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Synthetic Studies toward A-74528 and Synthesis of Cyclic Azobenzenes

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Erklärung

Diese Dissertation wurde im Sinne von § 7 der Promotionsordnung vom 28. November 2011 von Herrn Prof. Dr. Dirk Trauner betreut.

Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

München, den 14.01.2020

Martin Maier

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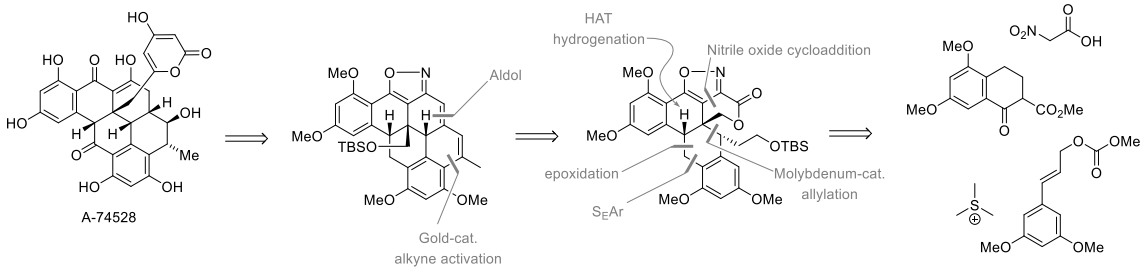
To my family and Pauline

Abstract

Part I: Synthetic studies toward A-74528

With thirty carbons A-74528 is one of the two largest type II polyketides known to date. It has a promising bioactivity linked to modulating RNAse L activity and mRNA degradation as part of the innate immune system and features a set of six contiguous stereocenters, which is atypical for this type of polyketide.

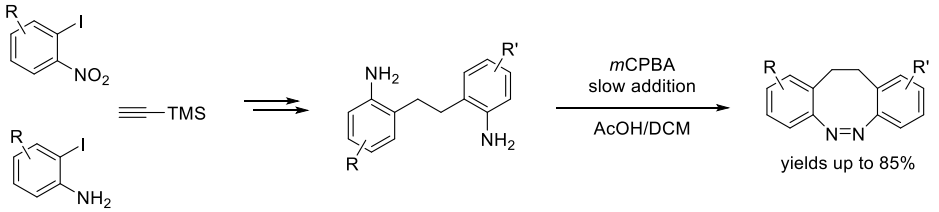
Two approaches toward the synthesis of A-74528 were investigated. A failed initial approach allowed identification of the most challenging reactions in the envisioned synthesis and supplied suitable model systems for studying the planned late-stage transformations. Following a revised approach, a highly advanced intermediate that already contains the full carbon skeleton of the hexacyclic core fragment of A-74528 was synthesized in a racemic fashion. Initial attempts to further evolve the most advanced synthetic intermediate toward the natural product failed and further investigations will be necessary. The key reactions of the revised approach is a highly diastereo- and regioselective molybdenum-catalyzed allylation, which enabled an efficient and convergent coupling of the two key building blocks, a ketoester and an allyl carbonate, and a gold-catalyzed alkyne activation forming the last ring system of the core fragment of A-74528.



Part II: Synthesis of cyclic azobenzenes

Diazocines, cyclic azobenzenes with an eight-membered ring, have distinct photophysical properties and are very promising to be useful photoswitches. However, there have been almost no applications of this type of azobenzene, due to the generally low-yielding synthesis and limited access to functionalized derivatives.

To enable the use of diazocines, a new synthetic approach based on the oxidative cyclization of dianiline precursors was developed. Furthermore, methods for the synthesis of the cyclization precursors as well as the late-stage derivatization of diazocines were developed. This allowed the preparation of more than forty, diversely functionalized diazocines. The yields of the oxidative cyclization proved to be predominantly good to moderate and in general significantly better than for all previously reported methods. The photophysical properties of the obtained diazocines were compared and several trends were identified.



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A special thanks goes to Dr. Andrii Shemet, Dr. Julius Reyes and Katharina Hüll for proofreading of this thesis and again to Andrii for continuing the efforts toward A-74528.

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In general, I want to thank all former and present member of the Trauner and Magauer research groups, who have contributed to the great working environment that I was allowed to experience.

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Finally, I do not want forget my housemate and research colleague Hugo Quintela Varela.

My biggest thanks go to my wife Pauline and my family for always supporting me.

Publications and conference contributions

Parts of this thesis have been published in peer-reviewed journals:

Maier, M. S.; Hüll, K.;* Reynders, M.;* Matsuura, B. S.;* Leippe, P.; Ko, T.; Schäffer, L.; Trauner, D. Oxidative Approach Enables Efficient Access to Cyclic Azobenzenes. *J. Am. Chem. Soc.* **2019**, *141*, 17295.

*These authors contributed equally to this work.

Parts of this thesis have been presented at scientific conferences:

Maier, M.; Hüll, K.; Matsuura, B.; Reynders, M.; Ko, T.;* Fehrentz, T.; Görldt, N.; Schäffer, L.; Klöcker, N.; Trauner, D. Sign Inversion in Photopharmacology: Modular Synthesis of Cyclic Azobenzenes (Poster Presentation). Artificial Molecular Switches and Motors Gordon Research Conference, Holderness, New Hampshire, USA, **2019**.

*The presentation was held by Tongil Ko.

Project Affiliation Disclosure

In this statement, I proclaim that the findings in the following thesis are the results of an effort involving more individuals than myself. Alongside the supervision of Prof. Dr. Dirk Trauner, here I list, in no particular order, the individuals that contributed to this work:

Part I: Synthetic studies toward A-74528

Georgios Toupalas (bachelor thesis), Jonas Feldmann (undergraduate student), Felix Richard Schäfer (bachelor thesis), Britta Weidinger (undergraduate student), Yudong Liu (undergraduate student)

Part II: Synthesis of cyclic azobenzenes

Katharina Hüll (photophysical characterization), Martin Reynders (synthetic method development), Bryan S. Matsuura (synthetic method development), Tongil Ko (undergraduate student), Lukas Schäffer (undergraduate student), Feng Yang (undergraduate student)

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Part I

Synthetic Studies toward
A-74528

1 Introduction

1.1 A-74528: 2'-PDE inhibitor and unusual polyketide

In 2004, a research group of the Sankyo company[a] reported their findings on a key enzyme of the 2-5A system and an inhibitor of a this enzyme.[1a] They identified a 2',5'-oligoadenylate phosphodiesterase (2'-PDE), which is involved in the deactivation of the 2-5A system. The 2-5A system is a pathway with antiviral and antitumor functions through unspecific RNA degradation by RNAse L. The RNAse L is activated by 2',5'-phospho-diester-linked oligoadenylates (2–5A) and the 2'-PDE degrades these oligoadenylates to AMP and ATP, which leads to deactivation of RNAse L. Thus, inhibitors of the 2'-PDE are potentially useful as antiviral and antitumor treatments. This was supported by the observations that overexpression of the 2'-PDE protected cells from interferon-induced antiproliferative activity and that viral replication was reduced by suppressing 2'-PDE activity with small interfering RNA or a 2'-PDE inhibitor. The 2'-PDE inhibitor that was used in these studies was a novel polyketide with a highly unusual structure isolated from *Streptomyces* sp. SANK 61196, which was named A-74528. It was possible to elucidate the complex structure of A-74528 (Figure 1) by extensive NMR experiments, while attempts to determine the structure and absolute configuration of A-74528 by X-ray crystallography failed.[1b] In the process, it was observed that the compound proved either unstable or unreactive toward chemical modification.

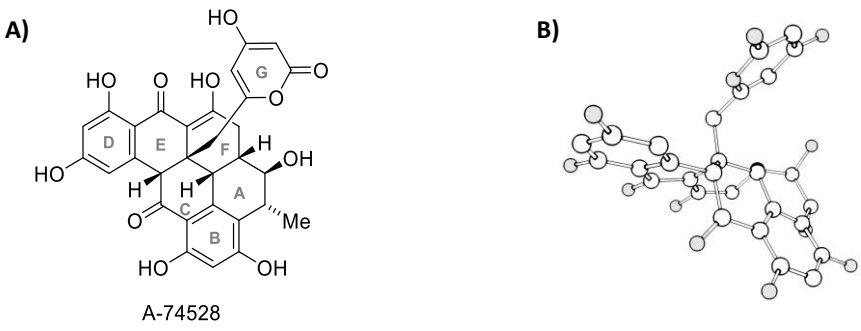


Figure 1 A) Structure of A-74528 and ring labels used in this work. **B)** Three-dimensional model of A-74528 (MMFF force field, hydrogen atoms omitted, pyrone moiety depicted in a random orientation).

A-74528 is a C_{30} polyketide, which consists of a hexacyclic main fragment that is connected to a 4-hydroxy-2-pyrone moiety through a methylene linker. The hexacyclic fragment contains a hydropyrene system with two adjoining aromatic rings. The aromatic rings and neighboring benzylic positions are highly oxidized, forming two acylresorcinol motifs. Apart from these two acylresorcinol motifs, the hexacyclic system is oxidized at two other positions, giving rise to a secondary alcohol and 1,3-diketone. As the hydrogens of all

[a]Now Daiichi Sankyo Company, Limited.

tertiary stereocenters at the ring junctions are oriented to the same side of the molecule or rather in the same direction, the hexacyclic fragment adopts a bent, L-shaped structure akin to an "open book". Both the extended sequence of contiguous stereocenters and the secondary alcohol found within A-74528 are unusual for this type polyketide. The former because aromatic polyketides of bacterial origin usually exhibit a smaller number and rather non-contiguous stereocenters. The latter because it does not follow the common 1,3-relation of oxygenated positions that is a consequence of the iterative biosynthesis of polyketides. Additionally, the sheer size of A-74528 is exceptional, with Fredericamycin A (Figure 2) being the only other known C_{30} type II polyketide.

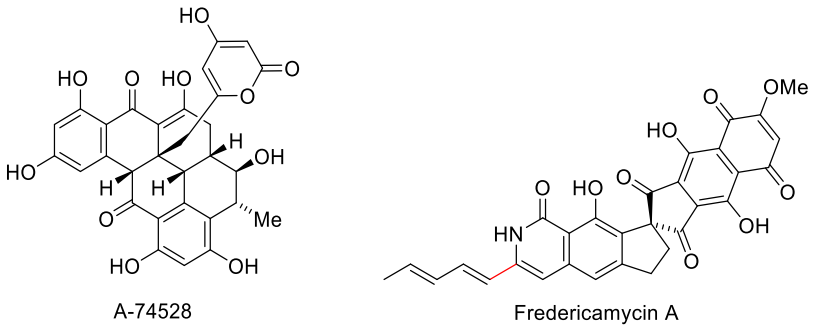
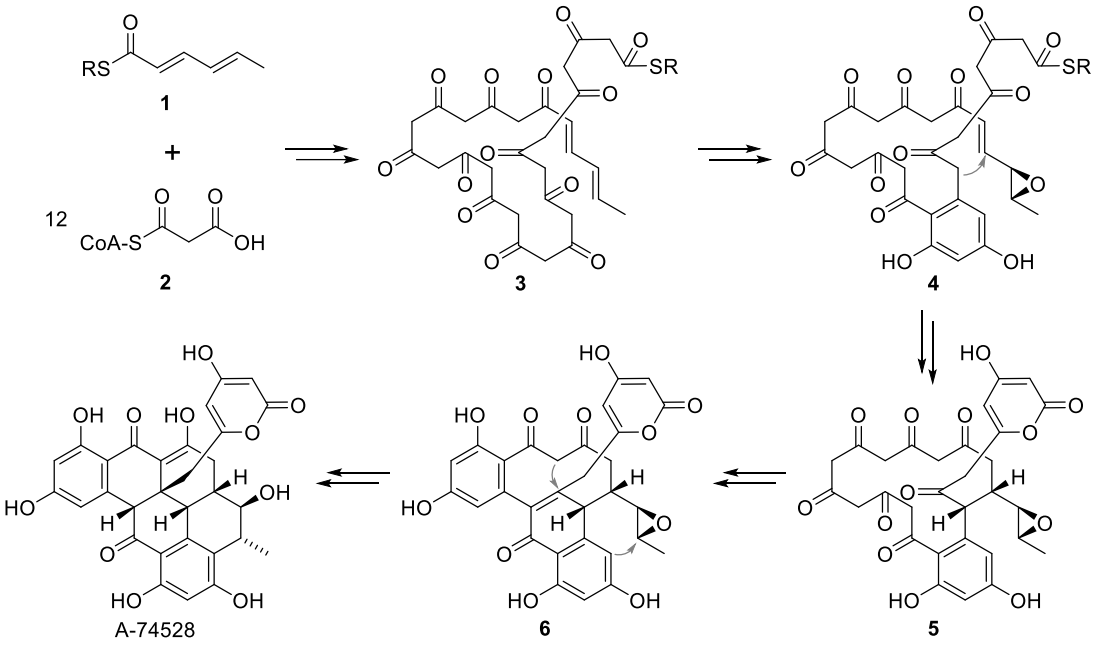


Figure 2 Comparison of the structures of A-74528 and Fredericamycin A.

The biosynthesis of A-74528 was investigated in detail by the group of Khosla.[2] These studies led to the identification of the gene cluster of the corresponding type II polyketide synthase, which showed a high level of homology to the biosynthetic machinery that produces Fredericamycin A. It was also found that many genes of the identified cluster are not necessary for the production of A-74528. Consequently, the set of necessary genes was identified and a minimal system for the biosynthesis of A-74528 was engineered. While the original *Streptomyces* strain and a heterologous *Streptomyces* host with the original gene cluster produced both Fredericamycin A and A-74528, the minimal system allowed the production of A-74528 in the absence of Fredericamycin A.

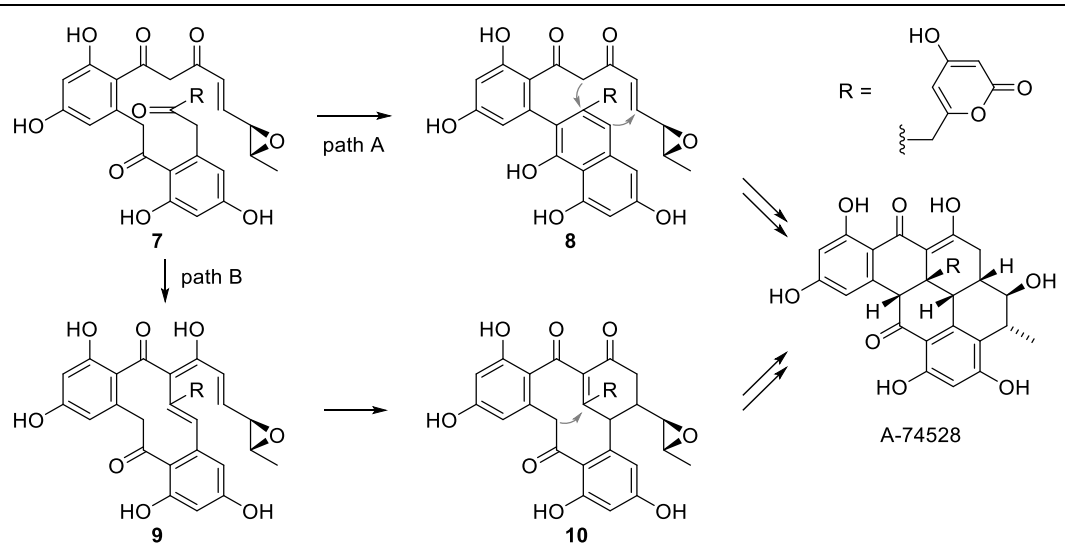
Based on their observations, the Khosla group also proposed a biosynthetic pathway, which explains the unusual position of the secondary alcohol as a result of an epoxidation and epoxide opening (Scheme 1).[2b] The other key steps in this proposal are two Michael additions that occur between intermediates **4** and **5** as well as **6** and A-74528. Together, these reactions would establish all six stereocenters. While the timing of the epoxidation and all cyclizations was purely speculative, it was assumed that an early epoxidation may serve to direct the regio- and stereoselectivity of the cyclization cascade. Starting from hexadienyl priming unit **1**, the following sequence of steps was assumed: Elongation of the priming unit **1** to the C_{30} intermediate **3**, epoxidation and formation of the first aromatic ring leading to resorcinol **4**, pyrone formation and the first Michael addition to afford

macrocycle **5**, formation of the second aromatic ring and aldol condensation to give enone **6**, epoxide opening and the second Michael addition to afford the final natural product A-74528.



Scheme 1 Selected intermediates of the biosynthetic pathway to A-75428 proposed by the group of Khosla (R = enzyme, CoA = Coenzyme A).

Several alternative biosynthetic intermediates were suggested by Trauner and Hager (Scheme 2).[3] They considered compound **7**, in which both aromatic rings and the pyrone are already present, to be a key intermediate.



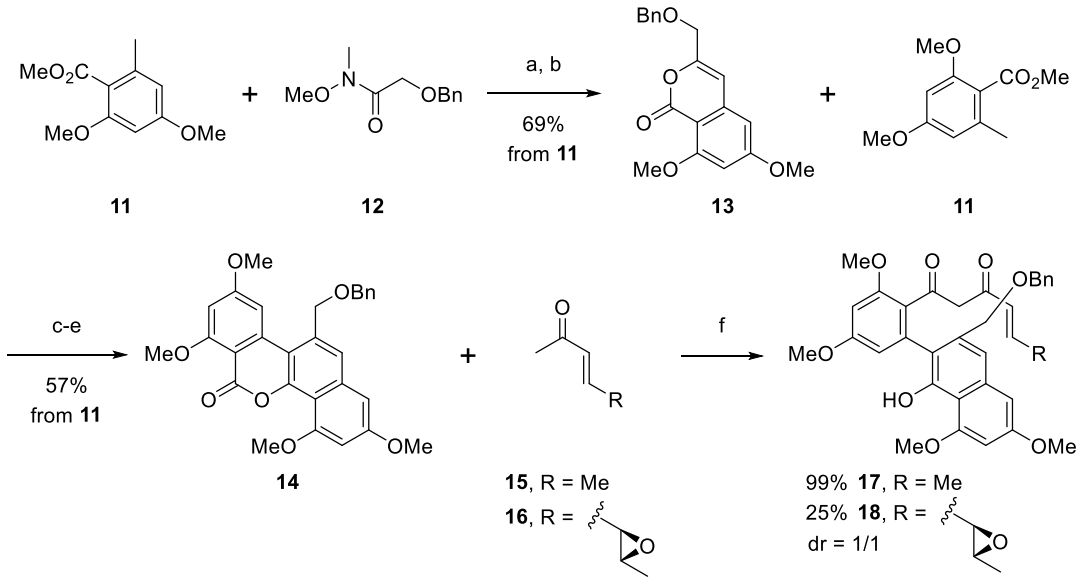
Scheme 2 Alternative biosynthetic intermediates toward A-74528 proposed by Trauner and Hager.

From intermediate **7** the cascade forming the final product could proceed in different ways, which would be initiated by first forming a 6-, 10-, 12- or 14-membered ring. Along these lines intermediates **8** and **9** were proposed. The former compound would lead to the

natural product through a dearomatizing double Michael addition (Scheme 2, path A) and the latter through a 6π-electrocyclization/Michael addition sequence (Scheme 2, path B).

1.2 Previous synthetic efforts

Currently, only one synthetic study toward A-74528 has been reported.[3] In this study, Trauner and Hager investigated a biomimetic approach toward A-74528 following one of their biosynthetic proposals (Scheme 2, path A). They employed orsellinic acid derivative **11** as a key building block, which allowed rapid access to precursors **17** and **18** for the presumed biomimetic cascade (Scheme 3).



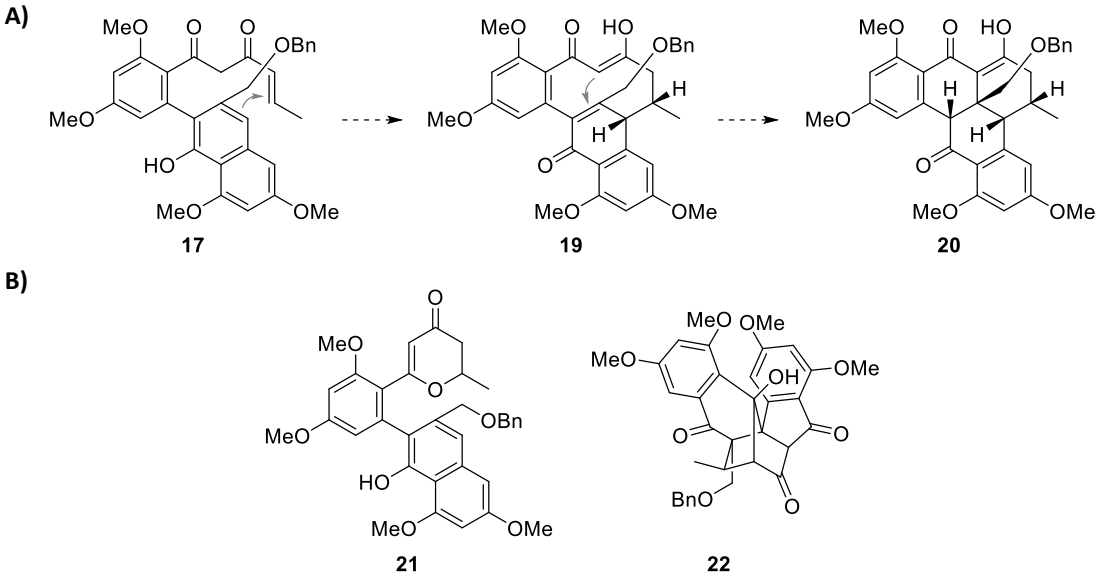
a) LDA, THF, −78 °C. b) DBU, DCM. c) LDA, THF, −78 °C. d) LiOH, water/MeOH. e) $(COCl)_2$, Et_3N, DMAP, DCM. f) KHMDS, THF, −78 °C.

Scheme 3 Biomimetic approach toward A-74528 by Trauner and Hager: Synthesis of cascade precursors.

By acylation of deprotonated orsellinic acid derivative **11** with Weinreb amide **12** and base-mediated cyclization, isocoumarin **13** was prepared in two steps. A second acylation of deprotonated orsellinic acid derivative **11** with isocoumarin **13**, followed by aldol condensation forming the naphthalene moiety and a hydrolysis/esterification sequence then afforded lactone **14**. From this shared intermediate two cascade precursors were prepared by Claisen condensation with unsaturated ketones **15** and **16**. This afforded diketone **17** and epoxy diketone **18** in a total yield over six steps of 39% and 10%, respectively.

As the truncated model compound **17** was easier accessible compared to epoxide **18** and does not contain the sensitive epoxide functionality, the proposed cyclization cascade was investigated with compound **17** (Scheme 4). Despite testing a broad range of conditions, the desired product **20,** which would result from a dearomatizing double Michael addition cascade, could not be observed. However, some noteworthy side products were isolated, such as dihydropyrone **21** and complex polycyclic structure **22**. Compound **21** is presumed

to result from an oxa-Michael addition and compound **22** is presumed to arise by an initial oxidation of the naphthalene moiety to the naphthoquinone followed by a sequence of two Michael additions and an Aldol addition.



Scheme 4 Biomimetic approach toward A-74528 by Trauner and Hager: **A)** Desired transformation. **B)** Observed products.

1.3 Project objectives

This part of the thesis describes the efforts toward the synthesis of A-74528. As highlighted in the preceding introduction, this polyketide is a molecule with the potential to be used to develop an antiviral or anticancer medicine and has an unusual and complex structure, which so far has not succumbed to total synthesis. All this makes A-74528 a challenging and intriguing synthetic target and provided the motivation to initiate the presented work.

Currently, there is no crystal structure of the natural product available and its absolute configuration is not known. A total synthesis of A-74528 should lead to the identification of the absolute configuration and conclusively prove the assigned structure, which is only based on spectroscopic data. To be able to provide the naturally occurring enantiomer the synthesis should be able to access both possible enantiomers of A-74528.

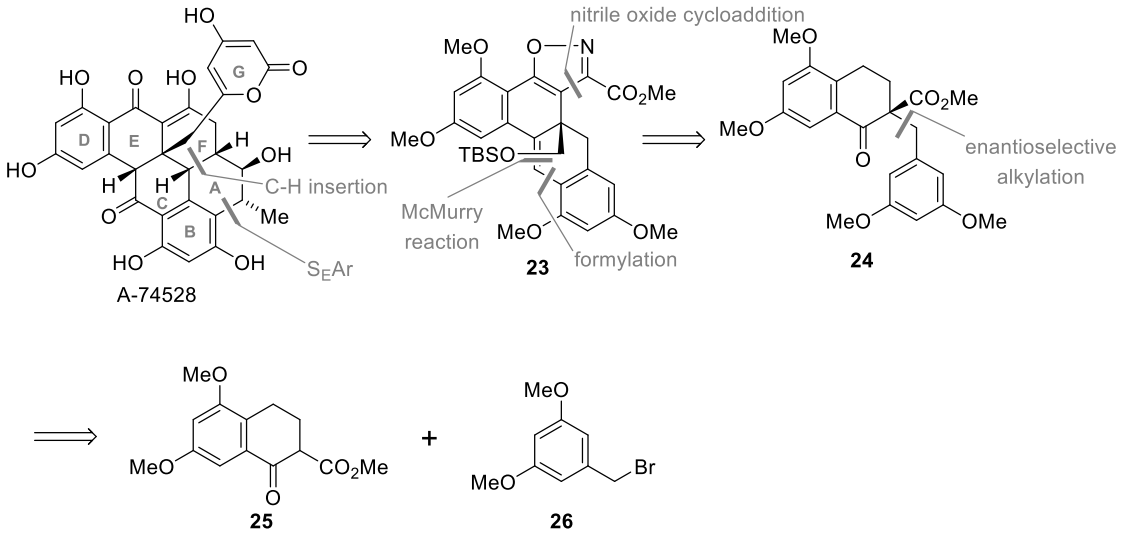
Apart from simply solving the synthetic challenge, the synthetic approach should be scalable and in principle allow the synthesis of various analogs of A-74528 to enable structure-activity relationship (SAR) studies. Providing a simplified, yet bioactive analog would be of interest, as well as a more chemically robust derivative, as A-74528 might suffer from instability under application conditions.[1b] Thus, contrary to previous efforts that focused on a biomimetic cascade reaction,[3] it was decided to follow a stepwise, non-biomimetic strategy.

2 First-generation approach

2.1 Synthetic strategy

Considering the limited stability of A-74528, it was expected that introducing potentially sensitive moieties, such as the 1,3-diketone or the pyrone, at a late stage or keeping them masked until the final steps of the synthesis would be prudent. Additionally, motifs like the secondary alcohol or the benzylic carbonyl groups should be introduced at a point that allows divergent access to derivatives for SAR-studies from late-stage intermediates. With respect to the stereochemistry of A-74528, it was envisioned that it would be possible to set the quaternary stereocenter early in the synthesis and that the configuration of all other stereocenters could be derived from the configuration of this key stereocenter.

Consequently, in a retrosynthetic analysis (Scheme 5) A-74528 was traced back to isoxazole **23**, which is missing the A- and F-rings. Assembling the F-ring would require forming a bond at a non-functionalized benzylic position. Although there is no good precedence, it was hoped that an intramolecular C-H-insertion[4] might be possible at this position. Alternatively, the benzylic position would need to be pre-functionalized, for example by a benzylic oxidation. With the F-ring formed, the A-ring was expected to be easily closed by an electrophilic aromatic substitution on the electron-rich dimethoxybenzene moiety.



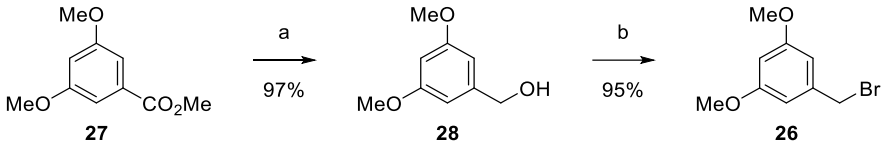
Scheme 5 Retrosynthetic analysis of A-74528.

Isoxazole **23** in turn could be derived from β-ketoester **24**, which requires a nitrile oxide cycloaddition and introduction of a one-carbon fragment to establish the stilbene motif as well as the C-ring. This was expected to be possible by a sequence of regioselective formylation and reductive carbonyl-carbonyl coupling.[5] To form the isoxazole moiety of intermediate **23** it was planned to employ a nitrile oxide cycloaddition. Ultimately, the

retrosynthetic analysis led to β-ketoester **25** and known benzyl bromide **26**[6] as the initial building blocks. Examples of the alkylation of β-ketoester both in high yields and with high enantiomeric excess have been reported for phase-transfer catalysis with chiral ammonium ions derived from binaphtyl[7a] compounds and cinchonine.[7b]

2.2 Synthesis of building blocks

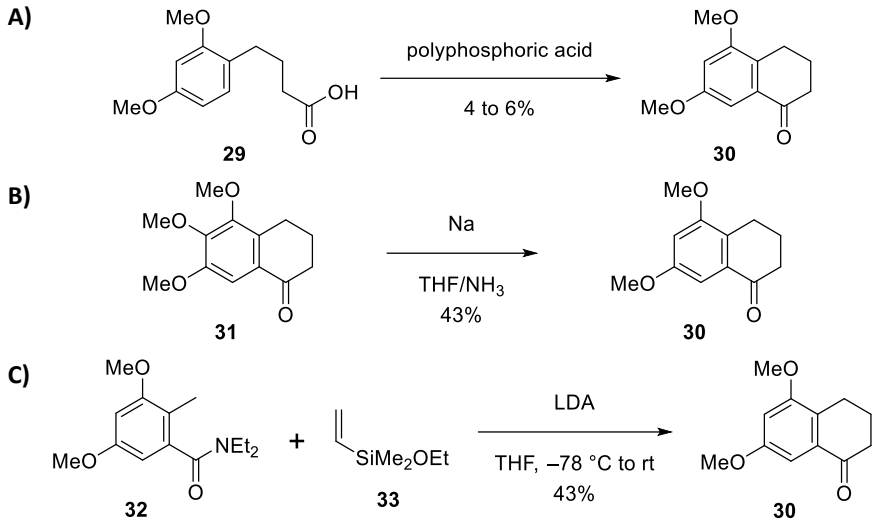
According to the conceived synthetic strategy, the first task was to establish a robust and scalable route to the key building blocks **25** and **26**. The benzyl bromide **26** was easily prepared by reduction of 3,5-dimethoxybenzoate **27** with lithium aluminum hydride, followed by treatment with phosphorous tribromide in an overall yield of 92% (Scheme 6). The obtained material was pure enough to be used without further purification and both reactions could be performed without problems on a scale of multiple tens of grams. The specific procedure for the reduction of methyl benzoate **27** was based on the conditions reported by Denmark[8] and scaled up to 80 grams per batch. While 3,5-dimethoxybenzoic acid would be a cheaper starting material compared to methyl ester **27**, this alternative substrate suffered specifically on large scales from its lower solubility in tetrahydrofuran and the vigorous formation of hydrogen upon contact with the reductant.



a) LAH, THF, 0 °C. b) PBr_3, DCM, 0 °C.

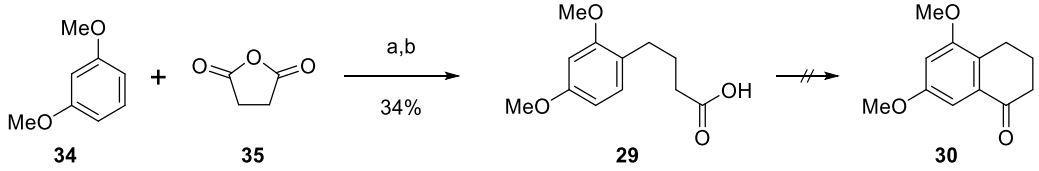
Scheme 6 Synthesis of benzyl bromide **26**.

Compared to the synthesis of the benzyl bromide building block, preparing the β-ketoester **25** proved more challenging. Initially, it was planned to prepare this building block by acylation of tetralone **30**, for which three approaches have been reported (Scheme 7).[9] None of reported synthesis of tetralone **30** were expected to be easily scalable, but the cyclization of phenylbutyric acid **29** to tetralone **30** was still further investigated (Scheme 8).



Scheme 7 Reported routes to tetralone **30**: **A)** Davies et al.[9b] **B)** Rao.[9c] **C)** Date et al.[9d]

Reaction of an excess of dimethoxybenzene **34** with succinic anhydride, followed by reduction at the benzylic position with triethylsilane in trifluoroacetic acid provided cyclization substrate **29**.[10] These two reactions proceeded in a rather disappointing overall yield of 34% and the product of the initial acylation step as well as the reduction product **29** were not conveniently purified. The cyclization of acid **29** to tetralone **30** was investigated with several reagents that had not not tested in the previous reports (Ms_2O, conc. H_2SO_4, TFAA/TFA, P_2O_5/MsOH, cyanuric chloride/$AlCl_3$/pyridine[11]), but the desired product was not obtained in any case. This was not surprising, as Davies et al. had already reported that acid **29** was a particularly bad substrate for the desired reaction and they had obtained the desired product **30** only in 4 to 6% yield.

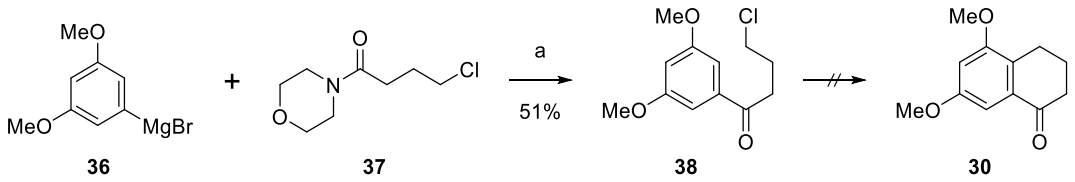


a) $AlCl_3$, DCM, 0 °C. b) Et_3SiH, TFA.

Scheme 8 Attempt to synthesize tetralone **30** from phenylbutyric acid **29**.

Considering that the acylation in *meta*-position with respect to the methoxy groups in acid **29** is problematic, it was assumed that a cyclization through an attack in the *para*-position might be more successful. Following this reasoning, alternative cyclization precursors were tested.

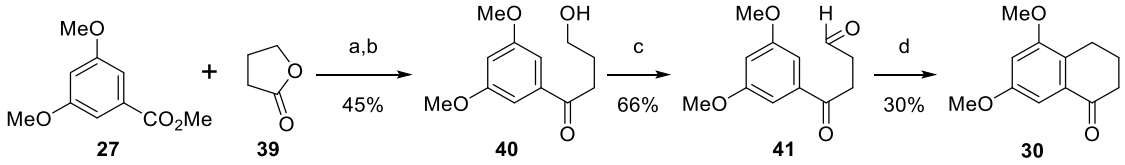
First, the chloride **38** was prepared from reaction of Grignard reagent **36** with known morpholine amide **37**[12] (Scheme 9) and exposed to various Lewis acids ($AlCl_3$, AgOTf, Ag_2O, $TiCl_4$, $InBr_3$). However, this did not afford the desired tetralone product.



a) THF, 0 °C to rt.

Scheme 9 Attempt to synthesize tetralone **30** from chloride **38**.

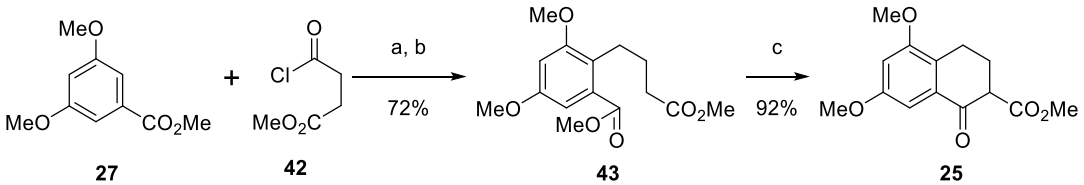
Second, the aldehyde **41** was prepared in three steps from methyl benzoate **27** and γ-butyrolactone and successfully cyclized to tetralone **30** (Scheme 10). Crossed Claisen condensation followed by decarboxylative lactone opening afforded alcohol **40**, which was oxidized to aldehyde **41** with Dess-Martin periodinane.[13] Finally, reductive cyclization upon treatment with trifluoroacetic acid and triethylsilane afforded the desired product **30** in an overall yield of 9%. As this yield was not assumed to be sufficient for preparing larger amounts of tetralone **30** and the results of the decarboxylative lactone opening were also varying significantly from batch to batch this route was abandoned.



a) LiHMDS, THF, −78 °C to rt. b) LiOH, H_2O/THF, 65 °C. c) DMP, DCM. d) Et_3SiH, TFA, DCM.

Scheme 10 Synthesis of tetralone **30** through aldehyde **41.**

As tetralone **30** had turned out to be a rather troublesome intermediate toward β-ketoester **25**, a more direct approach featuring a Dieckmann condensation as the key reaction was developed (Scheme 11). A Friedel-Crafts acylation of dimethoxy-benzoate **27** with acid chloride **42**, followed by ketone reduction with triethylsilane in trifluoroacetic acid[14] and treatment with potassium *tert*-butoxide led to desired compound **25** in 66% yield over three steps. This approach proved scalable and robust, easily providing multiple tens of grams of material.

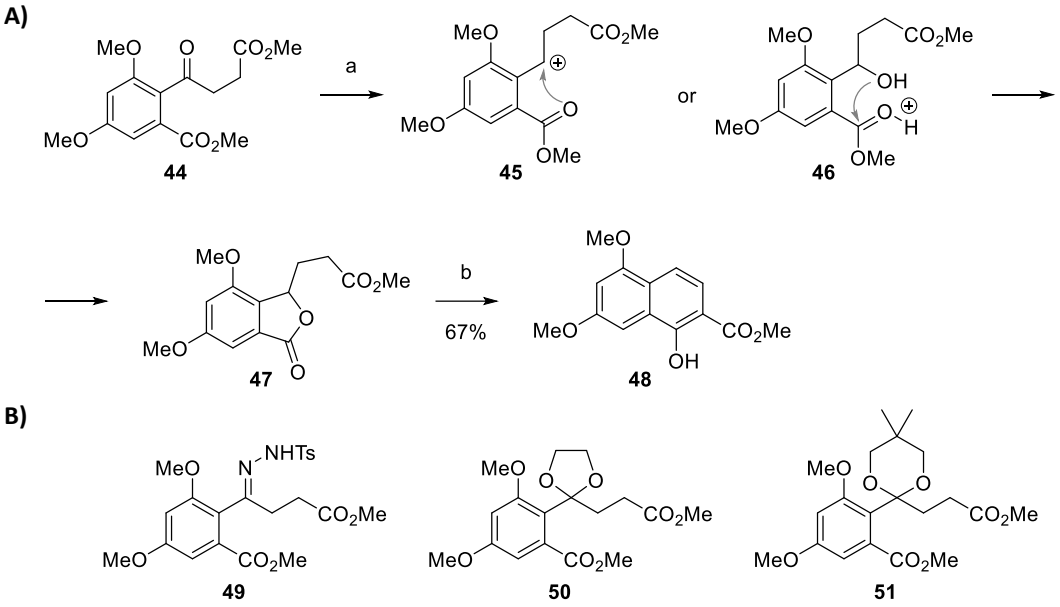


a) $AlCl_3$, DCE, 0 °C. b) Et_3SiH, TFA. c) KO*t*Bu, THF, 0 °C.

Scheme 11 Synthesis of β-ketoester **25**.

While the first and last step of this sequence have a yield of more than 90%, the reduction of ketone **44** (see Scheme 12) proved to be the most challenging step. The main issue during this reaction is the formation of lactone **47**, which could originate from either benzylic

cation **45** or carboxonium ion **46**. Apart from reducing the overall yield, the formation of side product **47** significantly complicates the purification and introduces the need for chromatography to remove side product **47** from desired reduction product **43**. While β-ketoester **25** can in principle be purified by crystallization, this was not sufficient to remove naphthalene **48**, which results from lactone **47** under the conditions of the Dieckmann condensation.



a) Et_3SiH, TFA. b) KO*t*Bu, THF, 0 °C.

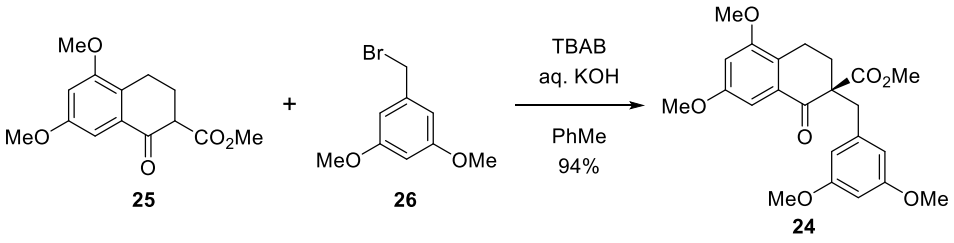
Scheme 12 A) Plausible mechanisms for the formation of lactone **47** from ketone **44** during ionic reduction and transformation to naphthalene. **48**. **B)** Failed alternative intermediates.

Typically, neat ketone **44** was treated with a slight excess of triethylsilane (2.4 eq.) followed by a larger excess of trifluoroacetic acid (10 eq.). This approach was practical and reliably provided the product **43** on a scale several tens of grams per batch. Attempts were made to optimize the reaction conditions and suppress the formation of lactone **47**, but no ideal solution to the problem could be established. Reducing the amount of trifluoroacetic acid and performing the reaction more dilute, for example by adding a small amount of dichloromethane, strongly increased the formation of side product **37**. Cooling the reaction did not clearly change the ratio of product to side product, but mainly lowered reaction rates. Only replacing trifluoroacetic acid with Lewis acids (TMSOTf, $BF_3{\cdot}OEt$, $TiCl_4$) led to a diminished amount of side product **47**. Especially titanium tetrachloride did perform quite well and allowed to obtain the product with an increased yield of roughly 85% on a small scale of several hundred milligrams. However, this was not further investigated, as the workup is significantly more complicated for the reaction with titanium tetrachloride and the reaction with trifluoroacetic acid had proven to be reliable on large scale and sufficiently efficient. Completely different conditions to reduce ketone **44**, for example through tosyl hydrazone **49**, and transformation of the ketone moiety to an acetal, like in compounds **50**

or **51**, were also tested. All of these attempts failed due to large amounts of unreacted substrate **44** remaining or no reaction occurring at all. This low reactivity can be assumed to be a consequence of the sterically congested surroundings of the benzylic ketone moiety.

2.3 Synthesis of a tetracyclic intermediate

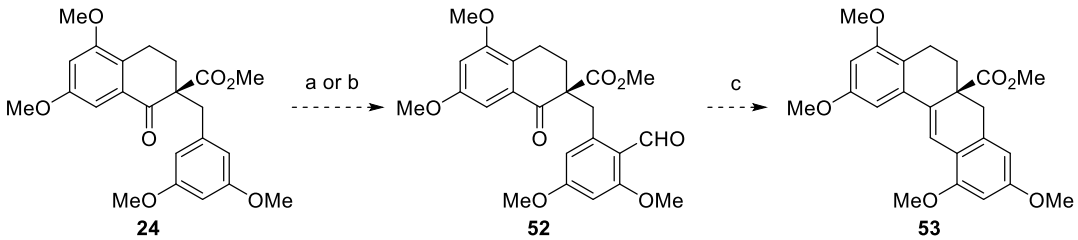
Having established a scalable and practical access to building blocks **25** and **26**, the next step was to join these fragments and form the C-ring of A-74528. Consequently, β-ketoester **25** was alkylated with benzyl bromide **26** in a biphasic system under phase-transfer catalysis with tetrabutylammonium bromide (Scheme 13).



Scheme 13 Joining of building blocks **25** and **26**.

This cleanly afforded the benzylation product **24** in a yield of more than 90% and in high purity after simple purification by washing with ethanol. Also, the reaction could be performed on a scale of more than ten grams product without any issues. An excess of benzyl bromide **26** (1.6 eq.) was required for an efficient conversion, but the excess material could easily be recovered. As described in section 2.1 this alkylation was planned to be the key enantioselective step in an enantioselective approach to A-74528. However, performing this reaction enantioselectively was postponed at this point, as it was deemed more reasonable to first establish the overall synthesis with the more easily available racemic material before focusing on providing enantiopure material.

Initial attempts to selectively formylate compound **24** with DMF/$POCl_3$[15a] or Cl_2CHOMe and $TiCl_4$/$AlCl_3$[15b] resulted in no reaction or a mixture of products and thus did not efficiently provide the desired formylation product **52**, which was planned to be cyclized to stilbene **53** under reductive conditions (Scheme 14).

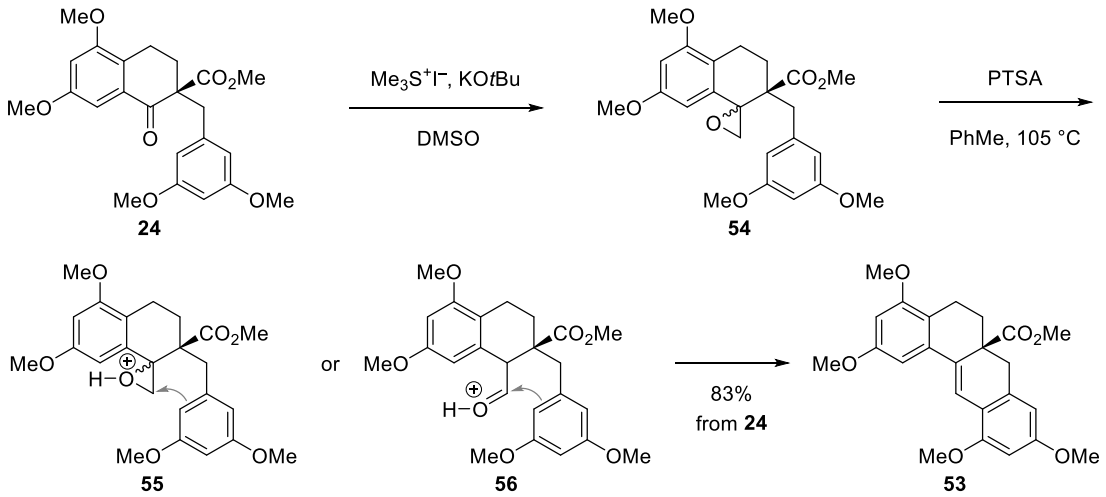


a) DMF/$POCl_3$. b) Cl_2CH_2OMe, $TiCl_4$ or $AlCl_3$. c) Zn, $TiCl_4$.

Scheme 14 Planned synthesis of stilbene **53** through regioselective formylation and reductive cyclization.

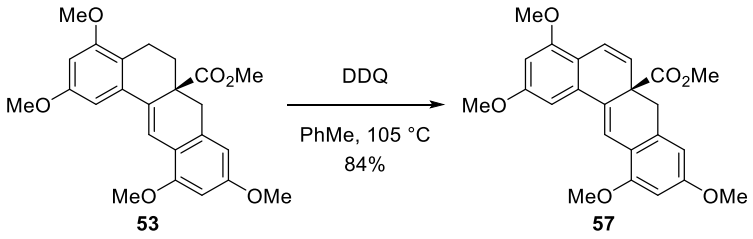
A more successful method to introduce a one carbon fragment and close the C-ring was transforming the ketone moiety of compound **24** to the epoxide **54** by treatment with trimethylsulfonium iodide[16] and potassium *tert*-butoxide, followed by acid-mediated transformation to stilbene **53** (Scheme 15).[17] This afforded the tetracyclic product **53** in 83% yield. Regarding the mechanism of the transformation two intramolecular electrophilic aromatic substitutions can be considered, either directly through attack of the epoxide as depicted for compound **55** or after rearrangement to aldehyde **56**. According to Baldwin's rules[18] the former would be a disfavored 6-*endo-tet* process, while the latter would be a favored 6-*exo-trig* process. Thus, the formation of stilbene **53** through aldehyde **56** may be considered more plausible.

In an early screening of conditions, strong hydrogen bond donor solvents (TFE, HFIP) and a variety of Brønsted acids (PPTS, TFA, CSA) and Lewis acids ($InBr_3$, $TiCl_4$, $BF_3{\cdot}OEt_2$, Tf_2O) in dichloromethane were tested for the formation of stilbene **53** from epoxide **54**. Due to the fluorescence of stilbene **53,** the different conditions could easily be checked for the presence of the desired product and analysis by thin-layer chromatography revealed that only $BF_3{\cdot}OEt_2$ resulted in clean conversion to the desired product. However, successive attempts to scale up the reaction with $BF_3{\cdot}OEt_2$ did only afford the product **53** in a low yield of about 20%. Suspecting that the mixture of compounds observed with Brønsted acids in the initial screening might be intermediates of the conversion of epoxide **54** to stilbene **53**, the reaction was tested with *para*-toluenesulfonic acid in toluene at elevated temperature, which afforded the stilbene **53** in good yield.



Scheme 15 Transformation of β-ketoester **24** to stilbene **53** and possible intermediates.

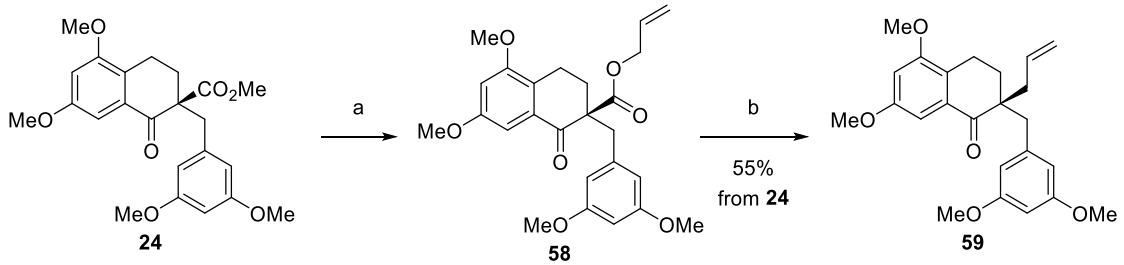
To prepare for successive transformations, stilbene **53** was dehydrogenated with DDQ, which afforded diene **57** in 84% yield.



Scheme 16 Dehydrogenation of stilbene **53**.

2.4 Decarboxylative allylation investigations

As an alternative to phase-transfer catalyzed alkylation as the enantioselective key reaction, palladium-catalyzed decarboxylative allylation[19] was also considered. To assess such an approach, allyl ester **58** was prepared from methyl ester **24** by treatment with titanium isopropoxide in allyl alcohol and further transformed to racemic decarboxylative allylation product **59** under palladium catalysis with a yield of 55% over two steps (Scheme 17). This showed that decarboxylative allylation may be a potential alternative to the currently followed strategy, but the access to allyl ester would need to be improved. Attempts to introduce the allyl ester earlier in the synthesis had failed. The main issues during transesterification were incomplete conversion of methyl ester **24** and formation of significant amounts of the corresponding isopropyl ester in addition to allyl ester **58**.

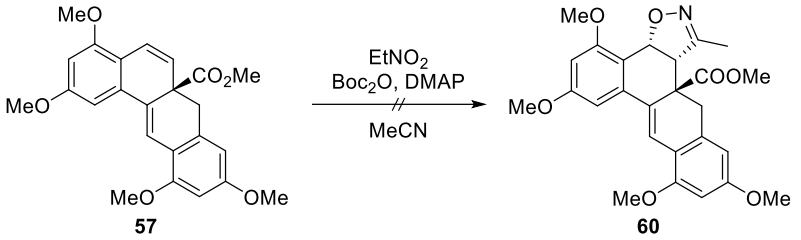


a) Ti(O*i*Pr)$_4$, allyl alcohol, 70 °C. b) Pd(PPh$_3$)$_4$, PhMe, 100 °C.

Scheme 17 Investigation of a decarboxylative allylation strategy.

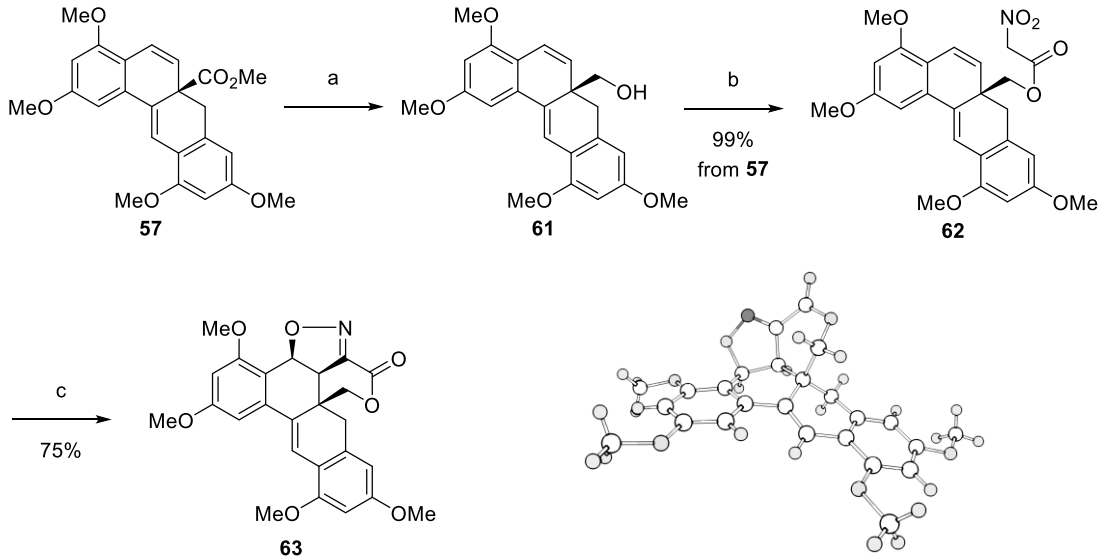
2.5 Nitrile oxide ycycloaddition

To install the 1,3-diketone of A-74528 in the masked form of an isoxazole and to set the stage for installing the F-ring system, it was now necessary to perform a selective nitrile oxide cycloaddition on the less substituted double bond of diene **57**. In a preliminary test reaction diene **57** was exposed to the nitrile oxide generated from nitroethane upon reaction with 4-(dimethylamino)pyridine and di-*tert*-butyl dicarbonate[20a] (Scheme 18). Predominantly unreacted starting material was left in the case of diene **57** instead of forming isoxazoline **60**, while a test reaction with styrene under the same conditions afforded the expected cycloaddition product 3-methyl-5-phenyl-2-isoxazoline. This showed that compound **57** did not easily undergo an intermolecular nitrile oxide cycloaddition.



Scheme 18 Initial intermolecular nitrile oxide cycloaddition test.

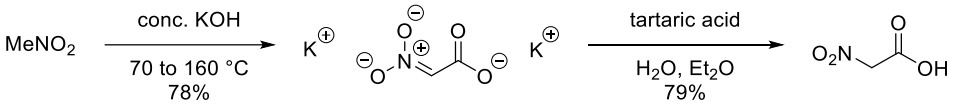
Thus, instead of an intermolecular reaction an intramolecular reaction was tested (Scheme 19). Ester **57** was reduced to alcohol **61** and then coupled with nitroacetic acid, which afforded cycloaddition precursor **62** in near perfect yield.



a) DIBAL-H, PhMe, 0 °C. b) Nitroacetic acid, DIC, THF/DCM, 0 °C. c) 4-Cl-PhNCO, Et_3N, PhMe, 105 °C.

Scheme 19 Formation nitroacetic acid ester **62** and isoxazoline **63**, with X-ray structure of isoxazoline **63**.

To achieve full conversion of alcohol **61** it was necessary to employ a significant excess of nitroacetic acid (2.2 eq.) as well as coupling reagent *N*,*N*′-diisopropylcarbodiimide (2.5 eq.). Also, the choice of solvent did play an important role for this step. While tetrahydrofuran is often employed for the formation of nitroacetic acid esters from alcohols after activation with carbodiimide reagents, it was found that dichloromethane gave much better results in our case. Surprisingly, attempts to improve the reaction outcome by addition of 4-(dimethylamino)pyridine rather resulted in a detrimental effect. The nitroacetic acid was prepared starting from nitromethane by treatment with concentrated potassium hydroxide according to the procedure by Zen et al.[21a] followed by acidifying the dipotassium salt with tartaric acid in a modified version of the procedure reported by Armarego[21b] (Scheme 20).



Scheme 20 Preparation of nitroacetic acid.

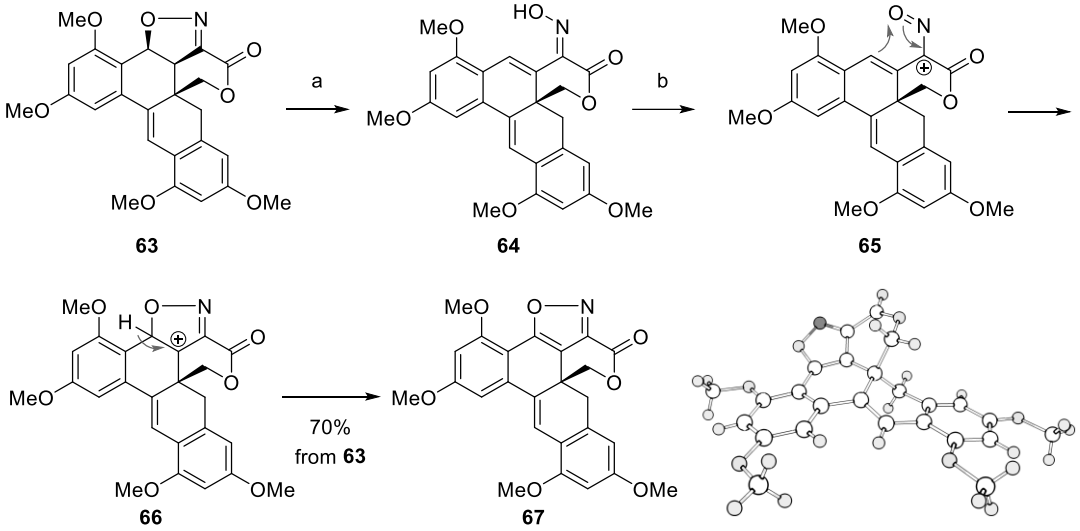
To transform the cycloaddition precursor **62** to the nitrile oxide and form isoxazoline **63**, a modification of the conditions developed by Mukaiyama[20b] was highly effective. Addition of 4-chlorophenyl isocyanate to a hot, dilute solution of triethylamine and compound **62** in toluene afforded isoxazoline **63** in a yield of 74%. The structure of isoxazoline **63** was confirmed by X-ray crystallography.

Surprisingly, compared to the catalytic amounts of base that are usually employed in the Mukaiyama conditions, it was necessary to use a superstoichiometric amount of triethylamine to reliably achieve full conversion of the starting material **62** in the cycloaddition. Therefore, the isocyanate was added slowly to avoid nitrile oxide dimerization. This slightly improved the yield compared to addition of the isocyanate in one batch. Alternative solvents (DCE) or reagents (Boc_2O/DMAP, TMSCl/Et_3N, DABCO)[20a,c,d] did result in the formation of increased amounts of side products or did not affect substrate **62** and no reaction occurred. A curious result was observed with di-*tert*-butyl dicarbonate and 4-(dimethylamino)pyridine. In this case the substrate **62** was consumed, but no product was formed. However, upon treatment with acid part of the resulting material was converted back to substrate **62**. Thus, a product carrying a *tert*-butyloxycarbonyl group seems to form but not to react further to the nitrile oxide.

The largest issue of the cycloaddition reaction was the purification. Initially, phenyl isocyanate was employed, which led to byproducts that were problematic to remove. Toluene diisocyanate was also tested but not found to be more practical overall, as the resulting chunks of polymeric byproducts complicated the workup and were sticking to the reaction vessel walls. Finally, it was noticed that the byproducts formed from 4-chlorophenyl isocyanate could be separated sufficiently well from cycloaddition product **63**.

2.6 Isoxazoline oxidation

After the cycloaddition the isoxazoline **63** had to be oxidized to the corresponding isoxazole, which was remarkably challenging. Simple treating isoxazoline **63** with standard oxidizing reagents (DDQ, *p*-chloranil, MnO_2)[22] either gave no reaction or the reaction was quite sluggish. A faster oxidation was observed upon using a combination of DDQ and a strong acid (PTSA), which was intended to increase the reactivity of the quinone oxidant. Finally, it was observed that the heterocyclic ring of isoxazoline **63** upon treatment with a sufficiently strong acid opens to form the unsaturated oxime **64**, which is much more susceptible to oxidation (Scheme 21).



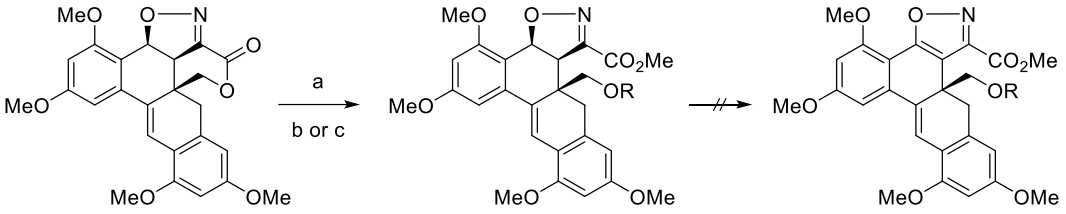
a) MsOH, $CHCl_3$ b) DDQ, PhH, 75 °C.

Scheme 21 Oxidation of isoxazoline **63** to isoxazole **67** with presumed intermediates and X-ray structure of isoxazole **67**.

As the yields proved to be higher and more reliable than by directly using a combination of DDQ and acid, the oxidation to the isoxazole was performed as a two-step procedure. First the isoxazoline **63** was treated with acid to obtain oxime **64**, which was then subjected to an aqueous workup to remove the acid followed by oxidation of the crude material. Using methanesulfonic acid in the first step and DDQ in the second step, this allowed to obtain isoxazole **67** in 70% yield. This overall yield is in the same range as the general values reported for the oxidation of unsaturated oximes to isoxazoles.[22] Using trifluoroacetic acid

for the transformation to the oxime did give similar results. A plausible mechanism for the oxidation would be the initial formation of nitroso-cation **65**, followed by electrocyclic ring closure to cation **66** and finally deprotonation to isoxazole **67**. The structure of isoxazole **67** was confirmed by X-ray crystallography.

To determine if the unexpected issues during the oxidation of isoxazoline **63** were a result of strain resulting from the presence of the lactone, the oxidation was also tested after methanolysis of the lactone moiety. Therefore, lactone **63** was converted to a methyl ester by treatment with catalytic amounts of 4-(dimethylamino)pyridine in methanol and the resulting free neopentylic alcohol was directly protected to obtain silyl ether **68** and pivalate **69**. However, these two compounds could not be oxidized more easily to the corresponding isoxazoles **23** and **70** than lactone **63** to isoxazole **67**. In both cases mixtures of products were obtained. In the case of silyl ether **68**, a major component was present in the mixture, but this compound was assumed to not be the desired product **23** based on inspection of the ^{1}H-NMR spectrum[a] of the crude reaction mixture. This was later confirmed by comparison to isoxazole **23** prepared through a different route (see page 21), which allowed to identify isoxazole **23** as a minor component of the mixture obtained upon reaction with DDQ.



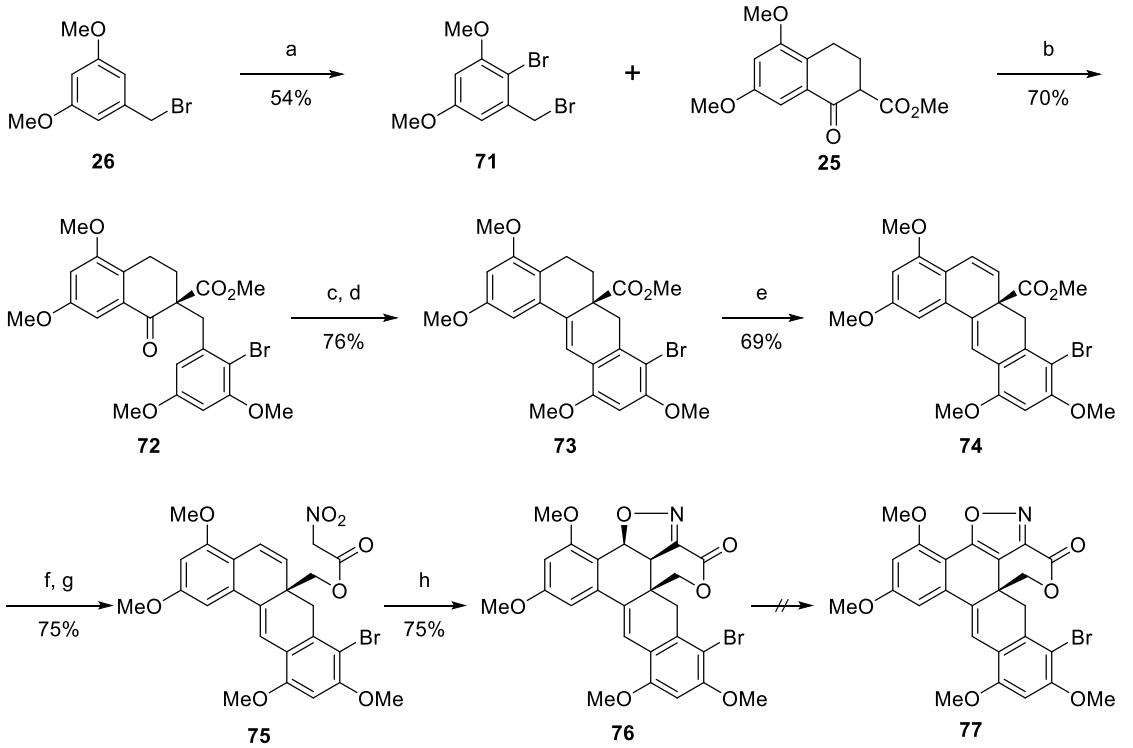
a) DMAP, MeOH, 60 °C. b) TBSCl, imidazole, DMF. c) PivCl, Et_3N, DMAP, DCM

Scheme 22 Isoxazoline oxidation attempts with silyl ether **68** and pivalate **69**.

[a]In $CDCl_3$.

2.7 Attempt to prepare a brominated analog

In parallel to developing the synthesis of isoxazole **67**, the brominated analog **77** was also pursued (Scheme 23). Such a brominated version would provide an additional functional handle that could facilitate the formation of the A- and F-ring systems of A-74528. Thus, bromoisoxazoline **76** was prepared using the same synthetic route as for the non-brominated isoxazole **77**, except for replacing benzyl bromide **26** with bromobenzyl bromide **71**, which was prepared from the former by reaction with *N*-bromosuccinimide.



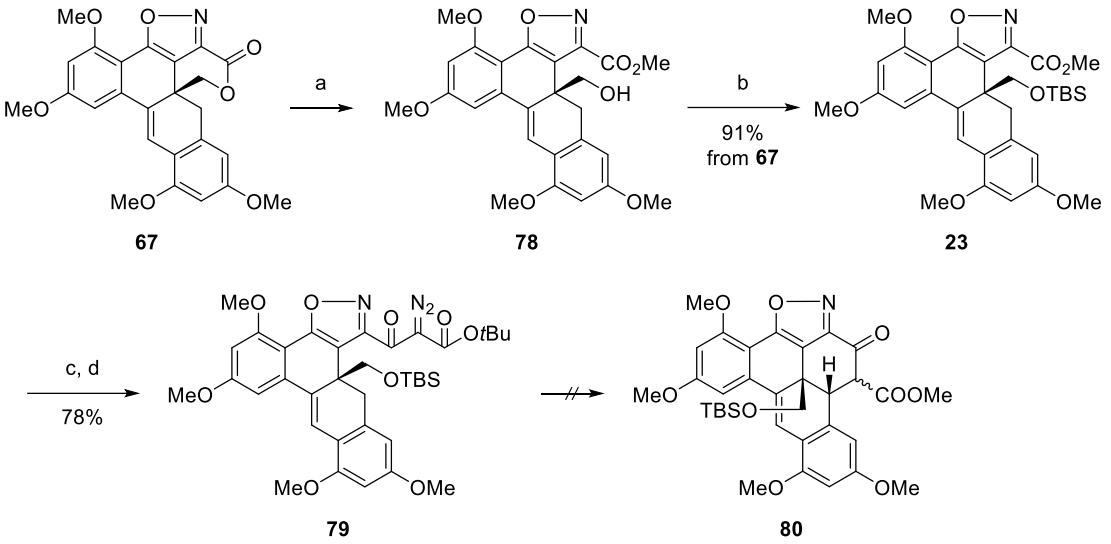
a) NBS, DCM, 0 °C to rt. b) TBAB, conc. KOH, PhMe. c) $Me_3S^+I^-$, KO*t*Bu, THF/DMSO. d) PTSA, PhMe, 105 °C. e) DDQ, PhMe, 105 °C. f) DIBAL-H, PhMe, 0 °C. g) DIC, nitroacetic acid, THF/DCM, 0 °C to rt. h) 4-Cl-PhNCO, Et_3N, PhMe, 105 °C.

Scheme 23 Synthesis of brominated isoxazoline **76** and inaccessible, desired isoxazole **77**.

Although isoxazoline **76** was still easily prepared in gram amounts, the yields were on average lower compared to the non-brominated analogs. The lower yields can be assumed to be connected to the significantly lower solubility of the brominated compounds, which did not pose a crucial problem until the oxidation of isoxazoline **76** to isoxazole **77**. This oxidation failed completely using the two-step procedure described in the preceding section, due to formation of an almost insoluble material after treatment with trifluoroacetic acid, which also did not become more soluble again after exposure to DDQ. It has to be mentioned here that the direct formation of bromoisoxazole **77** from isoxazole **67** with *N*-bromosuccinimide has also been tried and gave a complex mixture of compounds. In consequence, no further attempts toward bromoisoxazole **77** were performed.

2.8 Attempt to form F-ring

To form the next ring of the tetracyclic core of A-74528, lactone **67** was transformed to α-diazo-ketoester **79** in a four-step sequence with an overall yield of 71% (Scheme 24). After methanolysis of lactone **67** the resulting alcohol **78** was directly converted to silyl ether **23** without purification. Initial attempts to purify alcohol **78**, resulted in a significantly lower yield for the methanolysis step alone than for the two-step sequence, which indicates a limited stability of free alcohol **78**.



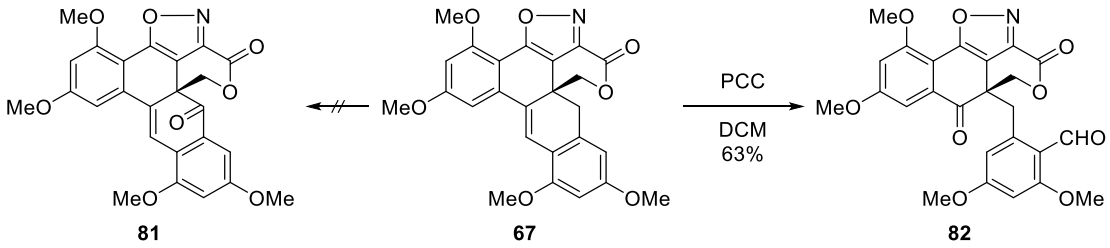
a) DMAP, MeOH/DCE, 60 °C. b) 2,6-lutidine, TBSOTf, DCM, 0 °C. c) AcO*t*Bu, LiHMDS, THF, –78 °C to rt. d) *p*ABSA, Et_3N, 0 °C to rt, DCM.

Scheme 24 Synthesis of α diazo-ketoester **79** and inaccessible, desired C-H insertion product **80**.

The C-H insertion precursor **79** was then prepared from methyl ester **23** by crossed Claisen condensation with *tert*-butyl acetate and diazo-transfer with 4-acetamido-benzenesulfonyl azide. Unfortunately, attempts to close the F-ring and form hexacycle **80** were not successful. Treatment with copper(II) triflate gave unspecific decomposition, while no reaction was observed with rhodium(II) acetate at room temperature and elevated temperatures also only resulted in decomposition. With other rhodium complexes ($Rh_2(OPiv)_4$, $Rh_2(TFA)_4$, $Rh_2(pfb)_4$) significant changes were observed by ^{1}H-NMR spectroscopy. However, these changes were not supporting the desired reaction, but rather the formation of polymeric material by intermolecular C-H insertion or cyclopropanation. The chemical shifts did not clearly change with respect to the substrate **80**, only the line shapes changed from sharp to very broad bands.

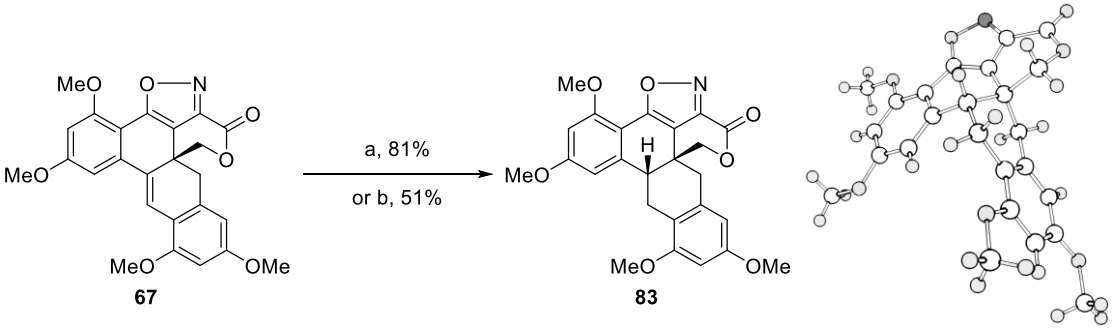
2.9 Benzylic oxidation and stilbene reduction

As the C-H insertion attempts had failed, the benzylic oxidation of lactone **67** was investigated next. Upon testing chromium reagents, it was observed that instead of forming the desired oxidation product **81**, the central stilbene double bond was cleaved (Scheme 25). Although such reactivity had been reported,[23] it was surprising how rapidly the reaction proceeded in the present case. Treatment with four equivalents of pyridinium chlorochromate at room temperature within one hour fully converted stilbene **67** to aldehyde **82** in a moderate yield of 63%. Aldehyde **82** was viewed as a potentially useful compound, but the yield of the stilbene cleavage did not prove consistent on small scale and was expected to be even lower on larger scales.



Scheme 25 Stilbene cleavage forming aldehyde **82** and desired benzylic oxidation product **81**.

A possibility to avoid the oxidative cleavage was to reduce the sensitive stilbene double bond (Scheme 26). Toward that end, reaction with a small excess of triethylsilane (1.2 eq.) in trifluoroacetic acid[24] at elevated temperatures afforded the reduced lactone **83**, which fortunately had the correct stereochemistry as confirmed by X-ray crystallography.



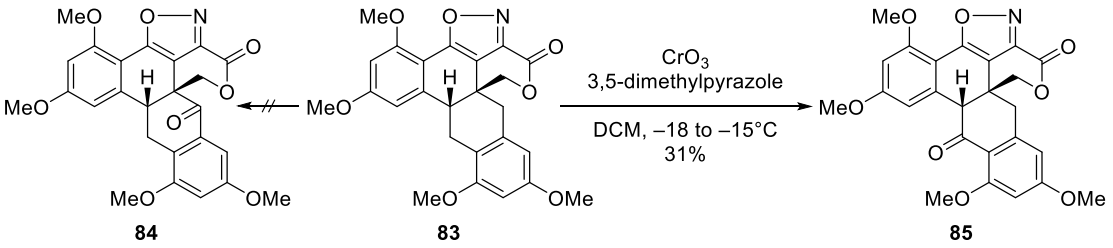
a) Et_3SiH, TFA, 70 °C. b) $PhSiH_3$, TBHP, $Mn(dpm)_3$, DCE/*i*PrOH.

Scheme 26 Stereoselective stilbene reduction and X-ray structure of reduction product **83**.

A main problem of this reduction was that depending on the amount of triethylsilane the reaction suffered either from incomplete conversion or the formation of an overreduction side product, which could not be reoxidized with DDQ. Due to the volatility of triethylsilane and the elevated reaction temperature this proved to be especially a problem on small scale but was less critical on larger scale. Attempts to effect the same transformation through metal catalyzed hydrogenation (Pd/C, $[Ir(cod)(PCy_3)(py)]PF_6$[25]) or diimide reduction

(potassium azodicarboxylate, tosyl hydrazide)[26] failed. In addition to the low reactivity of the stilbene moiety and potential side reactions due to cleavage of the lactone or reduction of the isoxazole, the rather low solubility of lactone **67** in many solvents proved to be an issue during searching conditions for the stilbene reduction. The low solubility was also problematic with respect to the only other method that was found to provide reduced lactone **83**, which was Shenvi's hydrogen atom transfer hydrogenation (HAT) method.[27a] Using a cobalt catalyst only traces of product were observed, but under manganese catalysis the product **83** was obtained in 51% yield. It is important to mention, that Shenvi's method was originally not tried, due to the solubility issues, and only tested in retrospective, after it had proven to be successful in the revised approach (see page 47).

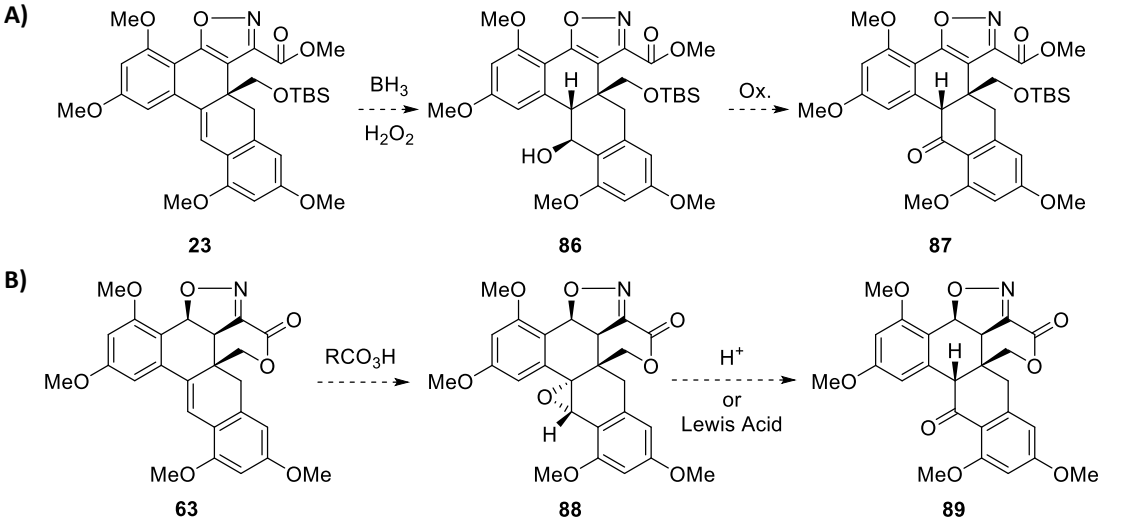
The reduced lactone **83** was then treated with chromium trioxide-2,5-dimethylpyrazole complex[28] at low temperature (Scheme 27). It was hoped that the benzylic oxidation might occur with such a regioselectivity that isomer **84** would be formed, which would be preferred to install the F-ring. However, it was considered more likely that regioisomer **85** would be obtained, which also was the observed product. The yield of 31% was rather low for this oxidation, but the reaction conditions as well as workup and purification have not been optimized yet. A main issue is the large excess of chromium reagent, that needs to be removed. Despite the rather low yield, chromium trioxide-2,5-dimethyl-pyrazole complex is still a reasonably effective reagent to prepare ketone **85** compared to pyridinium chlorochromate, as treatment of lactone **83** with pyridinium chlorochromate also predominantly afforded carbon-carbon cleavage products.



Scheme 27 Benzylic oxidation of lactone **83**.

As the benzylic ketone moiety of compound **85** is also present in A-74528, it was considered that stilbene reduction followed by benzylic oxidation would be a good strategy to install this carbonyl group and set the neighboring stereocenter in general. This was especially important, since the originally considered approaches had not proven to be as efficient as expected (Scheme 28). Initially, it was planned to introduce the benzylic ketone starting from a stilbene by hydroboration followed by oxidation (e. g. compounds **86** and **87**) or epoxidation followed by rearrangement to the ketone (e. g. compounds **88** and **89**). These two approaches had been tested using methyl ester **23** and isoxazoline **63** as model systems, for which preliminary experiments had shown that both epoxidation with

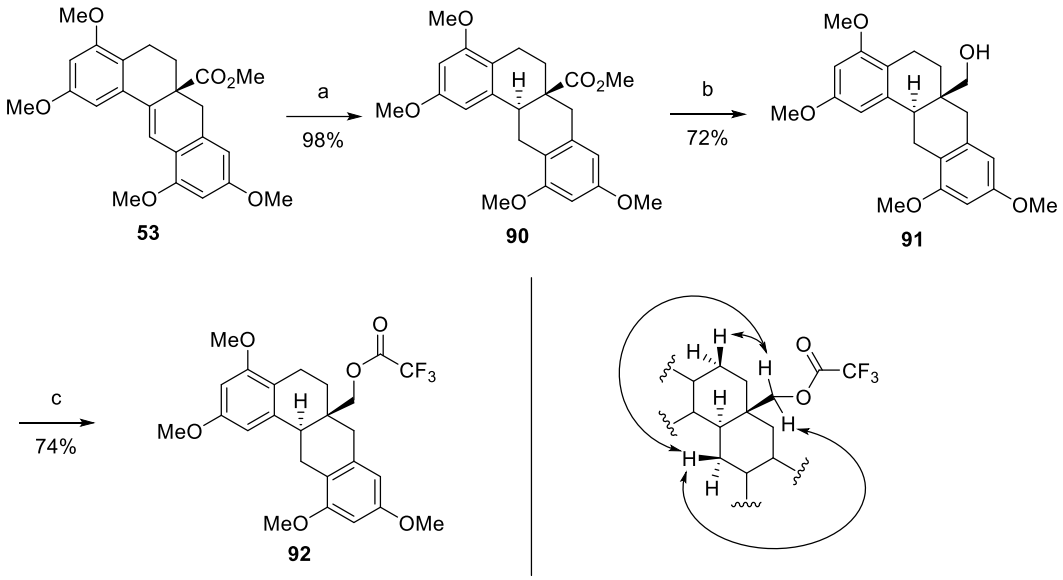
meta-chloroperoxybenzoic acid and hydroboration with borane–tetrahydrofuran proceeded rather sluggish. Furthermore, the small amounts of obtained material that were presumed to be alcohol **86** seemed to be unstable toward elimination and thereby being converted back to stilbene **23**.



Scheme 28 Envisioned approaches to install the benzylic ketone moiety.

At this point it was considered to revise the synthetic strategy in general, use the available material of the currently pursued route to perform further model studies and possibly prepare truncated analogs of A-74528. A key question of high importance in this respect was if the stereoselective stilbene reduction was also possible for other intermediates than lactone **67**. For that purpose, early intermediate **53** was subjected to reduction with Shenvi's HAT method[27a] and the reduction product **90** was converted to trifluoroacetate **92**, which allowed to determine the stereochemistry of the reduction by analysis of NOESY correlations (Scheme 29). Based on the observed correlations it was obvious that the reduction had occurred with the undesired stereochemistry, which led to the conclusion that the presence of the lactone moiety in stilbene **67** is crucial for the stereoselectivity of the stilbene reduction. As much more catalyst and reagents were necessary to achieve full conversion of substrate **53**, it also became clear that the presence of the lactone moiety increases the reactivity of the stilbene **67** toward reduction significantly.

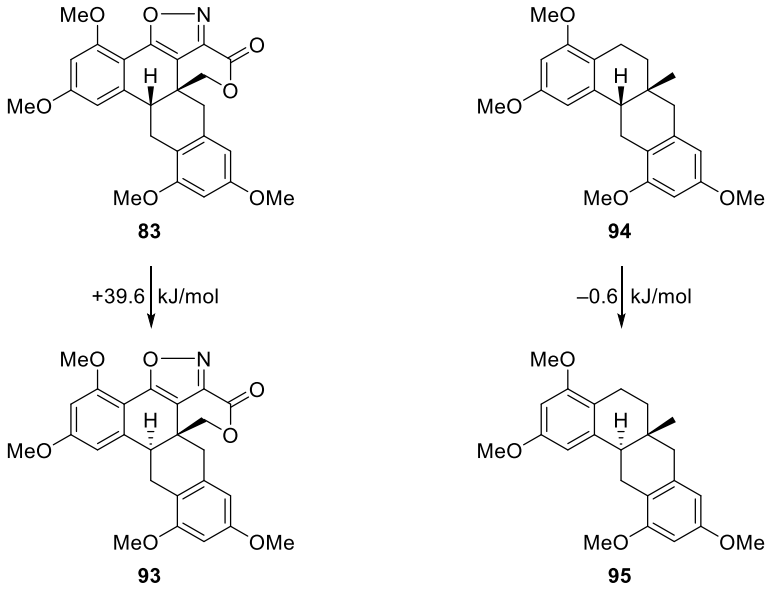
While the detailed investigation of the stereochemical outcome of the stilbene reduction based on trifluoroacetate **92** was performed after Shenvi's method had proven suitable (see page 47), initially only the stilbene reduction with triethylsilane in trifluoroacetic acid was tested. Contrary to the single product of the HAT hydrogenation of stilbene **53**, these conditions led to the formation of two products. The major product was the same compound obtained by the HAT hydrogenation. The minor product was assigned to the alternative diastereomer based on LC-MS data.



a) $PhSiH_3$, TBHP, $Mn(dpm)_3$, DCE/*i*PrOH. b) DIBAL-H, THF, 0 °C. c) TFAA, pyridine, DMAP, DCM, 0 °C to rt.

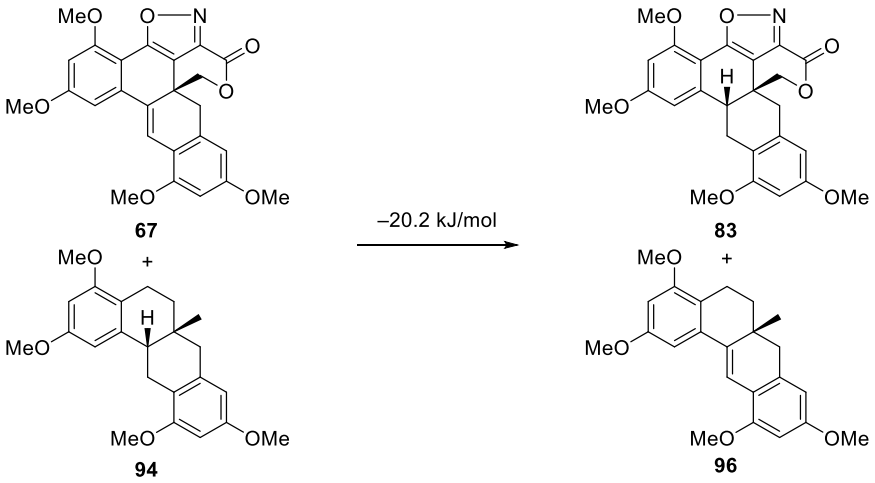
Scheme 29 Reduction of stilbene **53**, transformation to trifluoroacetate **92** and key NOESY correlations.

To further understand the observed selectivity of the stilbene reduction the energetics of the reaction were investigated by density functional theory (DFT) calculations with respect to the overall reaction as well as the reaction intermediates. To simplify the calculations the model compound **94** was chosen as a replacement for ester **53**. First the relative stabilities of desired and undesired epimers were compared (Scheme 30), which showed that the desired epimer **83** is roughly 40 kJ/mol more stable than the undesired epimer **93**. In contrast, without the strain imposed by the lactone moiety the undesired epimers **95** is virtually equal in energy to desired epimers **94**.



Scheme 30 Epimerization of lactone **83** and model compound **94** from the desired to the undesired isomer with reaction energies calculated at the DSD-PBEP86/def2-QZVPP//D3-PBE/def2-TZVP level.

Next, to quantify the release of strain during the hydrogenation of lactone **67** the reaction energy for the isodesmic dihydrogen transfer from model compound **94** to stilbene **67** was calculated (Scheme 31). As expected from the increasing reactivity of lactone **67** compared to stilbene **53**, this hypothetical reaction is exothermic by roughly 20 kJ/mol, which is a significant though not particularly large value.



Scheme 31 Dihydrogen transfer between lactone **67** and model compound **94** with reaction energy calculated at the DSD-PBEP86/def2-QZVPP//D3-PBE/def2-TZVP level.

Finally, the stability of the possible cationic or radical intermediates for both methods were compared (Figure 3). In general, several types of intermediates can be formed. The first type would be represented by structures **97** and **100**. In these cations, the correct stereochemistry is already present. The second type is found in structures **98** and **101**. Here the stereochemistry is not defined. The third and last type would exhibit the incorrect stereochemistry like the structures **99** and **102**.

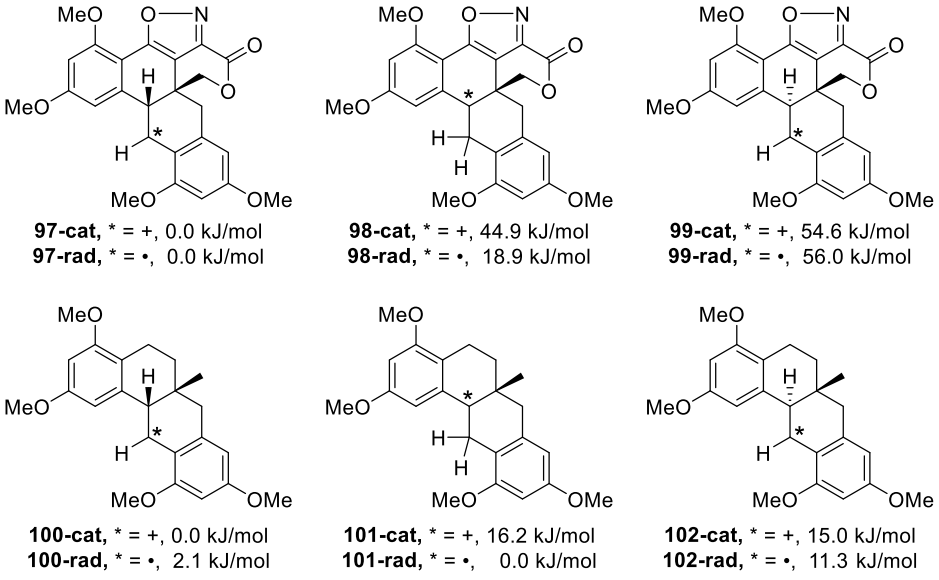


Figure 3 Relative energies of possible regioisomeric cationic and radical intermediates during a reduction of lactone **67** and model compound **96** with energies calculated at the DSD-PBEP86/def2-QZVPP//D3-PBE/def2-TZVP level.

For the reduction of lactone **67** following a cationic mechanism, the intermediate **97-cat** is clearly preferred by about 45 or 55 kJ/mol over **98-cat** and **99-cat**, with the undesired structure **99-cat** being more disfavored. The situation is similar without the lactone moiety, but the energetic differences of roughly 15 kJ/mol between intermediate **100-cat** and **101-cat** or **102-cat** are much smaller and the energies of intermediates **101-cat** and **102-cat** are almost the same.

In the case of radical intermediates, there are significant changes. The energetic ordering with the lactone moiety is still **97-rad** < **98-rad** < **99-rad**, but the energies of radicals **97-rad** and **98-rad** are now much closer with a gap of only 19 kJ/mol, while the difference between **97-rad** and **99-rad** did virtually not change. Without the lactone moiety, the radical **101-rad** is now even slightly more stable than radical **100-rad** and the difference to **102-rad** also decreased to about 10 kJ/mol.

To interpret the experimentally observed stereoselectivities based on the computational data and it is important to keep in mind that protonation of lactone **67** to cations **97-cat**, **98-cat** and **99-cat** should be reversible and the three isomers can be interconverting, while the corresponding radicals should not be interconverting. The same is true for ester **53**.

The high stereoselectivity of the reduction of lactone **67** can be explained by the relative stabilities resulting in a preference for the formation of **97-cat** and **97-rad**, which then react to product **83**. The presence of the species **98-cat**, **99-cat** and **99-rad** is highly unlikely, while the involvement of radical **98-rad** is unlikely but cannot be excluded, as **98-rad** might form due to a kinetic preference resulting from hydrogen delivery to the least hinder position. Still, for the conversion of **98-rad** to product **83** the thermodynamic preference over diastereomer **93** should be the dominant factor compared to steric effects, as both sides should be similarly shielded (see X-ray structure in Scheme 21).

While the DFT calculations showed that, in contrast to lactone **67,** there is no thermodynamic preference toward the desired diastereomer for the reduction of ester **53**, the current data is not sufficient to fully explain the inverted diastereoselectivity and further investigations would need to be performed for a conclusive answer. However, upon inspection of the structure of ester **53** that was determined by X-ray crystallography (Figure 4) it can be assumed that steric shielding through the ester moiety could be the key factor. All four rings of ester **53** are occupying the same plane, which makes this compound almost planar, except for the methyl ester moiety, which is sticking out of the main molecular plane in a perpendicular orientation. Thus, in a radical reaction the initial delivery of a hydrogen would rather occur from the side that is not shielded by the ester moiety. This would either directly set the wrong stereochemistry or, if a radical like **101-rad** is formed, the stereochemistry would be determined in the second hydrogen transfer. Such a radical like **101-rad** should be similarly planar like the initial substrate **53** and the shielding through the ester moiety would again be favoring the formation of the undesired diastereomer.

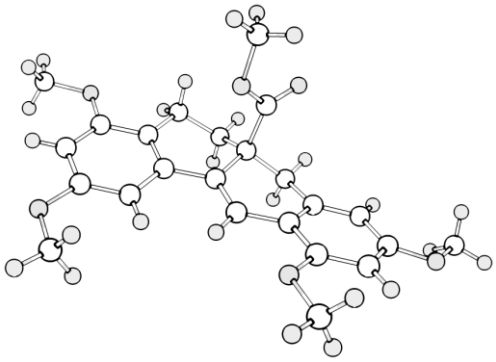
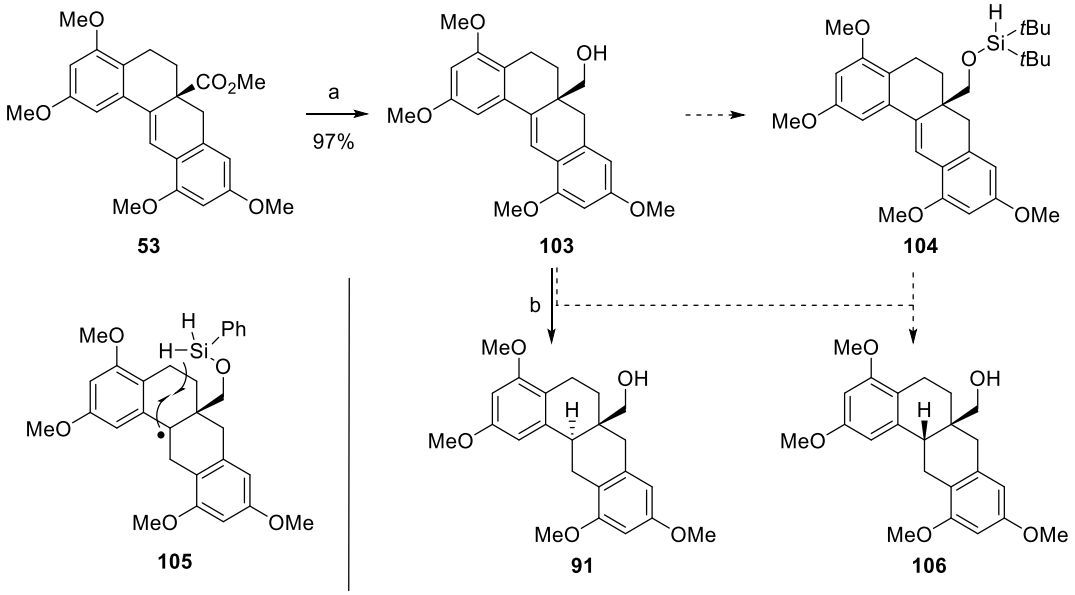


Figure 4. X-ray structure of ester **53**.

In the case of a cationic mechanism it would be easier to form a cation like **100-cat** despite any shielding, as the cationic isomers may rearrange rapidly into each other and could effectively be in equilibrium. This would agree with the observed minor product that had been mentioned earlier. Still, the hydride delivery to form the final product seems to to occur primarily from the opposing side with respect to the ester moiety. The reason for this could be that a cation like **100-cat** is less reactive toward hydrogen abstraction due to being more stabilized and/or that it adopts a bent, more shielded structure than an almost planar **102-cat** like structure. However, based on the available data and without investigating the actual transition states this explanation for the cationic reaction is rather speculative. Also, it needs to be considered that there may be differences between the simplified model system used in the calculations and the actual ester **53** as well as solvent effects that have not been considered in the current gas-phase calculations.

Concluding the investigation of the stilbene reduction, one final noteworthy observation was made. Upon reducing the alcohol **103** under hydrogen atom transfer conditions, it was observed that a mixture of products was formed (Scheme 32).



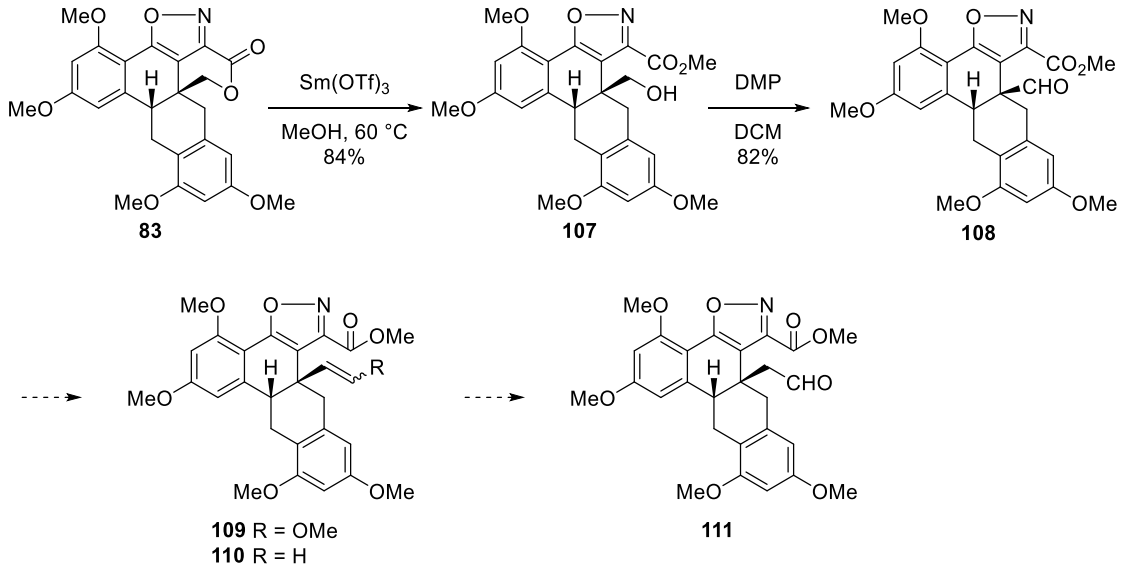
a) DIBAL-H, THF, 0 °C. b) $PhSiH_3$, TBHP, $Mn(dpm)_3$, DCE/*i*PrOH.

Scheme 32 Results and future directions for an intramolecular hydrogen atom transfer.

Compound **91** was identified as a major component in the mixture and the second product might be attributed to the formation of epimer **106**. Although this assignment is a preliminary speculation and needs to be further investigated, the assignment is quite plausible. While the observed result might be resulting from changes of conformation and steric shielding, an intermolecular hydrogen delivery like depicted for radical **105** could also be possible. According to a study by Shenvi[27b] isopropoxy(phenyl)silane, which is formed in situ under the employed conditions, may be the actual reductant in many HAT hydrogenations instead of phenyl silane. Thus, the formation of species **105** appears to be entirely reasonable as the primary alcohol **103** could react in the same way with phenylsilane as isopropanol. Additionally, the intermolecular hydrogen transfer shown in Scheme 32 would occur within a six-membered ring, which is typically not a disfavored structure. Further investigations based on this observation must be performed, as this could be a useful method complementing the established directed metal-catalyzed hydrogenation methods.[29] Preliminary experiments in this direction showed that the di-*tert*-butyl-silyl ether **104** would be a sufficiently stable reduction precursor and can be prepared by reaction with the corresponding silyl chloride.

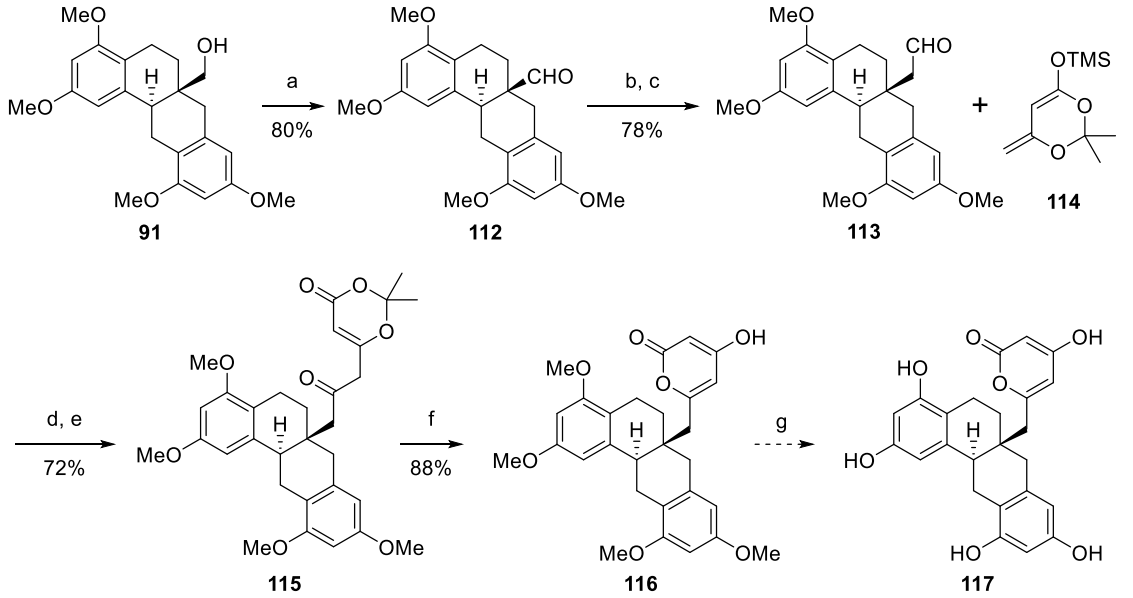
2.10 Model studies toward the pyrone moiety

Given the available intermediates that had been prepared at this point, the model studies toward the installation of the pyrone fragment commenced from lactone **83** (Scheme 33). Methanolysis to alcohol **107** catalyzed by samarium(III) triflate and oxidation with Dess-Martin periodinane afforded aldehyde **108** in 69% yield over two steps. This was a gratifying outcome, as preliminary attempts to oxidize alcohol **61** under the same conditions did not work well. This had raised concerns about the stability of alcohol **107** and aldehyde **108**, although they were expected to be more stable than alcohol **61** and the corresponding aldehyde.



Scheme 33 Synthesis of aldehyde **108** and intended homologation to aldehyde **111**.

The next step to install the pyrone was a homologation to aldehyde **111**. During trials to perform this homologation with aldehyde **108** it turned out that preparing alkenes **109** or **110** by Wittig olefination gave irreproducible results. It was presumed that this was related to side reactions caused by the presence of the methyl ester group. Thus, the sequence to install the pyrone was further investigate with alcohol **91** instead (Scheme 34).



a) DMP, DCM. b) KO*t*Bu, $MeOCH_2PPh_3Cl$, THF/DMSO. c) HCOOH, DCM. d) $BF_3{\cdot}OEt_2$, DCM, –78 °C. e) DMP, DCM. f) PhMe, 105 °C. g) BBr_3, DCM, –78 °C to rt.

Scheme 34 Synthesis of pyrone **116** and targeted deprotection product **117**.

Now, oxidation of alcohol **91** to aldehyde **112**, followed by olefination with (methoxymethyl)triphenylphosphonium chloride[30]/potassium *tert*-butoxide and enol ether cleavage with formic acid reliably afforded homologation product **113** in 62% yield from alcohol **91**. Then, the pyrone was installed in a three-step sequence according to the procedure reported by Bach[31] with slight modifications. Mukaiyama aldol addition of aldehyde **113** with silyl ketene acetal **114** mediated by boron trifluoride diethyl etherate followed by oxidation with Dess-Martin periodinane gave dioxinone **115** in a good yield of 72%. A standard aldol addition with the corresponding lithium enolate instead of Lewis acid mediated reaction with silyl ether **114** proved less efficient and suffered from incomplete conversion of the substrate aldehyde. Finally, by warming a toluene solution to 105 °C, dioxinone **115** was cleanly converted to pyrone **116**, which was easily isolated as it precipitated from the reaction mixture.

Having accessed pyrone **116**, the challenge of fully deprotecting all phenolic hydroxy groups was addressed. Therefore, compound **161** was treated with boron tribromide in dichloromethane and after aqueous workup the crude material was directly analyzed by LC-MS. The results agreed with all four methyl groups having been cleanly removed, forming polyphenol **117** without any detectable side products. However, according to the

mass of the crude material there were still significant impurities present. Thus, the crude product was subjected to column chromatography (silica, MeOH/DCM), which resulted in decomposition. As the deprotection of compound **161** has not be repeated at this point, further investigations are necessary.

2.11 Truncated analogs of A-74528

Regarding the synthesis of analogs of A-74528 for SAR studies, several of the compounds described within the preceding sections already contain a significant fraction of the carbon skeleton and functional groups present in the natural product itself. These compounds could give rise to simplified versions of the natural product. Furthermore, pursuing the synthesis of these compounds is expected to provide valuable information for the final steps of the synthesis of A-74528. Three targets that are considered most promising are depicted in Figure 5. First, diketone **118**. This compound might be derived from pyrone **116**, as the wrong stereochemistry should not be important due to the possibility of enolization. A second target would be polyphenol **119**, which should be accessible in the same manner as its epimer **117** (Scheme 34), except for the need to provide the alternate diastereoselectivity of the stilbene hydrogenation. A third target would be 1,3-diketone **120**, which is based on lactone **83**. Obviously, many other compounds could be considered. The three compounds depicted in Figure 5 are but one possible choice and based to a certain extent also on personal opinion.

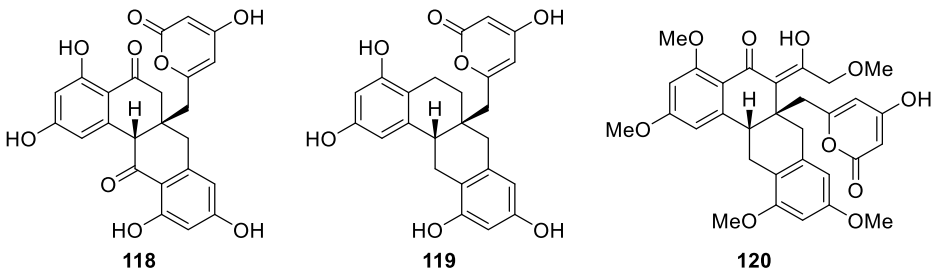
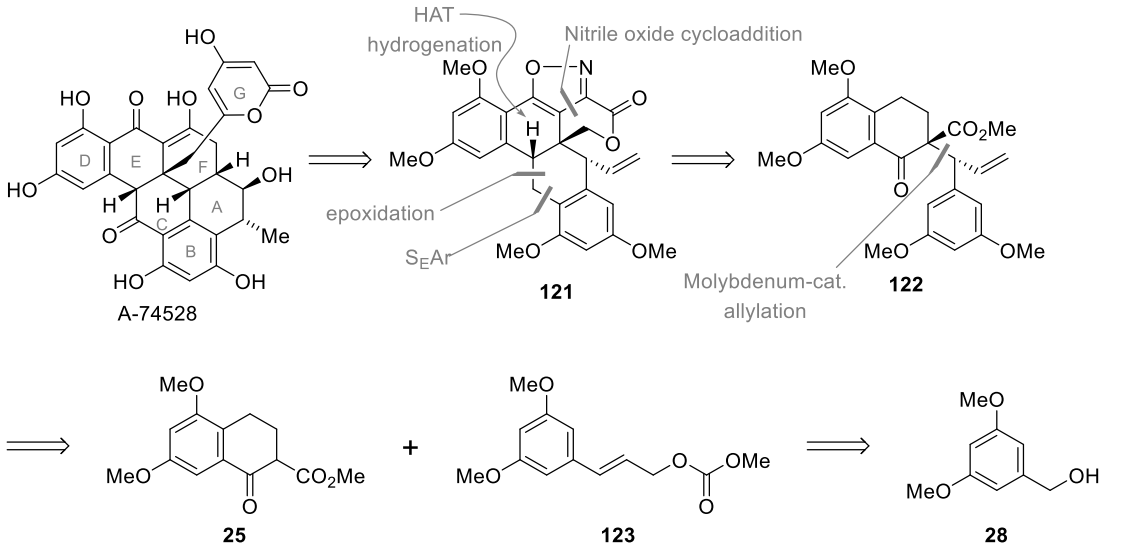


Figure 5 Examples of possible truncated analogs of A-74528.

3 Second-generation approach

3.1 Synthetic strategy

Having identified the functionalization of the benzylic position for the formation of the F-ring system as a key issue in the original strategy, an approach was devised that would avoid this issue and in addition be more convergent (Scheme 35). In the second-generation approach the envisioned key disconnection would now be a metal-catalyzed allylation to form β-ketoester **122** from already established building block **25** and known carbonate **123**[32] or a similar allyl donor. The carbonate **123** would be prepared from alcohol **28**, which was available from the previous route. Also, it was assumed that effectively all reactions that had been established previously in the first-generation approach could still be applied or at least adapted to the new approach.

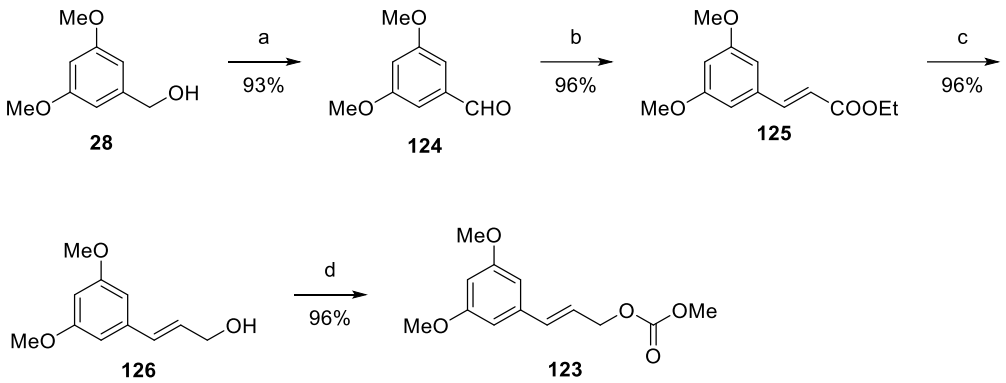


Scheme 35 Revised retrosynthetic Analysis of A-74528.

The new key reaction would require a challenging carbon-carbon bond formation to simultaneously establish an all-carbon quaternary stereocenter and a vicinal tertiary stereocenter in a stereoselective manner. Almost exactly the envisioned stereoselective coupling of β-ketoesters and cinnamyl carbonates to the branched allylation product was reported by Stoltz and coworkers, who developed an efficient protocol based on iridium catalysis.[33] An alternative methodology, which was pioneered by the group of Trost,[34] could be a molybdenum catalyzed allylation, although the number of examples for the allylation of β-ketoesters is very limited. The advantage of the molybdenum-based method would be the significantly cheaper metal and ligands that are either commercially available at low cost or readily prepared from easily available materials.

3.2 Synthesis of allyl donors

The investigations of the second-generation approach commenced with the preparation of several allyl building blocks, among which carbonate **123** was the most suitable for several reasons. Regarding efficient synthetic access, carbonate **123** turned out to be a good choice and was prepared with 82% overall yield in four steps from alcohol **28** (Scheme 36). Several methods were tested for the transformation to aldehyde **124**, among which oxoammonium-catalyzed oxidation was the most convenient. Phenyliodine(III) diacetate[35a] or oxygen in combination with copper catalysis[35b] proved to be suitable terminal oxidants, with the former being overall more reliable and practical. The remaining issue of this oxidation protocol was the removal of the catalyst and the byproduct iodobenzene, which was achieved through chromatography. As a majority of the reported preparations[36] of aldehyde **124** used pyridinium chlorochromate,[37] this reagent was also employed at first and typically afforded the product **124** in yields of more than 90%. Here, pre-stirring the chromium reagent with silica[38] made the reaction more reliable and easier to purify. However, other methods were preferred, due to the toxicity issues of chromium(VI) reagents. Finally, oxidation with activated dimethyl sulfoxide according to the Parikh-Doering method[39] was tested, which proved not to be more practical than the methods described above. However, it is recommended to try other alternatives in the future that might afford sufficiently pure material to avoid chromatographic purification (e.g. oxidation with manganese dioxide[40]). This is especially important, as the other reactions of the sequence depicted in Scheme 36 can in principle be performed without intermediate purifications. Following such an approach and relying on recrystallization from ethanol as the only purification of the final product, the carbonate **123** was obtained in 63% yield over three steps on a scale of multiple decagrams and the yield was increased by further 22% after purification of the material from the mother liquors by chromatography. Thus, the overall yield was only slightly reduced compared to purification after every reaction.

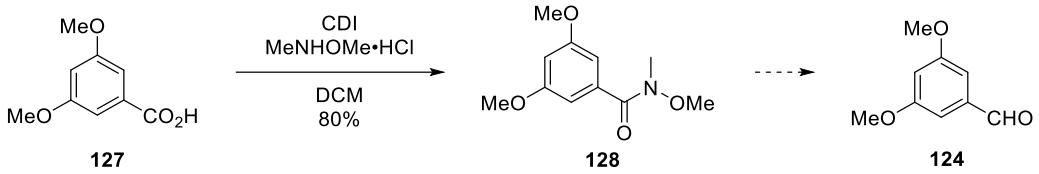


a) PIDA, TEMPO, DCM. b) triethyl phosphonoacetate, DBU. c) DIBAL-H, THF, 0 °C. d) DMAP, ClCOOMe, pyridine, DCM, 0 °C to rt.

Scheme 36 Synthesis of carbonate **123**.

Regarding the other reactions en route to carbonate **123**, a remarkably efficient and easily scalable protocol developed by Ando,[41] which is based on a neat reaction with DBU and triethyl phosphonoacetate, was used for the olefination of aldehyde **124** to unsaturated ester **125** and the reduction to cinnamyl alcohol **126** was conducted with diisobutylaluminum hydride. At the same temperature (0 °C) that was used for the reduction with diisobutylaluminum hydride, lithium aluminum hydride led to overreduction of the alkene moiety, although it was reported to afford the correct product **126** at a lower temperature(−78 °C).[42] Finally, the carboxylation of alcohol **126** with methyl chloroformate proceeded in near perfect yield when performed under catalysis by 4-(dimethylamino)pyridine and with pyridine as a base. Replacing pyridine by triethylamine or carboxylation of the salt formed by deprotonation with *n*-butyllithium proved less productive.

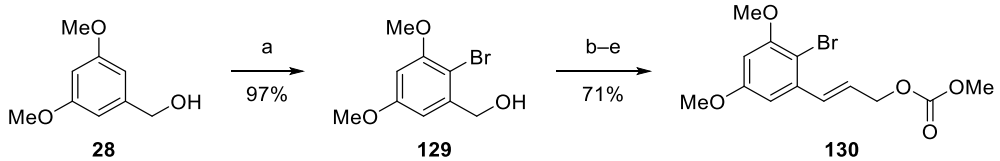
As a more redox-economic[43] alternative to the reduction-reoxidation based synthesis of aldehyde **124**, the reduction of Weinreb amide **128** was considered[44] (Scheme 37). This amide was prepared easily and without the need for chromatographic purification by carbonyldiimidazole-mediated[45] coupling of *N*,*O*-dimethyl-hydroxylamine with benzoic acid **127**, which also is a cheaper starting material than the corresponding methyl ester **27**. Initial trials showed that while the reduction on small scale with Red-Al® was successful, on larger scale with lithium aluminum hydride partial overreduction to alcohol **28** was observed.



127 **128** **124**

Scheme 37 Attempt to prepare aldehyde **124** through reduction of Weinreb amide **128**.

As a building block that provides an additional synthetic handle, the brominated carbonate **130** was prepared from alcohol **28** starting by treatment with *N*-bromo-succinimide to afford bromoalcohol **129** (Scheme 38). This was followed by a sequence of oxidation (PCC), olefination, reduction and carboxylation in the same manner as for non-brominated analog **123**, but with the overall yield of 71% being a bit smaller.

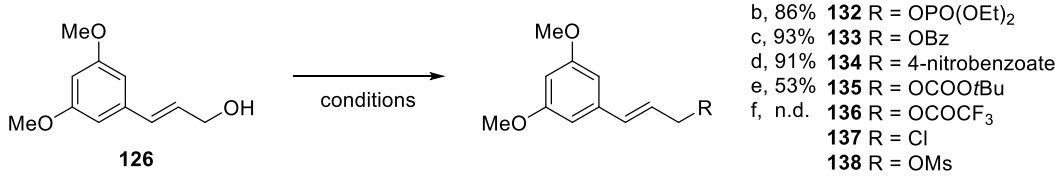


28 **129** **130**

a) NBS, DCM, 0 °C to rt. b) PCC, SiO_2, DCM. c) triethyl phosphonoacetate, DBU. d) DIBAL-H, THF, 0 °C. e) DMAP, ClCOOMe, pyridine, DCM, 0 °C to rt.

Scheme 38 Synthesis of carbonate **130**.

Apart from methyl carbonates, various other allyl donor species can be employed in metal-catalyzed allylations. Thus, several alternatives to carbonate **123** were prepared from alcohol **126** (Scheme 39). However, ultimately none of these alternative partners for the coupling with β-ketoester **25** was better suited to meet the necessary requirements than methyl carbonate **123**, which proved to be a perfectly stable, easy to purify solid and exhibited the desired reactivity in the allylation reaction (see Section 3.4).



a) DMAP, Ac_2O, Et_3N, DCM, 0 °C to rt. b) DMAP, $(EtO)_2POCl$, DCM, 0 °C to rt. c) BzCl, Et_3N, DCM, 0 °C to rt. d) 4-NO_2-PhCOCl, Et_3N, DCM, 0 °C to rt. e) Boc_2O, DMAP, DCM, 0 °C to rt. f) DMAP, TFAA, Et_3N, DCM, 0 °C to rt.

Scheme 39 Alternative allyl donor species.

For molybdenum catalyzed allylations, the two other prevalent types of allylic substrates apart from carbonates are acetates and phosphates.[46] In the present case, the corresponding compounds **131** and **132** were oils and had the disadvantage that they could not be purified by recrystallization. Furthermore, diethyl phosphate **132** suffered from significant decomposition during storage. Benzoate **133**, nitrobenzoate **134** and trifluoroacetate **136** were also prepared. While the first and the second compound were stable and conveniently handled solids, the third compound, or more precisely the material that was isolated and presumed to be trifluoroacetate **136**, was unstable to such an extent that it was not considered any further. Due to this instability and as their potential for an uncatalyzed background reaction was considered too large, other more reactive species such as allyl halide **137** or methanesulfonic acid ester **138** were excluded as viable allyl sources.

At last, as an alternative to the methyl version the *tert*-butyl carbonate **135** was prepared by reaction of alcohol **126** with di-*tert*-butyl dicarbonate and 4-(dimethylamino)pyridine. This afforded the product **135** as an oil in 53% yield. The poor yield was a result of about a third of alcohol **126** being consumed by the formation of symmetric carbonate **139** (Figure 6). The formation of such side products is a known issue that has been investigated by Basel and Hassner.[47]

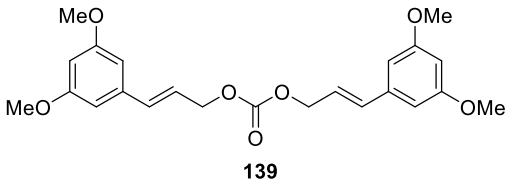


Figure 6 Symmetric carbonate side-product **139** formed during the synthesis of *tert*-butyl carbonate **135**.

3.3 Ligand synthesis

With all necessary building blocks at hand, the appropriate ligands (Figure 7) for the allylation reaction were the only missing ingredient preventing further investigation of the revised synthetic strategy. In the iridium-based protocol by the Stoltz group phosphoramidite **140** had proven uniquely successful.[33] However, ligand **140** itself as well as the tetrahydroquinoline building block necessary to prepare the ligand were not as easily available as pyridyl ligand **141-H**, or the respective building blocks for derivatives **141-Cl**, **141-OMe** and **141-PPY**. Additionally, the possibility to increase the scope of molybdenum-catalyzed allylations was found to be intriguing and it was decided to first focus on this metal and the respective ligands.

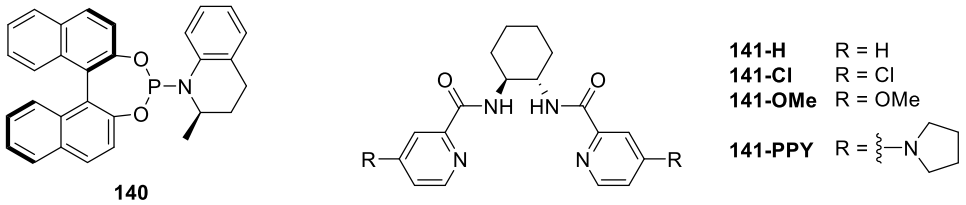
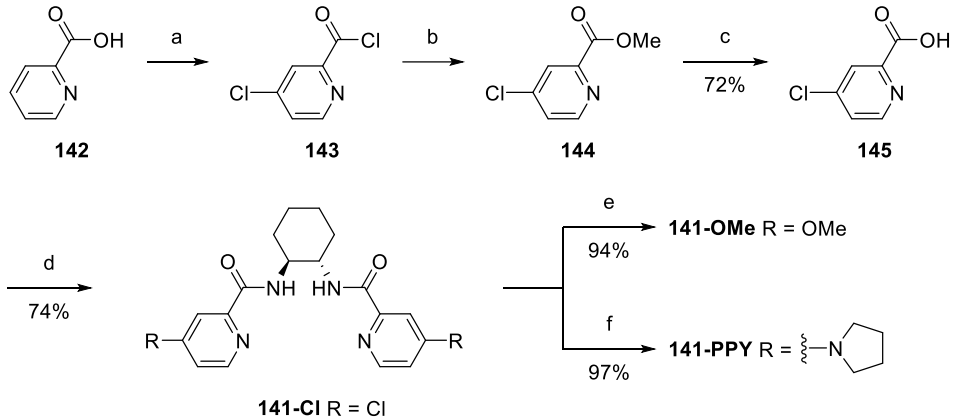


Figure 7 Ligands established for iridium-catalyzed allylation by the group of Stoltz[33] and for molybdenum-catalyzed allylation by Trost et al.[34c] and Moberg.[48]

While the (*R*,*R*)-enantiomer of ligand **141-H** was acquired from commercial sources, the three *para*-substituted derivatives **141-Cl**, **141-OMe** and **141-PPY** were prepared starting from picolinic acid (Scheme 40) following an approach similar to the route reported by Moberg.[48b]



a) NaBr, $SOCl_2$, reflux. b) MeOH. c) aq. NaOH. d) CDI, THF, 50°C. e) NaOMe, MeOH, reflux. f) pyrrolidine, PhMe, 85°C.

Scheme 40 Racemic synthesis of ligands **141-Cl**, **141-OMe** and **141-PPY**.

Conversion of picolinic acid to the acid chloride with concomitant *para*-chlorination followed by reaction with methanol afforded methyl ester **144**. The transformation to acid chloride **143** was achieved with a mixture of sulfonyl chloride and sodium bromide according to a protocol by Sundberg and Jiang.[49] The ester **144** was then hydrolyzed to

afford carboxylic acid **145** in an overall yield of 72% from picolinic acid. This indirect route was preferred over directly hydrolyzing the acid chloride **143**, as it simplified removal of impurities due to the higher solubility of ester **144** compared to acid **145**. The main problematic impurity is a badly soluble material that seems to be polymeric sulfur or a related compound, which is probably formed by reduction of thionyl chloride during the oxidative chlorination of the pyridine.

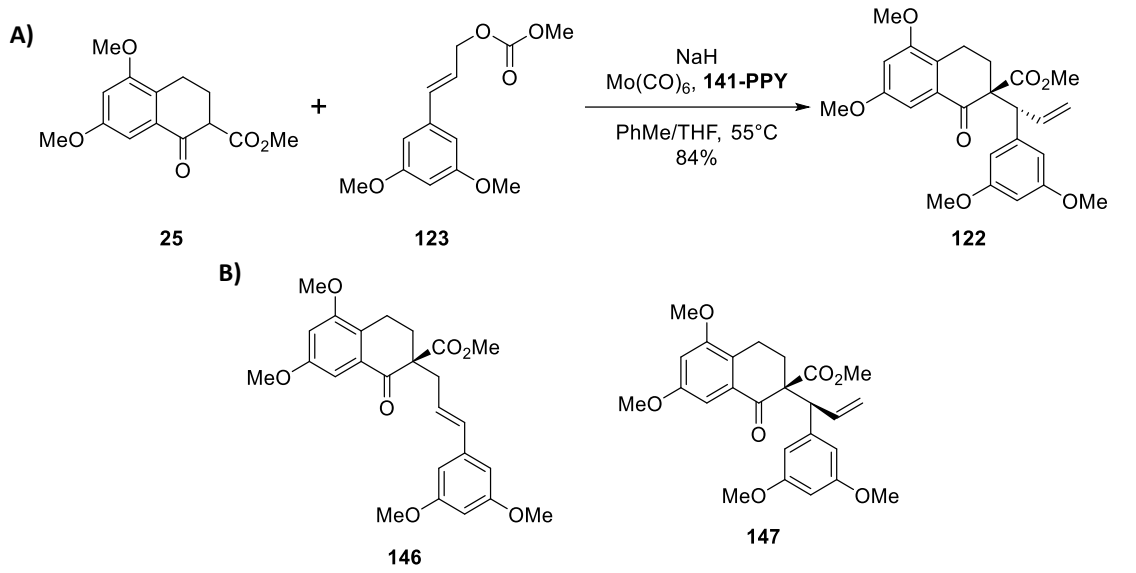
The picolinic acid **145** was then activated with carbonyldiimidazole according to Conlon et al.[50] and reacted with trans-1,2-diaminocyclohexane to form ligand **141-Cl**. As it was expected that large amounts of ligand would be needed, compound **141-Cl** was prepared in racemic form, which is significantly cheaper and made purification much easier. The racemic material could efficiently be converted into a solid and purified by treatment with ethanol. In contrast, the same conditions did not prevail for the material obtained with (*R*,*R*)- or (*S*,*S*)-1,2-diaminocyclohexane, which suffered from strong foaming to such a degree that it was not only an annoyance but rather a significant issue on a gram scale. Compared to the yield of 54% reported by Moberg for preparation of the (*R*,*R*)-form of ligand **141-Cl** from a mixture of sulphuric and hydrobromic acid salts of picolinic acid **145**, the current procedure afforded the racemic material in a higher yield of 74%.

Relying on nucleophilic aromatic substitution under microwave heating Moberg had reported yields of >99% based on crude material after aqueous workup for ligand **141-OMe** and after evaporation of the reaction mixture for ligand **141-PPY**. In the present case, the transformation of compound **141-Cl** to ligands **141-OMe** and **141-PPY** was accomplished in a slightly different way by simply refluxing with sodium methoxide in methanol or stirring with pyrrolidine in warm toluene, respectively. Both racemic ligands could be precipitated by appropriately diluting the reaction mixture and were isolated after washing and drying the precipitate in near perfect yield of 94% for ligand **141-OMe** and 97% for ligand **141-PPY**. The latter compound was easily prepared in quantities of more than 15 gram and turned out to be the most successful ligand for the allylation reaction (see Section 3.4),

At this point, further work toward an enantioselective synthesis of A-74528 was again postponed and it was decided to use the available racemic ligands to test the feasibility of the desired allylation and then investigate the successive steps with racemic material. In the case that enantioselectivity would later pose an issue for a molybdenum-catalyzed reaction, the iridium-catalyzed method by Stoltz[33] was considered to be a promising backup alternative.

3.4 Molybdenum-catalyzed allylation

After significant experimentation, conditions for the envisioned molybdenum-catalyzed coupling of β-ketoester **25** and carbonate **123** were found that allowed to prepare diastereomerically pure, branched allylation product **122** in 84% yield from carbonate **123** using only a small excess (1.3 eq.) of coupling partner **25** (Scheme 41). The reaction proceeded to full conversion using 8 mol% of molybdenum hexacarbonyl and 12 mol% of ligand **141-PPY**. The critical factors for the success of the reaction were the combination of ligand **141-PPY** with the base sodium hydride, which provided the desired regio- and diastereoselectivity, and conducting the reaction in a closed vessel, which allowed to reliably reach full conversion with the specified amounts of catalyst and ligand. It is noteworthy, that the catalyst loading is significantly lower than the values reported for comparable molybdenum-catalyzed allylations.[51] The same is true for the amount of nucleophilic coupling partner, for which often two or more equivalents are being used, also in the case of iridium-catalysis.[33]



Scheme 41 A) Synthesis of compound **122** by coupling of β-ketoester **25** and carbonate **123**. **B)** Side products resulting from undesired regio- and diastereoselectivity.

Regarding the optimization of the allylation reaction, the work by Trost et al. on the allylation of cyanoesters[51a] and the catalyst preparation procedure by Palucki et al.[52] provided a starting point. The search for an ideal protocol commenced with a comparison of allyl donors, which showed that phosphate **132** reacted significantly slower than carbonate **123** and acetate **131** did not react at all. This initial comparison was performed with the commercially available (*R*,*R*)-enantiomer of ligand **141-H**, excess bis(trimethylsilyl)acetamide as well as catalytic sodium hydride in tetrahydrofuran at 55 °C and afforded predominantly the linear allylation product **146**. In a successive screening with phosphate **132**, carbonate **123**, different bases (NaH, NaO*t*Bu, cat. NaH/BSA) and solvents (PhMe/85 °C, THF/55 °C), the largest fraction of branched product **122** was observed for

the combination of carbonate **123**, sodium hydride and toluene. Based on reports that more electron-rich ligands would give an increased regio- and diastereoselectivity,[48b,51a] the ligand was switched to pyrrolidinopyridine **141-PPY**, which further reduced the formation of undesired linear product **146**. To determine the influence of the enolate counterion, the lithium and potassium salts of β-ketoester **25** were also tested, using lithium and potassium tert-butoxide instead of sodium hydride. This either resulted in no reaction (*t*BuOLi) or an increased amount of linear side product **146** (*t*BuOK).

At this point it was attempted to scale up the reaction and reduce the amount of metal carbonyl, ligand **141-PPY** and β-ketoester **25**, which had been used in respective amounts of at least 15 mol%, 20 mol% and 2.2 equivalents. During this process it came to light, that the results with respect to conversion of carbonate **123**, as well as regio- and diastereo-selectivity were surprisingly fluctuating. Initially, it was presumed that these fluctuations would mainly be related to the reaction mixture being an inhomogeneous slurry resulting from the bad solubility of the sodium salt of β-ketoester **25** in toluene. Later, it was found that reliable results were observed when the reaction was performed in a closed vessel. This means without a balloon or a connection to an inert gas line for pressure release. One explanation for this result might be that a loss of carbon monoxide, which was observed to be necessary for closing the catalytic cycle in a related reaction by the group of Trost,[53] is avoided.

Thus, all further reactions were conducted in appropriately sealed vessel and the solvent was changed back to tetrahydrofuran, as it provided better solubility than toluene. Under these conditions the performance of the ligands **141-Cl**, **141-OMe** and **141-PPY** was compared. The ligands demonstrated an increasing selectivity for the branched allylation product with increasing electron-richness. The observed **146/122-**ratios[a] were 23/100, 13/100 and 5/100 for **141-Cl**, **141-OMe** and **141-PPY**, respectively. Alongside the increasing regioselectivity, an increasing reaction rate was observed. While 14% and 3% of carbonate **123**[b] were remaining with ligands **141-Cl** and **141-OMe**, ligand **141-PPY** resulted in full conversion within the same timeframe (22 hours).

Apart from linear allylation side product **146**, for which a pure sample had been obtained, another side product was formed, which was putatively assigned to be the diastereomeric coupling product **147**. Although no pure sample of this compound has been isolated, the assignment is supported by X-ray crystallography and NMR data. Crystals formed within the crude reaction mixture during the first scale-up attempts mentioned above were found to contain both diastereomers **147** and **122** in a ratio of 14/86 favoring the desired product. This ratio was close to the relative intensities of 13/100 that were

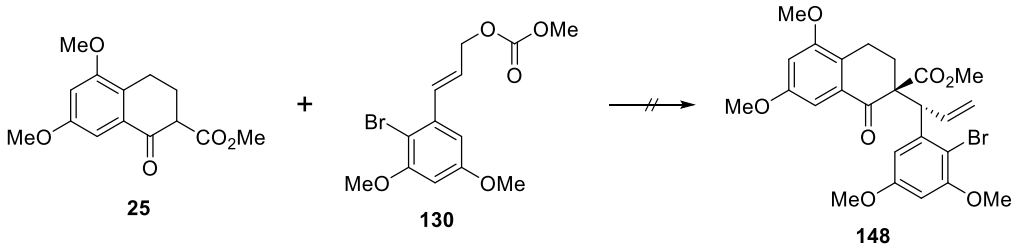
[a]Determined by ^{1}H-NMR($CDCl_3$) spectroscopy based on integration of the singulets at 3.67 ppm (**146**) and 3.56 ppm (**122**).
[b]Determined by ^{1}H-NMR($CDCl_3$) spectroscopy with dimethyl terephthalate as an internal standard based on integration of the singulet at 8.11 ppm (standard) and the doublet of doublets at 4.78 ppm (**123**).

observed by ^{1}H-NMR[a] for the doublet at 4.33 ppm, which corresponds to the proton at the tertiary stereocenter of compound **122,** and for a doublet at 4.10 ppm, which was assigned to correspond to the same proton in presumed epimer **147**. These **147**/**122** ratios were observed for a reaction in with ligand **141-PPY** in toluene at 85 °C, whereas in tetrahydrofuran at 55 °C a lower ratio of 6/100 was obtained. Surprisingly, the ligand did not seem to have a significant effect on this ratio and similar values were observed for both ligands **141-Cl** (4/100) and **141-OMe** (5/100).

In conclusion, the best results were obtained with ligand **141-PPY** and the reaction outcome was considered satisfactory with the current set of conditions. Therefore, the focus was put back on scaling up the reaction. As the reaction was supposed to be performed in a sealed vessel without pressure release, this was complicated by safety concerns due to the formation of gaseous byproducts from carbonate **123**. For that reason, alternative allyl donors that would not result in gaseous byproducts were tested again with the updated set of conditions. Still, even with the catalytic system based on ligand **141-PPY,** the use of phosphate **132** afforded significant linear product **146** and acetate **131** was too unreactive. Trying to increase the reactivity by using esters derived from more acidic carboxylic acids was moderately successful and benzoate **133** was at least partially converted to the coupling product **122**, but not to a synthetically useful extent. Notably, the nitrobenzoate **134,** which was expected to be more reactive, did not react at all. This may be a sign of an incompatibility of the molybdenum catalyst with the nitro group carried by benzoate **134**, although no such incompatibility was observed with a related catalyst.[51]

Having failed to solve the pressure issue by changing the reaction substrates, the alternative approach was to find a suitably stable reaction vessel. A simple modification of a regular pressure flask (see page 186) was found to be sufficient to conduct the reaction on a multi-gram scale. Purification on such a scale also proved to be convenient and effective. A simple filtration over silica to remove the catalyst complex followed by treatment with ethanol to remove excess β-ketoester **25** as well as side products **146** and **147** afforded pure product **122**.

Finally, attempts to access bromo derivative **130** in a similar manner were unsuccessful, with no reaction being observed (Scheme 42).

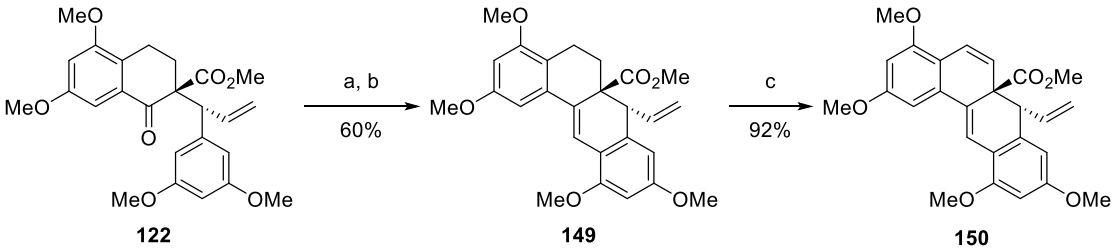


Scheme 42 Failed attempt to prepare brominated allylation product **148**.

[a]In $CDCl_3$.

3.5 Synthesis of the tetracyclic intermediate

With the success of the allylation reaction, it could now be tested if the reactions that had been established for the old strategy were suitable for the new substrates. Regarding the epoxidation of β-ketoester **122** and the successive cyclization, the previous conditions still worked (Scheme 43). However, compared to the 83% yield that had been obtained for stilbene **53** the moderate value of 60% for stilbene **149** was disappointing. The successive dehydrogenation was performed without issues and provided triene **150** in 92% yield.



a) $Me_3S^+I^-$, KO*t*Bu, THF/DMSO b) PTSA, PhMe, 105 °C. c) DDQ, PhMe, 65 °C.

Scheme 43 Synthesis of triene **150**.

At the stage of triene **150** the correct stereochemistry was unambigously determined by X-ray crystallography, which confirmed the correct orientation of the vinyl group (Figure 8). An X-ray structure was also obtained for the lactone **154** (Figure 8), which was identified as the major side-product (Scheme 44) during the cyclization to stilbene **150**.

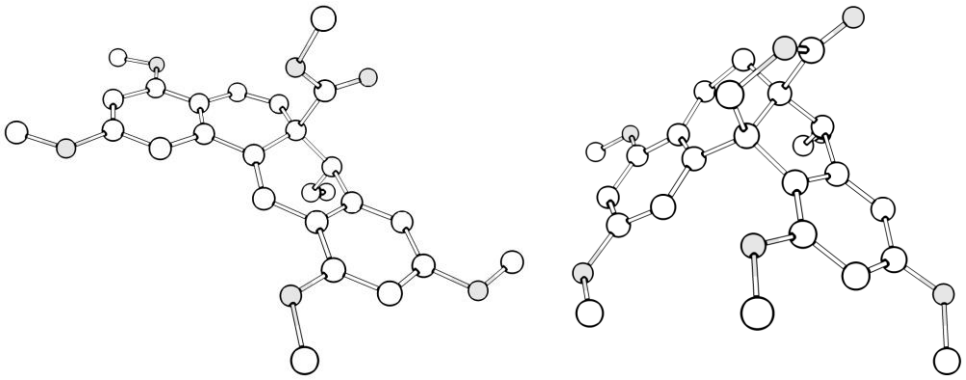
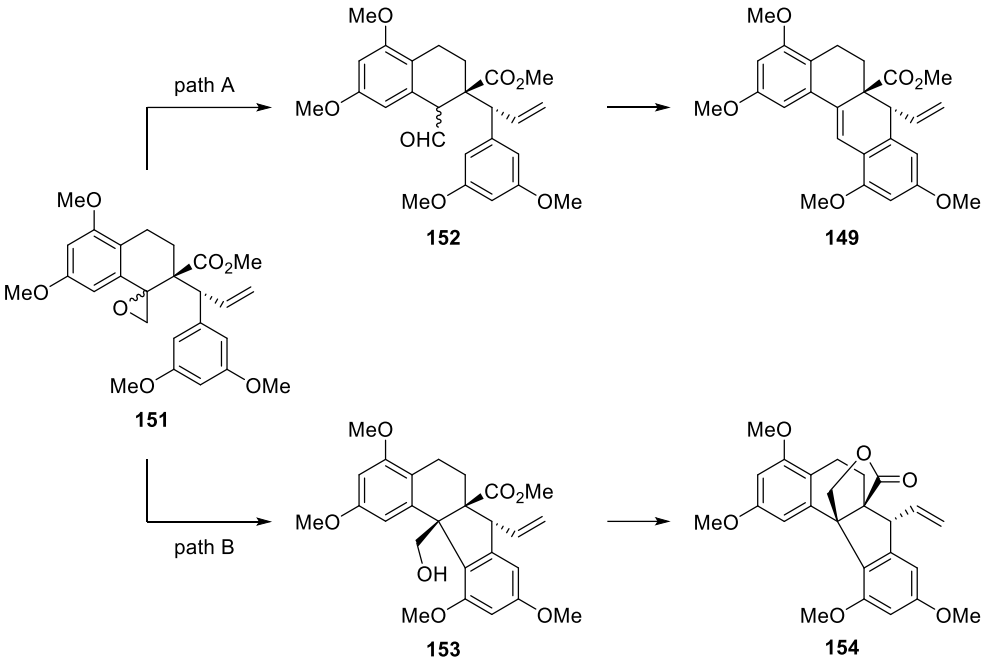


Figure 8 X-ray structures of triene **150** (left, hydrogen atoms have been omitted) and lactone **154** (right, hydrogen atoms have been omitted).

The reason for the formation of lactone **154**, for which no analogous side product was observed previously during the synthesis of stilbene **53**, is expected to be a gem-dimethyl type effect.[54] This means that, on the one hand, the additional vinyl substituent would increase the rate of cyclization to form alcohol **153**, which then leads to the formation of lactone **154** (Scheme 44, path B). On the other hand, the rate of rearrangement to aldehyde **152**, which is believed to be an intermediate (see reasoning on page 14) in the formation of stilbene **149** (Scheme 44, path A), would not profit from the presence of the vinyl substituent.



Scheme 44 Presumed intermediates leading to the formation of lactone **153** and stilbene **149**.

It could be considered that Scheme 44 implies that the transformations of epoxide **151** to aldehyde **152** and alcohol **153** are concerted processes and do not involve an intermediate. However, this is not necessarily the case and both transformations could involve a benzylic cation. This is of particular importance with respect to another factor that might be invoked as a possible explanation for the formation of lactone **154**, namely the relative configuration of the epoxide with respect to the neighboring quaternary carbon. While this configuration would not matter if a benzylic cation or a rearrangement to aldehyde **152** is involved, a concerted carbon-carbon bond formation and epoxide opening to alcohol **153** would only be possible for one epimer. However, this stereochemical factor seems not to be the crucial aspect, as the fraction of lactone **154** was highly dependent on the conditions of the reaction of epoxide **151** to stilbene **149**. This was observed in attempts to improve the reaction outcome.

Unfortunately, virtually all changes of the reaction conditions gave increasing amounts of side products. Conducting the reaction at lower temperature, solvents with a higher polarity (MeOH, DCE) and weaker acids (HCOOH) did strongly increase the amount of side product **154**. Using higher temperatures did lower the amount of side product **154**, but resulted in formation of other side products that were not observed before. Using trimethylsilyl triflate as a Lewis acid instead of Brønsted acid *para*-toluenesulfonic acid did not clearly change the reaction outcome. The only change that clearly reduced the amount of side product **154**, was conducting the reaction in less polar solvent (heptane) in combination with methanesulfonic acid. Still, this could not be exploited in a preparative sense, as additional issues resulted from the inhomogeneous reaction mixture. Thus, for the sake of focusing on the successive steps, the lower yield of the stilbene formation was accepted without conducting further investigations.

Albeit the amount of lactone **154** (typically in the range of 20 to 25% according to ^{1}H-NMR of the crude reaction mixture)[a] is actually lower than would be expected from the 60% yield of stilbene **149**, the truly irritating consequence of the formation of this side product is the loss of additional product **149** during purification. The only possible method that was found to cleanly remove lactone **154** was based on treatment with ethanol, which affords clean stilbene **149** at the cost of a lower yield. Column chromatography proved tedious to impossible and effectively inapplicable on a useful scale. Additionally, chromatography was also not appropriate to separate product **149** from the mixture of compounds contained in the mother liquors of the purification with ethanol. In an almost desperate attempt to recover further product **149** from this mixture, a sample was exposed to a mixture of methanol and sulfuric acid with the intent of opening the lactone and directly rearranging side product **154** to stilbene **149**. Sadly, instead of lactone **154** undergoing the transformation that was hoped for, only the desired product **149** decomposed, while lactone **154** seemed unaffected. Currently, the only reasonable solution toward separation of the mixture was to fully reduce everything and then separate the reduction products (Figure 9). The resulting mixture of diol **155**, and diastereomeric monoalcohols **156** and **157** was significantly easier to purify by column chromatography, although still not practical on multi-gram scale. All other attempts to open the lactone (e. g. aminolysis) and convert side product **154** into an easier separable species failed, which is not surprising considering the conformational restraints and steric shielding that stabilize this lactone.

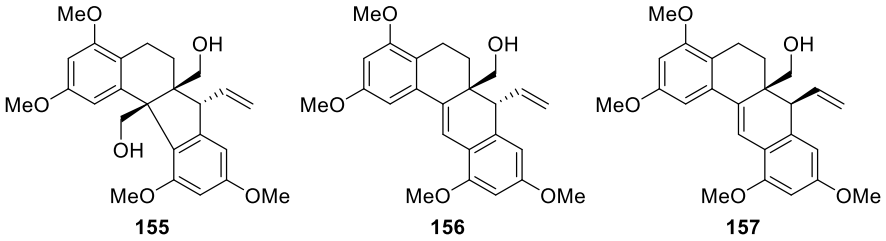
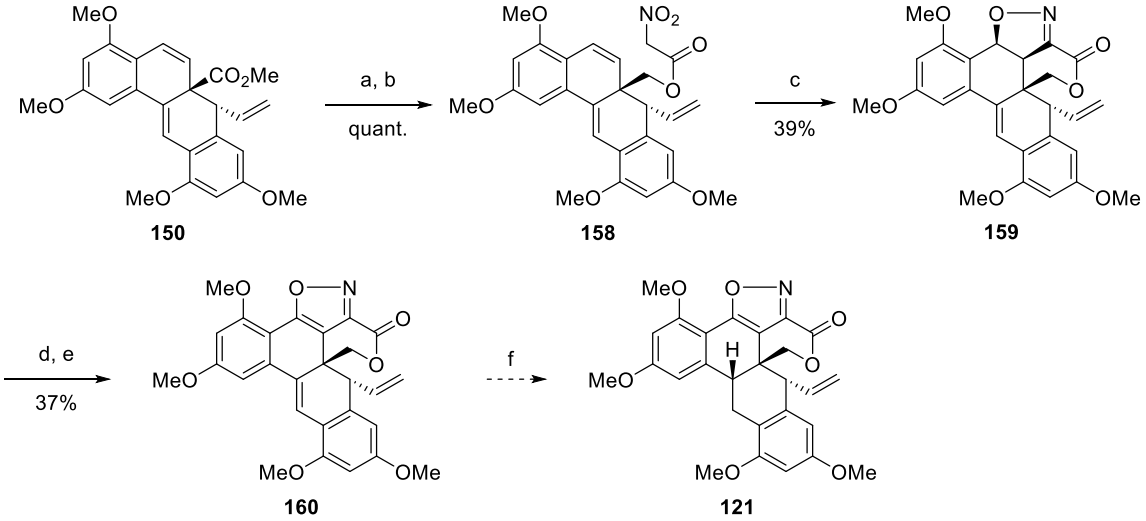


Figure 9 Compounds isolated after reduction of the mixture of compounds obtained during the purification of stilbene **149**.

[a]In $CDCl_3$. Based on integration of the singulet at 7.59 ppm (**149**) and the doublet at 6.96 ppm (**154**).

3.6 Nitrile oxide cycloaddition, isoxazoline oxidation and stilbene reduction

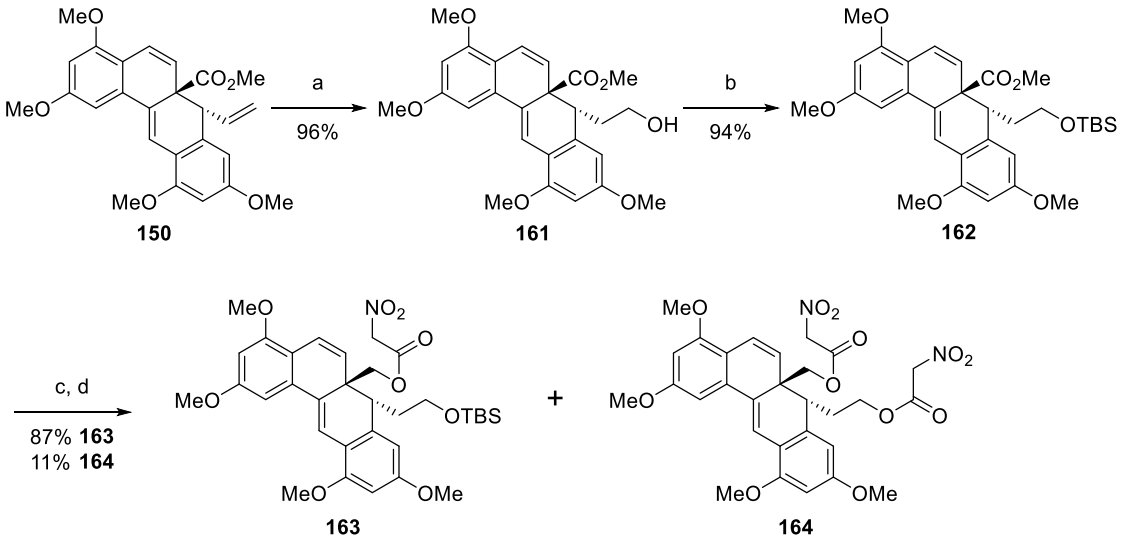
Next, the sequence of nitrile oxide cycloaddition, isoxazoline oxidation and stilbene reduction was investigated (Scheme 45). After unproblematic conversion of triene **150** to the new cycloaddition precursor **158**, it quickly became clear that the following reactions suffered heavily from the presence of the vinyl group. The yield of both the cycloaddition and oxidation steps was reproducibly lower than 40%. Thus, only one attempt was made for the reduction of stilbene **160** and the amount of impure material that was isolated showed that the yield of desired product **121** could be estimated to be less than 20%.



a) DIBAL-H, PhMe, 0 °C. b) DIC, nitroacetic acid, THF/DCM, 0 °C. c) Et_3N, 4-Cl-PhNCO, PhMe, 105 °C. d) TFA, DCM. e) DDQ, PhH, 75 °C. f) Et_3SiH, TFA, 70 °C.

Scheme 45 Nitrile oxide cycloaddition and related reactions in the presence of the free vinyl group.

Consequently, as the free vinyl group obviously posed a significant issue, a more appropriate cycloaddition precursor was prepared from triene **150** (Scheme 46).



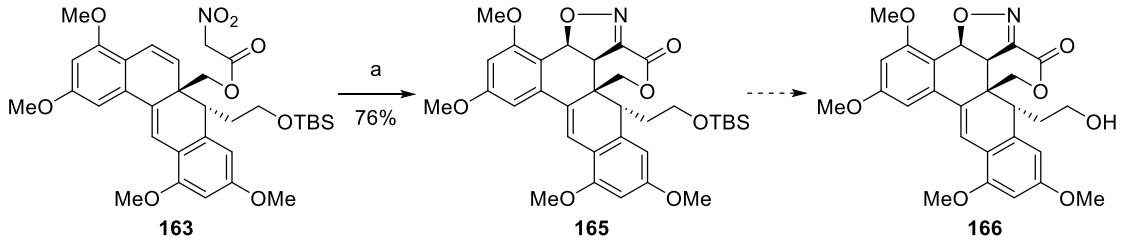
a) 9-BBN, then aq. NaOAc, H_2O_2, THF. b) TBSOTF, 2,6-lutidine, DCM, 0 °C. c) DIBAL-H, PhMe, 0 °C. d) DIC, nitroacetic acid, THF/DCM, 0 °C.

Scheme 46 Synthesis of nitroacetic acid ester **163**.

Selective hydroboration with 9-BBN followed by oxidation under mildly basic conditions with hydrogen peroxide and sodium acetate smoothly afforded alcohol **161**, which was then protected to obtain silyl ether **162**. Both steps proceeded in near ideal yields of 96% and 94% on a multi-gram scale. The possible choices for the protecting group were limited, as the protecting group would need to be stable against diisobutylaluminum hydride, could not interfere during the successive cycloaddition and should be removable in the presence of an isoxazole, preferentially under mild conditions. Furthermore, the acidic conditions of the previously established protocol for isoxazole oxidation and stilbene reduction should be tolerated. As these combined constraints are not effectively met by any standard protecting group, the choice fell on a silyl ether. This meant that the possibility of having to perform a protecting group switch was accepted. However, it was expected that the choice of a silyl ether in turn might be rewarded with increasing solubility, as the typically rather low solubility of many synthetic intermediates had posed an issue in the first-generation approach as well as in the current approach up to this point.

The reduction of ester **162** followed by acylation to nitroacetic ester **163** progressed in good yield of 87% with the missing material being recovered in the form of diester **164**. As nitroacetic acid is a significantly stronger acid (pK_A = 1.6)[55] than regular carboxylic acids, this side product resulting from the cleavage of the silyl ether group is not a surprising result. No attempts were made to recycle compound **164**, but it is expected that complete hydrolysis to the diol followed by selective silylation and esterification to transform this side product to ester **163** should be possible. A similarly selective silylation exploiting the low reactivity of the neopentylic alcohol has proven possible at a later stage in the synthesis (see page 49).

Without the presence of the unprotected vinyl group the nitrile oxide cycloaddition again took place in good yield affording isoxazoline **165** from nitroacetic acid ester **163** in 76% yield (Scheme 47).

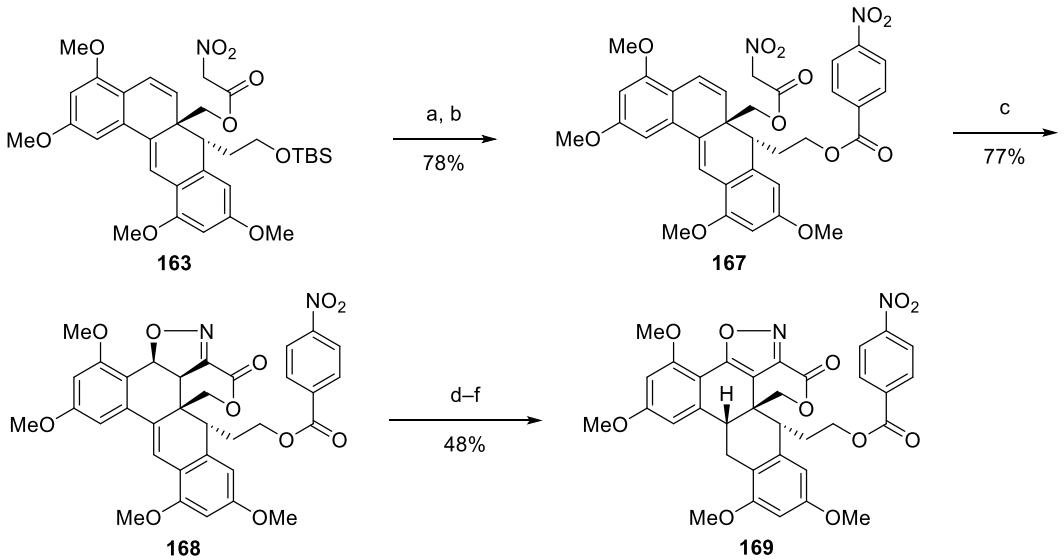


a) DIPEA, 4-Cl-PhNCO, PhMe, 105 °C.

Scheme 47 Nitrile oxide cycloaddition with silyl ether **163** and desired desilylation product **166**.

The previous conditions for the cycloaddition were improved in several key aspects. By switching from triethylamine to the less volatile base DIPEA, the issue of very low conversion with catalytic amounts of base was alleviated. This additionally did remove the need for slow addition of the isocyanate reagent, for which the employed amount could also be reduced from the previously employed significant excess (4 eq.) to a near stoichiometric quantity (2.4 eq.). This made the reaction more practical and in combination with the increased solubility resulting from the presence of the silyl ether protecting group allowed for an easier and more efficient purification of isoxazoline **165**. As the oxidation to the isoxazole was presumed to require conditions that were not compatible with the silyl ether protecting group, it was attempted to prepare alcohol **166** by treatment of silyl ether **165** with tetrabutylammonium fluoride to switch to an appropriate protecting group. This did not afford the desired product **166**, which was expected to be a result of the sensitivity of the lactone and/or isoxazoline rings. Acidic conditions to remove the silyl group were not considered viable, due to known potential of the isoxazoline moiety to open to the unsaturated oxime (see page 18). Thus, changing the protecting group at an earlier stage was expected to be a potential solution.

This expectation turned out to be true and silyl ether **163** could be deprotected with dilute, aqueous hydrochloric acid in tetrahydrofuran and then transformed into nitrobenzoate **167**with a yield of 78% over two steps (Scheme 48). Employing the established conditions, the successive conversion of cycloaddition precursor **167** to isoxazole **169** took place in an overall yield of 37%. The key to the success of the esterification was to activate the alcohol and form the ester by alkylation of a carboxylic acid through a Mitsunobu reaction. In contrast, acylation with acetic anhydride or pivaloyl chloride had failed and both reagents afforded a mixture of compounds.



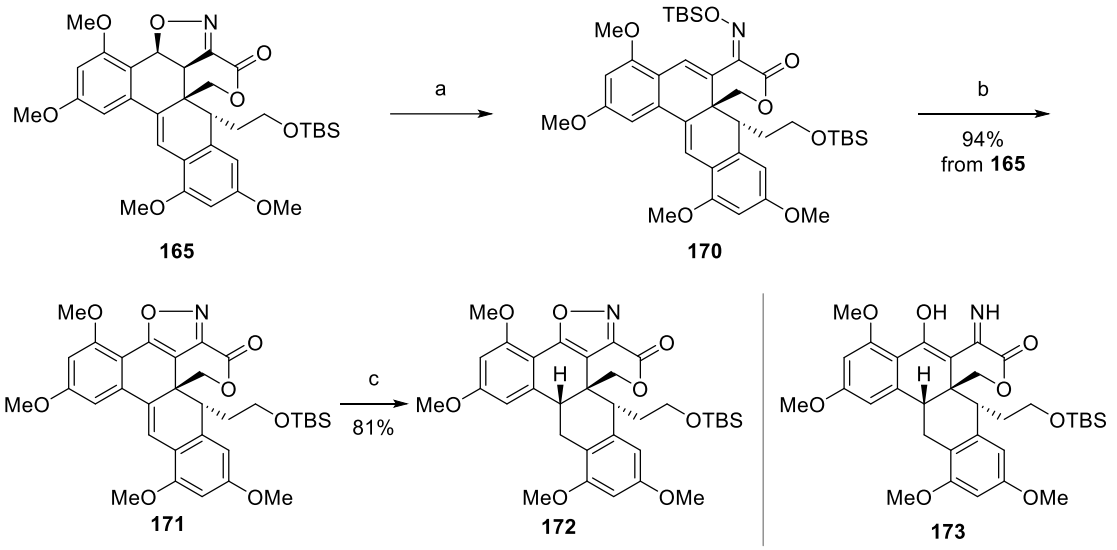
a) aq. HCl, THF. b) DIAD, PPh_3, 4-nitrobenzoic acid, THF. c) DIPEA, 4-Cl-PhNCO, PhMe, 105 °C. d) MsOH, $CHCl_3$. e) DDQ, PhH, 75 °C. f) Et_3SiH, TFA, 70 °C.

Scheme 48 Synthesis of nitrobenzoate **171**.

The stilbene reduction forming compound **169** cleanly afforded one diastereomer and the observed NOESY correlations agreed with the desired product. However, due to overlapping ^{1}H-NMR signals, the stereochemistry could not be confirmed unequivocally. Still, based on the selective reduction of lactone **67** it can be expected that the stereochemistry depicted for compound **169** in Scheme 48 is correct.

With the synthesis of compound **169**, the investigations following the revised synthetic strategy had reached a point where no information was available anymore from the first-generation approach for the successive reactions. Except, of course, for the benzylic oxidation conditions (Section 2.9) and the model studies for the pyrone formation (Section 2.10), which are both relevant for the final steps of the synthesis of A-74528. However, before proceeding with attempts to evolve isoxazole **169** further toward the natural product, it seemed worthwhile to revisit the conditions for the isoxazoline oxidation and stilbene reduction. Especially, as the need for switching between protecting groups was highly unsatisfactory.

Although it took some time to come up with an approach that seemed reasonable on paper, a surprisingly simple solution to fix the issue of the silyl ether instability during the isoxazole oxidation was found. The key idea was to open the isoxazoline to a silyl oxime instead of free oxime (Scheme 49). Treatment of isoxazoline **165** with TBS triflate without base followed by addition of 2,6-lutidine formed silyl oxime **170**, which was then oxidized to isoxazole **171** in a total yield of 94%. Thus, in addition to tolerating the silyl ether group, this new method increased the yield by roughly 25% compared to the value of 70% for oxidation of isoxazoline **63**.



a) TBSOTf then 2,6-lutidine, $CHCl_3$. b) DDQ, DCE, 75 °C. c) $PhSiH_3$, TBHP, $Mn(dpm)_3$, DCE/*i*PrOH.

Scheme 49 Conversion of isoxazoline **165** to isoxazole **172** and side-product **173**.

The improved yield of this isoxazole oxidation may be a consequence of an increased stability of silyl oxime **170**, as the free oximes **64** of the first-generation approach exhibited significant decomposition upon attempts of isolation and storage. Regarding the mechanism of the transformation of silyl oxime **170** to isoxazole **171**, it is assumed that it occurs through electrocyclization of a nitroso cation akin to intermediate **65** (see page 18). The ultimate fate of the silyl group was not determined, but it seems reasonable to expect that it would be transferred to the hydroquinone species formed from DDQ during the oxidation.

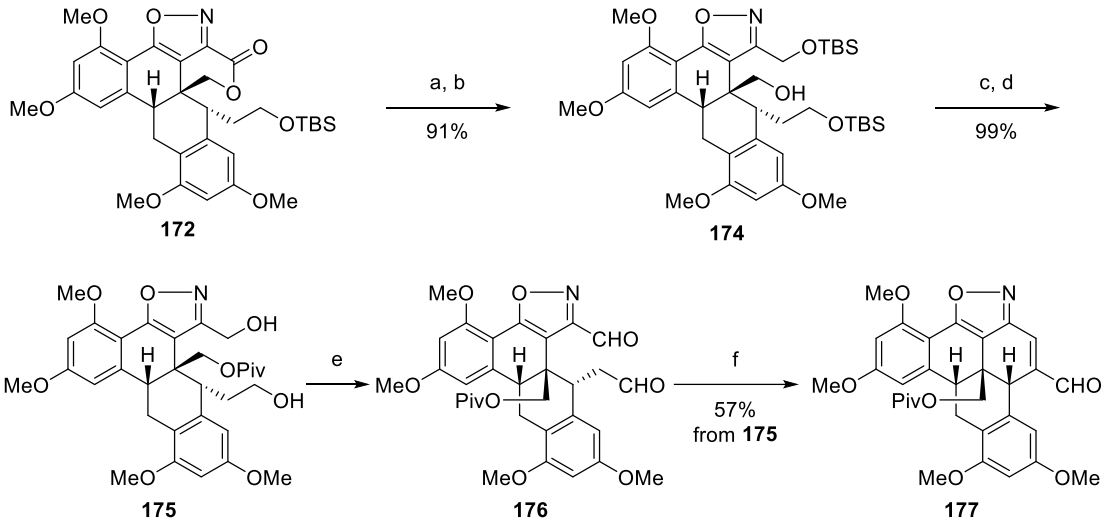
For the reduction of stilbene **171**, the improved solubility resulting from the silyl protecting group was again beneficial and allowed to efficiently employ Shenvi's HAT hydrogenation method[27a] (Scheme 49). Using a solvent consisting of a 1/5 mixture of isopropanol/1,2-dichloroethane allowed to conduct the reaction at a sufficient concentration of substrate **171** to provide high enough reaction rates for the reaction to finish on a timescale of hours. For the full conversion of substrate **171** with 10 mol% of $Mn(dpm)_3$ it was necessary to employ a larger amount phenylsilane (1.5 eq.) and *tert*-butyl hydroperoxide (2 eq.) than reported (1 and 1.5 eq.). The order of addition of reagents and catalyst as well as the degassing procedure was also modified with respect to the reported procedure. Addition of the silane and the peroxide by syringe to a degassed mixture of all the other reaction components was found to be more practical and reliable than to "degas the mixture for another 30 seconds" after addition of the solid catalyst as reported by Shenvi.[27a] Using this modified method, the stilbene reduction product **172** was obtained in 81% yield. Contrary to nitrobenzoate **169**, the NOESY spectrum allowed to clearly confirm that the silyl ether **172** exhibited the correct stereochemistry.

A side product that was formed during the stilbene reduction was identified to be imine **173**, which results from cleavage of the nitrogen-oxygen bond but only accounts for less than 5% of the missing material.[a] While the amount of side product **173** increased with larger amounts of phenylsilane and *tert*-butyl hydroperoxide, this effect was rather small. For example, using twice as much of both reagents only about 20% of side product **173** was observed. As this observation originates from an early small-scale test reaction, which also employed 50 mol% of catalyst, it shows that the method is quite robust against forming overreduction products.

[a]According to ^{1}H-NMR($CDCl_3$) spectroscopy of the crude reaction mixture with integration of the signals at 6.67 ppm (**172**) and 6.31 ppm (**173**).

3.7 F-ring formation

With access to lactone **172** secured, the formation of the F-ring system of A-74528 could be addressed. This was achieved through a six step sequence, which provided unsaturated aldehyde **177** in 51% yield and featured an aldol condensation for the key carbon-carbon bond formation to forge the F-ring system (Scheme 50).

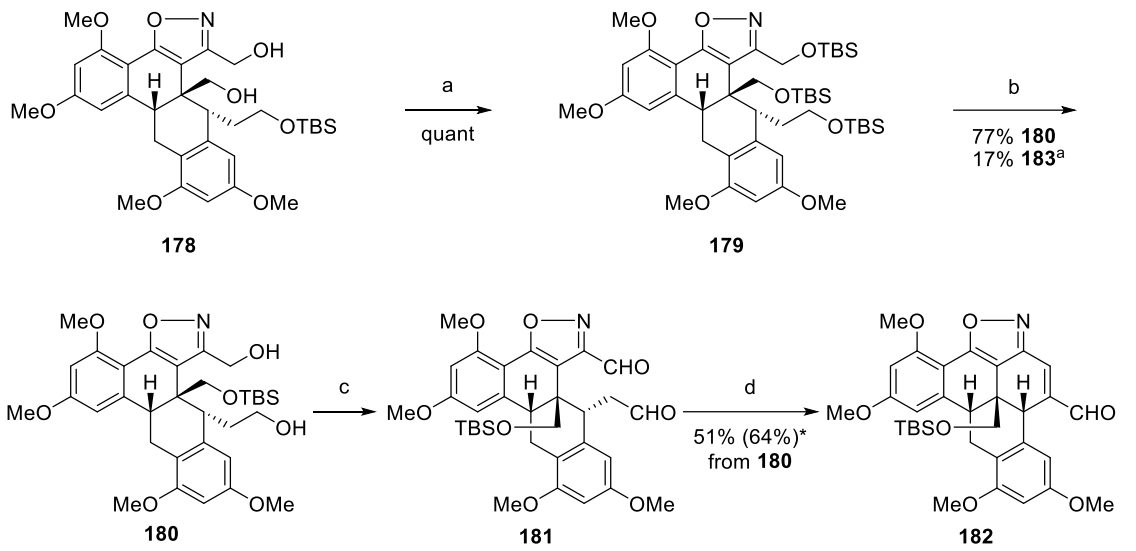


a) DIBAL-H, THF, 0 °C. b) TBSCl, imidazole, DCM, 0 °C to rt. c) PivCl, DMAP, DCM, 0 °C to rt. d) aq. HCl, THF. e) DMP, DCM. f) Bn_2NH_2TFA, PhMe, 60°C.

Scheme 50 Synthesis of unsaturated aldehyde **177**.

Starting with reduction by diisobutylaluminum hydride lactone **172** was converted into neopentylic alcohol **174** by a successive selective silylation at the less hindered position with TBS chloride/imidazole. Then, further protecting group manipulations afforded pivalate **175** in near quantitative yield, which was oxidized to dialdehyde **176** with Dess-Martin periodinane. Without any need for optimization of the reaction conditions, aldol condensation of dialdehyde **176** catalyzed by dibenzylammonium trifluoroacetate[56] directly afforded unsaturated aldehyde **177** in a respectable yield of 57%. An analysis of the NOESY correlations confirmed that during the sequence converting lactone **172** into unsaturated aldehyde **177** the configuration of all stereocenters was unaffected.

During initial trial reactions for the selective silylation an overreaction side product was obtained in addition to alcohol **174**. Upon attempting to recycle this side product it was noticed that a selective deprotecting of only two silyl groups was easily possible. This finding evolved into an efficient alternative to the route affording pivalate **177** and a four step sequence relying on a selective deprotection was developed to access unsaturated aldehyde **182** in 49% yield from diol **178** (Scheme 51) and, respectively, in five steps and 47% yield from lactone **172**.



a) TBSOTf, 2,6-lutidine, DCM, 0 °C to rt. b) aq. HCl, THF. c) DMP, DCM. d) Bn_2NH_2TFA, PhMe, 60°C. *after treatment of **185**[a] with MsCl, Et_3N, DMAP, DCM, 0 °C to rt, then DBU, PhMe, 60 °C.

Scheme 51 Synthesis of unsaturated aldehyde **182**. [a]See Figure 10.

While the overall yield for silyl ether **182** is lower than for pivalate **177**, this is virtually only a consequence of the formation of side product **183** (Figure 10). This triol formed during the desilylation step should be easily recycled to silyl ether **179**, although this has not been investigated yet. The advantage of the silyl ether **182** over pivalate **177** is that its synthesis requires one step less and, more importantly, a silyl protecting group is more suitable for the successive reactions than an ester.

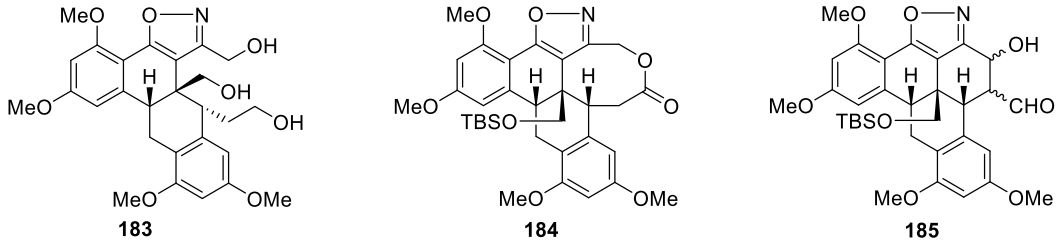


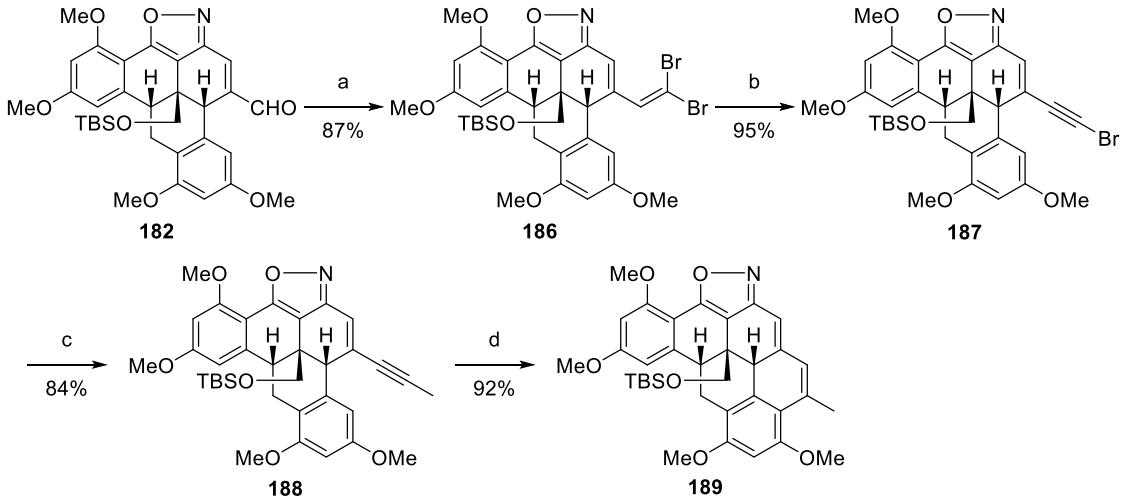
Figure 10 Side products isolated during the synthesis of aldehyde **182** from diol **177**.

One consequence resulting from changing the protecting group to a silyl ether was that under the same conditions the aldol condensation initially only afforded product **182** in a yield of 44%. However, additionally a mixture of compounds was isolated, which contained various diastereomers of aldol addition product **185** (Figure 10) according to LC-MS analysis. Consequently, after dehydration of this material by sulfonylation with methanesulfonyl chloride followed by exposure to DBU it was possible to isolate additional 13% of product **182**. Surprisingly, the DBU step seems not to have been necessary and elimination occurred directly during the sulfonylation, as it was not observed that the fraction of product **182** increased during the treatment with DBU. Apart from additional product, the eight-membered lactone **184** (Figure 10) was also isolated from the mixture of

compounds obtained after the dehydration step. This compound was traced back to be a side product formed during the oxidation of diol **180** to aldehyde **181**. Crude aldehyde **181** contained about 20%[a] of lactone **184** and for the pivalate route a similar compound was observed in hindsight, which made up about 15%[b] of the crude material for dialdehyde **176**. Thus, while the results were sufficient at the present to focus on successive reactions, optimization of the oxidation step to avoid formation of the lactone side products will be necessary in the future. As the lactone formation can be expected to proceed through the corresponding hemiacetal, the conditions should be modified to avoid acetalization, for example by using buffered Dess-Martin periodinane to compensate for the acidic character of the reagent. The same need for future optimization exists for the aldol condensation step. Here, it will be important to improve the conversion of aldol addition intermediates to the aldol condensation products, which may require a two-step approach, like for the aldol condensation product **182**.

3.8 A-ring formation and successive reactions

Having formed the F-ring, only one ring system of the hexacyclic core of A-74528 was missing. A concise sequence based on a Corey-Fuchs homologation[57a] and gold-catalyzed alkyne activation allowed to install this final ring and finish the carbon skeleton of the core fragment of A-74528 (Scheme 52).



a) CBr_4, PPH_3, Et_3N, DCM, 0 °C. b) NaHMDS, THF, −78 °C. c) *n*BuLi, MeI, THF, −78 °C to rt. d) $(Ph_3P)Au(NTf_2)$, PhMe, 80 °C.

Scheme 52 Synthesis of diene **189**.

[a]Determined by ^{1}H-NMR($CDCl_3$) spectroscopy based on integration of the singulet at 10.22 ppm and triplet at 9.32 ppm (**181**) versus the doublets at 5.53 and 5.06 ppm (**184**).
[b]Determined by ^{1}H-NMR($CDCl_3$) spectroscopy based on integration of the singulet at 10.21 ppm and triplet at 9.33 ppm (**176**) versus the doublets at 5.58 and 5.01 ppm (presumed lactone side product).

For the homologation of aldehyde **182,** a procedure by Grandjean, Pale and Chuche[57b] was used. This procedure uses triethylamine as an additive in the olefination step to avoid side reactions with electrophilic byproducts and performs the elimination of the 1,1-dibromoalkene to a bromoalkyne in a separate step. Compared to the original Corey-Fuchs approach, in which the 1,1-dibromoalkene **186** would be directly treated with *n*-butyllithium, it was expected that the separate elimination step should avoid problems resulting from lithiation at the aromatic rings. Following this homologation procedure, the methylate alkyne **188** was obtained after treatment with *n*-butyllithium and methyl iodide in a yield of 70% over three steps.

With all the carbons present, the next step was to form one more carbon-carbon bond to close the A-ring. Various similar examples were reported for the envisioned gold-catalyzed electrophilic bond formation between an alkyne and an aromatic ring.[58] Other metals are also able to catalyze such reactions, for example palladium, platinum, indium or mercury.[59] As the desired product **189** was not expected to be a highly robust molecule and as it was considered the mildest among these metals, gold catalysis was chosen to be tested first with the limited amount of material that was available. Among the gold catalysts that were at hand, triphenylphosphine gold triflimide was selected as it was the most practical, due to not needing an additional ingredient for activation. Luckily, the reaction with this catalyst in toluene at 80 °C cleanly converted alkyne **188** into diene **189** and upon scaling up to a multi-milligram scale a yield of 92% was obtained for this step and the structure of the product was confirmed by X-ray crystallography (Figure 11).

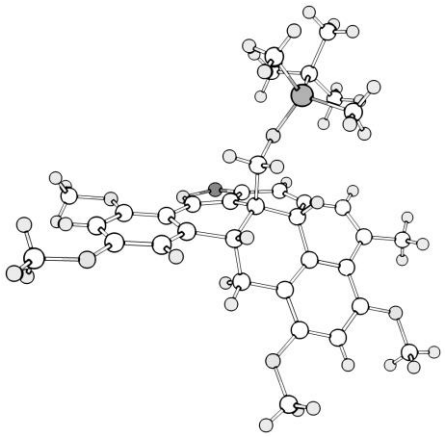
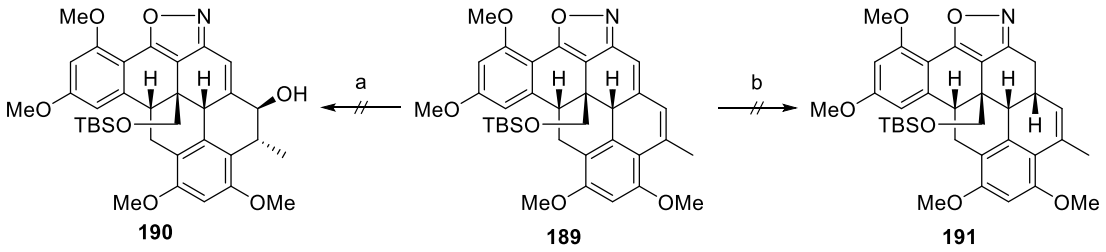


Figure 11 X-ray structure of diene **189.**

The successive reactions would need to differentiate between the two alkenes, install the secondary alcohol and establish the remaining stereocenters (Scheme 53). While the task of setting the correct stereochemistry at the intersection of the F- and A-ring was expected to be benefiting from strain disfavoring the undesired configuration, the configuration of the two stereocenters in the A-ring should be more challenging, as could not be expected to benefit from strain in similar manner.

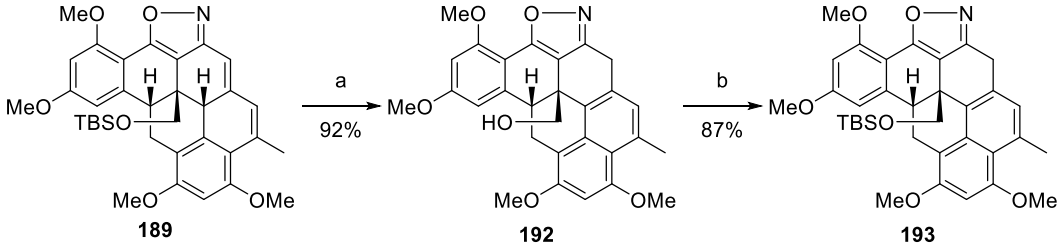
Although these investigations cannot be considered conclusive with respect to possible reactions and reaction conditions, unfortunately all attempts to further evolve diene **189** toward the natural product failed. Attempting to prepare alcohol **190** by hydroboration with 9-BBN or borane-tetrahydrofuran complex gave mainly unreacted starting material or a complex mixture, respectively. The previously successful manganese-catalyzed hydrogenation procedure also did not afford the desired selective reduction product **191**, but instead only minor amounts of the aromatized compound **193** (Scheme 54) were isolated among a complex mixture of compounds.



a) 9-BBN or BH_3·THF, then aq. NaOAc, H_2O_2 THF. b) $PhSiH_3$, TBHP, $Mn(dpm)_3$, DCE/*i*PrOH.

Scheme 53 Attempted reduction and hydroboration of diene **189**.

A clean sample of naphthalene **193** was obtained upon deprotection of the silyl ether **189** under basic conditions and direct reprotection of alcohol **192**, which suffered from rapid decomposition issues (Scheme 54). The naphthalene **193** was also a major product formed from diene **189** under irradiation with 427 nm light or extended exposure to ambient light.



a) TBAF·$3H_2O$, THF. b) TBSOTf, 2,6-lutidine, DCM, 0 °C.

Scheme 54 Aromatization of diene **189** to naphthalene **193**.

The aromatization of diene **189** had been a reason for concern from the beginning, based on a computational investigation (Figure 12). DFT calculations had predicted that the gold-catalyzed cyclization would be thermodynamically possible and for the conversion of model alkyne **194** to diene **195** a high reaction energy of more than 150 kJ/mol was calculated. Thus, any minor doubts of this cyclization being prevented by increasing strain in the cyclization product were dispersed. However, a comparison of the stability of epimers and regioisomers that might be formed from diene **195** showed that the undesired epimer **196** is similar in energy and that naphthalene **197** is more stable by about 70 kJ/mol. All other isomers were predicted to be less stable than the desired structure **195** by an extent that suggest that there was no need to worry about them.

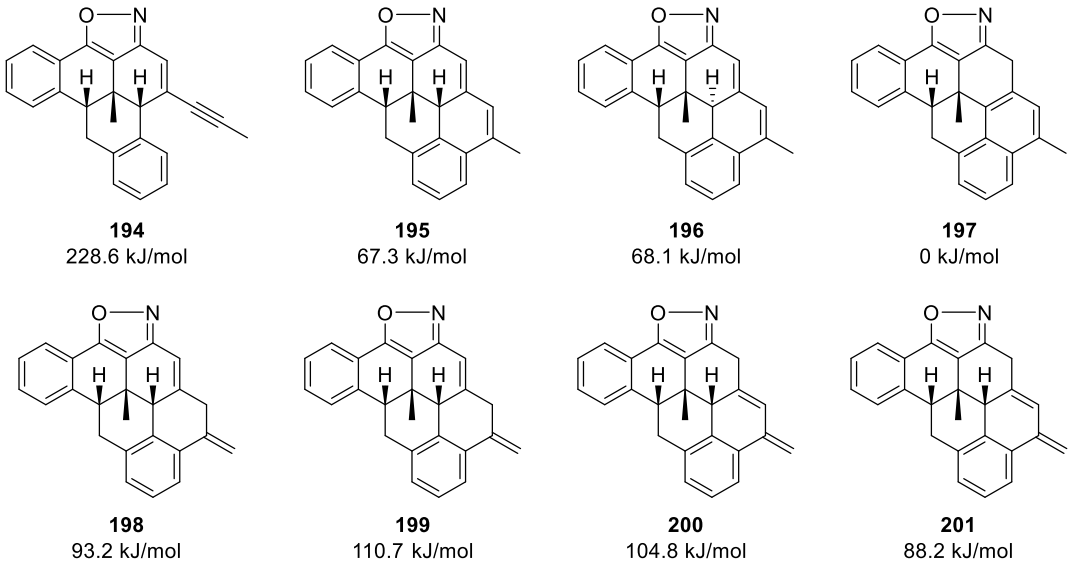
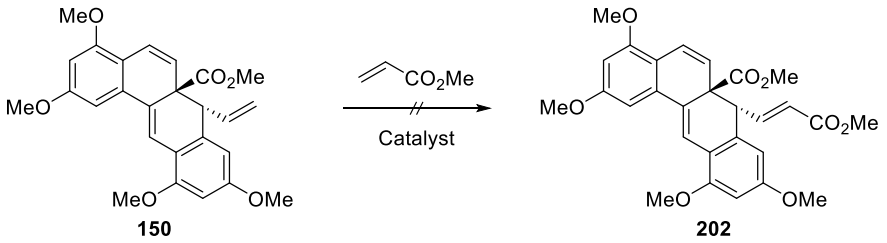


Figure 12 Relative energies of alkyne **194**, diene **195** and isomeric dienes calculated at the DSD-PBEP86/def2-QZVPP//D3-PBE/def2-TZVP level.

3.9 Attempts to modify triene 150 and diene 149

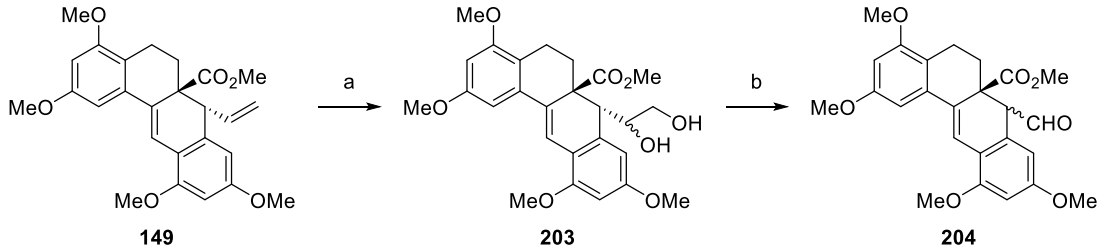
Before the summarizing the work toward A-74528 described in the preceding sections and considering future directions, the results of the investigations of alternative routes need to be reported. This will be the topic of this and the succeeding section, with this section focusing on attempts to modify triene **150** or diene **149**. The goal of these attempts was to test the possibility of forming the necessary additional carbon-carbon bonds toward the A- and F-ring at an early stage by modifying the vinyl substituent. However, the vinyl moiety of triene **150** exhibited a surprisingly low reactivity, which was first observed upon attempts to perform an alkene cross-metathesis with methyl acrylate (Scheme 55).



Scheme 55 Olefin cross-metathesis attempt with triene **150**.

Using various olefin metathesis catalysts (Grubbs I, Hoveyda-Grubbs I, Hoveyda-Grubbs II, Grubbs II + copper iodide[60]) no cross metathesis product **202** was observed and also no dimerization of triene **150** occurred. Thus, instead of an alkene metathesis a multiple-step approach based on oxidative cleavage of the vinyl group to an aldehyde followed by olefination was considered. In this case, the diene **149** was used as a starting material, to lower the potential for side reactions by reducing the number of alkene moieties in substrate.

For the oxidative cleavage of diene **149** to aldehyde **204** (Scheme 56) preliminary attempts of ozonolysis failed and only resulted in decomposition. Thus, a two-step cleavage by dihydroxylation and diol cleavage was tested. The reaction did only proceed very slowly under standard conditions with osmium tetroxide, but with a modified version of conditions reported for a "Sharpless-style racemic dihydroxylation"[61] the reaction finished within several days at room temperature. The resulting diol **203** was directly cleaved to aldehyde **204** with phenyliodine(III) diacetate according to the procedure by Nicolaou.[62] Several trial reactions under similar conditions were performed and in some instances the obtained material contained several aldehyde species. This was assumed to be a result of epimerization or an unwanted oxidation at different position in the molecule. Due to this observation and as the dihydroxylation step still required an unreasonably high amount of osmium tetroxide (0.15 eq.), the attempts to prepare aldehyde **204** were abandoned.

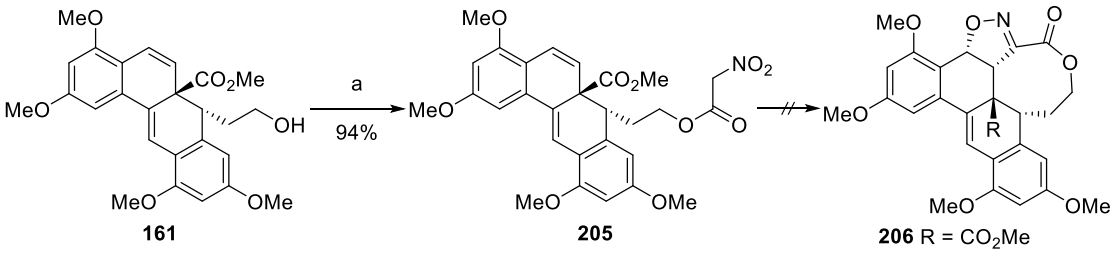


a) OsO_4, K_2CO_3, $K_3[Fe(CN)_6]$, DABCO, $MeSO_2NH_2$, *t*BuOH/DCE/water. b) PIDA, DCM.

Scheme 56 Conversion of diene **149** to aldehyde **204**.

3.10 Alternative nitrile oxide cycloaddition approaches

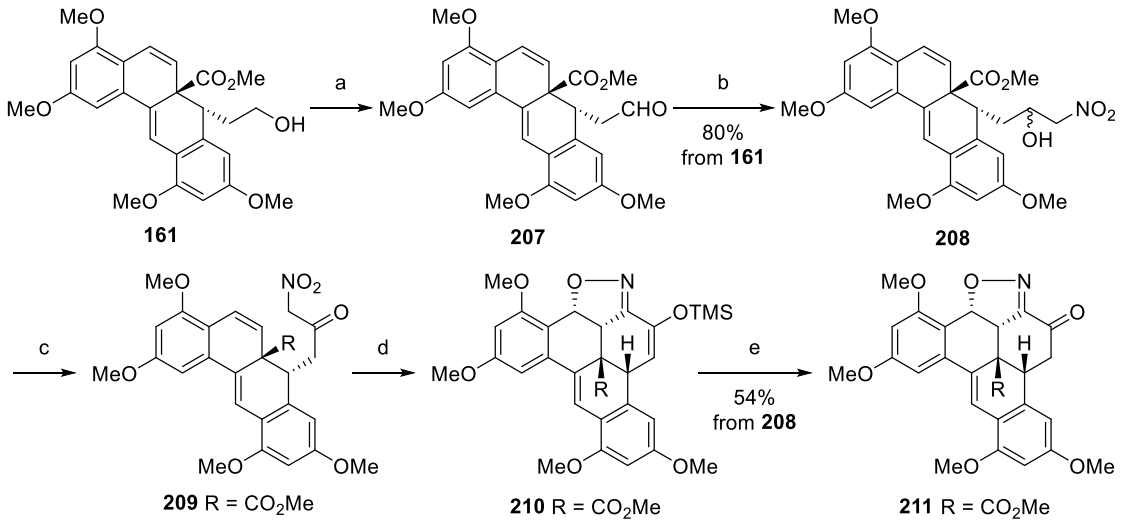
In the original strategy, only one position was available to attach a nitrile oxide precursor and perform an intramolecular nitrile oxide cycloaddition. While the same point of attachment has ultimately been the most successful, as described in the preceding sections, the revised strategy also offered possibilities to attach nitrile oxide precursors at different positions in the molecule. One quite obvious possibility is to prepare nitroacetic acid ester **205** from alcohol **161** (Scheme 57). However, no conditions were found that afforded the cycloaddition product **206**, which might be due to the eight-membered ring in isoxazole **206** being too strained or otherwise disfavored.



a) DIC, nitroacetic acid, THF/DCM, –18 to –15 °C, 94%.

Scheme 57 Attempted nitrile oxide cycloaddition to form eight-membered lactone **206**.

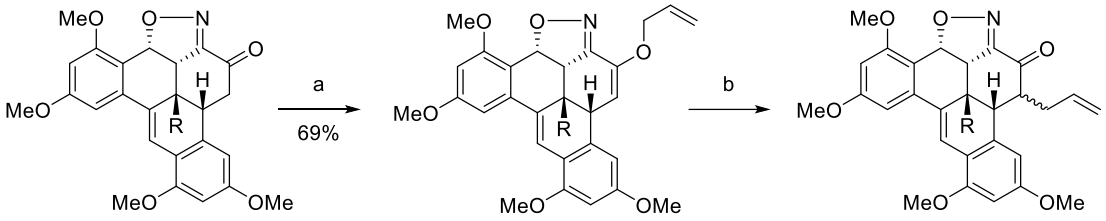
A more successful cycloaddition was possible with nitroketone **209**. In this case, a series of five reactions allowed to access isoxazoline **211** from alcohol **161** in 43% yield (Scheme 58). Oxidation of alcohol **161** under Parikh-Doering conditions[39] afforded aldehyde **207**, which was converted to nitroalcohol **208** in the same pot by concentrating the reaction mixture followed by adding nitromethane and triethylamine. This was an effective solution to avoid excessive decomposition of aldehyde **207**, which had proven highly unstable, and afforded nitroalcohol **208** in 80% yield as a mixture of epimers. Signs of decomposition were also observed for nitroketone **209**. Thus, after oxidization of nitroalcohol **208** with Dess-Martin periodinane, the crude nitroketone **209** was treated without delay with triethylamine and bis(trimethylsilyl)acetamide followed by stirring with silica. This sequence afforded isoxazoline **211** in 54% yield. With respect to the mechanism of this cycloaddition, both a nitrile oxide and a siloxynitronate could be involved.[63] Based on ^{1}H-NMR analysis of the crude reaction mixture before treatment with silica, it was assumed that isoxazoline **210** was observed and not a *N*-silyloxy-isoxazolidine that would be characteristic for the involvement of a siloxynitronate. The reason for stirring with silica was to cleave the silyl enol ether that was present in isoxazoline **210**, which could also decompose any *N*-silyloxy-isoxazolidine that was present at this point. The mild cleavage of the silyl enol ether was a significant advantage of using bis(trimethylsilyl)acetamide to initiate the cycloaddition, as related enol ether type species that cannot be cleaved mildly were observed with other reagents for the dehydration of nitro compounds (PhNCO, Boc_2O).



a) SO_3·pyridine, Et_3N, DCM/DMSO. b) Et_3N/$MeNO_2$. c) DMP, DCM. d) BSA, Et_3N, PhMe, 105 °C. d) SiO_2, water, DCM.

Scheme 58 Nitrile oxide cycloaddition route forming hexacycle **211** through nitroketone **209**.

Although the F-ring had been established in a rapid fashion, developing isoxazoline **211** further toward the natural product proved to be problematic. Neither treatment with DDQ nor the previously successful two-step procedure (see page 18) allowed oxidation to the isoxazole. Even though it has not been tested, based on previous results (Section 2.9) there is also reason to assume that a reduction of the stilbene moiety will be not be possible with the correct stereochemistry. Nevertheless, further investigations toward forming the A-ring system were pursued (Scheme 59).



211 R = CO_2Me **212** R = CO_2Me **213** R = CO_2Me

a) allyl bromide, K_2CO_3, DMF. b) mesitylene, 140°C.

Scheme 59 Further reactions with isoxazoline **211**.

To finish the hexacyclic core skeleton a three-carbon fragment was introduced by allylation with allyl bromide in decent yield of 69%. This alkylation afforded allyl enol ether **212**, but Claisen rearrangement at 140 °C in mesitylene afforded the desired α-allyl ketone **213**. However, the rearrangement product **213** was obtained as a mixture of rapidly equilibrating epimers, which could not be separated. To converge both epimers into one compound, the formation of the enol triflate was tested. This transformation was found to be proceeding sluggishly. Thus, further investigations of this route were stopped at this point.

4 Summary and future directions

The first part of this thesis described the efforts toward the total synthesis of the polyketide A-74528 culminating in the synthesis of diene **189**, which already contains the full carbon skeleton of the hexacyclic core fragment of the natural product (Figure 13).

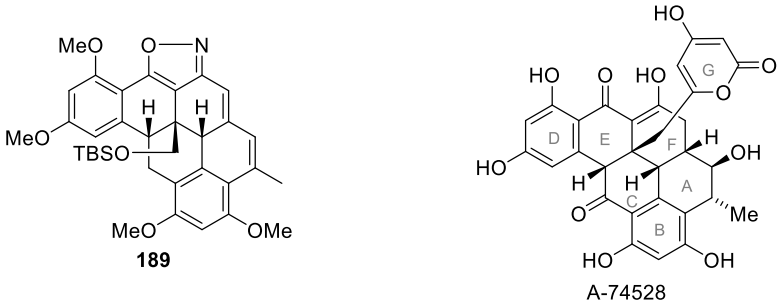
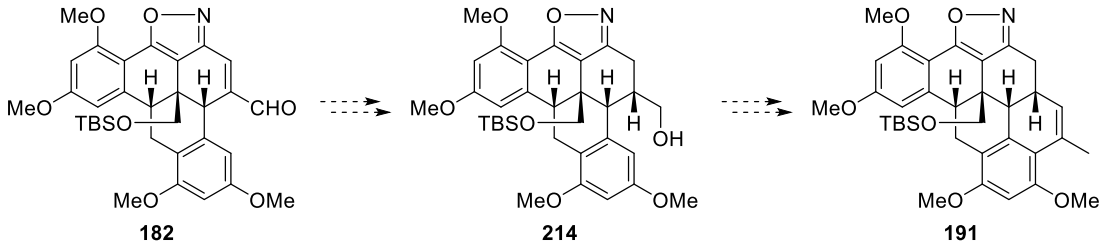


Figure 13 Diene **189** and A-74528.

Three of the six stereocenters of A-74528 are already present in diene **189** and the feasibility of several crucial transformations that are necessary to convert diene **189** to the natural product, such as the benzylic oxidation at C-ring and the installation of the pyrone moiety, has been confirmed with model compounds. However, a key challenge of future investigation will be to develop the diene moiety further toward the natural product and install the remaining stereocenters. Preliminary attempts toward this goal showed that an issue of diene **189** is a significant tendency to rearrange to a naphthalene. If this would turn out to make diene **189** a dead end, then it will be necessary to modify the current approach and take measures to prevent an aromatization. For example, this could be possible by an early reduction of the F-ring as depicted in Scheme 60, although achieving stereoselectivity in such a reduction may not be easy.



Scheme 60 Early F-ring reduction as a possible alternative direction for future investigations.

While it is undoubtedly the case that significant challenges remain to synthetically prepare A-74528, large progress toward the synthesis of this natural product has been made. Two approaches have been investigated and the knowledge gained from the original approach was vital for the success of the second-generation approach.

The key compounds to summarize the main results of the original approach (Section 2) are ketoester **25**, tetracycle **57** and isoxazole **83** (Figure 14). First, efficient access to

ketoester **25** was established through a Dieckmann condensation route. Then, tetracycle **57** was prepared from ketoester **25** and benzyl bromide **26**, starting with connecting the two fragments by a simple alkylation. Successively, a Corey-Chaykovsky epoxidation and acid catalyzed transformation of the resulting epoxide were the crucial reactions to form the C-ring. Finally, isoxazole **83** was prepared from tetracycle **57** with an intramolecular nitrile oxide cycloaddition as the key reaction. In the process, two discoveries of high strategic value were made. First, the oxidation of the cycloaddition product to the isoxazoline was identified as troublesome step and this problem was solved by developing a two-step approach. Second, it was recognized that the strain imposed by the lactone moiety allows to reduce the stilbene with the desired stereochemical outcome.

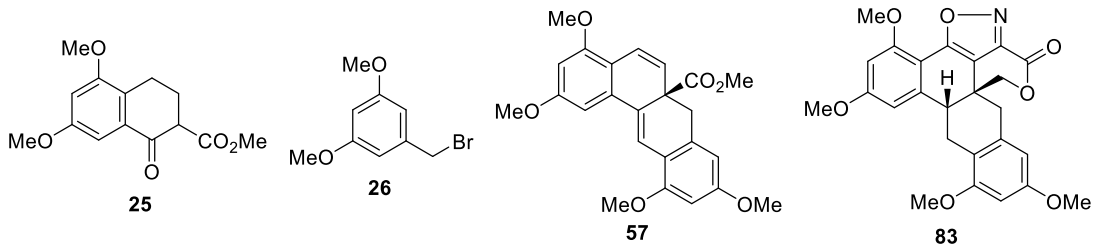


Figure 14 Key compounds of the first-generation approach.

Due to issues toward installing the F- and A-ring, the original approach was revised to enable the formation of these ring systems and also make the synthesis more convergent. As most of the chemistry of the original route could be reused, many of the key intermediates of the revised approach (Figure 15) shared direct relationship to respective intermediates of the original route. The major change in the revised approach was to replace benzyl bromide **26** by methyl carbonate **123** and perform a molybdenum-catalyzed allylation for the coupling with ketoester **25**. This afforded the branched allylation product **122** with high diastereo- and regioselectivity.

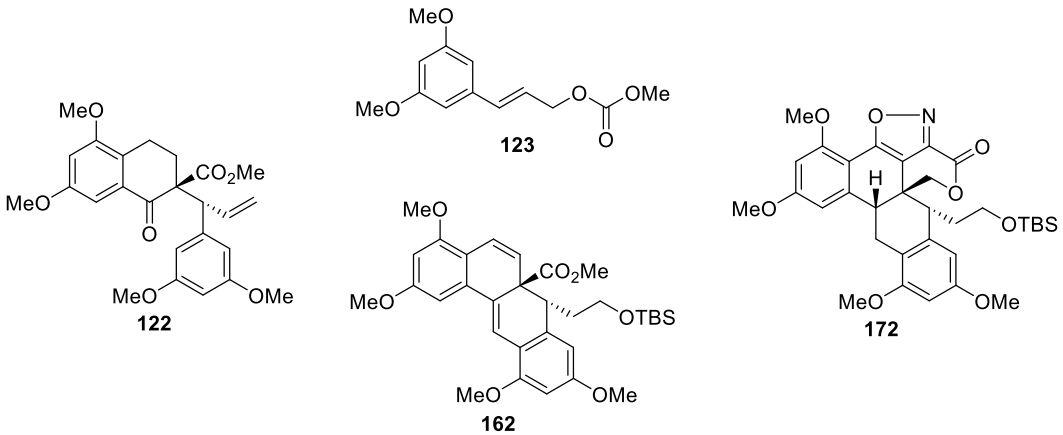


Figure 15 Key compounds of the second-generation approach, part 1.

To prepare diene **162** from coupling product **122** and for the further conversion to isoxazole **172** the same sequence as in the original approach proved suitable. The only changes were that an additional hydroboration/alcohol protection was part of the sequence and that the conditions for the isoxazole oxidation and stilbene reduction were adapted to be compatible with the silyl ether protecting group.

At this point the revised route diverged fully from the original route and the late-stage intermediates connecting isoxazole **172** and diene **189** were not related to previous intermediates (Figure 16). Lactone reduction and protecting group manipulation converted isoxazole **172** to diol **180**, which after alcohol oxidation and aldol condensation afforded unsaturated aldehyde **182**. Finally, diene **189** was obtained through homologation of aldehyde **182** to the methyl alkyne and a gold-catalyzed cyclization.

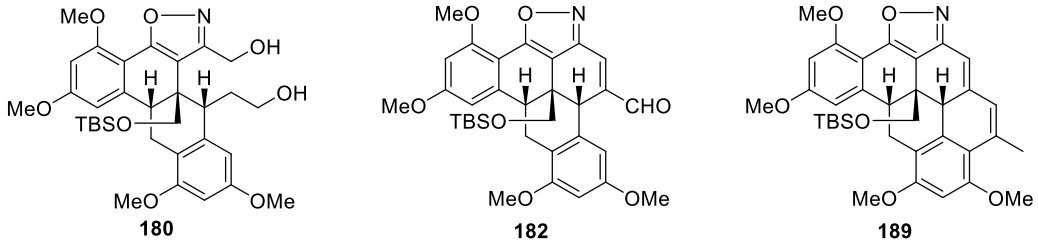


Figure 16 Key compounds of the second-generation approach, part 2.

With respect to the synthetic efficiency, the second-generation approach allowed to easily prepare more than 50 milligrams of diene **189** in a total of 29 steps with a 26 steps longest linear sequence. Starting from building blocks **25** and **123**, it took 21 steps to reach diene **189** and 17 steps to reach aldehyde **182**, with an overall yield of 5% and 8% respectively. In general, the synthetic route proved robust and scalable. The scalability has been confirmed by performing all reactions up to the formation of aldehyde **182** at least at a scale of several hundred milligrams. An important advantage with respect to scale-up is the low need for chromatographic purification, which can be avoided in many steps. In the cases where chromatographic purification cannot be avoided, the separation of product and impurities is typically easy. In cases where the separation is not efficient, highly pure product can be obtained after additional crystallization, precipitation or simply washing with an appropriate solvent. Thus, efficient access to large amounts of late-stage intermediates is possible, which will facilitate further investigations toward the final target. Preliminary data suggests that the currently lowest yielding steps (e.g. the formation of the C-ring or the oxidation/aldol condensation sequence) still have potential for optimization, which should allow to further improve the overall synthetic efficiency in future studies.

At last, it remains to be pointed out that the envisioned enantioselective key step has currently only been performed in a racemic fashion and additional efforts will be necessary toward an enantioselective synthesis of A-74528.

5 Computational methods

Generation of initial set of structures

Initial sets of conformers were obtained by a conformer search (no solvent, 200 kJ/mol energy window, mixed torsional/low-mode sampling) at the OPLS3e[64] force field level as implemented in the MacroModel applet within the Schrödinger suite of programs (Release 2019-1).[65]

For the compounds depicted in Scheme 30 and Scheme 31 a different approach based on manually generated conformers was followed, as it was expected that the conformations of the methoxy groups and the polycyclic backbone could be investigated separately. This would strongly lower the number of structures that needed to be investigated and consequently reduce the computational effort. Thus, the conformer structures of truncated analogs without the methoxy groups were determined (OPLS3e conformer search, structure optimization and energy calculation as described below). Then, the lowest energy conformer (OPLS3e conformer search, structure optimization and energy calculation as described below) was determined for lactone **67**. Based on the orientation of the methoxy group for lowest energy conformer of lactone **67** and the lowest energy conformers determined for the truncated compounds, new initial starting structures were prepared by attaching methoxy groups and then used in a second cycle of structure optimization and energy calculation as described below.

Initial structures for the radical and cationic species depicted in Figure 3 were prepared in a similar manner. Based on all conformeric structures obtained for the methoxy-truncated analogs of compounds **83** and **94** initial methoxy-truncated radical and cationic structures were prepared by deleting a hydrogen atom at one of the benzylic positions, producing three new structures per original conformer. These truncated structures were optimized as described below, then methoxy groups were added based on the lowest energy conformer of lactone **67** and a second cycle of structure optimization and energy calculation followed.

Structure optimization and frequency analysis

The initial structures were preoptimized at the PBE0[66]/def2-TZVP(-f)[67] level followed by a final optimization and frequency analysis at the PBE0/def2-TZVP level.

The resulting structures were checked for duplicates and confirmed to be energy minimum structures. If several of the initial structures had converged to the same optimized structure, then the duplicates structures were removed. If an imaginary frequency was observed, then the structure was deformed in both directions along the corresponding normal mode and the resulting structures were optimized. After the results were confirmed to be energy minimum structures, the obtained structures were included in the set of

optimized structures, except if they were duplicates of structures that were already part of the set.

These calculations were performed with the program ORCA[68] (Version 4.1.2) using the D3BJ dispersion correction[69] and the or RIJCOSX approximation[70] with the def2/JK auxiliary basis set[71] as well as tight convergence thresholds (TIGHTOPT, TIGHTSCF) and more accurate grid settings (GRID7, NOFINALGRID, GRIDX8, NOFINALGRIDX).

Energy calculation

Accurate energies for the PBE0/def2-TZVP-strcutures were calculated at the DSD-PBEP86[72]/def2-QZVPP level. The structures obtained for the lowest energy conformers are included in appendix 4.1.

These calculations were performed with the program ORCA (Version 4.1.2) using the D3BJ dispersion correction, the RIJCOSX approximation with the def2/JK auxiliary basis set, the RI-MP2 approximation[73] with the def2-QZVPP/C auxiliary basis sets[74] as well as tighter convergence thresholds (TIGHTSCF) and more accurate grid settings (GRID7, NOFINALGRID, GRIDX8, NOFINALGRIDX).

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Part II

Synthesis of Cyclic Azobenzenes

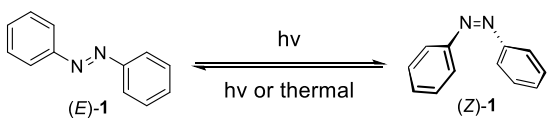
Note: As most of the content of this part of this thesis has been published in a peer-reviewed journal (see Section 2), the numbering used in this part of the thesis for compounds, tables, schemes, references, etc. follows the peer-reviewed publication as far as possible. This also applies to content within the experimental section and the appendix. Roman numerals have been used in cases where additional numbering was necessary.

1 Introduction

1.1 Azobenzene photoswitches

Azobenzene was first reported in 1834, when Mitscherlich[I] observed the formation of a red solid upon treatment of nitrobenzene with potassium hydroxide. Since then, azobenzene has become one of the most studied molecules in the history of organic chemistry. The interest in this molecule and its derivatives is based especially on two properties: its color and (*E*)-(*Z*) isomerization. First, compounds related to azobenzene currently are by far the most important class of commercial dyes.[II] Second, the two isomeric forms of azobenzene (Scheme I) exhibit distinct features. The isomerism results from the configuration of the diazene moiety linking the two aromatic rings of the molecule. In the (*E*) form the phenyl groups are pointing in two different directions and the molecule has a planar structure with C_{2h} symmetry.[III] In the (*Z*)-form the phenyl rings are oriented more toward the same direction and the molecule adopts a bent, non-planar structure of C_2 symmetry.[IIIa] Besides these structural characteristics as well as a consequence thereof, (*Z*)-azobenzene is also quite different from (*E*)-azobenzene in many other ways. The most important of these differences are the distinct UV-Vis spectra[IV] of both isomers as well as the about 50 kJ/mol higher energy[V] of the (*Z*)-form and its increased polarity with a dipole moment[VI] that is roughly 3 Debye higher than for the (*E*) form.

The (*E*)-(*Z*) isomerism of azobenzene was first noticed by Hartley in 1937,[VII] who observed that both (*E*)- and (*Z*)-azobenzene are converted into the respective other isomer when exposed to light (Scheme I). Hartley also observed that the (*Z*) form is metastable and slowly isomerizes thermally to (*E*) form.[VIII] The activation barrier of this process is roughly 100 kJ/mol and the half-life of (*Z*)-azobenzene is in the order of hours to days.[Vb,VIII]



Scheme I Isomers of azobenzene and isomerization processes between (*E*)- and (*Z*)-form.

While Hartley used polychromatic light for the photoisomerization, it was later discovered that there is a strong wavelength dependence of this process. Fischer *et al.* observed that the (*Z*/*E*) ratio would reach 91/9 by irradiation with 365 nm light and 12/88

with 405 nm light, but only 37/63 with broad-band irradiation.[IX] This wavelength dependence is a result of the differences in the absorption spectra of the two isomers.[IV] In the range above 250 nm the UV-Vis spectrum of (*E*)-azobenzene shows a strong absorption band with a maximum around 310-320 nm and a weak absorption band centered at about 440-450 nm. The strong band corresponds to a ππ*-transition and the weak band to a symmetry-forbidden nπ*-transition. For (*Z*)-azobenzene two analogous bands are found. In this case the nπ*-transition is allowed, which results in a stronger absorption compared to the (*E*) form. The nπ*-band is also shifted slightly to a shorter wavelength by approximately 10 nm. In contrast, the ππ*-band of the (*Z*) form is much weaker than for (*E*)-azobenzene and located at roughly 270-280 nm, which makes it significantly blue-shifted. In summary, this means that for certain wavelengths either the (*E*) or the (*Z*) isomer is more strongly absorbing than the other isomer, although there is still quite some overlap between the spectra due to the broadness of the absorption bands. These relative absorptions of the two isomers at certain wavelengths are connected to the (*Z*/*E*) ratios that are obtained upon irradiation. For example, at 365 nm the (*Z*) isomer has a much lower and at 405 nm a much higher absorption compared to the (*E*) isomer. This correlates with a high (*Z*) fraction upon 365 nm irradiation and a low (*Z*) fraction at 405 nm. In addition to the relative absorption, which is quantified by the extinction coefficient ε, the fraction of the excitations that lead to an isomerization, which is quantified by the quantum yield ϕ, has also to be taken into account. For a specific wavelength λ the (*Z*/*E*) ratio at which (*Z*)-to-(*E*) and (*E*)-to-(*Z*) photoisomerization are in an equilibrium, which is also called a photostationary state (PSS), is then given by the following equation.

$$\left(\frac{Z}{E}\right)_{\lambda} = \frac{\epsilon_{E,\lambda}}{\epsilon_{Z,\lambda}} \frac{\phi_{E\rightarrow Z,\lambda}}{\phi_{Z\rightarrow E,\lambda}}$$

The fact that azobenzene exhibits both photostationary states that can be rich in either (*E*) or in (*Z*) isomer makes it possible to efficiently and reversibly convert the (*E*) form to the (*Z*) form and *vice versa* by irradiation. This makes azobenzene a good candidate for use as a photoresponsive molecular switch or short a “photoswitch”. Photoswitches are of high interest to develop molecules whose properties can be controlled with light and light-responsive materials. Consequently, the photoisomerization of azobenzene and azobenzene-derived compounds has been heavily investigated,[X] which showed that the process is reliable for many derivatives under a wide range of conditions and azobenzenes are typically robust to fatigue over many cycles of switching. In combination with the typical ease of synthesis[XI] and the large changes in end-to-end distance upon isomerization, this arguably has made azobenzenes the photoswitch of choice among a variety of photoswitches,[XII] with a large number of applications in a broad range of fields.[3] Prominent areas of applications are light-controlled structural changes of peptides, proteins and

nucleic acids,[3a,b] photopharmacology using small molecules with photoswitchable bioactivity,[3b,c] light-responsive polymers[3d,] or light-activated catalysts.[3f,g]

Considering an ideal azobenzene photoswitch, the most obvious condition is that it should be possible to reach a high (Z/E) ratio for the (E)-to-(Z) photoisomerization, in the best case attaining pure (Z) isomer. Next, it should also be possible to efficiently convert the (Z) form back to the (E) form. It is important to remember that two processes can achieve this: thermal isomerization and photoisomerization. Thus, there is no single ideal photoswitch and rather two approaches have to be considered. Both approaches have advantages as well as disadvantages and each requires a specific type of azobenzene photoswitch. In an approach based on thermal isomerization, the azobenzene needs a sufficiently high rate of thermal (Z)-to-(E) relaxation. This fast-relaxing based approach has the key advantage that it is easy to obtain pure (E) isomer and that spatial control is straightforward, as the (Z)-isomer quickly decays outside the space that is irradiated. Also, the technical requirements are low, as it is only necessary to provide appropriate irradiation conditions for the (E)-to-(Z) isomerization. However, constant irradiation is required to keep the azobenzene in the (Z) configuration and thermal (Z)-to-(E) isomerization is competing with the (E)-to-(Z) photoisomerization, which can reduce the fraction of (Z) isomer that is achievable with a limited irradiation intensity. These issues are obviously less important with azobenzenes that are not rapidly relaxing thermally, a property that is also called “bistability”, and which require an approach based on (Z)-to-(E) photoisomerization. In this case it is obviously important that the photoisomerization is efficient for both (E)-to-(Z) and (Z)-to-(E). In the ideal case of quantitative conversion in both directions, it would then be optimal if there is no thermal (Z)-to-(E) relaxation. If such quantitative conversion cannot be achieved by photoisomerization a slow thermal relaxation could be beneficial to allow to obtain pure (E) isomer. A central issue of this approach is that it is typically not possible with common azobenzenes to obtain a quantitative or almost quantitative conversion in either direction by photoisomerization. To summarize, azobenzenes with quantitative photoisomerization in both directions and high bistability as well as azobenzenes that are thermally fast-relaxing and that can be quantitatively photoisomerized (E)-to-(Z) are two versions of an ideal azobenzene photoswitch.

Some examples that showcase the possibilities as well as the limitations of common azobenzenes are shown in Figure I. The compounds BzAQ, DENAQ and AFM 2-10, which were designed as potassium ion channel blockers, highlight optimization efforts toward a red-shifted UV-Vis absorption spectrum.[XIIIa,b] For biological applications this is a key issue of standard azobenzenes. The UV-light that is often necessary for photoisomerization can be damaging and also gets strongly absorbed by biological molecules. Light in the visible range is less damaging, but also does not allow to deeply penetrate the skin and tissue and

can get strongly absorbed by hemoglobin in the blood. Only in the near-infrared range the general tissue penetration is high enough to allow irradiation of deep tissue regions without an additional system for light delivery.

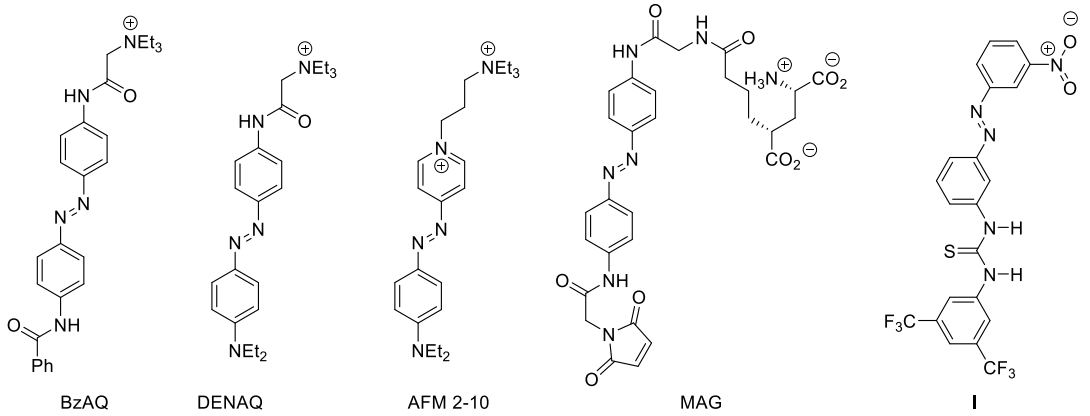


Figure I Examples of azobenzene-derived photoswitchable compounds: potassium ion-channel blockers BzAQ, DENAQ and inactive analog AFM 2-10; glutamate receptor agonist MAG; Michael addition catalyst thiourea **I**.

The traditional approach to red-shift the absorption bands of azobenzenes, or more specifically the ππ*-band, is to introduce substituents in the *para*-position of the aromatic rings. Electron-donating *para*-substituents can lead to large bathochromic shifts of the ππ*-excitation, while electron-withdrawing *para*-substituents only have a low effect on the ππ*-absorption bands.[XIV] In both cases the extent of the changes is related to the number and strength of the substituents and also an increase of the rate of the thermal (*Z*)-to-(*E*) isomerization is observed. Even more pronounced changes are obtained with push-pull type azobenzenes carrying a combination of electron-donating and electron-withdrawing groups. From unsubstituted azobenzene to BzAQ to DENAQ an efficient (*E*)-to-(*Z*) isomerization can be achieved by irradiation with light of increasingly longer wavelengths of 365, 380 and 480 nm, respectively. These values correlate with the absorption maxima of the increasingly electron-rich compounds. The push-pull type azobenzene AFM 2-10 absorbs even at 580 nm, but unfortunately is not acting as an ion channel blocker. Here, it is actually not an electron-withdrawing *para*-substituent that leads to a push-pull type system, but the electron-poor pyridinium system.

With respect to thermal isomerization, DENAQ is fast-relaxing and isomerizes on a second to millisecond timescale without needing irradiation, but BzAQ is not isomerizing fast enough and needs to be returned to the (*E*) form by irradiation with 500 nm light. A related example of a bistable azobenzenes with a well-investigated efficiency of the photoisomerization is the glutamate receptor agonist MAG, [XIIIc] for which the core azobenzene moiety is actually identical to BzAQ. MAG is an example for a tethered azobenzene photoswitch. Reaction of the maleimide moiety with a cysteine residue of the

target protein prevents diffusion of the compound and keeps the molecule in close proximity to the binding pocket, thereby allowing spatial precision upon irradiation of this bistable azobenzene. The thermal half-life of MAG is about 15 minutes and it can be isomerized with 380 nm light from (*E*) to (*Z*) and with 500 nm light from (*Z*) to (*E*), reaching 93% (*Z*) isomer and 83% (*E*) isomer, respectively. Thus, roughly 5-15% of the minor isomer are remaining for the photoisomerization in both directions. As BzAQ and MAG are used to control neuronal activity this is not a major concern. In these non-linear systems it is only necessary to reach a certain threshold to obtain the desired response and partial isomerization can be sufficient, but in other applications an incomplete conversion can lead to unwanted effects. Thiourea **I** (Figure I), which can catalyze the Michael addition of acetylacetone and provides photoswitchable catalytic activity, illustrates this case.[XV] Control over the catalytic activity is not complete as the reaction rate with pure, catalytically active (*E*) isomer of **I** is only about five times higher than with a mixture of (*E*) and (Z) isomer obtained under 365 nm irradiation. While the non-catalyzed background reaction also contributes to this, a major factor is the incomplete (*E*)-to-(*Z*) photoisomerization. Additionally, the catalyst **I** is not sufficiently thermally stable to be used without continuous irradiation due to a half-life of only three hours. To allow for a better control of the catalytic activity, it would be necessary to first increase the thermal half-life and second to improve the photostationary (*Z*/*E*) ratio.

Returning from these example azobenzenes to a more general perspective, it is obvious that there are key goals in the development of improved azobenzene photoswitches. For bistable and fast-relaxing azobenzenes these goals are partially overlapping, but also partially opposed. The most general objective is to increase the accessible (*Z*/*E*) ratio for the photoisomerization of the (*E*) isomer. Red-shifting the wavelength of light, which can affect this photoisomerization, is beneficial as well for many applications and therefore also a general aim. In the case of bistable azobenzenes, such a red-shift should not be accompanied by an increased thermal relaxation rate. This is a general issue for traditional azobenzenes with electron-donating and push-pull type substitution, which always result in both a bathochromic shift and an increased thermal relaxation. Furthermore, it is crucial for bistable azobenzenes to achieve an efficient photoisomerization back to the (*E*) isomer, which should also be possible with irradiation at a longer wavelength. Finally, on-demand modulation of the relaxation times is desirable. Increasing the thermal stability of the (*Z*) isomer of bistable azobenzenes allows to reduce illumination times and frequencies in pulsed illumination. For applications relying on fast-relaxing azobenzenes the efficiency of the (*Z*)-to-(*E*) photoisomerization is not as crucial, but it can be necessary to further increase the thermal relaxation rate.

The thermal relaxation rate, however, does not only depend on the azobenzene itself, but can also be strongly affected by the environment. Especially the behavior of rapidly relaxing push-pull azobenzenes[XIV] and tautomerizable azobenzenes[XV] is highly solvent dependent, while the changes for unsubstituted azobenzene itself are comparatively small.[VIII,XVII] Other factors that can increase the thermal isomerization rate are strain[XVIIIa] and catalysis by acids,[VIII,XVIIIb] metal salts[XVIIIb] and thiols.[XVIIIc] The UV-Vis spectra can also be affected by the solvent polarity, with the extent depending on the specific type of azobenzene.[XIX] Again, azobenzene itself is not strongly affected, but for some substituted azobenzenes and specifically push-pull azobenzenes the effect can be larger. In conclusion, to design new azobenzenes it is necessary to consider the effect of the environment in an actual application setting. For example, the reduction of azobenzenes to hydrazines by thiols can be a problem, especially for the (*Z*) isomers.[XVIIIc] The glutathione levels that are encountered in cells (0.5–10 mM)[XX] can be sufficient for this reduction, but in some settings azobenzenes can be surprisingly robust against reduction.[XXI]

Wanting to improve the (*E*)-to-(*Z*) and (*Z*)-to-(*E*) photoisomerization of azobenzenes, extinction coefficients and photoisomerization quantum yields also need to be considered. The relation between achievable (*Z*/*E*) ratio at the photostationary state and these two parameters has already been described in the preceding text for the example of unsubstituted azobenzene. Briefly said, to achieve a large fraction of a specific isomer of azobenzene by irradiation it is necessary that at the employed wavelength the desired isomer has a low extinction coefficient and/or a low quantum yield, while the undesired isomer has a high extinction coefficient and/or high quantum yield. In other words, at a specific wavelength the desired isomer should absorb light much less than the undesired isomer and most excitations of the undesired isomer should lead to transformation to the desired isomer, while excitation of the desired isomer should rather not result in transformation to the undesired isomer. Under these conditions the irradiation should result in depletion of the undesired isomer and accumulation of the desired isomer. If the quantum yields are ignored, this effectively simplifies to the condition that the absorption bands of both isomers should not overlap.

Considering the kinetics of the photoisomerization or rather the time that is necessary to reach the photostationary state, it would be beneficial to have a high extinction coefficient and a high quantum yield. Then, the light would be used most efficiently and only a small irradiation intensity would be necessary to obtain fast conversion from isomer to the other. However, this is only strictly true if just one isomer absorbs light at the wavelength that is utilized. As soon as there is any absorption by the other isomer this may result in inhomogeneous irradiation due to complete absorption of light, which is dependent on irradiation intensity and azobenzene concentration. For example, a solution of an

(*E*)-azobenzene in a vial is irradiated with a certain wavelength and the concentration is high enough so that the outer layers initially absorb all the light. Then, the absorbance of the outer layers drops continuously due to photoisomerization and the decreasing concentration of the (*E*)-azobenzene. Thus, the irradiation gradually reaches deeper into the solution. However, if the (*Z*) isomer is also absorbing at this wavelength, then the absorption in the outer layers at the photostationary state may still be high enough so that the light is completely absorbed and never reaches the deeper layers of the solution. Such behavior was for example reported for thiourea catalyst **I**.[XV] Even for irradiating only a small volume (NMR tube) of a solution of this compound at low concentration (2.5 mM) the fraction of (*Z*) isomer at the PSS increased from 56% to 70% upon further lowering the concentration (1.5 mM). Thus, depending on concentration, irradiated volume and the irradiation intensity both high and low extinction coefficient may be either beneficial or detrimental.

1.2 Recent progress toward improved azobenzene photoswitches

In the last decade several new types of azobenzene photoswitches have been developed, which have properties that are closer to the "ideal" photoswitch described in the preceding section than "traditional" azobenzenes. Still, there is significant room for improvement. The following short summary gives examples for important strategies to enhance the photophysical properties of azobenzenes and the respective remaining weaknesses as well as unsolved issues. These strategies are the use of heterocyclic azobenzenes, *ortho*-substitution and cyclic azobenzenes. This summary is not comprehensive, but the given examples (Figure II) are currently expected to be the most promising candidates for actual applications. In this context, while azobenzenes are arguably the most prominent type of photoswitch and have the largest numbers of applications, it is also important to mention that there is a variety of other photoswitchable scaffolds apart from azobenzenes.[XII]

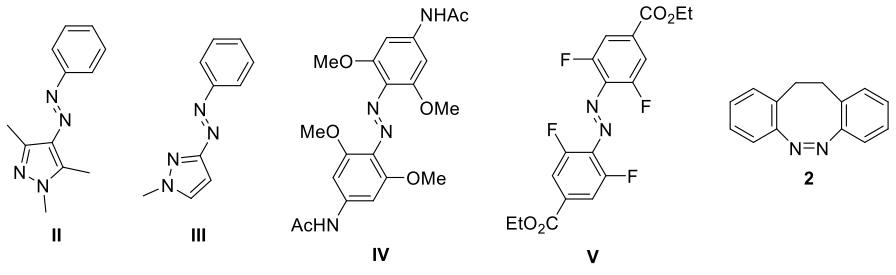


Figure II Examples of new types of azobenzene photoswitches.

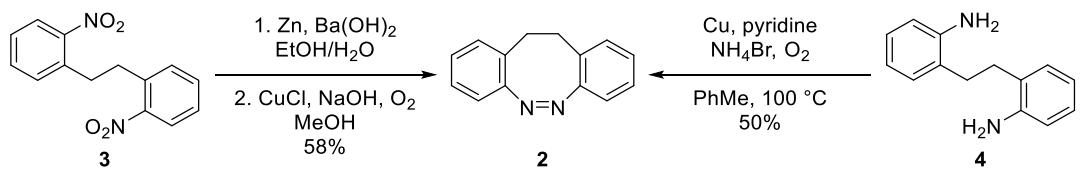
Among many heterocyclic azobenzenes[XXII] the arylazopyrazoles **II** and **III** developed by Fuchter and coworkers[4e,h] are standing out because of their excellent photophysical properties. In acetonitrile solution both compounds can be photoisomerized both to the (*Z*) isomer (355 nm) and back to the (*E*) isomer (532 nm) near quantitatively (≥97%). In

addition, the (*Z*) isomers of these compounds have long thermal half-lives (10 days for **II** and 74 days for **III**). A remaining issue of these compounds is the wavelength for an efficient (*E*)-to-(*Z*) isomerization, which still lies in the near-UV region.

Bidirectional photoisomerization with only visible light is possible with tetra-*ortho*-methoxy and tetra-*ortho*-fluoro substituted azobenzenes developed by the groups of Woolley[XXIII] and Hecht[4a,XXIV], which exhibit improved separation of the nπ*-bands of the (*E*) and (*Z*) isomers. For example, tetramethoxy azobenzene **IV** can be switched from (*E*) to (*Z*) and (*Z*) to (*E*) upon irradiation with 530–560 nm and 450–460 nm light and tetrafluoro azobenzene **V** with 500 nm and 410 nm light. Both compounds also display a high or very high thermal stability of the (*Z*) isomer (half-life of 164 days for **IV** in DMSO and 700 days for **V** in acetonitrile) and a range of photostationary (*Z*/*E*) ratios that are similar or better than comparable azobenzenes (80/20–15/85 for **IV** and 90/10–3/97 for **V**).

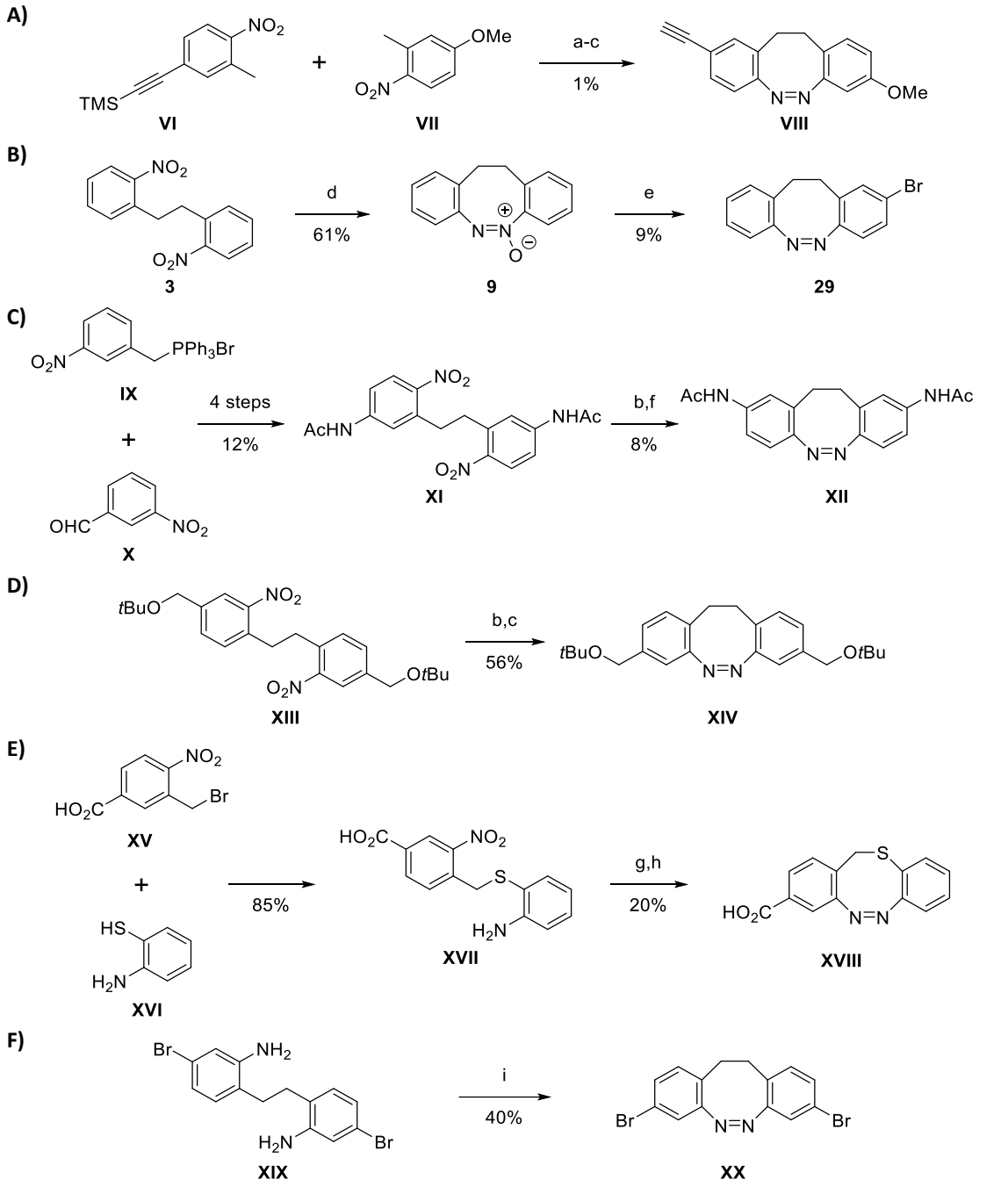
Diazocines, cyclic azobenzenes with an eight-membered ring, also have well-separated nπ*-bands for the (*E*) and (*Z*) isomers and can be isomerized efficiently in both directions with irradiation that is significantly red-shifted to compared traditional azobenzenes. This was observed by the groups of Herges and Temps, which reported (*Z*/*E*) ratios upon irradiation of a hexane solution of compound **2** of >10/90 at 370–400 nm and ≈100/0 at 480–550 nm.[5] Additionally, diazocines are unique by the (*Z*) form being the thermally preferred isomer and the thermal lifetime of the (*E*) form of diazocine **2** was found to be 4.5 hours.

Although a number of derivatives including heterocyclic versions have been prepared since the initial discovery of the unique properties of diazocine **2**, efficient synthetic access to this class of azobenzenes has not been achieved.[6–9] Moderate yields were reported for both a reductive and oxidative synthesis of the parent compound **2** (Scheme II).[6g,8a] To obtain reliable results for the reductive cyclization it was found to be beneficial to first transform dinitrodibenzyl **3** to the corresponding cyclic hydrazine and then reoxidize to diazocine **2**.



Scheme II Most efficient syntheses of diazocine **2**.

In contrast, derivatives of diazocine **2** and especially compounds suitable for application purposes, have been proven very problematic to prepare with the commonly employed, reductive cyclization approach (Scheme III).



a) KO*t*Bu, THF, 0 °C then Br_2. b) Zn, $Ba(OH)_2$, EtOH/H_2O, reflux. c) CuCl, NaOH, O_2, MeOH. d) Pb, pH = 9.5, MeOH. e) $AlBr_3$, CS_2. f) HgO, EtOH, reflux. g) Zn, NH_4, EtOH. h) $FeCl_3$, EtOH/H_2O, AcOH. i) Oxone, AcOH.

Scheme III Examples for the synthesis of substituted diazocines. A) Herges 2019.[7g] B) Yan 2012.[7a] C) Woolley 2012.[6e] D) Herges 2019.[6j] E) Herges 2019.[9d] F) Gorostiza, Hernando 2019.[8b]

The extension of the reductive synthesis of diazocine **2** to substituted analogs suffers from two issues: limited access to the 2,2′-dinitrodibenzyl cyclization precursors and typically poor yields of the cyclization. A good example for this issue is the very recent synthesis of diazocine **VIII**.[7g] Here an unselective, oxidative coupling of nitrotoluenes **VI** and **VII** has been used, which is not efficient to obtain the non-symmetrical coupling product and together with the low-yielding cyclization results in an overall yield of 1%.

An alternative approach to unsymmetrical diazocines was reported by the group of Yan.[7a] They prepared bromodiazocine **29** by deoxygenative bromination of azoxy compound **9**. However, with a total yield of 5% from dinitrodibenzyl **3** this approach does also not deliver satisfactory results.

Symmetrical diazocines are also usually problematic to prepare, as exemplified by the synthesis of diacetamido diazocine **XII**, which was prepared from building blocks **IX** and **X** in a five-step sequence with an overall yield of 1%.[6e] As for compound **VIII**, the cyclization is the lowest yielding step and proceeds with 8% yield. While the cyclization is typically problematic, there is also a small number of dinitrodibenzyl that have been cyclized in a yield similar to the unsubstituted parent system. An example for such a case is diether **XIII**, which can be cyclized to diazocine **XIV** in 56% yield.[6j]

Most recently, there have also been additional reports for oxidative approaches to diazocines. Herges et al. reported a Baeyer-Mills reaction for the synthesis of thioether diazocines such as compound **XVIII**, which was prepared in from benzyl bromide **XV** and thiol **XVI** in a total yield of 17%.[9d] Furthermore, dibromo diazocine **XX** was prepared by treatment of dianiline **XIX** with Oxone® in a yield of 40%.[8b]

Finally, contemporary efforts toward the development of improved photoswitches currently suffer from little systematic studies. Investigations of new photoswitches often only focus on a parent system or the investigated substitution patterns are limited to optimizing the photoswitching properties and the task of providing access to building blocks suitable for integration in larger, functional molecules is not addressed. This is quite problematic for developing applications based on a new and improved photoswitch, as the choice of an appropriate building block without loss of photoswitching performance can result in significant additional efforts. Furthermore, there are no standard conditions (e.g. solvent, light intensity, spectral distribution) to characterize the properties of newly prepared photoswitches, which makes comparing the actual performance to other systems often problematic. For example, the half-lives and (Z/E) ratios mentioned above for the compounds depicted in Figure II can hardly be compared as they are referring to solutions in hexane, acetonitrile or DMSO. Additionally, and often justified by solubility issues, there is only limited data on the behaviour in aqueous solution, which is crucial for biological applications. In this respect, a noteworthy study has been conducted by the group of Ravoo for arylazopyrazole derivatives related to compound **II**.

1.3 Project objectives

This part of the thesis describes the investigations toward an efficient and general synthetic approach to diazocines. As outlined above, this class of cyclic azobenzenes has unique photophysical properties and is a promising alternative to "traditional" azobenzenes but limited synthetic access has prevented application of these compounds and strongly limited the number of known derivatives.

Contrary to the commonly employed reductive cyclization approach, a synthesis based on an oxidative cyclization of 2,2′-ethylenedianilines has not been thoroughly investigated. Thus, it was chosen to optimize such an approach for the parent compound **2** and then attempt to extend the oxidative approach to substituted derivatives. The goal was to provide a scalable access to useful diazocine building blocks and also to diversely functionalized diazocines, which should allow a general study of the properties of substituted diazocines.

To allow access to a broad range of diazocines, it was necessary to establish a reliable, modular and general synthesis of substituted 2,2′-ethylenedianilines. It was envisioned that a cross-coupling approach featuring a Sonogashira coupling would be suitable in many cases. In addition to preparing diazocines from different cyclization precursors, it was also planned to increase the scope of accessible diazocines through late-stage derivatization.

2 Oxidative Approach Enables Efficient Access to Cyclic Azobenzenes

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Oxidative Approach Enables Efficient Access to Cyclic Azobenzenes

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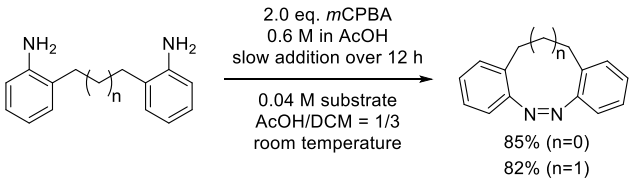
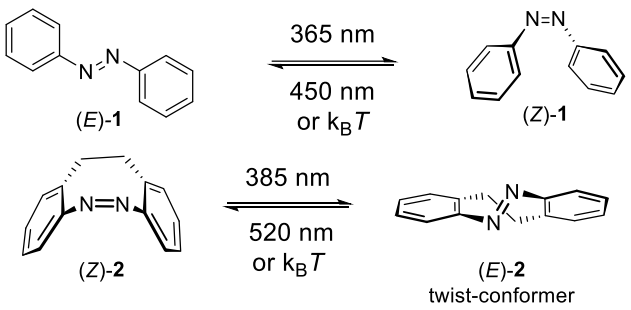
ABSTRACT



Azobenzenes are versatile photoswitches that have found widespread use in a variety of fields, ranging from photopharmacology to the material sciences. In addition to regular azobenzenes, the cyclic diazocines have recently emerged. Although diazocines have fascinating conformational and photophysical properties, their use has been limited by their synthetic accessibility. Herein, we present a general, high-yielding protocol that relies on the oxidative cyclization of dianilines. In combination with a modular substrate synthesis, it allows for rapid access to diversely functionalized diazocines on gram scales. Our work systematically explores substituent effects on the photoisomerization and thermal relaxation of diazocines. It will enable their incorporation into a wide variety of functional molecules, unlocking the full potential of these emerging photoswitches. The method can be applied to the synthesis of a new cyclic azobenzene with a nine-membered central ring and distinct properties.

INTRODUCTION

Azobenzene photoswitches contain a diaryl diazene moiety that can exist either in an (*E*) or in a (*Z*) configuration. In general, the elongated (*E*) or trans form is thermodynamically preferred and the bent (*Z*) or cis form is subject to gradual thermal isomerization (Scheme 1). The half-lives for this thermal relaxation range from picoseconds to days,[1] and photoswitches whose thermal relaxation is comparatively slow are often designated as "bistable". Irradiation of azobenzenes with monochromatic light establishes a photostationary state (PSS) that depends on both the extinction coefficients of the two isomers at a particular wavelength and their respective isomerization quantum yields. Photostationary states as high as $(Z)/(E) \simeq 90/10$ can be achieved, but are generally lower.[2] Because of their photostability, facile synthesis, and relatively low molecular weight, azobenzenes have become the photoswitch of choice in many applications. They have been successfully incorporated in photopharmaceuticals, in photoresponsive functional materials, such as polymers and hydrogels, or in catalysts that can be controlled with light.[3]



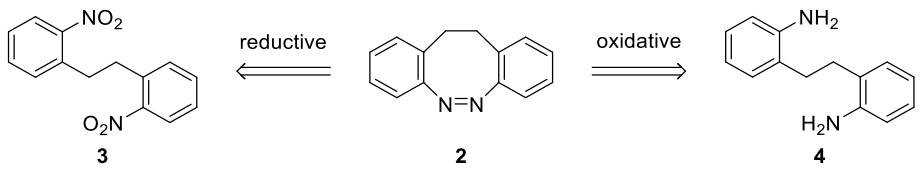
Scheme 1 Photoswitching of azobenzene[1] (**1**) compared to diazocine[5a] (**2**).

Despite their long history and popularity, there is still a need to tailor the properties of azobenzenes. One important direction is red shifting the action spectra while maintaining thermal bistability.[4] Significant progress toward this goal has been made by developing tetra-*ortho*-substituted azobenzenes, but these are marked by increased steric bulk and changes in dipole moment, which can interfere with their function. Another desirable feature are highly biased PSS, for both wavelengths that favor the (*Z*) isomer and those that give preference to the (*E*) isomer. Although thermal relaxation can revert azobenzenes fully to their (*E*) form, this process can be slow with bistable variants and the faster photochemical conversion to the (*E*) isomer is generally incomplete. Lastly, it can be useful to employ photoswitches that are bent in their default form, that is, in the absence of light, and become elongated upon irradiation. This is especially true in photopharmacology where tonic "dark activity" is often undesirable.

Cyclic azobenzenes, wherein the diazene unit is embedded in an eight-membered ring, meet many of these challenges. The parent compound of this class is 5,6-

dihydrodibenzo[c,g]-[1,2]diazocine ("diazocine"), which had already been discovered at the beginning of the last century.6a It received little attention, until recently, when its remarkable photophysical properties were recognized by Herges, Temps, and coworkers.[5] Contrary to regular azobenzenes, the thermodynamically preferred form of diazocines is the (*Z*) isomer because of the increased strain that the ring system imposes on the (*E*) isomer (Scheme 1). In addition, diazocines can be switched to more than 90% of the (*E*) isomer and quantitatively back to the (*Z*) isomer by irradiation with visible wavelengths around 400 and 520 nm, respectively.[5a]

Despite these remarkable photophysical properties, diazocines have found relatively few applications to date. The reason for this has been their limited availability due to lack of effective synthetic methods.[5a,6–9] Most reported diazocines have been synthesized by a reductive cyclization of 2,2′-dinitrodibenzyls (Scheme 2).[6,7,9a–c]



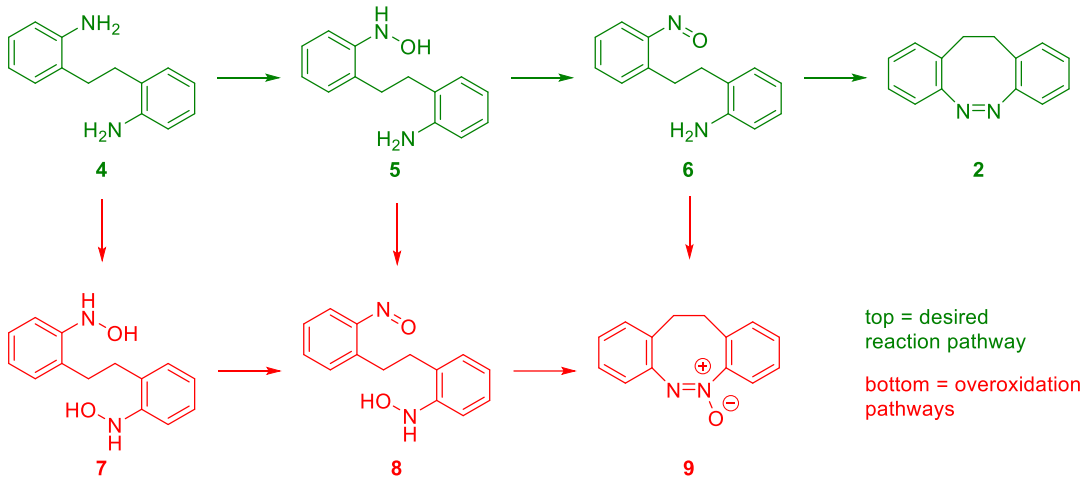
Scheme 2 Synthetic approaches toward the diazocine core.

Apart from low yields, a major limitation of the reductive cyclization is that it does not give straightforward access to unsymmetrical diazocines.[7,9a–c] In addition to the reductive cyclization approach, conditions based on oxidation of 2,2′-ethylenedianilines or hydroxylamine-aniline analogs have been reported, albeit with low to mediocre yields.[8,9c,9d] Very recently, an oxidative strategy has been applied in a synthesis of a photoswitchable glutamatederivative.[8b] However, the potential of the oxidative cyclization of 2,2′-ethylenedianilines has not been investigated systematically and a practical, generally applicable, and high-yielding protocol for the synthesis diazocines has been lacking.

RESULTS AND DISCUSSION

1. Mechanistic Considerations. Our investigation commenced with the optimization of reaction conditions for the oxidative cyclization of the commercially available 2,2′-ethylenedianiline **4** to the corresponding diazocine **2**. We considered four key requirements which needed to be fulfilled to make this an effective process (Scheme 3). First, it would be necessary to selectively oxidize 2,2′-ethylenedianiline **4** to 2-amino-2′-nitrosodibenzyl **6**, without formation of the dihydroxylamine **7** from intermediate **5**. Second, the cyclization of the nitroso-aniline **6** to diazocine **2** via a Baeyer-Mills reaction has to be faster than the oxidation to nitroso-hydroxylamine **8**. Third, the product diazocine **2** must not be oxidized further to form the azoxy compound **9**. Fourth, intermolecular

reactions leading to oligomeric or polymeric structures need to be suppressed. While temperature, concentration, and rate of addition of the oxidant are important considerations for optimization with respect to the second and fourth conditions, the other two conditions are more dependent on the inherent reactivity of the substrates. On the basis of our mechanistic scheme, we expected slow addition of the oxidant to be the most important parameter.



Scheme 3 Mechanistic considerations for an oxidative cyclization approach toward diazocines.

2. Development of Reaction Conditions. Most commonly, the oxidation of anilines to nitrosobenzenes is performed in a biphasic system of dichloromethane (DCM)/water using Oxone® as an oxidant. The ensuing Baeyer-Mills reaction is typically performed in acetic acid and mixtures of acetic acid with DCM or toluene. As these two sets of conditions are not compatible, we decided to use typical solvent systems of the Baeyer-Mills reaction, such as pure acetic acid or acetic acid/DCM, as the solvent and peroxycarboxylic acids as the oxidant. To simplify the workup, we initially focused on peracetic acid.

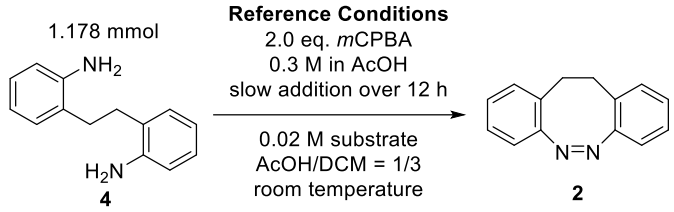
After optimization of oxidant addition rate, stoichiometry, and substrate concentrations, we were able to obtain diazocine **2** by the slow addition of 2 equivalents of peracetic acid in acetic acid to a dilute solution of 2,2′-ethylenedianiline **4** within a 12 hour period in a yield of more than 70%, which was already substantially superior to any previously reported value.[5a,6–9] However, we noticed several inconsistencies during the course of this initial optimization. The most important observations were a noticeably fluctuating yield, a highly detrimental effect of copper salts, and an unexpected relation between the obtained yields and the equivalents of peracetic acid that were employed.

We suspected the underlying issue to be the presence of considerable amounts of hydrogen peroxide in the commercial peracetic acid solutions. This “dormant oxidant” may either directly participate in the oxidation or slowly be transformed to peracetic acid, thus resulting in an incorrect stoichiometry. The effect can be expected to be more prominent

under conditions that should activate the hydrogen peroxide (e.g., the presence of transition metal ions), which agrees with the observed results. Additionally, we confirmed the reactivity of hydrogen peroxide in acetic acid by treatment of 2,2′-ethylenedianiline with urea hydrogen peroxide as a source of "dry" hydrogen peroxide. This led to the slow formation of diazocine, but could unfortunately not be developed into a synthetically practical procedure.

Building on the knowledge gained from our initial optimization with peracetic acid, we continued our search for optimal reaction conditions (Table 1). We did not perform an additional screening on the rate of addition as well as equivalents of oxidant and continued with the theoretically ideal stoichiometry of 2 equivalents of oxidant and the addition of oxidant within 12 hours.

Table 1 Optimization of the oxidative cyclization of 2,2′ ethylenedianiline – selected examples.



entry	Variation from reference conditions	yield[a]
1	none	86%
2	Solvent AcOH	75%
3	Solvent AcOH/DCM = 1/1	86%
4	Solvent AcOH/PhMe = 1/1	84%
5	Solvent AcOH/DCM = 1/9	81%
6	Entry 4 + 40 °C	82%
7	Entry 4 + 60 °C	76%
8	0.01 M substrate	85%
9	0.04 M substrate	85%
10	Entry 9 + 0.6 M *m*CPBA	86%
11	Entry 10 + 0.06 M substrate	79%
12	Entry 10 + catalytic Cu(II)	59%

[a]Determined by ^{1}H nuclear magnetic resonance (NMR) spectroscopy with dimethyl terephthalate as internal standard.

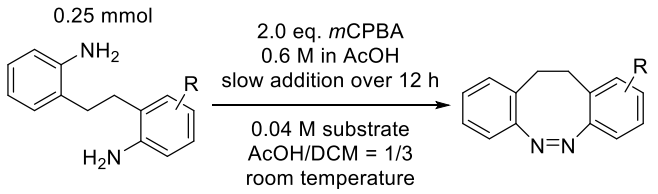
To identify a more reliable oxidant, we compared the most commonly employed commercially available percarboxylic acids. Among peracetic acid, *meta*-chloro-peroxybenzoic acid (*m*CPBA), and magnesium monoperoxyphthalate (MMPP), we found that *m*CPBA performed best. The use of *m*CPBA to prepare nitrosobenzenes from anilines is well precedented.[10] A screen of solvent mixtures revealed that diluting acetic acid with DCM or toluene resulted in a further increased yield, although a sizable fraction of acetic acid was

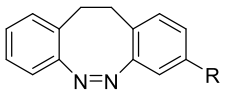
necessary for optimal results. Increasing the temperature proved to be slightly detrimental to the reaction outcome, while higher concentrations of the *m*CPBA solution (0.6 M) and substrate (0.04 M) were tolerated without a negative effect on the yield.

Copper salts were reported to be beneficial to the formation of azobenzenes by oxidative dimerization of anilines with peroxy acids.[11] However, we observed that addition of copper acetate reduced the yield and an increased amount of unreacted starting material remained. This supports our theory that our reaction does not depend on trace amounts of metal salts. Finally, we confirmed that the undesired overoxidation of diazocine **2** to azoxy compound **9** does not occur in the presence of unreacted dianiline **4** (see Supporting Information). This finding supports our initial reasoning about the importance of slow addition. Azoxy compound **9** does not primarily result from oxidation of desired product **2**, but forms through nitroso-hydroxylamine **8** (see Scheme 3).

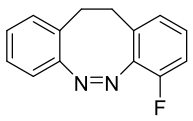
3. Investigation of Reaction Scope. After optimizing reaction conditions for the parent system, we applied our best protocol to various monosubstituted 2,2′-ethylenedianilines (compounds **10**–**30**, Table 2).

Table 2 Oxidative cyclization yields[a] of monosubstituted 2,2′-ethylenedianilines.

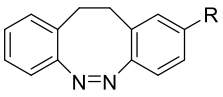




2, 85%	R = H
10, 85%	R = Me
11, 82%	R = CH_2CO_2Me
12, 74%	R = CH_2NHBoc
13, 58%	R = CF_3
14, 74%	R = CO_2Me
72%[b]	
15, 39%	R = CN
16, 68%	R = OMe
17, 73%	R = OAc
18, 62%	R = F



19, 46%



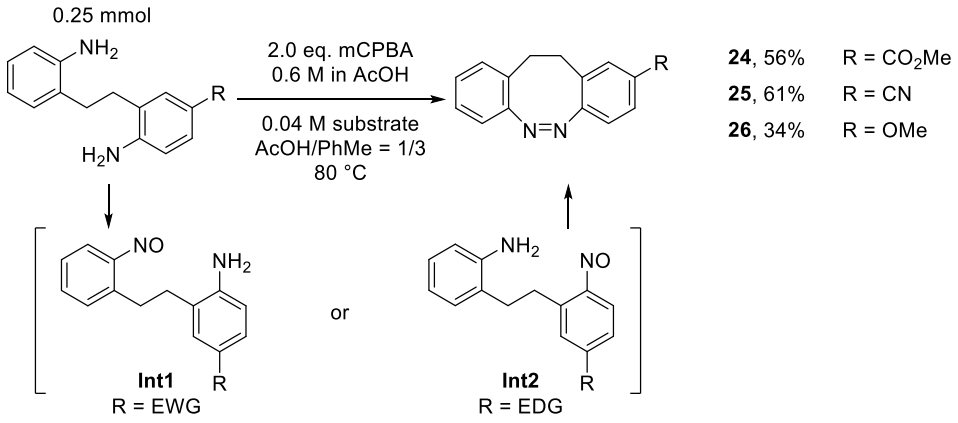
20, 82%	R = Me
21, 82%	R = CH_2CO_2Me
22, 69%	R = CH_2NHBoc
23, 37%	R = CF_3
24, 32%	R = CO_2Me
25, n.d.[c]	R = CN
26, 29%	R = OMe
27, 61%	R = OAc
28, 77%	R = F
29, 81%	R = Br
78%[d]	
30, 76%	R = I
75%[e]	

[a]Isolated yields are reported. [b]4.28 mmol scale. [c]Not determined. [d]7.90 mmol scale. [e]7.69 mmol scale.

For a majority of these compounds, we obtained the cyclization products in yields similar to or only slightly lower than those observed for the parent system. Substituents that only weakly affect the electronic nature of the arenes, such as most halogens and alkyl groups, had virtually no effect on the yield of the cyclization. The yields observed for the fluorinated compounds followed a trend, decreasing from *para*- to *meta*- to *ortho*-fluoro substitution.

Notably, the presence of both strongly electron-withdrawing and electron-donating substituents resulted in a significant reduction in yield. *para*-Substituted substrates gave generally lower yields than the corresponding *meta*-substituted ones, both for electron-withdrawing and electron-donating substituents. We reasoned that low-yielding substrates would undergo a highly selective oxidation of one of the two amino groups (see Scheme 4). In the corresponding intermediates **Int1** and **Int2**, the more nucleophilic aniline moiety is now oxidized, which leaves a deactivated aniline moiety in **Int1** and a deactivated nitrosobenzene moiety in **Int2**. This would make the subsequent Baeyer-Mills cyclization comparatively slow in both cases. Additionally, the tendency for intermolecular, instead of intramolecular, reactions would be increased, as the corresponding unreacted substrates carry a more reactive amino group than the intermediates **Int1** and **Int2**. These considerations led us to explore whether, instead of the slow addition protocol, one-batch addition and increased temperatures might be beneficial in these cases.

We tested this alternative protocol for the three compounds that were the most problematic for our slow addition method (Scheme 4). Gratifyingly, we now obtained the known[7a] *para*-cyano diazocine **25** in a respectable yield of 61%. The yield of the *para*-methyl ester diazocine **24** also was improved substantially to 56%. However, the *para*-methoxy product **26** was obtained only with slightly increased yield. A different factor seems to affect the yield in this case. The most probable explanation is the reactivity of *para*-alkoxy-nitrosobenzenes toward nucleophilic aromatic substitution.[12]

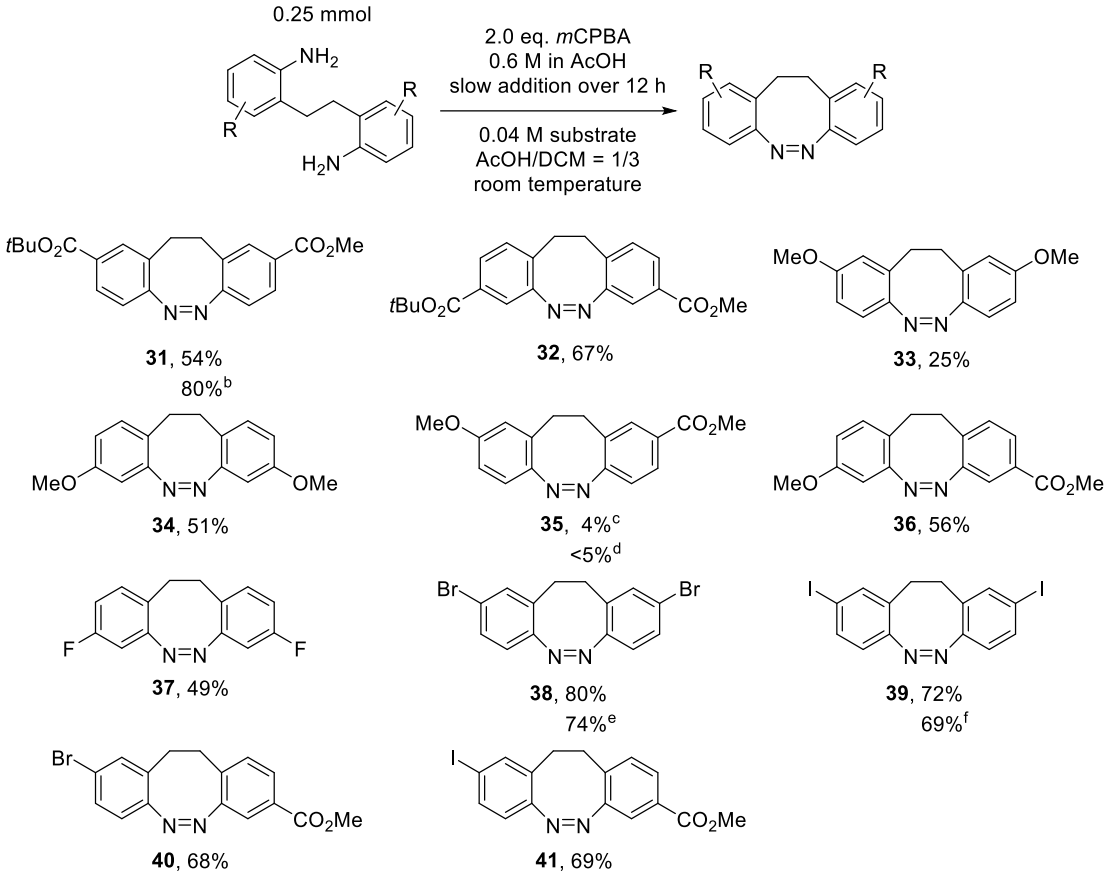


Scheme 4 Synthesis of diazocines using a one-batch addition protocol and presumed intermediates due to oxidation selectivity.

Next, we turned our attention toward disubstituted diazocines (compounds **31**–**41**, Table 3). Considering the large amount of combinatorial possibilities, we selected only a small number of examples. Our main goals were to obtain an appropriate set of disubstituted diazocines to investigate the photophysical properties of substituted diazocines, to determine the limitations of our approach, and to explore how substituent effects of the monosubstituted substrates extend to disubstituted substrates.

Employing our standard slow addition protocol, we observed that for most compounds the substituent effects were additive. The yields decreased compared to those of the corresponding monosubstituted analogs but remained in a synthetically useful range. A clear exception was found in the *para*-diester compound **31**, where the yield was significantly increased compared to that of the *para*-ester **24**. Performing the reaction at higher temperature further increased the yield to 80%, a level similar to that of the parent compound **5**. An example that shows a limitation of our approach, for both the slow and batch addition protocols, is the push–pull diazocine **35**. Still, we were able to obtain a sufficient quantity for photophysical characterization of this diazocine.

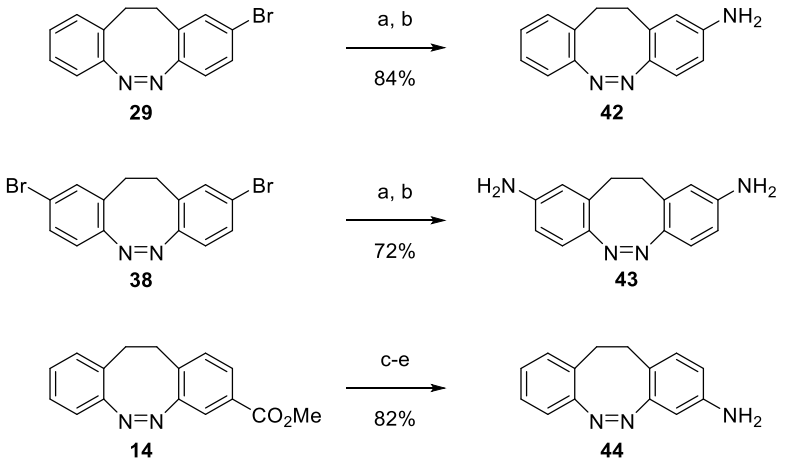
Table 3 Oxidative cyclization yields[a] of disubstituted 2,2'-ethylenedianilines.



[a]Isolated yields are reported. [b]80 °C. [c]0.832 mmol scale, 0.03 M substrate. [d]0.156 mmol scale, batch addition protocol. [e]7.16 mmol scale. [f]7.87 mmol scale.

4. Late-Stage Derivatization. Despite the large number of mono- and disubstituted diazocines accessible with our oxidative method, it could not readily deliver amino-substituted diazocines. Therefore, we developed a practical late-stage derivatization (Scheme 5). The known *para*-aminodiazocine **42**[7c] was synthesized in 84% yield from the *para*-bromo diazocine **29**[7a] by Buchwald-Hartwig coupling with *tert*-butyl carbamate, followed by deprotection of the *tert*-butyloxycarbonyl (Boc) group by treatment with tetra-*N*-butylammonium fluoride (TBAF).[13] Although the trifluoroacetic acid (TFA) protocol

could be used, TBAF afforded a cleaner product and avoided side reactions resulting from the presence of *tert*-butyl cations. The known *para*-diamino diazocine **43**[6e] was prepared in 72% yield in an identical fashion to the monoamino compound **42**. To access the *meta*-amino diazocine **44**, we started from *meta*-ester **14**. Ester hydrolysis followed by Curtius rearrangement in the presence of allyl alcohol, followed by removal of the allyloxycarbonyl (Alloc) group, gave the desired product **44** in 82% yield.

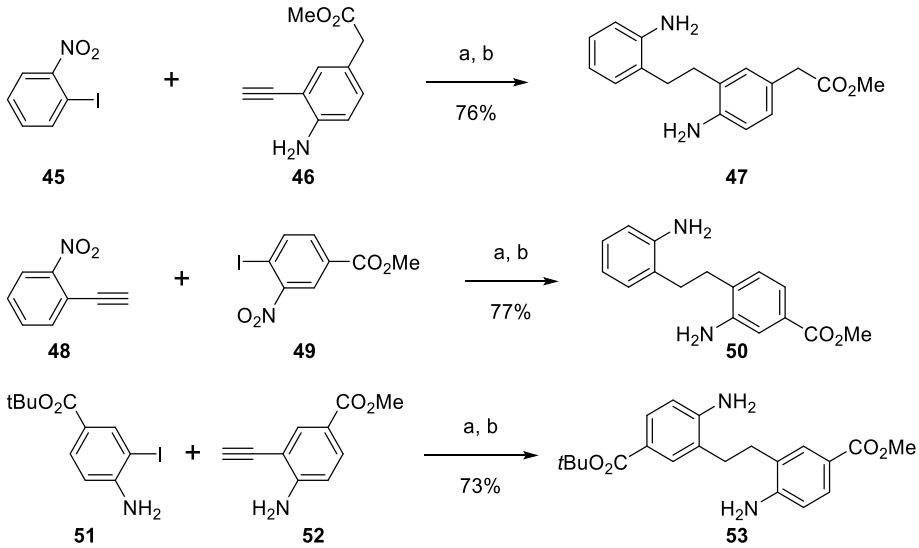


a) $BocNH_2$, Cs_2CO_3, XanthPhos Pd G3, 1,4-dioxane, 100 °C. b) TBAF·$3H_2O$, 2-methyltetrahydrofuran (Me-THF), 70 °C. c) LiOH, tetrahydrofuran (THF)/MeOH/H_2O. d) Allyl alcohol, DPPA, Et_3N, PhMe, rt to 80 °C. e) Pyrrolidine, $Pd(PPh_3)_4$, DCM.

Scheme 5 Late-stage diversification.

5. Cyclization Substrate Synthesis. A major advantage of the oxidative cyclization approach is the relative ease with which the requisite 2,2′-ethylenedianilines can be accessed. To this end, we developed a Sonogashira coupling strategy, which is exemplified in Scheme 6. Several combinations of alkynes and aryl halides are possible, pending on the nature of the coupling partners and their oxidation states.

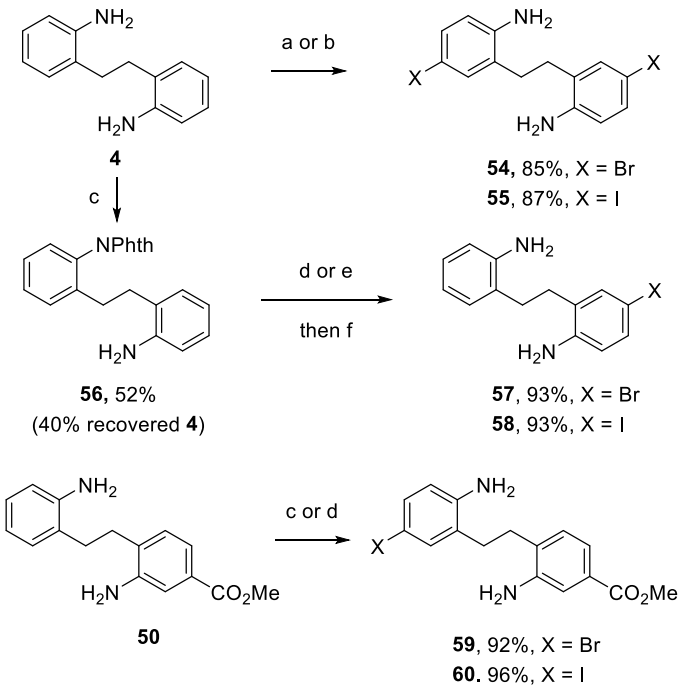
The first and most useful variant is based on the coupling of a 2-aminophenylacetylene with 2-iodonitrobenzene, as depicted for dianiline **47**. The second route proceeds through the coupling of a 2-nitrophenyl-acetylene with a 2-iodonitrobenzene, which is exemplified for compound **50**. In some cases, however, considerable decomposition of the 2-nitrophenylacetylenes was observed under the conditions of the Sonogashira coupling.[14] The third route involved the coupling of a 2-amino-phenylacetylene with a 2-iodoaniline as shown for dianiline **53**. This route is less general, as 2,2′-diaminodiphenylacetylenes tend to undergo cyclization to indoles.[15] Regarding the hydrogenation of the diarylacetylenes, we found that substrates must not contain any contaminants remaining from the Sonogashira reaction. Otherwise, we observed significant catalyst poisoning, resulting in unreasonably high catalyst loading.



a) $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, rt; then TMS acetylene. b) H_2, Pd/C, MeOH/DCM.

Scheme 6 Example 2,2' ethylenedianiline syntheses by Sonogashira coupling/hydrogenation.

Since our cross-coupling approach involves a hydrogenation step that is not compatible with aryl halides, we prepared several halo-substituted dianilines via electrophilic aromatic substitution (Scheme 7).



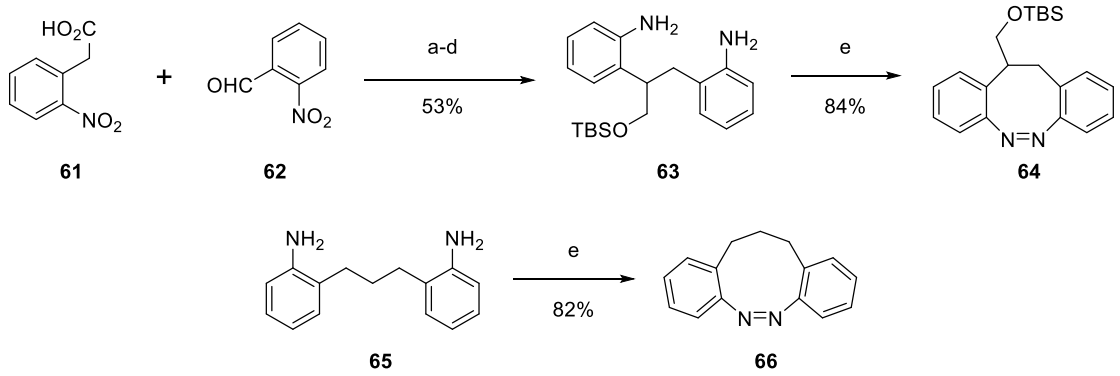
a) *N*-Bromosuccinimide (NBS) (2 eq.), DMSO. b) *N*-Iodosuccinimide (NIS) (2 eq.), dimethyl sulfoxide (DMSO). c) Phthalic anhydride, bis(trimethylsilyl)acetamide (BSA), PhMe, reflux. d) NBS (1 eq.), DMSO. e) NIS (1 eq.), DMSO. f) $N_2H_4 \cdot H_2O$, THF, reflux.

Scheme 7 Halogenation of 2,2' ethylenedianilines.

While the synthesis of the precursors leading to the symmetrical *para*-dihalogenated compounds **54** and **55** was straightforward, access to precursors of monohalo diazocines was more difficult. We initially used an unselective, statistical halogenation followed by

purification via chromatography and precipitation. However, to avoid the tedious separation of mono- and dihalogenation products, as well as unreacted substrate, we developed a more scalable and practical sequence. Desymmetrization of the commercially available dianiline **4** by protection of one amino group as the phthalimide, followed by highly selective halogenation of phthalimide **56** and deprotection, allowed to access the desired products **57** and **58** without any chromatographic purification. Selective halogenation could also be achieved by exploiting electronic differences in substituted dianilines. We tested this on ester **50**, which afforded the halogenation products **59** and **60** in high yield and without any undesired isomers.

6. New Cyclic Azobenzenes. Cyclic azobenzenes may be substituted not only on their arene moieties but also on their central ring.[7f,8b] Indeed, several heterodiazocines have recently emerged.[9] Confident in our new methodology, we have begun to explore cyclic azobenzenes with substitutions on the central bridge and with an increased ring size (Scheme 8).



a) Ac_2O, Et_3N, neat, 50 °C. b) EtOCOCl, Et_3N, THF then $NaBH_4$, H_2O. c) TBSOTf, 2,6-lutidine, DCM. d) H_2, Pd/C, MeOH/DCM. e) *m*CPBA in AcOH (2 eq., slow addition), AcOH/DCM = 1/3.

Scheme 8 Synthesis of new cyclic azobenzenes.

Condensation[16] of aldehyde **62** with acid **61**, followed by carboxylic acid reduction, *tert*-butyldimethylsilyl (TBS) protection, and hydrogenation afforded cyclization precursor **63** in 53% yield over four steps. The oxidative cyclization of the dianiline **63** to diazocine **64** proceeded in 84% yield, which is virtually the same efficiency as that for the unsubstituted parent system. The dianiline **65**[17] could be cyclized equally well to diazonine **66**, affording the first cyclic azobenzene that features a propylene bridge in the central ring. Both syntheses of dianilines **63** and **65** can in principle be adapted to allow access to symmetric and nonsymmetric substitution on the aromatic rings as well as to the halogenation strategy that we described in the previous section. Thus, the syntheses of diazocine **64** and diazonine **66** may be used as blueprints for new types of azobenzenes with interesting photophysical and pharmacological features.

7. Ultraviolet–Visible (UV–Vis) Spectroscopic Characterization. With more than 40 cyclic azobenzenes in hand, we turned toward their photophysical characterization to gain insight into the effects of substituents and backbone modifications on UV–vis spectra and photoswitching behavior. To determine the optimal wavelength (λ_{opt}) for a high (*Z*)/(*E*) ratio, we illuminated a 50 µM DMSO solution of each compound for 10 min in 20 nm increments from 540 to 360 nm and measured the resulting absorption spectra (Figures S4–S8).

For all diazocines, the lowest energy absorption was not significantly affected by substitution and typically centered around 400 nm for the (*Z*) isomer and around 490 nm for the (*E*) isomer. Like the parent compound **2**, the majority of the diazocines can be isomerized most efficiently to their thermodynamically less stable (*E*) form with 400 nm light (Table 4 and Table S1). A slightly longer wavelength of 420 nm or even 440 nm was required in the case of several electron-rich diazocines. The backbone-substituted compound 64 also did not show special features compared to the parent system **2**.

Finally, we also investigated the spectra and switching of the nine-membered diazonine **66**. Analogously to the eight-membered system, it could be isomerized to the (*E*) isomer with 400 nm irradiation and back to the (*Z*) isomer using 520 nm light. Interestingly, compared to that of the (*E*) isomer of diazocine **2**, the spectrum of the (*E*) isomer of diazonine **66** exhibits a notably higher absorbance for the band corresponding to the ππ*-transition, which also is found at a longer wavelength of 316 nm. Therefore, the spectrum of (*E*) diazonine resembles that of a regular (*E*) azobenzene, while the (*Z*) diazonine spectrum is similar to that of (*Z*) diazocine (Figure 1 and Table S3).

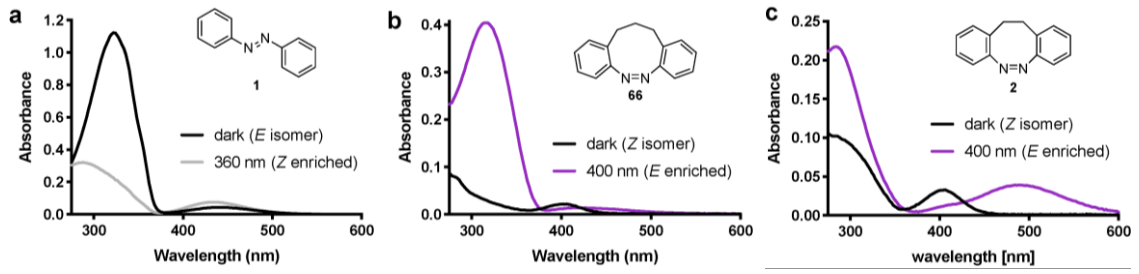
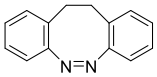
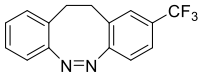
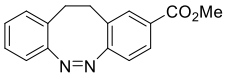
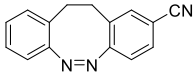
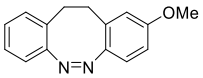
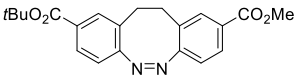
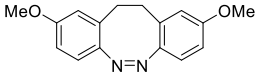
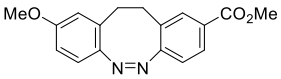
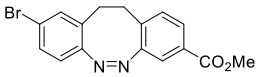
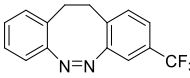
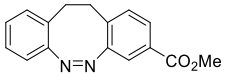
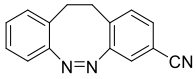
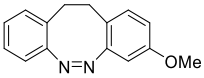
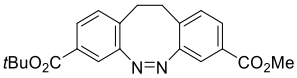
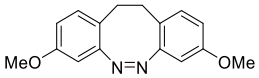
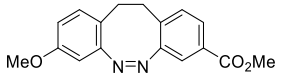
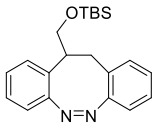
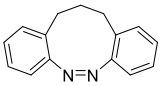


Figure 1 Comparison of UV–vis spectra of (a) azobenzene **1**, (b) diazonine **66**, and (c) diazocine **2** in the dark and under illumination. All spectra in DMSO, 50 µM.

Table 4 Photophysical properties of selected cyclic azobenzenes.

compound		λ_{opt}[a]	$T_{1/2}$	PSS (Z/E)[b]
	**2**	400 nm	9.4 h	12/88[c]
	**23**	400 nm	51 min	12/88[c]
	**24**	400 nm	14 min	14/86[c]
	**25**	400 nm	6 min	15/85[c]
	**26**	420 nm	3.0 h	33/67[c]
	**31**	400 nm	24 min	14/86[c]
	**33**	420 nm	3.5 h	32/68[c]
	**35**	420 nm	2.2 min	55/45[c]
	**40**	400 nm	4.7 h	14/86[c]
	**13**	400 nm	4.3 h	14/86[c]
	**14**	380 nm	6.7 h	14/86[c]
	**15**	400 nm	3.3 h	14/86[c]
	**16**	420 nm	10.4 h	45/55[d]
	**32**	400 nm	6.0 h	15/85[c]
	**34**	420 nm	11.2 h	55/45[d]
	**36**	420 nm	7.5 h	52/48[d]
	**64**	400 nm	14.2h	19/81[c]
	**66**	400 nm	n.d.[e]	14/86[c]

[a]For (*Z*) to (*E*) switching, determined by UV-Vis spectroscopy. [b]For (*Z*) to (*E*) switching, determined by ^{1}H-NMR spectroscopy in DMSO-d$_6$. [c]390 nm. [d]415 nm. [e]Not determined, no measurable isomerization within two weeks.

The comparatively small effect of substituents on the lowest energy absorption band of diazocines are not surprising since it results from a nπ*-excitation. A stronger effect was observed for the next absorption band at shorter wavelengths, which corresponds to a ππ*-transition. This band was notably redshifted for diazocines carrying electron-donating substituents (e.g., compounds **16** and **26**) or with a push–pull substitution. Increased overlap of the bands corresponding to ππ*- transitions of the (*E*) forms with the nπ*-transitions of the (*Z*) forms might be contributing to the poorer switching behavior observed for these diazocines (see PSS investigation by NMR spectroscopy below).

8. Thermal Relaxation. In respect to thermal relaxation, we observed broad variability (Table 4 and Table S1) with trends similar to regular azobenzenes. Thermal relaxation was monitored in 50 μM DMSO solution at 25 °C over a period of 24 h. Reduced half-lives for the (*E*) isomer were observed with electron-withdrawing groups in the *meta*-position as well as both electron-withdrawing and electron-donating groups in the *para*-position. Strong electron-withdrawing groups and push–pull substitution in *para*-position resulted in rapidly relaxing photoswitches. When comparing the effect of a substituent in *meta*-position to that of the same substituent in *para*-position, we found that *para*-substituted compounds were generally more affected than their *meta*-substituted counterparts. To determine the effect of water on the relaxation rates, we also investigated solutions in phosphate-buffered saline (PBS)/DMSO mixtures for three selected compounds (see Table S2). Surprisingly, we observed up to 2- or 3-times longer half-lives upon increasing the fraction of the aqueous component in the solvent mixture.

None of the aromatic substitutions resulted in a major increase in relaxation times compared to the parent system **2**. However, improved bistability could be achieved by changes in the central ring system. An increased thermal stability of the (*E*) form was observed for the ethylene-bridge-substituted diazocine **64**. For diazonine **66** no relaxation could be observed at room temperature after enrichment of the (*E*) isomer by both UV–vis (40 h) as well as NMR measurements (2 weeks). Still, diazonine **66** did fully relax to the (*Z*) isomer upon prolonged storage in the solid state in the dark. The high bistability of diazonine **66** is expected to be connected to the low energy difference between (*E*) and (*Z*) isomer, which is a consequence of the longer three-carbon bridge ($\Delta G_{Z\rightarrow E}$ = 10.6 kJ/mol in the gas phase and 17.4 kJ/mol in DMSO, see Tables S14 and S15).

9. PSS Investigation by NMR Spectroscopy. Having determined the best switching wavelengths and relaxation times, we turned toward determination of the PSS compositions (Table 4 and Table S1, Figure S3). We chose to determine the PSS as (*Z*)/(*E*) ratio observed with one-pulse ^{1}H-NMR spectroscopy measurements of 10 mM solutions in DMSO-d_6. The samples were first measured before illumination, then after 30 s of illumination with a 390 nm high-power light-emitting diode (LED), and after successive 30 s of illumination

with a 520 nm high-power LED (Prizmatix). We additionally tested the (*Z*)-to-(*E*) isomerization with a 460 nm high-power LED and a 415 nm Mic-LED (Prizmatix) for the compounds either where we had determined an optimal switching wavelength higher than 400 nm in our UV–vis experiments or where we observed poor (*Z*)/(*E*) ratios (>20/80) after 390 nm illumination.

Despite handling the samples without precautions to avoid exposure to ambient light, most samples contained no detectable (E) isomer and all diazocines showed an initial (*Z*)/(*E*) ratio of at least 97/3. For the (*Z*)-to-(*E*) isomerization upon irradiation with violet/blue light, we observed distinct differences between individual groups of diazocines. With the majority of the compounds, we were able to establish a PSS between 12/88 and 19/81. This included compounds with electron-withdrawing substituents, backbone substitution, some electron-donating substituents, and weakly interacting substituents, such as alkyl or halogen, which all showed excellent PSS. However, methoxy and most amino substituents lowered the (*E*) isomer fraction and more of the (*Z*) isomer remained. Furthermore, the push–pull combination of methoxy and methyl ester led to a drastic PSS deterioration, regardless of their position on the ring.

The photoisomerization from the (*E*) to the (*Z*) form was found to be highly effective for all diazocines. In all cases illumination with 520 nm led to quantitative isomerization to the thermodynamically favored (*Z*) form. This is an important distinction from regular azobenzenes. In summary, all tested diazocines can be reversibly isomerized with visible light.

For diazonine **66** we observed no (*E*) isomer before illumination and a PSS of 14/86 after illumination with 390 nm light. While this result for the (*Z*)-to-(*E*) isomerization was virtually identical to that of the unsubstituted diazocine **2**, a nonquantitative conversion was observed for the (*E*)-to-(*Z*) photoisomerization of diazonine **66** and only a (*Z*)/(*E*) ratio of 89/11 could be achieved with 520 nm light. Still, the value for the photoisomerization to the thermodynamically preferred form is better for diazonine **66** than for azobenzene **1**, which exhibited at best a PSS of 83/17 for (*Z*)-to-(*E*) isomerization in DMSO (Table S4).

Finally, it is important to mention that we had to reduce the concentration of azobenzene **1** for our NMR experiments from 10 to 1 mM, as we had observed a very low (*E*)-to-(*Z*) conversion at 10 mM. Probably this issue results from incomplete sample penetration during irradiation due to complete absorption of light. This issue is alleviated by the lower extinction coefficients of diazocine and diazonine. Thus, at least at the present concentrations, both diazocines and the diazonine allow for a more rapid and efficient establishment of the PSS than regular azobenzenes.

CONCLUSION

The broad implementation of diazocines as photoswitches with useful new functional properties has been limited by their poor synthetic accessibility. With this work, we have shown that the oxidative cyclization of dianilines can largely overcome this limitation. In combination with a modular cross-coupling approach to furnish the cyclization substrates, as well as late-stage functionalization, the oxidative protocol gives access to a wide variety of diazocines that are substituted on one or both aromatic rings. Additionally, we were able to prepare a diazonine with a nine-membered ring and a diazocine substituted on the ethylene bridge, which we consider the vanguard of new types of photoswitches.

Furthermore, we have compared the photophysical properties and thermal relaxation data of diazocines. This allowed us to identify substitution patterns that are tolerated without affecting the useful photoswitch characteristics of the parent system as well as the patterns that should be avoided because of their detrimental effects. On the basis of our results, it is also possible to tune the thermal relaxation of diazocines over a broad range. This knowledge will facilitate the choice of diazocines in a variety of applications.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b08794.

Synthetic procedures and characterization data; photophysical characterization; optimization of reaction conditions; synthetic recommendations; computational data (PDF)

X-ray crystallographic data for 38 (CIF)

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Notes

The authors declare no competing financial interest.

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3 Supporting Information for Oxidative Approach Enables Efficient Access to Cyclic Azobenzenes

3.1 Synthetic procedures and characterization data

The content of this section has been integrated in the experimental section (Section 2, general information, synthetic procedures and analytical data) and in the appendix (Section 3.2, NMR spectra).

3.2 Photophysical characterization

Protocols

UV-Vis Spectroscopy

UV-Vis spectra were recorded on a Varian Cary 60 Scan UV-Vis spectrometer equipped with a Peltier PCB-1500 Thermostat and an 18-cell holder using Brand disposable UV cuvettes (70-850 µL, 10 mm light path) by Brandtech Scientific Inc.. Sample preparation and all experiments were performed under red light conditions in a dark room. All UV-Vis measurements were performed with dimethyl sulfoxide (DMSO) as the solvent.

Determination of optimal switching wavelength: Light at different wavelengths was provided by an Optoscan Monochromator with an Optosource (75 mW lamp), which was controlled through a program written in Matlab (Figure S1). Irradiation to establish the photostationary state took place from the top through a fiber-optic cable. For each compound a 25 or 100 mM stock solution in DMSO was prepared and diluted to a 50 µM concentration prior to the experiment. First, a spectrum of the non-irradiated sample was acquired, then a spectrum with irradiation at 600 nm. If these two spectra did not overlap, the measurement was aborted and the light fiber readjusted, then a new run was started. Otherwise, spectra with illumination were acquired from 540 to 360 nm in 20 nm steps going from higher to lower wavelengths and illuminating 10 minutes for each wavelength.

wavelength	**time**
600 nm	10 s (dummy time at resting wavelength)
540 nm	600 s
520 nm	600 s
500 nm	600 s
480 nm	600 s
460 nm	600 s
440 nm	600 s
420 nm	600 s
400 nm	600 s
380 nm	600 s
360 nm	600 s

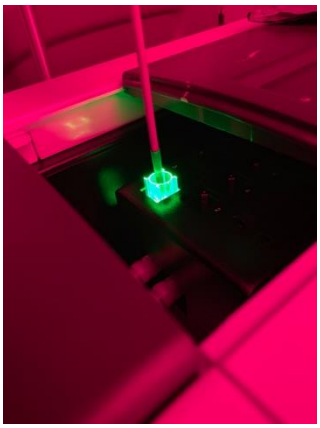


Figure S1 Left: Protocol for the determination of the optimal switching wavelength. Right: Picture of a sample being illuminated in the UV-Vis spectrometer.

Thermal relaxation: All samples were prepared by dilution of a 100 mM stock solution in DMSO to a 50 µM concentration with DMSO. Thermal isomerization half-lives at 25 °C were determined by measuring the absorption decay at 490 nm. The samples were irradiated for 1 minute with a 390 nm Prizmatix high power LED from the top, then data points were collected for 24 hours. For compounds **23**, **24**, **25**, **31**, **35**, **42** and **43**, the collection of data points was stopped earlier, due to their short relaxation times. Each sample was measured at least twice.

Photostationary state investigation by NMR spectroscopy

To determine the photostationary state compositions, one pulse proton ^{1}H-NMR spectroscopy was performed 600 MHz[a] at 10 mM concentration in DMSO-d_6 to ensure a low optical density and good signal-to-noise ratio. Samples were prepared by diluting 100 mM stock solutions in DMSO-d_6 and were handled without precautions under ambient light. Spectra were collected before illumination and after illumination for 30 seconds with Prizmatix high power LEDs (390, 460 and 520 nm) or Prizmatix Mic-LEDs (365 and 415 nm). Each sample was first illuminated at 390 nm followed by 520 nm[b] (see Figure S2). If necessary (see Table 4, main text and Figure S3) the samples were also irradiated with 415 nm or 460 nm light. Diazonine **66** was additionally irradiated at 365 nm. For the irradiation sequence of azobenzene **1** see Table S4.
The (*Z*)/(*E*)-ratio was determined by integration of baseline separated signals in the aromatic region. For compounds with a relaxation time shorter than 100 minutes (established through UV-Vis spectroscopy), ten spectra were collected every 20–60 seconds and the values extrapolated to the timepoint when the illumination of the sample was stopped.

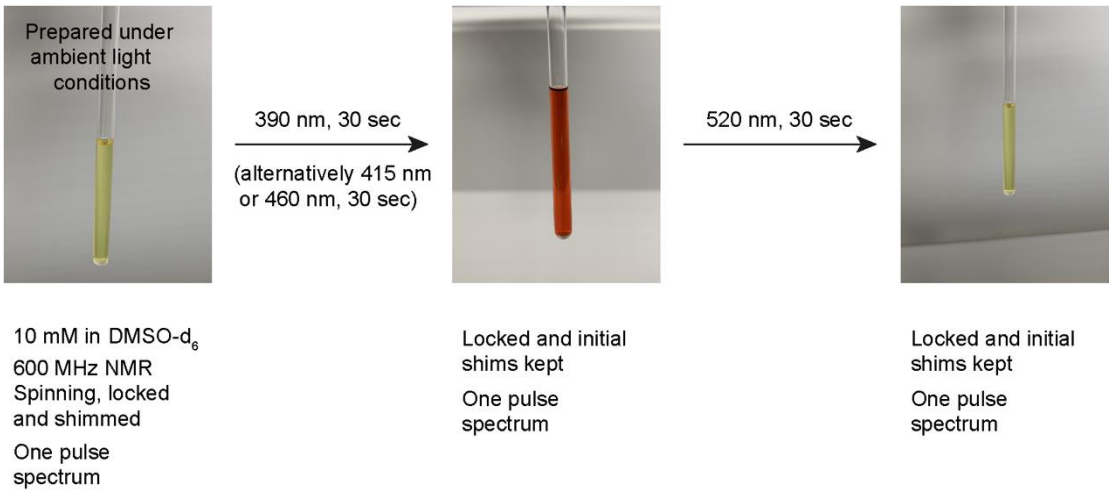
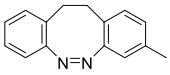
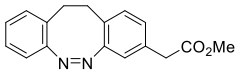
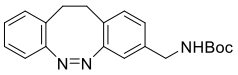
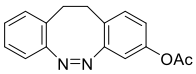
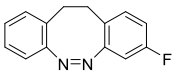
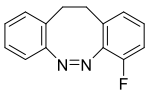
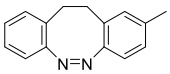
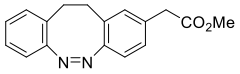
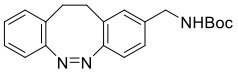
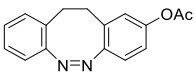
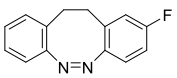
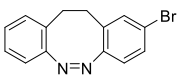
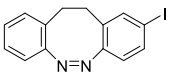
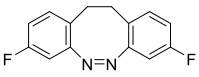
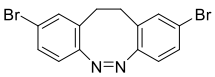
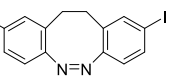
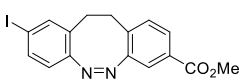
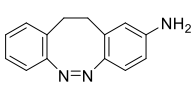


Figure S2 Workflow for the investigation of the photostationary states by ^{1}H-NMR spectroscopy.

[a]For details on NMR spectrometer see "General information" in section "Synthetic procedures and characterization".
[b]The most suitable range of wavelengths for (*E*) to (*Z*) switching of diazocine **2** was determined to lie between 480 nm and 540 nm by UV-Vis spectroscopy (see Figure S4).

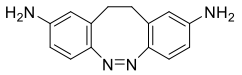
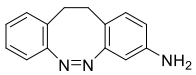
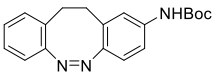
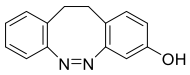
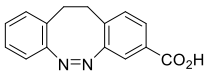
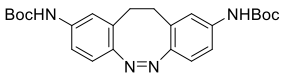
Summary of photophysical properties for characterization by UV-Vis and NMR spectroscopy

Table S1 Photophysical properties of diazocines.

compound		λ_{opt}[a]	$T_{1/2}$	PSS (Z/E)[b]
	**10**	400 nm	9.3 h	17/83[c]
	**11**	400 nm	8.9 h	14/86[c]
	**12**	400 nm	8.9 h	17/83[c]
	**17**	400 nm	8.0 h	15/85[c]
	**18**	400 nm	5.7 h	13/87[c]
	**19**	400 nm	11.0 h	15/85[c]
	**20**	400 nm	6.8 h	15/85[c]
	**21**	400 nm	7.9 h	14/86[c]
	**22**	400 nm	7.9 h	14/86[c]
	**27**	400 nm	8.7 h	17/83[c]
	**28**	400 nm	9.5 h	13/87[c]
	**29**	400 nm	5.6 h	14/86[c]
	**30**	400 nm	4.9 h	15/85[c]
	**37**	400 nm	5.9 h	15/85[c]
	**38**	400 nm	4.0 h	15/85[c]
	**39**	400 nm	3.2 h	19/81[c]
	**41**	400 nm	4.3 h	17/83[c]
	**42**	400 and 360 nm	16 min	85/15[c]

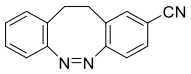
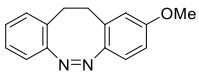
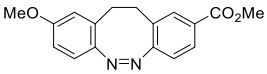
[a]For (*Z*) to (*E*) switching, determined by UV-Vis spectroscopy. [b]For (*Z*) to (*E*) switching, determined by ^{1}H-NMR spectroscopy in DMSO-d_6. [c]390 nm. [d]415 nm. [e]460 nm.

Table S1 (continued) Photophysical properties of diazocines.

compound		λ_{opt}[a]	$T_{1/2}$	PSS (Z/E)[b]
	**43**	440 nm	14 min	73/27[c]
	**44**	360 – 420 nm	13.2 h	61/39[c]
	**SI-95**	420 nm	2.1 h	44/56[d]
	**SI-96**	420 nm	11.3 h	61/39[c]
	**SI-97**	400 nm	8.6 h	12/88[c]
	**SI-98**	420 nm	3.0 h	15/85[e]

[a]For (*Z*) to (*E*) switching, determined by UV-Vis spectroscopy. [b]For (*Z*) to (*E*) switching, determined by ^{1}H-NMR spectroscopy in DMSO-d_6. [c]390 nm. [d]415 nm. [e]460 nm.

Table S2 Effect of water on thermal relaxation: Comparison of half-lives[a] for thermal (*E*) to (*Z*) isomerization of selected diazocines in DMSO and PBS/DMSO mixtures.

compound		$T_{1/2}$ DMSO	$T_{1/2}$ 50% PBS/DMSO	$T_{1/2}$ 90% PBS/DMSO
	**25**	6.4 min	6.9 min	13.4 min
	**26**	181.1 min	283.1 min	532.0 min
	**35**	1.9 min	2.3 min	4.6 min

[a]Determined according to the general protocol, but each sample was measured only once and the samples were prepared by diluting the DMSO stock solution with the specified solvent mixture instead of DMSO

Table S3 ππ*- and nπ*-absorption maxima of azobenzene **1**, diazonine **66** and diazocine **2** in DMSO (50 µM).

Transition	(E)-**1**[a]	(Z)-**1**[b]	(E)-**66**[c]	(Z)-**66**[a]	(E)-**2**[c]	(Z)-**2**[a]
ππ*	322 nm	280 nm	316 nm	280 nm	284 nm	286 nm
nπ*	444 nm	430 nm	426 nm	406 nm	494 nm	405 nm

[a]Non-irradiated sample. [b]After 360 nm illumination. [c]After 400 nm illumination.

Table S4 (*Z*)/(*E*) ratios of 1 mM azobenzene 1 in DMSO-d_6 determined by ^{1}H-NMR spectroscopy after 30 seconds of irradiation at different wavelengths.

Entry[a]	λ	PSS (*Z*/*E*)
1[b,c]	365 nm	17/83
2	non-irradiated sample	3/97
3[c]	365 nm	60/40
4[d]	415 nm	17/83[c]
5	390 nm	18/82
6	460 nm	23/77
7	520 nm	35/65

[a]The entries in this table refer to the same sample and are ordered from top to bottom according to the sequence of irradiation, except for the entry 1, which refers to a more concentrated sample that was measured separately.
[b]10 mM.
[c]The determination of the optimal wavelength for switching to (*Z*)-**1** by UV-Vis spectroscopy (see Figure S5) did not include wavelengths below 360 nm. Thus, at shorter wavelengths a higher conversion from (*E*)/(*Z*) may be possible.
[d]The optimal wavelength for switching to (*E*)-**1** determined by UV-Vis spectroscopy (see Figure S5) was 420 nm.

Supplementary figures

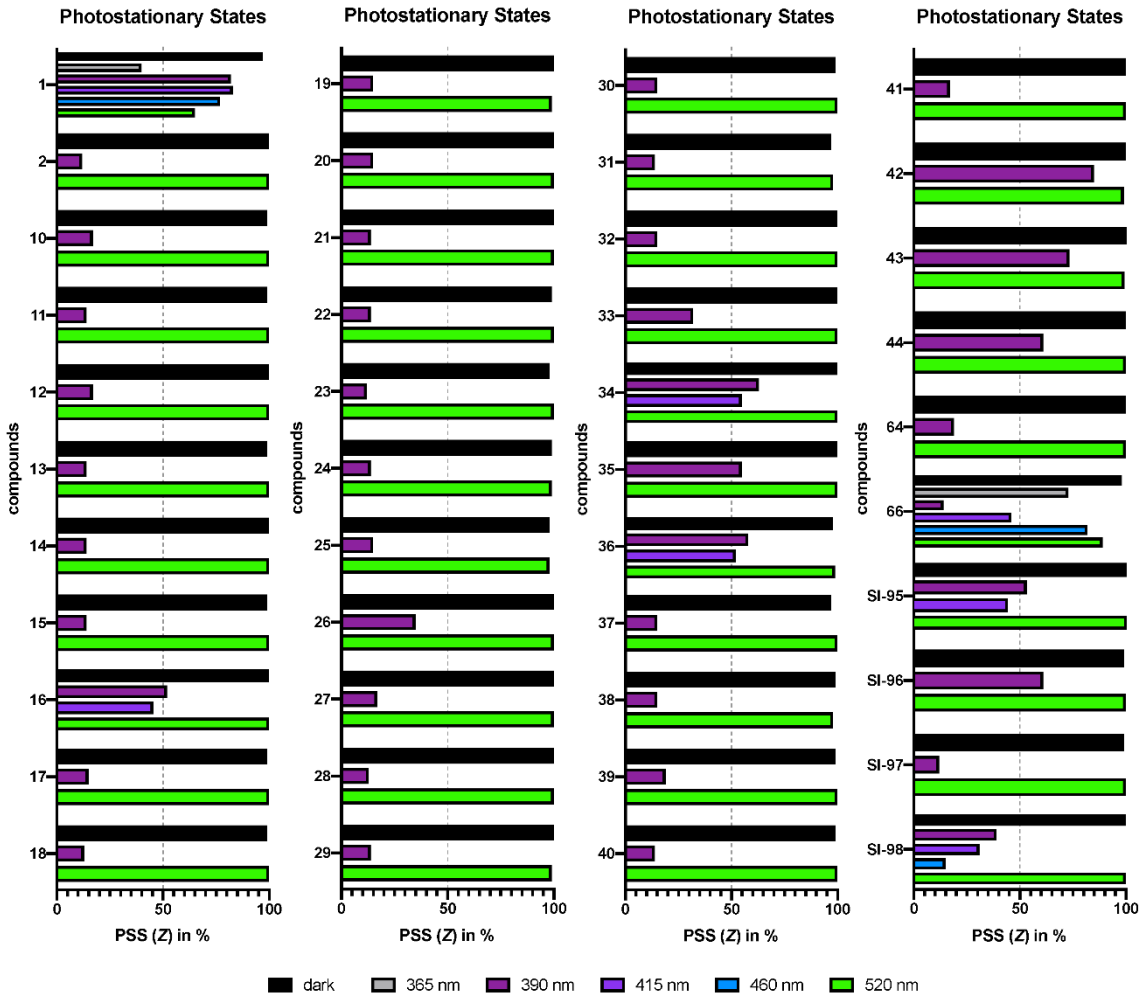


Figure S3 Overview of the fraction of (*Z*)-isomer determined by ^{1}H-NMR spectroscopy for the non-irradiated sample (prepared under ambient light conditions, labeled as "dark") and the PSS at different wavelengths. Values for 390 and 520 nm irradiation are depicted for all compounds and values for 365, 415 and 460 nm irradiation are shown for selected compounds or if a better PSS composition was obtained.

