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Biomimetic Synthesis of Complex Flavonoids from East Indian Dragon's Blood

&

Total Synthesis of Salimabromide

von

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aus

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Erklärung

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Eidesstattliche Versicherung

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TO MY PARENTS

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

- "*Biomimetic Synthesis of Complex Flavonoids Isolated from Daemonorops "Dragons Blood*" " M. Schmid, D. Trauner, *Angew. Chem. Int. Ed.* **2017**, *56*, 12332–12335.

  Highlighted as: **Very Important Paper**, Cover

  Highlighted in: E. M. Carreira, M. Hönig, *Synfacts* **2017**, *13*, 1009.

- "*Total Synthesis of Salimabromide: A Tetracyclic Polyketide from a Marine Myxobacterium*" M. Schmid, A. S. Grossmann, K. Wurst, T. Magauer, *J. Am. Chem. Soc.* **2018**, *140* (27), 8444–8447.

  Highlighted in: E. M. Carreira, N. Sievertsen, *Synfacts* **2018**, *14*, 887.

  Selected as ***Synfact of the Month*** *– September 2018*

- "*Ring-expansion approaches for the total synthesis of salimabromide*" M. Schmid,[†] A. S. Grossmann,[†] P. Mayer, T. Müller, T. Magauer, *Tetrahedron* **2019**, *https://doi.org/10.1016/j.tet.2019.03.010*, in press.

  [†] These authors contributed equally to this work.

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  Total Synthesis of Salimabromide: A tetracyclic brominated polyketide (poster)
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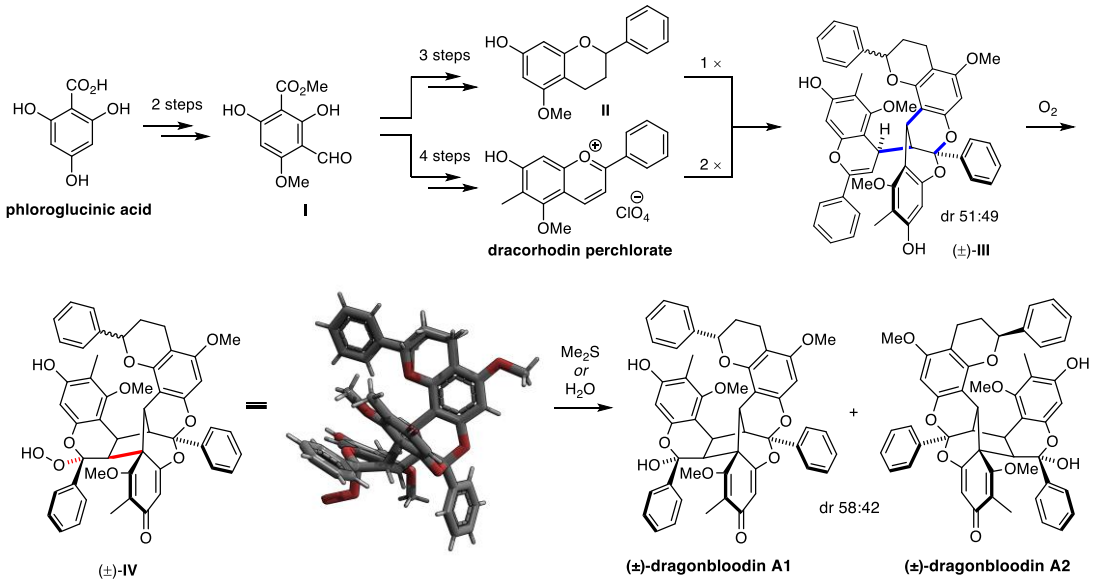
- **30. Irseer Naturstofftage**
  Oldschool Chemistry enables a Total Synthesis of Salimabromide (poster & presentation)
  Irsee, Germany, February 2018.

1 Abstract

Part I

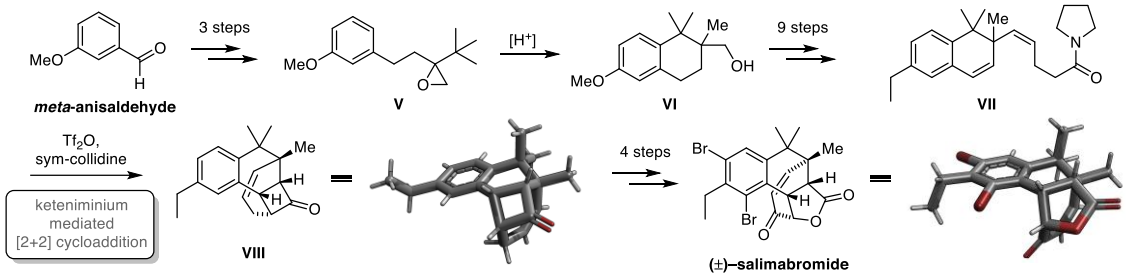
East Indian Dragon's blood – a resin from *Daemonorops draco* blume – has played and continues to play an enormous role in Traditional Chinese Medicine (TCM). This resin, highly priced in ancient times, is used against a variety of physical discomforts, in particular, to improve tissue generation, stimulate blood circulation and to alleviate pain. As a source of interesting and unique flavonoid natural products, renewed interest in finding biological active natural products has led to the recent isolation and characterization of the complex flavonoid trimers dragonbloodin A1 and A2. These remarkable natural products, with an unprecedented spiro hexadienone core represent the first representatives of a new class of trimeric flavonoids featuring the [3.3.1] bicyclic ketal moiety of A-type proanthocyanidins. Its densely functionalized and unique structure in combination with its unknown biogenetic origin render it a highly challenging and attractive synthetic target for biomimetic synthesis approaches. Starting from phloroglucinic acid the building blocks dracorhodin perchlorate and flavan **II** were synthesized in a divergent route *via* the shared intermediate **I**. Trimerization under buffered conditions in a biphasic system revealed the flav-2-en containing intermediates **III** as intermediates towards the dragonbloodins. Exceptional sensitivity against aerial oxidation led to the investigation of the exact autoxidation products and finally revealed an unprecedented cascade reaction forging the complex skeleton of dragonbloodin A1 & A2 accompanied by endoperoxide formation towards the diastereomers **IV**. Reduction or hydrolysis of these peroxo semiketals gave access to a mixture of both natural products in a racemic fashion.



Scheme 1-1: *Biomimetic total synthesis of dragonbloodin A1 and A2.*

Part II

The second part of this thesis describes the investigations on the total synthesis of salimabromide, a novel secondary metabolite from the marine myxobacterium strain *enhygromyxa salina SWB007*. While more than 100 natural products from terrestrial myxobacteria are known, only seven classes have been isolated from the marine counterpart. Salimabromide represents one of these classes and was only reported in 2013 from the König group. Bearing a fascinating and unprecedented carbon framework featuring two contiguous quaternary carbon centers and two aromatic bound bromide substituents, especially the difficulties in isolation and the resulting lack of material for biological studies render it an attractive and challenging target for total synthesis. Starting with inexpensive *meta*-anisaldehyde we were able to quickly access tetraline **VI** bearing both quarternary carbon centers by an unprecedented Wagner–Meerwein rearrangement/ Friedel–Crafts alkylation sequence of epoxide **V**. By subsequent well-orchestrated and high-yielding transformations, the ethyl side chain was introduced and all carbons of the framework assembled. A keteniminium mediated [2+2] cycloaddition affords tetracyclic cyclobutanone **VIII** in impressive regioselectivity and yield. A variety of late-stage oxidations including a regioselective directed Baeyer–Villiger oxidation finish the first successful total synthesis of salimabromide. By employing robust and scalable methodologies the route gives access to quantities of salimabromide in the three-digit milligram range and allows easy late-stage modifications for structure–activity relationship studies.



Scheme 1-2: *Total synthesis of salimabromide.*

2 Acknowledgments

For the last three years I have been part of two wonderful but very different groups. Since I will always remember these times with a smile on my face, I would like to thank and acknowledge all the people who made this time so educational, exciting and unforgettable.

First of all, I want to thank Prof. Dr. Dirk Trauner for giving me the opportunity to conduct my Ph.D. studies in his group. As I accomplished already one of my Master's research internships within the Trauner group under the supervision of Dr. Daniel Terwilliger, I was early fascinated by Prof. Trauner's patience for science, inspiration and humor. At this time I realized that I want to come back to this group after my Master studies and become a part of this wonderful synthesis family. Although my stay in his group was limited due to the movement of the Trauner group to the New York University, it was a very fascinating time and I wish him and all former colleagues all the best for their futures. Thanks also for entrusting me with the inspiring project of the dragonbloodins.

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Wein joined the Lab 3 and it was always a pleasure to have you around. Especially the ski trips will not be forgotten.

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3 List of Abbreviations

µW	microwave
Å	Ångstrom
Ac	acetyl
acac	acetylacetonate
AD-mix	asymmetric dihydroxylation mixture
Anis	*p*-anisaldehyd solution
ANR	anthocyanidin synthase
Ar	aryl
ATR	attenuated total reflection
BINAP	(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)
BINOL	1,1′-bi-2-naphthol
Bn	benzyl
Bu	butyl
Bz	benzoyl
CAM	ceric ammonium molybdate solution
CoA	Coenzyme A
cod	cyclooctadiene
COSY	homonuclear correlation spectroscopy
D	dextro
d	doublet (NMR spectroscopy)
dba	dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
dcype	1,2-Bis-(dicyclohexylphosphino)ethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DEAD	Diethyl azodicarboxylate
DFR	dihydroflavonol 4-reductase
DIBAL-H	diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMC	dimethylcarbonate
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dppf	1,1'-Bis(diphenylphosphino)ferrocene
E. coli	*Escherichia coli*
ee	enantiomeric excess
EI	electron impact ionization
ESI	elctro spray ionization
Et	ethyl
et al.	et alibi
F3’5’H	flavonoid 3’,5’-hydroxylase
F3’H	flavonoid 3’-hydroxylase
F3H	flavonoid 3-hydroxylase
FABP5	fatty acid binding protein 5
FT	fourier transformation
HFIP	1,1,1,3,3,3-hexafluoorisopropanol
HMBC	heterocnuclear multiple bond coherence
HMDS	bis(trimethylsilyl)amide
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
imH	imidazole
J	coupling constant (NMR spectroscopy)
L	Levo
LAR	leucoanthocyanidin reductase
LDA	lithium diisoproylamide
LDL	low-density lipoproteins
m	multiplet (NMR spectroscopy)
m	medium (IR spectroscopy)
m-CPBA	*meta*-Chloroperoxybenzoic acid
MDA	methyl dichloroacetate
Me	methyl
MOM	methoxymethyl
NADPH	Nicotinamide adenine dinucleotide phosphate (hydride)
NBS	*N*-Bromosuccinimide
NHC	*N*-heterocyclic carbene

NMO	*N*-Methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser enhancement spectroscopy
PA	proanthocyanidin
Ph	phenyl
PIDA	phenyliodine(III) diacetate
PIFA	phenyliodine bis(trifluoroacetate)
PKS	polyketide synthase
ppm	parts per million
PPO	polyphenol oxidase
p-Ts	*para*-methylphenylsulfonyl
q	quartet (NMR spectroscopy)
R	undefined residue
REM	rapid eye movement
R_f	retention factor
ROS	reactive oxygen species
s	strong (IR spectroscopy)
t	(tert-) teriary (isomer)
t	triplet (NMR spectroscopy)
TBAF	tetrabutylammoniumfluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TCM	Traditional Chinese Medicine
Tf	trifluoromethane sulfonyl
TFA	trifluoroacetyl /trifluoracetic acid
Tfacac	1,1,1-trifluoroacetylacetonate
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
TOCSY	total correlation spectroscopy
TPAP	tetrapropylammonium perruthenate
vs	very strong (IR spectroscopy)
w	weak (IR spectroscopy)
ent	enantiomer

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Chapter III

Experimental Part

Chapter I

Biomimetic Synthesis of Complex Flavonoids from East Indian Dragon's Blood

1 Introduction

1.1 Flavonoids in nature

Flavonoids undoubtedly play a central role in the family of natural products of plant origin. These molecules and their derivatives have served for a long time as colorful tools to investigate a variety of important plant problems, such as the regulation of gene expression. The Augustan monk Gregor Johann Mendel already used indirectly the flavonoid pathways in his experiments to investigate the segregation of visible traits in his hereditary studies on peas in the second half of the 19th century.[1] At the beginning of the 20th century, Bateson, Saunders and Punnett renewed the focus on these colorful studies that led to the hypothesis of genetic factors.[2] In respect to the chemical structures of flavonoids Morot was the first to reveal the pure organic nature of these molecules already in 1849.[3] 65 years later, Willstätter and colleagues revealed that the pigments of a large number of plant species all originated from the three anthocyanidins pelargonidin (**I.1**), cyanidin (**I.2**) and delphinidin (**I.3**) (Figure 1-1).[4] It was also Willstätter who described the chemical relationship to the flavonols, quercetin, myricetin, kaempferol and the presence of sugar and methoxy groups on these molecules. Bearing sugar moieties on the 3-OH group, these molecules are referred to anthocyanins, not to be confused with their aglycons. Together with his research on chlorophylls, these groundbreaking results were awarded with the Nobel Prize for Chemistry in 1915.

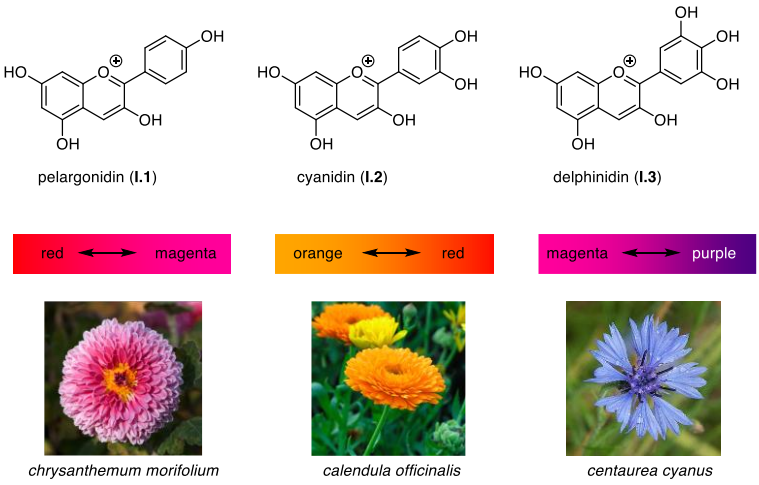


Figure 1-1: *Structures of anthocyanidins characterized by Willstätter and corresponding flowers.*

[1] G. Mendel, *Verh naturforschenden Vereines Brunn*, **1865**, 3–47.
[2] W. Bateson, E. R. Saunders, R. C. Punnett, *Proc. R. Soc. Lond. B Biol. Sci.*, **1906**, *77*, 236–238.
[3] F. S. Morot, *Ann. Sci. Nat. (Bot., Paris)*, **1849**, 160-235.
[4] R. Willstätter, A. E. Everest, *Justus Liebigs Ann. Chem.*, **1913**, *401*, 189–232, R. Willstätter, *Ber. Dtsch. Chem. Ges.*, **1914**, *47*, 2831–2874, R. Willstätter, E. K. Bolton, *Justus Liebigs Ann. Chem.*, **1915**, *408*, 42–61, R. Willstätter, F. J. Weil, *Justus Liebigs Ann. Chem.*, **1917**, *412*, 178–194.

1.2 Flavonoid subclasses

Flavonoids represent the largest class of polyphenols in nature with the characteristic diphenylpropane (C_6–C_3–C_6) structure in which a three-carbon chain connects two aromatic phenyl subunits (see Figure 1-2). This propane chain builds up a chromane through an ether bond towards a phenolic oxygen atom of the A–ring system. The B–ring is connected *via* a carbon-carbon bond at the C-2 position of the pyran (C–ring). The flavonoids can be divided into several subclasses, the seven largest of which represent the flavones (e.g. luteolin (**I.4**)), flavonols (e.g. kaempferol (**I.5**)), flavanones (e.g. naringenin (**I.6**)), flavanonols (e.g. taxifolin (**I.7**)), anthocyanidins (e.g. cyanidin (**I.2**) and luteolidin (**I.8**)), flavans (e.g. catechin (**I.9**)) and the constitutional isomeric isoflavones (e.g. genistein (**I.10**)). Their fully aromatic C–ring and the carbonyl group on C-4 characterize flavones and flavonols. As mostly yellow and sparely in water soluble compounds, they were already early used as dyes. Luteolin (**I.4**) is perhaps even the oldest European dye and is still used for dyeing leather.[5] Flavanones and Flavanonoles are dihydrogenated forms of both. The saturation of the double bond between C-2 and C-3 introduces a chirality center on the pyran ring at the C-2 position and in the case of flavanonols even a second one adjacent to the first. Due to the benzylic character of the C-2 position, some natural flavanones and flavanonols like naringenin (**I.6**) tend to racemize at pH values lower than 9.[6] The already mentioned anthocyanidins are the most colorful group of flavonoids and important natural pigments. Their intense color is based on the chromophoric benzopyrilium core. Molecules like the shown luteolidin (**I.8**) belong to the subclass of the 3-deoxyanthocyanidins, lacking the 3-OH group that is the usual anchor position for glycosylations in nature (compare Figure 1-1).

[5] H. B. Singh, K. A. Bharati, *Handbook of Natural Dyes and Pigments*, Elsevier, **2014.**
[6] M. Krause, R. Galensa, *Chromatographia*, **1991**, *32*, 69–72.

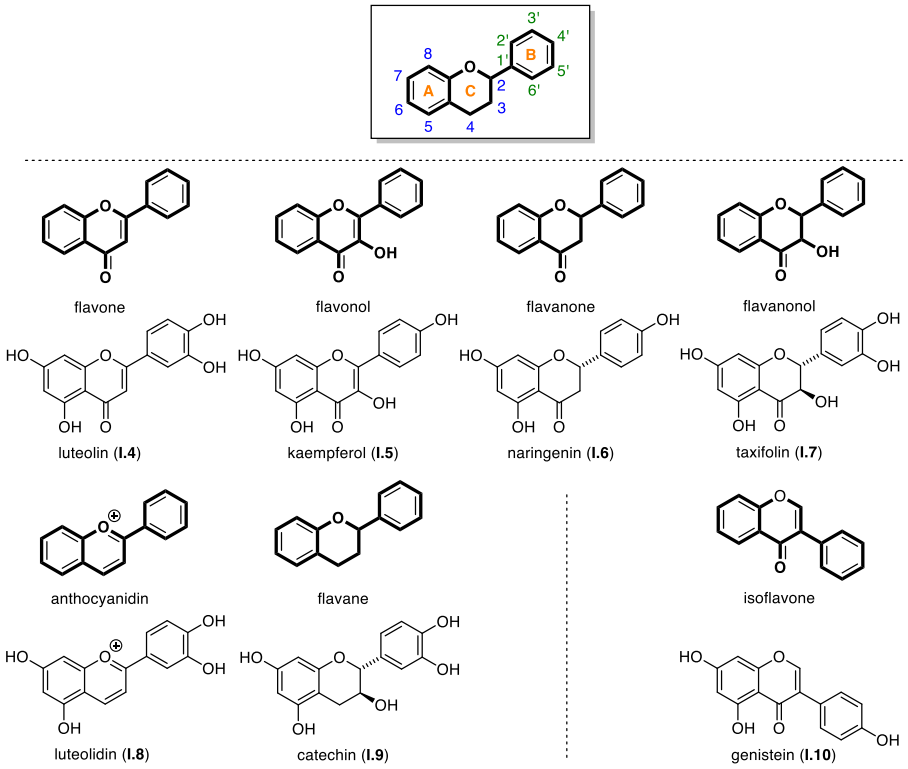


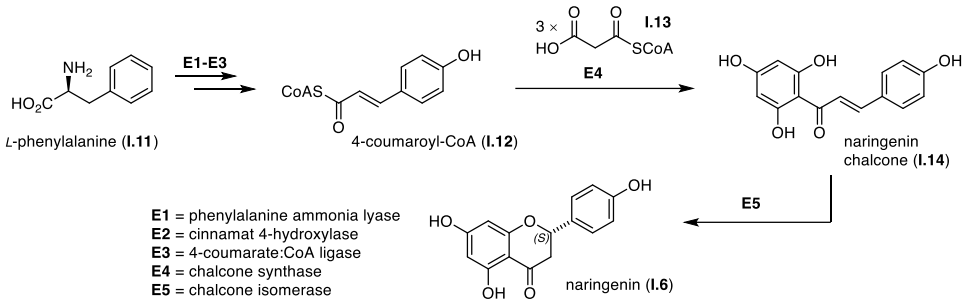
Figure 1-2: *Major classes of natural occurring monomeric flavonoids.*

Flavans that have a fully saturated chromane core structure represent in terms of volume probably the biggest class of natural occurring flavonoids. An important example is catechin (**I.9**), which belongs to the subfamily of flavan-3-ols and is a major building block of condensed tannins and precursor for theaflavins in fermentated black tea. In addition to these six classes, there are also several constitutional isomeric subgroups, of which the isoflavones belong to the most prominent one. These bear the B–ring substituent on the C-3 position instead of the C-2 position. This structural effect gives them completely different dietary effects. Due to a structural resemblance with estrogen derivatives and a resulting often similar hormonal effect, this class is also referred to as phytoestrogens. Consumption of appropriate plants containing these compounds can entail severe health risks.

1.3 Flavonoid significance in plants

Nature does not produce these compounds without any reason. These compounds play important roles in plants like acting as copigments, shielding the organism from dangerous UV radiation[7] and even contributing in some cases to male fertility by facilitating the pollen germination.[8] They also have roles against frost hardiness, drought resistance, help the plant in detoxification, and act as antimicrobial defensive compounds.[9] Due to the omnipresence of the flavonoids in everyday food like fruits, vegetables, chocolate, wine and tea, scientists were early on highly interested in the origin of these metabolites in the plants and intensively studied their biogenetic origin – the flavonoid pathway. Unsurprisingly, it is now one of the most well-studied secondary metabolite systems in the plant world. Stafford was able to prove that many of the enzymes involved originated early from the primary metabolism.[10] This development occurred during the rapid evolution that accompanied the movement of the plants from water to land. As part of the phenylpropanoid pathway, L-phenylalanine (**I.11**) that stems from the shikimate pathway is converted into 4-coumaroyl-CoA (**I.12**) by a lyase, a hydroxylase and a CoA ligase.[11] This building block brings the first aromatic core (C-ring) with it. The second one is synthesized by the chalcone synthase that uses malonyl-CoA (**I.13**) as a C_2 building block. The so formed naringenin chalcone (**I.14**) is closed by a chalcone isomerase that catalyzes the intramolecular Michael-addition in a highly stereoselective way favoring (2*S*)-naringenin (**I.6**) over (2*R*)-naringenin with a selectivity of around 100 000:1.[12] Being the central linker enzyme between the phenylpropanoid and the flavonoid pathway, it was also the first flavonoid pathway enzyme to be isolated from soy beans and described by Moustafa *et al.* in 1967.[13]

[7] K. G. Ryan, E. E. Swinny, C. Winefield, K. R. Markham, *Z. Naturforsch. C*, **2001**, *56*, 745–754.
[8] L. P. Taylor, E. Grotewold, *Curr. Opin. Plant. Biol.*, **2005**, *8*, 317–323.
[9] A. Samanta, G. Das, S. Das, *Int. J. Pharm. Sci. Tech.*, **2011**, *6*, 12–36.
[10] H. A. Stafford, *Plant Physiology*, **1991**, *96*, 680–685.
[11] C. M. Fraser, C. Chapple, *Arabidopsis Book*, **2011**, *9*, e0152.
[12] J. M. Jez, M. E. Bowman, R. A. Dixon, J. P. Noel, *Nat. Struct. Biol.*, **2000**, *7*, 786–791.
[13] E. Moustafa, *Phytochemistry*, **1967**, *6*, 625–632.



Scheme 1-1: *Phenylpropanoid pathway from L-phenylalanine* ***(I.11)*** *to naringenin* ***(I.6)****.*

For diversification of the flavanone thus formed, that is the central branching point of the flavonoid biogenesis, a variety of enzymes including hydroxylases, reductases and especially glucosyl transferases are responsible that today more than 6 500 different derivatives are known.[14]

1.4 Dietary effects on mammalians

Being an inevitable ingredient of daily food, scientists early started to investigate possible consumption effects of flavonoids on human health. Research in recent decades has shown that a flavonoid-rich diet can protect against a variety of diseases, including coronary – especially cardiovascular – diseases and even some cancers.[15] In particular, cranberry products, which are known for their high flavonoid content, are intensively advertised to the public for the prophylaxis and treatment of bladder diseases.[16] These positive health benefits are attributed especially to the antioxidative effect of the flavonoids. Reactive oxygen species (ROS) are permanently formed during normal aerobic metabolism despite the natural antioxidant defense mechanism involving superoxide dismutases and catalases. These species can cause severe damage to proteins, lipids and deoxyribonucleic acid (DNA) and are involved in cellular aging,[17] mutagenis,[18] carcinogenesis[19] and coronary heart diseases due to the damage they cause.[20] In this respect many studies could prove *in vitro* the potent peroxyl radical scavenging abilities of flavonoids for instance in the oxidation of lipids and low-density lipoproteins (LDLs).[21] In general, the protective effects of flavonoids in

[14] A. Samanta, G. Das, S. Das, *Int. J. Pharm. Sci. Tech.*, **2011**, *6*, 12–36.
[15] A. R. Ness, J. W. Powles, *Int. J. Epidemiol.*, **1997**, *26*, 1–13.
[16] G. Abeywickrama, S. C. Debnath, P. Ambigaipalan, F. Shahidi, *J. Agric. Food Chem.*, **2016**, *64*, 9342–9351.
[17] J. Sastre, F. V. Pallardó, J. Viña, *IUBMB life*, **2000**, *49*, 427–435.
[18] W. Takabe, E. Niki, K. Uchida, S. Yamada, K. Satoh, N. Noguchi, *Carcinogenesis*, **2001**, *22*, 935–941.
[19] S. Kawanishi, Y. Hiraku, S. Oikawa, *Mutat. Res.*, **2001**, *488*, 65–76.
[20] M. A. Khan, A. Baseer, *J. Pak. Med. Assoc.*, **2000**, *50*, 261–264.
[21] C. Castelluccio, G. Paganga, N. Melikian, G. P. Bolwell, J. Pridham, J. Sampson, C. Rice-Evans, *FEBS Lett.*, **1995**, *368*, 188–192, N. Salah, N. J. Miller, G. Paganga, L. Tijburg, G. P. Bolwell, C. Rice-Evans, *Arch. Biochem. Biophys.*, **1995**, *322*, 339–346.

biological systems can be ascribed next to the antioxidative effects to the ability of transferring free radical electrons, chelate cell-toxic metal catalysts,[22] regenerate Vitamin E radials[23] and the direct inhibition of oxidases[24].

1.5 Oligomeric flavonoids - proanthocyanidins

Flavonoids not only appear exclusively as monomers. In 1947 Jaques Masquelier, a French chemist, discovered and patented methods to isolate oligomeric and polymeric flavonoids from grape seeds during his Ph.D. studies.[25] These extracts are still commercially available as food additives and are market under the name Anthogenol®. These first characterized procyanidins are a subclass of the so-called proanthocyanidins or flavolanes and consist of polymeric chains of catechin (**I.9**) and epicatechin (**I.15**). These two flavan-3-ols are also the most common found building blocks in natural condensed tannins and proanthocyanidins. The name proanthocyanidin is based on the observation that oxidative depolymerization leads back to monomeric anthocyanidins. They can exist as chains but also branched molecules of condensed tannins (**I.20**) are known (indicated by dotted line in Figure 1-3). Condensed tannins refer generally to oligomeric proanthocyanidins that can reach molecular masses up to 20 000.[26] Proanthocyanidins are divided into a type-A and a type-B class. While in type-B proanthocyanidins the flavonoid subunits are connected *via* a single C-C bond (4→8 or 4→6) like in procyanidin B1 (**I.16**) or cinnamtannin A3 (**I.19**), the subunits in type-A proanthocyanidins are connected *via* an additional C-O bond (2→*O*-7 or 2→*O*-5) like in procyanidin A1 (**I.18**) or cinnamtannin B1 (**I.17**). This results in the characteristic bicyclic [3.3.1] ketal moiety of this type. Studies showed an anti-adhesion effect of type-A proanthocyanidins from cranberries against *E. coli* to the urinary tract epithelial cells, while type-B proanthocyanidins from grapes exhibited only minor activity.[27] Yet no sufficient clinical evidence was given that this effect helps to prevent bladder diseases.[28] Recently Takanashi *et al.* showed that type-B chains of

[22] M. Ferrali, C. Signorini, B. Caciotti, L. Sugherini, L. Ciccoli, D. Giachetti, M. Comporti, *FEBS Lett.*, **1997**, *416*, 123–129.
[23] R. Hirano, W. Sasamoto, A. Matsumoto, H. Itakura, O. Igarashi, K. Kondo, *J. Nutr. Sci. Vitaminol. (Tokyo)*, **2001**, *47*, 357–362.
[24] P. Cos, L. Ying, M. Calomme, J. P. Hu, K. Cimanga, B. van Poel, L. Pieters, A. J. Vlietinck, D. Vanden Berghe, *J. Nat. Prod.*, **1998**, *61*, 71–76.
[25] C. Izard, J. Masquelier, *C. R. Acad. Sci. Paris*, **1958**, *246*, p. 1454.
[26] P. Frutos, G. Hervás, F. J. Giráldez, A. R. Mantecón, *Span. J. Agric. Res.*, **2004**, *2*, p. 191.
[27] A. B. Howell, J. D. Reed, C. G. Krueger, R. Winterbottom, D. G. Cunningham, M. Leahy, *Phytochemistry*, **2005**, *66*, 2281–2291.
[28] R. G. Jepson, G. Williams, J. C. Craig, *Cochrane Database Syst. Rev.*, **2012**, *10*, CD001321.

epicatechin longer than trimers (e.g. **I.19**) exhibit strong anticancer effects while chains of the epimer catechin did not show any activity at all.[29]

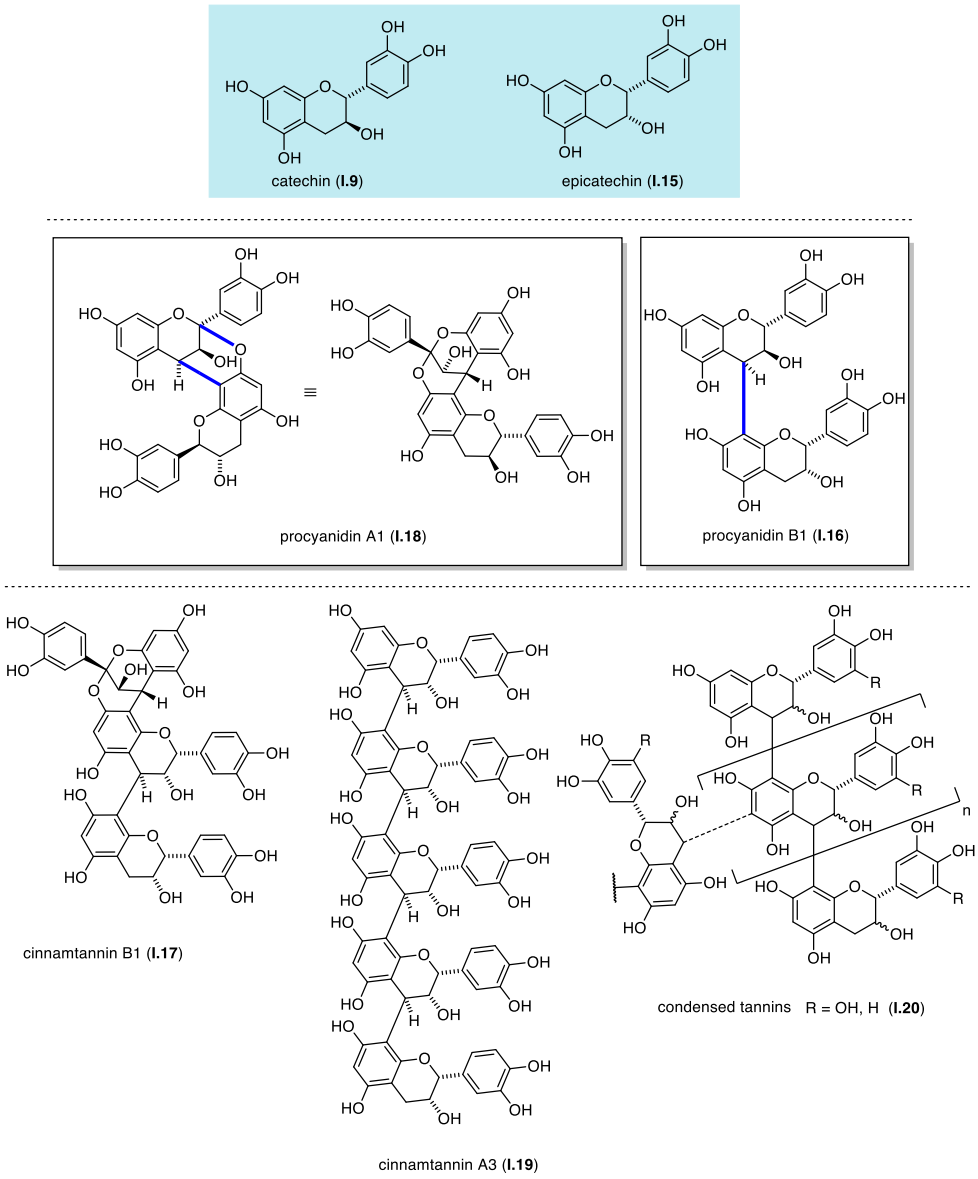


Figure 1-3: *Proanthocyanidins type-A and type-B from catechin* ***(I.9)*** *and epicatechin* ***(I.15)*** *building blocks.*

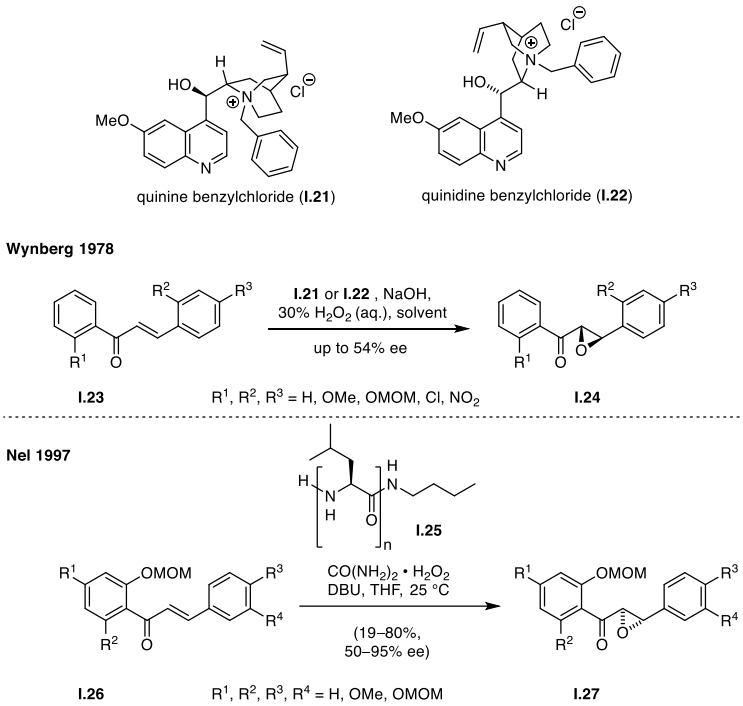
[29] K. Takanashi, M. Suda, K. Matsumoto, C. Ishihara, K. Toda, K. Kawaguchi, S. Senga, N. Kobayashi, M. Ichikawa, M. Katoh et al., *Sci. Rep.*, **2017**, *7*, p. 7791.

1.6 Asymmetric synthesis of flavonoids

Despite the omnipresence of flavonoids in nature, many interesting derivatives occur only in small quantities and cannot be isolated in larger amounts with justifiable effort. Synthetic approaches are essential for reliable access and asymmetric synthesis is due to the chiral center on C-2 all the more important. For this reason, the scientific community worked early on to synthesize these natural products and their derivatives stereoselectively. In particular, chalcones or dihydrochalcones are important intermediates for the synthesis of flavonoids. Their diphenylpropan frameworks are readily accessible *via* well-established routes comprising aldol-condensation of 2-hydroxyacetophenones and benzaldehydes.[30] Usually a condensation under basic conditions is preferred as under acidic conditions, the direct racemic formation of flavanones is observed. For an asymmetric synthesis, chalcone epoxides emerged early as important intermediates. Wynberg was the first to report quinine and quinidine benzyl chlorides (Scheme 1-2, **I.21** and **I.22**) as phase transfer catalysts for asymmetric epoxidation of electron poor olefins using readily available aqueous hydrogen peroxide as oxidant.[31] He showed that the enantiomeric excess was inversional proportional to the dielectric constant of the organic solvent and could synthesize chalcone epoxides (**I.24**) with up to 54% ee in toluene.[32] Despite the rather low enantiomeric excesses he proved the preferential formation of (α*S*,β*R*)-epoxides (not shown) for **I.22** and (αR,βS)-epoxides (shown) for **I.21** as catalysts respectively. These findings lead to a variety of investigations to enhance the enantiomeric excess of such epoxides although many methods were limited to non-chalcone substrates. Only a few years later, a breakthrough was achieved by Juliá by the development of triphasic epoxidation conditions exploiting amino acid polymers as chiral catalysts.[33] By using poly-(*S*)-alanine, enantiomeric excesses higher than 90% could be achieved. This method has been improved through collaboration with Colonna and has provided several efficient catalysts based on alanine, leucine and isoleucine.[34] Under the originally published triphasic conditions, epoxidation takes place at the interface between the insoluble polymer and the organic solvent (e.g. toluene). An aqueous hydrogen peroxide solution provides the necessary oxidizing agent. Unfortunately, this protocol still suffered from limitations such as unacceptably long reaction times, catalyst degradation and sometimes the need for continuous addition of base and oxidant. Many of these problems were solved by Roberts and Bentley, who switched to a two-phase non-aqueous system

[30] v. St. Kostanecki, G. Rossbach, *Ber. Dtsch. Chem. Ges.*, **1896**, *29*, 1488–1494.
[31] R. Helder, J. C. Hummelen, R.W.P.M. Laane, J. S. Wiering, H. Wynberg, *Tetrahedron Lett.*, **1976**, *17*, 1831–1834.
[32] H. Wynberg, B. Greijdanus, *J. Chem. Soc., Chem. Commun.*, **1978**, *0*, 427–428.
[33] S. Juliá, J. Guixer, J. Masana, J. Rocas, S. Colonna, R. Annuziata, H. Molinari, *J. Chem. Soc., Perkin Trans. 1*, **1982**, 1317–1324,S. Juliá, J. Masana, J. C. Vega, *Angew. Chem. Int. Ed.*, **1980**, *19*, 929–931.
[34] S. Colonna, H. Molinari, S. Banfi, S. Juliá, J. Masana, A. Alvarez, *Tetrahedron*, **1983**, *39*, 1635–1641.

with a non-nucleophilic base.[35] Nel further optimized these conditions for the epoxidation of hydroxylated chalcones (see Scheme 1-2).[36] In his method, carbamide peroxide was used together with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and the polyleucine catalyst **I.25** in tetrahydrofuran, which provides high amounts of chalcone epoxides of medium to high optical purity.

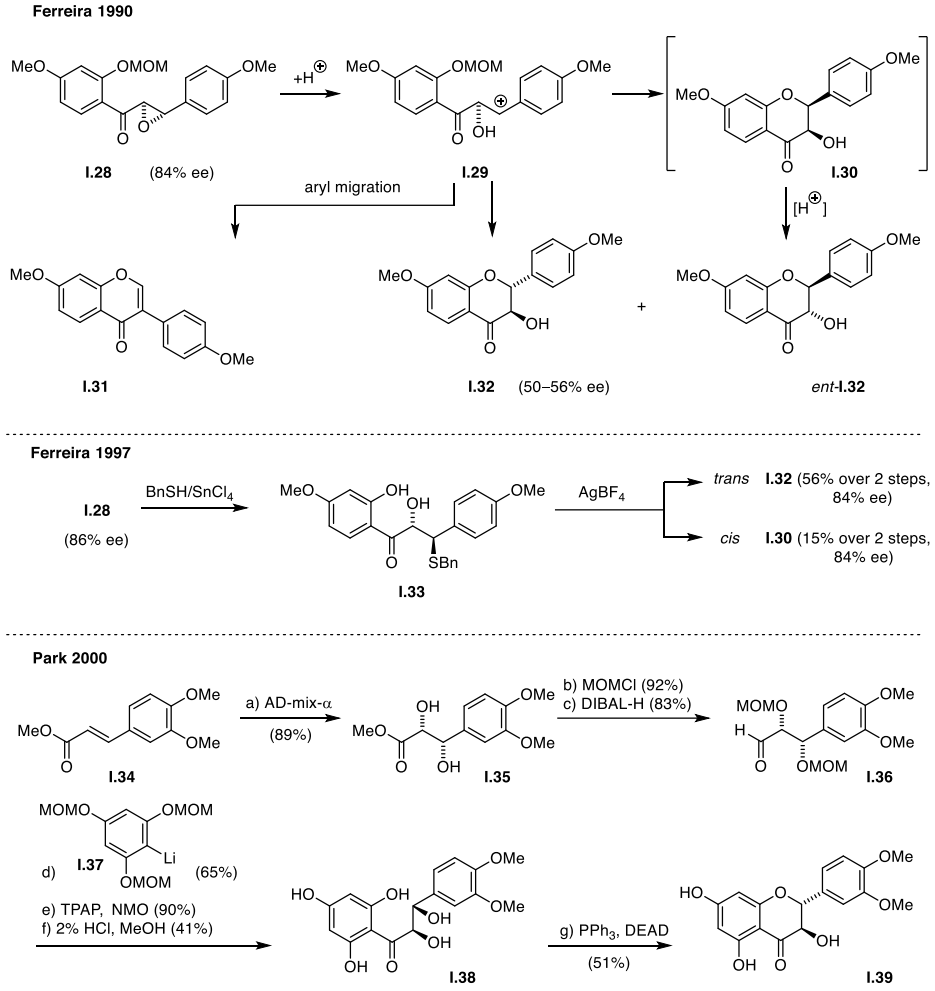


Scheme 1-2: *Asymmetric epoxidation of chalcones by Wynberg and Nel.* ***I.24*** *possesses the absolute stereochemistry derived from asymmetric induction by the catalyst* ***I.21.***

Since the chalcone epoxides contain a stereo center at the C-2 position, they are the key intermediates for an asymmetric flavonoid ring closure. The attempts by Ferreira and his colleagues to carry out acid-catalyzed cyclization reactions of exemplary **I.28** to produce *cis*- and *trans*-2,3-flavanonols were hampered by two main difficulties. On the one hand, aryl migration was observed, leading to isoflavone (**I.31**) formation, and on the other hand, instant epimerization of thermodynamically less stable (2*S*,3*R*)-*cis*-flavanonol (**I.30**), which forms the opposite enantiomer to the first formed (2*R*,3*R*)-*trans*-flavanonol (**I.32**), leading to an enormous decrease in optical purity.[37] By elegantly exploiting the nucleophilic and nucleofugic character of thiols he solved this problem shortly after.[38] Together with his coworkers the enantioenriched chalcone epoxides were

[35] P. A. Bentley, S. Bergeron, M. W. Cappi, D. E. Hibbs, M. B. Hursthouse, T. C. Nugent, R. Pulido, S. M. Roberts, L. Eduardo Wu, *Chem. Commun.*, **1997**, 739–740, M. E. Lasterra-Sánchez, U. Felfer, P. Mayon, S. M. Roberts, S. R. Thornton, C. J. Todd, *J. Chem. Soc., Perkin Trans. 1*, **1996**, *19*, 343–348.
[36] R. J.J. Nel, P. S. van Heerden, H. van Rensburg, D. Ferreira, *Tetrahedron Lett.*, **1998**, *39*, 5623–5626.
[37] J. A.N. Augustyn, C. B. Barend, Bezuidenhoudt, D. Ferreira, *Tetrahedron*, **1990**, *46*, 2651–2660.
[38] H. van Rensburg, P. S. van Heerden, B. C. B. Bezuidenhoudt, D. Ferreira, *Chem. Commun.*, **1996**, p. 2747.

converted into thioethers (**I.33**) by treatment with benzylthiol and tin tetrachloride. These conditions cleave also the methoxy methyl (MOM) protecting group *in situ*. Subsequently, the pyran ring was cyclized by treatment with thiophilic silver tetrafluoroborate, which resulted in high amounts of *trans*-flavanonols (**I.32**) and for the first time also *cis*-flavanonols (**I.30**) with complete retention of the optical purity.



Scheme 1-3: *Cyclization attempts of enantiomeric enriched chalcone epoxides towards cis- and trans-flavanonols and total synthesis of (2R,3R)-3′,4′-O,O-dimethyltaxifolin (**I.39**) by Park.*

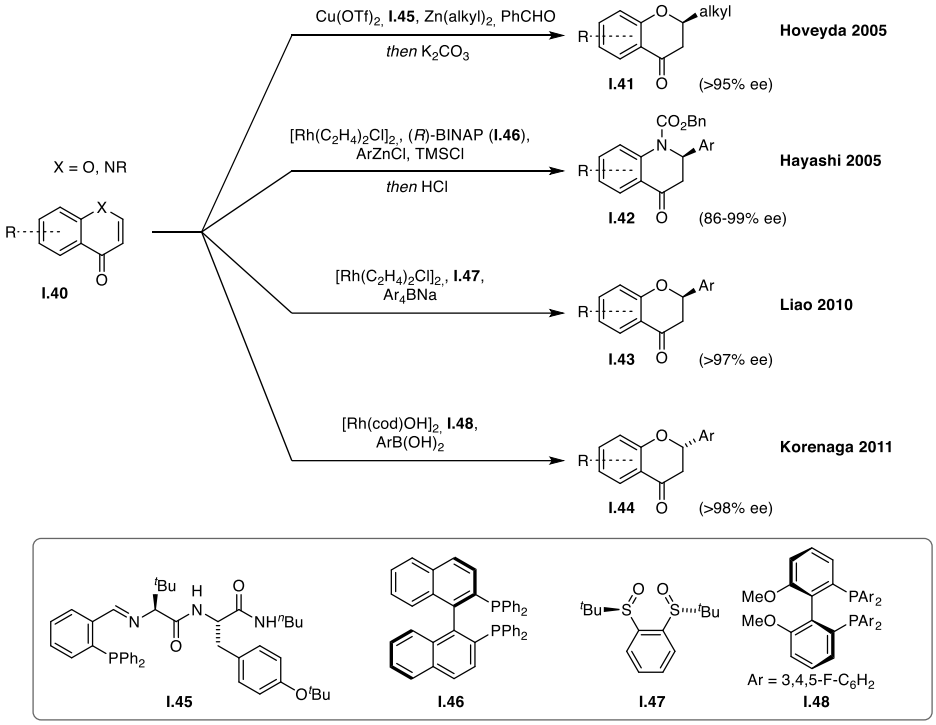
In 1992, Barry Sharpless introduced the new class of phthalazine ligands for the asymmetric dihydroxylation of alkenes that quickly arrived in the scientific community.[39] This exceptional stereoselective method was used by Park and coworkers as key-step in a highly enantioselective synthesis of pure (2*R*,3*R*)-3′,4′-*O*,*O*-dimethyltaxifolin (**I.39**).[40] To forge the B-ring, a Mitsunobu

[39] K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K. S. Jeong, H. L. Kwong, K. Morikawa, Z. M. Wang, *J. Org. Chem.*, **1992**, *57*, 2768–2771.
[40] S.-s. Jew, H.-a. Kim, S.-y. Bae, J.-h. Kim, H.-g. Park, *Tetrahedron Lett.*, **2000**, *41*, 7925–7928.

reaction afforded the desired *trans*-flavanonol in optical purity higher than 99%. The A-ring was convergently introduced by nucleophilic addition of protected and lithiated phloroglucinol **I.37** onto phenylpropanal **I.36** and subsequent Ley–Griffith oxidation.

A more general approach to enantioenriched flavanones and chromanones by an intermolecular conjugate addition of nucleophilic organometallic species was developed in the middle of the 2000's by different groups (Scheme 1-4). This is also one of the most convergent approaches to enantioenriched flavanones. While it has been frequently utilized for asymmetric tetralone synthesis previously, the application to chromones and flavones was limited before by the ease of phenoxide elimination after enolate formation. Hoveyda[41] and Hayashi[42] who both published methodologies in 2005 solved this issue by trapping the enolate either by an aldehyde electrophile or trimethylchlorosilane. Those trapping groups were removed in an additional step. Hoveyda employed an amino acid derived phosphine ligand **I.45** in cooperation with copper triflate. Yet this method was limited to alkyl zinc species and not applicable to flavanone synthesis. Hayashi employed rhodium with (*R*)-BINAP (**I.46**) instead and synthesized quinolones derivatives that shortly before have been identified as a new class of antimitotic antitumor agents.[43] Also Liao employed rhodium in his methodology five years later.[44] Tetraarylboronates as nucleophilic component enabled to run the reaction in an aqueous system that avoids the need of enolate trapping. Only electron deficient arylboronates suffered from low yields but still with ee values of around 97%. Novel was especially the C_2-symmetric chiral bis-sulfoxide ligand **I.47** in his methodology. A similar approach was reported by Korenaga and co-workers in early 2011.[45] Under their conditions the catalyst loadings were significantly reduced and turnover numbers up to 320 000 achieved. This was realized by combination of rhodium with the chiral highly electron-poor ligand (*R*)-MeO-F_{12}-BIPHEP (**I.48**). With this methodology, it was finally possible to employ easy accessible aryl boronic acids as nucleophiles.

[41] M. K. Brown, S. J. Degrado, A. H. Hoveyda, *Angew. Chem. Int. Ed.*, **2005**, *44*, 5306–5310.
[42] R. Shintani, T. Yamagami, T. Kimura, T. Hayashi, *Org. Lett.*, **2005**, *7*, 5317–5319.
[43] Y. Xia, Z. Y. Yang, P. Xia, K. F. Bastow, Y. Tachibana, S. C. Kuo, E. Hamel, T. Hackl, K. H. Lee, *J. Med. Chem.*, **1998**, *41*, 1155–1162.
[44] J. Chen, J. Chen, F. Lang, X. Zhang, L. Cun, J. Zhu, J. Deng, J. Liao, *J. Am. Chem. Soc.*, **2010**, *132*, 4552–4553.
[45] T. Korenaga, R. Maenishi, K. Hayashi, T. Sakai, *Adv. Synth. Catal.*, **2010**, *352*, 3247–3254.

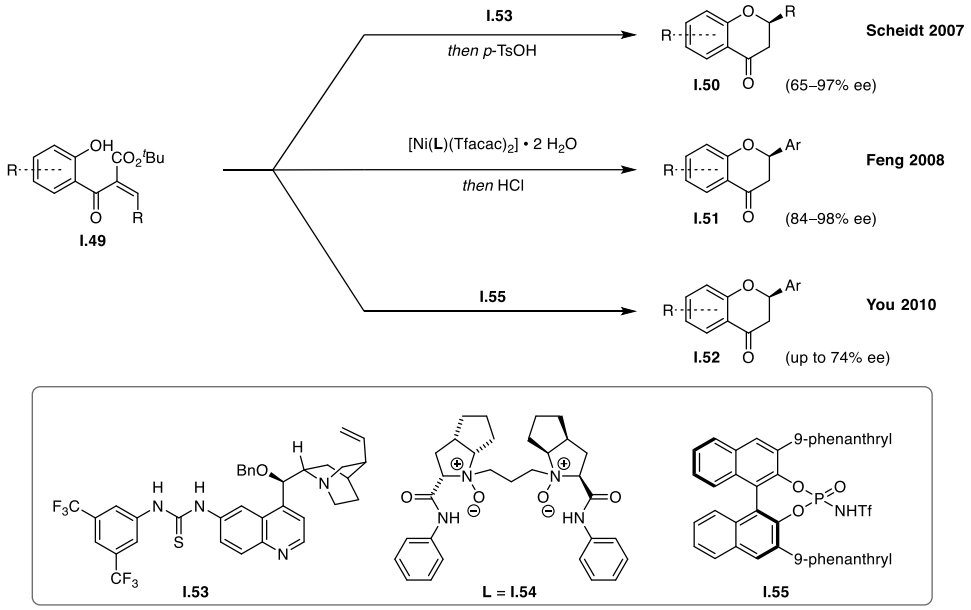


Scheme 1-4: *Asymmetric conjugate addition towards the synthesis of chromones and flavones.*

Next to those two approaches, scientists investigated many other ways to forge the important chiral C–ring of monomeric flavonoids. Next to approaches involving chiral pool compounds or kinetic resolutions that were already investigated by Corey,[46] especially the intramolecular Michael addition was extensively investigated by the scientific community (Scheme 1-5). In 2007, Scheidt and coworkers reported the first general catalytic and enantioselective synthesis of flavanones and chromanones from alkylidenes (**I.49**).[47] The intramolecular Michael addition towards the alkylidene is catalyzed by a chiral quinine derived thiourea catalyst **I.53**. The integrated *tert*-butyl ester provides a second Lewis-basic side for the organocatalyst and enhances the reactivity of the enone. Under mildly acidic conditions, the ester could be easily removed after the ring closing. The alkylidenes were generated by Knoevenagel condensation, after which the *E* diastereomer was separated and purified by recrystallization. This gave access to flavanones with excellent enantioselectivity. Based on transition metal catalysis Feng reported a method catalyzed by a chiral *N,N'*-dioxide nickel(II) complex employing the ligand **I.54**.[48] Noteworthy despite the general high yields, substrates containing electron-donating groups resulted in decreased optical purity of the corresponding flavanones. The same transformation was also achieved by You who showed the

[46] E. J. Corey, R. B. Mitra, *J. Am. Chem. Soc.*, **1962**, *84*, 2938–2941.
[47] M. M. Biddle, M. Lin, K. A. Scheidt, *J. Am. Chem. Soc.*, **2007**, *129*, 3830–3831.
[48] L. Wang, X. Liu, Z. Dong, X. Fu, X. Feng, *Angew. Chem. Int. Ed.*, **2008**, *47*, 8670–8673.

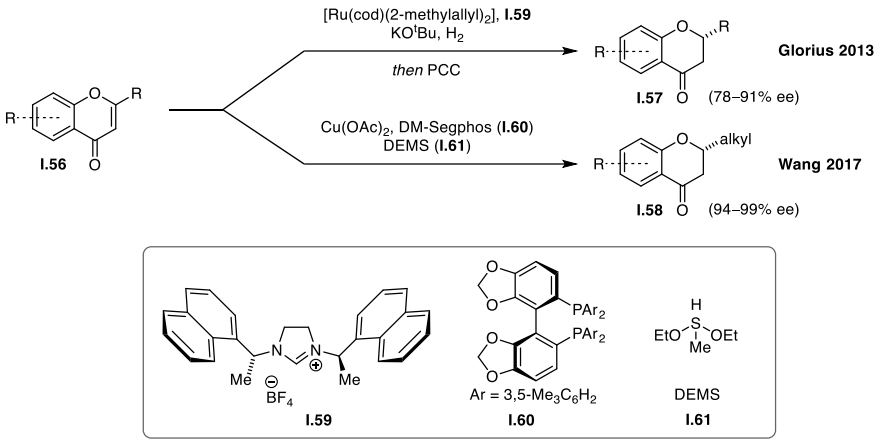
general applicability of BINOL derived phosphoric acid catalysts (**I.55**) to catalyze the intramolecular Michael addition affording flavanones in up to 74% ee.[49]



Scheme 1-5: *Asymmetric synthesis of flavanones and chromanones by intramolecular conjugate addition.*

The approach most recently developed is the asymmetric hydrogenation of flavones (Scheme 1-6). In 2013, Glorius and his team reported on the first asymmetric hydrogenation of flavones catalyzed by an N-heterocyclic carbene-(NHC(**I.59**))-ruthenium(II) complex with enantioselectivities of up to 97%.[50] In 2017 Wang reported on a complementary asymmetric methodology achieving a copper catalyzed conjugate reduction of chromones. Unfortunately despite the general high yields and enantioselectivities only chromones with an alkyl residue on the C-2 position could successfully be reduced.[51]

[49] Z. Feng, M. Zeng, Q. Xu, S. You, *Chin. Sci. Bull.*, **2010**, *55*, 1723–1725.
[50] D. Zhao, B. Beiring, F. Glorius, *Angew. Chem. Int. Ed.*, **2013**, *52*, 8454–8458.
[51] D. Xiong, W. Zhou, Z. Lu, S. Zeng, J. Wang, *Chem. Commun.*, **2017**, *53*, 6844–6847.



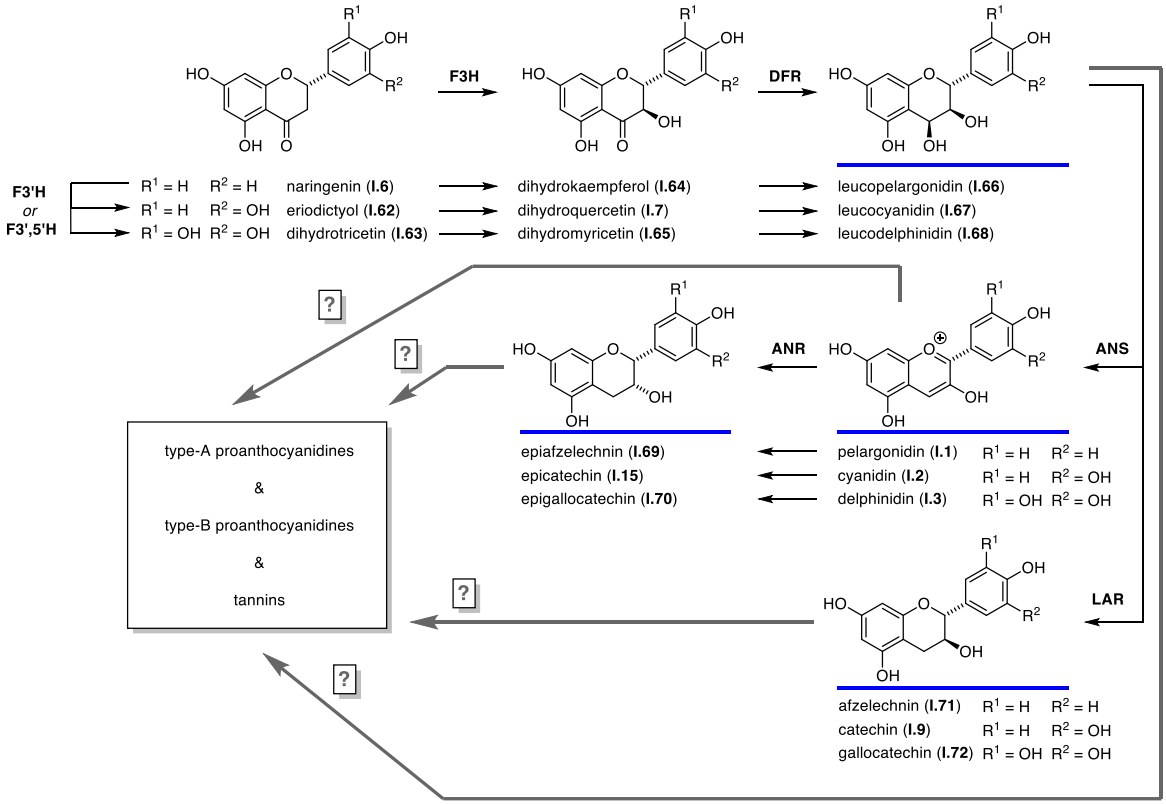
Scheme 1-6: *Asymmetric synthesis of flavanones and chromanones by enantioselective hydrogenation.*

1.7 Biogenesis of B-type proanthocyanidins

For an efficient biomimetic access to oligomeric and polymeric proanthocyanidins, their biological origin needs to be revealed in a first instance. As most procyanidins and tannins consist predominantly of the flavan-3-ols catechin (**I.9**) and epicatechin (**I.15**), their exact origin in the flavonoid pathway is of special interest and importance. To synthesize these epimers several enzymes are involved (Scheme 1-7). Starting from naringenin (**I.6**), the enzymes flavonoid 3'-hydroxylase (**F3'H**) or flavonoid 3',5'-hydroxylase (**F3'5'H**) adjust the hydroxylation pattern on the B-ring to synthesize eriodictyol (**I.62**) and dihydrotricetin (**I.63**). All of these three (2S)-flavanones can be oxidatively hydroxylated to yield dihydroflavonols (dihydrokaempferol (**I.64**), dihydroquercetin/taxifolin (**I.7**) and dihydromyricetin (**I.65**), respectively) by the flavonoid 3-hydroxylase (**F3H**). Subsequently the dihydroflavonol 4-reductase (**DFR**), a NADPH depending enzyme, reduces the dihydroflavonols to leucoanthocyanidins (leucopelargonidin (**I.66**), leucocyanidin (**I.67**) and leucodelphinidin (**I.68**), respectively).[52] This reduction is like the others highly specific and delivers (2*R*,3*S*,4*S*)-leucoanthocyanidins.[53] These molecules represent branching points for the synthesis of *cis*- and *trans*-flavan-3-ols. On the one hand, the anthocyanidin synthase (**ANS**) – an non-haem Fe^{2+} oxygenase – synthesizes the colored achiral anthocyanidins (pelargonidin (**I.1**), cyanidin (**I.2**), delphinidin (**I.3**), respectively) that can be converted into the *cis*-flavan-3-ols (epiafzelechnin (**I.69**), epicatechin (**I.15**), epigallocatechin (**I.70**), respectively) by the anthocyanidin reductase (**ANR**).[54] Yet for the synthesis of the *trans*-flavan-3-ols another route is purchased by nature. For this, the leucoanthocyanidin reductase (**LAR**) removes the benzylic

[52] S. Martens, T. Teeri, G. Forkmann, *FEBS Lett.*, **2002**, *531*, 453–458.
[53] P. Petit, T. Granier, B. L. d'Estaintot, C. Manigand, K. Bathany, J.-M. Schmitter, V. Lauvergeat, S. Hamdi, B. Gallois, *J. Mol. Biol.*, **2007**, *368*, 1345–1357.
[54] D.-Y. Xie, S. B. Sharma, N. L. Paiva, D. Ferreira, R. A. Dixon, *Science*, **2003**, *299*, 396–399.

hydroxyl group to yield the *trans*-flavan-3-ols (afzelechnin (**I.71**), catechin (**I.9**), gallocatechin (**I.72**), respectively) directly.[55] Thus, epicatechin (**I.15**) and catechin (**I.9**), the two dominant building blocks and potential precursors of proanthocyanidins are synthesized from two distinct pathway branches, employing two distinct enzymes and two different substrates although the difference between both is only a single stereocenter.



***Scheme 1-7**: Flavonoid pathway towards trans- and cis-flavan-3-ols, highlighting possible precursors for PA formation.*

For the formation of proanthocyanidins, the *cis*-flavan-3-ols, the *trans*-flavan-3-ols, the anthocyanidins and the leucoanthocyanidins were discussed as potential precursors (blue subscriptions and bold grey arrows in Scheme 1-7). Yet the exact mechanism *in vivo* is still controversially discussed and especially the roles of enzymatic and nonenzymatic steps remain in many cases unclear and may differ from molecule to molecule. Furthermore type-A and type-B PAs have to be distinguished in many cases. In 2005 Harper and coworkers reported their findings on the dependency of PA formation in the seed coat endothelium of *Arabidopsis thaliana* on a plasma

[55] G. J. Tanner, K. T. Francki, S. Abrahams, J. M. Watson, P. J. Larkin, A. R. Ashton, *J. Biol. Chem.*, **2003**, *278*, 31647–31656.

membrane H^+ ATPase.[56] Further studies support the hypothesis that such a H^+-ATPase or even P-type proton pumps could help acidify cytoplasmic or vacuolar compartments in which the PA-synthesis takes place in. In mechanistic terms, this supports the theory that the PA type-B C–C bond (4→8 or 4→6) is initially formed by the formation of a *para*-quinomethide from a leucoanthocyanidin that acts as an electrophile on the C-4 position. Nucleophilic attack of an electronrich flavan-3-ol forges subsequently the intermolecular bond of the type-B PA. The attack of similar nucleophilic leucoanthocyanidins instead of a flavan-3-ol enables oligo- and polymerization until a flavan-3-ol terminates the elongation.[57] Yet this theory lacks of explanation that epicatechin was found in many proanthocyanidins as starting and elongation unit.[58] To find a solution for this paradox, Haslam proposed that the initially formed *para*-quinomethides with the *trans*-stereochemistry of catechin (**I.74**) can be converted *via* flav-3-en-3-ol intermediates (**I.76**) to their *cis* counterparts (**I.78**) (Scheme 1-8).[59] This theory could not be proven *in vivo* yet, but is supported by experimental data from Creasey and Swain who showed already the synthesis of proanthocyanidins from leucocyanidin (**I.67**) with either catechin (**I.9**) or epicatechin (**I.15**) units *in vitro*.[60] A highly speculative route proposed by Dixon also involves the flav-3-en-3-ols (**I.76**) as intermediate yet generated by a different pathway.[61] A polyphenol oxidase (PPO) is proposed to oxidize the B-ring of *cis*- and *trans*-flavan-3-ols towards an *ortho*-quinone (**I.79**, **I.81**) first. These quinones oxidize subsequently the adjacent pyran ring to the flav-3-en-3-ol (**I.76**). However in the experimentally conducted PPO mediated oxidative polymerization of flavan-3-ols, researchers never obtained natural PAs but oligomers with bond connection towards the terminal B-ring and not towards the C-4 position of the C-ring.[62] In addition to these theories based on the leucoanthocyanidins and the flavan-3-ols, anthocyanidins and anthocyanins (glycosylated anthocyanidins) are potential precursors for PA formation as well what should not be forgotten (see chapter 1.9). They were shown to condense non enzymatically with nucleophilic flavonoid molecules due to their partially availability as quinomethides (anhydrobase) next to their flavylium form depending on the pH value. Especially in the case of wine this reaction is directly observable as this reaction causes a change of the tannin composition over time what is relevant for the mouth-feel and color.[63]

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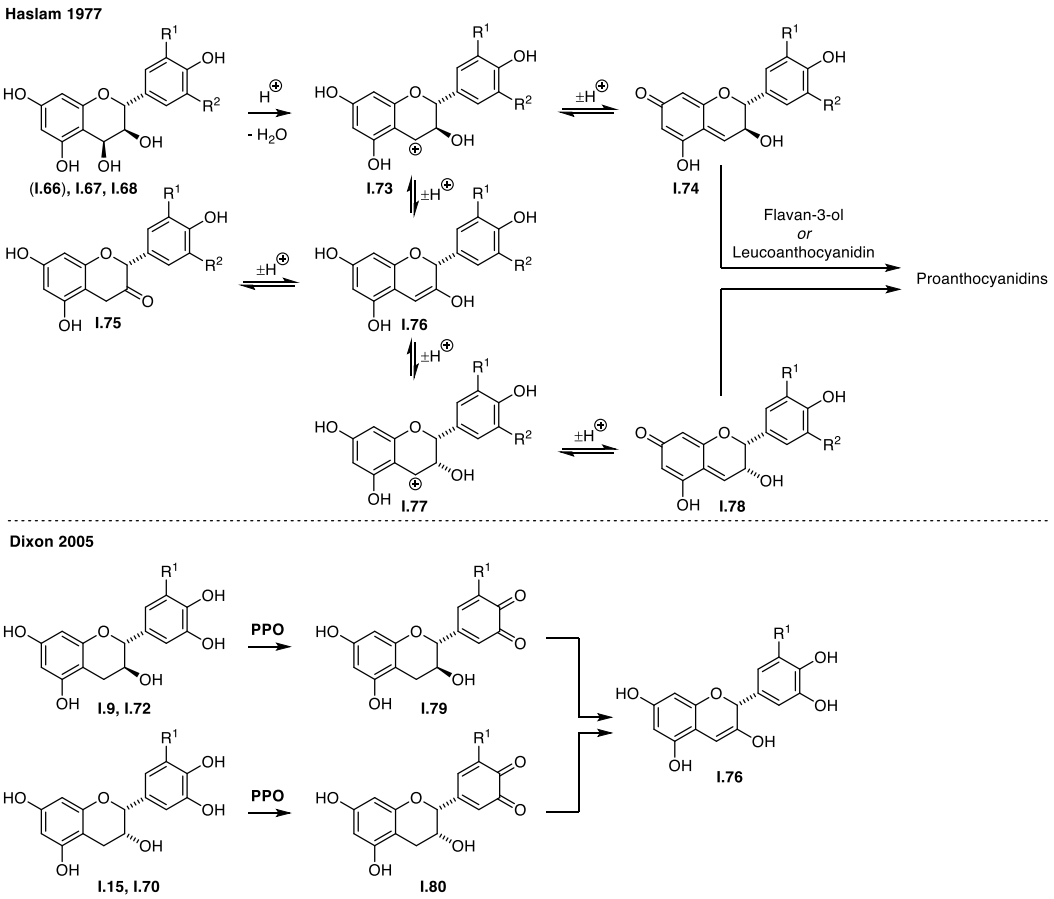
[56] I. R. Baxter, J. C. Young, G. Armstrong, N. Foster, N. Bogenschutz, T. Cordova, W. A. Peer, S. P. Hazen, A. S. Murphy, J. F. Harper, *Proc. Natl. Acad. Sci. U. S. A.*, **2005**, *102*, 2649–2654.
[57] M. A. S. Marles, H. Ray, M. Y. Gruber, *Phytochemistry*, **2003**, *64*, 367–383.
[58] L. J. Porter, *J. Chem. Educ.*, **1995**, *72*, 23-55.
[59] A. C. Fletcher, L. J. Porter, E. Haslam, R. K. Gupta, *J. Chem. Soc., Perkin Trans. 1*, **1977**, p. 1628, R. W. Hemingway, J. J. Karchesy, S. J. Branham (Eds.), *Chemistry and Significance of Condensed Tannins*, Springer, Boston, MA, **2014.**
[60] L. L. Creasy, T. Swain, *Nature*, **1965**, *208*, 151–153.
[61] R. A. Dixon, D.-Y. Xie, S. B. Sharma, *The New phytologist*, **2005**, *165*, 9–28.
[62] S. Guyot, J. Vercauteren, V. Cheynier, *Phytochemistry*, **1996**, *42*, 1279–1288.
[63] S. Vidal, D. Cartalade, J.-M. Souquet, H. Fulcrand, V. Cheynier, *J. Agric. Food Chem.*, **2002**, *50*, 2261–2266.



Scheme 1-8: *Proposed pathways of interconversion of the C-3 stereocenter of leucoanthocyanidins and flavan-3-ols by flav-3-en-3-ol intermediates.*

1.8 Synthetic approaches towards B-type proanthocyanidins

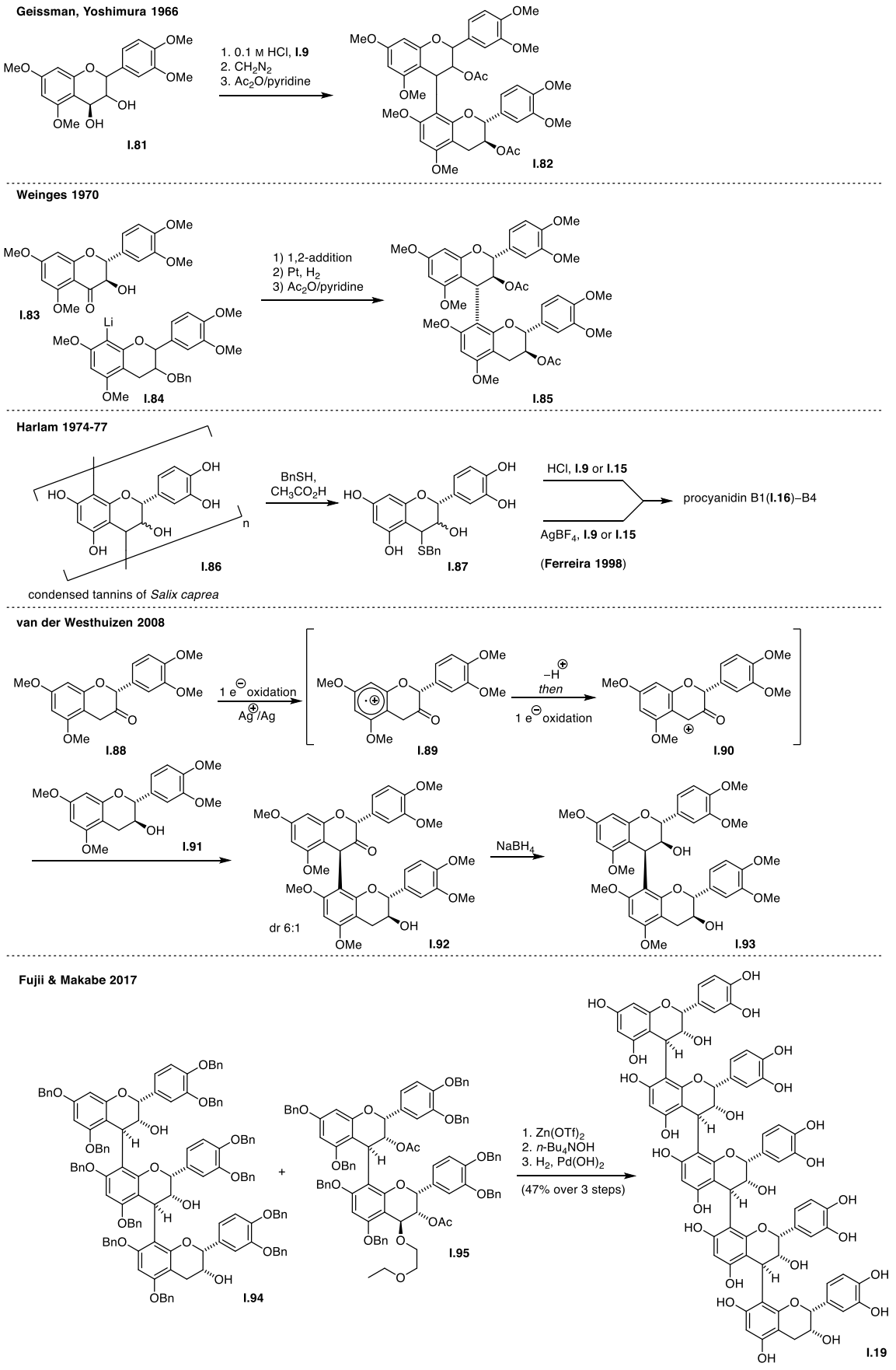
A first synthetic procyanidin derivative was afforded by Geissman and Yoshimura already in 1966 (Scheme 1-9).[64] By a mild acid catalyzed condensation a leucocyanidin derivative **I.81** with free phenolic catechin (**I.9**), they received the procyanidin derivative **I.82** after methylation and acetylation. Yet the absolute configuration was not fully elucidated as only a 60 MHz NMR spectrometer was used. A similar derivative but by a much less biomimetic approach was achieved by Weinges and coworkers four years later.[65] They forged the interflavonyl bond by 1,2-additon of a lithiated catechin derivative **I.84** onto tetra methylated taxifolin **I.83**. Subsequent removal of the benzyl protection groups by hydrogenation followed by methylation afforded a similar derivative identical to methylated procyanidin B3. The benzylic hydroxyl function was simultaneously removed in the hydrogenation step over Pearlman's catalyst. The work of Haslam resulted in the

[64] T. A. Geissman, N. N. Yoshimura, *Tetrahedron Lett.*, **1966**, *7*, 2669–2673.
[65] K. Weinges, J. Perner, H.-D. Marx, *Chem. Ber.*, **1970**, *103*, 2344–2349.

first synthesis of free phenolic procyanidins.[66] Tannins from *Salix caprea* and *Crataegus monogyna* (**I.86**) were converted to the 4β-benzylthiocatechin and –epicatechins (**I.87**) under by acetic acid acidified conditions. These were reacted in a further step with free catechin (**I.9**) and epicatechin (**I.15**) to afford the procyanidins B1 – B4. With a thiophilic Lewis acid, this dimerization can also be achieved under neutral condition what was shown by Ferreira who afforded procyanidins B1 (**I.16**) and B2 in up to 50% isolated yield.[67] With slight modifications of these general concepts a broad range of proanthocyanidins and B-type procyanidins are accessible *via* more or less biomimetic ways.[68] A rather new concept was pursuit by van der Westhuizen and coworkers in 2008.[69] They converted catechin into flavan-3-on **I.88** and showed that upon treatment with silver tetrafluoroborate in tetrahydrofuran as single electron oxidant, the benzylic position is oxidized into a cationic species **I.90**. This cation is trapped by nucleophilic tetra-*O*-methylcatechin **I.91** to afford a biflavonoid. By subsequent reduction with sodium borohydride octa-*O*-methylprocyanidin B3 derivative **I.92** was yielded favoring a 3,4-*cis* configuration.

Modern chromatography methods enable nowadays the selective synthesis and separation of proanthocyanidins in a broad range of monomeric units. Only in 2017 Makabe and Fujii reported the selective synthesis of proanthocyanidins with up to six flavonoid monomers employing zinc triflate as Lewis acid and leucoanthocyanidins with ethoxyethyl leaving groups (e.g. **I.95**) as substrate.[70] Their investigation revealed a strong difference between catechin derived proanthocyanidins and their epicatechin analogues. While epicatechin chains like cinnamtannin A3 (**I.19**) showed significant activity for suppression of cell growth and Fatty Acid Binding Protein 5 (FABP5) gene expression in human prostate cancer cells, their catechin counterparts did not show any activity at all.

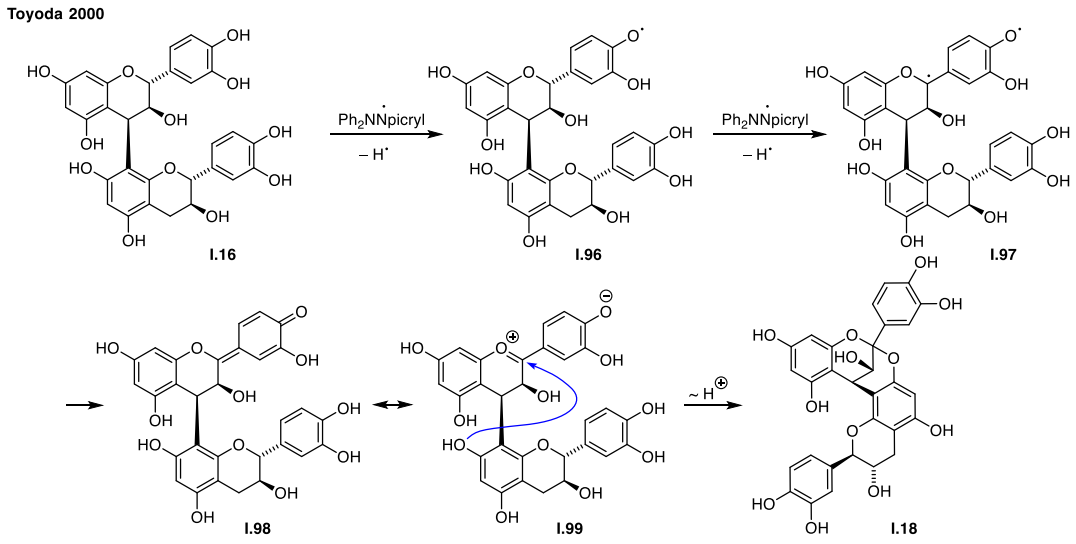
[66] A. C. Fletcher, L. J. Porter, E. Haslam, R. K. Gupta, *J. Chem. Soc., Perkin Trans. 1*, **1977**, p. 1628, E. Haslam, *J. Chem. Soc., Chem. Commun.*, **1974**, p. 594.
[67] P. J. Steynberg, R. J.J. Nel, H. van Rensburg, B. C.B. Bezuidenhoudt, D. Ferreira, *Tetrahedron*, **1998**, *54*, 8153–8158.
[68] D. Ferreira, C. M. Coleman, *Planta Med*, **2011**, *77*, 1071–1085.
[69] M. C. Achilonu, S. L. Bonnet, J. H. van der Westhuizen, *Org. Lett.*, **2008**, *10*, 3865–3868.
[70] K. Takanashi, M. Suda, K. Matsumoto, C. Ishihara, K. Toda, K. Kawaguchi, S. Senga, N. Kobayashi, M. Ichikawa, M. Katoh et al., *Sci. Rep.*, **2017**, *7*, p. 7791, M. Suda, W. Fujii, K. Takanashi, Y. Hattori, H. Makabe, *Synthesis*, **2014**, *46*, 3351–3355.



Scheme 1-9: *Approaches towards the synthesis of B-type proanthocyanidin derivatives.*

1.9 A-Type proanthocyanidins

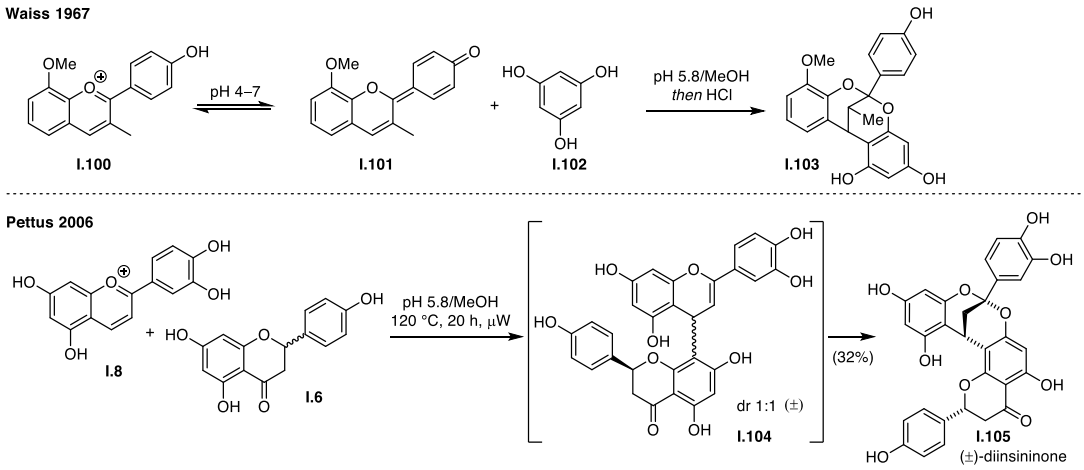
While in the proanthocyanidins the monomers are mostly linked only by a single C–C bond (4→8, 4→6), the A-type shows a second C–O bond (2→*O*-7) that closes the characteristic bicyclic [3.3.1] ketal core. Important examples are the procyanidins A1 (**I.18**) till A4. Two main ways have been suggested of exactly how this connection is created starting from B-type PAs. As these molecules are known to react with reactive oxygen species (ROS), especially the catechol ring is prone for oxidation. A first oxidation of the phenolic hydroxyl group is presumably followed by the abstraction of the hydrogen of the C-2 position on the pyran ring that results in the formation of a *para*-quinomethide (compare Scheme 1-10, **I.98**). This methide is stabilized by the oxygen of the pyran ring (**I.99**) and can be attacked by nucleophiles. In a 6-*exo*-*trig* fashion this can be the free C-7 hydroxyl group on the other flavonoid monomer. After tautomerism this would yield proanthocyanidins of the A-type (e.g. **I.18**). Toyoda and coworkers delivered evidence for this mechanism by oxidizing procyanidins B1 (**I.16**) with a diphenylpicrylhydrazyl radical in a water/ethanol mixture what yielded procyanidin A1 (**I.18**).[71] Yet this was not entirely new as the general concept has already been shown by Nishioka and coworkers who successfully converted B-type proanthocyanidins into the A-type by treatment with hydrogen peroxide and sodium bicarbonate in the 80's.[72] Toyoda calculated the bond dissociation energy (BDE) of the hydrogen atom at C-2 position to be 68.7 kcal/mol what is weak enough to be easily abstracted by radicals (compare BDE(methane) = 105 kcal/mol).



Scheme 1-10: *Radical oxidation of procyanidin B1 to A1 by diphenylpicrylhydrazyl radicals.*

[71] K. Kondo, M. Kurihara, K. Fukuhara, T. Tanaka, T. Suzuki, N. Miyata, M. Toyoda, *Tetrahedron Lett.*, **2000**, *41*, 485–488.
[72] S. Morimoto, G.-I. Nonaka, I. Nishioka, *Chem. Pharm. Bull.*, **1987**, *35*, 4717–4729.

As already mentioned anthocyanidins and anthocyanins are plausible substrates for the PA formation as well. Particularly in the case of A-type PAs, they gain even more importance as precursors compared to B-type PAs. Already Waiss showed in 1965 that anthocyanidins undergo formal [3+3] addition with electron-rich phloroglucinol (**I.101**) towards the typical bicyclic [3.3.1] ketal moiety of type-A PAs under a pH range from 4–7 (Scheme 1-11).[73] At an optimized pH value of 5.8 they observed the setting of an equilibrium of the flavylium ion and the corresponding quinomethide that was attacked by the C-nucleophilic phloroglucinol in a formal 1,8-fashion. Inspired by this work Pettus and coworkers synthesized the natural A-type PA diinsininone (**I.105**) in 2006 by exploiting this intrinsic reactivity from luteolidin (**I.8**) and racemic naringenin (**I.6**).[74] He could even prove that the C–C bond formation precedes the oxygen-carbon bond formation of the ketal by isolation of the non-ketalized type-B intermediate (**I.104**). In contrast to the first described pathway starting from B-type PAs, this ionic mechanism does not require any oxidation steps and is only dependent on the pH value. Important to note, diinsininone was received by Pettus as a single diastereomer in a racemic fashion. As already mentioned (see 1.2), flavanones tend to racemize under acidic conditions. While the nucleophilic addition of **I.6** towards **I.8** showed no preference and gave a 1:1 mixture of diastereomers (**I.104**), the stereocenter at the C-2 position of the flavanone moiety in the closed A-type PA was adjusted *in situ* by phenoxide elimination and Oxa-Michael addition in relative stereochemistry to the stereocenter set by the first nucleophilic attack.



Scheme 1-11: *Ionic formation of proanthocyanidin type-A skeletons from anthocyanidins and C-nucleophilic phenol derivatives.*

[73] L. Jurd, A. C. Waiss, *Tetrahedron*, **1965**, *21*, 1471–1483.
[74] C. Selenski, T. R. R. Pettus, *Tetrahedron*, **2006**, *62*, 5298–5307.

1.10 Dragon's blood as source of flavonoids

Flavonoids appear also in the resins of a variety of plants as important constituents. Dragon's blood is a deep red resin with remarkable pharmaceutical effects. Yet there is a certain degree of confusion as many red resins of different origins are called Dragon's blood in medical literature. Therefore, several kinds have to be strictly distinguished due to their different origins – these are especially East Indian Dragon's blood (from the fruit of *Daemonorops draco* (Willd.) Blume), West Indian Dragon's blood (exudates of *Pterocarpus draco* L.), Socotran or Zanzibar Dragon's blood (exudates of *Dracaena cinnabari* Balf. f.), Canary Dragon's blood (exudates formed from incisions of the trunk of *Dracaena draco* (L.) L.), Mexican Dragon's blood (resin of *Croton lechleri* Müll. Arg.) and Venezuelan Dragon's blood (resin of *Croton gossypifolium* Vahl).[75] The East Indian Dragon's blood from *Daemonorops draco* (palmaceae) is a famous traditional Chinese medicine and was highly priced in ancient times. For hundreds of years people have used it to heal wounds by improving the tissue regeneration, stimulating the blood circulation, pain alleviation and controlling of bleeding.[76] It is obtained as deep red teardrop-shaped lumps and is isolated by pacing the fruits in sacks and pounding them after what the pulp is treated with boiling water. The resin is subsequently kneaded into balls or long sticks.[77]. The first pigment isolated from Brockmann and Haase and reported almost simultaneously and independently from Hesse was dracorubin (**I.106**) in 1936, which is the most important pigment for the deep red color.[78] Yet this pigment was only characterized by its elemental analysis at the beginning. This anthocyanin derivative is a biflavonoid with the typical 4→8 and an unusual 5→7-*O* bond. Shortly after, the monomeric 3-deoxyanthocyanidin dracorhodin (**I.108**) – as second important red pigment was reported by Brockmann who was able to reveal its structure as well.[79] Novel mild isolation methods showed that up to 6.6% of the crude resin consist of this base labile 3-deoxyanthocyanidin what would significantly exceed the content of dracorubin (**I.106**).[80] Based on these results and further experiments from Brockmann, the structural elucidation of dracorubin was finally achieved by Whalley in 1950.[81] He was also the first to synthesize this pigment in 1976.[82] Five years earlier, Nasini and Salvadori reported six new optical active flavans including **I.110** and **I.111**, which are

[75] T. Sollmann, *J. Am. Pharm. Assoc. (Wash.)*, **1920**, *9*, 141–144.
[76] Chinese Pharmacopoeia Commission, *Pharmacopoeia of the People's Republic of China*, **2005**, p. 96.
[77] T. H. Barry, R. S. Morrell, A. A. Drummond, *The chemistry of the natural & synthetic resins*, Van Nostrand, New York, **1926.**
[78] H. Brockmann, R. Haase, *Ber. dtsch. Chem. Ges. A/B*, **1937**, *70*, 1733–1738, H. Brockmann, R. Haase, *Ber. dtsch. Chem. Ges. A/B*, **1936**, *69*, 1950–1954, G. Hesse, *Justus Liebigs Ann. Chem.*, **1936**, *524*, 14–24.
[79] H. Brockmann, H. Junge, *Ber. dtsch. Chem. Ges. A/B*, **1943**, *76*, 751–763.
[80] J. Shi, R. Hu, Y. Lu, C. Sun, T. Wu, *J. Sep. Sci.*, **2009**, *32*, 4040–4047.
[81] H. Brockmann, R. Haase, E. Freiensehner, *Ber. dtsch. Chem. Ges. A/B*, **1944**, *77*, 279–286, A. Robertson, W. B. Whalley, J. Yates, *J. Chem. Soc.*, **1950**, *0*, 3117–3123.
[82] E. O. P. Agbakwuru, W. B. Whalley, *J. Chem. Soc., Perkin Trans. 1*, **1976**, 1392–1394.

the reduced forms of **I.108** and **I.109**.[83] He also described interconversion of these flavans to the 3-deoxyanthocyanidins dracorhodin (**I.108**) and nordracorhodin (**I.109**) by oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and reduction with sodium borohydride respectively. In the case of **I.110** he even observed fast autoxidation towards **I.108** under air. A very interesting *ortho*-ester – dracooxepine **I.118** - was reported in 1989 by the same group.[84] Fine splitting in the ^{13}C-NMR spectra of this natural product revealed its almost 1:1 mixture of diastereomers. After dracoflavan A (**I.119**) in 1990,[85] the dracoflavan series of B – D (**I.112** – **I.117**) were the first A-type PAs isolated from East Indian Dragon's blood.[86] These three members all appear as pair of diastereomers. In 2009 the new series of daemonorols (e.g. **I.120** and **I.121**) were reported by Iinuma in which **I.110** or **I.111** are linked by a methylene bridge.[87] Next to these unique compounds other natural products like resin acids (e.g. abietic acid) were found in this Dragon's blood as well.[88]

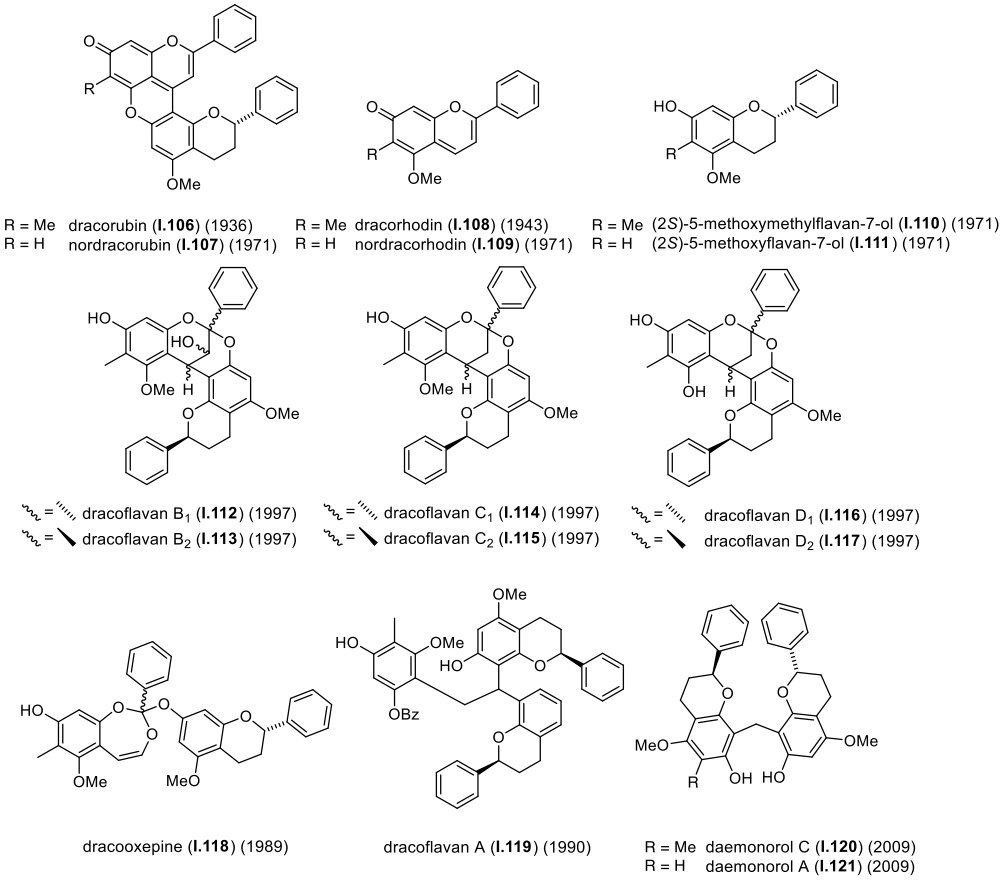


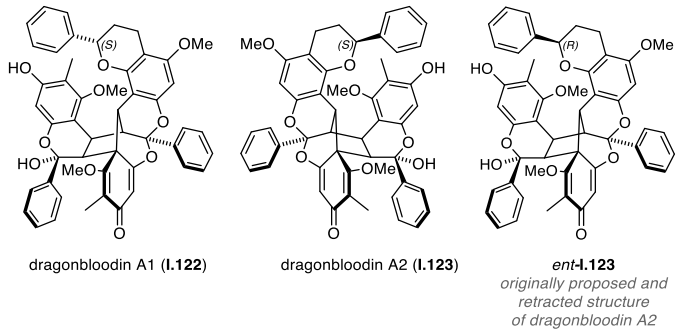
Figure 1-4: *Selection of characteristic natural products from daemonorops draco dragon's blood and the year of their first description.*

[83] G. Cardillo, L. Merlini, G. Nasini, P. Salvadori, *J. Chem. Soc., C*, **1971**, 3967–3970.
[84] G. Nasini, A. Arnone, L. Merlini, *Heterocycles*, **1989**, *29*, 1119–1125.
[85] A. Arnone, G. Nasini, L. Merlini, *J. Chem. Soc., Perkin Trans. 1*, **1990**, *29*, 2637–2640.
[86] A. Arnone, G. Nasini, O. Vajna de Pava, L. Merlini, *J. Nat. Prod.*, **1997**, *60*, 971–975.
[87] K.-i. Nakashima, N. Abe, F. Kamiya, T. Ito, M. Oyama, M. Iinuma, *Helv. Chim. Acta*, **2009**, *92*, 1999–2008.
[88] L. Merlini, G. Nasini, *J. Chem. Soc., Perkin Trans. 1*, **1976**, 1570–1576,G. Nasini, F. Piozzi, *Phytochemistry*, **1981**, *20*, 514–516.

1.11 Isolation of dragonbloodin A1 and A2

The instability of many of the flavonoid based components in dragon's blood - especially during the isolation steps - greatly increased the difficulty of purification and identification of new natural products. However, Wu tackled this challenge by advanced chiral chromatography methods whereupon two novel bioactive structural complex compounds were isolated, characterized and even evaluated in respect to their anti-inflammatory activity. The dragonbloodins A1 (**I.122**) and A2 (**I.123**) are the first complex flavonoid trimers that have been reported in 2016 bearing the same [3.3.1] bicyclic ketal core of A-type PAs (Scheme 1-12).[89] Isolated as an almost 1:1 mixture of diastereomers, separation was achieved by chiral column chromatography (ASTEC CELLULOSE DMP). Yet it was not possible to fully elucidate the structure by exclusive analysis of the complex NMR data. The structural elucidation was further complicated as both diastereomers proved to be even more unstable when separated from each other. Fortunately, crystalline material composed of a mixture of dragonbloodin A1 and A2 was relatively stable and a single crystal X-ray analysis finally revealed their complex structure. It is important to note that the relative stereochemistry is completely identical between **I.122** and **I.123** except the absolute (2*S*) configuration of the single flavan building block. Wu and coworkers solved the crystallographic data impeding the $P2_1/n$ space group instead of the $P2_1$ group that would have been an option as well. As in this used centrosymmetric space group both diastereomers appear merged as one molecule (formally **I.122** and *ent*-**I.123**) with the disordered position of the absolute (2*S*) stereocenter, this caused a severe misinterpretation of the absolute stereochemistry of dragonbloodin A2 (**I.123**). Simply spoken instead of assigning both diastereomers the same absolute stereochemistry on the (2*S*) center, all other centers were assumed to have the same absolute configuration. In turn Wu and coworkers came up with a proposed biogenesis to explain the interpreted (2*R*) configuration of *ent*-**I.123**. In respect to the correct absolute stereochemistry of **I.123**, that has recently been proven experimentally, too,[90] this proposed biogenesis is unreasonable. This mistake has been realized shortly after publication in April 2016 whereupon the paper was retracted in the beginning of June 2016.

[89] W.-K. Du, H.-Y. Hung, P.-C. Kuo, T.-L. Hwang, L.-C. Shiu, K.-B. Shiu, E.-J. Lee, S.-H. Tai, T.-S. Wu, *Org. Lett.*, **2016**, *18*, p. 3042.
[90] Z. Guo, Z. Wang, Y. Tang, *Org. Lett.*, **2018**, *20*, 1819–1823.



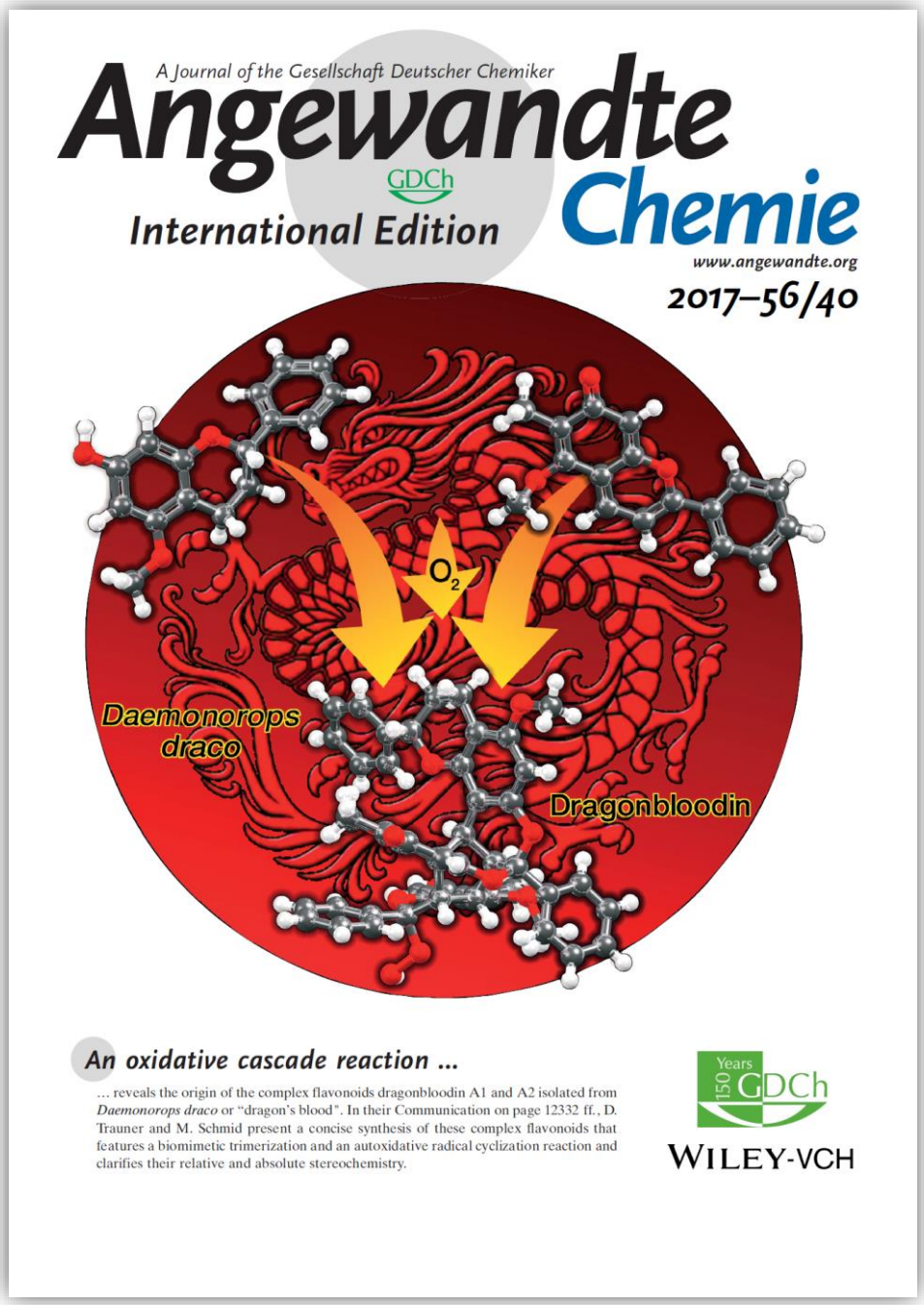
Scheme 1-12: *Structures of dragonbloodin A1 and A2 and the incorrect originally proposed structure ent-**I.123**.*

As our group has a strong expertise in biomimetic synthesis of complex natural products[91] we got quickly interested in these new molecules despite the formal retraction of the publication. Being outstanding and challenging targets for a biomimetic synthesis, we hoped to reveal the true biogenesis by exploiting biomimetic principles and intrinsic reactivity of the building blocks.

[91] B. Cheng, D. Trauner, *J. Am. Chem. Soc.*, **2015**, *137*, 13800–13803, P. Ellerbrock, N. Armanino, M. K. Ilg, R. Webster, D. Trauner, *Nat. Chem.*, **2015**, *7*, p. 879, R. Meier, S. Strych, D. Trauner, *Org. Lett.*, **2014**, *16*, 2634–2637, S. Strych, G. Journot, R. P. Pemberton, S. C. Wang, D. J. Tantillo, D. Trauner, *Angew. Chem. Int. Ed.*, **2015**, *54*, 5079–5083.

2 Results and Discussion

2.1 Biomimetic Synthesis of Complex Flavonoids Isolated from Daemonorops "Dragon's Blood"



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Biomimetic Synthesis of Complex Flavonoids Isolated from *Daemonorops* "Dragon's Blood"

*Matthias Schmid and Dirk Trauner**

Abstract: *The dragonbloodins are a pair of complex flavonoid trimers that have been isolated from the palm tree Daemonorops draco, one of the sources of the ancient resin known as "dragon's blood". We present a short synthesis that clarifies their relative configurations and sheds light on their origin in Nature. This synthesis features biomimetic cascade reactions that involve both ionic and radical intermediates. The biogenetic relationships between dracorhodin, the dracoflavans C, and the dragonbloodins A1 and A2 are discussed.*

The intensely red resin "dragon's blood" has been used in medicine since ancient times and across many cultures.[1] It can be obtained from several different plant sources, which has led to some confusion regarding its composition and pharmacology. A resin variety obtained from the palm tree *Daemonorops draco* has recently received renewed attention as a source of bioactive molecules. It was shown to have antiviral[2] and anticancer[3] effects as well as activity against osteoporosis,[4] diabetes,[5] inflammation,[6] and platelet aggregation.[7] Detailed investigations into its chemical components yielded a range of flavonoids of varying complexity (Figure 1). These comprise monomeric flavonoids such as (2*S*)-5-methoxyflavan-7-ol (**1**) and (2*S*)-5-methoxy-6-methylflavan-7-ol (**2**). Their oxidized congeners nordracorhodin (**3**) and dracorhodin (**4**), respectively, which are shown here as the anhydrobases, are largely responsible for the intense red color of dragon's blood. The monomeric flavonoids can dimerize in various ways to give rise to nordracorubin (**5**), dracorubin (**6**),[8] daemonorol A (**7**) and C (**8**),[9] dracooxepine (**9**),[10] and the diastereomeric dracoflavans C1 (**10a**) and C2 (**10b**).[11]

Recently, Wu and co-workers isolated the first flavonoid trimers from dragon's blood, namely dragonbloodin A1 (**11a**) and A2 (**11b**).[12] These highly complex molecules feature a unique skeleton with a central spiro[4.5]deca-8-oxo-6,9-diene core. The original report was retracted shortly after its publication because of doubts regarding the structure of dragonbloodin A2 and the biosynthesis proposed on the basis of this structure. The monomeric and dimeric flavonoids shown in Figure 1 all feature *S*-configured chromane moieties, which is consistent with their biosynthesis being catalyzed by chalcone isomerase.[13] This fact and the CD spectra of **11a** and **11b** led us to hypothesize that the dragonbloodins are not epimers but pseudoenantiomers that differ in seven of the eight stereocenters, with the exception being the 2*S* center of the chromane moiety. We now wish to report our own studies on the dragonbloodins, which clarify the relationship between dragonbloodin A1 and A2, and provide an effective synthetic entry through an oxidative biomimetic cascade.

Our proposed biosynthetic pathway, which links the monomers with the dimers and trimers, is shown in

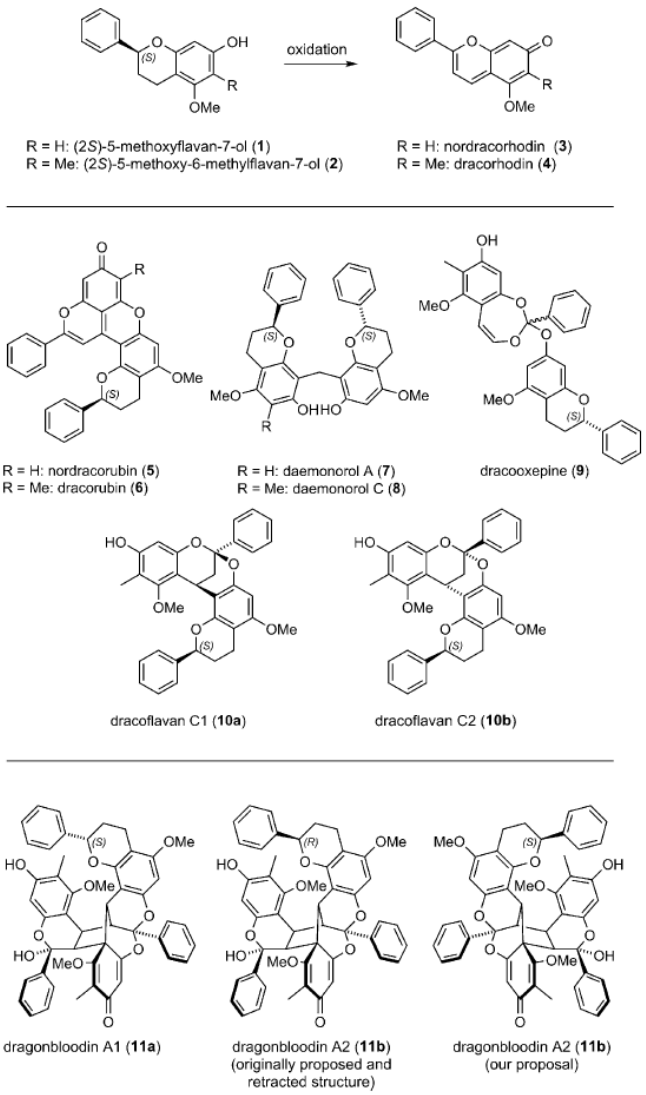

Figure 1. Natural flavonoids isolated from dragon's blood.

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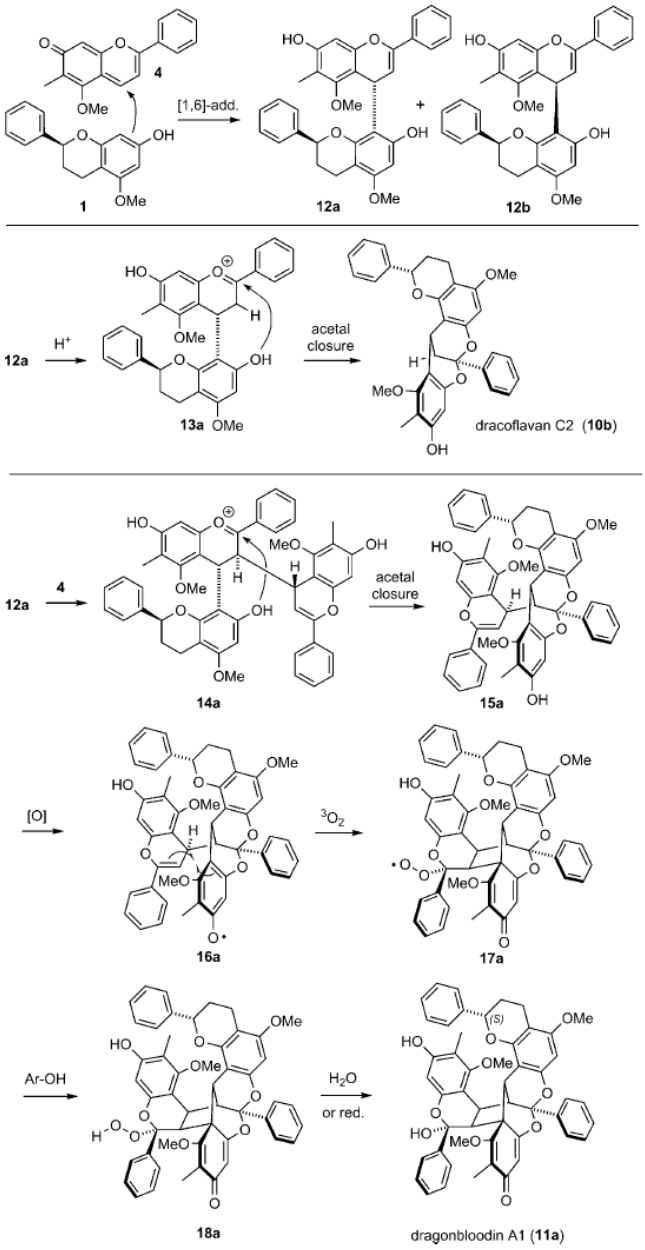
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201705390.

Scheme 1. A 1,6-addition of flavan-7-ol (**1**) to dracorhodin (**4**) would lead to the two diastereomeric intermediates **12a** and **12b**. This process is not catalyzed by an enzyme and occurs with low diastereoselectivity. The benzo-4*H*-pyrans **12a** and **12b** possess a nucleophilic vinyl ether moiety that can react with various electrophiles, the simplest of which is a proton. Accordingly, protonation of **12a** would yield oxocarbenium ion **13a**. Closure of the acetal would then afford dracoflavan C2 (**10b**). The analogous reaction of **12b** (not shown) would yield dracoflavan C1 (**10a**). Alternatively, enol ether **12a** could react with dracorhodin (**4**) as an electrophile, which would yield oxocarbenium ion **14a**. This second nucleophilic attack onto **4** can be expected to occur with a high degree of diastereoselectivity *trans* to the existing chromanol moiety. Closure of the acetal then yields **15a**, which still retains an enol ether moiety.