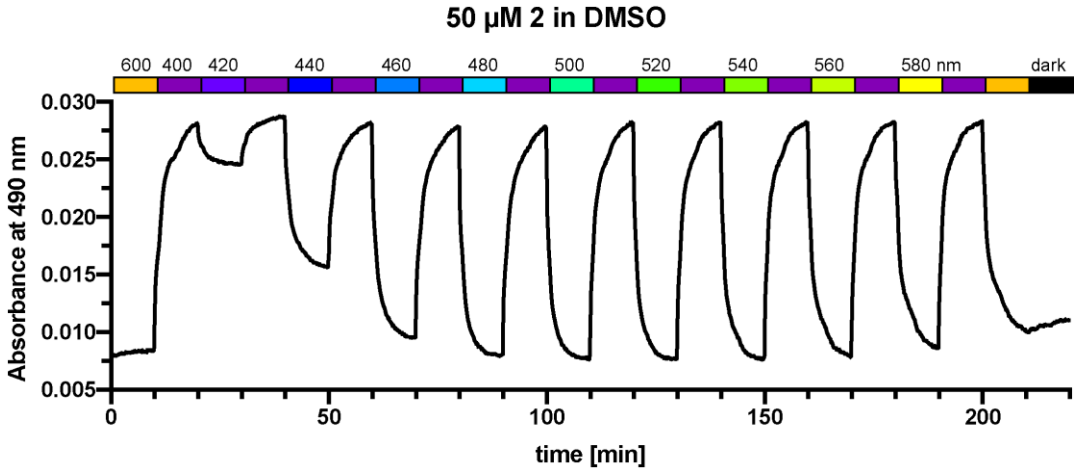


Figure S4 Determination of the ideal wavelength to switch diazocine **2** from (*E*) to (*Z*).

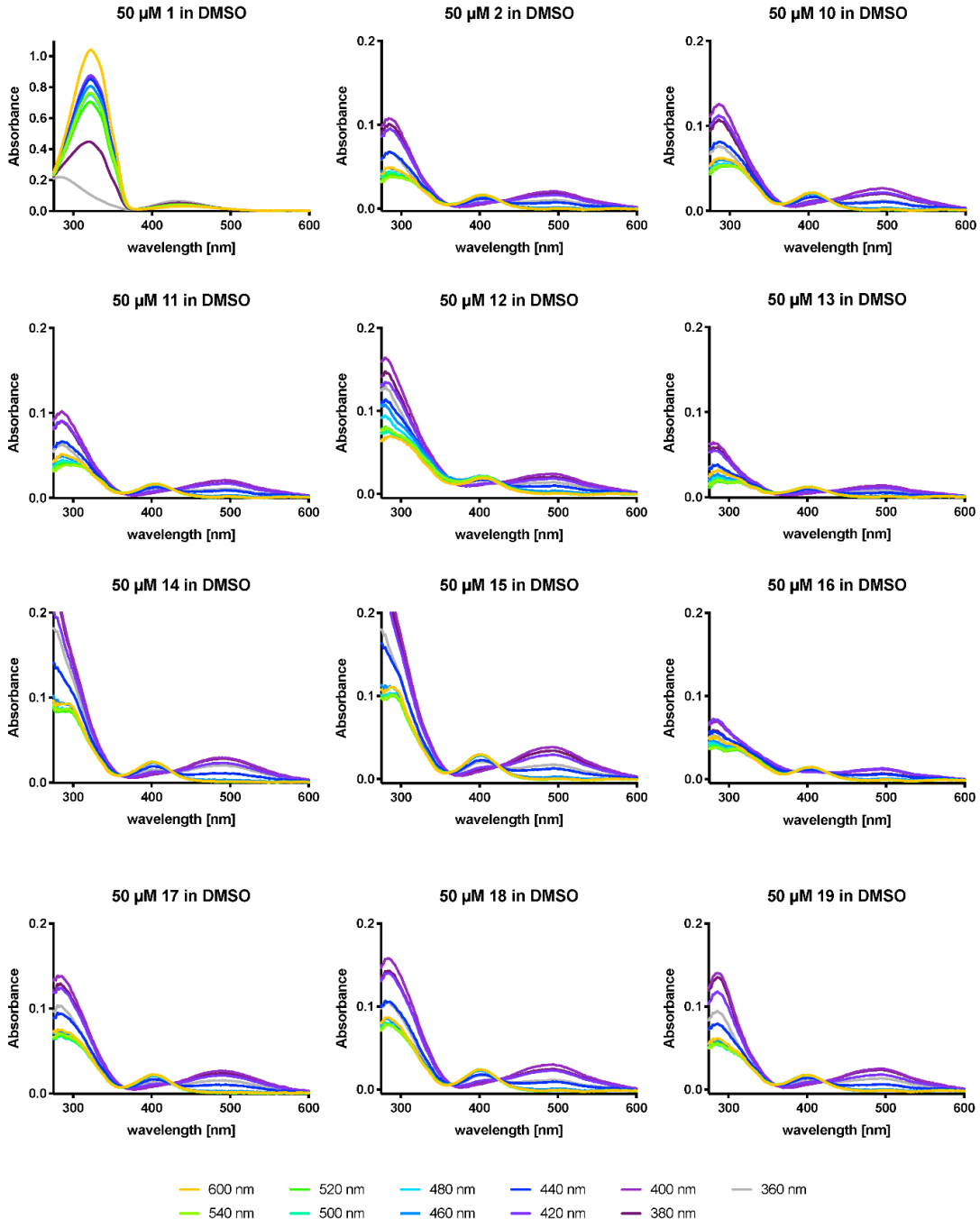


Figure S5 UV-Vis spectra of compounds **1**, **2**, **10**–**19**.

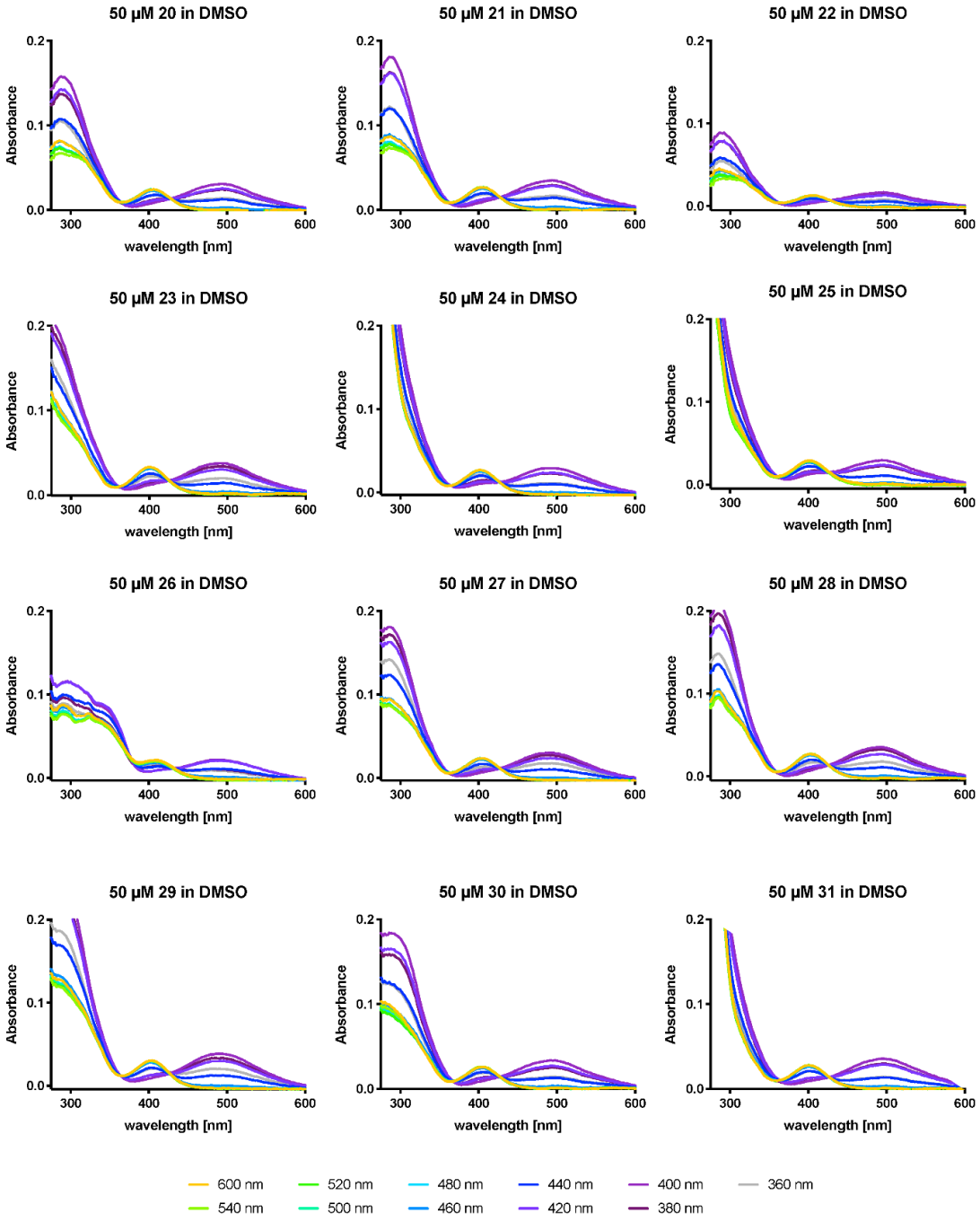


Figure S6 UV-Vis spectra of compounds **20**–**31**.

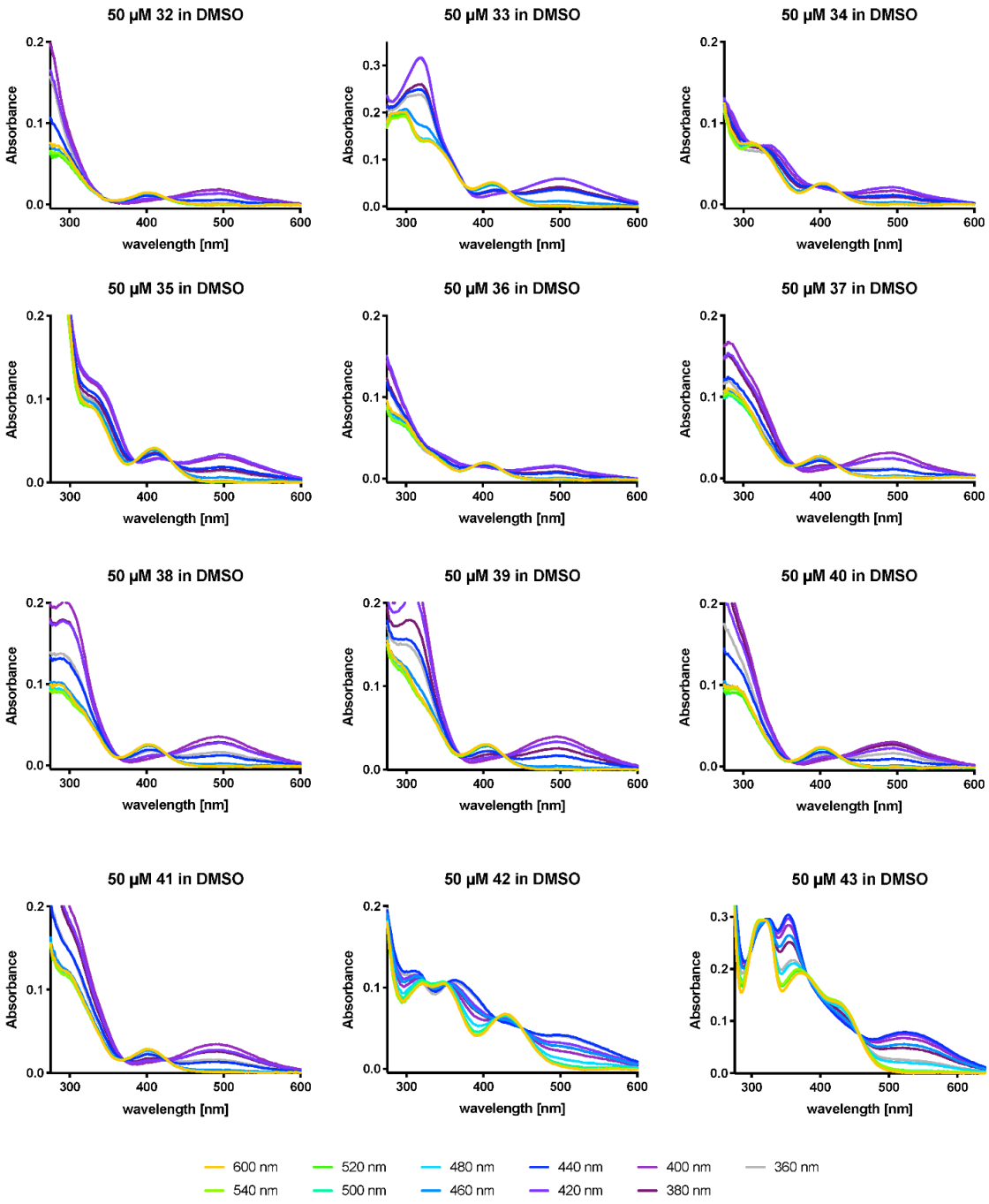


Figure S7 UV-Vis spectra of compounds **32**–**43**.

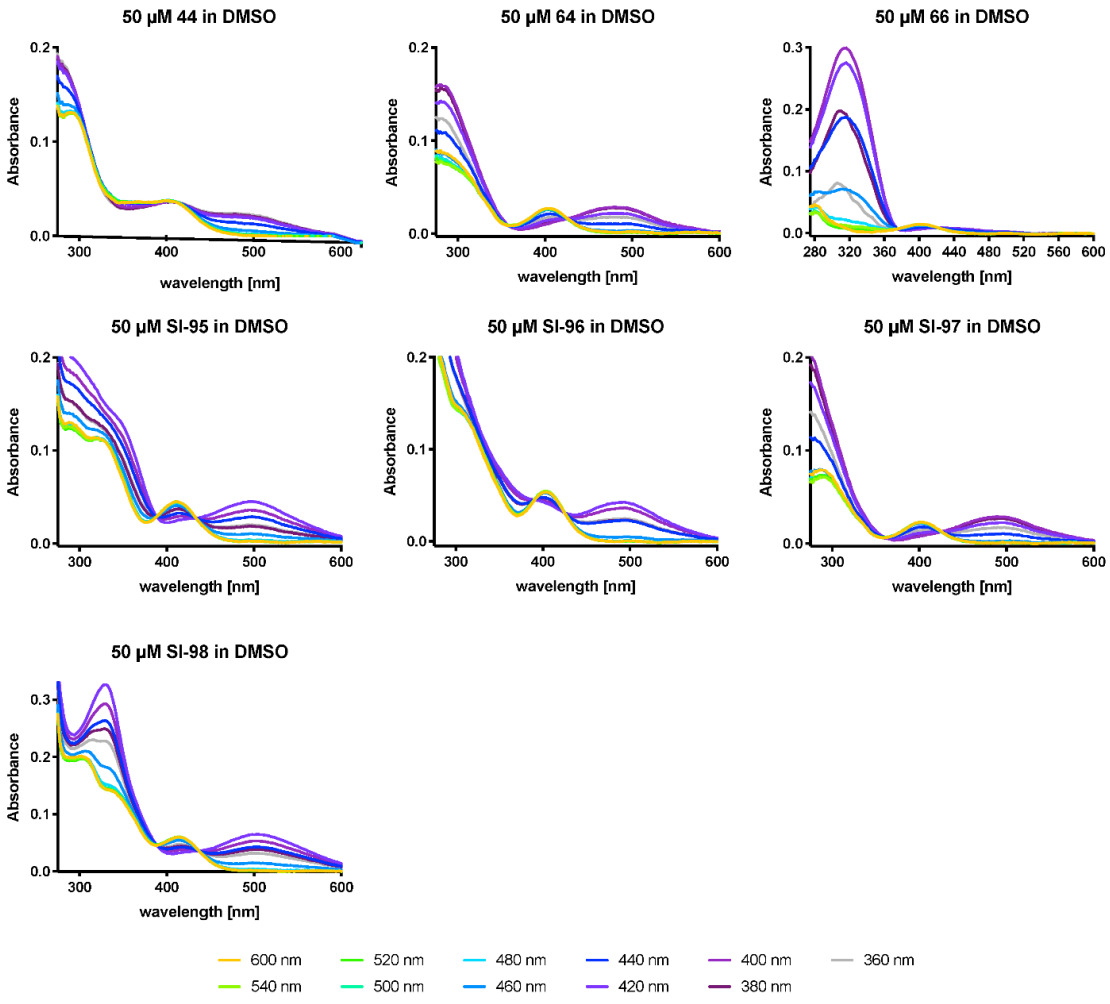
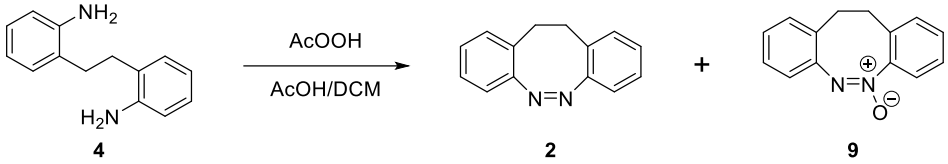


Figure S8 UV-Vis spectra of compounds **44, 64**, **66**, **SI-95**–**SI-98**.

3.3 Optimization of reaction conditions

Optimization with peracetic acid (AcOOH)

Reference procedure



4 2 9

A 0.33 M[a] solution of peracetic acid in acetic acid (3.00 mL, 1.00 mmol, 2.0 eq.) was added by syringe pump within a period of 12 hours to a solution of 2,2'-ethylenedianiline **4** (106 mg, 0.500 mmol, 1.0 eq.) in acetic acid/dichloromethane = 1/1 (25 mL) under rapid stirring. After the addition of the peracetic acid solution was complete, the mixture was stirred for at least one more hour. The volatiles were then removed under reduced pressure and dimethyl terephthalate (32.4 mg, 0.167 mmol, 0.33 eq.) and dichloromethane (20 mL) were added to the residue. The mixture was sonicated until all solids had dissolved. A sample (1 mL) was separated and the solvent removed under reduced pressure. The residue was dissolved in $CDCl_3$ and the solution analyzed by ^{1}H-NMR spectroscopy using a standard 16-scan experiment. The components of the mixture were quantified by integration of the following signals:

- dimethyl terephthalate: 3.95 ppm (s, 3H)
- 2,2'-ethylenedianiline (**4**): 6.68 ppm (dd, J = 7.7, 1.2 Hz, 2H)
- diazocine **2**: 6.82 ppm (dd, J = 7.7, 1.3 Hz, 2H)
- diazocine *N*-oxide **9**: 3.37 ppm (ddd, J = 14.2, 10.2, 5.5 Hz, 1H)

Table S5 Equivalents of oxidant.

Entry	Equivalents of AcOOH	Product **2**	Substrate **4**	Side-Product **9**
1	1.5	71%	6%	6%
2	1.7	73%	2%	6%
3	1.8	67%	0%	8%
4	1.9	69%	0%	10%
5	2.0	73%	1%	10%
6	2.1	69%	0%	16%
7	2.1	75%	3%	4%
8	2.5	27%	0%	60%

All reactions were performed and analyzed according to the reference procedure for the oxidation of 2,2'-ethylenedianiline **4** with peracetic acid, except for varying the equivalents of peracetic acid.

[a]For the titration of *m*CPBA and peracetic acid see "General information" in section "Synthetic procedures and characterization".

Table S6 Rate of oxidant addition.

Entry	Oxidant addition	Product **2**	Substrate **4**	Side-Product **9**
1	as one batch	55%	6%	18%
2	within 1 h	64%	3%	14%
3	within 3 h	66%	0%	16%
4	within 6 h	68%	1%	14%
5	within 12 h	73%	1%	10%

All reactions were performed and analyzed according to the reference procedure for the oxidation of 2,2'-ethylenedianiline **4** with peracetic acid, except for varying the rate of addition of peracetic acid.

Table S7 Solvent screen.

Entry	Solvent	Product **2**	Substrate **4**	Side-Product **9**
1	acetic acid	67%	1%	14%
2	acetic acid/dichloromethane= 1/1	73%	1%	10%
3	acetic acid/dimethylformamide = 1/1	53%	1%	30%
4	acetic acid/acetonitrile = 1/1	33%	0%	not determined

All reactions were performed and analyzed according to the reference procedure for the oxidation of 2,2'-ethylenedianiline **4** with peracetic acid, except for using different solvent mixtures.

Table S8 Substrate concentration.

Entry	Concentration	Product **2**	Substrate **4**	Side-Product **9**
1	0.01 M	64%	1%	14%
2	0.02 M	73%	1%	10%
3	0.04 M	67%	0%	14%
4	0.08 M	53%	0%	28%

All reactions were performed and analyzed according to the reference procedure for the oxidation of 2,2'-ethylenedianiline **4** with peracetic acid, except for varying the amount of solvent/concentration. The reported concentrations refer to 2,2' ethylenedianiline **4**.

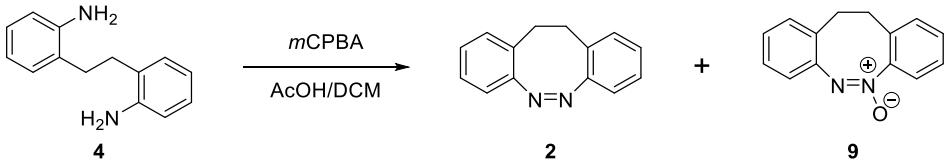
Table S9 Other parameters.

Entry	Variation from reference procedure	Product **2**	Substrate **4**	Side-Product **9**
1[a]	1.5 eq. of AcOOH	69%	not determined	not determined
2[a]	none	74%	not determined	not determined
3	solvent acetic acid, reaction at 80 °C	12%	1%	6%
4	36 hours stirring after oxidant addition	67%	0%	16%
5	with 0.05 eq. $Cu(OAc)_2$	19%	10%	12%

All reactions were performed and analyzed according to the reference procedure for the oxidation of 2,2'-ethylenedianiline **4** with peracetic acid, except for the specified variations.
[a]The reported yield for diazocine **2** is based on isolated material after purification, the amounts of compounds **4** and **9** were not determined.

Optimization with *meta*-chloroperoxybenzoic acid (*m*CPBA)

Reference procedure



A freshly prepared and titrated[a] 0.3 M solution of *m*CPBA (7.87 mL, 2.36 mmol, 2.0 eq.) in acetic acid was added by syringe pump within a period of 12 hours to a solution of 2,2'-ethylenedianiline **4** (250 mg, 1.18 mmol, 1.0 eq.) in acetic acid/dichloromethane = 1/3 (60 mL) under rapid stirring. After the complete addition of the *m*CPBA solution, the mixture was stirred for at least one more hour. The volatiles were then removed under reduced pressure and dimethyl terephthalate (76.1 mg, 0.392 mmol, 0.33 eq.) and dichloromethane (25 mL) were added to the residue. The mixture was sonicated until all solids had dissolved. A sample (500 µL) was separated and the solvent removed under reduced pressure. The residue was dissolved in $CDCl_3$ and the solution analyzed by ^{1}H-NMR spectroscopy using a 1-scan experiment. The components of the mixture were quantified by integration of the following signals:

- dimethyl terephthalate: 3.95 ppm (s, 3H)
- 2,2'-ethylenedianiline (**4**): 6.68 ppm (dd, J = 7.7, 1.2 Hz, 2H)
- diazocine **2**: 6.82 ppm (dd, J = 7.7, 1.3 Hz, 2H)
- diazocine *N*-oxide **9**: 3.37 ppm (ddd, J = 14.2, 10.2, 5.5 Hz, 1H)

Table S10 Oxidant comparison.

Entry	Oxidant	Product **2**	Substrate **4**	Side-Product **9**
1	*m*CPBA	75%	1%	10%
2	peracetic acid	72%	3%	6%
3	magnesium monoperoxyphthalate (MMPP)	65%	2%	4%

All reactions were performed and analyzed according to the reference procedure for the oxidation of 2,2'-ethylenedianiline **4** with mCPBA, except for pure acetic acid as the solvent and the specified oxidants instead of mCPBA.

[a]For the titration of *m*CPBA and peracetic acid see "General information" in section "Synthetic procedures and characterization".

Table S11 Solvent screen.

Entry	Solvent	Product **2**	Substrate **4**	Side-Product **9**
1	acetic acid	75%	1%	10%
2	acetic acid/dichloromethane = 1/1	85%	1%	6%
3	acetic acid/dichloromethane= 1/3	87%	2%	6%
4	acetic acid/dichloromethane = 1/9	81%	3%	8%
5	acetic acid/toluene= 1/1	83%	2%	6%
6	acetic acid/toluene= 1/9	76%	4%	8%
7	acetic acid/acetonitrile = 1/1	83%	2%	6%
8	acetic acid/tetrahydrofuran = 1/1	68%	3%	10%
9	acetic acid/methanol = 1/1	37%	9%	24%
10	acetic acid/dimethylformamide = 1/1	75%	3%	8%

All reactions were performed and analyzed according to the reference procedure for the oxidation of 2,2'-ethylenedianiline **4** with mCPBA, except for using different solvent mixtures.

Table S12 Substrate and oxidant concentration.

Entry	Concentration	Product **2**	Substrate **4**	Side-Product **9**
1	0.3 M *m*CPBA 0.01 M substrate	85%	2%	6%
2	0.3 M *m*CPBA 0.02 M substrate	87%	2%	6%
3	0.3 M *m*CPBA 0.04 M substrate	85%	2%	6%
4	0.6 M *m*CPBA 0.04 M substrate	86%	1%	8%
5	0.6 M *m*CPBA 0.06 M substrate	79%	2%	8%
6	0.6 M *m*CPBA 0.08 M substrate	76%	3%	8%

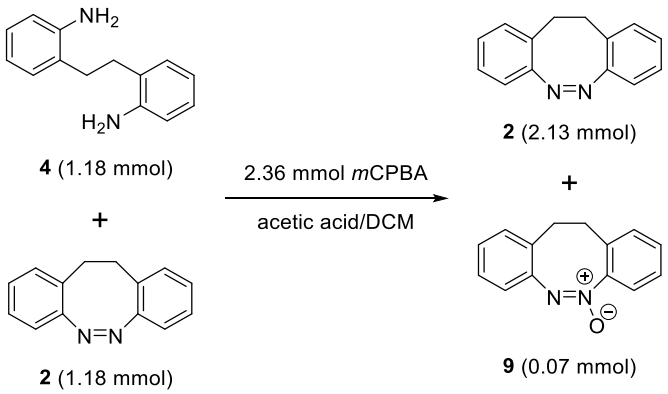
All reactions were performed and analyzed according to the reference procedure for the oxidation of 2,2'-ethylenedianiline **4** with mCPBA, except for varying the amount of solvent/concentration for both the reaction mixture and the oxidant solution.

Table S13 Other parameters.

Entry	Variation from reference procedure	Product **2**	Substrate **4**	Side-Product **9**
1	acetic acid/toluene= 1/1 reaction at 40 °C	82%	3%	4%
2	acetic acid/toluene= 1/1 reaction at 60 °C	78%	3%	4%
3	0.04 M substrate with 100 µL saturated $Cu(OAc)_2$ in acetic acid	60%	6%	8%

All reactions were performed and analyzed according to the reference procedure for the oxidation of 2,2'-ethylenedianiline **4** with mCPBA, except for the specified variations.

Investigation of the formation of azoxy side-product 9

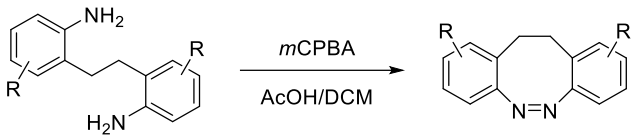


The reaction was performed and analyzed according to the reference procedure for the oxidation of 2,2'-ethylenedianiline **4** with *m*CPBA, but additionally diazocine **2** (1.18 mmol) was added to the reaction mixture before the addition of oxidant. Also, the reaction was performed at increased concentration (0.04 M) and with a more concentrated solution of *m*CPBA (0.6 M).

The analysis of the reaction mixture by ^{1}H-NMR spectroscopy showed that the amount of diazocine **2** (2.13 mmol) corresponded to a yield of 81% for the formation of the desired product **2** (0.95 mmol after subtraction of the amount of diazocine **2** that was added) from 2,2'-ethylenedianiline **4**. This value is close to the value to be expected (compare to Entry 4, Table S12), if the product **2** is not oxidized to side-product **9** in the presence of unreacted substrate **4**. Also, the quantity of the overoxidation product **9** (0.07 mmol corresponding to 6% of the amount of 2,2'-ethylenedianiline **4**) did not change. Thus, during the oxidation of dianiline **4** to diazocine **2** with *m*CPBA, the oxidation of diazocine **2** does not contribute strongly to the formation of azoxy compound **9**.

3.4 Synthetic recommendations

Oxidative cyclization of dianilines to diazocines



- While we did not experience any incidents of explosions during our experiments, we want to point out the potential hazards of concentrated solutions of *m*CPBA[17] and do not recommend using solutions with a higher concentration than 0.6 M. We advise caution when preparing and handling solutions of *m*CPBA.
- The solutions of *m*CPBA in acetic acid should be prepared freshly before use, as we observed a decreasing activity upon storage of the solutions. This loss of activity usually was accompanied by a change of color from colorless to yellow. In some cases, the *m*CPBA solution quickly turned yellow directly after preparation, which was related to the quality of the acetic acid. In such cases, the solutions were not suitable for use.
- Acetic acid was chosen as the solvent for the *m*CPBA solution as it was compatible with the plastic syringes that we used for the slow addition by syringe pump, which swell and leak after prolonged exposure to dichloromethane.
- Rapid and efficient stirring of the reaction mixture during addition of oxidant is essential to obtain good yields.
- For easier purification of the diazocine product by column chromatography, we recommend avoiding highly polar or poorly soluble derivatives in this step, if possible (Figure S9). For example, the silylated compound **64** was easy to purify compared to our initial target **SI-102**. Without the silyl protecting group, purification was tedious and plagued by bad separation during column chromatography. Compound **SI-103** was also difficult to purify, mainly due to its low solubility. In contrast, the less symmetric and more soluble analog **32** was easily purified.

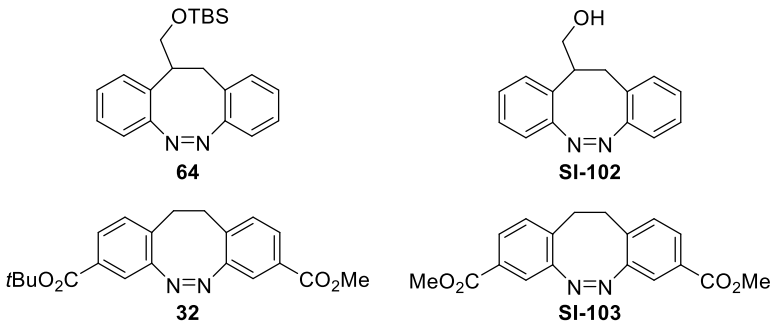
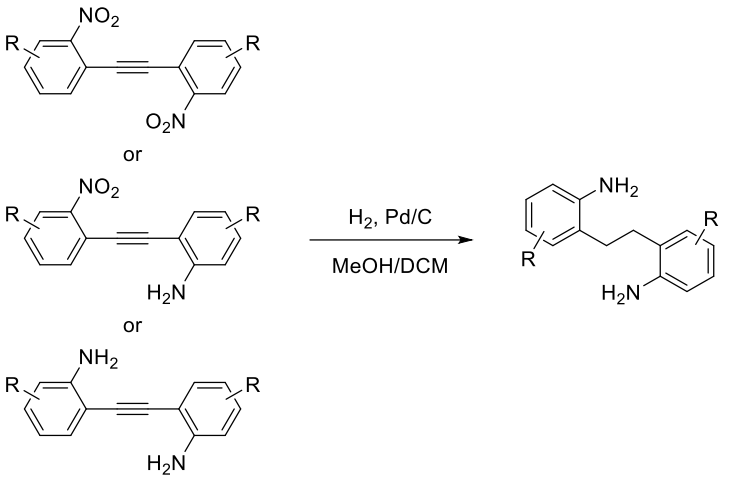


Figure S9 Examples of diazocines which were difficult to purify.

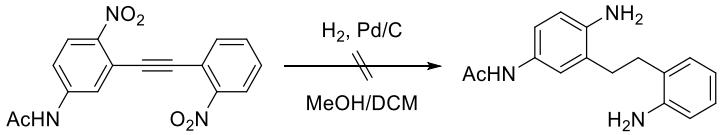
- We want to remind that, in addition to the examples given in the main text (see Scheme 4), it may be worthwhile to also investigate the one-batch addition approach in cases where a low or mediocre yield is observed with the slow addition method.
- We want to encourage the use of the oxidative cyclization even if a syringe pump for slow addition of the oxidant over an extended period is not available. While the yield can be expected to be lower with a faster addition, it may still be competitive to other methods and sufficient to obtain viable amounts of product (see Table S6).

Hydrogenation of diphenylacetylenes



- Early in our investigations to prepare ethylenedianilines by hydrogenation of nitro- or amino-substituted diphenylacetylenes, we often noticed issues with incomplete conversion or no reaction occurring at all. Typically, if the same material that had not reacted was recovered and resubjected to hydrogenation with a new batch of hydrogenation catalyst, good conversion was observed. We assumed that this was the result of catalyst poisoning by impurities remaining from the preceding reaction and found it could be avoided by using sufficiently pure substrate (for substrate purification see following section).
- In case of uncertainty about sufficient purity of a hydrogenation substrate, we recommend performing the hydrogenation first on a small test batch and purify the substrate again if no reaction or incomplete conversion is observed.
- After the hydrogenation we usually observed the presence of a strongly red colored byproduct, which appears regardless of starting material purity. This impurity was typically less polar than the dianiline product and in general could be removed without issues by column chromatography.

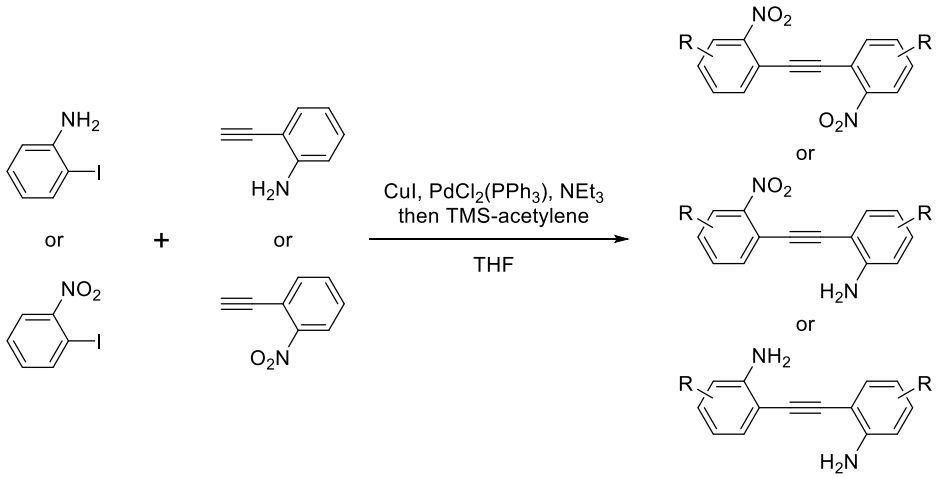
- For the hydrogenation of compound **SI-104** (Scheme S1), we observed that no desired product **SI-105** was formed, while the substrate was completely consumed. The obtained material could not be converted to the desired product by a second cycle of hydrogenation with fresh catalyst. This failed hydrogenation motivated us to prepare amino-substituted diazocines by late-stage modification of suitably functionalized diazocine precursors (see Scheme 5, main text), rather than introducing the amino group early in the synthesis.



SI-104 **SI-105**

Scheme S1 Failed hydrogenation of diphenylacetylene **SI-104**.

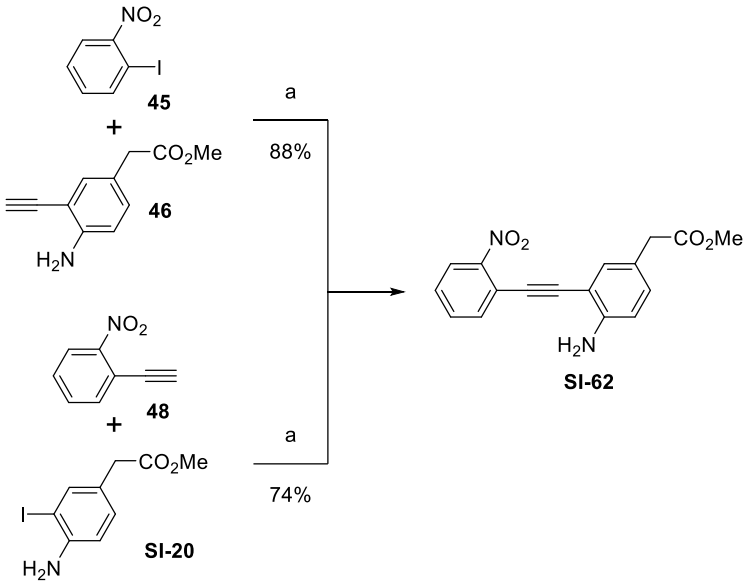
Sonogashira coupling to form diphenylacetylenes



- Apart from the three possible combinations of Sonogashira coupling described in the main text (see Scheme 6, main text), we also prepared a number of diphenylacetylenes by coupling of 2-nitrophenylacetylene **48** with a 2-iodoaniline (**SI-57**, **SI-59**, **SI-61**, **SI-65**, see section "Synthetic procedures and characterization"). The reason that we did prepare these compounds from building block **48**, was to avoid having to prepare each individual 2-aminophenylacetylene and the easy access to large amounts of compound **48**.

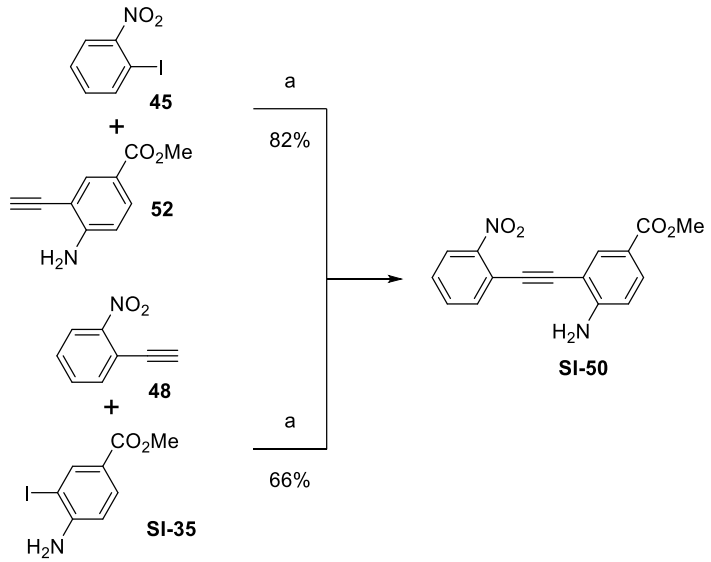
  Due to the slow decomposition of compound **48** under the Sonogashira coupling conditions, this approach is less efficient than the coupling of 2-iodonitrobenzenes with 2-aminophenylacetylenes. We did not observe decomposition of any of the 2-aminophenylacetylenes employed in this work (**SI-25**, **SI-28**, **46**, **52**, see section "Synthetic procedures and characterization") during Sonogashira coupling.

We also directly compared the results of the 2-nitrophenylacetylene and 2-aminophenylacetylene approach in two cases (Schemes S2 and S3), both of which verified that the 2-aminophenylacetylene route was superior.



a) $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, rt; then TMS acetylene.

Scheme S2 Comparison of the 2-nitrophenylacetylene (compounds **48** and **SI-20**) and 2-aminophenylacetylene approach (compounds **45** and **46**) – alternative Sonogashira coupling routes to diphenylacetylene **SI-62**.



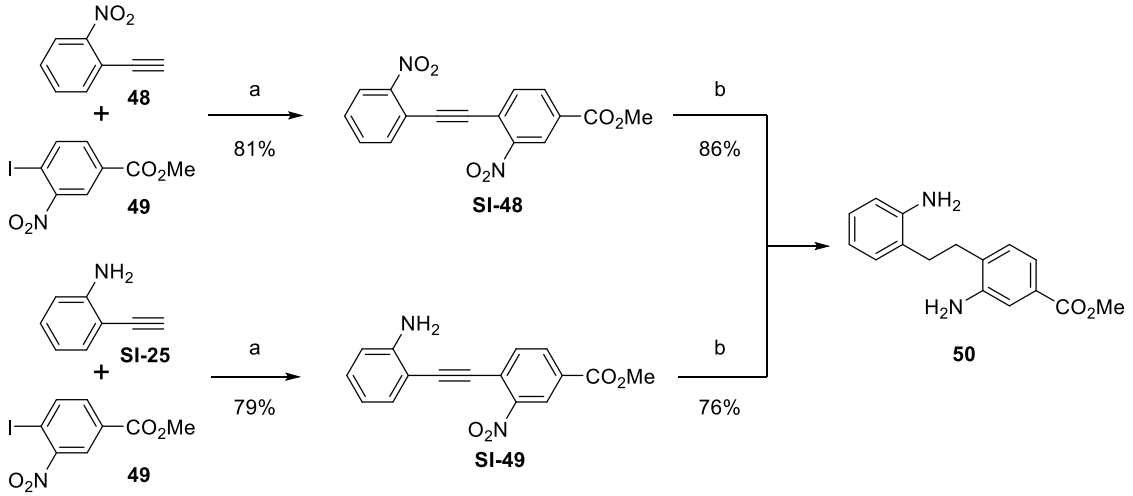
a) $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, rt; then TMS acetylene.

Scheme S3 Comparison of the 2-nitrophenylacetylene (compounds **48** and **SI-35**) and 2-aminophenylacetylene approach (compounds **45** and **52**) – alternative Sonogashira coupling routes to diphenylacetylene **SI-50**.

- Compared to the Sonogashira coupling of a 2-nitrophenylacetylene with a 2-iodoaniline, the coupling of a 2-nitrophenylacetylene with a 2-iodonitrobenzene undergoes less decomposition of the 2-nitrophenylacetylene building block. This is due to the increased overall reaction rate resulting from the higher reactivity of a 2-iodonitrobenzene in relation to a 2-iodoaniline. However, comparing the coupling of a 2-nitrophenylacetylene with a 2-iodonitrobenzene and the coupling of a 2-aminophenylacetylene with a 2-iodonitrobenzene is more complicated, as these reactions give different types of products. Therefore, the actual efficiency also depends on the ease of purification and the yields of the following reactions. For one example we directly compared these two routes, which we will refer to as the 2,2'-dinitrodiphenylacetylene and 2-amino-2'-nitro-diphenylacetylene approach in the following.

  For the investigated example (Scheme S4), the 2,2'-dinitrodiphenylacetylene approach proved slightly better, mostly due to a higher yield for the hydrogenation to ethylenedianiline **50** from intermediate **SI-48** than from intermediate **SI-49**. The coupling reaction afforded almost identical yields based on isolated amounts of **SI-48** and **SI-49**.

  The main reasons to choose the 2,2'-dinitrodiphenylacetylene route are the availability of the respective aryl iodide building blocks and the potentially advantageous properties of the 2,2'-dinitrodiphenylacetylenes with respect to purification (see below).



a) $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, rt; then TMS acetylene. b) H_2, Pd/C, MeOH/DCM.

Scheme S4 Comparison of 2,2'-dinitrodiphenylacetylene (via compound **SI-48**) and 2-amino-2'-nitro-diphenylacetylene approach (via compound **SI-49**) – alternative Sonogashira coupling/hydrogenation routes to ethylenedianiline **50**.

- In many cases (**SI-39**, **SI-41**, **SI-43**, **SI-45**, **SI-47**, **SI-59**, **SI-61**, see section "Synthetic procedures and characterization"), a reduced yield for Sonogashira couplings involving 2-nitrophenylacetylene **48** resulted from issues during product purification. This was due to the problematic removal of a dimerization side-product formed from compound **48**. We presume that either switching to a 2-amino-2'-nitro-diphenylacetylene approach by replacing 2-nitrophenylacetylene **48** with 2-aminophenylacetylene **SI-25** (**SI-39**, **SI-41**, **SI-43**, **SI-45**, **SI-47**) or switching from the 2-nitrophenylacetylene to the 2-aminophenylacetylene approach (**SI-59**, **SI-61**) will give significantly better results.
- During our preliminary investigations, a major issue that arose during the purification of the Sonogashira coupling products was the removal of unreacted aryl iodide. This was greatly simplified by converting unreacted aryl iodide to the corresponding TMS-phenylacetylene, which was in general easy to separate from the desired product. We want to point out that the addition of TMS-acetylene might not be necessary in all cases, especially if the aryl iodide is efficiently converted to the desired product and little aryl iodide is remaining. We did not investigate if the addition of TMS-acetylene has a detrimental effect in these cases.
- Regarding purification of the coupling products, we observed that after an aqueous workup a combination of column chromatography in dichloromethane followed by additional washing with an appropriate solvent, recrystallization, trituration or precipitation afforded very pure diphenylacetylenes in good yields and the successive hydrogenation proceeded without any issues.

  Alternatively, purification by only column chromatography in ethyl acetate/hexanes can be a viable alternative, if the respective diphenylacetylene is soluble enough in ethyl acetate/hexanes and too soluble for other methods of purification. Compound **SI-62** for example was purified in this way. Nevertheless, we recommend planning the synthesis of a diazocine in a way that the respective diphenylacetylene intermediate is soluble enough for efficient column chromatography but still amenable to crystallization/trituration.
- Depending on the nature of the *ortho*-substituents, the Sonogashira coupling products showed a distinctive behavior with respect to solubility and stability (Figure S10). 2-amino-2'-nitro-diphenylacetylenes (e.g. **SI-49** and **SI-62**) are strongly colored (orange to violet-red) and were generally sufficiently soluble to be purified efficiently by column chromatography. Additionally, many of these compounds could be obtained in very high purity by recrystallization from toluene. We did not observe any signs of decomposition for 2-amino-2'-nitro-diphenylacetylenes.

  Compared to 2-amino-2'-nitro-diphenylacetylenes the 2,2'-dinitrodiphenylacetylenes (e.g. **SI-48**) are less colored (colorless to yellow) and were also efficiently purified by

column chromatography. Washing the material obtained after chromatography with methanol proved to be a good method of purification for many compounds of this type, affording the product in high purity and good yields. Based on our observations, we presume that the 2,2'-dinitrodiphenylacetylenes tend to be less soluble than 2-amino-2'-nitro-diphenylacetylenes. This can be an advantage and was usually not a problem, except in extreme cases like phthalimide **SI-106** which was virtually insoluble in all solvents that we tried. We observed the formation of discoloration upon extended exposure to ambient light for some 2,2'-dinitrodiphenylacetylenes.

Finally, 2,2'-diaminodiphenylacetylenes (e.g. **SI-67**) are the least robust intermediates en route to diazocines. We found them to be more problematic to purify by chromatography and recrystallization or similar methods were usually not possible. Still, we found a noteworthy exception in compound **SI-67**, which proved to be a good synthetic intermediate that could be easily purified by precipitation from dichloromethane solution. In fact, we had prepared non-symmetric diester **SI-67** as a more soluble alternative to the symmetric analog **SI-107**, which proved impractical due to a very low solubility. We observed cyclization to indoles as common issue of 2,2'-diaminodiphenylacetylenes, thus we only recommend preparing 2,2'-diaminodiphenylacetylenes which are carrying additional electron-withdrawing substituents, such as example **SI-67**.

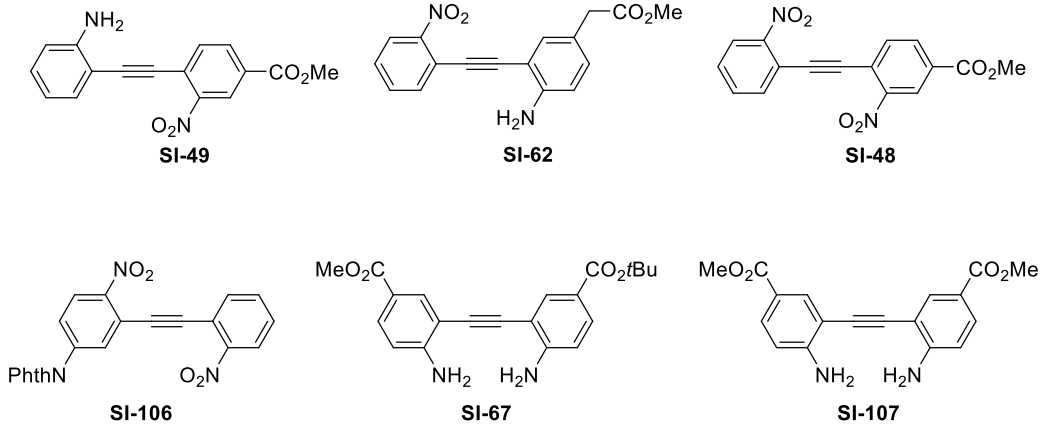


Figure S10 Examples of diphenylacetylenes with different levels of solubility.

- For the phenylacetylene building blocks we advise not to amplify their intrinsic tendency toward side reactions (Figure S11). Stated differently, this means that 2-nitrophenylacetylenes carrying additional electron-withdrawing substituents (e.g. compound **SI-108**) or 2-aminophenylacetylenes carrying additional electron-donating groups (e.g. compound **SI-109**) should possibly be avoided. For derivative **SI-108** we observed a decreased stability compared to unsubstituted compound **48**. In this case a better building block was compound **SI-28**, where the amino and ester group

compensate each other. A similar compensation exists for compound **SI-34**. While we did not investigate the corresponding analog **SI-109**, we expect it to be less stable than compound **SI-25**.

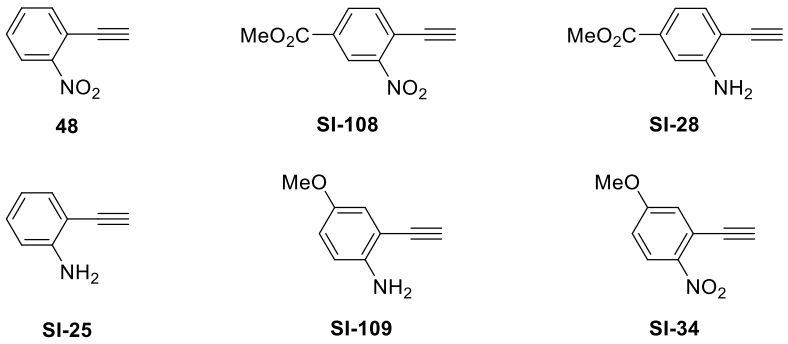


Figure S11 Phenylacetylene building blocks with different levels of stability.

- In conclusion, we recommend approaching the synthesis of a diphenylacetylenes in the following way: First, consider the availability and stability of building blocks. Second, if there is no clear reason not to follow the 2-amino-2'-nitro-diphenylacetylene route, investigate this route first. Third, if there are issues during purification, then attempt to modify your product to modulate the solubility and allow for a more efficient purification (e.g. change protecting groups or switch from a 2-amino-2'-nitro- to a 2,2'-dinitrodiphenylacetylene).

3.5 Computational data

Computational methods

Generation of initial set of structures

For both (*Z*) and (*E*) isomer of diazonine **66** an initial set of conformer structures was obtained by a conformer search (no solvent, 200 kJ/mol energy window, mixed torsional/low-mode sampling) at the OPLS3e[24] force field level as implemented in the MacroModel applet within the Schrödinger suite of programs (Release 2019-1).[25]

Preoptimization and generation of set of conformer structures

The sets of structures obtained at the force-field level were optimized at the B3LYP[26]/def2-TZVP(-f)[27] level and an initial selection of structures was performed. If several of the initial structures had converged to the same optimized structure, then the duplicates were removed from resulting set of optimized structures. If two enantiomeric structures were observed, then one was removed from the set of structures. Finally, structures with a relative energy higher than 50 kJ/mol compared to the lowest energy structure of the set were removed.
For the remaining structures the vibrational frequencies were calculated to confirm that energy minimum structures were obtained. If an imaginary frequency was observed, then the frequency analysis (and the optimization, if necessary) was repeated with increased grid accuracy and tighter convergence thresholds to confirm that the imaginary frequency did not result from numerical or convergence issues. If the imaginary frequency was still observed, then the structure was deformed in both directions along the corresponding normal mode and the resulting structures were optimized. After the results were confirmed to be energy minimum structures, the obtained structures were included in the set of optimized structures, except if they were duplicates of structures that were already part of the set.
These calculations were performed with the program ORCA[28] (Version 4.1.2) using the D3BJ dispersion correction[29] and the RI-JK (optimization) or RIJCOSX (frequency analysis) approximation[30] with the def2/JK auxiliary basis set[31] as well as standard convergence thresholds and grid accuracy (except for the situations involving imaginary frequencies).

Calculation of thermochemical corrections

The sets of structures obtained at the B3LYP/def2-TZVP(-f) level were optimized at the PBE0[32]/def2-TZVP level, followed by calculation of the corrections (zero-point vibrational energy, thermal vibrational/rotational/translational corrections, enthalpy correction, vibrational/rotational/translational entropic contributions) necessary to calculate thermochemical data (298.15 K, 1.00 atm).
These calculations were performed with the program ORCA (Version 4.1.2) using the D3BJ dispersion correction, the RIJCOSX approximation with the def2/JK auxiliary basis set and tight convergence thresholds (TIGHTOPT, TIGHTSCF) as well as more accurate grid settings (GRID7, NOFINALGRID, GRIDX8, NOFINALGRIDX).

Final structure optimization, energies and selection of structures

The structures optimized at the PBE0/def2-TZVP level were further optimized at the DSD-PBEP86[33]/def2-TZVP level (see Appendix 0), followed by the calculation of energies at the DSD-PBEP86/def2-QZVPP level. Based on these energies, structures within a window

of 20 kJ/mol were selected for further investigation.
Energies in the solvent DMSO (dielectric constant 47.2, refractive index 1.479) were calculated with the C-PCM continuum solvation model[34] based on gas-phase structures. These calculations were performed with the program ORCA (Version 4.1.2) using the D3BJ dispersion correction, the RIJCOSX approximation with the def2/JK auxiliary basis set, the RI-MP2 approximation[35] with the def2-TZVP/C (optimization) or def2-QZVPP/C (energies) auxiliary basis sets[36] as well as tighter convergence thresholds (TIGHTOPT, TIGHTSCF) and more accurate grid settings (GRID7, NOFINALGRID, GRIDX8, NOFINALGRIDX).

Calculation of UV-Vis spectroscopic data

Absorption wavelengths λ and oscillator strengths f_{osc} were calculated based on DSD-PBEP86/def2-TZVP structures at the CAM-B3LYP[37]/def2-TZVP level.
The values in the solvent DMSO (dielectric constant 47.2, refractive index 1.479) were calculated with the C-PCM continuum solvation model based on gas-phase structures. These calculations were performed with the program ORCA (Version 4.1.2) using the RIJCOSX approximation with the def2/JK auxiliary basis set, tighter convergence thresholds (VERYTIGHTSCF), more accurate grid settings (GRID7, NOFINALGRID, GRIDX8, NOFINALGRIDX) and the KDIIS algorithm.

Calculation of 1H-NMR spectroscopic data

^{1}H-NMR isotropic chemical shielding values σ_{iso} for the solvent chloroform (dielectric constant 4.9, refractive index 1.45) were calculated with the C-PCM continuum solvation model based on gas-phase DSD-PBEP86/def2-TZVP structures at the M06-L[38]/pcSseg-2[39] level.
These calculations were performed with the program ORCA (Version 4.1.2) using the RI approximation[40] with the def2/JK auxiliary basis set, tighter convergence thresholds (VERYTIGHTSCF) and more accurate grid settings (GRID7, NOFINALGRID).

Thermochemical data

Table S14 Calculated thermochemical data for the selected low energy conformers of the (*E*) and (*Z*) isomers of diazonine **66** based on gas-phase energies.

Structure	E_{abs}[a] [Hartree]	E_{rel}[a] [kJ/mol]	$(G-E)_{abs}$[b] [Hartree]	$E_{abs} + (G-E)_{abs} = G_{abs}$ [Hartree]	G_{rel} [kJ/mol]
(*Z*)-**66**	-688.559471800693	0.0	0.2183102	-688.3411616	0.0
(E)-**66** Conformer 1	-688.555630275080	10.1	0.2185064	-688.3371239	10.6
(E)-**66** Conformer 2	-688.553652403457	15.3	0.2188192	-688.3348332	16.62

[a]DSD-PBEP86/def2-QZVPP energies for DSD-PBEP86/def2-TZVP structures.
[b]PBE0/def2-TZVP thermochemical corrections.

Table S15 Calculated thermochemical data for the selected low energy conformers of the (*E*) and (*Z*) isomers of diazonine **66** based on energies in DMSO.

Structure	E_{abs}[a] [Hartree]	E_{rel}[a] [kJ/mol]	$(G-E)_{abs}$[b] [Hartree]	$E_{abs} + (G-E)_{abs} = G_{abs}$ [Hartree]	G_{rel} [kJ/mol]
(*Z*)-**66**	-688.571630180346	0.0	0.2183102	688.3533200	0.0
(E)-**66** Conformer 1	-688.565195322249	16.9	0.2185064	-688.346689	17.4
(E)-**66** Conformer 2	-688.563751179241	20.7	0.2188192	-6883449320	22.0

[a]C-PCM(DMSO)-DSD-PBEP86/def2-QZVPP energies for DSD-PBEP86/def2-TZVP structures.
[b]PBE0/def2-TZVP thermochemical corrections.

UV-Vis spectroscopic data

Table S16 Calculated UV-Vis spectroscopic data (CAM-B3LYP/def2 TZVP) for the selected low energy conformers of the (*E*) and (*Z*) isomers of diazonine **66** in the gas phase.

Structure	λ_1 [nm]	λ_2 [nm]	λ_3 [nm]	$f_{osc,1}$	$f_{osc,2}$	$f_{osc,3}$
(*Z*)-**66**	404.5	267.2	255.1	0.00173178	0.00089365	0.00306788
(E)-**66** Conformer 1	443.1	298.8	265.9	0.00137011	0.38348388	0.03296371
(E)-**66** Conformer 2	491.9	275.2	267.5	0.02664142	0.01049769	0.14249755

[a]DSD-PBEP86/def2-QZVPP energies for DSD-PBEP86/def2-TZVP structures.
[b]PBE0/def2-TZVP thermochemical corrections.

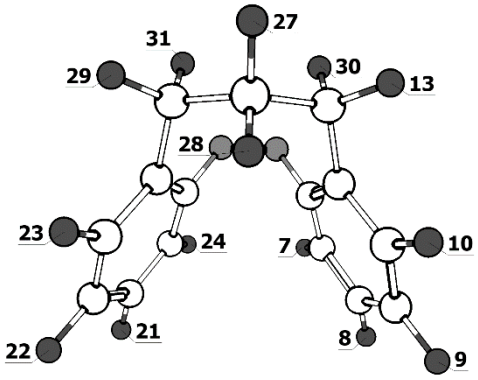
Table S17 Calculated UV-Vis spectroscopic data (CAM-B3LYP/def2 TZVP) for the selected low energy conformers of the (*E*) and (*Z*) isomers of diazonine **66** in DMSO.

Structure	λ_1 [nm]	λ_2 [nm]	λ_3 [nm]	$f_{osc,1}$	$f_{osc,2}$	$f_{osc,3}$
(*Z*)-**66**	402.0	287	285.5	0.00164899	0.00064917	0.00204008
(E)-**66** Conformer 1	438.0	311.6	280.1	0.00148663	0.35473728	0.03619080
(E)-**66** Conformer 2	485.7	288.9	278.9	0.02881543	0.01212332	0.12090563

[a]DSD-PBEP86/def2-QZVPP energies for DSD-PBEP86/def2-TZVP structures.
[b]PBE0/def2-TZVP thermochemical corrections.

^{1}H-NMR spectroscopic data

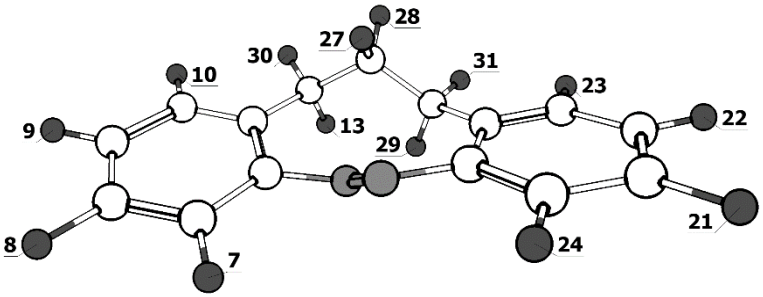
Table S18 Calculated ^{1}H-NMR spectroscopic data (M06-L/pcSseg-2) for the lowest energy conformer of the (*Z*) isomer of diazonine **66** in chloroform and comparison to experimental values for the thermally preferred isomer.



Nucleus[a]	σ_{iso}[b] [ppm]	$\sigma_{iso,TMS} - \sigma_{iso} = \delta$[c] [ppm]	δ_{avg}[d] [ppm]	δ_{exp}[e] [ppm]	$\delta_{avg} - \delta_{exp}$ [ppm]
28	30.675	1.345	1.34	1.37 (1)	-0.03
27	29.903	2.117	2.12	2.15 (1)	-0.03
30	29.817	2.203	2.21	2.39 (2)	-0.19
31	29.810	2.210	- - -	- - -	- - -
13	29.369	2.651	2.65	2.71 (2)	-0.06
29	29.368	2.652	- - -	- - -	- - -
24	25.584	6.436	6.44	6.38 (2)	0.06
7	25.576	6.444	- - -	- - -	- - -
9	25.010	7.010	7.01	6.89 (2)	0.12
22	25.010	7.010	- - -	- - -	- - -
21	24.970	7.050	7.05	6.93 (2)	0.12
8	24.967	7.053	- - -	- - -	- - -
10	24.925	7.095	7.09	6.96 (2)	0.13
23	24.925	7.095	- - -	- - -	- - -

[a]Numbering according to the xyz structural data given in a previous section. All nuclei (C, H, N) are included in the numbering. The numbering starts with 1.
[b]Isotropic chemical shielding.
[c]Chemical shift relative to tetramethylsilane.
[d]Averaged chemical shift for nuclei that are equivalent due to C_s symmetry.
[e]Measured at 600 MHz in $CDCl_3$, the corresponding number of protons is given in parentheses.

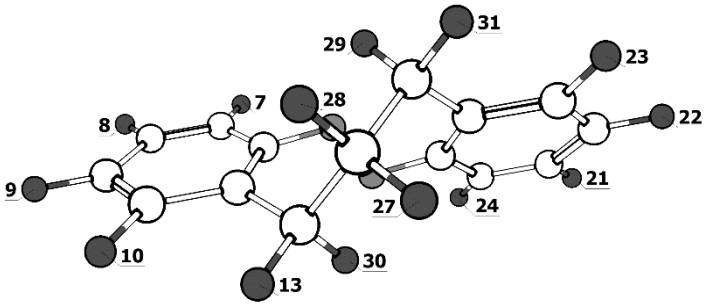
Table S19 Calculated ^{1}H-NMR spectroscopic data (M06-L/pcSseg-2) for the lowest energy conformer of the (*E*) isomers of diazonine **66** (Conformer 1) in chloroform.



Nucleus[a]	σ_{iso}[b] [ppm]	$\sigma_{iso,TMS} - \sigma_{iso} = \delta$[c] [ppm]
27	31.593	0.43
28	29.745	2.27
30	28.988	3.03
31	28.919	3.10
13	29.025	2.99
29	28.811	3.21
10	24.549	7.47
23	24.571	7.45
9	24.506	7.51
22	24.48	7.54
21	24.398	7.62
8	24.534	7.49
7	24.58	7.44
24	23.85	8.17

[a]Numbering according to the xyz structural data given in a previous section. All nuclei (C, H, N) are included in the numbering. The numbering starts with 1.
[b]Isotropic chemical shielding.
[c]Chemical shift relative to tetramethylsilane.

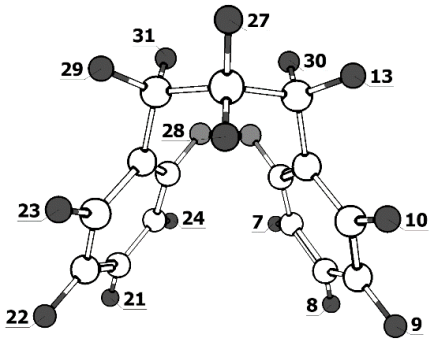
Table S20 Calculated ^{1}H-NMR spectroscopic data (M06-L/pcSseg-2) for the second lowest energy conformer of the (*E*) isomers of diazonine **66** (Conformer 2) in chloroform.



Nucleus[a]	σ_{iso}[b] [ppm]	$\sigma_{iso,TMS} - \sigma_{iso} = \delta$[c] [ppm]
27	30.123	1.90
28	30.122	1.90
13	29.819	2.20
31	29.818	2.20
30	28.451	3.57
29	28.442	3.58
22	24.627	7.39
9	24.626	7.39
10	24.531	7.49
23	24.53	7.49
8	24.46	7.56
21	24.46	7.56
7	24.311	7.71
24	24.31	7.71

[a]Numbering according to the xyz structural data given in a previous section. All nuclei (C, H, N) are included in the numbering. The numbering starts with 1.
[b]Isotropic chemical shielding.
[c]Chemical shift relative to tetramethylsilane.

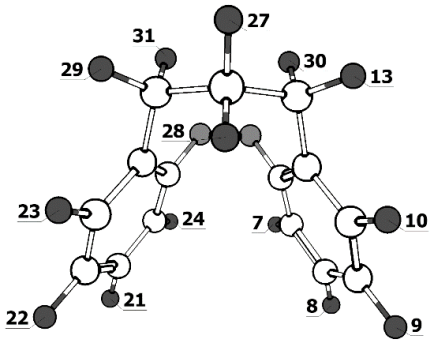
Table S21 Calculated ^{1}H-NMR coupling constants for the propylene fragment of the lowest energy conformer of the (*Z*) isomer of diazonine **66** and comparison to experimental values for the thermally preferred isomer.



Coupling nuclei[a]	$^{3}J_{calc}$ (ϕ)[b]	$^{3}J_{exp}$ (δ_{exp})[c]
27-13 and 27-29	6.3 Hz (44.9°)	5.6 Hz (2.15 ppm), 5.7 Hz (2.71 ppm)
27-30 and 27-31	2.8 Hz (70.6°)	not observed
28-13 and, 28-29	2.8 Hz (70.8°)	not observed
28-30 and 28-31	12.9 Hz (173.7°)	13.1 Hz (1.37 ppm) 13.2 Hz (2.39 ppm)

[a]Numbering according to the xyz structural data given in a previous section. All nuclei (C, H, N) are included in the numbering. The numbering starts with 1.
[b]Coupling constants calculated with the equation[41] 3JHCCH = 7 – cos φ + 5 cos 2φ based on DSD PBEP86/def2-TZVP structures. The corresponding unsigned dihedral angles are given in parentheses.
[c]Experimental 3J coupling constants with chemical shifts of the corresponding signals in parentheses.

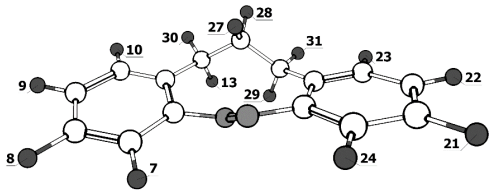
Table S22 Assignment of experimental ^{1}H-NMR (600 MHz, $CDCl_3$) signals and coupling constants for the propylene fragment of the thermally preferred isomer of diazonine **66** based on calculated coupling constants (see Table S21).



δ_{exp} [ppm]	Multiplicity	^{2}J (nuclei)	^{3}J (nuclei)	Integral	Nuclei[a]
2.71	dd	13.5 Hz (29-31, 13-30)	5.7 Hz (13-27, 27-29)	2	13, 29
2.39	t	13.2 (29-31, 13-30)	13.2 (28-30, 28-31)	2	30, 31
2.15	dt	12.0 Hz (27-28)	5.6 (13-27, 27-29)	1	27
1.37	q	13.1 Hz (27-28)	13.1 (28-30, 28-31)	1	28

[a]Numbering according to the xyz structural data given in a previous section. All nuclei (C, H, N) are included in the numbering. The numbering starts with 1.

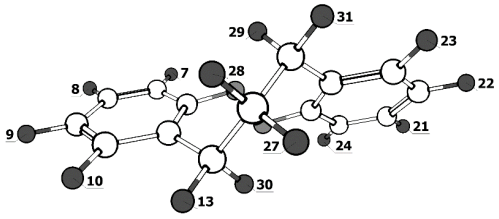
Table S23 Calculated ^{1}H-NMR coupling constants for the propylene fragment of the lowest energy conformer of the (*E*) isomers of diazonine **66** (Conformer 1).



Coupling nuclei[a]	$^{3}J_{calc}$ (ϕ)[b]
27-13	10.0 Hz (147.7°)
27-29	5.8 Hz (124.6°)
27-30,	2.3 Hz (97.3°)
27-31	5.1 Hz (120.4°)
28-13	2.3 Hz (98.0°)
28-29	5.1 Hz (120.8°)
28-30	10.2 Hz (17.0°)
28-31	10.9 Hz (5.8°)

[a]Numbering according to the xyz structural data given in a previous section. All nuclei (C, H, N) are included in the numbering. The numbering starts with 1.
[b]Coupling constants calculated with the equation[41] 3JHCCH = 7 – cos φ + 5 cos 2φ based on DSD PBEP86/def2-TZVP structures. The corresponding unsigned dihedral angles are given in parentheses.

Table S24 Calculated ^{1}H-NMR coupling constants for the propylene fragment of the second lowest energy conformer of the (*E*) isomers of diazonine **66** (Conformer 2).



Coupling nuclei[a]	$^{3}J_{calc}$ (ϕ)[b]
27-13,	4.6 Hz (55.7°)
27-31	4.3 Hz (57.8°)
27-29	12.8 Hz (171.7°)
27-30	4.2 Hz (58.2°)
28-13	4.3 Hz (58.0°)
28-31	4.6 Hz (55.8°)
28-29	4.3 Hz (58.1°)
28-30	12.8 Hz (171.8°)

[a]Numbering according to the xyz structural data given in a previous section. All nuclei (C, H, N) are included in the numbering. The numbering starts with 1.
[b]Coupling constants calculated with the equation[41] 3JHCCH = 7 – cos φ + 5 cos 2φ based on DSD PBEP86/def2-TZVP structures. The corresponding unsigned dihedral angles are given in parentheses.

3.6 Single-crystal X-Ray analysis of compound 38

The content of this section has not been included in this thesis.

4 References

For Sections 1 (Introduction) and 2 (Oxidative Approach Enables Efficient Access to Cyclic Azobenzenes)

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For Section 3 (Supporting information for: Oxidative Approach Enables Efficient Access to Cyclic Azobenzenes)

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Experimental Section

1 **Part I:** Synthetic studies toward A-74528

General information

Experimental conditions

All reactions were conducted with magnetic stirring at room temperature unless otherwise noted. Reactions at elevated temperatures were performed using an oil bath or aluminum block as the heat transfer medium, with the reported temperature corresponding to that of the heat transfer medium.

Chemicals

All chemicals were obtained from common vendors and used without further purification unless otherwise noted. With the exception of dimethyl sulfoxide, which was purchased from Oakwood Chemical in standard quality, all solvents were purchased with "certified ACS" or higher quality. Anhydrous solvents were prepared with a solvent purification system by filtration of HPLC grade solvents through alumina according to the method of Grubbs[1] or purchased from Acros Organics in AcroSeal™ bottles. Dess-Martin periodinane was prepared according to literature procedure.[2]

Chromatography

Retardation factors were determined by analytical thin-layer chromatography performed on pre-coated glass plates from Millipore Sigma (TLC Silica Gel 60 Plates, 250 µm layer thickness, F254 fluorescence indicator), with visualization by exposure to ultraviolet light (254 nm) or by staining with a basic potassium permanganate solution.
Column chromatography was performed with silica gel obtained from Millipore Sigma (Geduran® Si 60, 40 – 63 µm) or from Teledyne Isco (RediSep® Gold, 20 – 40 µm, spherical). Column chromatography was either performed manually or with an automated chromatography system (Teledyne Isco CombiFlash®).
High-performance liquid chromatography was performed with HPLC grade solvents on an Agilent 1260 Infinity series system (Preparative Pump, Preparative Pump Gradient Extension, Preparative Autosampler, Infinity II Diode Array Detector WR, 1290 Infinity Valve Drive, Fraction Collector prep scale) equipped with a Phenomenex Gemini® LC Column (5 µm, C18, 110 Å, 150×10 mm) and Phenomenex Gemini® SecurityGuard™ Prep Cartridge (C18, 10×10mm ID).

Nuclear magnetic resonance spectroscopy

Proton and carbon (^{1}H- and ^{13}C-) NMR spectra were recorded on Bruker Avance III (600/150 MHz, with TCI Cryoprobe™) and Avance III HD (400/100 MHz, with BBFO Cryoprobe™) spectrometers. All spectra were recorded at a temperature of 25 °C in 5 mm tubes in deuterated solvents purchased from Cambridge Isotope Laboratories, Inc. (chloroform-d or $CDCl_3$, 99.8% D; dimethyl sulfoxide-d_6 or DMSO-d_6, 99.9% D; methanol-d_4 or CD_3OD, 99.8% D; acetone-d_6, 99.9% D). For ^{1}H-NMR spectra chemical shifts (δ) in parts per million (ppm) relative to tetramethylsilane (δ = 0 ppm) are reported using the residual protic solvent ($CHCl_3$ in $CDCl_3$: δ = 7.26 ppm, DMSO-d_5 in DMSO-d_6: δ = 2.50 ppm, CHD_2OD in CD_3OD: δ = 3.31 ppm, acetone-d_5 in acetone-d_6: δ = 2.05 ppm) as an internal reference. For ^{13}C-NMR spectra, chemical shifts in ppm relative to tetramethylsilane (δ = 0 ppm) are reported using the central resonance of the solvent signal ($CDCl_3$: δ = 77.16 ppm, DMSO-d_6:

δ = 39.52 ppm, CD_3OD: δ = 49.00 ppm, acetone-d_6: δ = 29.84 ppm) as an internal reference. The abbreviations used for multiplicities and descriptors are s = singlet, d = doublet, t = triplet, q = quartet or combinations thereof, m = multiplet and br = broad. Patterns that cannot be clearly identified due to second-order effects, overlapping signals or for other reasons are referred to as multiplet or broad. The numbering used in the assignments of signals to nuclei refers to the numbering depicted in the corresponding reaction schemes and does not follow a specific convention. The assignments are based chemical shifts, coupling patterns and two-dimensional NMR spectra (COSY, HSQC, HMBC, NOESY), which were measured under the same conditions as the one-dimensional spectra. Diastereotopic protons were labeled as H_A and H_B with H_A corresponding to the more downfield-shifted signal. NMR spectral data was analyzed with the program MestreNova 12.0.3 developed by Mestrelab Research S. L.

Infrared spectroscopy

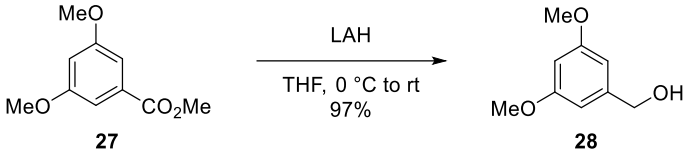
Infrared spectra were recorded on a Thermo-Fisher Nicolet 6700 Fourier Transform-IR spectrometer with Smart iTR™ attenuated total reflectance unit. Samples were either measured as a solid or as a thin film formed from a solution after evaporation of the solvent. IR data is reported as wave numbers with the unit cm^{-1}. The window of acquisition was 4000 to 700 cm^{-1}.

Mass spectrometry

A Shimadzu TQ 8040 GC-MS/FID systems with electron ionization ion source was used to obtain low-resolution mass spectra. High-resolution mass spectra using either an electrospray ionization or atmospheric pressure chemical ionization ion source were obtained with an Agilent 6224 Accurate Mass time-of-flight LC/MS system. High-resolution mass spectra using an electron ionization source were measured on a Thermo Finnigan MAT 95 system at the analytic section of the Department of Chemistry of the Ludwig Maximilian University of Munich. All reported data refers to positive ionization mode.

Experimental procedures and analytical data

Benzyl alcohol 28



To a suspension of lithium aluminum hydride (19.3 g, 510 mmol, 1 eq.) in anhydrous tetrahydrofuran (250 mL) under nitrogen atmosphere was added ester **27** (100 g, 510 mmol) in small portions within approx. 1 hour under ice bath cooling. After the addition was complete, the cooling bath was removed and the mixture was stirred overnight at room temperature. Then, ethyl acetate (50 mL), methanol (25 mL), water (200 mL) and diethyl ether (200 mL) were added carefully in the specified order and the mixture was stirred vigorously for 10 minutes. The resulting suspension was filtered, the solids were washed with several portions of diethyl ether (4×100 mL) and then discarded. The filtrate was washed with saturated, aqueous sodium chloride (200 mL), dried over magnesium sulfate and evaporated under reduced pressure to afford benzyl alcohol **28** (83.1 g, 494 mmol, 97%) as white solid, which was used without further purification.

R_f = 0.29 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 6.52 (dd, J = 2.3, 0.7 Hz, 2H), 6.38 (t, J = 2.3 Hz, 1H), 4.63 (s, 2H), 3.79 (s, 6H).

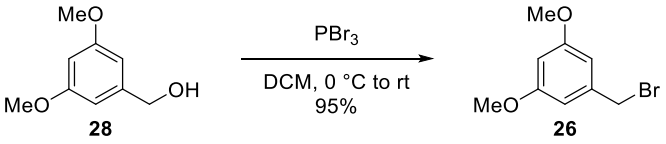
^{13}C-NMR (100 MHz, $CDCl_3$): 161.1, 143.5, 104.7, 99.8, 65.5, 55.5.

IR: 3352, 3000, 2939, 2838, 1595, 1458, 1428, 1345, 1318, 1295, 1262, 1203, 1148, 1058, 1035, 993, 952, 940, 918, 830, 703.

HRMS (APCI): $C_9H_{13}O_3$ [M+H] calc. 169.0859, found 169.0865.

The spectroscopic data agrees with previously reported values.[3]

Benzyl bromide 26



Phosphorus tribromide (20.3 mL, 214 mmol, 1.2 eq.) was added dropwise under ice bath cooling to a solution of alcohol **28** (30.0 g, 178 mmol) in anhydrous dichloromethane (450 mL) under nitrogen atmosphere. The mixture was stirred overnight with warming to room temperature. Then, saturated, aqueous sodium bicarbonate (300 mL) was added under ice bath cooling and the mixture was stirred carefully for approximately one hour, until no further gas evolved. During this time, the stirring rate was adjusted to keep the evolution of gas at a moderate level. Then, the layers were separated and the organic layer was washed with saturated, aqueous sodium bicarbonate (100 mL), dried over magnesium sulfate and evaporated under reduced pressure to afford benzyl bromide **26** (39.0 g, 169 mmol, 95%) as a white solid, which was used without further purification.

R_f = 0.54 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 6.54 (d, J = 2.3 Hz, 2H), 6.40 (t, J = 2.3 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 6H).

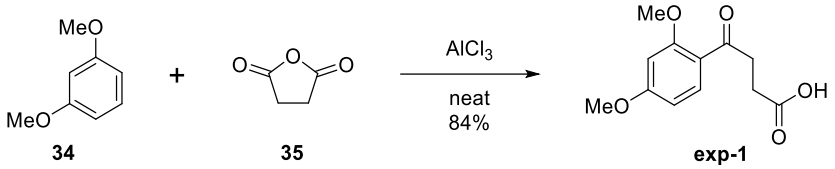
^{13}C-NMR (100 MHz, $CDCl_3$): 161.0, 139.9, 107.1, 100.7, 55.5, 33.8.

IR: 3060, 3003, 2967, 2936, 2895, 2837, 1614, 1589, 1474, 1457, 1445, 1430, 1321, 1206, 1155, 1116, 1068, 1057, 940, 866, 857, 823.

HRMS (APCI): $C_9H_{12}BrO_2$ [M+H] calc. 231.0015, found 231.0021.

The spectroscopic data agrees with previously reported values.[4]

Carboxylic acid **exp-1**



To a suspension of succinic anhydride (1.00 g, 9.99 mmol) in 1,3-dimethoxy-benzene (5.00 mL, 38.2 mmol, 3.8 eq.) was added aluminum chloride (2.67 g, 20.0 mmol, 2 eq.) under ice bath cooling. Then, the cooling bath was removed and the mixture was stirred at room temperature overnight, before ice (10 g) and 2 M hydrochloric acid (10 mL) were added. The resulting slurry was diluted with ethyl acetate (120 mL) and the layers were separated. The organic layer was washed with water (2×50 mL) and extracted with 1 M aqueous sodium hydroxide (50 mL). The washings as well as the organic layer were discarded and the basic extract was acidified with concentrated hydrochloric acid (5 mL). The resulting suspension was filtered and the filtrate was discarded. The solids were washed with water and dried to afford carboxylic acid **exp-1** (1.99 g, 8.35 mmol, 84%) as a white solid.

R_f = 0.41 (60% ethyl acetate in hexanes + 1% acetic acid).

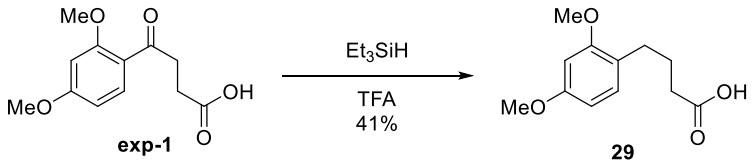
^{1}H-NMR (400 MHz, $CDCl_3$): 11.15 (br, 1H), 7.88 (d, J = 8.7 Hz, 1H), 6.53 (dd, J = 8.7, 2.3 Hz, 1H), 6.46 (d, J = 2.3 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.30 (t, J = 6.6 Hz, 2H), 2.73 (t, J = 6.6 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): 197.7, 178.7, 164.9, 161.4, 133.1, 120.2, 105.4, 98.4, 55.7, 55.6, 38.6, 28.8.

IR: 3014, 2978, 2939, 2839, 1706, 1658, 1600, 1571, 1503, 1489, 1473, 1458, 1440, 1419, 1402, 1368, 1325, 1315, 1297, 1277, 1257, 1232, 1215, 1190, 1170, 1124, 1079, 1047, 1031, 990, 918, 844, 823, 782, 729.

HRMS (APCI): $C_{12}H_{15}O_5$ [M+H] calc. 239.0914, found 239.0915.

Carboxylic acid **29**



To a solution of ketone **exp-1** (400 mg, 1.68 mmol) in trifluoroacetic acid (1.29 mL, 16.8 mmol, 10 eq.) was added triethylsilane (589 µL, 3.69 mmol, 2.2 eq.) and the mixture was stirred for 1.5 hours. Then, the volatiles were removed under reduced pressure and the residue was purified by column chromatography (45% diethyl ether in pentane) to afford a colorless oil that was dissolved in dichloromethane (10 mL). The dichloromethane solution was extracted with 0.2 M aqueous sodium hydroxide (10 mL) and the organic layer was

discarded. The aqueous extract was acidified with concentrated hydrochloric acid (5 mL), extracted with dichloromethane (10 mL) and discarded. The organic extract was dried over sodium hydroxide and evaporated under reduced pressure to afford carboxylic acid **29** (156 mg, 0.696 mmol, 41%) as a colorless solid.

R_f = 0.59 (60% ethyl acetate in hexanes + 1% acetic acid).

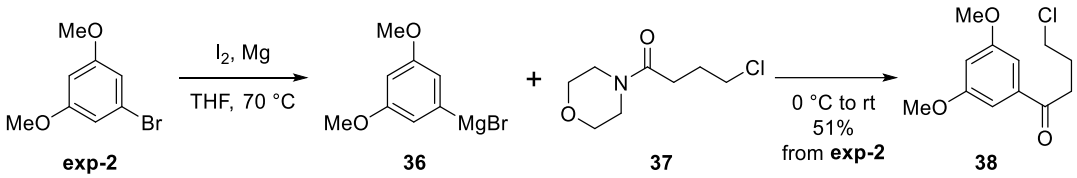
^{1}H-NMR (400 MHz, $CDCl_3$): 11.44 (s, 1H), 7.01 (d, J = 8.1 Hz, 1H), 6.44 (d, J = 2.4 Hz, 1H), 6.41 (dd, J = 8.1, 2.4 Hz, 1H), 3.79 (s, 3H), 3.79 (s, 3H), 2.61 (t, J = 7.4 Hz, 2H), 2.35 (t, J = 7.5 Hz, 2H), 1.90 (p, J = 7.5 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): 180.0, 159.5, 158.5, 130.4, 122.1, 103.9, 98.6, 55.5, 55.3, 33.5, 28.9, 25.1.

IR: 2999, 2936, 2835, 1702, 1612, 1587, 1506, 1455, 1438, 1417, 1287, 1259, 1206, 1152, 1122, 1112, 1036, 992, 934, 922, 832, 784, 747, 728, 706.

HRMS (APCI): $C_{12}H_{17}O_4$ [M+H] calc. 225.1121, found 225.1120.

Ketone **38**



Step 1: Aryl bromide **exp-2** (2.00 g, 9.21 mmol) was dissolved in anhydrous tetrahydrofuran (10 mL). A small part (1 mL) of the solution was added to a suspension of magnesium turnings (246 mg, 10.1 mmol, 1.1 eq.) and a small amount of iodine in anhydrous tetrahydrofuran (1 mL) under nitrogen atmosphere. Then, the mixture was warmed until the color of iodine faded and the remaining solution was added dropwise, followed by stirring at reflux for 3.5 hours. After cooling to room temperature, the resulting solution of Grignard reagent **36** without any remaining solids was drawn up in a syringe and directly used in the next sept.

Step 2: The solution of Grignard reagent **36** was added dropwise under ice bath cooling to a solution of morpholine amide **37**[5] (1.99 g, 10.1 mmol, 1.1 eq.) in anhydrous tetrahydrofuran (100 mL) under nitrogen atmosphere. Directly after the addition, the cooling bath was removed and the mixture was stirred for 1 hour at room temperature. Then, 1 M hydrochloric acid was added and the mixture was extracted with diethyl ether (2×40 mL). The combined organic layers were washed with saturated, aqueous sodium bicarbonate (60 mL), saturated, aqueous sodium chloride (60 mL), dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (12% diethyl ether in pentane) to afford ketone **38** (1.15 g, 4.73 mmol, 51%) as a colorless solid.

R_f = 0.71 (40% ethyl acetate in hexanes).

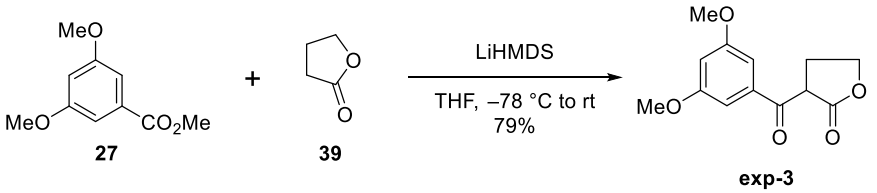
^{1}H-NMR (400 MHz, $CDCl_3$): 7.10 (d, J = 2.3 Hz, 1H), 6.66 (t, J = 2.3 Hz, 1H), 3.84 (s, 3H), 3.67 (t, J = 6.2 Hz, 1H), 3.13 (t, J = 7.0 Hz, 1H), 2.22 (p, J = 6.7 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 198.8, 161.0, 138.8, 106.0, 105.6, 55.7, 44.7, 35.6, 27.0.

IR: 2960, 2941, 2839, 1683, 1591, 1455, 1425, 1362, 1348, 1327, 1313, 1253, 1204, 1153, 1064, 1042, 1013, 992, 975, 940, 925, 841, 784, 726.

HRMS (ESI): $C_{12}H_{16}ClO_3$ [M+H] calc. 243.0784, found 243.0782.

Ketoester **exp-3**



To a solution ester **27** (1.50 g, 7.65 mmol) in anhydrous tetrahydrofuran (30 mL) under nitrogen atmosphere was added a 1.6 M tetrahydrofuran solution of LiHMDS (10.5 mL, 16.8 mmol, 2.2 eq.) under cooling with a dry ice/acetone bath, followed by dropwise addition of lactone **39** (594 µL, 7.80 mmol, 1 eq.). The mixture was stirred for 6.5 hours with warming to room temperature, then poured into a mixture of ice (50 g) and 2 M hydrochloric acid (20 mL) and stirred until all ice had dissolved. The resulting suspension was filtered and the filtrate was discarded. The solids were washed with water and dried to afford ketoester **exp-3** (1.50 g, 5.99 mmol, 79%) as a pale-red solid that was used without further purification.

An analytical sample of ketoester **exp-3** was purified by column chromatography (25% ethyl acetate in pentane), affording a white solid.

$\mathbf{R_f}$ = 0.30 (40% ethyl acetate in hexanes).

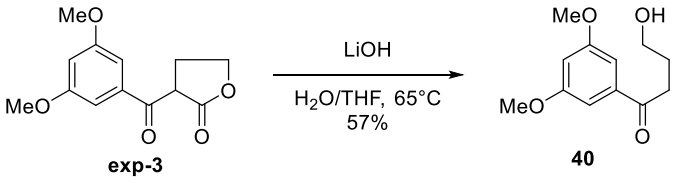
^{1}H-NMR (400 MHz, $CDCl_3$): 7.20 (d, J = 2.3 Hz, 2H), 6.70 (t, J = 2.3 Hz, 1H), 4.56 – 4.48 (m, 2H), 4.42 (ddd, J = 8.8, 8.1, 5.4 Hz, 1H), 3.84 (s, 6H), 2.83 (ddt, J = 13.2, 7.7, 5.5 Hz, 1H), 2.52 (dddd, J = 12.9, 9.3, 8.2, 7.1 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 193.1, 172.8, 161.1, 137.3, 107.3, 106.6, 67.9, 55.8, 48.3, 26.5.

IR: 2917, 1764, 1680, 1591, 1456, 1427, 1356, 1343, 1313, 1302, 1255, 1205, 1154, 1102, 1066, 1022, 1001, 953, 941, 925, 849, 820, 772.

HRMS (APCI): $C_{13}H_{15}O_5$ [M+H] calc. 251.0914, found 251.0916.

Alcohol **40**



A solution of lithium hydroxide monohydrate (369 mg, 8.79 mmol, 2.2 eq.) in water (30 mL) was added to a solution of ketoester **exp-3** (1.00 g, 3.99 mmol) in tetrahydrofuran (25 mL) under nitrogen atmosphere at 65 °C. The mixture was stirred for 2.5 hours, then cooled to room temperature. After addition of 1 M hydrochloric acid (11 mL), the mixture was extracted with diethyl ether (3×30 mL). The extracts were dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (40% ethyl acetate in pentane) to afford alcohol **40** (512 mg, 2.28 mmol, 57%) a colorless oil.

$\mathbf{R_f}$ = 0.17 (30% ethyl acetate in pentane).

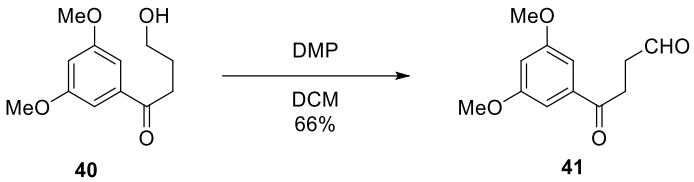
^{1}H-NMR (400 MHz, $CDCl_3$): 7.11 (d, J = 2.3 Hz, 2H), 6.65 (t, J = 2.3 Hz, 1H), 3.84 (s, 6H), 3.74 (t, J = 6.0 Hz, 2H), 3.09 (t, J = 6.9 Hz, 2H), 2.05 – 1.97 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): 200.3, 161.0, 138.9, 106.0, 105.5, 62.5, 55.7, 35.6, 27.1.

IR: 3371, 3094, 3001, 2940, 2839, 2085, 1680, 1591, 1455, 1425, 1348, 1312, 1293, 1253, 1204, 1151,1062, 1018, 992, 924, 840, 789, 716, 699, 677, 612.

LRMS (EI): $C_{12}H_{16}O_4$ [M+·] calc. 224.11, found 224.20.

Aldehyde **41**



40 **41**

To a solution of alcohol **40** (511 mg, 2.28 mmol) in anhydrous dichloromethane (12 mL) was added Dess-Martin periodinane (1.16 g, 2.74 mmol, 1.2 eq.) and the mixture was stirred for 2 hours. Then, dichloromethane (20 mL), 1 M aqueous sodium thiosulfate (10 mL) and saturated, aqueous sodium bicarbonate (10 mL) were added. After stirring for further 30 minutes, the layers were separated. The organic layer was washed with a 1/1 mixture (10 mL) of 1 M aqueous sodium thiosulfate and saturated, aqueous sodium bicarbonate, dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (25% diethyl ether in pentane) to afford aldehyde **41** (335 mg, 1.51 mmol, 66%) as a faint reddish solid.

$\mathbf{R_f}$ = 0.39 (40% ethyl acetate in hexanes).

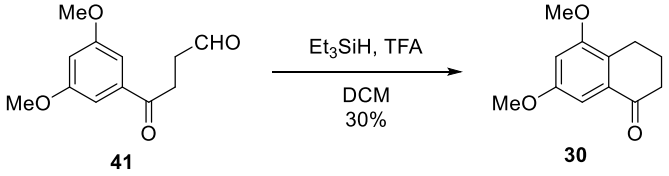
^{1}H-NMR (400 MHz, $CDCl_3$): 9.90 (s, 1H), 7.11 (d, J = 2.3 Hz, 2H), 6.66 (t, J = 2.3 Hz, 1H), 3.83 (s, 6H), 3.28 (t, J = 6.3 Hz, 2H), 2.92 (t, J = 6.3 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): 200.7, 197.6, 161.0, 138.5, 106.0, 105.7, 55.7, 37.8, 31.3.

IR: 2941, 2910, 2839, 1719, 1682, 1591, 1456, 1426, 1396, 1361, 1348, 1310, 1295, 1255, 1228, 1205, 1153, 1065, 1012, 992, 940, 925, 879, 842, 757.

HRMS (APCI): $C_{12}H_{15}O_4$ [M+H] calc. 223.0965, found 223.0966.

Tetralone **30**



41 **30**

To a solution of aldehyde **41** (50.0 mg, 225 µmol) in anhydrous dichloromethane (5 mL) were added triethylsilane (44 µL, 0.28 mmol, 1.2 eq.) and trifluoroacetic acid (260 µL, 3.38 mmol, 15 eq.). The mixture was stirred for 1 hour at room temperature, then the volatiles were removed under reduced pressure. The residue was purified by column chromatography (50% dichloromethane in pentane) to afford tetralone **30** (14.1 mg, 68.4 µmol, 30%.) as a colorless oil that solidified upon standing at room temperature.

$\mathbf{R_f}$ = 0.67 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.13 (d, J = 2.5 Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 2.81 (t, J = 6.1 Hz, 2H), 2.65 – 2.57 (m, 2H), 2.09 (p, J = 6.4 Hz, 2H).

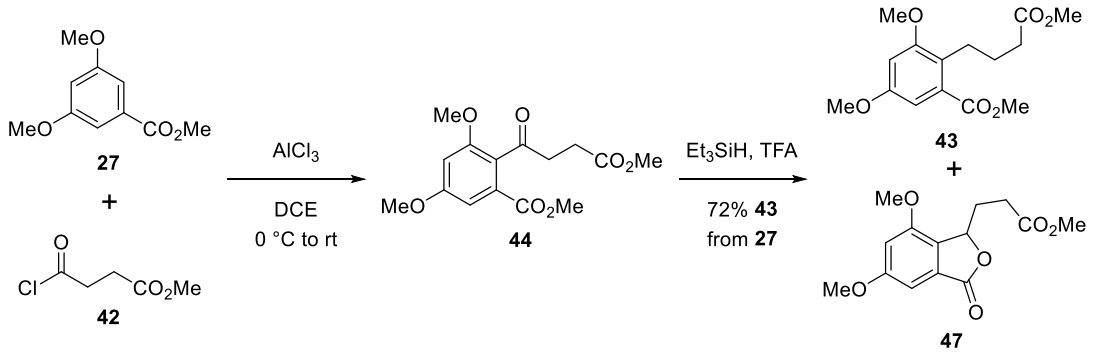
^{13}C-NMR (100 MHz, $CDCl_3$): 198.7, 158.9, 158.1, 134.0, 127.2, 104.2, 100.0, 55.9, 55.7, 39.1, 22.9, 22.5.

IR: 3003, 2945, 2901, 2837, 1677, 1602, 1485, 1463, 1455, 1434, 1426, 1362, 1346, 1330, 1284, 1262, 1242, 1208, 1186, 1180, 1165, 1129, 1062, 1033, 940, 914, 898, 862, 841, 802, 752, 717.

HRMS (APCI): $C_{12}H_{15}O_3$ [M+H] calc. 207.1016, found 207.1015.

The spectroscopic data and melting points reported by Rao[6] (67–68 °C, ^{1}H-NMR: 7.13, 6.61, 3.85 ppm) and Davies[7] et. al. (66–68 °C) agree with the observed spectroscopic data and melting point (68–71 °C). However, the spectroscopic data and melting point (150 °C) reported Date et al.[8] are do not agree with the results of this work. As the current data is also supported by two-dimensional NMR spectra, it is expected that the values reported by Date et al. are wrong.

Ketone **44**, diester **43** and lactone **47**



Step 1: To a solution of ester **27** (7.50 g, 38.2 mmol) and acid chloride **42** (8.63 g, 57.3 mmol, 1.5 eq.) in anhydrous 1,2-dichloroethane (500 mL) was added aluminum chloride (10.2 g, 76.5 mmol, 2 eq.) in 2 g portions within 5 minutes under ice bath cooling. The mixture was stirred for 3 hours, then the cooling bath was removed and stirring was continued at room temperature. After 2.5 hours, the mixture was poured onto water/ice (20 mL/30 g) and stirred until all ice had dissolved. Then, the layers were separated and the aqueous layer was extracted with dichloromethane (75 mL). The combined organic layers were washed with saturated, aqueous sodium bicarbonate (50 mL), saturated, aqueous sodium chloride (50 mL), dried over sodium sulfate and concentrated under reduced pressure to afford crude ketone **44** (12.2 g) as an orange solid, which was used without further purification.

Step 2: To crude ketone **44** were added successively triethylsilane (14.6 mL, 91.8 mmol, 2.4 eq.) and trifluoroacetic acid (29.5 mL, 382 mmol, 10 eq.). The mixture was stirred for 2.5 hours, then the volatiles were removed under reduced pressure. The residue, which contained diester **43** and lactone **47**, was purified by column chromatography (20% diethyl ether in pentane) to afford diester **43** (8.14 g, 27.5 mmol, 72%) as a colorless oil that solidified upon extended standing at room temperature.

Analytical data for ketone **44**

An analytical sample of ketone **44** was purified by column chromatography (30% ethyl acetate in pentane), affording a white solid.

$\mathbf{R_f}$ = 0.33 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.02 (d, J = 2.2 Hz, 1H), 6.63 (d, J = 2.3 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.70 (s, 3H), 3.13 (t, J = 7.3 Hz, 2H), 2.77 (t, J = 7.3 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): 203.5, 173.6, 166.4, 161.1, 157.3, 129.7, 126.2, 105.5, 103.1, 56.2, 55.8, 52.7, 51.8, 39.3, 28.4.

IR: 3002, 2952, 2843, 1720, 1639, 1601, 1579, 1455, 1436, 1422, 1329, 1295, 1249, 1215, 1174, 1149, 1065, 1049, 980, 950, 887, 844, 787, 763.

HRMS (ESI): $C_{15}H_{18}NaO_7$ [M+H] calc. 333.0945, found 333.0957.

Analytical data for diester **43**

R_f = 0.32 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 6.88 (d, J = 2.6 Hz, 1H), 6.57 (d, J = 2.5 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 3.65 (s, 3H), 2.90 – 2.84 (m, 2H), 2.34 (t, J = 7.7 Hz, 2H), 1.86 (p, J = 7.7 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): 174.4, 168.4, 159.1, 158.4, 131.8, 124.5, 105.1, 102.2, 55.8, 55.6, 52.2, 51.5, 34.1, 25.57, 25.55.

IR: 2998, 2951, 2840, 1722, 1603, 1584, 1483, 1460, 1434, 1421, 1350, 1315, 1275, 1237, 1199, 1153, 1131, 1068, 1055, 989, 941, 886, 844, 810, 787, 762.

HRMS (ESI): $C_{15}H_{20}NaO_6$ [M+Na] calc. 319.1152, found 319.1165.

Analytical data for lactone **47**

A sample of lactone **47** was obtained in a separate experiment under identical conditions and purified by column chromatography (0 to 30% ethyl acetate in hexanes).

R_f = 0.40 (40% ethyl acetate in hexanes), 0.13 (20% ethyl acetate in hexanes).

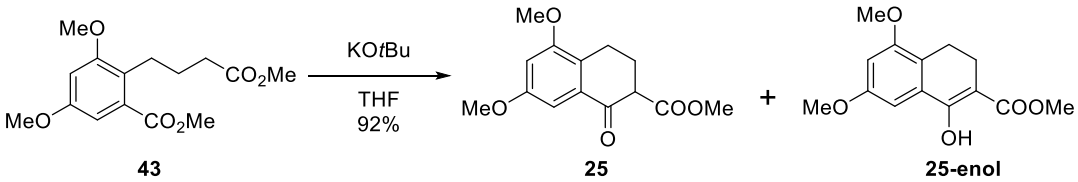
^{1}H-NMR (600 MHz, $CDCl_3$): 6.90 (d, J = 1.9 Hz, 1H), 6.66 (d, J = 1.9 Hz, 1H), 5.49 (dd, J = 8.1, 3.3 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.66 (s, 3H), 2.61 (dddd, J = 14.5, 9.6, 6.6, 3.3 Hz, 1H), 2.47 (ddd, J = 15.8, 9.1, 6.6 Hz, 1H), 2.40 (ddd, J = 16.6, 9.4, 5.5 Hz, 1H), 1.99 (dddd, J = 14.7, 9.3, 8.1, 5.6 Hz, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$): 173.4, 170.5, 162.8, 155.2, 130.3, 128.7, 105.0, 98.7, 79.4, 56.1, 55.9, 51.9, 29.5, 28.4.

IR: 2950, 2843, 1763, 1735, 1679, 1626, 1606, 1502, 1454, 1435, 1331, 1302, 1257, 1228, 1202, 1154, 1117, 1070, 1037, 991, 944, 892, 845, 768, 727, 704.

HRMS (ESI): $C_{14}H_{17}O_6$ [M+H] calc. 281.1020, found 281.1031.

Ketoester **25**



43 **25** **25-enol**

To a solution of potassium *tert*-butoxide (81.0 g, 722 mmol, 3 eq.) in anhydrous tetrahydrofuran (240 mL) under nitrogen atmosphere was dropwise added a solution of ester **43** (71.3 g, 241 mmol) in anhydrous tetrahydrofuran (80 mL) under ice bath cooling. The mixture was stirred for two hours, then poured onto ice-cold 2 M hydrochloric acid (650 mL) and the resulting suspension was filtered. The solids were washed with water (2×100 mL) followed by ethanol (100 mL) and dried to afford a mixture of tautomers **25** and **25-enol** (43.5 g, 165 mmol, 68%) as a white powder, which contained enol **25-enol** as the primary component (≈95% by ^{1}H-NMR). The combined filtrate and washings were extracted with ethyl acetate (2×150 mL). The extracts were washed with water (200 mL) and saturated, aqueous sodium chloride (200 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by recrystallization from ethanol to afford a mixture of tautomers **25** and **25-enol** (10.1 g, 38.2 mmol, 16%) in the

form of a white solid, which contained ketone **25** as the primary component (≈80% by ^{1}H-NMR). The mother liquors of the recrystallization were evaporated under reduced pressure. The residue was washed with ethanol and dried to afford further material (5.27 g, 19.9 mmol, 8%) as an off-white solid, which contained roughly equal amounts of the tautomers **25** and **25-enol**.

Analytical data for enol-tautomer 25-enol

^{1}H-NMR (400 MHz, $CDCl_3$): 12.45 (s, 1H), 6.99 (d, J = 2.4 Hz, 1H), 6.53 (d, J = 2.4 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 2.72 (dd, J = 9.0, 6.9 Hz, 2H), 2.51 (dd, J = 8.8, 7.1 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 173.3, 165.1, 159.2, 157.0, 131.4, 120.7, 101.5, 99.8, 97.3, 55.8, 55.7, 51.8, 20.3, 19.7.

IR: 3000, 2900, 2841, 1648, 1595, 1580, 1489, 1453, 1437, 1422, 1373, 1352, 1322, 1287, 1236, 1211, 1200, 1152, 1126, 1070, 1052, 1029, 1010, 941, 918, 900, 852, 828, 801, 769, 756, 731.

HRMS (ESI): $C_{14}H_{17}O_5$ [M+H] calc. 265.1071, found 265.1076.

Analytical data for keto-tautomer 25

R_f = 0.44 (20% ethyl acetate in hexanes).

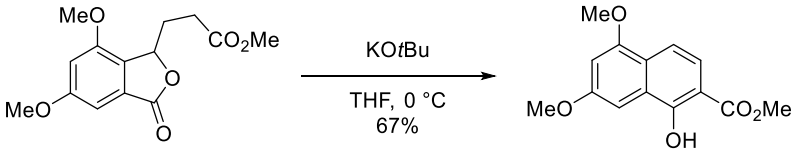
^{1}H-NMR (400 MHz, $CDCl_3$): 7.12 (d, J = 2.5 Hz, 1H), 6.63 (d, J = 2.5 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.77 (s, 3H), 3.58 (dd, J = 10.3, 4.7 Hz, 1H), 2.98 (ddd, J = 17.7, 5.9, 4.8 Hz, 1H), 2.73 (ddd, J = 17.7, 9.2, 4.9 Hz, 1H), 2.43 (dddd, J = 13.8, 10.3, 9.3, 4.8 Hz, 1H), 2.32 (ddt, J = 13.5, 5.9, 4.9 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 193.5, 170.9, 159.2, 157.9, 133.0, 126.4, 104.6, 100.4, 55.9, 55.7, 54.3, 52.4, 25.9, 20.9.

IR: 3001, 2951, 2840, 1739, 1682, 1650, 1605, 1583, 1487, 1453, 1434, 1366, 1326, 1312, 1283, 1241, 1211, 1196, 1149, 1128, 1116, 1072, 1042, 1005, 969, 940, 915, 889, 843, 768, 754, 728.

HRMS (ESI): $C_{14}H_{17}O_5$ [M+H] calc. 265.1071, found 265.1083.

Naphthalene 48



47 **48**

To potassium *tert*-butoxide (60.1 mg, 0.535 mmol, 3 eq.) in anhydrous tetrahydrofuran (0.5 mL) under nitrogen atmosphere was dropwise added a solution of lactone **47** (50 mg, 0.178 mmol) in anhydrous tetrahydrofuran (0.5 mL) under ice bath cooling. The mixture was stirred with cooling for 1.25 hours, before 2 M hydrochloric acid (2 mL) was added and the mixture was extracted with dichloromethane (3×2 mL). The extracts were dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (50 to 100% dichloromethane in hexanes) to afford naphthalene **48** (31.5 mg, 0.120 mmol, 67%) as a white solid.

R_f = 0.75 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 11.87 (s, 1H), 7.63 (d, J = 9.1 Hz, 1H), 7.60 (d, J = 8.9 Hz, 1H), 7.27 (d, J = 2.0 Hz, 1H), 6.63 (d, J = 2.2 Hz, 1H), 4.00 (s, 3H), 3.97 (s, 3H), 3.96 (s, 3H).

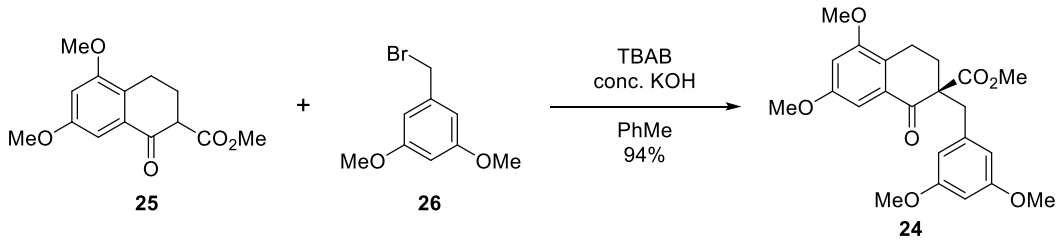
^{13}C-NMR (100 MHz, $CDCl_3$): 171.8, 159.5, 158.5, 156.4, 126.3, 125.2, 121.3, 112.8, 106.9, 100.9, 93.9, 55.8, 55.7, 52.4.

IR: 3109, 3004, 2957, 2940, 1663, 1606, 1590, 1506, 1465, 1443, 1432, 1408, 1332, 1284, 1248, 1230, 1198, 1168, 1144, 1066, 1049, 1011, 943, 925, 891, 839, 829, 801, 778, 738.

HRMS (APCI): $C_{14}H_{15}O_5$ [M+H] calc.263.0914, found 263.0914.

The spectroscopic data agrees with previously reported values.[9]

Ketoester **24**



Toluene (125 mL) was added to a mixture of ketoester **25** (7.00 g, 26.5 mmol), benzyl bromide **26** (9.79 g, 42.4 mmol, 1.6 eq.) and tetrabutylammonium bromide (854 mg, 2.65 mmol, 0.1 eq.) under nitrogen atmosphere and the mixture was stirred for several minutes until most solids had dissolved. Then, 50% aqueous potassium hydroxide (8 mL, 106 mmol, 4 eq.) was added and stirring was continued for 1 hour, before water (125 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (2×35 mL). The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. Ethanol (100 mL) was added to the residue and the mixture was warmed to reflux for several minutes. The mixture was cooled to room temperature, kept standing for several hours and filtered. The solids were washed with a minimal amount of ethanol and dried to afford ketoester **24** (10.3 g, 24.9 mmol, 94%) as a white solid.[a]

R_f = 0.39 (30% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.15 (d, J = 2.4 Hz, 1H), 6.58 (d, J = 2.5 Hz, 1H), 6.37 (d, J = 2.3 Hz, 2H), 6.31 (t, J = 2.3 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.75 (s, 6H), 3.65 (s, 3H), 3.35 (d, J = 13.6 Hz, 1H), 3.24 (d, J = 13.6 Hz, 1H), 2.87 (ddd, J = 18.1, 5.2, 3.7 Hz, 1H), 2.69 (ddd, J = 18.0, 11.1, 4.9 Hz, 1H), 2.49 (ddd, J = 13.8, 4.9, 3.6 Hz, 1H), 1.91 (ddd, J = 13.8, 11.1, 5.3 Hz, 1H).

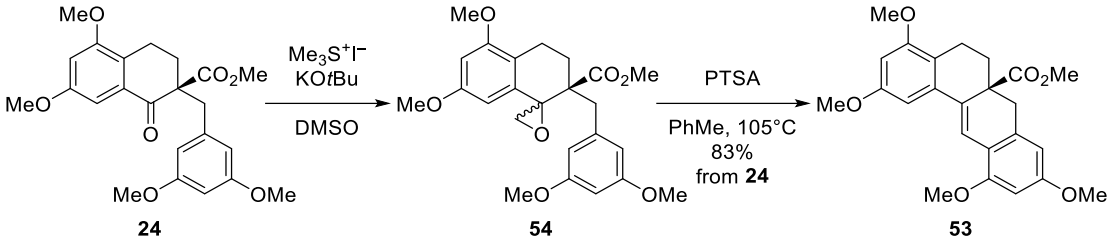
^{13}C-NMR (100 MHz, $CDCl_3$): 194.8, 171.9, 160.5, 159.1, 157.9, 138.9, 133.4, 125.9, 108.9, 104.2, 100.8, 98.8, 58.5, 55.8, 55.7, 55.4, 52.6, 40.4, 29.9, 19.5.

IR: 3002, 2949, 2837, 1729, 1685, 1605, 1594, 1487, 1455, 1428, 1367, 1347, 1336, 1284, 1240, 1203, 1194, 1149, 1135, 1050, 1010, 991, 928, 913, 886, 845, 771, 729.

HRMS (ESI): $C_{23}H_{26}NaO_7$ [M+Na] calc. 437.1571, found 437.1576.

[a]The filtrate consists mainly of unreacted benzyl bromide **26**, which can be recovered, if desired. Removal of the solvent and purification of the residue by column chromatography (30 to 50% dichloromethane in hexanes) typically recovers 80% or more of the excess benzyl bromide **26**.

Stilbene **53**



Step 1: To ketoester **24** (6.40 g, 15.5 mmol) and trimethyl sulfonium iodide (3.78 g, 18.5 mmol, 1.2 eq.) under nitrogen atmosphere was added anhydrous dimethyl sulfoxide (50 mL) and the mixture was warmed under stirring until all solids had dissolved. After cooling to room temperature, a freshly prepared solution of potassium *tert*-butoxide (1.82 g, 16.2 mmol, 1.05 eq.) in anhydrous dimethyl sulfoxide (17 mL) was added dropwise. The mixture was stirred for 20 minutes, then dichloromethane (150 mL), water (50 mL) and saturated, aqueous sodium chloride (200 mL) were added. The mixture was shaken thoroughly, the layers were separated and the aqueous layer was extracted with dichloromethane (2×100 mL). The combined organic layers were washed with water (2×100 mL), dried over sodium sulfate and evaporated under reduced pressure to afford crude epoxide **54**, which was directly used without further purification in the next step.

Step 2: Anhydrous toluene (70 mL) was added to crude epoxide **54**, then the mixture was warmed to 105°C and p-toluenesulfonic acid monohydrate (132 mg, 0.694 mmol, 0.045 eq.) was added. After stirring for 3 hours, the mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by column chromatography (66% dichloromethane in pentane) to afford stilbene **53** (5.27 g, 12.8 mmol, 83%) as an off-white solid.

$\mathbf{R_f}$ = 0.37 (30% ethyl acetate in hexanes).

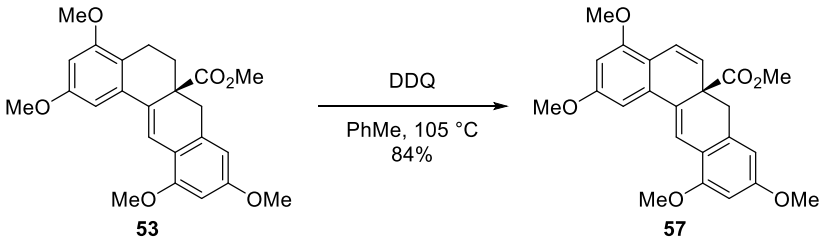
^{1}H-NMR (400 MHz, $CDCl_3$): 7.57 (s, 1H), 7.08 (d, J = 2.3 Hz, 1H), 6.39 – 6.28 (m, 3H), 3.89 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.49 (s, 3H), 3.31 (d, J = 15.5 Hz, 1H), 2.98 (ddd, J = 17.0, 4.7, 2.5 Hz, 1H), 2.85 (dt, J = 15.5, 1.0 Hz, 1H), 2.40 (ddd, J = 12.8, 4.7, 2.6 Hz, 1H), 2.28 (ddd, J = 17.4, 13.2, 4.6 Hz, 1H), 1.79 (td, J = 13.0, 4.7 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 176.2, 160.1, 158.7, 158.1, 156.7, 136.4, 134.9, 131.2, 118.5, 116.7, 116.3, 104.3, 98.6, 97.4, 96.8, 55.59, 55.56, 55.53, 55.45, 52.3, 47.1, 41.3, 34.1, 20.2.

IR: 2998, 2940, 2837, 1720, 1600, 1570, 1491, 1454, 1426, 1365, 1338, 1324, 1302, 1287, 1274, 1247, 1212, 1197, 1183, 1143, 1117, 1090, 1069, 1052, 1002, 980, 938, 906, 869, 825, 782, 771, 727.

HRMS (APCI): $C_{24}H_{27}O_6$ [M+H] calc. 412.1836, found 412.1839.

Diene **57**



To stilbene **53** (7.94 g, 19.3 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzo-quinone (5.05 g, 22.2 mmol, 1.15 eq.) under nitrogen atmosphere was added anhydrous toluene

(90 mL) and the mixture was stirred at 105 °C for 35 minutes. After cooling to room temperature, the mixture was filtered over silica (15 g), the silica was washed with dichloromethane (150 mL) and the solvent was removed under reduced pressure. Ethanol (100 mL) was added to the residue, the mixture was warmed to reflux for 15 minutes, then cooled to room temperature and filtered. The filtrate was discarded. The solids were washed with ethanol and dried to afford diene **57** (6.60 g, 16.2 mmol, 84%) as a yellow solid.

R_f = 0.31 (30% ethyl acetate in hexanes).

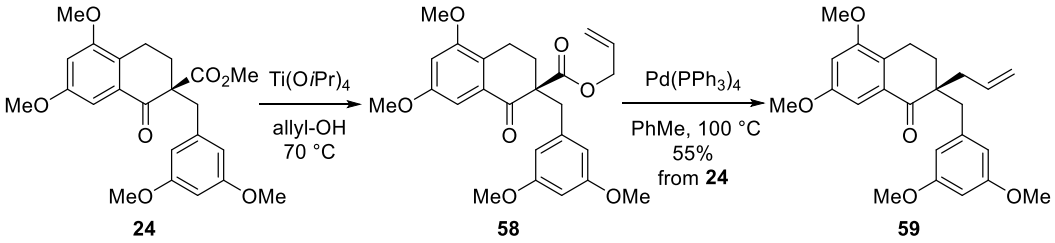
^{1}H-NMR (400 MHz, $CDCl_3$): 7.47 (s, 1H), 6.99 (d, J = 2.2 Hz, 1H), 6.92 (d, J = 9.7 Hz, 1H), 6.40 (d, J = 2.2 Hz, 1H), 6.34 (d, J = 2.2 Hz, 1H), 6.32 (d, J = 2.1 Hz, 1H), 5.65 (dd, J = 9.7, 1.0 Hz, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.82 (s, 3H), 3.47 (s, 3H), 3.39 (d, J = 15.8 Hz, 1H), 3.05 (d, J = 15.6 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 173.6, 160.5, 160.5, 156.9, 156.7, 135.0, 134.9, 130.7, 125.5, 121.5, 118.5, 116.5, 114.3, 104.4, 99.7, 97.7, 96.9, 55.7, 55.6, 55.6, 55.5, 52.7, 47.2, 39.4.

IR: 3000, 2940, 2904, 2837, 1721, 1638, 1596, 1568, 1491, 1454, 1426, 1387, 1328, 1304, 1289, 1254, 1236, 1218, 1204, 1172, 1142, 1111, 1086, 1051, 1042, 1002, 968, 946, 936, 906, 827, 795, 763, 727.

HRMS (APCI): $C_{24}H_{25}O_6$ [M+H] calc. 409.1646, found 409.1651.

Ketone **59**



Step 1: To a mixture of ketoester **24** (150 mg, 362 µmol) and allyl alcohol (495 µL, 7.24 mmol, 20 eq.) under nitrogen atmosphere was added titanium isopropoxide (268 µL, 905 µmol, 2.5 eq.) and the mixture was stirred at 70 °C for 48 hours. Then, half-saturated, aqueous ammonium chloride (2.5 mL) was added and the mixture was extracted with dichloromethane (3×5 mL). The extracts were dried over sodium sulfate, filtered over a short plug of silica and the silica was washed with ethyl acetate/pentane = 1/2. After removal of the volatiles under reduced pressure, crude allyl ester **58** (163 mg) was obtained as a colorless oil that was directly used without further purification.

Step 2: To crude ally ester **58** (163 mg) and tetrakis(triphenylphosphine)palladium (42.5 mg, 36.8 mmol, 0.1 eq.) under nitrogen atmosphere was added anhydrous, degassed[a] toluene (4 mL). The mixture was stirred at 100 °C for 3 hours. After cooling to room temperature, the mixture was the directly[b] purified by column chromatography (17% diethyl ether in pentane) to afford ketone **59** (79.0 mg, 199 µmol, 55%) as a colorless oil.

R_f = 0.53 (30% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.16 (d, J = 2.5 Hz, 1H), 6.60 (d, J = 2.5 Hz, 1H), 6.30 (s, 3H), 5.80 (ddt, J = 17.3, 10.2, 7.3 Hz, 1H), 5.13 – 5.02 (m, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.74 (s, 6H), 3.15 (d, J = 13.4 Hz, 1H), 2.90 – 2.73 (m, 2H), 2.69 (d, J = 13.4 Hz, 1H), 2.51 (ddt, J = 13.9, 6.8,

[a]By three cycles of freeze-pump-thaw.
[b]The reaction mixture was directly loaded onto the column.

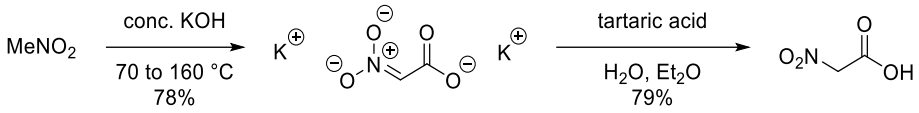
1.2 Hz, 1H), 2.20 (ddt, J = 14.1, 7.6, 1.2 Hz, 1H), 1.97 (ddd, J = 14.0, 6.5, 5.4 Hz, 1H), 1.88 (ddd, J = 13.9, 7.9, 5.7 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 201.0, 160.4, 159.1, 157.9, 140.1, 134.1, 133.3, 125.6, 118.6, 109.0, 103.9, 100.7, 98.4, 55.8, 55.7, 55.4, 49.1, 40.8, 39.6, 29.8, 18.6.

IR: 3000, 2936, 2837, 1677, 1638, 1605, 1595, 1486, 1462, 1429, 1366, 1338, 1314, 1283, 1204, 1148, 1057, 989, 935, 919, 843, 779, 732, 720.

HRMS (APCI): $C_{24}H_{29}O_5$ [M+H] calc. 398.2043, found 398.2045.

Nitroacetic acid[10]



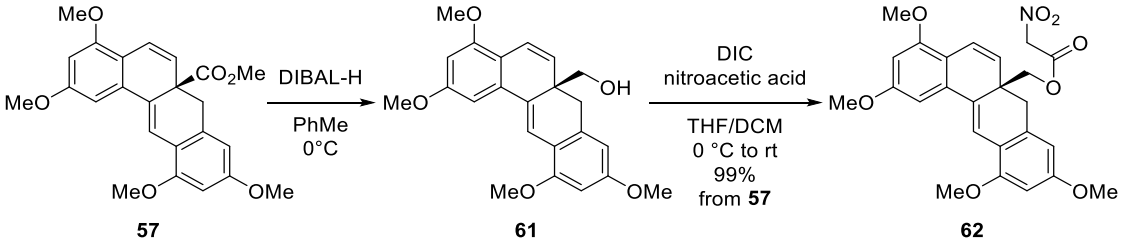
Step 1:[10a] To a solution of potassium hydroxide (128.7 g, 2.3 mol, 4 eq.) in water (65 mL) under nitrogen atmosphere at 70°C was dropwise added nitromethane (30.7 mL, 574 mmol) and the mixture was stirred for 30 minutes. Then, the temperature was increased to 160°C and stirring was continued for 3 hours, before the mixture was cooled to room temperature and filtered. The filtrate was discarded. The solids were washed with methanol (3×200 mL) and dried to afford nitroacetic acid dipotassium salt (40.5 g, 223 mmol, 78%) as a light-brown solid.

Step 2:[10b] To a mixture of nitroacetic acid dipotassium salt (17.5 g, 96.6 mmol), water (95 mL) and diethyl ether (200 mL) was added tartaric acid (59 g, 393 mmol, 4 eq.) in equal portions within 5 minutes under ice bath cooling. The mixture was stirred for additional 5 minutes, then filtered and the solids were discarded. The layers of filtrate were separated and the aqueous layer was extracted with diethyl ether (2×100 mL). The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. The residue was dried under high vacuum to afford nitroacetic acid (7.97 g, 75.9 mmol, 79%) as a yellowish solid, which was used without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$): 5.25 (s, 2H).

The spectroscopic data agrees with previously reported values.[11]

Nitroacetic acid ester 62



Step 1: To a suspension of diene **57** (2.93 g, 7.17 mmol) in anhydrous toluene (40 mL) under nitrogen atmosphere was added a 1 M toluene solution of diisobutylaluminum hydride (17.8 mL, 17.8 mmol, 2.5 eq.) under ice bath cooling. The mixture was stirred for 35 minutes, before methanol (2.5 mL) was carefully added to the resulting solution, followed by toluene (40 mL), water (40 mL) and saturated, aqueous potassium sodium tartrate (40 mL). The ice bath was removed and the mixture was stirred vigorously for 40 minutes, before enough ethyl acetate was added to dissolve all solids. The layers were

separated and the aqueous layer was extracted with ethyl acetate (80 mL). The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure to afford crude alcohol **61** as a yellow solid, which was directly used without further purification in the next step.

Step 2: To a solution of crude alcohol **61** in anhydrous dichloromethane (75 mL) under nitrogen atmosphere was added *N*,*N*′-diisopropylcarbodiimide (2.81 mL, 18.1 mmol, 2.5 eq.) under ice/brine bath cooling. Then, a solution of nitroacetic acid (see page 154, 1.68 g, 16.0 mmol, 2.2 eq.) in anhydrous tetrahydrofuran (35 mL) was added dropwise. After stirring overnight with warming to room temperature, the volatiles were removed under reduced pressure. The residue was purified by column chromatography (dichloromethane) to afford nitroacetic acid ester **62** (3.37 g, 7.21 mmol, 99%) as a brownish-yellow foam.

$\mathbf{R_f}$ = 0.31 (30% ethyl acetate in hexanes).

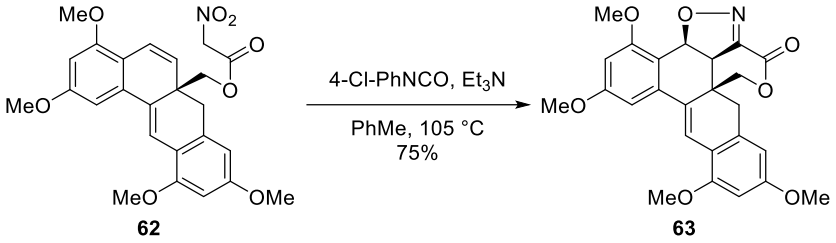
^{1}H-NMR (400 MHz, $CDCl_3$): 7.44 (s, 1H), 6.92 (d, J = 12.7 Hz, 1H), 6.91 (s, 1H), 6.36 (d, J = 2.2 Hz, 1H), 6.35 (s, 1H), 5.58 (dd, J = 9.7, 0.9 Hz, 1H), 4.83 (d, J = 14.4 Hz, 1H), 4.67 (d, J = 14.4 Hz, 1H), 4.19 (d, J = 10.4 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.87 (d, J = 10.4 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.10 (d, J = 16.2 Hz, 1H), 2.82 (d, J = 16.3 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 161.8, 160.7, 160.4, 156.8, 156.7, 134.7, 134.4, 131.4, 126.8, 121.3, 118.8, 116.0, 114.8, 104.9, 99.9, 97.9, 96.9, 75.9, 69.5, 55.8, 55.68, 55.66, 55.5, 38.9, 37.5.

IR: 3001, 2960, 2941, 2838, 1755, 1638, 1597, 1563, 1492, 1455, 1427, 1393, 1366, 1337, 1310, 1294, 1239, 1205, 1147, 1102, 1082, 1050, 1006, 983, 946, 937, 910, 874, 830, 784, 731.

HRMS (APCI): $C_{25}H_{26}NO_8$ [M+H] calc. 468.1653, found 468.1652.

Isoxazoline **63**



To ester **62** (640 mg, 1.37 mmol) in anhydrous toluene (15 mL) under nitrogen atmosphere was added triethylamine (380 µL, 2.74 mmol, 2 eq.) and the mixture was warmed to 105°C. Then, a solution of 4-chlorophenyl isocyanate (841 mg, 5.48 mmol, 4 eq.) in anhydrous toluene (1 mL) was added via syringe pump within 1 hour. After stirring for further 15 minutes, the mixture was cooled to room temperature and filtered. The solids were washed with dichloromethane (30 mL) and discarded. The filtrate was evaporated under reduced pressure and the residue was partially purified by column chromatography (66 to 100% dichloromethane in hexanes). Ethanol (10 mL) was added to the partially purified material, the mixture was warmed to reflux for several minutes, then cooled to room temperature and filtered. The filtrate was discarded. The solids were washed with ethanol (5 mL) and dried to afford isoxazoline **63** (461 mg, 1.03 mmol, 75%) as an off-white solid.

$\mathbf{R_f}$ = 0.60 (60% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.40 (s, 1H), 6.80 (d, J = 2.2 Hz, 1H), 6.48 (d, J = 2.2 Hz, 1H), 6.41 (d, J = 2.3 Hz, 1H), 6.38 (d, J = 2.1 Hz, 2H), 6.14 (d, J = 12.6 Hz, 1H), 4.00 (d, J = 11.8 Hz, 1H),

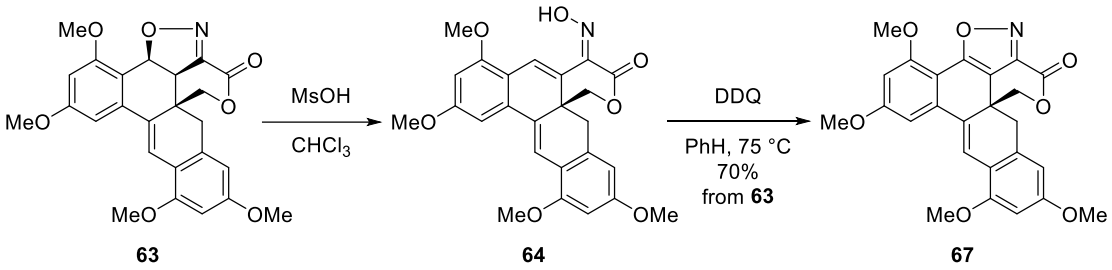
3.92 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.62 (d, J = 13.0 Hz, 2H), 3.58 (dd, J = 11.9, 2.0 Hz, 1H), 3.19 (d, J = 15.7 Hz, 1H), 2.91 (d, J = 15.7 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 161.6, 161.5, 161.2, 160.1, 157.1, 148.1, 134.7, 134.2, 126.4, 121.2, 115.2, 113.0, 105.2, 100.2, 99.1, 97.5, 79.0, 68.6, 56.3, 55.71, 55.68, 55.6, 50.0, 40.5, 36.8.

IR: 2961, 2938, 2838, 2253, 1755, 1605, 1576, 1492, 1453, 1426, 1376, 1365, 1359, 1340, 1302, 1276, 1243, 1226, 1215, 1203, 1153, 1108, 1092, 1047, 1011, 995, 974, 937, 908, 870, 827, 797, 775, 757, 724.

HRMS (APCI): $C_{25}H_{24}NO_7$ [M+H] calc. 450.1547, found 450.1546.

Isoxazole **67**



Step 1: To a solution of isoxazoline **63** (2.75 g, 6.12 mmol) in anhydrous chloroform (50 mL) was added methanesulfonic acid (795 µL, 12.2 mmol, 2 eq.) and the mixture was stirred for 20 minutes. Then, sodium acetate was added (2.01 g, 24.5 mmol, 4 eq.). The mixture was washed with water (50 mL) and saturated, aqueous sodium bicarbonate (10 mL) and the combined washings were extracted with ethyl acetate (3x50 mL). The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure to afford crude oxime **64** (3.04 g) as an orange-brown solid, which was directly used without further purification in the next step.

Step 2: To crude oxime **64** was added 2,3-dichloro-5,6-dicyano-1,4-benzo-quinone (1.53 g, 6.73 mmol, 1.1 eq.), followed by anhydrous benzene (50 mL) and the mixture was stirred at 75 °C for 45 minutes. After cooling to room temperature, the mixture was filtered over a short plug of silica and the silica was washed with dichloromethane until no further material eluted. The solvent was removed under reduced pressure and ethanol (50 mL) was added to the residue. The mixture was warmed to reflux for several minutes, then cooled to room temperature and filtered. The filtrate was discarded. The solids were washed with ethanol (10 mL) followed by diethyl ether (5 mL) and dried to afford isoxazole **67** (1.93 g, 4.31 mmol, 70%) as a brownish-orange solid.

Analytical data for oxime **64**

^{1}H-NMR (400 MHz, $CDCl_3$): 8.06 (s, 1H), 7.38 (s, 1H), 6.85 (d, J = 2.2 Hz, 1H), 6.34 (s, 2H), 6.32 (d, J = 2.2 Hz, 1H), 4.25 (d, J = 10.7 Hz, 1H), 4.21 (d, J = 10.6 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.24 (d, J = 16.0 Hz, 1H), 2.89 (d, J = 16.1 Hz, 1H).

Analytical data for isoxazole **67**

R_f = 0.60 (60% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.48 (s, 1H), 6.98 (d, J = 2.1 Hz, 1H), 6.44 – 6.40 (m, 2H), 6.36 (d, J = 2.2 Hz, 1H), 4.53 (d, J = 10.5 Hz, 1H), 3.99 (s, 3H, OMe), 3.91 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.28 (d, J = 15.7 Hz, 1H), 3.19 (d, J = 15.7 Hz, 1H).

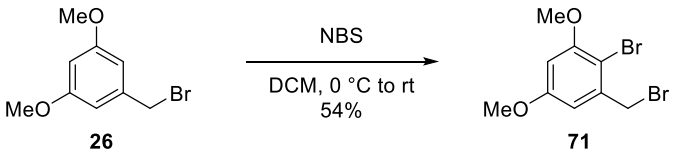
The HSQC spectrum showed that the signal of one proton of the CH_2O group is superimposed with the OMe signals at 3.91 and 3.88 ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): 165.9, 163.1, 162.1, 158.2, 157.9, 157.5, 149.8, 137.8, 133.7, 127.0, 124.1, 117.3, 115.9, 106.9, 105.4, 102.0, 97.6, 97.5, 72.9, 56.3, 55.8, 55.70, 55.68, 37.4, 35.2.

IR: 3003, 2941, 2839, 2254, 1762, 1651, 1605, 1563, 1488, 1455, 1427, 1321, 1291, 1241, 1209, 1146, 1120, 1094, 1079, 1049, 1028, 1003, 981, 955, 930, 908, 888, 845, 829, 792, 770, 727.

HRMS (APCI): $C_{25}H_{22}NO_7$ [M+H] calc. 448.1391, found 448.1396.

Benzyl bromide 71



To a solution of benzyl bromide **26** (5.00 g, 21.6 mmol) in anhydrous dichloromethane (40 mL) was added *N*-bromosuccinimide (3.85 g, 21.6 mmol, 1 eq.) in one portion under ice bath cooling and the mixture was stirred with warming to room temperature overnight. Then, the mixture was washed with water (2×40 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was partially purified by column chromatography (25% dichloromethane in hexanes). The resulting solids were washed with a small amount of ethanol and dried to afford benzyl bromide **71** (3.59 g, 11.6 mmol, 54%) as a white solid.

R_f = 0.45 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 6.62 (d, J = 2.7 Hz, 1H), 6.44 (d, J = 2.7 Hz, 1H), 4.60 (s, 2H), 3.87 (s, 3H), 3.81 (s, 3H).

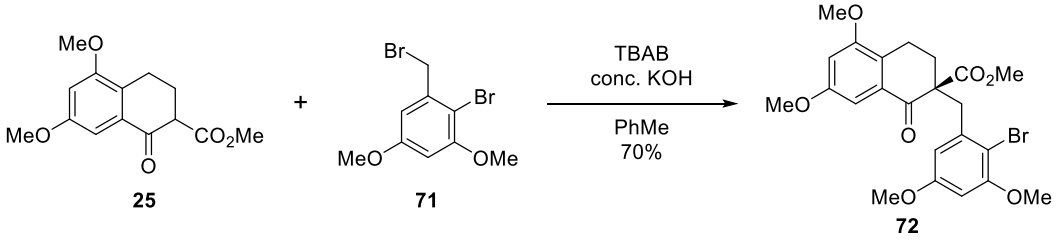
^{13}C-NMR (100 MHz, $CDCl_3$): 159.9, 157.3, 138.7, 107.2, 105.1, 100.1, 56.6, 55.8, 34.0.

IR: 2941, 2840, 1591, 1580, 1468, 1432, 1418, 1329, 1299, 1237, 1211, 1202, 1168, 1127, 1084, 1023, 944, 850, 822, 719.

LRMS (ESI): $C_9H_{10}Br_2O_2$ [$M^{+\cdot}$] calc. 309.9, 307.9, 311.9, found 309.9, 307.9, 311.9.

The spectroscopic data agrees with previously reported values.[12]

Ketoester 72



Toluene (60 mL) was added to a mixture of ketoester **25** (2.92 g, 11.1 mmol), benzyl bromide **71** (3.43 g, 11.1 mmol, 1 eq.) and tetrabutylammonium bromide (357 mg, 1.11 mmol, 0.1 eq.) under nitrogen atmosphere and the mixture was stirred for several minutes. Then, 50% aqueous potassium hydroxide (3.30 mL, 44.6 mmol, 4 eq.) was added and stirring was continued for 2 hours, before water (100 mL) and dichloromethane (100 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (2×25 mL). The combined organic layers were dried over magnesium sulfate and evaporated under reduced pressure. Ethanol (50 mL) was added to the residue.

The mixture was warmed to reflux for several minutes, cooled to room temperature, kept standing for several hours and filtered. The solids were washed with additional ethanol (2×10 mL) and dried to afford ketoester **72** (3.85 g, 7.80 mmol, 70%) as a white solid.

R_f = 0.36 (30% ethyl acetate in hexanes).

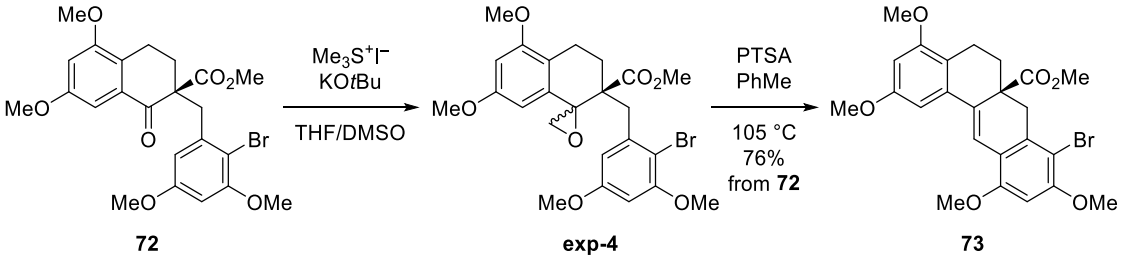
^{1}H-NMR (400 MHz, $CDCl_3$): 7.17 (d, J = 2.5 Hz, 1H), 6.58 (d, J = 2.4 Hz, 1H), 6.44 (d, J = 2.8 Hz, 1H), 6.35 (d, J = 2.8 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.78 (s, 3H), 3.75 (d, J = 13.9 Hz, 1H), 3.73 (s, 3H), 3.65 (s, 3H), 3.61 (d, J = 14.0 Hz, 1H), 2.91 – 2.78 (m, 1H), 2.69 – 2.57 (m, 2H), 2.00 – 1.89 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 194.9, 171.6, 159.3, 159.1, 157.9, 156.7, 138.7, 133.5, 126.1, 108.1, 107.3, 104.2, 100.8, 98.6, 58.7, 56.4, 55.8, 55.7, 55.5, 52.8, 38.8, 29.5, 19.5.

IR: 3007, 2942, 2839, 1724, 1684, 1606, 1580, 1482, 1453, 1430, 1367, 1337, 1315, 1285, 1237, 1211, 1199, 1160, 1134, 1086, 1075, 1059, 1046, 1023, 977, 937, 907, 848, 824, 808, 772, 728.

HRMS (ESI): $C_{23}H_{25}BrNaO_7$ [M+Na] calc. 515.0676, found 515.0687.

Stilbene **73**



Step 1: To ketoester **72** (3.78 g, 7.66 mmol) and trimethyl sulfonium iodide (2.03 g, 9.96 mmol, 1.3 eq.) under nitrogen atmosphere was added anhydrous dimethyl sulfoxide (40 mL). The suspension was stirred for several minutes before a 1 M tetrahydrofuran solution of potassium *tert*-butoxide (9.19 mL, 9.19 mmol, 1.2 eq.) was added dropwise. After stirring for 30 minutes, the resulting solution was poured onto a mixture of water (340 mL) and saturated, sodium chloride (60 mL). The mixture was stirred for several minutes, the resulting suspension was filtered and the filtrate was discarded. The solids were washed with water and then dissolved in dichloromethane (150 mL). The solution was washed with water (50 mL), dried over sodium sulfate and evaporated under reduced pressure to afford crude epoxide **exp-4**, which was directly used without further purification in the next step.

Step 2: Anhydrous toluene (70 mL) was added to crude epoxide **exp-4** and the mixture was warmed to 105°C. Then, p-toluenesulfonic acid monohydrate (146 mg, 0.768 mmol, 0.1 eq.) was added and the mixture was stirred for 15 minutes. After cooling to room temperature, the mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane (50 mL). The solution was washed with saturated, aqueous sodium bicarbonate (40 mL), dried over magnesium sulfate and evaporated under reduced pressure. Ethanol (70 mL) was added to the residue and the mixture was warmed to reflux for several minutes. After standing at room temperature overnight, the mixture was filtered and the filtrate was discarded. The solids were washed with ethanol (2×15 mL) and dried to afford stilbene **73** (2.86 g, 5.84 mmol, 76%) as an off-white solid.

R_f = 0.25 (30% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.55 (s, 1H), 7.06 (d, J = 2.3 Hz, 1H), 6.38 (s, 1H), 6.36 (d, J = 2.3 Hz, 1H), 3.93 (d, J = 15.8 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.89 (s, 3H), 3.50 (s, 3H), 2.99

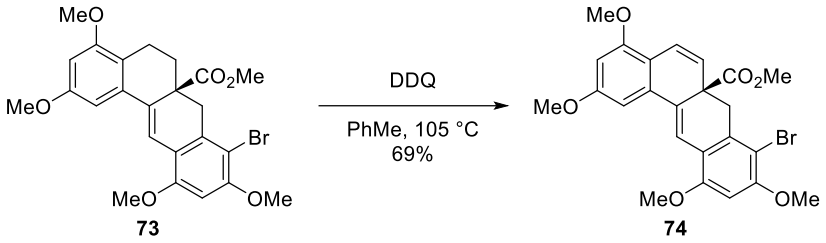
(ddd, J = 17.1, 4.7, 2.6 Hz, 1H), 2.64 (dd, J = 16.1, 0.8 Hz, 1H), 2.46 (ddd, J = 12.9, 4.7, 2.6 Hz, 1H), 2.32 (ddd, J = 17.4, 13.2, 4.6 Hz, 1H), 1.82 (td, J = 13.1, 4.7 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 175.4, 158.8, 158.1, 156.0, 155.7, 135.7, 134.3, 132.0, 118.8, 118.0, 115.9, 104.2, 98.8, 97.6, 94.8, 56.5, 55.9, 55.61, 55.56, 52.4, 46.9, 40.6, 33.7, 20.1.

IR: 2999, 2941, 2839, 1724, 1691, 1614, 1580, 1562, 1513, 1482, 1462, 1434, 1366, 1337, 1325, 1302, 1287, 1274, 1245, 1207, 1186, 1171, 1145, 1121, 1081, 1065, 1006, 978, 946, 910, 887, 839, 826, 808, 791, 776, 731.

HRMS (APCI): $C_{24}H_{26}BrO_6$ [M+H] calc. 489.0907, found 489.0904.

Diene **74**



To stilbene **73** (2.81 g, 5.74 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzo-quinone (1.43 g, 6.32 mmol, 1.1 eq.) was added anhydrous toluene (60 mL) and the mixture was stirred at 105 °C for 40 minutes. After cooling to room temperature, the mixture was filtered over silica (30 g), the silica was washed with dichloromethane (300 mL) and the solvent was removed under reduced pressure. Ethanol (100 mL) was added to the residue, the mixture was warmed to reflux for 15 minutes, then cooled to room temperature and filtered. The filtrate was discarded. The solids were washed with ethanol and dried to afford diene **74** (1.94 g, 3.98 mmol, 69%) as a yellow solid.

R_f = 0.21 (30% ethyl acetate in hexanes).

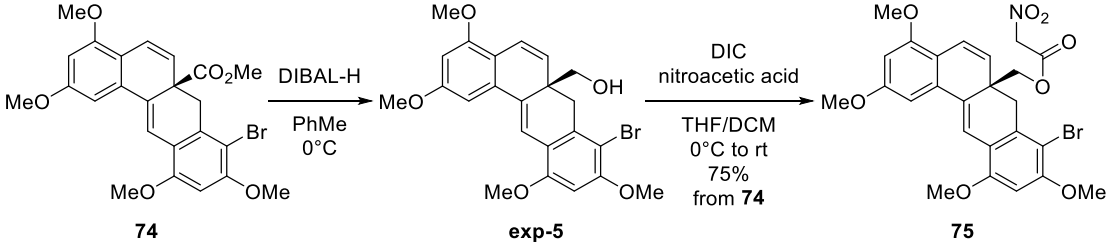
^{1}H-NMR (400 MHz, $CDCl_3$): 7.45 (s, 1H), 6.98 (d, J = 2.2 Hz, 1H), 6.94 (d, J = 9.7 Hz, 1H), 6.38 (s, 1H), 6.35 (d, J = 2.2 Hz, 1H), 5.73 (dd, J = 9.7, 1.0 Hz, 1H), 4.01 (d, J = 16.3 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 3.82 (s, 3H), 3.48 (s, 3H), 2.82 (d, J = 16.3 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 173.1, 160.6, 156.7, 156.3, 155.8, 134.3, 131.6, 125.2, 121.5, 118.0, 117.7, 114.4, 104.3, 99.9, 97.9, 94.7, 56.5, 55.9, 55.8, 55.6, 52.7, 47.2, 38.8.

IR: 3000, 2943, 2911, 2883, 2838, 1724, 1639, 1611, 1591, 1569, 1484, 1462, 1433, 1387, 1330, 1300, 1286, 1255, 1207, 1171, 1143, 1114, 1095, 1072, 1056, 1042, 1006, 966, 948, 937, 910, 898, 839, 828, 797, 768, 730.

HRMS (APCI): $C_{24}H_{24}BrO_6$ [M+H] calc. 487.0751, found 487.0747.

Nitroacetic acid ester **75**



Step 1: To a suspension of diene **74** (1.87 g, 3.84 mmol) in anhydrous toluene (20 mL) under nitrogen atmosphere was added a 1.49 M toluene solution of diisobutylaluminum

hydride (6.44 mL, 9.59 mmol, 2.5 eq.) under ice bath cooling. The mixture was stirred for 15 minutes, before methanol (1.5 mL) was carefully added to the resulting solution, followed by toluene (20 mL), water (20 mL) and saturated, aqueous potassium sodium tartrate (20 mL). The ice bath was removed and the mixture was stirred vigorously for 40 minutes, before ethyl acetate (60 mL) was added and the resulting suspension was filtered. The solids were washed with water (10 mL), followed by ethyl acetate (10 mL) and dried. The organic layer of the filtrate was separated, dried over sodium sulfate and evaporated under reduced pressure. The residue was combined with the previously separated solids. The obtained crude alcohol **exp-5** was a yellow solid, which was directly used without further purification in the next step.

Step 2: To a suspension of crude alcohol **exp-5** in anhydrous dichloromethane (50 mL) under nitrogen atmosphere was added *N*,*N*′-diisopropylcarbodiimide (1.49 mL, 9.59 mmol, 2.5 eq.) under ice bath cooling. Then, a solution of nitroacetic acid (see page 154, 887 mg, 8.44 mmol, 2.2 eq.) in anhydrous tetrahydrofuran (18 mL) was added dropwise. After stirring with warming to room temperature overnight, the volatiles were removed under reduced pressure. The residue was partially purified by column chromatography (33 to 100% dichloromethane in hexanes, then 2% acetone in dichloromethane) and ethanol (150 mL) was added to the partially purified material. The mixture was warmed to reflux for several minutes, then cooled to room temperature and filtered. The filtrate was discarded. The solids were washed with ethanol and dried to afford nitroacetic acid ester **75** (1.58 g, 2.98 mmol, 75%) as a yellow solid.

$\mathbf{R_f}$ = 0.17 (30% ethyl acetate in hexanes).

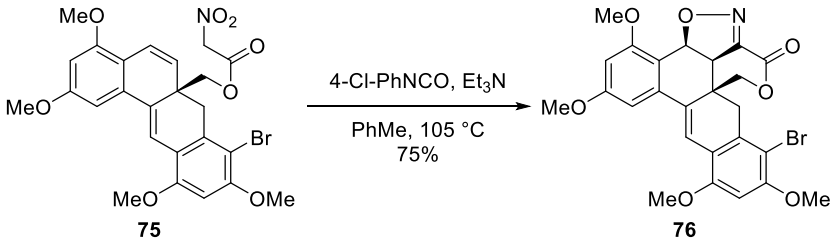
^{1}H-NMR (400 MHz, $CDCl_3$): 7.42 (s, 1H), 6.95 (d, J = 9.8 Hz, 1H), 6.90 (d, J = 2.2 Hz, 1H), 6.42 (s, 1H), 6.38 (d, J = 2.2 Hz, 1H), 5.67 (dd, J = 9.9, 0.9 Hz, 1H), 4.87 (d, J = 14.5 Hz, 1H), 4.80 (d, J = 14.5 Hz, 1H), 4.08 (d, J = 10.4 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.90 (s, 3H), 3.88 (d, J = 10.4 Hz, 1H), 3.84 (s, 3H), 3.45 (d, J = 16.9 Hz, 1H), 2.84 (d, J = 16.9 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 161.7, 160.4, 156.7, 156.6, 155.8, 133.8, 133.8, 132.3, 126.8, 121.3, 118.2, 117.2, 114.9, 104.9, 100.1, 98.1, 94.8, 75.9, 69.7, 56.6, 56.0, 55.8, 55.7, 38.9, 36.8.

IR: 3007, 2997, 2942, 2886, 2880, 2840, 1754, 1640, 1611, 1590, 1565, 1512, 1483, 1460, 1434, 1401, 1392, 1369, 1329, 1309, 1284, 1228, 1206, 1146, 1107, 1075, 1054, 1012, 975, 959, 944, 937, 910, 874, 831, 820, 782, 771, 731, 714.

HRMS (APCI): $C_{25}H_{25}BrNO_8$ [M+H] calc. 546.0758, found 546.0756.

Isoxazoline **76**



75 **76**

To ester **75** (1.36 g, 2.49 mmol) in anhydrous toluene (20 mL) was added triethylamine (414 µL, 2.99 mmol, 1.2 eq.) and the mixture was warmed to 105°C. Then, a solution of 4-chlorophenyl isocyanate (1.15 g, 7.47 mmol, 3 eq.) in anhydrous toluene (2 mL) was added via syringe pump within 1 hour. After stirring for further 2 hours, the mixture was

cooled to room temperature and directly[a] purified by column chromatography (dichloromethane). Ethanol (75 mL) was added to the resulting partially purified material, the mixture was warmed to reflux for several minutes, then cooled to room temperature and filtered. The filtrate was discarded. The solids were washed with ethanol (50 mL) and dried to afford isoxazoline **76** (990 mg, 1.87 mmol, 75%) as an off-white solid.

R_f = 0.45 (60% ethyl acetate in hexanes).

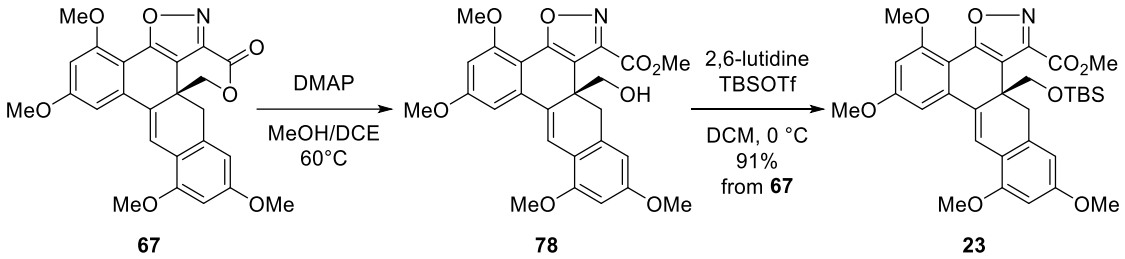
^{1}H-NMR (400 MHz, DMSO-d_6): 7.28 (s, 1H), 6.74 (s, 1H), 6.73 (d, J = 2.3 Hz, 1H), 6.64 (d, J = 2.2 Hz, 1H), 6.09 (d, J = 12.7 Hz, 1H), 4.06 (d, J = 12.7 Hz, 1H), 3.93 (s, 6H), 3.85 (s, 3H), 3.85 (s, 3H), 3.73 (d, J = 12.1 Hz, 1H), 3.64 (d, J = 16.8 Hz, 1H), 3.60 (dd, J = 12.0, 1.7 Hz, 1H), 2.78 (d, J = 16.6 Hz, 1H).

^{13}C-NMR (100 MHz, DMSO-d_6): 161.1, 161.0, 159.6, 156.5, 155.8, 148.9, 133.9, 133.2, 127.5, 119.7, 115.5, 113.0, 103.6, 99.7, 99.2, 95.9, 78.2, 68.3, 56.6, 56.2, 56.1, 55.4, 48.1, 38.6, 35.8.

IR: 2938, 2841, 2361, 2337, 2259, 2244, 1761, 1600, 1580, 1490, 1459, 1430, 1366, 1331, 1313, 1280, 1207, 1152, 1111, 1048, 999, 930, 911, 871, 830, 731.

HRMS (APCI): $C_{25}H_{23}BrNO_7$ [M+H] calc. 528.0652, found 528.0652.

Alcohol 78 and silyl ether 23



Step 1: To lactone **67** (500 mg, 1.12 mmol) and 4-dimethylaminopyridine (25.1 mg, 224 µmol, 0.2 eq.) under nitrogen atmosphere were added anhydrous 1,2-dichloroethane (15 mL) and anhydrous methanol (5 mL). The mixture was stirred for 2.5 hours at 60 °C. Then, the volatiles were removed under reduced pressure to afford crude alcohol **78**, which was directly used without further purification.

Step 2: To crude alcohol **78** under nitrogen atmosphere was added anhydrous dichloromethane (20 mL). The resulting solution was cooled with an ice bath and 2,6-lutidine (260 µL, 2.23 mmol, 2 eq.) was added. Then, *tert*-butyldimethylsilyl trifluoromethanesulfonate (385 µL, 1.68 mmol, 1.5 eq.) was added dropwise. The mixture was stirred under cooling for 2 hours, before being washed with saturated, aqueous sodium bicarbonate (20 mL). The aqueous washings were extracted with dichloromethane (20 mL) and the combined organic layers were dried over magnesium sulfate before being evaporated under reduced pressure. The residue was purified by column chromatography (dichloromethane) to afford silyl ether **23** (643 mg, 1.08 mmol, 91%) as a yellow solid.

Analytical data for alcohol 78

An analytical sample of alcohol **78** was obtained in a separate experiment under identical conditions to step 1 and purified by column chromatography (0 to 2% acetone in dichloromethane), affording a yellow solid.

R_f = 0.39 (60% ethyl acetate in hexanes).

[a]The reaction mixture was directly loaded onto the column.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.51 (s, 1H), 7.00 (d, J = 2.2 Hz, 1H), 6.44 (d, J = 2.1 Hz, 1H), 6.42 (d, J = 2.3 Hz, 1H), 6.33 (d, J = 2.0 Hz, 1H), 4.06 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H), 3.86 (s, 3H), 3.85 (d, J = 16.1 Hz, 1H), 3.84 (s, 3H), 3.69 – 3.56 (m, 2H), 3.05 (d, J = 16.1 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 166.8, 163.2, 162.5, 161.2, 157.8, 156.9, 152.8, 138.2, 135.0, 131.2, 120.8, 115.1, 114.2, 105.9, 105.0, 101.6, 98.0, 97.1, 66.6, 56.2, 55.7, 55.64, 55.62, 53.4, 41.8, 35.2.

IR: 3554, 3453, 2941, 2839, 1740, 1602, 1567, 1536, 1495, 1457, 1427, 1413, 1336, 1323, 1291, 1233, 1212, 1193, 1149, 1088, 1049, 1019, 1000, 964, 907, 870, 827, 813, 762, 728.

Analytical data for silyl ether **23**

R_f = 0.31 (30% ethyl acetate in hexanes).

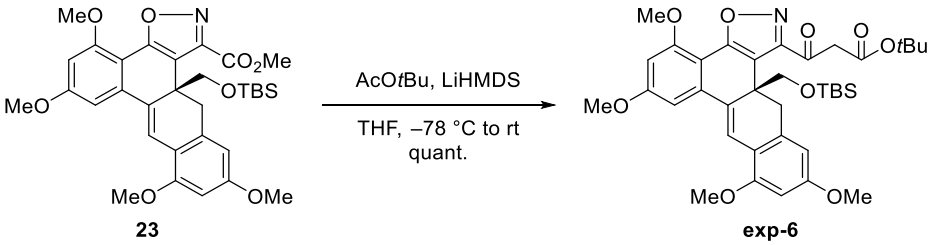
^{1}H-NMR (400 MHz, $CDCl_3$): 7.48 (s, 1H), 6.99 (d, J = 2.2 Hz, 1H), 6.41 (d, J = 2.2 Hz, 1H), 6.40 (d, J = 2.2 Hz, 1H), 6.32 (d, J = 2.1 Hz, 1H), 4.02 (s, 3H), 3.95 (s, 3H), 3.92 (s, 3H), 3.87 (d, J = 16.5 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.65 (d, J = 9.4 Hz, 1H), 3.56 (d, J = 9.3 Hz, 1H), 3.09 (d, J = 16.3 Hz, 1H), 0.55 (s, 9H), -0.29 (s, 3H), -0.32 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 166.9, 162.5, 162.2, 160.8, 157.7, 156.8, 152.9, 139.1, 135.6, 132.5, 119.9, 115.3, 114.9, 106.5, 104.9, 101.5, 97.7, 96.9, 67.2, 56.2, 55.7, 55.6, 55.6, 52.9, 41.8, 35.5, 25.6, 18.0, -5.6, -5.9.

IR: 2954, 2855, 2839, 1736, 1603, 1570, 1496, 1456, 1428, 1413, 1377, 1338, 1324, 1308, 1292, 1243, 1232, 1213, 1151, 1140, 1088, 1050, 1043, 1003, 970, 952, 906, 875, 834, 811, 793, 775, 726.

HRMS (APCI): $C_{32}H_{40}NO_8Si$ [M+H] calc. 594.2518, found 594.2508.

Ketoester **exp-6**



23 **exp-6**

A 1.3 M tetrahydrofuran solution lithium bis(trimethylsilyl)amide (130 µL, 168 µmol, 2.5 eq.) was added to anhydrous tetrahydrofuran (1 mL) under nitrogen atmosphere and the solution was cooled with a dry ice/acetone bath. Then, a solution of silyl ether **23** (40.0 mg, 67.4 µmol) and *tert*-butyl acetate (11 µL, 81 µmol, 1.2 eq.) in anhydrous tetrahydrofuran (3 mL) was added dropwise. Directly after the addition, the cooling bath was removed. After the mixture had stirred for 1 hour, saturated, aqueous ammonium chloride (3 mL) and water (2 mL) were added and the mixture was extracted with dichloromethane (5 mL). The organic extract was dried over sodium sulfate and evaporated under reduced pressure to afford ketoester **exp-6** (46 mg, 67.9 mmol, quant.) as a yellow film, which was used without further purification.

R_f = 0.48 (30% ethyl acetate in hexanes).

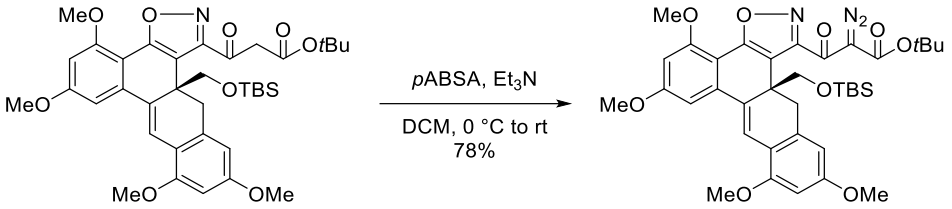
^{1}H-NMR (400 MHz, $CDCl_3$): 7.47 (s, 1H), 7.00 (d, J = 2.2 Hz, 1H), 6.43 – 6.39 (m, 2H), 6.32 (d, J = 2.0 Hz, 1H), 4.24 (d, J = 16.3 Hz, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.92 (d, J = 16.2 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.80 (d, J = 16.6 Hz, 1H), 3.70 (d, J = 9.3 Hz, 1H), 3.67 (d, J = 9.3 Hz, 1H), 3.03 (d, J = 16.4 Hz, 1H), 1.46 (s, 9H), 0.48 (s, 9H), -0.32 (s, 3H), -0.39 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 189.5, 168.0, 166.5, 162.3, 160.8, 157.9, 157.7, 156.8, 139.8, 135.7, 133.1, 119.8, 115.4, 114.4, 106.6, 104.8, 101.4, 97.6, 96.9, 82.2, 68.0, 56.2, 55.8, 55.7, 55.6, 49.0, 41.8, 35.5, 28.2, 25.5, 17.8, -5.6, -5.9.

IR: 3002, 2933, 2855, 2839, 1739, 1707, 1603, 1571, 1496, 1456, 1427, 1411, 1394, 1368, 1329, 1293, 1251, 1239, 1207, 1151, 1097, 1065, 1051, 1020, 1005, 960, 938, 911, 875, 835, 775, 763, 732.

HRMS (APCI): $C_{37}H_{48}NO_9Si$ [M+H] calc. 678.3093, found 678.3086.

Diazoester **79**



To a solution of ketoester **exp-6** (46.0 mg, 77.3 µmol) and 4-acetamido-benzenesulfonyl azide (33.4 mg, 139 µmol, 1.8 eq.) in anhydrous dichloromethane (5 mL) under nitrogen atmosphere was added triethylamine (19 µL, 0.14 mmol, 1.8 eq.) under ice bath cooling. After the mixture had stirred with warming to room temperature overnight, the volatiles were removed under reduced pressure and the residue was purified by column chromatography (75% dichloromethane in pentane) to afford diazoester **79** (36.0 mg, 60.6 µmol, 78%) as a yellow foam.

R_f = 0.42 (30% ethyl acetate in hexanes).

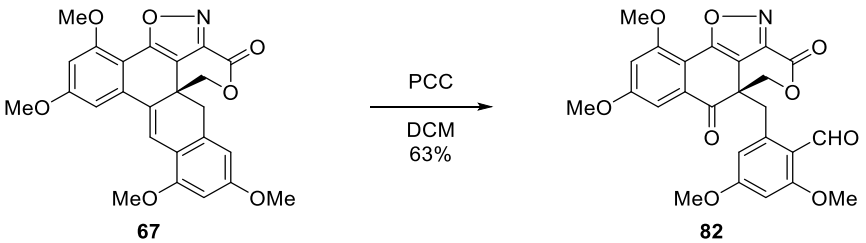
^{1}H-NMR (400 MHz, acetone-d_6): 7.55 (s, 1H), 7.02 (d, J = 2.2 Hz, 1H), 6.63 (d, J = 2.1 Hz, 1H), 6.45 (d, J = 2.3 Hz, 1H), 6.43 (d, J = 2.3 Hz, 1H), 3.98 (s, 3H), 3.94 (s, 3H), 3.90 (s, 3H), 3.83 (s, 3H), 3.66 (s, 2H), 3.34 (d, J = 16.3 Hz, 1H), 3.14 (dt, J = 16.3, 1.2 Hz, 1H), 1.44 (s, 9H), 0.57 (s, 9H), -0.25 (s, 3H), -0.27 (s, 3H).

^{13}C-NMR (100 MHz, acetone-d_6): 179.8, 166.6, 163.4, 162.1, 160.0, 158.6, 158.0, 157.9, 140.0, 135.9, 133.0, 120.5, 115.6, 114.6, 107.0, 106.0, 102.5, 98.3, 97.4, 83.9, 79.2, 69.3, 56.5, 56.1, 56.0, 55.8, 42.0, 36.5, 28.2, 25.9, 18.5, -5.61, -5.63.

IR: 3003, 2954, 2931, 2905, 2855, 2839, 2255, 2133, 1729, 1695, 1646, 1603, 1571, 1495, 1456, 1426, 1414, 1394, 1370, 1331, 1313, 1292, 1255, 1236, 1207, 1151, 1106, 1093, 1053, 1003, 968, 904, 876, 835, 794, 776, 762, 729.

HRMS (ESI): $C_{37}H_{46}N_3O_9Si$ [M+H] calc. 704.2998, found 704.3033.

Aldehyde **82**



To a solution of isoxazole **67** (30.0 mg, 67.1 µmol) in anhydrous dichloromethane (2 mL) was added pyridinium chlorochromate (57.8 mg, 268 µmol, 4 eq.). The mixture was stirred

for 1 hour and then directly[a] purified by column chromatography (1% acetone in dichloromethane) to afford aldehyde **82** (20.4 mg, 42.5 µmol, 63%) as yellow solid.

R_f = 0.31 (60% ethyl acetate in hexanes).

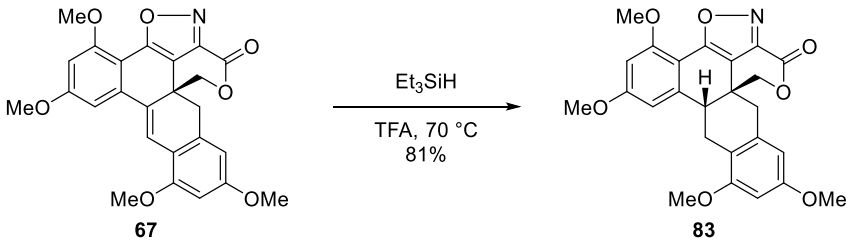
^{1}H-NMR (400 MHz, $CDCl_3$): 10.16 (s, 1H), 7.01 (d, J = 2.2 Hz, 1H), 6.71 (d, J = 2.2 Hz, 1H), 6.28 (d, J = 2.2 Hz, 1H), 6.10 (d, J = 2.2 Hz, 1H), 4.94 (d, J = 11.3 Hz, 1H), 4.34 (d, J = 13.1 Hz, 1H), 4.31 (d, J = 11.9 Hz, 1H), 3.98 (s, 3H), 3.90 (s, 3H), 3.81 (s, 3H), 3.74 (s, 3H), 3.34 (d, J = 12.6 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 197.4, 190.0, 165.4, 164.3, 163.3, 163.1, 156.8, 156.6, 149.6, 139.1, 134.1, 117.4, 117.3, 110.7, 110.2, 105.3, 104.6, 97.7, 74.3, 56.5, 56.1, 56.0, 55.7, 47.4, 38.7.

IR: 3135, 3092, 3082, 2941, 2842, 1765, 1690, 1670, 1596, 1571, 1523, 1487, 1454, 1434, 1358, 1319, 1280, 1246, 1205, 1153, 1111, 1094, 1083, 1050, 1030, 1006, 957, 911, 877, 839, 802, 789, 771, 757, 729.

HRMS (APCI): $C_{25}H_{22}NO_9$ [M+H] calc. 480.1289, found 480.1291.

Lactone 83



To stilbene **67** (220 mg, 491 µmol) under nitrogen atmosphere were added trifluoroacetic acid (940 µL, 12.3 mmol, 25 eq.) and triethylsilane (94 µL, 0.59 mmol, 1.2 eq.). The mixture was stirred at 70 °C for 25 minutes, then the volatiles were removed under reduced pressure and the residue was purified by column chromatography (dichloromethane) to afford lactone **83** (179 mg, 398 µmol, 81%) as a faint yellow solid.

R_f = 0.60 (60% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 6.55 – 6.47 (m, 1H), 6.42 (d, J = 2.0 Hz, 1H), 6.35 (d, J = 2.3 Hz, 1H), 6.13 (d, J = 2.3 Hz, 1H), 4.66 (d, J = 10.9 Hz, 1H), 4.49 (dd, J = 10.9, 1.9 Hz, 1H), 3.98 (s, 3H), 3.87 (s, 3H), 3.80 (s, 3H), 3.74 (s, 3H), 3.59 (d, J = 19.0 Hz, 1H), 3.18 (d, J = 6.0 Hz, 1H), 2.95 (d, J = 17.2 Hz, 1H), 2.65 (ddd, J = 18.9, 6.6, 1.8 Hz, 1H), 2.58 (d, J = 17.2 Hz, 1H).

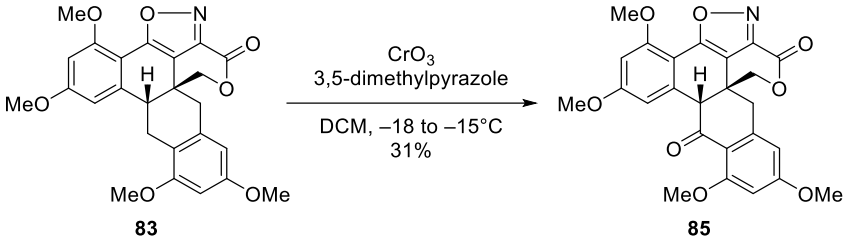
^{13}C-NMR (100 MHz, $CDCl_3$): 165.7, 163.6, 159.1, 158.5, 157.7, 157.6, 148.0, 141.5, 134.7, 120.4, 113.2, 107.9, 106.8, 104.5, 97.0, 95.9, 79.0, 56.2, 55.58, 55.56, 55.4, 41.8, 31.2, 31.0, 20.0.

IR: 2939, 2839, 1759, 1653, 1601, 1570, 1522, 1492, 1449, 1425, 1357, 1345, 1325, 1311, 1275, 1256, 1209, 1197, 1157, 1144, 1136, 1097, 1049, 1040, 1005, 977, 965, 955, 937, 906, 882, 854, 832, 794, 757, 725, 702.

HRMS (APCI): $C_{25}H_{24}NO_7$ [M+H] calc. 450.1547, found 450.1544.

[a]The reaction mixture was directly loaded onto the column.

Ketone **83**



83 **85**

Chromium trioxide flakes (334 mg, 3.34 mmol, 15 eq.) were dried with stirring in a flask under high vacuum until the color changed from violet to orange-red. Then, the flask was placed under nitrogen atmosphere, anhydrous dichloromethane (10 mL) was added and the mixture was cooled with an ice/brine bath. After stirring for several minutes, 3,5-dimethylpyrazole (321 mg, 3.34 mmol, 15 eq.) was added and the mixture was stirred for additional 25 minutes, before lactone **83** (100 mg, 222 µmol) was added. After stirring for 1 hour, the cold mixture was filtered over silica (12 g) and eluted with acetone/dichloromethane = 1/25. The solvent was removed under reduced pressure and the residue was purified by column chromatography (0 to 10% ethyl acetate in dichloromethane) to afford ketone **85** (31.5 mg, 68.0 µmol, 31%) as a yellow solid.

R_f = 0.21 (60% ethyl acetate in hexanes).

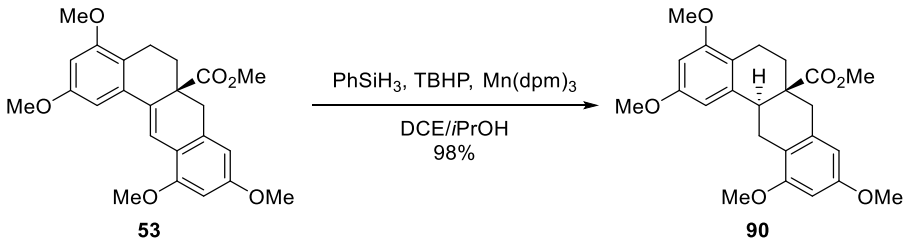
^{1}H-NMR (400 MHz, DMSO-d_6): 6.77 (d, J = 2.2 Hz, 1H), 6.58 (d, J = 2.3 Hz, 1H), 6.49 (s, 1H), 6.25 (s, 1H), 4.79 (d, J = 11.1 Hz, 1H), 4.49 (d, J = 11.0 Hz, 1H), 3.99 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 3.73 (s, 1H), 3.17 (d, J = 17.3 Hz, 1H), 2.85 (d, J = 17.1 Hz, 1H).

^{13}C-NMR (100 MHz, DMSO-d_6): 189.8, 164.7, 164.7, 163.4, 163.1, 157.3, 157.0, 148.3, 144.5, 136.5, 117.9, 113.8, 107.8, 106.7, 106.1, 98.0, 96.9, 76.9, 56.4, 56.0, 55.73, 55.72, 55.6, 33.7, 31.5.

IR: 2923, 2850, 1766, 1728, 1664, 1597, 1570, 1523, 1454, 1435, 1426, 1378, 1357, 1343, 1309, 1280, 1260, 1238, 1219, 1201, 1161, 1138, 1086, 1054, 1041, 1018, 996, 964, 954, 913, 837, 820, 798, 764, 732.

HRMS (ESI): $C_{25}H_{22}NO_8$ [M+H] calc. 464.1340, found 464.1349.

Ester **90**



53 **90**

To stilbene **53** (1.53 g, 3.73 mmol) and tris(2,2,6,6-tetramethyl-3,5-heptane-dionato)manganese(III) (676 mg, 1.12 mmol, 0.3 eq.) under nitrogen atmosphere were added anhydrous, degassed[a] 1,2-dichloroethane (23 mL), anhydrous, degassed* isopropanol (4.6 mL) and phenylsilane (1.84 mL, 14.9 mmol, 4 eq.). The mixture was stirred for several minutes, until a yellow solution was obtained. Then, a 5.5 M solution of *tert*-butyl hydroperoxide in decane (2.71 mL, 14.9 mmol, 4 eq.) was added dropwise in portions (approx. 1 mL). After each portion, the mixture began to boil slightly. At that point, the

[a]By sparging with nitrogen under sonication.

reaction vessel was cooled with an ice bath until the boiling stopped. Then, the cooling bath was removed again and the next portion was added. After the addition was finished and the mixture had stirred overnight, the volatiles were removed under reduced pressure and dichloromethane (15 mL) was added to the residue. The mixture was filtered over Celite® and the Celite® was washed with additional dichloromethane (40 mL). The dichloromethane was evaporated under reduced pressure and the residue was purified by column chromatography (0 to 2% methanol in dichloromethane) to afford ester **90** (1.51 g, 3.66 mmol, 98%) as a white solid.

R_f = 0.57 (40% ethyl acetate in hexanes).

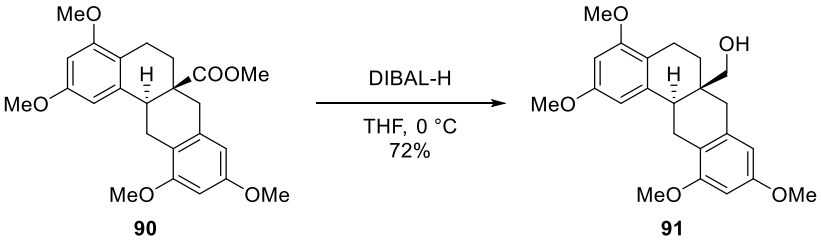
^{1}H-NMR (400 MHz, $CDCl_3$): 6.67 (d, J = 1.7 Hz, 1H), 6.34 (d, J = 2.1 Hz, 1H), 6.31 (d, J = 2.1 Hz, 1H), 6.25 (d, J = 2.0 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.46 (s, 3H), 3.40 (dd, J = 15.9, 5.4 Hz, 1H), 3.31 (d, J = 16.3 Hz, 1H), 3.11 – 2.92 (m, 2H), 2.92 – 2.75 (m, 2H), 2.43 – 2.29 (m, 2H), 1.85 – 1.73 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 174.6, 158.9, 158.6, 158.5, 157.6, 141.2, 135.8, 117.7, 116.7, 103.9, 102.3, 96.4, 95.4, 55.6, 55.41, 55.36, 55.3, 51.6, 45.3, 42.4, 41.4, 34.5, 25.8, 20.6.

IR: 2997, 2938, 2837, 1733, 1606, 1592, 1491, 1463, 1454, 1436, 1422, 1362, 1341, 1314, 1300, 1279, 1261, 1233, 1218, 1198, 1167, 1149, 1125, 1102, 1083, 1052, 1007, 992, 980, 944, 908, 827, 782, 774, 728.

HRMS (APCI): $C_{24}H_{29}O_6$ [M+H] calc. 413.1959, found 413.1961.

Alcohol 91



90 **91**

To a solution of ester **90** (1.36 g, 3.30 mmol) in anhydrous tetrahydrofuran (35 mL) under nitrogen atmosphere was dropwise added a 1.2 M toluene solution of diisobutylaluminum hydride (6.60 mL, 7.92 mmol, 2.4 eq.) under ice bath cooling. The mixture was stirred with warming to room temperature for 8 hours. Then, ethyl acetate (0.5 mL), methanol (0.5 mL) and saturated, aqueous sodium potassium tartrate (35 mL) were added carefully in the specified order. After stirring vigorously overnight, the mixture was extracted with ethyl acetate (3×20 mL). The extracts were washed with saturated, aqueous sodium chloride (2×60 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was partially purified by column chromatograph (0 to 2% methanol in dichloromethane) affording a yellow oil. Diethyl ether (5 mL) was added and the mixture was sonicated. The resulting suspension was filtered, the solids were washed with diethyl ether (8 mL) and the filtrate was discarded. The solids were dissolved in dichloromethane, the solution was diluted with hexanes and then evaporated under reduced pressure to afford alcohol **91** (908 mg, 2.36 mmol, 72%) as a white solid.

R_f = 0.34 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 6.62 (d, J = 1.5 Hz, 1H), 6.36 (d, J = 2.3 Hz, 1H), 6.33 (d, J = 2.4 Hz, 1H), 6.31 (d, J = 2.4 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.51 (d, J = 10.9 Hz, 1H), 3.45 (d, J = 10.6 Hz, 1H), 3.41 (dd, J = 17.3, 6.3 Hz, 1H), 3.06 (d, J = 16.7 Hz, 1H),

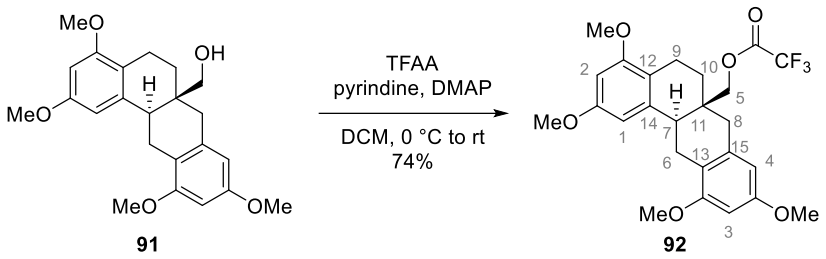
2.98 (dd, J = 12.5, 6.3 Hz, 1H), 2.82 (dd, J = 17.8, 5.6 Hz, 1H), 2.66 – 2.55 (m, 1H), 2.52 (d, J = 16.6 Hz, 1H), 2.32 – 2.21 (m, 2H), 1.47 (td, J = 13.0, 6.4 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 158.9, 158.9, 158.4, 158.0, 140.4, 137.1, 118.0, 117.1, 104.6, 102.9, 96.1, 95.5, 60.0, 55.6, 55.5, 55.45, 55.38, 41.3, 39.9, 35.7, 31.0, 24.7, 19.8.

IR: 3444, 2996, 2936, 2836, 1605, 1593, 1491, 1463, 1421, 1361, 1351, 1336, 1311, 1277, 1227, 1200, 1176, 1147, 1113, 1091, 1053, 987, 964, 944, 927, 909, 827, 808, 755, 730.

HRMS (APCI): $C_{23}H_{29}O_5$ [M+H] calc. 385.2010, found 385.2019.

Trifluoroacetic acid ester **92**



To a solution of alcohol **91** (51.0 mg, 133 µmol), 4-dimethylaminopyridine (3.2 mg, 27 µmol, 0.2 eq.) and pyridine (43 µL, 0.53 mmol, 4 eq.) in anhydrous dichloromethane (3 mL) under nitrogen atmosphere was dropwise added trifluoroacetic anhydride (37 µL, 0.26 mmol, 2 eq.) under ice bath cooling and the mixture was stirred with warming to room temperature overnight. Then, the mixture was diluted with dichloromethane (3 mL) and washed with water (5 mL) and 2 M hydrochloric acid (2×5 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (0 to 30% ethyl acetate in hexanes) to afford trifluoroacetic acid ester **92** (47.0 mg, 97.8 µmol, 74%) as a white solid.

The material after chromatography contained minor impurities. A highly pure sample for NOESY studies was obtained by precipitation from dichloromethane solution by addition of hexanes.

R_f = 0.68 (40% ethyl acetate in hexanes).

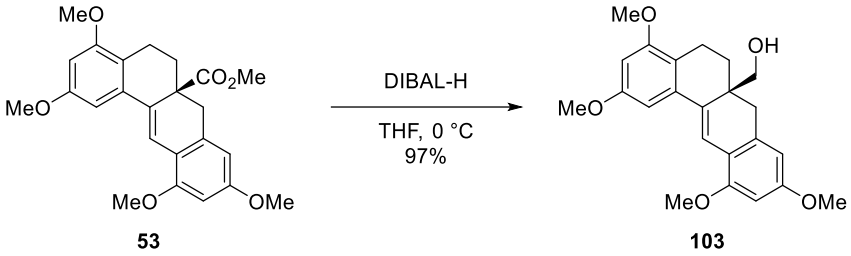
^{1}H-NMR (400 MHz, $CDCl_3$): 6.62 (br, 1H, 1-H), 6.37 (d, J = 2.3 Hz, 1H, 2-H), 6.35 (d, J = 2.4 Hz, 1H, 3-H), 6.27 (d, J = 2.4 Hz, 1H, 4-H), 4.24 (d, J = 11.0 Hz, 1H, 5-H_A), 4.14 (d, J = 11.1 Hz, 1H, 5-H_B), 3.86 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.48 (dd, J = 17.5, 6.4 Hz, 1H, 6-H_A), 3.05 (dd, J = 12.7, 6.4 Hz, 1H, 7-H), 2.95 (d, J = 16.8 Hz, 1H, 8-H_A), 2.85 (dd, J = 18.1, 6.2 Hz, 1H, 9-H_A), 2.66 (d, J = 16.8 Hz, 1H, 8-H_B), 2.44 (ddd, J = 18.2, 13.0, 6.0 Hz, 1H, 9-H_B), 2.30 (dd, J = 17.5, 12.7 Hz, 1H, 6-H_B), 2.22 (dd, J = 13.5, 6.1 Hz, 1H, 10-H_A), 1.59 (td, J = 13.2, 6.3 Hz, 1H, 10-H_B).

^{13}C-NMR (100 MHz, $CDCl_3$): 159.2 (C-OMe), 159.2 (C-OMe), 158.5 (C-OMe), 158.1 (C-OMe), 157.7 (q, J = 42.1 Hz, C=O), 139.2 (C14), 135.7 (C15), 117.1 (C12), 116.3 (C13), 114.7 (q, J = 285.8 Hz, CF_3), 104.5 (C4), 102.9 (C1), 96.4 (C3), 95.8 (C2), 66.7 (C5), 55.6 (OMe), 55.5 (OMe), 55.44 (OMe), 55.39 (OMe), 41.2 (C7), 40.1 (C8), 34.5 (C11), 31.1 (C10), 24.8 (C6), 19.5 (C9).

IR: 2938, 2839, 1782, 1606, 1592, 1492, 1463, 1456, 1437, 1422, 1401, 1365, 1333, 1312, 1278, 1253, 1216, 1201, 1146, 1105, 1092, 1054, 1010, 991, 970, 958, 939, 910, 828, 808, 775, 757, 731.

HRMS (APCI): $C_{25}H_{28}F_3O_6$ [M+H] calc. 481.1832, found 481.1836.

Alcohol **103**



To a solution of ester **53** (500 mg, 1.22 mmol) in anhydrous tetrahydrofuran (8 mL) under nitrogen atmosphere was dropwise added a 1.49 M toluene solution of diisobutylaluminum hydride (2.00 mL, 3.05 mmol, 2.5 eq.) under ice bath cooling. After stirring 2.5 hours, ethyl acetate (0.25 mL), methanol (0.5 mL) and saturated, aqueous sodium potassium tartrate (8 mL) were added carefully in the specified order. The cooling bath was removed and the mixture was stirred vigorously overnight. Then, the mixture was diluted with ethyl acetate (5 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (5 mL). The combined organic layers were washed with water (20 mL) and saturated, aqueous sodium chloride (20 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatograph (0 to 80% ethyl acetate in hexanes) to afford alcohol **103** (451 mg, 1.18 mmol, 97%) as a white solid.

R_f = 0.33 (40% ethyl acetate in hexanes).

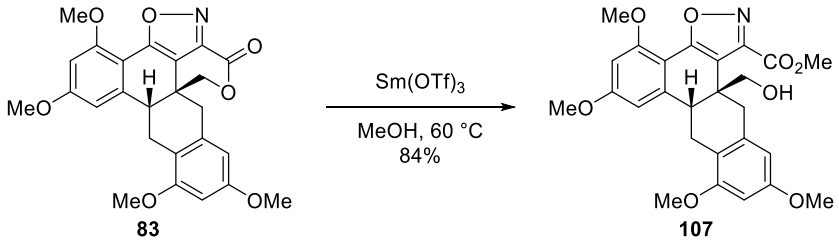
^{1}H-NMR (400 MHz, $CDCl_3$): 7.47 (s, 1H), 7.01 (d, J = 2.3 Hz, 1H), 6.37 (d, J = 2.3 Hz, 1H), 6.35 (d, J = 2.3 Hz, 1H), 6.32 (d, J = 2.3 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.82 (s, 4H), 3.82 (s, 3H), 3.48 (d, J = 11.1 Hz, 1H), 3.33 (d, J = 11.1 Hz, 1H), 3.01 (d, J = 15.9 Hz, 1H), 2.92 (ddd, J = 17.4, 5.3, 2.6 Hz, 1H), 2.71 (dd, J = 15.9, 1.4 Hz, 1H), 2.54 (ddd, J = 17.7, 13.0, 5.1 Hz, 1H), 2.25 (ddd, J = 13.2, 5.2, 2.6 Hz, 1H), 1.56 (td, J = 13.1, 5.3 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 160.1, 158.7, 158.4, 156.5, 137.0, 134.6, 133.4, 118.7, 116.5, 115.6, 105.1, 98.7, 97.3, 96.5, 61.6, 55.62, 55.61, 55.56, 55.5, 38.78, 38.75, 29.9, 19.2.

IR: 3418, 2937, 2836, 1599, 1569, 1490, 1454, 1425, 1363, 1338, 1325, 1308, 1293, 1282, 1234, 1210, 1196, 1181, 1147, 1099, 1073, 1052, 997, 938, 906, 875, 825, 764, 726.

HRMS (APCI): $C_{23}H_{27}O_5$ [M+H] calc. 383.1853, found 383.1859.

Ester **107**



To lactone **83** (103 mg, 231 µmol) and samarium(III) trifluoromethanesulfonate (13.8 mg, 23.1 µmol, 0.1 eq.) under nitrogen atmosphere was added anhydrous methanol (10 mL) and the suspension was stirred at 60 °C for 3 hours. The resulting solution was evaporated under reduced pressure and the residue was purified by column chromatography (2% acetone in dichloromethane) to afford ester **107** (93.1 mg, 193 µmol, 84%) as a yellow solid.

R_f = 0.39 (60% ethyl acetate in hexanes).

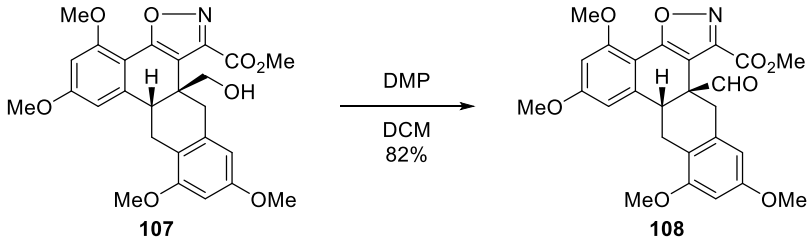
^{1}H-NMR (400 MHz, $CDCl_3$): 6.53 (d, J = 2.2 Hz, 1H), 6.42 (d, J = 2.2 Hz, 1H), 6.25 (d, J = 2.4 Hz, 1H), 6.19 (d, J = 2.3 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.87 (s, 3H), 3.76 (s, 3H), 3.74 (d, J = 12.4 Hz, 1H), 3.70 (d, J = 10.6 Hz, 1H), 3.67 (s, 3H), 3.51 (d, J = 10.7 Hz, 1H), 3.13 (dd, J = 10.5, 7.0 Hz, 1H), 3.04 (d, J = 16.7 Hz, 1H), 2.94 (dd, J = 17.9, 7.1 Hz, 1H), 2.20 (dd, J = 18.5, 10.7 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 167.8, 162.9, 162.5, 158.7, 157.9, 157.3, 153.7, 145.3, 136.1, 117.6, 113.0, 105.8, 105.3, 104.4, 97.2, 96.0, 68.7, 56.0, 55.6, 55.5, 55.2, 53.1, 42.8, 40.4, 33.2, 29.9.

IR: 3420, 3002, 2940, 2839, 1737, 1596, 1554, 1494, 1455, 1428, 1365, 1321, 1298, 1281, 1263, 1224, 1212, 1148, 1126, 1104, 1086, 1051, 1010, 981, 964, 948, 910, 829, 812, 795, 730.

HRMS (APCI): $C_{26}H_{28}NO_8$ [M+H] calc. 482.1809, found 482.1808.

Aldehyde **108**



107 **108**

To a solution of alcohol **107** (84.7 mg, 176 µmol) in anhydrous dichloromethane (3 mL) was added Dess-Martin periodinane (112 mg, 264 µmol, 1.5 eq.) and the mixture was stirred for 1 hour. Then, saturated, aqueous sodium bicarbonate (1 mL), 1 M aqueous sodium thiosulfate (1 mL), water (3 mL) and dichloromethane (2 mL) were added. After further 15 minutes of vigorous stirring, the layers were separated and the aqueous layer was extracted with dichloromethane (5 mL). The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (dichloromethane) to afford aldehyde **108** (69.0 mg, 144 µmol, 82%) as a yellow foam.

R_f = 0.61 (60% ethyl acetate in hexanes).

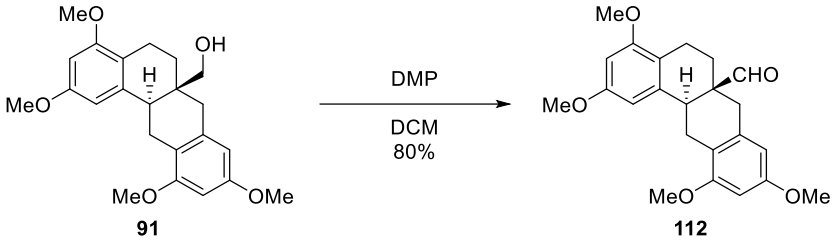
^{1}H-NMR (400 MHz, $CDCl_3$): 9.68 (s, 1H), 6.53 (d, J = 2.1 Hz, 1H), 6.41 (d, J = 2.2 Hz, 1H), 6.25 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 3.84 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H), 3.54 – 3.44 (m, 2H), 3.15 (d, J = 16.7 Hz, 1H), 2.87 (dd, J = 18.0, 6.6 Hz, 1H), 2.62 (dd, J = 18.0, 8.2 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 200.7, 168.7, 163.3, 161.4, 158.8, 158.0, 157.6, 152.9, 143.4, 134.7, 116.3, 110.5, 105.7, 105.5, 104.3, 97.2, 96.5, 56.1, 55.6, 55.5, 55.3, 53.0, 49.9, 41.1, 31.2, 27.1.

IR: 3002, 2941, 2839, 2253, 1732, 1596, 1556, 1494, 1454, 1445, 1428, 1365, 1320, 1299, 1282, 1264, 1233, 1214, 1159, 1147, 1123, 1100, 1082, 1049, 1031, 1010, 984, 964, 948, 908, 870, 830, 811, 794, 762, 728.

HRMS (APCI): $C_{26}H_{26}NO_8$ [M+H] calc. 480.1653, found 480.1654.

Aldehyde **112**



To a solution of alcohol **91** (769 mg, 2.00 mmol) in anhydrous dichloromethane (15 mL) was dropwise added a solution of Dess-Martin periodinane (1.06 g, 2.50 mmol, 1.25 eq.) in anhydrous dichloromethane (5.5 mL)[a,b] and the mixture was stirred for 1.5 hours. Then, saturated, aqueous sodium bicarbonate (10 mL) and 2 M aqueous sodium thiosulfate (10 mL) were added. After stirring vigorously for 1 hour, the layers were separated and the aqueous layer was extracted with dichloromethane (2×15 mL). The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. The residue was partially purified by column chromatography (dichloromethane) and the partially purified material was washed with diethyl ether to afford aldehyde **112** (528 mg, 1.60 mmol, 80%) as a white solid.

R_f = 0.55 (40% ethyl acetate in hexanes).

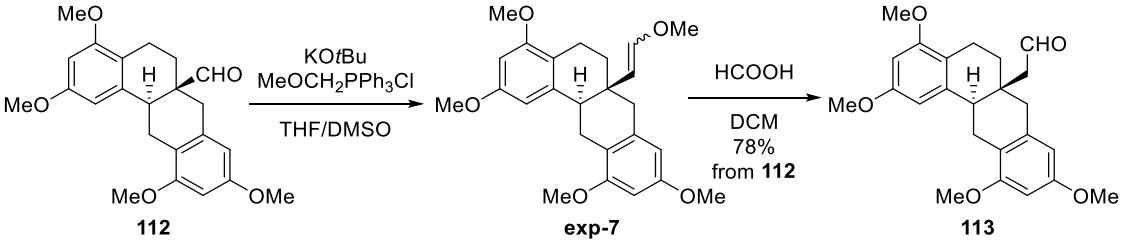
^{1}H-NMR (400 MHz, $CDCl_3$): 9.65 (s, 1H), 6.73 (d, J = 1.5 Hz, 1H), 6.38 (d, J = 2.1 Hz, 1H), 6.31 (d, J = 2.4 Hz, 1H), 6.27 (d, J = 2.4 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 3.57 (dd, J = 17.4, 6.5 Hz, 1H), 3.20 (d, J = 16.5 Hz, 1H), 3.13 (dd, J = 12.4, 6.4 Hz, 1H), 2.84 (ddd, J = 17.8, 6.4, 2.0 Hz, 1H), 2.74 – 2.64 (m, 2H), 2.52 (dddd, J = 17.9, 12.8, 6.4, 1.7 Hz, 1H), 2.25 (ddd, J = 13.3, 6.4, 2.0 Hz, 1H), 1.75 (td, J = 13.0, 6.5 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 206.2, 159.2, 158.9, 158.4, 157.9, 139.8, 135.9, 117.5, 116.8, 103.8, 102.7, 96.5, 95.9, 55.6, 55.44, 55.42, 55.36, 47.6, 39.6, 39.6, 32.2, 25.7, 20.0.

IR: 2999, 2935, 2837, 1719, 1592, 1490, 1456, 1423, 1360, 1312, 1278, 1200, 1147, 1088, 1052, 986, 908, 827, 728.

HRMS (ESI): $C_{23}H_{27}O_5$ [M+H] calc. 383.1853, found 383.1869.

Aldehyde **113**



Step 1: To a suspension of aldehyde **112** (515 mg, 1.35 mmol) and (methoxymethyl)-triphenylphosphonium chloride (1.02 g, 2.96 mmol, 2.2 eq.) in anhydrous dimethyl sulfoxide (13.5 mL) under nitrogen atmosphere was added a 1.66 M tetrahydrofuran solution of potassium *tert*-butoxide (1.60 mL, 2.66 mmol, 2 eq.) and the mixture was stirred for 5 hours. The resulting red solution was diluted with saturated, aqueous ammonium

[a]During preparing the solution of Dess-Martin periodinane some insoluble material remained, which was not added to reaction mixture.
[b]During the addition the mixture initially turned from colorless to yellow and toward the end from yellow to blue.

chloride (40 mL) and extracted with dichloromethane (3×30 mL). The extracts were washed with a 1/4 mixture of saturated, aqueous sodium chloride/water (2×50 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (0 to 20% ethyl acetate in hexanes) to afford enol ether **exp-7** as a roughly 1/1 mixture of diastereomers in the form of a yellowish oil that was used directly in the next step.

Step 2: Enol ether **exp-7** was dissolved in dichloromethane (12 mL). Formic acid (2 mL) was added and the mixture was stirred for 1 hour. Then, the mixture was diluted with dichloromethane (8 mL), washed with water (2×10 mL) and saturated, aqueous sodium bicarbonate (10 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was washed with diethyl ether to afford aldehyde **113** (415 mg, 1.05 mmol, 78%) as an off-white solid.

$\mathbf{R_f}$ = 0.56 (40% ethyl acetate in hexanes).

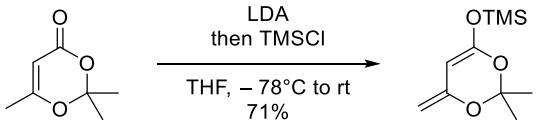
^{1}H-NMR (400 MHz, $CDCl_3$): 9.84 (t, J = 2.6 Hz, 1H), 6.62 (d, J = 1.6 Hz, 1H), 6.37 (d, J = 2.3 Hz, 1H), 6.34 (d, J = 2.4 Hz, 1H), 6.28 (d, J = 2.4 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.45 (dd, J = 17.5, 6.2 Hz, 1H), 3.07 (d, J = 16.7 Hz, 1H), 2.92 – 2.78 (m, 2H), 2.72 (d, J = 16.7 Hz, 1H), 2.54 (dddd, J = 18.0, 13.1, 6.2, 1.8 Hz, 1H), 2.41 – 2.20 (m, 4H), 1.63 (td, J = 13.3, 6.3 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 203.3, 159.12, 159.06, 158.5, 158.1, 140.0, 136.3, 117.1, 116.5, 104.5, 103.1, 96.3, 95.6, 55.6, 55.45, 55.43, 55.39, 43.4, 42.5, 41.1, 34.4, 33.1, 24.8, 19.8.

IR: 2997, 2935, 2914, 2837, 2251, 1715, 1656, 1605, 1592, 1491, 1462, 1454, 1422, 1361, 1351, 1336, 1307, 1277, 1257, 1228, 1199, 1176, 1147, 1130, 1102, 1091, 1053, 994, 968, 945, 934, 909, 827, 730.

HRMS (ESI): $C_{24}H_{29}O_5$ [M+H] calc. 397.2010, found 397.2026.

Silyl enol ether 114



exp-8 **114**

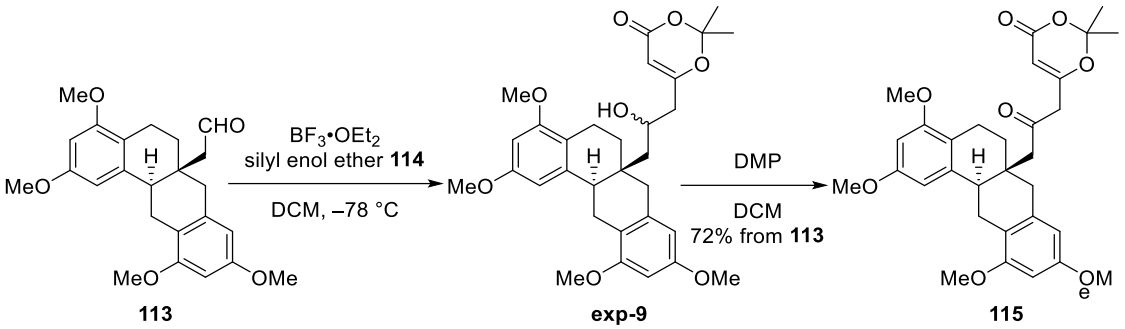
To a solution of diisopropylamine (3.25 mL, 23.2 mmol, 1.1 eq.) in anhydrous tetrahydrofuran (14 mL) under nitrogen atmosphere was dropwise added a 2.38 M hexane solution of *n*-butyllithium (9.75 mL, 23.2 mmol, 1.1 eq.) under ice bath cooling. The mixture was stirred for 20 minutes, then the ice bath was replaced by a dry ice/acetone bath and dioxinone **exp-8** (2.80 mL, 21.1 mmol)[a] was added dropwise. After stirring for 1 hour, chlorotrimethylsilane (3.20 mL, 25.2 mmol, 1.2 eq.) was added dropwise and stirring was continued for 45 minutes. Then, the cooling bath was removed, the mixture was stirred at room temperature for 1.5 hours and filtered over magnesium sulfate under nitrogen atmosphere. The solids were discarded and the filtrate was concentrated under reduced pressure. The residue was purified by distillation under reduced pressure (34–36 °C at 0.5 mbar) to afford silyl enol ether **114** (3.20 g, 14.9 mmol, 71%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 4.65 (s, 1H), 4.07 (d, J = 0.9 Hz, 1H), 3.88 (d, J = 1.0 Hz, 1H), 1.55 (s, 6H), 0.27 (s, 9H).

The spectroscopic data agrees with previously reported values.[13]

[a]The commercially available material was purified by column chromatography (0 to 20% diethyl ether in pentane) before use.

Dioxinone **115**



Step 1: To a solution of aldehyde **113** (350 mg, 0.883 mmol) under nitrogen atmosphere in anhydrous dichloromethane (7 mL) was added boron trifluoride diethyl etherate (163 µL, 1.32 mmol, 1.5 eq.) under cooling with a dry ice/acetone bath. The mixture was stirred for 3 minutes, before silyl enol ether **114** (567 mg, 2.65 mmol, 3 eq.) was added dropwise. After stirring for 2 hours, saturated, aqueous sodium bicarbonate (10 mL) and dichloromethane (13 mL) were added. The cooling bath was removed, the mixture was stirred for 30 minutes and the layers were separated. The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was partially purified by column chromatography (0 to 10% methanol in dichloromethane) to afford alcohol **exp-9** as an orange-yellow oil, which was directly used in the next step.

Step 2: To a solution of alcohol **exp-9** in dichloromethane (7 mL) under nitrogen atmosphere was dropwise added a solution of Dess-Martin periodinane (468 mg, 1.10 mmol, 1.25 eq.) in anhydrous dichloromethane (2.5 mL)[a,b] and the mixture was stirred for 45 minutes. Then, dichloromethane (10 mL), saturated, aqueous sodium bicarbonate (18 mL) and 2 M aqueous sodium thiosulfate (18 mL) were added. After stirring vigorously for 40 minutes, the layers were separated and the aqueous layer was extracted with dichloromethane (2×5 mL). The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. The residue was partially purified by column chromatography (0 to 5% ethyl acetate in dichloromethane). The partially purified material was dissolved in diethyl ether (4 mL), hexanes were added (4 mL), which resulted in separation of an oil, which solidified upon standing at room temperature. The solids were collected, washed with a minimal amount of diethyl ether and dried to afford dioxinone **115** (343 mg, 0.639 mmol, 72%) as an off-white solid

$\mathbf{R_f}$ = 0.33 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 6.60 (d, J = 1.3 Hz, 1H), 6.37 (d, J = 1.8 Hz, 1H), 6.34 (d, J = 2.3 Hz, 1H), 6.25 (d, J = 2.4 Hz, 1H), 5.16 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.42 (dd, J = 17.5, 6.3 Hz, 1H), 3.21 (d, J = 16.8 Hz, 1H), 3.12 (d, J = 15.9 Hz, 1H), 3.07 (d, J = 16.0 Hz, 1H), 2.88 – 2.75 (m, 2H), 2.62 (d, J = 16.8 Hz, 1H), 2.51 (dd, J = 13.2, 5.8 Hz, 1H), 2.45 – 2.24 (m, 4H), 1.57 (s, 6H).

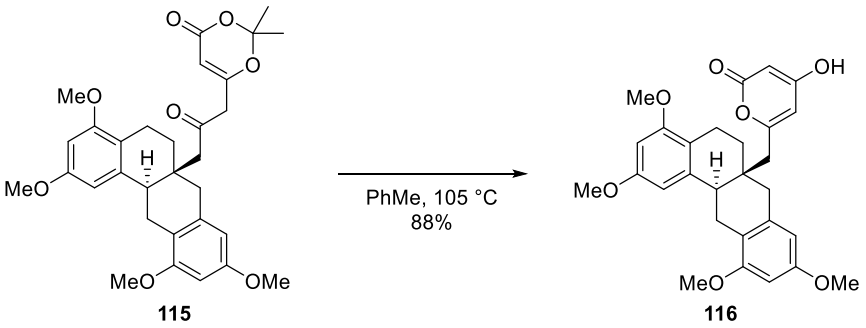
^{13}C-NMR (100 MHz, $CDCl_3$): 203.3, 164.6, 160.7, 159.2, 159.1, 158.5, 158.0, 140.0, 136.8, 117.2, 116.2, 107.1, 104.5, 103.2, 96.5, 96.2, 95.5, 55.6, 55.45, 55.38 (2×OMe), 48.9, 43.6, 41.5, 39.2, 34.2, 31.9, 24.92, 24.86, 24.8, 20.1.

[a]During preparing the solution of Dess-Martin periodinane some insoluble material remained, which was not added to reaction mixture.
[b]During the addition the mixture initially turned from faint yellow to yellow and toward the end from yellow to pink.

IR: 2937, 2916, 2838, 1720, 1635, 1605, 1592, 1492, 1462, 1455, 1421, 1390, 1371, 1309, 1273, 1254, 1228, 1200, 1147, 1109, 1093, 1080, 1051, 1015, 985, 963, 946, 935, 906, 828, 808, 727.

HRMS (ESI): $C_{31}H_{37}O_8$ [M+H] calc. 537.2483, found 537.2501.

Pyrone **116**



115 **116**

A suspension of dioxinone **115** (275 mg, 0.512 mmol) in anhydrous toluene (6 mL) was warmed to 105 °C and stirred for 30 minutes. Then, the mixture was cooled to room temperature and filtered. The filtrate was discarded. The solids were washed with a minimal amount of toluene and dried to afford pyrone **116** (215 mg, 0.449 mmol, 88%) as a white solid.

$\mathbf{R_f}$ = 0.28 (5% methanol in dichloromethane).

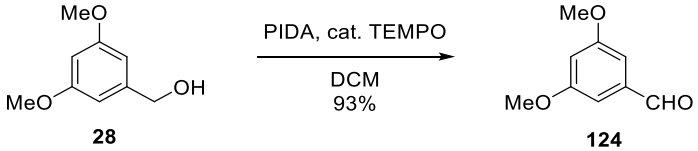
^{1}H-NMR (600 MHz, DMSO-d_6): 11.59 (br, 1H), 6.49 (d, J = 1.6 Hz, 1H), 6.46 (d, J = 2.3 Hz, 1H), 6.42 (d, J = 2.4 Hz, 1H), 6.28 (d, J = 2.3 Hz, 1H), 5.56 (d, J = 2.1 Hz, 1H), 5.21 (d, J = 2.1 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.74 (s, 3H), 3.37 (dd, J = 17.4, 6.4 Hz, 1H), 2.93 (dd, J = 12.2, 6.4 Hz, 1H), 2.79 – 2.63 (m, 3H), 2.53 (d, J = 16.3 Hz, 1H), 2.25 (dd, J = 16.8, 12.4 Hz, 1H), 2.12 (d, J = 14.1 Hz, 1H), 2.08 (d, J = 14.2 Hz, 1H), 1.83 (ddd, J = 13.7, 6.2, 1.6 Hz, 1H), 1.51 (td, J = 13.0, 7.1 Hz, 1H).

^{13}C-NMR (150 MHz, DMSO-d_6): 170.0, 164.5, 163.8, 158.59, 158.56, 157.9, 157.5, 139.3, 136.0, 115.8, 115.4, 104.9, 102.8, 102.3, 95.8, 95.5, 88.5, 55.28, 55.26, 55.1, 55.0, 42.0, 41.4, 34.3, 32.1, 30.6, 24.4, 19.3.

IR: 2935, 2925, 1695, 1663, 1607, 1593, 1568, 1492, 1453, 1424, 1362, 1309, 1277, 1249, 1231, 1201, 1148, 1107, 1082, 1054, 827.

HRMS (ESI): $C_{28}H_{31}O_7$ [M+H] calc. 479.2070, found 479.2064.

Aldehyde **124**



28 **124**

To a solution of alcohol **28** (5.00 g, 29.7 mmol) in dichloromethane were added 2,2,6,6-tetramethylpiperidinyloxyl (467 mg, 2.97 mmol, 0.1 eq.) and phenyliodine(III) diacetate (10.5 g, 32.7 mmol, 1.1 eq.). After stirring for two hours, the solution was washed with 2 M aqueous sodium thiosulfate (40 mL) and saturated, aqueous sodium bicarbonate (40 mL), then dried over sodium sulfate and the solvent removed under reduced pressure. The residue was purified by column chromatography (0 to 20% ethyl acetate in hexanes) to

afford aldehyde **124** (4.60 g, 27.7 mmol, 93%) as faint yellowish oil that solidified upon standing at room temperature.

R_f = 0.45 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 9.90 (s, 1H), 7.01 (d, J = 2.4 Hz, 2H), 6.70 (t, J = 2.3 Hz, 1H), 3.84 (s, 6H).

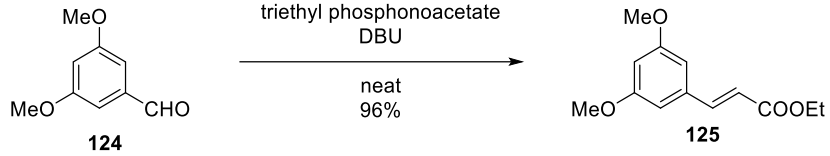
^{13}C-NMR (100 MHz, $CDCl_3$): 192.1, 161.4, 138.5, 107.3, 107.2, 55.8.

IR: 2964, 2942, 2841, 1699, 1653, 1605, 1592, 1560, 1525, 1457, 1431, 1386, 1351, 1316, 1298, 1250, 1233, 1205, 1155, 1063, 1053, 990, 968, 954, 936, 923, 844, 720, 712.

HRMS (EI): $C_9H_{10}O_3$ [$M^{+\cdot}$] calc. 166.0625, found 166.0622.

The spectroscopic data agrees with previously reported values.[14]

Ester **125**



To a mixture of aldehyde **124** (4.60 g, 27.7 mmol) and triethyl phosphonoacetate (5.77 mL, 29.1 mmol, 1.05 eq.) under nitrogen atmosphere was added 1,8-diazabicyclo[5.4.0]undec-7-ene (6.20 ml, 41.5 mmol, 1.5 eq.). After stirring overnight, ethyl acetate (50 ml) was added. The mixture was washed with water (25 mL), 2 M hydrochloric acid (25 mL), saturated, aqueous sodium bicarbonate (25 mL) and saturated, aqueous sodium chloride (25 mL), dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography (0 to 20% ethyl acetate in hexanes) to afford ester **125** (6.30 g, 26.7 mmol, 96%) as colorless oil that solidified upon standing at room temperature.

R_f = 0.45 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.60 (d, J = 16.0 Hz, 1H), 6.66 (d, J = 2.3 Hz, 2H), 6.49 (t, J = 2.3 Hz, 1H), 6.40 (d, J = 16.0 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.81 (s, 6H), 1.34 (t, J = 7.1 Hz, 3H).

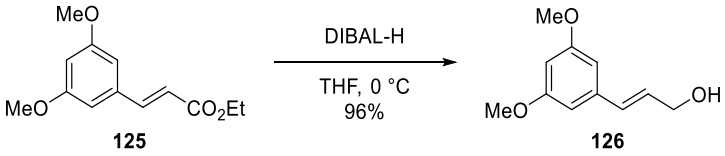
^{13}C-NMR (100 MHz, $CDCl_3$): 167.0, 161.1, 144.7, 136.5, 118.9, 106.1, 102.7, 60.7, 55.5, 14.4.

IR: 2977, 2960, 2939, 2904, 2839, 1706, 1639, 1590, 1457, 1427, 1392, 1367, 1354, 1338, 1318, 1307, 1278, 1240, 1205, 1174, 1152, 1116, 1095, 1062, 1034, 978, 940, 925, 834, 770, 730.

HRMS (ESI): $C_{13}H_{17}O_4$ [M+H] calc. 237.1121, found 237.1120.

The spectroscopic data agrees with previously reported values.[15]

Alcohol **126**



To a solution of ester **125** (6.30 g, 26.7 mmol) in anhydrous tetrahydrofuran (55 mL) under nitrogen atmosphere was dropwise added a 1.49 M toluene solution of diisobutylaluminum hydride (39.4 mL, 58.7 mmol, 2.2 eq.) under ice bath cooling within approximately 30 minutes. After stirring additional 50 minutes, ethyl acetate (2 mL), methanol (10 mL)

and saturated, aqueous sodium potassium tartrate (50 mL) were added carefully in the specified order. The ice bath was removed and the mixture was stirred vigorously overnight. Then, the layers were separated and the aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with water (40 mL) and saturated, aqueous sodium chloride (40°mL), dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography (0 to 30% ethyl acetate in dichloromethane) to afford alcohol **126** (4.96 g, 25.5 mmol, 96%) as a colorless oil that solidified upon standing at room temperature.

R_f = 0.26 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 6.54 (d, J = 2.3 Hz, 2H), 6.54 (dt, J = 15.8, 1.5 Hz, 1H), 6.40 – 6.29 (m, 2H), 4.31 (d, J = 5.4 Hz, 2H), 3.79 (s, 6H).

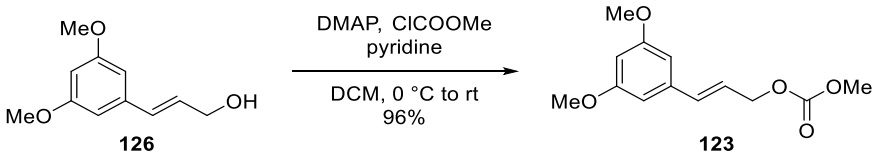
^{13}C-NMR (100 MHz, $CDCl_3$): 161.0, 138.9, 131.1, 129.2, 104.7, 100.0, 63.7, 55.4.

IR: 3338, 3000, 2936, 2837, 1589, 1456, 1424, 1343, 1323, 1299, 1269, 1241, 1203, 1148, 1092, 1058, 1012, 992, 964, 941, 926, 829, 781, 726.

HRMS (APCI): $C_{11}H_{15}O_3$ [M+H] calc. 195.1016, found 195.1018.

The spectroscopic data agrees with previously reported values.[16]

Carbonate 123



To a solution of alcohol **126** (453 mg, 2.33 mmol), 4-dimethylaminopyridine (47.5 mg, 0.233 mmol, 0.1 eq.) and pyridine (564 µL, 7.00 mmol, 3 eq.) in anhydrous dichloromethane (5 mL) under nitrogen atmosphere was dropwise added methyl chloroformate (361 µL, 4.66 mmol, 2 eq.) under ice bath cooling. The mixture was stirred with warming to room temperature overnight, then diluted with water (10 mL) and ethyl acetate (25 mL) under ice bath cooling. The layers were separated and the organic layer was washed with 1 M hydrochloric acid (10 mL) and saturated, aqueous sodium chloride (10 mL). After drying over magnesium sulfate, the solvent was removed under reduced pressure and the residue was purified by column chromatography (60% to 100% dichloromethane in pentane). The carbonate **123** (562 mg, 2.23 mmol, 96%) was obtained as a colorless oil that solidified upon standing at room temperature.

R_f = 0.37 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 6.62 (dt, J = 15.6, 1.3 Hz, 1H), 6.54 (d, J = 2.3 Hz, 2H), 6.39 (t, J = 2.3 Hz, 1H), 6.27 (dt, J = 15.8, 6.4 Hz, 1H), 4.78 (dd, J = 6.4, 1.3 Hz, 2H), 3.81 (s, 3H), 3.79 (s, 6H).

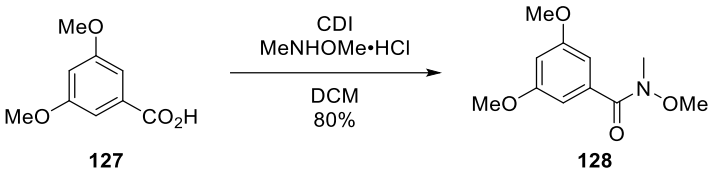
^{13}C-NMR (100 MHz, $CDCl_3$): 161.1, 155.8, 138.2, 134.8, 123.1, 104.9, 100.6, 68.4, 55.5, 55.0.

IR: 2957, 2839, 1744, 1590, 1452, 1441, 1427, 1379, 1349, 1333, 1253, 1203, 1150, 1121, 1059, 1022, 1011, 966, 939, 903, 830, 790, 719.

HRMS (ESI): $C_{13}H_{17}O_5$ [M+H] calc. 253.1071, found 253.1066.

The spectroscopic data agrees with previously reported values.[17]

Weinreb amide **128**



127 **128**

To a suspension of benzoic acid **127** (10.0 g, 54.9 mmol) in dichloromethane (90 mL) was added carbonyldiimidazole (11.1 g, 68.6 mmol, 1.25 eq.) in portions within roughly 5 minutes. After each portion, the mixture was stirred until the vigorous evolution of gas had subsided, before the next portion was added. After the complete addition of the carbonyldiimidazole, the mixture was stirred for 3 hours, before N,O-dimethyl-hydroxylamine hydrochloride (6.43 g, 65.9 mmol, 1.2 eq.) was added and stirring was continued overnight. Then, the mixture was filtered. The solids were washed with dichloromethane and discarded. The filtrate was evaporated under reduced pressure. Water (60 mL) and diethyl ether (60 mL) were added to the residue, the mixture was shaken thoroughly and the layers were separated. The organic layer was washed with water (30 mL), 2 M hydrochloric acid (30 mL) and saturated, aqueous sodium chloride (30 mL), dried over sodium sulfate and evaporated under reduced pressure to afford Weinreb amide **128** (9.94 g, 44.1 mmol, 80%) as yellowish oil.

$\mathbf{R_f}$ = 0.21 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 6.78 (d, J = 2.3 Hz, 2H), 6.53 (t, J = 2.3 Hz, 1H), 3.80 (s, 6H), 3.59 (s, 3H), 3.33 (s, 3H).

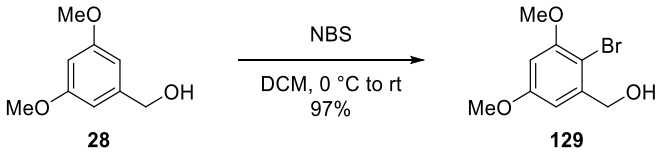
^{13}C-NMR (100 MHz, $CDCl_3$): 169.7, 160.5, 136.1, 106.1, 102.9, 61.3, 55.6, 34.1.

IR: 3001, 2963, 2937, 2839, 1644, 1589, 1536, 1454, 1424, 1373, 1341, 1326, 1311, 1292, 1254, 1204, 1153, 1062, 1045, 1002, 990, 925, 847, 802, 748.

HRMS (APCI): $C_{11}H_{16}NO_4$ [M+H] calc. 226.1074, found 226.1075.

The spectroscopic data agrees with previously reported values.[18]

Alcohol **129**



28 **129**

To a solution of alcohol **28** (5.00 g, 29.7 mmol) in anhydrous dichloromethane (40 mL) was added *N*-bromosuccinimide (5.29 g, 29.7 mmol, 1 eq.) in one portion under ice bath cooling. The mixture was stirred with warming to room temperature overnight. Then, the mixture was washed with water (2×40 mL) and dried over sodium sulfate. Removal of the solvent under reduced pressure afforded alcohol **129** (7.15 g, 28.9 mmol, 97%) as a faint yellowish solid, which was used without further purification.

$\mathbf{R_f}$ = 0.40 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 6.70 (d, J = 2.7 Hz, 1H), 6.44 (d, J = 2.7 Hz, 1H), 4.73 (s, 2H), 3.87 (s, 3H), 3.82 (s, 3H).

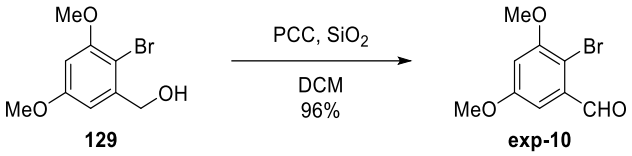
^{13}C-NMR (100 MHz, $CDCl_3$): 160.2, 156.7, 141.9, 104.9, 102.4, 99.1, 65.5, 56.5, 55.7.

IR: 3272, 3081, 2999, 2961, 2938, 2838, 1709, 1587, 1453, 1429, 1419, 1359, 1326, 1288, 1247, 1223, 1199, 1158, 1122, 1097, 1070, 1037, 1020, 954, 919, 835, 793.

HRMS (EI): $C_9H_{11}O_3Br$ [$M^{+\cdot}$] calc. 245.9887, found 245.9881.

The spectroscopic data agrees with previously reported values.[19]

Aldehyde **exp-10**



Silica (7.33 g) and pyridinium chlorochromate (7.33 g, 34.0 mmol, 1.2 eq.) were suspended in anhydrous dichloromethane (35 mL). The suspension was stirred for 10 min, before a solution of alcohol **129** (7.00 g, 28.3 mmol) in anhydrous dichloromethane (50 mL) was added dropwise. After the mixture had stirred for 6 hours, diethyl ether (250 mL) was added. Stirring was continued for 5 minutes, then the mixture was filtered over a small plug of silica. The silica was washed with additional diethyl ether (100 mL) and discarded. The filtrate was evaporated under reduced pressure to afford aldehyde **exp-10** (6.66 g, 27.2 mmol, 96%) as a green-brown solid, which was used without further purification.

$\mathbf{R_f}$ = 0.45 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 10.41 (s, 1H), 7.04 (d, J = 2.9 Hz, 1H), 6.71 (d, J = 2.9 Hz, 1H), 3.91 (s, 3H), 3.85 (s, 3H).

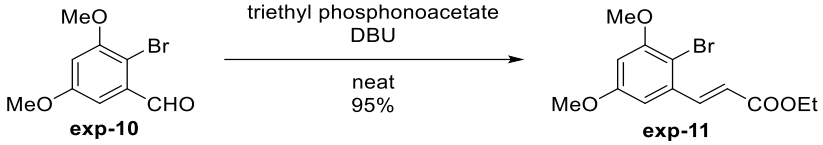
^{13}C-NMR (100 MHz, $CDCl_3$): 192.2, 160.1, 157.2, 134.9, 109.3, 106.0, 103.6, 56.8, 56.0.

IR: 3090, 3010, 2969, 2941, 2891, 2844, 1679, 1584, 1539, 1507, 1449, 1431, 1388, 1332, 1290, 1221, 1200, 1160, 1075, 1021, 970, 921, 842, 720.

HRMS (EI): $C_9H_9O_3Br$ [$M^{+\cdot}$] calc. 243.9730, found 243.9729.

The spectroscopic data agrees with previously reported values.[20]

Ester **exp-11**



To a mixture of aldehyde **exp-10** (5.91 g, 24.1 mmol) and triethyl phosphonate (5.02 mL, 25.3 mmol, 1.05 eq.) under nitrogen atmosphere was added 1,8-Diazabicyclo[5.4.0]undec-7-ene (5.41 ml, 36.2 mmol, 1.5 eq.). After stirring overnight, ethyl acetate (60 ml) was added. The mixture was washed with water (2×40 mL), 2 M hydrochloric acid (40 mL), 2 M aqueous sodium hydroxide (40 mL) and saturated, aqueous sodium chloride (40 mL), dried over magnesium sulfate. Removal of the solvent under reduced pressure afforded ester **exp-11** (7.25 g, 23.0 mmol, 95%) as an orange-brownish solid, which was used without further purification.

$\mathbf{R_f}$ = 0.38 (20% ethyl acetate in hexanes).

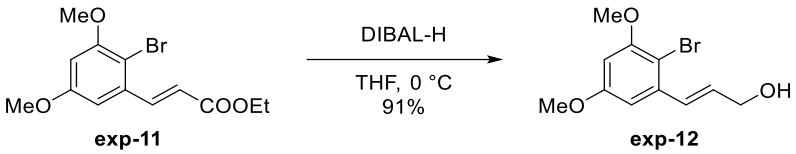
^{1}H-NMR (400 MHz, $CDCl_3$): 8.09 (d, J = 15.9 Hz, 1H), 6.71 (d, J = 2.7 Hz, 1H), 6.51 (d, J = 2.7 Hz, 1H), 6.35 (d, J = 15.9 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 166.5, 159.8, 157.2, 143.6, 136.2, 121.6, 106.5, 103.4, 101.4, 60.8, 56.6, 55.7, 14.4.

IR: 2977, 2939, 2840, 1708, 1636, 1576, 1451, 1432, 1417, 1392, 1367, 1349, 1339, 1301, 1285, 1266, 1238, 1203, 1175, 1161, 1081, 1022, 975, 944, 930, 868, 831, 770, 735.

HRMS (ESI): $C_{13}H_{16}BrO_4$ [M+H] calc. 315.0226, found 315.0216.

Alcohol **exp-12**



exp-11 **exp-12**

To a solution of ester **exp-11** (7.69 g, 24.4 mmol) in anhydrous tetrahydrofuran (40 mL) under nitrogen atmosphere was dropwise added a 1.49 M toluene solution of diisobutylaluminum hydride (36.0 mL, 53.6 mmol, 2.2 eq.) under ice bath cooling within approximately 10 minutes. After stirring additional 20 minutes, methanol (2 mL) was added carefully, followed by saturated, aqueous sodium potassium tartrate (40 mL), water (10 mL) and ethyl acetate (60 mL). The ice bath was removed and the mixture was stirred vigorously overnight. Then, the layers were separated and the aqueous layer was extracted with ethyl acetate (2×60 mL). The combined organic layers were washed with water (80 mL) and saturated, aqueous sodium chloride (80°mL), dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography (0 to 100% dichloromethane in hexanes to 2% acetone in dichloromethane) to afford alcohol **exp-12** (6.12 g, 22.4 mmol, 92%) as a faint brown oil that solidified upon standing at room temperature.

R_f = 0.26 (40% ethyl acetate in hexanes).

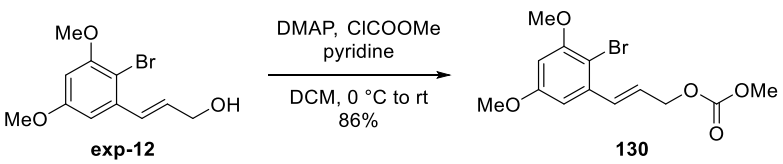
^{1}H-NMR (400 MHz, $CDCl_3$): 7.01 (dt, J = 15.7, 1.6 Hz, 1H), 6.67 (d, J = 2.7 Hz, 1H), 6.42 (d, J = 2.8 Hz, 1H), 6.29 (dt, J = 15.7, 5.6 Hz, 1H), 4.36 (dd, J = 5.6, 1.7 Hz, 2H), 3.87 (s, 3H), 3.82 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 159.7, 156.9, 138.3, 132.0, 130.3, 104.7, 103.2, 99.3, 63.7, 56.5, 55.7.

IR: 3320, 3002, 2961, 2937, 2838, 1574, 1449, 1415, 1330, 1283, 1232, 1201, 1160, 1091, 1076, 1020, 963, 932, 827, 726.

HRMS (APCI): $C_{11}H_{14}BrO_3$ [M+H] calc. 273.0121, found 273.0122.

Carbonate **130**



exp-12 **130**

To a solution of alcohol **exp-12** (5.00 g, 18.4 mmol), 4-dimethylaminopyridine (225 mg, 1.84 mmol, 0.1 eq.) and pyridine (4.45 mL, 55.1 mmol, 3 eq.) in anhydrous dichloromethane (40 mL) under nitrogen atmosphere was dropwise added methyl chloroformate (2.85 mL, 36.8 mmol, 2 eq.) under ice bath cooling. The mixture was stirred with warming to room temperature overnight, then diluted with water (80 mL) and ethyl acetate (120 mL) under ice bath cooling. The layers were separated and the organic layer was washed with 1 M

hydrochloric acid (80 mL), water (80 mL) and saturated, aqueous sodium chloride (80 mL). After drying over magnesium sulfate, the solvent was removed in vacuo and the residue was purified by recrystallization from ethanol to afford carbonate **130** (4.62 g, 14.0 mmol, 76%) as white solid. Additional product **130** (575 mg, 1.74 mmol, 10%) in the form of a white solid was obtained from the mother liquors of the recrystallization after removal of the solvent in vacuo, purification of the residue by column chromatography (0 to 66% dichloromethane in hexanes) and a second recrystallization from ethanol.

$\mathbf{R_f}$ = 0.31 (20% ethyl acetate in hexanes).

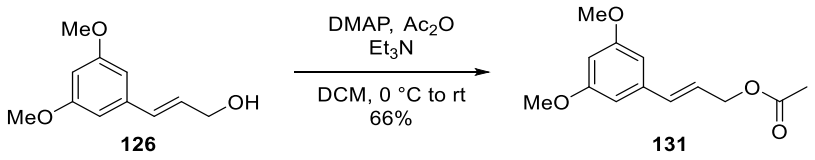
^{1}H-NMR (400 MHz, $CDCl_3$): 7.08 (dt, J = 15.8, 1.4 Hz, 1H), 6.65 (d, J = 2.7 Hz, 1H), 6.43 (d, J = 2.7 Hz, 1H), 6.22 (dt, J = 15.8, 6.3 Hz, 1H), 4.82 (dd, J = 6.4, 1.5 Hz, 2H), 3.86 (s, 3H), 3.82 (s, 5H).

^{13}C-NMR (100 MHz, $CDCl_3$): 159.7, 157.0, 155.7, 137.7, 133.9, 125.8, 104.9, 103.2, 99.7, 68.2, 56.5, 55.7, 55.1.

IR: 2956, 1744, 1578, 1447, 1417, 1379, 1345, 1335, 1254, 1202, 1161, 1120, 1080, 1045, 1022, 965, 941, 900, 830, 790.

HRMS (ESI): $C_{13}H_{15}BrNaO_5$ [M+Na] calc. 352.9995, found 352.9995.

Acetate **131**



To a solution of alcohol **126** (400 mg, 2.06 mmol), 4-dimethylaminopyridine (25.2 mg, 0.206 mmol, 0.1 eq.) and triethylamine (573 µL, 74.12 mmol, 2 eq.) in anhydrous dichloromethane (8 mL) under nitrogen atmosphere was dropwise added acetic anhydride (369 µL, 3.91 mmol, 1.9 eq.) under ice bath cooling. The mixture was stirred with warming to room temperature overnight, then the volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate (30 mL). The solution was washed with 2 M hydrochloric acid (20 mL), saturated, aqueous sodium bicarbonate (20 mL) and saturated, aqueous sodium chloride (20 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (0% to 40% ethyl acetate in hexanes) to afford acetate **131** (322 mg, 1.36 mmol, 66%) as a colorless oil.

$\mathbf{R_f}$ = 0.36 (20% ethyl acetate in hexanes).

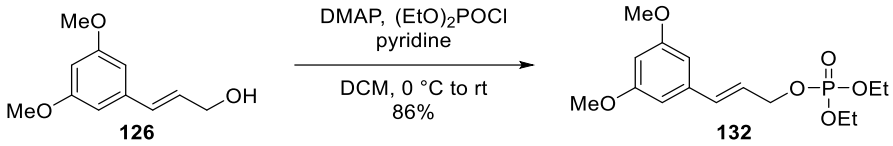
^{1}H-NMR (400 MHz, $CDCl_3$): 6.58 (dt, J = 15.9, 1.4 Hz, 1H), 6.54 (d, J = 2.3 Hz, 2H), 6.39 (t, J = 2.3 Hz, 1H), 6.26 (dt, J = 15.9, 6.4 Hz, 1H), 4.72 (dd, J = 6.4, 1.4 Hz, 2H), 3.79 (s, 6H), 2.10 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 170.9, 161.0, 138.3, 134.2, 123.9, 104.8, 100.5, 65.0, 55.5, 21.1.

IR: 2940, 2839, 1734, 1700, 1662, 1653, 1589, 1457, 1426, 1380, 1363, 1347, 1331, 1300, 1263, 1225, 1204, 1150, 1110, 1059, 1023, 990, 963, 926, 896, 831, 720.

HRMS (ESI): $C_{13}H_{17}O_4$ [M+H] calc. 237.1121, found 237.1114.

Phosphate **132**



To a solution of alcohol **126** (400 mg, 2.06 mmol), 4-dimethylaminopyridine (25.2 mg, 0.206 mmol, 0.1 eq.) and pyridine (199 µL, 2.47 mmol, 1.2 eq.) in anhydrous dichloromethane (8 mL) under nitrogen atmosphere was dropwise added diethyl chlorophosphate (327 µL, 391 mmol, 1.1 eq.) under ice bath cooling. The mixture was stirred with warming to room temperature overnight, then the volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate (30 mL). The solution was washed with 2 M hydrochloric acid (2×20 mL), saturated, aqueous sodium bicarbonate (20 mL) and saturated, aqueous sodium chloride (20 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (30% to 100% ethyl acetate in hexanes) to afford phosphate **132** (582 mg, 1.76 mmol, 86%) as a colorless oil.

R_f = 0.24 (20% ethyl acetate in dichloromethane).

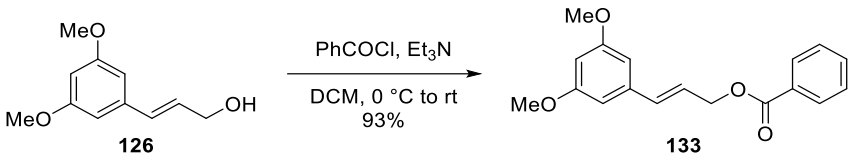
^{1}H-NMR (400 MHz, $CDCl_3$): 6.60 (dt, J = 15.7, 1.5 Hz, 1H), 6.54 (d, J = 2.2 Hz, 2H), 6.39 (t, J = 2.3 Hz, 1H), 6.28 (dt, J = 15.8, 6.2 Hz, 1H), 4.75 – 4.66 (m, 2H), 4.13 (dq, J = 7.9, 7.1 Hz, 4H), 3.79 (s, 6H), 1.34 (td, J = 7.1, 1.0 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): 161.1, 138.2, 133.9, 124.3 (d, J = 6.8 Hz), 104.9, 100.5, 67.86 (d, J = 5.4 Hz), 64.0 (d, J = 5.8 Hz), 55.5, 16.3 (d, J = 6.7 Hz).

IR: 2982, 2938, 2910, 2840, 1590, 1457, 1427, 1393, 1370, 1348, 1333, 1261, 1204, 1151, 1102, 1058, 1015, 992, 965, 843, 819, 799, 747.

HRMS (ESI): $C_{15}H_{23}NaO_6P$ [M+H] calc. 353.1124, found 353.1124.

Benzoate **133**



To a solution of alcohol **126** (500 mg, 2.57 mmol) and triethylamine (448 µL, 3.22 mmol, 1.25 eq.) in anhydrous dichloromethane (8 mL) under nitrogen atmosphere was dropwise added benzoyl chloride (359 µL, 3.09 mmol, 1.2 eq.) under ice bath cooling. The mixture was stirred with warming to room temperature overnight, then diluted with dichloromethane (12 mL) and washed with 1 M hydrochloric acid (20 mL). The aqueous washings were extracted with dichloromethane (2×10 mL), the combined layers dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography (0% to 40% ethyl acetate in hexanes) to afford benzoate **133** (717 mg, 2.40 mmol, 93%) as a colorless oil that solidified upon standing at room temperature.

R_f = 0.43 (20% ethyl acetate in hexanes).

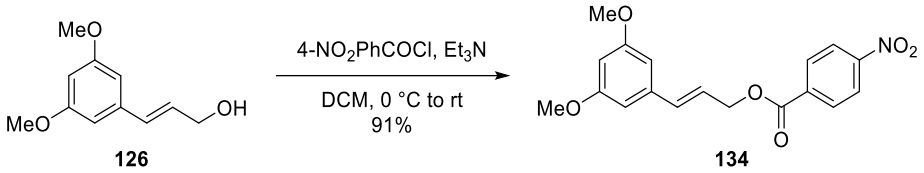
^{1}H-NMR (400 MHz, $CDCl_3$): 8.12 – 8.06 (m, 2H), 7.57 (ddt, J = 8.7, 6.9, 1.4 Hz, 1H), 7.48 – 7.43 (m, 2H), 6.68 (dt, J = 15.6, 1.4 Hz, 1H), 6.58 (d, J = 2.3 Hz, 2H), 6.45 – 6.34 (m, 2H), 4.98 (dd, J = 6.3, 1.4 Hz, 2H), 3.80 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): 166.5, 161.1, 138.4, 134.3, 133.2, 130.3, 129.8, 128.5, 124.0, 104.8, 100.6, 65.5, 55.5.

IR: 3001, 2939, 2838, 1714, 1659, 1642, 1590, 1536, 1530, 1492, 1452, 1426, 1376, 1347, 1332, 1314, 1266, 1204, 1175, 1151, 1113, 1067, 1026, 1003, 989, 966, 938, 926, 847, 830, 806, 710.

HRMS (ESI): $C_{18}H_{19}O_4$ [M+H] calc. 299.1278, found 299.1277.

Nitrobenzoate **134**



To a solution of alcohol **126** (500 mg, 2.57 mmol) and triethylamine (448 µL, 3.22 mmol, 1.2 eq.) in anhydrous dichloromethane (3 mL) under nitrogen atmosphere was dropwise added a solution of 4-nitrobenzoyl chloride (573 mg, 3.09 mmol, 1.2 eq.) in anhydrous dichloromethane (3 mL) under ice bath cooling. Directly after the addition the cooling bath was removed and the mixture was stirred at room temperature overnight. Then, the mixture was diluted with dichloromethane (10 mL), washed with 1 M hydrochloric acid (20 mL) and the aqueous washings were extracted with dichloromethane (2×10 mL). The combined organic layers were dried over sodium sulfate, ethanol (25 mL) was added and the dichloromethane was evaporated under reduced pressure. The remaining suspension in ethanol was filtered and the solids were washed with additional ethanol (10 mL). The filtrate was discarded and the solids were dried under reduced pressure to afford nitrobenzoate **134** (802 mg, 2.34 mmol, 91%) as a yellow solid.

R_f = 0.40 (dichloromethane).

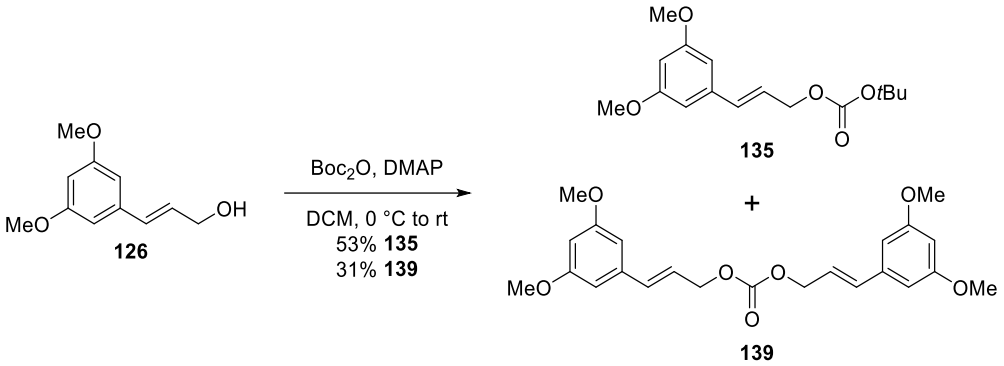
^{1}H-NMR (400 MHz, $CDCl_3$): 8.32 – 8.27 (m, 2H), 8.27 – 8.22 (m, 2H), 6.69 (dt, J = 15.9, 1.3 Hz, 1H), 6.57 (d, J = 2.2 Hz, 2H), 6.43 – 6.34 (m, 2H), 5.02 (dd, J = 6.6, 1.3 Hz, 2H), 3.80 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): 164.6, 161.1, 150.7, 138.0, 135.7, 135.4, 130.9, 123.7, 123.0, 104.9, 100.7, 66.5, 55.5.

IR: 3003, 2941, 2839, 1720, 1590, 1525, 1455, 1427, 1411, 1380, 1347, 1321, 1299, 1265, 1204, 1152, 1118, 1101, 1064, 1014, 965, 925, 872, 857, 838, 804, 784, 718.

HRMS (APCI): $C_{18}H_{18}NO_6$ [M+H] calc. 344.1129, found 344.1129.

Carbonates **135** and **139**



A solution of alcohol **126** (400 mg, 2.06 mmol) in anhydrous dichloromethane (3 mL) was added dropwise under ice bath cooling to a solution of di-*tert*-butyl dicarbonate (899 mg, 4.12 mmol, 2 eq.) and 4-dimethylaminopyridine (50.3 mg, 0.412 mmol, 0.2 eq.) in anhydrous dichloromethane (5 mL) under nitrogen atmosphere. The mixture was stirred with warming to room temperature overnight, then the volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate (30 mL). The solution was washed with 2 M hydrochloric acid (20 mL), saturated, aqueous sodium bicarbonate (20 mL) and saturated, aqueous sodium chloride (20 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (0% to 25% ethyl acetate in hexanes) to afford carbonate **135** (319 mg, 1.08 mmol, 53%) as a colorless oil and side-product **139** (133 mg, 0.321 mmol, 31%) as a colorless oil.

Analytical data for carbonate **135**

R_f = 0.48 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 6.60 (dt, J = 15.8, 1.4 Hz, 1H), 6.54 (d, J = 2.2 Hz, 2H), 6.39 (t, J = 2.3 Hz, 1H), 6.27 (dt, J = 15.8, 6.4 Hz, 1H), 4.71 (dd, J = 6.4, 1.3 Hz, 2H), 3.79 (s, 6H), 1.50 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): 161.0, 153.5, 138.4, 134.4, 123.6, 104.8, 100.5, 82.4, 67.4, 55.5, 27.9.

IR: 3001, 2979, 2938, 2839, 1737, 1591, 1530, 1458, 1426, 1394, 1381, 1369, 1349, 1333, 1272, 1252, 1205, 1151, 1117, 1087, 1061, 1014, 1005, 967, 927, 853, 831, 793, 765, 721.

HRMS (ESI): $C_{16}H_{23}O_5$ [M+H] calc. 295.1540, found 295.1540.

Analytical data for carbonate **139**

R_f = 0.22 (20% ethyl acetate in hexanes).

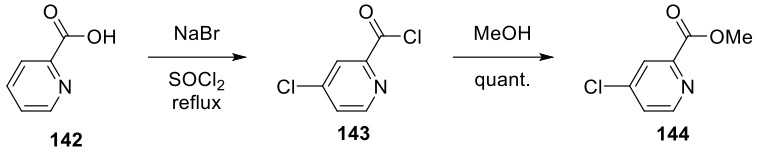
^{1}H-NMR (400 MHz, $CDCl_3$): 6.63 (dt, J = 15.8, 1.4 Hz, 1H), 6.55 (d, J = 2.3 Hz, 2H), 6.39 (t, J = 2.3 Hz, 1H), 6.29 (dt, J = 15.8, 6.4 Hz, 1H), 4.81 (dd, J = 6.4, 1.4 Hz, 2H), 3.79 (s, 5H).

^{13}C-NMR (100 MHz, $CDCl_3$): 161.1, 155.0, 138.2, 134.9, 123.1, 104.9, 100.7, 68.5, 55.5.

IR: 3000, 2938, 2838, 1740, 1589, 1455, 1426, 1391, 1370, 1347, 1332, 1244, 1203, 1149, 1111, 1059, 1008, 990, 966, 922, 830, 788, 729.

HRMS (ESI): $C_{22}H_{27}O_5$ [M+H] calc. 371.1853, found 371.1843.

Chloropicolinate **144**



To picolinic acid (25.0 g, 203 mmol) and sodium bromide (41.8 g, 406 mmol, 2 eq.) was added thionyl chloride (100 ml, 1.38 mol, 6.8 eq.) and the mixture was stirred at reflux for 5 hours. Then, the volatiles were removed under reduced pressure and anhydrous toluene (10 mL) was added to the residue. The mixture was cooled with an ice bath and anhydrous methanol (100 mL) was added carefully in small portions at an appropriate rate to keep the vigorous evolution of gas at an acceptable level. During the addition of methanol, the mixture initially turned into a thick slurry, which became more fluid again after the addition of further methanol. After the addition of methanol, the mixture was stirred with warming to room temperature overnight and the methanol was evaporated under reduced pressure. Saturated, aqueous sodium bicarbonate (300 mL) was added to the residue and the mixture was extracted with ethyl acetate (3×150 mL). The extracts were washed with saturated, aqueous sodium chloride (100 mL), dried over magnesium sulfate and evaporated under reduced pressure to afford chloropicolinate **144** (35.6 g, 207 mmol, quantitative) as a red-brown oil that solidified upon standing at room temperature. The crude material was used without further purification.

$\mathbf{R_f}$ = 0.38 (50% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.64 (dd, J = 5.2, 0.6 Hz, 1H), 8.13 (dd, J = 2.1, 0.6 Hz, 1H), 7.49 (dd, J = 5.2, 2.0 Hz, 1H), 4.01 (s, 3H).

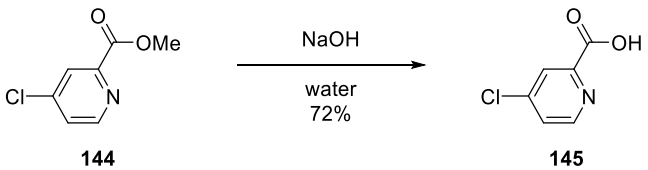
^{13}C-NMR (100 MHz, $CDCl_3$): 164.8, 150.8, 149.4, 145.6, 127.3, 125.8, 53.5.

IR: 3097, 3086, 2959, 1716, 1675, 1576, 1558, 1457, 1440, 1394, 1304, 1266, 1241, 1215, 1193, 1147, 1094, 1088, 994, 966, 896, 848, 782, 750, 703.

HRMS (ESI): $C_7H_7ClNO_2$ [M+H] calc. 172.0160, found 172.0162.

The spectroscopic data agrees with previously reported values.[21]

Chloropicolinic acid **145**



To methyl ester **144** (28.4 g, 166 mmol) was added 2 M aqueous sodium hydroxide (210 mL) and the mixture was stirred overnight. Then, 2 M aqueous hydrochloric acid (210 mL) was added. After stirring 25 minutes, the mixture was filtered and the filtrate was discarded. The solids were washed with water (25 mL), diethyl ether (3×25 mL) and dried to afford chloropicolinic acid **145** (18.7 g, 119 mmol, 72%) as light-brown solid.

^{1}H-NMR (400 MHz, DMSO-d_6): 8.68 (dd, J = 5.2, 0.6 Hz, 1H), 8.05 (dd, J = 2.1, 0.5 Hz, 1H), 7.79 (dd, J = 5.3, 2.1 Hz, 1H).

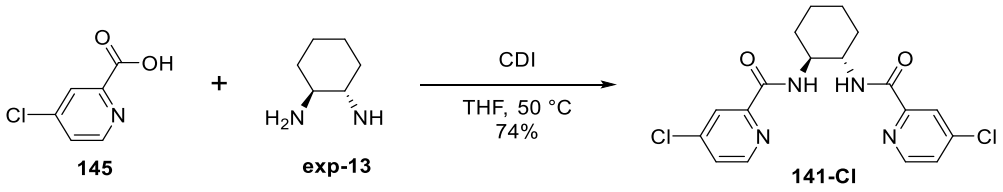
^{13}C-NMR (100 MHz, DMSO-d_6): 165.1, 151.0, 150.2, 144.0, 127.0, 124.7.

IR: 3085, 1700, 1588, 1558, 1445, 1399, 1281, 1269, 1242, 1010, 989, 972, 905, 858, 844, 791, 730.

HRMS (APCI): $C_6H_5ClNO_2$ [M+H] calc. 158.0003, found 158.0008.

The spectroscopic data agrees with previously reported values.[22]

Ligand **141-Cl**



A mixture of carboxylic acid **145** (16.7 g, 106 mmol, 2.2 eq.) and carbonyldiimidazole (16.4 g, 0.101 mmol, 2.1 eq.) in anhydrous tetrahydrofuran (172 mL) under nitrogen atmosphere was stirred for 5 minutes at room temperature and then warmed to 50 °C. After stirring for 2 hours, racemic trans-1,2-Diaminocyclohexane (**exp-13**, 5.78 mL, 48.1 mmol) was added and stirring at 50 °C was continued. After 6.5 hours, the mixture was cooled to room temperature and the solvent was removed under reduced pressure. Water (200 mL) was added to the residue, the mixture was stirred overnight and filtered. The solids were washed with additional water (2×50 mL) and the filtrate was discarded. Then, the solids were dissolved in dichloromethane and the remaining insoluble material was discarded. The dichloromethane solution was dried over sodium sulfate and filtered over a short plug of silica. The silica was washed with additional dichloromethane and 5% ethyl acetate in dichloromethane until no further material eluted. The solvent was removed under reduced pressure. The residue was suspended in ethanol (150 mL), warmed to reflux for 15 minutes and kept at 0 °C for 1 hour. The resulting suspension was filtered and the solids were washed with additional ethanol (2×10 mL) to afford ligand **141-Cl** (12.8 g 32.5 mmol, 68%) as an off-white solid. Additional product **141-Cl** (1.20 g, 3.05 mmol, 6%) was isolate from the filtrate after removal of the solvent under reduced pressure and purification of the residue by column chromatography (0 to 40% ethyl acetate in hexanes).

$\mathbf{R_f}$ = 0.51 (50% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.42 (dd, J = 5.3, 0.6 Hz, 2H), 8.22 – 8.09 (m, 2H), 8.05 (dd, J = 2.1, 0.6 Hz, 2H), 7.35 (dd, J = 5.2, 2.1 Hz, 2H), 4.14 – 3.94 (m, 2H), 2.29 – 2.11 (m, 2H), 1.92 – 1.73 (m, 2H), 1.63 – 1.33 (m, 4H).

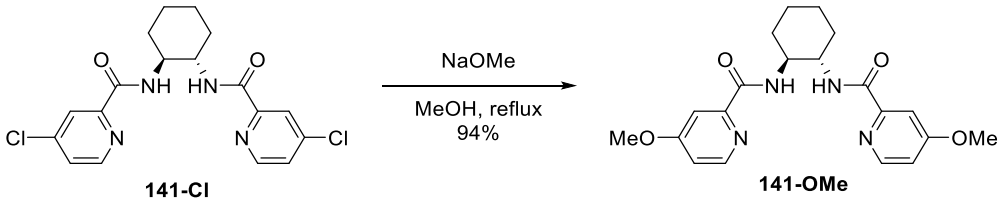
^{13}C-NMR (100 MHz, $CDCl_3$): 163.5, 151.3, 149.2, 145.7, 126.3, 122.9, 53.6, 32.7, 24.9.

IR: 3342, 2930, 2857, 1653, 1578, 1554, 1517, 1461, 1451, 1395, 1366, 1349, 1338, 1321, 1286, 1266, 1231, 1209, 1169, 1139, 1095, 1064, 1047, 994, 959, 938, 904, 878, 859, 847, 836, 795, 782, 747, 730.

HRMS (ESI): $C_{18}H_{19}Cl_2N_4O_2$ [M+H] calc. 393.0880, found 393.0896.

The spectroscopic data agrees with previously reported values.[23]

0Ligand **141-OMe**



To a suspension of chloropyridine **141-Cl** (1.00 g, 2.54 mmol) in anhydrous methanol (10 mL) under nitrogen atmosphere was added a 25% solution of sodium methoxide in methanol (5.4 mL, 20.3 mmol, 8 eq.) and the mixture was warmed to reflux. After stirring for 15 hours, the mixture was cooled to room temperature and the volatiles were removed under reduced pressure. Ammonium chloride (816 mg, 15.3 mmol, 6 eq.) and water (25 mL) were added to the residue and the mixture was stirred for 30 minutes. Then, the mixture was filtered, the solids were washed with water and dried to afford ligand **141-OMe** (923 mg, 2.40 mmol, 94%) as a faint brown solid.

$\mathbf{R_f}$ = 0.38 (5% methanol in dichloromethane).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.30 (d, J = 5.6 Hz, 2H), 8.27 – 8.16 (m, 2H), 7.60 (d, J = 2.6 Hz, 2H), 6.83 (dd, J = 5.6, 2.6 Hz, 2H), 4.09 – 3.95 (m, 2H), 3.83 (s, 6H), 2.26 – 2.14 (m, 2H), 1.88 – 1.76 (m, 2H), 1.58 – 1.37 (m, 4H).

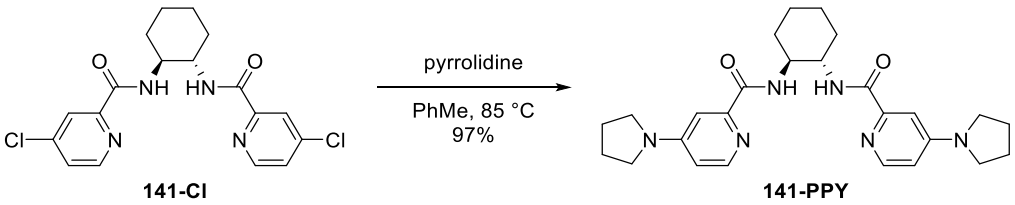
^{13}C-NMR (100 MHz, $CDCl_3$): 166.9, 164.6, 152.0, 149.4, 112.8, 107.5, 55.7, 53.4, 32.7, 24.9.

IR: 3357, 2936, 2857, 1659, 1597, 1567, 1521, 1481, 1462, 1442, 1372, 1322, 1306, 1282, 1251, 1225, 1143, 1105, 1032, 994, 921, 897, 878, 839, 808, 787, 774, 731, 704.

HRMS (ESI): $C_{20}H_{25}N_4O_4$ [M+H] calc. 385.1870, found 385.1875.

The spectroscopic data agrees with previously reported values.[24]

Ligand **141-PPY**



A mixture of chloropyridine **141-Cl** (14.2 g, 36.1 mmol), pyrrolidine (15 mL, 181 mmol, 5 eq.) and anhydrous toluene (14 mL) was stirred at 85 °C under nitrogen atmosphere for 44 hours. After cooling to room temperature, the mixture was diluted with diethyl ether (120 mL) and water (120 mL). Then, the mixture was stirred vigorously for 7.5 hours and the resulting suspension was filtered. The filtrate was discared. The solids were washed with water (2×50 mL) and diethyl ether (2×50 mL), then thoroughly dried at 80 °C under high vacuum to afford ligand **141-PPY** (16.2 g, 35.0 mmol, 97%) as an off-white powder.

$\mathbf{R_f}$ = 0.28 (5% methanol in dichloromethane).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.34 – 8.16 (m, 2H), 8.07 (d, J = 5.8 Hz, 2H), 7.21 (d, J = 2.5 Hz, 2H), 6.32 (dd, J = 5.8, 2.6 Hz, 2H), 4.12 – 3.90 (m, 2H), 3.39 – 3.21 (m, 8H), 2.23 – 2.13 (m, 2H), 2.03 – 1.92 (m, 8H), 1.86 – 1.72 (m, 2H), 1.52 – 1.35 (m, 4H).

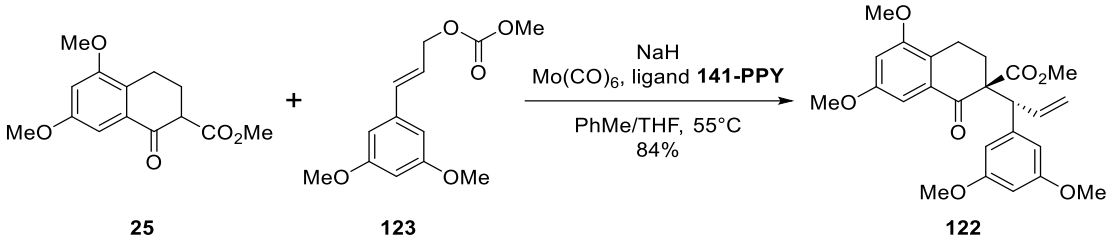
^{13}C-NMR (100 MHz, $CDCl_3$): 165.6, 152.6, 150.0, 148.2, 108.3, 105.7, 53.1, 47.2, 32.8, 25.4, 24.9.

IR: 3351, 2933, 2856, 1661, 1636, 1604, 1515, 1484, 1460, 1391, 1350, 1321, 1287, 1275, 1249, 1230, 1181, 1154, 1111, 1006, 981, 922, 868, 862, 837, 819, 785, 768, 728.

HRMS (ESI): $C_{26}H_{35}N_6O_2$ [M+H] calc. 463.2816, found 463.2810.

The spectroscopic data agrees with previously reported values.[23]

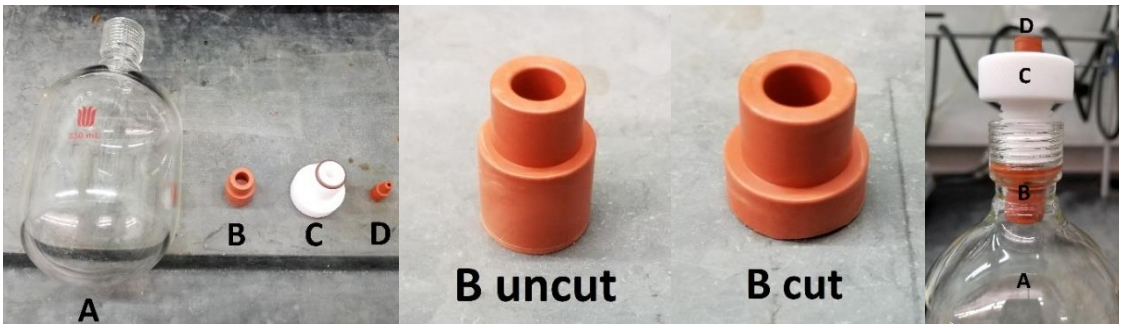
Ketoester **122**



Catalyst preparation: Molybdenum hexacarbonyl (528 mg, 2.00 mmol, 0.08 eq.) and racemic ligand **141-PPY** (1.38 g, 3.00 mmol, 0.12 eq.) were placed in a 40 mL 24-400 screw-cap vial, which was closed with an open-top cap with a PTFE/silicone septum. The vial was evacuated and refilled with argon three times. Anhydrous, degassed[a] toluene (13 mL) was added, the vial was disconnected from the argon line and the sealed vial was stirred at 85 °C behind a blast shield for 4 hours. The resulting solution was taken up in a syringe and directly used for the coupling of carbonate **123** and tetralone **25**.

Coupling: Carbonate **123** (6.31 g, 25.0 mmol), ketoester **25** (8.59 g, 32.5 mmol, 1.3 eq.) and a 60% suspension of sodium hydride in paraffin oil (1.35 g, 33.8 mmol, 1.35 eq.) were placed in a 350 mL pressure vessel, which was closed as described below. The vessel was evacuated and refilled with argon three times. Then, anhydrous, degassed* tetrahydrofuran (100 mL) was added, the mixture was stirred until no more gas evolved and kept at room temperature until the catalyst solution was injected. After the addition of the catalyst solution, the vessel was disconnected from the argon line and the sealed vessel was stirred at 55 °C for 52 hours behind a blast shield. Then, the pressure vessel was carefully vented through a needle and the reaction mixture was purified as described below.

Assembly of the reaction vessel:



The 350 mL pressure vessel with #15 opening (item **A**, highest pressure 88 psig) was closed with a 14/20 natural rubber septum (item **B**). To properly fit into the opening of the pressure vessel a part of the sleeve of the septum was cut off (**B uncut → B cut**). The septum was held in place by a threaded PTFE plug with a hole in the middle (item **C**, PTFE connecting adapter #15 ACE-thread to 8-425 GPI thread by Ace Glass Inc., product # 13290-11). This allows to access the inside of the pressure vessel with a needle through the septum. The outer opening of the hole in the PTFE plug was sealed with 8 mm OD natural

[a]By three cycles of evacuating/refilling with argon under sonication.

rubber septum, to create an addition barrier between the inside of the pressure vessel and the outside atmosphere. The space between both rubber septa was evacuated and refilled with protective gas in the same way as the inside of the pressure vessel.

Purification: Two batches of catalyst preparation and coupling as described above were performed in parallel and combined for purification. Silica (30 g) was added to the combined reaction mixtures of both batches and the volatiles were removed under reduced pressure. Then, the residue was suspended in dichloromethane (50 mL), filtered over additional silica (20 g) and the silica was washed with dichloromethane (450 mL). The dichloromethane was evaporated and ethanol (200 mL) was added to the residue. The mixture was warmed to reflux for several minutes, then kept at room temperature overnight and filtered. The filtrate was discarded. The solids were washed with ethanol (25 mL) and dried to afford ketoester **122** (18.4 g, 41.8 mmol, 84%) as a white solid.

$\mathbf{R_f}$ = 0.61 (40% ethyl acetate in hexanes).

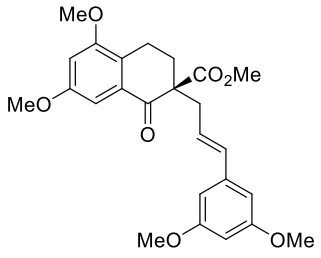
^{1}H-NMR (400 MHz, $CDCl_3$): 7.12 (d, J = 2.5 Hz, 1H), 6.58 (d, J = 2.3 Hz, 2H), 6.56 (d, J = 2.5 Hz, 1H), 6.36 – 6.26 (m, 2H), 5.18 – 5.08 (m, 2H), 4.33 (d, J = 10.0 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.76 (s, 6H), 3.56 (s, 3H), 2.91 (ddd, J = 18.2, 5.6, 3.3 Hz, 1H), 2.79 (ddd, J = 18.2, 11.0, 4.8 Hz, 1H), 2.55 (ddd, J = 13.7, 4.8, 3.3 Hz, 1H), 2.01 (ddd, J = 13.8, 11.1, 5.6 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 193.5, 170.0, 160.4, 159.0, 157.9, 142.2, 136.6, 133.7, 125.6, 117.8, 108.5, 104.2, 100.9, 98.8, 62.3, 55.8, 55.6, 55.4, 53.7, 52.5, 28.4, 19.9.

IR: 3000, 2950, 2837, 1729, 1687, 1604, 1594, 1503, 1487, 1456, 1430, 1367, 1347, 1328, 1283, 1230, 1199, 1152, 1127, 1055, 992, 964, 909, 884, 846, 787, 769, 729.

HRMS (ESI): $C_{25}H_{29}O_7$ [M+H] calc. 441.1908, found 441.1919.

Ketoester **146**



146

A sample of ketoester **146** was isolated during the optimization of the reaction conditions for the coupling of carbonate **123** and ketoester **25**. In the specific experiment, the reaction was conducted similar to the procedure described on page 186, except that the reaction was performed in toluene at 85 °C and not in a sealed vessel. For purification, the reaction mixture was evaporated and the residue was purified by repeated column chromatograph (0 to 30% and 0 to 15% ethyl acetate in hexanes), which afforded impure ketoester **146**. A pure sample was obtained by precipitation from dichloromethane solution by addition of hexanes, which afforded a white solid.

$\mathbf{R_f}$ = 0.55 (40% ethyl acetate in hexanes).

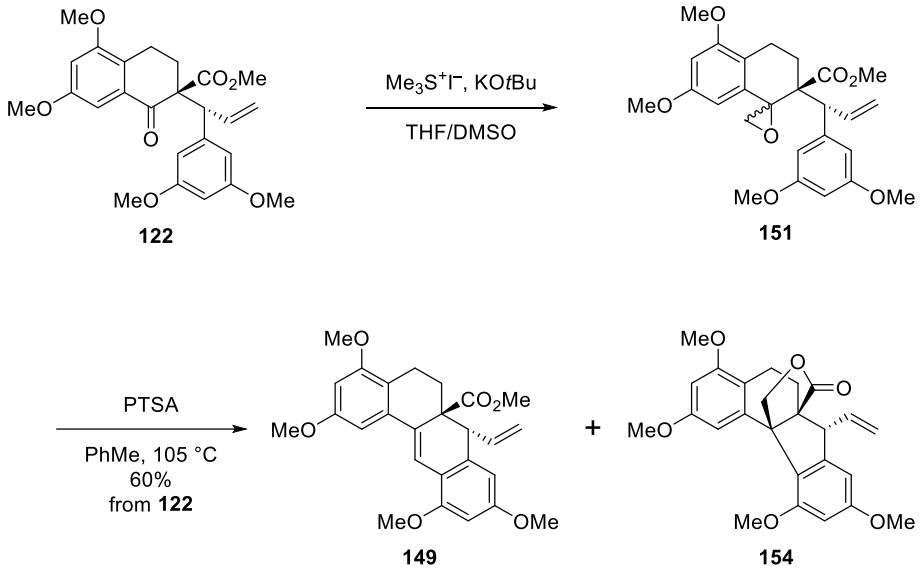
^{1}H-NMR (400 MHz, $CDCl_3$): 7.15 (d, J = 2.5 Hz, 1H), 6.61 (d, J = 2.4 Hz, 1H), 6.49 (d, J = 2.2 Hz, 2H), 6.41 (d, J = 15.8 Hz, 1H), 6.33 (t, J = 2.3 Hz, 1H), 6.22 (dt, J = 15.7, 7.4 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.78 (s, 6H), 3.67 (s, 3H), 2.89 (dt, J = 18.0, 5.1 Hz, 1H), 2.83 (dt, J = 7.5, 1.2 Hz, 2H), 2.75 (ddd, J = 18.1, 9.8, 4.9 Hz, 1H), 2.54 (dt, J = 13.8, 4.9 Hz, 1H), 2.11 (ddd, J = 13.8, 9.9, 5.3 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 195.4, 172.2, 161.0, 159.3, 157.9, 139.3, 134.0, 133.2, 125.9, 125.8, 104.5, 104.3, 100.7, 99.8, 57.8, 55.8, 55.7, 55.5, 52.6, 38.0, 30.4, 19.4.

IR: 3000, 2950, 2838, 1731, 1687, 1650, 1642, 1601, 1591, 1536, 1530, 1510, 1487, 1455, 1426, 1367, 1332, 1285, 1242, 1203, 1153, 1087, 1060, 972, 933, 910, 890, 847, 828, 773, 731, 702.

HRMS (ESI): $C_{25}H_{29}O_7$ [M+H] calc. 441.1908, found 441.1919.

Stilbene **149** and lactone **154**



Step 1: To a suspension of ketoester **122** (16.0 g, 36.3 mmol) and trimethyl sulfonium iodide (8.66 g, 42.4 mmol, 1.17 eq.) under nitrogen atmosphere in anhydrous dimethyl sulfoxide (75 mL) was added a 1.66 M tetrahydrofuran solution of potassium *tert*-butoxide (24.4 mL, 40.5 mmol, 1.12 mmol) in five equal portions in intervals of 10 minutes. After the addition, the mixture was stirred for 25 minutes. The resulting solution was diluted with water (320 mL) and saturated, aqueous sodium chloride (80 mL) and extracted with dichloromethane (200 mL and 2×100 mL). The extracts were washed with water (2×150 mL), dried over sodium sulfate and evaporated under reduced pressure to afford crude epoxide **151** as an off-white solid, which was directly used without further purification in the next step.

Step 2: To a solution of crude epoxide **151** in toluene (75 mL) at 105 °C was added p-toluenesulfonic acid monohydrate (734 mg, 3.86 mmol, 0.11 eq.) and the mixture was stirred for 35 minutes. Then, the reaction mixture was cooled to room temperature, filtered over silica (40 g) and the silica was washed with dichloromethane (350 mL). The solvent was removed under reduced pressure, ethanol (350 mL) was added to the residue and the mixture was warmed to reflux for one hour. After standing at room temperature overnight, the mixture was filtered, the filtrate was discarded and the solids were dried, which afforded stilbene **149** that still contained lactone **154** as a minor impurity and that was further purified as described above.

Purification: Two batches of epoxidation and stilbene formation had been performed in parallel and the impure stilbene **149** (10.6 g and 11.1 g for the individual batches) from both batches was combined. The combined material was treated again with ethanol (350 mL) in the same manner as described above to afford pure stilbene **154** (18.4 g, 43.5 mmol, 60%) as a white solid.

Analytical data for stilbene **149**

R_f = 0.57 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.59 (s, 1H), 7.08 (d, J = 2.2 Hz, 1H), 6.35 (d, J = 2.2 Hz, 1H), 6.33 (d, J = 2.4 Hz, 1H), 6.31 (d, J = 2.3 Hz, 1H), 5.69 (dt, J = 17.0, 9.8 Hz, 1H), 5.21 (ddd, J = 17.0, 1.9, 0.6 Hz, 1H), 4.95 (dd, J = 10.0, 1.9 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.80 (d, J = 9.7 Hz, 1H), 3.48 (s, 3H), 3.03 (ddd, J = 15.4, 4.4, 2.0 Hz, 1H), 2.25 – 2.07 (m, 2H), 1.89 (td, J = 13.3, 12.7, 4.4 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 176.6, 160.4, 158.7, 158.0, 157.0, 139.5, 136.8, 135.3, 129.2, 118.8, 117.1, 116.1, 115.8, 104.4, 98.5, 97.4, 97.2, 55.6, 55.4, 53.5, 52.4, 50.5, 30.4, 20.2.

IR: 3000, 2949, 2837, 1721, 1599, 1570, 1491, 1463, 1455, 1426, 1364, 1338, 1322, 1302, 1287, 1278, 1234, 1213, 1195, 1168, 1148, 1120, 1089, 1058, 999, 981, 961, 946, 912, 874, 861, 827, 792, 764, 731.

HRMS (ESI): $C_{26}H_{29}O_6$ [M+H] calc. 437.1959, found 437.1965.

Analytical data for lactone **154**

An analytical sample of lactone **154** was obtained from the mother liquors of the purification of ketoester **149** in a separate experiment. The mother liquors were evaporated under reduced pressure and column chromatography (0 to 30% ethyl acetate in hexanes) of the residue afforded impure lactone **154**. A pure sample was obtained by precipitation from dichloromethane solution by addition of hexanes, which afforded a white solid.

R_f = 0.51 (40% ethyl acetate in hexanes).

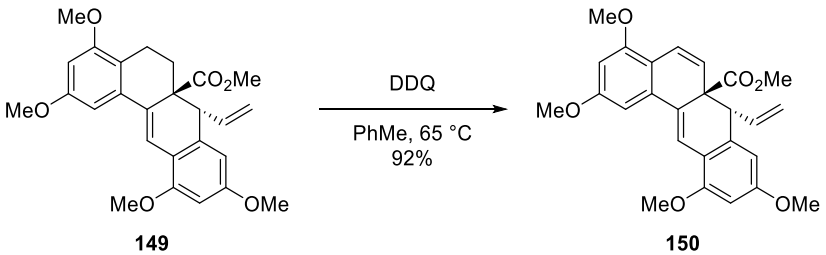
^{1}H-NMR (400 MHz, $CDCl_3$): 6.96 (d, J = 2.4 Hz, 1H), 6.44 (d, J = 2.1 Hz, 1H), 6.36 (d, J = 2.4 Hz, 1H), 6.30 (d, J = 2.1 Hz, 1H), 5.36 – 5.17 (m, 2H), 5.16 (d, J = 9.2 Hz, 1H), 4.96 (dd, J = 9.1, 2.5 Hz, 1H), 4.10 (d, J = 9.1 Hz, 1H), 4.09 (d, J = 9.2 Hz, 1H), 3.94 (s, 4H), 3.79 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H), 3.03 (ddd, J = 16.8, 7.1, 5.7 Hz, 1H), 2.51 (ddd, J = 16.8, 8.2, 5.9 Hz, 1H), 2.10 (ddd, J = 13.3, 7.0, 5.8 Hz, 1H), 2.00 (ddd, J = 14.2, 8.2, 5.8 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 183.3, 162.0, 158.9, 157.5, 157.2, 147.9, 139.6, 138.1, 122.6, 117.3, 117.0, 104.5, 101.6, 99.2, 97.1, 75.0, 58.1, 57.7, 57.5, 55.7, 55.6, 55.3, 55.2, 26.1, 20.1.

IR: 2939, 2837, 1762, 1606, 1585, 1487, 1462, 1454, 1436, 1424, 1363, 1330, 1322, 1308, 1285, 1240, 1201, 1177, 1150, 1111, 1077, 1057, 1021, 1003, 984, 946, 907, 832, 780, 763, 726.

HRMS (ESI): $C_{25}H_{27}O_6$ [M+H] calc. 423.1802, found 423.1806.

Triene **150**



149 **150**

To stilbene **149** (16.9 g, 38.7 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzo-quinone (9.67 g, 42.6 mmol, 1.1 eq.) under nitrogen atmosphere was added anhydrous toluene (155 mL). The mixture was stirred until all solids had been properly suspended, then warmed to 65°C. After stirring for 3 hours, the mixture was cooled to room temperature and filtered. The solids were washed thoroughly with several portions of dichloromethane

(425 mL total) and discarded. The filtrate was evaporated under reduced pressure, ethanol (200 mL) was added to the residue, the mixture was sonicated for 15 minutes and filtered. The solids were washed with ethanol (30 mL) and dried to afford diene **150** (14.8 g, 34.1 mmol, 88%) as a yellow solid. The filtrate was evaporated under reduced pressure and the residue purified by column chromatography (70 to 100% dichloromethane in hexanes and 0 to 10% ethyl acetate in dichloromethane) to afford additional diene **150** (680 mg, 1.57 mmol, 4%) as a yellow foam.

$\mathbf{R_f}$ = 0.53 (40% ethyl acetate in hexanes).

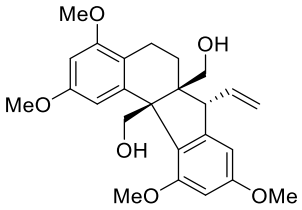
^{1}H-NMR (400 MHz, $CDCl_3$): 7.46 (s, 1H), 6.96 (d, J = 2.2 Hz, 1H), 6.88 (d, J = 9.8 Hz, 1H), 6.34 (d, J = 2.3 Hz, 1H), 6.30 (d, J = 2.2 Hz, 1H), 6.29 (d, J = 2.3 Hz, 1H), 5.92 (ddd, J = 17.0, 10.1, 8.4 Hz, 1H), 5.58 (dd, J = 9.9, 1.1 Hz, 1H), 5.06 (ddd, J = 17.0, 1.8, 1.0 Hz, 1H), 4.99 (ddd, J = 10.1, 1.8, 0.8 Hz, 1H), 4.00 (d, J = 8.4 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.51 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 173.6, 160.8, 160.5, 157.0, 156.8, 137.7, 136.8, 134.3, 129.0, 124.7, 121.9, 118.0, 116.5, 115.6, 113.9, 104.6, 99.3, 97.8, 97.2, 55.7, 55.61, 55.55, 55.5, 52.9, 52.2, 51.8.

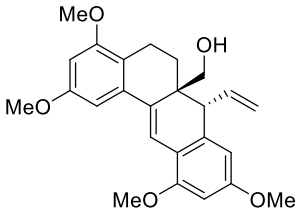
IR: 3001, 2939, 2836, 1719, 1633, 1595, 1568, 1491, 1454, 1424, 1387, 1324, 1304, 1288, 1217, 1204, 1166, 1142, 1116, 1082, 1071, 1051, 1027, 994, 972, 947, 907, 828, 801, 784, 760, 727.

HRMS (ESI): $C_{26}H_{27}O_6$ [M+H] calc. 435.1802, found 435.1813.

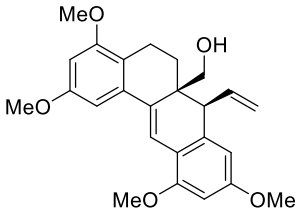
Diol 155, alcohol 156 and alcohol 157



155



156



157

A sample (2.2 g, combined material from several experiments) of the mixture of compounds obtained from the mother liquors of the purification of stilbene **149** (see page 188) was reduced according to the same procedure as ester **53** (see page 168), but with an excess of diisobutylaluminum hydride (10 eq.). Several mixtures of solvents (ethyl acetate/hexanes, ethyl acetate/dichloromethane, methanol/dichloromethane) and different gradients were tested for separating the resulting mixture of diol **155** and stilbenes **156** and **157**. None of these conditions proved suitable to separate the mixture on a multi-gram scale with reasonable effort, but pure samples of all three compounds were obtained.

Analytical data for diol 155

$\mathbf{R_f}$ = 0.40 (5% methanol in dichloromethane), 0.18 (40% ethyl acetate in hexanes)

^{1}H-NMR (400 MHz, $CDCl_3$): 6.93 (d, J = 2.4 Hz, 1H), 6.39 – 6.27 (m, 3H), 5.64 (dt, J = 16.7, 9.7 Hz, 1H), 5.28 (dd, J = 17.0, 2.2 Hz, 1H), 5.14 (d, J = 9.9 Hz, 1H), 4.16 (d, J = 12.8 Hz, 1H), 4.12 (d, J = 12.5 Hz, 1H), 3.86 (d, J = 8.3 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.77 – 3.73 (m, 7H), 3.55 (d, J = 12.3 Hz, 1H), 2.65 (dt, J = 17.9, 6.4 Hz, 1H), 2.51 (dt, J = 17.8, 7.6 Hz, 1H), 1.84 – 1.65 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): 160.8, 158.2, 157.7, 157.3, 148.2, 139.2, 137.6, 124.7, 119.7, 118.2, 105.3, 102.2, 98.1, 96.4, 66.9, 64.13, 58.7, 55.5, 55.4, 55.35, 55.32, 54.7, 53.0, 24.4, 19.7.

IR: 3322, 2998, 2936, 2836, 1605, 1588, 1485, 1462, 1453, 1439, 1418, 1384, 1362, 1331, 1299, 1280, 1244, 1198, 1144, 1105, 1090, 1053, 997, 907, 831, 764, 726.

HRMS (ESI): $C_{25}H_{30}NaO_6$ [M+Na] calc. 449.1935, found 449.1924.

Analytical data for stilbene **156**

R_f = 0.39 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.48 (s, 1H), 7.02 (d, J = 2.3 Hz, 1H), 6.37 (d, J = 2.3 Hz, 1H), 6.35 (d, J = 2.2 Hz, 1H), 6.33 (d, J = 2.3 Hz, 1H), 5.82 (dt, J = 16.9, 9.8 Hz, 1H), 5.15 (dd, J = 16.9, 2.0 Hz, 1H), 4.90 (dd, J = 10.0, 2.0 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.54 (d, J = 10.0 Hz, 1H), 3.52 (d, J = 8.3 Hz, 1H), 3.32 (d, J = 11.3 Hz, 1H), 2.97 (ddd, J = 17.1, 5.1, 2.8 Hz, 1H), 2.48 (ddd, J = 17.4, 12.9, 4.8 Hz, 1H), 2.01 (ddd, J = 13.6, 4.9, 2.8 Hz, 1H), 1.75 (td, J = 13.2, 5.1 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 160.5, 158.7, 158.3, 156.7, 139.8, 138.1, 135.1, 131.5, 119.0, 115.6, 115.3, 115.1, 105.3, 98.6, 97.3, 96.8, 61.7, 55.64, 55.61, 55.60, 55.5, 51.4, 41.6, 25.3, 19.3.

IR: 3437, 3000, 2938, 2836, 1611, 1598, 1568, 1490, 1462, 1424, 1363, 1339, 1321, 1301, 1279, 1210, 1181, 1148, 1097, 1070, 1055, 1031, 1014, 999, 970, 939, 909, 890, 829, 763, 731.

HRMS (APCI): $C_{25}H_{29}O_5$ [M+H] calc. 409.2010, found 409.2012.

Analytical data for stilbene **157**

R_f = 0.46 (40% ethyl acetate in hexanes).

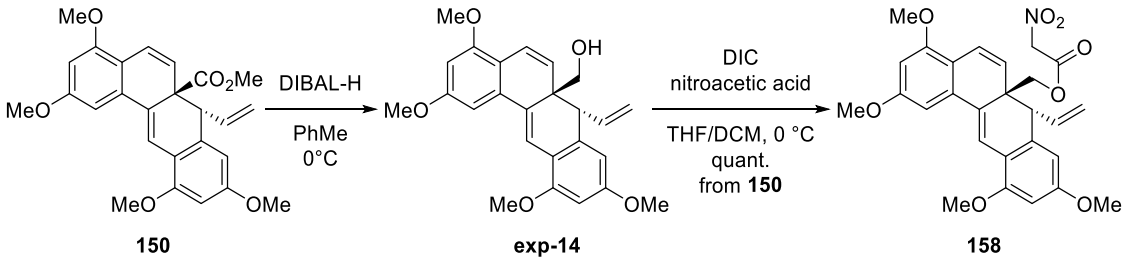
^{1}H-NMR (400 MHz, $CDCl_3$): 7.56 (s, 1H), 7.04 (d, J = 2.3 Hz, 1H), 6.45 (s, 1H), 6.36 (d, J = 2.2 Hz, 1H), 6.34 (d, J = 2.3 Hz, 1H), 6.26 (dt, J = 17.1, 10.1 Hz, 1H), 5.45 (dd, J = 10.1, 2.2 Hz, 1H), 5.24 (dd, J = 17.1, 2.2 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.64 – 3.51 (m, 2H), 3.45 (d, J = 10.1 Hz, 1H), 2.91 (ddd, J = 17.3, 5.4, 2.8 Hz, 1H), 2.49 (ddd, J = 17.6, 12.9, 5.1 Hz, 1H), 2.30 (ddd, J = 13.5, 5.2, 2.8 Hz, 1H), 1.58 (td, J = 13.0, 5.3 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 160.4, 158.7, 158.3, 156.4, 140.0, 136.7, 134.8, 133.4, 120.2, 118.7, 115.9, 115.7, 104.2, 99.0, 97.3, 96.3, 63.5, 55.7, 55.63, 55.57, 55.5, 55.2, 41.4, 30.4, 19.5.

IR: 3498, 2936, 2835, 1598, 1569, 1488, 1461, 1454, 1423, 1365, 1334, 1318, 1299, 1214, 1198, 1143, 1104, 1080, 1054, 1001, 977, 937, 907, 880, 824, 787, 728.

HRMS (APCI): $C_{25}H_{29}O_5$ [M+H] calc. 409.2010, found 409.2002.

Nitroacetic acid ester **158**



150 **exp-14** **158**

Step 1: To a solution of triene **150** (5.85 g, 13.4 mmol) in anhydrous toluene (75 mL) under nitrogen atmosphere was added a 1.49 M solution of diisobutylaluminum hydride in toluene (19.8 mL, 29.5 mmol, 2.2 eq.) under ice bath cooling. The mixture was stirred for 35 minutes, before methanol (2 mL) was carefully added to the resulting solution, followed by water (25 mL) and saturated, aqueous potassium sodium tartrate (75 mL). The ice bath

was removed and the mixture was stirred vigorously for 30 minutes at room temperature, before enough ethyl acetate was added to dissolve all solids. Then, the layers were separated and the aqueous layer was extracted with ethyl acetate (2×75 mL). The combined organic layers were washed with saturated, aqueous sodium chloride (100 mL), dried over sodium sulfate and evaporated under reduced pressure to afford crude alcohol **exp-14** as a brownish-yellow solid, which was directly used without further purification in the next step.

Step 2: To a solution of crude alcohol **exp-14** in anhydrous dichloromethane (100 mL) under nitrogen atmosphere was added *N*,*N*′-diisopropylcarbodiimide (6.23 mL, 40.2 mmol, 3 eq.) under ice bath cooling. Then, a solution of nitroacetic acid (see page 154, 3.52 g, 33.5 mmol, 2.5 eq.) in anhydrous tetrahydrofuran (65 mL) was added dropwise. After stirring for 2 hours, the cooling bath was removed and the volatiles were evaporated under reduced pressure. The residue was purified by column chromatography (0 to 100% dichloromethane in hexanes) to afford nitroacetic acid ester **158** (6.70 g, 13.6 mmol, quantitative) as a yellow foam.

$\mathbf{R_f}$ = 0.46 (40% ethyl acetate in hexanes).

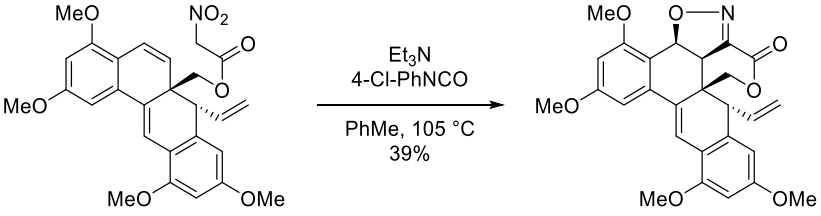
^{1}H-NMR (400 MHz, $CDCl_3$): 7.42 (s, 1H), 6.88 (d, J = 1.8 Hz, 1H), 6.86 (d, J = 5.8 Hz, 1H), 6.33 (d, J = 3.7 Hz, 1H), 6.33 (s, 1H), 6.28 (d, J = 2.3 Hz, 1H), 5.96 (ddd, J = 17.0, 10.0, 8.4 Hz, 1H), 5.55 (dd, J = 10.0, 1.0 Hz, 1H), 5.03 (ddd, J = 17.0, 1.7, 1.0 Hz, 1H), 4.96 (ddd, J = 10.1, 1.7, 0.6 Hz, 1H), 4.91 (d, J = 14.4 Hz, 1H), 4.79 (d, J = 14.4 Hz, 1H), 4.35 (d, J = 10.4 Hz, 1H), 4.04 (d, J = 10.4 Hz, 1H), 3.88 (s, 4H), 3.87 (s, 3H), 3.83 (s, 3H), 3.81 (s, 4H), 3.38 (d, J = 8.5 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 161.8, 161.1, 160.4, 156.9, 156.8, 137.4, 137.1, 133.8, 129.9, 126.2, 121.4, 118.3, 115.9, 114.9, 114.5, 105.3, 99.6, 98.0, 97.2, 76.0, 70.3, 55.8, 55.7, 55.6, 55.5, 51.0, 43.2.

IR: 3003, 2940, 2838, 1755, 1633, 1595, 1563, 1491, 1454, 1425, 1405, 1394, 1367, 1325, 1305, 1285, 1236, 1218, 1205, 1144, 1101, 1077, 1049, 993, 946, 907, 829, 813, 787, 768, 728.

HRMS (ESI): $C_{27}H_{28}NO_8$ [M+H] calc. 494.1809, found 494.1795.

Isoxazoline **159**



158 **159**

To a solution of 4-chlorophenyl isocyanate (644 mg, 4.19 mmol, 4 eq.) in anhydrous toluene (5 mL) under nitrogen atmosphere at 105 °C was added within 2 hours by syringe pump a solution of triene **158** (517 mg, 1.05 mmol) and triethylamine (290 µL, 2.10 mmol, 2 eq.) in anhydrous toluene (5 mL). The mixture was stirred for additional 2 hours, cooled to room temperature and the volatiles were removed under reduced pressure. Dichloromethane (10 mL) was added to the residue and the mixture was filtered. The solids were washed with additional dichloromethane (10 mL) and discarded. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography (dichloromethane) followed by recrystallization from ethanol to afford isoxazoline **159** (192 mg, 0.404 mmol, 39%) as brownish-yellow solid.

$\mathbf{R_f}$ = 0.36 (40% ethyl acetate in hexanes).

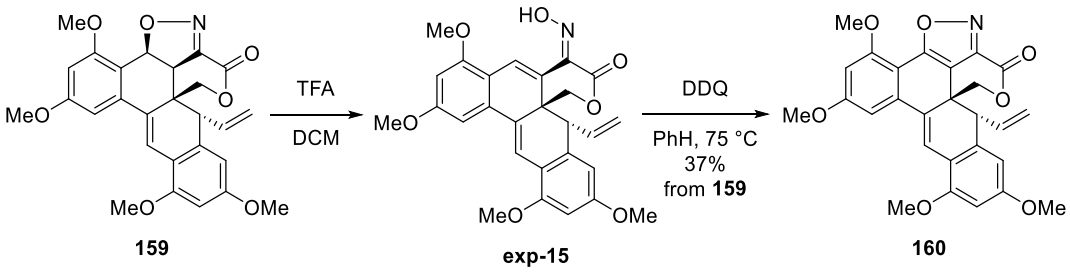
^{1}H-NMR (400 MHz, $CDCl_3$): 7.43 (s, 1H), 6.85 (d, J = 2.3 Hz, 1H), 6.50 (d, J = 2.3 Hz, 1H), 6.40 (d, J = 2.3 Hz, 1H), 6.39 (d, J = 2.3 Hz, 1H), 6.08 (d, J = 12.7 Hz, 1H), 5.73 (dt, J = 17.0, 9.8 Hz, 1H), 5.32 (dd, J = 17.0, 1.5 Hz, 1H), 5.15 (dd, J = 10.0, 1.5 Hz, 1H), 4.23 (d, J = 12.0 Hz, 1H), 4.15 (d, J = 12.8 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 3.71 (d, J = 12.0 Hz, 1H), 3.55 (d, J = 9.7 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 161.8, 161.7, 161.5, 160.1, 157.2, 148.1, 137.4, 135.8, 134.0, 124.6, 120.6, 119.4, 113.9, 112.6, 105.4, 99.7, 99.2, 97.7, 79.1, 69.4, 56.3, 55.72, 55.68, 55.6, 52.9, 44.8, 40.2.

IR: 3002, 2939, 2839, 1759, 1692, 1681, 1609, 1597, 1580, 1570, 1536, 1492, 1455, 1425, 1403, 1368, 1327, 1303, 1278, 1240, 1215, 1204, 1149, 1109, 1090, 1049, 1036, 1011, 988, 914, 877, 830, 799, 761, 730.

HRMS (ESI): $C_{27}H_{26}NO_7$ [M+H] calc. 476.1704, found 476.1724.

Isoxazole **160**



Step 1: To a solution of isoxazoline **159** (107 mg, 225 mmol) in anhydrous dichloromethane (5 mL) was added trifluoroacetic acid (208 µL, 2.70 mmol, 12 eq.). The mixture was stirred for 2.5 hours at 35°C, then poured onto saturated, aqueous sodium bicarbonate (20 mL) and ethyl acetate (30 mL). The mixture was shaken thoroughly and the layers were separated. The organic layer was washed with saturated, aqueous sodium bicarbonate (10 mL) and saturated, aqueous sodium chloride (10 mL), dried over sodium sulfate and evaporated under reduced pressure to afford crude oxime **exp-15** as orange film, which was directly used without further purification in the next step.

Step 2: To crude oxime **exp-15** and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (61.3 mg, 0.270 mmol, 1.2 eq.) under nitrogen atmosphere was added anhydrous toluene (15 mL) and the mixture was stirred at 80 °C for 10 minutes. Then, the mixture was cooled to room temperature, filtered over a short plug of silica and the silica was washed with 1/50 acetone/dichloromethane until no further material eluted. The solvent was removed under reduced pressure and ethanol (25 mL) was added to the residue. The mixture was warmed to reflux for several minutes, then kept at room temperature overnight and filtered. The filtrate was discarded. The solids were washed with a minimal amount of ethanol and dried to afford isoxazole **160** (40.0 mg, 84.1 mmol, 37%) as an orange solid.

R_f = 0.33 (40% ethyl acetate in hexanes).

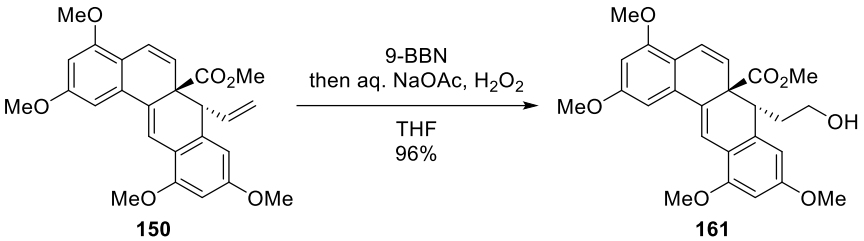
^{1}H-NMR (400 MHz, $CDCl_3$): 7.47 (s, 1H), 6.96 (d, J = 2.1 Hz, 1H), 6.40 (d, J = 2.1 Hz, 1H), 6.38 (d, J = 2.3 Hz, 1H), 6.36 (d, J = 2.3 Hz, 1H), 5.86 (ddd, J = 17.2, 10.2, 7.3 Hz, 1H), 4.99 (dt, J = 10.3, 1.1 Hz, 1H), 4.88 (dt, J = 17.0, 1.3 Hz, 1H), 4.63 (d, J = 10.6 Hz, 1H), 4.04 (d, J = 10.6 Hz, 1H), 3.99 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 3.85 (s, 3H), 3.76 (d, J = 7.3 Hz, 1H) .

^{13}C-NMR (100 MHz, $CDCl_3$): 167.0, 163.0, 162.3, 158.2, 158.0, 157.7, 149.4, 138.4, 136.3, 134.8, 125.0, 123.6, 119.0, 115.7, 114.9, 106.8, 105.8, 101.9, 97.8, 97.7, 73.9, 56.3, 55.8, 55.73, 55.70, 49.4, 40.0.

IR: 3005, 2965, 2941, 2839, 1763, 1688, 1650, 1605, 1592, 1564, 1491, 1458, 1425, 1323, 1303, 1293, 1238, 1208, 1151, 1101, 1077, 1048, 1029, 998, 957, 941, 912, 877, 831, 794, 762, 732.

HRMS (ESI): $C_{27}H_{24}NO_7$ [M+H] calc. 474.1547, found 474.1558.

Alcohol **161**



To a solution triene **150** (15.5 g, 35.7 mmol) in anhydrous tetrahydrofuran (200 mL) under nitrogen atmosphere was added a 0.5 M tetrahydrofuran solution of 9-borabicyclo-[3.3.1]nonane (78.5 mL, 39.2 mmol, 1.1 eq.) and the mixture was stirred overnight. Then, 20% aqueous sodium acetate (100 mL) and 30% hydrogen peroxide (23 mL) were added carefully under ice bath cooling. The cooling bath was removed and the mixture was stirred vigorously for 1 hour, diluted with water (400 mL) and extracted with dichloromethane (3×200 mL). The extracts were dried over sodium sulfate, evaporated under reduced pressure and hexane (430 mL) and ethanol (60 mL) were added to the remaining orange oil. The mixture was warmed to reflux until all of the oil had been consumed and a large amount of solids had formed. Then, the mixture was cooled to room temperature and filtered. The filtrate was discarded. The solids were washed with hexanes and dried to afford alcohol **161** (15.5 g, 34.3 mmol, 96%) as a yellow solid.

$\mathbf{R_f}$ = 0.35 (6% acetone in dichloromethane).

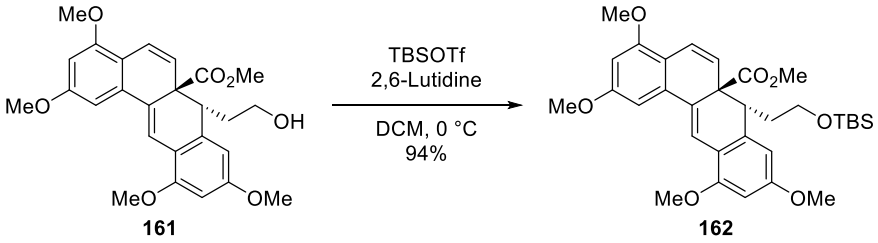
^{1}H-NMR (400 MHz, $CDCl_3$): 7.45 (s, 1H), 6.97 (d, J = 2.2 Hz, 1H), 6.91 (d, J = 9.8 Hz, 1H), 6.36 (d, J = 2.3 Hz, 1H), 6.30 (d, J = 2.2 Hz, 1H), 6.28 (d, J = 2.3 Hz, 1H), 5.58 (d, J = 9.9 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.59 (ddd, J = 11.0, 6.6, 4.4 Hz, 1H), 3.54 – 3.46 (m, 4H), 3.44 (dd, J = 11.2, 3.4 Hz, 1H), 2.00 (dddd, J = 13.9, 8.7, 6.8, 3.3 Hz, 1H), 1.69 (dddd, J = 13.9, 10.6, 5.8, 4.4 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 173.9, 160.6, 160.2, 157.1, 156.8, 138.8, 134.1, 129.2, 124.2, 122.6, 117.9, 115.4, 114.0, 105.5, 99.2, 97.8, 96.9, 60.9, 55.7, 55.6, 55.52, 55.50, 53.1, 52.8, 43.3, 33.2.

IR: 3001, 2940, 2838, 1720, 1639, 1596, 1568, 1491, 1455, 1425, 1388, 1338, 1289, 1219, 1205, 1149, 1121, 1090, 1051, 993, 946, 932, 910, 887, 872, 829, 803, 786, 764, 730.

HRMS (ESI): $C_{26}H_{29}O_7$ [M+H] calc. 453.1908, found 453.1916.

Silyl ether **162**



To a solution alcohol **161** (7.00 g, 15.5 mmol) and 2,6-lutidine (2.15 mL, 18.6 mmol, 1.2 eq.) in anhydrous dichloromethane (75 mL) under nitrogen atmosphere was dropwise added *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.90 mL, 18.6 mmol, 1.1 eq.) under ice bath cooling. The mixture was stirred for 1.5 hours, before additional 2,6-lutidine (0.350 mL, 3.02 mmol, 0.2 eq.) and *tert*-butyl-dimethylsilyl trifluoromethanesulfonate (0.700 mL, 3.05 mmol, 0.2 eq.) were added dropwise. Stirring under ice bath cooling was continued for further 50 minutes. Then, the mixture was diluted with dichloromethane (50 mL), washed with 2 M hydrochloric acid (100 mL), dried over sodium sulfate and evaporated under reduced pressure. Hexanes (150 mL) were added to the residue, the mixture was sonicated for 20 minutes and filtered. The filtrate was discarded. The solids were washed with hexanes and dried to afford silyl ether **162** (8.27 g, 14.6 mmol,94%) as a yellow solid.

R_f = 0.63 (40% ethyl acetate in hexanes).

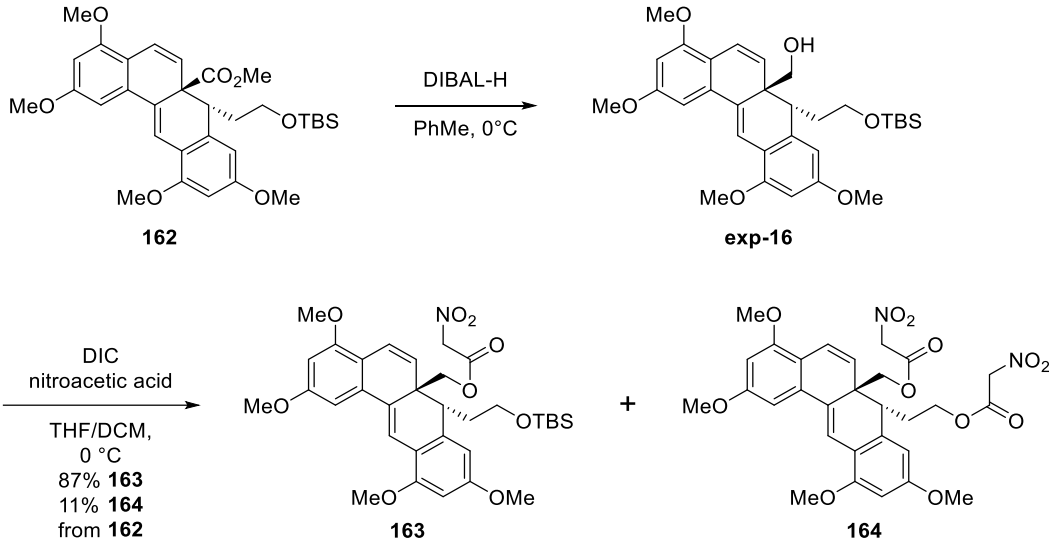
^{1}H-NMR (400 MHz, $CDCl_3$): 7.44 (s, 1H), 6.97 (d, J = 2.2 Hz, 1H), 6.91 (dd, J = 9.8, 0.6 Hz, 1H), 6.37 (d, J = 2.3 Hz, 1H), 6.30 (d, J = 2.2 Hz, 1H), 6.27 (d, J = 2.3 Hz, 1H), 5.57 (dd, J = 9.9, 1.1 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.58 – 3.38 (m, 6H), 1.97 (dtd, J = 13.0, 6.7, 3.4 Hz, 1H), 1.54 (dddd, J = 13.6, 11.1, 5.2, 3.6 Hz, 1H), 0.91 (s, 9H), 0.02 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): 174.1, 160.5, 160.1, 156.9, 156.8, 139.2, 134.2, 129.2, 124.5, 122.4, 117.9, 115.4, 114.1, 105.6, 99.2, 97.8, 96.9, 60.6, 55.7, 55.6, 55.5, 55.4, 53.1, 52.8, 42.8, 33.2, 26.1, 18.4, -5.0, -5.1.

IR: 3000, 2951, 2934, 2855, 2838, 1722, 1639, 1596, 1568, 1491, 1462, 1425, 1387, 1329, 1307, 1286, 1217, 1204, 1166, 1144, 1086, 1050, 1026, 1005, 962, 948, 938, 907, 889, 830, 801, 775, 729.

HRMS (ESI): $C_{32}H_{43}O_7Si$ [M+H] calc. 567.2773, found 567.2785.

Nitroacetic acid ester **163** and diester **164**



Step 1: To a suspension of ester **162** (7.60 g, 13.4 mmol) in anhydrous toluene (65 mL) under nitrogen atmosphere was dropwise added a 1.2 M solution of diisobutylaluminum hydride in toluene (23.5 mL, 28.2 mmol, 2.1 eq.) under ice bath cooling. The resulting solution was stirred for 1.5 hours, before ethyl acetate (4 mL), methanol (3.5 mL), and saturated, aqueous potassium sodium tartrate (65 mL) were added carefully in the specified order. The cooling bath was removed and the mixture was stirred vigorously for 45 minutes. Then, the layers were separated and the aqueous layer was extracted with toluene (2×50 mL). The combined organic layers were washed with water (65 mL) and saturated, aqueous sodium chloride (65 mL), dried over sodium sulfate and evaporated under reduced pressure to afford crude alcohol **exp-16** as yellow foam, which was directly used without further purification in the next step.

Step 2: To a solution of crude alcohol **exp-16** in anhydrous dichloromethane (90 mL) was added *N*,*N*′-diisopropylcarbodiimide (6.20 mL, 40.0 mmol, 3 eq.) under ice/brine bath cooling. Then, a solution of nitroacetic acid (see page 154, 4.23 g, 40.3 mmol, 3 eq.) in anhydrous tetrahydrofuran (23 mL) was added via syringe pump within 25 minutes. The mixture was stirred for one hour, then the cooling bath as removed and the mixture was filtered. The solids were washed with dichloromethane and discarded. The filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography (0 to 40% ethyl acetate in hexanes), which afforded diester **164** (879 mg, 1.47 mmol, 11%) in the form of an orange-yellow foam and ester **163** with minor impurities. Diethyl ether (25 mL) was added to impure ester **163**, the mixture was sonicated for several minutes and filtered. The solids were washed with diethyl ether (2×5 mL) and dried to afford ester **163** (2.11 g, 3.37 mmol, 25%) as a yellow solid. The filtrate was evaporated under reduced pressure, hexanes (40 mL) were added, the mixture was sonicated for several minutes and filtered. The solids were washed with hexanes and dried to afford additional ester **163** (4.50 g, 7.19 mmol, 54%) in the form of a yellow solid. The filtrate was evaporated under reduced pressure and the residue purified again by column chromatography (0 to 40% ethyl acetate in hexanes) to afford further ester **163** (660 mg, 1.05 mmol, 8%) as an orange-yellow foam.

Analytical data for nitroacetic acid ester **163**

R_f = 0.58 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.39 (s, 1H), 6.90 (d, J = 10.0 Hz, 1H), 6.87 (d, J = 2.2 Hz, 1H), 6.34 (d, J = 2.3 Hz, 1H), 6.32 (d, J = 2.2 Hz, 1H), 6.31 (d, J = 2.4 Hz, 1H), 5.53 (dd, J = 10.0, 1.1 Hz, 1H), 4.89 (d, J = 14.4 Hz, 1H), 4.81 (d, J = 14.4 Hz, 1H), 4.33 (d, J = 10.3 Hz, 1H), 4.07 (d, J = 10.3 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.52 (ddd, J = 9.9, 6.3, 3.3 Hz, 1H), 3.39 (td, J = 10.2, 4.7 Hz, 1H), 2.92 (dd, J = 10.9, 3.0 Hz, 1H), 1.99 (dddd, J = 13.4, 9.7, 6.4, 3.1 Hz, 1H), 1.61 (dddd, J = 13.9, 11.0, 4.6, 3.3 Hz, 1H), 0.92 (s, 9H), 0.03 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): 161.9, 160.4, 160.3, 156.9, 156.8, 138.5, 133.9, 130.2, 126.2, 121.8, 118.1, 114.7, 106.4, 99.4, 97.9, 96.9, 76.0, 70.9, 60.2, 55.8, 55.6, 55.5, 44.1, 41.0, 33.9, 26.1, 18.4, -5.07, -5.14.

IR: 3001, 2951, 2933, 2884, 2855, 2839, 1756, 1642, 1596, 1564, 1491, 1462, 1425, 1407, 1387, 1330, 1309, 1287, 1253, 1219, 1205, 1147, 1103, 1094, 1053, 1006, 978, 939, 911, 890, 833, 810, 776, 733.

HRMS (ESI): $C_{33}H_{44}NO_9Si$ [M+H] calc. 626.2780, found 626.2774.

Analytical data for diester **164**

R_f = 0.31 (40% ethyl acetate in hexanes).

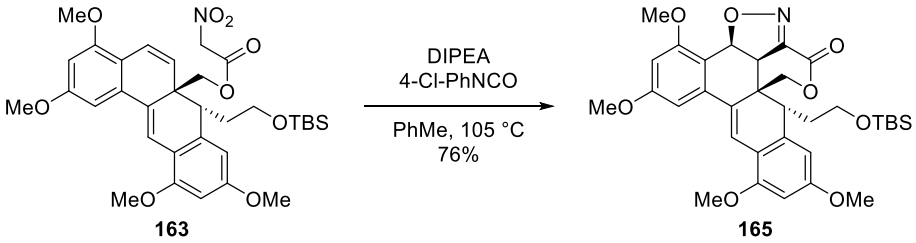
^{1}H-NMR (400 MHz, $CDCl_3$): 7.40 (s, 1H), 6.91 (d, J = 10.0 Hz, 1H), 6.86 (d, J = 2.2 Hz, 1H), 6.43 – 6.26 (m, 2H), 6.22 (d, J = 2.2 Hz, 1H), 5.53 (d, J = 10.0 Hz, 1H), 5.24 (d, J = 14.4 Hz, 1H), 5.17 (d, J = 14.4 Hz, 1H), 5.04 (d, J = 14.4 Hz, 1H), 4.96 (d, J = 14.4 Hz, 1H), 4.29 (d, J = 10.3 Hz, 1H), 4.20 (ddd, J = 10.1, 5.9, 3.8 Hz, 1H), 4.11 (td, J = 10.6, 4.5 Hz, 1H), 4.05 (d, J = 10.3 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 2.78 (dd, J = 11.1, 3.1 Hz, 1H), 2.22 – 2.10 (m, 1H), 1.85 (ddt, J = 15.0, 11.1, 4.2 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 161.7, 161.6, 160.7, 160.5, 157.2, 156.9, 136.8, 133.4, 129.5, 125.3, 122.2, 118.3, 114.6, 114.5, 106.0, 99.5, 98.1, 97.4, 76.5, 76.2, 70.1, 65.1, 55.8, 55.67, 55.65, 55.6, 43.8, 41.0, 29.7.

IR: 2941, 2840, 1752, 1641, 1596, 1561, 1491, 1462, 1456, 1426, 1406, 1369, 1333, 1312, 1286, 1238, 1205, 1148, 1108, 1083, 1050, 1013, 979, 946, 937, 911, 878, 832, 790, 732.

HRMS (ESI): $C_{29}H_{31}N_2O_{12}$ [M+H] calc. 599.1872, found 599.1862.

Isoxazoline **165**



To ester **163** (6.46 g, 10.3 mmol) and 4-chlorophenyl isocyanate (3.80 g, 24.8 mmol, 2.4 eq.) in anhydrous toluene (205 mL) under nitrogen atmosphere was added diisopropylethylamine (270 µL, 1.55 mmol, 0.15 eq.). The mixture was stirred at 105°C for 60 hours, with addition of further diisopropylethylamine after 12 hours (270 µL, 1.55 mmol, 0.15 eq.) and 36 h(540 µL, 3.10 mmol, 0.3 eq.). Then, the mixture was cooled to room temperature and filtered. The solids were washed with toluene and discarded. The filtrate was evaporated under reduced pressure and the residue was partially purified by column chromatography (0 to 40% ethyl acetate in hexanes) yielding a brown-red solid. The partially purified material was dissolved in dichloromethane and the solvent was removed under reduced pressure, providing an orange-red oil. Diethyl ether (30 mL) was added and the mixture was sonicated until all of the oil had dissolved. Upon standing at

room temperature for several minutes a white solid formed. The mixture was kept at room temperature until no further material crystallized and then filtered. The solids were washed with diethyl ether and dried to afford isoxazole **165** (3.96 g, 6.52 mmol, 63%) as a yellow solid. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography (0 to 50% ethyl acetate in hexanes) to afford additional product **165** (828 mg, 1.36 mmol, 13%) as an orange foam.

$\mathbf{R_f}$ = 0.48 (40% ethyl acetate in hexanes).

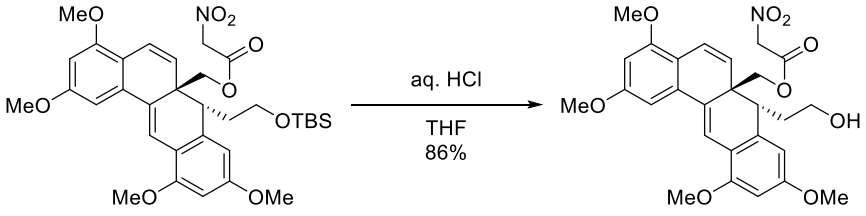
^{1}H-NMR (400 MHz, $CDCl_3$): 7.38 (s, 1H), 6.84 (d, J = 2.2 Hz, 1H), 6.47 (d, J = 2.2 Hz, 1H), 6.39 (d, J = 2.3 Hz, 1H), 6.37 (d, J = 2.3 Hz, 1H), 6.18 (d, J = 12.7 Hz, 1H), 4.18 (d, J = 12.0 Hz, 1H), 4.01 (d, J = 12.7 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.67 (d, J = 12.1 Hz, 1H), 3.55 (ddd, J = 10.1, 5.9, 3.1 Hz, 1H), 3.47 (td, J = 10.2, 4.1 Hz, 1H), 3.05 (dd, J = 10.0, 2.0 Hz, 1H), 1.75 (dddd, J = 16.1, 10.3, 6.0, 2.0 Hz, 1H), 1.45 (ddt, J = 13.7, 9.9, 3.7 Hz, 1H), 0.89 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 161.8, 161.5, 161.0, 160.2, 157.3, 148.2, 139.8, 134.0, 125.1, 120.4, 113.7, 112.8, 106.1, 99.4, 99.1, 97.2, 79.0, 70.0, 60.3, 56.3, 55.7, 55.6, 45.3, 43.0, 41.2, 33.3, 26.1, 18.35, -5.1, -5.2.

IR: 2951, 2934, 1760, 1608, 1598, 1580, 1567, 1529, 1492, 1457, 1426, 1368, 1329, 1319, 1303, 1278, 1258, 1242, 1215, 1203, 1150, 1117, 1100, 1074, 1052, 1028, 1010, 988, 906, 873, 833, 809, 776, 726.

HRMS (ESI): $C_{33}H_{42}NO_8Si$ [M+H] calc. 608.2681, found 608.2674.

Alcohol **exp-17**



To a solution of silyl ether **163** (496 mg, 0.793 mmol) in tetrahydrofuran (10.5 mL) was added 2 M hydrochloric acid (3.5 mL) and the mixture was stirred for 45 minutes. Then, water (10 mL) was added and the mixture was extracted with dichloromethane (10 mL and 2×5 mL). The extracts were dried over sodium sulfate and evaporated under reduced pressure. Ethanol (5 mL) and hexanes (20 mL) were added to the residues, the mixture was sonicated for several minutes and filtered. The filtrate was discarded. The solids were washed with small amounts of ethanol and hexanes and dried to afford alcohol **exp-17** (347 mg, 0.678 mmol, 86%) as a yellow solid.

$\mathbf{R_f}$ = 0.38 (5% methanol in dichloromethane).

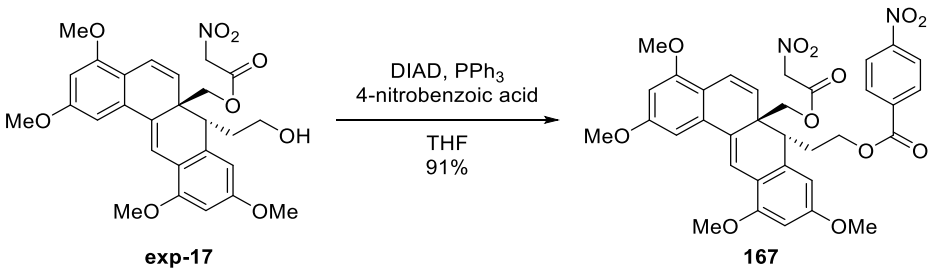
^{1}H-NMR (400 MHz, $CDCl_3$): 7.40 (s, 1H), 6.91 (d, J = 10.0 Hz, 1H), 6.86 (d, J = 2.2 Hz, 1H), 6.35 – 6.30 (m, 3H), 5.55 (dd, J = 10.0, 1.1 Hz, 1H), 4.91 (d, J = 14.4 Hz, 1H), 4.83 (d, J = 14.4 Hz, 1H), 4.34 (d, J = 10.4 Hz, 1H), 4.06 (d, J = 10.4 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.58 (ddd, J = 10.7, 6.6, 4.2 Hz, 1H), 3.46 (ddd, J = 10.6, 9.1, 5.5 Hz, 1H), 2.87 (dd, J = 10.9, 3.3 Hz, 1H), 2.01 (dddd, J = 14.0, 9.6, 6.6, 3.3 Hz, 1H), 1.78 (dddd, J = 13.9, 10.8, 5.5, 4.2 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 161.8, 160.5, 160.4, 157.0, 156.8, 138.1, 133.8, 130.1, 125.8, 122.0, 118.1, 114.7, 114.6, 106.3, 99.4, 98.0, 96.8, 76.1, 70.7, 60.6, 55.8, 55.65, 55.58, 44.1, 41.6, 33.9.

IR: 3001, 2939, 2888, 2839, 1754, 1597, 1564, 1491, 1457, 1425, 1394, 1367, 1334, 1309, 1287, 1236, 1206, 1148, 1106, 1083, 1050, 971, 946, 910, 884, 833, 788, 765, 731, 705.

HRMS (ESI): $C_{27}H_{30}NO_9$ [M+H] calc. 512.1915, found 512.1929.

Diester 167



exp-17 **167**

To a suspension of alcohol **exp-17** (219 mg, 0.428 mmol), 4-nitrobenzoic acid (78.7 mg, 0.471 mmol, 1.1 eq.) and triphenylphosphine (124 mg, 0.473 mmol, 1.1 eq.) in anhydrous tetrahydrofuran (4 mL) under nitrogen atmosphere was dropwise added diisopropyl azodicarboxylate (89 µL, 0.45 mmol, 1.05 eq.) and the mixture was stirred for 45 minutes. Then, the volatiles were evaporated under reduced pressure and the residue was purified by column chromatography (0 to 20% ethyl acetate in dichloromethane) to afford diester **167** (256 mg, 0.388 mmol, 91%) as an orange-yellow solid.

$\mathbf{R_f}$ = 0.41 (40% ethyl acetate in hexanes).

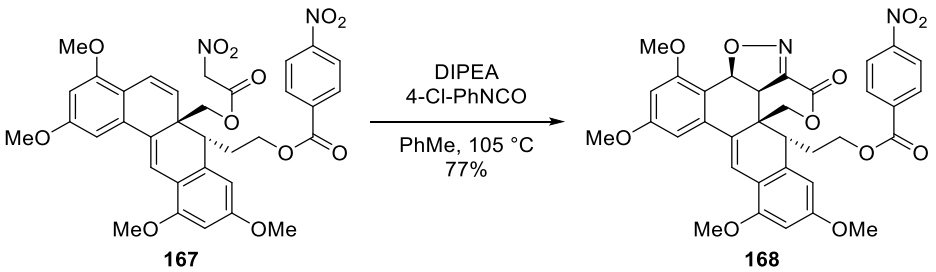
^{1}H-NMR (400 MHz, $CDCl_3$): 8.33 – 8.25 (m, 2H), 8.24 – 8.15 (m, 2H), 7.43 (s, 1H), 6.93 (d, J = 10.0 Hz, 1H), 6.87 (d, J = 2.0 Hz, 1H), 6.32 (d, J = 2.2 Hz, 1H), 6.30 (d, J = 2.3 Hz, 1H), 6.25 (d, J = 2.2 Hz, 1H), 5.58 (d, J = 10.0 Hz, 1H), 4.98 (d, J = 14.4 Hz, 1H), 4.91 (d, J = 14.4 Hz, 1H), 4.33 (d, J = 10.3 Hz, 1H), 4.33 – 4.24 (m, 1H), 4.17 (ddd, J = 11.1, 9.3, 5.4 Hz, 1H), 4.05 (d, J = 10.4 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 2.90 (dd, J = 10.9, 3.4 Hz, 1H), 2.23 (dddd, J = 15.4, 9.5, 6.3, 3.4 Hz, 1H), 2.03 (ddt, J = 15.6, 10.4, 5.0 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 164.7, 161.5, 160.7, 160.5, 157.1, 156.8, 150.7, 137.1, 135.7, 133.5, 130.9, 129.7, 125.3, 123.7, 122.2, 118.3, 114.7, 114.5, 106.3, 99.5, 98.0, 97.1, 76.2, 70.3, 64.1, 55.8, 55.7, 55.6, 55.5, 44.0, 42.0, 29.9.

IR: 2960, 2940, 2839, 1755, 1720, 1603, 1562, 1526, 1491, 1455, 1425, 1412, 1384, 1333, 1311, 1273, 1241, 1220, 1205, 1147, 1121, 1103, 1082, 1050, 1035, 1014, 973, 947, 937, 909, 873, 831, 785, 765, 719.

HRMS (ESI): $C_{34}H_{33}N_2O_{12}$ [M+H] calc. 661.2028, found 661.2017.

Isoxazoline 168



167 **168**

To ester **167** (300 mg, 0.454 mmol) and 4-chlorophenyl isocyanate (106 mg, 1.04 mmol, 2.3 eq.) in anhydrous toluene (9 mL) under nitrogen atmosphere at 105°C was added diisopropylethylamine (20 µL, 0.115 mmol 0.25 eq.). The mixture was stirred for 8.5 hours,

diisopropylethylamine (20 µL, 0.115 mmol 0.25 eq.) was added and stirring was continued for 16.5 hours. Then, mixture was cooled to room temperature and filtered. The solids were washed with toluene and discarded. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography (0 to 100% ethyl acetate in hexanes) to afford isoxazoline **168** (225 mg, 0.350 mmol, 77%) as a yellow solid.

R_f = 0.30 (40% ethyl acetate in hexanes).

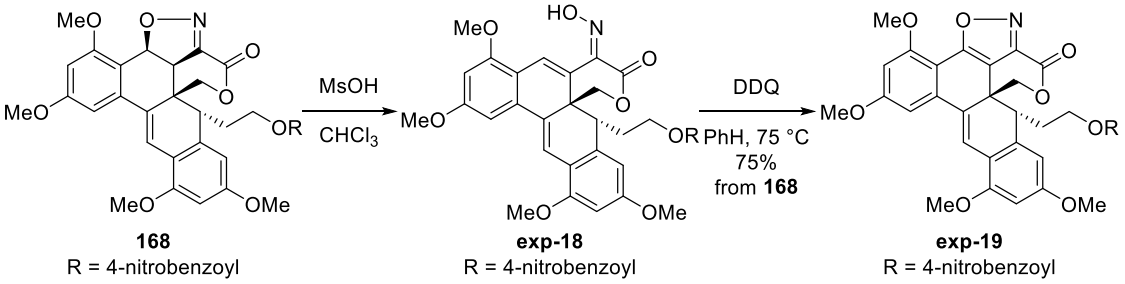
^{1}H-NMR (400 MHz, $CDCl_3$): 8.32 – 8.26 (m, 2H), 8.15 – 8.09 (m, 2H), 7.43 (s, 1H), 6.85 (d, J = 2.2 Hz, 1H), 6.48 (d, J = 1.8 Hz, 1H), 6.38 (d, J = 1.9 Hz, 1H), 6.36 (d, J = 2.4 Hz, 1H), 6.21 (d, J = 12.7 Hz, 1H), 4.34 – 4.16 (m, 3H), 3.93 (d, J = 12.6 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.89 (s, 3H), 3.81 (s, 3H), 3.69 (d, J = 12.2 Hz, 1H), 3.01 (dd, J = 10.9, 2.7 Hz, 1H), 2.11 – 2.00 (m, 1H), 1.87 (ddt, J = 15.2, 10.6, 5.2 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 164.5, 161.6, 161.5, 161.1, 160.1, 157.4, 150.7, 147.6, 137.6, 135.2, 133.6, 130.6, 124.5, 123.7, 120.4, 113.6, 112.4, 106.2, 99.4, 99.1, 97.4, 78.8, 69.7, 63.7, 56.2, 55.61, 55.58, 55.5, 45.1, 43.8, 41.1, 28.3.

IR: 3003, 2940, 2840, 2255, 1757, 1721, 1685, 1608, 1598, 1580, 1569, 1526, 1491, 1456, 1425, 1335, 1319, 1301, 1274, 1241, 1215, 1203, 1150, 1118, 1103, 1061, 1048, 1028, 1014, 978, 909, 873, 831, 795, 784, 772, 720.

HRMS (ESI): $C_{34}H_{31}N_2O_{11}$ [M+H] calc. 643.1922, found 643.1919.

Isoxazole **exp-19**



168
R = 4-nitrobenzoyl

exp-18
R = 4-nitrobenzoyl

exp-19
R = 4-nitrobenzoyl

Step 1: To a solution of isoxazoline **168** (42.2 mg, 65.7 µmol) in anhydrous chloroform (1 mL) was added methanesulfonic acid (9 µL, 0.139 mmol, 2 eq.). The mixture was stirred for 35 minutes, additional methanesulfonic acid (9 µL, 0.139 mmol, 2 eq.) was added and stirring was continued for 30 minutes. Then, the mixture was poured onto water (3 mL) and saturated, sodium bicarbonate (2 mL). Ethyl acetate (5 mL) was added and the mixture was shaken thoroughly. The layers were separated and the aqueous layer was extracted with ethyl acetate (2×5 mL). The combined organic layers were washed with saturated, aqueous sodium chloride (10 mL), dried over sodium sulfate and evaporated under reduced pressure to afford crude oxime **exp-18** as an orange-brown solid, which was directly used without further purification in the next step.

Step 2: To crude oxime **exp-18** was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (16.4 mg, 72.2 µmol, 1.1 eq.), followed by anhydrous benzene (5 mL) and the mixture was stirred at 75 °C for 40 minutes. Then, the mixture was cooled to room temperature, filtered over silica and the silica was washed with dichloromethane until no further material eluted. The solvent was removed under reduced pressure and ethanol (10 mL) was added to the residue. The mixture was warmed to reflux for several minutes, then cooled with an ice bath and filtered. The solids were washed with diethyl ether (2 mL) and dried to afford isoxazole **169** (12.8 mg, 20.0 µmol, 30%) as an orange solid. The filtrate was evaporated under reduced pressure and purified by column chromatography (dichloromethane) to afford additional product **exp-19** (19.3 mg, 30.1 µmol, 45%) as an orange foam.

R_f = 0.28 (40% ethyl acetate in hexanes).

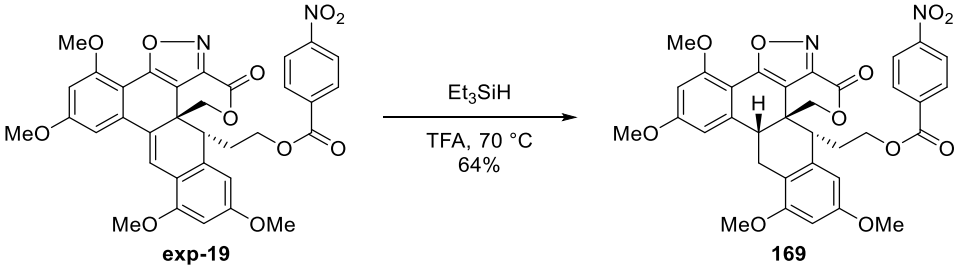
^{1}H-NMR (400 MHz, $CDCl_3$): 8.31 – 8.22 (m, 2H), 8.14 – 7.99 (m, 2H), 7.52 (s, 1H), 6.99 (d, J = 2.1 Hz, 1H), 6.42 (d, J = 2.1 Hz, 1H), 6.34 (d, J = 2.2 Hz, 1H), 6.33 (d, J = 2.3 Hz, 1H), 4.62 (d, J = 10.6 Hz, 1H), 4.36 – 4.22 (m, 2H), 4.04 (d, J = 10.5 Hz, 1H), 4.00 (s, 3H), 3.92 (s, 3H), 3.88 (s, 3H), 3.80 (s, 3H), 3.25 (dd, J = 9.9, 4.5 Hz, 1H), 2.17 – 1.96 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): 167.3, 164.6, 163.3, 162.0, 158.1, 158.0, 157.9, 150.7, 149.4, 138.3, 136.6, 135.3, 130.8, 125.1, 123.7, 123.4, 115.1, 114.2, 106.7, 106.5, 102.0, 97.8, 97.6,73.9, 63.8, 56.3, 55.84, 55.75, 55.6, 41.7, 40.3, 28.7.

IR: 3004, 2963, 2941, 2839, 2255, 1764, 1722, 1685, 1653, 1605, 1564, 1527, 1490, 1457, 1436, 1425, 1389, 1322, 1274, 1238, 1209, 1152, 1119, 1102, 1074, 1049, 1029, 1014, 994, 979, 954, 909, 873, 833, 792, 784, 766, 756, 720.

HRMS (ESI): $C_{34}H_{29}N_2O_{11}$ [M+H] calc. 641.1766, found 641.1765.

Isoxazole **169**



To stilbene **exp-19** (40.0 mg, 62.4 µmol) under nitrogen atmosphere were added trifluoroacetic acid (120 µL, 1.56 mmol, 25 eq.) and triethylsilane (11 µL, 69 µmol, 1.1 eq.). The mixture was stirred at 70 °C for 45 minutes, additional triethylsilane (3 µL, 19 µmol, 0.3 eq.) was added and stirring at 70 °C was continued for 20 minutes. Then, the volatiles were removed under reduced pressure and the residue was purified by column chromatography (0 to 5% ethyl acetate in dichloromethane) to afford isoxazole **169** (25.5 mg, 39.7 µmol, 64%) as a faint yellow solid.

R_f = 0.25 (40% ethyl acetate in hexanes).

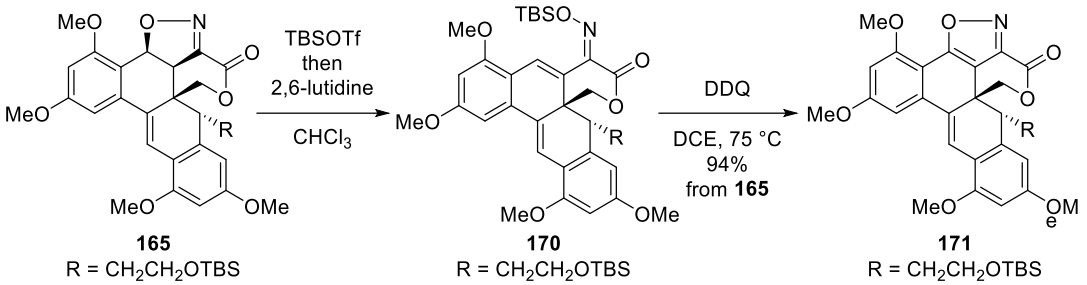
^{1}H-NMR (400 MHz, $CDCl_3$): 8.24 (m, 2H), 8.01 – 7.90 (m, 2H), 6.72 (s, 1H), 6.46 (d, J = 2.1 Hz, 1H), 6.38 (d, J = 2.3 Hz, 1H), 6.27 (d, J = 2.3 Hz, 1H), 4.22 – 4.12 (m, 3H), 4.06 – 4.00 (m, 4H), 3.91 (s, 3H), 3.85 (s, 3H), 3.78 – 3.68 (m, 4H), 3.24 – 3.15 (m, 2H), 2.97 (dd, J = 17.0, 6.0 Hz, 1H), 1.87 (dtd, J = 14.2, 7.1, 3.2 Hz, 1H), 1.66 (ddt, J = 14.2, 11.4, 4.9 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 167.2, 164.5, 163.8, 159.4, 158.0, 157.84, 157.76, 150.7, 148.7, 146.1, 138.9, 135.3, 130.7, 123.7, 116.1, 113.2, 107.2, 106.7, 105.8, 97.8, 96.1, 80.4, 64.1, 56.2, 55.8, 55.6, 55.5, 42.9, 38.4, 37.6, 28.1, 23.4.

IR: 2957, 2924, 2853, 1763, 1722, 1685, 1657, 1600, 1572, 1527, 1496, 1454, 1437, 1425, 1350, 1312, 1273, 1246, 1199, 1149, 1120, 1102, 1065, 1042, 1013, 965, 943, 908, 873, 838, 796, 784, 760, 719.

HRMS (APCI): $C_{34}H_{31}N_2O_{11}$ [M+H] calc. 643.1922, found 643.1921.

Silyl oxime **170** and isoxazole **171**



Step 1: To a solution of isoxazoline **165** (1.88 g, 3.09 mmol) in anhydrous chloroform (60 mL) under nitrogen atmosphere was dropwise added *tert*-butyldimethylsilyl trifluoromethanesulfonate (852 µL, 3.71 mmol, 1.2 eq.). The mixture was stirred for 25 minutes, 2,6-lutidine (537 µL, 4.64 mmol, 1.5 eq.) was added and stirring was continued for 1 hour. Then, the mixture was diluted with dichloromethane (50 mL), washed with water (60 mL), 2 M hydrochloric acid (2×60 mL) and again water (60 mL), dried over sodium sulfate and evaporated under reduced pressure to afford crude silyl oxime **170** as an orange-yellow solid, which was directly used without further purification in the next step.

Step 2: To a solution of crude silyl oxime **170** in anhydrous dichloroethane (40 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (738 mg, 3.25 mmol, 1.05 eq.). The mixture was stirred at 75°C for 18 hours, then cooled to room temperature and filtered. The solids were washed with dichloromethane and discarded. The filtrate was evaporated under reduced pressure and the residue was partially purified by column chromatography (0 to 100% ethyl acetate in hexanes). Diethyl ether (20 mL) was added to the partially purified material, the mixture was sonicated and filtered. The solids were washed with diethyl ether (2×5 mL) and dried to afford isoxazole **171** (1.67 g, 2.76 mmol, 89%) as an orange-yellow solid. The filtrate was evaporated under reduced pressure and the residue was again purified by column chromatography (0 to 40% ethyl acetate in hexanes) to afford additional product **171** (88.0 mg, 0.145 mmol, 5%) as an orange solid.

Analytical data for silyl oxime **170**

A sample of silyl oxime **170** was obtained in a separate experiment under identical conditions and purified by column chromatography (0 to 20% ethyl acetate in hexanes).

$\mathbf{R_f}$ = 0.62 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.11 (s, 1H), 7.33 (s, 1H), 6.83 (d, J = 2.2 Hz, 1H), 6.36 (d, J = 2.3 Hz, 1H), 6.30 (d, J = 2.3 Hz, 1H), 6.28 (d, J = 2.2 Hz, 1H), 4.35 (d, J = 10.6 Hz, 1H), 4.28 (d, J = 10.7 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.47 (ddd, J = 10.3, 6.8, 3.6 Hz, 1H), 3.34 (td, J = 9.8, 5.6 Hz, 1H), 3.06 (dd, J = 10.7, 3.8 Hz, 1H), 1.95 – 1.70 (m, 2H), 1.04 (s, 9H), 0.85 (s, 9H), 0.35 (s, 3H), 0.31 (s, 3H), -0.04 (s, 3H), -0.04 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 162.0, 161.0, 160.9, 158.2, 156.8, 147.0, 136.6, 134.4, 127.6, 126.5, 122.3, 119.1, 114.3, 113.9, 106.4, 99.1, 97.8, 97.7, 70.5, 60.3, 55.7, 55.60, 55.58, 42.7, 40.2, 32.5, 26.09, 26.07, 25.9, 18.2, 18.0, -4.99, -5.02, -5.04, -5.3.

IR: 2950, 2929, 2894, 2886, 2856, 2840, 1742, 1596, 1567, 1491, 1461, 1425, 1383, 1360, 1331, 1306, 1289, 1252, 1236, 1219, 1204, 1168, 1148, 1102, 1076, 1038, 1002, 987, 955, 937, 909, 828, 809, 787, 775, 731.

HRMS (ESI): $C_{39}H_{56}NO_8Si_2$ [M+H] calc. 722.3539, found 722.3539.

Analytical data for isoxazole **171**

$\mathbf{R_f}$ = 0.40 (40% ethyl acetate in hexanes).

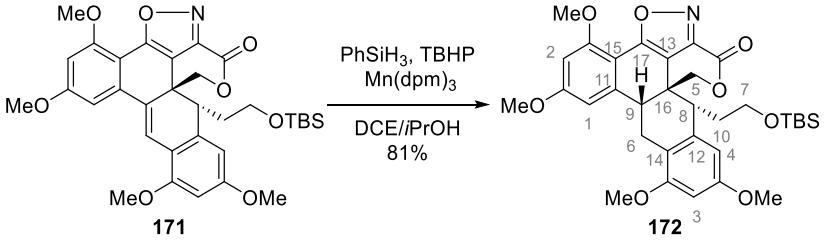
^{1}H-NMR (400 MHz, $CDCl_3$): 7.46 (s, 1H), 6.97 (d, J = 2.2 Hz, 1H), 6.44 (d, J = 2.3 Hz, 1H), 6.41 (d, J = 2.1 Hz, 1H), 6.35 (d, J = 2.3 Hz, 1H), 4.60 (d, J = 10.6 Hz, 1H), 4.03 – 3.97 (m, 4H), 3.91 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.55 – 3.35 (m, 3H), 1.84 – 1.63 (m, 2H), 0.85 (s, 9H), -0.03 (s, 3H), -0.05 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 167.0, 163.0, 161.8, 158.0, 158.0, 157.6, 149.5, 138.5, 137.8, 125.4, 123.1, 115.7, 114.5, 106.9, 106.5, 101.8, 97.7, 97.5, 74.1, 60.1, 56.3, 55.8, 55.7, 55.6, 40.4, 40.1, 32.5, 26.0, 18.3, -5.1, -5.3.

IR: 2950, 2931, 2885, 2856, 2840, 1765, 1653, 1604, 1592, 1564, 1489, 1459, 1435, 1425, 1388, 1323, 1297, 1253, 1236, 1205, 1175, 1150, 1101, 1075, 1050, 1029, 998, 982, 954, 907, 832, 810, 792, 776, 757, 728.

HRMS (ESI): $C_{33}H_{40}NO_8Si$ [M+H] calc. 606.2518, found 606.2524.

Isoxazole **172**



To stilbene **171** (2.50 g, 4.13 mmol), tris(2,2,6,6-tetramethyl-3,5-heptanedionato)-manganese(III) (250 mg, 0.413 mmol, 0.1 eq.), anhydrous, degassed[a] 1,2-dichloroethane (50 mL) and anhydrous, degassed[1] isopropanol (10 mL) under nitrogen atmosphere was added phenylsilane (764 µL, 0.670 mmol, 1.5 eq.) and the mixture was stirred for 5 minutes. Then, a 5.5 M solution of *tert*-butyl hydroperoxide (1.50 mL, 8.25 mmol, 2 eq.) was added dropwise, the mixture was stirred for 1.5 hours and evaporated under reduced pressure. The residue was partially purified by column chromatography (0 to 100% ethyl acetate in hexanes). Diethyl ether (20 mL) was added to the partially purified material, the mixture was sonicated and filtered. The solids were washed with diethyl ether (2×5 mL) and dried to afford isoxazole **172** (1.94 g, 3.19 mmol, 77%) as a yellowish solid. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography (0 to 40% ethyl acetate in hexanes) and again treated with diethyl ether to afford additional product **172** (102 mg, 0.168 mmol, 4%) as a yellow solid.

R_f = 0.43 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 6.67 (br, 1H, 1-H), 6.43 (d, J = 2.1 Hz, 1H, 2-H), 6.41 (d, J = 2.3 Hz, 1H, 3-H), 6.36 (d, J = 2.4 Hz, 1H, 3-H), 4.18 (d, J = 10.7 Hz, 1H, 5-H_A), 4.04 (d, J = 10.7 Hz, 1H, 5-H_B), 4.00 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.55 (dd, J = 17.1, 9.8 Hz, 1H, 6-H_A), 3.35 – 3.31 (m, 2H, 7-H), 3.27 (dd, J = 11.0, 3.4 Hz, 1H, 8-H), 3.14 (dd, J = 9.7, 5.3 Hz, 1H, 9-H), 3.01 (dd, J = 17.1, 5.3 Hz, 1H, 6-H_B), 1.54 (dtd, J = 13.3, 8.0, 3.3 Hz, 1H, 10-H_A), 1.26 (ddt, J = 13.3, 11.3, 4.4 Hz, 1H, 10-H_B), 0.79 (s, 9H, *t*Bu), -0.09 (s, 3H, SiMe), -0.13 (s, 3H, SiMe).

^{13}C-NMR (100 MHz, $CDCl_3$): 167.0 (C=O), 163.6 (C-OMe), 159.0 (C-OMe), 157.9 (C=N), 157.8 (C-OMe), 157.6 (C-OMe), 148.7 (C17), 146.0 (C11), 139.8 (C12), 116.8 (C9), 113.2 (C14), 107.5 (C15), 106.4 (C1), 105.9 (C4), 97.6 (C3), 96.0 (C2), 80.7 (C5), 60.5 (C7), 56.2 (OMe),

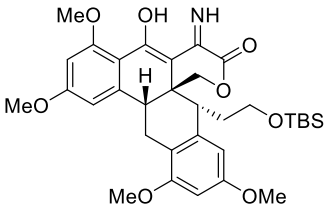
[a]By sparging with nitrogen under sonication.

55.7 (OMe), 55.54 (OMe), 55.51 (OMe), 40.8 (C8), 38.9 (C9), 37.2 (C16), 32.5 (C10), 25.9 (*t*Bu), 22.8 (C6), 18.2 (*t*Bu), -5.2 (SiMe), -5.3(SiMe).

IR: 3002, 2951, 2930, 2884, 2855, 1764, 1718, 1700, 1684, 1654, 1600, 1571, 1495, 1452, 1436, 1424, 1388, 1353, 1311, 1277, 1254, 1200, 1147, 1102, 1061, 1044, 1005, 981, 965, 948, 910, 883, 834, 811, 796, 776, 760, 730, 705.

HRMS (ESI): $C_{33}H_{42}NO_8Si$ [M+H] calc. 608.2674, found 608.2677.

Imine **173**



172

Imine **173** was observed as a side-product of the reduction of isoxazole **172** (see page 203). A sample of imine **173** was obtained in a separate experiment under identical conditions and purified by column chromatography (0 to 50% ethyl acetate in hexanes).

$\mathbf{R_f}$ = 0.45 (5% methanol in dichloromethane).

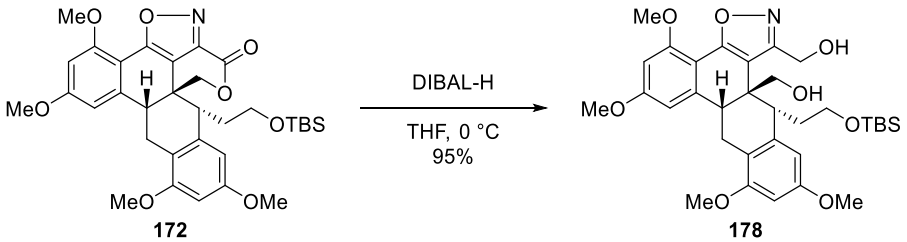
^{1}H-NMR (400 MHz, $CDCl_3$): 6.43 (s, 1H), 6.37 (d, J = 2.2 Hz, 1H), 6.35 (d, J = 2.3 Hz, 1H), 6.31 (d, J = 2.4 Hz, 1H), 4.34 (d, J = 10.5 Hz, 1H), 4.27 (d, J = 10.5 Hz, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H), 3.59 (d, J = 18.7 Hz, 1H), 3.48 – 3.33 (m, 2H), 3.31 (dd, J = 9.3, 4.1 Hz, 1H), 3.19 (d, J = 6.9 Hz, 1H), 2.64 (dd, J = 18.8, 7.1 Hz, 1H), 1.49 – 1.37 (m, 1H), 0.82 (s, 9H), 0.77 – 0.66 (m, 1H), -0.06 (s, 3H), -0.08 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 187.7, 164.3, 163.6, 162.0, 158.7, 158.4, 146.0, 140.6, 138.9, 117.8, 112.1, 111.5, 105.7, 103.3, 96.9, 96.3, 75.7, 61.0, 56.3, 55.5, 55.40, 55.37, 38.1, 38.0, 37.0, 36.5, 25.9, 20.7, 18.1, -5.2, -5.3.

IR: 3469, 3290, 2952, 2931, 2893, 2883, 2856, 1735, 1632, 1596, 1582, 1492, 1461, 1420, 1385, 1361, 1329, 1310, 1283, 1241, 1200, 1155, 1084, 1051, 1032, 1007, 985, 939, 912, 887, 862, 832, 777, 730.

HRMS (APCI): $C_{33}H_{44}NO_8Si$ [M+H] calc. 610.2831, found 610.2819.

Diol **178**



172 **178**

To a solution of lactone **172** (2.00 g, 3.29 mmol) in anhydrous tetrahydrofuran (35 mL) under nitrogen atmosphere was added a 1.2 M toluene solution of diisobutylaluminum hydride (6.00 mL, 7.20 mmol, 2.2 eq.) under ice bath cooling. The mixture was stirred for 35 minutes, then ethyl acetate (1 mL), methanol (1 mL) and saturated, aqueous sodium potassium tartrate (35 mL) were added carefully in the specified order. After stirring vigorously overnight, the tetrahydrofuran was evaporated under reduced pressure. The residue was diluted with water (40 mL) and extracted with dichloromethane (50 mL and

2×20 mL). The extracts were dried over sodium sulfate and evaporated under reduced pressure. The residue was partially purified by column chromatography (0 to 2.5% methanol in dichloromethane). Diethyl ether (20 mL) was added to the partially purified material, the mixture was sonicated and filtered. The solids were washed with diethyl ether (2×5 mL) and dried to afford diol **178** (1.70 g, 2.78 mmol, 84%) as a white solid. The filtrate was evaporated under reduced pressure and diethyl ether (2 mL) and hexanes (2 mL) were added to the residue. The mixture was sonicated, filtered and the filtrate was discarded. The solids were washed with a minimal amount of diethyl ether and dried to afford additional product **178** (216 mg, 0.353 mmol, 11%) as a yellowish solid.

R_f = 0.31 (5% methanol in dichloromethane).

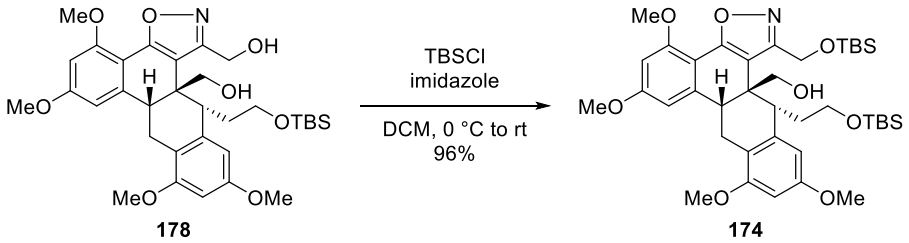
^{1}H-NMR (400 MHz, $CDCl_3$): 6.65 (d, J = 1.7 Hz, 1H), 6.40 – 6.35 (m, 2H), 6.33 (d, J = 2.3 Hz, 1H), 4.83 (d, J = 13.1 Hz, 1H), 4.78 (d, J = 13.1 Hz, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.69 (d, J = 11.7 Hz, 1H), 3.53 – 3.39 (m, 3H), 3.36 – 3.30 (m, 2H), 3.21 (dd, J = 10.4, 3.1 Hz, 1H), 2.79 (dd, J = 15.5, 6.5 Hz, 1H), 1.67 – 1.56 (m, 1H), 1.39 – 1.28 (m, 1H), 0.86 (s, 9H), -0.02 (s, 3H), -0.04 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 166.9, 162.3, 159.4, 158.7, 157.6, 157.4, 145.2, 141.0, 115.8, 110.9, 106.9, 105.5, 105.3, 96.7, 96.3, 68.9, 60.9, 56.8, 56.1, 55.6, 55.54, 55.50, 44.8, 41.9, 39.1, 33.4, 26.1, 25.5, 18.4, -5.2, -5.3.

IR: 3513, 3276, 2999, 2952, 2932, 2883, 2856, 2840, 1767, 1653, 1598, 1571, 1495, 1452, 1430, 1423, 1388, 1359, 1337, 1309, 1285, 1256, 1206, 1162, 1149, 1083, 1051, 1006, 982, 939, 910, 833, 810, 776, 730.

HRMS (ESI): $C_{33}H_{46}NO_8Si$ [M+H] calc. 612.2987, found 612.2985.

Alcohol **174**



To a solution of diol **178** (200 mg, 0.327 mmol) and imidazole (27.8 mg, 0.409 mmol, 1.25 eq.) in anhydrous dichloromethane (4 mL) under nitrogen atmosphere was dropwise added a solution of *tert*-butyldimethylsilyl chloride (54.2 mg, 0.360 mmol, 1.1 eq.) in anhydrous dichloromethane (1 mL) under ice bath cooling. The mixture was stirred with warming to room temperature overnight, then washed with water (5 mL) and the aqueous washings were extracted with dichloromethane (2×5 mL). The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (0 to 100% ethyl acetate in hexanes) to afford alcohol **174** (229 mg, 0.315 mmol, 96%) as a white foam.

R_f = 0.61 (40% ethyl acetate in hexanes).

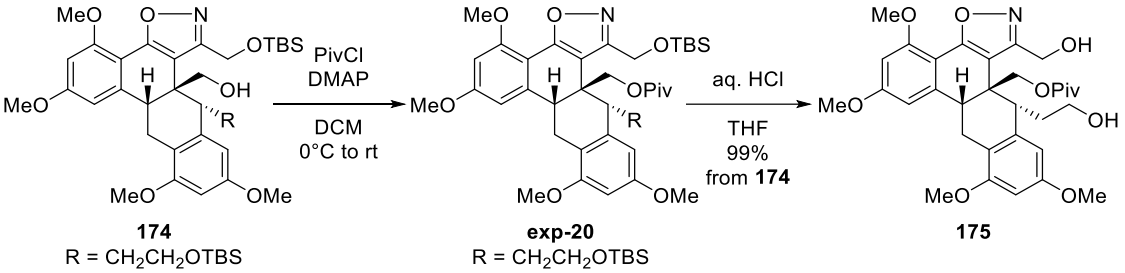
^{1}H-NMR (400 MHz, $CDCl_3$): 6.66 (s, 1H), 6.38 (d, J = 2.2 Hz, 1H), 6.35 (d, J = 2.4 Hz, 1H), 6.31 (d, J = 2.4 Hz, 1H), 4.86 (d, J = 11.7 Hz, 1H), 4.78 (d, J = 11.7 Hz, 1H), 3.95 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.73 (dd, J = 12.0, 6.4 Hz, 1H), 3.66 – 3.60 (m, 1H), 3.50 (dd, J = 17.1, 8.6 Hz, 1H), 3.38 (dd, J = 11.9, 8.9 Hz, 1H), 3.31 – 3.23 (m, 2H), 3.05 (dd, J = 10.4, 3.3 Hz, 1H), 2.93 (dd, J = 17.1, 6.3 Hz, 1H), 1.60 – 1.48 (m, 1H), 1.30 – 1.16 (m, 1H), 0.91 (s, 9H), 0.85 (s, 9H), 0.20 (s, 3H), 0.14 (s, 3H), -0.05 (s, 3H), -0.09 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 167.4, 162.3, 158.5, 158.1, 157.7, 157.3, 145.6, 141.0, 115.3, 111.3, 107.3, 105.6, 105.3, 96.6, 96.2, 68.5, 60.6, 57.4, 56.1 (OMe), 55.6 (2×OMe), 55.4 (OMe), 45.1, 42.6, 37.8, 33.6, 26.0, 25.9, 24.2, 18.4, 18.3, -5.0 (SiMe), -5.27 (SiMe), -5.28 (SiMe), -5.32 (SiMe).

IR: 3435, 3000, 2952, 2929, 2884, 2856, 1599, 1572, 1494, 1463, 1453, 1432, 1389, 1360, 1339, 1311, 1285, 1256, 1205, 1163, 1150, 1080, 1070, 1056, 1005, 960, 939, 913, 835, 778, 733.

HRMS (ESI): $C_{39}H_{60}NO_8Si_2$ [M+H] calc. 726.3852, found 726.3875.

Diol **175**



174
R = CH_2CH_2OTBS

exp-20
R = CH_2CH_2OTBS

175

Step 1: To a solution of alcohol **174** (171 mg, 0.236 mmol) and 4-dimethyl-aminopyridine (63.3 mg, 0.518 mmol, 2.2 eq.) in anhydrous dichloromethane (3 mL) under nitrogen atmosphere was dropwise added pivaloyl chloride (58 µL, 0.471 mmol, 2 eq.) under ice bath cooling and the mixture was stirred for 5 minutes. Then, the cooling bath was removed and stirring was continued at room temperature for 1.5 hours, before dichloromethane (6 mL) was added. The mixture was washed with saturated, aqueous sodium bicarbonate (6 mL), 2 M hydrochloric acid (2×6mL) and water (6 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was partially purified by column chromatography (0 to 25% ethyl acetate in hexanes) to afford pivaloyl ester **exp-20** as white foam, which was directly used without further purification in the next step.

Step 2: To a solution of pivaloyl ester **exp-20** in tetrahydrofuran (3 mL) was added 1 M hydrochloric acid (1 mL). The mixture was stirred overnight, then diluted with water and extracted with ethyl acetate (3×4 mL). The extracts were washed with water (6 mL), saturated, aqueous sodium bicarbonate (6 mL) and saturated, aqueous sodium chloride (6 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (0 to 5% methanol in dichloromethane) to afford diol **175** (137 mg, 0.234 mmol, 99%) as white foam.

R_f = 0.25 (5% methanol in dichloromethane).

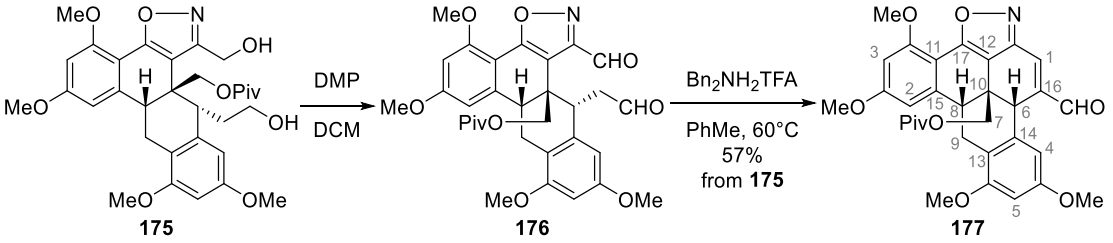
^{1}H-NMR (400 MHz, $CDCl_3$): 6.65 (dd, J = 2.3, 1.0 Hz, 1H), 6.39 (d, J = 2.1 Hz, 1H), 6.37 (d, J = 2.4 Hz, 1H), 6.35 (d, J = 2.4 Hz, 1H), 4.90 (d, J = 13.2 Hz, 1H), 4.71 (d, J = 13.3 Hz, 1H), 4.60 (d, J = 11.3 Hz, 1H), 3.94 (s, 3H), 3.86 (s, 3H), 3.85 (s, 4H), 3.79 (s, 3H), 3.51 (t, J = 7.2 Hz, 1H), 3.46 – 3.30 (m, 3H), 3.25 (dd, J = 10.0, 3.5 Hz, 1H), 2.96 (dd, J = 16.7, 7.1 Hz, 1H), 1.66 (dddd, J = 14.5, 9.1, 5.6, 3.5 Hz, 1H), 1.27 (ddt, J = 14.3, 8.6, 4.7 Hz, 1H), 0.90 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): 178.4, 166.4, 162.3, 159.8, 158.9, 157.7, 157.3, 144.3, 141.3, 114.8, 111.5, 107.1, 105.6, 105.5, 97.0, 96.2, 70.1, 60.4, 56.7, 56.1 (OMe), 55.6 (2×OMe), 55.5 (OMe), 42.9, 42.7, 39.6, 38.9, 34.5, 27.0, 24.7.

IR: 3357, 2938, 2839, 2253, 1722, 1598, 1572, 1495, 1479, 1452, 1424, 1398, 1329, 1308, 1283, 1206, 1148, 1108, 1083, 1051, 1040, 979, 940, 906, 832, 812, 785, 765, 727.

HRMS (ESI): $C_{32}H_{40}NO_9$ [M+H] calc. 582.2698, found 582.2720.

Aldehyde **177**



Step 1: To a suspension of diol **175** (94.0 mg, 0.162 mmol) in anhydrous dichloromethane (1 mL) was added a solution[a] of Dess-Martin periodinane (411 mg, 0.970 mmol, 6 eq.) in dichloromethane (3 mL) and the mixture was stirred for 1.5 hours. Then, 2 M aqueous sodium thiosulfate (3 mL) and saturated, aqueous sodium bicarbonate (3 mL) were added and the mixture was stirred vigorously for 1 hour. The layers were separated and the aqueous layer was extracted with dichloromethane (2×3 mL). The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure to afford crude dialdehyde **176**, which was directly used without further purification in the next step.

Step 2: Dialdehyde **176** and dibenzylammonium trifluoroacetate[b] (7.6 mg, 24 µmol, 0.15 eq.) in anhydrous toluene (1.6 mL) were stirred at 60 °C overnight. Then, the solvent was removed under reduced pressure and the residue was purified by column chromatography (2 cycles, 0 to 2% methanol in dichloromethane and 0 to 50% ethyl acetate in hexanes) to afford aldehyde **177** (51.5 mg, 92.0 mmol, 57%) as a yellow solid.

$\mathbf{R_f}$ = 0.40 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 9.95 (s, 1H, CHO), 7.53 (s, 1H, 1-H), 6.56 (d, J = 2.2 Hz, 1H, 2-H), 6.45 (d, J = 2.2 Hz, 1H, 3-H), 6.43 (d, J = 2.3 Hz, 1H, 4-H), 6.24 (d, J = 2.3 Hz, 1H, 5-H), 4.69 (s, 1H, 6-H), 3.97 (s, 3H, OMe), 3.93 (d, J = 11.1 Hz, 1H, 7-H_A), 3.88 (s, 3H, OMe), 3.79 (d, J = 11.1 Hz, 1H, 7-H_B), 3.71 (s, 3H, OMe), 3.69 (s, 3H, OMe), 3.17 (dd, J = 11.6, 5.8 Hz, 1H, 8-H), 3.03 (dd, J = 17.2, 5.8 Hz, 1H, 9-H_A), 2.15 (ddd, J = 17.2, 11.7, 1.4 Hz, 1H, 9-H_B), 1.09 (s, 9H, *t*Bu).

^{13}C-NMR (100 MHz, $CDCl_3$): 194.5 (H-C=O), 178.4 (O-C=O), 163.8 (C=N), 163.0 (C-OMe), 159.0 (C-OMe), 157.6 (C-OMe), 157.5 (C-OMe), 155.6 (C17), 149.7 (C16), 145.6 (C15), 136.6 (C14), 133.6 (C1), 116.9 (C13), 111.8 (C12), 107.7 (C2), 106.3 (C11), 103.9 (C4), 97.3 (C3), 96.8 (C5), 67.2 (C7), 56.2 (OMe), 55.7 (OMe), 55.5 (OMe), 55.4 (OMe), 42.5 (C8), 39.0 (C10), 36.4 (C6), 35.1 (*t*Bu), 27.8 (C9), 27.2 (*t*Bu).

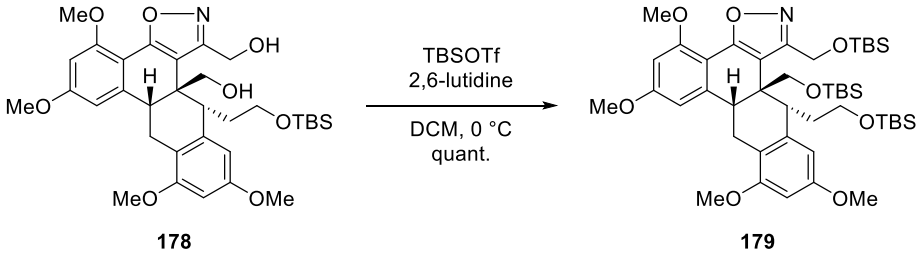
IR: 2969, 2939, 2906, 2839, 1728, 1683, 1652, 1602, 1570, 1518, 1492, 1480, 1456, 1435, 1424, 1397, 1365, 1316, 1283, 1210, 1199, 1151, 1120, 1090, 1073, 1048, 985, 971, 957, 943, 910, 835, 815, 769, 754, 731.

HRMS (ESI): $C_{32}H_{34}NO_8$ [M+H] calc. 560.2279, found 560.2282.

[a]During preparing the solution of Dess-Martin periodinane some insoluble material remained, which was not added to reaction mixture.

[b]Prepared by mixing dibenzyl amine (300 µL) and trifluoroacetic acid (120 µL) in diethyl ether (2 mL) under ice bath cooling. The resulting precipitate was washed with diethyl ether, dried and used without further purification.

Tris-silyl ether **179**



To a solution of diol **178** (1.5 g, 2.45 mmol) and 2,6-lutidine (1.14 mL, 9.84 mmol, 4 eq.) in anhydrous dichloromethane (20 mL) under nitrogen atmosphere was dropwise added *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.35 mL, 5.88 mmol, 2.4 eq.) under ice bath cooling. After stirring for 2.5 hours, dichloromethane (80 mL) was added and the cooling bath was removed. Then, the mixture was washed with saturated, aqueous sodium bicarbonate (100 mL), 2 M hydrochloric acid (2×100 mL) and water (100 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (0 to 10% ethyl acetate in hexanes) to afford tris-silyl ether **179** (2.06 g, 2.45 mmol, quantitative) as an off-white foam.

$\mathbf{R_f}$ = 0.47 (20% ethyl acetate in hexanes).

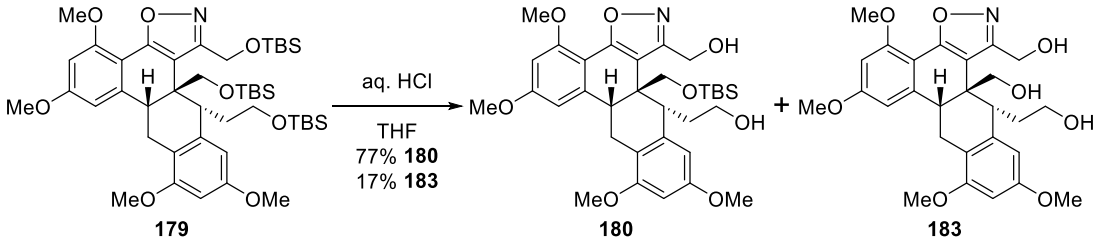
^{1}H-NMR (400 MHz, $CDCl_3$): 6.62 (dd, J = 2.2, 1.0 Hz, 1H), 6.37 (d, J = 2.2 Hz, 1H), 6.33 (d, J = 2.3 Hz, 1H), 6.22 (d, J = 2.3 Hz, 1H), 4.85 (d, J = 12.4 Hz, 1H), 4.76 (d, J = 12.4 Hz, 1H), 3.93 (s, 3H), 3.87 (d, J = 10.1 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 3.53 (t, J = 7.3 Hz, 1H), 3.45 (d, J = 10.0 Hz, 1H), 3.38 (td, J = 9.7, 4.7 Hz, 1H), 3.27 (ddd, J = 10.0, 8.8, 7.0 Hz, 1H), 3.20 (dd, J = 17.4, 7.8 Hz, 1H), 2.96 (dd, J = 17.3, 6.8 Hz, 1H), 2.89 (dd, J = 9.8, 3.7 Hz, 1H), 1.70 (dddd, J = 13.3, 10.0, 6.8, 3.7 Hz, 1H), 1.33 (dtd, J = 13.8, 9.1, 4.6 Hz, 1H), 0.96 (s, 9H), 0.76 (s, 9H), 0.67 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H), -0.12 (s, 6H), -0.14 (s, 3H), -0.15 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 166.1, 162.0, 159.7, 158.4, 157.7, 157.1, 145.1, 142.0, 115.8, 112.6, 107.8, 105.5, 105.2, 96.3, 96.1, 67.5, 62.8, 58.1, 56.0, 55.6, 55.5, 55.4, 44.5, 42.7, 38.8, 35.0, 26.2, 26.0, 25.8, 24.6, 18.6, 18.3, 18.1, -4.9, -5.0, -5.18, -5.24, -5.3, -5.4.

IR: 2954, 2929, 2884, 2856, 1599, 1572, 1493, 1463, 1432, 1423, 1389, 1361, 1338, 1324, 1311, 1286, 1255, 1207, 1163, 1148, 1081, 1054, 1005, 961, 939, 907, 832, 814, 775, 728.

HRMS (APCI): $C_{45}H_{74}NO_8Si_3$ [M+H] calc. 840.4717, found 840.4707.

Diol **180** and triol **183**



To a solution of silyl ether **179** (400 mg, 0.476 mmol) in tetrahydrofuran (6 mL) was added 1 M hydrochloric acid (2 mL) and the mixture was stirred for 4 hours. Then, 2 M sodium hydroxide (0.4 mL) and saturated, sodium bicarbonate (5 mL) were added. The tetrahydrofuran was evaporated under reduced pressure and the residue was extracted with dichloromethane (3×4 mL). The extracts were dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (0 to 10% methanol in dichloromethane) to afford diol **180** (224 mg, 0.366 mmol, 77%) and

triol **183** (39.6 mg,79.6 µmol, 17%), which were both obtained in the form of a yellowish solid.

Analytical data for diol 180

R_f = 0.29 (5% methanol in dichloromethane).

^{1}H-NMR (400 MHz, $CDCl_3$): 6.62 (d, J = 1.5 Hz, 1H), 6.41 – 6.35 (m, 3H), 4.87 (s, 2H), 3.94 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 3.70 (d, J = 9.9 Hz, 1H), 3.45 – 3.28 (m, 5H), 3.24 (t, J = 7.4 Hz, 1H), 2.86 (dd, J = 16.3, 7.8 Hz, 1H), 1.74 (dddd, J = 14.6, 9.1, 5.8, 3.3 Hz, 1H), 1.30 (ddt, J = 14.5, 10.3, 4.1 Hz, 1H), 0.70 (s, 9H), -0.10 (s, 3H), -0.12 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 165.7, 162.1, 160.5, 158.7, 157.6, 157.2, 144.5, 141.9, 115.7, 112.4, 107.3, 105.8, 105.6, 96.8, 96.2, 69.6, 60.7, 57.0, 56.1, 55.59, 55.56, 55.5, 44.6, 41.4, 40.1, 34.7, 25.8, 25.4, 18.3, -5.41, -5.44.

IR: 3359, 2954, 2930, 2884, 2856, 2840, 1599, 1572, 1494, 1462, 1452, 1423, 1390, 1359, 1336, 1309, 1285, 1257, 1206, 1162, 1148, 1107, 1083, 1051, 1007, 984, 961, 939, 906, 833, 813, 776, 727.

HRMS (ESI): $C_{33}H_{46}NO_8Si$ [M+H] calc. 612.3017, found 612.2987.

Analytical data for triol 183

R_f = 0.13 (5% methanol in dichloromethane).

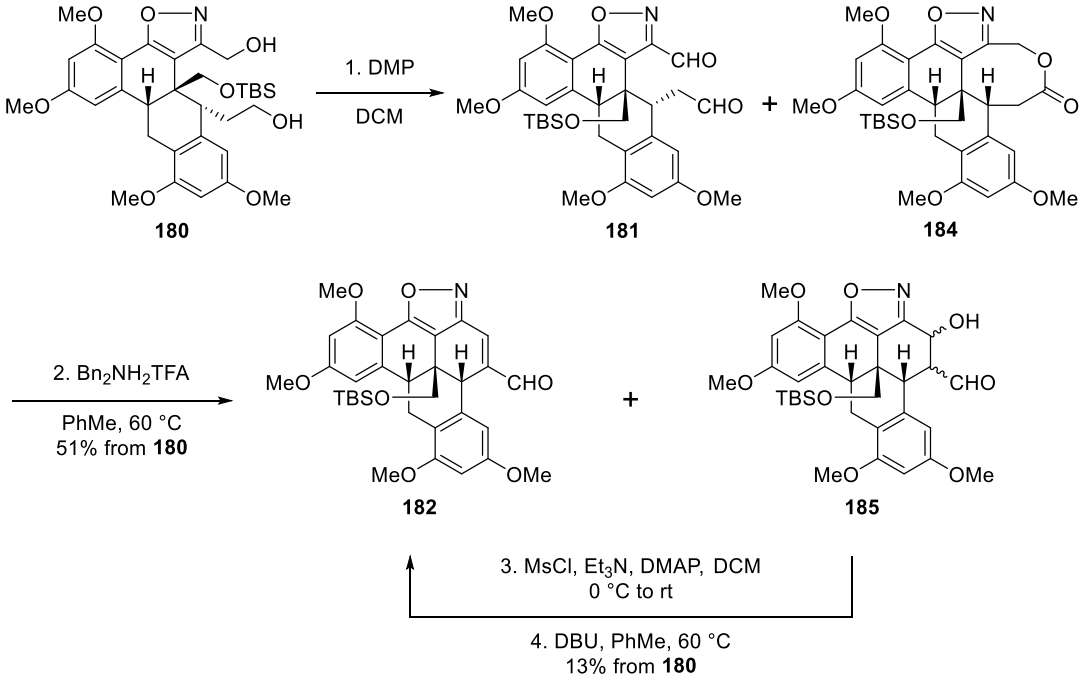
^{1}H-NMR (400 MHz, CD_3OD): 6.66 (dd, J = 2.2, 1.0 Hz, 1H), 6.53 (d, J = 2.2 Hz, 1H), 6.44 (d, J = 2.3 Hz, 1H), 6.33 (d, J = 2.3 Hz, 1H), 4.82 (d, J = 13.0 Hz, 1H), 4.78 (d, J = 13.1 Hz, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.85 (d, J = 11.4 Hz, 1H), 3.78 (s, 3H), 3.56 – 3.43 (m, 2H), 3.32 (d, J = 12.2 Hz, 1H), 3.29 – 3.17 (m, 2H), 3.04 (dd, J = 10.5, 3.7 Hz, 1H), 2.98 (dd, J = 16.3, 5.7 Hz, 1H), 1.54 (dtd, J = 13.7, 7.9, 3.7 Hz, 1H), 1.21 (dddd, J = 13.6, 10.9, 6.3, 4.8 Hz, 1H).

^{13}C-NMR (100 MHz, CD_3OD): 167.9, 164.1, 161.3, 160.1, 159.1, 158.6, 146.5, 142.4, 115.9, 113.1, 108.0, 107.0, 106.4, 97.5, 97.1, 68.4, 61.1, 57.1, 56.4, 56.0, 55.9, 55.7, 45.7, 44.2, 39.1, 35.1, 25.2.

IR: 3443, 3312, 2933, 2883, 2831, 1613, 1598, 1565, 1493, 1468, 1449, 1426, 1343, 1328, 1308, 1299, 1291, 1255, 1229, 1205, 1161, 1148, 1110, 1098, 1084, 1075, 1056, 1036, 1018, 995, 975, 951, 940, 905, 873, 865, 857, 834, 803, 792, 760, 727.

HRMS (APCI): $C_{27}H_{32}NO_8$ [M+H] calc. 498.2122, found 498.2125.

Aldehyde **182** and lactone **184**



Step 1: To a solution of diol **180** (1.09 g, 1.78 mmol) in anhydrous dichloromethane (20 mL) was added a 0.46 M[a] dichloromethane solution of Dess-Martin periodinane (9.70 mL, 4.46 mmol, 2.5 eq.) and the mixture was stirred for 1.5 hours. Then, 2 M aqueous sodium thiosulfate (20 mL) and saturated, aqueous sodium bicarbonate (20 mL) were added and the mixture was stirred vigorously for 1 hour. The layers were separated and the aqueous layer was extracted with dichloromethane (2×20 mL). The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure to afford crude dialdehyde **181**, which was directly used without further purification in the next step.

Step 2: A mixture of crude dialdehyde **181**, dibenzylammonium trifluoroacetate[b] (83.1 mg, 0.267 mmol, 0.15 eq.) and anhydrous toluene (25 mL) was stirred at 60 °C overnight. Then, the solvent was removed under reduced pressure and the residue was subjected to column chromatography (0 to 5% ethyl acetate in dichloromethane to 5% methanol in dichloromethane). This afforded impure aldehyde **182** and a mixture of compounds containing lactone **184** and multiple diastereomers of hydroxyaldehyde **185**, which was converted to aldehyde **182** as described below. The impure aldehyde **182** was further purified by column chromatography (0 to 20% ethyl acetate in hexanes) to afford pure aldehyde **182** (540 mg, 0.916 mmol, 51%) as a yellow solid.

Step 3/4: To the mixture of compounds obtained in step 2 and 4-dimethylaminopyridine (43.5 mg, 0.356 mmol) under nitrogen atmosphere were added anhydrous dichloromethane (10 mL) and triethylamine (1.24 mL, 8.91 mmol). Then, methanesulfonyl chloride (414 µL, 5.35 mmol) was added dropwise under ice bath cooling. After stirring for 1 hour, the cooling bath was removed and stirring was continued overnight. Then, the mixture was diluted with dichloromethane (40 mL), washed with saturated, aqueous sodium bicarbonate (60 ml), 2 M hydrochloric acid (2×60 mL) and water (60 mL), dried

[a]The activity of the solution was determined based on the conversion measured by ^{1}H-NMR spectroscopy for the oxidation of an excess of 3.5-dimethoxybenzyl alcohol.
[b]Prepared by mixing dibenzyl amine (300 µL) and trifluoroacetic acid (120 µL) in diethyl ether (2 mL) under ice bath cooling. The resulting precipitate was washed with diethyl ether, dried and used without further purification.

over sodium sulfate and evaporated under reduced pressure.
The residue was placed under nitrogen atmosphere and anhydrous toluene (20 mL) and 1,8 -diaza-bicyclo(5.4.0)undec-7-ene (400 µL, 2.68 mmol, 1.5 eq.) were added. After stirring for 2 hours at 60 °C, toluene (15 mL) was added. The mixture was washed with water (30 mL), 2 M hydrochloric acid (15 mL) and saturated, aqueous sodium chloride (15 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (0 to 5% ethyl acetate in dichloromethane) to afford aldehyde **182** (135 mg, 0.229 mmol, 13%) as a yellow film and impure lactone **184**.

Analytical data for aldehyde 182

R_f = 0.55 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 9.95 (s, 1H), 7.49 (s, 1H), 6.59 (d, J = 2.2 Hz, 1H), 6.48 – 6.42 (m, 2H), 6.23 (d, J = 2.3 Hz, 1H), 4.87 (s, 1H), 3.97 (s, 3H), 3.88 (s, 3H), 3.71 (s, 3H), 3.68 (s, 3H), 3.39 – 3.27 (m, 3H), 3.00 (dd, J = 17.2, 5.9 Hz, 1H), 2.13 (ddd, J = 17.2, 11.8, 1.4 Hz, 1H), 0.80 (s, 9H), -0.11 (s, 3H), -0.12 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 194.7, 163.6, 162.7, 158.8, 157.4, 157.3, 155.8, 150.0, 146.3, 137.6, 133.8, 117.2, 113.1, 107.6, 106.7, 104.0, 97.2, 96.5, 64.8, 56.1, 55.7, 55.43, 55.36, 41.2, 36.8, 35.3, 27.9, 25.9, 18.4, -5.53, -5.56.

IR: 2932, 2855, 1684, 1652, 1601, 1457, 1423, 1363, 1313, 1255, 1198, 1152, 1088, 958, 906, 836, 779, 726.

HRMS (ESI): $C_{33}H_{40}NO_7Si$ [M+H] calc. 590.2569, found 590.2585.

Analytical data for lactone 184

An analytical sample of lactone **184** was purified by reverse-phase HPLC,[a] which afforded a yellow foam.

R_f = 0.46 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 6.60 (d, J = 2.3 Hz, 1H), 6.45 (d, J = 2.2 Hz, 1H), 6.43 (d, J = 2.3 Hz, 1H), 6.27 (d, J = 2.1 Hz, 1H), 5.53 (d, J = 14.9 Hz, 1H), 5.06 (d, J = 14.8 Hz, 1H), 4.12 (t, J = 6.3 Hz, 1H), 3.94 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.71 (s, 3H), 3.65 (d, J = 10.4 Hz, 1H), 3.36 (dd, J = 14.7, 7.2 Hz, 1H), 3.30 (dd, J = 12.1, 5.3 Hz, 1H), 3.18 (d, J = 10.5 Hz, 1H), 3.05 (dd, J = 14.7, 5.3 Hz, 1H), 2.85 (dd, J = 17.4, 5.4 Hz, 1H), 2.37 (dd, J = 17.3, 12.1 Hz, 1H), 0.83 (s, 9H), -0.04 (s, 3H), -0.14 (s, 3H).

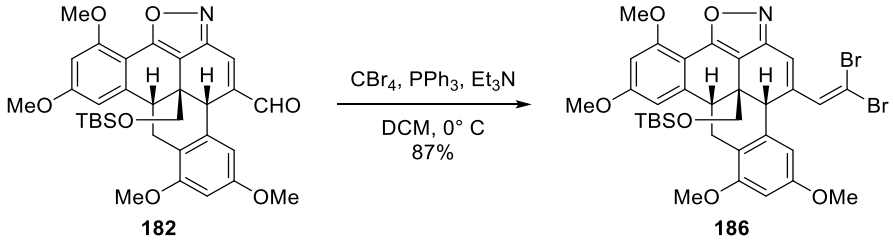
^{13}C-NMR (100 MHz, $CDCl_3$): 175.2, 167.7, 162.7, 158.8, 158.7, 157.7, 157.1, 144.7, 139.4, 118.3, 110.1, 105.7, 105.5, 103.6, 97.6, 95.7, 64.5, 62.1, 56.0 (OMe), 55.6 (2×OMe), 55.4 (OMe), 45.3, 44.6, 39.8, 34.5, 28.8, 25.9, 18.4, -5.5, -5.6.

IR: 3000, 2952, 2930, 2885, 2855, 2255, 1748, 1693, 1678, 1666, 1657, 1597, 1548, 1536, 1530, 1494, 1462, 1453, 1426, 1390, 1367, 1326, 1301, 1259, 1231, 1209, 1200, 1151, 1135, 1116, 1083, 1060, 1049, 1005, 990, 971, 958, 937, 910, 895, 868, 835, 815, 781, 731, 706.

HRMS (APCI): $C_{33}H_{42}NO_8Si$ [M+H] calc. 608.2674, found 608.2664.

[a] 10 mL/min; solvent A: water with 0.1% formic acid; solvent B: acetonitrile with 0.1% formic acid; gradient/%B: 30 to 70 in 1 min, 70 to 85 in 7 min, 85 to 100 in 2 min, 100 for 1 min.

Dibromoalkene **186**



To a solution of tetrabromomethane (207 mg, 0.624 mmol, 1.5 eq.) in anhydrous dichloromethane (2.5 mL) under nitrogen atmosphere was dropwise added a solution of triphenylphosphine (327 mg, 1.25 mmol, 3 eq.) in anhydrous dichloromethane (4 mL) under ice bath cooling. The mixture was stirred for 40 minutes, then a solution of aldehyde **182** (245 mg, 0.415 mmol) and triethylamine (58 µL, 0.42 mmol, 1 eq.) in anhydrous dichloromethane (4 mL) was added dropwise. After stirring for further 2 hours, the cooling bath was removed and mixture was directly[a] subjected to column chromatography (0 to 5% ethyl acetate in dichloromethane) to afford dibromoalkene **186** (270 mg, 0.362 mmol, 87%) as a yellowish solid.

R_f = 0.62 (40% ethyl acetate in hexanes).

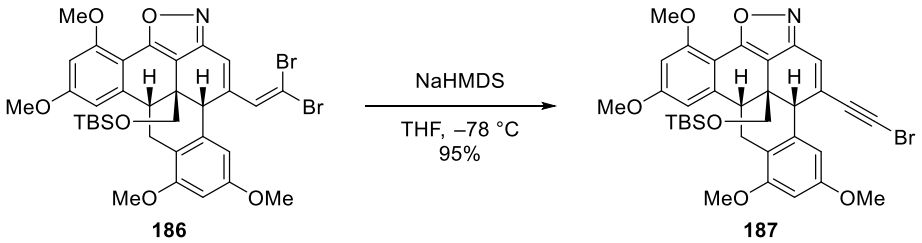
^{1}H-NMR (400 MHz, $CDCl_3$): 7.35 (s, 1H), 7.00 (s, 1H), 6.64 (d, J = 2.3 Hz, 1H), 6.56 (d, J = 2.2 Hz, 1H), 6.43 (d, J = 2.3 Hz, 1H), 6.26 (d, J = 2.3 Hz, 1H), 4.32 (s, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.68 (s, 3H), 3.45 (d, J = 9.9 Hz, 1H), 3.38 – 3.30 (m, 2H), 2.97 (dd, J = 17.0, 5.9 Hz, 1H), 2.20 (dd, J = 16.9, 11.6 Hz, 1H), 0.83 (s, 9H), -0.07 (s, 3H), -0.08 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 162.5, 162.4, 158.6, 157.5, 157.1, 156.1, 145.9, 145.0, 140.4, 137.5, 118.2, 117.8, 110.8, 107.6, 107.0, 102.9, 97.2, 97.0, 91.9, 64.3, 56.1 (OMe), 55.7 (OMe), 55.5 (2×OMe), 41.5, 41.3, 37.1, 27.8, 26.0, 18.5, -5.30, -5.37.

IR: 3000, 2951, 2927, 2853, 1767, 1725, 1656, 1599, 1570, 1518, 1491, 1455, 1436, 1421, 1389, 1361, 1312, 1284, 1256, 1212, 1198, 1151, 1118, 1086, 1074, 1058, 1026, 1006, 972, 959, 932, 907, 887, 834, 814, 776, 730, 707.

HRMS (ESI): $C_{34}H_{40}Br_2NO_6Si$ [M+H] calc. 744.0986, found 744.0987.

Bromoalkyne **187**



To a solution of dibromoalkene **186** (100 mg, 0.134 mmol) in anhydrous tetrahydrofuran (3 mL) under nitrogen atmosphere was dropwise added a 2 M tetrahydrofuran solution of sodium bis(trimethylsilyl)amide (134 µL, 0.268 mmol, 2 eq.) under dry ice/acetone bath cooling. The mixture was stirred for 30 minutes, before saturated, aqueous ammonium chloride (1 mL) was added and the cooling bath was removed. Then, the mixture was diluted with water (4 mL) and extracted with ethyl acetate (3×4 mL). The extracts were dried over sodium sulfate and evaporate under reduced pressure. The residue was purified

[a]The reaction mixture was directly loaded onto the column.

by column chromatography (0 to 20% ethyl acetate in hexanes) to afford bromoalkyne **187** (84.5 mg, 0.127 mmol, 95%) as an off-white foam/colorless film.

R_f = 0.58 (40% ethyl acetate in hexanes).

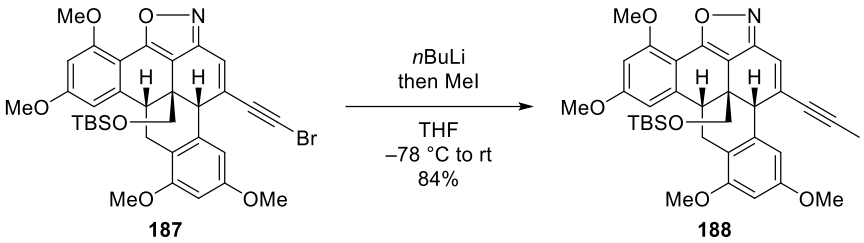
^{1}H-NMR (400 MHz, $CDCl_3$): 7.25 (d, J = 2.3 Hz, 1H), 6.99 (d, J = 1.0 Hz, 1H), 6.56 (d, J = 2.2 Hz, 1H), 6.43 (d, J = 2.2 Hz, 1H), 6.27 (d, J = 2.3 Hz, 1H), 4.24 (s, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.69 (s, 3H), 3.45 (d, J = 9.8 Hz, 1H), 3.33 (d, J = 9.9 Hz, 1H), 3.27 (dd, J = 11.9, 5.6 Hz, 1H), 2.95 (dd, J = 16.9, 5.6 Hz, 1H), 2.14 (ddd, J = 16.9, 12.0, 1.3 Hz, 1H), 0.84 (s, 9H), -0.04 (s, 3H), -0.06 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 162.5, 162.4, 158.5, 157.3, 157.1, 155.8, 145.8, 137.4, 131.7, 123.3, 117.6, 110.5, 107.6, 106.9, 103.9, 97.2, 97.0, 83.7, 64.7, 56.1, 55.7, 55.55, 55.46, 55.4, 42.7, 41.6, 37.0, 27.6, 26.0, 18.5, -5.4, -5.5.

IR: 3001, 2951, 2931, 2900, 2854, 2176, 1654, 1600, 1568, 1516, 1491, 1454, 1436, 1421, 1389, 1363, 1313, 1286, 1255, 1211, 1198, 1151, 1133, 1117, 1087, 1075, 1053, 1026, 1006, 988, 973, 958, 931, 907, 835, 811, 777, 753, 731, 711.

HRMS (ESI): $C_{34}H_{39}BrNO_6Si$ [M+H] calc. 664.1725, found 664.1732.

Alkyne **187**



To a solution of bromoalkyne **187** (70 mg, 105 µmol) in anhydrous tetrahydrofuran (2.5 mL) under nitrogen atmosphere was dropwise added a 2.35 M hexane/cyclohexane solution of *n*-butyllithium (58 µL, 0.14 mmol, 1.3 eq.) under dry ice/acetone bath cooling. The mixture was stirred for 10 minutes, then iodomethane (33 µL, 0.53 mmol, 5 eq.) was added. Stirring was continued for 15 minutes, before the cooling bath was removed. After stirred for 1 hour, saturated, aqueous ammonium chloride (1 mL) and water (4 mL) were added and the mixture was extracted with ethyl acetate (4 mL and 2×2 mL). The extracts were washed with saturated, aqueous sodium chloride (6 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (0 to 20% ethyl acetate in hexanes) to afford alkyne **188** (53.0 mg, 88.4µmol, 84%) as a white foam/colorless film.

R_f = 0.55 (40% ethyl acetate in hexanes).

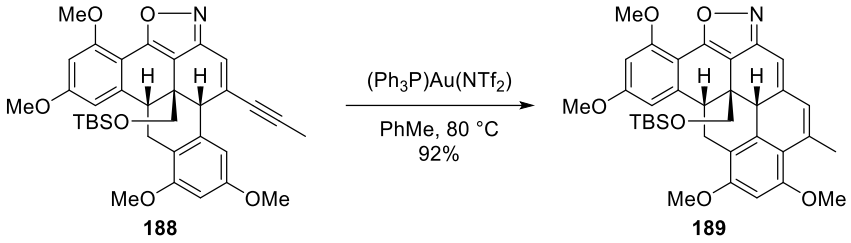
^{1}H-NMR (400 MHz, $CDCl_3$): 7.39 (d, J = 2.4 Hz, 1H), 6.85 (s, 1H), 6.56 (d, J = 2.2 Hz, 1H), 6.43 (d, J = 2.2 Hz, 1H), 6.26 (d, J = 2.4 Hz, 1H), 4.22 (s, 1H), 3.95 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.69 (s, 3H), 3.45 (d, J = 9.8 Hz, 1H), 3.36 – 3.27 (m, 2H), 2.96 (dd, J = 17.0, 5.8 Hz, 1H), 2.23 – 2.09 (m, 4H), 0.84 (s, 9H), -0.04 (s, 3H), -0.06 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 162.3, 162.2, 158.3, 157.2, 157.0, 156.2, 145.9, 138.0, 133.0, 120.6, 117.5, 110.6, 107.6, 107.1, 104.3, 97.1, 96.6, 91.9, 83.9, 64.3, 56.1, 55.6, 55.4, 55.3, 42.8, 41.3, 36.8, 27.7, 26.0, 18.5, 4.8, -5.3, -5.4.

IR: 2951, 2930, 2901, 2854, 1655, 1601, 1568, 1515, 1491, 1454, 1436, 1421, 1363, 1312, 1285, 1254, 1211, 1198, 1150, 1132, 1117, 1087, 1074, 1051, 1028, 1006, 988, 973, 943, 934, 907, 834, 811, 776, 759, 729.

HRMS (ESI): $C_{35}H_{42}NO_6Si$ [M+H] calc. 600.2776, found 600.2802.

Diene **189**



To alkyne **188** (52.0 mg, 86.7 µmol) and triphenylphosphinegold(I) bis(trifluoromethanesulfonyl)imidate (6.4 mg, 8.7 µmol, 0.1 eq.) under nitrogen atmosphere was added anhydrous toluene (3 mL) and the mixture was stirred at 80 °C for 5 hours. Then, the mixture was cooled to room temperature, filtered over silica and the silica was washed with 5% ethyl acetate in dichloromethane. The solvent was removed under reduced pressure and the residue was purified by column chromatography (0 to 20% ethyl acetate in hexanes) to afford diene **189** (48.0 mg, 80.0 µmol, 92%) as a yellow solid.

$\mathbf{R_f}$ = 0.49 (40% ethyl acetate in hexanes).

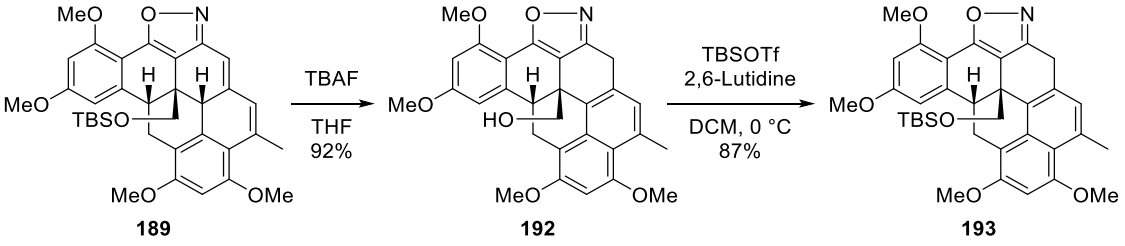
^{1}H-NMR (400 MHz, $CDCl_3$): 6.60 (d, J = 2.3 Hz, 1H), 6.43 (d, J = 2.3 Hz, 1H), 6.30 (q, J = 1.4 Hz, 1H), 6.26 (s, 1H), 6.20 (d, J = 2.2 Hz, 1H), 4.22 (s, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H), 3.48 (d, J = 9.7 Hz, 1H), 3.41 (dd, J = 12.7, 5.8 Hz, 1H), 3.33 (d, J = 9.7 Hz, 1H), 3.07 (dd, J = 16.4, 5.8 Hz, 1H), 2.35 (d, J = 1.5 Hz, 3H), 2.22 (ddd, J = 16.4, 12.7, 1.7 Hz, 1H), 0.79 (s, 9H), -0.10 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): 162.0, 160.7, 157.2, 156.9, 156.4, 156.3, 149.6, 145.0, 137.0, 137.0, 126.7, 117.2, 115.7, 110.3, 108.7, 108.0, 107.3, 97.2, 94.0, 66.6, 56.09, 56.05, 55.7, 55.5, 41.8, 40.3, 35.3, 27.2, 26.0, 23.8, 18.5, -5.3, -5.4.

IR: 3000, 2953, 2926, 2853, 1731, 1661, 1602, 1571, 1504, 1490, 1455, 1436, 1423, 1389, 1379, 1362, 1315, 1287, 1257, 1211, 1199, 1152, 1120, 1084, 1051, 1006, 996, 970, 942, 904, 852, 836, 814, 778, 753, 734, 721.

HRMS (ESI): $C_{35}H_{42}NO_6Si$ [M+H] calc. 600.2776, found 600.2786.

Naphthalene **193**



Step 1: To a solution of silyl ether **189** (22.0 mg, 36.7 µmol) in tetrahydrofuran (0.75 mL) was added tetrabutylammonium fluoride trihydrate (23.2 mg, 73.4 µmol, 2 eq.) and the mixture was stirred under nitrogen atmosphere for 2 hours. Then, water (4 mL) was added and the mixture was extracted with dichloromethane (3×4 mL). The extracts were dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (0 to 2.5% methanol in dichloromethane) to afford alcohol **192** (16.4 mg, 33.8 µmol, 92%) as a red-orange solid.

Step 2: To a solution of alcohol **192** (13 mg, 26.8 µmol) and 2,6-lutidine (16 µL, 0.13 mmol, 5 eq.) in anhydrous dichloromethane (1 mL) under nitrogen atmosphere was dropwise added *tert*-butyldimethylsilyl trifluoromethanesulfonate (15 µL, 67 µmol, 2.5 eq.) under ice

bath cooling. After stirring for 1 hour, saturated, aqueous sodium bicarbonate (5 mL) was added and the cooling bath was removed. The mixture was stirred for several minutes and then extracted with dichloromethane (3×4 mL). The extracts were dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (0 to 1% methanol in dichloromethane) to afford naphthalene **193** (14.0 mg, 23.3 µmol, 87%) as a yellow film.

Analytical data for alcohol 192

R_f = 0.39 (5% methanol in dichloromethane).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.02 (s, 1H), 6.78 (d, J = 2.3 Hz, 1H), 6.59 (s, 1H), 6.43 (d, J = 2.2 Hz, 1H), 4.25 (d, J = 19.5 Hz, 1H), 4.02 (d, J = 19.6 Hz, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 3.92 (s, 6H), 3.80 (dd, J = 13.9, 5.7 Hz, 1H), 3.62 (dd, J = 14.3, 5.6 Hz, 1H), 3.39 (dd, J = 10.7, 6.6 Hz, 1H), 3.30 (dd, J = 10.7, 6.8 Hz, 1H), 2.82 (s, 3H), 2.22 (t, J = 14.1 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 162.1, 161.8, 160.6, 157.7, 156.9, 153.7, 145.1, 134.3, 134.0, 132.5, 129.6, 127.7, 119.8, 114.1, 110.7, 108.0, 107.5, 97.0, 94.6, 72.2, 56.9, 56.1, 55.7, 55.6, 43.7, 40.5, 29.4, 28.4, 24.5.

Analytical data for naphthalene 193

R_f = 0.51 (40% ethyl acetate in hexanes).

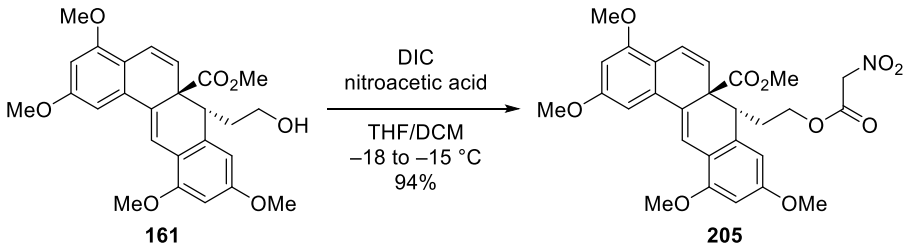
^{1}H-NMR (600 MHz, $CDCl_3$): 7.00 (s, 1H), 6.77 (d, J = 2.2 Hz, 1H), 6.57 (s, 1H), 6.41 (d, J = 2.2 Hz, 1H), 4.22 (d, J = 19.1 Hz, 1H), 4.00 (d, J = 19.5 Hz, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.92 (s, 3H), 3.91 (s, 3H), 3.72 (dd, J = 14.1, 5.6 Hz, 1H), 3.59 (dd, J = 14.3, 5.6 Hz, 1H), 3.33 (d, J = 9.4 Hz, 1H), 3.24 (d, J = 9.4 Hz, 1H), 2.80 (s, 3H), 2.21 (t, J = 14.2 Hz, 1H), 0.51 (s, 9H), -0.35 (s, 3H), -0.43 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): 161.8, 161.6, 160.5, 157.7, 156.7, 153.5, 145.7, 134.1, 133.8, 132.5, 130.4, 127.6, 119.8, 115.0, 111.0, 108.0, 107.8, 96.8, 94.6, 72.3, 57.0, 56.2, 55.8, 55.6, 44.0, 40.5, 29.3, 28.4, 25.5, 24.4, 17.9, -5.8, -6.0.

IR: 2952, 2928, 2852, 1673, 1650, 1603, 1594, 1572, 1510, 1492, 1459, 1437, 1420, 1399, 1384, 1361, 1339, 1312, 1290, 1278, 1255, 1210, 1204, 1181, 1159, 1113, 1097, 1078, 1072, 1057, 1022, 1005, 988, 973, 937, 907, 834, 812, 775, 728.

HRMS (APCI): $C_{35}H_{42}NO_6Si$ [M+H] calc. 600.2776, found 600.2774.

Nitroacetic acid ester 205



To a solution of alcohol **161** (270 mg, 0.597 mmol) in anhydrous dichloromethane (6 mL) under nitrogen atmosphere was added *N*,*N*′-diisopropylcarbodiimide (6.23 mL, 40.2 mmol, 3 eq.). Then, a solution of nitroacetic acid (see page 154, 3.52 g, 33.5 mmol, 2.5 eq.) in anhydrous tetrahydrofuran (5 mL) was added dropwise under ice/brine bath cooling. After stirring for 2 hours, the cooling bath was removed and the volatiles were evaporated under reduced pressure. The residue was purified by column chromatography (0 to 2% acetone in dichloromethane) to afford nitroacetic acid ester **205** (303 mg, 0.562 mmol, 94%) as a yellow solid.

R_f = 0.33 (40% ethyl acetate in hexanes).

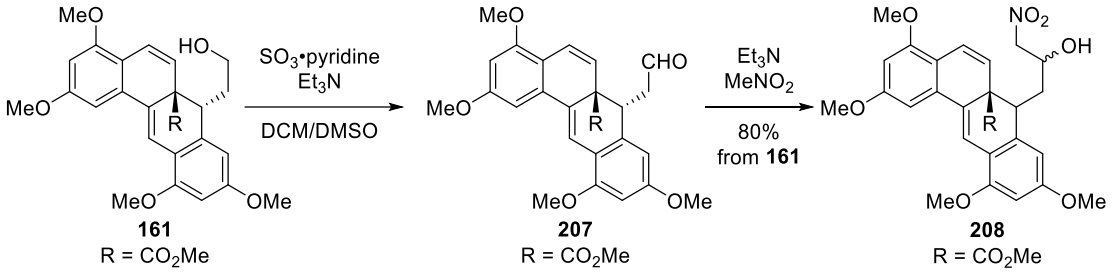
^{1}H-NMR (400 MHz, $CDCl_3$): 7.44 (s, 1H), 6.95 (d, J = 2.3 Hz, 1H), 6.93 (d, J = 9.8 Hz, 1H), 6.31 (d, J = 2.2 Hz, 1H), 6.30 (d, J = 2.3 Hz, 1H), 6.24 (d, J = 2.3 Hz, 1H), 5.52 (d, J = 9.8 Hz, 1H), 5.15 (d, J = 14.4 Hz, 1H), 5.09 (d, J = 14.4 Hz, 1H), 4.24 – 4.07 (m, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 3.81 (s, 6H), 3.50 (s, 3H), 3.33 (dd, J = 11.2, 3.4 Hz, 1H), 2.12 (dddd, J = 16.0, 9.7, 6.7, 3.4 Hz, 1H), 1.84 (ddt, J = 16.1, 10.7, 5.1 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): 173.6, 161.8, 160.7, 160.5, 157.2, 156.9, 137.4, 133.9, 128.8, 123.4, 123.1, 117.9, 115.2, 113.8, 105.2, 99.2, 97.9, 97.3, 76.4, 65.5, 55.7, 55.63, 55.55, 55.5, 52.98, 52.95, 43.3, 28.8.

IR: 3001, 2941, 2839, 1752, 1719, 1641, 1595, 1563, 1491, 1455, 1425, 1388, 1371, 1332, 1310, 1286, 1218, 1204, 1143, 1122, 1092, 1050, 1028, 1011, 947, 936, 908, 889, 830, 802, 767, 728.

HRMS (ESI): $C_{28}H_{30}NO_{10}$ [M+H] calc. 540.1864, found 540.1838.

Nitroalcohol 208



To a solution of alcohol **161** (400 mg, 0.884 mmol) and triethylamine (612 µL, 4.42 mmol, 5 eq.) in anhydrous dichloromethane (9 mL) under nitrogen atmosphere was added a solution of sulfur trioxide pyridine complex (352 mg, 2.21 mmol, 2.5 eq.) in anhydrous dimethyl sulfoxide (1.8 mL) and the mixture was stirred for 50 minutes. Then, the volatiles were removed under reduced pressure and nitromethane (3.6 mL) and triethylamine (1.8 mL) were added. The mixture was stirred for additional 3 hours, concentrated under reduced pressure and dichloromethane (25 mL) and 1 M hydrochloric acid (20 mL) were added to the residue. The mixture was shaken thoroughly, the layers were separated and the aqueous layer was extracted with dichloromethane (10 mL). The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (0 to 2.5% acetone in dichloromethane) to afford nitroalcohol **208** (359 mg, 0.702 mmol, 80%) as diastereomeric mixture (ratio ≈ 5/3 by ^{1}H-NMR) in the form of a yellow solid.

Analytical data for minor diastereomer of nitroalcohol 208

R_f = 0.52 (4% acetone in dichloromethane).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.46 (s, 1H), 6.97 – 6.91 (m, 2H), 6.35 (d, J = 2.3 Hz, 1H), 6.31 (d, J = 2.1 Hz, 1H), 6.30 (d, J = 2.3 Hz, 1H), 5.51 (dd, J = 9.8, 1.1 Hz, 1H), 4.46 (dd, J = 12.4, 2.3 Hz, 1H), 4.43 – 4.34 (m, 1H), 4.30 (dd, J = 12.4, 8.7 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.50 (s, 3H), 3.38 (dd, J = 9.6, 4.5 Hz, 1H), 2.14 (d, J = 4.2 Hz, 1H), 1.96 (ddd, J = 14.4, 6.0, 4.5 Hz, 1H), 1.79 (ddd, J = 14.4, 9.7, 6.9 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 173.4, 160.8, 160.8, 157.4, 157.0, 138.5, 133.9, 128.9, 123.5, 123.0, 117.9, 115.4, 113.7, 104.5, 99.3, 98.0, 97.4, 80.5, 68.5, 55.8, 55.7, 55.59, 55.58, 53.4, 53.0, 44.0, 35.0.

IR: 2941, 2839, 1721, 1604, 1597, 1569, 1554, 1492, 1462, 1426, 1385, 1336, 1287, 1221, 1206, 1152, 1119, 1090, 1052, 1005, 992, 937, 910, 888, 831, 804, 732.

HRMS (ESI): $C_{27}H_{30}NO_9$ [M+H] calc. 512.1915, found 512.1904.

Analytical data for major diastereomer of nitroalcohol **208**

R_f = 0.40 (4% acetone in dichloromethane).

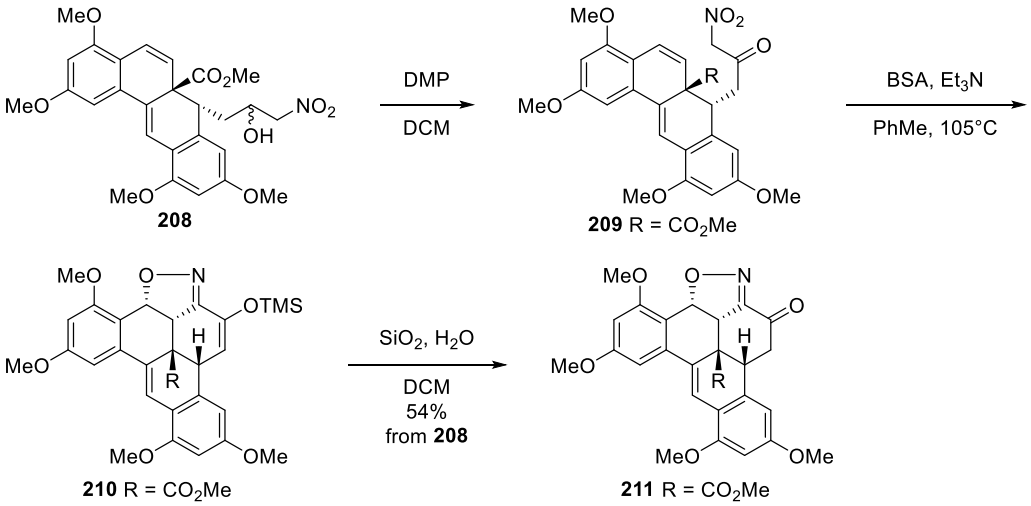
^{1}H-NMR (400 MHz, $CDCl_3$): 7.45 (s, 1H), 6.96 (d, J = 2.2 Hz, 1H), 6.92 (dd, J = 9.8, 0.6 Hz, 1H), 6.44 (d, J = 2.3 Hz, 1H), 6.31 (d, J = 2.2 Hz, 2H), 5.56 (dd, J = 9.8, 1.1 Hz, 1H), 4.24 (dd, J = 13.8, 9.0 Hz, 1H), 4.14 (dd, J = 13.7, 2.3 Hz, 1H), 4.11 – 4.02 (m, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.64 (dd, J = 11.9, 3.0 Hz, 1H), 3.51 (s, 3H), 2.73 (d, J = 4.4 Hz, 1H), 1.83 (ddd, J = 14.1, 11.1, 3.1 Hz, 1H), 1.53 (ddd, J = 14.0, 11.9, 2.3 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 173.5, 160.7, 160.5, 157.2, 156.9, 137.7, 133.9, 129.1, 123.7, 123.1, 117.9, 115.2, 113.9, 105.9, 99.3, 97.9, 97.1, 81.0, 66.2, 55.75, 55.66, 55.57, 53.0, 52.9, 42.1, 33.6.

IR: 2940, 2839, 1721, 1639, 1602, 1569, 1554, 1491, 1463, 1426, 1385, 1340, 1289, 1221, 1206, 1151, 1119, 1085, 1051, 1031, 1004, 909, 896, 831, 804, 732.

HRMS (ESI): $C_{27}H_{30}NO_9$ [M+H] calc. 512.1915, found 512.1913.

Isoxazoline **211**



Step 1: To a solution of alcohol **208** (1.03 g, 2.02 mmol) in anhydrous dichloromethane (40 mL) under nitrogen atmosphere was dropwise added a solution of Dess-Martin periodinane (1.03 g, 2.43 mmol, 1.2 eq.) in anhydrous dichloromethane (5 mL)[a] and the mixture was stirred for 5 minutes. Then, saturated, aqueous sodium bicarbonate (20 mL) and 10% aqueous sodium thiosulfate (10 mL) were added. After stirring vigorously for 15 minutes, dichloromethane (20 mL) and water (30 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (40 mL). The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure to afford crude nitroketone **209** as an orange-yellow solid, which was directly used without further purification in the next step.

Step 2: To a suspension of crude nitro ketone **209** in anhydrous toluene (50 mL) under nitrogen atmosphere were added triethylamine (550 µL, 3.96 mmol, 2 eq.) and

[a]During preparing the solution of Dess-Martin periodinane some insoluble material remained, which was not added to reaction mixture.

bis(trimethylsilyl)acetamide (1.94 mL, 7.93 mmol, 4 eq.) and the resulting solution was stirred at 105 °C for 18 hours. Then, the volatiles were evaporated under reduced pressure and the residue was dissolved in dichloromethane (75 mL). The solution was washed with 1 M hydrochloric acid and the aqueous washings were extracted with dichloromethane (25 mL). The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure to afford crude silyl enol ether **210** as a brown oil, which was directly used without further purification in the next step.

Step 3: To a solution of crude silyl enol ether **210** in dichloromethane (75 mL) were added silica (5 g) and water (0.25 mL). After the mixture had stirred overnight, the solvent was removed under reduced pressure and the residue[a] was partially purified by column chromatography (0 to 2% acetone in dichloromethane). Ethanol (30 mL) was added to the partially purified material, the mixture was warmed to reflux for several minutes, stored at −20 °C overnight and filtered. The solids were washed with a minimal amount of ethanol and dried to afford isoxazole **211** (291 mg, 0.592 mmol, 29%) as a yellow solid. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography (0 to 2% acetone in dichloromethane) to afford additional product **211** (246 mg, 0.501 mmol, 25%) as a yellow solid.

$\mathbf{R_f}$ = 0.45 (5% methanol in dichloromethane).

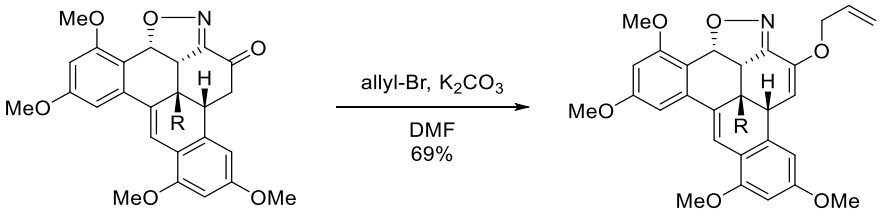
^{1}H-NMR (400 MHz, $CDCl_3$): 7.77 (s, 1H), 7.02 (d, J = 2.2 Hz, 1H), 6.43 (d, J = 2.2 Hz, 1H), 6.38 – 6.31 (m, 2H), 6.13 (d, J = 10.5 Hz, 1H), 4.32 (d, J = 10.5 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.76 (dd, J = 12.7, 5.1 Hz, 1H), 3.46 (s, 3H), 2.71 (dd, J = 17.7, 5.1 Hz, 1H), 2.57 (dd, J = 17.7, 12.8 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 191.1, 173.2, 161.4, 160.1, 157.8, 152.0, 139.1, 135.2, 123.0, 118.8, 113.9, 112.3, 103.8, 98.8, 98.5, 97.4, 77.8, 56.1, 55.7, 55.6, 53.3, 48.9, 46.8, 45.7, 44.0.

IR: 3004, 2941, 2840, 1712, 1598, 1579, 1521, 1492, 1457, 1428, 1400, 1370, 1339, 1321, 1285, 1233, 1215, 1200, 1152, 1112, 1098, 1058, 1045, 1009, 974, 935, 912, 878, 829, 793, 761, 731.

HRMS (ESI): $C_{27}H_{26}NO_8$ [M+H] calc. 492.1653, found 492.1663.

Allyl ether 212



211 R = CO_2Me **212** R = CO_2Me

To suspension of ketone **211** (64 mg, 0.130 mmol) and potassium carbonate (54.0 mg, 0.391 mmol, 3 eq.) in anhydrous dimethylformamide (2 mL) under nitrogen atmosphere was added allyl bromide (17 µL, 0.20 mmol, 1.5 eq.). The mixture was stirred for 3 hours, diluted with dichloromethane (5 mL), washed with water (4×5 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (0 to 1% acetone in dichloromethane) to afford allyl ether **212** (47.5 mg, 89.4 µmol, 69%) as yellow solid.

$\mathbf{R_f}$ = 0.50 (5% methanol in dichloromethane).

[a]The residue was suspended in dichloromethane and directly loaded onto the column.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.61 (s, 1H), 6.89 (d, J = 2.2 Hz, 1H), 6.39 (d, J = 2.2 Hz, 1H), 6.38 (d, J = 2.3 Hz, 1H), 6.36 (d, J = 2.3 Hz, 1H), 5.99 (d, J = 9.4 Hz, 1H), 5.88 (ddt, J = 17.2, 10.7, 5.4 Hz, 1H), 5.24 (dq, J = 17.2, 1.7 Hz, 1H), 5.15 (d, J = 10.5 Hz, 1H), 4.72 (d, J = 2.4 Hz, 1H), 4.28 (d, J = 9.5 Hz, 1H), 4.25 – 4.22 (m, 2H), 4.13 (d, J = 2.2 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.86 (s, 3H), 3.46 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 173.3, 161.2, 160.8, 160.2, 157.1, 150.7, 144.7, 138.2, 135.7, 132.0, 124.8, 118.4, 117.9, 115.2, 114.0, 109.3, 103.9, 99.3, 98.6, 97.0, 74.6, 68.9, 56.1 (OMe), 55.7 (OMe), 55.6 (2×OMe), 53.0, 49.1, 47.4, 45.8.

IR: 3003, 2940, 2839, 2250, 1722, 1598, 1574, 1494, 1455, 1426, 1368, 1338, 1326, 1294, 1283, 1232, 1213, 1197, 1171, 1150, 1133, 1098, 1088, 1061, 1045, 1017, 991, 981, 935, 908, 893, 880, 837, 800, 775, 728.

HRMS (ESI): $C_{30}H_{30}NO_8$ [M+H] calc. 532.1966, found 532.1981.

2 Part II: Synthesis of cyclic azobenzenes

General information

General experimental conditions

All reactions were conducted with magnetic stirring at room temperature unless otherwise noted. Reactions at elevated temperatures were performed using an oil bath or aluminum block as the heat transfer medium, with the reported temperature corresponding to that of the heat transfer medium.

Chemicals

All chemicals were obtained from common vendors and used without further purification unless otherwise noted. With the exception of dimethyl sulfoxide, which was purchased from Oakwood Chemical in standard quality, all solvents were purchased with "certified ACS" or higher quality. Anhydrous solvents were prepared with a solvent purification system by filtration of HPLC grade solvents through alumina according to the method of Grubbs[1] or purchased from Acros Organics in AcroSeal™ bottles.

Titration of peroxy acids

Titrations were performed as duplicates and the averaged value of both titrations was used. ***meta*-Chloroperoxybenzoic acid (*m*CPBA):** To an ice-cold mixture of 5 wt% aqueous sulfuric acid (50 mL) and 10 wt% aqueous potassium iodide (1–2 mL) was added a solution of *m*CPBA in acetic acid (500 µL). The mixture was titrated with 0.1 M aqueous sodium thiosulfate until the brown color almost disappeared, then 1 wt% aqueous starch (1–2 mL) was added. The titration with sodium thiosulfate was continued until the black-blue color disappeared and a white suspension was obtained. The concentration of the solution of *m*CPBA (c_{mCPBA}) directly corresponds to the necessary total volume of sodium thiosulfate solution ($V_{Na2S2O3}$) by the following relation:

$$c_{mCPBA} = (V_{Na2S2O3} / 10\ mL) * mol/L$$

Peracetic acid: The reported content of peroxy acid in the commercial solution of peracetic acid in acetic acid was confirmed by the same method as for *m*CPBA, but before the titration of the peroxy acid with sodium thiosulfate, the hydrogen peroxide was decomposed by titration with cerium (IV) ammonium sulfate against ferroin as the indicator.

Chromatography

Retardation Factors (R_f) were determined by analytical thin-layer chromatography (TLC) performed on pre-coated glass plates from Millipore Sigma (TLC Silica Gel 60 Plates, 250 µm layer thickness, F254 fluorescence indicator), with visualization by exposure to ultraviolet light (254 nm) or by staining with a basic potassium permanganate solution.
Column chromatography was performed with silica gel obtained from Millipore Sigma (Geduran® Si 60, 40 – 63 µm) or from Teledyne Isco (RediSep® Gold, 20 – 40 µm, spherical). Column chromatography was either performed manually or with an automated chromatography system (Teledyne Isco CombiFlash®).
High-performance liquid chromatography (HPLC) was performed with HPLC grade solvents on an Agilent 1260 Infinity series system (Preparative Pump, Preparative Pump Gradient

Extension, Preparative Autosampler, Infinity II Diode Array Detector WR, 1290 Infinity Valve Drive, Fraction Collector prep scale) equipped with a Phenomenex Gemini® LC Column (5 µm, C18, 110 Å, 150×30 mm, AXIATM Packed) and Phenomenex Gemini® SecurityGuard™ Prep Cartridge (C18, 15×30mm ID).

Nuclear magnetic resonance (NMR) spectroscopy

Proton and carbon (^{1}H- and ^{13}C-) NMR spectra were recorded on Bruker Avance III (600/150 MHz, with TCI Cryoprobe™) and Avance III HD (400/100 MHz, with BBFO Cryoprobe™) spectrometers. Fluorine (^{19}F) NMR spectra were recorded on a Bruker Avance III spectrometer (400 MHz for ^{1}H and 377 MHz for ^{19}F, with BB(F)O probe). All spectra were recorded at a temperature of 25 °C in 5 mm tubes in deuterated solvents purchased from Cambridge Isotope Laboratories, Inc. (chloroform-d or $CDCl_3$, 99.8% D; dimethyl sulfoxide-d_6 or DMSO-d_6, 99.9% D; methanol-d_4 or CD_3OD, 99.8% D). For ^{1}H-NMR spectra chemical shifts (δ) in parts per million (ppm) relative to tetramethylsilane (δ = 0 ppm) are reported using the residual protic solvent ($CHCl_3$ in $CDCl_3$: δ = 7.26 ppm, DMSO-d_5 in DMSO-d_6: δ = 2.50 ppm, CHD_2OD in CD_3OD: δ = 3.31 ppm) as an internal reference. For ^{13}C-NMR spectra, chemical shifts in ppm relative to tetramethylsilane (δ = 0 ppm) are reported using the central resonance of the solvent signal ($CDCl_3$: δ = 77.16 ppm, DMSO-d_6: δ = 39.52 ppm, CD_3OD: δ = 49.00 ppm) as an internal reference. For ^{19}F-NMR spectra chemical shifts in ppm are reported relative to trichlorofluoromethane (δ = 0 ppm) with absolute referencing (Ξ = 94.094011) using the ^{1}H-NMR signal of residual protic solvent as an internal reference. The abbreviations used for multiplicities and descriptors are s = singlet, d = doublet, t = triplet, q = quartet or combinations thereof, m = multiplet and br = broad. NMR spectral data was analyzed with the program MestreNova.

Infrared (IR) spectroscopy

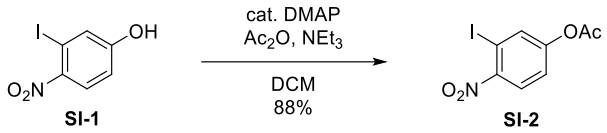
IR spectra were recorded on a Thermo-Fisher Nicolet 6700 Fourier Transform-IR spectrometer with Smart iTR™ attenuated total reflectance (ATR) unit. Samples were either measured as a solid or as a thin film formed from a solution after evaporation of the solvent. IR data is reported as wave numbers with the unit cm^{-1}. The window of acquisition was 4000 to 700 cm^{-1}.

Mass spectrometry (MS)

A Shimadzu TQ 8040 GC-MS/FID systems with electron ionization (EI) ion source was used to obtain low-resolution mass spectra (LRMS). High-resolution mass spectra (HRMS) were obtained with an Agilent 6224 Accurate Mass time-of-flight (TOF) LC/MS system using either an electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) ion source. All reported data refers to positive ionization mode.

Syntheses of aryl iodide building blocks

3-iodo-4-nitrophenyl acetate (SI-2)



Anhydrous dichloromethane (40 mL) and triethylamine (1.84 mL, 13.2 mmol, 1.4 eq.) were added to 4-dimethylaminopyridine (58 mg, 0.47 mmol, 0.05 eq.) and 3-iodo-4-nitrophenol[2] (**SI-1**, 2.50 g, 9.43 mmol, 1.0 eq.) under nitrogen atmosphere. The resulting solution was cooled with an ice-bath and acetic anhydride (1.25 mL, 13.2 mmol, 1.4 eq.) was added dropwise. The cooling bath was removed and the mixture was stirred for six hours at room temperature. The resulting dark green solution was diluted with dichloromethane (60 mL), washed successively with 2 M aqueous hydrochloric acid (60 mL) and saturated aqueous sodium hydrogen carbonate (60 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure, the remaining green oil taken up in dichloromethane (20 mL), filtered over a short plug of silica (4 g) and eluted with additional dichloromethane (2×20 mL). After removal of the solvent under reduced pressure, a yellow oil was obtained that solidified upon standing at room temperature to afford the title compound (2.55 g, 8.31 mmol, 88%) as a yellow solid.

R_f = 0.32 (20% ethyl acetate in hexanes).

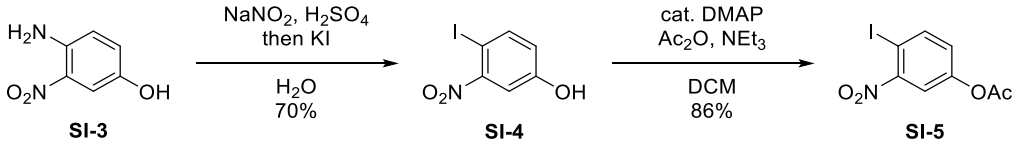
^{1}H-NMR (400 MHz, DMSO-d_6): 8.04 (d, J = 8.8 Hz, 1H), 7.96 (d, J = 2.4 Hz, 1H), 7.42 (dd, J = 8.8, 2.4 Hz, 1H), 2.29 (s, 3H).

^{13}C-NMR (100 MHz, DMSO-d_6): 168.6, 152.8, 150.6, 134.4, 126.3, 123.0, 88.7, 20.8.

IR: 3087, 3022, 1757, 1590, 1577, 1530, 1468, 1421, 1371, 1346, 1298, 1258, 1208, 1180, 1035, 1005, 919, 889, 862, 840, 809, 751, 714.

LRMS (GC-EI): 307 [$M^{+\bullet}$].

4-iodo-3-nitrophenyl acetate (SI-5)



Step1: A mixture of 4-amino-3-nitrophenol (**SI-3**, 20.0 g, 130 mmol, 1.0 eq.), water (285 mL) and concentrated sulfuric acid (15 mL) was warmed to dissolve the solids, then cooled with an ice-bath. A solution of sodium nitrite (10.3 g, 149 mmol, 1.15 eq.) in water (34 mL) was added dropwise within approx. one hour under vigorous stirring. After stirring for additional 40 minutes, a solution of potassium iodide (32.2 g, 195 mmol, 1.5 eq.) was added dropwise and the mixture was stirred with warming to room temperature overnight. The resulting precipitate was collected, washed with plenty of water and dried. Purification of the precipitate by column chromatography (20% ethyl acetate in hexanes) afforded 4-iodo-3-nitrophenol (24.2 g, 91.2 mmol, 70%) as a yellow solid.

Step2: Anhydrous dichloromethane (83 mL) and triethylamine (3.67 mL, 26.4 mmol, 1.4 eq.) were added to 4-dimethylaminopyridine (115 mg, 0.941 mmol, 0.05 eq.) and 4-iodo-3-nitrophenol (**SI-4**, 5.00 g, 18.9 mmol, 1.0 eq.) under nitrogen atmosphere. The resulting solution was cooled with an ice-bath and acetic anhydride (2.49 mL, 26.4 mmol,

1.4 eq.) was added dropwise. The mixture was then stirred with warming to room temperature for nine and a half hours. The resulting yellow solution was washed successively with 2 M aqueous hydrochloric acid (40 mL), water (40 mL) and saturated aqueous sodium hydrogen carbonate (40 mL) and dried over sodium sulfate. After removal of the solvent under reduced pressure, the title compound (5.00 g, 16.3 mmol, 86%) was obtained as a yellow solid.

R_f = 0.32 (20% ethyl acetate in hexanes).

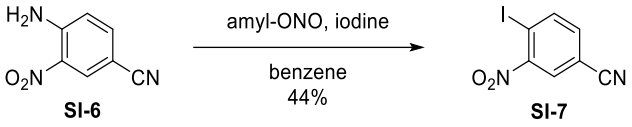
^{1}H-NMR (400 MHz, $CDCl_3$): 8.03 (d, J = 8.6 Hz, 1H), 7.70 (d, J = 2.6 Hz, 1H), 7.09 (dd, J = 8.6, 2.7 Hz, 1H), 2.33 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 168.4, 153.2, 151.0, 142.6, 127.3, 119.6, 82.0, 21.1.

IR: 3094, 3078, 1752, 1572, 1523, 1468, 1434, 1351, 1297, 1284, 1260, 1200, 1143, 1099, 1044, 1014, 953, 895, 860, 828, 801, 753, 716.

LRMS (GC-EI): 307 [$M^{+\bullet}$].

4-iodo-3-nitrobenzonitrile (SI-7)



To 4-amino-3-nitrobenzonitrile (**SI-6**, 3.00 g, 18.4 mmol, 1.0 eq.) and iodine (2.57 g, 10.1 mmol, 0.55 eq.) under nitrogen atmosphere was added anhydrous benzene (10 mL), followed by amyl nitrite (2.59 mL, 19.3 mmol, 1.05 eq.). The dark, red-black suspension was stirred until the substrate was consumed according to ^{1}H-NMR spectroscopy. The resulting red suspension was diluted with hexanes (20 mL) and sonicated. The solids were collected, washed with additional hexanes (50 mL) and the filtrate was discarded. The solids were dissolved in dichloromethane and the insoluble residue was discarded. After removal of the solvent under reduced pressure and purification of the crude material by column chromatography (0 to 50% dichloromethane in hexanes) the title compound (2.23 g, 8.14 mmol, 44%) was obtained as a yellow solid.

R_f = 0.37 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.22 (d, J = 8.2 Hz, 1H), 8.12 (d, J = 1.9 Hz, 1H), 7.51 (dd, J = 8.2, 1.9 Hz, 1H).

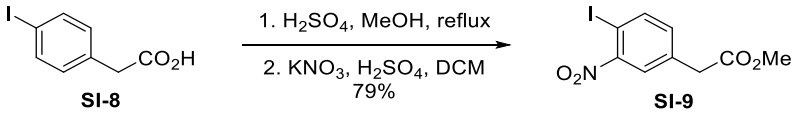
^{13}C-NMR (100 MHz, $CDCl_3$): 153.4, 143.5, 135.6, 128.5, 116.1, 113.7, 92.8.

IR: 3091, 3066, 3037, 3009, 2235, 1596, 1548, 1529, 1464, 1348, 1286, 1265, 1202, 1147, 1024, 927, 912, 843, 787, 748.

LRMS (GC-EI): 274 [$M^{+\bullet}$].

The spectroscopic data agrees with previously reported values.[3]

methyl 2-(4-iodo-3-nitrophenyl)acetate (SI-9)



Step1: Concentrated sulfuric acid (850 µL, 15.4 mmol, 0.4 eq.) was added dropwise to a solution of 2-(4-iodophenyl)acetic acid (**SI-8**, 8.20 g, 31.3 mmol, 1.0 eq.) in methanol

(50 mL). The mixture was stirred at reflux overnight, then the volatiles were removed under reduced pressure. The residue was taken up in ethyl acetate (100 mL), washed with saturated aqueous sodium chloride (50 mL), saturated aqueous sodium hydrogen carbonate (50 mL), again saturated aqueous sodium chloride (50 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure to afford methyl 2-(4-iodophenyl)acetate (8.35 g, 30.2 mmol, 96%) as a yellow oil, which was used without further purification.

Step2: Concentrated sulfuric acid (2.5 mL, 47.5 mmol, 9.5 eq.) was added to potassium nitrate (5.06 g, 50 mmol, 10.0 eq.) in a round-bottom flask. The slurry was stirred for 15 minutes, then sonicated for ten minutes. After placing the flask in an ice-bath, anhydrous dichloromethane (25 mL) was added and the mixture was stirred vigorously for five minutes. Methyl 2-(4-iodophenyl)acetate (1.38 g, 5.00 mmol, 1.0 eq.) in anhydrous dichloromethane (8 mL) was then added dropwise and the mixture was stirred vigorously with warming to room temp overnight. The mixture was poured onto 10 wt% aqueous sodium sulfate (40 mL), the layers were separated and the aqueous layer was extracted with dichloromethane (25 mL). The combined organic layers were washed with 10 wt% aqueous sodium sulfate (40 mL), dried over sodium sulfate and the solvent removed under reduced pressure. The residue was purified by column chromatography (50 to 80% dichloromethane in hexanes) to afford the title compound (1.31 g, 4.08 mmol, 82%) as a yellow oil, which contained several minor impurities and was used without further purification.

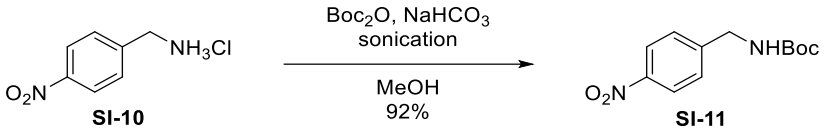
The NMR spectroscopic data is reported for the main component of the mixture.

$\mathbf{R_f}$ = 0.36 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.98 (d, J = 8.1 Hz, 1H), 7.80 (d, J = 2.2 Hz, 1H), 7.20 (dd, J = 8.1, 2.2 Hz, 1H), 3.72 (s, 3H), 3.67 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): 170.4, 153.1, 142.1, 135.9, 134.6, 126.5, 84.7, 52.6, 40.1.

tert-butyl (4-nitrobenzyl)carbamate (SI-11)



Di-*tert*-butyl dicarbonate (5.79 g, 26.5 mmol, 1.0 eq.), methanol (133 mL), 4-nitrobenzyl-amine hydrochloride (**SI-10**, 5.00 g, 26.5 mmol, 1.0 eq.) and sodium hydrogen carbonate (6.68 g, 79.5 mmol, 3.0 eq.) were successively added into a round bottom flask and the mixture was sonicated for 90 minutes. Then the solids were filtered off, washed with additional methanol (2×20 mL) and discarded. The filtrate was concentrated under reduced pressure, diethyl ether (100 mL) was added to the residue and the mixture was filtered again. The solid were washed with additional diethyl ether (50 mL) and discarded. The solvent was removed from the filtrate under reduced pressure to afford the title compound (6.14 g, 24.3 mmol, 92%) as a yellow solid.

$\mathbf{R_f}$ = 0.20 (20% ethyl acetate /hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.18 (d, J = 8.7 Hz, 2H), 7.44 (d, J = 8.6 Hz, 2H), 5.04 (br, 1H), 4.41 (d, J = 6.3 Hz, 2H), 1.46 (s, 9H).

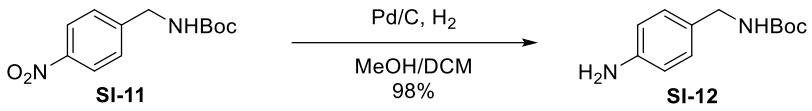
^{13}C-NMR (100 MHz, $CDCl_3$): 156.0, 147.3, 146.8, 128.0, 124.0, 80.3, 44.1, 28.5.

IR: 3324, 2983, 2935, 1687, 1606, 1514, 1453, 1427, 1393, 1365, 1349, 1320, 1296, 1285, 1266, 1251, 1162, 1142, 1110, 1044, 1028, 1014, 961, 937, 868, 858, 837, 798, 768, 741, 725, 701.

HRMS (ESI): $C_{12}H_{17}N_2O_4$ [M+H] calc. 253.1183, found 253.1177.

The spectroscopic data agrees with previously reported values.[4]

tert-butyl (4-aminobenzyl)carbamate (SI-12)



Palladium on carbon (10 wt%, 406 mg) and *tert*-butyl (4-nitrobenzyl)carbamate (**SI-11**, 3.85 g, 15.3 mmol) were placed in a round bottom flask and wetted with dichloromethane (10 mL). Methanol (90 mL) was added and the flask was evacuated and refilled with hydrogen for two times. The mixture was stirred for two days under a balloon of hydrogen, then diluted with dichloromethane and a small amount of Celite® was added. After further stirring for several minutes, the mixture was filtered over a pad of Celite® and the Celite® was washed with additional dichloromethane. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (0 to 20% ethyl acetate in dichloromethane) to afford the title compound (3.32 g, 14.9 mmol, 98%) as a yellow solid.

R_f = 0.24 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.10 – 7.03 (m, 2H), 6.66 – 6.61 (m, 2H), 4.73 (br, 1H), 4.18 (d, J = 5.8 Hz, 2H), 3.66 (br, 2H), 1.45 (s, 9H).

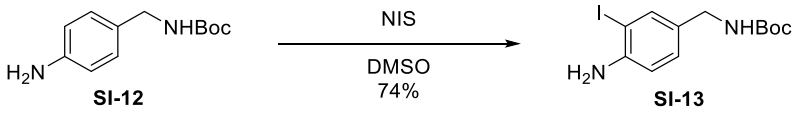
^{13}C-NMR (100 MHz, $CDCl_3$): 156.0, 145.8, 129.0, 128.9, 115.3, 79.4, 44.5, 28.6.

IR: 3354, 3004, 2977, 2930, 1691, 1625, 1517, 1455, 1439, 1392, 1365, 1344, 1266, 1248, 1162, 1045, 1024, 943, 926, 913, 863, 847, 782, 764, 729, 702.

HRMS (ESI): $C_{12}H_{19}N_2O_2$ [M+H] calc. 223.1441, found 223.1450.

The spectroscopic data agrees with previously reported values.[5]

tert-butyl (4-amino-3-iodobenzyl)carbamate (SI-13)



To a solution of *tert*-butyl (4-aminobenzyl)carbamate (**SI-12**, 1.52 g, 6.84 mmol, 1.0 eq.) in dimethyl sulfoxide (25 mL) was added *N*-iodosuccinimide (1.58 g, 7.01 mmol, 1.025 eq.) in one portion. After stirring overnight, the mixture was diluted with water/saturated aqueous sodium chloride = 4/1 (50 mL) and extracted with dichloromethane (3×30 mL). The extracts were washed with 2 M aqueous sodium thiosulfate/saturated aqueous sodium hydrogen carbonate = 1/1 (50 mL), followed by water/saturated aqueous sodium chloride = 4/1 (2×50 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue purified by column chromatography (0 to 30% ethyl acetate in hexanes) to afford the title compound (1.76 g, 5.06 mmol, 74%) as a yellow oil.

R_f = 0.19 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.55 (d, J = 2.0 Hz, 1H), 7.06 (d, J = 7.8 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 4.72 (br, 1H), 4.15 (d, J = 5.8 Hz, 2H), 4.06 (br, 2H), 1.46 (s, 9H).

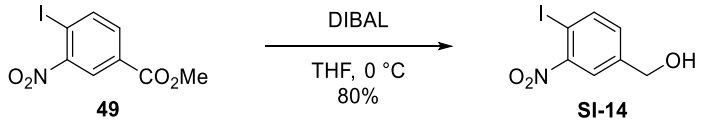
^{13}C-NMR (100 MHz, $CDCl_3$): 155.9, 146.2, 138.2, 130.7, 129.1, 114.8, 84.1, 79.7, 43.7, 28.6.

IR: 3347, 3208, 3004, 2977, 2931, 1693, 1617, 1500, 1455, 1434, 1410, 1392, 1366, 1333, 1304, 1274, 1250, 1204, 1166, 1079, 1048, 1028, 947, 933, 919, 879, 857, 820, 783, 763, 717.

HRMS (ESI): $C_{12}H_{18}IN_2O_2$ [M+H] calc. 349.0407, found 349.0415.

The spectroscopic data agrees with previously reported values.[6]

(4-iodo-3-nitrophenyl)methanol (**SI-14**)



A 1.49 M solution of diisobutylaluminum hydride (13.4 mL, 20.0 mmol, 2.05 eq.) was added dropwise to a solution of methyl 4-iodo-3-nitrobenzoate (**49**, 3.00 g, 9.77 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (50 mL) under ice-bath cooling and nitrogen atmosphere. The mixture was stirred for 30 minutes, then methanol (2 mL) was added, followed by saturated aqueous potassium sodium tartrate (50 mL). The cooling bath was removed and the mixture was stirred vigorously for one and a half hours, then diluted with water (30 mL) and extracted with ethyl acetate (3×30 mL). The extracts were washed with saturated aqueous sodium chloride (60 mL), dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography (0 to 10% ethyl acetate in dichloromethane) and a yellow oil that solidified upon standing at room temperature was obtained. Further purification by precipitation from dichloromethane solution by addition of hexanes afforded the title compound (2.19 g, 7.85 mmol, 80%) as a yellow solid.

R_f = 0.26 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, DMSO-d_6): 8.05 (d, J = 8.1 Hz, 1H), 7.85 (d, J = 1.9 Hz, 1H), 7.35 (dd, J = 8.2, 2.0 Hz, 1H), 5.51 (t, J = 5.7 Hz, 1H), 4.54 (d, J = 5.7 Hz, 2H).

^{13}C-NMR (100 MHz, DMSO-d_6): 153.2, 145.0, 140.8, 131.5, 122.4, 85.0, 61.3.

^{1}H-NMR (400 MHz, $CDCl_3$): 8.00 (d, J = 8.1 Hz, 1H), 7.87 (d, J = 1.9 Hz, 1H), 7.29 – 7.23 (m, 2H), 4.76 (s, 2H).

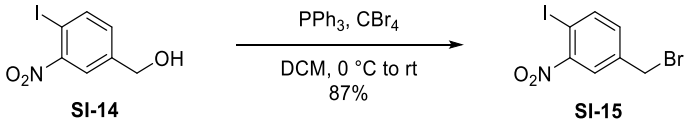
^{13}C-NMR (100 MHz, $CDCl_3$): 153.3, 143.1, 142.0, 131.4, 123.5, 84.5, 63.5.

IR: 3353, 3260, 3095, 3065, 2940, 2879, 1602, 1560, 1522, 1471, 1456, 1433, 1405, 1346, 1320, 1288, 1268, 1232, 1214, 1148, 1038, 1028, 1019, 985, 973, 895, 836, 827, 804, 750, 732, 725.

HRMS (APCI): $C_7H_7INO_3$ [M+H] calc. 279.9465, found 279.9468.

The spectroscopic data agrees with previously reported values.[7]

4-(bromomethyl)-1-iodo-2-nitrobenzene (**SI-15**)



To a mixture of (4-iodo-3-nitrophenyl)methanol (**SI-14**, 2.03 g, 7.28 mmol, 1.0 eq.), triphenylphosphine (2.19 g, 8.37 mmol, 1.15 eq.) and anhydrous dichloromethane (60 mL)

was added dropwise a solution of carbon tetrabromide (2.78 g, 8.37 mmol, 1.15 eq.) in anhydrous dichloromethane (10 mL) under ice-bath cooling. The mixture was stirred with warming to room temperature for three hours, then the solvent was removed under reduced pressure. The residue was purified by column chromatography (0 to 30% ethyl acetate in hexanes) to afford the title compound (2.16 g, 6.32 mmol, 87%) as a yellow oil that solidified upon standing at room temperature.

R_f = 0.52 (20% ethyl acetate in hexanes).

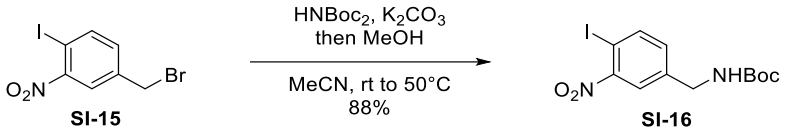
^{1}H-NMR (400 MHz, $CDCl_3$): 8.02 (d, J = 8.2 Hz, 1H), 7.89 (d, J = 2.2 Hz, 1H), 7.30 (dd, J = 8.2, 2.2 Hz, 1H), 4.45 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): 153.2, 142.6, 139.8, 133.8, 125.9, 86.1, 30.3.

IR: 3089, 3032, 1596, 1559, 1525, 1470, 1440, 1395, 1353, 1330, 1296, 1267, 1224, 1208, 1121, 1022, 931, 896, 875, 834, 807, 750.

LRMS (GC-EI): 341 [$M^{+\bullet}$], 343 [$M^{+\bullet}$].

tert-butyl (4-iodo-3-nitrobenzyl)carbamate (SI-16)



A mixture of 4-(bromomethyl)-1-iodo-2-nitrobenzene (**SI-15**, 2.80 g, 8.19 mmol, 1.05 eq.), di-*tert*-butyl-iminodicarboxylate (1.69 g, 7.78 mmol, 1.0 eq.), potassium carbonate (2.26 g, 16.4 mmol, 2.1 eq.) and anhydrous acetonitrile (28 mL) was stirred at room temperature overnight. Then methanol (28 mL) was added, the mixture was stirred at 50 °C for two more days and the volatiles were removed under reduced pressure. The residue was dissolved in dichloromethane (40 mL) and water (40 mL), the layers were separated and the aqueous layer was extracted with additional dichloromethane (2×20 mL). The combined organic layers were dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography (0 to 20% ethyl acetate in hexanes) to afford the title compound (2.59 g, 6.84 mmol, 88%) as a yellow solid.

R_f = 0.23 (20% ethyl acetate in hexanes).

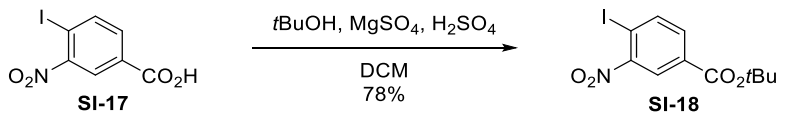
^{1}H-NMR (400 MHz, $CDCl_3$): 7.97 (d, J = 8.1 Hz, 1H), 7.77 (d, J = 2.1 Hz, 1H), 7.20 (dd, J = 8.1, 2.1 Hz, 1H), 5.02 (br, 1H), 4.33 (d, J = 6.3 Hz, 2H), 1.45 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): 155.9, 153.2, 142.1, 141.7, 132.4, 124.2, 84.4, 80.5, 43.5, 28.5.

IR: 3344, 2977, 2932, 2870, 2362, 1688, 1600, 1562, 1531, 1470, 1454, 1425, 1392, 1366, 1350, 1275, 1250, 1164, 1050, 1020, 945, 925, 911, 886, 860, 823, 803, 782, 763, 750, 727.

HRMS (ESI): $C_{12}H_{15}IN_2NaO_4$ [M+Na] calc. 400.9969, found 400.9976.

tert-butyl 4-iodo-3-nitrobenzoate (SI-18)



A mixture of concentrated sulfuric acid (727 µL, 13.7 mmol, 1.0 eq.), magnesium sulfate (6.57 g, 54.6 mmol, 4.0 eq.) and dichloromethane (40 mL) was stirred for five minutes, then a solution of *tert*-butanol (6.44 mL, 68.3 mmol, 5.0 eq.) and 4-iodo-3-nitrobenzoic acid (**SI-17**, 4.00 g, 13.7 mmol, 1.0 eq.) in dichloromethane (15 mL) was added slowly. The

mixture was stirred for two days, then filtered. The filtrate was washed with 2 M aqueous sodium hydroxide (100 mL), dried over sodium sulfate and the solvent removed under reduced pressure. The residue was purified by column chromatography (0 to 80% dichloromethane in hexanes) to afford the title compound (3.71 g, 10.6 mmol, 78%) as a yellow solid.

R_f = 0.65 (20% ethyl acetate in hexanes).

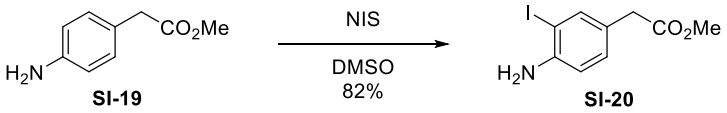
^{1}H-NMR (400 MHz, $CDCl_3$): 8.35 (d, J = 2.0 Hz, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.82 (dd, J = 8.2, 2.0 Hz, 1H), 1.60 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): 163.2, 153.3, 142.2, 133.6, 133.5, 126.0, 91.5, 83.1, 28.2.

IR: 2979, 2935, 1716, 1598, 1560, 1534, 1477, 1458, 1393, 1368, 1352, 1299, 1245, 1169, 1149, 1128, 1118, 1021, 916, 845, 838, 767, 743, 726, 714.

LRMS (GC-EI): 349 [$M^{+\bullet}$].

methyl 2-(4-amino-3-iodophenyl)acetate (SI-20)



To a solution of methyl 2-(4-aminophenyl)acetate (**SI-19**, 5.00 g, 30.3 mmol, 1.0 eq.) in dimethyl sulfoxide (100 mL) was added *N*-iodosuccinimide (6.98 g, 31.0 mmol, 1.025 eq.) in one portion. The solution was stirred overnight, then diluted with water/saturated aqueous sodium chloride = 4/1 (200 mL) and extracted with dichloromethane (3×100 mL). The extracts were washed with water/saturated aqueous sodium chloride = 4/1 (2×150 mL), dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography (0 to 20% ethyl acetate in hexanes) to afford the title compound (7.25 g, 24.9 mmol, 82%) as an orange oil that solidified upon extended storage at −20 °C.

R_f = 0.26 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.55 (d, J = 2.0 Hz, 1H), 7.06 (dd, J = 8.2, 2.1 Hz, 1H), 6.70 (d, J = 8.2 Hz, 1H), 4.07 (br, 2H), 3.68 (s, 3H), 3.47 (s, 2H).

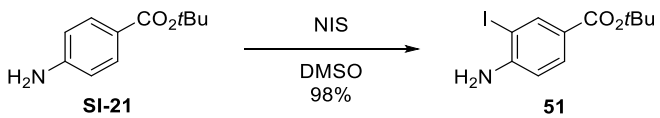
^{13}C-NMR (100 MHz, $CDCl_3$): 172.2, 146.0, 139.5, 130.4, 125.5, 114.7, 84.1, 52.2, 39.7.

IR: 3452, 3360, 2949, 1728, 1616, 1561, 1497, 1435, 1410, 1339, 1307, 1265, 1220, 1196, 1156, 1032, 1012, 932, 899, 873, 856, 822, 804, 743, 726, 707.

HRMS (ESI): $C_9H_{11}INO_2$ [M+H] calc. 292.9861, found 292.9867.

The spectroscopic data agrees with previously reported values.[8]

tert-butyl 4-amino-3-iodobenzoate (51)



To a solution of *tert*-butyl 4-aminobenzoate (**SI-21**, 6.00 g,31.0 mmol, 1.0 eq.) in dimethyl sulfoxide (100 mL) was added *N*-iodosuccinimide (7.16 g, 31.8 mmol, 1.025 eq.) in one portion. After stirring overnight, the mixture was diluted with water/saturated aqueous sodium chloride = 4/1 (250 mL) and extracted with dichloromethane (3×100 mL). The

extracts were washed with water/saturated aqueous sodium chloride = 4/1 (2×100 mL), dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was taken up in dichloromethane/hexane = 1/1 (200 mL), filtered over a plug of silica (20 g) and the silica washed with additional dichloromethane/hexane = 1/1 (100 mL). Removal of the solvent under reduced pressure afforded the title compound (9.70 g, 30.4 mmol, 98%) as a red-brown oil, which solidified upon standing at room temperature.

R_f = 0.42 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.26 (d, J = 1.9 Hz, 1H), 7.76 (dd, J = 8.4, 1.9 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 4.46 (br, 2H), 1.56 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): 164.6, 150.4, 140.9, 131.2, 123.4, 113.2, 82.3, 80.8, 28.4.

IR: 3466, 3356, 2975, 2930, 1686, 1612, 1589, 1498, 1473, 1455, 1403, 1392, 1367, 1291, 1249, 1168, 1149, 1119, 1027, 907, 884, 849, 828, 766, 730.

HRMS (ESI): $C_{11}H_{15}INO_2$ [M+H] calc. 320.0142, found 320.0143.

Syntheses of monoaryl acetylenes

General procedure – Sonogashira coupling

To the aryl iodide substrate (1.0 eq.), copper iodide (0.025 eq.) and bis(triphenylphosphine)palladium(II) dichloride (0.025 eq.) were added anhydrous tetrahydrofuran (2 mL per 1 mmol aryl iodide), triethylamine (2.0 eq.) and trimethylsilylacetylene (1.5 eq.) successively under a nitrogen atmosphere. The mixture was stirred overnight, then the volatiles were removed under reduced pressure. Hexanes were added to the residue, the mixture was sonicated and filtered. The solids were washed with additional hexanes and discarded. The filtrate was concentrated under reduced pressure and purified as specified.

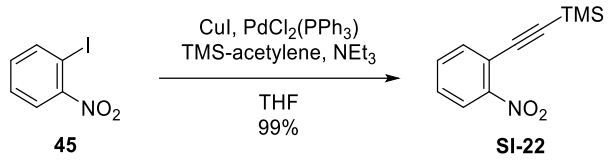
General procedure – desilylation with potassium carbonate

To a solution of silylacetylene substrate (1.0 eq.) in methanol (2.25 mL per 1 mmol substrate) was added potassium carbonate (1.0 eq.) and the mixture was stirred until the substrate was consumed according to TLC. The mixture was then diluted with dichloromethane and filtered. The solids were washed with additional dichloromethane and discarded. The filtrate was washed with water and the aqueous washes were extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, the solvent was removed under reduced pressure and the residue purified as specified.

General procedure – desilylation with triethylamine trihydrofluoride

To a solution of silylacetylene substrate (1.0 eq.) in tetrahydrofuran (3.5 mL per 1 mmol substrate) was added triethylamine trihydrofluoride (0.5 eq.) and the mixture was stirred until the substrate was consumed according to TLC. The mixture was then diluted with diethyl ether, washed with saturated aqueous sodium hydrogen carbonate and the aqueous washes were extracted with diethyl ether. The combined organic layers were washed with saturated aqueous sodium chloride, the solvent was removed under reduced pressure and the residue purified as specified.

trimethyl((2-nitrophenyl)ethynyl)silane (**SI-22**)



Prepared from 1-iodo-2-nitrobenzene (**45**, 10.0 g, 40.2 mmol) according to the general Sonogashira coupling procedure, but with a reduced amount of trimethylsilylacetylene (1.25 eq.).
The crude was dissolved in hexane (100 mL), filtered over a short plug of silica (10 g) and eluted with additional hexanes (50 mL). After removal of the solvent under reduced pressure, the title compound (8.71 g, 39.7 mmol, 99%) was obtained as an orange-red oil that was used without further purification.

R_f = 0.62 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.01 (dd, J = 8.3, 1.3 Hz, 1H), 7.65 (dd, J = 7.8, 1.5 Hz, 1H), 7.55 (td, J = 7.6, 1.3 Hz, 1H), 7.45 (ddd, J = 8.2, 7.4, 1.5 Hz, 1H), 0.28 (s, 9H).

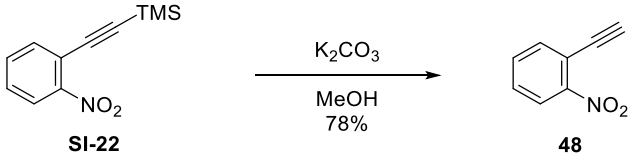
^{13}C-NMR (100 MHz, $CDCl_3$): 150.3, 135.2, 132.8, 129.0, 124.6, 118.5, 103.9, 99.5, -0.2.

IR: 2961, 2162.6, 1606, 1569, 1525, 1477, 1343, 1250, 1221, 1083, 870, 841, 815, 783, 760, 744.

HRMS (APCI): $C_{11}H_{14}NO_2Si$ [M+H] calc. 220.0788, found 220.0792.

The spectroscopic data agrees with previously reported values.[9]

1-ethynyl-2-nitrobenzene (**48**)



Prepared from trimethyl((2-nitrophenyl)ethynyl)silane (**SI-22**, 8.71 g, 39.7 mmol) according to the general procedure for desilylation with potassium carbonate.
The crude was dissolved in dichloromethane (100 mL), the solution filtered over a plug of silica (5 g) and the silica washed with additional dichloromethane (50 mL). The solvent was removed under reduced pressure and the residue was purified by precipitation from dichloromethane solution by addition of hexanes to afford the title compound (4.53 g, 30.8 mmol, 78%) as a brownish-grey to off-white solid.

R_f = 0.51 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.04 (dd, J = 8.2, 1.3 Hz, 1H), 7.70 (dd, J = 7.7, 1.5 Hz, 1H), 7.59 (td, J = 7.6, 1.3 Hz, 1H), 7.50 (ddd, J = 8.2, 7.4, 1.5 Hz, 1H), 3.51 (s, 1H).

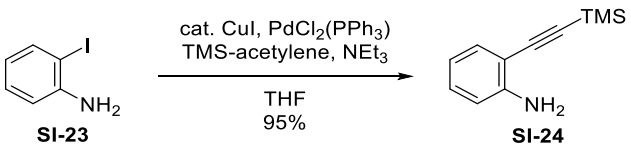
^{13}C-NMR (100 MHz, $CDCl_3$): 150.4, 135.7, 133.0, 129.5, 124.7, 117.6, 85.3, 78.7.

IR: 3255, 3106, 2105, 1608, 1567, 1513, 1477, 1452, 1439, 1385, 1344, 1306, 1260, 1230, 1203, 1169, 1146, 1080, 958, 872, 860, 786, 772, 741.

HRMS (APCI): $C_8H_6NO_2$ [M+H] calc. 148.0393, found 148.0386.

The spectroscopic data agrees with previously reported values.[10]

2-((trimethylsilyl)ethynyl)aniline (SI-24)



Prepared from 2-iodoaniline (**SI-23**, 10.0 g, 45.7 mmol) according to the general Sonogashira coupling procedure.
The crude was dissolved in hexane (100 mL), filtered over a short plug of silica (10 g) and eluted with additional hexanes (50 mL). After removal of the solvent under reduced pressure, the title compound (8.23 g, 43.5 mmol, 95%) was obtained as an orange-red oil that was used without further purification.

R_f = 0.62 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.29 (ddd, J = 7.7, 1.6, 0.5 Hz, 1H), 7.11 (ddd, J = 8.1, 7.3, 1.6 Hz, 1H), 6.70 – 6.63 (m, 2H), 4.22 (br, 2H), 0.27 (s, 9H).

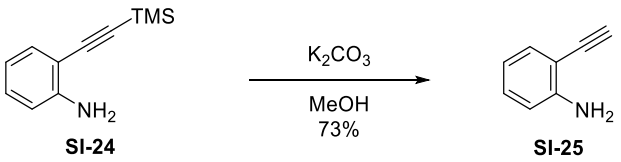
^{13}C-NMR (100 MHz, $CDCl_3$): 148.4, 132.4, 130.0, 117.9, 114.3, 107.9, 101.9, 99.9, 0.3.

IR: 3478, 3382, 2958, 2145, 1612, 1572, 1489, 1453, 1311, 1249, 1230, 1210, 1157, 1137, 1030, 870, 837, 776, 745.

HRMS (ESI): $C_{11}H_{16}NSi$ [M+H] calc. 190.1047, found 190.1041.

The spectroscopic data agrees with previously reported values.[11]

2-ethynylaniline (SI-25)



Prepared from 2-((trimethylsilyl)ethynyl)aniline (**SI-24**, 8.23 g, 43.5 mmol) according to the general procedure for desilylation with potassium carbonate.
The crude was purified by column chromatography (0 to 10% ethyl acetate in hexanes) to afford the title compound (3.74 g, 31.9 mmol, 73%) as an orange-yellow oil.

R_f = 0.42 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.32 (dd, J = 7.6, 1.6 Hz, 1H), 7.14 (ddd, J = 8.7, 7.5, 1.6 Hz, 1H), 6.71 – 6.66 (m, 2H), 4.24 (br, 2H), 3.38 (s, 1H).

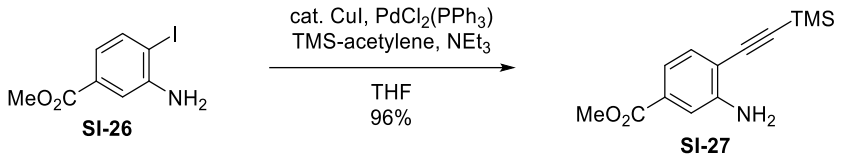
^{13}C-NMR (100 MHz, $CDCl_3$): 148.7, 132.8, 130.3, 117.9, 114.4, 106.7, 82.6, 80.8.

IR: 3471, 3377, 3276, 2096, 1612, 1566, 1490, 1452, 1314, 1258, 1158, 1143, 1029, 939, 870, 844, 747.

HRMS (ESI): C_8H_8N [M+H] calc. 118.0651, found 118.0646.

The spectroscopic data agrees with previously reported values.[12]

methyl 3-amino-4-((trimethylsilyl)ethynyl)benzoate (SI-27)



Prepared from methyl 3-amino-4-iodobenzoate (**SI-26**, 5.00 g, 18.0 mmol) according to the general Sonogashira coupling procedure.
The crude was purified by column chromatography (0 to 10% ethyl acetate in hexanes) to afford the title compound (4.31 g, 17.4 mmol, 97%) as an orange solid.

R_f = 0.45 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.36 (dd, J = 1.4, 0.6 Hz, 1H), 7.34 (dd, J = 8.0, 0.6 Hz, 1H), 7.31 (dd, J = 8.0, 1.4 Hz, 1H), 4.34 (br, 2H), 3.88 (s, 3H), 0.27 (s, 9H).

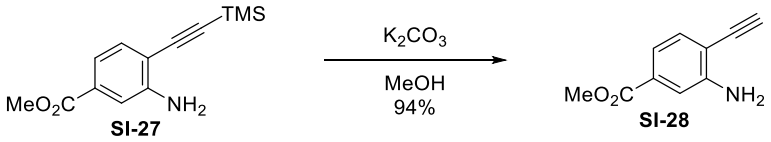
^{13}C-NMR (100 MHz, $CDCl_3$): 166.9, 148.2, 132.3, 131.1, 118.7, 115.0, 112.1, 102.9, 101.0, 52.3, 0.1.

IR: 3471, 3362, 2955, 2144, 1710, 1619, 1561, 1499, 1441, 1327, 1296, 1272, 1247, 1210, 1139, 1107, 1064, 995, 917, 896, 839, 803, 785, 759, 730.

HRMS (ESI): $C_{13}H_{18}NO_2SI$ [M+H] calc. 248.1101, found 248.1092.

The spectroscopic data agrees with previously reported values.[13]

methyl 3-amino-4-ethynylbenzoate (SI-28)



Prepared from methyl 3-amino-4-((trimethylsilyl)ethynyl)benzoate (**SI-27**, 3.97 g, 16.0 mmol) according to the general procedure for desilylation with potassium carbonate, but with an increased amount of methanol (4.5 mL per 1 mmol substrate).
The crude was dissolved in dichloromethane (40 mL), the solution filtered over a plug of silica (4 g) and the silica washed with additional dichloromethane (40 mL). The solvent was removed under reduced pressure to afford the title compound (2.64 g, 15.1 mmol, 94%) as a yellow solid.

R_f = 0.28 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.37 (d, J = 1.6 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.32 (dd, J = 8.0, 1.5 Hz, 1H), 4.37 (br, 2H), 3.88 (s, 3H), 3.50 (s, 1H).

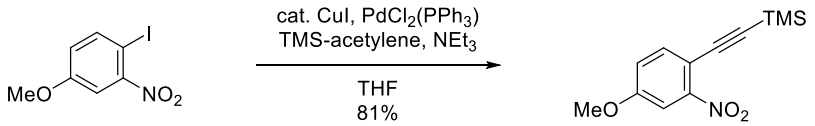
^{13}C-NMR (100 MHz, $CDCl_3$): 166.9, 148.5, 132.7, 131.5, 118.7, 115.2, 110.9, 84.9, 80.0, 52.3.

IR: 3476, 3377, 3276, 3252, 2952, 1709, 1626, 1602, 1563, 1501, 1462, 1434, 1297, 1277, 1242, 1195, 1139, 1106, 1062, 984, 956, 937, 910, 880, 859, 838, 798, 761, 732, 709.

HRMS (ESI): $C_{10}H_{10}NO_2$ [M+H] calc. 176.0706, found 176.0700.

The spectroscopic data agrees with previously reported values.[13]

((4-methoxy-2-nitrophenyl)ethynyl)trimethylsilane (SI-30)



SI-29 SI-30

Prepared from 1-iodo-4-methoxy-2-nitrobenzene (**SI-29**, 3.00 g, 10.8 mmol) according to the general Sonogashira coupling procedure.
The crude was purified by column chromatography (0 to 5% ethyl acetate in hexanes) to afford the title compound (2.19 g, 8.78 mmol, 81%) as a yellow oil that solidified upon standing at room temperature.

R_f = 0.54 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.55 (d, J = 8.7 Hz, 1H), 7.51 (d, J = 2.7 Hz, 1H), 7.08 (dd, J = 8.7, 2.7 Hz, 1H), 3.88 (s, 3H), 0.26 (s, 9H).

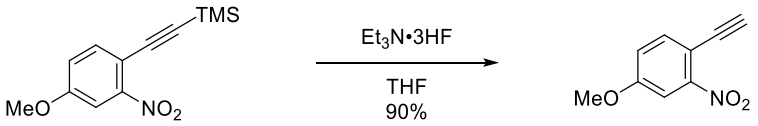
^{13}C-NMR (100 MHz, $CDCl_3$): 159.7, 151.2, 136.2, 119.6, 110.7, 109.3, 101.5, 99.6, 56.1, -0.1.

IR: 2960, 2900, 2842, 2158, 1723, 1617, 1560, 1530, 1496, 1460, 1441, 1415, 1345, 1309, 1297, 1273, 1248, 1219, 1211, 1186, 1142, 1107, 1072, 1030, 918, 856, 838, 817, 791, 780, 758, 701.

HRMS (ESI): $C_{12}H_{16}NO_3Si$ [M+H] calc. 250.0894, found 250.0903.

The spectroscopic data agrees with previously reported values.[14]

1-ethynyl-4-methoxy-2-nitrobenzene (SI-31)



SI-30 SI-31

Prepared from ((4-methoxy-2-nitrophenyl)ethynyl)trimethylsilane (**SI-30**, 2.07 g, 8.30 mmol) according to the general procedure for desilylation with triethylamine trihydrofluoride.
The crude was dissolved in dichloromethane (10 mL), the solution filtered over a plug of silica (2 g) and the silica washed with additional dichloromethane (20 mL). The solvent was removed under reduced pressure and the residue was purified by precipitation from dichloromethane solution by addition of hexanes to afford the title compound (1.33 g, 7.51 mmol, 90%) as a yellow solid.

R_f = 0.43 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.59 (d, J = 8.6 Hz, 1H), 7.54 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.7, 2.7 Hz, 1H), 3.89 (s, 3H), 3.39 (s, 1H).

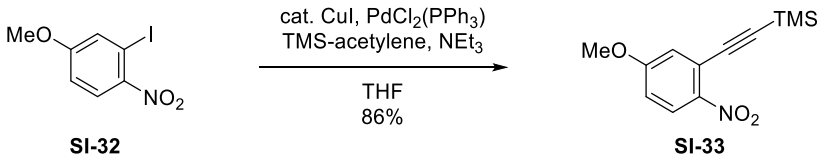
^{13}C-NMR (100 MHz, $CDCl_3$): 160.1, 151.4, 136.6, 119.7, 109.6, 109.5, 83.3, 78.7, 56.2.

IR: 3283, 3079, 1617, 1561, 1524, 1491, 1465, 1456, 1440, 1424, 1351, 1303, 1274, 1243, 1202, 1184, 1147, 1069, 1035, 951, 917, 888, 859, 825, 810, 762, 718.

HRMS (ESI): $C_9H_8NO_3$ [M+H] calc. 178.0499, found 178.0490.

The spectroscopic data agrees with previously reported values.[14]

((5-methoxy-2-nitrophenyl)ethynyl)trimethylsilane (SI-33)



SI-32 SI-33

Prepared from 2-iodo-4-methoxy-1-nitrobenzene (**SI-32**, 3.00 g, 10.8 mmol) according to the general Sonogashira coupling procedure.
The crude was purified by column chromatography (0 to 5% ethyl acetate in hexanes) to afford the title compound (2.31 g, 9.26 mmol, 86%) as a yellow oil that solidified upon standing at room temperature.

R_f = 0.51 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.06 (d, J = 9.2 Hz, 1H), 7.07 (d, J = 2.8 Hz, 1H), 6.90 (dd, J = 9.2, 2.8 Hz, 1H), 3.89 (s, 3H), 0.28 (s, 9H).

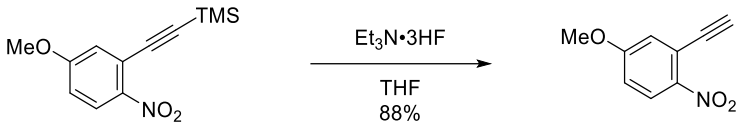
^{13}C-NMR (100 MHz, $CDCl_3$): 162.8, 143.3, 127.1, 120.8, 119.2, 115.0, 103.8, 100.1, 56.2, --0.2.

IR: 2960, 2900, 2162, 1601, 1582, 1574, 1516, 1479, 1460, 1443, 1409, 1336, 1292, 1276, 1248, 1195, 1167, 1090, 1080, 1026, 949, 937, 836, 755, 701.

HRMS (ESI): $C_{12}H_{16}NO_3Si$ [M+H] calc. 250.0894, found 250.0892.

The spectroscopic data agrees with previously reported values.[15]

2-ethynyl-4-methoxy-1-nitrobenzene (SI-34)



SI-33 SI-34

Prepared from ((5-methoxy-2-nitrophenyl)ethynyl)trimethylsilane (**SI-33**, 2.18 g, 8.74 mmol) according to the general procedure for desilylation with triethylamine trihydrofluoride.
The crude was dissolved in dichloromethane (15 mL), the solution filtered over a plug of silica (2 g) and the silica washed with additional dichloromethane (30 mL). The solvent was removed under reduced pressure and the residue was purified by precipitation from dichloromethane solution by addition of hexanes to afford the title compound (1.36 g, 7.68 mmol, 88%) as a yellow solid.

R_f = 0.37 (20% ethyl acetate in hexanes).

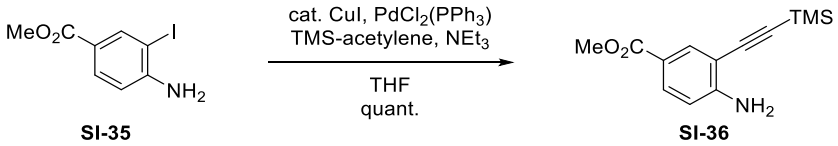
^{1}H-NMR (400 MHz, $CDCl_3$): 8.10 (d, J = 9.2 Hz, 1H), 7.12 (d, J = 2.8 Hz, 1H), 6.95 (dd, J = 9.2, 2.8 Hz, 1H), 3.90 (s, 3H), 3.52 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 163.0, 143.3, 127.3, 120.0, 119.9, 115.2, 85.1, 79.2, 56.2.

IR: 3259, 2104, 1609, 1572, 1504, 1477, 1459, 1437, 1408, 1372, 1345, 1322, 1291, 1242, 1192, 1162, 1085, 1024, 947, 919, 877, 857, 837, 820, 751, 721.

HRMS (ESI): $C_9H_8NO_3$ [M+H] calc. 178.0499, found 178.0498.

methyl 4-amino-3-((trimethylsilyl)ethynyl)benzoate (SI-36)



Prepared from methyl 4-amino-3-iodobenzoate (**SI-35**, 4.00 g, 14.4 mmol) according to the general Sonogashira coupling procedure, but with a modified workup. Due to the low solubility of the product in hexanes, the residue after removal of the reaction solvent was washed with diethyl ether instead of hexanes.
The crude was dissolved in dichloromethane (40 mL), the solution filtered over a short plug of silica (5 g), the silica washed with additional dichloromethane (40 mL) and the solvent removed under reduced pressure. The residue was purified by precipitation from dichloromethane solution by addition of hexanes to yield the title compound (2.34 g, 9.46 mmol, 66%) as a brown solid. The mother liquors of the precipitation were concentrated under reduced pressure and the residue was purified by column chromatography (0 to 20% ethyl acetate in hexanes) to afford additional product (1.24 g, 5.01 mmol, 35%) in the form of a brown solid.

R_f = 0.44 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.01 (d, J = 1.8 Hz, 1H), 7.79 (ddd, J = 8.5, 2.1, 0.8 Hz, 1H), 6.66 (dd, J = 8.6, 0.7 Hz, 1H), 4.65 (br, 2H), 3.85 (s, 3H), 0.26 (s, 9H).

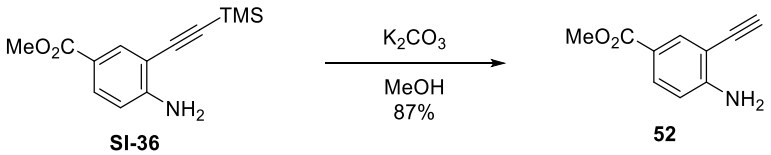
^{13}C-NMR (100 MHz, $CDCl_3$): 166.7, 152.0, 134.7, 131.7, 119.4, 113.3, 107.2, 100.7, 100.6, 51.9, 0.2.

IR: 3482, 3353, 3210, 2954, 2148, 1703, 1625, 1596, 1504, 1440, 1425, 1407, 1340, 1325, 1294, 1247, 1222, 1207, 1187, 1155, 1107, 993, 912, 863, 842, 788, 760, 730, 703.

HRMS (ESI): $C_{13}H_{18}NO_2Si$ [M+H] calc. 248.1101, found 248.1095.

The spectroscopic data agrees with previously reported values.[13]

methyl 4-amino-3-ethynylbenzoate (52)



Prepared from methyl 4-amino-3-((trimethylsilyl)ethynyl)benzoate (**SI-36**, 3.33 g, 13.5 mmol) according to the general procedure for desilylation with potassium carbonate, but with an increased amount of methanol (5 mL per 1 mmol substrate).
The crude was dissolved in dichloromethane (50 mL), the solution filtered over a plug of silica (4 g) and the silica washed with additional dichloromethane (80 mL). The solvent was removed under reduced pressure and the residue was purified by precipitation from dichloromethane solution by addition of hexanes to afford the title compound (2.07 g, 11.8 mmol, 87%) as a yellow solid.

R_f = 0.24 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.03 (d, J = 2.0 Hz, 1H), 7.81 (dd, J = 8.6, 2.0 Hz, 1H), 6.67 (d, J = 8.6 Hz, 1H), 4.68 (br, 2H), 3.85 (s, 3H), 3.39 (s, 1H).

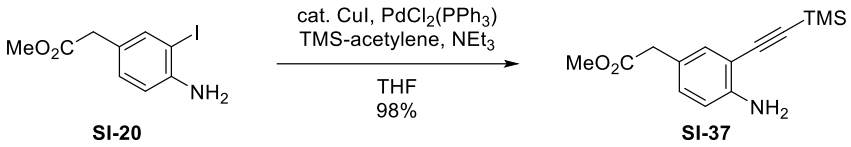
^{13}C-NMR (100 MHz, $CDCl_3$): 166.6, 152.3, 135.1, 132.0, 119.4, 113.4, 105.9, 83.1, 79.6, 51.9.

IR: 3439, 3329, 3249, 3208, 2950, 1693, 1654, 1624, 1600, 1570, 1505, 1456, 1430, 1419, 1334, 1296, 1259, 1213, 1190, 1143, 1101, 978, 960, 913, 836, 808, 783, 764, 732.

HRMS (ESI): $C_{10}H_{10}NO_2$ [M+H] calc. 176.0706, found 176.0701.

The spectroscopic data agrees with previously reported values.[13]

methyl 2-(4-amino-3-((trimethylsilyl)ethynyl)phenyl)acetate (SI-37)



Prepared from methyl 2-(4-amino-3-iodophenyl)acetate (**SI-20**, 2.00 g, 6.87 mmol) according to the general Sonogashira coupling procedure.
The crude was purified by column chromatography (0 to 10% ethyl acetate in hexanes) to afford the title compound (1.76 g, 6.77 mmol, 98%) as a red oil.

R_f = 0.39 (20% ethyl acetate in hexanes).

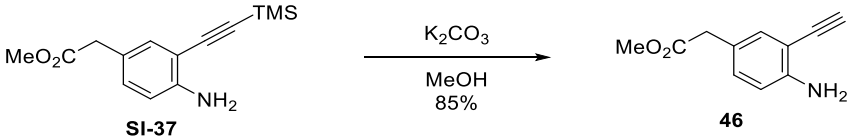
^{1}H-NMR (400 MHz, $CDCl_3$): 7.21 (d, J = 1.9 Hz, 1H), 7.03 (dd, J = 8.3, 2.2 Hz, 1H), 6.64 (d, J = 8.2 Hz, 1H), 4.20 (br, 2H), 3.67 (s, 3H), 3.46 (s, 2H), 0.25 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): 172.4, 147.4, 133.0, 131.0, 123.2, 114.5, 108.1, 101.6, 100.1, 52.1, 40.2, 0.2.

IR: 3476, 3376, 2953, 2899, 2142, 1733, 1653, 1621, 1570, 1502, 1457, 1436, 1300, 1285, 1249, 1195, 1147, 1099, 1014, 960, 924, 840, 760, 736.

HRMS (ESI): $C_{14}H_{20}NO_2Si$ [M+H] calc. 262.1258, found 262.1250.

methyl 2-(4-amino-3-ethynylphenyl)acetate (46)



Prepared from methyl 2-(4-amino-3-((trimethylsilyl)ethynyl)phenyl)acetate (**SI-37**, 1.65 g, 6.26 mmol) according to the general procedure for desilylation with potassium carbonate, but with an increased amount of methanol (4 mL per 1 mmol substrate).
The crude was dissolved in dichloromethane (20 mL), the solution filtered over a plug of silica (4 g) and the silica washed with additional dichloromethane (40 mL). The solvent was removed under reduced pressure to afford the title compound (1.01 g, 5.34 mmol, 85%) as a yellow oil.

R_f = 0.21 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.23 (d, J = 2.1 Hz, 1H), 7.06 (dd, J = 8.3, 2.1 Hz, 1H), 6.66 (d, J = 8.3 Hz, 1H), 4.22 (br, 2H), 3.68 (s, 3H), 3.48 (s, 2H), 3.37 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 172.4, 147.8, 133.3, 131.2, 123.3, 114.7, 106.9, 82.7, 80.5, 52.1, 40.2.

IR: 3468, 3373, 3278, 2952, 2096, 1725, 1623, 1576, 1559, 1502, 1457, 1435, 1311, 1268, 1199, 1154, 1012, 950, 902, 843, 825, 807, 748.

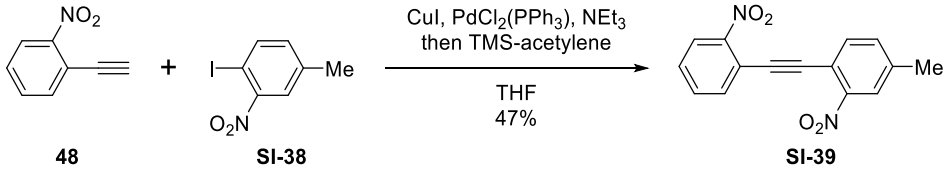
HRMS (ESI): $C_{11}H_{12}NO_2$ [M+H] calc. 190.0863, found 190.0859.

Syntheses of diaryl acetylenes

General procedure – Sonogashira coupling

To the aryl acetylene (1.1 eq.), aryl iodide (1.0 eq.), copper iodide (0.025 eq.) and bis(triphenylphosphine)palladium(II) dichloride (0.025 eq.) were successively added anhydrous tetrahydrofuran (2.5 mL per 1 mmol aryl iodide) and triethylamine (2.0 eq.) under a nitrogen atmosphere. The mixture was then stirred overnight and analyzed by ^{1}H-NMR spectroscopy. If necessary, stirring was further continued until no remaining aryl acetylene was observed. After all of the aryl acetylene was consumed, trimethylsilylacetylene (0.25 eq.) was added and the mixture was stirred overnight again. The solvent was then removed under reduced pressure, dichloromethane (30 mL) and water (10 mL) were added to the residue and the mixture was filtered. If remaining solids were present, they were analyzed by ^{1}H-NMR spectroscopy and kept for further purification, if significant amounts of the desired product were present. The layers of the filtrate were separated, the aqueous layer was extracted with dichloromethane (2×5 mL) and the combined organic layers were dried over magnesium sulfate. The solvent was removed under reduced pressure, the residue combined with any previously separated solids and purified as specified.

4-methyl-2-nitro-1-((2-nitrophenyl)ethynyl)benzene (SI-39)



48 **SI-38** **SI-39**

Prepared from 1-iodo-4-methyl-2-nitrobenzene (**SI-38**, 1.00 g, 3.80 mmol) and 1-ethynyl-2-nitrobenzene (**48**, 615 mg, 4.18 mmol) according to the general Sonogashira coupling procedure.
The crude was purified by column chromatography (0 to 100% dichloromethane in hexanes) and the resulting brown solid dissolved in boiling toluene (40 mL). The solution was cooled to room temperature, filtered over a short plug of silica and the silica was washed with additional toluene. After removal of the solvent under reduced pressure, the residue was recrystallized from a small amount of toluene to afford the title compound (504 mg, 1.79 mmol, 47%) as a yellow solid.

R_f = 0.34 (50% dichloromethane in hexanes).

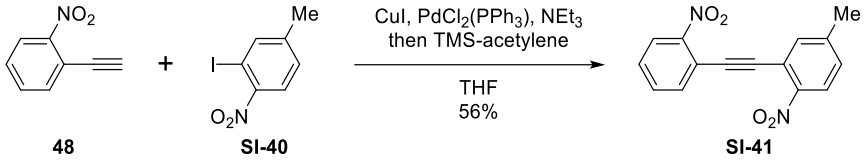
^{1}H-NMR (400 MHz, $CDCl_3$): 8.13 (dd, J = 8.3, 1.3 Hz, 1H), 7.94 (d, J = 1.8 Hz, 1H), 7.81 (dd, J = 7.7, 1.5 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.64 (td, J = 7.6, 1.3 Hz, 1H), 7.52 (ddd, J = 8.7, 7.5, 1.5 Hz, 1H), 7.45 (dd, J = 8.0, 1.7 Hz, 1H), 2.49 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 149.5, 149.4, 140.9, 135.3, 135.2, 134.1, 133.2, 129.5, 125.3, 124.9, 118.4, 115.2, 92.4, 91.2, 21.5.

IR: 1604, 1566, 1558, 1520, 1473, 1457, 1438, 1419, 1405, 1375, 1343, 1285, 1254, 1143, 922, 864, 829, 799, 784, 762, 743.

HRMS (ESI): $C_{15}H_{11}N_2O_4$ [M+H] calc. 283.0713, found 283.0727.

4-methyl-1-nitro-2-((2-nitrophenyl)ethynyl)benzene (**SI-41**)



48 SI-40 SI-41

Prepared from 2-iodo-4-methyl-1-nitrobenzene (**SI-40**, 1.00 mg, 3.80 mmol) and 1-ethynyl-2-nitrobenzene (**48**, 615 mg, 4.18 mmol) according to the general Sonogashira coupling procedure.

The crude was purified by column chromatography (0 to 75% dichloromethane in hexanes) and the resulting brown solid dissolved in boiling toluene (40 mL). The solution was cooled to room temperature, filtered over a short plug of silica and the silica was washed with additional toluene. After removal of the solvent under reduced pressure, the residue was washed with methanol and further purified by two more cycles of column chromatography (0 to 40% ethyl acetate in hexanes, 0 to 40% dichloromethane in hexanes) to afford the title compound (598 mg, 2.12 mmol, 56%) as a yellowish solid.

$\mathbf{R_f}$ = 0.32 (50% dichloromethane in hexanes).

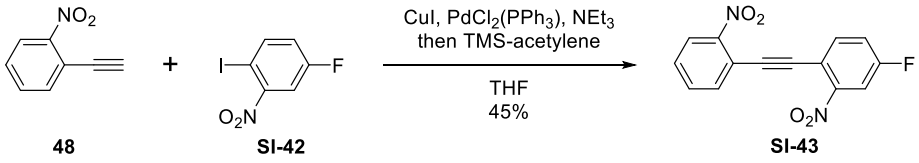
^{1}H-NMR (400 MHz, $CDCl_3$): 8.13 (dd, J = 8.3, 1.3 Hz, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.83 (dd, J = 7.8, 1.5 Hz, 1H), 7.65 (td, J = 7.6, 1.3 Hz, 1H), 7.61 (dd, J = 2.0, 0.9 Hz, 1H), 7.53 (ddd, J = 8.3, 7.5, 1.5 Hz, 1H), 7.31 (ddd, J = 8.5, 2.0, 0.8 Hz, 1H), 2.46 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 149.5, 147.3, 144.7, 135.7, 135.4, 133.3, 130.4, 129.6, 125.1, 124.9, 118.3, 118.1, 92.6, 91.5, 21.4.

IR: 1609, 1585, 1567, 1517, 1488, 1457, 1439, 1375, 1338, 1291, 1250, 1211, 1167, 1148, 1083, 939, 887, 858, 840, 786, 756, 744, 701.

HRMS (ESI): $C_{15}H_{11}N_2O_4$ [M+H] calc. 283.0713, found 283.0721.

4-fluoro-2-nitro-1-((2-nitrophenyl)ethynyl)benzene (**SI-43**)



48 SI-42 SI-43

Prepared from 4-fluoro-1-iodo-2-nitrobenzene (**SI-42**, 1.00 g, 3.75 mmol) and 1-ethynyl-2-nitrobenzene (**48**, 606 mg, 4.12 mmol) according to the general Sonogashira coupling procedure.

The crude was purified by column chromatography (0 to 100% dichloromethane in hexanes) and the resulting brown solid dissolved in boiling toluene (40 mL). The solution was cooled to room temperature, filtered over a short plug of silica and the silica was washed with additional toluene. After removal of the solvent under reduced pressure, the residue was washed with methanol and recrystallized from a small amount of toluene to afford the title compound (488 mg, 1.70 mmol, 45%) as a dark brown solid.

$\mathbf{R_f}$ = 0.36 (50% dichloromethane in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.15 (dd, J = 8.3, 1.3 Hz, 1H), 7.88 (dd, J = 8.3, 2.6 Hz, 1H), 7.84 (dd, J = 8.7, 5.4 Hz, 1H), 7.82 (dd, J = 7.7, 1.3 Hz, 1H), 7.66 (td, J = 7.6, 1.3 Hz, 1H), 7.55 (ddd, J = 8.3, 7.4, 1.5 Hz, 1H), 7.40 (ddd, J = 8.7, 7.3, 2.6 Hz, 1H).

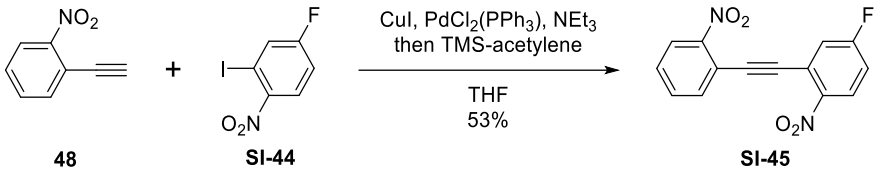
^{13}C-NMR (100 MHz, $CDCl_3$): 162.0 (d, J = 256.0 Hz), 150.3 (d, J = 8.5 Hz), 149.5, 137.1 (d, J = 8.1 Hz), 135.3, 133.3, 129.8, 125.0, 121.1 (d, J = 21.9 Hz), 118.0, 114.5 (d, J = 4.0 Hz), 112.9 (d, J = 27.1 Hz), 92.0 (d, J = 1.9 Hz), 91.1 (d, J = 1.4 Hz).

^{19}F-NMR (377 MHz, $CDCl_3$): -105.72 (ddd, J = 8.3, 7.2, 5.5 Hz).

IR: 3096, 1604, 1577, 1567, 1521, 1500, 1474, 1458, 1438, 1409, 1343, 1282, 1272, 1211, 1166, 1131, 945, 886, 866, 834, 807, 785, 760, 743.

HRMS (ESI): $C_{14}H_8FN_2O_4$ [M+H] calc. 287.0463, found 287.0476.

4-fluoro-1-nitro-2-((2-nitrophenyl)ethynyl)benzene (**SI-45**)



Prepared from 4-fluoro-2-iodo-1-nitrobenzene (**SI-44**, 1.00 g, 3.75 mmol) and 1-ethynyl-2-nitrobenzene (**48**, 606 mg, 4.12 mmol) according to the general Sonogashira coupling procedure.
The crude was purified by column chromatography (0 to 100% dichloromethane in hexanes) and the resulting brown solid dissolved in boiling toluene (40 mL). The solution was cooled to room temperature, filtered over a short plug of silica and the silica was washed with additional toluene. After removal of the solvent under reduced pressure, the residue was recrystallized from a small amount of toluene to afford the title compound (570 mg, 1.99 mmol, 53%) as a dark brown solid.

R_f = 0.31 (50% dichloromethane in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.21 (dd, J = 9.2, 5.0 Hz, 1H), 8.16 (dd, J = 8.3, 1.3 Hz, 1H), 7.84 (dd, J = 7.7, 1.5 Hz, 1H), 7.68 (td, J = 7.6, 1.3 Hz, 1H), 7.57 (ddd, J = 8.2, 7.5, 1.5 Hz, 1H), 7.50 (dd, J = 8.3, 2.8 Hz, 1H), 7.22 (ddd, J = 9.2, 7.1, 2.8 Hz, 1H).

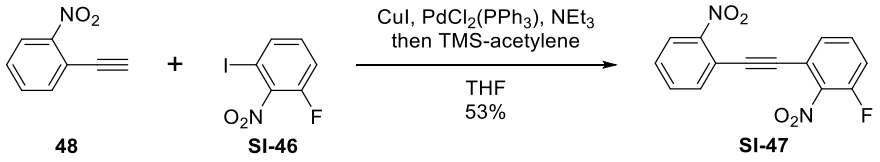
^{13}C-NMR (100 MHz, $CDCl_3$): 164.7 (d, J = 258.5 Hz), 149.6, 145.7, 135.4, 133.4, 130.1, 127.8 (d, J = 10.2 Hz), 125.1, 121.9 (d, J = 24.9 Hz), 121.0 (d, J = 11.0 Hz), 117.7, 117.1 (d, J = 23.4 Hz), 93.4, 90.9 (d, J = 2.3 Hz).

^{19}F-NMR (377 MHz, $CDCl_3$): -103.24 (ddd, J = 8.3, 7.0, 5.1 Hz).

IR: 1613, 1578, 1522, 1489, 1466, 1439, 1411, 1341, 1330, 1294, 1252, 1212, 1166, 1145, 1129, 1085, 1070, 962, 909, 874, 859, 841, 798, 785, 755, 744, 701.

HRMS (ESI): $C_{14}H_8FN_2O_4$ [M+H] calc. 287.0463, found 287.0466.

1-fluoro-2-nitro-3-((2-nitrophenyl)ethynyl)benzene (**SI-47**)



Prepared from 1-fluoro-3-iodo-2-nitrobenzene (**SI-46**, 1.00 g, 3.75 mmol) and 1-ethynyl-2-nitrobenzene (**48**, 606 mg, 4.12 mmol) according to the general Sonogashira coupling procedure.
The crude was purified by column chromatography (0 to 75% dichloromethane in hexanes) and the resulting brown solid dissolved in boiling toluene (40 mL). The solution was cooled

to room temperature, filtered over a short plug of silica and the silica was washed with additional toluene. After removal of the solvent under reduced pressure, the residue was recrystallized from a small amount of toluene to afford the title compound (567 mg, 1.98 mmol, 53%) as a greyish-red solid.

R_f = 0.36 (50% dichloromethane in hexanes).

^{1}H-NMR (600 MHz, $CDCl_3$): 8.15 (dd, J = 8.2, 1.3 Hz, 1H), 7.73 (dd, J = 7.7, 1.5 Hz, 1H), 7.66 (td, J = 7.6, 1.3 Hz, 1H), 7.58 – 7.51 (m, 3H), 7.30 (ddd, J = 9.6, 7.6, 2.1 Hz, 1H).

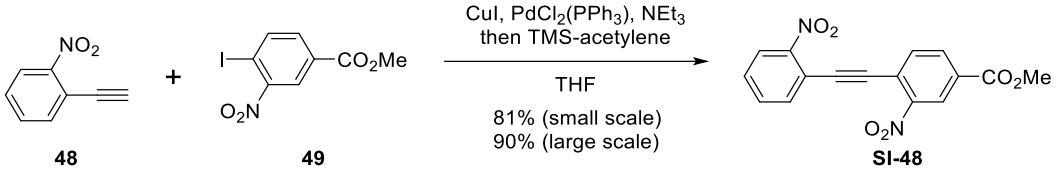
^{13}C-NMR (150 MHz, $CDCl_3$): 154.1 (d, J = 259.7 Hz), 149.5, 140.8 (d, J = 13.9 Hz), 135.4, 133.4, 132.4 (d, J = 8.8 Hz), 130.1, 129.5 (d, J = 3.6 Hz), 125.1, 118.6, 118.2 (d, J = 19.6 Hz), 117.3, 92.4, 88.9 (d, J = 4.1 Hz).

^{19}F-NMR (377 MHz, $CDCl_3$): -120.92 (dd, J = 9.4, 4.1 Hz).

IR: 3072, 1608, 1580, 1568, 1526, 1489, 1464, 1439, 1357, 1343, 1298, 1257, 1146, 1083, 995, 860, 796, 785, 743.

HRMS (ESI): $C_{14}H_8FN_2O_4$ [M+H] calc. 287.0463, found 287.0464.

methyl 3-nitro-4-((2-nitrophenyl)ethynyl)benzoate (SI-48)



48 **49** **SI-48**

Small scale: Prepared from methyl 4-iodo-3-nitrobenzoate (**49**, 1.00 g, 3.26 mmol) and 1-ethynyl-2-nitrobenzene (**48**, 527 mg, 3.58 mmol) according to the general Sonogashira coupling procedure, but with a reduced amount of trimethylsilylacetylene (0.2 eq.). Additional tetrahydrofuran (4 mL) was added after three hours to increase the fluidity of the reaction mixture, which had turned into a thick slurry.
The crude was purified by column chromatography (0 to 100% dichloromethane in hexanes) and the resulting brown solid dissolved in boiling toluene (40 mL). The solution was cooled to room temperature, filtered over a short plug of silica and the silica was washed with additional toluene. After removal of the solvent under reduced pressure, the residue was washed with methanol to afford the title compound (856 mg, 2.62 mmol, 81%) as an off-white solid.

Large scale: Prepared from methyl 4-iodo-3-nitrobenzoate (**49**, 4.00 g, 13.0 mmol) and 1-ethynyl-2-nitrobenzene (**48**, 2.11 g, 14.3 mmol) according to the general Sonogashira coupling procedure, but with an increased volume of tetrahydrofuran (4 mL per 1 mmol of aryl iodide), a reduced amount of trimethylsilylacetylene (0.1 eq.) and modified workup. After removal of the reaction solvent, the residue was dissolved in water (100 mL) and dichloromethane (120 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2×40 mL). The combined organic layers were dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography (dichloromethane) and the resulting brownish solid triturated with methanol to afford the title compound (3.83 g, 11.7 mmol, 90%) as an off-white solid.

R_f = 0.47 (dichloromethane).

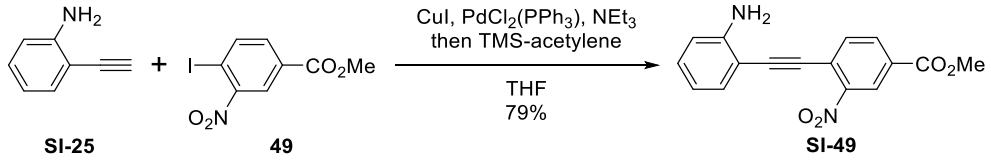
^{1}H-NMR (400 MHz, $CDCl_3$): 8.77 (d, J = 1.6 Hz, 1H), 8.28 (dd, J = 8.1, 1.7 Hz, 1H), 8.17 (dd, J = 8.3, 1.3 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.84 (dd, J = 7.8, 1.5 Hz, 1H), 7.68 (td, J = 7.6, 1.3 Hz, 1H), 7.58 (ddd, J = 8.3, 7.5, 1.5 Hz, 1H), 3.99 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 164.6, 149.6, 149.5, 135.6, 135.5, 133.6, 133.4, 131.3, 130.2, 126.1, 125.1, 122.1, 117.7, 95.1, 91.3, 53.1.

IR: 1731, 1617, 1567, 1559, 1522, 1472, 1457, 1433, 1399, 1343, 1289, 1237, 1193, 1147, 1121, 976, 898, 863, 852, 832, 820, 787, 771, 756, 743.

HRMS (ESI): $C_{16}H_{11}N_2O_6$ [M+H] calc. 327.0612, found 327.0617.

methyl 4-((2-aminophenyl)ethynyl)-3-nitrobenzoate (SI-49)



Prepared from methyl 4-iodo-3-nitrobenzoate (**49**, 1.00 g, 3.26 mmol) and 2-ethynylaniline (**SI-25**, 420 mg, 3.58 mmol) according to the general Sonogashira coupling procedure, but with a reduced amount of trimethylsilylacetylene (0.2 eq.).
The crude was purified by column chromatography (0 to 100% dichloromethane in hexanes) and the resulting red solid recrystallized from toluene to afford the title compound (481 mg, 1.62 mmol, 50%) as a red solid. The mother liquors of the recrystallization were filtered over a short plug of silica, the silica was washed with ethyl acetate/toluene = 1/10 and the solvent was removed under reduced pressure. The residue was washed with methanol to obtain additional product (284 mg, 959 µmol, 29%) in the form of a red solid.

R_f = 0.28 (dichloromethane).

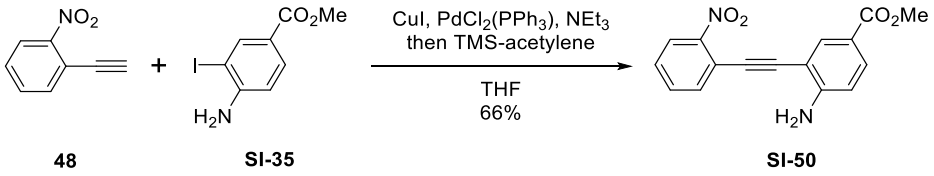
^{1}H-NMR (400 MHz, $CDCl_3$): 8.79 (d, J = 1.7 Hz, 1H), 8.23 (dd, J = 8.2, 1.7 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.39 (dd, J = 7.7, 1.6 Hz, 1H), 7.21 (ddd, J = 8.3, 7.3, 1.5 Hz, 1H), 6.76 – 6.67 (m, 2H), 4.73 (br, 2H), 3.98 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 164.8, 150.1, 148.2, 134.6, 133.6, 132.9, 131.9, 129.8, 126.4, 123.6, 117.7, 114.6, 105.8, 99.2, 91.0, 53.0.

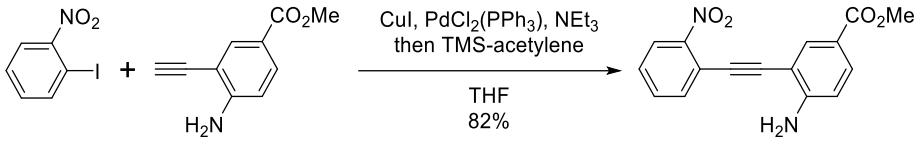
IR: 3481, 3381, 2197, 2182, 1722, 1707, 1617, 1598, 1555, 1521, 1499, 1475, 1457, 1435, 1338, 1307, 1283, 1258, 1237, 1191, 1149, 1115, 1073, 978, 911, 844, 821, 770, 747, 729.

HRMS (ESI): $C_{16}H_{13}N_2O_4$ [M+H] calc. 297.087, found 297.0869.

methyl 4-amino-3-((2-nitrophenyl)ethynyl)benzoate (SI-50)



2-nitrophenylacetylene route: Prepared from methyl 4-amino-3-iodobenzoate (**SI-36**, 1.00 g, 3.61 mmol) and 1-ethynyl-2-nitrobenzene (**48**, 584 mg, 3.97 mmol) according to the general Sonogashira coupling procedure, but with an increased amount of trimethylsilylacetylene (0.6 eq.).
The crude was purified by column chromatography (0 to 100% dichloromethane in hexanes) and the resulting dark red solid recrystallized from toluene to afford the title compound (704 mg, 2.38 mmol, 66%) as a red solid.



45 52 SI-50

2-aminephenylacetylene route: Prepared from 1-iodo-2-nitrobenzene (**45**, 940 mg, 3.77 mmol) and methyl 4-amino-3-ethynylbenzoate (**52**, 727 mg, 4.15 mmol) according to the general Sonogashira coupling procedure.
The crude was purified by column chromatography (0 to 100% dichloromethane in hexanes) and the resulting dark red solid recrystallized from toluene to afford the title compound (921 mg, 3.11 mmol, 82%) as a red solid.

$\mathbf{R_f}$ = 0.20 (dichloromethane).

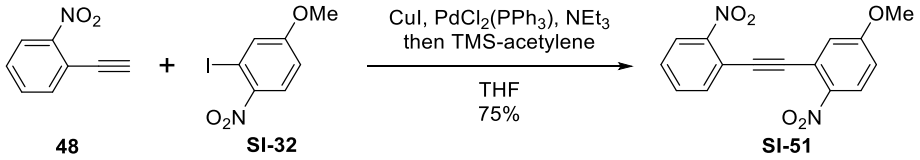
^{1}H-NMR (400 MHz, $CDCl_3$): 8.18 (dd, J = 8.3, 1.3 Hz, 1H), 8.11 (d, J = 2.0 Hz, 1H), 7.85 (dd, J = 8.6, 2.0 Hz, 1H), 7.75 (dd, J = 7.8, 1.5 Hz, 1H), 7.64 (td, J = 7.6, 1.3 Hz, 1H), 7.47 (ddd, J = 8.7, 7.4, 1.5 Hz, 1H), 6.71 (d, J = 8.6 Hz, 1H), 5.16 (br, 2H), 3.87 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 166.6, 153.2, 148.4, 135.1, 134.6, 133.6, 132.7, 128.6, 125.3, 119.2, 119.1, 113.6, 105.7, 94.1, 91.3, 51.9.

IR: 3481, 3377, 2195, 1710, 1615, 1599, 1563, 1511, 1479, 1457, 1437, 1338, 1296, 1249, 1192, 1168, 1153, 1137, 1103, 1079, 1038, 996, 961, 908, 877, 859, 831, 807, 790, 762, 742, 728.

HRMS (ESI): $C_{16}H_{13}N_2O_4$ [M+H] calc. 297.0870, found 297.0882.

4-methoxy-1-nitro-2-((2-nitrophenyl)ethynyl)benzene (SI-51)



48 SI-32 SI-51

Prepared from 2-iodo-4-methoxy-1-nitrobenzene (**SI-32**, 1.00 g, 3.58 mmol) and 1-ethynyl-2-nitrobenzene (**48**, 580 mg, 3.94 mmol) according to the general Sonogashira coupling procedure.
The product was purified by column chromatography (0 to 75% dichloromethane in hexanes) and the resulting brown solid dissolved in boiling toluene (40 mL). The solution was cooled to room temperature, filtered over a short plug of silica and the silica was washed with additional toluene. After removal of the solvent under reduced pressure, the residue was washed with methanol to afford the title compound (795 mg, 2.67 mmol, 75%) as an orange-yellow solid.

$\mathbf{R_f}$ = 0.18 (50% dichloromethane in hexanes).

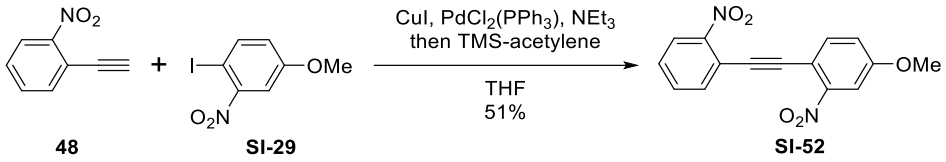
^{1}H-NMR (400 MHz, $CDCl_3$): 8.18 (d, J = 9.2 Hz, 1H), 8.14 (dd, J = 8.3, 1.3 Hz, 1H), 7.85 (dd, J = 7.7, 1.5 Hz, 1H), 7.66 (td, J = 7.6, 1.3 Hz, 1H), 7.54 (ddd, J = 8.3, 7.5, 1.5 Hz, 1H), 7.23 (d, J = 2.8 Hz, 1H), 6.98 (dd, J = 9.2, 2.8 Hz, 1H), 3.94 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 163.2, 149.5, 142.6, 135.5, 133.3, 129.7, 127.4, 125.0, 120.4, 119.0, 118.2, 115.8, 92.7, 91.9, 56.3.

IR: 1611, 1573, 1512, 1473, 1457, 1441, 1412, 1342, 1312, 1302, 1264, 1230, 1188, 1169, 1089, 1074, 1025, 875, 859, 839, 827, 784, 754, 745.

HRMS (ESI): $C_{15}H_{11}N_2O_5$ [M+H] calc. 299.0662, found 299.0670.

4-methoxy-2-nitro-1-((2-nitrophenyl)ethynyl)benzene (SI-52)



48 SI-29 SI-52

Prepared from 1-iodo-4-methoxy-2-nitrobenzene (**SI-29**, 1.00 g, 3.58 mmol) and 1-ethynyl-2-nitrobenzene (**48**, 580 mg, 3.94 mmol) according to the general Sonogashira coupling procedure.
The crude was purified by column chromatography (0 to 75% dichloromethane in hexanes) and the resulting brown solid dissolved in boiling toluene (40 mL). The solution was cooled to room temperature, filtered over a short plug of silica and the silica was washed with additional toluene. After removal of the solvent under reduced pressure, the residue was recrystallized from methanol and purified further by two more cycles of column chromatography (0 to 50% ethyl acetate in hexanes, 0 to 50% dichloromethane in hexanes) to afford the title compound (542 mg, 1.82 mmol, 51%) as a yellow solid.

$\mathbf{R_f}$ = 0.23 (50% dichloromethane in hexanes).

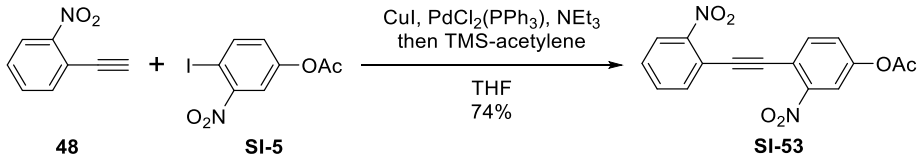
^{1}H-NMR (400 MHz, $CDCl_3$): 8.12 (dd, J = 8.3, 1.3 Hz, 1H), 7.80 (dd, J = 7.8, 1.5 Hz, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.65 – 7.61 (m, 2H), 7.50 (ddd, J = 8.2, 7.4, 1.5 Hz, 1H), 7.18 (dd, J = 8.6, 2.7 Hz, 1H), 3.92 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 160.4, 150.6, 149.4, 136.4, 135.2, 133.2, 129.2, 124.9, 120.0, 118.6, 110.2, 109.8, 92.5, 90.5, 56.2.

IR: 1604, 1565, 1517, 1474, 1439, 1420, 1341, 1299, 1274, 1229, 1194, 1163, 1146, 1067, 1032, 992, 956, 918, 895, 864, 829, 795, 783, 759, 741.

HRMS (ESI): $C_{15}H_{11}N_2O_5$ [M+H] calc. 299.0662, found 299.0667.

3-nitro-4-((2-nitrophenyl)ethynyl)phenyl acetate (SI-53)



48 SI-5 SI-53

Prepared from 4-iodo-3-nitrophenyl acetate (**SI-5**, 1.20 g, 3.91 mmol) and 1-ethynyl-2-nitrobenzene (**48**, 633 mg, 4.30 mmol) according to the general Sonogashira coupling procedure.
The crude was purified by column chromatography (0 to 75% dichloromethane in hexanes) and the resulting brown solid dissolved in boiling toluene (40 mL). The solution was cooled to room temperature, filtered over a short plug of silica and the silica was washed with additional toluene and dichloromethane. After removal of the solvent under reduced pressure, the residue was washed with methanol to afford the title compound (888 mg, 2.72 mmol, 70%) as an off-white solid. Additional product (50 mg, 0.15 mmol, 4%) in the form of a greyish-brown solid was obtained from the washings after removal of the solvent under reduced pressure and recrystallization of the residue from toluene.

$\mathbf{R_f}$ = 0.50 (dichloromethane).

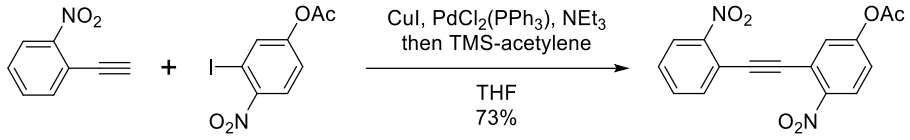
^{1}H-NMR (400 MHz, $CDCl_3$): 8.14 (d, J = 8.2 Hz, 1H), 7.95 (d, J = 2.4 Hz, 1H), 7.87 – 7.78 (m, 2H), 7.66 (t, J = 7.6 Hz, 1H), 7.54 (t, J = 7.7 Hz, 1H), 7.44 (dd, J = 8.6, 2.4 Hz, 1H), 2.36 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 168.4, 150.9, 149.8, 149.5, 136.2, 135.4, 133.3, 129.8, 127.0, 125.0, 118.8, 118.1, 115.6, 92.2, 91.5, 21.1.

IR: 3102, 1763, 1603, 1567, 1523, 1498, 1473, 1438, 1410, 1369, 1341, 1300, 1282, 1257, 1215, 1202, 1170, 1144, 1080, 1066, 1046, 1019, 956, 906, 880, 863, 841, 830, 803, 784, 762, 743.

HRMS (ESI): $C_{16}H_{11}N_2O_6$ [M+H] calc. 327.0612, found 327.0615.

4-nitro-3-((2-nitrophenyl)ethynyl)phenyl acetate (SI-54)



48 SI-2 SI-54

Prepared from 3-iodo-4-nitrophenyl acetate (**SI-2**, 1.20 g, 3.91 mmol) and 1-ethynyl-2-nitrobenzene (**48**, 633 mg, 4.30 mmol) according to the general Sonogashira coupling procedure.
The crude was purified by column chromatography (0 to 75% dichloromethane in hexanes) and the resulting brown solid recrystallized from toluene to afford the title compound (588 mg, 1.80 mmol, 46%) as a brownish-grey solid. The mother liquors of the recrystallization were filtered over a short plug of silica, the silica was washed with additional toluene and the solvent was removed under reduced pressure. The residue was washed with methanol to obtain additional product (350 mg, 1.07 mmol, 27%) in the form of an off-white solid.

R_f = 0.48 (dichloromethane).

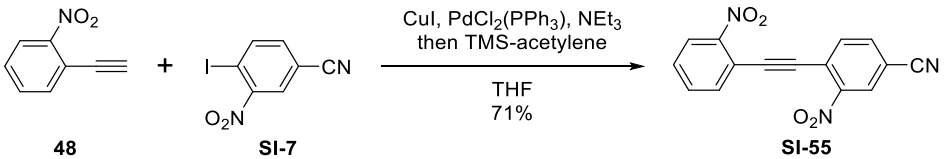
^{1}H-NMR (400 MHz, $CDCl_3$): 8.19 (d, J = 9.0 Hz, 1H), 8.15 (dd, J = 8.2, 1.3 Hz, 1H), 7.83 (dd, J = 7.7, 1.5 Hz, 1H), 7.67 (td, J = 7.6, 1.3 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.30 (dd, J = 9.0, 2.6 Hz, 1H), 2.37 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 168.3, 154.0, 149.6, 146.6, 135.5, 133.4, 129.9, 128.1, 126.6, 125.0, 123.2, 120.0, 117.9, 93.0, 91.3, 21.2.

IR: 3109, 3076, 1764, 1613, 1577, 1568, 1518, 1490, 1470, 1439, 1406, 1369, 1343, 1292, 1256, 1191, 1145, 1137, 1088, 1073, 1038, 1011, 962, 903, 876, 859, 834, 783, 758, 744, 729.

HRMS (ESI): $C_{16}H_{11}N_2O_6$ [M+H] calc. 327.0612, found 327.0617.

3-nitro-4-((2-nitrophenyl)ethynyl)benzonitrile (SI-55)



48 SI-7 SI-55

Prepared from 4-iodo-3-nitrobenzonitrile (**SI-7**, 1.00 g, 3.65 mmol) and 1-ethynyl-2-nitrobenzene (**48**, 591 mg, 4.01 mmol) according to the general Sonogashira coupling procedure.
The crude was purified by column chromatography (0 to 75% dichloromethane in hexanes) and the resulting brown solid recrystallized from toluene to afford the title compound (764 mg, 2.61 mmol, 71%) as a brownish-yellow solid.

R_f = 0.49 (dichloromethane).

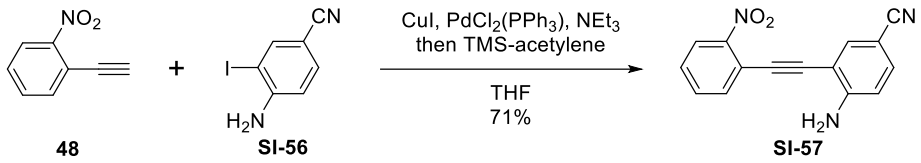
^{1}H-NMR (400 MHz, $CDCl_3$): 8.44 (dd, J = 1.6, 0.6 Hz, 1H), 8.19 (dd, J = 8.3, 1.3 Hz, 1H), 7.95 (dd, J = 8.1, 0.5 Hz, 1H), 7.91 (dd, J = 8.1, 1.6 Hz, 1H), 7.84 (dd, J = 7.7, 1.5 Hz, 1H), 7.71 (td, J = 7.6, 1.3 Hz, 1H), 7.61 (ddd, J = 8.2, 7.5, 1.5 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 149.6, 149.3, 136.3, 135.9, 135.6, 133.5, 130.7, 128.7, 125.2, 122.6, 117.2, 116.3, 113.3, 96.9, 90.4.

IR: 3088, 3077, 2233, 2215, 1763, 1616, 1567, 1549, 1522, 1474, 1439, 1403, 1342, 1302, 1280, 1266, 1215, 1199, 1145, 1086, 1012, 963, 921, 864, 844, 832, 787, 763, 743.

HRMS (ESI): $C_{15}H_7N_3NaO_4$ [M+Na] calc. 316.0329, found 316.0334.

4-amino-3-((2-nitrophenyl)ethynyl)benzonitrile (SI-57)



Prepared from 4-amino-3-iodobenzonitrile (**SI-56**, 1.00 mg, 4.10 mmol) and 1-ethynyl-2-nitrobenzene (**48**, 663 mg, 4.51 mmol) according to the general Sonogashira coupling procedure, but with an increased amount of trimethylsilylacetylene (0.4 eq.).
The crude was purified by column chromatography (0 to 100% dichloromethane in hexanes) and the resulting red-brown solid recrystallized from toluene to afford the title compound (765 mg, 2.91 mmol, 71%) as a brownish-orange solid.

R_f = 0.34 (dichloromethane).

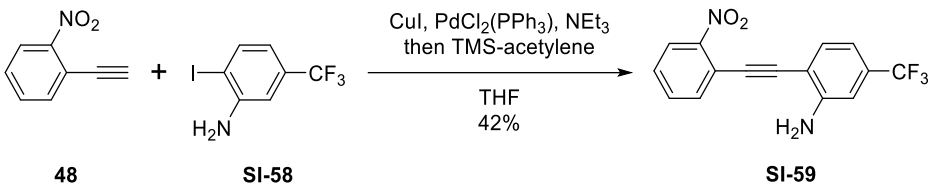
^{1}H-NMR (400 MHz, $CDCl_3$): 8.20 (dd, J = 8.3, 1.3 Hz, 1H), 7.75 (dd, J = 7.8, 1.5 Hz, 1H), 7.70-7.65 (m, 2H), 7.51 (ddd, J = 8.8, 7.4, 1.5 Hz, 1H), 7.40 (dd, J = 8.6, 2.0 Hz, 1H), 6.73 (d, J = 8.6 Hz, 1H), 5.27 (br, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): 152.7, 148.6, 136.9, 134.7, 134.3, 133.7, 129.1, 125.4, 119.4, 118.7, 114.3, 106.7, 99.9, 92.4, 92.1.

IR: 3474, 3375, 3220, 3103, 3072, 2216, 2201, 1621, 1599, 1566, 1515, 1504, 1477, 1437, 1422, 1337, 1294, 1270, 1252, 1195, 1160, 1146, 905, 859, 823, 808, 785, 742.

HRMS (ESI): $C_{15}H_{10}N_3O_2$ [M+H] calc. 264.0768, found 264.0763.

2-((2-nitrophenyl)ethynyl)-5-(trifluoromethyl)aniline (SI-59)



Prepared from 2-iodo-5-(trifluoromethyl)aniline (**SI-58**, 900 mg, 3.14 mmol) and 1-ethynyl-2-nitrobenzene (**48**, 507 mg, 3.45 mmol) according to the general Sonogashira coupling procedure.
The crude was purified by column chromatography (0 to 50% dichloromethane in hexanes) and the resulting brown-orange solid dissolved in boiling toluene (40 mL). The solution was cooled to room temperature, filtered over a short plug of silica and the silica was washed with additional toluene. After removal of the solvent under reduced pressure, the residue

was recrystallized from a small amount of toluene to afford the title compound (407 mg, 1.33 mmol, 42%) as an orange solid.

R_f = 0.35 (50% dichloromethane in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.18 (dd, J = 8.3, 1.3 Hz, 1H), 7.75 (dd, J = 7.8, 1.5 Hz, 1H), 7.65 (td, J = 7.6, 1.3 Hz, 1H), 7.54 – 7.43 (m, 2H), 6.96 (s, 1H), 6.92 (d, J = 8.1 Hz, 1H), 4.88 (br, 2H).

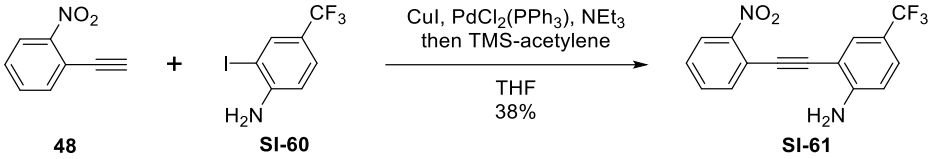
^{13}C-NMR (100 MHz, $CDCl_3$): 149.6, 148.7, 134.7, 133.5, 133.0, 132.6 (q, J = 32.2 Hz), 128.9, 125.3, 124.0 (q, J = 272.6 Hz), 118.9, 113.8 (q, J = 3.8 Hz), 110.90 (q, J = 3.9 Hz), 109.5 (q, J = 1.4 Hz), 93.52 (q, J = 0.8 Hz), 92.3.

^{19}F-NMR (377 MHz, $CDCl_3$): -63.34 (s).

IR: 3492, 3386, 2198, 1617, 1564, 1518, 1472, 1448, 1338, 1286, 1252, 1168, 1150, 1119, 1110, 1088, 1047, 928, 879, 866, 815, 789, 745, 706.

HRMS (ESI): $C_{15}H_{10}F_3N_2O_2$ [M+H] calc. 307.0689, found 307.0693.

2-((2-nitrophenyl)ethynyl)-4-(trifluoromethyl)aniline (SI-61)



48 SI-60 SI-61

Prepared from 2-iodo-4-(trifluoromethyl)aniline (**SI-60**, 1.00 g, 3.48 mmol) and 1-ethynyl-2-nitrobenzene (**48**, 564 mg, 3.83 mmol) according to the general Sonogashira coupling procedure, but with an increased amount of trimethylsilylacetylene (0.4 eq.).
The crude was purified by column chromatography (0 to 50% dichloromethane in hexanes) and the resulting brown-orange solid dissolved in boiling toluene (40 mL). The solution was cooled to room temperature, filtered over a short plug of silica and the silica was washed with additional toluene. After removal of the solvent under reduced pressure, the residue was recrystallized from a small amount of toluene to afford the title compound (400 mg, 1.31 mmol, 38%) as an orange solid.

R_f = 0.33 (50% dichloromethane in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.19 (dd, J = 8.3, 1.2 Hz, 1H), 7.75 (dd, J = 7.8, 1.5 Hz, 1H), 7.70 – 7.62 (m, 2H), 7.49 (td, J = 7.8, 7.3, 1.5 Hz, 1H), 7.39 (dd, J = 8.6, 2.1 Hz, 1H), 6.76 (d, J = 8.6 Hz, 1H), 5.05 (s, 2H).

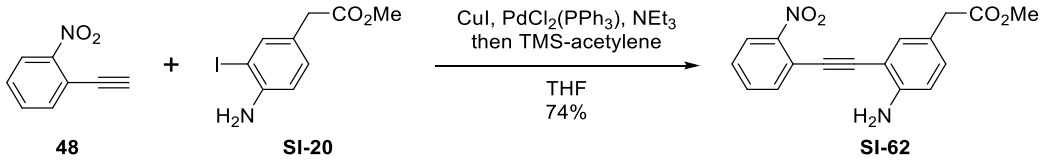
^{13}C-NMR (100 MHz, $CDCl_3$): 152.0, 148.5, 134.6, 133.6, 130.0 (q, J = 4.0 Hz), 128.8, 127.9 (q, J = 3.6 Hz), 125.3, 124.5 (q, J = 270.6 Hz), 119.5 (q, J = 33.1 Hz), 119.0, 114.0, 105.9, 93.6, 91.6.

^{19}F-NMR (377 MHz, $CDCl_3$): -61.50 (s).

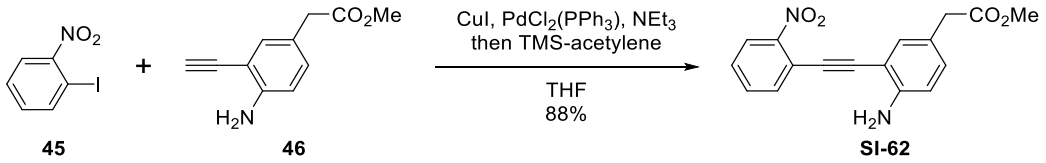
IR: 3471, 3371, 2204, 1625, 1600, 1570, 1562, 1509, 1477, 1337, 1329, 1312, 1286, 1269, 1253, 1147, 1111, 1083, 1072, 906, 861, 831, 789, 745.

HRMS (ESI): $C_{15}H_{10}F_3N_2O_2$ [M+H] calc. 307.0689, found 307.0692.

methyl 2-(4-amino-3-((2-nitrophenyl)ethynyl)phenyl)acetate (SI-62)



2-nitrophenylacetylene route: Prepared from methyl 2-(4-amino-3-iodophenyl)acetate (**SI-20**, 1.00 g, 3.44 mmol) and 1-ethynyl-2-nitrobenzene (**48**, 557 mg, 3.78 mmol) according to the general Sonogashira coupling procedure, but with an increased amount of trimethylsilylacetylene (0.5 eq.).
The crude was purified by two cycles of column chromatography (0 to 100% dichloromethane in hexanes, 0 to 40% ethyl acetate in hexanes) to afford the title compound (794 mg, 2.56 mmol, 74%) as a red solid.



2-aminophenylacetylene route: Prepared from 1-iodo-2-nitrobenzene (**45**, 855 mg, 3.43 mmol) and methyl 2-(4-amino-3-ethynylphenyl)acetate (**46**, 715 mg, 3.78 mmol) according to the general Sonogashira coupling procedure.
The crude was purified by column chromatography (0 to 100% dichloromethane in hexanes) and the resulting brown solid dissolved in boiling toluene (40 mL). The solution was cooled to room temperature, filtered over a short plug of silica and the silica was washed with additional toluene and dichloromethane. After removal of the solvent under reduced pressure, the title compound (954 mg, 3.01 mmol, 88%) was obtained as a red solid.

R_f = 0.55 (5% ethyl acetate in dichloromethane).

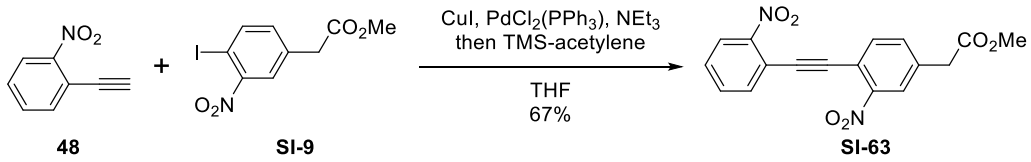
^{1}H-NMR (400 MHz, $CDCl_3$): 8.15 (dd, J = 8.3, 1.3 Hz, 1H), 7.72 (dd, J = 7.8, 1.5 Hz, 1H), 7.62 (td, J = 7.6, 1.3 Hz, 1H), 7.45 (ddd, J = 8.8, 7.4, 1.5 Hz, 1H), 7.31 (d, J = 2.1 Hz, 1H), 7.10 (dd, J = 8.3, 2.1 Hz, 1H), 6.69 (d, J = 8.3 Hz, 1H), 4.68 (br, 2H), 3.69 (s, 3H), 3.51 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): 172.4, 148.8, 148.5, 134.5, 133.4, 133.1, 132.2, 128.3, 125.2, 122.9, 119.5, 114.7, 106.5, 95.1, 91.0, 52.2, 40.2.

IR: 3475, 3378, 2950, 2192, 1728, 1623, 1603, 1565, 1516, 1502, 1477, 1435, 1336, 1315, 1295, 1260, 1217, 1195, 1154, 1145, 1079, 1038, 1011, 957, 905, 876, 857, 825, 806, 784, 741.

HRMS (ESI): $C_{17}H_{15}N_2O_4$ [M+H] calc. 311.1026, found 311.1038.

methyl 2-(3-nitro-4-((2-nitrophenyl)ethynyl)phenyl)acetate (SI-63)



48 SI-9 SI-63

Prepared from methyl 2-(4-iodo-3-nitrophenyl)acetate (**SI-9**, 1.31 g, 4.08 mmol) and 1 -ethynyl-2-nitrobenzene (**48**, 660 mg, 449 mmol) according to the general Sonogashira coupling procedure.

The crude was purified by column chromatography (0 to 100% dichloromethane in hexanes) and the resulting brown solid dissolved in boiling toluene (40 mL). The solution was cooled to room temperature, filtered over a short plug of silica and the silica was washed with additional toluene and dichloromethane. After removal of the solvent under reduced pressure, the residue was washed with methanol to afford the title compound (840 mg, 2.47 mmol, 61%) as a faint yellow solid. Additional material was isolated from the washings. The solvent was removed under reduced pressure, the residue dissolved in hexanes/dichloromethane = 1/3, the solution filtered over a short plug of silica and the solvent again removed under reduced pressure. The residue was purified by precipitation from dichloromethane solution by addition of hexanes to afford further title compound (86 mg, 0.25 mmol, 6%) in the form of a brownish solid.

R_f = 0.35 (dichloromethane).

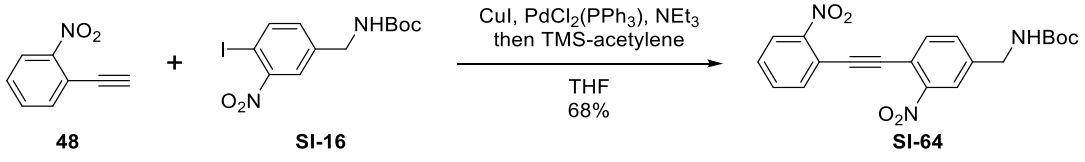
^{1}H-NMR (400 MHz, $CDCl_3$): 8.13 (dd, J = 8.2, 1.2 Hz, 1H), 8.07 (d, J = 1.7 Hz, 1H), 7.82 (dd, J = 7.7, 1.5 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.65 (td, J = 7.6, 1.3 Hz, 1H), 7.58 (dd, J = 8.0, 1.8 Hz, 1H), 7.53 (ddd, J = 8.7, 7.5, 1.5 Hz, 1H), 3.75 (s, 3H), 3.74 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 170.5, 149.5, 149.4, 136.4, 135.45, 135.39, 134.3, 133.3, 129.7, 125.9, 125.0, 118.2, 117.0, 92.2, 91.9, 52.6, 40.6.

IR: 1730, 1606, 1567, 1556, 1520, 1475, 1439, 1419, 1341, 1289, 1268, 1252, 1235, 1222, 1199, 1177, 1145, 995, 904, 864, 841, 832, 813, 785, 762, 743.

HRMS (ESI): $C_{17}H_{13}N_2O_6$ [M+H] calc. 341.0768, found 341.0752.

tert-butyl (3-nitro-4-((2-nitrophenyl)ethynyl)benzyl)carbamate (SI-64)



48 SI-16 SI-64

Prepared from *tert*-butyl (4-iodo-3-nitrobenzyl)carbamate (**SI-16**, 750 mg, 1.98 mmol) and 1-ethynyl-2-nitrobenzene (**48**, 321 mg, 2.18 mmol) according to the general Sonogashira coupling procedure.

The crude was purified by column chromatography (0 to 100% dichloromethane in hexanes) and the resulting brown solid dissolved in toluene (40 mL). The solution was filtered over a short plug of silica and the silica was washed with additional toluene and dichloromethane. After removal of the solvent under reduced pressure, the residue was washed with methanol to afford the title compound (531 mg, 1.34 mmol, 68%) as an off-white solid.

R_f = 0.49 (5% ethyl acetate in dichloromethane).

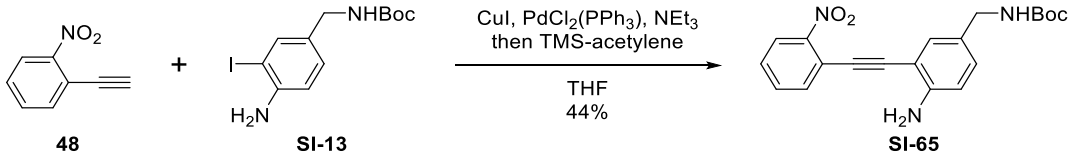
^{1}H-NMR (400 MHz, $CDCl_3$): 8.13 (dd, J = 8.3, 1.2 Hz, 1H), 8.05 (d, J = 1.7 Hz, 1H), 7.82 (dd, J = 7.8, 1.5 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.65 (td, J = 7.6, 1.3 Hz, 1H), 7.57 (dd, J = 8.0, 1.7 Hz, 1H), 7.53 (ddd, J = 8.7, 7.6, 1.5 Hz, 1H), 5.08 (br, 1H), 4.42 (d, J = 6.3 Hz, 2H), 1.47 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): 156.0, 149.6, 149.5, 142.2, 135.6, 135.4, 133.3, 131.9, 129.7, 125.0, 123.4, 118.2, 116.9, 92.0, 91.9, 80.5, 43.9, 28.5.

IR: 3341, 2979, 1689, 1606, 1568, 1558, 1524, 1475, 1457, 1438, 1429, 1412, 1392, 1366, 1342, 1290, 1252, 1168, 1052, 946, 931, 864, 832, 785, 762, 744.

HRMS (ESI): $C_{20}H_{20}N_3O_6$ [M+H] calc. 398.1347, found 398.1353.

tert-butyl (4-amino-3-((2-nitrophenyl)ethynyl)benzyl)carbamate (SI-65)



48 SI-13 SI-65

Prepared from *tert*-butyl (4-amino-3-iodobenzyl)carbamate (**SI-13**, 904 mg, 2.60 mmol) and 1-ethynyl-2-nitrobenzene (**48**, 420 mg, 2.86 mmol) according to the general Sonogashira coupling procedure, but with an increased amount of trimethylsilylacetylene (1.0 eq.).
The crude was purified by column chromatography (0 to 100% dichloromethane in hexanes to 4% methanol in dichloromethane) and the resulting dark red solid recrystallized from toluene to afford the title compound (234 mg, 638 µmol, 25%) as a red solid. Additional material was isolated from the mother liquors of the recrystallization. The solvent was removed under reduced pressure and the residue washed with methanol to afford additional product (80 mg, 0.22 mmol, 8%) in the form of a red solid. The washings were concentrated under reduced pressure. The residue was subjected to column chromatography (0 to 66% ethyl acetate in hexanes) and washed with methanol to afford another portion of the title compound (106 mg, 289 µmol, 11%) as a red solid.

R_f = 0.31 (5% ethyl acetate in dichloromethane).

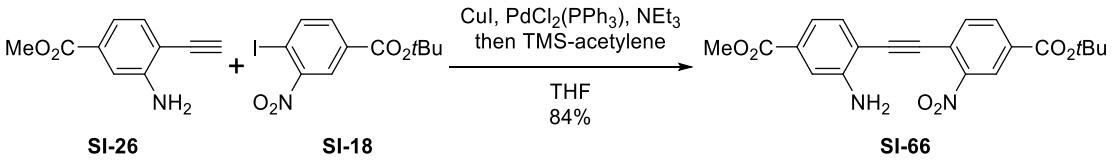
^{1}H-NMR (400 MHz, $CDCl_3$): 8.17 (dd, J = 8.3, 1.2 Hz, 1H), 7.73 (dd, J = 7.8, 1.5 Hz, 1H), 7.63 (td, J = 7.6, 1.3 Hz, 1H), 7.46 (ddd, J = 8.7, 7.4, 1.5 Hz, 1H), 7.32 (d, J = 2.1 Hz, 1H), 7.12 (dd, J = 8.4, 2.0 Hz, 1H), 6.70 (d, J = 8.3 Hz, 1H), 4.81 – 4.60 (br, 3H), 4.19 (d, J = 5.8 Hz, 2H), 1.47 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): 155.9, 149.0, 148.5, 134.5, 133.4, 131.8, 131.0, 128.3, 128.0, 125.2, 119.5, 114.7, 106.4, 95.1, 91.0, 79.6, 44.2, 28.6.

IR: 3477, 3375, 3353, 2972, 2930, 2187, 1682, 1622, 1607, 1566, 1521, 1506, 1477, 1437, 1392, 1366, 1353, 1339, 1321, 1298, 1269, 1249, 1207, 1164, 1120, 1045, 1030, 959, 860, 825, 781, 735.

HRMS (ESI): $C_{20}H_{22}N_3O_4$ [M+H] calc. 368.1605, found 368.1613.

tert-butyl 4-((2-amino-4-(methoxycarbonyl)phenyl)ethynyl)-3-nitrobenzoate (**SI-66**)



SI-26 **SI-18** **SI-66**

Prepared from *tert*-butyl 4-iodo-3-nitrobenzoate (**SI-18**, 1.40 g, 4.01 mmol) and methyl 3-amino-4-ethynylbenzoate (**SI-26**, 773 mg, 4.41 mmol) according to the general Sonogashira coupling procedure, but with a reduced amount of trimethylsilylacetylene (0.20 eq.). The crude was purified by column chromatography (0 to 100% dichloromethane in hexanes) and the resulting brown-orange solid recrystallized from toluene to afford the title compound (1.03 g, 2.60 mmol, 65%) as an orange solid. The mother liquors were filtered over a short plug of silica, the silica was washed with additional toluene and dichloromethane and the solvent removed under reduced pressure. The residue was washed with methanol to afford additional product (306 mg, 772 µmol, 19%) in the form of an orange solid.

R_f = 0.57 (5% ethyl acetate in dichloromethane).

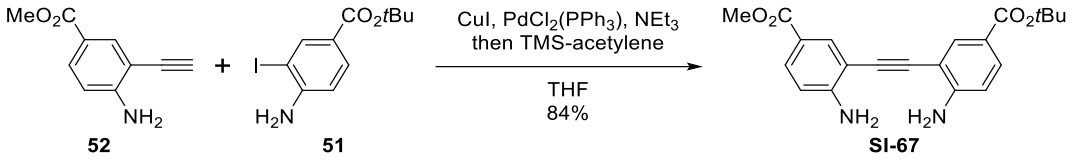
^{1}H-NMR (400 MHz, $CDCl_3$): 8.74 (d, J = 1.6 Hz, 1H), 8.23 (dd, J = 8.2, 1.7 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 1.4 Hz, 1H), 7.37 (dd, J = 8.0, 1.5 Hz, 1H), 4.86 (br, 2H), 3.93 (s, 3H), 1.65 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): 166.8, 163.2, 149.7, 148.5, 134.6, 133.6, 132.8, 132.6, 132.4, 126.2, 122.3, 118.3, 115.4, 109.9, 97.1, 92.7, 83.0, 52.4, 28.2.

IR: 3473, 3370, 2981, 2193, 1703, 1614, 1552, 1525, 1509, 1481, 1456, 1432, 1396, 1367, 1339, 1311, 1303, 1269, 1234, 1166, 1154, 1117, 1104, 1061, 984, 913, 885, 843, 825, 794, 761, 753, 729.

HRMS (ESI): $C_{21}H_{21}N_2O_6$ [M+H] calc. 397.1394, found 397.1399.

tert-butyl 4-amino-3-((2-amino-5-(methoxycarbonyl)phenyl)ethynyl)benzoate (**SI-67**)



52 **51** **SI-67**

Prepared from *tert*-butyl 4-amino-3-iodobenzoate (**51**, 1.30 g, 4.07 mmol) and methyl 4-amino-3-ethynylbenzoate (**52**, 785 mg, 4.48 mmol) according to the general Sonogashira coupling procedure.

The crude was purified by two cycles of column chromatography (0 to 10% ethyl acetate in dichloromethane and 0 to 35% ethyl acetate in hexanes). The resulting brownish solids were further purified by precipitation from dichloromethane solution by addition of hexanes to afford the title compound (1.25 g, 3.41 mmol, 84%) as a white solid.

R_f = 0.23 (5% ethyl acetate in dichloromethane).

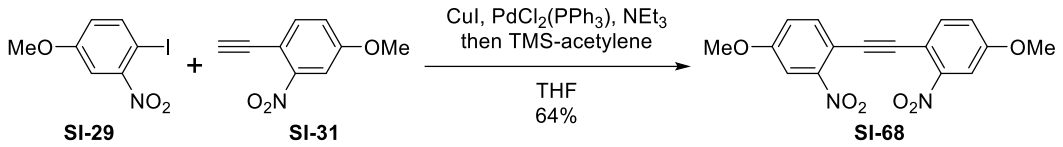
^{1}H-NMR (400 MHz, DMSO-d_6): 8.00 (d, J = 2.1 Hz, 1H), 7.92 (d, J = 2.1 Hz, 1H), 7.65 (dd, J = 8.6, 2.1 Hz, 1H), 7.59 (dd, J = 8.6, 2.1 Hz, 1H), 6.74 (t, J = 8.6 Hz, 2H), 6.35 (br, 2H), 6.28 (br, 2H), 3.77 (s, 3H), 1.52 (s, 9H).

^{13}C-NMR (100 MHz, DMSO-d_6): 165.8, 164.7, 153.2, 152.9, 134.5, 134.3, 130.82, 130.77, 118.1, 116.2, 113.2, 113.0, 105.4, 105.2, 90.5, 90.2, 79.5, 51.4, 28.0.

IR: 3475, 3360, 2977, 2950, 2932, 1689, 1616, 1571, 1505, 1474, 1455, 1435, 1392, 1368, 1336, 1295, 1244, 1191, 1168, 1148, 1123, 1110, 1092, 1051, 990, 962, 946, 907, 850, 832, 795, 768, 731.

HRMS (ESI): $C_{21}H_{23}N_2O_4$ [M+H] calc. 367.1652, found 367.1662.

1,2-bis(4-methoxy-2-nitrophenyl)ethyne (SI-68)



Prepared from 1-iodo-4-methoxy-2-nitrobenzene (**SI-29**, 1.00 g, 3.58 mmol) and 1-ethynyl-4-methoxy-2-nitrobenzene (**SI-31**, 698 mg, 3.94 mmol) according to the general Sonogashira coupling procedure, but with a modified workup due to the very low solubility of the product.

After removal of the reaction solvent, the residue was suspended in dichloromethane (30 mL) and water (10 mL), the mixture was filtered and the filtrate was discarded. The solids were purified by column chromatography (0 to 100% dichloromethane in hexanes to 5% ethyl acetate in dichloromethane) and the resulting brownish-yellow solids were washed with methanol as well as a small amount of dichloromethane to afford the title compound (747 mg, 2.28 mmol, 64%) as a yellow solid.

$\mathbf{R_f}$ = 0.56 (dichloromethane).

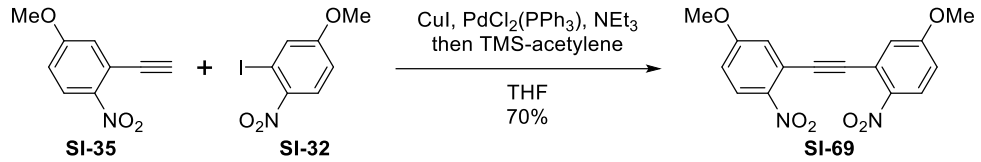
^{1}H-NMR (400 MHz, $CDCl_3$): 7.71 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 2.6 Hz, 2H), 7.17 (dd, J = 8.7, 2.7 Hz, 2H), 3.92 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): 160.1, 150.4, 136.2, 120.1, 110.7, 109.7, 90.8, 56.2.

IR: 1617, 1559, 1530, 1469, 1456, 1447, 1418, 1345, 1330, 1302, 1271, 1225, 1193, 1151, 1070, 1034, 952, 921, 887, 825, 778, 760.

HRMS (ESI): $C_{16}H_{13}N_2O_6$ [M+H] calc. 329.0768, found 329.0772.

1,2-bis(5-methoxy-2-nitrophenyl)ethyne (SI-69)



Prepared from 2-iodo-4-methoxy-1-nitrobenzene (**SI-32**, 1.00 g, 3.58 mmol) and 2-ethynyl-4-methoxy-1-nitrobenzene (**SI-35**, 698 mg, 3.94 mmol) according to the general Sonogashira coupling procedure.

The crude was purified by column chromatography (0 to 100% dichloromethane in hexanes) and the resulting brown-yellow solids recrystallized from toluene to afford the title compound (728 mg, 2.22 mmol, 62%) as an off-white solid. Additional material was obtained from the mother liquors of the recrystallization. The solvent was removed under reduced pressure, the residue dissolved in hexanes/dichloromethane = 1/3, filtered over a short plug of silica and the solvent was again removed under reduced pressure. The residue was further purified by precipitation from dichloromethane solution by addition of hexane to afford additional product (96 mg, 0.29 mmol, 8%) in the form of a yellow solid.

$\mathbf{R_f}$ = 0.52 (dichloromethane).

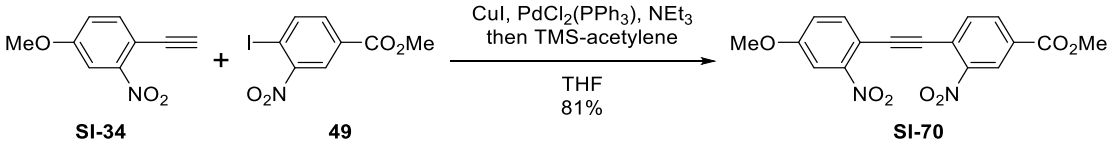
^{1}H-NMR (400 MHz, DMSO-d_6): 8.23 (d, J = 9.2 Hz, 2H), 7.36 (d, J = 2.8 Hz, 2H), 7.24 (dd, J = 9.3, 2.9 Hz, 2H), 3.94 (s, 6H).

^{13}C-NMR (100 MHz, DMSO-d_6): 162.9, 141.8, 127.7, 119.2, 118.9, 116.2, 91.5, 56.5.

IR: 1605, 1583, 1540, 1502, 1467, 1457, 1412, 1353, 1334, 1310, 1293, 1259, 1229, 1181, 1155, 1092, 1021, 965, 936, 913, 905, 871, 856, 843, 777, 759, 746, 706.

HRMS (ESI): $C_{16}H_{13}N_2O_6$ [M+H] calc. 329.0768, found 329.0766.

methyl 4-((4-methoxy-2-nitrophenyl)ethynyl)-3-nitrobenzoate (SI-70)



SI-34 49 SI-70

Prepared from methyl 4-iodo-3-nitrobenzoate (**49**, 1.00 g, 3.26 mmol) and 1-ethynyl-4-methoxy-2-nitrobenzene (**SI-34**, 635 mg, 3.58 mmol) according to the general Sonogashira coupling procedure.
The crude was purified by column chromatography (0 to 75% dichloromethane in hexanes). The resulting brownish-yellow solid was purified further by precipitation from dichloromethane solution by addition of methanol to afford the title compound (943 mg, 2.65 mmol, 81%) as a yellow solid.

R_f = 0.42 (dichloromethane).

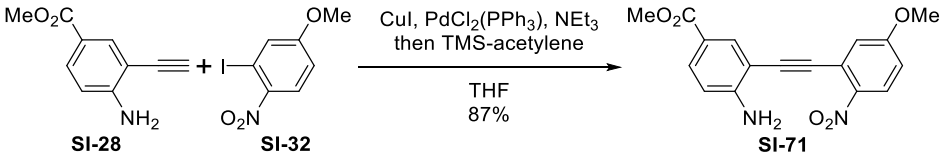
^{1}H-NMR (400 MHz, $CDCl_3$): 8.76 (d, J = 1.7 Hz, 1H), 8.26 (dd, J = 8.1, 1.7 Hz, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.66 (d, J = 2.6 Hz, 1H), 7.20 (dd, J = 8.7, 2.6 Hz, 1H), 3.99 (s, 3H), 3.94 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 164.7, 160.9, 150.7, 149.3, 136.6, 135.4, 133.5, 130.8, 126.0, 122.6, 120.0, 110.0, 109.6, 95.7, 90.0, 56.3, 53.0.

IR: 3085, 2955, 2904, 2847, 2211, 1733, 1684, 1653, 1610, 1559, 1530, 1483, 1457, 1437, 1404, 1345, 1302, 1276, 1239, 1232, 1193, 1152, 1116, 1065, 1032, 971, 918, 887, 880, 856, 827, 795, 770, 756, 726.

HRMS (ESI): $C_{17}H_{13}N_2O_7$ [M+H] calc. 357.0717, found 357.0717.

methyl 4-amino-3-((5-methoxy-2-nitrophenyl)ethynyl)benzoate (SI-71)



SI-28 SI-32 SI-71

Prepared from 2-iodo-4-methoxy-1-nitrobenzene (**SI-32**, 500 mg, 1.79 mmol) and methyl 4-amino-3-ethynylbenzoate (**SI-28**, 345 mg, 1.97 mmol) according to the general Sonogashira coupling procedure.
The crude was purified by column chromatography (0 to 10% ethyl acetate in dichloromethane) and the resulting orange solid was recrystallized from toluene to afford the title compound (507 mg, 1.55 mmol, 87%) as an orange solid.

R_f = 0.55 (5% ethyl acetate in dichloromethane).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.21 (d, J = 9.3 Hz, 1H), 8.13 (d, J = 2.0 Hz, 1H), 7.86 (dd, J = 8.6, 2.0 Hz, 1H), 7.16 (d, J = 2.8 Hz, 1H), 6.94 (dd, J = 9.3, 2.8 Hz, 1H), 6.71 (d, J = 8.6 Hz, 1H), 5.23 (br, 2H), 3.95 (s, 3H), 3.88 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 166.6, 163.5, 153.4, 141.6, 135.1, 132.8, 127.8, 121.6, 119.1, 118.0, 115.2, 113.5, 105.7, 94.1, 91.9, 56.3, 51.9.

IR: 3484, 3380, 2190, 1734, 1713, 1705, 1622, 1610, 1595, 1581, 1560, 1532, 1507, 1497, 1457, 1437, 1398, 1339, 1302, 1281, 1241, 1187, 1137, 1114, 1102, 1075, 1027, 1016, 995, 949, 919, 909, 848, 827, 802, 761, 754, 728.

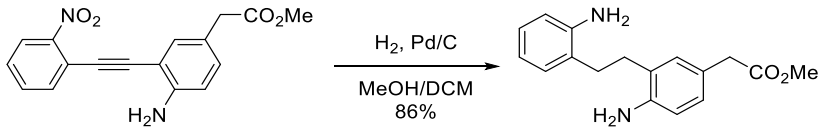
HRMS (ESI): $C_{17}H_{14}N_2NaO_5$ [M+Na] calc. 349.0795, found 349.081.

Syntheses of 2,2'-ethylenedianilines

General procedure – hydrogenation

The diarylacetylene substrate and palladium on charcoal (10 wt%, 106 mg per 1 mmol of substrate) were placed in a round bottom flask and wetted with dichloromethane (2.25 mL per 1 mmol of substrate) to reduce the risk of fire. After the addition of methanol (10 mL per 1 mmol substrate), the flask was evacuated and refilled with hydrogen twice. The mixture was stirred under a balloon of hydrogen until the reaction had finished according to ^{1}H-NMR spectroscopy. The flask was then evacuated and refilled with nitrogen. The mixture was diluted with dichloromethane (10 mL per 1 mmol of substrate), a small portion of Celite® was added and stirring was continued for several minutes. The mixture was filtered over a plug of Celite® and the Celite® was washed with additional dichloromethane. The solvent was removed under reduced pressure and the residue was purified as specified.

methyl 2-(4-amino-3-(2-aminophenethyl)phenyl)acetate (**47**)



SI-62 **47**

Prepared from methyl 2-(4-nitro-3-((2-nitrophenyl)ethynyl)phenyl)acetate (**SI-62**, 1.15 g, 3.71 mmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 50% ethyl acetate in dichloromethane) to afford the title compound (909 mg, 3.20 mmol, 86%) as a faint brown oil that solidified upon standing at room temperature to give an off-white solid.

R_f = 0.33 (40% ethyl acetate in dichloromethane).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.09 – 7.02 (m, 2H), 7.00 – 6.94 (m, 2H), 6.75 (td, J = 7.4, 1.2 Hz, 1H), 6.67 (dd, J = 7.8, 1.2 Hz, 1H), 6.63 (d, J = 7.9 Hz, 1H), 3.68 (s, 3H), 3.57 (br, 4H), 3.51 (s, 2H), 2.84 – 2.73 (m, 4H).

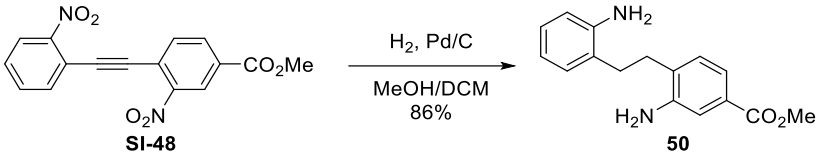
^{13}C-NMR (100 MHz, $CDCl_3$): 172.8, 144.5, 143.5, 130.5, 129.6, 128.2, 127.4, 126.6, 126.3, 124.4, 119.1, 116.2, 116.0, 52.1, 40.5, 31.1.[a]

IR: 3433, 3360, 3227, 3020, 3006, 2948, 2867, 1724, 1623, 1583, 1496, 1455, 1434, 1266, 1198, 1153, 1078, 1060, 1039, 1012, 956, 906, 824, 803, 750, 729.

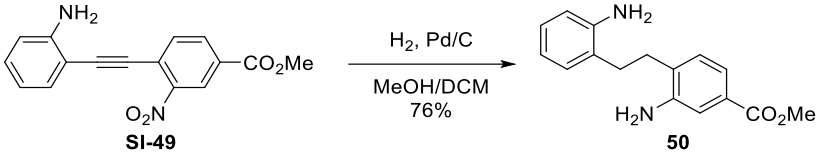
HRMS (ESI): $C_{17}H_{21}N_2O_2$ [M+H] calc. 285.1598, found 285.1600.

[a]The signal at 31.1 ppm corresponds to two carbons.

methyl 3-amino-4-(2-aminophenethyl)benzoate (**50**)



From substrate SI-48: Prepared from methyl 3-nitro-4-((2-nitrophenyl)ethynyl)-benzoate (**SI-48**, 725 mg, 2.22 mmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 30% ethyl acetate in dichloromethane) to afford the title compound (519 mg, 1.92 mmol, 86%) as a white solid.



From substrate SI-49: Prepared from methyl 4-((2-aminophenyl)ethynyl)-3-nitro-benzoate (**SI-49**, 650 mg, 2.19 mmol) according to the general hydrogenation procedure. The crude was purified by column chromatography (0 to 25% ethyl acetate in dichloromethane) to afford the title compound (451 mg, 1.67 mmol, 76%) as a white solid.

R_f = 0.45 (40% ethyl acetate in dichloromethane).

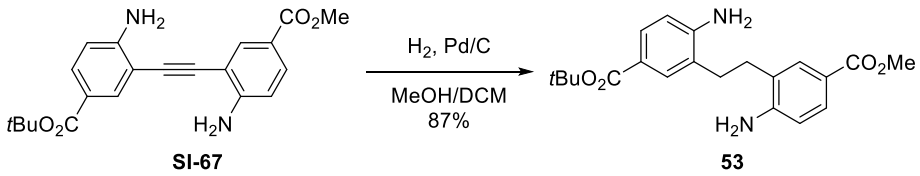
^{1}H-NMR (400 MHz, $CDCl_3$): 7.41 (dd, J = 7.8, 1.7 Hz, 1H), 7.34 (d, J = 1.7 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H), 7.06 (td, J = 7.6, 1.6 Hz, 1H), 7.02 (dd, J = 7.5, 1.6 Hz, 1H), 6.74 (td, J = 7.4, 1.2 Hz, 1H), 6.68 (dd, J = 7.9, 1.2 Hz, 1H), 3.88 (s, 3H), 3.64 (br, 4H), 2.88 – 2.78 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 167.4, 144.6, 144.3, 131.5, 129.72, 129.67, 129.2, 127.6, 125.9, 120.2, 119.2, 116.6, 116.1, 52.1, 31.0, 30.8.

IR: 3449, 3433, 3023, 2949, 2869, 1707, 1624, 1578, 1497, 1455, 1438, 1297, 1244, 1199, 1157, 1144, 1110, 1067, 1040, 995, 931, 909, 887, 852, 830, 793, 757.

HRMS (ESI): $C_{16}H_{19}N_2O_2$ [M+H] calc. 271.1441, found 271.1446.

tert-butyl 4-amino-3-(2-amino-5-(methoxycarbonyl)phenethyl)benzoate (**53**)



Prepared from *tert*-butyl 4-amino-3-((2-amino-5-(methoxycarbonyl)phenyl)ethynyl)-benzoate (**SI-67**, 1.14 g, 3.10 mmol) according to the general hydrogenation procedure, but with a modified workup. During the filtration to remove the palladium on charcoal the filter Celite® had to be washed with a large amount of dichloromethane/methanol = 1/1, due to the low solubility of the product.
The crude was dissolved in tetrahydrofuran and filtered over a short plug of silica (4 g), eluting with a small amount of additional tetrahydrofuran. The solvent was removed under reduced pressure and the residue washed with dichloromethane to afford the title compound (999 mg, 2.70 mmol, 87%) as a white solid.

R_f = 0.62 (40% ethyl acetate in dichloromethane).

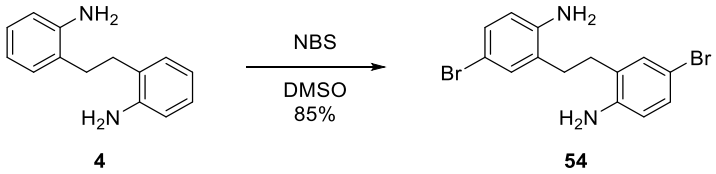
^{1}H-NMR (400 MHz, DMSO-d_6): 7.61 (d, J = 2.1 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.47 (dd, J = 8.4, 2.1 Hz, 1H), 6.64 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 5.79 (s, 2H), 5.71 (s, 2H), 3.73 (s, 3H), 2.69 (s, 4H), 1.48 (s, 9H).

^{13}C-NMR (100 MHz, DMSO-d_6): 166.5, 165.5, 151.2, 150.8, 130.8, 130.7, 128.7, 128.6, 123.8, 123.7, 118.1, 116.1, 113.4, 113.2, 78.8, 51.1, 29.08, 29.06, 28.0.

IR: 3445, 3348, 3254, 3237, 2977, 1680, 1640, 1600, 1506, 1470, 1452, 1437, 1427, 1386, 1364, 1352, 1309, 1291, 1267, 1242, 1194, 1175, 1150, 1111, 997, 950, 911, 858, 831, 805, 794, 767, 708.

HRMS (ESI): $C_{21}H_{26}N_2NaO_4$ [M+Na] calc. 393.1785, found 393.1798.

2,2'-(ethane-1,2-diyl)bis(4-bromoaniline) (**54**)



4 **54**

To a solution of 2,2'-ethylenedianiline (**4**, 1.00 g, 4.71 mmol, 1.0 eq.) in dimethyl sulfoxide (15 mL) was added *N*-bromosuccinimide (1.72 g, 9.66 mmol, 2.05 eq.) in three portions within 10 minutes. After the mixture had stirred overnight, dichloromethane (10 mL) and water (60 mL) were added. The mixture was stirred for additional 30 minutes, then the precipitate was collected, washed with a small amount of methanol and dried to afford the title compound (1.10 g, 2.97 mmol, 63%) as a faint brown solid. Saturated, aqueous sodium chloride (10 mL) was added to the filtrate and the mixture was extracted with dichloromethane (50 mL and 2×25 mL). The organic extracts were washed with a mixture of saturated, aqueous sodium chloride/water = 1/4 (2×100 mL), dried over sodium sulfate and the solvent removed under reduced pressure. The residue was purified by column chromatography (0 to 100% dichloromethane in hexanes) to afford additional product (380 mg, 1.03 mmol, 22%) as a faint brown solid.

R_f = 0.38 (20% ethyl acetate in dichloromethane).

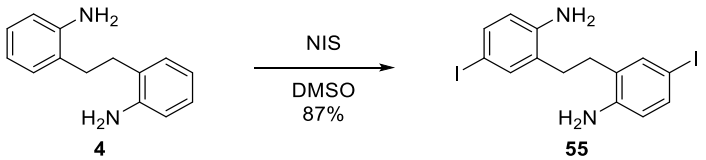
^{1}H-NMR (400 MHz, $CDCl_3$): 7.18 – 7.12 (m, 4H), 6.58 – 6.54 (m, 2H), 3.62 (br, 4H), 2.72 (s, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 143.4, 132.1, 130.2, 128.0, 117.5, 110.8, 30.7.

IR: 3443, 3365, 3081, 3041, 2945, 2927, 2865, 1617, 1574, 1484, 1463, 1412, 1311, 1289, 1271, 1193, 1160, 1119, 1076, 938, 908, 884, 872, 814, 784, 748, 731.

HRMS (ESI): $C_{14}H_{15}Br_2N_2$ [M+H] calc. 368.9597, found 368.9589.

2,2'-(ethane-1,2-diyl)bis(4-iodoaniline) (**55**)



4 **55**

To a solution of 2,2'-ethylenedianiline (**4**, 1.00 g, 4.71 mmol, 1.0 eq.) in dimethyl sulfoxide (15 mL) was added *N*-iodosuccinimide (2.17 g, 9.66 mmol, 2.05 eq.) in three portions within 10 minutes. After the mixture had stirred overnight, dichloromethane (10 mL) and water (60 mL) were added. The mixture was stirred for additional 30 minutes, then the precipitate

was collected, washed with a small amount of dichloromethane, followed by a small amount of methanol and dried to afford the title compound (1.59 g, 3.43 mmol, 73%) as a reddish-brownish solid. Saturated, aqueous sodium chloride (10 mL) was added to the filtrate and the mixture was extracted with dichloromethane (50 mL and 2×25 mL). The organic extracts were washed with a mixture of saturated, aqueous sodium chloride/water = 1/4 (2×100 mL), dried over sodium sulfate and the solvent removed under reduced pressure. The residue was purified by column chromatography (0 to 100% dichloromethane in hexanes) to afford additional product (310 mg, 668 µmol, 14%) as a red-brown solid.

R_f = 0.43 (20% ethyl acetate in dichloromethane).

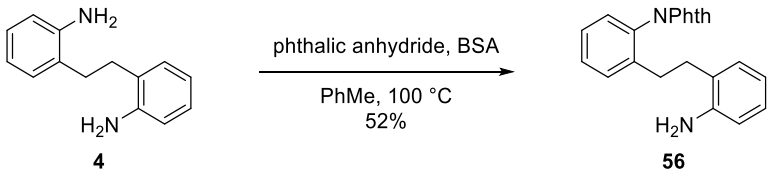
^{1}H-NMR (400 MHz, $CDCl_3$): 7.34 – 7.30 (m, 4H), 6.48 – 6.44 (m, 2H), 3.63 (br, 4H), 2.69 (s, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 144.2, 138.0, 136.2, 128.6, 118.1, 80.3, 30.6.

IR: 3431, 3353, 3078, 3033, 2943, 2927, 2865, 1616, 1567, 1483, 1463, 1405, 1310, 1291, 1272, 1192, 1164, 1122, 1070, 941, 885, 863, 814, 780, 748, 732, 709.

HRMS (ESI): $C_{14}H_{15}I_2N_2$ [M+H] calc. 464.9319, found 464.9313.

Phthalimide **56**



Preparation of the mono-phthalimide: To a warm solution of 2,2'-ethylenedianiline (**4**, 5.00 g, 23.6 mmol, 1.0 eq.) in toluene (23.5 mL) was added bis(trimethylsilyl)acetamide (6.00 mL, 24.3 mmol, 1.03 eq.), followed by phthalic anhydride (3.49 g, 23.6 mmol, 1.0 eq.). The mixture was stirred for 6.5 hours at 100 °C, then cooled to room temperature and concentrated under reduced pressure. Dichloromethane (60 mL) was added to the residue and the mixture was washed with 2 M aqueous sodium hydroxide (50 mL) and water (2×50 mL). After drying over sodium sulfate, the resulting solution was concentrated under reduced pressure. Diethyl ether (50 mL) was added to the oily residue and the mixture was sonicated until the oily layer had fully dissolved and large amounts of a yellow solids had formed, then the mixture was cooled with an ice-bath for two hours. Next, the solids were collected and washed with a small amount of additional diethyl ether. The filtrate, which mainly consisted of unreacted substrate and only minor amounts of the product, was kept for the recovery of starting material. The solids were dissolved in dichloromethane (30 mL) and the minor quantities of poorly soluble white solids were filtered off and discarded. The obtained solution was treated with a 4 M solution of hydrogen chloride in 1,4-dioxane (3.5 mL, 14.1 mmol, 0.6 eq.), sonicated until the mixture had turned into a thick slurry and cooled with an ice-bath for one hour. Then, the slurry was diluted with dichloromethane (15 mL), the solids were collected and washed with more dichloromethane (40 mL). The filtrate, which was almost exclusively the doubly protected side-product (not depicted), was also kept for the recovery of starting material. The solids were suspended in dichloromethane (30 mL) and saturated, aqueous sodium carbonate (30 mL). The suspension was stirred with the rate of stirring adjusted appropriately to keep the evolution of gas at a controlled level. After all solids had dissolved, 2 M aqueous sodium hydroxide (10 mL) was added, the layers were mixed thoroughly, separated and the organic layer was dried over sodium sulfate. Removal of the solvent under reduced pressure then afforded the title compound (4.19 g, 12.2 mmol, 52%) as a yellow solid.

Recovery of starting material: The diethyl ether solution of the first precipitation and the dichloromethane solution of the second precipitation were combined and the solvent was removed under reduced pressure. Tetrahydrofuran (30 mL) and hydrazine monohydrate (1.15 mL, 23.6 mmol, 1.0 eq.) were added to the residue. The mixture was stirred at reflux for three hours, cooled to room temperature and filtered. The solids were washed with additional tetrahydrofuran (2×10 mL) and discarded. The filtrate was diluted with water (20 mL) and the tetrahydrofuran was removed under reduced pressure. An oily layer separated, which solidified upon keeping the mixture at room temperature overnight. The solids were collected, washed with water and dried, to obtain the recovered substrate (**4**, 1.98 g, 9.33 mmol, 40%) as a reddish solid.

$\mathbf{R_f}$ = 0.88 (20% ethyl acetate in dichloromethane).

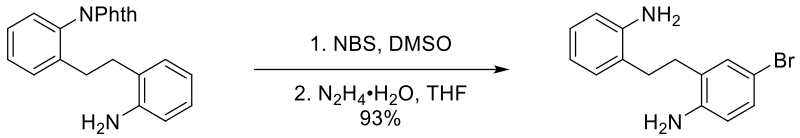
^{1}H-NMR (400 MHz, $CDCl_3$): 7.99 – 7.92 (m, 2H), 7.84 – 7.78 (m, 2H), 7.46 – 7.33 (m, 3H), 7.21 (dd, J = 7.6, 1.8 Hz, 1H), 6.98 (ddt, J = 8.3, 4.2, 1.9 Hz, 2H), 6.66 (td, J = 7.4, 1.2 Hz, 1H), 6.56 (dd, J = 8.2, 1.3 Hz, 1H), 3.54 (br, 2H), 2.84 – 2.72 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 168.1, 144.5, 140.3, 134.6, 132.1, 130.5, 130.2, 129.8, 129.7, 129.3, 127.5, 127.4, 125.4, 123.9, 118.8, 115.7, 32.2, 31.2.

IR: 3466, 3377, 3062, 3028, 2940, 2870, 1784, 1766, 1744, 1711, 1624, 1583, 1495, 1466, 1454, 1380, 1313, 1285, 1221, 1172, 1161, 1112, 1083, 909, 888, 856, 794, 756, 719, 701.

HRMS (APCI): $C_{22}H_{19}N_2O_2$ [M+H] calc. 343.1441, found 343.1433.

2-(2-aminophenethyl)-4-bromoaniline (**57**)



56 **57**

Bromination: To a solution of mono-phthalimide **56** (2.50 g, 7.30 mmol, 1.0 eq.) in anhydrous dimethyl sulfoxide (21 mL) was added *N*-bromosuccinimide (1.30 g, 7.30 mmol, 1.0 eq.) in one portion. After the mixture had stirred for two hours, saturated, aqueous sodium chloride/water = 1/4 (50 mL) was added and the mixture was extracted with dichloromethane (30 mL and 2×15 mL). The extracts were washed with saturated, aqueous sodium chloride/water = 1/4 (2×50 mL) and dried over sodium sulfate. The solution was then filtered over a short plug of silica (5 g) and eluted with additional dichloromethane (25 mL). The solvent was removed under reduced pressure and the residue was used without further purification.

Phthalimide cleavage: To the bromination product were added tetrahydrofuran (37 mL) and hydrazine monohydrate (2.13 mL, 43.8 mmol, 6.0 eq.) and the mixture was stirred at reflux for two hours. After cooling to room temperature, the mixture was filtered. The solids were washed with additional tetrahydrofuran (2×10 mL) and discarded. Water (20 mL) was added to the filtrate, the tetrahydrofuran removed under reduced pressure and the residue extracted with diethyl ether (30 mL and 2×15 mL). The extracts were washed with saturated, aqueous sodium chloride (30 mL), dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by precipitation from dichloromethane solution by addition of hexanes to afford the title compound (1.98 g, 6.80 mmol, 93%) as an off-white solid.

$\mathbf{R_f}$ = 0.34 (20% ethyl acetate in dichloromethane).

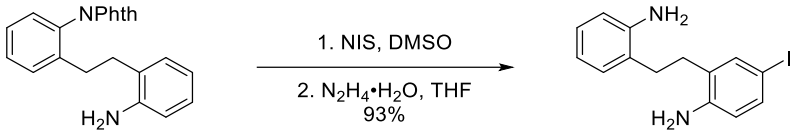
^{1}H-NMR (400 MHz, $CDCl_3$): 7.19 (d, J = 2.3 Hz, 1H), 7.13 (dd, J = 8.4, 2.4 Hz, 1H), 7.10 – 7.01 (m, 2H), 6.75 (td, J = 7.4, 1.2 Hz, 1H), 6.69 (dd, J = 7.8, 1.2 Hz, 1H), 6.54 (d, J = 8.4 Hz, 1H), 3.60 (br, 4H), 2.82 – 2.72 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 144.3, 143.6, 132.1, 130.0, 129.7, 128.5, 127.6, 125.9, 119.3, 117.4, 116.1, 110.7, 31.1, 30.8.

IR: 3433, 3353, 3225, 3061, 3021, 2936, 2868, 1618, 1583, 1486, 1455, 1435, 1409, 1312, 1271, 1198, 1180, 1159, 1145, 1083, 1058, 1039, 933, 876, 859, 813, 751, 704.

HRMS (ESI): $C_{14}H_{16}BrN_2$ [M+H] calc. 291.0491, found 291.0498.

2-(2-aminophenethyl)-4-iodoaniline (**58**)



56 **58**

Iodination: To a solution of mono-phthalimide **56** (2.50 g, 7.30 mmol, 1.0 eq.) in anhydrous dimethyl sulfoxide (21 mL) was added *N*-iodosuccinimide (1.64 g, 7.30 mmol, 1.0 eq.) in one portion. After the mixture had stirred for three hours, saturated, aqueous sodium chloride/water = 1/4 (50 mL) was added and the mixture was extracted with dichloromethane (30 mL and 2×15 mL). The extracts were washed with saturated, aqueous sodium chloride/water = 1/4 (2×50 mL) and dried over sodium sulfate. The solution was then filtered over a short plug of silica (5 g) and eluted with additional dichloromethane (25 mL). The solvent was removed under reduced pressure and the residue was used without further purification.

Phthalimide cleavage: To the iodination product were added tetrahydrofuran (37 mL) and hydrazine monohydrate (2.13 mL, 43.8 mmol, 6 eq.) and the mixture was stirred at reflux for two hours. After cooling to room temperature, the mixture was filtered. The solids were washed with additional tetrahydrofuran (2×10 mL) and discarded. Water (20 mL) was added to the filtrate, the tetrahydrofuran removed under reduced pressure and the residue extracted with diethyl ether (30 mL and 2×15 mL). The extracts were washed with saturated, aqueous sodium chloride (30 mL), dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by precipitation from dichloromethane solution by addition of hexanes to afford the title compound (1.98 g, 6.80 mmol, 93%) as a brownish-yellow solid.

$\mathbf{R_f}$ = 0.38 (20% ethyl acetate in dichloromethane).

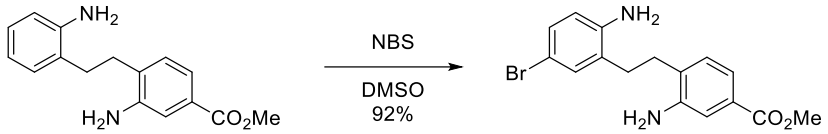
^{1}H-NMR (400 MHz, $CDCl_3$): 7.36 (d, J = 2.1 Hz, 1H), 7.31 (dd, J = 8.3, 2.1 Hz, 1H), 7.10 – 7.00 (m, 2H), 6.75 (td, J = 7.4, 1.2 Hz, 1H), 6.69 (dd, J = 7.9, 1.2 Hz, 1H), 6.44 (d, J = 8.3 Hz, 1H), 3.61 (br, 4H), 2.81 – 2.70 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 144.32, 144.29, 137.9, 136.0, 129.7, 129.1, 127.6, 125.9, 119.3, 118.0, 116.1, 80.2, 31.1, 30.6.

IR: 3430, 3350, 3227, 3059, 3020, 2936, 2867, 1617, 1582, 1571, 1484, 1455, 1434, 1403, 1361, 1310, 1269, 1198, 1161, 1146, 1057, 1039, 933, 907, 874, 856, 812, 750.

HRMS (ESI): $C_{14}H_{16}IN_2$ [M+H] calc. 339.0353, found 339.0351.

methyl 3-amino-4-(2-amino-5-bromophenethyl)benzoate (59)



50 59

To a solution of methyl 3-amino-4-(2-aminophenethyl)benzoate (**50**, 400 mg, 1.48 mmol, 1.0 eq.) in dimethyl sulfoxide (6 mL) was added *N*-bromosuccinimide (270 mg, 1.52 mmol, 1.025 eq.) in one portion. After the mixture had stirred overnight, saturated, aqueous sodium chloride/water = 1/4 (30 mL) was added and the mixture was extracted with dichloromethane (3×15 mL). The extracts were washed with saturated, aqueous sodium chloride/water = 1/4 (2×20 mL), dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography (0 to 20% ethyl acetate in dichloromethane) to afford the title compound (474 mg, 1.36 mmol, 92%) as a brownish solid.

R_f = 0.43 (40% ethyl acetate in dichloromethane).

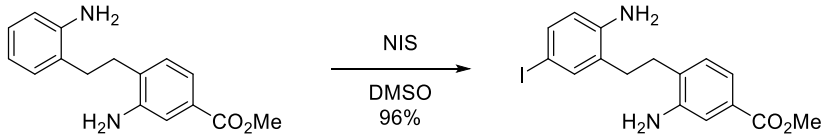
^{1}H-NMR (400 MHz, $CDCl_3$): 7.40 (dd, J = 7.8, 1.7 Hz, 1H), 7.35 (d, J = 1.7 Hz, 1H), 7.16 (d, J = 2.3 Hz, 1H), 7.13 (dd, J = 8.3, 2.4 Hz, 1H), 7.08 (d, J = 7.8 Hz, 1H), 6.54 (d, J = 8.3 Hz, 1H), 3.89 (s, 3H), 3.66 (br, 4H), 2.85 – 2.72 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 167.3, 144.4, 143.5, 132.1, 130.9, 130.2, 129.7, 129.4, 128.0, 120.4, 117.5, 116.8, 110.8, 52.1, 31.0, 30.4.

IR: 3449, 3366, 3233, 3023, 2999, 2948, 2872, 1703, 1621, 1577, 1507, 1488, 1436, 1410, 1295, 1240, 1197, 1145, 1109, 1082, 996, 907, 878, 853, 813, 762, 730.

HRMS (ESI): $C_{16}H_{18}BrN_2O_2$ [M+H] calc. 349.0546, found 349.0537.

methyl 3-amino-4-(2-amino-5-iodophenethyl)benzoate (60)



50 60

To a solution of methyl 3-amino-4-(2-aminophenethyl)benzoate (**50**, 400 mg, 1.48 mmol, 1.0 eq.) in dimethyl sulfoxide (6 mL) was added *N*-iodosuccinimide (341 mg, 1.52 mmol, 1.025 eq.) in one portion. After the mixture had stirred overnight, saturated, aqueous sodium chloride/water = 1/4 (30 mL) was added and the mixture was extracted with dichloromethane (3×15 mL). The extracts were washed with saturated, aqueous sodium chloride/water = 1/4 (2×20 mL), dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography (0 to 20% ethyl acetate in dichloromethane) to afford the title compound (563 mg, 1.42 mmol, 96%) as a red solid.

R_f = 0.42 (40% ethyl acetate in dichloromethane).

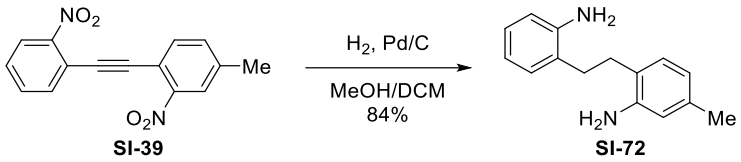
^{1}H-NMR (400 MHz, $CDCl_3$): 7.40 (dd, J = 7.8, 1.7 Hz, 1H), 7.36 (d, J = 1.7 Hz, 1H), 7.34 (d, J = 2.1 Hz, 1H), 7.31 (dd, J = 8.3, 2.1 Hz, 1H), 7.08 (d, J = 7.8 Hz, 1H), 6.44 (d, J = 8.2 Hz, 1H), 3.89 (s, 3H), 3.67 (br, 4H), 2.86 – 2.68 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 167.3, 144.4, 144.2, 138.0, 136.1, 131.0, 129.7, 129.4, 128.6, 120.4, 118.1, 116.8, 80.2, 52.1, 31.1, 30.2.

IR: 3447, 3368, 3325, 2997, 2947, 2870, 1703, 1621, 1577, 1507, 1486, 1436, 1404, 1362, 1295, 1241, 1198, 1147, 1109, 1065, 996, 907, 886, 813, 762, 730.

HRMS (ESI): $C_{16}H_{18}IN_2O_2$ [M+H] calc. 397.0407, found 397.0397.

2-(2-aminophenethyl)-5-methylaniline (SI-72)



SI-39 SI-72

Prepared from 4-methyl-2-nitro-1-((2-nitrophenyl)ethynyl)benzene (**SI-39**, 387 mg, 1.37 mmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 30% ethyl acetate in dichloromethane) to afford the title compound (260 mg, 1.15 mmol, 84%) as an off-white solid.

R_f = 0.33 (20% ethyl acetate in dichloromethane).

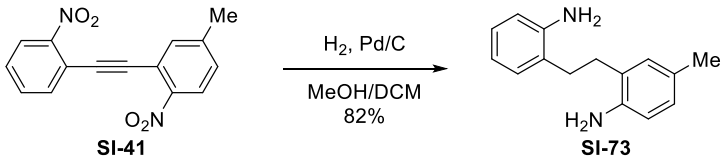
^{1}H-NMR (400 MHz, $CDCl_3$): 7.11 – 7.04 (m, 2H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.77 (td, *J* = 7.4, 1.2 Hz, 1H), 6.69 (dd, *J* = 7.9, 1.2 Hz, 1H), 6.61 – 6.57 (m, 1H), 6.52 (d, *J* = 1.7 Hz, 1H), 3.55 (br, 4H), 2.79 (s, 4H), 2.27 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 144.4, 144.3, 137.1, 129.60, 129.55, 127.3, 126.5, 123.5, 120.0, 119.1, 116.7, 116.0, 31.3, 30.8, 21.2.

IR: 3428, 3350, 3221, 3020, 3006, 2919, 2859, 1619, 1579, 1511, 1495, 1455, 1422, 1377, 1296, 1273, 1198, 1159, 1060, 1038, 997, 989, 943, 908, 863, 798, 749.

HRMS (ESI): $C_{15}H_{19}N_2$ [M+H] calc. 227.1543, found 227.1550.

2-(2-aminophenethyl)-4-methylaniline (SI-73)



SI-41 SI-73

Prepared from 4-methyl-1-nitro-2-((2-nitrophenyl)ethynyl)benzene (**SI-41**, 470 mg, 1.67 mmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 30% ethyl acetate in dichloromethane) to afford the title compound (310 mg, 1.37 mmol, 82%) as an off-white solid.

R_f = 0.25 (20% ethyl acetate in dichloromethane).

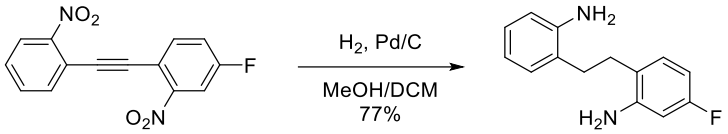
^{1}H-NMR (400 MHz, $CDCl_3$): 7.12 – 7.02 (m, 2H), 6.91 (d, J = 2.0 Hz, 1H), 6.87 (dd, J = 8.0, 2.1 Hz, 1H), 6.76 (td, J = 7.4, 1.2 Hz, 1H), 6.68 (dd, J = 7.9, 1.2 Hz, 1H), 6.60 (d, J = 7.9 Hz, 1H), 3.51 (br, 4H), 2.85 – 2.73 (m, 4H), 2.24 (s, 3H) .

^{13}C-NMR (100 MHz, $CDCl_3$): 144.5, 141.8, 130.3, 129.6, 128.4, 127.8, 127.4, 126.7, 126.5, 119.1, 116.2, 116.0, 31.4, 31.2, 20.6.

IR: 3425, 3350, 3220, 3060, 3020, 3006, 2919, 2860, 1621, 1583, 1504, 1495, 1455, 1379, 1314, 1267, 1156, 1059, 1038, 1005, 930, 907, 880, 850, 814, 749, 703.

HRMS (ESI): $C_{15}H_{19}N_2$ [M+H] calc. 227.1543, found 227.1549.

2-(2-aminophenethyl)-5-fluoroaniline (**SI-74**)



SI-43 **SI-74**

Prepared from 4-fluoro-2-nitro-1-((2-nitrophenyl)ethynyl)benzene (**SI-43**, 335 mg, 1.17 mmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 30% ethyl acetate in dichloromethane) to afford the title compound (207 mg, 899 µmol, 77%) as a grey-brown solid.

R_f = 0.38 (20% ethyl acetate in dichloromethane).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.11 – 7.02 (m, 2H), 6.97 (dd, J = 8.3, 6.4 Hz, 1H), 6.76 (td, J = 7.4, 1.3 Hz, 1H), 6.69 (dd, J = 7.8, 1.2 Hz, 1H), 6.43 (td, J = 8.4, 2.6 Hz, 1H), 6.37 (dd, J = 10.5, 2.6 Hz, 1H), 3.62 (br, 4H), 2.82 – 2.73 (m, 4H).

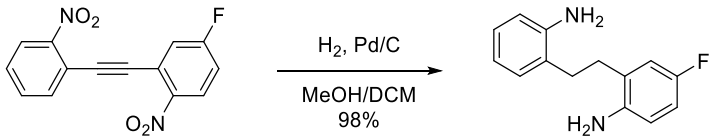
^{13}C-NMR (100 MHz, $CDCl_3$): 162.4 (d, J = 241.8 Hz), 145.9 (d, J = 10.4 Hz), 144.4, 130.7 (d, J = 9.7 Hz), 129.7, 127.5, 126.2, 121.8 (d, J = 2.7 Hz), 119.3, 116.1, 105.3 (d, J = 21.1 Hz), 102.5 (d, J = 24.5 Hz), 31.2 (d, J = 1.1 Hz), 30.4.

^{19}F-NMR (377 MHz, $CDCl_3$): -116.38 (ddd, J = 10.5, 8.5, 6.4 Hz).

IR: 3455, 3370, 3062, 3029, 2929, 2867, 2838, 1620, 1592, 1495, 1453, 1432, 1320, 1307, 1279, 1202, 1179, 1158, 1132, 1116, 1065, 1035, 1006, 990, 966, 929, 907, 837, 787, 749, 733, 709.

HRMS (ESI): $C_{14}H_{16}FN_2$ [M+H] calc. 231.1292, found 231.1293.

2-(2-aminophenethyl)-4-fluoroaniline (**SI-75**)



SI-45 **SI-75**

Prepared from 4-fluoro-1-nitro-2-((2-nitrophenyl)ethynyl)benzene (**SI-45**, 399 mg, 1.39 mmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 40% ethyl acetate in dichloromethane) to afford the title compound (315 mg, 1.37 mmol, 98%) as a brownish solid.

R_f = 0.21 (20% ethyl acetate in dichloromethane).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.09 – 7.03 (m, 2H), 6.81 (dd, J = 9.4, 2.9 Hz, 1H), 6.79 – 6.73 (m, 2H), 6.69 (dd, J = 7.8, 1.2 Hz, 1H), 6.60 (dd, J = 8.6, 4.9 Hz, 1H), 3.51 (br, 4H), 2.85 – 2.74 (m, 4H).

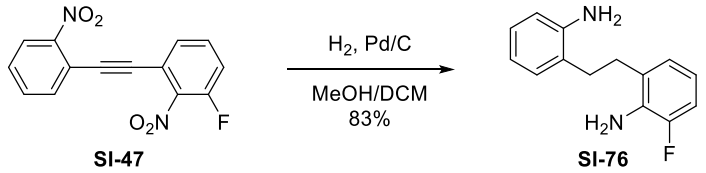
^{13}C-NMR (100 MHz, $CDCl_3$): 156.7 (d, J = 236.2 Hz), 144.4, 140.4 (d, J = 2.2 Hz), 129.7, 128.2 (d, J = 6.6 Hz), 127.6, 125.8, 119.2, 116.8 (d, J = 7.8 Hz), 116.0, 115.9 (d, J = 22.1 Hz), 113.6 (d, J = 22.1 Hz), 31.05 (d, J = 1.4 Hz), 30.98.

^{19}F-NMR (377 MHz, $CDCl_3$): -126.11 (ddd, J = 9.5, 8.2, 4.9 Hz).

IR: 3416, 3397, 3315, 3211, 3064, 3034, 2898, 2842, 1625, 1585, 1496, 1456, 1445, 1262, 1252, 1235, 1201, 1184, 1149, 1136, 1066, 1045, 957, 930, 872, 853, 813, 785, 773, 749, 718.

HRMS (ESI): $C_{14}H_{16}FN_2$ [M+H] calc. 231.1292, found 231.1295.

2-(2-aminophenethyl)-6-fluoroaniline (SI76)



Prepared from 1-fluoro-2-nitro-3-((2-nitrophenyl)ethynyl)benzene (**SI-47**, 456 mg, 1.59 mmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 20% ethyl acetate in dichloromethane) to afford the title compound (305 mg, 1.32 mmol, 83%) as a brown solid.

R_f = 0.58 (20% ethyl acetate in dichloromethane).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.10 – 7.03 (m, 2H), 6.93 – 6.85 (m, 2H), 6.76 (td, J = 7.4, 1.2 Hz, 1H), 6.72 – 6.64 (m, 2H), 3.62 (br, 4H), 2.83 (h, J = 3.1 Hz, 4H).

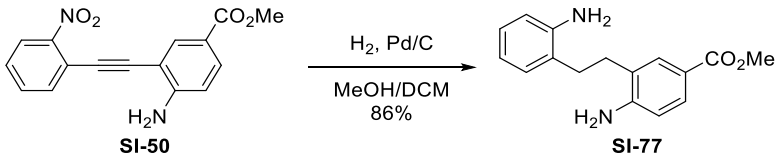
^{13}C-NMR (100 MHz, $CDCl_3$): 152.1 (d, J = 237.8 Hz), 144.3, 132.8 (d, J = 12.2 Hz), 129.7, 128.9 (d, J = 2.9 Hz), 127.5, 126.1, 124.7 (d, J = 2.9 Hz), 119.2, 118.2 (d, J = 7.8 Hz), 116.1, 113.1 (d, J = 19.2 Hz), 31.2, 30.7 (d, J = 2.9 Hz).

^{19}F-NMR (377 MHz, $CDCl_3$): -134.91 (dd, J = 10.7, 5.4 Hz).

IR: 3443, 3360, 3217, 3064, 3024, 2932, 2867, 1623, 1581, 1495, 1475, 1456, 1315, 1262, 1222, 1160, 1137, 1068, 1039, 930, 910, 880, 852, 748, 728, 704.

HRMS (ESI): $C_{14}H_{16}FN_2$ [M+H] calc. 231.1292, found 231.1295.

methyl 4-amino-3-(2-aminophenethyl)benzoate (SI-77)



Prepared from methyl 4-amino-3-((2-nitrophenyl)ethynyl)benzoate (**SI-50**, 1.48 g, 5.00 mmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 20% ethyl acetate in dichloromethane) to afford the title compound (1.16 g, 4.29 mmol, 86%) as an off-white solid.

R_f = 0.50 (40% ethyl acetate in dichloromethane).

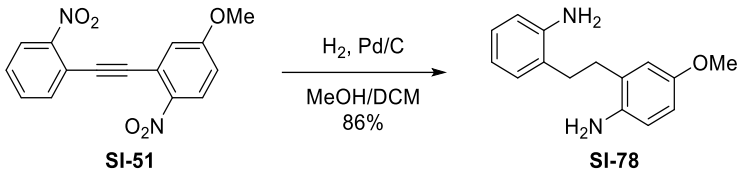
^{1}H-NMR (400 MHz, $CDCl_3$): 7.82 (d, J = 2.0 Hz, 1H), 7.74 (dd, J = 8.3, 2.1 Hz, 1H), 7.11 – 7.01 (m, 2H), 6.75 (td, J = 7.4, 1.2 Hz, 1H), 6.70 (dd, J = 7.8, 1.2 Hz, 1H), 6.62 (d, J = 8.3 Hz, 1H), 3.86 (s, 3H), 3.81 (br, 4H), 2.88 – 2.75 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 167.4, 149.2, 144.2, 131.5, 129.7, 129.6, 127.6, 126.2, 125.1, 120.1, 119.4, 116.2, 114.7, 51.8, 31.2, 30.6.

IR: 3467, 3424, 3338, 3211, 2942, 1680, 1634, 1620, 1604, 1576, 1506, 1496, 1456, 1429, 1368, 1335, 1304, 1278, 1253, 1191, 1164, 1134, 1112, 1068, 1040, 1006, 988, 956, 930, 910, 864, 850, 825, 795, 768, 751, 710.

HRMS (ESI): $C_{16}H_{19}N_2O_2$ [M+H] calc. 271.1441, found 271.1444.

2-(2-aminophenethyl)-4-methoxyaniline (SI-78)



SI-51 SI-78

Prepared from 4-methoxy-1-nitro-2-((2-nitrophenyl)ethynyl)benzene (**SI-51**, 687 mg, 2.30 mmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 50% ethyl acetate in dichloromethane) to afford the title compound (482 mg, 1.99 mmol, 86%) as a dark red oil.

R_f = 0.23 (40% ethyl acetate in dichloromethane).

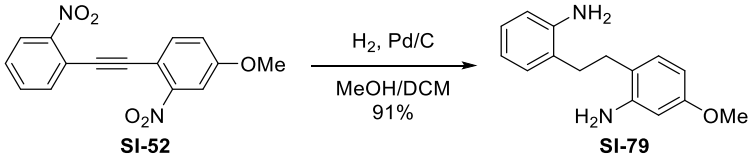
^{1}H-NMR (400 MHz, $CDCl_3$): 7.09 – 7.03 (m, 2H), 6.75 (td, J = 7.4, 1.2 Hz, 1H), 6.70 – 6.61 (m, 4H), 3.74 (s, 3H), 3.42 (br, 4H), 2.84 – 2.76 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 153.2, 144.5, 138.0, 129.7, 128.3, 127.4, 126.2, 119.1, 117.3, 115.9, 115.6, 112.6, 55.8, 31.5, 31.3.

IR: 3421, 3349, 3222, 3021, 2936, 2867, 2831, 1620, 1583, 1497, 1455, 1431, 1320, 1239, 1192, 1156, 1040, 930, 908, 813, 751.

HRMS (ESI): $C_{15}H_{19}N_2O$ [M+H] calc. 243.1492, found 243.1489.

2-(2-aminophenethyl)-5-methoxyaniline (SI-79)



SI-52 SI-79

Prepared from 4-methoxy-2-nitro-1-((2-nitrophenyl)ethynyl)benzene (**SI-52**, 397 mg, 1.33 mmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 30% ethyl acetate in dichloromethane) to afford the title compound (295 mg, 1.22 mmol, 92%) as a red oil.

R_f = 0.37 (40% ethyl acetate in dichloromethane).

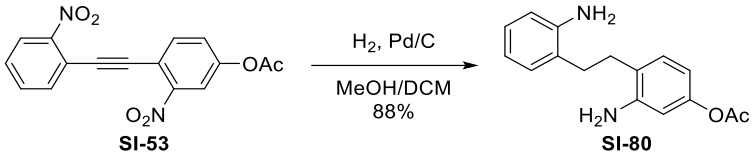
^{1}H-NMR (400 MHz, $CDCl_3$): 7.10 – 7.03 (m, 2H), 6.96 (d, J = 8.3 Hz, 1H), 6.76 (td, J = 7.5, 1.3 Hz, 1H), 6.70 – 6.65 (m, 1H), 6.32 (dd, J = 8.3, 2.5 Hz, 1H), 6.25 (d, J = 2.6 Hz, 1H), 3.76 (s, 3H), 3.54 (br, 4H), 2.84 – 2.70 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 159.2, 145.5, 144.4, 130.4, 129.7, 127.3, 126.5, 119.2, 119.0, 116.0, 104.3, 101.8, 55.3, 31.4, 30.5.

IR: 3432, 3358, 3223, 3062, 3021, 3002, 2935, 2864, 2834, 1618, 1582, 1509, 1496, 1455, 1320, 1292, 1208, 1163, 1078, 1030, 986, 958, 943, 909, 836, 789, 751, 704.

HRMS (ESI): $C_{15}H_{19}N_2O$ [M+H] calc. 243.1492, found 243.1495.

3-amino-4-(2-aminophenethyl)phenyl acetate (SI-80)



Prepared from 3-nitro-4-((2-nitrophenyl)ethynyl)phenyl acetate (**SI-53**, 925 mg, 2.84 mmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 25% ethyl acetate in dichloromethane) to afford the title compound (678 mg, 2.51 mmol, 88%) as a brown solid.

R_f = 0.39 (40% ethyl acetate in dichloromethane).

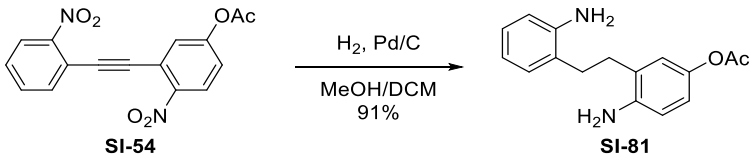
^{1}H-NMR (400 MHz, $CDCl_3$): 7.09 – 7.02 (m, 3H), 6.75 (td, J = 7.4, 1.2 Hz, 1H), 6.68 (dd, J = 8.2, 1.2 Hz, 1H), 6.46 (dd, J = 8.2, 2.3 Hz, 1H), 6.41 (d, J = 2.3 Hz, 1H), 3.63 (br, 4H), 2.83 – 2.72 (m, 4H), 2.27 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 169.8, 150.0, 145.5, 144.4, 130.2, 129.6, 127.5, 126.2, 123.9, 119.2, 116.0, 111.7, 108.8, 31.0, 30.6, 21.3.

IR: 3433, 3366, 3323, 2935, 1749, 1623, 1606, 1590, 1498, 1456, 1431, 1369, 1318, 1280, 1217, 1180, 1156, 1042, 1014, 990, 972, 932, 906, 850, 800, 752, 707.

HRMS (ESI): $C_{16}H_{19}N_2O_2$ [M+H] calc. 271.1441, found 271.1441.

4-amino-3-(2-aminophenethyl)phenyl acetate (SI-81)



Prepared from 4-nitro-3-((2-nitrophenyl)ethynyl)phenyl acetate (**SI-54**, 789 mg, 2.42 mmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 50% ethyl acetate in dichloromethane) to afford the title compound (597 mg, 2.21 mmol, 91%) as an off-white solid.

R_f = 0.34 (40% ethyl acetate in dichloromethane).

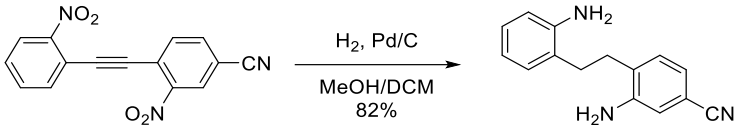
^{1}H-NMR (400 MHz, $CDCl_3$): 7.08 – 7.03 (m, 2H), 6.82 (d, J = 2.7 Hz, 1H), 6.79 – 6.73 (m, 2H), 6.68 (dd, J = 8.3, 1.2 Hz, 1H), 6.64 (d, J = 8.5 Hz, 1H), 3.55 (br, 4H), 2.84 – 2.72 (m, 4H), 2.26 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 170.3, 144.4, 143.2, 142.3, 129.7, 127.5, 127.4, 126.0, 122.3, 120.2, 119.2, 116.4, 116.1, 31.0, 30.9, 21.2.

IR: 3432, 3361, 3229, 3063, 3024, 2935, 2869, 1748, 1624, 1583, 1497, 1456, 1430, 1368, 1317, 1208, 1150, 1041, 1015, 960, 933, 907, 819, 752.

HRMS (ESI): $C_{16}H_{19}N_2O_2$ [M+H] calc. 271.1441, found 271.1444.

3-amino-4-(2-aminophenethyl)benzonitrile (SI-82)



Prepared from 3-nitro-4-((2-nitrophenyl)ethynyl)benzonitrile (**SI-55**, 655 mg, 2.23 mmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 20% ethyl acetate in dichloromethane) to afford the title compound (434 mg, 1.83 mmol, 82%) as a faint red solid.

R_f = 0.33 (20% ethyl acetate in dichloromethane).

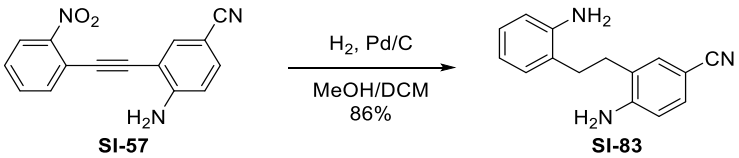
^{1}H-NMR (400 MHz, $CDCl_3$): 7.10 (d, J = 7.8 Hz, 1H), 7.07 (td, J = 7.8, 1.5 Hz, 2H), 6.99 (ddd, J = 8.7, 7.5, 1.6 Hz, 2H), 6.88 (d, J = 1.6 Hz, 1H), 6.74 (td, J = 7.5, 1.2 Hz, 1H), 6.70 (dd, J = 7.9, 1.2 Hz, 1H), 3.71 (br, 4H), 2.89 – 2.75 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 145.2, 144.2, 131.4, 130.4, 129.7, 127.8, 125.5, 122.5, 119.5, 119.4, 118.2, 116.2, 110.8, 30.8, 30.7.

IR: 3453, 3368, 3227, 3063, 3030, 2941, 2870, 2224, 1624, 1583, 1570, 1497, 1456, 1421, 1318, 1289, 1190, 1158, 1142, 1060, 1040, 992, 957, 937, 908, 869, 804, 753.

HRMS (ESI): $C_{15}H_{16}N_3$ [M+H] calc. 238.1339, found 238.1348.

4-amino-3-(2-aminophenethyl)benzonitrile (SI-83)



Prepared from 4-amino-3-((2-nitrophenyl)ethynyl)benzonitrile (**SI-57**, 1.21 g, 4.60 mmol) according to the general hydrogenation procedure.
The crude was purified by precipitation from dichloromethane solution by addition of hexanes to afford the title compound (810 mg, 3.41 mmol, 74%) as an off-white solid. Additional material was isolated from the mother liquors of the precipitation. The solvent was removed under reduced pressure and the residue purified by column chromatography (0 to 20% ethyl acetate in dichloromethane) to obtain additional product (127 mg, 535 µmol, 12%) in the form of an off-white solid.

R_f = 0.39 (20% ethyl acetate in dichloromethane).

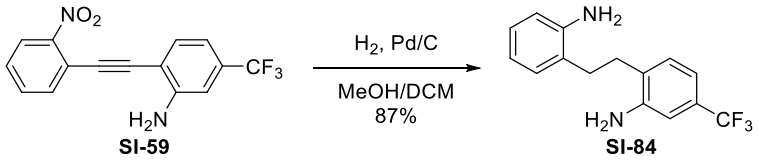
^{1}H-NMR (400 MHz, $CDCl_3$): 7.34 – 7.30 (m, 2H), 7.07 (td, J = 7.6, 1.6 Hz, 1H), 6.98 (dd, J = 7.5, 1.6 Hz, 1H), 6.74 (td, J = 7.4, 1.2 Hz, 1H), 6.70 (dd, J = 7.9, 1.2 Hz, 1H), 6.61 (d, J = 8.2 Hz, 1H), 4.07 (br, 2H), 3.52 (br, 2H), 2.83 – 2.74 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 148.8, 144.1, 133.6, 131.8, 129.8, 127.8, 126.0, 125.6, 120.3, 119.5, 116.4, 115.2, 100.7, 30.8, 30.2.

IR: 3463, 3374, 3224, 3063, 3032, 2941, 2909, 2869, 2215, 1626, 1604, 1584, 1572, 1503, 1456, 1427, 1305, 1273, 1233, 1215, 1162, 1135, 1068, 1042, 929, 896, 855, 825, 753, 728, 711.

HRMS (ESI): $C_{15}H_{16}N_3$ [M+H] calc. 238.1339, found 238.1348.

2-(2-aminophenethyl)-5-(trifluoromethyl)aniline (SI-84)



Prepared from 2-((2-nitrophenyl)ethynyl)-5-(trifluoromethyl)aniline (**SI-59**, 367 mg, 1.20 mmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 10% ethyl acetate in dichloromethane) to afford the title compound (292 mg, 1.04 mmol, 87%) as a light-brown solid.

R_f = 0.43 (20% ethyl acetate in dichloromethane).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.14 (d, J = 7.8 Hz, 1H), 7.07 (td, J = 7.6, 1.6 Hz, 1H), 7.03 (dd, J = 7.5, 1.6 Hz, 1H), 6.97 (ddd, J = 7.8, 1.9, 0.8 Hz, 1H), 6.88 (d, J = 1.8 Hz, 1H), 6.75 (td, J = 7.4, 1.2 Hz, 1H), 6.70 (dd, J = 7.9, 1.2 Hz, 1H), 3.70 (br, 4H), 2.89 – 2.74 (m, 4H).

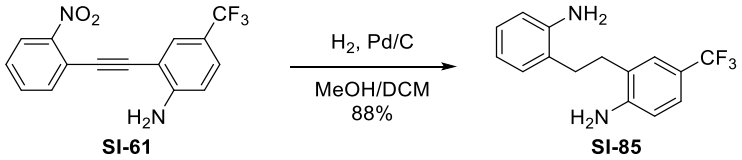
^{13}C-NMR (100 MHz, $CDCl_3$): 144.8, 144.3, 130.0, 129.8 (q, J = 1.3 Hz), 129.7, 129.6 (q, J = 32.1 Hz), 127.6, 125.8, 124.4 (q, J = 272.0 Hz), 119.4, 116.2, 115.4 (q, J = 4.0 Hz), 112.1 (q, J = 3.8 Hz), 30.82, 30.78.

^{19}F-NMR (377 MHz, $CDCl_3$): -62.54 (s).

IR: 3411, 3396, 3310, 3194, 3065, 3051, 2900, 1625, 1586, 1512, 1496, 1458, 1436, 1428, 1331, 1297, 1252, 1187, 1161, 1093, 1062, 1047, 987, 964, 920, 883, 811, 788, 750.

HRMS (ESI): $C_{15}H_{16}F_3N_2$ [M+H] calc. 281.1260, found 281.1262.

2-(2-aminophenethyl)-4-(trifluoromethyl)aniline (SI-85)



Prepared from 2-((2-nitrophenyl)ethynyl)-4-(trifluoromethyl)aniline (**SI-61**, 353 mg, 1.15 mmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 10% ethyl acetate in dichloromethane) to afford the title compound (284 mg, 1.01 mmol, 88%) as a white solid.

R_f = 0.40 (20% ethyl acetate in dichloromethane).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.32 – 7.27 (m, 2H), 7.07 (td, J = 7.6, 1.6 Hz, 1H), 7.03 (dd, J = 7.6, 1.5 Hz, 1H), 6.75 (td, J = 7.4, 1.2 Hz, 1H), 6.70 (dd, J = 7.9, 1.2 Hz, 1H), 6.67 (d, J = 8.2 Hz, 1H), 3.76 (br, 4H), 2.81 (s, 4H).

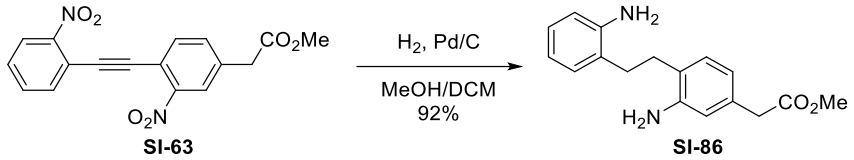
^{13}C-NMR (100 MHz, $CDCl_3$): 147.6 (q, J = 1.2 Hz), 144.2, 129.7, 127.7, 126.7 (q, J = 3.8 Hz), 125.9, 125.7, 125.0 (q, J = 270.7 Hz), 124.6 (q, J = 3.9 Hz), 120.6 (q, J = 32.3 Hz), 119.4, 116.2, 115.0, 31.0, 30.7.

^{19}F-NMR (377 MHz, $CDCl_3$): -61.08 (s).

IR: 3421, 3322, 3256, 3209, 2902, 1626, 1587, 1511, 1498, 1458, 1426, 1330, 1294, 1263, 1248, 1185, 1139, 1095, 1077, 933, 907, 895, 862, 831, 791, 757, 737, 703.

HRMS (ESI): $C_{15}H_{16}F_3N_2$ [M+H] calc. 281.1260, found 281.1260.

methyl 2-(3-amino-4-(2-aminophenethyl)phenyl)acetate (SI-86)



Prepared from methyl 2-(3-nitro-4-((2-nitrophenyl)ethynyl)phenyl)acetate (**SI 63**, 803 mg, 2.36 mmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 40% ethyl acetate in dichloromethane) to afford the title compound (617 mg, 2.17 mmol, 92%) as a yellowish oil that solidified upon standing a room temperature to form an off-white solid.

R_f = 0.32 (40% ethyl acetate in dichloromethane).

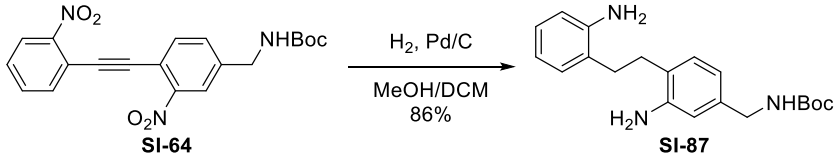
^{1}H-NMR (400 MHz, $CDCl_3$): 7.09 – 7.03 (m, 2H), 7.02 (d, J = 7.6 Hz, 1H), 6.75 (td, J = 7.4, 1.2 Hz, 1H), 6.70 – 6.64 (m, 2H), 6.61 (d, J = 1.8 Hz, 1H), 3.69 (s, 3H), 3.58 (br, 4H), 3.52 (s, 2H), 2.88 – 2.69 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 172.4, 144.6, 144.4, 133.1, 129.8, 129.6, 127.4, 126.3, 125.3, 119.9, 119.2, 116.6, 116.0, 52.1, 41.0, 31.1, 30.8.

IR: 3435, 3363, 3230, 3061, 3020, 2949, 2867, 1727, 1623, 1580, 1554, 1511, 1496, 1455, 1433, 1195, 1155, 1060, 1039, 1013, 968, 933, 904, 850, 752.

HRMS (ESI): $C_{17}H_{21}N_2O_2$ [M+H] calc. 285.1598, found 285.1601.

tert-butyl (3-amino-4-(2-aminophenethyl)benzyl)carbamate (SI-87)



Prepared from *tert*-butyl (3-nitro-4-((2-nitrophenyl)ethynyl)benzyl)carbamate (**SI-64**, 409 mg, 1.03 mmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 20% ethyl acetate in dichloromethane) to afford the title compound (303 mg, 887 µmol, 86%) as a reddish solid.

R_f = 0.21 (40% ethyl acetate in dichloromethane).

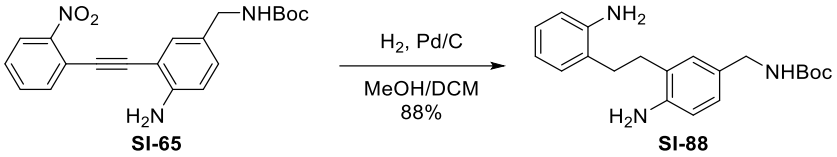
^{1}H-NMR (400 MHz, $CDCl_3$): 7.10 – 7.03 (m, 2H), 7.02 (d, J = 7.7 Hz, 1H), 6.75 (td, J = 7.4, 1.2 Hz, 1H), 6.68 (dd, J = 8.2, 1.2 Hz, 1H), 6.65 (dd, J = 7.6, 1.7 Hz, 1H), 6.60 (s, 1H), 4.77 (br, 1H), 4.21 (d, J = 5.9 Hz, 2H), 3.58 (br, 4H), 2.78 (s, 4H), 1.47 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): 156.0, 144.7, 144.4, 138.2, 129.9, 129.6, 127.4, 126.3, 125.5, 119.2, 118.1, 116.0, 115.0, 79.5, 44.6, 31.1, 30.8, 28.6.