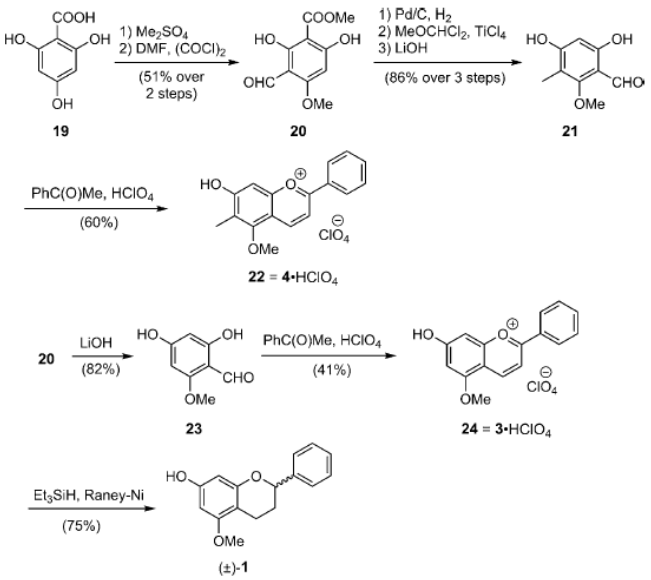


Scheme 1. Proposed biogenesis of the dracoflavans and dragonbloodins.

To account for the formation of the dragonbloodins, we propose an autoxidation mechanism. The phenolate corresponding to **15a** is initially oxidized to the phenoxy radical **16a**. Intramolecular addition to the enol ether moiety generates the spirocyclohexadienone and gives a stabilized benzylic radical (not shown) that reacts with triplet oxygen to yield the hydroperoxy radical **17a**. This intermediate abstracts a hydrogen atom from the next phenol, completing the radical chain (see the Supporting Information for details). The resultant hydroperoxide **18a** is either reduced or, more likely, undergoes hydrolysis to generate dragonbloodin A1 (**11a**). The analogous oxidative cascade starting from **12b** would yield the pseudoenantiomeric trimer dragonbloodin A2 (**11b**).

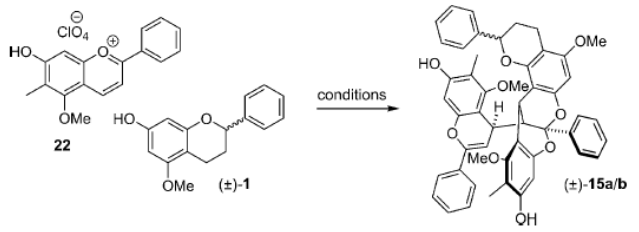
To test our hypothesis experimentally, we first synthesized the flavonoid monomers **1** and **4**. Dracorhodin (**4**) and simple congeners thereof have been the subject of many previous studies, and our optimized approach largely follows an established route.[14] Thus 2,4,6-trihydroxybenzoic acid (**19**) was converted into aromatic aldehyde **20** by selective methylation and formylation. Reduction of the formyl group with palladium on charcoal, Rieche formylation, and ester cleavage followed by decarboxylation then gave aldehyde **21** in excellent yield. We found that the use of LiOH instead of NaOH prevented deformylation, which was otherwise a significant side reaction. Condensation of **21** with acetophenone promoted by perchloric acid cleanly afforded dracorhodin as the flavylium perchlorate salt **22**. Racemic 5-methoxyflavan-7-ol (**1**) was also synthesized from aldehyde **20**, which was hydrolyzed and decarboxylated to afford **23**. An analogous condensation with acetophenone gave surprisingly low yields of nordracorhodin perchlorate **24** when compared to dracorhodin perchlorate **22**. Hydrogenation of the flavylium salt **24** with PtO_2 or Pd/C as the catalyst also gave only poor yields of **1**. By contrast, reduction with Raney nickel and triethylsilane proved to be effective, affording racemic **1** in high purity. Interestingly, substitution of the perchlorate anion with hexafluorophosphate led to a dramatic drop in yield for this reduction.

With both monomeric flavonoid building blocks in hand, we proceeded to synthesize the dimeric dracoflavans **10a** and **10b** (Scheme 2). Taking inspiration from the work of Pettus,[15] we dissolved a mixture of flavylium salt **22** and racemic flavanol **1** in aqueous phosphate buffer (pH 5.8) and methanol and heated the mixture to 110 °C in a closed vial. This directly afforded the dracoflavans **10a** and **10b** in a 56:44 ratio, which is virtually identical to the ratio in which the two diastereomers have been found in Nature. We were never able to isolate the putative intermediates **12a**/**12b** (Scheme 1) but we consistently found traces of trimeric side products that clearly stemmed from the reaction of one equivalent of chromanol **1** and two equivalents of anhydrobase **4**. These were ultimately identified as **15a** and **15b** (51:49 d.r.), which is in accordance with our biogenetic hypothesis (Scheme 1). An extensive screening of solvents and conditions increased the combined yield of the trimers to 76 % (see Table 1). Interestingly, a large excess of **1** was required to obtain good yields although it is the minor building block in the formation of the trimers. Compounds **15a**/**15b** proved to be highly sensitive,



Scheme 2. Synthesis of the flavonoid building blocks dracorhodin perchlorate (**22**) and 5-methoxyflavan-7-ol (**1**).

Table 1: Reaction optimization of the biomimetic trimerization.

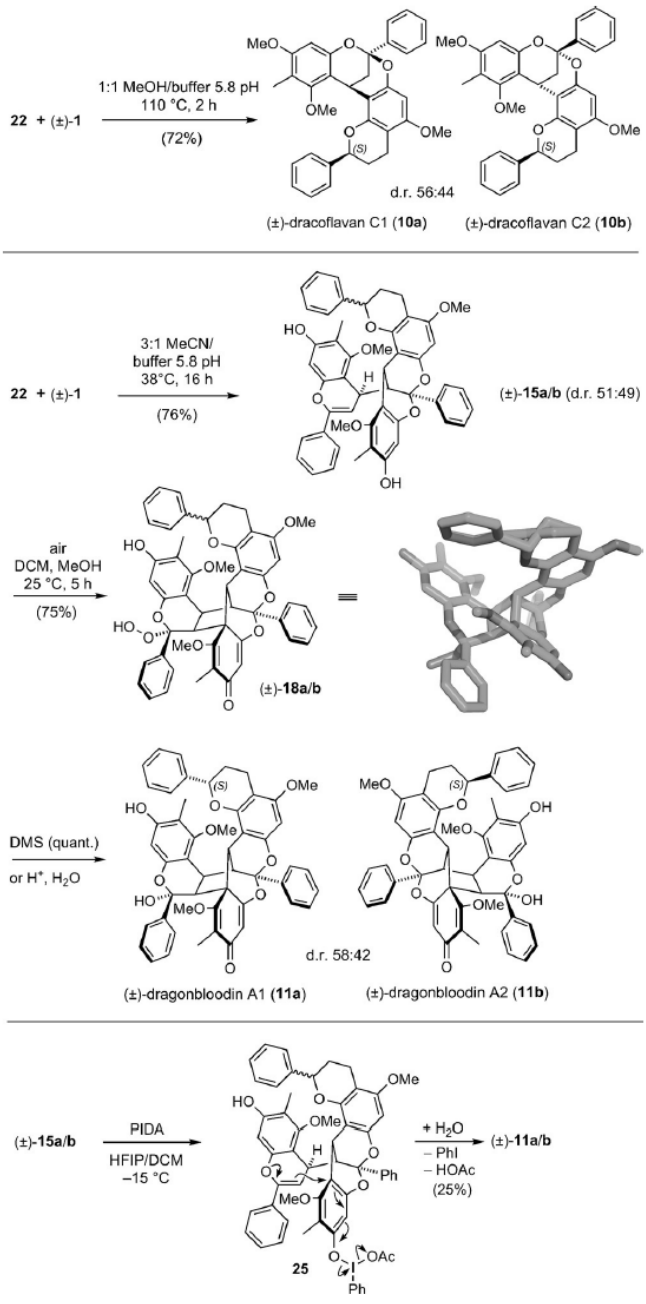


Entry	22/1	Additives	Solvent	*T* [°C]	Yield [%][a]
1	1:1.5	Na_3PO_4	MeOH	RT to 65	0
2	1:1.5	Na_3PO_4/4 Å M.S.[17]	toluene	RT	traces
3	1:6	buffer pH 5.8[c]	MeOH	RT	14
4	1:4	buffer pH 5.8[c]	HFIP	RT	0
5	1:4	buffer pH 5.8[c]	DMF	RT	traces
6	1:4	buffer pH 5.8[c]	MeCN	RT	60–63[b]
7	1:4	buffer pH 5.8[c]	MeCN	38	76[b]
8	1:3	buffer pH 5.8[c]	MeCN	45	32[b]

[a] Determined by NMR spectroscopy after 15–20 h reaction time. [b] Yield of isolated product. [c] Ratio of the solvent and aqueous 0.1 M pH 5.8 phosphate buffer: 3:1 (v/v), [**22**] = 0.025 M. HFIP = hexafluoroisopropanol, M.S. = molecular sieves.

and we quickly realized that they were unstable towards air during attempts of separation and purification. We therefore deliberately exposed them to oxygen. When a solution of **15a/15b** in DCM with 3% MeOH was stirred in the presence of air, we were able to isolate large quantities of a material that was stable towards column chromatography on silica gel. A crystal suitable for X-ray structure analysis revealed this compound to be the hydroperoxy hemiacetal (±)-**18a/18b**. It is important to note that this crystal contains four distinct molecules, that is, the two enantiomers of both pseudoenantiomeric diastereomers.[16] The structure depicted in Scheme 3 shows an average of the hydroperoxides corresponding to natural dragonbloodin A1 and the unnatural enantiomer of dragonbloodin A2. The hydroperoxides **18a/18b** were cleanly reduced with dimethyl sulfide (DMS) to provide the dragonbloodins **11a/11b**. Perhaps more relevant to the biosynthesis, we noted that during HPLC purification, the hydroperoxide **18a/18b** underwent clean hydrolysis to provide the dragonbloodins **11a** and **11b**. The spectra of our racemic molecules matched those obtained for the natural products by Wu and co-workers.[12]

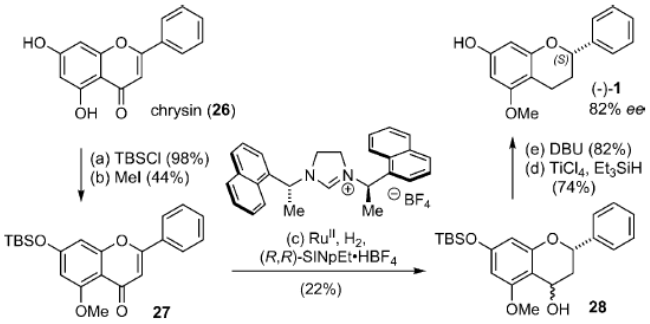
Although these results implied the role of molecular oxygen, we also explored further oxidants that would be able to effect an umpolung of the nucleophilic phenol and provide the spirocyclohexadienone.[18] Treatment of **23a/23b** with [bis(trifluoroacetoxy)iodo]benzene (PIFA) failed to yield **11a/11b** and only cleaved the trimer to afford dracorhodin



Scheme 3. Synthesis of the dracoflavans C (**10a** and **10b**) and dragonbloodins A (**11a** and **11b**). DMS = dimethyl sulfide, HFIP = hexafluoroisopropanol, PIDA = (diacetoxyiodo)benzene.

as the main product. Under less acidic conditions using (diacetoxyiodo)benzene (PIDA), however, we were able to isolate dragonbloodin A (**11a**/**11b**), albeit in low yield (Scheme 3). The oxidative cyclization presumably proceeds via iodine(III) intermediate **25**, which undergoes intramolecular nucleophilic attack by the enol ether moiety followed by interception with water.

The absolute configuration of the dragonbloodins can be inferred from the *S* configuration of their biosynthetic precursor, compound **1**. Our asymmetric synthesis of this compound is based on the asymmetric hydrogenation of flavones and chromones developed by Glorius and co-workers (Scheme 4).[19] Selective TBS protection and methylation



Scheme 4. Asymmetric synthesis of (*S*)-5-methoxyflavan-7-ol (**1**).

of the commercially available flavonoid chrysin (**26**) afforded the requisite substrate **27**. Hydrogenation with Ru(cod)(η^3-methylallyl)$_2$ and the NHC ligand (*R*,*R*)-SINpEt·HBF$_4$ as the catalyst afforded the flavan-4-ol **28**, albeit in low yield. Reductive removal of the benzylic hydroxy group under ionic conditions and deprotection then afforded (2*S*)-(−)-**1** with an *ee* of 82%. Chrysin can also be used as a convenient source for (±)-**1** (see the Supporting Information).

In summary, we have achieved the first synthesis of the highly complex flavonoid trimers dragonbloodin A1 and A2 in racemic form and developed a formal asymmetric synthesis. A practical and scalable route to dracorhodin, nordracorhodin, and the corresponding flavanol has also been developed. Our synthesis clarified the biogenetic and stereochemical relationships between the more complex components of *Daemonorops draco* "dragon's blood" and identified dragonbloodin A2 (**11b**) as a pseudoenantiomer of dragonbloodin A1 (**11a**). It also revealed how the umpolung of highly electron-rich phenols can be achieved in the absence of oxidizing enzymes, namely by autoxidation. Finally, our work is another demonstration for the power of biomimetic reaction cascades, which can be highly efficient even when multiple intermolecular steps are involved.[20]

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Conflict of interest

The authors declare no conflict of interest.

Keywords: autoxidation · biomimetic synthesis · cascade reactions · natural products · total synthesis

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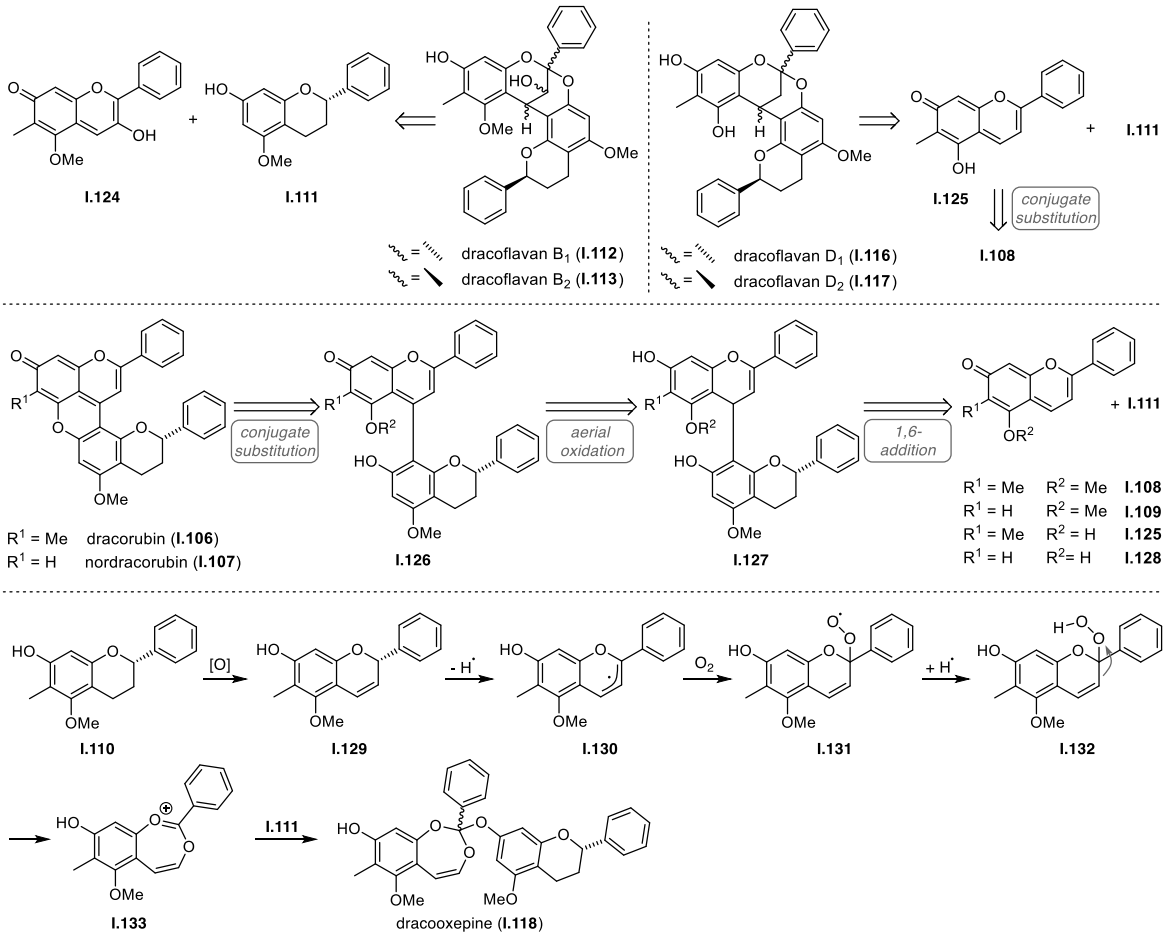
3 Conclusion & Outlook

The successful total synthesis of dragonbloodin A1 (**I.122**), A2 (**I.123**) and the dracoflavans C1 (**I.114**), C2 (**I.115**) by biomimetic approaches revealed some interesting aspects of the nature of these complex flavonoids. With these new insights it is necessary to review the other flavonoids once again. During the synthesis of the dracoflavans C the observed ratio between both diastereomers, identical to nature's, suggests that the formation of these A-type PAs occurs most probably in nature without any enzymatic assistance that could control the diastereoselectivity of one being prefered. Yet the question rises if the other A-type PAs dracoflavan B (**I.112**, **I.113**) and D (**I.116**, **I.117**) might be formed by such an ionic non-enzymatic mechanism as well. In such a case the anthocyanidin **I.124** needs to be anticipated for the dracoflavan B biogenesis. Although such a molecule was not observed yet, the anticipation of this molecule bearing the additional hydroxyl group on the C-3 position fits perfectly to the structural similarity to the anthocyanidins pelargonidin (**I.1**), anthocyanidin (**I.2**) and delphinidin (**I.3**) and is reasonable in respect to the flavonoid pathway. Dracoflavan D lacks the same OH group like dracoflavan C. A similar retrosynthetical cleavage of this A-type PA leads to flavan-7-ol **I.110** and to a demethylated dracorhodin **I.125**. Theoretically an enzymatic demethylation of dracoflavan C is plausible yet would be surprising as the methoxy groups are usually put on the flavonoid monomers after the chalcone isomerase step. This would implicate a methylation with subsequent removal a few steps later. More reasonable is the assumption that the methoxy group of dracorhodin is replaced *in situ* by a conjugate addition of water and methanol elimination. An aspect that also has an influence on biogenetic consideration of the other flavonoids is the extraordinary sensitivity of the trimeric flav-3-en (see abstract – **III**) towards aerial oxidation. This intermediate proved to be so unstable in dichloromethane that it reacted within a few hours under air to the endoperoxide of dragonbloodin A (see abstract – **IV**). As initial experiments towards the dragonbloodins A aimed on the synthesis of the proposed intermediate **I.127** (R^1, R^2 = Me), these new results shine light on this molecule from a different point of view. Most probably this flav-3-en is similar or even more sensitive towards aerial oxidation what might lead to instant oxidation to the 4-flavanyl-anthocyanidin **I.126** (R^1, R^2 = Me) for what reason it probably could never be observed. This molecule bears a fascinating structure of a linked dimer between an electronpoor *para*-quinomethide and an electronrich flavan. As a 1,6- or a 1,8-addition of the 7-OH group onto the quinone structure is sterically impossible, a 1,4- conjugate addition/substitution is the only way how it can react intramoleculary to balance these electronic differences. By such a proposed conjugate substitution of the 5-methoxy group, the dracorubins (**I.106** and **I.107**) are formed following an enthropically favored path. This assumption further increases the crucial role played by the molecule **I.127**. According to this proposal it can not only interact with a proton electrophile towards the dracoflavans C (**I.114** and **I.115**) or a dracorhodin electrophile towards the dragonbloodins A (**I.122**

and **I.123**), electrophilic oxygen or reactive oxygen species open a third pathway that leads to the dracorubins (**I.106** and **I.107**). The sensitivity of **I.110** and the observed endoperoxide formation of the trimeric flav-2-en give also hints onto the dracooxepine (**1.118**) biogenesis pathway. We suggest that the oxidation of **I.110** towards dracorhodin (**I.108**) occurs *via* flav-3-en **I.129** or a flav-2-en (not shown). By a radical hydrogen abstraction, **I.130** should occur as an instable intermediate that might quickly add triplett oxygen from the air under the right conditions and upon reduction by exemplary another flavonoid form the endoperoxide **I.132**. Under the acidic conditions caused by the resin acids, a formal Baeyer–Villiger oxidation can be formulated, what leads to the dioxepinium cation **I.133**. Trapping by **I.111** leads to dracooxepine (**1.118**). Further studies and calculations on the exact oxidation mechanisms involed in the formation of the appearing flavonoids in dragon's blood could shine more light on their biogenesis and enable in future efficient synthesis routes to the different members.



Scheme 3-1: *Proposed biogenesis routes of flavonoids related to dragonbloodin A1 (**I.122**) and A2 (**I.123**).*

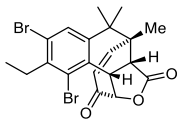
Chapter II

Total Synthesis of Salimabromide

1 Introduction

1.1 Salimabromide

Dragonbloodin A1 (**I.122**) and A2 (**I.123**), as complex trimers of flavonoids, belong in a broader sense to the family of polyketide natural products. This classification is based on the biosynthesis of both which involves the chalcone synthase in the synthesis of the monomeric flavonoid building blocks. This enzyme employs malonyl-CoA building units to build up the phloroglucinol A-ring of the flavonoids and belongs to the polyketide synthases (PKS). PKSs are a family of enzyme complexes and multi-domain enzymes, that appear in bacteria, fungi, plants and a few animal lineages and are responsible for a huge class of secondary metabolites in nature.[92] Furthermore, the chalcone synthase belongs to the PKS type III family. In contrast to the type I and type II, this class doesn't employ an acyl carrier protein and appears rather seldom in nature. In addition, the chalcone synthase was the first ever characterized PKS type III by Hahlbrock in 1972.[93] They were thought to only appear in plants, involed in chalcone and stilbene syntheses, until the first PKS type III in bacteria was found just at the beginning of this millenium.[94] The first representative in fungi was reported by Kitamoto and coworkers in 2005.[95] In 2013 König and coworkers reported on a novel natural product from a marine myxobacterium with unprecedented skeleton. Salimabromide (**II.1**), the so-named natural product, seems to be synthesized by the bacterium employing just such a PKS type III.[96] A very special structural characteristic besides the presumed PKS type III origin, are the bromide substituents on the arene core.



salimabromide (**II.1**)

Figure 1-1: *Structure of salimabromide (**II.1**).*

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In the vast universe of natural products that have been isolated and characterized, halogenated compounds are a small group, but with essential impact. More than 5000 compounds are known to date and each year several hundreds are added to this number.[97] Due to the omnipresence of chloride and bromide ions in sea water it is unsurprising that most of them are of maritime origin. A variety of organisms like bacteria, fungi, lichen, plants but especially marine organisms of all types have the capabilities to incorporate halide substituents onto organic frameworks. Nevertheless humans have a certain need of halide as well that is used for important metabolites and signal molecules in the body. Probably the most prominent and well-known molecules in public are the tyroid hormones (represented as thyroxine (**II.2**) in Figure 1-2) that are iodinated tyrosin derivatives. Iodine has found its way to many households, either for daily consumption by the use of iodized table salt or as backup supply in the event of radioactive emergency cases. However, less people are aware of the need for bromine. One example is bromoacetoacetate ester **II.3** which was isolated from humans cerebrospinal fluid and was shown to play a role in the activation of the rapid eye movement (REM) sleeping phase.[98] In the drug sector, brominated molecules still play a minor role compared to fluorine and chlorine containing compounds, too. However, an often prescribed sedative-hypnotic thienotriazolodiazepine – yet synthetic – drug is brotizolam (**II.4**), that is used in the treatment of severe or debilitating insomnia.[99] The exact role of natural occuring halogen-containing compounds in their mother organism is often not known, yet antifeedant or defense functions against other organisms have been reported. Besides, some derivatives seem also to have regulatory hormone and signaling activities.[100]

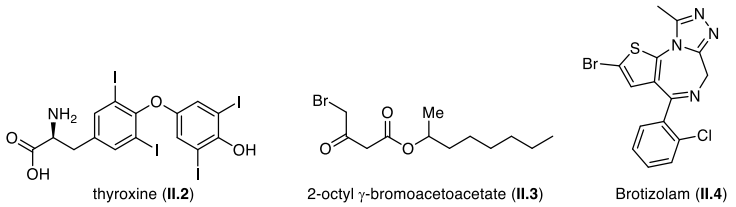

Figure 1-2: *Important bioactive organohalogen compounds.*

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1.2 Isolation of salimabromide

As part of their project on microorganisms of the intertidal zone, König and coworkers were able to isolate an *enhygromyxa salina* strain in a mud sample from the coast of the German Baltic Sea island Prerow. Although these myxobacteria were hitherto called "unculturable",[101] König and coworkers managed to cultivate these bacteria in an aquaculture. They observed a persistent antibiotic activity of this strain towards gram-positive microorganisms whereupon they had a closer look into the metabolites of this bacterium. On a large scale aquaculture and under addition of an adsorption resin they found minute amounts of a hitherto unknown molecule (0.5 mg in 64 L aquaculture). Intensive analysis lead to the structural elucidation of salimabromide (**II.1**). This molecule is the first natural product isolated from the *Plesiocystis/Enhygromyxa* clade (suborder *Nannocystineae*) of obligatory marine myxobacteria. It shows no resemblance to any other known natural product and provides several unique features. The tetracyclic system consists of a fivefold substituted arene with two bromide substituents annealed to a cyclohexane that bears two adjacent quarternary carbon centers, one of which is a stereocenter. This cyclohexane is bridged by an enone moiety and annealed to a γ-butyrolactone representing the fourth ring. Yet the bromide substituents and the ethyl group are the most uncommon features. From a structural and chemical point of view, salimabromide (**II.1**) should be in principle a product of a polyketide synthase (PKS) and one or two halogenases. König therefore had also a look into the genome sequence of its parent strain *enhygromyxa salina* SWB007. Bioinformatic analysis of the obtained whole-genome sequences found a halogenase-encoding gene adjacent to sequences coding for a PKS type III system. Further studies were addressed afterwards, but did not reveal any hints towards the unusual rearrangement reactions so far that must be responsible for the formation of the unique carbon skeleton of salimabromide. With 0.5 mg of salimabromide in hand, first bioassay tests revealed a moderate antibiotic activity against gram-positive *arthrobacter cristallopoietes*. Yet due to the lack of material, more extensive evaluation essays could not be conducted yet. Further aquacultur experiments from König to isolate more material even failed. The lack of material for further evaluation tests and the unique skeleton render it a very appealling and challenging target for natural product synthesis that is worth striving for. Earlier attempts to synthesize salimabromide (**II.1**) by Menche and coworkers have already revealed synthetic obstacles towards its skeleton what in fact prohibited a successful synthesis until recently.[102]

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2 Results and discussion

2.1 Total Synthesis of Salimabromide: A Tetracyclic Polyketide from a Marine Myxobacterium

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Total Synthesis of Salimabromide: A Tetracyclic Polyketide from a Marine Myxobacterium

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Supporting Information

ABSTRACT: Salimabromide is an antibiotic polyketide that was previously isolated from the obligate marine myxobacterium *Enhygromyxa salina*, and its densely functionalized and conformationally rigid tetracyclic framework is unprecedented in nature. Herein we report the first chemical synthesis of the target structure by employing a series of well-orchestrated, robust transformations, highlighted by an acid-promoted, powerful Wagner–Meerwein rearrangement/Friedel–Crafts cyclization sequence to forge the two adjacent quaternary carbon centers embedded in the tetrahydronaphthalene. A high-yielding ketiminium mediated [2+2]-cycloaddition was also utilized for the simultaneous construction of the remaining three stereocenters.

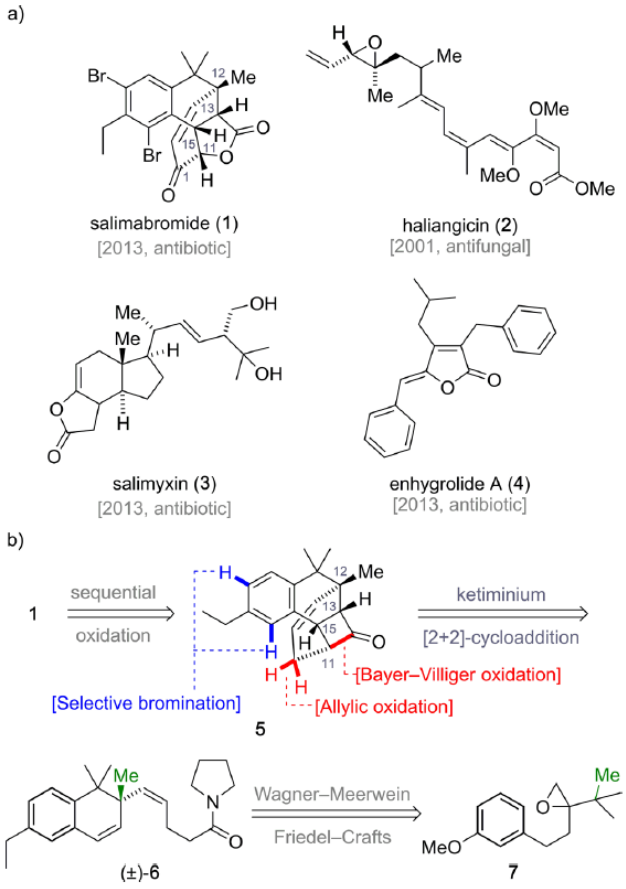
Myxobacteria of terrestrial origin produce an abundance of structurally complex secondary metabolites with notable biological activities. Prominent examples include epothilone, corallopyronin and soraphen.[1] Marine myxobacteria, on the other hand, have eluded their cultivation and isolation on many occasions and constitute a largely unexplored treasure trove of bioactive molecules.[2] Haliangincin (**2**), which was reported in seminal work by Fudou in 2001,[3] represents the first natural product isolated from a strictly marine myxobacterium (Scheme 1a). Following this early report, only a handful of new marine myxobacterium molecules have appeared in the literature,[2] and in 2013, König disclosed the isolation of salimabromide (**1**) in minute quantities (0.5 mg from 64 L of culture) from the obligate marine bacterium *Enhygromxya salina*.[4] Although a broad biological screening campaign was impossible at this stage, **1** was shown to possess inhibitory activity against *Arthrobacter crystallopoietes* (16 μg mL^{-1}).

From a structural point of view, salimabromide (**1**) contains an unprecedented tetracyclic ring-architecture that contains four consecutive stereocenters, one of which is quaternary. Additionally, the brominated tetrahydronaphthalene core is bridged at C12 and C15 to form a highly substituted and synthetically challenging seven-membered carbocycle.[5] The conformational flexibility of this subunit is further reduced by fusion to a five-membered lactone.

The structure for **1** was exclusively deduced from extensive NMR measurements. Though this only confirmed the connectivity, the absolute stereochemistry was determined by comparison of calculated and measured CD spectra.

Despite considerable progress of the Menche group,[5] no total synthesis of salimabromide (**1**) has been accomplished to date. In light of these considerations, we set out to develop a practical synthetic route to enable rapid access to **1** and fully

Scheme 1. (a) Structural Diversity Produced by Marine Myxobacteria and (b) Key Retrosynthetic Bond Disconnections for Salimabromide (1)



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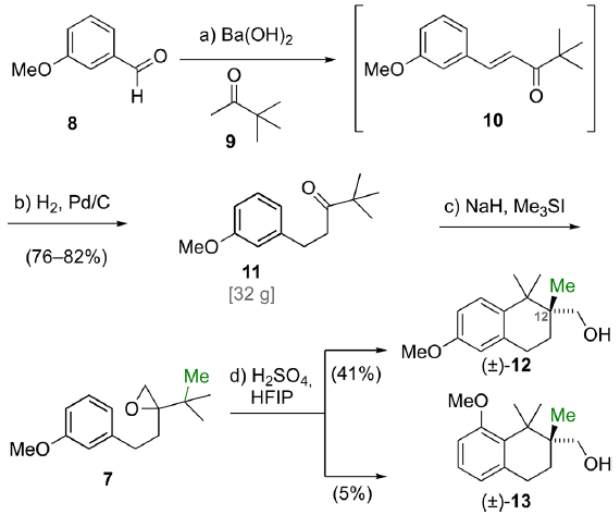
synthetic derivatives thereof. Herein we describe a streamlined synthesis of **1** employing a series of robust chemical transformations. The successful realization of this route allowed us to produce 1.9 g of a highly advanced intermediate in a single batch from which salimabromide (**1**) was prepared in only three steps.

Our retrosynthetic bond disconnections were guided by our desire to rapidly generate molecular complexity and to install the individual stereocenters via a minimum number of synthetic operations (Scheme 1b). We planned to first install the pivotal C12 quaternary carbon center and utilize this handle for the subsequent one-step construction of the stereotriad along C11, C13 and C15. For this purpose and in analogy to the logic of two-phase terpene (bio)synthesis,[6] salimabromide (**1**) was first reduced to tetracycle **5**. This intermediate was designed to eliminate steric hindrance and cross-reactivity of the bromine substituents en route to the tetracyclic carbon framework of **1**. Compound **5** contains the retron for a powerful ketiminium mediated [2+2]-cycloaddition[7] to produce the simplified dihydronaphthalene **6**. Further C−C bond disconnections involving truncation of the side chain and a retro-Friedel−Crafts cyclization/Wagner−Meerwein[8] rearrangement sequence provided epoxide **7**.

We commenced our synthesis with the Claisen−Schmidt condensation of commercially available 3-methoxybenzaldehyde **8** with pinacolone **9** (Scheme 2). Though slow reactions

Scheme 2. Synthesis of the Tetrahydronaphthalene Framework via Consecutive Wagner−Meerwein Rearrangement and Friedel−Crafts Cyclization



[a]Reagents and conditions: (a) [$Ba(OH)_2 \cdot H_2O$, C-200], pinacolone **9**, EtOH, 78 °C; (b) Pd/C, H_2, EtOAc, 23 °C, 76−82% over two steps; (c) NaH, DMSO, 70 °C, then Me_3SI, 0 to 23 °C; (d) H_2SO_4, HFIP, 23 °C, 41% for **12**, 5% for **13** over two steps.

(48 h) and moderate yields (48%) were observed for standard bases such as sodium or potassium hydroxide, the use of activated barium hydroxide [$Ba(OH)_2 \cdot H_2O$, C-200][9] led to rapid consumption of the reactants and clean conversion to the condensation product **10**. On large scale, **10** was best obtained by simple filtration of the reaction mixture using a pad of Celite and evaporation of excess ethanol and pinacolone **9**. The following heterogeneous hydrogenation (1 atm H_2, Pd/C, EtOAc) was conducted on large-scale and reproducibly provided **11** in good yield (76−83% over two steps, 32 g). Exposure of **11** to standard Corey−Chaykovsky conditions (NaDMSO, Me_3SI, 0 to 23 °C)[10] effected clean conversion to epoxide **7**. With **7** in hand, we investigated the crucial rearrangement-cyclization sequence. We found that exposure of **7** to hexanes/sulfuric acid or dichloromethane/titanium(IV) chloride was low-yielding for **12** (~30%) and afforded substantial amounts of the undesired *ortho*-product **13** (~10%). Further screening revealed 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP, 0.1 M), a strong hydrogen-bond donor and weak nucleophile,[11] as the solvent of choice and concentrated sulfuric acid as the optimal catalyst (10 mol %). Under these conditions, the *para*-product **12** was formed with very good regioselectivity (**12**:**13** = 8:1). The remainder of the mass balance corresponds to a complex mixture of byproducts.[12] Similar results were obtained when the reaction was conducted in a hexameric resorcinarene capsule.[13] In agreement with related Lewis-acid catalyzed semipinacol and Wagner−Meerwein rearrangements,[14] a high level of stereoselectivity should be possible for the initial rearrangement step. Evidence was obtained when a solution of enantiomerically enriched **7** (82% ee) in dichloromethane was exposed to titanium(IV) chloride at −78 °C. Under these conditions, an enantiomeric excess of 70% was obtained for **12** (see Supporting Information for details). This result provides an opportunity to access **1** in an asymmetric fashion.

Having successfully installed the crucial C12 quaternary stereocenter in only four steps, we turned our attention to the remaining functionalization of **12** (Scheme 3). To begin, the primary alcohol was protected as its *tert*-butyldiphenylsilyl (TBDPS) ether, and styrene **14** was then formed via exposure to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 2 equiv).[15] The use of substochiometric amounts of DDQ (30 mol %) in combination with manganese(IV) oxide (6 equiv) or alternative oxidation agents such as chloranil, Pd/C or electrochemical methods (4 V, chloranil, Pt/Pt, 0.1 M $LiClO_4$, MeCN) were ineffective.

The TBDPS group was crucial for the stability of the silyl ether under the reaction conditions, and the presence of the electron-donating methoxy substituent was beneficial for the oxidation.[16]

For the installation of the missing ethyl substituent, we initially investigated the direct coupling of **14** using nickel (e.g., $Ni(acac)_2$, dcype, EtMgBr, MgI_2, PhMe, 100 °C; $Ni(cod)_2$, dcype, EtMgI, MgI_2, PhMe, 100 °C).[17] Because our substrate proved to be remarkably unreactive under these conditions, we decided to replace the methoxy substituent with a more reactive triflate. For the removal of the methyl ether, freshly prepared lithium diphenylphosphide (Ph_2PH, *n*-BuLi) was found to be optimal.[18] The free phenol was then converted to the triflate upon exposure to the Hendrickson−McMurray reagent ($PhNTf_2$)[19] to afford **15** in quantitative yield. Standard Negishi cross-coupling ($Pd(dppf)Cl_2$, $ZnEt_2$, dioxane, 70 °C)[20] enabled clean installation of the missing ethyl substituent (92%), and cleavage of the silyl ether (TBAF, THF, 23 °C) gave alcohol **16** (99%). The remaining carbon-chain was introduced in a three-step sequence beginning with the oxidation of **16** using Dess−Martin periodinane[21] (96%), followed by a high-yielding, *Z*-selective Wittig olefination and amide formation (pyrrolidine, 100 °C) to provide **6** (85%).

With robust access to the dihydronaphthalene **6**, we proceeded to investigate the key-step of our synthesis: a ketiminium ion mediated [2+2]-cycloaddition[7] to construct

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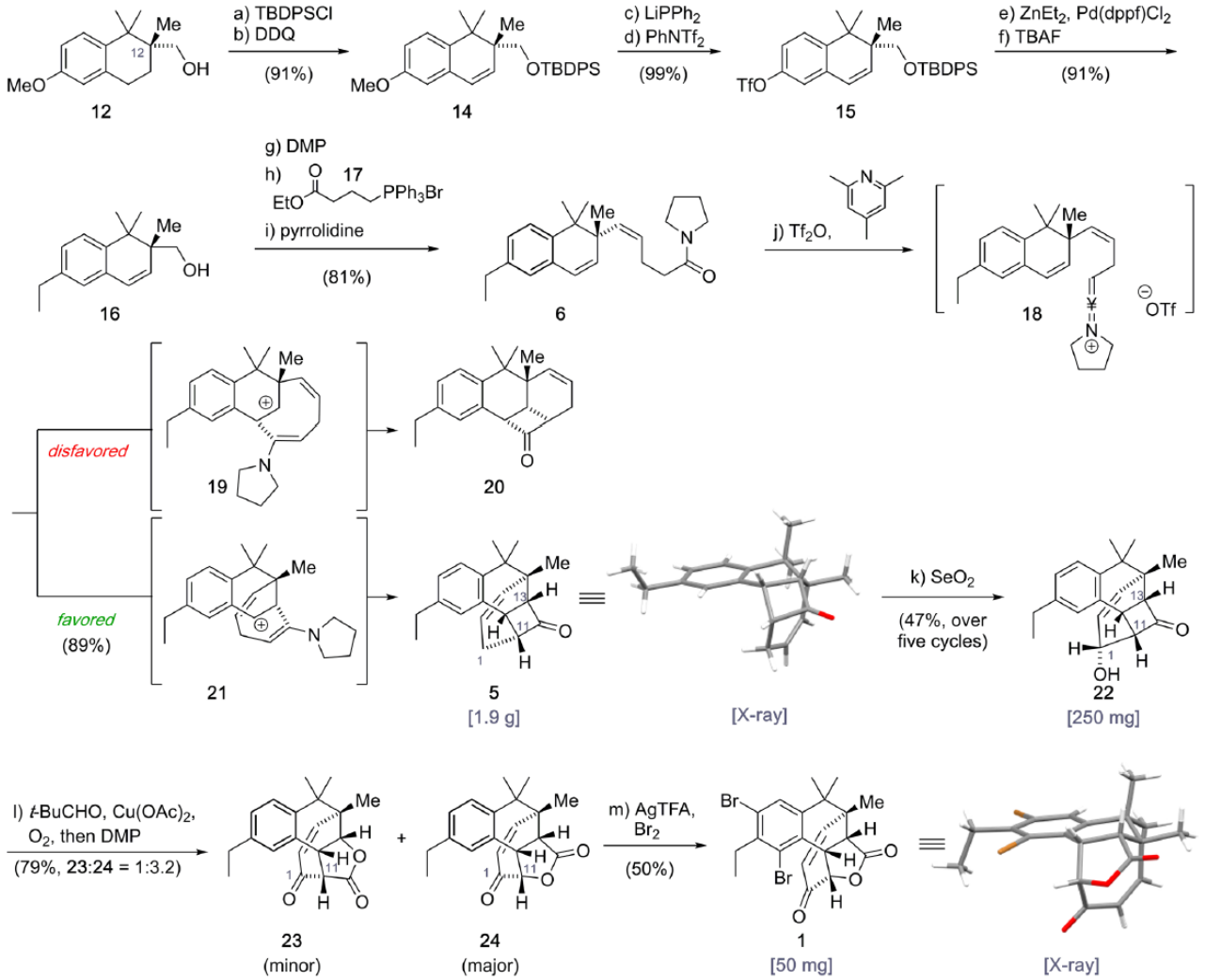
Scheme 3. Total Synthesis of Salimabromide[a]



[a]Reagents and conditions: (a) TBDPSCl, imidazole, DMAP, DMF, 23 °C; (b) DDQ, dioxane, 93 °C, 91% over two steps; (c) $LiPPh_2$, THF, 60 °C; (d) $PhNTf_2$, NEt_3, THF, 23 °C, 99% over two steps; (e) $ZnEt_2$, $Pd(dppf)Cl_2$, dioxane, 70 °C, 92%; (f) TBAF, THF, 23 °C, 99%; (g) DMP, K_2CO_3, CH_2Cl_2, 0 to 23 °C, 96%; (h) NaHMDS, **17**, THF, −78 to +23 °C, 85%; (i) pyrrolidine, 100 °C, 99%; (j) Tf_2O, 2,4,6-collidine, $ClCH_2CH_2Cl$, 80 °C, 89%; (k) SeO_2, SiO_2, dioxane, 120 °C, 47% over five cycles; (l) *t*-BuCHO, $Cu(OAc)_2$, O_2 (1 atm), $ClCH_2CH_2Cl$, 23 °C, then DMP, $NaHCO_3$, CH_2Cl_2, 79%, **23**:**24** = 1:3.2; (m) AgTFA, Br_2, CF_3COOH, 50%.

the seven-membered carbocycle and complete the tetracyclic carbon framework. Under optimized conditions, a solution of amide **6** and *sym*-collidine (1.2 equiv) in dichloroethane was slowly added to a refluxing solution of freshly distilled trifluoromethanesulfonic anhydride (1.2 equiv) in dichloroethane (0.1 M). The cycloaddition produced the tetracycle **5** with almost perfect regio- and diastereoselectivity in excellent yield (89%, 1.9 g). The exact mechanism, concerted (synchronous/asynchronous) or stepwise, has been a matter of debate for many decades.[7] Depending on the substitution pattern on both the alkene and the ketiminium salt, either of the two pathways might be operational.[22] The greater resonance stabilization of the benzylic cation **21** versus **19** was envisioned to govern the regioselectivity favoring formation of **5**.

Having installed the crucial stereocenters, we were poised to tackle the remaining challenges: regioselective oxidation of the carbon-framework and bromination of the arene subunit. When **5** (500 mg) was treated with selenium dioxide (dioxane, 120 °C, 6 h) in the presence of silicon dioxide (>230 mesh) to prevent agglomeration, the diastereomerically pure allylic alcohol **22** was formed together with unreacted **5**. Extended reaction times were detrimental as overoxidation and decomposition started to prevail. Subjection of recovered **5** (76%) to the reaction conditions enabled us to prepare 250 mg of **22** after five cycles (47%, ~15% for the first cycle).[23] Subsequent Baeyer−Villiger oxidation using standard conditions (*m*-CPBA, $NaHCO_3$, CH_2Cl_2) gave two regioisomeric lactones, which were directly oxidized (DMP, $NaHCO_3$, CH_2Cl_2) to afford **23** and **24** in a ratio of 1.4:1 in 84% combined yield. Separation of **23** and **24** was readily accomplished by flash column chromatography. To improve this undesired outcome, further optimization of the oxidant was performed. Interestingly, exposure of **22** to *t*-BuCHO (5 equiv) in the presence of molecular oxygen (1 atm) and copper(II) acetate (1 equiv) gave **24** as the major product

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(79%, **23**:**24** = 1:3.2).[24] The directing effect of the free hydroxy group was crucial as the corresponding methyl ether led to lower regioselectivity (1:1.1) only slightly favoring the desired regioisomer (compare **24**). It is also noteworthy that replacement of *t*-BuCHO with *m*-CPBA in the Baeyer–Villiger step under otherwise identical conditions was even less efficient and only poor regioselectivity (**23**:**24** = 1.2:1) was obtained. For the introduction of the missing bromine substituents, **24** was exposed to a panel of brominating agents (e.g., Br_2, $CHCl_3$; NBS, HOAc; $BnMe_3NBr_3$, $ZnBr_2$, HOAc). Under these conditions, formation of **1** was only observed in trace amounts if at all. Finally, we found that treating a solution of **24** in trifluoroacetic acid (0.1 M) with silver(I) trifluoroacetate (3 equiv) and elemental bromine (3 equiv) enabled the desired bromination (50%) and thus completed the synthesis of salimabromide (**1**, 50 mg).[25] The analytical data for **1** (^{1}H NMR, ^{13}C NMR, HRMS) fully matched those reported for the natural compound. Additionally, the structure of **1** was unambiguously validated by single-crystal X-ray diffraction analysis.

In summary, we have completed the first total synthesis of salimabromide, a unique tetracyclic polyketide. The highlights of the developed route are (1) a powerful Wagner–Meerwein rearrangement/Friedel–Crafts cyclization sequence to forge the tetrahydronaphthalene skeleton and (2) a high-yielding ketiminium mediated (2+2)-cycloaddition to set the remaining three stereocenters. The overall sequence benefits from a series of practical transformations that can be also conducted on large scale. The robustness of the developed synthesis is evident from the fact that more than 1.9 g of a highly advanced intermediate were prepared in a single batch.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b06228.

Experimental details and spectroscopic data (PDF)
X-ray crystallographic data for **1**, **5**, **23** and **24** (CIF)

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Notes

The authors declare no competing financial interest.

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2.2 Ring-Expansion Approaches for the Total Synthesis of Salimabromide

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Ring-Expansion Approaches for the Total Synthesis of Salimabromide

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ABSTRACT

We describe the evolution of a synthetic strategy for the construction of the marine polyketide salimabromide. Combining a bicyclo[3.1.0]hexan-2-one ring-expansion to build up a functionalized naphthalene and an unprecedented rearrangement/cyclization cascade, enabled synthesis of a dearomatized tricyclic subunit of the target compound. Alternatively, an intramolecular keteniminium [2+2]-cycloaddition and subsequent Baeyer–Villiger ring-expansion gave access to the sterically encumbered architecture of salimabromide. Sequential oxidation of the carbon framework finally enabled the total synthesis of this unusual natural product.

1. Introduction

Myxobacteria are a unique class of δ-proteobacteria with an elaborate ability for intercellular communication [1]. In an impressive process of cooperative morphogenesis, these rod-shaped gliding bacteria can aggregate and pile up on starvation conditions, forming so-called fruiting bodies. Within the maturing fruiting body, the cells differentiate into myxospores that are resistant to desiccation. Most myxobacteria also have a fascinating predatory activity on other microorganisms and can lyse a variety of bacteria and fungi to feed on the lysis products [2]. More than 100 natural product scaffolds with a broad range of biological activities were isolated from terrestrial myxobacteria since the last three decades [3]. Only in 1998, the first member of currently ten known marine myxobacterial strains was reported by Iizuka [4]. Difficulties in the cultivation of these bacteria complicate the isolation of natural products and only seven natural product classes have been identified so far (Figure 1) [5]. These include enhygrolide A (**1**) and B (**2**) [6], enhygromic acid (**3**) [7], haliamide (**4**) [8], haliangicins (**5**) [9], salimyxins (**6**) [6] and salimabromide (**7**) [10].

Of those seven classes, the organobromine compound salimabromide (**7**) contains a unique C_{20} framework that does not show any resemblance to other known natural products. Its tetrahydronaphthalene moiety features two contiguous quaternary carbon centers, one of which is asymmetric, and is annealed to a γ-butyrolactone. An enone motif connects the lactone and the saturated half of the tetrahydronaphthalene. The two bromides are located on the aromatic half, resulting in a penta-substituted arene with an uncommon ethyl side chain. First biological screens were limited as only 0.5 mg of **7** could be isolated [10]. However, they

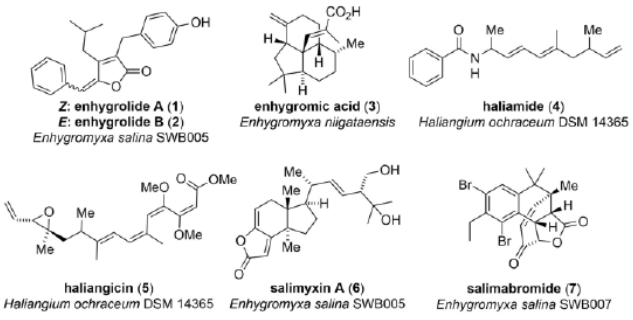
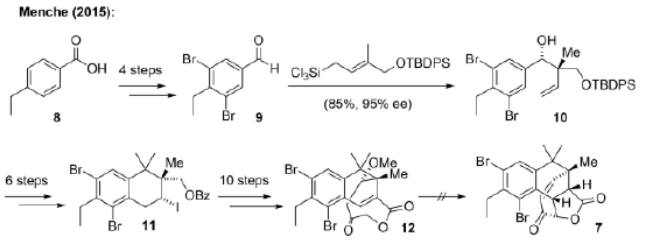


Figure 1 | Natural product classes from marine myxobacteria.

revealed a moderate antibiotic activity against *Arthrobacter cristallopoedes* with a MIC value of 16 μg mL^{-1}.

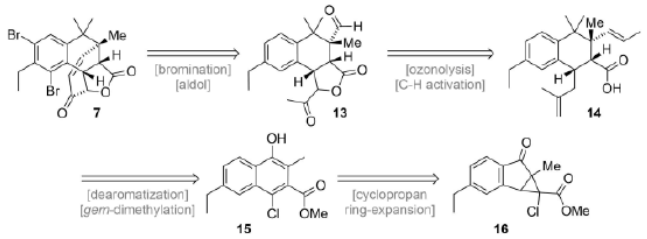
The group of Menche began first synthetic studies shortly after the isolation of **7** in 2013 [11]. In their approach, the crucial quaternary stereocenter was set via an asymmetric Denmark crotylation (95% ee) employing aldehyde **9**. It is interesting to note that **9**, derived from acid **8** in four steps, already contains the sterically demanding bromide substituents. The alcohol **10** was converted to the tetraline **11** within further six steps. For the introduction of the remaining carbon atoms, an additional ten steps were required to give the eight-membered lactone **12**. Unfortunately, the final ring closure of the γ-butyrolactone by an intramolecular Michael-addition as well as the elimination of the neopentylic methoxy group could not be achieved at this stage.



Scheme 1 | Synthetic studies towards salimabromide (**7**) by Menche. TBDPS = *tert*-butyldiphenylsilyl; Bz = benzoyl.

2. Results and discussion

In our retrosynthetic analysis, we envisioned a complementary approach to the one developed by Menche and decided to introduce the bromide substituents of **7** at the very end of the synthesis (Scheme 2). This decision was based on the hypothesis

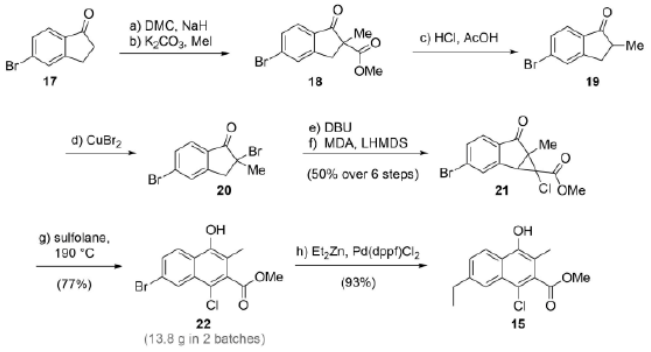


Scheme 2 | Initial retrosynthesis of salimabromide (**7**).

that the biosynthesis involves a late-stage bromination and on steric arguments [10]. The enone of **7** was disconnected via a dynamic kinetic aldol reaction to provide **13** [12]. Further disconnection was accomplished by removal of the lactone and masking of the aldehyde function as an alkene to give **14**. For the construction of **14**, a dearomatization sequence of **15** was planned. Guided by our previously developed ring-expansion methodology, we envisioned to directly trace back **15** to **16** [13–15].

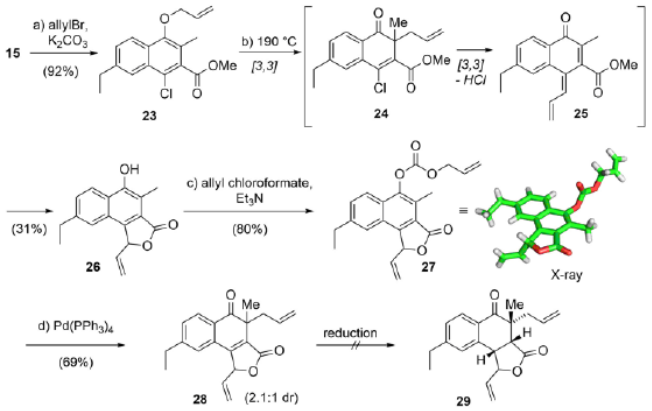
2.1. First Generation Route

We commenced our synthesis with commercially available 5-bromo-1-indanone (**17**) (Scheme 3). From there, cyclopropanated indanone **21** was generated in six steps involving a three-step methylation procedure (**17** to **18** to **19**) [16,17], a bromination with



Scheme 3 | Synthesis of naphthol **15** by fragmentation of cyclopropanated indanone **21**. a) DMC, NaH, THF, 0 to 70 °C; b) K_2CO_3, MeI, DMSO, 0 to 23 °C; c) HCl (37%), AcOH, 100 °C; d) $CuBr_2$, EtOAc/$CHCl_3$, 70 °C; e) DBU, benzene, 0 to 23 °C; f) MDA, LHMDS, THF, –78 °C, 50% over 6 steps; g) sulfolane, 190 °C, 77%; h) Et_2Zn, Pd(dppf)Cl_2, 1,4-dioxane, 0 to 90 °C, 93%. DMC = dimethylcarbonate, DMSO = dimethylsulfoxide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, MDA = methyl dichloroacetate, LHMDS = lithium bis(trimethylsilyl)amide, dppf = 1,1'-Bis(diphenylphosphino)ferrocene.

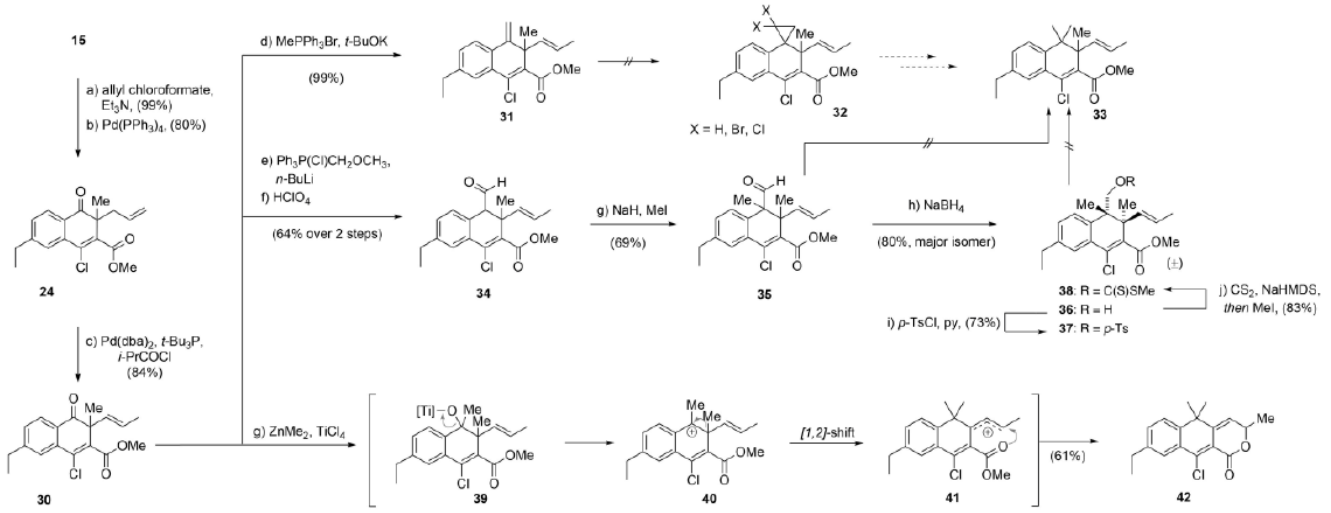
copper(II) bromide (**19** to **20**) [18,19] followed by elimination and subsequent cyclopropanation with methyl dichloroacetate (MDA, **20** to **21**) [13,20]. The fragmentation was conducted in sulfolane at 190 °C affording naphthol **22** in good yield (77%) on gram-scale [13]. Negishi cross-coupling using freshly prepared diethylzinc introduced the ethyl side chain of **15** in excellent yield [21]. To achieve the dearomatization of the naphthalene we pursued the sequence shown in Scheme 4. First, **15** was allylated under



Scheme 4 | A tandem Claisen/Cope-rearrangement of phenyl allyl ether **23** and dearomatization of **26**. a) Allyl bromide, K_2CO_3, DMF, 65 °C, 90%; b) sulfolane, 190 °C, 31%; c) allyl chloroformate, Et_3N, THF, 0 °C, 80%; d) $Pd(PPh_3)_4$, toluene/*n*-hexane (9:1), 45 °C, 69%. THF = tetrahydrofuran, DMF = *N*,*N*-dimethylformamide.

standard conditions (allyl bromide, K_2CO_3, DMF, 65 °C) to give **23** in 92% yield. Heating a solution of **23** in sulfolane at 190 °C induced a tandem Claisen/Cope-rearrangement/cyclization sequence to afford – via the intermediacy of **24** and *p*-quinomethide **25** – the lactone **26** in 31% yield. For the crucial dearomatization, **26** was converted to its allyl carbonate **27** [22]. Exposure to palladium(0) induced the decarboxylative allylation to provide **28** as a mixture of two diastereomers (69%, dr = 2.1:1) [23]. Unfortunately, all attempts to selectively reduce the enone to **29** lead to decomposition, no reaction, isomerization of the vinyl group or reduction of the ketone [24–26].

We therefore decided to go back to **15** and first concentrate on the installation of the *gem*-dimethyl group (Scheme 5). For this purpose, **15** was dearomatized following an analogous procedure as above. In this way, the dearomatized product **24** was obtained in good yields (79% over two steps). Isomerization of the allylic double bond – required for the intended ozonolysis towards **13** – was accomplished by conditions developed by Skrydstrup ($Pd(dba)_2$, *t*-Bu_3P, *i*-PrCOCl, PhMe) in 84% yield [27]. With **31** in hand, we investigated introduction of the *gem*-dimethyl group. First, Wittig olefination proceeded smoothly to give **32** [28]. Unfortunately we were not able to cyclopropanate this alkene by employing the Simmons–Smith protocol (CH_2I_2, $ZnEt_2$) [29], the use of dichlorocarbene or dibromocarbene [30]. In a second approach, a Kluge–Wittig reaction/hydrolysis sequence gave aldehyde **34** which was α-methylated. Noteworthy, rigorous degassing of the solvent (THF) was mandatory to avoid competing oxidation of the enolate and diminished yields of **35**. Attempts to directly reduce this aldehyde by the protocol of Wolff–Kishner [31] or the formation of a thioacetal followed by nickel catalyzed hydrogenation (Mozingo protocol) [32] failed. Therefore, **34** was reduced to the primary alcohol **36**. While it was possible to tosylate this alcohol (**36** to **37**), **33** could not be generated by reduction with lithium aluminum hydride even under elevated temperature (60 °C). Finally, a radical Barton–McCombie deoxygenation of **38**



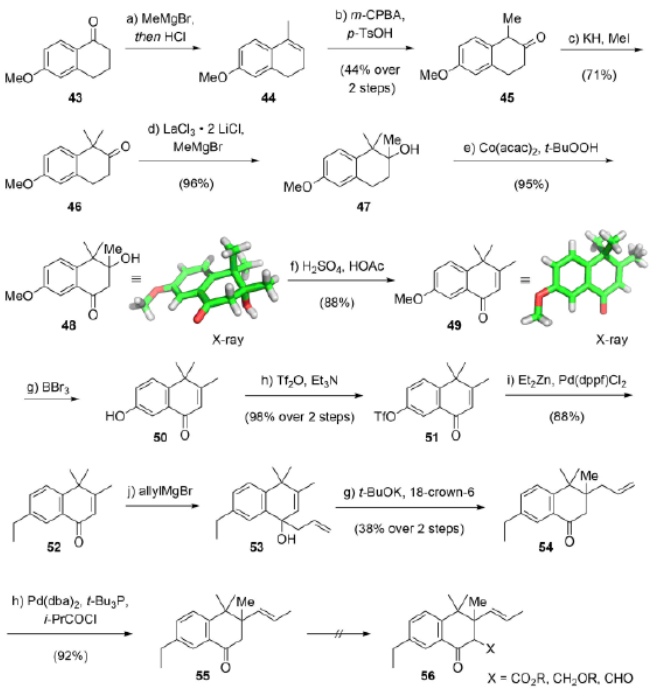
Scheme 5 | Attempts towards the *gem*-dimethylation of dearomatized naphthol **30**. a) Allyl chloroformate, Et_3N, THF, 0 °C, 99%; b) $Pd(PPh_3)_4$, toluene/*n*-hexane (10:1), 45 °C, 80%; c) $Pd(dba)_2$, *t*-Bu_3P, *i*-PrCOCl, toluene, 80 °C, 84%; d) $MePPh_3Br$, *t*-BuOK, THF, 0 to 23 °C, 99%; e) $Ph_3P(Cl)CH_2OCH_3$, *n*-BuLi, THF, 0 to 23 °C, 81%; f) $HClO_4$, Et_2O, 23 °C, 79%; g) NaH, MeI, THF, 0 to 23 °C, 69%; h) $NaBH_4$, MeOH, 0 °C, 80%; i) *p*-TsCl, pyridine, 23 °C, 73%; j) CS_2, NaHMDS, THF, −78 to −65 °C, 83%; g) $TiCl_4$, $ZnMe_2$, CH_2Cl_2, 0 °C, 61%. dba = dibenzylideneacetone, *p*-Ts = *p*-toluenesulfonyl, NaHMDS = sodium bis(trimethylsilyl)amide, py = pyridine.

was investigated [33]. However, the intended product was not formed but a complex product mixture was obtained. Direct dimethylation of the ketone using Reetz conditions [34] failed as the strongly Lewis acidic conditions induced a Wagner–Meerwein rearrangement (**39** to **40** to **41**) to give **42** as the sole product [35].

2.2 Second Generation Route

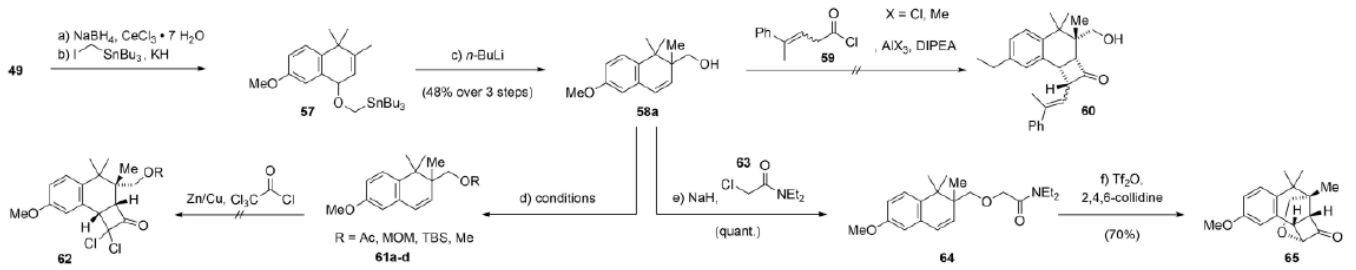
Realizing that introduction of the two quaternary carbon centers is highly problematic at this stage of the synthesis, we abandoned the indanone ring-expansion route and tried to set both centers at an earlier stage. Starting with commercially available methoxytetralone **43**, addition of methylmagnesium bromide and acid-mediated elimination gave known **44** [36]. Epoxidation with concomitant Meinwald-rearrangement afforded ß-tetralone **45** in 44% yield over two steps [37]. Methylation under thermodynamic control using potassium hydride as the base set the *gem*-dimethyl group and afforded tetralone **46** [38]. The vicinal methyl group of **47** was introduced by Grignard addition employing Knochel's conditions ($LaCl_3 \cdot 2$ LiCl, MeMgBr) [39]. Benzylic oxidation with cobalt acetylacetonate [40] gave clean **48** [41] and subsequent acid-mediated elimination afforded enone **49** [42] in good yield [43]. A three-step procedure, involving demethylation, triflation [44] and Negishi cross-coupling [21] with diethylzinc was used to replace the methoxy with an ethyl group yielding **52** (via **50** and **51**, 86% over three steps). Allylation with allylmagnesium bromide (**52** to **53**) followed by an anionic oxy-Cope rearrangement set the quaternary stereocenter of **54** [45,46]. For the isomerization of the allyl group, Skrydrup's conditions again proved to be the method of choice affording **55** in 92% yield [27]. Surprisingly, despite extensive efforts tetralone **55** proved to be reluctant to react at its α-position. We examined several α-acylation and alkylation procedures to introduce the carboxylate for the γ-butyrolactone, however, no carbon-carbon bond formation to give **56** was observed. We reasoned that steric hindrance by the adjacent quaternary stereocenter impedes nucleophilic attack of the enolate.

As steric hindrance prevented α-functionalization of the ketone, we considered an alternative [2+2]-cycloaddition strategy using the readily available **49** (Scheme 7). Conversion of **49** to **58a**



Scheme 6| Synthesis of tetralone **55**. a) MeMgBr, THF, 0 °C, *then* HCl, 23 °C; b) *m*-CPBA, CH_2Cl_2/TFE, *p*-TsOH, 0 °C, 44% over 2 steps; c) KH, MeI, THF, 0 to 23 °C, 71%; d) MeMgBr, $LaCl_3 \cdot 2$ LiCl, THF, 0 °C, 96%; e) $Co(acac)_2$, *t*-BuOOH, Me_2CO, 23 °C, 95%; f) H_2SO_4, AcOH, 100 °C, 88%; g) BBr_3, CH_2Cl_2, −78 to 0 °C; h) Tf_2O, Et_3N, CH_2Cl_2, −78 to 23 °C, 98% over two steps; i) Et_2Zn, $Pd(dppf)Cl_2$, 1,4-dioxane, 90 °C, 88%; j) allylMgBr, THF, 0 °C; g) *t*-BuOK, 18-crown-6, THF, 0 to 23 °C, 38% over 2 steps; h) $Pd(dba)_2$, *t*-Bu_3P, *i*-PrCOCl, toluene, 80 °C, 92%. *m*-CPBA = *meta*-chloroperoxybenzoic acid, TFE = 2,2,2-trifluoroethanol, acac = acetylacetonate, Tf = trifluoromethanesulfonate, 18-crown-6 = 1,4,7,10,13,16-hexaoxacyclooctadecane.

proceeded uneventfully via the intermediacy of **57** and involved a Wittig–Still rearrangement to construct the quaternary stereocenter (48% over three steps) [47,48]. We envisioned the primary alcohol to serve as a handle to control the facial selectivity of the ketene [2+2]-cycloaddition. First, we investigated the use of

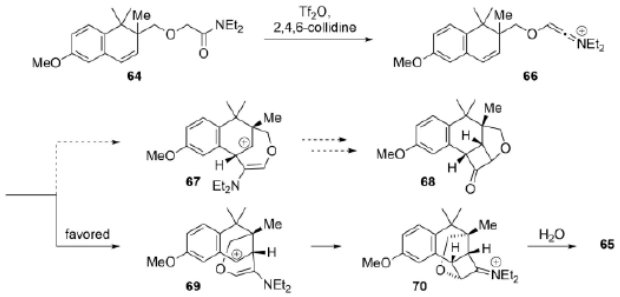


Scheme 7 Investigation of the [2+2]-cycloadditon on **58**. a) $NaBH_4$, $CeCl_3 \cdot 7\ H_2O$, MeOH, 0 °C; b) KH, ICH_2SnBu_3, THF, 0 °C; c) *n*-BuLi, –78 to –45 °C, 48% over 3 steps; d) **61a:** Ac_2O, NEt_3, CH_2Cl_2, 0 °C, 86%; **61b:** DIPEA, MOMCl, CH_2Cl_2, 0 °C, 94%; **61c:** TBSCl, imH, DMF, 0 to 23 °C, 68%; **61d:** NaH, MeI, DMF, 0 to 23 °C, 80%; e) NaH, $ClCH_2CONEt_2$, $(CH_2OMe)_2$, 0 to 23 °C, 97%; e) Tf_2O, 2,4,6-collidine, $(CH_2Cl)_2$, 80 °C, then K_2CO_3, Me_2CO, 70 °C, 70%. DIPEA = *N*,*N*-diisopropylethylamine, DMP = Dess–Martin periodinane, TBS = *tert*-butyldimethylsilyl, MOM = methoxymethyl, Ac = acetyl, imH = imidazole.

Lewis acids ($AlMe_3$; $MeAlCl_2$) to control the trajectory of the ketene derived from **59** via coordination to the alkoxide. Unfortunately, no cycloaddition product **60** was observed and only traces of the corresponding ester together with polymeric byproducts were formed. Protection of the primary alcohol (**61a-d** = Ac, MOM, TBS, Me) and cycloaddition with dichloroketene to give **62** was equally unproductive.

Facing the problems of ketene oligo-and polymerization we resorted to keteniminium salts, which are known to be more electrophilic and reluctant to dimerization [49,50]. Treatment of **58** with 2-chloro-*N*,*N*-diethylacetamide (**63**) gave **64**. We were pleased to see that upon treatment with freshly distilled trifluoromethanesulfonic anhydride and *sym*-collidine at 80 °C, **64** underwent the intramolecular cycloaddition to the iminium salt **70**. The cycloaddition product **65** was formed after hydrolysis in 70% yield and excellent regioselectivity affording exclusively the 6/4- instead of the 5/4-system. The regioselectivity finds its basis in a stepwise mechanism presumably proceeding via the benzylic cation **69** (Scheme 8). This cation should be favored over the secondary cation **67** leading to regioisomer **68**.

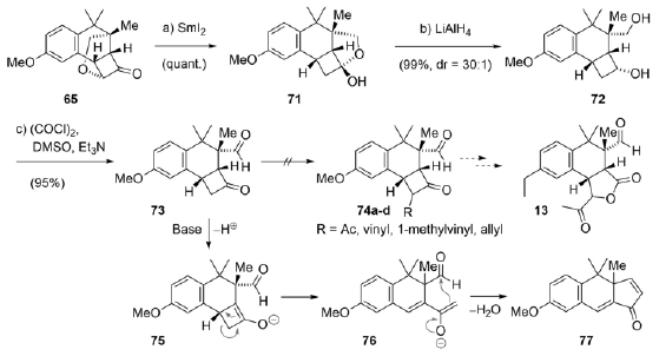
With **65** in hand, we cleaved the ether bridge by treatment with



Scheme 8 | Proposed mechanism of the intramolecular [2+2]-cycloaddition of keteniminium ion **64.**

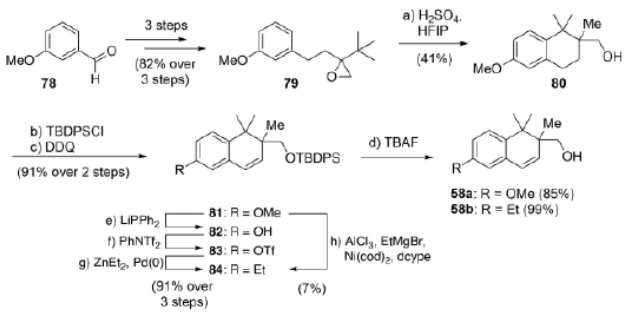
samarium iodide to give lactol **71** (Scheme 9) [51]. Reduction with lithium aluminum hydride afforded diol **72** and oxidation under Swern conditions provided cyclobutanone **73** in 95% yield. All efforts to functionalize the cyclobutanone ring and to convert **73** to **74a-d** failed. Under basic conditions formation of **77** was observed in minor amounts. We believe that **77** is formed via ring-opening of the enolate **75** (stepwise or electrocyclic) and subsequent aldol condensation of **76**.

At this point, we realized that synthesis of **13**, the key-substrate for the intended kinetic dynamic aldol condensation, might not be possible via the investigated routes. Therefore, we reassessed our strategy once again. Encouraged by the high selectivity of the keteniminium mediated cycloaddition of **64** we decided to



Scheme 9 | Synthesis of cyclobutanone **71** a) SmI_2, THF/MeOH, 0 °C, quant.; b) $LiAlH_4$, Et_2O, 0 °C, 99%; c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 to 23 °C, 95%.

investigate an [2+2]-cycloaddition approach using a carbon chain tether (Scheme 10) [52]. For this purpose, we resorted to alcohol **58a**. Since synthesis of **58a** was rather low-yielding so far, we considered other synthetic options to get rapid access to the tetraline core. Inspired by the work of El-Fouty [53] and our desire to rapidly introduce both quaternary carbon centers, we envisioned the synthesis of **80** by a Wagner–Meerwein cyclization sequence of epoxide **79**. [54] When conducting this reaction in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), 41% of the desired product could be isolated, giving access to large amounts of **80** in four steps involving only two purification steps [54]. For the oxidation to the styrene **81** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

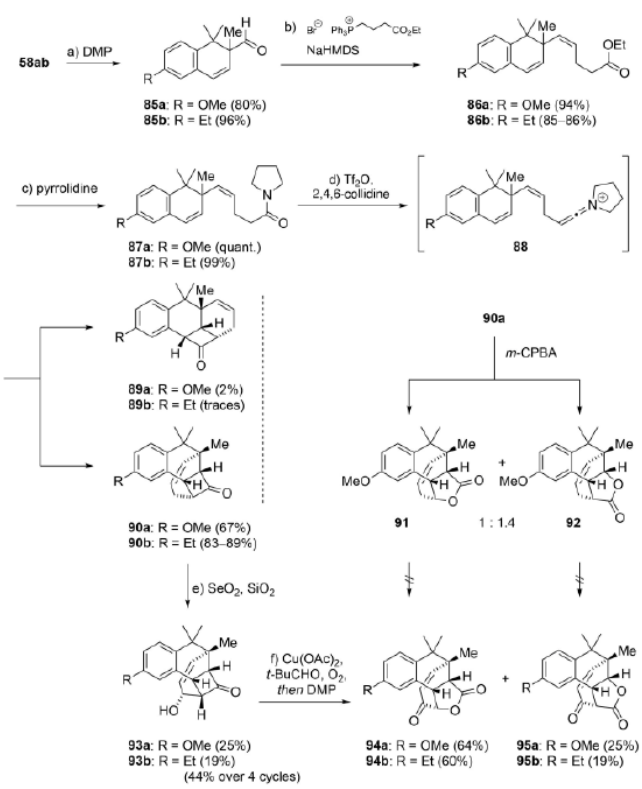


Scheme 10 | Second generation approach to **58ab**. a) H_2SO_4, HFIP, 23 °C, 41%; b) TBDPSCl, imidazole, DMAP, DMF, 23 °C; c) DDQ, 1,4-dioxane, 93 °C, 91% over two steps; d) TBAF, THF, 23 °C, 85–99%; e) $LiPPh_2$, THF, 60 °C; f) $PhNTf_2$, NEt_3, THF, 23 °C, 99% over two steps; g) $ZnEt_2$, $Pd(dppf)Cl_2$, 1,4-dioxane, 70 °C, 92%; h) $AlCl_3$, EtMgBr, $Ni(cod)_2$, dcype, PhMe, *i*-Pr_2O, 100 °C, 7%. HFIP = 1,1,1,3,3,3-hexafluoroisopropanol, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, cod = 1,5-cyclooctadiene, dcype = 1,2-bis(dicyclohexylphosphino)ethane.

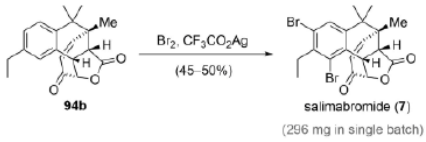
(DDQ), protection of the free alcohol was mandatory as otherwise tetrahydrofuran formation was observed. Deprotection of **81** using tetrabutylammonium fluoride completed the synthesis of **58a**. This sequence shortens the route from nine to seven steps, uses inexpensive reagents and enables large scale synthesis of **58a**. In addition, **81** was used for the installation of the ethyl side chain. A four-step protocol involving demethylation, triflate formation, Negishi cross-coupling using diethylzinc (**82** to **83** to **84**) and cleavage of the silyl protecting group gave **58b**. We also investigated the direct nickel(0)-catalyzed coupling of **81** using the conditions developed by Rueping and Schoenebeck [55]. Under these conditions **84** was only formed in low yields (7%).

With **58a** and **58b** in hand, we continued with the cycloaddition approach. Dess–Martin periodinane (DMP) gave aldehyde **85ab** in 80–96% yield (Scheme 11). A *Z*-selective Wittig olefination [56] afforded ester **86ab** that could be converted into amide **87ab** by heating in neat pyrrolidine [57]. We were pleased to see that **87ab** underwent the envisioned [2+2] cycloaddition in good yields (67% for **90a**, 82–89% for **90b**) and excellent regioselectivity (> 30:1). Only 2% of the undesired [2+2] product **89a** and trace amounts of **89b** were formed. We later found that a very similar approach was investigated by Menche [58,59]. Having successfully built up the full carbon framework of salimabromide (**7**), only Baeyer–Villiger oxidation to expand the cyclobutanone to the γ-butyrolactone and allylic oxidation of the alkene to give the enone were left. Baeyer–Villiger oxidation of the cyclobutanone **90a** promoted by *meta*-chloroperoxybenzoic acid (*m*-CPBA) proceeded smoothly, however, the undesired regioisomer **92** prevailed (**91**:**92** = 1:1.4). As separation of this mixture was impossible at this stage, we directly investigated the allylic oxidation. Efforts to realize the oxidation with rhodium (e.g. bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] [60]) or manganese based catalysts (e.g $Mn(OAc)_3$ [61]) in combination with *tert*-butylhydroperoxide were unsuccessful. The use of bromine or selenium dioxide did not lead to any functionalization of the desired position. Next, we tried inversion of the overall sequence and investigated the allylic oxidation first. Exposure of **90a** to a large excess of selenium dioxide (10 equiv) in the presence of fine quartz sand – to prevent selenium dioxide from agglomeration [62] – and terminating the reaction at around 40% conversion to avoid overoxidation, gave **93a** in 25% yield. This alcohol was converted to the lactones **94a** and **94b** by careful treatment with an equimolar amount of *m*-CPBA followed by DMP oxidation of the allylic alcohol. While we were pleased to observe the desired oxidation, we were confronted with an unfavorable regioselectivity (**94a**:**95a** = 1:1.4). Employing conditions previously developed by Bolm ($Cu(OAc)_2$, *t*-BuCHO, O_2) we were able to invert this ratio to favor the desired lactone **94a** (**94a**:**95a** = 2.5:1) [63–65]. Since the overall route using **58b** turned out to be more efficient, we turned our attention to the completion of the synthesis using **90b**. While allylic oxidation of **90b** proceeded with comparable yields, we observed in the Baeyer–Villiger oxidation of **93b** the formation of many sideproducts and a significant drop of selectivity on scales larger than 50 mg. Despite a balanced ratio of the regioisomeric lactones (**94b**:**95b** = 1:1), we found that copper(I) thiophene carboxylate in wet benzene, followed by DMP oxidation in dichloromethane gives reproducible yields of both **94b** and **95b** even on gram scale (see Experimental for details).

Introduction of the remaining bromine substituents was accomplished by treatment of **94b** with bromine and silver trifluoroacetate to give 296 mg of salimabromide (**7**) in a single batch (Scheme 12). The use of silver trifluoroacetate to form highly reactive trifluoroacetyl hypobromite was essential [66,67]. Other bromination reagents (NBS; n-$Bu_4NBr_3/ZnCl_2$; $Br_2/FeBr_3$) only lead to monobromination or decomposition of **94b** [54]. The analytical data for synthetic salimabromide matched those reported in the literature [10].



Scheme 11 | Synthesis of the carbon skeleton of salimabromide (**7**). a) DMP, CH_2Cl_2, 0 to 23 °C; b) NaHMDS, $Ph_3P(Br)(CH_2)_3CO_2Et$, THF, –78 to 23 °C; c) pyrrolidine, 100 °C; d) Tf_2O, 2,4,6-collidine, $(CH_2Cl)_2$, 80 °C, *then* CCl_4, H_2O, reflux; e) SeO_2, SiO_2, 1,4-dioxane, 120–125 °C; f) $Cu(OAc)_2$, *t*-BuCHO, O_2, $(CH_2Cl)_2$, 23 °C, *then* DMP, 0 to 23 °C.



Scheme 12 | Total synthesis of salimabromide. Br_2, CF_3CO_2Ag, TFA, 0 °C, 45–50%.

3. Conclusion

We presented two complementary strategies for the total synthesis of salimabromide. In our initial route we targeted a highly-substituted keto-aldehyde that was thought to be synthesized via ring-expansion of a cyclopropanated indanone and subsequent dearomatization. Although both key-transformations were realized, efforts to introduce the *gem*-dimethyl group as well as the stereocenters connecting the lactone and the tetrahydronaphthalene core failed. In our second approach, we relied on a [2+2]-cycloaddition to construct the carbon skeleton. While intermolecular cycloaddition reactions were unsuccessful, an intramolecular keteniminium [2+2]-cycloaddition showed to be high-yielding and proceeded with excellent regioselectivity. Three regioselective oxidations (allylic, Baeyer–Villiger, late-stage bromination) enabled completion of the total synthesis in 18 steps (longest linear sequence). The developed route allowed production of 296 mg of salimabromide in a single batch.

Experimental

All reactions were performed in flame-dried glassware fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred *via* syringe or stainless-steel cannula through rubber septa. Solids were added under inert gas counter flow or were dissolved in appropriate solvents. Low temperature-reactions were carried out in a Dewar vessel filled with a cooling agent: acetone/dry ice (−78 °C), water/ice (0 °C). Reaction temperatures above room temperature were conducted in a heated oil bath. The reactions were magnetically stirred and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC), using aluminum plates precoated with silica gel (0.25 mm, 60-Å pore size, Merck) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), were stained by submersion in aqueous potassium permanganate solution ($KMnO_4$), ceric ammonium molybdate solution (CAM) or *p*-anisaldehyde solution (Anis), and were developed by heating with a heat gun. Flash-column chromatography was performed as described by Still [68] employing silica gel (60 Å, 40–63 µm, Merck KGaA). The yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) pure material. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled under nitrogen atmosphere from sodium and benzophenone or sodium/potassium alloy prior to use. Dichloromethane (CH_2Cl_2), Acetonitrile (MeCN), acetone and methanol (MeOH) were purchased from Acros Organics as 'extra dry' reagents and used as received. All other reagents and solvents were purchased from chemical suppliers (Sigma-Aldrich, TCI, Acros Organics, Alfa Aesar, Strem Chemicals, ABCR, Fluorochem) and were used as received. Solvents for extraction, crystallization and flash column chromatography were purchased in technical grade and distilled under reduced pressure prior to use. The molarity of *n*-butyllithium and *tert*-butyllithium solutions was determined by titration against diphenylacetic acid as an indicator (average of three determinations). **NMR spectra** were measured on a Bruker Avance III HD 400 MHz spectrometer equipped with a CryoProbeTM, Bruker Avance Neo 400 MHz spectrometer, Bruker Avance II 600MHz spectrometer, Bruker AXR300, a Varian VXR400 S, Bruker AMX600 or Bruker Avance HD 800. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual proton in the NMR solvent ($CHCl_3$: δ 7.26, acetone-d_5: δ 2.05, C_6D_5H: δ 7.16). Carbon chemical shifts are expressed in parts per million (δ scale, assigned carbon atom) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.16, acetone-d_6: δ 29.84, 206.26, C_6D_6: δ 128.06). ^1H NMR spectroscopic data are reported as follows: Chemical shift in ppm (multiplicity, coupling constants J (Hz), integration intensity, assigned proton). The multiplicities are abbreviated with s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). In case of combined multiplicities, the multiplicity with the larger coupling constant is stated first. Except for multiplets, the chemical shift of all signals, as well for centrosymmetric multiplets, is reported as the center of the resonance range. Additionally to ^1H and ^{13}C NMR measurements, 2D NMR techniques such as homonuclear correlation spectroscopy (COSY), total correlation spectroscopy (TOCSY), heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond coherence (HMBC) were used to assist signal assignment. For further elucidation of 3D structures of the products, nuclear Overhauser enhancement spectroscopy (NOESY) was conducted. Coupling constants J are reported in Hz. All raw fid files were processed and the spectra analyzed using the program MestReNOVA 9.0 from Mestrelab Research S. L. All **mass spectra** were measured by the analytic section of the Department of Chemistry, Ludwig-Maximilians-Universität München and the group of Thomas Müller at the Department of Chemisty, Leopold-Franzens Universität Innsbruck. Mass spectra were recorded on the following spectrometers (ionization mode in brackets): MAT 95 (EI), MAT 90 (ESI) from Thermo Finnigan GmbH and Q Exactive Orbitrap (ESI) from Thermo Fisher Scientific. Mass spectra were recorded in high-resolution. The method used is reported at the relevant section of the experimental section. **IR spectra** were recorded on a PerkinElmer Spectrum BX II FT-IR system. If required, substances were dissolved in CH_2Cl_2 or $CDCl_3$ prior to direct application on the ATR unit. Data are represented as follows: frequency of absorption (cm^{-1}) and intensity of absorption (vs = very strong, s = strong, m = medium, w = weak, br = broad).

*3.1. Methyl 5-bromo-2-methyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**18**)*

To a suspension of sodium hydride (60% dispersion in mineral oil, 19.9 g, 497 mmol, 2.00 equiv) and dimethyl carbonate (39.9 mL, 474 mmol, 2.00 equiv) in tetrahydrofuran (470 mL) in a 3-necked 1-liter round bottom flask fitted with a reflux condenser, dropping funnel and thermometer was added 5-bromo-1-indanone (**17**) (50.0 g, 237 mmol, 1 equiv) in tetrahydrofuran (680 mL) at 0 °C over 45 min. The dark brown reaction mixture was stirred at 0 °C for 30 min, warmed very slowly to 23 °C and carefully heated to 70 °C for 15 h. The solution was cooled to 0 °C and diluted with saturated aqueous ammonium chloride solution (200 mL), aqueous hydrogen chloride solution (2 M; 200 mL) and diethyl ether (300 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 400 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (300 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered through a short pad of Celite® and the filtrate was concentrated. The crude product **S1** was afforded as a dark brown solid and was used without additional purification for the next step. To crude I.71 in dry dimethyl sulfoxide (240 mL) was added potassium carbonate (65.5 g, 474 mmol, 2.00 equiv) portionwise at 0 °C. After dropwise addition of methyl iodide (29.5 mL, 474 mmol, 2.00 equiv) the dark green slurry was stirred at 23 °C for 2 h. The excess methyl iodide was removed by distillation (23 °C, 50 mbar). The reaction mixture was cooled to 0 °C, diluted with saturated aqueous ammonium chloride solution (100 mL), water (100 mL) and ethyl acetate (250 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 400 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (300 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered through a short pad of Celite® and the filtrate was concentrated. The crude product **18** was afforded as a dark brown solid and was used without additional purification for the next step. An analytical pure sample of **18** was obtained by flash column chromatography on silica gel (9% ethyl acetate in hexanes). **Analytical data for 18: TLC** (20% ethyl acetate in hexanes), R_f = 0.40 (UV, $KMnO_4$). **^1H NMR** (400 MHz, $CDCl_3$) δ: 7.63 (s, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.51 (d, J = 8.6 Hz, 1H), 3.69 (s, 1H), 3.64 (s, 3H), 2.95 (d, J = 17.3 Hz, 1H), 1.48 (s, 3H). **^{13}C NMR** (101 MHz, CDCl3) δ: 202.1, 172.0, 154.2, 133.5, 131.6, 130.9, 129.8, 126.1, 56.1, 52.9, 39.6, 21.0. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2953 (*w*), 1742 (*s*), 1710 (*vs*), 1594 (*s*), 1579 (*m*), 1428 (*m*), 1317 (*m*), 1266 (*s*), 1200 (*s*), 1177 (*s*), 1095 (*m*), 1057 (*m*), 964 (*s*), 919 (*m*), 830 (*m*), 769 (*m*), 668 (*m*), 593 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{12}H_{11}O_3{}^{81}Br$ $[M]^+$: 283.9866; found: 283.9875.

*3.2. 5-bromo-2-methyl-2,3-dihydro-1H-inden-1-one (**19**)*

Crude **18** was dissolved in water (82 mL), glacial acetic acid (400 mL) and aqueous hydrogen chloride solution (37%, 125 mL, 924 mmol, 3.90 equiv). The reaction mixture was heated to 100 °C for 16 h. After cooling to 23 °C, the solution was diluted with dichloromethane (300 mL) and water (300 mL) and was carefully neutralized by portionwise addition of sodium bicarbonate (250 g) and aqueous sodium hydroxide solution (10%, 300 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 400 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered through a short pad of Celite® and the filtrate was concentrated. The crude product **19** was afforded as a dark brown solid and was used without additional purification for the next step. An analytical pure sample of **19** was obtained by flash column chromatography on silica gel (2% ethyl acetate in hexanes). **Analytical data for 19: TLC** (20% ethyl acetate in hexanes), R_f = 0.56 (UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.63 – 7.56 (m, 2H), 7.49 (d, *J* = 8.1 Hz, 1H), 3.37 (dd, *J* = 18.1, 8.8 Hz, 1H), 2.70 (dt, *J* = 12.1, 3.5 Hz, 2H), 1.29 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 208.2, 155.2, 135.3, 131.1, 130.1, 129.9, 125.3, 42.1, 34.7, 16.3. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2964 (*w*), 2930 (*w*), 1707 (*vs*), 1594 (*vs*), 1572 (*m*), 1412 (*m*), 1318 (*m*), 1265 (*m*), 1199 (*m*), 1055 (*m*), 963 (*s*), 882 (*m*) 858 (*m*), 825 (*m*), 764 (*m*), 676 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{10}H_9O^{81}Br$ $[M]^+$: 225.9811; found: 225.9814.

*3.3. 2,5-Dibromo-2-methyl-2,3-dihydro-1H-inden-1-one (**20**)*

To a solution of crude indanone **19** in ethyl acetate (1 L) and chloroform (1 L), was added copper(II) bromide (106 g, 474 mmol, 2.00 equiv). The green suspension was heated to 70 °C and while stirring with a KPG stirrer. After 22 h, the mixture was allowed to cool to 23 °C, filtered through a short pad of Celite® and the filtrate was concentrated. The crude product **20** was used without additional purification for the next step. An analytical pure sample of **20** was obtained by flash column chromatography on silica gel (2% ethyl acetate in hexanes). **Analytical data for 20: TLC** (20% ethyl acetate in hexanes), R_f = 0.57 (UV). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.72 (d, *J* = 8.2 Hz, 1H), 7.61 (s, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 3.77 (d, *J* = 18.3 Hz, 1H), 3.47 (d, *J* = 18.3 Hz, 1H), 1.96 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 199.2, 150.7, 132.1, 131.7, 131.4, 129.8, 127.0, 59.2, 46.1, 26.8. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 1723 (*vs*), 1596 (*s*), 1575 (*w*), 1423 (*w*), 1320 (*m*), 1266 (*w*), 1210 (*w*), 1057 (*m*), 973 (*m*), 900 (*w*), 857 (*w*), 831 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{10}H_8O^{79}Br_2$ $[M]^+$: 301.8936; found: 301.8937.

*3.4. Methyl 3-bromo-1-chloro-6a-methyl-6-oxo-1,1a,6,6a-tetrahydrocyclopropa[a]indene-1-carboxylate (**21**)*

To crude indanone **20** in benzene (474 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (106 mL, 711 mmol, 3.00 equiv) at 0 °C. After 5 min, the solution was warmed to 23 °C and was stirred for 45 min. The reaction mixture was diluted with saturated aqueous ammonium chloride solution (100 mL) and diethyl ether (200 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 300 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered through a short pad of Celite® and the filtrate was concentrated (>200 mbar). The crude indenone **S2** was afforded as a yellow-brown oil and was used immediately without additional purification for the next step. *Note: Indenones undergo facile polymerizations and should therefore be used immediately after preparation. For safety reasons the cyclopropanation was carried out in two parallel batches. The crude material of both batches was subsequently combined and purified together.* To a stirred solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 137 mL, 137 mmol, 1.15 equiv) in tetrahydrofuran (119 mL) in a 3-necked 2 liter round bottom flask fitted with a reflux condenser, dropping funnel and thermometer, was added methyl dichloroacetate (12.9 mL, 125 mmol, 1.05 equiv) over 30 min at −78 °C. After stirring for 105 min, a solution of crude indenone **S2** in tetrahydrofuran (238 mL) was added over 1.5 h and after the addition, the reaction mixture was allowed to warm slowly to 23 °C. After 16 h, the mixture was cooled to 0 °C and diluted with saturated aqueous ammonium chloride solution (200 mL) and ethyl acetate (300 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 300 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (2 to 3% ethyl acetate in hexanes) to obtain **21** (38.9 g, 50% over 6 steps, inconsequential mixture of diastereomers) as a yellow solid. **Analytical data for 21:** *Note: Traces of the minor diastereomer are visible in the ^{1}H and ^{13}C NMR spectra, but solely the resonances of the major diastereomer are listed below.* **TLC** (20% ethyl acetate in hexanes), R_f = 0.47 (UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.67 (s, 1H), 7.54 (s, 2H), 3.86 (s, 3H), 3.71 (s, 1H), 1.51 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 197.3, 165.9, 149.4, 134.5, 132.2, 129.9, 129.8, 125.3, 64.9, 53.9, 42.8, 37.3, 9.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954 (*w*), 1717 (*vs*), 1597 (*s*), 1579 (*m*), 1435 (*m*), 1356 (*w*), 1283 (*m*), 1260 (*s*), 1237 (*s*), 1206 (*m*), 1162 (*m*), 1107 (*w*), 1055 (*m*), 988 (*w*), 952 (*m*), 938 (*m*), 889 (*m*), 836 (*m*), 788 (*w*), 777 (*w*), 738 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{13}H_{10}O_3{}^{79}Br^{35}Cl$ $[M]^+$: 327.9496; found: 327.9505.

*3.5. Methyl 7-bromo-1-chloro-4-hydroxy-3-methyl-2-naphthoate (**22**)*

Note: The reaction was carried out in two parallel batches. The crude material of both batches was subsequently combined and purified together. A solution of **21** (8.90 g, 27.0 mmol, 1 equiv) in sulfolane (54 mL) was heated to 190 °C for 5.5 h and then cooled to 23 °C. The reaction mixture was diluted with diethyl ether (200 mL) and water (200 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 300 mL). The combined organic layers were washed successively with saturated aqueous sodium chloride solution (200 mL) and water (3 × 300 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (14% ethyl acetate in hexanes) to provide **22** (13.8 g, 77%) as a brown solid. **Analytical data for 22: TLC** (20% ethyl acetate in hexanes), R_f = 0.18 (UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.18 (s, 1H), 7.94 (d, *J* = 8.9 Hz, 1H), 7.57 (d, *J* = 8.9 Hz, 1H), 5.65 (s, 1H), 4.02 (s, 3H), 2.25 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 168.5, 148.4, 133.5, 130.6, 130.5, 126.8, 124.2, 123.8, 122.2, 118.9, 115.0, 53.2, 13.3. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3330 (*w*), 2951 (*w*), 1695 (*vs*), 1619 (*w*), 1583 (*m*), 1558 (*w*), 1439 (*s*), 1378 (*m*), 1361 (*m*), 1275 (*vs*), 1247 (*vs*), 1177 (*m*), 1111 (*m*), 1074 (*m*), 1053 (*m*), 962 (*m*), 927 (*s*), 874 (*m*), 863 (*m*), 823 (*vs*), 761 (*m*), 741 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{13}H_{10}O_3{}^{79}Br^{35}Cl$ $[M]^+$: 327.9496; found: 327.9492.

*3.6. Methyl 1-chloro-7-ethyl-4-hydroxy-3-methyl-2-naphthoate (**15**)*

Note: The reaction setup has to be flame-dried very carefully, since otherwise the yield decreases significantly. To [1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) dichloride (400 mg, 0.546 mmol, 0.0180 equiv) was added a solution of **22**

(10.0 g, 30.3 mmol, 1 equiv) in 1,4-dioxane (25 mL). The red suspension was cooled to 0 °C and a freshly prepared solution of diethylzinc (1 M in toluene, 60.1 mL, 60.7 mmol, 2.00 equiv) was added very carefully over 30 min. After the addition, the dark red mixture was allowed to warm to 23 °C over 30 min and the beige suspension was then heated carefully to 90 °C. After 3 h, it was cooled to 0 °C and methanol (20 mL) was added dropwise. Water (100 mL) and aqueous hydrochloric acid solution (2 M, 100 mL) were added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 200 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered through a short pad of Celite® and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (9% ethyl acetate in hexanes) to obtain **15** (7.82 g, 93%) as a red-brown oil. **Analytical data for 15: TLC** (20% ethyl acetate in hexanes), R_f = 0.31 (UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.05 (d, *J* = 8.6 Hz, 1H), 7.97 (q, *J* = 0.9 Hz, 1H), 7.45 (dd, *J* = 8.7, 1.7 Hz, 1H), 5.37 (s, 1H), 4.03 (s, 3H), 2.86 (q, *J* = 7.6 Hz, 2H), 2.32 (s, 3H), 1.63 (s, 1H), 1.36 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 168.6, 148.2, 143.7, 132.7, 130.0, 128.3, 123.9, 122.7, 121.6, 119.6, 113.1, 52.9, 29.3, 15.6, 13.1. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3475 (*w*), 2362 (*m*), 1715 (*s*), 1438 (*m*), 1387 (*m*), 1293 (*m*), 1239 (*vs*), 1053 (*m*), 668 (*m*) cm^{-1}.**HRMS** (EI) calcd for $C_{15}H_{15}O_3{}^{35}Cl$ $[M]^+$: 278.0704; found: 278.0699.

*3.7. Methyl 4-(allyloxy)-1-chloro-7-ethyl-3-methyl-2-naphthoate (**23**)*

To a solution of **15** (100 mg, 0.359 mmol, 1 equiv) in dimethylformamide (1.2 mL) were successively added potassium carbonate (74.4 mg, 0.538 mmol, 1.50 equiv) and allyl bromide (34.2 µL, 47.7 mmol, 1.10 equiv) and the reaction mixture was heated to 65 °C. After 1.5 h, water (10 mL) and diethyl ether (15 mL) were added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with aqueous hydrochloric acid solution (2 M, 30 mL) and saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to yield **23** (103 mg, 90%) as a colorless oil. **Analytical data for 23: TLC** (20% ethyl acetate in hexanes), R_f = 0.58 (UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.02 (s, 1H), 8.01 (d, *J* = 6.6 Hz, 1H), 7.45 (dd, *J* = 8.6, 0.9 Hz, 1H), 6.18 (ddt, *J* = 17.1, 11.6, 5.9 Hz, 1H), 5.50 (d, *J* = 17.2 Hz, 1H), 5.33 (d, *J* = 10.4 Hz, 1H), 4.45 (d, *J* = 6.6 Hz, 2H), 4.01 (s, 3H), 2.85 (q, *J* = 7.3 Hz, 2H), 2.37 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 168.2, 152.1, 143.6, 133.6, 133.3, 130.4, 129.0, 127.9, 123.4, 123.0 (2C), 122.6, 118.0, 75.2, 52.8, 29.3, 15.6, 13.5. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2965 (*w*), 1736 (*vs*), 1598 (*w*), 1436 (*m*), 1385 (*m*), 1330 (*m*), 1315 (*m*), 1280 (*m*), 1231 (*s*), 1214 (*m*), 1170 (*m*), 1113 (*m*), 1051 (*s*), 991 (*m*), 972 (*m*), 937 (*m*), 877 (*m*), 833 (*m*), 757 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{18}H_{19}O_3{}^{35}Cl$ $[M]^+$: 318.1017; found: 318.1020.

*3.8. 8-Ethyl-5-hydroxy-4-methyl-1-vinylnaphtho[1,2-c]furan-3(1H)-one (**26**)*

A solution of **23** (1.56 g, 4.90 mmol, 1 equiv) in sulfolane (10 mL) was heated to 190 °C. After 2 h, water (100 mL) and diethyl ether (100 mL) were added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed successively with water (5 × 100 mL) and saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **26** (407.7 mg, 31%) as a yellow solid. **Analytical data for 26: TLC** (20% ethyl acetate in hexanes), R_f = 0.23 (UV, CAM, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.22 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 1.0 Hz, 1H), 7.53 (dd, *J* = 8.7, 1.7 Hz, 1H), 6.04 (d, *J* = 7.8 Hz, 1H), 5.92 (ddd, *J* = 17.0, 9.9, 7.7 Hz, 1H), 5.75 (d, *J* = 16.8 Hz, 1H), 5.52 (d, *J* = 10.3 Hz, 1H), 5.50 (s, 1H), 2.83 (q, *J* = 7.5 Hz, 2H), 2.70 (s, 3H), 1.32 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 171.4, 150.8, 143.4, 140.0, 134.7, 129.8, 126.6, 125.8, 123.1, 122.0, 121.7, 121.2, 112.4, 80.7, 29.1, 15.4, 9.2. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3418 (*w*), 2966 (*w*), 1733 (*vs*), 1582 (*w*), 1469 (*w*), 1395 (*w*), 1371 (*w*), 1299 (*w*), 1262 (*w*), 1198 (*w*), 1013 (*m*), 977 (*m*), 939 (*w*), 834 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{17}H_{16}O_3$ $[M]^+$: 268.1094; found: 268.1074.

*3.9. Allyl (8-ethyl-4-methyl-3-oxo-1-vinyl-1,3-dihydronaphtho[1,2-c]furan-5-yl) carbonate (**27**)*

To a solution of **26** (500 mg, 1.86 mmol, 1 equiv) in tetrahydrofuran (9.3 mL) was added triethylamine (0.363 mL, 2.61 mmol, 1.40 equiv). After 10 min, the reaction mixture was cooled to 0 °C and allyl chloroformate (0.238 mL, 2.24 mmol, 1.20 equiv) was added. After 15 min, water (100 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (70 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (9% ethyl acetate in hexanes) to afford **27** (528 mg, 80%) as a light-yellow solid. **Analytical data for 27: TLC** (20% ethyl acetate in hexanes), R_f = 0.35 (UV, CAM, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.90 (d, *J* = 8.7 Hz, 1H), 7.71 (d, *J* = 0.8 Hz, 1H), 7.57 (dd, *J* = 8.7, 1.6 Hz, 1H), 6.10 (d, *J* = 7.7 Hz, 1H), 6.10 – 5.88 (m, 2H), 5.80 (d, *J* = 16.7 Hz, 1H), 5.56 (d, *J* = 9.9 Hz, 1H), 5.48 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.39 (dq, *J* = 10.4, 1.1 Hz, 1H), 4.81 (dt, *J* = 5.8, 1.3 Hz, 2H), 2.83 (q, *J* = 7.6 Hz, 2H), 2.66 (s, 3H), 1.31 (d, *J* = 7.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 170.4, 153.0, 146.1, 145.7, 143.8, 134.0, 131.3, 131.0, 128.5, 126.7, 124.4, 122.3, 122.3, 122.1, 121.8, 120.1, 80.7, 69.8, 29.1, 15.4, 10.6. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2921 (*w*), 1746 (*vs*), 1610 (*w*), 1411 (*w*), 1356 (*w*), 1304 (*w*), 1232 (*s*), 1196 (*m*), 1147 (*m*), 1027 (*m*), 1013 (*m*), 972 (*m*), 938 (*m*), 924 (*m*), 886 (*m*), 840 (*m*), 778 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{21}H_{20}O_5$ $[M]^+$: 352.1305; found: 352.1309.

*3.10. 4-Allyl-8-ethyl-4-methyl-1-vinyl-1,4-dihydronaphtho[1,2-c]furan-3,5-dione (**28**)*

Tetrakis(triphenylphosphine)palladium(0) (32.8 mg, 0.0284 mmol, 0.100 equiv) was added to a Schlenk flask and the flask was purged with argon. Carbonate **27** (100 mg, 0.284 mmol, 1 equiv) was added and the flask was purged with argon. The reactants were dissolved in degassed toluene (7.5 mL) and degassed *n*-hexanes (0.75 mL) and stirred at 45 °C for 45 min. The reaction mixture was filtered through a plug of silica gel and rinsed thoroughly with diethyl ether (100 mL). The filtrate was concentrated and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to obtain **28** (60 mg, 69%, mixture of diastereomers) as a yellow oil. *Note: A small sample of the diastereomeric mixture was used to separate the diastereomers by flash column chromatography on silica gel (5% ethyl acetate in hexanes).* **Analytical data for the major isomer 28: TLC** (20% ethyl acetate in hexanes), R_f = 0.29 (UV, $KMnO_4$). **^{1}H NMR** (800 MHz, $CDCl_3$) δ: 8.11 (d, *J* = 8.0 Hz,

1H), 7.43 (dd, J = 8.0, 1.7 Hz, 1H), 7.28 – 7.26 (m, 1H), 5.89 (ddd, J = 17.0, 10.0, 7.9 Hz, 1H), 5.77 (d, J = 8.4 Hz, 1H), 5.76 (d, J = 17.0 Hz, 1H), 5.57 (d, J = 10.0 Hz, 1H), 5.33 (dddd, J = 16.8, 10.1, 8.2, 6.6 Hz, 1H), 4.97 (dq, J = 16.9, 1.3 Hz, 1H), 4.80 (dd, J = 10.1, 1.9 Hz, 1H), 2.96 (dd, J = 13.5, 8.2 Hz, 1H), 2.81 (dd, J = 13.5, 6.5 Hz, 1H), 2.74 (qd, J = 7.5, 2.9 Hz, 2H), 1.53 (s, 3H), 1.28 (d, J = 7.6 Hz, 3H). **^{13}C NMR** (201 MHz, $CDCl_3$) δ: 200.8, 170.0, 153.0, 151.7, 133.5, 132.8, 132.4, 131.4, 130.7, 128.9, 128.3, 124.4, 122.5, 118.7, 80.5, 48.6, 42.6, 29.2, 23.1, 15.0. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2920 (*m*), 2363 (*w*), 1756 (*vs*), 1679 (*m*), 1600 (*m*), 1456 (*w*), 1378 (*w*), 1239 (*m*), 1015 (*m*), 853 (*w*), 797 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{20}H_{20}O_3$ $[M]^+$: 308.1407; found: 308.1410.

*3.11. Methyl 4-(((allyloxy)carbonyl)oxy)-1-chloro-7-ethyl-3-methyl-2-naphthoate (**S3**)*

To a solution of **15** (4.00 g, 14.4 mmol, 1 equiv) in tetrahydrofuran (72 mL) was added triethylamine (2.79 mL, 20.1 mmol, 1.40 equiv), the mixture was cooled to 0 °C and allyl chloroformate (1.83 mL, 17.2 mmol, 1.20 equiv) was added. After 10 min, saturated aqueous ammonium chloride solution (100 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with saturated aqueous hydrogen chloride solution (100 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The product **S3** (5.15 g, 99%) was obtained as an orange oil and used without further purification. **Analytical data for S3: TLC** (20% ethyl acetate in hexanes), R_f = 0.43 (UV, $KMnO_4$). **^{1}H NMR** (599 MHz, $CDCl_3$) δ: 8.05 (d, J = 1.8 Hz, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.49 (dd, J = 8.7, 1.7 Hz, 1H), 6.24 – 5.78 (m, 1H), 5.46 (dq, J = 16.9, 1.5 Hz, 1H), 5.37 (dq, J = 10.6, 1.3 Hz, 1H), 4.88 – 4.59 (m, 2H), 4.01 (s, 3H), 2.85 (q, J = 7.6 Hz, 2H), 2.29 (s, 3H), 1.33 (t, J = 7.5 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ: 167.6, 152.9, 144.1, 143.8, 132.8, 131.1, 130.2, 129.9, 126.5, 126.2, 123.3, 123.1, 121.3, 120.0, 69.8, 52.9, 29.3, 15.6, 13.6. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2361 (*m*), 1764 (*m*), 1736 (*m*), 1437 (*w*), 1232 (*vs*), 940 (*w*), 668 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{19}H_{20}O_5{}^{35}Cl$ $[M]^+$: 362.0916; found: 362.0917.

*3.12. methyl 3-allyl-1-chloro-7-ethyl-3-methyl-4-oxo-3,4-dihydronaphthalene-2-carboxylate (**24**)*

Tetrakis(triphenylphosphine)palladium(0) (669 mg, 0.579 mmol, 7.00 mol%) was added to a Schlenk flask and the flask was purged with argon. **S3** (3.00 g, 8.27 mmol, 1 equiv) was added and the flask was purged with argon. Degassed toluene (219 mL) and degassed *n*-hexane (22 mL) were added and the solution was stirred at 45 °C for 15 h. The reaction mixture was filtered through a plug of silica gel and the plug was thoroughly rinsed with diethyl ether (200 mL). The filtrate was concentrated and the residue was purified by flash column chromatography on silica gel (2% ethyl acetate and 1% acetic acid in hexanes) to obtain **24** (2.1 g, 80%) as a light-yellow oil. **Analytical data for 24: TLC** (20% ethyl acetate in hexanes), R_f = 0.44 (UV, $KMnO_4$) **^{1}H NMR** (599 MHz, $CDCl_3$) δ: 8.00 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 1.6 Hz, 1H), 7.34 (dd, J = 8.2, 1.7 Hz, 1H), 5.74 – 5.32 (m, 1H), 4.99 (dt, J = 17.0, 1.6 Hz, 1H), 4.93 – 4.77 (m, 1H), 3.91 (s, 3H), 2.76 (p, J = 7.6 Hz, 3H), 2.52 (dd, J = 13.7, 6.5 Hz, 1H), 1.41 (s, 3H), 1.30 (t, J = 7.7 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ: 198.4, 166.4, 151.9, 137.9, 134.4, 132.2, 129.7, 127.7, 127.6, 127.5, 125.4, 118.8, 52.5, 52.3, 44.2, 29.3, 23.7, 15.0. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2970 (*w*), 1729 (*vs*), 1679 (*m*), 1598 (*m*), 1453 (*w*), 1434 (*m*), 1284 (*m*), 1248 (*m*), 1231 (*m*), 1195 (*m*), 1044 (*w*), 994 (*w*), 924 (*w*), 848 (*w*) 701 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{18}H_{19}O_3{}^{35}Cl$ $[M]^+$: 318.1017; found: 318.1016.