IR: 3405, 3344, 3233, 3021, 3004, 2977, 2931, 2868, 1693, 1623, 1581, 1509, 1497, 1455, 1432, 1391, 1366, 1271, 1249, 1163, 1046, 1029, 989, 967, 930, 910, 866, 751, 731.

HRMS (ESI): $C_{20}H_{28}N_3O_2$ [M+H] calc. 342.2176, found 342.2173.

tert-butyl (4-amino-3-(2-aminophenethyl)benzyl)carbamate (SI-88)



Prepared from *tert*-butyl (4-amino-3-((2-nitrophenyl)ethynyl)benzyl)carbamate (**SI-65**, 310 mg, 844 µmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 40% ethyl acetate in dichloromethane) to afford the title compound (255 mg, 747 µmol, 89%) as a brownish-yellow foam.

R_f = 0.30 (40% ethyl acetate in dichloromethane).

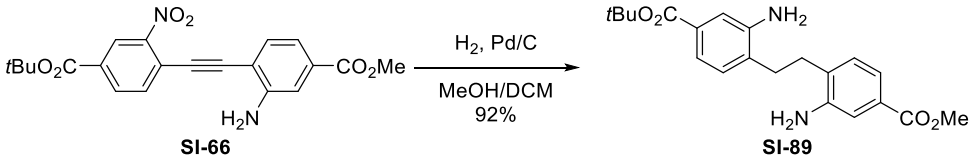
^{1}H-NMR (400 MHz, $CDCl_3$): 7.10 – 7.01 (m, 2H), 6.99 – 6.92 (m, 2H), 6.74 (td, J = 7.4, 1.3 Hz, 1H), 6.68 (dd, J = 7.8, 1.2 Hz, 1H), 6.63 (d, J = 7.9 Hz, 1H), 4.66 (br, 1H), 4.17 (d, J = 5.6 Hz, 2H), 3.59 (br, 4H), 2.78 (s, 4H), 1.47 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): 155.9, 144.4, 143.7, 129.7, 129.3, 129.2, 127.5, 126.9, 126.5, 126.2, 119.2, 116.04, 115.99, 79.4, 44.5, 31.11, 31.07, 28.6.

IR: 3352, 3005, 2976, 2931, 2867, 1692, 1623, 1583, 1497, 1455, 1433, 1391, 1365, 1268, 1247, 1159, 1045, 1027, 909, 860, 823, 750, 729.

HRMS (ESI): $C_{20}H_{28}N_3O_2$ [M+H] calc. 342.2176, found 342.2173.

tert-butyl 3-amino-4-(2-amino-4-(methoxycarbonyl)phenethyl)benzoate (SI-89)



Prepared from *tert*-butyl 4-((2-amino-4-(methoxycarbonyl)phenyl)ethynyl)-3-nitrobenzoate (**SI-66**, 1.22 g, 3.08 mmol) according to the general hydrogenation procedure. The crude was purified by column chromatography (0 to 25% ethyl acetate in dichloromethane) to afford the title compound (1.05 g, 2.83 mmol, 92%) as a yellowish solid.

R_f = 0.48 (40% ethyl acetate in dichloromethane).

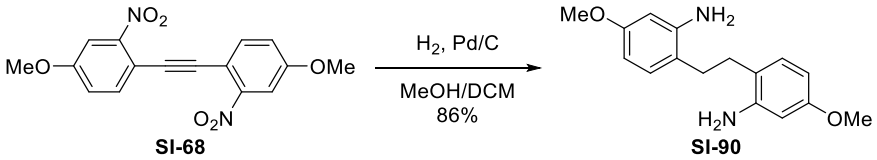
^{1}H-NMR (400 MHz, $CDCl_3$): 7.38 (dd, J = 7.8, 1.7 Hz, 1H), 7.34 (dd, J = 7.8, 1.7 Hz, 1H), 7.33 (d, J = 1.7 Hz, 1H), 7.28 (d, J = 1.7 Hz, 1H), 7.06 (d, J = 7.8 Hz, 1H), 7.02 (d, J = 7.8 Hz, 1H), 3.88 (s, 3H), 3.69 (br, 4H), 2.84 (s, 4H), 1.57 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): 167.4, 166.0, 144.5, 144.3, 131.3, 131.0, 130.4, 129.8, 129.7, 129.4, 120.34, 120.29, 116.8, 116.7, 80.9, 52.1, 30.81, 30.77, 28.3.

IR: 3450, 3368, 3234, 2976, 2950, 2934, 1698, 1625, 1577, 1507, 1477, 1437, 1427, 1392, 1368, 1297, 1243, 1165, 1110, 1068, 998, 956, 908, 889, 849, 827, 796, 786, 764, 732.

HRMS (ESI): $C_{21}H_{27}N_2O_4$ [M+H] calc. 371.1965, found 371.1954.

6,6'-(ethane-1,2-diyl)bis(3-methoxyaniline) (SI-90)



SI-68 SI-90

Prepared from 1,2-bis(4-methoxy-2-nitrophenyl)ethyne (**SI-68**, 628 mg, 1.91 mmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 40% ethyl acetate in dichloromethane) to afford the title compound (447 mg, 1.64 mmol, 86%) as a brownish-yellow solid.

R_f = 0.34 (40% ethyl acetate in dichloromethane).

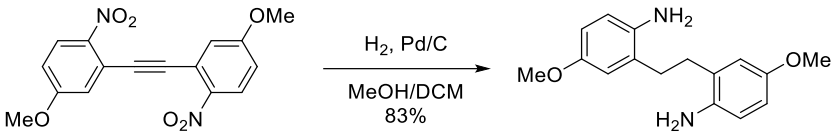
^{1}H-NMR (400 MHz, $CDCl_3$): 6.95 (d, J = 8.3 Hz, 2H), 6.32 (dd, J = 8.2, 2.6 Hz, 2H), 6.24 (d, J = 2.5 Hz, 2H), 3.76 (s, 6H), 3.57 (br, 4H), 2.71 (s, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 159.2, 145.5, 130.5, 119.1, 104.2, 101.8, 55.3, 30.8.

IR: 3447, 3365, 3004, 2962, 2934, 2862, 2835, 1623, 1612, 1586, 1509, 1465, 1455, 1445, 1425, 1330, 1293, 1265, 1251, 1212, 1168, 1154, 1138, 1081, 1066, 1025, 959, 939, 909, 833, 799, 770, 758, 736, 718.

HRMS (ESI): $C_{16}H_{21}N_2O_2$ [M+H] calc. 273.1598, found 273.1597.

2,2'-(ethane-1,2-diyl)bis(4-methoxyaniline) (SI-91)



SI-69 SI-91

Prepared from 1,2-bis(5-methoxy-2-nitrophenyl)ethyne (**SI-69**, 690 mg, 2.10 mmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 5% methanol in dichloromethane) to afford the title compound (474 mg, 1.74 mmol, 83%) as a grey-brown solid.

R_f = 0.13 (40% ethyl acetate in dichloromethane).

^{1}H-NMR (400 MHz, $CDCl_3$): 6.77 – 6.54 (m, 6H), 3.73 (s, 6H), 3.32 (br, 4H), 2.78 (s, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 153.2, 138.0, 128.1, 117.2, 115.6, 112.6, 55.9, 31.6.

^{1}H-NMR (600 MHz, DMSO-d_6): 6.63 (s, 2H), 6.58 (d, J = 8.5 Hz, 2H), 6.53 (d, J = 8.4 Hz, 2H), 4.42 (s, 4H), 3.61 (s, 6H), 2.63 (s, 4H).

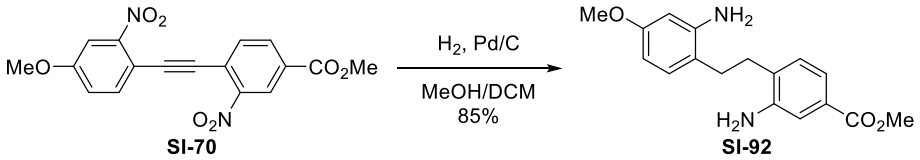
^{13}C-NMR (150 MHz, DMSO-d_6): 151.06, 139.74, 126.96, 115.67, 115.05, 111.82, 55.23, 30.14.

IR: 3417, 3355, 3221, 2998, 2938, 2832, 1610, 1587, 1501, 1465, 1450, 1431, 1323, 1274, 1240, 1212, 1155, 1039, 933, 852, 813, 734, 714.

HRMS (ESI): $C_{16}H_{21}N_2O_2$ [M+H] calc. 273.1598, found 273.1597.

The spectroscopic data agrees with previously reported values.[16]

methyl 3-amino-4-(2-amino-4-methoxyphenethyl)benzoate (SI-92)



Prepared from methyl 4-((4-methoxy-2-nitrophenyl)ethynyl)-3-nitrobenzoate (**SI-70**, 704 mg, 1.98 mmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 50% ethyl acetate in dichloromethane) to afford the title compound (502 mg, 1.67 mmol, 85%) as an off-white solid.

R_f = 0.36 (40% ethyl acetate in dichloromethane).

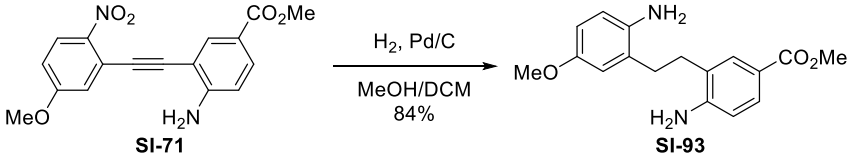
^{1}H-NMR (400 MHz, $CDCl_3$): 7.40 (dd, J = 7.8, 1.7 Hz, 1H), 7.33 (d, J = 1.7 Hz, 1H), 7.09 (d, J = 7.8 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 6.29 (dd, J = 8.3, 2.5 Hz, 1H), 6.24 (d, J = 2.5 Hz, 1H), 3.88 (s, 3H), 3.75 (s, 3H), 3.63 (br, 4H), 2.85 – 2.72 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 167.4, 159.3, 145.4, 144.6, 131.7, 130.5, 129.7, 129.1, 120.3, 118.4, 116.7, 104.3, 101.8, 55.3, 52.1, 31.4, 30.2.

IR: 3442, 3366, 3229, 2999, 2948, 2835, 1704, 1620, 1577, 1508, 1464, 1436, 1293, 1240, 1205, 1165, 1144, 1109, 1031, 996, 958, 908, 888, 832, 794, 762, 729.

HRMS (ESI): $C_{17}H_{21}N_2O_3$ [M+H] calc. 301.1547, found 301.1553.

methyl 4-amino-3-(2-amino-5-methoxyphenethyl)benzoate (SI-93)



Prepared from methyl 4-amino-3-((5-methoxy-2-nitrophenyl)ethynyl)benzoate (**SI-71**, 791 mg, 2.42 mmol) according to the general hydrogenation procedure.
The crude was purified by column chromatography (0 to 25% ethyl acetate in dichloromethane) to afford the title compound (614 mg, 2.04 mmol, 84%) as an off-white solid.

R_f = 0.33 (40% ethyl acetate in dichloromethane).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.81 (d, J = 2.0 Hz, 1H), 7.74 (dd, J = 8.3, 2.1 Hz, 1H), 6.69 – 6.63 (m, 3H), 6.62 (d, J = 8.3 Hz, 1H), 3.95 (br, 2H), 3.86 (s, 3H), 3.72 (s, 3H), 3.55 (br, 2H), 2.80 (s, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 167.4, 153.4, 149.2, 137.7, 131.5, 129.6, 128.3, 124.9, 120.0, 117.7, 115.6, 114.6, 112.7, 55.8, 51.7, 31.6, 30.8.

IR: 3431, 3407, 3340, 3240, 2988, 2951, 2832, 1684, 1640, 1606, 1587, 1503, 1468, 1448, 1437, 1334, 1298, 1252, 1221, 1197, 1155, 1114, 1069, 1052, 1037, 999, 929, 906, 857, 827, 806, 768, 735, 708.

HRMS (ESI): $C_{17}H_{21}N_2O_3$ [M+H] calc. 301.1547, found 301.1547.

Syntheses of diazocines[a]

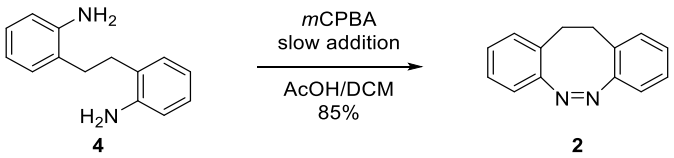
General procedure – slow addition

A freshly prepared and titrated (0.57 – 0.62 M) solution of *m*CPBA (500 µmol, 2.0 eq.) in acetic acid was added by syringe pump within a period of 12 hours under rapid stirring to a solution of a 2,2'-ethylenedianiline substrate (250 µmol, 1.0 eq.) in acetic acid/dichloromethane = 1/3 (6.25 mL). After the complete addition of the *m*CPBA solution, the mixture was stirred for at least one more hour. The solvent was then removed under reduced pressure, the residue taken up in ethyl acetate (10 mL) and washed with saturated, aqueous sodium hydrogen carbonate (2×5 mL), followed by saturated, aqueous sodium chloride (5 mL). The solution was dried over sodium sulfate, the solvent was removed under reduced pressure and the residue was purified by column chromatography as specified.

General procedure – one-batch addition

A freshly prepared and titrated (0.57 – 0.62 M) solution of *m*CPBA (500 µmol, 2.0 eq.) in acetic acid was added in one batch to a solution of a 2,2'-ethylenedianiline substrate (250 µmol, 1.0 eq.) in acetic acid/toluene = 1/3 (6.25 mL). The mixture was stirred for 15 minutes, then warmed to 80 °C and stirred overnight. The solvent was then removed under reduced pressure, the residue taken up in ethyl acetate (10 mL) and washed with saturated, aqueous sodium hydrogen carbonate (2×5 mL) followed by saturated, aqueous sodium chloride (5 mL). The solution was dried over sodium sulfate, the solvent was removed under reduced pressure and the residue was purified by column chromatography as specified.

(Z)-11,12-dihydrodibenzo[c,g][1,2]diazocine (**2**)



Prepared from 2,2'-ethylenedianiline (**4**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 5% ethyl acetate in hexanes) to afford the title compound (44.2 mg, 212 µmol, 85%) as a yellow solid after purification.

R_f = 0.44 (10% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.13 (ddd, J = 7.8, 7.0, 1.8 Hz, 2H), 7.01 (td, J = 7.3, 1.3 Hz, 2H), 6.97 (dd, J = 7.7, 1.7 Hz, 2H), 6.82 (dd, J = 7.8, 1.2 Hz, 2H), 3.09 – 2.68 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 155.6, 129.7, 128.2, 127.2, 126.8, 118.8, 31.8.

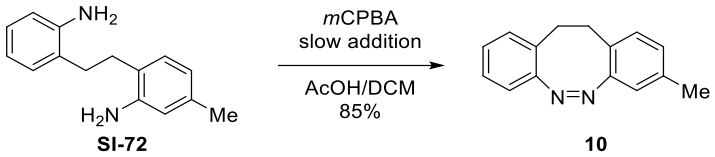
IR: 3072, 3057, 3021, 2959, 2892, 2860, 1801, 1570, 1519, 1479, 1443, 1156, 1089, 1038, 975, 942, 857, 805, 763, 742.

HRMS (ESI): $C_{14}H_{13}N_2$ [M+H] calc. 209.1073, found 209.1080.

The spectroscopic data agrees with previously reported values.[18]

[a]While we did not observe any related issues in our experiments, we want to point out the potential explosion hazard of concentrated solutions of *m*CPBA[17] and do not recommend using solutions with a higher concentration than 0.6 M. We advise caution when preparing and handling solutions of *m*CPBA.

(Z)-3-methyl-11,12-dihydrodibenzo[c,g][1,2]diazocine (**10**)



Prepared from 2-(2-aminophenethyl)-5-methylaniline (**SI-72**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 5% ethyl acetate in hexanes) to afford the title compound (47.1 mg, 212 µmol, 85%) as a brown-yellow solid.

R_f = 0.43 (10% ethyl acetate in hexanes).

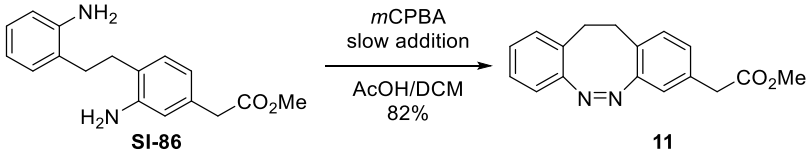
^{1}H-NMR (400 MHz, $CDCl_3$): 7.13 (ddd, J = 7.7, 7.0, 1.8 Hz, 1H), 7.02 (td, J = 7.3, 1.3 Hz, 1H), 6.98 (dd, J = 7.6, 1.8 Hz, 1H), 6.87 – 6.82 (m, 2H), 6.80 (ddd, J = 7.7, 1.8, 0.7 Hz, 1H), 6.65 – 6.62 (m, 1H), 3.07 – 2.60 (m, 4H), 2.23 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 155.6, 155.5, 136.6, 129.68, 129.66, 128.4, 128.0, 127.1, 126.7, 125.0, 119.3, 118.9, 31.8, 31.6, 21.1.

IR: 3063, 3041, 3018, 2945, 2920, 2896, 2852, 1612, 1571, 1519, 1495, 1479, 1456, 1446, 1379, 1169, 1158, 1143, 1087, 1038, 979, 947, 934, 896, 884, 849, 810, 752, 722.

HRMS (ESI): $C_{15}H_{15}N_2$ [M+H] calc. 223.1230, found 223.1230.

methyl (Z)-2-(11,12-dihydrodibenzo[c,g][1,2]diazocin-3-yl)acetate (**11**)



Prepared methyl 2-(3-amino-4-(2-aminophenethyl)phenyl)acetate (**SI-86**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 15% ethyl acetate in hexanes) to afford the title compound (57.5 mg, 205 µmol, 82%) as a yellow oil.

R_f = 0.27 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.13 (td, *J* = 7.4, 1.6 Hz, 1H), 7.02 (td, *J* = 7.4, 1.3 Hz, 1H), 6.98 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.95 – 6.90 (m, 2H), 6.83 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.75 (d, *J* = 1.4 Hz, 1H), 3.65 (s, 3H), 3.50 (s, 2H), 3.07 – 2.68 (m, 4H).

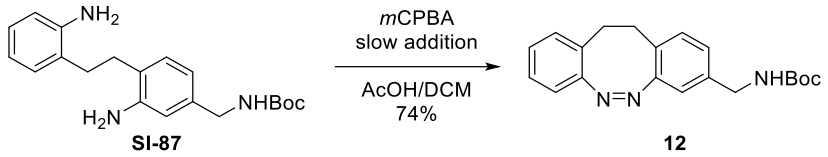
^{13}C-NMR (100 MHz, $CDCl_3$): 171.6, 155.5,[a] 132.7, 130.1, 129.7, 128.11, 128.05, 127.2, 127.1, 126.8, 119.8, 118.9, 52.2, 40.6, 31.7, 31.6.

IR: 3063, 3045, 2950, 2899, 2847, 1735, 1612, 1569, 1520, 1494, 1479, 1458, 1435, 1417, 1340, 1258, 1194, 1161, 1088, 1037, 1014, 949, 934, 908, 896, 851, 822, 791, 754, 722.

HRMS (ESI): $C_{17}H_{17}N_2O_2$ [M+H] calc. 281.1285, found 281.1282.

[a]The 155.5 ppm signal is corresponding to two carbons.

tert-butyl (Z)-((11,12-dihydrodibenzo[c,g][1,2]diazocin-3-yl)methyl)carbamate (**12**)



SI-87 **12**

Prepared from *tert*-butyl (3-amino-4-(2-aminophenethyl)benzyl)carbamate (**SI-87**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 30% ethyl acetate in hexanes) to afford the title compound (62.8 mg, 186 µmol, 74%) as a brownish-yellow solid.

R_f = 0.22 (20% ethyl acetate in hexanes).

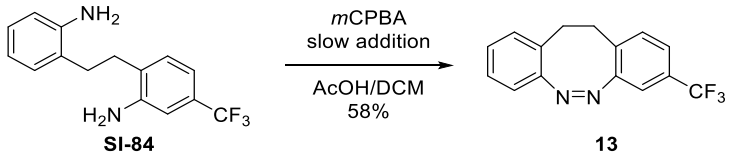
^{1}H-NMR (400 MHz, $CDCl_3$): 7.13 (td, J = 7.5, 1.6 Hz, 1H), 7.01 (td, J = 7.4, 1.3 Hz, 1H), 6.97 (dd, J = 7.6, 1.6 Hz, 1H), 6.95 – 6.90 (m, 2H), 6.83 (dd, J = 7.8, 1.3 Hz, 1H), 6.74 (s, 1H), 4.77 (br, 1H), 4.44 – 4.04 (m, 2H), 3.07 – 2.67 (m, 4H), 1.44 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): 155.9, 155.6, 155.5, 137.9, 130.1, 129.7, 128.1, 127.24, 127.19, 126.9, 126.2, 119.0, 117.8, 79.8, 44.1, 31.7, 31.6, 28.5.

IR: 3337, 3064, 3003, 2975, 2927, 2871, 2854, 1693, 1612, 1568, 1479, 1455, 1415, 1391, 1365, 1334, 1269, 1248, 1165, 1103, 1087, 1048, 1028, 946, 911, 887, 862, 819, 782, 753, 730.

HRMS (ESI): $C_{20}H_{24}N_3O_2$ [M+H] calc. 338.1863, found 338.1877.

(Z)-3-(trifluoromethyl)-11,12-dihydrodibenzo[c,g][1,2]diazocine (**13**)



SI-84 **13**

Prepared from 2-(2-aminophenethyl)-5-(trifluoromethyl)aniline (**SI-84**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 10% ethyl acetate in hexanes) to afford the title compound (40.0 mg, 145 µmol, 58%) as a brownish-yellow solid.

R_f = 0.41 (10% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.27 (d, J = 7.9 Hz, 1H), 7.17 (td, J = 7.6, 1.5 Hz, 1H), 7.11 (d, J = 8.1 Hz, 1H), 7.08 (s, 1H), 7.04 (td, J = 7.5, 1.3 Hz, 1H), 6.99 (d, J = 7.0 Hz, 1H), 6.86 (dd, J = 7.8, 1.3 Hz, 1H), 3.14 – 2.65 (m, 4H).

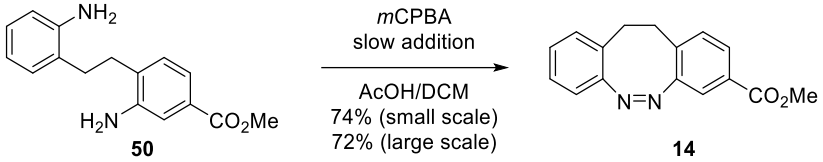
^{13}C-NMR (100 MHz, $CDCl_3$): 155.4, 155.3, 132.5 (q, J = 1.3 Hz), 130.5, 129.8, 129.4 (q, J = 33.0 Hz), 127.6, 127.4, 127.3, 123.9 (q, J = 3.7 Hz), 123.7 (q, J = 272.3 Hz), 118.9, 116.3 (q, J = 3.9 Hz), 31.9, 31.4.

^{19}F-NMR (377 MHz, $CDCl_3$): -62.63 (s).

IR: 1617, 1522, 1507, 1498, 1479, 1458, 1444, 1437, 1411, 1326, 1272, 1212, 1170, 1155, 1123, 1090, 1072, 1038, 980, 947, 929, 898, 872, 847, 826, 753, 724.

HRMS (ESI): $C_{15}H_{12}F_3N_2$ [M+H] calc. 277.0947, found 277.0953.

methyl (Z)-11,12-dihydrodibenzo[c,g][1,2]diazocine-3-carboxylate (**14**)



Small scale: Prepared from methyl 3-amino-4-(2-aminophen-ethyl)benzoate (**50**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 20% ethyl acetate in hexanes) to afford the title compound (49.0 mg, 184 µmol, 74%) as a yellow solid.

Large scale: Prepared from methyl 3-amino-4-(2-aminophen-ethyl)benzoate (**50**, 1.16 g, 4.29 mmol) according to the general procedure with slow addition of *m*CPBA. The reaction vessel and amount of *m*CPBA-solution/solvent were scaled accordingly and the workup/purification were modified as follows:
After removal of the solvent, the residue was taken up in ethyl acetate (70 mL), washed with saturated, aqueous sodium hydrogen carbonate (2×60 mL), saturated, aqueous sodium chloride (60 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography[a] (0 to 15% ethyl acetate in hexanes) to afford a fraction of impure product and clean title compound (564 mg, 2.12 mmol, 49%) as a yellow solid. Additional product (189 mg, 710 µmol, 17%) in the form of a yellow solid could be isolated from the impure fraction by precipitation from dichloromethane solution by addition of hexanes. The mother liquors of the precipitation were concentrated under reduced pressure and the residue purified by column chromatography (0 to 15% ethyl acetate in hexanes) to afford further title compound (65 mg, 0.24 mmol, 6%) as a yellow solid.

$\mathbf{R_f}$ = 0.21 (10% ethyl acetate in hexanes).

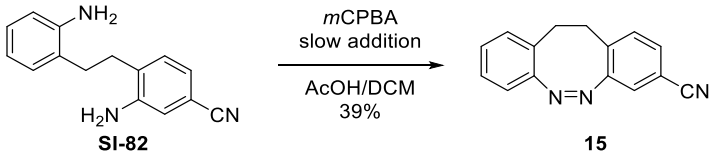
^{1}H-NMR (400 MHz, $CDCl_3$): 7.68 (dd, J = 7.9, 1.8 Hz, 1H), 7.49 (d, J = 1.7 Hz, 1H), 7.13 (td, J = 7.5, 1.6 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.01 (td, J = 7.4, 1.3 Hz, 1H), 6.96 (dd, J = 7.7, 1.5 Hz, 1H), 6.84 (dd, J = 7.7, 1.3 Hz, 1H), 3.85 (s, 3H), 3.08 – 2.70 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 166.3, 155.42, 155.40, 133.8, 130.0, 129.8, 129.0, 128.2, 127.6, 127.4, 127.1, 120.2, 118.9, 52.3, 32.0, 31.5.

IR: 3062, 2950, 2897, 2844, 1717, 1608, 1568, 1521, 1478, 1434, 1404, 1284, 1255, 1193, 1157, 1118, 1096, 985, 948, 929, 908, 873, 851, 840, 785, 751, 730.

HRMS (ESI): $C_{16}H_{15}N_2O_2$ [M+H] calc. 267.1128, found 267.1132.

(Z)-11,12-dihydrodibenzo[c,g][1,2]diazocine-3-carbonitrile (**15**)



Prepared from 3-amino-4-(2-aminophenethyl)benzonitrile (**SI-82**) according to the general procedure with slow addition of *m*CPBA.

[a]Unreacted substrate **50** eluted with 15 to 100% ethyl acetate in hexanes and a significant amount of substrate **50** (76 mg, 0.28 mmol, 7%) could be recovered after additional purification by column chromatography (0 to 20% ethyl acetate in dichloromethane).

The crude was purified by column chromatography (0 to 15% ethyl acetate in hexanes) to afford the title compound (22.5 mg, 96.5 µmol, 39%) as a yellow solid.

R_f = 0.31 (20% ethyl acetate in hexanes).

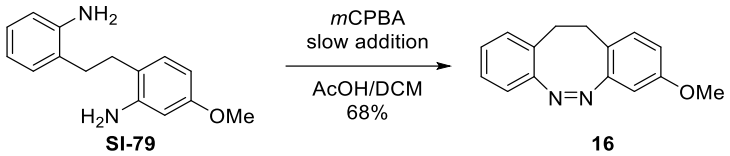
^{1}H-NMR (400 MHz, $CDCl_3$): 7.30 (dd, J = 7.9, 1.7 Hz, 1H), 7.19 (td, J = 7.6, 1.4 Hz, 1H), 7.12 – 7.08 (m, 2H), 7.05 (td, J = 7.5, 1.3 Hz, 1H), 6.97 (dd, J = 7.7, 1.4 Hz, 1H), 6.86 (dd, J = 7.8, 1.3 Hz, 1H), 3.11 – 2.73 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 155.8, 155.3, 134.4, 130.8, 130.7, 129.9, 127.8, 127.4, 127.2, 122.5, 118.8, 118.1, 111.0, 32.1, 31.4.

IR: 3059, 3033, 2956, 2920, 2876, 2853, 2230, 1602, 1555, 1522, 1488, 1475, 1451, 1431, 1393, 1350, 1208, 1163, 1101, 1084, 1035, 981, 945, 932, 905, 893, 853, 823, 749.

HRMS (ESI): $C_{15}H_{12}N_3$ [M+H] calc. 234.1026, found 234.1028.

(Z)-3-methoxy-11,12-dihydrodibenzo[c,g][1,2]diazocine (**16**)



Prepared from 2-(2-aminophenethyl)-5-methoxyaniline (**SI-79**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 7.5% ethyl acetate in hexanes) to afford the title compound (40.4 mg, 170 µmol, 68%) as a yellow solid.

R_f = 0.27 (10% ethyl acetate in hexanes).

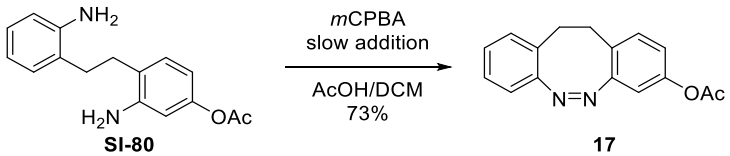
^{1}H-NMR (400 MHz, $CDCl_3$): 7.14 (td, J = 7.5, 1.6 Hz, 1H), 7.02 (td, J = 7.4, 1.3 Hz, 1H), 6.98 (dd, J = 7.6, 1.6 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.83 (dd, J = 7.7, 1.3 Hz, 1H), 6.55 (dd, J = 8.4, 2.6 Hz, 1H), 6.37 (d, J = 2.6 Hz, 1H), 3.71 (s, 3H), 3.02 – 2.65 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 158.3, 156.3, 155.5, 130.8, 129.7, 128.4, 127.2, 126.7, 120.2, 118.9, 113.1, 104.1, 55.5, 31.9, 31.1.

IR: 3063, 3003, 2940, 2897, 2835, 1607, 1570, 1518, 1493, 1479, 1462, 1441, 1417, 1316, 1279, 1268, 1244, 1208, 1187, 1169, 1143, 1101, 1086, 1033, 947, 932, 900, 876, 835, 811, 751, 723.

HRMS (ESI): $C_{15}H_{15}N_2O$ [M+H] calc. 239.1179, found 239.1190.

(Z)-11,12-dihydrodibenzo[c,g][1,2]diazocin-3-yl acetate (**17**)



Prepared from 3-amino-4-(2-aminophenethyl)phenyl acetate (**SI-80**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 15% ethyl acetate in hexanes) to afford the title compound (48.5 mg, 182 µmol, 73%) as a yellow solid.

R_f = 0.32 (20% ethyl acetate in hexanes).

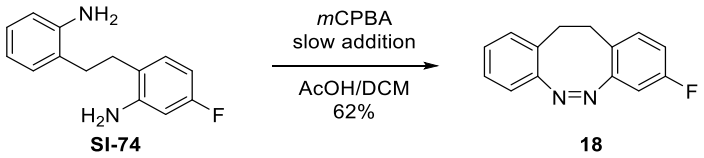
^{1}H-NMR (400 MHz, $CDCl_3$): 7.15 (td, *J* = 7.5, 1.5 Hz, 1H), 7.03 (td, *J* = 7.4, 1.3 Hz, 1H), 6.98 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.83 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.77 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.61 (d, *J* = 2.4 Hz, 1H), 3.06 – 2.66 (m, 4H), 2.23 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 169.1, 155.9, 155.4, 149.2, 130.7, 129.8, 127.9, 127.4, 127.0, 125.8, 120.2, 118.8, 112.3, 31.6, 31.5, 21.2.

IR: 2898, 2852, 1759, 1603, 1580, 1520, 1486, 1461, 1435, 1411, 1368, 1261, 1195, 1181, 1135, 1101, 1083, 1041, 1012, 981, 948, 920, 894, 846, 816, 752, 730.

HRMS (ESI): $C_{16}H_{15}N_2O_2$ [M+H] calc. 267.1128, found 267.1137.

(Z)-3-fluoro-11,12-dihydrodibenzo[c,g][1,2]diazocine (**18**)



Prepared from 2-(2-aminophenethyl)-5-fluoroaniline (**SI-74**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 7.5% ethyl acetate in hexanes) to afford the title compound (34.9 mg, 154 µmol, 62%) as a yellow solid.

R_f = 0.40 (10% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.16 (td, *J* = 7.5, 1.5 Hz, 1H), 7.03 (td, *J* = 7.5, 1.3 Hz, 1H), 6.97 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.94 (dd, *J* = 8.5, 5.6 Hz, 1H), 6.83 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.71 (td, *J* = 8.4, 2.7 Hz, 1H), 6.56 (dd, *J* = 8.6, 2.6 Hz, 1H), 3.07 – 2.68 (m, 4H).

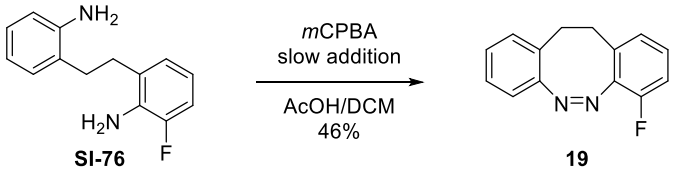
^{13}C-NMR (100 MHz, $CDCl_3$): 161.2 (d, J = 246.9 Hz), 156.4 (d, J = 7.7 Hz), 155.4, 131.1 (d, J = 8.2 Hz), 129.9, 128.0, 127.4, 127.0, 124.1 (d, J = 3.5 Hz), 118.9, 114.1 (d, J = 21.2 Hz), 106.3 (d, J = 24.4 Hz), 31.8, 31.1.

^{19}F-NMR (377 MHz, $CDCl_3$): -115.02 (td, J = 8.4, 5.5 Hz).

IR: 3080, 3056, 2952, 2925, 2897, 2849, 1603, 1584, 1524, 1489, 1463, 1441, 1405, 1284, 1262, 1243, 1227, 1183, 1171, 1158, 1132, 1099, 1077, 1040, 993, 982, 944, 909, 887, 866, 853, 825, 816, 758, 722.

HRMS (ESI): $C_{14}H_{12}FN_2$ [M+H] calc. 227.0979, found 227.0983.

(Z)-4-fluoro-11,12-dihydrodibenzo[c,g][1,2]diazocine (**19**)



Prepared from 2-(2-aminophenethyl)-6-fluoroaniline (**SI-76**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 7.5% ethyl acetate in hexanes) to afford the title compound (25.9 mg, 114 µmol, 46%) as a yellow solid.

R_f = 0.39 (10% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.17 (td, J = 7.6, 1.4 Hz, 1H), 7.07 – 6.95 (m, 3H), 6.89 (dd, J = 7.8, 1.4 Hz, 1H), 6.83 (ddd, J = 9.5, 8.3, 1.2 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 3.06 – 2.72 (m, 4H).

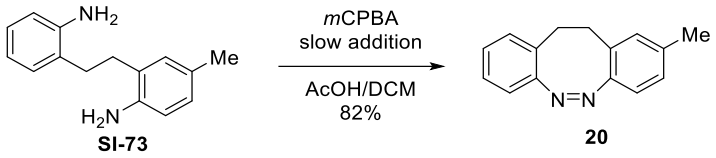
^{13}C-NMR (100 MHz, $CDCl_3$): 155.9, 152.0 (d, J = 247.7 Hz), 142.9 (d, J = 14.0 Hz), 131.5 (d, J = 1.4 Hz), 130.0, 128.4 (d, J = 7.9 Hz), 127.9, 127.5, 127.1, 124.7 (d, J = 3.3 Hz), 118.3, 114.1 (d, J = 19.2 Hz), 31.5 (d, J = 2.2 Hz), 31.8.

^{19}F-NMR (377 MHz, $CDCl_3$): -125.24 (dd, J = 9.4, 5.3 Hz).

IR: 3073, 3057, 3021, 2958, 2946, 2923, 2895, 2871, 2855, 1611, 1577, 1519, 1468, 1454, 1444, 1251, 1180, 1167, 1158, 1148, 1064, 1041, 1018, 975, 955, 906, 864, 847, 784, 750, 729.

HRMS (ESI): $C_{14}H_{12}FN_2$ [M+H] calc. 227.0979, found 227.0977.

(Z)-2-methyl-11,12-dihydrodibenzo[c,g][1,2]diazocine (**20**)



Prepared from 2-(2-aminophenethyl)-4-methylaniline (**SI-73**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 5% ethyl acetate in hexanes) to afford the title compound (45.5 mg, 205 µmol, 82%) as a yellow solid.

R_f = 0.42 (10% ethyl acetate in hexanes).

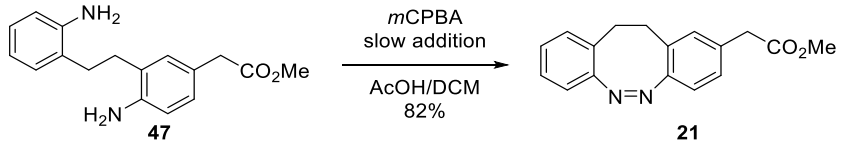
^{1}H-NMR (400 MHz, $CDCl_3$): 7.13 (ddd, J = 7.7, 6.9, 1.9 Hz, 1H), 7.05 – 6.97 (m, 2H), 6.93 (dd, J = 8.2, 1.3 Hz, 1H), 6.83 (dd, J = 7.5, 1.1 Hz, 1H), 6.77 (br, 1H), 6.74 (d, J = 7.9 Hz, 1H), 3.12 – 2.61 (m, 4H), 2.20 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 155.7, 153.3, 136.8, 130.4, 129.6, 128.3, 127.8, 127.4, 127.1, 126.8, 119.1, 118.9, 32.0, 31.7, 21.0.

IR: 3062, 3016, 2919, 2896, 2852, 1608, 1572, 1515, 1479, 1459, 1445, 1378, 1235, 1148, 1089, 1037, 982, 947, 931, 885, 862, 811, 752, 731.

HRMS (ESI): $C_{15}H_{15}N_2$ [M+H] calc. 223.1230, found 223.1238.

methyl (Z)-2-(11,12-dihydrodibenzo[c,g][1,2]diazocin-2-yl)acetate (**21**)



Prepared from methyl (Z)-2-(11,12-dihydrodibenzo[c,g][1,2]diazocin-2-yl)acetate (**47**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 20% ethyl acetate in hexanes) to afford the title compound (57.4 mg, 205 µmol, 82%) as a yellow oil.

R_f = 0.25 (20% ethyl acetate in hexanes).

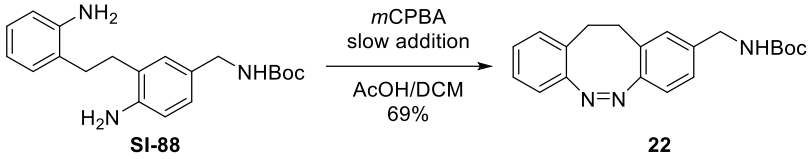
^{1}H-NMR (400 MHz, $CDCl_3$): 7.14 (ddd, J = 7.8, 7.0, 1.7 Hz, 1H), 7.07 – 6.98 (m, 2H), 6.98 (dd, J = 7.6, 1.7 Hz, 1H), 6.89 (d, J = 1.8 Hz, 1H), 6.84 (dd, J = 7.7, 1.3 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 3.66 (s, 3H), 3.47 (s, 2H), 3.11 – 2.61 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 171.8, 155.6, 154.5, 132.8, 130.7, 129.7, 128.4, 128.1, 127.7, 127.2, 126.9, 119.5, 119.0, 52.2, 40.6, 32.0, 31.6.

IR: 3063, 3020, 2950, 2898, 2360, 2340, 1734, 1607, 1574, 1520, 1480, 1458, 1434, 1328, 1257, 1196, 1152, 1089, 1036, 1014, 947, 910, 896, 863, 847, 821, 788, 754.

HRMS (ESI): $C_{17}H_{17}N_2O_2$ [M+H] calc. 281.1285, found 281.1282.

tert-butyl (Z)-((11,12-dihydrodibenzo[c,g][1,2]diazocin-2-yl)methyl)carbamate (**22**)



SI-88 **22**

Prepared from *tert*-butyl (3-amino-4-(2-aminophenethyl)benzyl)carbamate (**SI-88**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 30% ethyl acetate in hexanes) to afford the title compound (58.4 mg, 173 µmol, 69%) as a yellow solid.

R_f = 0.20 (20% ethyl acetate in hexanes).

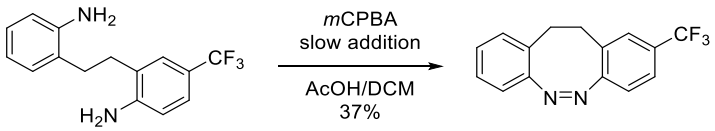
^{1}H-NMR (400 MHz, $CDCl_3$): 7.14 (td, J = 7.5, 1.7 Hz, 1H), 7.06 – 6.96 (m, 3H), 6.88 (d, J = 1.8 Hz, 1H), 6.83 (dd, J = 7.9, 1.2 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 4.72 (br, 1H), 4.31 – 4.02 (m, 2H), 3.18 – 2.60 (m, 4H), 1.44 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): 155.9, 155.6, 154.7, 137.8, 129.8, 128.9, 128.4, 128.1, 127.2, 126.9, 125.9, 119.4, 118.9, 79.8, 44.2, 32.0, 31.6, 28.5.

IR: 3340, 3063, 3003, 2975, 2929, 1694, 1512, 1482, 1456, 1391, 1365, 1336, 1271, 1249, 1166, 1108, 1089, 1048, 1030, 942, 908, 862, 819, 782, 755, 732.

HRMS (ESI): $C_{20}H_{24}N_3O_2$ [M+H] calc. 338.1863, found 338.1879.

(Z)-2-(trifluoromethyl)-11,12-dihydrodibenzo[c,g][1,2]diazocine (**23**)



SI-85 **23**

Prepared from 2-(2-aminophenethyl)-4-(trifluoromethyl)aniline (**SI-85**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 10% ethyl acetate in hexanes) to afford the title compound (25.4 mg, 91.9 µmol, 37%) as a yellow solid.

R_f = 0.33 (10% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.38 (dd, J = 8.2, 1.8 Hz, 1H), 7.25 (d, J = 1.7 Hz, 1H), 7.16 (td, J = 7.6, 1.5 Hz, 1H), 7.05 (td, J = 7.4, 1.3 Hz, 1H), 6.99 (dd, J = 7.7, 1.4 Hz, 1H), 6.92 (d, J = 8.2 Hz, 1H), 6.86 (dd, J = 7.8, 1.3 Hz, 1H), 3.12 – 2.75 (m, 4H).

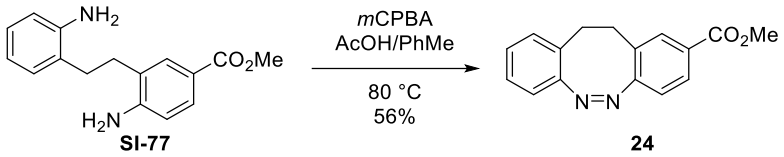
^{13}C-NMR (100 MHz, $CDCl_3$): 158.01 (q, J = 1.2 Hz), 155.4, 130.0, 129.3, 129.2 (q, J = 32.6 Hz), 127.7, 127.4, 127.2, 126.9 (q, J = 3.7 Hz), 124.0 (q, J = 3.8 Hz), 123.8 (q, J = 272.1 Hz), 119.4, 118.8, 31.8, 31.6.

^{19}F-NMR (377 MHz, $CDCl_3$): -62.44 (s).

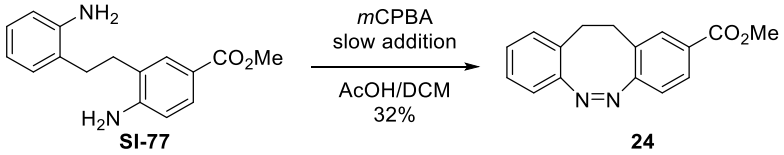
IR: 1613, 1581, 1523, 1479, 1462, 1447, 1422, 1324, 1277, 1204, 1158, 1121, 1094, 1072, 1040, 989, 946, 925, 904, 876, 865, 824, 757, 741.

HRMS (ESI): $C_{15}H_{12}F_3N_2$ [M+H] calc. 277.0947, found 277.0955.

methyl (Z)-11,12-dihydrodibenzo[c,g][1,2]diazocine-2-carboxylate (**24**)



One-batch addition: Prepared from methyl 4-amino-3-(2-aminophenethyl)-benzoate (**SI-77**) according to the general procedure with one-batch addition of *m*CPBA.
The crude was purified by column chromatography (0 to 15% ethyl acetate in hexanes) to afford the title compound (37.1 mg, 139 µmol, 56%) as a yellow solid.



Slow addition: Prepared from methyl 4-amino-3-(2-aminophenethyl)-benzoate (**SI-77**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 15% ethyl acetate in hexanes) to afford the title compound (21 mg, 79.8 µmol, 32%) as a yellow solid.

$\mathbf{R_f}$ = 0.22 (10% ethyl acetate in hexanes).

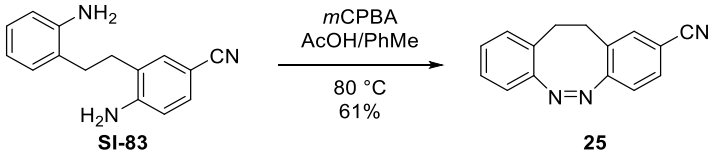
^{1}H-NMR (400 MHz, $CDCl_3$): 7.79 (dd, J = 8.1, 1.7 Hz, 1H), 7.69 (d, J = 1.7 Hz, 1H), 7.13 (td, J = 7.5, 1.5 Hz, 1H), 7.01 (tt, J = 7.4, 1.0 Hz, 1H), 6.96 (dd, J = 7.7, 1.4 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.83 (dd, J = 7.7, 1.3 Hz, 1H), 3.84 (d, J = 0.7 Hz, 3H), 3.08 – 2.71 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 166.4, 159.2, 155.5, 131.3, 130.0, 128.83, 128.81, 128.3, 127.7, 127.5, 127.0, 118.8, 118.7, 52.3, 31.7, 31.6.

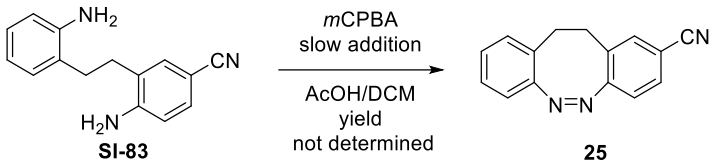
IR: 2950, 2900, 2849, 1716, 1604, 1575, 1522, 1478, 1458, 1435, 1414, 1347, 1288, 1257, 1204, 1194, 1162, 1114, 1099, 1085, 1038, 1003, 967, 947, 913, 878, 866, 835, 766, 749, 730.

HRMS (ESI): $C_{16}H_{15}N_2O_2$ [M+H] calc. 267.1128, found 267.1132.

(Z)-11,12-dihydrodibenzo[c,g][1,2]diazocine-2-carbonitrile (**25**)



One-batch addition: Prepared from 4-amino-3-(2-aminophenethyl)benzonitrile (**SI-83**) according to the general procedure with one-batch addition of *m*CPBA.
The crude was purified by column chromatography (0 to 15% ethyl acetate in hexanes) to afford the title compound (35.3 mg, 151 µmol, 61%) as a yellow solid.



Slow addition: Prepared from 4-amino-3-(2-aminophenethyl)benzonitrile (**SI-83**) according to the general procedure with slow addition of *m*CPBA.
The reaction mixture was analyzed by ^{1}H-NMR spectroscopy, which showed the presence of a mixture of the desired product **25** as a minor component and the presumed nitroso-aniline intermediate as a major component with a ratio of approximately 1/10.

R_f = 0.35 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.41 (dd, J = 8.1, 1.7 Hz, 1H), 7.29 (d, J = 1.6 Hz, 1H), 7.17 (td, J = 7.6, 1.4 Hz, 1H), 7.06 (td, J = 7.5, 1.3 Hz, 1H), 6.98 (dd, J = 7.7, 1.3 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.84 (dd, J = 7.8, 1.3 Hz, 1H), 3.10 – 2.73 (m, 4H).

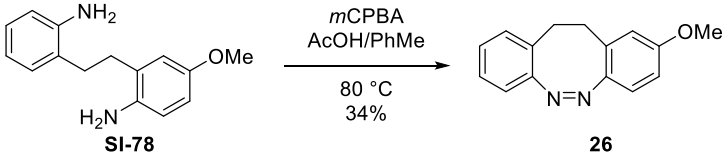
^{13}C-NMR (100 MHz, $CDCl_3$): 158.8, 155.4, 133.6, 130.8, 130.2, 130.0, 127.9, 127.3, 127.1, 119.6, 118.7, 118.3, 111.0, 31.4.[a]

IR: 3065, 3031, 2950, 2924, 2900, 2853, 2228, 1602, 1565, 1518, 1478, 1461, 1446, 1407, 1296, 1223, 1173, 1157, 1106, 1090, 1038, 998, 949, 904, 865, 823, 798, 756, 731.

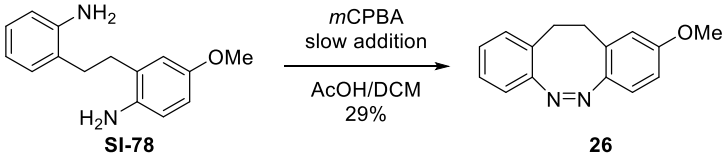
HRMS (ESI): $C_{15}H_{12}N_3$ [M+H] calc. 234.1026, found 234.1022.

The spectroscopic data agrees with previously reported values.[19]

(Z)-2-methoxy-11,12-dihydrodibenzo[c,g][1,2]diazocine (26)



One-batch addition: Prepared from 2-(2-aminophenethyl)-4-methoxyaniline (**SI-78**) according to the general procedure with one-batch addition of *m*CPBA
The crude was purified by column chromatography (0 to 7.5% ethyl acetate in hexanes) to afford the title compound (20.1 mg, 84.4 µmol, 34%) as a yellow solid.



Slow addition: Prepared from 2-(2-aminophenethyl)-4-methoxyaniline (**SI-78**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 7.5% ethyl acetate in hexanes) to afford the title compound (17.4 mg, 73.0 µmol, 29%) as a yellow solid.

R_f = 0.23 (10% ethyl acetate in hexanes).

[a]The 31.4 ppm signal is corresponding to two carbons.

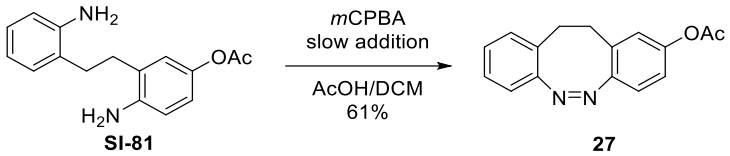
^{1}H-NMR (400 MHz, $CDCl_3$): 7.14 (ddd, J = 7.8, 6.8, 2.0 Hz, 1H), 7.07 – 6.97 (m, 2H), 6.86 – 6.78 (m, 2H), 6.67 (dd, J = 8.6, 2.6 Hz, 1H), 6.49 (d, J = 2.6 Hz, 1H), 3.70 (s, 3H), 3.06 – 2.64 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 158.3, 155.6, 149.2, 129.7, 129.6, 128.3, 127.1, 126.8, 121.0, 119.0, 114.8, 112.0, 55.4, 32.5, 31.6.

IR: 3062, 3002, 2937, 2836, 2361, 1602, 1576, 1513, 1483, 1462, 1424, 1308, 1278, 1244, 1197, 1173, 1155, 1108, 1092, 1037, 993, 948, 928, 878, 849, 814, 757, 724.

HRMS (ESI): $C_{15}H_{15}N_2O$ [M+H] calc. 239.1179, found 239.1187.

(Z)-11,12-dihydrodibenzo[c,g][1,2]diazocin-2-yl acetate (**27**)



SI-81 **27**

Prepared from 4-amino-3-(2-aminophenethyl)phenyl acetate (**SI-81**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 15% ethyl acetate in hexanes) to afford the title compound (40.3 mg, 151 µmol, 61%) as a yellow solid.

R_f = 0.28 (20% ethyl acetate in hexanes).

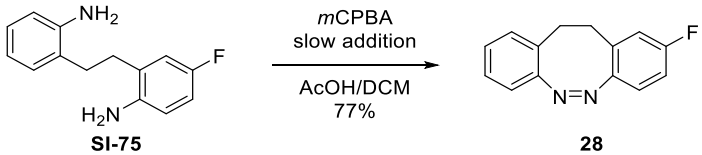
^{1}H-NMR (400 MHz, $CDCl_3$): 7.15 (td, J = 7.5, 1.5 Hz, 1H), 7.03 (td, J = 7.4, 1.3 Hz, 1H), 6.98 (dd, J = 7.6, 1.5 Hz, 1H), 6.89 (dd, J = 8.5, 2.2 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 6.83 (dd, J = 7.7, 1.2 Hz, 1H), 6.75 (d, J = 2.2 Hz, 1H), 3.10 – 2.66 (m, 4H), 2.23 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 169.2, 155.5, 152.9, 149.1, 129.8, 129.7, 127.8, 127.4, 127.0, 122.5, 120.3, 119.9, 118.9, 32.0, 31.5, 21.2.

IR: 1757, 1604, 1579, 1518, 1479, 1432, 1367, 1276, 1195, 1161, 1147, 1105, 1087, 1042, 1014, 940, 918, 901, 872, 859, 817, 756, 727.

HRMS (ESI): $C_{16}H_{15}N_2O_2$ [M+H] calc. 267.1128, found 267.1136.

(Z)-2-fluoro-11,12-dihydrodibenzo[c,g][1,2]diazocine (**28**)



SI-75 **28**

Prepared from 2-(2-aminophenethyl)-4-fluoroaniline (**SI-75**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 7.5% ethyl acetate in hexanes) to afford the title compound (43.4 mg, 192 µmol, 77%) a yellow solid.

R_f = 0.38 (10% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.15 (td, J = 7.5, 1.6 Hz, 1H), 7.04 (td, J = 7.4, 1.3 Hz, 1H), 6.99 (dd, J = 7.6, 1.5 Hz, 1H), 6.88 – 6.78 (m, 3H), 6.74 – 6.66 (m, 1H), 3.15 – 2.59 (m, 4H).

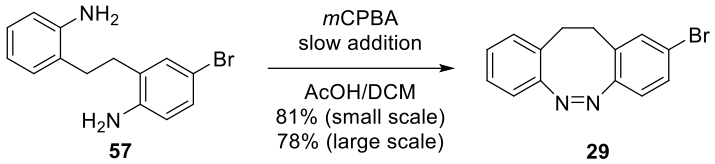
^{13}C-NMR (100 MHz, $CDCl_3$): 161.1 (d, J = 246.1 Hz), 155.5, 151.6, 130.7 (d, J = 7.7 Hz), 129.7, 127.8, 127.4, 127.0, 120.9 (d, J = 8.8 Hz), 118.8, 116.3 (d, J = 22.3 Hz), 113.8 (d, J = 22.7 Hz), 32.0 (d, J = 1.4 Hz), 31.5.

^{19}F-NMR (377 MHz, $CDCl_3$): -115.81 (ddd, J = 9.2, 7.4, 5.9 Hz).

IR: 3057, 3021, 2953, 2924, 2897, 2872, 2854, 1608, 1583, 1517, 1480, 1460, 1445, 1419, 1274, 1239, 1198, 1180, 1156, 1144, 1102, 1086, 1042, 1005, 974, 946, 932, 902, 890, 853, 814, 751, 724, 711.

HRMS (ESI): $C_{14}H_{12}FN_2$ [M+H] calc. 227.0979, found 227.0978.

(Z)-2-bromo-11,12-dihydrodibenzo[c,g][1,2]diazocine (**29**)



Small scale: Prepared from 2-(2-aminophenethyl)-4-bromoaniline (**57**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 5% ethyl acetate in hexanes) to afford the title compound (58.4 mg, 203 µmol, 81%) as a yellow solid.

Large scale: Prepared from 2-(2-aminophenethyl)-4-bromoaniline (**57**, 2.30 g, 7.90 mmol) according to the general procedure with slow addition of *m*CPBA. The reaction vessel and amount of *m*CPBA-solution/solvent were scaled accordingly and the workup/purification were modified as follows:
After removal of the solvent, the residue was taken up in ethyl acetate (70 mL), washed with saturated, aqueous sodium hydrogen carbonate (2×60 mL), saturated, aqueous sodium chloride (60 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography (0 to 5% ethyl acetate in hexanes) to afford a fraction of impure product and clean title compound (558 mg, 1.94 mmol, 25%) as a yellow solid. Additional product (865 mg, 3.01 mmol, 38%) in the form of a yellow solid was isolated from the impure fraction by crystallization from dichloromethane followed by washing the obtained solids with diethyl ether. The washings were concentrated under reduced pressure and the residue was further purified by column chromatography (0 to 5% ethyl acetate in hexanes) followed by washing of the resulting solids with a mixture of diethyl ether/hexanes to afford further product (342 mg, 1.19 mmol, 15%) as a yellow solid.

$\mathbf{R_f}$ = 0.43 (10% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.24 (dd, J = 8.3, 2.1 Hz, 1H), 7.20 – 7.11 (m, 2H), 7.05 (td, J = 7.4, 1.3 Hz, 1H), 6.99 (dd, J = 7.7, 1.4 Hz, 1H), 6.83 (dd, J = 7.8, 1.2 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 3.11 – 2.61 (m, 4H).

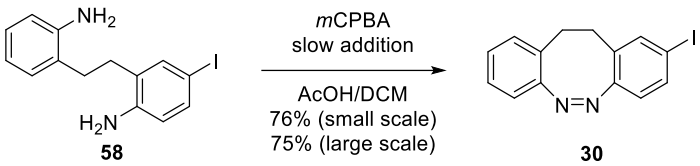
^{13}C-NMR (100 MHz, $CDCl_3$): 155.4, 154.3, 132.5, 130.6, 129.88, 129.86, 127.6, 127.5, 127.1, 120.8, 120.4, 118.8, 31.8, 31.5.

IR: 3064, 3017, 2948, 2895, 1587, 1573, 1563, 1520, 1468, 1398, 1161, 1110, 1093, 1076, 1037, 986, 947, 921, 888, 861, 814, 753, 722.

HRMS (ESI): $C_{14}H_{12}BrN_2$ [M+H] calc. 287.0178, found 287.0188.

The spectroscopic data agrees with previously reported values.[19]

(Z)-2-iodo-11,12-dihydrodibenzo[c,g][1,2]diazocine (**30**)



Small scale: Prepared from 2-(2-aminophenethyl)-4-iodoaniline (**58**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 5% ethyl acetate in hexanes) to afford the title compound (63.8 mg, 191 µmol, 76%) as a yellow solid.

Large scale: Prepared from 2-(2-aminophenethyl)-4-iodoaniline (**58**, 2.60 g, 7.69 mmol) according to the general procedure with slow addition of *m*CPBA. The reaction vessel and amount of *m*CPBA-solution/solvent were scaled accordingly and the workup/purification were modified as follows:
After removal of the solvent, the residue was taken up in ethyl acetate (70 mL), washed with saturated, aqueous sodium hydrogen carbonate (2×60 mL), saturated, aqueous sodium chloride (60 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography (0 to 5% ethyl acetate in hexanes) to afford a fraction of impure product and clean title compound (831 mg, 2.49 mmol, 32%) as a yellow solid. Additional product (955 mg, 2.86 mmol, 37%) in the form of a yellow solid was isolated from the impure fraction by washing with diethyl ether. The washings were concentrated under reduced pressure and the residue was purified by crystallization from dichloromethane followed by again washing the resulting solids with diethyl ether to afford further title compound (162 mg, 485 µmol, 6%) as a yellow solid.

$\mathbf{R_f}$ = 0.43 (10% ethyl acetate in hexanes).

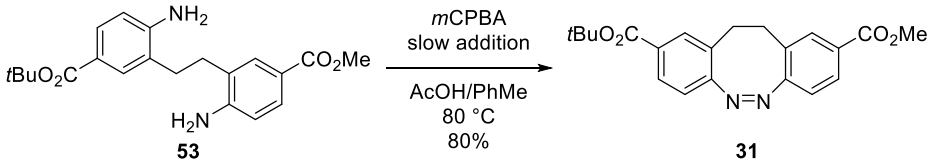
^{1}H-NMR (400 MHz, $CDCl_3$): 7.44 (dd, J = 8.3, 1.8 Hz, 1H), 7.34 (d, J = 1.8 Hz, 1H), 7.16 (td, J = 7.5, 1.5 Hz, 1H), 7.05 (td, J = 7.5, 1.3 Hz, 1H), 7.00 (dd, J = 7.6, 1.5 Hz, 1H), 6.83 (dd, J = 7.8, 1.3 Hz, 1H), 6.58 (d, J = 8.2 Hz, 1H), 3.07 – 2.61 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 155.4, 155.0, 138.4, 135.8, 130.7, 129.9, 127.6, 127.5, 127.1, 120.9, 118.9, 91.9, 31.6, 31.5.

IR: 3063, 3017, 2948, 2894, 1581, 1556, 1520, 1466, 1392, 1345, 1164, 1109, 1093, 1036, 981, 946, 920, 889, 861, 814, 753, 722.

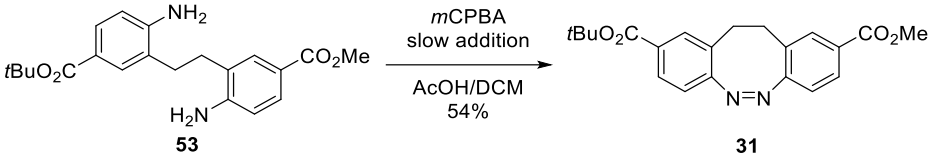
HRMS (ESI): $C_{14}H_{12}IN_2$ [M+H] calc. 335.0040, found 335.0051.

2-(*tert*-butyl) 9-methyl (Z)-11,12-dihydrodibenzo[c,g][1,2]diazocine-2,9-dicarboxylate (**31**)



Modified procedure: Prepared from *tert*-butyl 4-amino-3-(2-amino-5-(methoxy-carbonyl)phenethyl)benzoate (**53**) according to the general procedure with slow addition of *m*CPBA, but at an increased reaction temperature of 80 °C and in the solvent-mixture acetic acid/toluene = 1/3 instead of acetic acid/dichloromethane.

The crude was purified by column chromatography (0 to 15% ethyl acetate in hexanes) to afford the title compound (73.5 mg, 201 µmol, 80%) as a yellow solid.



Standard procedure: Prepared from *tert*-butyl 4-amino-3-(2-amino-5-(methoxy-carbonyl)phenethyl)benzoate (**53**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 15% ethyl acetate in hexanes) to afford the title compound (49.3 mg, 135 µmol, 54%) as a yellow solid.

R_f = 0.41 (20% ethyl acetate in hexanes).

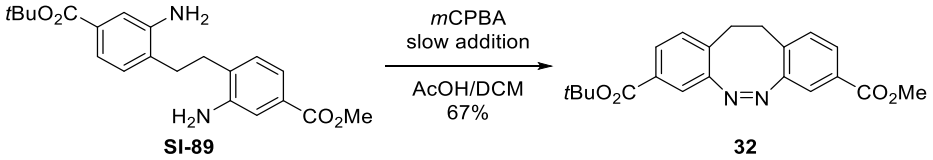
^{1}H-NMR (400 MHz, $CDCl_3$): 7.80 (dd, J = 8.2, 1.7 Hz, 1H), 7.74 (dd, J = 8.2, 1.7 Hz, 1H), 7.69 (d, J = 1.7 Hz, 1H), 7.60 (d, J = 1.7 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 3.85 (s, 3H), 3.09 – 2.80 (m, 4H), 1.54 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): 166.3, 164.9, 159.0, 158.6, 131.6, 131.3, 131.0, 129.1, 128.5, 128.41, 128.39, 128.0, 118.7, 118.6, 81.5, 52.3, 31.5, 31.4, 28.3.

IR: 2977, 2952, 2934, 1712, 1605, 1577, 1475, 1457, 1436, 1419, 1407, 1393, 1368, 1343, 1291, 1257, 1202, 1159, 1114, 1005, 972, 917, 849, 825, 807, 771, 758, 731.

HRMS (ESI): $C_{21}H_{23}N_2O_4$ [M+H] calc. 367.1652, found 367.1665.

3-(*tert*-butyl) 8-methyl (Z)-11,12-dihydrodibenzo[c,g][1,2]diazocine-3,8-dicarboxylate (32)



Prepared from *tert*-butyl 3-amino-4-(2-amino-4-(methoxycarbonyl)-phenethyl)benzoate (**SI-89**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 15% ethyl acetate in hexanes) to afford the title compound (61.0 mg, 166 µmol, 67%) as a yellow solid.

R_f = 0.30 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.70 (dd, J = 8.0, 1.8 Hz, 1H), 7.64 (dd, J = 7.9, 1.7 Hz, 1H), 7.54 (d, J = 1.7 Hz, 1H), 7.47 (d, J = 1.7 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 3.87 (s, 3H), 3.14 – 2.78 (m, 4H), 1.55 (s, 9H).

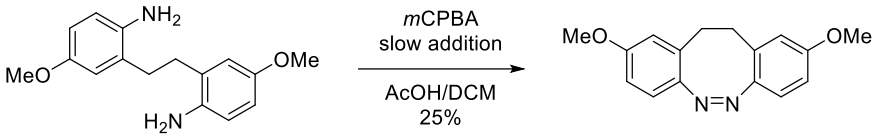
^{13}C-NMR (100 MHz, $CDCl_3$): 166.2, 164.8, 155.2, 155.0, 133.1, 132.3, 131.2, 130.0, 129.9, 129.3, 128.5, 128.4, 120.5, 120.3, 81.7, 52.4, 31.7,[a] 28.3.

IR: 2977, 2952, 2933, 1715, 1607, 1568, 1475, 1457, 1436, 1407, 1394, 1368, 1291, 1261, 1251, 1192, 1155, 1130, 1113, 1087, 985, 914, 849, 806, 784, 760, 732.

HRMS (ESI): $C_{21}H_{23}N_2O_4$ [M+H] calc. 367.1652, found 367.1667.

[a]The 31.7 ppm signal is corresponding to two carbons.

(Z)-2,9-dimethoxy-11,12-dihydrodibenzo[c,g][1,2]diazocine (**33**)



SI-91 **33**

Prepared from 2,2'-(ethane-1,2-diyl)bis(4-methoxyaniline) (**SI-91**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 15% ethyl acetate in hexanes) to afford the title compound (16.5 mg, 61.5 µmol, 25%) as a yellow solid.

R_f = 0.19 (20% ethyl acetate in hexanes).

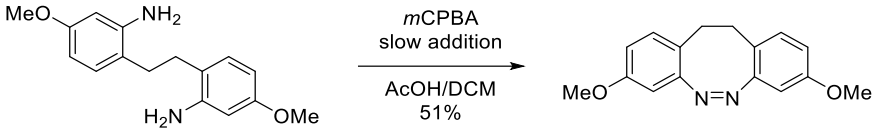
^{1}H-NMR (400 MHz, $CDCl_3$): 6.81 (d, J = 8.6 Hz, 2H), 6.68 (dd, J = 8.6, 2.7 Hz, 2H), 6.52 (d, J = 2.6 Hz, 2H), 3.72 (s, 6H), 2.82 (s, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 158.3, 149.2, 129.8, 121.1, 114.6, 112.0, 55.4, 32.2.

IR: 3000, 2936, 2835, 1601, 1573, 1483, 1462, 1427, 1312, 1276, 1241, 1192, 1169, 1153, 1106, 1033, 992, 940, 888, 815, 799, 732, 703.

HRMS (ESI): $C_{16}H_{17}N_2O_2$ [M+H] calc. 269.1285, found 269.1297.

(Z)-3,8-dimethoxy-11,12-dihydrodibenzo[c,g][1,2]diazocine (**34**)



SI-90 **34**

Prepared from 6,6'-(ethane-1,2-diyl)bis(3-methoxyaniline) (**SI-90**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 10% ethyl acetate in hexanes) to afford the title compound (34.4 mg, 128 µmol, 51%) as a yellow solid.

R_f = 0.34 (20% ethyl acetate in hexanes).

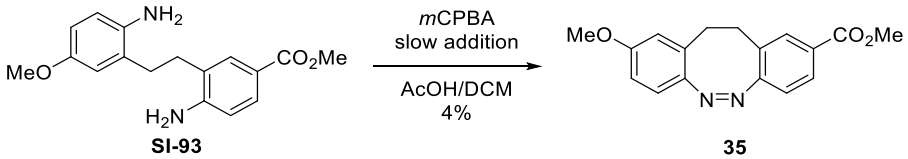
^{1}H-NMR (400 MHz, $CDCl_3$): 6.87 (d, J = 8.4 Hz, 2H), 6.57 (dd, J = 8.4, 2.6 Hz, 2H), 6.38 (d, J = 2.6 Hz, 2H), 3.72 (s, 6H), 2.97 – 2.59 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 158.2, 156.2, 130.7, 120.4, 113.1, 104.2, 55.5, 31.1.

IR: 3065, 3014, 2924, 2853, 1604, 1571, 1533, 1493, 1464, 1453, 1442, 1403, 1318, 1253, 1209, 1185, 1139, 1093, 1077, 1030, 977, 951, 940, 910, 890, 855, 842, 810, 734, 704.

HRMS (ESI): $C_{16}H_{17}N_2O_2$ [M+H] calc. 269.1285, found 269.1293.

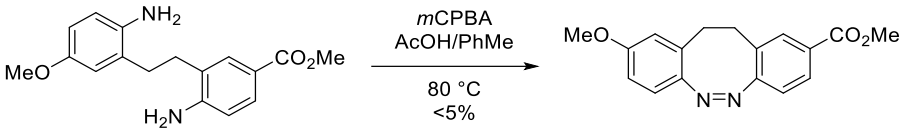
methyl (Z)-9-methoxy-11,12-dihydrodibenzo[c,g][1,2]diazocine-2-carboxylate (**35**)



SI-93 **35**

Slow addition: Prepared from methyl 4-amino-3-(2-amino-5-methoxyphenethyl)-benzoate (**SI-93**, 250 mg, 832 µmol) according the general procedure with slow addition of *m*CPBA, but at higher dilution (0.03 M). The reaction vessel and amount of

*m*CPBA-solution/solvent were scaled accordingly and the workup/purification were modified as follows:
After removal of the solvent, the residue was taken up in ethyl acetate (20 mL), washed with saturated, aqueous sodium hydrogen carbonate (2×10 mL), saturated, aqueous sodium chloride (10 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography (0 to 20% ethyl acetate in hexanes) followed by reverse-phase HPLC (72 mL/min; solvent A: water with 0.1% formic acid; solvent B: acetonitrile with 0.1% formic acid; gradient/%B: 20 to 60 in 1 min, 60 to 70 in 5 min, 70 to 100 in 10 s, 100 for 1 min 50 s) to afford the title compound (9.6 mg, 32 µmol, 4%) as a yellow film.



SI-93 35

One-batch addition: Prepared from methyl 4-amino-3-(2-amino-5-methoxyphenethyl)-benzoate (**SI-93**, 47.0 mg, 156 µmol) according to the general procedure with one-batch addition of *m*CPBA. The amount of *m*CPBA-solution/solvent were scaled accordingly. The crude was purified by column chromatography (0 to 20% ethyl acetate in hexanes) to afford a mixture of compounds (2.1 mg, 7.1 µmol, 5%), which contained the title compound and significant impurities, as a yellow film.

R_f = 0.19 (20% ethyl acetate in hexanes).

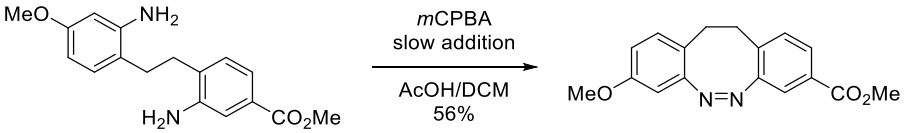
^{1}H-NMR (400 MHz, $CDCl_3$): 7.80 (dd, J = 8.2, 1.7 Hz, 1H), 7.71 (d, J = 1.7 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.82 (d, J = 8.6 Hz, 1H), 6.67 (dd, J = 8.6, 2.6 Hz, 1H), 6.47 (d, J = 2.6 Hz, 1H), 3.86 (s, 3H), 3.70 (s, 3H), 3.10 – 2.64 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 166.5, 159.4, 158.6, 149.2, 131.2, 129.2, 129.0, 128.8, 128.3, 120.9, 118.9, 114.9, 112.2, 55.4, 52.3, 32.3, 31.3.

IR: 3001, 2950, 2848, 2838, 1717, 1603, 1576, 1513, 1485, 1462, 1435, 1343, 1289, 1255, 1245, 1199, 1157, 1114, 1037, 1004, 971, 916, 890, 874, 838, 809, 785, 764, 731.

HRMS (ESI): $C_{17}H_{17}N_2O_3$ [M+H] calc. 297.1234, found 297.1244.

methyl (Z)-8-methoxy-11,12-dihydrodibenzo[c,g][1,2]diazocine-3-carboxylate (**36**)



SI-92 36

Prepared from methyl 3-amino-4-(2-amino-4-methoxyphenethyl)benzoate (**SI-92**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 15% ethyl acetate in hexanes) to afford the title compound (41.8 mg, 141 µmol, 56%) as a yellow solid.

R_f = 0.21 (20% ethyl acetate in hexanes).

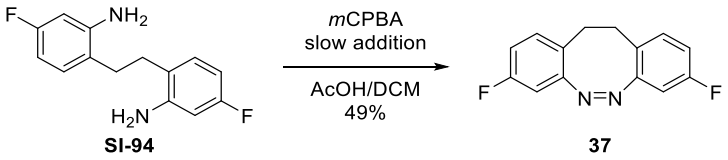
^{1}H-NMR (600 MHz, $CDCl_3$): 7.69 (dd, J = 7.9, 1.7 Hz, 1H), 7.49 (d, J = 1.8 Hz, 1H), 7.06 (d, J = 7.9 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 6.55 (dd, J = 8.4, 2.6 Hz, 1H), 6.38 (d, J = 2.6 Hz, 1H), 3.86 (s, 3H), 3.71 (s, 3H), 3.04 – 2.66 (m, 4H).

^{13}C-NMR (150 MHz, $CDCl_3$): 166.3, 158.5, 156.1, 155.3, 134.0, 130.8, 130.0, 128.9, 128.2, 120.2, 119.6, 113.4, 104.1, 55.5, 52.3, 32.1, 30.8.

IR: 3068, 3004, 2952, 2922, 2854, 2844, 1717, 1677, 1653, 1635, 1605, 1570, 1524, 1496, 1467, 1454, 1435, 1398, 1296, 1263, 1193, 1160, 1145, 1116, 1090, 1081, 1029, 989, 971, 951, 938, 912, 871, 842, 817, 779, 760, 733.

HRMS (ESI): $C_{17}H_{17}N_2O_3$ [M+H] calc. 297.1234, found 297.1245.

(Z)-3,8-difluoro-11,12-dihydrodibenzo[c,g][1,2]diazocine (**37**)



Prepared from 6,6'-(ethane-1,2-diyl)bis(3-fluoroaniline) (**SI-94**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 10% ethyl acetate in hexanes) to afford the title compound (29.7 mg, 122 µmol, 49%) as a yellow solid.

R_f = 0.34 (10% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 6.94 (dd, J = 8.4, 5.5 Hz, 2H), 6.74 (td, J = 8.3, 2.6 Hz, 2H), 6.57 (dd, J = 8.5, 2.7 Hz, 2H), 3.02 – 2.64 (m, 4H).

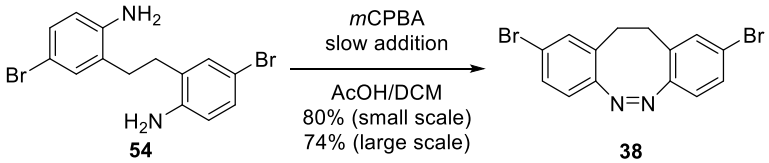
^{13}C-NMR (100 MHz, $CDCl_3$): 161.3 (d, J = 247.5 Hz), 156.1 (d, J = 7.9 Hz), 131.3 (d, J = 8.3 Hz), 123.9 (d, J = 3.6 Hz), 114.3 (d, J = 21.3 Hz), 106.3 (d, J = 24.6 Hz), 31.0.

^{19}F-NMR (377 MHz, $CDCl_3$): -114.65 (dd, J = 8.5, 5.7 Hz).

IR: 3059, 3041, 2966, 2909, 2870, 2855, 1604, 1587, 1523, 1483, 1461, 1406, 1262, 1241, 1202, 1183, 1173, 1129, 1087, 1077, 986, 975, 952, 928, 906, 879, 843, 816, 803, 737, 710.

HRMS (ESI): $C_{14}H_{11}F_2N_2$ [M+H] calc. 245.0885, found 245.0887.

(Z)-2,9-dibromo-11,12-dihydrodibenzo[c,g][1,2]diazocine (**38**)



Small scale: Prepared from 2,2'-(ethane-1,2-diyl)bis(4-bromoaniline) (**54**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (50% dichloromethane in hexanes) to afford the title compound (72.9 mg, 199 µmol, 80%) as a yellow solid.

Large scale: Prepared from 2,2'-(ethane-1,2-diyl)bis(4-bromoaniline) (**54**, 2.65 g, 7.16 mmol) according to the general procedure with slow addition of *m*CPBA. The reaction vessel and amount of *m*CPBA-solution/solvent were scaled accordingly and the workup/purification were modified as follows:
After removal of the solvent, the residue was taken up in ethyl acetate (70 mL), washed with saturated, aqueous sodium hydrogen carbonate (2×60 mL), saturated, aqueous sodium chloride (60 mL) and dried over sodium sulfate. The solvent was removed under reduced

pressure and the residue was purified by column chromatography[a] (25 to 50% dichloromethane in hexanes). The resulting brownish-yellow solid was washed with diethyl ether to afford the title compound (1.86 g, 5,08 mmol, 71%) as a yellow solid. The washings were concentrated under reduced pressure, the residue was crystallized from dichloromethane and the obtained solids again washed with diethyl ether to afford additional product (91.2 mg, 249 µmol, 3%) as a yellow solid.

R_f = 0.42 (10% ethyl acetate in hexanes).

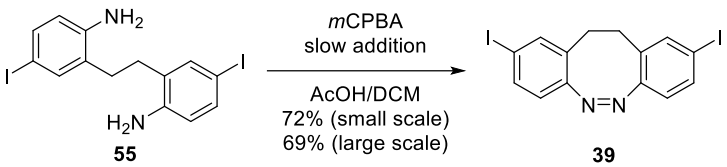
^{1}H-NMR (400 MHz, $CDCl_3$): 7.28 (dd, J = 8.4, 2.0 Hz, 2H), 7.16 (d, J = 2.0 Hz, 2H), 6.72 (d, J = 8.4 Hz, 2H), 3.04 – 2.65 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 154.2, 132.6, 130.2, 130.0, 120.8, 120.7, 31.4.

IR: 3077, 3045, 3012, 2972, 2944, 2912, 2895, 2874, 1759, 1584, 1559, 1517, 1500, 1466, 1432, 1389, 1268, 1218, 1201, 1185, 1159, 1104, 1084, 1073, 989, 951, 920, 893, 881, 861, 817, 797, 735.

HRMS (ESI): $C_{14}H_{11}Br_2N_2$ [M+H] calc. 364.9284, found 364.9287.

(Z)-2,9-diiodo-11,12-dihydrodibenzo[c,g][1,2]diazocine (**39**)



Small scale: Prepared from 2,2'-(ethane-1,2-diyl)bis(4-iodoaniline) (**55**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (50% dichloromethane in hexanes) to afford the title compound (82.8 mg, 180 µmol, 72%) as a yellow solid.

Large scale: Prepared from 2,2'-(ethane-1,2-diyl)bis(4-iodoaniline) (**55**, 3.65 g, 7.87 mmol) according to the general procedure with slow addition of *m*CPBA. The reaction vessel and amount of *m*CPBA-solution/solvent were scaled accordingly and the workup/purification were modified as follows:
After removal of the solvent, the residue was treated with ethyl acetate (100 mL) The remaining solids were filtered off and kept for purification. The filtrate was washed with saturated, aqueous sodium hydrogen carbonate (2×60 mL), saturated, aqueous sodium chloride (60 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue combined with the previously separated solids. Purification by column chromatography[b] (25 to 50% dichloromethane in hexanes) gave a brown solid, which was washed with diethyl ether to afford the title compound (2.38 g, 5.17 mmol, 66%) as a yellow solid. The washings were concentrated under reduced pressure and the residue was again purified by column chromatography (0 to 50% dichloromethane in hexanes) and successive washing with diethyl ether to afford additional product (93 mg, 0.20 mmol, 3%) in the form of a brownish-yellow solid.

[a]Unreacted substrate **54** eluted with 20% ethyl acetate in dichloromethane and a significant amount of substrate **54** (110 mg, 301 µmol, 4%) could be recovered after additional purification by column chromatography (0 to 10% ethyl acetate in dichloromethane).
[b]Unreacted substrate **55** eluted with 20% ethyl acetate in dichloromethane and a significant amount of substrate **55** (169 mg, 364 µmol, 5%) could be recovered after additional purification by column chromatography (0 to 10% ethyl acetate in dichloromethane).

R_f = 0.44 (10% ethyl acetate in hexanes).

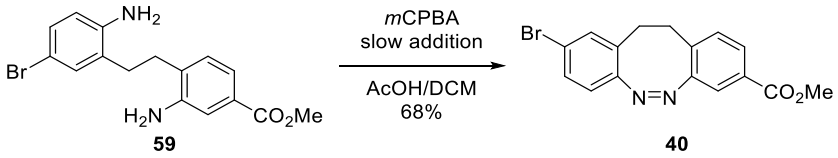
^{1}H-NMR (400 MHz, $CDCl_3$): 7.48 (dd, J = 8.2, 1.8 Hz, 2H), 7.36 (d, J = 1.8 Hz, 2H), 6.59 (d, J = 8.2 Hz, 2H), 3.02 – 2.62 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 154.8, 138.5, 136.1, 130.0, 120.9, 92.4, 31.2.

IR: 2939, 2909, 2895, 2872, 2854, 1576, 1554, 1524, 1487, 1465, 1382, 1341, 1283, 1269, 1166, 1099, 1064, 986, 946, 904, 896, 882, 859, 826, 807, 791, 732.

HRMS (ESI): $C_{14}H_{11}I_2N_2$ [M+H] calc. 460.9006, found 460.9010.

methyl (Z)-9-bromo-11,12-dihydrodibenzo[c,g][1,2]diazocine-3-carboxylate (**40**)



Prepared from methyl 3-amino-4-(2-amino-4-bromophenethyl)benzoate (**59**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 1% methanol in dichloromethane) to afford the title compound (59.0 mg, 171 µmol, 68%) as a yellow solid.

R_f = 0.21 (10% ethyl acetate in hexanes).

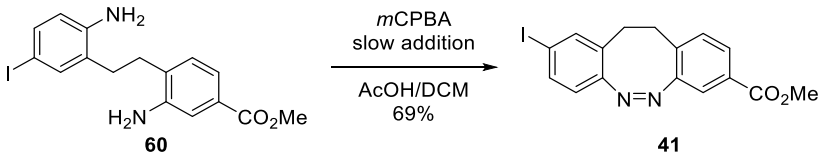
^{1}H-NMR (400 MHz, $CDCl_3$): 7.72 (dd, J = 8.0, 1.7 Hz, 1H), 7.49 (d, J = 1.7 Hz, 1H), 7.26 (dd, J = 8.3, 2.0 Hz, 1H), 7.13 (d, J = 2.0 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 8.3 Hz, 1H), 3.87 (s, 3H), 3.07 – 2.66 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 166.2, 155.3, 154.2, 133.1, 132.5, 130.2, 130.1, 129.9, 129.3, 128.6, 120.8, 120.7, 120.2, 52.4, 31.6, 31.4.

IR: 3068, 2994, 2947, 2898, 2876, 2844, 1716, 1677, 1607, 1587, 1564, 1522, 1492, 1467, 1435, 1405, 1393, 1282, 1259, 1222, 1194, 1175, 1158, 1119, 1105, 1074, 993, 975, 945, 926, 908, 889, 880, 867, 847, 805, 784, 760, 730.

HRMS (ESI): $C_{16}H_{14}BrN_2O_2$ [M+H] calc. 345.0233, found 345.0228.

methyl (Z)-9-iodo-11,12-dihydrodibenzo[c,g][1,2]diazocine-3-carboxylate (**41**)



Prepared from methyl 3-amino-4-(2-amino-4-iodophenethyl)benzoate (**60**) according to the general procedure with slow addition of *m*CPBA.
The crude was purified by column chromatography (0 to 1% methanol in dichloromethane) to afford the title compound (67.5 mg, 172 µmol, 69%) as a yellow solid.

R_f = 0.21 (10% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.72 (dd, J = 7.9, 1.7 Hz, 1H), 7.49 (d, J = 1.8 Hz, 1H), 7.45 (dd, J = 8.2, 1.8 Hz, 1H), 7.33 (d, J = 1.8 Hz, 1H), 7.09 (d, J = 7.9 Hz, 1H), 6.60 (d, J = 8.2 Hz, 1H), 3.87 (s, 3H), 3.07 – 2.65 (m, 4H).

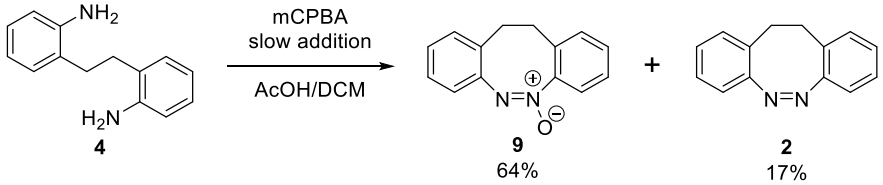
^{13}C-NMR (100 MHz, $CDCl_3$): 166.2, 155.3, 154.9, 138.4, 136.1, 133.1, 130.1, 130.0, 129.3, 128.6, 120.9, 120.2, 92.2, 52.4, 31.6, 31.3.

IR: 2949, 2925, 2898, 2849, 1720, 1685, 1608, 1580, 1566, 1560, 1522, 1465, 1435, 1406, 1389, 1288, 1264, 1194, 1158, 1119, 1104, 1086, 986, 928, 910, 884, 870, 841, 806, 782, 761, 732.

HRMS (ESI): $C_{16}H_{14}IN_2O_2$ [M+H] calc. 393.0094, found 393.0091.

Synthesis of diazocine-*N*-oxides

(E)-11,12-dihydrodibenzo[c,g][1,2]diazocine 5-oxide (**9**)



A freshly prepared and titrated (0.59 M) solution of *m*CPBA in acetic acid (14.0 mL, 8.27 mmol, 3.0 eq.) was added by syringe pump within a period of 12 hours to a solution of 2,2'-ethylenedianiline (**4**, 585 mg, 2.76 mmol, 1.0 eq.) in acetic acid/dichloromethane = 1/3 (6.25 mL) under rapid stirring. After the complete addition of the *m*CPBA solution, the mixture was stirred for one more hour, then the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (100 mL), the solution washed with saturated aqueous sodium hydrogen carbonate (100 mL and 50 mL), saturated aqueous sodium chloride (50 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue purified by column chromatography (0 to 100% dichloromethane in hexanes) to afford the title compound (398 mg, 1.77 mmol, 64%) as an off-white solid. Additionally, diazocine **2** (100 mg, 480 µmol, 17%) was isolated in the form of a yellow solid.

$\mathbf{R_f}$ = 0.58 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.22 – 7.07 (m, 4H), 7.06 – 6.98 (m, 3H), 6.93 (d, J = 7.8 Hz, 1H), 3.37 (ddd, J = 14.2, 10.2, 5.5 Hz, 1H), 3.23 (ddd, J = 14.8, 10.2, 4.6 Hz, 1H), 2.97 (ddd, J = 14.2, 10.0, 4.7 Hz, 1H), 2.87 (ddd, J = 14.3, 10.0, 5.5 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 148.9, 146.2, 131.9, 131.7, 130.5, 130.4, 129.7, 127.9, 127.4, 127.3, 121.82, 121.75, 31.3, 30.3.

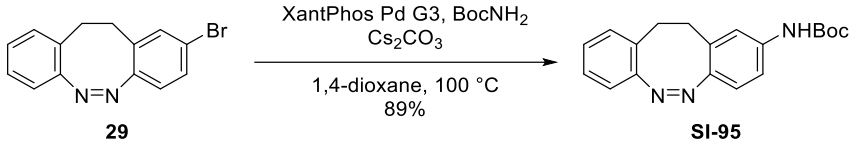
IR: 3062, 3025, 2953, 2938, 2897, 1483, 1466, 1444, 1370, 1345, 1311, 1295, 1263, 1243, 1217, 1186, 1175, 1159, 1135, 1111, 1077, 1036, 992, 983, 951, 930, 908, 890, 874, 778, 766, 749.

HRMS (ESI): $C_{14}H_{13}N_2O$ [M+H] calc. 225.1022, found 225.1026.

The spectroscopic data agrees with previously reported values.[19]

Derivatization of diazocines

tert-butyl (Z)-(11,12-dihydrodibenzo[c,g][1,2]diazocin-2-yl)carbamate (SI-95)



29 **SI-95**

To (Z)-2-bromo-11,12-dihydrodibenzo[c,g][1,2]diazocine (**29**, 750 mg, 2.61 mmol, 1.0 eq.), XantPhos Pd G3[a] (62 mg, 65 µmol, 0.025 eq.), cesium carbonate (1.19 g, 3.66 mmol, 1.4 eq.) and *tert*-butyl carbamate (367 mg, 3.13 mmol, 1.2 eq.) under nitrogen atmosphere was added anhydrous, degassed[b] 1,4-dioxane (8.7 mL). The mixture was warmed to 100 °C and stirred overnight. After removal of the volatiles under reduced pressure, dichloromethane (15 mL) and water (20 mL) were added. The layers were separated and the organic layer washed with additional water (20 mL), then filtered over a small plug Celite®, dried over sodium sulfate and the solvent removed under reduced pressure. The residue was purified by column chromatography (0 to 20% ethyl acetate in hexanes) to afford the title compound (755 mg, 2.33 mmol, 89%) as a yellow foam.

R_f = 0.66 (40% ethyl acetate in hexanes).

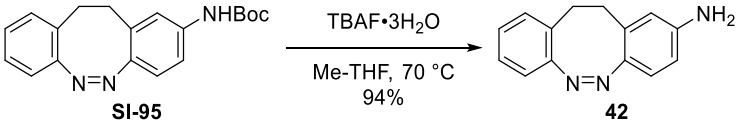
^{1}H-NMR (400 MHz, $CDCl_3$): 7.16 – 7.10 (m, 2H), 7.05 – 6.97 (m, 3H), 6.82 (dd, J = 7.8, 1.3 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.37 (br, 1H), 2.85 (br, 4H), 1.47 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): 155.6, 152.6, 150.9, 137.3, 129.7, 129.2, 128.2, 127.2, 126.8, 120.3, 118.99, 118.96, 116.6, 80.9, 32.3, 31.6, 28.4.

IR: 3310, 2977, 1723, 1705, 1609, 1588, 1521, 1481, 1463, 1447, 1416, 1392, 1367, 1349, 1316, 1287, 1264, 1234, 1155, 1109, 1092, 1055, 1031, 1005, 910, 891, 872, 852, 820, 800, 753, 730.

HRMS (ESI): $C_{19}H_{22}N_3O_2$ [M+H] calc. 324.1707, found 324.1720.

(Z)-11,12-dihydrodibenzo[c,g][1,2]diazocin-2-amine (**42**)



SI-95 **42**

To *tert*-butyl (Z)-(11,12-dihydrodibenzo[c,g][1,2]diazocin-2-yl)carbamate (**SI-95**, 100 mg, 309 µmol, 1.0 eq.) and tetrabutylammonium fluoride trihydrate (488 mg, 1.55 mmol, 5.0 eq.) under nitrogen atmosphere was added anhydrous 2-methyltetrahydrofuran (4 mL) and the mixture was stirred overnight at 70 °C. After cooling to room temperature, the mixture was diluted with saturated aqueous sodium hydrogen carbonate (10 mL) and extracted with ethyl acetate (3×5 mL). The extracts were washed with saturated aqueous sodium chloride (10 mL), dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography (0 to 30% ethyl acetate in hexanes) to afford the title compound (64.7 mg, 290 µmol, 94%) as a yellow solid.

R_f = 0.23 (40% ethyl acetate in hexanes).

[a][(4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methane-sulfonate

[b]Three cycles of evacuating under sonication and refilling with nitrogen.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.13 (ddd, J = 7.8, 6.8, 2.0 Hz, 1H), 7.06 – 6.98 (m, 2H), 6.81 (dd, J = 7.7, 1.2 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 6.44 (dd, J = 8.3, 2.4 Hz, 1H), 6.27 (d, J = 2.4 Hz, 1H), 3.56 (br, 2H), 2.82 (br, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 155.8, 147.9, 145.4, 129.4, 129.3, 128.6, 127.0, 126.7, 121.4, 119.0, 115.5, 113.4, 32.5, 31.5.

^{1}H-NMR (600 MHz, DMSO-d_6): 7.15 (td, J = 7.6, 1.4 Hz, 1H), 7.10 (dd, J = 7.5, 1.4 Hz, 1H), 7.05 (td, J = 7.4, 1.2 Hz, 1H), 6.76 (dd, J = 7.9, 1.2 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 6.35 (dd, J = 8.4, 2.3 Hz, 1H), 6.18 (d, J = 2.3 Hz, 1H), 5.13 (br, 2H), 2.83 – 2.51 (m, 4H).

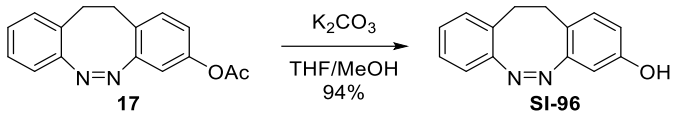
^{13}C-NMR (150 MHz, DMSO-d_6): 155.5, 147.9, 145.4, 129.4, 128.7, 128.4, 126.6, 126.5, 121.0, 118.5, 113.7, 111.9, 31.9, 30.7.

IR: 3444, 3345, 3219, 2945, 2922, 2897, 1604, 1503, 1438, 1308, 1256, 1158, 1107, 1083, 1038, 981, 907, 878, 815, 727.

HRMS (ESI): $C_{14}H_{14}N_3$ [M+H] calc. 224.1182, found 224.1191.

The spectroscopic data agrees with previously reported values.[20]

(Z)-11,12-dihydrodibenzo[c,g][1,2]diazocin-3-ol (SI-96)



To a solution of (Z)-11,12-dihydrodibenzo[c,g][1,2]diazocin-3-yl acetate (**17**, 540 mg, 2.03 mmol, 1.0 eq.) in a mixture of tetrahydrofuran (3 mL) and methanol (9 mL) was added potassium carbonate (280 mg, 2.03 mmol, 1.0 eq.) and the mixture was stirred for 20 minutes. Then dichloromethane (30 mL) was added and the mixture was filtered. The solids were washed with additional dichloromethane (20 mL) and discarded. The filtrate was washed with 2 wt% aqueous citric acid (50 mL) and the washings were extracted with additional dichloromethane (2×15 mL). The combined organic phases were dried over sodium sulfate and the solvent was removed under reduced pressure. The residue crystallized partially upon standing at room temperature overnight. The resulting yellow solids were collected and washed with a minimal amount of dichloromethane to afford the title compound (324 mg, 1.44 mmol, 71%) as a yellow solid. The dichloromethane washings were concentrated under reduced pressure and the residue was purified by column chromatography (0 to 5% methanol in dichloromethane) to afford additional product (103 mg, 459 µmol, 23%) in the form of a yellow solid.

R_f = 0.50 (40% ethyl acetate in hexanes).

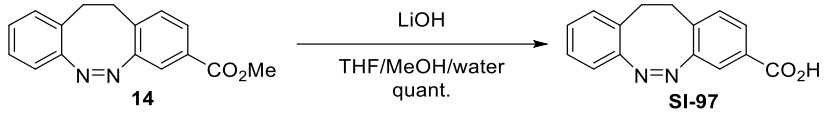
^{1}H-NMR (400 MHz, $CDCl_3$): 7.14 (td, J = 7.5, 1.5 Hz, 1H), 7.03 (td, J = 7.4, 1.3 Hz, 1H), 6.98 (dd, J = 7.6, 1.5 Hz, 1H), 6.83 (d, J = 4.5 Hz, 1H), 6.81 (d, J = 4.0 Hz, 1H), 6.50 (dd, J = 8.3, 2.6 Hz, 1H), 6.33 (d, J = 2.6 Hz, 1H), 5.24 (br, 1H), 3.13 – 2.48 (m, 4H)

^{13}C-NMR (100 MHz, $CDCl_3$): 156.2, 155.3, 154.3, 131.0, 129.8, 128.4, 127.3, 126.8, 120.5, 118.9, 114.5, 105.9, 31.9, 31.0.

IR: 3220, 3066, 3023, 2948, 2897, 2844, 2791, 2736, 2681, 1610, 1582, 1521, 1498, 1480, 1443, 1331, 1279, 1233, 1167, 1139, 1102, 1082, 1038, 981, 946, 911, 880, 842, 817, 754.

HRMS (ESI): $C_{14}H_{13}N_2O$ [M+H] calc. 225.1022, found 225.1026.

(Z)-11,12-dihydrodibenzo[c,g][1,2]diazocine-3-carboxylic acid (SI-97)



Methyl (Z)-11,12-dihydrodibenzo[c,g][1,2]diazocine-3-carboxylate (**14**, 650 mg, 2.44 mmol, 1.0 eq.) was dissolved in tetrahydrofuran (7 mL), then methanol (7 mL), water (7 mL) and lithium hydroxide (164 mg, 6.85 mmol, 2.8 eq.) were added. The mixture was sonicated until all lithium hydroxide had dissolved. After additional stirring for two and a half hours, the mixture was concentrated under reduced pressure, removing most tetrahydrofuran and methanol. The residue was acidified with 2 M aqueous hydrochloric acid (4 mL), the resulting precipitate collected, washed with water and dried to afford the title compound (619 mg, 2.45 mmol, quant.) as a yellow solid.

R_f = 0.23 (5% methanol in dichloromethane).

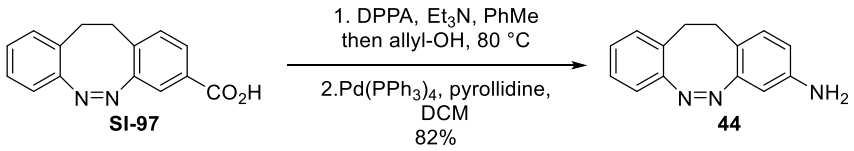
^{1}H-NMR (400 MHz, DMSO-d_6): 13.07 (br, 1H), 7.60 (dd, J = 7.9, 1.8 Hz, 1H), 7.32 (d, J = 1.7 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.18 (ddd, J = 7.7, 6.8, 1.9 Hz, 1H), 7.12 – 7.01 (m, 2H), 6.89 (dd, J = 7.8, 1.2 Hz, 1H), 2.94 – 2.79 (m, 4H).

^{13}C-NMR (100 MHz, DMSO-d_6): 166.4, 155.0, 154.9, 133.5, 130.4, 129.8, 129.5, 127.9, 127.6, 127.3, 127.0, 119.1, 118.3, 31.0, 30.6.

IR: 3061, 3017, 2952, 2898, 2661, 2548, 1691, 1608, 1567, 1480, 1421, 1290, 1257, 1159, 1126, 1083, 909, 839, 754.

HRMS (ESI): $C_{15}H_{13}N_2O_2$ [M+H] calc. 253.0972, found 253.0978.

(Z)-11,12-dihydrodibenzo[c,g][1,2]diazocin-3-amine (**44**)



Step1: To a solution of (Z)-11,12-dihydrodibenzo[c,g][1,2]diazocine-3-carboxylic acid (**SI-97**, 300 mg, 1.19 mmol, 1.0 eq.) in anhydrous toluene (10 mL) under nitrogen atmosphere were added successively diphenylphosphoryl azide (308 µL, 1.43 mmol, 1.2 eq.) and triethylamine (248 µL, 1.78 mmol, 1.5 eq.). After stirring for 35 minutes, allyl alcohol (243 µL, 3.57 mmol, 3.0 eq.) was added and the mixture stirred at 80 °C overnight. The volatiles were then removed under reduced pressure and the residue was purified by column chromatography (0 to 20% ethyl acetate in hexanes) to afford allyl (Z)-(11,12-dihydrodibenzo[c,g][1,2]diazocin-3-yl)carbamate as an orange oil.

Step2: To a solution of allyl (Z)-(11,12-dihydrodibenzo[c,g][1,2]diazocin-3-yl)carbamate and palladium-tetrakis(triphenylphosphine) (27 mg, 24 µmol, 0.02 eq.) in dichloromethane (5 mL) was added pyrrolidine (245 µL, 2.97 mmol, 2.5 eq.) and the mixture was stirred for one and a half hours. The volatiles were then removed under reduced pressure and the residue was purified by column chromatography (0 to 5% ethyl acetate in dichloromethane) to afford the title compound (218 mg, 976 µmol, 82% over 2 steps) as a yellow solid.

R_f = 0.32 (40% ethyl acetate in hexanes).

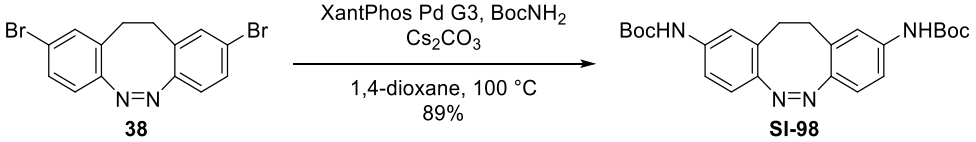
^{1}H-NMR (400 MHz, $CDCl_3$): 7.13 (td, J = 7.5, 1.6 Hz, 1H), 7.01 (td, J = 7.4, 1.3 Hz, 1H), 6.97 (dd, J = 7.7, 1.6 Hz, 1H), 6.81 (dd, J = 7.8, 1.3 Hz, 1H), 6.73 (d, J = 8.1 Hz, 1H), 6.32 (dd, J = 8.2, 2.4 Hz, 1H), 6.15 (d, J = 2.4 Hz, 1H), 3.57 (br, 2H), 3.04 – 2.54 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 156.3, 155.6, 144.9, 130.7, 129.7, 128.6, 127.0, 126.6, 118.9, 118.2, 114.3, 105.2, 32.0, 31.0.

IR: 3443, 3349, 3223, 3063, 3044, 3017, 2945, 2895, 2847, 1621, 1609, 1570, 1517, 1499, 1479, 1457, 1437, 1304, 1276, 1246, 1170, 1147, 1102, 1081, 1038, 980, 945, 909, 876, 840, 815, 789, 752, 728.

HRMS (ESI): $C_{14}H_{14}N_3$ [M+H] calc. 224.1182, found 224.1187.

di-*tert*-butyl (11,12-dihydrodibenzo[c,g][1,2]diazocine-2,9-diyl)(Z)-dicarbamate (SI-98)



To (Z)-2,9-dibromo-11,12-dihydrodibenzo[c,g][1,2]diazocine (**38**, 400 mg, 1.09 mmol, 1.0 eq.), XantPhos Pd G3[a] (26 mg, 27 µmol, 0.025 eq.), cesium carbonate (997 mg, 3.06 mmol, 2.8 eq.) and *tert*-butyl carbamate (307 mg, 2.62 mmol, 2.4 eq.) under nitrogen atmosphere was added anhydrous, degassed[b] 1,4-dioxane (3.6 mL). The mixture was warmed to 100 °C and stirred overnight. The volatiles were then removed under reduced pressure, followed by the addition of dichloromethane (15 mL) and water (20 mL). The layers were separated, the organic layer was washed with water (20 mL), filtered over a small plug of Celite® and dried over sodium sulfate. The solvent was removed under reduced pressure, dichloromethane (2 mL) was added, the mixture was sonicated and filtered. The solids were washed with a small amount of dichloromethane to afford the title compound (265 mg, 604 µmol, 55%) as a yellow solid. The filtrate was concentrated under reduced pressure and the residue purified by column chromatography (0 to 5% ethyl acetate in dichloromethane) to afford further product (163 mg, 372 µmol, 34%) in the form of a brownish-yellow solid.

R_f = 0.55 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.14 (br, 2H), 7.03 (dd, J = 8.5, 2.3 Hz, 2H), 6.78 (d, J = 8.5 Hz, 2H), 6.41 (br, 2H), 2.81 (br, 4H), 1.48 (s, 18H).

^{13}C-NMR (100 MHz, $CDCl_3$): 152.7, 150.9, 137.3, 129.3, 120.4, 118.9, 116.6, 80.8, 32.0, 28.4.

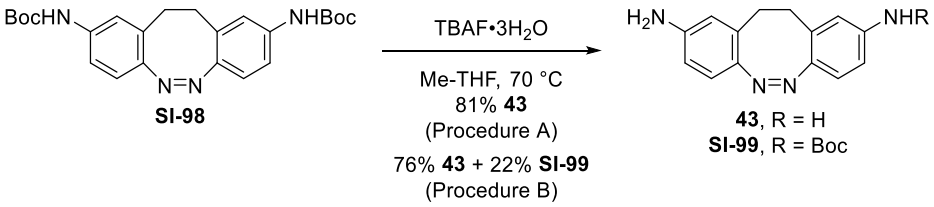
IR: 3311, 2978, 1700, 1609, 1588, 1521, 1456, 1408, 1393, 1367, 1346, 1317, 1286, 1234, 1153, 1100, 1054, 1030, 1005, 908, 895, 884, 869, 826, 809, 771, 730.

HRMS (ESI): $C_{24}H_{31}N_4O_4$ [M+H] calc. 439.2340, found 439.2347.

[a][(4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate

[b]Three cycles of evacuating under sonication followed by refilling with nitrogen.

(Z)-11,12-dihydrodibenzo[c,g][1,2]diazocine-2,9-diamine (**43**)



Procedure A: To di-*tert*-butyl (11,12-dihydrodibenzo[c,g][1,2]diazocine-2,9-diyl)(Z)-dicarbamate (**SI-98**, 20 mg, 46 µmol, 1.0 eq.) and tetrabutylammonium fluoride trihydrate (216 mg, 684 µmol, 15.0 eq.) under nitrogen atmosphere was added anhydrous 2-methyltetrahydrofuran (0.5 mL) and the mixture was stirred at 70 °C for 18 hours. After cooling to room temperature, the mixture was diluted with saturated aqueous sodium hydrogen carbonate (10 mL) and extracted with ethyl acetate (3×5 mL). The extracts were washed with saturated aqueous sodium chloride (10 mL), dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography (70 to 100% ethyl acetate in hexanes) to afford the title compound (8.8 mg, 37 µmol, 81%) as a yellow solid.

Procedure B: To di-*tert*-butyl (11,12-dihydrodibenzo[c,g][1,2]diazocine-2,9-diyl)(Z)-dicarbamate (**SI-98**, 100 mg, 228 µmol, 1.0 eq.) and tetrabutylammonium fluoride trihydrate (719 mg, 2.28 mmol, 10.0 eq.) under nitrogen atmosphere was added anhydrous 2-methyltetrahydrofuran (4 mL) and the mixture was stirred at 70 °C overnight. After cooling to room temperature, the mixture was diluted with saturated aqueous sodium hydrogen carbonate (10 mL) and extracted with ethyl acetate (3×5 mL). The extracts were washed with saturated aqueous sodium chloride (10 mL), dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography (0 to 100% ethyl acetate in hexanes) to afford the title compound (41.1 mg, 172 µmol, 76%) as an orange-yellow solid. Additionally, *tert*-butyl (Z)-(9-amino-11,12-dihydro-dibenzo[c,g][1,2]diazocin-2-yl)carbamate (**SI-99**, 16.9 mg, 49.9 µmol, 22%) was isolated in the form of a yellow solid.

Analytical Data for (Z)-11,12-dihydrodibenzo[c,g][1,2]diazocine-2,9-diamine (**43**)

R_f = 0.44 (ethyl acetate).

^{1}H-NMR (400 MHz, $CDCl_3$): 6.71 (d, J = 8.3 Hz, 2H), 6.45 (dd, J = 8.4, 2.4 Hz, 2H), 6.30 (d, J = 2.4 Hz, 2H), 3.57 (br, 4H), 2.73 (s, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): 147.8, 145.3, 129.8, 121.6, 115.3, 113.3, 32.1.

^{1}H-NMR (400 MHz, CD_3OD): 6.61 (d, J = 8.4 Hz, 2H), 6.50 (dd, J = 8.4, 2.4 Hz, 2H), 6.39 (d, J = 2.4 Hz, 2H), 2.70 (br, 4H).

^{13}C-NMR (100 MHz, CD_3OD): 148.4, 147.8, 131.3, 122.3, 116.2, 114.3, 32.9.

^{1}H-NMR (400 MHz, DMSO-d_6): 6.54 (d, J = 8.3 Hz, 2H), 6.35 (dd, J = 8.4, 2.3 Hz, 2H), 6.22 (d, J = 2.3 Hz, 2H), 5.07 (s, 4H), 2.56 (s, 4H).

^{13}C-NMR (100 MHz, DMSO-d_6): 147.5, 145.37, 129.16, 121.20, 113.45, 111.81, 31.62.

IR: 3416, 3321, 3200, 3046, 2938, 2894, 2841, 1603, 1495, 1353, 1307, 1254, 1158, 1106, 999, 954, 870, 812, 731.

HRMS (ESI): $C_{14}H_{15}N_4$ [M+H] calc. 239.1291, found 239.1299.

The ^{1}H-NMR data agrees with previously reported values[21] (CD_3OD), while the ^{13}C-NMR data differs. All signals are shifted by +1.4 to 1.5 ppm with respect to the reported values and instead of the reported eight signals, we only observed seven signals.

Analytical Data for *tert*-butyl (Z)-(9-amino-11,12-dihydrodibenzo[c,g][1,2]diazocin-2-yl)-carbamate (SI-99)

R_f = 0.47 (66% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.20 (br, 1H), 6.99 (dd, J = 8.5, 2.3 Hz, 1H), 6.77 (d, J = 8.5 Hz, 1H), 6.71 (d, J = 8.3 Hz, 1H), 6.45 (dd, J = 8.3, 2.4 Hz, 1H), 6.40 (br, 1H), 6.27 (d, J = 2.4 Hz, 1H), 3.58 (br, 2H), 2.79 (br, 4H), 1.49 (s, 9H).

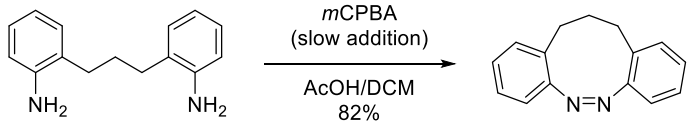
^{13}C-NMR (100 MHz, $CDCl_3$): 152.7, 151.0, 147.8, 145.5, 137.1, 129.7, 129.4, 121.5, 120.4, 118.8, 116.5, 115.5, 113.4, 80.8, 32.2, 32.0, 28.4.

IR: 3344, 3232, 2978, 2935, 1708, 1606, 1518, 1412, 1367, 1315, 1236, 1155, 1055, 906, 820, 726.

HRMS (ESI): $C_{19}H_{23}N_4O_2$ [M+H] calc. 339.1816, found 339.1825.

Syntheses of new cyclic azobenzenes

(Z)-12,13-dihydro-11H-dibenzo[c,h][1,2]diazonine (66)



65 **66**

A freshly prepared and titrated (0.62 M) solution of *m*CPBA in acetic acid (806 µL, 0.500 mmol, 2.0 eq.) was added by syringe pump within a period of 12 hours to a solution of 2,2'--(propane-1,3-diyl)dianiline (**65**, 56.6 mg, 0.250 mmol, 1.0 eq.) in acetic acid/dichloromethane = 1/3 (6.25 mL) under rapid stirring. After the complete addition of the *m*CPBA solution, the mixture was stirred for one more hour, then the volatiles were removed under reduced pressure. The residue was dissolved in ethyl acetate (10 mL), the solution washed with saturated aqueous sodium hydrogen carbonate (2×5 mL), saturated aqueous sodium chloride (5 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue purified by column chromatography (0 to 5% ethyl acetate in hexanes) to afford the title compound (45.6 mg, 0.205 mmol, 82%) as an orange solid. The initially obtained material consisted of a mixture of isomers, which converged to one isomer upon storage as a solid, also resulting in a change of color from orange to yellow.

R_f = 0.64 (20% ethyl acetate in hexanes).

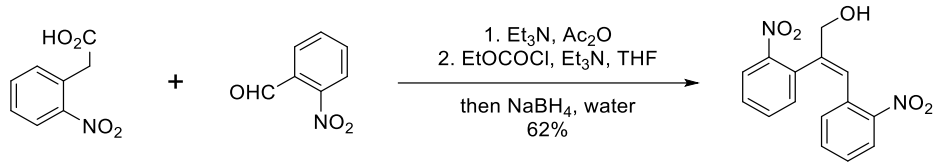
^{1}H-NMR (600 MHz, $CDCl_3$): 6.96 (td, J = 7.5, 1.6 Hz, 2H), 6.93 (dd, J = 7.7, 1.6 Hz, 2H), 6.89 (td, J = 7.4, 1.3 Hz, 2H), 6.38 (dd, J = 7.7, 1.3 Hz, 2H), 2.71 (dd, J = 13.5, 5.7 Hz, 2H), 2.39 (t, J = 13.2 Hz, 2H), 2.15 (dt, J = 12.0, 5.6 Hz, 1H), 1.37 (q, J = 13.1 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): 155.4, 130.3, 129.7, 126.5, 126.1, 117.4, 31.5, 30.1.

IR: 3064, 3014, 2928, 2857, 1598, 1575, 1515, 1478, 1462, 1441, 1351, 1335, 1314, 1285, 1257, 1232, 1203, 1156, 1148, 1100, 1085, 1045, 1017, 977, 959, 949, 939, 912, 870, 846, 836, 804, 785, 748, 733, 703.

HRMS (ESI): $C_{15}H_{15}N_2$ [M+H] calc. 223.1230, found 223.1233.

E)-2,3-bis(2-nitrophenyl)prop-2-en-1-ol (SI-100)



61 62 SI-100

Step 1:[22] A mixture of 2-(2-nitrophenyl)acetic acid (**61**, 2.00 g, 11.0 mmol, 1.0 eq.), 2-nitrobenzaldehyde (**62**, 1.67 g, 11.0 mmol, 1.0 eq.), triethylamine (1.69 mL, 12.1 mmol, 1.1 eq.) and acetic anhydride (11.0 mL, 117 mmol, 10.6 eq.) was stirred at 50 °C for one day. After cooling to room temperature, the mixture was diluted with water (45 mL) and stirred vigorously for one hour. Then the aqueous phase was decanted, water (80 mL) and 10 wt% aqueous ammonia (20 mL) were added to the residue, the mixture was briefly brought to boil, cooled to room temperature and filtered again. The solids were discarded and the filtrate was acidified with half-concentrated hydrochloric acid (10 mL). The resulting precipitate was collected and recrystallized from dichloromethane to afford (E)-2,3-bis(2-nitro-phenyl)acrylic acid (427 mg, 1.36 mmol, 12%) as an off-white solid. The mother liquors of the recrystallization were diluted with hexanes and more precipitate formed, which was collected to yield additional product (2.05 g, 6.52 mmol, 59%) in the form of a faint brown solid.

Step 2: To a solution of (E)-2,3-bis(2-nitrophenyl)acrylic acid (1.20 g, 3.82 mmol, 1.0 eq.) and triethylamine (664 µL, 4.77 mmol, 1.25 eq.) in anhydrous tetrahydrofuran (19 mL) under nitrogen atmosphere was dropwise added ethyl chloroformate (456 µL, 4.77 mmol, 1.25 eq.) with ice-bath cooling. The mixture was stirred for one hour and 20 minutes, then sodium borohydride (578 mg, 15.3 mmol, 4.0 eq.) was added, followed by the careful addition of water (0.5 mL). The mixture was stirred open to ambient atmosphere for several minutes until the evolution of gas had subsided, then additional water (6.5 mL) was added. After stirring for two more hours and warming to approx. 5 °C, the mixture was carefully acidified with 2 M aqueous hydrochloric acid (10 mL), diluted with water (40 mL) and extracted with ethyl acetate (3×20 mL). The extracts were washed with saturated aqueous sodium hydrogen carbonate (40 mL), saturated aqueous sodium chloride (40 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure und the residue purified by column chromatography (0 to 2% methanol in dichloromethane) to afford the title compound (994 mg, 3.31 mmol, 87%) as a yellow oil.

R_f = 0.32 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, DMSO-d_6): 7.97 – 7.90 (m, 2H), 7.60 (td, *J* = 7.5, 1.3 Hz, 1H), 7.49 (ddd, *J* = 8.1, 7.5, 1.5 Hz, 1H), 7.39 – 7.34 (m, 2H), 7.28 – 7.25 (m, 1H), 7.04 – 7.02 (m, 1H), 6.99 – 6.94 (m, 1H), 5.43 (t, *J* = 5.6 Hz, 1H), 4.25 (dd, J = 5.6, 1.8 Hz, 2H).

^{13}C-NMR (100 MHz, DMSO-d_6): 148.6, 148.0, 142.8, 133.5, 133.0, 132.7, 132.2, 131.5, 131.1, 129.1, 128.3, 124.3, 124.2, 121.6, 64.4.

^{1}H-NMR (400 MHz, $CDCl_3$): 8.00 – 7.92 (m, 2H), 7.45 (td, J = 7.5, 1.4 Hz, 1H), 7.38 (ddd, J = 8.0, 7.4, 1.6 Hz, 1H), 7.31 – 7.23 (m, 2H), 7.18 – 7.12 (m, 2H), 7.05 – 6.99 (m, 1H), 4.50 (d, J = 5.0 Hz, 2H), 1.85 (t, J = 6.2 Hz, 1H).

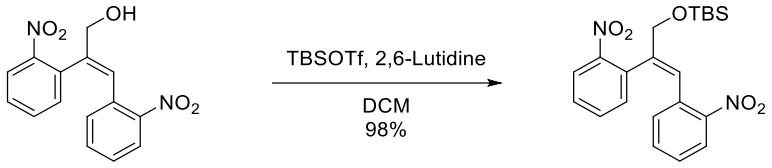
^{13}C-NMR (100 MHz, $CDCl_3$): 148.9, 148.3, 141.9, 133.8, 133.5, 133.1, 132.5, 132.3, 131.6, 129.0, 128.3, 124.8, 124.6, 124.5, 66.9.

IR: 1608, 1571, 1516, 1481, 1439, 1340, 1298, 1262, 1210, 1163, 1144, 1098, 1077, 1062, 1040, 1005, 978, 961, 909, 890, 852, 786, 750, 735, 704.

HRMS (ESI): $C_{15}H_{12}N_2NaO_5$ [M+Na] calc. 323.0638, found 323.0647.

The spectroscopic data agrees with previously reported values.[23]

(E)-((2,3-bis(2-nitrophenyl)allyl)oxy)(*tert*-butyl)dimethylsilane (SI-101)



SI-100 **SI-101**

To a solution of (E)-2,3-bis(2-nitrophenyl)prop-2-en-1-ol (**SI-100**, 856 mg, 2.40 mmol, 1.0 eq.) in anhydrous dichloromethane (20 mL) were added 2,6-lutidine (416 µL, 3.59 mmol, 1.5 eq.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (687 µL, 2.99 mmol, 1.25 eq.) under ice-bath cooling. The mixture was stirred with ice-bath cooling for two hours, then diluted with dichloromethane (10 mL), washed with 2 M aqueous hydrochloric acid (20 mL), saturated aqueous sodium hydrogen carbonate (20 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue purified by column chromatography (0 to 10% ethyl acetate in hexanes) to afford the title compound (969 mg, 2.34 mmol, 98%) as a yellow oil.

R_f = 0.49 (20% ethyl acetate in hexanes).

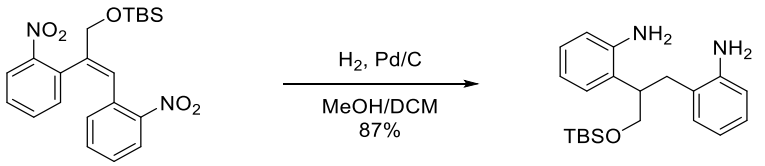
^{1}H-NMR (400 MHz, DMSO-d_6): 7.98 – 7.92 (m, 2H), 7.62 (td, *J* = 7.5, 1.3 Hz, 1H), 7.51 (ddd, *J* = 8.7, 7.5, 1.5 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.29 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.07 – 7.04 (m, 1H), 7.00 – 6.93 (m, 1H), 4.45 (d, *J* = 1.8 Hz, 2H), 0.84 (s, 9H), 0.05 (s, 6H).

^{13}C-NMR (100 MHz, DMSO-d_6): 148.6, 148.0, 141.4, 133.5, 133.1, 132.3, 132.0, 131.2, 131.0, 129.3, 128.4, 124.3, 124.2, 121.8, 65.7, 25.7, 17.9, -5.6.

IR: 2954, 2928, 2884, 2856, 1609, 1572, 1521, 1471, 1463, 1440, 1408, 1390, 1343, 1297, 1254, 1213, 1188, 1163, 1126, 1085, 1055, 1019, 1005, 959, 939, 881, 869, 851, 836, 816, 779, 748, 737, 706.

HRMS (ESI): $C_{21}H_{26}N_2NaO_5Si$ [M+Na] calc. 437.1503, found 437.1503.

2,2'-(3-((*tert*-butyldimethylsilyl)oxy)propane-1,2-diyl)dianiline (63)



SI-101 **63**

Palladium on carbon (10 wt%, 89.9 mg) and (E)-((2,3-bis(2-nitrophenyl)allyl)oxy)-(*tert*-butyl)dimethylsilane (**SI-101**, 350 mg, 0.844 mmol) were placed in a round bottom flask and wetted with a minimal amount of dichloromethane. Methanol (20 mL) was added, the flask evacuated and refilled with hydrogen. After one day of stirring under a balloon of hydrogen, the mixture was diluted with dichloromethane and a small amount of Celite® was added. The mixture was stirred further for several minutes, then filtered over a pad of Celite® and the Celite® washed with additional dichloromethane. The solvent was removed under reduced pressure and the residue purified by column chromatography (0 to 70% ethyl acetate in hexanes) to afford the title compound (263 mg, 0.738 mmol, 87%) as a yellow oil.

R_f = 0.45 (40% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.11 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.02 (tt, *J* = 7.7, 1.6 Hz, 2H), 6.87 (dd, *J* = 7.5, 1.6 Hz, 1H), 6.78 (td, *J* = 7.5, 1.3 Hz, 1H), 6.68 – 6.59 (m, 3H), 3.86 (dd, *J* = 9.6, 6.6

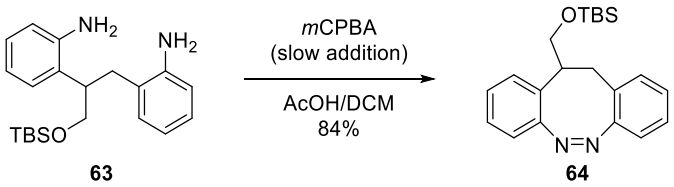
Hz, 1H), 3.74 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.68 (br, 4H), 3.25 – 3.11 (m, 2H), 2.70 (dd, *J* = 13.4, 6.9 Hz, 1H), 0.90 (s, 9H), -0.01 (s, 3H), -0.01 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 144.93, 144.86, 130.9, 128.6, 127.43, 127.41, 127.2, 125.1, 119.2, 118.5, 116.5, 115.6, 66.3, 41.6, 33.9, 26.1, 18.4, -5.5.

IR: 3440, 3357, 3024, 2953, 2927, 2896, 2884, 2856, 1621, 1583, 1496, 1470, 1455, 1408, 1389, 1361, 1304, 1273, 1253, 1217, 1158, 1095, 1070, 1004, 954, 938, 908, 834, 814, 776, 747, 729.

HRMS (ESI): $C_{21}H_{33}N_2OSi$ [M+H] calc. 357.2357, found 357.2355.

2,2'-(3-((*tert*-butyldimethylsilyl)oxy)propane-1,2-diyl)dianiline (**64**)



A freshly prepared and titrated (0.605 M) solution of *m*CPBA in acetic acid (826 µL, 0.500 mmol, 2.0 eq.) was added by syringe pump within a period of 12 hours to a solution of 2,2'-(3-((*tert*-butyldimethyl-silyl)oxy)propane-1,2-diyl)dianiline (**63**, 89.1 mg, 0.250 mmol, 1.0 eq.) in acetic acid/dichloromethane = 1/3 (6.25 mL) under rapid stirring. After the complete addition of the *m*CPBA solution, the mixture was stirred for three more hours, then the volatiles were removed under reduced pressure. The residue was dissolved in ethyl acetate (10 mL), the solution washed with saturated aqueous sodium hydrogen carbonate (2×5 mL), saturated aqueous sodium chloride (5 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue purified by column chromatography (0 to 5% ethyl acetate in hexanes) to afford the title compound (74.4 mg, 0.211 mmol, 84%) as an orange solid. The isolated material consisted of a 1/10 mixture of compounds, which were tentatively assigned to be two non-interconverting conformers differing in the orientation of the CH_2OTBS group.

The NMR spectroscopic data is reported for the main component of the mixture.

R_f = 0.69 (20% ethyl acetate in hexanes).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.17 – 7.08 (m, 3H), 7.05 (td, *J* = 7.4, 1.4 Hz, 1H), 6.98 (td, *J* = 7.4, 1.3 Hz, 1H), 6.92 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.88 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.80 (dd, *J* = 7.9, 1.3 Hz, 1H), 3.69 (d, *J* = 6.9 Hz, 2H), 3.14 (ddt, *J* = 10.8, 8.4, 7.0 Hz, 1H), 2.87 (dd, *J* = 13.8, 8.5 Hz, 1H), 2.40 (dd, *J* = 13.8, 10.8 Hz, 1H), 0.86 (s, 9H), -0.02 (s, 3H), -0.05 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): 155.6, 154.8, 132.1, 129.6, 128.6, 128.4, 127.3, 127.03, 126.98,[a] 120.0, 118.3, 67.4, 50.4, 33.5, 26.0, 18.4, -5.4, -5.5.

IR: 2953, 2927, 2884, 2855, 1471, 1462, 1439, 1407, 1384, 1361, 1252, 1212, 1177, 1155, 1098, 1060, 1035, 1006, 986, 947, 940, 909, 833, 814, 796, 775, 761, 736.

HRMS (ESI): $C_{21}H_{29}N_2OSi$ [M+H] calc. 353.2044, found 353.2059.

[a]The signal at 126.98 ppm corresponds to two carbons.

3 References

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For Section 2 (Part II: Synthesis of cyclic azobenzenes)

See page 135.

Appendix

1 Glossary

2–5A 2’,5’ phospho-diester-linked oligoadenylates

9-BBN 9-borabicyclo[3.3.1]nonane

Ac acetyl

Alloc allyloxycarbonyl

AMP adenosine monophosphate

APCI atmospheric pressure chemical ionization

ATP adenosine triphosphate

ATR attenuated total reflectance

Boc tert-butyloxycarbonyl

BSA bis(trimethylsilyl)acetamide

Bz benzoyl

CDI carbonyldiimidazole

cod 1,5-cyclooctadiene

conc. concentrated

COSY homonuclear correlation spectroscopy

CSA camphorsulfonic acid

Cy cyclohexyl

DABCO 1,4-diazabicyclo[2.2.2]octane

DBU 1,8 diazabicyclo[5.4.0]undec-7-ene

DCE 1,2-dichloroethane

DCM dichloromethane

DDQ 2,3-dichloro-5,6-dicyano-1,4-benzo-quinone

DFG German Research Foundation

DFT density functional theory

DIAD diisopropyl azodicarboxylate

DIBAL-H diisobutylaluminum hydride

DIC N,N′-diisopropylcarbodiimide

DIPEA diisopropylethylamine

DMAP 4-dimethylaminopyridine

DMF dimethylformamide

DMP Dess-Martin periodinane

DMSO dimethyl sulfoxide

dpm 2,2,6,6-tetramethyl-3,5-heptanedionato

DPPA diphenylphosphoryl azide

EDG electron-donating group

EI electron ionization

eq. equivalents

ESI electrospray ionization

Et ethyl

EWG electron-withdrawing group

FID flame ionization detector

Grubbs I first-generation Grubbs catalyst benzylidene-bis(tricyclohexylphosphino)-dichlororuthenium

Grubbs II second-generation Grubbs catalyst [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethylene)-(tricyclohexylphosphino)ruthenium

HAT hydrogen atom transfer

HFIP hexafluoroisopropanol

HMBC heteronuclear multiple bond coherence

Hoveyda Grubbs I First-generation Hoveyda–Grubbs catalyst dichloro(o-isopropoxyphenylmethylene)(tricyclohexylphosphine)ruthenium(II)

Hoveyda Grubbs II Second-generation Hoveyda–Grubbs catalyst [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro-(o-isopropoxyphenylmethylene)ruthenium

HPLC high-performance liquid chromatography

HR high resolution

HSQC heteronuclear single quantum coherence

***i*Pr** isopropyl

IR infrared

LAH lithium aluminum hydride

LC liquid chromatography

LDA lithium diisopropylamide

LED light-emitting diode

LiHMDS lithium bis(trimethylsilyl)amide

LR low resolution

mCPBA *meta*-chloroperoxybenzoic acid

Me methyl

MMPP magnesium monoperoxyphthalate

MS mass spectrometry

Ms Methanesulfonyl

NaHMDS sodium bis(trimethylsilyl)amide

NBS *N*-bromosuccinimide

***n*Bu** *n*-butyl

NIH National Institutes of Health

NIS *N*-iodosuccinimide

NMR nuclear magnetic resonance

NOESY nuclear Overhauser enhancement correlation spectroscopy

Tf trifluoromethanesulfonyl

***p*ABSA** 4 acetamido-benzenesulfonyl azide

PBS phosphate-buffered saline

PCC pyridinium chlorochromate

PDE phosphodiesterase

pfb heptafluorobutyrate

Ph phenyl

Phth phthaloyl

PIDA phenyliodine(III) diacetate

Piv pivaloyl

PPTS pyridinium *p*-toluenesulfonate

PSS photostationary state

PTSA *p*-toluenesulfonic acid

R_f retardation factors

RNA ribonucleic acid

rt room temperature

SAR structure-activity relationship

TBAB tetrabutylammonium bromide

TBAF tetrabutylammonium fluoride

TBHP *tert*-butyl hydroperoxide

TBS *tert*-butyldimethylsilyl

***t*Bu** *tert*-butyl

TEMPO 2,2,6,6-tetramethylpiperidinyloxyl

Tf trifluoromethanesulfonyl

TFA trifluoroacetic acid or trifluoroacetate

TFAA trifluoroacetic anhydride

TFE trifluoroethanol

THF tetrahydrofuran

TLC thin-layer chromatography

TMS trimethylsilyl

TOF time-of-flight

UV ultraviolet

Vis visible

Xanthphos 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

2 X-ray crystallographic data

2.1 Part I: Synthetic studies toward A-74528

General information

The structures depicted in the preceding sections were generated with the program Chemcraft based on xyz-files extracted from the res- or cif-file with the program Mercury.[1] Data collection and structure solution/refinement for compounds **53**, **63**, **67**, **83**, **150** and **154** was performed by Dr. Peter Mayer at the Ludwig Maximilian University of Munich. The programs CrysAlisPro[2] (Oxford diffractometer) or Bruker SAINT[3] and SADABS[4] (Bruker diffractometers) were applied for the integration, scaling and multi-scan absorption correction of the data. The structures were solved by direct methods with SIR97[5] and refined by least-squares methods against F2 with SHELXL-97.[6] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. Plotting of thermal ellipsoids for compounds **53**, **63**, **67**, **83**, **150** and **154** depicted in the following was carried out using the program Ortep-3[7] for Windows.
Data collection and structure solution/refinement for compound **189** was performed by Dr. Chunhua Hu at New York University using a Bruker APEX-II CCD system. The Bruker SAINT[3] software package was applied for the integration, scaling and multi-scan absorption correction of the data. The structure was solved by direct methods with SHELXT[8] and refined by least-squares methods against F2 with SHELXL-2018/3.[9] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. Plotting of thermal ellipsoids for compound **189** depicted in the following was carried out using the program Diamond.[10]

References

(1) Macrae, C. F.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Shields, G. P.; Taylor, R.; Towler, M.; van de Streek, J. Mercury: visualization and analysis of crystal structures. *J. Appl. Cryst.* **2006**, *39*, 453.

(2) Agilent **2014**. CrysAlis PRO. Agilent Technologies Ltd, Yarnton, Oxfordshire, England.

(3) Bruker **2012**. SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.

(4) Bruker **2001**. SADABS. Bruker AXS Inc., Madison, Wisconsin, USA.

(5) Altomare, A., Burla, M. C., Camalli, M., Cascarano, G. L., Giacovazzo, C., Guagliardi, A., Moliterni, A. G. G., Polidori, G.; Spagna, R. SIR97: a new tool for crystal structure determination and refinement. *J. Appl. Cryst.* **1999**, *32*, 115.

(6) Sheldrick, G. M. Crystal structure refinement with SHELXL. *Acta Cryst.* **2015**. *C71*, 3.

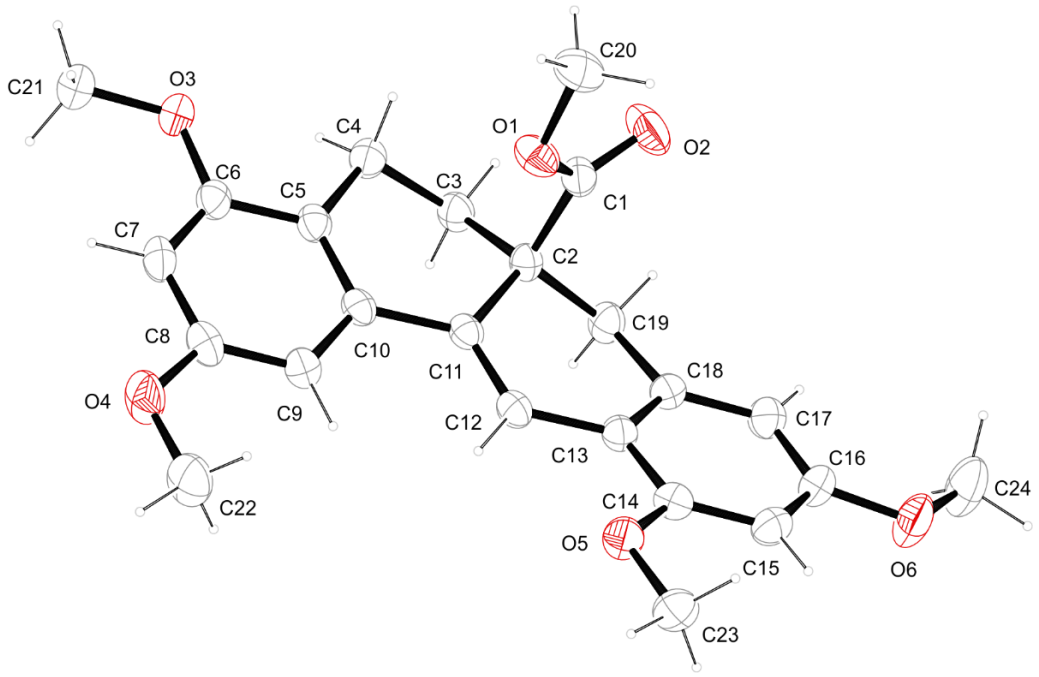
(7) Farrugia, L. J. WinGX and ORTEP for Windows: an update. *J. Appl. Cryst.* **2012**, *45*, 849.

(8) Sheldrick, G. M. SHELXT – Integrated space-group and crystal-structure determination. *Acta Cryst.* **2015**, *A71*, 3.

(9) Sheldrick, G. M. Crystal structure refinement with SHELXL. *Acta Cryst.* **2015,** *C71*, 3

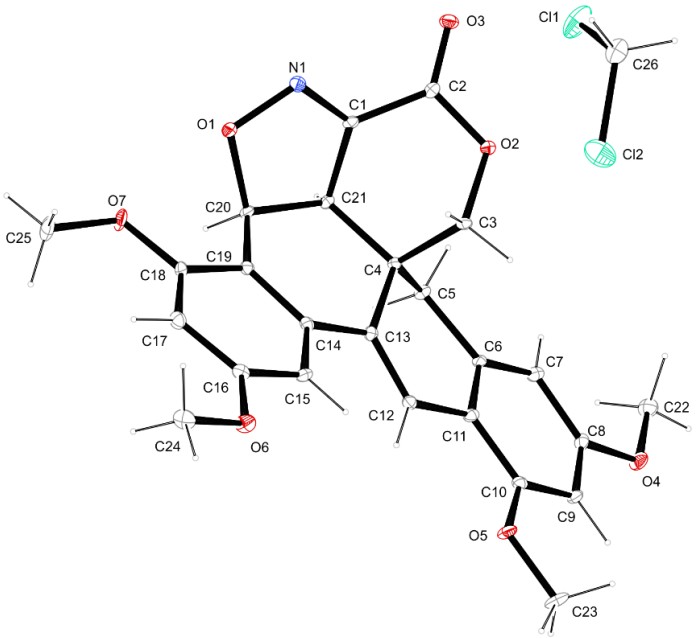
(10) Brandenburg, K. **1999**. DIAMOND. Crystal Impact GbR, Bonn, Germany.

Compound **53**



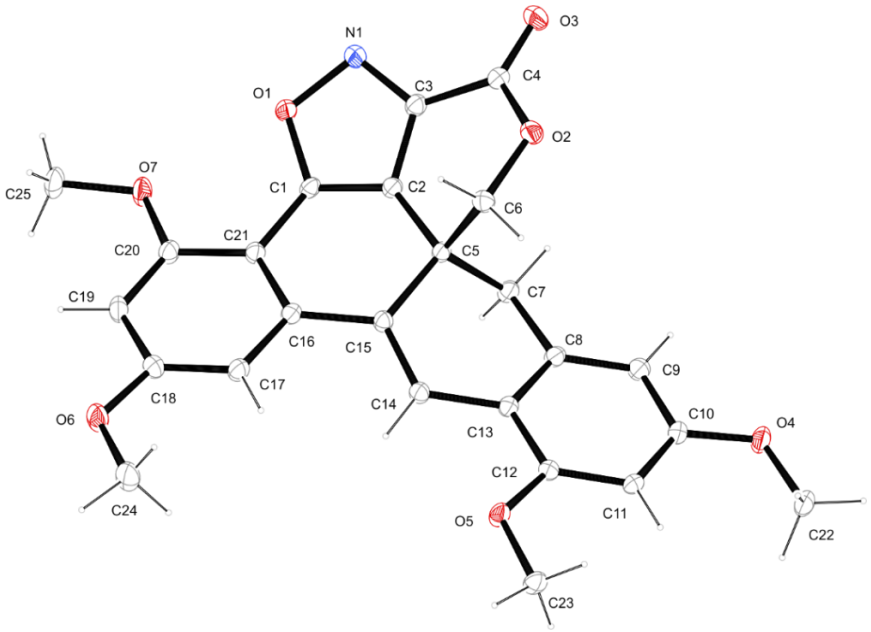
identification code	C24H26O6_uo006_trauner
net formula	$C_{24}H_{26}O_6$
M_r/g mol^{-1}	410.45
crystal size/mm	0.431 × 0.349 × 0.258
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	'P 21/c'
a/Å	9.9674(6)
b/Å	21.3935(10)
c/Å	10.1381(6)
α/°	90
β/°	110.797(7)
γ/°	90
V/Å^3	2021.0(2)
Z	4
calc. density/g cm^{-3}	1.349
μ/mm^{-1}	0.096
absorption correction	'multi-scan'
transmission factor range	0.99175–1.00000
refls. measured	11656
R_{int}	0.0324
mean σ(I)/I	0.0419
θ range	4.241–26.368
observed refls.	3069
x, y (weighting scheme)	0.0440, 0.4881
hydrogen refinement	constr
refls in refinement	4126
parameters	276
restraints	0
$R(F_{obs})$	0.0449
$R_w(F^2)$	0.1122
S	1.025
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.224
min electron density/e Å^{-3}	−0.195

Compound **63**



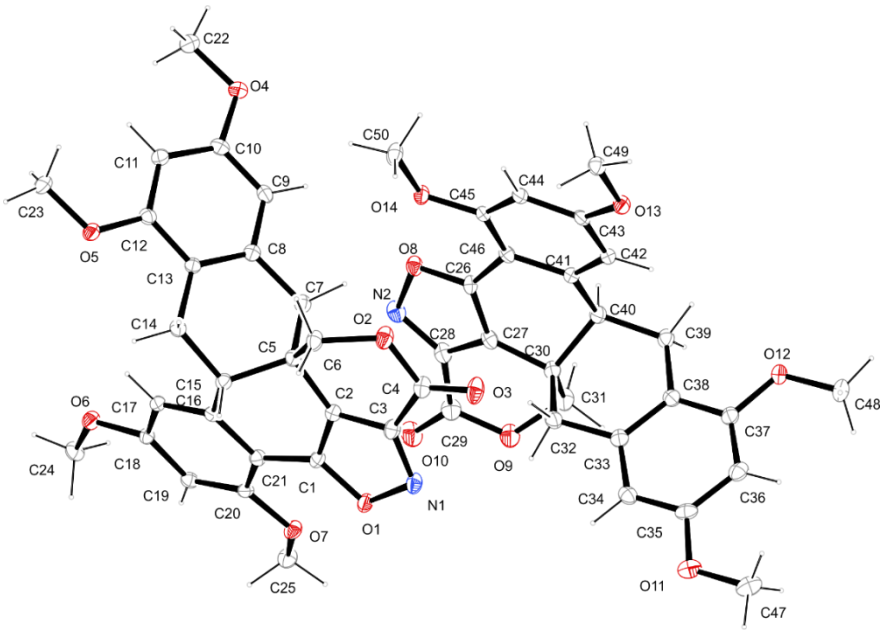
identification code	C25H23NO7_CH2Cl2_tv404_trauner
net formula	$C_{26}H_{25}Cl_2NO_7$
M_r/g mol^{-1}	534.37
crystal size/mm	0.100 × 0.060 × 0.040
T/K	100(2)
radiation	MoKα
diffractometer	'Bruker D8Venture'
crystal system	triclinic
space group	'P -1'
a/Å	9.6421(5)
b/Å	11.0129(5)
c/Å	11.8736(6)
α/°	95.0345(16)
β/°	102.8496(17)
γ/°	97.6363(15)
V/Å^3	1209.34(10)
Z	2
calc. density/g cm^{-3}	1.467
μ/mm^{-1}	0.317
absorption correction	multi-scan
transmission factor range	0.8553–0.9580
refls. measured	14075
R_{int}	0.0411
mean σ(I)/I	0.0424
θ range	3.131–25.37
observed refls.	3490
x, y (weighting scheme)	0.0464, 1.7450
hydrogen refinement	constr
refls in refinement	4427
parameters	329
restraints	0
$R(F_{obs})$	0.0462
$R_w(F^2)$	0.1193
S	1.026
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.491
min electron density/e Å^{-3}	−0.535

Compound **67**



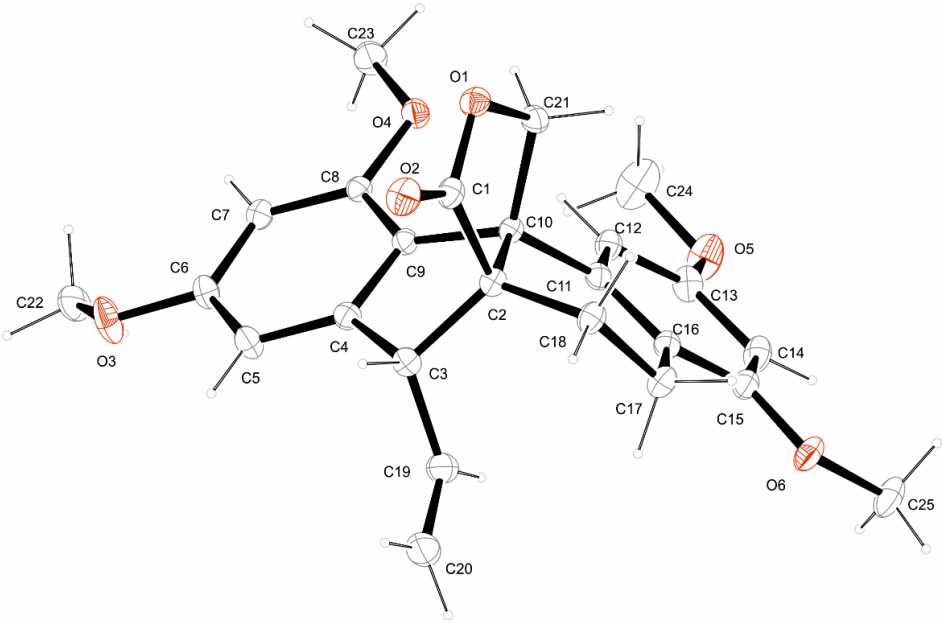
identification code	C25H21NO7_uo014_trauner
net formula	$C_{25}H_{21}NO_7$
M_r/g mol^{-1}	447.43
crystal size/mm	0.484 × 0.445 × 0.365
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	triclinic
space group	'P -1'
a/Å	8.4941(6)
b/Å	10.9645(8)
c/Å	12.3172(9)
α/°	68.162(7)
β/°	74.824(6)
γ/°	79.407(6)
V/Å^3	1022.90(14)
Z	2
calc. density/g cm^{-3}	1.453
μ/mm^{-1}	0.107
absorption correction	'multi-scan'
transmission factor range	0.97011–1.00000
refls. measured	5681
R_{int}	0.0161
mean σ(I)/I	0.0355
θ range	4.413–26.371
observed refls.	3283
x, y (weighting scheme)	0.0520, 0.2218
hydrogen refinement	constr
refls in refinement	4132
parameters	302
restraints	0
$R(F_{obs})$	0.0413
$R_w(F^2)$	0.1108
S	1.04
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.244
min electron density/e Å^{-3}	−0.223

Compound **83**



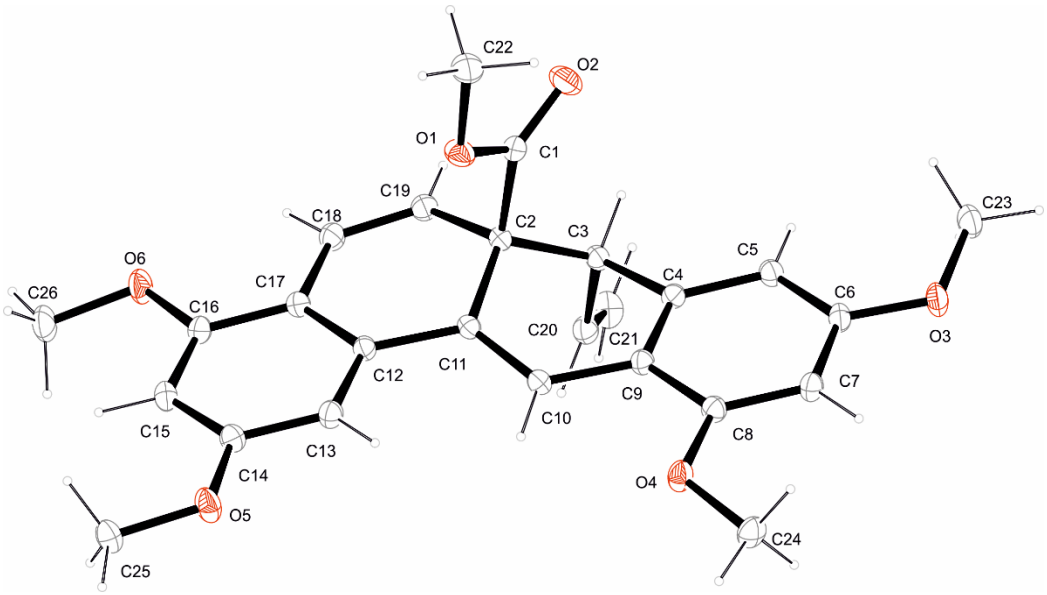
identification code	C25H23NO7_uv160_trauner
net formula	$C_{25}H_{23}NO_7$
M_r/g mol^{-1}	449.44
crystal size/mm	0.100 × 0.070 × 0.020
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21/n 1'
a/Å	7.5094(5)
b/Å	26.7265(19)
c/Å	20.8946(14)
α/°	90
β/°	94.478(2)
γ/°	90
V/Å^3	4180.7(5)
Z	8
calc. density/g cm^{-3}	1.428
μ/mm^{-1}	0.105
absorption correction	Multi-Scan
transmission factor range	0.8743–0.9585
refls. measured	50766
R_{int}	0.1015
mean σ(I)/I	0.0681
θ range	3.202–26.368
observed refls.	5674
x, y (weighting scheme)	0.0464, 1.8499
hydrogen refinement	constr
refls in refinement	8527
parameters	603
restraints	0
$R(F_{obs})$	0.0564
$R_w(F^2)$	0.1251
S	1.029
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.224
min electron density/e Å^{-3}	−0.252

Compound **154**



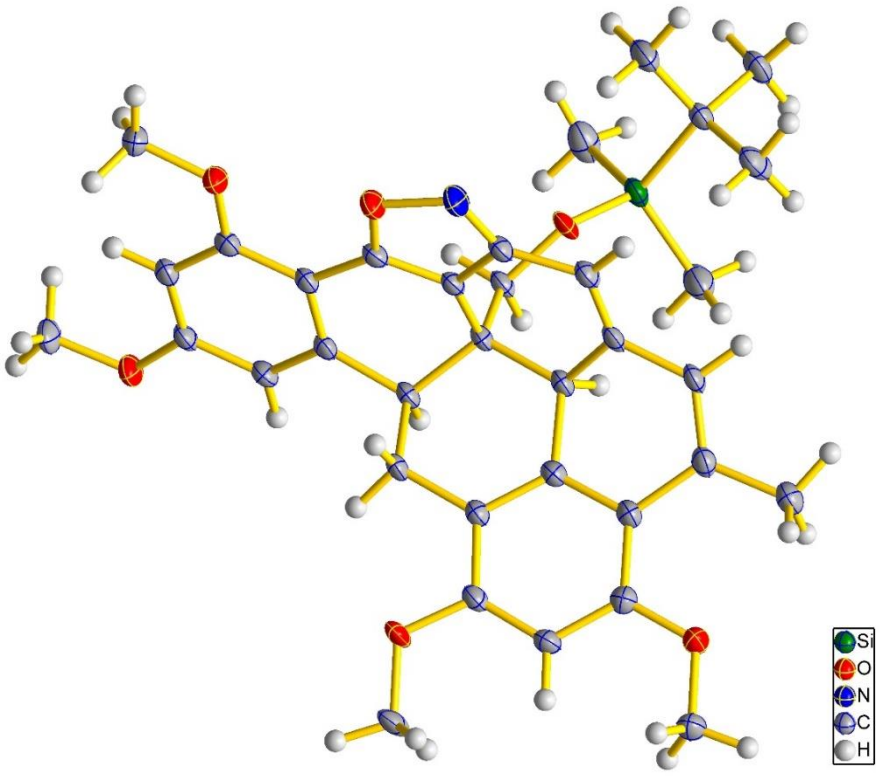
identification code	C25H26O6_uv556_trauner
net formula	$C_{25}H_{26}O_6$
M_r/g mol^{-1}	422.46
crystal size/mm	0.100 × 0.070 × 0.050
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	triclinic
space group	'P -1'
a/Å	8.4504(2)
b/Å	9.5743(2)
c/Å	13.8868(3)
α/°	72.9990(10)
β/°	85.5420(10)
γ/°	76.9410(10)
V/Å^3	1046.57(4)
Z	2
calc. density/g cm^{-3}	1.341
μ/mm^{-1}	0.095
absorption correction	Multi-Scan
transmission factor range	0.9384–0.9705
refls. measured	27075
R_{int}	0.0379
mean σ(I)/I	0.0335
θ range	3.263–30.507
observed refls.	5163
x, y (weighting scheme)	0.0689, 0.3424
hydrogen refinement	constr
refls in refinement	6364
parameters	284
restraints	0
$R(F_{obs})$	0.0436
$R_w(F^2)$	0.1383
S	1.105
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.5
min electron density/e Å^{-3}	−0.391

Compound **150**



identification code	C26H26O6_uv555_trauner
net formula	$C_{26}H_{26}O_6$
M_r/g mol^{-1}	434.47
crystal size/mm	0.100 × 0.090 × 0.080
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	triclinic
space group	'P -1'
a/Å	7.6291(3)
b/Å	8.4554(3)
c/Å	16.5462(6)
α/°	81.9640(10)
β/°	86.9560(10)
γ/°	83.3040(10)
V/Å^3	1048.92(7)
Z	2
calc. density/g cm^{-3}	1.376
μ/mm^{-1}	0.097
absorption correction	Multi-Scan
transmission factor range	0.8926–0.9705
refls. measured	26648
R_{int}	0.0438
mean σ(I)/I	0.0387
θ range	3.247–30.508
observed refls.	5254
x, y (weighting scheme)	0.0596, 0.3368
hydrogen refinement	constr
refls in refinement	6371
parameters	294
restraints	0
$R(F_{obs})$	0.0417
$R_w(F^2)$	0.1236
S	1.059
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.449
min electron density/e Å^{-3}	−0.234

Compound **189**

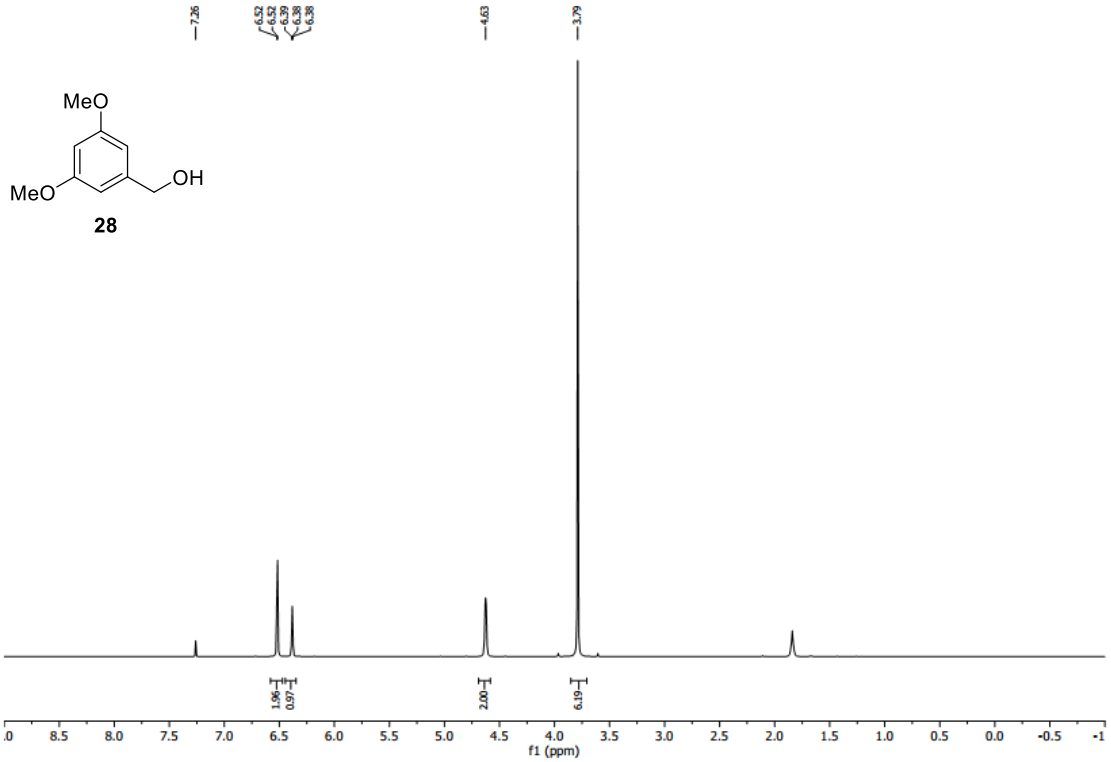


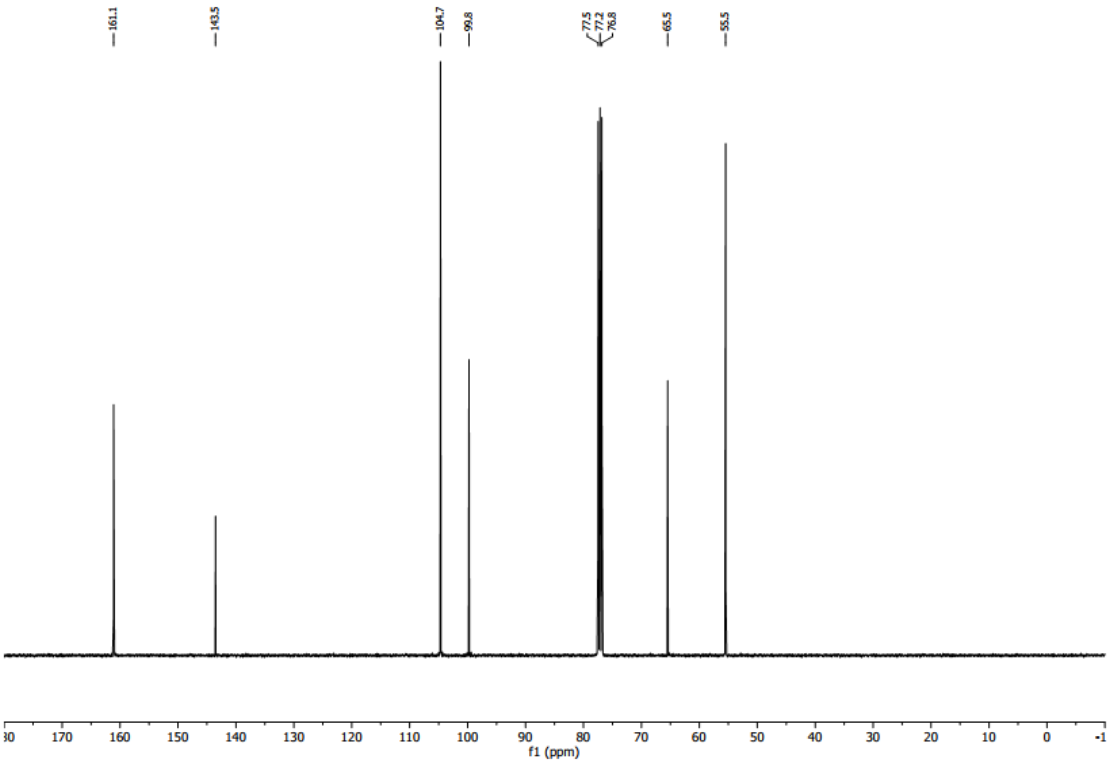
Identification code	19dtr2h	
Empirical formula	C35 H41 N O6 Si	
Formula weight	599.78	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.6309(10) Å	a= 86.7341(18)°.
	b = 11.2029(15) Å	b= 86.6911(18)°.
	c = 18.778(2) Å	g = 74.6194(17)°.
Volume	1543.8(4) Å3	
Z	2	
Density (calculated)	1.290 Mg/m3	
Absorption coefficient	0.123 mm-1	
F(000)	640	
Crystal size	0.360 x 0.240 x 0.090 mm3	
Theta range for data collection	1.887 to 28.285°.	
Index ranges	-10<=h<=10, -14<=k<=14, -25<=l<=25	
Reflections collected	22647	
Independent reflections	7640 [R(int) = 0.0501]	
Completeness to theta = 25.242°	100.00%	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7457 and 0.5948	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	7640 / 0 / 398	
Goodness-of-fit on F2	1.046	
Final R indices [I>2sigma(I)]	R1 = 0.0517, wR2 = 0.1353	
R indices (all data)	R1 = 0.0715, wR2 = 0.1452	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.397 and -0.433 e.Å-3	

3 NMR spectra

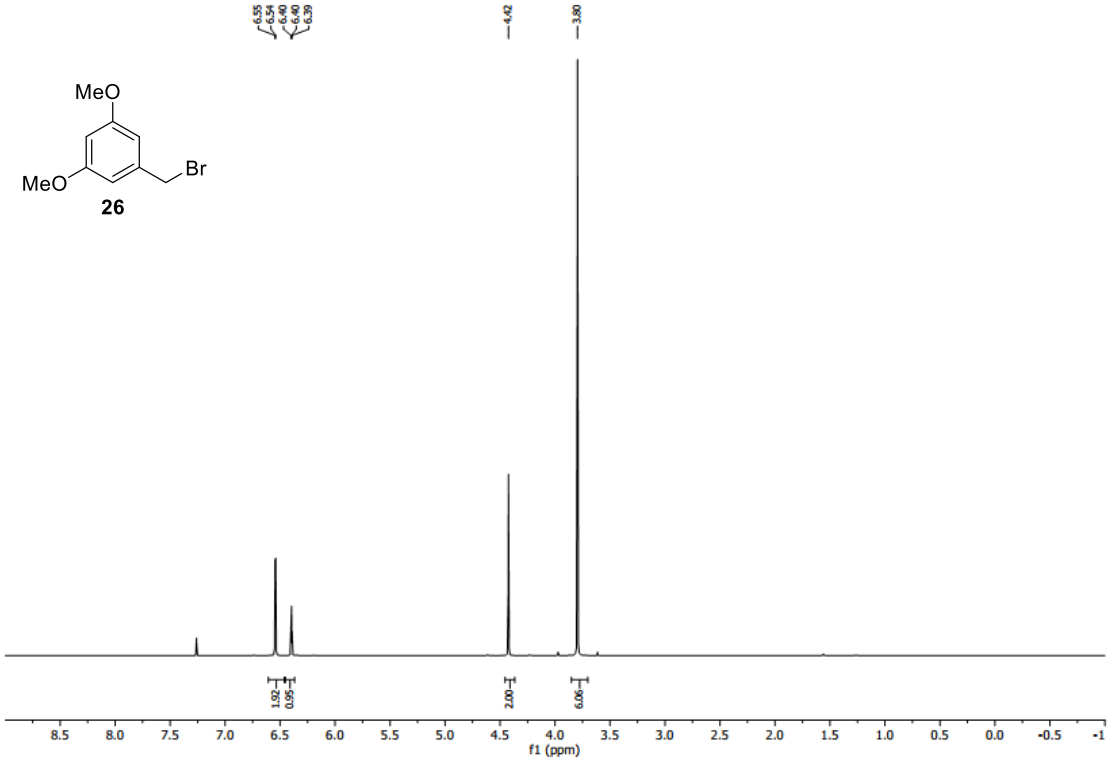
3.1 **Part I:** Synthetic studies toward A-74528

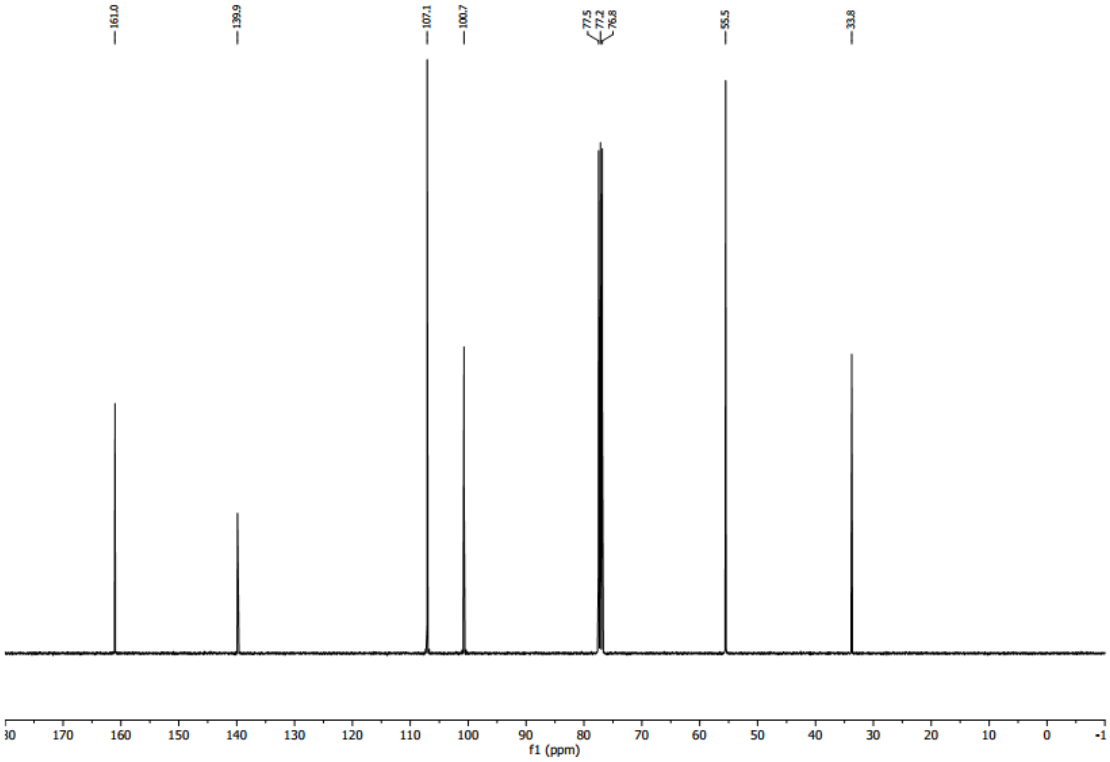
Compound **28** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



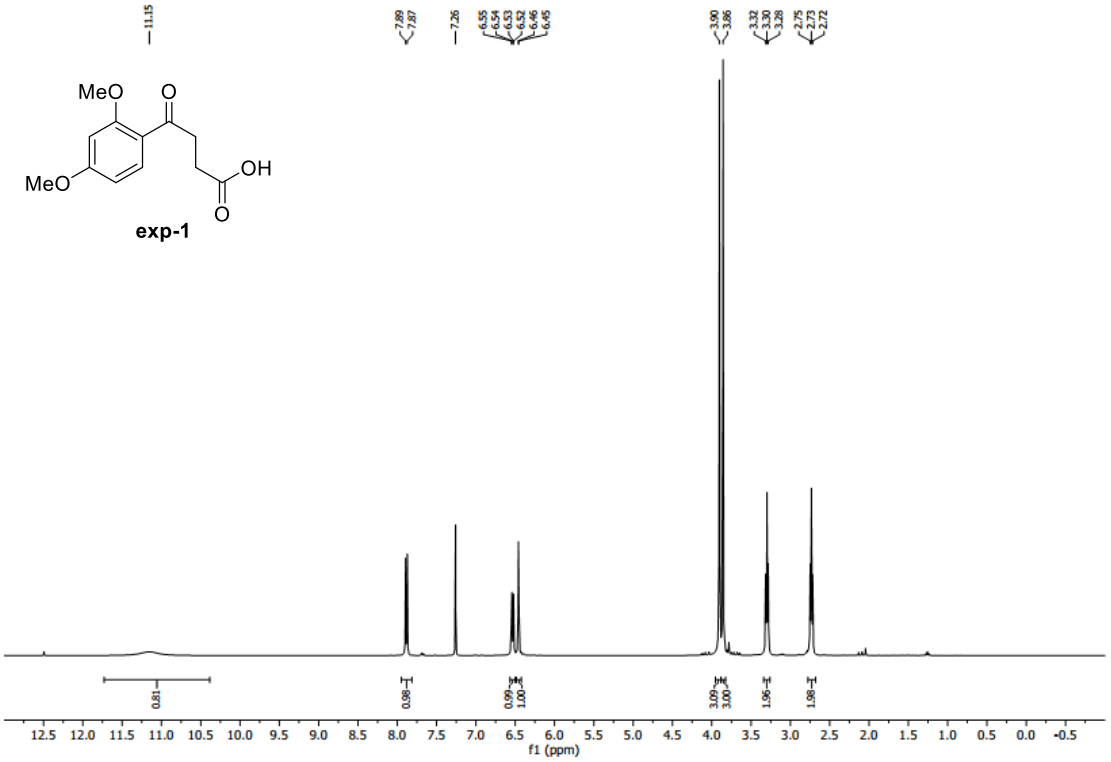


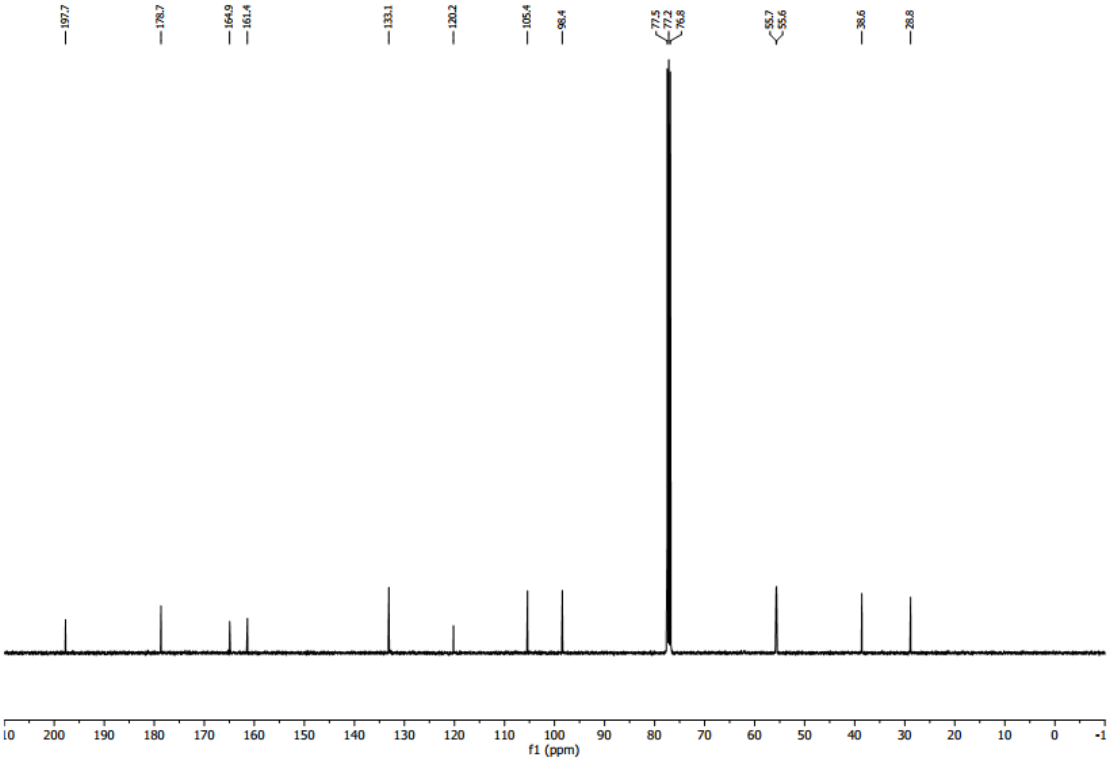
Compound **26** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



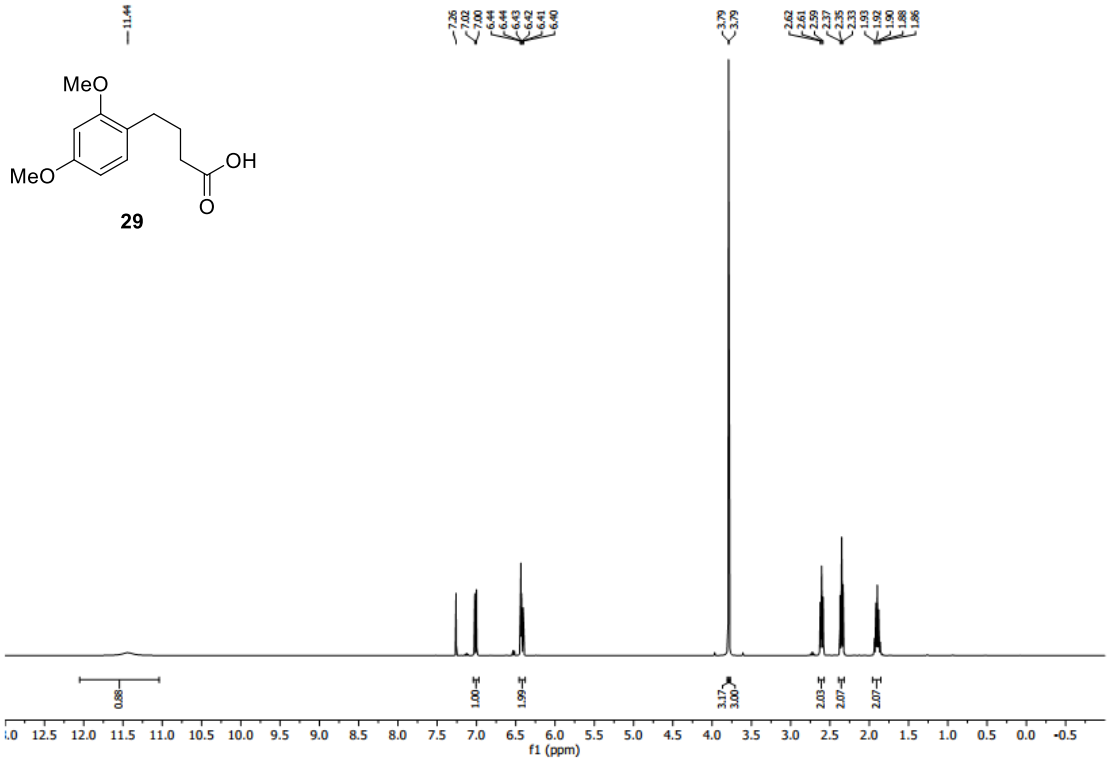


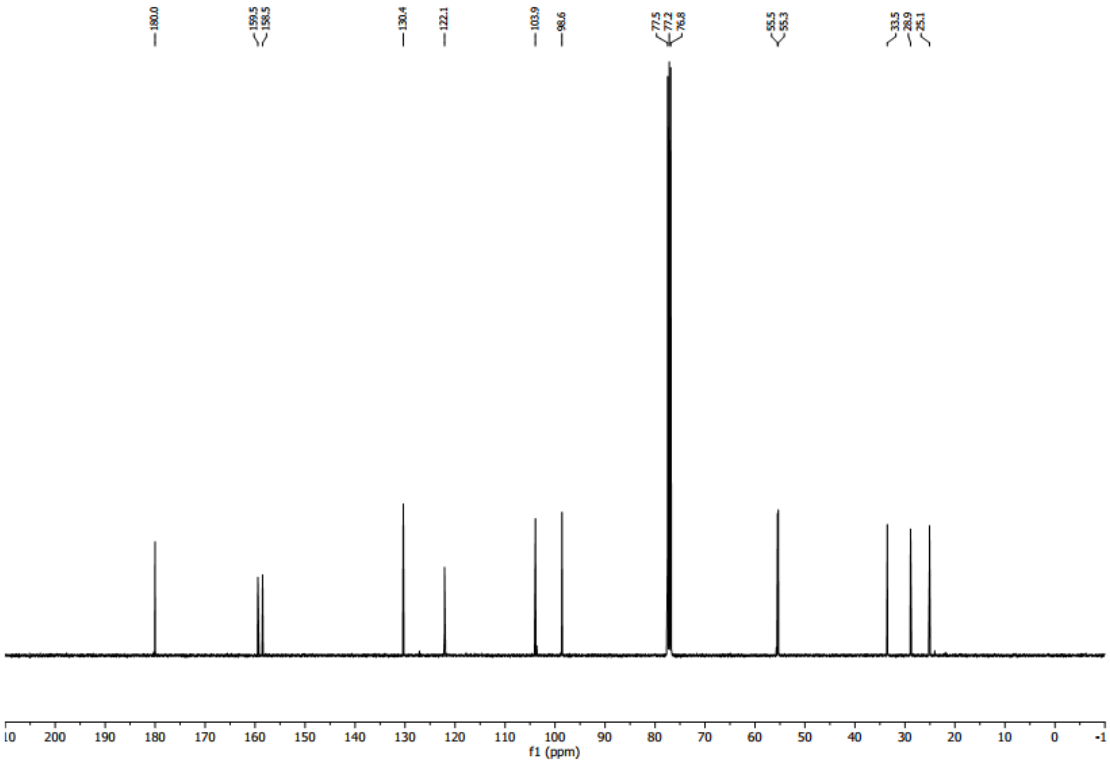
Compound **exp-1** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



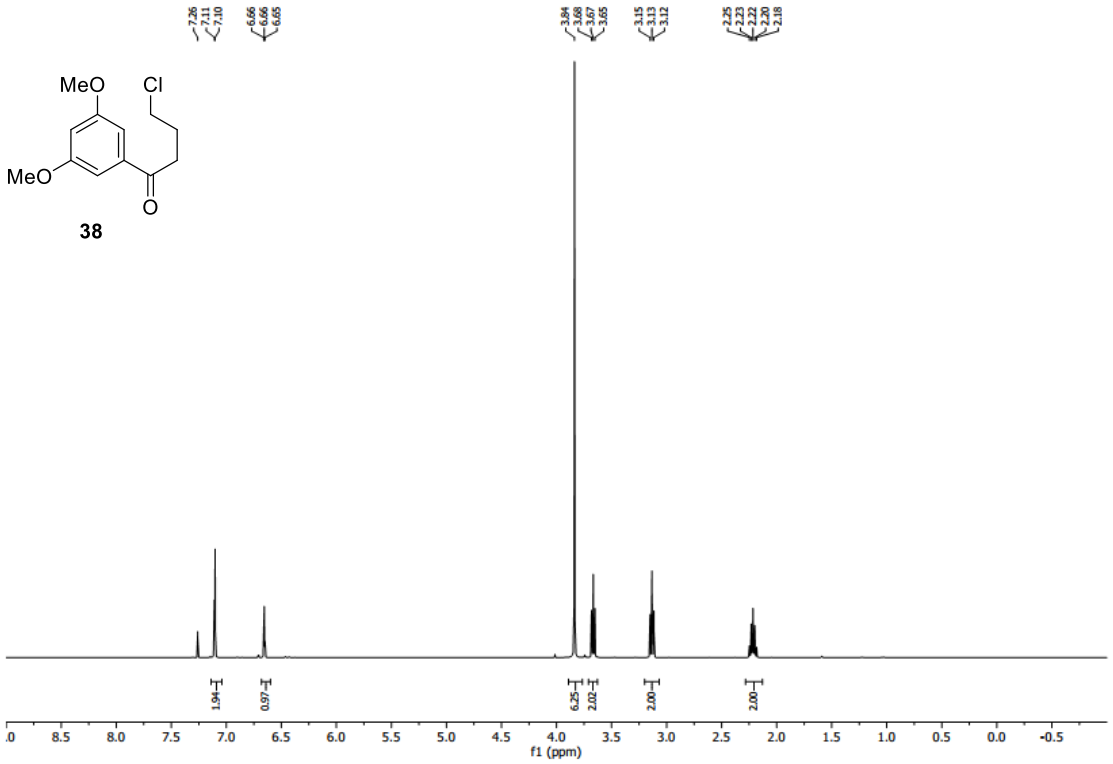


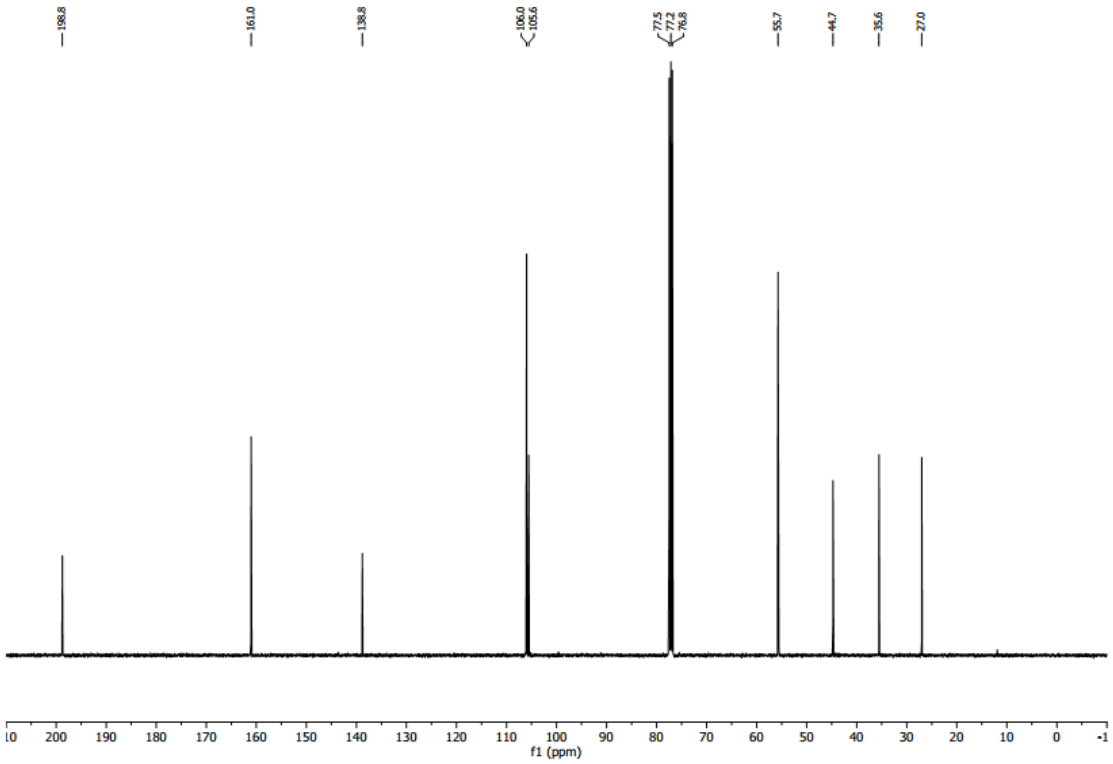
Compound **29** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



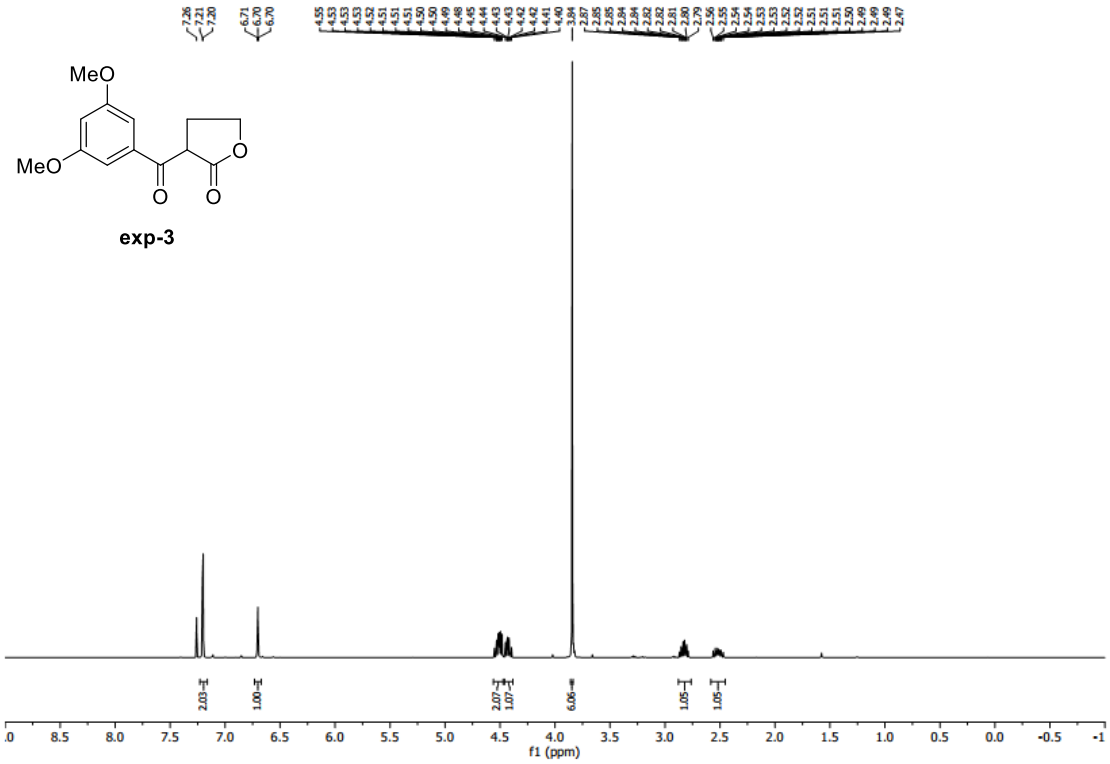


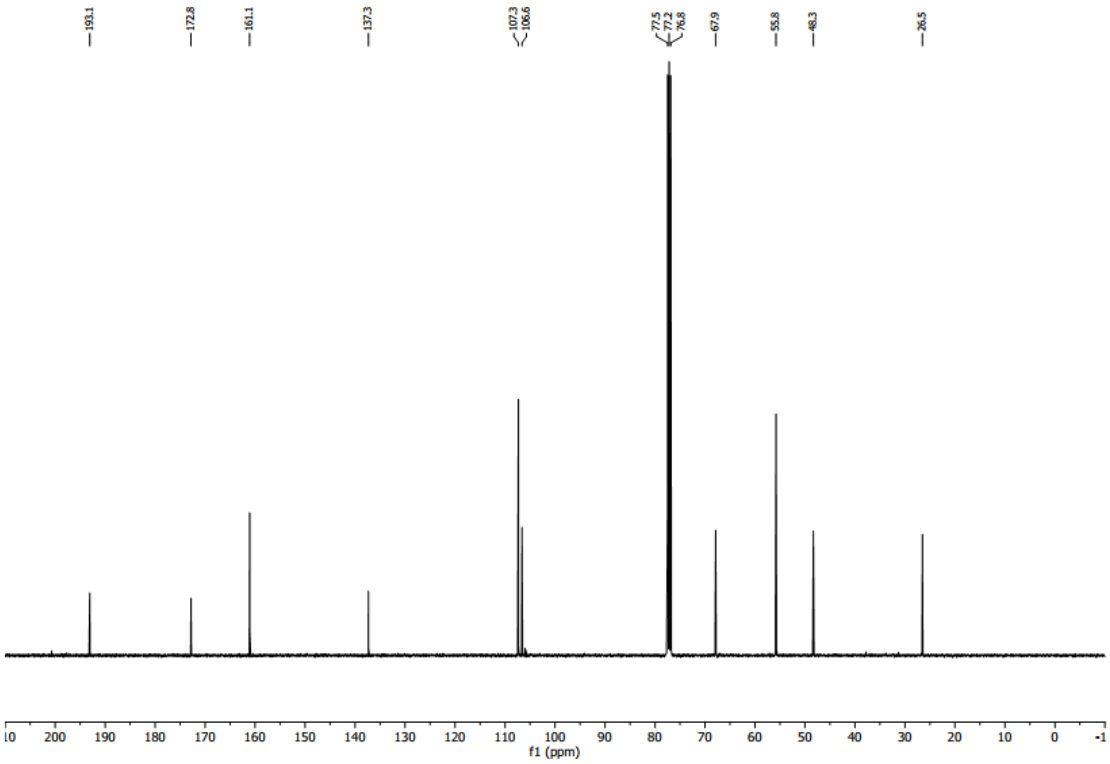
Compound **38** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



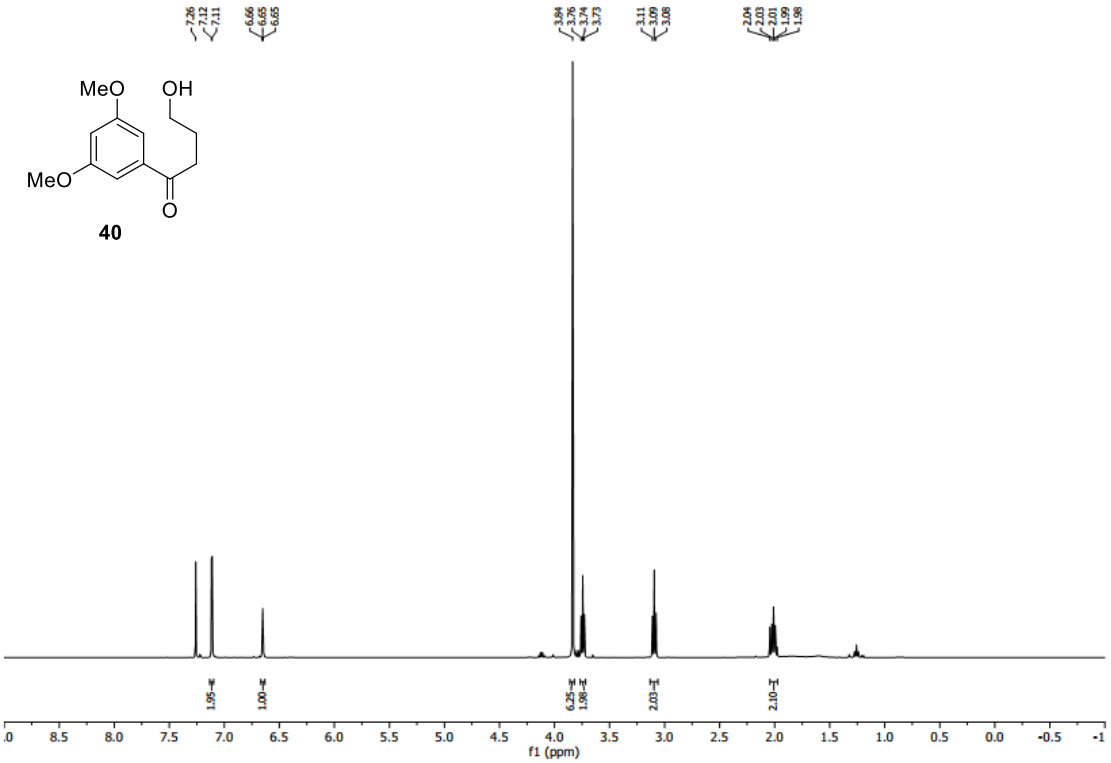


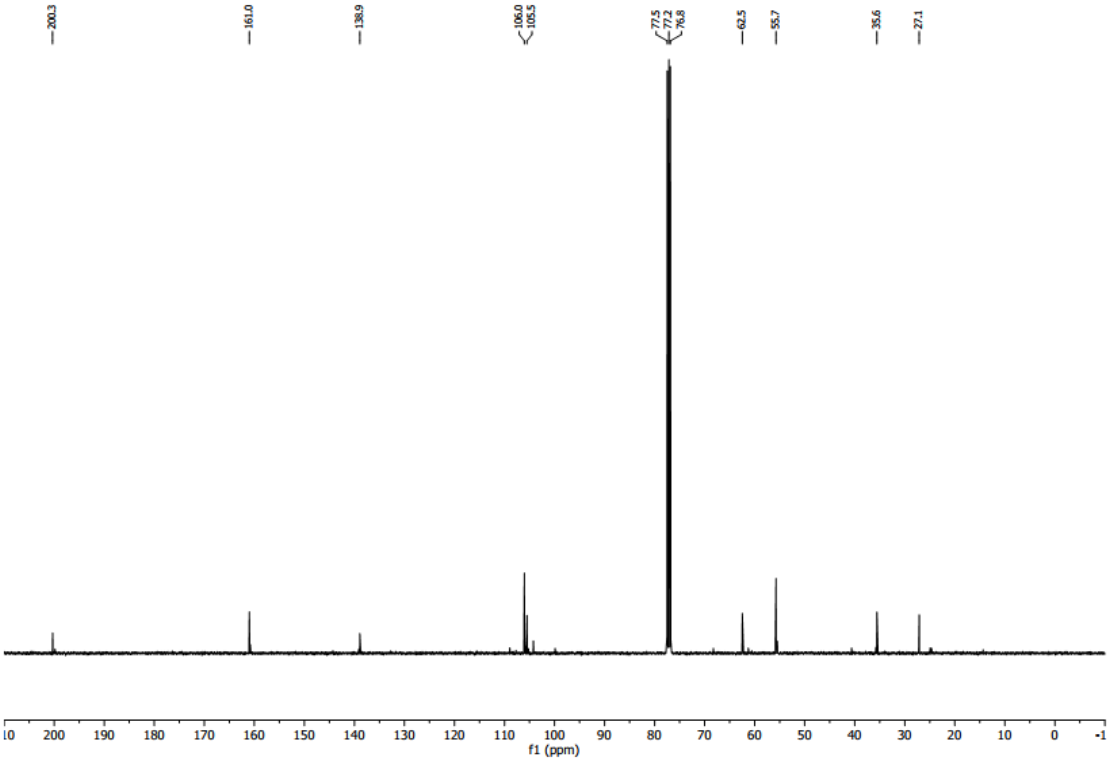
Compound **exp-3** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



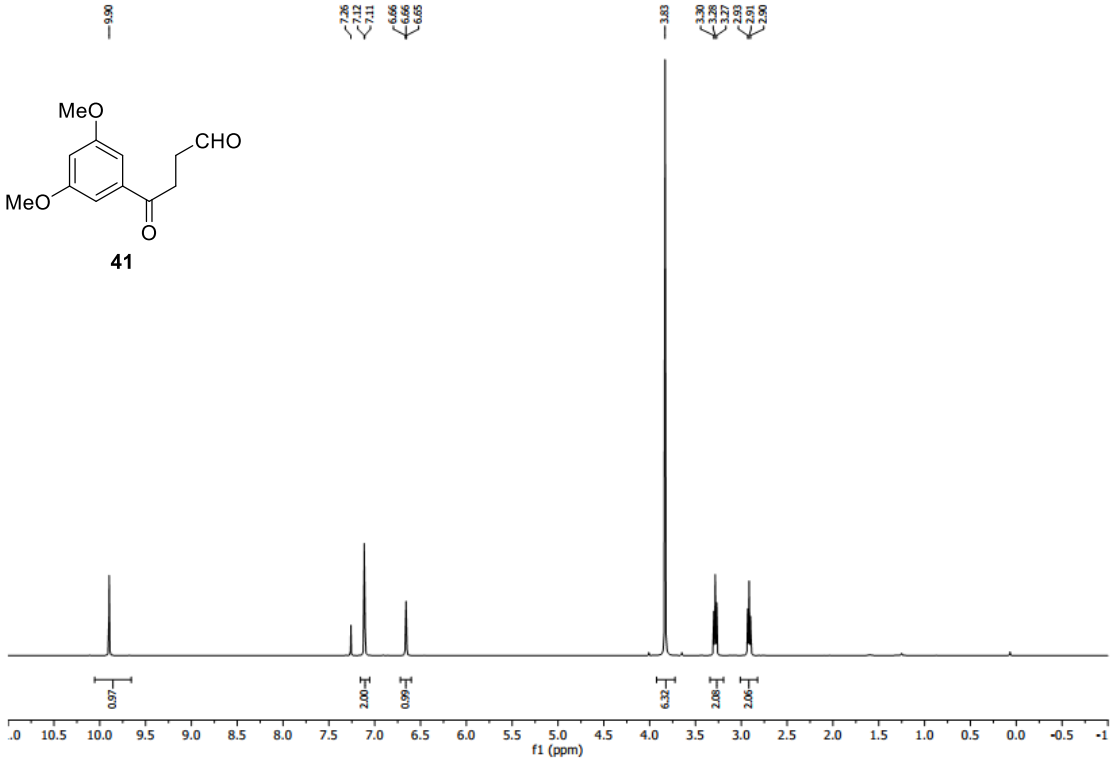


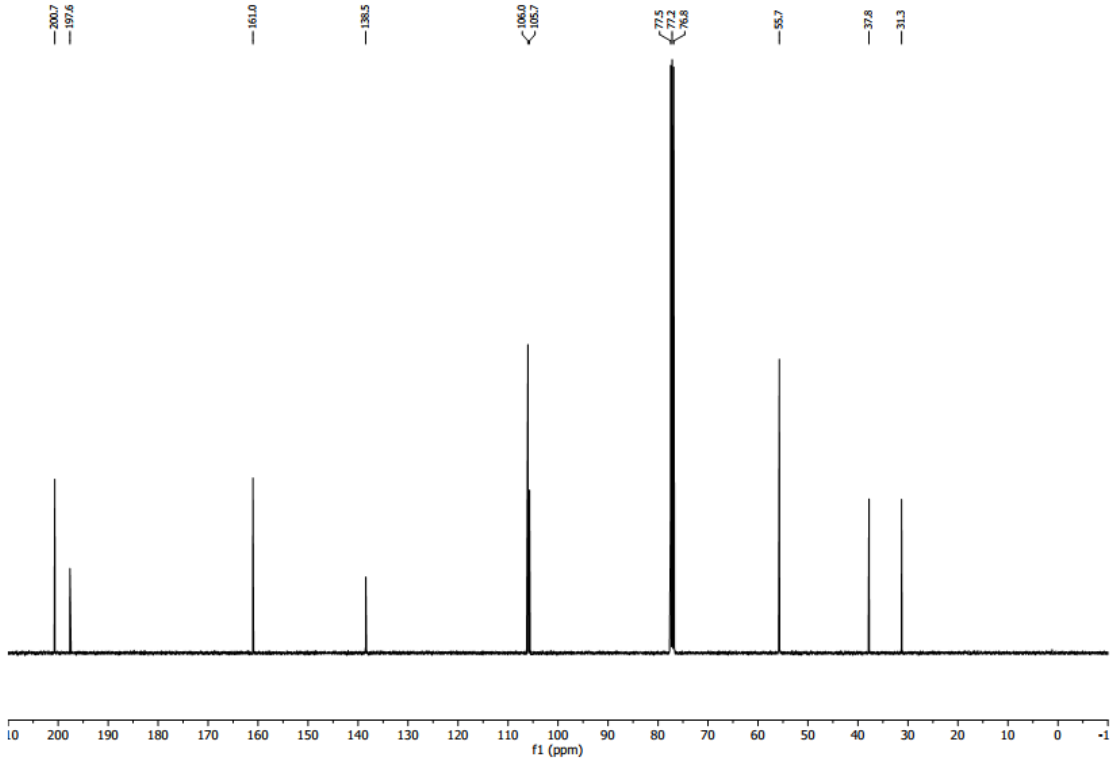
Compound **40** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



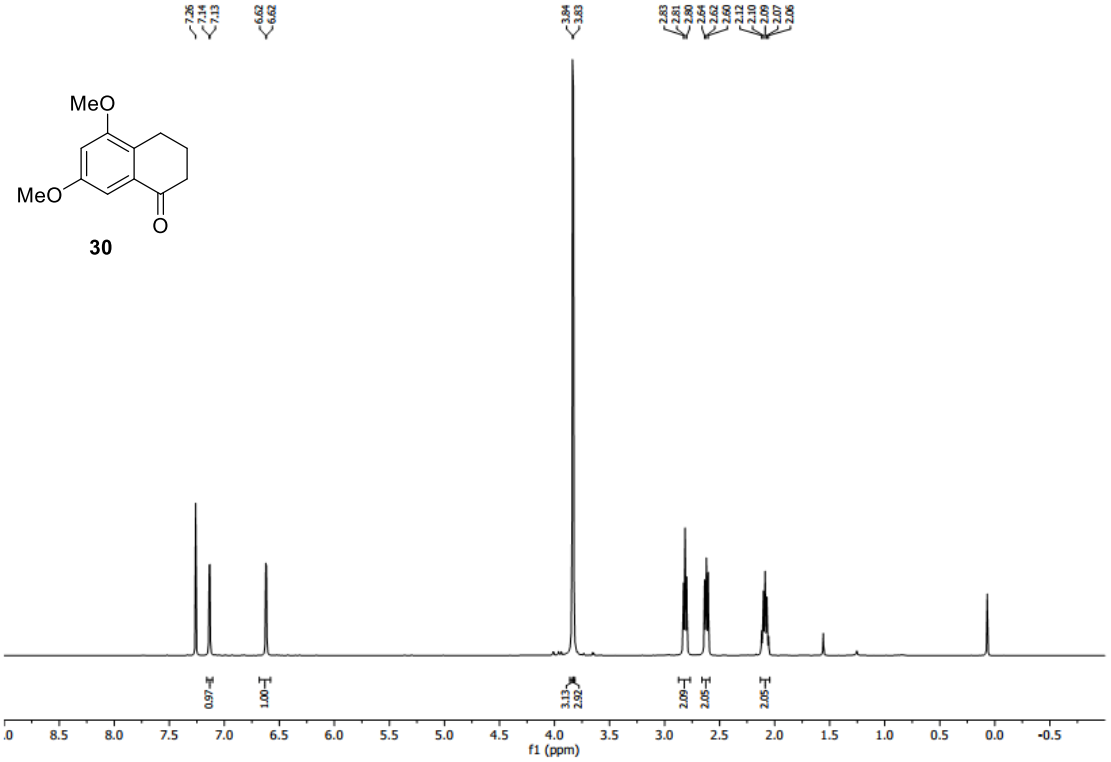


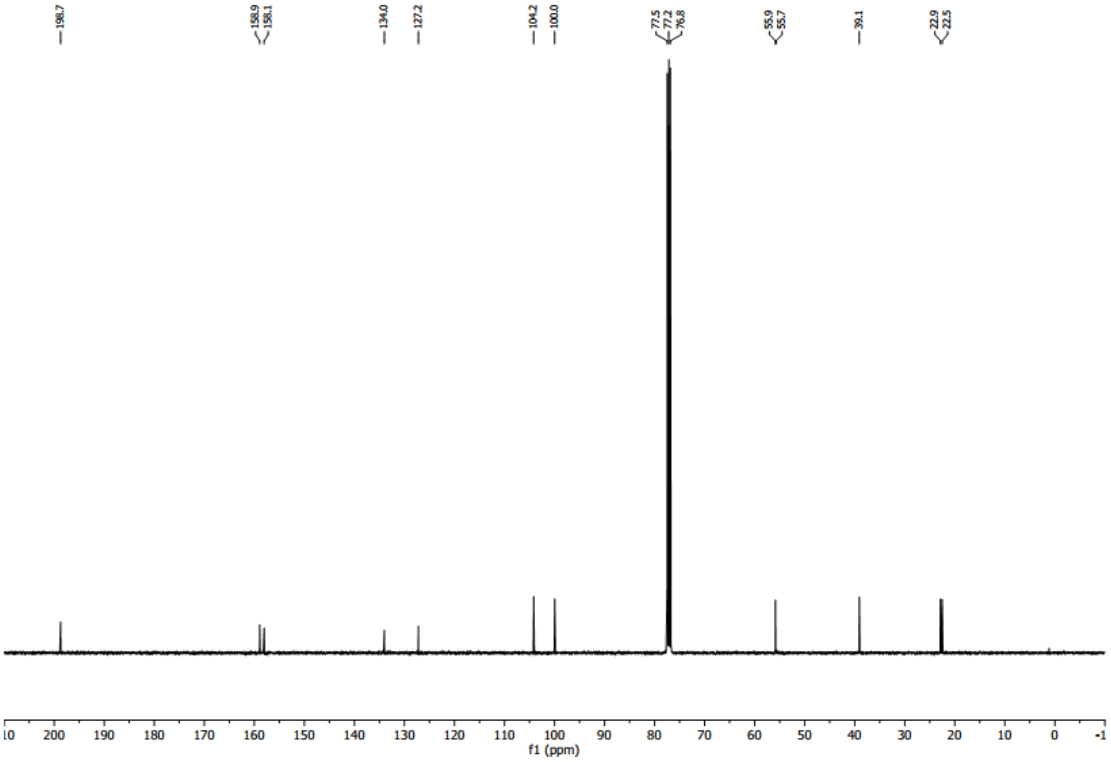
Compound **41** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



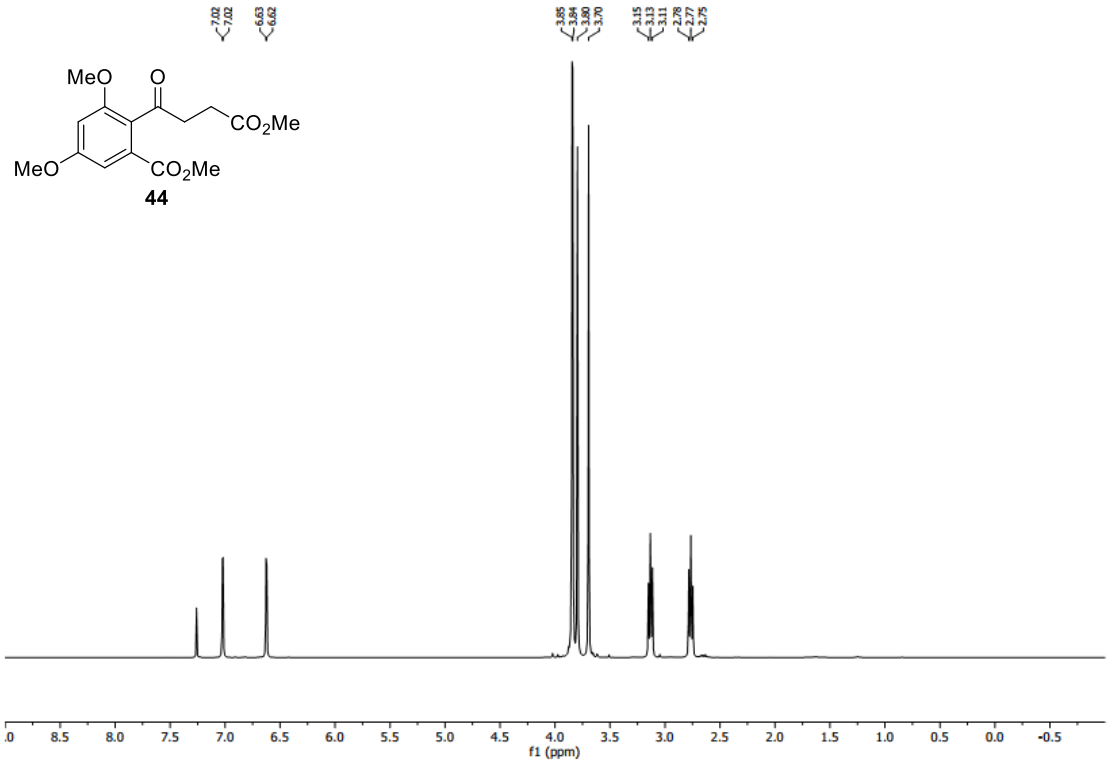


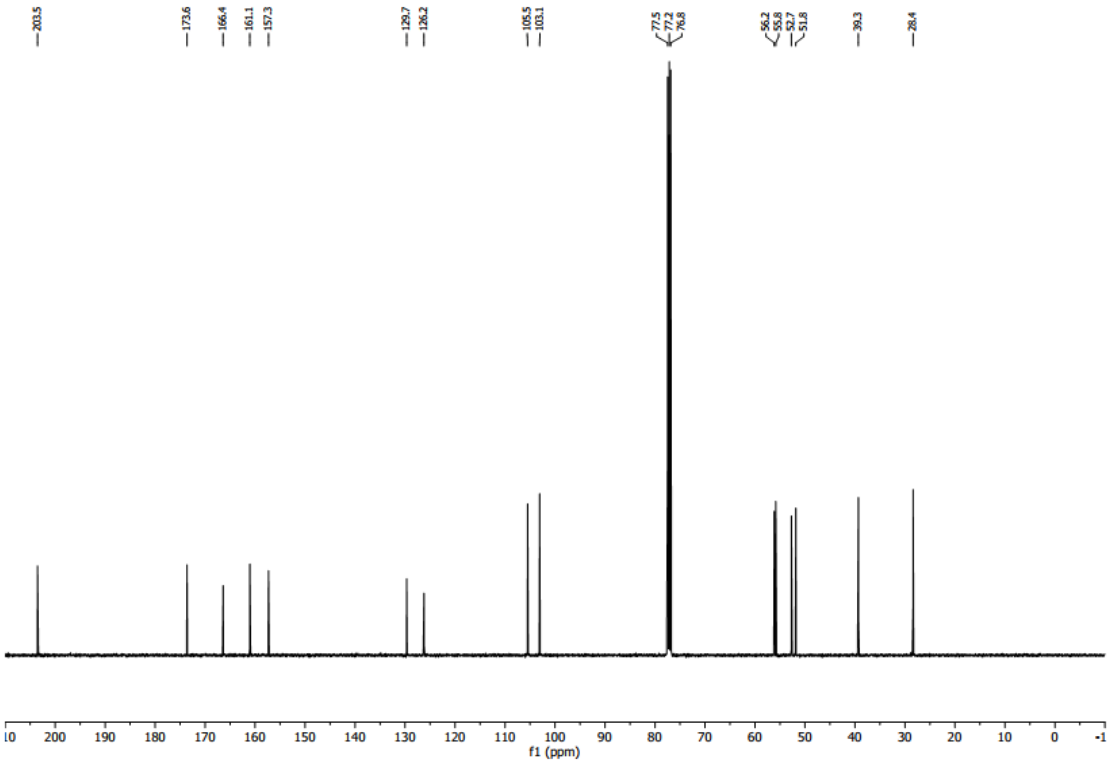
Compound **30** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



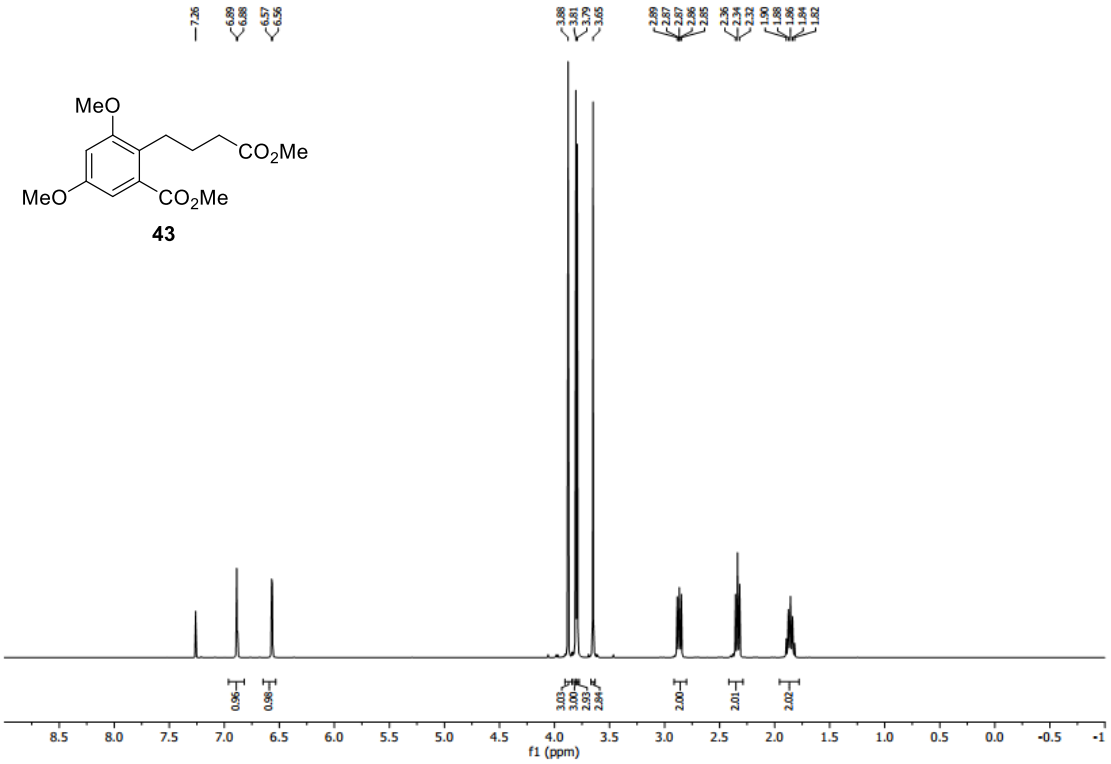


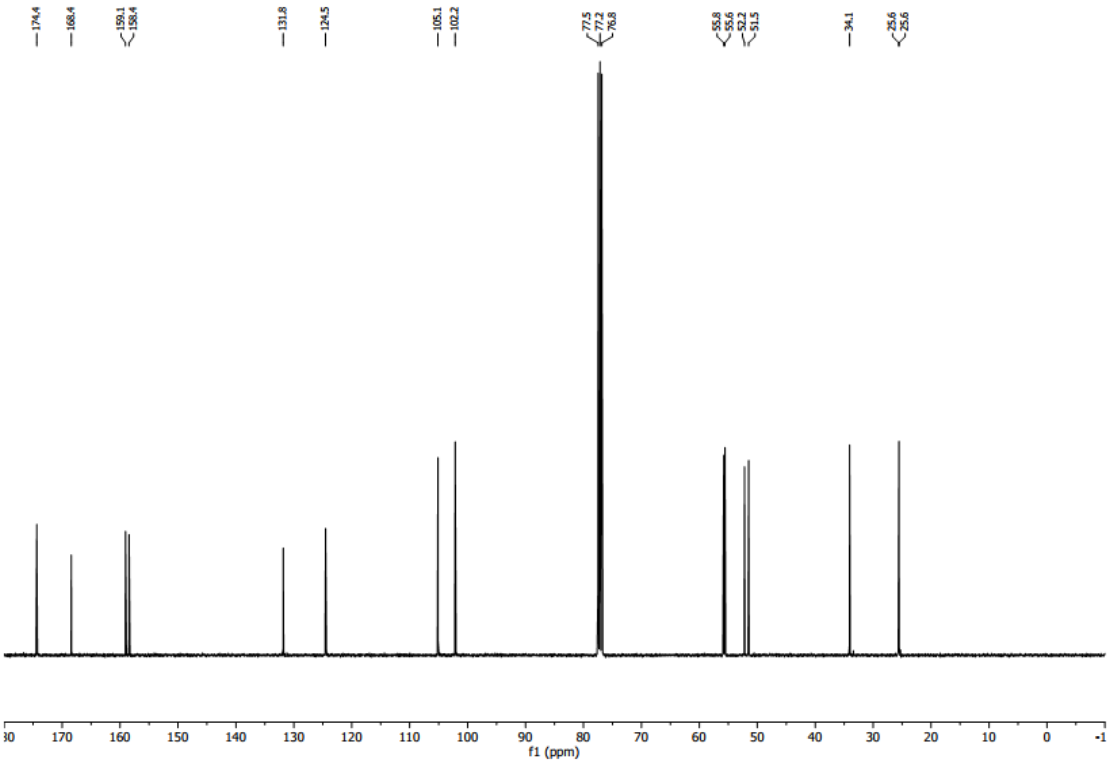
Compound **44** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



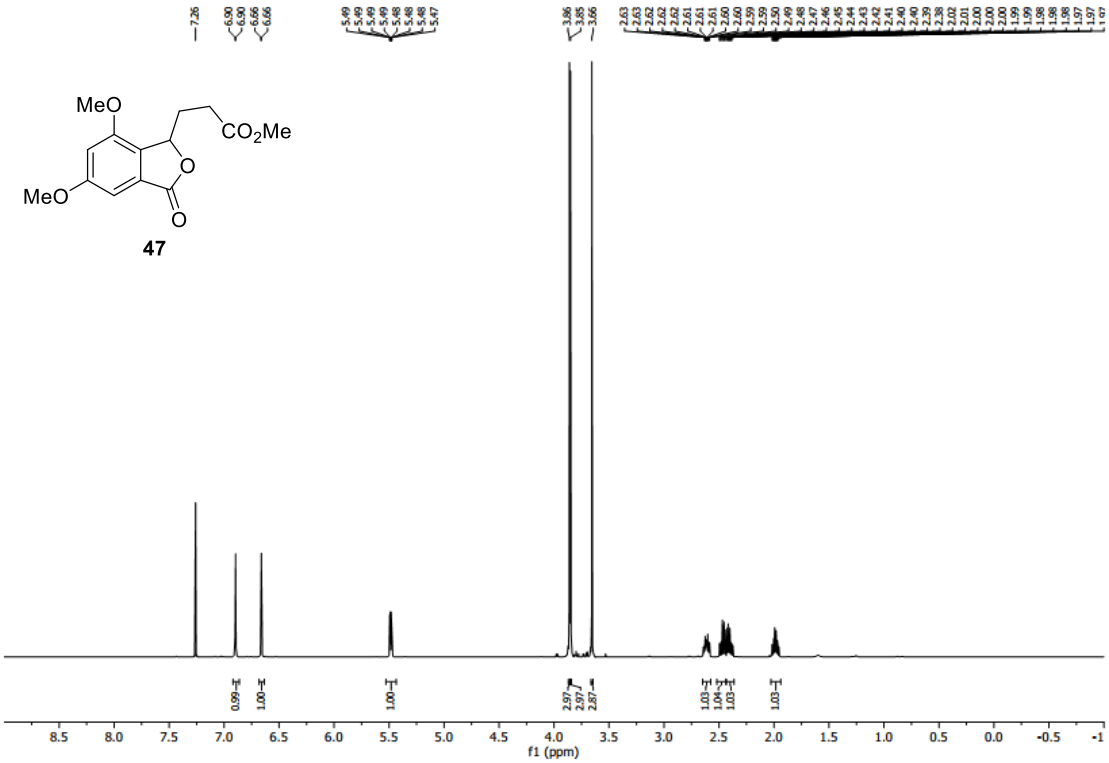


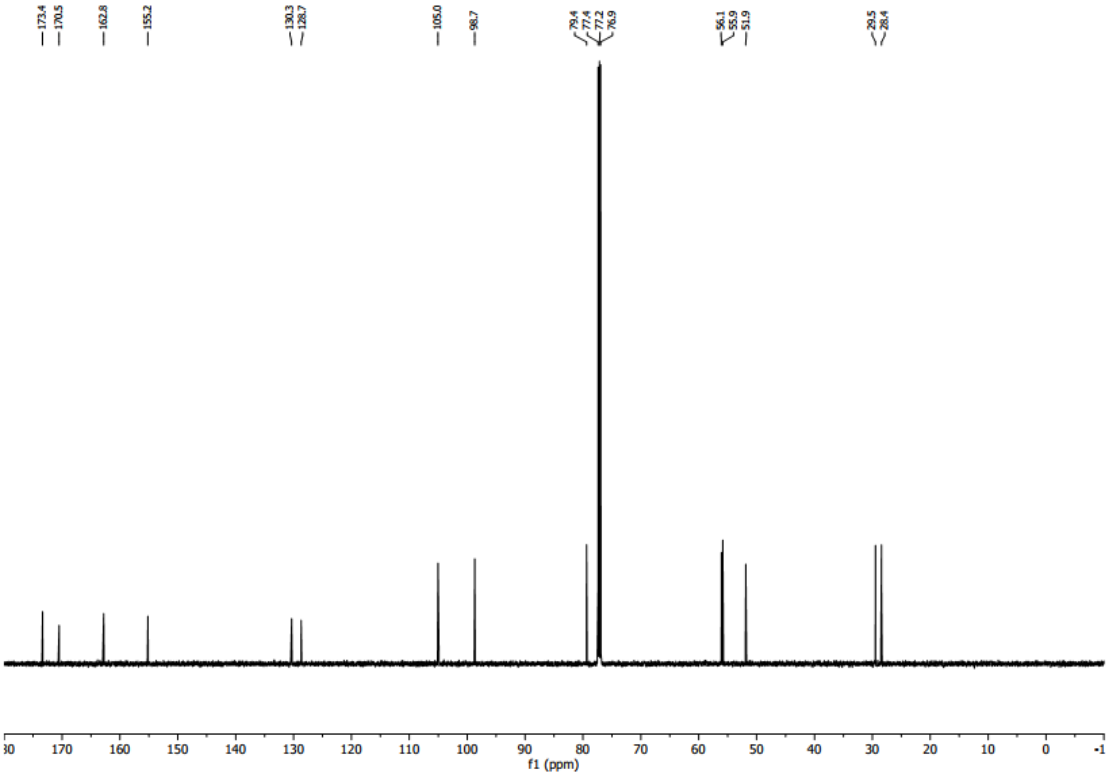
Compound **43** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



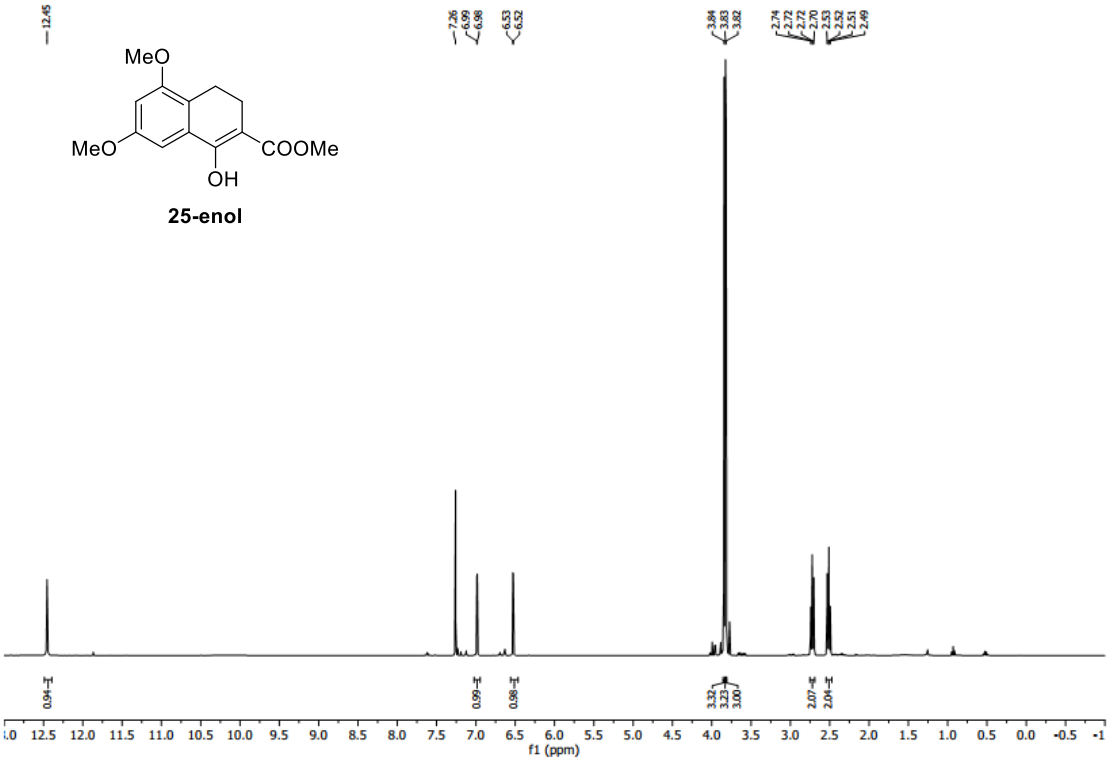


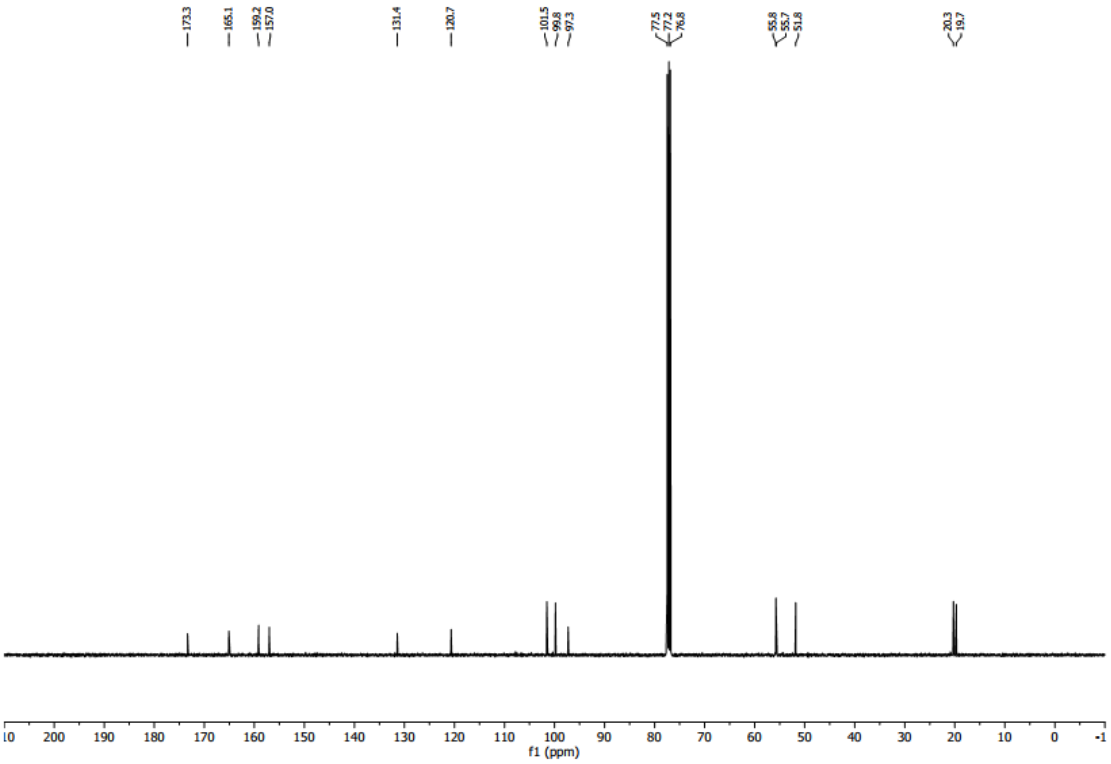
Compound **47** – **^{1}H-NMR** (600 MHz) and **^{13}C-NMR** (150 MHz) in $CDCl_3$



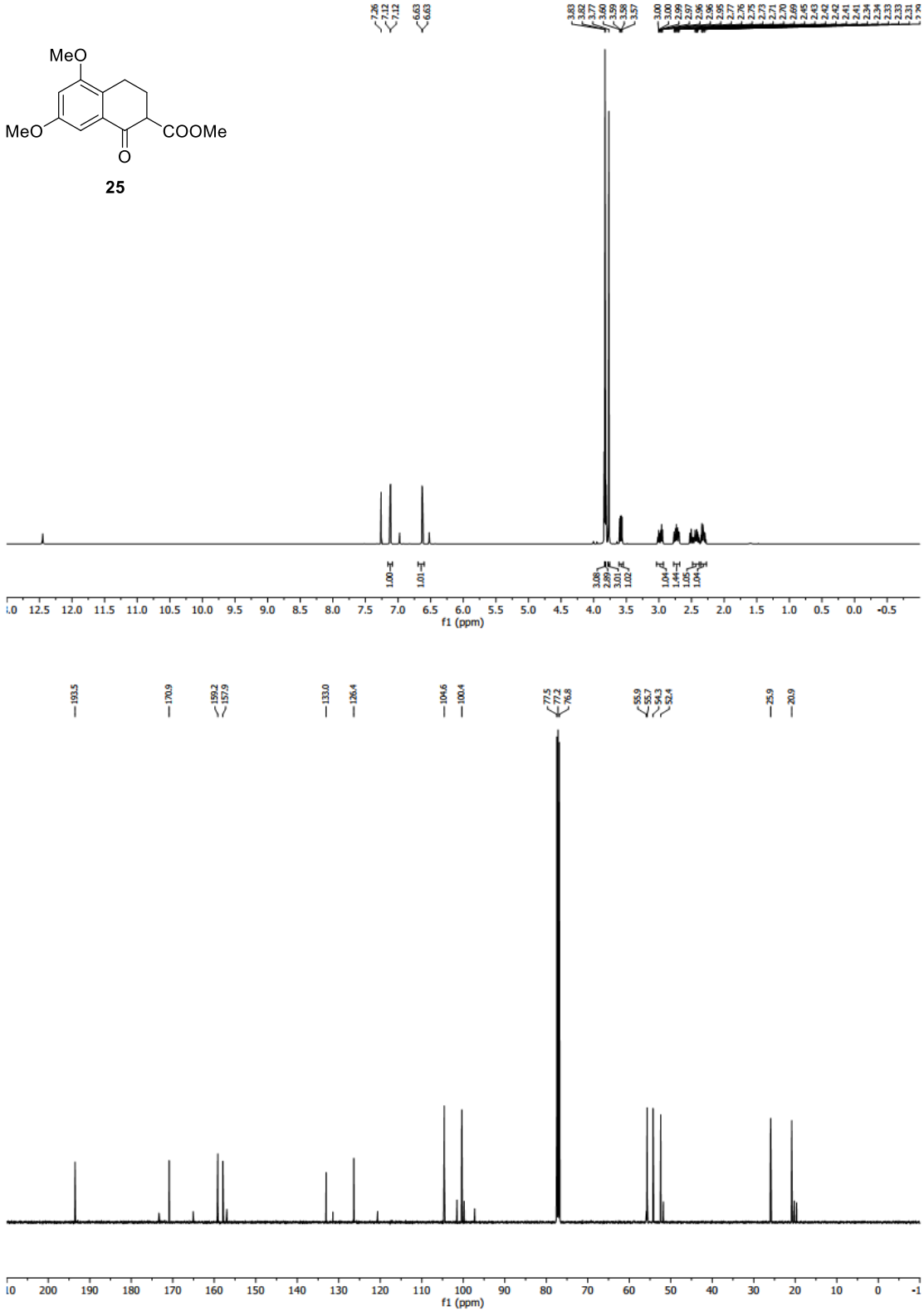


Compound **25-enol** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

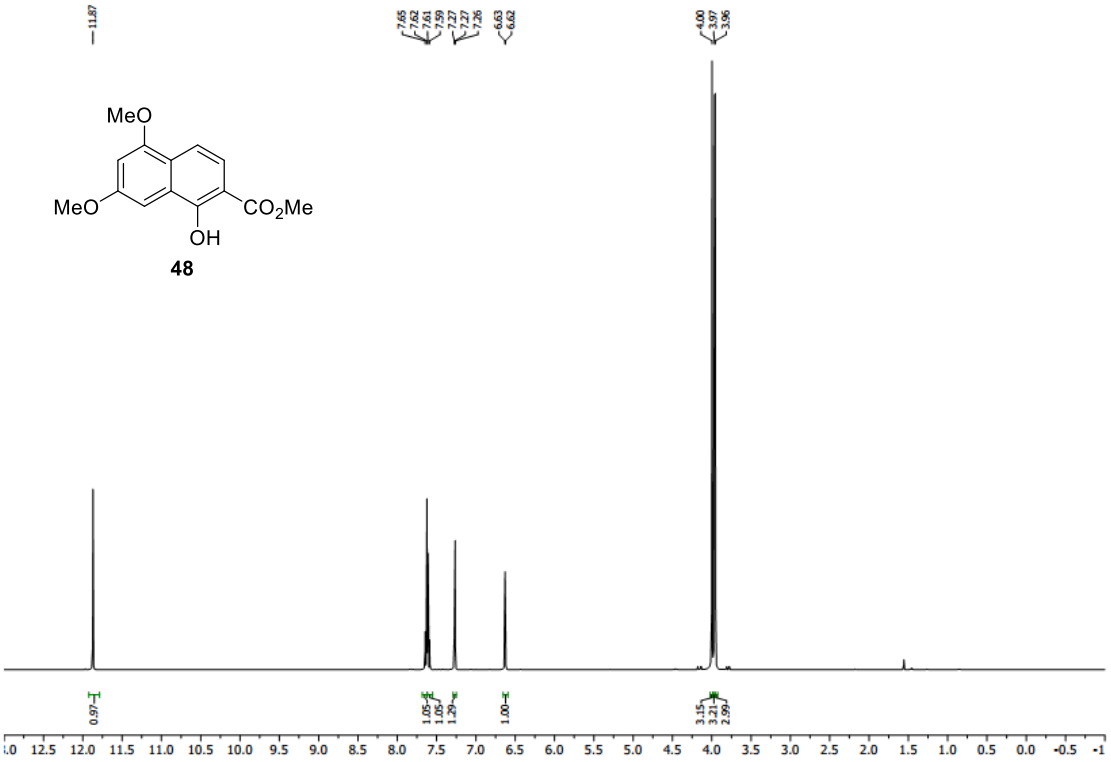


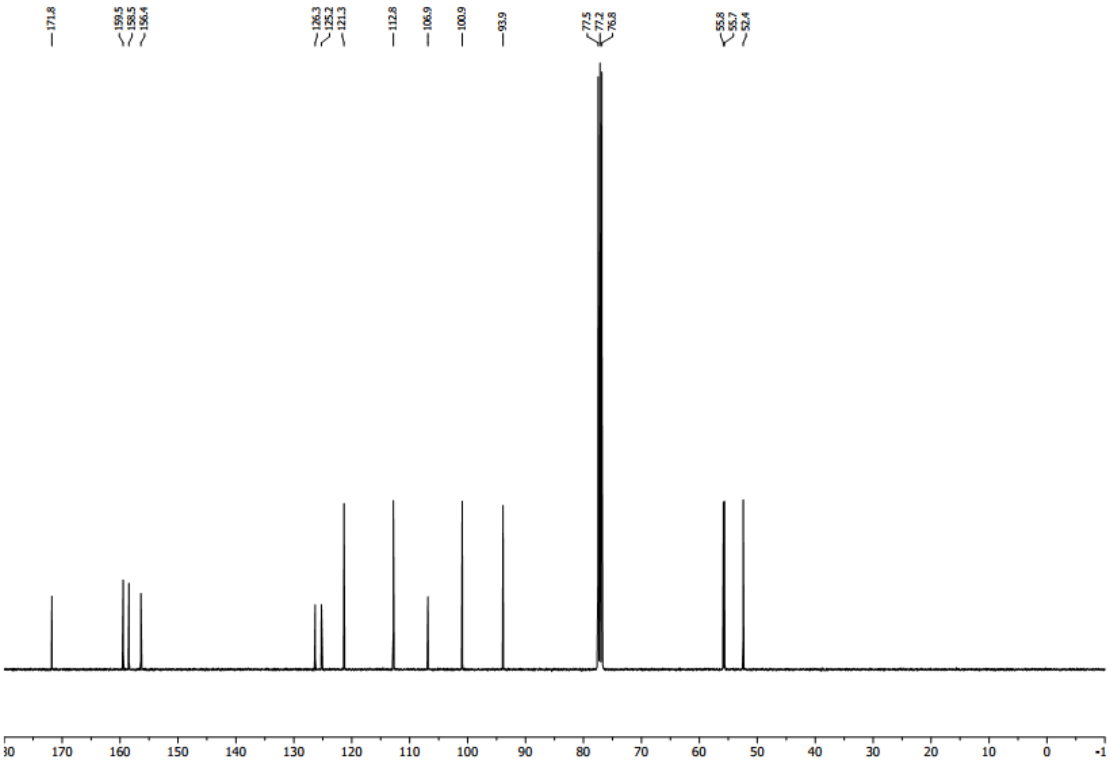


Compound **25** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

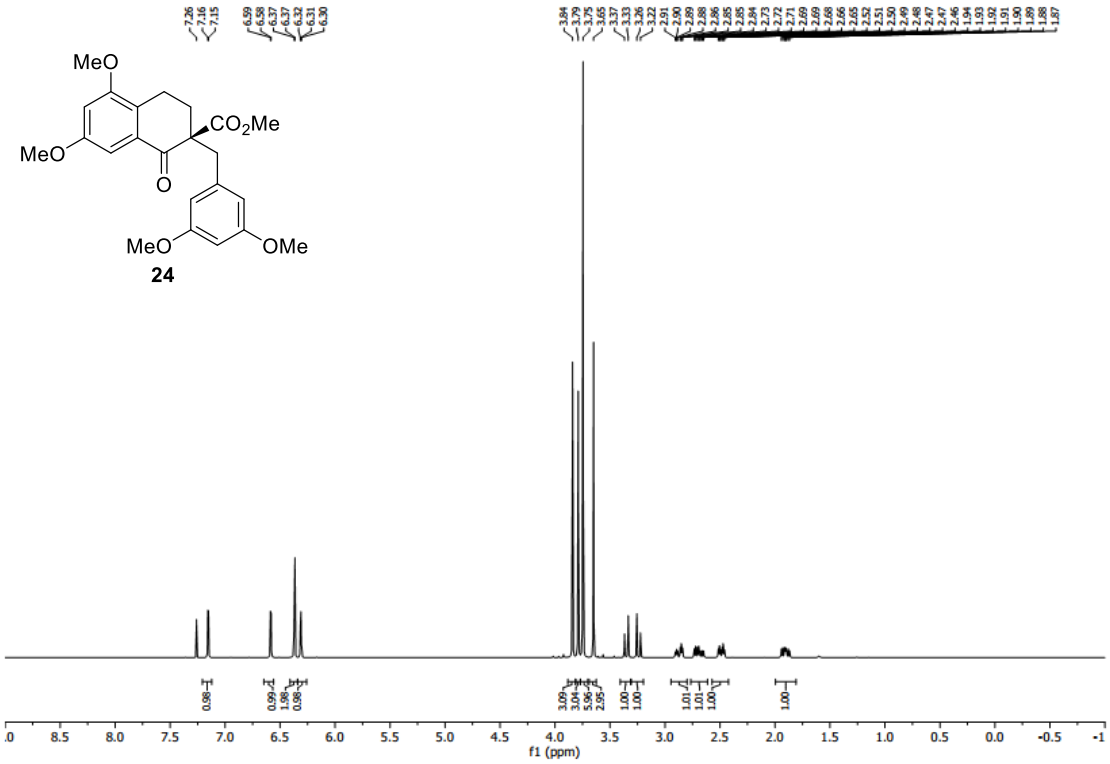


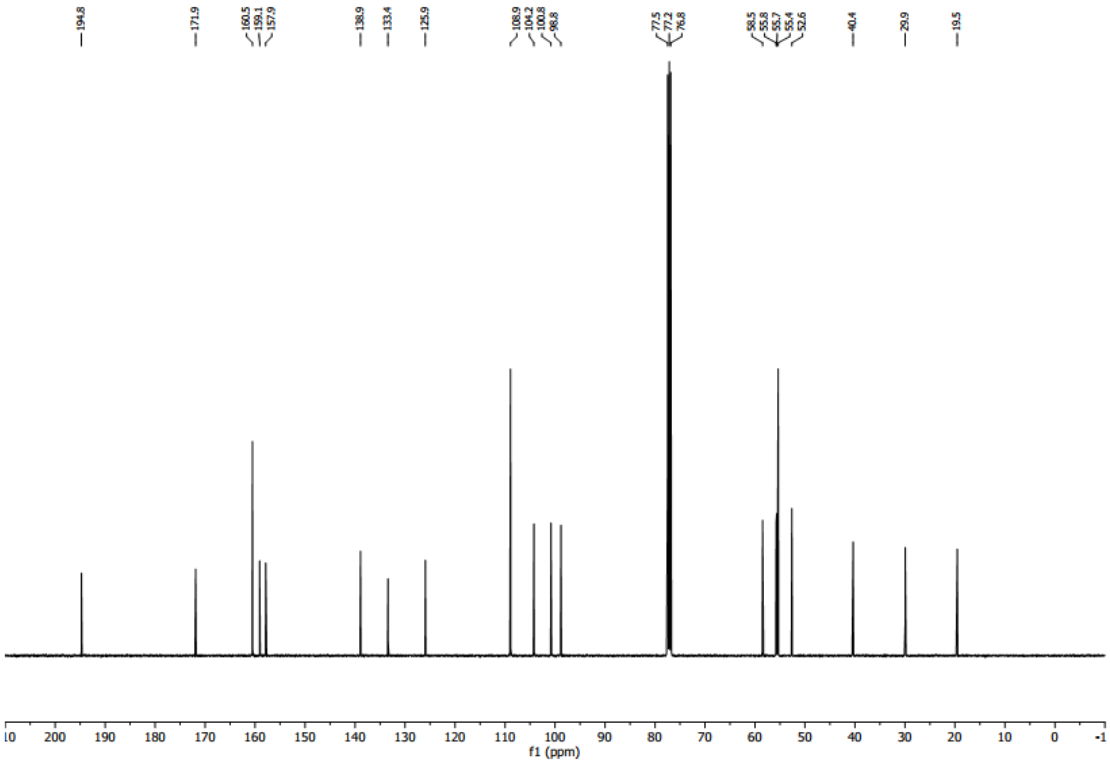
Compound **48** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



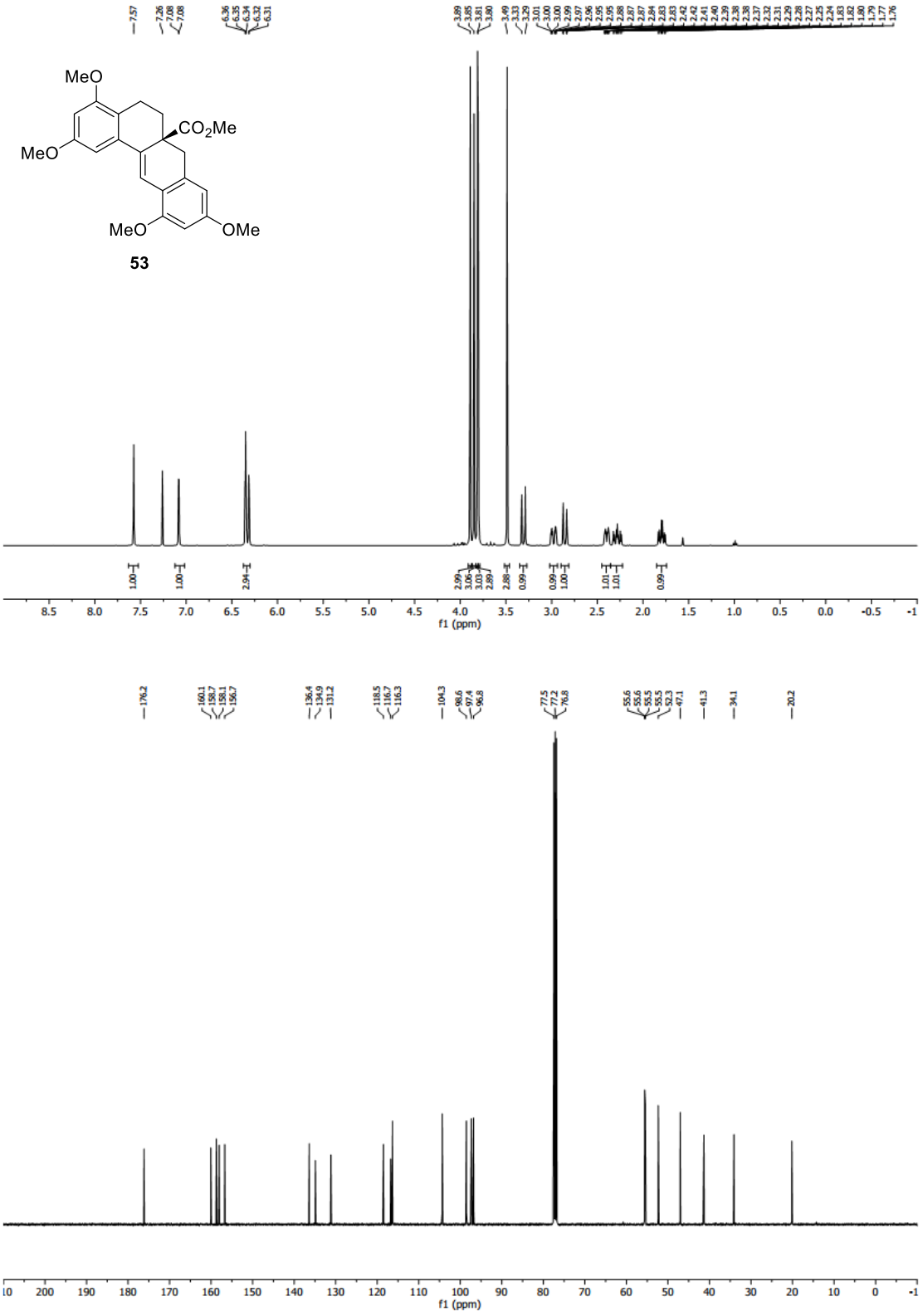


Compound **24** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

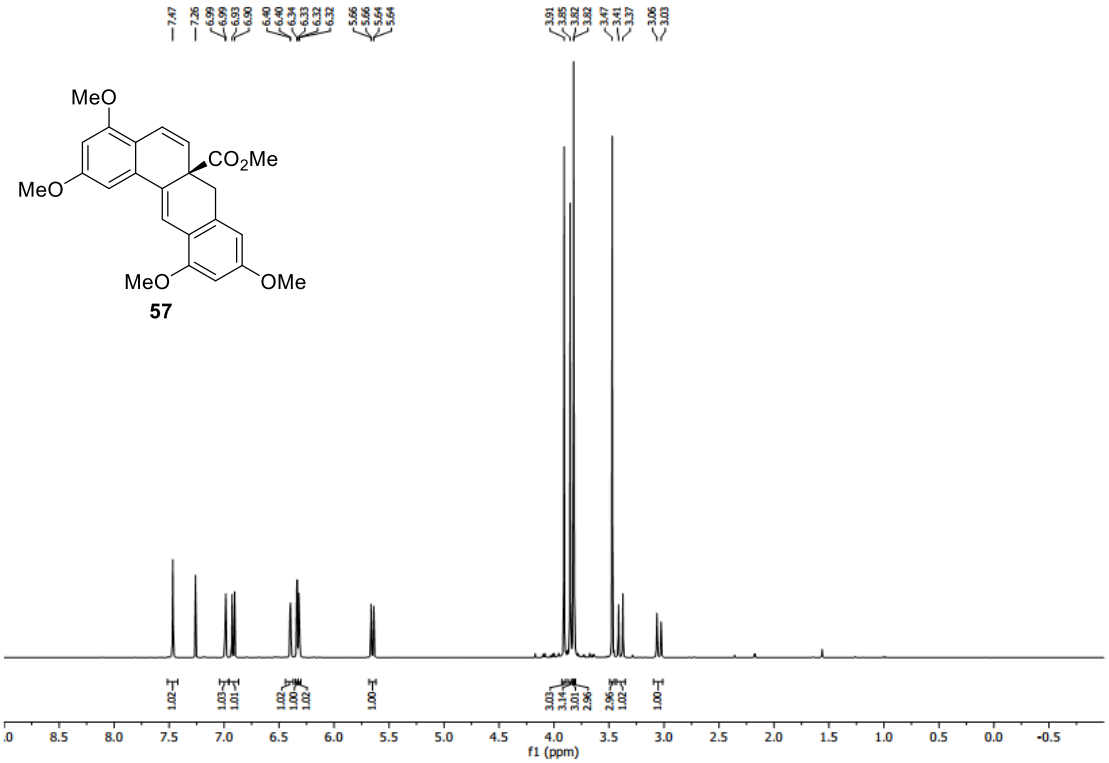


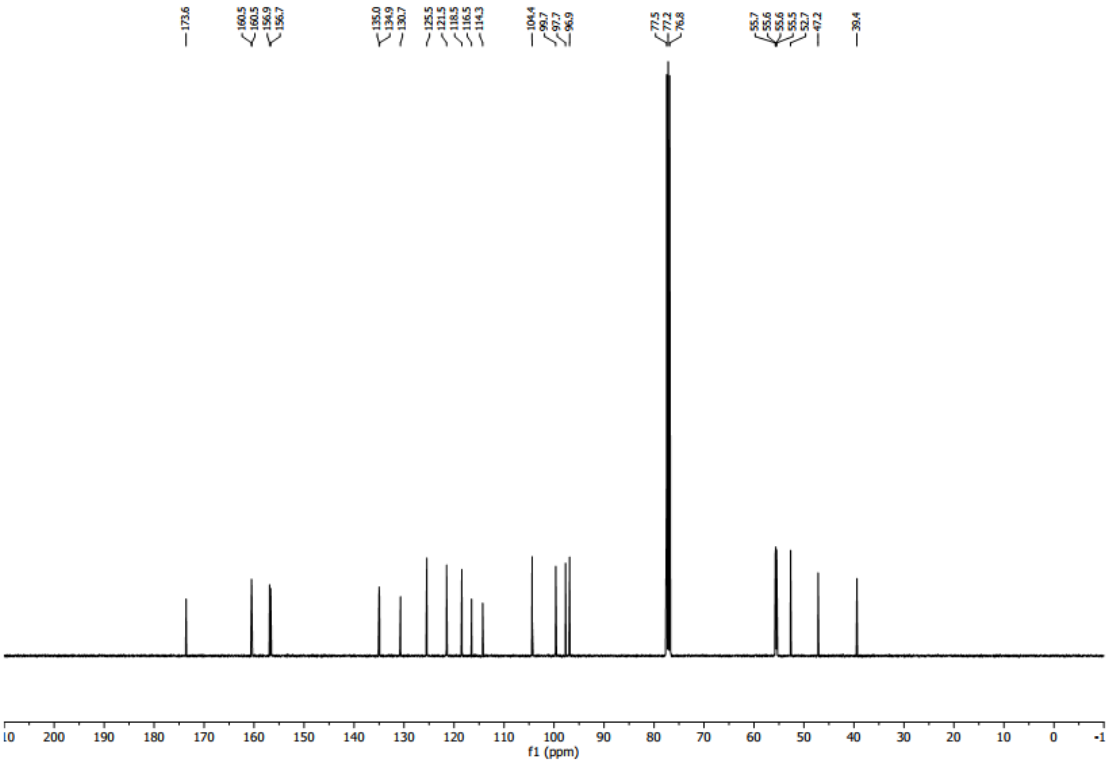


Compound **53** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

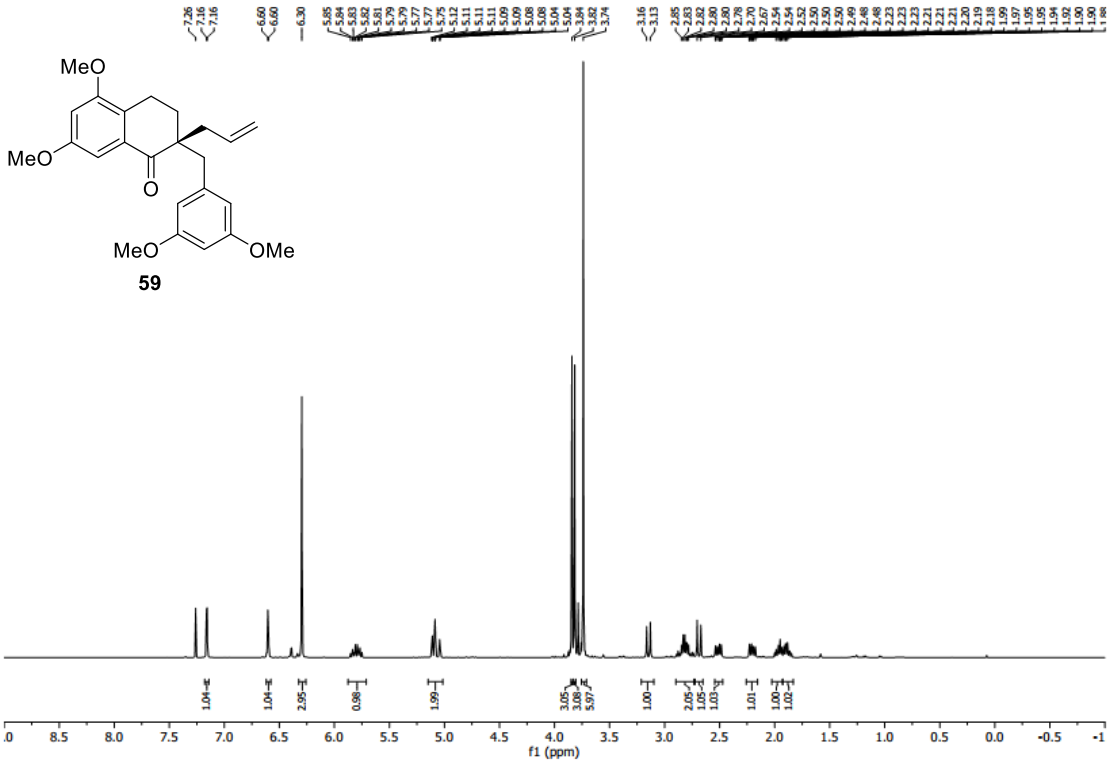


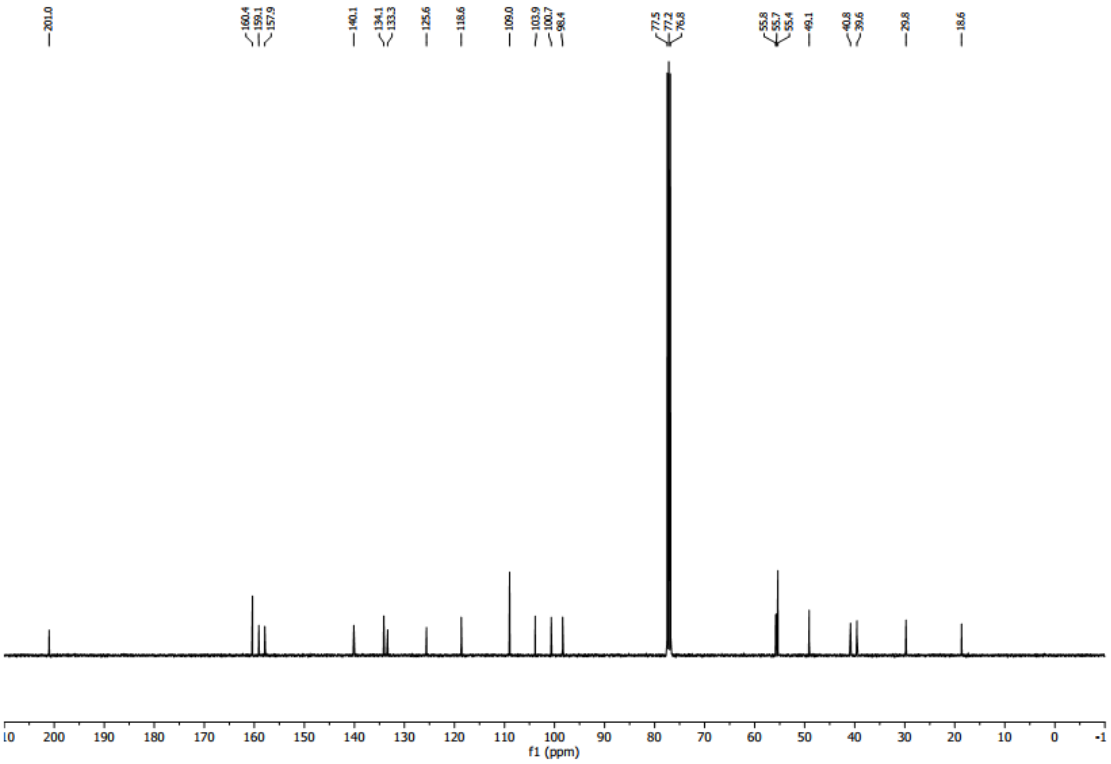
Compound **57** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



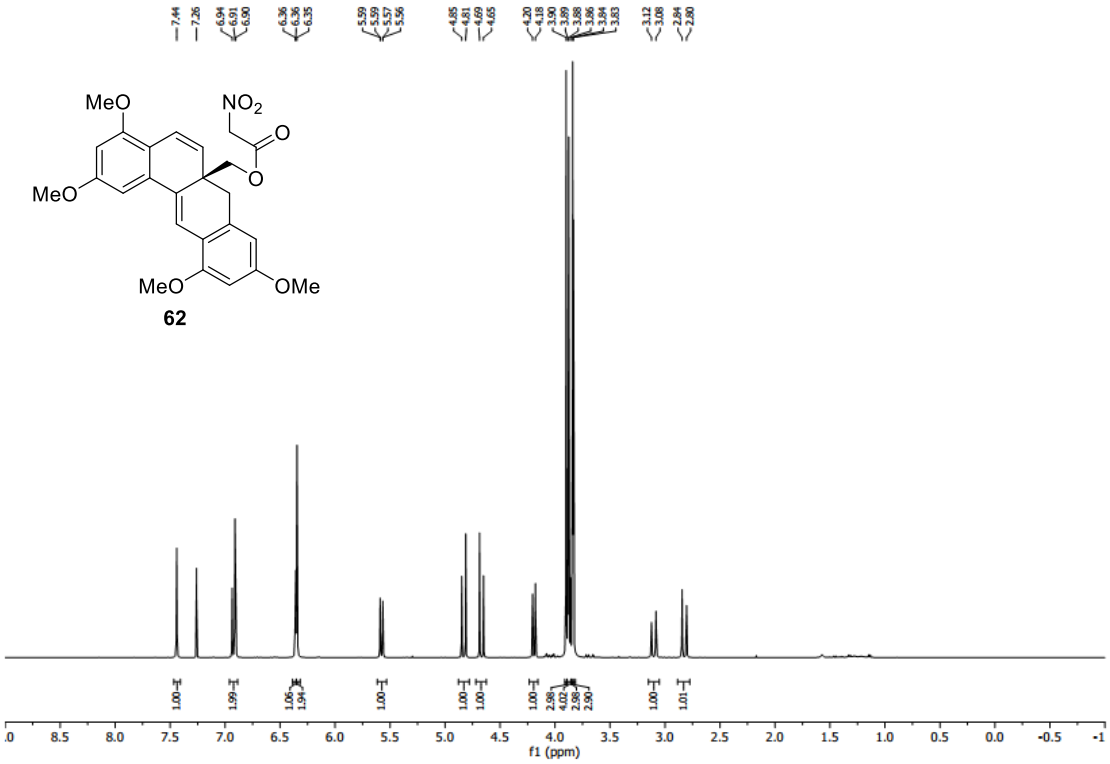


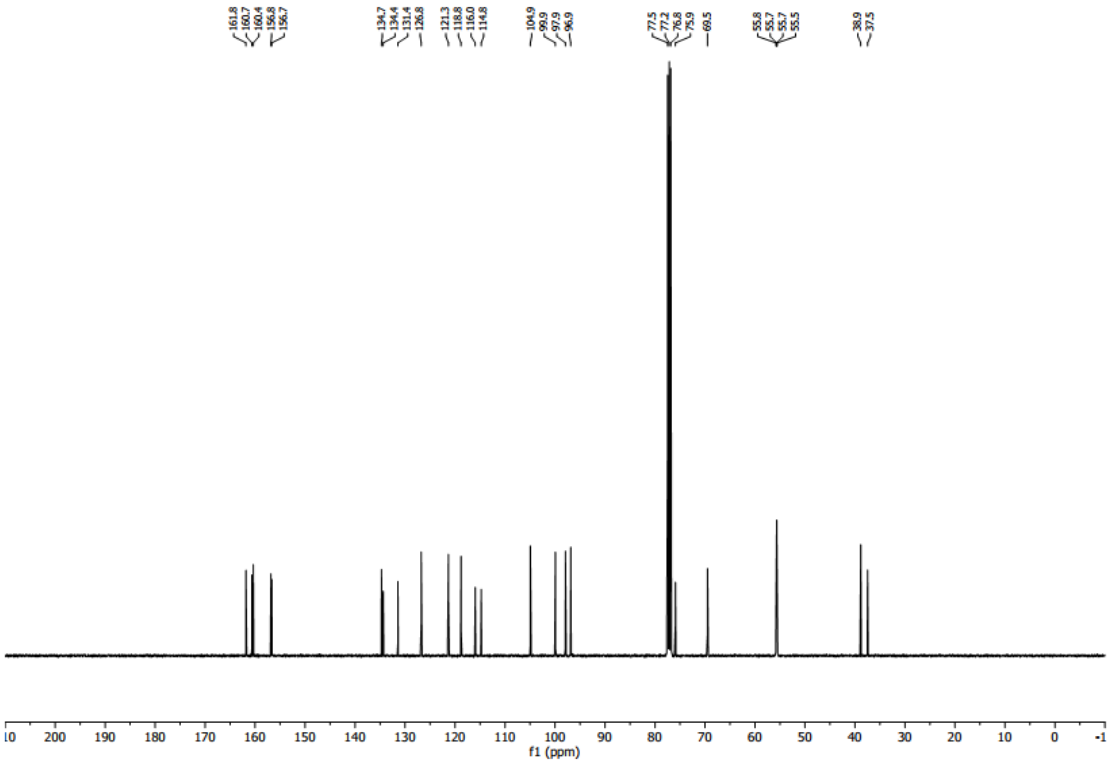
Compound **59** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



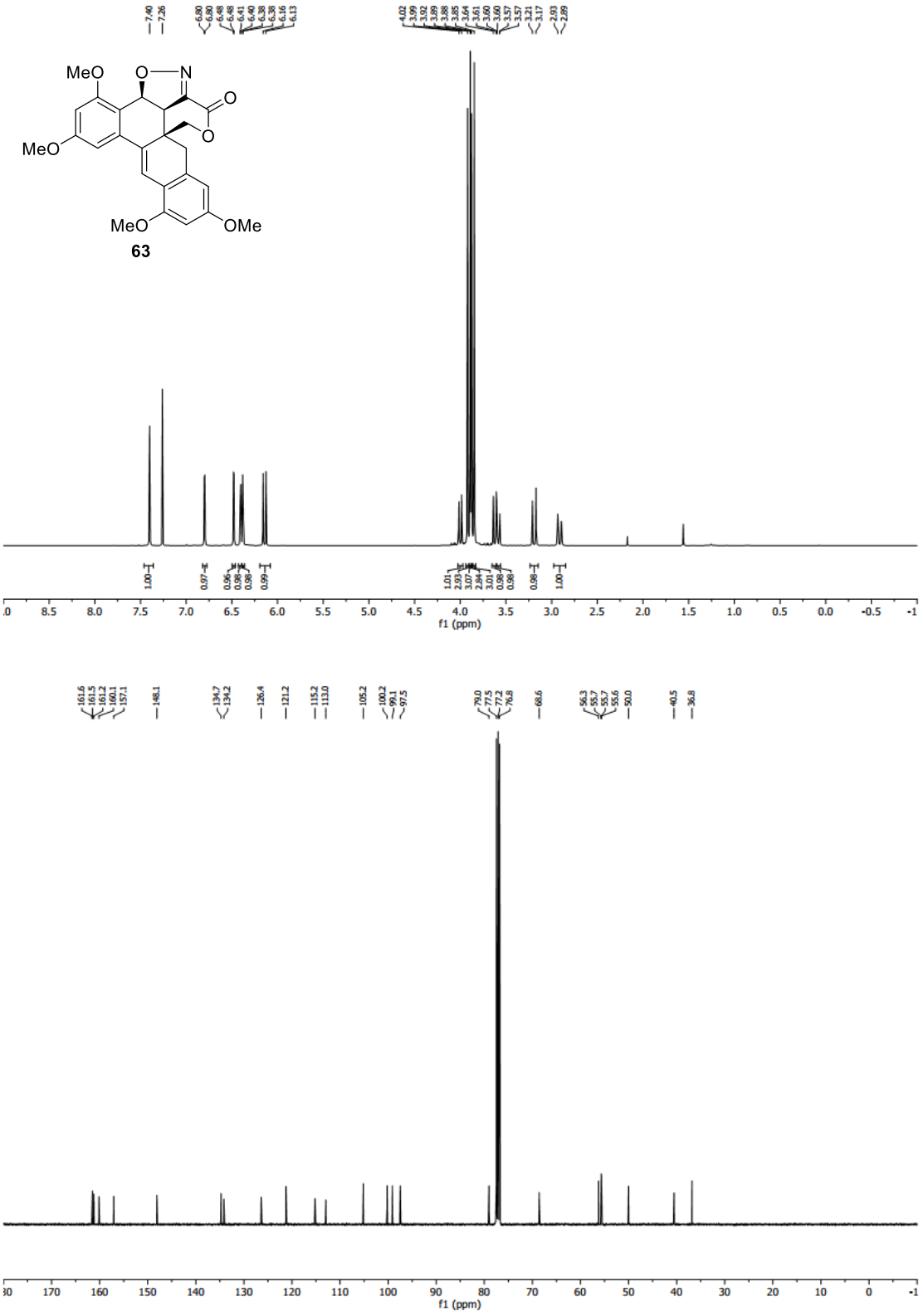


Compound **62** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

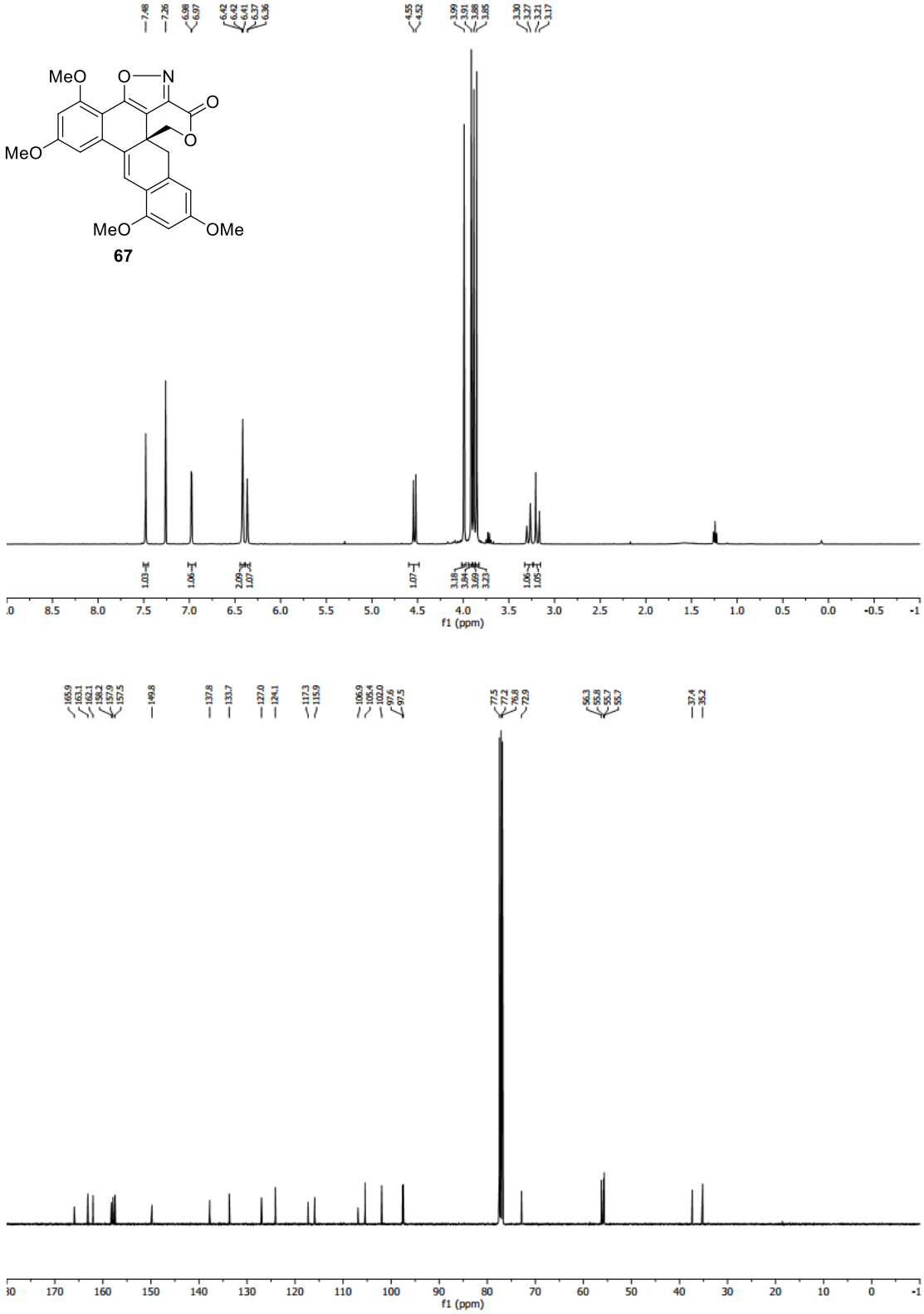




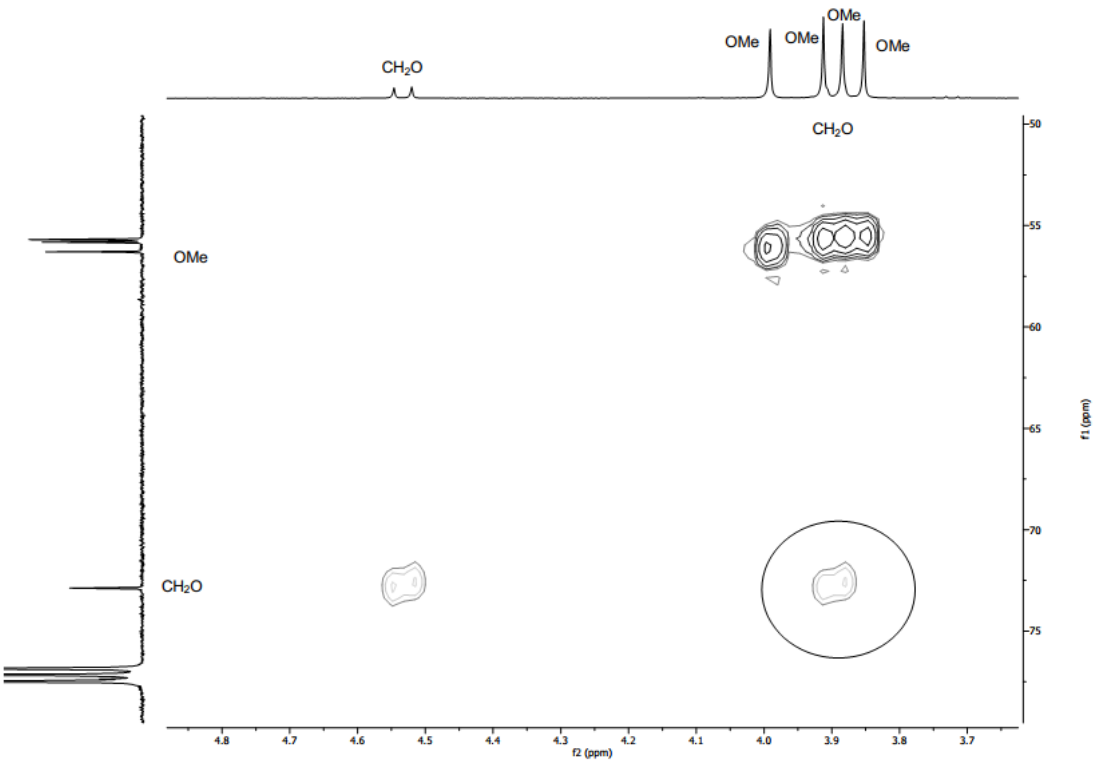
Compound **63** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

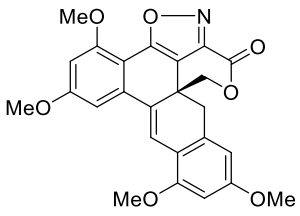


Compound **67** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



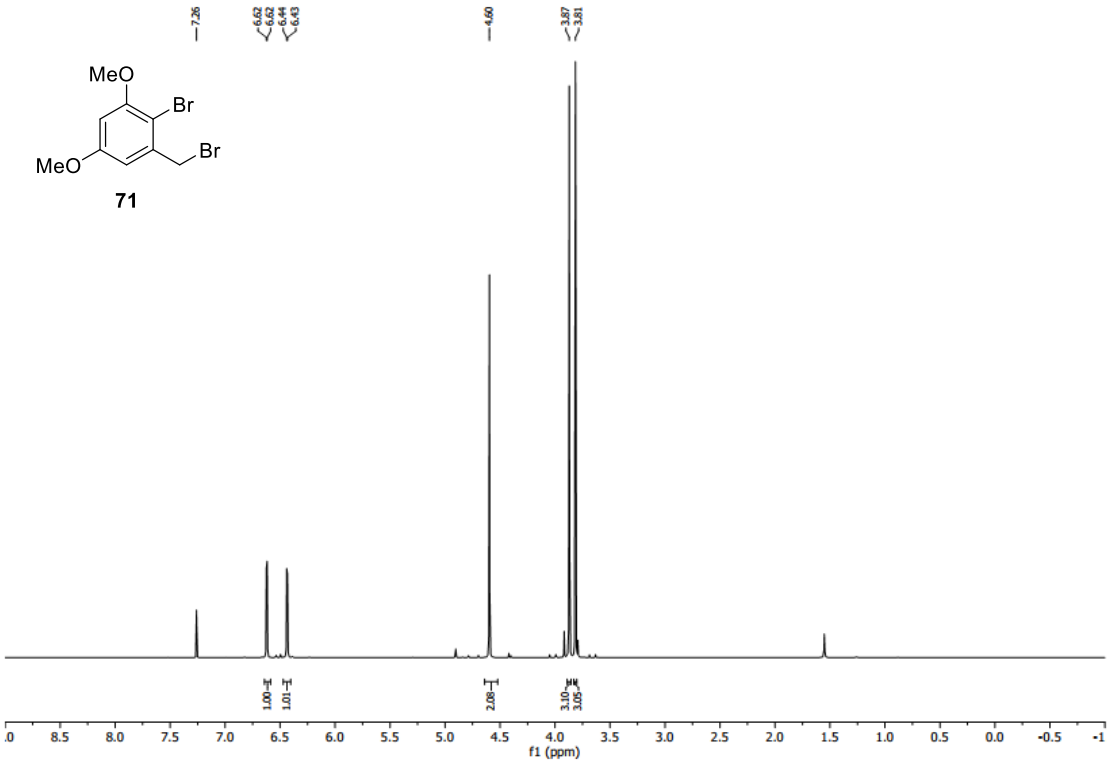
Compound **67** – HSQC (400 MHz) in $CDCl_3$

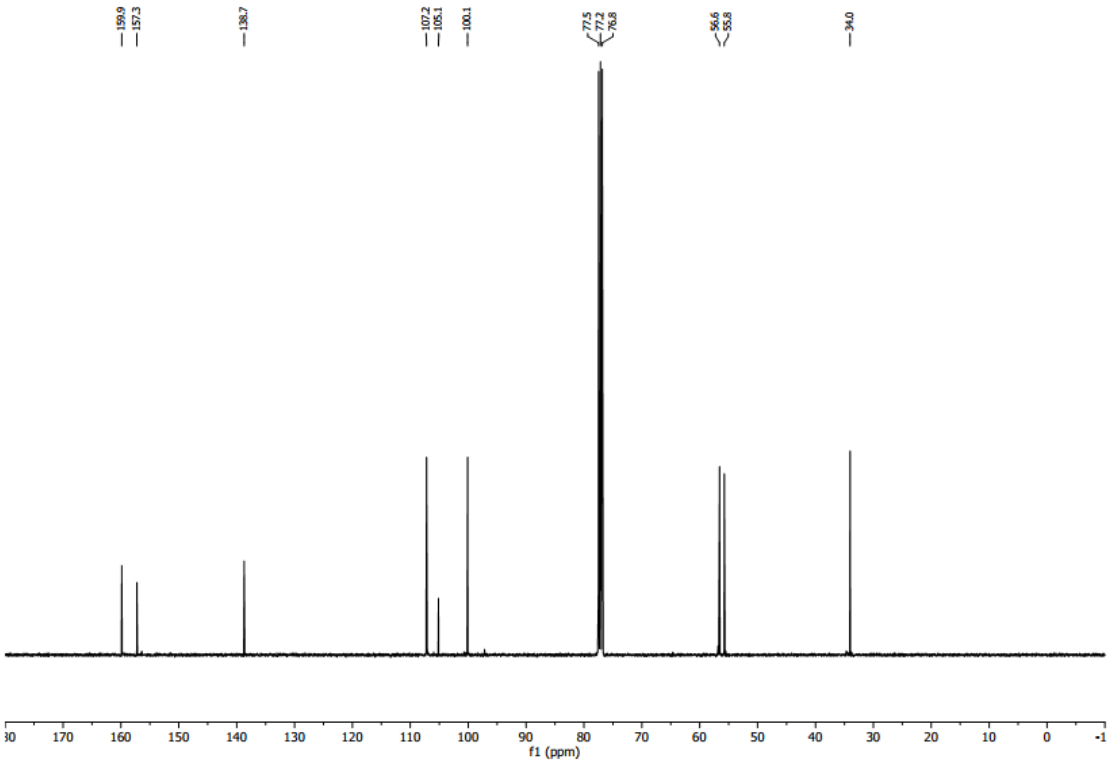




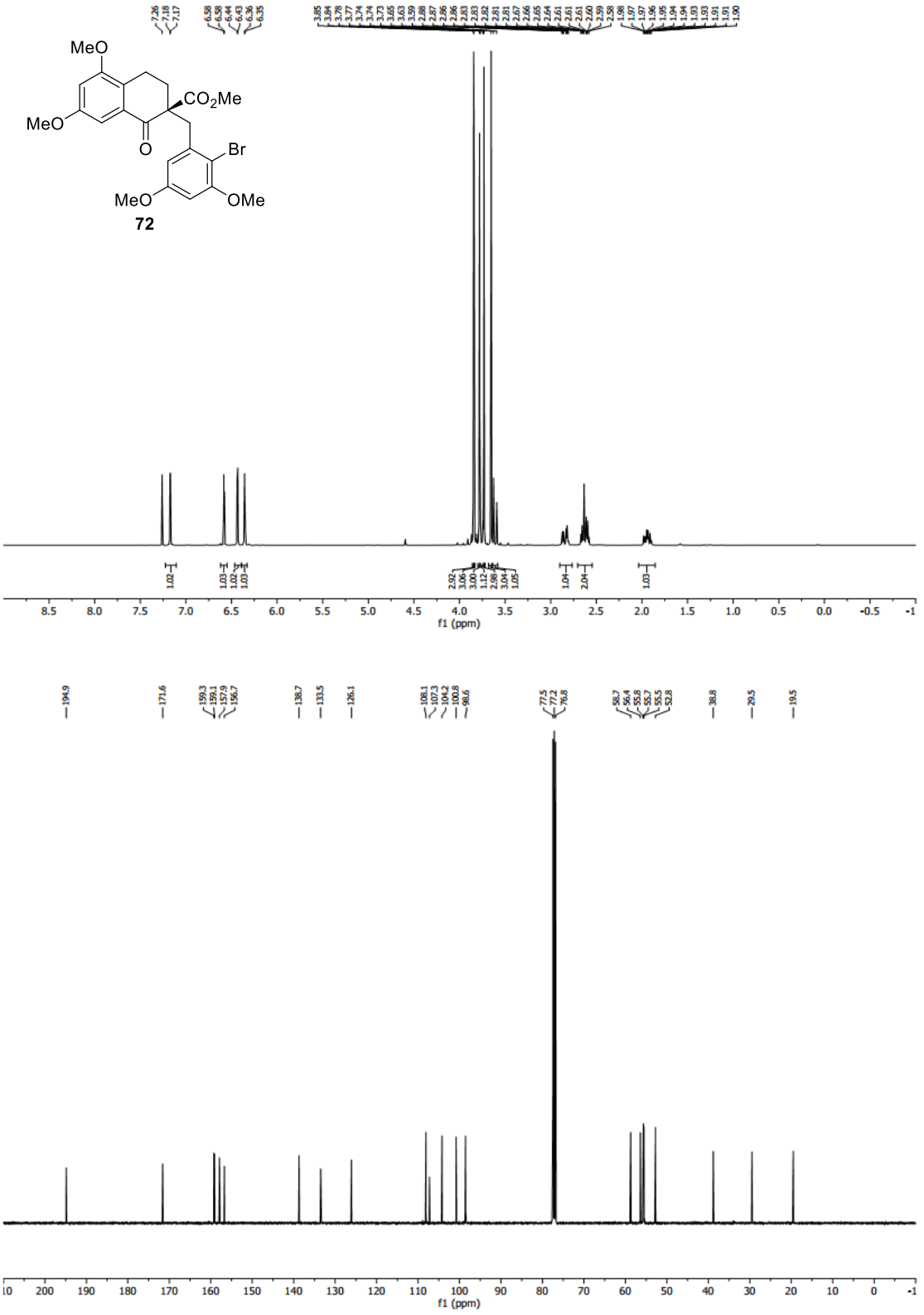
67

Compound **71** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

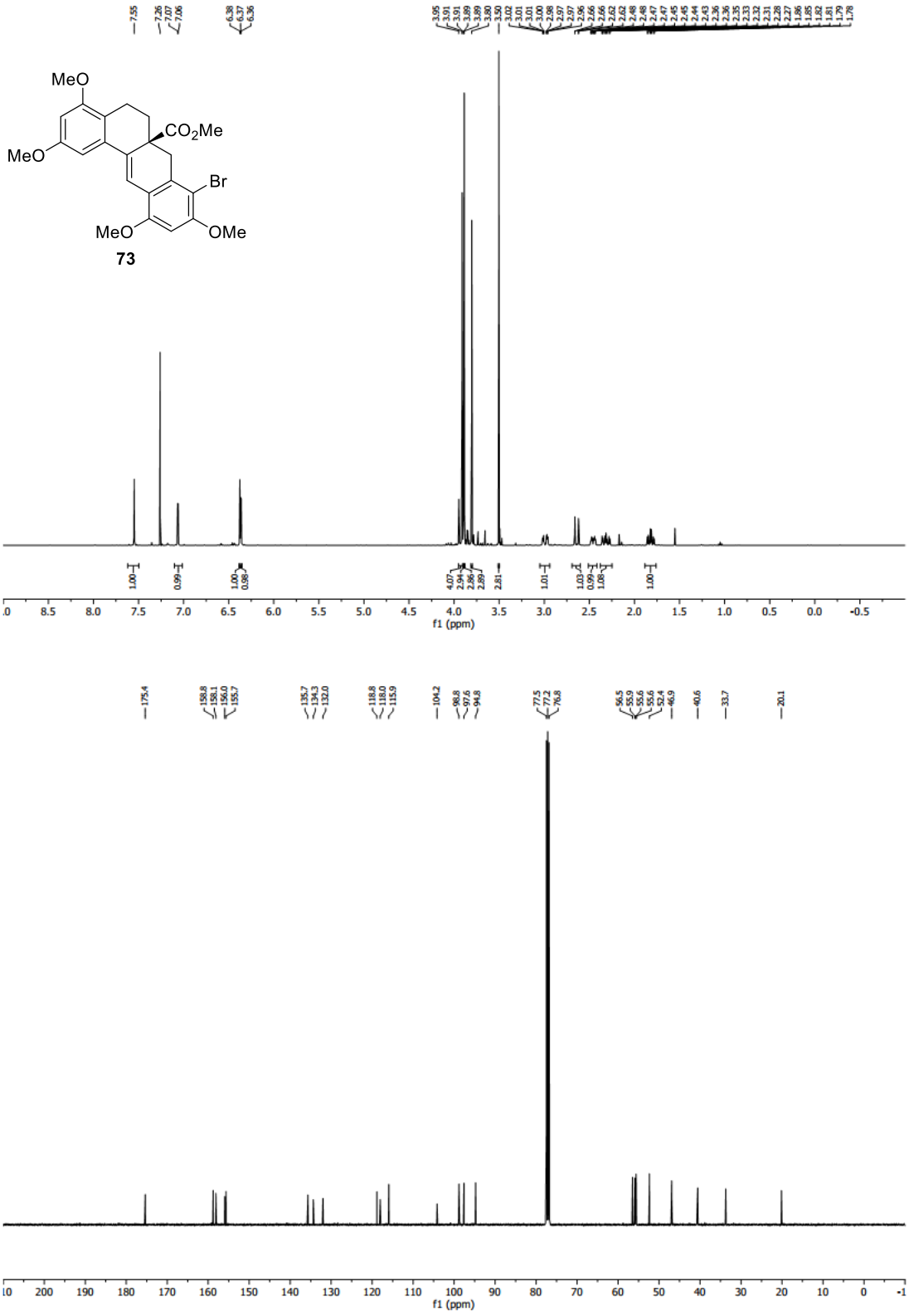




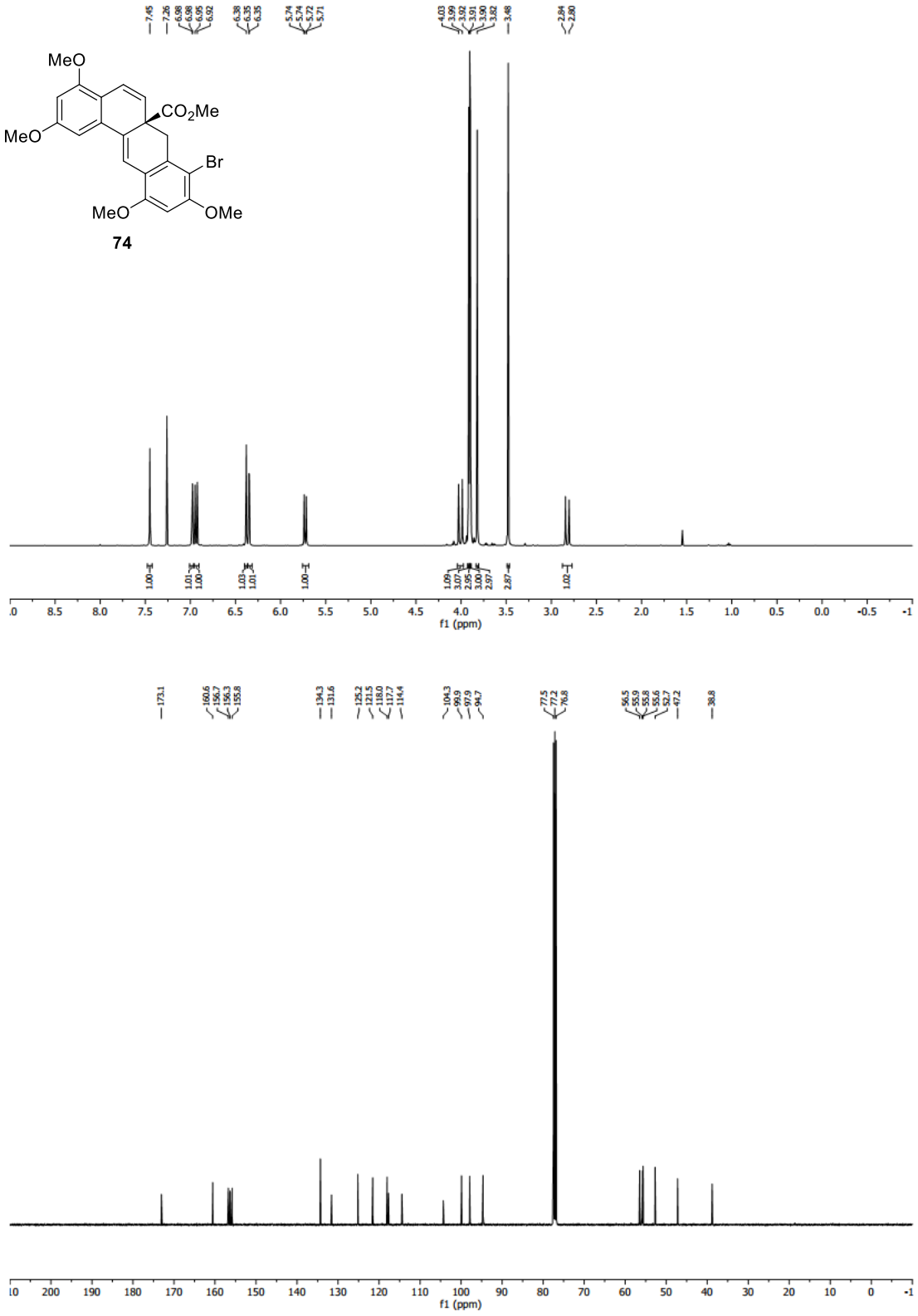
Compound **72** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



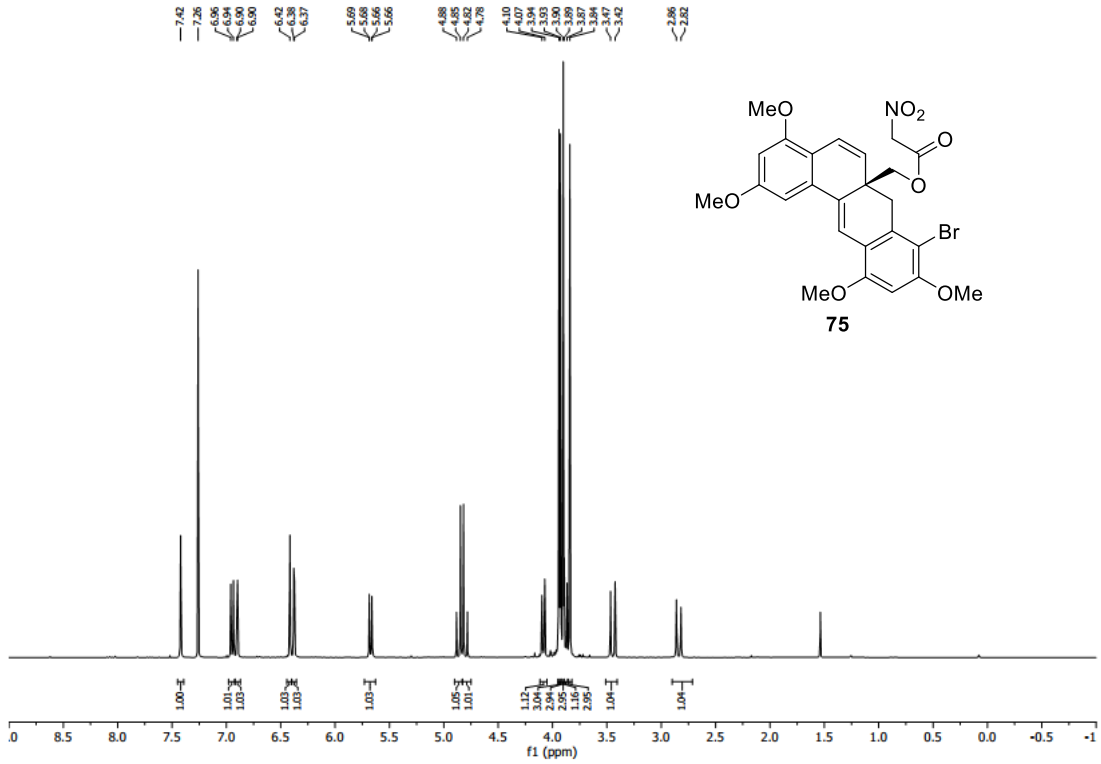
Compound **73** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

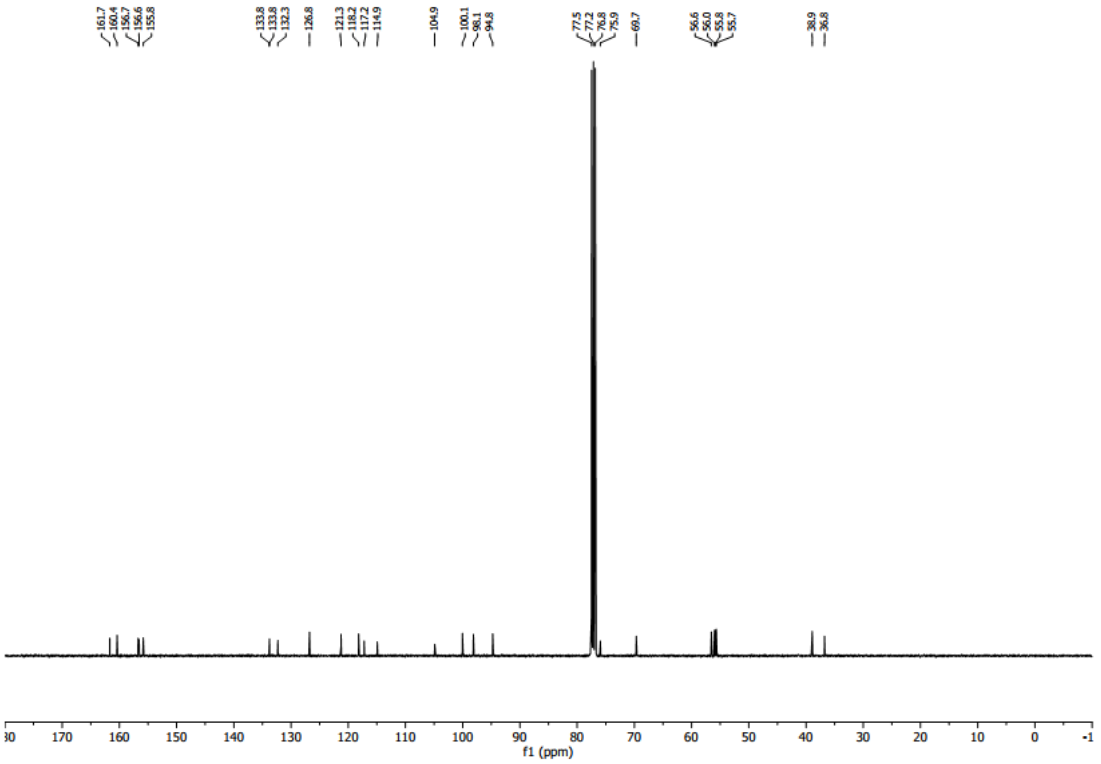


Compound **74** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

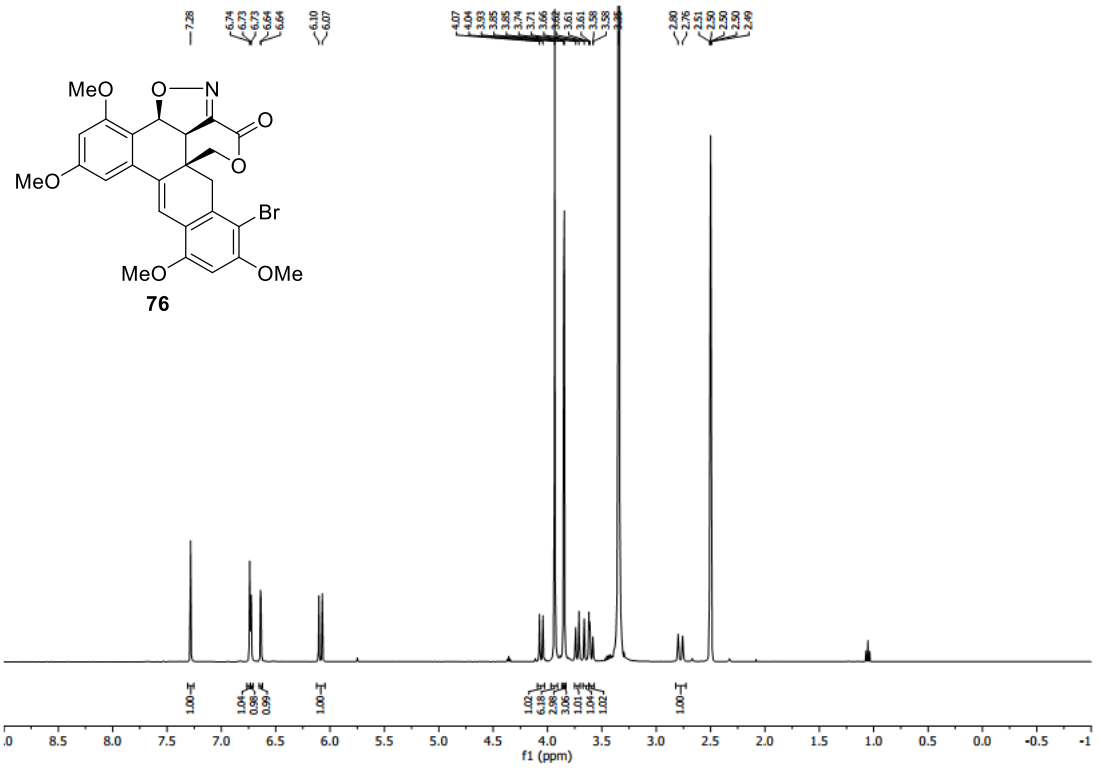


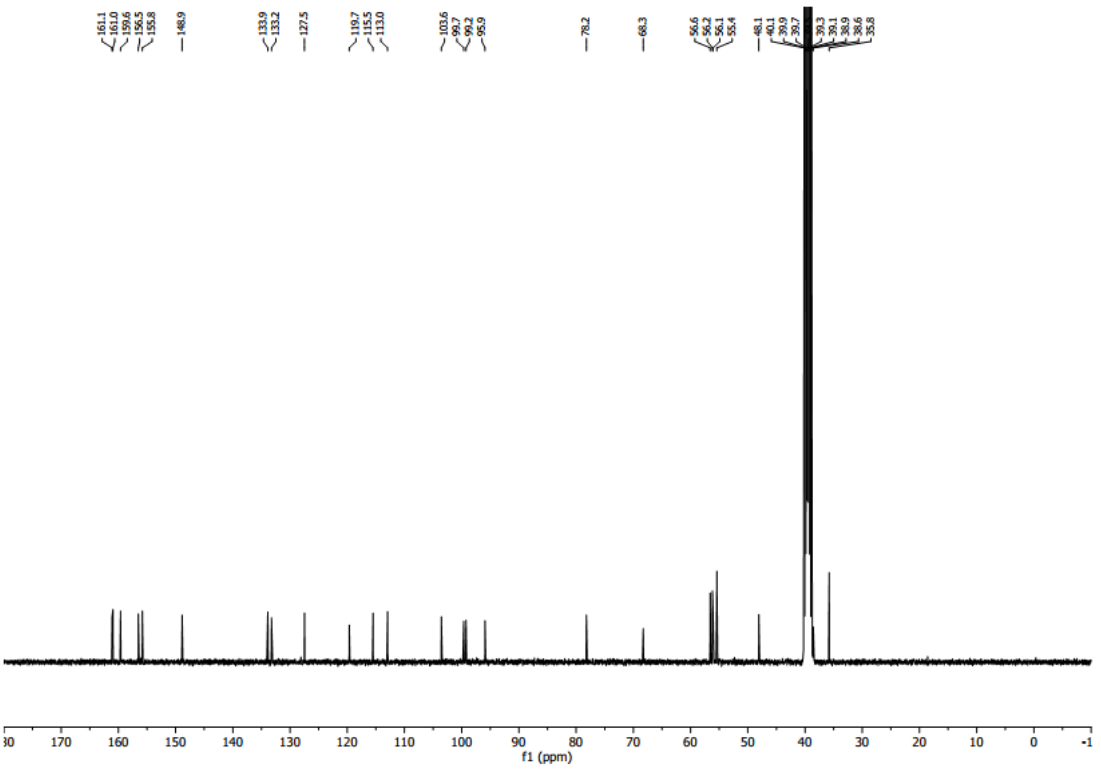
Compound **75** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



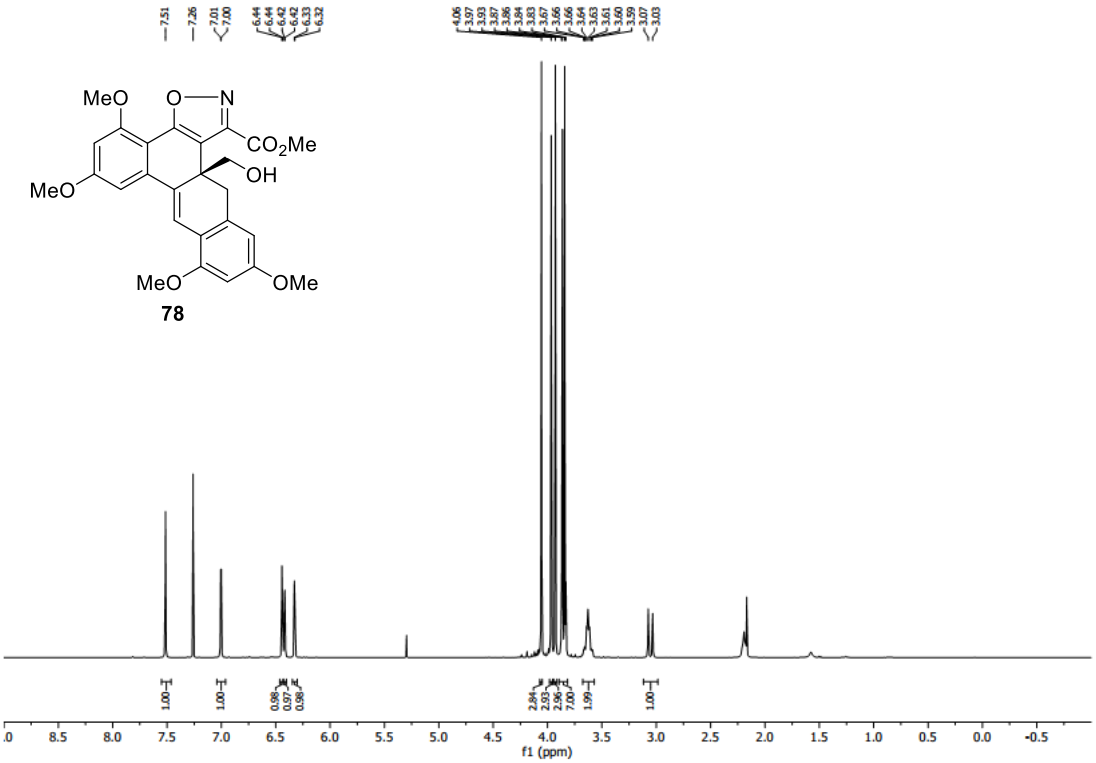


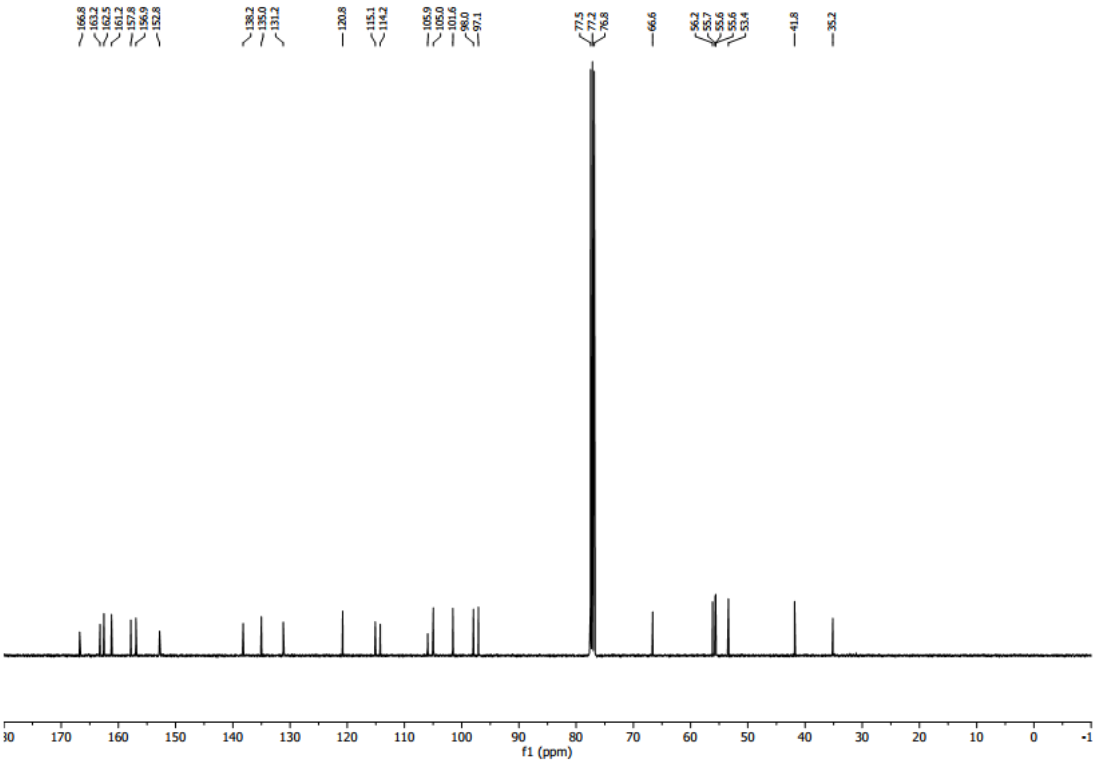
Compound **76** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in DMSO-d_6



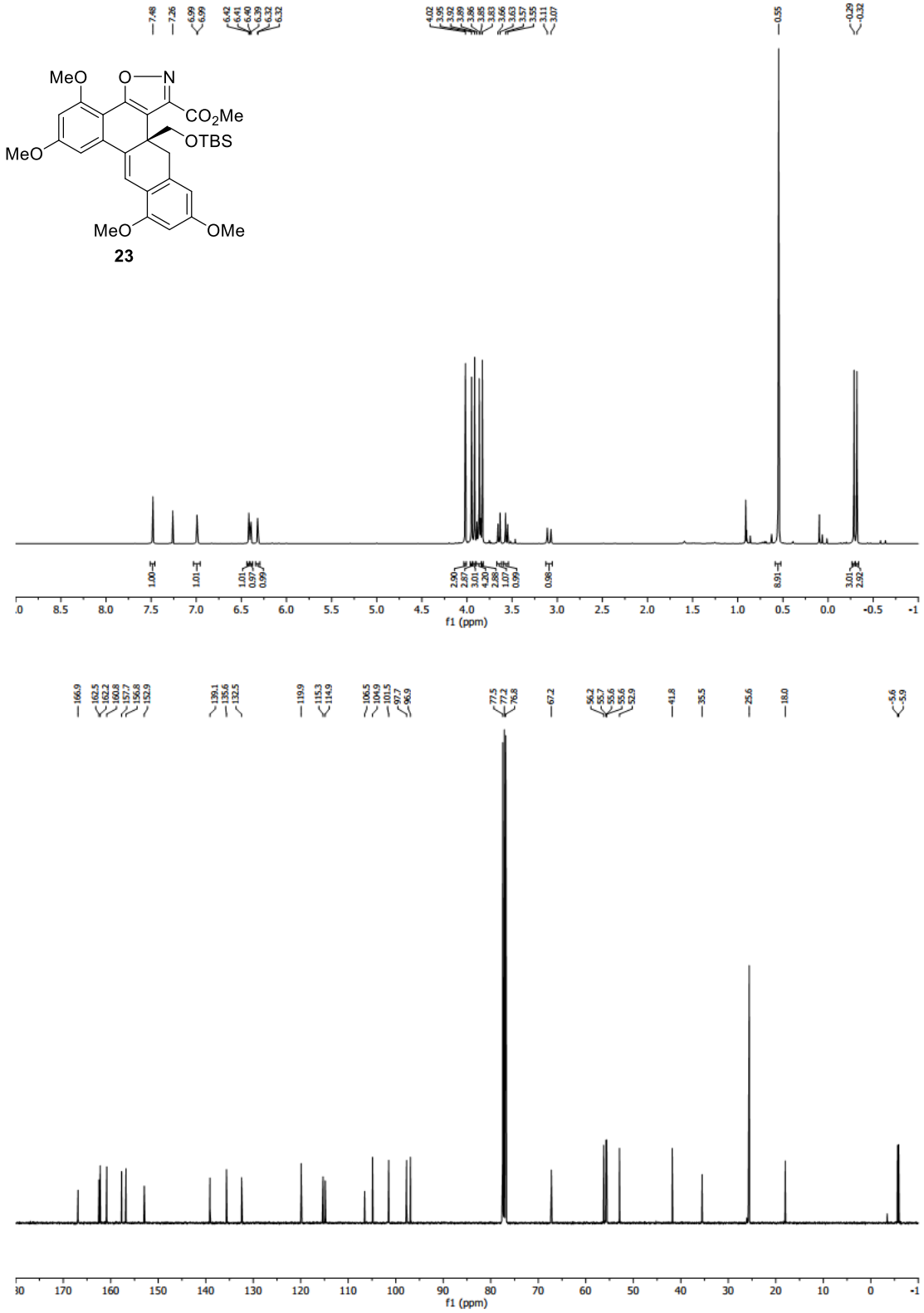


Compound **78** – ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) in $CDCl_3$

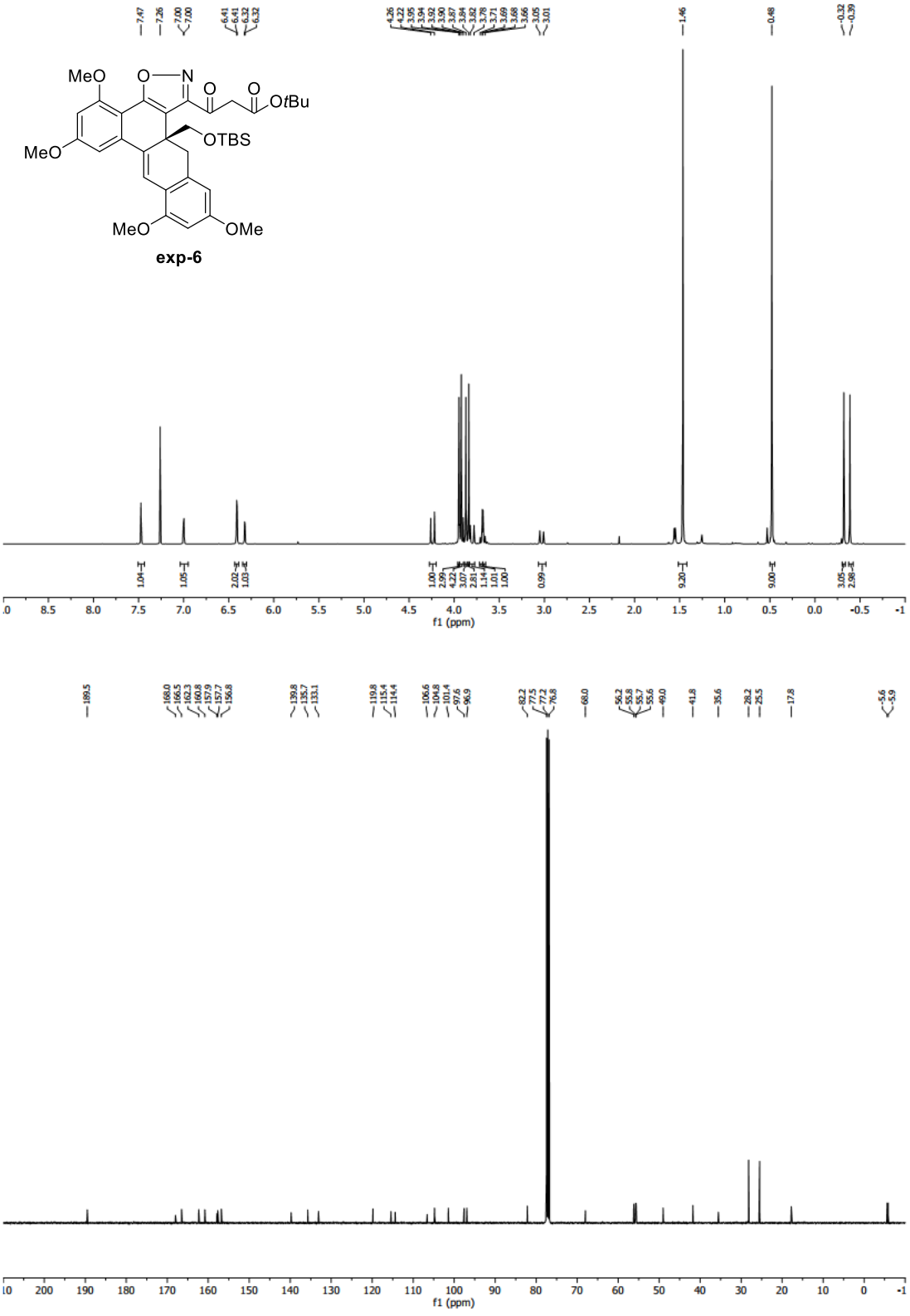




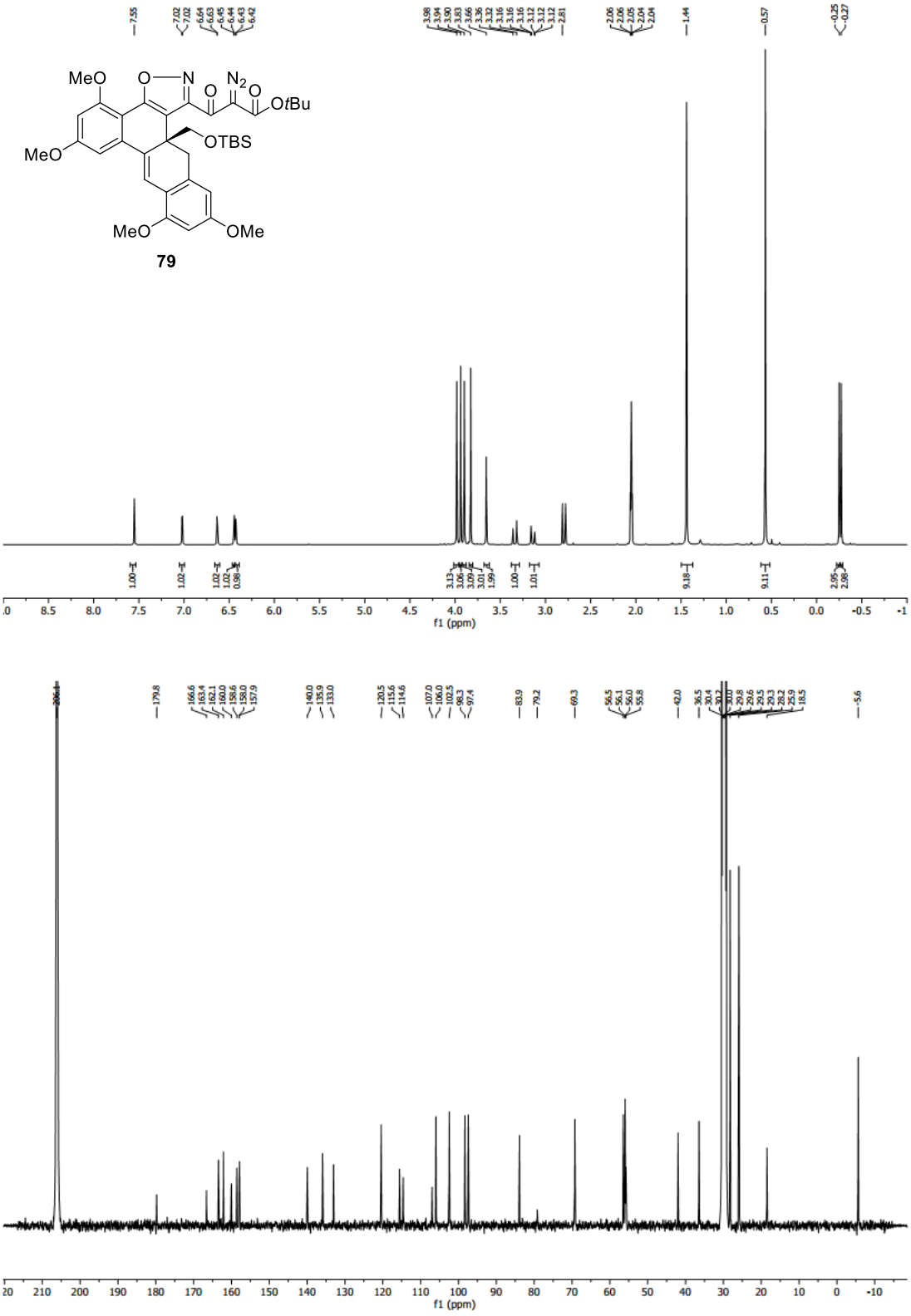
Compound **23** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



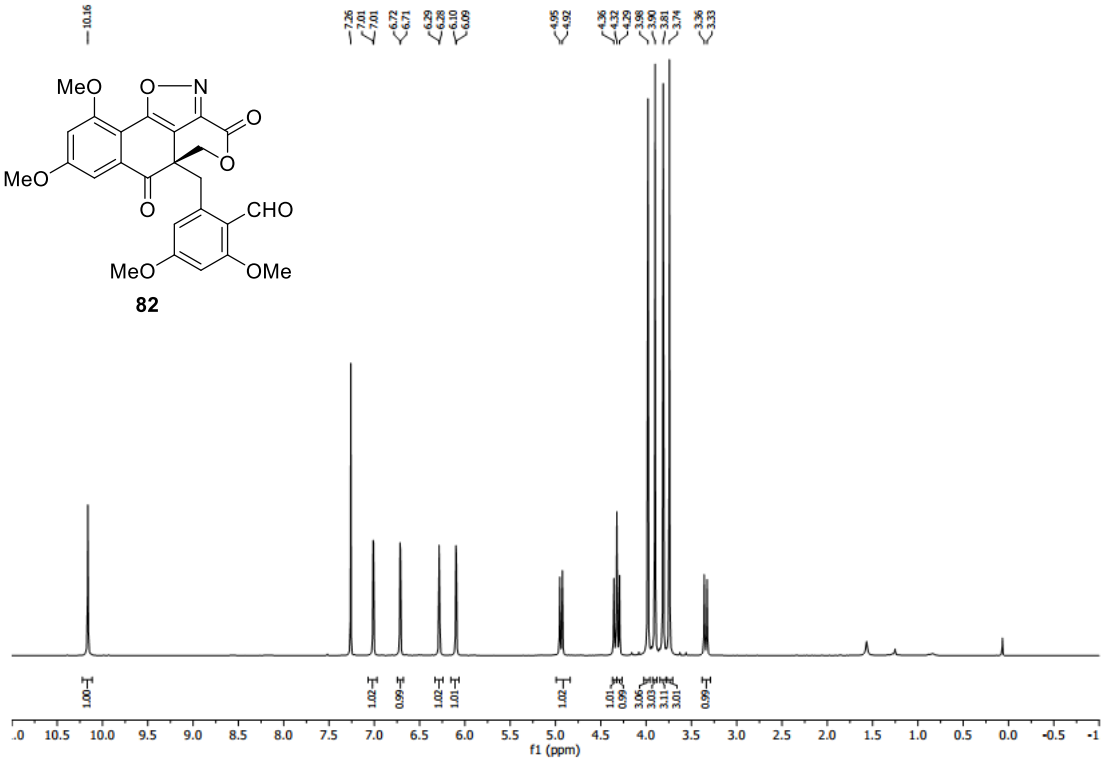
Compound **exp-6** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

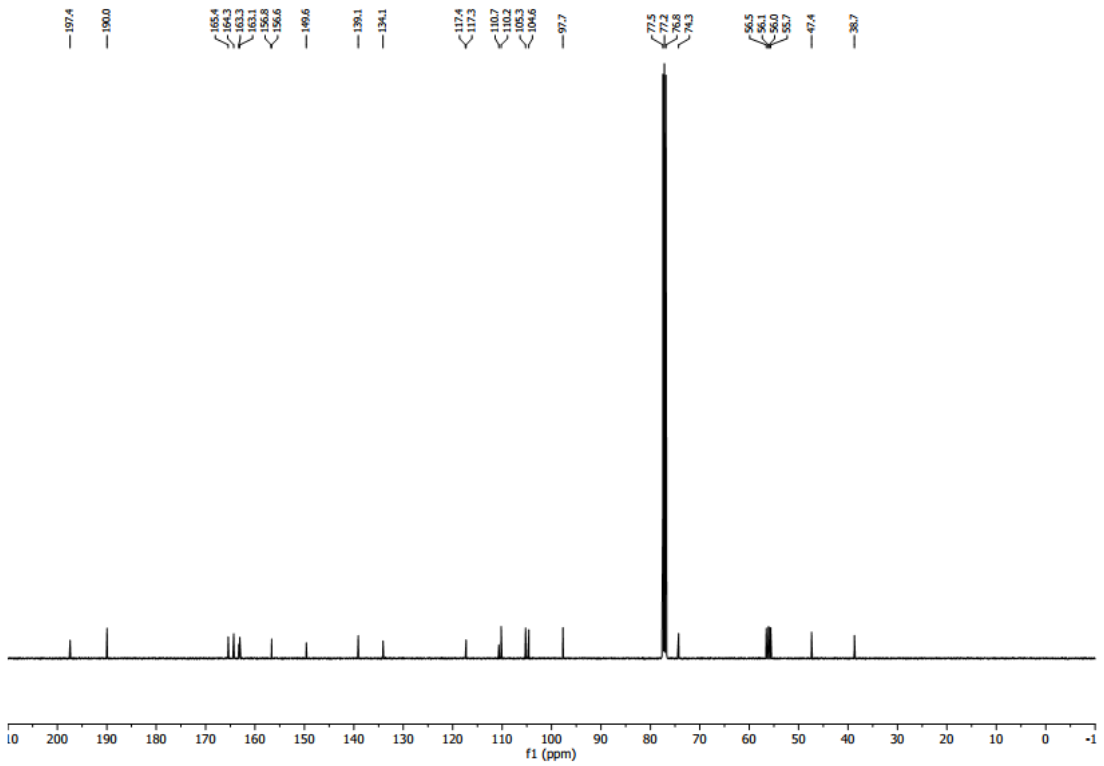


Compound **79** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in acetone-d_6

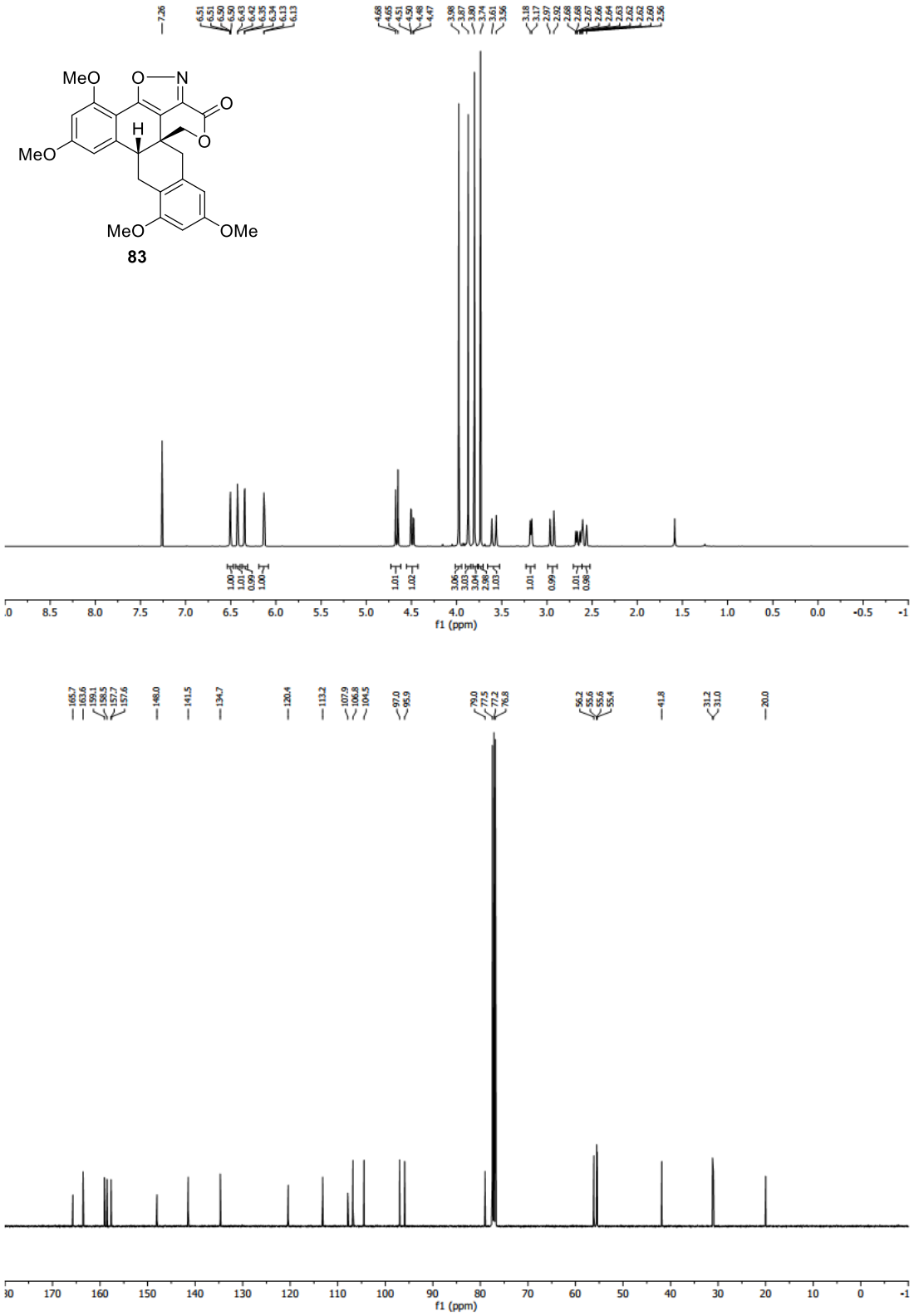


Compound **82** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

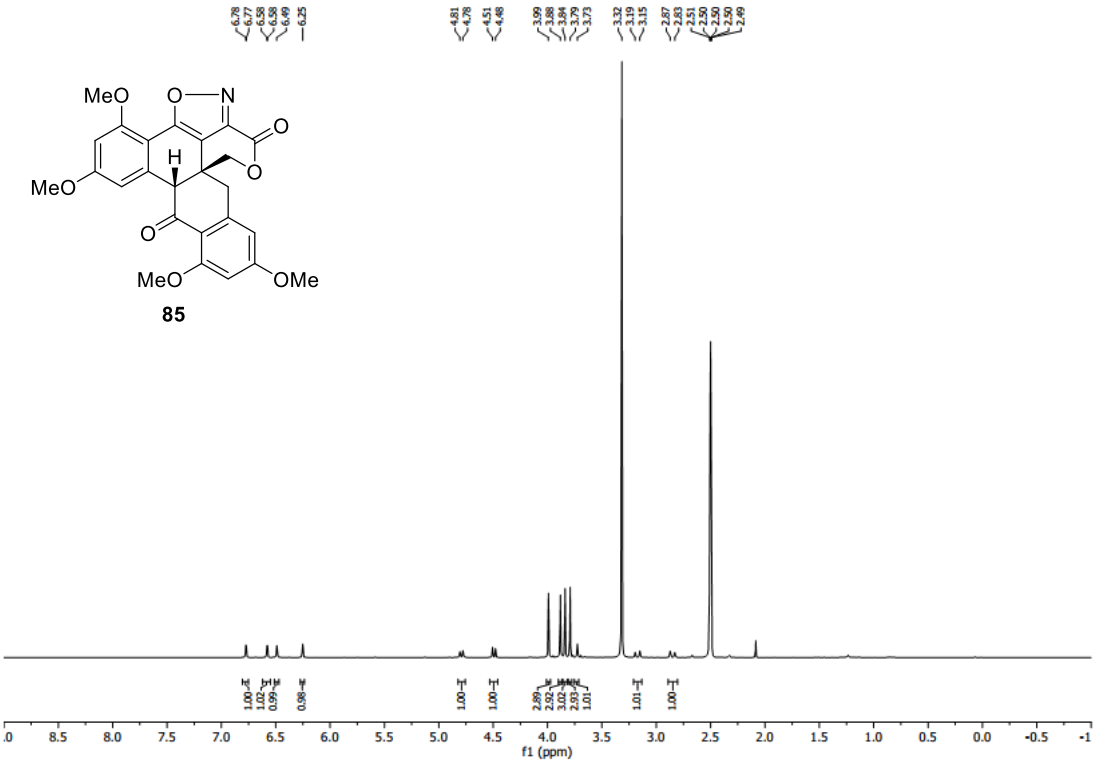


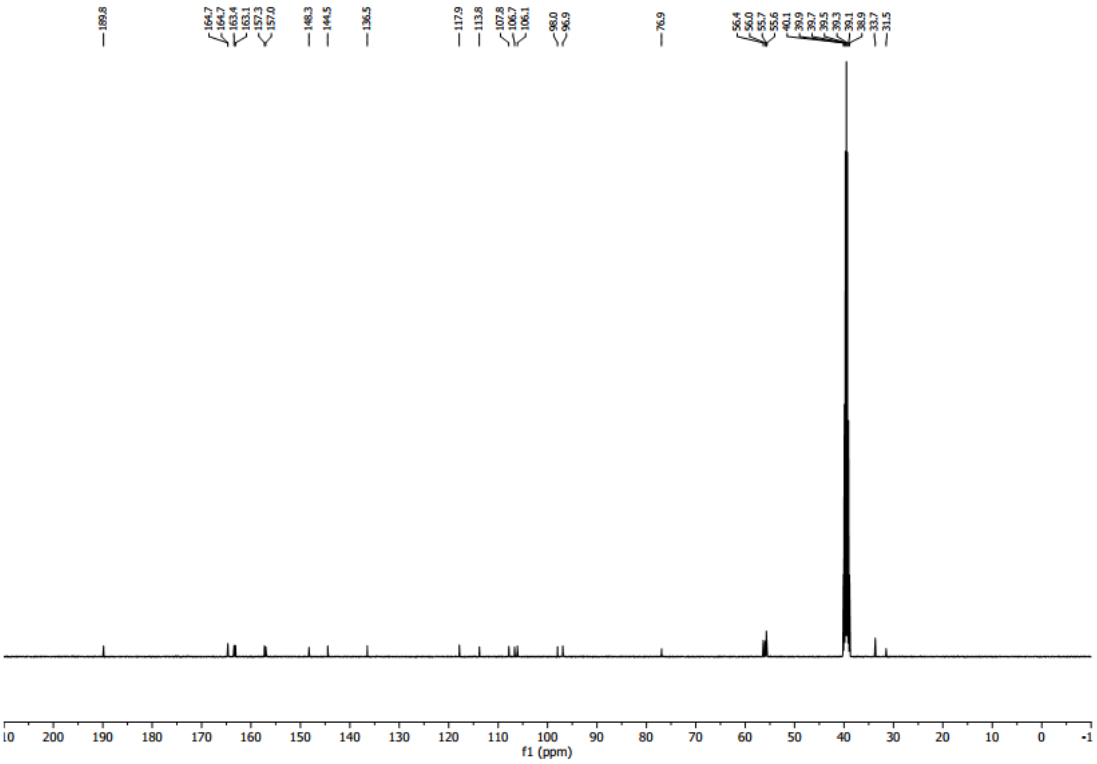


Compound **83** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

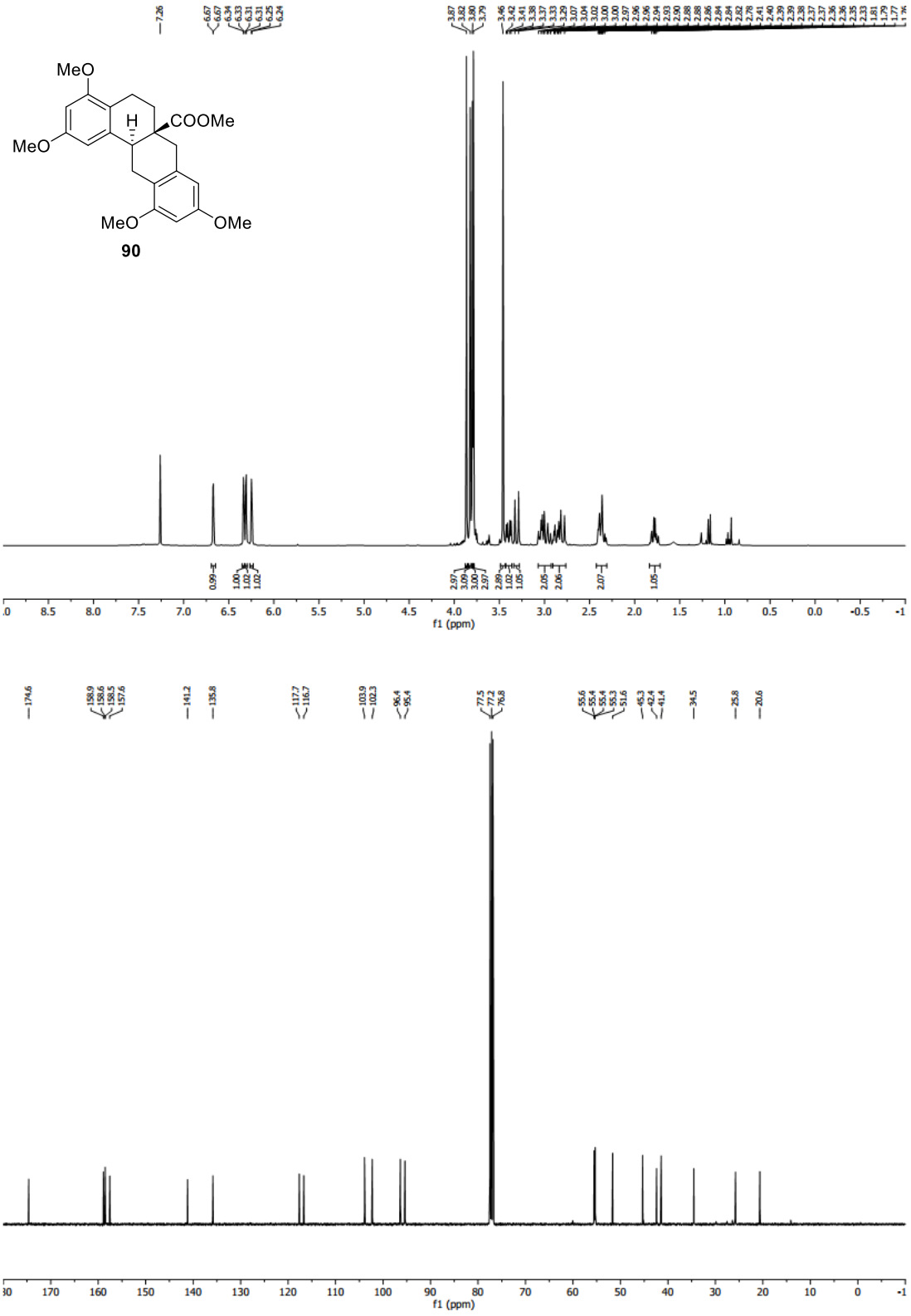


Compound **85** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in DMSO-d_6

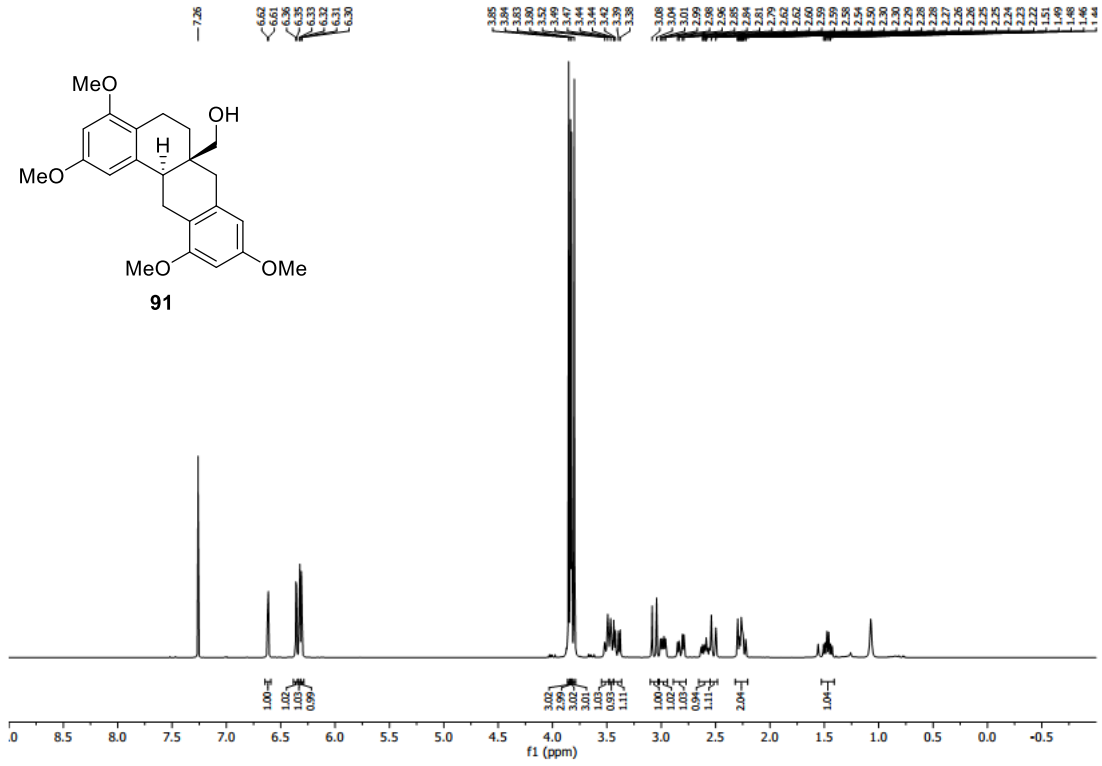


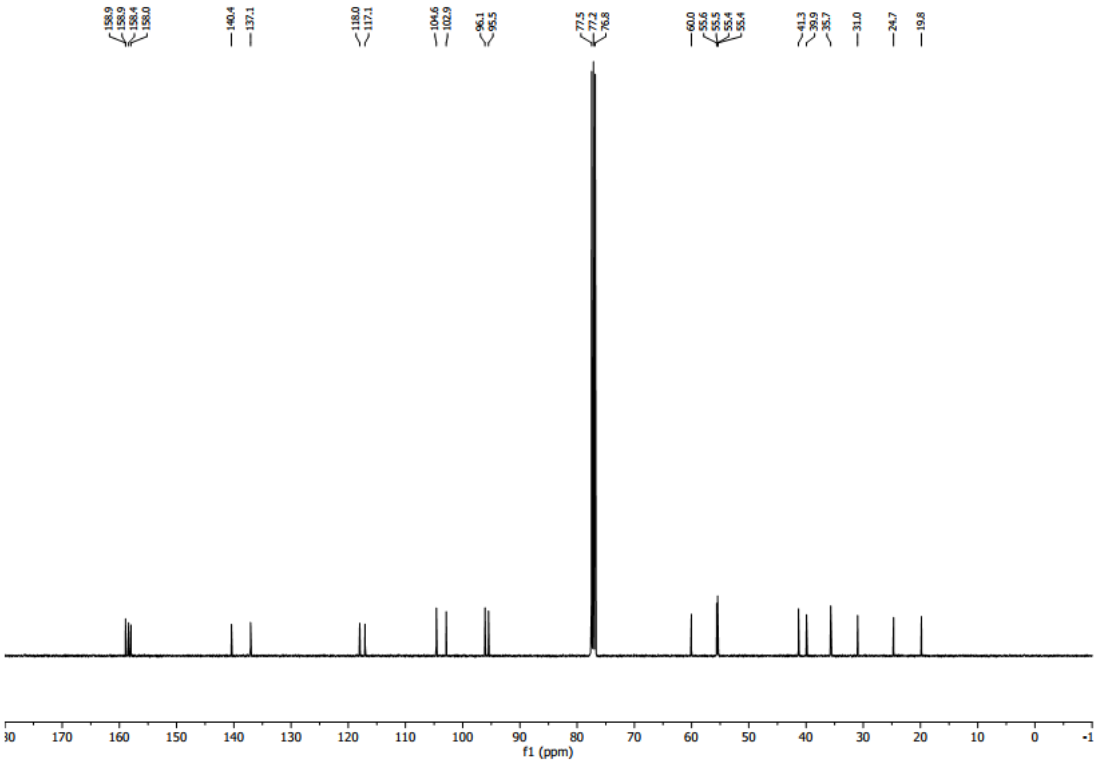


Compound **90** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

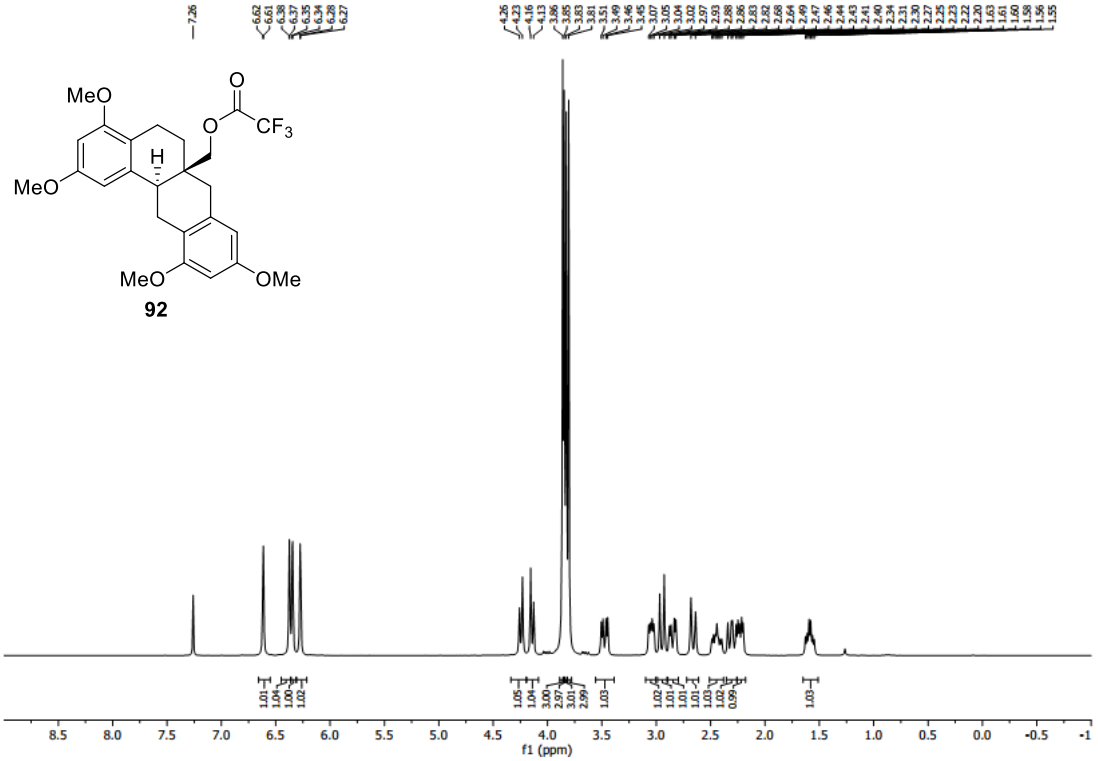


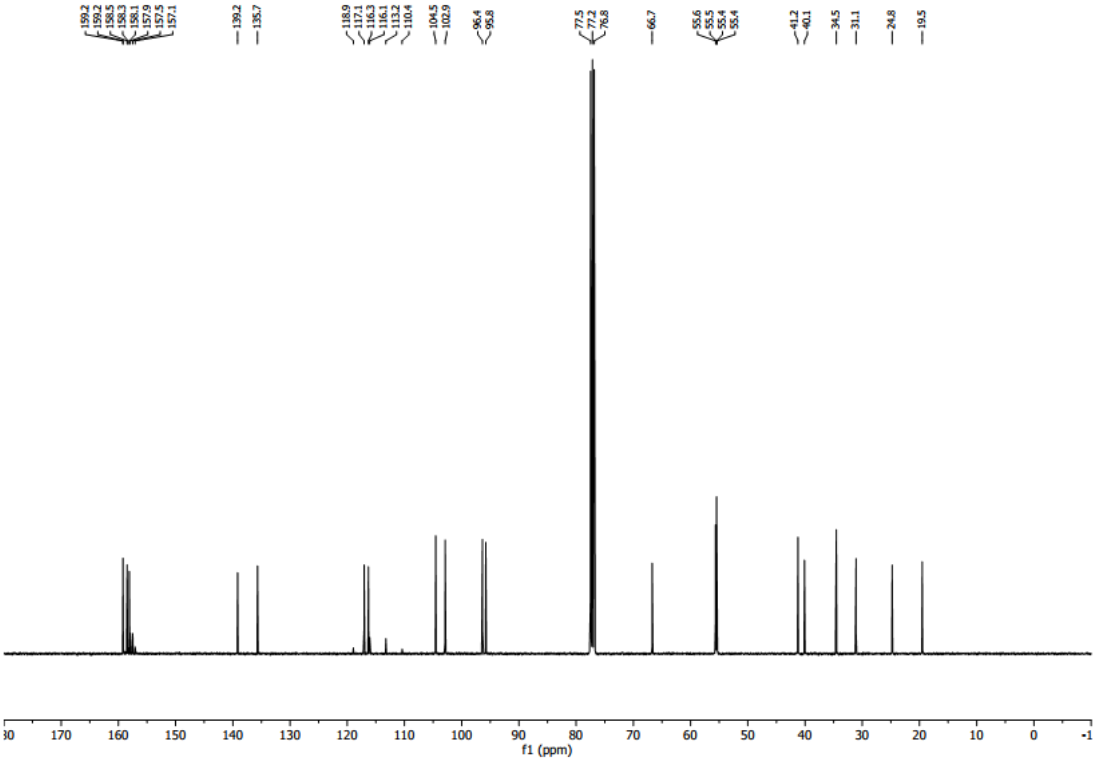
Compound **91** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



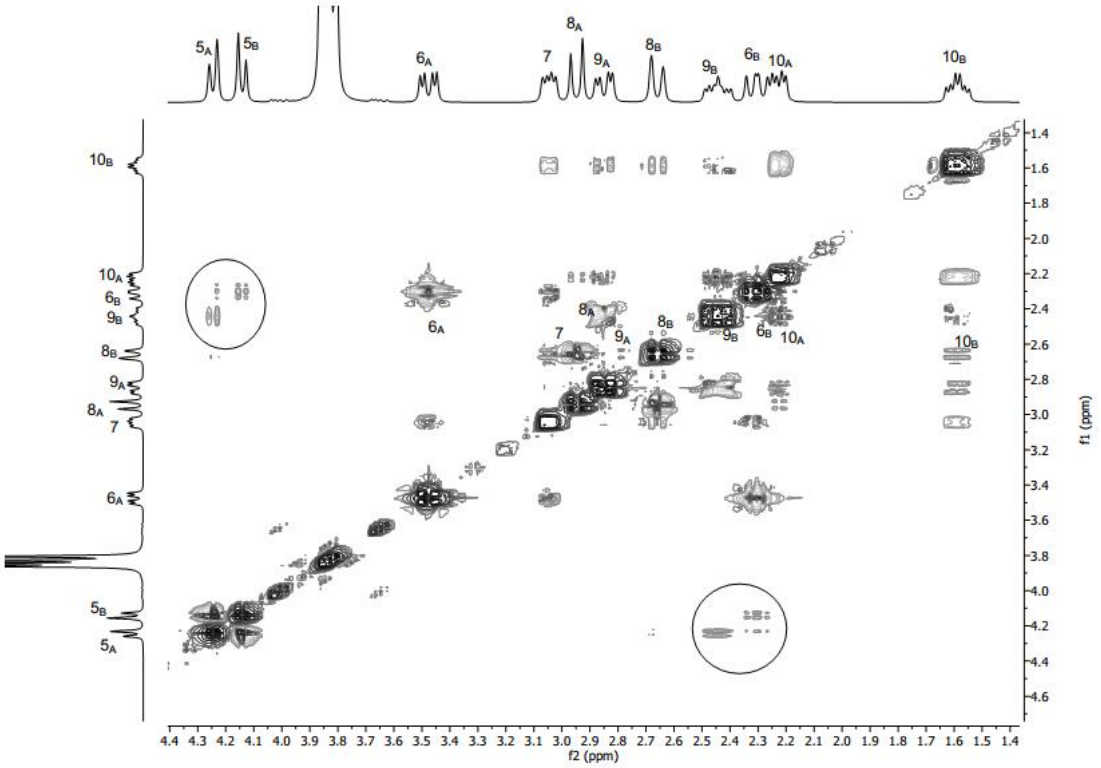


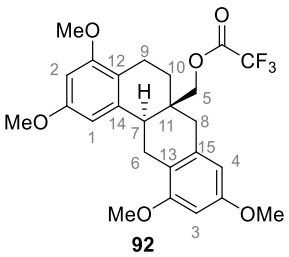
Compound **92** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



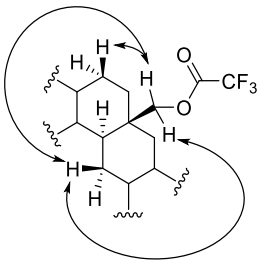


Compound **92** – **NOESY** (400 MHz) in $CDCl_3$

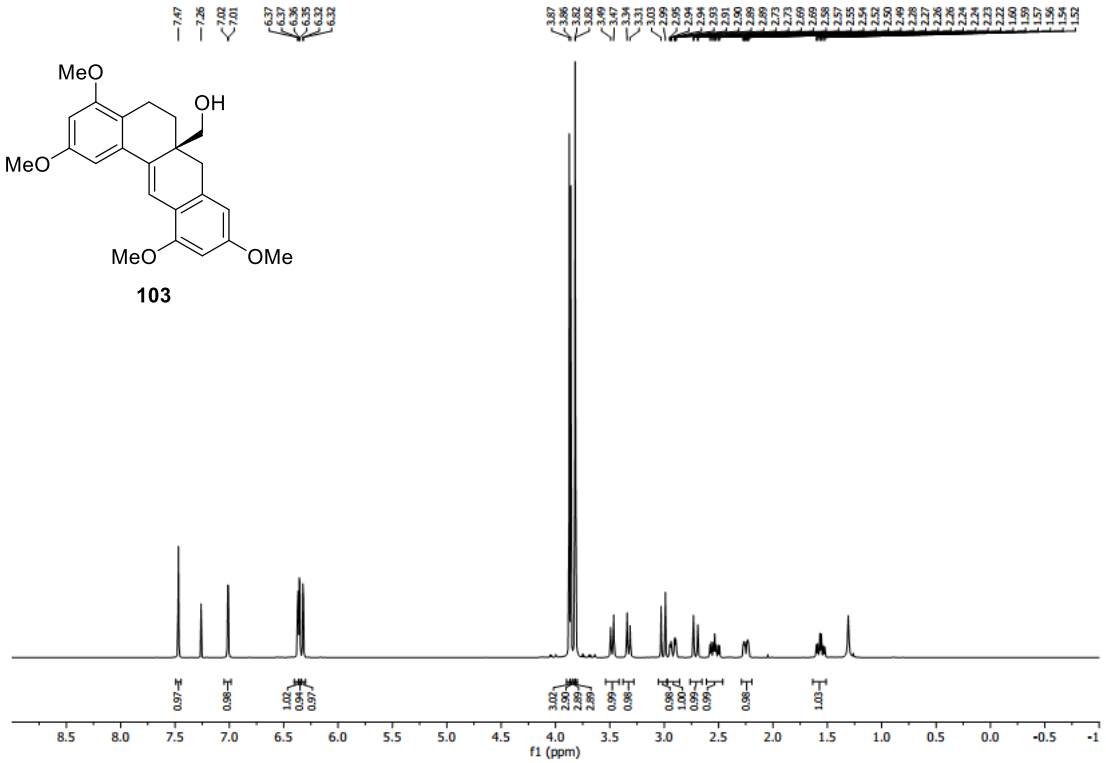




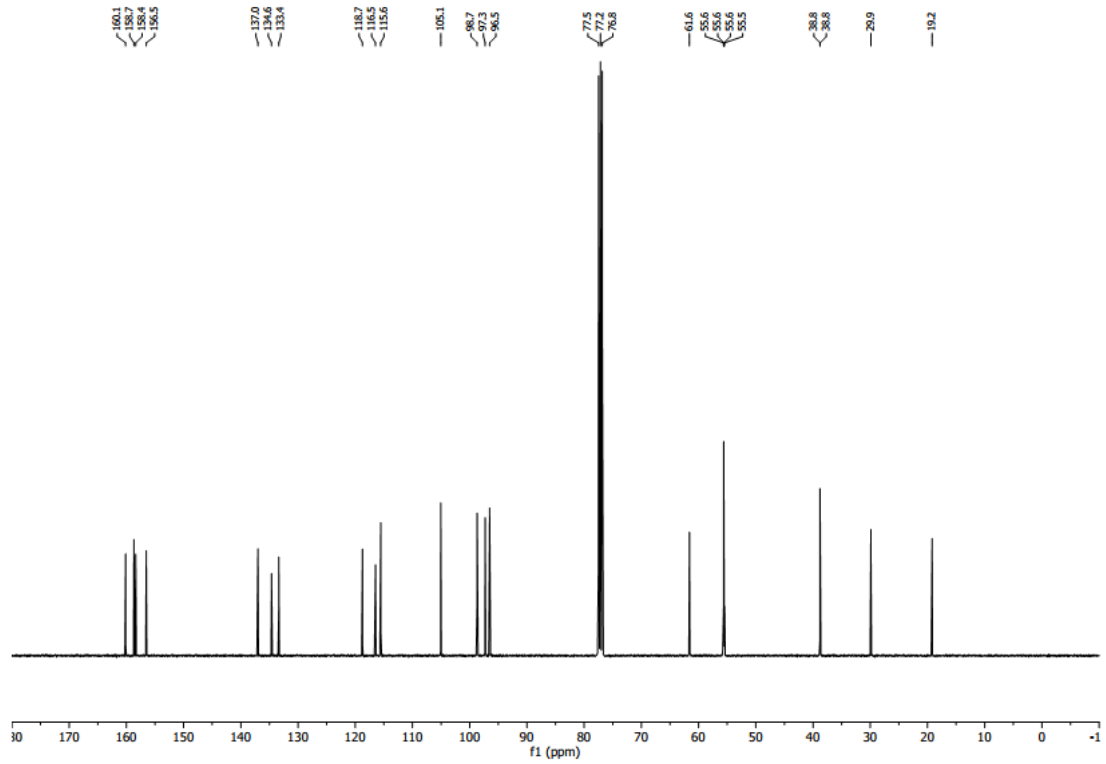
92



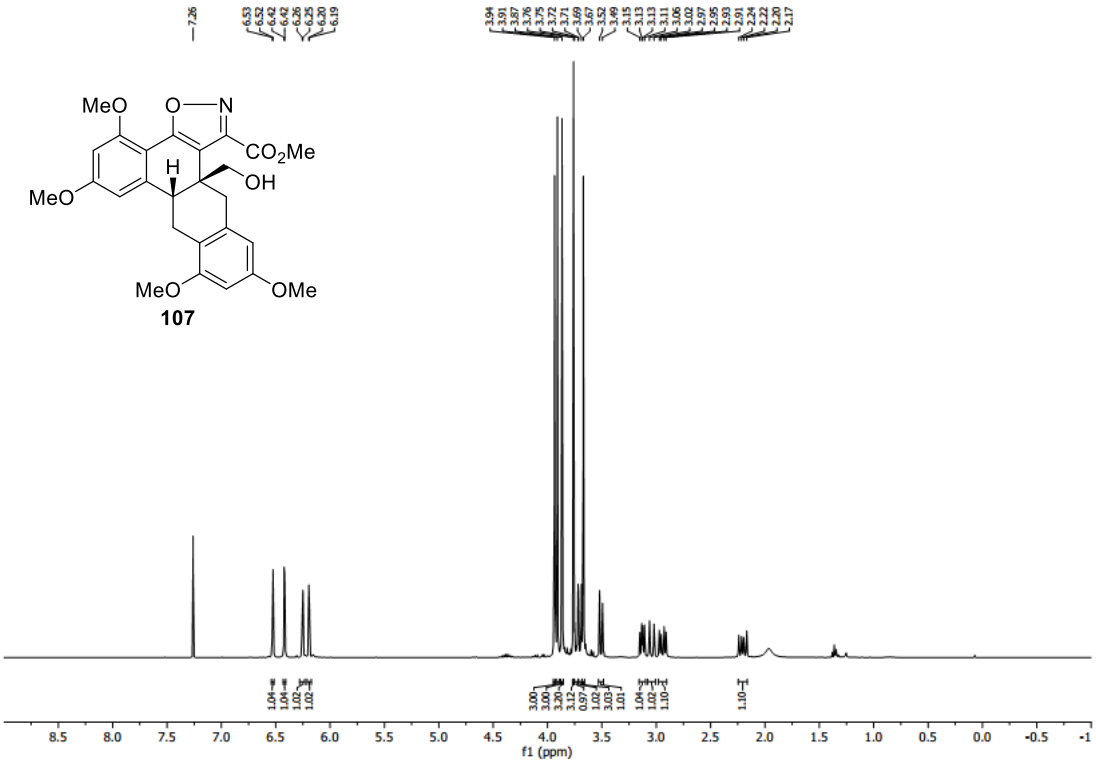
Compound **103** – ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) in $CDCl_3$

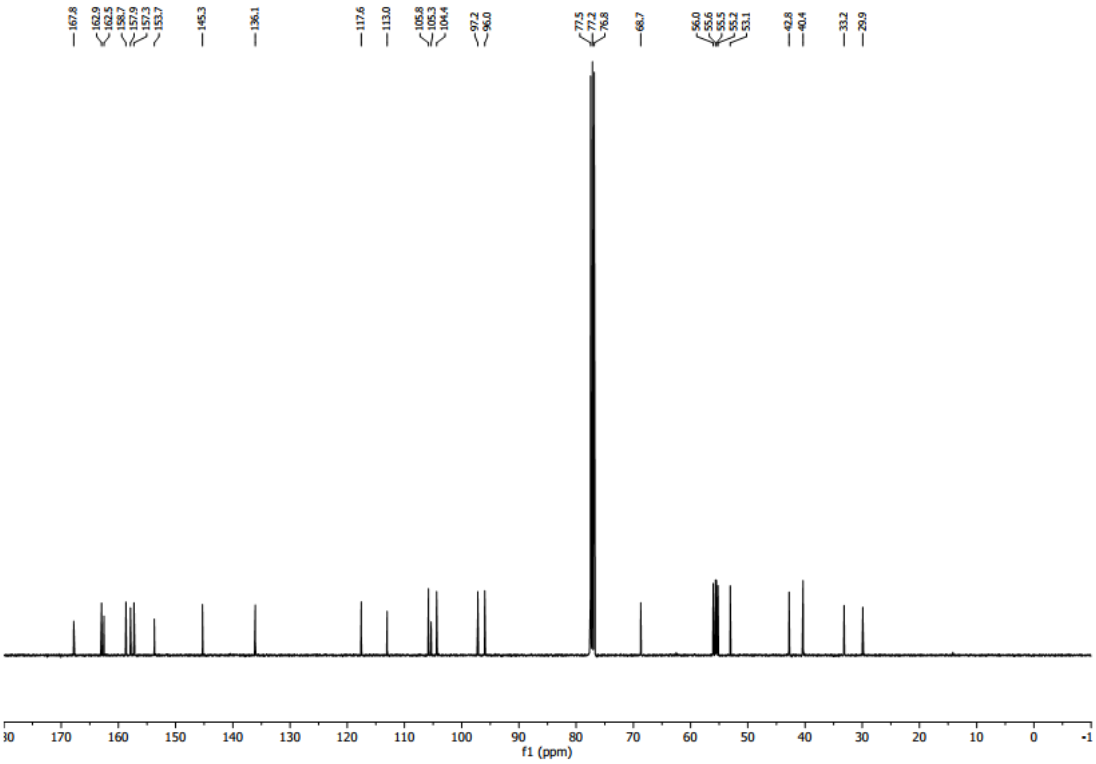


103

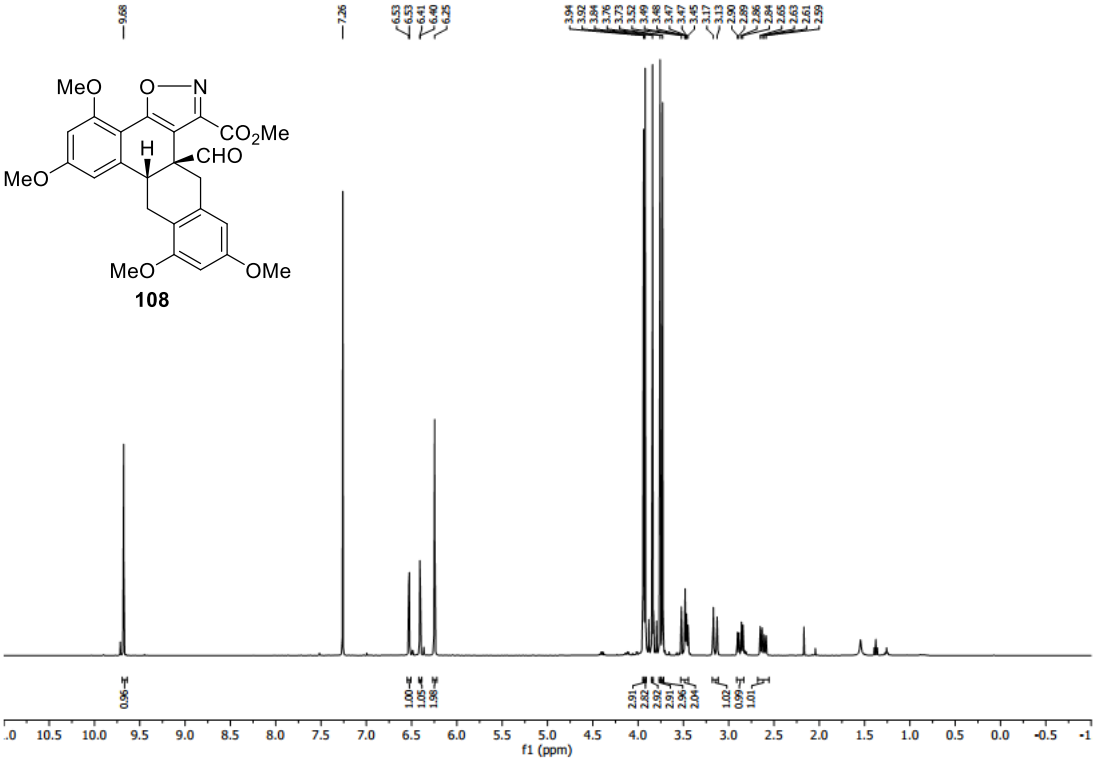


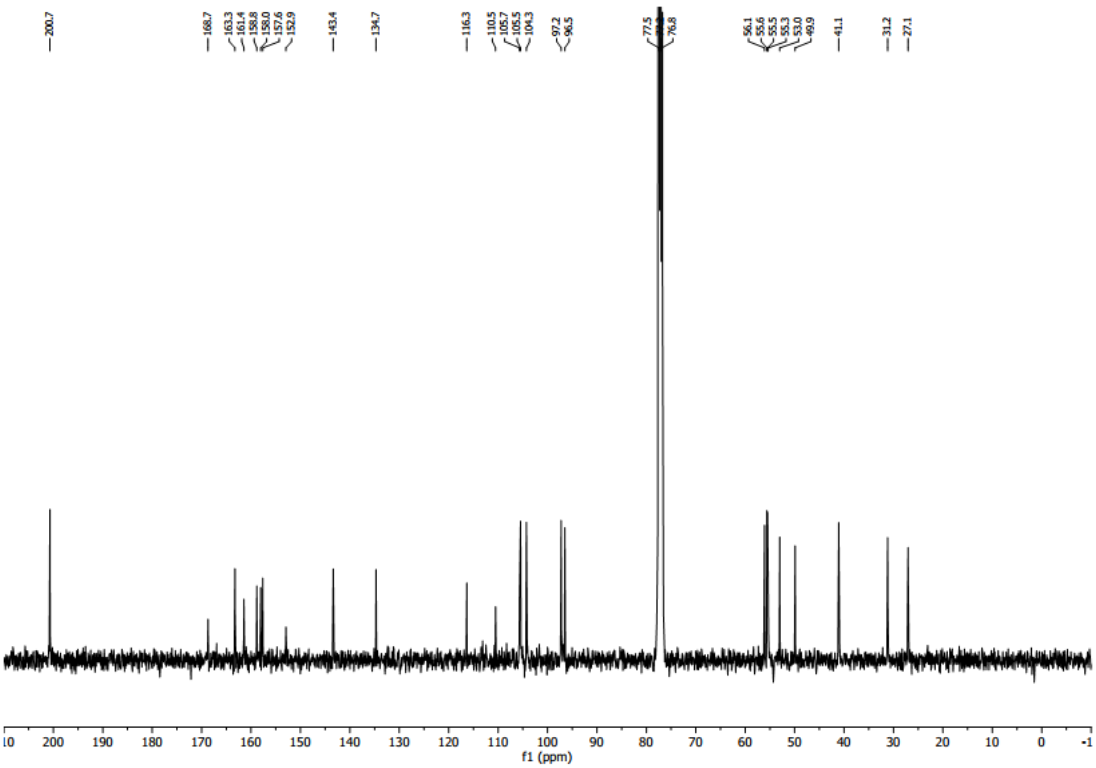
Compound **107** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



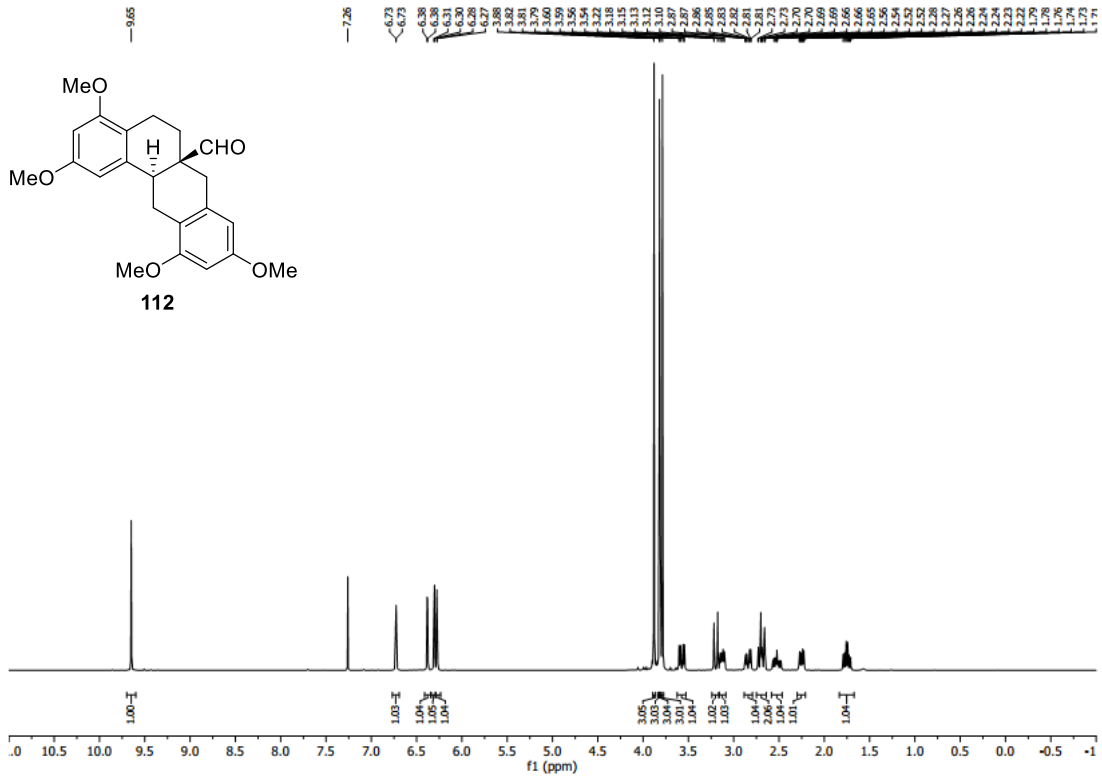


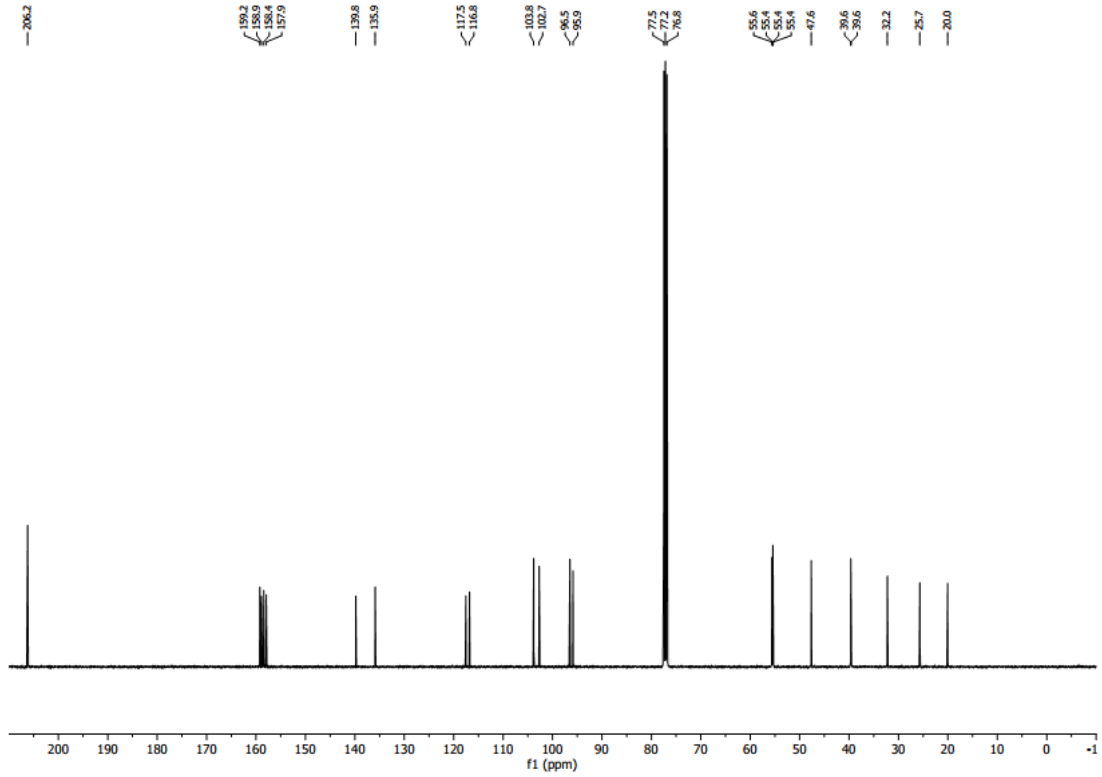
Compound **108** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



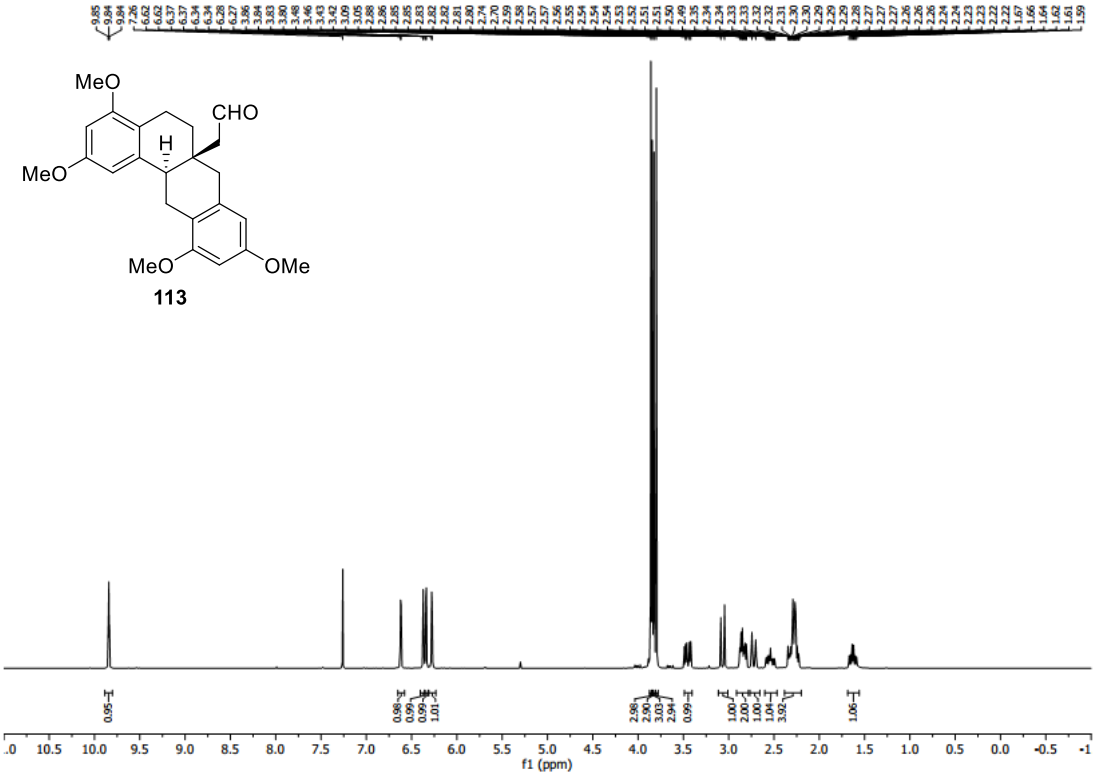


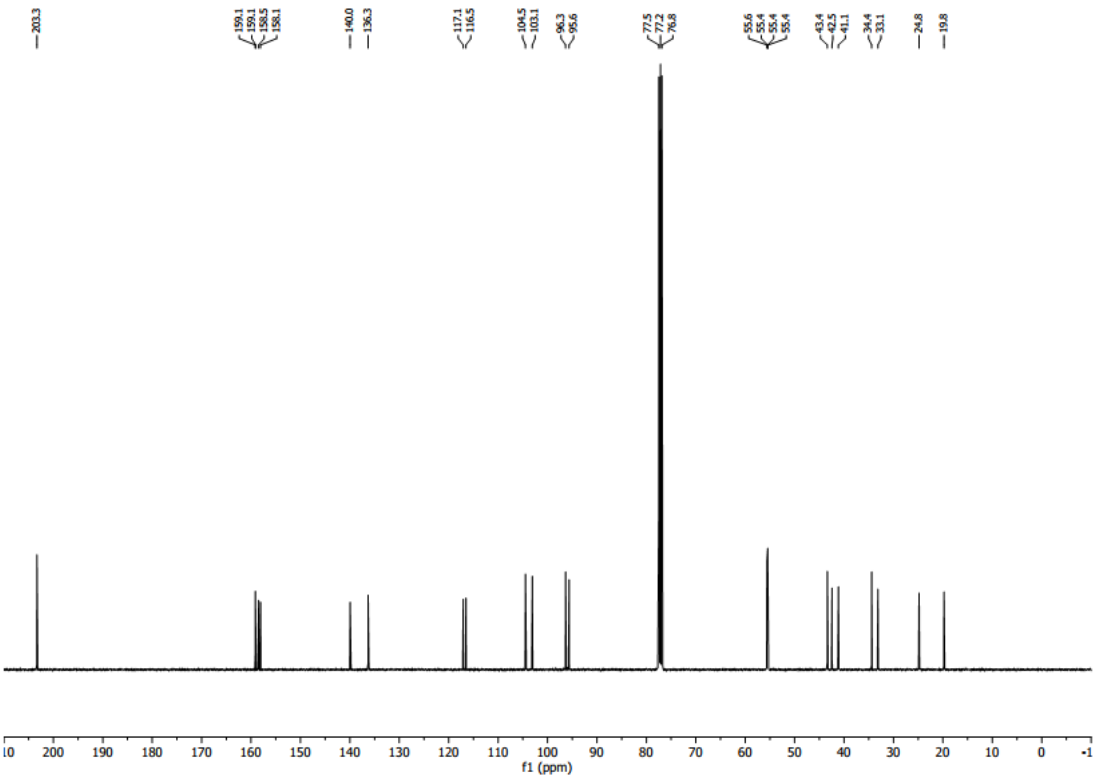
Compound **112** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



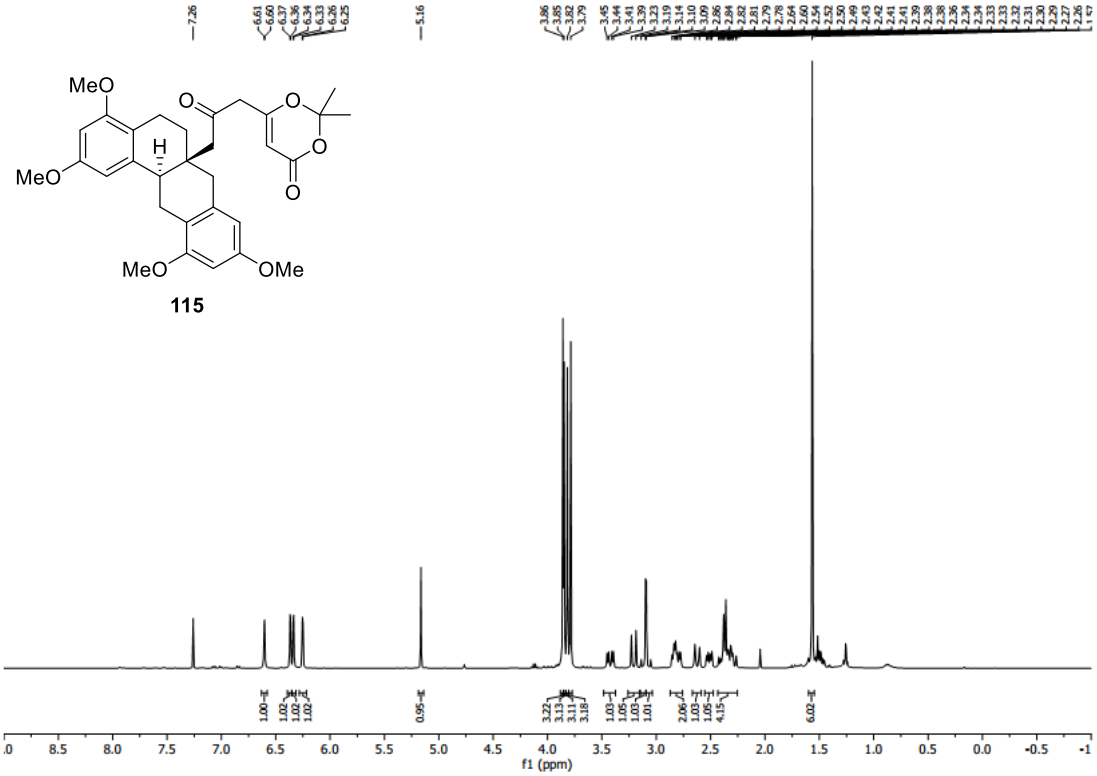


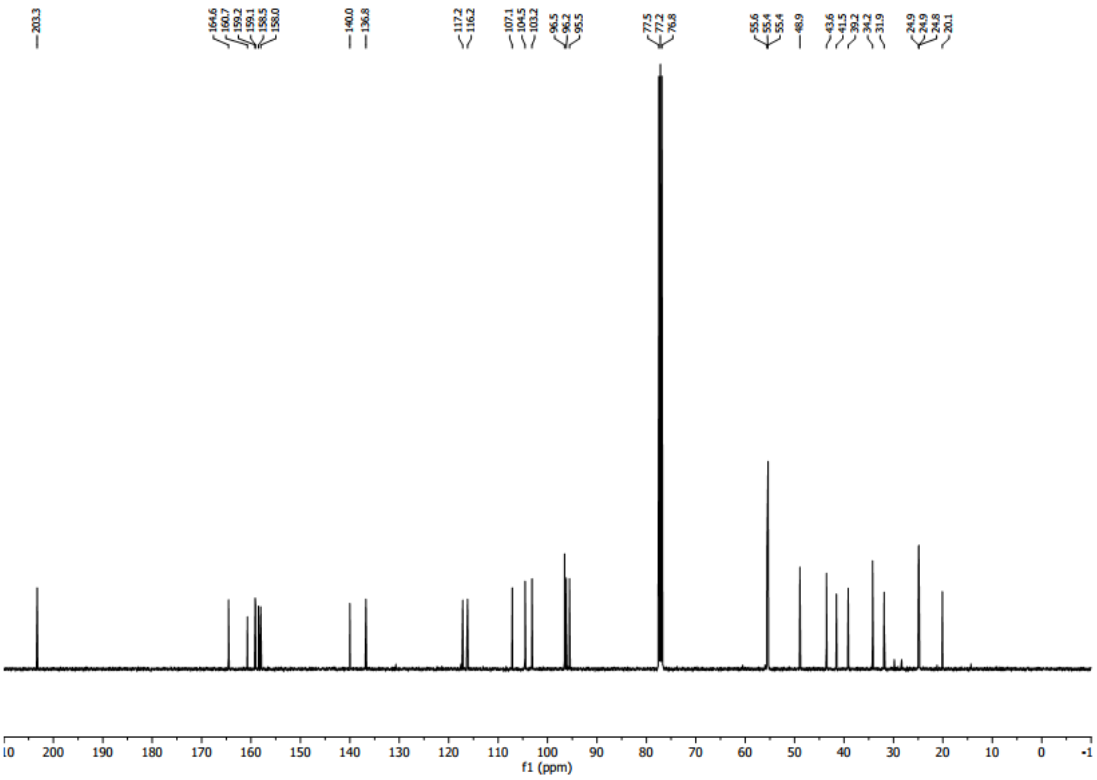
Compound **113** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



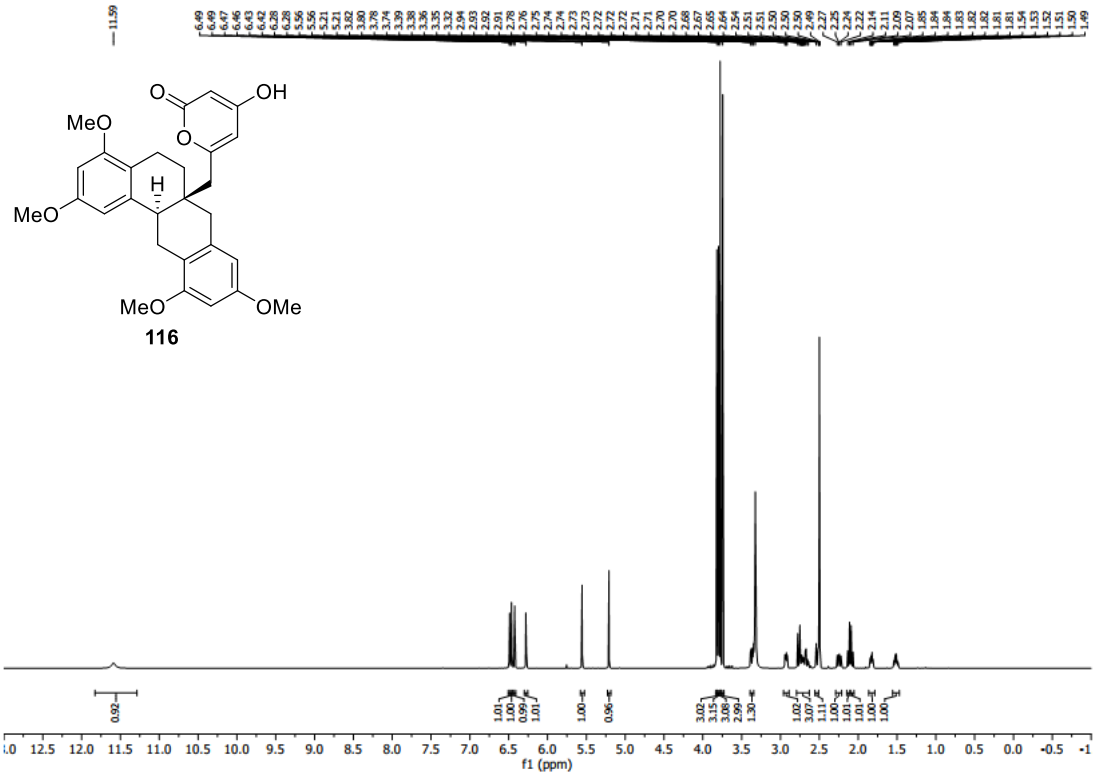


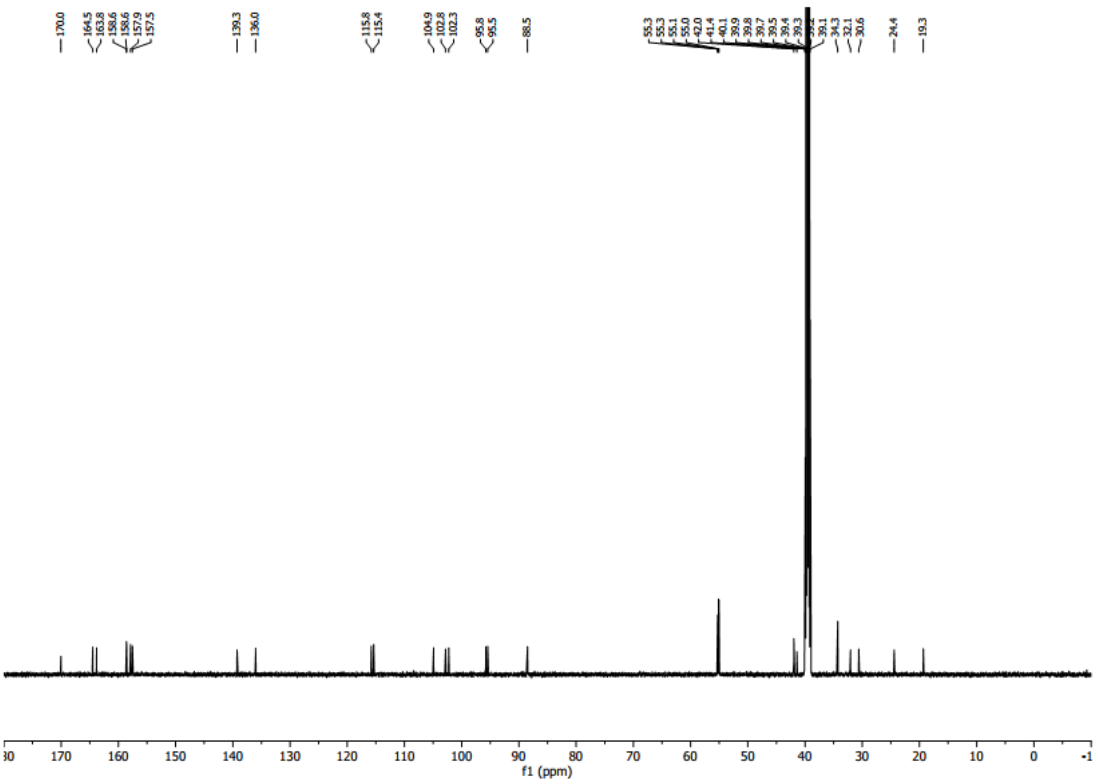
Compound **115** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



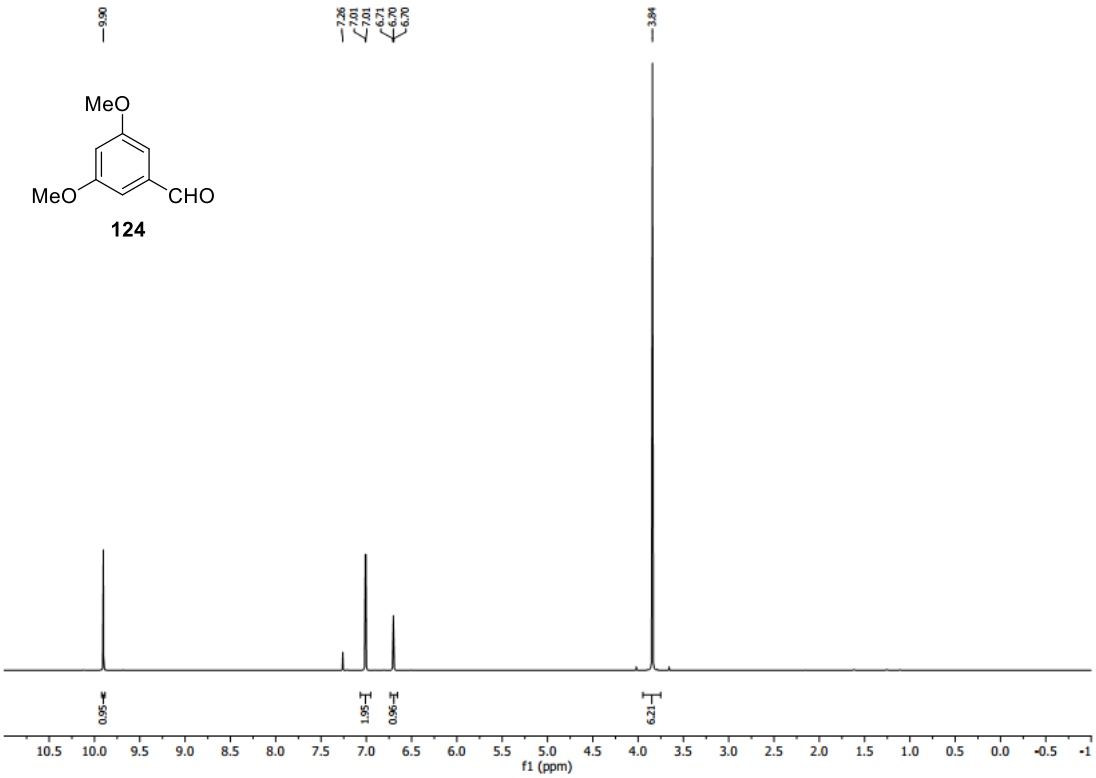


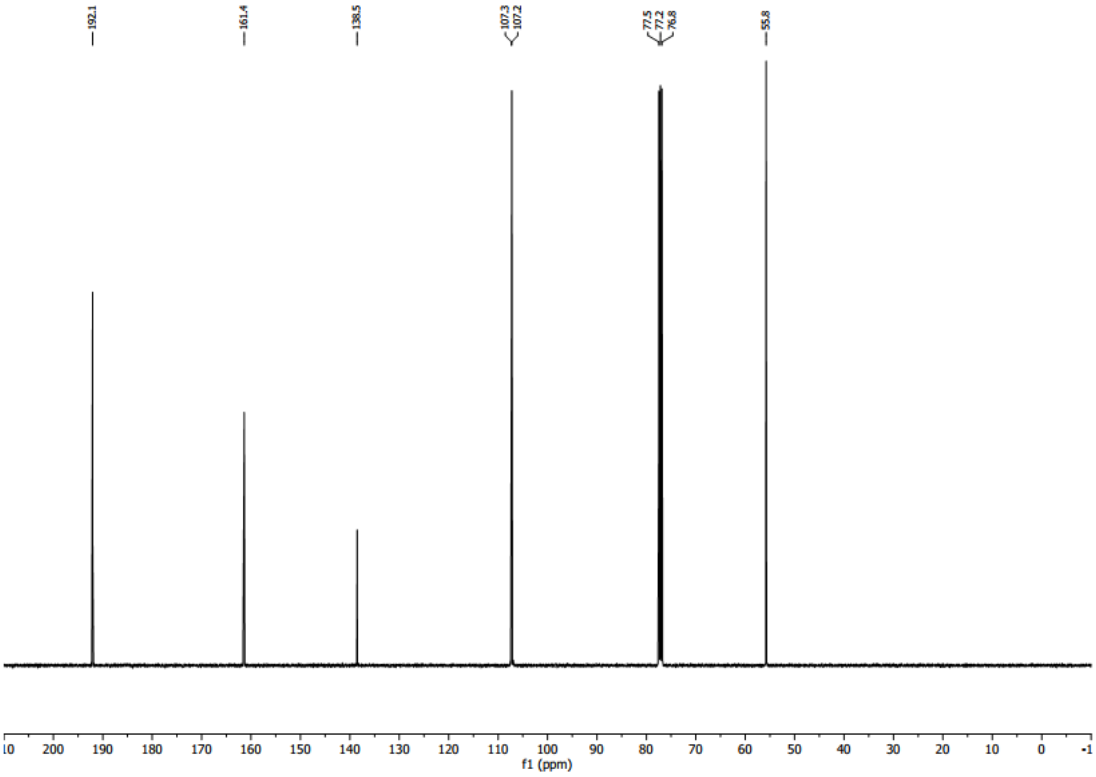
Compound **116** – **^{1}H-NMR** (600 MHz) and **^{13}C-NMR** (150 MHz) in DMSO-d_6



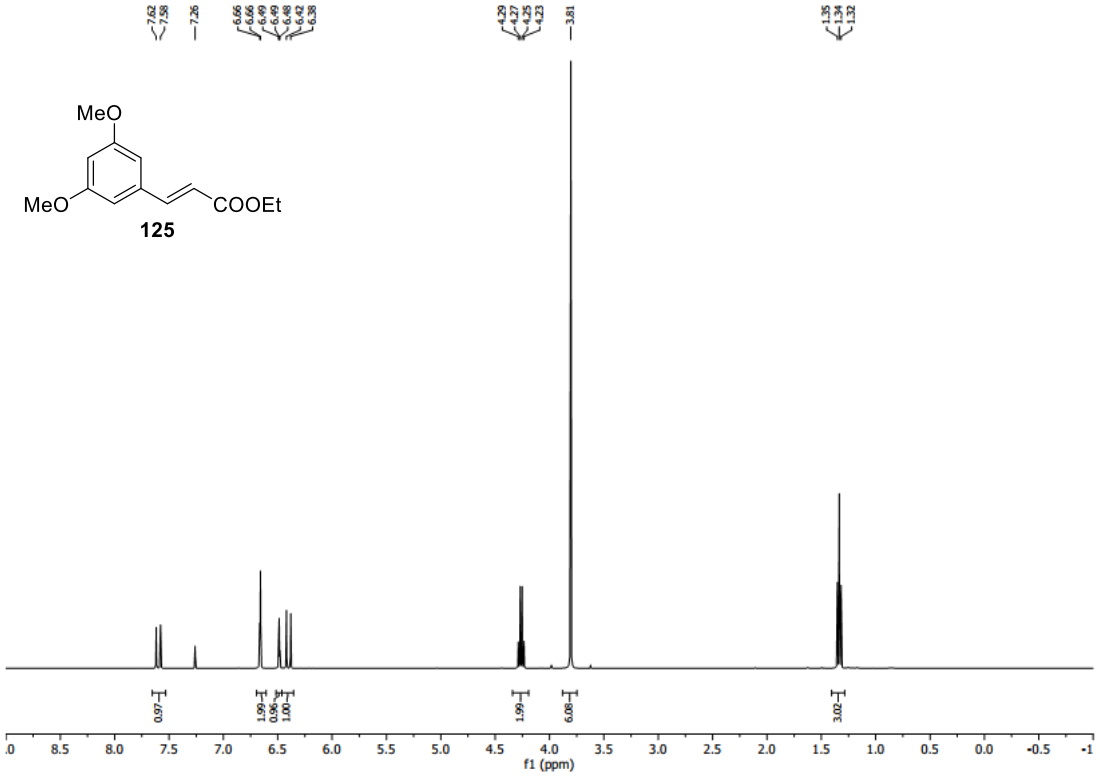


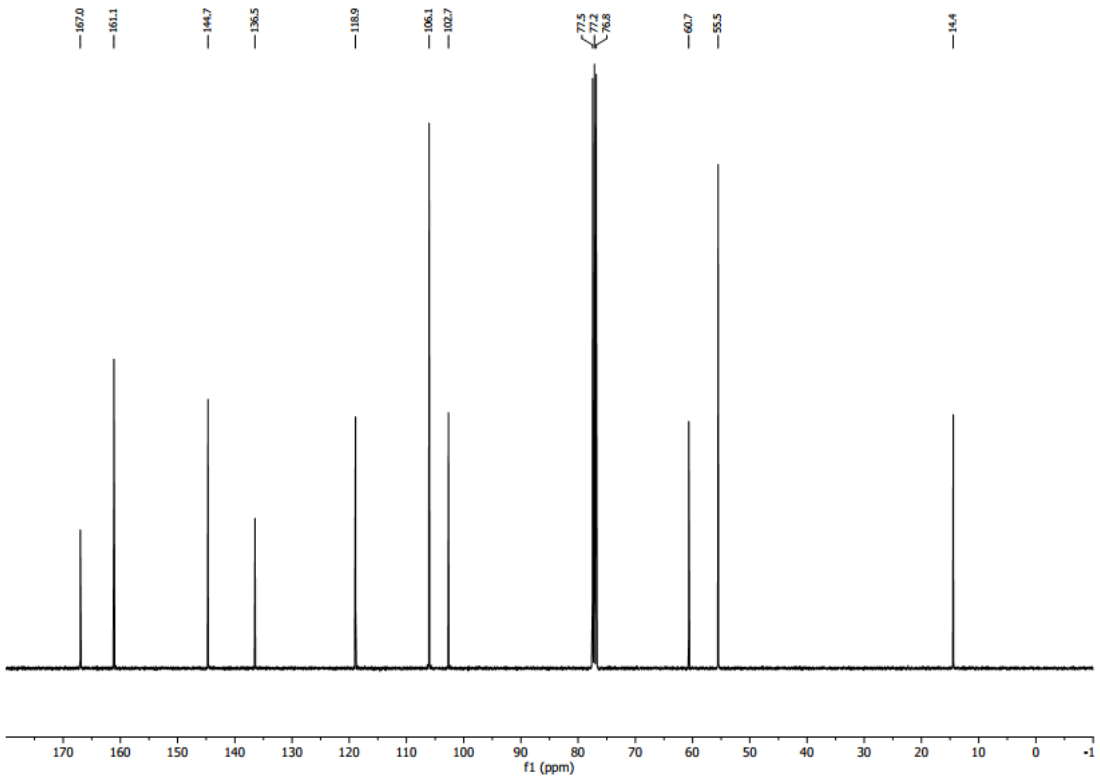
Compound **124** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



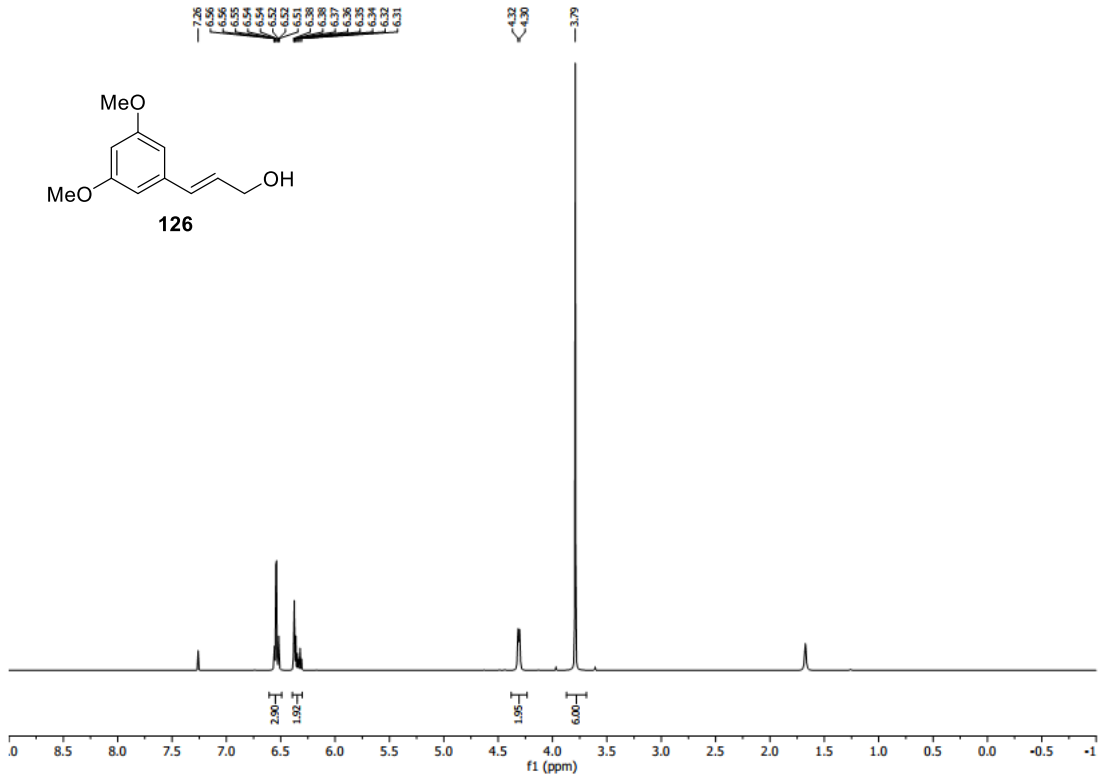


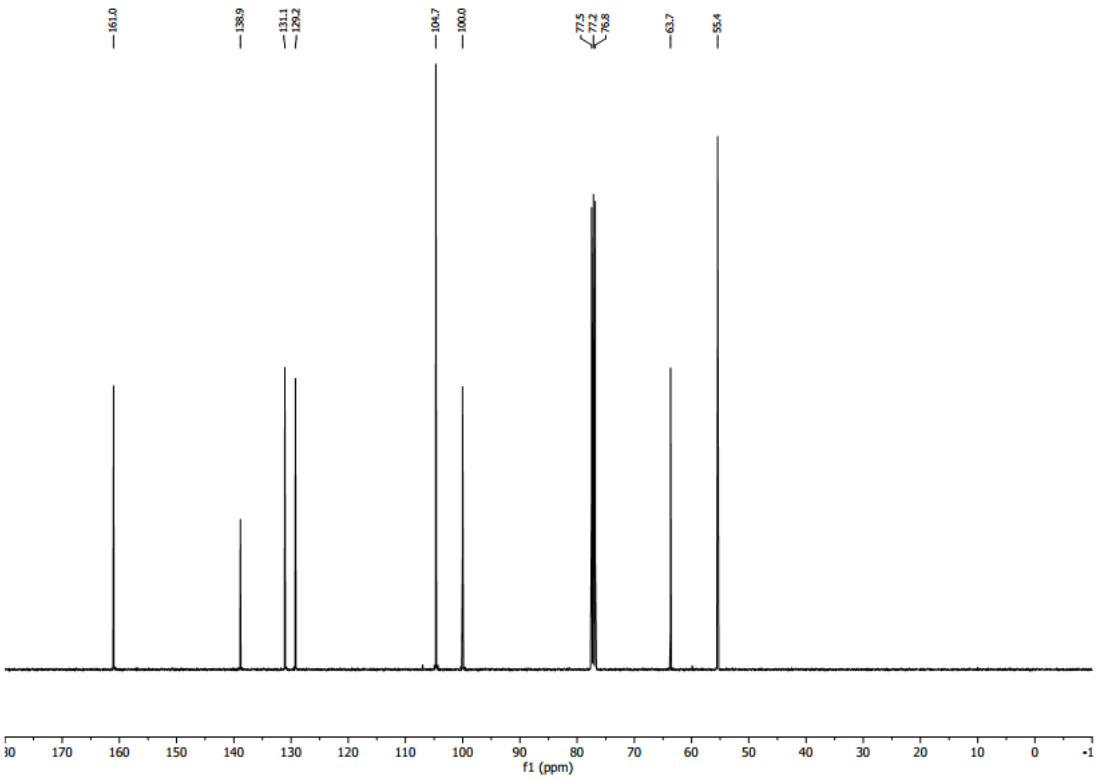
Compound **125** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



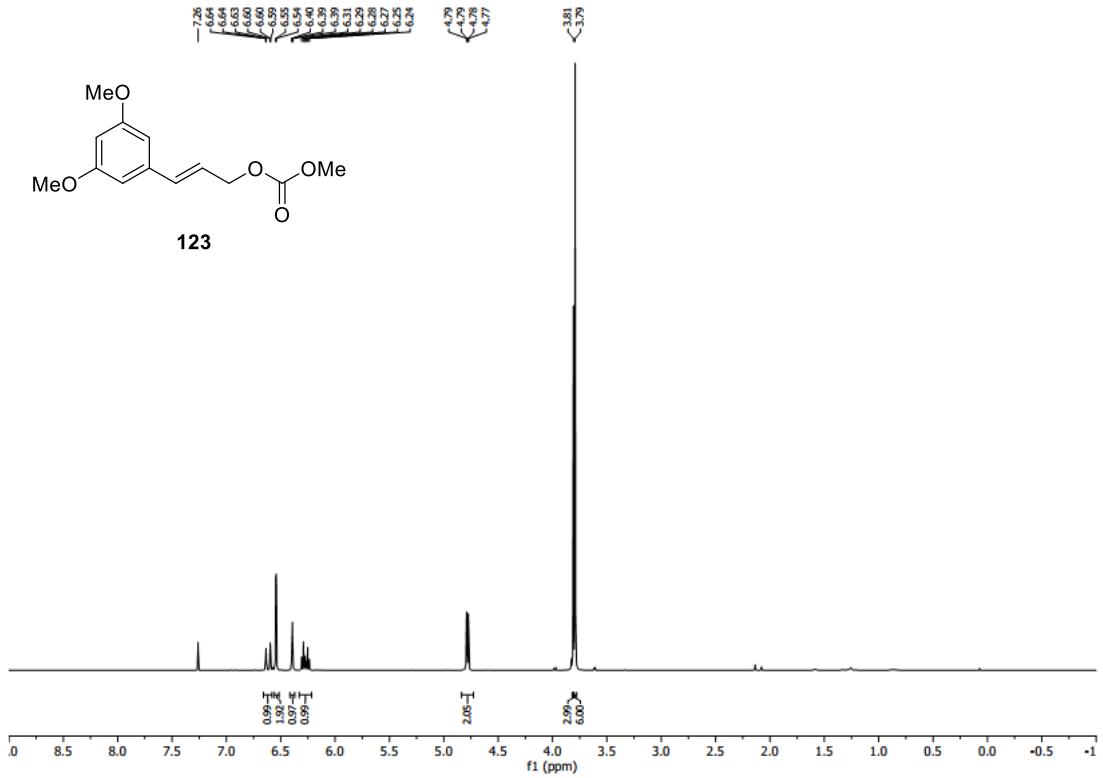


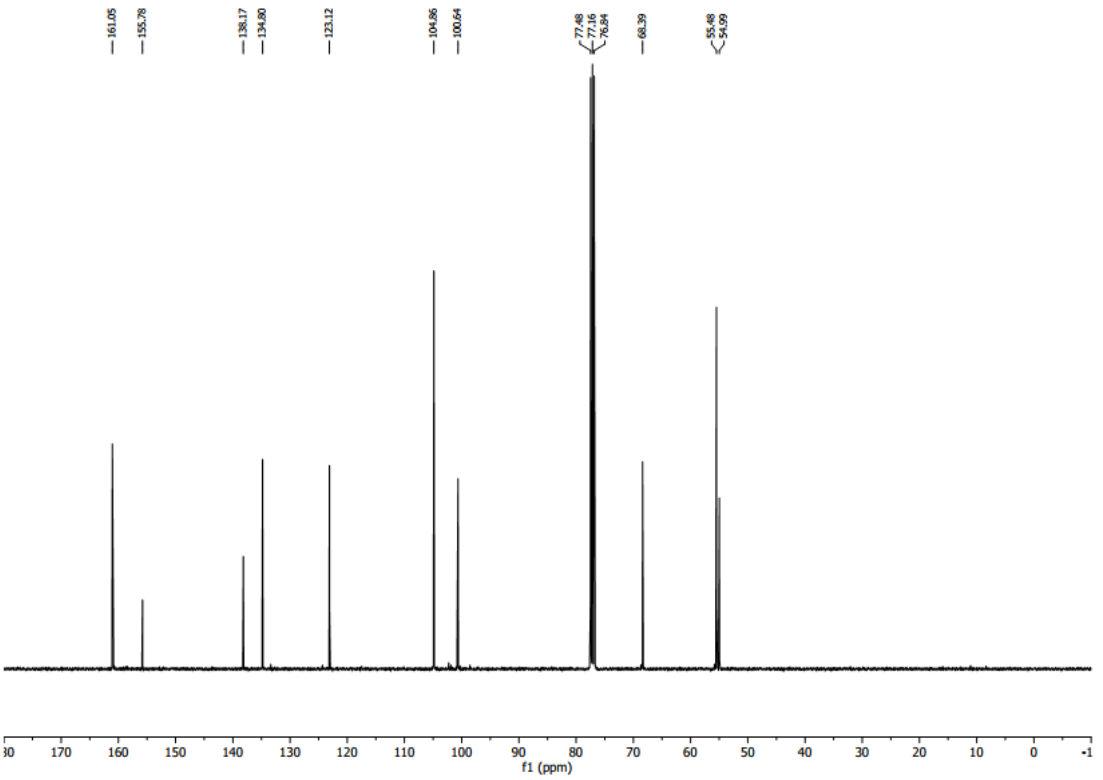
Compound **126** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



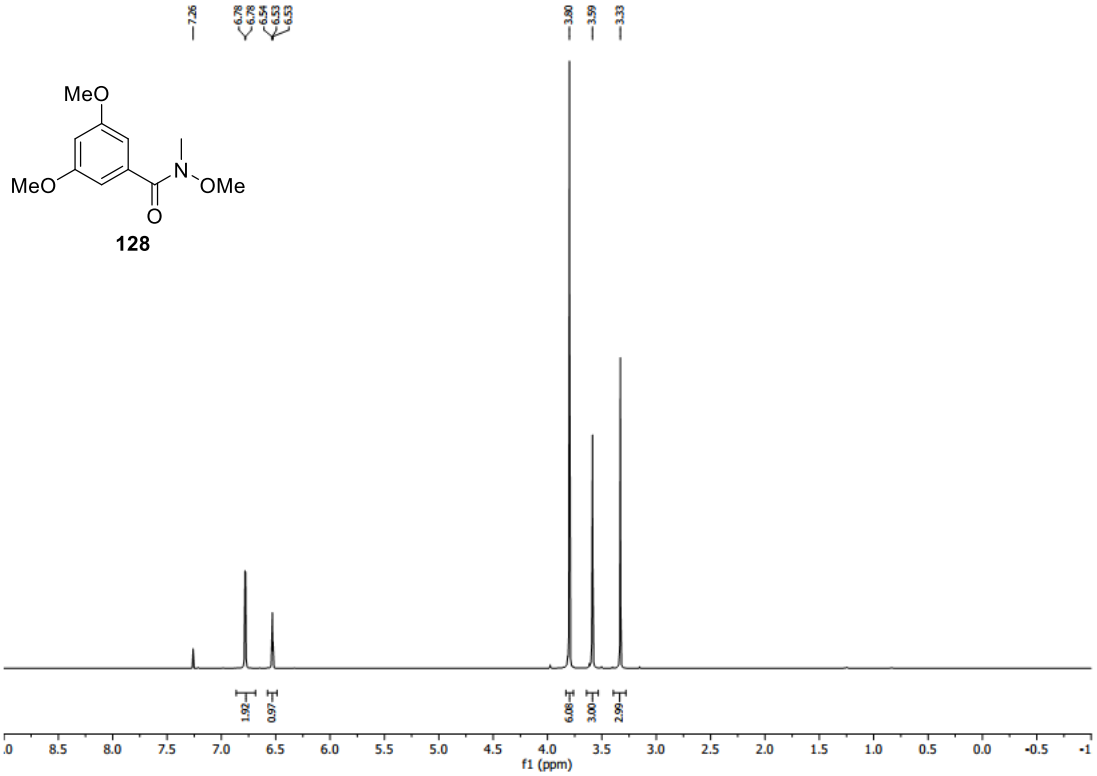


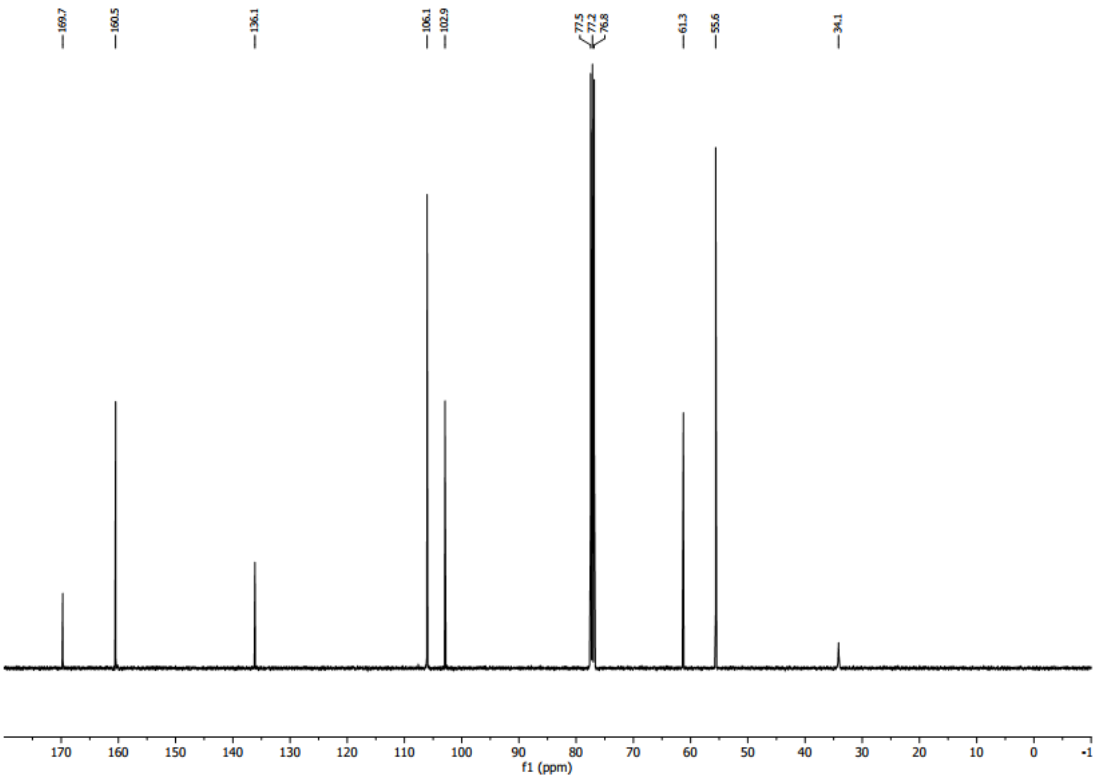
Compound **123** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



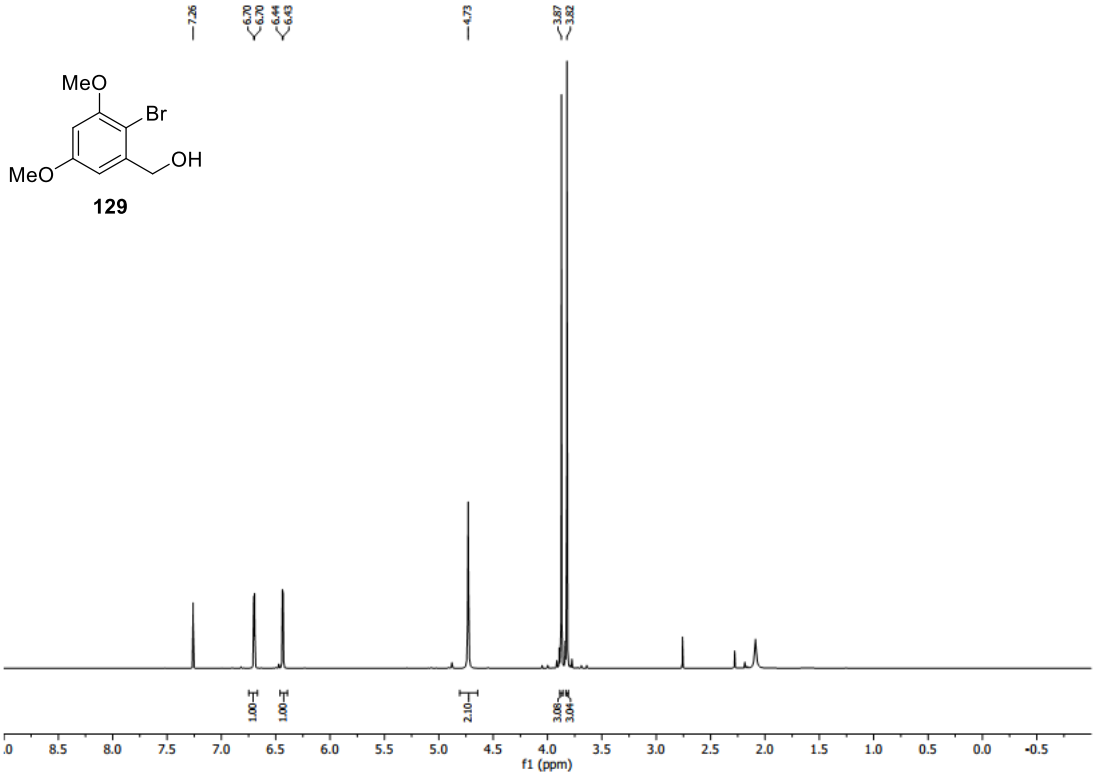


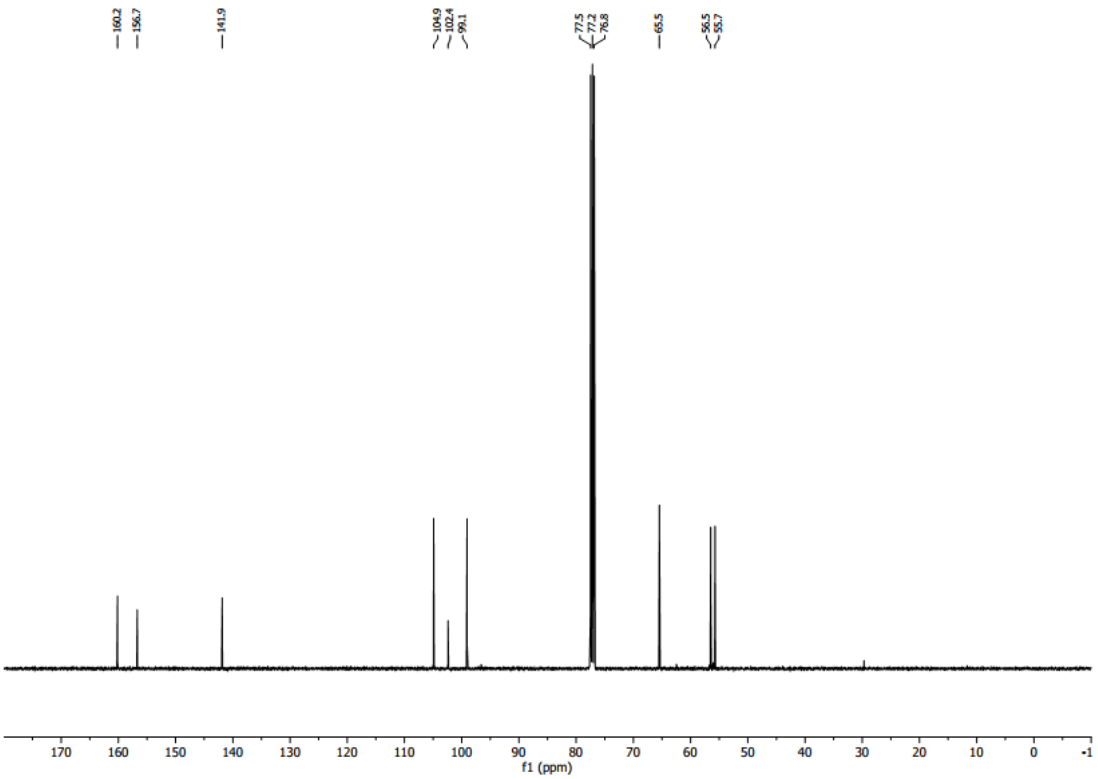
Compound **128** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



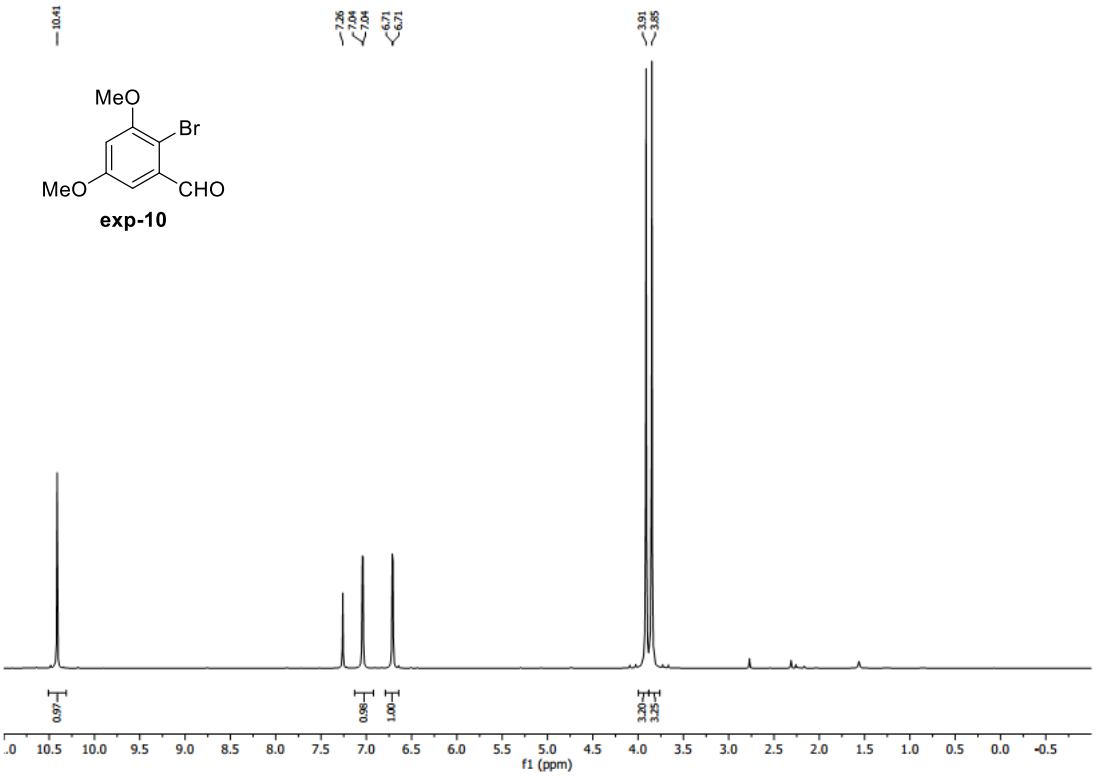


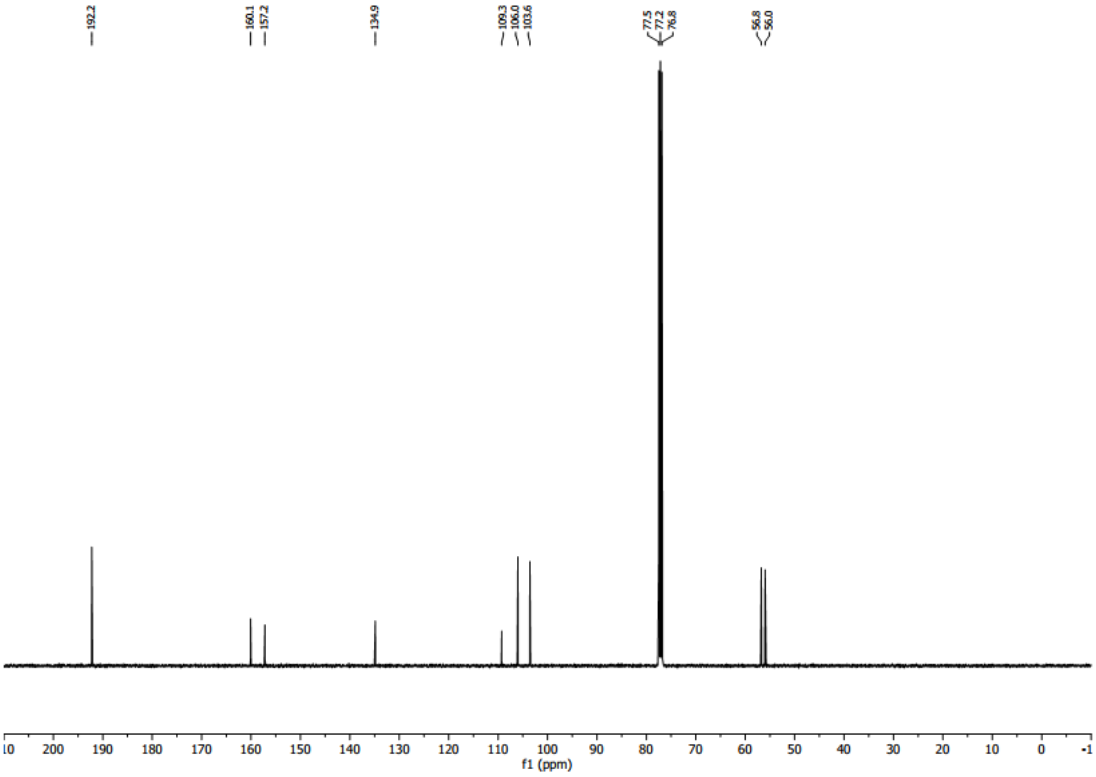
Compound **129** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



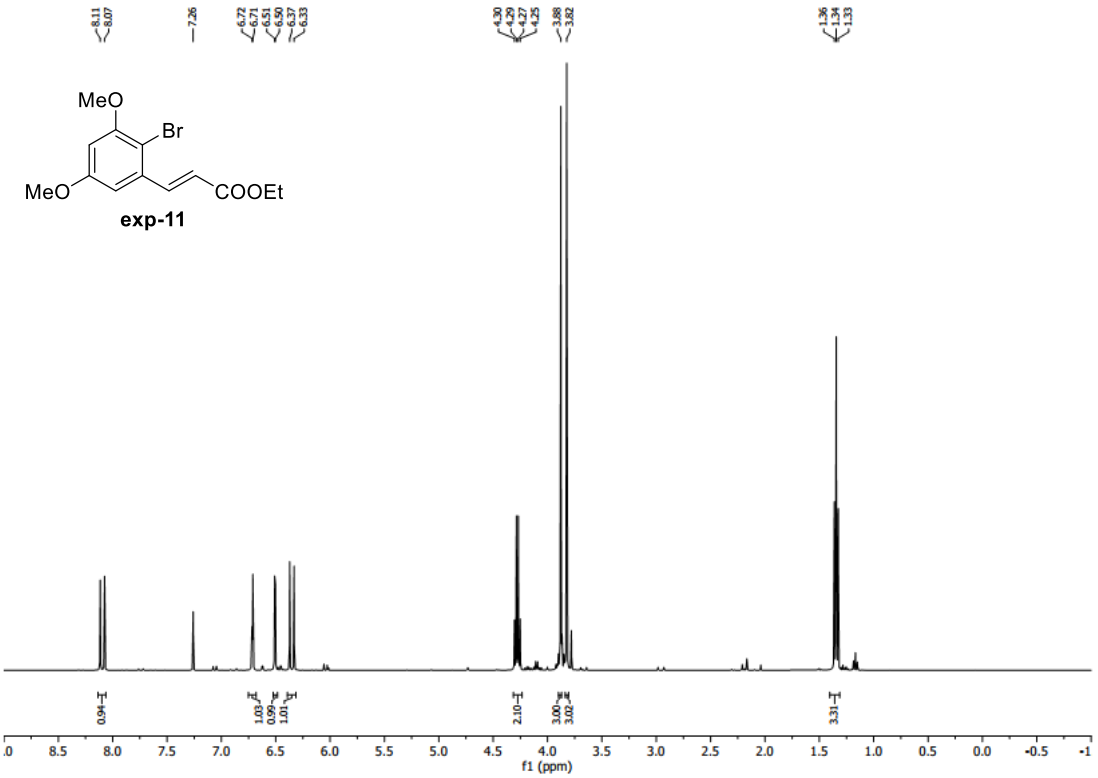


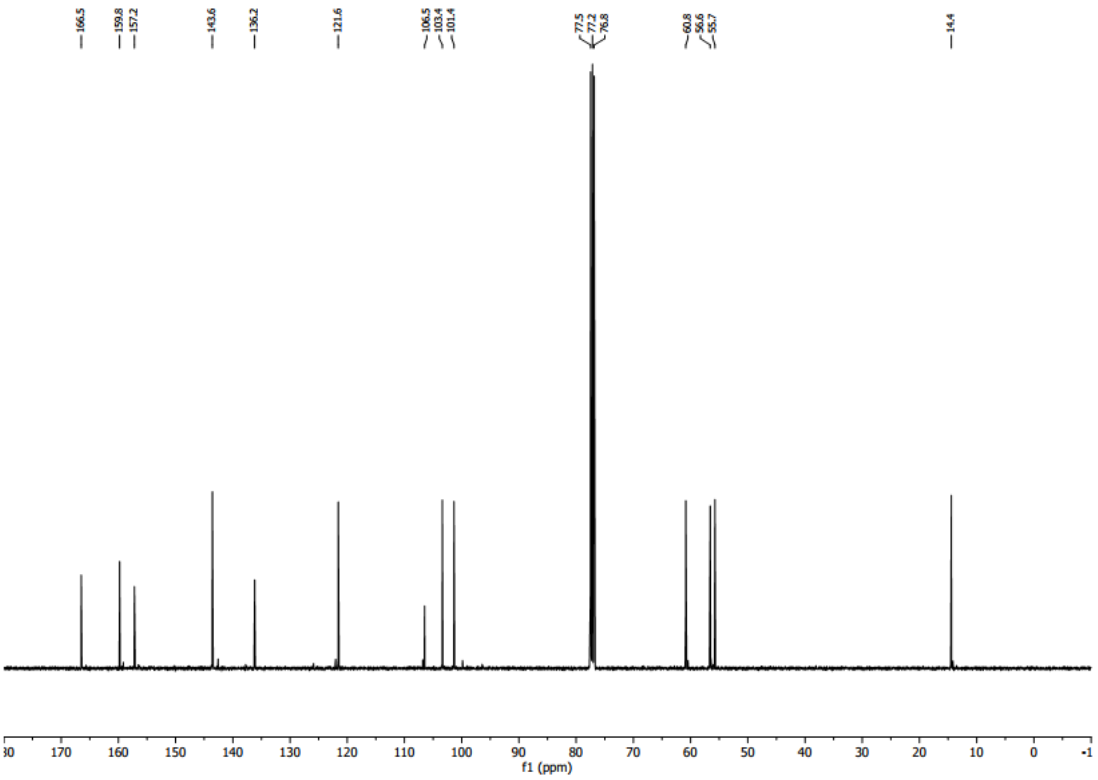
Compound **exp-10** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



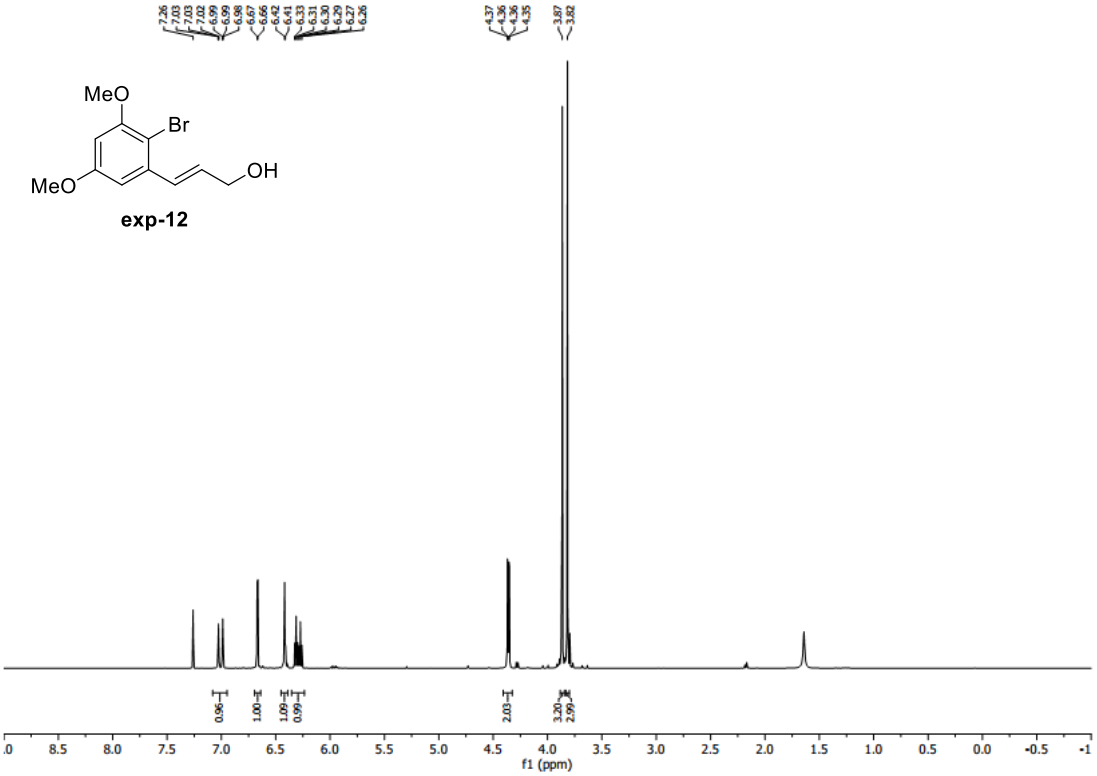


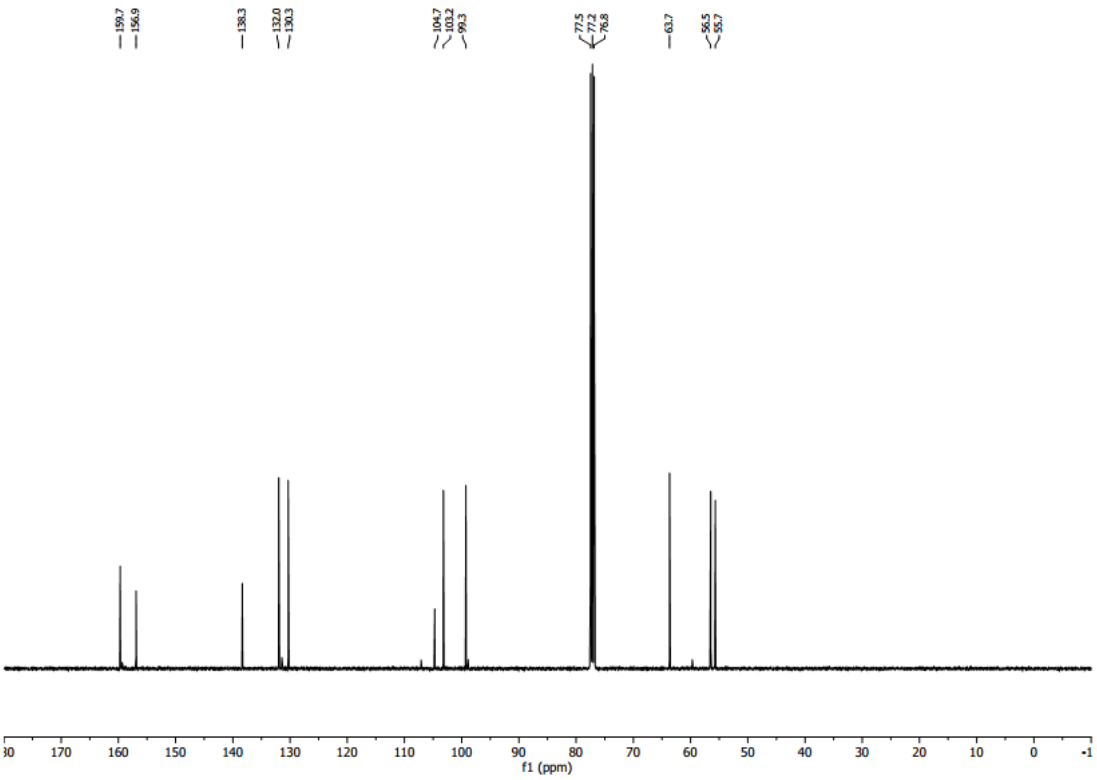
Compound **exp-11** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



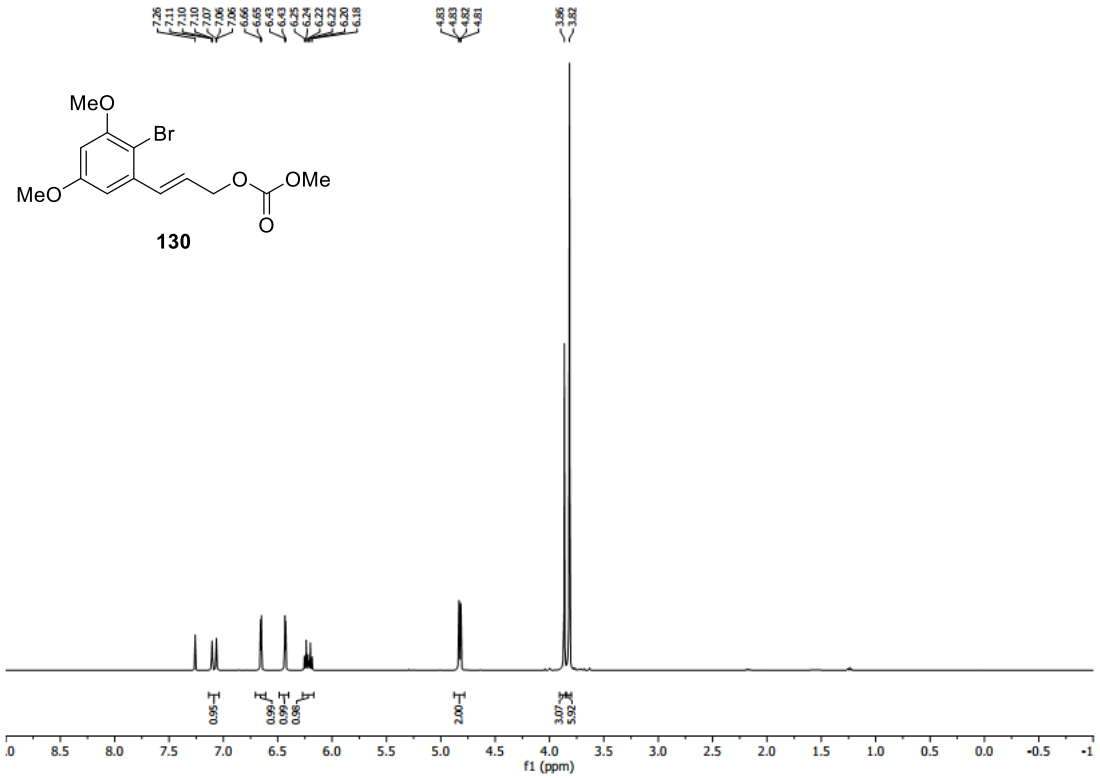


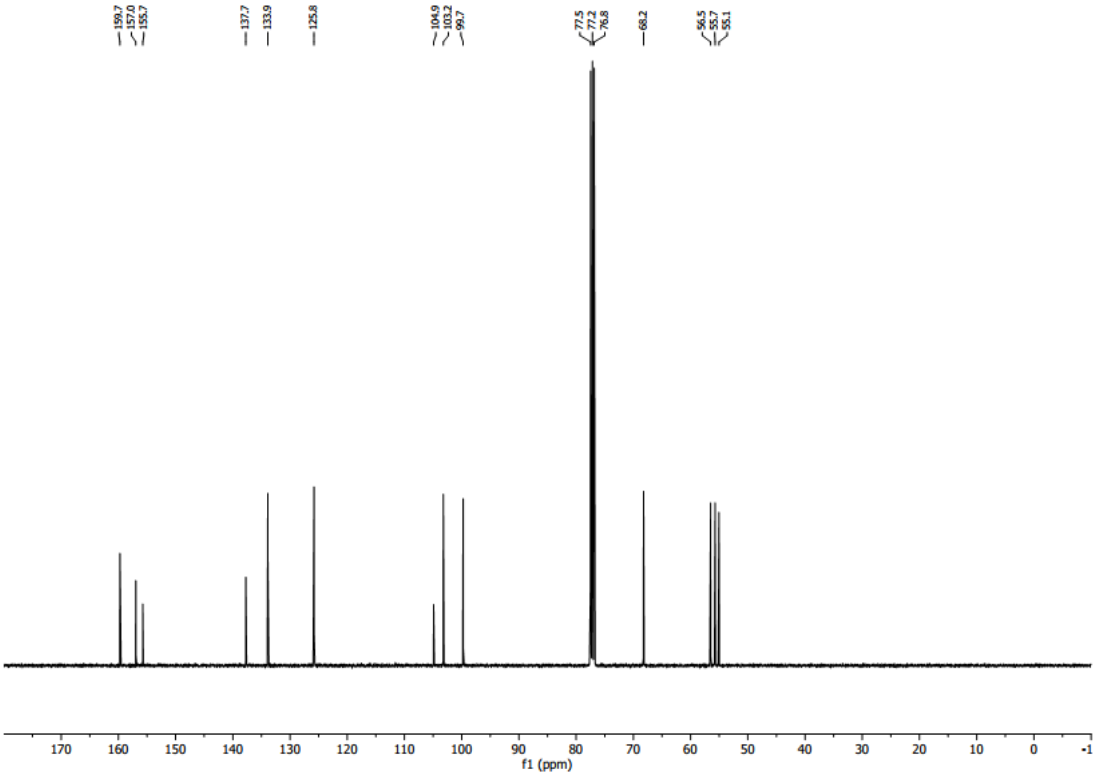
Compound **exp-12** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



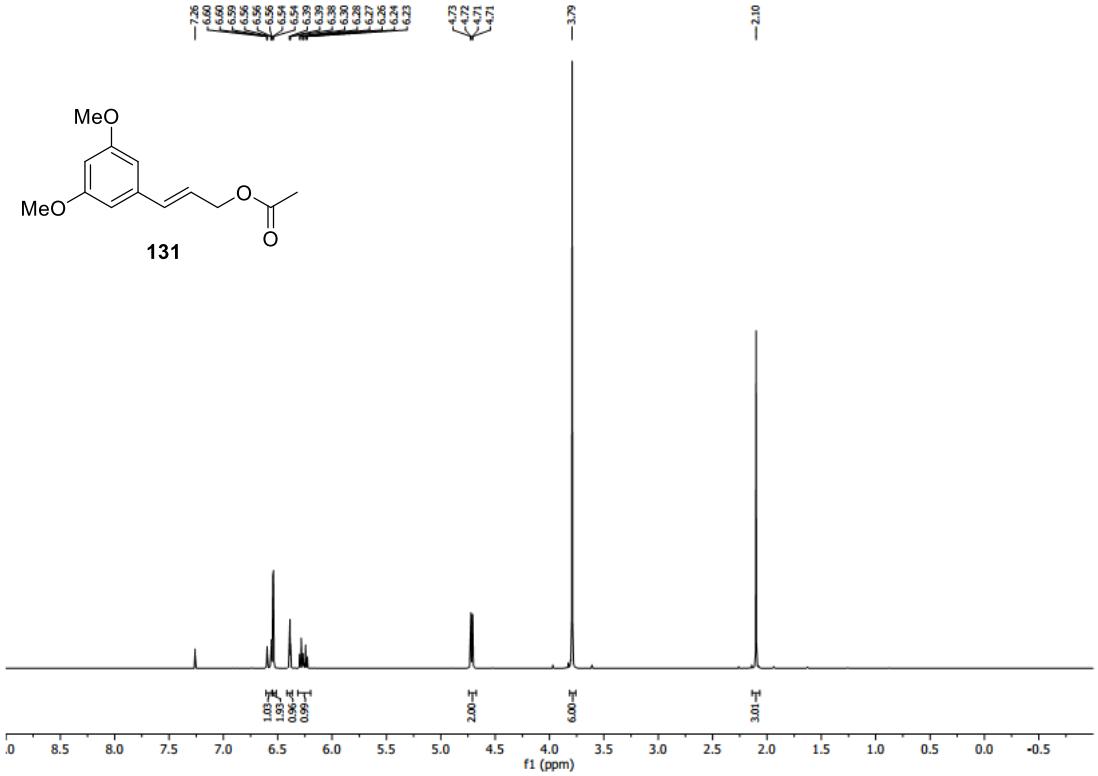


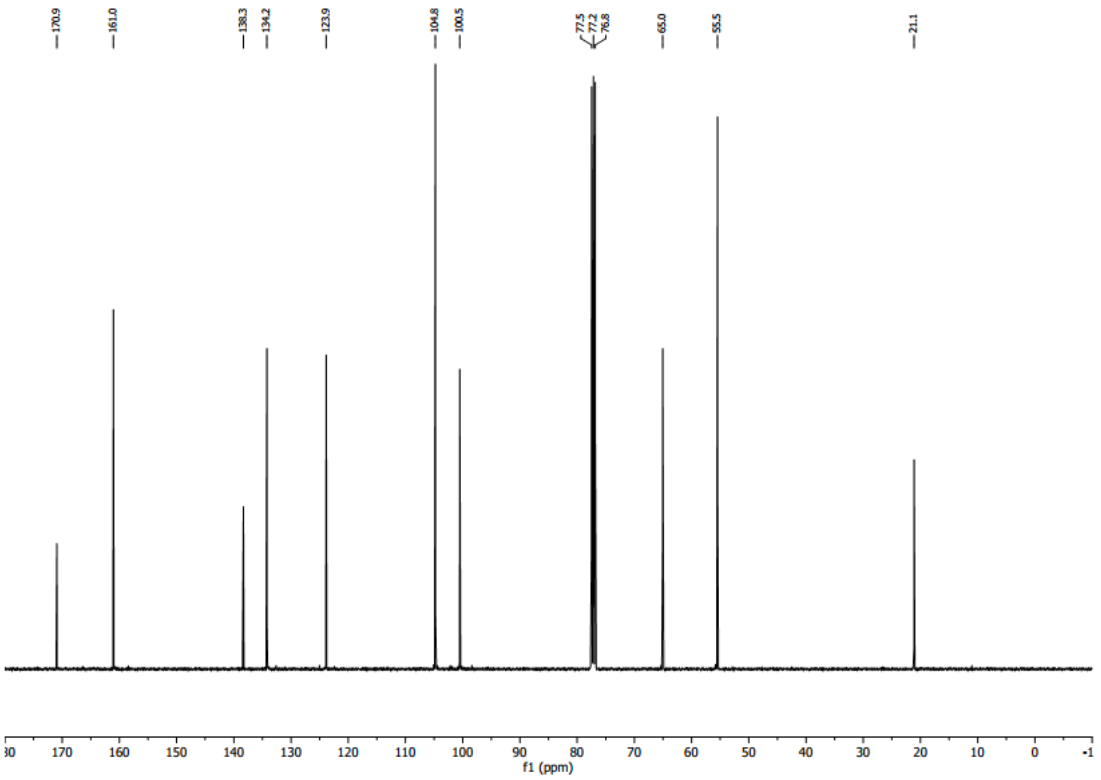
Compound **130** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



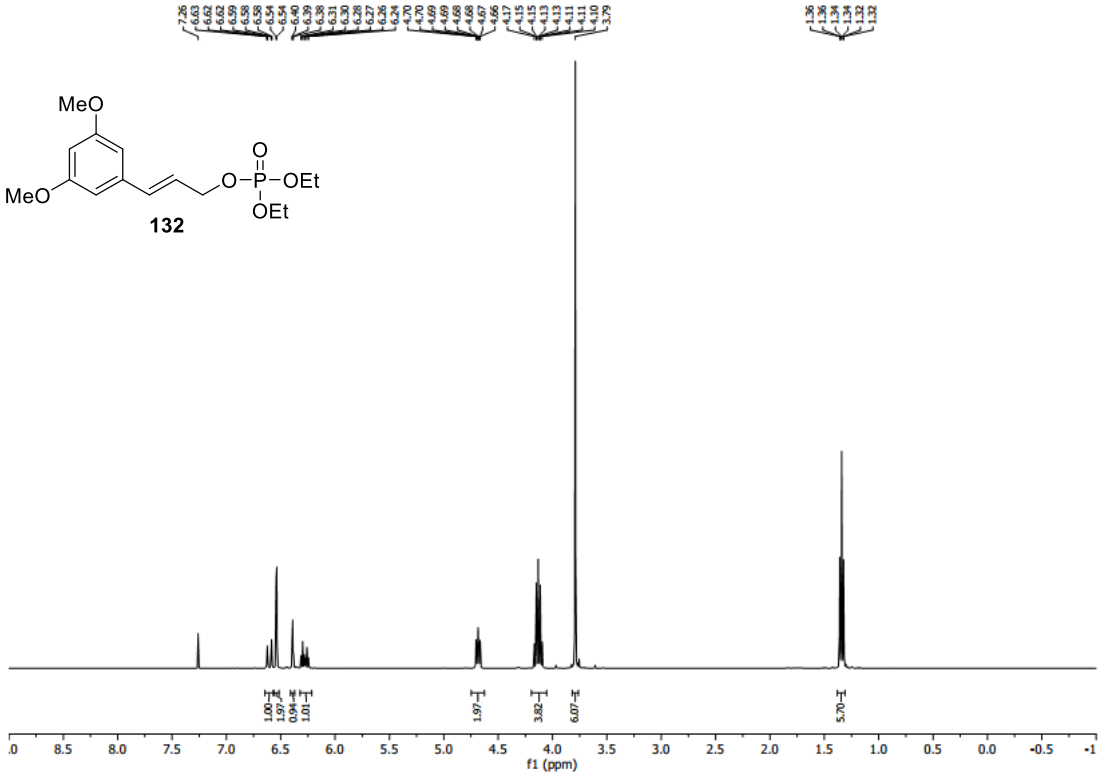


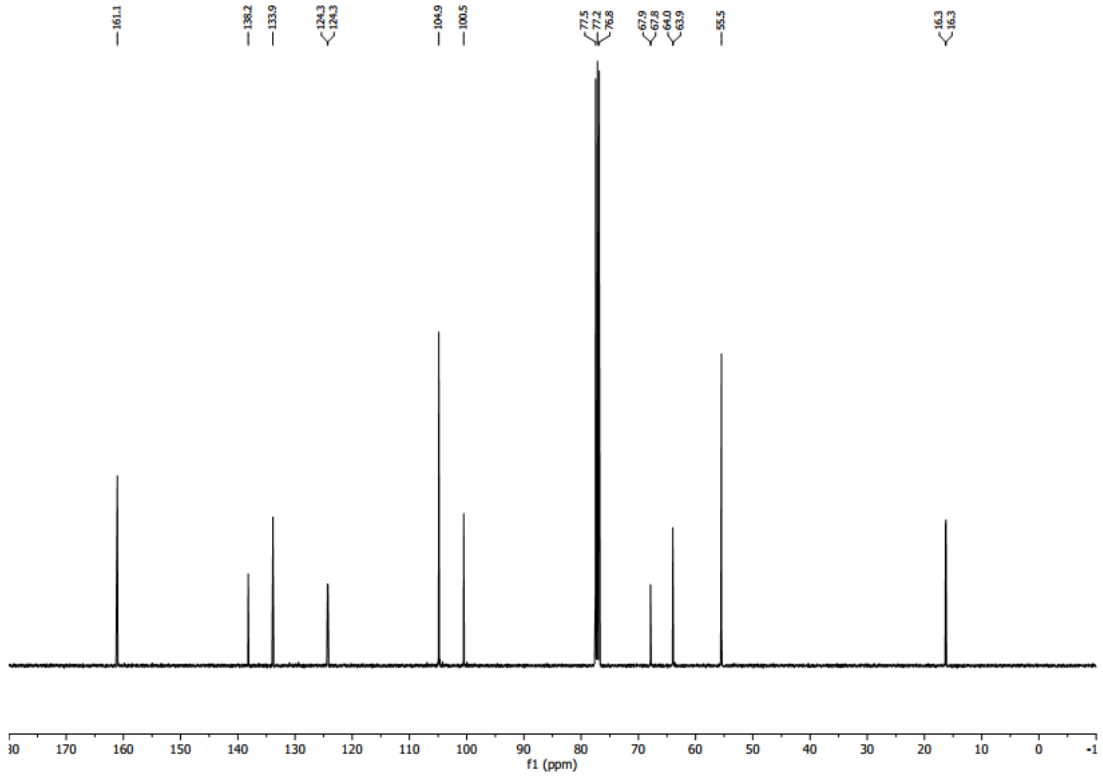
Compound **131** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



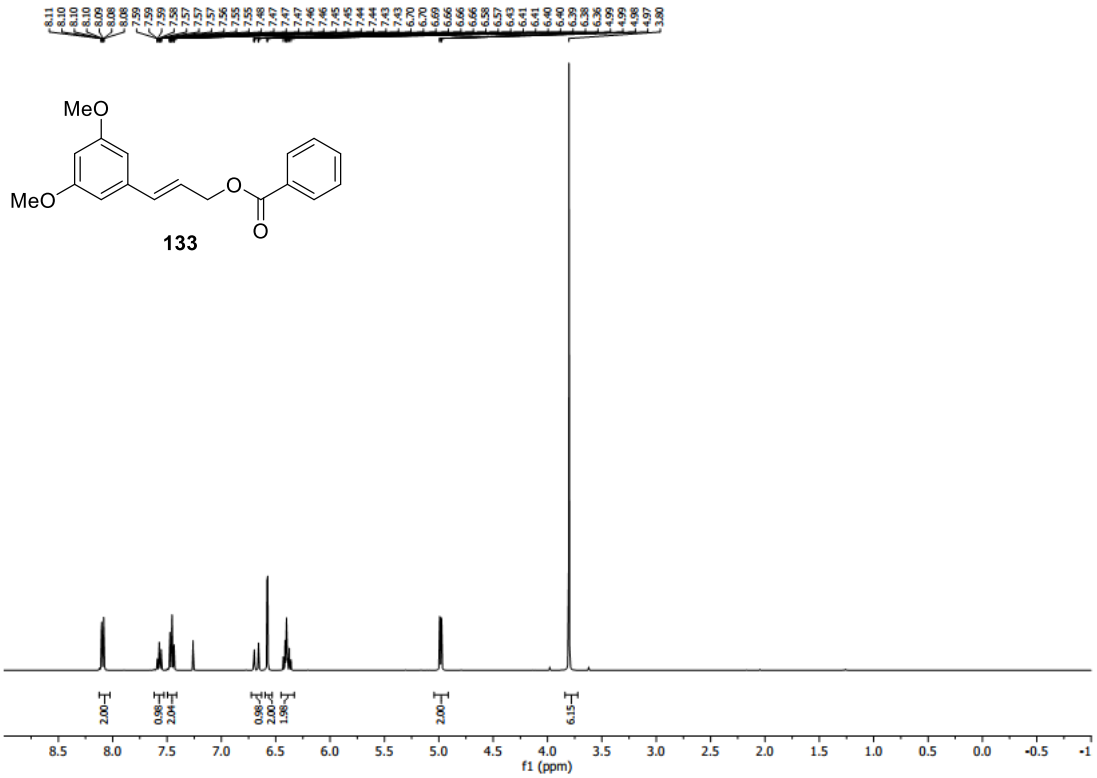


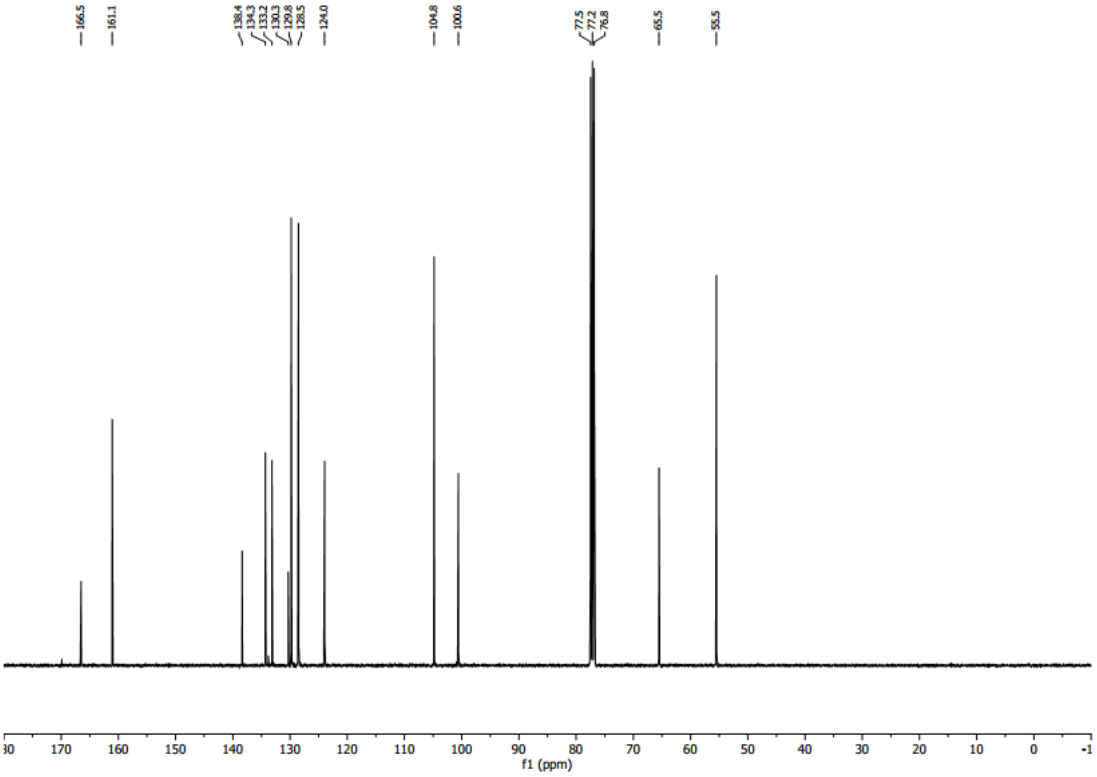
Compound **132** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



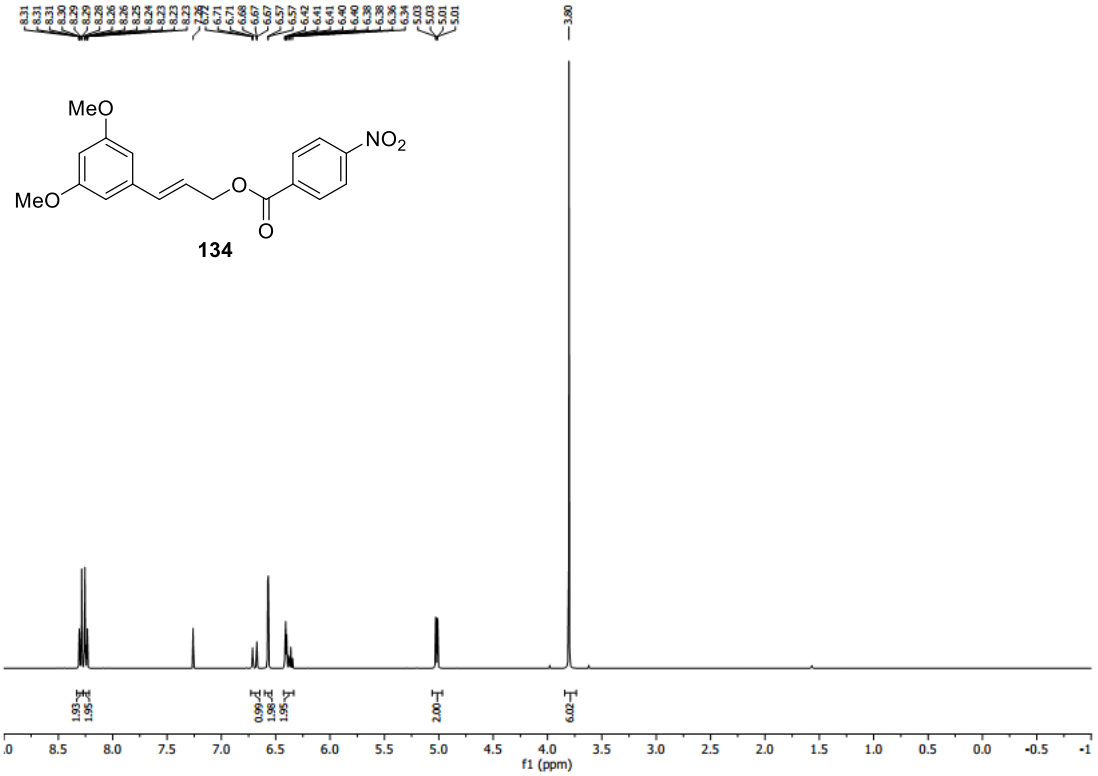


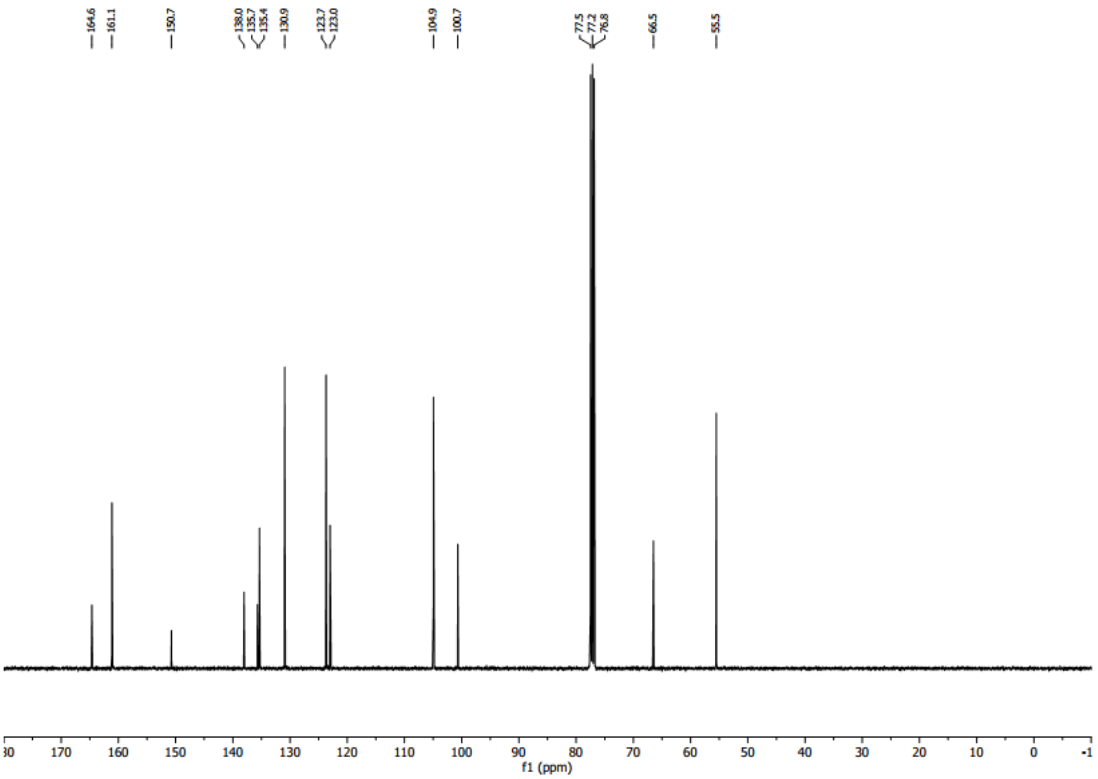
Compound **133** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



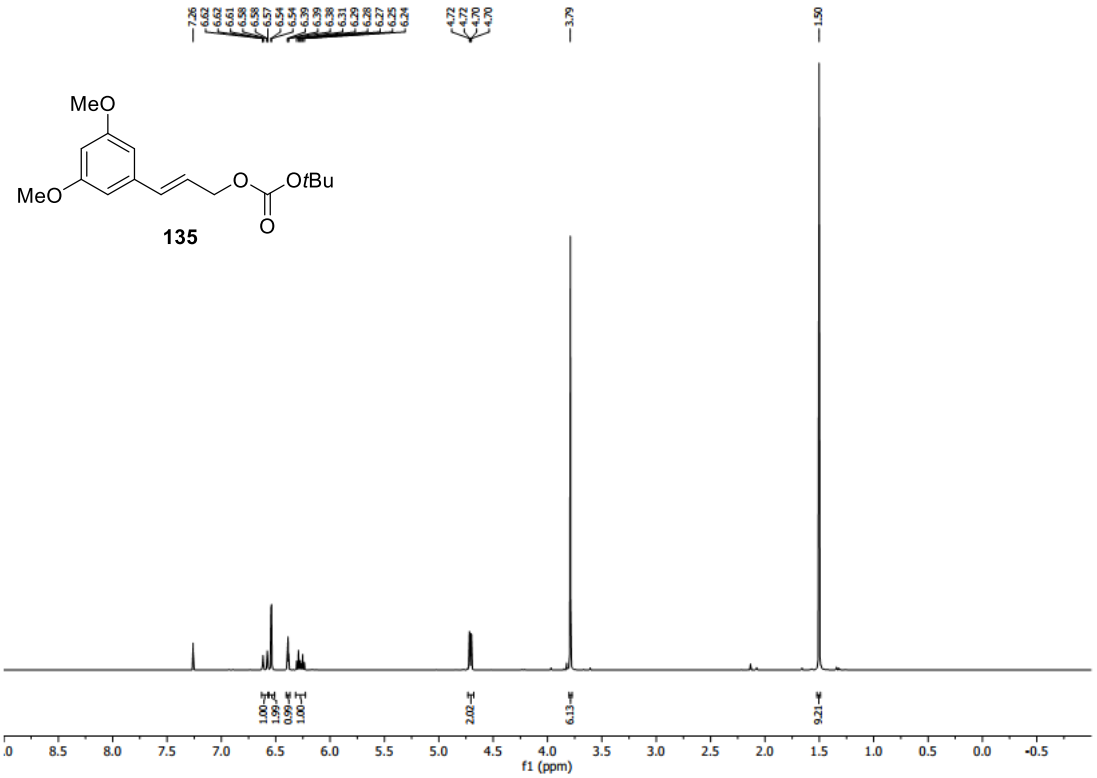


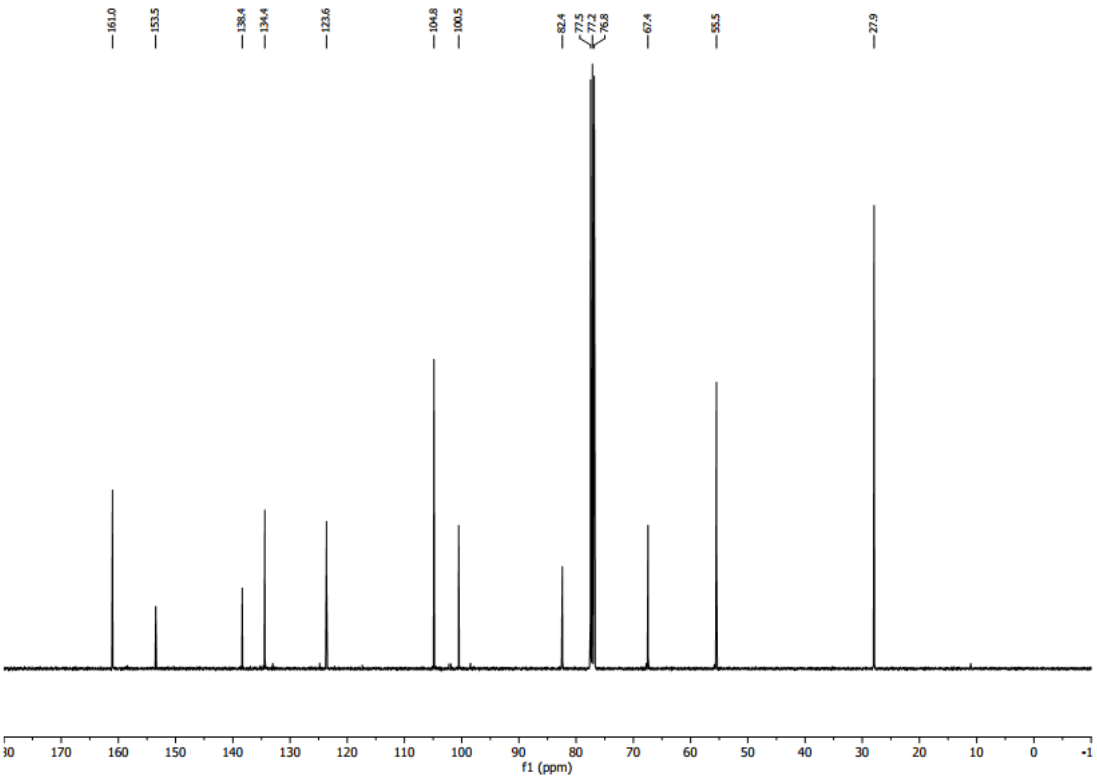
Compound **134** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



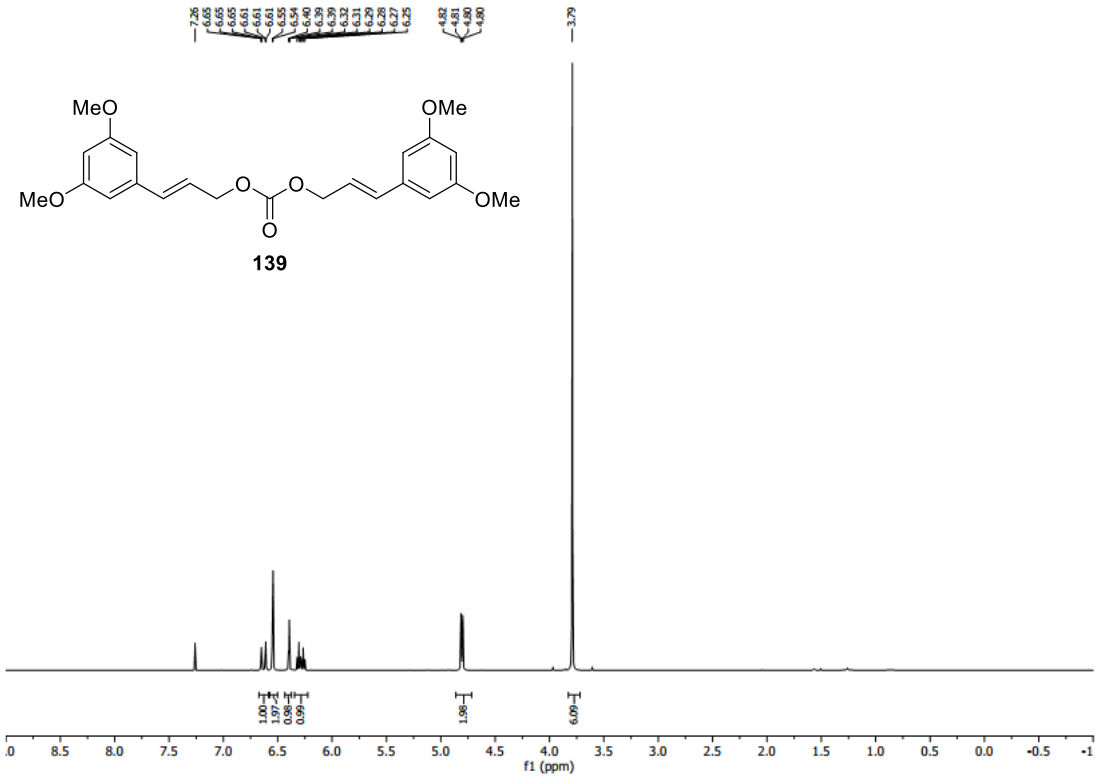


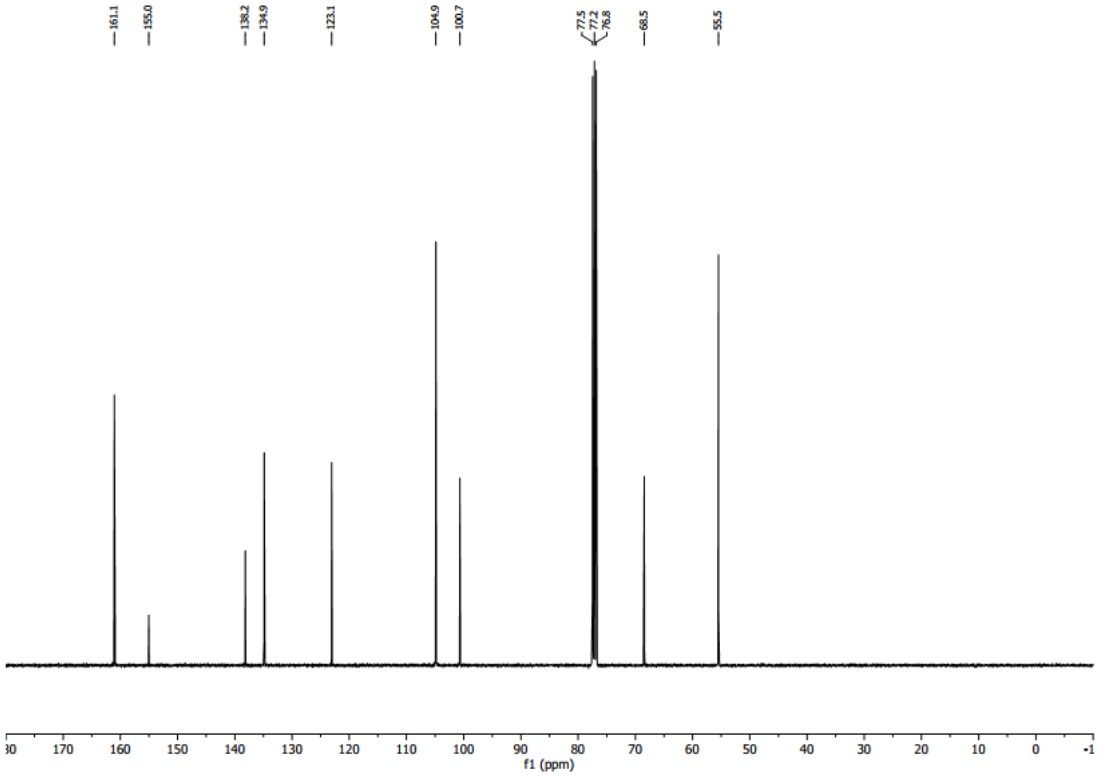
Compound **135** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



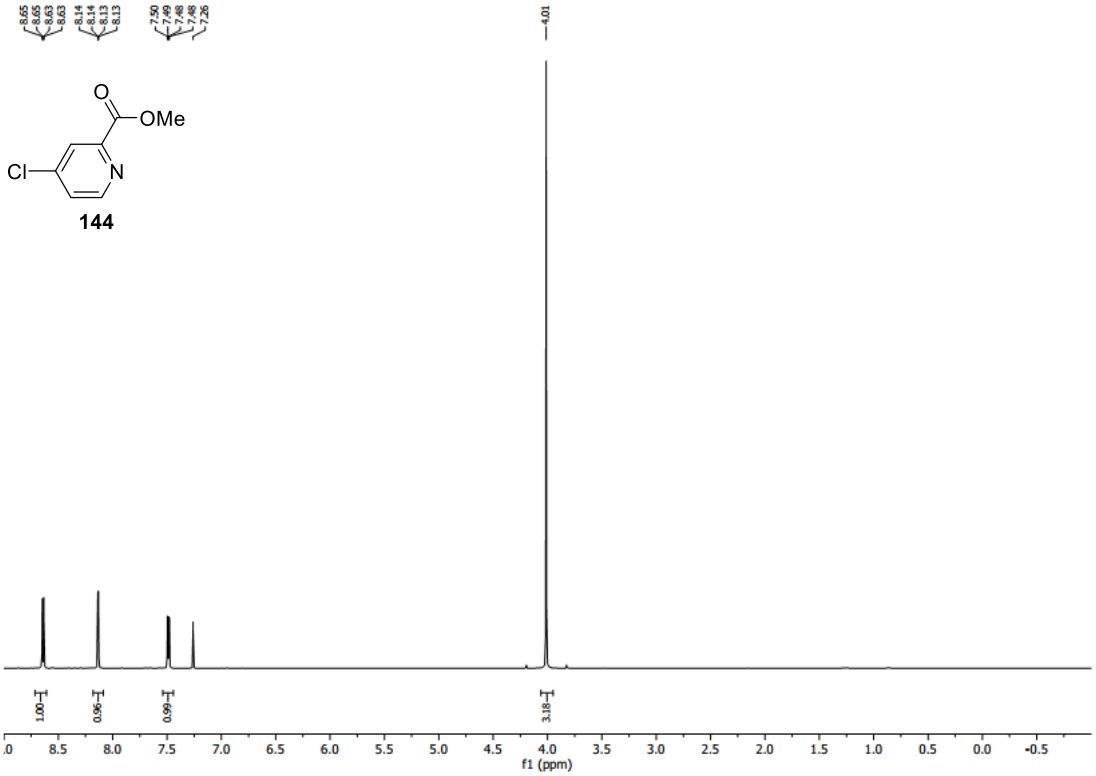


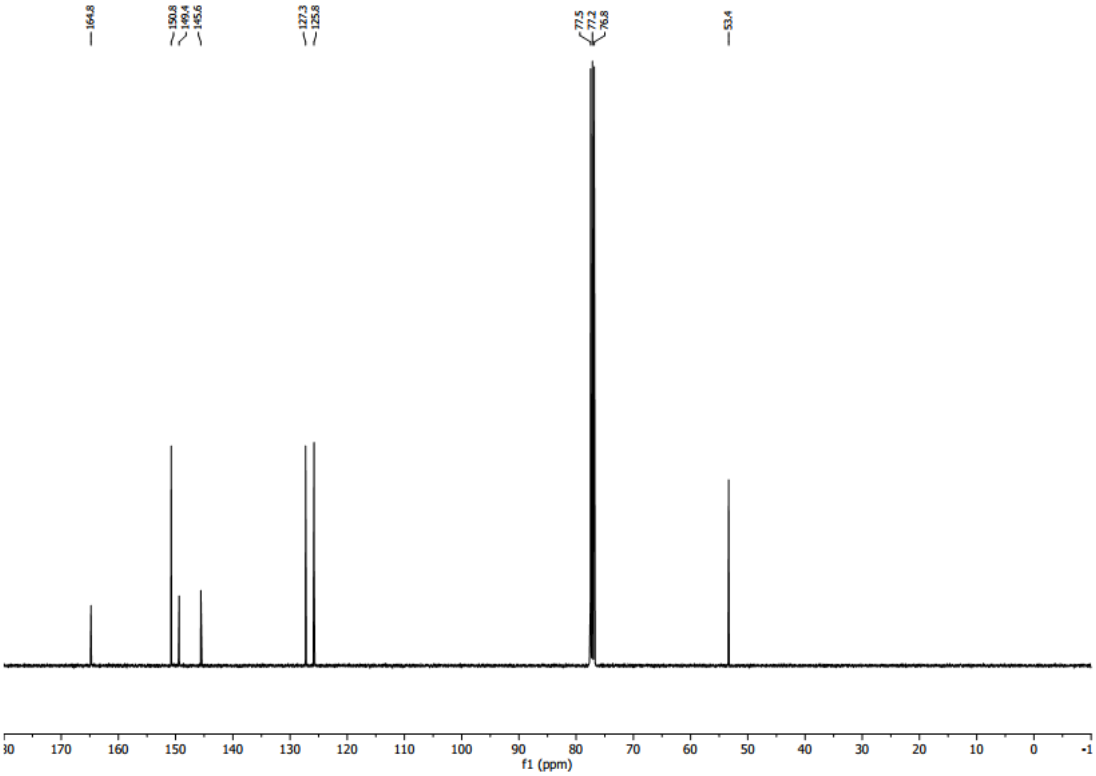
Compound **139** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



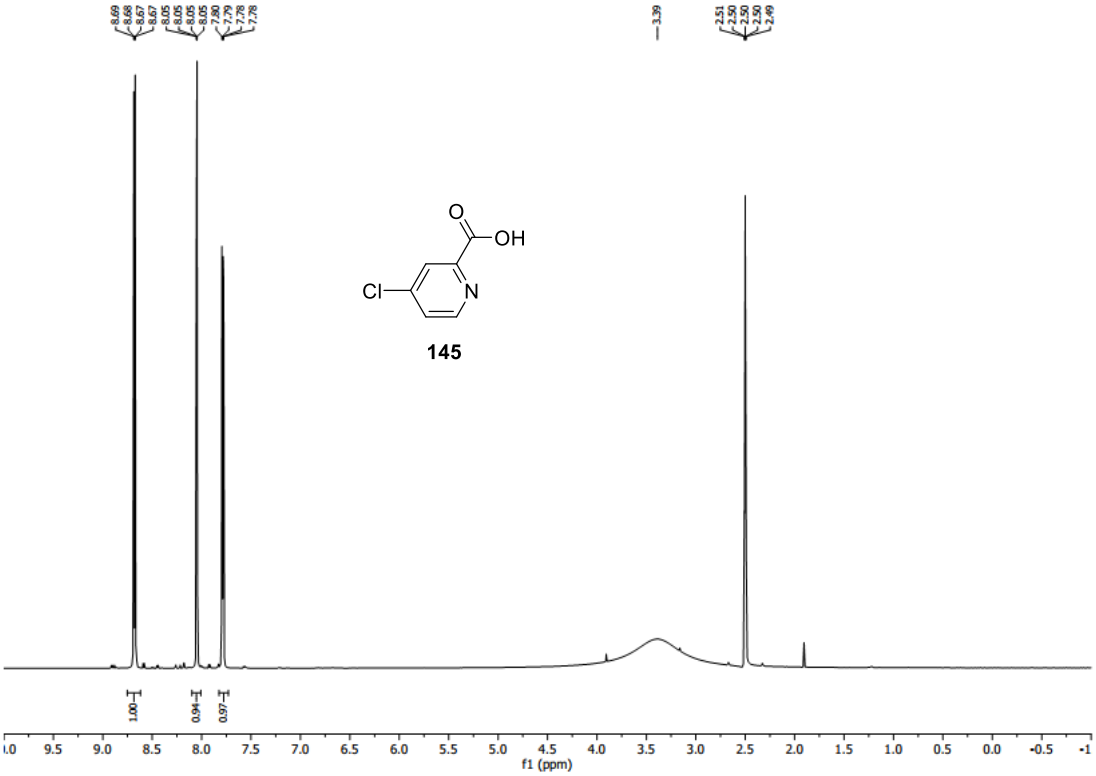


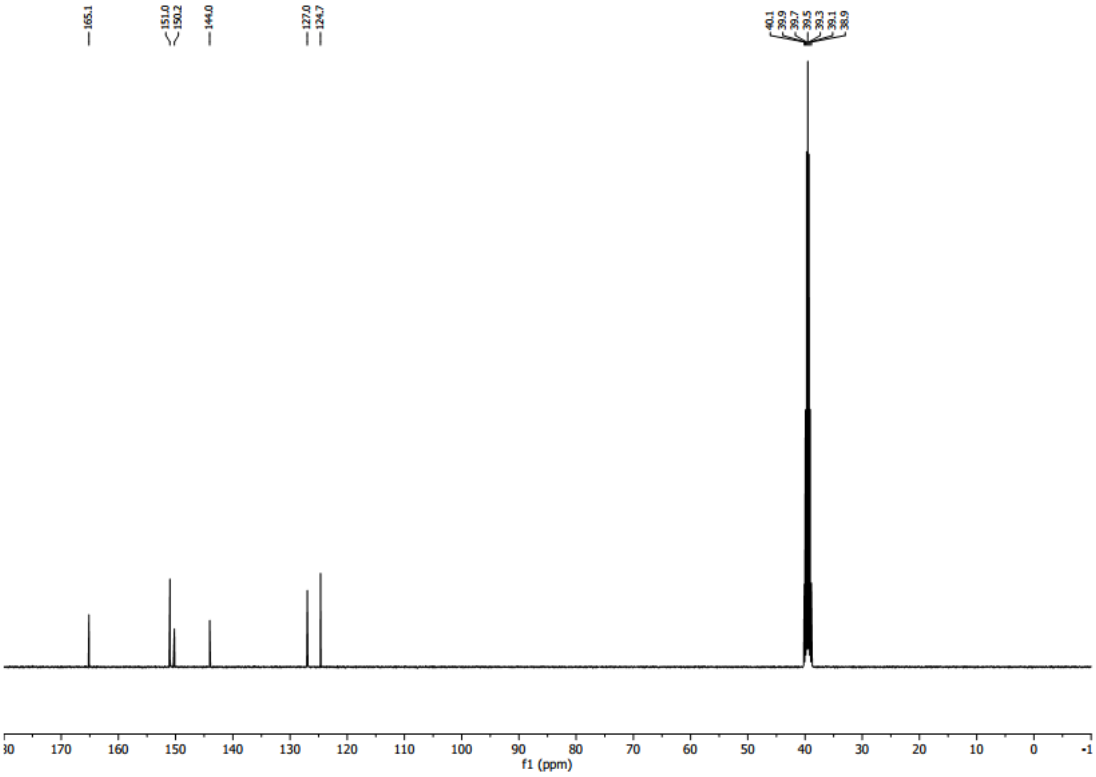
Compound **144** – ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) in $CDCl_3$



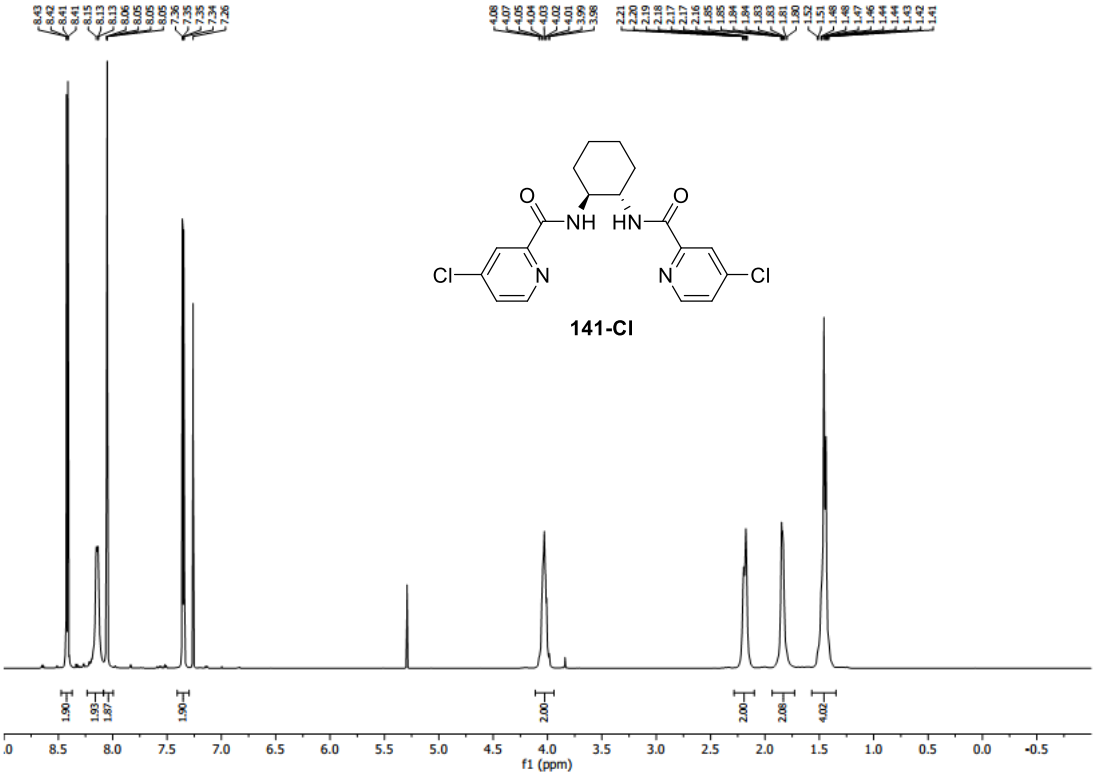


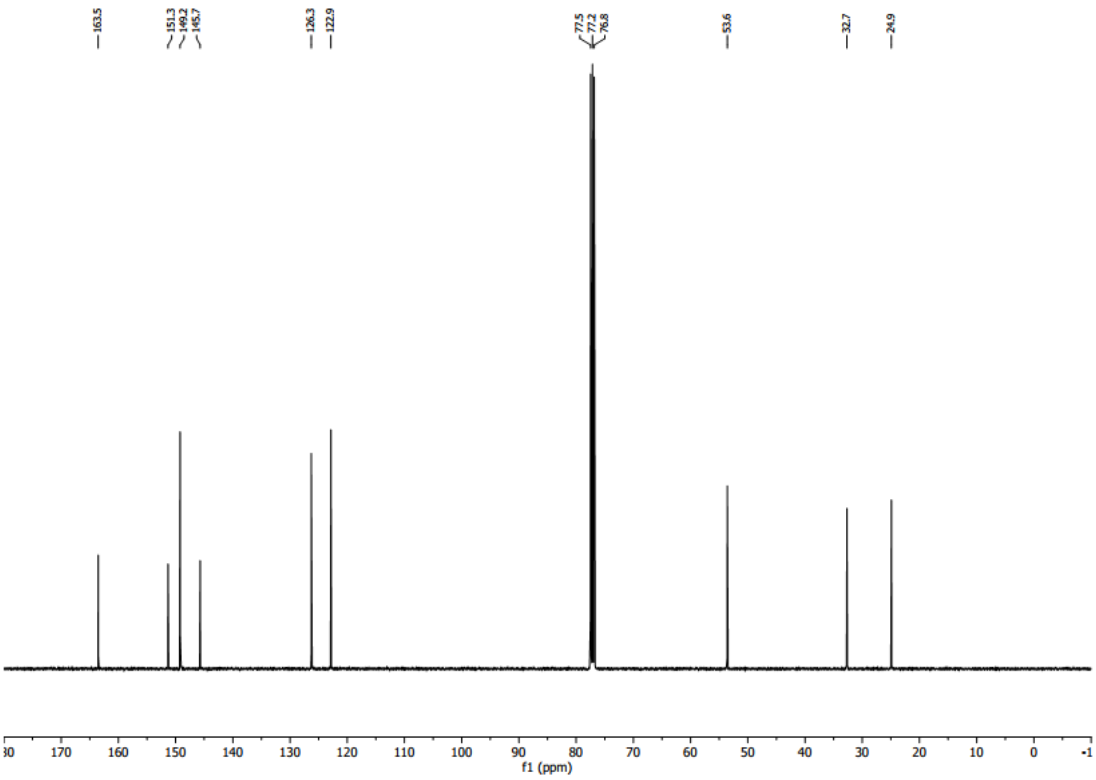
Compound **145** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in DMSO-d_6



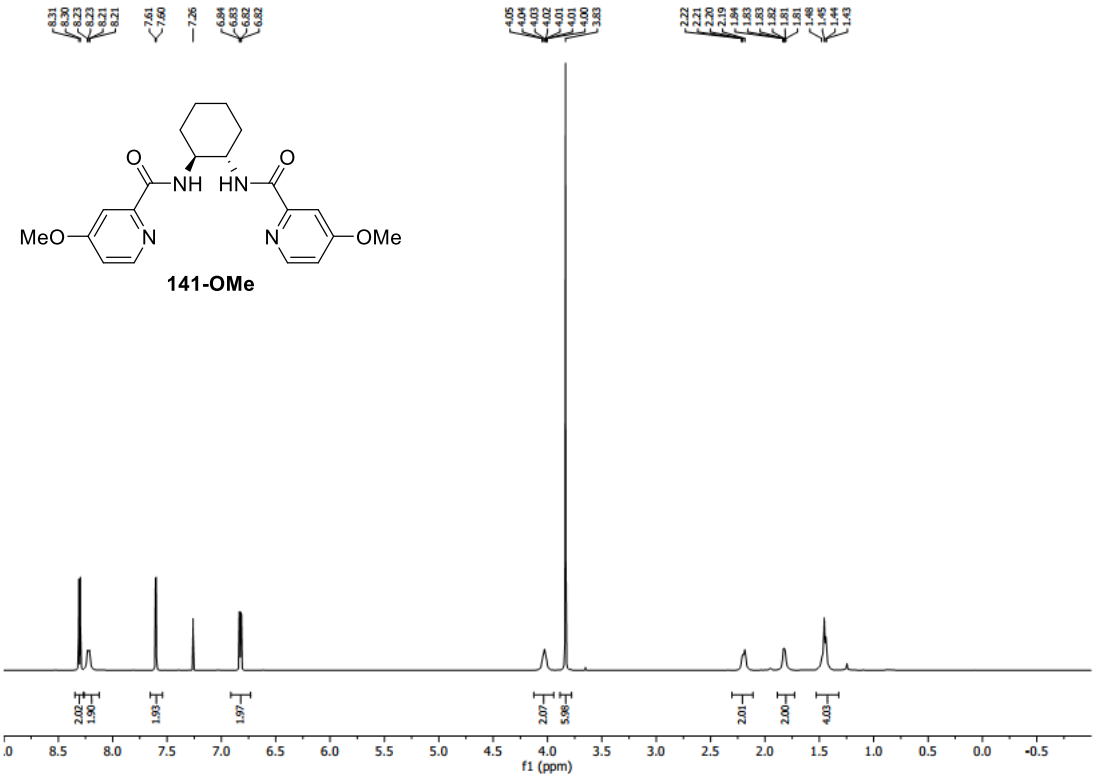


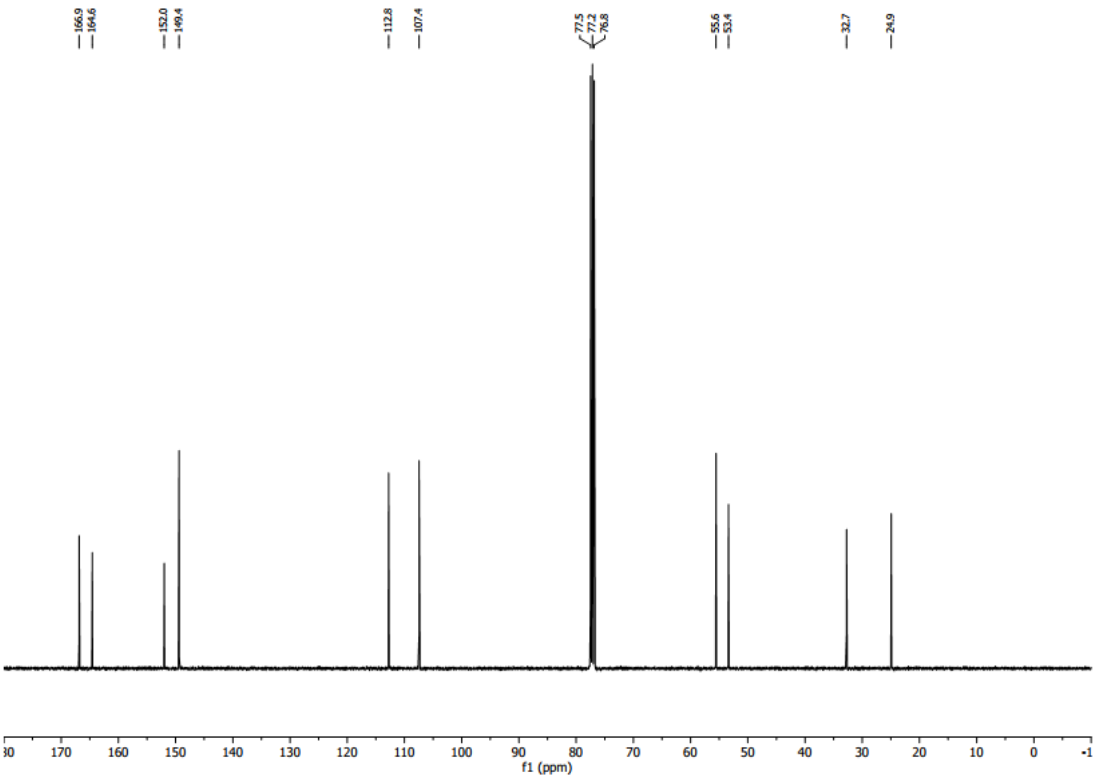
Compound **141-Cl** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



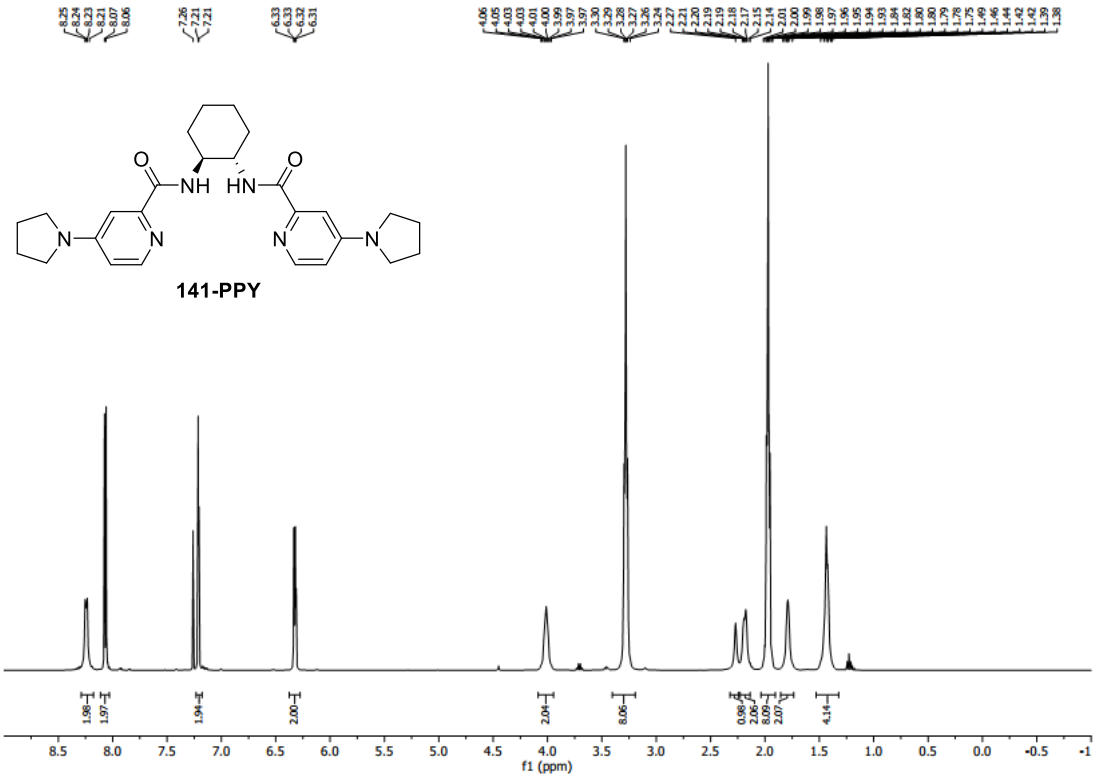


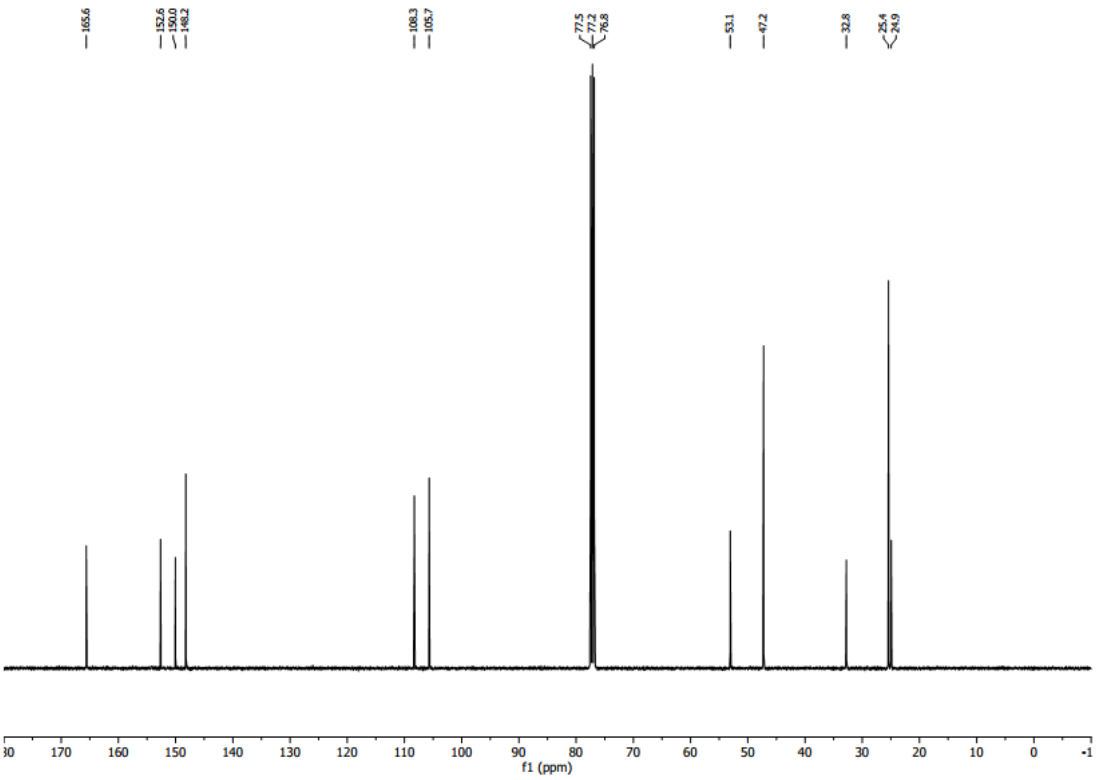
Compound **141-OMe** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



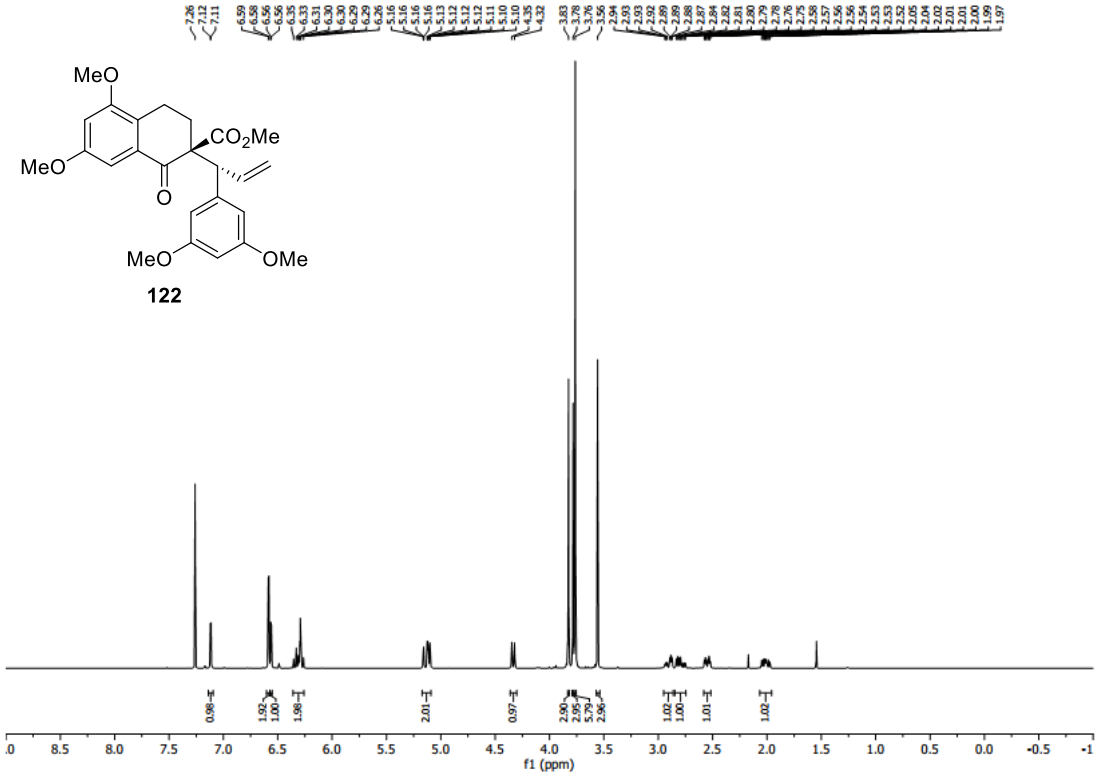


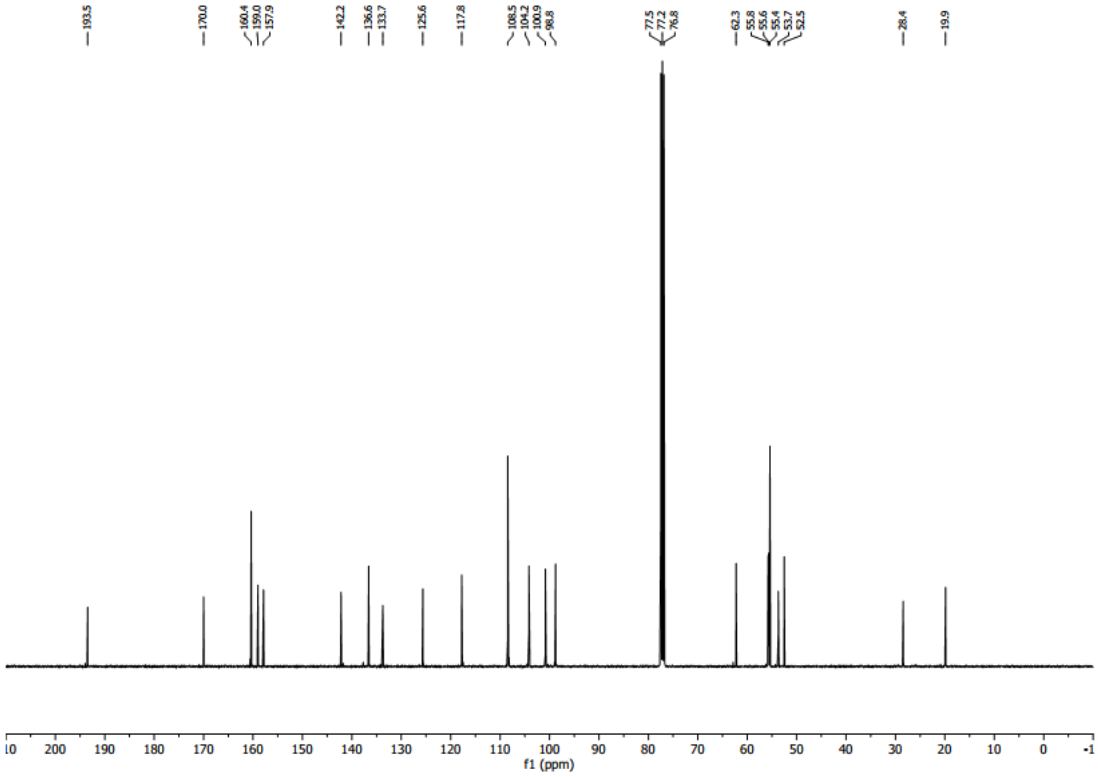
Compound **141-PPY** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



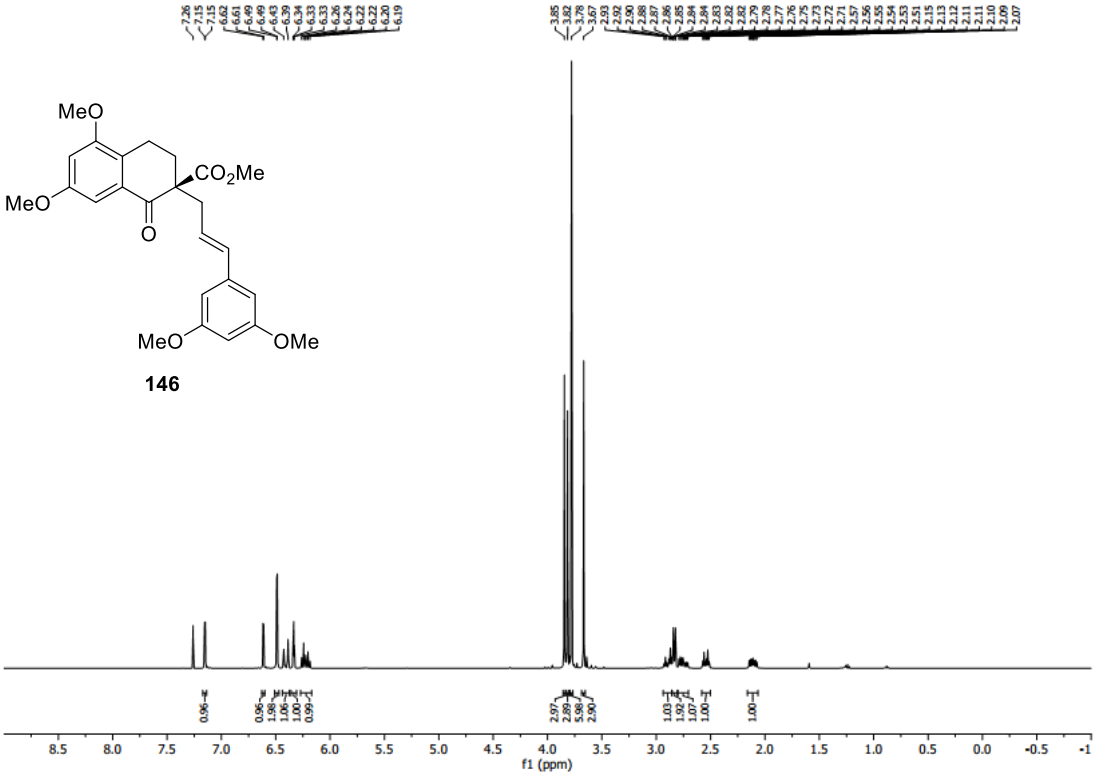


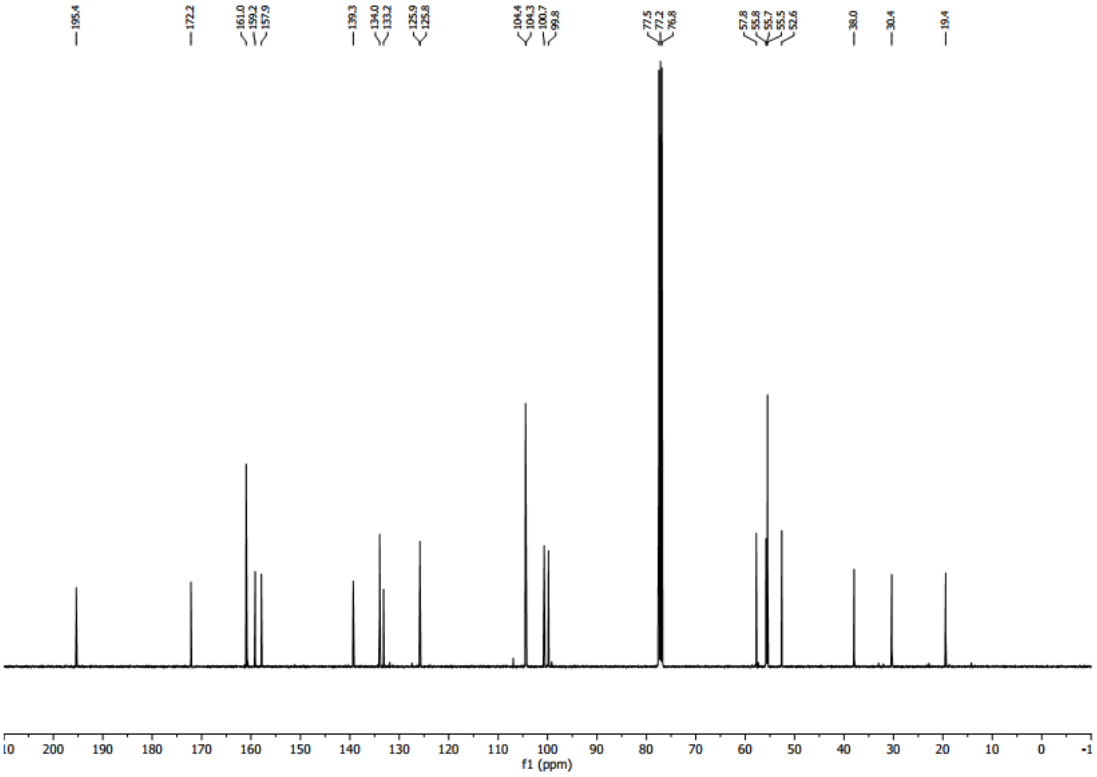
Compound **122** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



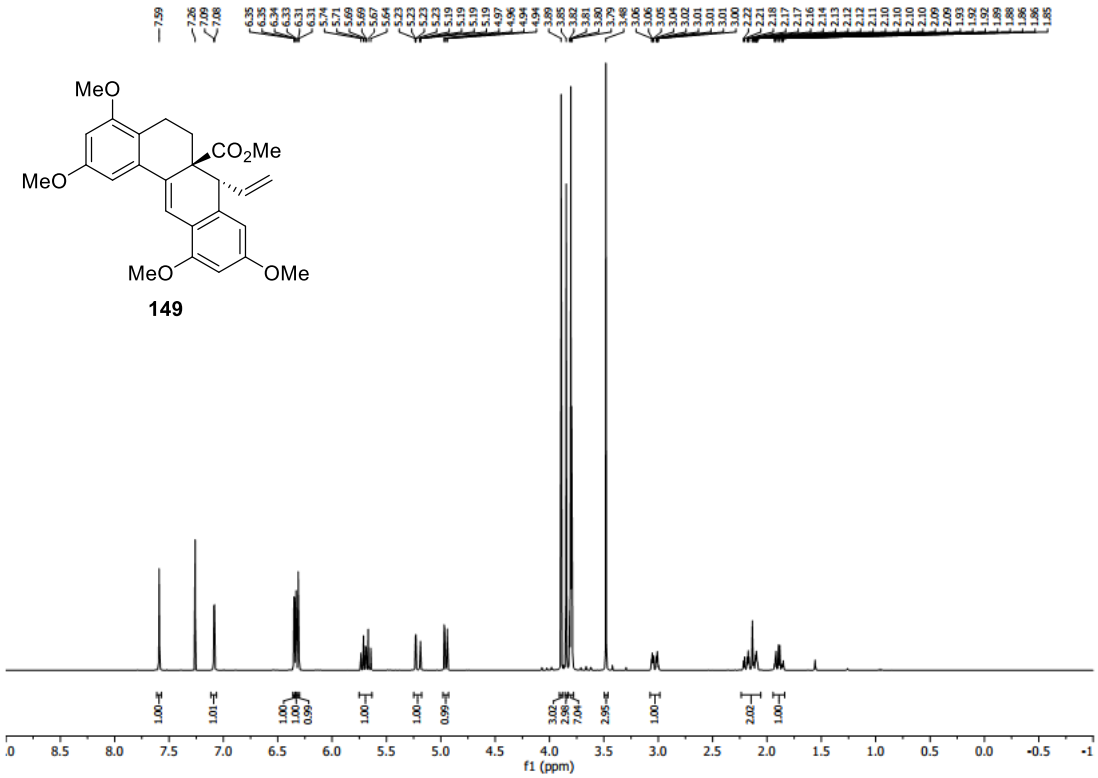


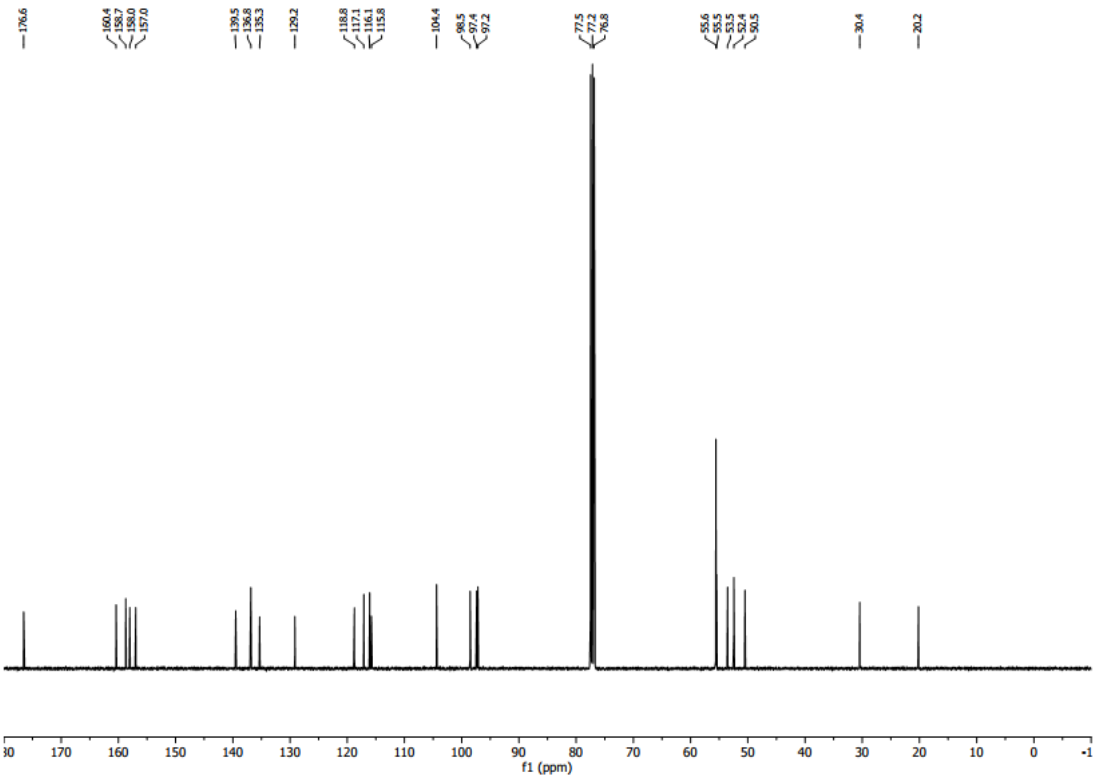
Compound **146** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



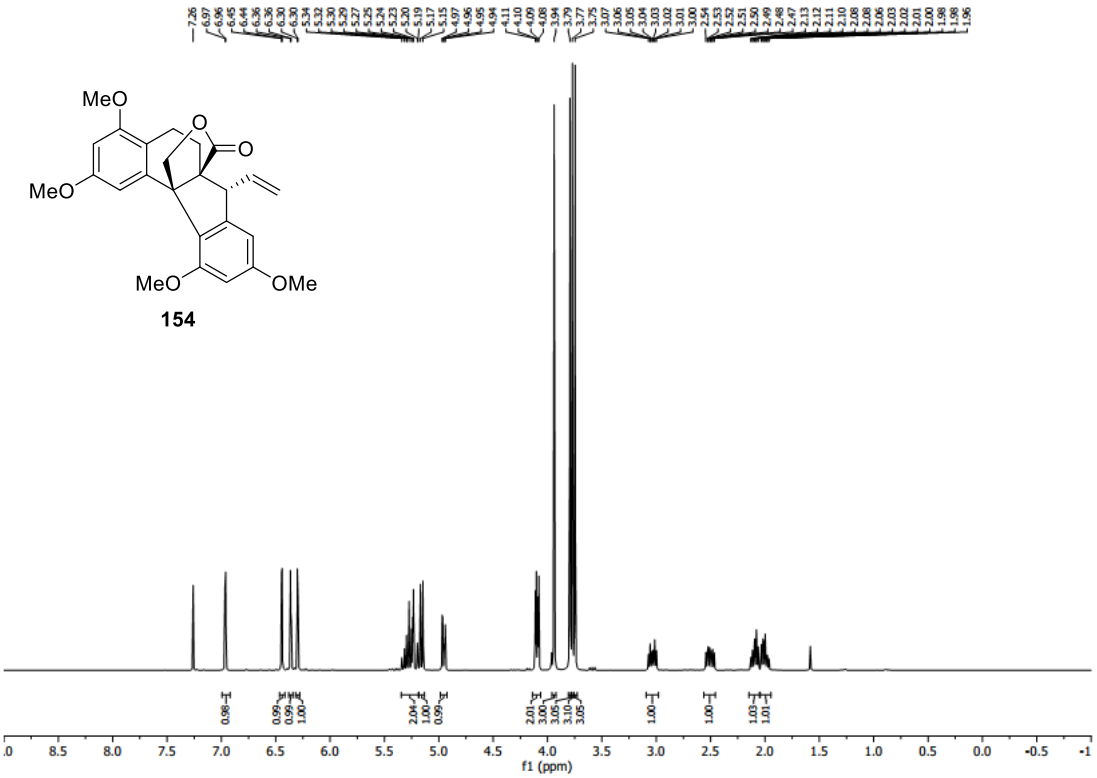


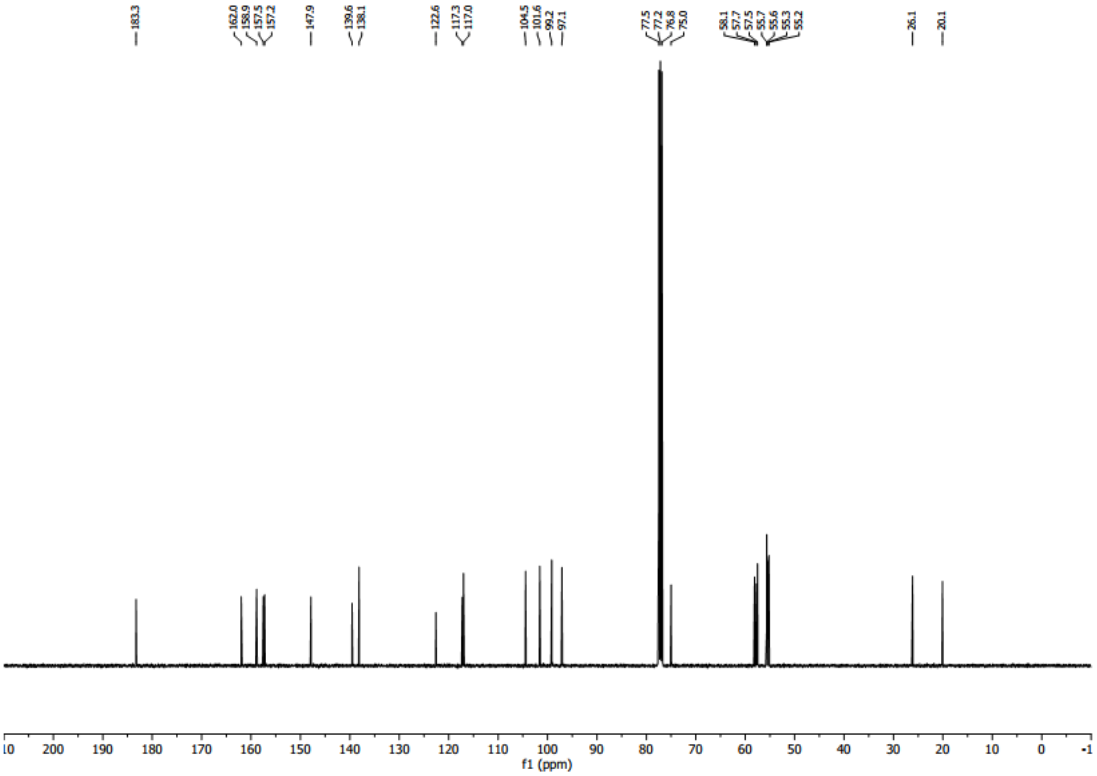
Compound **149** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



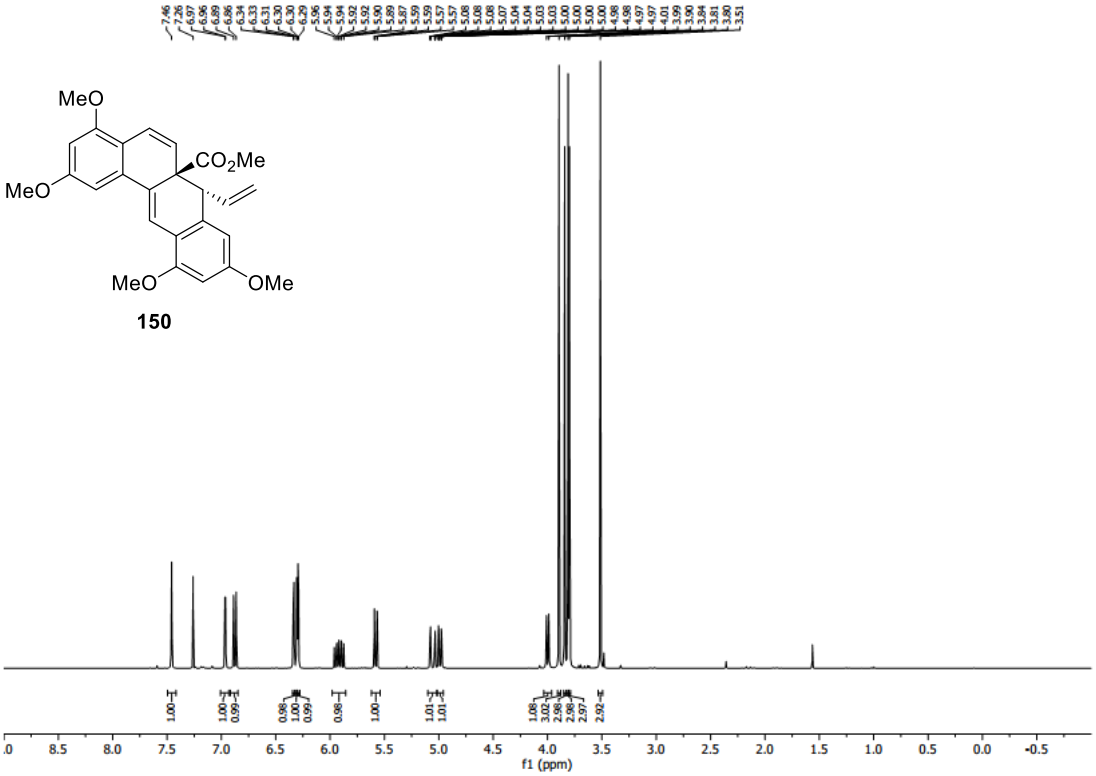


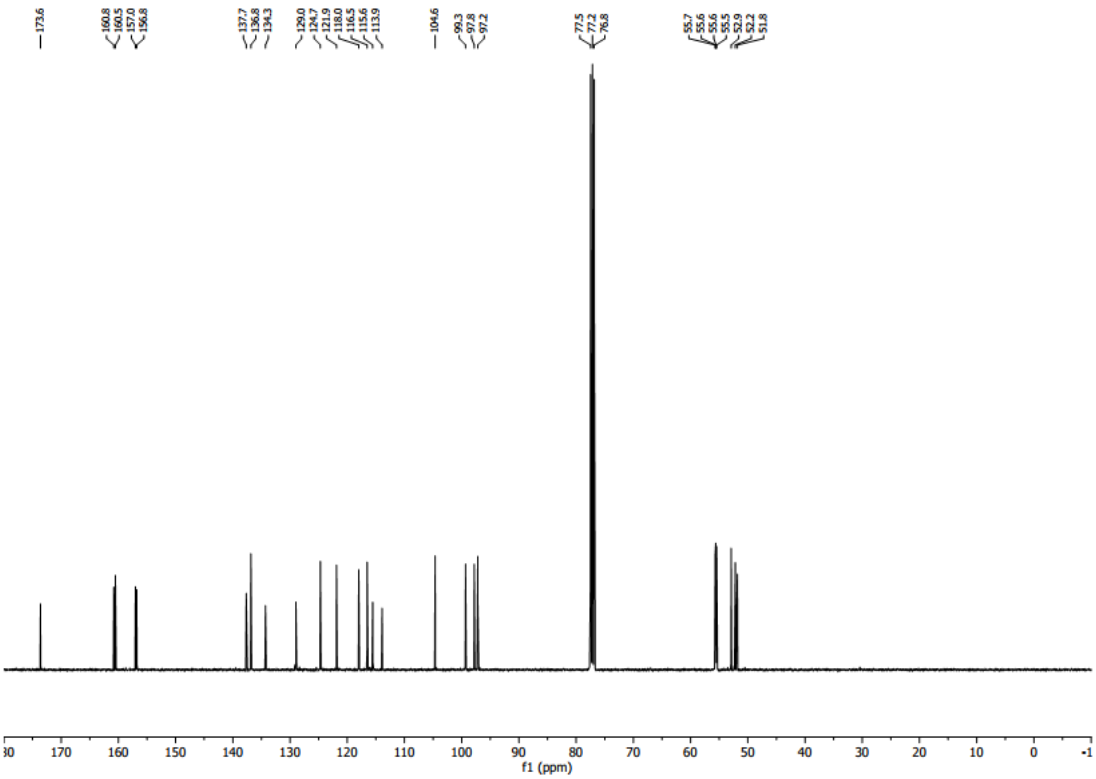
Compound **154** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



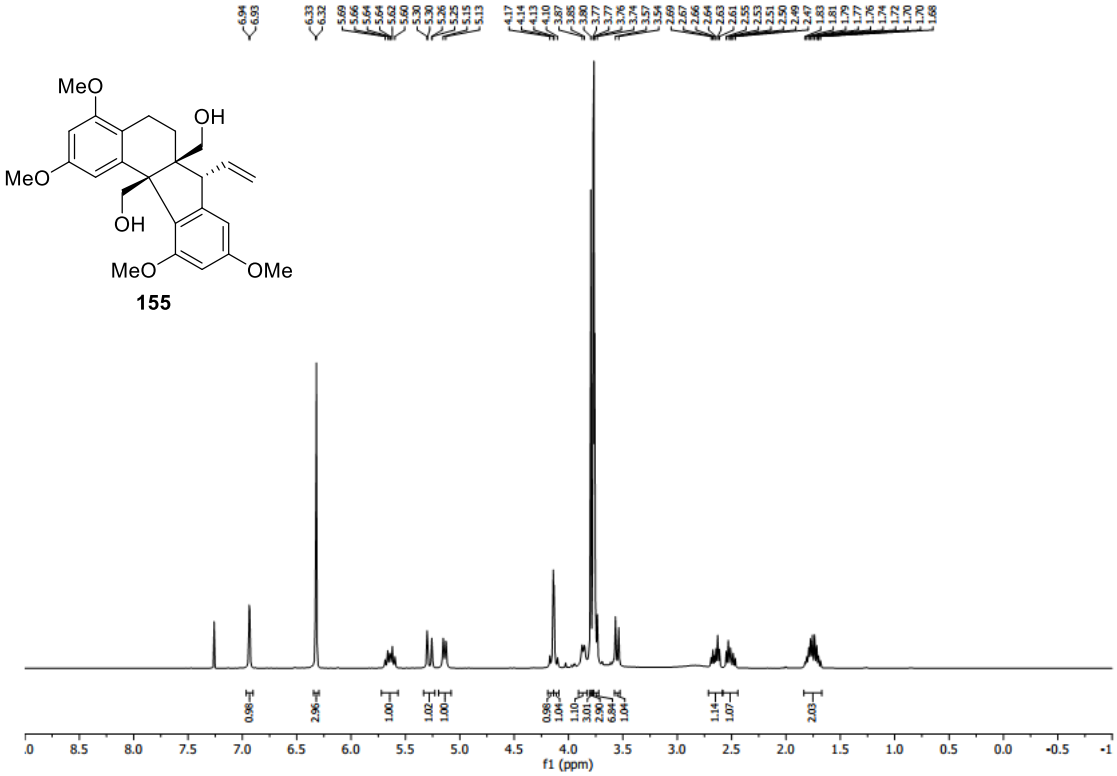


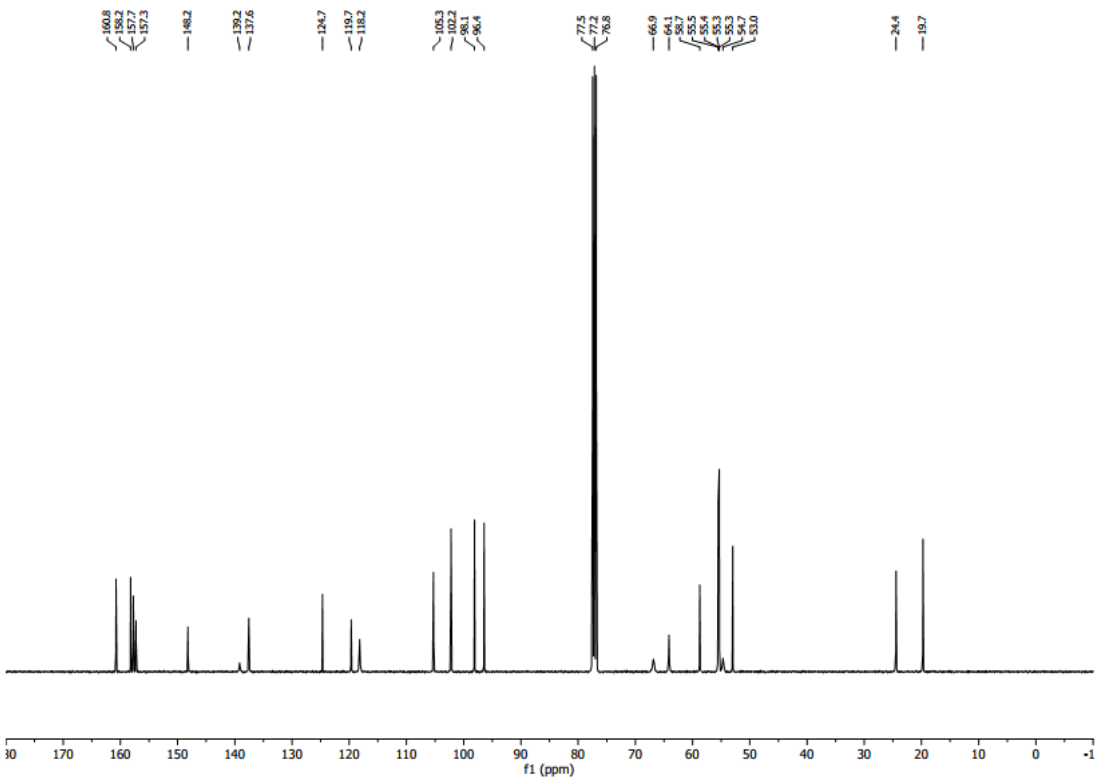
Compound **150** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



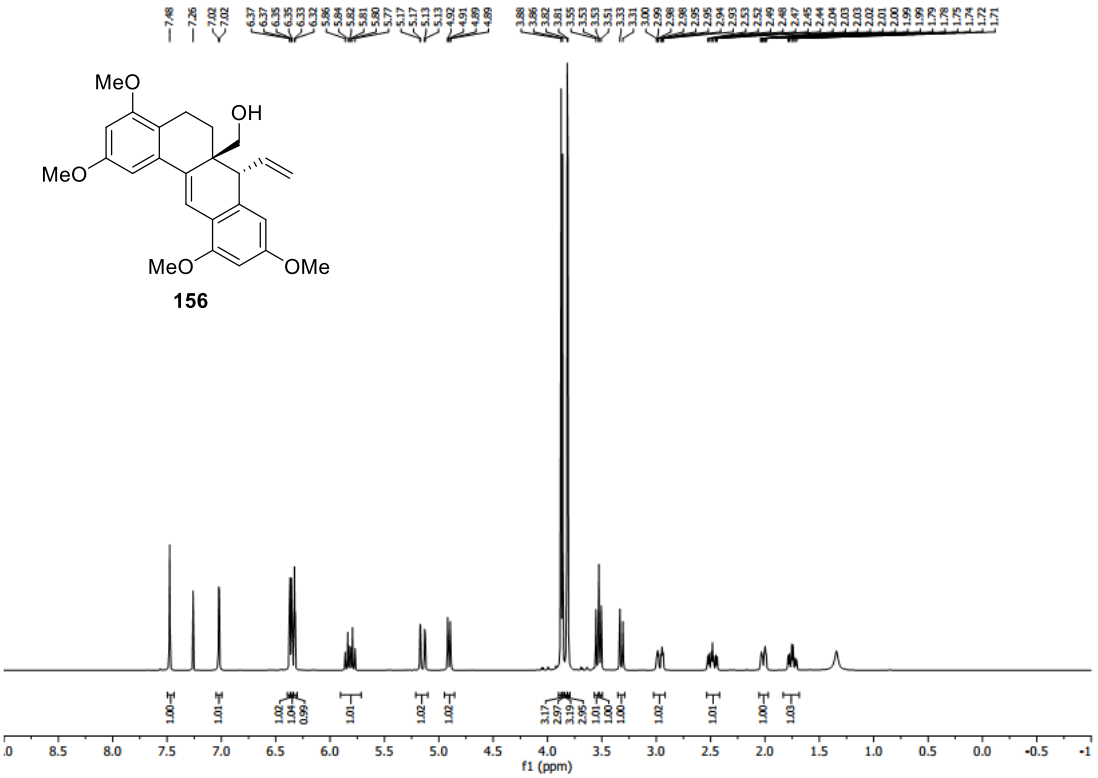


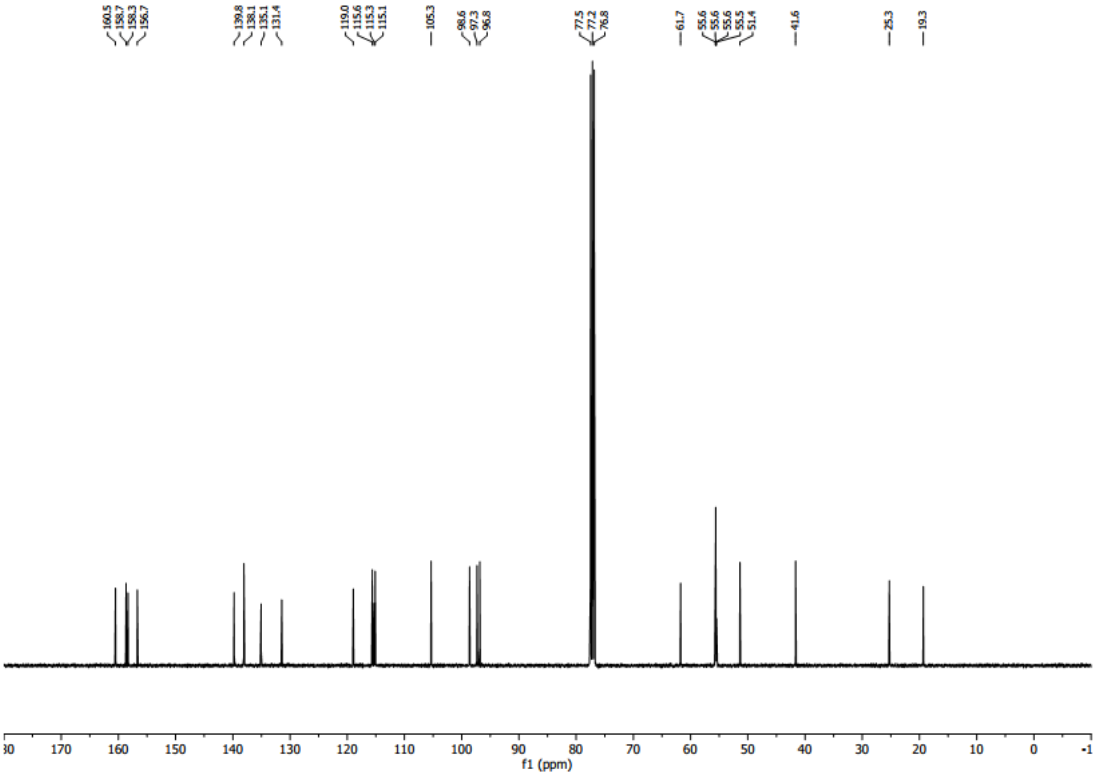
Compound **155** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



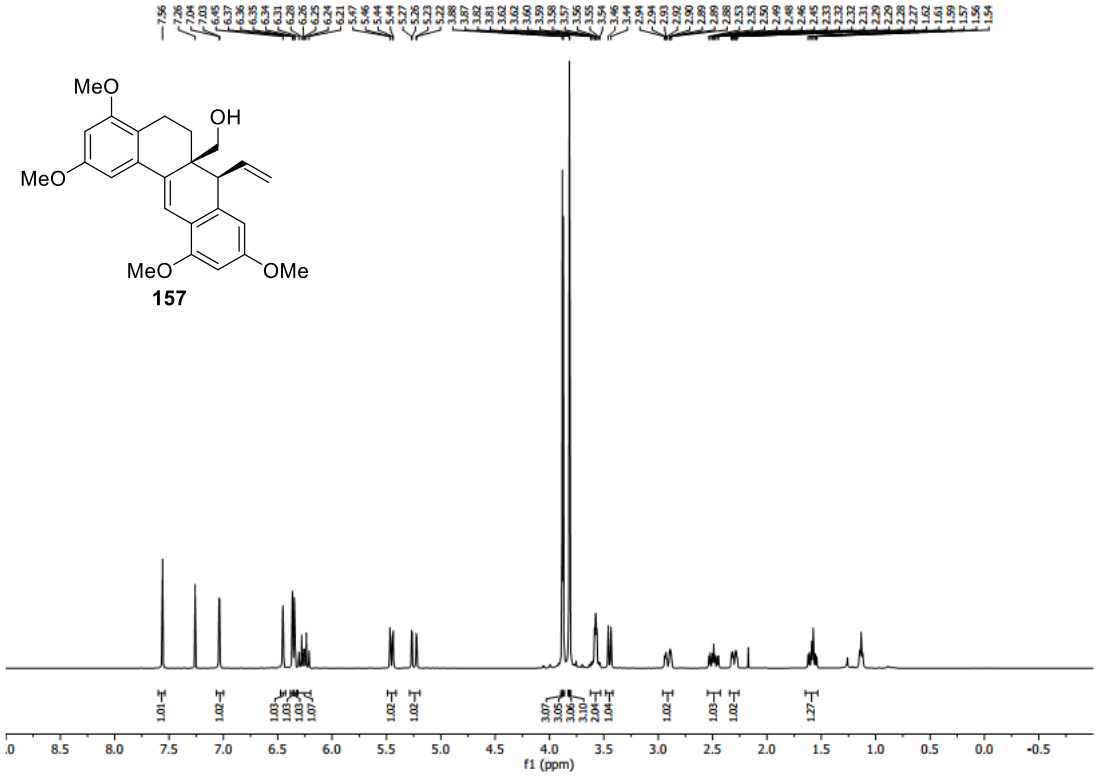


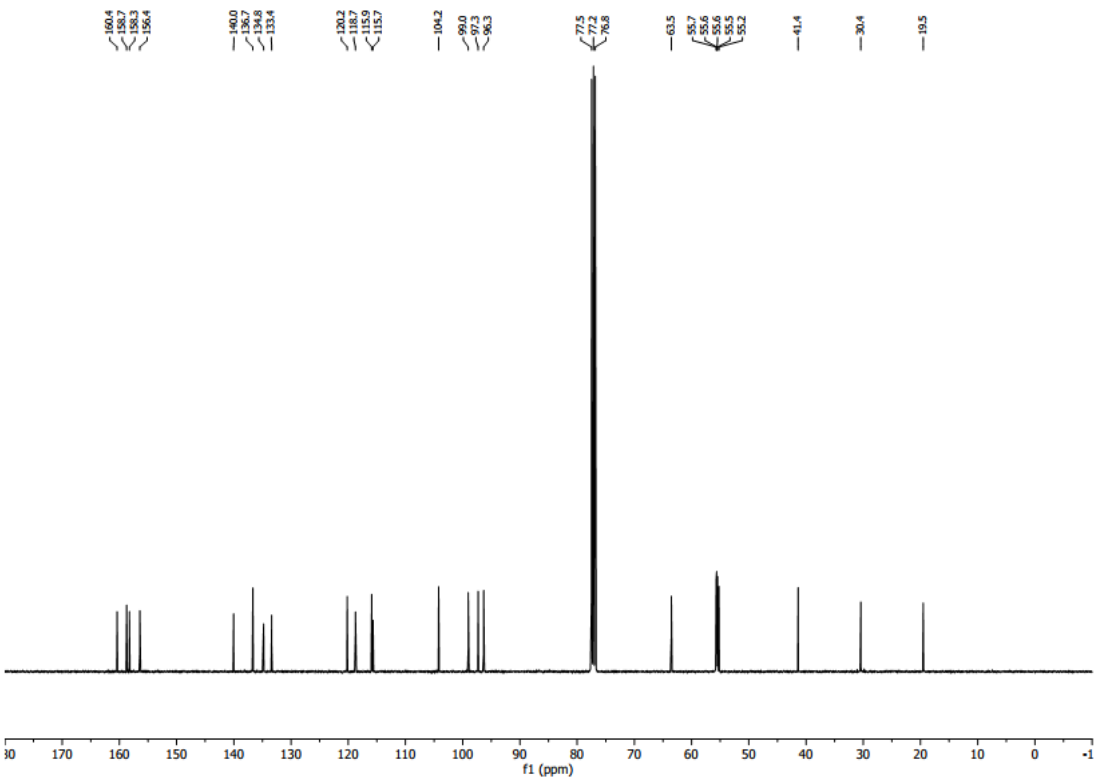
Compound **156** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



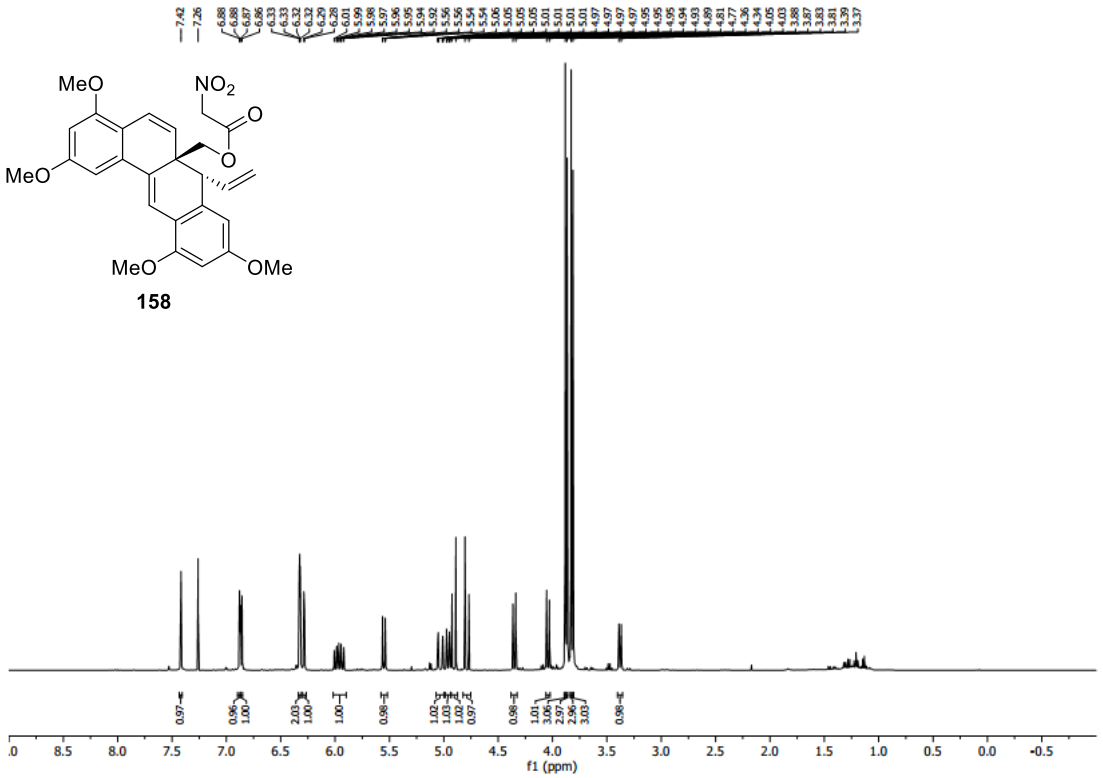


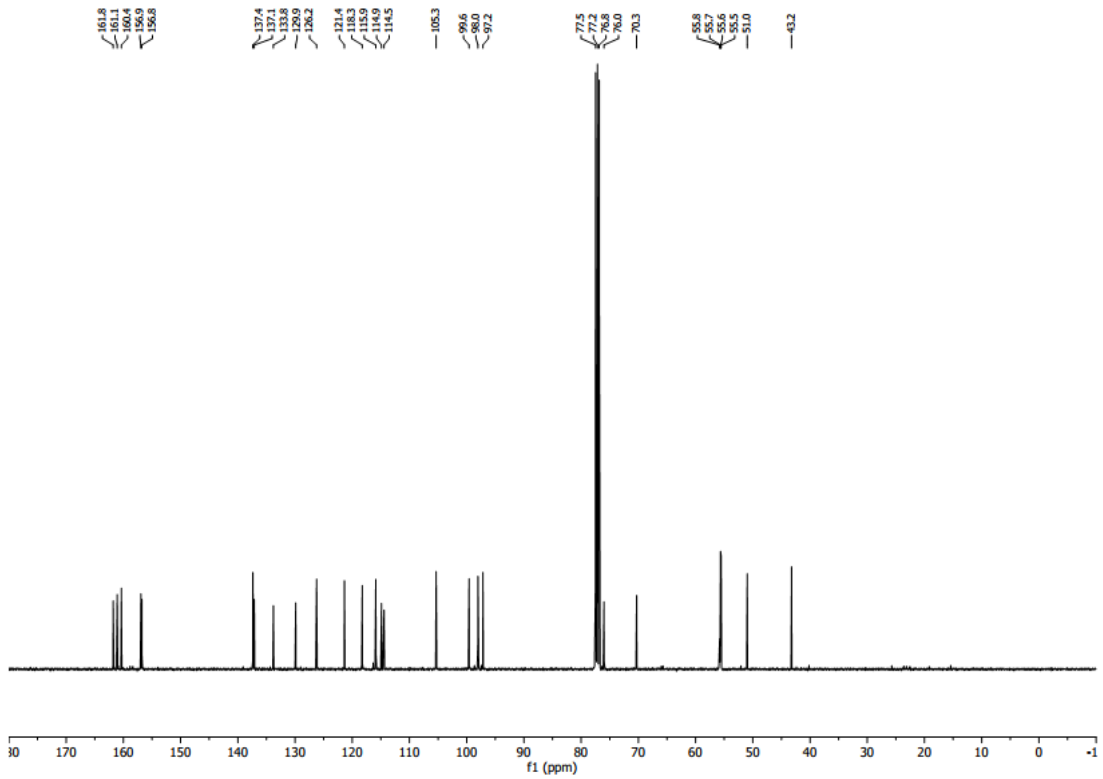
Compound **157** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



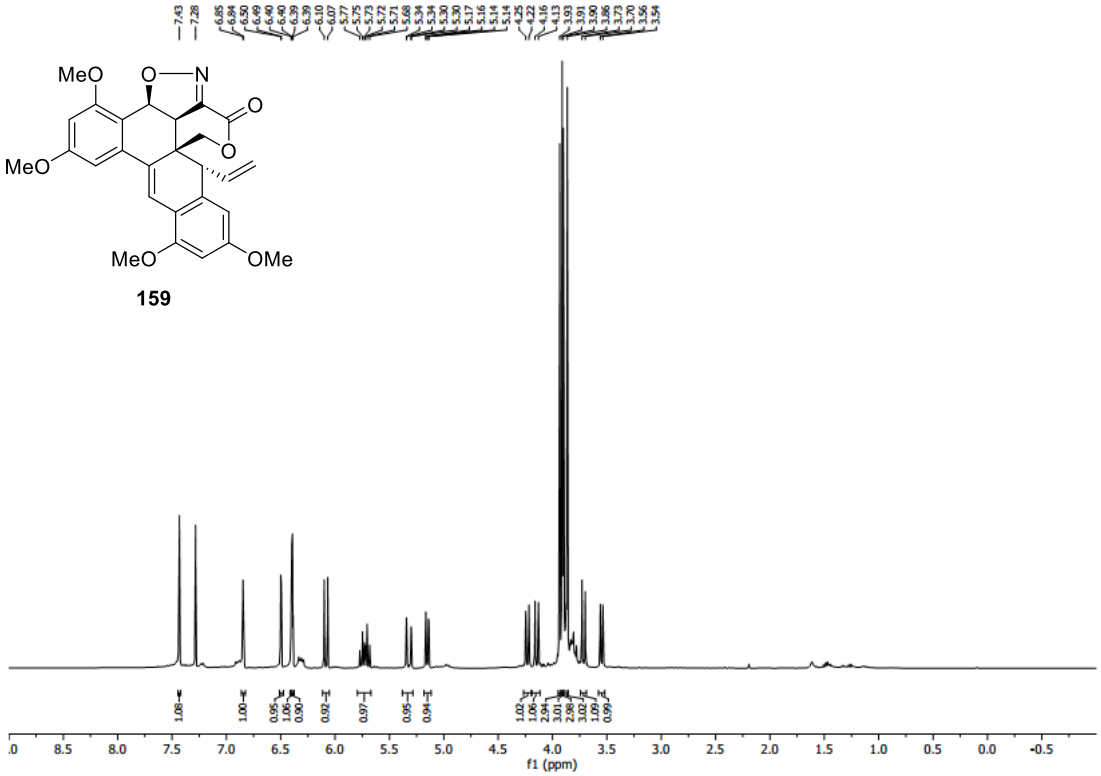


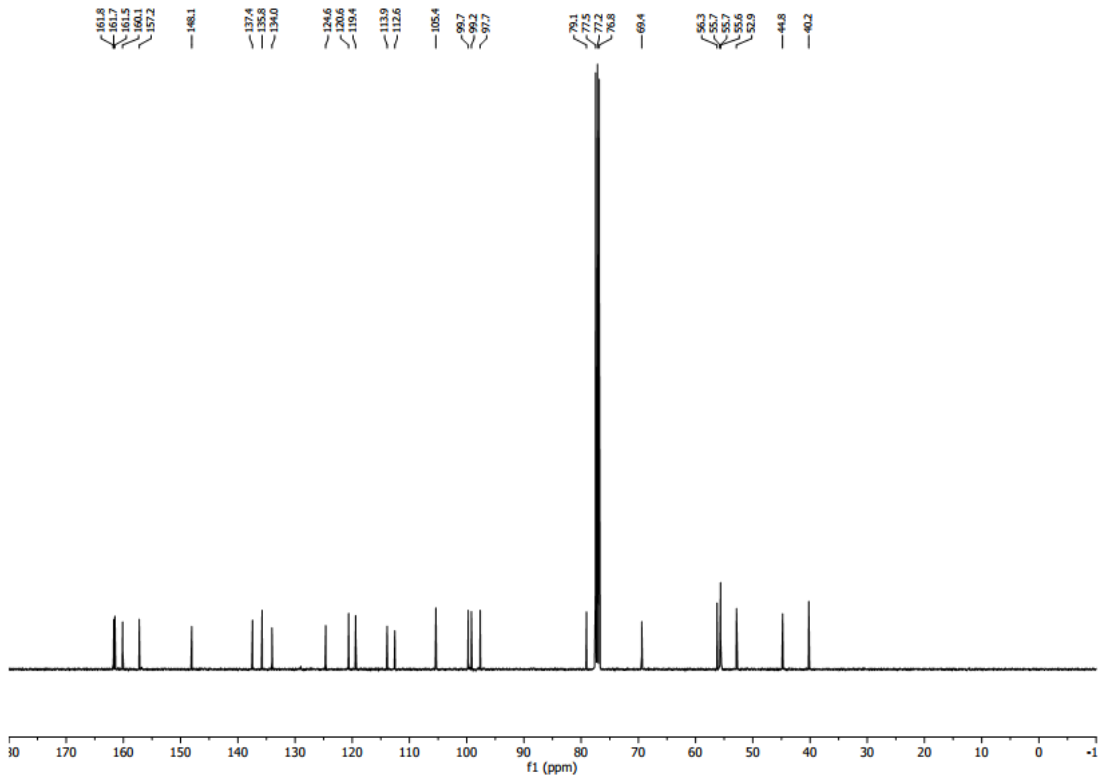
Compound **158** – ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) in $CDCl_3$



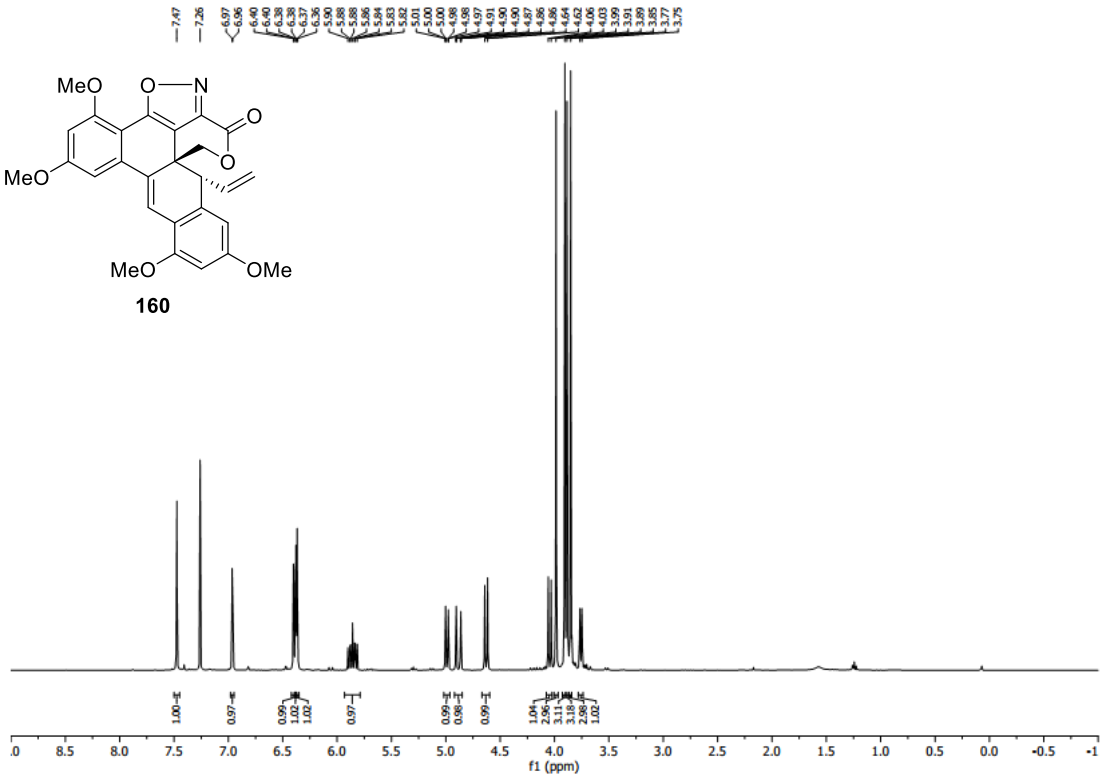


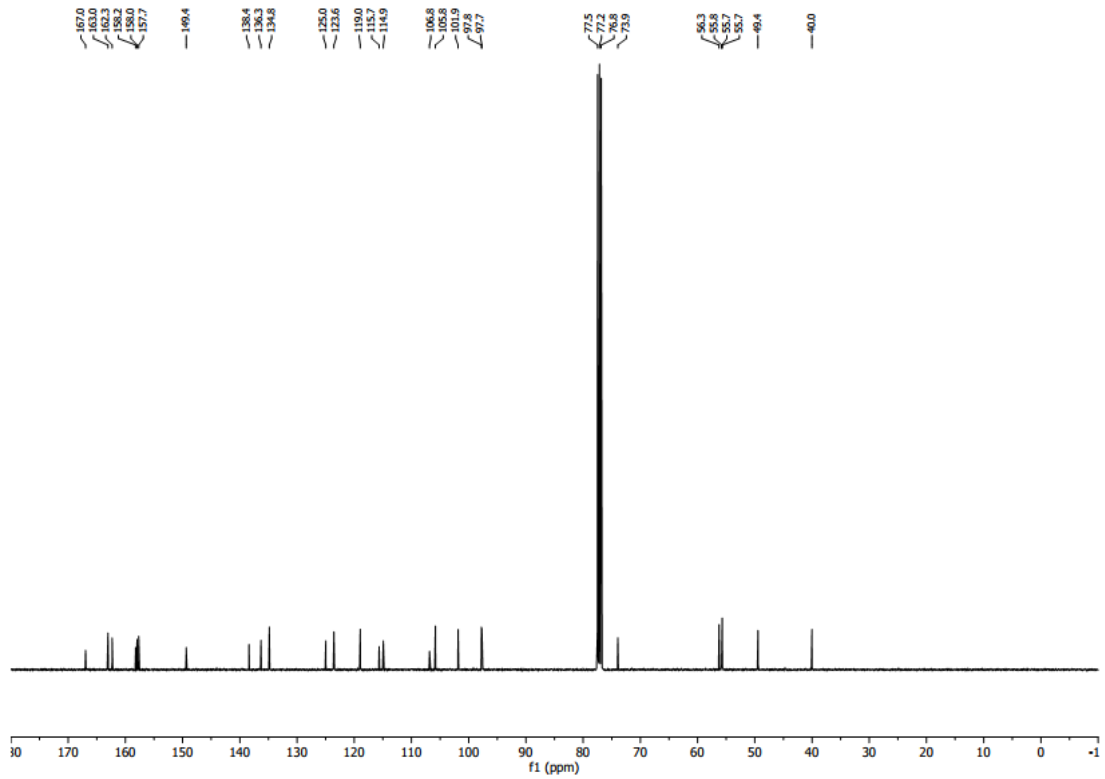
Compound **159** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



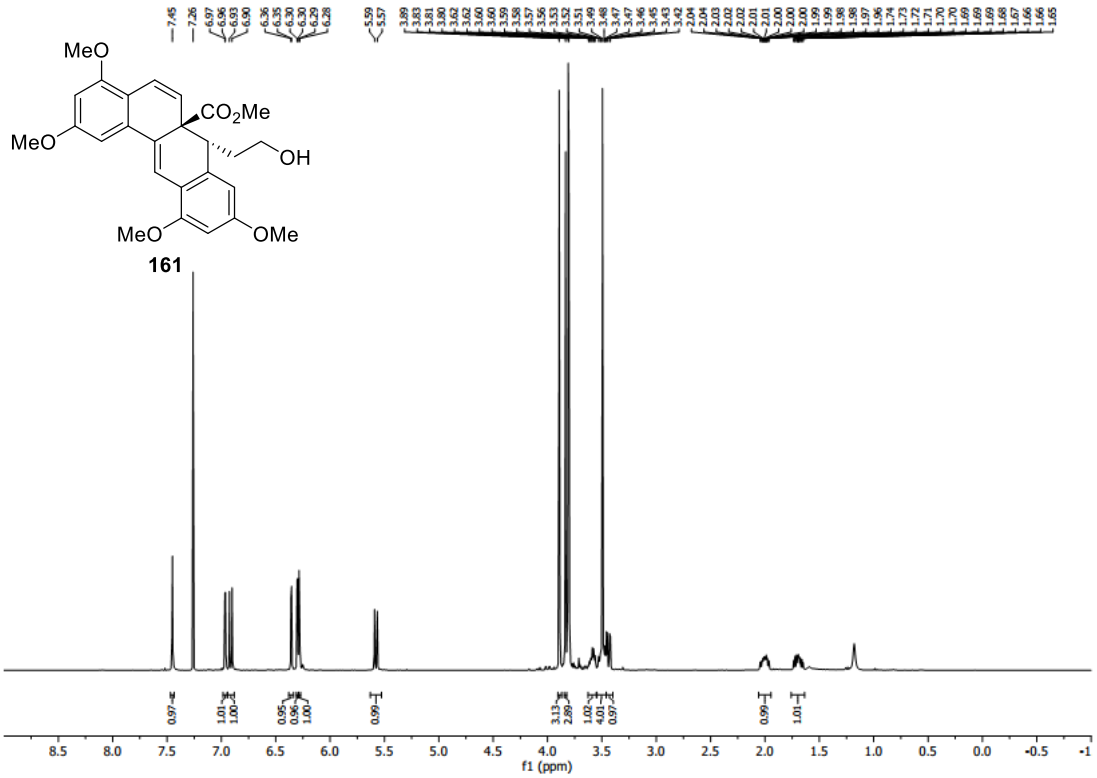


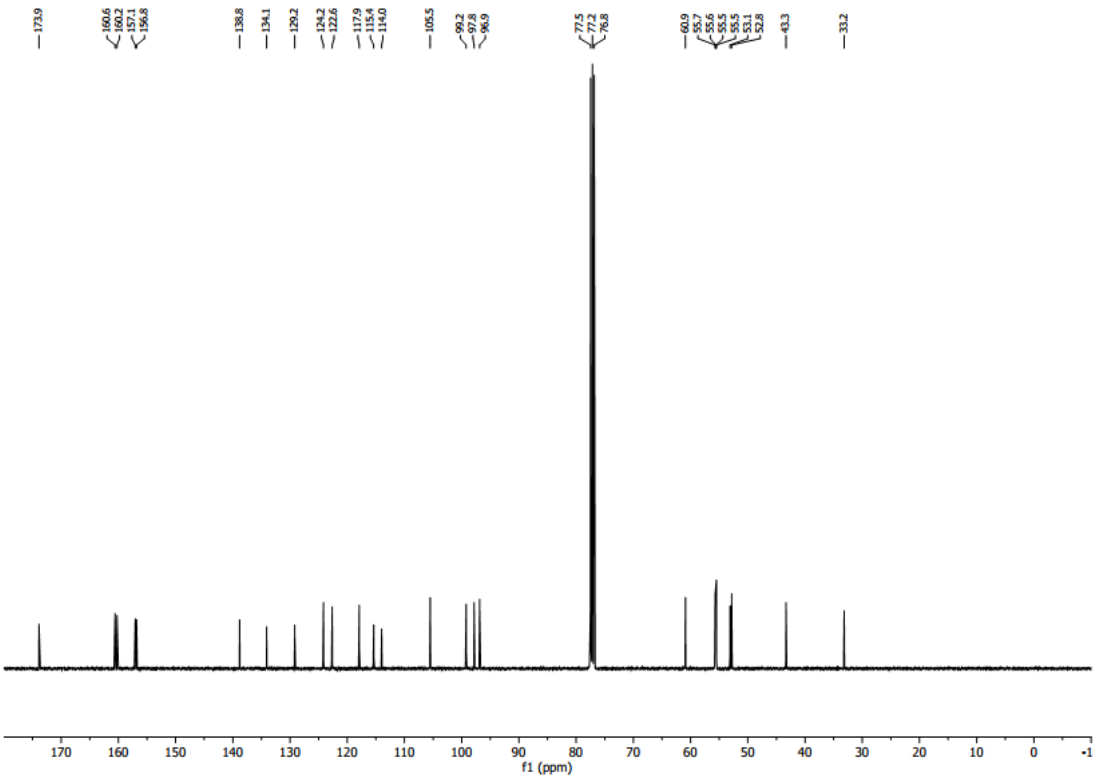
Compound **160** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



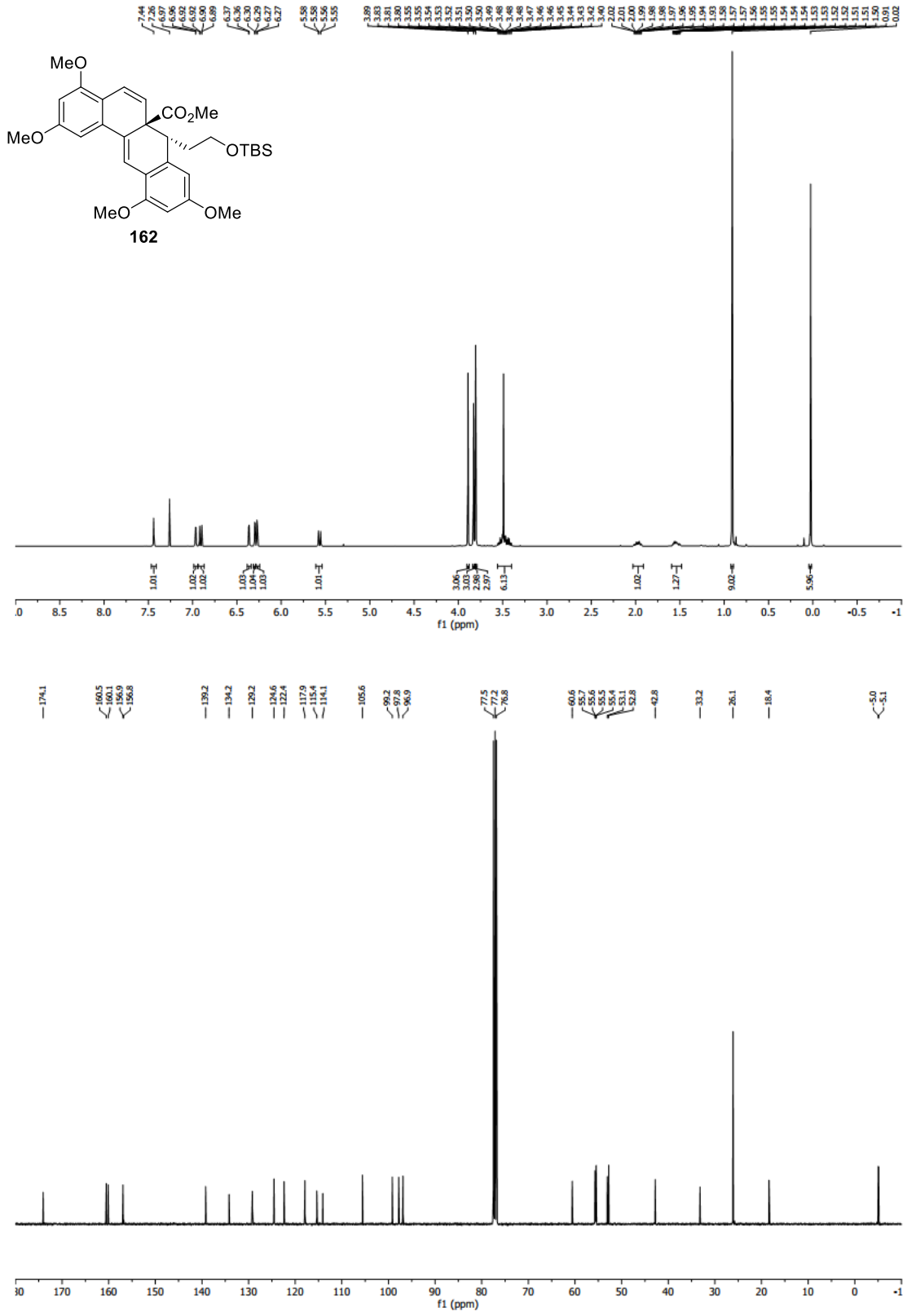


Compound **161** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

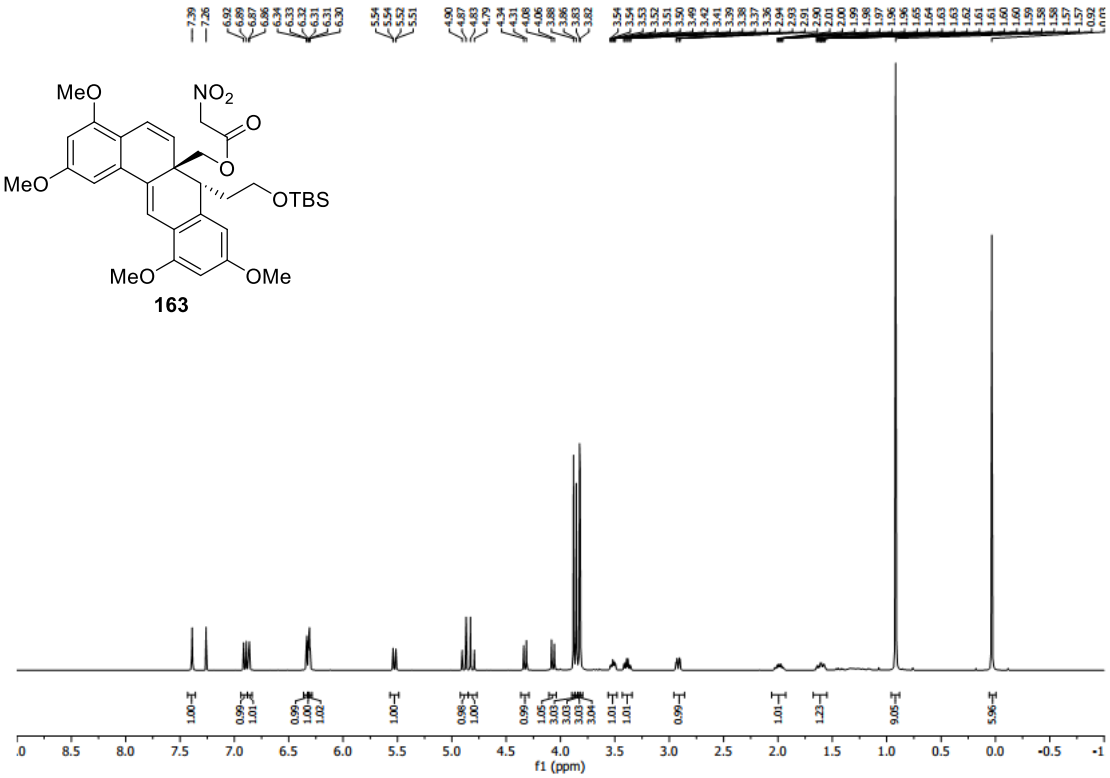


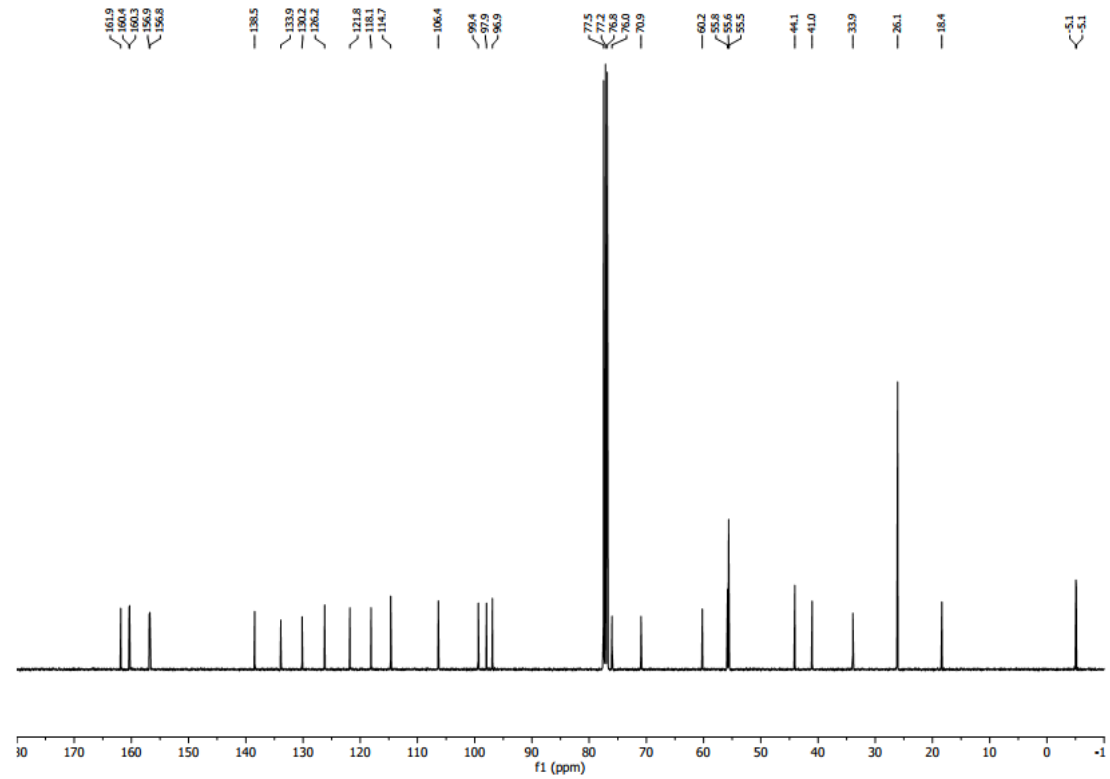


Compound **162** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

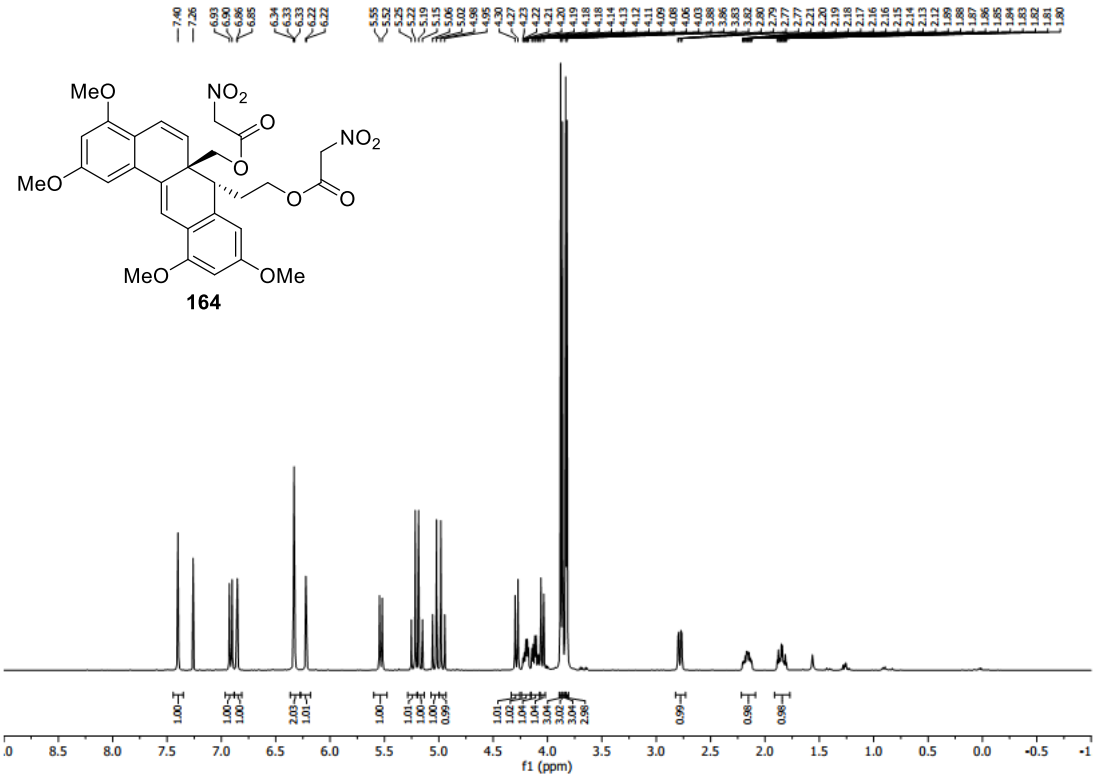


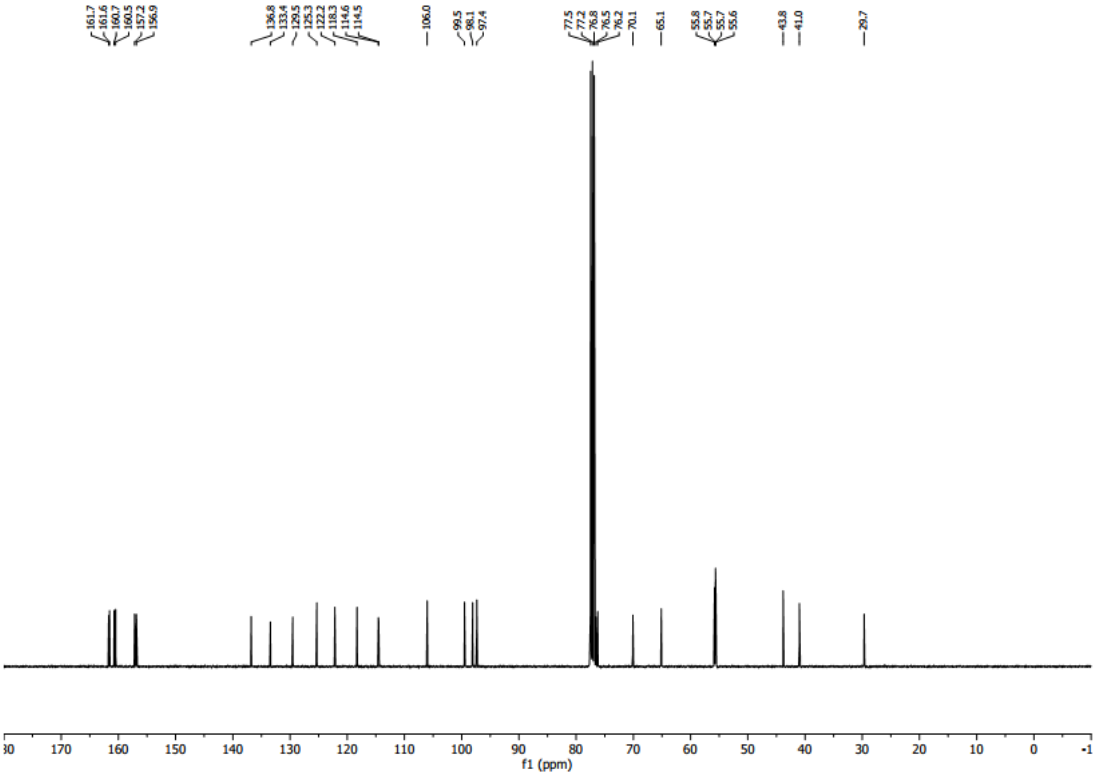
Compound **163** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



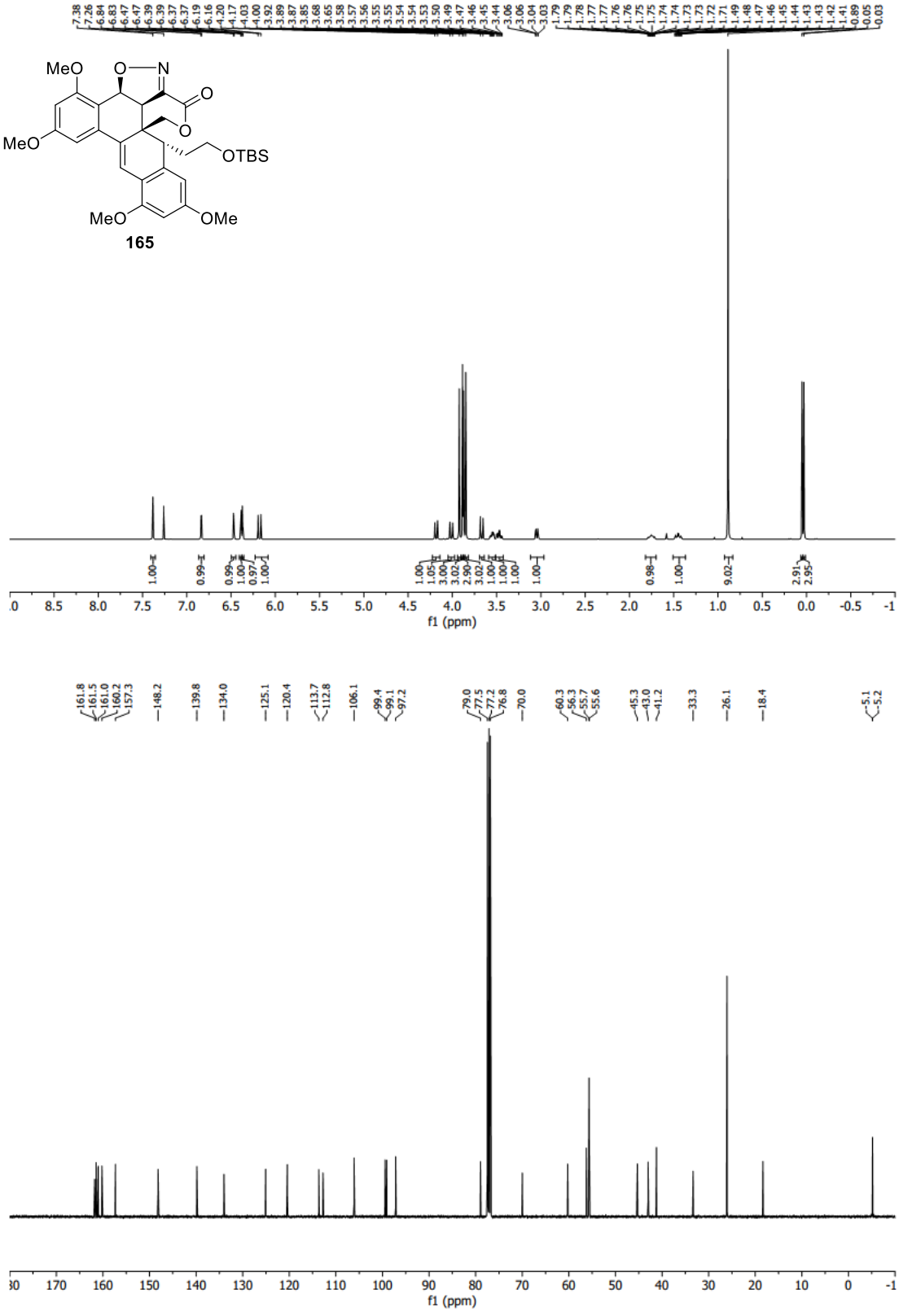


Compound **164** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

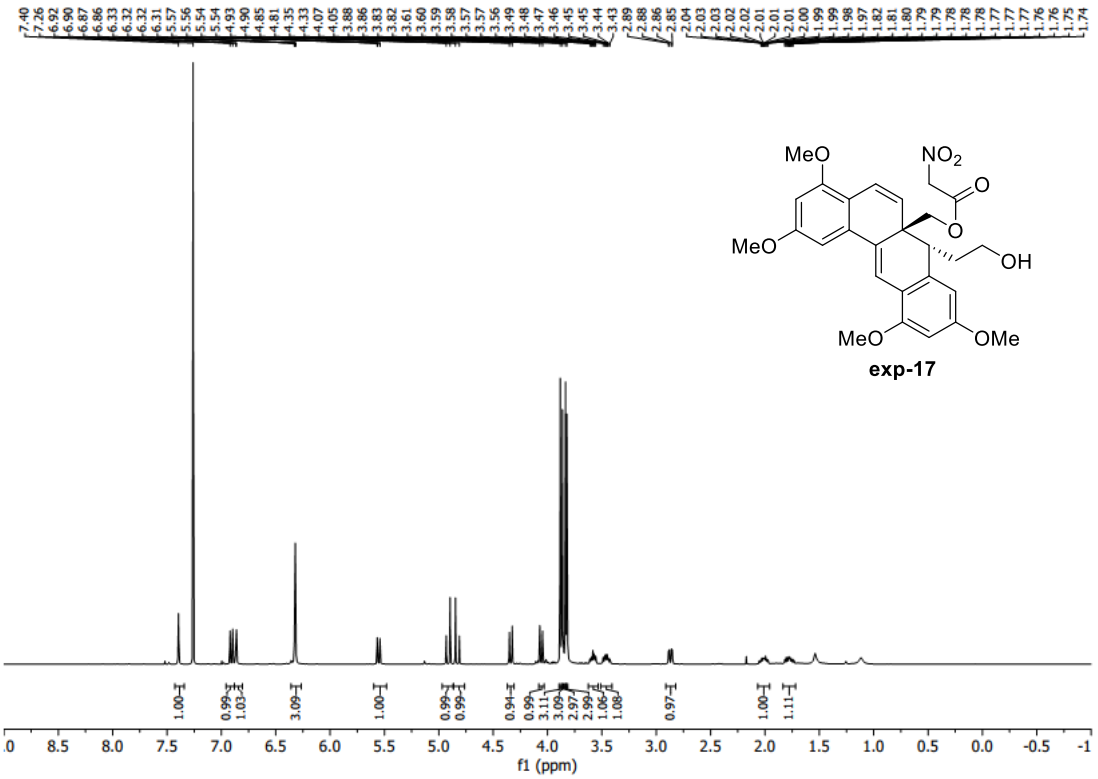


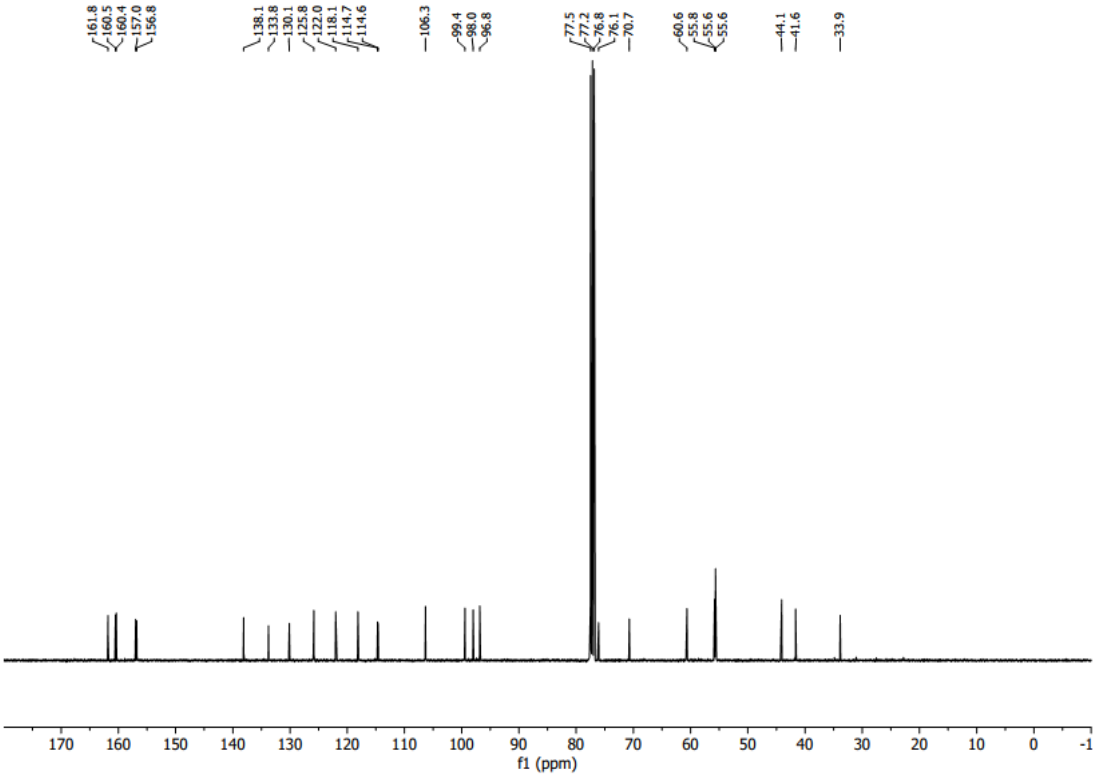


Compound **165** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

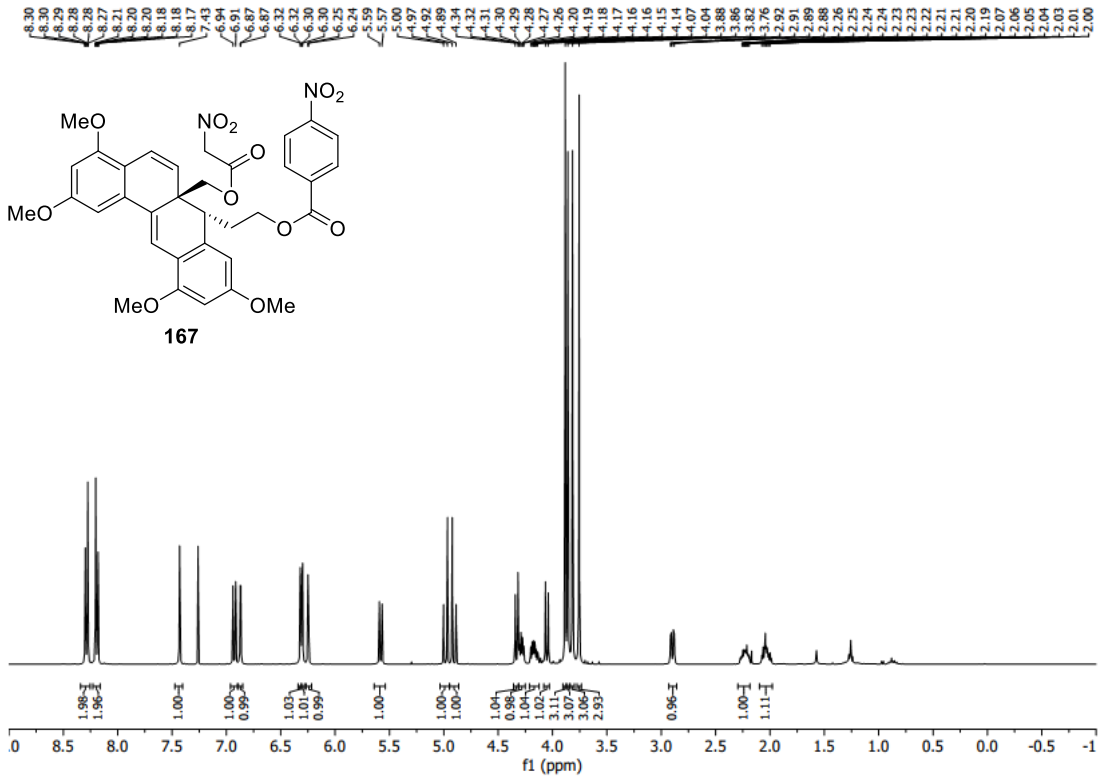


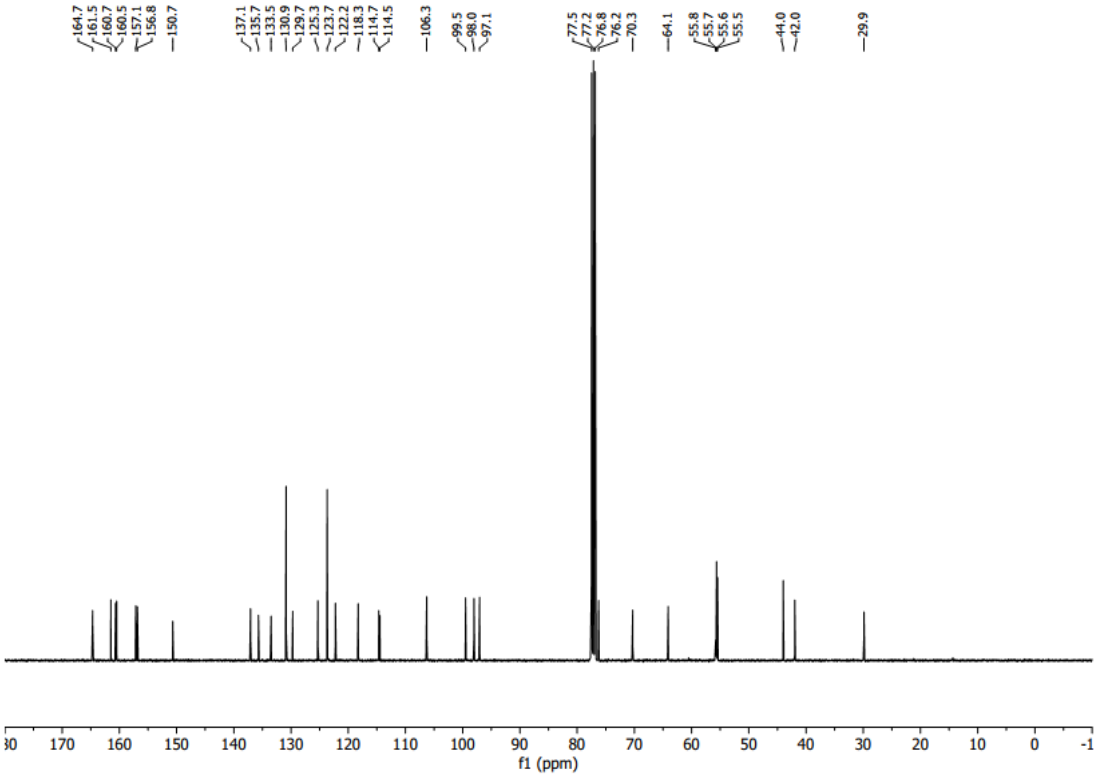
Compound **exp-17** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



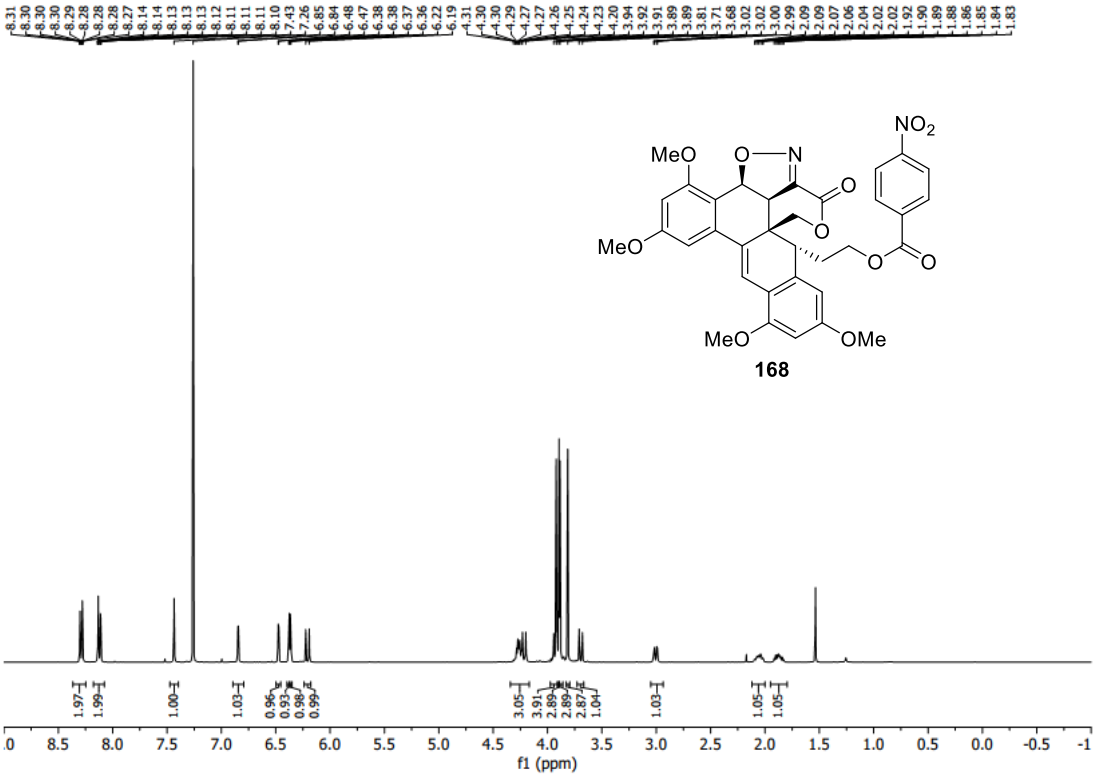


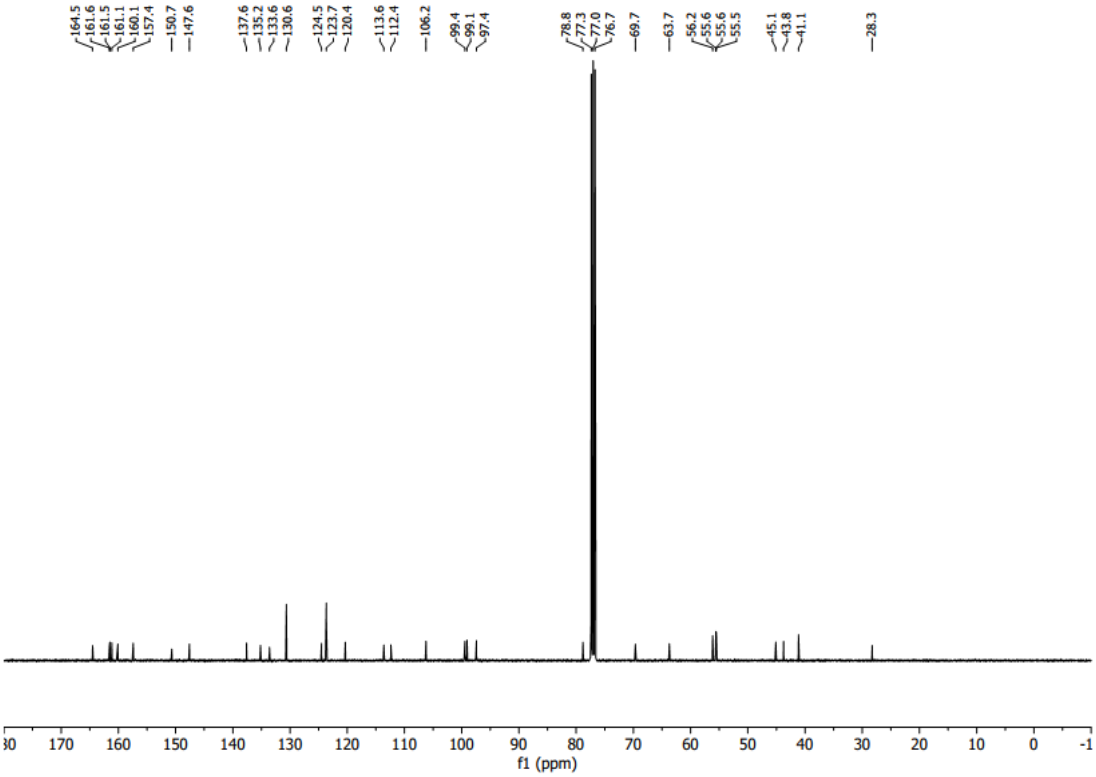
Compound **167** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