*3.13. Methyl (E)-1-chloro-7-ethyl-3-methyl-4-oxo-3-(prop-1-en-1-yl)-3,4-dihydronaphthalene-2-carboxylate (**30**)*

To bis(dibenzylidenacetone)palladium(0) (113 mg, 0.0196 mmol, 10.0 mol%) was added a solution of **24** (625 mg, 1.96 mmol, 1 equiv) in degassed toluene (5.3 mL), tri-*t*-butylphosphine (1 M in toluene, 0.196 mL, 0.196 mmol, 10.0 mol%) and then isobutyryl chloride (0.078 M in degassed toluene, 2.51 mL, 0.196 mmol, 10.0 mol%). The reaction mixture was heated to 80 °C for 41 h, diluted with ethyl acetate (50 mL) and then concentrated. The residue was purified by flash column chromatography on silica gel (2% ethyl acetate and 1% acetic acid in hexanes) to afford **30** (523 mg, 84%) as a yellow oil. **Analytical data for 30:** *Note: The product* **30** *could not be separated from traces of remaining starting material* **24** *since both were co-polar during column chromatography.* **TLC** (20% ethyl acetate in hexanes), R_f = 0.56 (UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.96 (d, J = 7.9 Hz, 1H), 7.65 (d, J = 1.6 Hz, 1H), 7.33 (dd, J = 7.9, 1.6 Hz, 1H), 5.67 (dq, J = 15.6, 6.5 Hz, 1H), 5.43 (dq, J = 15.4, 1.6 Hz, 1H), 3.85 (s, 3H), 2.76 (q, J = 7.6 Hz, 2H), 1.65 (dd, J = 6.5, 1.6 Hz, 3H), 1.52 (s, 3H), 1.29 (t, J = 7.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 197.0, 166.4, 151.9, 137.8, 134.3, 129.8, 129.7, 128.4, 128.2, 127.3, 127.3, 125.6, 54.2, 52.4, 29.4, 21.5, 18.2, 15.2. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2967 (*w*), 1729 (*vs*), 1683 (*s*), 1598 (*s*), 1447 (*m*), 1433 (*m*), 1373 (*w*), 1270 (*vs*), 1230 (*s*), 1198 (*s*), 1121 (*m*), 1061 (*m*), 1043 (*s*), 983 (*m*), 958 (*s*), 846 (*m*), 806 (*m*), 698 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{18}H_{19}O_3{}^{35}Cl$ $[M]^+$: 318.1017; found: 318.1014.

*3.14. Methyl (E)-1-chloro-7-ethyl-3-methyl-4-methylene-3-(prop-1-en-1-yl)-3,4-dihydronaphthalene-2-carboxylate (**31**)*

To a solution of methyltriphenylphosphonium bromide (1.03 g, 2.89 mmol, 2.00 equiv) in tetrahydrofuran (14 mL) was added potassium *tert*-butoxide (324 mg, 2.89 mmol, 2.00 equiv). After 1.5 h, the reaction mixture was cooled to 0 °C, a solution of **30** (460 mg, 1.44 mmol, 1 equiv) in tetrahydrofuran (9 mL) was added and the reaction mixture was allowed to warm to 23 °C. After 4 h, water (70 mL) was added, the layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 70 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to yield **31** (455 mg, 99%) as a yellow oil. **Analytical data for 31: TLC** (20% ethyl acetate in hexanes), R_f = 0.56 (UV, CAM, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.48 (d, J = 1.7 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.16 (dd, J = 7.9, 1.8 Hz, 1H), 5.67 – 5.56 (m, 2H), 5.44 (s, 1H), 5.18 (s, 1H), 3.80 (s, 3H), 2.68 (q, J = 7.6 Hz, 2H), 1.77 – 1.66 (m, 3H), 1.42 (s, 3H), 1.26 (t, J = 7.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 167.5, 148.3, 144.8, 136.8, 133.3, 132.2, 129.4, 128.8, 128.3, 125.8, 125.3, 124.7, 112.7, 52.1, 47.3, 28.9, 23.7, 18.2, 15.6. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2966 (*w*), 1755 (*vs*), 1602 (*w*), 1485 (*w*), 1432 (*m*), 1264 (*s*), 1235 (*s*), 1193 (*m*), 1154 (*m*), 1091 (*w*), 1043 (*m*), 962 (*m*), 898 (*m*), 836 (*m*), 737 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{19}H_{21}O_2{}^{35}Cl$ $[M]^+$: 316.1225; found: 316.1222.

*3.15. Methyl-1-chloro-7-ethyl-4-(methoxymethylene)-3-methyl-3-((E)-prop-1-en-1-yl)-3,4-dihydronaphthalene-2-carboxylate (**S4**).*

To a suspension of (methoxymethyl)triphenylphosphonium chloride (1.19 g, 3.48 mmol, 3.70 equiv) in tetrahydrofuran (4.7 mL) was added *n*-butyllithium (2.36 M in hexanes, 1.24 mL, 2.92 mmol, 3.10 equiv) over 5 min at 0 °C. After the addition was completed, the reaction mixture was warmed to 23 °C, stirred at this temperature for 20 min and then cooled to 0 °C. A solution of **30** (300 mg, 0.941 mmol, 1 equiv) in tetrahydrofuran (4.7 mL) was added and the reaction mixture was warmed to 23 °C. After 2 h,

saturated aqueous ammonium chloride solution (15 mL) was added and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 × 20 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (15 mL). The washed organic solution was dried over sodium sulfate and the dried solution was filtered and concentrated. The residue was purified by flash column chromatography on silica gel (2% ethyl acetate in hexanes) to afford **S4** (265 mg, 81%, inconsequential 1:1 mixture of diastereomers) as a light-yellow oil. **Analytical data for S4:** *Note: Singals marked with an asterisk belong to the same diastereomer.* **TLC** (20% ethyl acetate in hexanes), R_f = 0.47 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.81 (d, *J* = 8.0 Hz, 1H)*, 7.48 (d, *J* = 1.9 Hz, 1H)*, 7.46 (d, *J* = 1.9 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.15 (dd, *J* = 8.0, 1.9 Hz, 1H)*, 7.07 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.43 (s, 1H), 6.14 (s, 1H)*, 5.73 – 5.63 (m, 1H), 5.62 – 5.57 (m, 1H+1H*), 5.46 (dq, *J* = 15.4, 6.4 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H)*, 3.70 (s, 3H)*, 3.66 (s, 3H), 2.64 (qd, *J* = 7.6, 5.4 Hz, 2H+2H*), 1.75 – 1.67 (m, 3H)*, 1.64 (dd, *J* = 6.4, 1.6 Hz, 3H), 1.54 (s, 3H), 1.38 (s, 3H)*, 1.24 (td, *J* = 7.6, 3.6 Hz, 3H+3H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 167.6, 167.5*, 146.8, 145.9*, 142.8, 142.7*, 136.6, 136.6*, 134.6, 133.3*, 131.8, 129.3*, 129.1, 128.9*, 128.7*, 128.7*, 128.5, 128.5*, 128.0, 125.9*, 124.9, 124.7*, 123.4, 123.0, 116.6, 116.4*, 60.8*, 60.7, 52.0, 52.0*, 45.6, 45.3*, 28.9, 28.7*, 24.0*, 23.0, 18.2*, 18.0, 15.6*, 15.6. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2965 (*m*), 1748 (*vs*), 1641 (*s*), 1432 (*m*), 1260 (*s*), 1239 (*s*), 1145 (*m*), 1103 (*m*), 1043 (*m*), 977 (*m*), 833 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{20}H_{23}O_3{}^{35}Cl$ $[M]^+$: 346.1330; found: 346.1330.

*3.16. Methyl (E)-1-chloro-7-ethyl-4-formyl-3-methyl-3-(prop-1-en-1-yl)-3,4-dihydronaphthalene-2-carboxylate (**34**)*

To **S4** (265 mg, 0.764 mmol, 1 equiv) in diethyl ether (13 mL) was added perchloric acid (70% in water, 0.395 mL, 4.56 mmol, 6.00 equiv) and the reaction mixture was vigorously stirred for 19 h. The mixturw was diluted with diethyl ether (15 mL) and water (15 mL), and then sodium bicarbonate (400 mg) was carefully added. The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with saturated sodium chloride solution (15 mL), dried over sodium sulfate and the dried solution was filtered and concentrated. The residue was purified by flash column chromatography on Davisil© (2% ethyl acetate in hexanes) to yield **34** (202 mg, 79%, inconsequential mixture of diastereomers) as a colorless oil. **Analytical data for 34:** *Note: The singals, which could be assigned to the major diastereomer, are marked with an asterisk.* **TLC** (20% ethyl acetate in hexanes), R_f = 0.47 (UV, CAM, $KMnO_4$). **^{1}H NMR** (599 MHz, C_6D_6) δ: 9.62 (d, *J* = 4.5 Hz, 1H), 9.54 (d, *J* = 4.5 Hz, 1H)*, 7.63 (d, *J* = 11.9 Hz, 1H+1H*), 6.88 – 6.63 (m, 2H+2H*), 5.77 – 5.59 (m, 1H), 5.51 (dqd, *J* = 15.3, 6.5, 2.4 Hz, 1H+1H*), 5.33 (dd, *J* = 15.6, 2.1 Hz, 1H*), 3.44 (app d, *J* = 4.06 Hz, 3H+3H*), 3.23 (d, *J* = 4.7 Hz, 1H)*, 3.18 (d, *J* = 4.9 Hz, 1H), 2.31 (dq, *J* = 19.5, 7.5 Hz, 2H+2H*), 1.41 (dd, *J* = 6.7, 1.6 Hz, 3H), 1.29 – 1.25 (m, 9H*), 0.99 (t, *J* = 7.7 Hz, 3H), 0.96 (t, *J* = 7.7 Hz, 3H)*. **^{13}C NMR** (151 MHz, C_6D_6) δ: 198.0, 197.6*, 166.7*, 145.2, 145.1*, 136.5, 135.1*, 133.3, 131.4, 131.1, 130.6, 130.1, 129.8, 129.3, 129.2, 128.6, 128.5, 125.9, 125.5, 63.0, 62.3*, 51.7*, 51.6, 43.8, 42.8*, 28.9, 28.8*, 23.0, 21.6*, 18.1, 17.9*, 15.5, 15.4*. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2967 (*w*), 1724 (*vs*), 1603 (*w*), 1434 (*w*), 1266 (*s*), 1203 (*w*), 1046 (*w*), 964 (*w*), 834 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{19}H_{21}O_3{}^{35}Cl$ $[M]^+$: 332.1174; found: 332.1155.

*3.17. methyl (E)-1-chloro-7-ethyl-4-formyl-3,4-dimethyl-3-(prop-1-en-1-yl)-3,4-dihydronaphthalene-2-carboxylate (**35**)*

To sodium hydride (60% dispersion in mineral oil, 32.9 mg, 0.823 mmol, 2.00 equiv) was added a degassed solution of **34** (137 mg, 0.412 mmol, 1 equiv) and methyl iodide (0.256 mL, 4.12 mmol, 10.0 equiv) in tetrahydrofuran (5.9 mL) at 0 °C. The solution was allowed to warm to 23 °C and after 5.5 h, saturated aqueous ammonium chloride solution (10 mL) was added. The layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (toluene) to obtain **35** (98 mg, 69%) as a light-yellow oil. **Analytical data for 35: TLC** (20% ethyl acetate in hexanes), R_f = 0.45 (UV, CAM, $KMnO_4$). **^{1}H NMR** (800 MHz, C_6D_6) δ: 9.82 (s, 1H), 7.68 (d, *J* = 1.9 Hz, 1H), 6.87 (d, *J* = 7.9 Hz, 1H), 6.83 (dd, *J* = 7.9, 1.9 Hz, 1H), 5.50 – 5.30 (m, 2H), 3.43 (s, 3H), 2.33 (q, *J* = 7.6 Hz, 2H), 1.35 (s, 3H), 1.34 – 1.30 (m, 3H), 1.24 (s, 3H), 1.00 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (201 MHz, C_6D_6) δ: 199.8, 166.7, 144.5, 141.5, 136.1, 133.2, 131.1, 130.3, 129.9, 127.3, 127.1, 125.9, 56.2, 51.6, 46.2, 28.7, 18.1, 18.0, 15.4, 14.0. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2969 (*w*), 2362 (*w*), 1731 (*vs*), 1605 (*w*), 1434 (*w*), 1373 (*w*), 1268 (*m*), 1154 (*w*), 1102 (*w*), 1042 (*w*), 968 (*w*), 890 (*w*), 816 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{20}H_{23}O_3{}^{35}Cl$ $[M]^+$: 346.1330; found: 346.1341.

*3.18. methyl (E)-1-chloro-7-ethyl-4-(hydroxymethyl)-3,4-dimethyl-3-(prop-1-en-1-yl)-3,4-dihydronaphthalene-2-carboxylate (**36**)*

To a solution of **35** (15.0 mg, 0.0432 mmol, 1 equiv) in methanol (0.4 mL) was added sodium borohydride (2.45 mg, 0.0649 mmol, 1.50 equiv) at 0 °C. After 25 min, saturated aqueous ammonium chloride solution (10 mL) was added. The layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (11% ethyl acetate in hexanes) to obtain **I.143** (12 mg, 80%, major isomer) as a colorless oil. **Analytical data for 36:** *Note: Signals in the ^{13}C NMR which could only be assigned by cross-coupling in the HMBC are marked with an asterisk. The relative stereochemistry was assigned by NOE correlations of* **36**: **TLC** (20% ethyl acetate in hexanes), R_f = 0.21 (UV, CAM, ANIS, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.53 (d, *J* = 1.7 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.18 (dd, *J* = 7.9, 1.9 Hz, 1H), 5.50 (dt, *J* = 18.0, 6.4 Hz, 1H), 5.34 (d, *J* = 15.6 Hz, 1H), 3.90 (dd, *J* = 10.9, 3.9 Hz, 1H), 3.82 (s, 3H), 3.51 (t, *J* = 9.8 Hz, 1H), 2.67 (q, *J* = 7.6 Hz, 2H), 1.60 (dd, *J* = 6.3, 1.5 Hz, 3H), 1.30 (s, 3H), 1.26 (t, *J* = 7.6 Hz, 3H), 1.21 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 167.6, 143.3, 135.9, 131.0, 129.9, 129.2, 127.9*, 127.4*, 126.0, 125.4, 66.0, 52.2, 46.5, 45.8, 29.9, 28.6, 18.3, 16.4*, 16.4, 15.5. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3430 (*w*), 2964 (*m*), 1731 (*vs*), 1629 (*w*), 1607 (*w*), 1433 (*m*), 1375 (*w*), 1268 (*vs*), 1196 (*w*), 1151 (*m*), 1040 (*s*), 968 (*m*), 890 (*w*), 833 (*w*), 723 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{20}H_{25}O_3{}^{35}Cl$ $[M]^+$: 348.1487; found: 348.1492.

*3.19. methyl (E)-1-chloro-7-ethyl-3,4-dimethyl-3-(prop-1-en-1-yl)-4-((tosyloxy)methyl)-3,4-dihydronaphthalene-2-carboxylate (**37**)*

To **36** (14.0 mg, 0.0401 mmol, 1 equiv) and *p*-toluene-sulfonyl chloride (23.0 mg, 0.120 mmol, 3.00 equiv) was added pyridine (0.3 mL). After stirring for 48 h, the reaction mixture was diluted with saturated aqueous ammonium chloride solution (15 mL), the layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the

filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (14% ethyl acetate in hexanes) to afford **37** (14.8 mg, 73%) as a colorless oil. **Analytical data for 37:** *Note: Due to severe signal broadening in the NMR spectra some signals are missing or possess inaccurate integrals. Signals in the ^{13}C NMR which could only be assigned by cross-coupling in the HMBC are marked with an asterisk.* **TLC** (20% ethyl acetate in hexanes), R_f = 0.31 (UV, ANIS, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.29 (s, 1H), 7.21 – 7.10 (m, 4H), 5.44 (dq, *J* = 15.4, 6.4 Hz, 1H), 5.20 (s, 1H), 4.08 (s, 2H), 3.77 (s, 3H), 2.66 (q, *J* = 7.6 Hz, 2H), 2.41 (s, 3H), 1.55 (d, *J* = 4.9 Hz, 3H), 1.27 (t, *J* = 7.6 Hz, 6H), 1.16 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ: 167.2, 144.5, 143.3, 135.1*, 132.2, 129.8, 129.3, 129.1, 128.1, 127.8, 125.0, 72.6, 52.1, 46.6*, 44.1, 29.9*, 28.6, 21.8, 18.2, 16.7, 15.5. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2965 (*w*), 1729 (*s*), 1628 (*w*), 1451 (*w*), 1434 (*w*), 1361 (*m*), 1269 (*m*), 1189 (*s*), 1176 (*vs*), 1097 (*m*), 1041 (*m*), 979 (*s*), 912 (*m*), 830 (*s*), 813 (*s*), 731 (*m*), 666 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{27}H_{31}O_5{}^{35}ClS$ $[M]^+$: 502.1575; found: 502.1574.

*3.20. methyl (E)-1-chloro-7-ethyl-3,4-dimethyl-4-((((methylthio)carbonothioyl)oxy)methyl)-3-(prop-1-en-1-yl)-3,4-dihydronaphthalene-2-carboxylate (**38**)*

To a solution of **36** (12.0 mg, 0.0344 mmol, 1 equiv) in tetrahydrofuran (0.26 mL) was added sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 0.172 mL, 0.172 mmol, 5.00 equiv) at −78 °C. After 30 min, carbon disulfide (0.0415 mL, 0.688 mmol, 20.0 equiv) was added and the reaction was allowed to warm to −65 °C. After 30 min, methyl iodide (0.0428 mL, 0.688 mmol, 20.0 equiv) was added and the reaction mixture was stirred for 75 min. Saturated aqueous ammonium chloride solution (15 mL) was added, the layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to obtain **38** (12.6 mg, 83%) as a colorless oil. **Analytical data for 38:** *Note: Due to severe signal broadening in the NMR spectra some signals are missing or possess inaccurate integrals. Signals in the ^{13}C NMR which could only be assigned by cross-coupling in the HMBC are marked with an asterisk.* **TLC** (20% ethyl acetate in hexanes), R_f = 0.50 (UV, ANIS, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.58 – 7.44 (m, 1H), 7.18 (d, *J* = 1.2 Hz, 2H), 5.64 – 5.37 (m, 2H), 4.75 (s, 2H), 3.81 (s, 3H), 2.67 (q, *J* = 7.8 Hz, 2H), 2.45 (s, 3H), 1.65 (d, *J* = 6.1 Hz, 3H), 1.36 (s, 3H), 1.31 – 1.18 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 215.5, 167.4, 143.4, 137.3*, 135.8*, 130.2, 129.7, 129.5, 128.2, 125.3, 77.0*, 52.1, 47.2*, 44.7, 28.6, 18.9, 18.4, 17.2, 15.5, 10.6*. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2964 (*w*), 1730 (*vs*), 1607 (*w*), 1488 (*w*), 1449 (*w*), 1432 (*m*), 1375 (*w*), 1268 (*s*), 1253 (*s*), 1209 (*s*), 1153 (*m*), 1067 (*vs*), 1041 (*m*), 967 (*m*), 911 (*w*), 832 (*w*), 731 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{22}H_{27}O_3{}^{35}ClS_2$ $[M]^+$: 438.1085; found: 438.1077.

*3.21. 10-Chloro-8-ethyl-3,5,5-trimethyl-3,5,9,9a-tetrahydro-1H-benzo[g]isochromen-1-one (**42**)*

To titanium(IV) chloride (1 M in dichloromethane, 0.941 mL, 0.941 mmol, 6.00 equiv) in a Schlenk tube, which was wrapped in aluminum foil, was added dimethylzinc (15wt% in toluene, 0.784 mL, 0.941 mmol, 6.00 equiv) over 5 min at 0 °C. After 25 min, a solution of **30** (50.0 mg, 0.157 mmol, 1 equiv) in dichloromethane (1.6 mL) was added over 5 min. The reaction mixture was stirred for 8 h at 0 °C before saturated aqueous ammonium chloride solution (10 mL) was added. The layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (2% ethyl acetate and 1% acetic acid in hexanes) to yield **42** (29 mg, 61%) as a light-yellow oil. **Analytical data for 42: TLC** (20% ethyl acetate in hexanes), R_f = 0.23 (UV, CAM, $KMnO_4$). **^{1}H NMR** (599 MHz, $CDCl_3$) δ: 7.85 (d, *J* = 1.9 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.24 (dd, *J* = 8.0, 1.9 Hz, 1H), 5.94 (d, *J* = 2.9 Hz, 1H), 5.03 (qd, *J* = 6.8, 3.2 Hz, 1H), 2.69 (q, *J* = 7.7 Hz, 2H), 1.48 (s, 3H), 1.47 (d, *J* = 7.0 Hz, 3H), 1.43 (s, 3H), 1.26 (t, *J* = 7.7 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ: 163.6, 143.1, 143.0, 142.6, 136.8, 130.7, 130.2, 127.6, 123.8, 123.3, 117.9, 74.5, 38.3, 28.9, 28.6, 27.2, 22.1, 15.6. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2967 (*m*), 1729 (vs), 1556 (*m*), 1463 (*m*), 1379 (*m*), 1379 (*m*), 1286 (*m*), 1210 (*m*), 1159 (*m*), 895 (*w*), 835 (*w*), 835 (*w*), 786 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{18}H_{19}O_2{}^{35}Cl$ $[M]^+$: 302.7975; found: 302.1071.

*3.22. 7-methoxy-4-methyl-1,2-dihydronaphthalene (**44**)*

To 6-methoxy-3,4-dihydronaphthalen-1(2H)-one (**43**) (10.0 g, 56.7 mmol, 1 equiv) in tetrahydrofuran (100 mL) was added methylmagnesium bromide solution (3 M in diethyl ether, 28.4 mL, 85.1 mmol, 1.50 equiv) at 0 °C. The ice bath was removed after the addition and the reaction mixture was stirred for 17 h. The mixture was cooled to 0 °C and aqueous hydrochloric acid solution (2 M, 200 mL) was added until pH=2. The reaction was stirred for 5 h, diluted with water (100 mL) and the layers were separated. The aqueous phase was extracted with diethyl ether (3 × 200 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (200 mL), the washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was used without further purification. An analytical pure sample of **44** was obtained by flash column chromatography on silica gel (2% ethyl acetate in hexanes). **Analytical data for 44: TLC** (20% ethyl acetate in hexanes), R_f = 0.63 ($KMnO_4$, ANIS). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.16 (d, *J* = 8.2 Hz, 1H), 6.88 – 6.62 (m, 2H), 5.73 (ddd, *J* = 6.0, 3.8, 1.6 Hz, 1H), 3.81 (s, 3H), 2.75 (t, *J* = 8.0 Hz, 2H), 2.29 – 2.16 (m, 2H), 2.03 (q, *J* = 1.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 158.5, 138.3, 131.9, 129.2, 124.0, 123.0, 113.7, 110.9, 55.4, 29.0, 23.3, 19.5. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2932 (*w*), 1605 (*m*), 1496 (*s*), 1427 (*m*), 1302 (*m*), 1249 (*vs*), 1141 (*s*), 1032 (*s*), 867 (*m*), 819 (*s*), 674 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{12}H_{14}O$ $[M]^+$: 174.1039; found: 174.1041.

*3.23. 6-methoxy-1-methyl-3,4-dihydronaphthalen-2(1H)-one (**45**)*

To a solution of crude **44** in dichloromethane (283 mL) and 2,2,2-trifluoroethanol (71 mL) were added 3-chloroperoxybenzoic acid (75% in water, 16.3 g, 70.9 mmol, 1.25 equiv) and *p*-toluenesulfonic acid monohydrate (13.5 g, 70.9 mmol, 1.25 equiv) subsequently at 0 °C. After stirring for 20 min, saturated aqueous sodium bicarbonate solution (200 mL) and dichloromethane (200 mL) were added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 200 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (6% ethyl acetate in hexanes) to obtain **45** (4.76 g, 44% over 2 steps) as a yellow oil. **Analytical data for 45: TLC** (20% ethyl acetate in hexanes), R_f = 0.45 ($KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.11 (d, *J* = 8.3 Hz, 1H), 6.83 – 6.76 (m, 2H), 3.81 (s, 3H), 3.47 (qd, *J* = 6.9, 0.9 Hz, 1H), 3.15 – 2.91 (m, 2H), 2.62 (dt, *J* = 17.5, 5.9 Hz, 1H), 2.48 (ddd, *J* = 17.5, 9.0, 6.1 Hz, 1H), 1.45 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 212.5, 158.5, 138.1, 130.1, 127.3, 113.3, 112.3, 55.4, 46.8, 37.3, 28.4, 14.6. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2937 (*w*), 1713 (*vs*), 1610 (*m*), 1579 (*w*), 1497 (*s*), 1454 (*m*), 1261

(*s*), 1160 (*m*), 1037 (*m*), 864 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{12}H_{14}O_2$ $[M]^+$: 190.0988; found: 190.0994.

*3.24. 6-methoxy-1,1-dimethyl-3,4-dihydronaphthalen-2(1H)-one (**46**)*

To a suspension of freshly washed potassium hydride (4.55 g, 114 mmol, 1.20 equiv) in degassed tetrahydrofuran (40 mL) was added a degassed solution of **45** (18.0 g, 94.6 mmol, 1 equiv) in tetrahydrofuran (500 mL) over 25 min at 0 °C. After 20 min, the ice bath was removed and the reaction mixture was stirred at 23 °C. After 1 h, the mixture was cooled to 0 °C, methyl iodide (11.8 mL, 189 mmol, 2.00 equiv) was added and the ice bath was removed after the addition. After 25 min at 23 °C, the mixture was again cooled to 0 °C, saturated aqueous ammonium chloride solution (200 mL) and ethyl acetate (100 mL) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (6% ethyl acetate in hexanes) to afford **46** (13.6 g, 71%) as a yellow oil. **Analytical data for 46: TLC** (20% ethyl acetate in hexanes), R_f = 0.39 ($KMnO_4$, ANIS, UV). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.29 (s, 1H), 6.84 (ddd, *J* = 8.7, 2.8, 0.7 Hz, 1H), 6.73 (d, *J* = 2.6 Hz, 1H), 3.83 (s, 3H), 3.09 (t, *J* = 6.9 Hz, 2H), 2.79 – 2.63 (m, 2H), 1.44 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 215.0, 158.1, 136.6, 135.8, 127.4, 113.3, 112.9, 55.4, 47.4, 37.3, 28.9, 27.2 (2C). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2968 (*w*), 1709 (*vs*), 1609 (*m*), 1500 (*s*), 1464 (*m*), 1307 (*m*), 1265 (*s*), 1228 (*m*), 1138 (*m*), 1035 (*s*), 814 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{13}H_{16}O_2$ $[M]^+$: 204.1145; found: 204.1133.

*3.25. 6-methoxy-1,1,2-trimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (**47**)*

To a solution of **46** (2.74 g, 13.4 mmol, 1 equiv) in tetrahydrofuran (13 mL) was added lanthanum(III) chloride bis(lithium chloride) complex solution (0.3 M in tetrahydrofuran, 44.7 mL, 13.4 mmol, 1 equiv). After 1 h, the solution was cooled to 0 °C and methylmagnesium bromide solution (3 M in diethyl ether, 6.71 mL, 20.1 mmol, 1.50 equiv) was added dropwise over 20 min (syringe pump). After 20 min, saturated aqueous ammonium chloride solution (50 mL) and diethyl ether (50 mL) were added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (14% ethyl acetate in hexanes) to obtain **47** (2.83 g, 96%) as a colorless oil. **Analytical data for 47: TLC** (20% ethyl acetate in hexanes), R_f = 0.23 (ANIS). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.27 (d, *J* = 8.7 Hz, 1H), 6.75 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.60 (d, *J* = 2.7 Hz, 1H), 3.78 (s, 3H), 2.98 (dt, *J* = 17.6, 7.1 Hz, 1H), 2.81 (dt, *J* = 17.5, 6.8 Hz, 1H), 2.04 – 1.79 (m, 2H), 1.32 (s, 3H), 1.27 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 157.4, 137.4, 135.5, 128.1, 113.0, 112.8, 73.7, 55.3, 41.5, 32.8, 27.1, 27.0, 25.4, 24.3. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3470 (*w*), 2969 (*m*), 1608 (*m*), 1499 (*vs*), 1464 (*m*), 1373 (*w*), 1315 (*m*), 1237 (*s*), 1084 (*m*), 1037 (*s*), 911 (*m*), 818 (*s*) cm^{-1}. **HRMS** (EI) calcd for $C_{14}H_{20}O_2$ $[M]^+$: 220.1458; found: 220.1452.

*3.26. 3-hydroxy-7-methoxy-3,4,4-trimethyl-3,4-dihydronaphthalen-1(2H)-one (**48**)*

To a solution of **47** (843 mg, 3.83 mmol, 1 equiv) in dry acetone (7.7 mL) was added cobalt(II) acetylacetonate (197 mg, 0.765 mmol, 0.200 equiv). To the resulting purple suspension was added dropwise *tert*-butyl hydroperoxide (5.5 M in decane, 2.78 mL, 15.3 mmol, 4.00 equiv). After 2 d, saturated aqueous ammonium chloride solution (20 mL) and ethyl acetate (20 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to afford **48** (854 mg, 95%) as a green oil. **TLC** (20% ethyl acetate in hexanes), Rf = 0.056 (ANIS, UV). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.50 (d, *J* = 3.0 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 7.14 (dd, *J* = 8.7, 3.0 Hz, 1H), 3.84 (s, 3H), 2.89 (s, 2H), 1.44 (s, 3H), 1.38 (s, 3H), 1.33 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 196.8, 158.2, 143.5, 131.8, 127.8, 122.6, 109.1, 75.7, 55.7, 55.6, 50.0, 42.5, 24.7, 24.6. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3483 (*m*), 2975 (*m*), 1677 (*vs*), 1608 (*s*), 1493 (*s*), 1418 (*m*), 1325 (*s*), 1291 (*vs*), 1262 (*s*), 1087 (*m*), 1032 (*s*), 883 (*w*), 830 (*w*), 705 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{14}H_{18}O_3$ $[M]^+$: 234.1250; found: 234.1249.

*3.27. 7-methoxy-3,4,4-trimethylnaphthalen-1(4H)-one (**49**)*

A mixture of **48** (270 mg, 1.15 mmol, 1 equiv) in acetic acid (11.5 mL) and sulfuric acid (97%, 30 µL) was heated to 100 °C for 10 min. After cooling to 23 °C, the reaction mixture was diluted with water (30 mL) and dichloromethane (50 mL). Sodium bicarbonate was slowly added until pH=7. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to obtain **49** (220 mg, 88%) as a yellow solid. **Analytical data for 49: TLC** (60% ethyl acetate in hexanes), R_f = 0.50 ($KMnO_4$, UV). **^{1}H NMR** (800 MHz, $CDCl_3$) δ: 7.63 (d, *J* = 3.0 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.16 (dd, *J* = 8.7, 3.0 Hz, 1H), 6.32 (q, *J* = 1.3 Hz, 1H), 3.88 (s, 3H), 2.14 (d, *J* = 1.3 Hz, 3H), 1.48 (s, 6H). **^{13}C NMR** (201 MHz, $CDCl_3$) δ: 184.5, 165.9, 158.2, 144.1, 131.7, 127.9, 126.6, 121.4, 107.6, 55.7, 40.3, 28.7 (2C), 20.3. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2975 (*w*), 1657 (*vs*), 1608 (*m*), 1497 (*s*), 1425 (*s*), 1296 (*s*), 1230 (*w*), 1032 (*w*), 870 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{14}H_{16}O_2$ $[M]^+$: 216.1145; found: 216.1145.

*3.28. 5,5,6-trimethyl-8-oxo-5,8-dihydronaphthalen-2-yl trifluoromethanesulfonate (**51**)*

To a solution of **49** (200 mg, 0.925 mmol, 1 equiv) in dichloromethane (4.6 mL) was added dropwise boron tribromide (1 M, in dichloromethane, 4.62 mL, 4.62 mmol, 5 equiv) at −78 °C. The reaction mixture was allowed to warm to 0 °C over 2 h and methanol (3 mL) was added dropwise. Water (40 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product **50** was used in the next step without further purification. To a solution of crude **50** in dichloromethane (4.6 mL) was added triethylamine at −78 °C and the mixture was stirred for 5 min before trifluoromethanesulfonic anhydride (0.230 mL, 1.39 mmol, 1.50 equiv) was added over 10 min. The reaction was allowed to warm to 23 °C over 3 h and saturated aqueous sodium bicarbonate solution (15 mL) and dichloromethane (20 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (14% ethyl acetate in

hexanes) to afford **51** (302 mg, 98% over 2 steps) as a yellow solid. **Analytical data for 41: TLC** (33% ethyl acetate in hexanes), R_f = 0.26 ($KMnO_4$, UV). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.05 (d, *J* = 2.9 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.47 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.36 (t, *J* = 1.3 Hz, 1H), 2.17 (d, *J* = 1.3 Hz, 3H), 1.53 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 182.5, 166.2, 151.1, 148.4, 132.8, 129.2, 126.4, 125.3, 118.9 (q, *J* = 320.3 Hz) 118.8, 40.7, 28.7 (2C), 20.5. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2980 (*w*), 1660 (*s*), 1579 (*w*), 1486 (*w*), 1421 (*s*), 1314 (*m*), 1290 (*m*), 1204 (*vs*), 1137 (*vs*), 1109 (*m*), 918 (*vs*), 875 (*m*), 841 (*s*), 811 (*s*), 767 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{14}H_{13}O_4F_3S$ $[M]^+$: 334.0481; found: 334.0490.

*3.29. 7-ethyl-3,4,4-trimethylnaphthalen-1(4H)-one (**52**)*

Note: The reaction setup has to be flame-dried very carefully, since the yield otherwise decreases significantly. To [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (41.1 mg, 0.0562 mmol, 0.0180 equiv) was added a solution of **51** (1.04 g, 3.12 mmol, 1 equiv) in 1,4-dioxane (2.6 mL). The red suspension was cooled to 0 °C and diethylzinc solution (15wt% in toluene, 4.27 mL, 6.25 mmol, 2.00 equiv) was added dropwise. After stirring for 10 min, the yellow solution was heated to 90 °C for 70 min, cooled to 0 °C and treated with methanol (5 mL). Water (15 mL) was added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with aqueous hydrogen chloride solution (2 M, 20 mL) and saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (17% ethyl acetate in hexanes) to obtain **52** (590 mg, 88%) as a yellow oil. **TLC** (20% ethyl acetate in hexanes), R_f = 0.35 ($KMnO_4$, UV). **^{1}H NMR** (599 MHz, $CDCl_3$) δ: 8.01 (d, *J* = 2.1 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.42 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.32 (d, *J* = 1.5 Hz, 1H), 2.71 (q, *J* = 7.6 Hz, 2H), 2.13 (d, *J* = 1.1 Hz, 3H), 1.49 (s, 6H), 1.27 (t, *J* = 7.7 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ: 184.9, 165.6, 148.8, 142.6, 132.5, 130.4, 126.8, 126.5, 125.2, 40.4, 28.7, 28.5, 20.3, 15.5. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2971 (*m*), 2873 (*w*), 1657 (*vs*), 1610 (*m*), 1462 (*w*), 1427 (*m*), 1307 (*m*), 1270 (*w*), 1117 (*w*), 1011 (*w*), 876 (*m*), 837 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{15}H_{18}O_2$ $[M]^+$: 214.1352; found: 214.1351.

*3.30. 3-allyl-7-ethyl-3,4,4-trimethyl-3,4-dihydronaphthalen-1(2H)-one (**54**)*

To a solution of **52** (590 mg, 2.75 mmol, 1 equiv) in tetrahydrofuran (5.5 mL) was added dropwise allylmagnesium bromide solution (1 M in diethyl ether, 4.13 mL, 4.13 mmol, 1.50 equiv) at 0 °C. After 1 h, the mixture was cooled to 0 °C and saturated aqueous sodium bicarbonate solution (10 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product **53** was used without further purification. A mixture of 18-crown-6 (1.45 g, 5.50 mmol, 2.00 equiv) and potassium *tert*-butoxide (617 mg, 5.50 mmol, 2.00 equiv) in tetrahydrofuran (46 mL) was stirred at 0 °C for 1 h. A solution of crude **53** in tetrahydrofuran (10 mL) was added over 10 min and after complete addition, the reaction mixture was allowed to warm to 23 °C. After 2 h, saturated aqueous sodium bicarbonate solution (40 mL) and dichloromethane (40 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 40 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (2% ethyl acetate in hexanes) to obtain **54** (270 mg, 38% over 2 steps) as a yellow oil. **Analytical data for 54: TLC** (20% ethyl acetate in hexanes), R_f = 0.59 ($KMnO_4$, UV). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.84 (s, 1H), 7.38 (s, 2H), 5.78 (ddt, *J* = 15.0, 10.1, 7.5 Hz, 1H), 5.08 (dd, *J* = 10.1, 2.0 Hz, 1H), 4.98 (d, *J* = 17.0 Hz, 1H), 2.66 (q, *J* = 7.6 Hz, 2H), 2.60 (s, 2H), 2.17 – 2.13 (m, 2H), 1.35 (s, 3H), 1.34 (s, 3H), 1.25 (t, *J* = 7.6 Hz, 3H), 0.99 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 198.4, 149.9, 142.1, 134.5, 134.2, 131.3, 126.4, 125.7, 118.6, 46.1, 41.2, 40.9, 40.4, 28.3, 20.9, 15.4. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2969 (*s*), 1683 (*vs*), 1639 (*w*), 1611 (*m*), 1456 (*m*), 1376 (*m*), 1296 (*m*), 1263 (*m*), 1093 (*m*), 999 (*m*), 913 (*m*), 835 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{18}H_{24}O$ $[M]^+$: 256.1822; found: 256.1820.

*3.31. (E)-7-ethyl-3,4,4-trimethyl-3-(prop-1-en-1-yl)-3,4-dihydronaphthalen-1(2H)-one (**55**)*

To bis(dibenzylidenacetone)palladium(0) (66.1 mg, 0.115 mmol, 10.0 mol%) was added subsequently a solution of **54** (295 mg, 1.15 mmol, 1 equiv) in degassed toluene (3.3 mL), tri-*t*-butylphosphine (1 M in toluene, 0.115 mL, 0.115 mmol, 10.0 mol%) and isobutyryl chloride (0.078 M in degassed toluene, 1.47 mL, 0.115 mmol, 10.0 mol%). The reaction mixture was heated to 80 °C for 2 d, diluted afterwards with ethyl acetate (30 mL) and concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **55** (272 mg, 92%) as a yellow oil. **Analytical data for 55: TLC** (20% ethyl acetate in hexanes), R_f = 0.58 ($KMnO_4$, UV). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.86 (d, *J* = 1.9 Hz, 1H), 7.40 – 7.33 (m, 2H), 5.61 (d, *J* = 15.7 Hz, 1H), 5.47 (dq, *J* = 15.6, 6.2 Hz, 1H), 2.83 (d, *J* = 17.3 Hz, 1H), 2.66 (q, *J* = 7.6 Hz, 2H), 2.53 (d, *J* = 17.4 Hz, 1H), 1.67 (d, *J* = 6.2 Hz, 3H), 1.33 (s, 3H), 1.28 (s, 3H), 1.24 (t, *J* = 7.6 Hz, 3H), 1.06 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 198.6, 149.7, 142.0, 135.9, 134.1, 130.9, 126.4, 125.8, 124.5, 48.1, 43.5, 40.6, 28.3, 26.8, 24.5, 21.7, 18.5, 15.4. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2968 (*m*), 2936 (*w*), 1683 (*vs*), 1611 (*w*), 1491 (*w*), 1452 (*w*), 1376 (*w*), 1290 (*w*), 1264 (*w*), 1096 (*w*), 975 (*w*), 834 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{18}H_{24}O$ $[M]^+$: 256.1822; found: 256.1821.

*3.32. (6-methoxy-1,1,2-trimethyl-1,2-dihydronaphthalen-2-yl)methanol (**58a**)*

To a solution of **48** (870 mg, 4.02 mmol, 1 equiv) in methanol (34 mL) were added cerium(III) chloride heptahydrate (1.65 g, 4.42 mmol, 1.10 equiv) and sodium borohydride (228 mg, 6.03 mmol, 1.50 equiv) respectively at 0 °C. After 1 h, the mixture was diluted with pH7 buffer solution (20 mL) and dichloromethane (20 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was used immediately without further purification. *Note: The product is very sensitive toward acidic conditions. Therefore, it was used immediately in the next step.* To washed potassium hydride (242 mg, 6.03 mmol, 1.50 equiv) was added a solution of the crude alcohol in tetrahydrofuran (60 mL) at 0 °C. After 10 min, a solution of tributyl(iodomethyl)stannane (1.91 g, 4.42 mmol, 1.10 equiv) in tetrahydrofuran (15 mL) was added. After 105 min, the mixture was diluted with pH7 buffer solution (30 mL) and dichloromethane (30 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product **57** was used immediately without further purification. To a solution of crude **57** in tetrahydrofuran (80 mL) was added *n*-butyllithium (2.51 M in hexanes, 2.08 mL, 5.23 mmol, 1.30 equiv) dropwise over 5 min at −78 °C. The

reaction was allowed to warm to −45 °C over 2 h and was diluted with saturated aqueous ammonium chloride solution (30 mL) and water (20 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 × 40 mL) and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (17% ethyl acetate in hexanes) to obtain **58a** (450 mg, 48% over three steps) as a yellow oil. **Analytical data for 58a: TLC** (25% ethyl acetate in hexanes), R_f = 0.26 ($KMnO_4$, CAM, UV). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.18 (d, *J* = 8.5 Hz, 1H), 6.73 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.59 (d, *J* = 2.8 Hz, 1H), 6.46 (d, *J* = 9.6 Hz, 1H), 5.68 (d, *J* = 9.6 Hz, 1H), 3.79 (s, 3H), 3.62 (d, *J* = 10.8 Hz, 1H), 3.39 (d, *J* = 10.8 Hz, 1H), 1.29 (s, 4H), 1.13 (s, 3H), 1.09 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 157.9, 137.3, 135.5, 133.3, 127.3, 125.2, 112.9, 112.2, 67.8, 55.3, 43.0, 38.6, 25.8, 21.6, 17.7. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3409 (*m*), 2969 (*m*), 2877 (*w*), 1746 (*w*), 1602 (*m*), 1490 (*m*), 1309 (*m*), 1259 (*vs*), 1154 (*w*), 1035 (*vs*), 777 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{15}H_{20}O_2$ [M]$^+$: 232.1458; found: 232.1458.

*3.33. 6-Methoxy-1,1,2-trimethyl-1,2-dihydronaphthalen-2-yl)methyl acetate (**61a**)*

To a solution of **58a** (10.0 mg, 0.0430 mmol, 1 equiv) in dichloromethane (0.43 mL) were added triethylamine (17.9 µL, 0.129 mmol, 3.00 equiv), acetic anhydride (10.5 µl, 0.112 mmol, 2.60 equiv) and 4-dimethylaminopyridine (0.526 mg, 0.00430 mmol, 0.100 equiv) at 0 °C. After 30 min, the reaction mixture was diluted with saturated aqueous sodium bicarbonate solution (10 mL), the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to afford **61a** (10.2 mg, 86%) as a colorless oil. **Analytical data for 61a: TLC** (20% ethyl acetate in hexanes), R_f = 0.31 (UV, CAM).**^{1}H NMR** (599 MHz, $CDCl_3$) δ: 7.18 (d, *J* = 8.3 Hz, 1H), 6.72 (dd, *J* = 8.3, 2.8 Hz, 1H), 6.58 (d, *J* = 2.7 Hz, 1H), 6.39 (d, *J* = 9.7 Hz, 1H), 5.67 (d, *J* = 9.5 Hz, 1H), 4.01 (q, *J* = 10.7 Hz, 2H), 3.78 (s, 3H), 1.94 (s, 3H), 1.27 (s, 3H), 1.18 (s, 3H), 1.07 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ: 171.4, 158.0, 136.8, 135.1, 133.2, 126.7, 125.2, 112.8, 112.2, 68.6, 55.4, 41.4, 39.0, 24.7, 22.5, 21.0, 17.8. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2971 (*m*), 1738 (*s*), 1603 (*m*), 1491 (*m*), 1375 (*m*), 1260 (*s*), 1237 (*vs*), 1154 (*m*), 1034 (*s*), 856 (*s*), 777 (*s*) cm^{-1}.**HRMS** (EI) calcd for $C_{17}H_{22}O_3$ [M]$^+$: 274.1563; found: 274.1564.

*3.34. 6-Methoxy-2-((methoxymethoxy)methyl)-1,1,2-trimethyl-1,2-dihydronaphthalene (**61b**)*

To a solution of **58a** (20.0 mg, 0.0861 mmol, 1 equiv) in dichloromethane (0.43 mL) were added *N*,*N*-diisopropylethylamine (59.6 µL, 0.344 mmol, 4.00 equiv), 4-dimethylaminopyridine (1.05 mg, 0.008641 mmol, 0.100 equiv) and chloromethyl methyl ether (22.9 µL, 0.301 mmol, 3.50 equiv) respectively at 0 °C. The reaction mixture was allowed to warm to 23 °C and after 4 h, saturated aqueous ammonium chloride solution (10 mL) was added. The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to provide **61b** (22.3 mg, 94%) as a colorless oil. **Analytical data for 61b: TLC** (20% ethyl acetate in hexanes), R_f = 0.43 (UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.18 (dd, *J* = 8.4, 0.6 Hz, 1H), 6.72 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.58 (d, *J* = 2.8 Hz, 1H), 6.37 (d, *J* = 9.6 Hz, 1H), 5.77 (d, *J* = 9.6 Hz, 1H), 4.59 – 4.52 (m, 2H), 3.79 (s, 3H), 3.45 (s, 2H), 3.32 (s, 3H), 1.22 (s, 3H), 1.19 (s, 3H), 1.10 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 158.0, 137.0, 136.6, 133.5, 125.7, 125.2, 112.5, 112.1, 97.0, 72.3, 55.3, 55.3, 42.0, 39.1, 24.3, 22.9, 17.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2968 (*w*), 2931 (*w*), 1602 (*w*), 1464 (*w*), 1309 (*w*), 1260 (*m*), 1149 (*m*), 1105 (*m*), 1037 (*vs*), 916 (*w*), 854 (*w*), 776 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{17}H_{24}O_3$ [M]$^+$: 276.1720; found: 276.1715.

*3.35. tert-Butyl((6-methoxy-1,1,2-trimethyl-1,2-dihydronaphthalen-2-yl)methoxy)dimethyl-silane (**61c**)*

To a solution of **58a** (20.0 mg, 0.0861 mmol, 1 equiv) in dimethylformamide (0.21 mL) were added imidazole (11.7 mg, 0.172 mmol, 2.00 equiv) and *tert*-butyldimethylsilyl chloride (19.5 mg, 0.129 mmol, 1.50 equiv) at 0 °C and the reaction was allowed to warm to 23 °C. After 20 h, saturated aqueous ammonium chloride solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to obtain **61c** (20.2 mg, 68%) as a colorless oil. **Analytical data for 61c: TLC** (20% ethyl acetate in hexanes), R_f = 0.68 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.17 (dd, *J* = 8.4, 0.6 Hz, 1H), 6.71 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.56 (d, *J* = 2.8 Hz, 1H), 6.33 (d, *J* = 9.6 Hz, 1H), 5.71 (d, *J* = 9.6 Hz, 1H), 3.79 (s, 3H), 3.51 (s, 2H), 1.21 (d, *J* = 3.6 Hz, 6H), 1.02 (s, 3H), 0.86 (s, 9H), -0.03 (d, *J* = 2.4 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 157.8, 137.5, 137.1, 133.7, 125.6, 125.1, 112.4, 111.9, 67.0, 55.3, 43.1, 39.0, 26.0, 24.5, 23.2, 18.4, 17.6, -5.4, -5.4. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955 (*m*), 2928 (*m*), 2855 (*w*), 1602 (*w*), 1463 (*m*), 1360 (*w*), 1309 (*w*), 1259 (*s*), 1072 (*s*), 1038 (*s*), 1005 (*m*), 849 (*vs*), 835 (*vs*), 773 (*vs*), 668 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{21}H_{34}O_2Si$ [M]$^+$: 346.2323; found: 346.2322.

*3.36. 6-Methoxy-2-(methoxymethyl)-1,1,2-trimethyl-1,2-dihydronaphthalene (**61d**)*

To a solution of **58a** (20.0 mg, 0.0861 mmol, 1 equiv) in dimethylformamide (0.43 mL) was added sodium hydride (60% dispersion in mineral oil, 6.89 mg, 0.172 mmol, 2.00 equiv) at 0 °C. After 15 min, methyl iodide (9.65 mL, 0.155 mmol, 1.80 equiv) was added and the mixture was allowed to warm to 23 °C over 2.5 h. Saturated aqueous ammonium chloride solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to provide **61d** (17 mg, 80%) as a colorless oil. **Analytical data for 61d: TLC** (20% ethyl acetate in hexanes), R_f = 0.61 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.18 (d, *J* = 8.4 Hz, 1H), 6.72 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.59 (d, *J* = 2.7 Hz, 1H), 6.37 (d, *J* = 9.6 Hz, 1H), 5.75 (d, *J* = 9.6 Hz, 1H), 3.79 (s, 3H), 3.33 – 3.22 (m, 5H), 1.22 (s, 3H), 1.18 (s, 3H), 1.09 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 157.9, 137.0, 136.9, 133.5, 125.5, 125.2, 112.5, 112.0, 77.4, 59.5, 55.3, 42.2, 39.1, 24.4, 22.8, 17.8. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2970 (*m*), 2932 (*m*), 1886 (*m*), 1602 (*m*), 1572 (*m*), 1489 (*m*), 1464 (*m*), 1361 (*w*), 1309 (*m*), 1282 (*m*), 1261 (*vs*), 1194 (*m*), 1154 (*m*), 1105 (*vs*), 1089 (*s*), 1037 (*s*), 982 (*w*), 871 (*w*), 777 (*m*) cm^{-1}.**HRMS** (EI) calcd for $C_{16}H_{22}O_2$ [M]$^+$: 246.1620; found: 246.1614.

*3.37. N,N-diethyl-2-((6-methoxy-1,1,2-trimethyl-1,2-dihydronaphthalen-2-yl)methoxy)acetamide (**64**)*

To a solution of **58a** (100 mg, 0.430 mmol, 1 equiv) in 1,2-dimethoxyethane (2.2 mL) was added sodium hydride (60% dispersion in mineral oil, 51.6 mg, 1.29 mmol, 3.00 equiv) at 0 °C and after 20 min 2-chloro-*N*,*N*-diethylacetamide (88.7 µL, 0.646 mmol, 1.50 equiv). The reaction was allowed to warm slowly to 23 °C over 17 h and diluted with saturated aqueous ammonium chloride solution (10 mL) and water (5 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 × 15 mL) and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to afford **64** (144 mg, 97%) as a colorless oil. **Analytical data for 64: TLC** (33% ethyl acetate in hexanes), R_f = 0.17 (UV, CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.16 (d, *J* = 8.4 Hz, 1H), 6.70 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.56 (d, *J* = 2.7 Hz, 1H), 6.34 (d, *J* = 9.6 Hz, 1H), 5.78 (d, *J* = 9.7 Hz, 1H), 4.04 (q, *J* = 13.2 Hz, 2H), 3.78 (s, 3H), 3.47 – 3.25 (m, 6H), 1.26 – 1.04 (m, 15H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 168.5, 157.9, 136.9, 136.7, 133.4, 125.6, 125.2, 112.4, 112.0, 76.0, 71.3, 55.3, 42.3, 41.1, 39.8, 39.0, 24.3, 22.8, 17.9, 14.4, 12.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2971 (*m*), 2935 (*m*), 2874 (*w*), 1645 (*vs*), 1603 (*m*), 1572 (*w*), 1464 (*m*), 1431 (*m*), 1381 (*w*), 1362 (*w*), 1309 (*m*), 1261 (*vs*), 1222 (*m*), 1153 (*m*), 1102 (*m*), 1088 (*m*), 1036 (*m*), 947 (*w*), 871 (*w*), 791 (*w*), 779 (*w*), 734 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{21}H_{31}O_3N$ [M]$^+$: 345.2298; found: 345.2295.

*3.38. 7-methoxy-3,4,4-trimethyl-2a,3,4,8b-tetrahydro-1,3-(epoxymethano)cyclobuta[a]naphthalen-2(1H)-one (**65**)*

To a solution of **64** (60.0 mg, 0.174 mmol, 1 equiv) in 1,2-dichloroethane (6 mL) were added 2,4,6-collidine (11.7 µL, 0.868 mmol, 5.00 equiv) and trifluoromethanesulfonic anhydride (1 M in dichloromethane, 0.868 mL, 0.868 mmol, 5.00 equiv) and the reaction mixture was heated to 80 °C. After 75 min, potassium carbonate (120 mg, 0.868 mmol, 5.00 equiv), acetone (6 mL) and water (6 mL) were added and the mixture was heated to 70 °C. After 2 h, aqueous hydrochloric acid solution (2 M, 20 mL) was added and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (14% ethyl acetate in hexanes) to yield **65** (33 mg, 70%) as a yellow oil. **Analytical data for 65: TLC** (25% ethyl acetate in hexanes), R_f = 0.41 (CAM, ANIS, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.36 (d, *J* = 8.7 Hz, 1H), 6.83 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.69 (d, *J* = 2.8 Hz, 1H), 4.66 (dd, *J* = 6.7, 4.3 Hz, 1H), 4.05 (dt, *J* = 12.1, 0.9 Hz, 1H), 3.80 (s, 3H), 3.50 (d, *J* = 12.1 Hz, 1H), 3.41 (tt, *J* = 6.1, 0.7 Hz, 1H), 3.27 (dd, *J* = 6.0, 4.3 Hz, 1H), 1.41 (s, 3H), 1.08 (s, 3H), 1.06 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 204.8, 158.0, 139.1, 130.3, 126.3, 113.7, 113.6, 93.0, 71.9, 64.2, 55.3, 45.9, 38.1, 35.8, 30.9, 21.5, 20.8. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2975 (*m*), 2865 (*w*), 1780 (*vs*), 1610 (*m*), 1501 (*m*), 1465 (*m*), 1316 (*w*), 1260 (*m*), 1249 (*m*), 1153 (*w*), 1053 (*m*), 1037 (*m*), 908 (*m*), 818 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{17}H_{20}O_3$ [M]$^+$: 272.1407; found: 272.1406.

*3.39. 7-methoxy-3a,4,4-trimethyl-3,3a,4,8b-tetrahydro-1H-benzo[f]cyclobuta[cd]isobenzofuran-1a(1a1H)-ol (**71**)*

To a degassed solution of **65** (12.0 mg, 0.0441 mmol, 1 equiv) in tetrahydrofuran (1.2 mL) and methanol (0.6 mL) was added dropwise a solution of samarium(II) iodide (0.1 M in tetrahydrofuran, 3.52 mL, 0.352 mmol, 8.00 equiv) at 0 °C. After 1 h, water (10 mL) and aqueous hydrochloric acid solution (2 M, 10 mL) were added and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to afford **71** (12 mg, quant.) as a colorless oil. **Analytical data for 71: TLC** (33% ethyl acetate in hexanes), R_f = 0.26 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.24 (d, *J* = 8.8 Hz, 1H), 6.73 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.58 (d, *J* = 2.7 Hz, 1H), 3.78 (s, 3H), 3.68 (d, *J* = 8.9 Hz, 1H), 3.51 (d, *J* = 8.9 Hz, 1H), 3.34 (td, *J* = 10.4, 5.0 Hz, 1H), 3.05 (ddd, *J* = 12.9, 11.2, 1.7 Hz, 1H), 2.75 – 2.66 (m, 2H), 2.23 (dd, *J* = 13.0, 5.1 Hz, 1H), 1.28 (s, 6H), 1.06 (s, 3H). **^{13}C NMR** (101 MHz, CDCl3) δ: 157.8, 139.4, 136.8, 126.1, 112.8, 112.3, 106.4, 76.7, 55.3, 53.6, 46.6, 44.2, 37.9, 29.5, 23.6, 22.2, 21.9. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3391 (*w*), 2971 (*m*), 1608 (*m*), 1575 (*w*), 1502 (*m*), 1424 (*w*), 1364 (*w*), 1284 (*s*), 1254 (s), 1216 (*w*), 1158 (*m*), 1125 (*w*), 1037 (*vs*), 867 (*m*), 815 (*m*), 728 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{17}H_{22}O_3$ [M]$^+$: 274.1563; found: 274.1572.

*3.40. 3-(hydroxymethyl)-7-methoxy-3,4,4-trimethyl-1,2,2a,3,4,8b-hexahydrocyclobuta[a]naphthalen-2-ol (**72**)*

To a solution of **71** (12.0 mg, 0.0437 mmol, 1 equiv) in diethyl ether (3 mL) was added lithium aluminum hydride (16.6 mg, 0.437 mmol, 10.0 equiv) at 0 °C and the reaction mixture was allowed to slowly warm to 23 °C. After 4 h, the reaction mixture was diluted with saturated aqueous ammonium chloride solution (15 mL), the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to yield **72** (12 mg, 99%, d.r. = 30:1) as a colorless oil. **Analytical data for 72: TLC** (50% ethyl acetate in hexanes), R_f = 0.20 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.09 (d, *J* = 8.5 Hz, 1H), 6.66 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.59 (d, *J* = 2.7 Hz, 1H), 4.52 (dt, *J* = 9.7, 8.1 Hz, 1H), 3.77 (s, 3H), 3.55 – 3.44 (m, 2H), 3.35 (s, 2H), 3.12 (q, *J* = 8.9 Hz, 1H), 3.03 (dt, *J* = 12.0, 6.0 Hz, 1H), 2.90 (dtd, *J* = 11.3, 8.0, 3.3 Hz, 1H), 2.00 (q, *J* = 10.1 Hz, 1H), 1.31 (s, 3H), 1.18 (s, 3H), 1.02 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 158.2, 140.7, 137.0, 124.9, 112.3, 111.1, 65.5, 65.1, 55.3, 49.8, 42.9, 41.1, 40.1, 27.9, 27.3, 21.5, 18.7. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3217 (*m*), 2970 (*m*), 2934 (*m*), 1606 (*m*), 1576 (*w*), 1495 (*m*), 1465 (*m*), 1365 (*w*), 1310 (*m*), 1247 (*s*), 1198 (*m*), 1112 (*m*), 1031 (*vs*), 849 (*m*), 808 (*m*), 735 (*s*), 703 (*m*) cm^{-1}. **HRMS** (EI) calcd for $C_{17}H_{24}O_3$ [M]$^+$: 276.1720; found: 276.1726.

*3.41. 7-methoxy-3,4,4-trimethyl-2-oxo-1,2,2a,3,4,8b-hexahydrocyclobuta[a]naphthalene-3-carbaldehyde (**73**)*

To a solution of oxalyl chloride (2 M in dichloromethane, 151 µL, 0.302 mmol, 2.20 equiv) in dichloromethane (1.5 mL) was added dimethyl sulfoxide (47.9 µL, 0.674 mmol, 4.90 equiv) at −78 °C. After stirring for 3 min, a solution of **72** (38.0 mg, 0.137 mmol, 1 equiv) dichloromethane (1 mL) was added and after further 25 min triethylamine (191 µL, 1.37 mmol, 10.0 equiv) was added. The reaction mixture was stirred for 10 min at −78 °C and was then directly warmed to 23 °C. After 10 min, saturated aqueous sodium bicarbonate solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash

column chromatography on silica gel (20% ethyl acetate in hexanes, triethylamine pretreated silica gel) to obtain **73** (35.5 mg, 95%) as a colorless oil. *Note: Signals in the ^{13}C NMR which could only be assigned by cross-coupling in the HMBC are marked with an asterisk.* **Analytical data for 73: TLC** (20% ethyl acetate in hexanes), R_f = 0.18 (ANIS). **^{1}H NMR** (400 MHz, C_6D_6) δ: 9.12 (br s, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.68 – 6.59 (m, 2H), 3.31 (s, 3H), 3.24 (br s, 1H), 3.08 (ddd, *J* = 17.2, 9.6, 3.8 Hz, 1H), 2.95 (tdt, *J* = 9.6, 6.0, 1.1 Hz, 1H), 2.83 (ddd, *J* = 10.3, 3.7, 2.8 Hz, 1H), 1.05 (s, 3H), 1.01 (s, 3H), 0.73 (s, 3H). **^{13}C NMR** (101 MHz, C_6D_6) δ: 206.7, 202.2, 159.2, 140.3, 135.5, 125.4, 113.4, 112.3, 63.9, 55.9, 54.7, 53.1, 39.7, 26.3, 25.9, 21.7*, 16.3. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2973 (*w*), 2933 (*w*), 2728 (*w*), 1774 (*vs*), 1718 (*s*), 1607 (*m*), 1574 (*w*), 1494 (*m*), 1465 (*m*), 1388 (*m*), 1298 (*m*), 1249 (*s*), 1155 (*m*), 1087 (*m*), 1034 (*s*), 854 (*w*), 820 (*w*) cm^{-1}. **HRMS** (ESI) calcd for $C_{17}H_{20}O_3$ [M]$^+$: 272.1407; found: 272.1409.

3.42. 7-methoxy-3a,4,4-trimethyl-3a,4-dihydro-1H-cyclopenta[b]naphthalen-1-one (77)

To a solution of **73** (5.00 mg, 0.0184 mmol, 1 equiv) in tetrahydrofuran (0.2 mL) was added lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 22.0 µL, 0.0220 mmol, 1.20 equiv) at −78 °C. After 1 h, freshly distilled trimethylsilyl chloride (over CaH_2, 3.52 µL, 0.0275 mmol, 1.50 equiv) was added and the mixture was allowed to warm to 23 °C. After 3 h, dichloromethane (5 mL) was added, the reaction mixture was filtered through a small plug of Celite® and the filtrate was concentrated. The residue was used without further purification. To acetone (2.03 µL, 0.0276 mmol, 1.50 equiv) in dichloromethane (0.1 mL) was added titanium(IV) chloride (3.04 µL, 0.0276 mmol, 1.50 equiv) followed by the addition of a solution of crude product in dichloromethane (0.3 mL) at −78 °C. The reaction mixture was allowed to warm to 23 °C over 17 h. pH7 Buffer solution (10 mL) and diethyl ether (10 mL) were added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to provide trace amounts of **77** as colorless oil. **Analytical data for 77: TLC** (20% ethyl acetate in hexanes), R_f = 0.26 (UV, CAM, $KMnO_4$). **^{1}H NMR** (400 MHz, C_6D_6) δ: 7.20 (s, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.86 (dd, *J* = 6.0, 1.1 Hz, 1H), 6.78 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.63 (d, *J* = 2.8 Hz, 1H), 6.24 (d, *J* = 6.0 Hz, 1H), 3.27 (s, 3H), 1.08 (s, 3H), 0.76 (s, 3H), 0.69 (s, 3H). **^{13}C NMR** (101 MHz, C_6D_6) δ: 194.6, 162.4, 158.9, 143.1, 139.3, 136.4, 133.0, 126.1, 124.4, 115.9, 115.0, 54.9, 49.9, 39.6, 26.3, 20.4, 20.3. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2966 (*w*), 2929 (*w*), 1689 (*vs*), 1645 (*vs*), 1605 (*m*), 1566 (*m*), 1482 (*w*), 1465 (*w*), 1372 (*w*), 1322 (*w*), 1249 (*m*), 1229 (*vs*), 1205 (*w*), 1146 (*w*), 1082 (*w*), 1057 (*w*), 1036 (*m*), 853 (*w*), 816 (*s*), 709 (*w*) cm^{-1}. **HRMS** (EI) calcd for $C_{17}H_{18}O_3$ [M]$^+$: 254.1301; found: 254.1301.

*3.43. 6-methoxy-1,1,2-trimethyl-1,2-dihydronaphthalene-2-carbaldehyde (**85a**)*

To a solution of alcohol **58a** (1.17 g, 5.04 mmol, 1 equiv) in dry dichloromethane (50 mL) was added potassium carbonate (1.39 g, 10.1 mmol, 2.00 equiv) and Dess–Martin periodinane (4.27 g, 10.1 mmol, 2.00 equiv) at 0 °C. The suspension was stirred at 0 °C for 30 min and at 23 °C for 1.5 h. Excess Dess–Martin periodinane was quenched by addition of saturated aqueous sodium bicarbonate solution (35 mL) and saturated aqueous sodium thiosulfate solution (20 mL). The organic layer was separated and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over sodium sulfate and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1% ethyl acetate in cyclohexane initially, grading to 5% ethyl acetate in cyclohexane) afforded aldehyde **85a** (0.92 g, 80%) as a colorless oil. **Analytical data for 85a: TLC** (10% ethyl acetate in cyclohexane) R_f = 0.37 (UV) **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.35 (s, 1H), 7.20 (d, *J* = 8.5 Hz, 1H), 6.77 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.65 – 6.61 (m, 2H), 5.49 (d, *J* = 9.5 Hz, 1H), 3.80 (s, 3H), 1.28 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.8, 158.4, 135.4, 133.1, 130.6, 129.9, 125.6, 113.6, 112.8, 55.4, 54.8, 38.7, 25.3, 22.5, 14.3. **IR** (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3032 (*w*), 2971 (*w*), 2871 (*w*), 2833 (*w*), 2715 (*w*), 1715 (*s*), 1634 (*w*), 1601 (*m*), 1570 (*m*), 1495 (*m*), 1463 (*m*), 1427 (*m*), 1386 (*w*), 1363 (*w*), 1308 (*m*), 1283 (*m*), 1259 (*s*), 1223 (*m*), 1192 (*w*), 1175 (*m*), 1153 (*m*), 1093 (*m*), 1034 (*s*), 961 (*w*), 933 (*w*), 908 (*m*), 871 (*m*), 856 (*m*), 818 (*m*), 791 (*w*), 773 (*s*), 754 (*w*), 731 (*s*), 712 (*m*), 683 (*w*), 621 (*w*), 582 (*w*), 553 (*w*), 527 (*m*), 498 (*w*), 431 (*w*) cm^{-1}. **HRMS** (ESI) calcd for $C_{15}H_{18}NaO_2$ [M+Na]$^+$: 253.1199; found: 253.1185.

*3.44. ethyl (Z)-5-(6-methoxy-1,1,2-trimethyl-1,2-dihydronaphthalen-2-yl)pent-4-enoate (**86a**)*

To a stirred suspension of [3-(ethoxycarbonyl)propyl]triphenylphosphonium bromide (2.85 g, 6.23 mmol, 1.60 equiv) in tetrahydrofuran (25 mL) was added sodium bis(trimethylsilyl)amide (1.0 M in THF, 7.1 mL, 7.1 mmol, 1.8 equiv) at 0 °C. The orange mixture was stirred for 30 min at 0 °C and was then cooled to −78 °C. A solution of aldehyde **85a** (0.90 g, 3.90 mmol, 1 equiv) in tetrahydrofuran (4.2 mL) was added slowly. After 15 min, the reaction was allowed to warm to 23 °C and stirred at 23 °C for 4 h. Excess amide was quenched by addition of saturated aqueous ammonium chloride solution (21 mL). The mixture was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (70 mL) and the washed solution was dried over sodium sulfate. The solution was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) to afford the title compound **86a** (1.20 g, 94%) as a colorless oil. **Analytical data for 86a: TLC** (10% ethyl acetate in cyclohexane) R_f = 0.45 (UV) **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.18 (d, *J* = 8.5 Hz, 1H), 6.72 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.58 (d, *J* = 2.7 Hz, 1H), 6.31 (d, *J* = 9.6 Hz, 1H), 5.99 (d, *J* = 9.6 Hz, 1H), 5.46 (d, *J* = 12.0 Hz, 1H), 5.36 (dt, *J* = 12.0, 7.2 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 2.73 – 2.62 (m, 1H), 2.50 (tdd, *J* = 14.7, 7.2, 1.3 Hz, 1H), 2.37 (t, *J* = 7.5 Hz, 2H), 1.28 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.16 (s, 3H), 1.09 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 173.1, 157.9, 139.0, 136.5, 135.7, 133.2, 129.7, 125.2, 124.6, 112.3, 112.0, 60.4, 55.2, 45.1, 40.9, 34.7, 26.1, 24.9, 22.5, 21.6, 14.3. **IR** (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2972 (*m*), 2937 (*w*), 2873 (*w*), 2833 (*w*), 1732 (*s*), 1636 (*w*), 1602 (*m*), 1571 (*w*), 1489 (*m*), 1464 (*m*), 1427 (*w*), 1371 (*m*), 1308 (*m*), 1281 (*m*), 1259 (*s*), 1214 (*m*), 1171 (*k*), 1151 (*s*), 1089 (*m*), 1062 (*w*), 1035 (*s*), 910 (*m*), 871 (*m*), 856 (*m*), 818 (*m*), 778 (*m*), 730 (*s*), 648 (*w*), 631 (*w*), 597 (*w*), 554 (*w*), 473 (*w*), 433 (*w*) cm^{-1}. **HRMS** (ESI) calcd for $C_{21}H_{28}NaO_3$ [M+Na]$^+$: 351.1931, found: 351.1926.

*3.45. (Z)-5-(6-methoxy-1,1,2-trimethyl-1,2-dihydronaphthalen-2-yl)-1-(pyrrolidin-1-yl)pent-4-en-1-one (**87a**)*

The ester **86a** (1.20 g, 3.65 mmol, 1 equiv) was dissolved in dry and colorless pyrrolidine (4.5 mL, 55 mmol, 15 equiv) in a pressure tube under argon. The tube was sealed and heated at 100 °C. The reaction mixture was stirred for 65 h and was then cooled to 23 °C. Excess pyrrolidine was removed under reduced pressure. Purification by flash column chromatography on silica gel (50% ethyl acetate in cyclohexane) afforded the title compound

87a (1.38 g, quant.) as a pale-yellow oil. **Analytical data for 87a: TLC** (50% ethyl acetate in cyclohexane) R_f = 0.27 (CAM) **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.17 (d, *J* = 8.4 Hz, 1H), 6.71 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.57 (d, *J* = 2.7 Hz, 1H), 6.29 (d, *J* = 9.6 Hz, 1H), 6.00 (d, *J* = 9.6 Hz, 1H), 5.46 – 5.36 (m, 2H), 3.78 (s, 3H), 3.47 (t, *J* = 6.8 Hz, 2H), 3.40 (t, *J* = 6.8 Hz, 2H), 2.73 – 2.62 (m, 1H), 2.59 – 2.47 (m, 1H), 2.31 (t, *J* = 7.7 Hz, 2H), 1.99 – 1.89 (m, 2H), 1.89 – 1.80 (m, 2H), 1.27 (s, 3H), 1.16 (s, 3H), 1.08 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 171.1, 157.9, 139.4, 136.8, 135.4, 133.5, 130.7, 125.3, 124.6, 112.4, 112.0, 55.3, 46.8, 45.8, 45.2, 41.0, 35.3, 26.3, 26.2, 25.1, 24.6, 22.6, 21.7. **IR** (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2969 (*m*), 2872 (*w*), 2833 (*w*), 1641 (*s*), 1602 (*m*), 1571 (*w*), 1489 (*m*), 1433 (*s*), 1380 (*w*), 1359 (*w*), 1340 (*w*), 1309 (*w*), 1282 (*w*), 1260 (*s*), 1225 (*w*), 1192 (*w*), 1171 (*w*), 1152 (*w*), 1089 (*w*), 1035 (*m*), 870 (*w*), 857 (*w*), 818 (*w*), 780 (*w*), 727 (*w*), 632 (*w*), 549 (*w*), 421 (*w*) cm^{-1}. **HRMS** (ESI) calcd for $C_{23}H_{31}NNaO_2$ $[M+Na]^+$: 376.2247, found: 376.2240

*3.46. 7-methoxy-3,4,4-trimethyl-2a,3,4,8b-tetrahydro-3,1-prop[1]enocyclobuta[a]naphthalen-2(1H)-one (**90a**)*

To a vigorously stirred solution of freshly distilled trifluoromethanesulfonic anhydride (0.77 mL, 4.55 mmol, 1.20 equiv) in dry 1,2-dichloroethane (47 mL) at 80 °C was added dropwise a solution of amide **87a** (1.34 g, 3.79 mmol, 1 equiv) and 2,4,6-collidine (0.60 mL, 4.55 mmol, 1.20 equiv) in 1,2-dichloroethane (47 mL) via a dropping funnel over a period of 2 h. The initial yellowish reaction mixture turned red-brownish, stirring was continued at 80 °C for 24 h and was cooled to 23 °C. The dark red-brownish reaction mixture was concentrated under reduced pressure. To the crude iminium salt was added tetrachloromethane (20 mL) and water (20 mL) and the dark brown mixture was heated at reflux at 80 °C for 5 h under an atmosphere of argon. The organic layer was separated and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) afforded cyclobutanone **90a** (0.72 g, 67%) as a pale yellow solid and cyclobutanone **89a** (0.02 g, 2%) as a colorless oil. **Analytical Data for 90a: TLC** (10% ethyl acetate in cyclohexane) R_f = 0.21 (UV, CAM) **^{1}H NMR** (400 MHz, Acetone-d_6) δ: 7.20 (d, *J* = 8.4 Hz, 1H), 6.75 – 6.67 (m, 2H), 5.37 (ddt, *J* = 12.5, 2.7, 1.8 Hz, 1H), 5.11 (dddd, *J* = 12.5, 5.1, 2.6, 1.1 Hz, 1H), 3.75 (s, 3H), 3.72 (d, *J* = 8.2 Hz, 1H), 3.67 – 3.60 (m, 1H), 3.48 (ddd, *J* = 8.3, 6.6, 1.9 Hz, 1H), 2.21 (dtd, *J* = 18.5, 5.1, 1.6 Hz, 1H), 1.98 (dq, *J* = 18.5, 2.8 Hz, 1H), 1.37 (s, 3H), 1.24 (s, 3H), 1.10 (s, 3H). **^{13}C NMR** (101 MHz, Acetone-d_6) δ: 209.2, 158.2, 139.7, 136.7, 134.5, 126.6, 126.5, 114.8, 112.9, 64.9, 61.7, 55.3, 41.5, 41.1, 30.6, 28.3, 27.6, 21.9, 21.9. **IR** (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2969 (*w*), 2909 (*w*), 2834 (*w*), 1776 (*s*), 1608 (*w*), 1576 (*w*), 1497 (*w*), 1464 (*w*), 1424 (*w*), 1387 (*w*), 1370 (*w*), 1324 (*w*), 1304 (*w*), 1281 (*w*), 1255 (*m*), 1246 (*m*), 1220 (*w*), 1160 (*w*), 1112 (*w*), 1090 (*w*), 1062 (*w*), 1037 (*w*), 975 (*w*), 929 (*w*), 857 (*w*), 822 (*w*), 760 (*w*), 701 (*w*), 688 (*w*), 601 (*w*), 570 (*w*), 483 (*w*), 410 (*w*) cm^{-1}. **HRMS** (ESI) calcd for $C_{19}H_{22}NaO_2$ $[M+Na]^+$: 305.1512, found: 305.1472. **Analytical Data for 89a: TLC** (10% ethyl acetate in cyclohexane) R_f = 0.27 (UV, CAM) **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.10 (d, *J* = 8.6 Hz, 1H), 6.84 (dd, *J* = 2.8, 1.2 Hz, 1H), 6.63 (ddd, *J* = 8.6, 2.8, 1.0 Hz, 1H), 5.46 (ddd, *J* = 10.4, 6.7, 1.9 Hz, 1H), 5.42 (ddd, *J* = 10.2, 2.9, 1.5 Hz, 1H), 4.28 (dt, *J* = 9.8, 2.0 Hz, 1H), 3.71 (s, 3H), 3.62 (dddd, *J* = 9.9, 7.0, 3.2, 1.7 Hz, 1H), 3.04 (td, *J* = 9.8, 1.5 Hz, 1H), 2.28 (ddd, *J* = 16.9, 6.7, 1.8 Hz, 1H), 2.06 (dddd, *J* = 17.0, 7.0, 2.9, 2.0 Hz, 1H), 1.34 (s, 3H), 1.11 (s, 3H), 1.02 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ: 212.6, 157.8, 137.5, 134.9, 130.9, 126.2, 125.1, 112.4, 112.0, 58.9, 55.7, 55.3, 39.9, 38.7, 34.6, 25.5, 22.1, 21.9, 20.4. **IR** (ATR, $CDCl_3$) $\tilde{\nu}_{max}$ 3034 (*w*), 2969 (*m*), 2838 (*w*), 1775 (*s*), 1606 (*m*), 1575 (*w*), 1496 (*m*), 1464 (*w*), 1400 (*w*), 1383 (*w*), 1369 (*w*), 1320 (*w*), 1302 (*m*), 1257 (*m*), 1229 (*m*), 1178 (*w*), 1158 (*w*), 1141 (*w*), 1117 (*w*), 1091 (*w*), 1037 (*m*), 1016 (*w*), 956 (*w*), 927 (*w*), 868 (*w*), 850 (*w*), 815 (*w*), 757 (*w*), 731 (*w*), 698 (*m*), 589 (*w*), 560 (*w*), 526 (*w*), 507 (*w*), 479 (*w*), 442 (*w*) cm^{-1}. **HRMS** (ESI) calcd for $C_{19}H_{22}NaO_2$ $[M+Na]^+$: 305.1512, found: 305.1465.

*3.47. 11-hydroxy-7-methoxy-3,4,4-trimethyl-2a,3,4,8b-tetrahydro-3,1-prop[1]enocyclobuta[a]naphthalen-2(1H)-one (**93a**)*

To finely grinded selenium dioxide (2.13 g, 19.2 mmol, 10.0 equiv) and oven-dried (100 °C) fine white quartz sand (2.19 g, 19.0 equiv, particle size >230mesh) in a flame-dried pressure tube (15 mL) equipped with a magnetic stirring bar was added cyclobutanone **90a** (541 mg, 1.92 mmol, 1 equiv). After sparging with argon for 10 min, dry 1,4-dioxane (9.6 mL) was added. The tube was sealed and the vigorously stirred reaction mixture was heated at 125 °C (700 rpm) for 7 h. The reaction mixture was cooled to 23 °C and filtered through a pad of Celite®. The Celite® plug was washed with ethyl acetate (200 mL) and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1% ethyl acetate in cyclohexane initially, grading to 10% ethyl acetate in cyclohexane, grading to 25% ethyl acetate in cyclohexane, grading to 50% ethyl acetate in cyclohexane) afforded slightly impure **93a** (165 mg) as an orange foam. Cyclobutanone **90a** (294 mg, 54%) was recovered. Purification of the impure product **93a** by flash column chromatography (10% ethyl acetate in dichloromethane) afforded the allylic alcohol **93a** (142 mg, 25%) as a colorless sticky foam. **Analytical Data for 93a: TLC** (25% ethyl acetate in cyclohexane) R_f = 0.30 (UV, CAM) **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.19 (d, *J* = 8.7 Hz, 1H), 6.75 (ddd, *J* = 8.7, 2.8, 0.7 Hz, 1H), 6.66 (dd, *J* = 2.8, 0.9 Hz, 1H), 5.42 (dt, *J* = 12.6, 1.8 Hz, 1H), 5.34 (ddd, *J* = 12.7, 2.5, 1.9 Hz, 1H), 4.04 – 3.97 (m, 1H), 3.83 (dddd, *J* = 8.6, 6.4, 4.3, 1.9 Hz, 1H), 3.78 (s, 3H), 3.73 (t, *J* = 8.5 Hz, 1H), 3.48 (ddd, *J* = 8.3, 6.6, 1.7 Hz, 1H), 1.98 (d, *J* = 9.4 Hz, 1H), 1.39 (s, 3H), 1.28 (s, 3H), 1.09 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 208.5, 157.5, 138.6, 135.8, 132.3, 130.0, 126.2, 113.9, 112.8, 68.1, 67.5, 64.7, 55.3, 42.5, 40.5, 28.4, 27.7, 22.0, 21.9. **IR** (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3420 (*w br*), 2971 (*w*), 2909 (*w*), 2836 (*w*), 2251 (*w*), 1771 (*s*), 1607 (*m*), 1575 (*w*), 1496 (*m*), 1477 (*w*), 1464 (*w*), 1425 (*w*), 1388 (*w*), 1371 (*w*), 1325 (*w*), 1309 (*w*), 1244 (*m*), 1174 (*m*), 1163 (*m*), 1128 (*w*), 1107 (*w*), 1090 (*w*), 1057 (*w*), 1032 (*s*), 974 (*w*), 908 (*m*), 879 (*m*), 852 (*w*), 816 (*m*), 775 (*m*), 726 (*s*), 701 (*m*), 688 (*m*), 647 (*m*), 588 (*m*), 552 (*w*), 529 (*w*), 492 (*w*), 453 (*w*) cm^{-1}. **HRMS** (ESI) calcd for $C_{19}H_{22}NaO_3$ $[M+Na]^+$: 321.1461, found: 321.1416.

*3.48. 8-methoxy-4,5,5-trimethyl-3a,4,5,9b-tetrahydro-4,1-prop[1]enonaphtho[1,2-c]furan-3,12(1H)-dione (**94a**)*

To a solution of allylic alcohol **93a** (50.0 mg, 0.168 mmol, 1 equiv) in 1,2-dichloroethane (4.4 mL) was added pivalaldehyde (0.09 mL, 0.8 mmol, 5 equiv) and copper(II) acetate monohydrate (33.5 mg, 0.168 mmol, 1.00 equiv). The flask was capped with a septum and sparged with oxygen gas from a balloon for 2 min. The solution was stirred under oxygen at 23 °C until monitoring by thin layer chromatography indicated full conversion of the starting material (1.5 h). Sodium bicarbonate (70.4 mg, 0.838 mmol, 5.00 equiv) and Dess–Martin periodinane (142 mg, 0.335 mmol, 2.00 equiv) were added and the reaction was stirred at 23 °C. After 1 h, an additional portion of Dess-Martin periodinane (142 mg, 0.335 mmol, 2.00 equiv) was added and the reaction was stirred at 23 °C for 1 h. Excess Dess–Martin periodinane was quenched by addition of saturated aqueous sodium bicarbonate solution (9 mL) and saturated aqueous sodium thiosulfate solution (4.5 mL). The mixture was extracted with dichloromethane (3 × 25 mL). The

combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane initially, grading to 25% ethyl acetate in cyclohexane) afforded a mixture of lactones **94a** and **95a**. Separation by slow flash column chromatography on silica gel (5% ethyl acetate in cyclohexane initially, grading to 10% ethyl acetate in cyclohexane) afforded lactone **94a** (34 mg, 64%) and lactone **95a** (13 mg, 25%) as both colorless crystalline solids. **Analytical Data for 94a: TLC** (25% ethyl acetate in cyclohexane) R_f = 0.27 (UV, CAM) **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.21 (d, *J* = 8.8 Hz, 1H), 6.78 (ddd, *J* = 8.9, 2.8, 0.6 Hz, 1H), 6.61 (dd, *J* = 2.8, 0.8 Hz, 1H), 6.10 (dd, *J* = 13.1, 1.5 Hz, 1H), 5.63 (dd, *J* = 13.1, 1.9 Hz, 1H), 5.03 (dd, *J* = 8.6, 2.0 Hz, 1H), 4.05 (t, *J* = 8.7 Hz, 1H), 3.75 (s, 3H), 3.15 (dd, *J* = 8.7, 1.5 Hz, 1H), 1.58 (s, 3H), 1.42 (s, 3H), 1.21 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 195.8, 176.9, 158.2, 148.2, 135.7, 128.4, 127.6, 126.2, 114.9, 113.0, 84.6, 55.4, 45.7, 43.7, 42.3, 39.6, 28.6, 22.2, 21.4. **IR** (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2978 (*w*), 2838 (*w*), 1776 (*s*), 1680 (*s*), 1612 (*m*), 1579 (*w*), 1503 (*m*), 1479 (*w*), 1466 (*m*), 1427 (*w*), 1392 (*w*), 1377 (*w*), 1368 (*w*), 1331 (*w*), 1314 (*m*), 1284 (*m*), 1258 (*s*), 1242 (*s*), 1206 (*m*), 1180 (*m*), 1155 (*s*), 1109 (*m*), 1090 (*w*), 1065 (*w*), 1028 (*s*), 992 (*w*), 958 (*w*), 923 (*w*), 905 (*w*), 877 (*w*), 825 (*s*), 753 (*m*), 722 (*w*), 704 (*w*), 692 (*w*), 666 (*w*), 602 (*w*), 563 (*w*), 547 (*w*), 498 (*w*), 457 (*w*), 432 (*w*) cm^{-1}. **HRMS** (ESI) calcd for $C_{19}H_{20}NaO_4$ $[M+Na]^+$: 335.1254, found: 335.1194. **Analytical Data for 95a: TLC** (25% ethyl acetate in cyclohexane) R_f = 0.20 (UV) **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.18 (d, *J* = 8.8 Hz, 1H), 6.78 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.59 (dd, *J* = 2.8, 0.8 Hz, 1H), 6.04 (dd, *J* = 13.2, 1.8 Hz, 1H), 5.70 (dd, *J* = 13.2, 1.7 Hz, 1H), 5.10 (dd, *J* = 8.2, 1.8 Hz, 1H), 4.18 (t, *J* = 8.5 Hz, 1H), 3.90 (dd, *J* = 8.8, 1.7 Hz, 1H), 3.75 (s, 3H), 1.49 (s, 3H), 1.43 (s, 3H), 1.25 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 192.2, 171.6, 158.3, 148.0, 135.6, 130.8, 127.9, 127.3, 114.9, 113.6, 81.5, 60.1, 55.4, 49.2, 43.2, 40.6, 28.6, 23.2, 19.0. **IR** (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2977 (*w*), 2927 (*w*), 1774 (*s*), 1673 (*m*), 1612 (*m*), 1578 (*w*), 1502 (*m*), 1465 (*w*), 1426 (*w*), 1392 (*w*), 1374 (*w*), 1358 (*w*), 1341 (*w*), 1316 (*w*), 1260 (*m*), 1243 (*m*), 1204 (*w*), 1159 (*m*), 1091 (*w*), 1065 (*w*), 1019 (*m*), 958 (*w*), 925 (*w*), 865 (*w*), 844 (*w*), 813 (*w*), 783 (*w*), 753 (*w*), 705 (*w*), 656 (*w*), 607 (*w*), 546 (*w*), 514 (*w*), 497 (*w*), 447 (*w*) cm^{-1}. **HRMS** (ESI) calcd for $C_{19}H_{20}NaO_4$ $[M+Na]^+$: 335.1254, found: 335.1199.

*3.49. tert-butyl((6-ethyl-1,1,2-trimethyl-1,2-dihydronaphthalen-2-yl)methoxy)diphenylsilane (**84**)*

To aluminum chloride (133 mg, 1.00 mmol, 3.00 equiv) in an oven dried Schlenk flask was added dry toluene (1.0 mL) and ethyl magnesium bromide solution (3 M in diethylether, 1.00 mL, 3.00 mmol, 12.0 equiv). The suspension was irradiated in an ultrasonic bath for 15 min. To a second Schlenk flask equipped with a magnetic stirring bar was added bis(1,5-cyclooctadiene)nickel(0) (5.8 mg, 21 µmol, 25 mol%) and 1,2-bis(dicyclohexylphosphino)ethane (8.9 mg, 21 µmol, 25 mol%) and protected dehydrotetraline **81** (45.0 mg, 95.6 µmol, 1 equiv) in a glovebox. Toluene (0.5 mL) and diisopropyl ether (0.5 mL) were added. The suspension of aluminum chloride and ethyl magnesium bromide (0.50 mL, 0.50 mmol $AlEt_3$, 5.2 equiv) was transferred to this solution. The resulting bright yellow suspension was heated to 100 °C for 19 h and then cooled to 23 °C. Excess ethyl metal species were quenched by slow addition of saturated aqueous potassium sodium tartrate solution (5 mL) and the biphasic mixture was stirred for 2 h at 23 °C. The aqueous phase was separated and extracted with ethyl acetate (3 × 5 mL). The combined organic phases were washed with saturated aqueous sodium chloride solution (5 mL) and dried over sodium sulfate. The dried solution was filtered and concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to provide ethyl tetraline **84** (3.1 mg, 7%) as a colorless oil. **Analytical Data for 84:** The physical data were identical in all respects to those previously reported [54].

*3.50. tert-butyl((6-ethyl-1,1,2-trimethyl-1,2-dihydronaphthalen-2-yl)methoxy)diphenylsilane (**84**)*

To a solution of triflate **83** (15.0 g, 25.5 mmol, 1 equiv) in dry dioxane (130 mL) was added [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (250 mg, 0.34 mmol, 1.3 mol%). The orange suspension was cooled to 0 °C causing partial crystallization of the solvent. Diethylzinc (1 M in hexanes, 38.2 mL, 38.2 mmol, 1.50 equiv) was added and the ice bath was removed. When all dioxane was melted again, a yellow clear solution was formed. The reaction mixture was heated at 70 °C for 1 h and was then cooled to 0 °C. Excess diethylzinc of the brownish solution was quenched by addition of methanol (20 mL), water (100 mL) and saturated aqueous ammonium chloride solution (100 mL). The mixture was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL) and the washed solution was dried over sodium sulfate. The filtrate was concentrated under reduced pressure, passed through a plug of silica (5% ethyl acetate in cyclohexane) and used without further purification in the next step. **Analytical Data for 84:** The physical data were identical in all respects to those previously reported [54].

*3.51. (6-ethyl-1,1,2-trimethyl-1,2-dihydronaphthalen-2-yl)methanol (**58b**)*

To a stirred solution of protected alcohol **84** (ca. 25.5 mmol, 1 equiv) in tetrahydrofuran (130 mL) was added a solution of tetrabutylammonium fluoride (1 M in THF, 35 mL, 35 mmol, 1.4 equiv) at 0 °C. The ice bath was removed after 15 min and the reaction was stirred at 23 °C for 18 h. Excess fluoride was quenched by addition of water (50 mL). The reaction was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over sodium sulfate. The filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1% ethyl acetate in cyclohexane initially, grading to 5% ethyl acetate in cyclohexane) afforded the title compound **58b** (5.9 g, 99%) as a colorless viscous oil. **Analytical Data for 58b:** The physical data were identical in all respects to those previously reported [54].

*3.52. 6-ethyl-1,1,2-trimethyl-1,2-dihydronaphthalene-2-carbaldehyde (**85b**)*

To a solution of oxalyl chloride (4.4 mL, 50 mmol, 2.0 equiv) in dichloromethane (250 mL) was added a solution of dimethyl sulfoxide (4.4 mL, 63 mmol, 2.5 equiv) in dichloromethane dropwise at –78 °C. The mixture was stirred for 30 min before a solution of alcohol **58b** (5.8 g, 25 mmol, 1 equiv) in dichloromethane (25 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 1 h before triethylamine (17 mL, 0.13 mol, 5.0 equiv) was added. The reaction was stirred for 30 min at –78 °C and 4 h at 23 °C. Excess base was quenched by the addition of saturated aqueous ammonium chloride solution (100 mL). The biphasic mixture was extracted with diethyl ether (3 × 200 mL). The combined organic layers were washed with concentrated aqueous sodium chloride solution (200 mL) and dried over sodium sulfate. The dried solution was filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane) afforded aldehyde **85b** as colorless oil (5.7 g, 99%). **Analytical**

Data for 85b: The physical data were identical in all respects to those previously reported [54].

*3.53. ethyl (Z)-5-(6-ethyl-1,1,2-trimethyl-1,2-dihydronaphthalen-2-yl)pent-4-enoate (**86b**)*

To a stirred suspension of [3-(ethoxycarbonyl)propyl]triphenylphosphonium bromide (17 g, 38 mmol, 1.50 equiv) in tetrahydrofuran (150 mL) was added sodium bis(trimethylsilyl)amide (1.0 M in THF, 12.6 mL, 12.6 mmol, 1.70 equiv) at 0 °C. The yellow-orange mixture was stirred for 30 min at 0 °C and was then cooled to −78 °C. A solution of aldehyde **85b** (5.7 g, 25 mmol, 1 equiv) in tetrahydrofuran (20 mL) was added slowly. After 15 min, the reaction was allowed to warm to 23 °C and stirred at 23 °C for 5 h. Excess amide was quenched by addition of saturated aqueous ammonium chloride solution (100 mL). The mixture was extracted with diethyl ether (3 × 300 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL) and the washed solution was dried over sodium sulfate. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane) to afford the title compound **86b** (7.0 g, 86%) as a colorless oil. **Analytical Data for 86b:** The physical data were identical in all respects to those previously reported [54].

*3.54. (Z)-5-(6-ethyl-1,1,2-trimethyl-1,2-dihydronaphthalen-2-yl)-1-(pyrrolidin-1-yl)pent-4-en-1-one (**87b**)*

The ester **86b** (7.0 g, 21 mmol, 1 equiv) was dissolved in dry and colorless pyrrolidine (26 mL, 0.32 mol, 15 equiv) in a pressure tube under argon. The tube was sealed and heated at 100 °C. The reaction mixture was stirred for 60 h and then allowed to cool to 23 °C. Excess pyrrolidine was removed under reduced pressure. Purification by flash column chromatography on silica gel (50% ethyl acetate in cyclohexane) afforded the title compound **87b** (7.5 g, 99%) as a pale-yellow oil. **Analytical Data for 87b:** The physical data were identical in all respects to those previously reported [54].

*3.55. 7-ethyl-3,4,4-trimethyl-2a,3,4,8b-tetrahydro-3,1-prop[1]enocyclobuta[a]- naphthalen-2(1H)-one (**90b**)*

To a vigorously stirred solution of freshly distilled trifluoromethanesulfonic anhydride (4.50 mL, 26.8 mmol, 1.30 equiv) in dry 1,2-dichloroethane (270 mL) at 80 °C was added dropwise a solution of amide **87b** (7.25 g, 20.6 mmol, 1 equiv) and 2,4,6-collidine (3.54 mL, 26.8 mmol, 1.30 equiv) in 1,2-dichloroethane (270 mL) via a dropping funnel over a period of 3.5 h. The initial yellowish reaction mixture turned red-brownish, stirring was continued at 80 °C for 20 h and then the reaction mixture was concentrated under reduced pressure. To the crude iminium salt was added tetrachloromethane (100 mL) and water (100 mL) and the dark brown mixture was heated at reflux at 80 °C for 5 h under an atmosphere of argon. The organic layer was separated and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over sodium sulfate and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane grading to 10% ethyl acetate in cyclohexane) afforded cyclobutanone **90b** (4.8 g, 83%) as a pale yellowish oil that solidified upon storage. **Analytical Data for 90b:** The physical data were identical in all respects to those previously reported [54].

*3.56. 7-ethyl-11-hydroxy-3,4,4-trimethyl-2a,3,4,8b-tetrahydro-3,1- prop[1]enocyclobuta[a]naphthalen-2(1H)-one (**93b**)*

To finely grinded selenium dioxide (21 g, 0.19 mol, 10 equiv) and oven-dried (100 °C) fine white quartz sand (21 g, 0.35 mol, 19 eq, particle size >230 mesh) in a flame-dried pressure tube equipped with a magnetic stirring bar was added cyclobutanone **90b** (5.2 g, 19 mmol, 1 equiv). After sparging with nitrogen for 5 min, dry 1,4-dioxane (93 mL) was added. The tube was sealed and the vigorously stirred reaction mixture was heated at 120 °C for 6 h. The reaction mixture was cooled to 23 °C and filtered through a pad of Celite®. The Celite® was washed with ethyl acetate (200 mL) and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1% ethyl acetate in cyclohexane initially, grading to 10% ethyl acetate in cyclohexane, grading to 25% ethyl acetate in cyclohexane, grading to 50% ethyl acetate in cyclohexane) afforded slightly impure **93b** (1.21 g) as an orange oil. Cyclobutanone **90b** (3.38 g, 65%) was recovered and used in the next cycle following the same procedure. After four cycles, the product fractions were combined and collectively purified by flash column chromatography on silica gel (dichloromethane grading to 10% ethyl acetate in dichloromethane) to afford the allylic alcohol **93b** (2.42 g, 44%) as a slightly yellow wax. **Analytical Data for 93b:** The physical data were identical in all respects to those previously reported [54].

*3.57. 8-ethyl-4,5,5-trimethyl-3a,4,5,9b-tetrahydro-4,1-prop[1]enonaphtho[1,2- c]furan-3,12(1H)-dione (**94b**)*

A flask charged with allylic alcohol **93b** (1.27 g, 4.29 mmol, 1 equiv) and copper(I) thiophene-2-carboxylate (82 mg, 0.43 mmol, 0.10 equiv) was sparged with oxygen for 5 min. Water saturated benzene (11 mL) was added and the suspension was stirred till the allylic alcohol was solved completely. Pivaldehyde (3.26 mL, 30.0 mmol, 7 equiv) was added in seven portions (1 equivalent/hour). The green-blueish reaction mixture was stirred after complete addition at 23 °C for 18 h. Another portion of copper(I) thiophene-2-carboxylate (82 mg, 0.43 mmol, 0.10 equiv) was added and the mixture was stirred for 5 h. Excess peroxy-species were quenched by the addition of saturated aqueous sodium thiosulfate solution (5 mL) and saturated aqueous sodium bicarbonate solution (25 mL). The biphasic mixture was extracted with dichloromethane (4 × 30 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered and concentrated under reduced pressure. The crude product was solved in dichloromethane (40 mL). Sodium bicarbonate (1.08 g, 12.9 mmol, 3.00 equiv) and Dess–Martin periodinane (3.64 g, 8.58 mmol, 2.00 equiv) were added at 0 °C. The reaction was stirred for 15 min at 0 °C and 1.5 h at 23 °C. Excess periodinane was quenched by the addition of saturated aqueous sodium thiosulfate solution (10 mL) and saturated aqueous sodium bicarbonate solution (50 mL). The biphasic mixture was extracted with dichloromethane (4 × 30 mL). The combined organic layers were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane) afforded lactone **94b** (445 mg, 33%) and regioisomeric lactone **95b** (433 mg, 32%) as both colorless crystalline solids. **Analytical Data for 94b and 95b:** The physical data were identical in all respects to those previously reported [54].

*3.58. Salimabromide (**7**)*

A flask charged with lactone **94b** (438 mg, 1.41 mmol, 1 equiv) and silver trifluoroacetate (935 mg, 4.23 mmol, 3.00 equiv) was sparged with nitrogen. Trifluoroacetic acid (10 mL) was added and the mixture was stirred at 0 °C until a clear solution was formed. Bromine (0.22 mL, 4.2 mmol, 3.0 equiv) was added dropwise under rigorous stirring. The white-orange suspension was stirred for 10 min at 0 °C. Excess bromine and trifluoroacetic acid were quenched by the addition of saturated aqueous sodium thiosulfate

solution (10 mL) and saturated aqueous sodium bicarbonate solution (250 mL). The suspension was extracted with dichloromethane (4 × 50 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel afforded salimabromide (**7**) (296 mg, 45%) and monobrominated product (7-bromo) (115 mg, 21%) as both colorless crystalline solids. The physical data were identical in all respects to those previously reported [10,54].

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Author contributions

† M.S. and A.S.G. contributed equally

Supplementary data

Supplementary data related to this article can be found at "XY".

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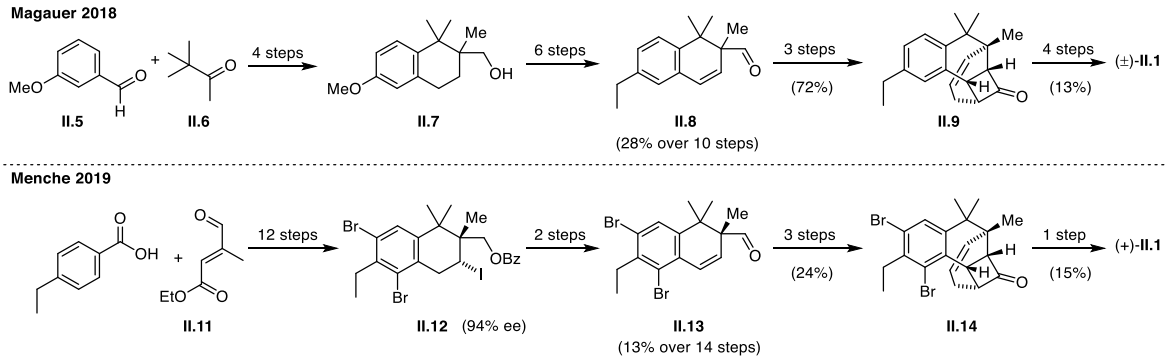
2.3 Conclusion & Outlook - derivative synthesis of salimabromide

This first successful total synthesis of salimabromide (**II.1**) features a route with several advantages. Especially in view of the very recently finished synthesis of salimabromide by Menche following the same strategy of a keteniminium mediated cycloaddition and a late-stage oxidation strategy of the carbon framework, several aspects become very evident.[103] The setting of the quarternary carbon centers in the early phase of the route required a multi-step protocol that we could avoid by developing an unprecedented reaction cascade featuring a Wagner–Meerwein rearrangement of an epoxide followed by an intramolecular Friedel–Crafts alkylation. This afforded tetraline **II.7** in a racemic fashion in only four steps. However, Menche pursued an enantioselective pathway and was able to synthesize the brominated derivative **II.12** within twelve steps in an optical purity of 94% ee by employing an asymmetric Denmark crotylation.[104] To reach a comparable intermediate, our route required further six steps to afford **II.6** in 28% yield over ten steps. Yet this substrate still lacks the bromide substitutents in comparison to **II.13**. Unfortunately these seem to highly influence the subsequent three step sequence of chain elongation by Wittig olefination, amide formation and [2+2] cycloaddition. This structural variation lead to a yield drop of 2/3 in the route of Menche compared to the less unsubstituted **II.8** towards **II.9**, synthesized by our group. From here on we followed a four step sequence including a tedious allylic oxidation affording salimabromide in 13% over four steps. Menche could generate salimabromide in a single step from **II.14** by performing the allylic oxidation and the Baeyer–Villiger oxidation in a one-pot procedure in 15% yield.



Scheme 2-1: *Comparative overview between the asymmetric total synthesis of Menche and our racemic route.*

Considering a late-stage bromination in our route, the corresponding lactone **II.15** is a very important branching point for structure–activity relationship (SAR) studies of the core skeleton

[103] A. Palm, C. Knopf, B. Schmalzbauer, D. Menche, *Org. Lett.*, **2019**, *21*, 1939–1942.
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(Figure 2-1). Major aspects include the role of the bromide substituents and the ethyl side chain on the arene core. As a byproduct during the bromination with silvertrifluoroacetate and elemental bromine, we observed the mono-brominated derivative **II.16**, that can give indications about the role of the second bromide substituent. Non-brominated **II.15** might give interesting insights as well. With the methoxy derivative **II.17** in hand, we could synthesize derivative **II.18**, that bears only the structural difference of an oxygen linker instead of a methylene unit. During the Baeyer-Villiger oxidation towards **II.15**, lactone **II.19** was formed as an undesired byproduct. Assuming that the carbonyl groups of the enone and the lactone act as hydrogen bonding acceptors in enzyme pockets, it is noteworthy that the distance between these two oxygen atoms diverges only by 1.52 Ångstrom in **II.19** compared to lactone **II.15**. This structural similarity prompted us to synthesize derivatives **II.20**, **II.21** and **II.22** in order to compare their bioactivity to salimabromide (**II.1**) and to learn more about its unique structure.

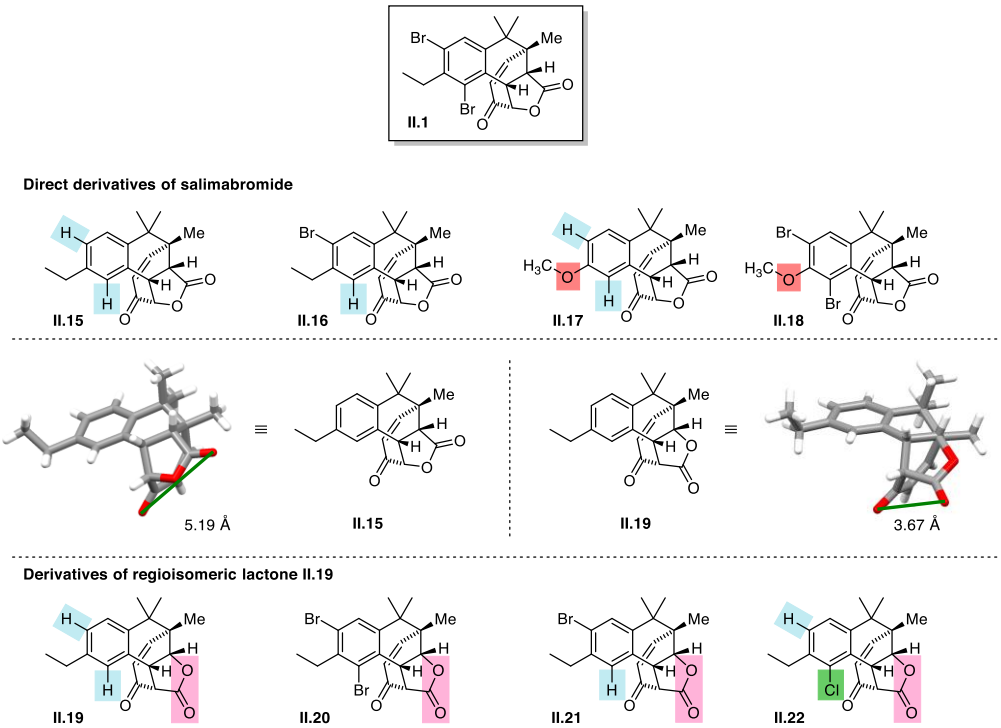


Figure 2-1: *Derivatives of salimabromide for structure-activity relationship studies. Structural differences in comparison to salimabromide (**II.1**) highlighted by colored boxes.*

A very interesting and important finding was done by Menche in his succesfull asymmetric total synthesis of salimabromide (**II.1**). During chiral HPLC analysis of his synthetic material in order to compare its absolute stereochemistry to the natural product, they discovered an almost racemic appearance of natural salimabromide. In the sample that was received directly from König, analysis revealed an ee value of only 4% for the original isolated salimabromide sample from 2013. On the

one hand, this finding raises further questions about the biogenesis of salimabromide and its unique carbon skeleton but increases the impact of our racemic route for further bioactivity studies, on the other hand.

Chapter III

Experimental Part

1 Supporting information to chapter I – 2.1

1.1 General experimental details

All reactions were carried out with magnetic stirring, and if moisture or air sensitive, under nitrogen or argon atmosphere using standard Schlenk techniques in oven-dried glassware (150 °C oven temperature). If required glassware was further dried under vacuum with a heat-gun at 650 °C. External bath temperatures were used to record all reaction temperatures. Low temperature reactions were carried out in a Dewar vessel filled with acetone/dry ice (T between –78 °C and 0 °C) or distilled water/ice (0 °C). High temperature reactions were conducted using a heated silicon oil bath in reaction vessels equipped with a reflux condenser or in a pressure tube. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled over sodium and benzophenone prior to use. Dichloromethane (CH_2Cl_2), was distilled over calcium hydride under a nitrogen atmosphere. All other solvents were purchased from Acros Organics as 'extra dry' reagents. All other reagents with a purity > 95% were obtained from commercial sources (Sigma Aldrich, Acros, Alfa Aesar and others) and used without further purification.

Flash column chromatography was carried out with Merck silica gel 60 (0.040-0.063 mm). Analytical thin layer chromatography (TLC) was carried out using Merck silica gel 60 F254 glass-backed plates and visualized under UV light at 254 nm. Staining was performed with ceric ammonium molybdate (CAM) or by staining with an aqueous anisaldehyde solution and subsequent heating.

NMR spectra (^{1}H NMR and ^{13}C NMR) were recorded in deuterated chloroform ($CDCl_3$), benzene (C_6D_6), acetone (acetone-d_6), dimethylsulfoxide (DMSO-d_6) or methanol (MeOD-d_4) on a Bruker Avance III HD 400 MHz spectrometer equipped with a CryoProbe™, a Varian VXR400 S spectrometer, a Bruker AMX600 spectrometer or a Bruker Avance III HD 800 MHz spectrometer equipped with a CryoProbe™ and are reported as follows: chemical shift δ in ppm (multiplicity, coupling constant *J* in Hz, number of protons) for ^{1}H NMR spectra and chemical shift δ in ppm for ^{13}C NMR spectra. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, br = broad, m = multiplet, or combinations thereof. Residual solvent peaks of $CDCl_3$ (δ_H = 7.26 ppm, δ_C = 77.16 ppm), C_6D_6 (δ_H = 7.16 ppm, δ_C = 128.06 ppm), DMSO-d_6 (δ_H = 2.50 ppm, δ_C = 39.52 ppm), acetone-*d6* (δ_H = 2.05 ppm, δ_C = 29.84 ppm) and MeOD-d_4 (δ_H = 3.31 ppm, δ_C = 49.00 ppm) were used as internal reference. NMR spectra were assigned using information ascertained from COSY, HMBC, HSQC and NOESY experiments.

High resolution mass spectra (HRMS) were recorded on a Varian MAT CH7A or a Varian MAT 711 MS instrument by electron impact (EI) or electrospray ionization (ESI) techniques at the Department of Chemistry, Ludwig-Maximilians-University Munich.

Infrared spectra (IR) were recorded from 4000 cm^{-1} to 600 cm^{-1} on a PERKIN ELMER Spectrum BX II, FT-IR instrument. For detection a SMITHS DETECTION DuraSampl*IR* II Diamond ATR sensor was used. Samples were prepared as a neat film or a thin powder S3 layer. IR data in frequeny of absorption (cm^{-1}) is reported as follows: w = weak, m = medium, s = strong, br = broad or combinations thereof.

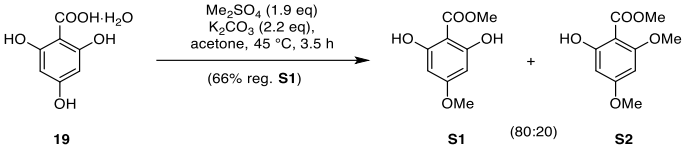
Melting Points were measured with a BÜCHI Melting Point B-450 instrument in open glass capillaries and are uncorrected.

Optical rotation values were recorded on an Anton Paar MCP 200 polarimeter. The specific rotation is calculated as follows: $[\alpha]_D^{25} = \frac{\propto \times 100}{c \times d}$. Thereby, the wavelength λ is reported in nm and the measuring temperature in °C. α represents the recorded optical rotation, *c* the concentration of the analyte in 10 mg/mL and *d* the length of the cuvette in dm. Thus, the specific rotation is given in 10^{-1}·deg·cm^2 ·g^{-1} . Use of the sodium *D* line (λ = 589 nm) is indicated by *D* instead of the wavelength in nm. The sample concentration as well as the solvent is reported in the relevant section of the experimental part.

X-ray diffraction analysis was carried out by Dr. Peter Mayer (Ludwig-Maximilians-Universität München). The data collections were performed an a Bruker D8Venture using MoKα-radiation (λ = 0.71073 Å, graphite monochromator). The CrysAlisPro software (version 1.171.33.41) was applied for the integration, scaling and multi-scan absorption correction of the data. The structures were solved by direct methods with SIR9713 and refined by least-squares methods against F2 with SHELXL-97.14. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. Further details are summarized in the tables at the different sections. Plotting of thermal ellipsoids in this document and in the main text was carried out using Ortep-3 for Windows.