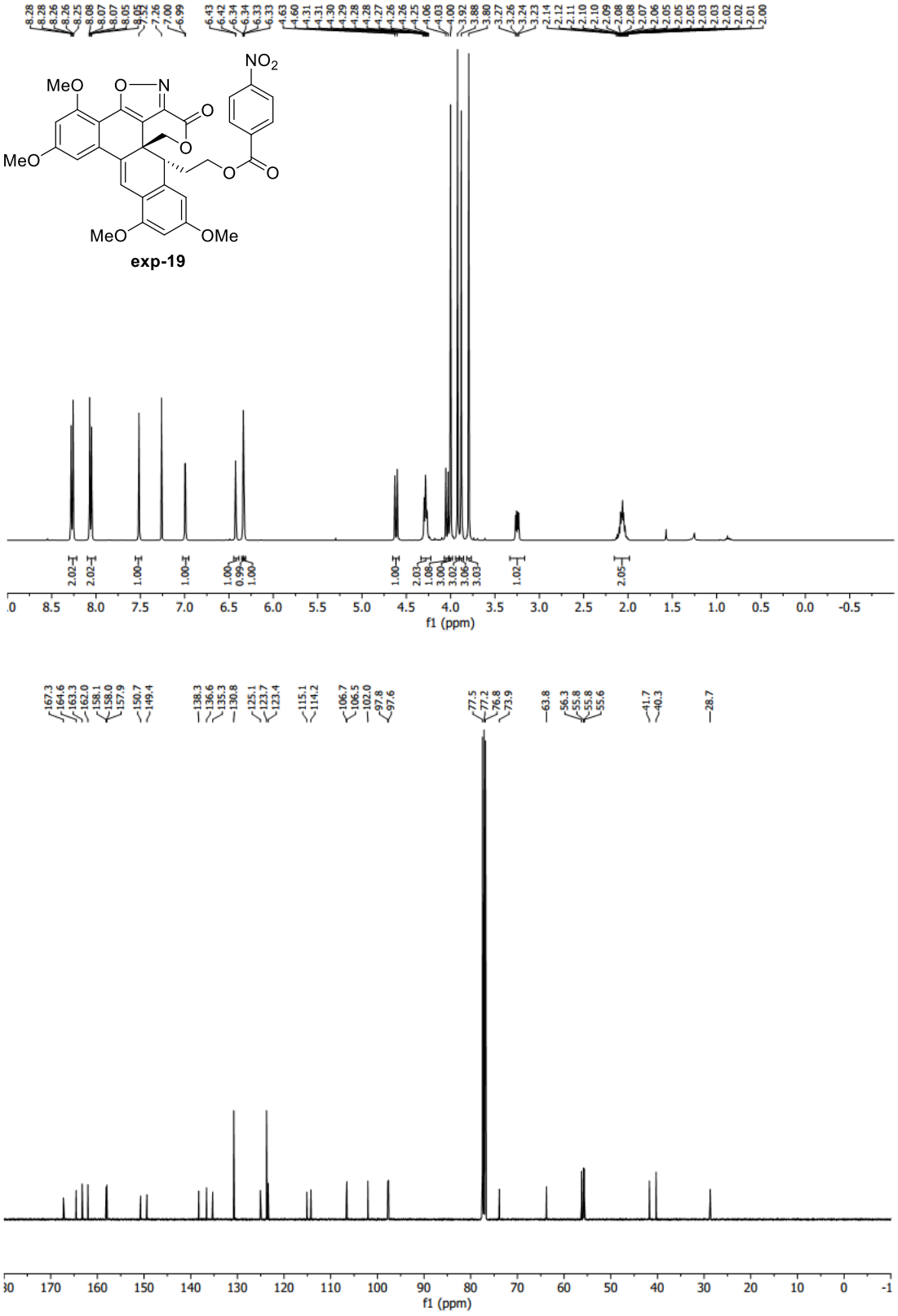


Compound **168** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

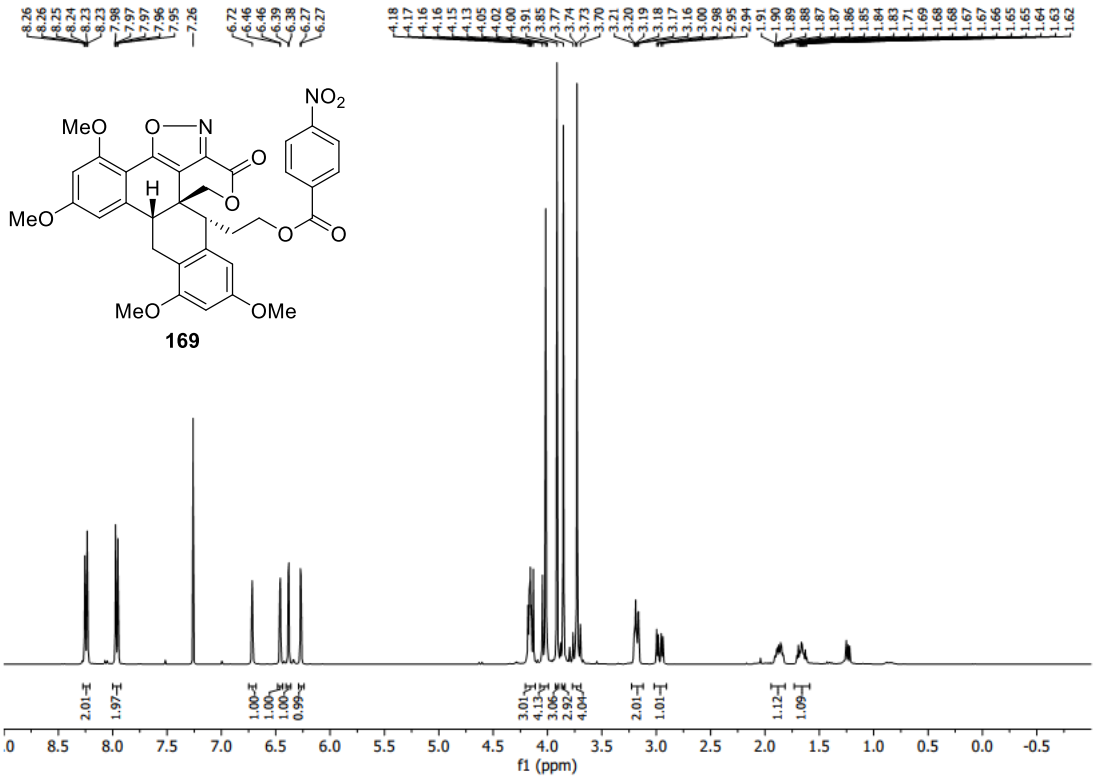


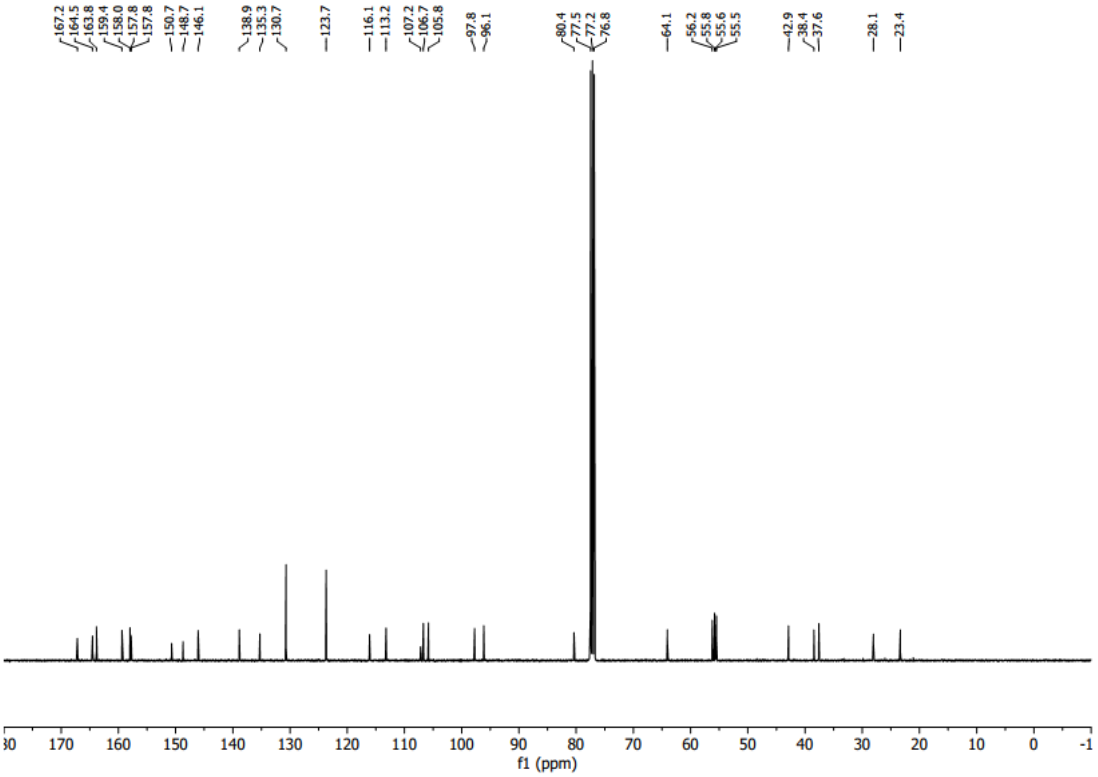


Compound **exp-19** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

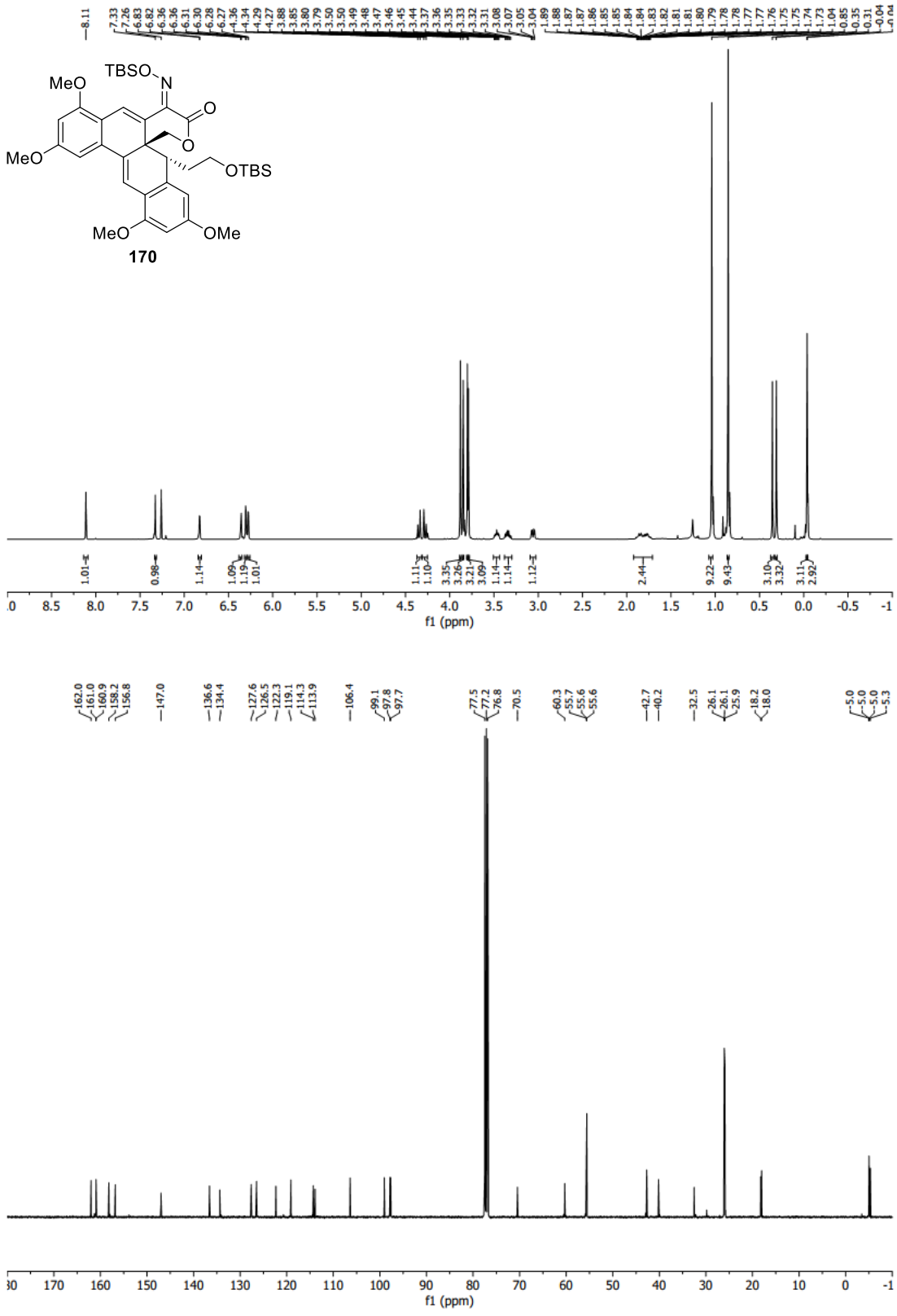


Compound **169** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

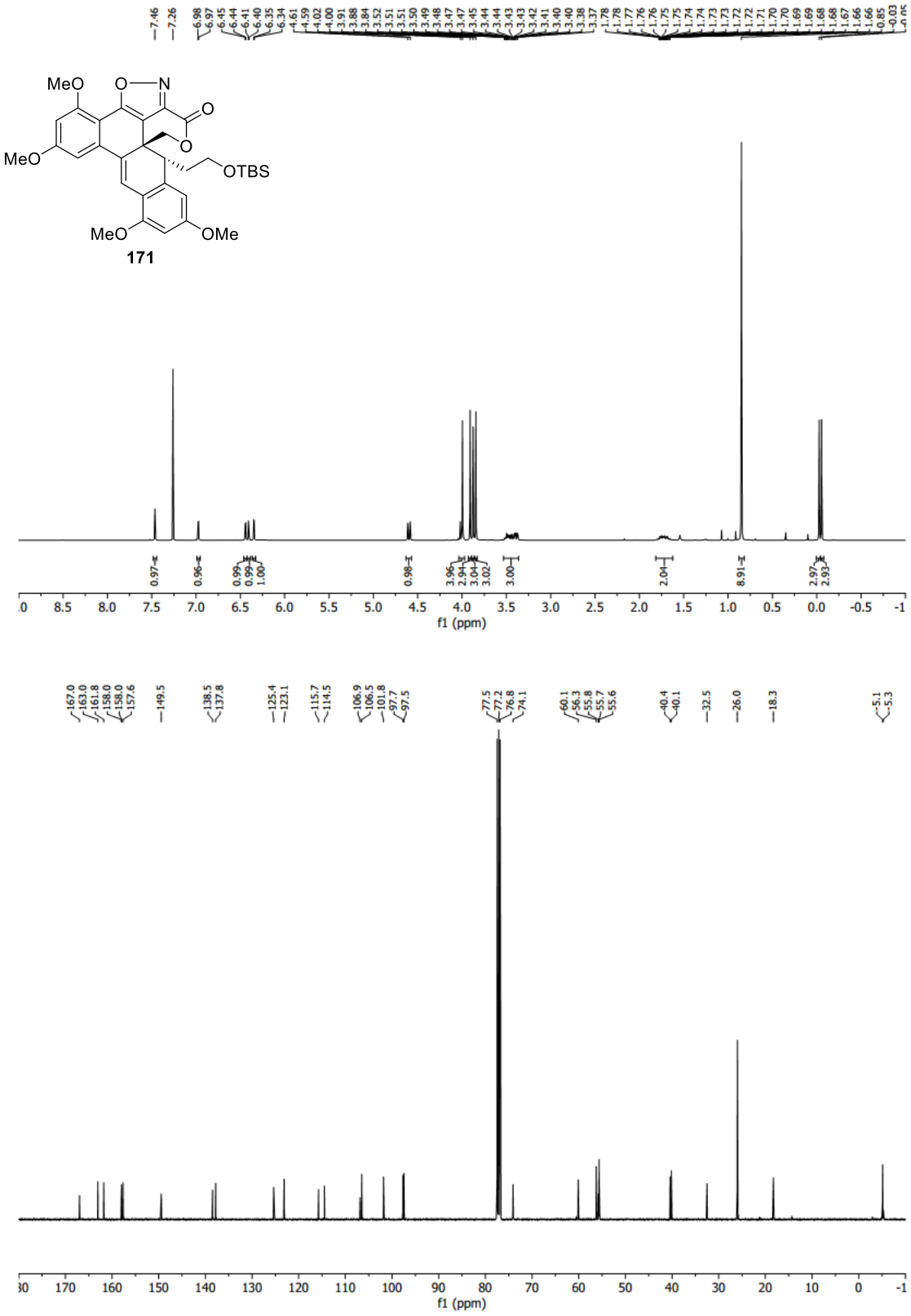




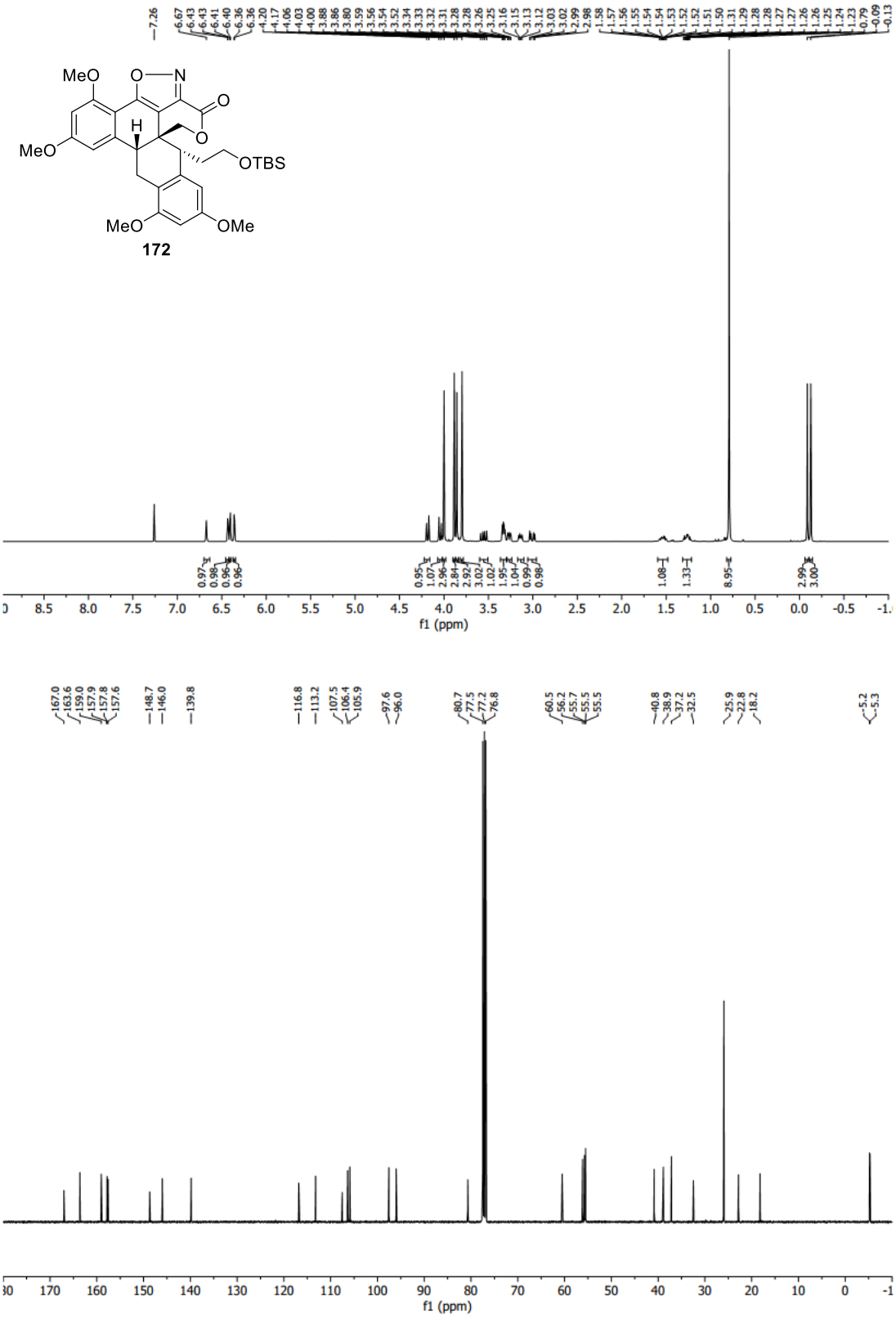
Compound **170** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



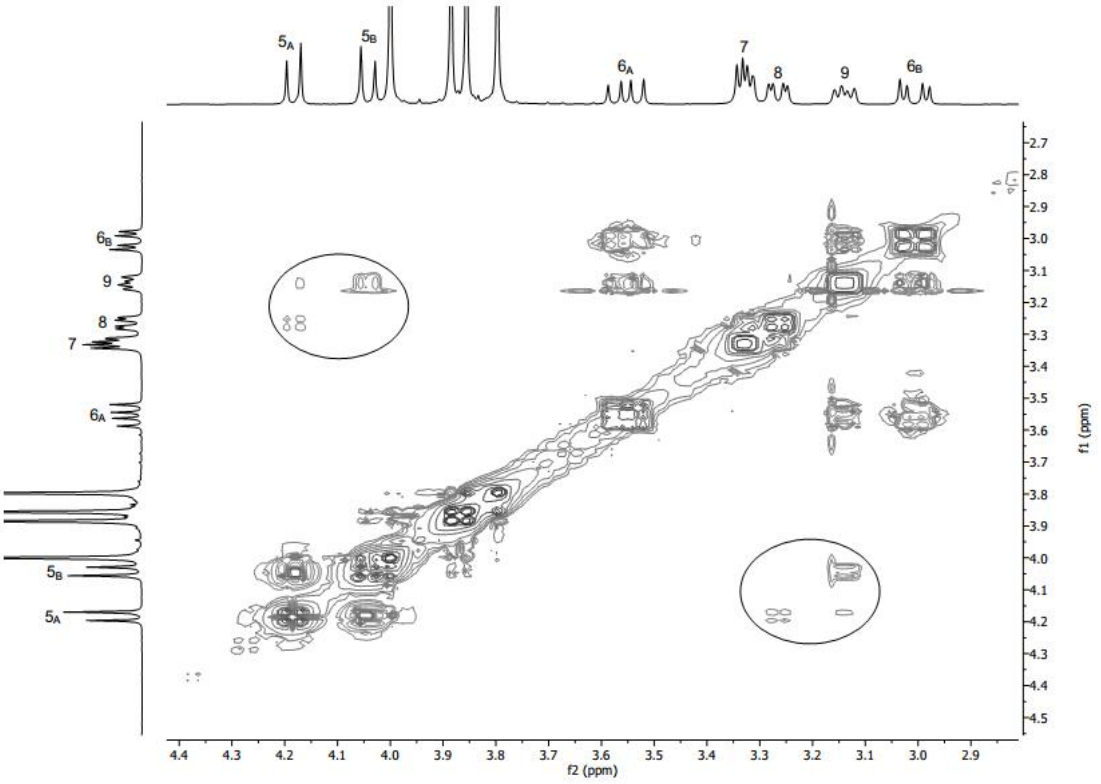
Compound **171** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

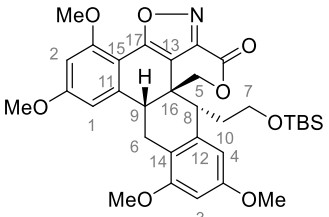


Compound **172** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



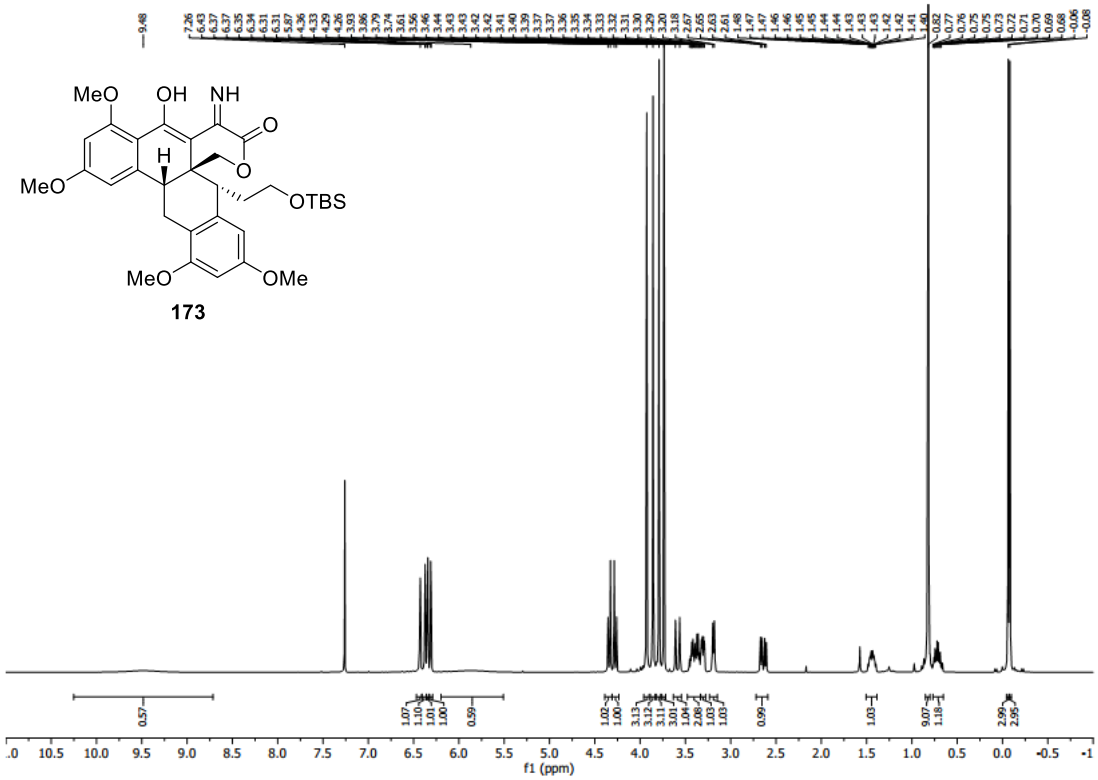
Compound **172** – **NOESY** (400 MHz) in $CDCl_3$

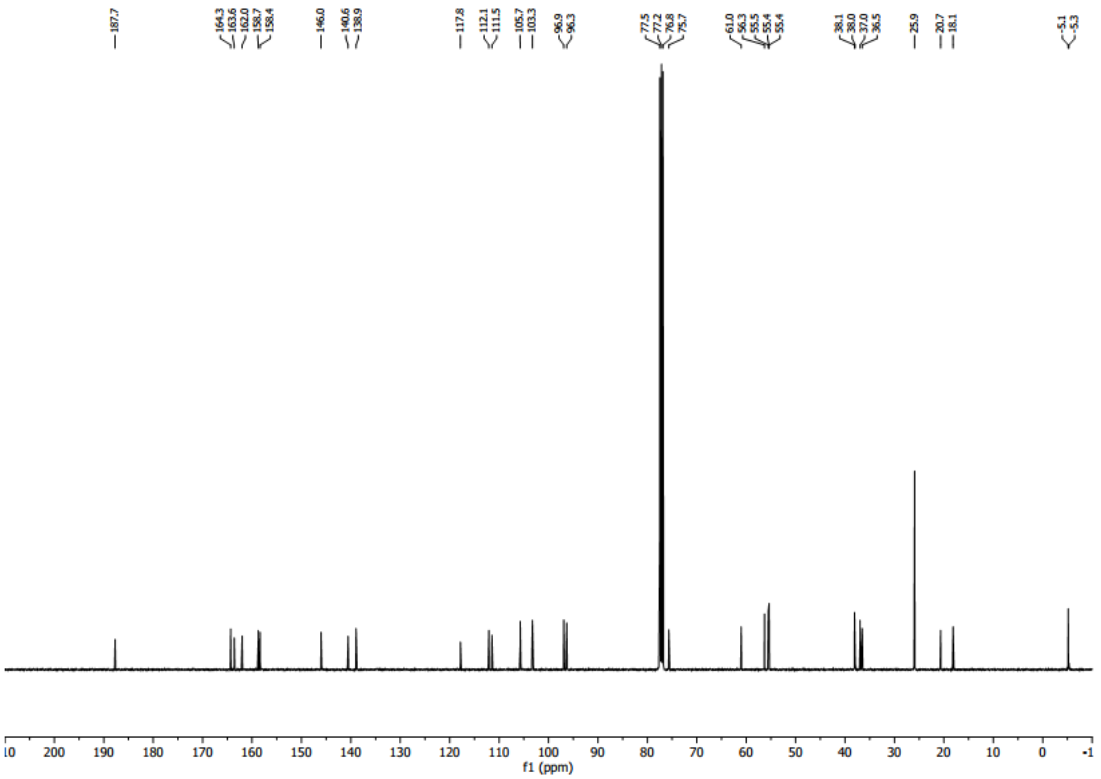




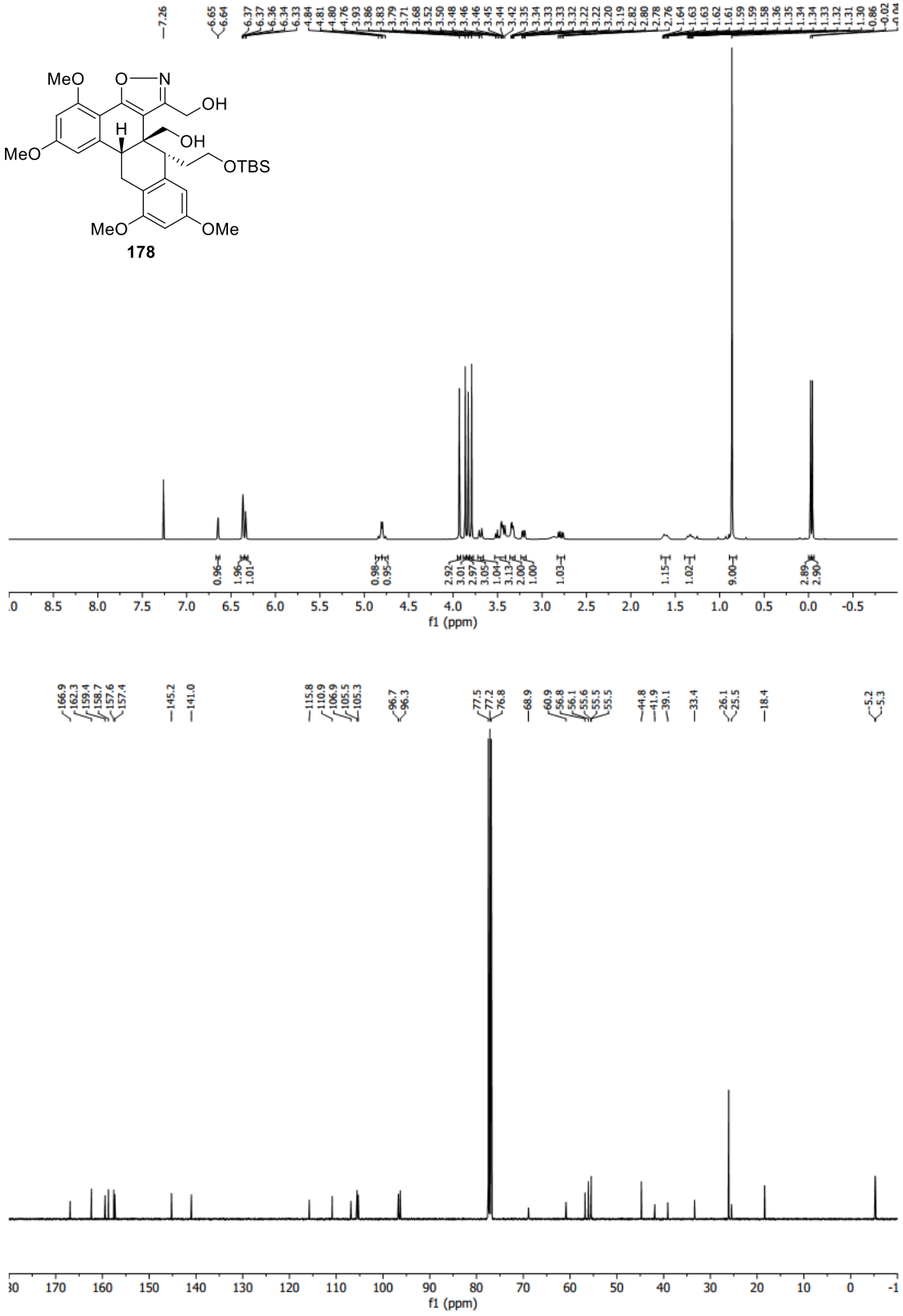
172

Compound **173** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

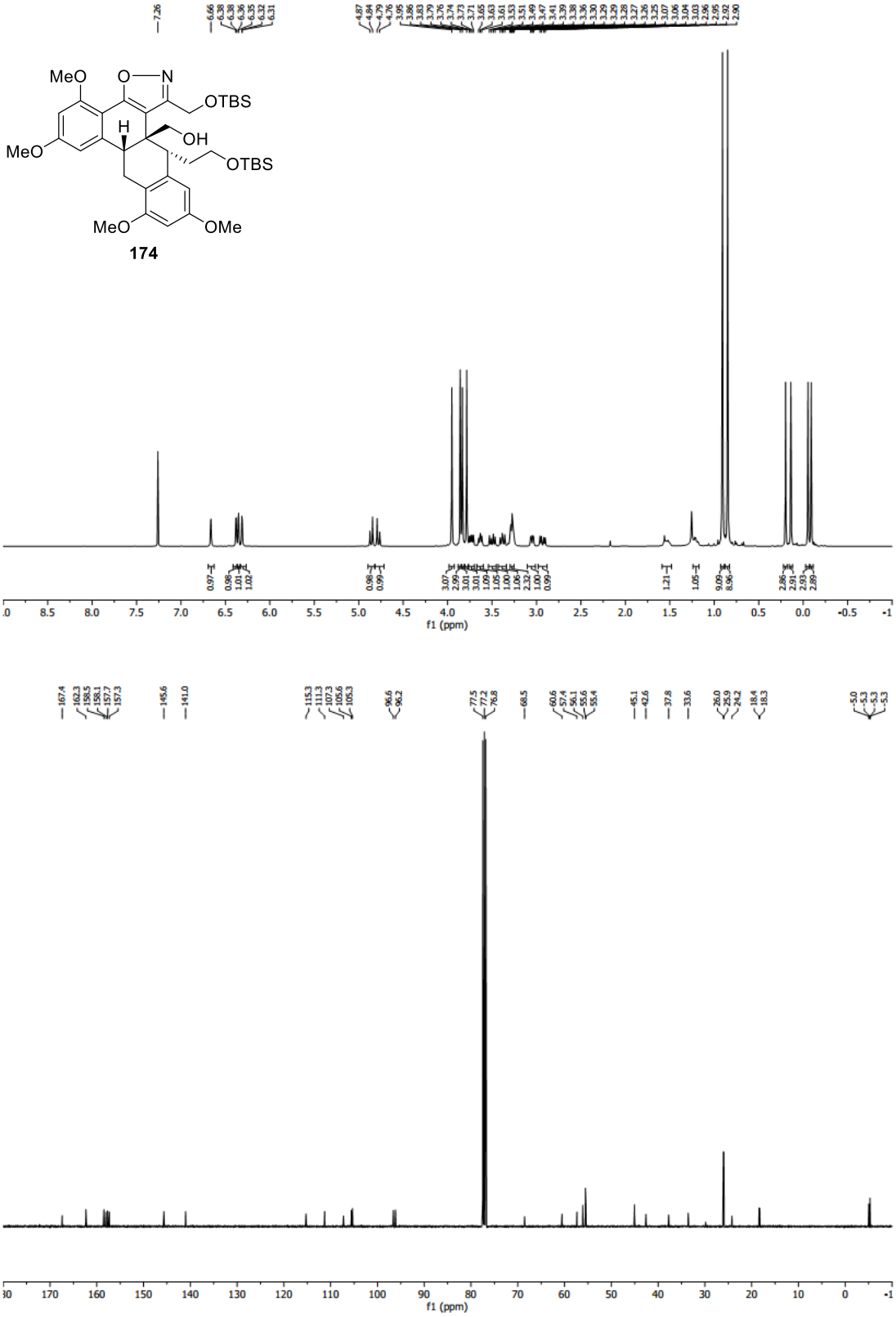




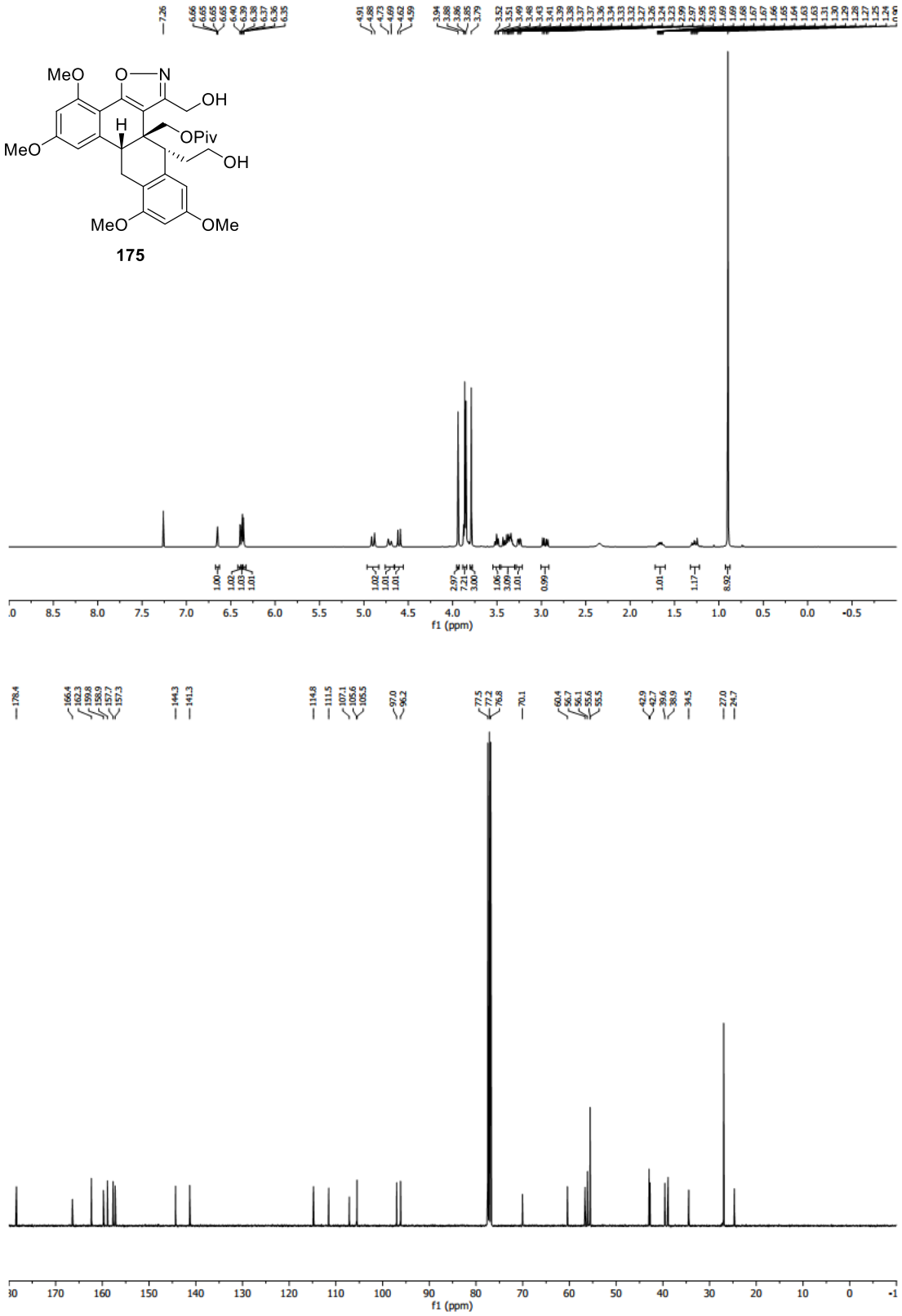
Compound **178** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



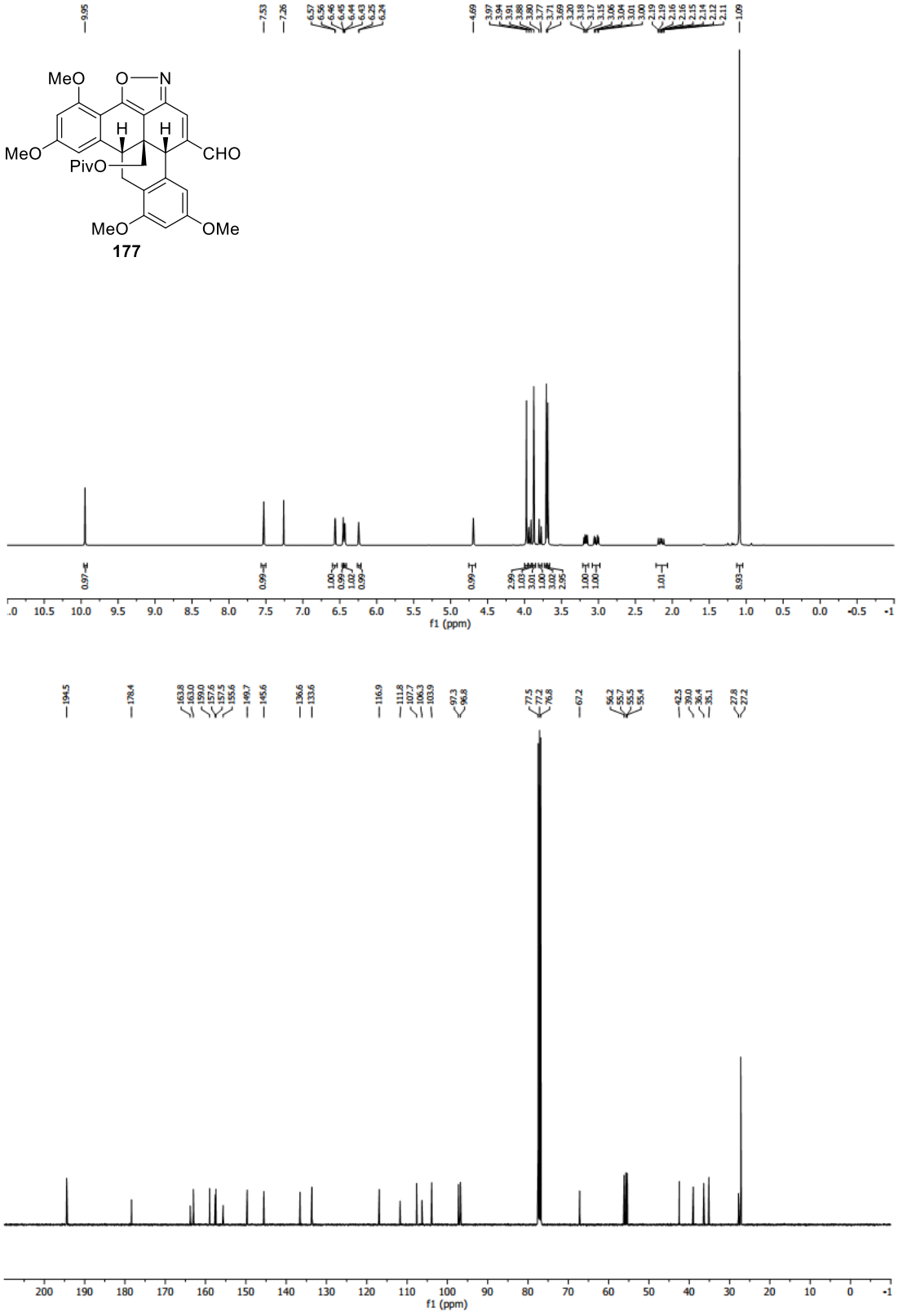
Compound **174** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



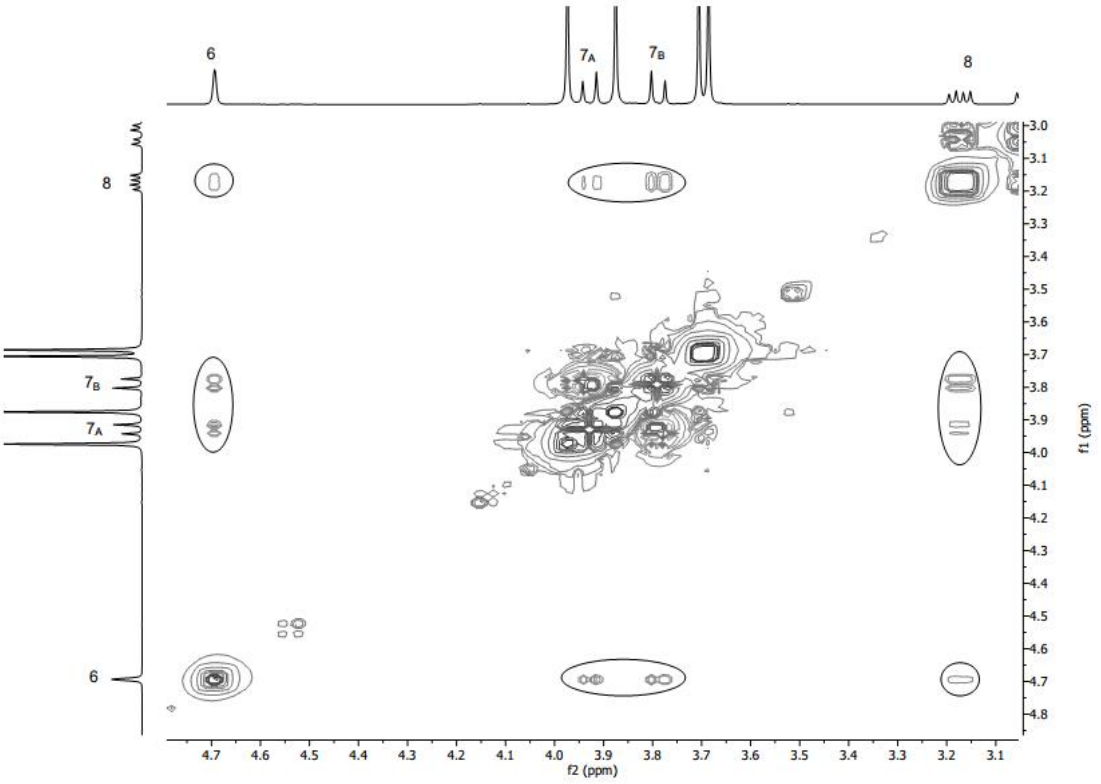
Compound **175** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

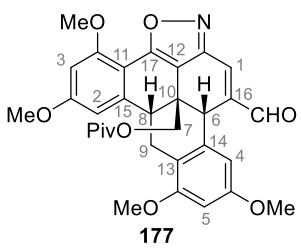


Compound **177** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

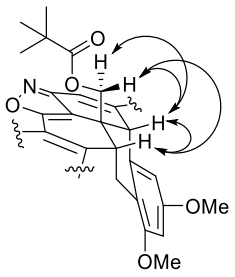


Compound **177** – **NOESY** (400 MHz) in $CDCl_3$

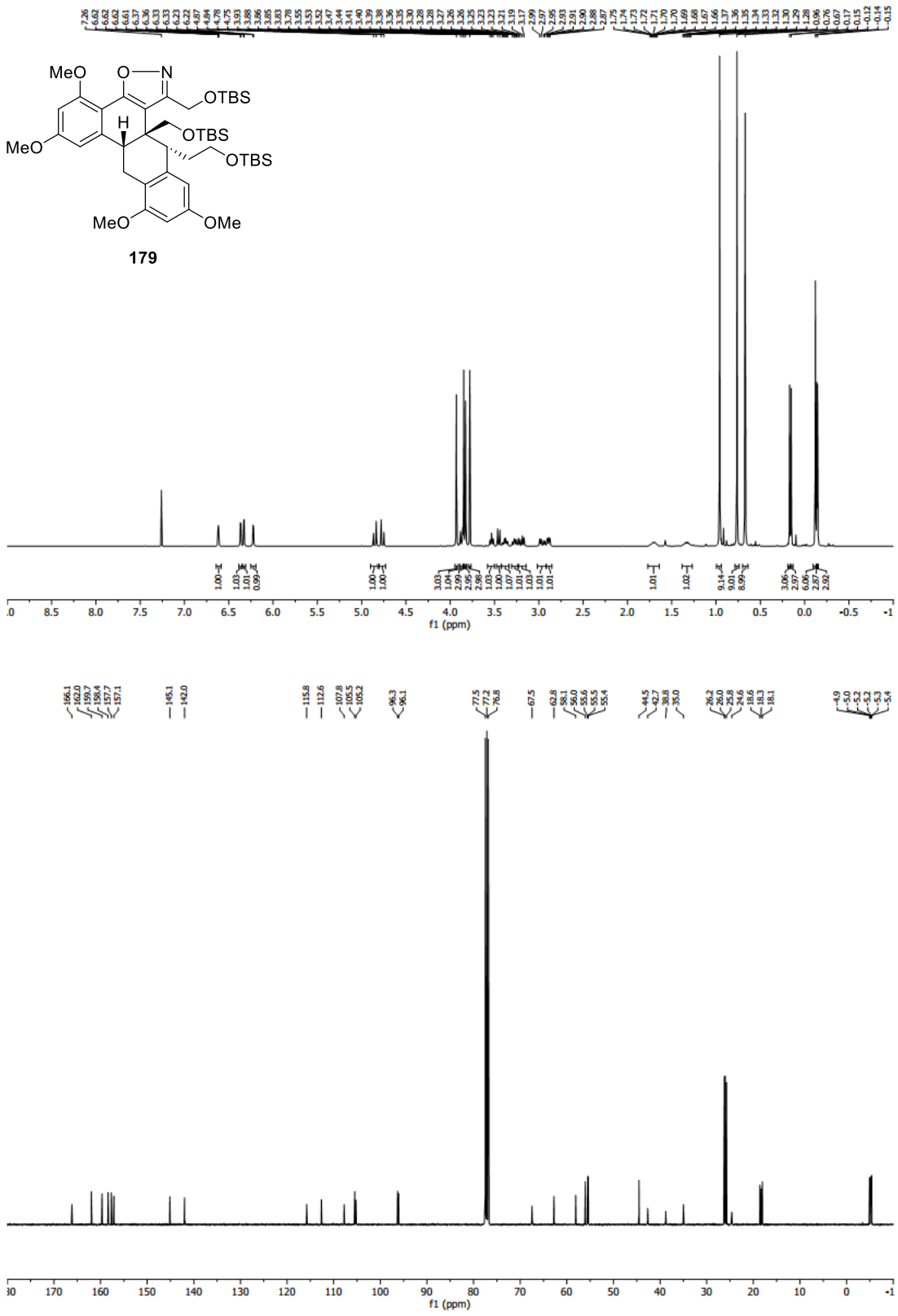




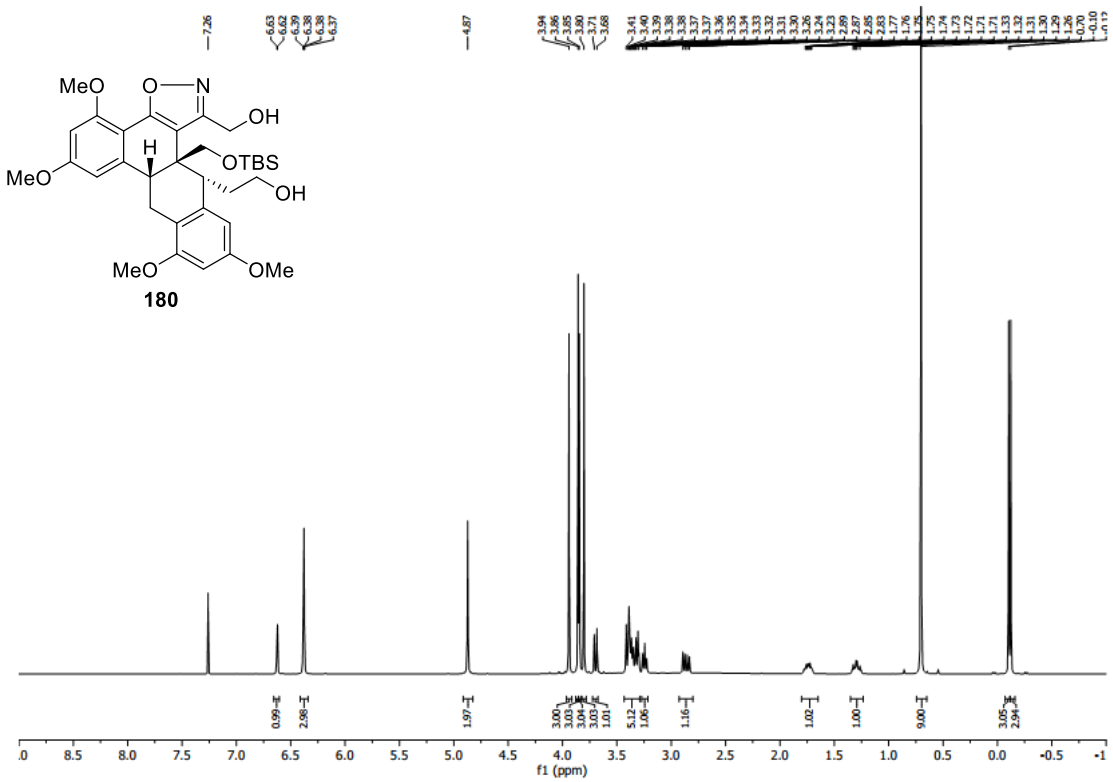
177

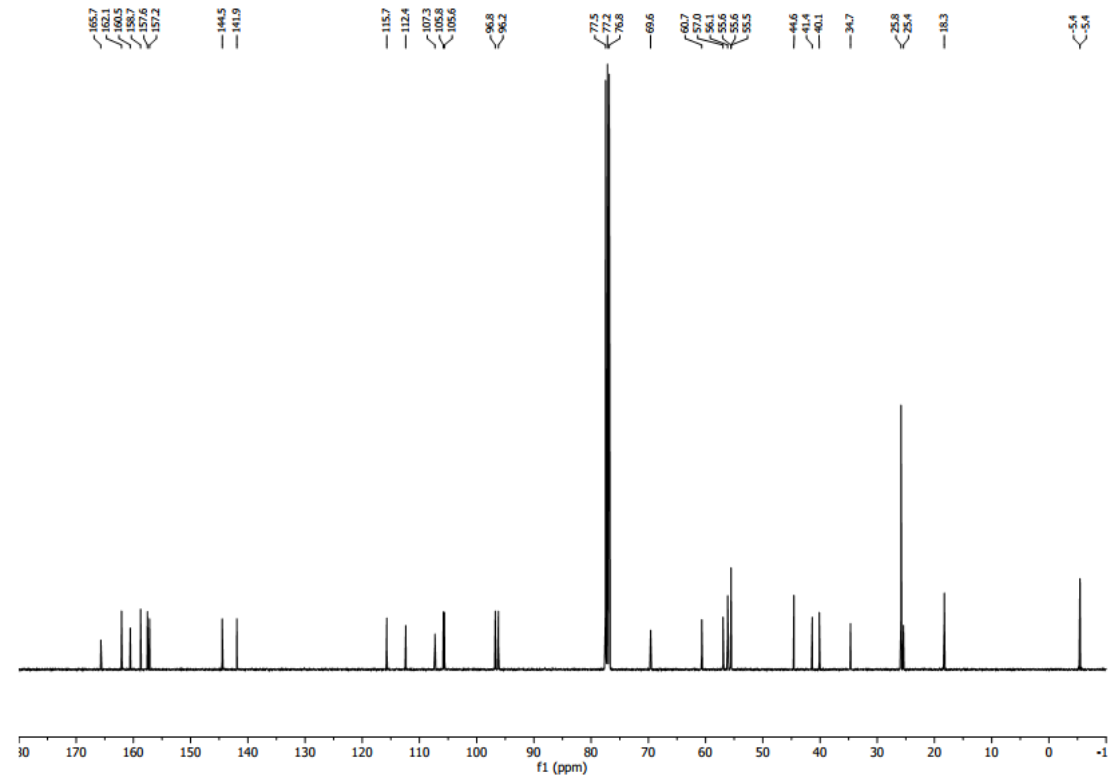


Compound **179** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

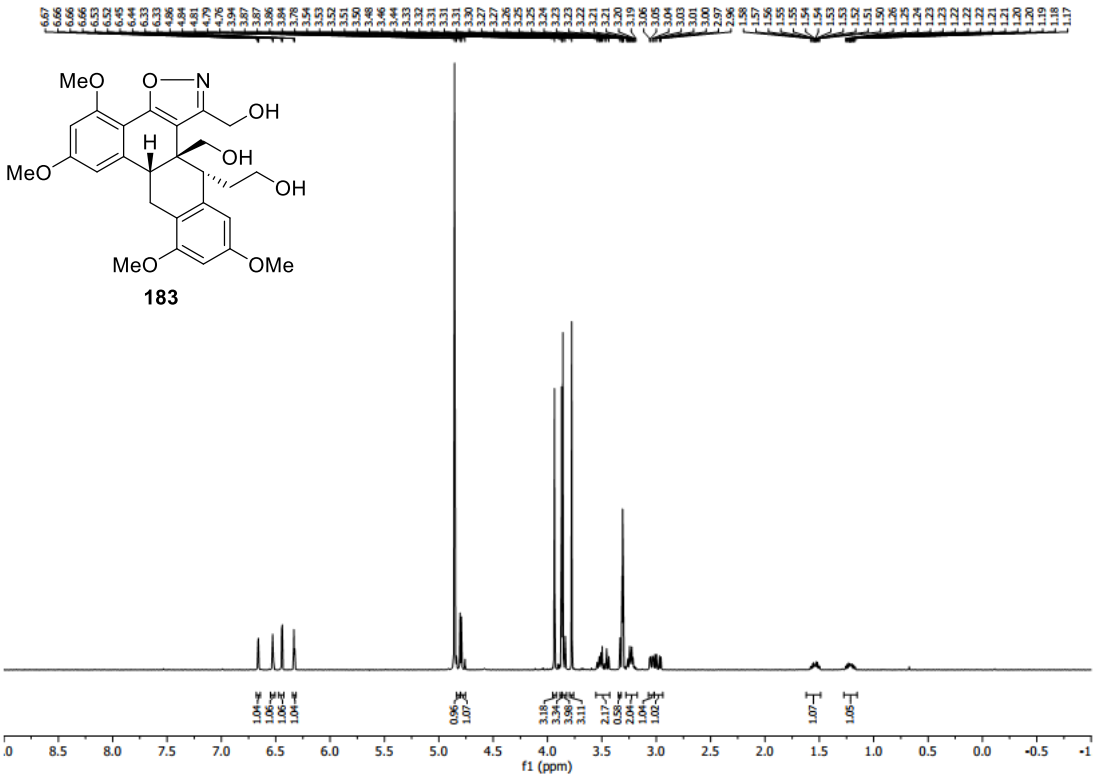


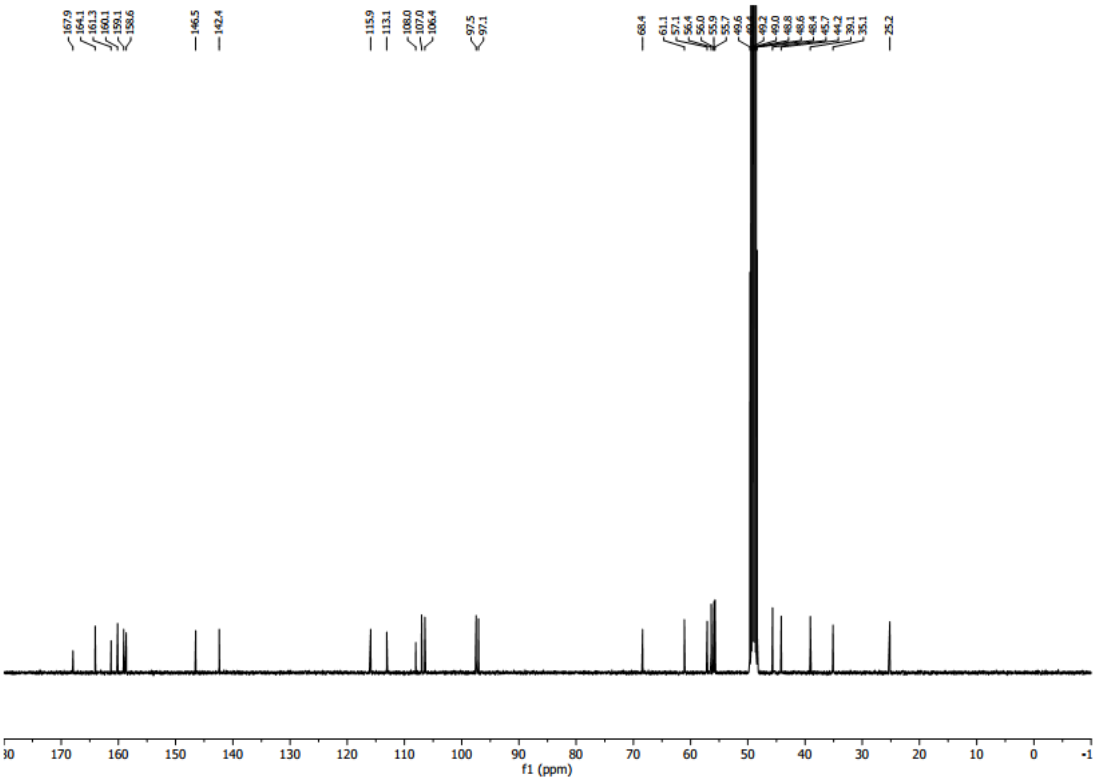
Compound **180** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



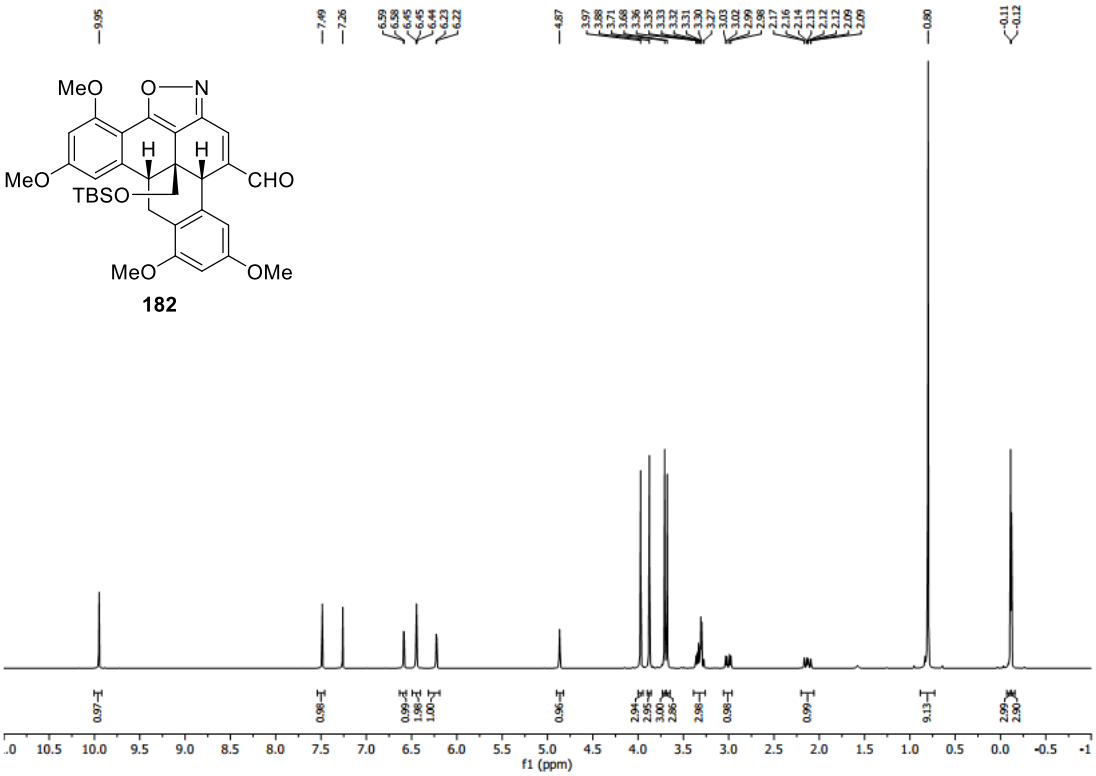


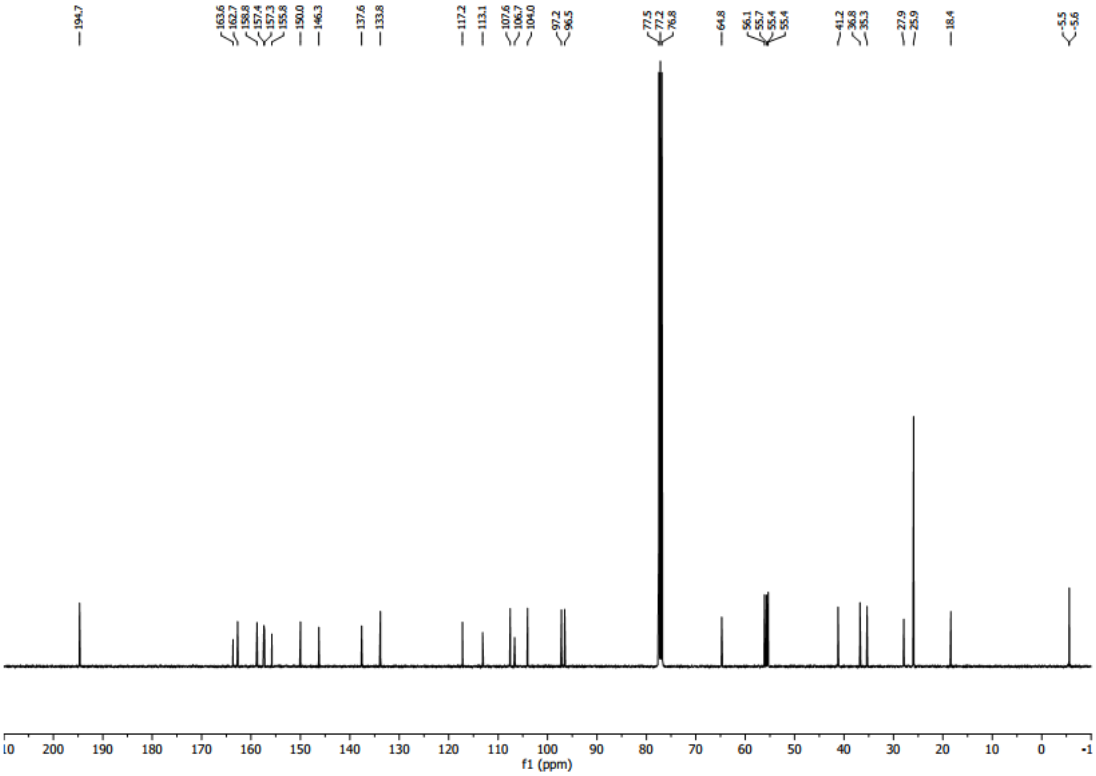
Compound **183** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in CD_3OD



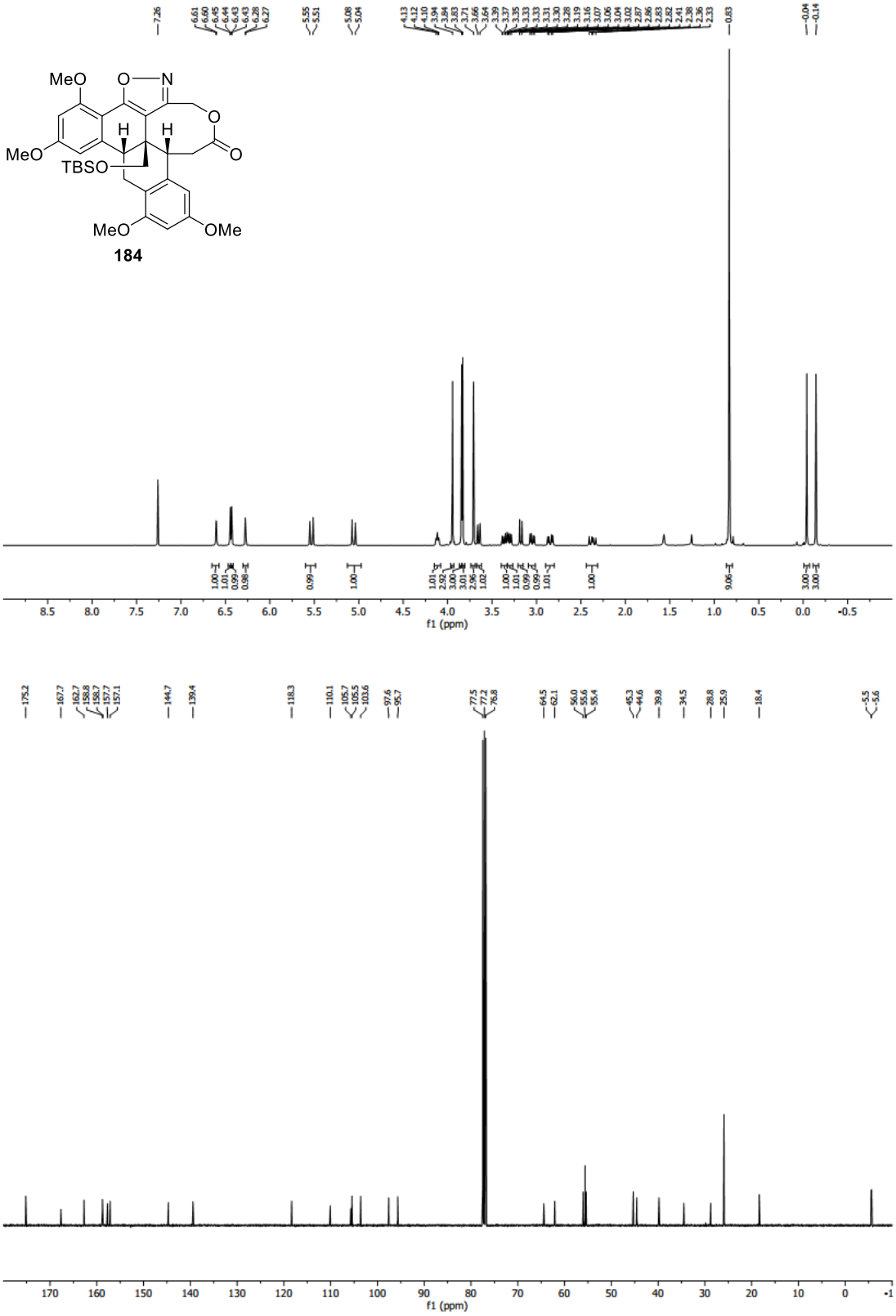


Compound **182** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

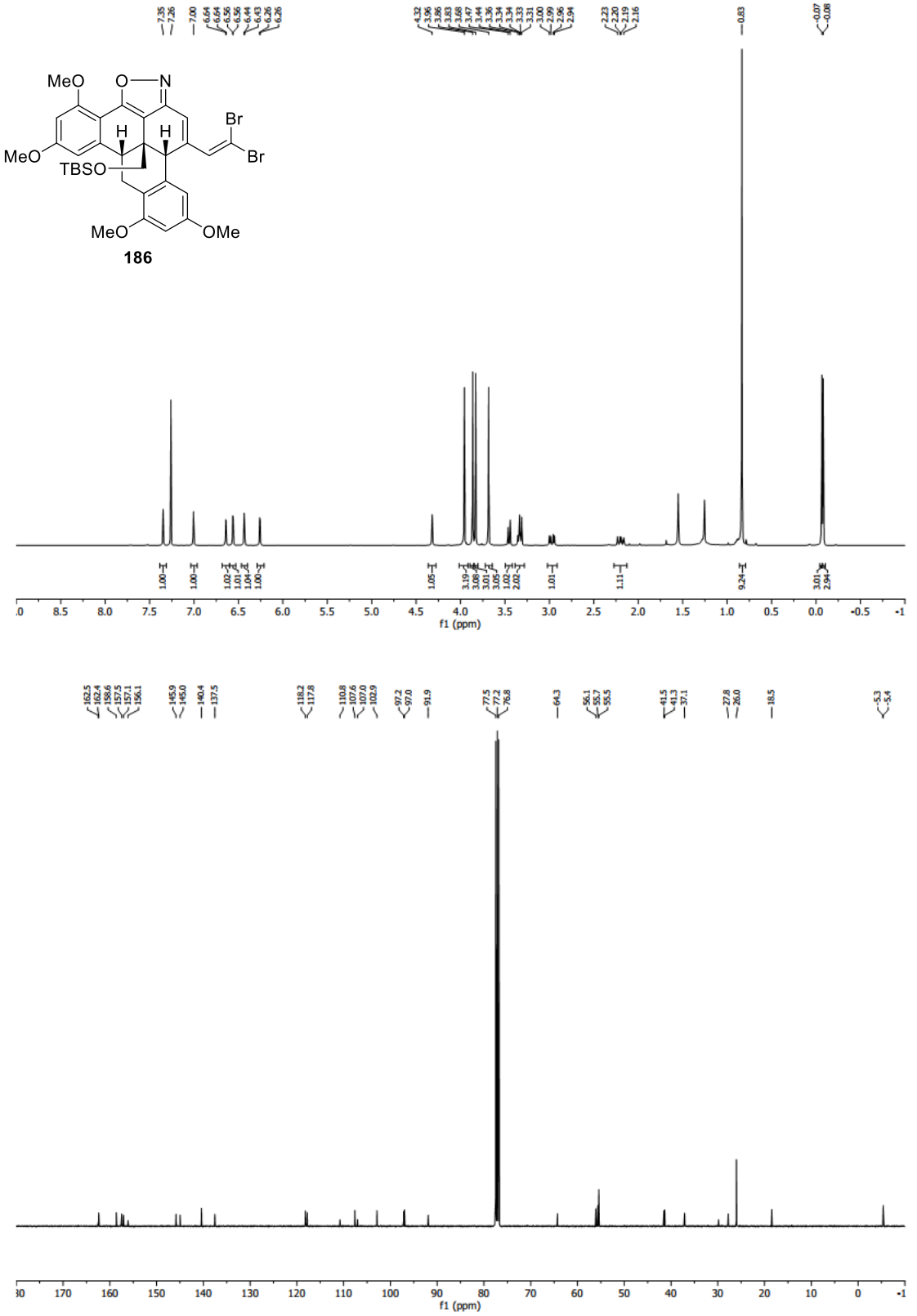




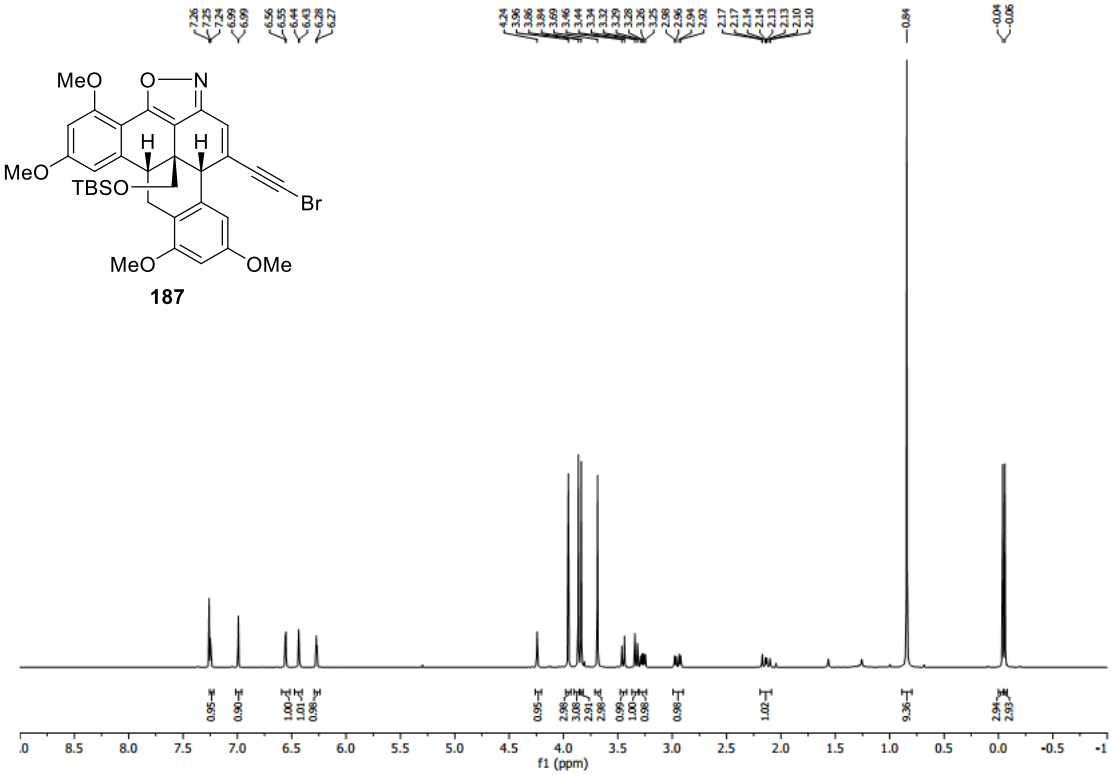
Compound **184** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



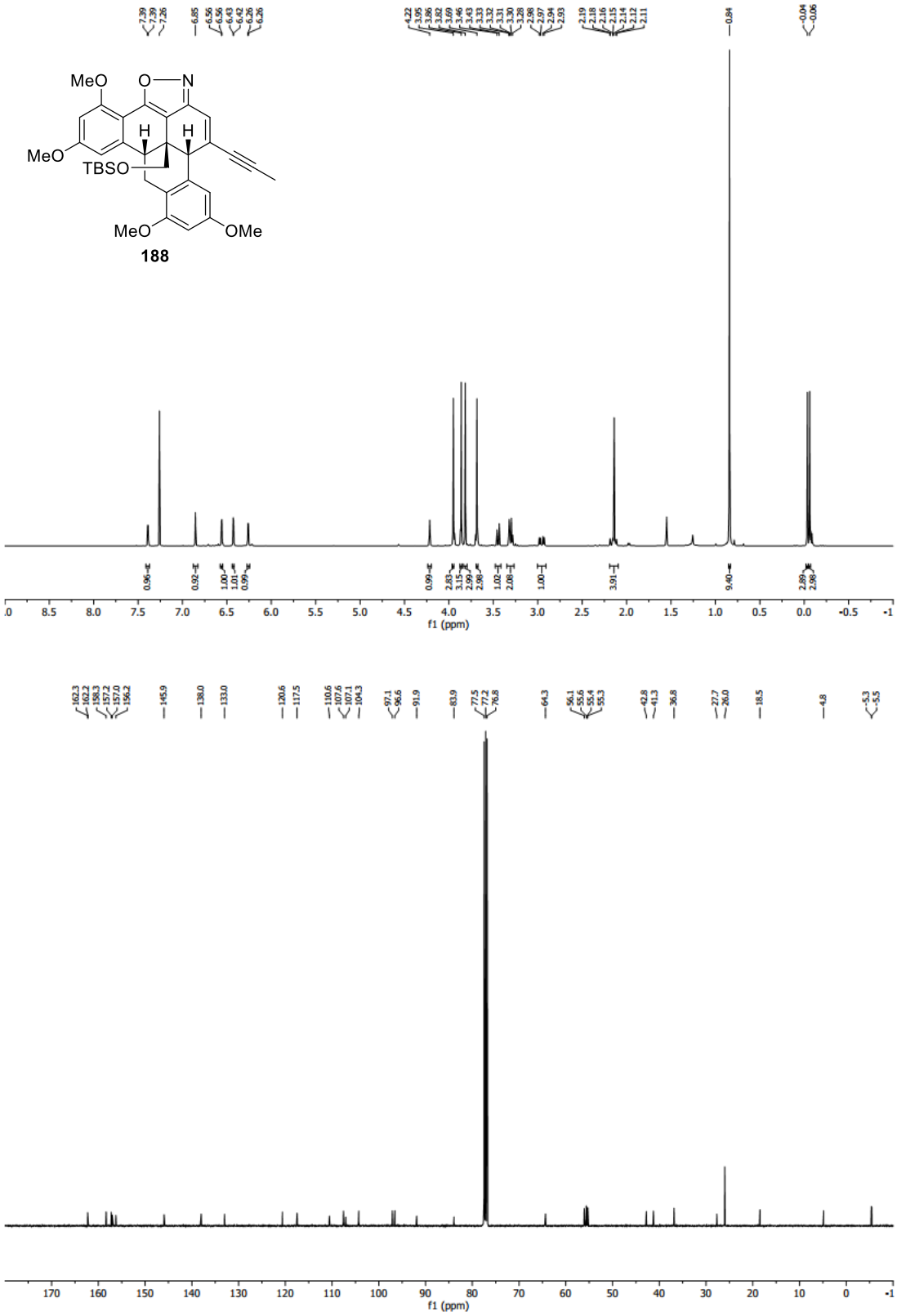
Compound **186** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



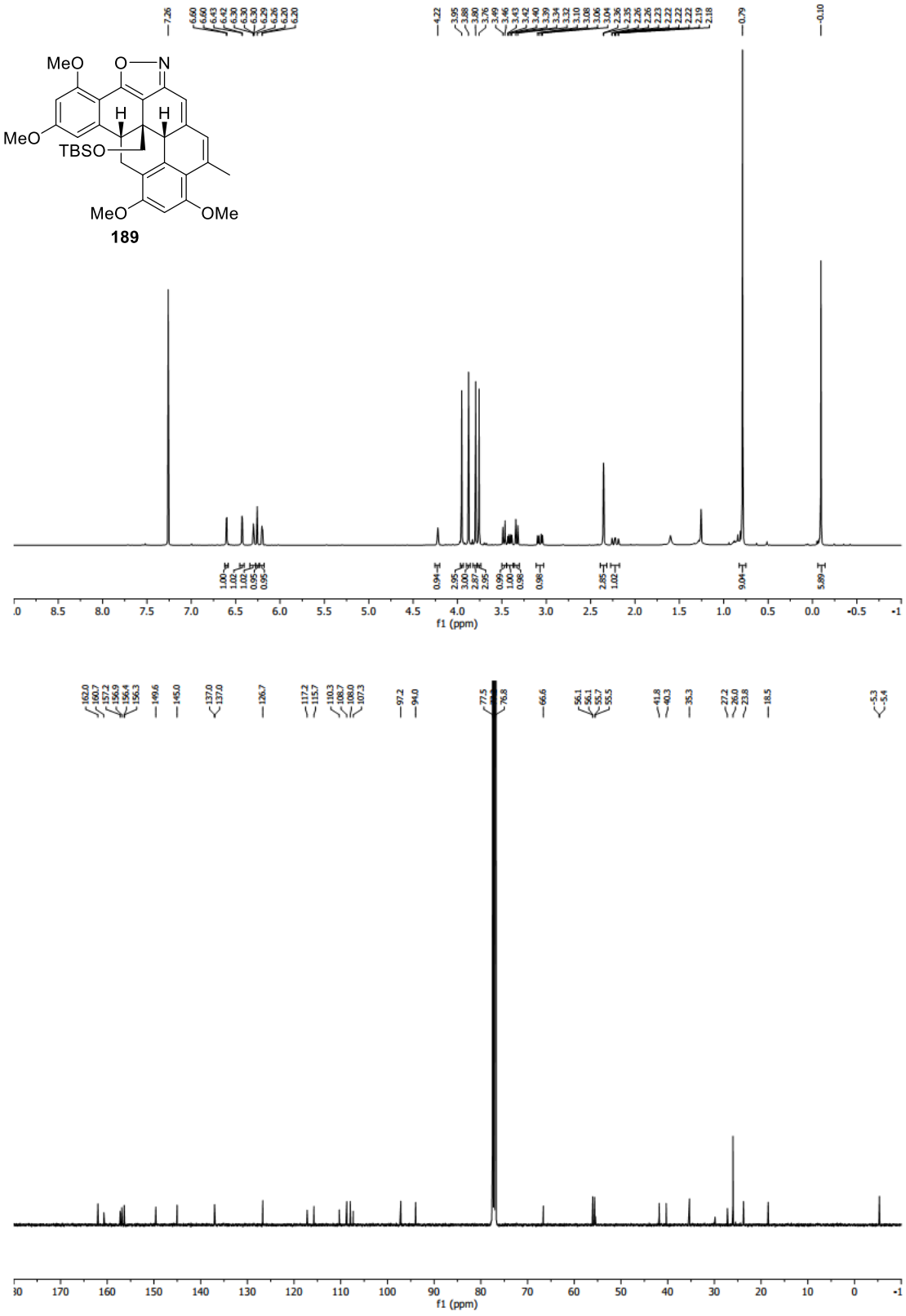
Compound **187** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



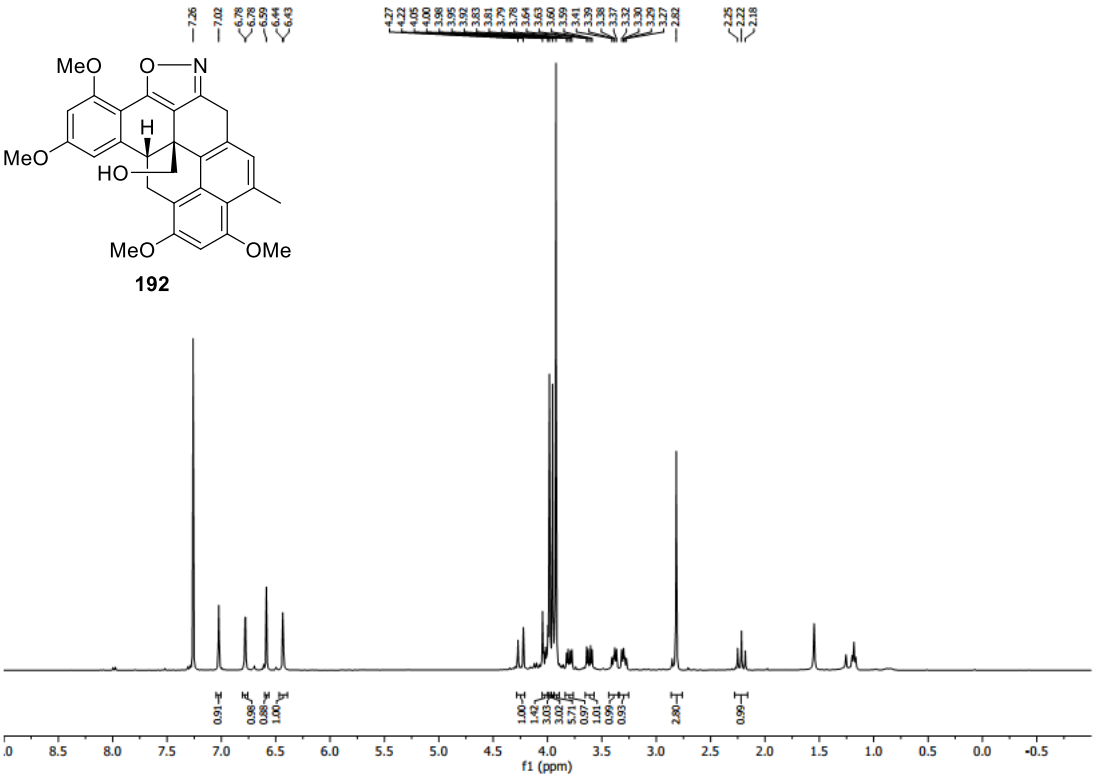
Compound **188** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

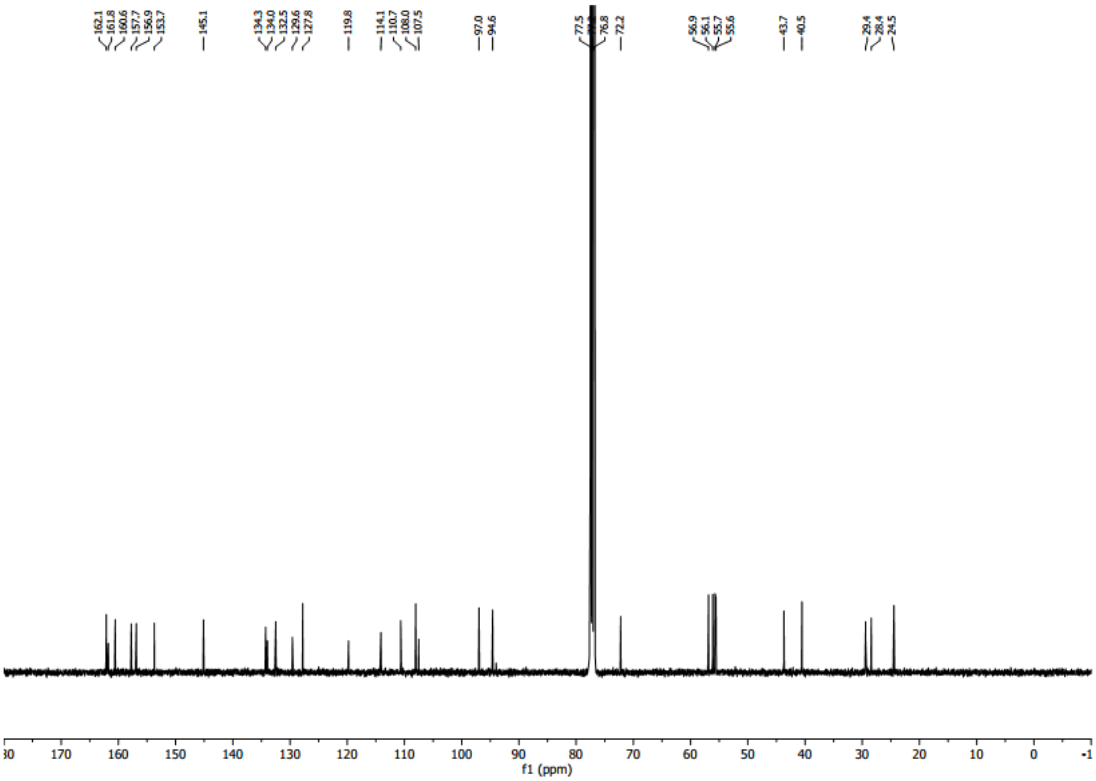


Compound **189** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

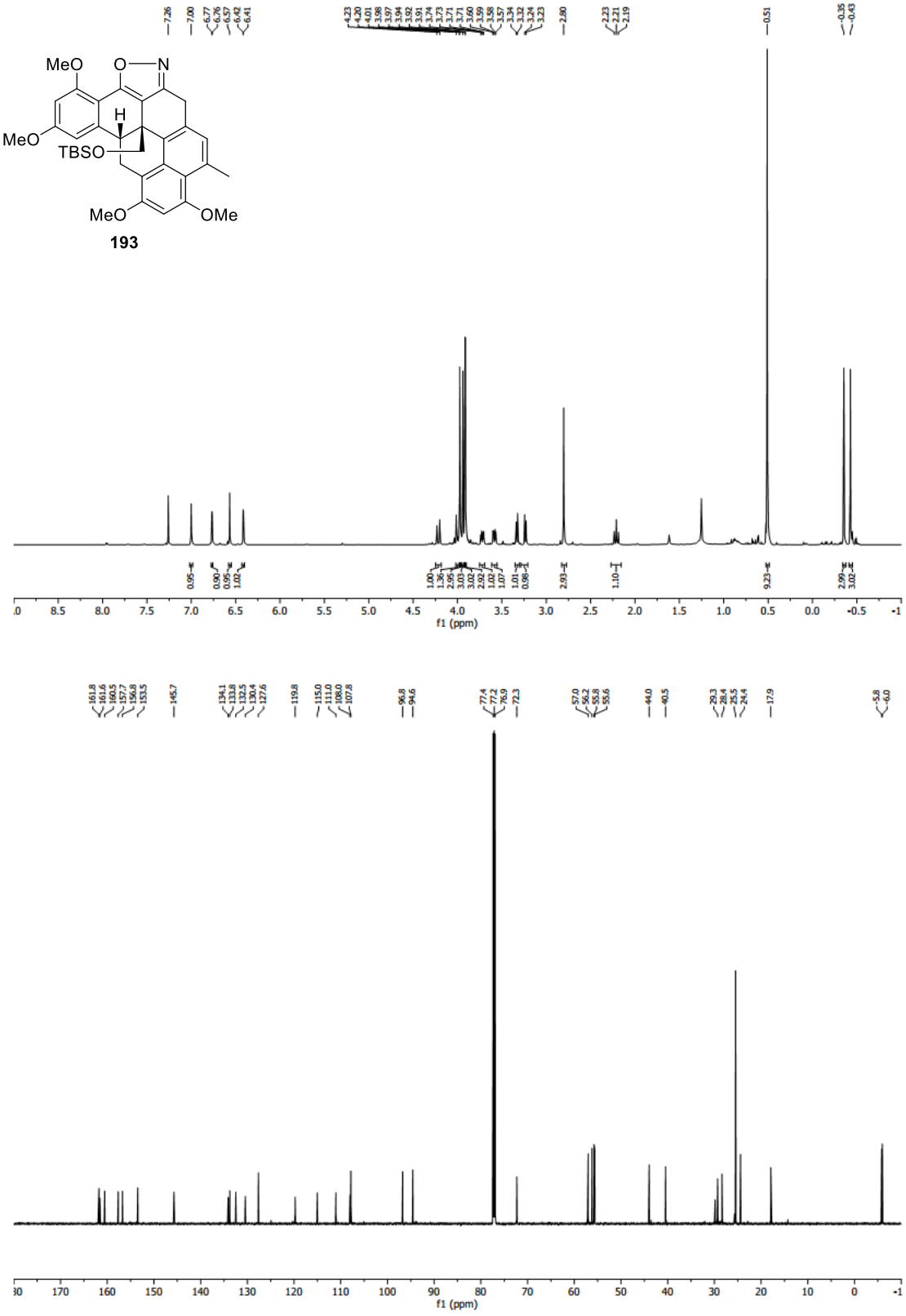


Compound **192** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

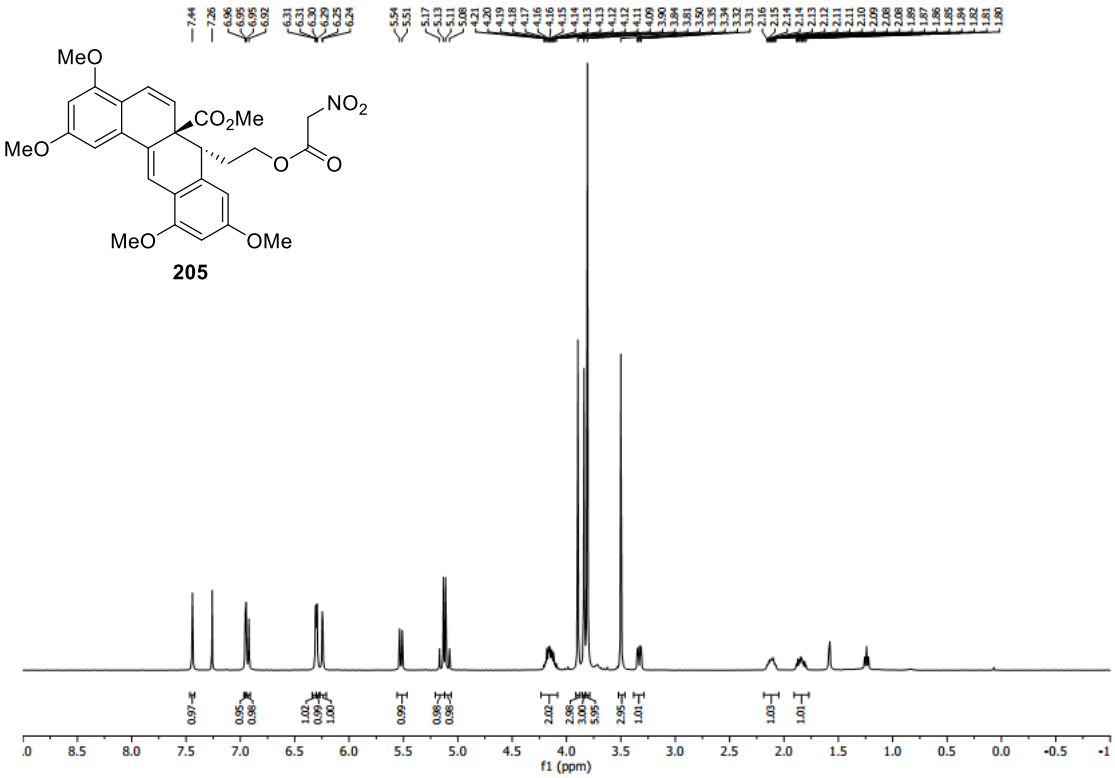


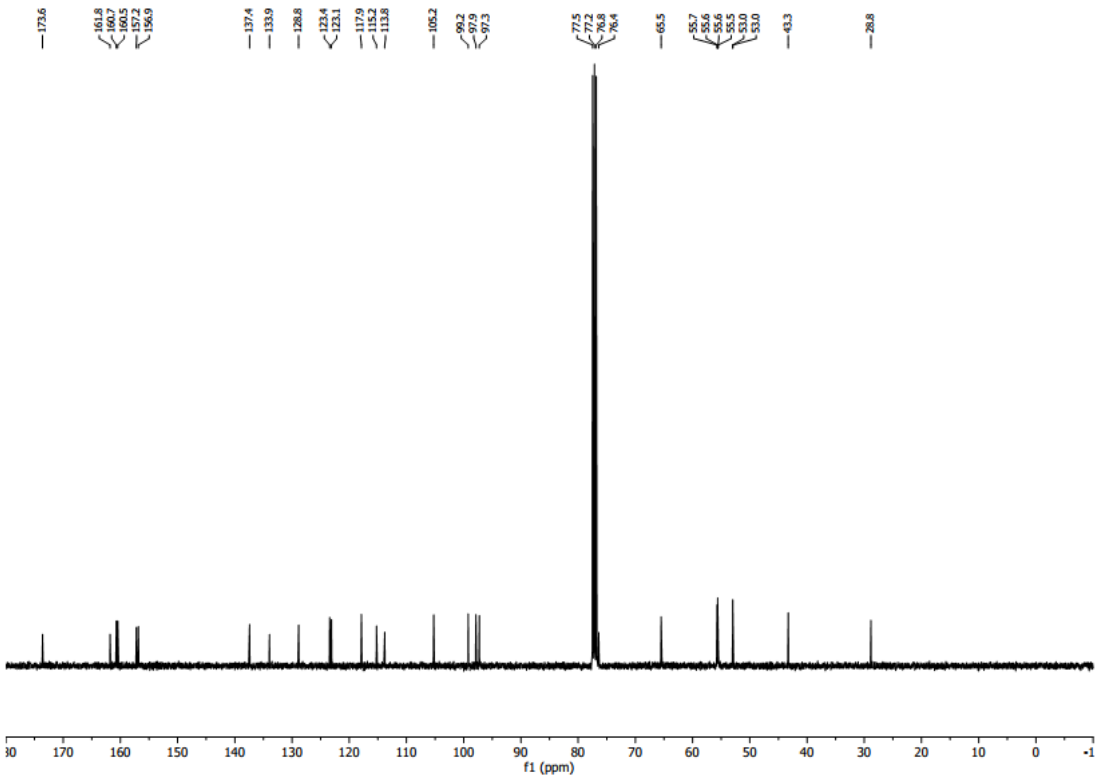


Compound **193** – **^{1}H-NMR** (600 MHz) and **^{13}C-NMR** (150 MHz) in $CDCl_3$

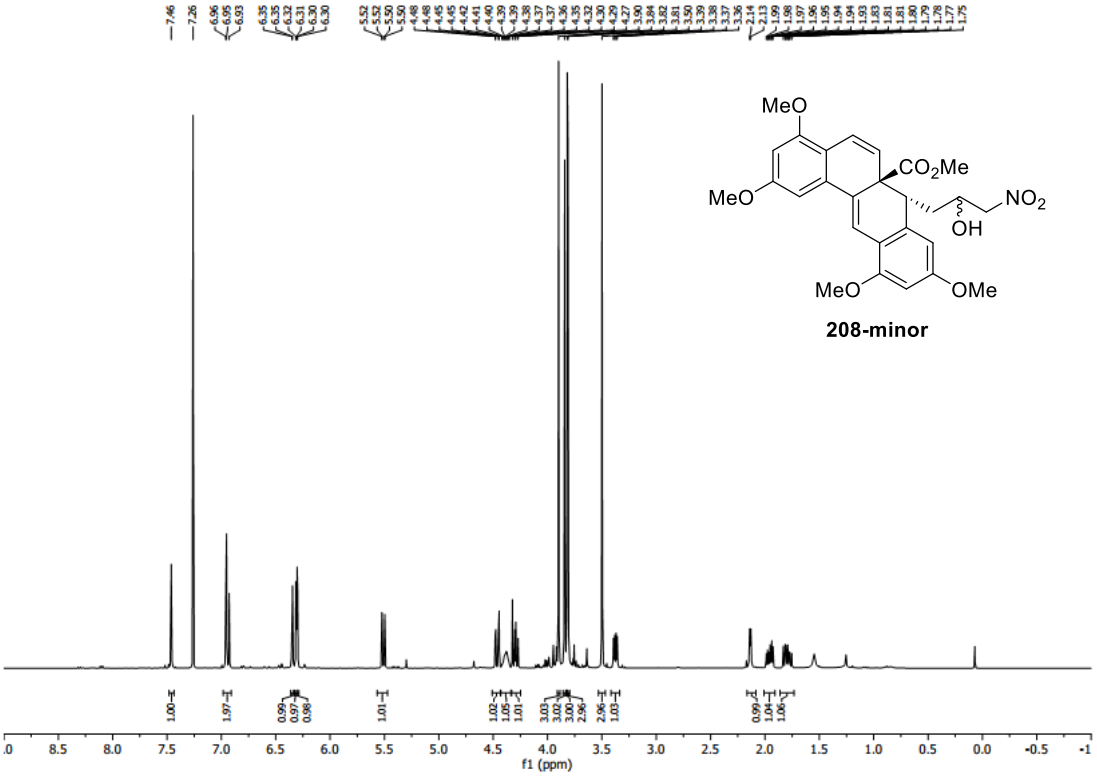


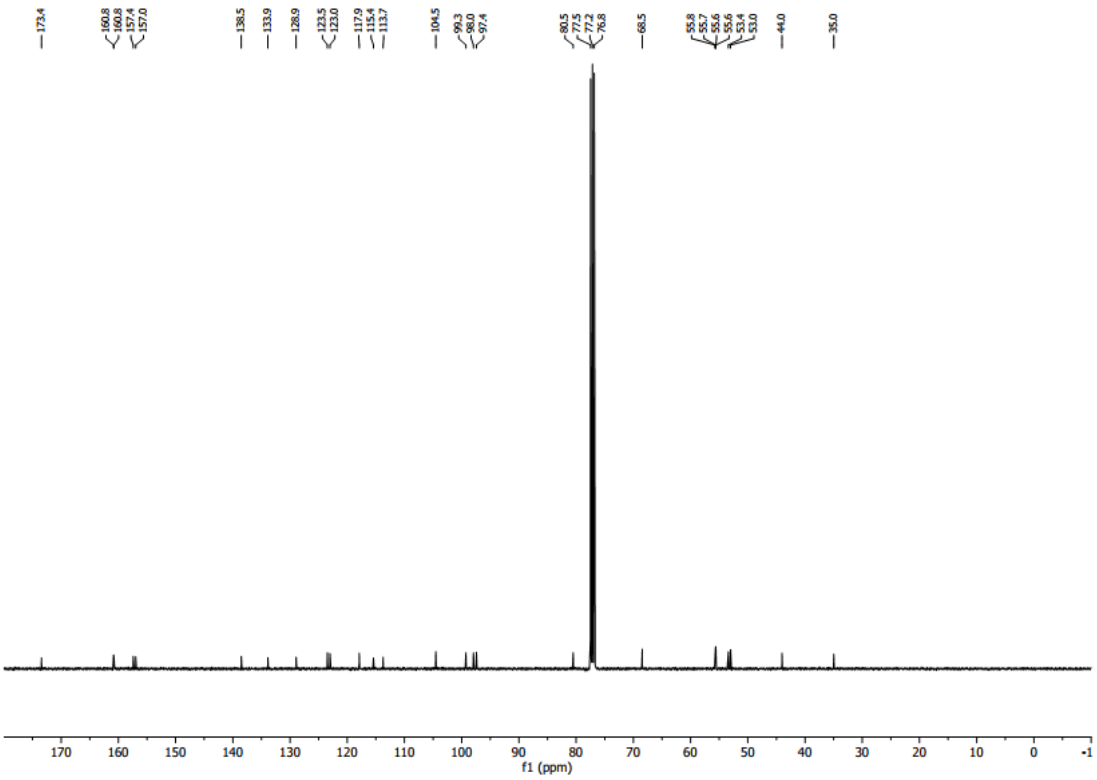
Compound **205** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



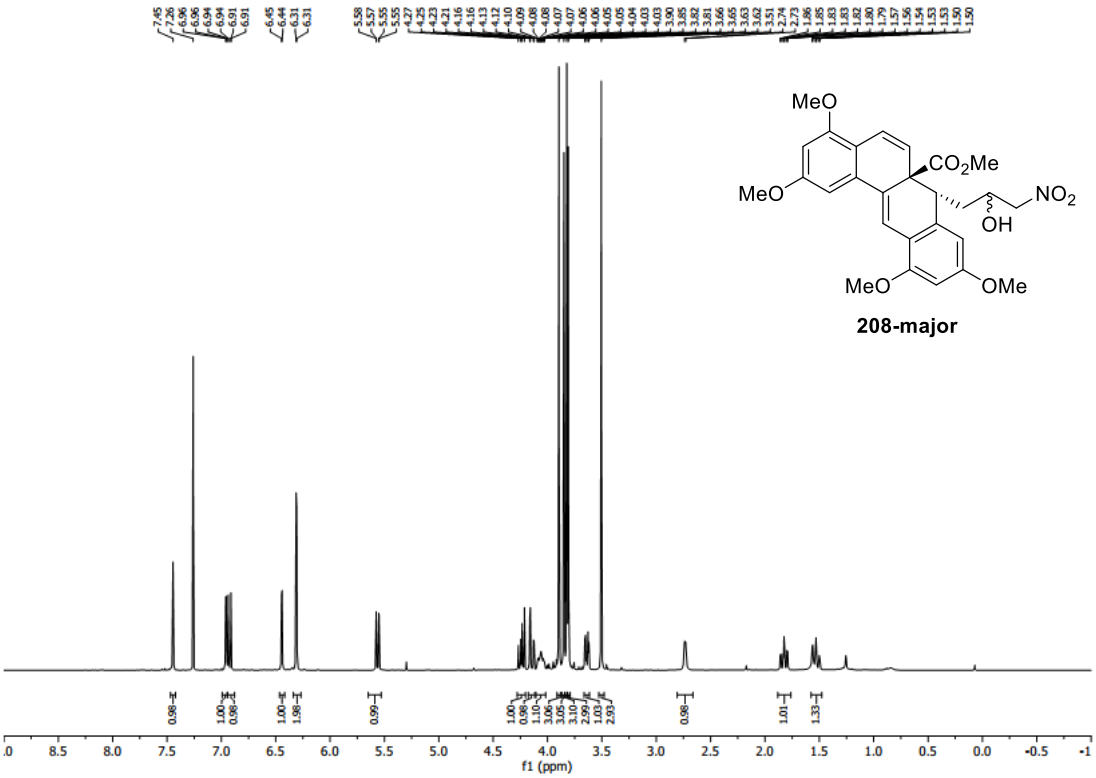


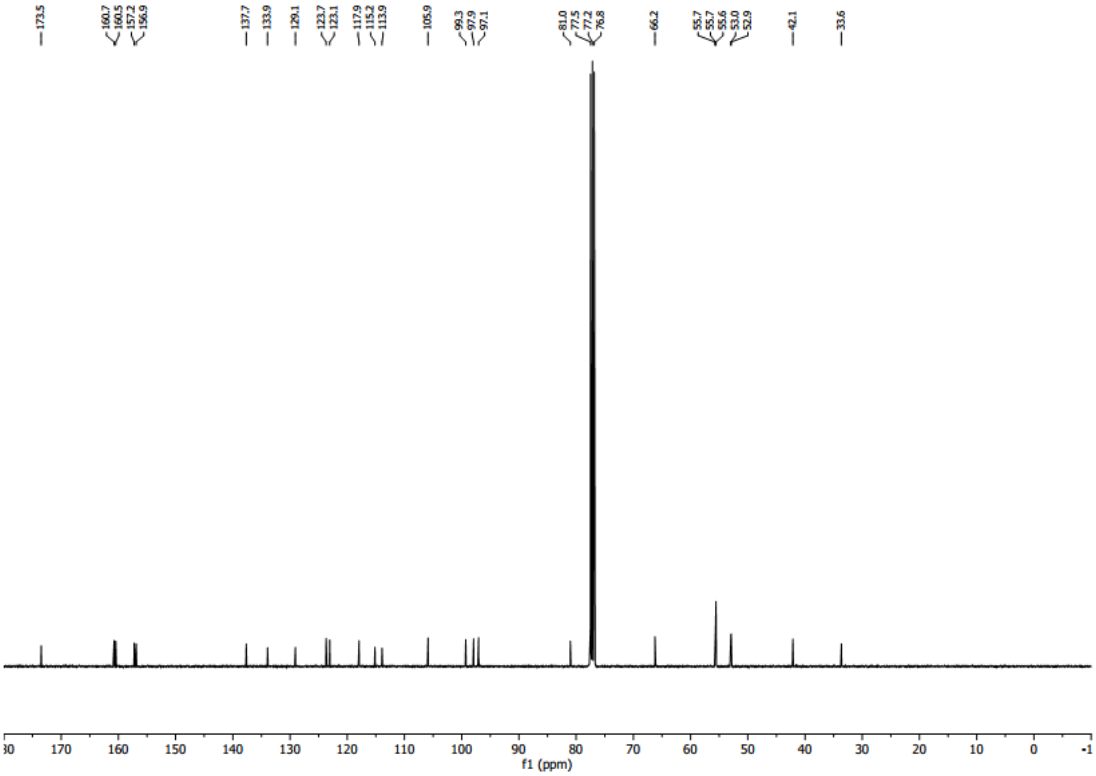
Compound **208-minor** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



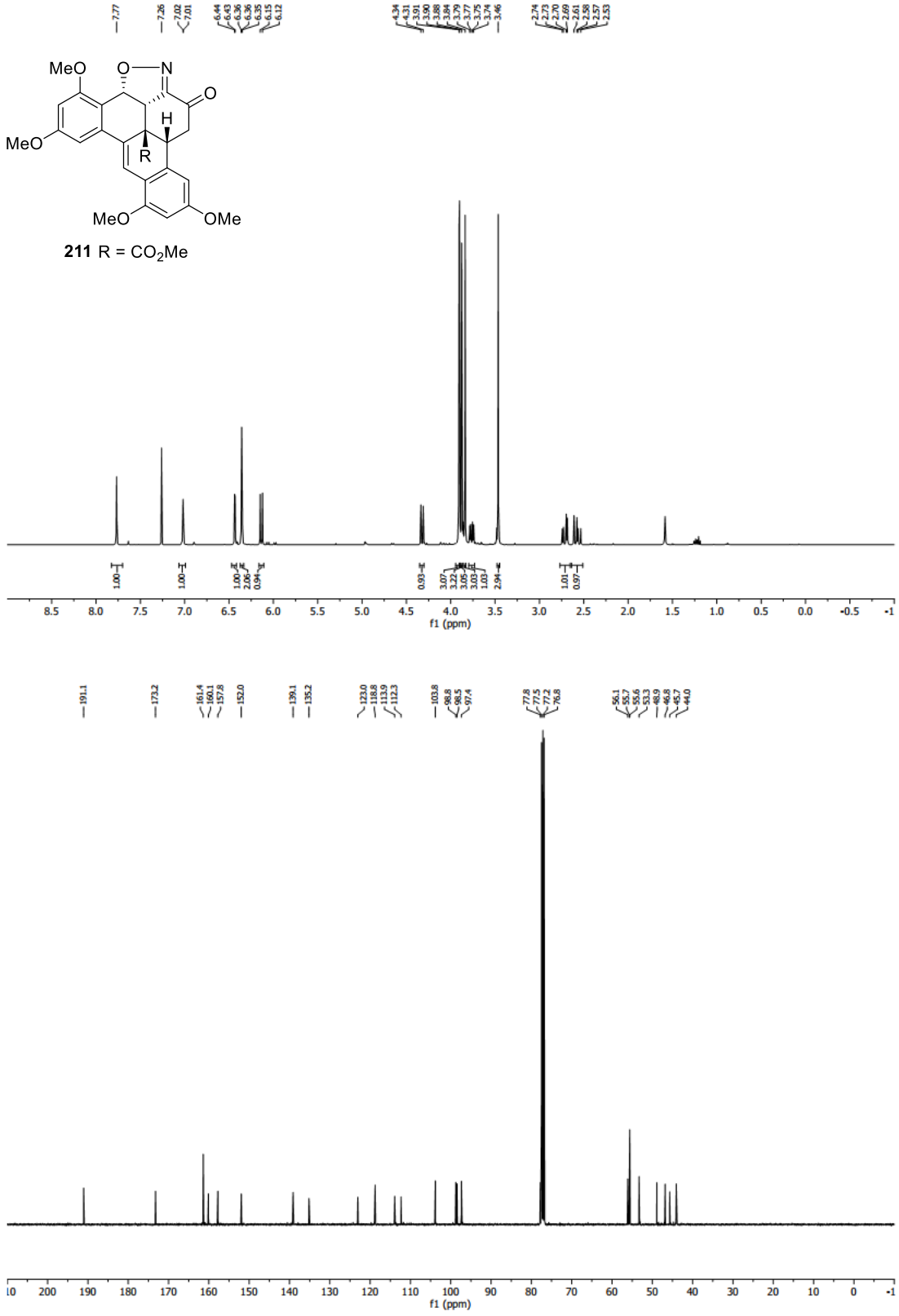


Compound **208-major** – ^{1}**H-NMR** (400 MHz) and ^{13}**C-NMR** (100 MHz) in $CDCl_3$

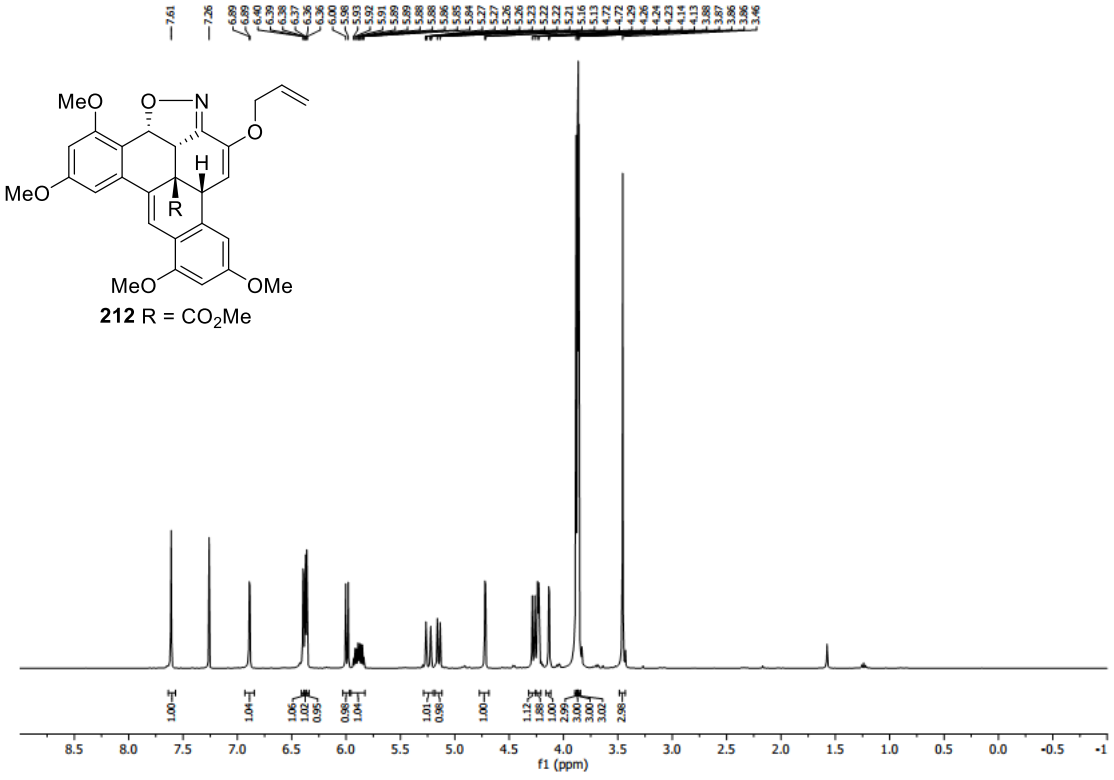


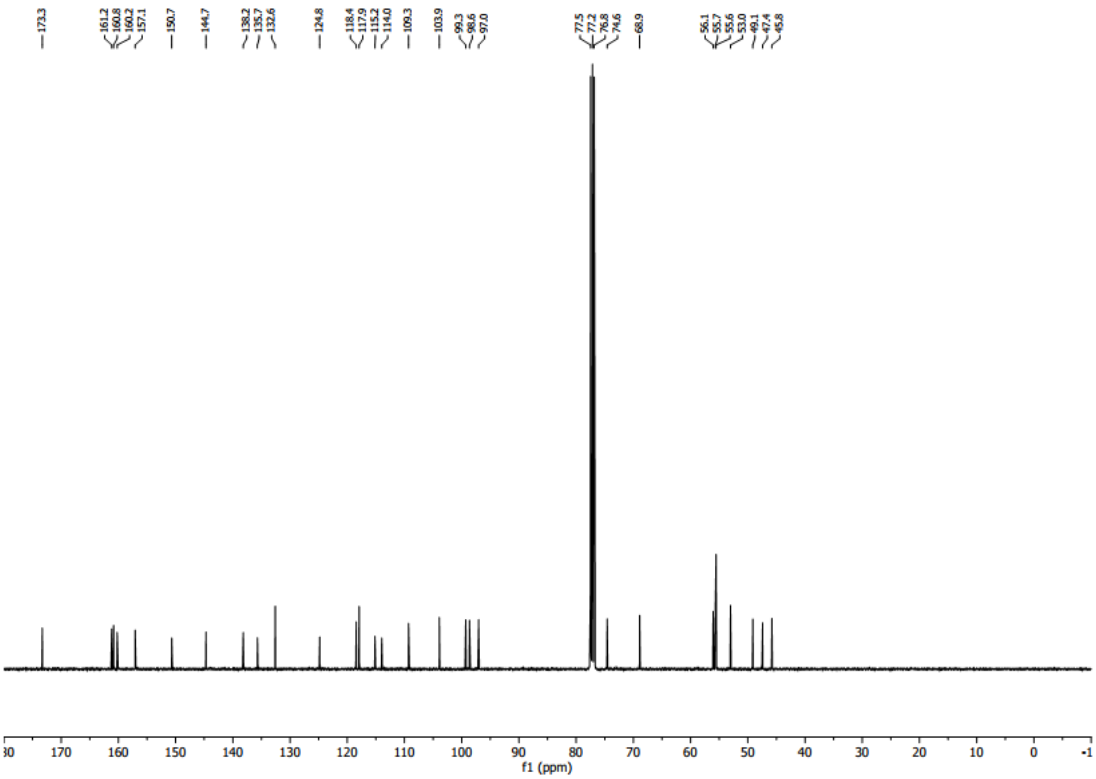


Compound **211** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



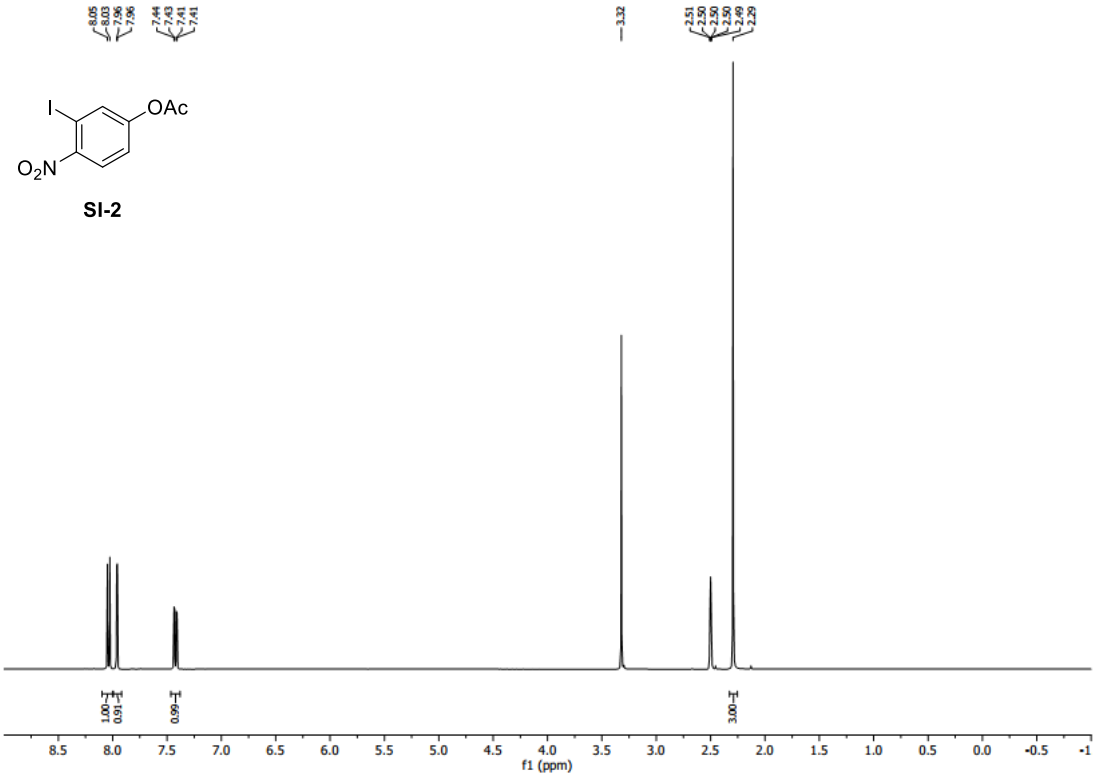
Compound **212** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

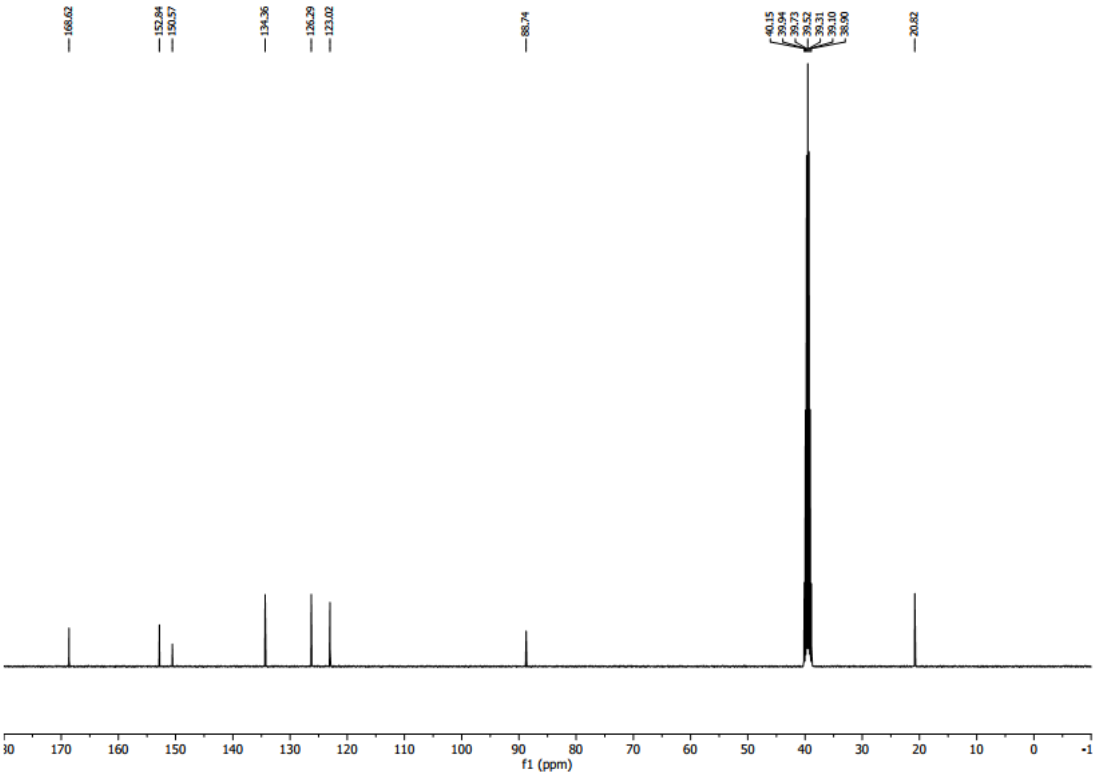




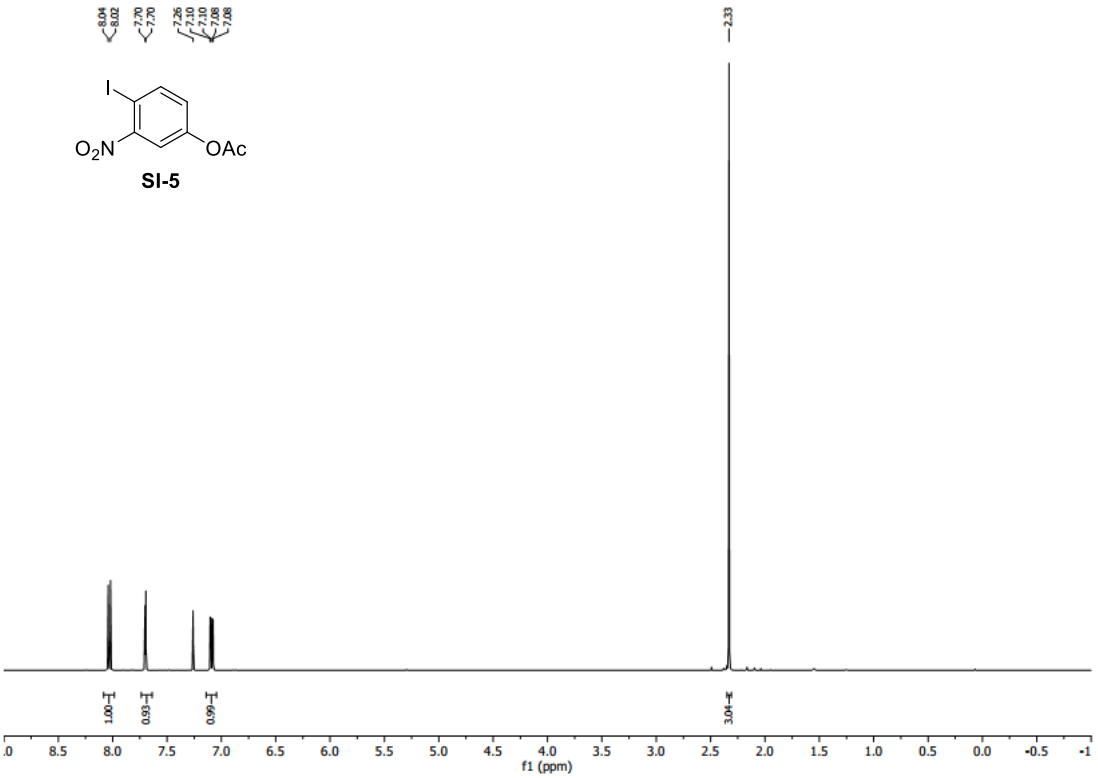
3.2 **Part II:** Synthesis of cyclic azobenzenes

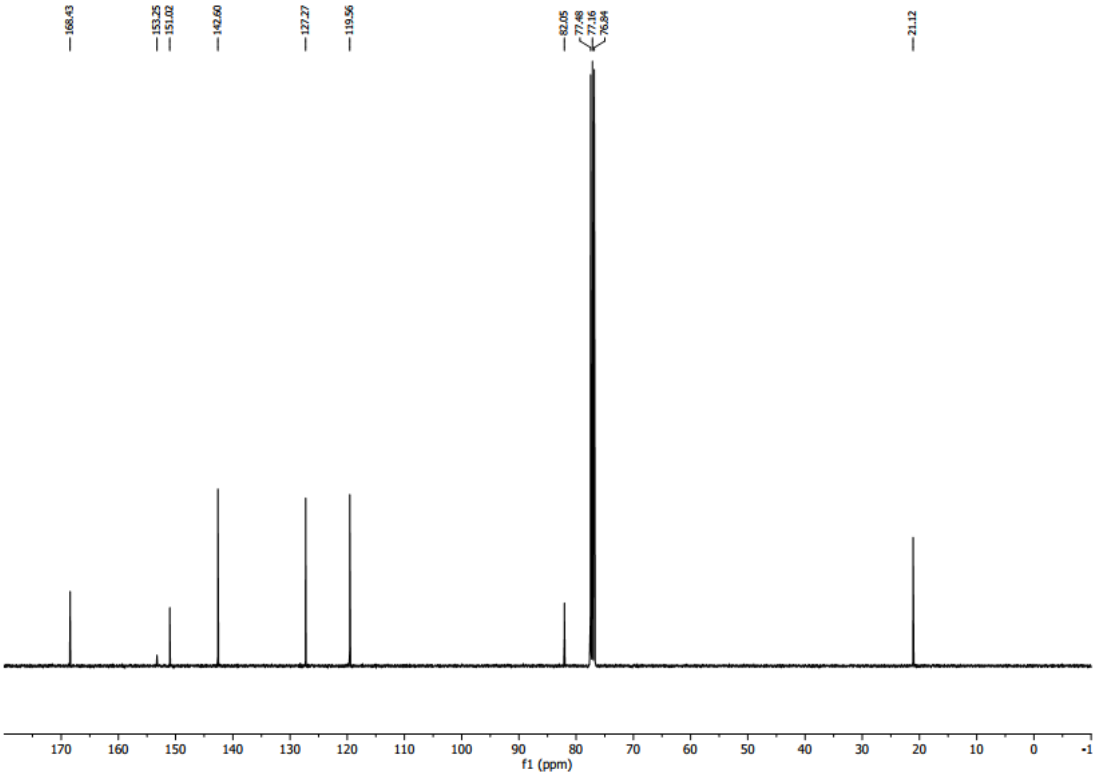
Compound **SI-2** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in DMSO-d_6



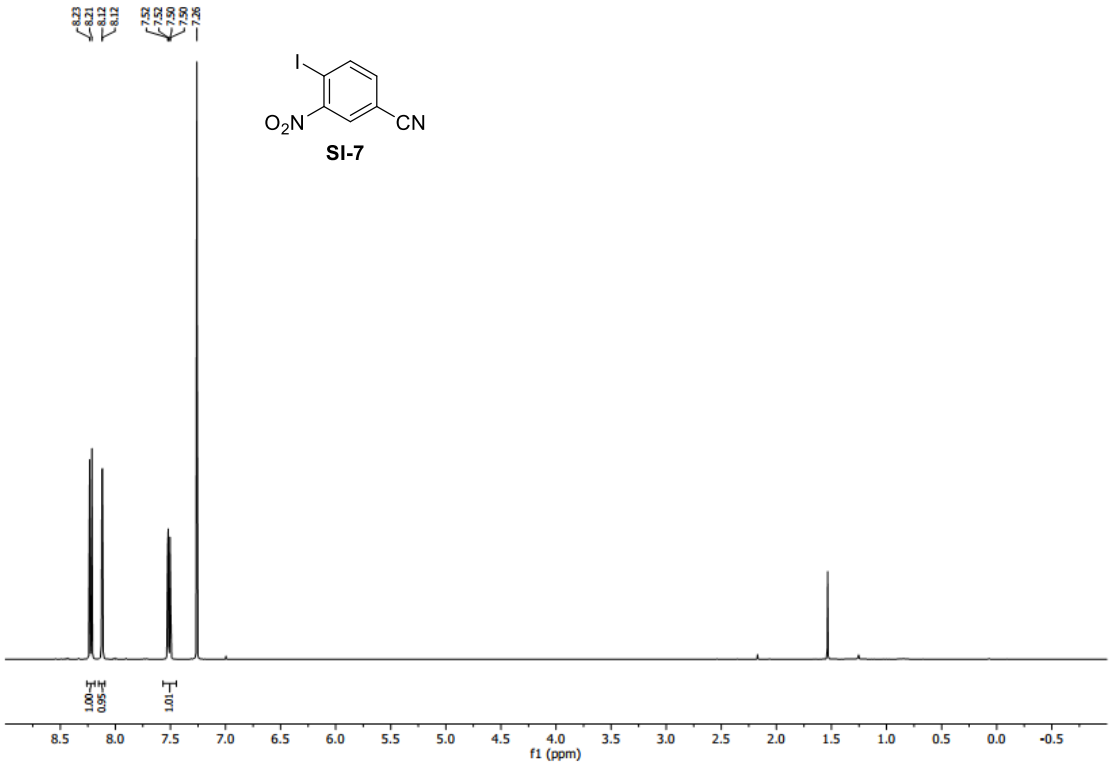


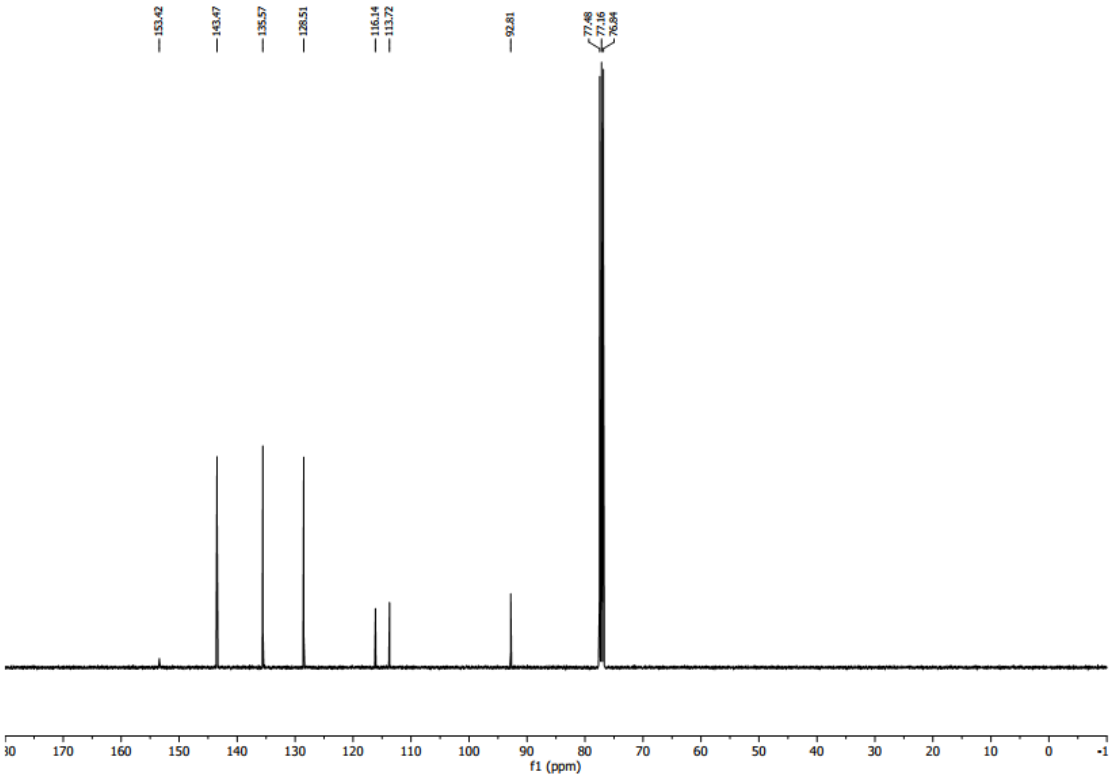
Compound **SI-5** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



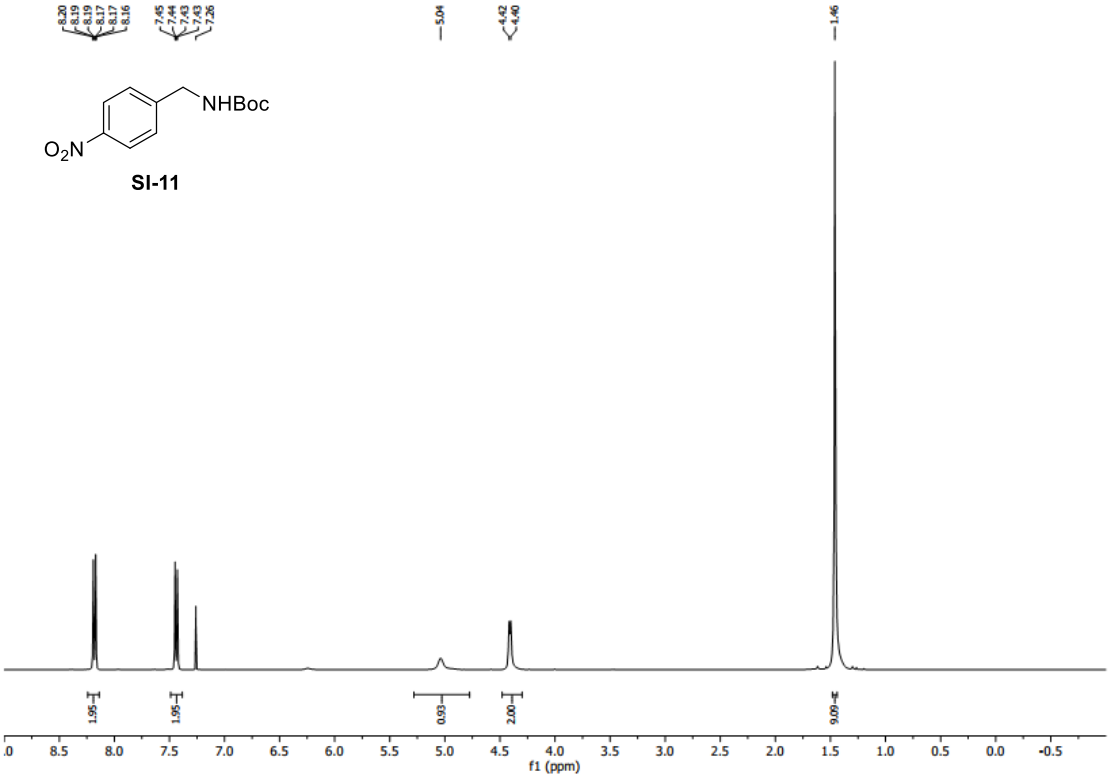


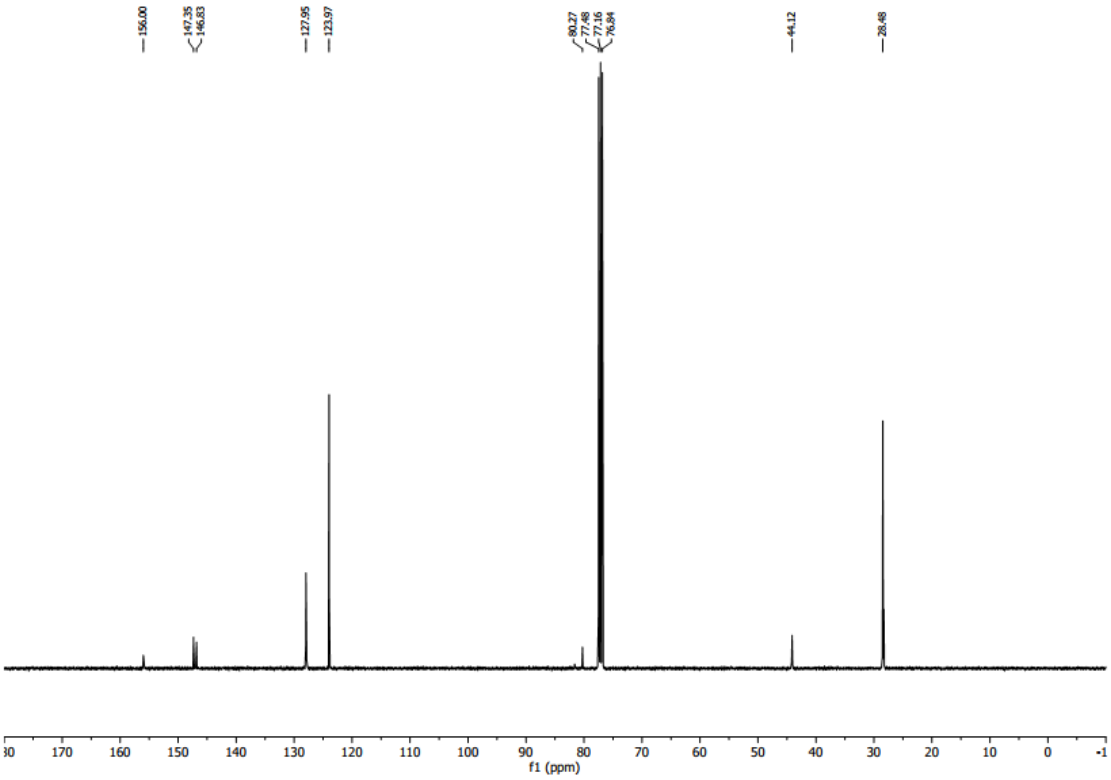
Compound **SI-7** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



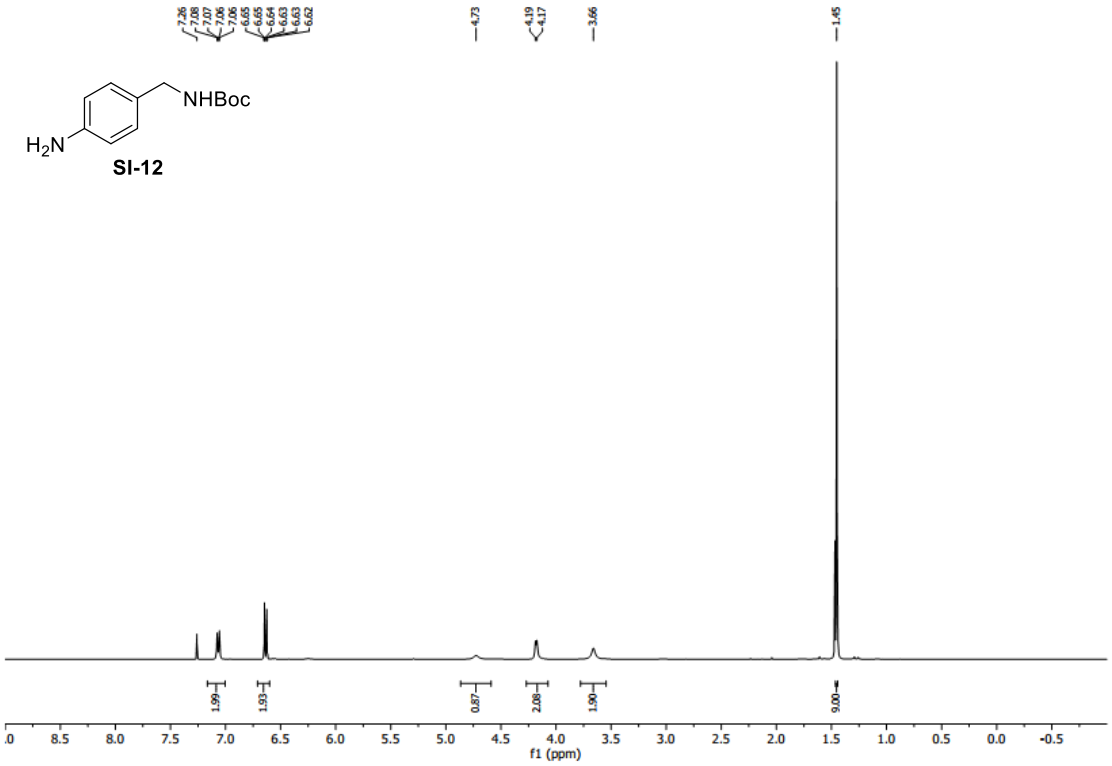


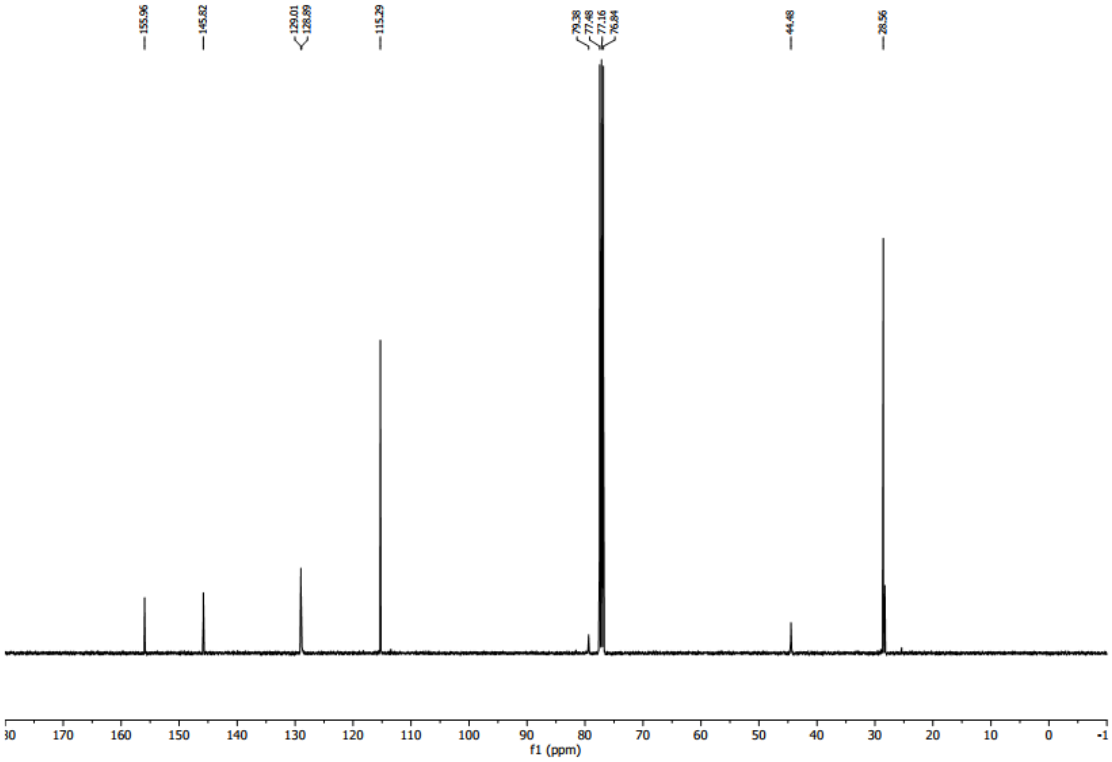
Compound **SI-11** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



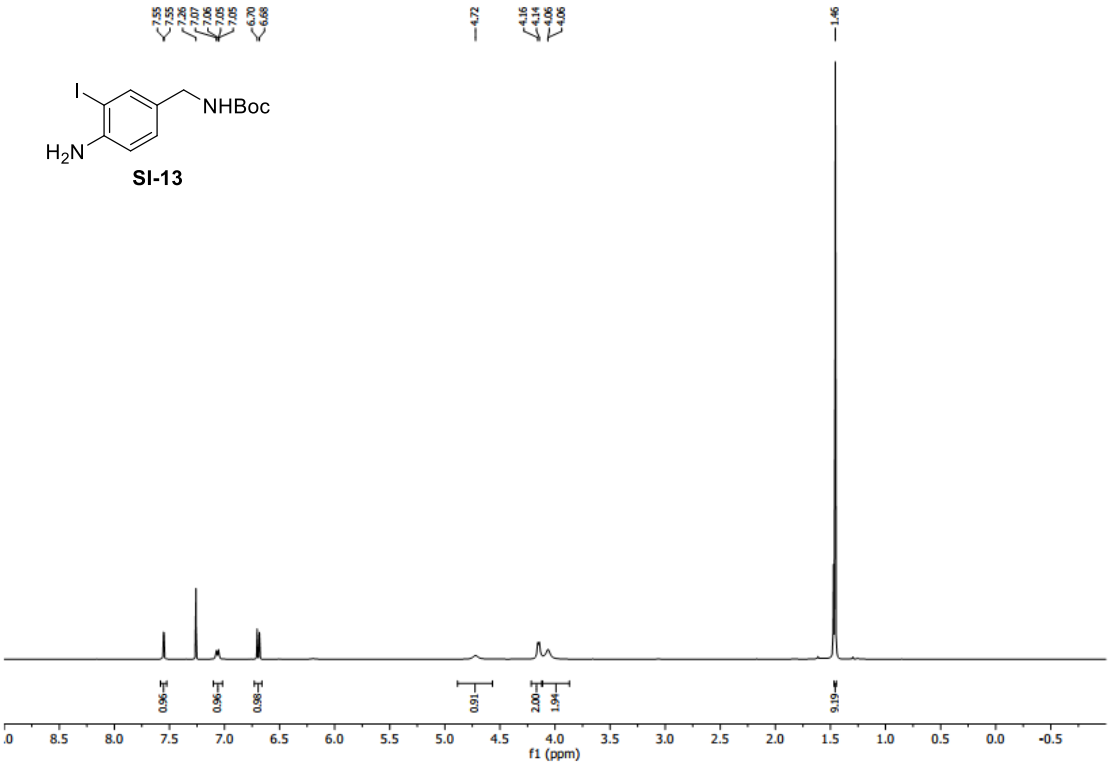


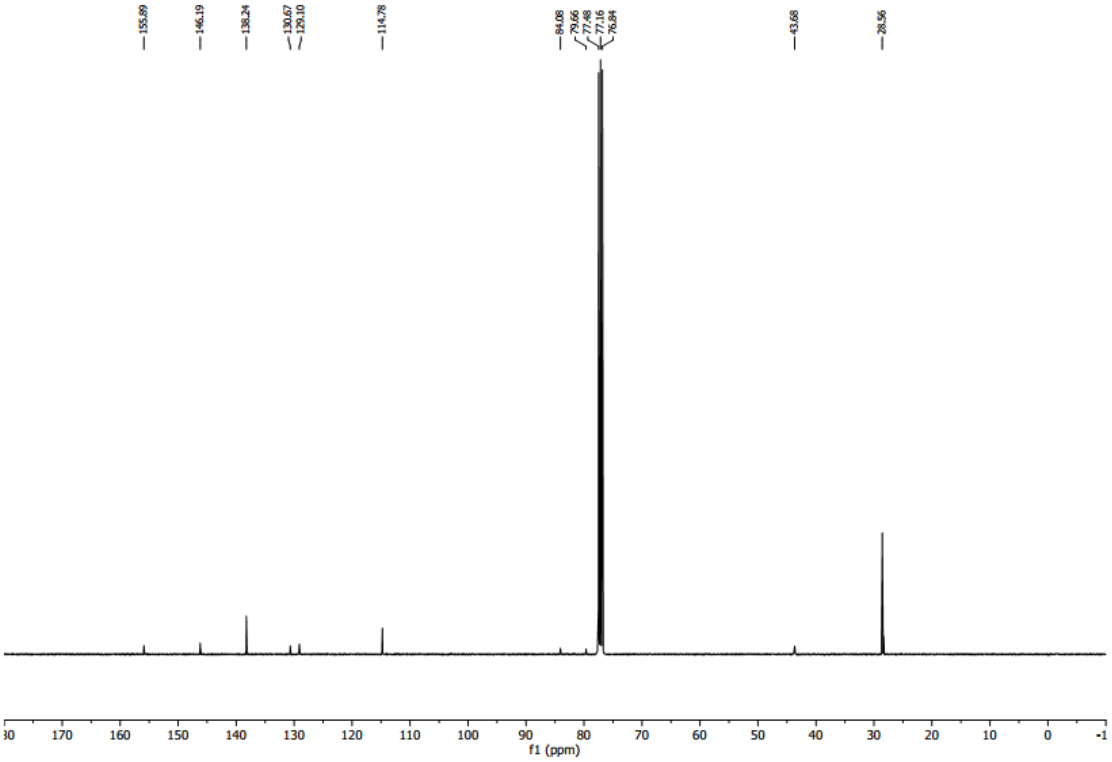
Compound **SI-12** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$





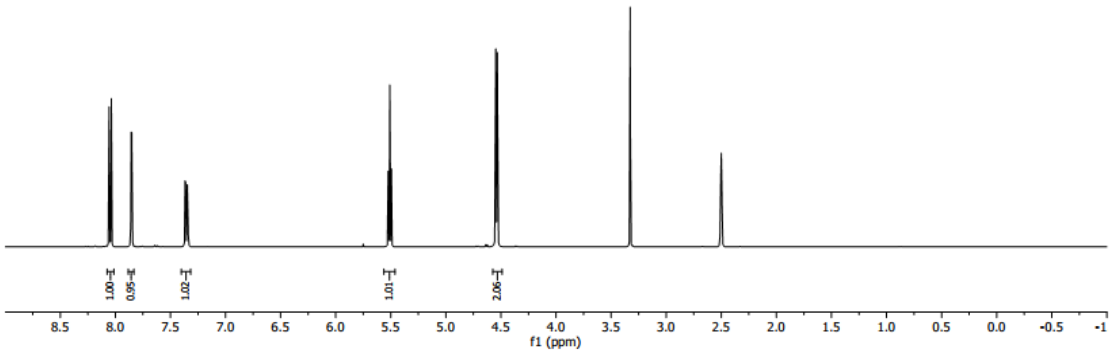
Compound **SI-13** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

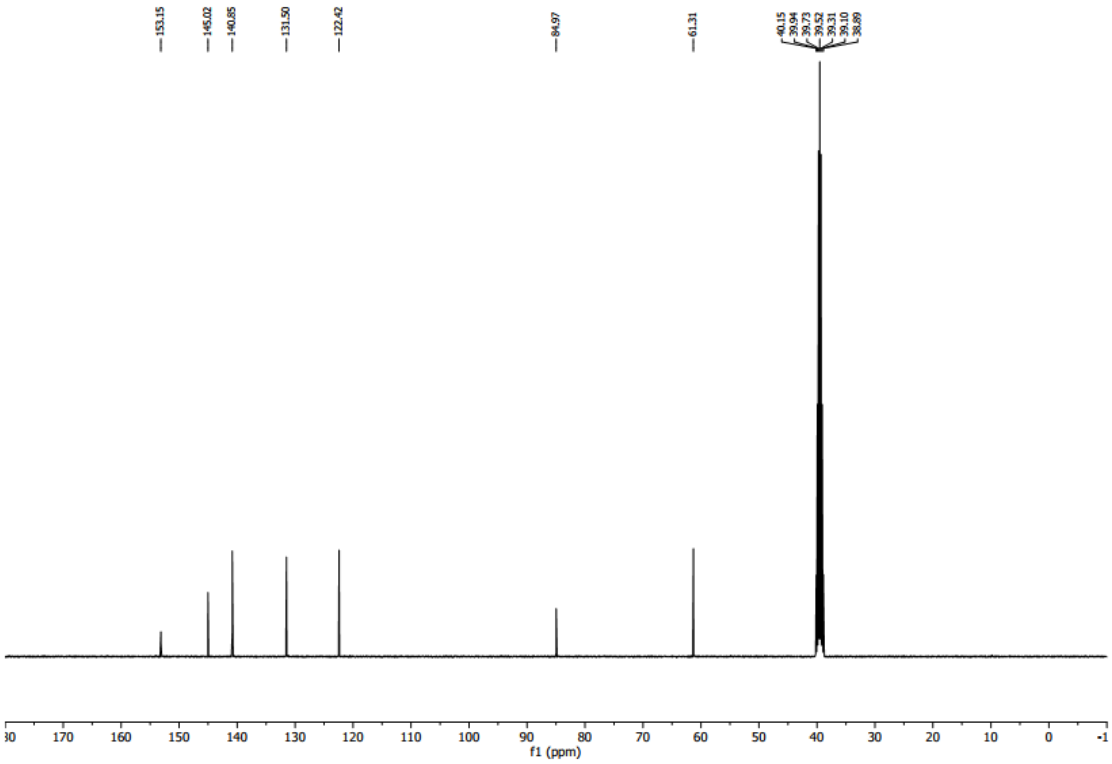




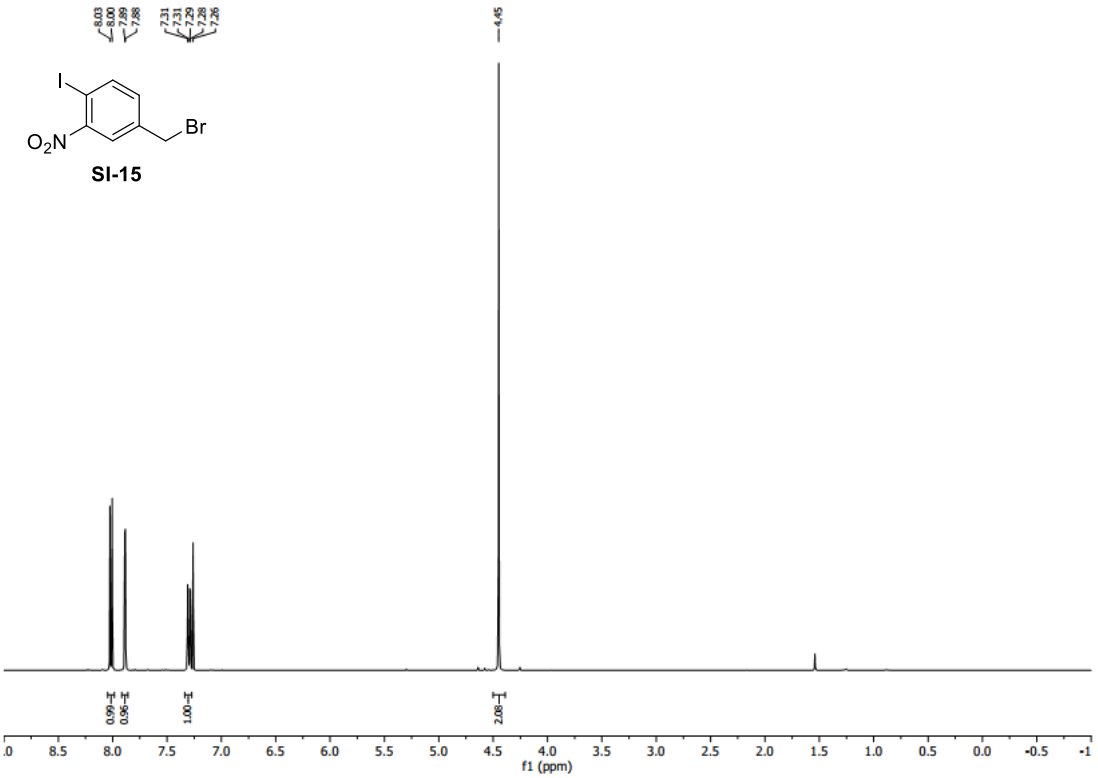
Compound **SI-14** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in DMSO-d_6

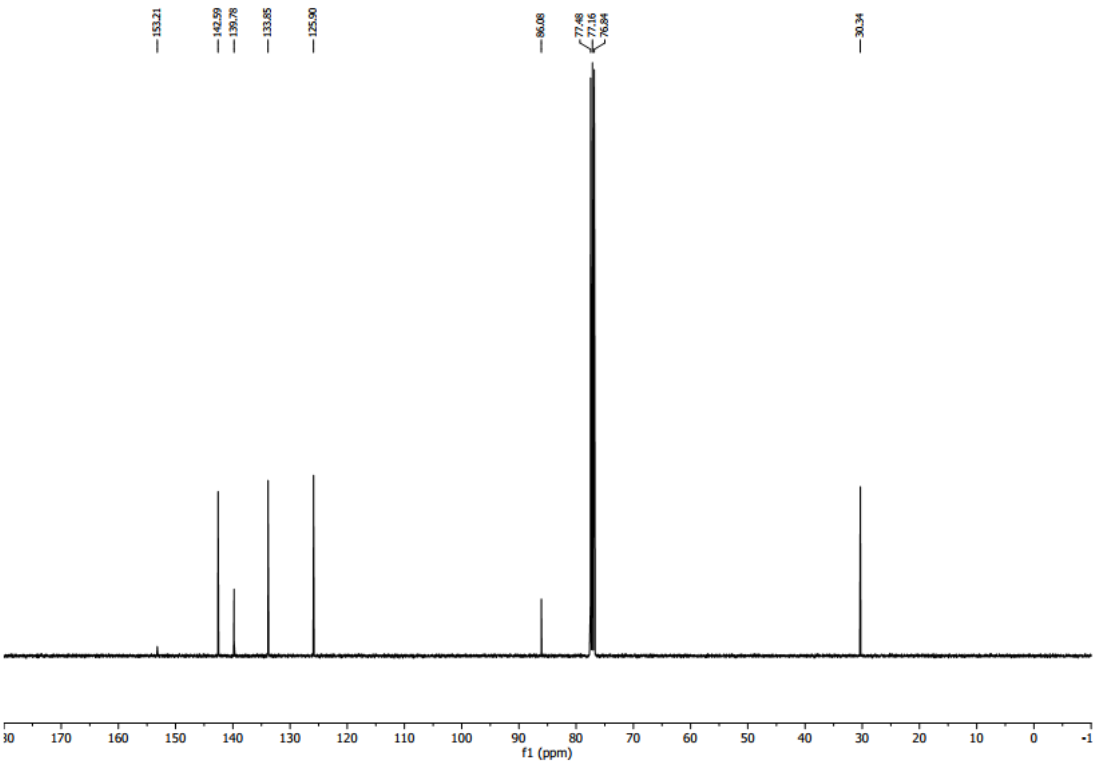
SI-14



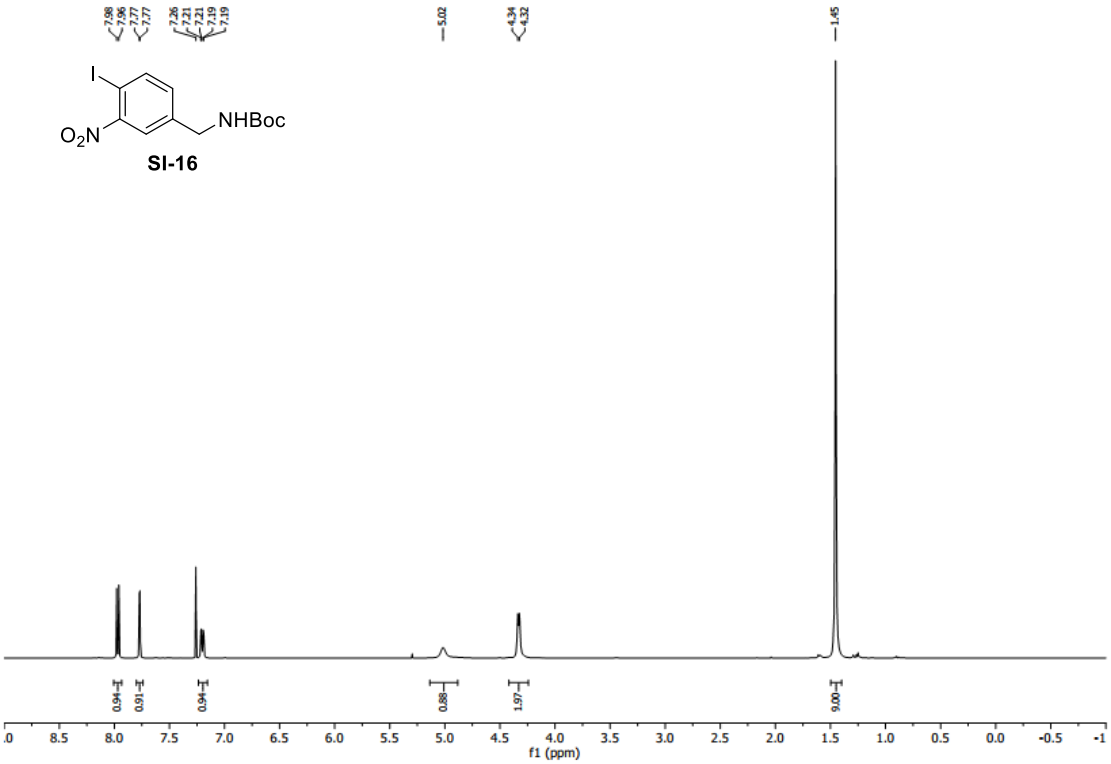


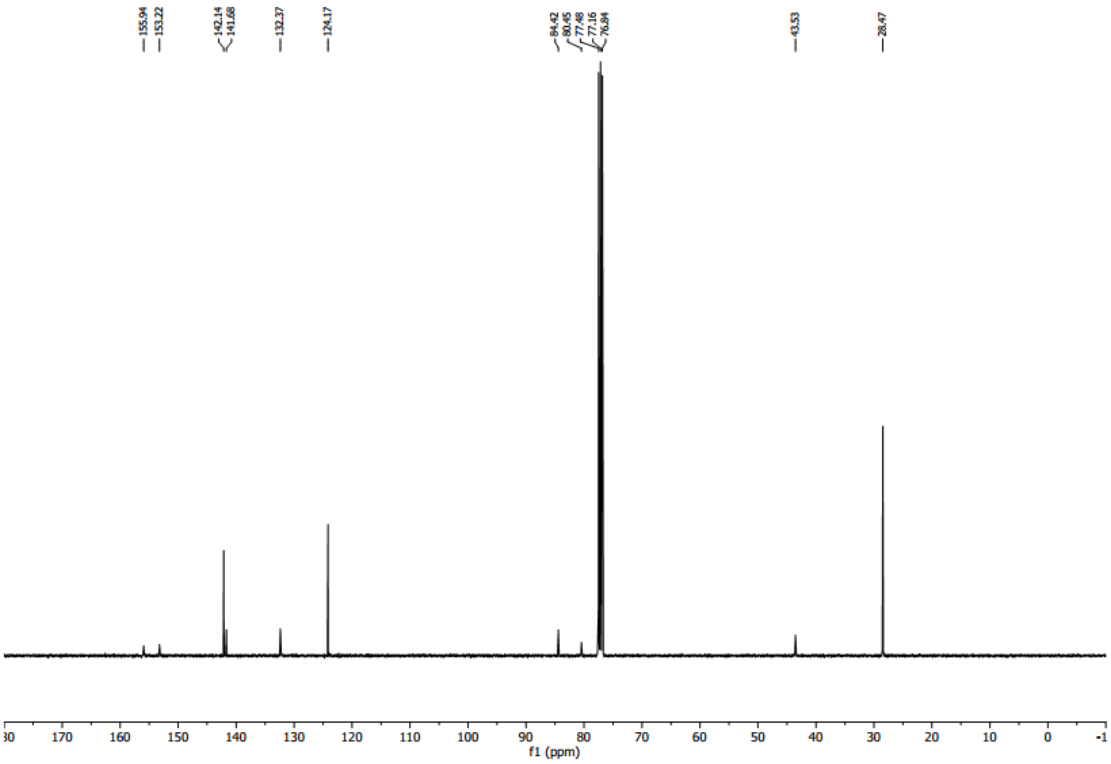
Compound **SI-15** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



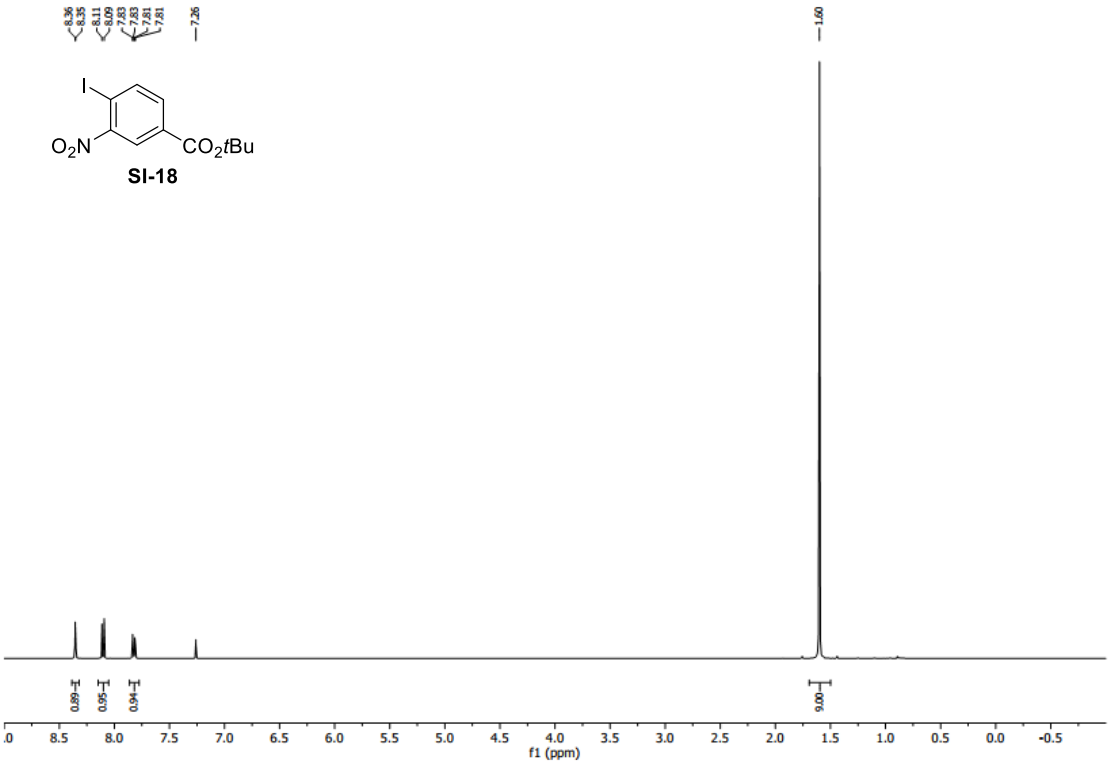


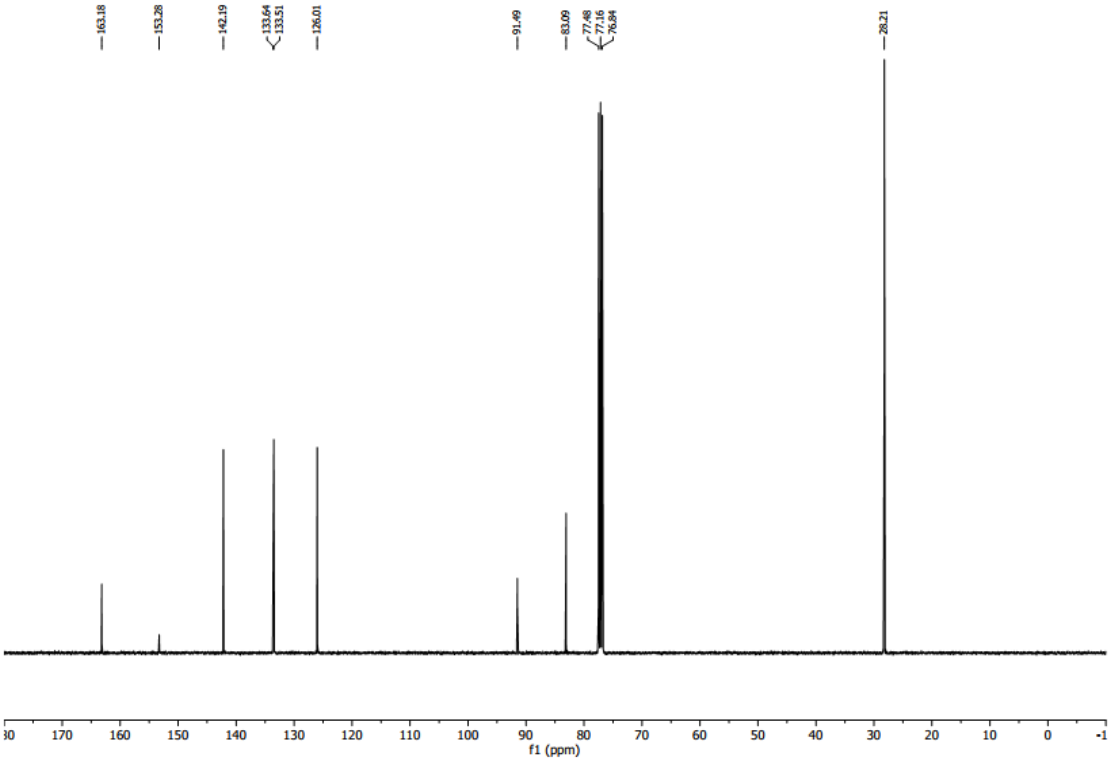
Compound **SI-16** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



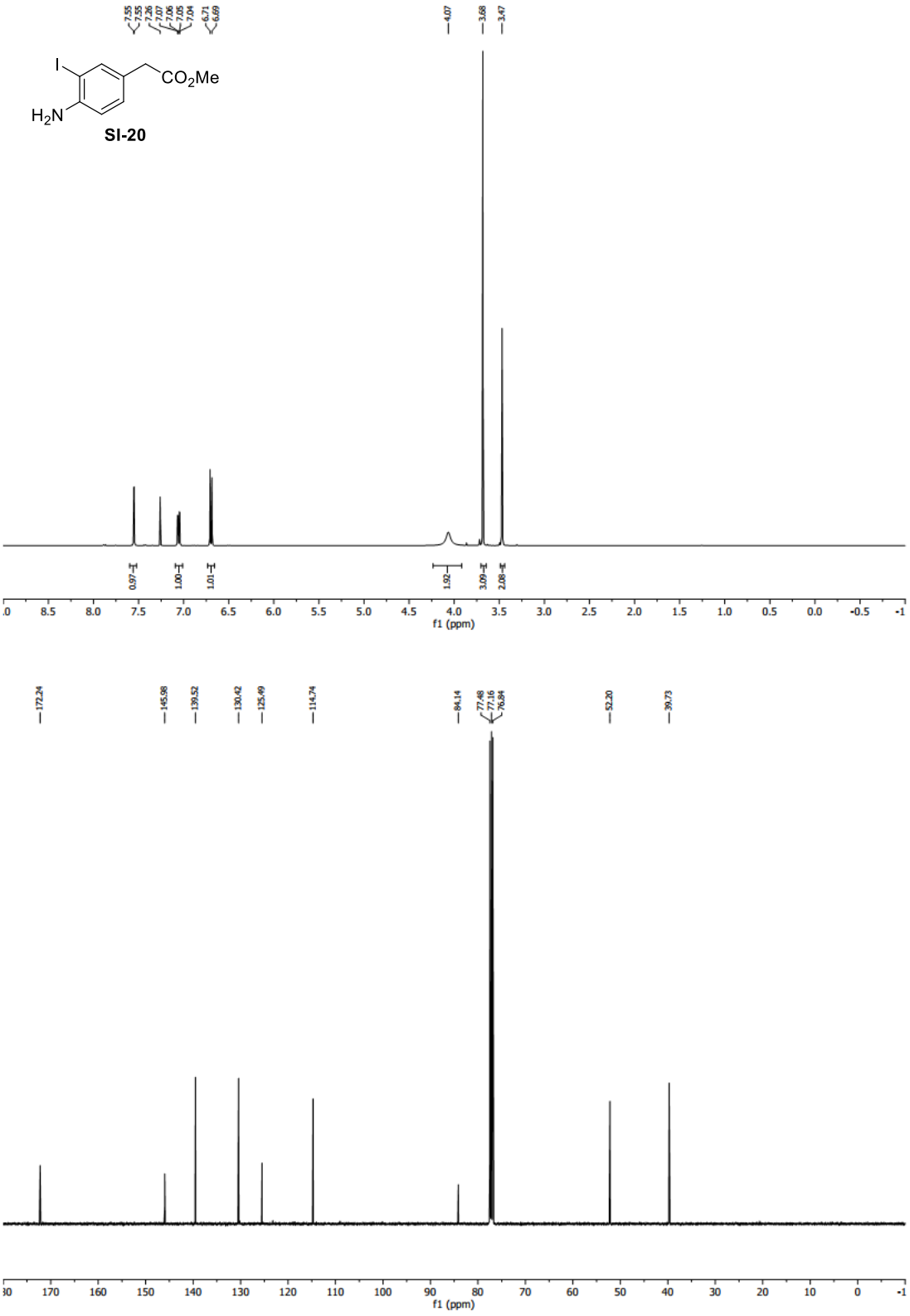


Compound **SI-18** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

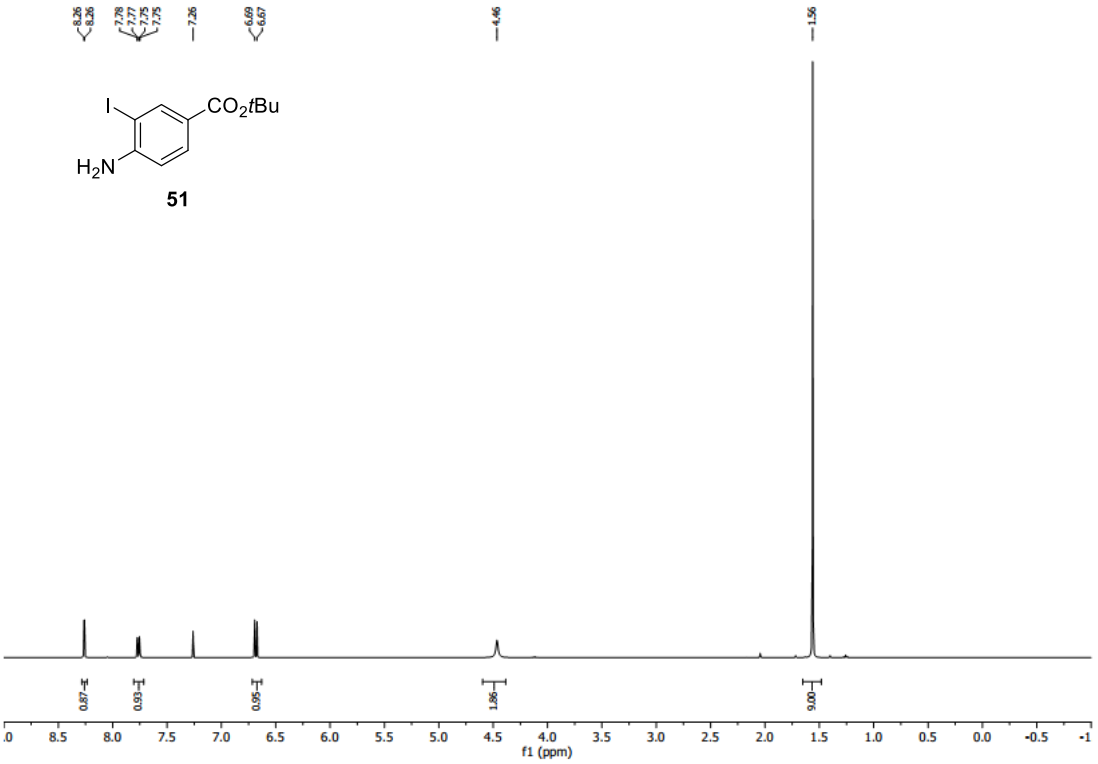


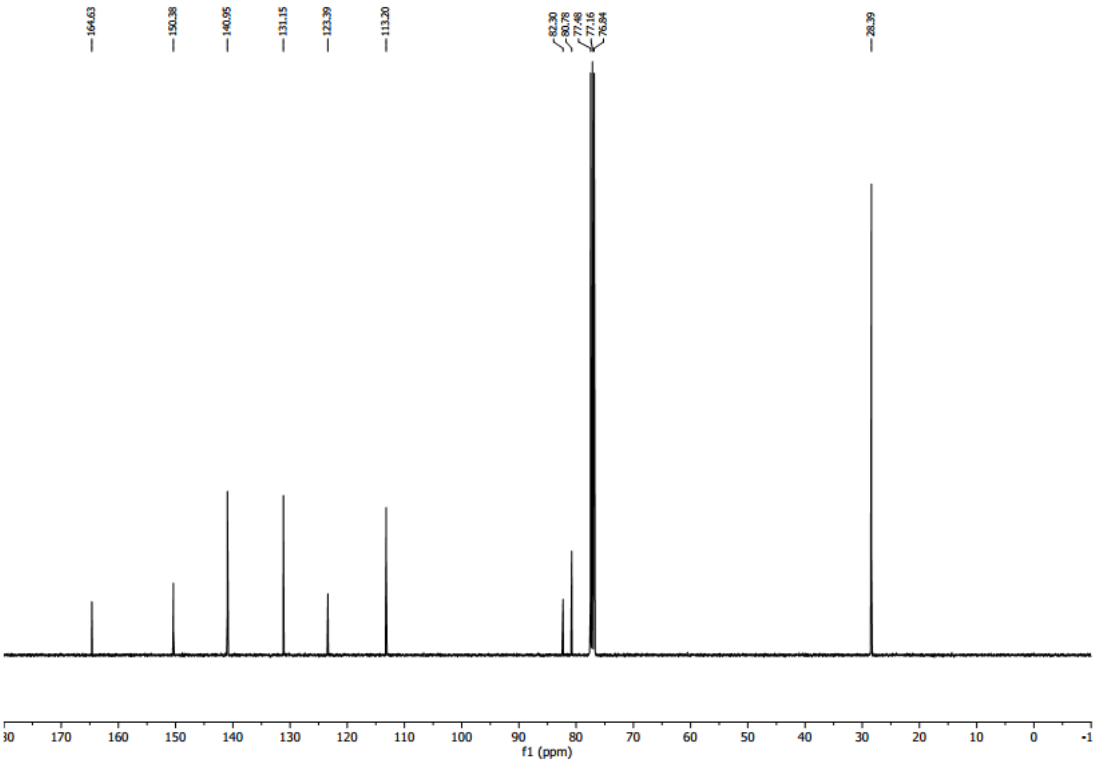


Compound **SI-20** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

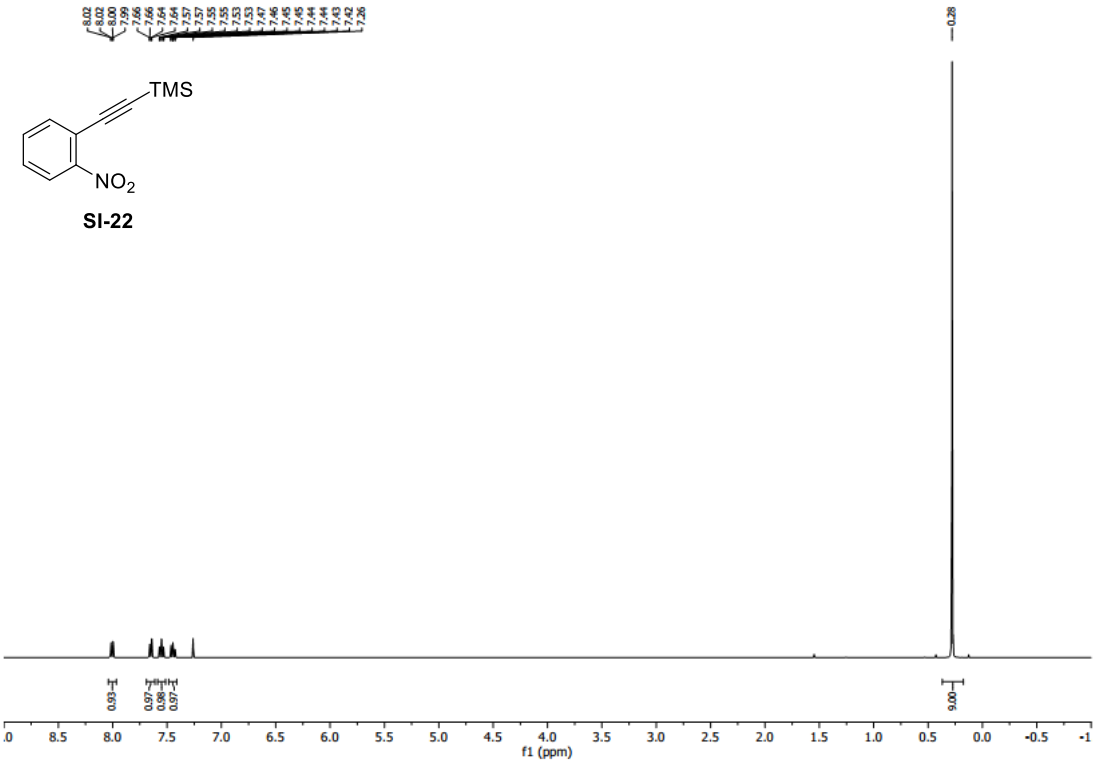


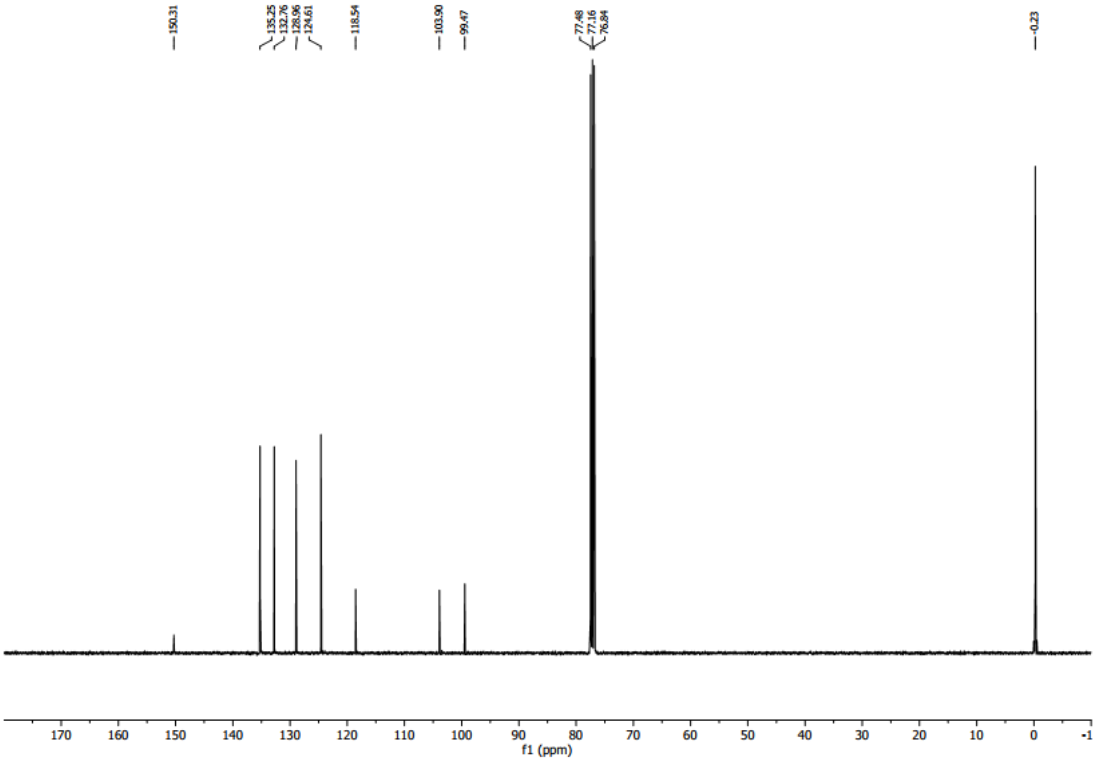
Compound **51** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



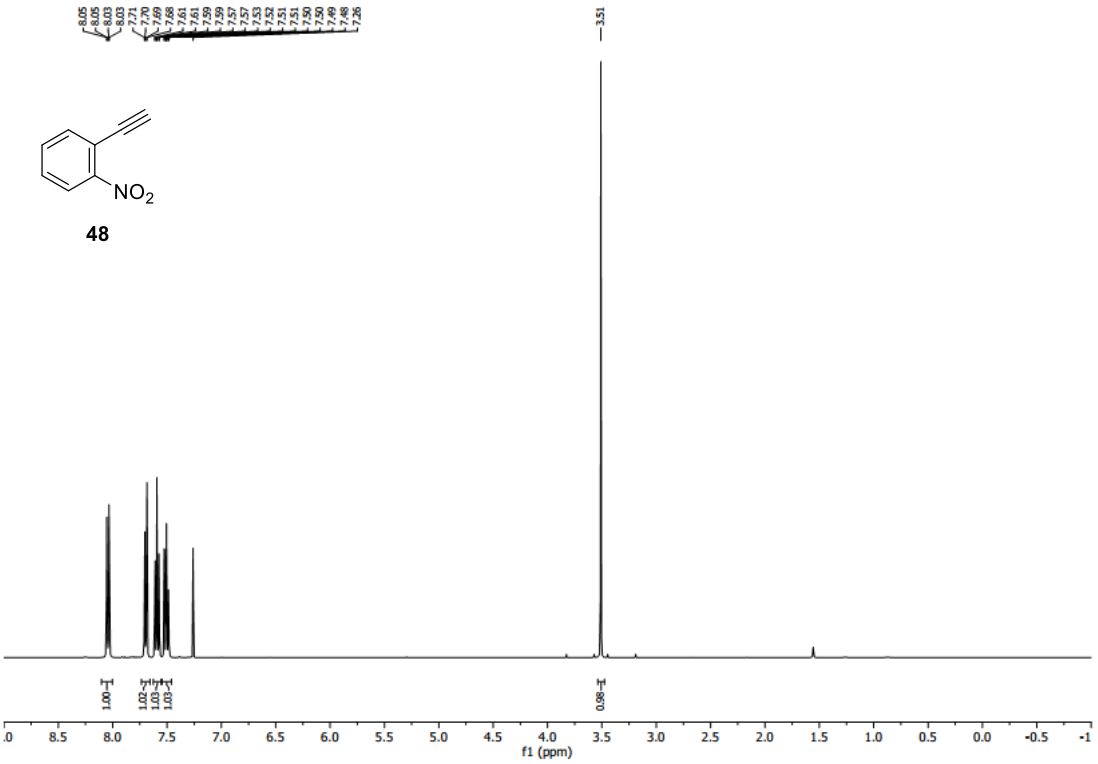


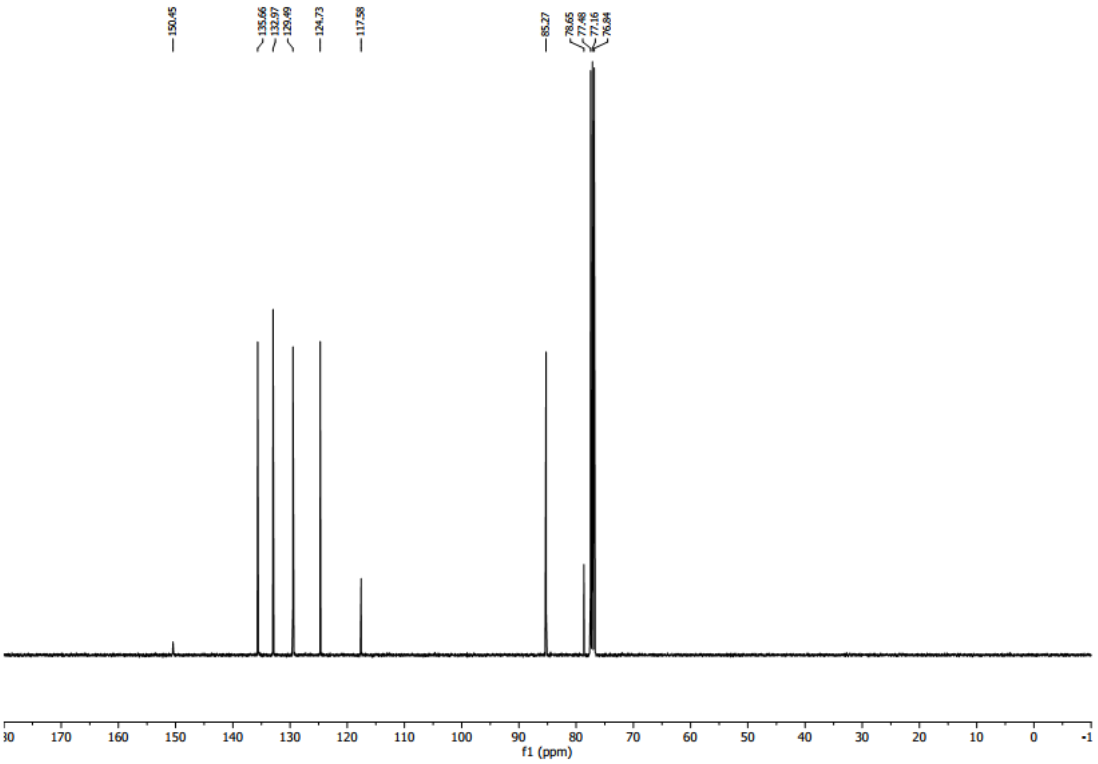
Compound **SI-22** – ^{1}**H-NMR** (400 MHz) and ^{13}**C-NMR** (100 MHz) in $CDCl_3$



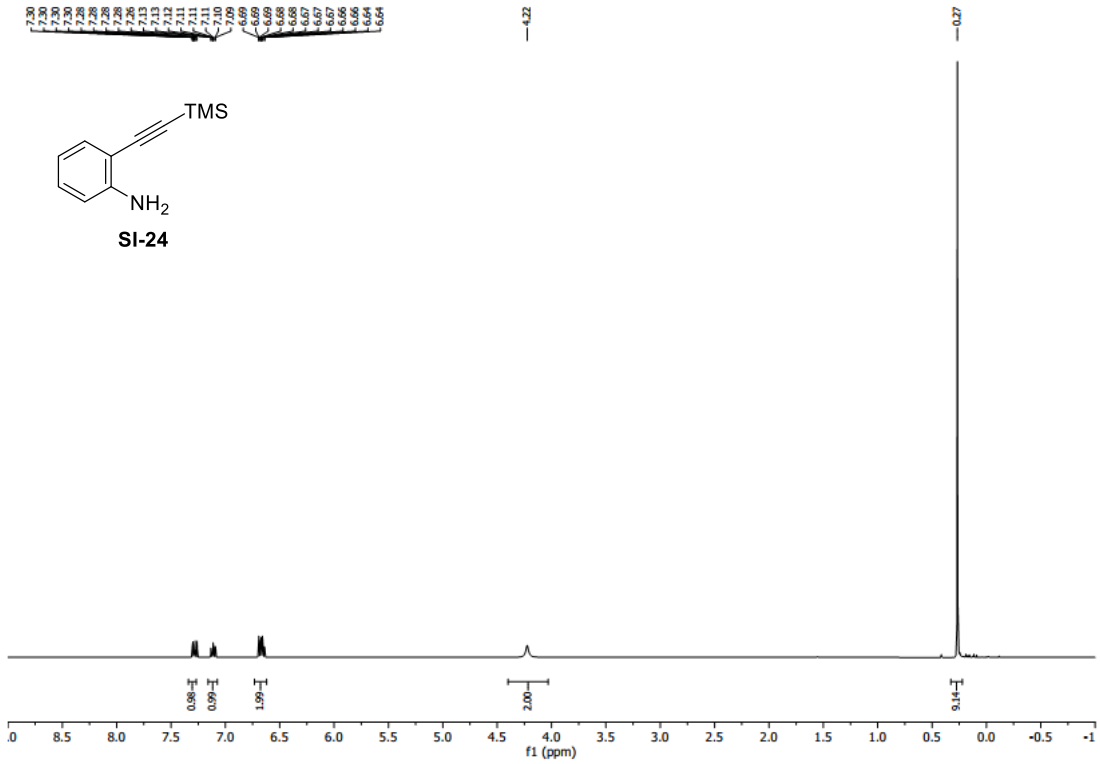


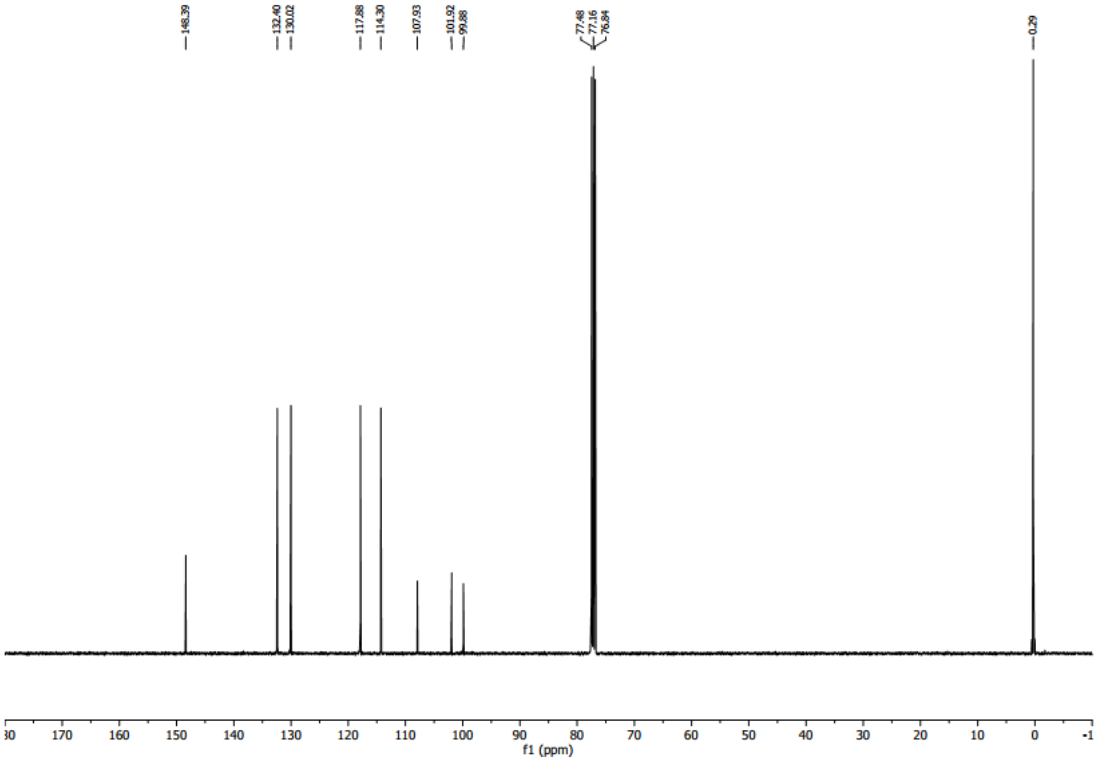
Compound **48** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



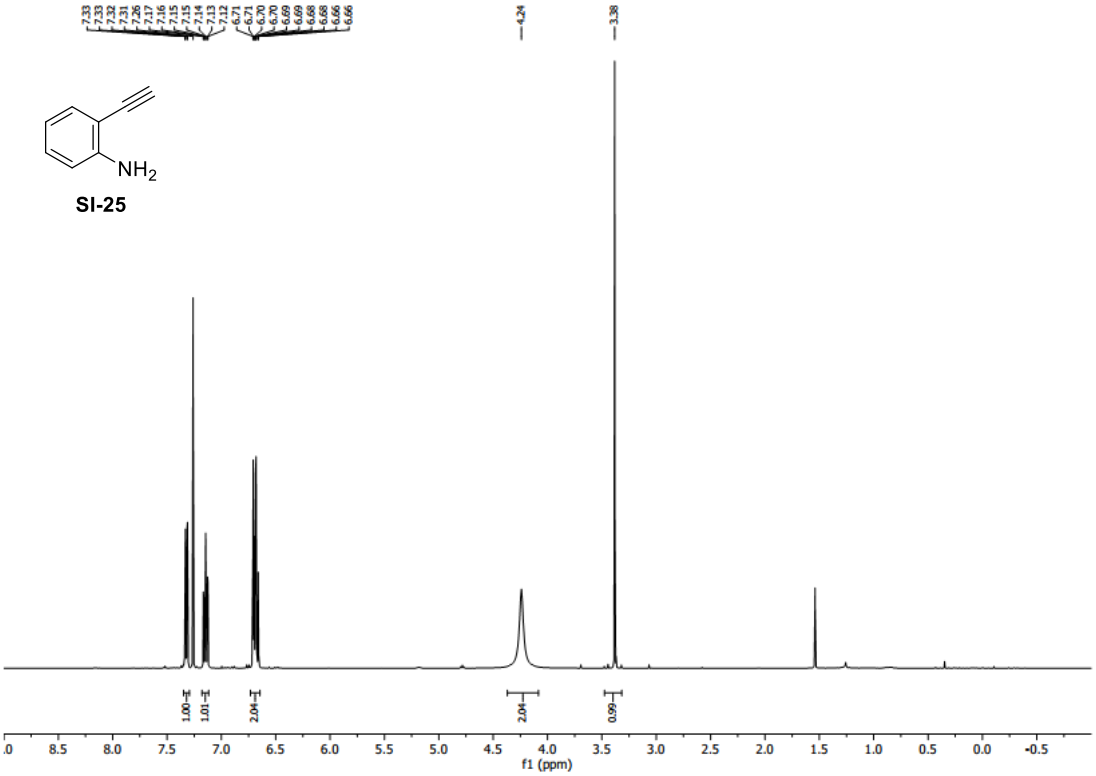


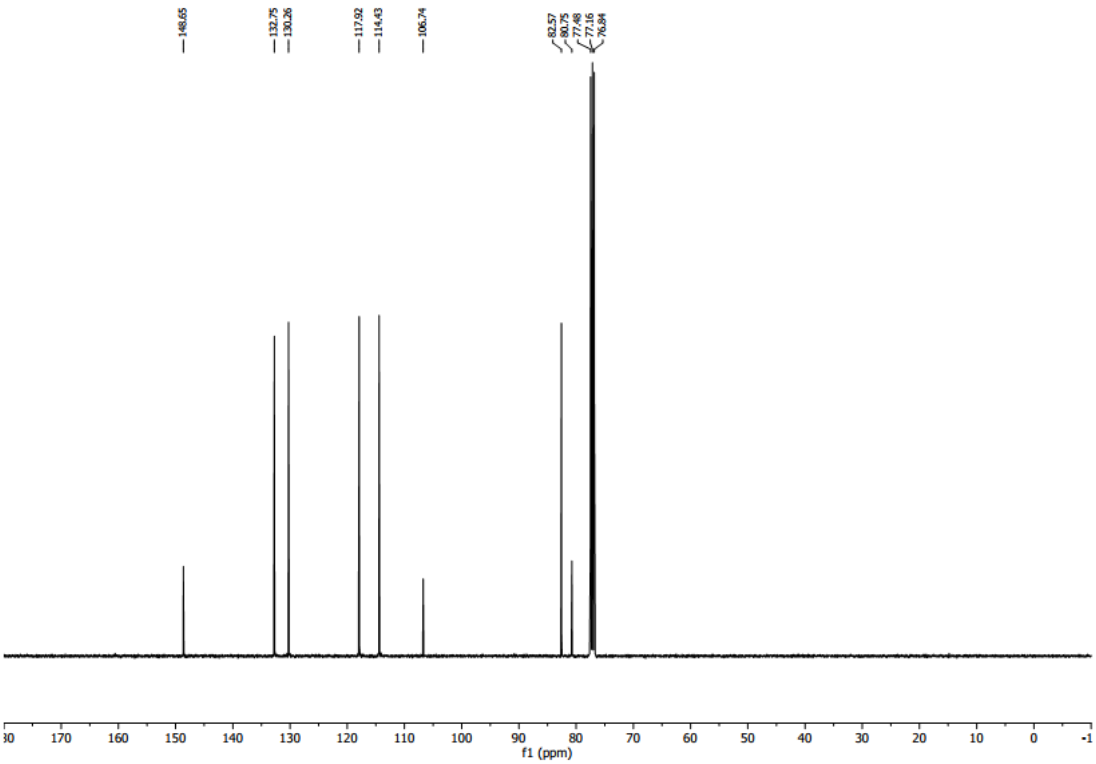
Compound **SI-24** – ^{1}**H-NMR** (400 MHz) and ^{13}**C-NMR** (100 MHz) in $CDCl_3$



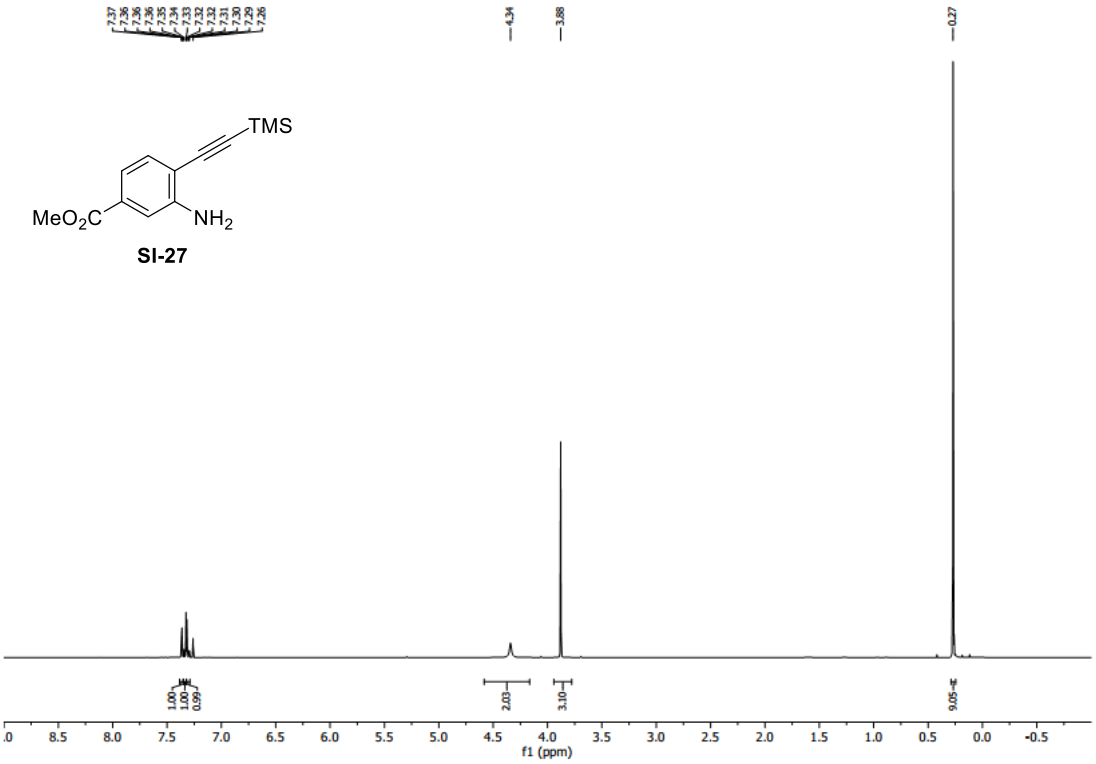


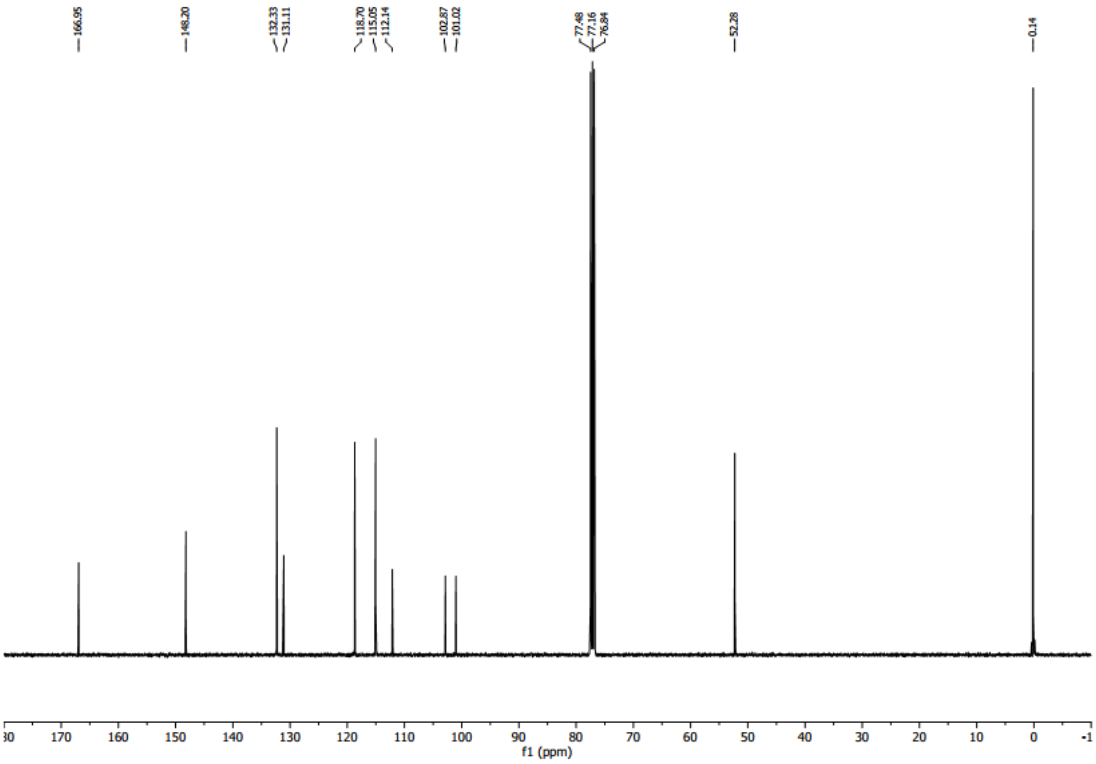
Compound **SI-25** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



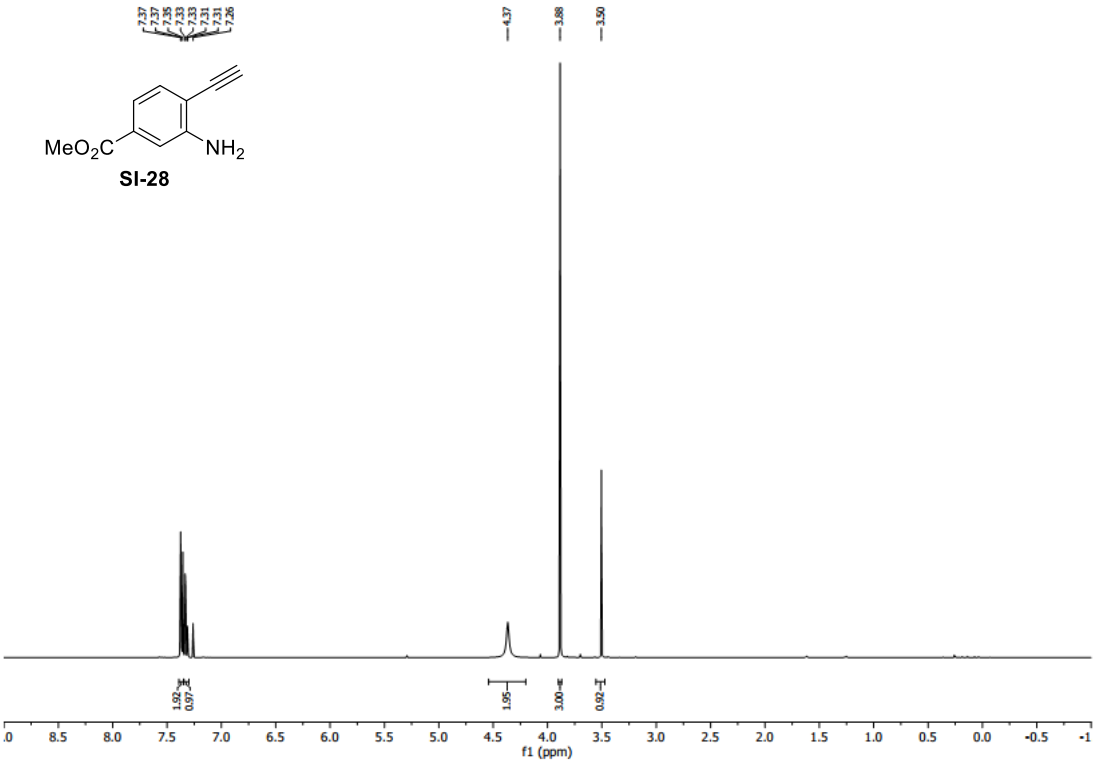


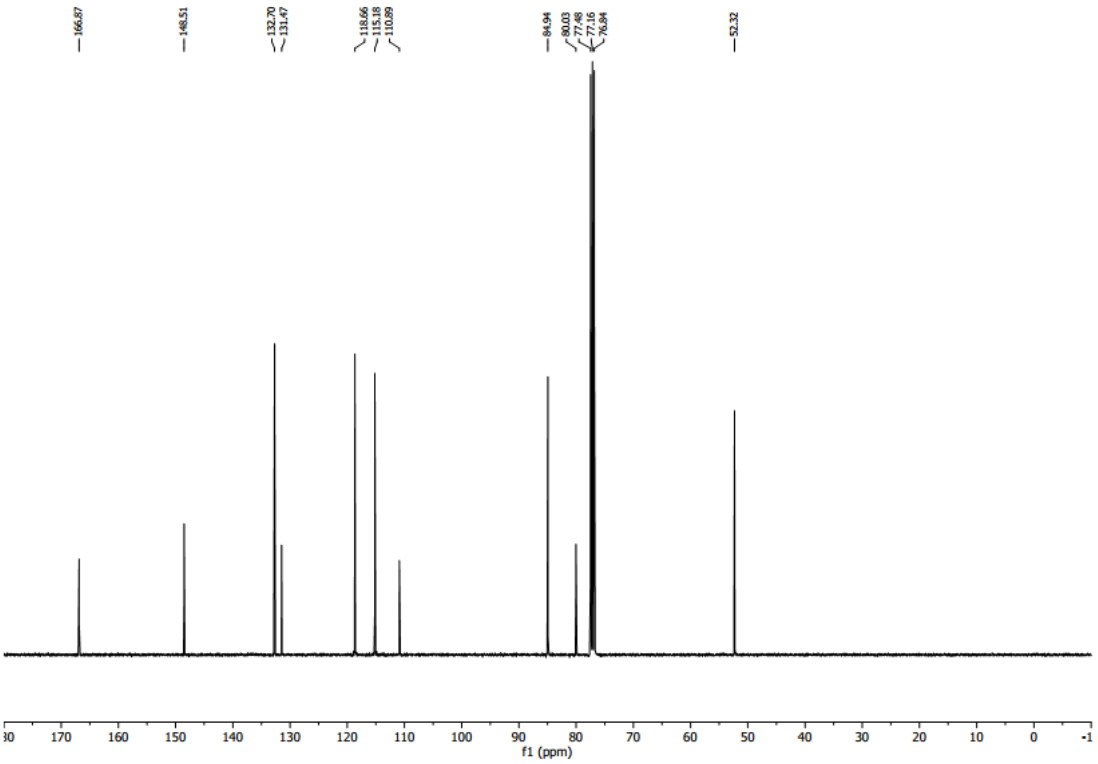
Compound **SI-27** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



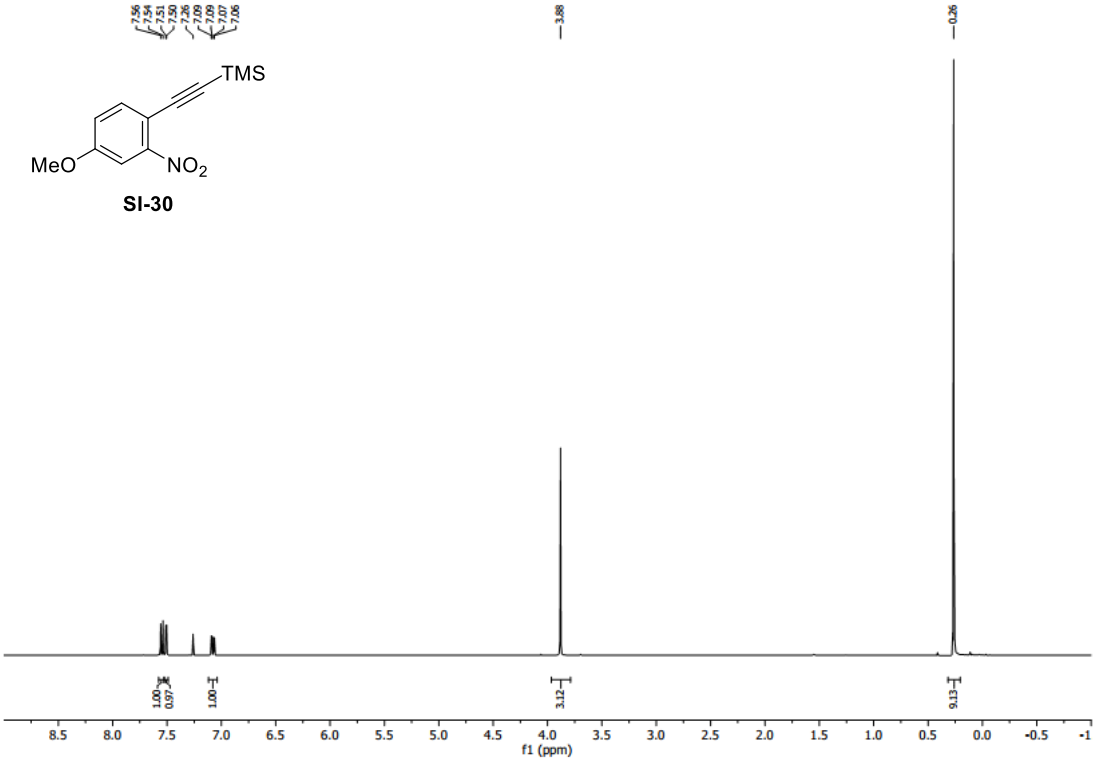


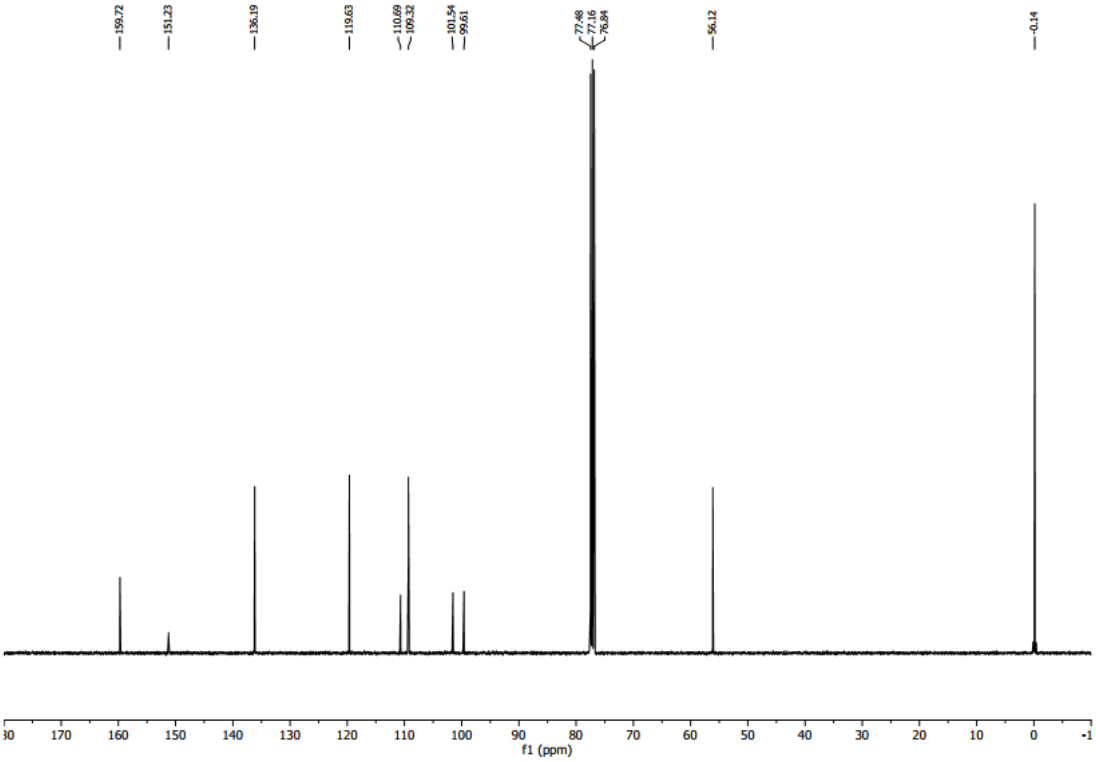
Compound **SI-28** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



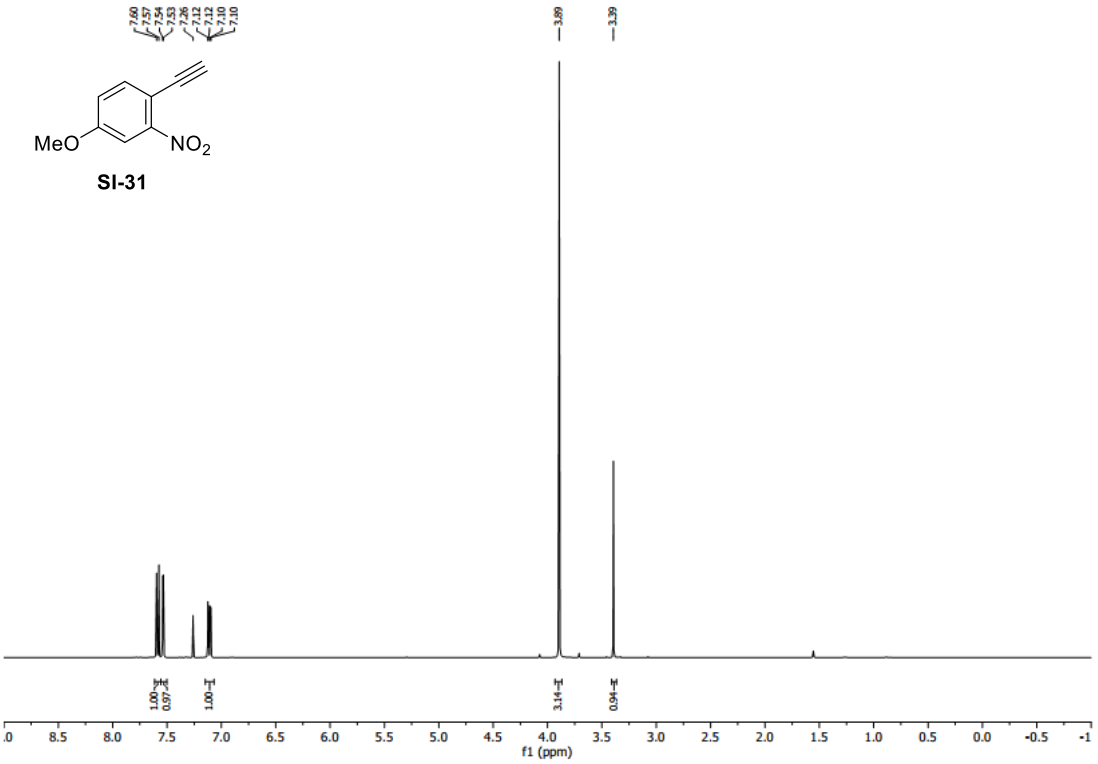


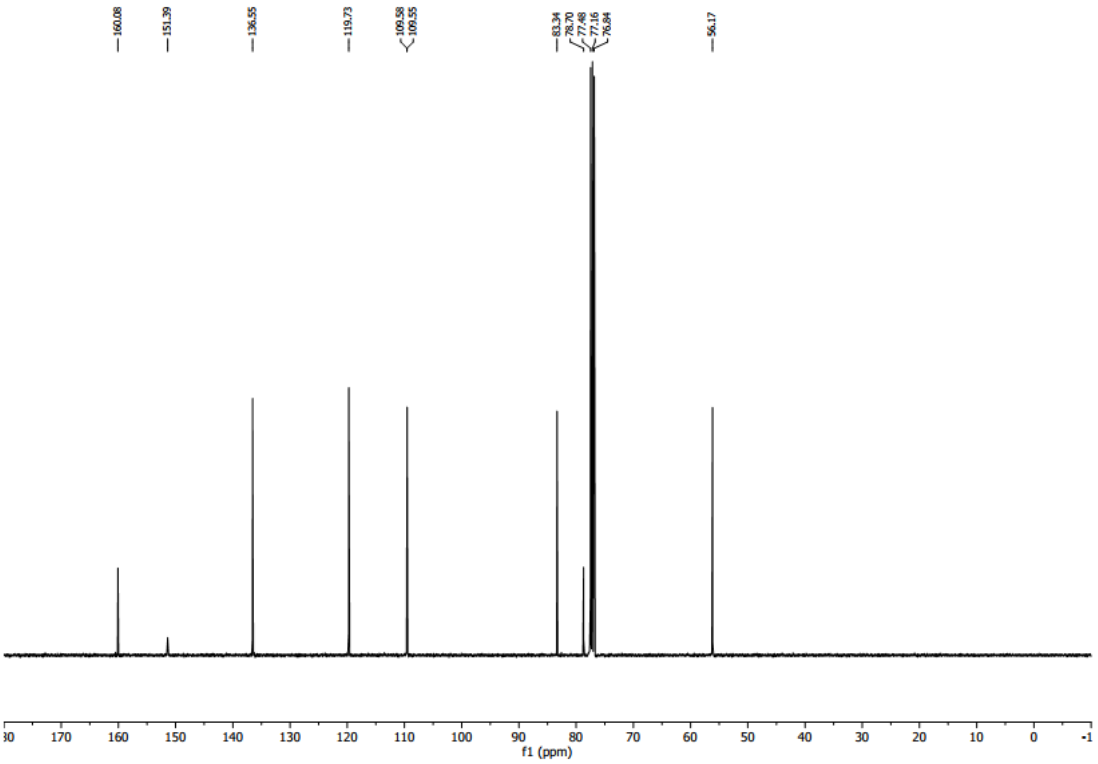
Compound **SI-30** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



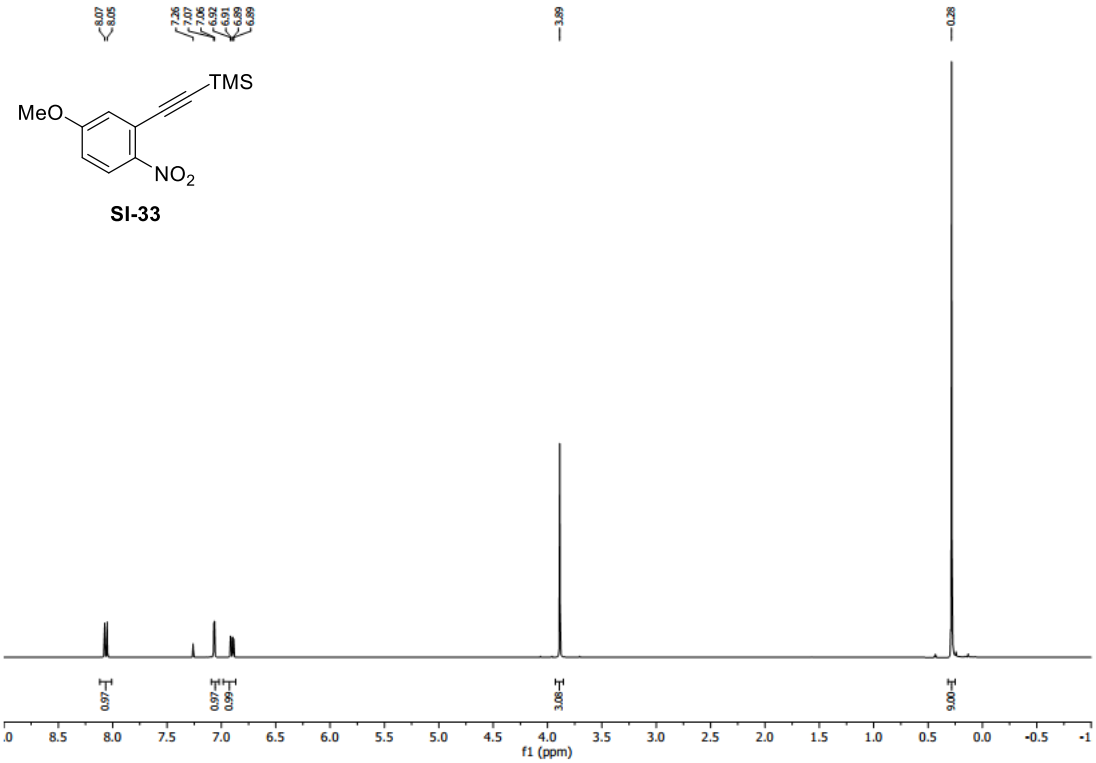


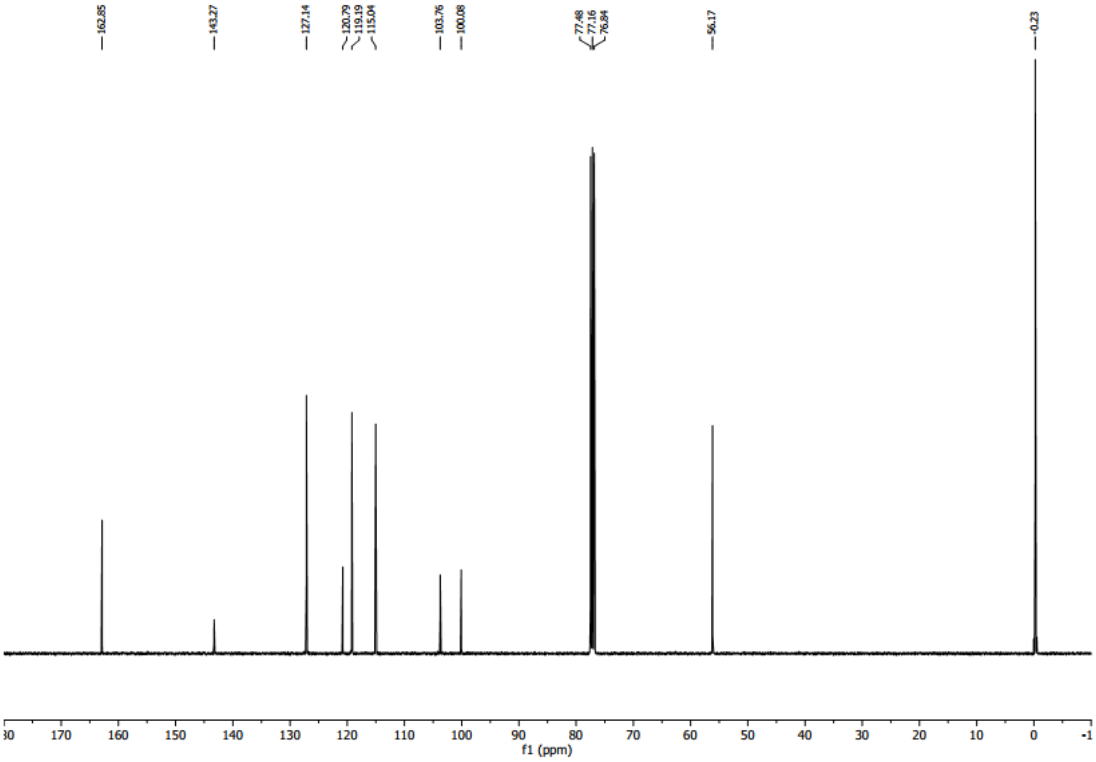
Compound **SI-31** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



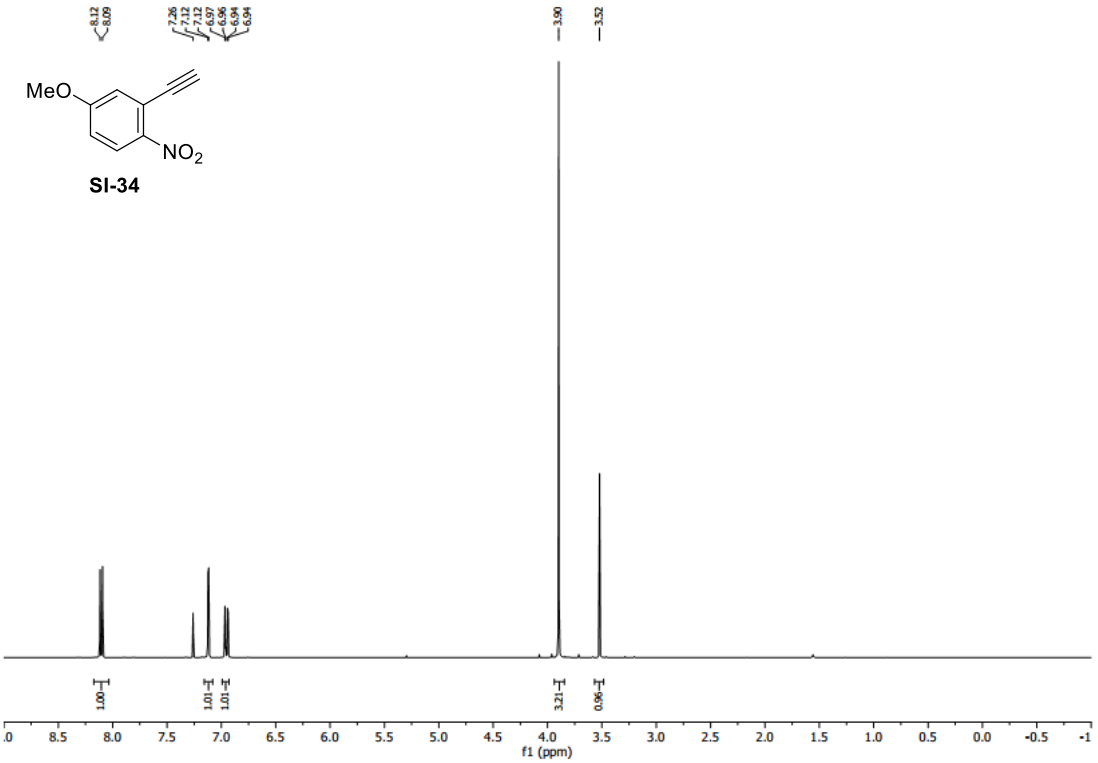


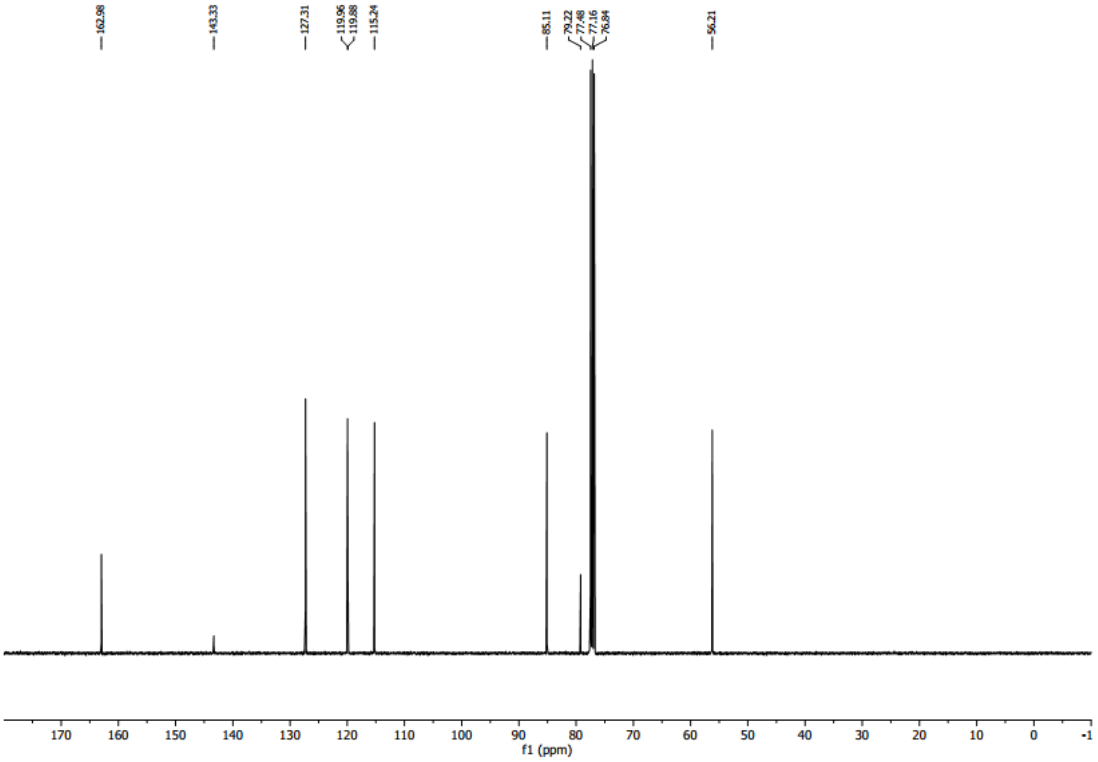
Compound **SI-33** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



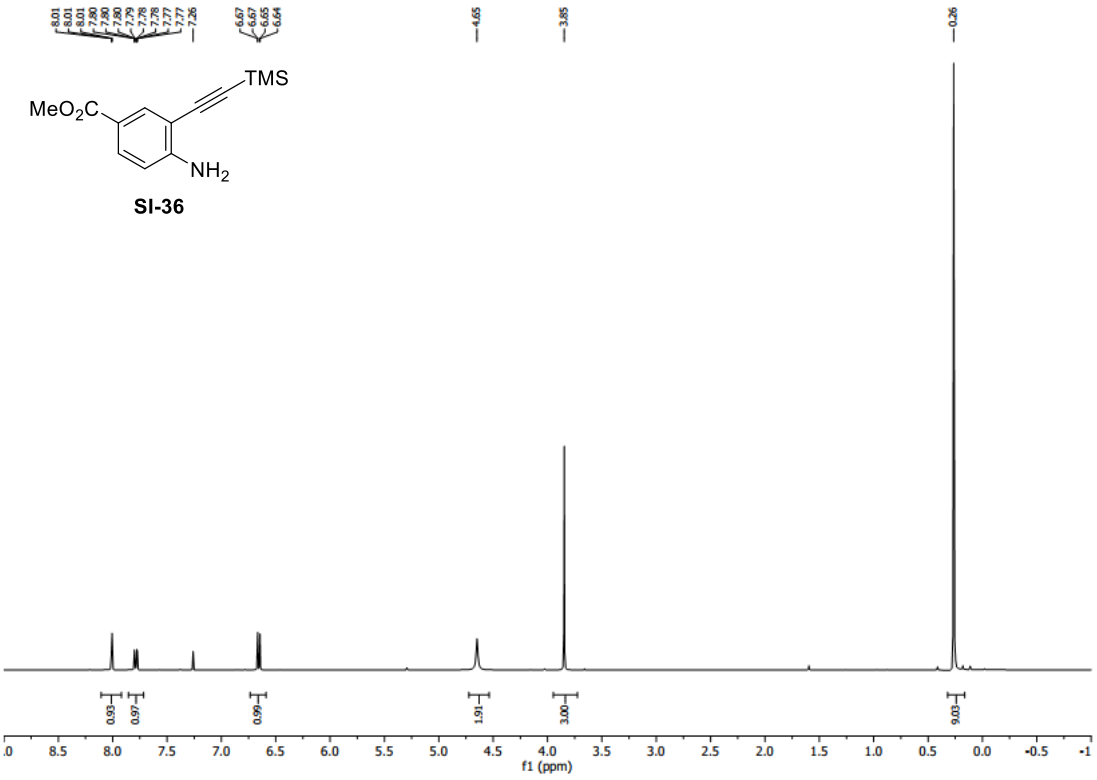


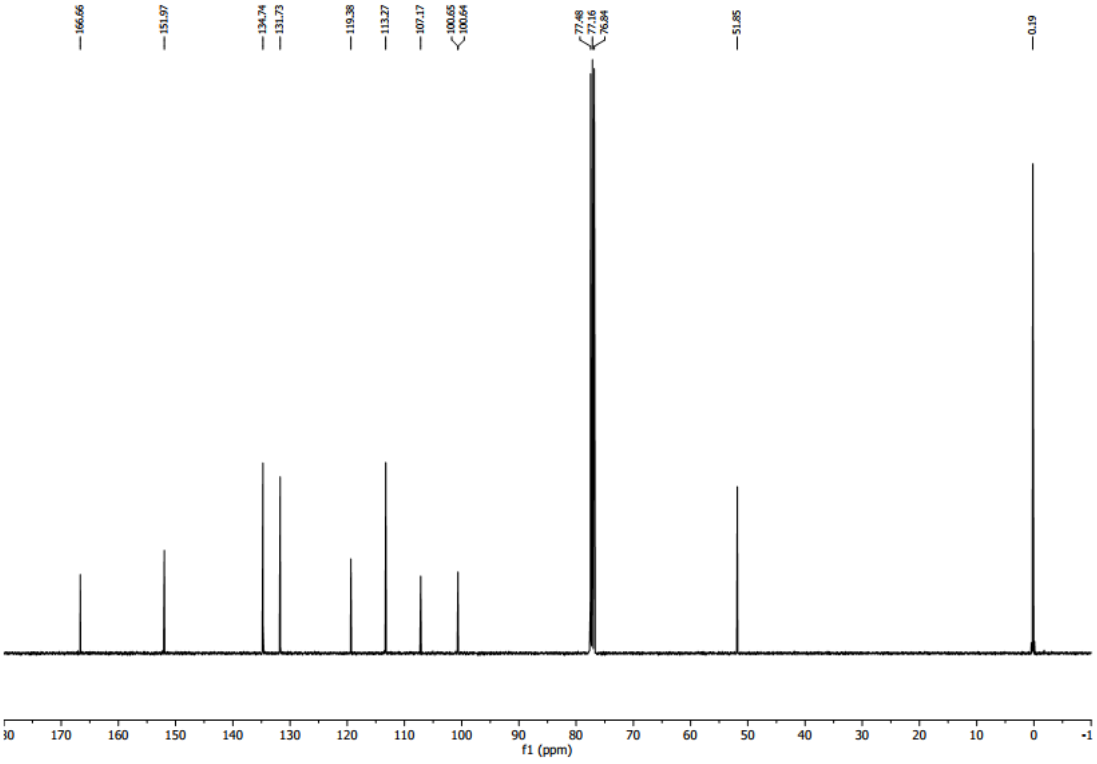
Compound **SI-34** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



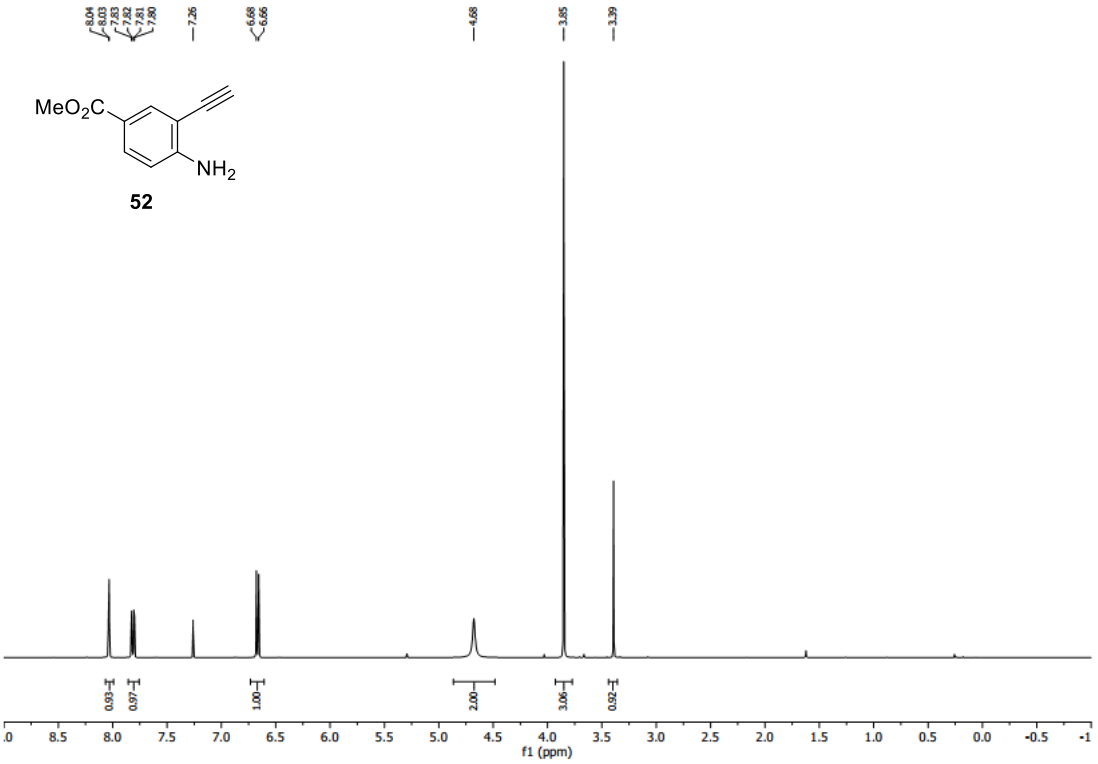


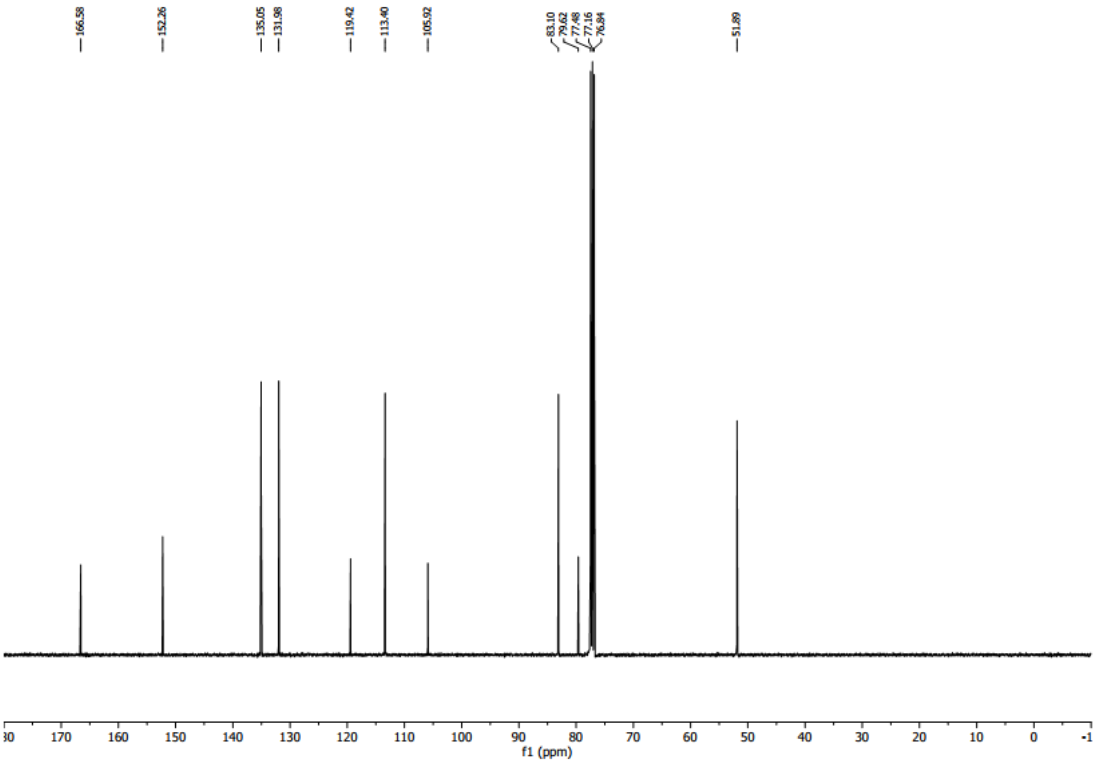
Compound **SI-36** – ^{1}**H-NMR** (400 MHz) and ^{13}**C-NMR** (100 MHz) in $CDCl_3$



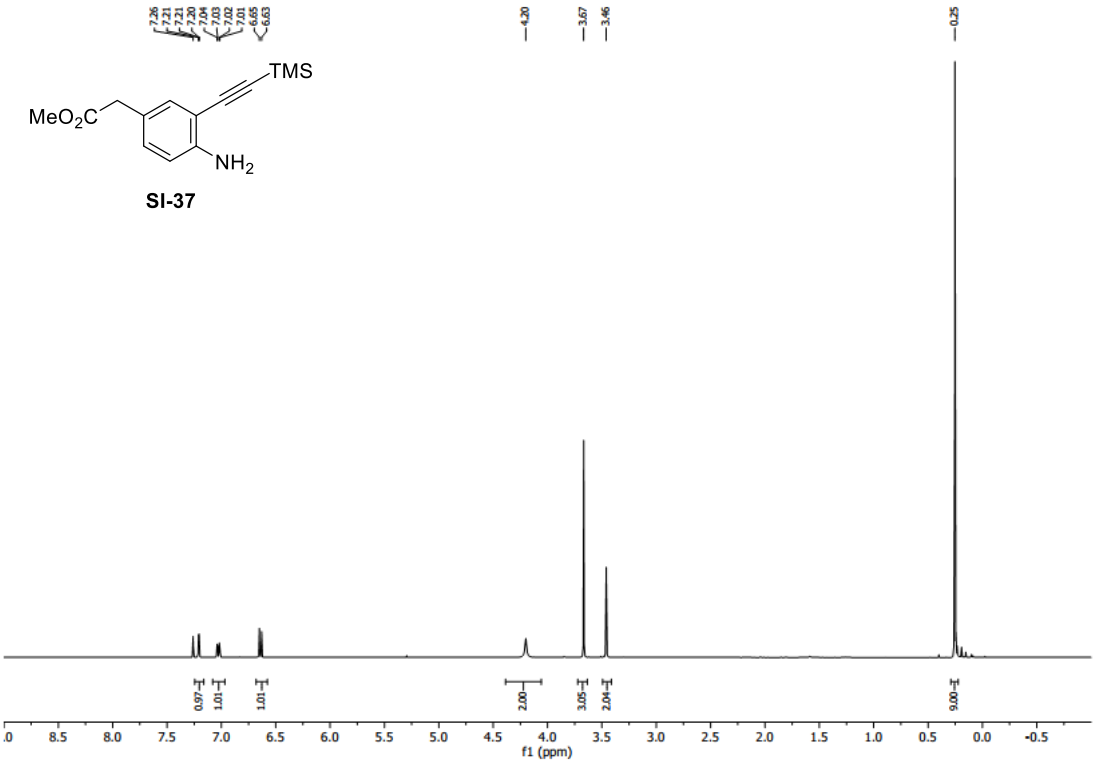


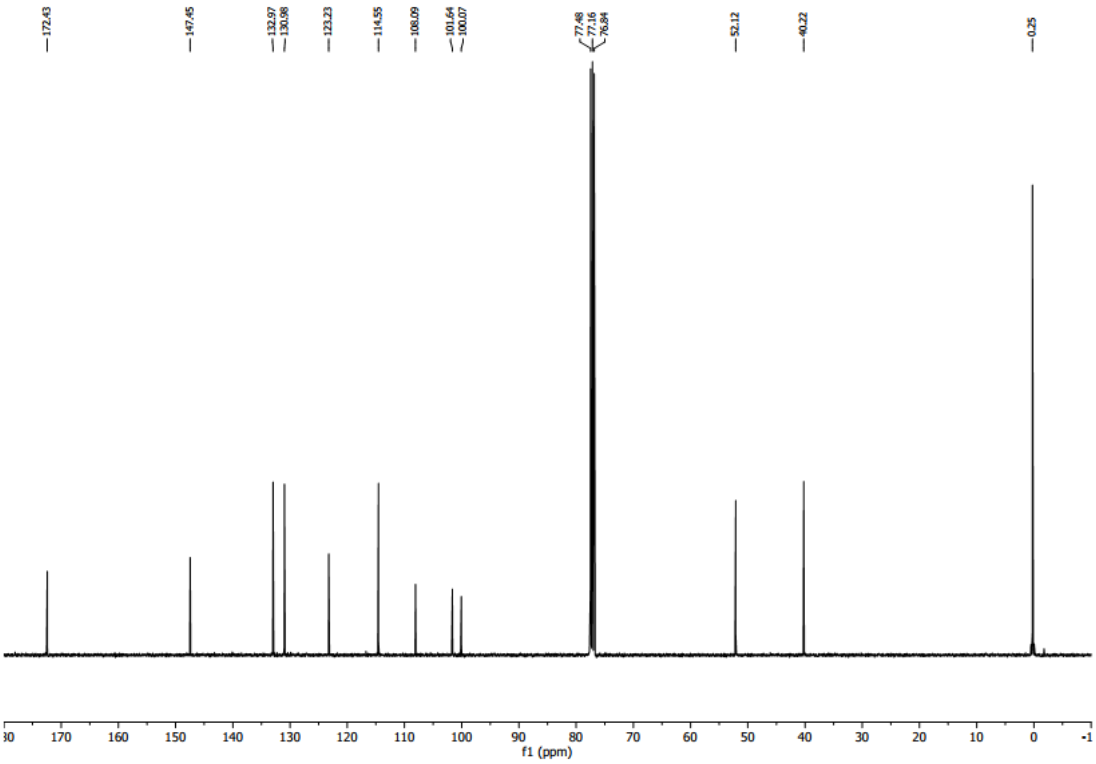
Compound **52** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



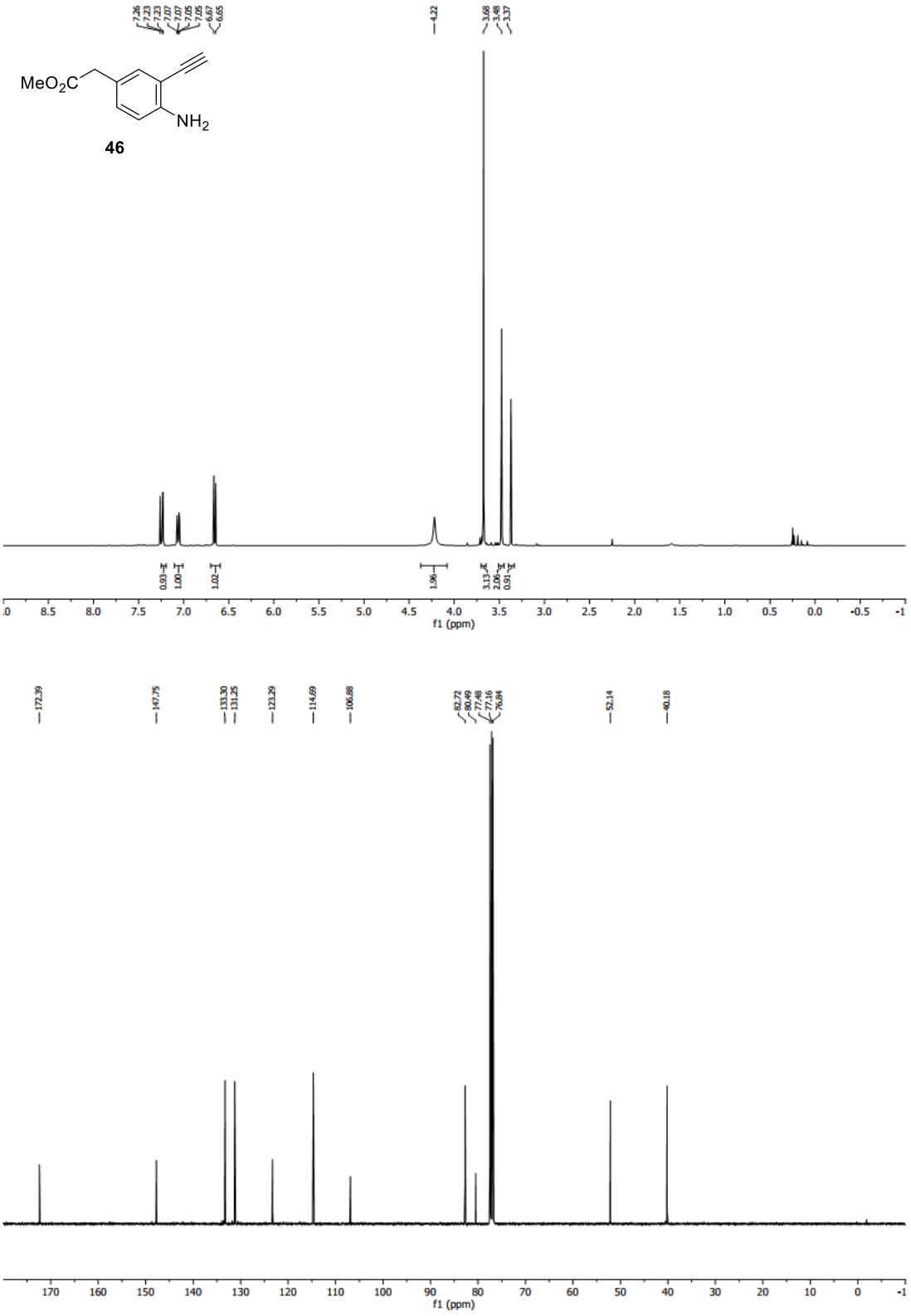


Compound **SI-37** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

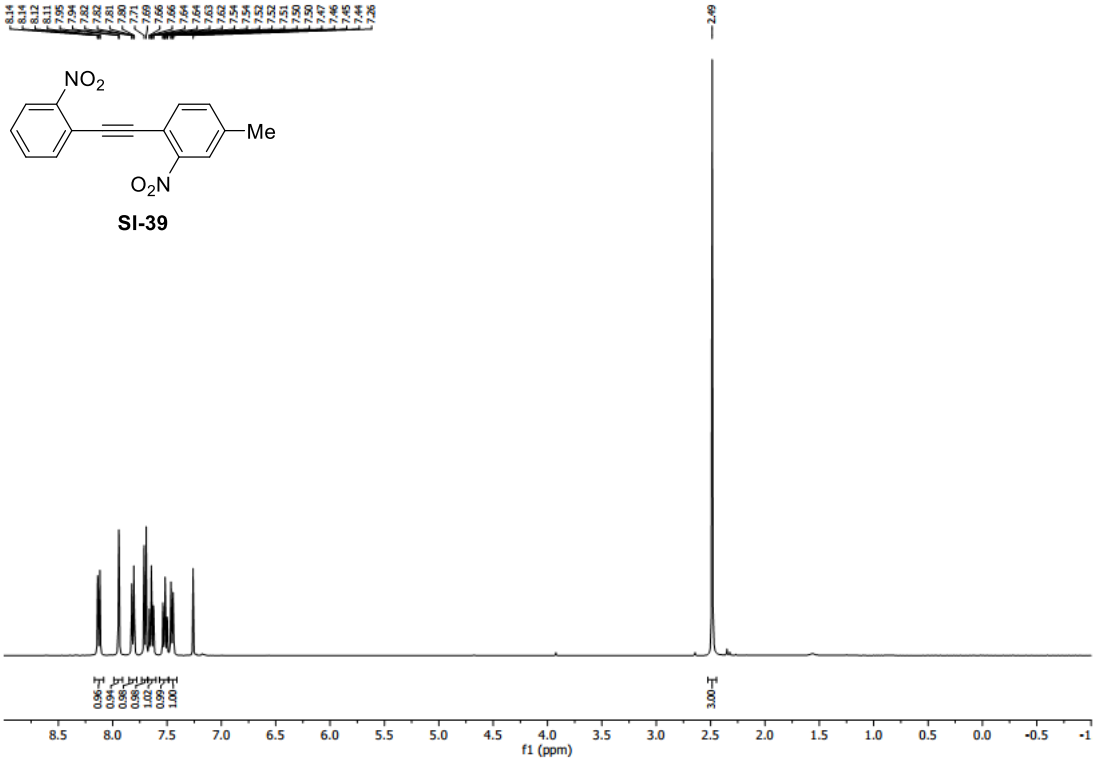


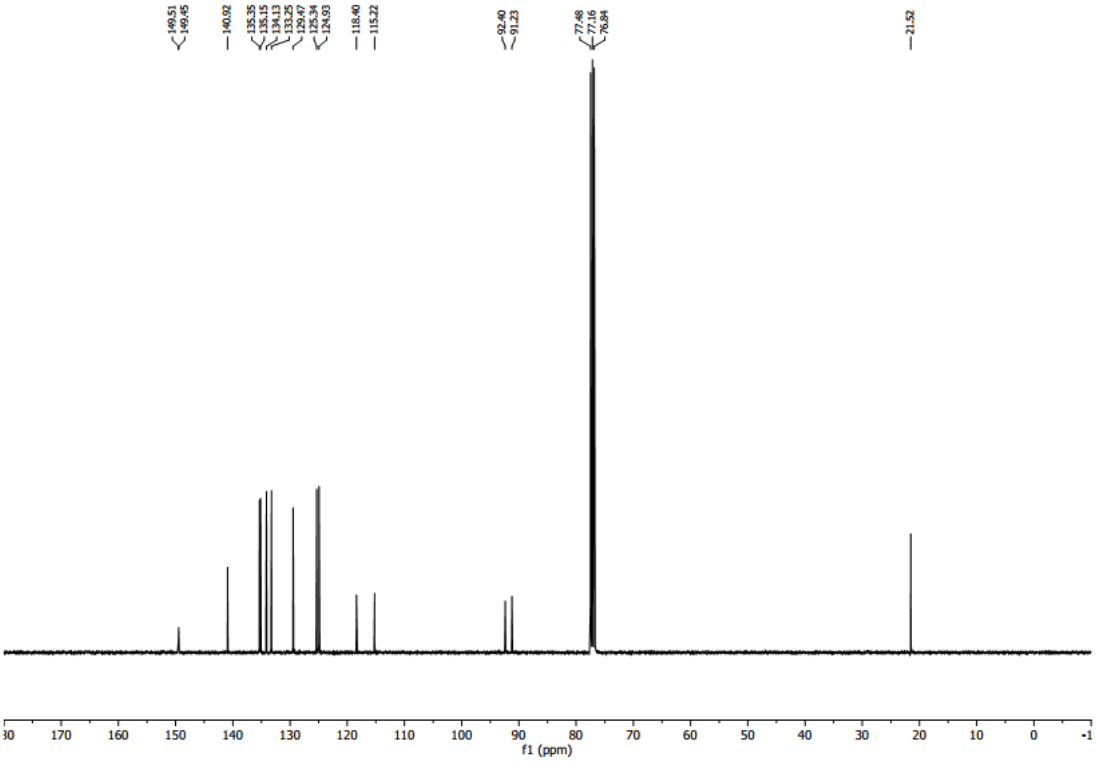


Compound **46** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

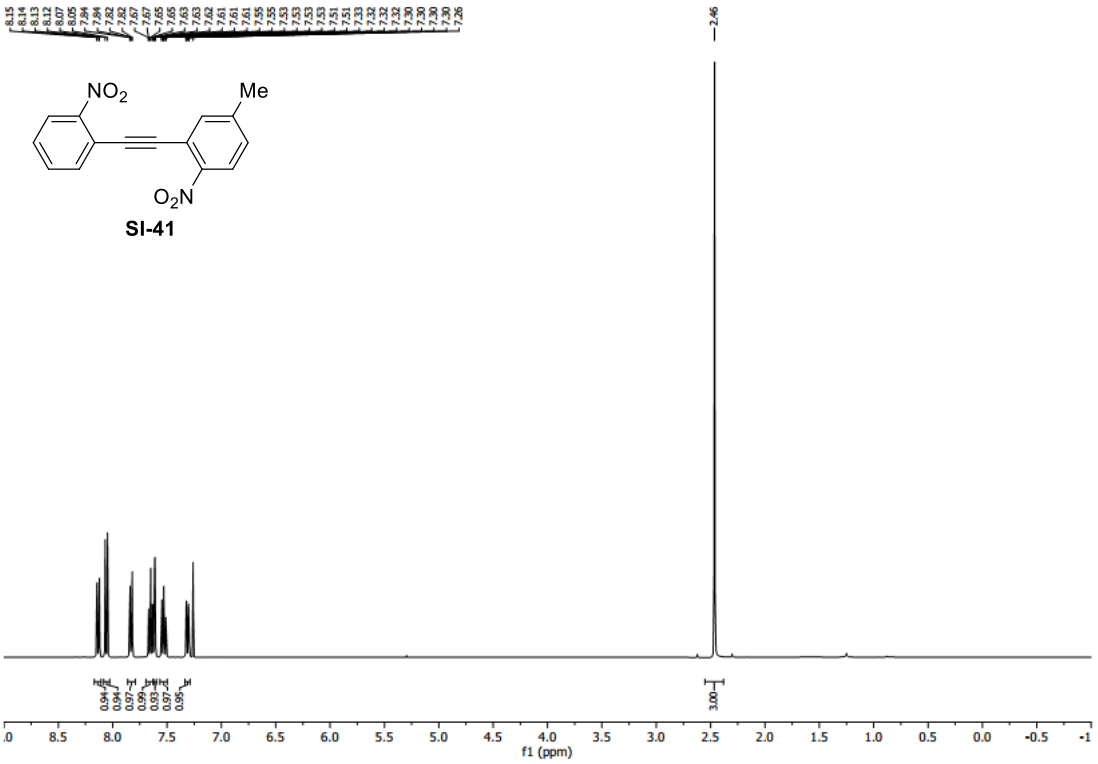


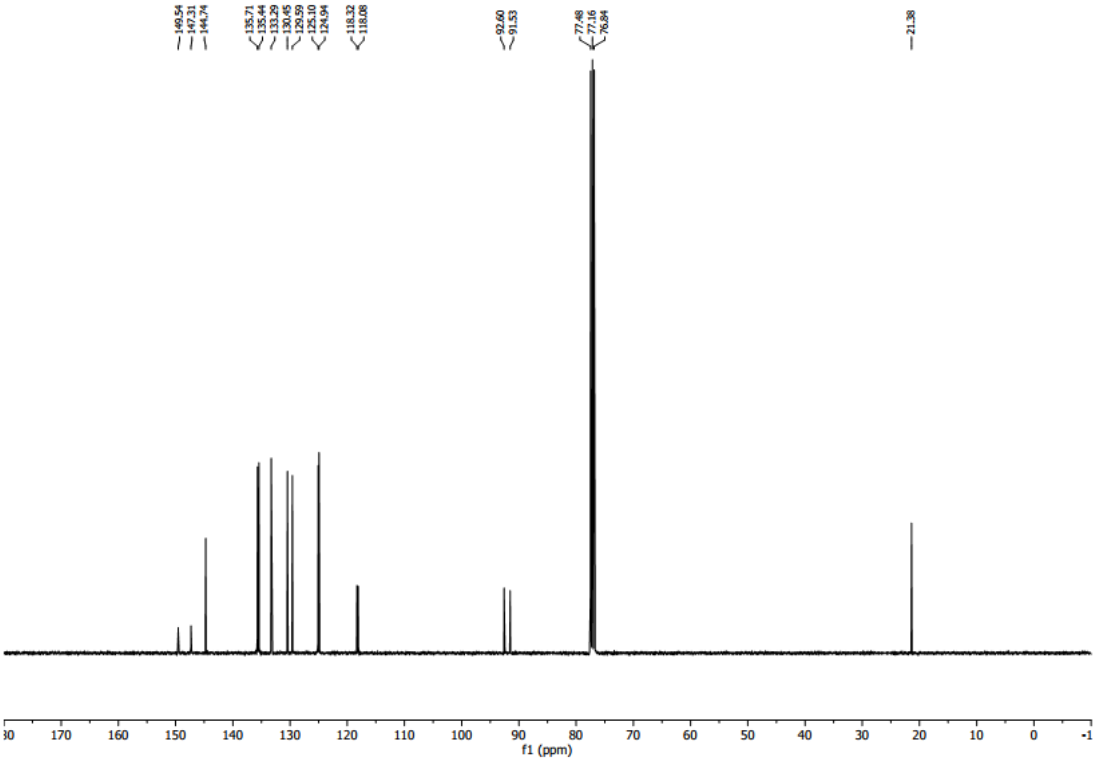
Compound **SI-39** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



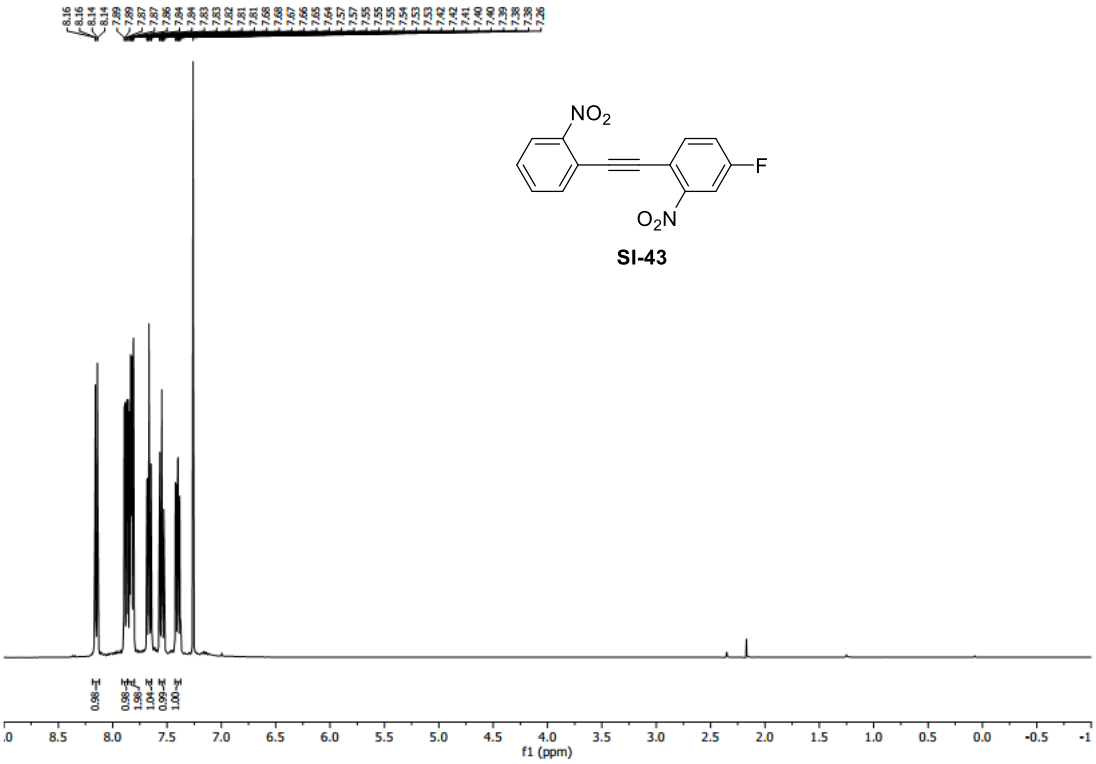


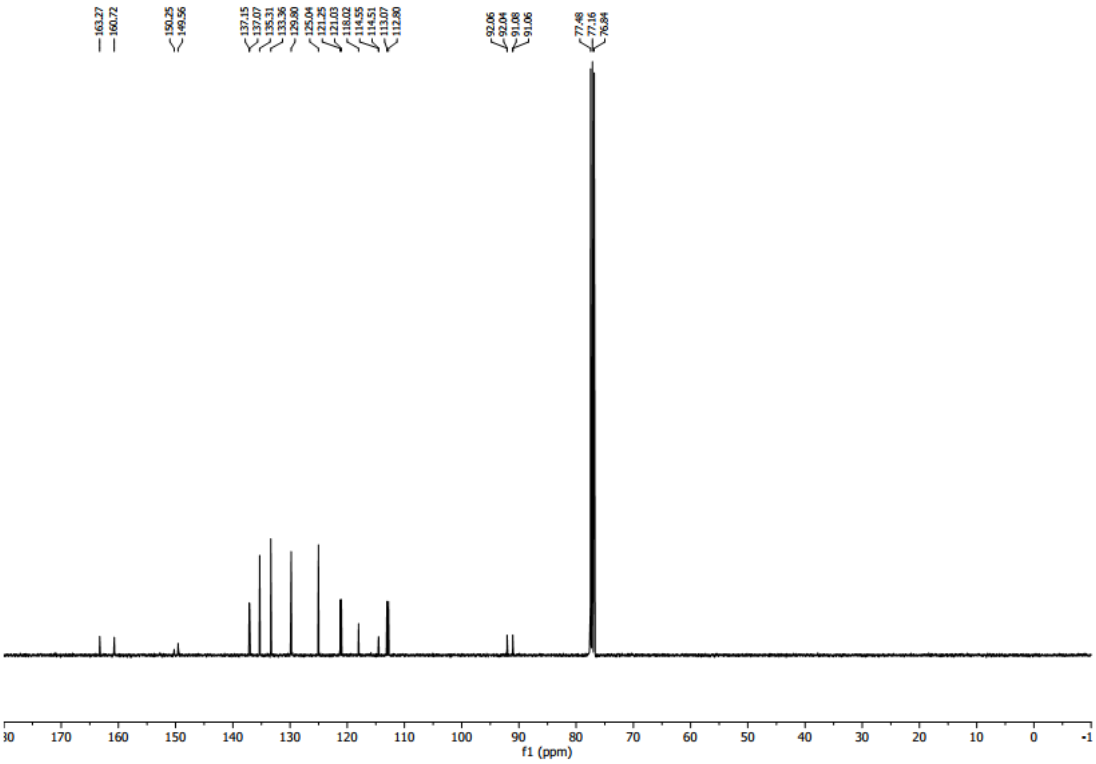
Compound **SI-41** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



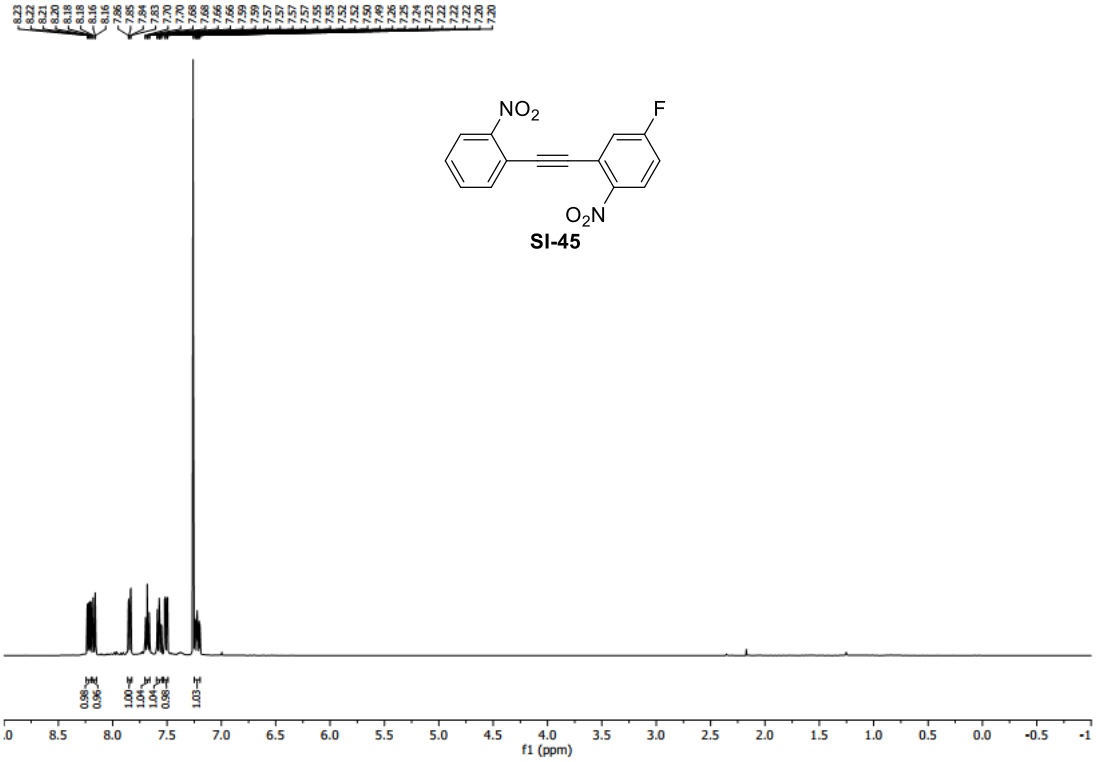


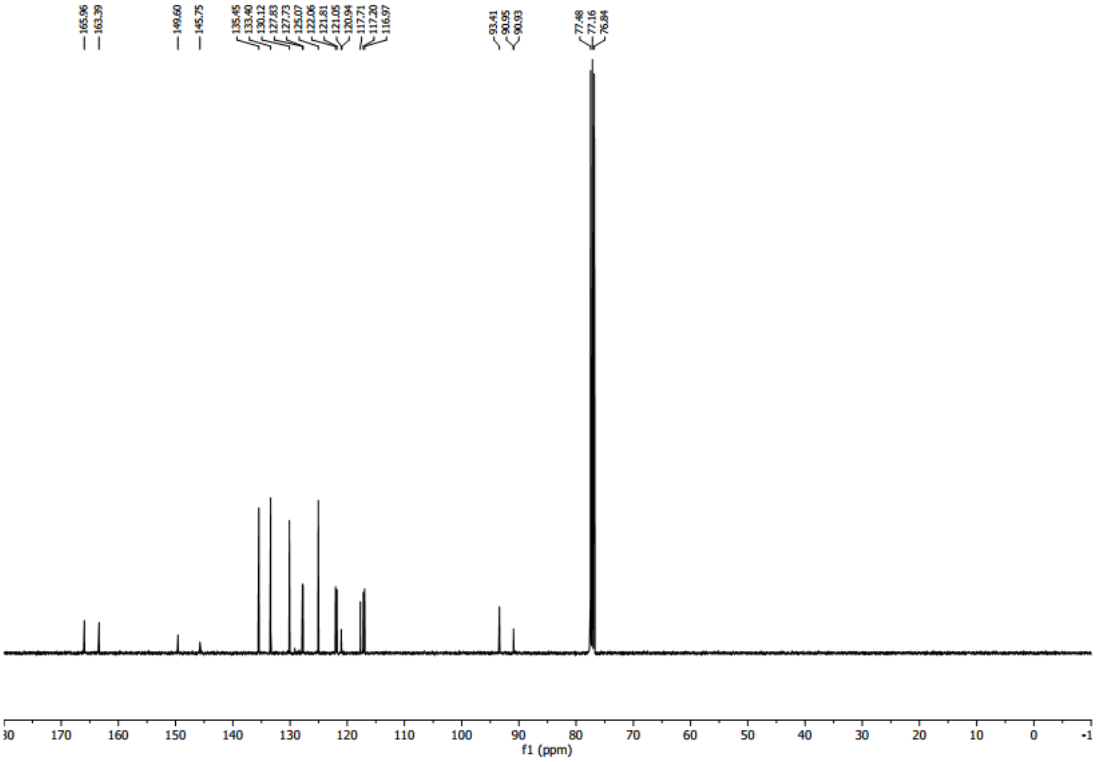
Compound **SI-43** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



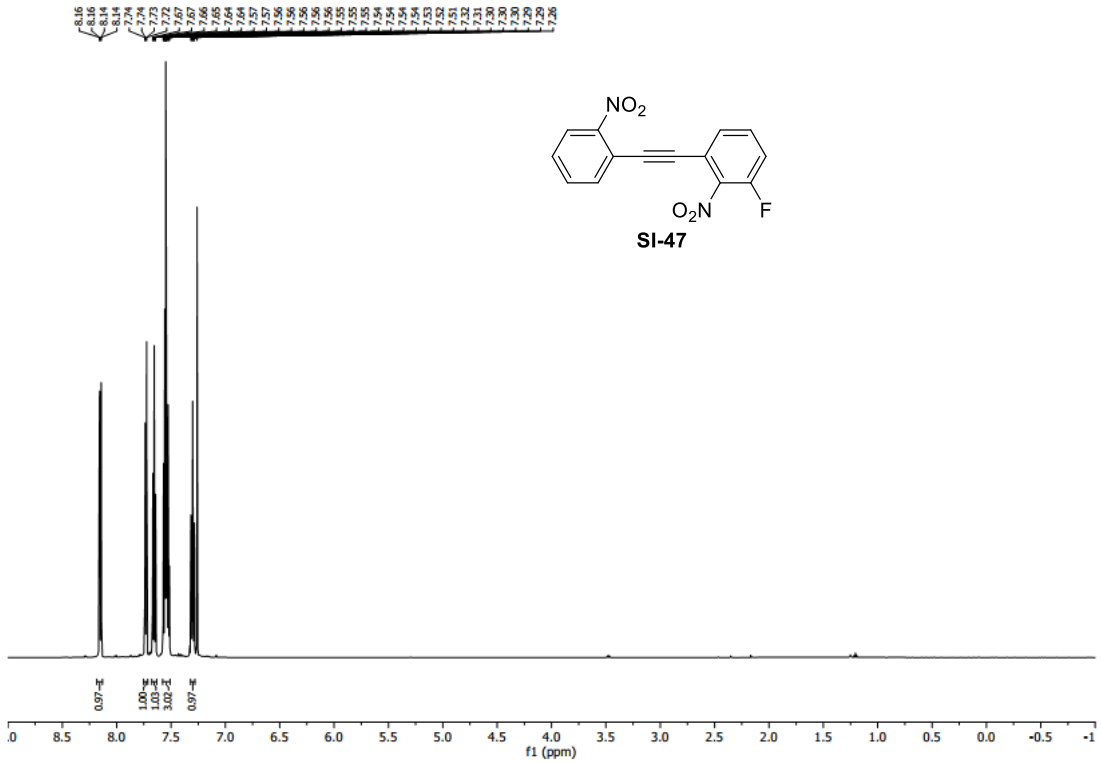


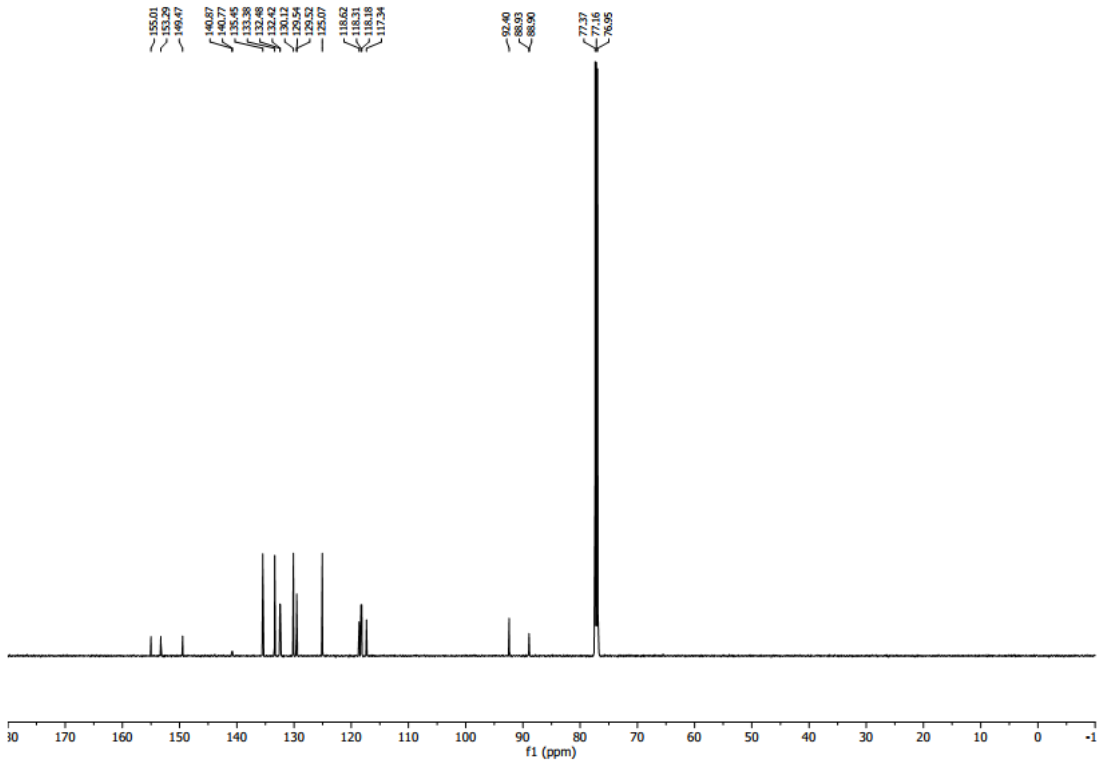
Compound **SI-45** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



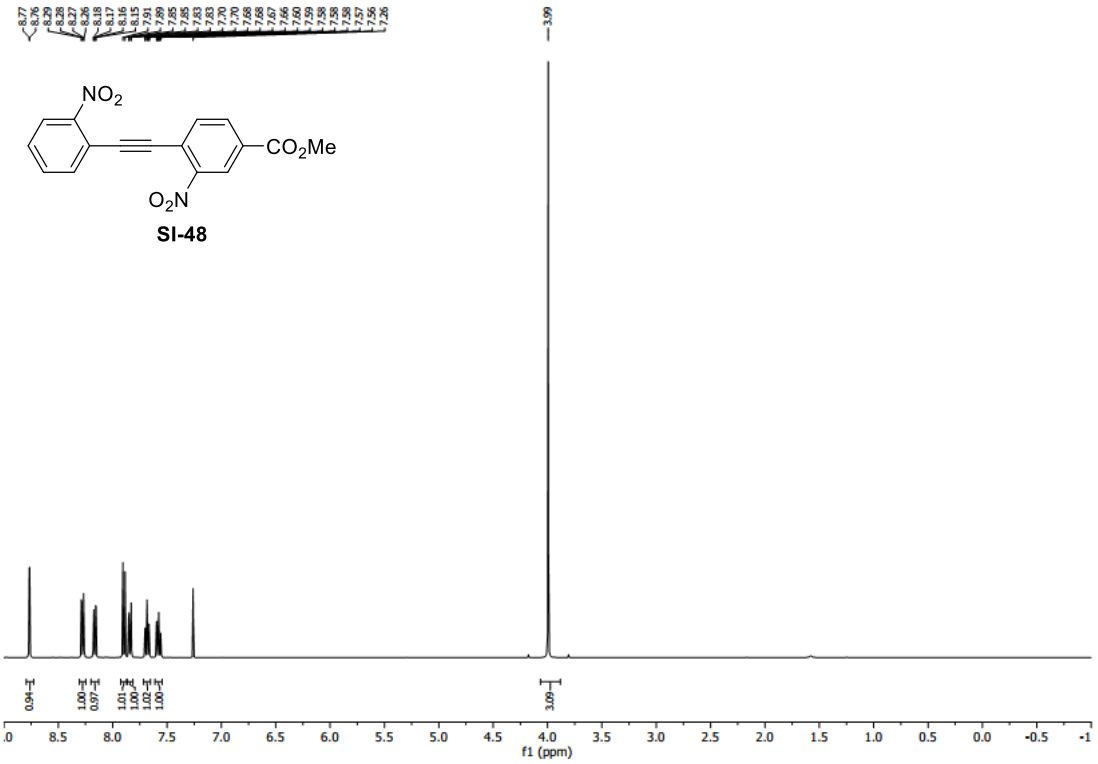


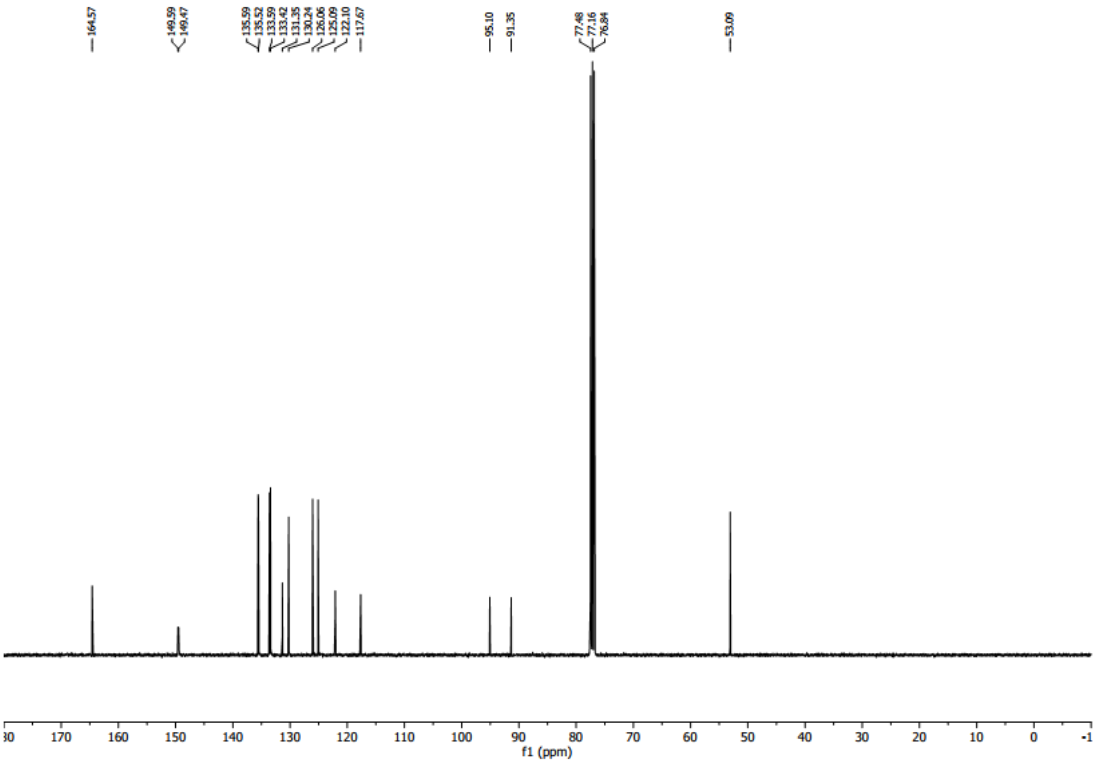
Compound **SI-47** – **^{1}H-NMR** (600 MHz) and **^{13}C-NMR** (150 MHz) in $CDCl_3$



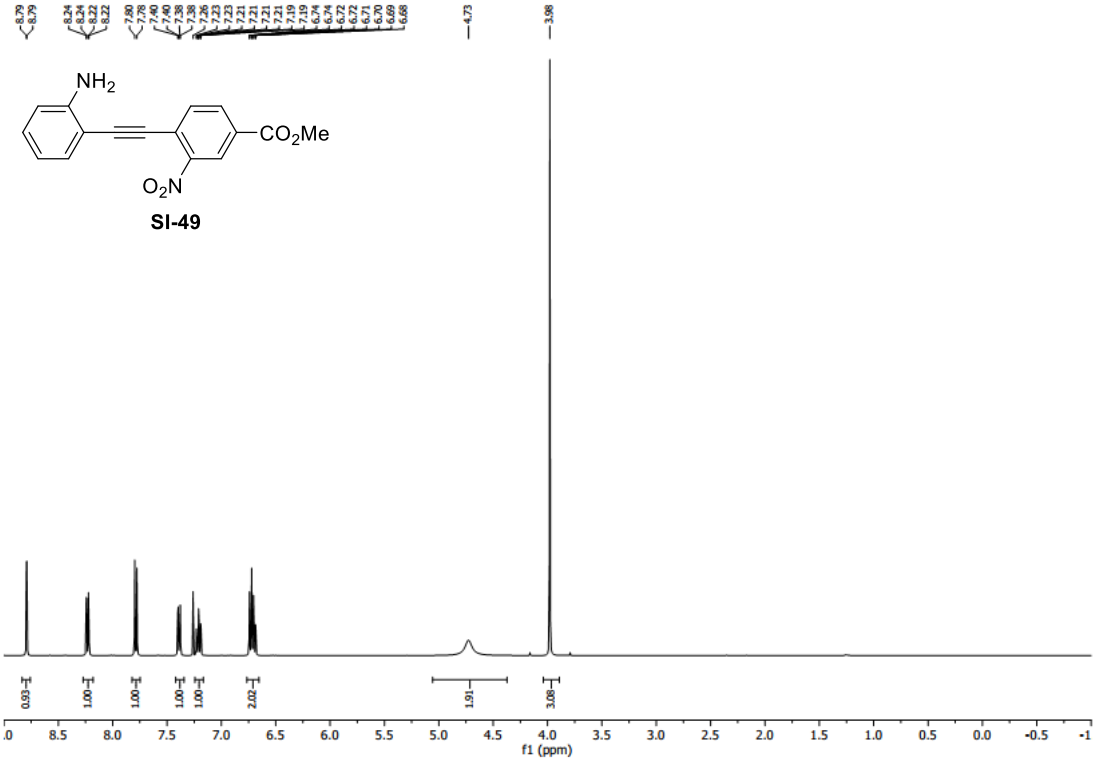


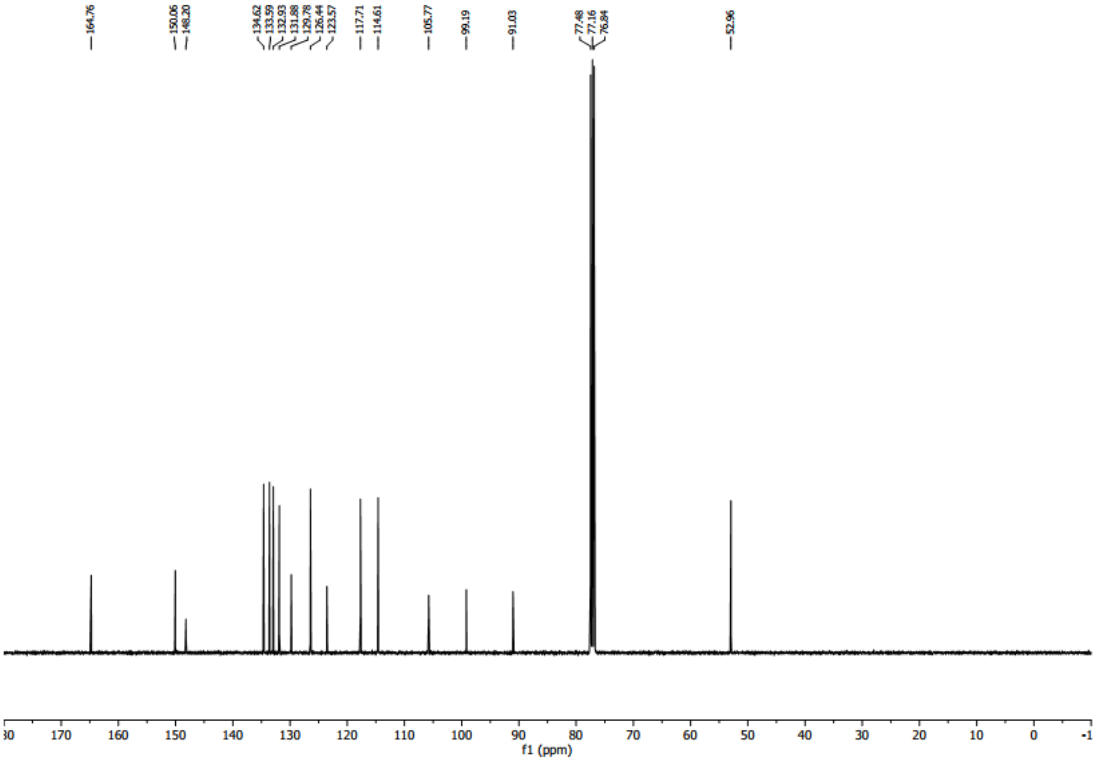
Compound **SI-48** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



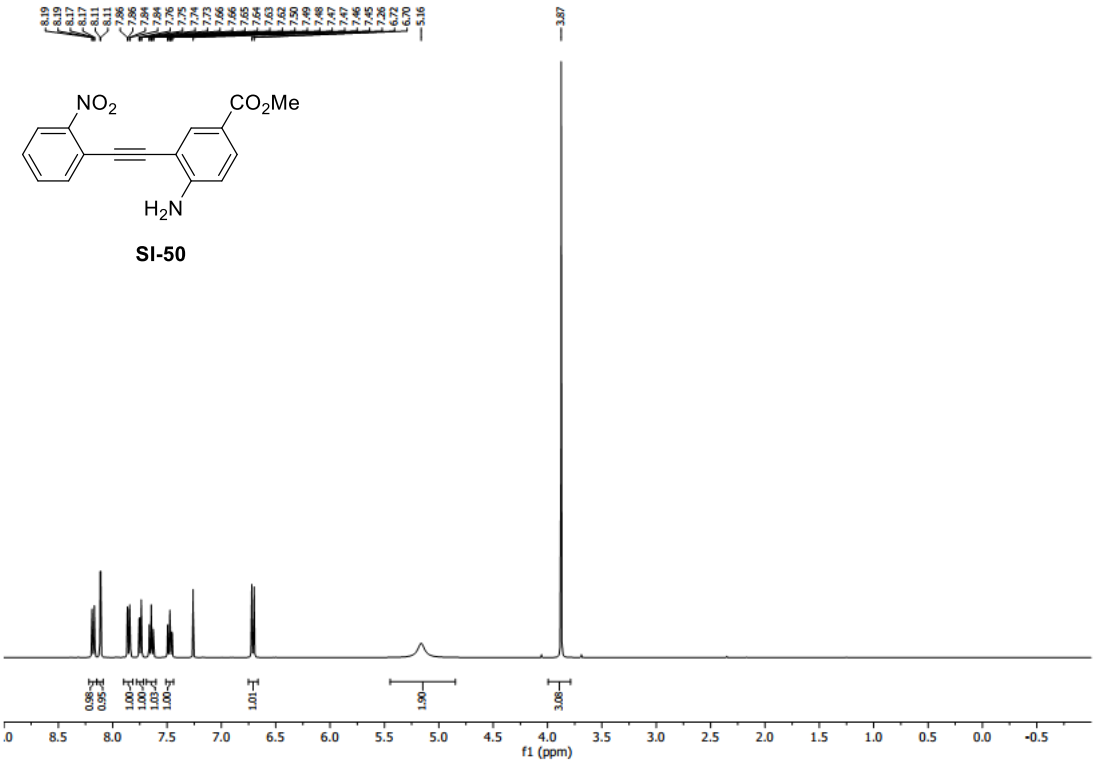


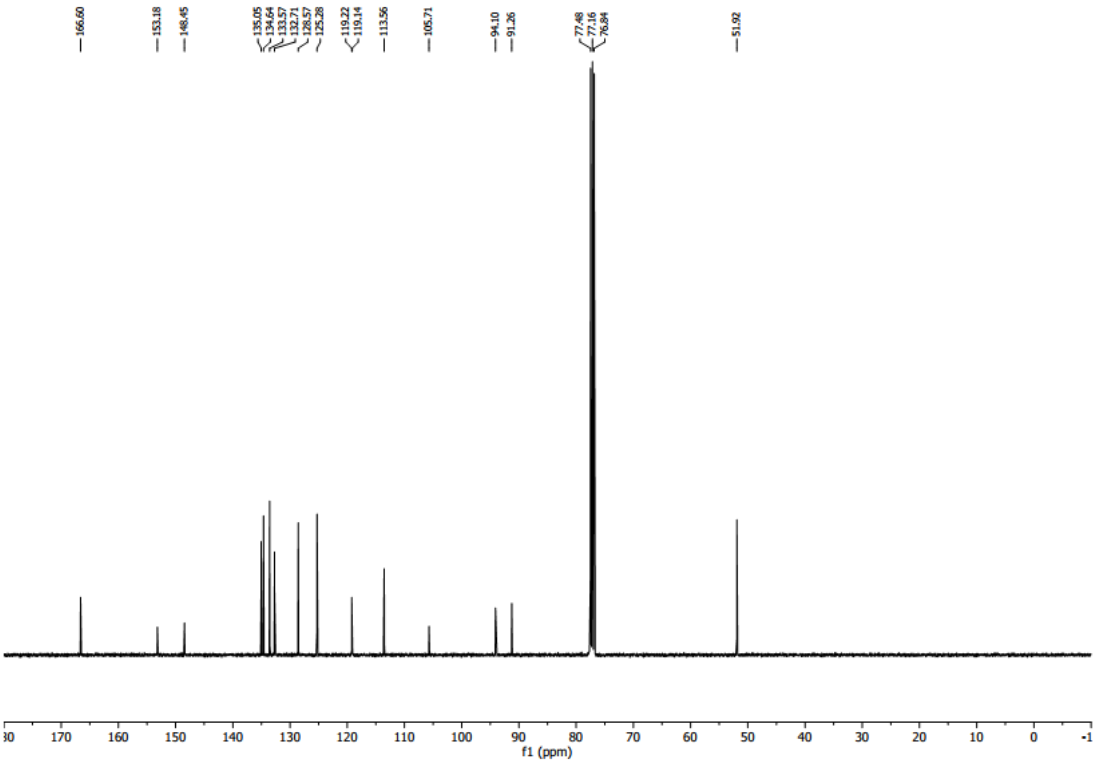
Compound **SI-49** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



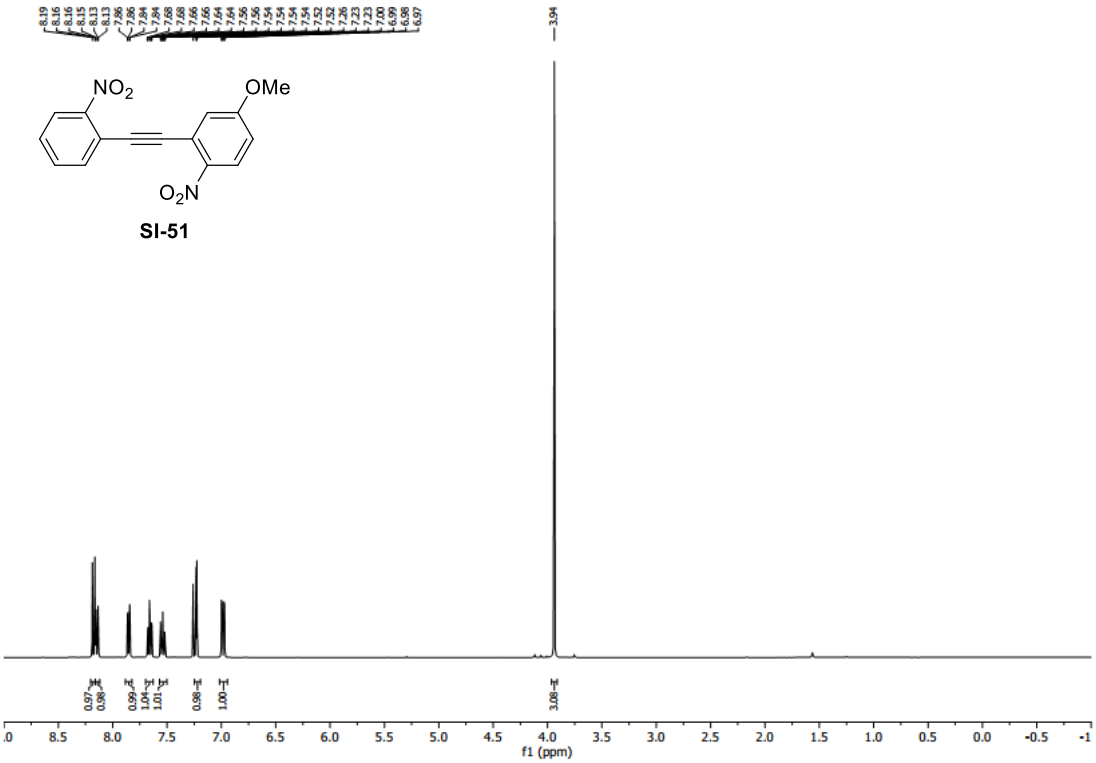


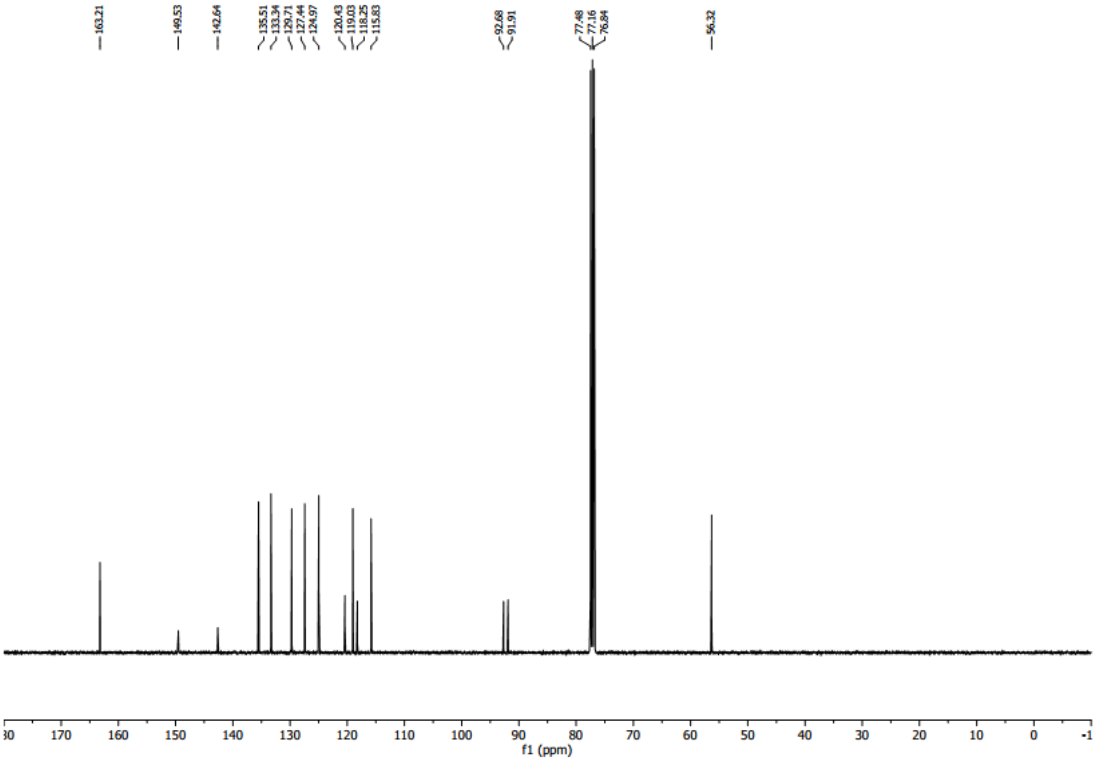
Compound **SI-50** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



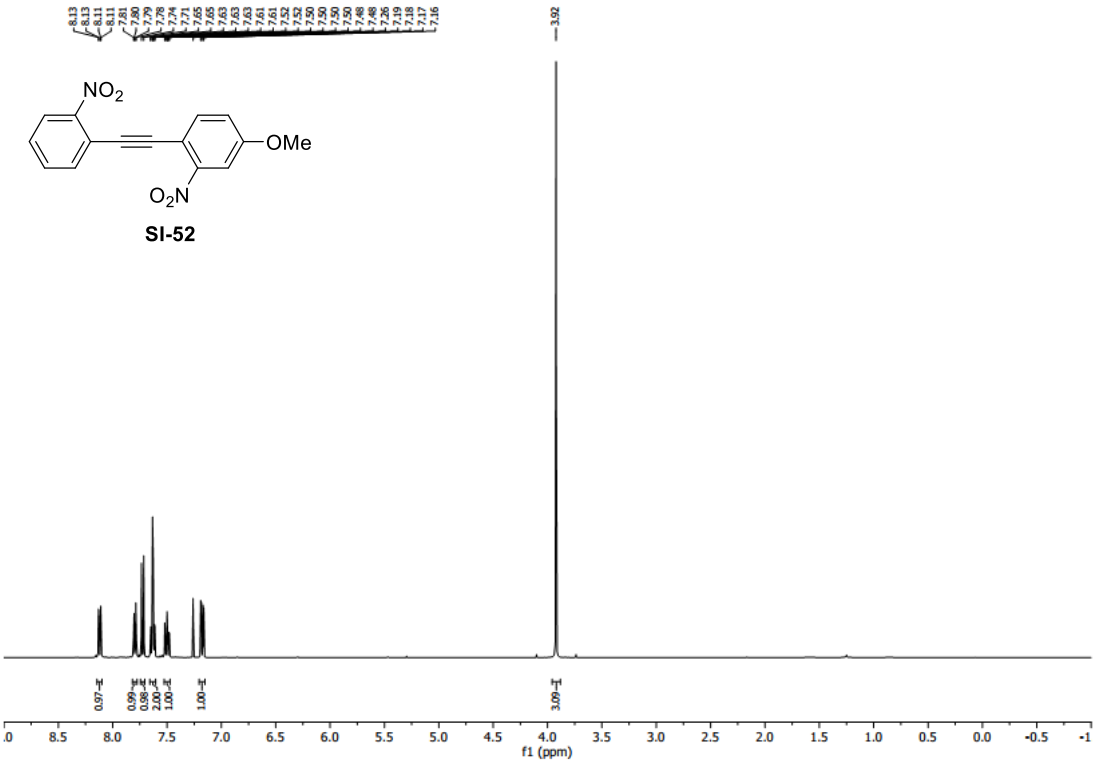


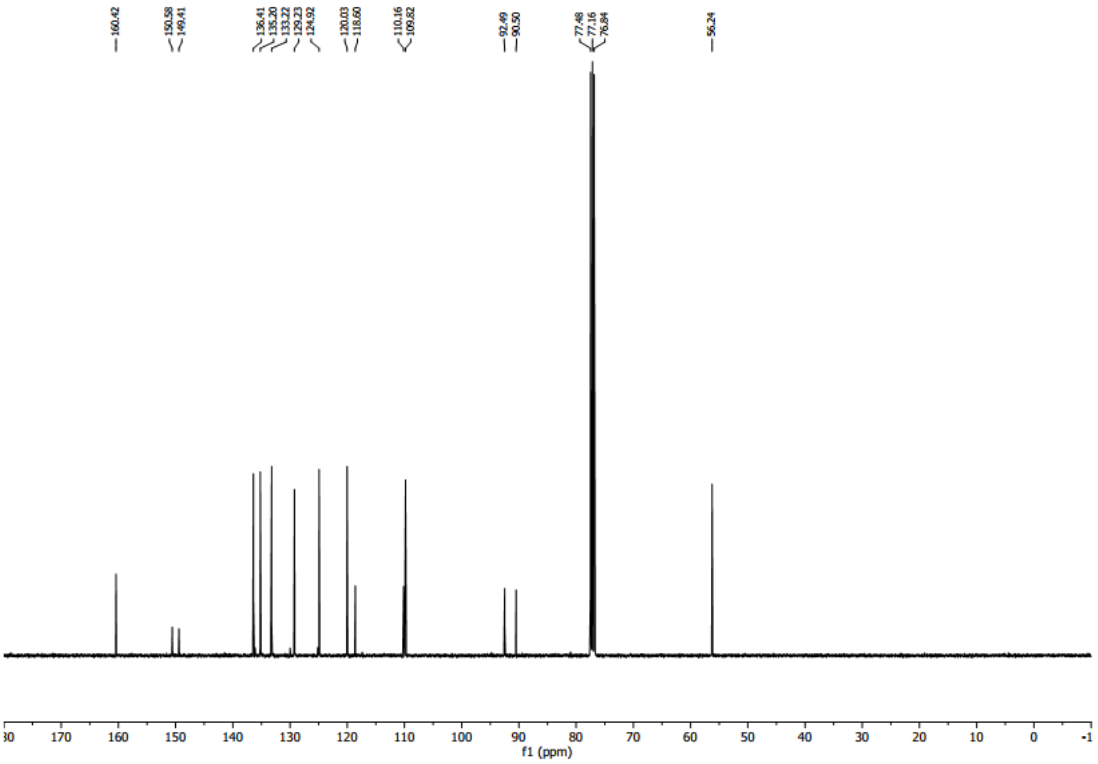
Compound **SI-51** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



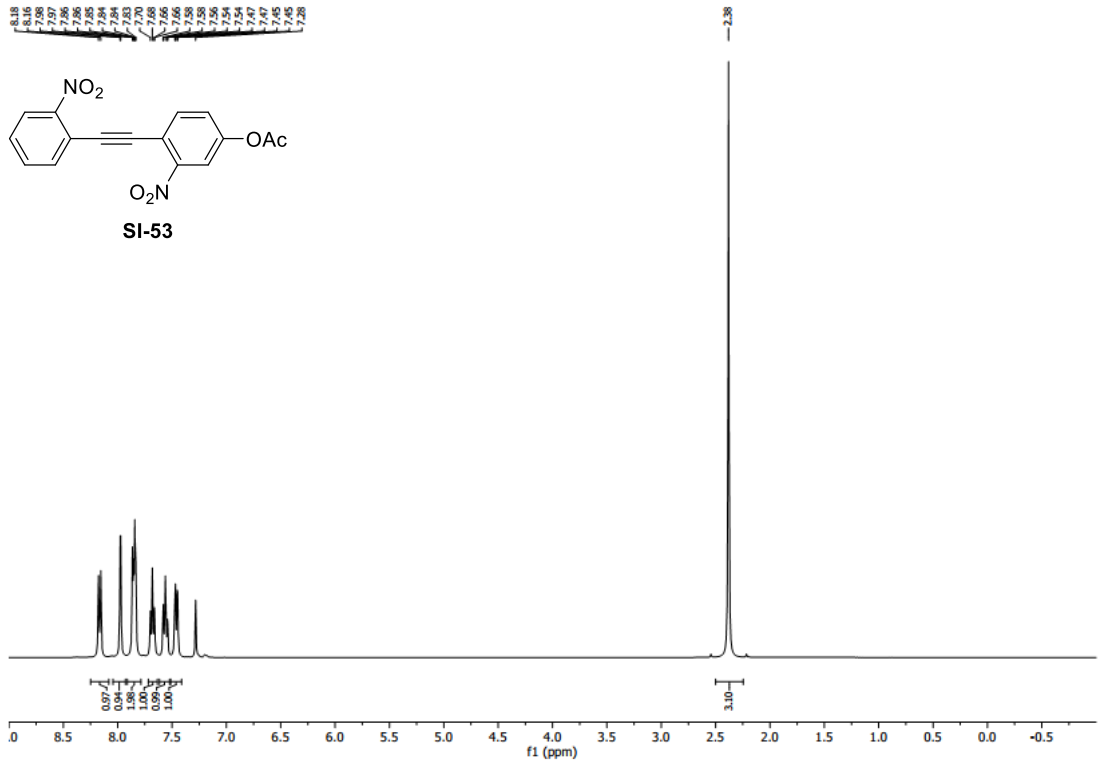


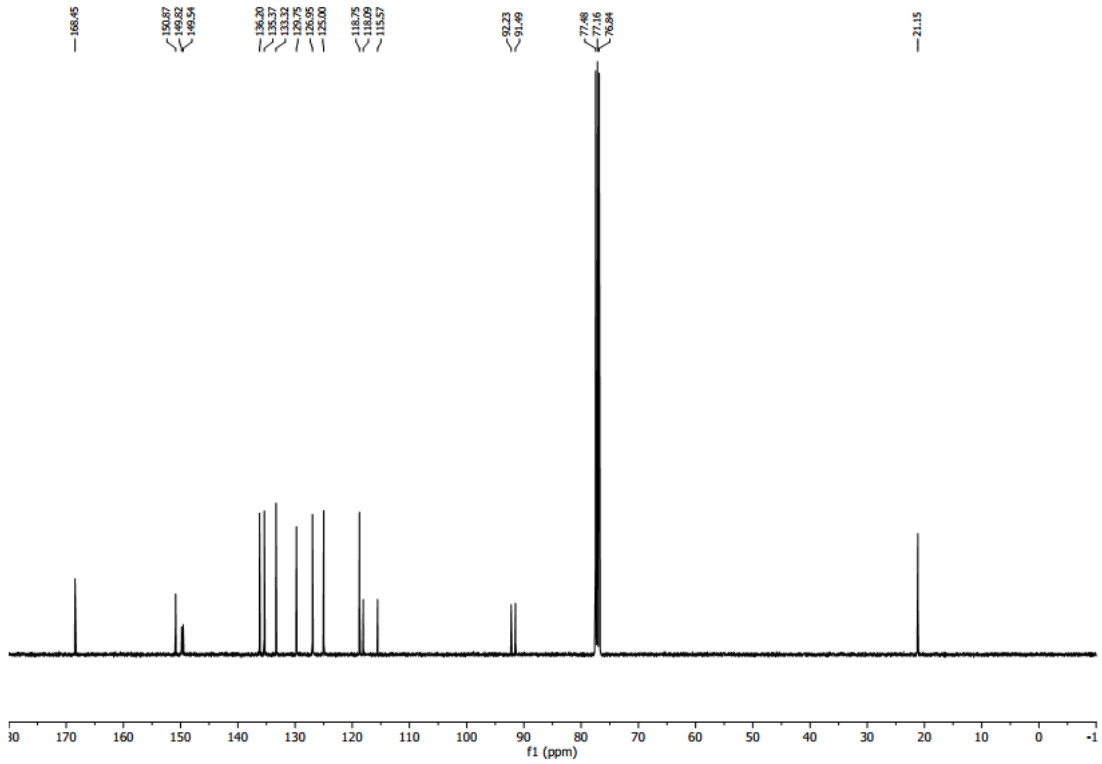
Compound **SI-52** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



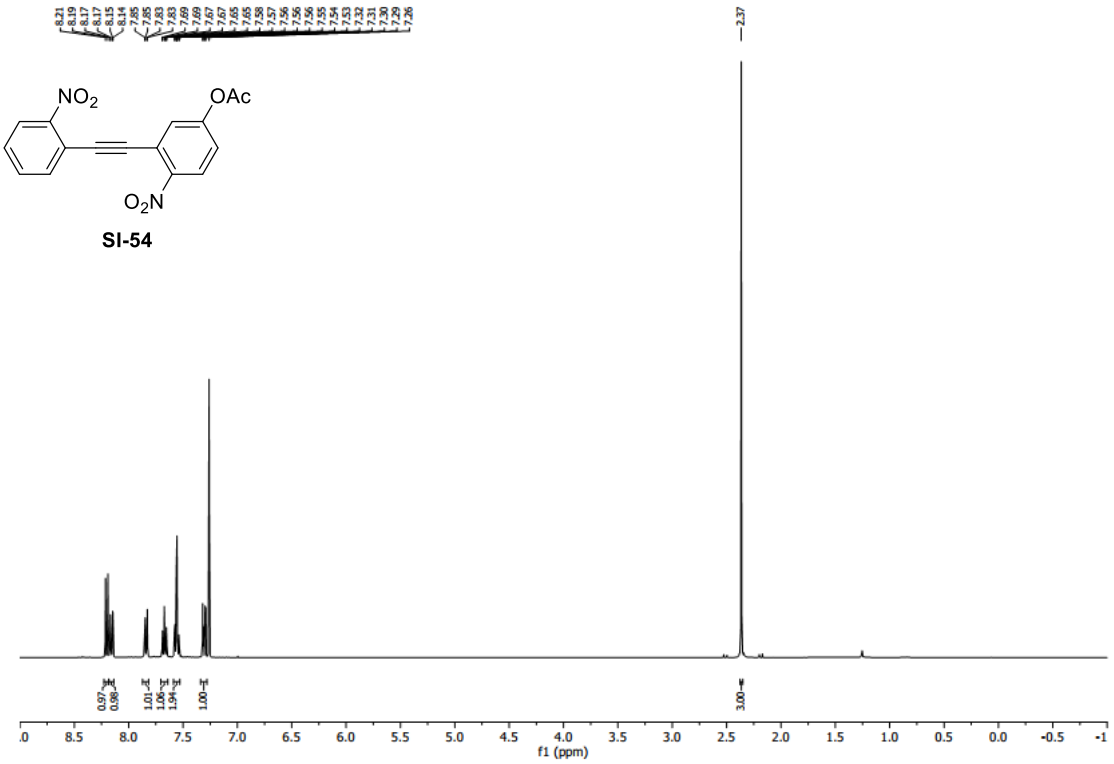


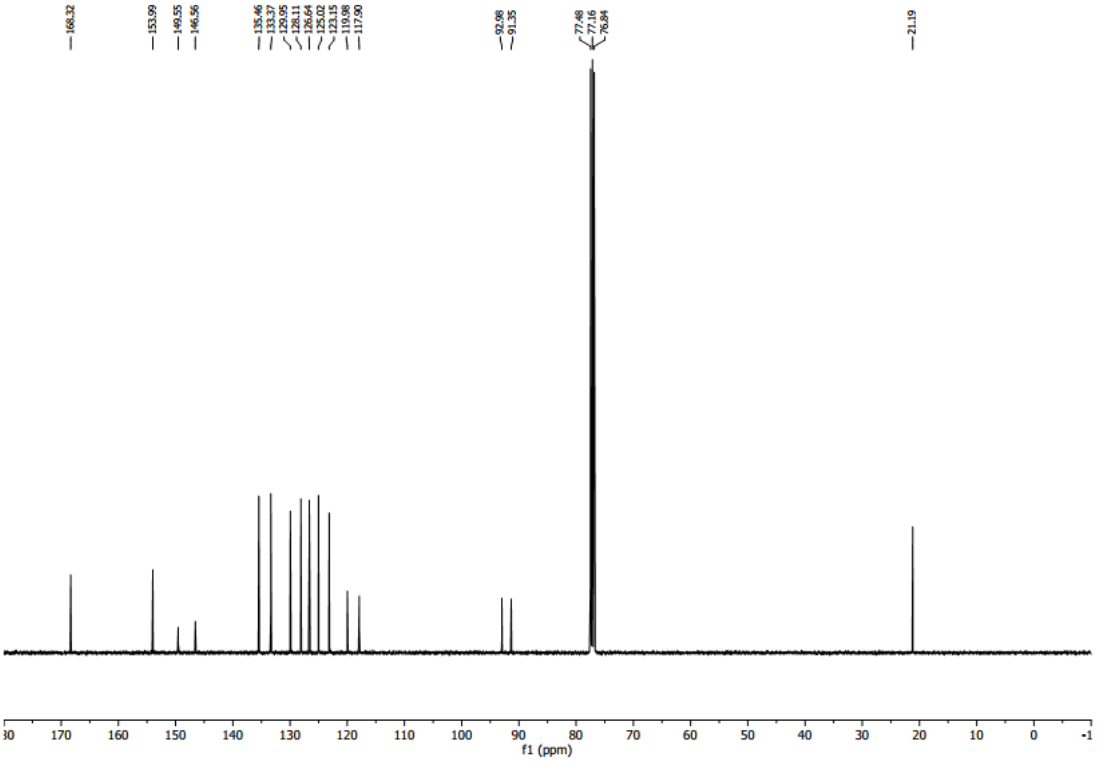
Compound **SI-53** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



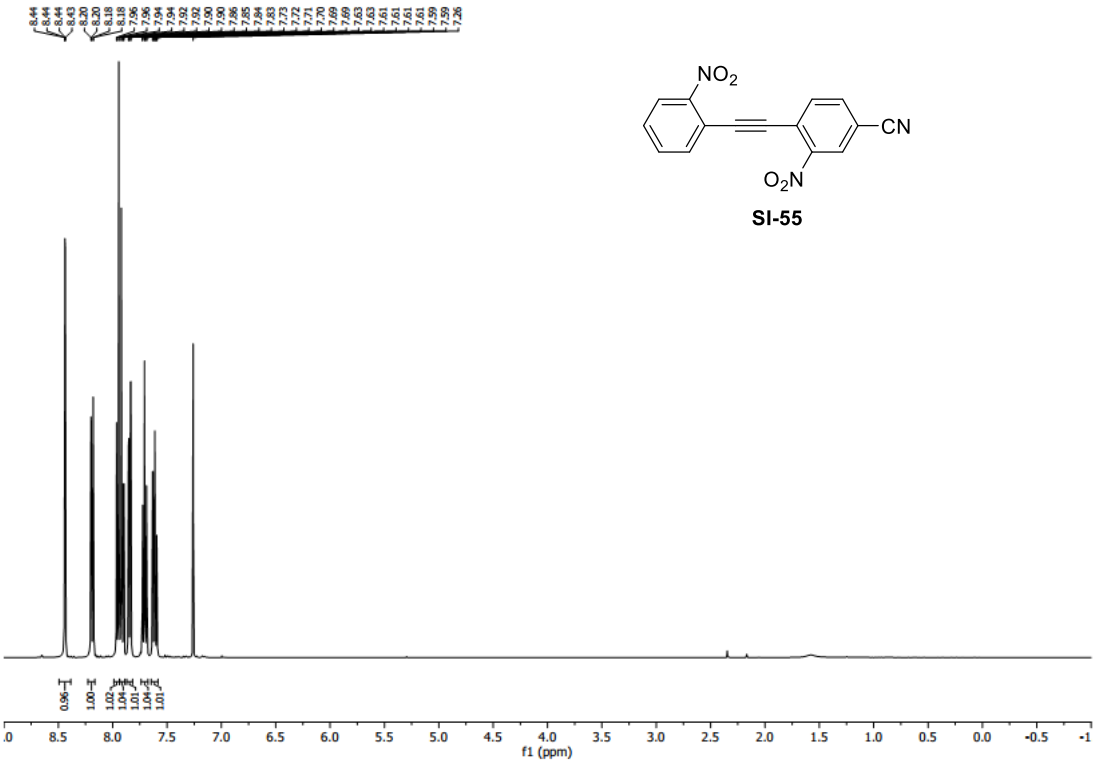


Compound **SI-54** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

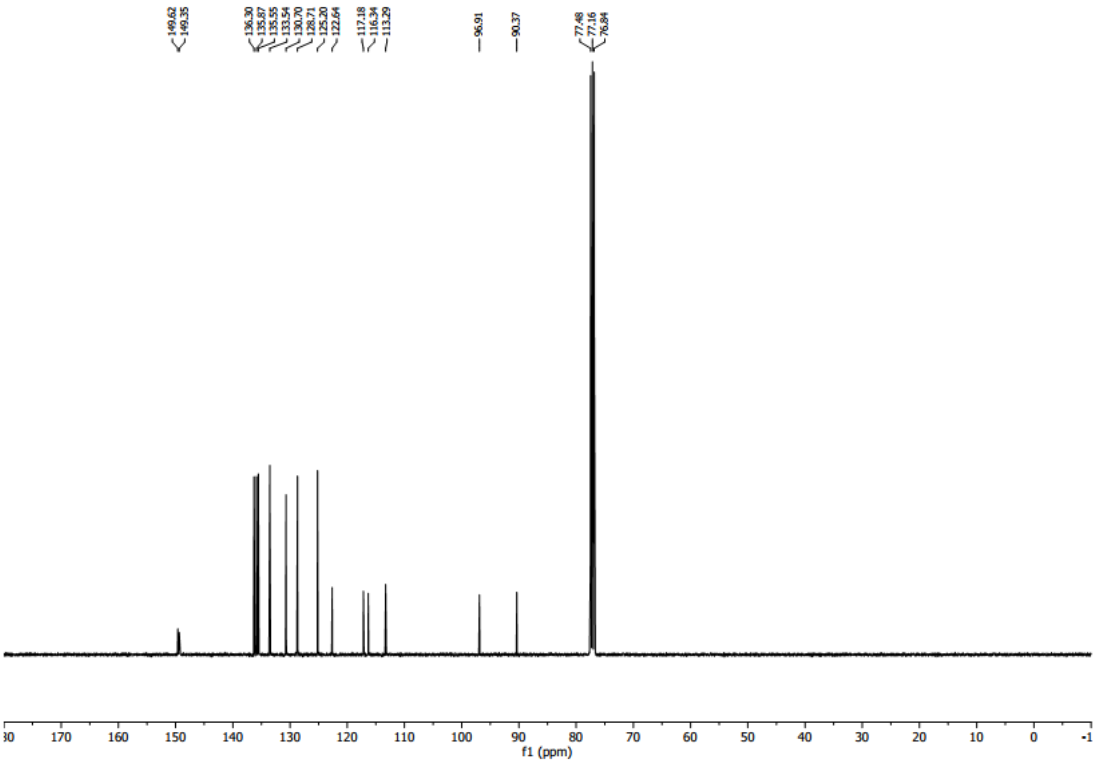




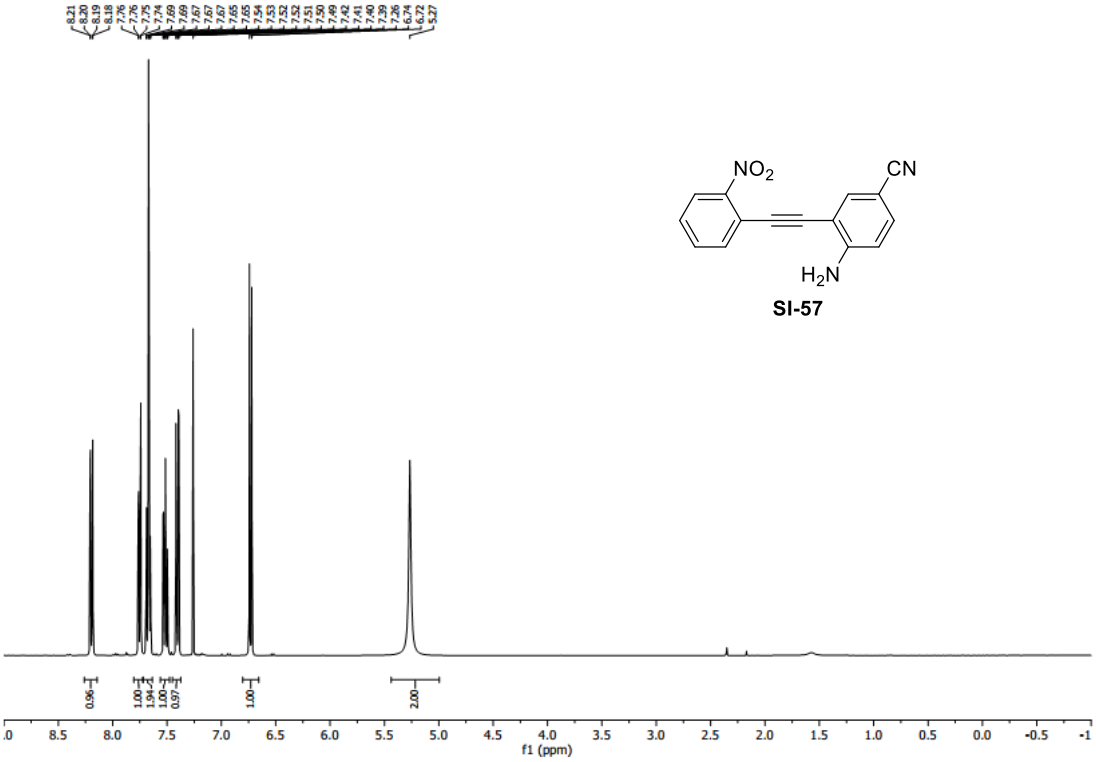
Compound **SI-55** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

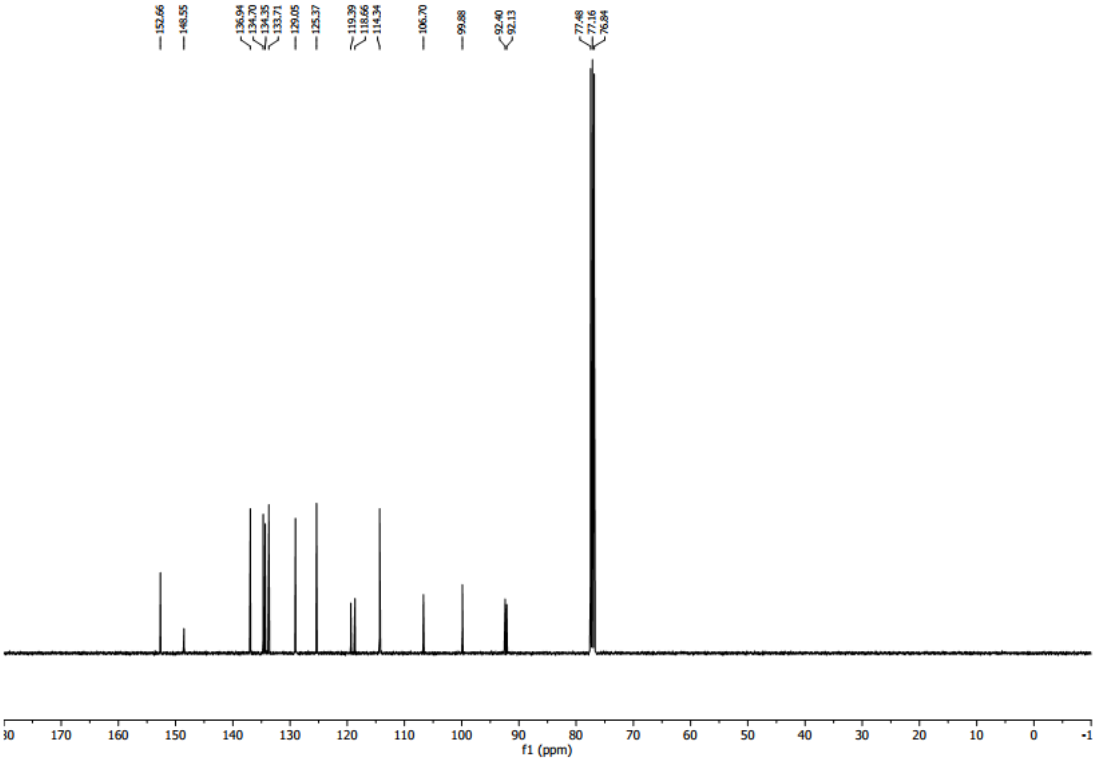


SI-55

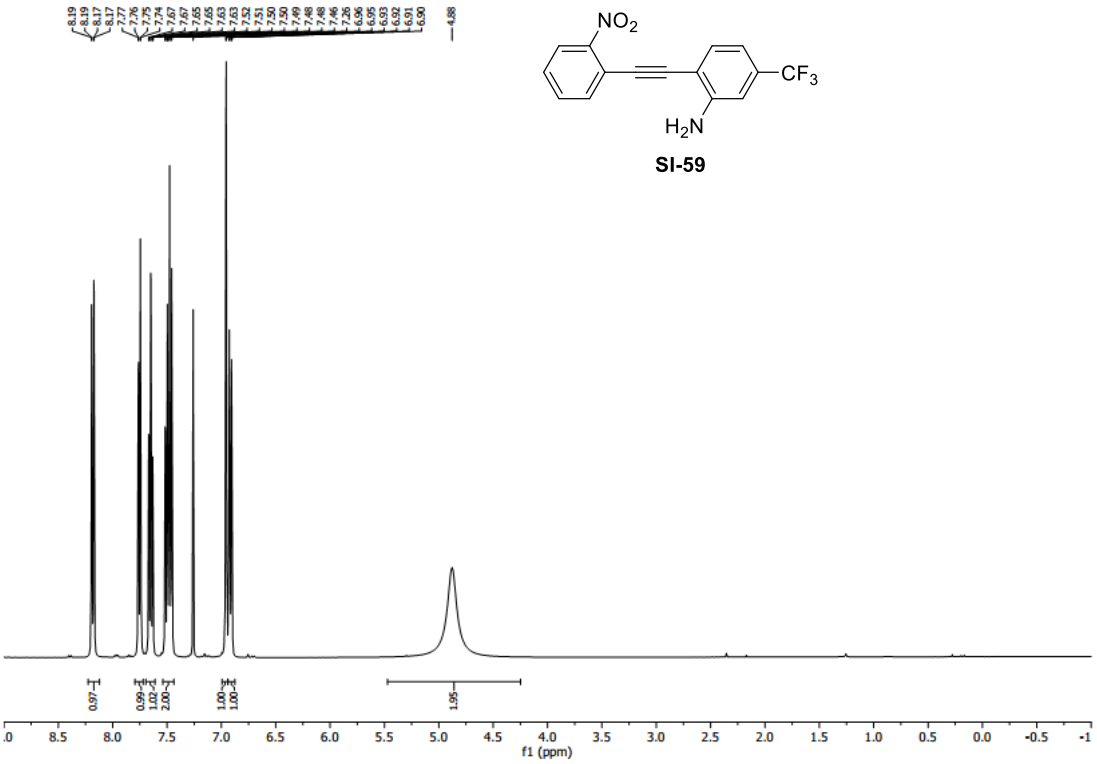


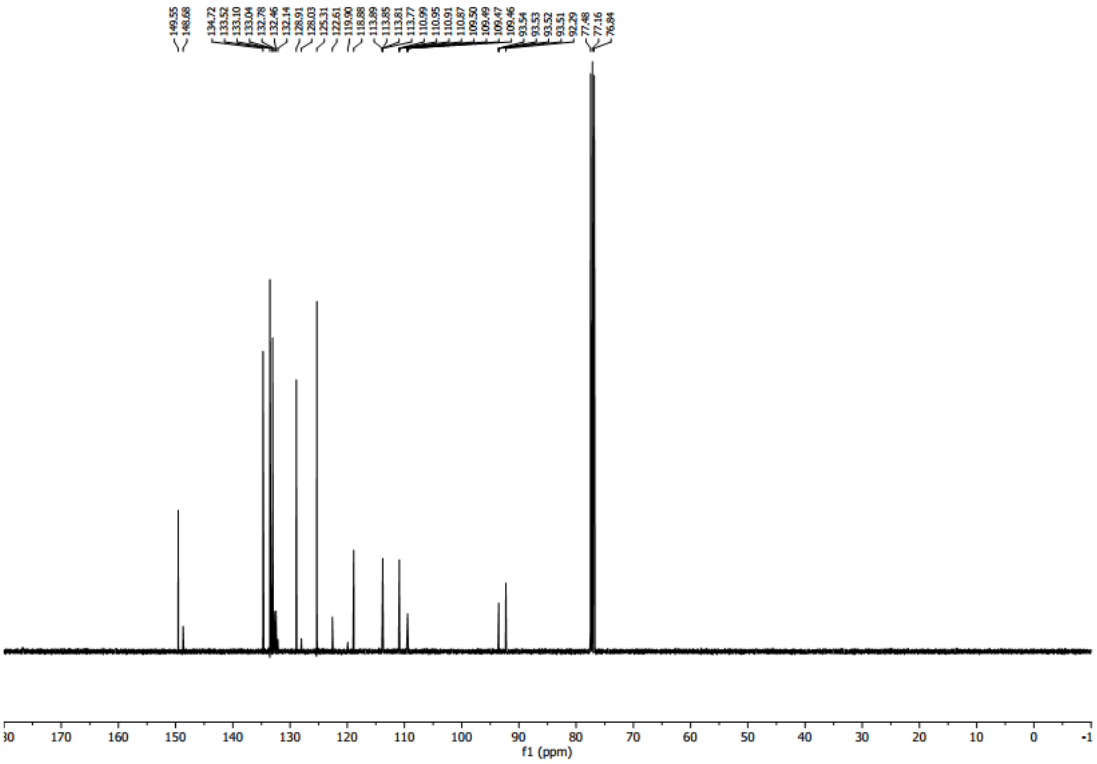
Compound **SI-57** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



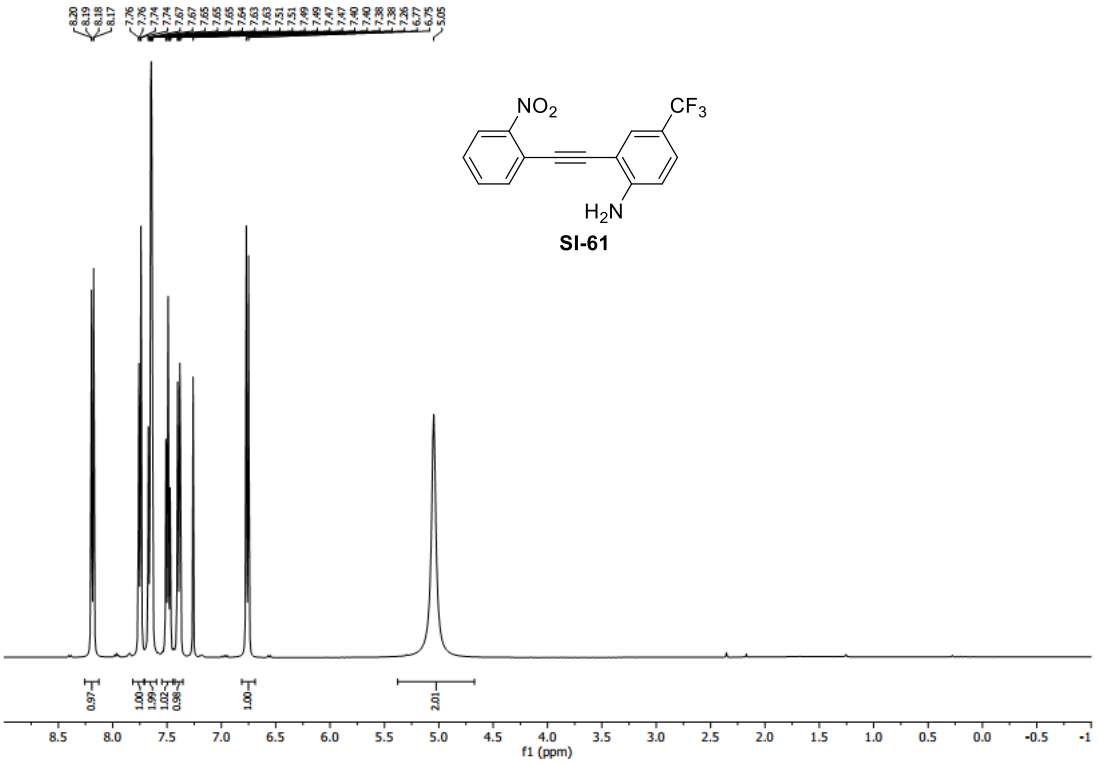


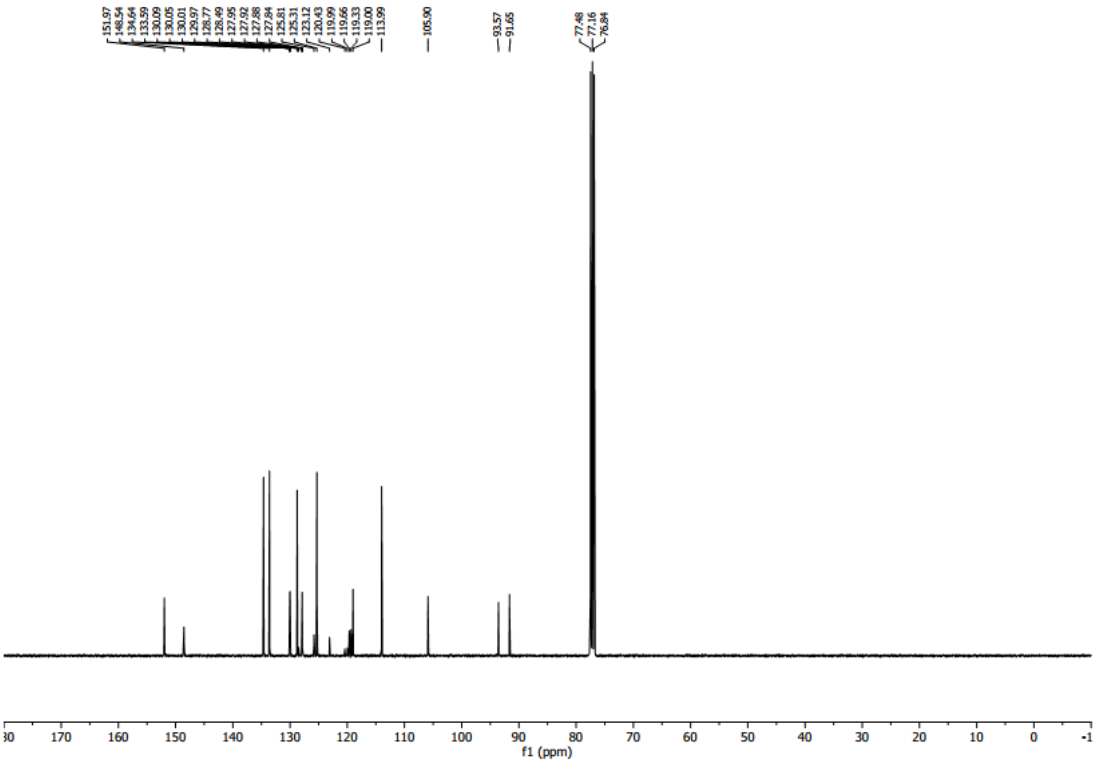
Compound **SI-59** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



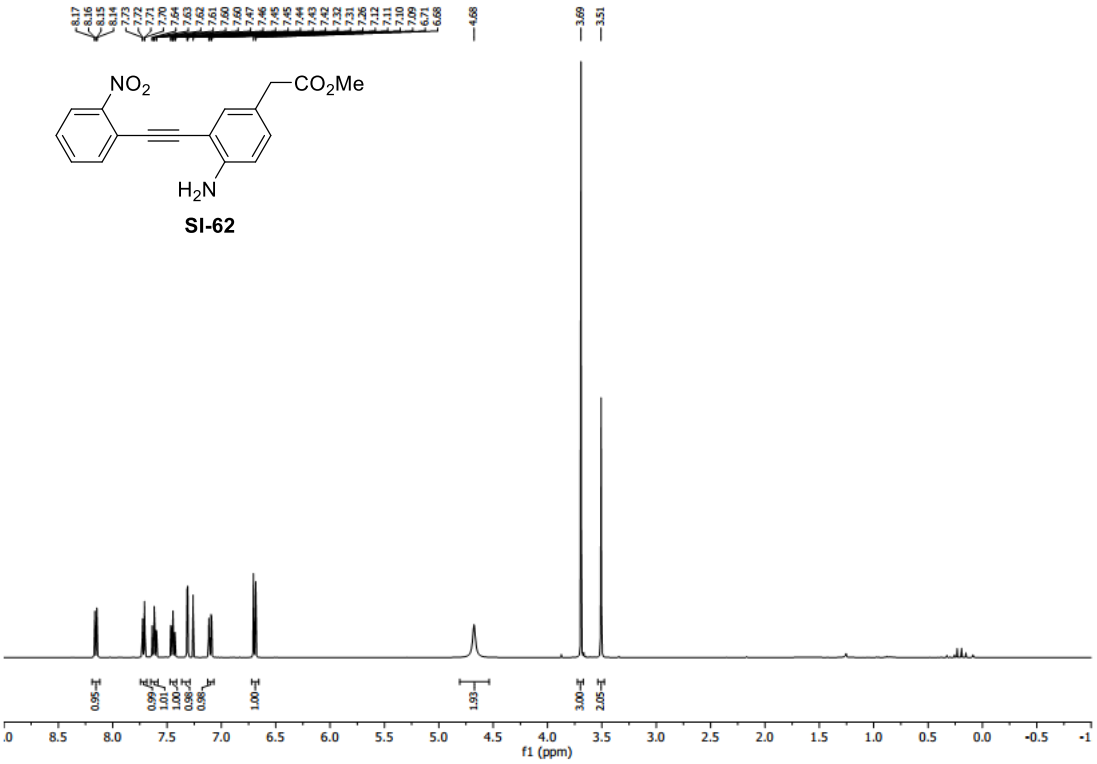


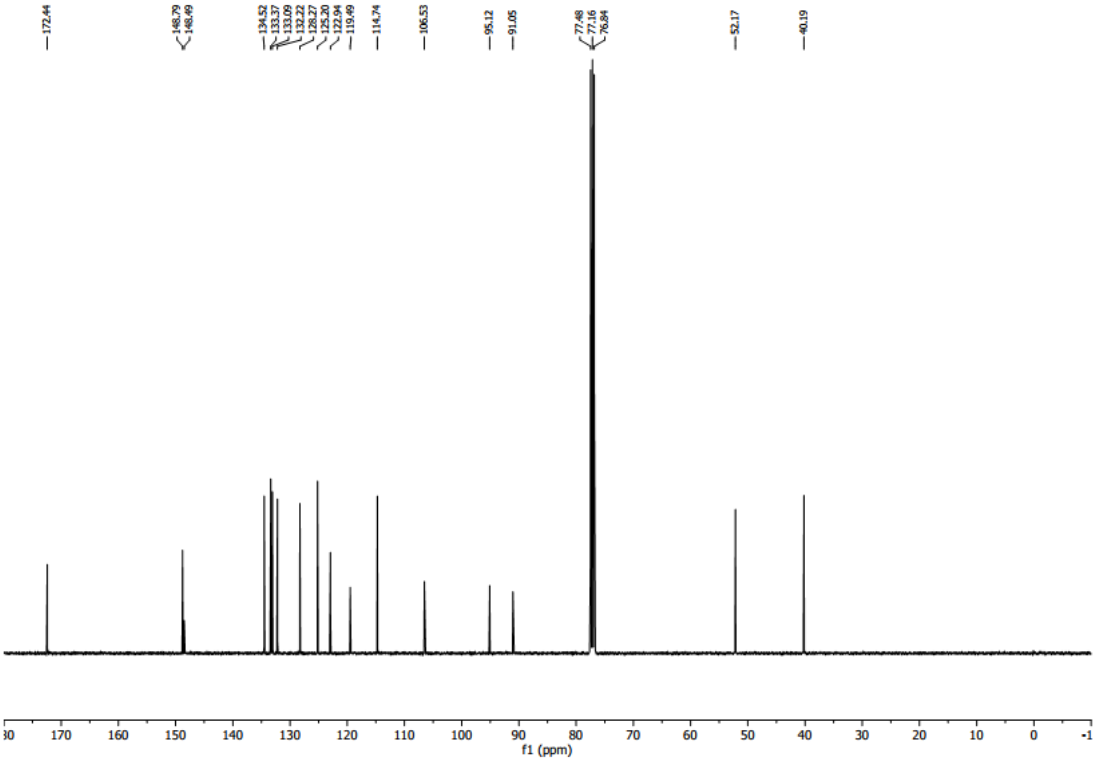
Compound **SI-61** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



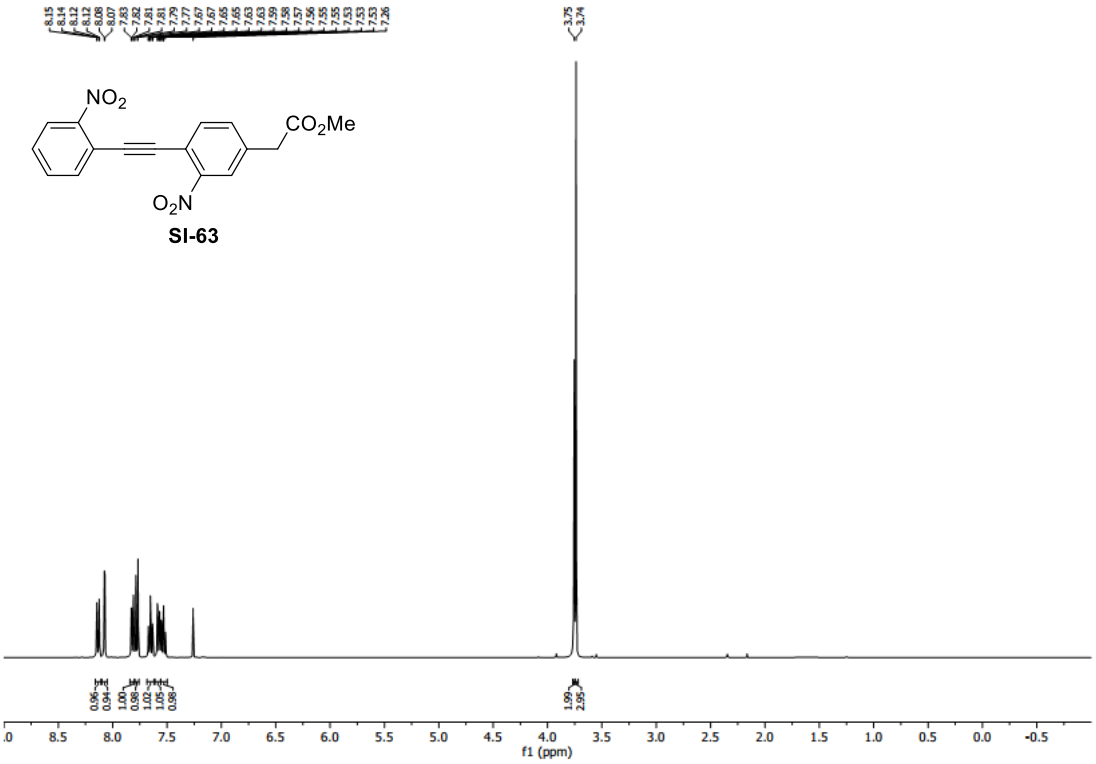


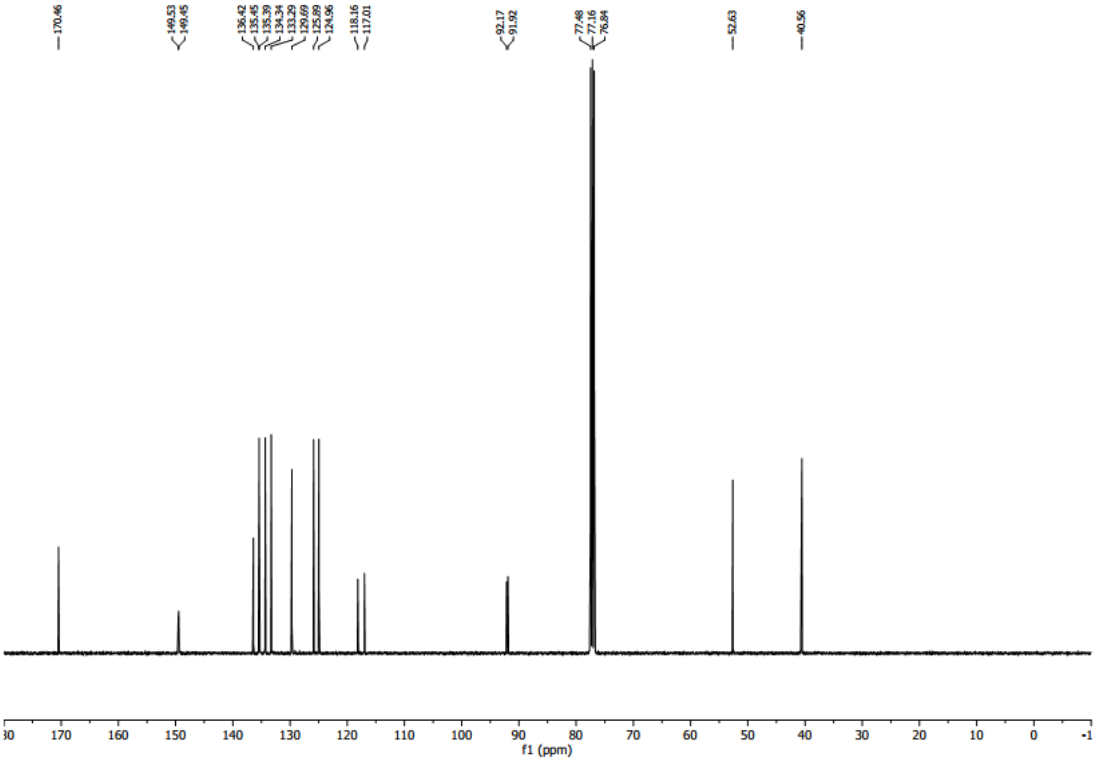
Compound **SI-62** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



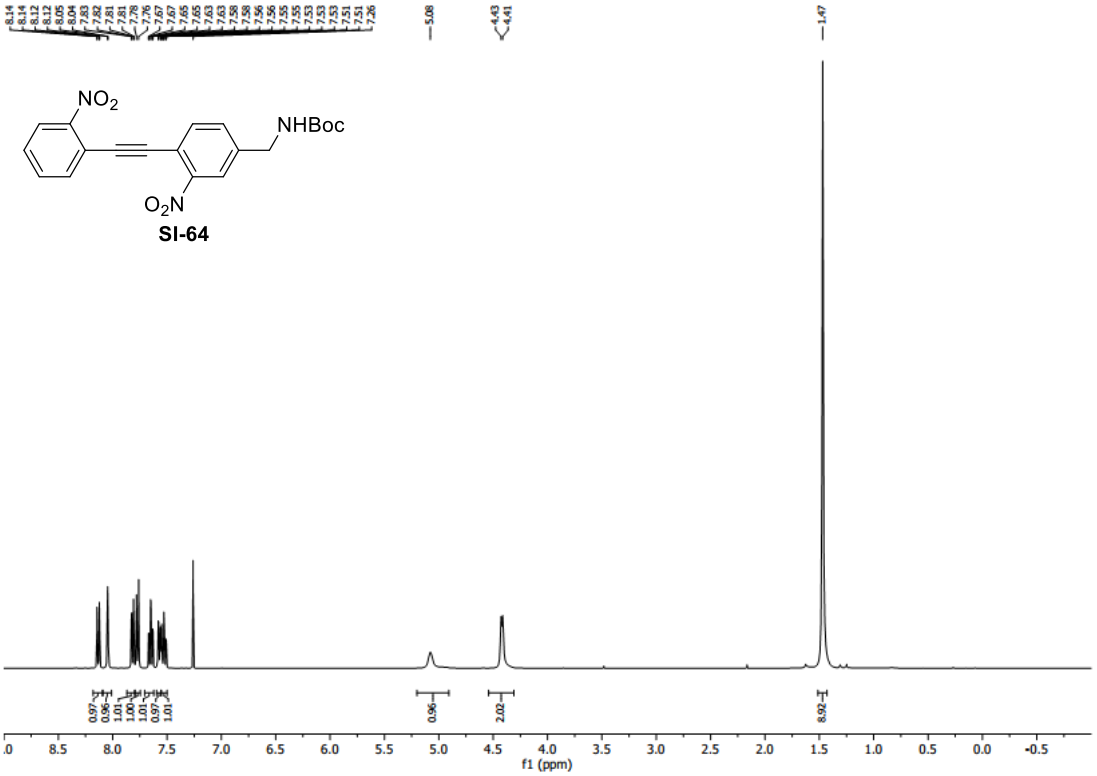


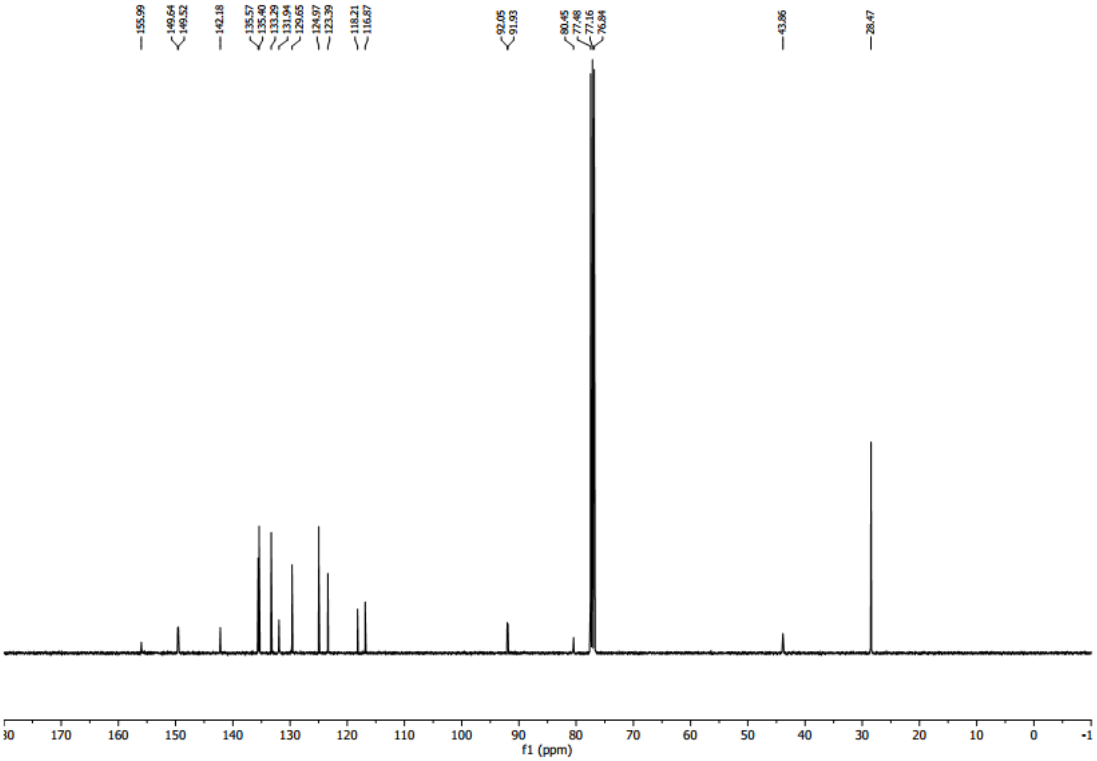
Compound **SI-63** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



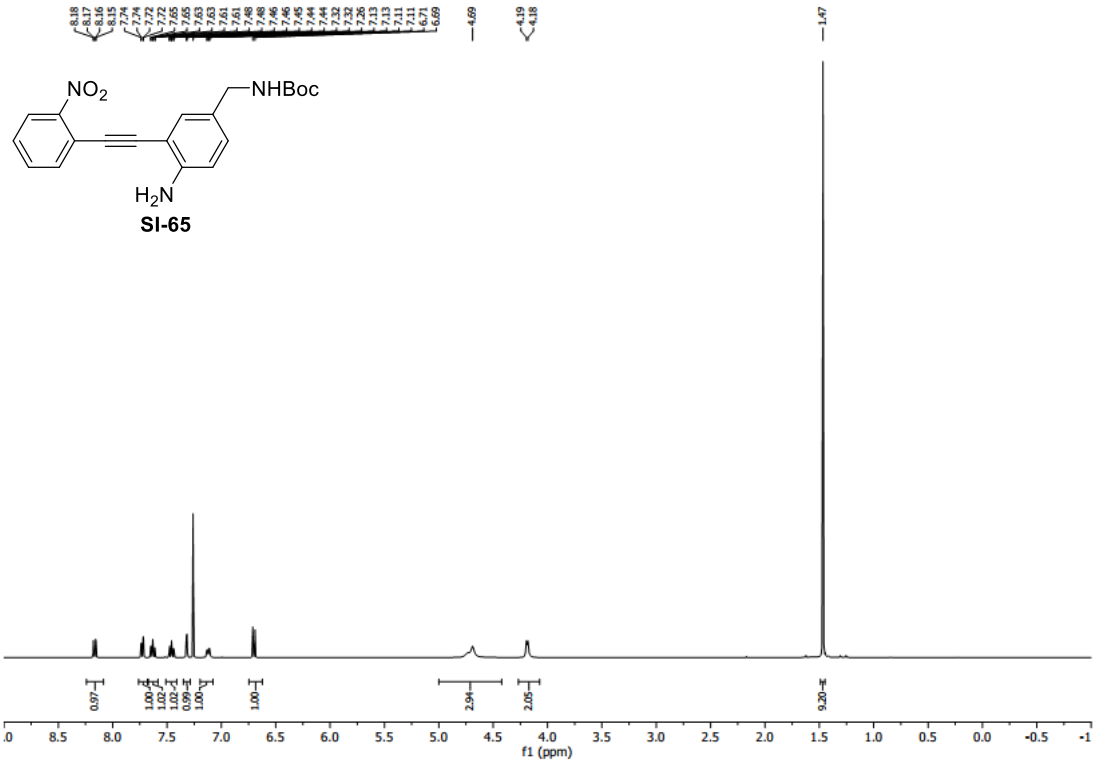


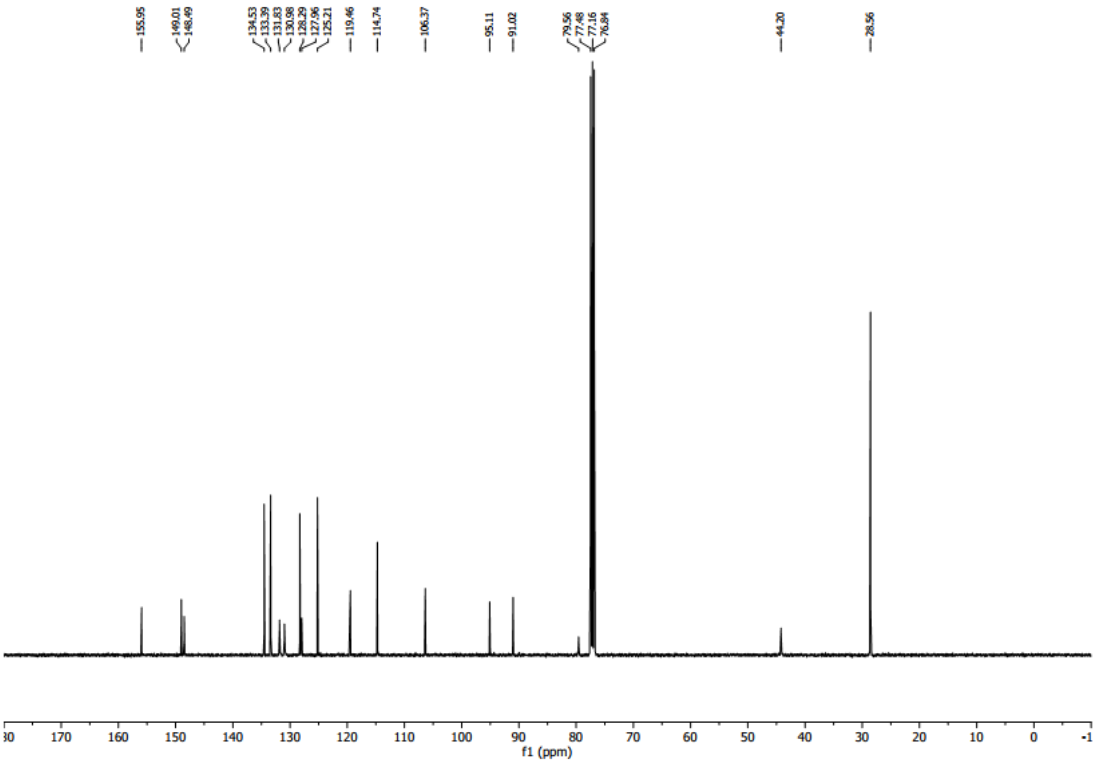
Compound **SI-64** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



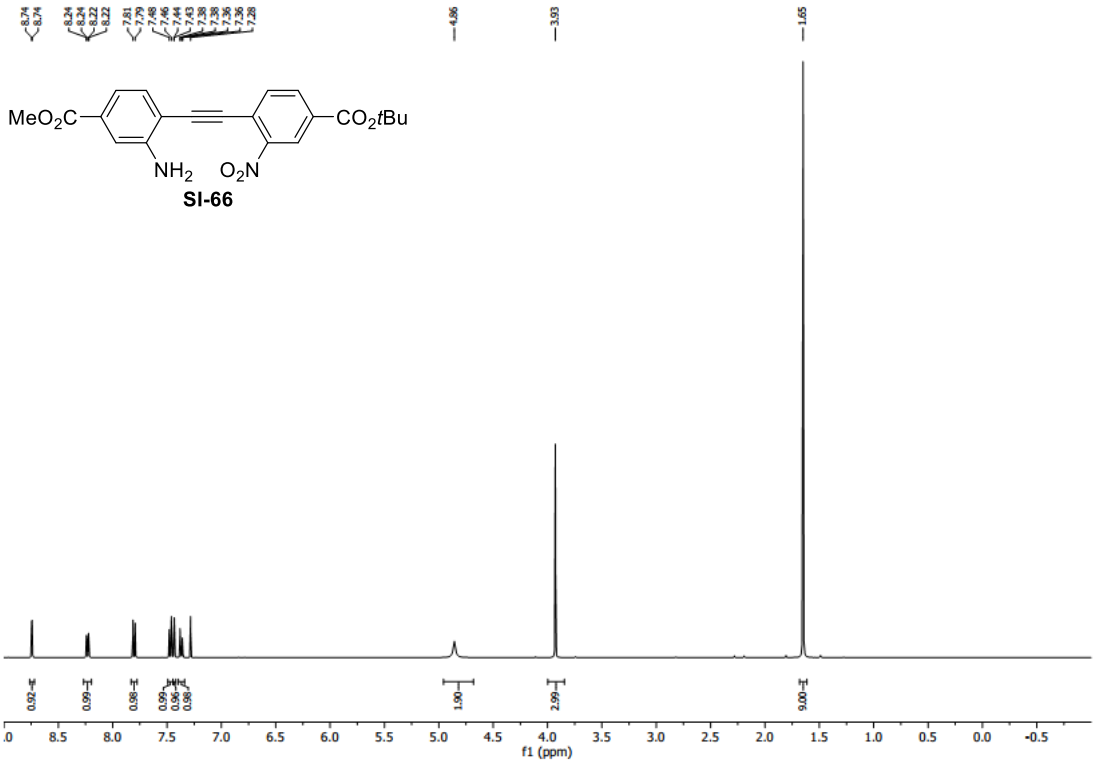


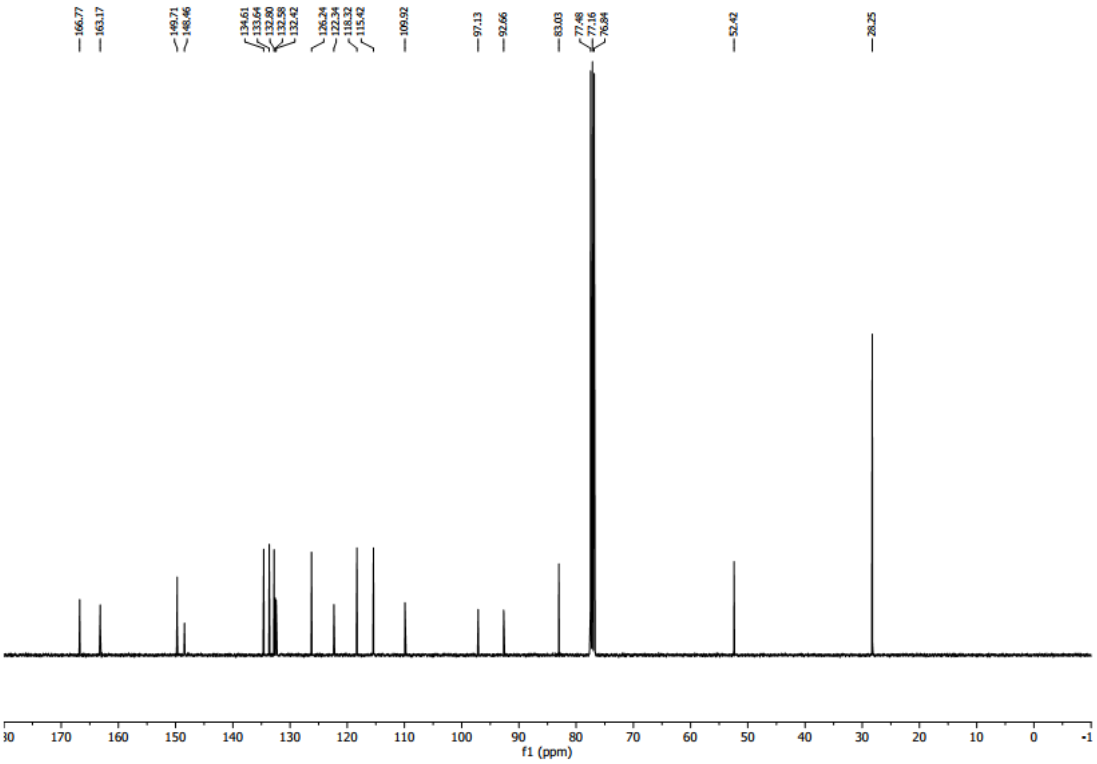
Compound **SI-65** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



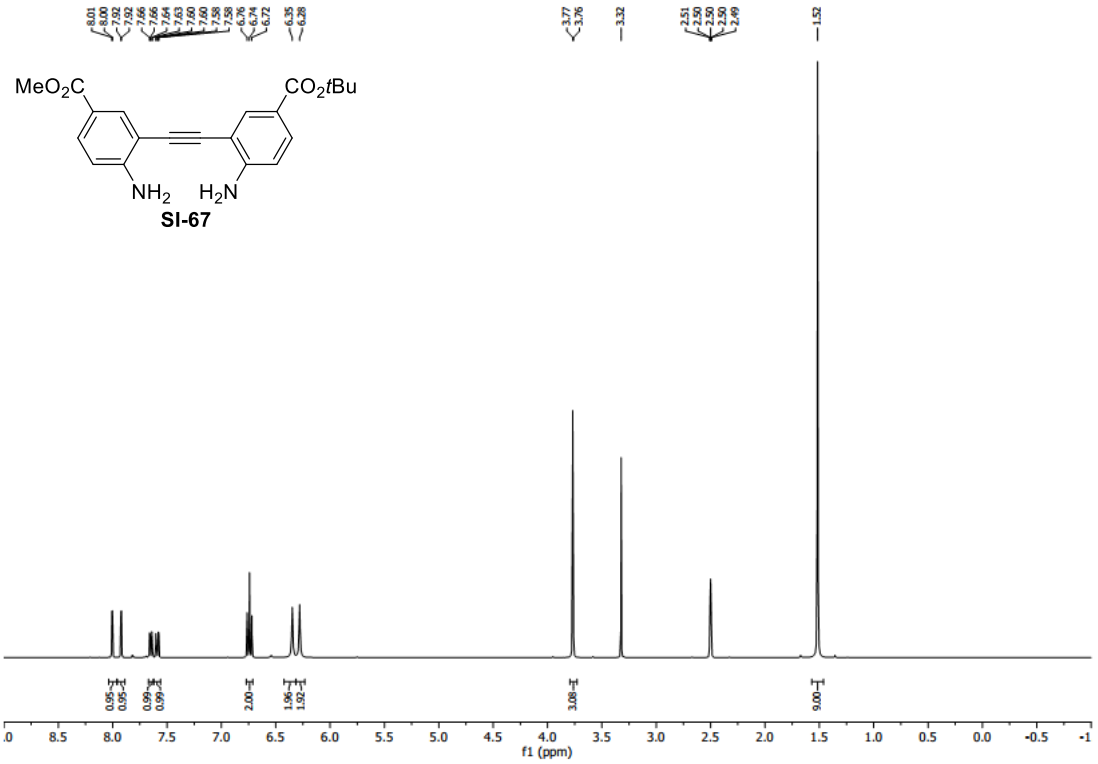


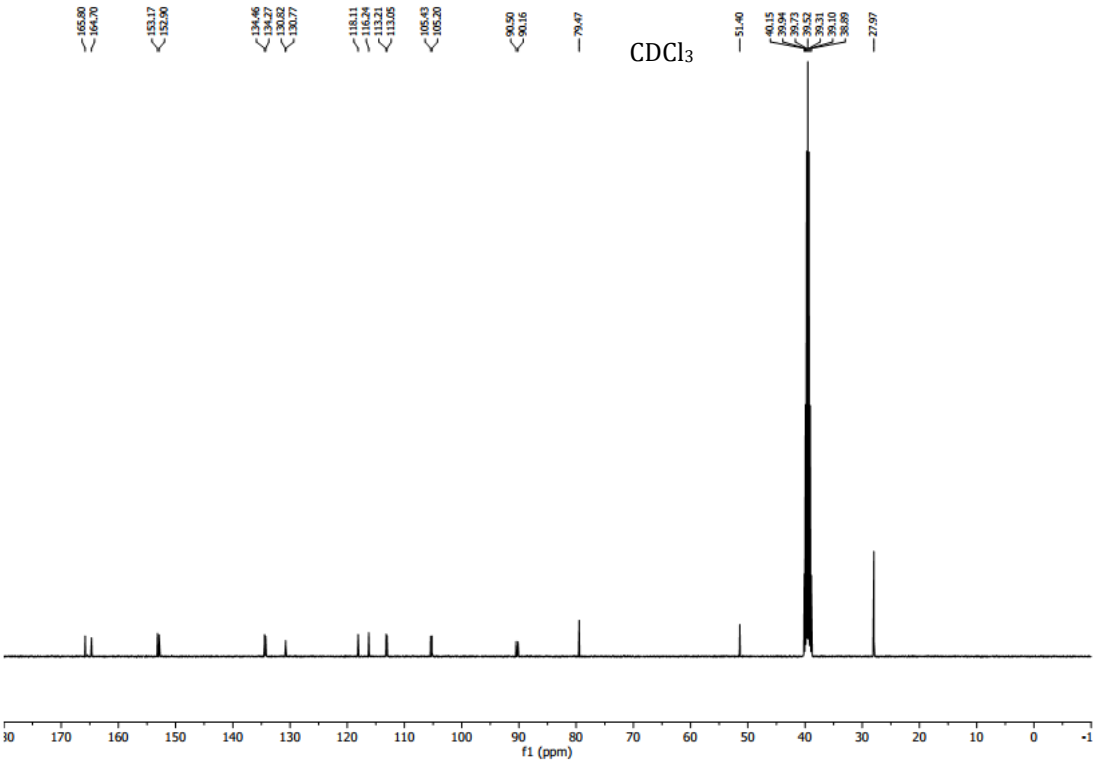
Compound **SI-66** – ^{1}**H-NMR** (400 MHz) and ^{13}**C-NMR** (100 MHz) in $CDCl_3$



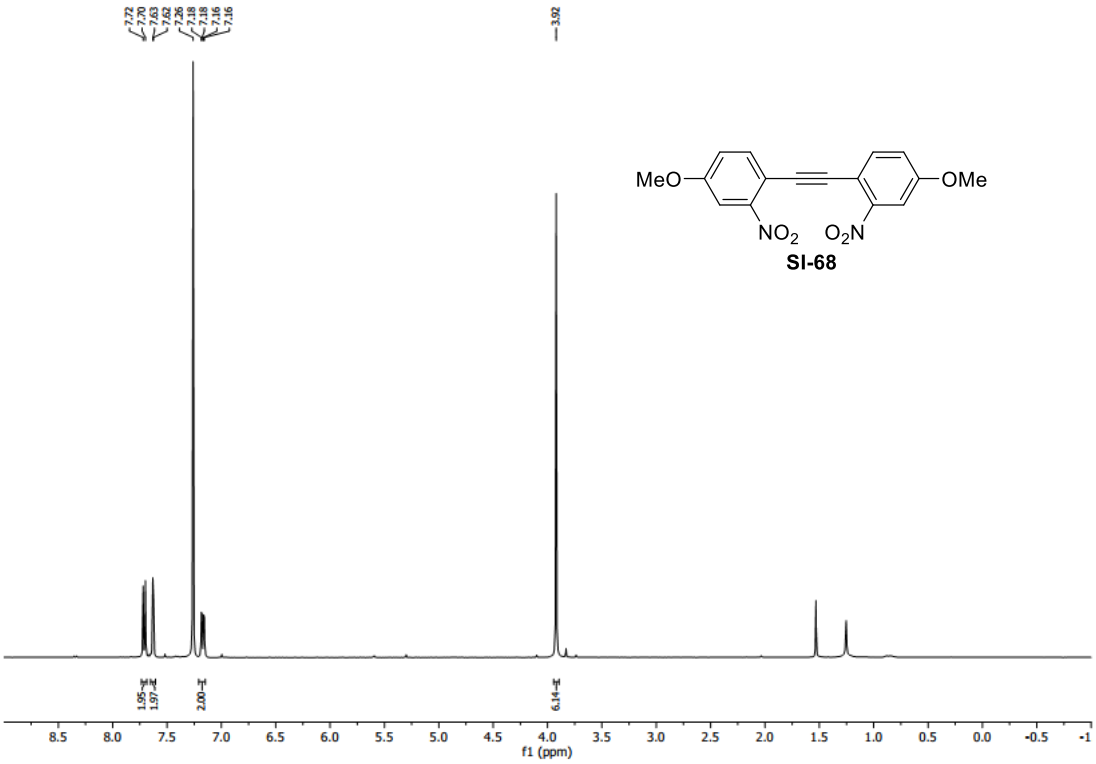


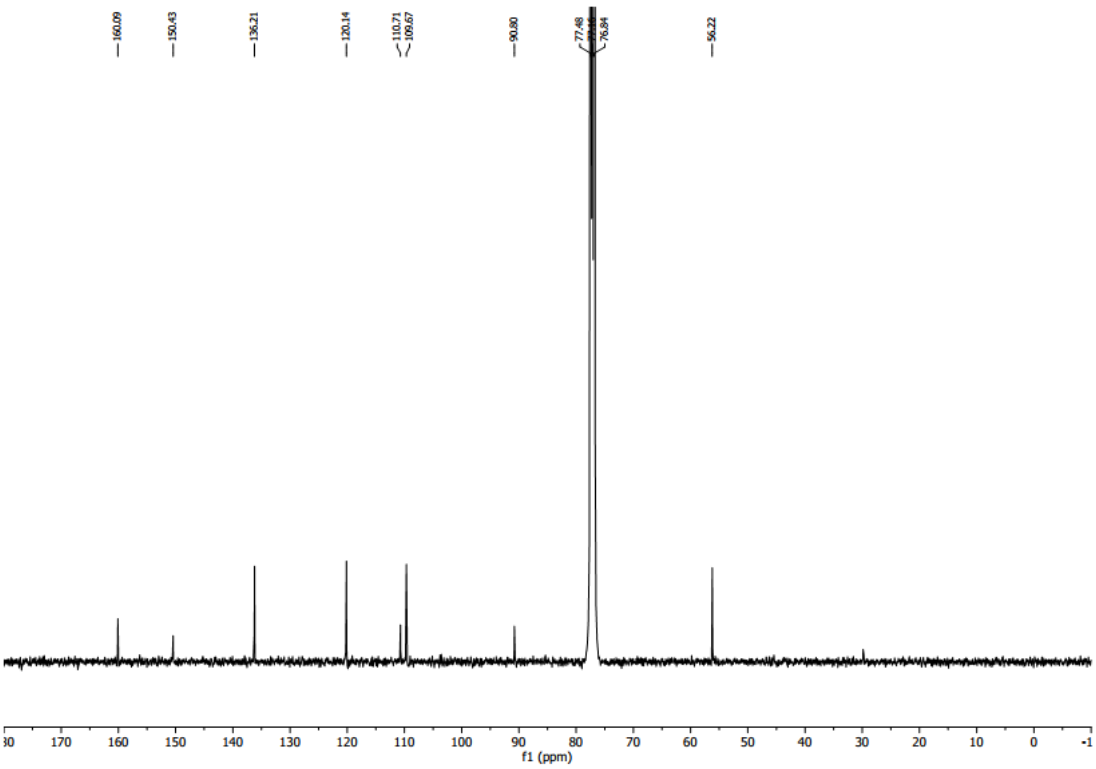
Compound **SI-67** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in DMSO-d_6



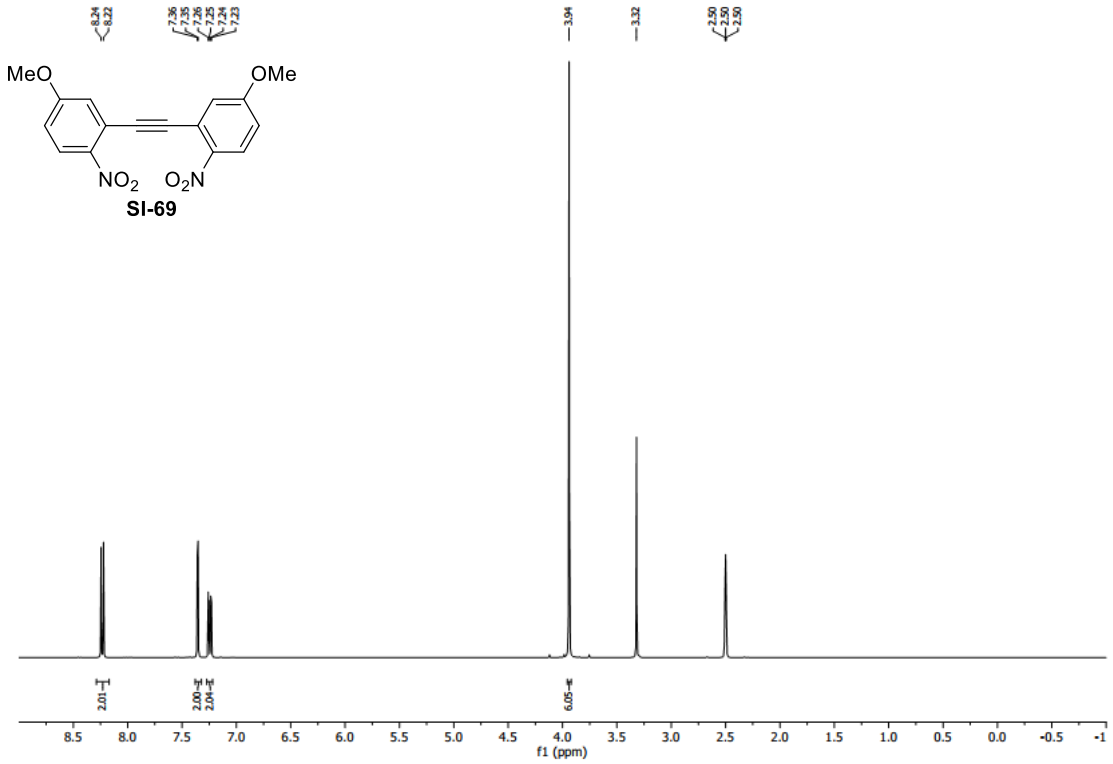


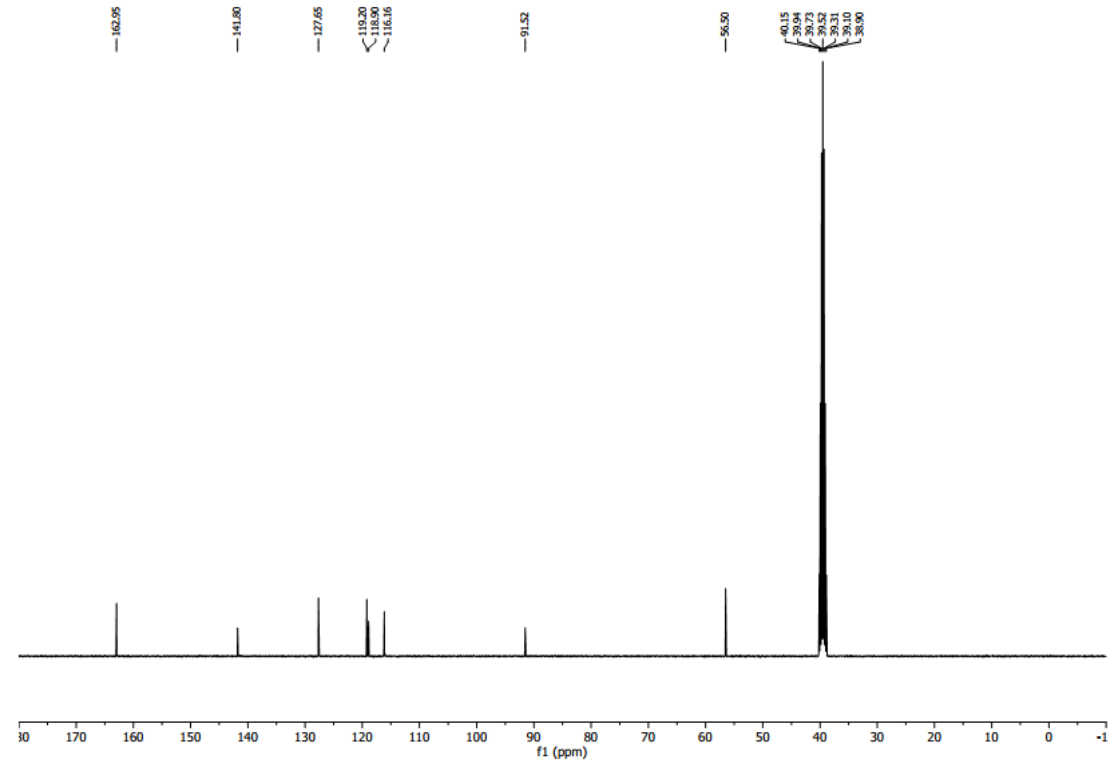
Compound **SI-68** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



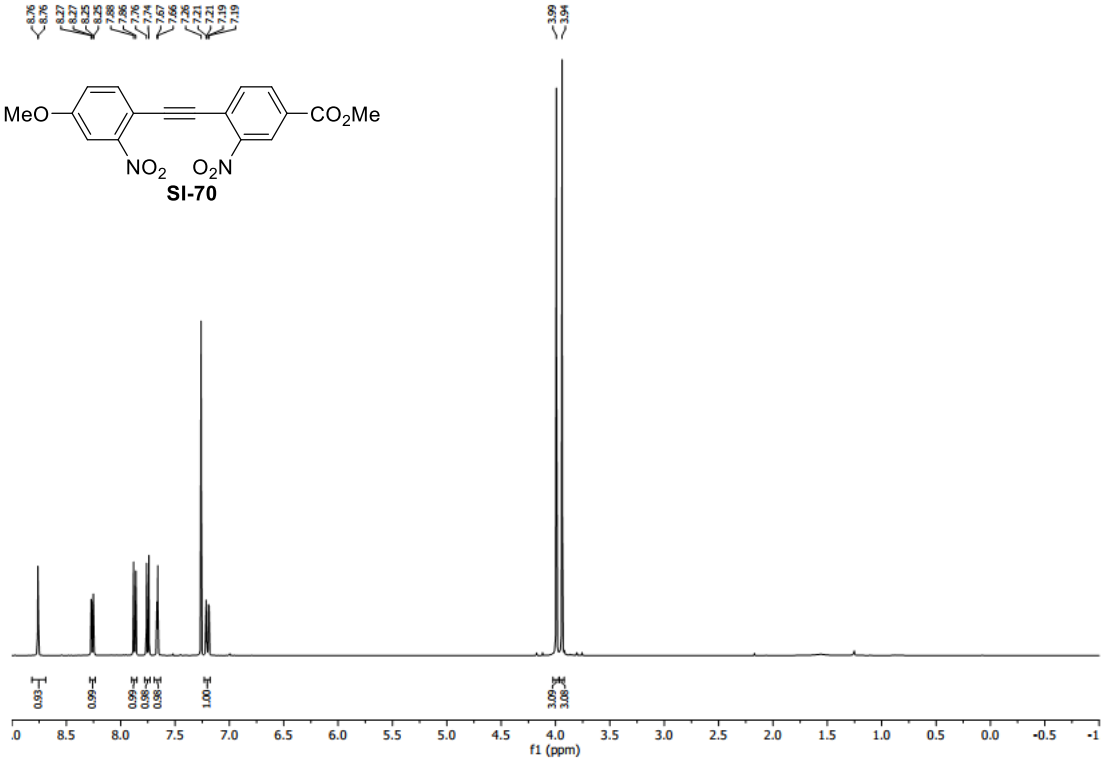


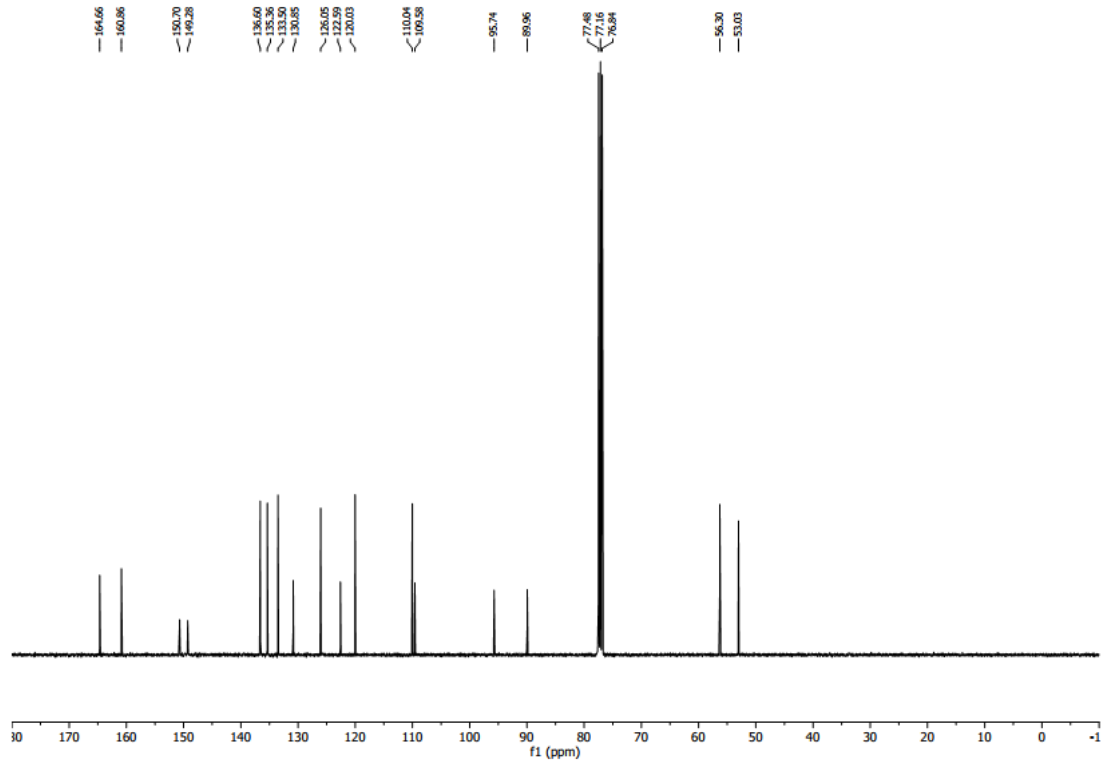
Compound **SI-69** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in DMSO-d_6



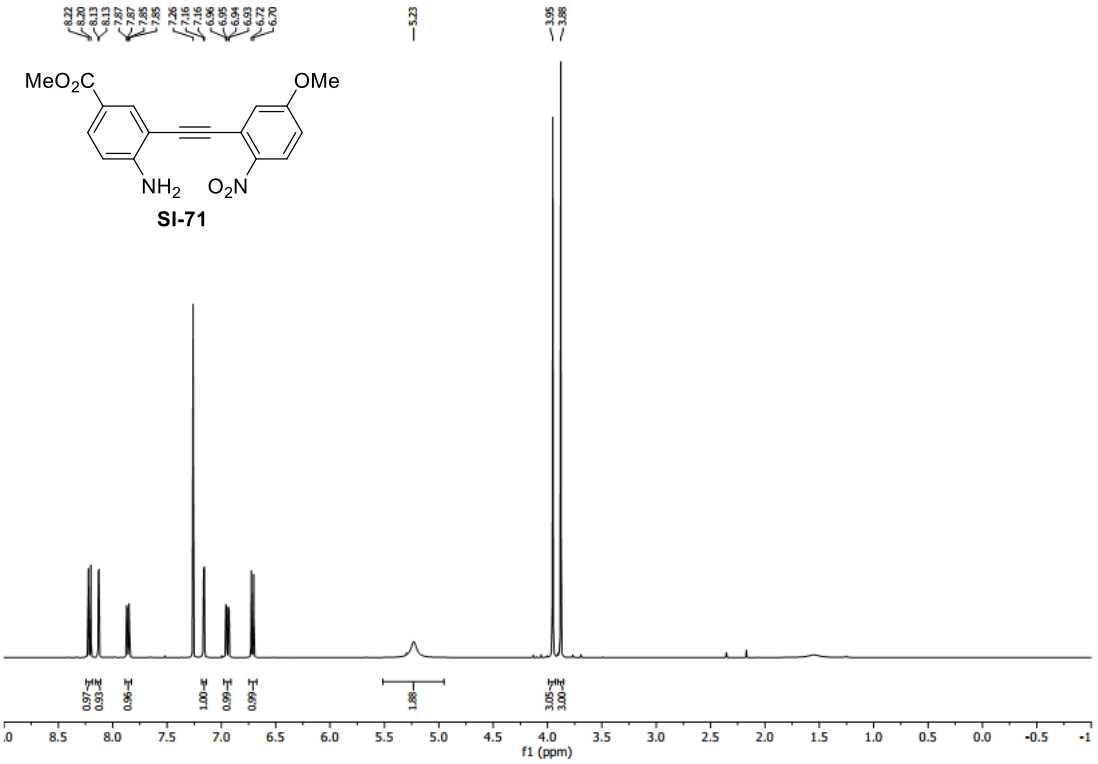


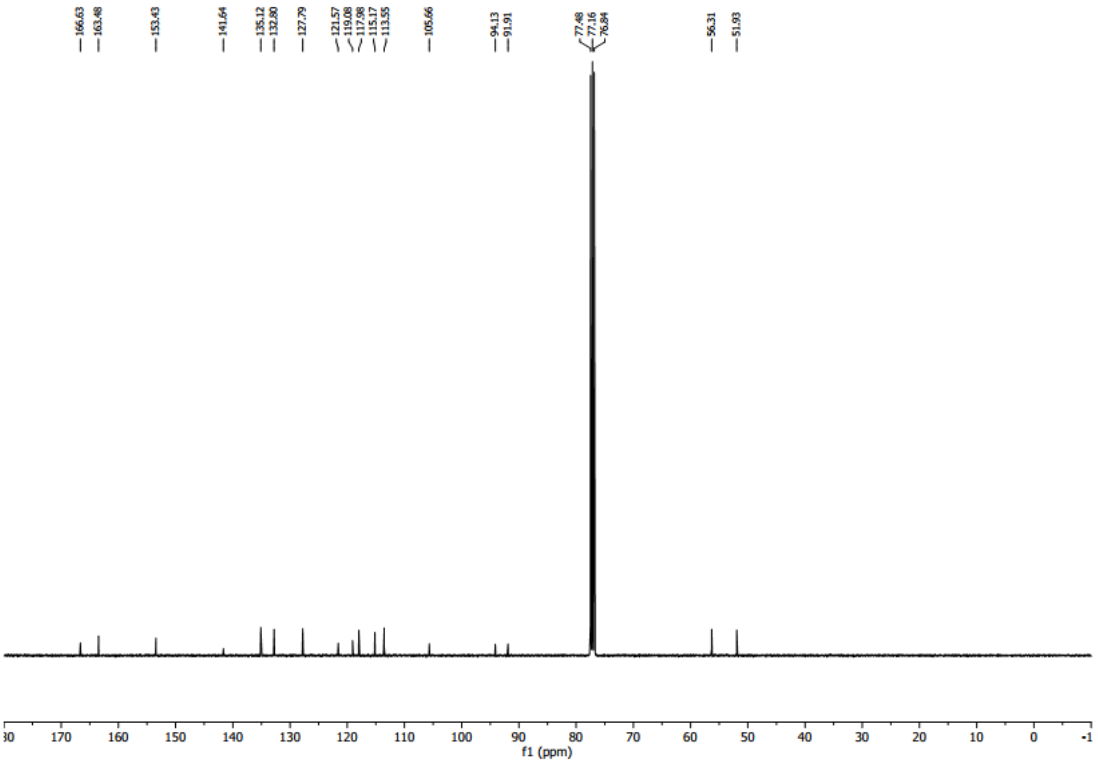
Compound **SI-70** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



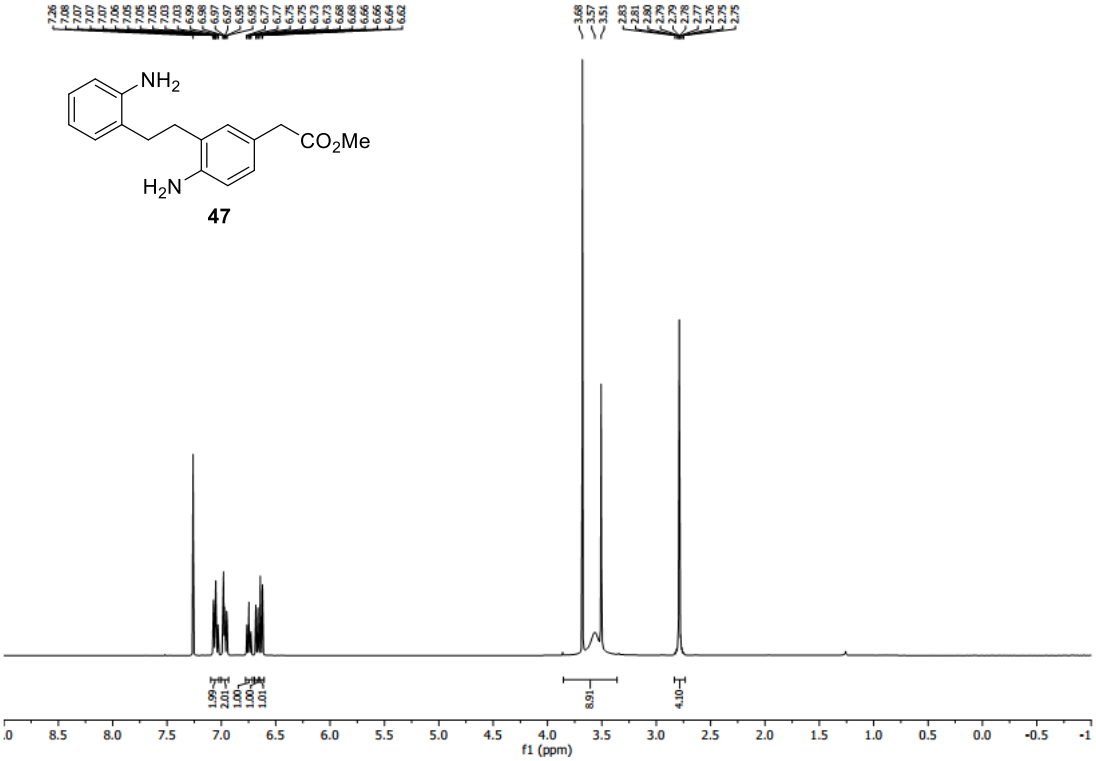


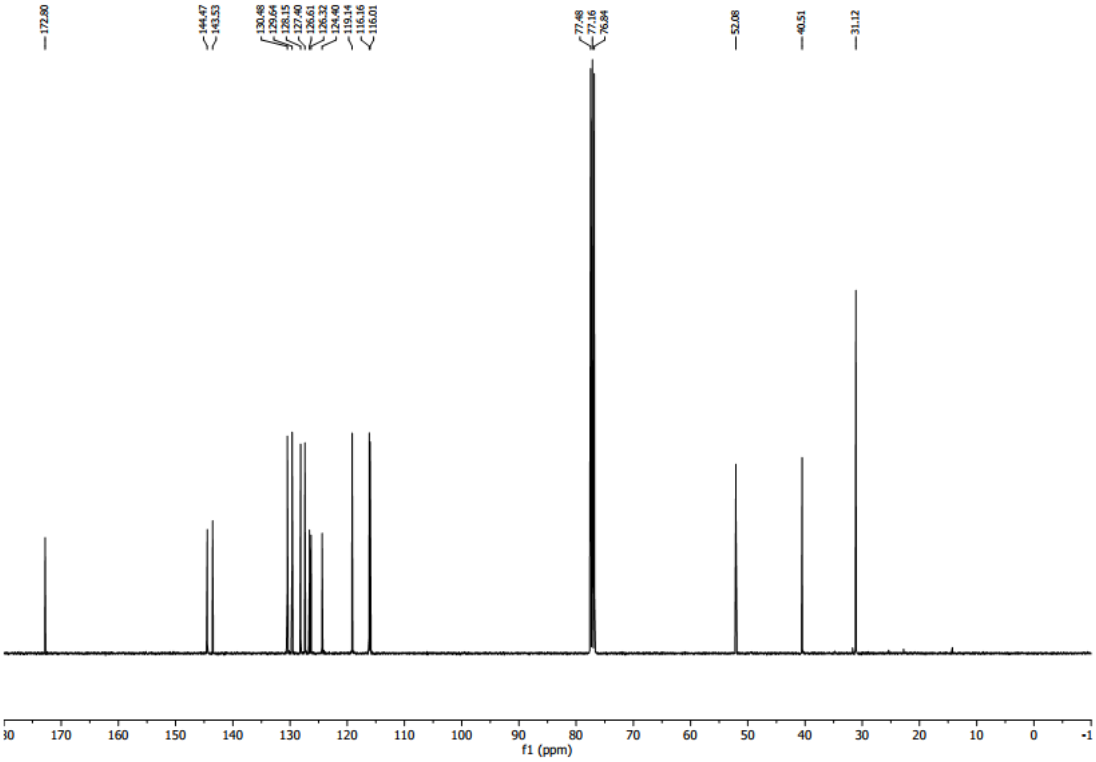
Compound **SI-71** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



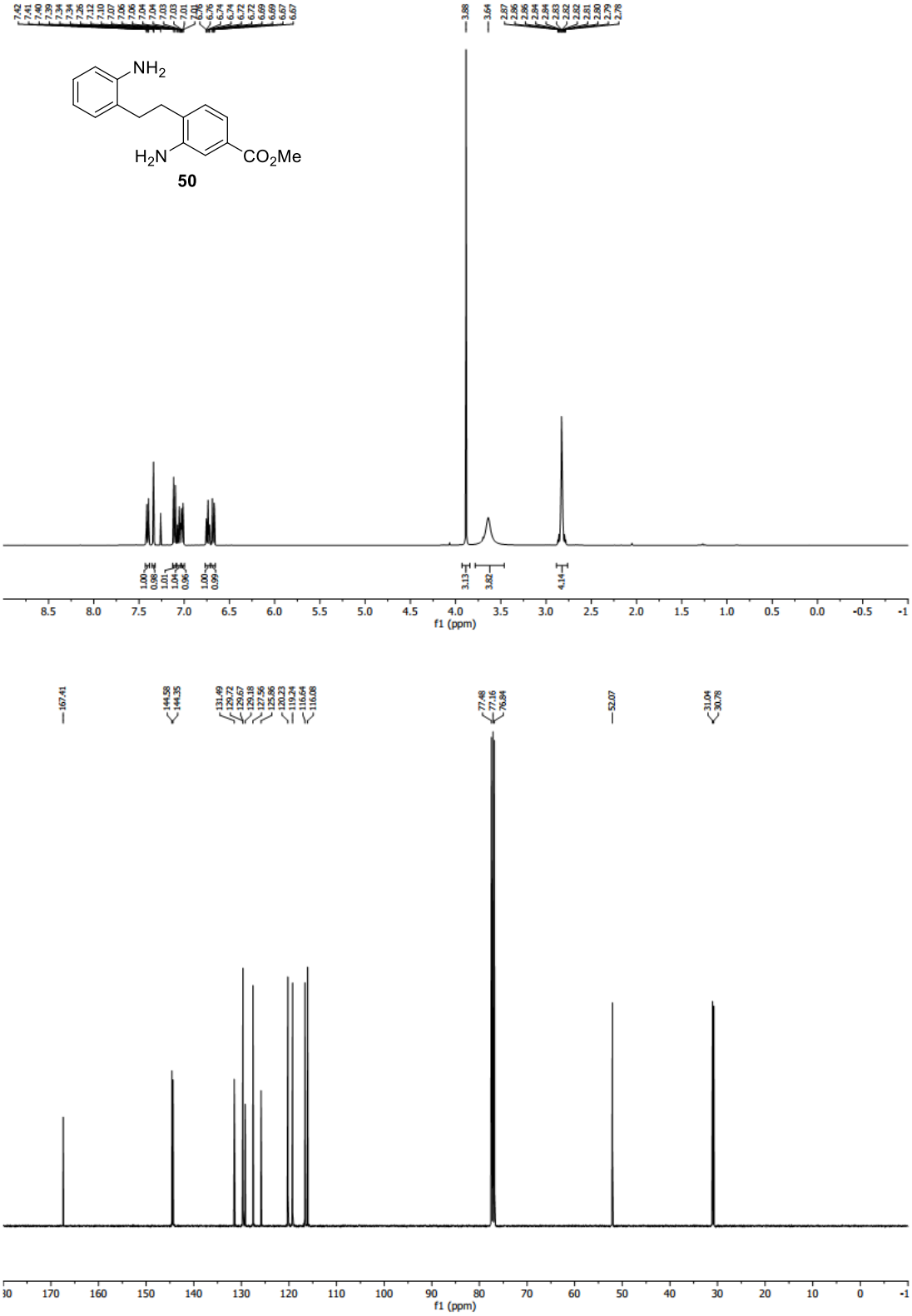


Compound **47** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

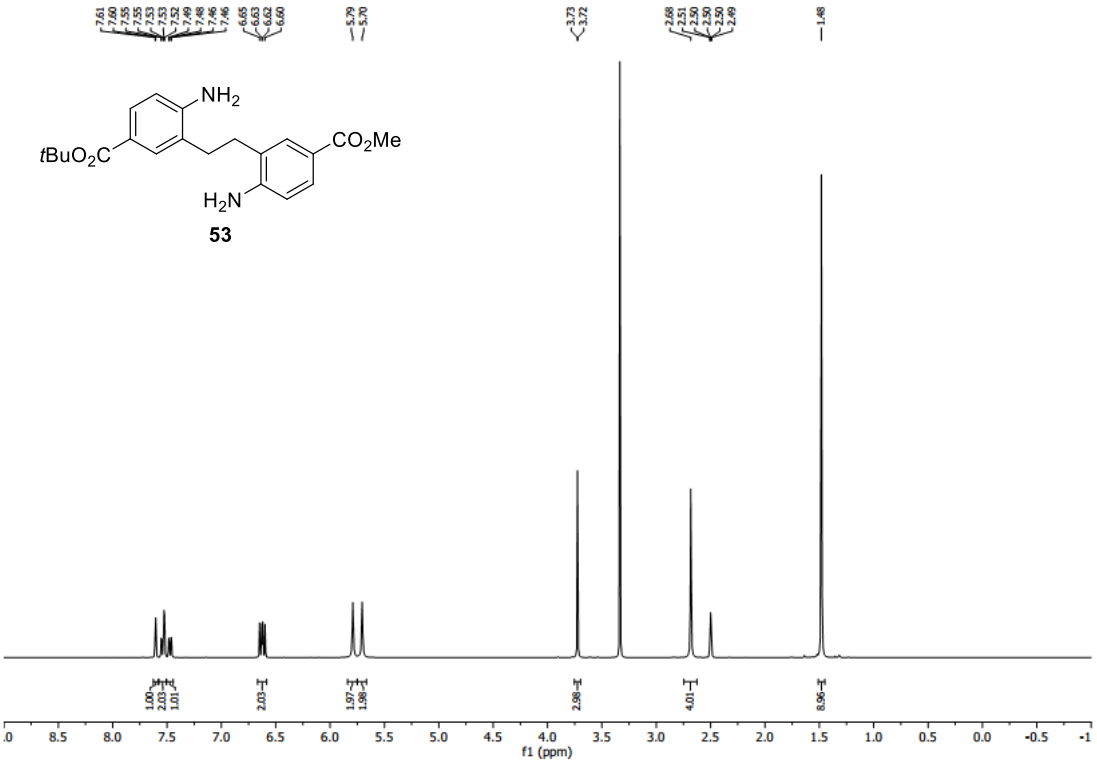


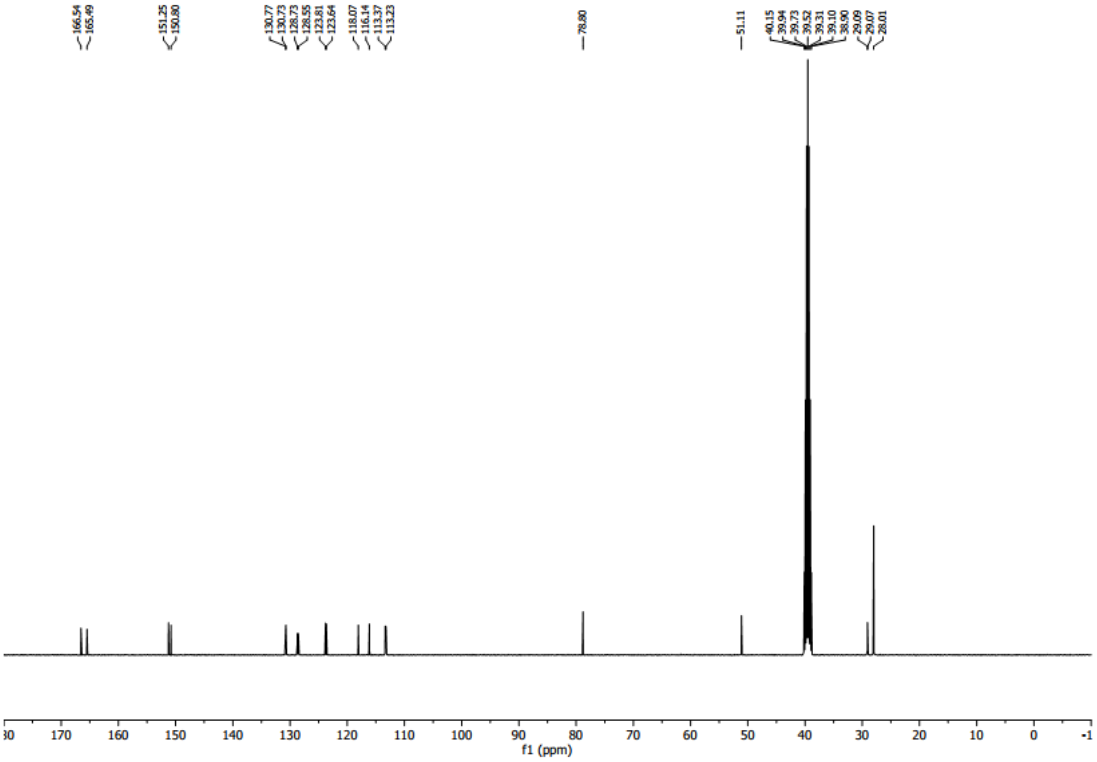


Compound **50** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

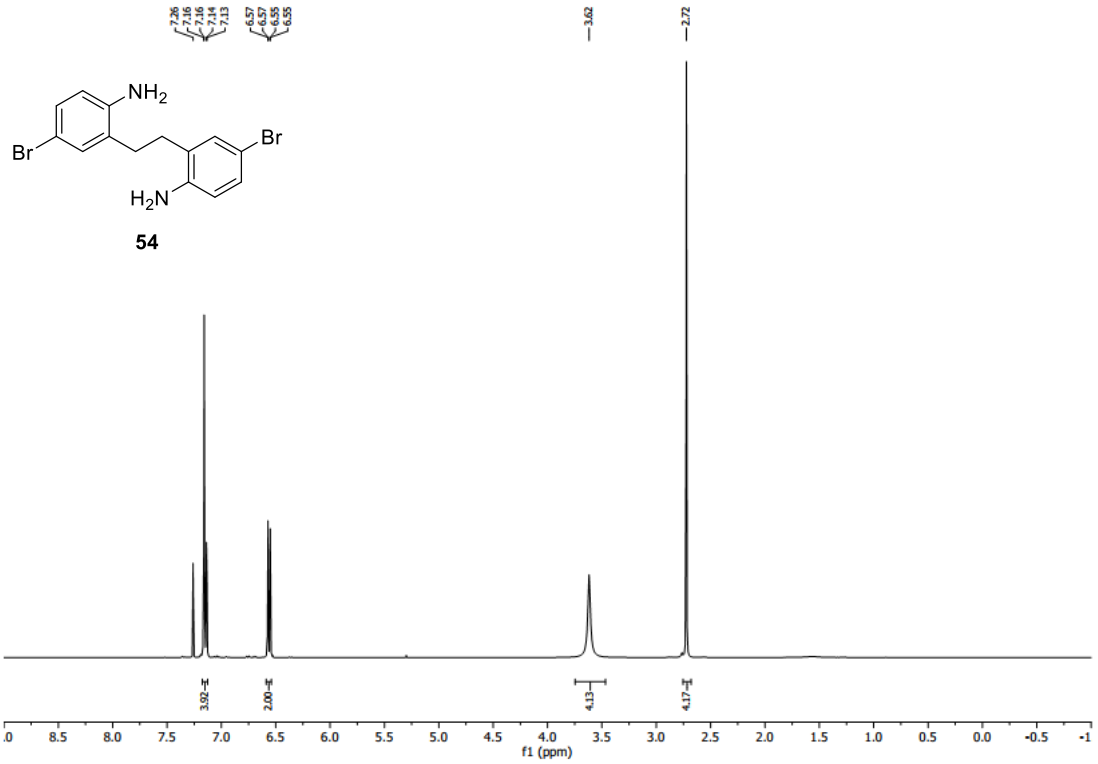


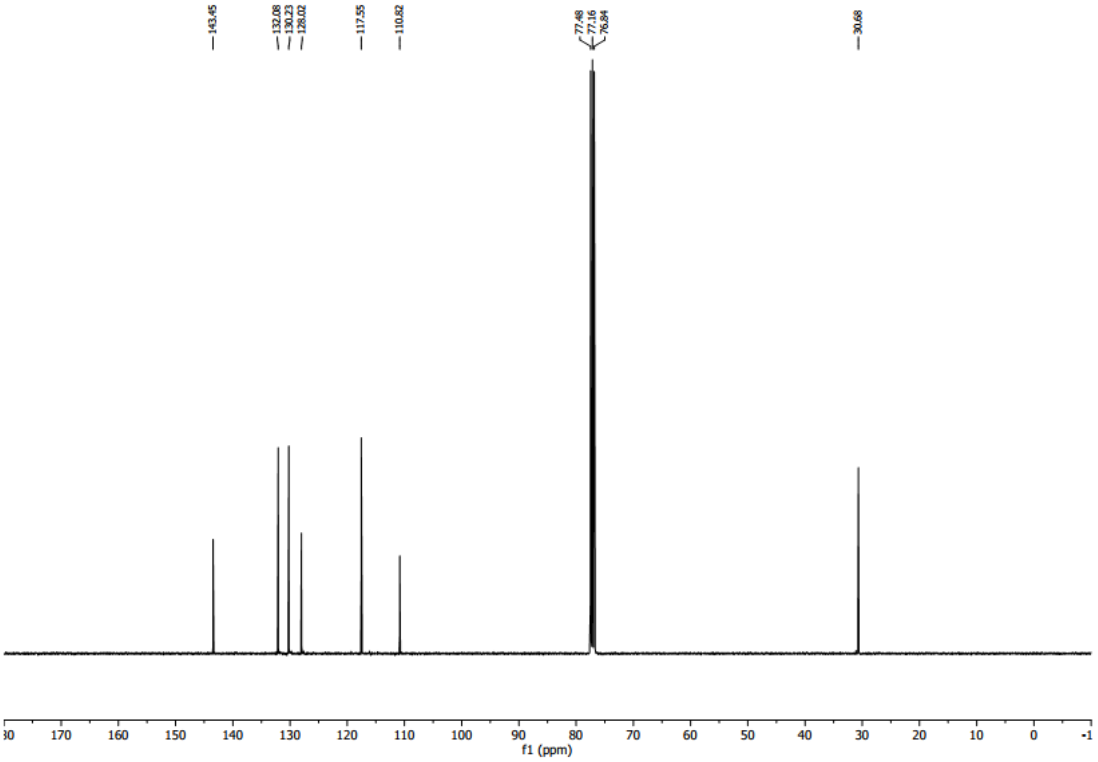
Compound **53** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in DMSO-d_6



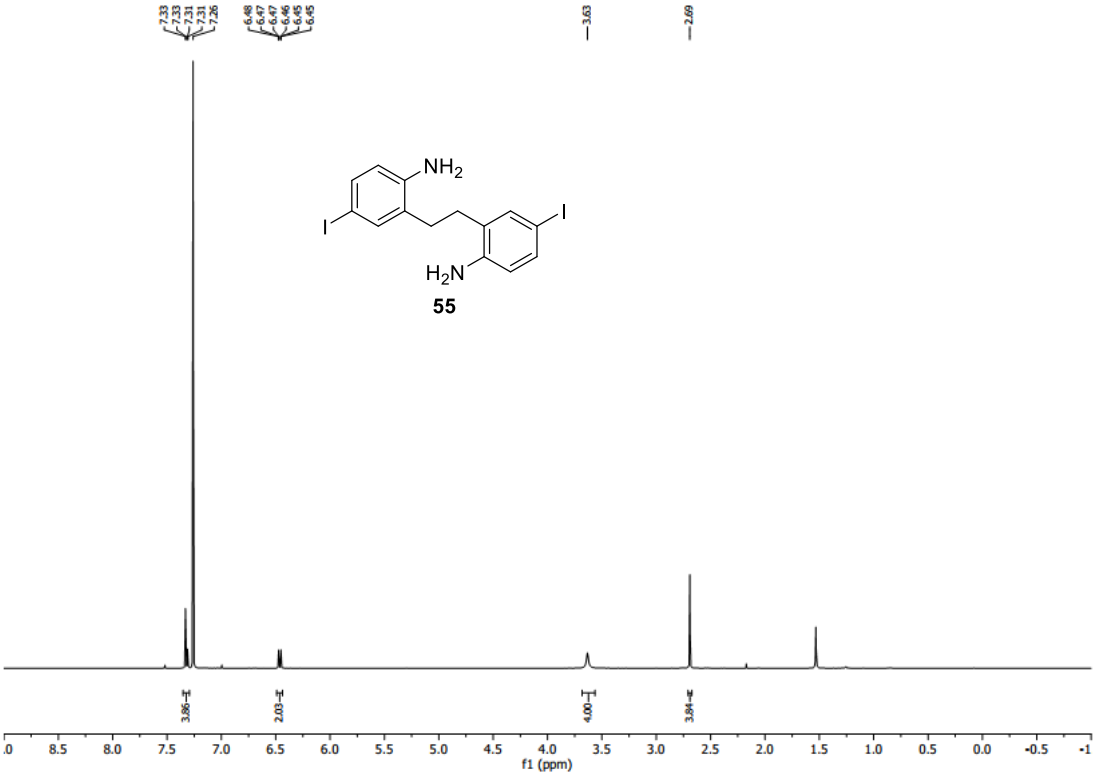


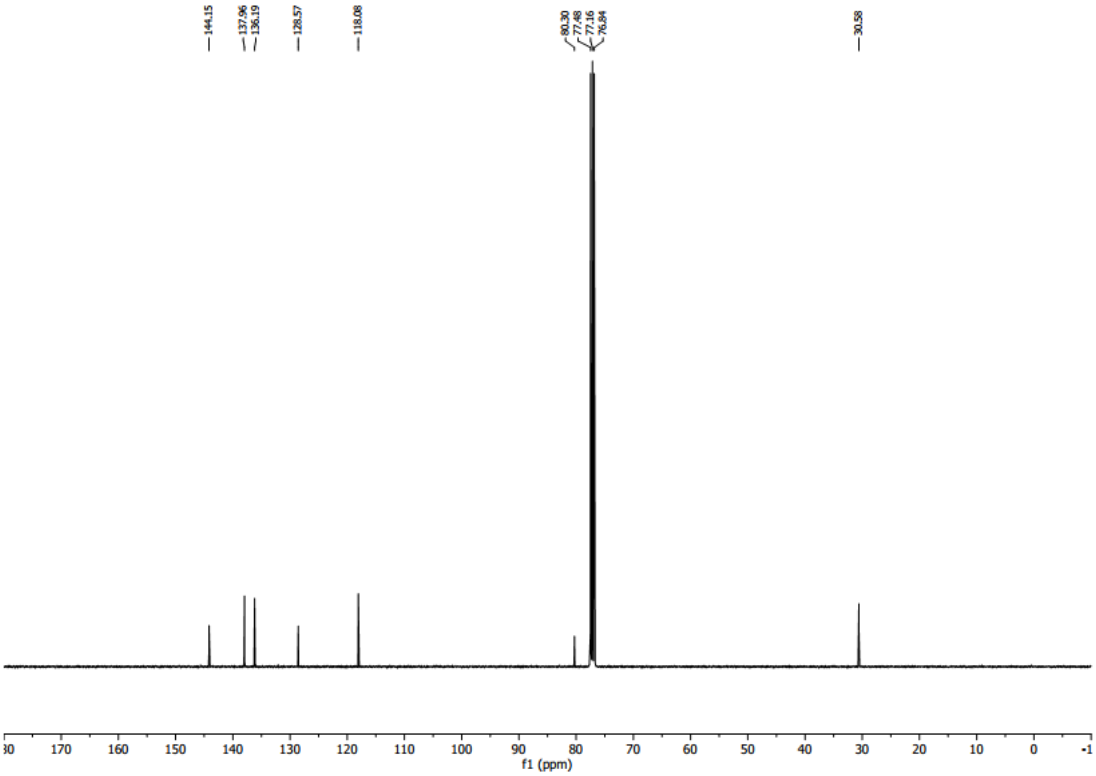
Compound **54** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



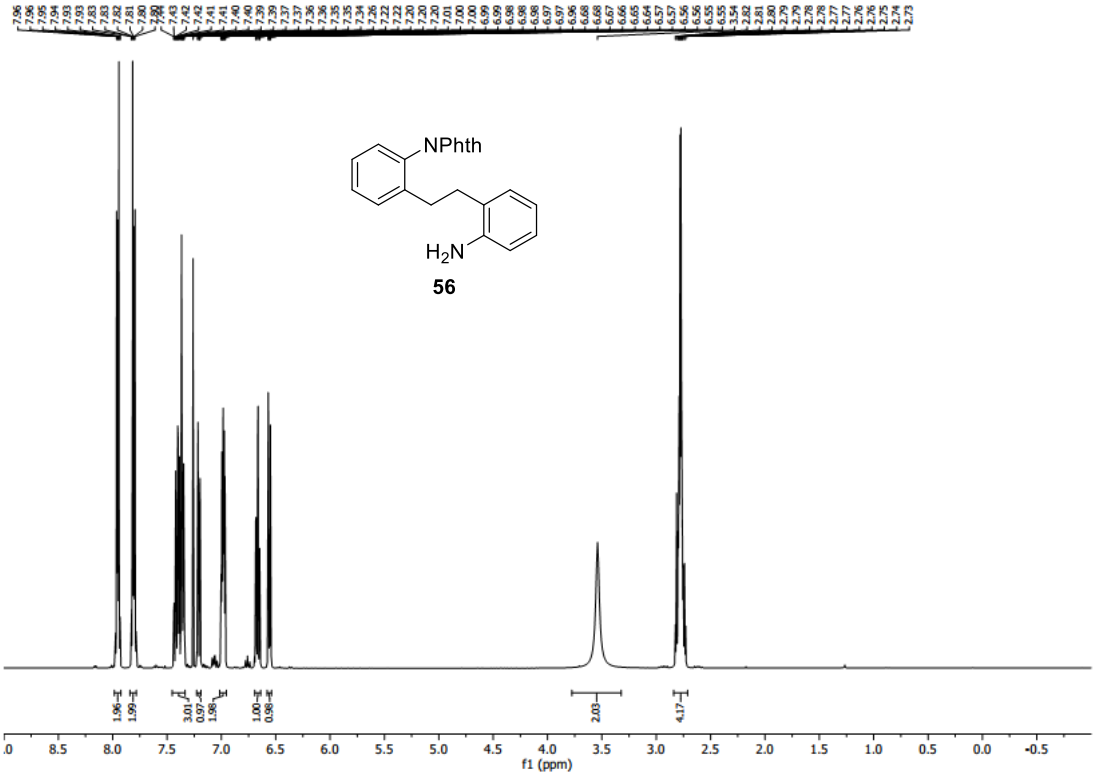


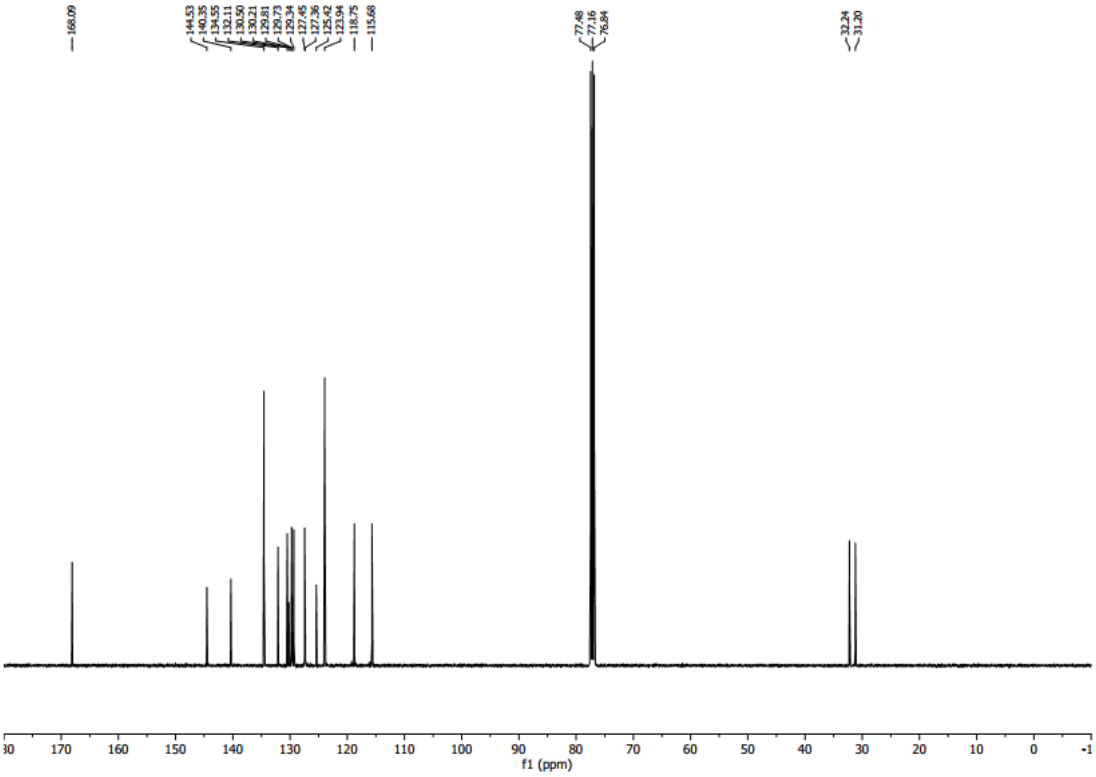
Compound **55** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



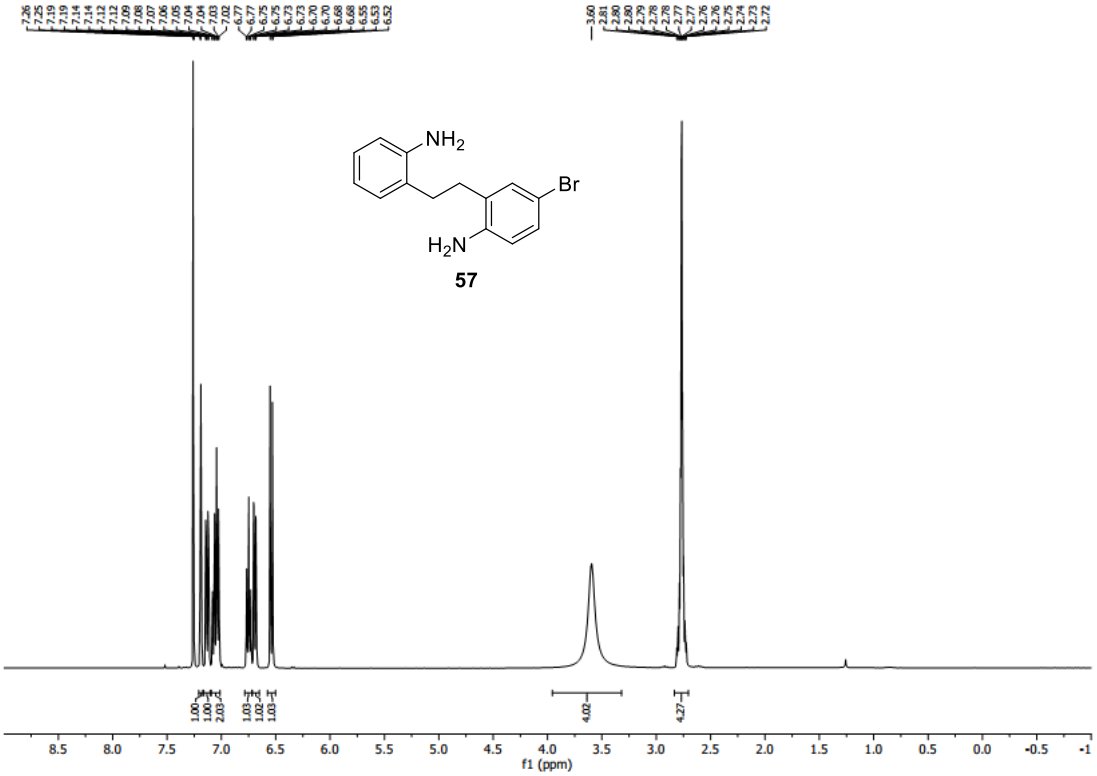


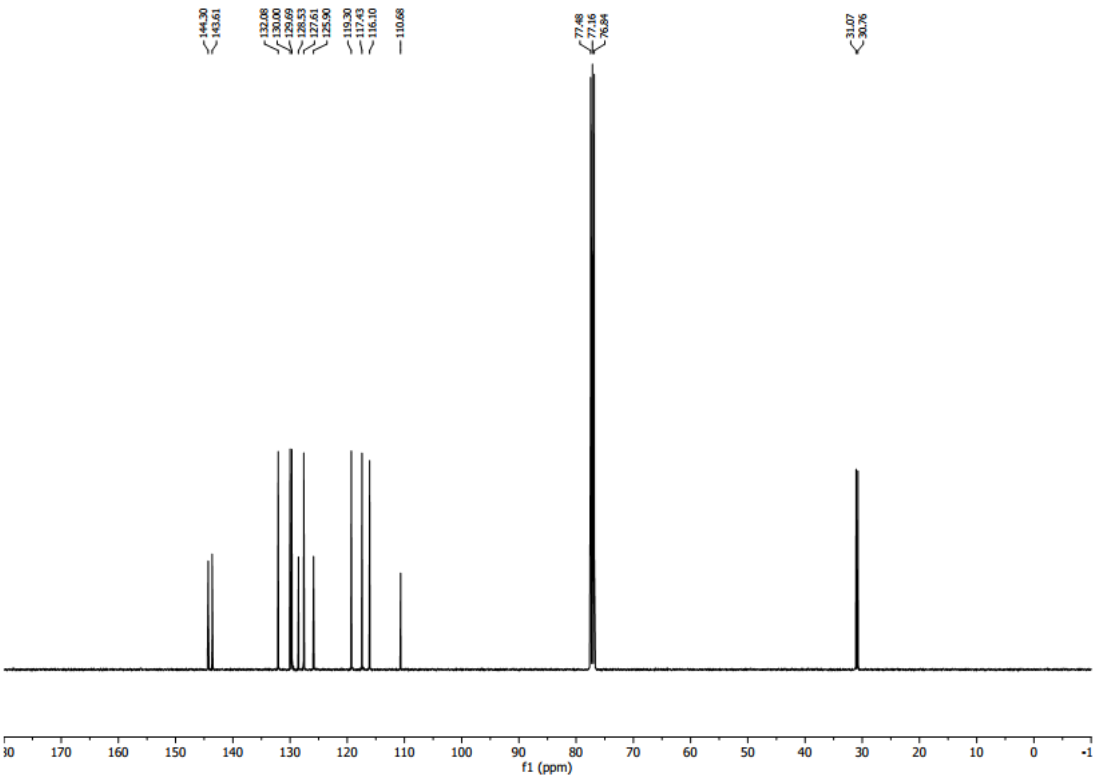
Compound **56** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



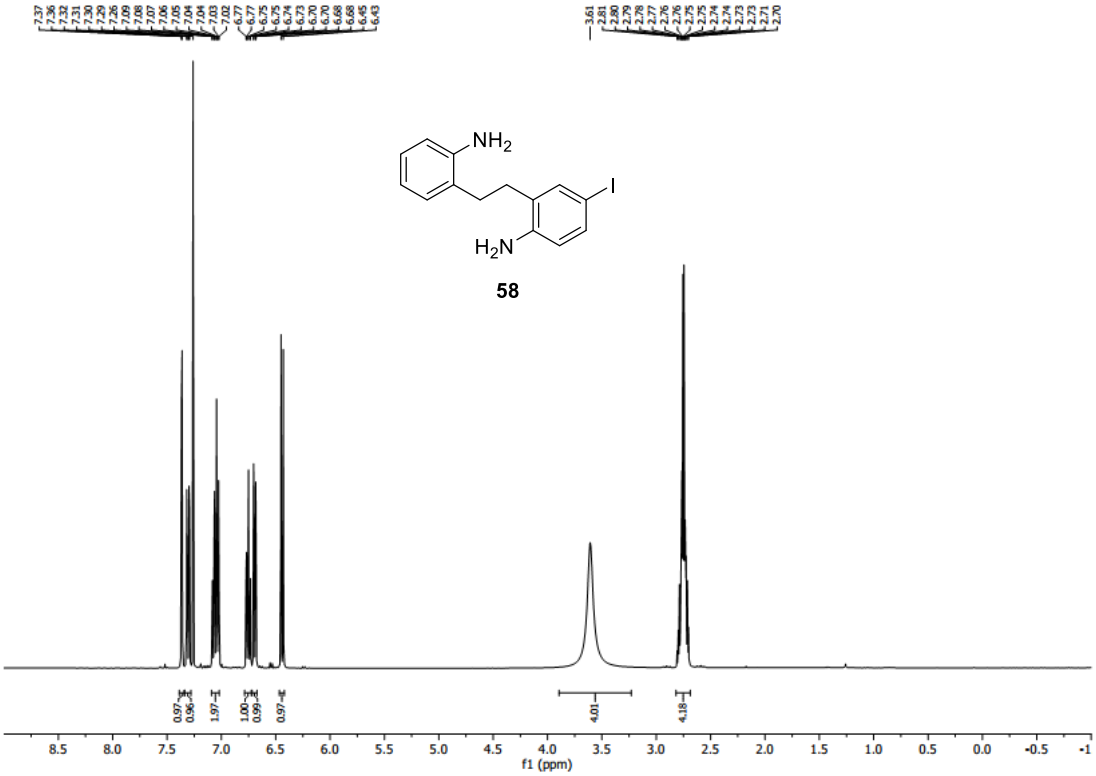


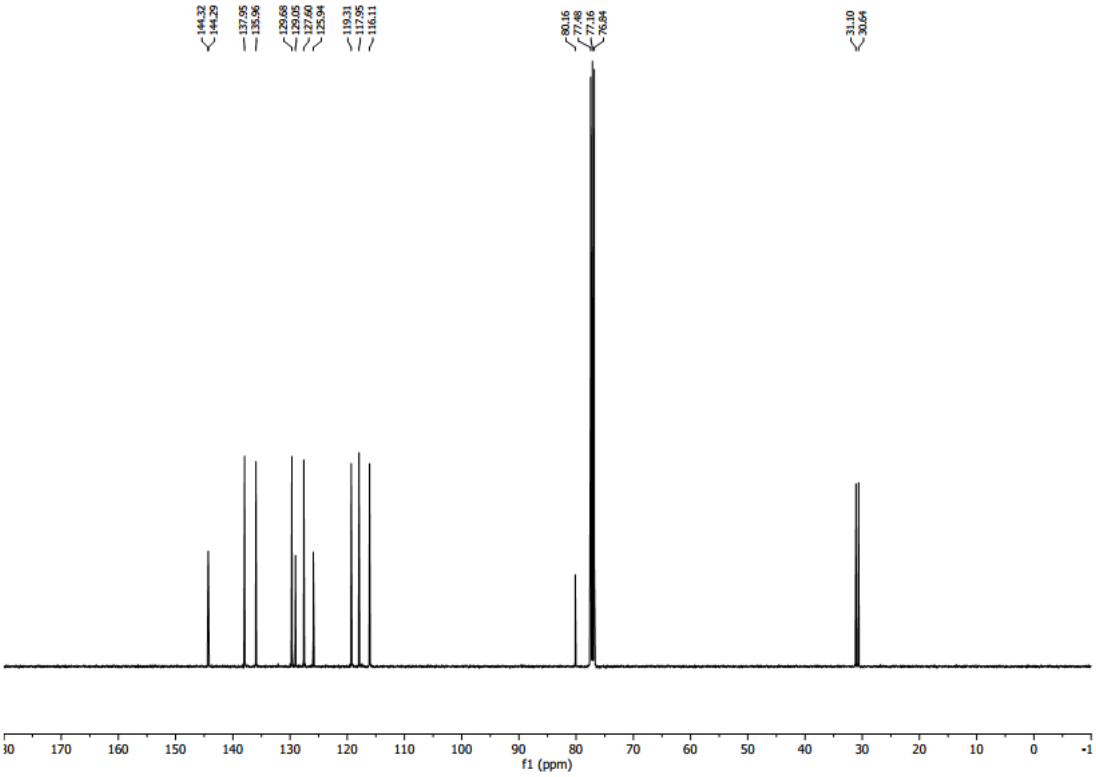
Compound **57** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



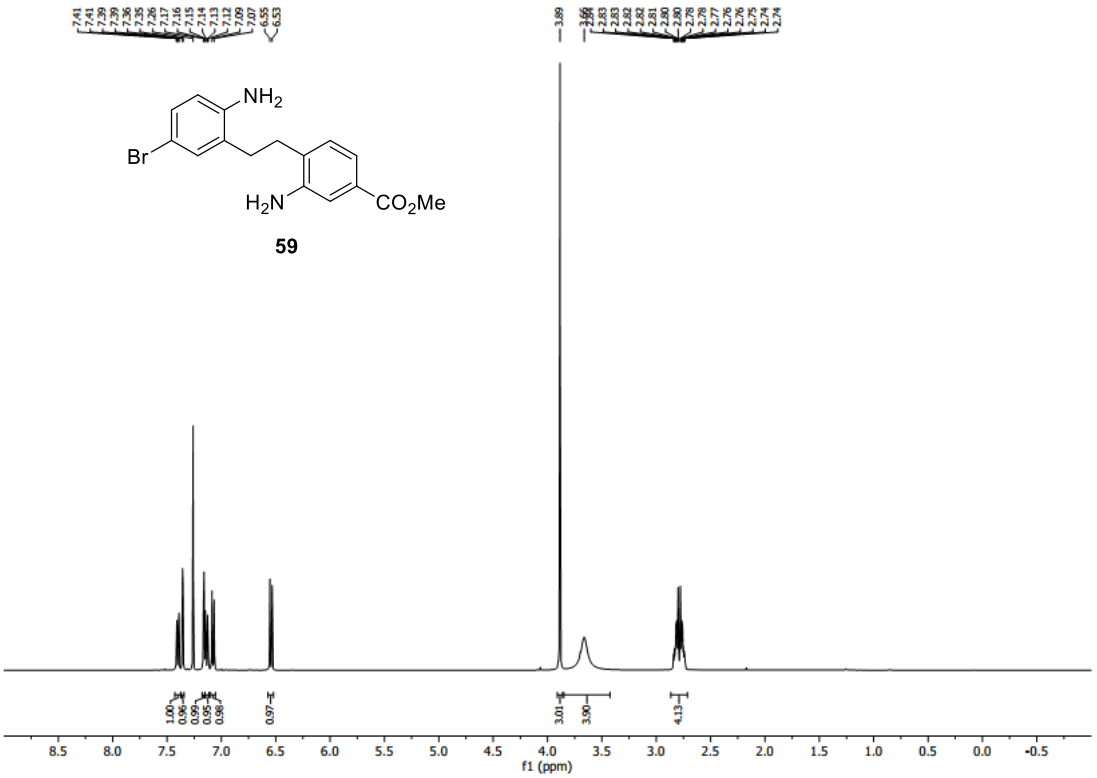


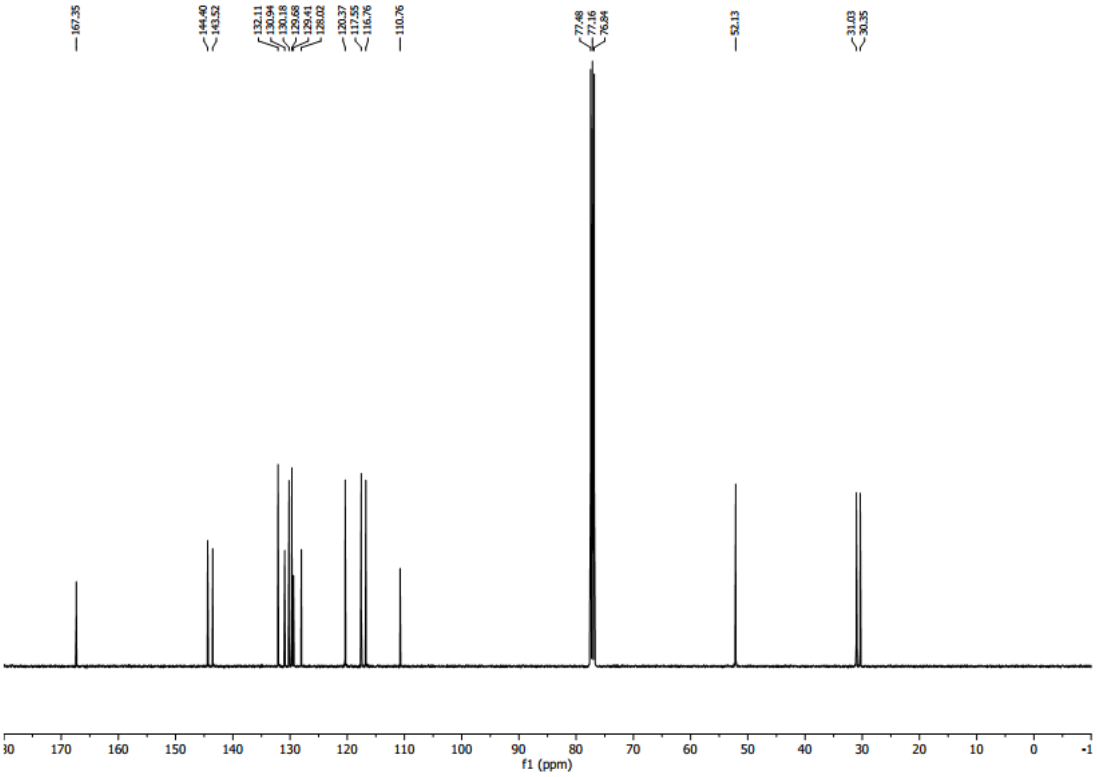
Compound **58** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



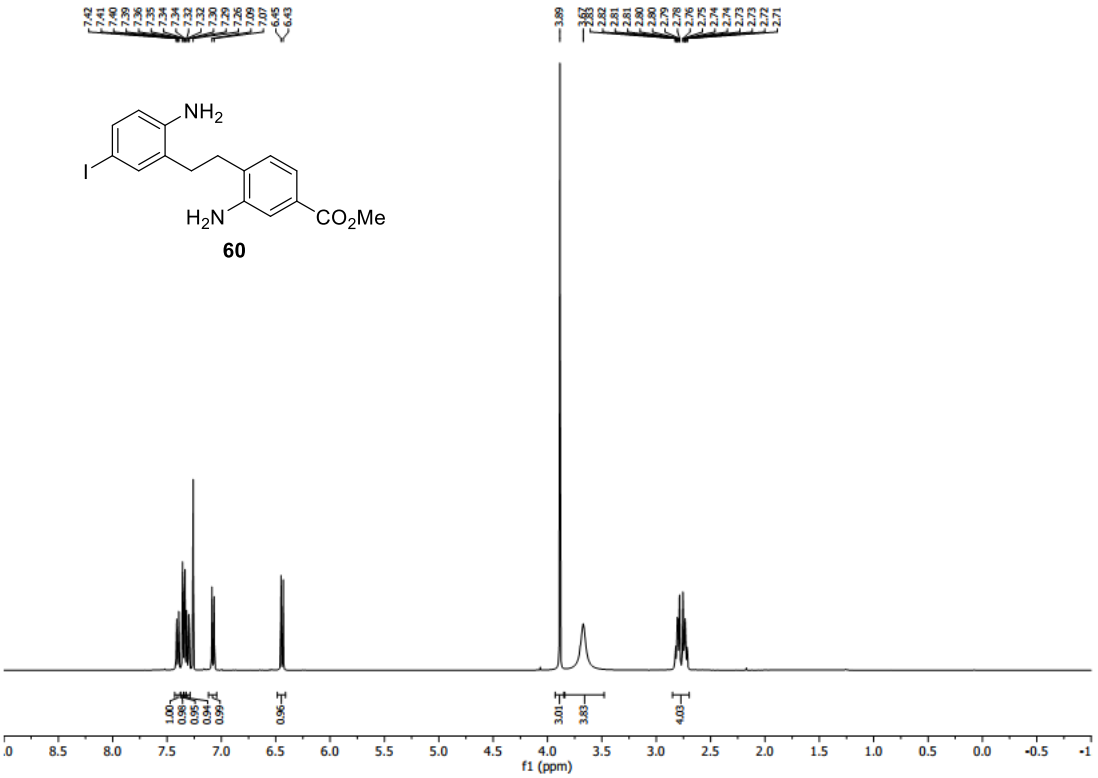


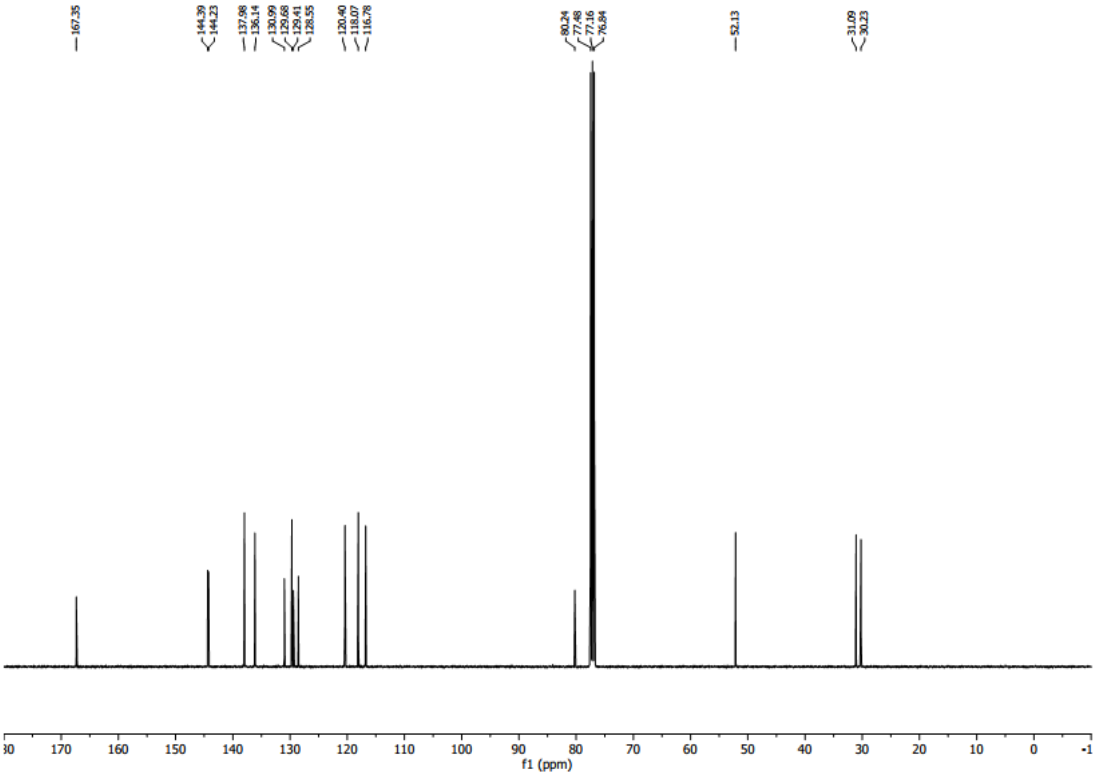
Compound **59** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



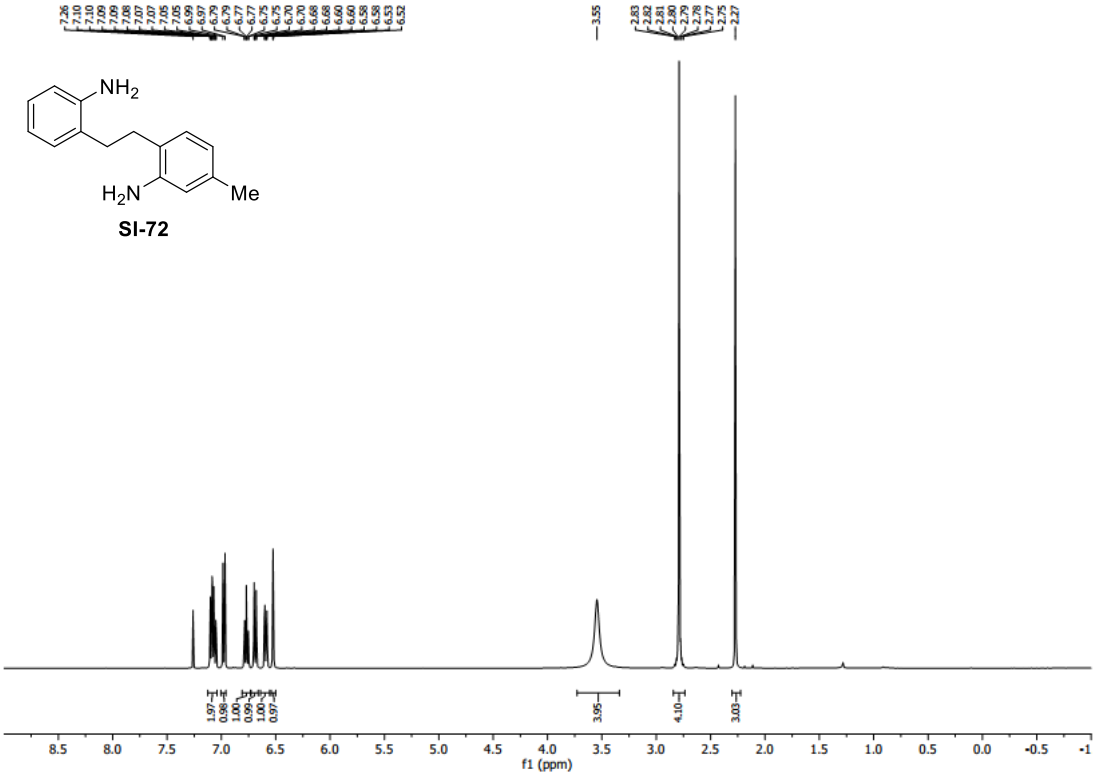


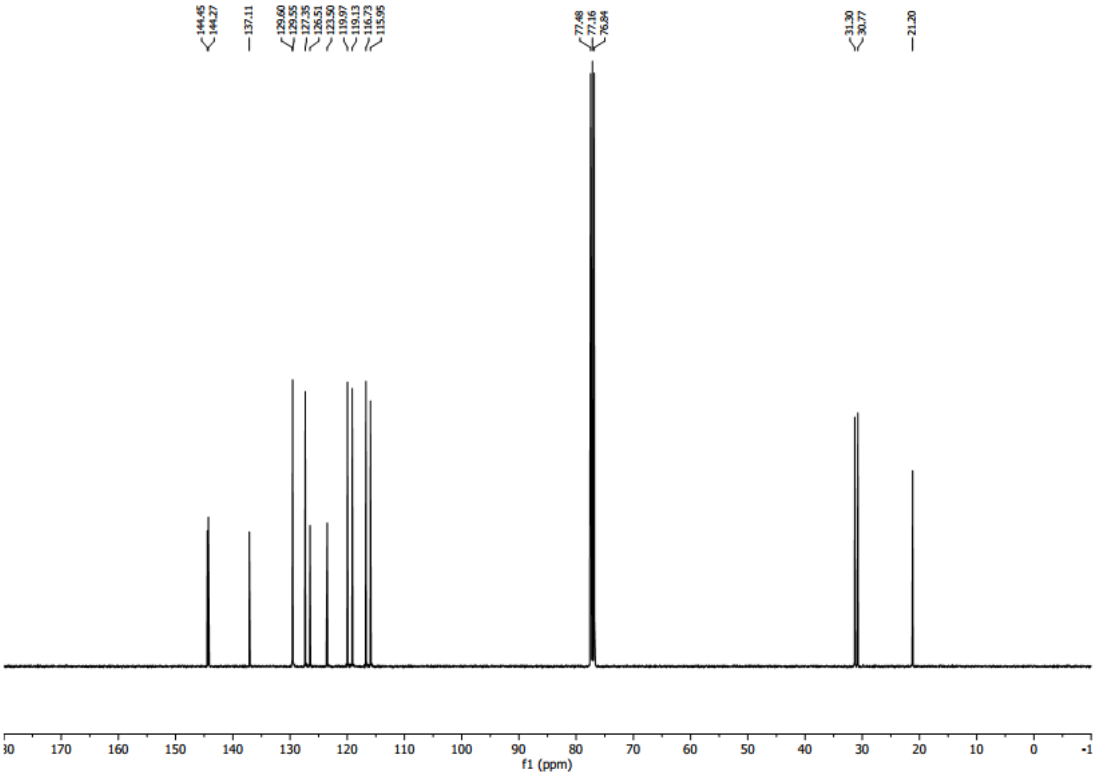
Compound **60**– **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



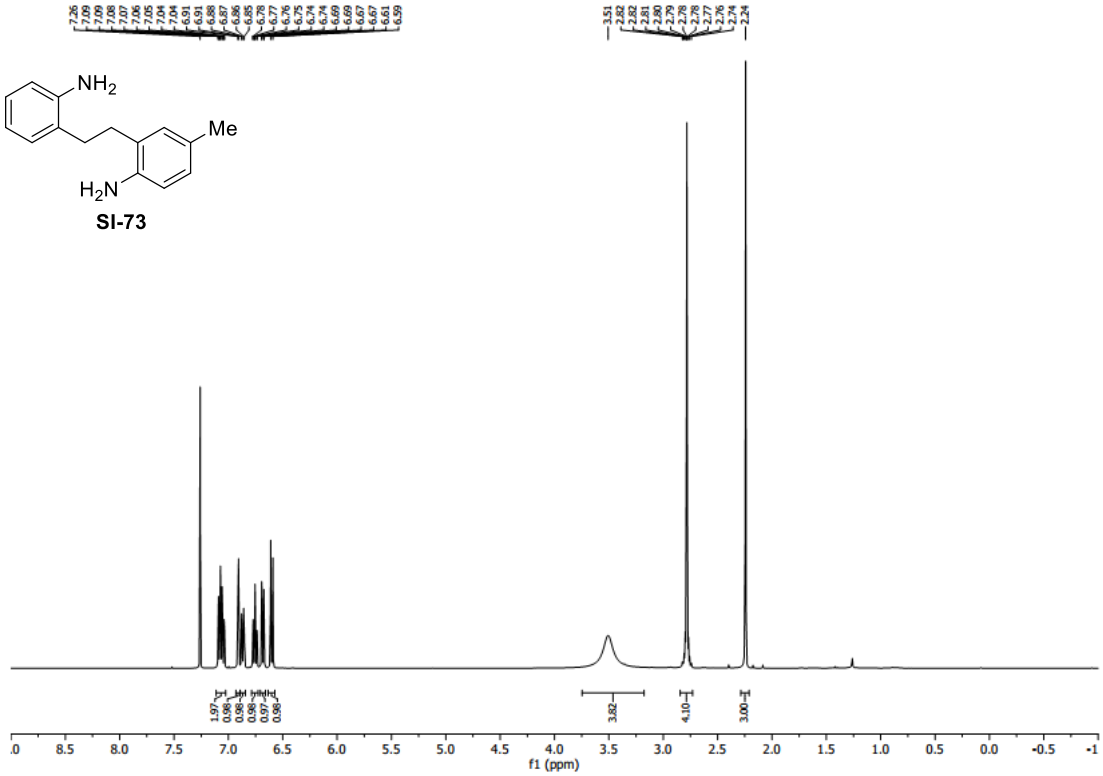


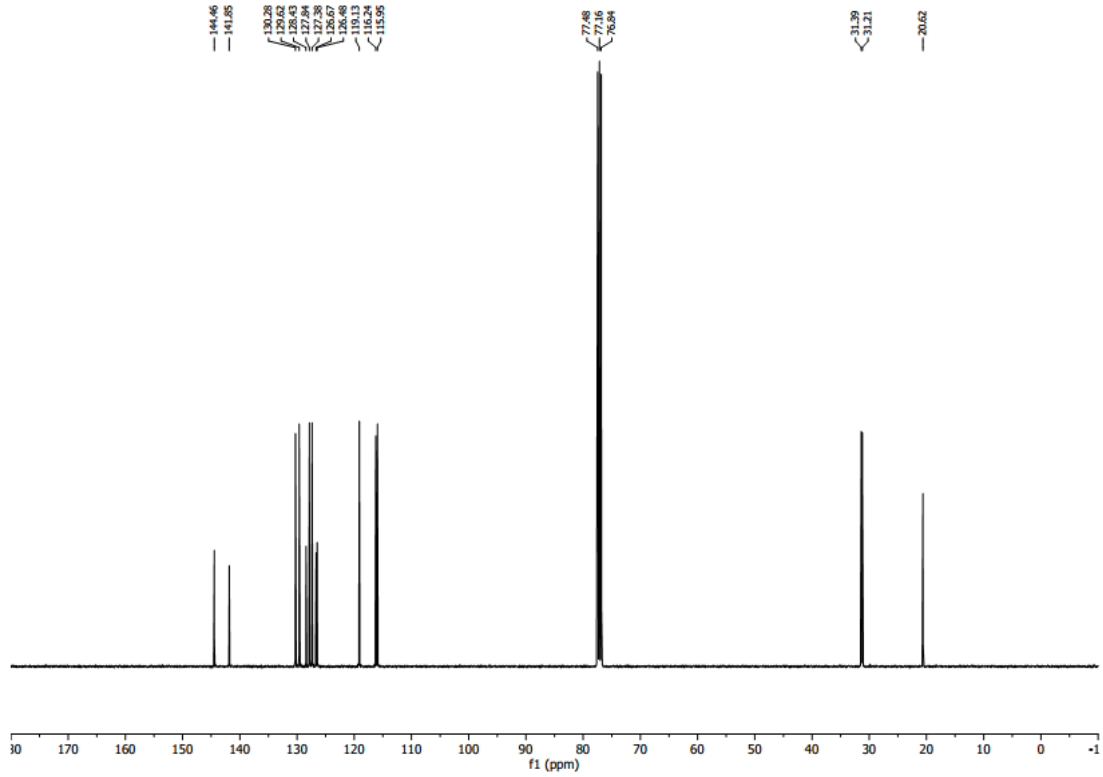
Compound **SI-72** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



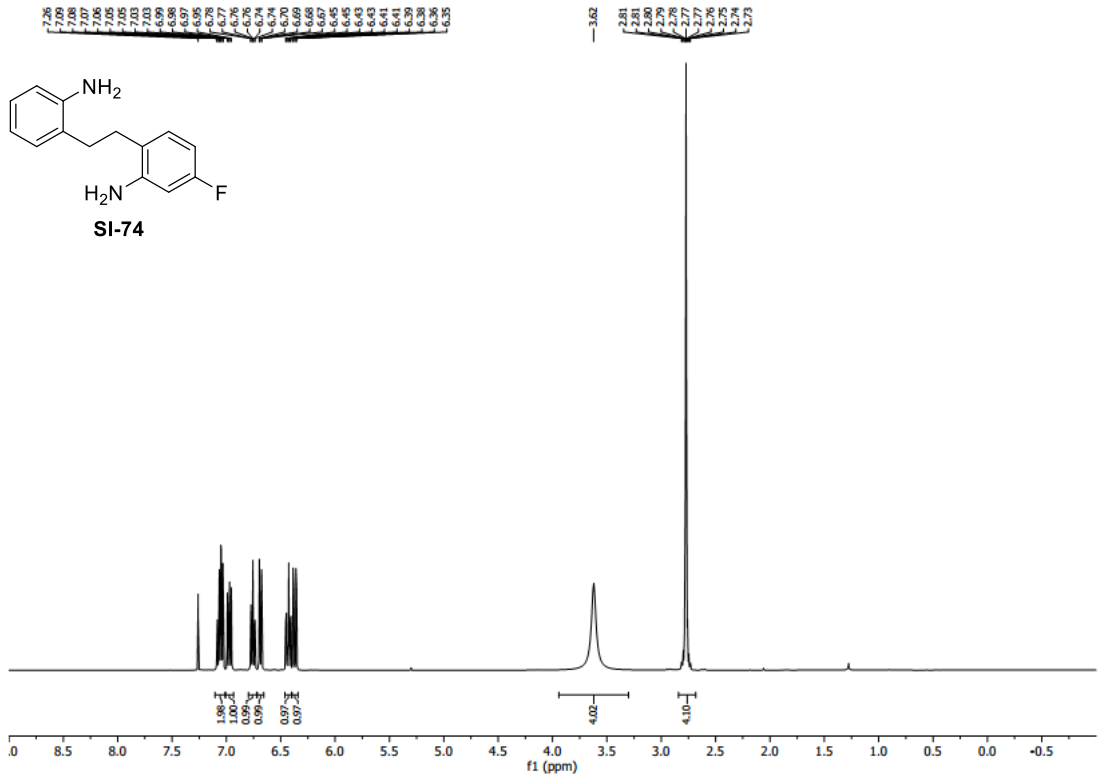


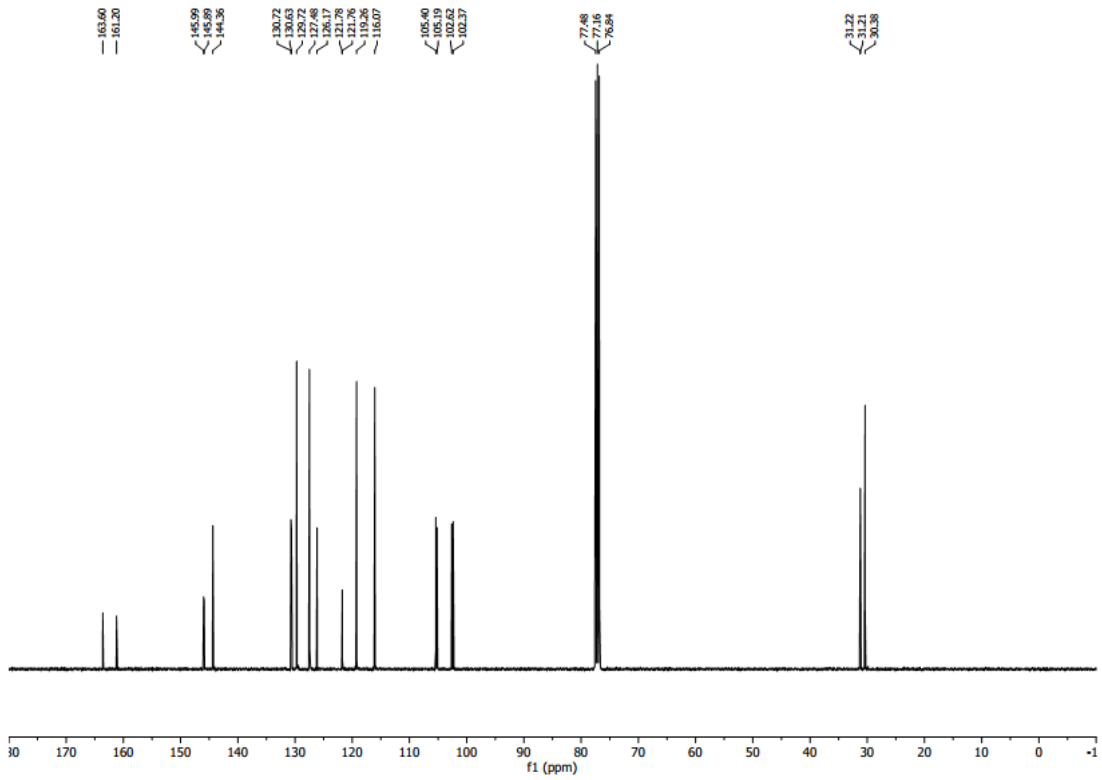
Compound **SI-73** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



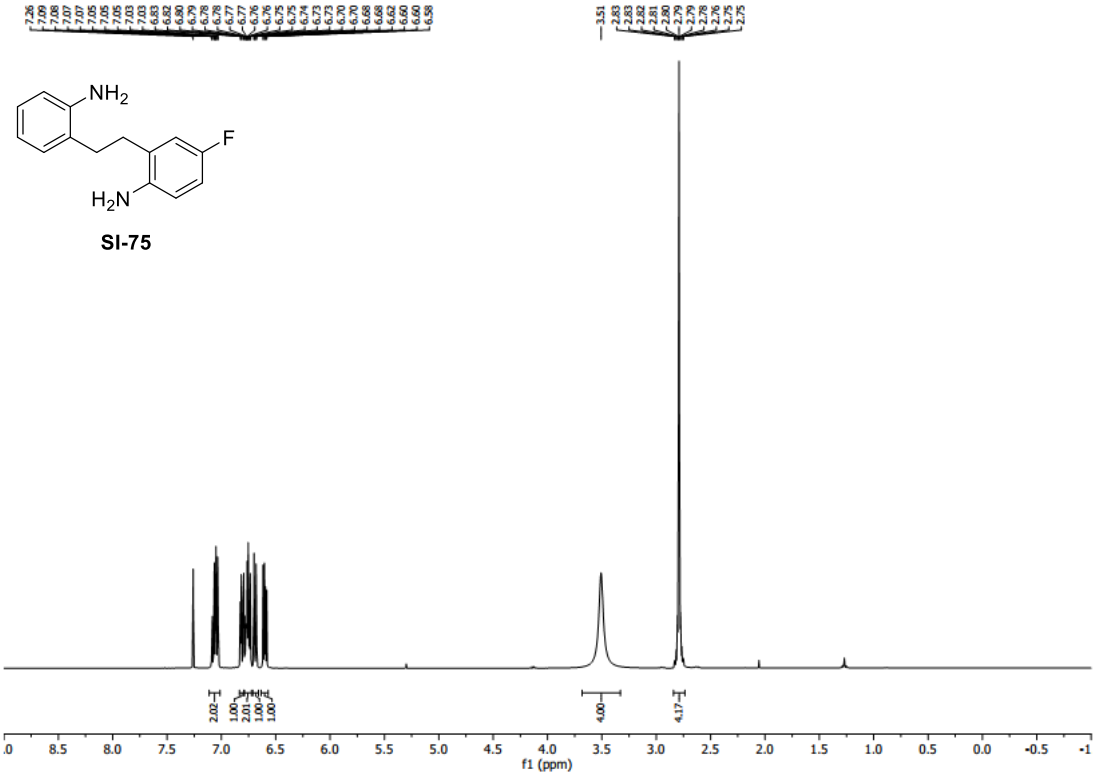


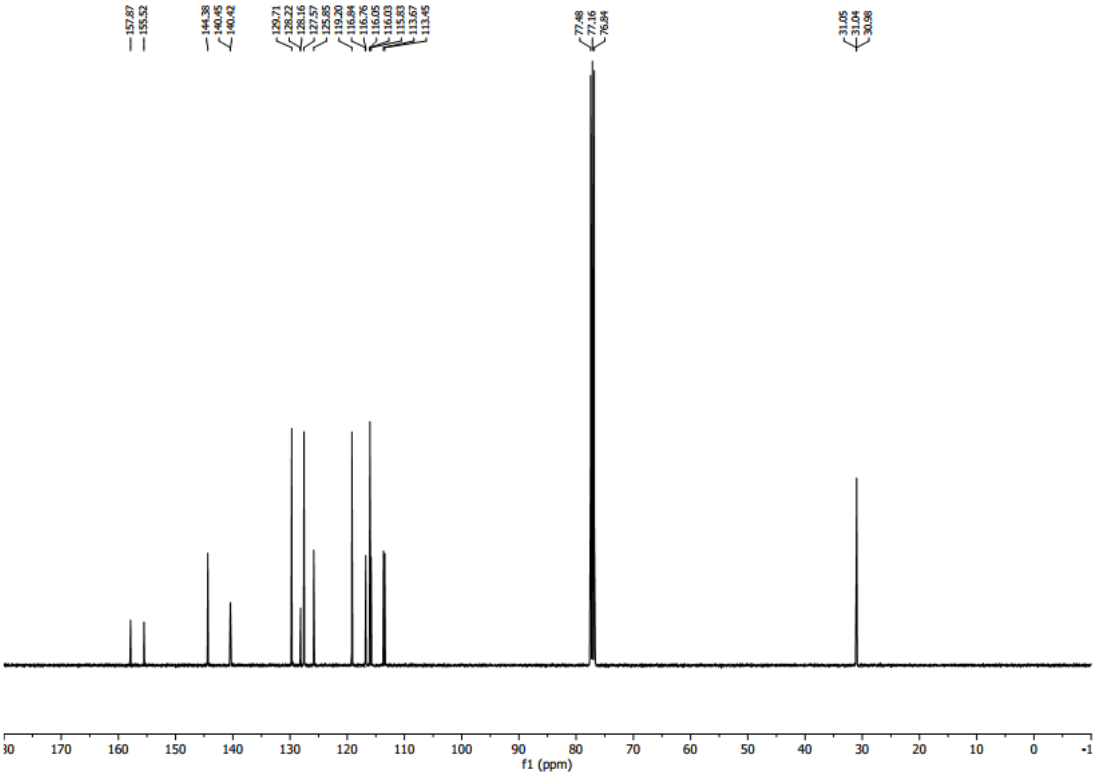
Compound **SI-74** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



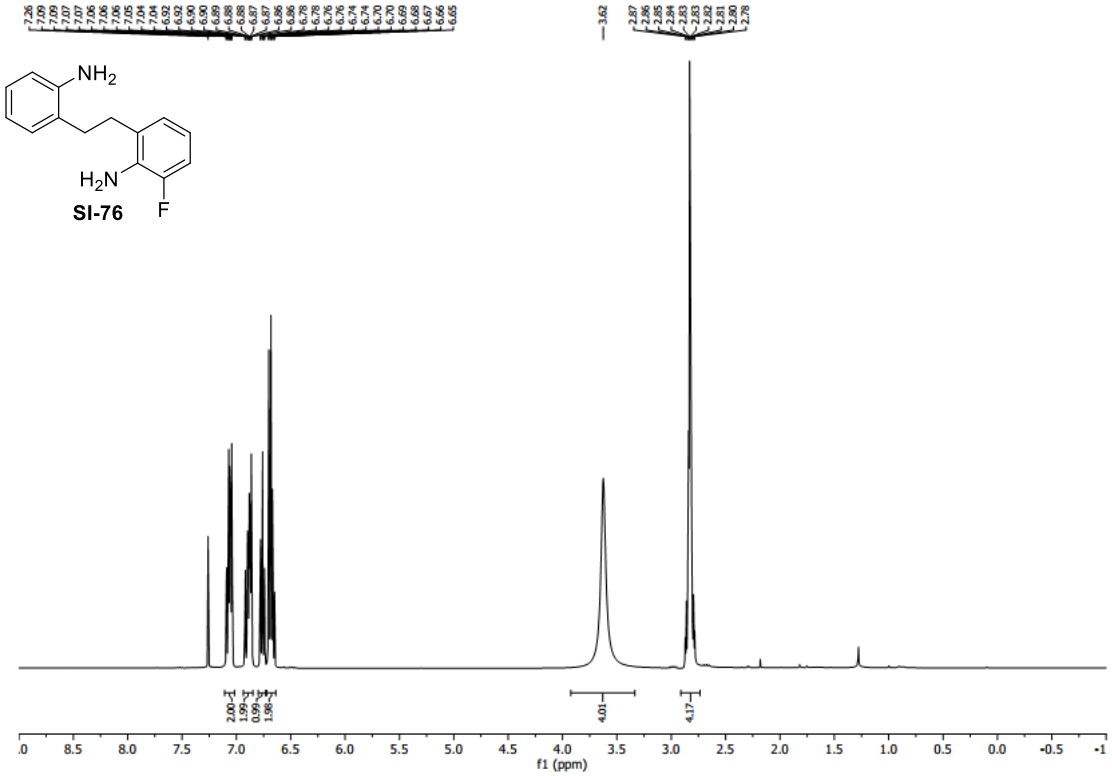


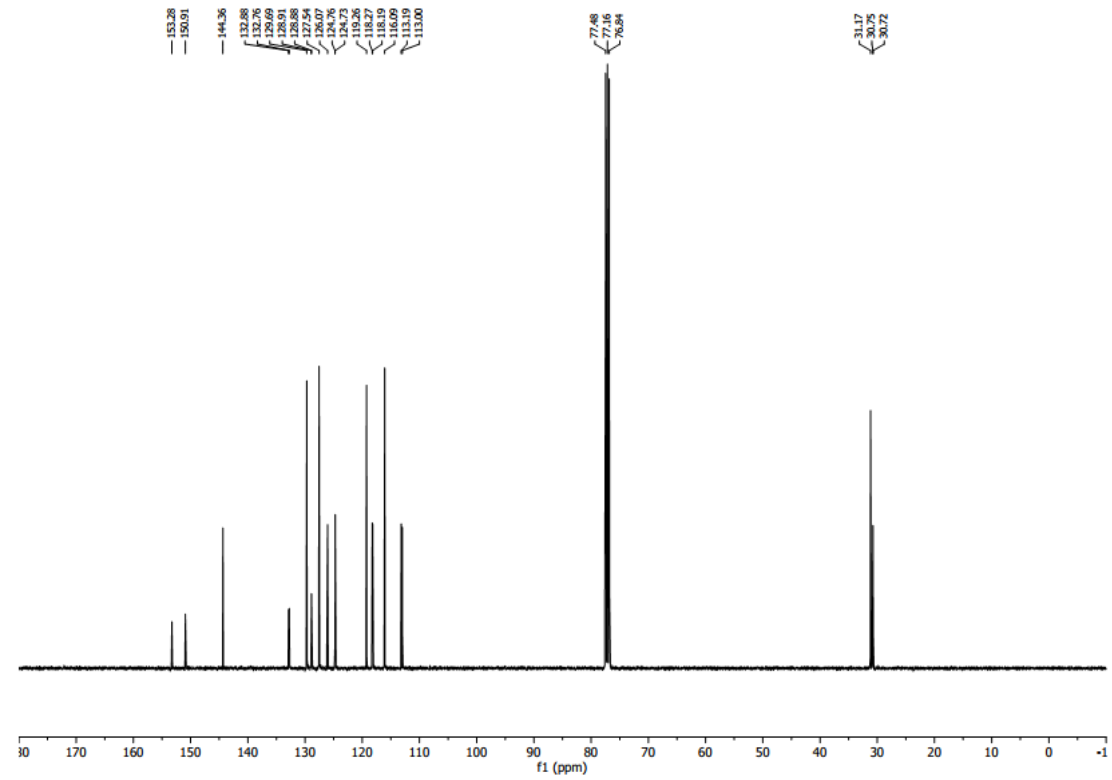
Compound **SI-75** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



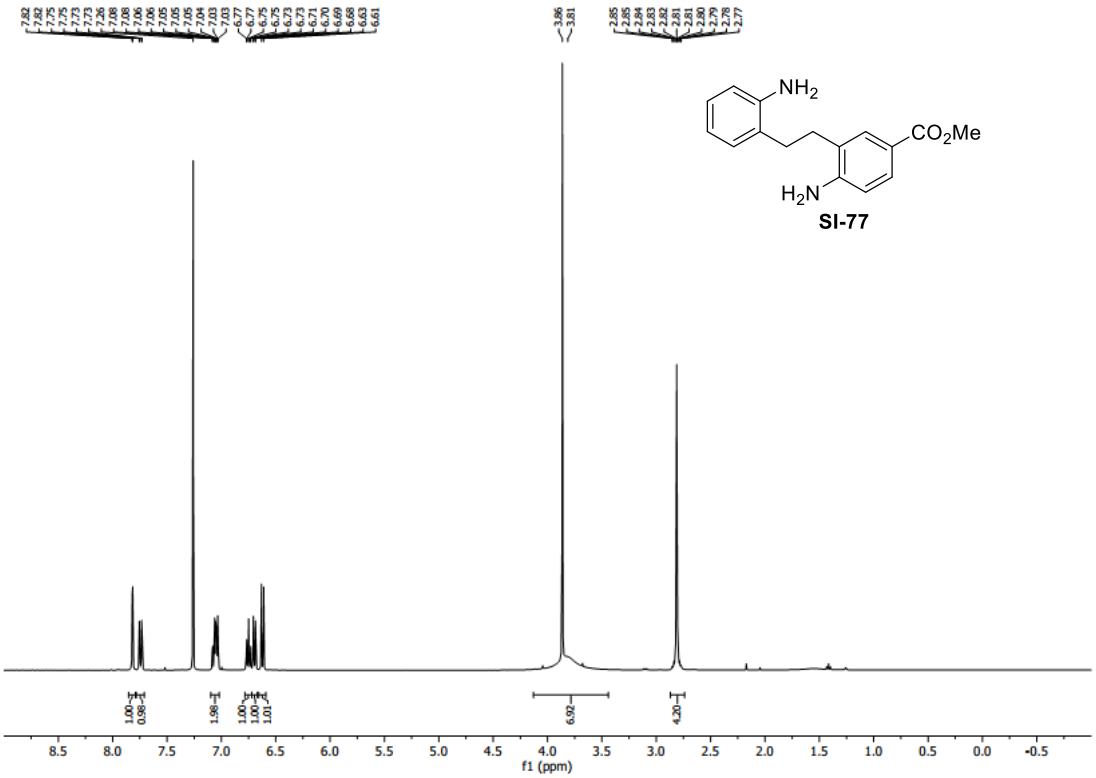


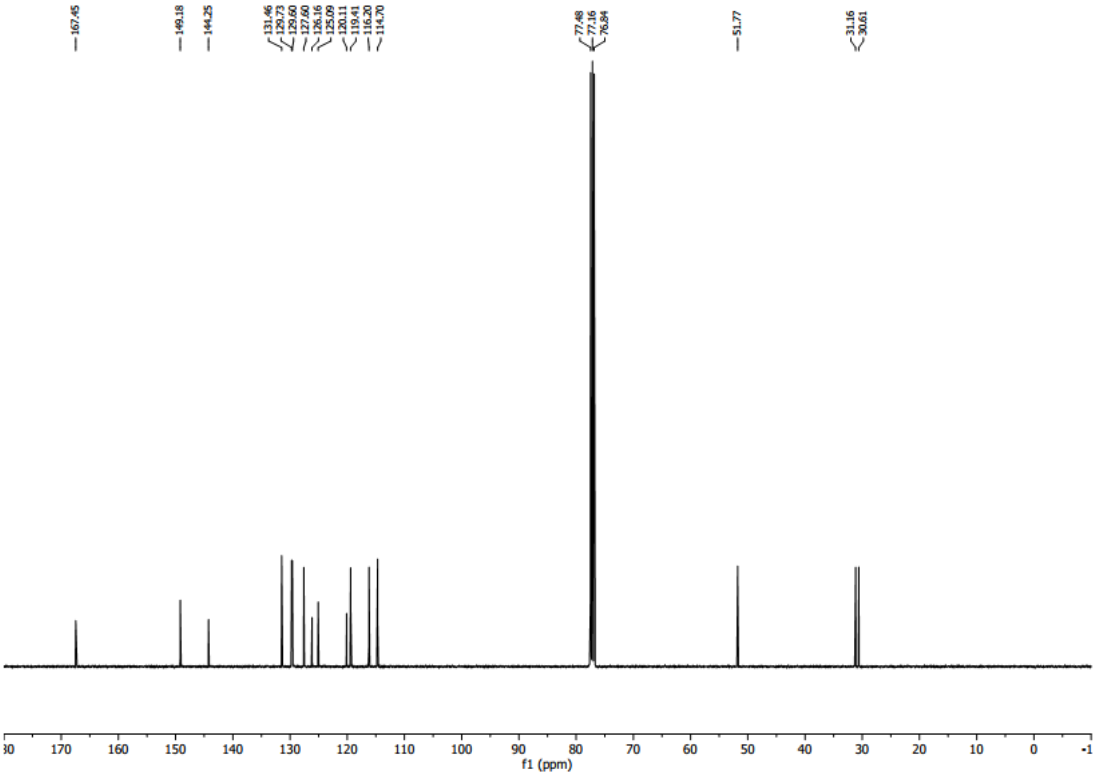
Compound **SI-76** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



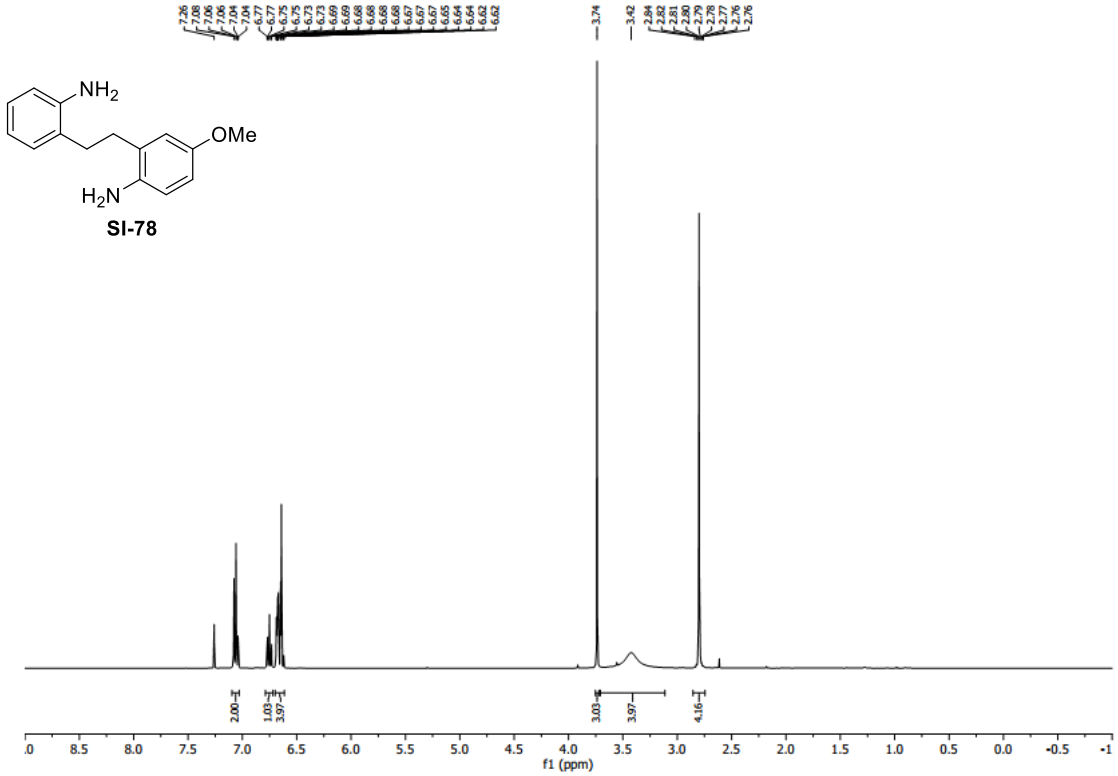


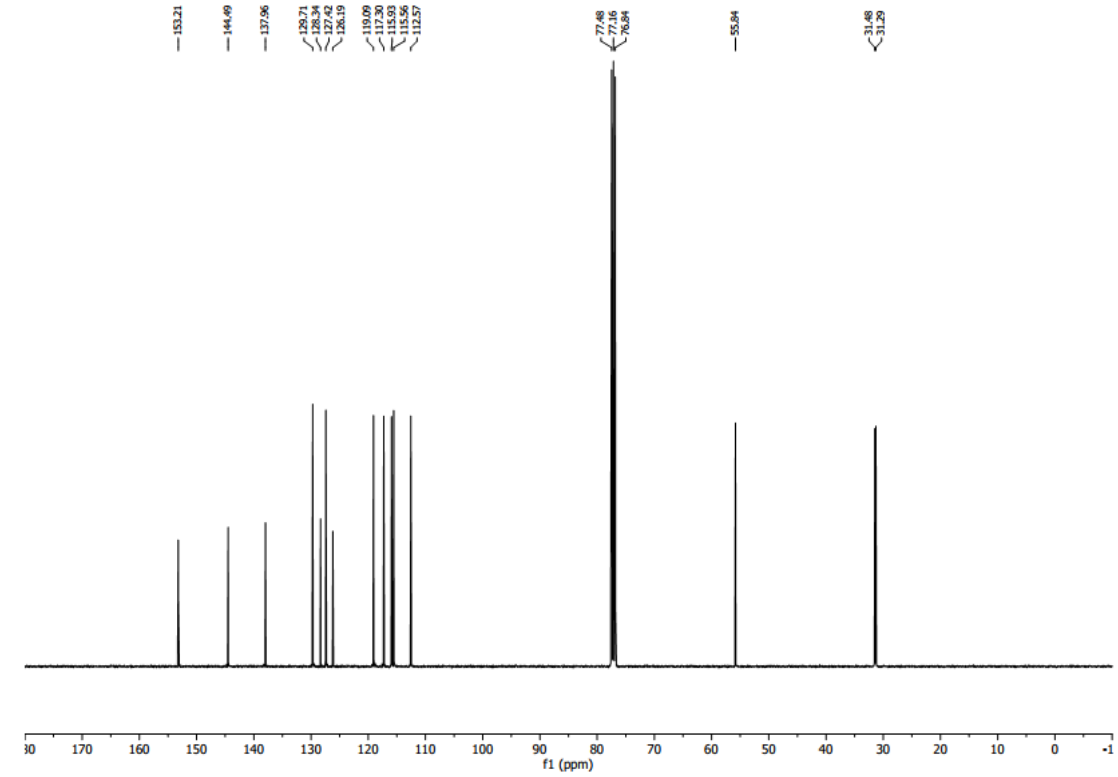
Compound **SI-77** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



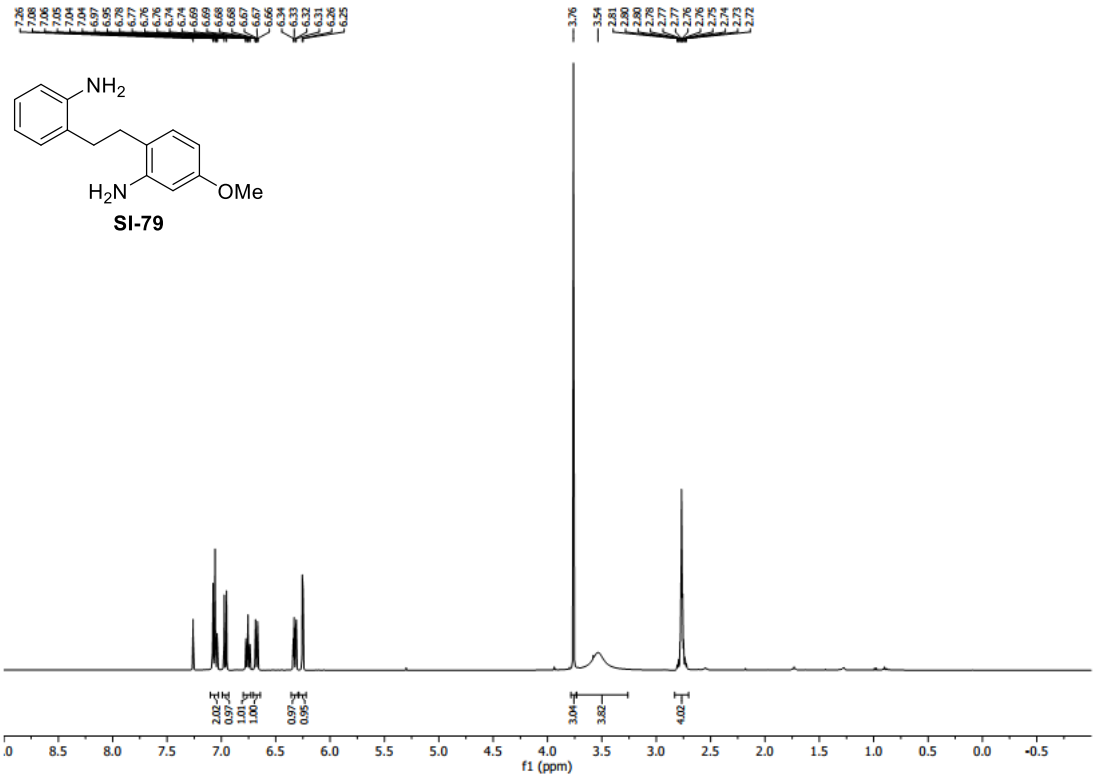


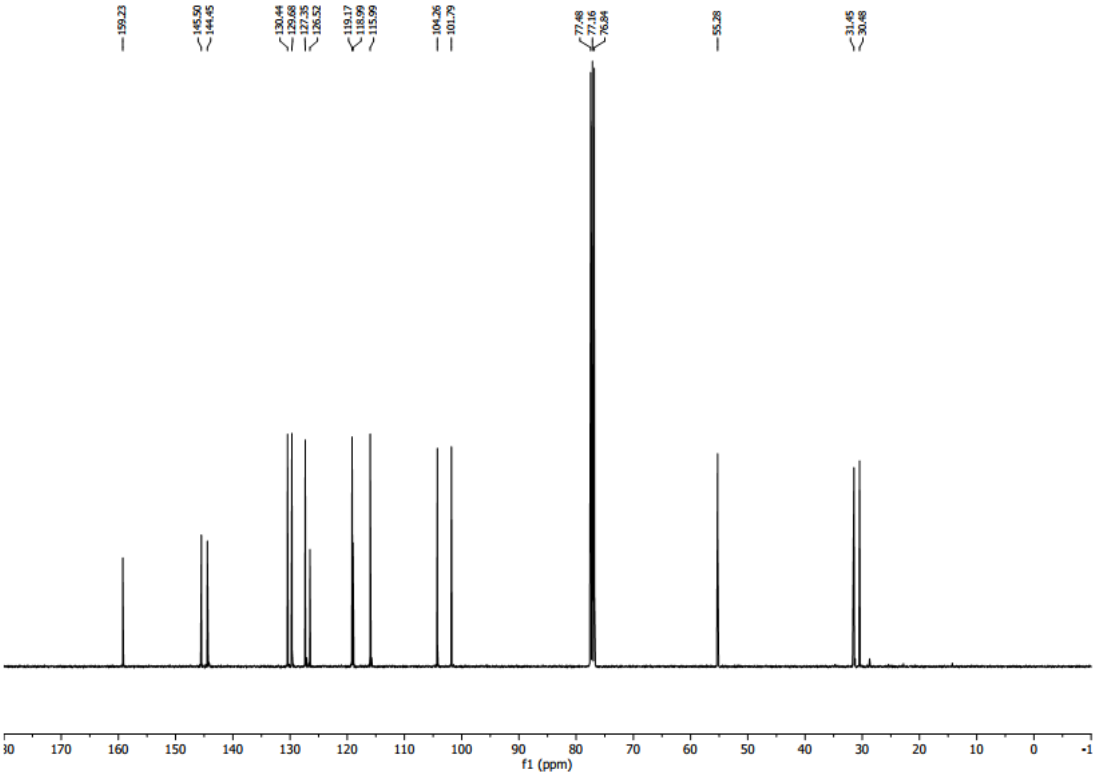
Compound **SI-78** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



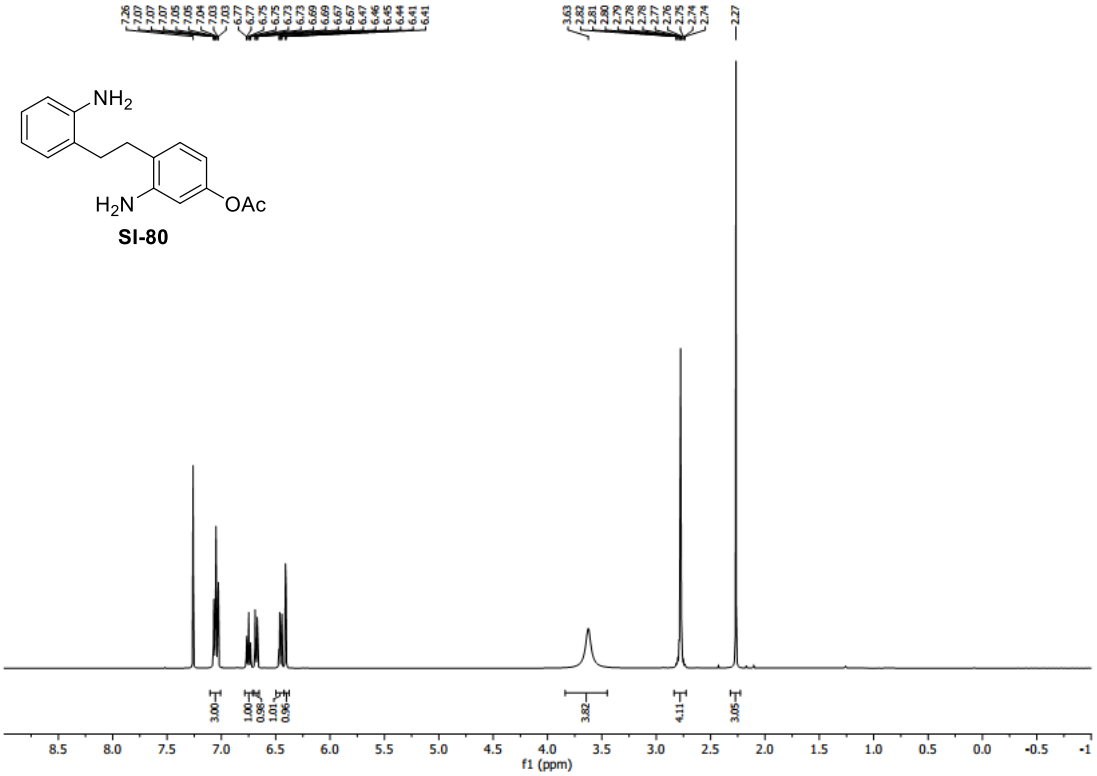


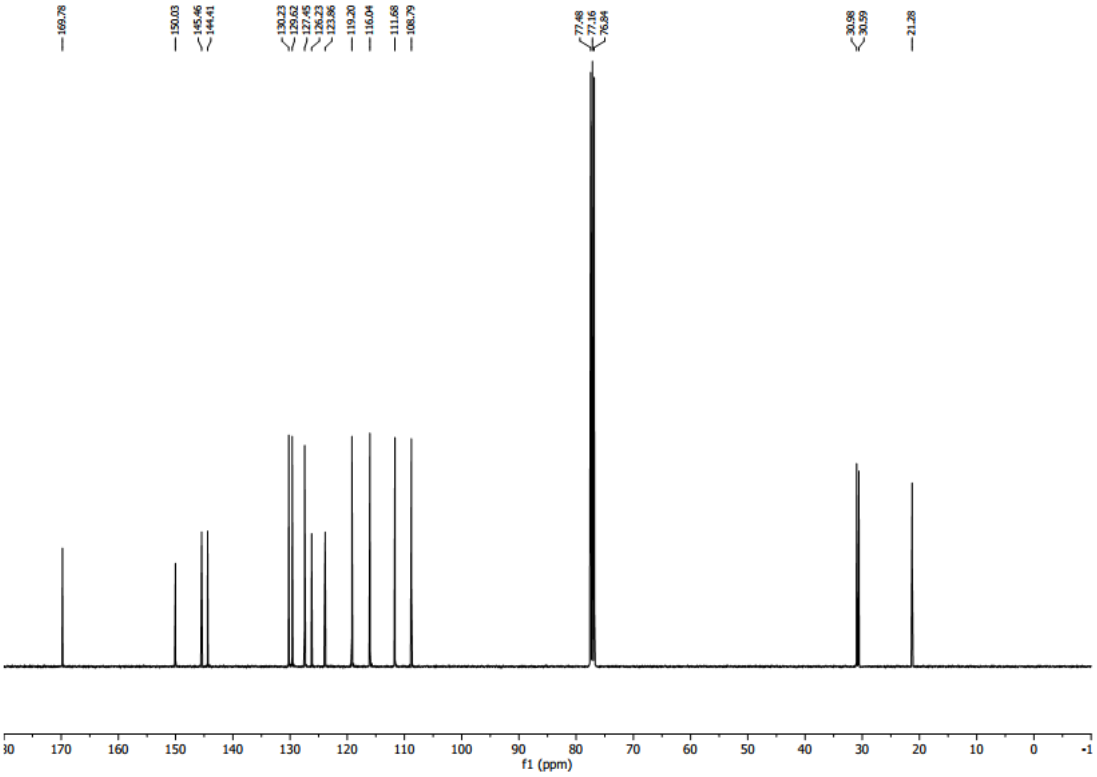
Compound **SI-79** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



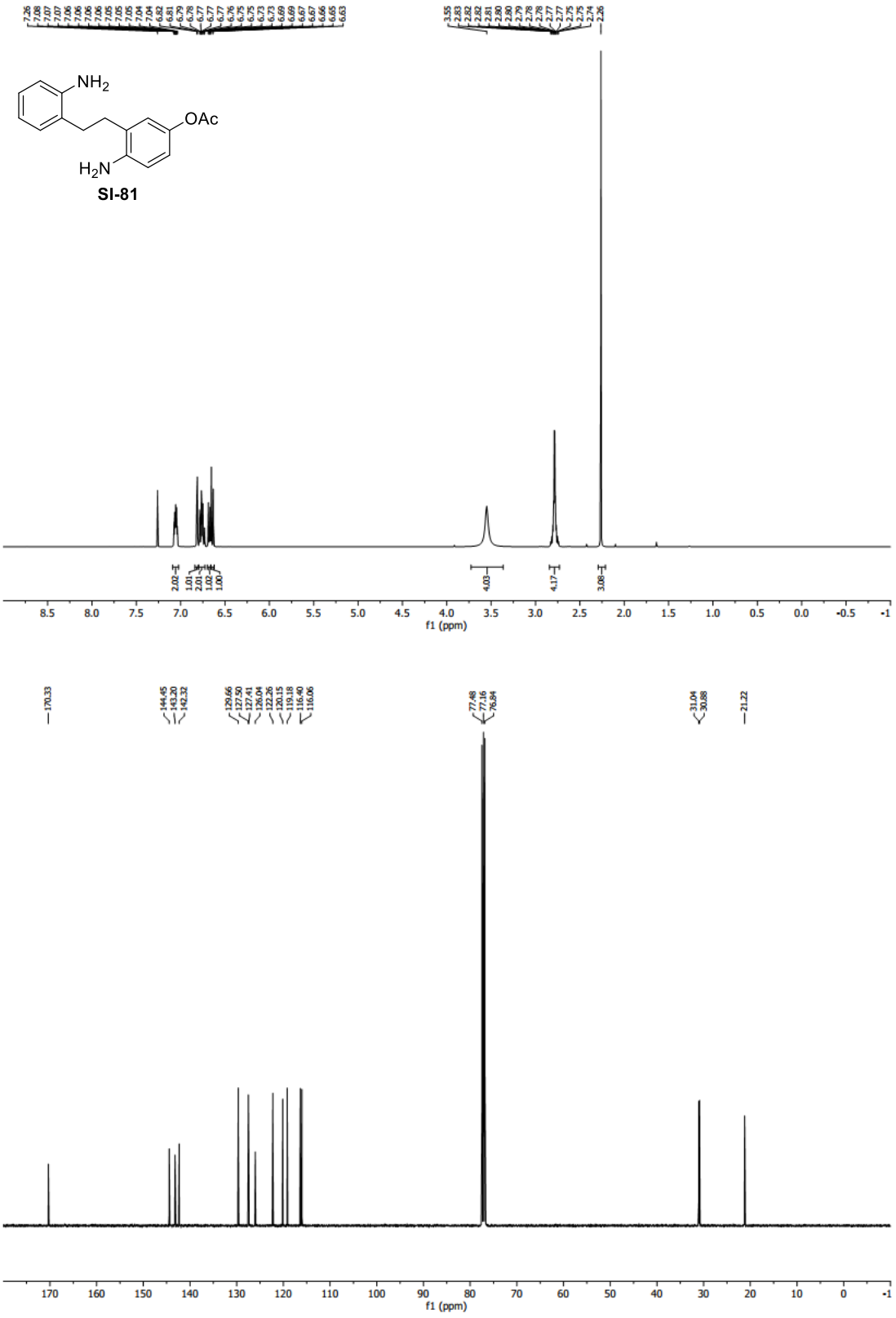


Compound **SI-80** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

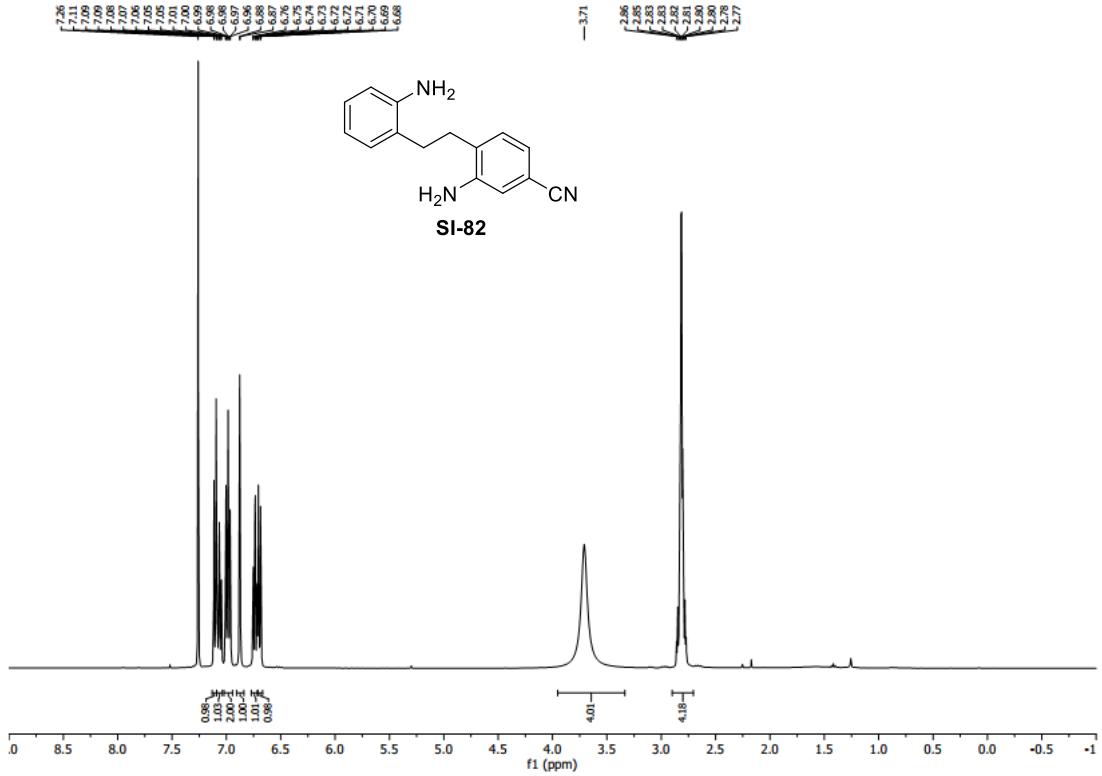


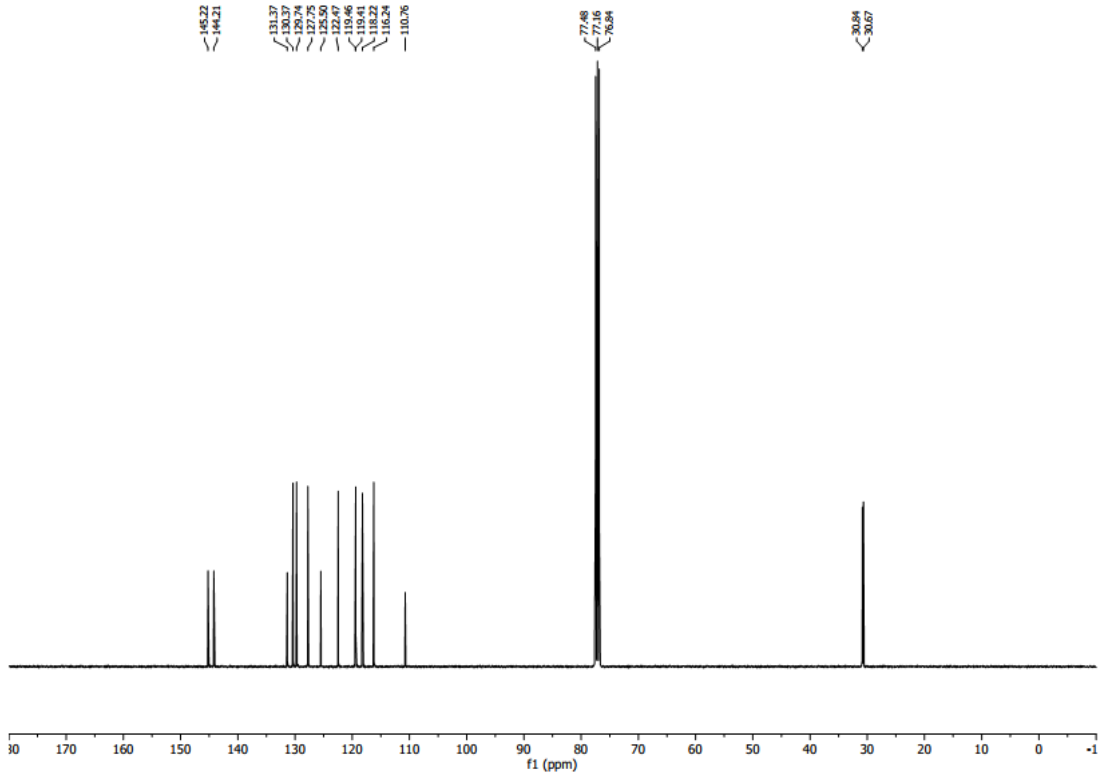


Compound **SI-81** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$

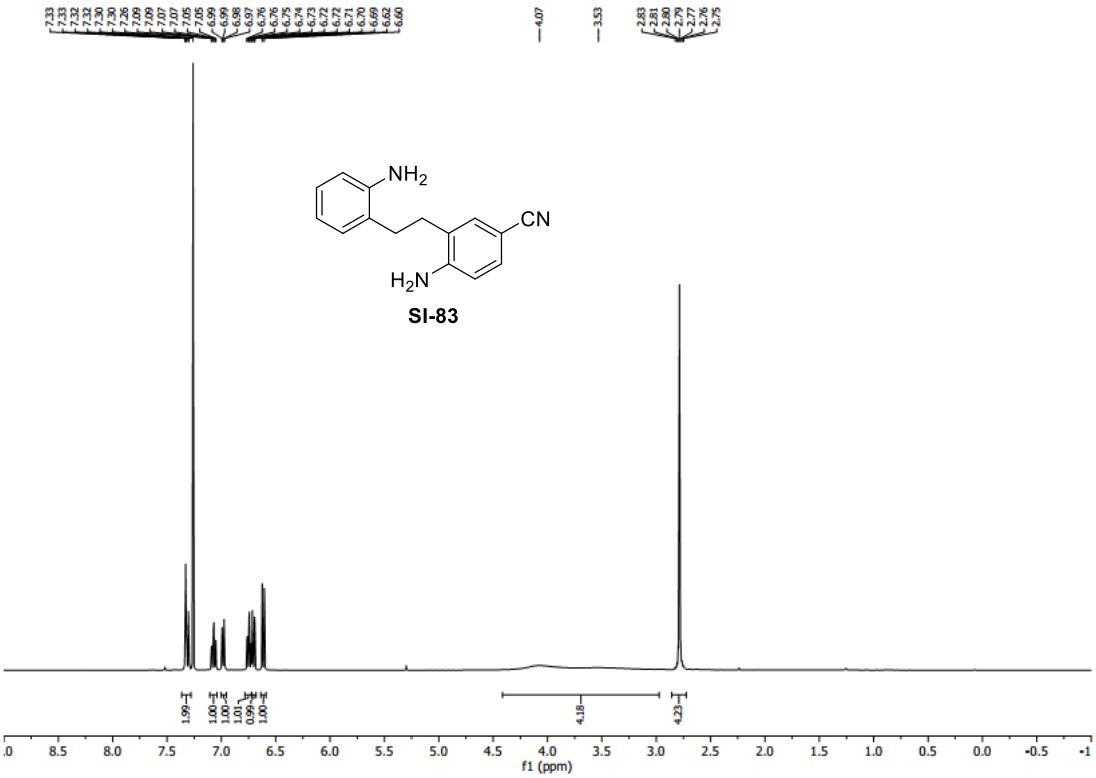


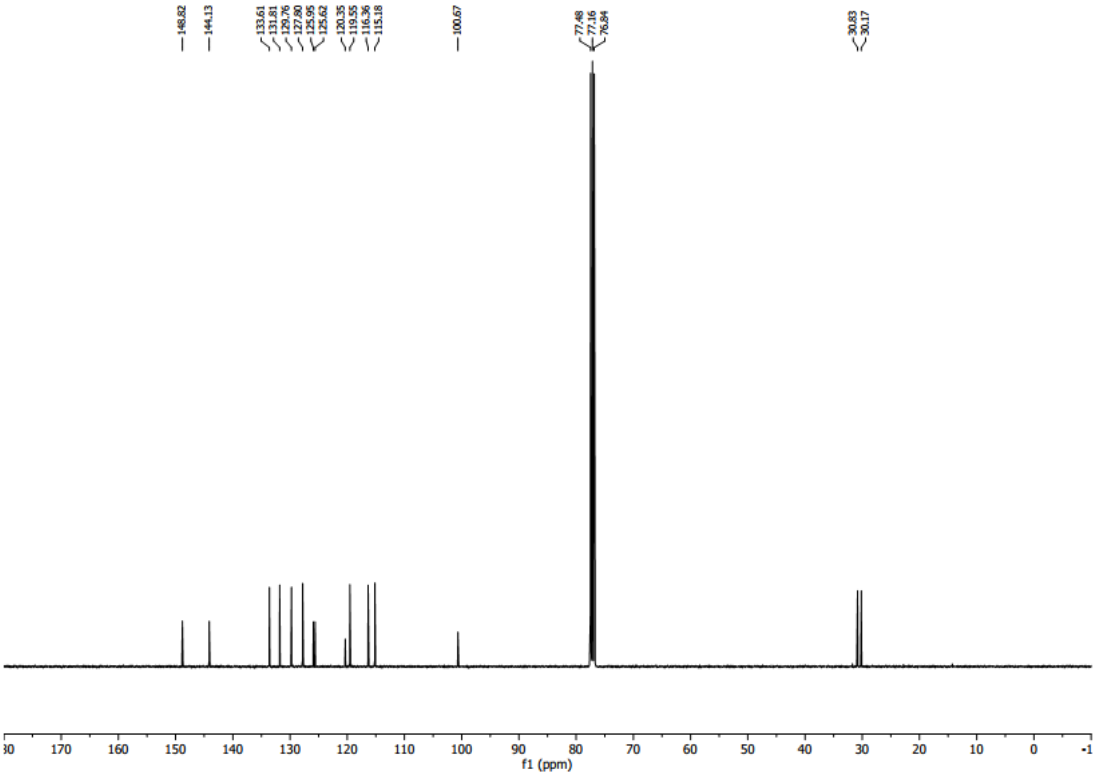
Compound **SI-82** – ^{1}**H-NMR** (400 MHz) and ^{13}**C-NMR** (100 MHz) in $CDCl_3$



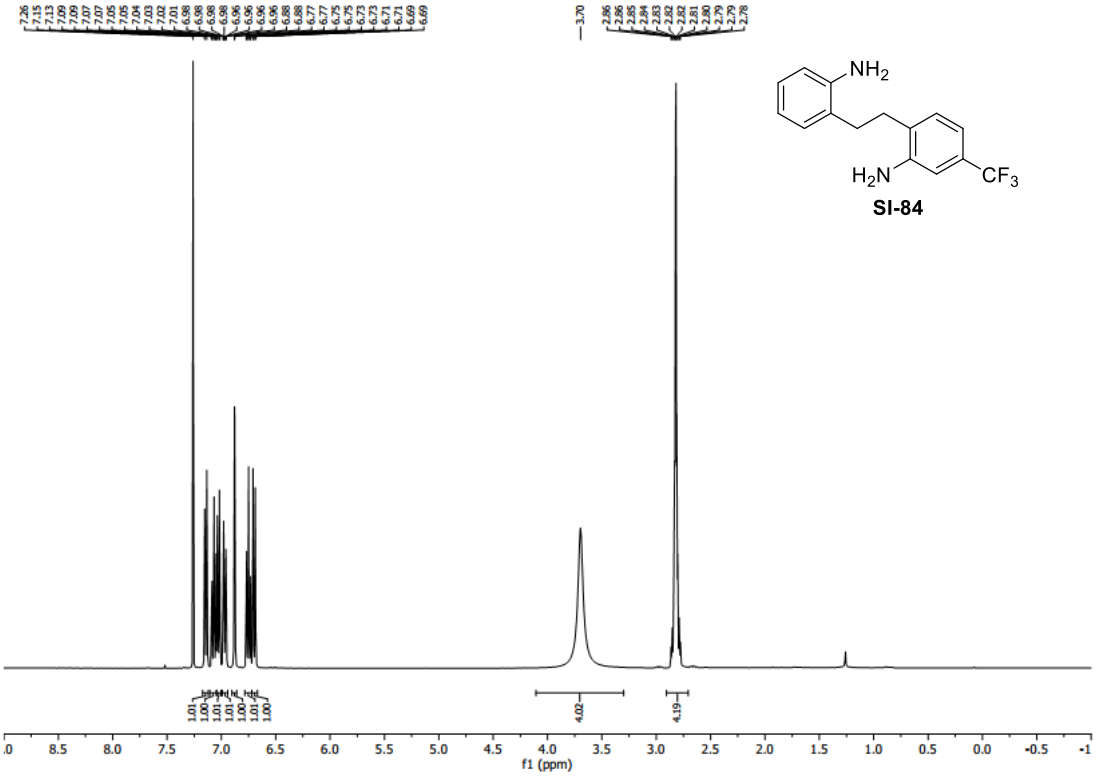


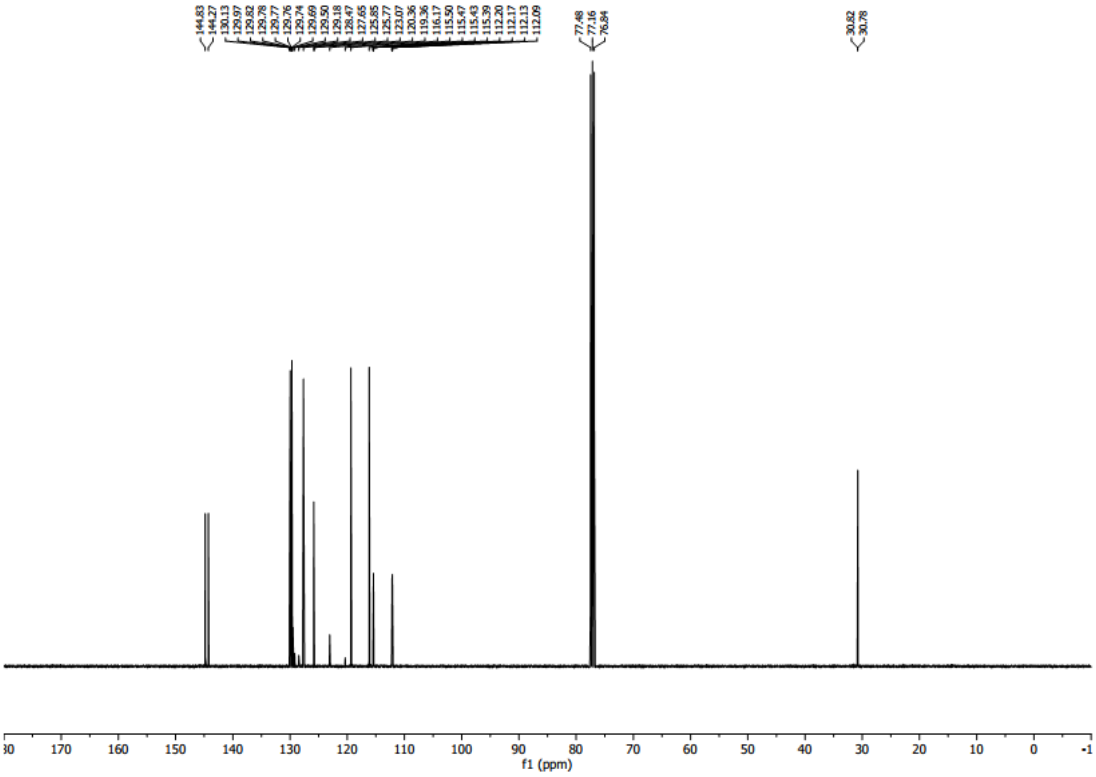
Compound **SI-83** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



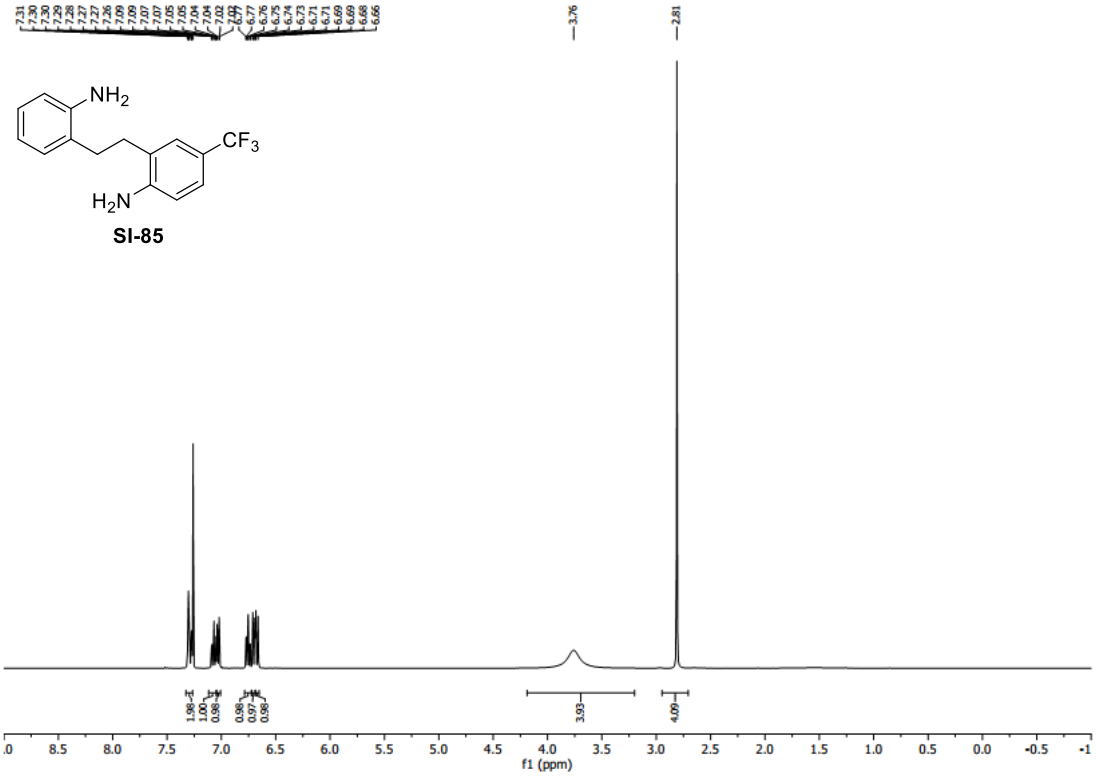


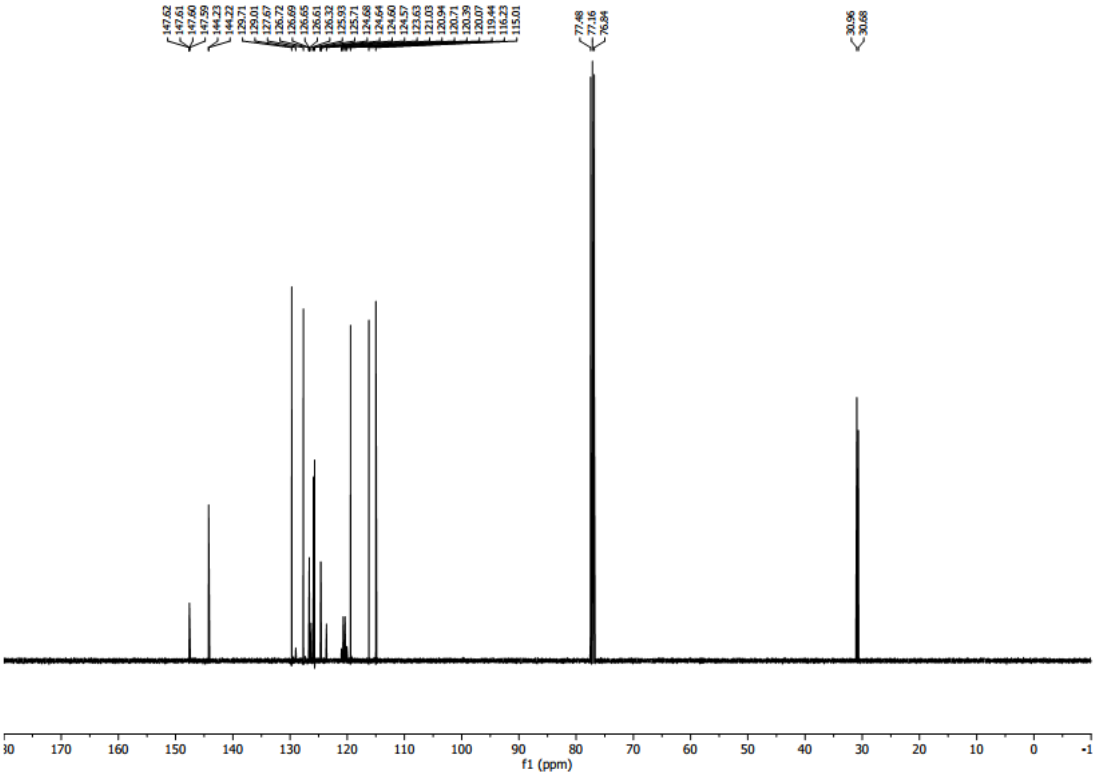
Compound **SI-84** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



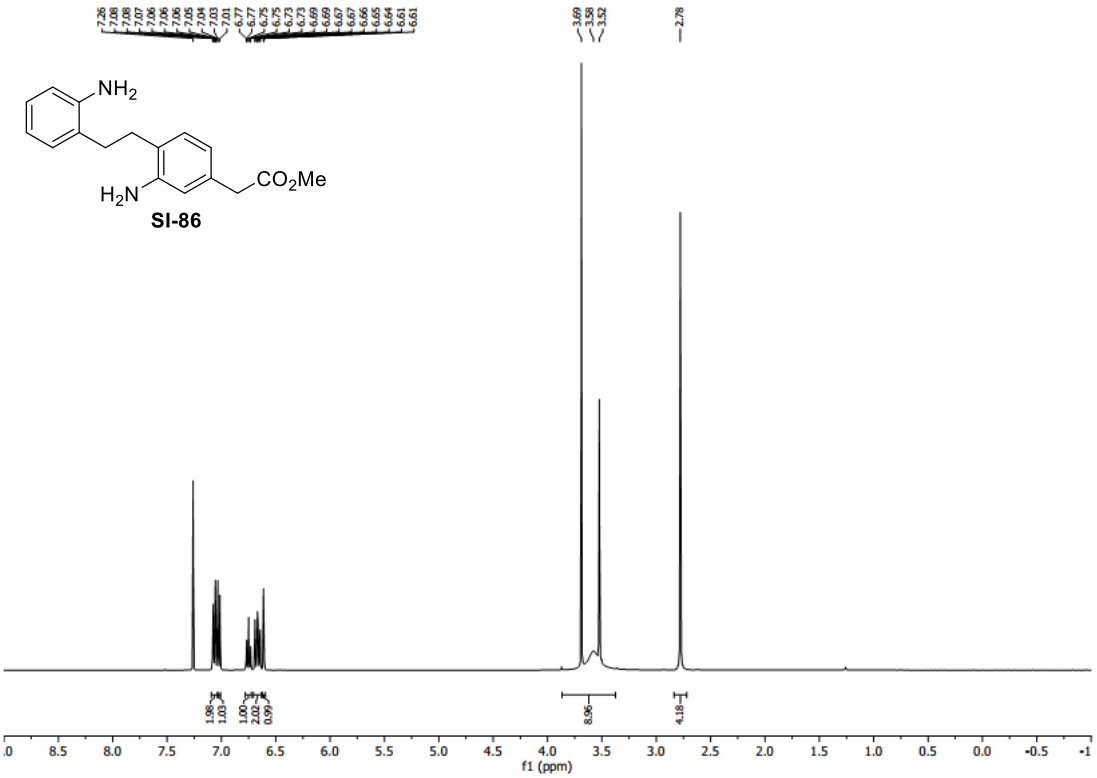


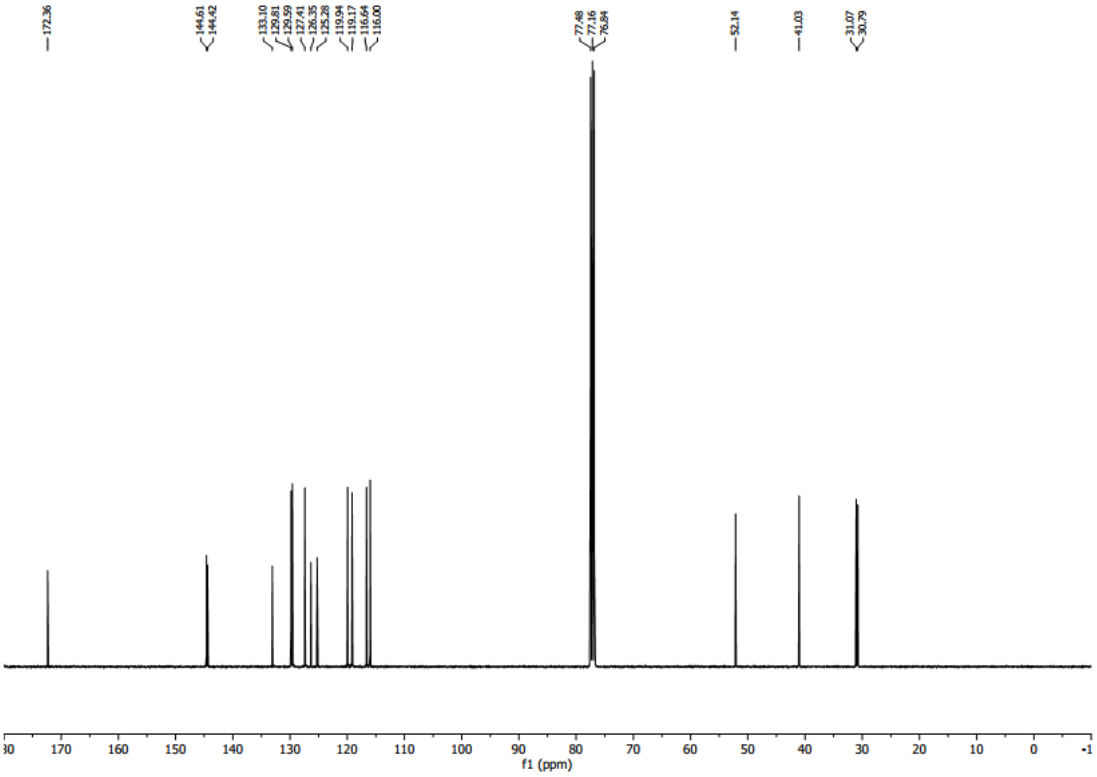
Compound **SI-85** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



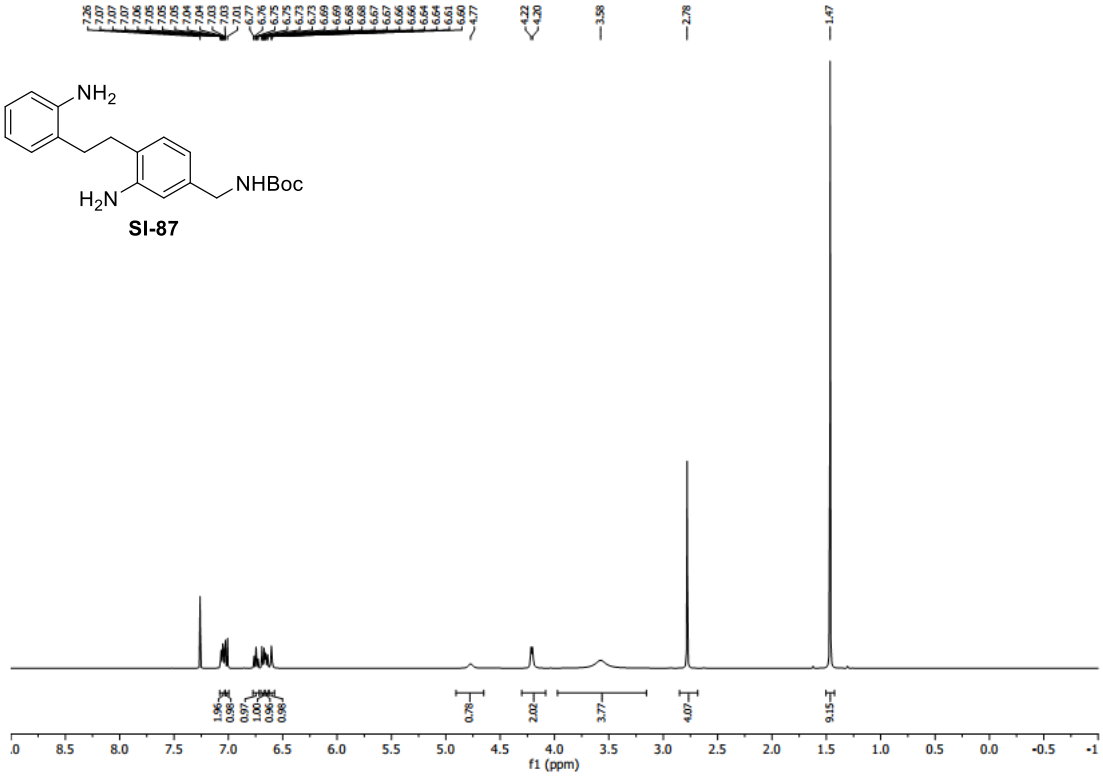


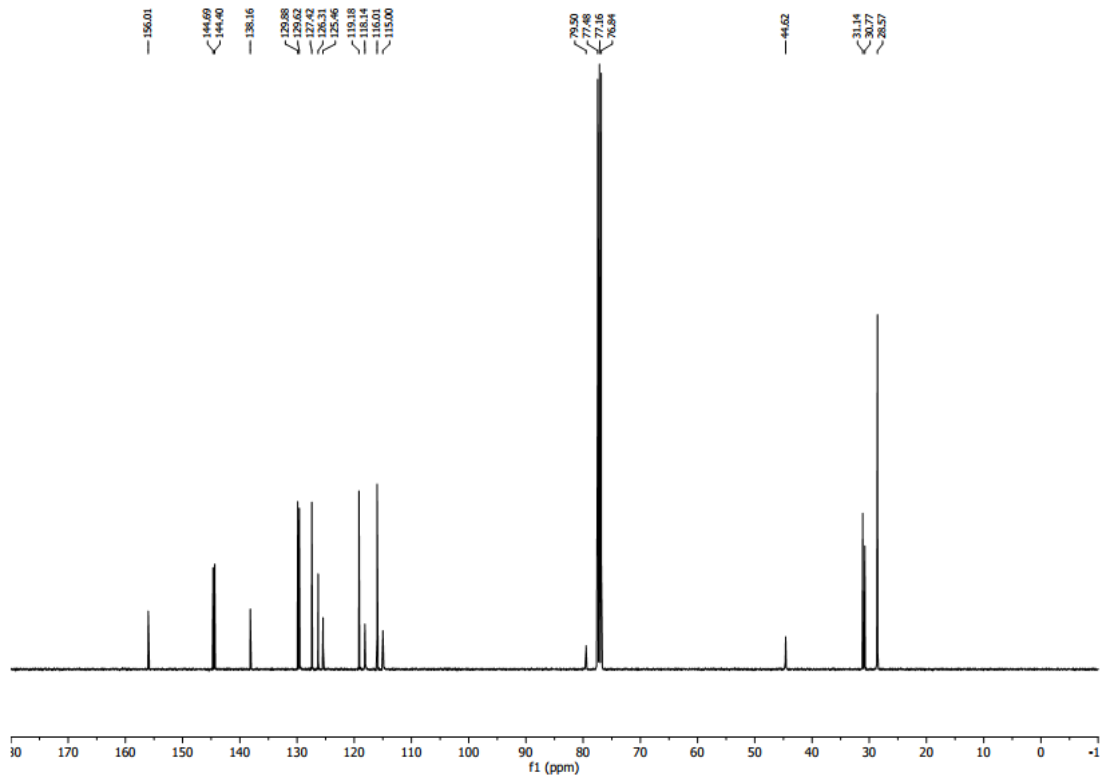
Compound **SI-86** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



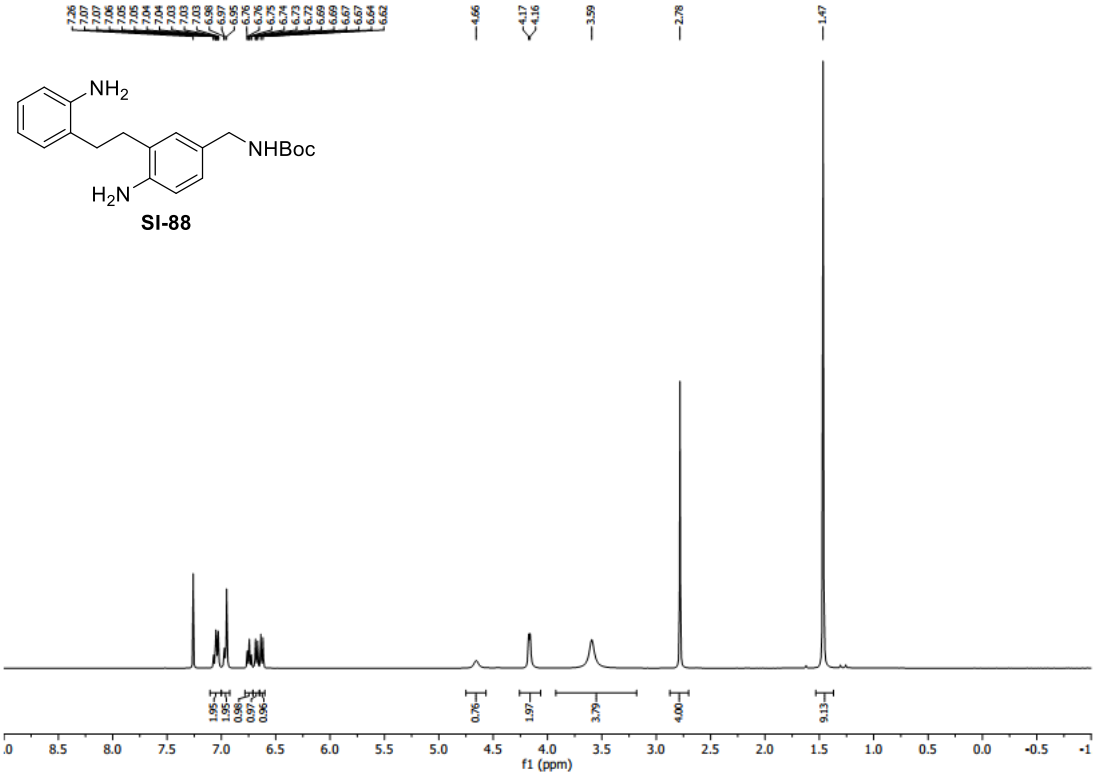


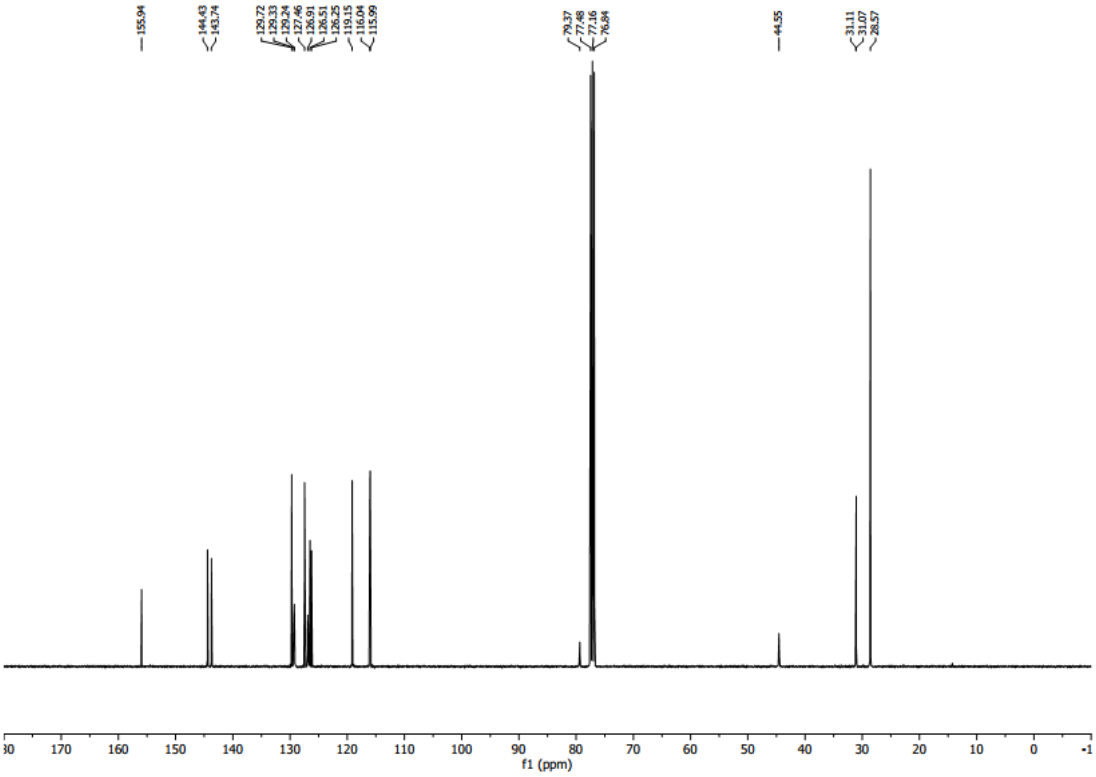
Compound **SI-87** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



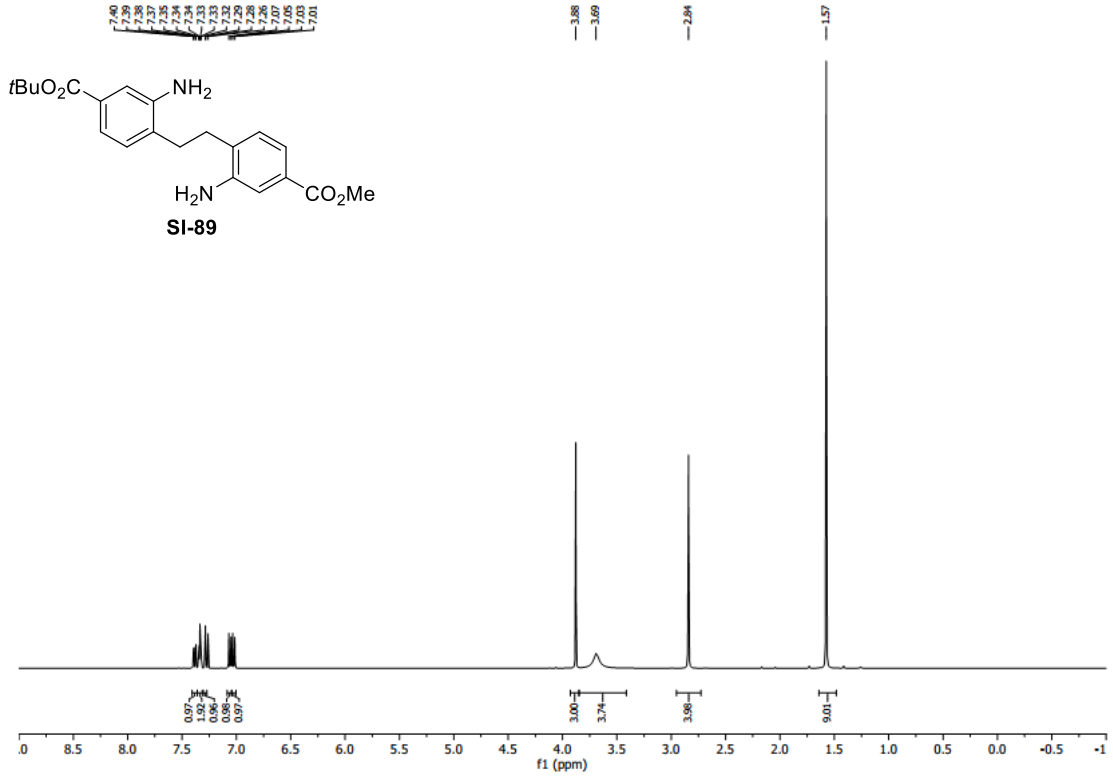


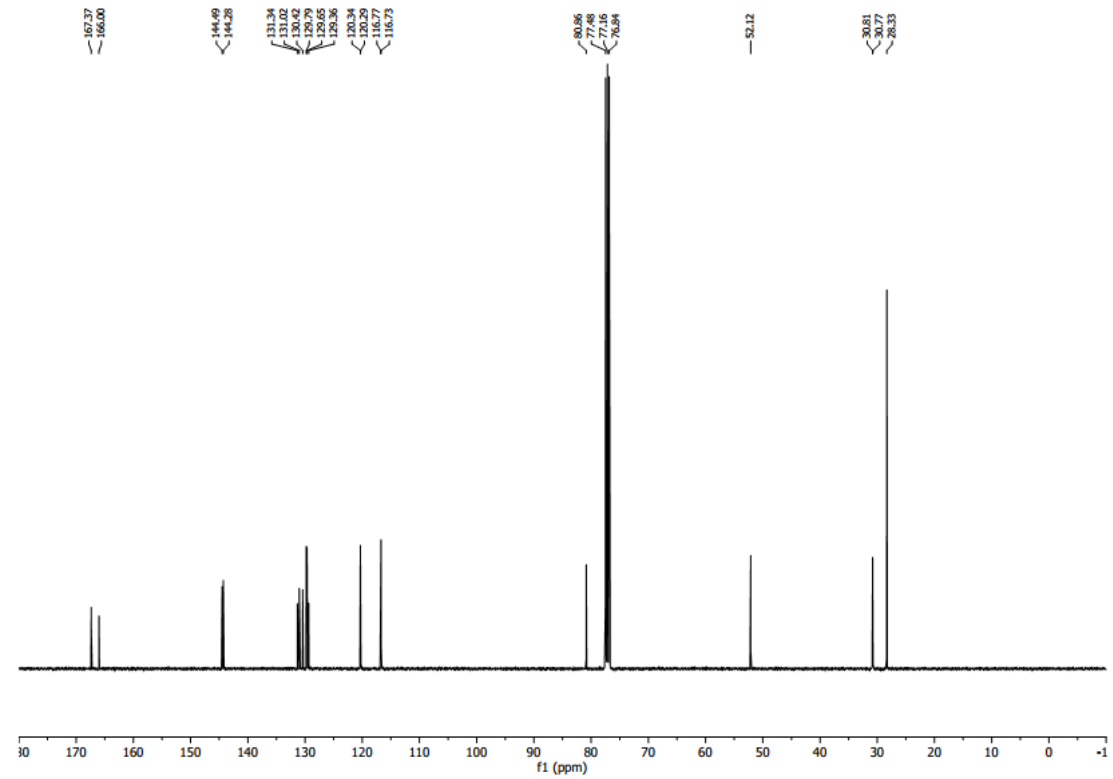
Compound **SI-88** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



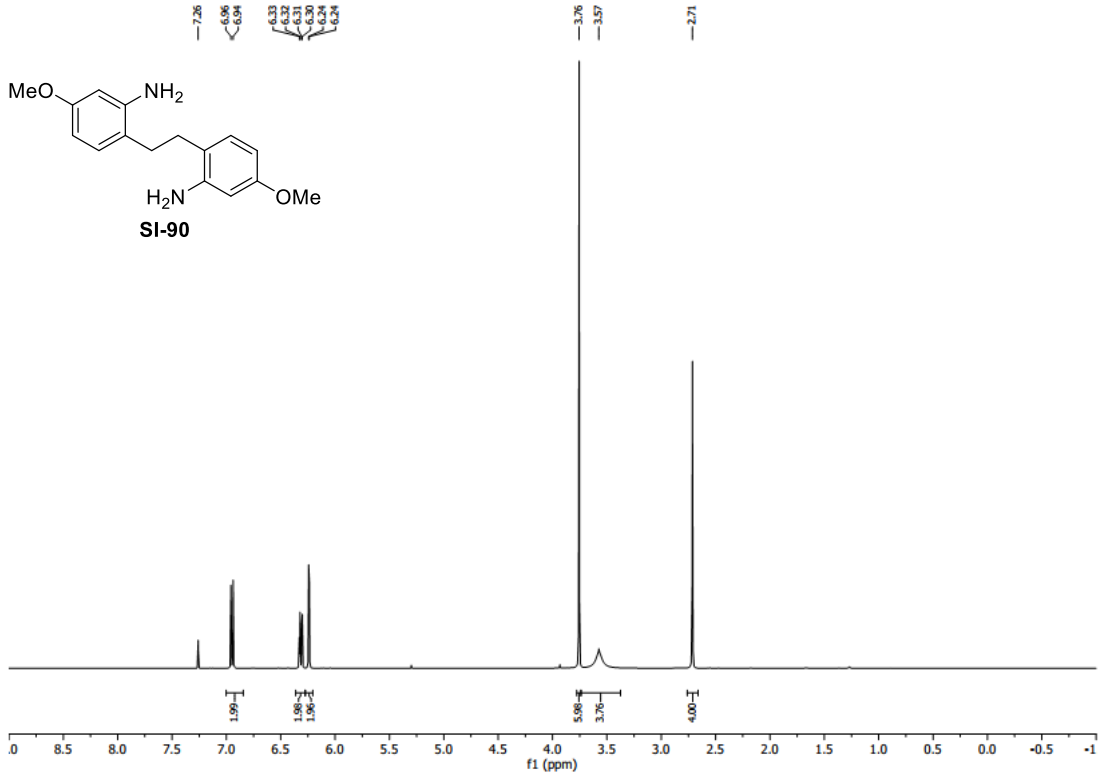


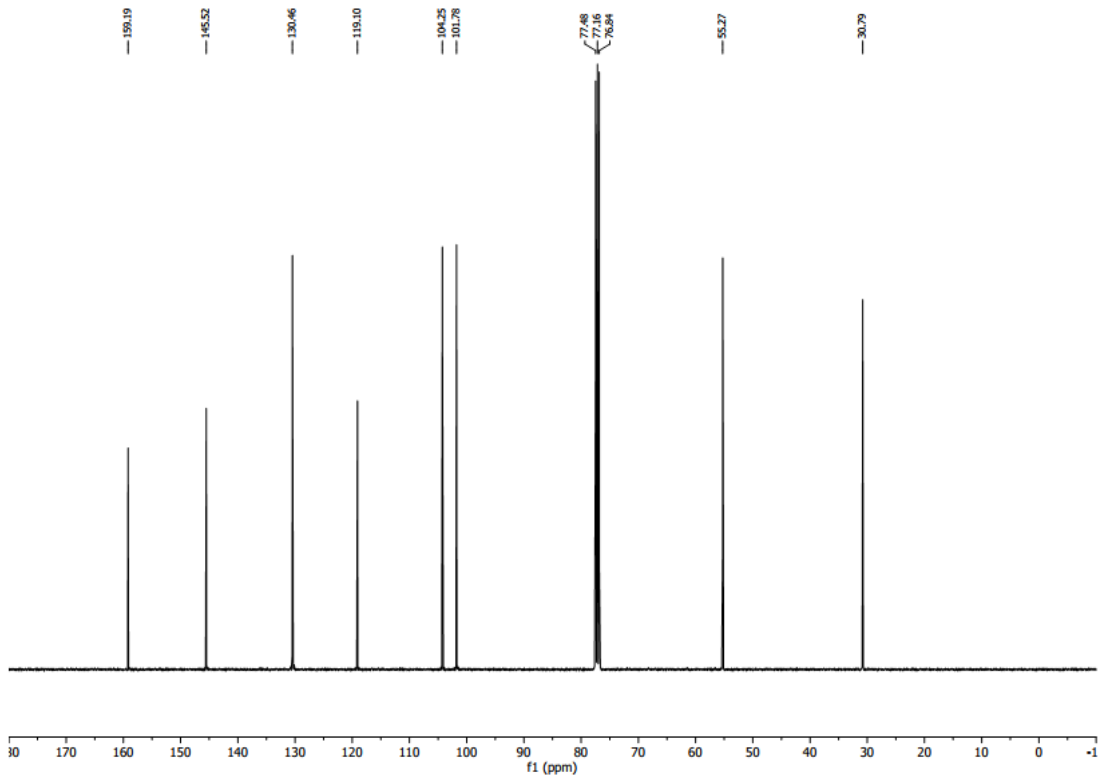
Compound **SI-89** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



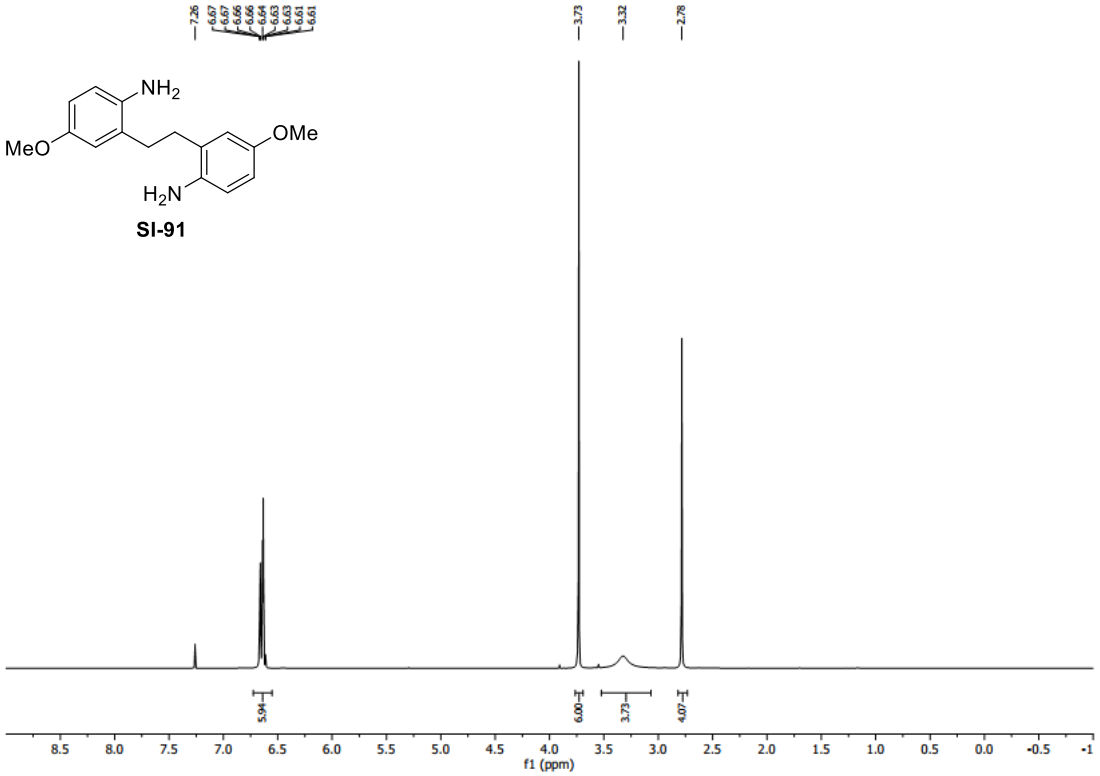


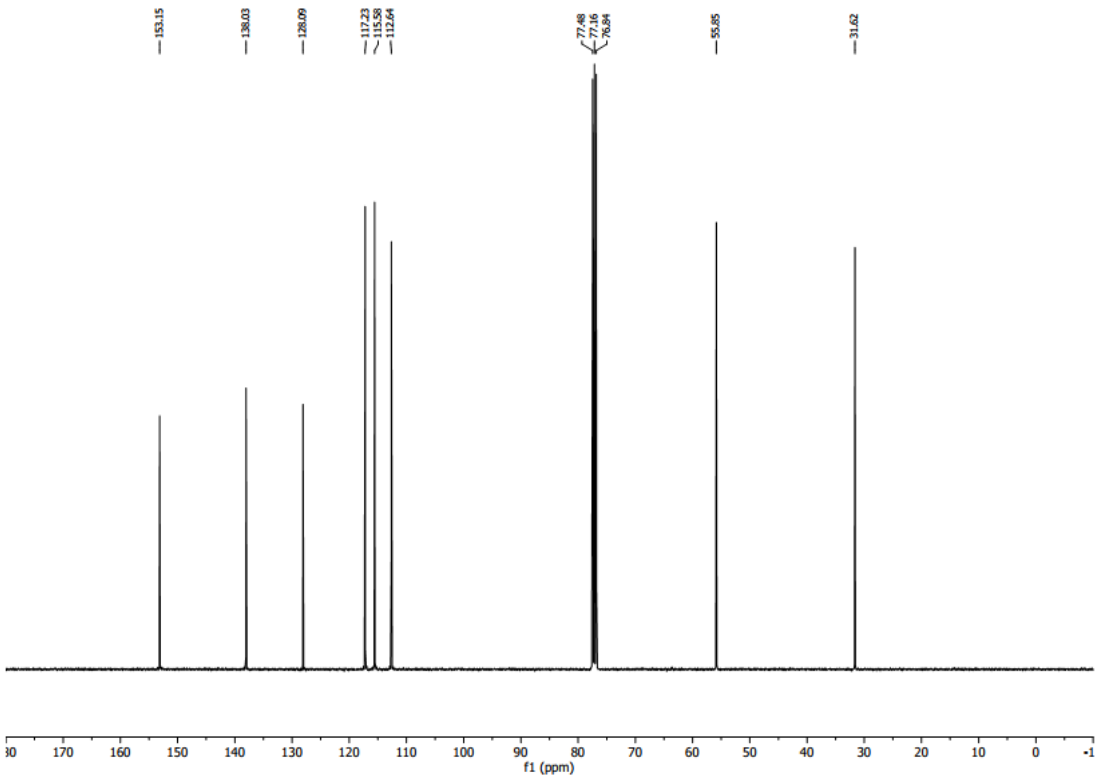
Compound **SI-90** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



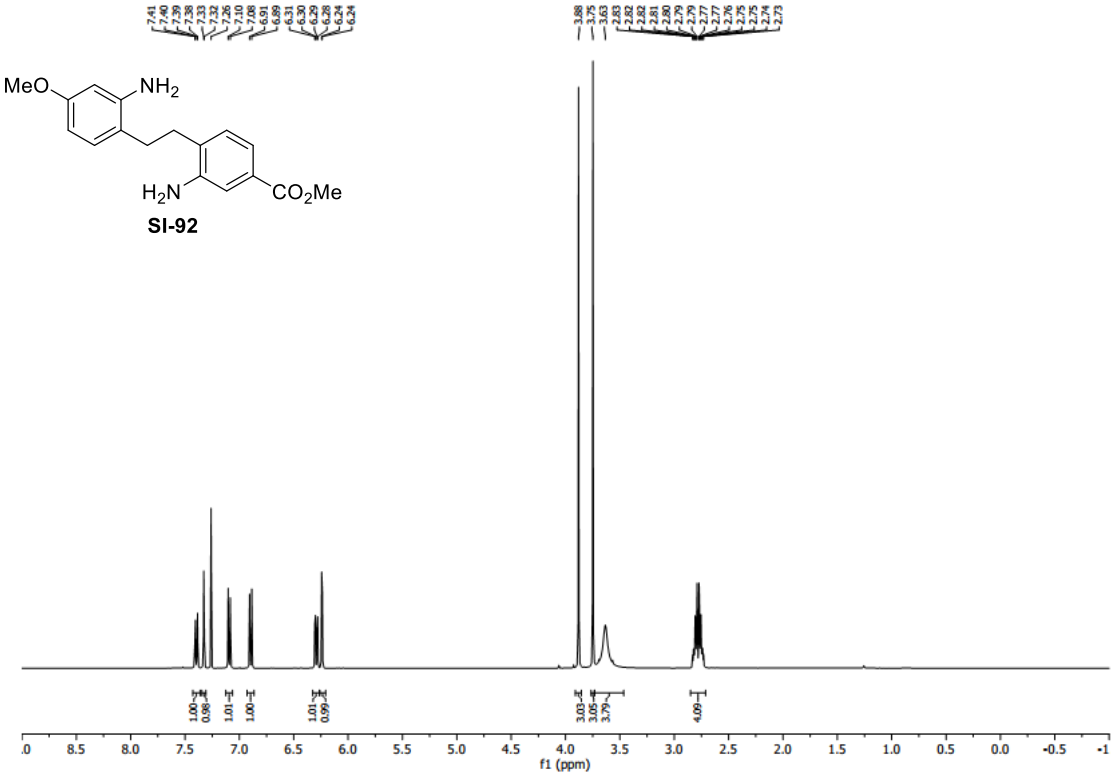


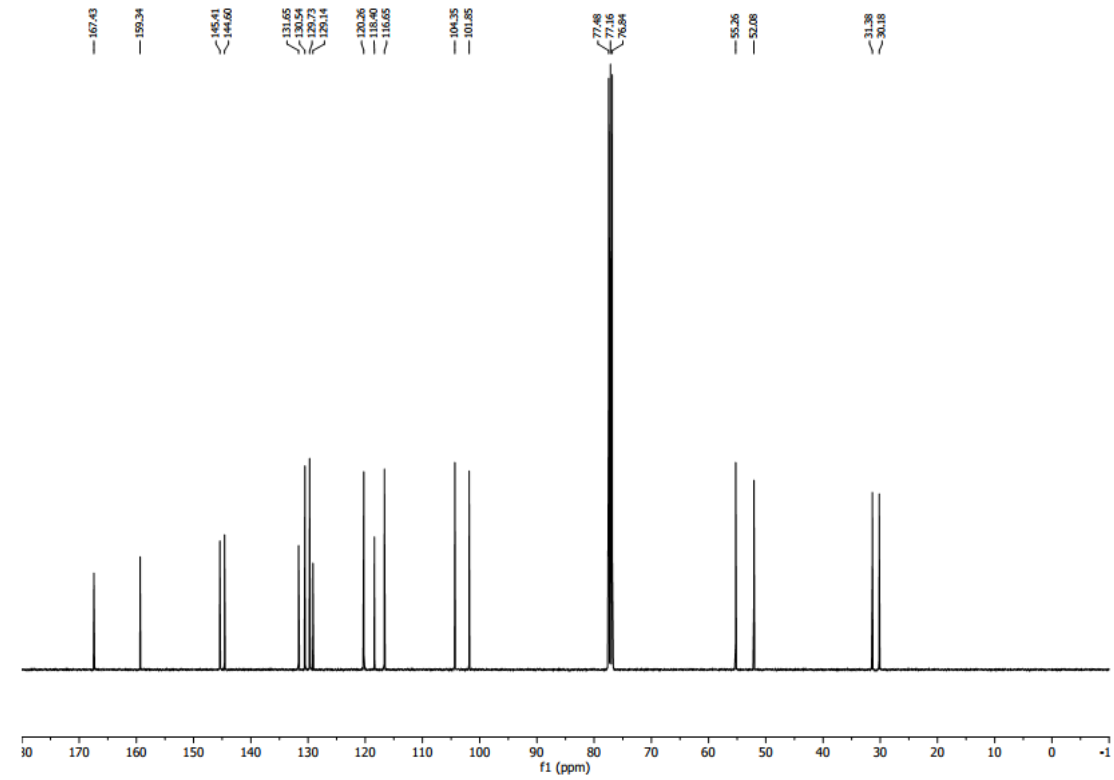
Compound **SI-91** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



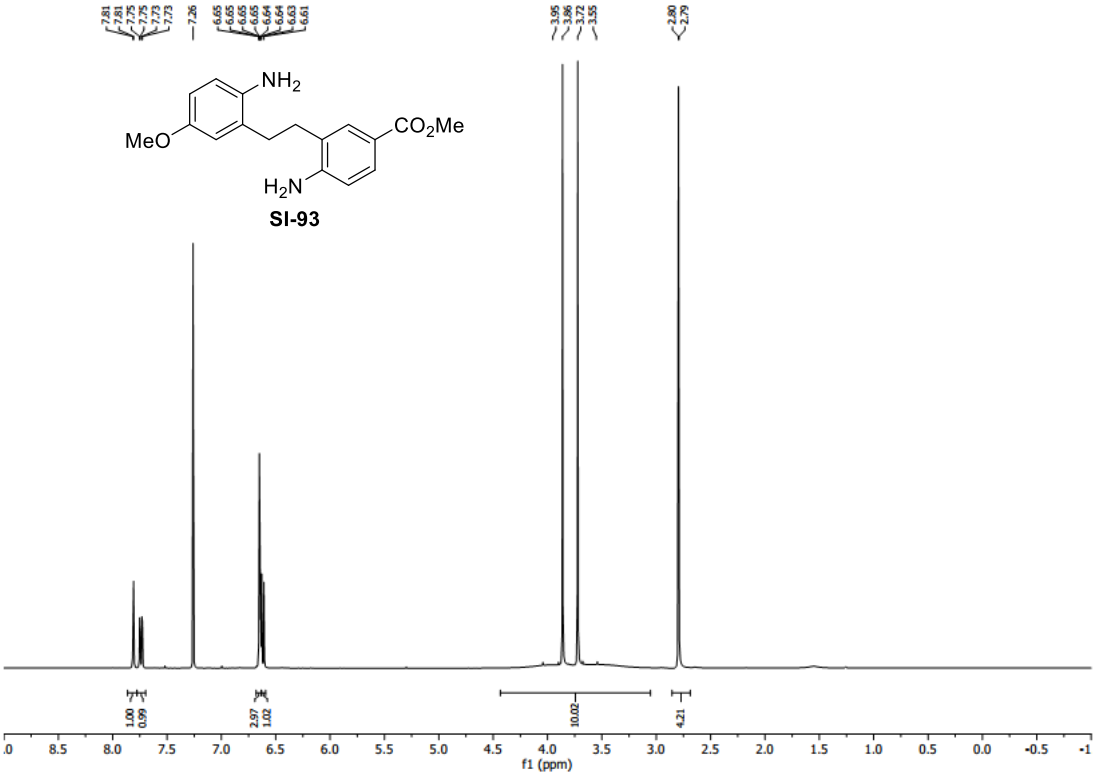


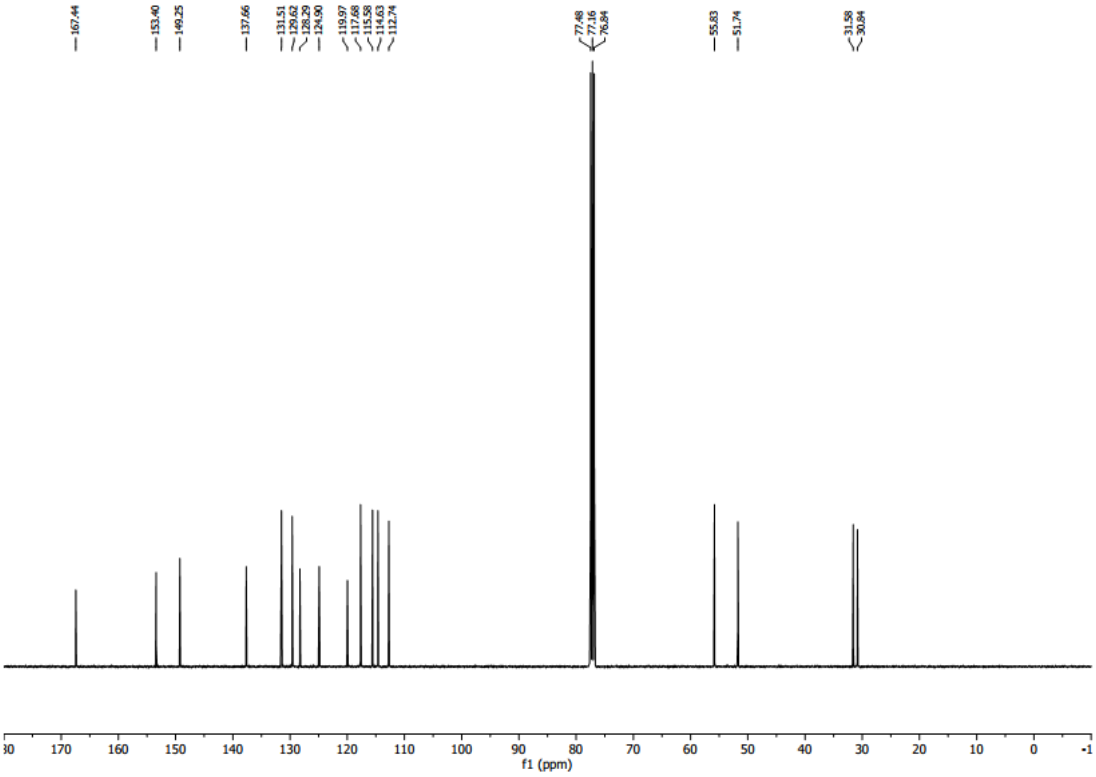
Compound **SI-92** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



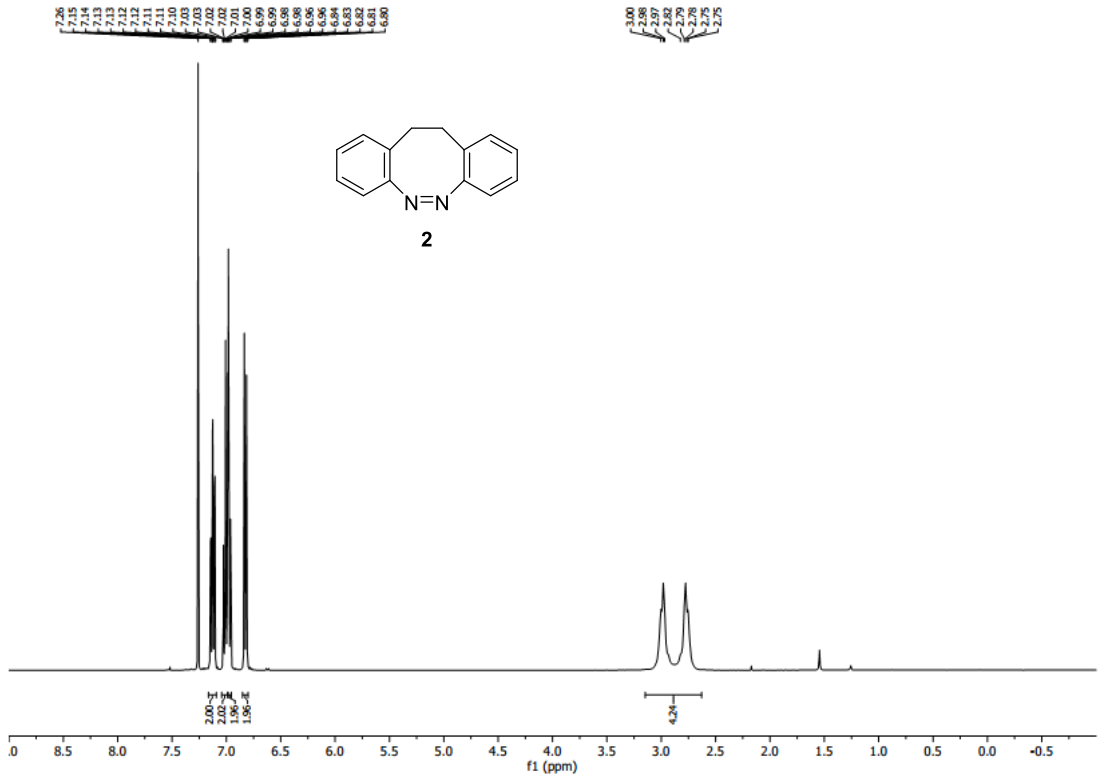


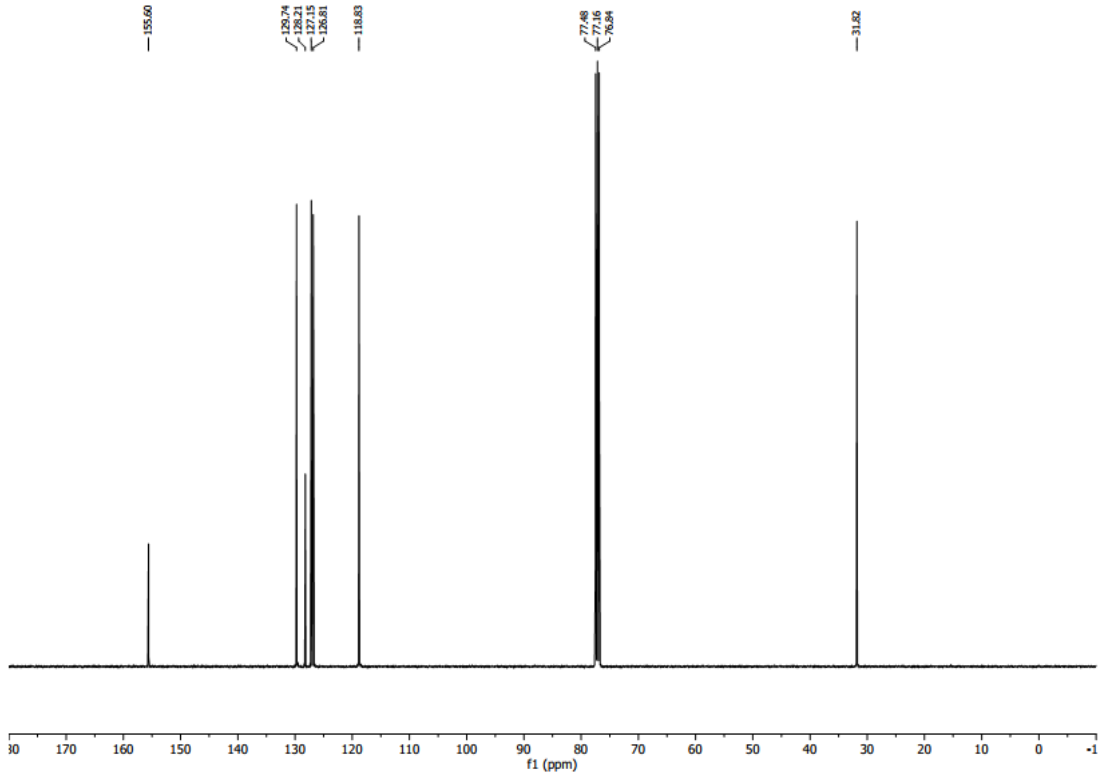
Compound **SI-93** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



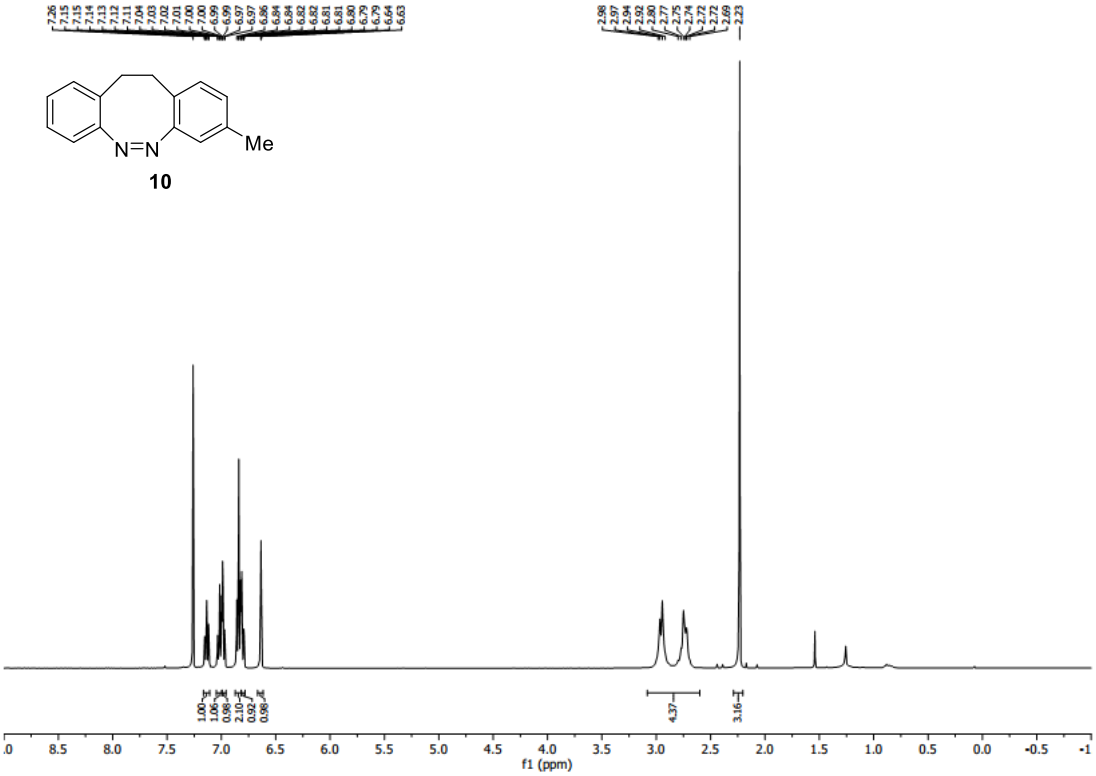


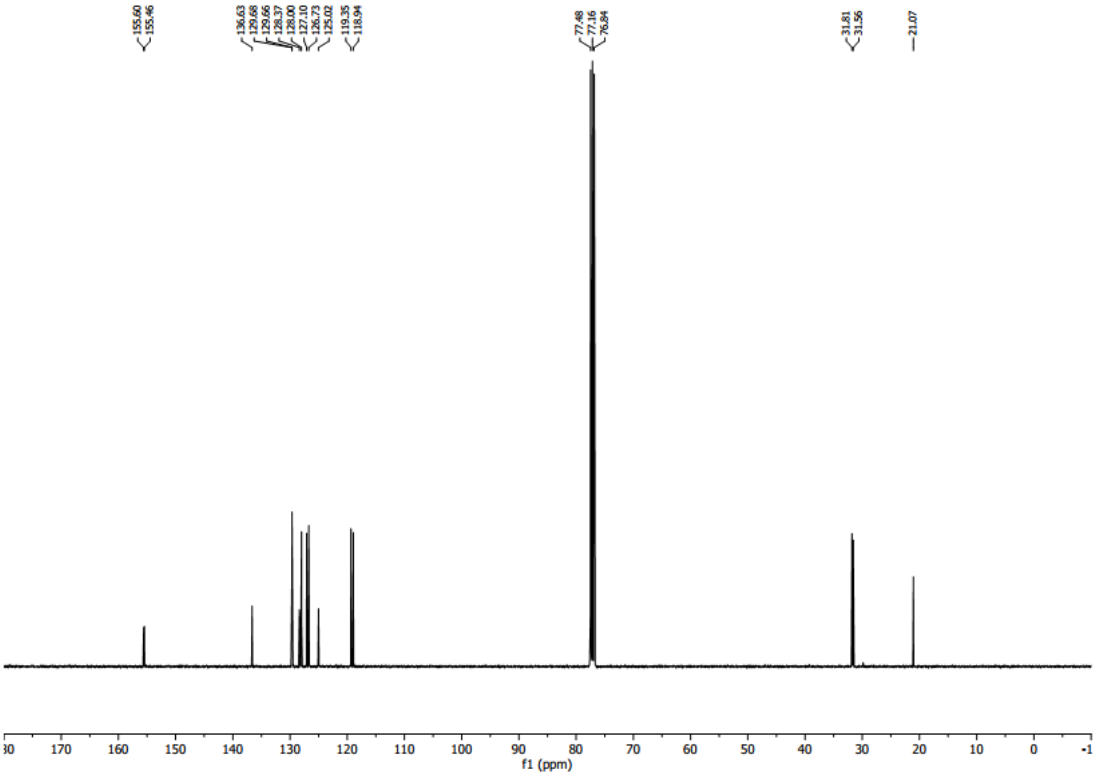
Compound **2** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



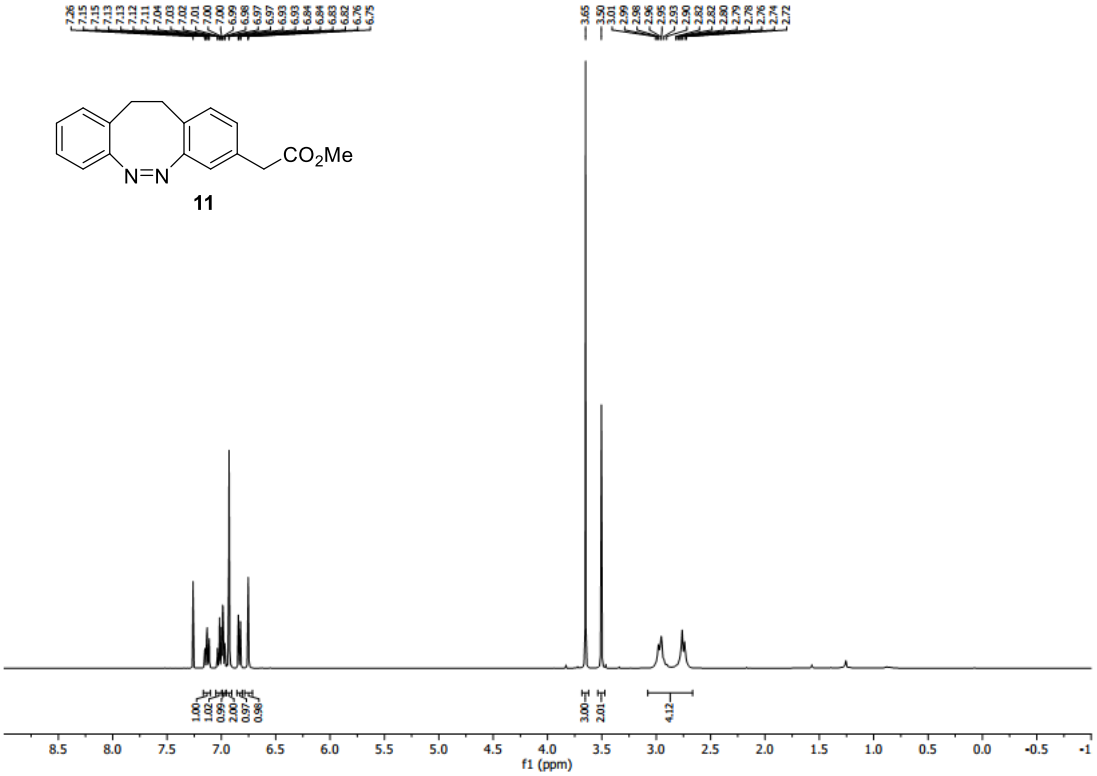


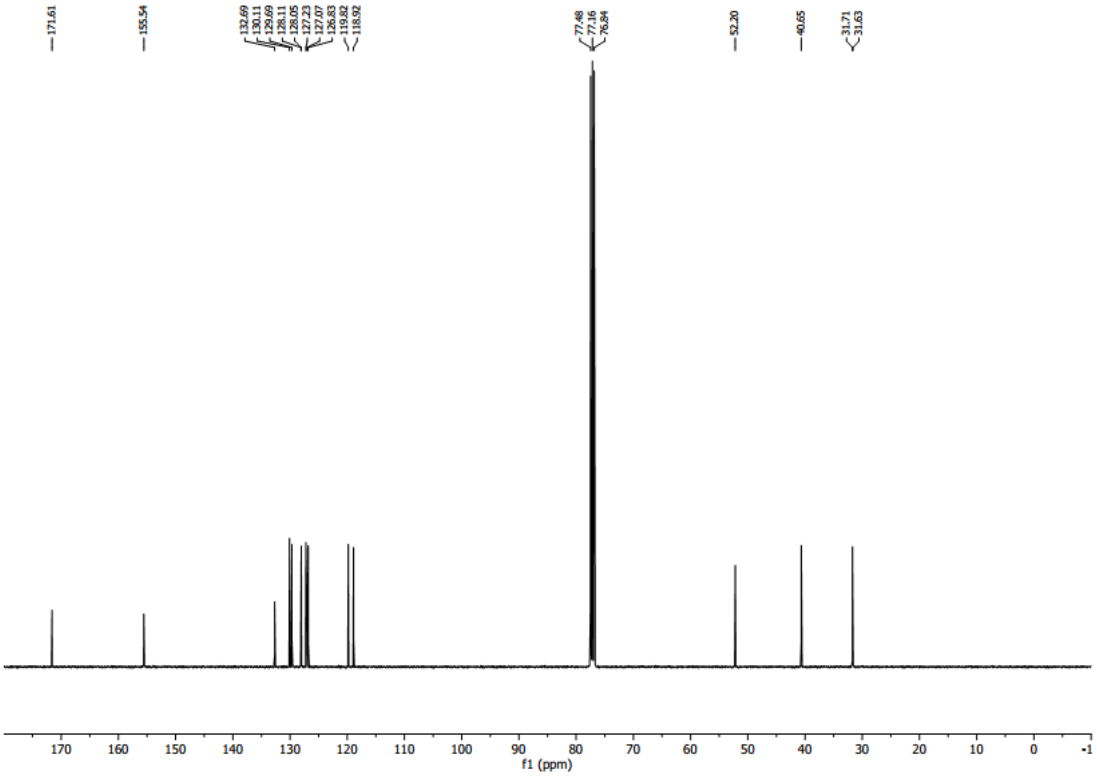
Compound **10** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



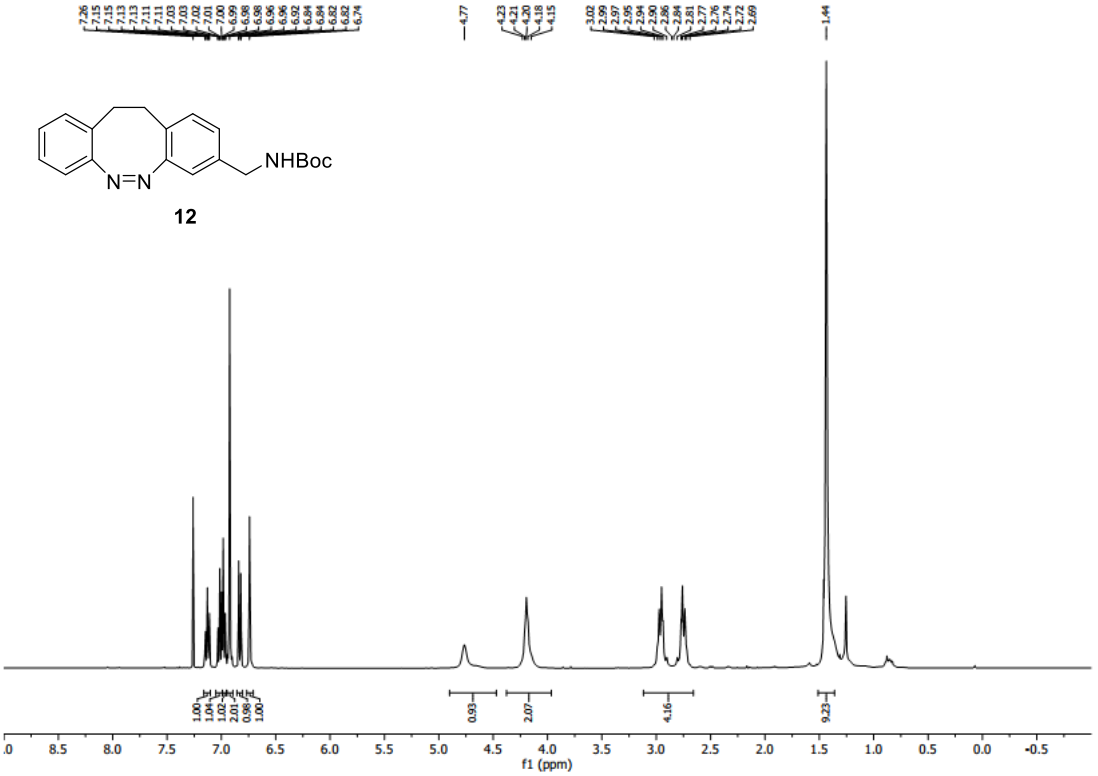


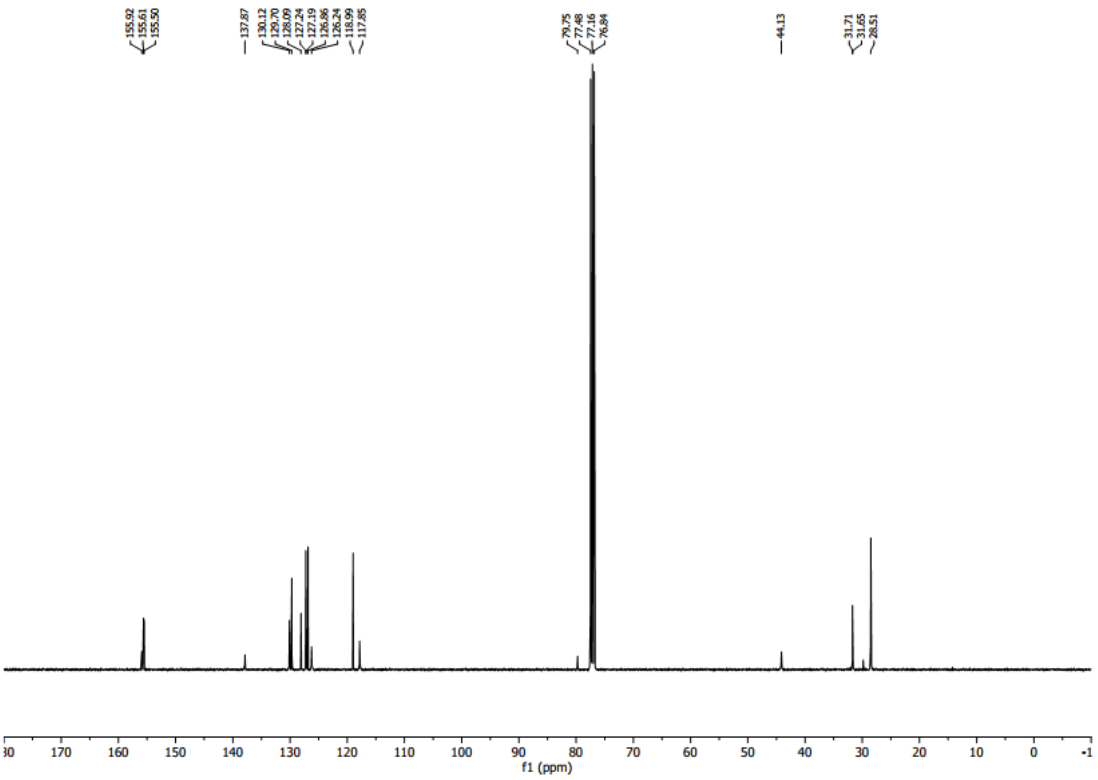
Compound **11** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



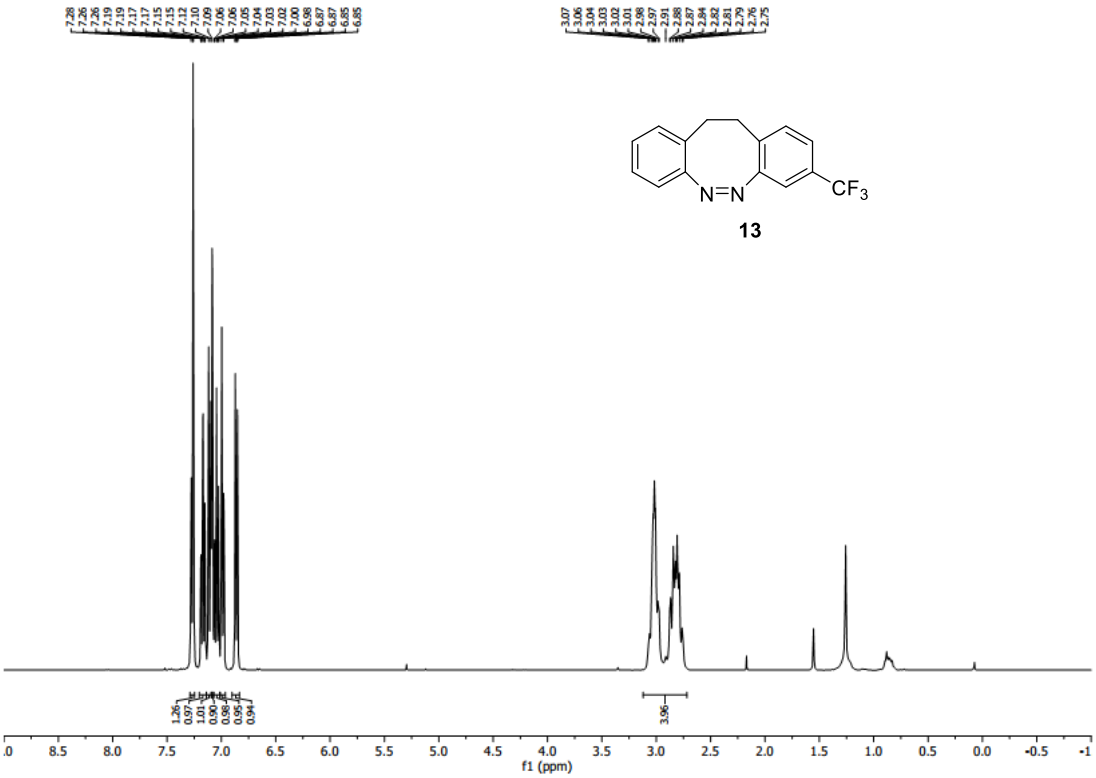


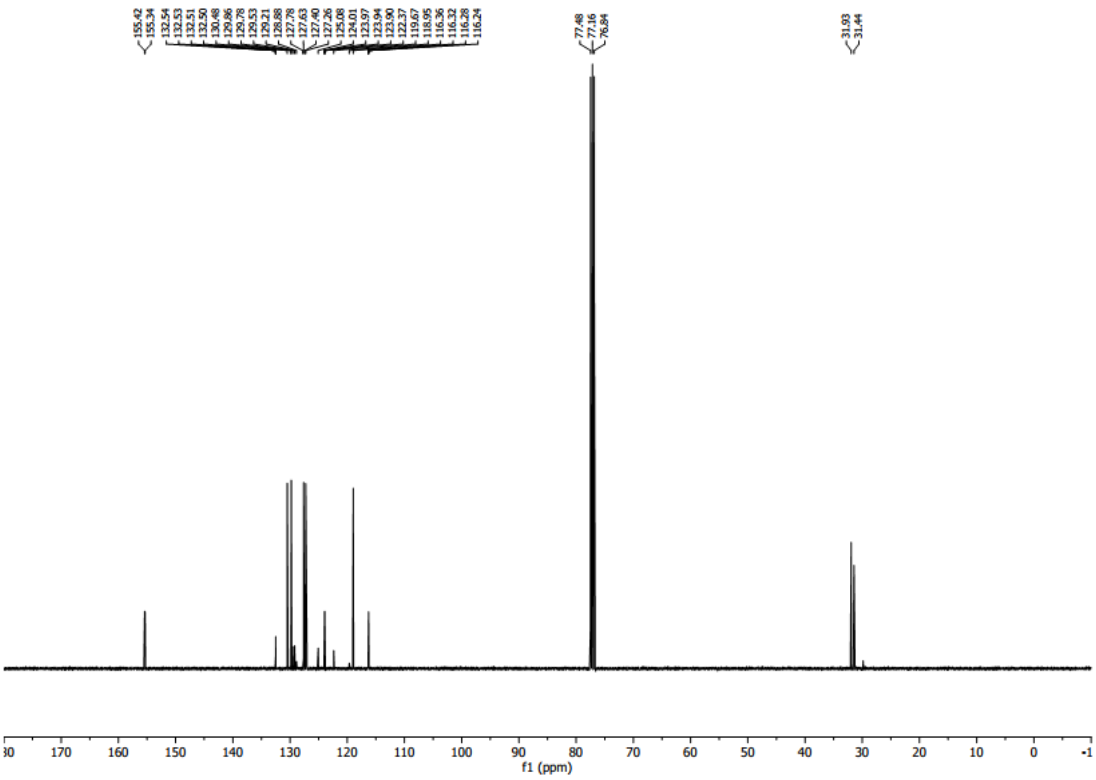
Compound **12** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



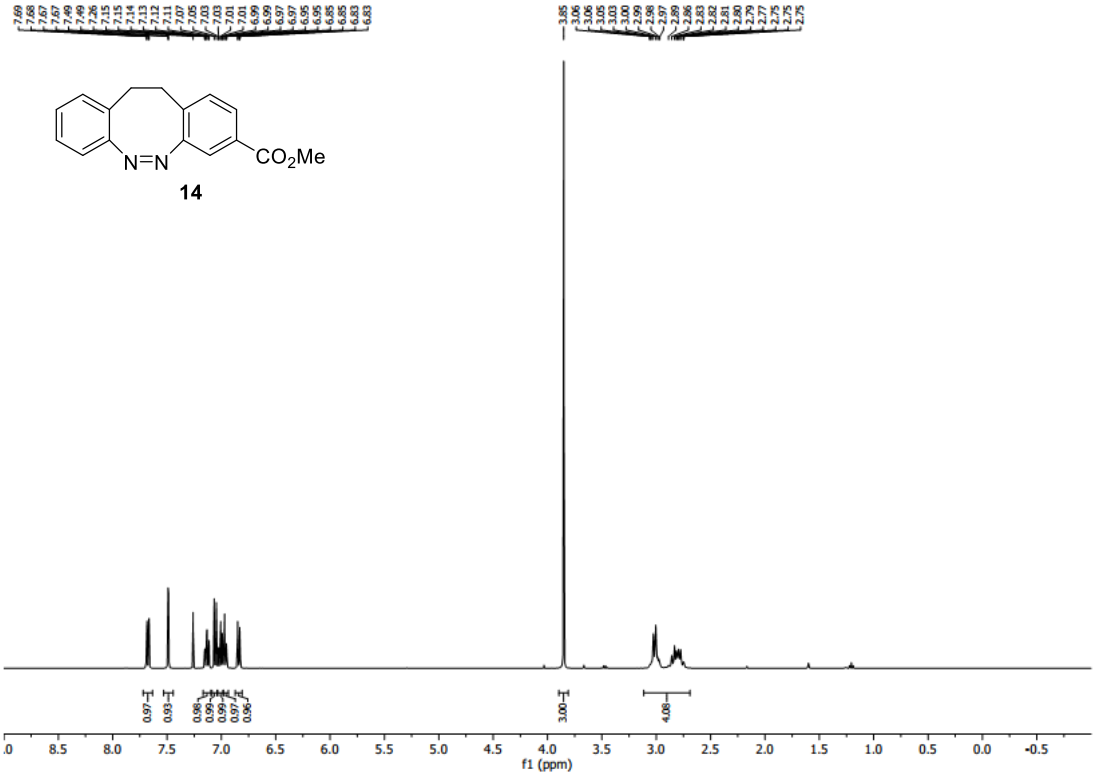


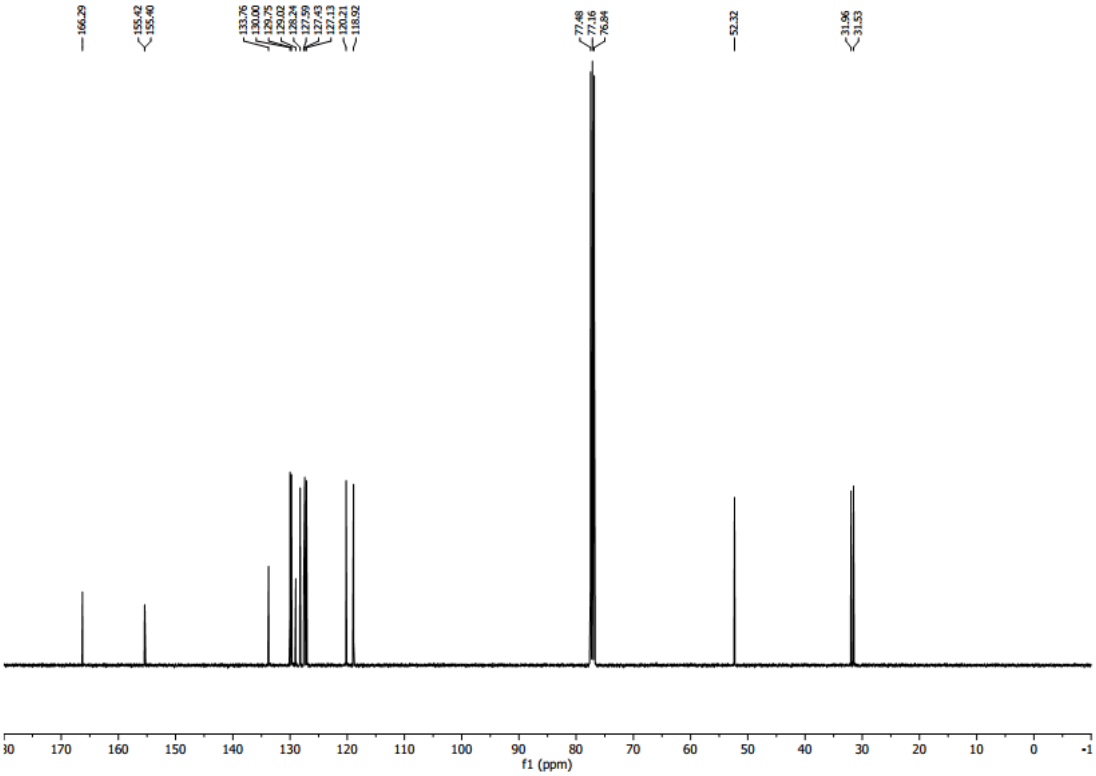
Compound **13** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



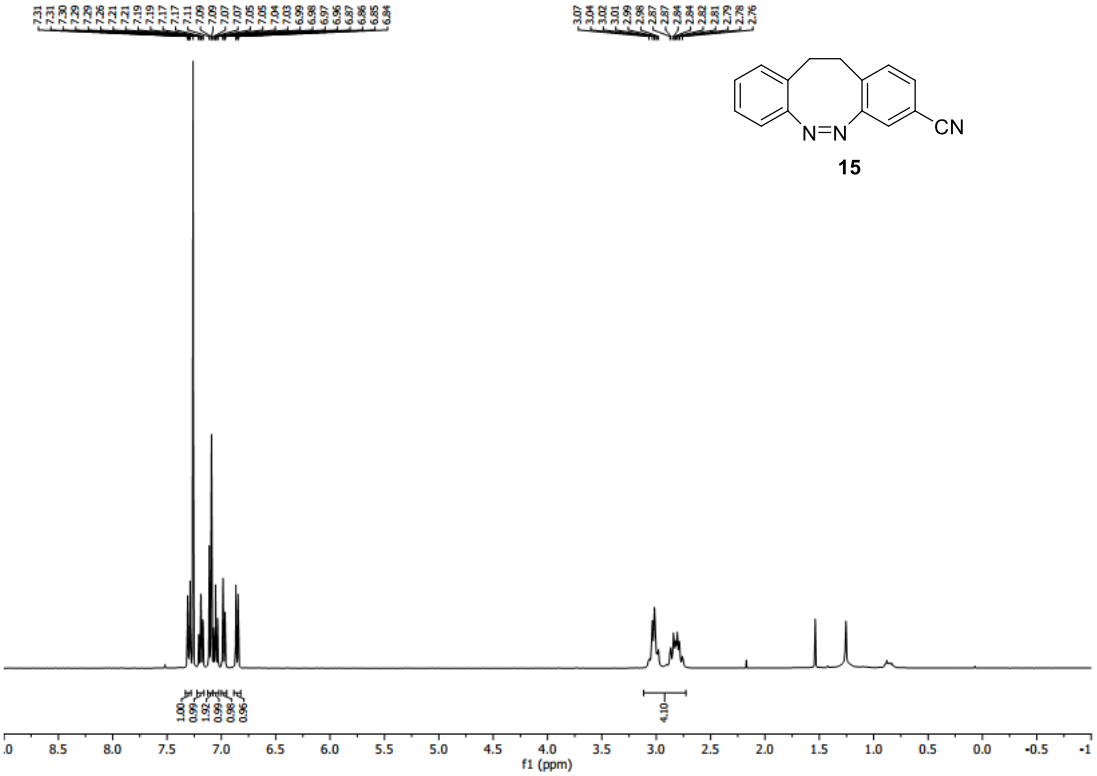


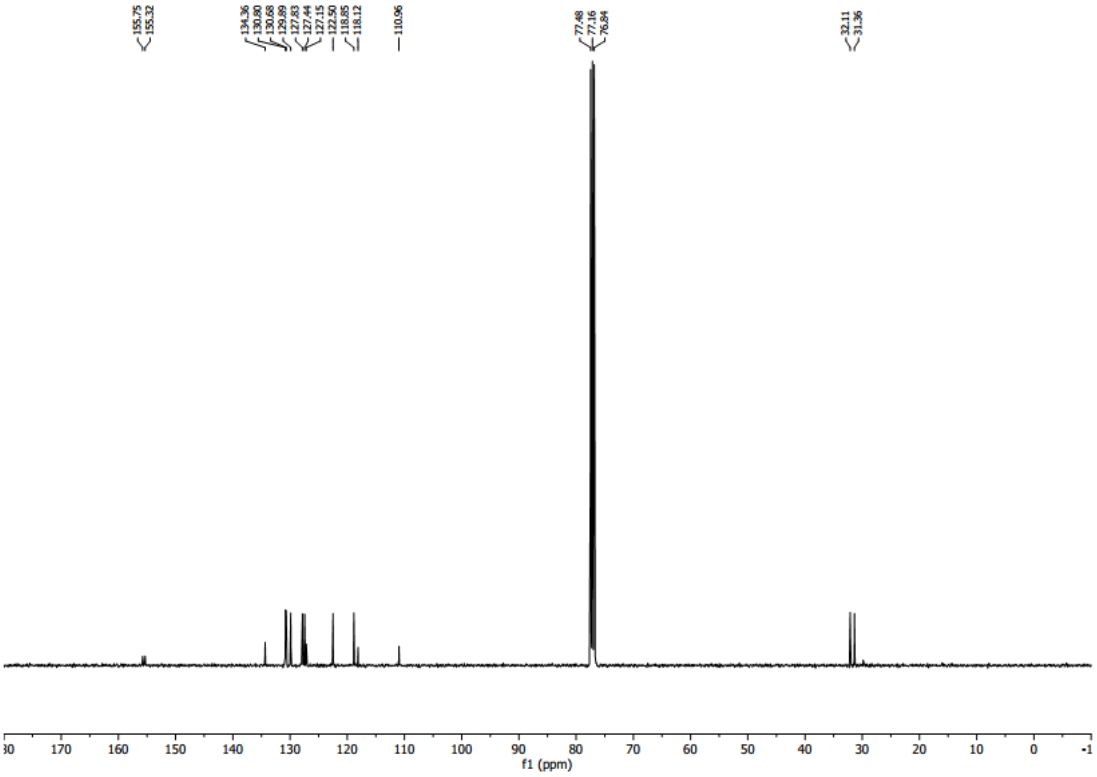
Compound **14** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