High Pressure hydrogenation experiments were carried out by Mario Wiesenfeldt (Westfälische Wilhelms-Universität Münster, group of Prof. Dr. Frank Glorius) in Berghof high pressure Reactors using hydrogen gas.

All yields are isolated, unless otherwise specified.

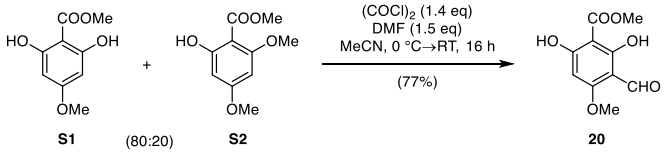


Ester S1 To a stirred suspension of 2,4,6-trihydroxybenzoic acid hydrate (**19**) (10.2 g, 54.0 mmol, 1.00 eq) and potassium carbonate (16.4 g, 119 mmol, 2.20 eq) in acetone (300 mL) at 45 °C was added dimethyl sulfate (9.7 mL,12.9 g, 103 mmol, 1.90 eq). The solution was stirred for 3.5 h and water (120 mL) was added subsequently. The mixture was stirred another 30 min at 45 °C and extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were washed with brine (300 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by FCC (4:1→3:1; hexane: ethyl acetate) to afford a mixture of **S1** and **S2** (8.88 g, 66% in respect to **S1**) in a ratio of 80:20 as a colorless crystalline solid.

R_f: 0.31 (hexanes:EtOAc 4:1), **m.p.** 103–111 °C (Lit.: 114 – 116 °C for pure **S1**)
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (br s, 2H), 6.03 (s, 2H), 4.03 (s, 3H), 3.78 (s, 3H) ppm.
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.76, 166.53, 162.44 (br), 94.55, 94.02, 55.58, 52.64 ppm.
IR (ATR): $\tilde{\nu}_{max}$= 3408 (m), 3021 (w), 2961 (w), 2853 (w), 1644 (s), 1579 (s), 1511 (m), 1483 (w), 1444 (w), 1427 (m), 1344 (m), 1309 (m), 1252 (s), 1181 (s), 1145 (s), 1102 (s), 1071 (s), 1031 (s), 961 (m), 938 (m), 821 (s), 790 (m), 722 (m), 697 (m), 660 (w) cm^{-1}
HRMS (EI): calc. for $C_9H_{10}O_5$ $[M]^+$: 198.0523, found: 198.0531.

The reported data match those previously reported.[105]

An analytical pure sample was received by deformylation of **20**. The melting point measured is valid for the received mixture with **S2**.



Aldehyde 20 To a solution of **S1** (8.25 g, 80% pure, 33.3 mmol, 1.0 eq) in dry acetonitrile (105 mL) under N_2 at 0 °C was added dry DMF (3.87 mL, 3.65 g, 49.9 mmol, 1.5 eq). Oxalyl chloride (3.93 mL, 5.81 g, 45.8 mmol, 1.4 eq) was added dropwise, what caused a strong gas evolution. The clear solution was stirred for 30 min at 0 °C and 15 h at RT. The formed colorless precipitate was filtered off, washed with acetonitrile, suspended in water (100 mL) and heated for 2 h at 100 °C

[105] B. S. Balgir, L. N. Mander, S. T. K. Mander, *Austr. J. Chem.*, **1973**, *26*, 2459–2472.

under N_2. The suspension was cooled to 0 °C and the solid was filtered off, washed with water and dried under reduced pressure to afford aldehyde **20** (5.82 g, 26.6 mmol, 77%) as off-white solid.

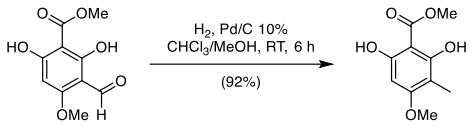
R_f: 0.38 (hexanes:EtOAc 3:1), **m.p.** 173 °C (Lit: 177 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ 14.28 (s, 1H), 12.94 (s, 1H), 10.04 (s, 1H), 5.98 (s, 1H), 3.98 (s, 3H), 3.91 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.93, 172.38, 171.51, 168.54, 166.99, 104.91, 95.56, 91.50, 56.34, 52.79 ppm.

IR (ATR): $\tilde{\nu}_{max}$= 2961 (w), 1715 (w), 1658 (m), 1606 (s), 1579 (s), 1470 (w), 1440 (s), 1406 (m), 1389 (w), 1338 (s), 1285 (m), 1248 (s), 1206 (s), 1170 (s), 1127 (m), 1098 (s), 988 (m), 956 (w), 933 (m), 886 (s), 837 (m), 813 (s), 790 (m), 737 (w), 705 (m) 677 (w) cm^{-1}

HRMS (EI): calc. for $C_{10}H_{10}O_6$ $[M]^+$: 226.0472, found: 226.0477.



20 S3

Cresol S3 To a solution of **20** (226 mg, 1.00 mmol, 1.0 eq) in a mixture of $CHCl_3$ and MeOH (2:1, 5 mL) was added Pd/C 10% (0.10 eq, 106 mg). The gas volume was replaced by hydrogen by evacuating and refilling (3 ×). The suspension was vigourously stirred for 6 h at RT. Subsequently the reaction mixture was filtered over a plug of celite, washed with ethyl acetate and concentrated under reduced pressure. The crude product was purified by FCC (6:1→5:1, hexanes:EtOAc) to afford the product **S3** (195 mg, 0.92 mmol, 92%) as a colorless solid.

R_f: 0.43 (hexanes:EtOAc 3:1), **m.p.** 132.4 °C (Lit[106]: 132–133 °C)

^{1}H NMR (400 MHz, Benzene-d_6) δ 10.15 (b s, 2H), 6.11 (s, 1H), 3.20 (s, 3H), 3.02 (s, 3H), 2.34 (s, 3H) ppm.

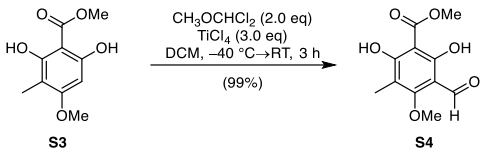
^{13}C NMR (101 MHz, C_6D_6) δ 170.24, 164.83, 161.51, 159.56, 105.01, 94.12, 91.82, 55.09, 51.55, 7.95 ppm.

IR (ATR): $\tilde{\nu}_{max}$= 3411 (m), 2960 (w), 1656 (s), 1638 (s), 1583 (s), 1502 (w), 1451 (m), 1435 (m), 1413 (w), 1390 (w), 1365 (w), 1344 (m), 1314 (m), 1246 (s), 1204 (m), 1197 (m), 1156 (s), 1134 (s), 1079 (s), 1001 (w), 979 (m), 938 (m), 864 (w), 806 (s), 794 (s), 778 (w), 754 (s), 722 (w), 681 (m), 666 (m) cm^{-1}

[106] A. Robertson, W. B. Whalley, *J. Chem. Soc.*, **1950**, *0*, 1882–1884.

HRMS (EI): calc. for $C_{10}H_{12}O_6$ $[M]^+$: 212.0679, found: 212.0678.

The reported data match those previously reported.[107]



Aldehyde S4 To a solution of **S3** (212 mg, 1.00 mmol, 1.0 eq) and 1,1-dichlorodimethyl ether (178 µL, 230 mg, 2.00 mmol, 2.0 eq) in DCM (4.00 mL) was added neat titanium tetrachloride (331 µL, 569 mg, 3.00 mmol, 3.0 eq) at −35 °C. The cooling bath was removed and the red solution was allowed to warm up to RT under stirring. The reaction was monitored by TLC and quenched with 10% $HCl_{(aq)}$ (5 mL) after 3 h. The crude reaction mixture was extracted with EtOAc (3 ×), washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Crude aldehyde **S4** (237 mg, 0.99 mmol, 99%) was obtained as an off-white solid.

R_f: 0.47 (hexanes:EtOAc 3:1), **m.p.** 120.6–123.3 °C (Lit:[108] 122 °C)

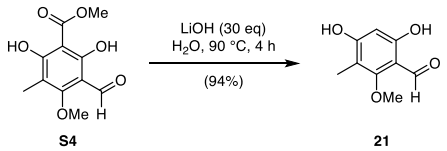
^{1}H NMR (400 MHz, $CDCl_3$) δ 13.82 (s, 1H), 13.11 (s, 1H), 10.00 (s, 1H), 4.00 (s, 3H), 3.88 (s, 3H), 2.09 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.78, 171.72, 170.81, 166.32, 166.02, 110.87, 107.85, 98.15, 63.11, 52.96, 8.33 ppm.

IR (ATR): $\tilde{\nu}_{max}$= 2930 (w), 2695 (w), 1640 (s), 1583 (s), 1439 (m), 1423 (m), 1394 (m), 1377 (m), 1353 (m), 1335 (m), 1285 (m), 1230 (s), 1159 (s), 1117 (s), 1086 (m), 1025 (w), 989 (m), 958 (s), 928 (m), 890 (w), 830 (s), 804 (s), 758 (w), 715 (w) 700 (w) cm^{-1}

HRMS (EI): calc. for $C_{10}H_{12}O_6$ $[M]^+$: 240.0628, found: 240.0624.

The reported data match those previously reported.[109]

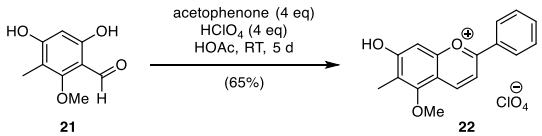


Aldehyde 21 Ester **S4** (961 mg, 4.00 mmol, 1.0 eq) and $LiOH{\cdot}H_2O$ (5.04 g, 120 mmol, 30 eq) were dissolved in water (120 mL). The flask was purged with nitrogen for 5 min. The reaction mixture

[107] G. P. Schiemenz, H. Behrens, C. P. Ebert, K. Maienschein, J.-M. Schröder, *Z. Naturforsch. B*, **1985**, *40*, 681–692.
[108] A. Robertson, W. B. Whalley, *J. Chem. Soc.*, **1950**, *0*, 1882–1884.
[109] G. P. Schiemenz, H. Behrens, C. P. Ebert, K. Maienschein, J.-M. Schröder, *Z. Naturforsch. B*, **1985**, *40*, 681–692.

was stirred for 4 h at 90 °C in an oil bath. After complete consumption of the starting material (monitored by TLC) the mixture was cooled to RT and acidified by addition of $HCl_{(aq)}$ (~65 mL, 2 M, Attention: Gas evolution at the end!). The precipitate was filtered off, washed with water and dried under reduced pressure. The aqueous filtrate was extracted with DCM (3 ×). The combined organic phases were dried over Na_2SO_4, combined with the solid and the solvents were removed under reduced pressure. The crude product was purified by FCC (DCM:MeOH, 97:3) to afford aldehyde **21** (683 mg, 3.75 mmol, 94%) as an off-white crystalline solid.

R_f: 0.27 (hexanes:EtOAc 3:1), **m.p.** 176.3–177 °C (decomposition starts at 165 °C)
^{1}H NMR (400 MHz, MeOD) δ 9.95 (s, 1H), 6.09 (s, 1H), 3.83 (s, 3H), 2.02 (s, 3H) ppm.
^{13}C NMR (101 MHz, MeOD) δ 193.61, 167.26, 164.39, 164.32, 111.33, 109.46, 99.01, 63.53, 8.19 ppm.
IR (ATR): $\tilde{\nu}_{max}$= 3194 (br, w), 2938 (w), 1605 (s), 1474 (m), 1373 (s), 1353 (m), 1313 (m), 1262 (s), 1244 (s), 1178 (m), 1151 (s), 1095 (s), 1007 (m), 934 (m), 878 (w), 825 (m), 804 (w), 746 (s), 663 (m) cm^{-1}
HRMS (EI): calc. for $C_9H_{10}O_4$ $[M]^+$: 182.0574, found: 182.0580.



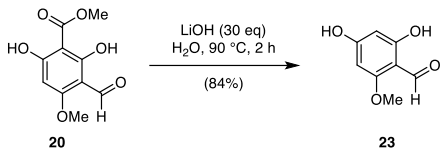
Dracorhodin perchlorate 22 Aldehyde **21** (650 mg, 3.57 mmol, 1.0 eq) was suspended in acetic acid (7.14 mL). Acetophenone (1.71 g, 1.66 mL, 14.3 mmol, 4.0 eq) and $HClO_{4(aq)}$ (11.6 M, 1.23 mL, 4.0 eq) were added and the mixture was stirred at RT for 5 days. The bright orange solid was filtered off, washed with Et_2O and dried *in vacuo*. Dracorhodin perchlorate **22** (846 mg, 65%) was obtained as fine orange crystals.

m.p. 238 °C (decomp., Lit:[110] 227–230 °C)
^{1}H NMR (400 MHz, MeOD) δ 9.31 (d, *J* = 8.6 Hz, 1H), 8.46 – 8.39 (m, 3H), 7.86 – 7.80 (m, 1H), 7.74 (t, *J* = 7.7 Hz, 2H), 7.37 (s, 1H), 4.08 (s, 3H), 2.38 (s, 3H) ppm.
^{13}C NMR (101 MHz, MeOD) δ 172.48, 172.11, 159.62, 158.72, 151.23, 136.78, 131.20, 130.69, 130.03, 125.56, 118.19, 113.30, 99.25, 64.12, 9.83 ppm.
IR (ATR): $\tilde{\nu}_{max}$= 3071 (w br), 1630 (m), 1596 (w), 1583 (w), 1532 (s), 1446 (m), 1388 (s), 1336 (s), 1301 (m), 1270 (w), 1242 (s), 1196 (m), 1168 (w), 1097 (s), 1043 (s), 1015 (s), 996 (s), 950

[110] A. Robertson, W. B. Whalley, J. Yates, *J. Chem. Soc.*, **1950**, *0*, 3117–3123.

(m), 930 (m), 911 (m), 881 (w), 846 (ss), 787 (s), 754 (s), 706 (w), 683 (m), 668 (w) cm^{-1}

HRMS (ESI): calc. for $C_{17}H_{15}O_3$ $[M\text{-}ClO_4]^+$: 267.1016, found: 267.1014.



Aldehyde 23 Ester **20** (226 mg, 1.00 mmol, 1.0 eq) and $LiOH{\cdot}H_2O$ (1.26 g, 30.0 mmol, 30 eq) were suspended in water (30 mL) in a 50 mL flask. The flask was capped with a septa and purged with nitrogen for 5 min. The mixture was stirred in an oil bath at 90 °C. The reaction turned into a clear yellow solution after approx. 45 minutes. After complete consumption of the starting material indicated by TLC the reaction was cooled to RT after 2 h and acidified carefully with $HCl_{(aq)}$ (~17 mL, 2 M, Attention: Gas evolution at the end!). The precipitated crude product was extracted with DCM (4 ×), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by FCC (DCM:MeOH, 97:3) afforded aldehyde **23** (141 mg, 84%) as colorless crystalline needles.

R_f: 0.13 (hexanes:EtOAc 3:1), **m.p.** 209 °C (decomp., Lit:[5] 203 °C)

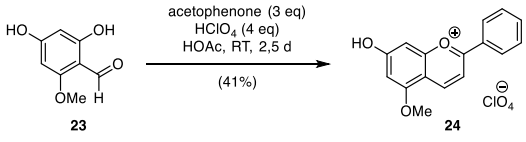
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (s, 1H), 10.95 (s, 1H), 9.94 (s, 1H), 5.98 (d, J = 2.0 Hz, 1H), 5.86 (d, J = 2.0 Hz, 1H), 3.81 (s, 3H) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ 190.72, 167.46, 165.17, 163.98, 104.61, 94.99, 91.23, 55.94 ppm.

IR (ATR): $\tilde{\nu}_{max}$= 3185 (m br), 2584 (w), 1632 (s), 1600 (s), 1584 (s), 1535 (w), 1498 (s), 1476 (s), 1450 (m), 1436 (m), 1380 (w), 1352 (w), 1283 (s), 1227 (s), 1206 (s), 1185 (s), 1161 (s9, 1108 (s), 959 (m), 833 (m), 818 (m), 788 (s), 738 (m), 726 (s), 695 (s), 654 (w) cm^{-1}

HRMS (EI): calc. for $C_8H_8O_4$ $[M]^+$: 168.0417, found: 168.0418.

The reported data match those previously reported.[111]



Nordracorhodin perchlorate 24 Aldehyde **23** (841 mg, 5.00 mmol, 1.0 eq) was suspended in acetic acid (10.0 mL). Acetophenone (1.80 g, 1.75 mL, 15.0 mmol, 3.0 eq) and $HClO_{4(aq)}$ (11.6 M, 1.72 mL, 4.0 eq) were added and the mixture was stirred at RT for 2.5 h. The solid was filtered off,

[111] W. Bradley, R. Robinson, G. Schwarzenbach, *J. Chem. Soc.*, **1930**, *0*, 793–817.

washed with Et_2O and dried *in vacuo*. Nordracorhodin perchlorate **24** (730 mg, 41%) was afforded as a red powder.

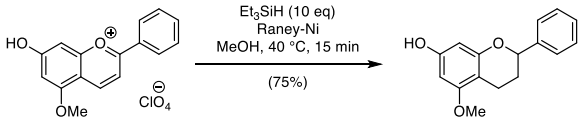
m.p. 245 °C (decomp.)

^{1}H NMR (400 MHz, MeOD) δ 9.31 (dd, *J* = 8.5, 0.7 Hz, 1H), 8.43 – 8.38 (m, 2H), 8.29 (d, *J* = 8.5 Hz, 1H), 7.86 – 7.80 (m, 1H), 7.76 – 7.70 (m, 2H), 7.13 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.86 (d, *J* = 1.9 Hz, 1H), 4.15 (s, 3H) ppm.

^{13}C NMR (101 MHz, MeOD) δ 174.43, 172.25, 161.51, 161.36, 150.76, 136.70, 131.16, 130.67, 129.89, 116.21, 111.97, 101.61, 96.86, 58.04 ppm.

IR (ATR): $\tilde{\nu}_{max}$= 3175 (w br), 3107 (w), 1712 (w), 1642 (s), 1582 (m), 1572 (), 1537 (s), 1500 (w), 1462 (w), 1448 (w), 1437 (w), 1391 (m), 1368 (m), 1337 (s), 1303 (m), 1260 (m), 1240 (s), 1213 (s), 1196 (m), 1180 (m), 1159 (m), 1124 (s), 1109 (s), 1098 (s), 1047 (s), 997 (m), 961 (w), 925 (m), 853 (m), 842 (w), 821 (m), 786 (m), 745 (m), 719 (w), 686 (s), 655 (w) cm^{-1}

HRMS (ESI): calc. for $C_{16}H_{13}O_3$ [*M-ClO$_4$*]$^+$: 253.0860, found: 253.0857.



24 **1**

Flavanol 1 Nordracorhodin perchlorate **24** (556 mg, 1.58 mmol, 1.0 eq) was dissolved in MeOH (80 mL). The flask was capped, purged with nitrogen for 5 min and heated in an oil bath at 40 °C. When the temperature was reached, triethylsilane (1.83 g, 2.52 mL, 15.8 mmol, 10 eq) was added und vigorous stirring, followed by a suspension of Raney-Nickel in water (1 mL, excess). A strong gas evolution was observed accompanied by a decolorization of the orange solution. The reaction was stirred for 15 min at 40 °C and filtered over a plug of celite (Attention: Raney-Ni is pyrophoric!) and washed with ethylacetate. The solvents were removed under reduced pressure and the crude product was purified by FCC (hexanes:ethyl acetate, 3:1) to afford 5-methoxyflavan-7-ol **1** (307 mg, 75%) as a colorless sticky oil. Storage under air reddens the compound due to rearomatizative oxidation. Trituration under hexanes leads to crystallization of the oil affording a colorless solid.

R_f: 0.28 (hexanes:EtOAc 3:1), **m.p.** 95.5–96.7 °C (Lit: 94 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.37 (m, 4H), 7.36 – 7.30 (m, 1H), 6.07 (d, *J* = 2.3 Hz, 1H), 6.04 (d, *J* = 2.3 Hz, 1H), 5.17 (s, 1H), 4.99 (dd, *J* = 10.3, 2.2 Hz, 1H), 3.78 (s, 3H), 2.75 (ddd, *J* =

16.7, 5.8, 3.2 Hz, 1H), 2.64 (ddd, *J* = 16.8, 11.0, 6.1 Hz, 1H), 2.20 (ddt, *J* = 13.6, 5.8, 2.9 Hz, 1H), 2.01 (dtd, *J* = 13.7, 10.7, 5.9 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.78, 156.33, 155.12, 141.67, 128.61, 127.95, 126.15, 103.52, 96.21, 91.60, 77.84, 55.60, 29.59, 19.30 ppm.

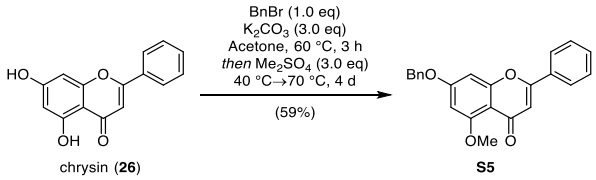
IR (ATR): $\tilde{\nu}_{max}$= 3384 (w br), 2935 (w), 2847 (w), 1601 (s), 1497 (s), 1468 (s), 1366 (w), 1341 (w), 1308 (w), 1267 (w), 1198 (m), 1177 (m), 1138 (s), 1106 (s), 1068 (m) 1045 (m), 1029 (w), 1013 (m), 984 (w), 964 (w), 907 (m), 889 (w), 817 (m), 759 (m), 733 (m), 699 (m) cm^{-1}

HRMS (EI): calc. for $C_{16}H_{16}O_3$ $[M]^+$: 256.1094, found: 256.1089.

The reported data match those previously reported.[112]

Nordracorhodin hexafluorophosphate, that was obtained in 61% yield by a similiar procedure as Nordracorhodin perchlorate **24** (41%) afforded under the same reductive conditions only 21% of the flavanol **1**.

Flavanol **1** could also be obtained by an unoptimized procedure starting with commercially available chrysin in only two steps.



Protected Chrysin S5 To a suspension of chrysin (**26**) (10.2 g, 40.0 mmol, 1.0 eq) and K_2CO_3 (16.6 g, 120 mmol, 3.0 eq) in acetone (120 mL) was added benzyl bromide (6.84 g, 4.75 mL, 40.0 mmol, 1.0 eq). The reaction mixture was stirred for 3 h at 60 °C. After TLC indicated complete consumption of the starting material, the reaction mixture was cooled to 40 °C and dimethyl sulfate (11.38 mL, 15.14 g, 120 mmol, 3.0 eq) was added. The reaction mixture was stirred for 1 day before the temperature was risen to 70 °C. It was stirred for another 3 days at this temperature. The suspension was filtered and the filtrate was concentrated under reduced pressure. The filter cake was combined with the residue and stirred with a mixture of DCM and water. The aqueous phase was acidified with $HCl_{(aq)}$ (2 M) till the pH value was around 2 and extracted after phase separation with DCM (2 × 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by FCC (1. DCM/MeOH 97/3; 2. Ethyl acetate) to afford the product **S5** (8.44 g, 23.6 mmol, 59%) as a colorless solid.

[112] A. Robertson, W. B. Whalley, J. Yates, *J. Chem. Soc.*, **1950**, *0*, 3117–3123.

R_f: 0.25 (EtOAc), **m.p.** 183.2–185.6 °C (Lit: 178–180 °C)

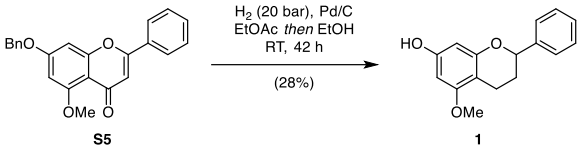
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92 – 7.84 (m, 2H), 7.56 – 7.33 (m, 8H), 6.73 (s, 1H), 6.67 (d, *J* = 2.1 Hz, 1H), 6.47 (d, *J* = 2.0 Hz, 1H), 5.16 (s, 2H), 3.95 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.77, 163.29, 161.08, 160.89, 160.00, 135.75, 131.61, 131.37, 129.08, 128.95, 128.65, 127.80, 126.11, 109.54, 109.17, 96.92, 93.86, 70.69, 56.64 ppm.

IR (ATR): $\tilde{\nu}_{max}$= 2063 (w br), 2363 (w), 1644 (s), 1606 (s), 1578 (m), 1488 (m), 1463 (m), 1449 (m), 1422(w), 1389 (w), 1346 (s), 1303 (w), 1262 (w), 11213 (m), 1190 (m), 1164 (s), 1119 (s), 1101 (m), 1016 (w), 1032 (w), 906 (w), 847 (w), 823 (w), 766 (m), 695 (m) cm^{-1}

HRMS (EI): calc. for $C_{23}H_{18}O_4$ $[M]^+$: 358.1200, found: 358.1202.

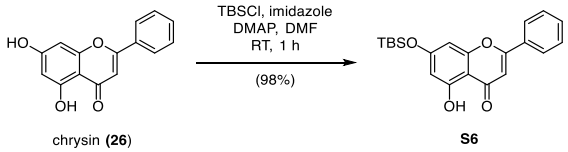
The reported data match those previously reported.[113]



Flavanol 1 Protected Chrysin **S5** (2.84 g, 7.92 mmol, 1.0 eq) and Pd/C 10% (211 mg, 0.198 mmol, 0.025 eq) were suspended in EtOAc (32 mL). The suspension was placed in a steel autoclave that was pressurized to 20 bar H_2 after purging and releasing with hydrogen (10 bars × 3). The suspension was stirred at RT for 18 h. The pressure was released, the solvent was removed under reduced pressure and the crude mixture was resuspended in EtOH (30 mL). The reaction mixture was placed back in the steel reactor and pressurized to 20 bar H_2 according the same procedure as before. The mixture was stirred for 24 h at RT. The pressure was released, the crude solution filtered over a plug of celite and concentrated under reduced pressure. The crude product was purified by FCC (DCM/MeOH; 97:3) to afford flavan-7-ol **4** (558 mg, 28%) as a colorless sticky oil. Storage under air reddens the compound due to rearomatizative oxidation. Trituration under hexanes leads to crystallization of the oil affording a colorless solid.

See previous experiments for analytical data.

[113] T. E. Adams, M. El Sous, B. C. Hawkins, S. Hirner, G. Holloway, M. L. Khoo, D. J. Owen, G. P. Savage, P. J. Scammells, M. A. Rizzacasa, *J. Am. Chem. Soc.*, **2009**, *131*, 1607–1616.



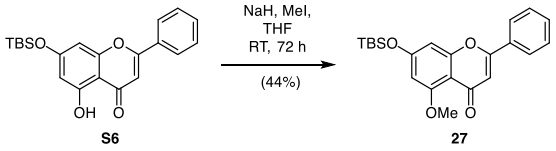
TBS ether S6 Chrysin (**26**) (0.76 g, 3.00 mmol, 1.0 eq), imidazole (266 mg, 3.9 mmol, 1.3 eq) and 4-dimethylaminopyridine (3.7 mg, 0.03 mmol, 0.01 eq) were dissolved in dry DMF (15 mL). To the clear solution was added *tert*-butyldimethylsilyl chloride (0.59 g, 3.9 mmol, 1.3 eq) under argon. The solution was stirred for 1 h at RT. After complete conversion monitored by TLC, the reaction was quenched by addition of diethyl ether (100 mL) and water (15 mL). The aqueous phase was disposed and the organic phase was washed with water (5 × 5 mL) and brine (10 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by FCC (hexanes:ethyl acetate, 6:1) afforded TBS ether **S6** (1.08 g, 98%) as a yellow crystalline solid.

R_f: 0.82 (hexanes:EtOAc 3:1), **m.p.** 146.8 - 147.5 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.69 (s, 1H), 7.92 – 7.85 (m, 3H), 7.58 – 7.48 (m, 3H), 6.67 (s, 1H), 6.46 (d, *J* = 1.9 Hz, 1H), 6.31 (d, *J* = 1.9 Hz, 1H), 1.00 (s, 9H), 0.28 (s, 6H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 182.72, 164.12, 162.51, 162.20, 157.76, 131.97, 131.48, 129.21, 126.45, 106.36, 105.99, 104.09, 98.96, 25.68, 18.39, −4.19 ppm.

HRMS (ESI): calc. for $C_{21}H_{25}O_4Si^+$ $[M+H]^+$: 369,15166, found: 369,15145.



Methylated chrysin 27 NaH (60% in mineral oil, 60 mg, 1.5 mmol, 1.5 eq) was suspended in a flame-dried flask in dry hexane (3 mL) under argon. After stirring for 15 minutes, the organic phase was carefully removed. To the washed sodium hydride was added dry THF (10 mL). The suspension was cooled to 0 °C and TBS protected chrysin **S6** (369 mg, 1.0 mmol, 1.0 eq) was added. The reaction mixture was stirred for 15 minutes at RT before methyl iodide (426 mg, 187 µL, 3.0 mmol, 3.0 eq) was added. The ice bath was removed and the solution was stirred at RT for 72 h before the reaction was quenched by addition of saturated $NH_4Cl_{(aq)}$ solution. The mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by FCC (1. DCM/MeOH, 97:3, 2. Ethyl acetate) afforded the title compound **27** (166 mg, 44%) as a colorless solid.

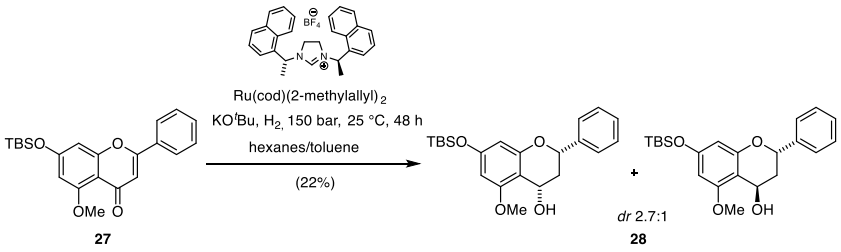
R_f: 0.41 (EtOAc), **m.p.** 151.6–152.2 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 (dd, *J* = 6.5, 2.7 Hz, 2H), 7.46 – 7.38 (m, 3H), 6.60 (s, 1H), 6.48 (d, *J* = 1.9 Hz, 1H), 6.26 (d, *J* = 1.9 Hz, 1H), 3.90 (s, 3H), 0.96 (s, 9H), 0.25 (s, 6H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.56, 160.93, 160.61, 160.53, 159.35, 131.40, 131.09, 128.81, 125.85, 109.59, 108.81, 100.41, 100.21, 56.34, 25.51, 18.18, −4.34 ppm.

IR (ATR): $\tilde{\nu}_{max}$= 2954 (m), 2930 (m), 2858 (m), 1643 (s), 1604 8s9, 1578 (w), 1566 (w), 1462 8w9, 1448 (m), 1416 (m), 1383 (w), 1343 (s), 1310 (w), 1285 (w), 1258 (m), 1212 (m), 1165 (s), 1117 (s), 1098 (w), 1051 (m), 1032 (w), 999 (m), 958 (w), 837 (s), 783 8m), 767 (m), 690 (m), 676 (w) cm^{-1}.

HRMS (ESI): calc. for $C_{22}H_{27}O_4Si^+$ $[M+H]^+$: 383,16731, found: 383,16672.



Flavan-4-ol 28 To a flame-dried Schlenk tube equipped with a magnetic stirring bar was added bis(2-methylallyl)(1,5-cyclooctadiene)ruthenium(II) (9.6 mg, 0.03 mmol, 0.1 eq), (*R*,*R*)-SINpEt·HBF_4 (29.8 mg, 0.064 mmol, 0.12 eq) and potassium *t*-butanolate (10.0 mg; 0.090 mmol, 0.27 eq) in a glove box. The mixture was suspended in dry hexane (1 mL) and stirred at 70 °C for 14 h under argon. The afforded yellow catalyst suspension was transferred to a flame-dried vial equipped with a magnetic stirring bar and protected chrysin **27** (115 mg, 0.30 mmol, 1.0 eq). The suspension was diluted with dry hexane (2 mL) and dry toluene (3 mL) and placed in a high-pressure stainless-steel autoclave filled with argon. The autoclave was closed and carefully pressurized/depressurized with hydrogen gas thrice before the reaction pressure of 150 bar was adjusted. The reaction mixture was stirred for 48 h in a tempered metal block at 25 °C before the pressure was carefully released. The crude mixture was filtered over a plug of silica and flushed with diethyl ether. Purification by FCC (hexanes:ethyl acetate, 6:1) afforded compound **28** (25.6 mg, 22%) as a colorless oil with a *dr* of 2.7:1.

R_f: 0.54 (***cis***), 0.49 (***trans***) (hexanes:EtOAc 3:1),

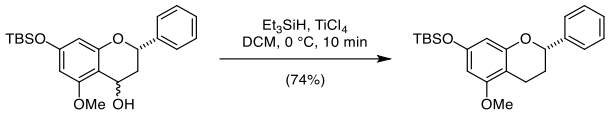
For the major product (***Cis***-product) **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.50 – 7.31 (m, 5H), 6.08 (d, *J* = 1.8 Hz, 1H), 6.04 (d, *J* = 2.0 Hz, 1H), 5.29 – 5.22 (m, 1H), 5.01 (s, 1H), 3.94 (s, 1H), 3.86 (s, 3H), 2.51 (dd, *J* = 13.4, 7.2 Hz, 1H), 2.30 – 2.16 (m, 1H), 0.98 (s, 9H), 0.21 (s, 6H) ppm.

For the major product (***Cis***-product) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.24, 156.74, 156.45,

140.49, 128.74, 128.34, 126.45, 108.01, 101.47, 96.93, 77.22, 63.57, 55.75, 37.98, 25.80, 18.31, −4.27 ppm.

IR (ATR): $\tilde{\nu}_{max}$= 3562 (m), 2956 (m), 2930 (m), 2886 (m), 2858 (m), 1613 (s), 1584 (s), 1490 (m), 1429 (m), 1452 (m), 1390 (w), 1363 (m), 1342 (w), 1318 (w), 1283 (w), 1254 8m), 1209 (m), 1187 (m), 1153 (s), 1114 (w), 1045 (m), 1016 (w), 957 (w), 840 (s), 782 (m), 759 (w), 699 (m) cm^{-1}.

HRMS (EI): calc. for $C_{22}H_{30}O_4Si^+$ $[M]^+$: 386,1908, found: 386,1903.



Chromane S7 Flavan-4-ol **28** (10.8 mg, 27.9 µmol, 1.0 eq) was dissolved under nitrogen in dry DCM (280 µL). The solution was cooled to 0 °C and triethyl silane (13.5 µL, 84 µmol, 3.0 eq) was added. Titanium tetrachloride (1 M in DCM, 84 µL, 84 µmol, 3.0 eq) was added dropwise and the orange-red solution was stirred for 10 minutes. The reaction was quenched by addition of saturated $NaHCO_{3(aq)}$ solution (0.5 mL). The reaction mixture was extracted with EtOAc (3 × 1 mL). The organic phases were combined, filtered through celite and dried over Na_2SO_4. Purification by FCC (hexanes: ethyl acetate, 9:1) afforded chromane **S7** (7.7 mg, 74%) as a colorless oil.

R_f: 0.52 (hexanes:EtOAc, 9:1),

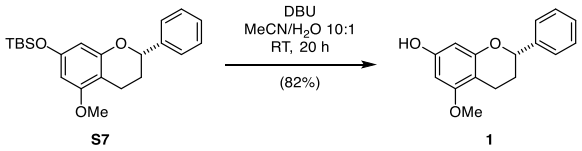
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 – 7.28 (m, 5H), 6.09 (d, *J* = 1.9 Hz, 1H), 6.00 (d, *J* = 1.9 Hz, 1H), 4.97 (dd, *J* = 10.3, 1.6 Hz, 1H), 3.78 (s, 3H), 2.74 (ddd, *J* = 16.7, 5.7, 3.0 Hz, 1H), 2.64 (ddd, *J* = 16.8, 11.0, 6.1 Hz, 1H), 2.19 (ddt, *J* = 12.9, 5.4, 2.4 Hz, 1H), 2.07 – 1.94 (m, 1H), 0.98 (s, 9H), 0.21 (s, 6H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.43, 156.20, 155.20, 141.88, 128.62, 127.93, 126.21, 104.18, 100.91, 96.07, 77.80, 55.56, 29.73, 25.86, 19.47, 18.34, −4.25 ppm.

IR (ATR): $\tilde{\nu}_{max}$= 2954 (m), 2930 (m), 2857 (m), 1613 (s), 1590 (s), 1494 (m), 1450 (m), 1422 (w), 1363 (w), 1254 (w), 1201 (m), 1177 (m), 1151 (s), 1114 8s), 1048 (w), 1019 (w), 967 (w), 854 (s), 841 (s), 780 (m), 758 (w), 699 (m) cm^{-1}.

HRMS (EI): calc. for $C_{22}H_{30}O_3Si^+$ $[M]^+$: 370,19587, found: 370,1954

$[\alpha]_D^{20}$ = −10.1 (c = 0.375, $CHCl_3$)



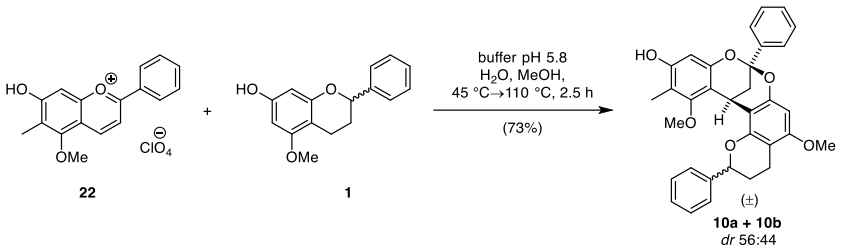
(−)-Methoxyflavanol 1 To a solution of chromane **S7** (7.4 mg, 20 µmol, 1.0 eq) in acetonitrile (200 µL) and water (20 µL) was added DBU (3.0 µL, 20 µmol, 1.0 eq) and the reaction mixture was stirred at RT for 20 h. The reaction was quenched by addition of saturated $NH_4Cl_{(aq)}$ solution and extracted with ethyl acetate (3 ×1 mL). The organic phases were combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by FCC (hexanes:ethylacetate, 9:1) afforded 5-methoxy flavan-7-ol (**1**) (4.2 mg, 82%) as a colorless sticky oil.

Analytical data was identical with racemic product. See racemic synthesis for details.

82% *ee* (HPLC conditions: Chiralcel IA column, heptane/i-PrOH = 97/3, 1.0 mL/min, λ = 269 nm, t_R(major) = 24.0 min, t_R(minor) = 28.2 min),

$[\alpha]_D^{20}$ = −5.7 (c = 0.42, $CHCl_3$)

[Lit][114]: −6.35 (c = 1.94, $CHCl_3$) for natural (2*S*)-5-methoxyflavan-7-ol



Dracoflavan C 10a/b To flavanol **1** (70.0 mg, 273 µmol, 6.0 eq) and dracorhodin perchlorate **22** (16.7 mg, 45.5 µmol, 1.0 eq) was given water (200 µL), MeOH (400 µL) and phosphate buffer 5.8 pH (0.1 M, 200 µL). The addition of the buffer lead to the formation of a red suspension. The vial was capped and placed in a metal block at 45 °C. The reaction mixture was heated up to 110 °C during 30 min and stirred at this temperature for 2 h. The deep-red suspension was cooled down, diluted with water and extracted with EtOAc (3 ×). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The reaction mixture was purified by four FCC purification steps (1. hexanes:ethyl acetate 9:1→6:1, 2./3. DCM:MeOH 98:1, 4. Toluene/EtOAc 10:1) to afford next to recovered flavanol **1** (47.4 mg, 4.1 eq) dracoflavan C (**10a/b**) (17.3 mg, 73%) as a colorless solid in a diastereomeric ratio of 56:44 (**10a**:**10b**). Storage under air leads to reddening of the product.

[114] G. Cardillo, L. Merlini, G. Nasini, P. Salvadori, *J. Chem. Soc., C*, **1971**, 3967–3970.

R_f: 0.42 (hexanes:EtOAc 3:1), **m.p.** ~130 °C (decomp. starts at 100 °C; Lit[115]: 90–95 °C)

^{1}H NMR (800 MHz, Acetone-d_6) δ 8.24 (s, 1H), 8.20 (s, 1H), 7.73 – 7.70 (m, 6H), 7.62 – 7.60 (m, 2H), 6.34 (s, 1H), 6.32 (s, 1H), 6.23 (s, 1H), 6.22 (s, 1H), 5.12 (dd, *J* = 10.4, 2.2 Hz, 1H), 5.02 (dd, *J* = 10.6, 1.8 Hz, 1H), 4.77 (t, *J* = 3.1 Hz, 1H), 4.70 (t, *J* = 3.1 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.53 (s, 3H), 3.38 (s, 3H), 2.73 (ddd, *J* = 16.7, 5.8, 2.9 Hz, 1H), 2.70 – 2.62 (m, 4H), 2.60 (s, 1H), 2.28 (dd, *J* = 13.1, 3.3 Hz, 1H), 2.26 (dd, *J* = 13.2, 3.2 Hz, 2H), 2.25 – 2.22 (m, 2H), 2.20 (dd, *J* = 13.1, 3.0 Hz, 1H), 2.15 (dd, *J* = 13.2, 3.0 Hz, 1H) (m, 1H), 2.14 (s, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 1.98 (s, 3H), 2.00 – 1.93 (m, 2H) ppm.

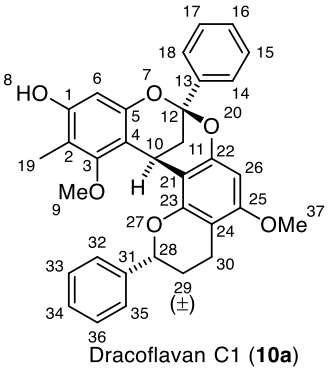
^{13}C NMR (201 MHz, Acetone) δ 157.80, 157.69, 157.66, 157.65, 156.07, 156.01, 153.11, 153.00, 152.79, 152.46, 152.31, 152.06, 143.53, 143.29, 143.24, 142.95, 129.30, 129.11, 129.01, 128.97, 128.34, 128.30, 127.34, 126.95, 126.57, 126.55, 112.48, 112.33, 111.46, 111.36, 108.93, 108.87, 104.66, 104.45, 99.69, 99.68, 99.58, 99.57, 99.14, 99.02, 92.34, 92.29, 78.97, 78.18, 61.04, 60.65, 55.82, 55.79, 35.42, 35.31, 30.62, 30.59, 30.51, 21.98, 21.95, 20.69, 20.20, 9.17, 9.14 ppm.

IR (ATR): $\tilde{\nu}_{max}$= 3408 (w br), 2939 (w), 1612 (s), 1486 (m), 1464 (m), 1448 (m), 1426 (m), 1336 (m), 1278 (w), 1196 (m), 1176 (w), 1114 (s), 1101 (s), 1027 (w), 1011 (w), 970 (w), 955 (w), 910 (m), 808 (w), 762 (m), 732 (m), 699 (m) cm^{-1}

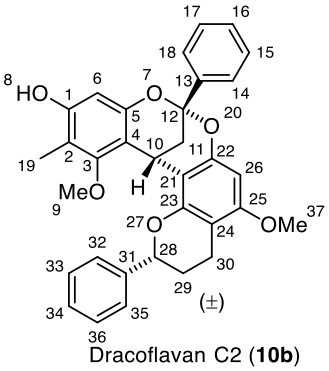
HRMS (ESI): calc. for $C_{33}H_{31}O_6^+$ $[M+H]^+$: 523.2115, found: 523.2117.

Dracoflavan C was characterized as diastereomeric mixture.

[115] A. Arnone, G. Nasini, O. Vajna de Pava, L. Merlini, *J. Nat. Prod.*, **1997**, *60*, 971–975.



Dracoflavan C1 (**10a**)



Dracoflavan C2 (**10b**)

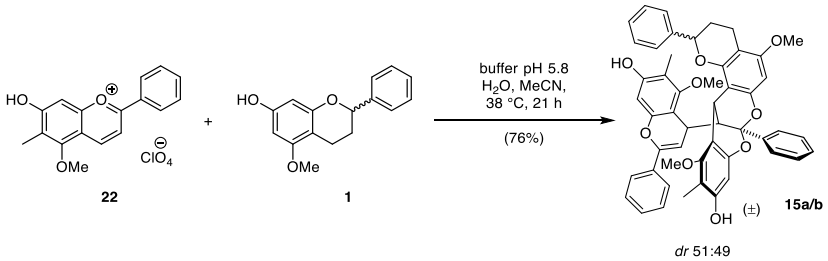
^{1}H NMR comparison with isolated natural product[116]

No.	^{1}H NMR Isolation (acetone-d_6, 250 MHz) dracoflavan C1 (**10a**)	^{1}H NMR Synthetic (acetone-d_6, 800 MHz)	Δ ppm	^{1}H NMR Isolation (acetone-d_6, 250 MHz) dracoflavan C2 (**10b**)	^{1}H NMR Synthetic (acetone-d_6, 800 MHz)	Δ ppm
6	(6.34)	6.34 (s, 1H)	±0.00	(6.32)	6.32 (s, 1H)	±0.00
8	(8.31)	8.24 (s, 1H)	–0.07	(8.27)	8.20 (s, 1H)	–0.07
9	3.52	3.53 (s, 3H)	+0.01	3.37	3.38 (s, 3H)	+0.01
10	4.69 (J = 3.1 Hz)	4.70 (t, J = 3.1 Hz, 1H)	+0.01	4.76 (J = 3.1 Hz)	4.77 (t, J = 3.1 Hz, 1H)	+0.01
11	2.24 (J = 13.2, 3.1 Hz), 2.13 (J = 13.2, 3.1 Hz)	2.26 (dd, J = 13.2, 3.2 Hz, 2H), 2.15 (J = 13.2, 3.0 Hz)	+0.02, +0.02	2.28 (J = 13.2, 3.1 Hz), 2.19 (J = 13.2, 3.1 Hz)	2.28 (dd, J = 13.1, 3.3 Hz, 1H), 2.20 (dd, J = 13.1, 3.0 Hz, 1H)	±0.00, +0.01
14	7.72	7.73 – 7.70	n.d.	7.72	7.73 – 7.70	n.d.
15	7.5 – 7.3	7.5 – 7.3 (m)	n.d.	7.5 – 7.3	7.5 – 7.3 (m)	n.d.
16	7.5 – 7.3	7.5 – 7.3 (m)	n.d.	7.5 – 7.3	7.5 – 7.3 (m)	n.d.
17	7.5 – 7.3	7.5 – 7.3 (m)	n.d.	7.5 – 7.3	7.5 – 7.3 (m)	n.d.
18	7.72	7.73 – 7.70 (m)	+0.01	7.72	7.73 – 7.70	+0.01
19	2.09	2.09 (s, 3H)	±0.00	1.98	1.98 (s, 3H)	±0.00
26	(6.23)	6.23 (s, 1H)	±0.00	(6.22)	6.22 (s, 1H)	±0.00
28	4.99 (J = 10.6, 2.2 Hz)	5.02 (dd, J = 10.6, 1.8 Hz, 1H)	+0.03	5.11 (J = 10.5, 2.4 Hz)	5.12 (dd, J = 10.4, 2.2 Hz, 1H)	+0.01
29	2.25 (J = 2.2 Hz), 1.96 (J = 10.6 Hz)	2.25 – 2.22 (m), 2.00 – 1.93 (m)	n.d.	2.25 (J = 6,1, 3.1, 2.4 Hz), 1.96 (J = 11.1, 10.5, 6.2 Hz)	2.25 – 2.22 (m), 2.00 – 1.93 (m)	n.d.
30	2.69, 2.66	2.70 – 2.62 (m)	n.d.	2.72 (J = 16.8, 6.2, 3.1 Hz), 2.65 (J = 16.8, 11.1, 6.1 Hz)	2.73 (ddd, J = 16.7, 5.8, 2.9 Hz, 1H), 2.66 – 2.62 (m)	+0.01, n.d.
32	7.70	7.73 – 7.70 (m)	n.d.	7.61	7.62 – 7.60 (m, 2H)	n.d.
33	7.5 – 7.3	7.5 – 7.3 (m)	n.d.	7.5 – 7.3	7.5 – 7.3 (m)	n.d.
34	7.5 – 7.3	7.5 – 7.3 (m)	n.d.	7.5 – 7.3	7.5 – 7.3 (m)	n.d.
35	7.5 – 7.3	7.5 – 7.3 (m)	n.d.	7.5 – 7.3	7.5 – 7.3 (m)	n.d.
36	7.70	7.73 – 7.70 (m)	n.d.	7.61	7.62 – 7.60 (m, 2H)	n.d.
37	(3.77)	3.78 (s, 3H)	+0.01	(3.76)	3.77 (s, 2H)	+0.01

[116] A. Arnone, G. Nasini, O. Vajna de Pava, L. Merlini, *J. Nat. Prod.*, **1997**, *60*, 971–975.

^{13}C NMR comparison with isolated natural product[9]

^{13}C NMR Isolation [ppm] (Acetone-d^6, 62.9 MHz)	^{13}C NMR Synthetic [ppm] (Acetone-d^6, 201 MHz)	Δ ppm
157.77	157.80,	+0.03
157.63	157.69, 157.66, 157.65	+0.06, +0.03, +0.02
156.07	156.07	±0.00
155.99	156.01	+0.02
153.08	153.11	+0.03
152.98	153.00	+0.02
152.77	152.79	+0.02
152.43	152.46	+0.03
152.28	152.31	+0.03
152.04	152.06	+0.02
143.50	143.53	+0.03
143.21	143.29, 143.24	+0.08, +0.03
142.92	142.95	+0.03
129.30	129.30	±0.00
129.11	129.11	±0.00
128.99	129.01, 128.97	+0.02, –0.02
128.33	128.34, 128.30	+0.01, –0.03
127.31	127.34	+0.03
126.93	126.95	+0.02
126.54	126.55	+0.01
112.42	112.48	+0.06
112.28	112.33	+0.05
111.45	111.46	+0.01
111.28	111.36	+0.08
108.90	108.93	+0.03
108.83	108.87	+0.04
104.63	104.66	+0.03
104.48	104.45	+0.03
99.66	99.69, 99.68	+0.03 +0.02
99.56	99.58, 99.57	+0.02, +0.01
99.12	99.14	+0.02
98.98	99.02	+0.04
92.31	92.34	+0.03
92.26	92.29	+0.03
78.93	78.97	+0.04
78.14	78.18	+0.04
61.04	61.04	±0.00
60.65	60.65	±0.00
55.78	55.82, 55.79	+0.04, +0.01
35.37	35.42	+0.05
35.27	35.31	+0.04
30.62	30.62, 30.59, 30.51	±0.00, –0.03, –0.11
21.92	21.98, 21.95	+0.06, +0.03
20.68	20.69	+0.01
20.19	20.20	+0.01
9.16	9.17, 9.14	+0.01, –0.02



Benzopyran 15a/b To a solution of flavanol **1** (103 mg, 400 µmol, 4.0 eq) and dracorhodin perchlorate **22** (36.7 mg, 100 µmol, 1.0 eq) in acetonitrile (1.50 mL) under N_2 was given aqueous phosphate buffer 5.8 pH (0.1 M, 0.5 mL) under vigorous stirring whereupon the color of the solution reddened. The reaction mixture was stirred for 21 h at 38 °C. Approximately ¾ of the organic solvent was removed by a stream of nitrogen what caused a phase separation. The mixture was extracted with EtOAc (3×), washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by FCC (hexanes:ethyl acetate, 3:1, loading:toluene) afforded next to recovered flavanol **1** (90 mg, 3.5 eq), benzopyran **15a/b** (29.9 mg, 76%) as an colorless –fast reddening, air sensitive solid in a diasteromeric ratio of 51:49. Concentration after purification by chromatography is carried out at 0°C under reduced pressure.

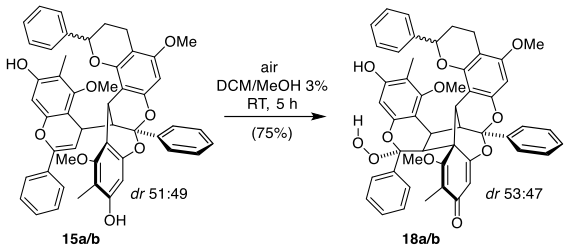
R_f: 0.25 (hexanes:EtOAc 3:1), **m.p.** 135 °C (decomp.)

^{1}H NMR (599 MHz, DMSO-d_6) δ 9.73 (s, 1H), 9.62 (s, 1H), 9.28 (s, 1H), 9.28 (s, 1H), 7.82 – 7.77 (m, 4H), 7.62 – 7.57 (m, 4H), 7.53 – 7.48 (m, 2H), 7.42 – 7.36 (m, 4H), 7.31 (dd, *J* = 18.8, 7.8 Hz, 4H), 7.23 (q, *J* = 6.1 Hz, 2H), 7.16 (dt, *J* = 16.3, 7.7 Hz, 6H), 6.98 – 6.94 (m, 4H), 6.43 (s, 1H), 6.43 (s, 1H), 6.43 (s, 1H), 6.36 (s, 1H), 6.15 (s, 1H), 6.13 (s, 1H), 5.29 (d, *J* = 5.5 Hz, 1H), 5.27 (d, *J* = 5.4 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 4.75 (d, *J* = 10.8 Hz, 1H), 4.33 (s, 1H), 4.21 (s, 1H), 3.69 (s, 3H), 3.67 (s, 3H), 3.48 (ddd, *J* = 7.1, 5.5, 1.8 Hz, 2H), 2.96 (s, 3H), 2.89 (s, 3H), 2.87 (s, 3H), 2.86 (s, 3H), 2.58 – 2.51 (m, 6H), 2.26 – 2.20 (m, 1H), 2.12 – 2.07 (m, 1H), 1.94 (s, 3H), 1.89 (s, 3H), 1.88 – 1.81 (m, 1H), 1.67 – 1.60 (m, 1H), 1.59 (s, 3H), 1.57 (s, 3H) ppm.

^{13}C NMR (151 MHz, DMSO-d_6) δ 156.24, 156.05, 155.99, 155.77, 155.68, 155.02, 152.21, 151.88, 150.70, 150.62, 150.37, 149.79, 149.59, 148.95, 148.54, 148.33, 142.25, 140.57, 140.25, 140.15, 133.58, 128.65, 128.31, 128.20, 128.05, 127.64, 127.02, 126.58, 126.35, 124.86, 124.30, 112.86, 111.70, 111.66, 111.33, 111.19, 110.06, 109.90, 105.84, 105.65, 103.21, 102.69, 100.99, 100.71, 98.78, 98.69, 98.15, 98.08, 97.99, 91.09, 76.35, 75.51, 59.52, 58.69, 58.52, 55.41, 47.88, 47.33, 40.06, 29.55, 29.53, 29.44, 26.34, 21.72, 21.55, 19.31, 18.72, 8.88, 8.67, 8.61 ppm.

IR (ATR): $\tilde{\nu}_{max}$= 3413 (br m), 2939 (m), 2362 (w), 1613 (s), 1493 (m), 1464 (m), 1450 (m), 1425 (m), 11344 (w), 1321 (m), 1300 (m), 1242 (m), 1195 (m), 1120 (s), 1102 (s), 1032 (w), 1006 (w), 964 (m), 901 (w), 828 (w), 765 (m), 763 (m), 699 (m) cm^{-1}

HRMS (EI): calc. for $C_{50}H_{44}O_9$ $[M]^+$: 788.2985, found: 788.3004.



Dragonbloodin Peroxide 18a/b A solution of benzopyran **15a/b** (16.8 mg, 21.3 µmol, 1.0 eq) in DCM/MeOH (97:3, 2.1 mL) was stirred under air at RT in a capped vial until TLC indicated complete consumption of the starting material. After 5 h, the solvent was blown off by a stream of nitrogen. The crude product was purified by FCC (DCM/MeOH 97:3) to afford **18a/b** (13.1 mg, 75%) as a colorless solid with a *dr* of 53:47. A crystal suitable for X-Ray analysis was obtained from $CDCl_3$/hexanes.

Attempted separation by HPLC (acetonitrile/water: 80/20) directly affords dragonbloodin A (11a/b) due to hydrolysis.

R_f: 0.26 (hexanes:EtOAc 1:1), **m.p.** >200 °C (decomposition)

^{1}H NMR (800 MHz, Acetone-d_6**) δ 10.28 (s, 1H), 10.24 (s, 1H), 8.54 (s, 1H), 8.54 (s, 1H), 7.91 – 7.88 (m, 4H), 7.66 – 7.62 (m, 4H), 7.56 (tq, *J* = 7.2, 1.2 Hz, 2H), 7.30 – 7.15 (m, 18H), 7.05 (d, *J* = 7.2 Hz, 2H), 6.47 (s, 1H), 6.46 (s, 1H), 6.11 (s, 1H), 6.08 (s, 1H), 5.43 (s, 1H), 5.43 (s, 1H), 5.32 (t, *J* = 4.0 Hz, 1H), 5.06 (dd, *J* = 9.3, 2.9 Hz, 1H), 3.99 (d, *J* = 4.5 Hz, 1H), 3.86 (d, *J* = 4.5 Hz, 1H), 3.85 (d, *J* = 9.0 Hz, 1H), 3.79 (d, *J* = 9.1 Hz, 1H), 3.72 (s, 6H), 3.61 (d, *J* = 8.8 Hz, 1H), 3.59 (d, *J* = 8.8 Hz, 1H), 3.26 (d, *J* = 4.6 Hz, 1H), 3.25 (s, 3H), 3.24 (d, *J* = 4.6 Hz, 1H), 2.94 (s, 3H), 2.93 (s, 3H), 2.87 (s, 3H), 2.55 – 2.43 (m, 3H), 2.10 – 2.03 (m, 2H), 2.03 (s, 3H), 2.00 (s, 3H), 2.00 – 1.98 (m, 1H), 1.98 – 1.96 (m, 1H), 1.77 – 1.69 (m, 1H), 1.19 (s, 3H), 0.71 (s, 3H) ppm.

^{13}C NMR (201 MHz, Acetone) δ 187.99, 187.77, 171.78, 171.61, 163.82, 163.24, 158.59, 158.54, 157.67, 157.55, 156.54, 154.46, 154.10, 153.30, 153.16, 151.77, 151.67, 143.33, 141.77, 139.92, 139.90, 138.18, 137.70, 129.94, 129.91, 129.21, 129.18, 129.14, 129.05, 128.93, 128.17, 127.90, 127.51, 127.46, 126.64, 126.36, 113.53, 112.86, 112.45, 112.43, 109.18, 109.10, 106.74, 106.09, 105.13, 104.89, 104.84, 104.72, 104.43, 104.35, 101.04, 100.94, 100.81, 100.75, 91.95, 91.89, 78.04, 77.46, 59.49, 58.86, 55.75, 55.28, 55.03, 50.12, 49.72, 48.93, 48.32, 38.84, 38.71, 36.09, 35.80, 32.63, 30.19*, 26.92, 23.32, 19.06, 16.21, 14.35, 9.57, 9.52, 8.79, 8.76 ppm.

IR (ATR): $\tilde{\nu}_{max}$= 3250 (m br), 2923 (m), 2853 (w), 1675 (m), 1602 (s), 1581 (s), 1462 (w), 1446(m), 1344 (m), 1313 (w), 1238 (m), 1198 (w), 1176 (m), 1123 (s), 1089 (s), 1001 (m), 956

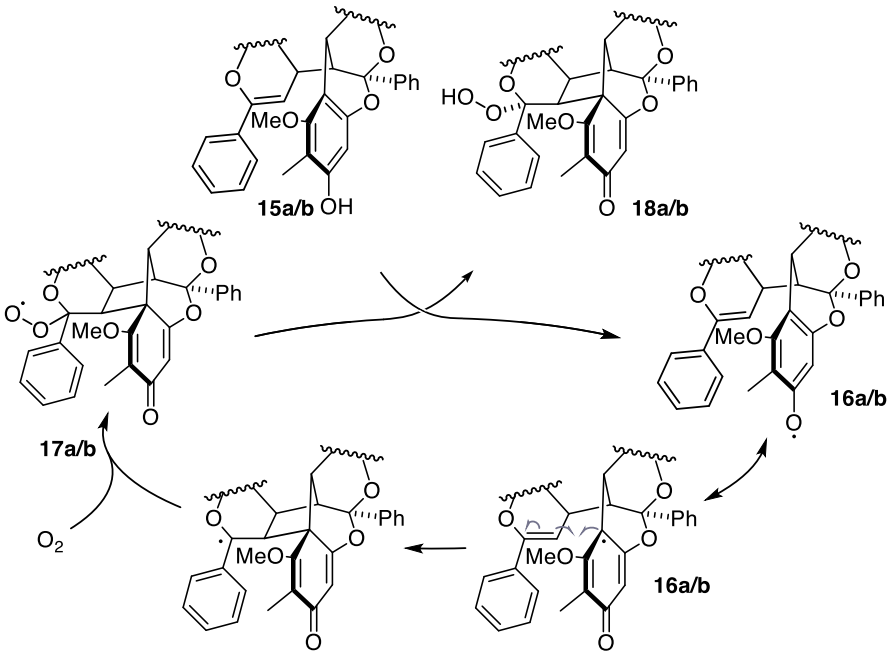
(m), 910 (w), 832 (w), 748 (m), 697 (s) cm^{-1}

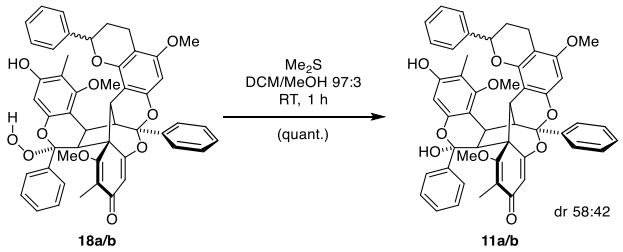
HRMS (ESI): calc. for $C_{50}H_{45}O_{11}$ $[M+H]^+$: 821.2956, found: 821.2964

*assigned by HSQC data

solubility in acetone-*d6* is very low compared to dragonbloodin A (11a/b**).

Proposed autoxidation mechanism of the formation of **18a/b.**





Dragonbloodin A 11a/b To a solution of peroxy compound **18a/b** (2.0 mg, 2.4 µmol, 1.0 eq) in DCM/MeOH (97/3, 250 µL) was added dimethylsulfide (0.9 µL, 12 µmol, 5.0 eq). The solution was stirred at RT for 1 h. The organic solvents were removed under reduced pressure to afford dragonbloodin A **11a/b** (2.0 mg, quantitative crude) as a colorless solid that reddens slowly under air.

R_f: 0.28 (hexanes:EtOAc 1:1), **m.p.** >200 °C (decomposition)

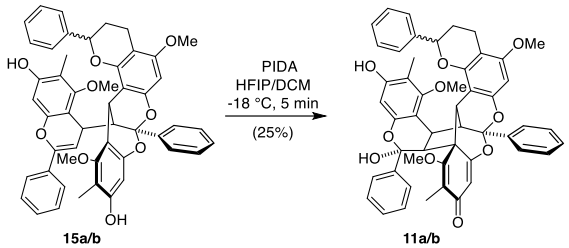
^{1}H NMR (400 MHz, Acetone-d_6) δ 8.44 (s, 1H), 8.43 (s, 1H), 7.93 – 7.88 (m, 4H), 7.67 – 7.61 (m, 4H), 7.59 – 7.52 (m, 2H), 7.33 – 7.14 (m, 18H), 7.08 – 7.03 (m, 2H), 6.42 (s, 2H), 6.11 (s, 1H), 6.08 (s, 1H), 5.45 (s, 1H), 5.45 (s, 1H), 5.44 (s, 1H), 5.44 (s, 1H), 5.31 (t, *J* = 3.4 Hz, 1H), 5.03 (dd, *J* = 9.4, 2.7 Hz, 1H), 4.04 (d, *J* = 4.6 Hz, 1H), 3.91(d, *J* = 8.5 Hz, 1H), 3.91 (d, *J* = 5.0 Hz, 1H), 3.88 (d, *J* = 8.8 Hz, 1H), 3.77 (d, *J* = 8.8 Hz, 1H), 3.75 (d, *J* = 9.2 Hz, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.23 (d, *J* = 4.7 Hz, 1H), 3.22 (d, *J* = 4.9 Hz, 1H), 3.21 (s, 3H), 2.93 (s, 3H), 2.90 (s, 6H), 2.62 – 2.40 (m, 3H), 2.02 (s, 3H), 1.99 (s, 3H), 2.11 – 1.95 (m, 4H), 1.77 – 1.65 (m, 1H), 1.19 (s, 3H), 0.72 (s, 3H) ppm.

^{13}C NMR (201 MHz, Acetone) δ 188.18, 187.93, 172.33, 172.18, 164.60, 163.89, 158.53, 158.50, 157.88, 157.74, 156.44, 154.47, 154.14, 153.34, 153.20, 152.76, 152.67, 143.40, 142.54, 142.22, 141.82, 140.12, 140.09, 129.86, 129.84, 129.15, 129.12, 128.71, 128.61, 128.06, 127.88, 127.55, 127.50, 126.69, 126.38, 113.40, 112.94, 111.76, 111.75, 109.90, 109.80, 106.63, 105.94, 105.05, 104.98, 104.92, 104.63, 101.37, 101.20, 100.96, 100.76, 97.28, 97.23, 91.95, 91.89, 78.02, 77.43, 59.52, 59.45, 58.86, 55.75, 55.73, 55.09, 54.85, 52.91, 52.26, 49.93, 49.58, 38.91, 38.80, 36.21, 35.88, 30.43, 26.94, 19.21, 16.35, 9.61, 9.60, 8.78, 8.74 ppm.

IR (ATR): $\tilde{\nu}_{max}$= 3332 (w, br), 2958 (m), 2363 (w), 2333 (w), 1670 (s), 1617 (s), 1595 (s), 1492 (m), 1463 (w) 1449 8m), 1424 (w), 1367 (w), 1349 (m), 1312 (w), 1264 (w), 1239 (m), 1211 (m), 1200 (m9, 1178 (m), 1121 (s), 1091 (s), 1011 (m), 978 (w9, 954 8m), 916 (w), 892 (w), 806 (w), 760 (w), 699 (m), 668 (w) cm^{-1}

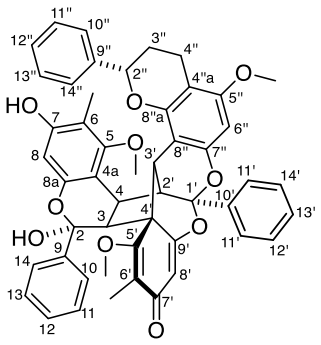
HRMS (ESI): calc. for $C_{50}H_{45}O_{10}$ $[M+H]^+$: 805.30072, found: 805.30136

The reduction of **18a/b** towards dragonbloodin A (**11a/b**) can be conducted in the same step as the oxidation of **15a/b** towards **18a/b** without any significant drop in yield. Yet this is not recommendable as dragonbloodin A proved to be less column stable than **18a/b**.

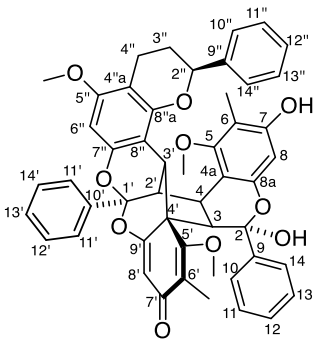


Dragonbloodin A 11a/b To a suspension of benzopyran **15a/b** (24.3 mg, 30.8 µmol, 1.0 eq) in DCM/HFIP (hexafluoro-*iso*-propanol) (3/5, 1.60 mL) was added (Diacetoxyiodo)benzene (10.9 mg, 33.9 µmol, 1.1 eq) as a solution in HFIP (600 µL) at -18 °C. The solution was stirred for 5 minutes and quenched by the addition of acetone. The solvents were removed under reduced pressure and the crude mixture was purified by FCC (DCM/MeOH: 99/1) to afford the title compound **11a/b** (6.2 mg. 25%) as a reddish solid.

See previous experiments for analytical data.



Dragonbloodin A1 (**11a**)



Dragonbloodin A2 (**11b**)

^{1}H- NMR comparison with isolated natural product[117]

No.	^{1}H NMR Isolation (400 MHz, Acetone-d_6) Dragonbloodin A1 (**11a**) [ppm]	^{1}H NMR synthetic (400 MHz, Acetone-d_6) [ppm]	Δ ppm	^{1}H NMR Isolation (400 MHz, Acetone-d_6) Dragonbloodin A2 (**11b**) [ppm]	^{1}H NMR synthetic (400 MHz, Acetone-d_6) [ppm]	Δ ppm
3	3.90(d, J = 9.1 Hz)	3.91 (d, J = 8.8 Hz)	+0.01	3.86 (d, J = 9.1 Hz)	3.87 (d, J = 9.1 Hz)	+0.01
4	3.75(d, J = 9.1 Hz)	3.76 (d, J = 8.9 Hz)	+0.01	3.74 (d, J = 9.1 Hz)	3.75 (d, J = 8.9 Hz)	+0.01
8	6.40(s)	6.41 (s)	+0.01	6.40 (s)	6.41 (s)	+0.01
10	7.30 – 7.25 (m)	7.33 – 7.19 (m)	n.d.	7.18 – 7.14 (m)	7.30 – 7.12 (m)	n.d.
11	7.30 – 7.25 (m)	7.33 – 7.19 (m)	n.d.	7.18 – 7.14 (m)	7.30 – 7.12 (m)	n.d.
12	7.30 – 7.25 (m)	7.33 – 7.19 (m)	n.d.	7.18 – 7.14 (m)	7.30 – 7.12 (m)	n.d.
13	7.30 – 7.25 (m)	7.33 – 7.19 (m)	n.d.	7.18 – 7.14 (m)	7.30 – 7.12 (m)	n.d.
14	7.30 – 7.25 (m)	7.33 – 7.19 (m)	n.d.	7.18 – 7.14 (m)	7.30 – 7.12 (m)j	n.d.
2-OH	5.41(s)	5.44 (s)	+0.03	5.41 (s)	5.43 (s)	+0.02
5-OMe	2.93(s)	2.94 (s)	+0.01	2.92 (s)	2.93 (s)	+0.01
6-Me	2.01(s)	2.02 (s)	+0.01	1.98 (s)	1.99 (s)	+0.01
7-OH	8.33(s)	8.44 (s)	+0.11	8.28 (s, br)	8.49 (s)	+0.21
2′	3.21(d, J = 4.6 Hz)	3.22 (d, J = 4.6 Hz)	+0.01	3.21 (d, J = 4.9 Hz)	3.22 (d, J = 5.3 Hz)	+0.01
3′	4.03(d, J = 4.6 Hz)	4.03 (d, J = 4.6 Hz)	+0.01	3.90 (d, J = 4.9 Hz)	3.90 (d, J = 4.7 Hz)	±0.00
8′	5.42(s)	5.44 (s)	+0.02	5.42 (s)	5.45 (s)	+0.03
11′	7.89(d, J = 7.4 Hz)	7.90 (d, J = 7.7 Hz)	+0.01	7.90 (d, J = 7.4 Hz)	7.90 (d, J = 7.4 Hz)	±0.00
12′	7.63 (t, J = 7.7 Hz)	7.64 (t, J = 7.6 Hz)	+0.01	7.64 (t, J = 7.7 Hz)	7.65 (t, J = 7.6 Hz)	+0.01
13′	7.55(t, J = 7.7 Hz)	7.56 (t, J = 7.3 Hz)	+0.01	7.55 (t, J = 7.7 Hz)	7.56 (t, J = 7.3 Hz)	+0.01
14′	7.63(t, J = 7.7 Hz)	7.64 (t, J = 7.6 Hz)	+0.01	7.64 (t, J = 7.7 Hz)	7.65 (t, J = 7.6 Hz)	+0.01
15′	7.89(d, J = 7.4 Hz)	7.90 (d, J = 7.7 Hz)	+0.01	7.90 (d, J = 7.6 Hz)	7.90 (d, J = 7.4 Hz)	±0.00
5′-OMe	2.89(s)	2.90 (s), (assigned by HSQC)	+0.01	3.20 (s)	3.21 (s)	+0.01
6′-Me	1.17(s)	1.18 (s)	+0.01	0.70 (s)	0.71 (s)	+0.01
2′′	5.02(dd, J = 9.2, 2.6 Hz)	5.03 (dd, J = 9.4, 2.2 Hz)	+0.01	5.31 (dd, J = 5.2, 4.0 Hz)	5.31 (t, J = 3.3 Hz)	±0.00
3′′	2.05 – 2.01(m) 1.71(m)	2.12 – 2.00 (m) (assigned by HSQC) 1.79 – 1.64 (m)	n.d.	2.05 – 1.98 (m) 2.05 – 1.98 (m)	2.11 – 1.95 (m) (assigned by HSQC)	n.d.
4′′	2.53 (ddd, J = 16.0, 5.7, 4.6 Hz) 2.45(ddd, J = 17.2,10.5, 5.9 Hz)	2.58 – 2.41 (m)	n.d.	2.50 (ddd, J = 16.8, 6.2, 4.9 Hz), 1.94-1.98 (m)	2.55 – 2.47 (m) 2.02 – 1.93 (m)	n.d.
6′′	6.07(s)	6.08 (s)	+0.01	6.10 (s)	6.11 (s)	+0.01
10′′	7.23 – 7.20(m)	7.33 – 7.19 (m)	n.d.	7.05 (d, J = 7.1 Hz)	7.06 (d, J = 6.8 Hz)	+0.01
11′′	7.23 – 7.20(m)	7.33 – 7.19 (m)	n.d.	7.24 – 7.19 (m)	7.30 – 7.12 (m)	n.d.
12′′	7.25 – 7.24(m)	7.33 – 7.19 (m)	n.d.	7.24 – 7.19 (m)	7.30 – 7.12 (m)	n.d.

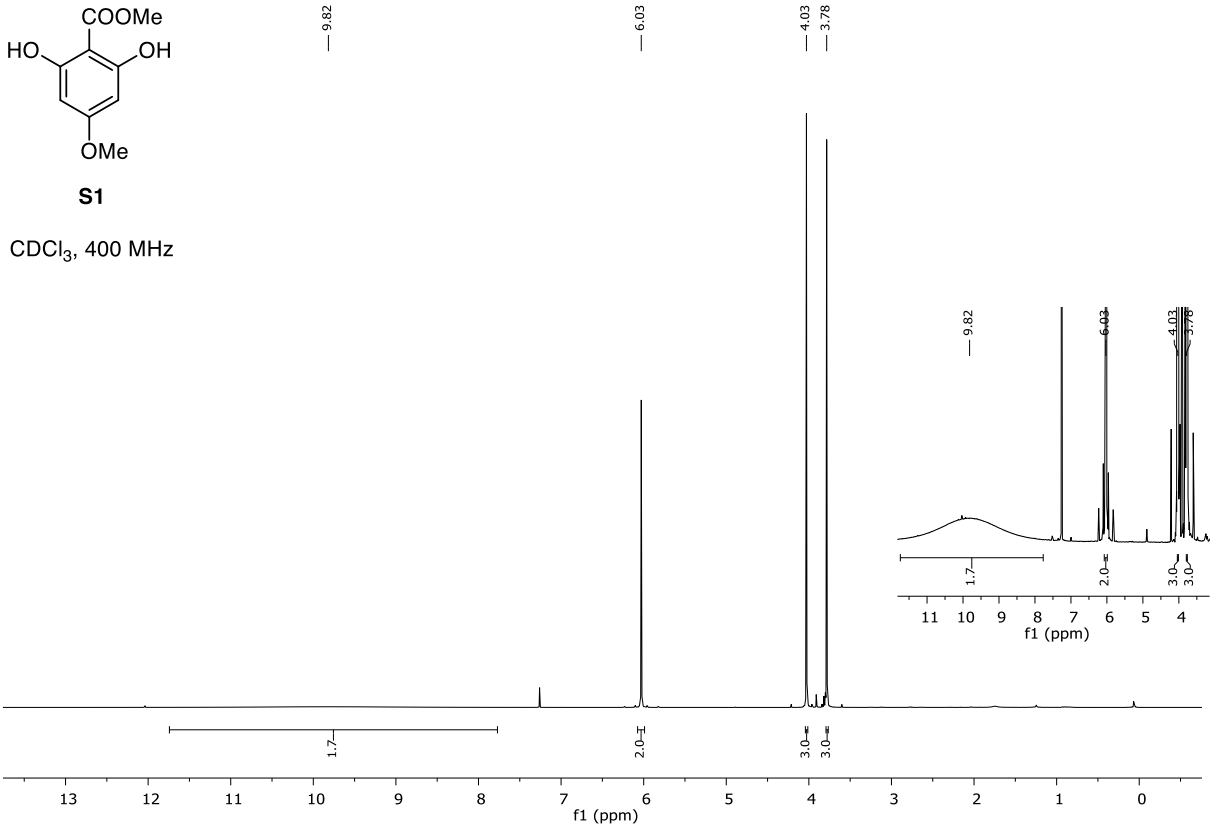
[117] W.-K. Du, H.-Y. Hung, P.-C. Kuo, T.-L. Hwang, L.-C. Shiu, K.-B. Shiu, E.-J. Lee, S.-H. Tai, T.-S. Wu, *Org. Lett.*, **2016**, *18*, p. 3042.

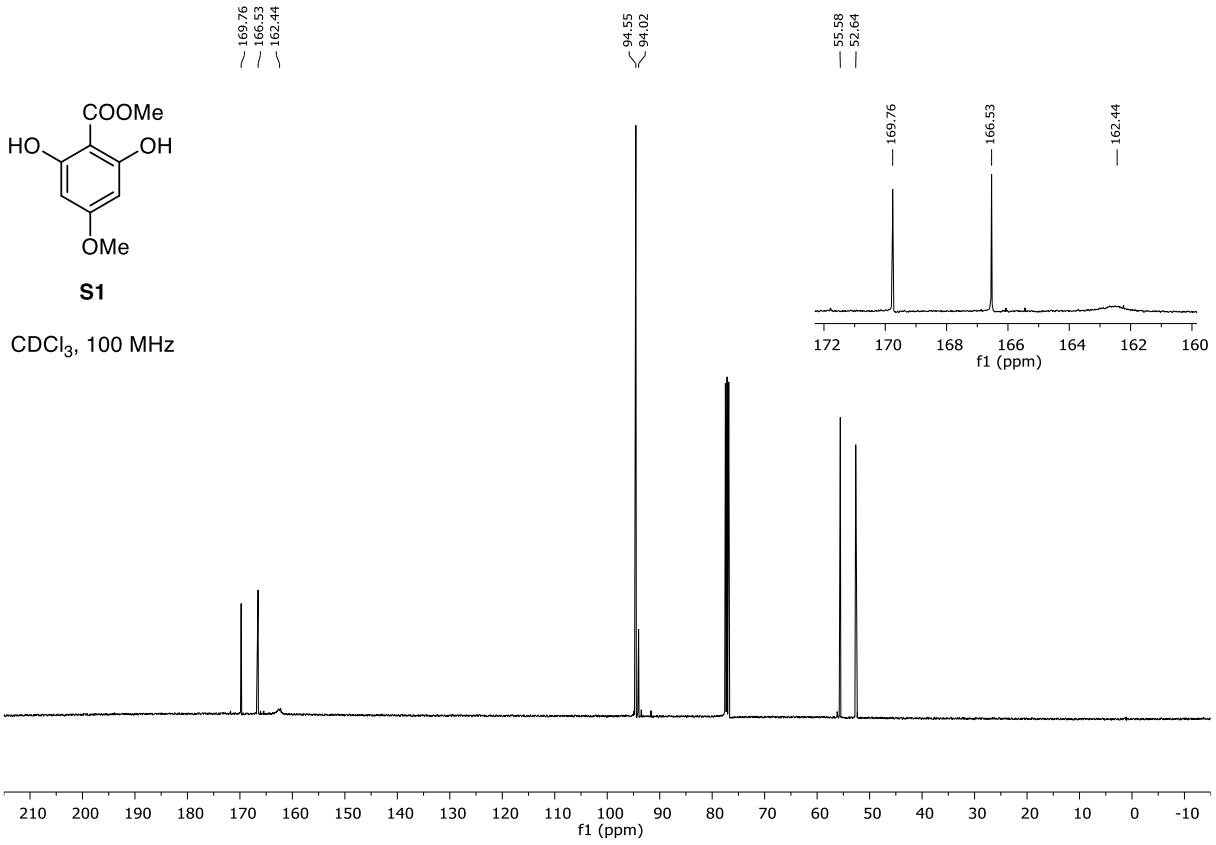
13″	7.23 – 7.20 (m)	7.33 – 7.19 (m)	n.d.	7.24 – 7.19 (m)	7.30 – 7.12 (m)	n.d.
14″	7.23 – 7.20(m)	7.33 – 7.19 (m)	n.d.	7.05 (d, J = 7.1 Hz)	7.06 (d, J = 6.8 Hz)	+0.01
5′′-OMe	3.71 (s)	3.72 (s)	+0.01	3.71 (s)	3.71 (s)	±0.00

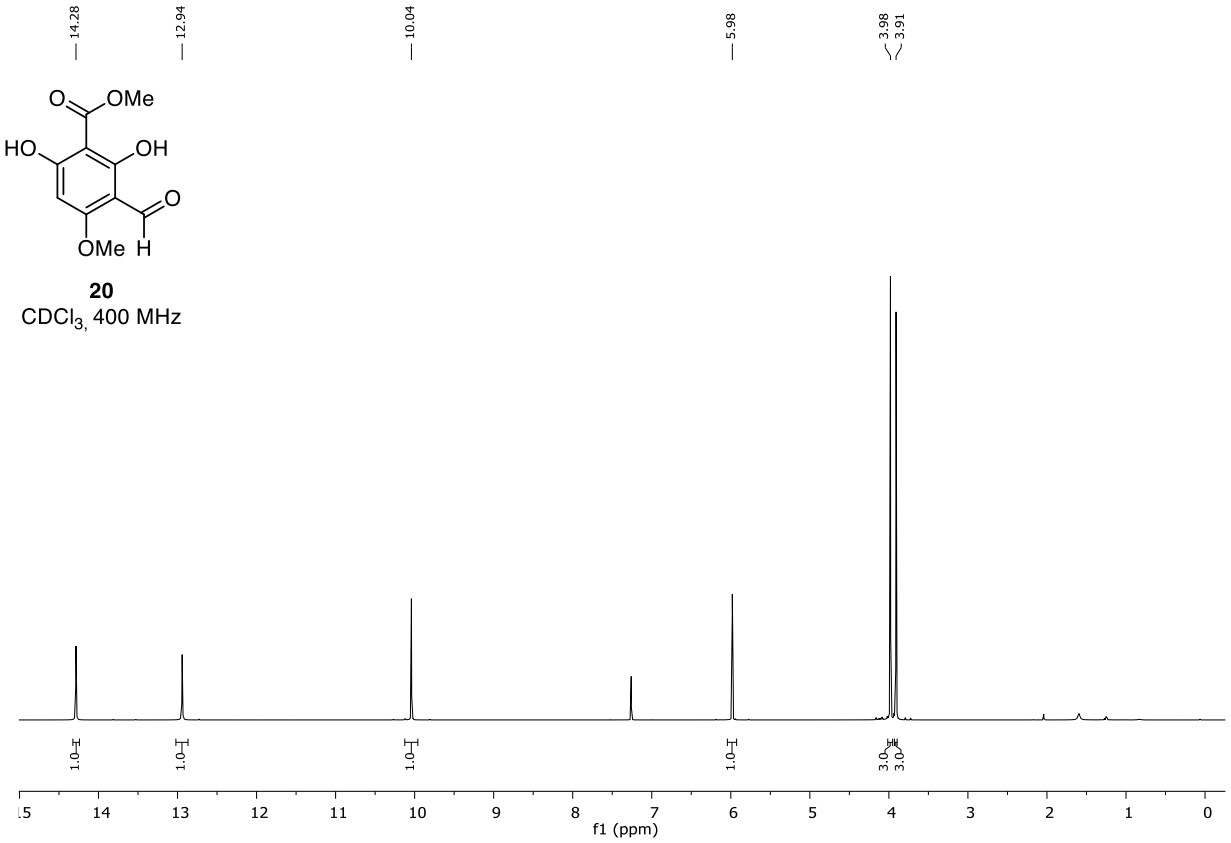
^{13}C-NMR comparison with isolated natural product

No.	^{13}C NMR Isolation (100 MHz, Acetone-d_6) Dragonbloodin A1 (**11a**) [ppm]	^{13}C NMR (201 MHz) synthetic [ppm]	Δ ppm	1H NMR Isolation (100 MHz, Acetone-d_6) Dragonbloodin A2 (**11b**) [ppm]	^{13}C NMR (201 MHz) synthetic [ppm]	Δ ppm
2	96.91 (s)	97.24	+0.35	96.85 (s)	97.18	+0.33
3	51.85 (d)	52.21	+0.36	52.52 (d)	52.87	+0.35
4	35.81 (d)	36.17	+0.36	35.49 (d)	35.83	+0.34
4a	109.59 (s)	109.86	+0.27	109.49 (s)	109.70	+0.21
5	157.37 (s)	157.69	+0.32	157.51 (s)	157.81	+0.30
6	111.36 (s)	111.71	+0.35	111.38 (s)	111.72	+0.34
7	156.04 (s)	156.43	+0.39	156.03 (s)	156.44	+0.41
8	100.37 (d)	100.72	+0.35	100.57 (d)	100.92	+0.35
8a	152.40 (d)	152.73	+0.33	152.31 (d)	152.63	+0.32
9	143.04 (s)	143.36	+0.32	141.45 (s)	141.78	+0.33
10	128.76 (d)	126.36, 128.11, 129.10	+0.34, n.d.	128.80	126.35, 128.03, 129.14	+0.34, n.d.
11	128.76 (d)	126.36, 128.11, 129.10	+0.34, n.d.	128.80	126.35, 128.03, 129.14	+0.34, n.d.
12	128.76 (d)	126.36, 128.11, 129.10	+0.34, n.d.	128.80	126.35, 128.03, 129.14	+0.34, n.d.
13	128.76 (d)	126.36, 128.11, 129.10	+0.34, n.d.	128.80	126.35, 128.03, 129.14	+0.34, n.d.
14	128.76 (d)	126.36, 128.11, 129.10	+0.34, n.d.	128.80	126.35, 128.03, 129.14	+0.34, n.d.
5-OMe	59.08 (q)	59.42	+0.34	59.08	59.41	+0.33
6-Me	8.42 (q)	8.77	+0.35	8.38	8.73	+0.35
1′	104.58 (s)	104.94	+0.36	104.52 (s)	104.90	+0.38
2′	49.20 (d)	49.55	+0.35	49.56 (s)	49.91	+0.35
3′	38.49 (d)	38.86	+0.37	38.40 (d)	38.76	+0.36
4′	54.68 (s)	55.05	+0.37	54.42 (s)	54.80	+0.38
5′	164.17 (s)	164.60	+0.43	163.43 (s)	163.91	+0.48
6′	112.55 (s)	112.90	+0.35	113.02 (s)	113.35	+0.33
7′	187.71 (s)	188.16	+0.45	187.43 (s)	187.97	+0.54
8′	106.30 (d)	106.60	+0.30	105.60 (d)	105.87	+0.27
9′	171.74 (s)	172.16	+0.42	171.89 (s)	172.35	+0.46
10′	139.72 (s)	140.05	+0.33	139.75 (s)	140.06	+0.31
11′	127.15 (d)	127.49	+0.34	127.20 (d)	127.53	+0.33
12′	128.80 (d)	129.10	+0.30	128.80 (d)	129.14	+0.34
13′	129.49 (d)	129.83	+0.34	129.52 (d)	129.86	+0.34
14′	128.80 (d)	129.10	+0.30	128.80 (d)	129.14	+0.34
15′	127.15 (d)	127.49	+0.34	127.20 (d)	127.53	+0.33
5′-OMe	59.16 (q)	59.51	+0.35	58.50 (q)	58.85	+0.35
6′-Me	9.24 (q)	9.59	+0.35	9.24 (q)	9.58	+0.34
2′′	77.64 (d)	77.99	+0.35	77.02 (d)	77.37	+0.35
3′′	29.97 (t)	30.4 (assigned by HSQC)	+0.4	26.56 (t)	26.91	+0.35
4′′	18.85 (t)	19.19	+0.34	15.92 (t)	16.25	+0.33
4′′a	104.22 (s)	104.58	+0.36	104.64 (s)	104.90	+0.26
5′′	158.11 (s)	158.46	+0.35	158.15 (s)	158.48	+0.33
6′′	91.56 (d)	91.91	+0.35	91.50 (d)	91.84	+0.34
7′′	152.83 (s)	153.16	+0.33	152.97 (s)	153.29	+0.32
8′′	100.97 (s)	101.32	+0.35	100.80 (s)	101.14	+0.34
8′′a	153.77 (s)	154.11	+0.34	154.07 (s)	154.41	+0.34
9′′	141.84 (s)	142.19	+0.36	142.17 (s)	142.51	+0.34
10′′	126.03 (d)	126.42	+0.39	126.29 (d)	126.62	+0.33
11′′	127.70 (d)	128.03	+0.33	127.50 (d)	127.85	+0.35
12′′	128.36 (d)	128.70	+0.34	128.25 (d)	128.58	+0.33
13″	127.70 (d)	128.03	+0.33	127.50 (d)	127.85	+0.35
14″	126.03 (d)	126.42	+0.39	126.29 (d)	126.62	+0.33
5′′-OMe	55.38 (q)	55.73	+0.35	55.36 (q)	55.71	+0.35

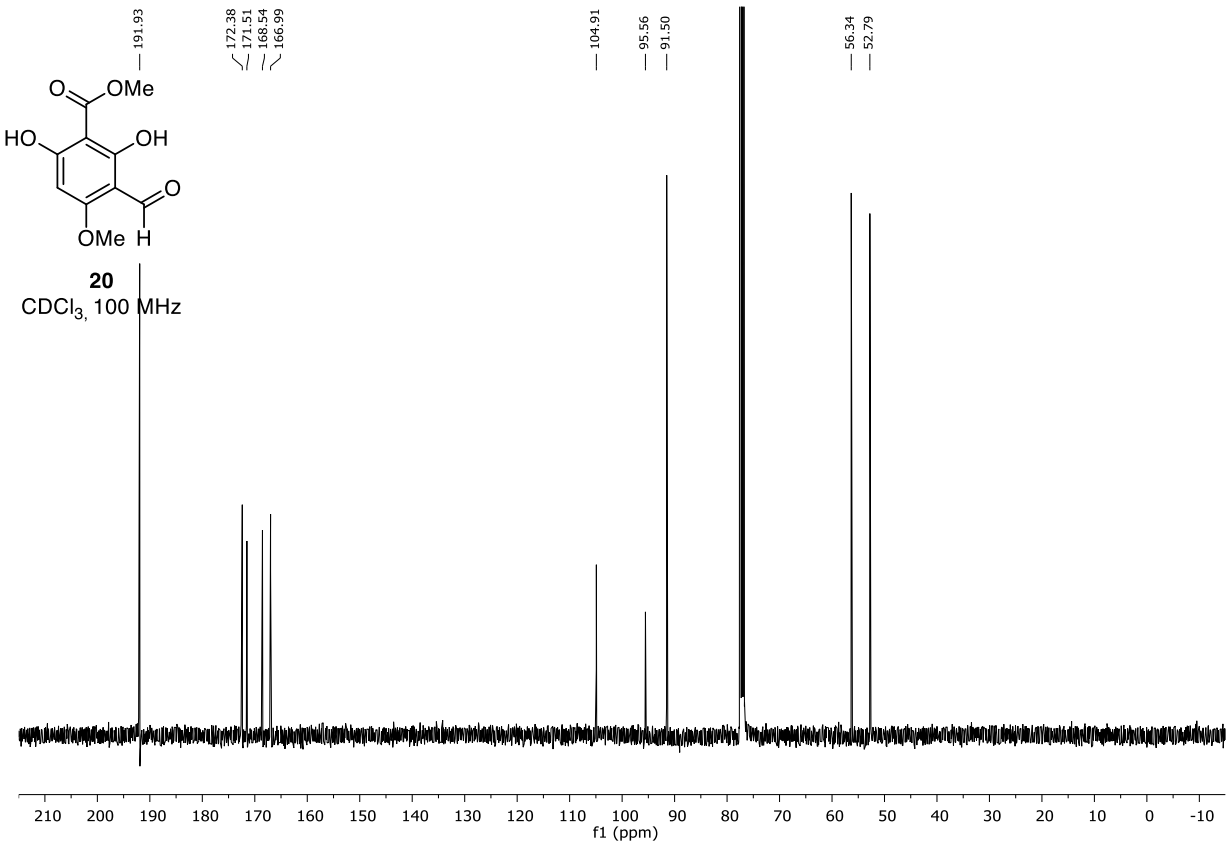
1.2 NMR spectra



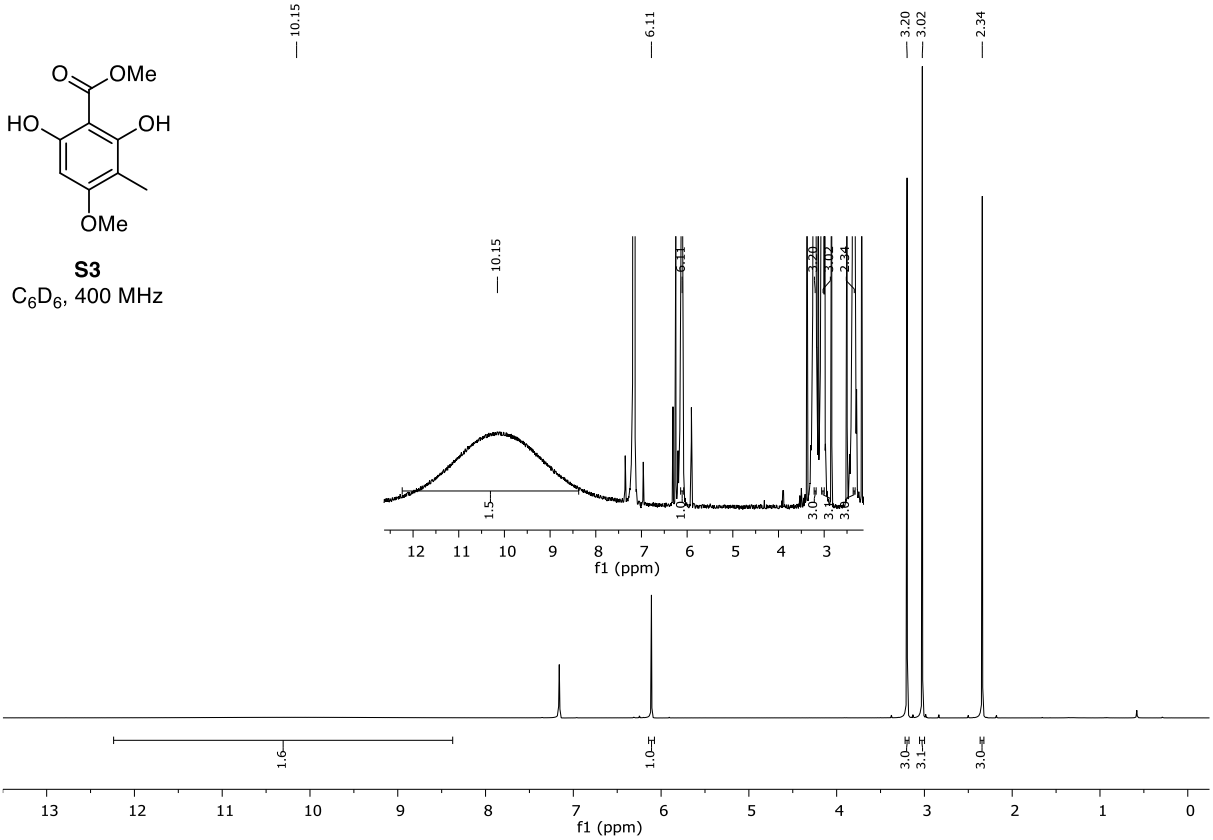




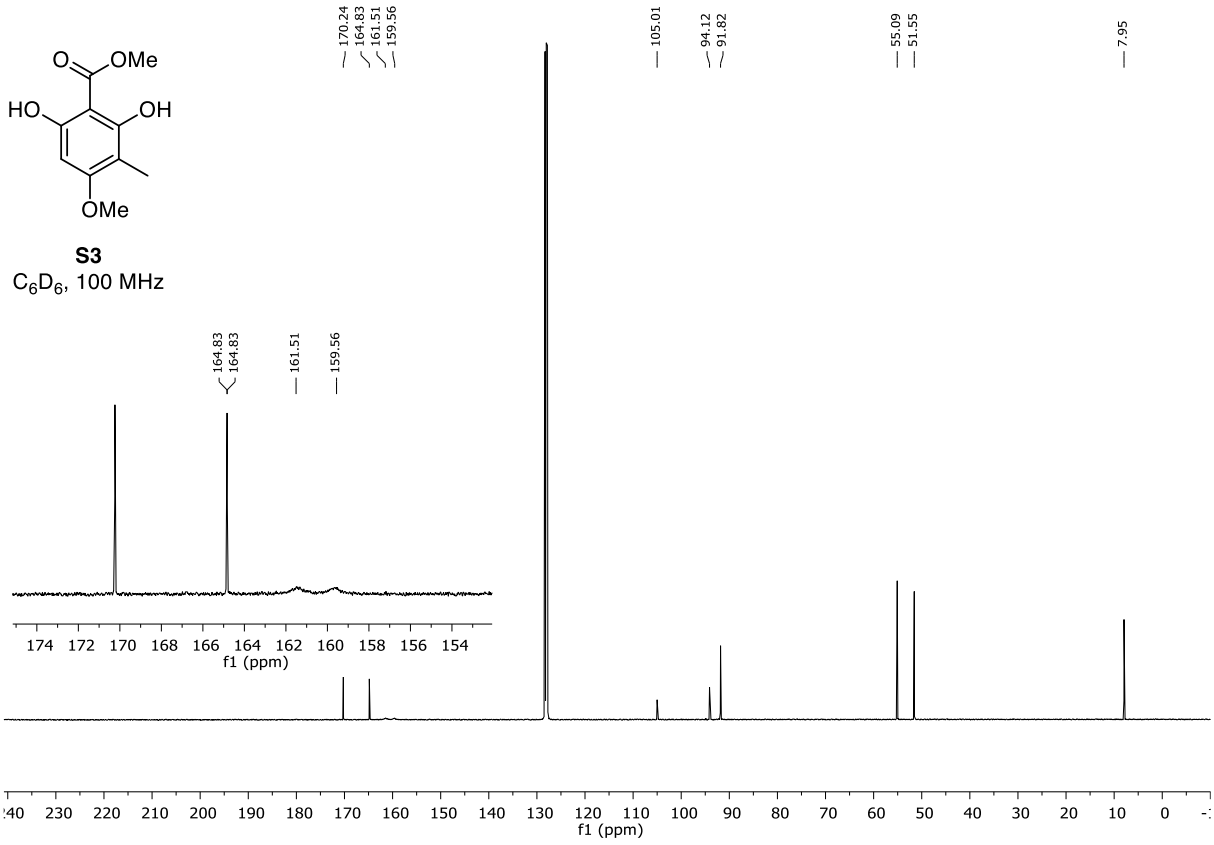
20
$CDCl_3$, 400 MHz



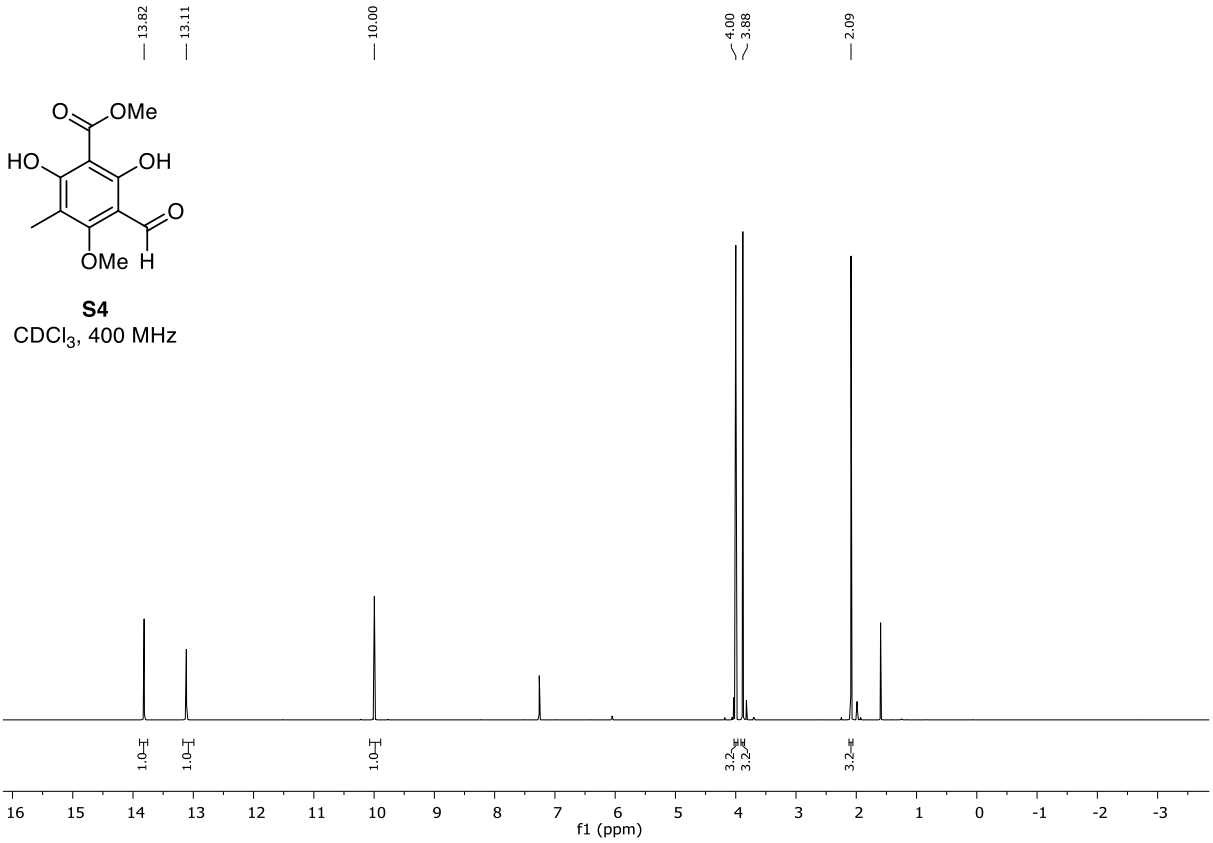
20
$CDCl_3$, 100 MHz



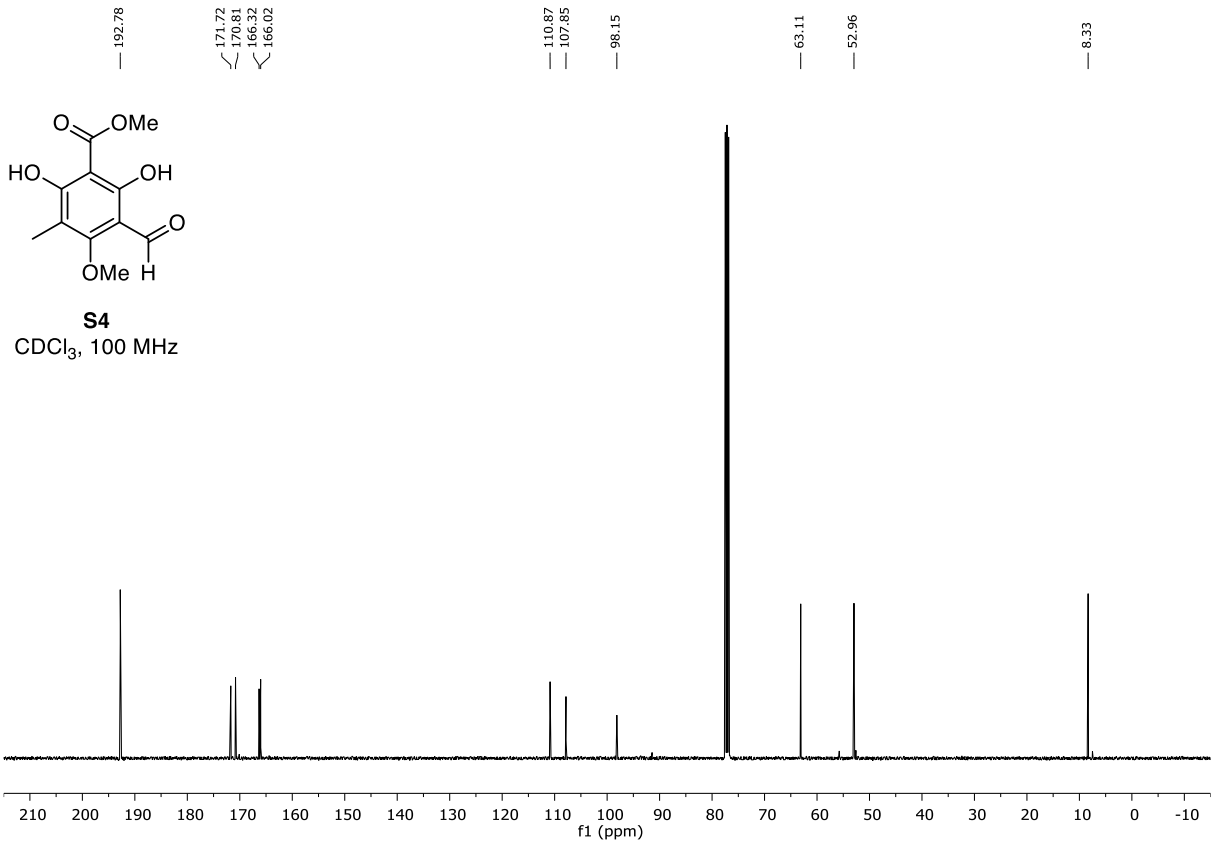
S3
C_6D_6, 400 MHz



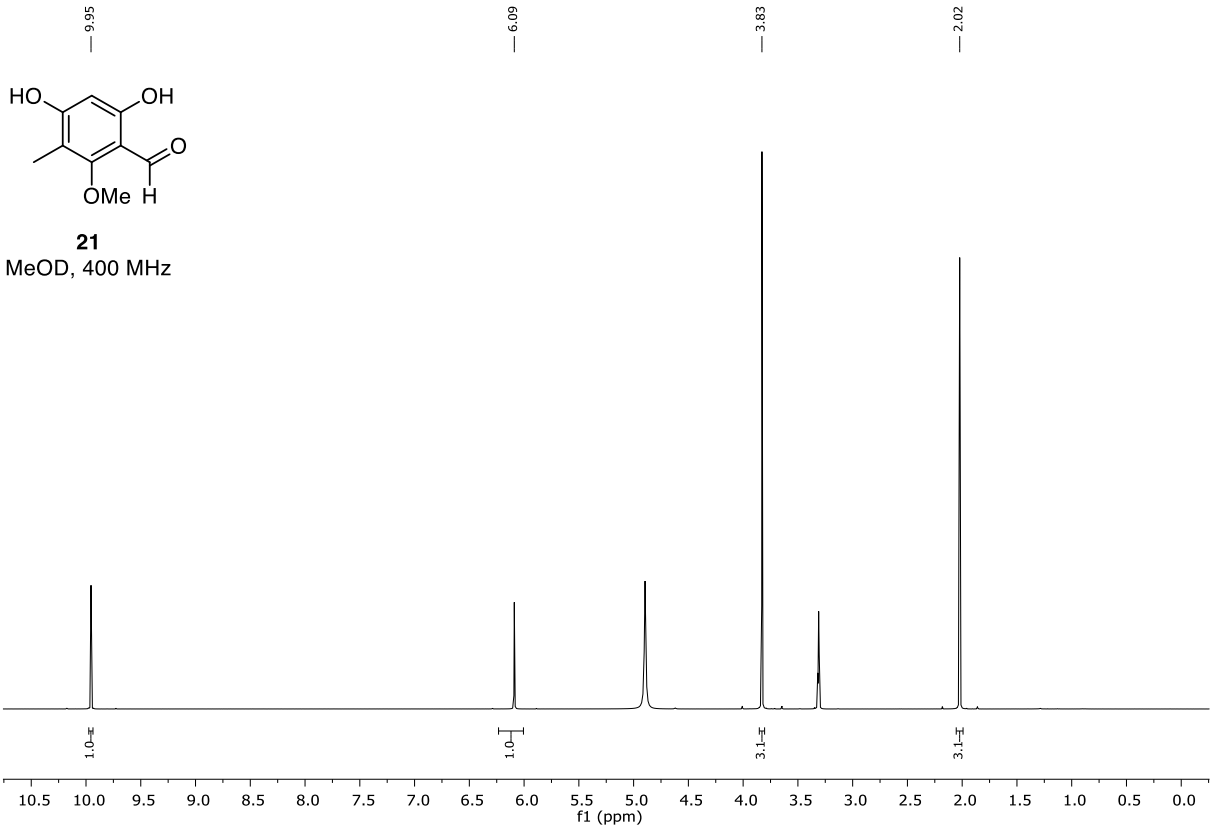
S3
C_6D_6, 100 MHz

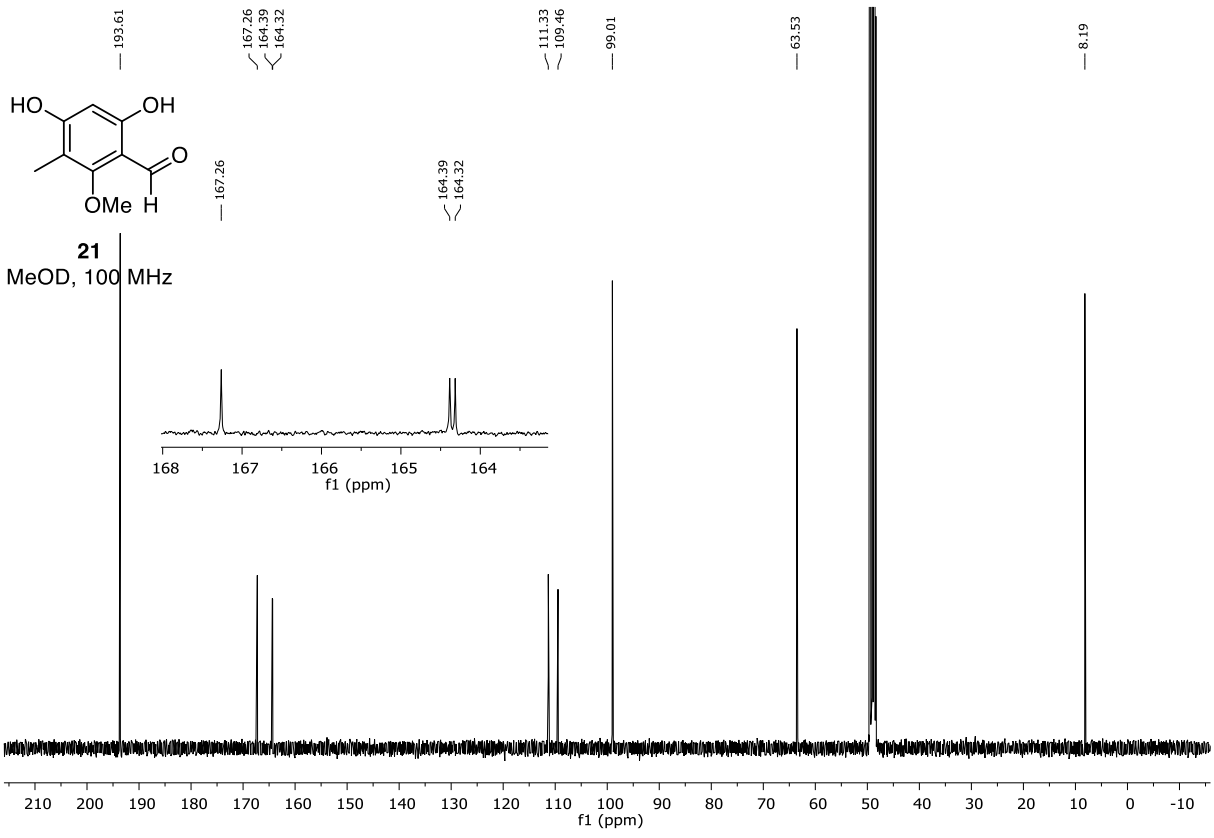


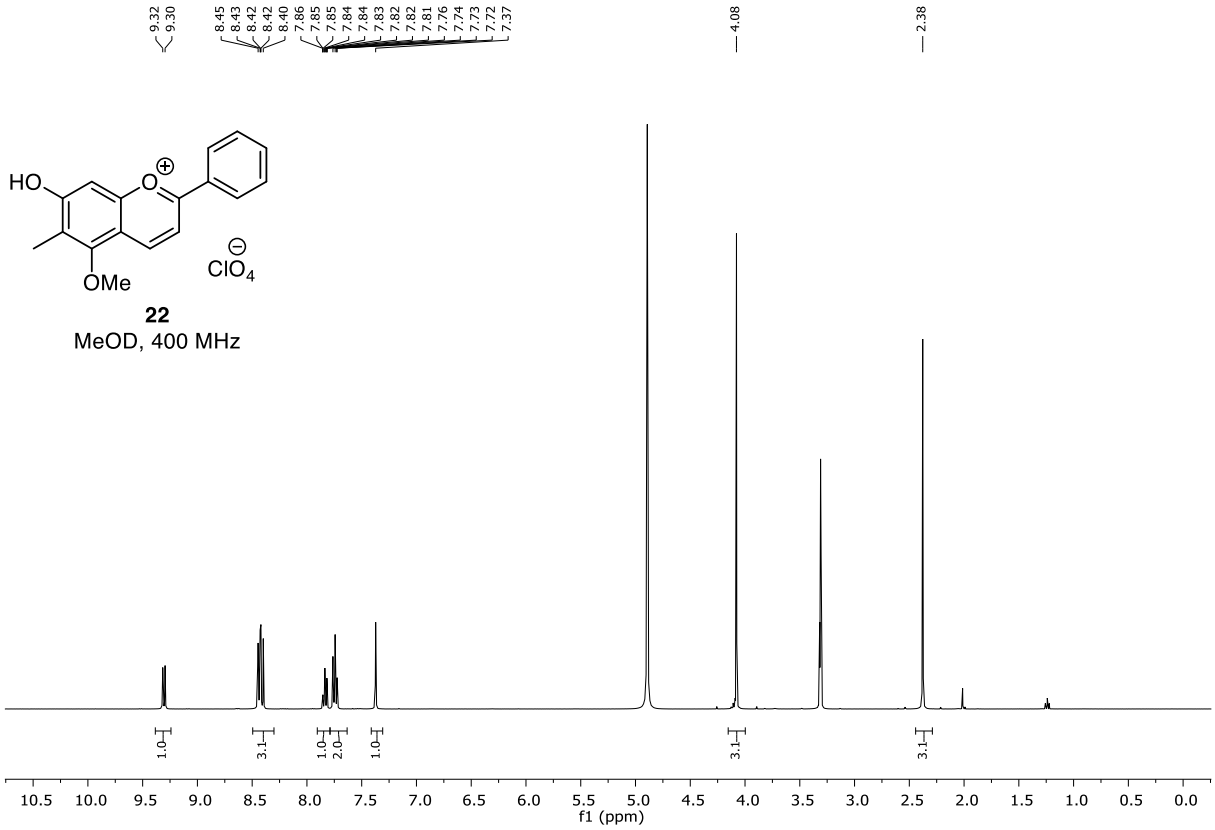
S4
$CDCl_3$, 400 MHz



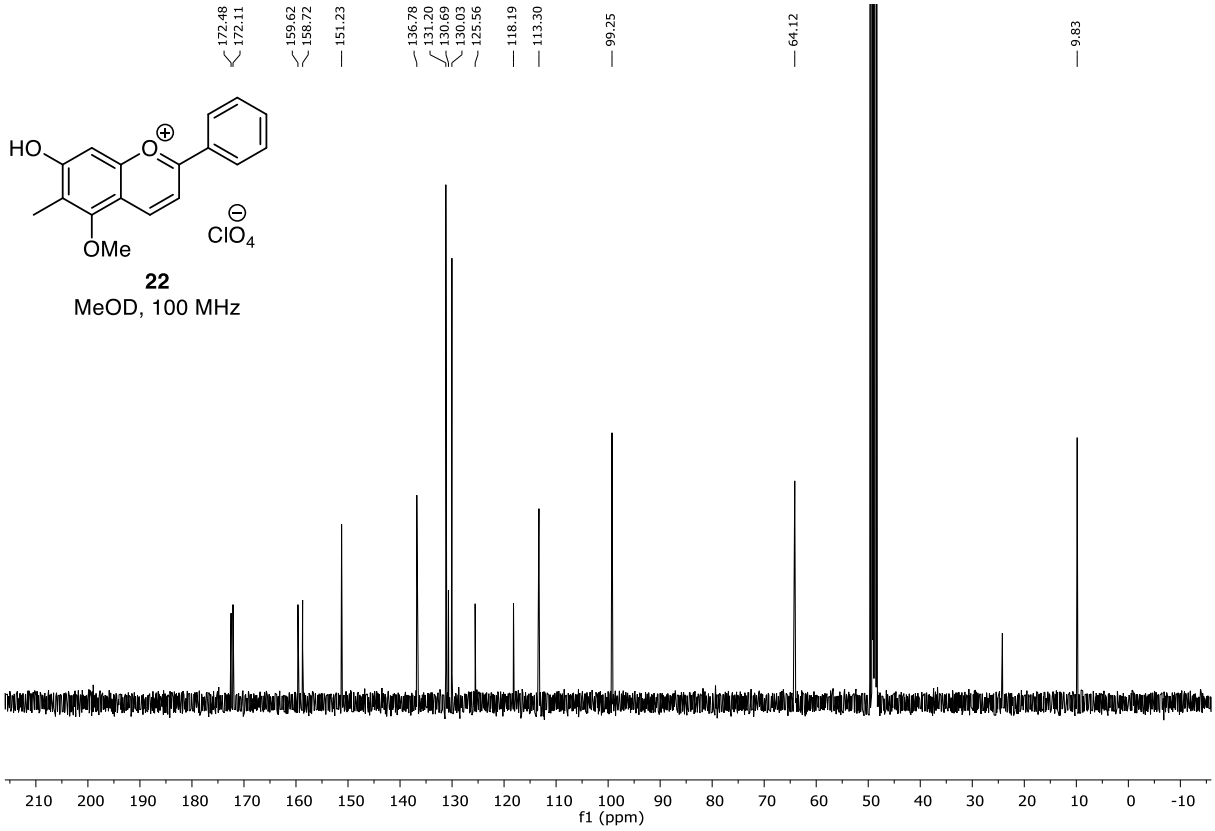
S4
$CDCl_3$, 100 MHz


9.95
6.09
3.83
2.02
HO
OH
O
OMe H
21
MeOD, 400 MHz
1.0
1.0
3.1
3.1
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

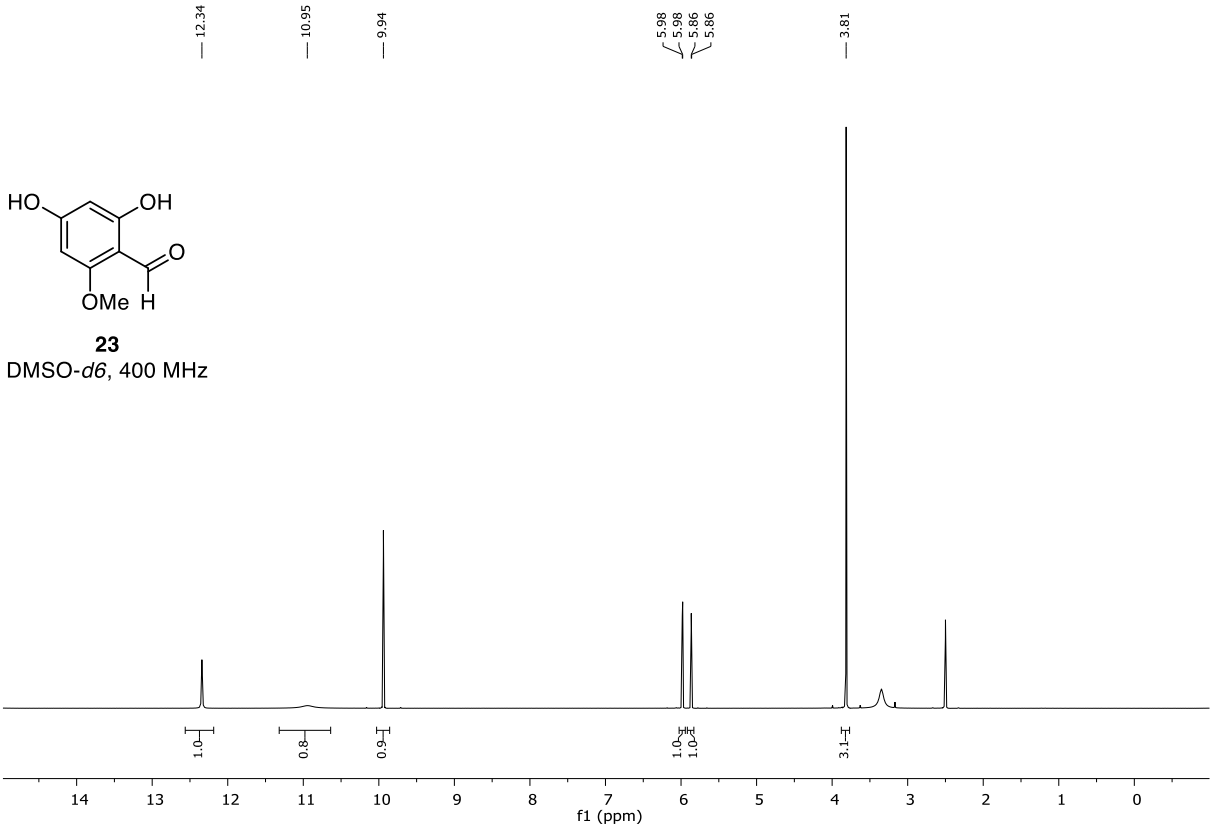

193.61
167.26
164.39
164.32
111.33
109.46
99.01
63.53
8.19
HO
OH
O
OMe H
21
MeOD, 100 MHz
167.26
164.39
164.32
168 167 166 165 164
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



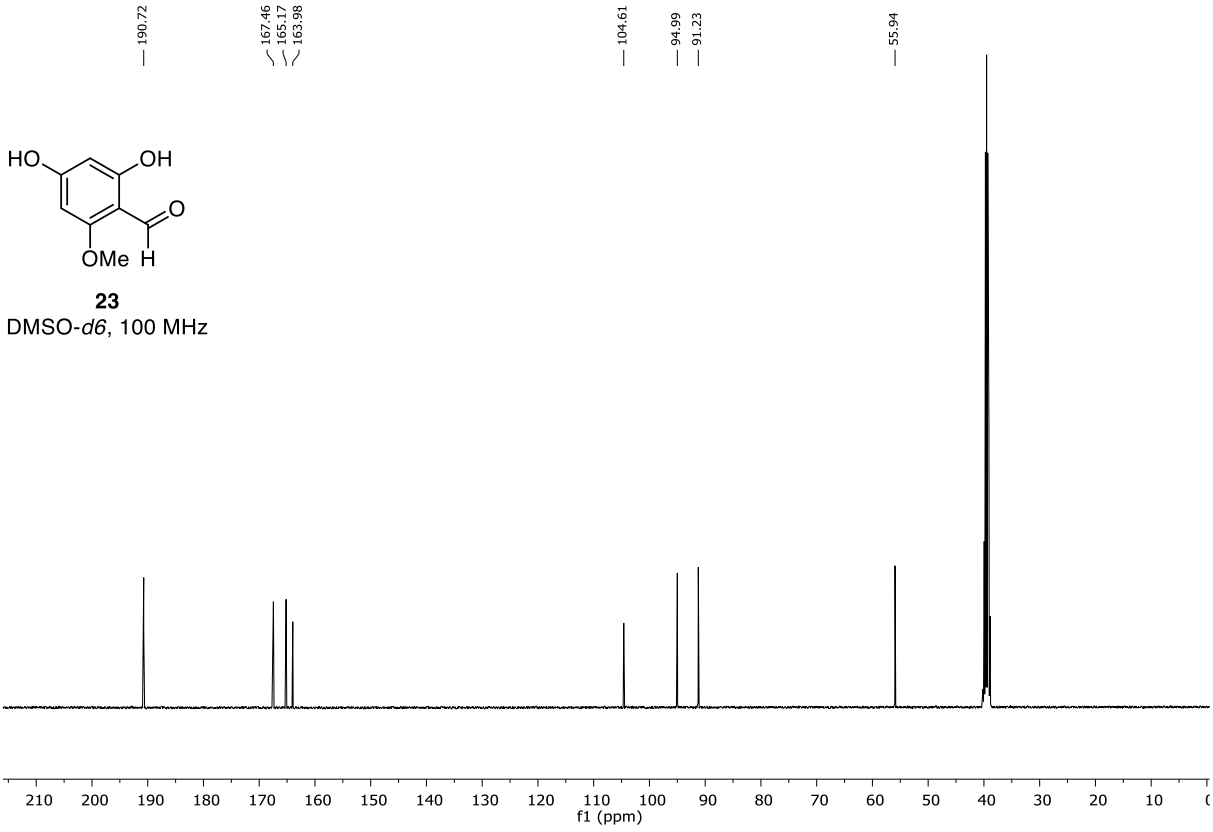
22
MeOD, 400 MHz



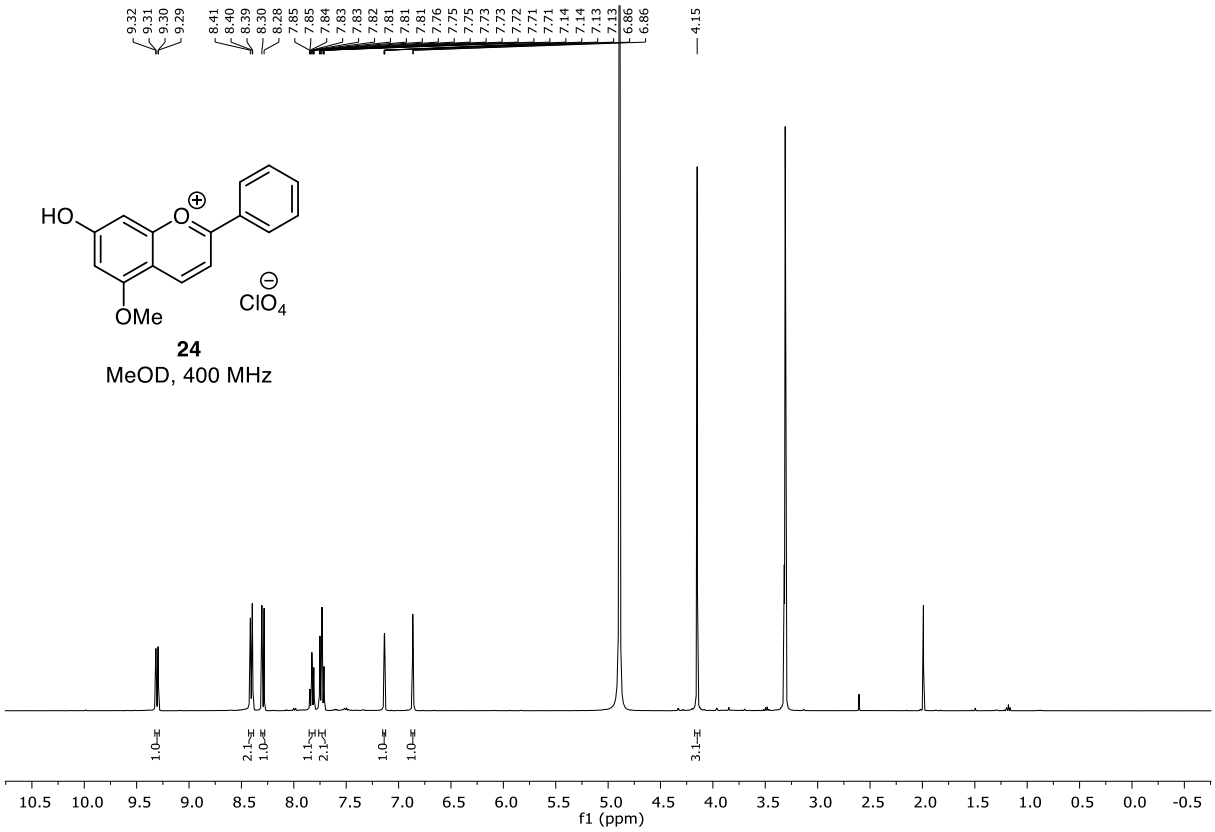
22
MeOD, 100 MHz



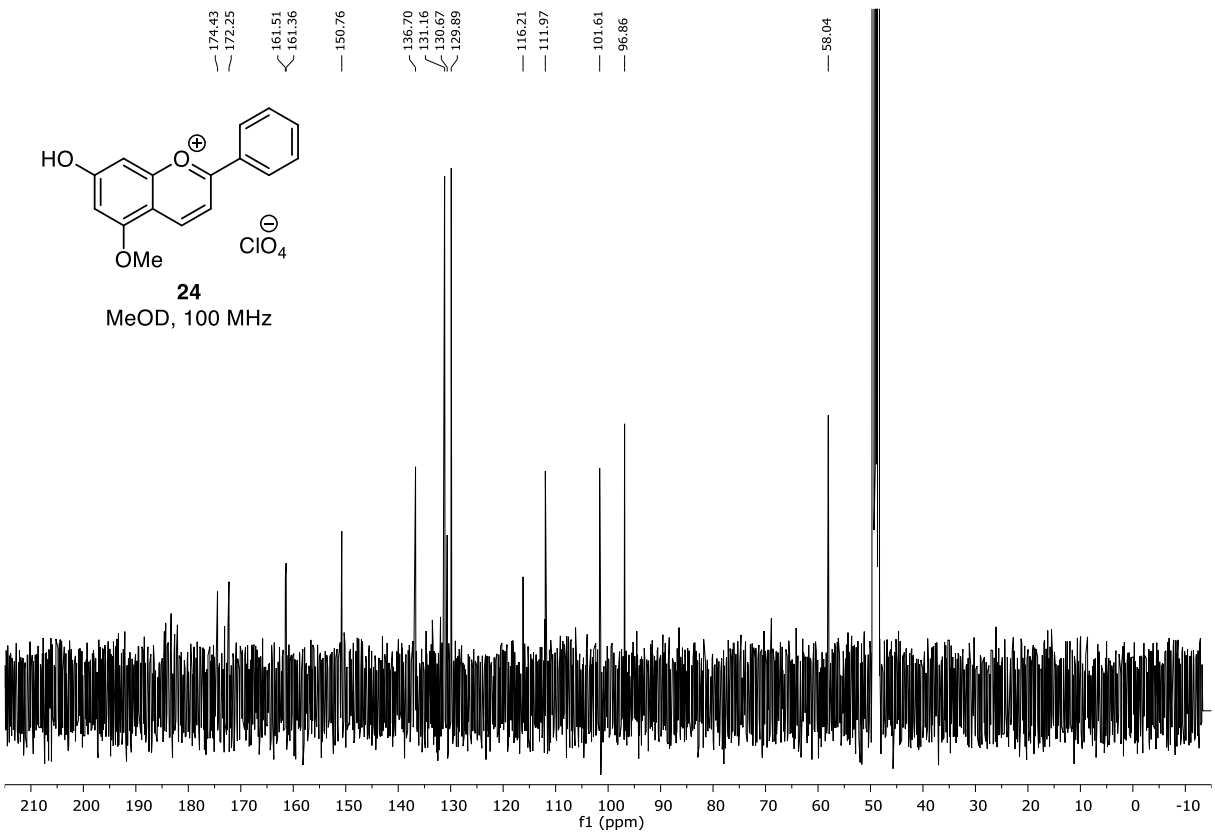
23
DMSO-*d6*, 400 MHz



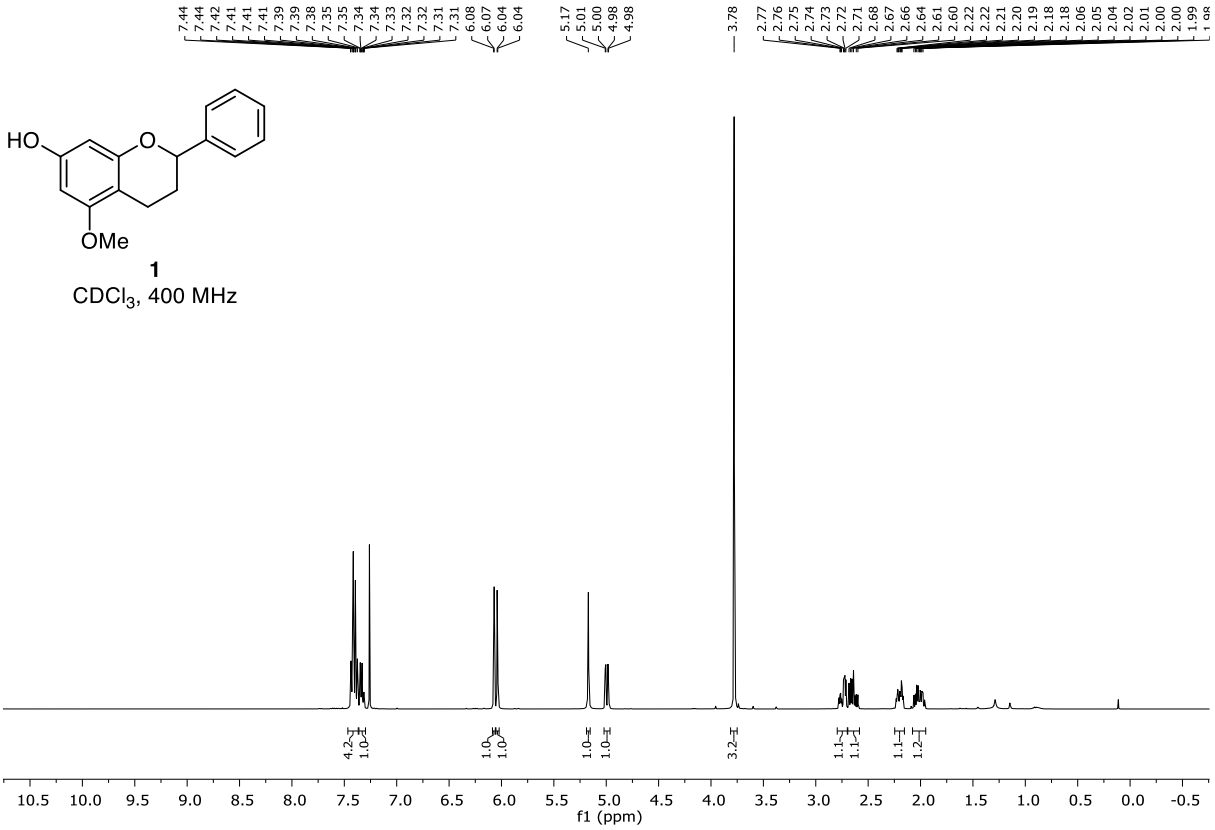
23
DMSO-*d6*, 100 MHz

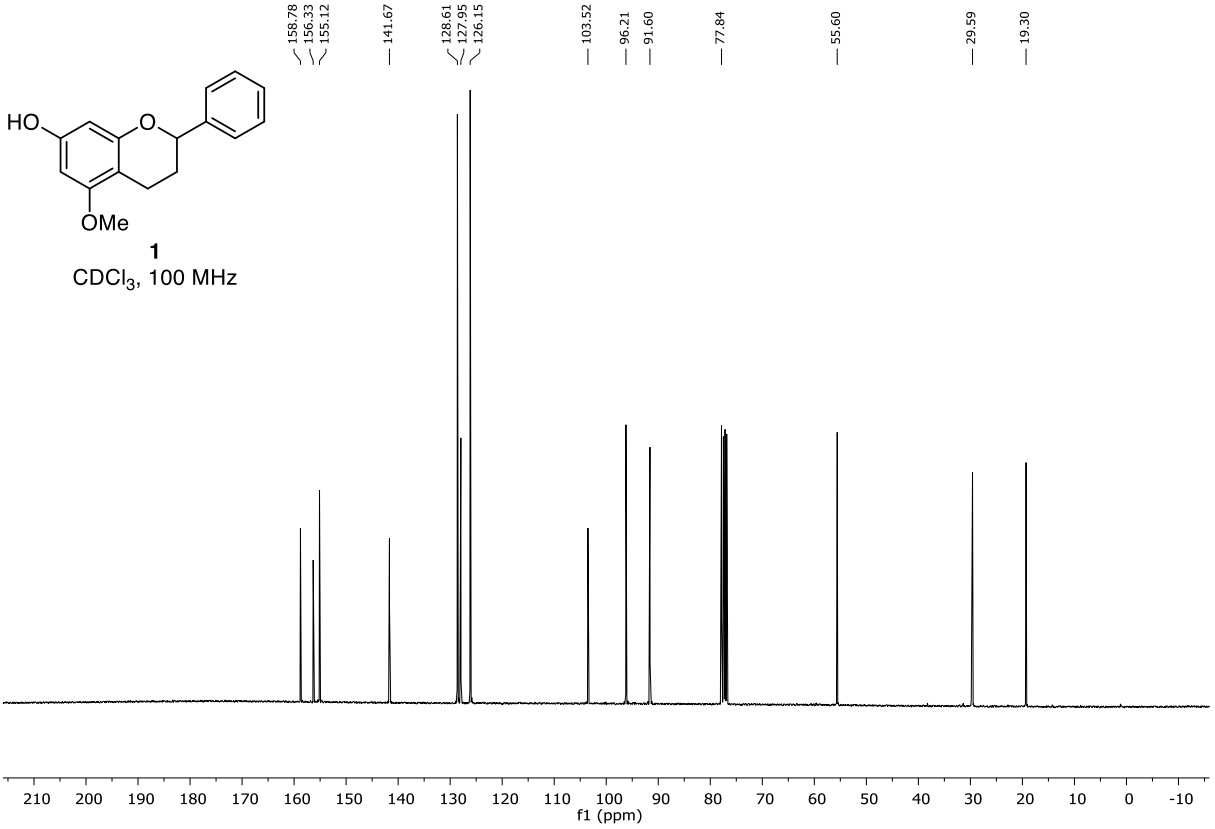


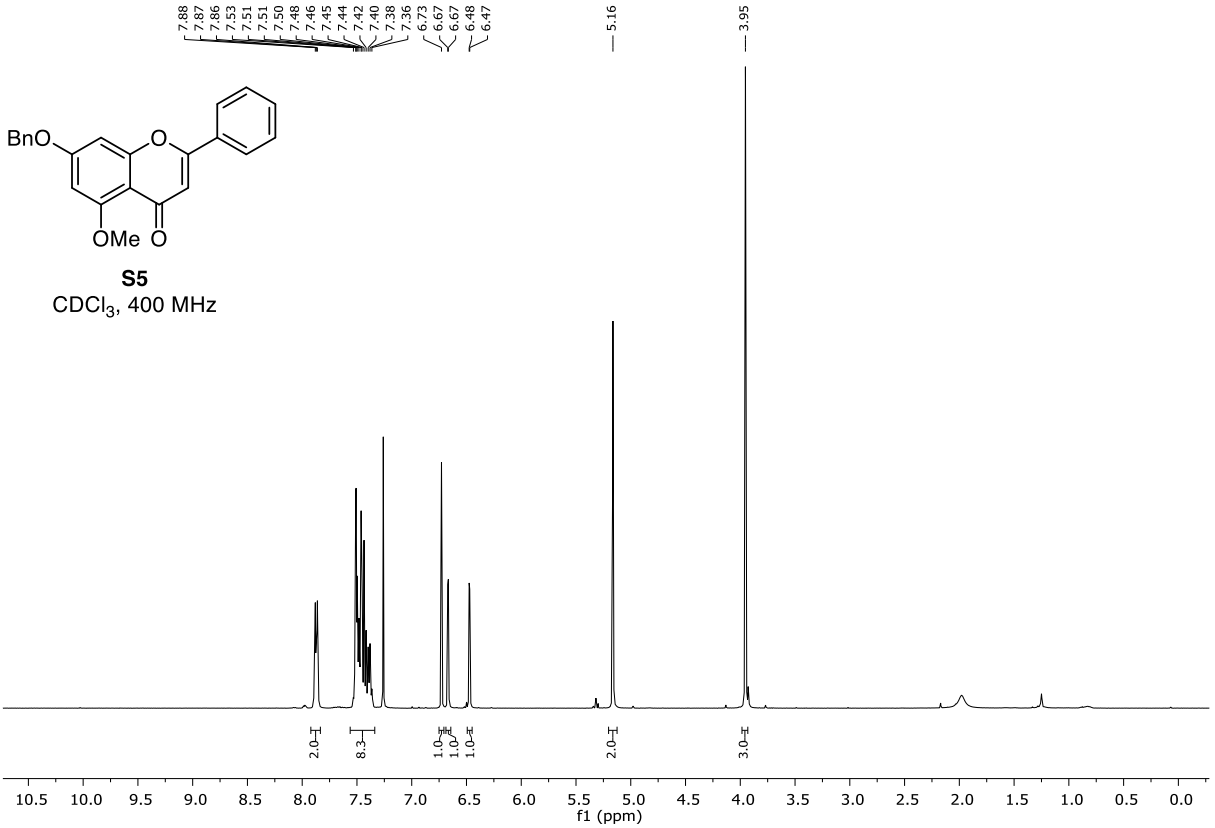
24
MeOD, 400 MHz



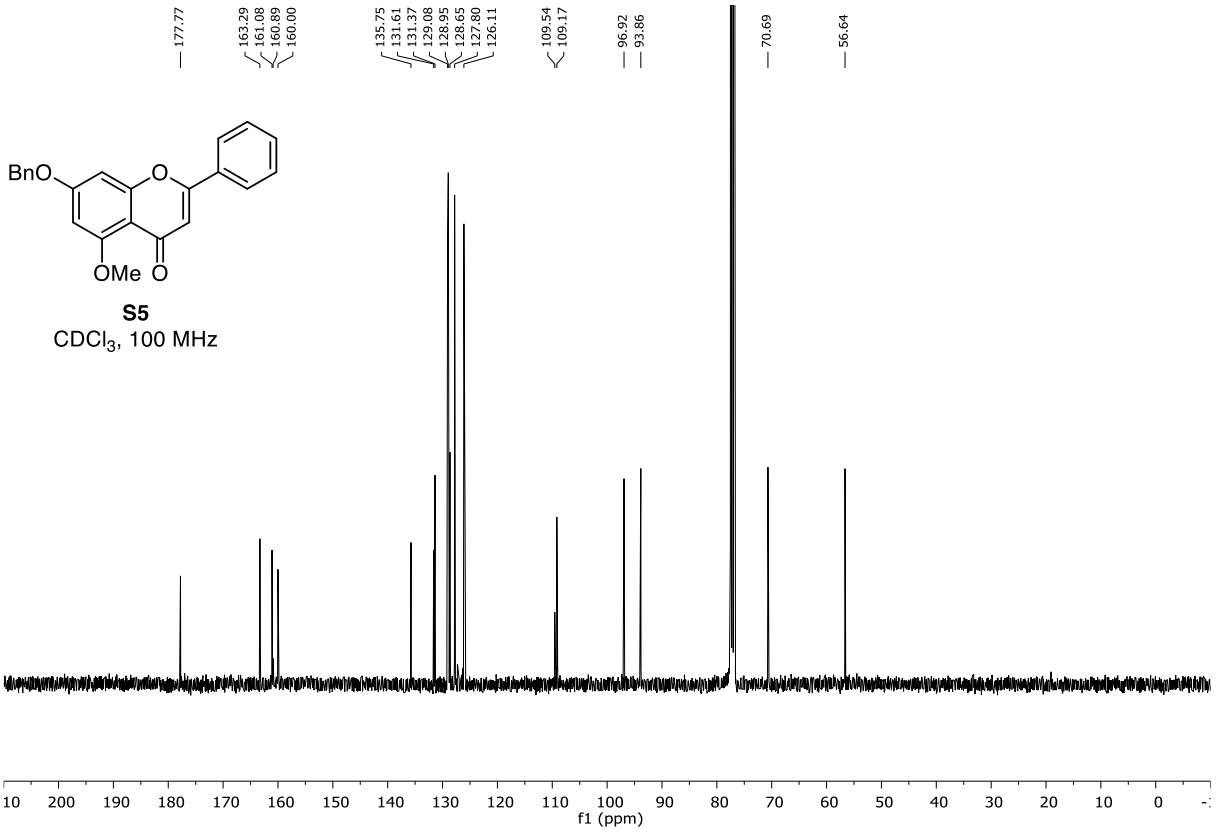
24
MeOD, 100 MHz


HO
O
OMe
1
CDCl3, 400 MHz
f1 (ppm)

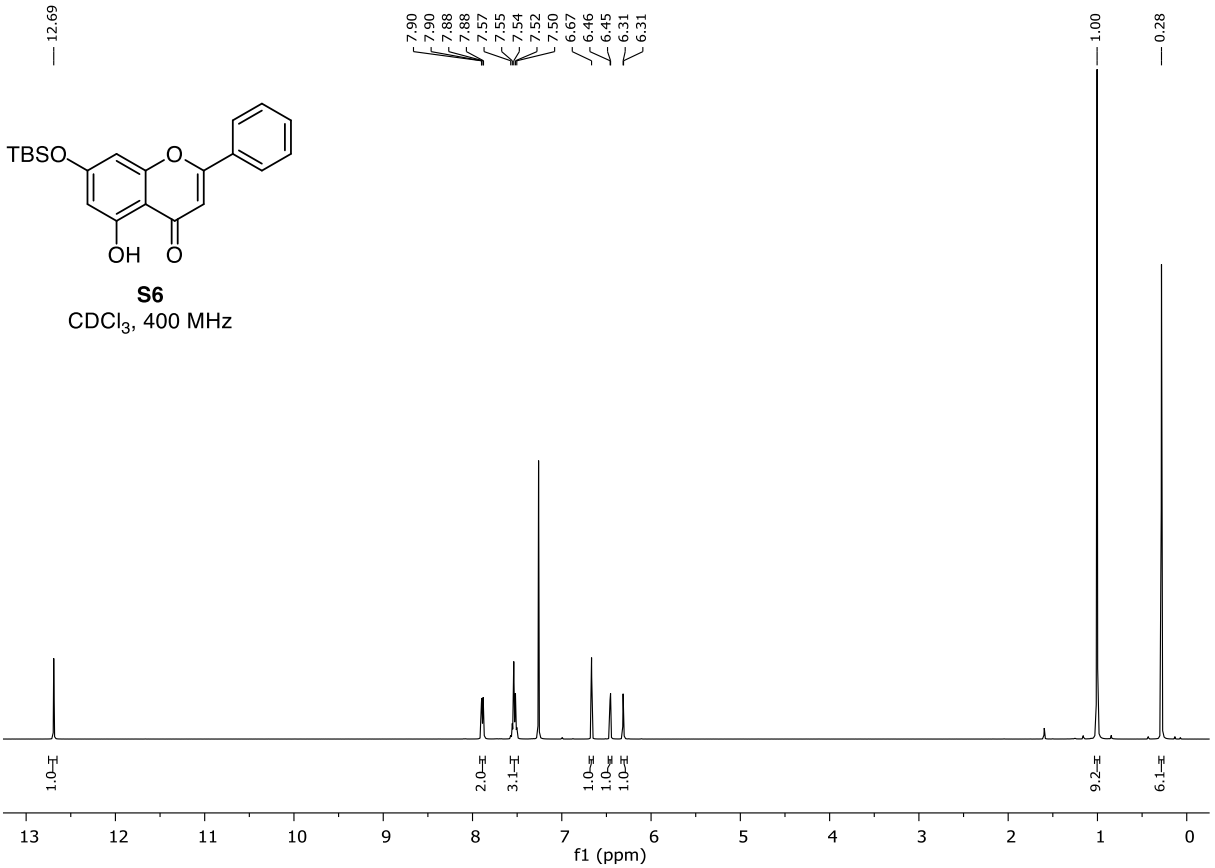

HO
O
OMe
1
CDCl3, 100 MHz
f1 (ppm)



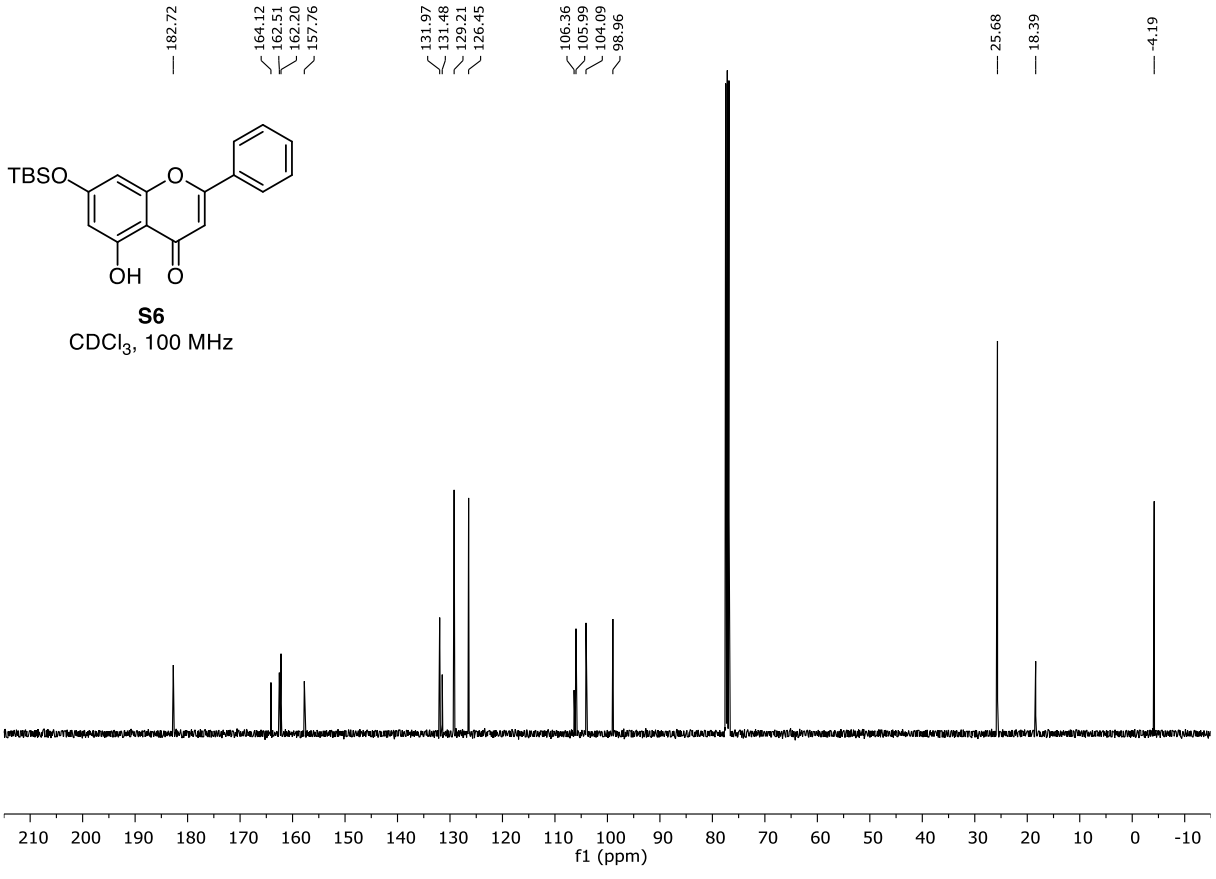
S5
$CDCl_3$, 400 MHz



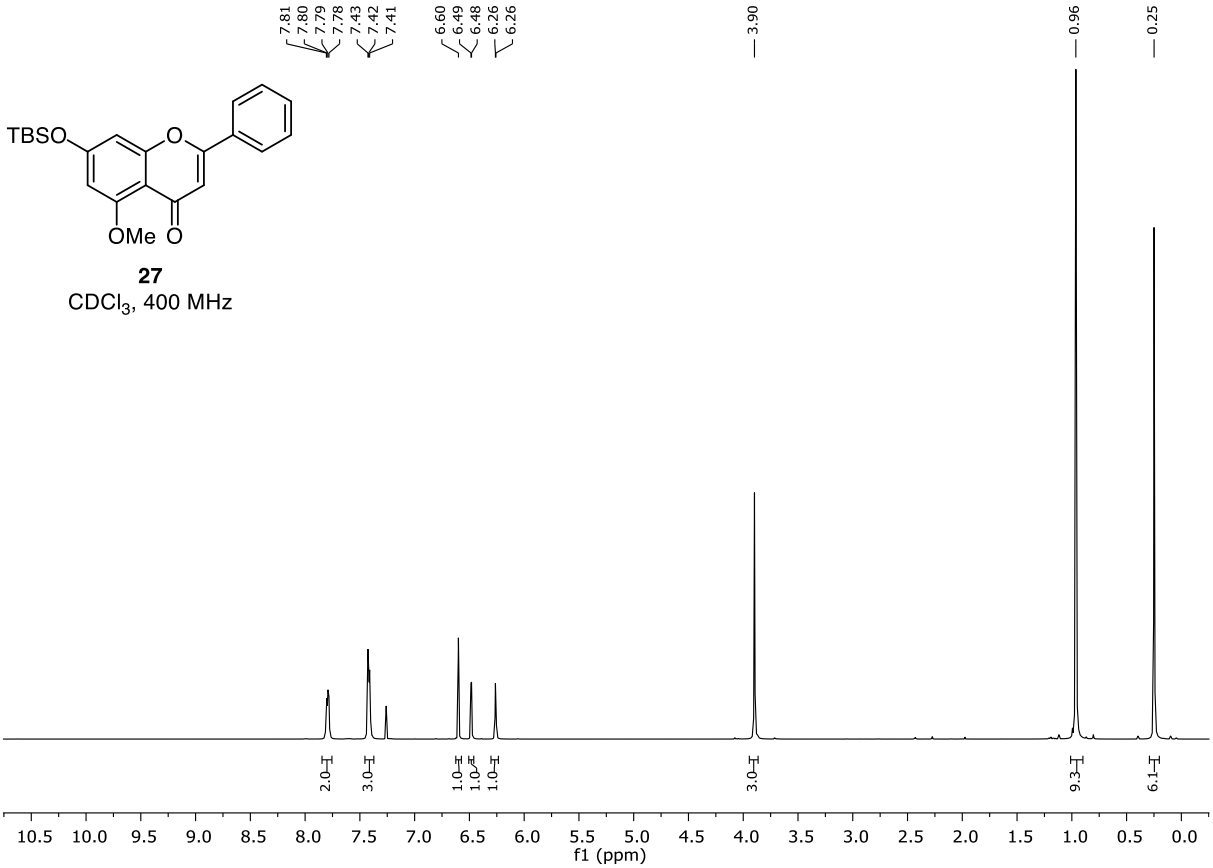
S5
$CDCl_3$, 100 MHz



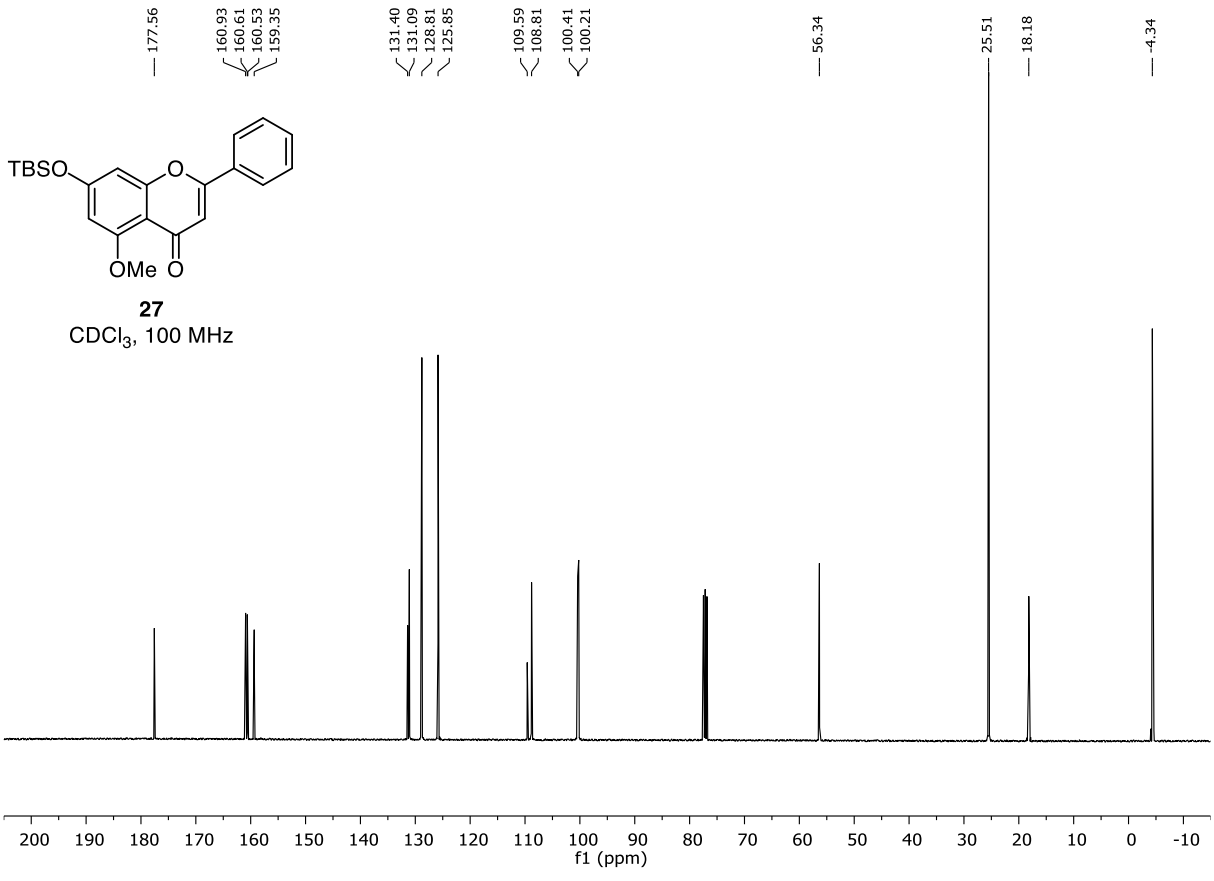
S6
$CDCl_3$, 400 MHz



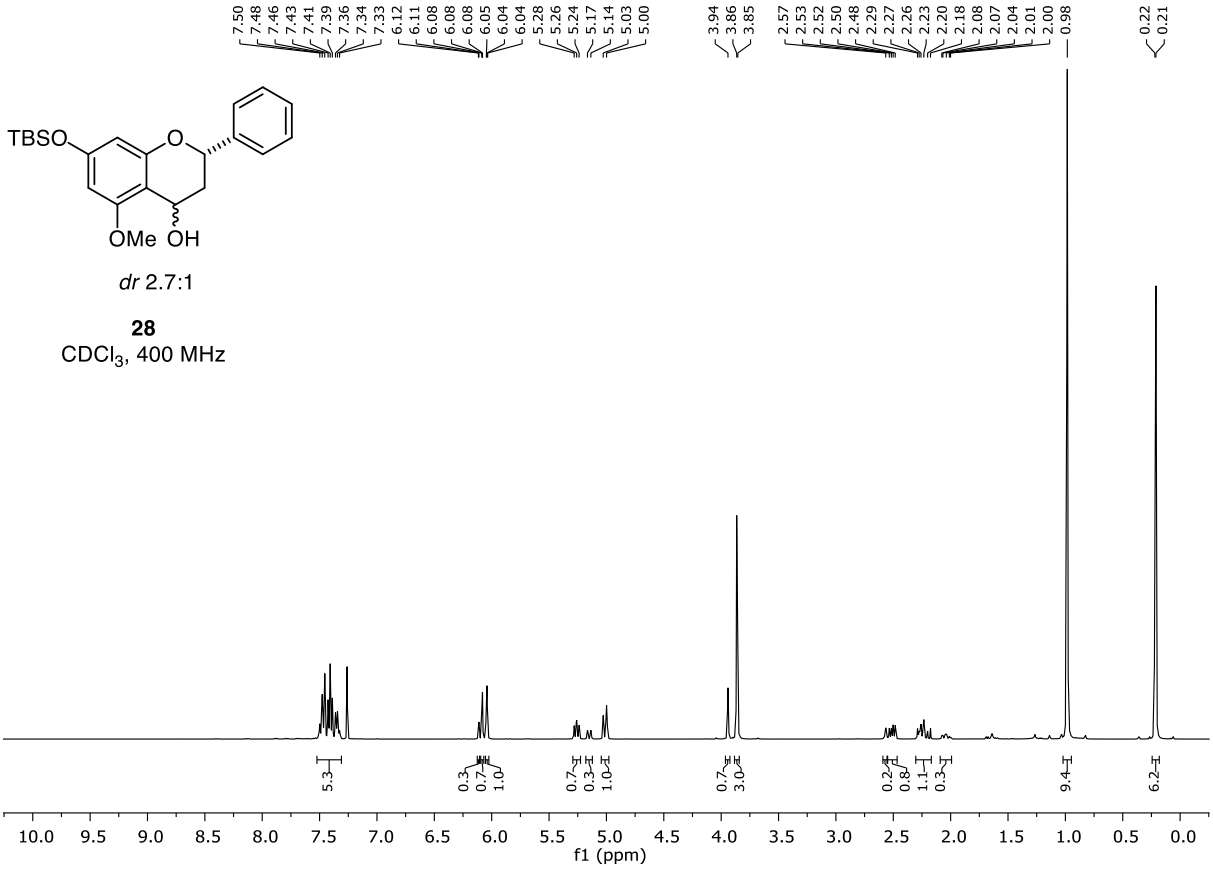
S6
$CDCl_3$, 100 MHz

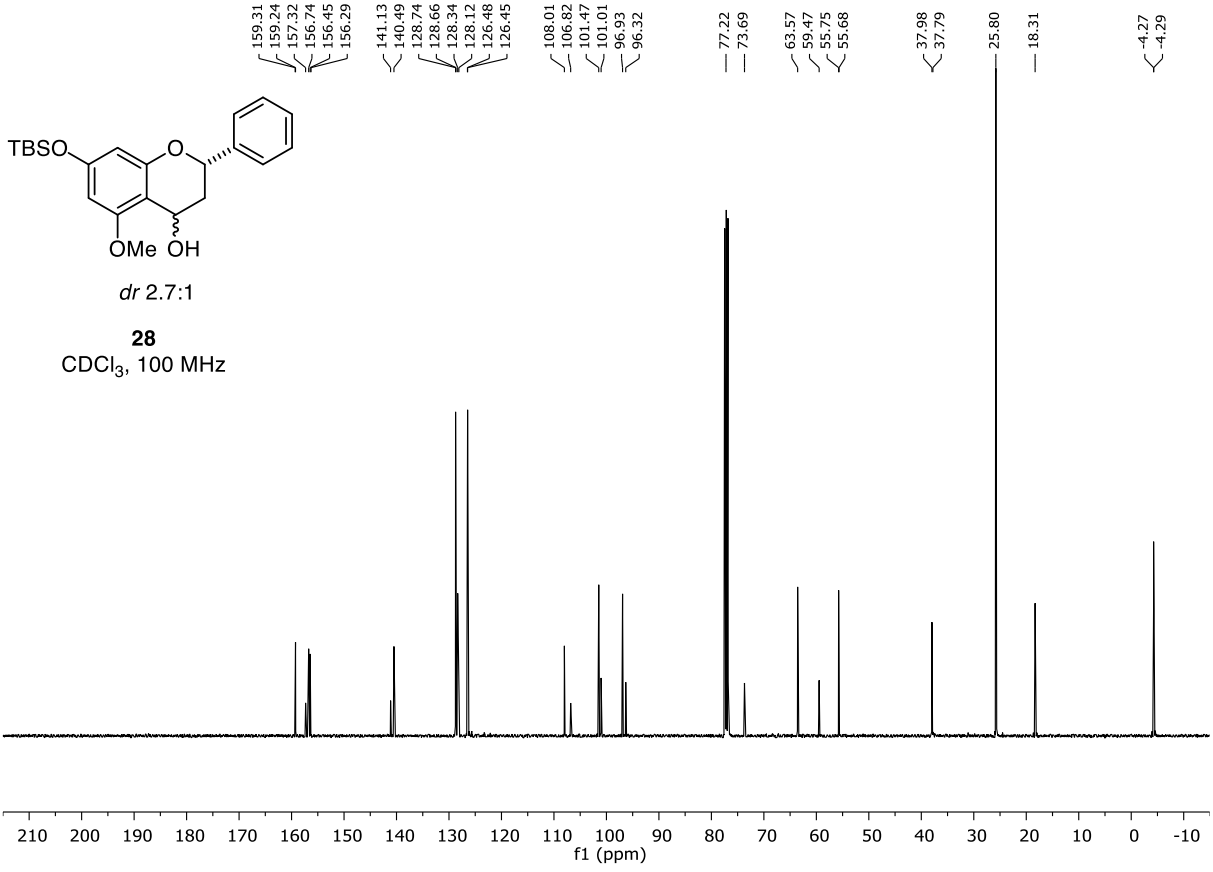


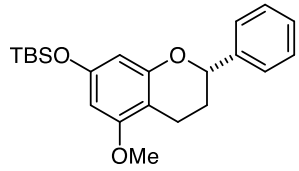
27
$CDCl_3$, 400 MHz



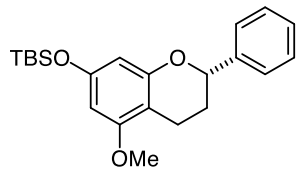
27
$CDCl_3$, 100 MHz


TBSO
OMe OH
dr 2.7:1
28
CDCl3, 400 MHz
f1 (ppm)

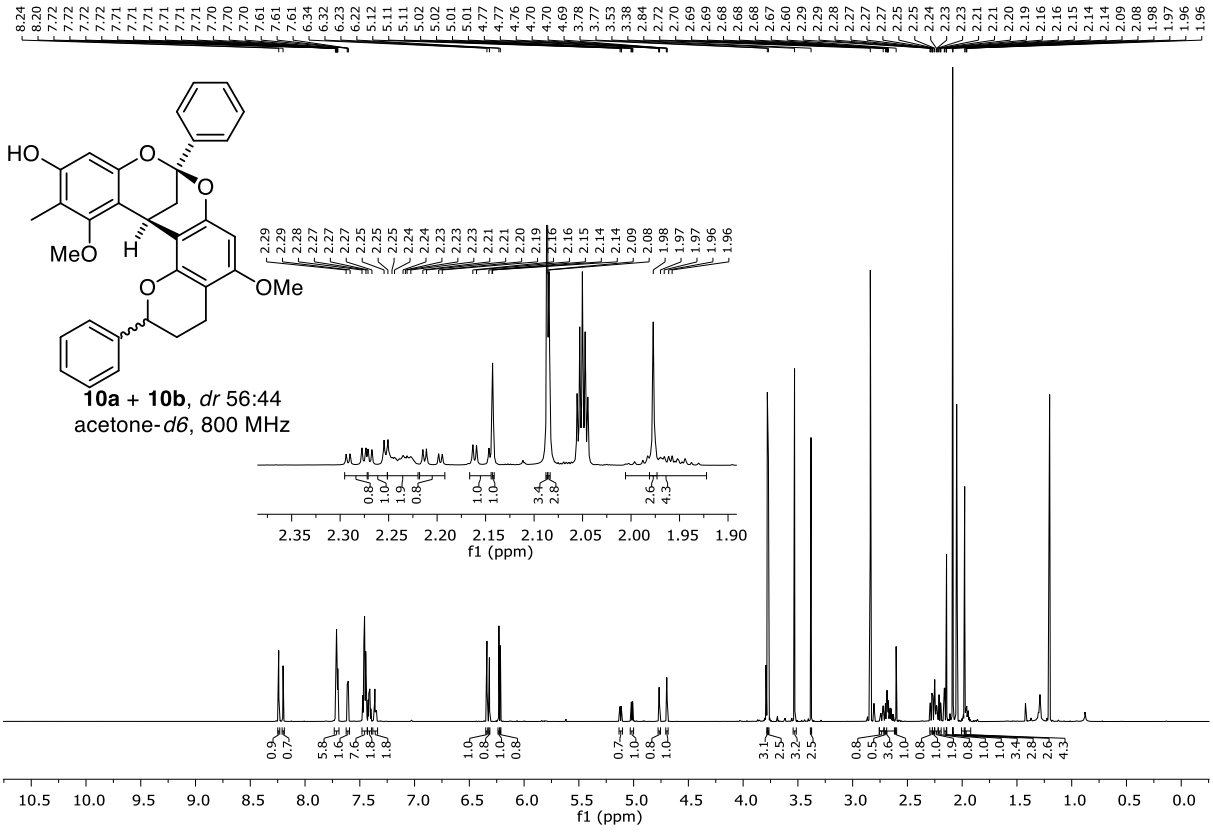

TBSO
OMe OH
dr 2.7:1
28
CDCl3, 100 MHz
f1 (ppm)

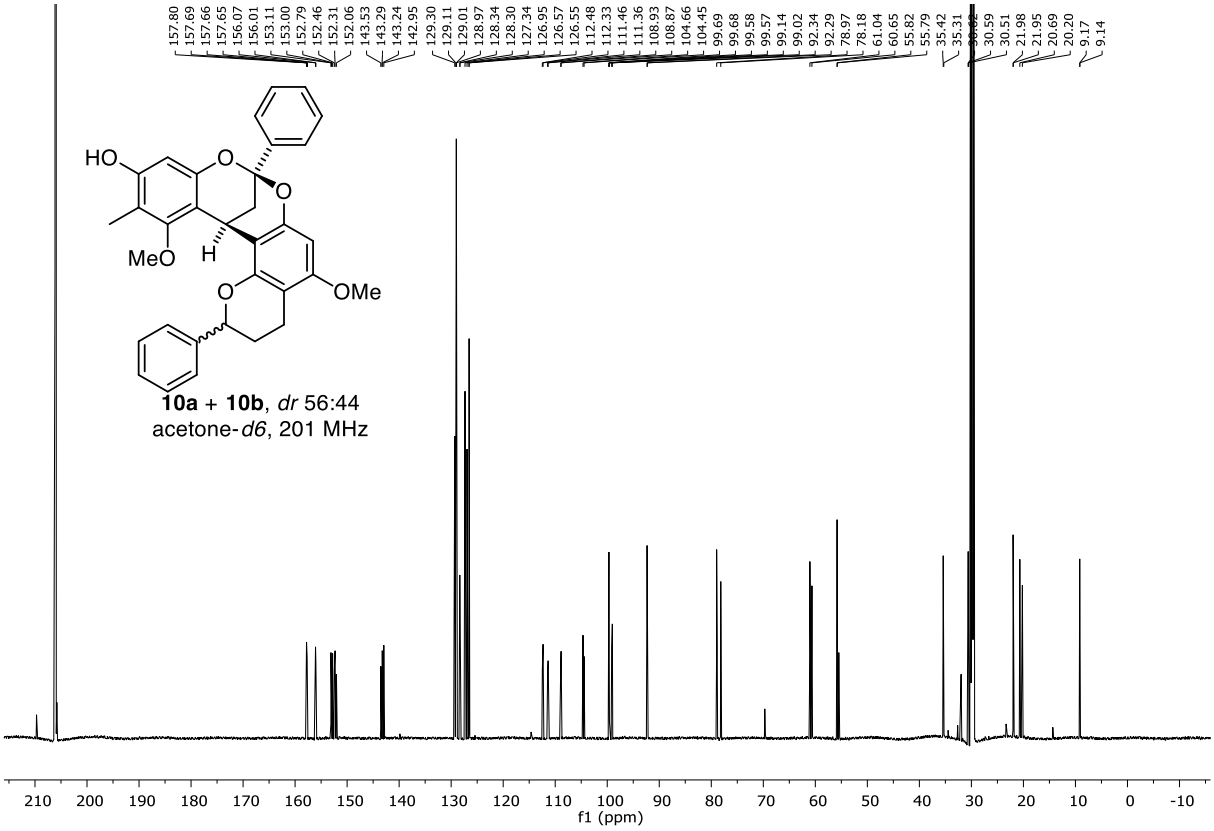


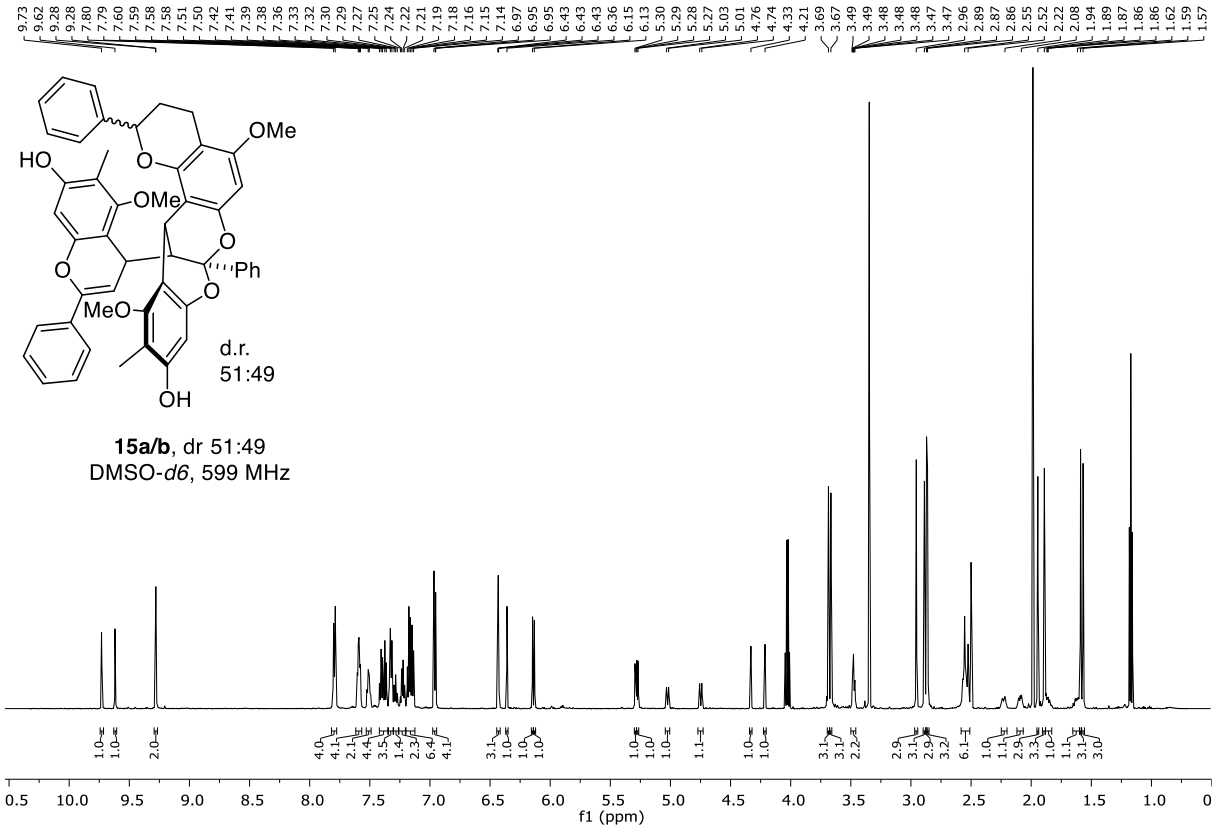
S7
$CDCl_3$, 400 MHz

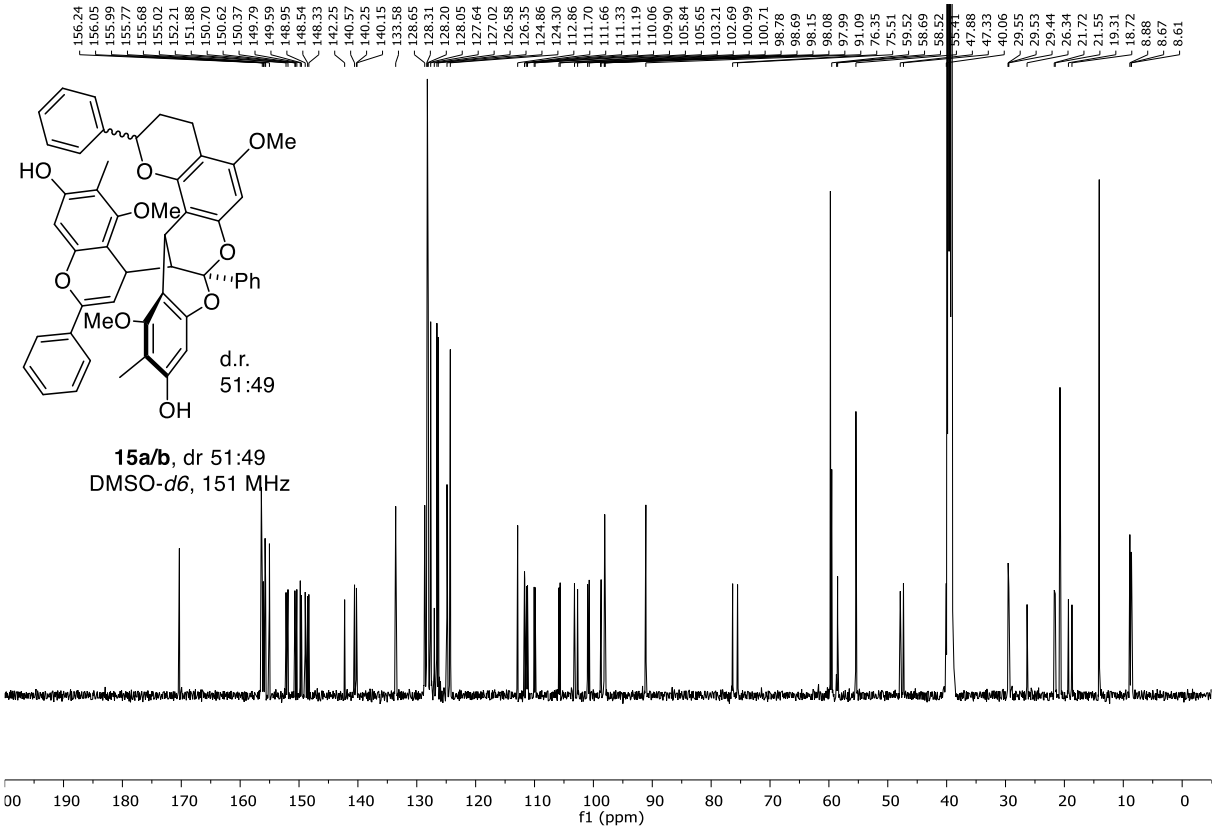


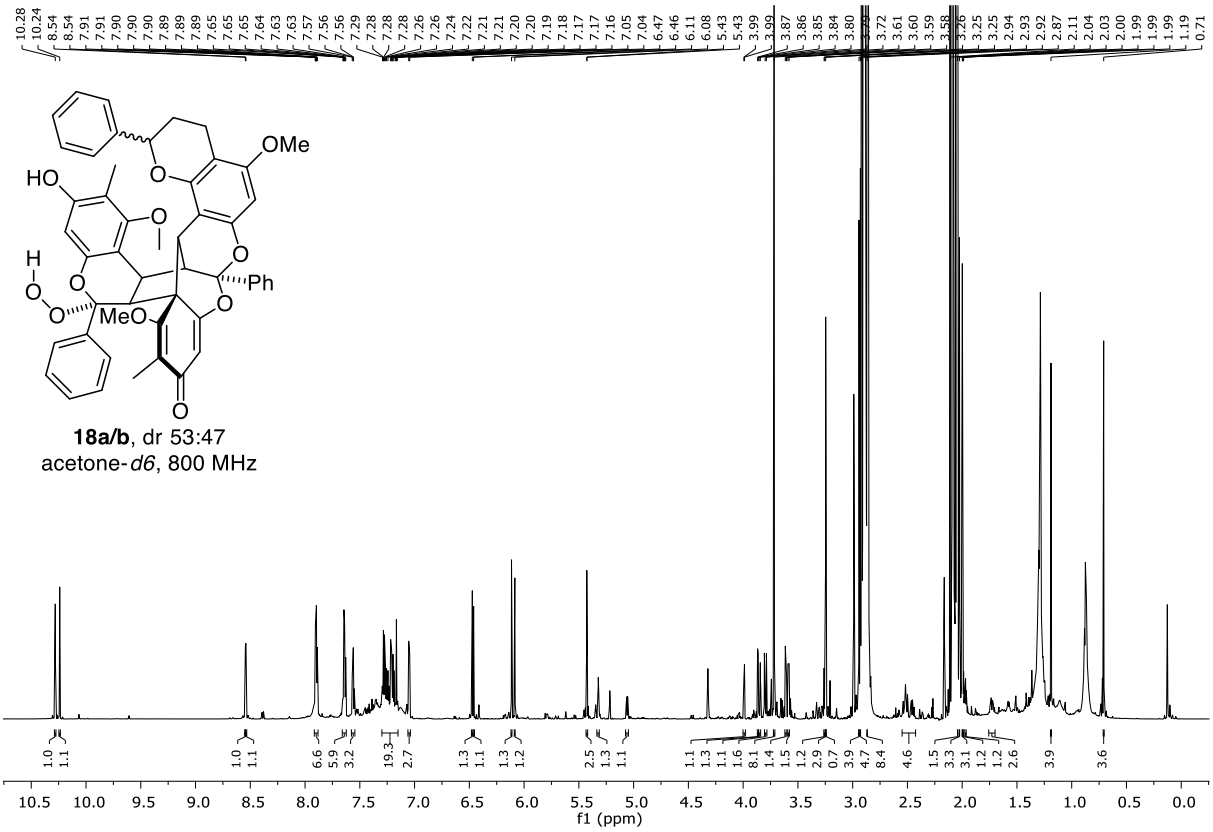
S7
$CDCl_3$, 100 MHz


HO
MeO
H
OMe
10a + 10b, dr 56:44
acetone-d6, 800 MHz
f1 (ppm)

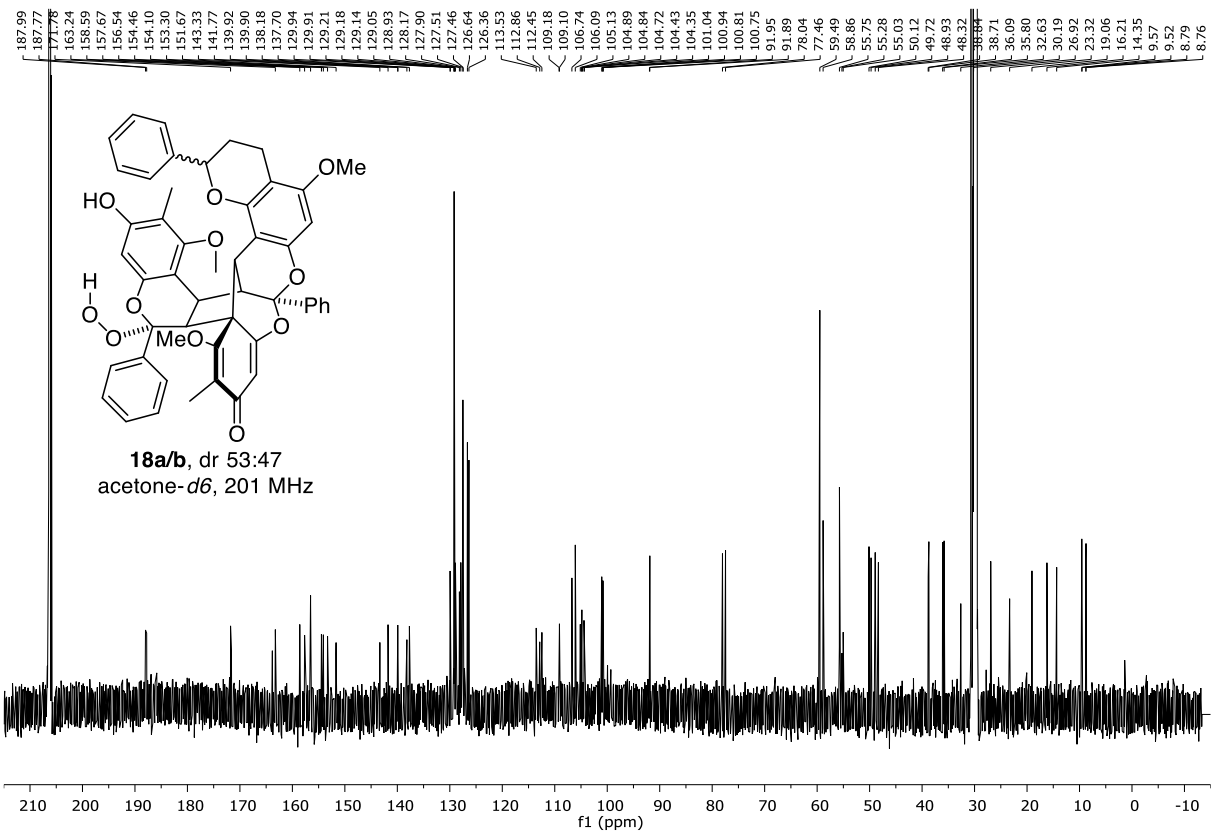

HO
MeO
H
OMe
10a + 10b, dr 56:44
acetone-d6, 201 MHz
f1 (ppm)


HO
OMe
OMe
O
O
O
Ph
MeO
d.r.
51:49
OH
15a/b, dr 51:49
DMSO-d6, 599 MHz
f1 (ppm)


HO
OMe
OMe
O
O
O
Ph
MeO
d.r.
51:49
OH
15a/b, dr 51:49
DMSO-d6, 151 MHz
f1 (ppm)

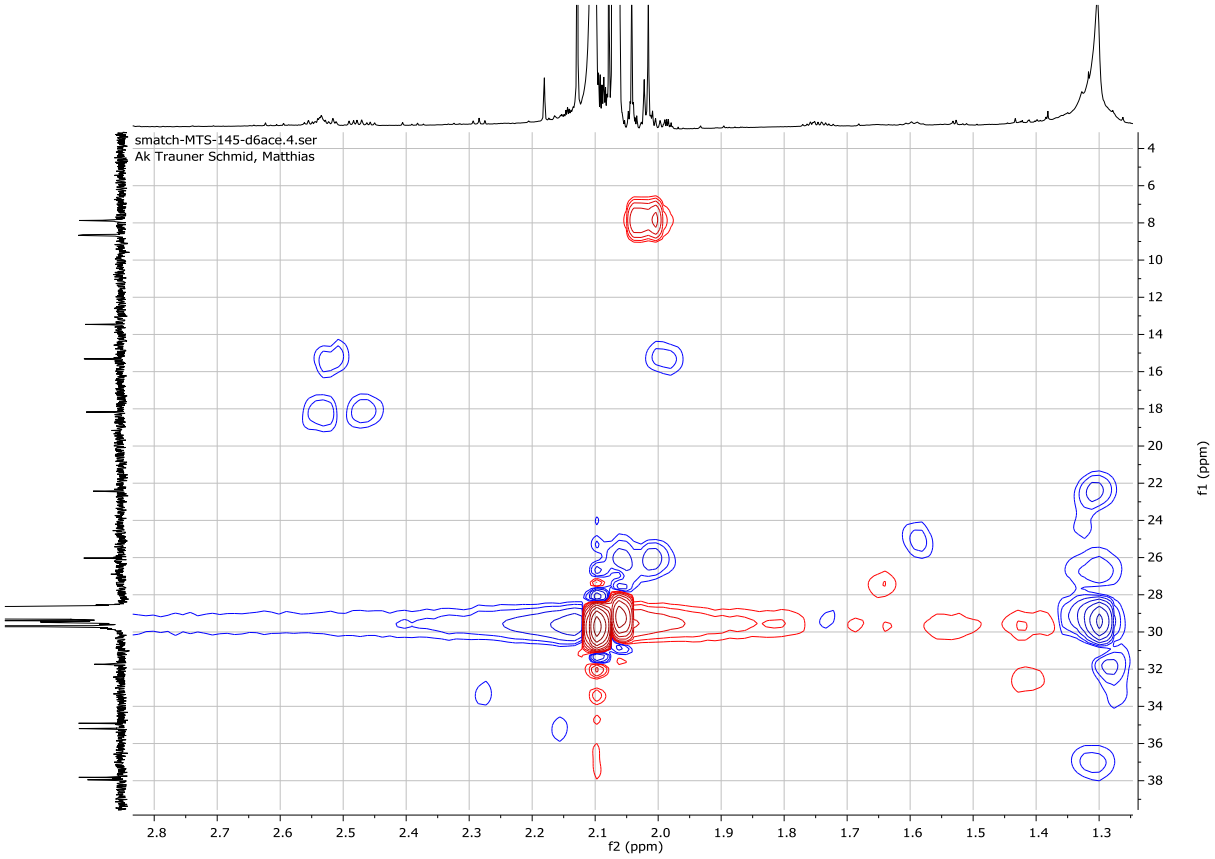


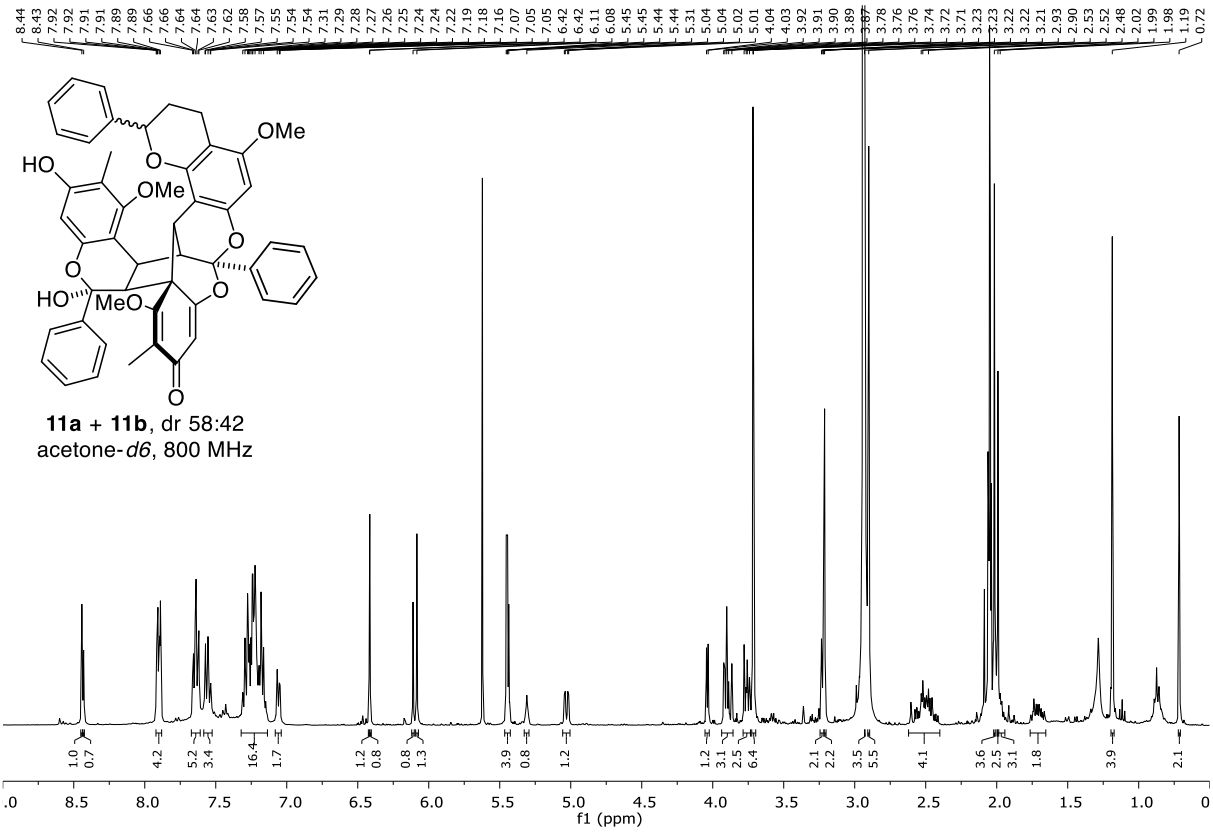
18a/b, dr 53:47
acetone-*d6*, 800 MHz

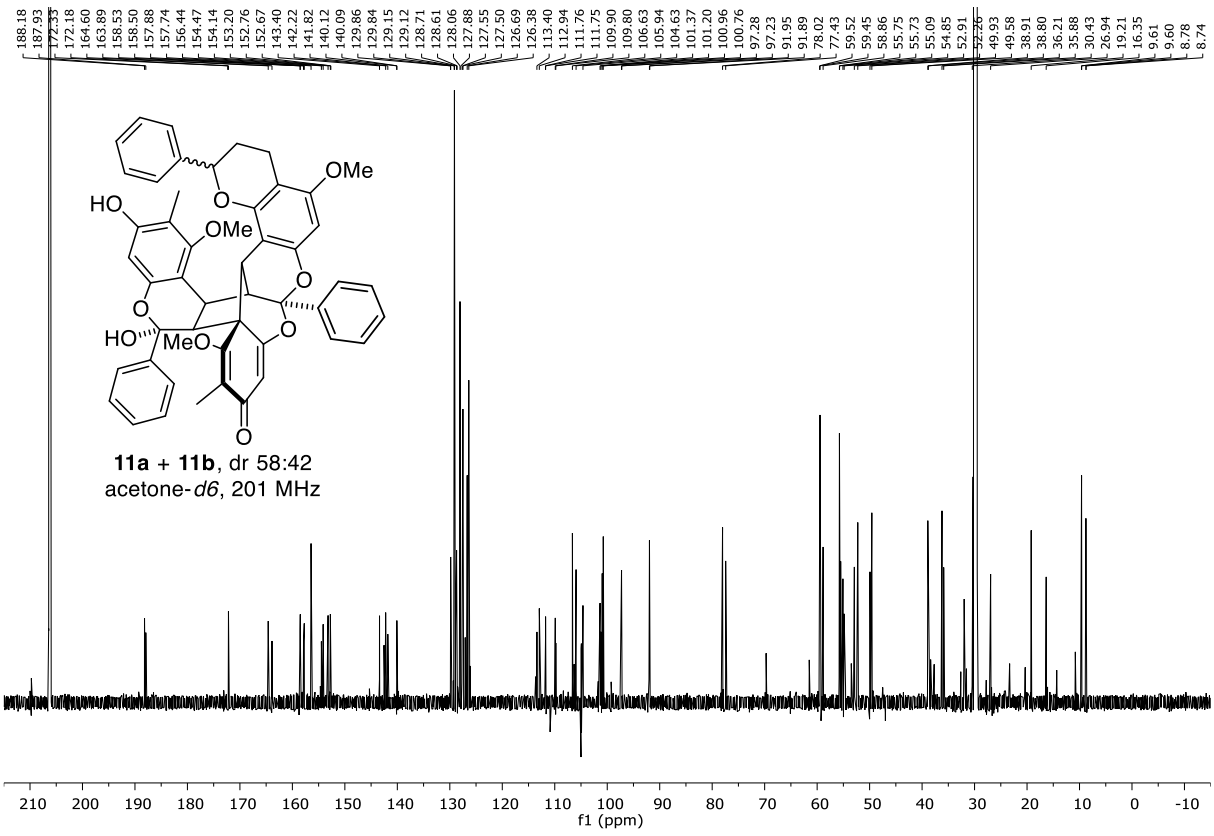


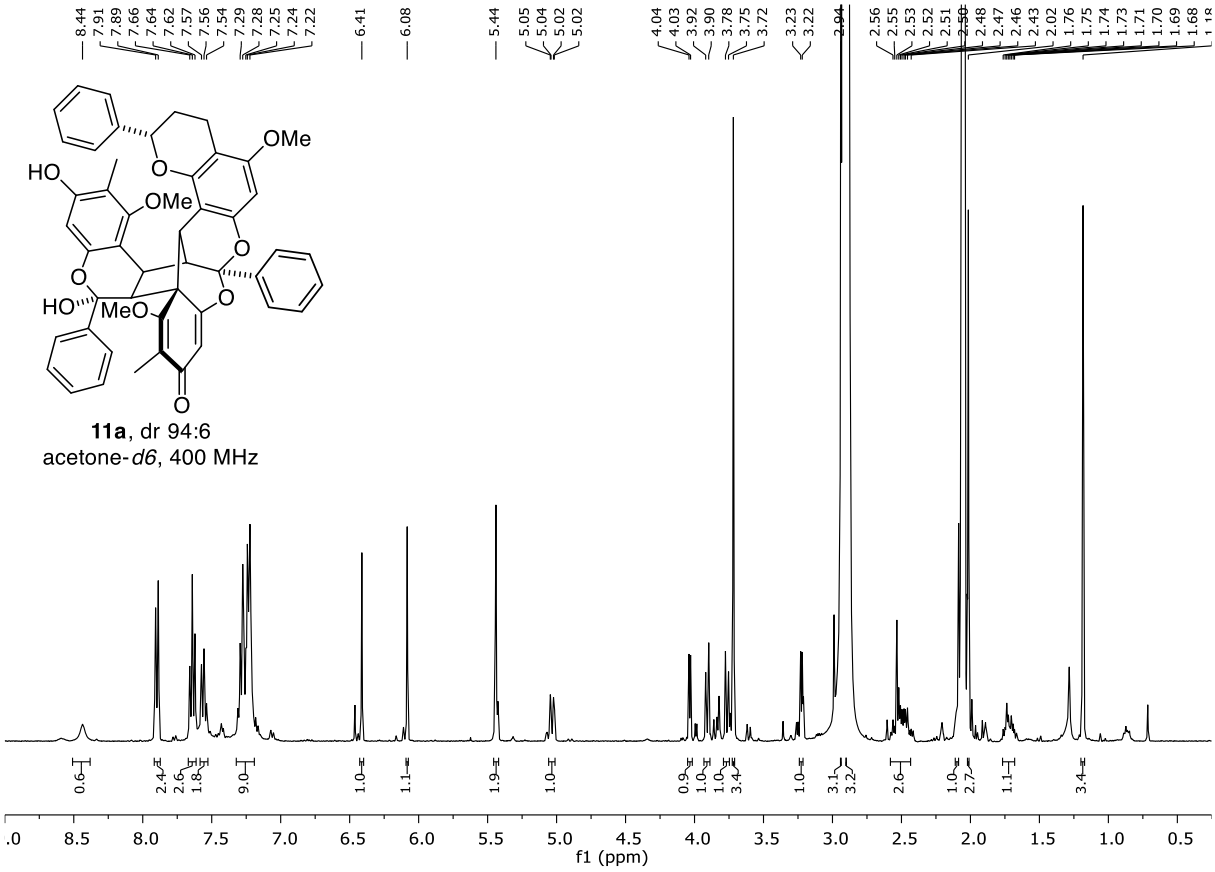
18a/b, dr 53:47
acetone-*d6*, 201 MHz

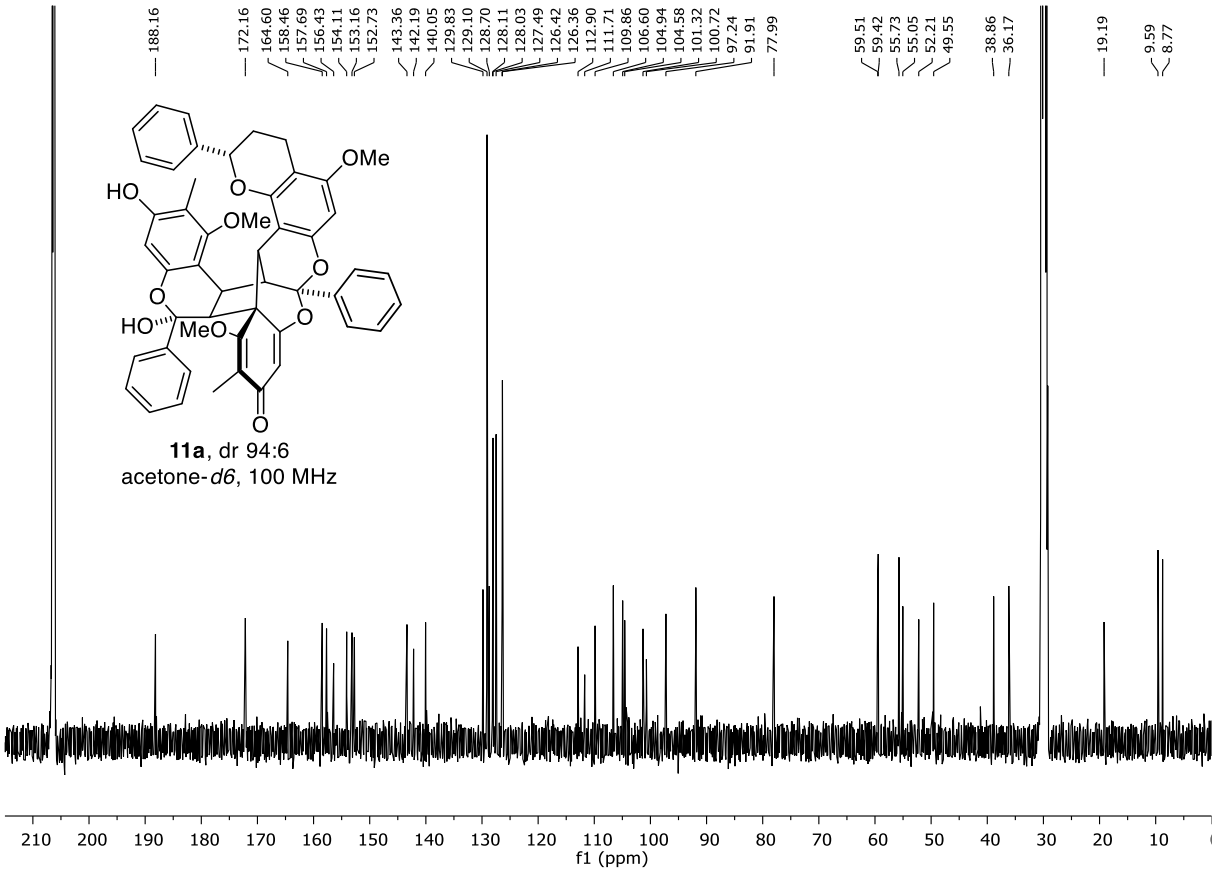
HSQC **18a/b**


smatch-MTS-145-d6ace.4.ser
Ak Trauner Schmid, Matthias
f2 (ppm)
f1 (ppm)

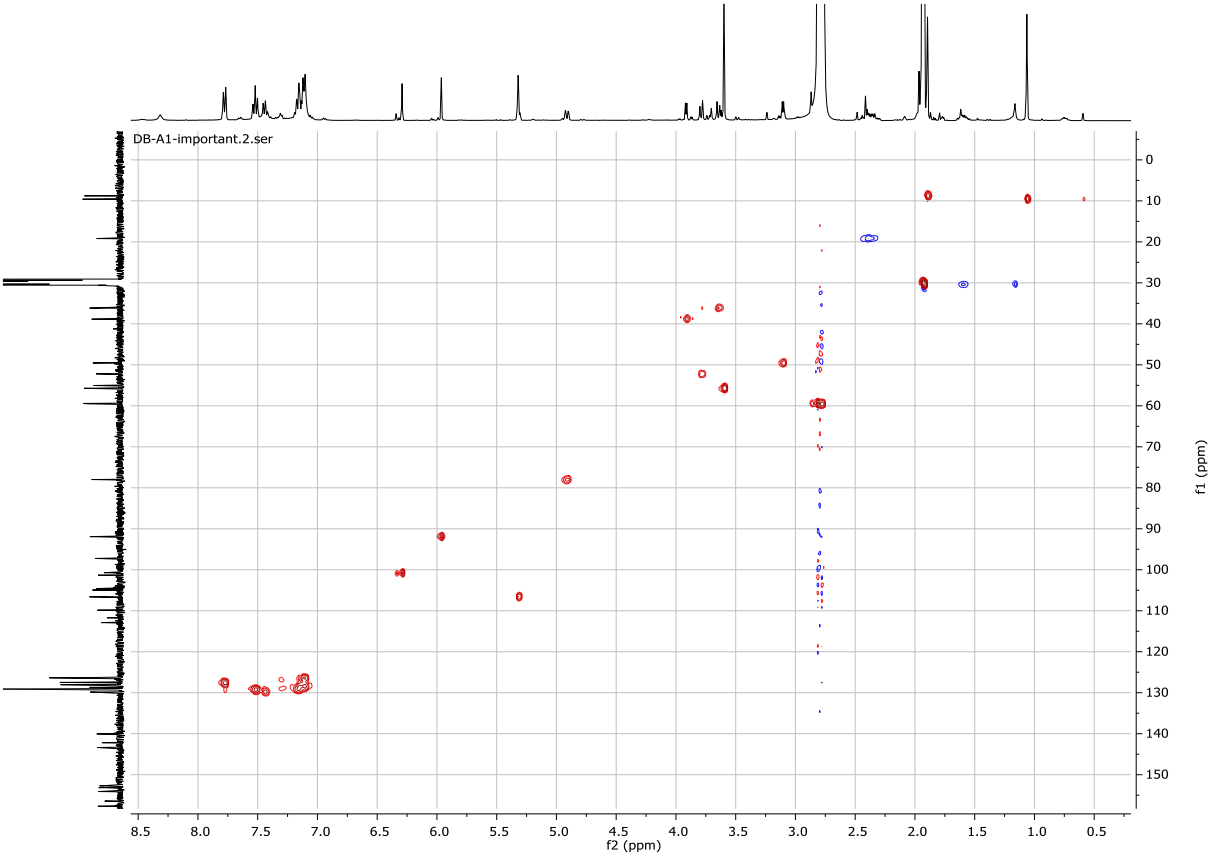

OMe
HO
O
OMe
O
O
HO
MeO
O
O
11a + 11b, dr 58:42
acetone-d6, 800 MHz
f1 (ppm)


OMe
HO
O
OMe
O
O
HO
MeO
O
O
11a + 11b, dr 58:42
acetone-d6, 201 MHz
f1 (ppm)

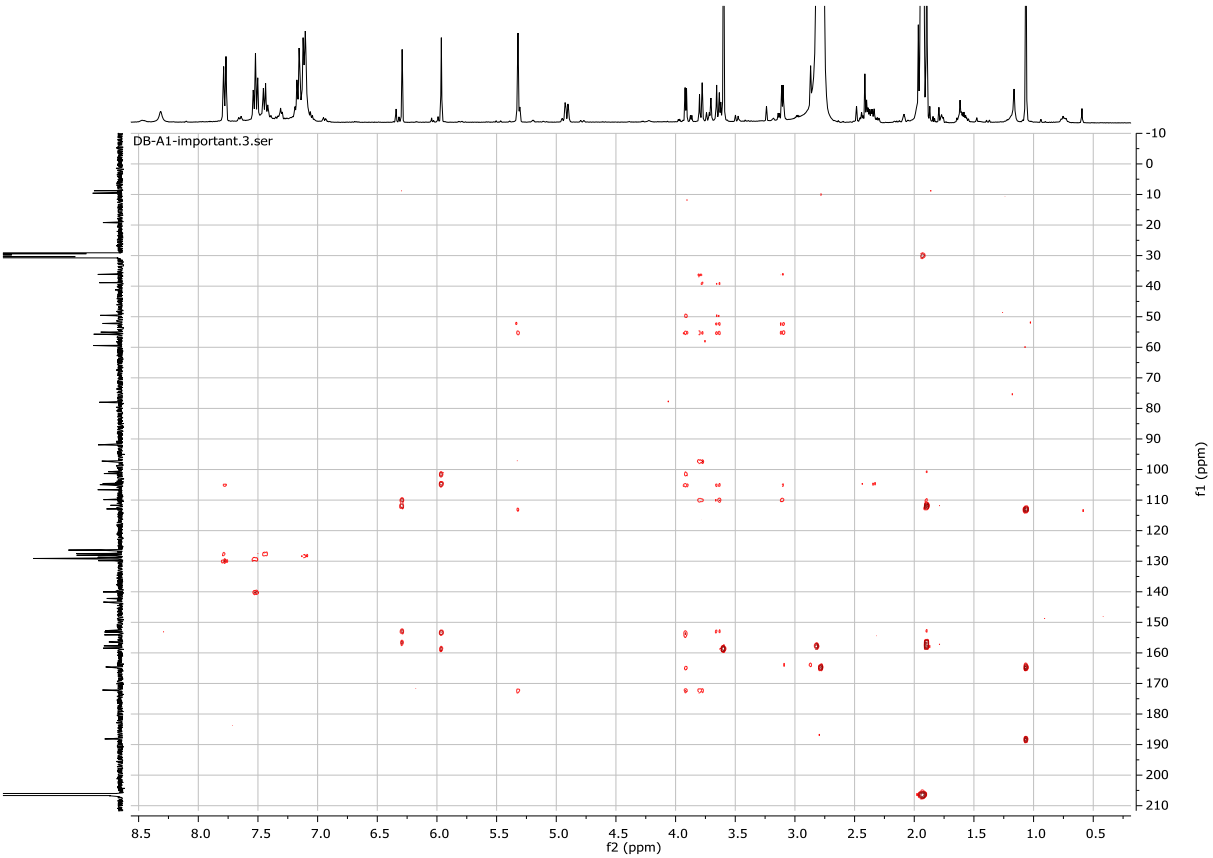

11a, dr 94:6
acetone-d6, 400 MHz
f1 (ppm)


11a, dr 94:6
acetone-d6, 100 MHz
f1 (ppm)

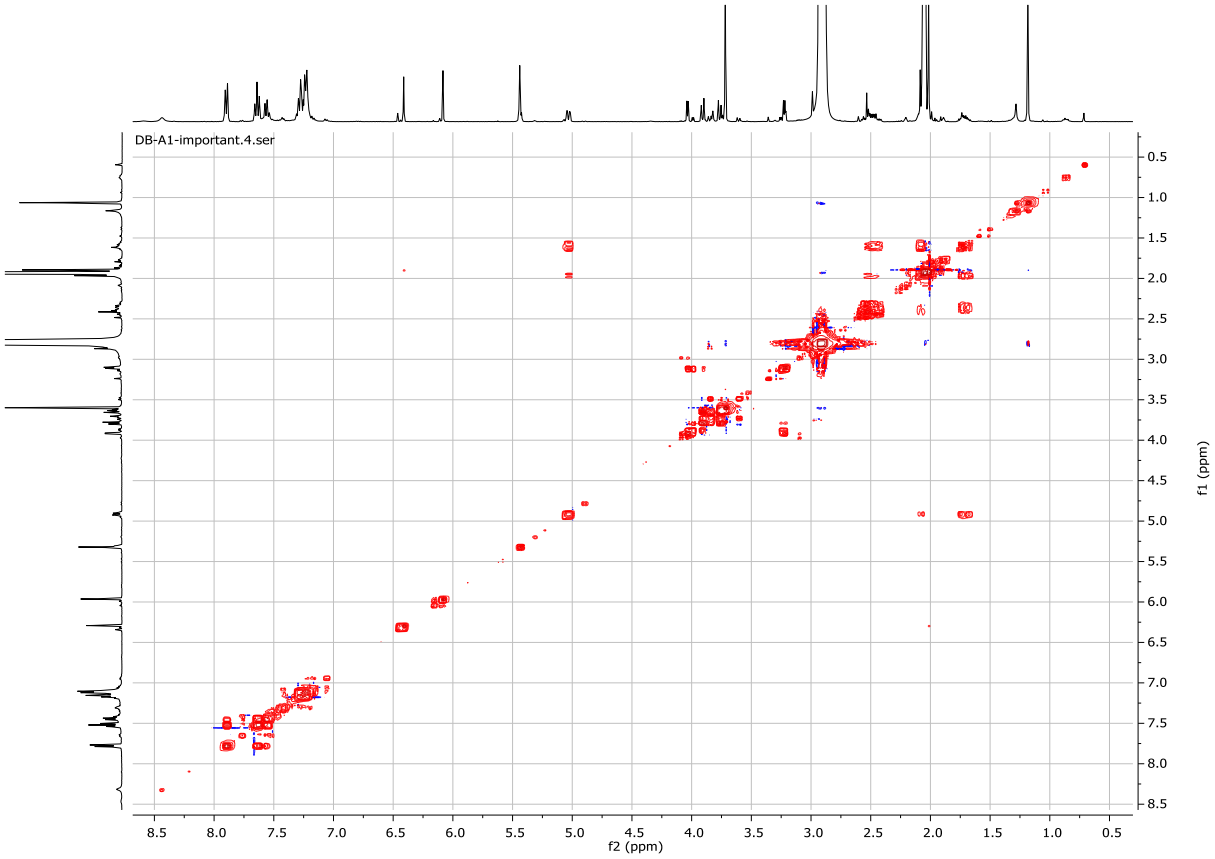
HSQC **11a**

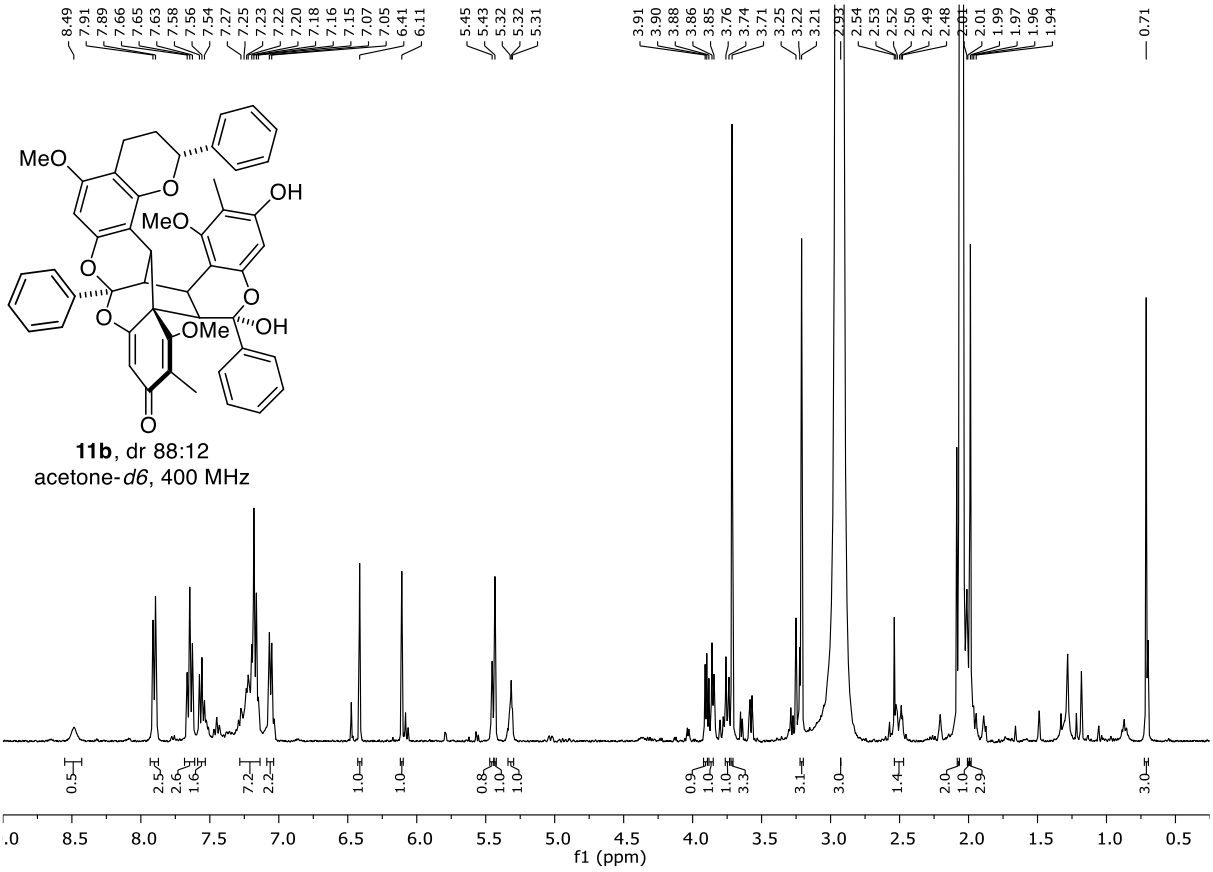


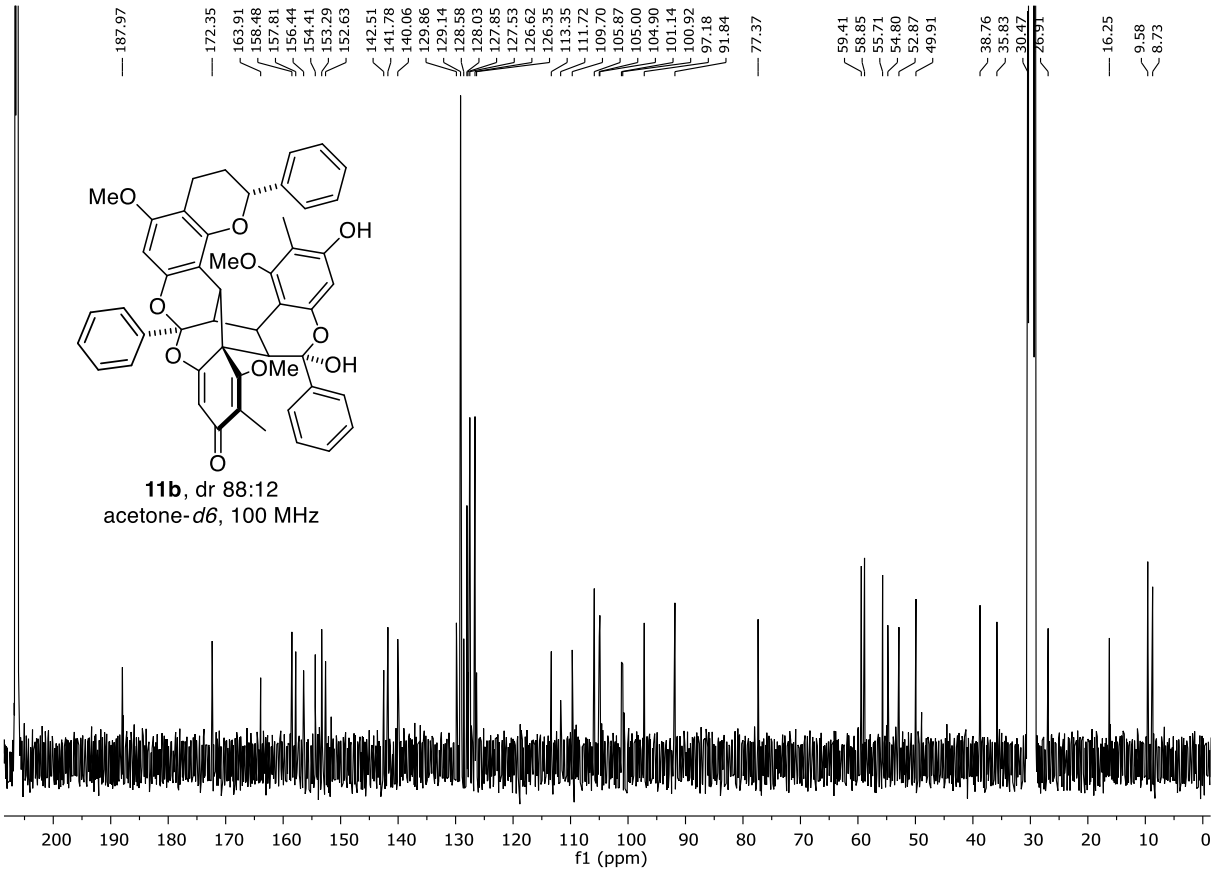
HMBC **11a**



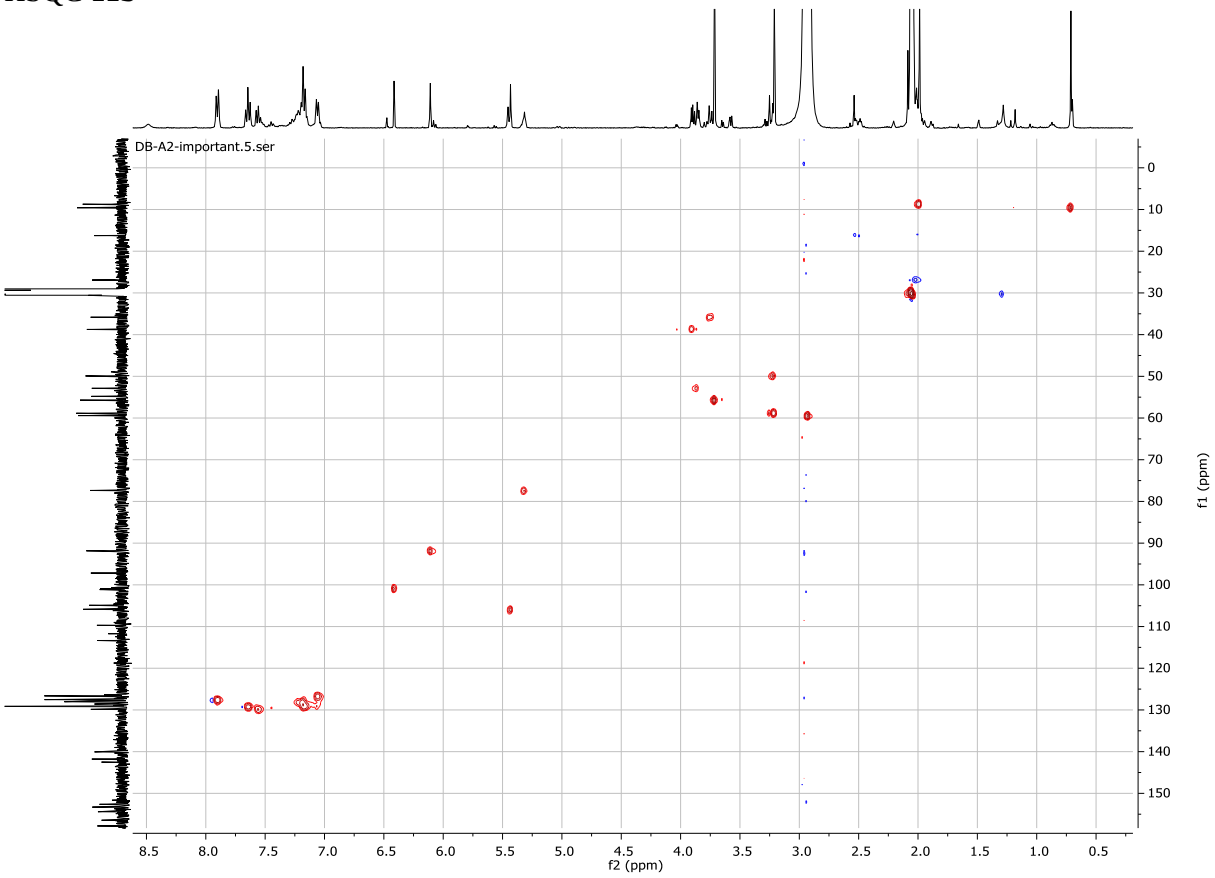
COSY **11a**



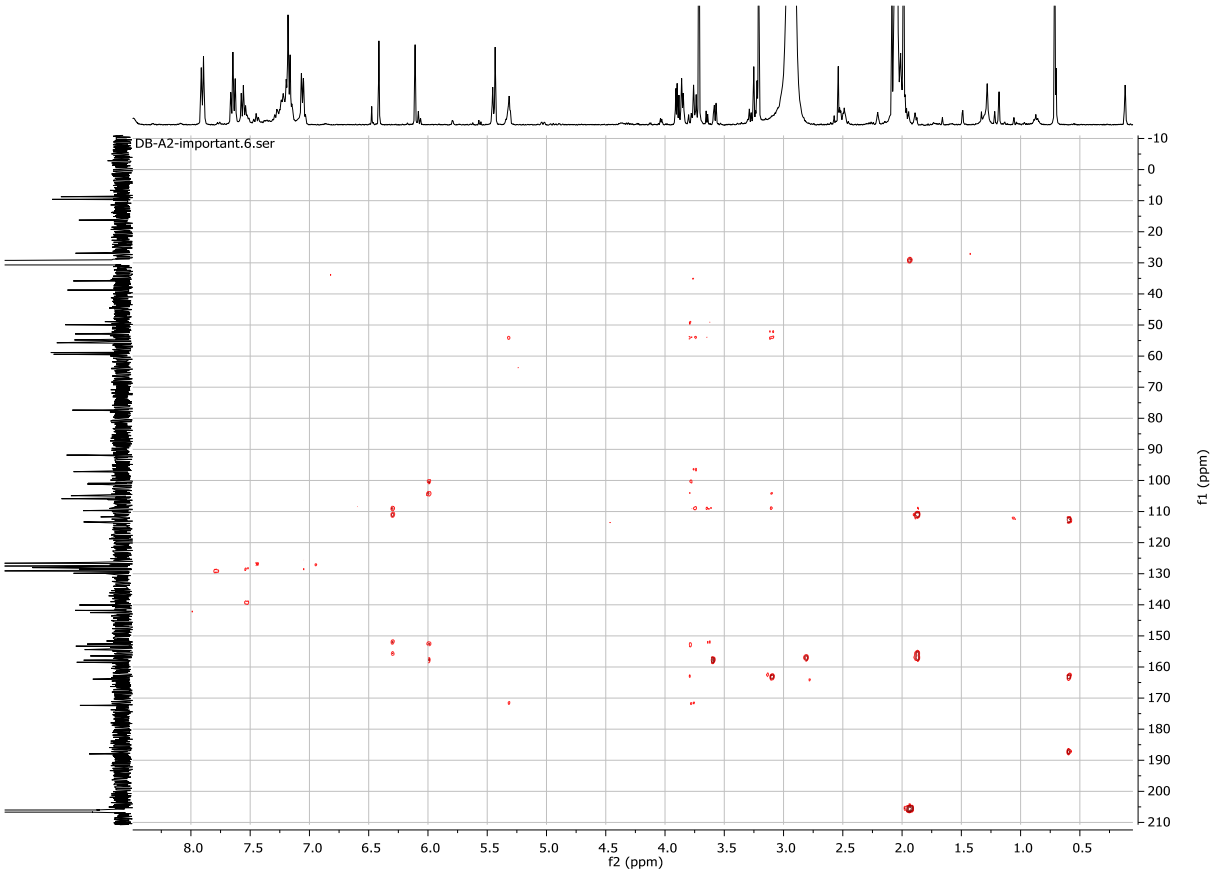

MeO
OH
MeO
OMe
OH
O
11b, dr 88:12
acetone-d6, 400 MHz
f1 (ppm)


MeO
OH
MeO
OMe
OH
O
11b, dr 88:12
acetone-d6, 100 MHz
f1 (ppm)

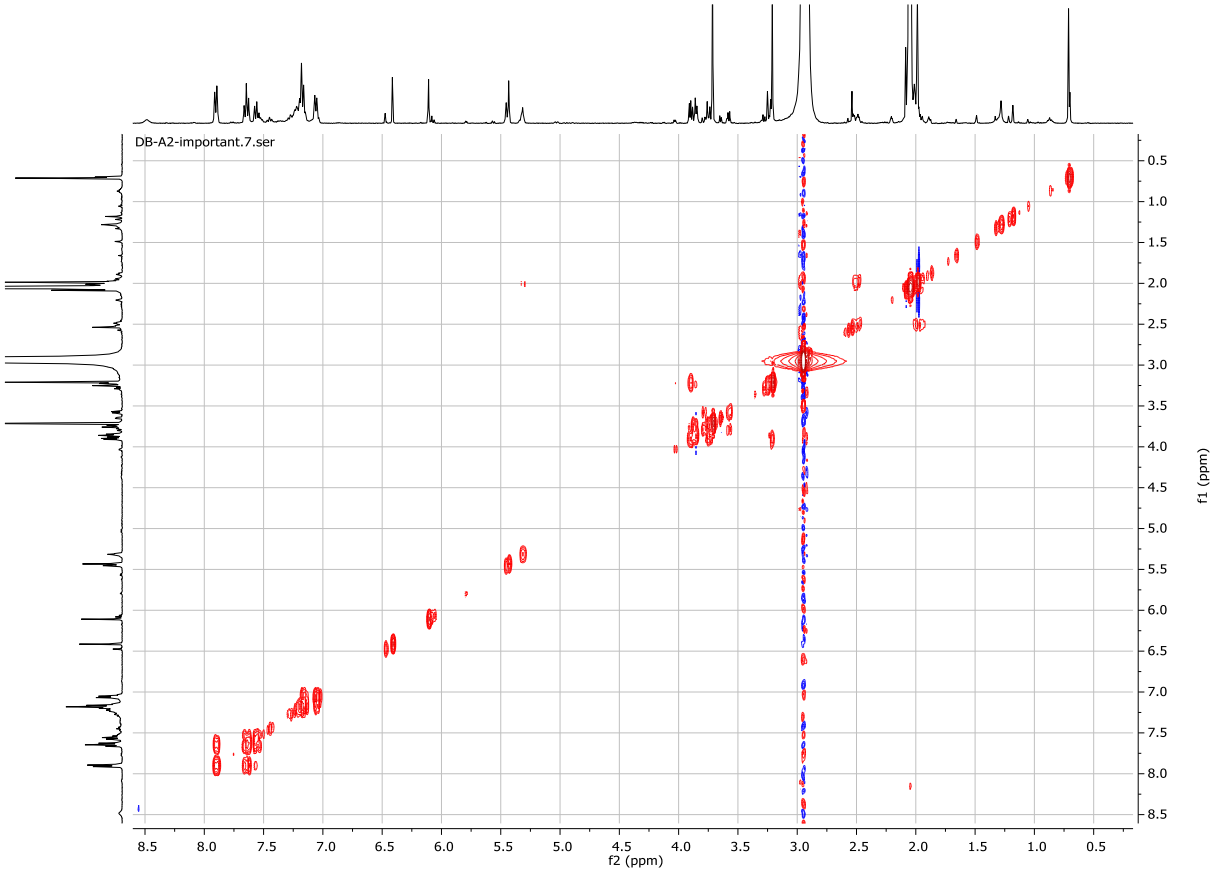
HSQC **11b**



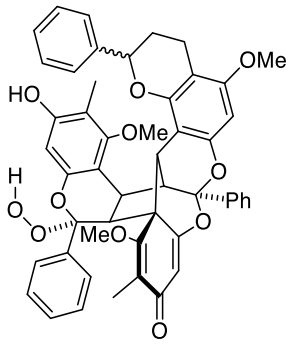
HMBC **11b**



COSY **11b**



1.3 X-Ray crystallographic analysis data



18a/b

Dragonbloodin peroxide (**18a/b**)	
net formula	$C_{50}H_{44}O_{11}$
M_r/g mol^{-1}	820.85
crystal size/mm	0.100 × 0.090 × 0.020
T/K	100(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P b c a'
a/Å	18.3069(8)
b/Å	20.2298(7)
c/Å	26.5416(10)
α/°	90
β/°	90
γ/°	90
V/Å^3	9829.5(7)
Z	8
calc. density/g cm^{-3}	1.109
μ/mm^{-1}	0.078
absorption correction	Multi-Scan
transmission factor range	0.8689–0.9593
refls. measured	68880
R_{int}	?
mean σ(I)/I	0.0657
θ range	3.255–26.37
observed refls.	6328
x, y (weighting scheme)	0.1195, 0.0000
hydrogen refinement	constr
refls in refinement	10043
parameters	576
restraints	0
R(F_{obs})	0.0671
$R_w(F^2)$	0.2048
S	1.045
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.330
min electron density/e Å^{-3}	–0.286

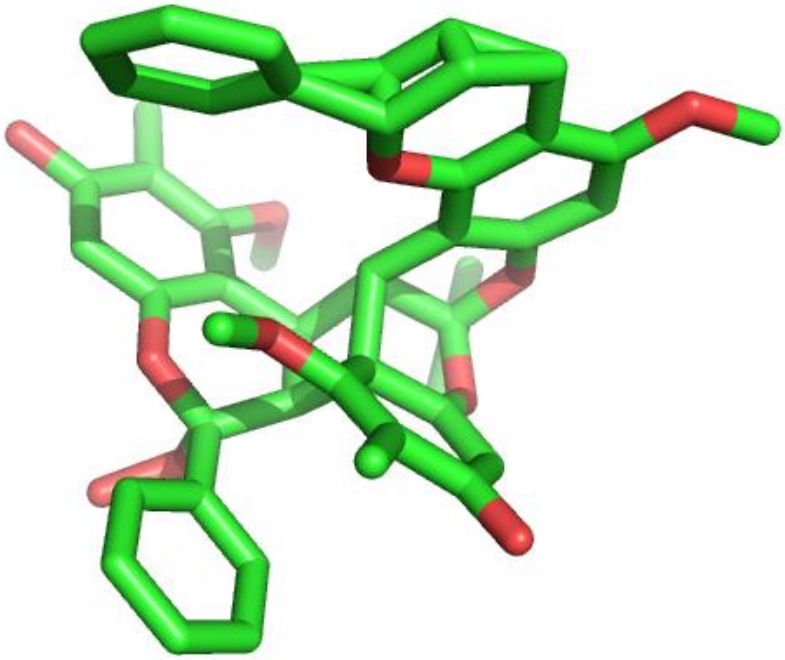
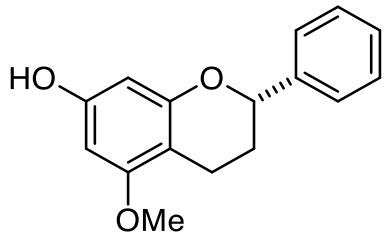
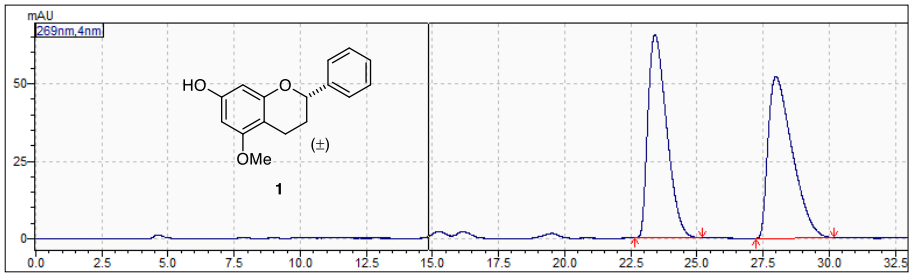


Figure 1-1: *Crystal structure of dragonbloodin A1 and the unnatural A2 enantionmer with structural disorder on the flavan moiety.*

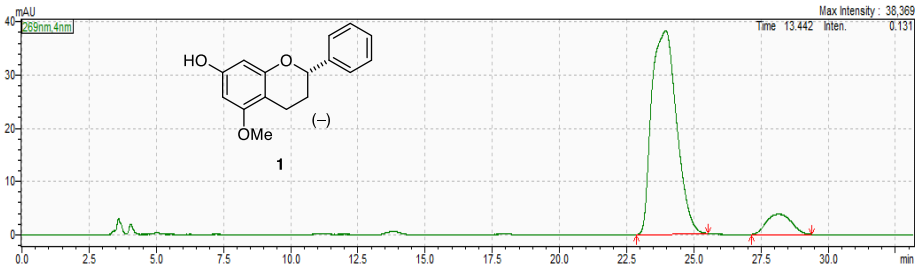
1.4 Chiral HPLC data



1



Peak#	Ret. Time	Area	Height	ID#	Area%	Name
1	23.418	3239777	65659		49.441	
2	27.992	3313003	52141		50.559	
Total		6552780	117799		100.000	



Peak#	Ret. Time	Area	Height	ID#	Area%	Name
1	23.956	2460776	38263		90.848	
2	28.166	247884	3797		9.152	
Total		2708660	42060		100.000	

2 Supporting information for chapter II – 2.1

2.1 General experimental details

All reactions were carried out with magnetic stirring, and if moisture or air sensitive, under nitrogen or argon atmosphere using standard Schlenk techniques in oven-dried glassware (100 °C oven temperature). If required glassware was further dried under vacuum with a heat-gun at 650 °C. External bath thermometers were used to record all reaction temperatures. Low temperature reactions were carried out in a Dewar vessel filled with acetone/dry ice (T between –78 °C and 0 °C) or distilled water/ice (0 °C). High temperature reactions were conducted using a heated silicon oil bath or a metal block in reaction vessels equipped with a reflux condenser or in a pressure tube. Tetrahydrofuran (THF) was distilled over sodium/potassium alloy prior to use. All other solvents were purchased from Acros Organics as 'extra dry' reagents. All other reagents with a purity > 95% were obtained from commercial sources (Sigma Aldrich, Acros, Alfa Aesar and others) and used without further purification unless otherwise stated.