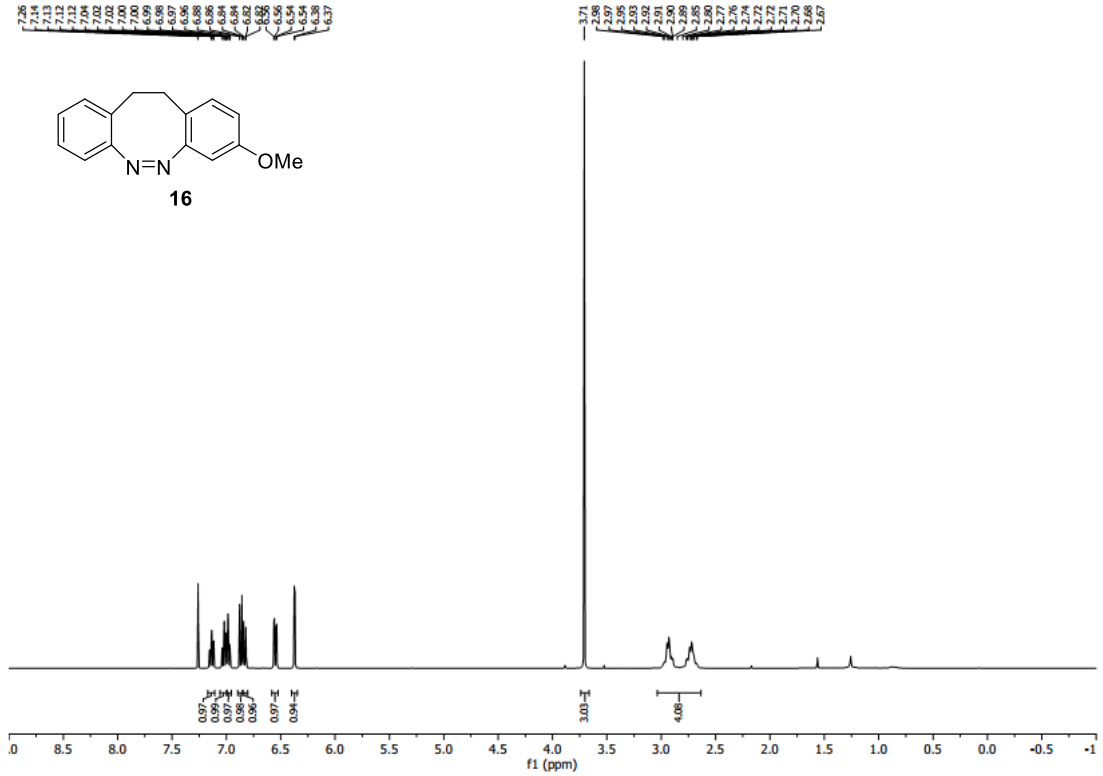


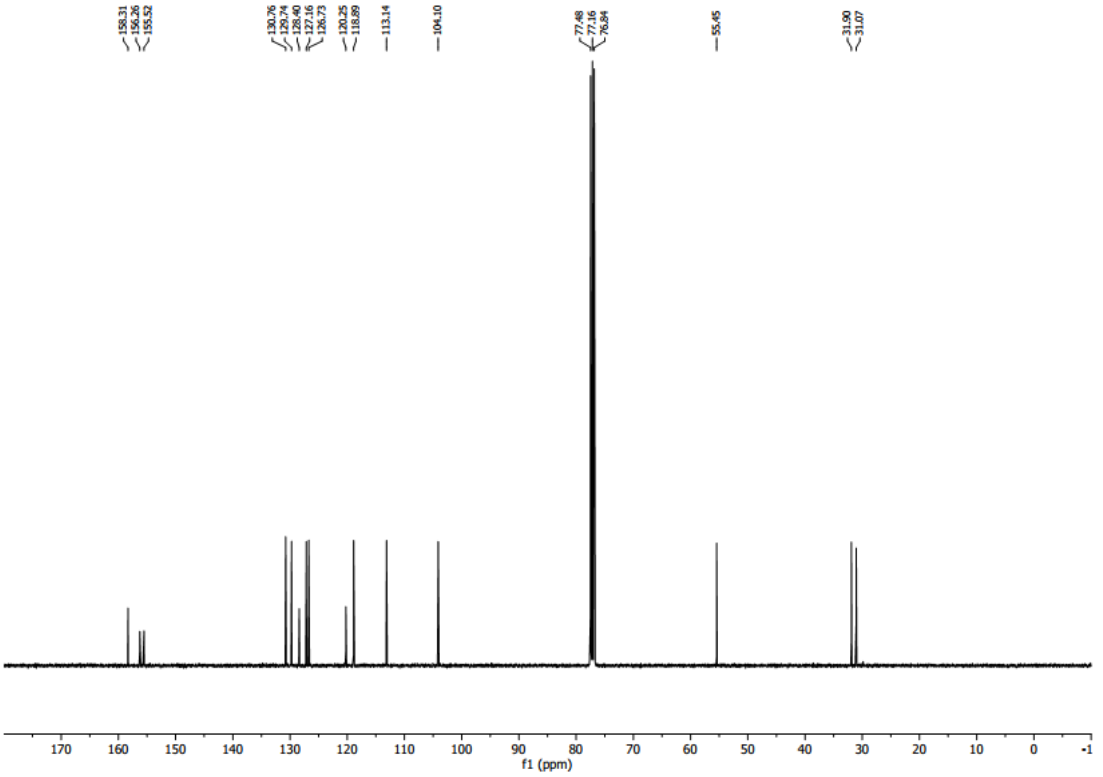
Compound **15** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



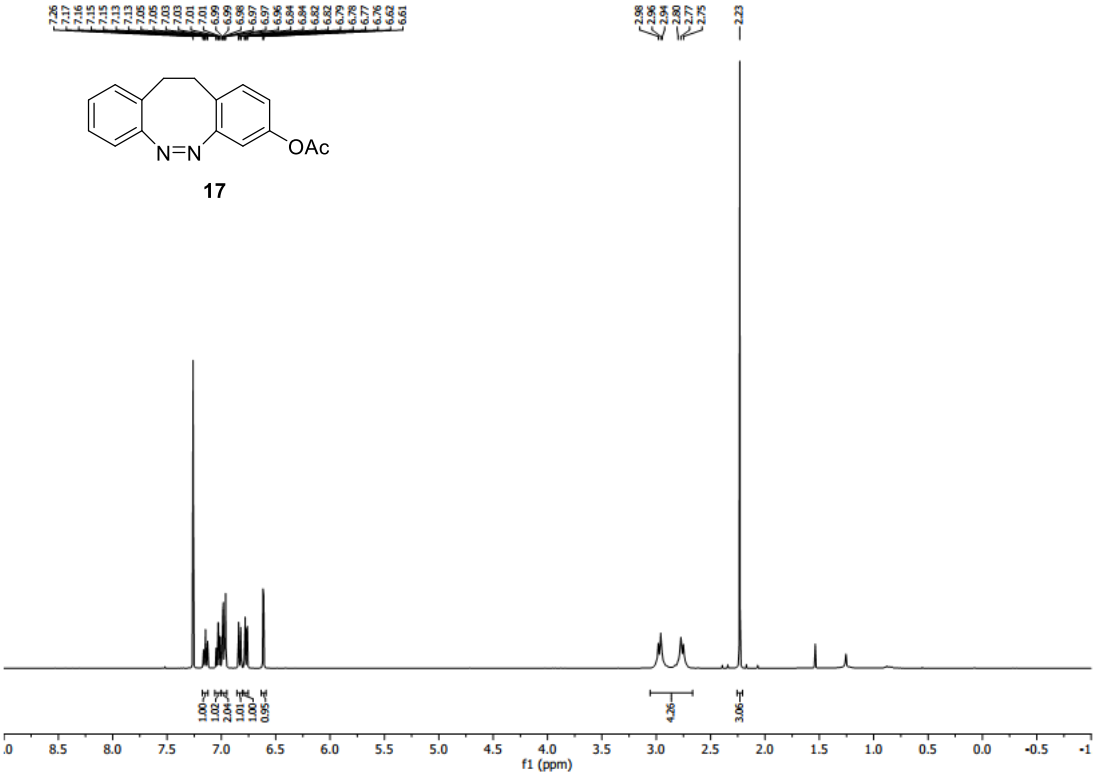


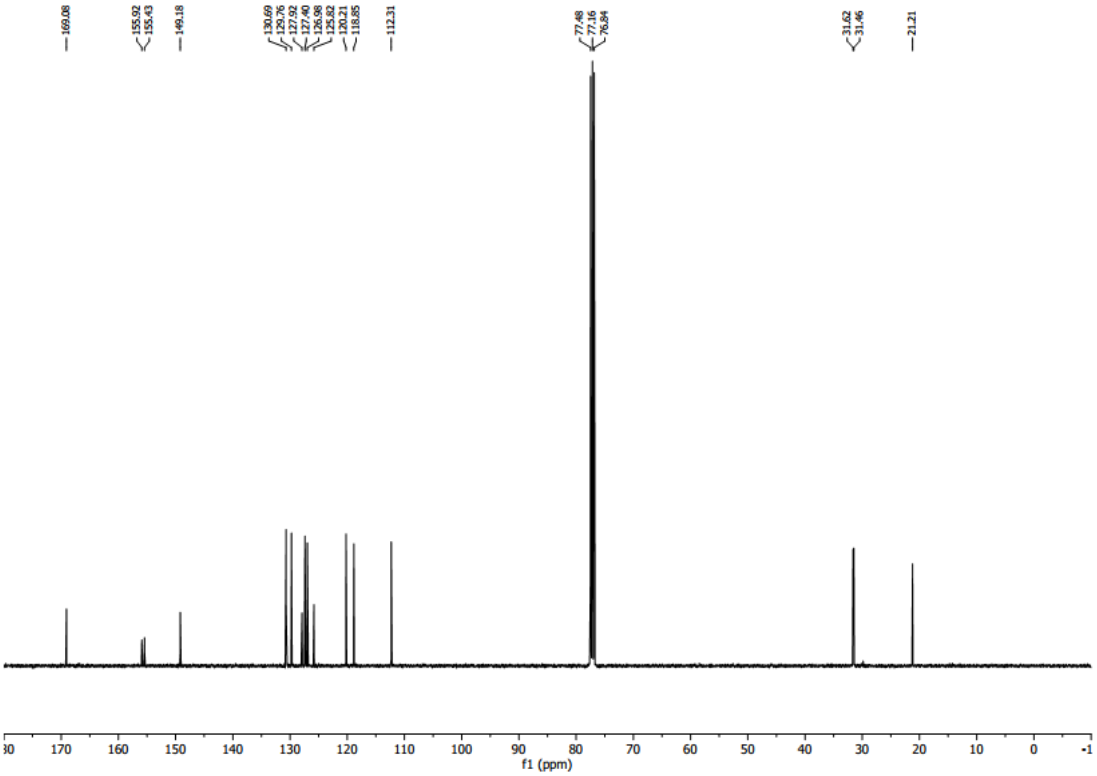
Compound **16** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



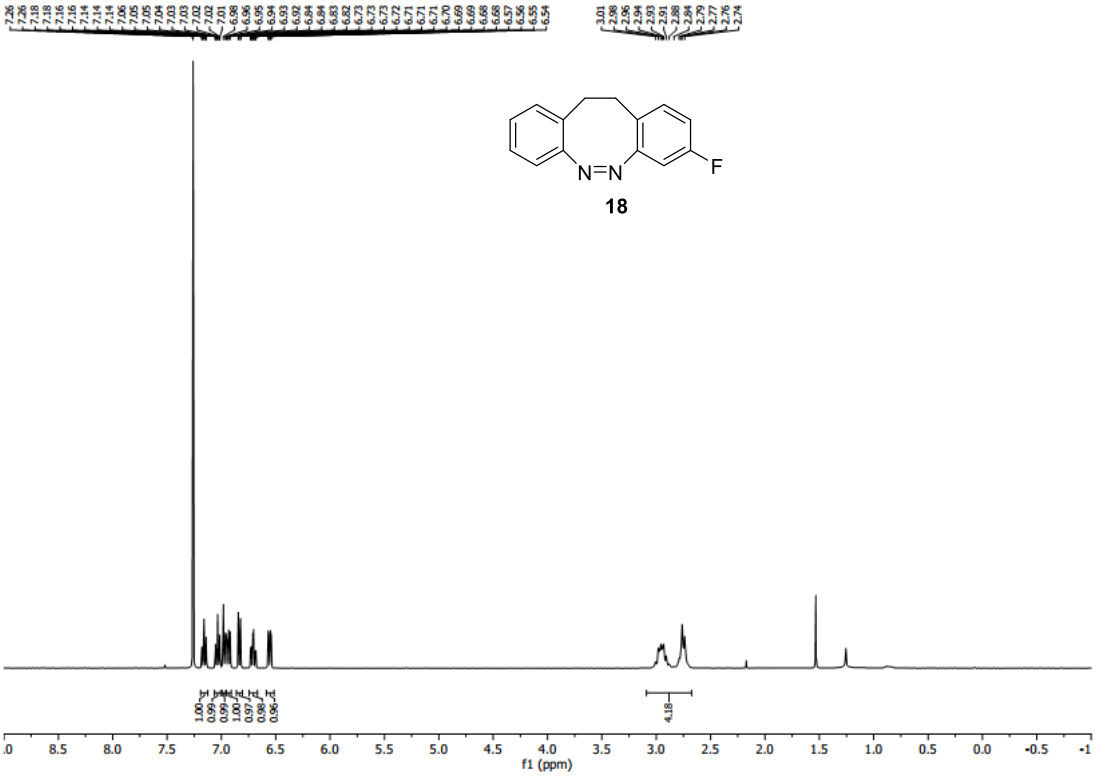


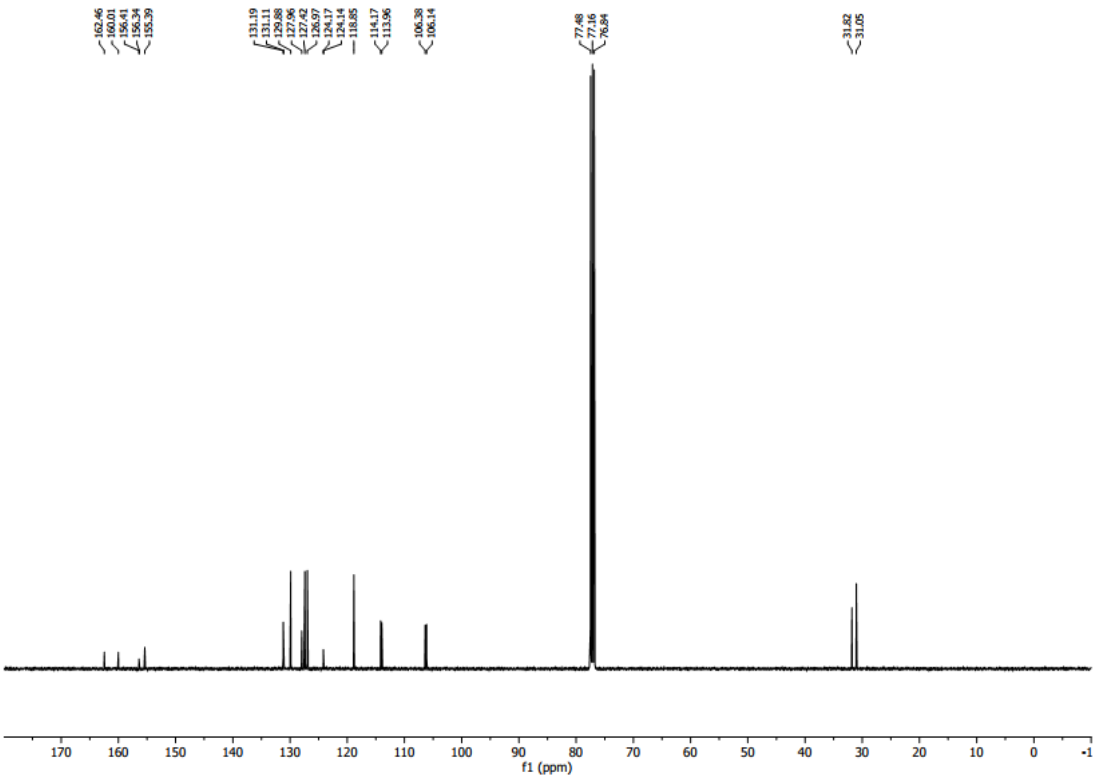
Compound **17** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



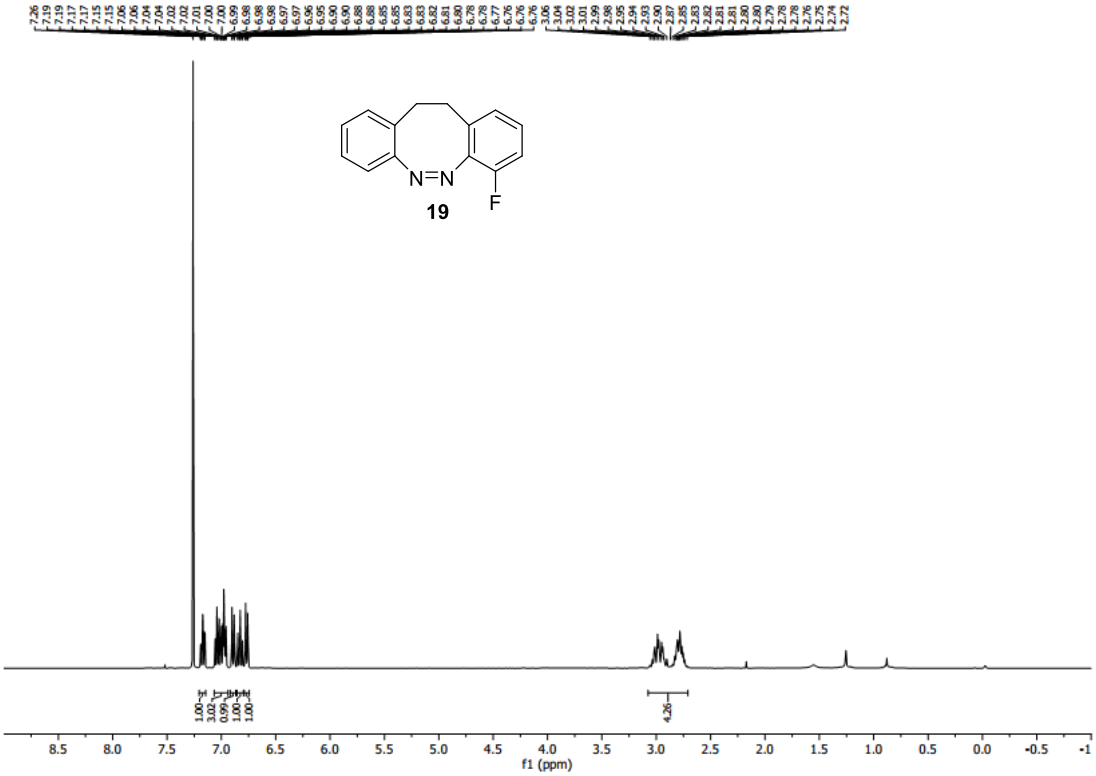


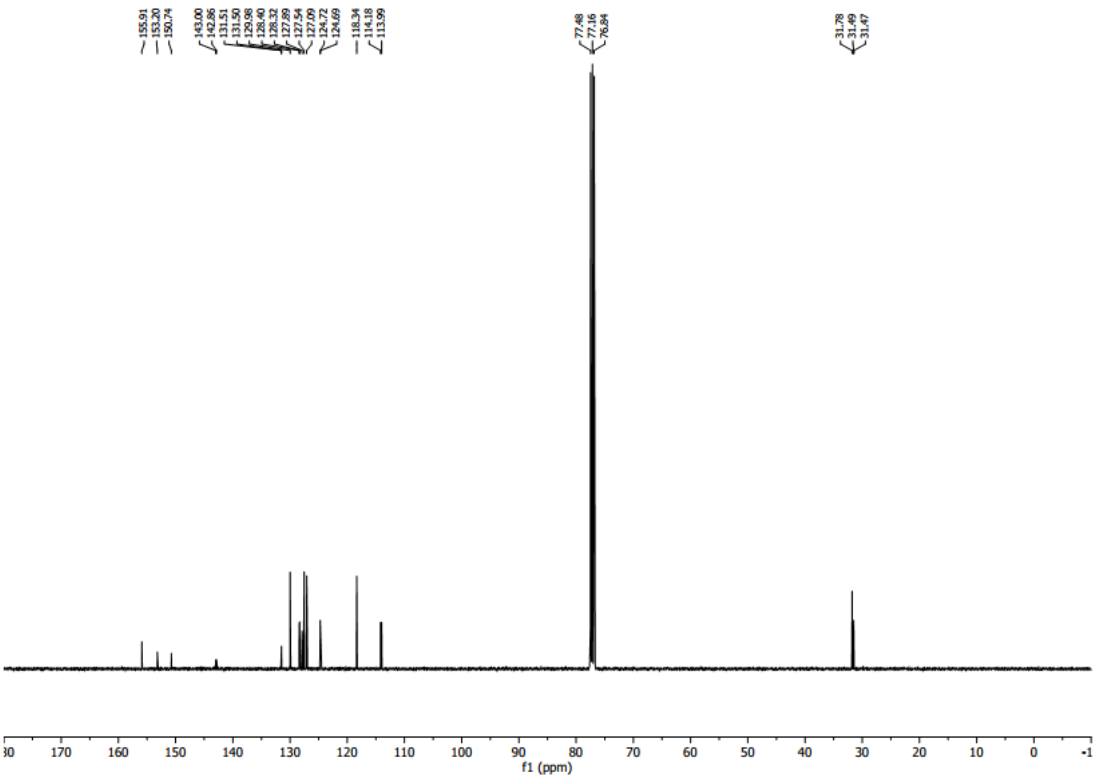
Compound **18** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



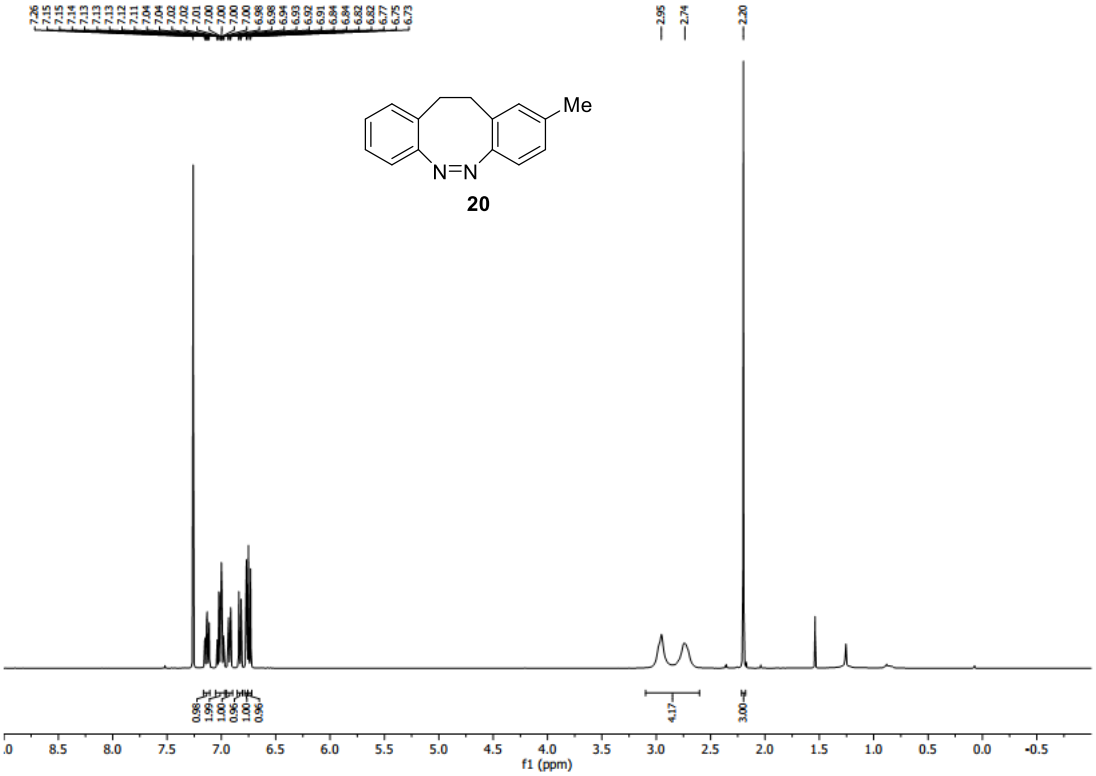


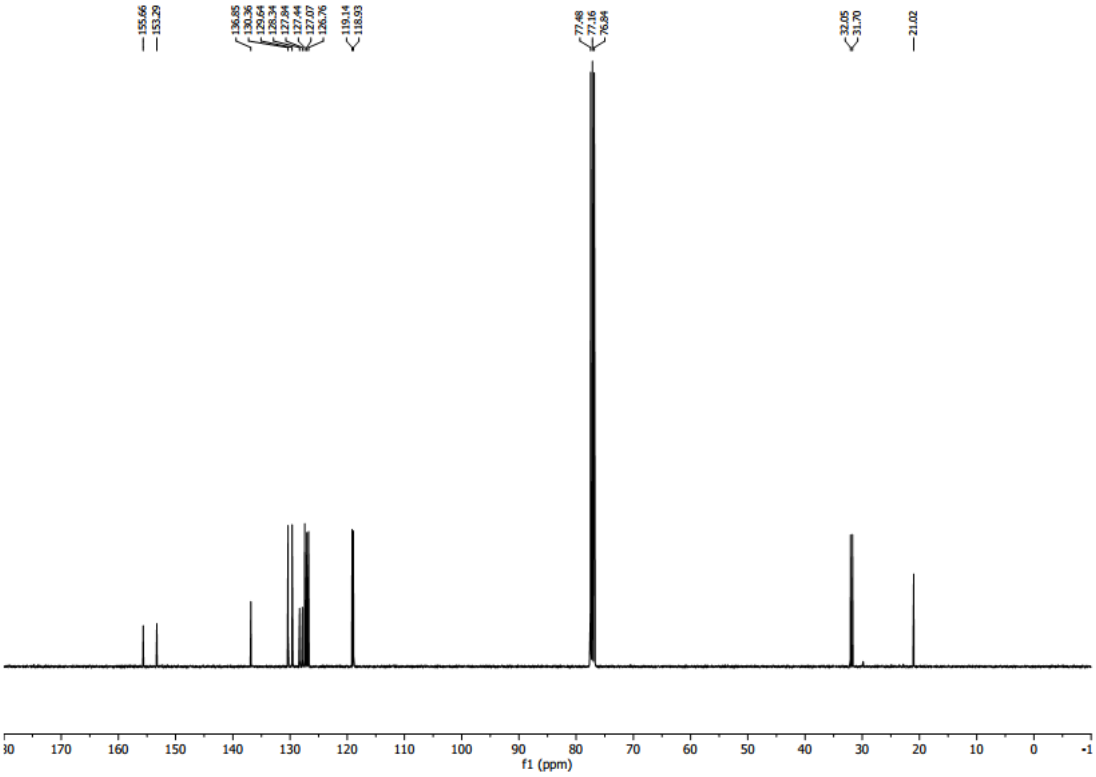
Compound **19** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



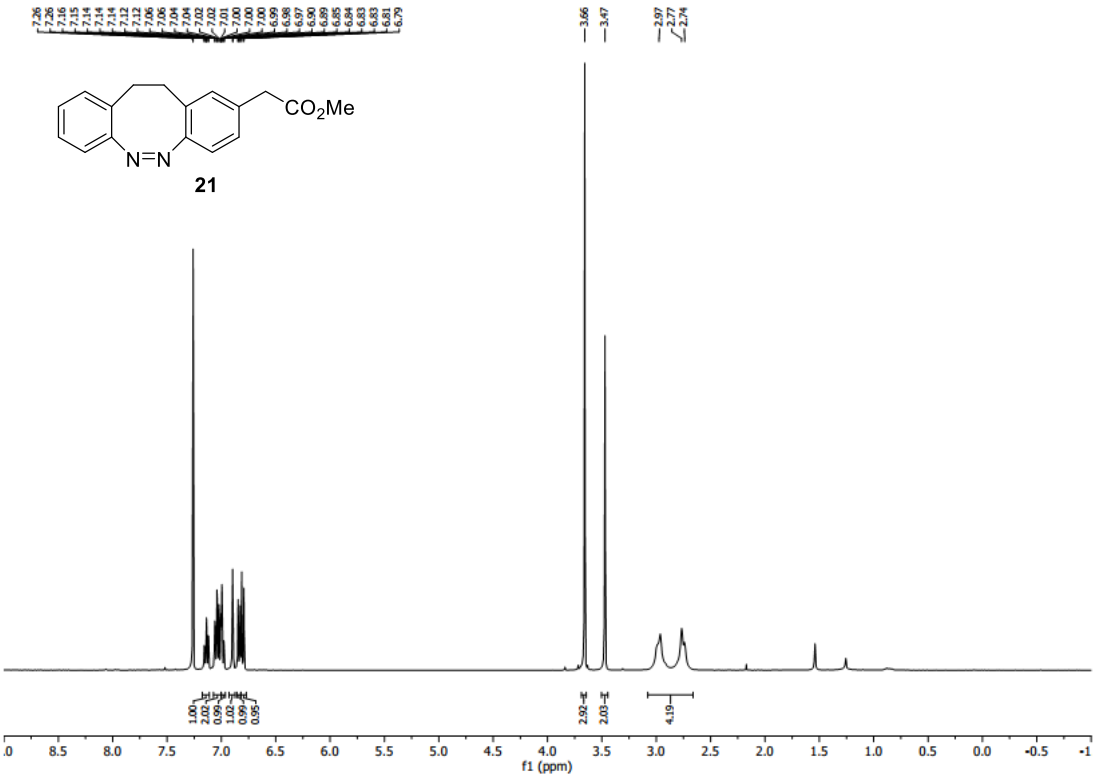


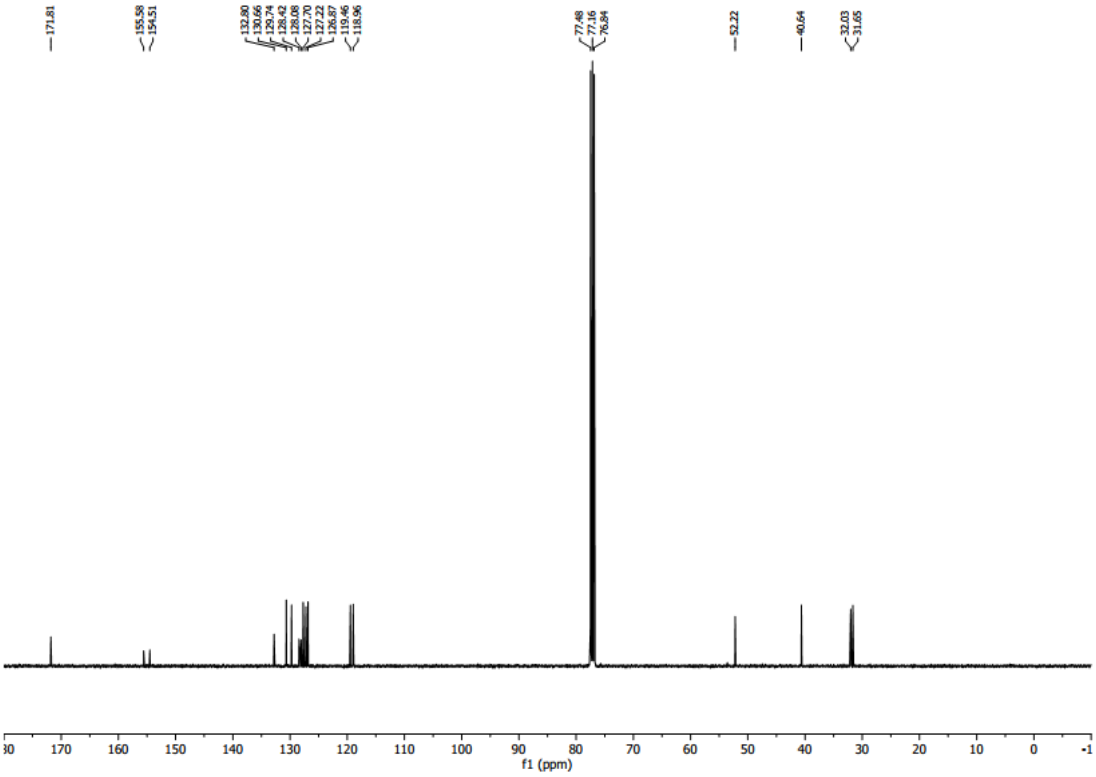
Compound **20** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



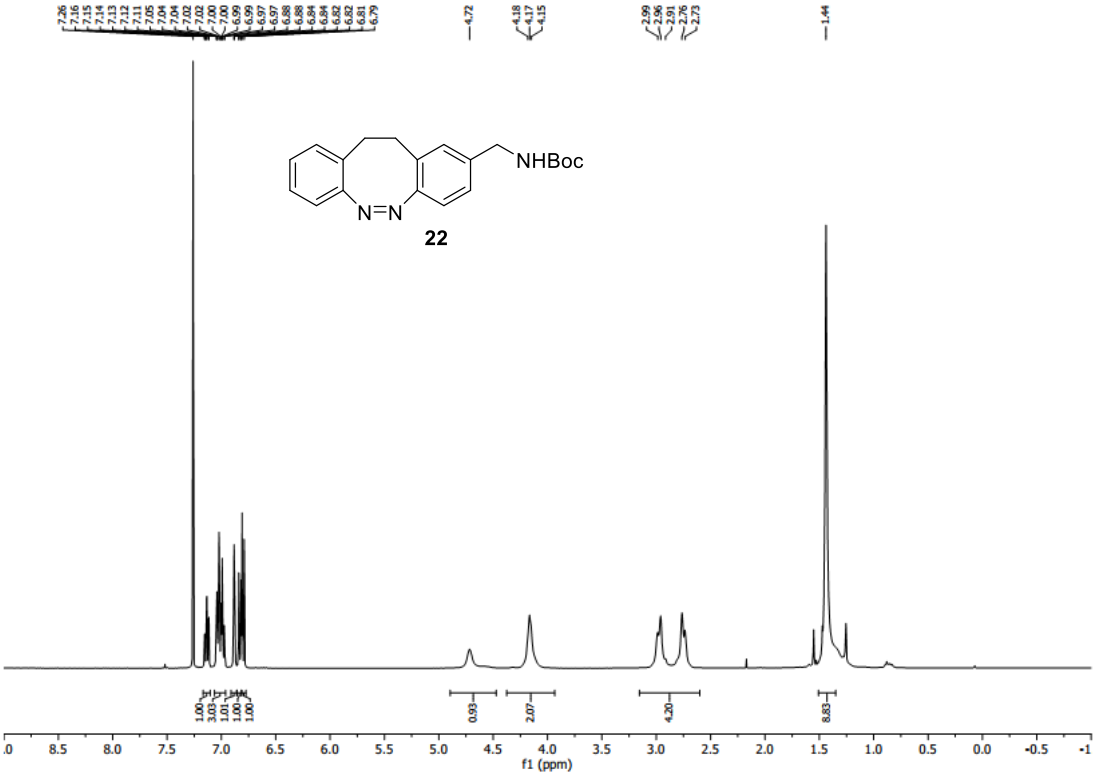


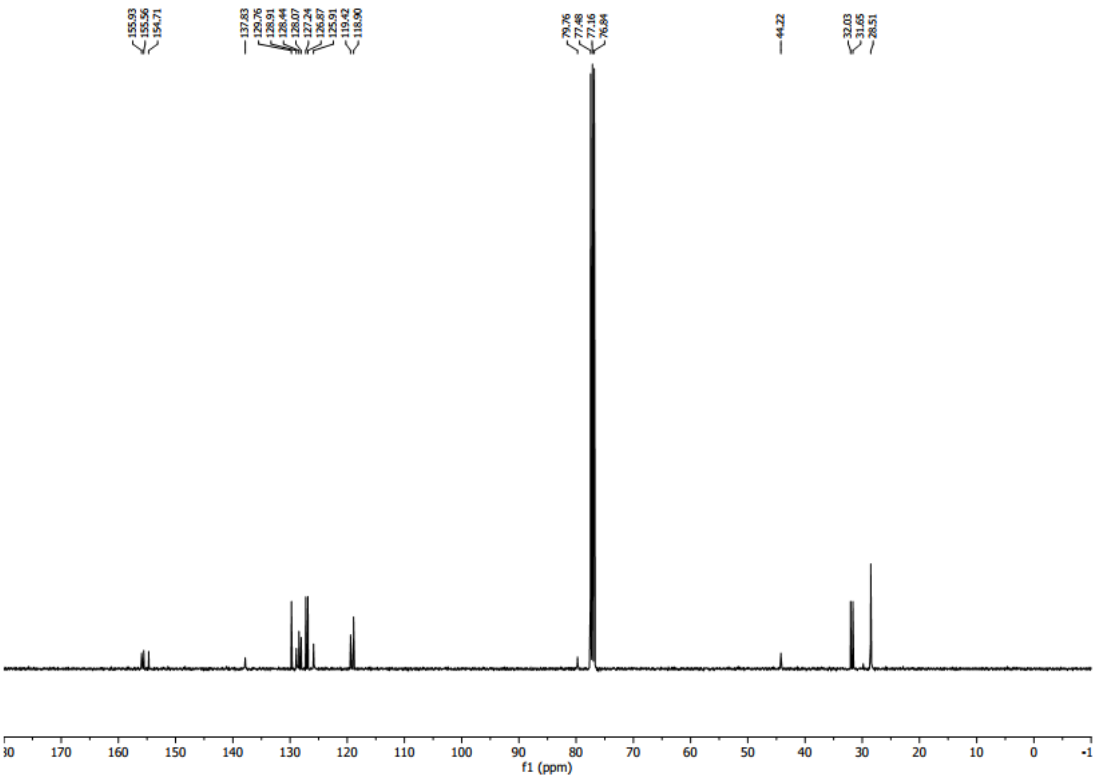
Compound **21** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



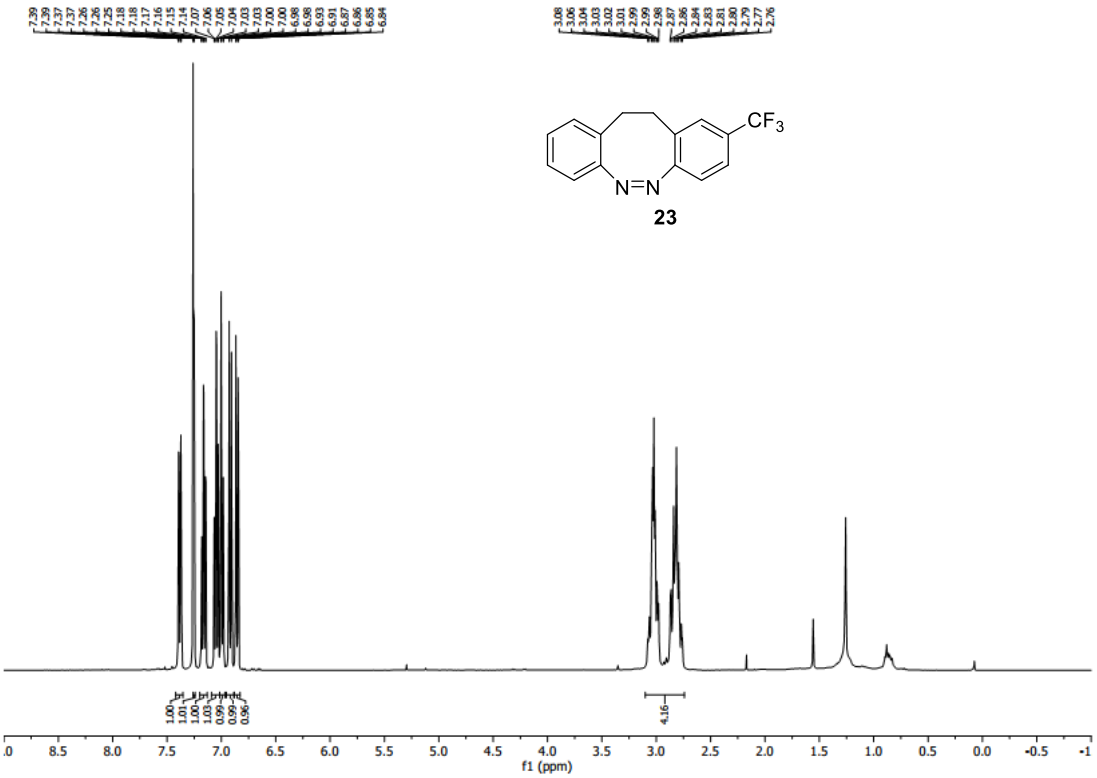


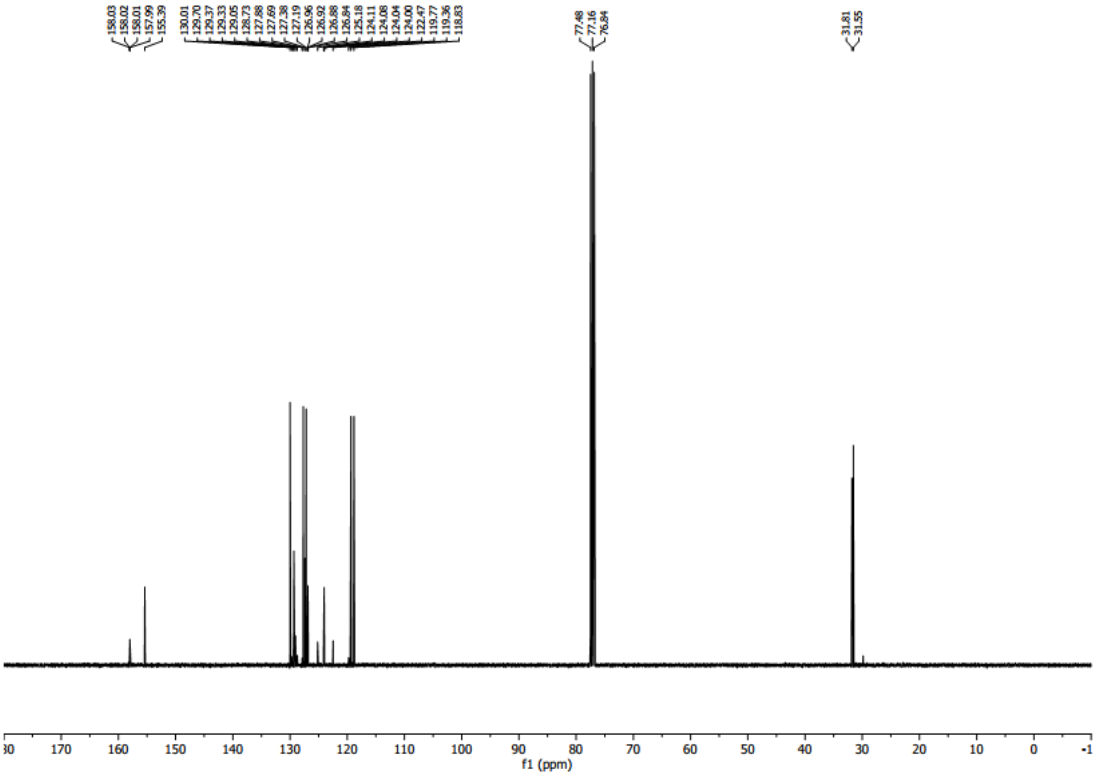
Compound **22** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



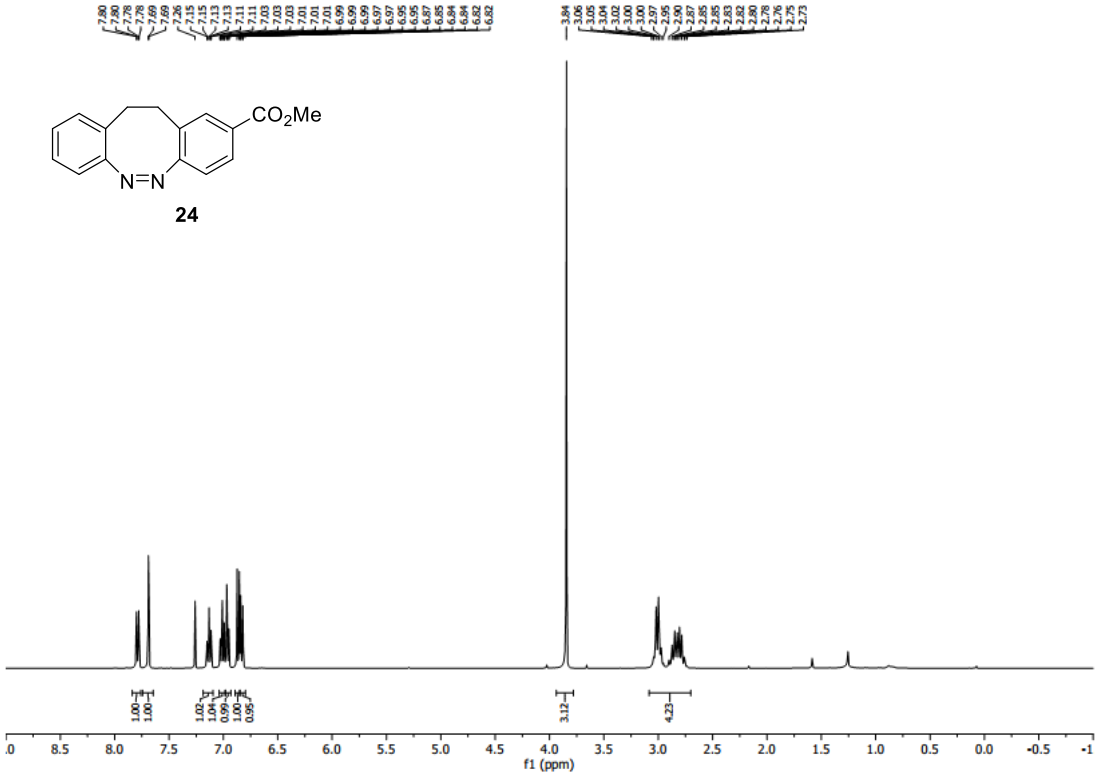


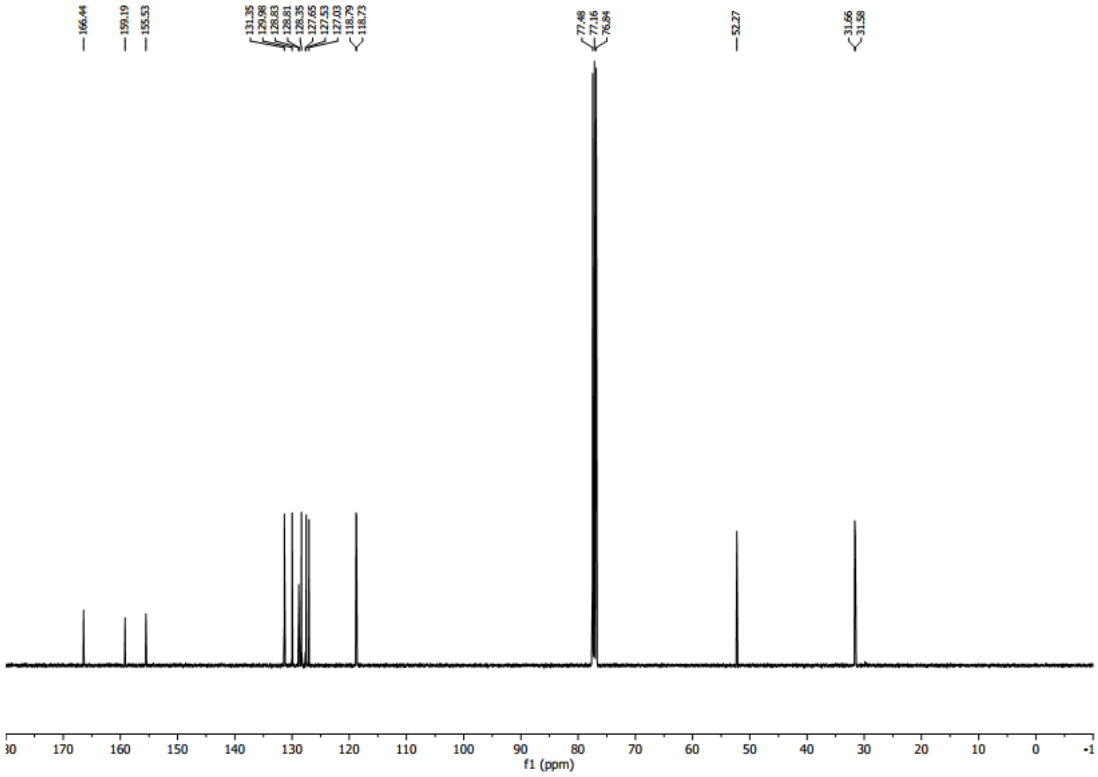
Compound **23** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



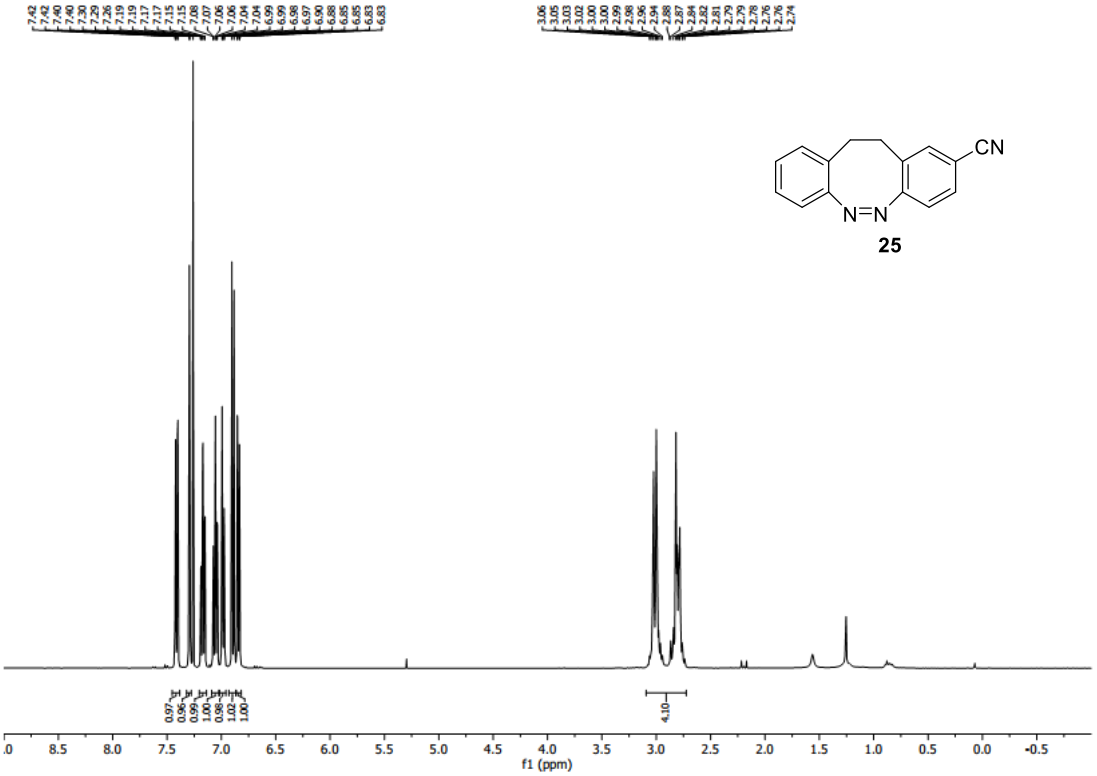


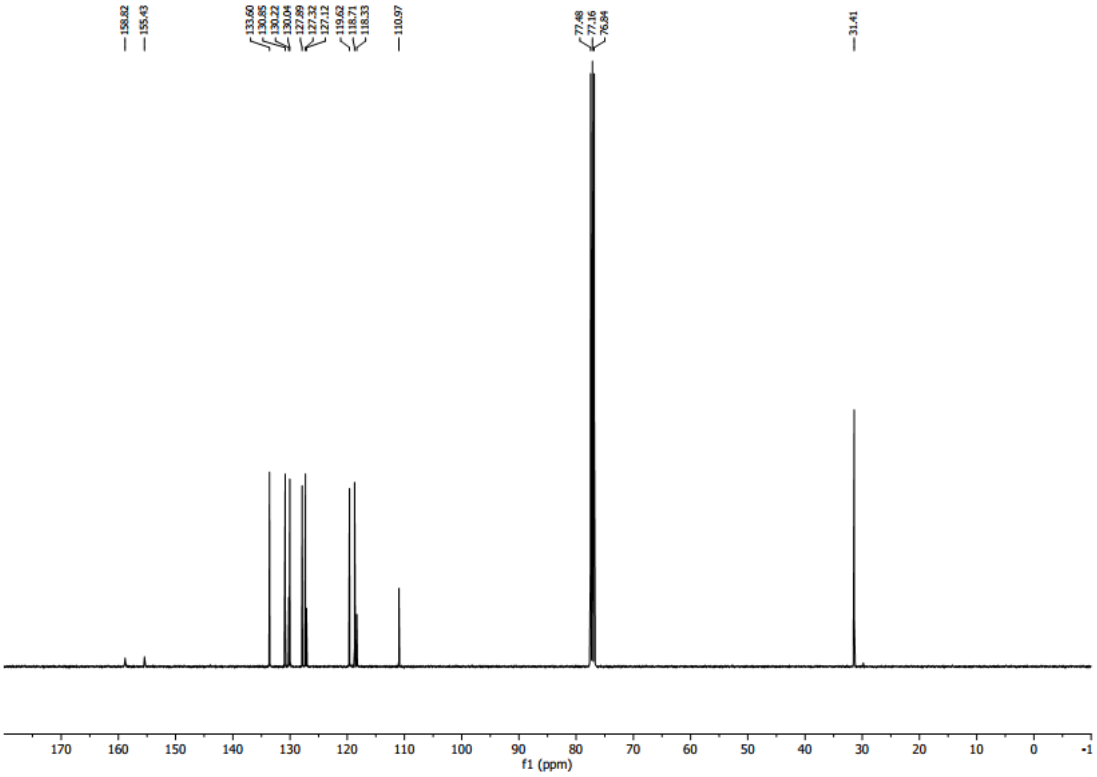
Compound **24** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



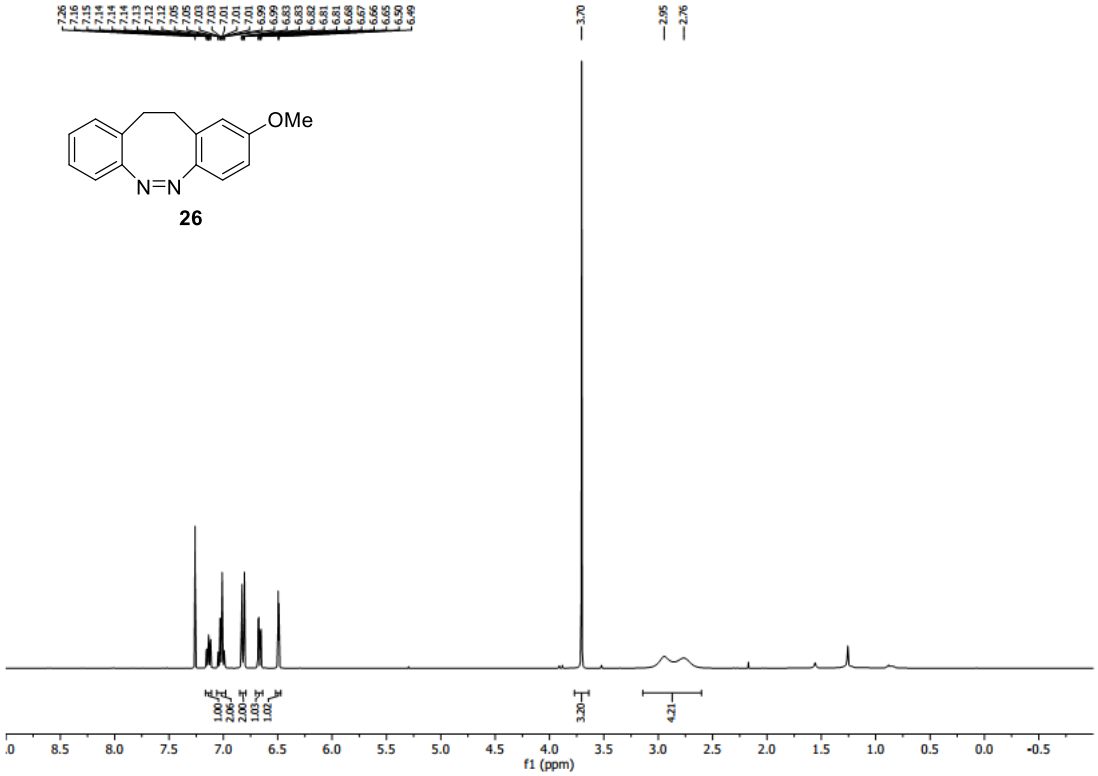


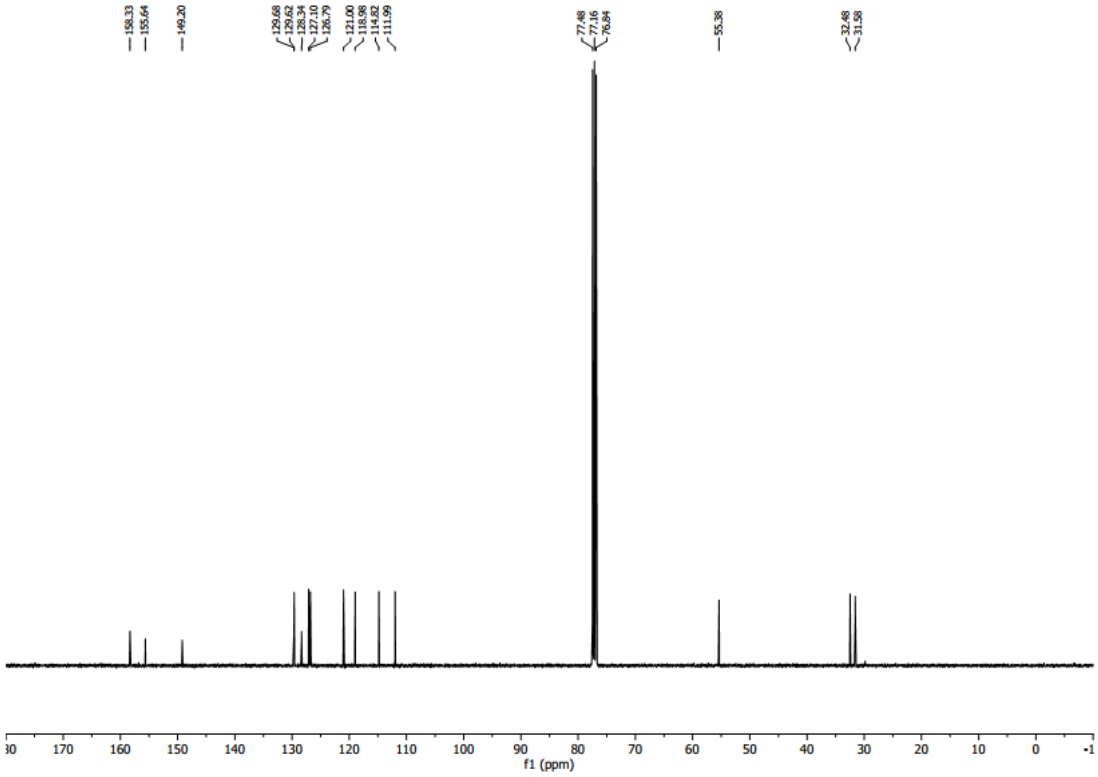
Compound **25** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



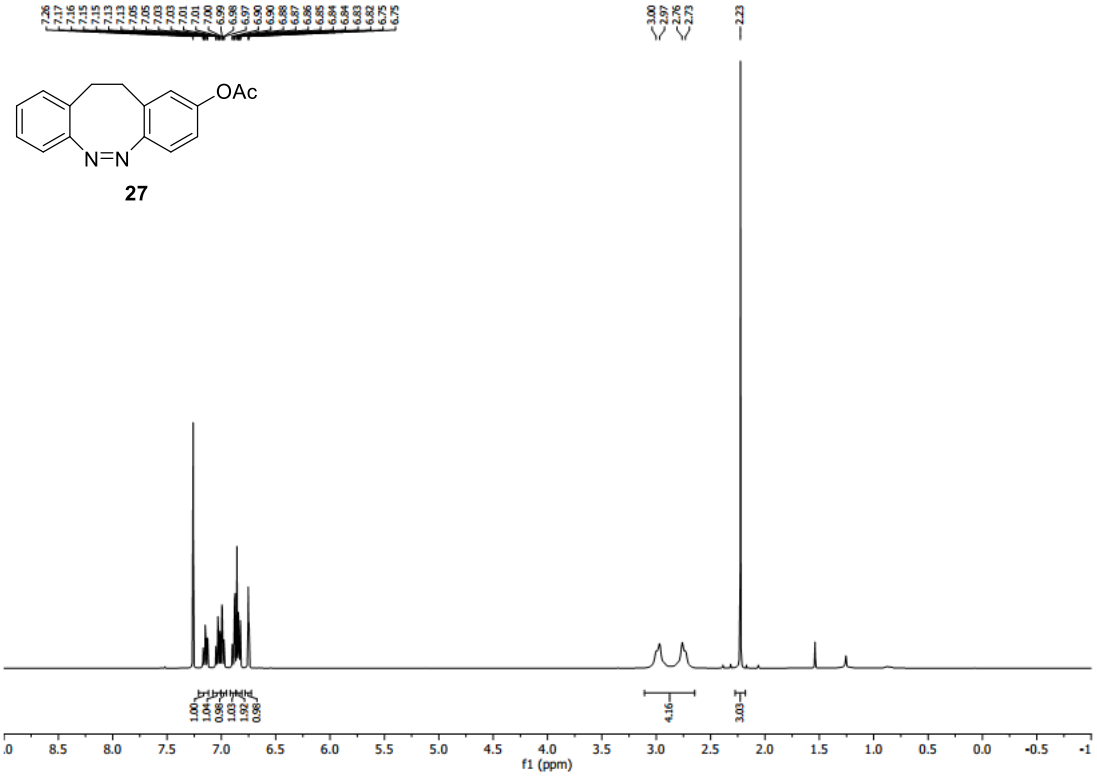


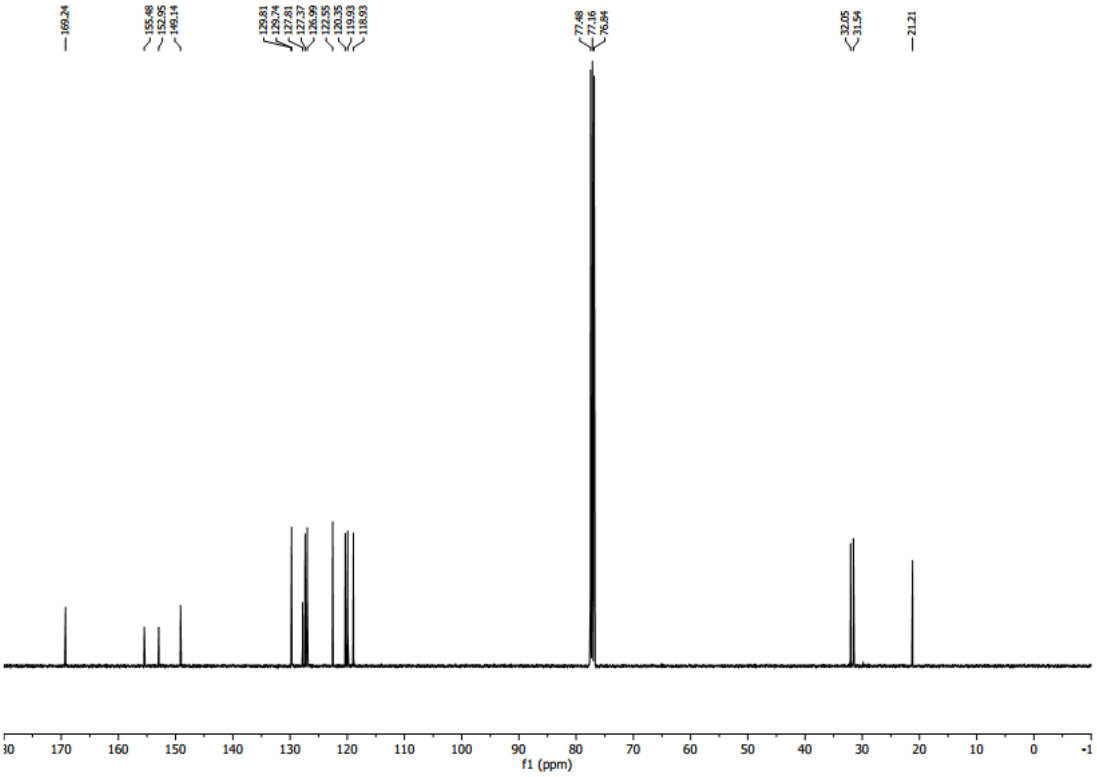
Compound **26** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



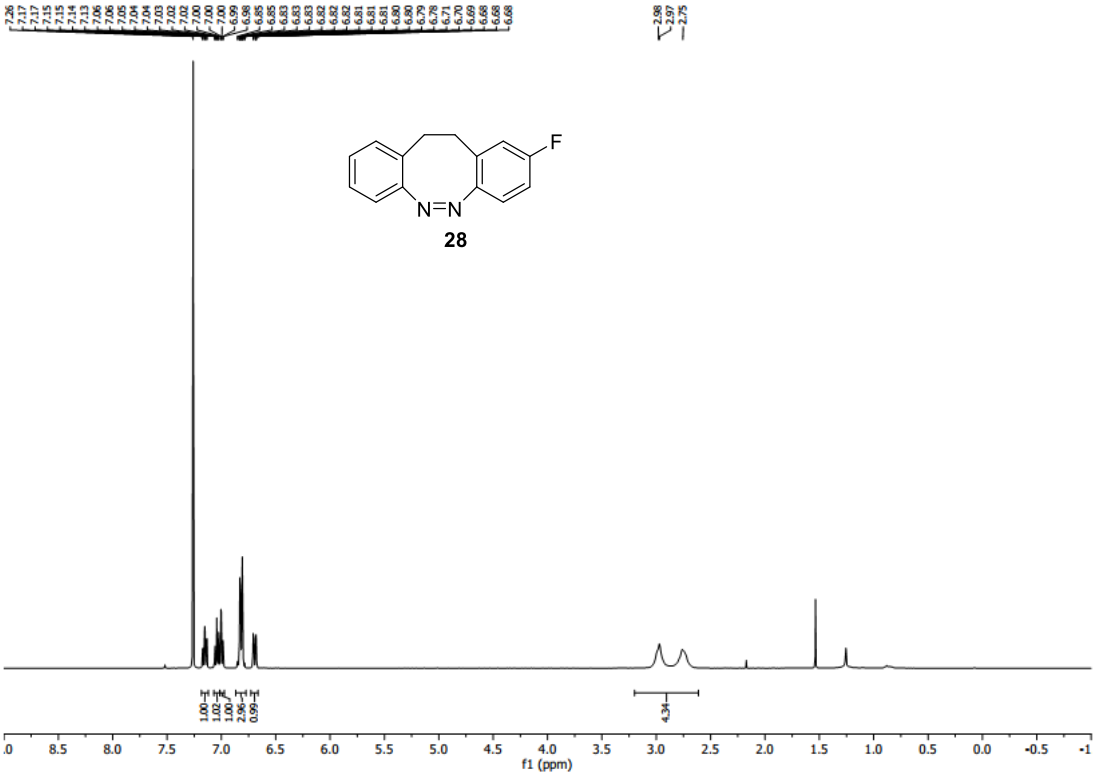


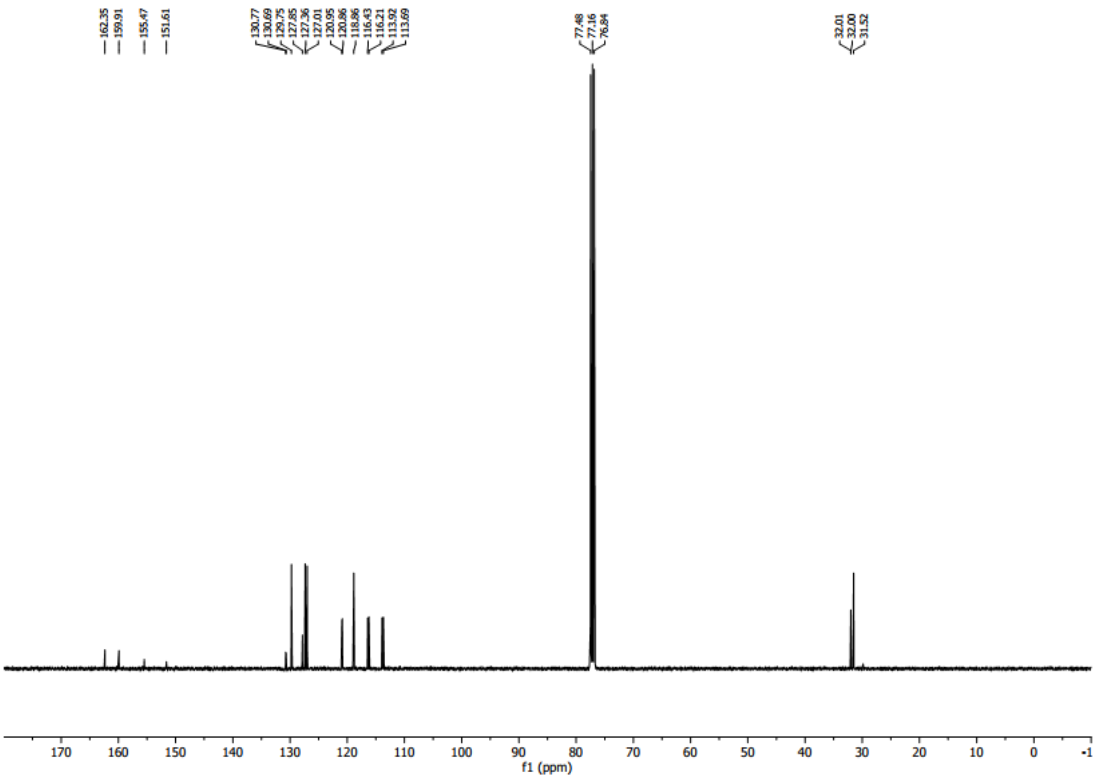
Compound **27** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



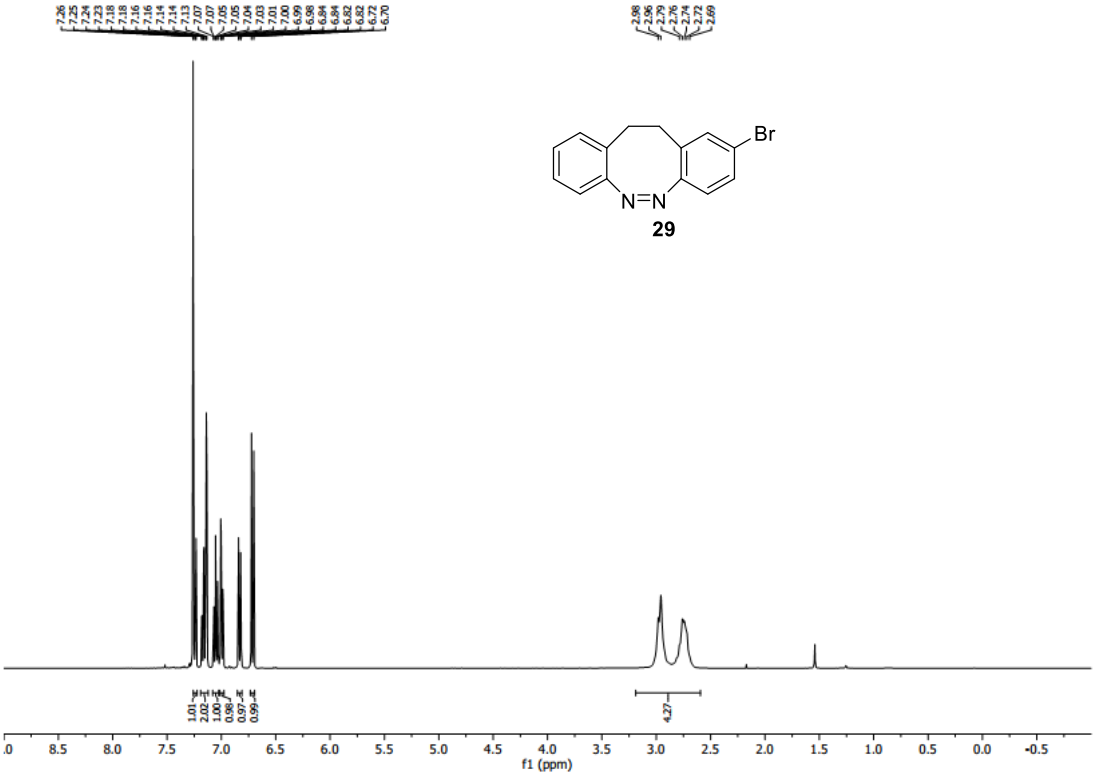


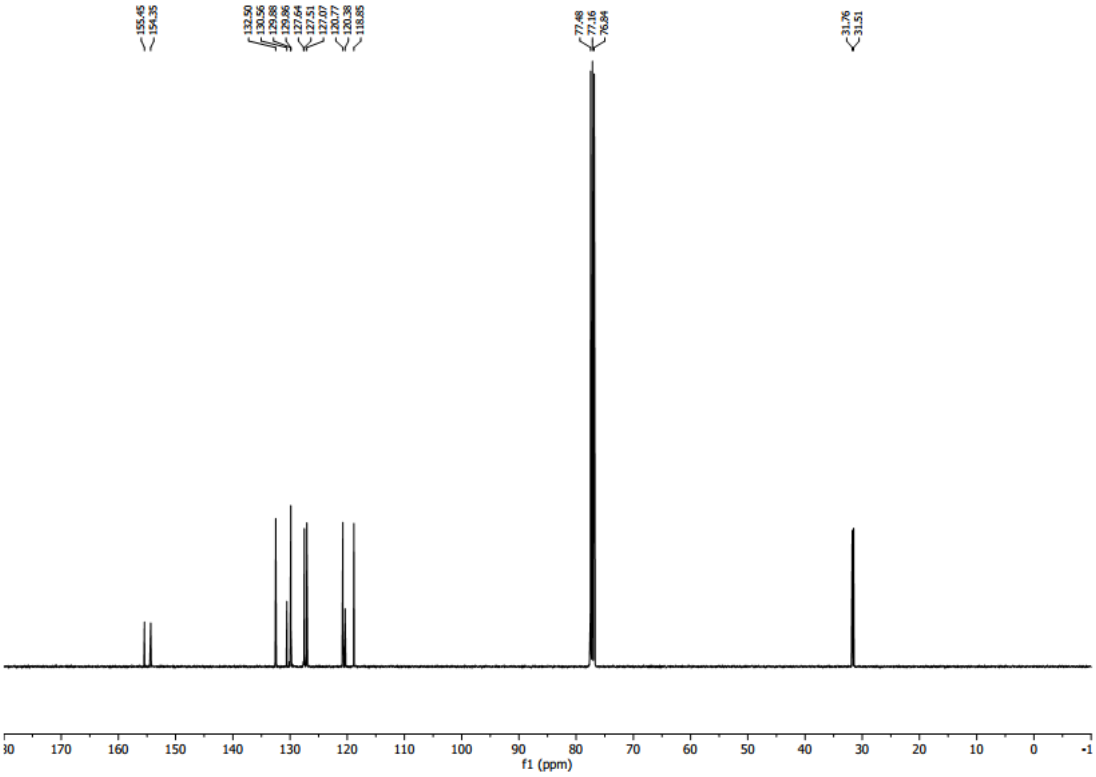
Compound **28** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



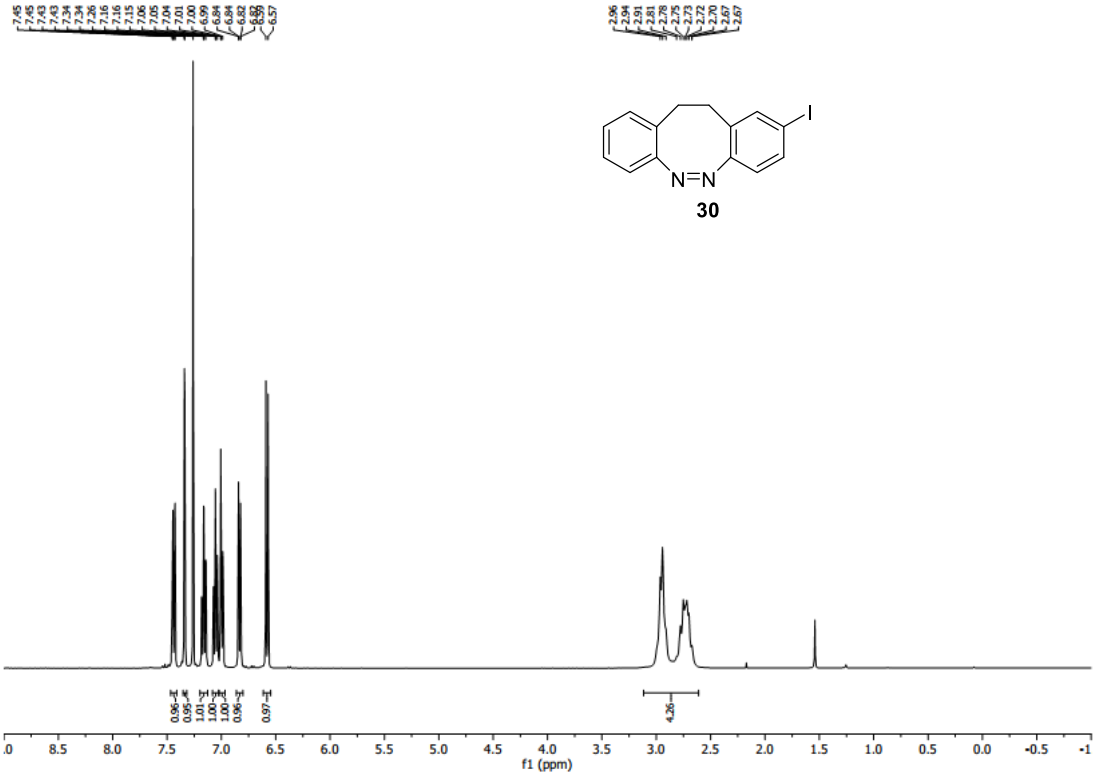


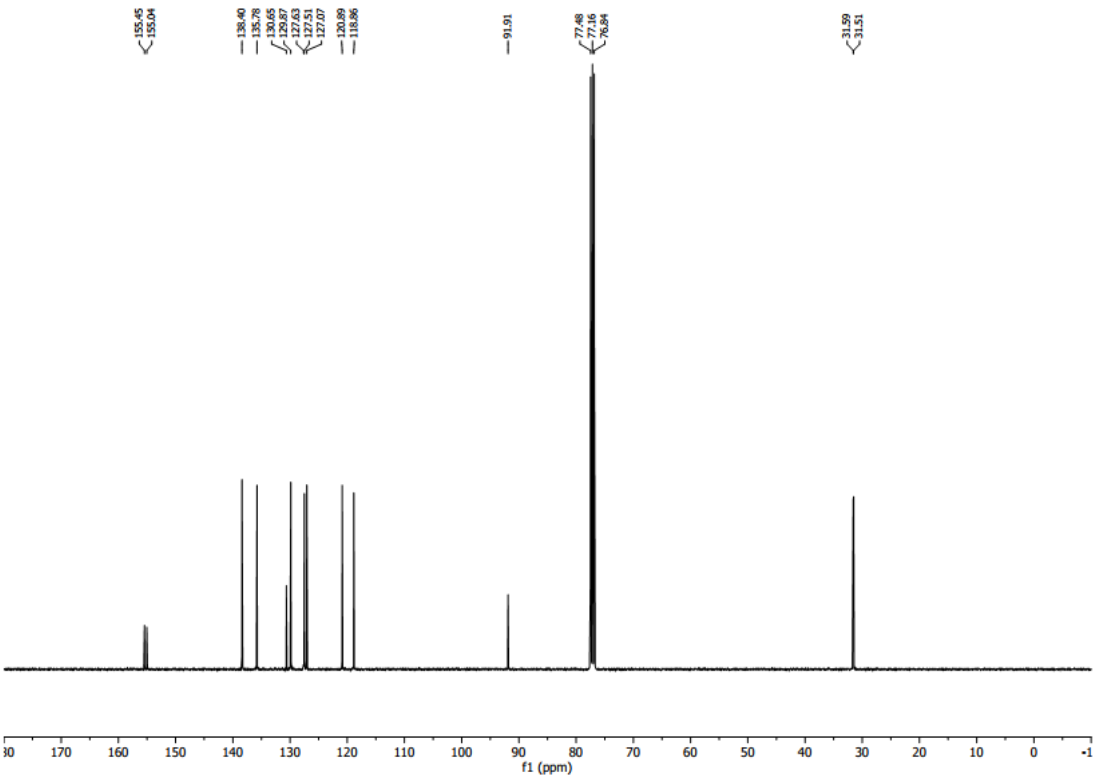
Compound **29** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



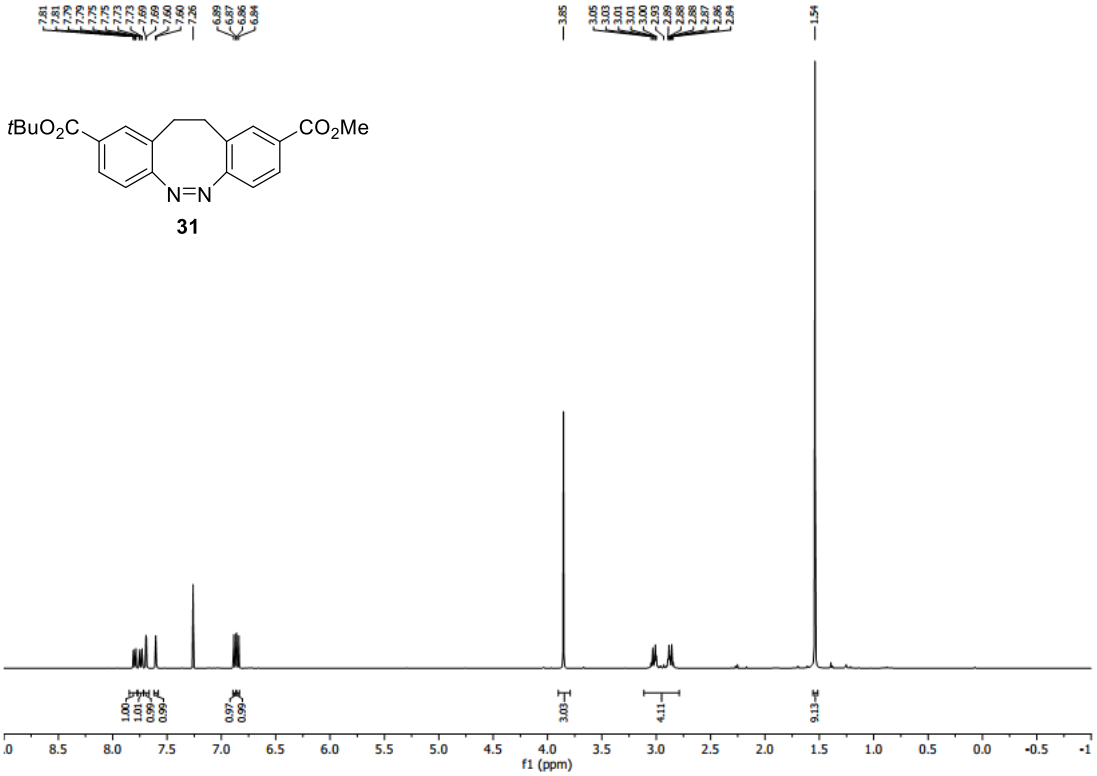


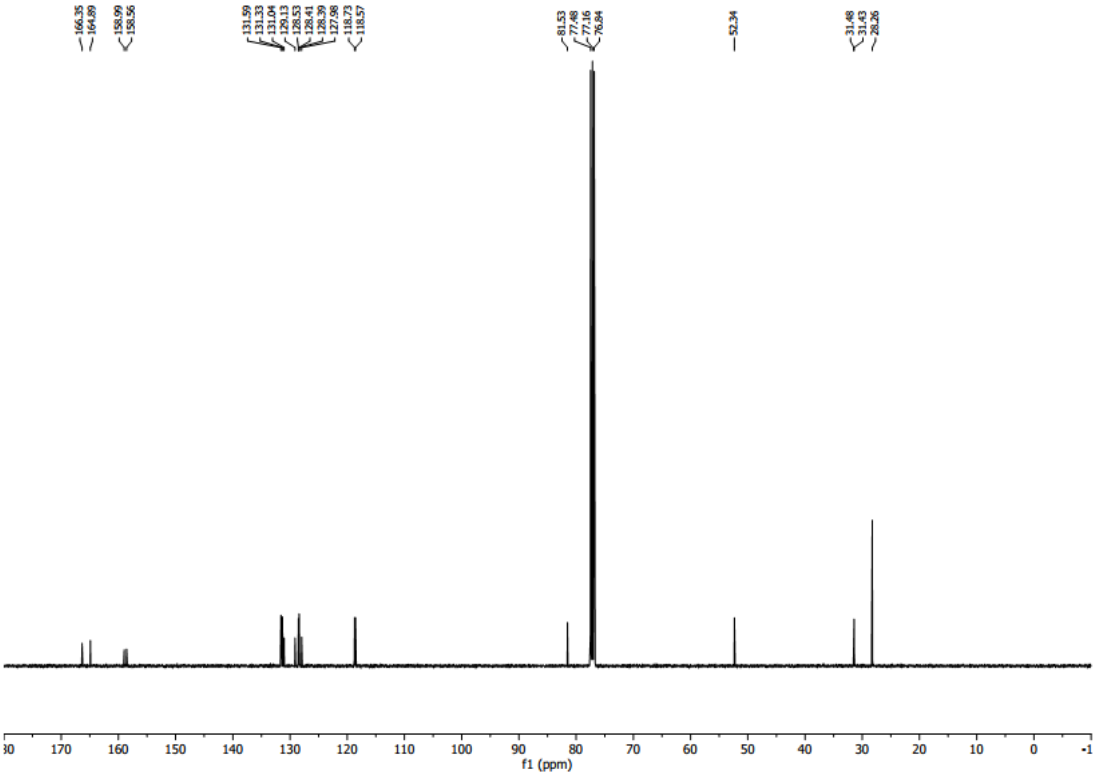
Compound **30** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



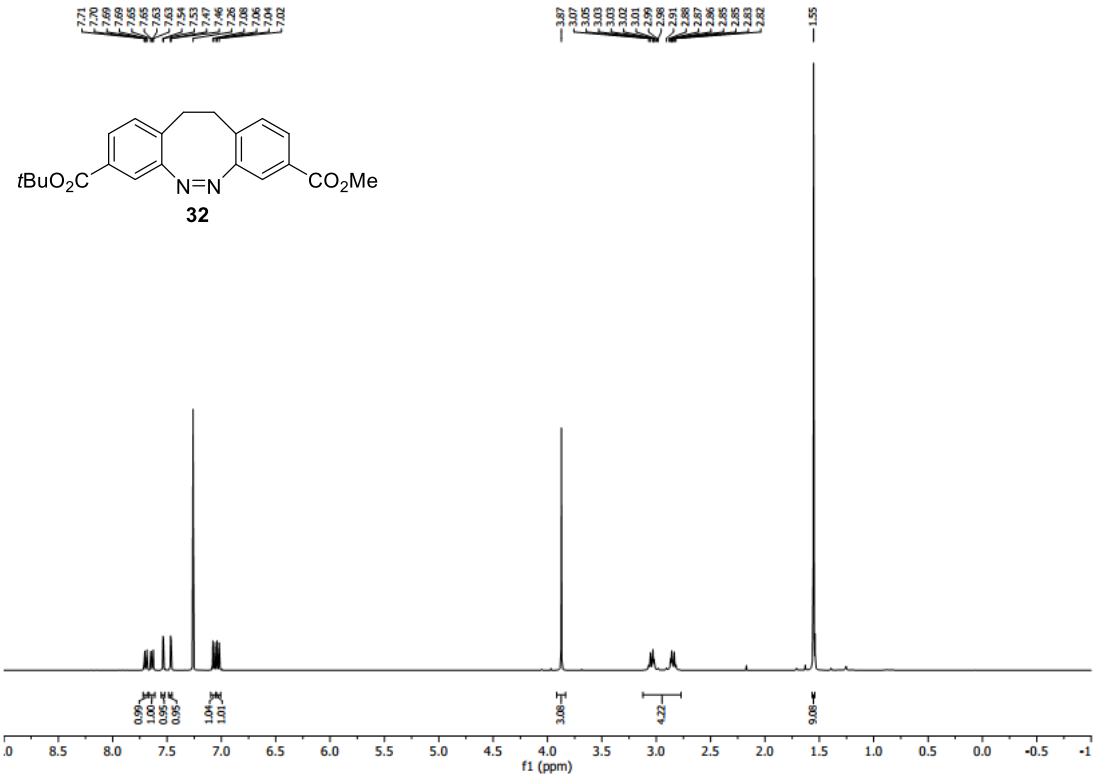


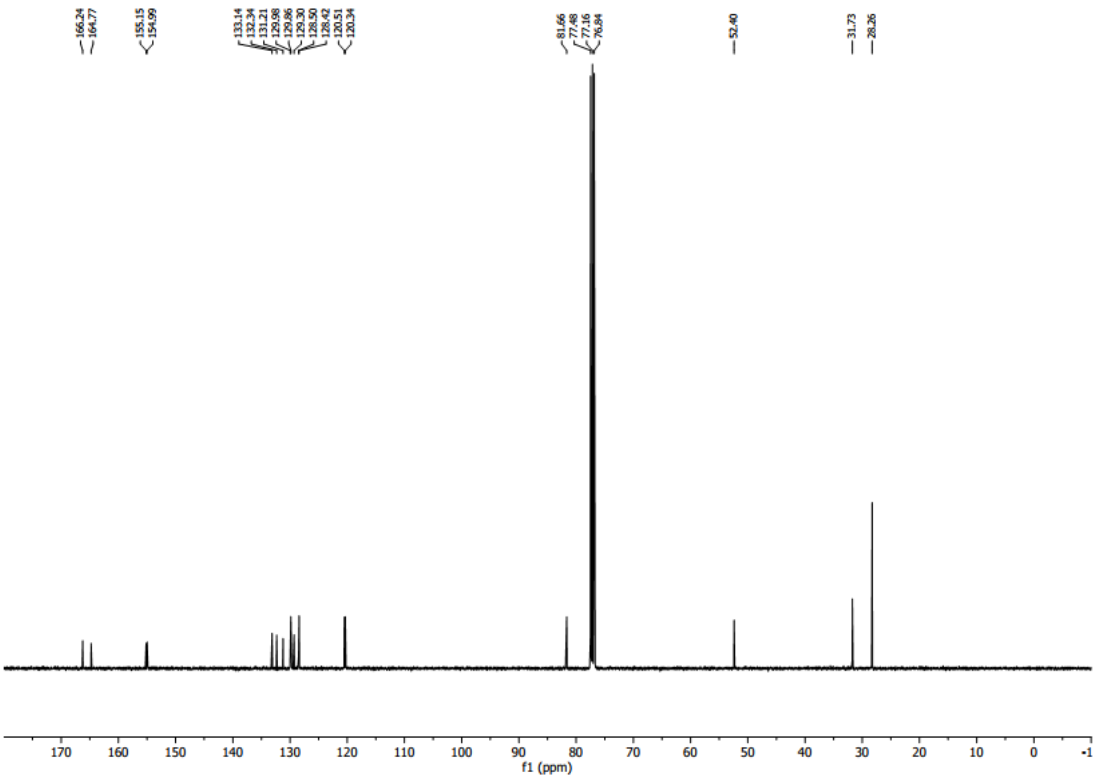
Compound **31** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



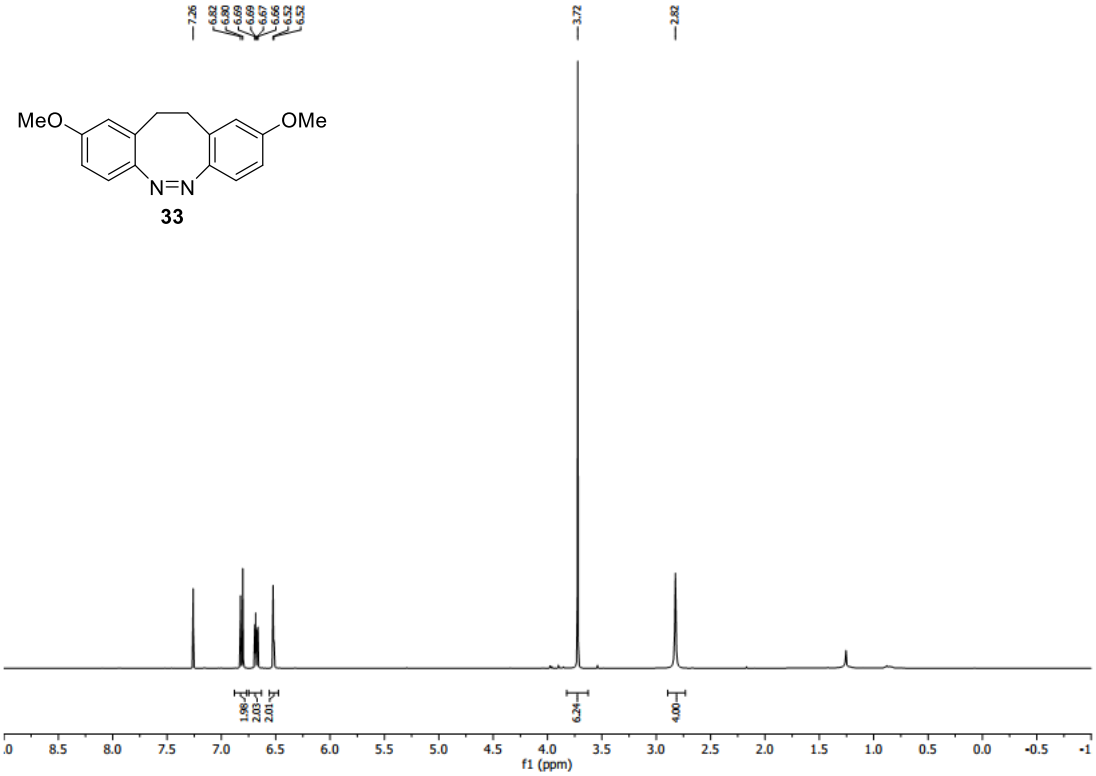


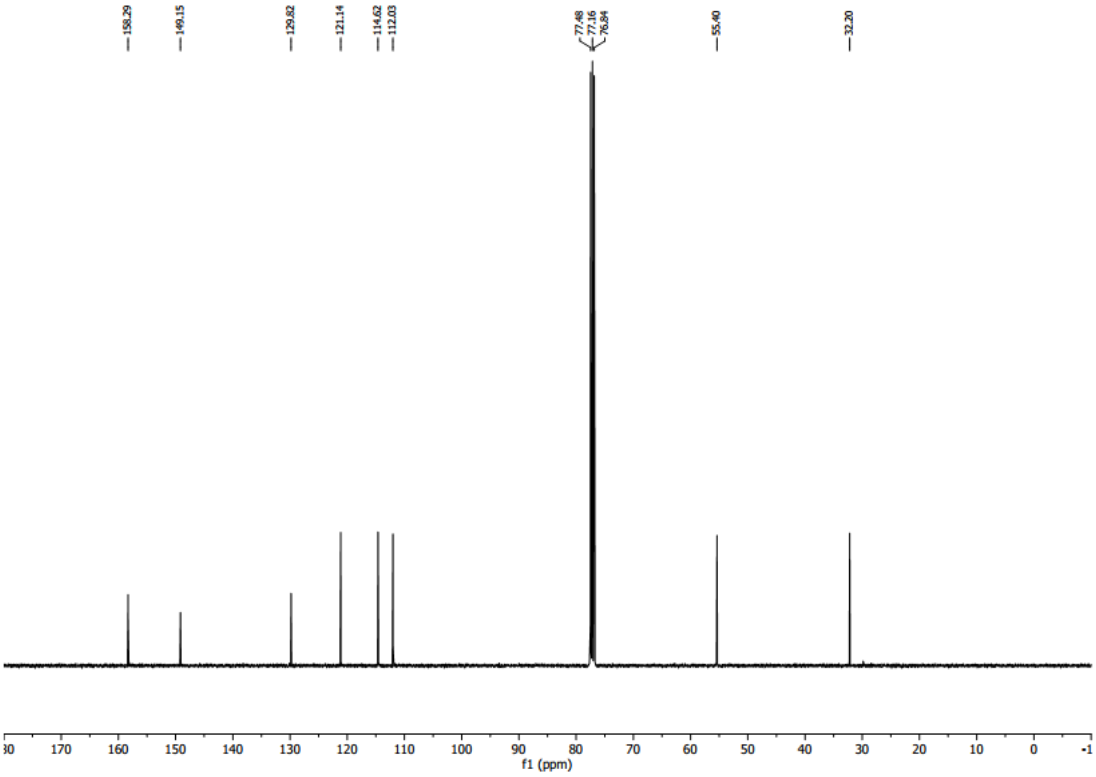
Compound **32** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



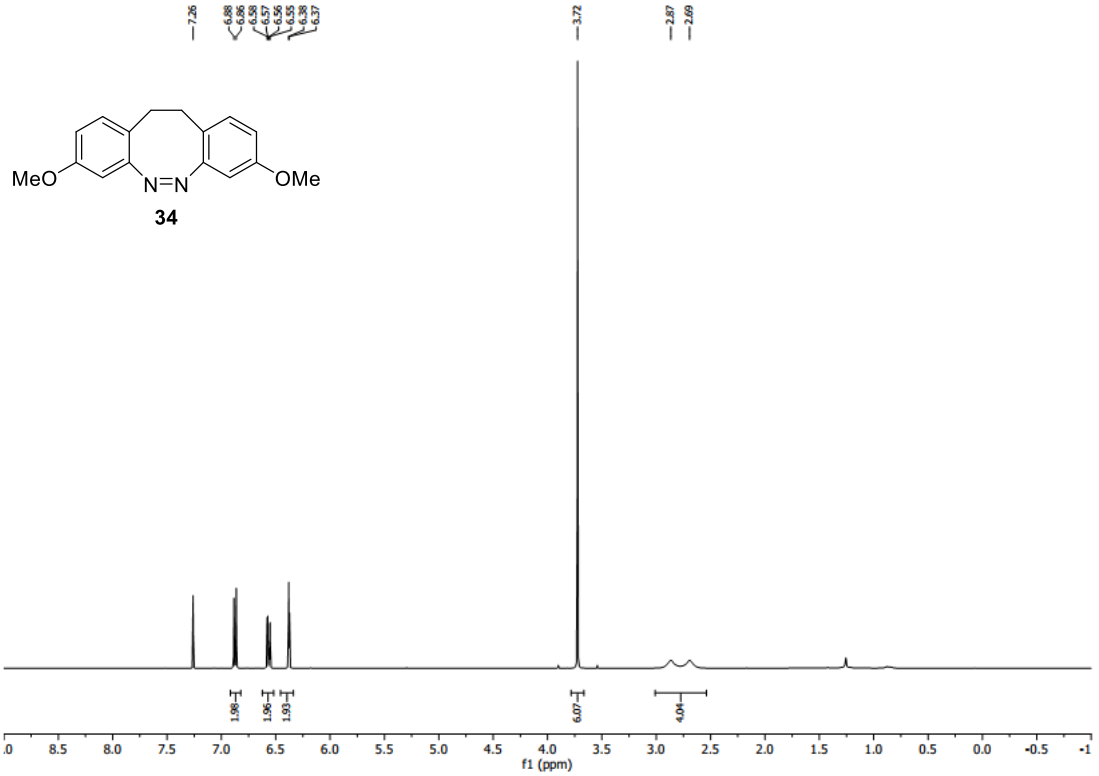


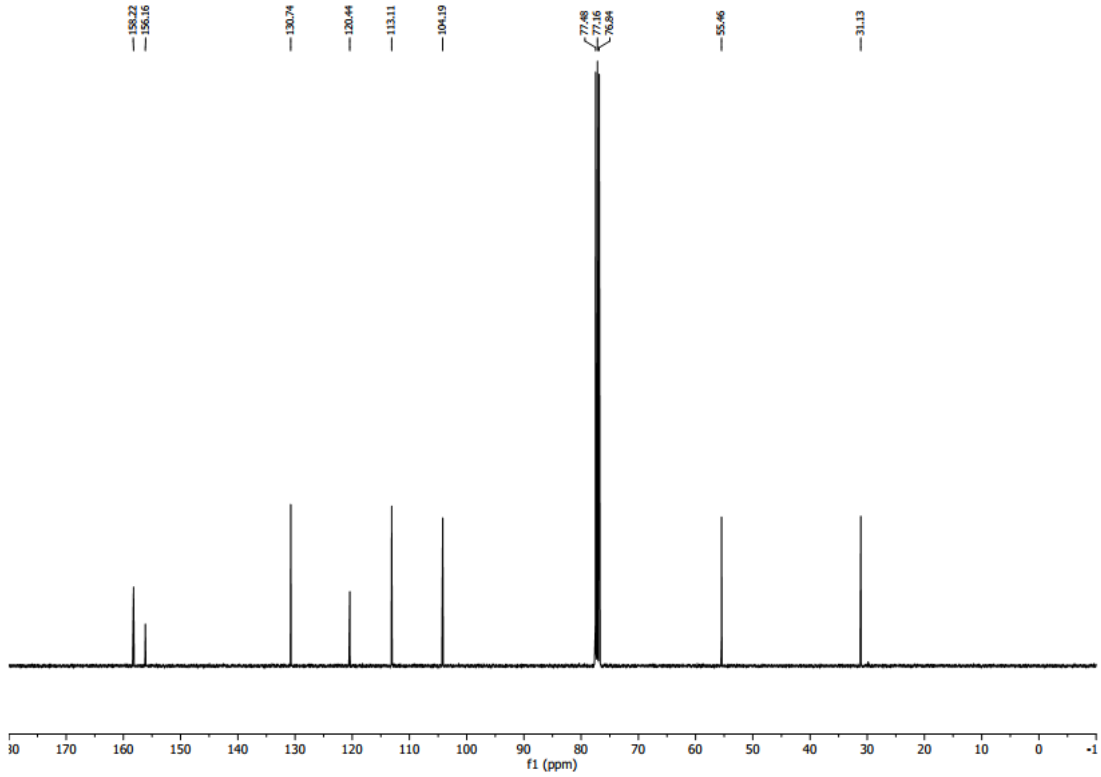
Compound **33** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



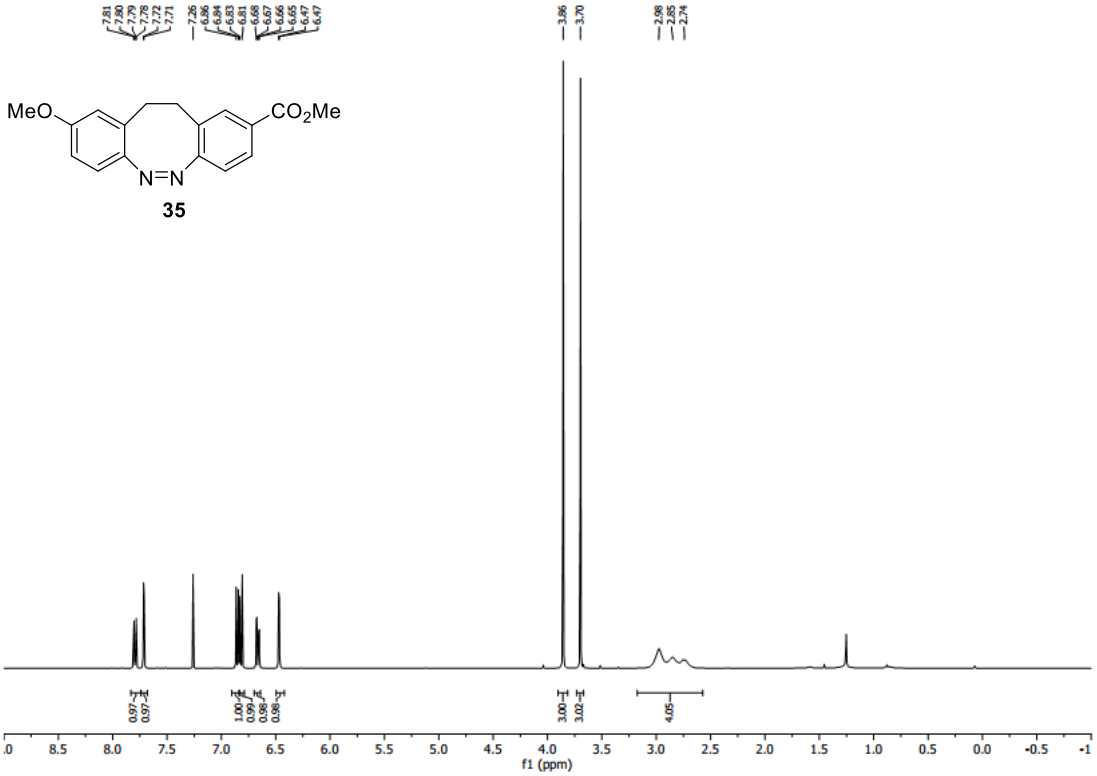


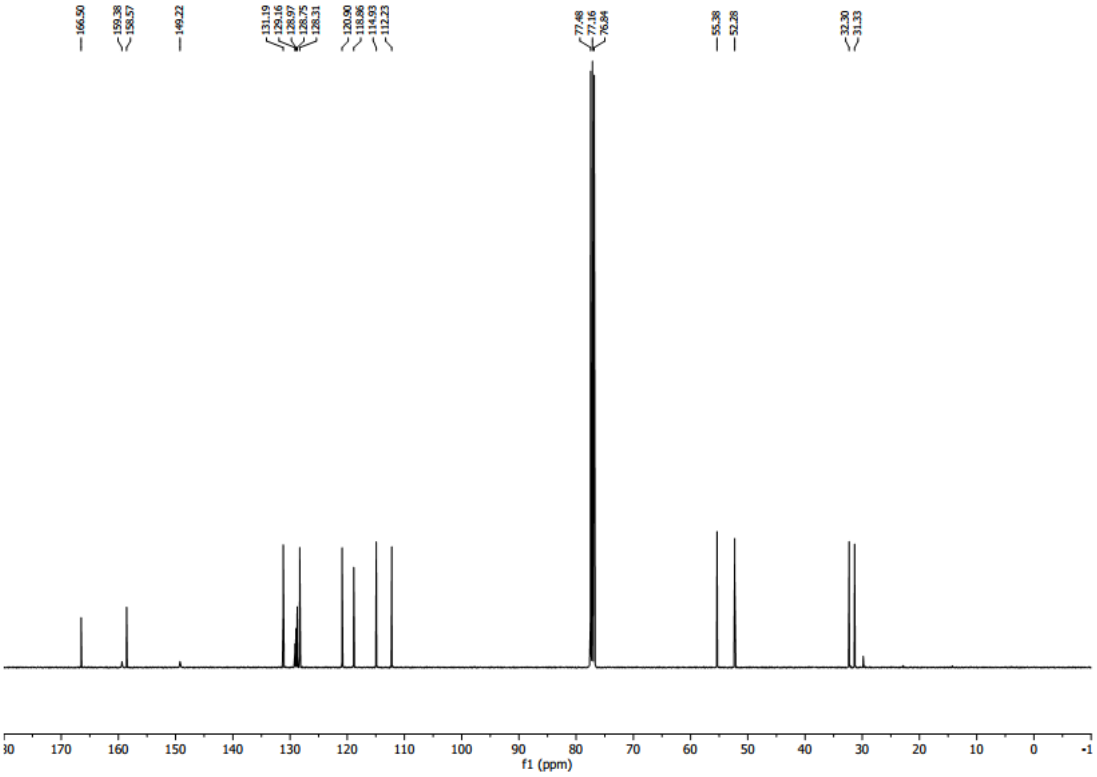
Compound **34** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



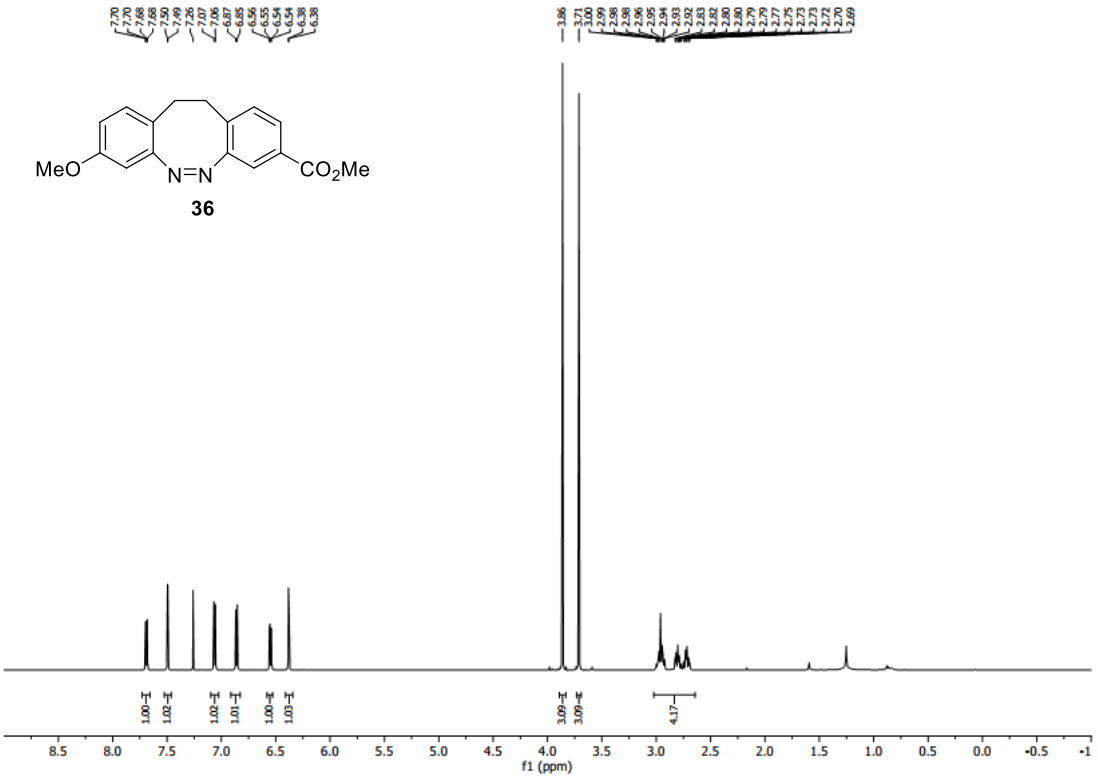


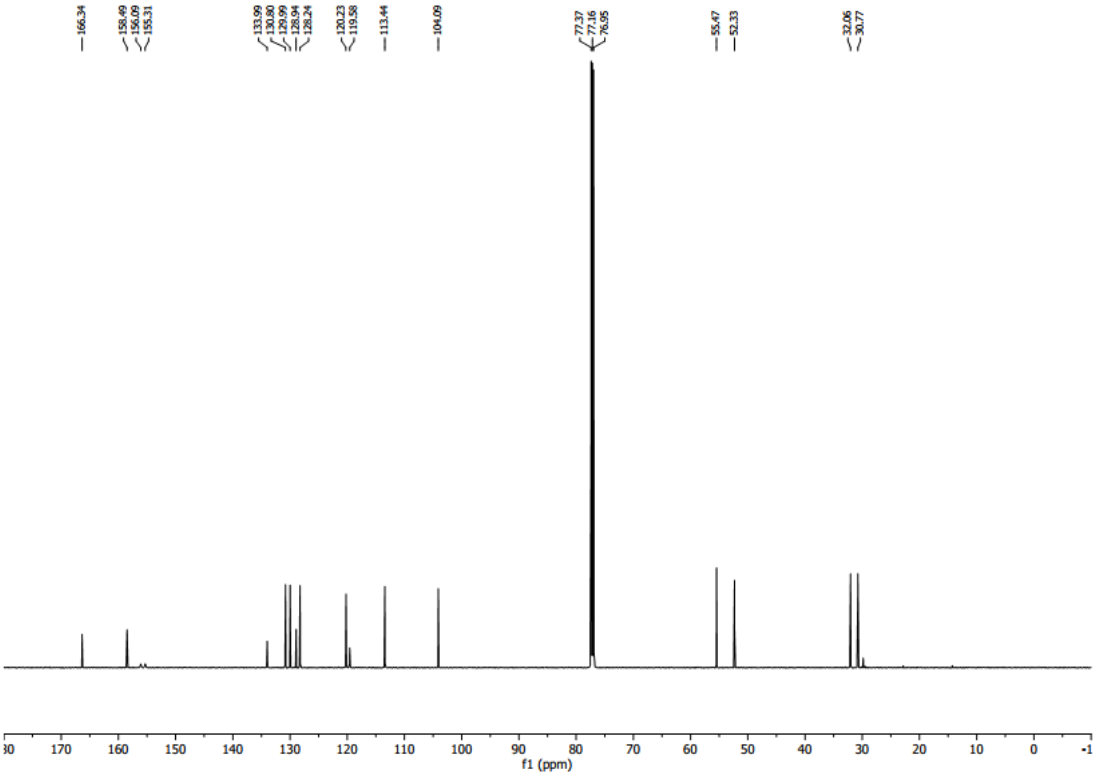
Compound **35** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



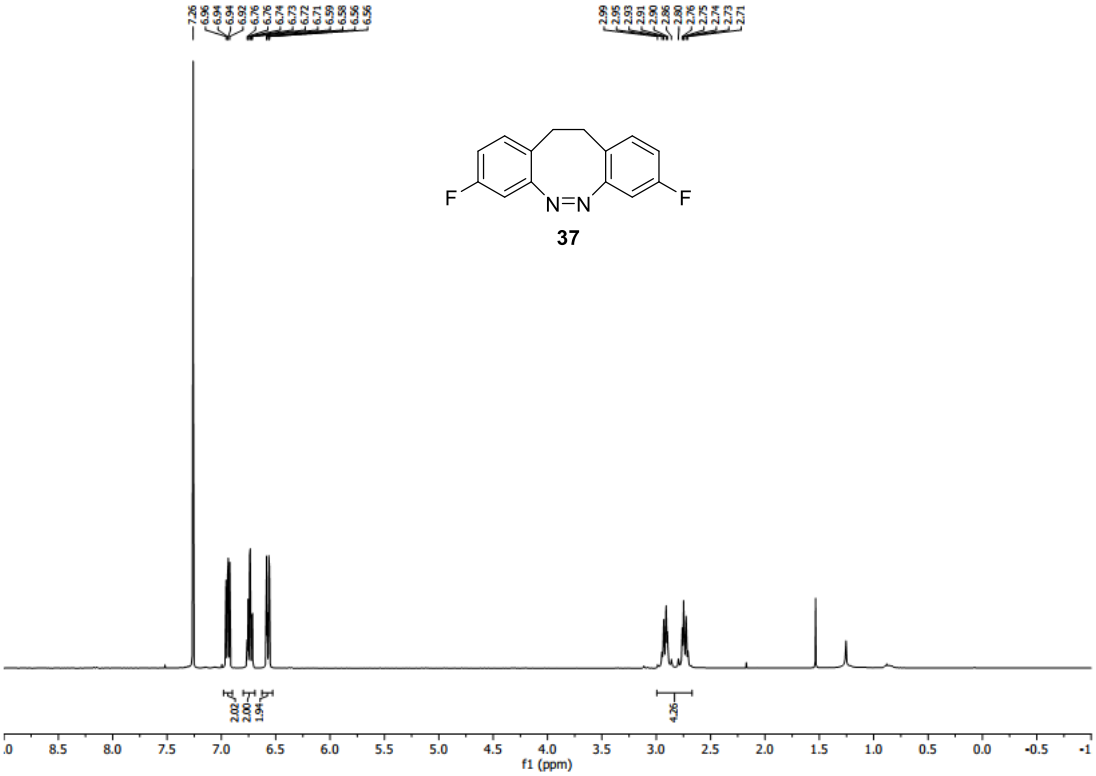


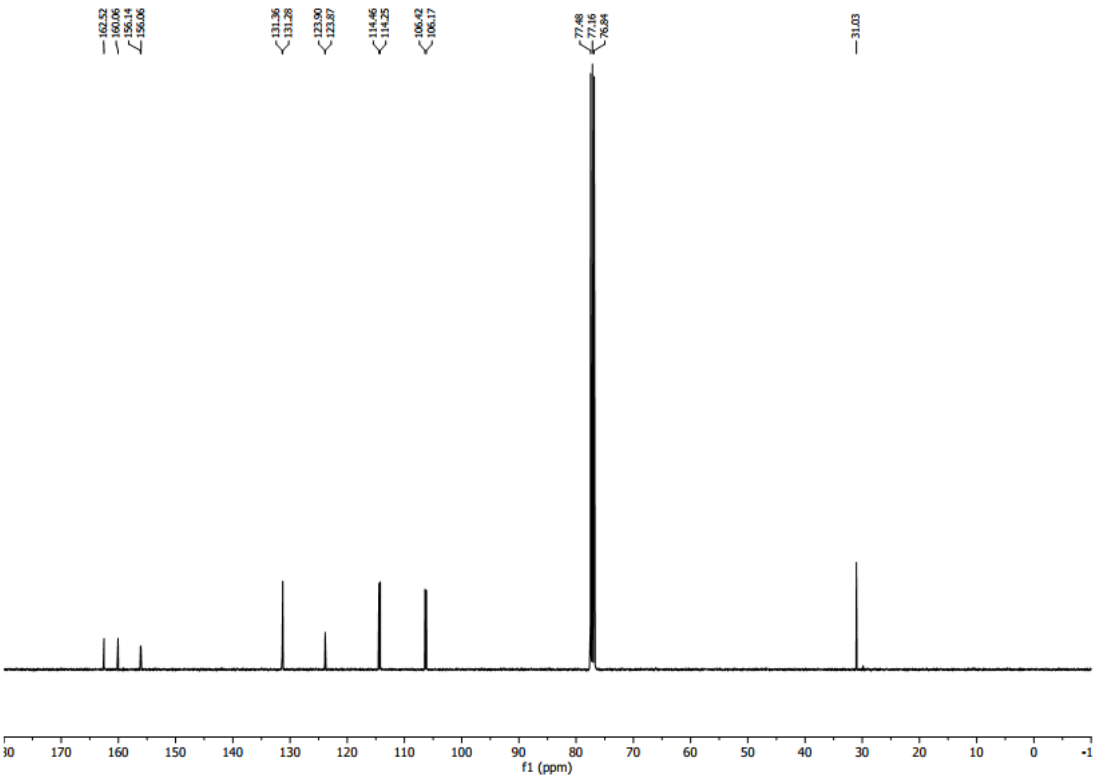
Compound **36** – **^{1}H-NMR** (600 MHz) and **^{13}C-NMR** (150 MHz) in $CDCl_3$



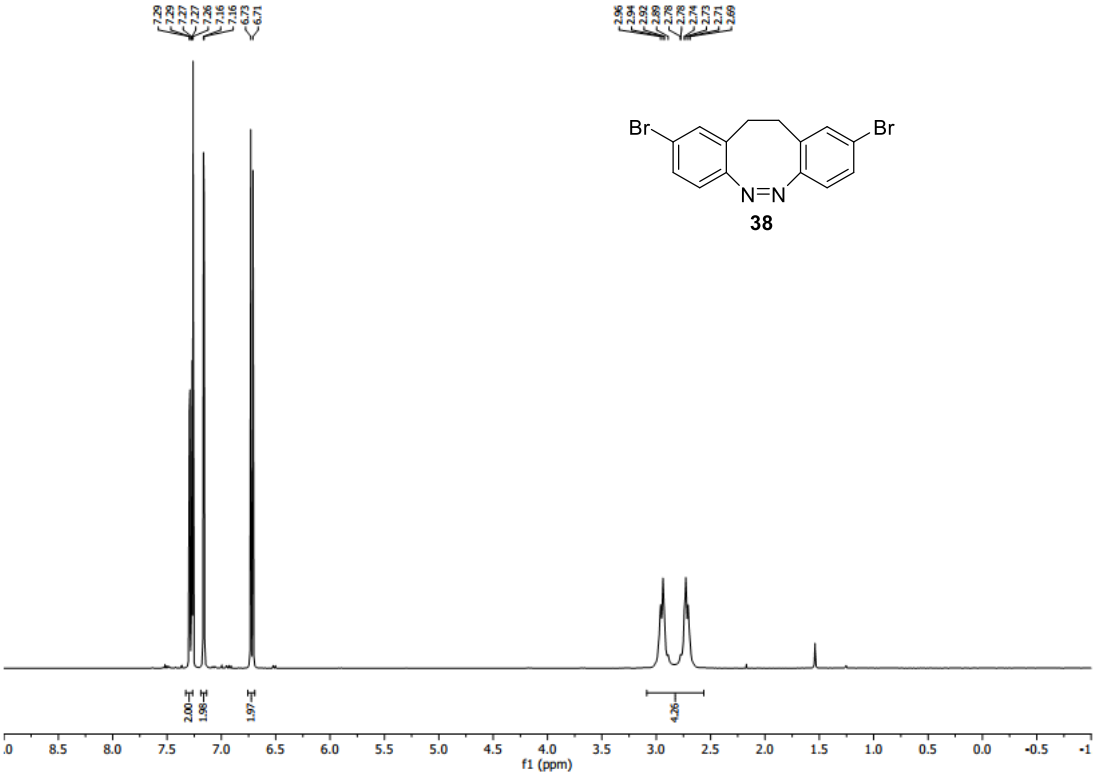


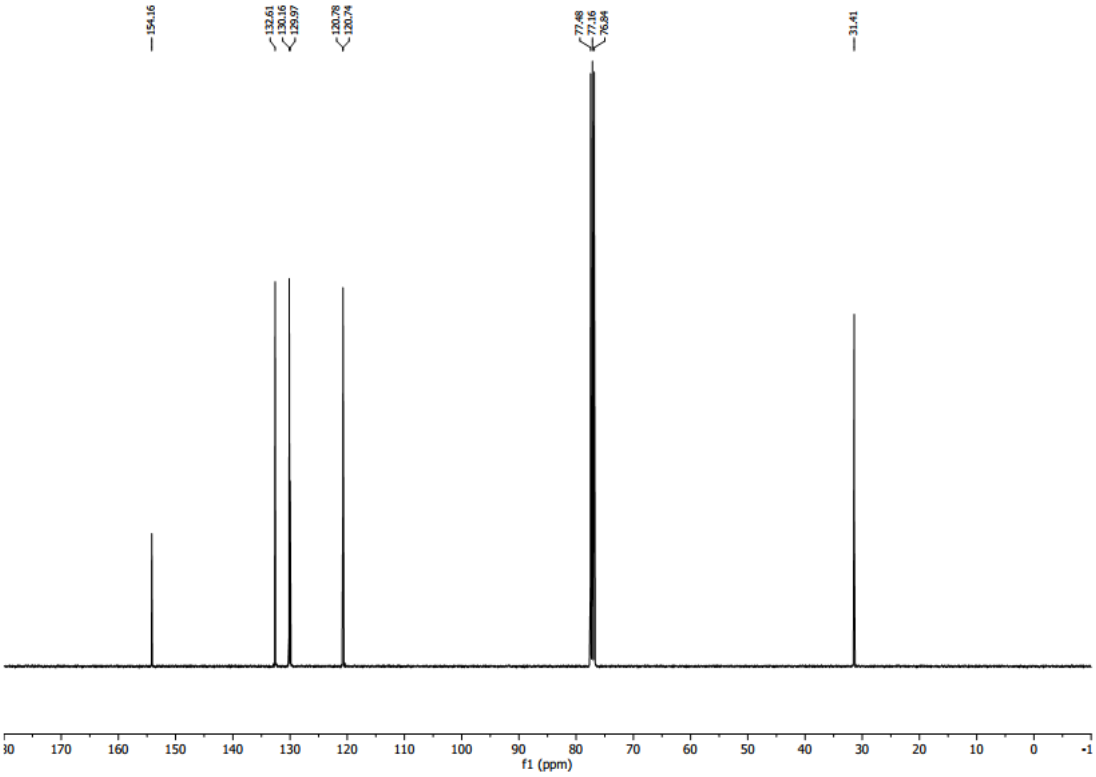
Compound **37** – ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) in $CDCl_3$



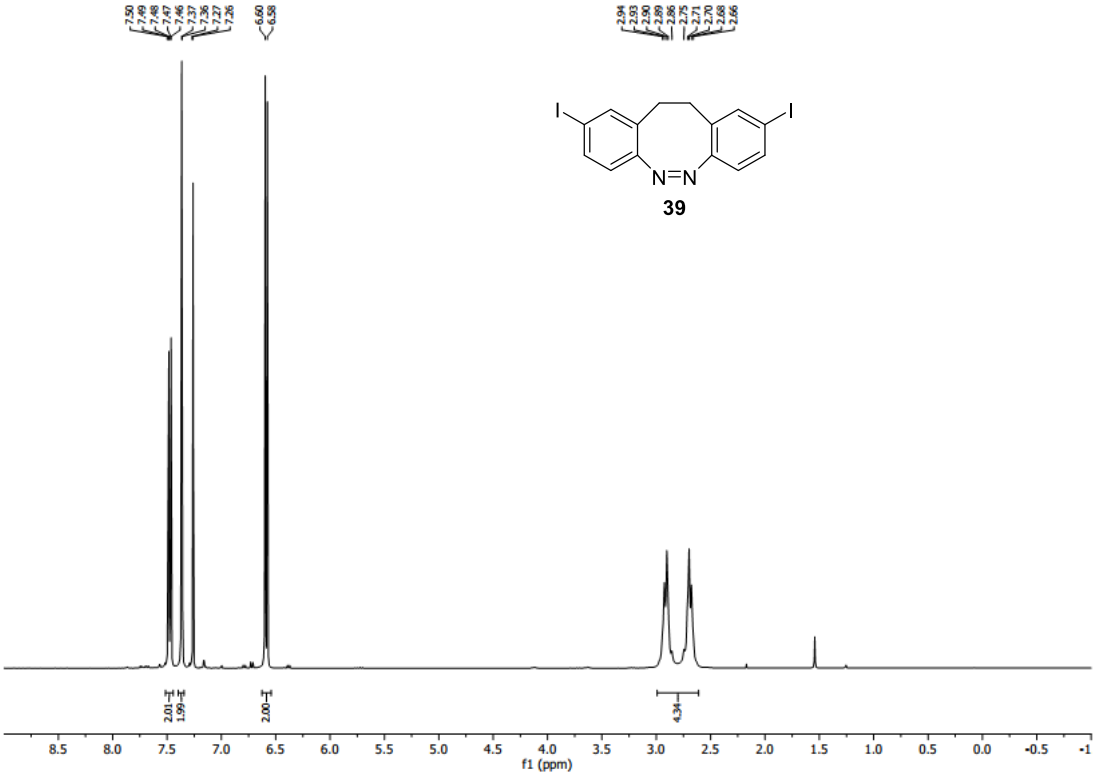


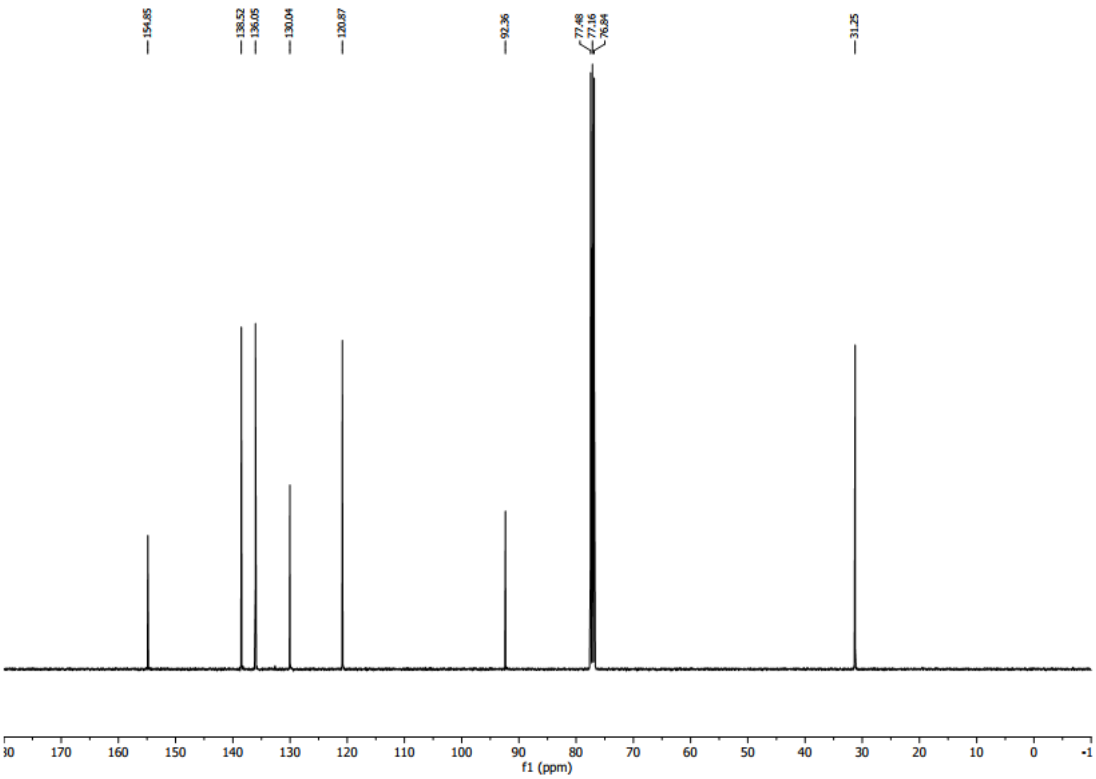
Compound **38** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



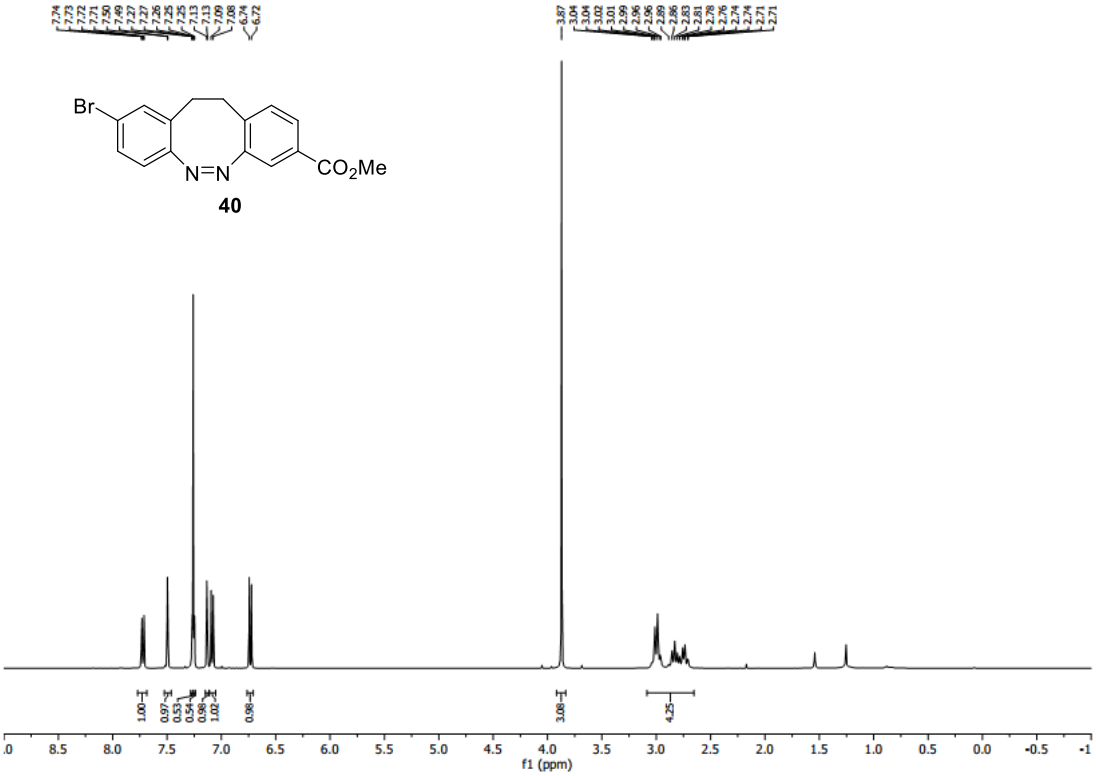


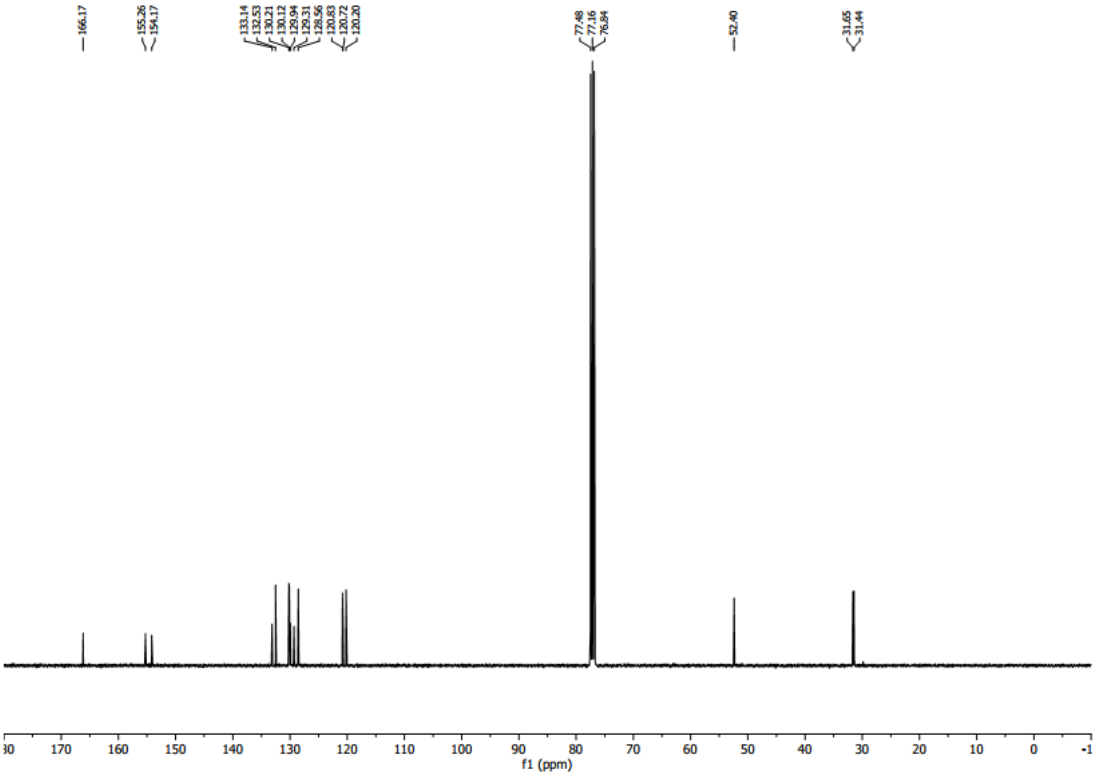
Compound **39** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



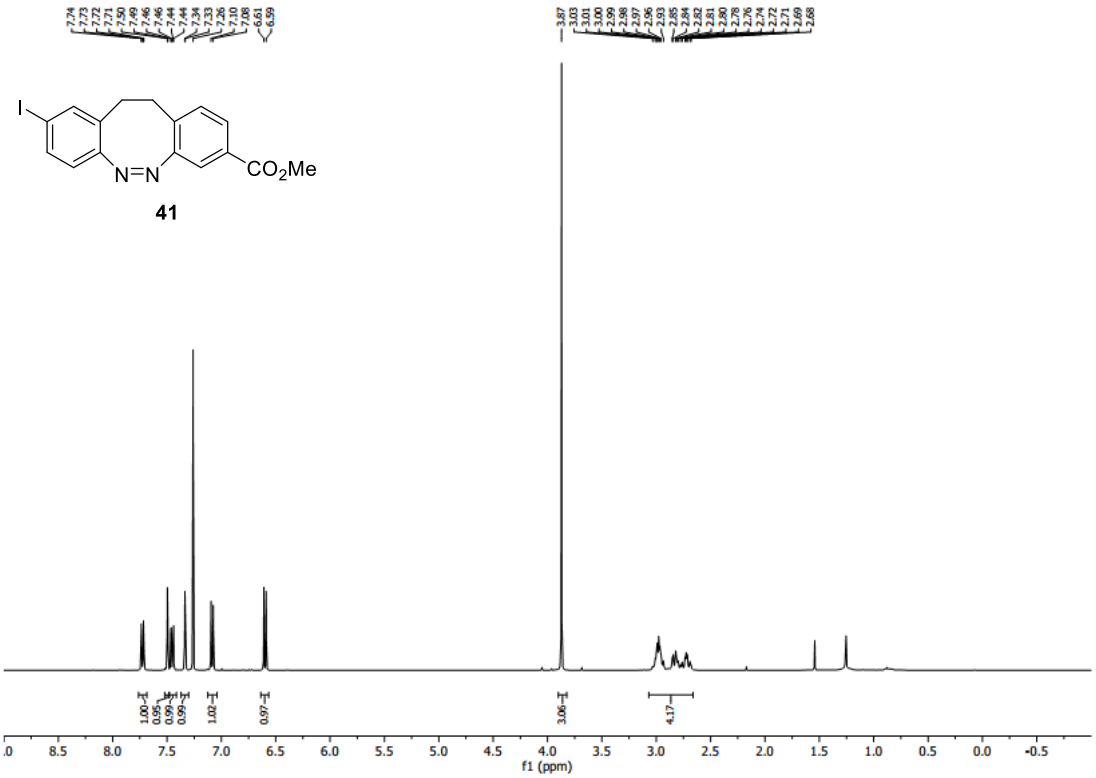


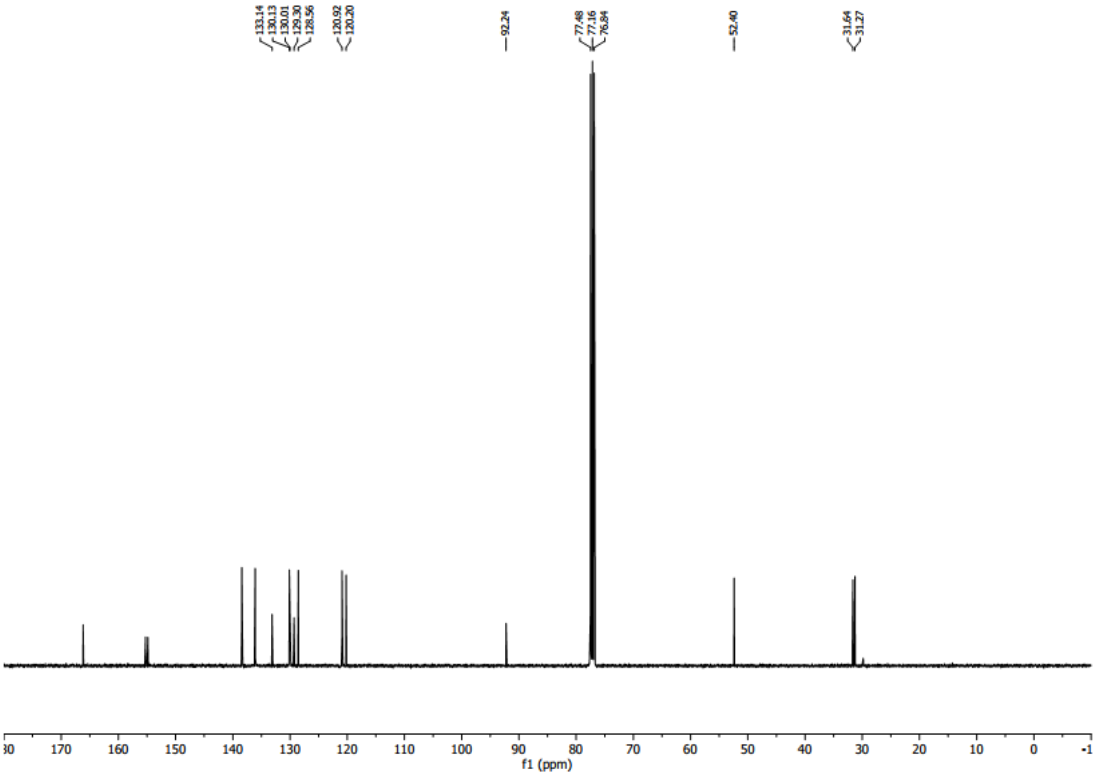
Compound **40** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



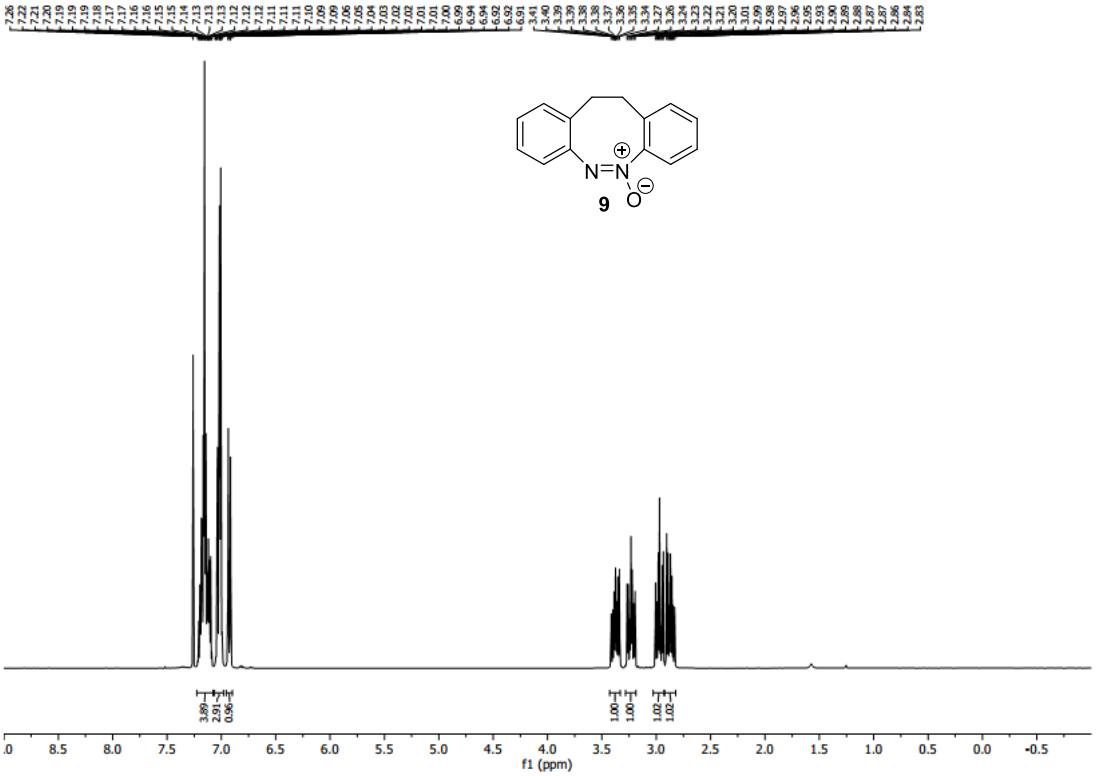


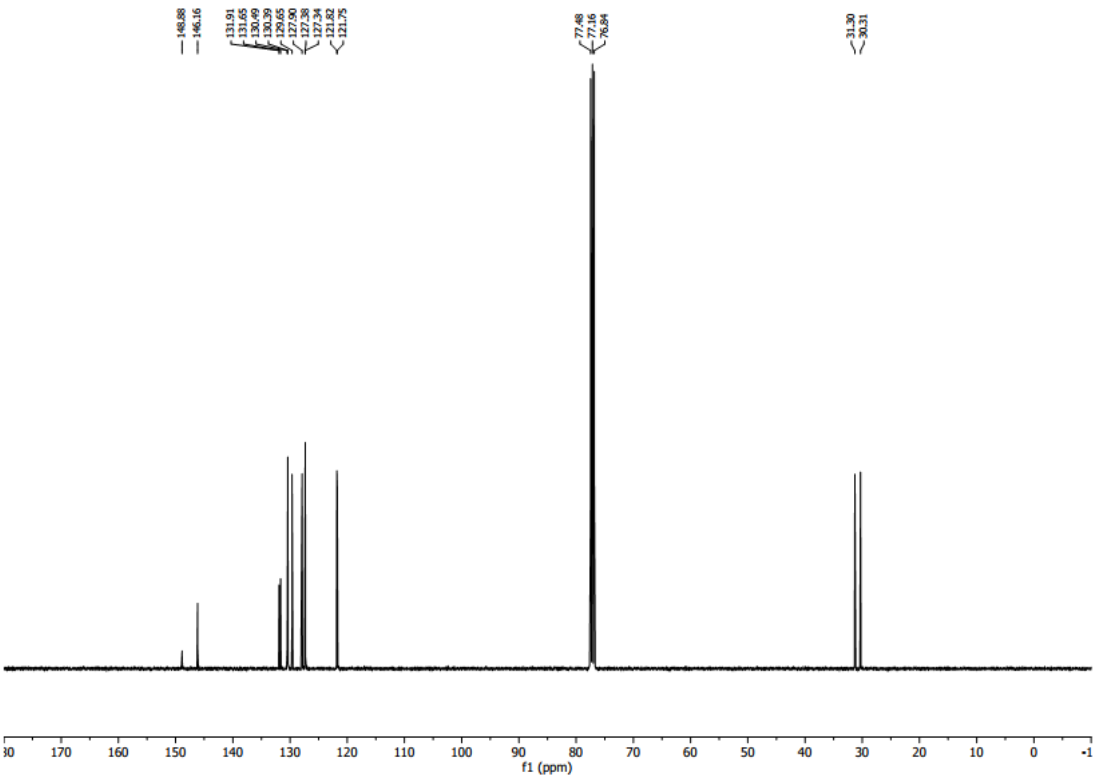
Compound **41** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



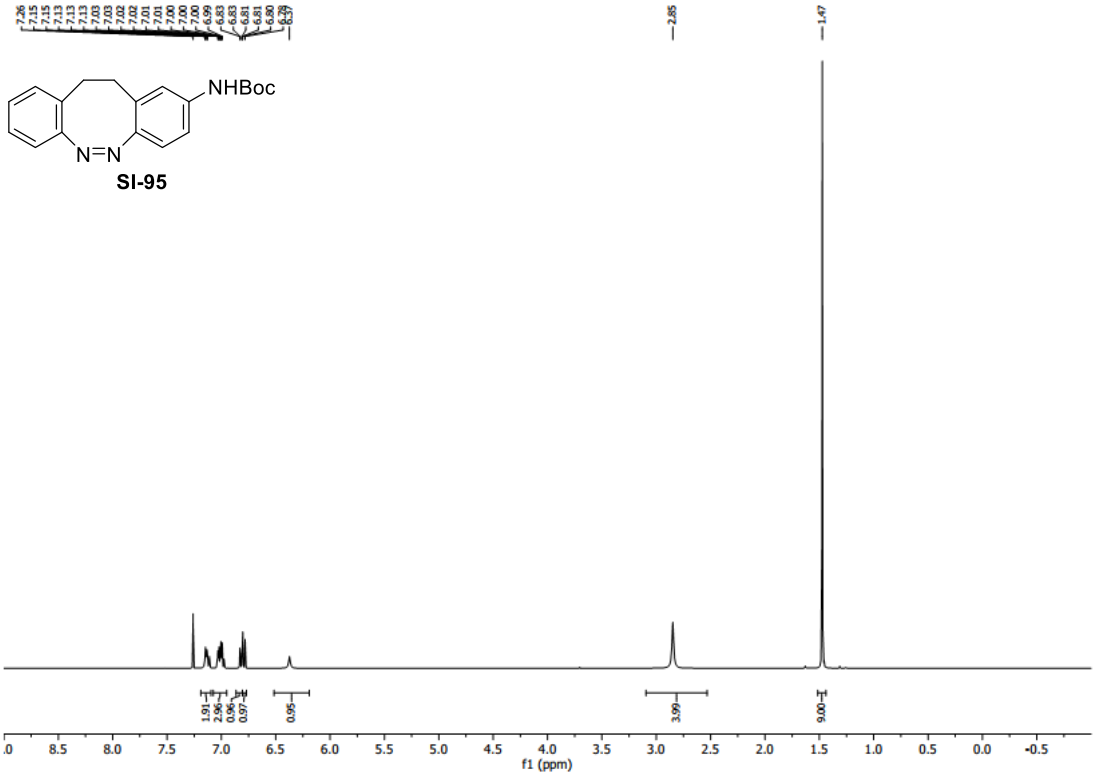


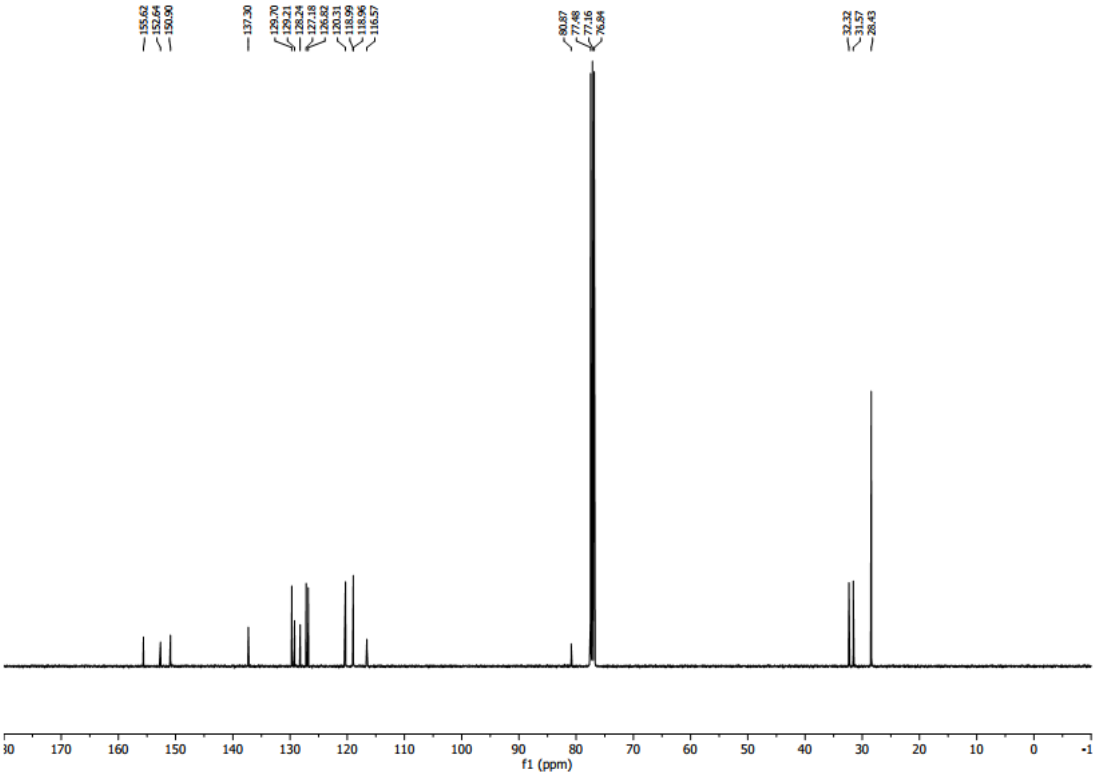
Compound **9** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



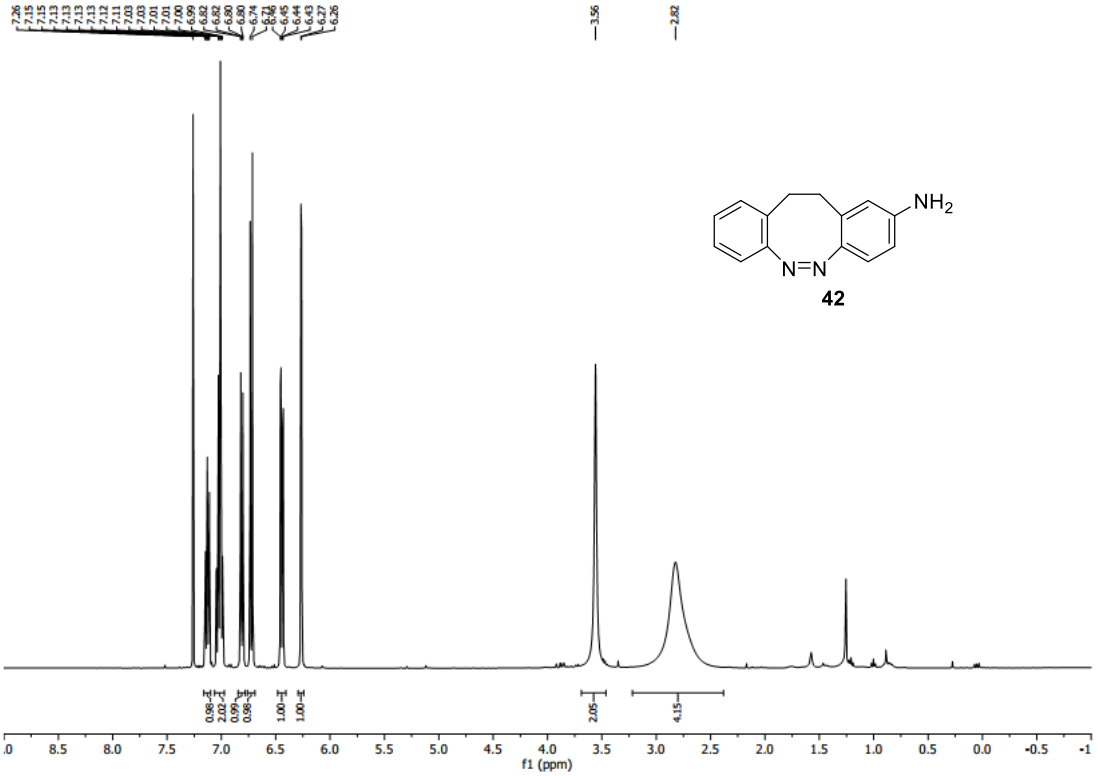


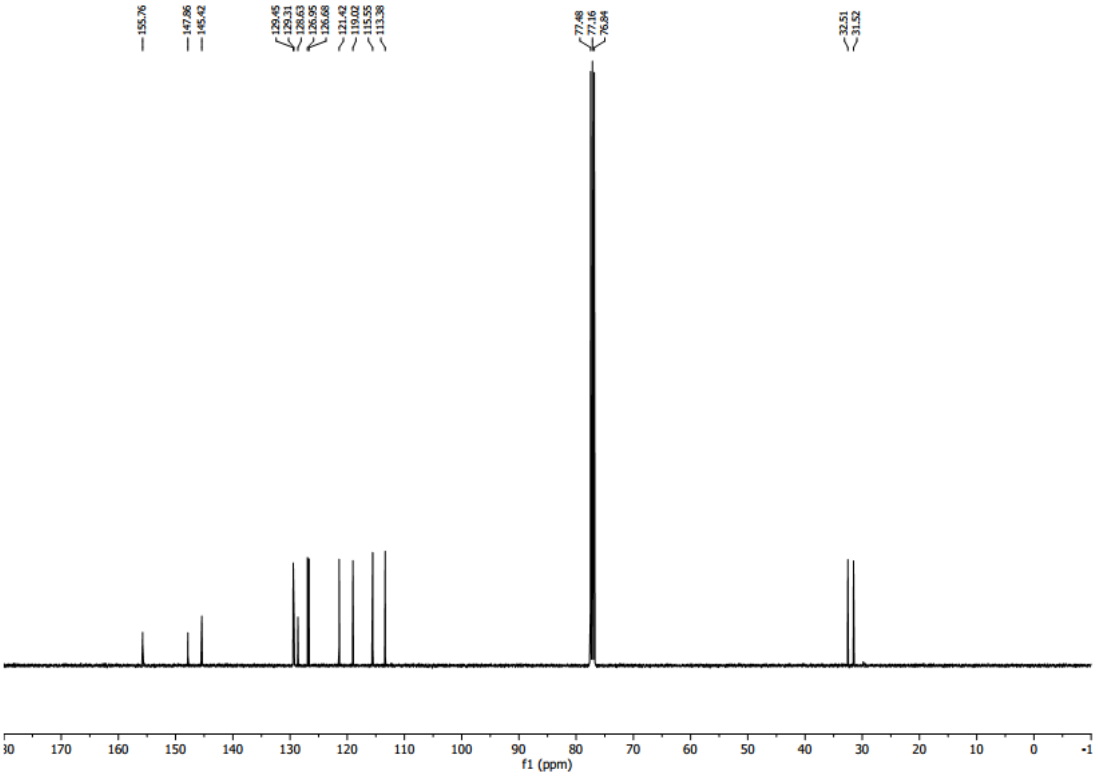
Compound **SI-95** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



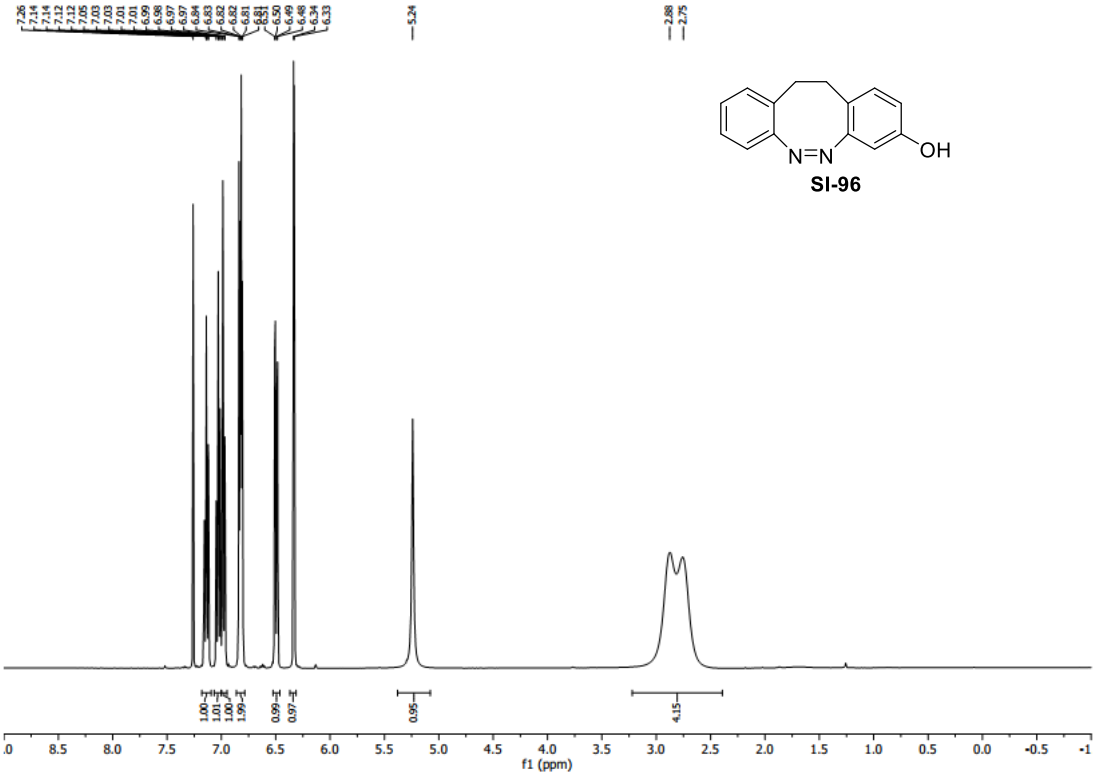


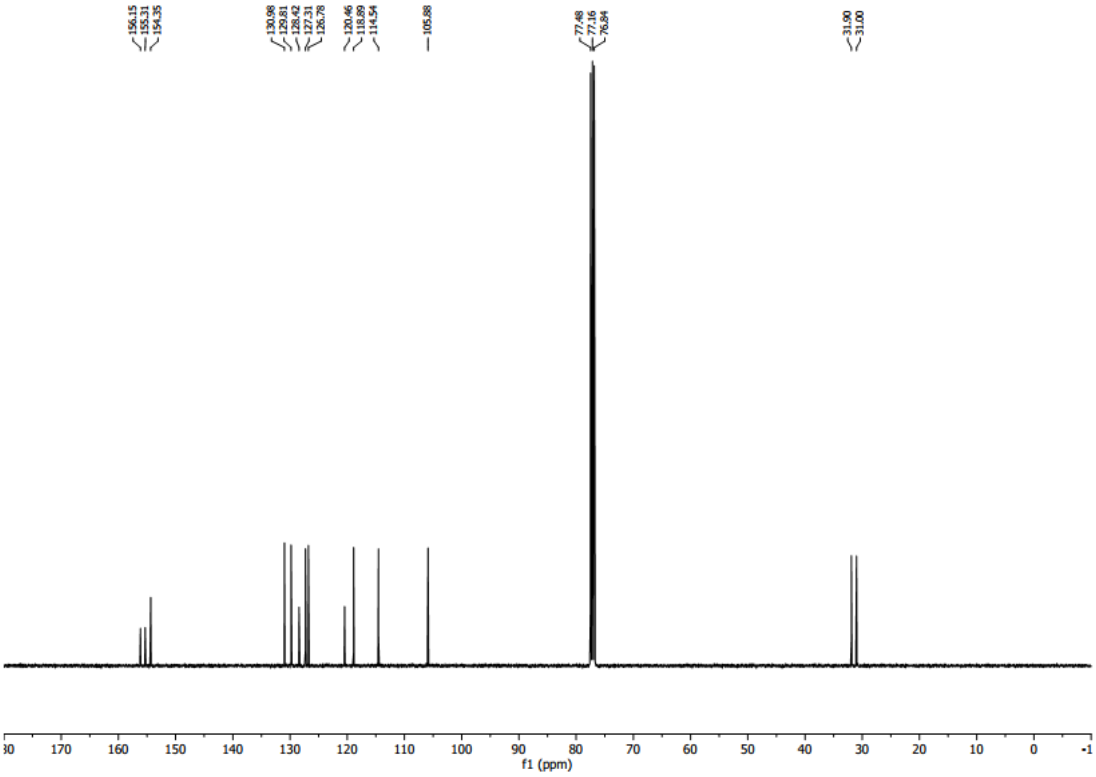
Compound **42** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



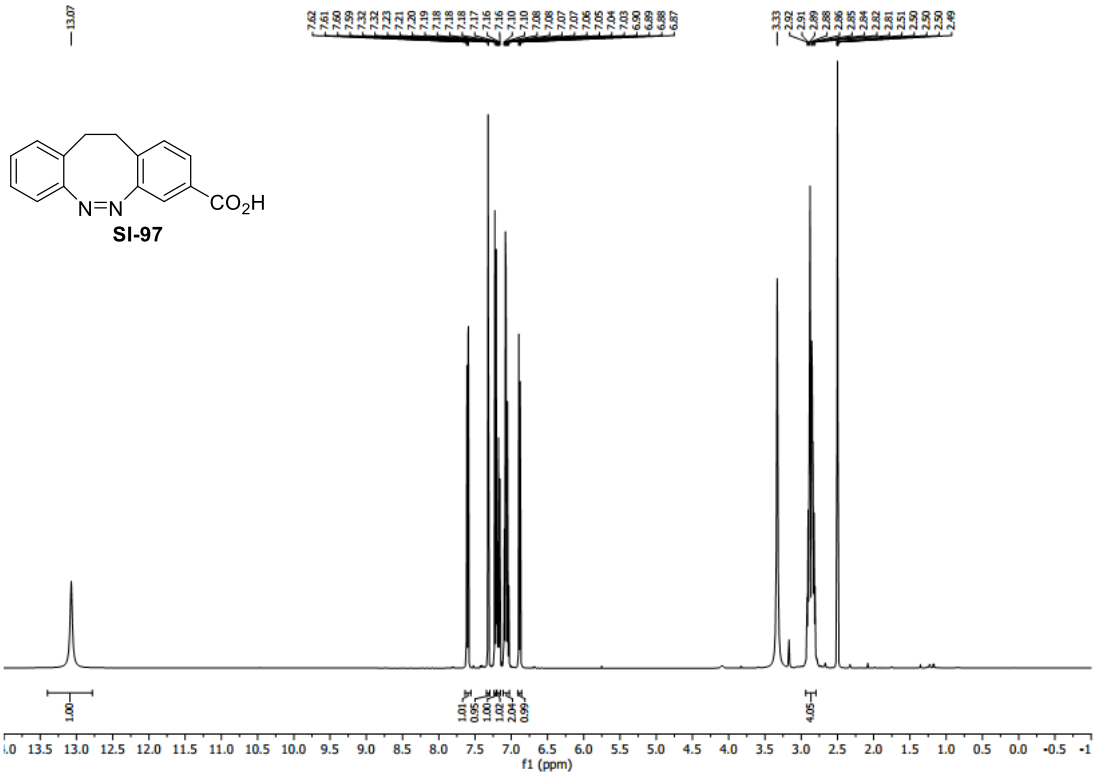


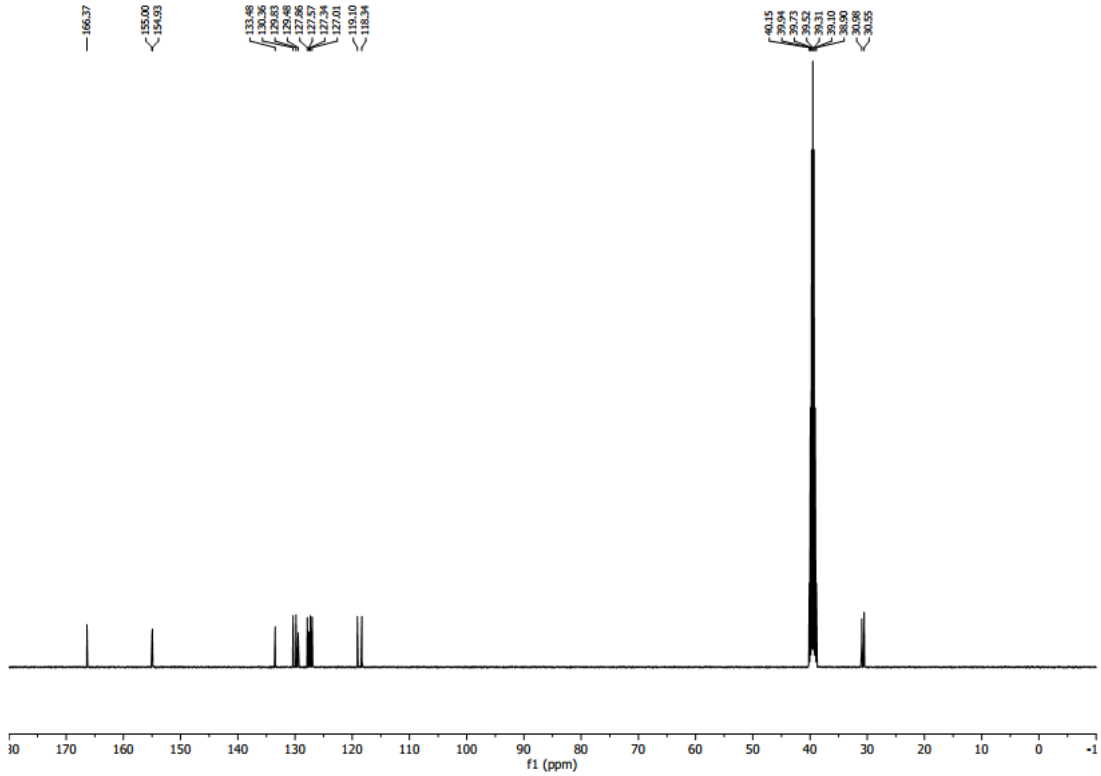
Compound **SI-96** – ^{1}**H-NMR** (400 MHz) and ^{13}**C-NMR** (100 MHz) in $CDCl_3$



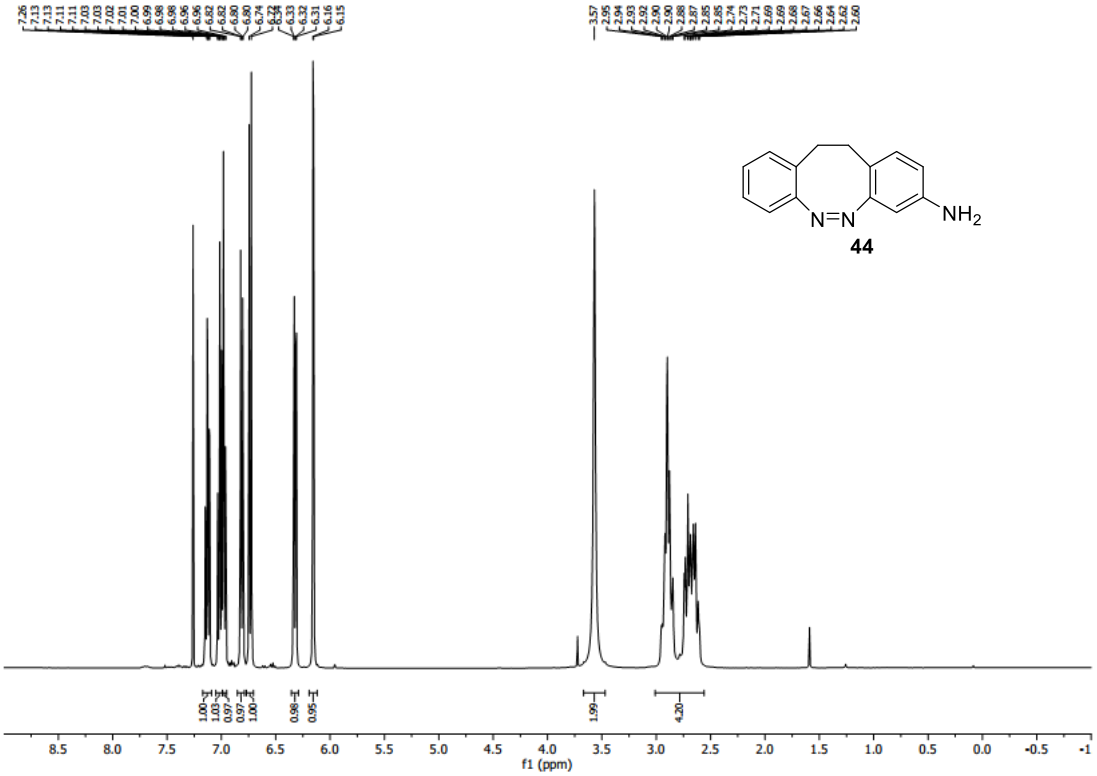


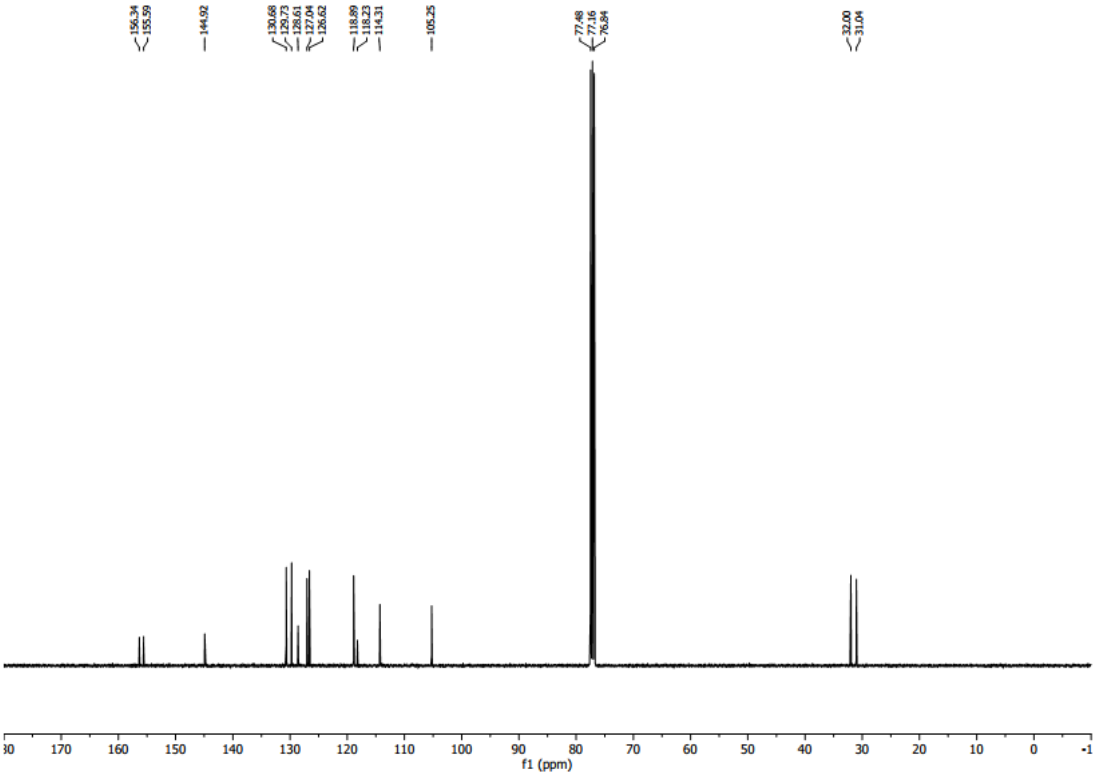
Compound **SI-97** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in DMSO-d_6



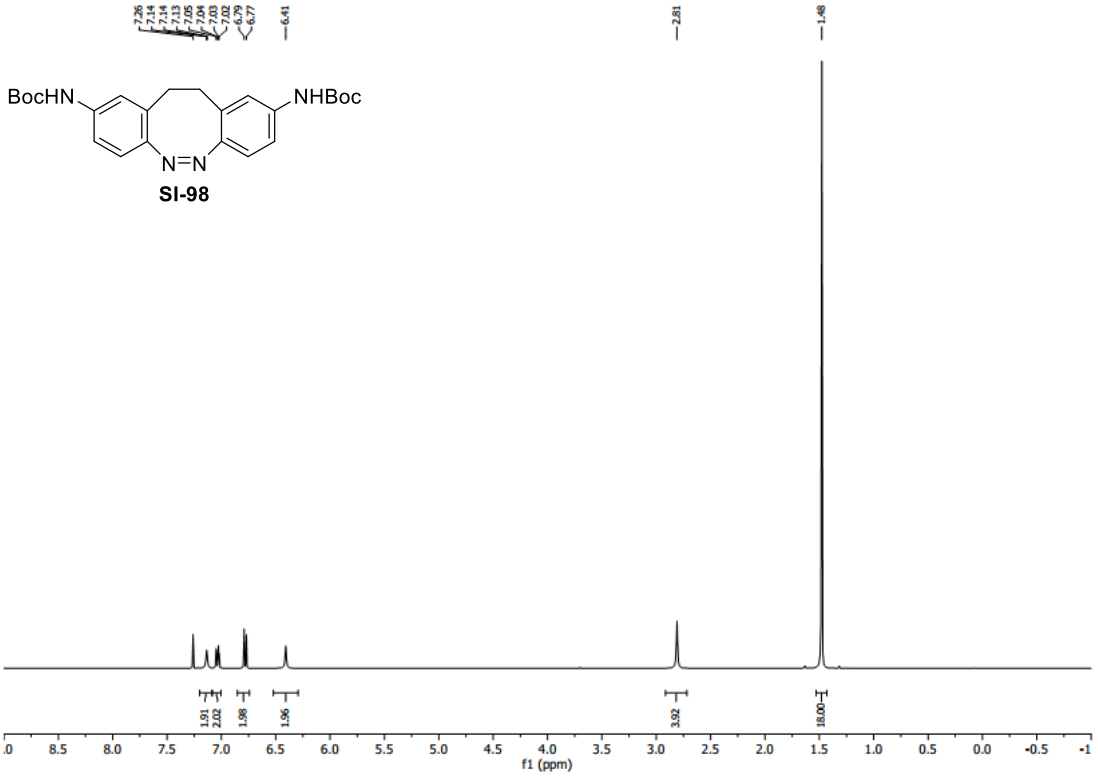


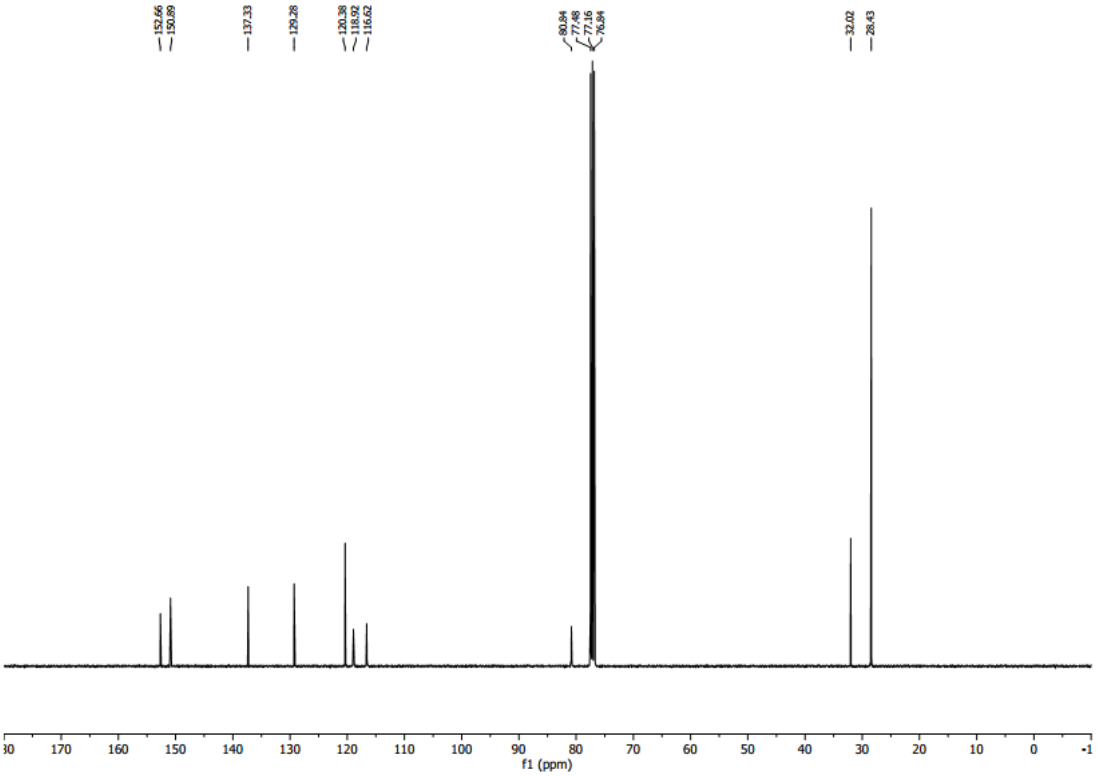
Compound **44** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



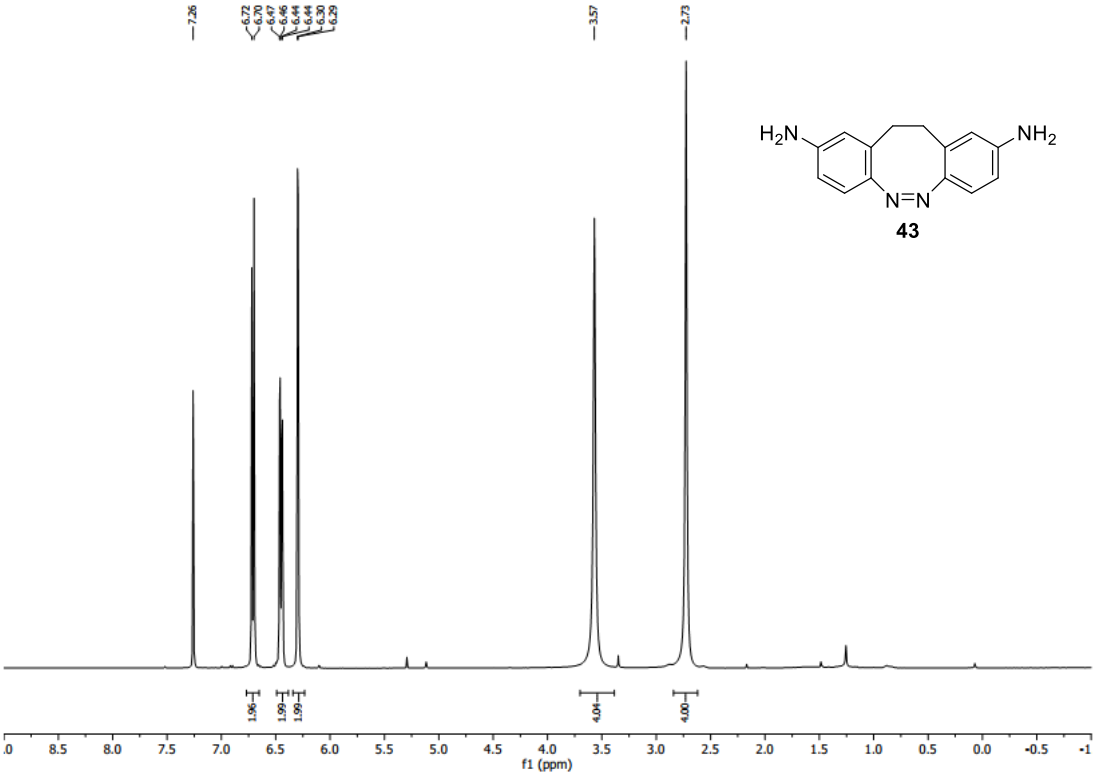


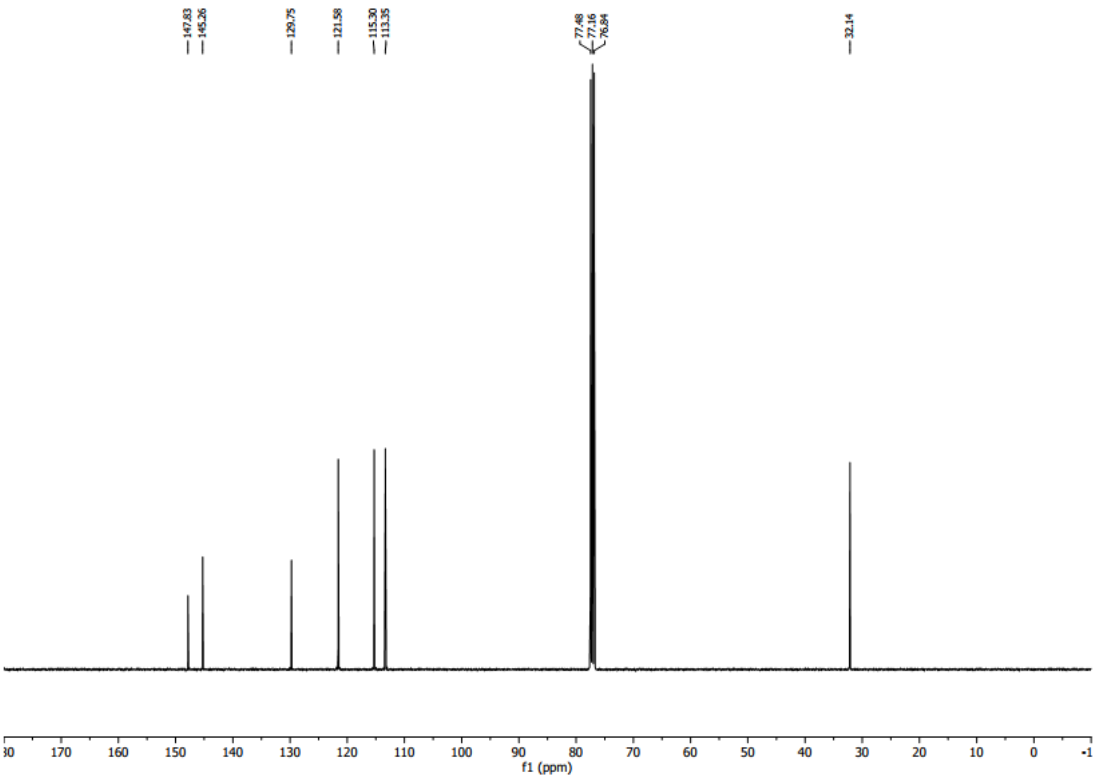
Compound **SI-98** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



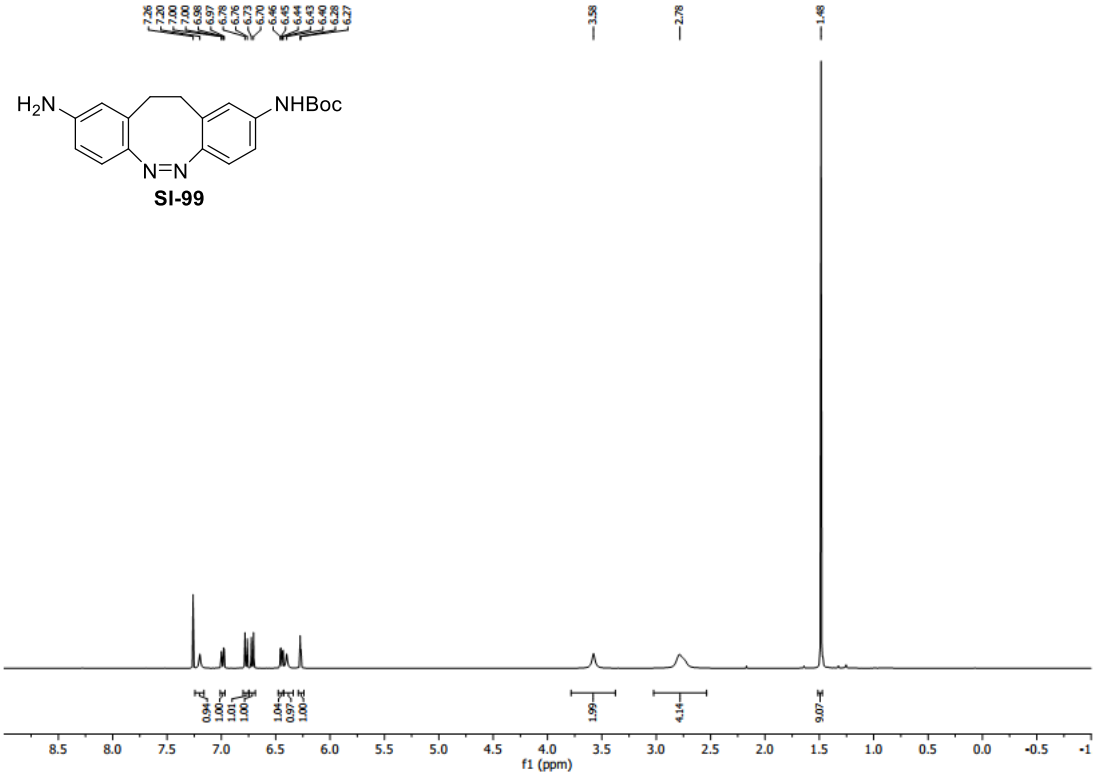


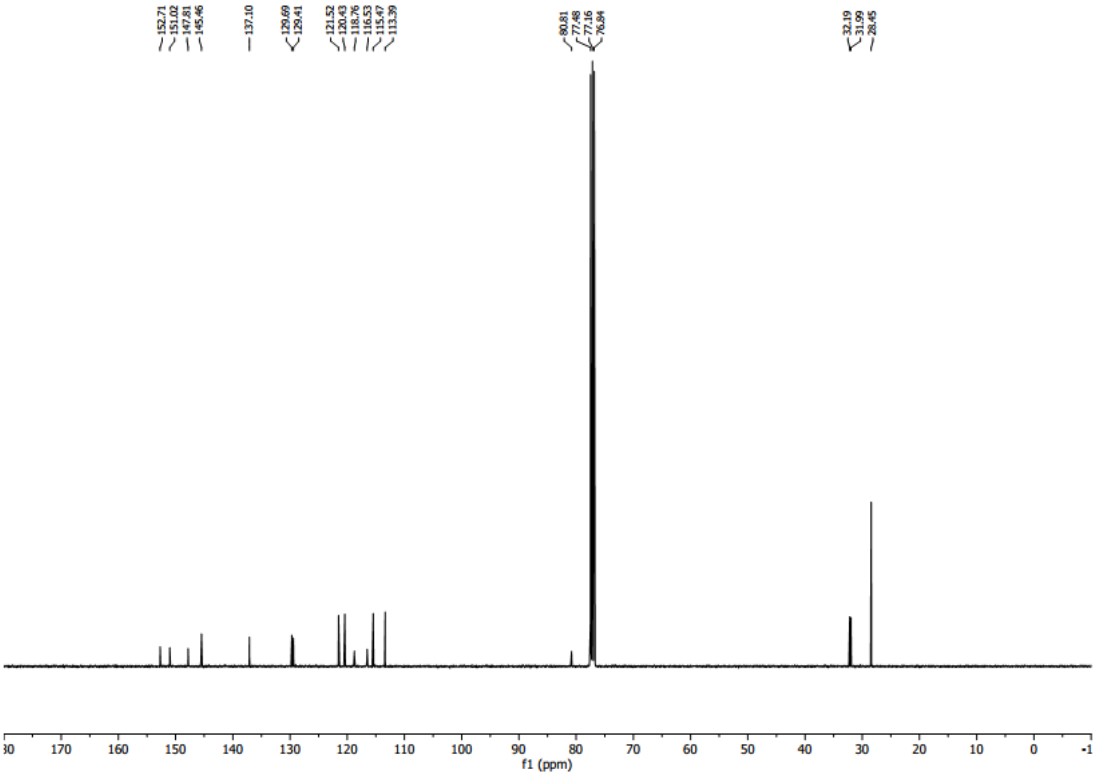
Compound **43** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



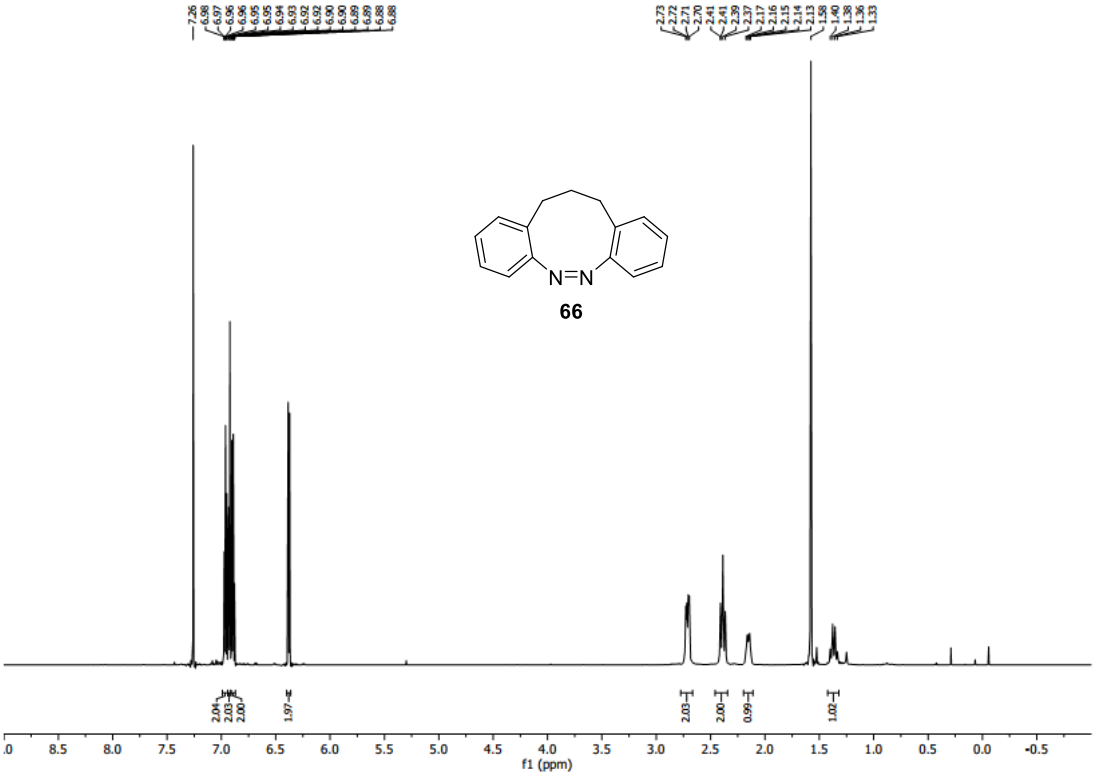


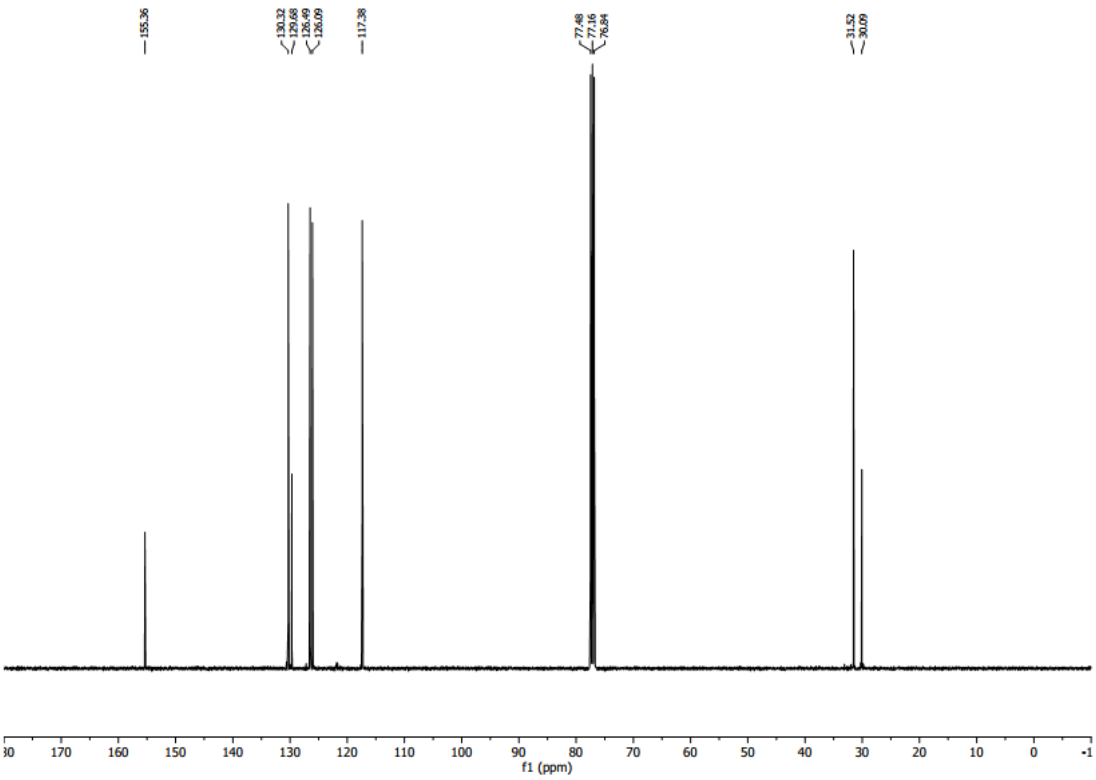
Compound **SI-99** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



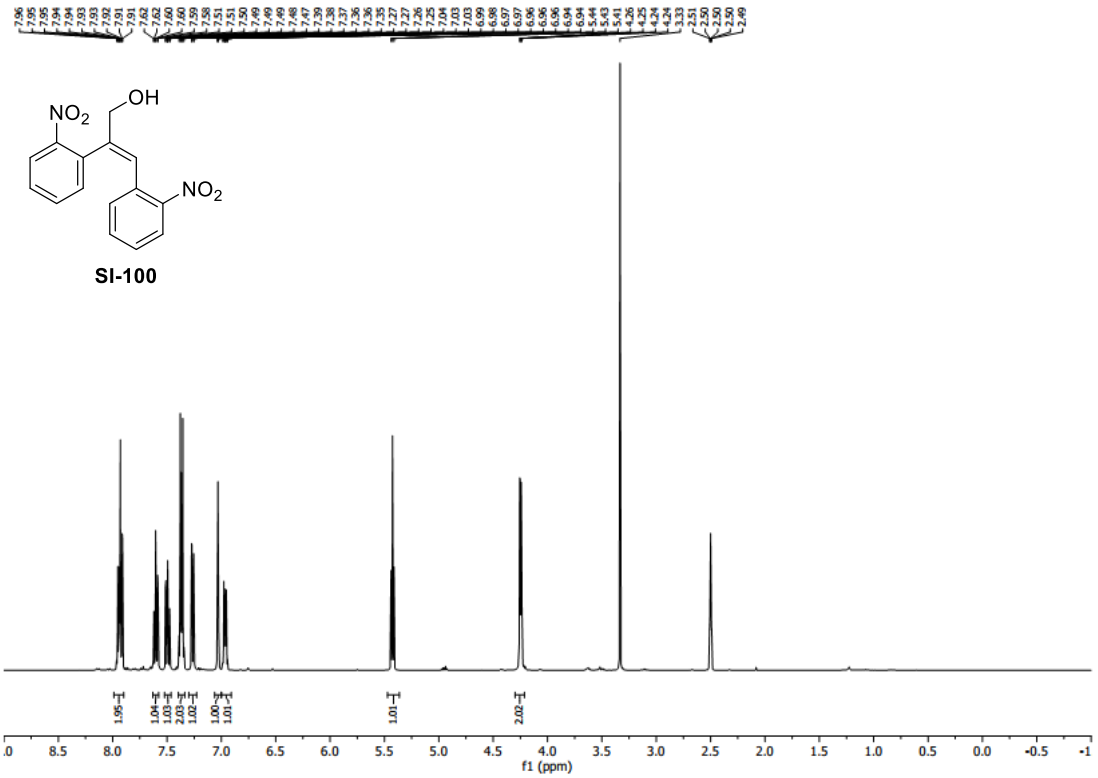


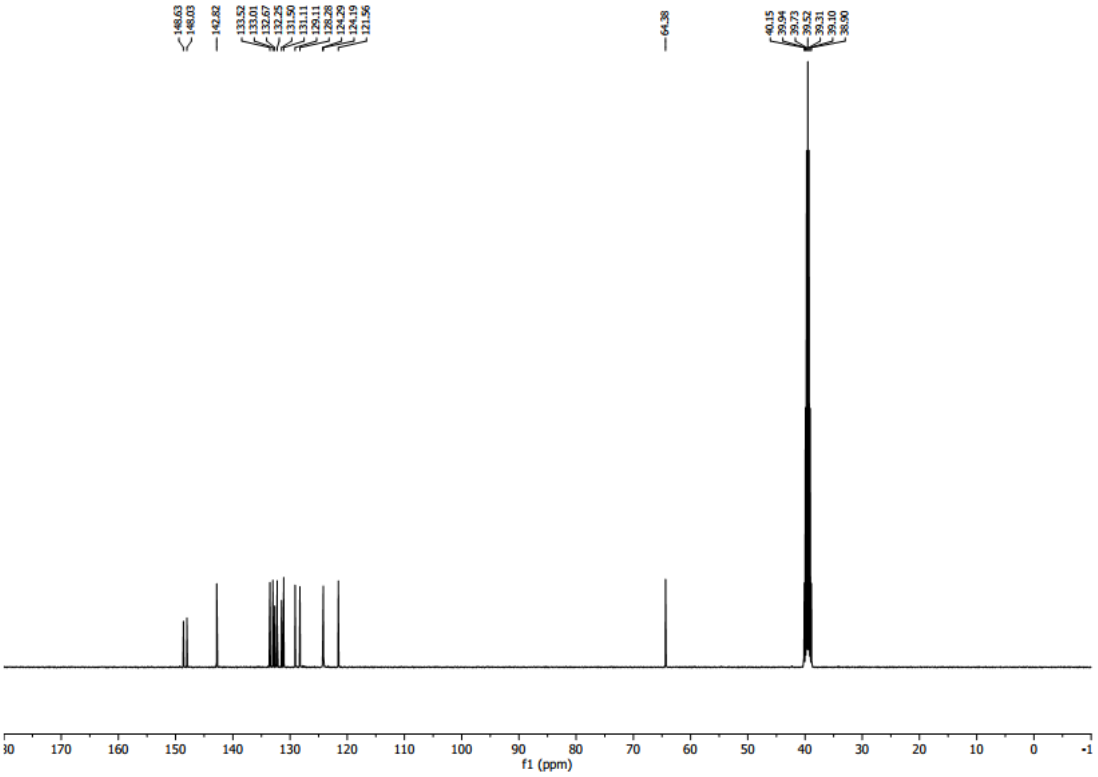
Compound **66** – **^{1}H-NMR** (600 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



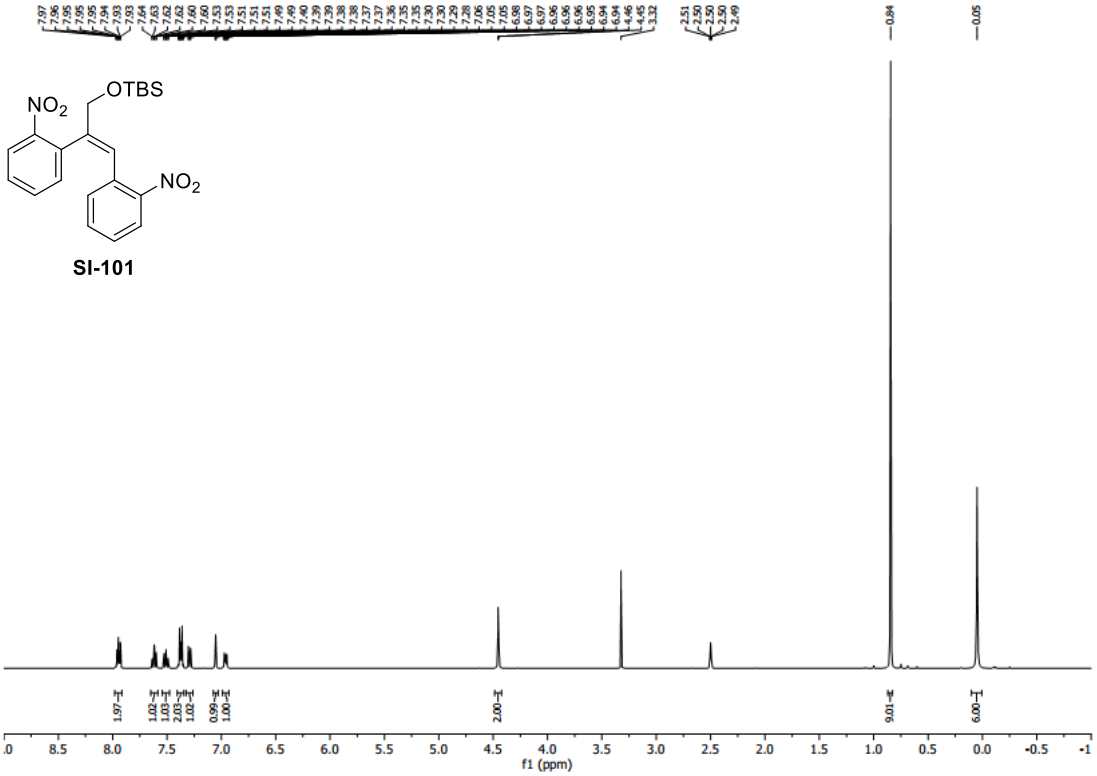


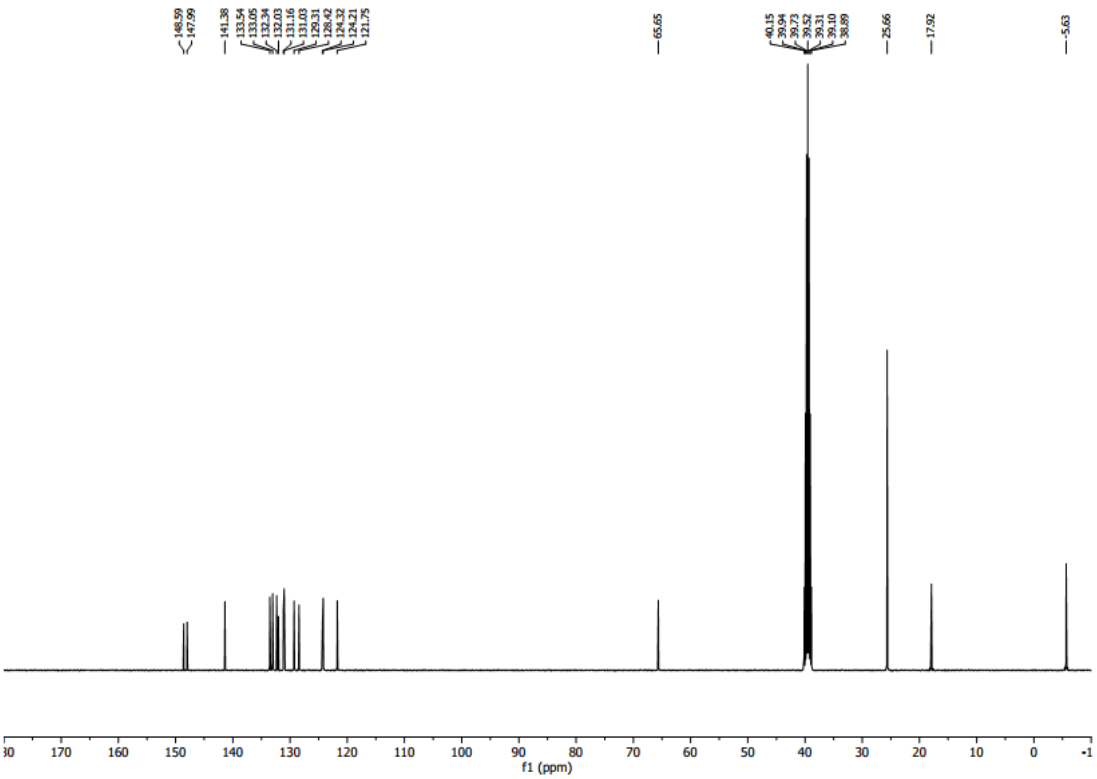
Compound **SI-100** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in DMSO-d_6



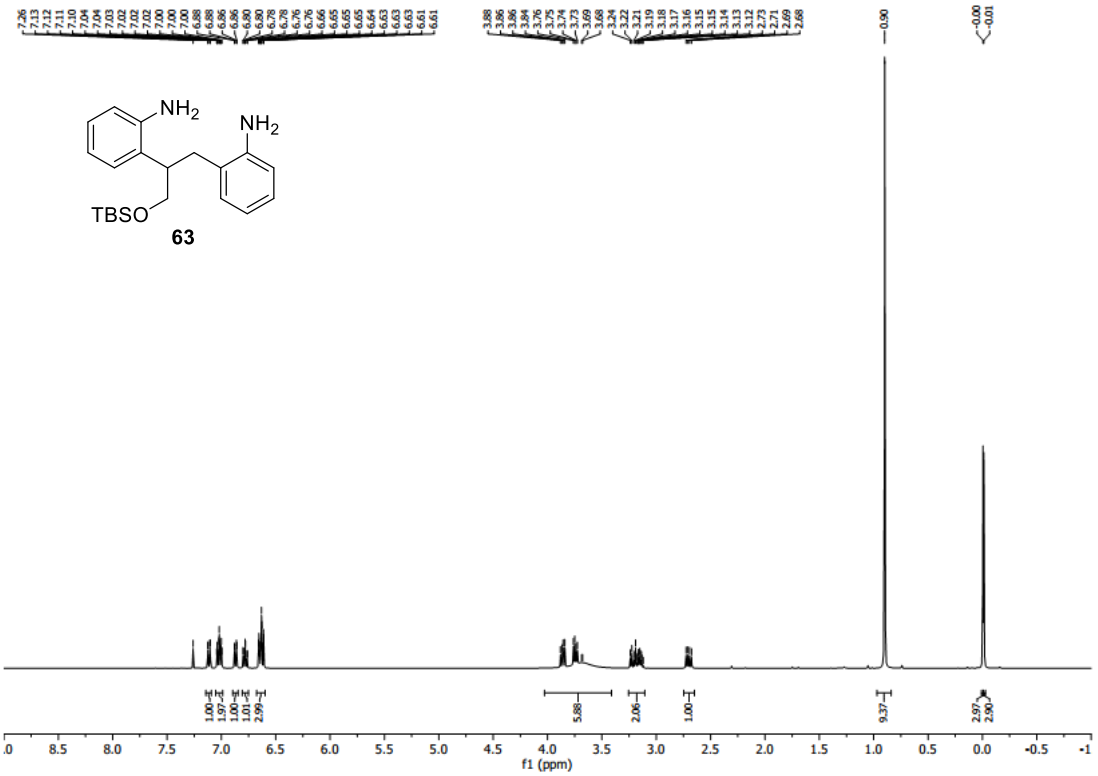


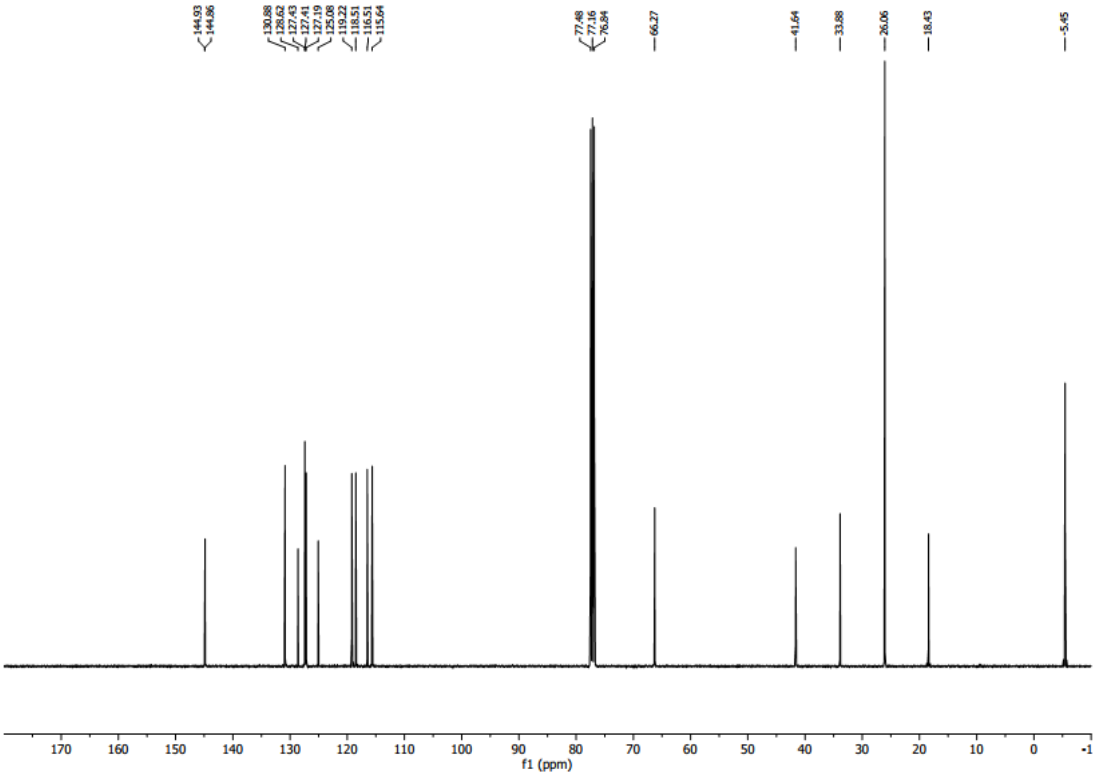
Compound **SI-101** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in DMSO-d_6



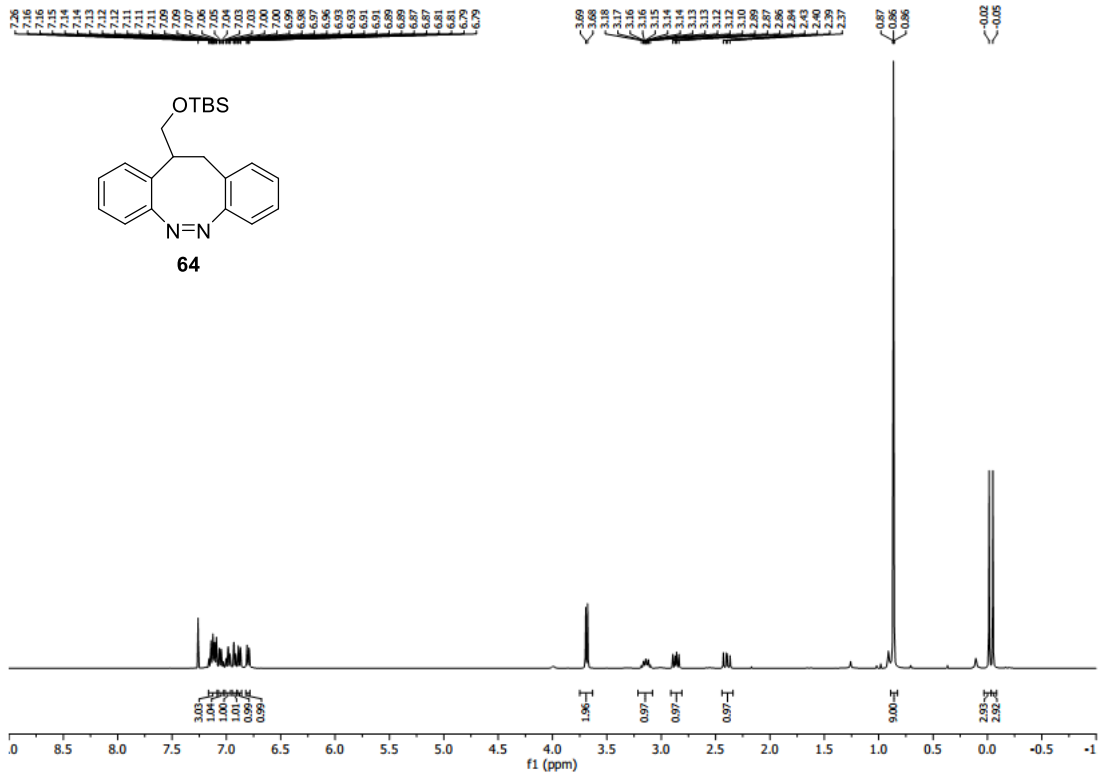


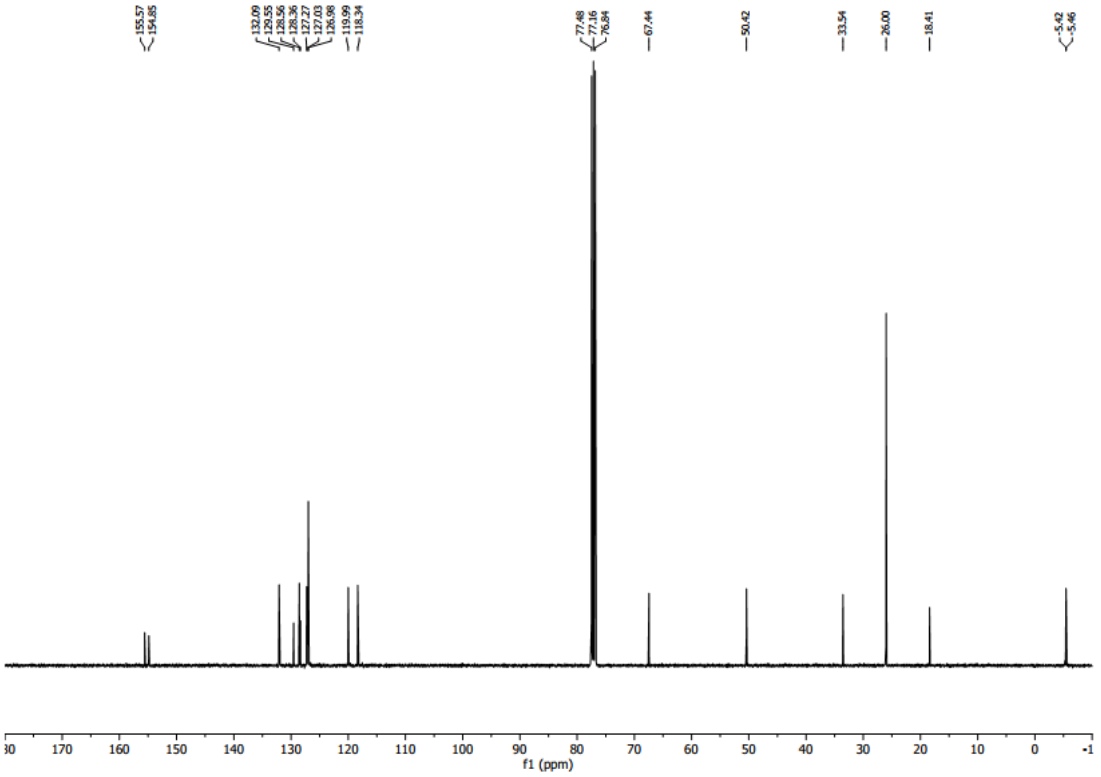
Compound **63** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$





Compound **64** – **^{1}H-NMR** (400 MHz) and **^{13}C-NMR** (100 MHz) in $CDCl_3$



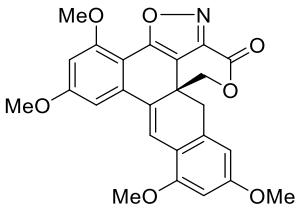


4 Computational structures

4.1 **Part I:** Synthetic studies toward A-74528

PBE0/def2-TZVP structures with DSD-PBEP86/def2-QZVPP energies (a.u.)

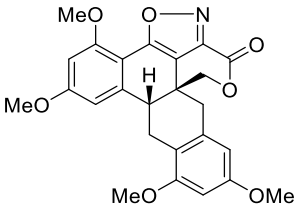
Compound **67** (−1544.709201458335 Eh)



67

C	1.05711836707722	0.88897811054529	0.54747205976019
C	2.11928925275188	1.06644161959864	-0.26269753358040
C	-0.11967632519442	1.78430434144321	0.50362867429463
C	-0.32503345485208	2.60289253138787	-0.60970837383382
C	-1.37246735079026	3.50715983859941	-0.63832788752562
C	-2.24838974791286	3.62461533467019	0.44026155402111
C	-2.07759798388907	2.80724450322813	1.54040322990500
C	-1.02737063278507	1.87231154673963	1.58220425320878
C	-0.87724714792207	0.87813982456829	2.61411400711912
C	0.11771702869283	-0.03478063731617	2.60790462141826
C	1.20067162719676	-0.18016307757107	1.62655402375697
C	2.60554213061143	-0.07994703612948	2.22567225538039
C	-0.34577020744696	-1.06412886593559	3.43089021497876
N	-1.48790463082611	-0.76106773254186	3.99911366058788
O	-1.81822479132311	0.47920122665338	3.49330176815787
C	4.82713431043377	-0.91542258029808	1.37482153131652
C	5.75852016650257	-1.01031724966648	0.34552020529798
C	5.51109325892065	-0.41881275129066	-0.89329076064997
C	4.32040667532202	0.25073719080266	-1.10716969547741
C	3.35476395641839	0.33685284984193	-0.08814046787834
C	3.63677679249984	-0.24243405620720	1.14960121535811
H	0.32982131723928	2.51203288948261	-1.46181930682210
H	-3.04833165097471	4.34775610008794	0.37768728277815
H	2.74210737836677	-0.83091865312286	3.00544589396594
O	-1.63162727123925	4.32397887844851	-1.67983565667697
O	-2.87688582493164	2.83369840876673	2.61846196764383
H	6.26452546456413	-0.51777624653868	-1.66155946548468
O	3.99434054153291	0.84060389871365	-2.27713531122969
O	6.93213911703724	-1.66491414028297	0.44544673179588
H	2.10698341328648	1.81386693640058	-1.04477220967777
H	5.00830057718524	-1.36523399551172	2.34135547096448
H	2.71706784864819	0.90413168870042	2.69706064208240
C	0.31924166498054	-2.38431258180436	3.38321778729818
O	0.29686732735165	-3.24215564763861	4.21046358936623
C	0.97404417233106	-1.62574760618938	1.13821771129002
O	1.03511886975441	-2.55455786528718	2.23759207504798
H	1.75287514504314	-1.95765931761986	0.45333223525017
H	0.00088031154956	-1.70672925131089	0.64687061681801
C	-0.77539311100139	4.26457676463117	-2.79605548825620
C	-3.99012191373407	3.69506422221990	2.60522468768182
C	4.93074956358549	0.79220660394085	-3.32688374643182
C	7.22440174535442	-2.31748971506369	1.65927977266731
H	-1.15102221737754	5.00011340451158	-3.50465153498648
H	0.25446224591514	4.51778152578658	-2.52334410712012
H	-0.79214248044591	3.27376421954573	-3.26167746610004
H	-4.50799908344100	3.52814194097995	3.54724077686344
H	-3.68317950708679	4.74397703430009	2.53992713670160
H	-4.66280867754660	3.46108644855161	1.77393028735043
H	4.48339471732324	1.33386583248231	-4.15817742241359
H	5.87234558661489	1.27439592135236	-3.04527647927164
H	5.13084135227102	-0.23929564851875	-3.63406589125195
H	8.19021777127498	-2.79885303368700	1.51848198507476
H	7.29256312295309	-1.60670749515540	2.48913805092359
H	6.47217119013072	-3.07699645229325	1.89475082854280

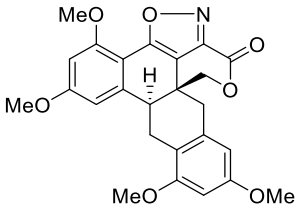
Compound **83** (−1545.928764597686 Eh)



83

C	1.18177875508534	0.72215545405566	1.01947714402924
C	2.57571317168020	1.20941717614492	0.67788988096620
C	0.07965353580122	1.78230008243016	0.99369943714799
C	0.31702537796106	3.04553104186419	0.47786326744626
C	-0.72018369626562	3.96912976268029	0.38910453110762
C	-2.01013748181096	3.63598256317412	0.79189846341768
C	-2.25674585678740	2.38047229457336	1.32102916959661
C	-1.21568962036593	1.44779763299661	1.44259234812383
C	-1.30998951935974	0.17740232827360	2.11935805400645
C	-0.20027086530771	-0.45139899205844	2.56151939132969
C	1.18576272108712	-0.00618484626466	2.37361488428616
C	1.63147966452532	0.95531913279709	3.47719743256978
C	-0.64873051362645	-1.65290239009502	3.09808950619815
N	-1.95662595866399	-1.75808350380560	3.02102988789676
O	-2.37404091327612	-0.59331173397015	2.40297052202751
C	3.45182874011011	2.50883052137869	4.14973344834518
C	4.50001891340428	3.36246593842459	3.85979697862711
C	4.93354018099456	3.52176594508668	2.54241626004876
C	4.30170707408057	2.82128975443563	1.53418887369951
C	3.22376196344455	1.96015381542834	1.80350923159816
C	2.81346876256927	1.81393604080783	3.11869516557380
H	1.31138834601864	3.31436404388978	0.15754893880236
H	-2.78600281757386	4.38223700450458	0.69915789266802
H	1.84068898683459	0.39010146772938	4.39007441762962
O	-0.56258094085491	5.22324691817561	-0.07878944065722
O	-3.45760506840241	1.97620178356138	1.76613647582131
H	5.76001053547809	4.19203481874709	2.35396085303388
O	4.65756365528341	2.91163290565448	0.22968215210615
O	5.17212437215011	4.08942588419661	4.78037585080898
H	2.57108561811167	1.81302072538050	-0.23059387140046
H	3.10538975325631	2.37065602544959	5.16531126736096
H	0.78986541186088	1.61520362060218	3.71519781465153
C	0.33925723157758	-2.60007202570374	3.65377400726978
O	0.11995422732892	-3.57165525875273	4.30815873695367
C	1.98819367208244	-1.30755355089616	2.35649828757299
O	1.62459156742532	-2.21308261285386	3.41286114014842
H	3.05486601851573	-1.13667313896696	2.50286145474459
H	1.84006703092429	-1.81658853072433	1.39773583584374
H	0.88496106294399	-0.02230674655533	0.26731505435589
H	3.19008615741236	0.33745422191035	0.42060220987482
C	0.73223404623851	5.63089460440709	-0.45787777416699
C	-4.54085324401911	2.87217133298094	1.67726725804072
C	5.73803279932873	3.74725215364173	-0.10524190655905
C	4.75687529785086	3.98840810857957	6.12085568815135
H	0.64100451672981	6.66775962687781	-0.77531342570300
H	1.43196708963271	5.56827056105313	0.38163315238949
H	1.11300208978502	5.03087744801662	-1.29064577346372
H	-5.40212374451318	2.34093154354672	2.07654642169017
H	-4.36245418016078	3.77379202984653	2.27202596396666
H	-4.73842363995509	3.15500695373191	0.63848087439270
H	5.85925274167544	3.66975703033380	-1.18426124956736
H	5.53737507209394	4.79003047428040	0.16272816098020
H	6.66063000610987	3.42293094140034	0.38680788583888
H	5.40698810417451	4.64905157100601	6.69144192462524
H	3.71713893160658	4.31060460861546	6.24191478928869
H	4.86162485776935	2.96564543797563	6.49789505446454

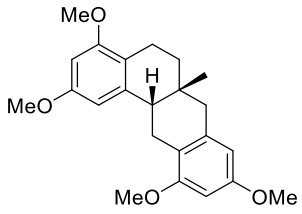
Compound **93** (−1545.913587827412 Eh)



93

C	1.21970417395105	1.18155895452607	0.80292323495156
C	1.99492513184585	0.94453513351747	-0.47859207676064
C	-0.11203299782459	1.89855384005341	0.67102986055757
C	-0.38464899547663	2.65263780022573	-0.46207354748317
C	-1.52601985649562	3.44642659179855	-0.51539406845210
C	-2.40314795147527	3.50427549199084	0.56214868871037
C	-2.14724804532815	2.74794311817181	1.69222500254779
C	-1.00833803465267	1.92619234410345	1.75594313457098
C	-0.77592890665429	0.94335332208862	2.78724722827381
C	0.23415866285967	0.04160401752775	2.73275210959282
C	1.26426088338482	-0.08457263120979	1.69047504051352
C	2.70823250984446	-0.17679847973344	2.19007781897160
C	-0.22704107949058	-1.03288236111243	3.50042171251432
N	-1.35817746549082	-0.76212337721080	4.10379312616004
O	-1.69650917979312	0.50306702807538	3.66973269325519
C	4.91466021327207	-0.83504933997668	1.22935996377678
C	5.81431089736733	-0.92184020794245	0.18164692122307
C	5.48462016718982	-0.40327289465198	-1.07113628852140
C	4.25098367413255	0.18967855608193	-1.25493014440842
C	3.32166608142618	0.29121357464643	-0.20567555495035
C	3.67271850489077	-0.22672328553064	1.03318196365912
H	0.29818506447140	2.62819886936342	-1.29695687913537
H	-3.27140332964390	4.14217815980094	0.48348627021394
H	2.84835526965514	-1.06283563061915	2.81214700555554
O	-1.86221328045849	4.20848556952946	-1.57540100041817
O	-2.94226388350978	2.73692915575886	2.77228787601049
H	6.20886146952793	-0.49396819343425	-1.86806882924528
O	3.84019258911193	0.70587827290099	-2.43787120360650
O	7.03217698132005	-1.50175695404018	0.26458603199047
H	2.17917902985120	1.88887194677811	-0.99597805684441
H	5.14596036664917	-1.24680843209512	2.20247377770490
H	2.91793820845593	0.68821160687223	2.82784179587516
C	0.37485916466586	-2.36863108627203	3.29680971076669
O	0.39683441150650	-3.28673187788365	4.05619469640103
C	0.88980336966454	-1.43991767358614	1.06868519485464
O	0.94762796239826	-2.48145788734371	2.06683831023191
H	1.59859273479883	-1.76369724195820	0.30735072612910
H	-0.11606447421988	-1.40708029524603	0.63946857242563
H	1.81485428168086	1.89945880907629	1.38702086092107
H	1.40889494401938	0.33696898658786	-1.18023534555325
C	-1.00405435799389	4.20865815922419	-2.69211487382311
C	-4.13299250672600	3.48747671245283	2.73676549778184
C	4.72096547113191	0.63356789356088	-3.53233075186618
C	7.40239933920833	-2.07095961840287	1.49714513673720
H	-1.45744621204822	4.87740093638017	-3.42106565076269
H	-0.00831035499582	4.58120896315622	-2.43050875518826
H	-0.91273954938050	3.20850150693458	-3.12781537175659
H	-4.63072115267779	3.30300705077196	3.68630102614845
H	-3.92652481231158	4.55786120345869	2.63602436398268
H	-4.78239995523218	3.16371148576604	1.91725616963237
H	4.20527862147921	1.10038346018453	-4.36969922674261
H	5.65147502215516	1.17549890718762	-3.33377074837017
H	4.95690040884731	-0.40477118672293	-3.78699482394771
H	8.39514662649294	-2.49281812635111	1.35148565274834
H	7.44328089433814	-1.31690374812774	2.29029310181043
H	6.71152325028526	-2.86719689910201	1.79339292063595

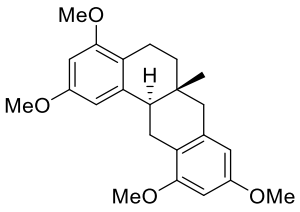
Compound **94** (−1192.704372736338 Eh)



94

C	1.43564820182246	0.31597012705492	1.14473548348519
C	2.34509245564200	0.60404893971712	-0.05674338150681
C	0.17975069174100	1.13300809293590	0.99077760863056
C	-0.85417281063800	0.63619892524005	0.19364705001475
C	-1.98627757412202	1.40081278382385	-0.02181979923737
C	-2.09952405878622	2.66312647159331	0.55909288582404
C	-1.07170166611073	3.13881746352244	1.35206976209212
C	0.09120722125848	2.38422686451088	1.58053171102408
C	1.15250422311966	2.93414101531091	2.49169168807986
C	2.41789840070058	2.08690670536565	2.56449492781227
C	2.12592626189090	0.58927530455571	2.48531242005600
C	3.41298855766557	-0.22569935053931	2.56022330272441
C	5.65335822406091	-0.47367952938652	1.49314103478780
C	6.48484993542759	-0.45337004841548	0.38932726154638
C	5.97958626483285	-0.10451608320959	-0.86350601920923
C	4.64244496845400	0.22106762925937	-0.98682393421625
C	3.77603493647482	0.19991101958296	0.12073749344401
C	4.30022756061033	-0.14899206556641	1.35239695270526
H	-0.74710342155840	-0.34676775752550	-0.24591743010876
H	-2.99987162761377	3.23176929987039	0.37488284081480
H	3.14550043399967	-1.27807715831275	2.72349257586659
O	-3.04196320875087	1.01223535802285	-0.77790871578496
O	-1.10761428350171	4.34708197836626	1.96468917885499
H	6.65920363174727	-0.09282141154804	-1.70369635464834
O	4.07321987024474	0.58388104378581	-2.16134422714932
O	7.80699602759427	-0.74991859539604	0.41859713737006
H	2.30398202249483	1.67551238151043	-0.28606993286316
H	6.02795390275011	-0.73663014059716	2.47357202240196
H	3.97985925183609	0.07767864487002	3.44722813553606
C	1.22952167084223	0.15531937757098	3.64021035212506
H	0.28108985700005	0.69371352008566	3.64881052734764
H	1.72863935702778	0.32802253665913	4.59830808022332
H	0.71698886089500	3.04301275407116	3.49217466020745
H	3.09836077385863	2.35614350458961	1.75192029088650
H	1.00420200112839	-0.91238161273275	3.56776106168784
H	1.16392850542186	-0.74669086959354	1.12221624095105
H	1.92640324322993	0.12048128104254	-0.94327470840032
H	1.40237569270010	3.95396220496562	2.18555654370732
H	2.95209741787867	2.30772385020942	3.49423260105571
C	-2.98180454342941	-0.25942529047899	-1.37185815576596
C	-2.24284785258829	5.15131147989432	1.76801482525272
C	4.88425888601431	0.60187154102181	-3.30887282644591
C	8.36525621817798	-1.10388115808337	1.65833241194639
H	-3.91183704955863	-0.38315686289985	-1.92438470857249
H	-2.13707212122396	-0.34068989808570	-2.06485870996107
H	-2.90197865638308	-1.05105169477306	-0.61861972402162
H	-2.07349929569468	6.06335935699773	2.33804263857331
H	-2.37604837722425	5.40495237879421	0.71082194362670
H	-3.15095927949271	4.66051808730707	2.13433429573941
H	4.23861349425352	0.89886800108797	-4.13368151549961
H	5.70141972982497	1.32471546830002	-3.21163336671447
H	5.30576242850863	-0.38739095320528	-3.51762904353240
H	9.41966757566049	-1.30251993275872	1.47358735184454
H	8.27416601433214	-0.29075065772231	2.38683659603113
H	7.89509105555394	-2.00443432066574	2.06864065936074

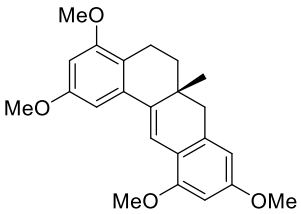
Compound **95** (−1192.704620019985 Eh)



95

C	1.03243158358195	2.61617688947865	3.63335105421049
C	1.91233446101924	3.83948437730486	3.40010526985468
C	-0.44832662627905	2.94126020725524	3.64777768615376
C	-0.87039056797137	4.18365358662096	4.13606526646585
C	-2.21569730966774	4.49717421928089	4.17880349095498
C	-3.16697505217316	3.58438074384209	3.72857109945624
C	-2.74356733728059	2.36151209491131	3.24634464456757
C	-1.38275333721814	2.01203655373682	3.20803991978845
C	-1.00415277159166	0.66254717134376	2.67221796262358
C	0.44941182972367	0.31930113218869	2.93126708813020
C	1.37882744073184	1.49224517106267	2.64781093949373
C	2.81750900216976	1.06907659734609	2.91663888115580
C	5.14908338874312	1.93826656241321	2.71337813413044
C	6.07122483582446	2.96730443535193	2.74621103524438
C	5.65323090806429	4.27723129178040	2.98124017417077
C	4.31103500531298	4.53260951667709	3.18545726999407
C	3.35620619925697	3.50065928604324	3.17392711929741
C	3.79485507349329	2.20921152741623	2.93195095598028
H	-0.13624358807495	4.89736702734289	4.47701818073332
H	-4.20940504086608	3.86659571067322	3.76734267271498
H	3.12989756703774	0.33215790948124	2.16876130396046
O	-2.71118557655266	5.67321466855151	4.63643784171221
O	-3.59438107046754	1.41716906088554	2.77565065457340
H	6.40104979922828	5.05724815753160	2.99166489835605
O	3.81892656158223	5.77574253186769	3.40852991401768
O	7.40327755319835	2.81195528588873	2.55444137680167
H	1.85097165758771	4.51897903835175	4.25305409651990
H	5.45245078113255	0.91811050180600	2.51782112218306
H	2.85818639905359	0.55357639751138	3.88537051711472
C	1.23675336192433	1.95182291962278	1.19814819700576
H	2.00699912568365	2.67945812788792	0.93626753799985
H	0.26368614655899	2.41153434693715	1.01514382489590
H	-1.21669027007384	0.63181545441397	1.59686833883198
H	0.57670072135382	0.02770518938063	3.98064136806682
H	1.34263345609944	1.09918802485599	0.52144971617487
H	1.28250608805818	2.22582729043234	4.63140614757330
H	1.52928964509505	4.41469603087994	2.54829494618842
H	-1.65596838848663	-0.09791237703666	3.11028267904504
H	0.74427973190800	-0.54466920464425	2.32593300401303
C	-1.79058303849185	6.63592608892503	5.08278318615717
C	-4.97008882936490	1.70033249663486	2.79686571770013
C	4.72818759240931	6.84696780591421	3.43707923395955
C	7.88300124144437	1.50786765571441	2.34630402766015
H	-2.37801740847161	7.49730442811348	5.39672134772593
H	-1.20523747564281	6.26933077337456	5.93339551894902
H	-1.10536657931978	6.93806350900490	4.28315241212535
H	-5.46754072444523	0.82564643897863	2.38090125849200
H	-5.32939985879366	1.86897273224194	3.81780975084624
H	-5.20884718362902	2.57661485732142	2.18471815492615
H	4.13931633000358	7.74202144328225	3.63086643304119
H	5.46956298275675	6.72274079198089	4.23374333060424
H	5.24791499910526	6.95662527753267	2.47927667501961
H	8.96372362374676	1.59299090255363	2.24526115579982
H	7.64957891057565	0.85498689948027	3.19452888388073
H	7.46917403139715	1.06739444227128	1.43250658295762

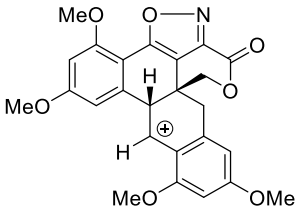
Compound **96** (−1191.492496593007 Eh)



96

C	2.29586304461822	2.24652167093573	0.25614740139516
C	2.62142974877952	1.12270044485637	-0.41056113612219
C	1.15095563819309	3.09648007535764	-0.10873923055973
C	0.29086311664901	2.71587093968669	-1.15528229183913
C	-0.80712406800250	3.48255422396134	-1.47406809577862
C	-1.09181761928967	4.64869001185503	-0.76065697485344
C	-0.25276776392239	5.02036522889311	0.26873096898132
C	0.88279512539634	4.26350671997266	0.60793652273420
C	1.75162488335734	4.73897358355601	1.73139429223252
C	3.12273751956418	4.10371864999172	1.68833621181268
C	3.06330861125828	2.58977780620266	1.51983007471491
C	4.49556860539856	2.06959166184287	1.41811717051940
C	5.57364187250942	-0.20778431979627	1.46410304377251
C	5.65426923251115	-1.50273869427344	0.96967070195489
C	4.75854164501269	-1.94456610356999	-0.00347275340951
C	3.77628477905756	-1.08956044249292	-0.47106334725202
C	3.66569468431517	0.22235633530535	0.02803338618723
C	4.58533455247996	0.64208936656155	0.98556235535172
H	0.48394539916638	1.80407838230895	-1.69750573926718
H	-1.96767800084364	5.21877718875072	-1.03494089177881
H	5.00642426493041	2.21485960174609	2.37482442084473
O	-1.68818478666376	3.18402055170518	-2.46059406539089
O	-0.45717861559412	6.12656387950133	1.02523294473064
H	4.85819932399362	-2.95946162432063	-0.36103666540351
O	2.86757812527028	-1.44700392968137	-1.40698427393000
O	6.56884239864425	-2.41485160179145	1.37218367262395
H	2.06321613332324	0.81299855661242	-1.28329637419245
H	6.26726774653494	0.15487008659139	2.21089409520122
H	5.03044442060683	2.68066336338317	0.67780303081268
C	2.35067499790526	1.93373914190843	2.70655556627020
H	2.83088793063879	2.21656006673175	3.64868437105864
H	1.30163387293733	2.23052403370473	2.75149695554892
H	1.83752903180300	5.82709075854067	1.68782086822382
H	3.68281122968840	4.34702184247374	2.59737931013456
H	2.38560118821728	0.84613502894433	2.61603616863052
H	1.26220410175940	4.52855827132447	2.69038833119016
H	3.68493386380902	4.51973054530419	0.84496304957891
C	-1.46585286178606	2.00890740138006	-3.19731807151573
C	-1.56941864023816	6.93084677013735	0.72654555469371
C	2.94747553308379	-2.74227075814374	-1.94678555792438
C	7.50669799265083	-2.01646481833120	2.34098686251672
H	-2.26732864039255	1.95320311349266	-3.93222795941577
H	-0.50164844650128	2.03474225008929	-3.71692933120761
H	-1.50072419052750	1.12090409652966	-2.55648746982761
H	-1.54753365163350	7.75657319981676	1.43591085173224
H	-1.51590539255151	7.32814276490103	-0.29280426345624
H	-2.50754623689101	6.37814648099407	0.84519467436289
H	2.14984737486195	-2.81464439419663	-2.68423325612431
H	3.91078182281609	-2.91310640694114	-2.43900272625779
H	2.79748491081338	-3.50690923419773	-1.17726734134438
H	8.14048351285583	-2.88205009769173	2.52605266063955
H	8.12488446685721	-1.18635235867767	1.98256374679576
H	7.01814621256967	-1.72178931174524	3.27587855160492

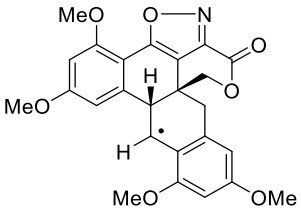
Compound **97-cat** (−1545.066773698803 Eh)



97-cat

C	1.12923918271832	1.06078224682012	1.14076366510078
C	2.37645698155979	1.84106933954726	0.96506376166012
C	-0.12737711484130	1.94110871557871	0.95108903790732
C	-0.03544275054982	3.14690207965120	0.27187362517488
C	-1.19423572623534	3.87641069443945	-0.00210165009947
C	-2.44014930619199	3.40949305597603	0.40385915893424
C	-2.53730466393344	2.21403078913385	1.09392548601607
C	-1.37968956516024	1.46500670856627	1.37761441317067
C	-1.35849446973992	0.24328752498723	2.13713943592126
C	-0.21043991744258	-0.25384523944357	2.64330131734098
C	1.13900750537706	0.28787426366430	2.47246854909529
C	1.54368968177997	1.24003646705115	3.60401702885395
C	-0.55903161502163	-1.48147795787333	3.20545667133896
N	-1.84399322513228	-1.71285046752335	3.08696118201102
O	-2.34812782685630	-0.61795553169976	2.41236596863386
C	3.76940908312418	2.08725213564751	4.34040264229624
C	5.00785061763765	2.71200477008969	4.03940264078420
C	5.34046269842794	3.11230496348189	2.73439438621567
C	4.45923467276770	2.87668199742949	1.71381533266073
C	3.20002227783879	2.19769227362195	1.98143427218981
C	2.87527802956982	1.85074348707679	3.34646922267721
H	0.92080591099102	3.52076640566111	-0.06346406456035
H	-3.31016870492486	4.00515793738259	0.16789900901208
H	1.53357170216558	0.72309932486425	4.56456727594977
H	6.29446187174871	3.59586030443699	2.58324475506322
H	2.67023102943941	2.11171302367414	-0.04371505446165
H	3.53430516650573	1.80331201734203	5.35665231992794
H	0.79760110881631	2.04291200006593	3.65855208610702
C	0.49197260915894	-2.32128448141502	3.81611180619429
O	0.35652972799790	-3.27306946970452	4.51026452351727
C	2.01613310576038	-0.97183154265647	2.45192067663555
O	1.75009045045086	-1.82187731036628	3.56685599554781
H	3.08257155760512	-0.75074702307744	2.52071010205469
H	1.83521301688946	-1.52059975470017	1.52161577097749
H	1.08760301935487	0.32385627310768	0.32450648022603
C	0.01640543284766	5.56384153501833	-1.14070522767360
H	-0.23295039809597	6.49356894762413	-1.64668378113934
H	0.70968705314887	5.77497683550714	-0.32010674086585
H	0.48487231761756	4.87991656857524	-1.85542245944096
C	-4.88670110689414	2.39514762736570	1.29880937830190
H	-5.67172849626771	1.79847022309076	1.75613156176093
H	-4.86572194180837	3.38721513915382	1.75828431411707
H	-5.07568273051406	2.48679848520288	0.22585948584663
C	5.89222474999297	3.83222434456056	0.09147069317732
H	5.83817660137841	3.98101397023704	-0.98302199530622
H	5.99432908180395	4.79504900411132	0.59593401422918
H	6.73535684914335	3.18256899515435	0.33432175413705
C	5.71335755680566	2.61362085866203	6.31387522867762
H	6.60959792767206	2.94558743255211	6.82933047201323
H	4.84180983181329	3.13277499839864	6.71489542994766
H	5.60371382095370	1.53336725437669	6.41769248655724
O	-1.20305494555974	5.04337595091779	-0.65995658924112
O	-3.68017387278547	1.69616094781758	1.54332887446614
O	4.66257517192183	3.20858652069567	0.45706694837262
O	5.91752097517032	2.96461434014051	4.94135832198753

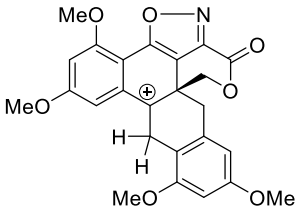
Compound **97-rad** (−1545.278124730801 Eh)



97-rad

C	1.14617694944666	0.93358457373195	1.09435839722775
C	2.44310379158337	1.62615765913507	0.86705146263366
C	-0.09051858686195	1.83973034337916	0.94197355813718
C	0.03356568153982	3.06386752603520	0.30530882981241
C	-1.09550870733622	3.84283201524631	0.07009739794681
C	-2.35773583027857	3.40721810827628	0.46389422441322
C	-2.48846411243274	2.19300766562221	1.11517075391328
C	-1.35863571696474	1.39875070424858	1.36451428816601
C	-1.35316190472974	0.16932627210324	2.11546826915594
C	-0.20766175000577	-0.33977825420778	2.61608100666264
C	1.14868425742317	0.19439631519295	2.44603169080437
C	1.55425975619741	1.16777178983531	3.55562645455750
C	-0.56903237515329	-1.56587094445892	3.16946550429378
N	-1.85776156494801	-1.79001337408096	3.05250725887009
O	-2.35416048802408	-0.68528477761701	2.38615016866617
C	3.70753929013632	2.18472069372151	4.32313548799692
C	4.92008177139301	2.81128983526736	4.06029510658676
C	5.32153974857715	3.05281931426712	2.73965795775701
C	4.51304542553282	2.66934908687318	1.69787776593071
C	3.25521877589127	2.02996960882452	1.93038657704937
C	2.88017793404523	1.80808384793751	3.27812067523542
H	1.01530241132953	3.39755220396165	0.00217051966170
H	-3.20658942853724	4.04406385885187	0.26089492295175
H	1.57374984528888	0.64957872575737	4.51750345559105
H	6.27468339965170	3.53739304120825	2.58222681971270
H	3.39231137418651	1.98417454070126	5.33852759311055
H	0.77904552105139	1.94012143837542	3.62931884166364
C	0.47571952407373	-2.42330431296698	3.76608169711545
O	0.31513521417512	-3.38870385334461	4.44680699458284
C	2.02826772867548	-1.05749644689108	2.43914598513494
O	1.73118855530710	-1.95471500784079	3.52383809605112
H	3.08420324474336	-0.81943773451722	2.56182693683674
H	1.89352249999554	-1.59506586818811	1.49489424031240
H	1.01907903235652	0.16530560654862	0.31623661431633
H	2.77527525999929	1.80833194537120	-0.14562022593716
C	0.18975180298220	5.53621721266786	-0.96109841835928
H	-0.00508864954217	6.50274833246965	-1.42166910998031
H	0.87332867121595	5.66770308564752	-0.11637141208111
H	0.65095032448852	4.87109662054051	-1.69807318326383
C	-4.82291871091775	2.46385344517350	1.35525205351619
H	-5.63556866519025	1.89243316952471	1.79856144031168
H	-4.75350401951473	3.43933550472019	1.84731987085844
H	-5.02059800102209	2.60851936585832	0.28841244139246
C	6.06516643828899	3.45351527422566	0.09905613839227
H	6.12864403816008	3.49210288155995	-0.98676567623386
H	6.12796444658626	4.46937529350666	0.50253073591561
H	6.89656150652043	2.85829611543846	0.49031886840705
C	5.44809631723826	3.00046513799761	6.35490056036143
H	6.26489802221630	3.41087263130043	6.94545486621565
H	4.51665476944846	3.50993801503079	6.62217720687683
H	5.34897763959358	1.93135164814631	6.56863818658709
O	-1.06154164435540	5.04492381700130	-0.53851128542605
O	-3.65631181767449	1.70240840290038	1.56066907973839
O	4.82585295718089	2.85945224047693	0.40017195101966
O	5.78765434296891	3.22504516945359	5.00663648283064

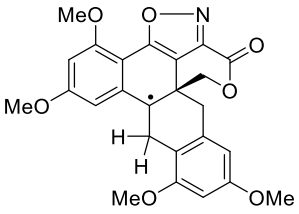
Compound **98-cat** (−1545.049671731896 Eh)



98-cat

C	0.87809353669511	0.75929937680492	0.43010293478914
C	1.81098687877216	0.65390902901569	-0.70748995356043
C	-0.07354814187081	1.79580805473877	0.56673051653826
C	-0.15112677113188	2.82078310639102	-0.41080500482711
C	-1.09467328538601	3.81684378261926	-0.30216817685362
C	-1.99116585193459	3.83444657770043	0.78310332440700
C	-1.95073776825593	2.86402464063133	1.76332697231933
C	-0.99553985301657	1.83117142014607	1.67984776253912
C	-0.91208099606710	0.77040806926960	2.61760245270103
C	0.05317874120342	-0.17038132966646	2.51389804494095
C	1.08129567505915	-0.24670177020150	1.49779976547606
C	2.50657931405331	0.11441330090749	2.06082040548233
C	-0.33695301111070	-1.18753090299752	3.38560628604278
N	-1.43118639860060	-0.86003003277322	4.02826090035447
O	-1.79087177086101	0.37969402566835	3.55972167943746
C	4.83671752654796	-0.42288896550480	1.33394816088802
C	5.79094234544806	-0.55524123382797	0.32990693525045
C	5.44923268890581	-0.31916692544558	-1.00370576145672
C	4.15826071754992	0.04795805525639	-1.32794405781515
C	3.19389889046897	0.20707601703226	-0.32105121877451
C	3.54508493733242	-0.03254555550396	0.99348019786123
H	0.53109311815044	2.82188020820989	-1.24398830809442
H	-2.70836129821751	4.64372020615322	0.82277736404233
H	2.69292318830705	-0.57176167401860	2.88858857860134
H	6.21568878185173	-0.44911700298518	-1.75442563264872
H	1.86339829197949	1.56413306011005	-1.30179250367587
H	5.07965509867238	-0.62812503874259	2.36727670119477
H	2.48387964914008	1.12629668591617	2.47639962080933
C	0.39903188619229	-2.47171683539921	3.37211605825674
O	0.37936120099811	-3.32877570814537	4.18821947149128
C	1.07236881165196	-1.75536725482757	1.11641170463991
O	1.22455388749408	-2.56103402675781	2.27897933209077
H	1.91374706426532	-2.01126691901913	0.47571206595044
H	0.13321693460993	-1.99716015685568	0.61151228737935
H	1.37153510771868	-0.09679020328779	-1.39072629521142
C	-0.40510702558174	4.88599144589321	-2.29559123915081
H	-0.71386226439124	5.76980059676116	-2.84723114368579
H	0.64194592662290	4.99048071099218	-1.99742480327940
H	-0.53109067169389	4.00065697481220	-2.92525978864940
C	-3.74562928322875	3.82361077211330	2.97611719555849
H	-4.27597890654982	3.56910073969108	3.88949097331233
H	-3.28424454716519	4.80903261610457	3.08146087080590
H	-4.44303459476771	3.82131691056951	2.13444357623648
C	4.64116488971251	0.10172193059453	-3.64714069695576
H	4.08579859365892	0.30741361694150	-4.55917096723577
H	5.47742273344755	0.80107853753841	-3.56363756118741
H	5.02033590220922	-0.92329625557891	-3.67464126541393
C	7.47996186502517	-1.19281440248065	1.85972330321154
H	8.53008592498613	-1.46603767376915	1.79113989714906
H	7.37660581881665	-0.30810342804546	2.49478208953138
H	6.91731370896754	-2.02595486254600	2.29110405287055
O	-1.25168236410006	4.82200155964278	-1.16020639527362
O	-2.75610495805454	2.81723007200079	2.81676711166582
O	3.72399433687815	0.27531035885013	-2.58169272206747
O	7.06052578859300	-0.92420430069616	0.53681490199197

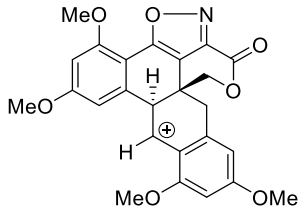
Compound **98-rad** (−1545.270908119341 Eh)



98-rad

C	1.04371747523620	1.49654766405688	1.44150606820749
C	2.35943738638312	2.06781676713779	1.03441749065898
C	-0.19782340373095	1.99482588051677	0.96290256209484
C	-0.23112040519172	3.03209454716714	-0.00256708272628
C	-1.42863431889921	3.53378379352710	-0.46301585164259
C	-2.65410632031907	3.04675330366772	0.01016940065401
C	-2.66124193756809	2.02776707839795	0.94423134396329
C	-1.46099864594315	1.48066357094218	1.41745130459966
C	-1.38487390753539	0.35407922471113	2.29559299831669
C	-0.20553595945585	-0.09268147951267	2.77777690523598
C	1.12462674926262	0.46470940657422	2.53310080342287
C	1.72623233511974	1.16437429155406	3.76929529068570
C	-0.48244296160274	-1.36104034836309	3.28683217745275
N	-1.75935502929449	-1.65051183179155	3.20073267101779
O	-2.33472451153168	-0.55916260828824	2.58148599100162
C	4.01689234602244	1.87622144896297	4.47166188023101
C	5.25967884433638	2.41721564508214	4.19094891204565
C	5.57119080190310	2.82643186478918	2.89389912089543
C	4.62607865170014	2.69303331161597	1.89526109770738
C	3.35362917460912	2.16258982532608	2.16181478084949
C	3.06713893885104	1.75866127717371	3.45469129184651
H	0.69471322418549	3.42451807855153	-0.39015570079874
H	-3.56320924918019	3.48476105139881	-0.37517634201388
H	1.81704195738579	0.44660205956048	4.58863437442019
H	6.55434476317985	3.23557007288097	2.70980737702312
H	2.24716641020841	3.06165655293861	0.59815938984380
H	3.76522996400189	1.53174297799233	5.46555008098985
H	1.02693839192782	1.93911972835504	4.09942134039788
C	0.63514667368086	-2.23332241694857	3.70267052218652
O	0.58348441638565	-3.20149736646019	4.39571599334591
C	1.95030457401804	-0.79459523226339	2.20280884579630
O	1.83501195281813	-1.78922769668521	3.23464749429569
H	3.01758513748849	-0.58484817058497	2.14283806535809
H	1.60825345556905	-1.21952925188361	1.25478324386352
H	2.79904382144418	1.46244924721309	0.22598552550830
C	-0.34898125687384	5.06412255739285	-1.90623517482233
H	-0.65820752199851	5.82616401221041	-2.61899684513906
H	0.25719259572261	5.52742358524546	-1.12075351558209
H	0.24832676017277	4.30618980910006	-2.42371189807661
C	-5.02271813925642	1.98863167005254	1.01415131851619
H	-5.78006162575253	1.41766823133056	1.54701120889993
H	-5.13602162462874	3.05173659771889	1.24971967466606
H	-5.14728643114670	1.84024329326550	-0.06313533381486
C	6.11633139480525	3.54478236399123	0.26678398474930
H	6.09121016461462	3.73823705773932	-0.80405691039686
H	6.34194467608030	4.47539173357493	0.79770498903113
H	6.89742442475786	2.80900400593999	0.48354163293776
C	5.99194892112265	2.17116980273951	6.42193264147655
H	6.89293252954912	2.39776055487977	6.98894984922475
H	5.14619835107586	2.71440574507422	6.85657930245642
H	5.79321965836221	1.09561430267602	6.47356097496889
O	-1.53469906959213	4.51536302689852	-1.38307822699125
O	-3.78158741712279	1.49521135916006	1.45915464486175
O	4.84248175041725	3.05405628145168	0.60846247581079
O	6.24493106422608	2.58415174224615	5.10073584048870

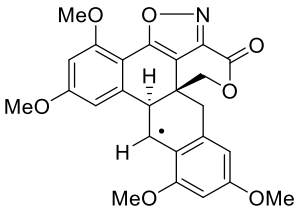
Compound **99-cat** (−1545.045963396560 Eh)



99-cat

C	1.24544856087401	1.23164813929921	0.89317306873110
C	2.18610118472485	1.10508285737193	-0.23291014660083
C	-0.09358600782774	1.91128007759016	0.66315176829201
C	-0.32186408349797	2.67638610124619	-0.46869035135164
C	-1.48920948949473	3.43545192469256	-0.56638028862385
C	-2.41793215934958	3.44285055127415	0.46819075185302
C	-2.19389188057844	2.68565852286034	1.60438367497992
C	-1.02844194308559	1.89921741989995	1.71246821225283
C	-0.80223994681065	0.93461979485295	2.76202900430774
C	0.24204365009494	0.06750027809226	2.77687031812145
C	1.29139763477376	-0.05799346177514	1.75582659299020
C	2.73700915433015	-0.14522301250579	2.26432705327460
C	-0.22297167108967	-1.01636724926187	3.53216111534650
N	-1.38758429666145	-0.77129442974953	4.07535219963479
O	-1.74289269404273	0.47561634181517	3.60775878942248
C	4.84369813569561	-0.96586815983894	1.21156083095847
C	5.72079015890344	-1.03748763821104	0.09807397581836
C	5.43689531530794	-0.38479423743307	-1.11224778218398
C	4.27295194231105	0.32587441336638	-1.23694090042180
C	3.35141092833154	0.41290075537955	-0.11834765185330
C	3.69023208495641	-0.25495992040371	1.11752415499622
H	0.39769899190296	2.71435682620633	-1.27186323165870
H	-3.30204735513921	4.05336604242771	0.35548067630457
H	2.87714334893494	-0.98711371932409	2.94198583375968
H	6.15119435461624	-0.48150824588861	-1.91670920472867
H	1.97851450348293	1.58811684417510	-1.17992465710603
H	5.08310361449736	-1.48645419313655	2.12835073537557
H	2.96683030987254	0.76488383611780	2.83376042267003
C	0.42499561021612	-2.33511411186639	3.36408248454254
O	0.47832342901504	-3.24274195173055	4.12532696346116
C	0.92669193712768	-1.41827397330485	1.12929312063586
O	1.03694175340800	-2.43428321541687	2.13496526787415
H	1.61362753042381	-1.73994073390803	0.34552076472272
H	-0.08774409129301	-1.39288416446097	0.72187011232011
H	1.75341384934261	1.95618138857815	1.56208498831125
C	-0.88649611807213	4.27643858769326	-2.69663262395390
H	-1.33664537232389	4.94677335980238	-3.42489606528968
H	0.07514335516497	4.68851697011630	-2.37437998684155
H	-0.73424460417766	3.29537097252922	-3.15774464390537
C	-4.23211934210548	3.37828748350299	2.58359510007927
H	-4.75047196861986	3.17218665807637	3.51641777593994
H	-4.03141139227937	4.45034061373113	2.50502931500342
H	-4.85054036124641	3.05353937540677	1.74235917860577
C	4.73154453233085	0.91864092302822	-3.48204173055184
H	4.21866754292721	1.50687710271609	-4.23740779391616
H	5.70587004225403	1.36152102037582	-3.26616020030640
H	4.84804550904663	-0.11009151437642	-3.82870763634572
C	7.23752134356769	-2.45478658117936	1.26822439974041
H	8.17618677149886	-2.92742629289592	0.99458631846611
H	7.39307645432402	-1.78411486403438	2.11453857361311
H	6.49496677318399	-3.21690067769395	1.50883649520074
O	-1.79596067866038	4.20217886071337	-1.62084594146132
O	-3.02642876098027	2.63930324990681	2.64233208336394
O	3.89680244543264	0.96168913331060	-2.32700597555248
O	6.83754146446141	-1.71563407775922	0.11024469168316

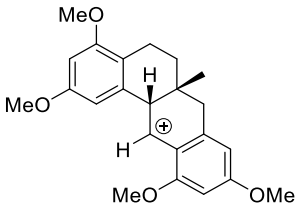
Compound **99-rad** (−1545.256808457824 Eh)



99-rad

C	1.23288258708550	1.21471563437291	0.85457491772028
C	2.09324199714499	1.01079247276179	-0.33835940708827
C	-0.10341472386148	1.90900930546068	0.67964191553765
C	-0.32533792347279	2.71043961945274	-0.43040508838558
C	-1.47215715166254	3.49317366840544	-0.50726662435949
C	-2.40751224299573	3.48729614632928	0.52200969383682
C	-2.19414314562603	2.69338160224188	1.63481755652906
C	-1.04344803115445	1.88977725088721	1.72651991472168
C	-0.81846046863904	0.90752730088524	2.75973083801879
C	0.22604003017529	0.04203337331289	2.75172906937562
C	1.28426156037671	-0.06214071982419	1.73569920205005
C	2.73148974801894	-0.13327690209956	2.24069784401371
C	-0.23318739296139	-1.04842135421671	3.49955197957739
N	-1.39665141151092	-0.81603073148880	4.05434839024374
O	-1.75854815425936	0.43753846349908	3.60535400974862
C	4.89849836988654	-0.87210908398739	1.23254044137424
C	5.77126238087108	-0.98670486177016	0.15747604395971
C	5.43516151315861	-0.44312266264337	-1.08918512506016
C	4.23542002203079	0.20612521195038	-1.25121040327576
C	3.32015699332184	0.35419969171437	-0.16576639946109
C	3.69119310175163	-0.20799220475755	1.08118473884258
H	0.40997517680112	2.74610368083261	-1.21863543681734
H	-3.28072554207462	4.11578056896307	0.42514526476197
H	2.87792026843495	-1.00069321210537	2.88689970552306
H	6.14075716212677	-0.56237319156192	-1.89911358668152
H	1.81816854893456	1.36761719338223	-1.31836433116146
H	5.13621027619189	-1.31332637114890	2.19141023566739
H	2.93278400271197	0.75247282455194	2.85322943275531
C	0.41208585310756	-2.36652550061184	3.31082562601251
O	0.44661119205495	-3.28306497908194	4.07185054452334
C	0.94270964770433	-1.41750008734126	1.09627458584591
O	1.01018174389986	-2.46179319962095	2.09230645461733
H	1.66459868169986	-1.72100298546923	0.34029645644638
H	-0.05819765475975	-1.39946439516719	0.65566873513253
H	1.76194129971585	1.94232123432143	1.49732642666160
C	-0.82310452661701	4.39322570479655	-2.59415471593008
H	-1.23884076655797	5.09891464412680	-3.31061571254722
H	0.14191467434704	4.76656432489207	-2.23654583139458
H	-0.67662018024337	3.42554309431537	-3.08457966997963
C	-4.23267792886441	3.37880542198175	2.61163448204155
H	-4.77134639654329	3.15797339609197	3.53056015579311
H	-4.02813008766721	4.45300938826886	2.55868178568082
H	-4.84285724620114	3.08235569508448	1.75255452324382
C	4.67180350789627	0.62305479917137	-3.53622796097169
H	4.16040558879572	1.11816795081938	-4.35962844407419
H	5.63664823536886	1.11123228366201	-3.36420384188975
H	4.83978919780473	-0.42776712641776	-3.79320165092766
C	7.34331626024863	-2.21703337234816	1.42038864442577
H	8.31367384758467	-2.67616116303898	1.24131592566611
H	7.43634455511558	-1.47432901868128	2.21949279801123
H	6.62917335389226	-2.98848248991173	1.72584690504646
O	-1.75877388472294	4.30436071338294	-1.54483315347379
O	-3.04028794622382	2.63263323678895	2.67359387598526
O	3.82792811821786	0.74713063778502	-2.41745953620173
O	6.96247231014203	-1.61805992119847	0.20417880028964

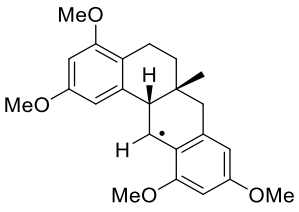
Compound **100-cat** (−1191.860675788449 Eh)



100-cat

C	1.36833000066488	0.15508811757816	1.28256441721891
C	2.26349890706153	0.12760372114830	0.10392462718320
C	0.21444463027954	1.09289657417778	0.98306442313891
C	-0.77762089883233	0.64798341515799	0.10565725355224
C	-1.82301416306887	1.49458620933635	-0.22209741432412
C	-1.88405199052637	2.77678205654976	0.32970733499268
C	-0.90164225233148	3.19475658029291	1.20334447850802
C	0.18396280939905	2.35742033500985	1.54080702529968
C	1.19936855671511	2.84486156677301	2.52858870722706
C	2.43732464687657	1.97000009615551	2.59730473327775
C	2.10882614854016	0.47534729887399	2.58803819543682
C	3.39794103593189	-0.34697273881468	2.63045313808504
C	5.62249449152206	-0.22418589590573	1.50201374963718
C	6.39124752395993	-0.11200203366831	0.31762225932601
C	5.79524905987973	0.04582592094510	-0.94261502891094
C	4.42900656621918	0.11061835565375	-1.03575814570420
C	3.61743851756293	0.01787548728086	0.16171512780050
C	4.26512284864634	-0.16865671637999	1.43177902800847
H	-0.72960847866060	-0.35791933013294	-0.29134406623692
H	-2.71972928382744	3.40627545077118	0.05903898768634
H	3.13436681950000	-1.41240399522192	2.69115860391923
H	6.44443246986232	0.12129170374508	-1.80257051452094
H	6.10906855329408	-0.36297470996525	2.45726172117372
H	3.96322866841648	-0.11704106513218	3.53695148070104
C	1.24622029267618	0.09745883748491	3.78388040837187
H	0.28455700269001	0.61062976812257	3.75991081980667
H	1.74791721896895	0.36152167418326	4.71786657431593
H	0.72591312569074	2.91079925287773	3.51505755793309
H	3.08829300854831	2.20284253420700	1.74814216972603
H	1.04942807795670	-0.97758690692902	3.79949338916690
H	0.94981385700584	-0.86393666271869	1.36255843857477
H	1.79211345620181	0.23078939304607	-0.86853395221376
H	1.48282045859559	3.87136760116845	2.28535779899444
H	3.00966211177909	2.20620803158884	3.49929293523942
C	-2.83859569313159	-0.11026200099611	-1.62655221269243
H	-3.72673369233731	-0.15795257587780	-2.25264357436457
H	-1.95086952234966	-0.27365039811995	-2.24678252428649
H	-2.89570884262062	-0.88928075915994	-0.85947405148657
C	-1.93339746325787	5.30607678893832	1.48389998393445
H	-1.73249612732000	6.20721222655913	2.05880158271272
H	-1.94208824529733	5.54843880224402	0.41703731298470
H	-2.90713376728967	4.90072984886580	1.77398734843990
C	4.48323993624154	0.39425011652445	-3.38291396192573
H	3.73069899167038	0.52417708398668	-4.15539587087514
H	5.13942846189235	1.26664159498957	-3.35477292320824
H	5.06262143850798	-0.51067072870244	-3.57738616197130
C	8.43548355549744	-0.28715899156664	1.52455793427668
H	9.48148748662975	-0.26842476231304	1.23282092477473
H	8.22465552903428	0.54592889240166	2.19701132303416
H	8.20345798760878	-1.23842766316076	2.00621889863911
O	-2.83212818356467	1.17562063668580	-1.05080010713763
O	-0.89155302224216	4.40387501657397	1.79238809414258
O	3.76310635063152	0.27294941341298	-2.15990813974230
O	7.70130102449890	-0.14772246854539	0.30816986236033

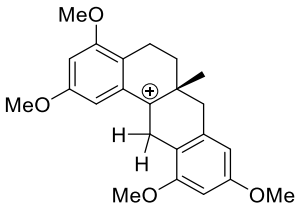
Compound **100-rad** (−1192.052366183052 Eh)



100-rad

C	1.49372814765909	0.15598422198182	1.38767376069239
C	2.35707771022484	0.17800183682646	0.16478435248231
C	0.21904824664337	0.92598836399313	1.12215985697639
C	-0.77465712348991	0.30221109263678	0.36124288699337
C	-1.93804648717440	0.98276476325145	0.05618912825314
C	-2.12684880316195	2.28763889524853	0.51191591075783
C	-1.14109895908275	2.88725801086308	1.27180780137468
C	0.05591012149302	2.21975037643501	1.58759217007938
C	1.07635017817091	2.90845233550827	2.44512891276210
C	2.40488905315966	2.17372182156277	2.50702377197302
C	2.23524549598583	0.66047753257027	2.63497374229616
C	3.60190391936499	-0.02084183610700	2.70434846118838
C	5.80995966782933	0.20149577193623	1.53633447521546
C	6.55987902630051	0.29839705131665	0.37112260238620
C	5.92644143499969	0.34043650170212	-0.87765100887252
C	4.55465780177236	0.29364360272274	-0.95243442708327
C	3.75221524473722	0.19396314502075	0.22572026197487
C	4.42706021230063	0.14099658773410	1.46653352829432
H	-0.61186639922247	-0.71260633820367	0.02260474747061
H	-3.05103532944292	2.78841035553436	0.26084816032958
H	3.44104666600287	-1.09310499142099	2.88382862523006
H	6.54956029507470	0.41835882236262	-1.75736843161415
H	6.28773084400418	0.16650214987789	2.50679586490164
H	4.15320619695961	0.35591614723006	3.57210359283249
C	1.44962561479997	0.30493517442614	3.89069534959386
H	1.36822702994807	-0.78038622297255	3.99755634512022
H	0.43707756991011	0.71113745752355	3.86379550351413
H	0.66063147603403	3.02794144776215	3.45325394433829
H	2.98171783697626	2.38212201173791	1.60192064501499
H	1.94897706236314	0.69385854775467	4.78278516438703
H	1.19779717721568	-0.88801302878016	1.58676923188807
H	1.86906023442590	0.20863332482993	-0.79988963036597
H	1.22902138471764	3.92811938237512	2.08175270082310
H	2.99574496887204	2.54760363656629	3.34981658012073
C	-2.81746847662217	-0.84329399811406	-1.15243122832307
H	-3.72869204933355	-1.06652449772619	-1.70503120714348
H	-1.95651679818769	-0.93361915915265	-1.82395839016434
H	-2.70731287313378	-1.56203907986723	-0.33294814179553
C	-2.40114384369698	4.88091697531398	1.44642274886167
H	-2.28062838690134	5.85562991141686	1.91638005308194
H	-2.50190239760553	5.01105266085897	0.36353538066775
H	-3.30689869883070	4.40277182303593	1.83477554085991
C	4.59907454887656	0.46222293925216	-3.30697469015779
H	3.86588940224250	0.49830522414905	-4.11078061141468
H	5.19546494023675	1.38064769177961	-3.31958479782509
H	5.26090537741474	-0.39727417417327	-3.45826185465195
C	8.60231366278206	0.33818092477069	1.55562413641364
H	9.66068140820975	0.40499661226662	1.30953150737054
H	8.32445307957596	1.18731231075826	2.18932343866284
H	8.41698318925219	-0.59228246667110	2.10310981089008
O	-2.96011141518076	0.46886215850839	-0.67073560177519
O	-1.24989526301947	4.14302039342265	1.76867269978765
O	3.86813894610362	0.34297046124708	-2.11279335652794
O	7.91122813144655	0.36197533711770	0.33198998185416

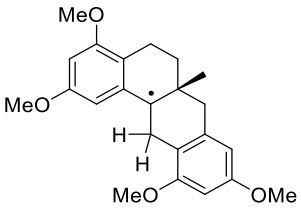
Compound **101-cat** (−1191.854486674039 Eh)



101-cat

C	1.68887164874259	0.19724517688606	1.55726445548707
C	2.19914133993879	-1.04626003289452	0.96835665512500
C	0.69619053349464	1.01496898347941	0.94620342247921
C	0.05317328341692	0.59075700087721	-0.24175113092833
C	-0.94453413291758	1.36522293915803	-0.78558534641144
C	-1.32910900138612	2.55838871888850	-0.15647352715725
C	-0.71147050201502	2.97471909957854	1.00779541692910
C	0.32869771565643	2.22054808183265	1.57526505369436
C	0.98233513662111	2.71212101300789	2.82112395445678
C	2.33661623353427	2.07858466401498	3.04365462741218
C	2.30877351938430	0.56250981230107	2.88179588655399
C	3.75991468541749	0.04281639563299	2.89110272428439
C	5.47465202317033	0.81208012554547	1.17352194650381
C	5.79656682562380	0.97050936037385	-0.17905274823171
C	4.93358323110922	0.51654672195862	-1.18479477417726
C	3.75416974304413	-0.11524092276478	-0.85101111857703
C	3.44731849972189	-0.32724493101119	0.51034013921390
C	4.29687018984002	0.17551131991584	1.50178446171940
H	0.35209854217059	-0.32578009106248	-0.72195176888898
H	-2.12382225126873	3.13207849339687	-0.61418499225964
H	3.79488238170054	-1.00711141568571	3.20274334809813
H	5.23186335293165	0.67564454212183	-2.21108766574482
H	1.63427139601978	-1.45445055061182	0.14036816667277
H	6.11488646081076	1.20198020198424	1.95209724422023
H	4.35005238439852	0.60551913682347	3.61528962656091
C	1.46987651153647	-0.10940421361647	3.97777013729004
H	1.43790776253887	-1.19260758256445	3.84497856379940
H	0.44399573376128	0.25987987424566	3.99066852188704
H	0.31503301042168	2.51881337708799	3.67060025643396
H	3.05068945177869	2.48711170742377	2.32036172645601
H	1.92090254892724	0.09785338782619	4.95047890051880
H	2.41343240621067	-1.82325476248389	1.70257409320631
H	1.06745841907210	3.79927015935106	2.77419931955050
H	2.71183708074480	2.32431926542285	4.03999036416105
C	-1.29647679583918	-0.12057241055419	-2.58452531629804
H	-1.94521631131695	-0.15737976021539	-3.45620940171308
H	-0.25078946080037	-0.11802133944019	-2.90836893521755
H	-1.48359237030016	-0.99628843022618	-1.95540818047770
C	-2.04602948360517	4.92973646693921	1.13027667172091
H	-2.12499817313643	5.77629215505658	1.80768655782563
H	-1.77569680789406	5.28619390342282	0.13202649884165
H	-3.00579794047033	4.40691320073470	1.08949587861813
C	3.16627759875479	-0.44616614295092	-3.11677261158054
H	2.34375610293643	-0.91521871837768	-3.65146795197932
H	3.23191916331371	0.60887923299007	-3.39507686212144
H	4.09955754281950	-0.95512844037202	-3.36981569228890
C	7.84629699662744	2.04290288377030	0.32924142891595
H	8.66734737297431	2.45239199463039	-0.25340839429122
H	7.41518168310749	2.82965846600481	0.95410381364256
H	8.21530570173823	1.22811356444561	0.95729565374352
O	-1.62113684183731	1.07375901125804	-1.90557113313535
O	-1.03398761864526	4.09767253198935	1.66501809995494
O	2.87058567068998	-0.58995858305388	-1.73777225620950
O	6.90156780673122	1.56917535750880	-0.61498380828849

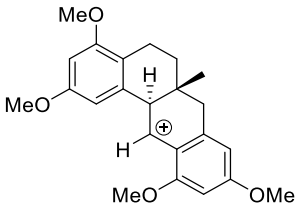
Compound **101-rad** (−1192.053180120036 Eh)



101-rad

C	0.91024723206941	2.77625558696847	3.20200030854158
C	1.90383667904459	3.85984662829175	3.46918114510080
C	-0.46573011553785	3.00137398718119	3.46703494053462
C	-0.88776867468119	4.22254483621042	4.05565908427526
C	-2.22123262951746	4.45400202155299	4.29520883399184
C	-3.18757879966126	3.50164128132038	3.95248845765647
C	-2.78384946110458	2.31323662549527	3.36563978439398
C	-1.43607329573017	2.03334466860866	3.12507119969737
C	-1.03872910083679	0.73166769480145	2.50292896703931
C	0.39585160517385	0.37725397777605	2.83659273521151
C	1.37339089566856	1.51095130647831	2.53902271897081
C	2.74876861477645	1.12174700948285	3.09067176235919
C	5.09322557435376	1.93119416156111	2.70323909680313
C	6.01575993354171	2.96039308030739	2.62769493800646
C	5.61204132501102	4.28154189069761	2.81729743717361
C	4.28258661299101	4.55419227032749	3.08209827508552
C	3.33223164474655	3.52552997932222	3.16877509499268
C	3.75678547383281	2.22213981500286	2.98239101601658
H	-0.15141003733167	4.96734697217402	4.31340116501195
H	-4.22436360807890	3.72996356036639	4.15274870648042
H	3.11013504066198	0.23043686051197	2.56809271031007
H	6.36025736955035	5.05834500348916	2.74960507325534
H	1.82940874330700	4.17656270737170	4.52062460041480
H	5.38497821967199	0.90073992991237	2.55005399079087
H	2.63123075591451	0.83960804170433	4.14452316080581
C	1.48399135714985	1.74367115637213	1.02442575570661
H	2.20622657096313	2.53159533433526	0.80384175965329
H	0.52363708332990	2.04153478941362	0.60097687491003
H	-1.17707646210727	0.77989024414868	1.41524621031981
H	0.46239129565203	0.14048710948552	3.90442504013863
H	1.81626874293532	0.82858342552034	0.52361855821914
H	1.62903347438021	4.76142707787217	2.90513432407228
H	-1.71211816057778	-0.05738128148344	2.84408911039285
H	0.70377906194697	-0.51969667142328	2.28917039655003
C	-1.79232216772503	6.59970083050029	5.17918358067642
H	-2.37549974935431	7.42124923826810	5.59210502613916
H	-1.06371982679946	6.26313722591751	5.92515876409986
H	-1.25486599561193	6.94893484801677	4.29051163008304
C	-5.02492574344884	1.56132494961387	3.22865674176269
H	-5.54277929014371	0.67964775710573	2.85423148537003
H	-5.22869510781933	1.67153448604345	4.29935201979609
H	-5.39575962329051	2.44722060362008	2.70189782577357
C	4.70173162364811	6.88210068158033	3.14303061599722
H	4.11809325624716	7.78722978960580	3.30268791082053
H	5.50231968375141	6.83351583548752	3.88880078120380
H	5.14600389607204	6.90917587089000	2.14241162405610
C	7.80086116619984	1.47660381473101	2.19684720390990
H	8.87277571799383	1.55363203521862	2.02265438089761
H	7.62308562968080	0.86751907327848	3.08985579401531
H	7.32963820862889	0.99195840603671	1.33471678435327
O	-2.71077978863004	5.58613452875519	4.85953118004341
O	-3.65873893543457	1.34853544879360	2.98251407132111
O	3.80585492652399	5.80733427320399	3.27792892627908
O	7.33458915800364	2.79083922217552	2.36915042051913

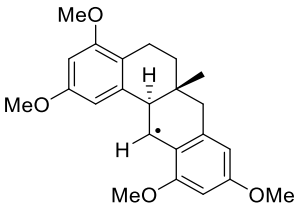
Compound **102-cat** (−1191.854945186171 Eh)



102-cat

C	1.03906425667271	2.54942437813249	3.68605173994743
C	2.03052892729812	3.63829958922809	3.64804500543362
C	-0.42003931629554	2.95695137652066	3.65880238941972
C	-0.81393528894752	4.20020680108025	4.16146253591950
C	-2.15721119082932	4.54280647830517	4.17295694260961
C	-3.11285351519146	3.65757126162766	3.67683258660188
C	-2.71171553659410	2.43062471121538	3.18969372410685
C	-1.35410155464894	2.04783475894686	3.18594271855502
C	-1.00589056496549	0.68794825282145	2.65558133708861
C	0.43335818723154	0.28744543953148	2.92269458674512
C	1.39544297669347	1.44076564332986	2.67677855174661
C	2.82622597244641	1.00510605969569	2.98168897600713
C	5.10800624015989	1.93892282065131	2.61046113019876
C	6.00702653116138	3.03142280414854	2.62781362577276
C	5.58957299480936	4.32672100853198	2.96858314584802
C	4.27821686497592	4.54643922319029	3.30211180452078
C	3.33724609088343	3.44335264747855	3.31308409513369
C	3.80363492728415	2.13113337286452	2.94825168671858
H	-0.08897224046853	4.88988416065595	4.56744610251032
H	-4.14934417230193	3.96259305907024	3.69523784604617
H	3.14636577749939	0.21544285855035	2.29728343600664
H	6.32737158373260	5.11531476460514	2.95076067156899
H	1.72786594088690	4.64453798937666	3.91313953339151
H	5.45156424882509	0.95350348154114	2.32817337427040
H	2.85187177072209	0.57066078063972	3.99216250677224
C	1.28758548878246	1.93445874271262	1.23584261064483
H	2.02641321056374	2.70450862298899	1.00526436156477
H	0.30201301528058	2.35360670158572	1.03363911593263
H	-1.21551051216250	0.65953818993397	1.58048926425467
H	0.54094838626831	-0.04127957153269	3.96282256213849
H	1.45030679099744	1.10250924233983	0.54667884902139
H	1.20825225691590	2.09779165546964	4.68630519407017
H	-1.68327406637696	-0.05090394329259	3.08977822489625
H	0.70700358936732	-0.56382105636802	2.29233286401534
C	-1.73097963469591	6.65082892042585	5.15460501391878
H	-2.32605112430177	7.50431880271349	5.47204963642545
H	-1.18565446998822	6.25200795695777	6.01667209336175
H	-1.01842535309455	6.97441321162667	4.38803196545771
C	-4.94152755699437	1.80826698606927	2.69389144899564
H	-5.43457580952194	0.94078206014628	2.26104000510285
H	-5.31074006302774	1.96666953232266	3.71143787353115
H	-5.15793570433367	2.69078160454949	2.08481397926991
C	4.63501214257140	6.86355918581049	3.61575802176005
H	4.00515982931815	7.70552674305932	3.88851552769407
H	5.43534040748868	6.74637559621138	4.34940474199696
H	5.05306000897192	7.02121460399285	2.61929373897381
C	7.83315727334683	1.65601115498354	1.96507227492523
H	8.88612426763222	1.84643720435668	1.77922971300627
H	7.72584834411143	0.94422615542325	2.78514714066202
H	7.36189411396345	1.27327385344532	1.05826428857596
O	-2.64067843079789	5.70772416691151	4.64119163509823
O	-3.56037527683507	1.51345612196616	2.69306949776336
O	3.77983943300576	5.72411876304448	3.62298633724927
O	7.27756953250536	2.92168507040668	2.32363196675297

Compound **102-rad** (−1192.048888345290 Eh)



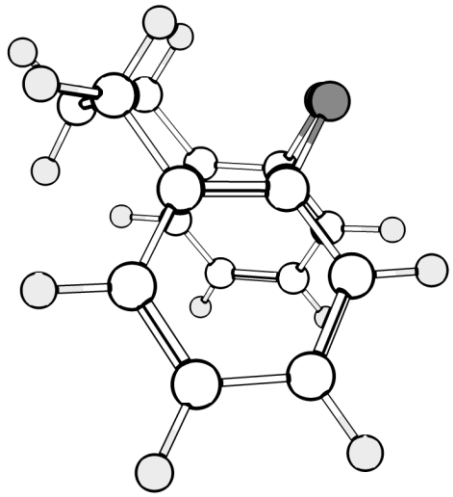
102-rad

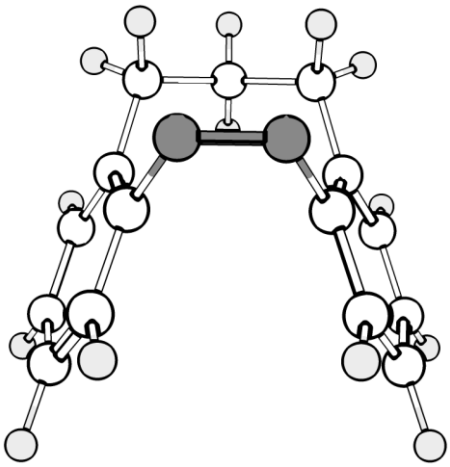
C	1.03431279800715	2.57229030249394	3.68363335056973
C	1.99337785310335	3.70818757876825	3.57572910688681
C	-0.43473375074045	2.94284740095221	3.65535649790439
C	-0.84747713524007	4.16812702662154	4.18864448971233
C	-2.18918176393635	4.49978641048081	4.21354279057870
C	-3.14212669072785	3.62084536949814	3.70386050889577
C	-2.72656831791732	2.40921644311886	3.18728016565041
C	-1.37041828768784	2.04026941611634	3.16548428353614
C	-1.00274302285998	0.69626217675288	2.60511057159138
C	0.43749299327423	0.30936079668204	2.88774816939229
C	1.39378422844260	1.47224206165685	2.66712495793477
C	2.82549745086104	1.03548751768201	2.96615824592620
C	5.13843320004441	1.94122753940325	2.65465112296524
C	6.04375329550902	2.99324483699073	2.65051536706718
C	5.61445492450167	4.29646508664206	2.93103987901450
C	4.29268953985088	4.53413384271643	3.22370200743495
C	3.33920977216141	3.47141321998309	3.26816999789466
C	3.80555567629604	2.17162970175227	2.96183393462580
H	-0.11241973134598	4.84629216141774	4.59461079820159
H	-4.18096119030432	3.91717381192401	3.73151383113266
H	3.14030150293792	0.27655221678886	2.24210876783555
H	6.35057143994361	5.08737814122964	2.90467070549161
H	1.67583186577669	4.72477388984305	3.74914639290756
H	5.45280973270535	0.93414491332199	2.41280262096893
H	2.84122929489613	0.54647716196984	3.95012933429641
C	1.29361869327500	1.98285061683233	1.23208437445380
H	2.04679414046946	2.74546823373402	1.03099159541065
H	0.31522716960728	2.42245736135714	1.03160373672853
H	-1.18994752730894	0.69567667645197	1.52486688398636
H	0.53301870783050	-0.02420640455409	3.92792359182350
H	1.44899553633911	1.15879500013832	0.52968698162129
H	1.19647968925716	2.10667625312474	4.67403916565139
H	-1.68153141043611	-0.05973198822327	3.00847633431127
H	0.72646259246923	-0.53788275682599	2.25665234771312
C	-1.75775804324836	6.59413738296973	5.21386357071954
H	-2.34170387263918	7.44994913466593	5.54884916925243
H	-1.19352587992897	6.18904948099598	6.06119386297119
H	-1.05390683053940	6.91789604115318	4.43928076993327
C	-4.95407927860880	1.79628965251498	2.67935749160421
H	-5.45727309098181	0.94250083200079	2.22840484535786
H	-5.32656852693369	1.93781599522846	3.69970252049454
H	-5.17125458263428	2.69488428056996	2.09202486636136
C	4.68227255647785	6.85453986866676	3.42887503252079
H	4.08762701339110	7.73983259827182	3.64757815572175
H	5.48270145507445	6.76441018522417	4.17106772804979
H	5.12645317381277	6.95292260213532	2.43269061349486
C	7.85785588327657	1.58108271053182	2.11047511673696
H	8.92792813094604	1.69370698721166	1.94505471802492
H	7.69192656685340	0.90651153805960	2.95730089169814
H	7.39796878430369	1.15068861525147	1.21428865323341
O	-2.68008775275522	5.66012820491828	4.71316817814267
O	-3.58214928431589	1.49415024789449	2.66975670679277
O	3.79933361033901	5.76250535845959	3.49021298354226
O	7.36284669905669	2.86976626643393	2.37586121523176

4.2 **Part II:** Synthesis of cyclic azobenzenes

DSD-PBEP86/def2-TZVP structures

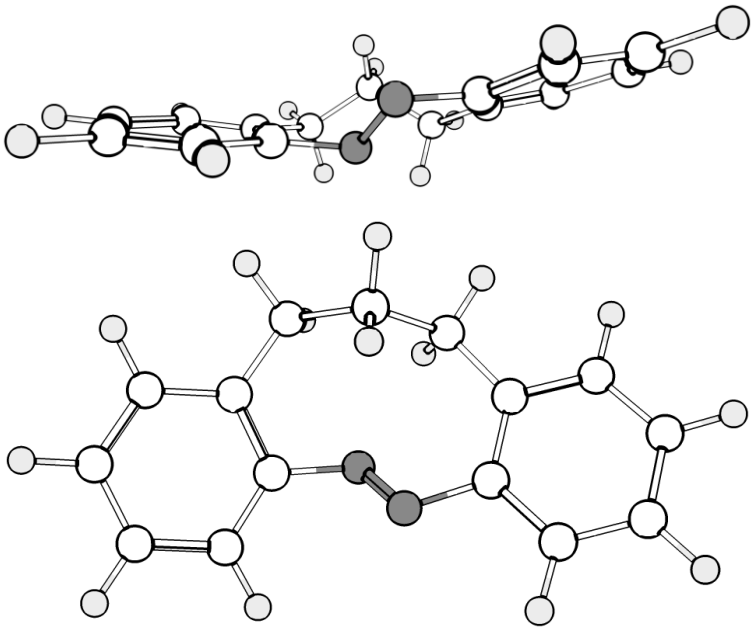
Diazonine **64** – (*Z*)-Isomer





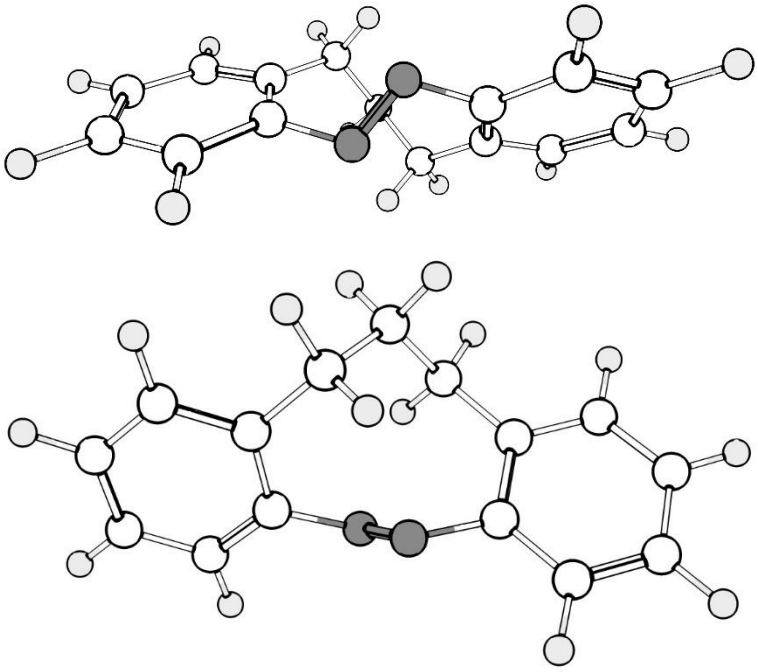
C	1.75453927582878	3.26463785600660	-0.94444192972661
C	2.46145681237406	3.51191568783089	-2.12214678626832
C	3.37082886514675	4.56152854823285	-2.22168789658449
C	3.62595225624516	5.35842796394234	-1.11313820418058
C	2.95648315681740	5.11342348122949	0.08317454607782
C	2.02683773295940	4.08297680003579	0.15470539623758
H	3.87410064270917	4.74220072460240	-3.16518911323993
H	4.34141632490879	6.16967253805755	-1.18524855842691
H	3.14618455196303	5.73380357862834	0.95161258468081
H	1.48653202621612	3.90754927943493	1.08078482756525
C	0.72009034630845	2.17396428064781	-0.84388499564958
C	1.22443374577455	0.84007812483020	-0.27683453713164
H	-0.08068623960106	2.53685783473934	-0.19168897401549
C	2.08464753187819	-0.00047979719304	-1.23002024941795
C	6.14440987941360	1.34817767503878	-1.82532522808172
C	5.81783761993169	0.55681567308825	-0.72695291672066
C	4.50655942360974	0.13320450731536	-0.54759584963956
C	3.49158729834532	0.49704915495822	-1.43606331441300
C	3.83978115568103	1.31557077126680	-2.51151677846430
C	5.15447819364873	1.72102841789841	-2.72533476801640
H	7.16697786626203	1.67125201825215	-1.98407872327674
H	6.58557604367986	0.25739153789267	-0.02268049536178
H	4.25641701029512	-0.50438096073958	0.29575868312345
H	5.39015481447951	2.32822432838844	-3.59244904407269
N	2.18549548052324	2.72792823426510	-3.30056707163289
N	2.84126480761742	1.68149307905263	-3.48545569551276
H	0.34630328889333	0.24176550656669	-0.01059930503877
H	1.77718250587180	1.02183691615135	0.65211986444984
H	2.14855412380001	-1.01433714491360	-0.82223710104065
H	0.26840734162958	1.99840265537378	-1.82587021049914
H	1.57439611678920	-0.08297927088094	-2.19544815572219

Diazonine **64** – (*E*)-Isomer, Conformer1



C	3.75697053401696	-0.07361462974328	-1.44577440065177
C	4.24036037219384	1.00340534739195	-2.20046980852809
C	5.48854913269542	0.99045172718327	-2.80995468085858
C	6.28133937652000	-0.14624531155375	-2.69126387148176
C	5.83123997558678	-1.22907509337483	-1.93938178305939
C	4.58709338051769	-1.18493334576785	-1.31246756277033
H	5.81585351834149	1.85805443406544	-3.37158720509183
H	7.25101148608813	-0.18426330713516	-3.17461750817229
H	6.45325982925824	-2.11133425168266	-1.83684947543512
H	4.25462855962993	-2.02783116739324	-0.71410045255540
C	2.39627694626580	-0.00166053076644	-0.78454685686892
C	2.03881127348821	1.31359512913670	-0.04090395404452
H	1.62711044878061	-0.18871359450035	-1.54408226558639
C	1.09101675893738	2.27833140421050	-0.81373637812947
C	2.19426612755113	6.45496544120007	-1.37277034491089
C	0.96875117138081	6.08379952014891	-0.82792449202933
C	0.66192411586634	4.73776659594959	-0.65104891766504
C	1.53545931163378	3.71324446931163	-1.02661081743031
C	2.76853187367767	4.11820951448325	-1.58790122718584
C	3.10052774825294	5.46621628675988	-1.72512438790264
H	2.44775564370794	7.50099641436428	-1.50015349897095
H	0.25456220151644	6.84124317102794	-0.52423291848292
H	-0.29030398709453	4.46743321370764	-0.20513347487784
H	4.08096074892433	5.71101905586568	-2.11880521357054
N	3.32643967802777	2.07931240571784	-2.22286236069082
N	3.79701221652459	3.19159770298188	-1.89657975583544
H	2.95245067849255	1.82764352612720	0.26757044605793
H	1.53104010288446	1.03924541943784	0.88876485467526
H	0.86190017671352	1.83762431383471	-1.78592854531827
H	2.33648912191795	-0.83867469936034	-0.08248132280642
H	0.14311147770180	2.33329083837171	-0.26854181982206

Diazonine **64** – (*E*)-Isomer, Conformer2



C	4.12853948944478	0.43631140827020	-1.11381448028756
C	4.37868239360611	1.13079770886046	-2.31330760489423
C	5.10297193267017	0.56480507938685	-3.35684383670321
C	5.65972497002977	-0.69849834516434	-3.20219335367223
C	5.43580121383380	-1.40738349869652	-2.02533733489944
C	4.67105710528852	-0.84584821236714	-1.00612391632028
H	5.23026691558041	1.12802884862150	-4.27485036755684
H	6.24851308705021	-1.13408731226455	-4.00135518227804
H	5.85042621121091	-2.40152655700399	-1.90178783730584
H	4.49636611896631	-1.41245621320490	-0.09648916546113
C	3.30657874060210	1.00999302148206	0.02550435306687
C	1.78666442706638	1.17809521830796	-0.18762533052135
H	3.41436340379807	0.31673359761824	0.86621701763662
C	1.22042941626966	2.10401894644128	-1.28582325339569
C	2.07886998511382	6.35533049592133	-1.03100374550330
C	0.79478085753509	5.86828757816363	-0.80399152350801
C	0.54163995272767	4.50135683509605	-0.88169582486321
C	1.54340263868435	3.58466803134703	-1.20755253758502
C	2.83024036769249	4.10875340599821	-1.43798380860204
C	3.10653887375690	5.46656250328903	-1.32074338464732
H	2.28220798613616	7.41802352031138	-0.96490434252525
H	-0.01059536692068	6.55156496651040	-0.55896772641859
H	-0.46246163572410	4.13327170518094	-0.69384892973059
H	4.12433623838902	5.81080804685985	-1.46821585705272
N	3.67983343444575	2.35037721075557	-2.50470273187892
N	3.88668220339753	3.17295628376882	-1.58089002079359
H	1.37894917147416	1.50940281652757	0.77481342297552
H	1.36141570431657	0.18530222990916	-0.37686334906561
H	1.48668233948460	1.71631968377944	-2.26928851605603
H	3.73918309673330	1.95372678967403	0.35830111374056
H	0.13100872734015	2.01940420662046	-1.21403194589355

Tetramethylsilane

Si	-3.70160221816959	-1.91610479556786	0.00019773291943
C	-1.82347643922137	-1.91625118462848	0.00015083360409
C	-4.32715265539049	-1.40102085778054	-1.69409495215974
C	-4.32734014349785	-0.70633511030499	1.29324757257854
C	-4.32709394107019	-3.64109853720526	0.40083752753768
H	-1.42844703017073	-0.92265104121052	-0.23141658937512
H	-1.42872452753147	-2.61363102912977	-0.74466775638692
H	-1.42851208521753	-2.21270157008923	0.97638735041670
H	-3.97748359977121	-4.36908232285645	-0.33722866432113
H	-5.42063565147697	-3.67305264004121	0.40832032544929
H	-3.97738336416647	-3.96937603010436	1.38412639331742
H	-3.97848388085198	0.30946738231616	1.08501564660131
H	-3.97727702582798	-0.98056757221753	2.29282608795880
H	-5.42089038678714	-0.68469169501312	1.31742417817950
H	-3.97674679157487	-0.39836891515157	-1.95637964540164
H	-5.42070289918986	-1.39056644022878	-1.72506650512640
H	-3.97840736008430	-2.08933764078649	-2.46966953579181