Flash column chromatography (FCC) was carried out with Merck silica gel 60 (0.040–0.063 mm). Analytical thin layer chromatography (TLC) was carried out using Merck silica gel 60 F254 glass-backed plates or aluminum foils and visualized under UV light at 254 nm. Staining was performed with ceric ammonium molybdate (CAM) or by staining with an aqueous anisaldehyde solution and subsequent heating.

NMR spectra (^{1}H NMR and ^{13}C NMR) were recorded in deuterated chloroform ($CDCl_3$) or methanol (MeOD-d_4) on a Bruker Avance III HD 400 MHz spectrometer equipped with a CryoProbe™, a Bruker Avance Neo 400 MHz spectrometer, an Agilent 500 DD2 500 MHz spectrometer or a Bruker Avance II 600 MHz spectrometer and are reported as follows: chemical shift δ in ppm (multiplicity, coupling constant *J* in Hz, number of protons) for ^{1}H NMR spectra and chemical shift δ in ppm for ^{13}C NMR spectra. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, br = broad, m = multiplet, or combinations thereof. Residual solvent peaks of $CDCl_3$ (δ_H = 7.26 ppm, δ_C = 77.16 ppm) and MeOD-d_4 (δ_H = 3.31 ppm, δ_C = 49.00 ppm) were used as internal reference. NMR spectra were assigned using information ascertained from COSY, HMBC, HSQC and NOESY experiments.

High resolution mass spectra (HRMS) were recorded on a Varian MAT CH7A or a Varian MAT 711 MS instrument by electron impact (EI) or electrospray ionization (ESI) techniques at the Department of Chemistry, Ludwig-Maximilians-University Munich or a Thermo Scientific™ LTQ

Orbitrap XL™ Hybrid Ion Trap-Orbitrap Mass Spectrometer at the Institute of Organic Chemistry and Center for Molecular Biosciences, University of Innsbruck.

Infrared spectra (IR) were recorded from 4000 cm^{-1} to 450 cm^{-1} on a Bruker™ ALPHA FT-IR Spectrometer from Bruker. Samples were prepared as a neat film or a film by evaporation of a solution in $CDCl_3$. IR data in frequency of absorption (cm^{-1}) is reported as follows: *w* = weak, *m* = medium, *s* = strong, *br* = broad or combinations thereof.

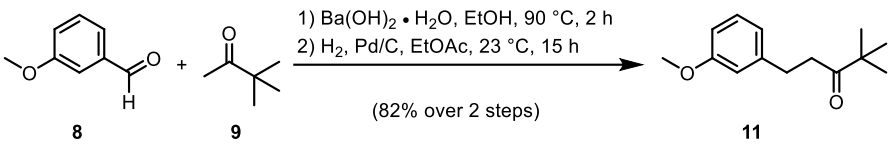
Melting Points were measured with a SRS MPA120 EZ-Melt Melting Point Apparatus in open glass capillaries and are uncorrected.

Optical rotation values were recorded on a Schmidt+Haensch UniPol L1000 Peltier polarimeter. The specific rotation is calculated as follows: $[\alpha]_{\lambda}^{T} = \frac{\propto \times 100}{c \times d}$. Thereby, the wavelength λ is reported in nm and the measuring temperature in °C. α represents the recorded optical rotation, *c* the concentration of the analyte in 10 mg/mL and *d* the length of the cuvette in dm. Thus, the specific rotation is given in 10^{-1}·deg·cm^2 g^{-1}. Use of the sodium *D* line (λ = 589 nm) is indicated by *D* instead of the wavelength in nm. The sample concentration as well as the solvent is reported in the relevant section of the experimental part.

X-ray diffraction analysis was carried out by Prof. Dr. Klaus Wurst at the Institute of Inorganic and Theoretical Chemistry and Center for Molecular Biosciences, University of Innsbruck. The data collections were performed on a Bruker D8Quest using MoKα-radiation (λ = 0.71073 Å, Incoatec Microfocus). The Bruker Apex III software was applied for the integration, scaling and multi-scan absorption correction of the data. The structures were solved by direct methods with SHELXTL-XT-2014 and refined by least-squares methods against F2 with SHELXL-2014/7. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. Further details are summarized in the tables at the different sections. Plotting of thermal ellipsoids in this document and in the main text was carried out using MERCURY for Windows.

All yields are isolated, unless otherwise specified.

1-(3-methoxyphenyl)-4,4-dimethylpentan-3-one (**11**)



To a solution of *m*-anisaldehyde (**8**) (8.95 mL, 73.4 mmol, 1 equiv) and pinacolone (**9**) (13.8 mL, 110 mmol, 1.50 equiv) in ethanol (37 mL) under argon was added finely grinded barium hydroxide monohydrate (C-200, 1.89 g, 11.0 mmol, 0.150 equiv), which was prepared by drying barium hydroxide octahydrate at 200 °C in an oven for 3 h. The mixture was heated to 90 °C and after 2 h, the reaction mixture was cooled to 23 °C, concentrated under reduced pressure, diluted with ethyl acetate (460 mL) and filtered over a short pad of Celite®. To this solution was added palladium on charcoal (10% palladium on activated charcoal, 0.781 g, 0.734 mmol, 1.00 mol%) and the resulting suspension was sparged with hydrogen gas for 20 min. Stirring under hydrogen atmosphere was continued for 15 h, then Celite® was added and the mixture was filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to yield saturated ketone **11** (13.3 g, 82% over 2 steps) as a colorless oil.

The same reaction was conducted also on larger scale: *m*-anisaldehyde (26.0 g, 191 mmol). Hereby the amount of palladium was reduced to 0.20 mol% (10% palladium on activated charcoal, 0.41 g), that afforded the ketone **11** (32.0 g) in 76% yield.

TLC (20% ethyl acetate in hexanes): R_f: 0.54 (UV)

mp: 15.1 °C

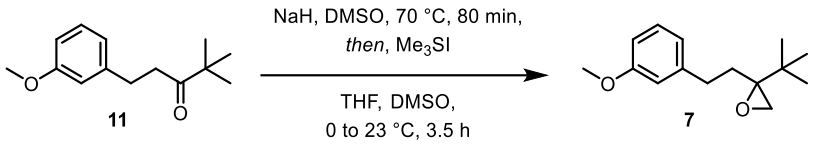
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.16 (m, 1H), 6.78 (dt, *J* = 7.7, 1.2 Hz, 1H), 6.76 – 6.72 (m, 2H), 3.79 (s, 3H), 2.88 – 2.76 (m, 4H), 1.11 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 215.0, 159.7, 143.3, 129.5, 120.8, 114.2, 111.4, 55.2, 44.2, 38.5, 30.2, 26.4.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3315 (*m*), 3297 (*m*), 3256 (*m*), 3183 (*m*), 3106 (*m*), 2957 (*m*), 2835 (*m*), 2707 (*m*), 2617 (*m*), 2125 (*w*), 1703 (*w*), 1651 (*m*), 1584 (*s*), 1517 (*s*), 1476 (*vs*), 1394 (*s*), 1364 (*s*), 1317 (*w*), 1226 (*s*), 1151 (*vs*), 1125 (*s*), 1099 (*s*), 1025 (*s*), 978 (*s*), 928 (*s*), 787 (s), 762 (*s*), 723 (*s*) cm^{-1}.

HRMS (EI): calcd for $C_{14}H_{20}O_2$ $[M]^+$: 220.1458; found: 220.1459.

2-(*tert*-butyl)-2-(3-methoxyphenethyl)oxirane (**7**)



Sodium hydride (60% in mineral oil, 7.40 g, 184 mmol, 1.60 equiv) was washed with *n*-hexane (20 mL) in a dry 1-liter three-neck bottom flask equipped with a mechanical stirrer for 10 min. The solvent was removed *via* syringe and dry dimethyl sulfoxide (90 mL) was added. The suspension was heated under strong hydrogen evolution at 70 °C for 80 min. The green-brownish solution was cooled to 23 °C, diluted with tetrahydrofuran (95 mL) and the solution was then cooled in an aceton/dry ice bath to −15 °C. A stirred suspension of trimethylsulfonium iodide (35.2 g, 172 mmol, 1.50 equiv) in dimethylsulfoxide (90 mL) was added *via* canula at a rate that the temperature did not exceed 0 °C. The reaction was stirred for 2 min and a solution of ketone **11** (25.3 g, 115 mmol, 1 equiv) in tetrahydrofuran (18 mL) was added slowly *via* syringe. The flask of the ketone was rinsed with tetrahydrofuran (3 × 7 mL) and the reaction solution was stirred for 15 min at 0 °C and 1 h at 23 °C. Excess base was quenched by addition of water (900 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (4 × 200 mL), the combined organic layers were washed with saturated aqueous sodium chloride solution (3 × 200 mL) and the washed solution was dried over sodium sulfate. The filtrate was concentrated under reduced pressure and the crude product (26.7 g) was used without further purification in the next step assuming full conversion. An analytically pure sample of the colorless oil was received by purification by flash column chromatography on silica gel (5% ethyl acetate in hexanes).

TLC (20% ethyl acetate in hexanes): R_f: 0.57 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23 – 7.17 (m, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 6.76 – 6.71 (m, 2H), 3.80 (s, 3H), 2.78 (d, *J* = 4.2 Hz, 1H), 2.67 (d, *J* = 4.2 Hz, 1H), 2.54 (ddd, *J* = 13.5, 11.5, 5.1 Hz,

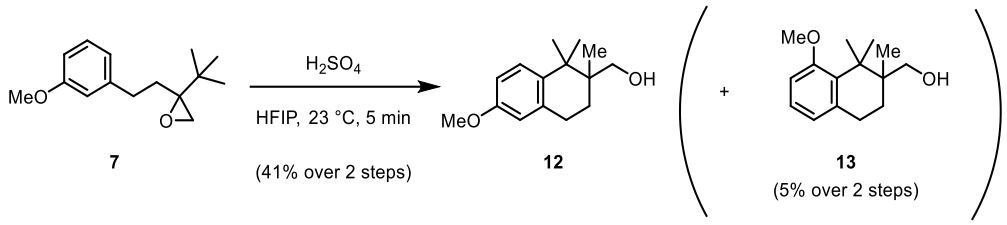
1H), 2.44 (ddd, *J* = 13.5, 11.6, 5.8 Hz, 1H), 2.13 (ddd, *J* = 14.6, 11.6, 5.8 Hz, 1H), 2.02 (ddd, *J* = 14.6, 11.7, 5.1 Hz, 1H), 0.97 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.8, 144.0, 129.5, 120.8, 114.3, 111.2, 63.5, 55.3, 48.1, 34.1, 31.4, 30.8, 26.2.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2958 (*m*), 2872 (*w*), 2835 (*w*), 1602 (*s*), 1585 (*s*), 1490 (*s*), 1465 (*s*),1455 (*s*), 1436 (*m*), 1394 (*w*), 1364 (*w*), 1284 (*w*), 1261 (*vs*), 1166 (*s*), 1153 (*vs*), 1055 (*s*), 1039 (*vs*),910 (*m*), 836 (*m*), 777 (*vs*), 745 (*m*), 696 (*vs*) cm^{-1}.

HRMS (ESI): calcd for $C_{15}H_{22}O_2$ $[M]^+$: 234.1614; found: 234.1621.

(6-methoxy-1,1,2-trimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (**12**)



The crude epoxide **7** (26.7 g, 114 mmol, 1 equiv) was divided into three equal batches and sequentially subjected to the reaction conditions.

To a vigorously stirred solution of sulfuric acid (0.20 mL, 3.8 mmol, 10 mol%) in 1,1,1,3,3,3-hexafluoro-2-propanol (485 mL) was added dropwise crude epoxide **7** (8.9 g, 38 mmol, 1 equiv) over a period of 5 min. The colorless liquid turned instantly yellow on the addition of the first drops and became finally burgundy. The reaction solution was stirred for further 5 min whereupon excess acid was quenched by addition of potassium carbonate (2.0 g, 14 mmol, 0.35 equiv), what caused a color change over red to grey. The reaction mixture was stirred for 5 min and concentrated under reduced pressure (250 mbar, 40 °C water bath temperature) to recover 1,1,1,3,3,3-hexafluoro-2-propanol (450 ml). The turquoise crude product was combined with the crude products from the other two batches, water (500 mL) was added and the mixture was extracted with ethyl acetate (3 × 300 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (300 mL) and the washed solution was dried over sodium sulfate. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford tetraline **12** (10.9 g, 41% over 2 steps) as colorless viscous oil that slowly solidified upon storage. Besides the *para*-product **12**,

ortho-product **13** (1.36 g, 5% over 2 steps) was afforded as a colorless viscous oil that slowly solidified upon storage.

Analytical data of **12**:

TLC (25% ethyl acetate in hexanes): R_f: 0.37 (CAM)

mp: 80.5 – 81.4 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (d, *J* = 8.9 Hz, 1H), 6.74 (dd, *J* = 8.7, 2.9 Hz, 1H), 6.58 (d, *J* = 2.7 Hz, 1H), 3.78 (s, 3H), 3.57 (d, *J* = 10.8 Hz, 1H), 3.54 (d, *J* = 10.8 Hz, 1H), 2.88 – 2.68 (m, 2H), 1.87 – 1.65 (m, 2H), 1.45 (s, 1H), 1.23 (s, 3H), 1.20 (s, 3H), 0.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.0, 138.3, 136.7, 128.0, 112.9, 112.6, 67.3, 55.2, 39.2, 38.7, 27.9, 27.2, 26.6, 25.4, 19.1.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3358 (*m*), 2973 (*m*), 2956 (*m*), 2929 (*m*), 1609 (*s*), 1500 (*s*) 1459 (*s*), 1448 (*s*), 1432 (*m*), 1361 (*m*), 1317 (*s*), 1246 (*s*), 1232 (*s*), 1198 (*m*), 1164 (*m*), 1084 (*m*), 1047 (*s*), 1033 (*vs*), 1022 (*vs*), 993 (*s*), 948 (*m*), 889 (*m*), 848 (*s*), 823 (*vs*), 754 (*m*), 714 (*m*) cm^{-1}.

HRMS (EI): calcd for $C_{15}H_{22}O_2$ $[M]^+$: 234.1614; found: 234.1617.

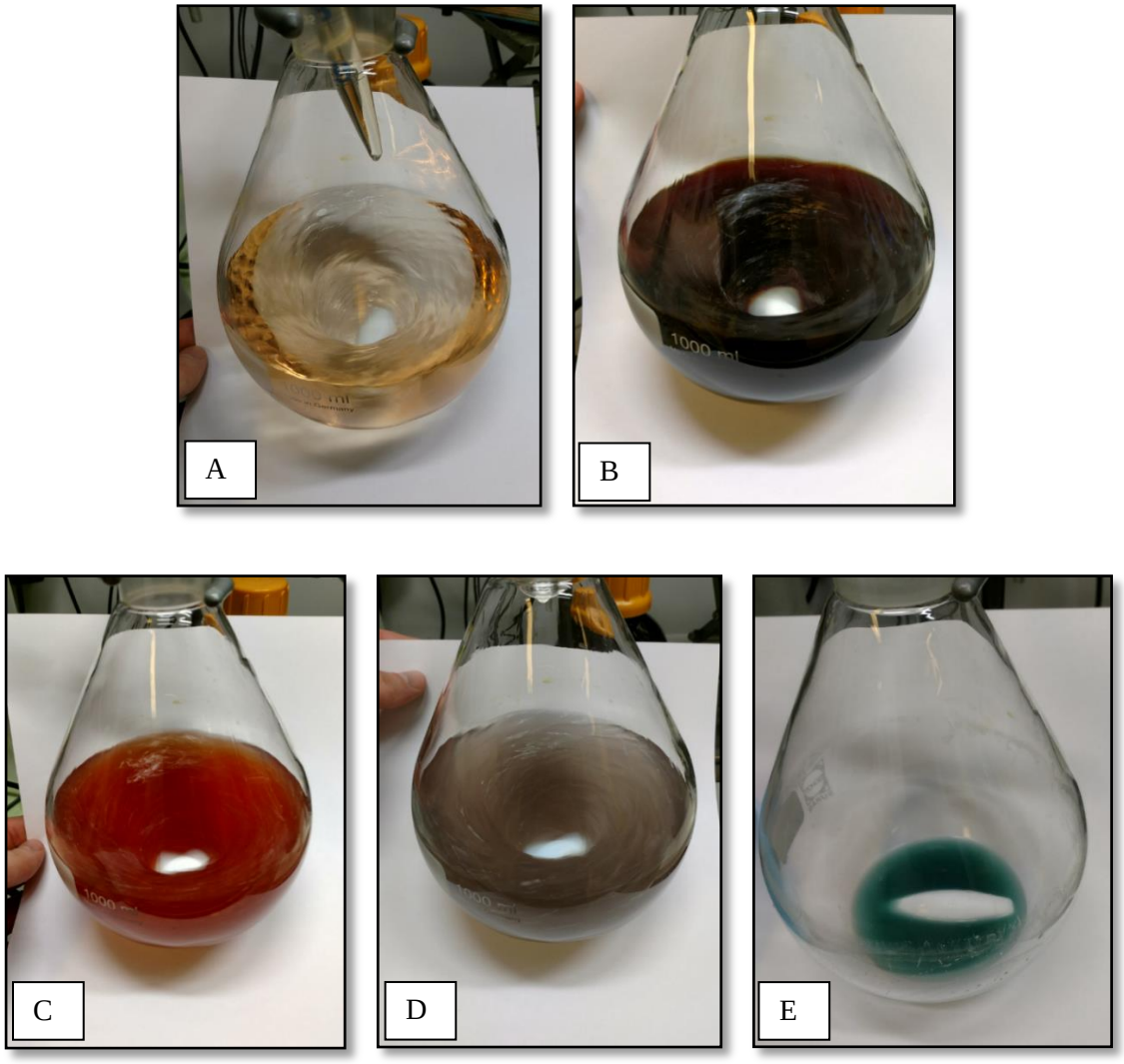


Figure 2-1: A = Addition of substrate (**7**) to HFIP/H_2SO_4; B =After complete addition of the substrate and 5 minutes of stirring; C = 10 seconds after addition of K_2CO_3, D = 5 minutes after K_2CO_3 addition; E = crude *product after removal of HFIP at 250 mbar, 40 °C.*

Analytical data of **13**:

TLC (25% ethyl acetate in hexanes): R_f: 0.47 (CAM)

mp: 71.5 – 74.4 °C

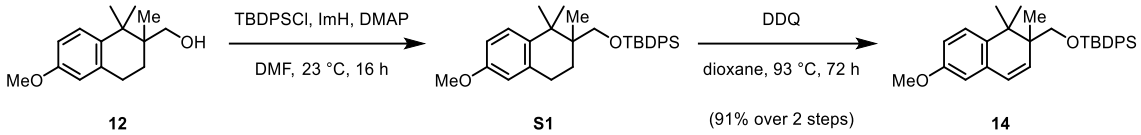
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.08 (t, *J* = 7.8 Hz, 1H), 6.74 – 6.68 (m, 2H), 3.80 (s, 3H), 3.59 (s, 2H), 2.92 – 2.70 (m, 3H), 1.80 – 1.61 (m, 2H), 1.35 (s, 3H), 1.32 (s, 3H), 0.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.5, 138.1, 133.9, 126.1, 122.1, 109.5, 66.9, 55.2, 40.5, 39.3, 27.2, 26.9, 23.5, 21.9, 18.9.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3384 (*w*), 2969 (*m*), 2938 (*m*), 1576 (*m*), 1452 (*s*), 1436 (*s*), 1362 (*m*), 1248 (*vs*), 1191 (*m*), 1109 (*m*), 1074 (*s*), 1058 (*s*), 1022 (*vs*), 1005 (*s*), 953 (*m*), 880 (m), 811 (*m*), 779 (*s*), 754 (*s*), 740 (*vs*) cm^{-1}.

HRMS (EI) calcd for $C_{15}H_{22}O_2$ $[M]^+$: 234.1614; found: 234.1616.

tert-butyl((6-methoxy-1,1,2-trimethyl-1,2-dihydronaphthalen-2-yl)methoxy)-diphenylsilane (**14**)



12 **S1** **14**

To a solution of alcohol **12** (8.92 g, 38.1 mmol, 1 equiv), *N*,*N*-dimethyl-4-aminopyridine (93 mg, 0.76 mmol, 2.0 mol%) and imidazole (4.66 g, 68.5 mmol, 1.80 equiv) in *N*,*N*-dimethylformamide (95 mL) was added dropwise *tert*-butyl(chloro)diphenylsilane (15.4 mL, 57.1 mmol, 1.50 equiv). The solution was stirred at 23 °C for 16 h and then excess *tert*-butyl(chloro)diphenylsilane was hydrolyzed by the addition of water (50 mL). The mixture was extracted with diethyl ether (500 mL). The organic layer was washed with water (2 × 50 mL) and saturated aqueous sodium chloride solution (2 × 50 mL). The organic layer was dried over sodium sulfate and the filtrate was concentrated under reduced pressure. The crude product **S1** was used without further purification in the next step.

To the solution of crude silyl ether **S1** in dry 1,4-dioxane (95 mL) was added 2,3-dichloro-4,5-dicyano-1,3-benzoquinone (13.0 g, 57.2 mmol, 1.50 equiv). The dark solution was stirred at 93 °C for 48 h. An additional portion of 2,3-dichloro-4,5-dicyano-1,3-benzoquinone (4.3 g, 19.1 mmol, 0.5 eq) was added and the reaction was stirred for further 24 h at 93 °C. Subsequently the solution was cooled to 23 °C and poured into cyclohexane (900 mL). The resulting suspension was filtered through a plug of Celite® and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (1% ethyl acetate in cyclohexane) afforded dihydronaphthalene **14** (16.3 g, 91%) as a colorless liquid.

TLC (10% ethyl acetate in cyclohexane): R_f: 0.61 (CAM)

mp: 99.2 – 100.6 °C

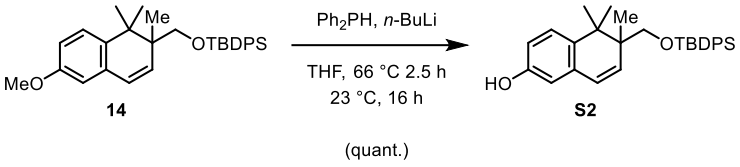
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 – 7.59 (m, 4H), 7.45 – 7.31 (m, 6H), 7.16 (d, *J* = 8.5 Hz, 1H), 6.71 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.59 (d, *J* = 2.8 Hz, 1H), 6.38 (d, *J* = 9.6 Hz, 1H), 5.84 (d, *J* = 9.6 Hz, 1H), 3.81 (s, 3H), 3.65 (d, *J* = 9.6 Hz, 1H), 3.57 (d, *J* = 9.6 Hz, 1H), 1.19 (s, 6H), 1.13 (s, 3H), 1.03 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.9, 137.4, 137.0, 135.9, 135.8, 133.9, 133.8, 133.7, 129.6, 129.6, 127.7, 127.7, 125.9, 125.1, 112.4, 112.0, 67.8, 55.4, 43.4, 38.9, 27.0, 24.7, 22.9, 19.5, 17.9.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3071 (*w*), 3031 (*w*), 2961 (*s*), 2931 (*s*), 2857 (*m*), 1603 (*m*), 1572 (*m*), 1489 (*m*), 1471 (*m*), 1428 (*m*), 1390 (*w*), 1361 (*m*), 1309 (*m*), 1282 (*m*), 1261 (*s*), 1228 (*w*), 1192 (*w*), 1153 (*m*), 1111 (*s*), 1073 (*s*), 1038 (*m*), 1007 (*w*), 976 (*w*), 936 (*w*), 872 (*w*), 855 (*w*), 821 (*s*) 790 (*w*), 775 (*w*), 740 (*m*), 702 (*s*), 658 (*w*), 612 (*m*), 560 (*w*), 504 (*s*), 490 (*m*), 433 (*w*) cm^{-1}.

HRMS (ESI) calcd for $C_{31}H_{38}NaO_2Si$ $[M+Na]^+$: 493.2533; found: 493.2481.

6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5,5,6-trimethyl-5,6-dihydronaphthalen-2-ol (**S2**)



To a solution of diphenylphosphane (17.8 mL, 103 mmol, 3.00 equiv) in dry tetrahydrofuran (170 mL) was added dropwise *n*-butyllithium (2.5 M in hexane, 41 mL, 103 mmol, 3.00 equiv) at 0 °C. The deep red solution was stirred for 30 minutes at 0 °C and then warmed up to 23 °C. The red solution was transferred to a flask containing methyl ether **14** (16.1 g, 34.2 mmol, 1 equiv) and the flask was equipped with a reflux condenser. The reaction was heated at reflux at 75 °C for 2.5 h and was then stirred for 16 h at 23 °C. Excess phosphide was quenched by the addition of saturated aqueous ammonium chloride solution (100 mL). The mixture was extracted with diethyl ether (3 × 200 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed solution was dried over sodium sulfate and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) afforded the title compound **S2** (15.7 g, quant.) as a colorless viscous oil.

TLC (10% ethyl acetate in cyclohexane): R_f: 0.28 (CAM)

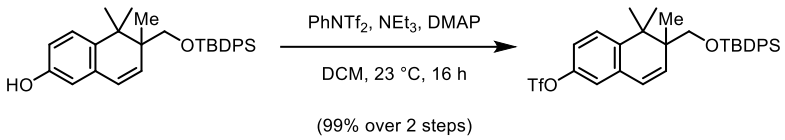
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (m, 4H), 7.46 – 7.32 (m, 6H), 7.11 (d, *J* = 8.3 Hz, 1H), 6.63 (dd, *J* = 8.3, 2.8 Hz, 1H), 6.52 (d, *J* = 2.7 Hz, 1H), 6.35 (d, *J* = 9.7 Hz, 1H), 5.84 (d, *J* = 9.6 Hz, 1H), 4.74 (s, 1H), 3.65 (d, *J* = 9.6 Hz, 1H), 3.58 (d, *J* = 9.6 Hz, 1H), 1.19 (s, 6H), 1.13 (s, 3H), 1.04 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 153.6, 137.6, 137.1, 135.9, 135.8, 133.9, 133.9, 133.7, 129.6, 129.6, 127.7, 127.7, 125.6, 125.3, 113.9, 113.3, 67.8, 43.4, 38.9, 27.0, 24.7, 22.9, 19.5, 17.9.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3339 (*m br*), 2962 (*m*), 2930 (*m*), 2857 (*m*), 1605 (*m*), 1576 (*m*), 1471 (*m*), 1427 (*m*), 1387 (*m*), 1361 (*m*), 1287 (*w*), 1265 (*m*), 1155 (*m*), 1105 (*s*), 1069 (*s*), 1007 (*w*), 958 (*w*), 908 (*m*), 867 (*m*), 819 (*s*), 790 (*m*), 732 (*s*), 700 (*s*), 659 (*m*), 612 (*s*), 543 (*w*), 503 (*s*), 489 (*s*), 434 (*w*) cm^{-1}.

HRMS (ESI) calcd for $C_{30}H_{37}O_2Si$ $[M+H]^+$: 457.2557; found: 457.2553.

6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5,5,6-trimethyl-5,6-dihydronaphthalen-2-yl trifluoromethanesulfonate (**15**)



To a solution of phenol **S2** (15.6 g, 34.2 mmol, 1 equiv) and *N*,*N*-dimethylpyridin-4-amine (0.42 g, 3.4 mmol, 0.10 equiv) in dichloromethane (70 mL) was added triethylamine (6.67 mL, 47.8 mmol, 1.40 equiv) and *N*-Phenyl-bis(trifluoromethanesulfonimide) (14.65 g, 41.0 mmol, 1.2 equiv). The solution was stirred at 23 °C for 16 h. Excess amine was quenched by addition of saturated aqueous ammonium chloride solution (100 mL) and the mixture was extracted with dichloromethane (3 × 150 mL). The combined organic layers were dried over sodium sulfate and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (1% ethyl acetate in cyclohexane initially, grading to 3% ethyl acetate in cyclohexane) to afford the title compound **15** (20.2 g, 99% over 2 steps) as a colorless wax, that crystallized upon storage at 23 °C after several days.

TLC (10% ethyl acetate in cyclohexane): R_f: 0.62 (CAM)

mp: 94.7 – 96.2 °C

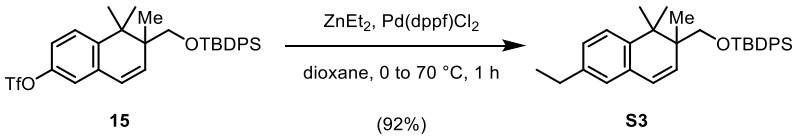
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.57 (m, 4H), 7.47 – 7.33 (m, 6H), 7.30 (d, *J* = 8.6 Hz, 1H), 7.05 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.91 (d, *J* = 2.7 Hz, 1H), 6.41 (d, *J* = 9.7 Hz, 1H), 5.90 (d, *J* = 9.7 Hz, 1H), 3.62 (d, *J* = 9.8 Hz, 1H), 3.53 (d, *J* = 9.8 Hz, 1H), 1.27 (s, 3H), 1.20 (s, 3H), 1.13 (s, 3H), 1.00 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.0, 145.6, 138.7, 135.8, 134.9, 133.6, 133.4, 129.7, 127.7, 125.8, 124.8, 119.6, 118.9 (q, *J* = 320.9 Hz), 118.5, 67.9, 43.3, 39.4, 26.8, 25.0, 22.3, 19.3, 17.9.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3072 (*w*), 2964 (*m*), 2932 (*m*), 2858 (*m*), 1602 (*w*), 1574 (*w*), 1473 (*m*), 1421 (*s*), 1363 (*m*), 1251 (*m*), 1212 (*s*), 1111 (*s*), 1074 (*s*), 1008 (*w*), 947 (*s*), 900 (*m*), 878 (*s*), 848 (*s*), 819 (*s*), 789 (*w*), 777 (*w*), 736 (*s*), 700 (*s*), 646 (*w*), 603 (*s*), 574 (*w*), 502 (*s*), 488 (*s*) 435 (*m*) cm^{-1}.

HRMS (ESI) calcd for $C_{31}H_{35}F_3NaO_4SSi$ $[M+Na]^+$: 611.1870; found: 611.1863.

tert-butyl((6-ethyl-1,1,2-trimethyl-1,2-dihydronaphthalen-2-yl)methoxy)-diphenylsilane (**S3**)



15 (92%) **S3**

To a solution of triflate **15** (5.00 g, 8.49 mmol, 1 equiv) in dry dioxane (70 mL) was added [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (124 mg, 0.17 mmol, 2 mol%). The orange suspension was cooled to 0 °C causing partial crystallization of the solvent. Diethylzinc (1 M in hexanes, 17.0 mL, 17.0 mmol, 2.00 equiv) was added and the ice bath was removed. When all dioxane was melted again, a yellow clear solution was formed. The reaction mixture was heated at 70 °C for 1 h and was then cooled to 0 °C. Excess diethylzinc of the brownish solution was quenched by addition of methanol (10 mL), water (50 mL) and saturated aqueous ammonium chloride solution (50 mL). The mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over sodium sulfate. The filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (1% ethyl acetate in cyclohexane) afforded the title compound **S3** (3.65 g, 92%) as a colorless viscous oil.

TLC (10% ethyl acetate in cyclohexane): R_f: 0.68 (CAM)

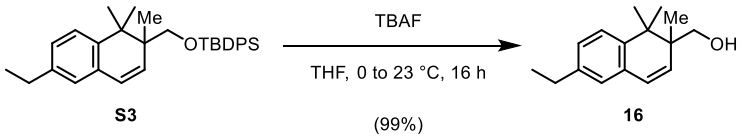
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.66 (m, 4H), 7.50 – 7.37 (m, 6H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.07 (dd, *J* = 7.9, 1.9 Hz, 1H), 6.93 (d, *J* = 1.8 Hz, 1H), 6.48 (d, *J* = 9.6 Hz, 1H), 5.87 (d, *J* = 9.6 Hz, 1H), 3.72 (d, *J* = 9.6 Hz, 1H), 3.64 (d, *J* = 9.6 Hz, 1H), 2.68 (q, *J* = 7.6 Hz, 2H), 1.32 (t, *J* = 7.6 Hz, 3H), 1.28 (s, 3H), 1.28 (s, 3H), 1.20 (s, 3H), 1.10 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4, 141.6, 136.0, 135.9, 135.8, 133.9, 133.8, 132.4, 129.6, 129.6, 127.7, 127.6, 127.1, 126.2, 126.0, 124.0, 67.9, 43.3, 39.1, 28.4, 27.0, 24.7, 22.8, 19.4, 18.0, 15.6.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3070 (*w*), 3020 (*w*), 2962 (*s*), 2930 (*s*), 2857 (*m*), 1589 (*w*), 1503 (*w*), 1490 (*w*), 1471 (*w*), 1462 (*m*), 1428 (*w*), 1390 (*w*), 1361 (*w*), 1247 (*w*), 1208 (*w*), 1111 (*s*), 1008 (*s*), 976 (*w*), 938 (*w*), 888 (*w*), 824 (*s*), 792 (*w*), 740 (*m*), 701 (*s*), 650 (*w*), 612 (*m*), 504 (*s*), 490 (*m*), 436 (*w*) cm^{-1}.

HRMS (ESI) calcd for $C_{32}H_{40}NaOSi$ $[M+Na]^+$: 491.2741; found: 491.2741.

(6-ethyl-1,1,2-trimethyl-1,2-dihydronaphthalen-2-yl)methanol (**16**)



S3 **16**

To a stirred solution of protected alcohol **S3** (3.61 g, 7.70 mmol, 1 equiv) in tetrahydrofuran (50 mL) was added a solution of tetrabutylammonium fluoride (1 M in THF, 10.0 mL, 10.0 mmol, 1.30 equiv) at 0 °C. The ice bath was removed after 15 min and the reaction was stirred at 23 °C for 16 h. Excess fluoride was quenched by addition of water (50 mL). The reaction was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over sodium sulfate. The filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1% ethyl acetate in cyclohexane initially, grading to 5% ethyl acetate in cyclohexane) afforded the title compound **16** (1.78 g, 99%) as a colorless viscous oil.

TLC (10% ethyl acetate in cyclohexane): R_f: 0.17 (CAM)

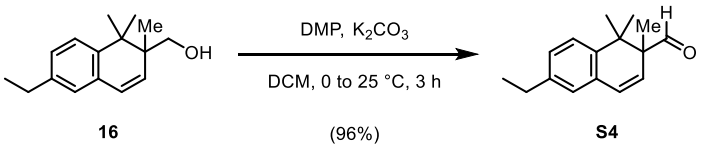
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 7.9 Hz, 1H), 7.03 (dd, *J* = 7.9, 1.9 Hz, 1H), 6.86 (d, *J* = 1.8 Hz, 1H), 6.49 (d, *J* = 9.6 Hz, 1H), 5.64 (d, *J* = 9.6 Hz, 1H), 3.62 (d, *J* = 10.8 Hz, 1H), 3.39 (d, *J* = 10.8 Hz, 1H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.30 (s, 3H), 1.23 (t, *J* = 7.6 Hz, 3H), 1.14 (s, 3H), 1.10 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4, 141.9, 134.5, 132.0, 127.6, 126.2, 124.1, 67.9, 42.9, 38.9, 28.3, 25.7, 21.4, 17.7, 15.5.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3371 (*br s*), 3022 (*w*), 2964 (*s*), 2931 (*m*), 2874 (*m*), 1607 (*w*), 1491 (*m*), 1461 (*m*), 1383 (*m*), 1361 (*m*), 1327 (*w*), 1285 (*w*), 1244 (*w*), 1154 (*w*), 1093 (*w*), 1078 (*m*), 1027 (*s*), 972 (*w*), 951 (*w*), 888 (*s*), 825 (*s*), 782 (*s*), 741 (*s*), 701 (*m*), 575 (*w*), 519 (*w*), 486 (*w*), 418 (*w*) cm^{-1}.

HRMS (ESI) calcd for $C_{16}H_{22}NaO$ $[M+Na]^+$: 253.1563; found: 253.1563.

6-ethyl-1,1,2-trimethyl-1,2-dihydronaphthalene-2-carbaldehyde (**S4**)



16 **S4**

To a solution of alcohol **16** (1.77 g, 7.68 mmol, 1 equiv) in dry dichloromethane (80 mL) was added potassium carbonate (2.12 g, 15.4 mmol, 2.00 equiv) and Dess–Martin periodinane (6.52 g, 15.4 mmol, 2.00 equiv) at 0 °C. The suspension was stirred at 0 °C for 15 min and at 25 °C for 3 h. Excess Dess–Martin periodinane was quenched by addition of saturated aqueous sodium bicarbonate solution (50 mL) and saturated aqueous sodium thiosulfate solution (30 mL). The organic layer was separated and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over sodium sulfate and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1% ethyl acetate in cyclohexane initially, grading to 5% ethyl acetate in cyclohexane) afforded aldehyde **S4** (1.69 g, 96%) as a colorless oil.

TLC (5% ethyl acetate in cyclohexane): R_f: 0.48 (UV)

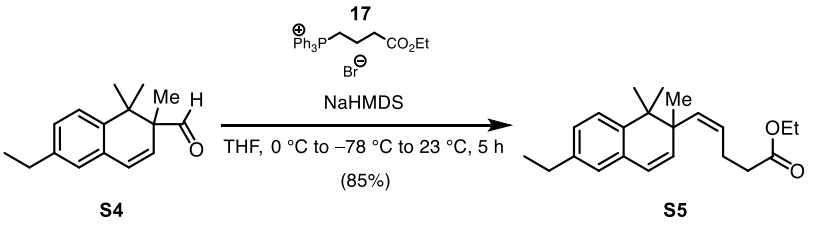
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.08 (dd, *J* = 7.9, 1.9 Hz, 1H), 6.90 (d, *J* = 1.8 Hz, 1H), 6.66 (d, *J* = 9.5 Hz, 1H), 5.46 (d, *J* = 9.5 Hz, 1H), 2.62 (q, *J* = 7.6 Hz, 2H), 1.30 (s, 3H), 1.25 (t, *J* = 7.6 Hz, 3H), 1.21 (s, 3H), 1.19 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.7, 142.6, 140.6, 131.8, 130.8, 129.0, 128.3, 126.7, 124.4, 54.7, 38.9, 28.3, 25.2, 22.3, 15.4, 14.3.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2967 (*s*), 2932 (*m*), 2872 (*w*), 2820 (*w*), 2715 (*w*), 1716 (*s*), 1606 (*w*), 1491 (*m*), 1455 (*m*), 1386 (*m*), 1363 (*m*), 1328 (*w*), 1286 (*w*), 1246 (*m*), 1185 (*w*), 1159 (*w*), 1096 (*m*), 1078 (*m*), 1011 (*w*), 983 (*w*), 889 (*w*), 873 (*s*), 826 (*s*), 792 (*m*), 778 (*s*), 754 (*m*), 732 (*s*), 701 (*m*), 579 (*m*), 528 (*m*), 503 (*m*), 414 (*w*) cm^{-1}.

HRMS (ESI) calcd for $C_{16}H_{20}NaO$ $[M+Na]^+$: 251.1406; found: 251.1408.

ethyl (*Z*)-5-(6-ethyl-1,1,2-trimethyl-1,2-dihydronaphthalen-2-yl)pent-4-enoate (**S5**)



S4 **S5**

To a stirred suspension of [3-(ethoxycarbonyl)propyl]triphenylphosphonium bromide (**17**) (5.08 g, 11.1 mmol, 1.50 equiv) in tetrahydrofuran (44 mL) was added sodium bis(trimethylsilyl)amide (1.0 M in THF, 12.6 mL, 12.6 mmol, 1.70 equiv) at 0 °C. The yellow-orange mixture was stirred for 30 min at 0 °C and was then cooled to −78 °C. A solution of aldehyde **S4** (1.69 g, 7.41 mmol, 1 equiv) in tetrahydrofuran (7 mL) was added slowly. After 15 min, the reaction was allowed to warm to 23 °C and stirred at 23 °C for 5 h. Excess amide was quenched by addition of saturated aqueous ammonium chloride solution (40 mL). The mixture was extracted with diethyl ether (3 × 150 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL) and the washed solution was dried over sodium sulfate. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane) to afford the title compound **S5** (2.06 g, 85%) as a colorless oil.

TLC (5% ethyl acetate in cyclohexane): R_f: 0.19 (CAM)

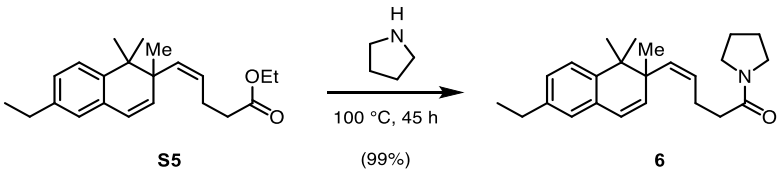
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 7.9 Hz, 1H), 7.05 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.88 (d, *J* = 1.7 Hz, 1H), 6.37 (d, *J* = 9.6 Hz, 1H), 5.99 (d, *J* = 9.6 Hz, 1H), 5.50 (d, *J* = 12.0 Hz, 1H), 5.40 (dt, *J* = 12.0, 7.2 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.80 – 2.65 (m, 1H), 2.64 (q, *J* = 7.6 Hz, 2H), 2.61 – 2.50 (m, 1H), 2.40 (t, *J* = 7.5 Hz, 2H), 1.33 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 7.6 Hz, 3H), 1.21 (s, 3H), 1.13 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 141.6, 141.5, 138.0, 135.8, 132.0, 129.7, 127.0, 125.9, 124.7, 124.1, 60.3, 45.0, 41.2, 34.7, 28.3, 26.0, 24.9, 22.5, 21.5, 15.4, 14.3.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2966 (*s*), 2932 (*m*), 2872 (*m*), 1736 (*s*), 1606 (*w*), 1491 (*w*), 1491 (*w*), 1458 (*m*), 1372 (*m*), 1248 (*m*), 1161 (*s*), 1092 (*w*), 1079 (*m*), 1041 (*w*), 889 (*w*), 826 (*m*), 792 (*w*), 760 (*w*), 739 (*w*), 700 (*w*) cm^{-1}.

HRMS (ESI) calcd for $C_{22}H_{31}O_2$ $[M+H]^+$: 327.2319; found: 327.2324.

(*Z*)-5-(6-ethyl-1,1,2-trimethyl-1,2-dihydronaphthalen-2-yl)-1-(pyrrolidin-1-yl)pent-4-en-1-one (**6**)



S5 **6**

The ester **S5** (2.05 g, 6.28 mmol, 1 equiv) was dissolved in dry and colorless pyrrolidine (7.7 mL, 94 mmol, 15 equiv) in a pressure tube under argon. The tube was sealed and heated at 100 °C. The reaction mixture was stirred for 45 h and then allowed to cool to 23 °C. Excess pyrrolidine was removed under reduced pressure. Purification by flash column chromatography on silica gel (50% ethyl acetate in cyclohexane) afforded the title compound **6** (2.23 g, 99%) as a pale yellow oil.

TLC (50% ethyl acetate in cyclohexane): R_f: 0.24 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 7.9 Hz, 1H), 7.00 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.83 (d, *J* = 1.7 Hz, 1H), 6.31 (d, *J* = 9.6 Hz, 1H), 5.97 (d, *J* = 9.6 Hz, 1H), 5.47 – 5.36 (m, 2H), 3.46 (t, *J* = 6.9 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 2.75 – 2.63 (m, 1H), 2.59 (q, *J* = 7.6 Hz, 2H), 2.60 – 2.47 (m,

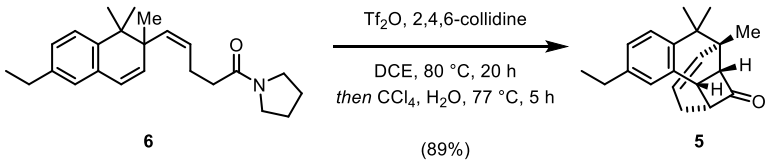
1H), 2.31 (t, *J* = 7.7 Hz, 2H), 1.93 (p, *J* = 6.6 Hz, 2H), 1.83 (p, *J* = 6.6 Hz, 2H), 1.28 (s, 3H), 1.22 (t, *J* = 7.6 Hz, 3H), 1.16 (s, 3H), 1.08 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 141.7, 138.4, 135.3, 132.1, 130.6, 126.9, 125.9, 124.7, 124.2, 46.7, 45.7, 45.0, 41.2, 35.2, 28.3, 26.2, 26.1, 25.0, 24.5, 22.5, 21.5, 15.4.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2965 (*s*), 2931 (*m*), 2870 (*m*), 1639 (*s*), 1490 (*w*), 1427 (*s*), 1380 (*m*), 1359 (*m*), 1340 (*m*), 1252 (*w*), 1226 (*m*), 1192 (*m*), 1167 (*m*), 1117 (*w*), 1090 (*w*), 1078 (*m*), 1034 (*w*), 986 (*w*), 986 (*w*), 913 (*w*), 888 (*m*), 857 (*w*), 825 (*s*), 781 (*m*), 763 (*m*), 725 (*s*), 699 (*m*), 628 (*w*), 544 (*w*), 521 (*m*), 424 (*w*) cm^{-1}.

HRMS (ESI) calcd for $C_{24}H_{34}NO$ $[M+H]^+$: 352.2635; found: 352.2635.

7-ethyl-3,4,4-trimethyl-2a,3,4,8b-tetrahydro-3,1-prop[1]enocyclobuta[*a*]-naphthalen-2(1*H*)-one (**5**)



6 **5**

To a vigorously stirred solution of freshly distilled trifluoromethanesulfonic anhydride (1.38 mL, 8.25 mmol, 1.20 equiv) in dry 1,2-dichloroethane (80 mL) at 80 °C was added dropwise a solution of amide **6** (2.23 g, 6.34 mmol, 1 equiv) and 2,4,6-collidine (1.09 mL, 8.25 mmol, 1.2 equiv) in 1,2-dichloroethane (80 mL) *via* a dropping funnel over a period of 5 h. The initial yellowish reaction mixture turned red-brownish, stirring was continued at 80 °C for 20 h and then the reaction mixture was concentrated under reduced pressure. To the crude iminium salt was added tetrachloromethane (30 mL) and water (30 mL) and the dark brown mixture was heated at reflux at 80 °C for 5 h under an atmosphere of argon. The organic layer was separated and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over sodium sulfate and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) afforded cyclobutanone **5** (1.59 g, 89%) as a pale yellowish oil that solidified upon storage.

TLC (10% ethyl acetate in cyclohexane): R_f: 0.43 (CAM)

mp: 68.4 – 69.1 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.0 Hz, 1H), 7.06 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.93 (d, *J* = 1.6 Hz, 1H), 5.41 (ddt, *J* = 12.4, 2.5, 1.6 Hz, 1H), 5.18 (ddd, *J* = 12.5, 4.9, 2.6 Hz, 1H), 3.74 – 3.64 (m, 2H), 3.54 (td, *J* = 7.4, 1.7 Hz, 1H), 2.64 (q, *J* = 7.6 Hz, 2H), 2.33 (dt, *J* = 18.4, 4.9 Hz, 1H), 1.99 (dq, *J* = 18.2, 2.6 Hz, 1H), 1.43 (s, 3H), 1.32 (s, 3H), 1.26 (t, *J* = 7.6 Hz, 3H), 1.16 (s, 3H).

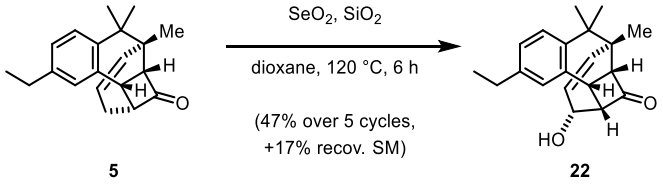
^{13}C NMR (101 MHz, $CDCl_3$) δ: 210.1, 144.1, 141.1, 135.9, 131.8, 128.4, 126.2, 125.8, 124.8, 64.4, 61.0, 40.8, 40.8, 29.7, 28.3, 28.0, 27.0, 21.8, 21.6, 15.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2965 (*m*), 2936 (*w*), 2251 (*w*), 1772 (*s*), 1612 (*w*), 1496 (*w*), 1477 (*w*), 1462 (*w*), 1418 (*w*), 1387 (*w*), 1371 (*w*) 1318 (*w*), 1240 (*w*), 1219 (*w*), 1184 (*w*), 1113 (*w*), 1087 (*w*), 1063 (*w*), 1013 (*w*), 968 (*w*), 944 (*w*), 908 (*s*), 857 (*w*), 825 (*m*), 793 (*w*), 758 (*m*), 728 (*s*), 702 (*w*), 687 (*m*), 647 (*m*), 608 (*w*), 590 (*w*), 562 (*w*), 512 (*w*), 480 (*m*), 447 (*w*) cm^{-1}.

HRMS (ESI): calcd for $C_{20}H_{24}NaO$ $[M+Na]^+$: 303.1719; found: 303.1717.

The structure was validated by single crystal X-ray analysis (see X-ray section).

7-ethyl-11-hydroxy-3,4,4-trimethyl-2a,3,4,8b-tetrahydro-3,1-prop[1]enocyclobuta[*a*]naphthalen-2(1*H*)-one (**22**)



5 **22**

To finely grinded selenium dioxide (2.0 g, 18 mmol, 10 equiv) and oven-dried (100 °C) fine white quartz sand (2.0 g, 19 eq, particle size >230 mesh) in a flame-dried pressure tube (15 mL) equipped with a magnetic stirring bar was added cyclobutanone **5** (500 mg, 1.78 mmol, 1.0 eq). After sparging with nitrogen for 5 min, dry 1,4-dioxane (9 mL) was added. The tube was sealed and the vigorously stirred reaction mixture was heated at 115 °C (700 rpm) for 3 h. The temperature was raised to 120 °C. After 3 h, the reaction mixture was cooled to 23 °C and filtered through a pad of Celite®. The Celite® was washed with ethyl acetate (200 mL) and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1% ethyl acetate in cyclohexane initially, grading to 10% ethyl acetate in cyclohexane, grading to 25% ethyl acetate in cyclohexane, grading to 50% ethyl acetate in cyclohexane) afforded slightly impure **22** (80 mg) as an orange oil. Cyclobutanone **5** (380 mg, 76%) was recovered and used in the next cycle. After five cycles, the product fractions were combined and collectively purified by flash column chromatography (10% ethyl acetate in dichloromethane) to afford the allylic alcohol **22** (252 mg, 47%) as a colorless wax.

cycle	1	2	3	4	5
recovered SM **5** [mg]	380	261	180	125	85

TLC (10% ethyl acetate in cyclohexane): R_f: 0.25 (CAM)

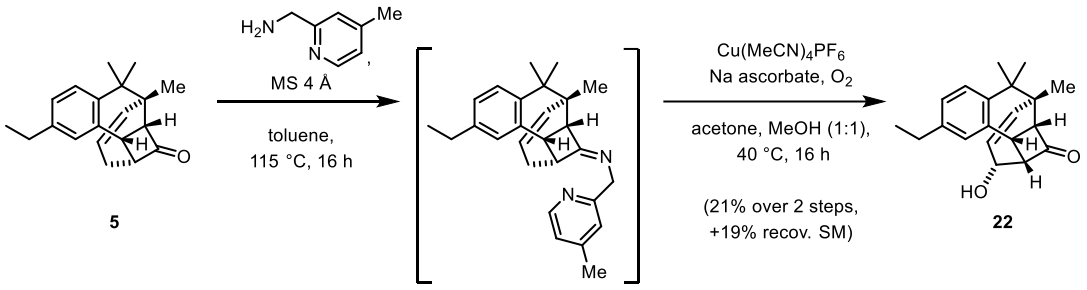
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.1 Hz, 1H), 7.03 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.96 (d, *J* = 1.4 Hz, 1H), 5.42 (dt, *J* = 12.7, 1.8 Hz, 1H), 5.33 (dt, *J* = 12.7, 2.2 Hz, 1H), 3.94 (s, 1H), 3.84 (dddd, *J* = 8.6, 6.4, 4.2, 1.9 Hz, 1H), 3.74 (t, *J* = 8.4 Hz, 1H), 3.49 (ddd, *J* = 8.2, 6.7, 1.6 Hz, 1H), 2.60 (q, *J* = 7.6 Hz, 2H), 2.17 (s, 1H), 1.41 (s, 3H), 1.29 (s, 3H), 1.22 (t, *J* = 7.6 Hz, 3H), 1.10 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.7, 143.6, 141.6, 135.7, 130.8, 130.1, 128.3, 126.6, 125.0, 68.2, 67.5, 64.7, 42.4, 40.7, 28.3, 28.1, 27.6, 22.0, 21.8, 15.5.

IR (Diamond-ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3434 (br m), 2967 (m), 2932 (w), 2247 (w), 1772 (s), 1612 (w), 1497 (w), 1497 (w), 1462 (m), 1388 (m), 1372 (w), 1319 (m), 1240 (w), 1138 (m), 1108 (w), 1087 (w) 1025 (s), 970 (w), 907 (s), 852 (w), 825 (m), 774 (m), 727 (s), 687 (m), 647 (m), 558 (m), 543 (w), 490 (w), 457 (w)

HRMS (ESI): calcd for $C_{20}H_{24}NaO_2$ $[M+Na]^+$: 319.1669; found: 319.1666.

Schönecker oxidation of **5**:[118]



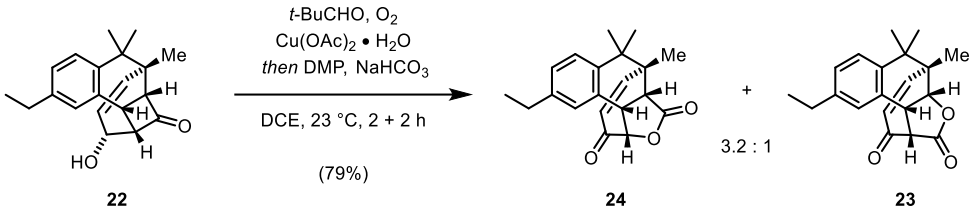
To flame-dried 4 Å molecular sieves (1.00 g, 500 w%) in a Schlenk flask was added cyclobutanone **5** (200 mg, 0.711 mmol, 1 equiv), dry toluene (3 mL) and (4-methylpyridin-2-yl)methanamine (260 mg, 2.14 mmol, 3.00 equiv). The flask was heated to 115 °C and stirred for 16 h. Subsequently the reaction was cooled to 23 °C and diluted with diethyl ether (20 mL). The mixture was washed with saturated aqueous ammonium chloride solution (2 × 20 mL), saturated aqueous sodium bicarbonate solution (20 mL) and saturated aqueous sodium chloride solution (20 mL). The organic layer was dried over sodium sulfate and the filtrate was concentrated under reduced pressure. To the crude imine in a round-bottom flask was added sodium ascorbate (410 mg, 2.07 mmol, 3.00 equiv) and tetrakis(acetonitrile)copper(I) hexafluorophosphate (515 mg, 1.38 mmol, 2.00 equiv). The flask was capped with a septum and sparged with nitrogen for 2 min. Acetone (2.0 mL) and methanol (2.0 mL) were added and the brownish suspension was stirred at 23 °C for 5 min. Oxygen gas from a balloon was sparged through the solution for 5 min whereupon the color changed to dark green-blueish. The flask was heated to 40 °C and stirred for 16 h under an atmosphere of oxygen. Ethyl acetate (3 mL) and saturated aqueous sodium ethylenediaminetetraacetate solution (7 mL, ca. pH 10) were added and the biphasic system was stirred at 23 °C for 1 h. The mixture was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were concentrated under reduced pressure. To the brown residue was added

[118] Y. Y. See, A. T. Herrmann, Y. Aihara, P. S. Baran, *J. Am. Chem. Soc.*, **2015**, *137*, 13776–13779.

tetrachloromethane (15 mL) and water (15 mL). The biphasic system was stirred vigorously at 23 °C for 22 h and extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over sodium sulfate and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane initially, grading to 10% ethyl acetate in cyclohexane, grading to 25% ethyl acetate in cyclohexane) afforded next to recovered cyclobutanone **5** (38 mg, 19%) the allylic alcohol **22** (44 mg, 21%) as a yellow wax.

The analytical data matched those obtained by selenium dioxide oxidation (see above).

8-ethyl-4,5,5-trimethyl-3a,4,5,9b-tetrahydro-4,1-prop[1]enonaphtho[1,2-*c*]furan-3,12(1*H*)-dione (**24**)

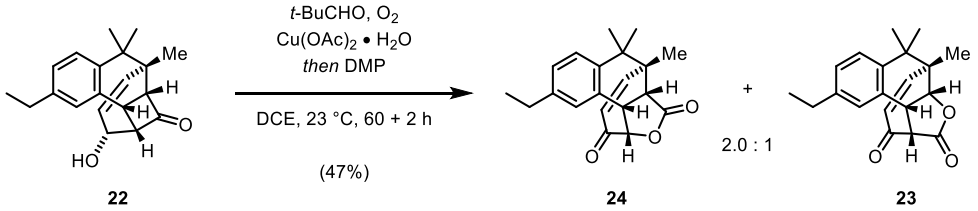


To a solution of allylic alcohol **22** (11.3 mg, 38 µmol, 1 equiv) in 1,2-dichloroethane (1 mL) was added pivalaldehyde (20 µL, 0.19 mmol, 5.0 equiv) and copper(II) acetate monohydrate (7.1 mg, 38 µmol, 1.0 equiv). The flask was capped with a septum and sparged with oxygen gas from a balloon for 2 min. The solution was stirred under oxygen at 23 °C until monitoring by thin layer chromatography indicated full conversion of the starting material (2 h). Sodium bicarbonate (16 mg, 0.19 mmol, 5.0 equiv) and Dess–Martin periodinane (32 mg, 76 µmol, 2.0 equiv) were added and the reaction was stirred at 23 °C. After 1.5 h, an additional portion of Dess-Martin periodinane (32 mg, 76 µmol, 2.0 equiv) was added and the reaction was stirred at 23 °C for 1 h. Excess Dess–Martin periodinane was quenched by addition of saturated aqueous sodium bicarbonate solution (2 mL) and saturated aqueous sodium thiosulfate solution (1 mL). The mixture was extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried over sodium sulfate and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane) afforded a mixture of lactones **24** and **23** (9.4 mg, 79%, ratio **24**:**23** = 3.2:1).

Table 1: Selected examples for the Baeyer-Villiger oxidation of **22**

Entry	conditions	scale [mg]	time [h]	yield (24 + 23)	ratio 24 : 23
1	mCPBA (1.2 equiv), then DMP	84 mg	1 + 2	83%	1.0 : 1.4
2	MeCHO, $Cu(OAc)_2$, O_2	5 mg		no reaction	
3	PhCHO, $Cu(OAc)_2$, O_2	5 mg		no reaction	
4	t-BuCHO, $Cu(OAc)_2$, O_2, then DMP	5 mg	3 + 2	n.d.	3.2 : 1.0
5	t-BuCHO (5 equiv), $Cu(OAc)_2$, O_2, then DMP	11 mg	2 + 2	78%	3.2 : 1.0
	1-Adamantanecarbaldehyde (5 equiv), $Cu(OAc)_2$, O_2, then DMP	5 mg		n.d	3.2 : 1.0
6	$MeCO_3H$, $Cu(OAc)_2$, then DMP	5 mg	1 + 2	n.d.	1.0 : 1.2
7	mCPBA, $Cu(OAc)_2$, then DMP	5 mg	1 + 2	n.d.	1.0 : 1.2

8	t-BuCHO (5 equiv), $Cu(OAc)_2$, O_2, then DMP	247 mg	60 + 2	47%	2.0 : 1.0



22 **24** **23**

Large-Scale Oxidation:

To a solution of allylic alcohol **22** (247 mg, 0.83 mmol, 1 equiv) in 1,2-dichloroethane (21 mL) was added pivalaldehyde (0.45 mL, 4.2 mmol, 5.0 equiv) and copper(II) acetate monohydrate (166 mg, 0.83 mmol, 1.00 equiv). The flask was capped with a septum and sparged with oxygen gas from a balloon for 5 min. The solution was stirred under oxygen at 23 °C until monitoring by thin layer chromatography indicated full conversion of the starting material (60 h). Sodium bicarbonate (350 mg, 4.12 mmol, 5.0 equiv) and Dess–Martin periodinane (1.4 g, 3.3 mmol, 4.0 equiv) were added and the solution was stirred for 2 h at 23 °C. Excess DessMartin periodinane was quenched by addition of saturated aqueous sodium bicarbonate solution (30 mL) and saturated aqueous sodium thiosulfate solution (10 mL). The mixture was extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over sodium sulfate and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane initially, grading to 25% ethyl acetate in cyclohexane) afforded a mixture of lactones **24** and **23** (122 mg, 47%, ratio **24**:**23** = 2.0:1). Separation by slow flash column chromatography on silica gel (5% ethyl acetate in cyclohexane initially, grading to 10% ethyl acetate in cyclohexane) afforded lactone **24** (83 mg, 32%) and lactone **23** (34 mg, 14%) as both colorless crystalline solids.

Analytical data of lactone **24**:

TLC (25% ethyl acetate in cyclohexane): R_f: 0.45 (UV)

mp: 138.0 – 139.1 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.2 Hz, 1H), 7.06 (dd, *J* = 8.2, 1.4 Hz, 2H), 6.93 (d, *J* = 1.4 Hz, 1H), 6.10 (dd, *J* = 13.1, 1.3 Hz, 1H), 5.61 (dd, *J* = 13.1, 1.9 Hz, 1H), 5.04 (dd, *J* = 8.6,

1.9 Hz, 1H), 4.06 (t, *J* = 8.7 Hz, 1H), 3.15 (dd, *J* = 8.8, 1.2 Hz, 1H), 2.57 (q, *J* = 7.6 Hz, 2H), 1.59 (s, 3H), 1.43 (s, 3H), 1.22 (s, 3H), 1.19 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.9, 177.0, 148.2, 142.9, 140.8, 128.5, 127.7, 127.1, 126.3, 126.2, 84.7, 45.6, 43.7, 42.5, 39.4, 28.5, 28.2, 22.1, 21.4, 15.4.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2966 (*s*), 2930 (*m*), 1776 (*s*), 1681 (*s*), 1615 (*m*), 1502 (*w*), 1479 (*w*), 1455 (*w*), 1423 (*w*), 1408 (*w*), 1391 (*w*), 1377 (*w*), 1368 (*w*), 1332 (*w*), 1317 (*m*), 1283 (*w*), 1265 (*w*), 1245 (*w*), 1205 (*m*), 1173 (*w*), 1158 (*w*), 1143 (*w*), 1124 (*w*), 1112 (*w*), 1085 (*w*), 1067 (*m*), 1026 (*w*), 981 (*w*), 950 (*w*), 916 (*m*), 897 (*w*), 825 (*w*), 732 (*w*), 705 (*w*), 690 (*w*), 655 (*w*), 503 (*w*), 589 (*w*), 563 (*w*), 494 (*w*), 476 (*w*), 452 (*w*), 407 (*w*) cm^{-1}.

HRMS (ESI): calcd for $C_{20}H_{22}NaO_3$ $[M+Na]^+$: 333.1461; found: 333.1452.

The structure was validated by single crystal X-ray analysis (see X-ray section).

Analytical data of lactone **23**:

TLC (25% ethyl acetate in cyclohexane): R_f: 0.38 (UV)

mp: 189.3 – 190.5 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.2 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.92 (s, 1H), 6.04 (d, *J* = 13.2 Hz, 1H), 5.69 (d, *J* = 13.2 Hz, 1H), 5.11 (d, *J* = 8.2 Hz, 1H), 4.19 (t, *J* = 8.5 Hz, 1H), 3.92 (d, *J* = 8.8 Hz, 1H), 2.57 (q, *J* = 7.6 Hz, 2H), 1.50 (s, 3H), 1.45 (s, 3H), 1.26 (s, 3H), 1.19 (t, *J* = 7.6 Hz, 3H).

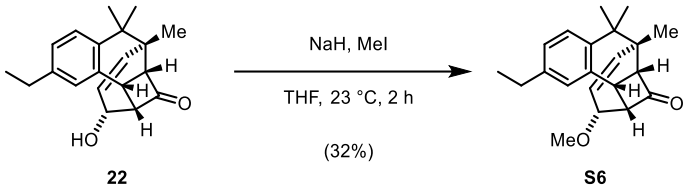
^{13}C NMR (126 MHz, $CDCl_3$) δ 192.4, 171.7, 147.9, 143.1, 140.7, 129.5, 128.5, 128.3, 127.9, 126.0, 81.6, 60.2, 49.2, 43.5, 40.5, 28.6, 28.2, 23.1, 19.1, 15.4.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2967 (*m*), 2933 (*w*), 1774 (*s*), 1672 (*s*), 1615 (*w*), 1573 (*w*), 1500 (*w*), 1479 (*w*), 1454 (*w*), 1416 (*w*), 1391 (*w*), 1374 (*w*), 1359 (*w*), 1342 (*w*),1315 (*w*), 1300 (*w*), 1275 (*w*), 1259 (*w*), 1221 (*w*), 1204 (*w*), 1187 (*m*), 1161 (*s*), 1146 (*w*), 1125 (*w*), 1068 (*w*), 1017 (*s*), 950 (*w*), 908 (*s*), 868 (*w*), 854 (*w*), 827 (*m*), 809 (*w*), 781 (*m*), 727 (*s*), 677 (*w*), 647 (*m*), 611 (*w*), 597 (*w*), 568 (*w*), 540 (*w*), 520 (*w*), 493 (*w*), 475 (*w*), 447 (*w*), 408 (*w*) cm^{-1}.

HRMS (ESI): calcd for $C_{20}H_{22}NaO_3$ $[M+Na]^+$: 333.1461; found: 333.1459

The structure was validated by single crystal X-ray analysis (see X-ray section).

7-ethyl-11-methoxy-3,4,4-trimethyl-2a,3,4,8b-tetrahydro-3,1-prop[1]enocyclobuta[*a*]naphthalen-2(1*H*)-one (**S6**)



22 **S6**

To a suspension of sodium hydride (60% in mineral oil, 6.1 mg, 0.15 mmol, 3.0 equiv) in tetrahydrofuran (0.50 mL) was added allylic alcohol **22** (15 mg, 0.050 mmol, 1 equiv). The suspension was stirred at 23 °C for 30 min and methyl iodide (10 µL, 0.15 mmol, 3.0 equiv) was added. The reaction mixture was stirred at 23 °C for 2 h. Excess base was quenched by addition of saturated aqueous ammonium chloride solution (0.5 mL). The mixture was extracted with dichloromethane (3 × 1 mL) and the combined organic layers were dried over sodium sulfate. The filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (1% ethyl acetate in cyclohexane initially, grading to 10% ethyl acetate in cyclohexane) afforded the ether **S6** (5.1 mg, 32%) as a colorless oil.

TLC (25% ethyl acetate in cyclohexane): R_f: 0.48 (CAM)

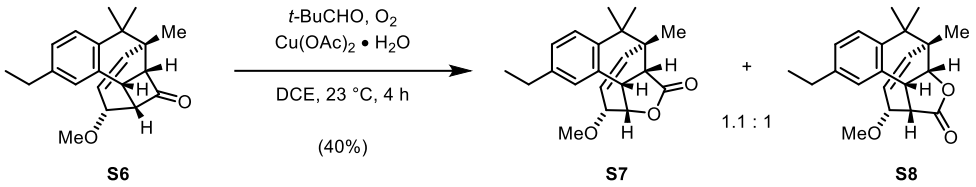
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.1 Hz, 1H), 7.04 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.95 (d, *J* = 1.3 Hz, 1H), 5.48 (dt, *J* = 12.8, 1.9 Hz, 1H), 5.35 (dt, *J* = 12.8, 2.2 Hz, 1H), 3.91 – 3.86 (m, 1H), 3.72 (t, *J* = 8.5 Hz, 1H), 3.59 (dt, *J* = 4.0, 2.3 Hz, 1H), 3.47 (ddd, *J* = 8.1, 6.6, 1.6 Hz, 1H), 3.32 (s, 3H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.41 (s, 3H), 1.29 (s, 3H), 1.23 (t, *J* = 7.6 Hz, 3H), 1.09 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.0, 144.0, 141.6, 136.5, 130.8, 128.6, 128.2, 126.8, 125.2, 76.4, 65.0, 64.9, 56.2, 42.3, 40.7, 28.4, 28.0, 27.8, 22.2, 21.9, 15.6.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2966 (*s*), 2933 (*w*), 2877 (*w*), 2829 (*w*), 1776 (*s*), 1740 (*w*), 1689 (*w*), 1662 (*w*), 1611 (*w*), 1570 (*w*), 1497 (*w*), 1462 (*m*), 1420 (*w*), 1388 (*w*), 1371 (*w*), 1323 (*w*), 1281 (*w*), 1260 (*w*), 1242 (*w*), 1184 (*m*), 1086 (*s*), 1022 (*w*), 987 (*w*), 969 (*w*), 948 (*w*), 920 (*w*), 850 (*w*), 825 (*w*), 804 (*m*), 774 (*w*), 732 (*w*), 688 (*w*), 643 (*w*), 589 (*w*), 543 (*w*), 492 (*w*), 459 (*w*), 430 (*w*) cm^{-1}.

HRMS (ESI): calcd for $C_{21}H_{26}NaO_2$ $[M+Na]^+$: 333.1825; found: 333.1802

8-ethyl-12-methoxy-4,5,5-trimethyl-3a,4,5,9b-tetrahydro-4,1-prop[1]enonaphtho[1,2-c]furan-3(1H)-one (**S7**)



To a solution of cyclobutanone **S6** (5.0 mg, 0.016 mmol, 1 equiv) in 1,2-dichloroethane (0.40 mL) was added pivalaldehyde (9 µL, 0.08 mmol, 5 equiv) and copper(II) acetate hydrate (3.2 mg, 0.016 mmol, 1.0 equiv). The vial was sparged with oxygen gas from a balloon for 2 min and stirred under an oxygen atmosphere for 16 h (ca. 50% conversion of **S6**). The mixture was flushed through a pad of silica (100% ethyl acetate). The filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) afforded a mixture of lactones **S7** and **S8** (2.1 mg, 40%, ratio **S7**:**S8** = 1.1:1) as a colorless film. Separation by flash column chromatography on silica gel (1% ethyl acetate in cyclohexane initially, grading to 10% ethyl acetate in cyclohexane) afforded **S7** (0.7 mg, 13%) as a colorless film.

Analytical data of **S7** (major regioisomer):

TLC (25% ethyl acetate in cyclohexane): R_f: 0.31 (CAM)

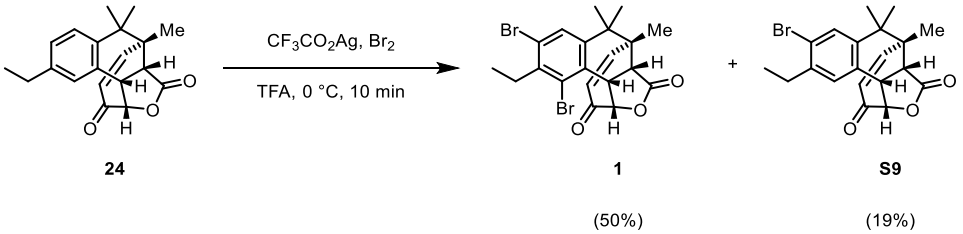
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.2 Hz, 1H), 7.11 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.98 (d, *J* = 1.7 Hz, 1H), 5.42 (ddd, *J* = 13.2, 2.5, 1.6 Hz, 1H), 5.23 (dt, *J* = 13.2, 2.0 Hz, 1H), 5.16 (dt, *J* = 8.8, 2.2 Hz, 1H), 4.02 (t, *J* = 8.8 Hz, 1H), 3.38 (q, *J* = 2.2 Hz, 1H), 3.34 (s, 3H), 2.96 (dd, *J* = 8.8, 1.5 Hz, 1H), 2.64 (q, *J* = 7.6 Hz, 2H), 1.48 (s, 3H), 1.43 (s, 3H), 1.25 (t, *J* = 7.6 Hz, 3H), 1.15 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8, 142.7, 142.2, 134.9, 129.6, 127.6, 127.2, 126.9, 124.5, 80.8, 79.9, 56.8, 43.4, 43.3, 41.8, 39.7, 29.0, 28.2, 22.4, 21.6, 15.6.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2971 (s) 2930 (w), 2823 (w), 1770 8s), 1688 (w), 16114 (w), 1502 (w), 1461 (w), 1423 (w), 1391 (w), 1366 (w), 1310 (w), 1278 (w), 1247 (w), 1187 (w), 1177 (m), 1147 (m), 1136 (w), 1099 (s), 1068 (w), 1019 (m), 976 (w), 948 (w), 929 (w), 894 (w), 849 (w), 828 (m), 777 (w), 743 (w), 712 (w), 689 (w), 658 (w), 623 (w), 584 (w), 539 (w), 519 (w), 496 (w), 475 (w), 438 (w), 426 (w), 410 (w) cm^{-1}.

HRMS (ESI): calcd for $C_{21}H_{26}NaO_3$ $[M+Na]^+$: 349.1774; found: 349.1749.

Salimabromide (**1**)



24 **1** (50%) **S9** (19%)

To a vigorously stirred solution of lactone **24** (65 mg, 0.21 mmol, 1 equiv) and silver(I) trifluoroacetate (139 mg, 0.63 mmol, 3.0 equiv) in trifluoroacetic acid (2.0 mL) was added bromine (32 µL, 0.63 mmol, 3.0 equiv) at 0 °C. The instantly formed milky suspension was stirred at 0 °C for 10 min. Excess bromine and trifluoroacetic acid was quenched by addition of saturated aqueous sodium bicarbonate solution (140 mL) and saturated aqueous sodium thiosulfate solution (10 mL). The suspension was extracted with dichloromethane (4 × 20 mL). The combined organic layers were dried over sodium sulfate and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane) afforded salimabromide **1** (49.4 mg, 50%) and mono-brominated lactone **S9** (15.4 mg, 19%) as both crystalline colorless solids.

Analytical data of salimabromide **1**:

TLC (25% ethyl acetate in cyclohexane): R_f: 0.56 (UV)

mp: 251.2 – 252.4 °C (slight decomposition already)

^{1}H NMR (600 MHz, MeOD) δ 7.63 (s, 1H), 6.32 (dd, *J* = 13.1, 1.4 Hz, 1H), 5.67 (dd, *J* = 13.1, 2.0 Hz, 1H), 5.62 (dd, *J* = 8.3, 2.0 Hz, 1H), 4.41 (t, *J* = 8.3 Hz, 1H), 3.35 (dd, *J* = 8.4, 1.4 Hz, 1H), 3.07 (qd, *J* = 7.5, 4.0 Hz, 2H), 1.59 (s, 3H), 1.49 (s, 3H), 1.23 (s, 3H), 1.15 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (151 MHz, MeOD) δ 197.7, 177.9, 149.8, 147.5, 142.7, 131.5, 130.1, 128.1, 126.5, 125.7, 83.5, 45.8, 45.2, 44.7, 42.6, 31.9, 29.1, 22.5, 21.8, 12.7.

The solubility in MeOD is very low!

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 6.12 (dd, J = 13.1, 1.3 Hz, 1H), 5.68 (dd, *J* = 13.2, 1.7 Hz, 1H), 5.66 (dd, *J* = 8.4, 1.8 Hz, 1H),4.22 (t, *J* = 8.4 Hz, 1H), 3.15 (dd, *J* = 8.4, 1.4 Hz, 1H), 3.09 – 2.95 (m, 2H), 1.59 (s, 3H), 1.45 (s, 3H), 1.20 (s, 3H), 1.14 (t, J = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 176.1, 147.4, 145.5, 142.2, 130.4, 127.9, 127.4, 126.1, 125.4, 82.1, 44.6, 44.2, 43.6, 41.7, 31.3, 29.2, 22.5, 21.7, 12.4.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2955 (*w*), 2924 (*s*), 2853 (*m*), 1783 (*s*), 1736 (*w*), 1685 (*s*), 1618 (*w*), 1578 (*w*), 1532 (*w*), 1463 (*m*), 1440 (*w*), 1392 (*w*), 1380 (*w*), 1324 (*w*), 1311 (*w*), 1280 (*w*), 1262 (*w*), 1219 (*m*), 1177 (*m*), 1159 (*s*), 1127 (*w*), 1111 (*w*), 1063 (*m*), 1034 (*s*), 979 (*m*), 948 (*w*), 908 (*s*), 875 (*w*), 825 (*s*), 793 (*m*), 731 (*s*), 648 (*w*), 624 (*w*), 586 (*w*), 558 (*w*), 501 (*w*), 486 (*w*), 449 (*w*) cm^{-1}.

HRMS (ESI): calcd for $C_{20}H_{21}Br_2O_3$ $[M+H]^+$: 468.9832; found: 468.9825

The structure was validated by single crystal X-ray analysis (see X-ray section).

Analytical data of **S9**:

TLC (25% ethyl acetate in cyclohexane): R_f: 0.51 (UV)

mp: 155.2 – 157.8 °C

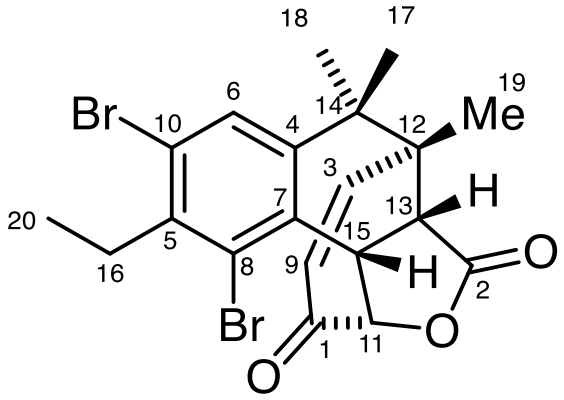
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 6.96 (s, 1H), 6.10 (dd, *J* = 13.1, 1.4 Hz, 1H), 5.64 (dd, *J* = 13.1, 1.9 Hz, 1H), 5.03 (dd, *J* = 8.6, 1.9 Hz, 1H), 4.02 (t, *J* = 8.8 Hz, 1H), 3.14 (dd, *J* = 8.8, 1.4 Hz, 1H), 2.67 (q, *J* = 7.5 Hz, 2H), 1.59 (s, 3H), 1.43 (s, 3H), 1.22 (s, 3H), 1.18 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.6, 176.6, 147.8, 143.2, 142.3, 130.7, 129.2, 126.8, 126.5, 124.8, 84.4, 45.5, 43.6, 42.6, 39.1, 28.9, 28.5, 22.1, 21.3, 14.2.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2967 (m), 2932 (w), 2873 (w), 1781 (s), 1683 (s), 1616 (w), 1556 (w), 1480 (w), 1462 (w), 1394 (w), 1370 (w), 1315 (w), 1261 (m), 1236 (w), 1204 (w), 1156 (s), 1124 (w), 1092 (m), 1070 (m), 1028 (s), 983 (w), 951 (w), 906 (m), 874 (w), 825 (s9, 800 (s), 732 (s), 697 (w), 648 (w), 616 (w), 577 (w), 542 (w), 521 (w), 471 (w) cm^{-1}.

HRMS (ESI): calcd for $C_{20}H_{21}NaBrO_3$ $[M+Na]^+$: 411.0566; found: 411.0539.

NMR comparison data of Salimabromide (1)[119]

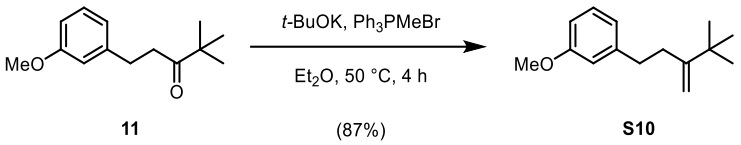


No.	^{1}H NMR (500 MHz, MeOD) isolated Salimabromide (**1**) [ppm]	^{1}H NMR (600 MHz, MeOD) synthetic Salimabromide (**1**) [ppm]	Δ ppm	^{13}C NMR (125 MHz, MeOD) isolated Salimabromide (**1**) [ppm]	^{13}C NMR (150 MHz, MeOD) synthetic Salimabromide (**1**) [ppm]	Δ ppm
1				197.7	197.7	±0.0
2				177.9	177.9	±0.0
3	6.35 (d, J = 13.1 Hz, 1H)	6.32 (dd, J = 13.1, 1.4 Hz, 1H)	–0.03	149.8	149.8	±0.0
4				147.6	147.6	±0.0
5				142.7	142.7	±0.0
6	7.65 (s, 1H)	7.63 (s, 1H)	–0.02	131.5	131.5	±0.0
7				130.1	130.1	±0.0
8				128.1	128.1	±0.0
9	5.70 (d, J = 13.1 Hz, 1H)	5.67 (dd, J = 13.1, 2.0 Hz, 1H)	–0.03	126.5	126.5	±0.0
10				125.7	125.7	±0.0
11	5.65 (d, J = 8.5 Hz, 1H)	5.62 (dd, J = 8.3, 2.0 Hz, 1H)	–0.03	83.5	83.5	±0.0
12				45.8	45.8	±0.0
13	3.38 (d, J = 8.5 Hz, 1H)	3.35 (dd, J = 8.4, 1.4 Hz, 1H)	–0.03	45.2	45.2	±0.0
14				44.7	44.7	±0.0
15	4.44 (t, J = 8.5 Hz, 1H)	4.41 (t, J = 8.3 Hz, 1H)	–0.03	42.6	42.6	±0.0
16	3.09 (q, J = 7.6 Hz, 2H)	3.07 (qd, J = 7.5, 4.0 Hz, 2H)	–0.02	31.9	31.9	±0.0
17	1.25 (s, 3H)	1.23 (s, 3H)	–0.02	29.1	29.1	±0.0
18	1.52 (s, 3H)	1.49 (s, 3H)	–0.03	22.5	22.5	±0.0
19	1.61 (s, 3H)	1.59 (s, 3H)	–0.02	21.8	21.8	±0.0
20	1.17 (t, J = 7.6 Hz, 3H)	1.15 (t, J = 7.5 Hz, 3H)	–0.02	12.7	12.7	±0.0

[119] S. Felder, S. Dreisigacker, S. Kehraus, E. Neu, G. Bierbaum, P. R. Wright, D. Menche, T. F. Schäberle, G. M. König, *Chem. Eur. J.*, **2013**, *19*, 9319–9324.

Asymmetric Synthesis of **12**

1-(4,4-dimethyl-3-methylenepentyl)-3-methoxybenzene (**S10**)



11 (87%) **S10**

To a suspension of potassium *tert*-butoxide (1.83 g, 16.3 mmol, 1.80 equiv) in diethyl ether (33 mL) was added methyltriphenylphosphonium bromide (5.84 g, 16.3 mmol, 1.80 equiv) at 0 °C. The yellow suspension was stirred for 15 min at 0 °C. The reaction was then concentrated at 40 °C under a stream of nitrogen for 1 h. Subsequently ketone **11** (2.00 g, 9.08 mmol, 1 equiv) was added and the slurry was stirred at 50 °C for 4 h. The reaction mixture was cooled to 23 °C and excess base was quenched by addition of saturated aqueous ammonium chloride solution (100 mL). The reaction mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL) and the washed solution was dried over sodium sulfate. The filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (1% ethyl acetate in cyclohexane) afforded alkene **S10** (1.73 g, 87%) as a colorless oil.

TLC (5% ethyl acetate in cyclohexane): R_f: 0.52 (UV)

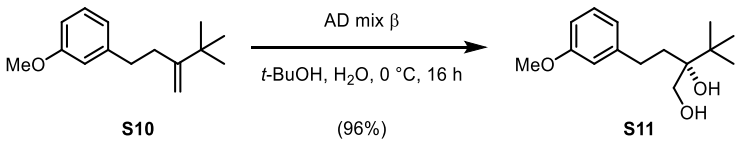
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 2.2 Hz, 1H), 6.76 (dd, *J* = 8.1, 2.5 Hz, 1H), 4.94 (q, *J* = 0.8 Hz, 2H), 4.81 (q, *J* = 1.2 Hz, 2H), 3.82 (s, 3H), 2.81 – 2.71 (m, 2H), 2.36 (dd, *J* = 10.4, 6.2 Hz, 2H), 1.10 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 157.7, 144.5, 129.4, 120.9, 114.4, 111.1, 106.3, 55.2, 36.4, 35.9, 33.3, 29.4.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2955 (s), 2910 (w), 2869 (w), 2834 (w), 1633 (m), 601 (s), 1584 (s), 1488 (s), 1464 (s), 1455 (s), 1436 (w), 1387 (w), 1361 (m), 1313 (w), 1261 (s), 1201 (w), 1191 (w), 1152 (s), 1081 (w), 1053 (ss), 996 (w), 960 (w), 890 (s), 847 (w), 776 (s), 750 (m), 693 (s), 637 (w), 572 (w), 541 (m), 503 (w), 479 (w), 451 (m) cm^{-1}.

HRMS (ESI): calcd for $C_{15}H_{23}O$ $[M+H]^+$: 219.1743 found: 219.1734.

(*R*)-2-(3-methoxyphenethyl)-3,3-dimethylbutane-1,2-diol (**S11**)



Potassium hexacyanoferrate(III) (9.9 g, 30 mmol, 6.0 equiv), potassium carbonate (4.1 g, 30 mmol, 5.0 equiv), potassium osmate(VI) dihydrate (11 mg, 30 µmol, 0.6 mol%) and hydroquinidine 1,4-phthalazinediyl diether (75 mg, 96 µmol, 1.9 mol%) were finely grinded in a mortar and the obtained powder was added to a mixture of water (30 mL) and *t*-butanol (30 mL). The suspension was sonicated for 30 min and then cooled to 0 °C. Methanesulfonamide (0.95 g, 10 mmol, 1.7 equiv) was added, followed by alkene **S10** (1.09 g, 4.99 mmol, 1 equiv). The suspension was vigorously stirred for 16 h at 0 °C until analysis by thin layer chromatography indicated full conversion of the alkene **S10**. The reaction was allowed to warm to 23 °C and sodium sulfite (6.5 g) was added. The reaction mixture was stirred for 1 h followed by addition of aqueous sodium hydroxide solution (1 M, 30 mL). The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL) and the washed solution was dried over sodium sulfate. The filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (25% ethyl acetate in cyclohexane initially, grading to 50% ethyl acetate in cyclohexane) afforded diol **S11** (1.21 g, 96%) as a colorless oil that crystallized upon storage.

TLC (50% ethyl acetate in cyclohexane): R_f: 0.39 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (t, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 2.2 Hz, 1H), 6.75 (dd, *J* = 8.1, 2.4 Hz, 1H), 3.80 (s, 3H), 3.79 – 3.75 (m, 1H), 3.66 (dd, *J* = 11.0, 6.0 Hz, 1H), 2.83 – 2.67 (m, 2H), 2.55 (t, *J* = 5.3 Hz, 1H), 2.44 (s, 1H), 1.95 (ddd, *J* = 14.1, 11.4, 5.7 Hz, 1H), 1.82 (ddd, *J* = 14.1, 11.5, 5.9 Hz, 1H), 0.99 (s, 9H).

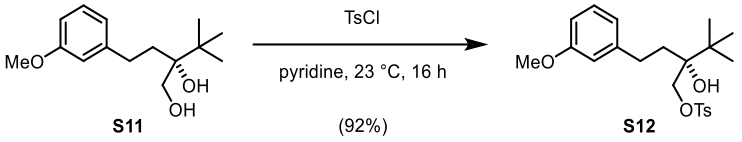
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 144.8, 129.5, 120.9, 114.3, 111.1, 76.4, 64.3, 55.2, 37.8, 36.5, 31.0, 25.6.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3444 (*br s*), 2958 (*s*), 2836 (*w*), 1601 (*m*), 1584 (*m*), 1488 (*m*), 1455 (*m*), 1436 (*w*), 1395 (*w*), 1368 (*w*), 1314 (*w*), 1258 (*s*), 1192 (*w*), 1153 (*s*), 1037 (*s*), 908 (*s*), 777 (*m*), 730 (*s*), 694 (*s*), 648 (*m*), 556 (*w*), 488 (*w*), 454 (*w*) cm^{-1}.

HRMS (ESI): calcd for $C_{15}H_{24}NaO_3$ $[M+Na]^+$: 275.1618 found: 275.1604.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +1.6 (c = 1.03, CH_2Cl_2).

(*R*)-2-hydroxy-2-(3-methoxyphenethyl)-3,3-dimethylbutyl 4-methylbenzene-sulfonate (**S12**)



To a solution of diol **S11** (86 mg, 0.34 mmol, 1 equiv) in pyridine (1.0 mL) at 0 °C was added 4-methylbenzene-1-sulfonyl chloride (130 mg, 0.682 mmol, 2.00 equiv) in one portion. The solution was stirred at 23 °C for 16 h. Subsequently the reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (25% ethyl acetate in cyclohexane) afforded the title compound (128 mg, 92%) as a colorless oil.

TLC (50% ethyl acetate in cyclohexane): R_f: 0.51 (CAM)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.19 (t, *J* = 7.8 Hz, 1H), 6.76 – 6.68 (m, 3H), 4.13 (d, *J* = 9.9 Hz, 1H), 4.07 (d, *J* = 9.9 Hz, 1H), 3.80 (s, 3H), 2.63 (ddd, *J* = 13.3, 9.9, 7.2 Hz, 1H), 2.52 (ddd, *J* = 13.3, 10.3, 7.0 Hz, 1H), 2.45 (s, 3H), 1.94 – 1.83 (m, 3H), 0.95 (s, 9H).

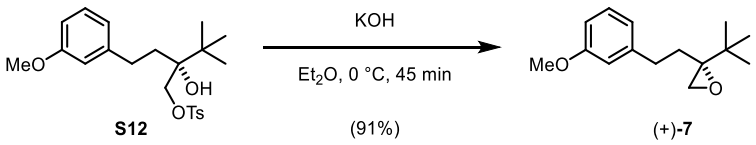
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 145.2, 144.0, 132.6, 130.1, 129.5, 128.1, 120.8, 114.3, 111.3, 75.8, 71.4, 55.2, 37.9, 35.1, 30.3, 25.6, 21.7.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3548 (*m br*), 2961 (*m*), 2836 (*w*), 1599 (*m*), 1585 (*m*), 1487 (*m*), 1455 (*w*), 1437 (*w*), 1399 (*w*), 1358 (*m*), 1290 (*w*), 1260 (*m*), 1212 (*w*), 1189 (*w*), 1174 (*s*), 1154 (*w*), 1120 (*w*), 1096 (*m*), 1044 (*m*), 1019 (*w*), 975 (*s*), 953 (*s*), 840 (*s*), 813 (*s*), 783 (*m*), 736 (*m*), 696 (*m*), 665 (*s*), 579 (*m*), 554 (*s*), 528 (*s*), 477 (*w*), 450 (*w*) cm^{-1}.

HRMS (ESI): calcd for $C_{15}H_{24}NaO_3$ $[M+Na]^+$: 429.1706 found: 429.1650.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −17.0 (c = 0.79, CH_2Cl_2).

(*R*)-2-(*tert-butyl*)-2-(3-methoxyphenethyl)oxirane (**7**)



To a solution of tosylate **S12** (116 mg, 0.285 mmol, 1 equiv) in diethyl ether (1.0 mL) was added freshly grinded potassium hydroxide (65 mg, 1.2 mmol, 4.0 equiv) in one portion at 0 °C. The suspension was stirred for 45 min at 0 °C until analysis by thin layer chromatography indicated full conversion of the tosylate **S12**. The reaction solution was directly purified by flash column chromatography on silica gel (1% ethyl acetate in cyclohexane) to afford epoxide **7** (61 mg, 91%) as a colorless oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +8.0 (c = 0.77, CH_2Cl_2).

82% ee (HPLC conditions: Chiralcel IA column, heptane/EtOAc = 99.7/0.3, 1.5 mL/min, λ = 272 nm, t_R(minor) = 8.6 min, t_R(major) = 9.8 min)

The analytical data matched those obtained by direct epoxidation of **11**.

(6-methoxy-1,1,2-trimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (**12**)

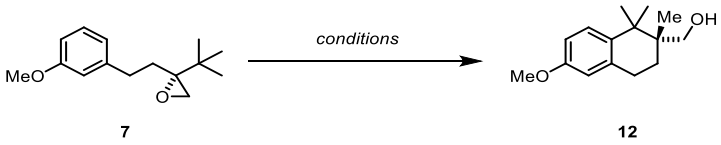
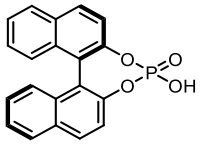


Table 2: Rearrangement of enantioenriched **7** towards **12** under different conditions.

Entry*	conditions	ee of 7	comments	ee of 12
1	HFIP, H_2SO_4, 23 °C, 5 min	82%		38%
2	n-hexane, H_2SO_4, 23 °C, 5 min	82%		39%
3	n-hexane, H_2SO_4, –78 °C, 2.5 h, warm to 23 °C, 5 min	82%	solubility of H_2SO_4 at -78 °C is very low, probably no reaction till warm up	37%
4	DCM, $TiCl_4$, 23 °C, 10 min	82%		59%
5	DCM, $TiCl_4$, –78 °C, 1 h, warm to 23 °C, 5 min	82%	25% yield	**70%**

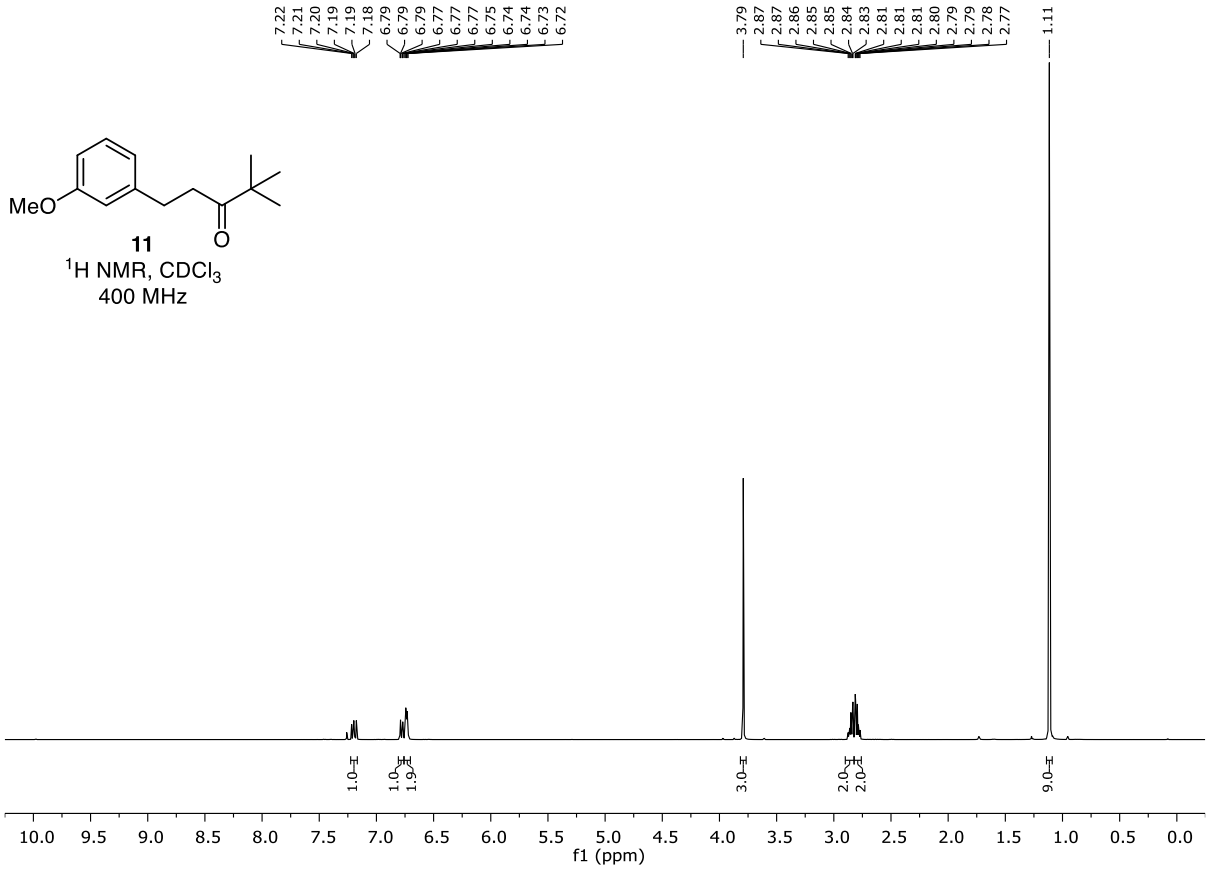
6	DCM, **S13**, –78 °C, 4 h, warm to 23 °C, 16 h	0%	only very minor traces of product detectable, >90% of **7**	ca. 0%

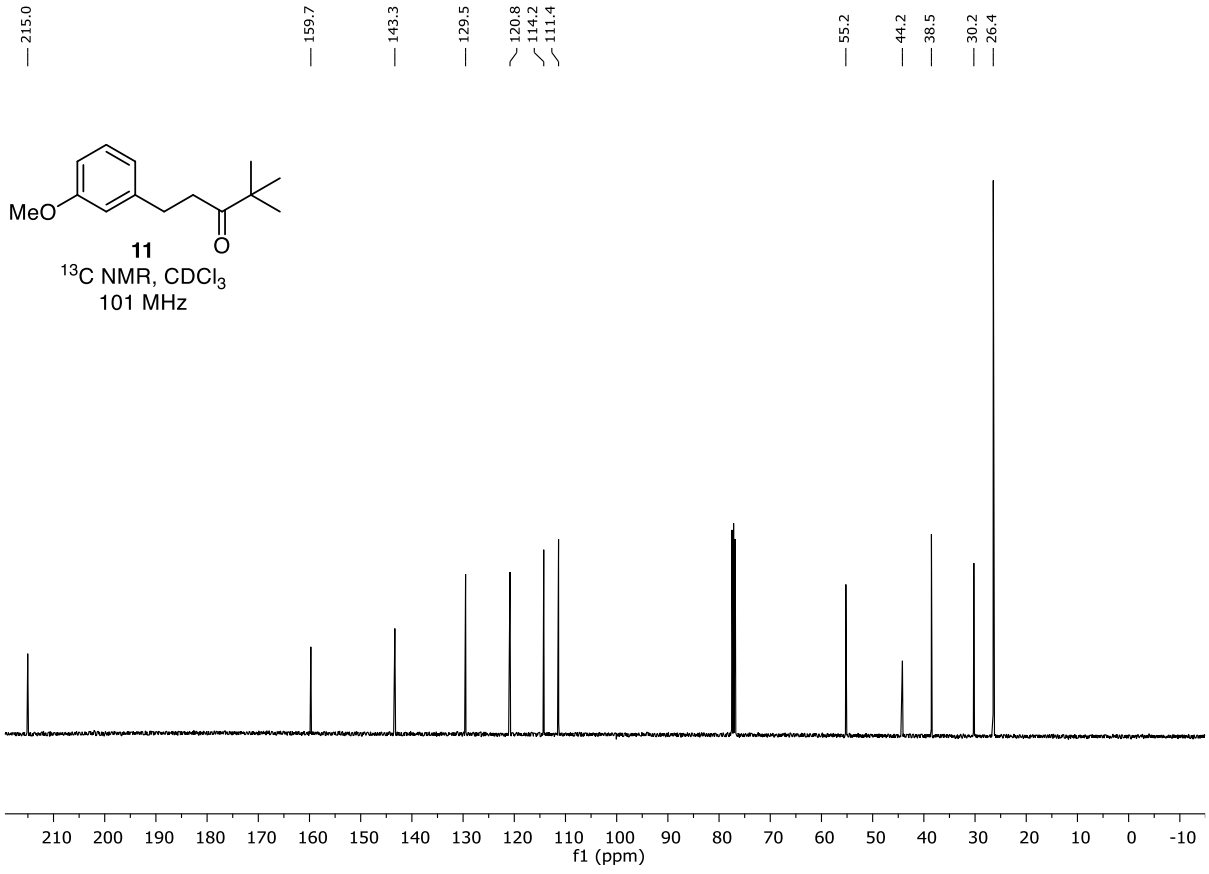
S13 = 

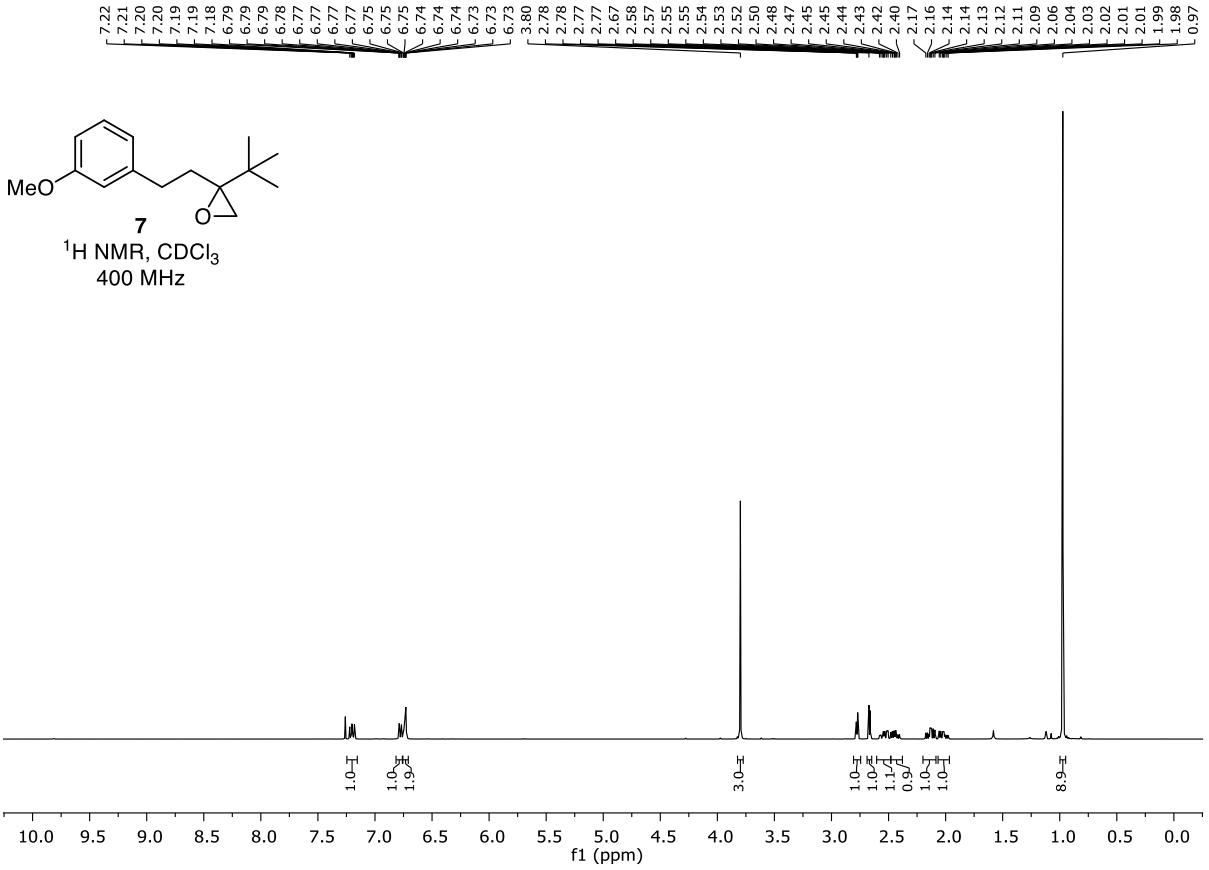
, *all reactions were performed on a 3 till 5 mg scale

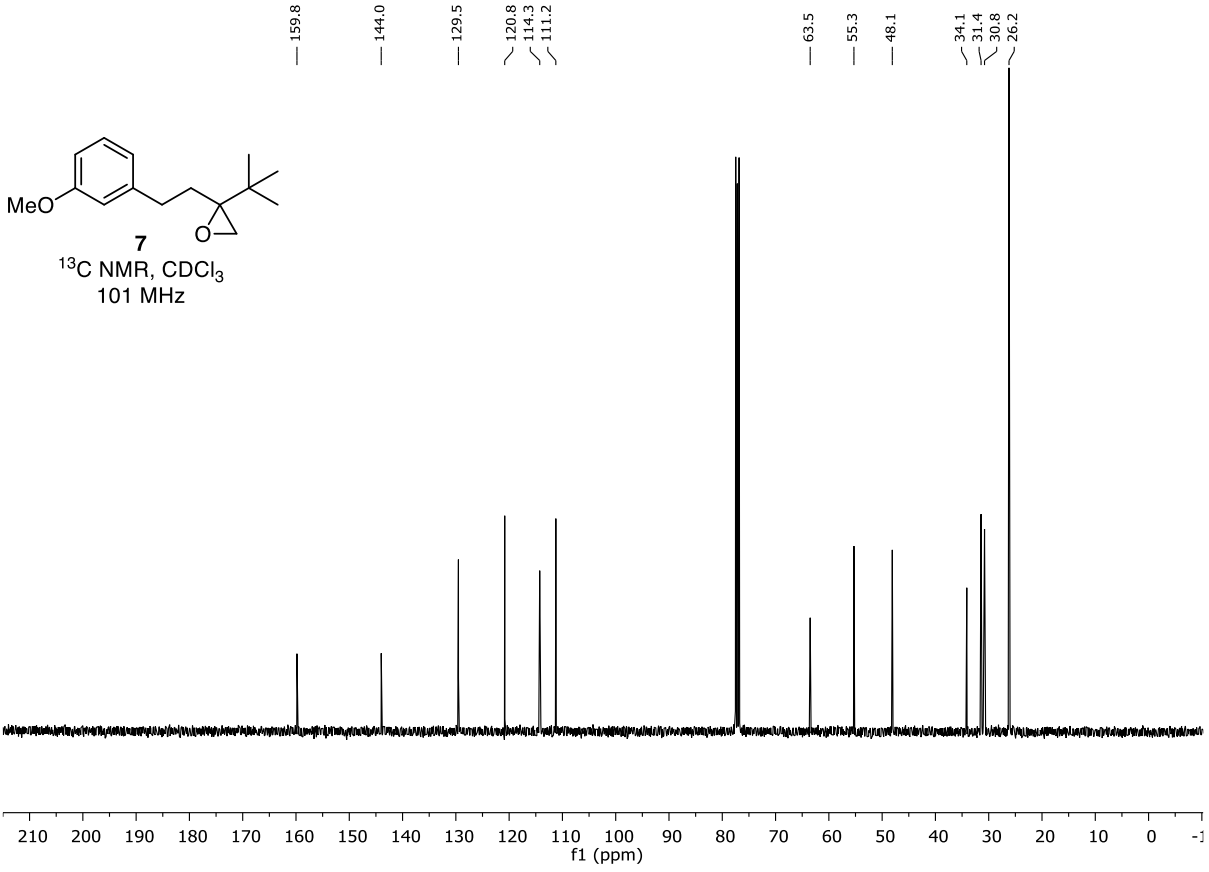
HPLC conditions: Chiralcel IA column, heptane/*i*-PrOH = 99/1, 1.5 mL/min, λ = 210 nm, t_R (minor) = 17.7 min, t_R(major) = 18.7 min

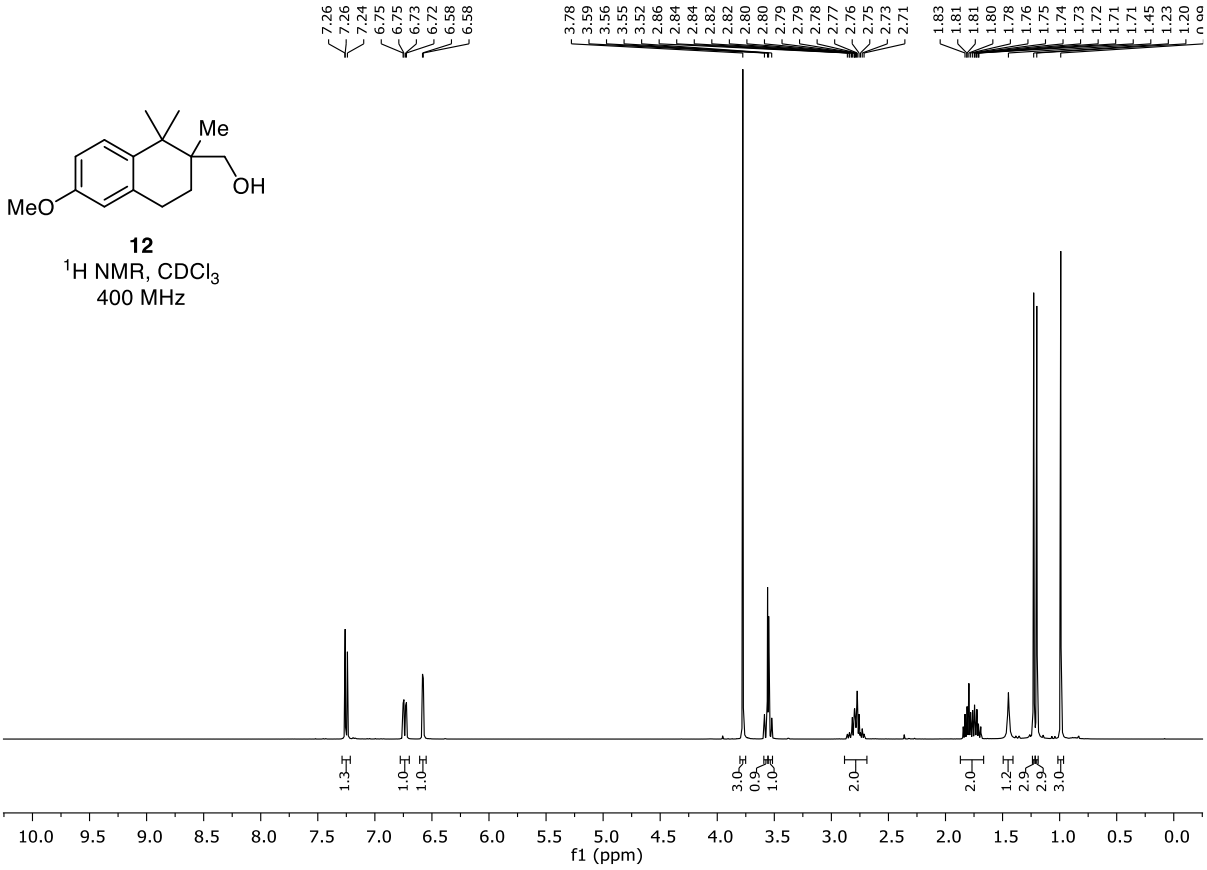
2.2 NMR spectra

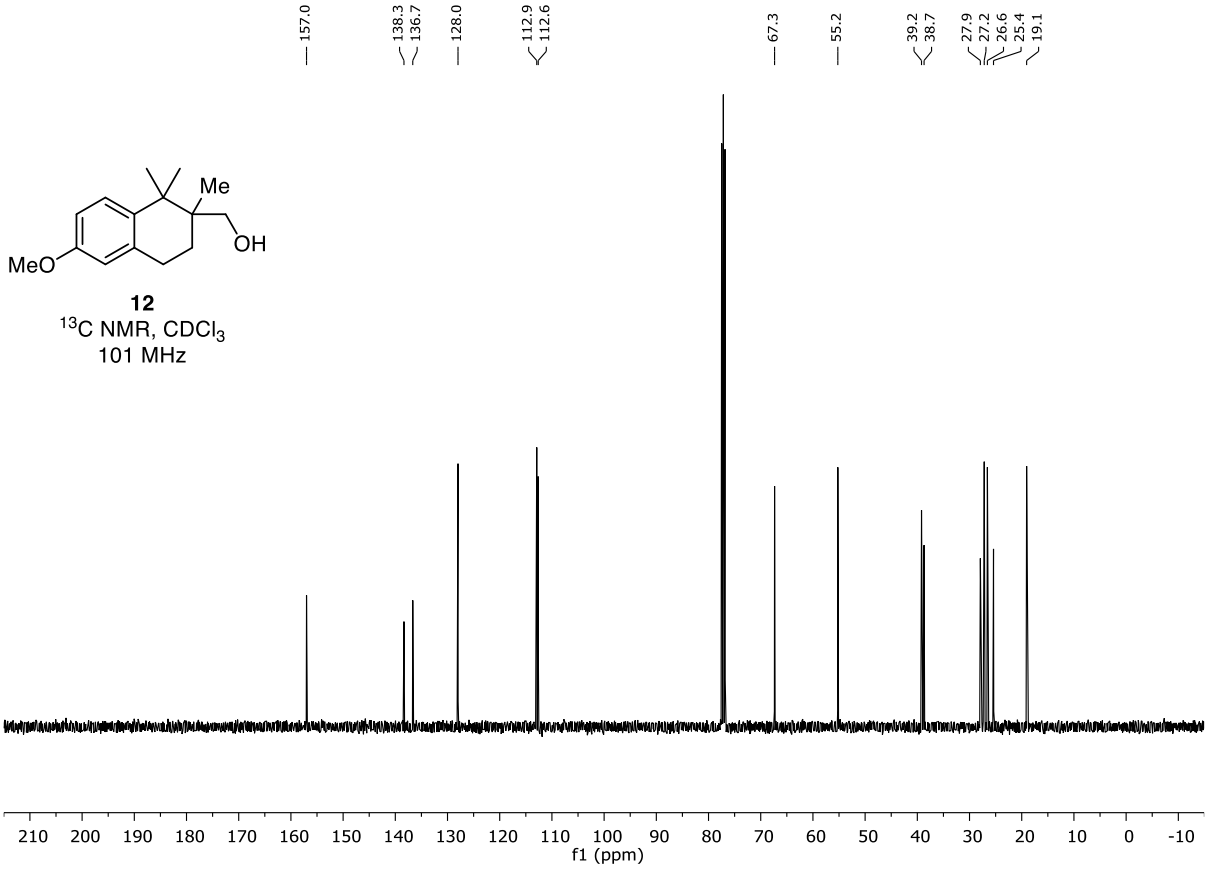


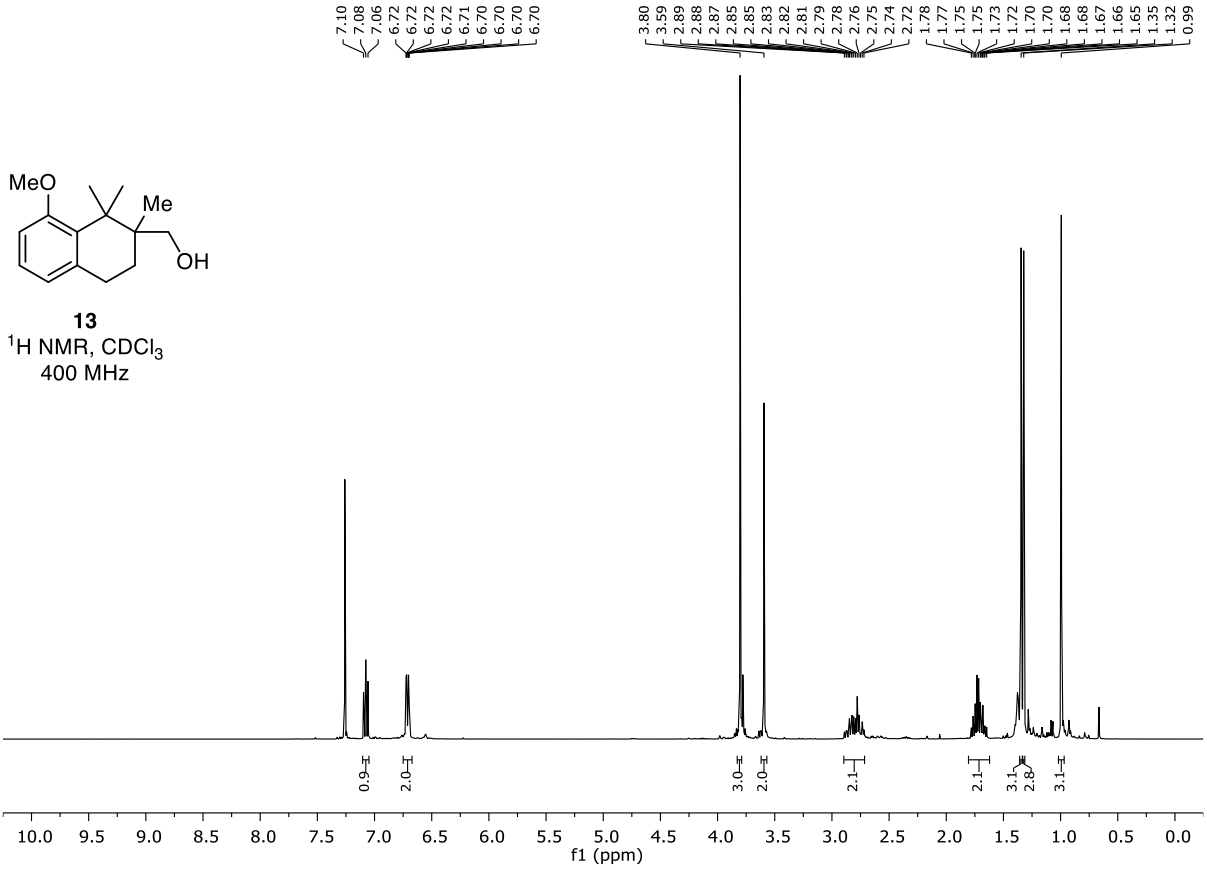



MeO
O
7
1H NMR, CDCl3
400 MHz
f1 (ppm)

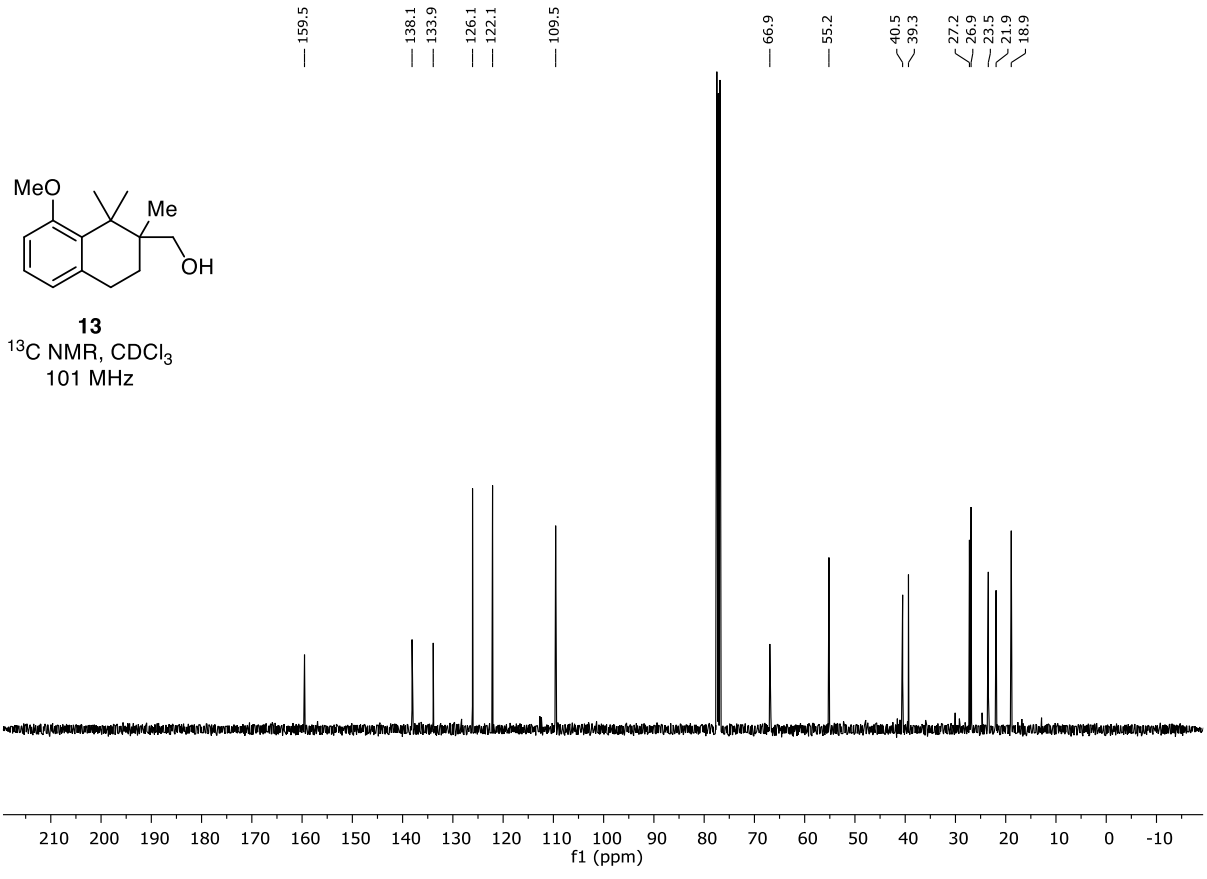

MeO
O
7
13C NMR, CDCl3
101 MHz
f1 (ppm)


Me
OH
MeO
12
^{1}H NMR, $CDCl_3$
400 MHz
f1 (ppm)

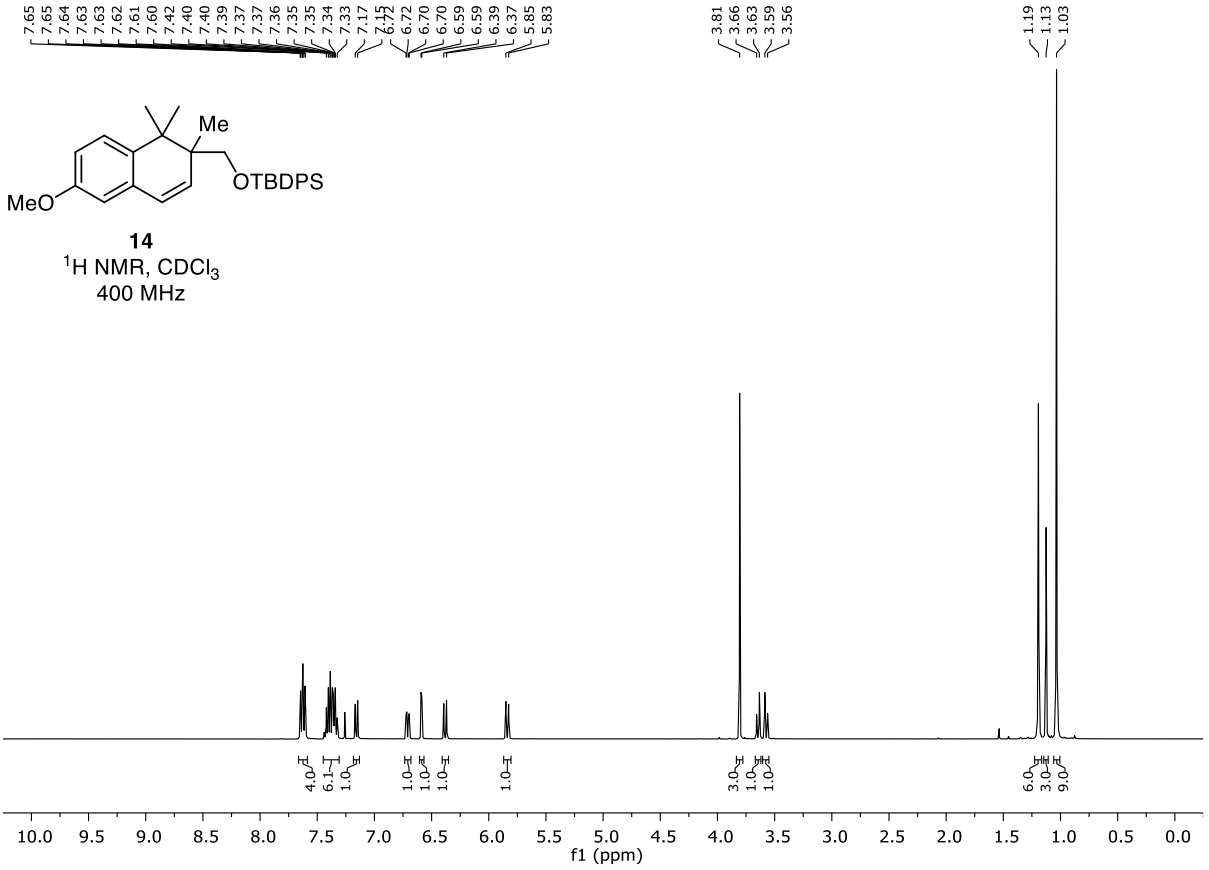

Me
OH
MeO
12
^{13}C NMR, $CDCl_3$
101 MHz
f1 (ppm)



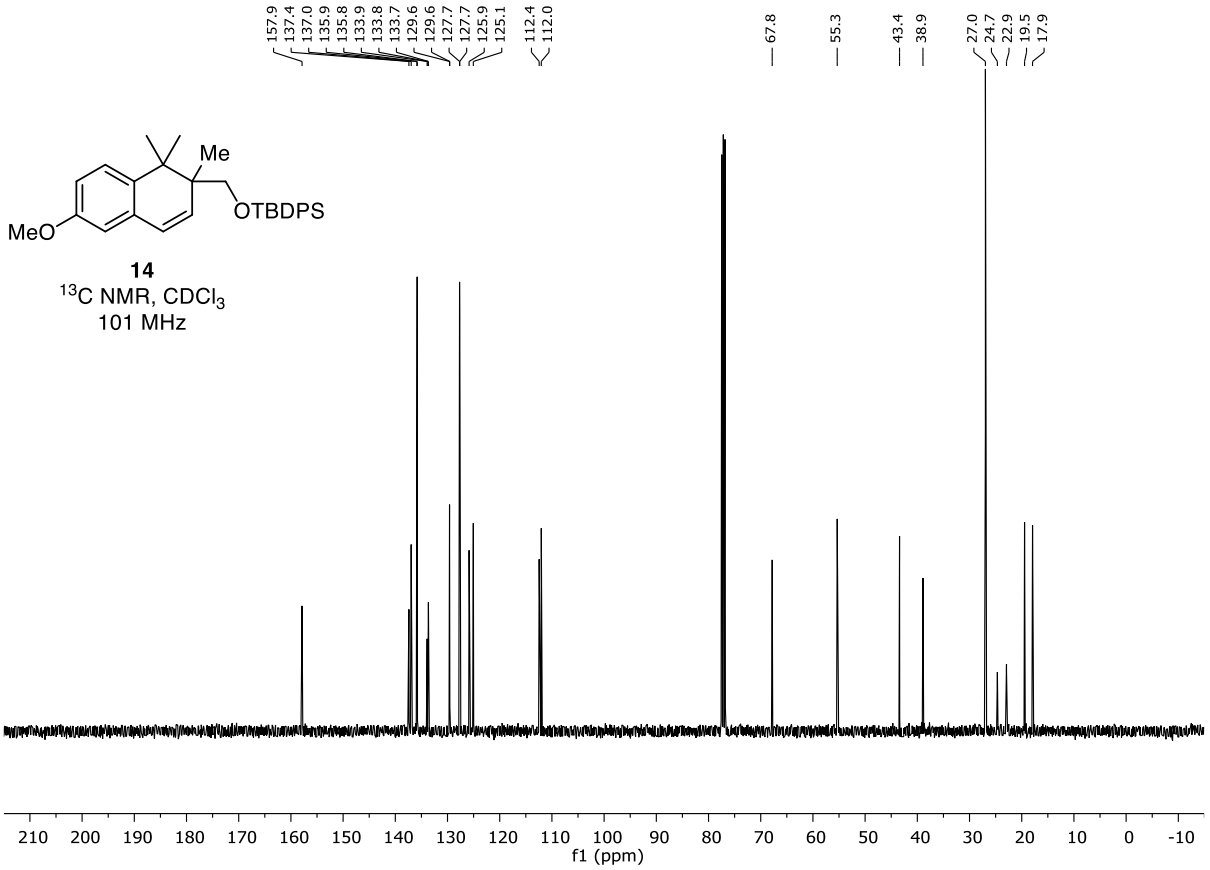
13
^{1}H NMR, $CDCl_3$
400 MHz



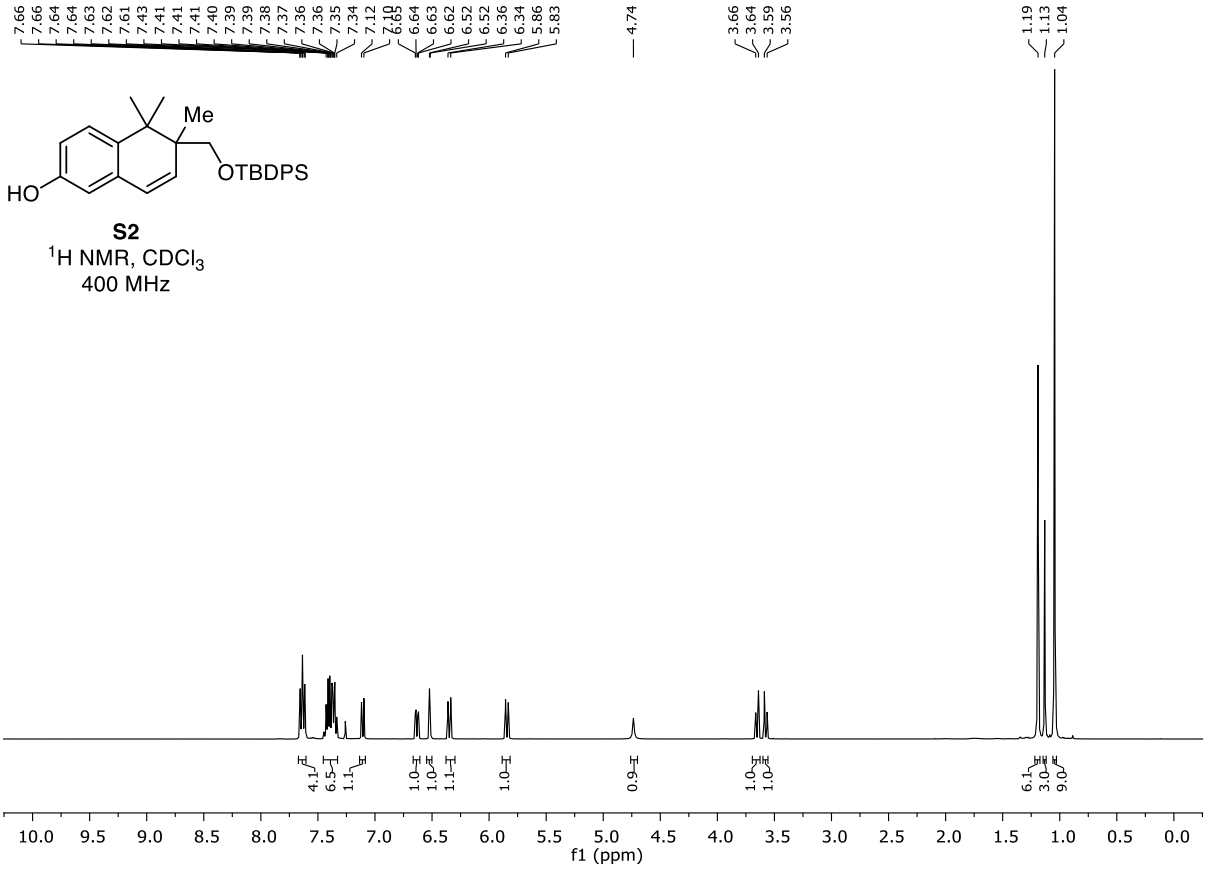
13
^{13}C NMR, $CDCl_3$
101 MHz



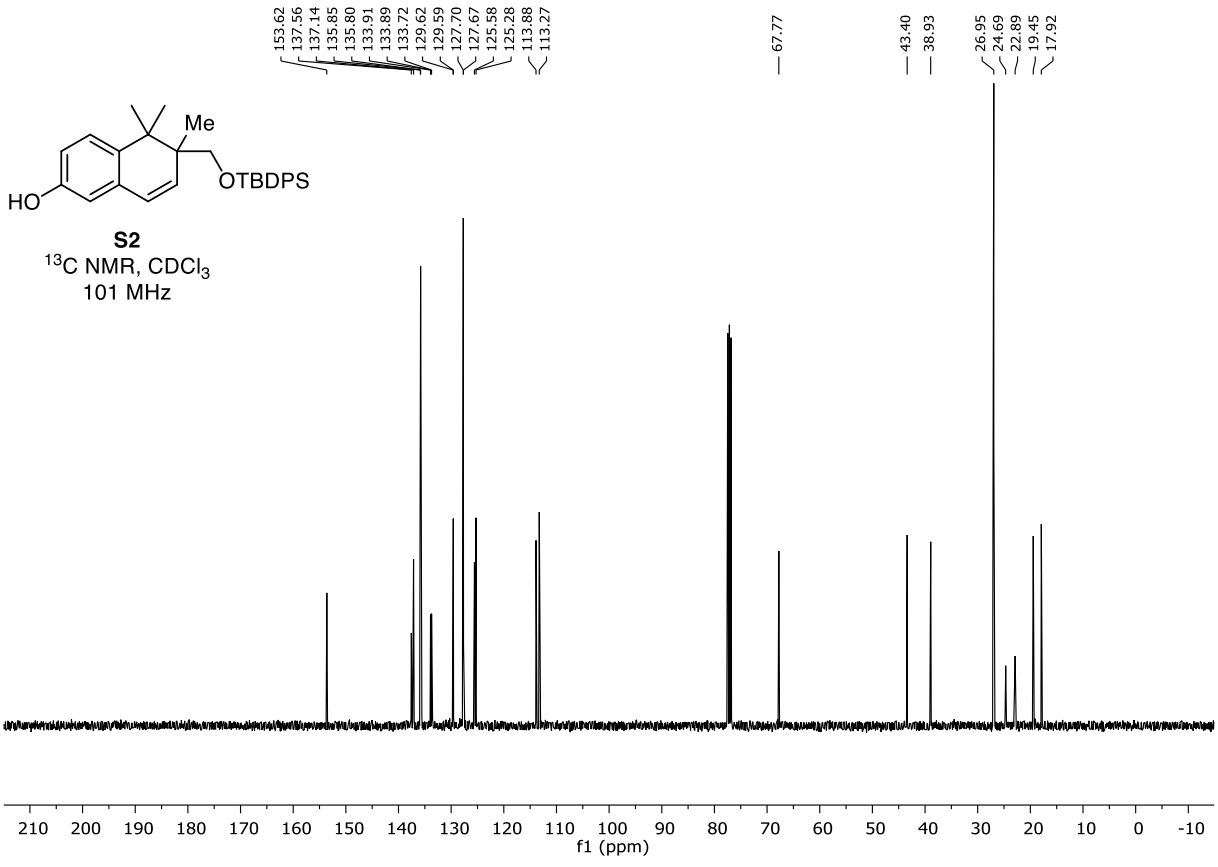
14
^{1}H NMR, $CDCl_3$
400 MHz



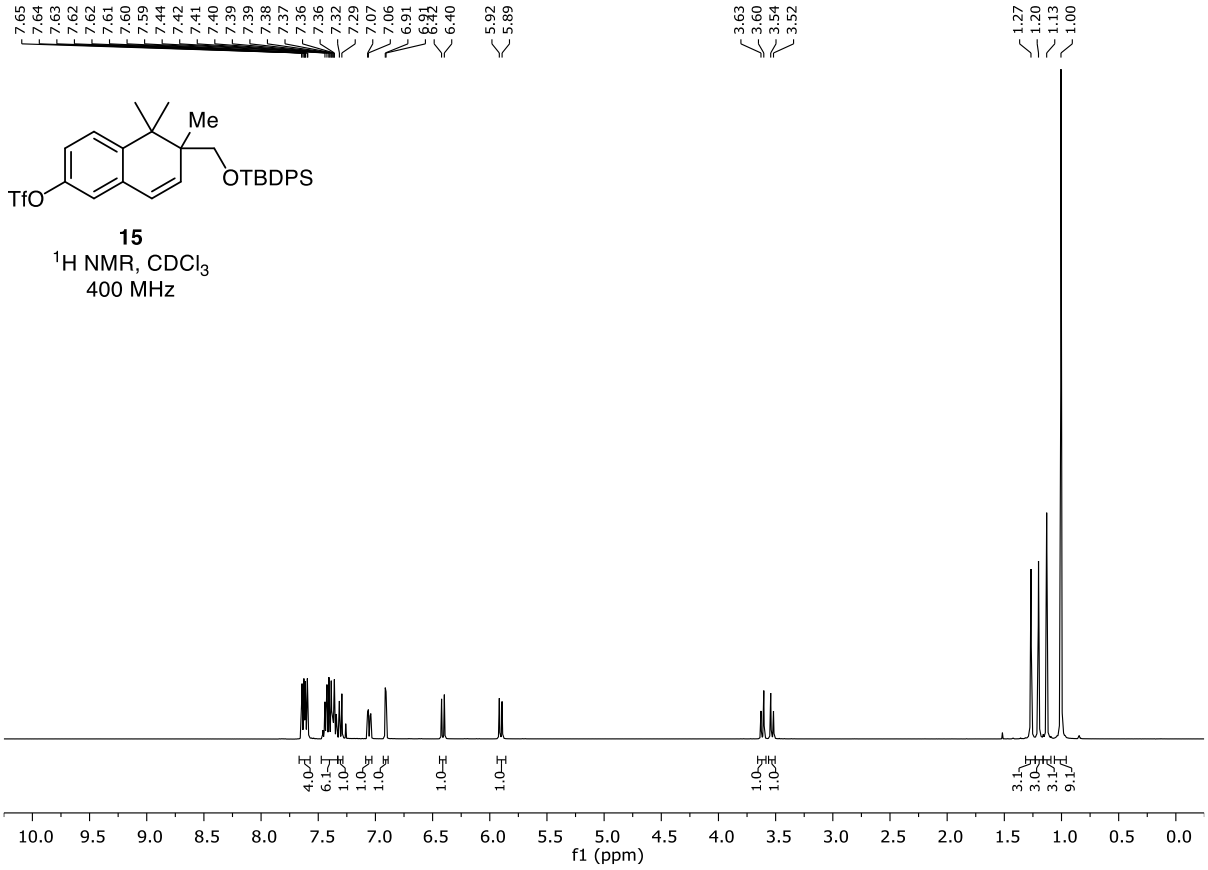
14
^{13}C NMR, $CDCl_3$
101 MHz



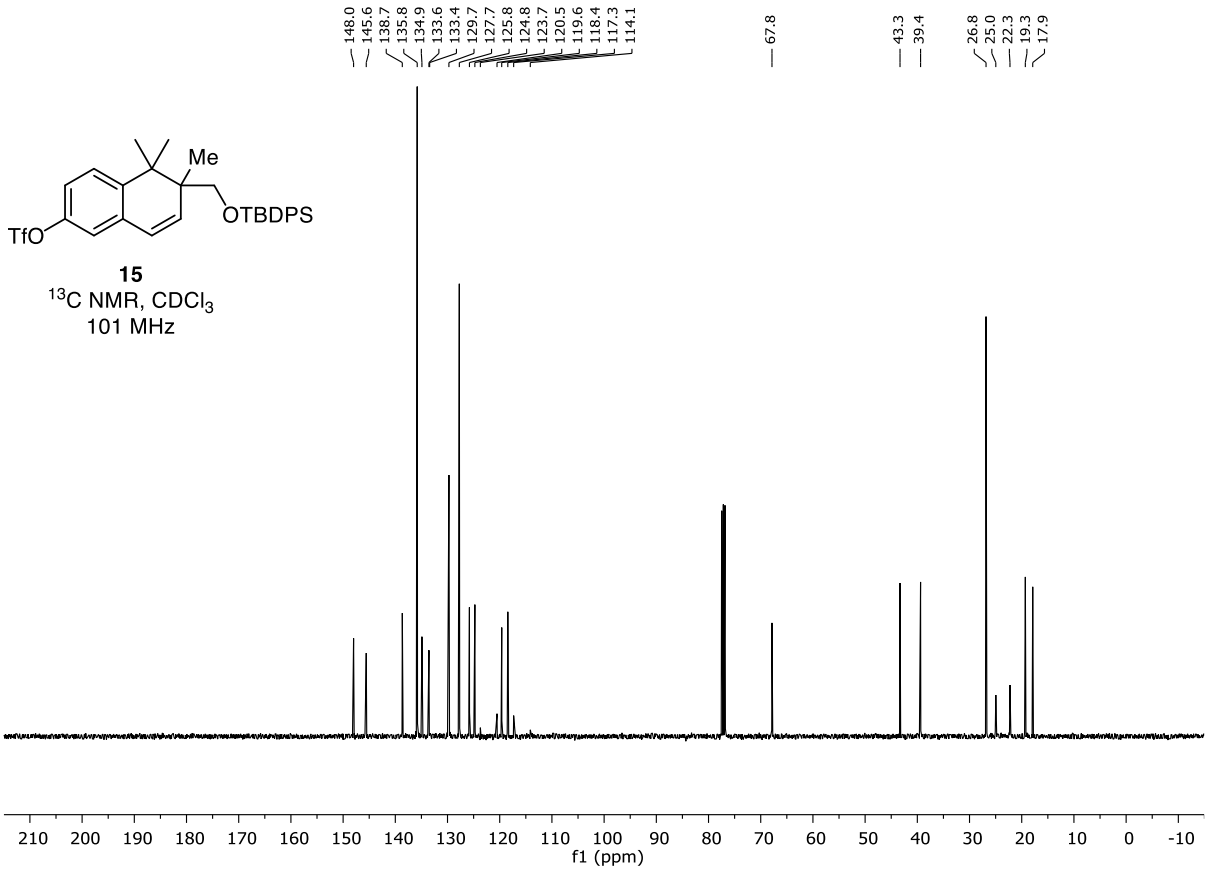
S2
^{1}H NMR, $CDCl_3$
400 MHz



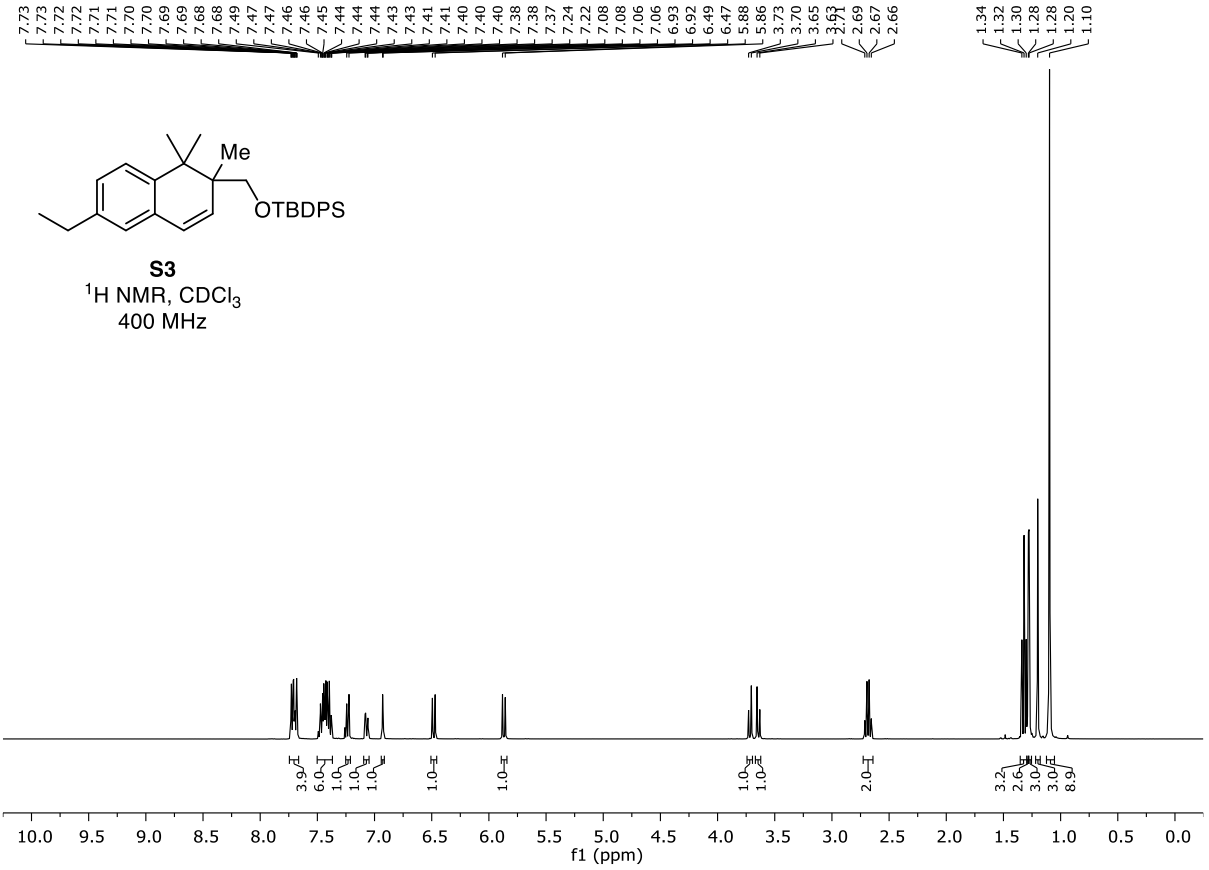
S2
^{13}C NMR, $CDCl_3$
101 MHz



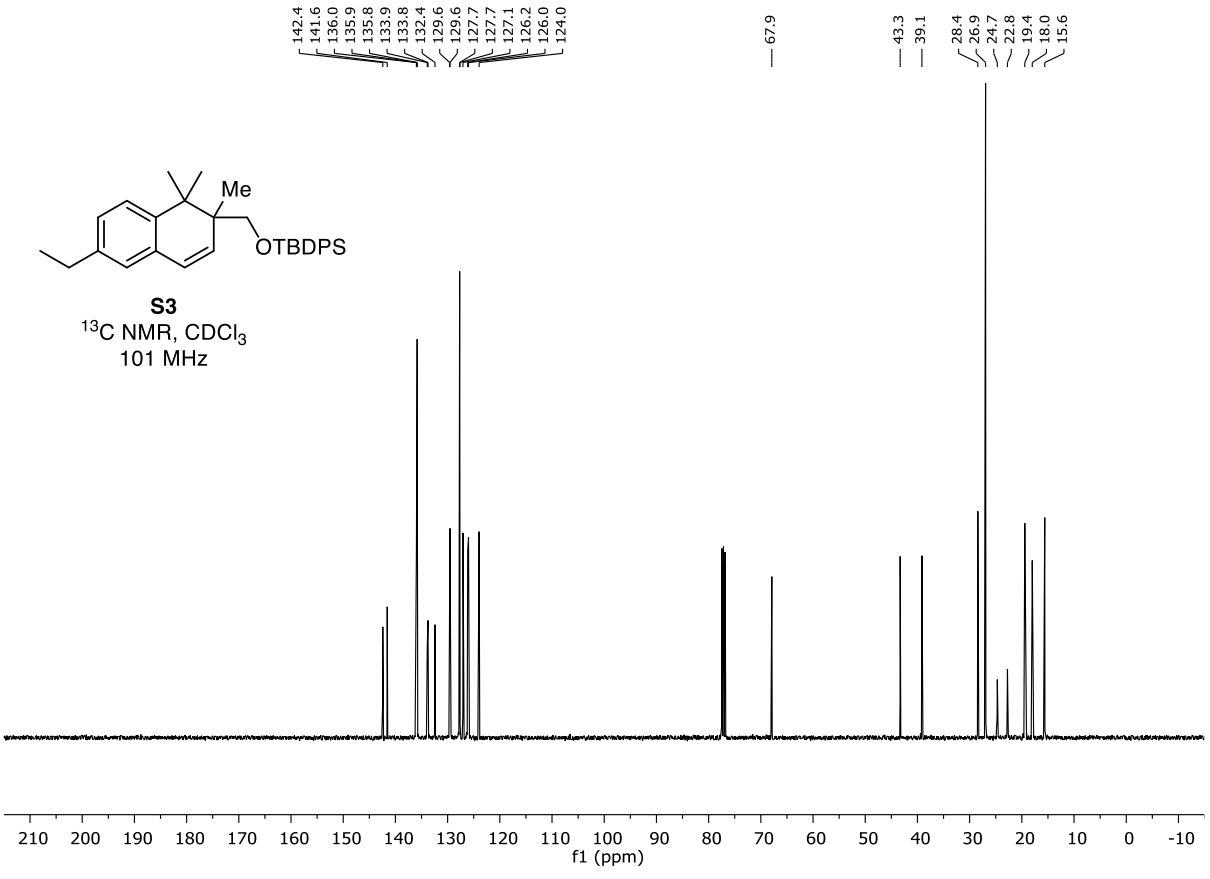
15
^{1}H NMR, $CDCl_3$
400 MHz



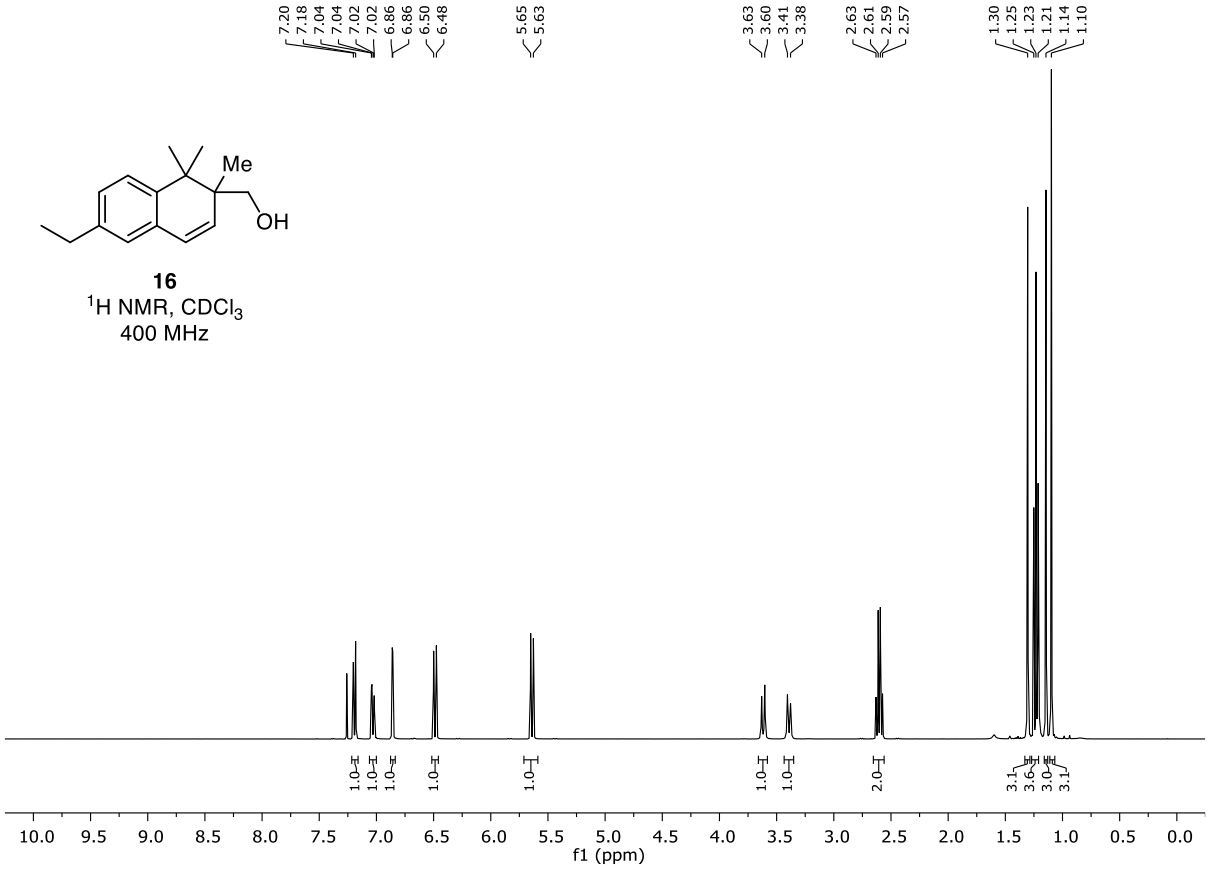
15
^{13}C NMR, $CDCl_3$
101 MHz



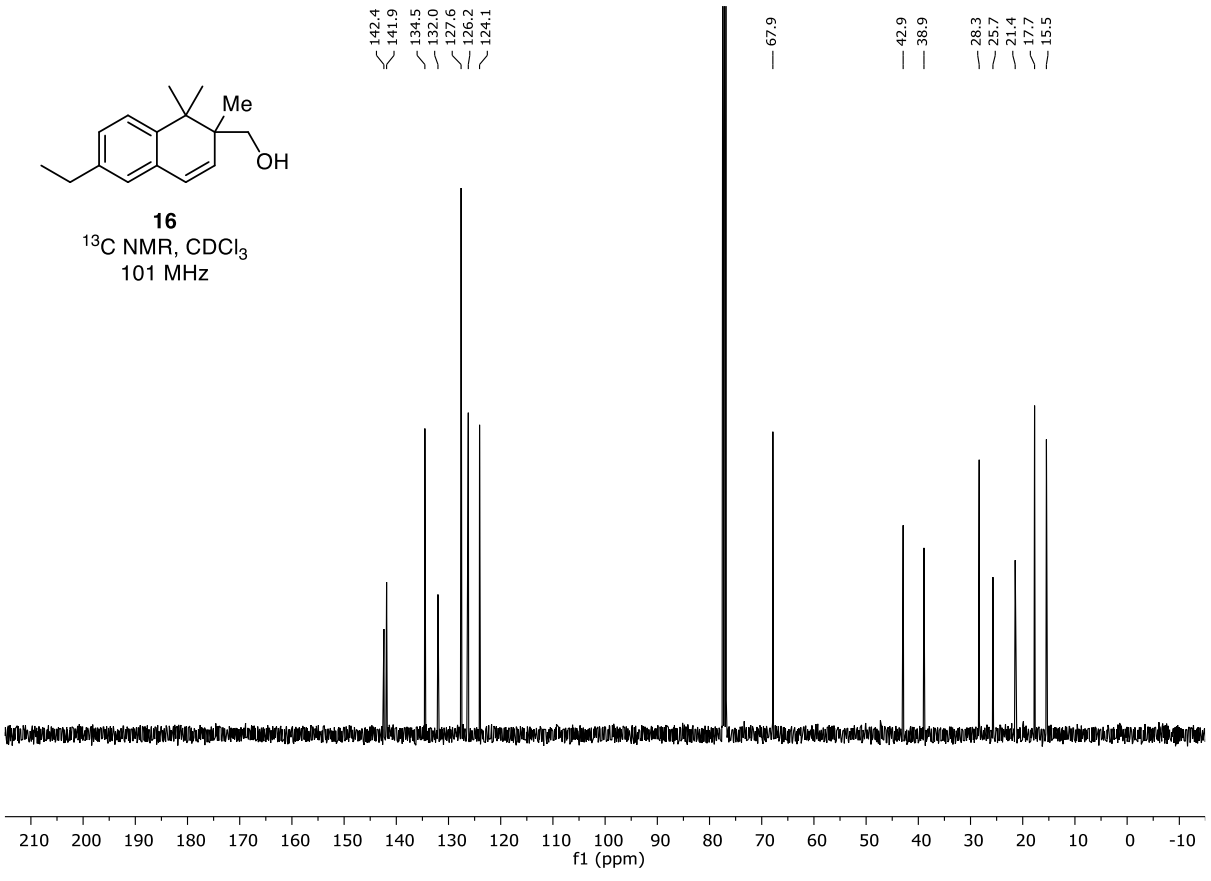
S3
^{1}H NMR, $CDCl_3$
400 MHz



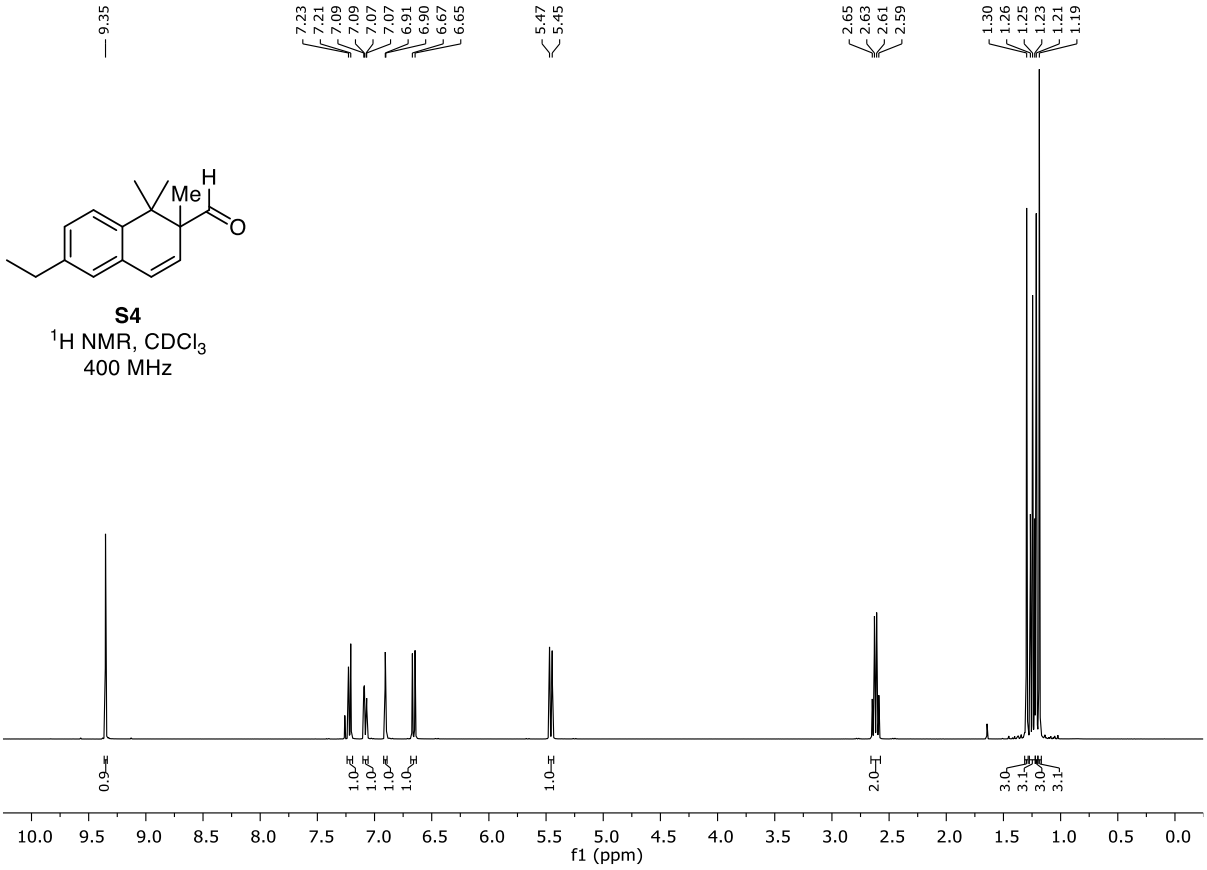
S3
^{13}C NMR, $CDCl_3$
101 MHz



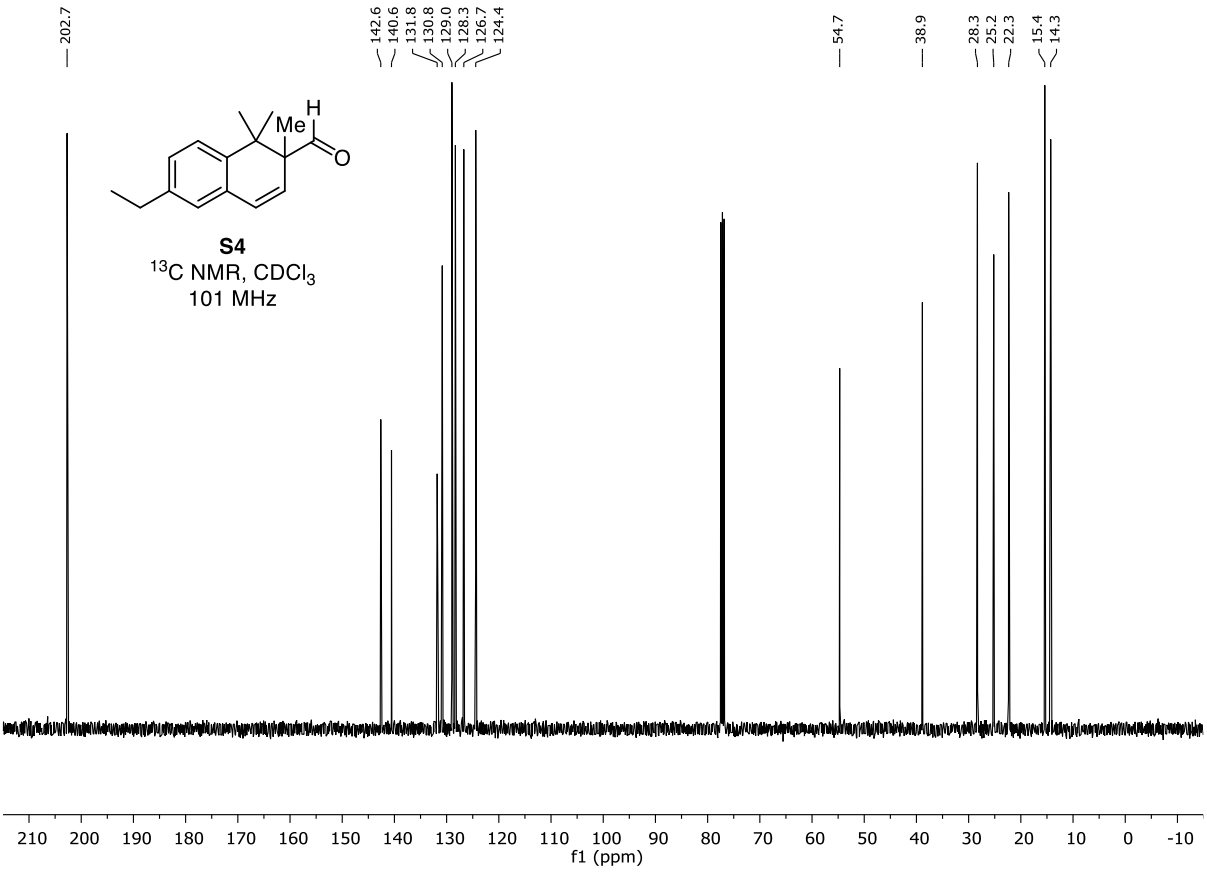
16
^{1}H NMR, $CDCl_3$
400 MHz



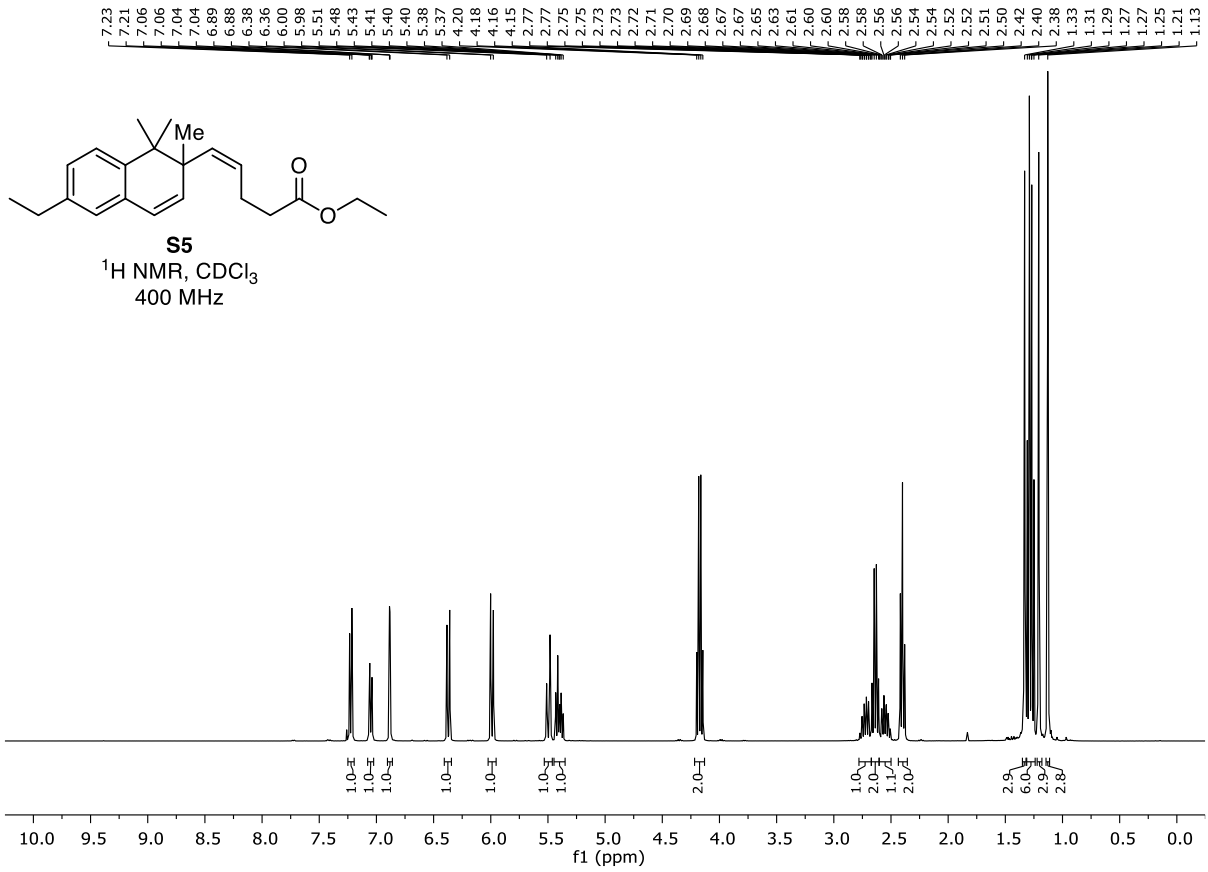
16
^{13}C NMR, $CDCl_3$
101 MHz

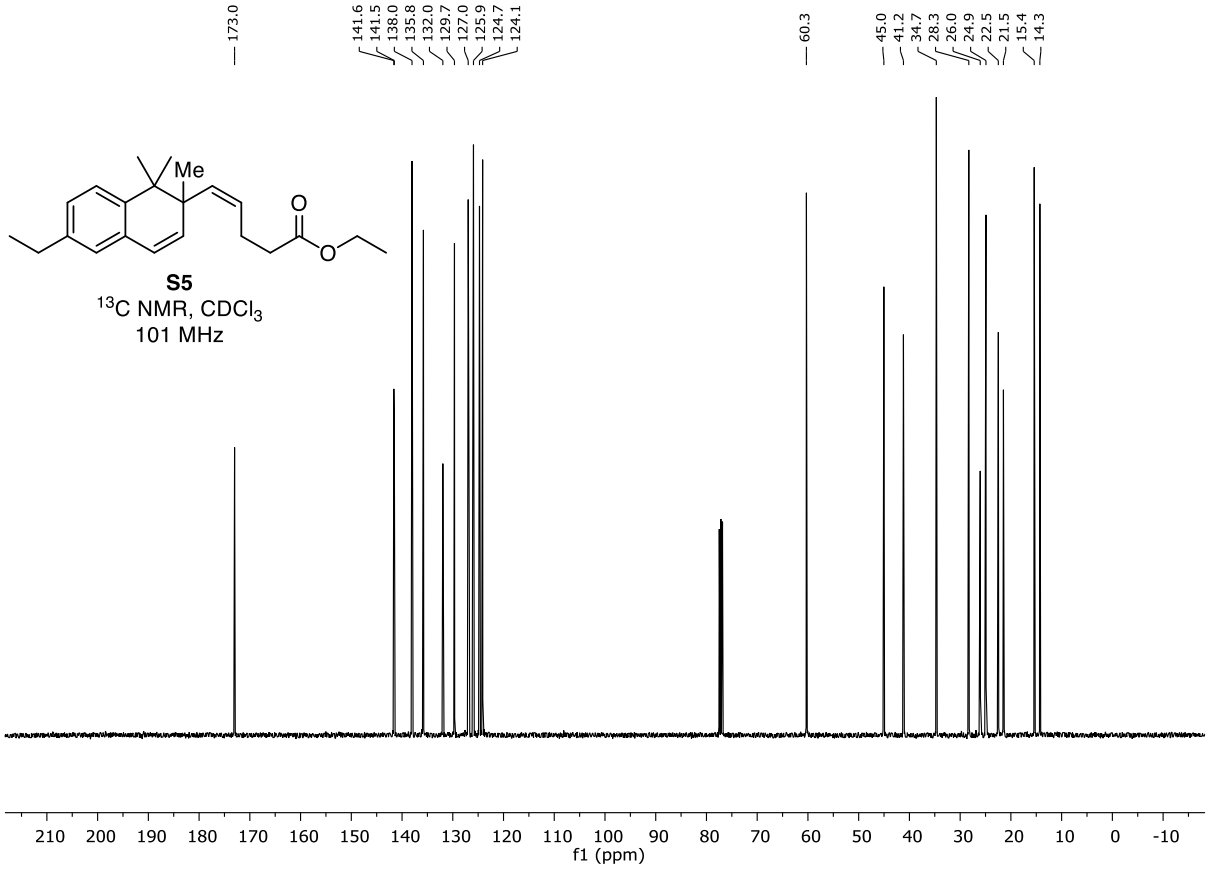


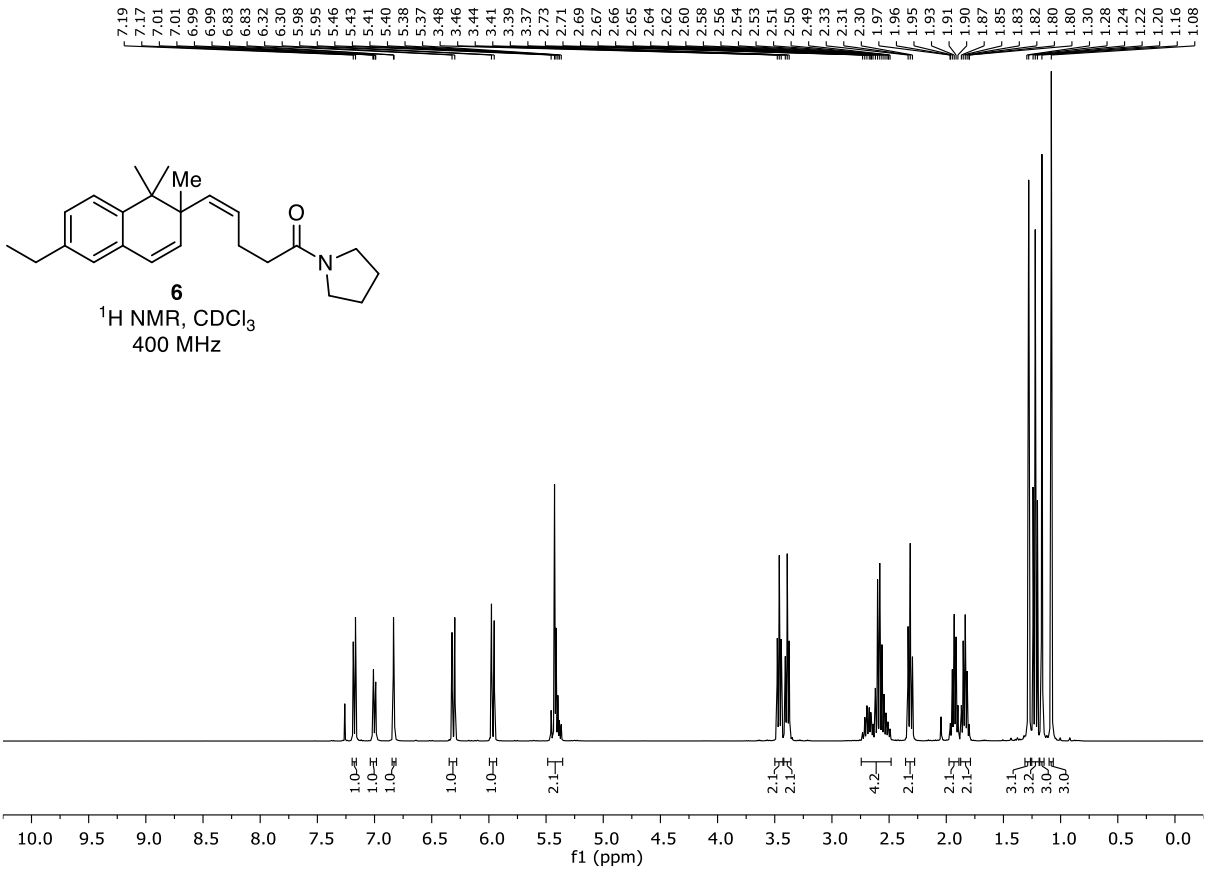
S4
^{1}H NMR, $CDCl_3$
400 MHz

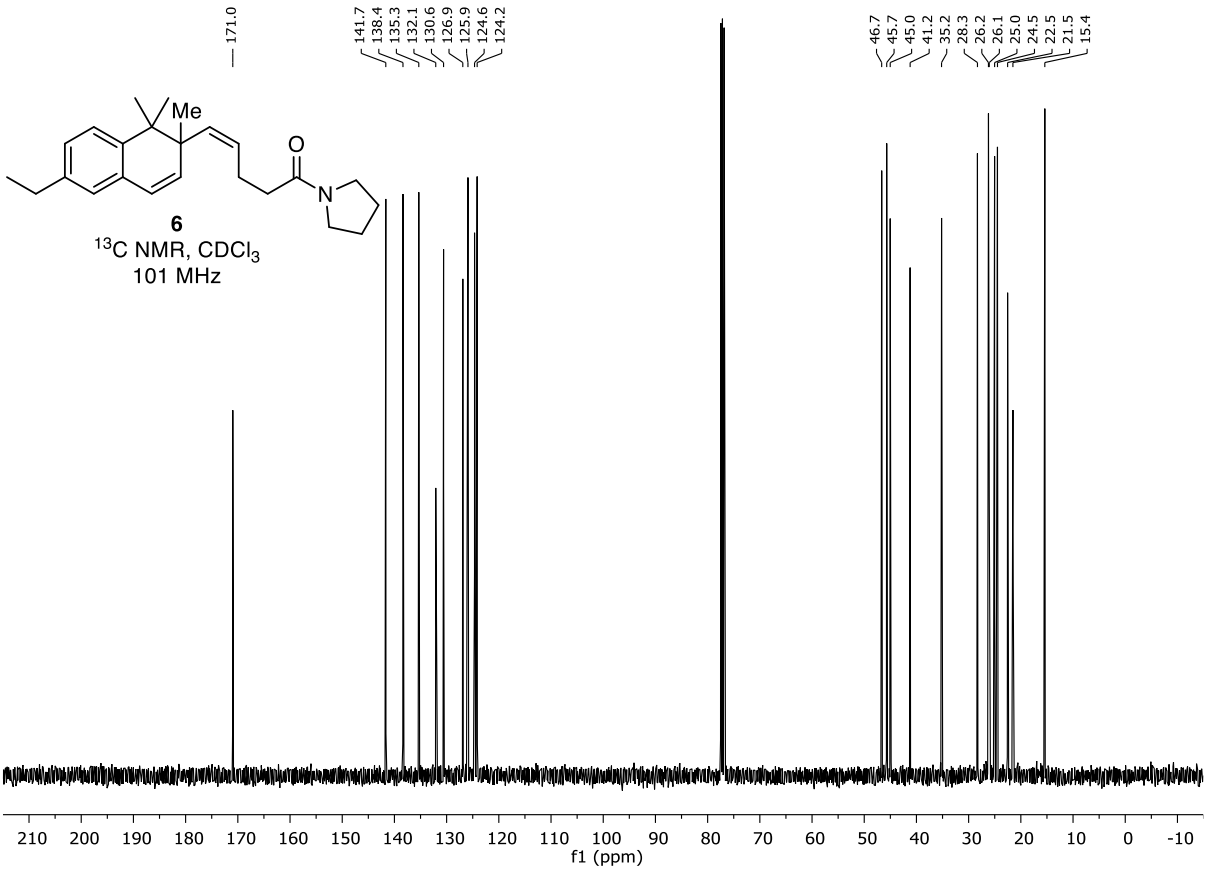


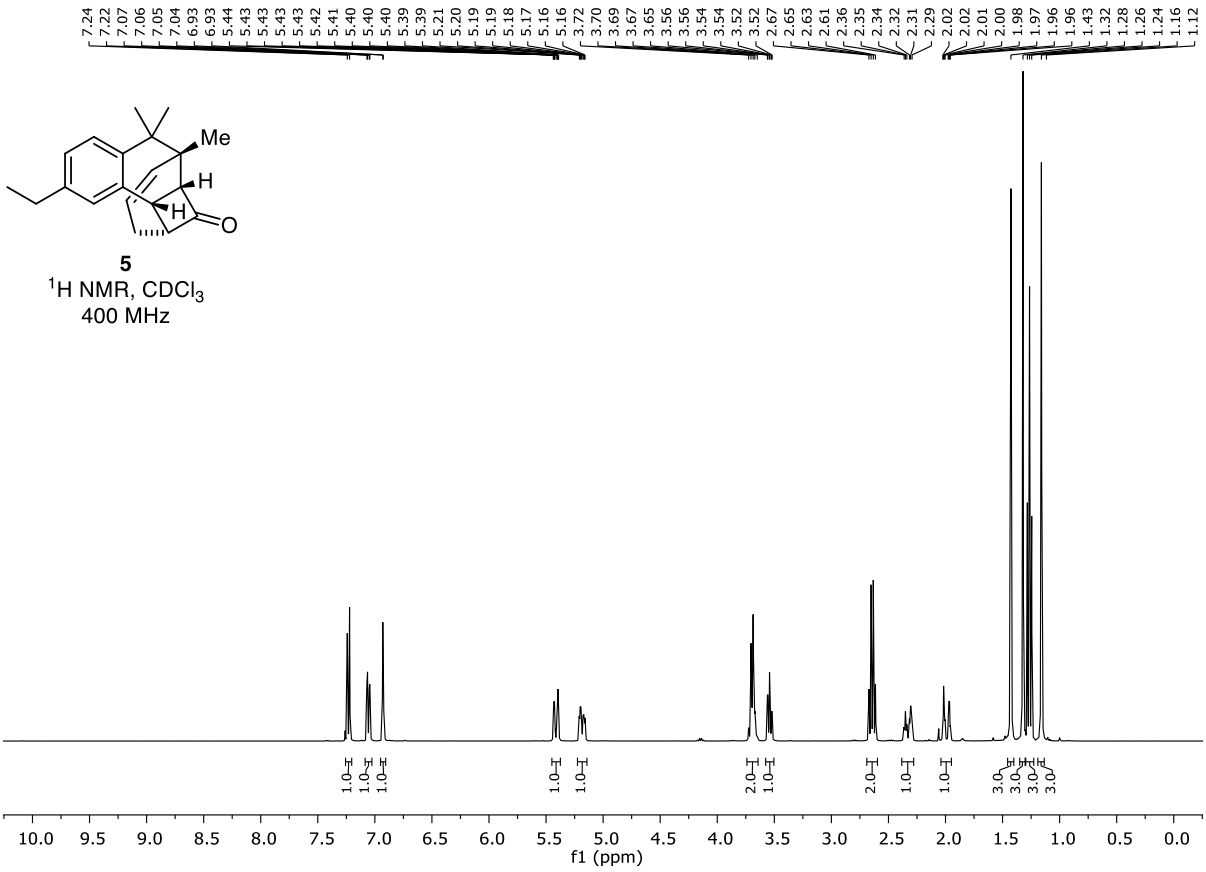
S4
^{13}C NMR, $CDCl_3$
101 MHz

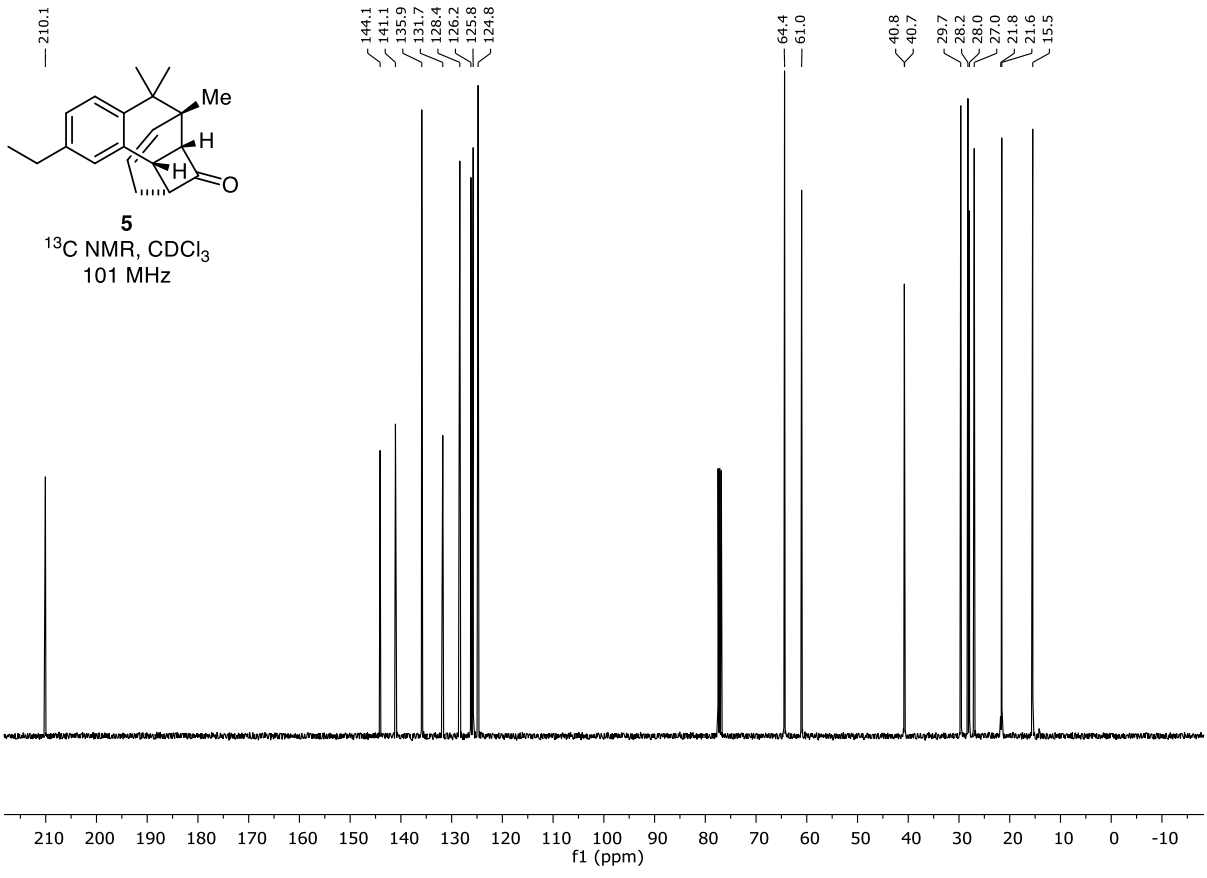

Me
O
O
S5
1H NMR, CDCl3
400 MHz
f1 (ppm)

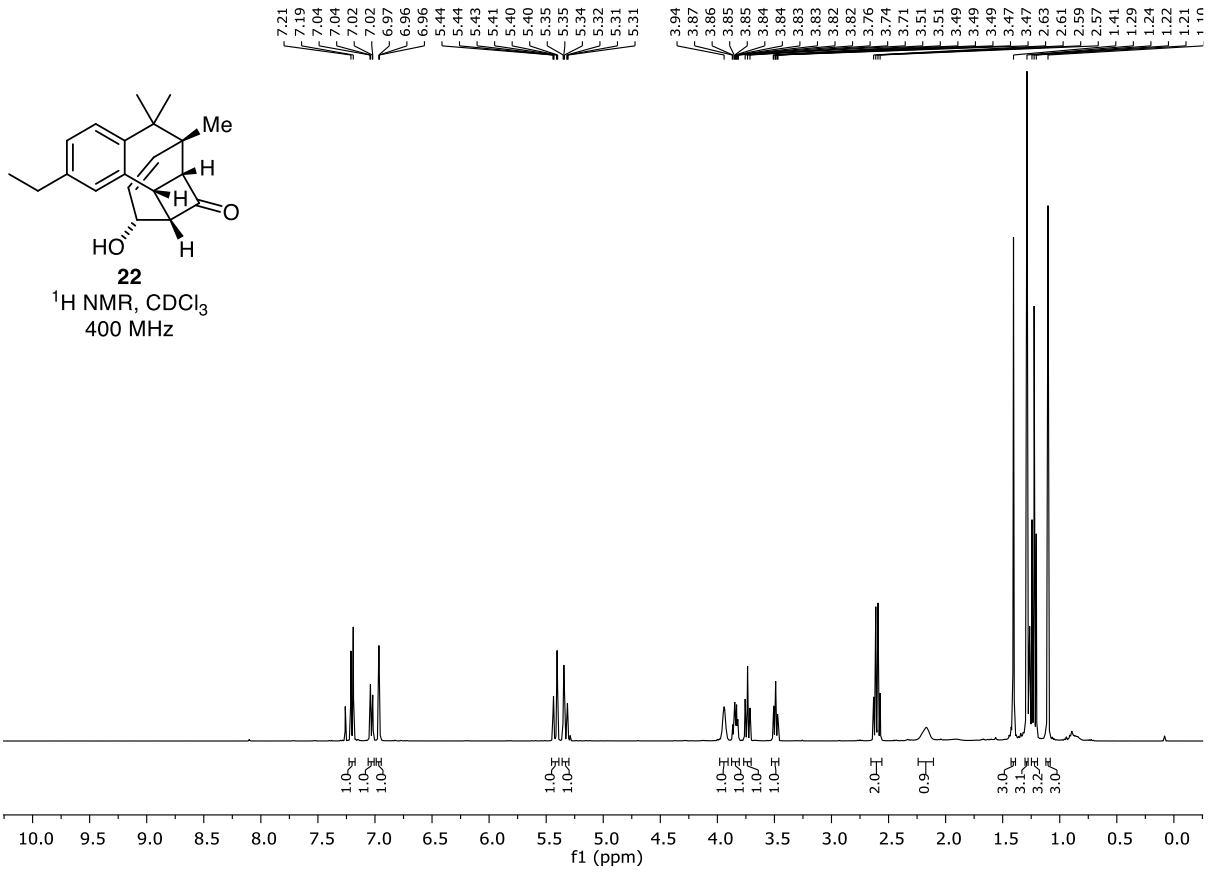

Me
O
O
S5
13C NMR, CDCl3
101 MHz
f1 (ppm)

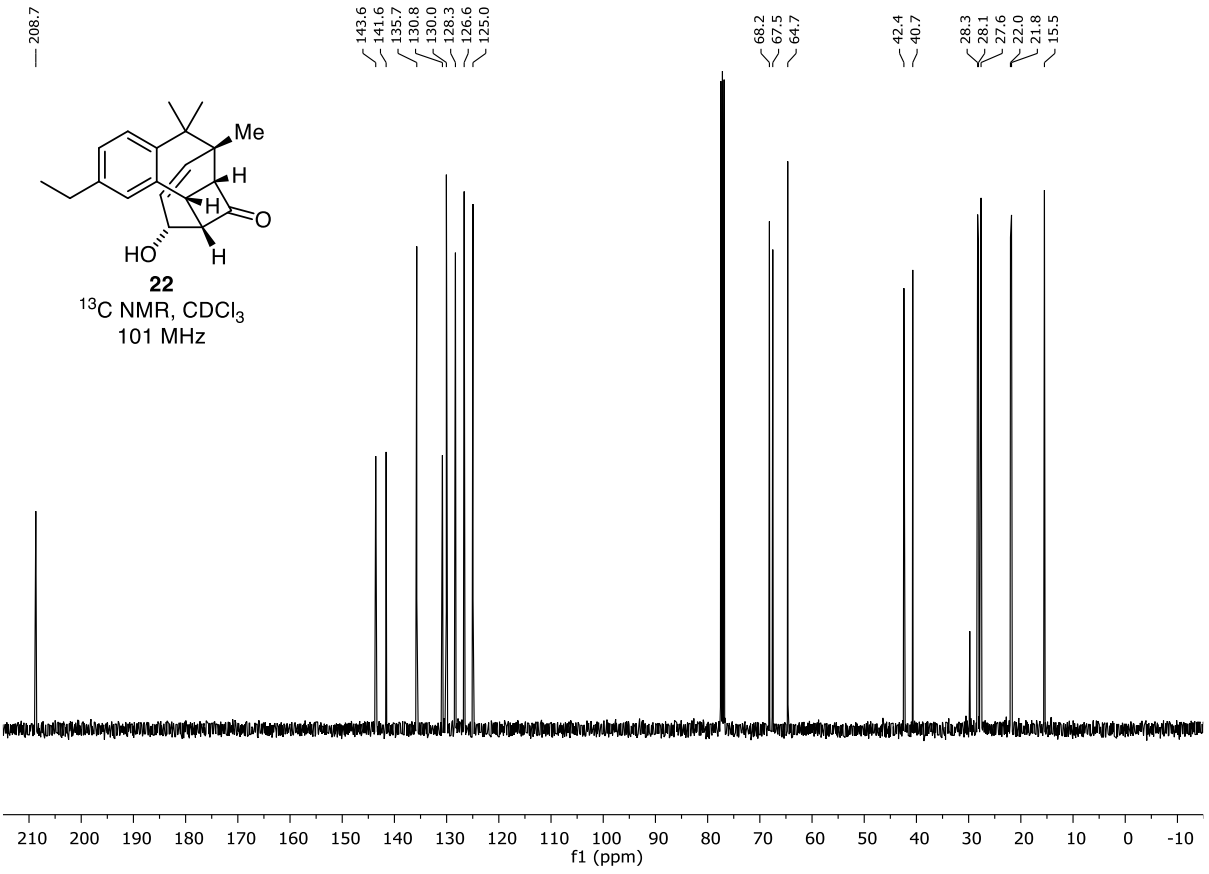

Me
O
N
6
1H NMR, CDCl3
400 MHz
f1 (ppm)

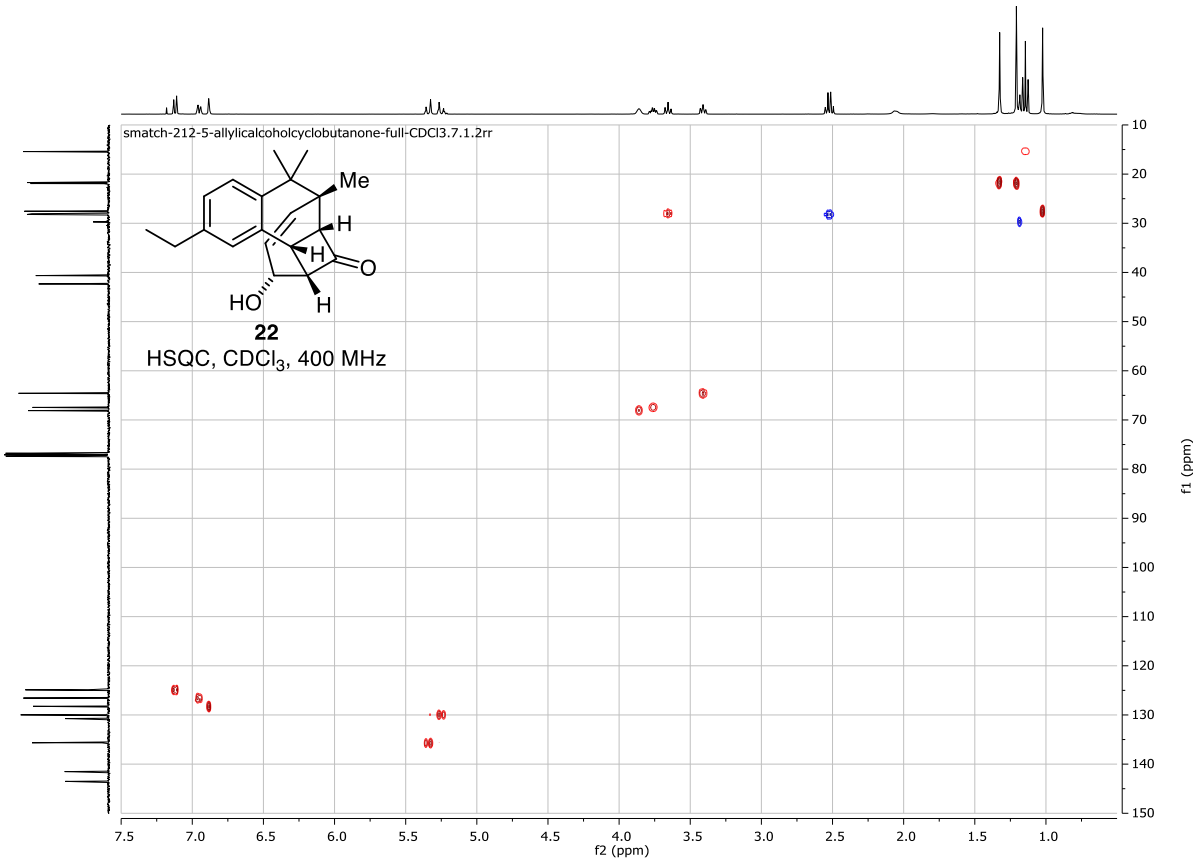

Me
O
N
6
13C NMR, CDCl3
101 MHz
f1 (ppm)

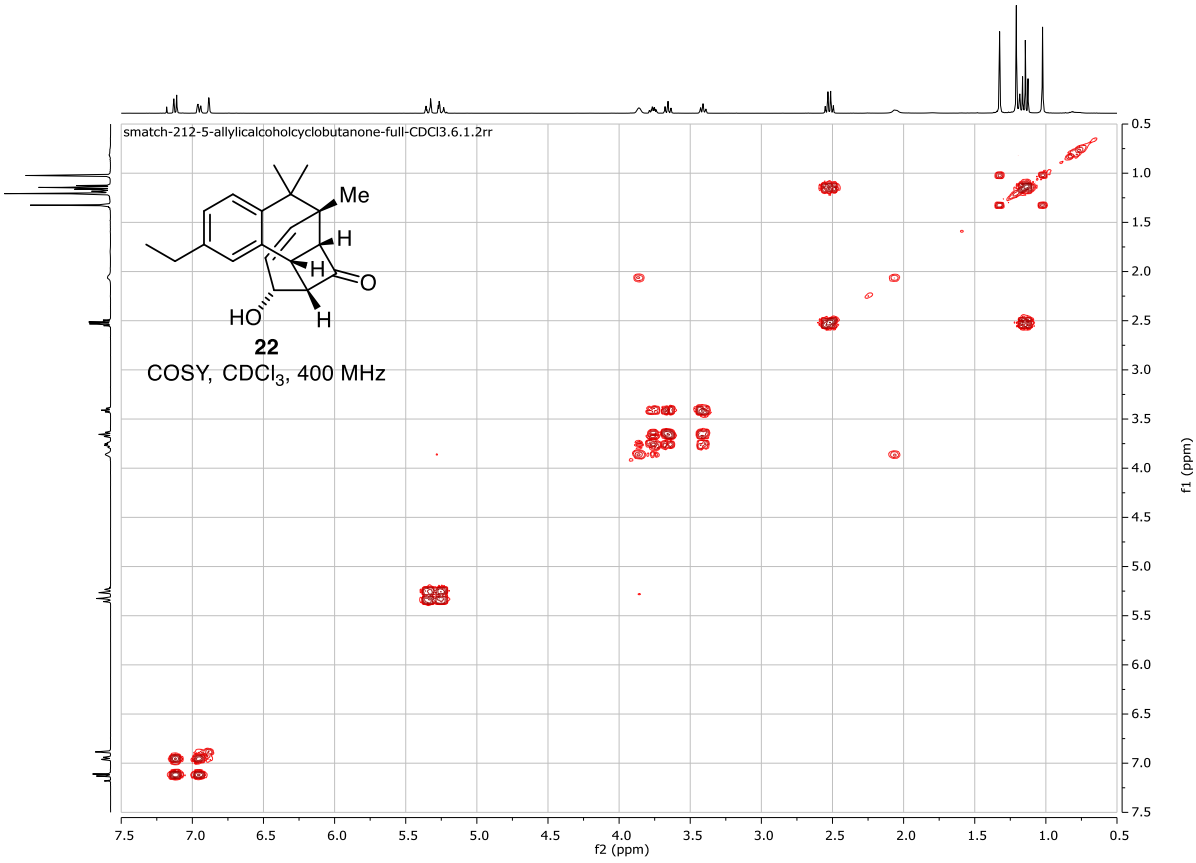

Me
H
H
O
5
1H NMR, CDCl3
400 MHz
f1 (ppm)

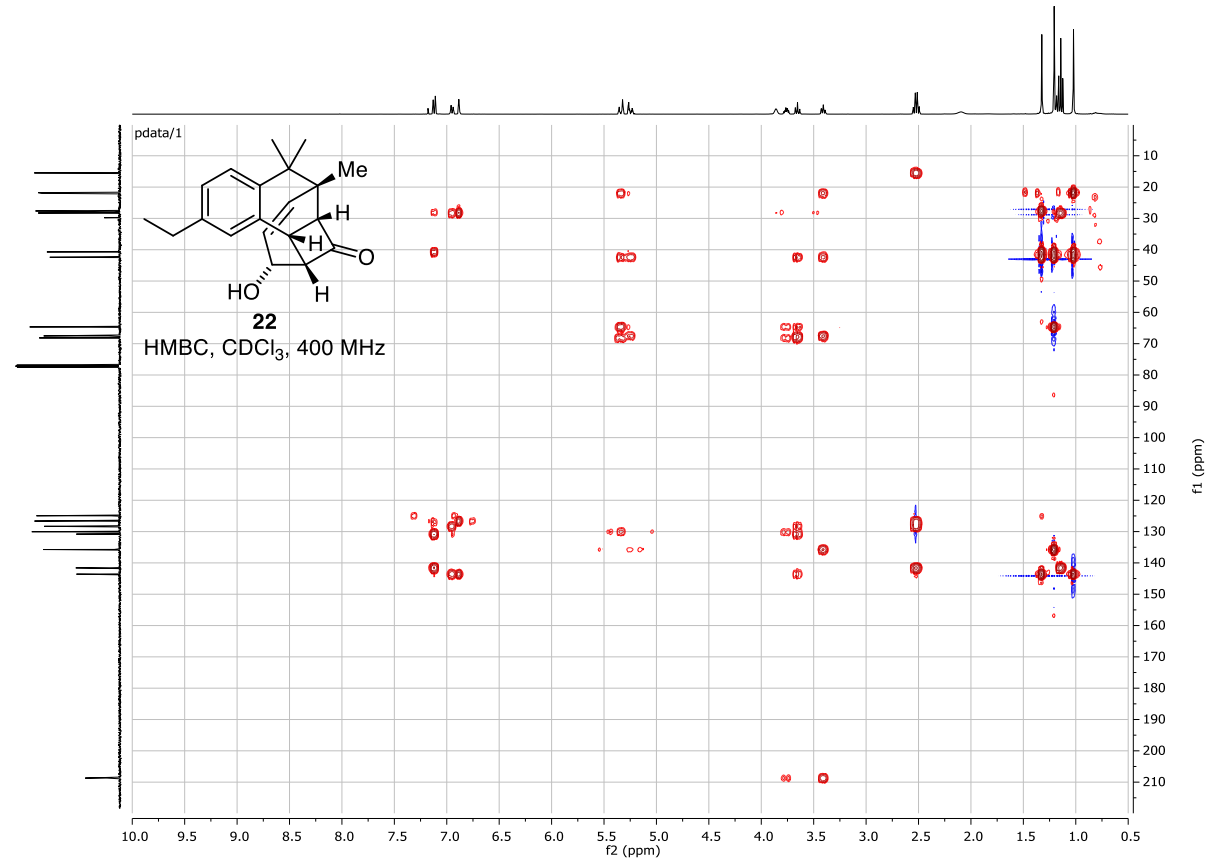

Me
H
H
O
5
13C NMR, CDCl3
101 MHz
f1 (ppm)

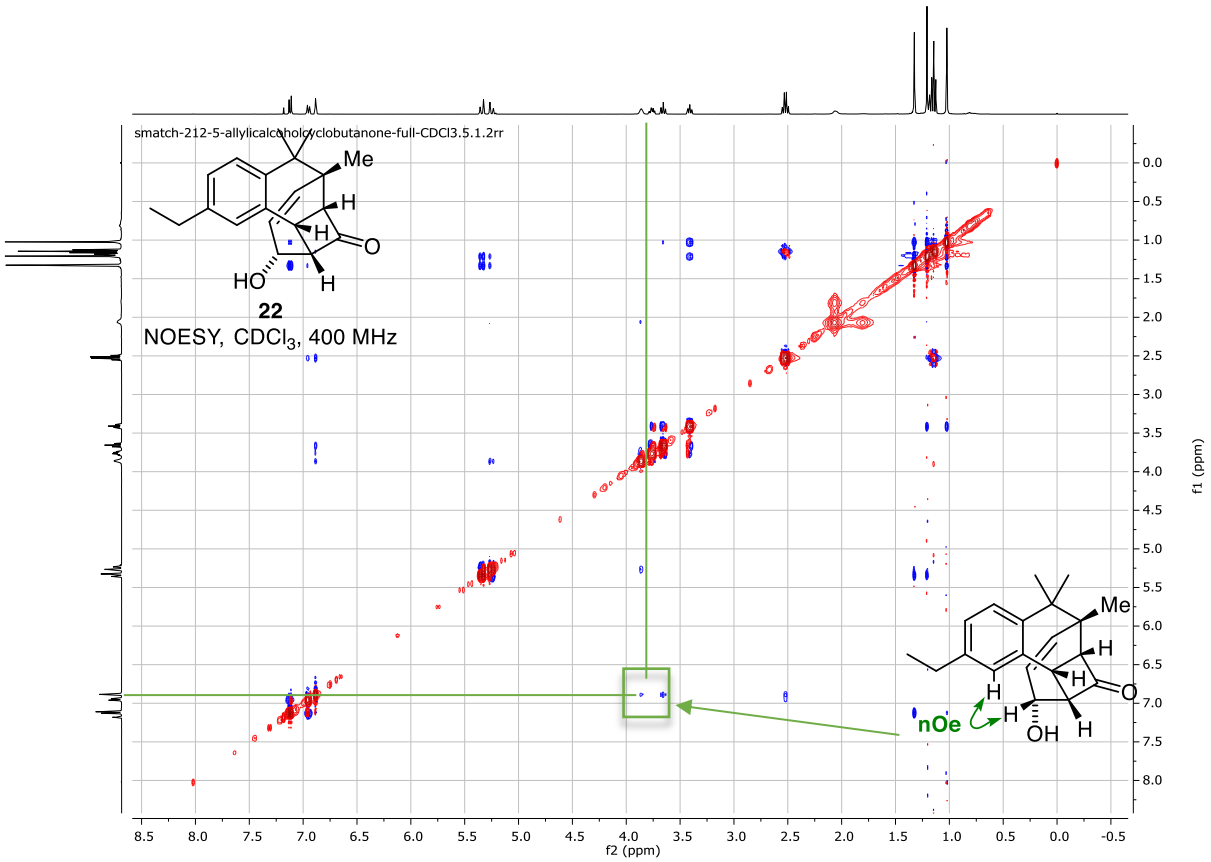

Me
H
H
O
HO
H
22
^{1}H NMR, $CDCl_3$
400 MHz
f1 (ppm)

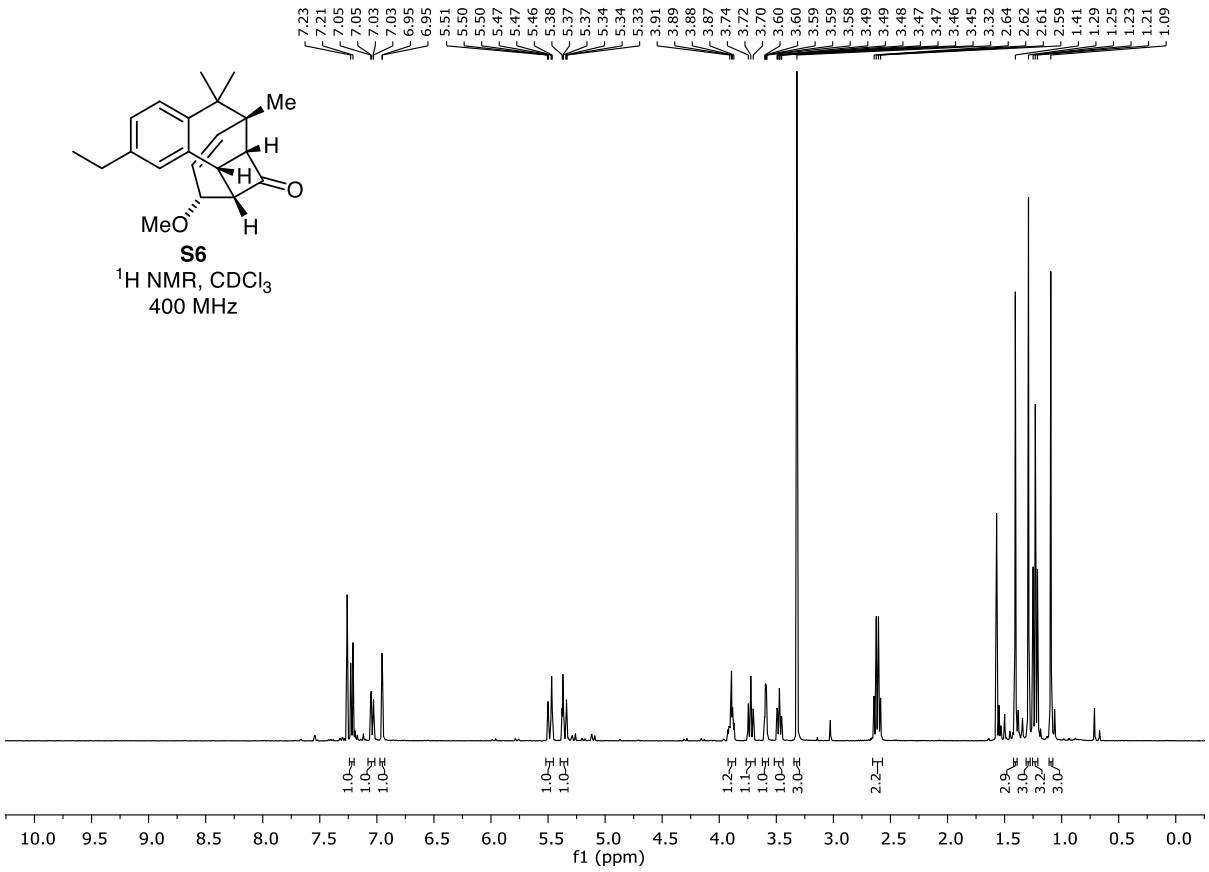

Me
H
H
O
HO
H
22
^{13}C NMR, $CDCl_3$
101 MHz
f1 (ppm)

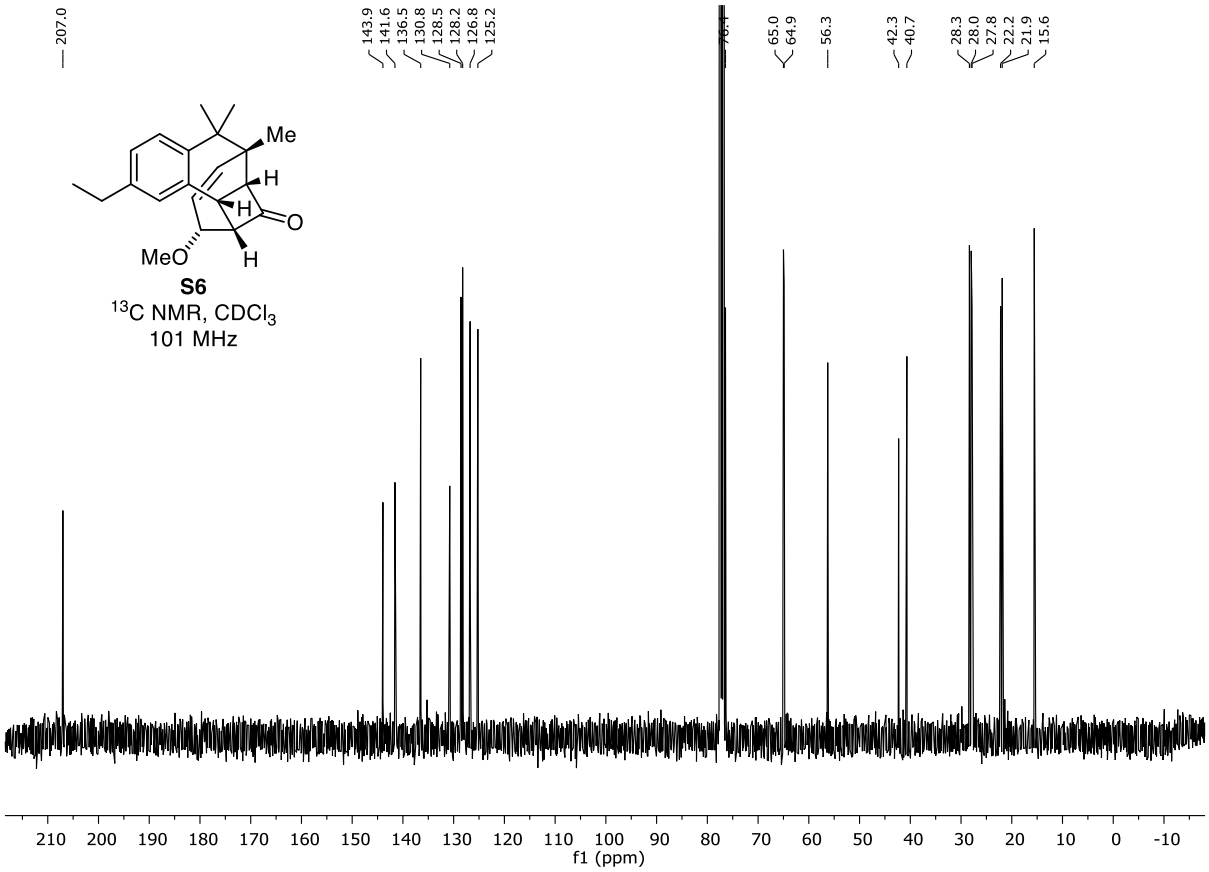

smatch-212-5-allylicalcoholcyclobutanone-full-CDCl3.7.1.2rr
Me
H
H
O
HO
H
22
HSQC, CDCl3, 400 MHz
f2 (ppm)
f1 (ppm)

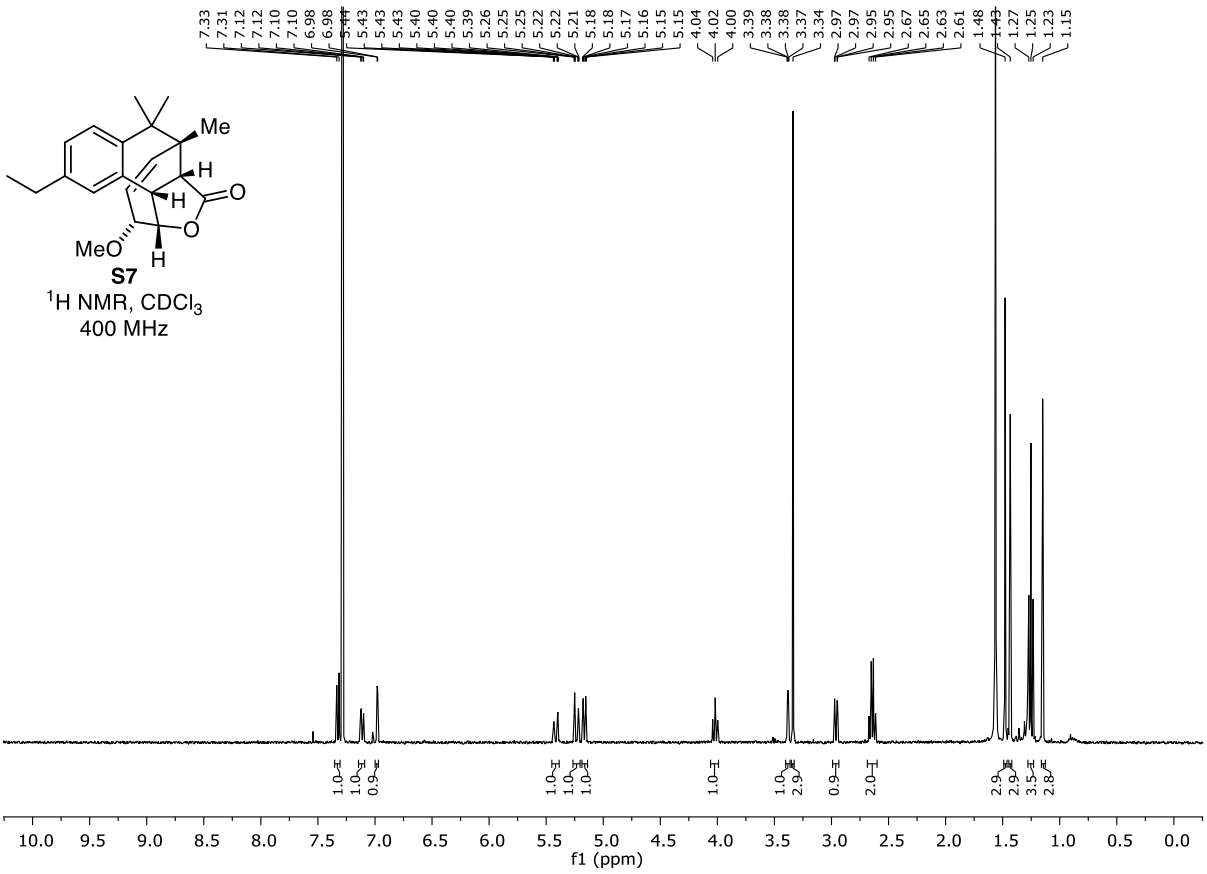

smatch-212-5-allylicalcoholcyclobutanone-full-CDCl3.6.1.2rr
Me
H
H
O
HO
H
22
COSY, CDCl3, 400 MHz
f2 (ppm)
f1 (ppm)

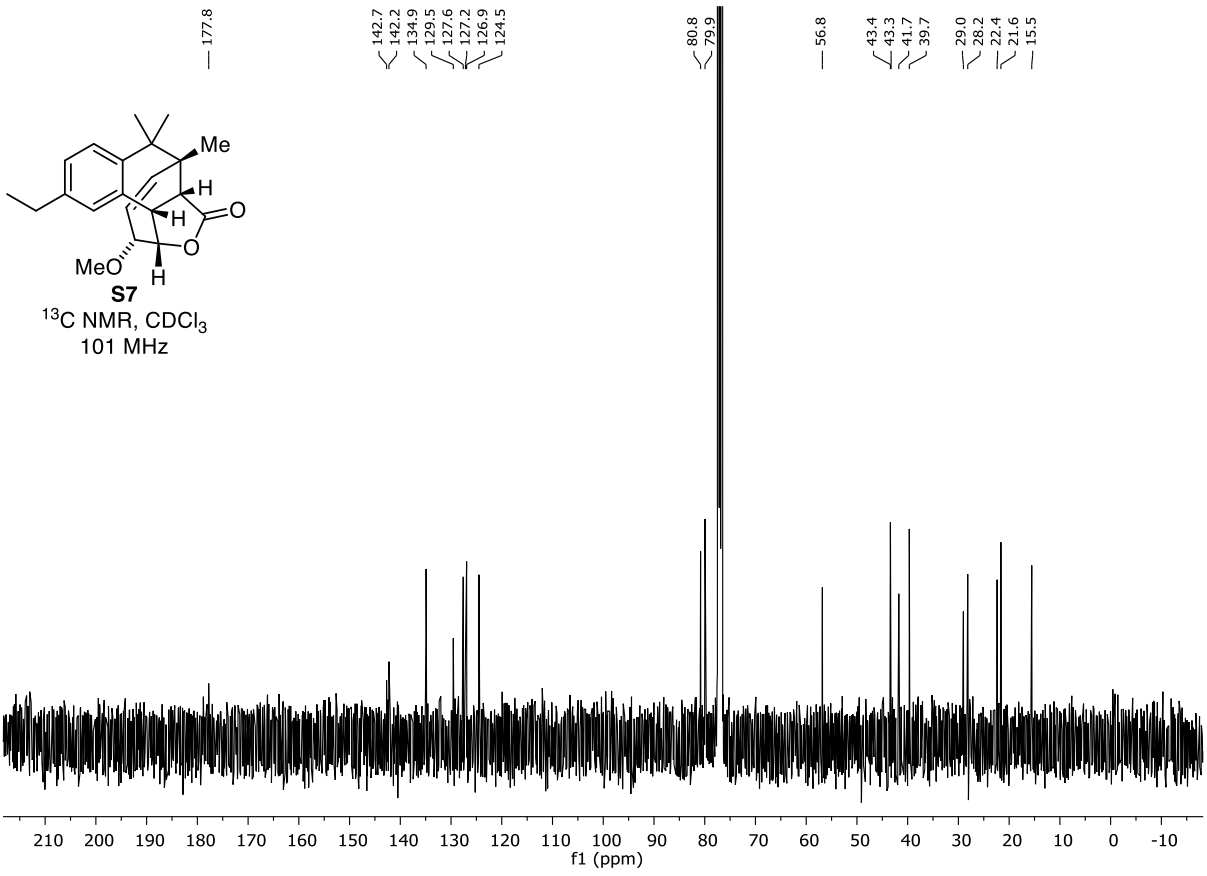

pdata/1
Me
H
H
O
HO
H
22
HMBC, CDCl3, 400 MHz
f2 (ppm)
f1 (ppm)

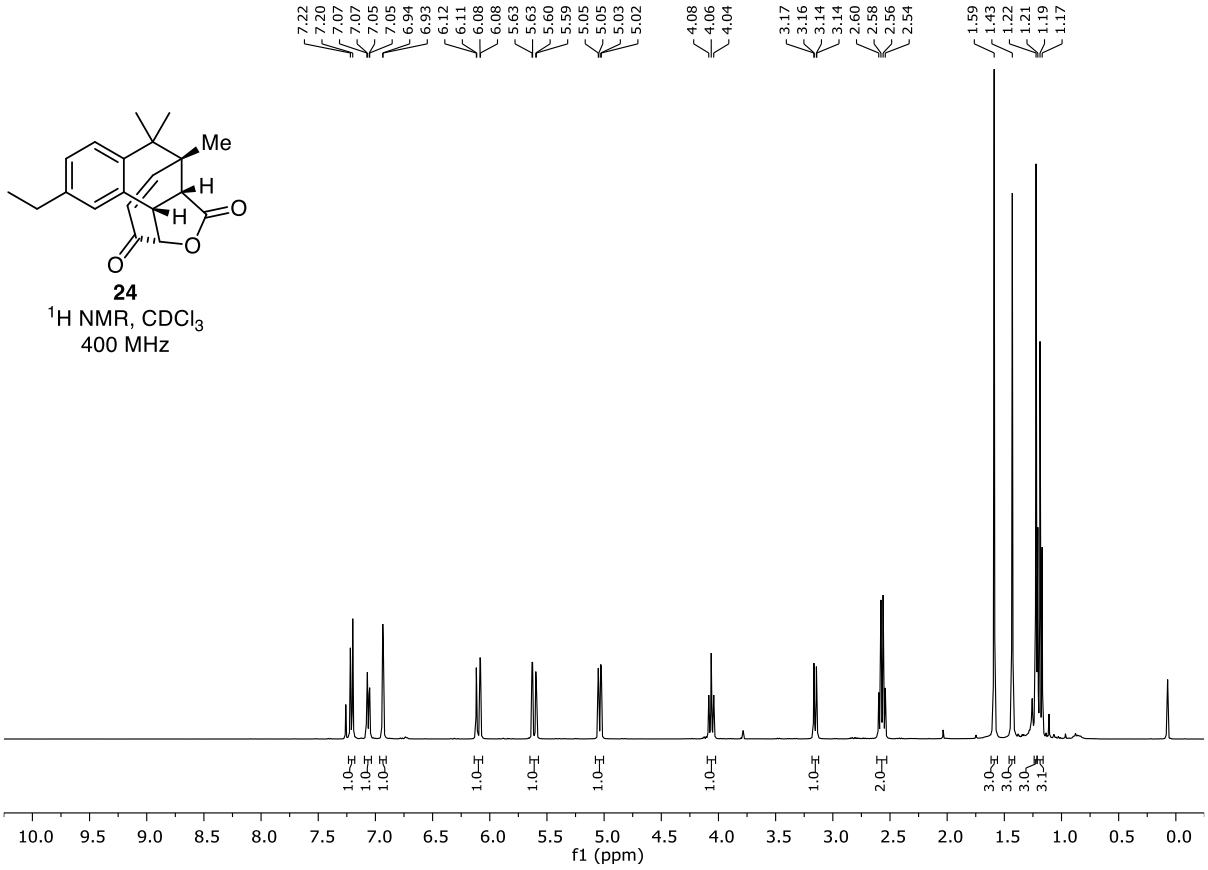

smatch-212-5-allylicalcoholcyclobutanone-full-CDCl3.5.1.2rr
Me
H
H
O
HO
H
22
NOESY, CDCl3, 400 MHz
nOe
f2 (ppm)
f1 (ppm)

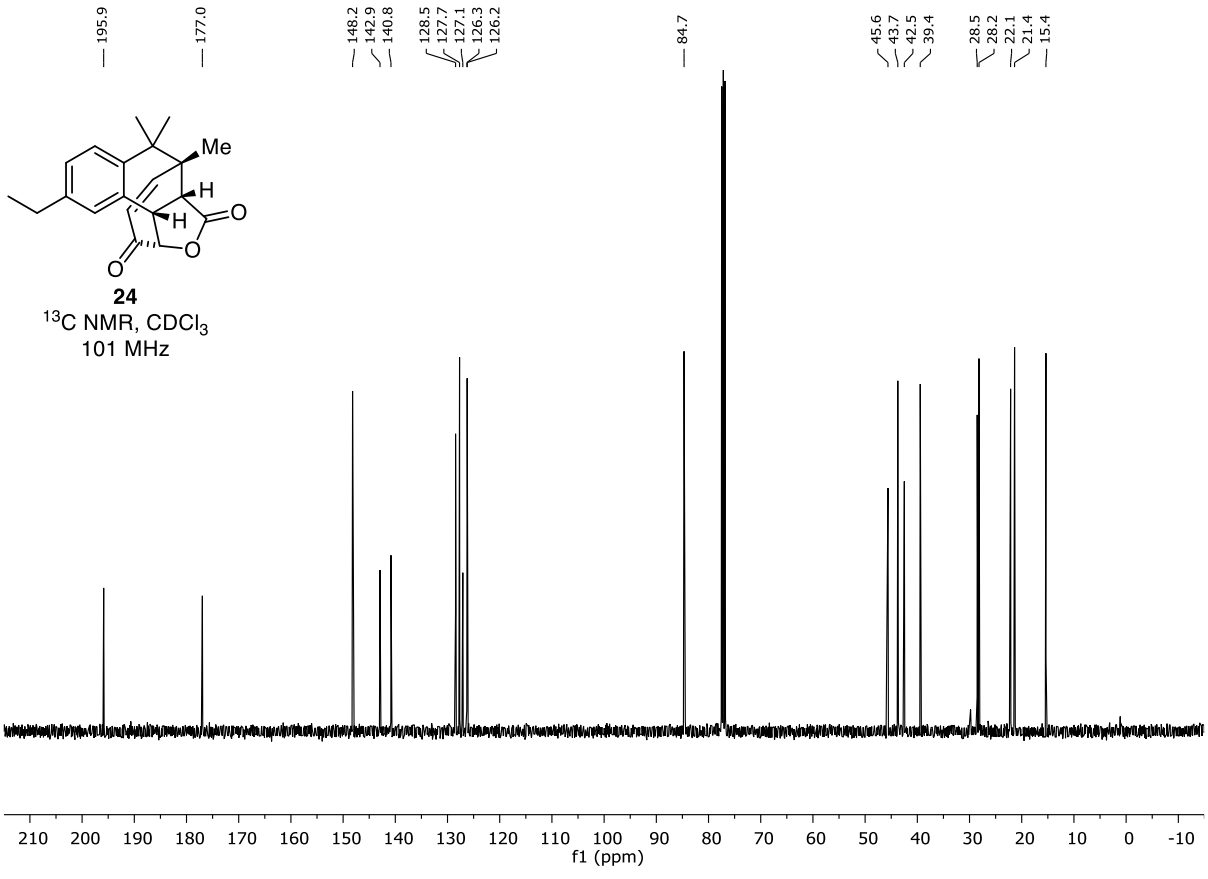

Me
H
H
O
MeO
H
S6
1H NMR, CDCl3
400 MHz
f1 (ppm)

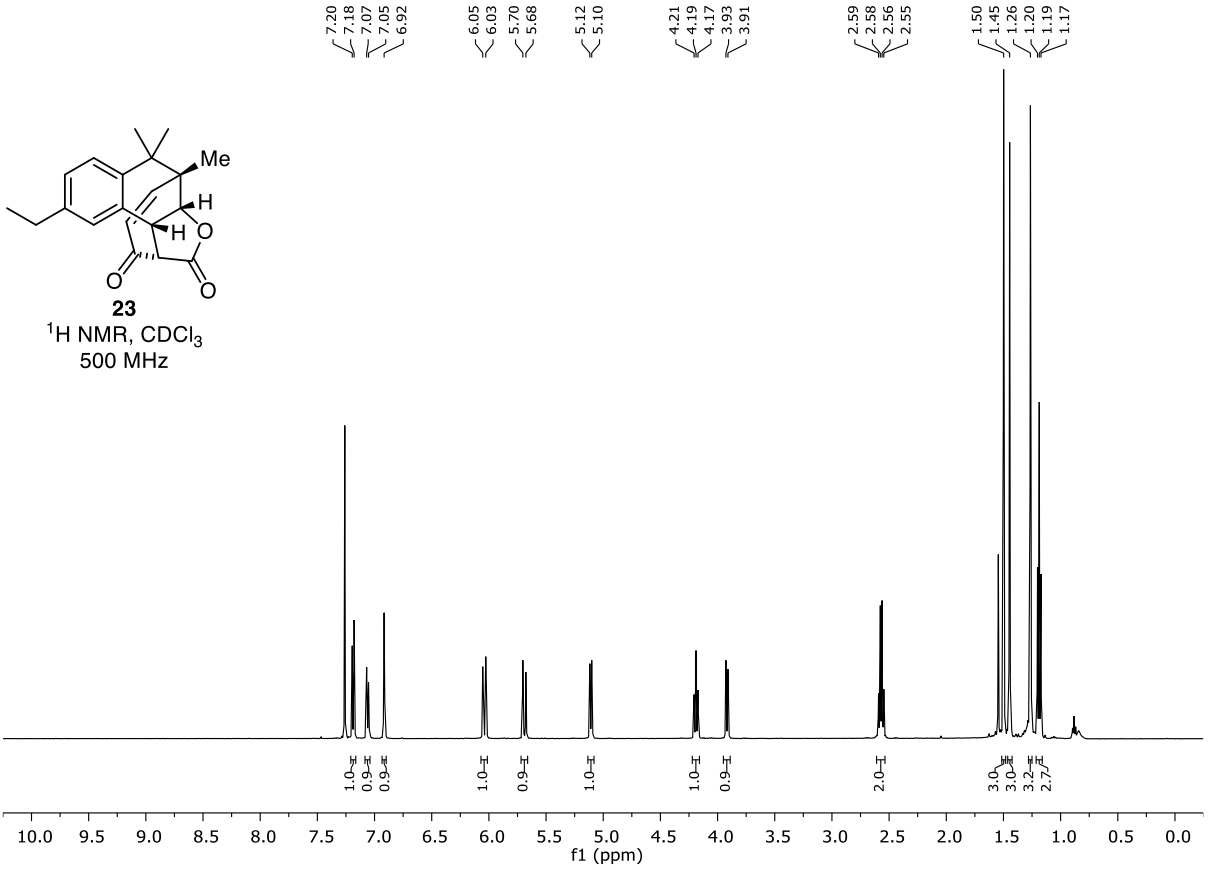

Me
H
H
O
MeO
H
S6
13C NMR, CDCl3
101 MHz
f1 (ppm)

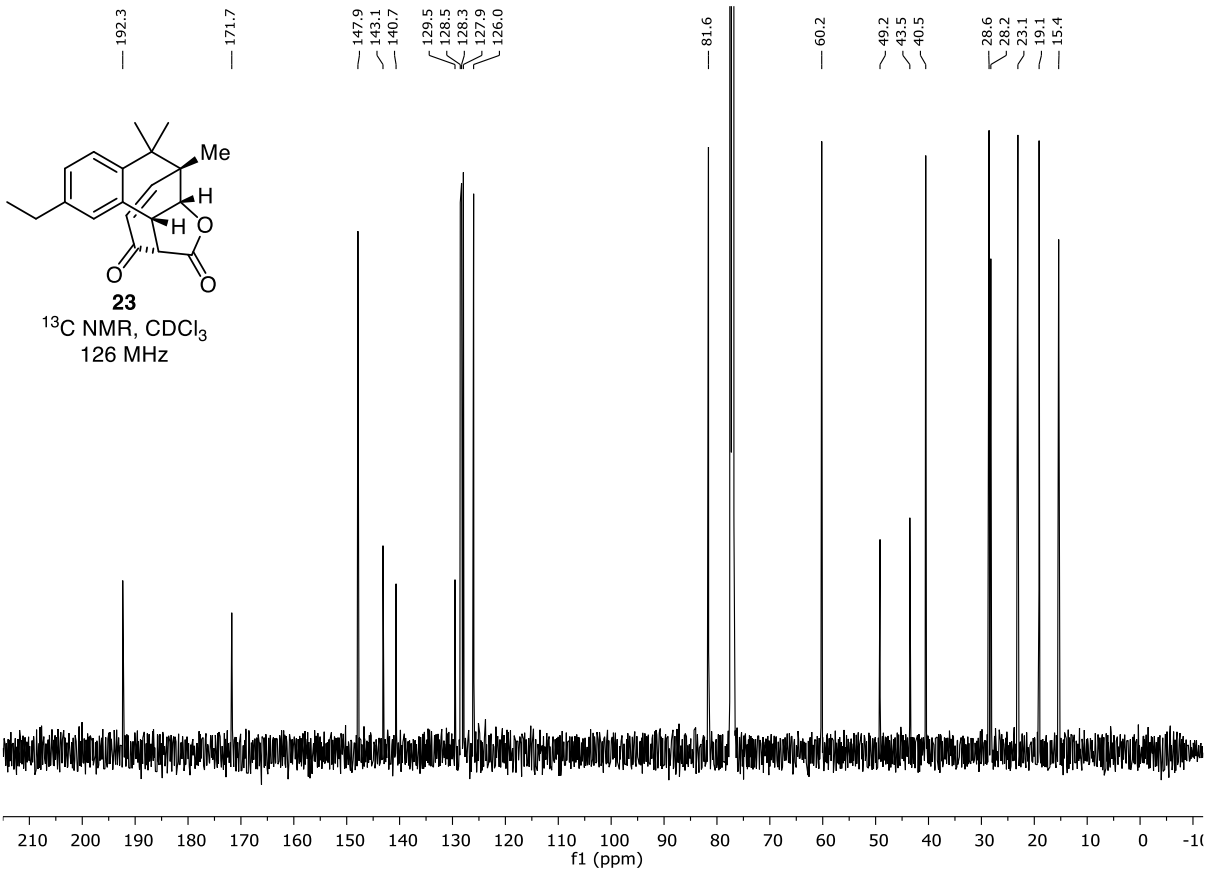

Me
H
H
O
O
MeO
H
S7
^{1}H NMR, CDCl$_3$
400 MHz
f1 (ppm)

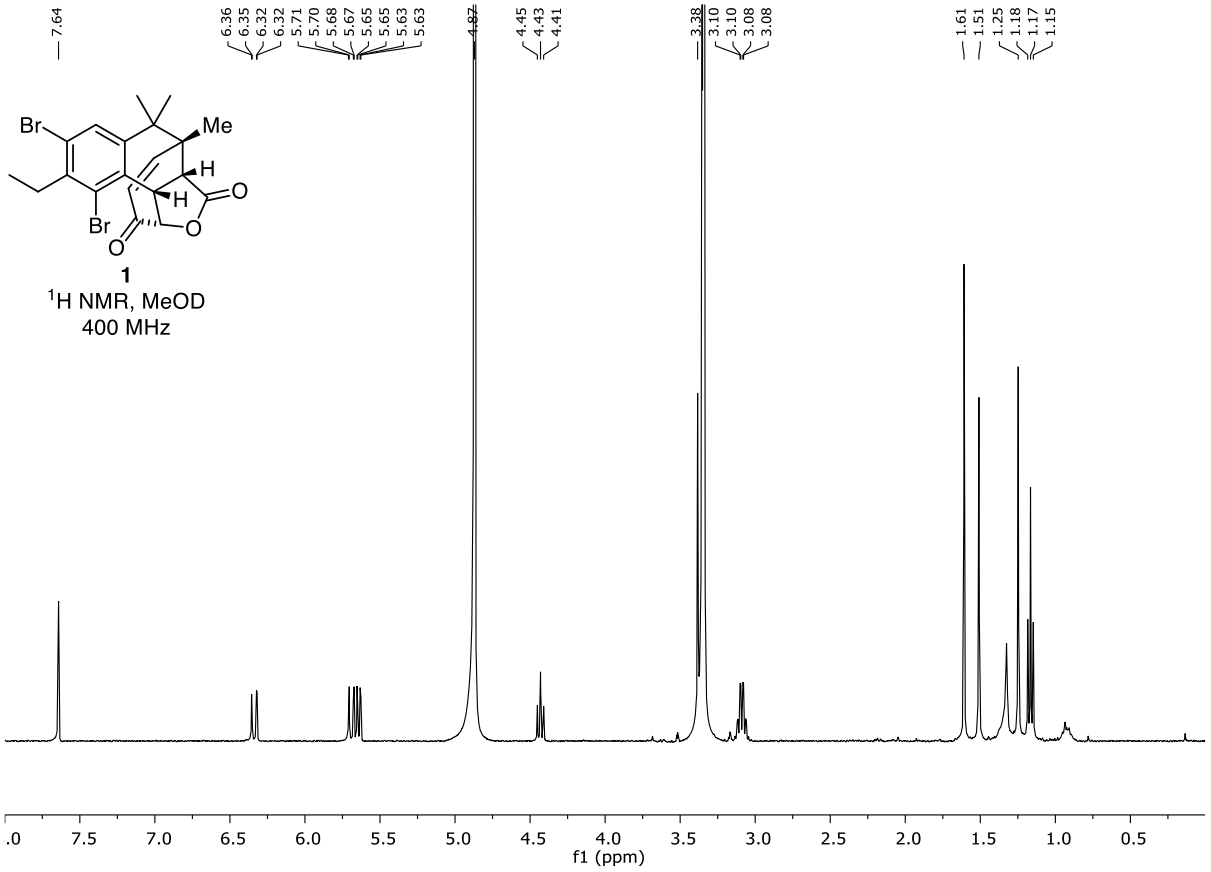

Me
H
H
O
O
MeO
H
S7
^{13}C NMR, CDCl$_3$
101 MHz
f1 (ppm)


Me
H
H
O
O
O
24
1H NMR, CDCl3
400 MHz
7.22
7.20
7.07
7.07
7.05
7.05
6.94
6.93
6.12
6.11
6.08
6.08
5.63
5.63
5.60
5.59
5.05
5.05
5.03
5.02
4.08
4.06
4.04
3.17
3.16
3.14
3.14
2.60
2.58
2.56
2.54
1.59
1.43
1.22
1.21
1.19
1.17
1.0
1.0
1.0
1.0
1.0
1.0
1.0
1.0
2.0
3.0
3.0
3.1
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


Me
H
H
O
O
O
24
13C NMR, CDCl3
101 MHz
195.9
177.0
148.2
142.9
140.8
128.5
127.7
127.1
126.3
126.2
84.7
45.6
43.7
42.5
39.4
28.5
28.2
22.1
21.4
15.4
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.20
7.18
7.07
7.05
6.92
6.05
6.03
5.70
5.68
5.12
5.10
4.21
4.19
4.17
3.93
3.91
2.59
2.58
2.56
2.55
1.50
1.45
1.26
1.20
1.19
1.17
Me
H
H
O
O
O
23
1H NMR, CDCl3
500 MHz
1.0
0.9
0.9
1.0
0.9
1.0
1.0
0.9
2.0
3.0
3.0
3.2
2.7
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


192.3
171.7
147.9
143.1
140.7
129.5
128.5
128.3
127.9
126.0
81.6
60.2
49.2
43.5
40.5
28.6
28.2
23.1
19.1
15.4
Me
H
H
O
O
O
23
13C NMR, CDCl3
126 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



^{1}H NMR spectrum of salimabromide in [D_4]MeOH (500 MHz)

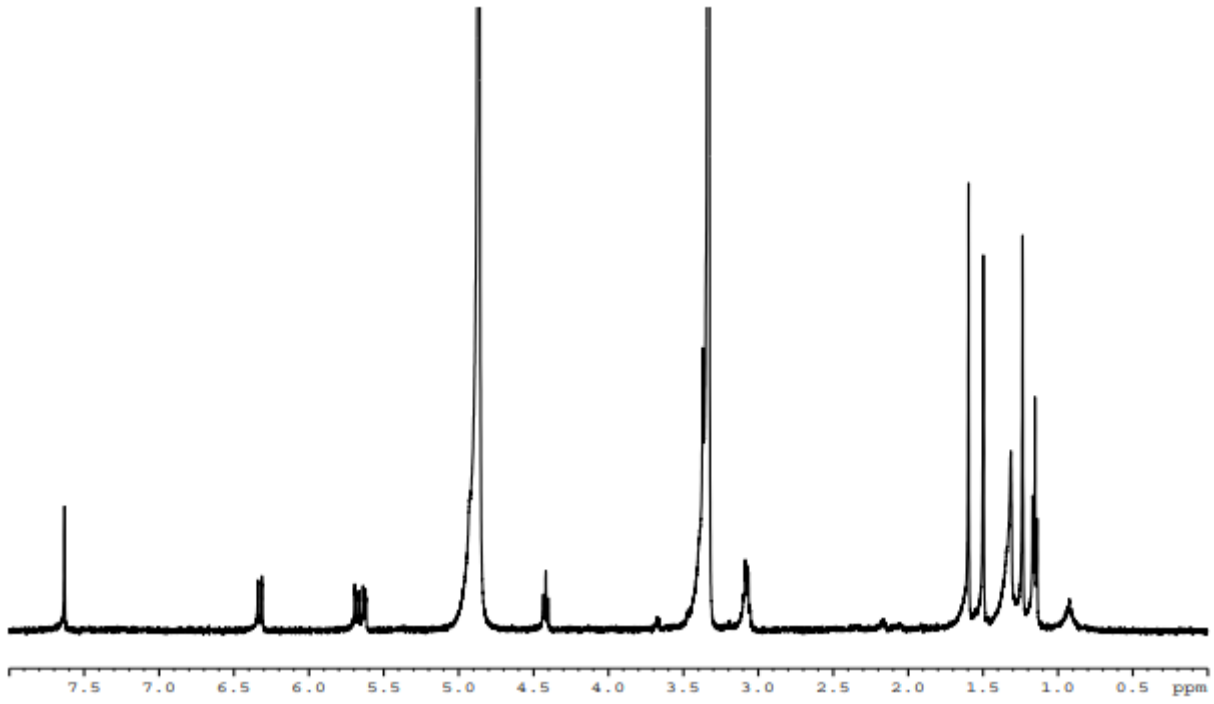
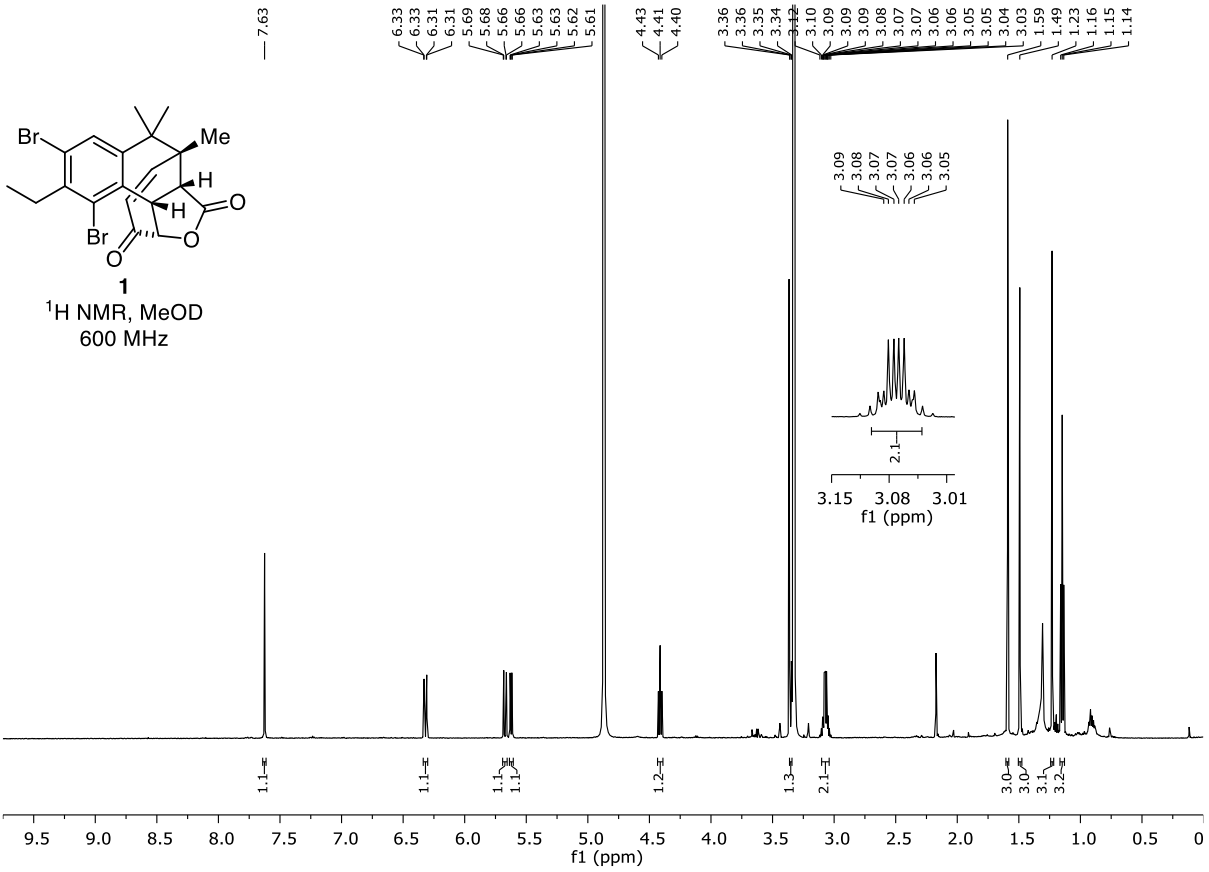
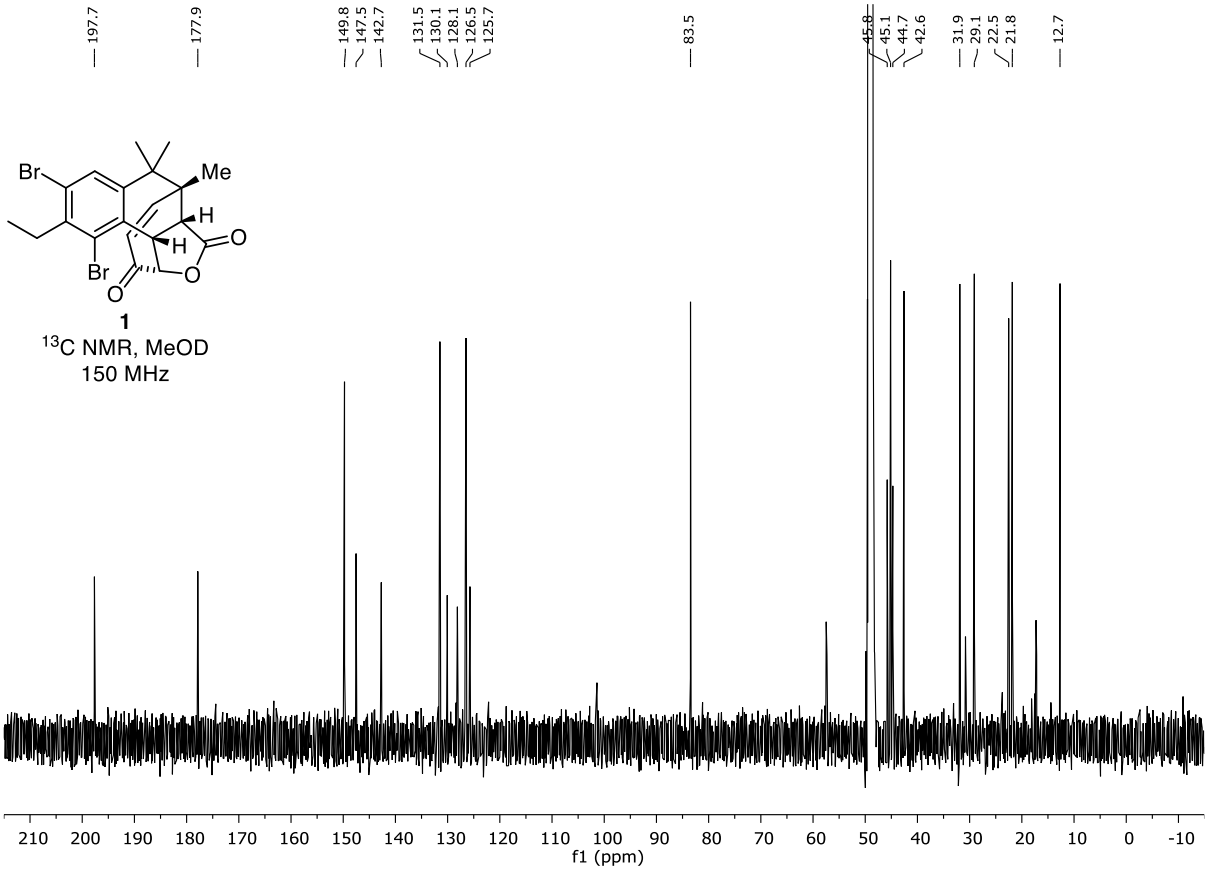
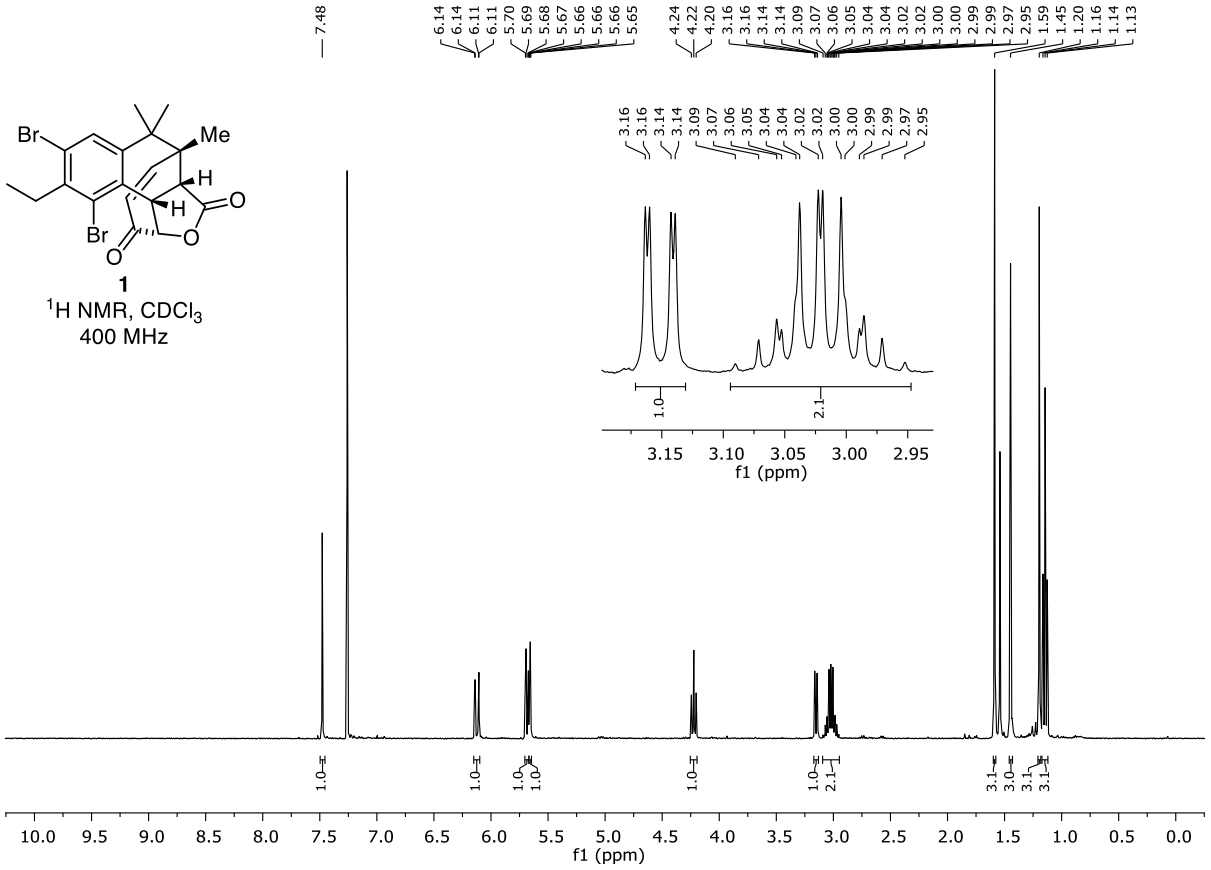


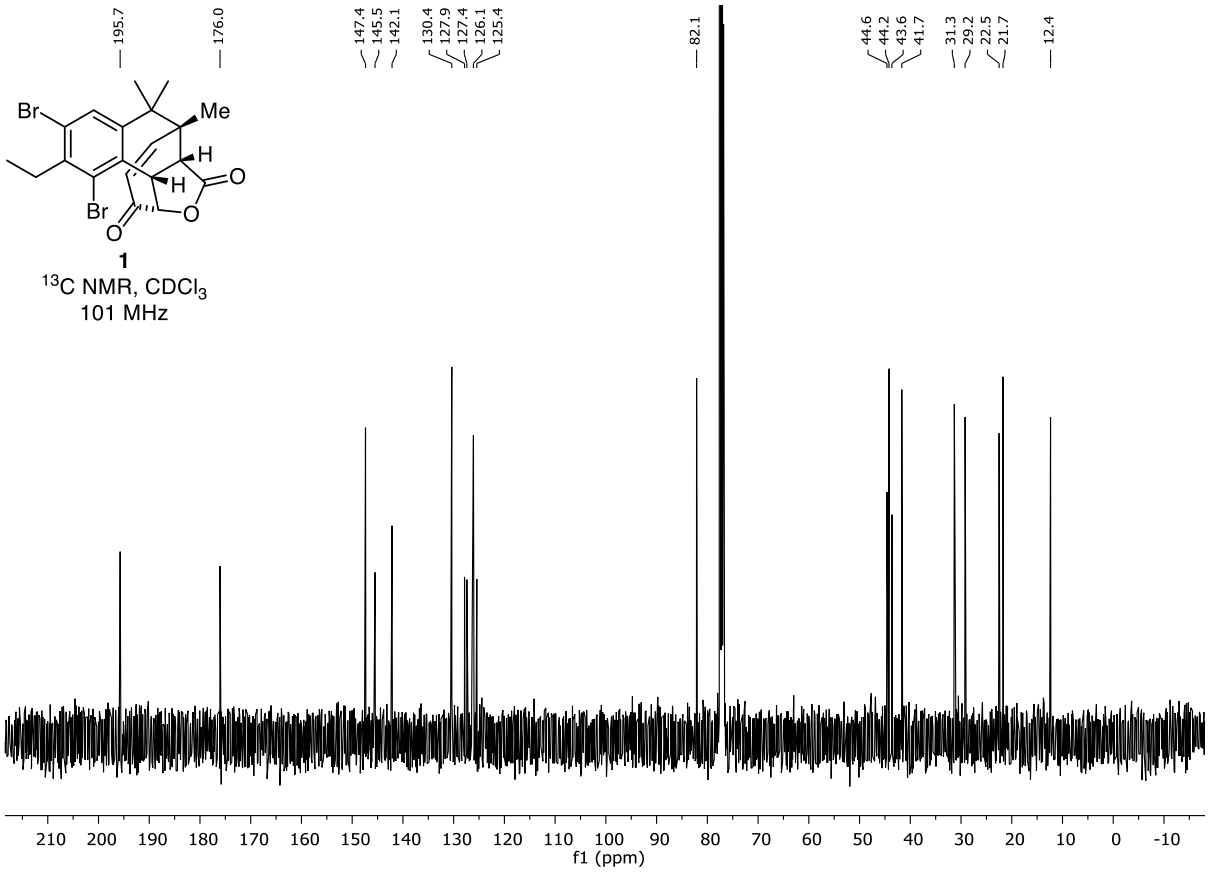
Figure 2-2: Original ^{1}H-NMR spectra of salimabromide (**1**) published by König et. al.[120]

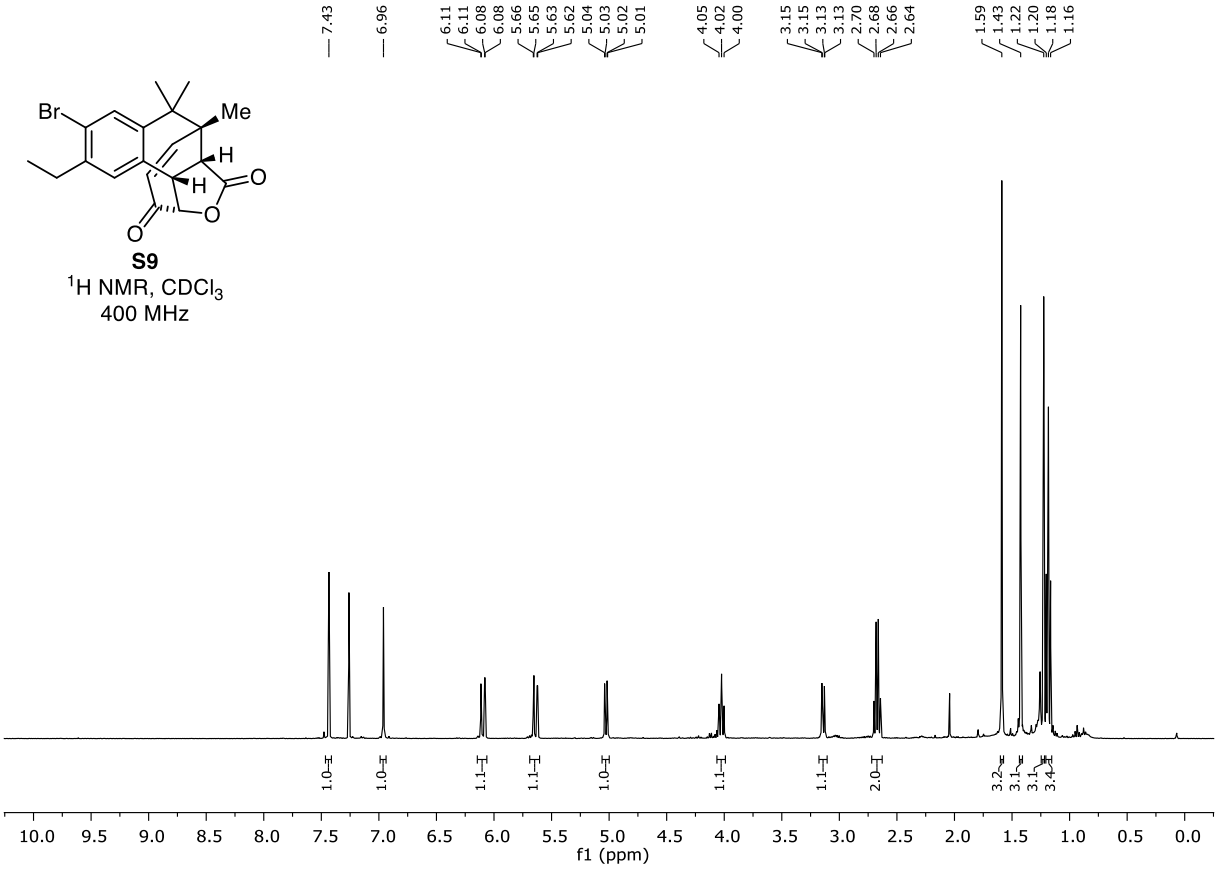
[120] S. Felder, S. Dreisigacker, S. Kehraus, E. Neu, G. Bierbaum, P. R. Wright, D. Menche, T. F. Schäberle, G. M. König, *Chem. Eur. J.*, **2013**, *19*, 9319–9324.


Br
Me
H
H
O
Br
O
O
1
1H NMR, MeOD
600 MHz
7.63
6.33
6.31
5.69
5.68
5.66
5.63
5.62
5.61
4.43
4.41
4.40
3.36
3.35
3.34
3.10
3.09
3.08
3.07
3.06
3.05
3.04
3.03
1.59
1.49
1.23
1.16
1.15
1.14
2.1
3.15 3.08 3.01
f1 (ppm)
1.1
1.1
1.1
1.1
1.2
1.3
2.1
3.0
3.0
3.1
3.2
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)

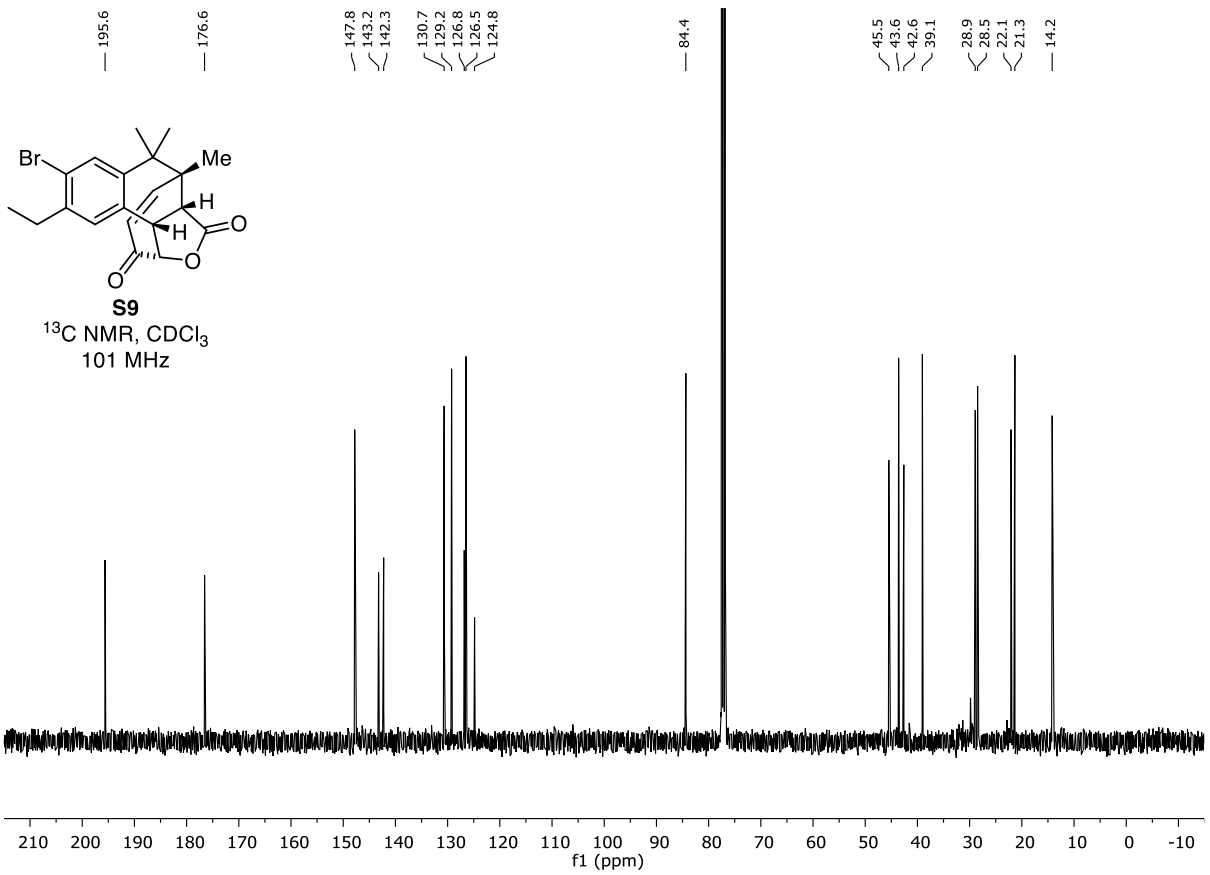

197.7
177.9
149.8
147.5
142.7
131.5
130.1
128.1
126.5
125.7
83.5
45.8
45.1
44.7
42.6
31.9
29.1
22.5
21.8
12.7
Br
Me
H
H
O
Br
O
O
1
13C NMR, MeOD
150 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Br
Me
H
H
O
Br
O
O
1
^{1}H NMR, $CDCl_3$
400 MHz
f1 (ppm)

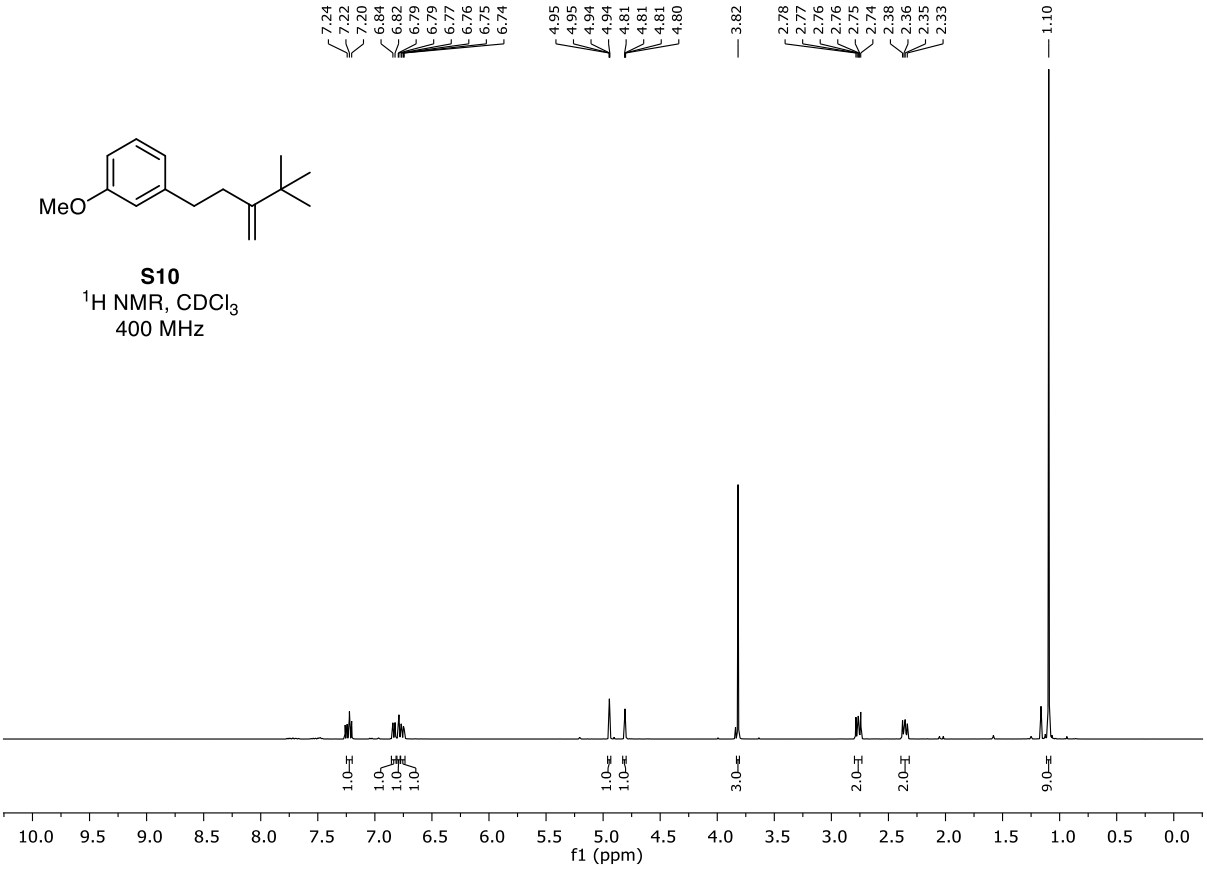

Br
Me
H
H
O
Br
O
O
1
^{13}C NMR, $CDCl_3$
101 MHz
f1 (ppm)



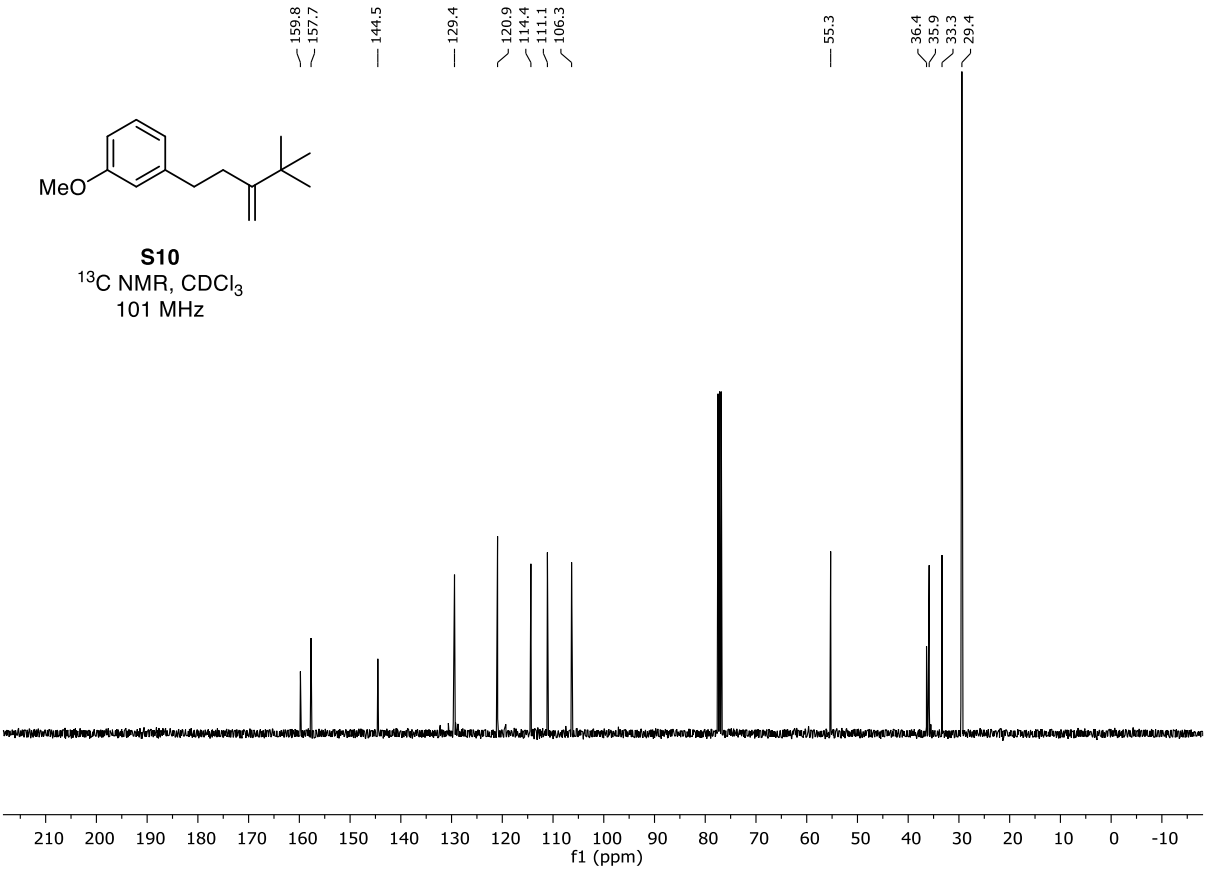
S9
^{1}H NMR, $CDCl_3$
400 MHz



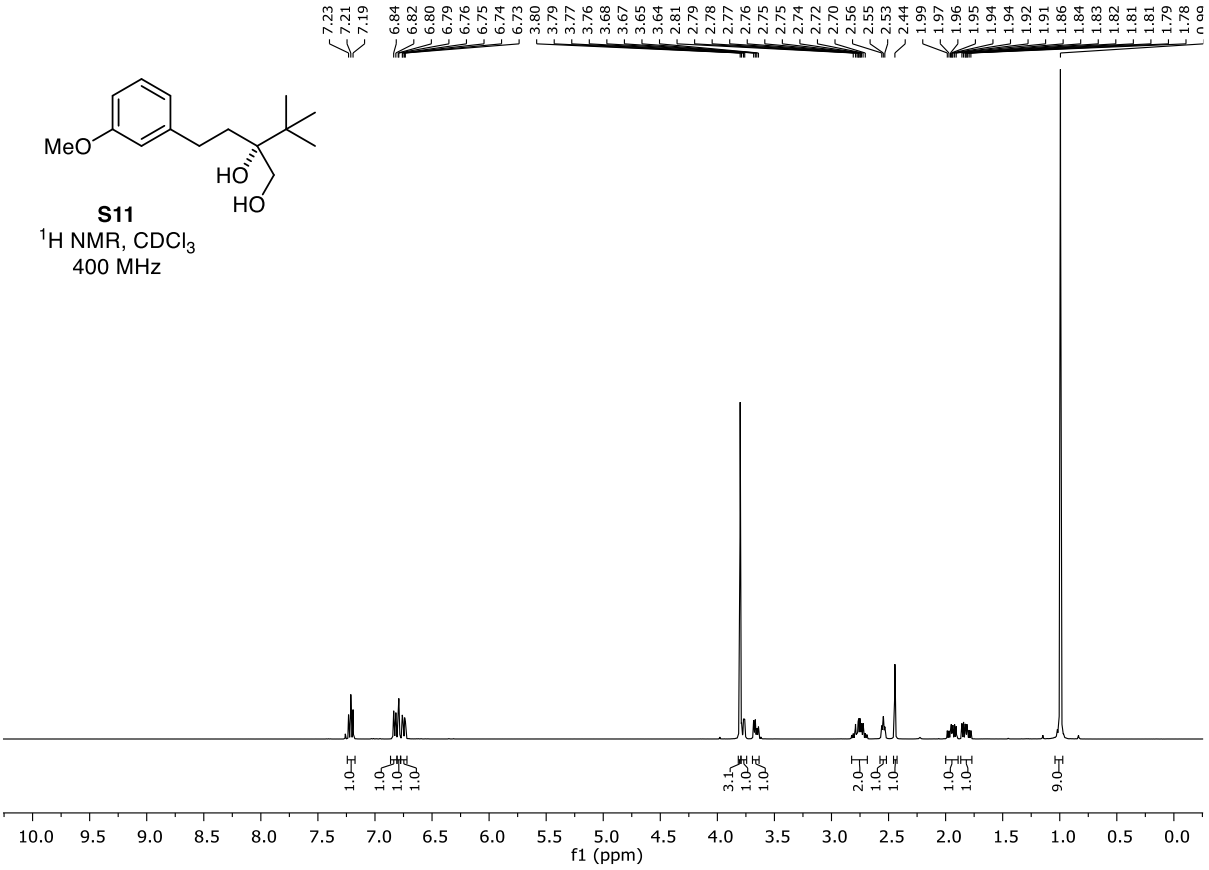
S9
^{13}C NMR, $CDCl_3$
101 MHz

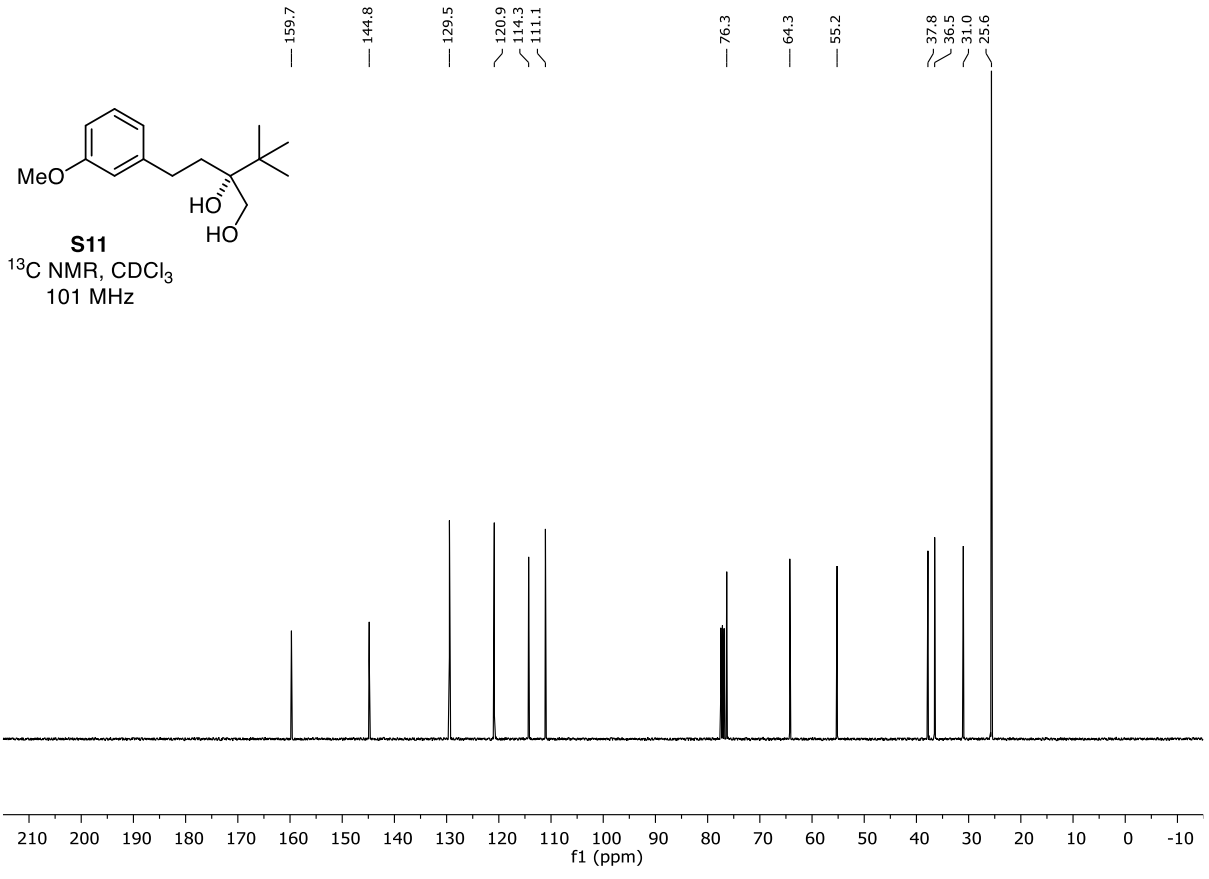


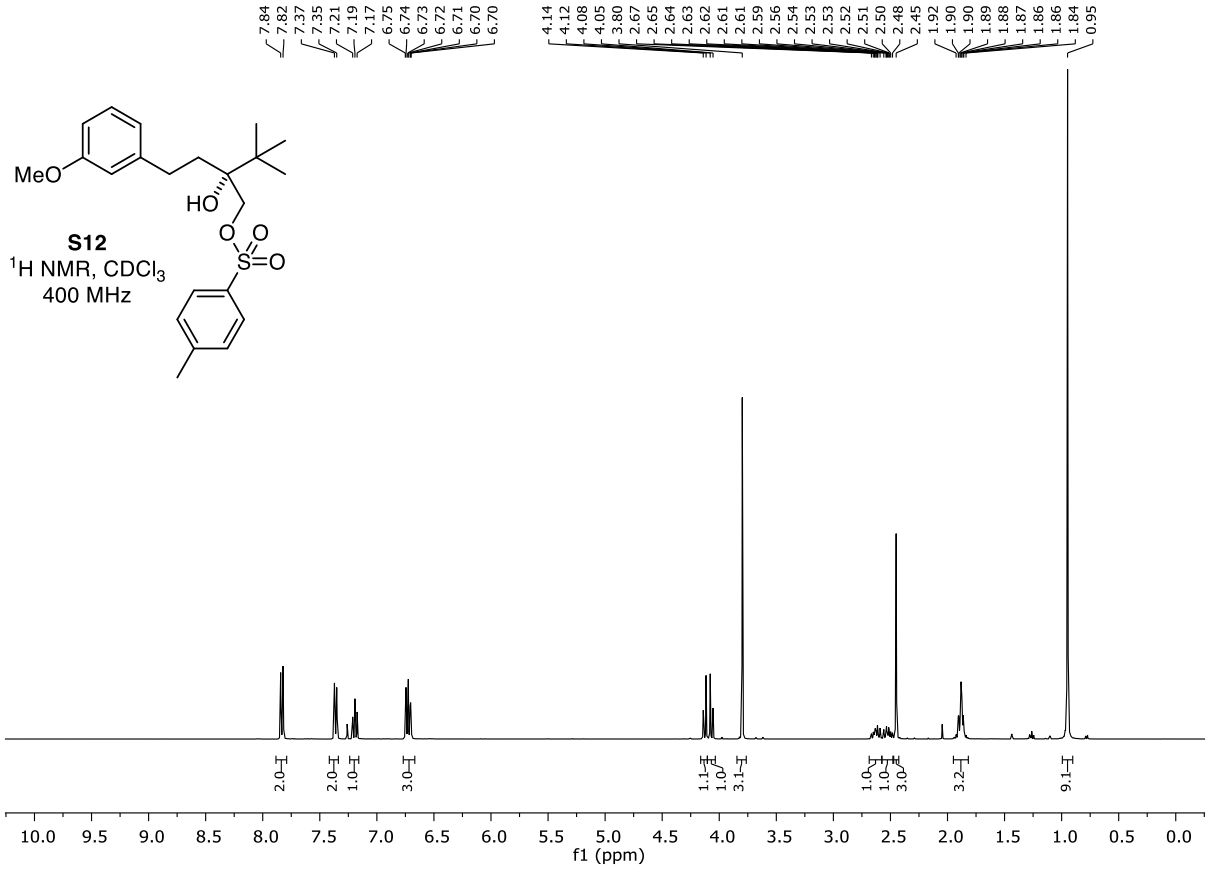
S10
^{1}H NMR, $CDCl_3$
400 MHz

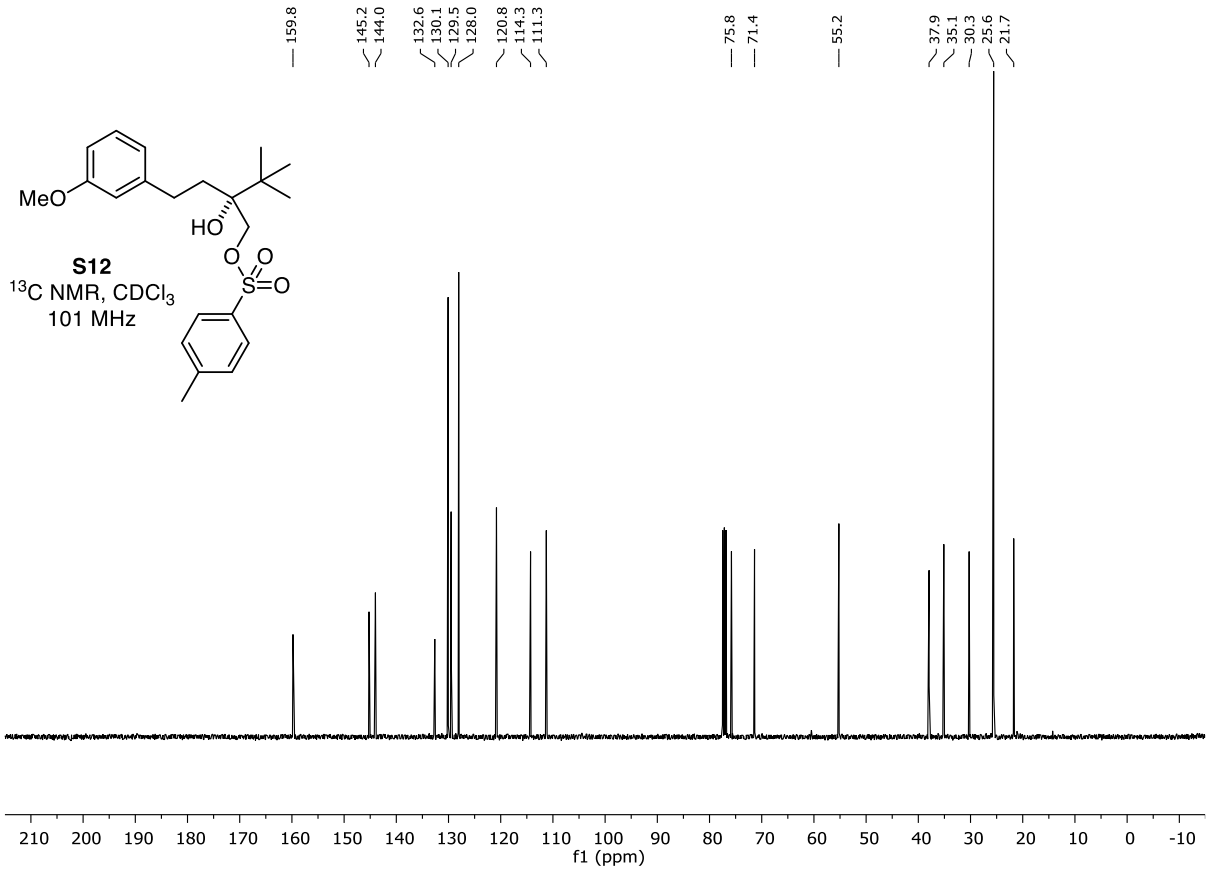


S10
^{13}C NMR, $CDCl_3$
101 MHz


MeO
HO
HO
S11
1H NMR, CDCl3
400 MHz
f1 (ppm)

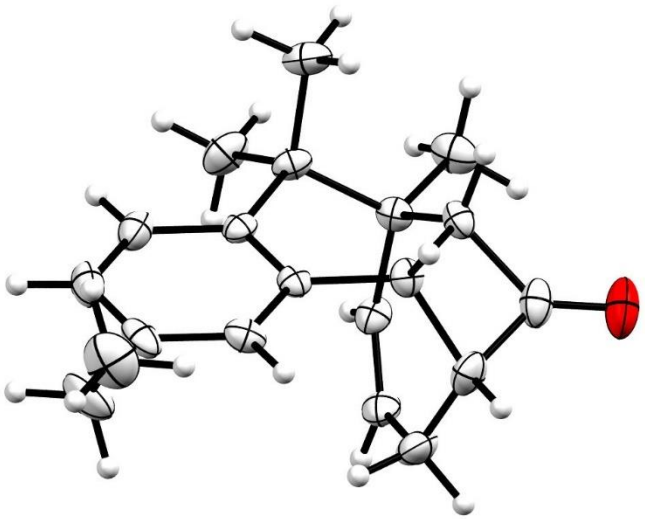

MeO
HO
HO
S11
13C NMR, CDCl3
101 MHz
f1 (ppm)


MeO
HO
O
O
S=O
S12
1H NMR, CDCl3
400 MHz
f1 (ppm)


MeO
HO
O
O
S=O
S12
13C NMR, CDCl3
101 MHz
f1 (ppm)

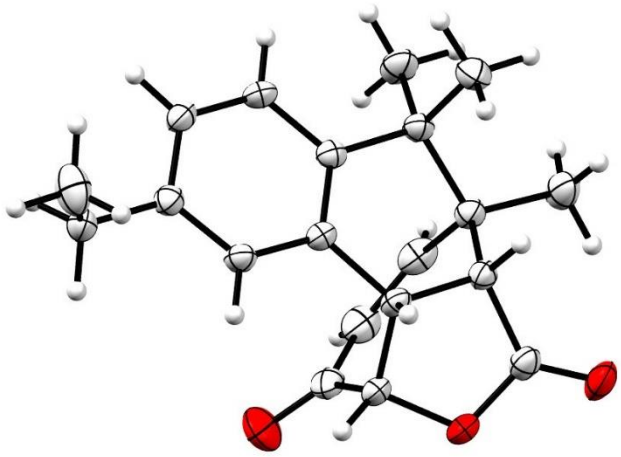
2.3 X–Ray crystallographic analysis data

Cyclobutanone (**5**)



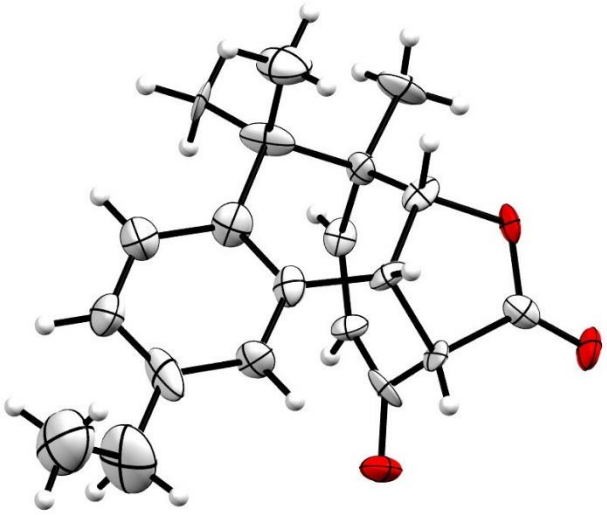
Identification code	mar1810
Empirical formula	$C_{20}H_{24}O$
Formula weight	280.39
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$ (no. 14)
Unit cell dimensions	a = 9.9024(4) Å α= 90°. b = 17.7073(8) Å β= 100.9080(10)° c = 8.9301(3) Å γ = 90°.
Volume	1537.55(11) $Å^3$
Z	4
Density (calculated)	1.211 Mg/m^3
Absorption coefficient	0.072 mm^{-1}
F(000)	608
Crystal size	0.220 x 0.160 x 0.120 mm^3
Theta range for data collection	2.094 to 24.998°.
Index ranges	-11<=h<=11, -21<=k<=21, -10<=l<=10
Reflections collected	16633
Independent reflections	2713 [R(int) = 0.0310]
Completeness to theta = 25.242°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.988 and 0.973
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2713 / 3 / 203
Goodness-of-fit on F^2	1.028
Final R indices [I>2sigma(I)]	R1 = 0.0449, wR2 = 0.1109
R indices (all data)	R1 = 0.0547, wR2 = 0.1174
Absolute structure parameter	0.032(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.363 and -0.238 $e.Å^{-3}$

Lactone (**24**)



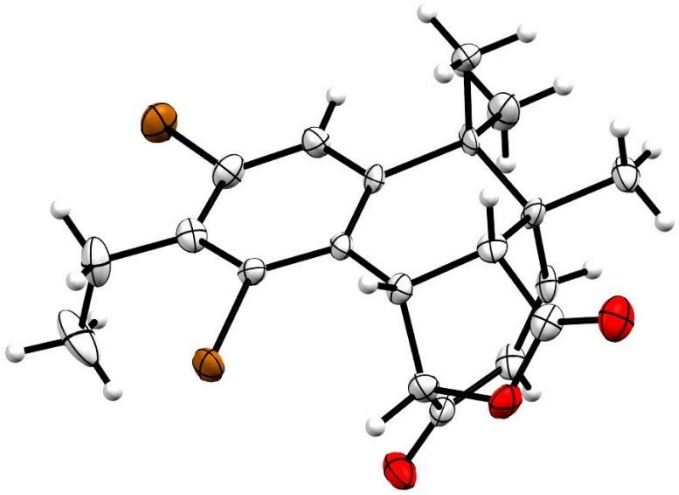
Identification code	mar187
Empirical formula	$C_{20}H_{22}O_3$
Formula weight	310.37
Temperature	183(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1 (no. 2)
Unit cell dimensions	a = 10.2423(9) Å α= 88.506(3)°. b = 11.5267(11) Å β= 80.899(3)°. c = 14.1776(14) Å γ = 76.244(3)°.
Volume	1605.2(3) $Å^3$
Z	4
Density (calculated)	1.284 Mg/m^3
Absorption coefficient	0.085 mm^{-1}
F(000)	664
Crystal size	0.180 x 0.180 x 0.080 mm^3
Theta range for data collection	2.316 to 24.998°.
Index ranges	-12<=h<=12, -13<=k<=13, -16<=l<=16
Reflections collected	40208
Independent reflections	5650 [R(int) = 0.0328]
Completeness to theta = 25.242°	99.9%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.958 and 0.942
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5650 / 0 / 416
Goodness-of-fit on F^2	1.031
Final R indices [I>2sigma(I)]	R1 = 0.0395, wR2 = 0.0993
R indices (all data)	R1 = 0.0498, wR2 = 0.1053
Extinction coefficient	0.0198(15)
Largest diff. peak and hole	0.277 and -0.370 $e.Å^{-3}$

Lacton (**23**)



Identification code	mar183
Empirical formula	$C_{20}H_{22}O_3$
Formula weight	310.37
Temperature	183(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	Pc (no. 7)
Unit cell dimensions	a = 27.498(6) Å α= 90°. b = 7.6508(18) Å β= 90.715(6)°. c = 15.583(4) Å γ = 90°.
Volume	3278.1(14) $Å^3$
Z	8
Density (calculated)	1.258 Mg/m^3
Absorption coefficient	0.083 mm^{-1}
F(000)	1328
Crystal size	0.180 x 0.180 x 0.060 mm^3
Theta range for data collection	2.222 to 24.000°.
Index ranges	-31<=h<=31, -8<=k<=8, -17<=l<=17
Reflections collected	26356
Independent reflections	9751 [R(int) = 0.0664]
Completeness to theta = 25.242°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.972 and 0.963
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9751 / 2 / 830
Goodness-of-fit on F^2	1.314
Final R indices [I>2sigma(I)]	R1 = 0.1179, wR2 = 0.3162
R indices (all data)	R1 = 0.1484, wR2 = 0.3419
Absolute structure parameter	0.1(10)
Extinction coefficient	0.008(3)
Largest diff. peak and hole	0.912 and -0.480 $e.Å^{-3}$

Salimabromide (**1**)

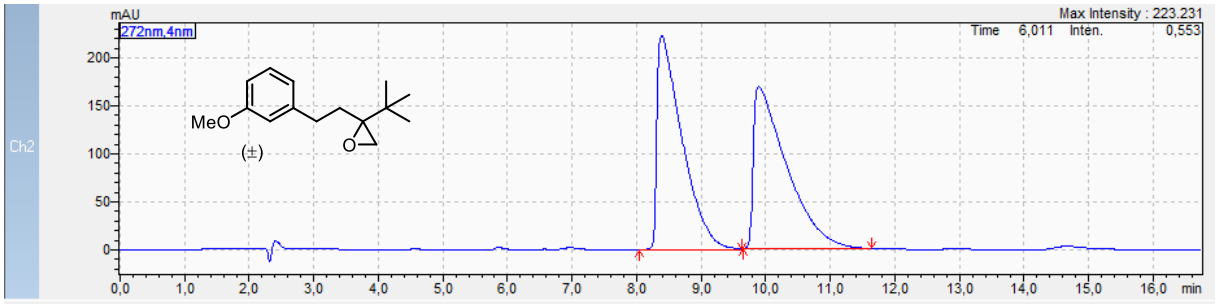


Identification code	mar185
Empirical formula	$C_{20}H_{20}Br_2O_3$
Formula weight	468.18
Temperature	183(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$Pca2_1$ (no. 29)
Unit cell dimensions	a = 17.2220(6) Å α= 90°. b = 9.8655(4) Å β= 90°. c = 20.9582(8) Å γ = 90°.
Volume	3560.9(2) $Å^3$
Z	8
Density (calculated)	1.747 Mg/m^3
Absorption coefficient	4.570 mm^{-1}
F(000)	1872
Crystal size	0.140 x 0.080 x 0.035 mm^3
Theta range for data collection	2.365 to 25.498°.
Index ranges	-20<=h<=18, -11<=k<=11, -25<=l<=25
Reflections collected	59510
Independent reflections	6607 [R(int) = 0.0402]
Completeness to theta = 25.242°	99.9%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.825 and 0.673
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6607 / 1 / 452
Goodness-of-fit on F^2	1.051
Final R indices [I>2sigma(I)]	R1 = 0.0324, wR2 = 0.0784
R indices (all data)	R1 = 0.0376, wR2 = 0.0813
Absolute structure parameter	0.287(13)
Extinction coefficient	n/a
Largest diff. peak and hole	1.255 and -1.083 $e.Å^{-3}$

2.4 Chiral HPLC data

Epoxide **7**

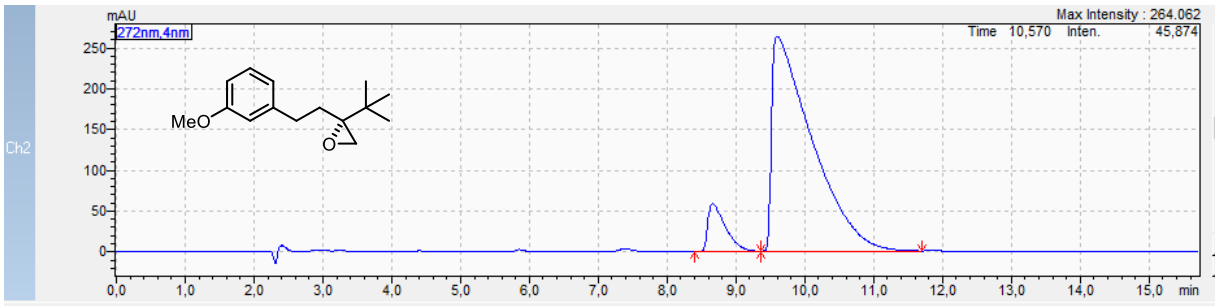
HPLC conditions: Chiralcel IA column, heptane/EtOAc = 99.7/0.3, 1.5 mL/min, λ = 272 nm, t_R (minor) = 8.6 min, t_R(major) = 9.8 min



Results View - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	8,388	6012699	223050		0,000				49,858
2	9,894	6046991	168397	M	0,000				50,142
Total		12059690	391447		0,000				100,000



Results View - Peak Table

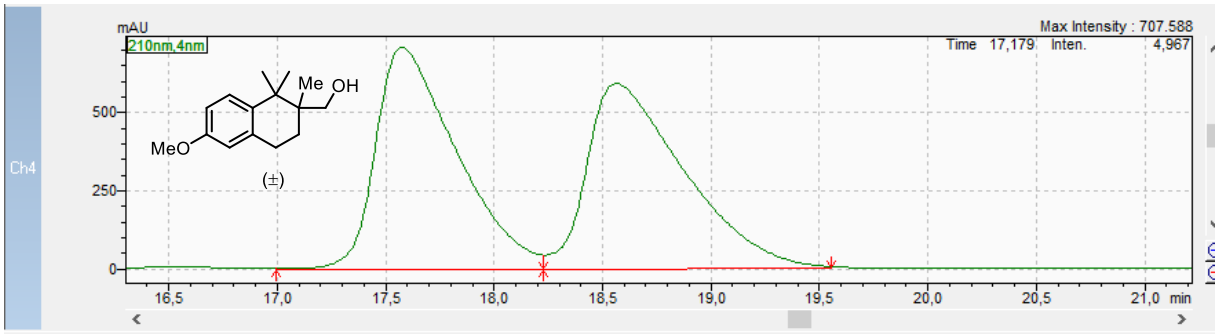
Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	8,663	1056128	58983		0,000				8,905
2	9,604	10804000	263596	V	0,000				91,095
Total		11860127	322580		0,000				100,000

Tetraline **12**

HPLC conditions: Chiralcel IA column, heptane/*i*-PrOH = 99/1, 1.5 mL/min, λ = 210 nm, t_R (minor) = 17.7 min, t_R(major) = 18.7 min

Racemic **12**

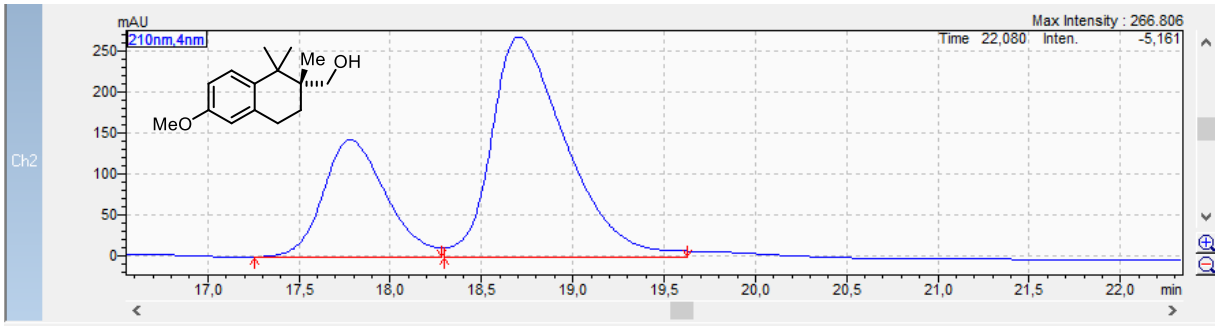


Results View - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	17,575	18356513	707344		0,000				49,754
2	18,564	18538374	592707	M	0,000				50,246
Total		36894887	1300051		0,000				100,000

HFIP, H_2SO_4, 23 °C, 5 min

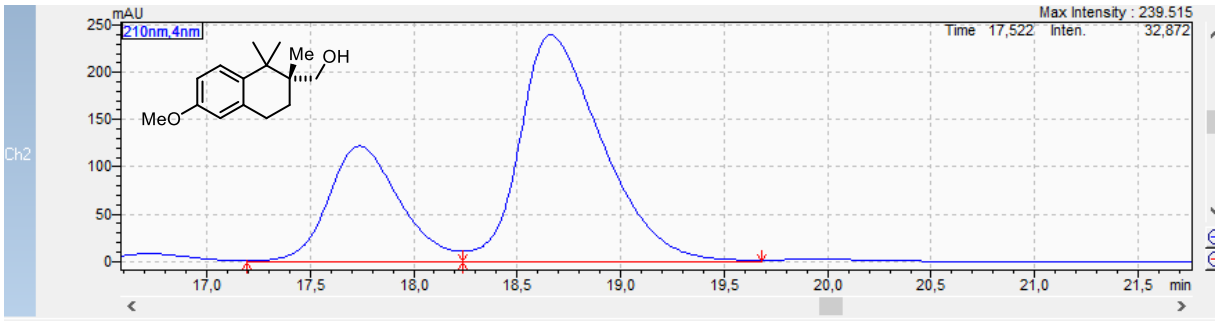


Results View - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	17,780	3380513	142590	M	0,000				30,777
2	18,703	7603464	268290	M	0,000				69,223
Total		10983977	410880		0,000				100,000

n-Hexane, H_2SO_4, 23 °C, 5 min

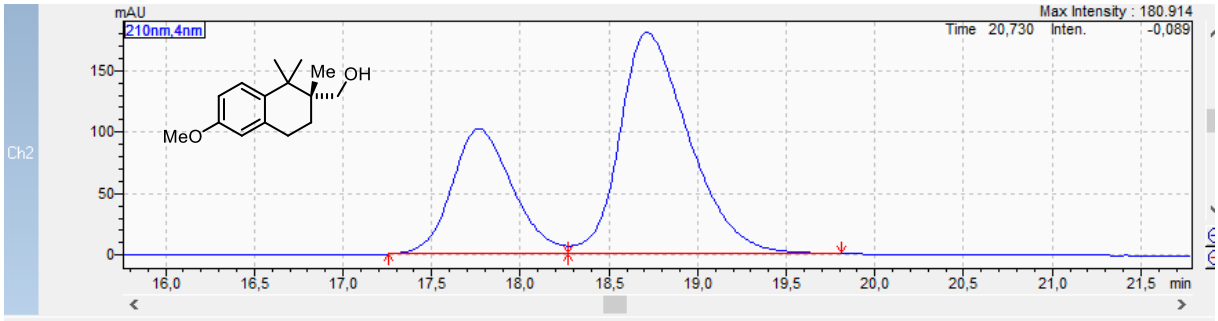


Results View - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	17,738	2926852	122253		0,000				30,543
2	18,662	6655797	239812	V	0,000				69,457
Total		9582648	362065		0,000				100,000

n-Hexane, H_2SO_4, –78 °C (2.5 h,), then slowly to 23 °C, 5 min

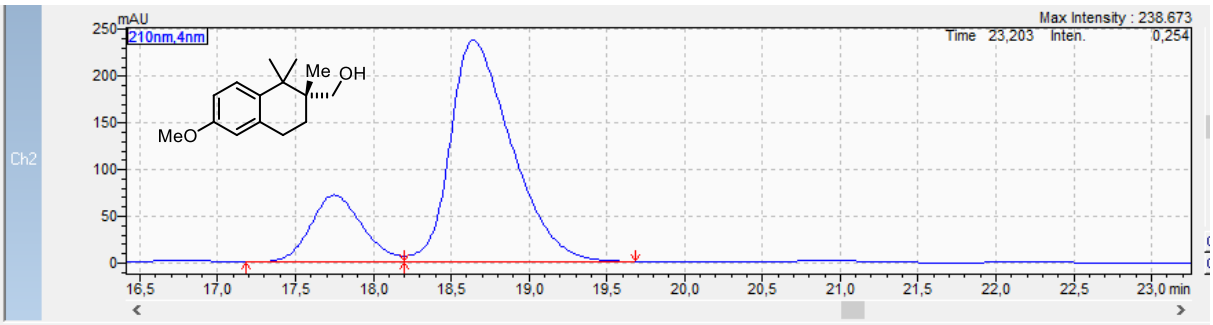


Results View - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	17,766	2412896	101585	M	0,000				33,050
2	18,715	4887938	179791	V M	0,000				66,950
Total		7300834	281377		0,000				100,000

DCM, $TiCl_4$, 23 °C, 10 min

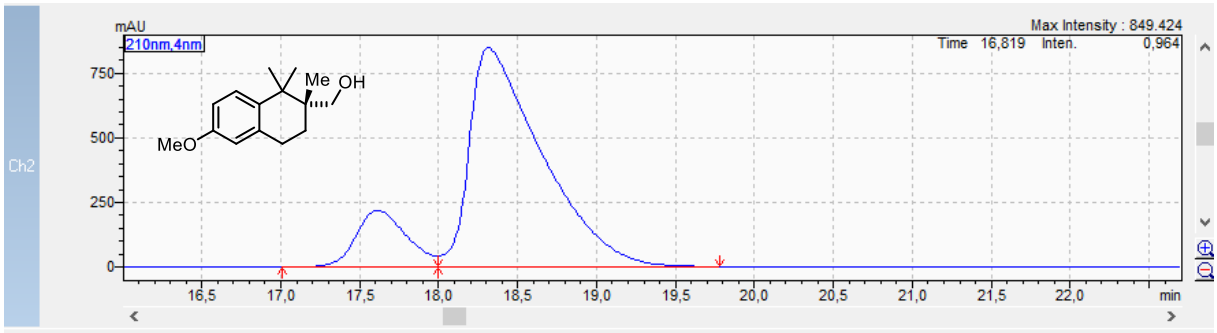


Results View - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	17,749	1667299	71998		0,000				20,398
2	18,642	6506724	237488	V M	0,000				79,602
Total		8174023	309487		0,000				100,000

DCM, $TiCl_4$, –78 °C, 1 h, then slowly to 23 °C, 5 min

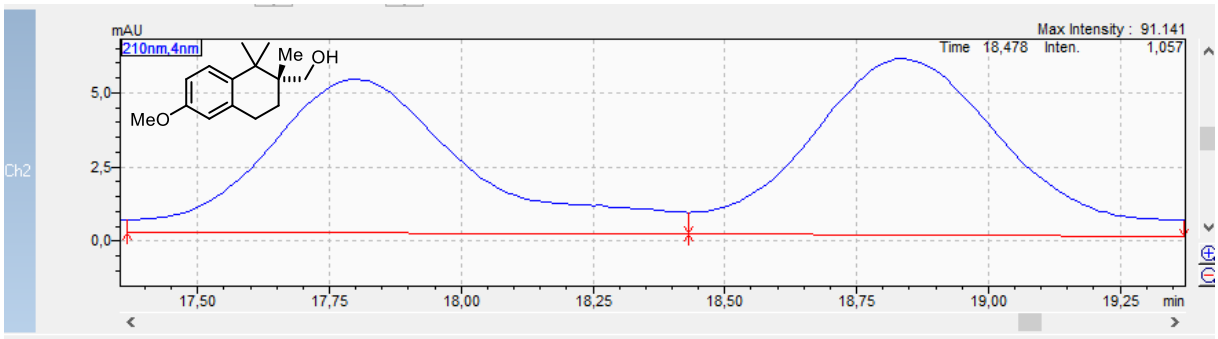


Results View - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	17,613	4864090	218864		0,000				15,231
2	18,315	27072403	848175	V M	0,000				84,769
Total		31936493	1067038		0,000				100,000

(R)-(–)-1,1′-Binaphthyl-2,2′-diyl hydrogenphosphate, DCM, –78 °C, 3 h, then 23 °C, 16 h



Results View - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	17,802	138326	5168		0,000				47,350
2	18,834	153806	5928	V	0,000				52,650
Total		292132	11096		0,000				100,000

3 Supporting information for chapter II – 2.2

3.1 X-Ray crystallographic analysis data

The X-ray intensity data of **27**, **48** and **49** were measured at 100 K on a Bruker D8 Venture TXS system equipped with a multilayer mirror optics monochromator and a Mo Kα rotating-anode X-ray tube (λ = 0.71073 Å). The frames were integrated with SAINT [1], the data were corrected for absorption effects using the Multi-Scan method (SADABS) [2]. The structures were solved and refined using the Bruker SHELXTL Software Package [3]. In 48, the coordinates of the O-bound hydrogen atom were restrained to refine to a O-H distance of 0.83 Å, the temperature factor was refined freely. All other hydrogen atoms were calculated in ideal geometry riding on their parent atoms.

The figures below were created with ORTEP [4].

Single-crystal X-ray analysis of compound 27:

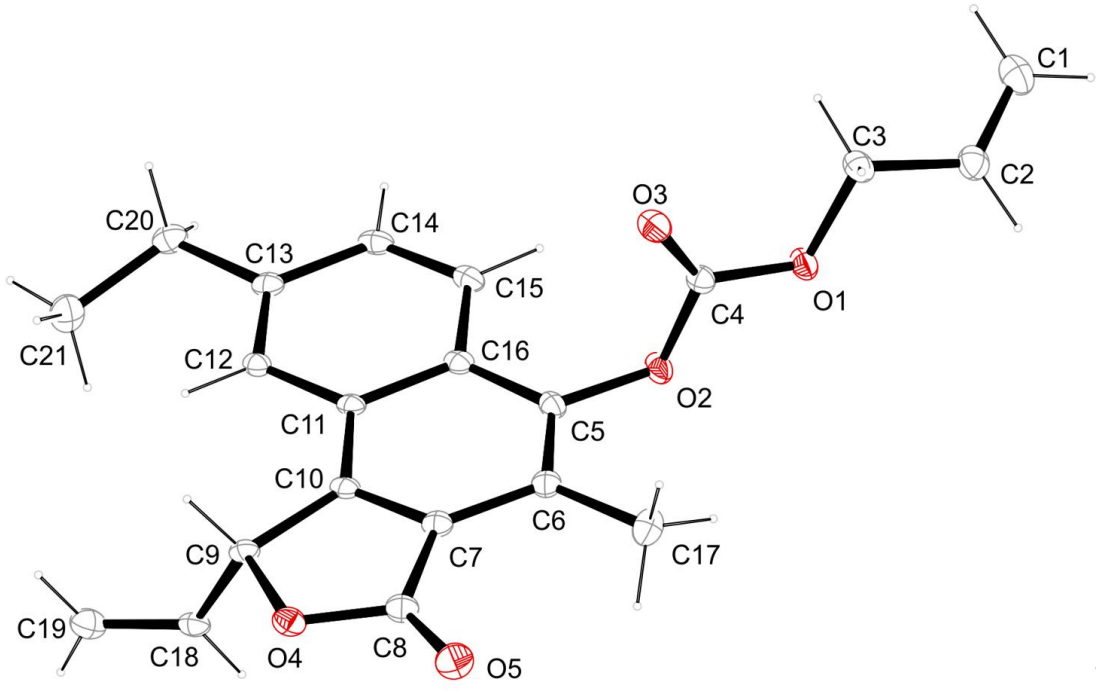


Fig. 1 The molecular structure of **27** (ORTEP drawing at the 50% ellipsoid probability level).

net formula	$C_{21}H_{20}O_5$
M_r/g mol^{-1}	352.37
crystal size/mm	0.100 × 0.090 × 0.010

T/K	100(2)
radiation	MoKα
diffractometer	'Bruker D8Venture'
crystal system	monoclinic
space group	'C 2/c'
a/Å	30.2456(18)
b/Å	7.6603(4)
c/Å	18.2737(11)
α/°	90
β/°	122.731(2)
γ/°	90
V/Å^3	3561.6(4)
Z	8
calc. density/g cm^{-3}	1.314
μ/mm^{-1}	0.094
absorption correction	multi-scan
transmission factor range	0.8940–0.9580
refls. measured	18840
R_{int}	0.0480
mean σ(I)/I	0.0356
θ range	3.202–25.38
observed refls.	2358
x, y (weighting scheme)	0.0393, 2.6371
hydrogen refinement	constr
refls in refinement	3250
parameters	237
restraints	0
$R(F_{obs})$	0.0402
$R_w(F^2)$	0.0956
S	1.058
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.223
min electron density/e Å^{-3}	−0.210

Single-crystal X-ray analysis of compound 48:

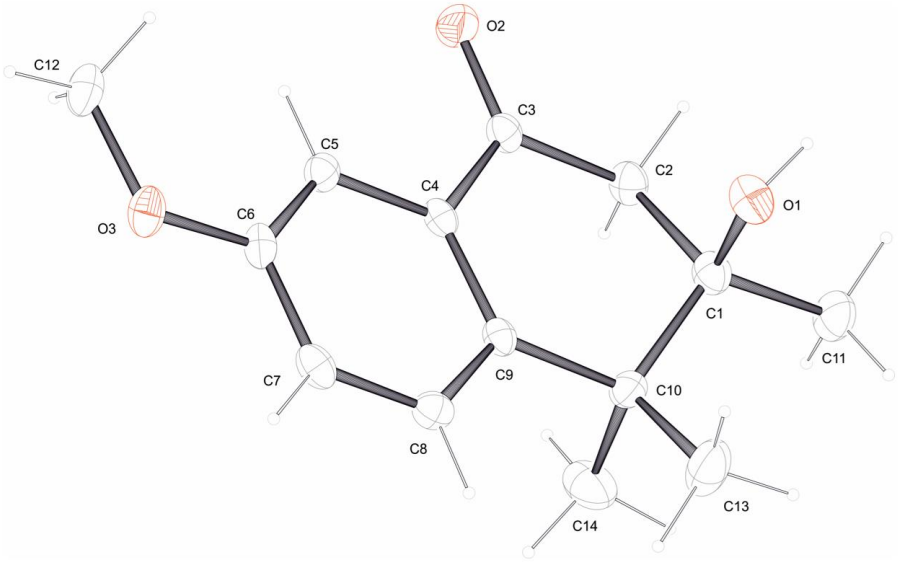


Fig. 2 The molecular structure of **48** (ORTEP drawing at the 50% ellipsoid probability level).

net formula	$C_{14}H_{18}O_3$
M_r/g mol^{-1}	234.28
crystal size/mm	0.090 × 0.040 × 0.030
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21/n 1'
a/Å	7.0271(3)
b/Å	17.0529(7)
c/Å	10.0184(4)
α/°	90
β/°	91.650(2)
γ/°	90
V/Å^3	1200.03(9)
Z	4
calc. density/g cm^{-3}	1.297
μ/mm^{-1}	0.090
absorption correction	Multi-Scan
transmission factor range	0.9017–0.9705
refls. measured	18124
R_{int}	0.0421
mean σ(I)/I	0.0268
θ range	3.137–26.365
observed refls.	2013
x, y (weighting scheme)	0.0528, 1.1304

hydrogen refinement	H(C) constr, H(O) restr
refls in refinement	2450
parameters	162
restraints	1
$R(F_{obs})$	0.0561
$R_w(F^2)$	0.1404
S	1.116
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.496
min electron density/e Å^{-3}	−0.358

Single-crystal X-ray analysis of compound 49:

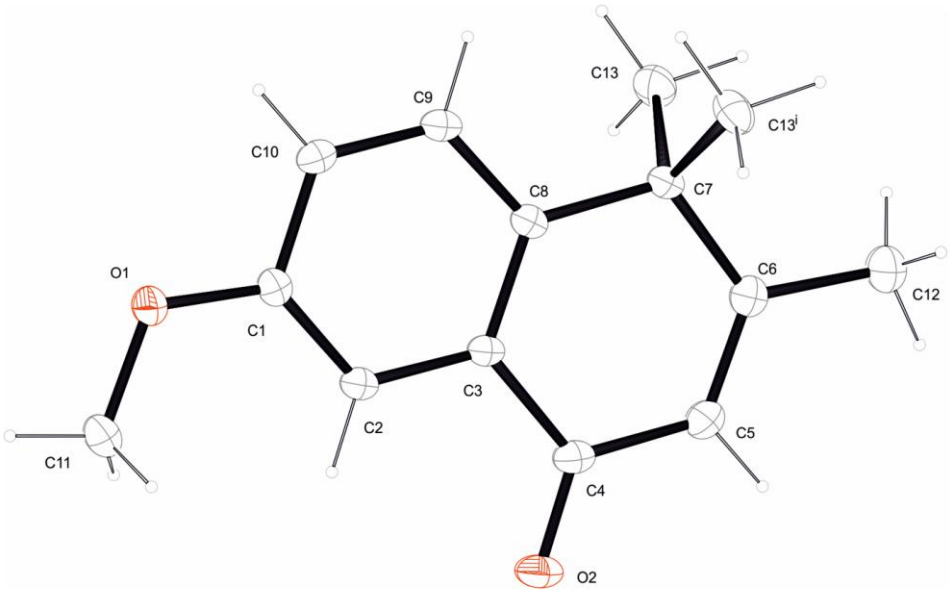


Fig. 3 The molecular structure of **49** (ORTEP drawing at the 50% ellipsoid probability level).

net formula	$C_{14}H_{16}O_2$
M_r/g mol^{-1}	216.27
crystal size/mm	0.090 × 0.070 × 0.030
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P n m a'
a/Å	15.3960(5)
b/Å	7.0864(2)
c/Å	10.4521(3)
α/°	90
β/°	90
γ/°	90
V/Å^3	1140.35(6)
Z	4
calc. density/g cm^{-3}	1.260
μ/mm^{-1}	0.083
absorption correction	Multi-Scan
transmission factor range	0.9123–0.9705
refls. measured	12854
R_{int}	0.0310
mean σ(I)/I	0.0191
θ range	3.287–28.272

observed refls.	1332
x, y (weighting scheme)	0.0630, 0.3244
hydrogen refinement	constr
refls in refinement	1533
parameters	97
restraints	0
$R(F_{obs})$	0.0394
$R_w(F^2)$	0.1145
S	1.065
shift/error_{max}	0.001
max electron density/e $Å^{-3}$	0.402
min electron density/e $Å^{-3}$	−0.210

References

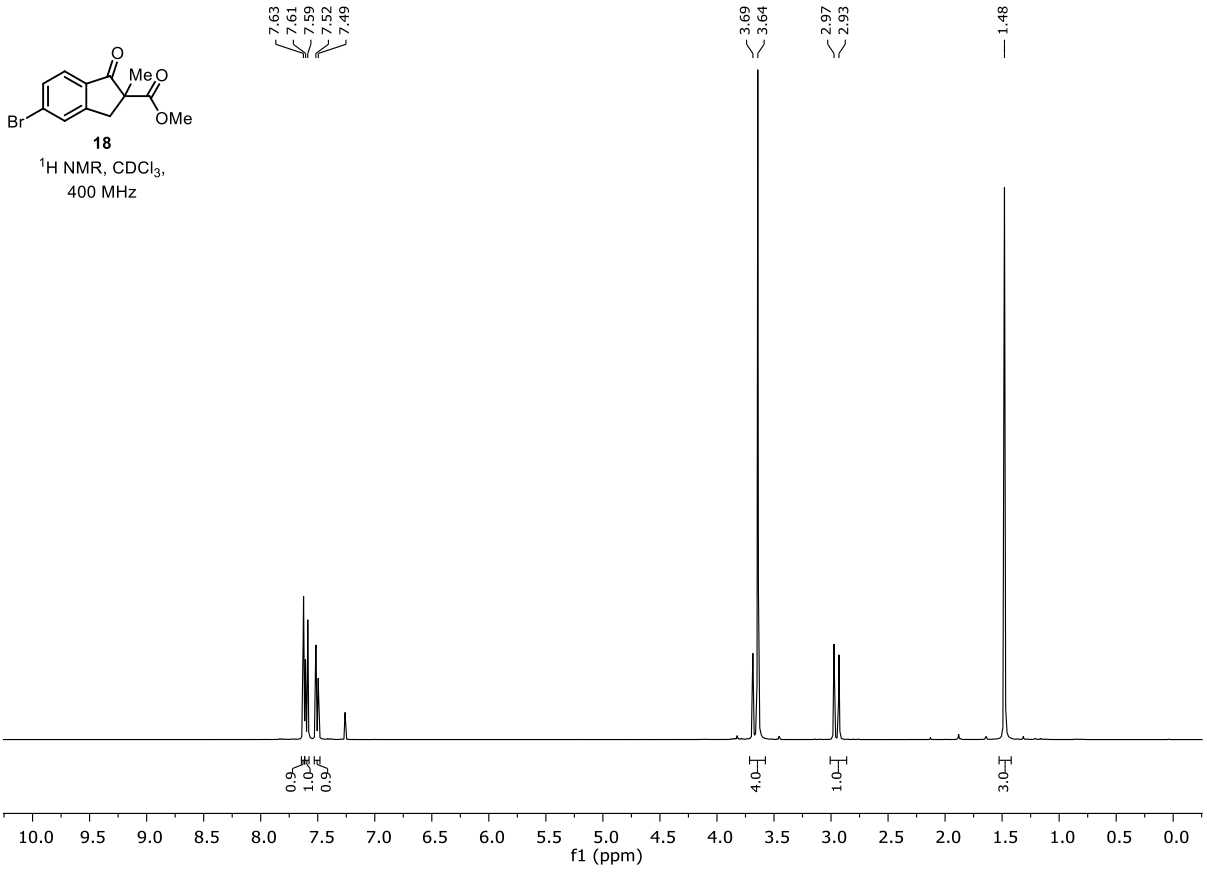
[1] Bruker (2015). *SAINT*. Bruker AXS Inc., Madison, Wisconsin, USA.

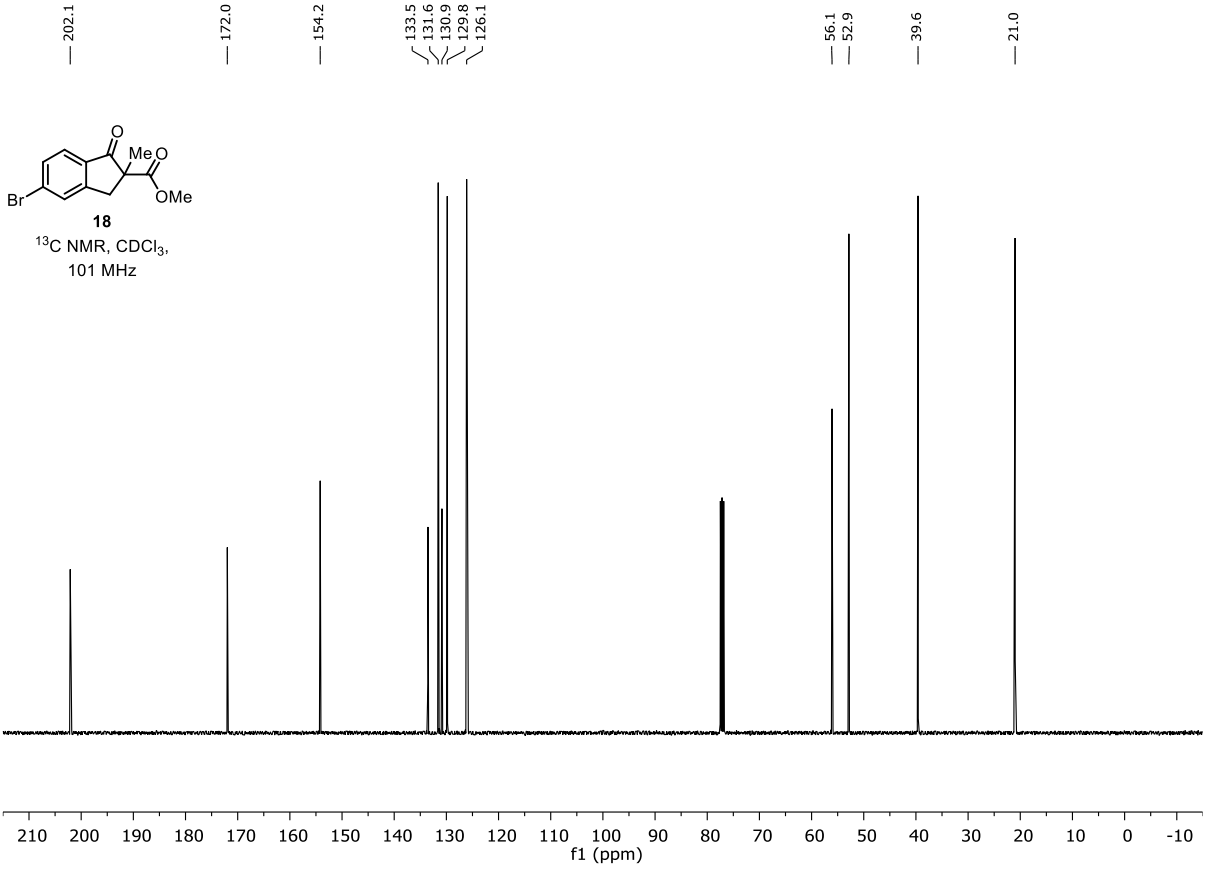
[2] Bruker (2001). *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA.

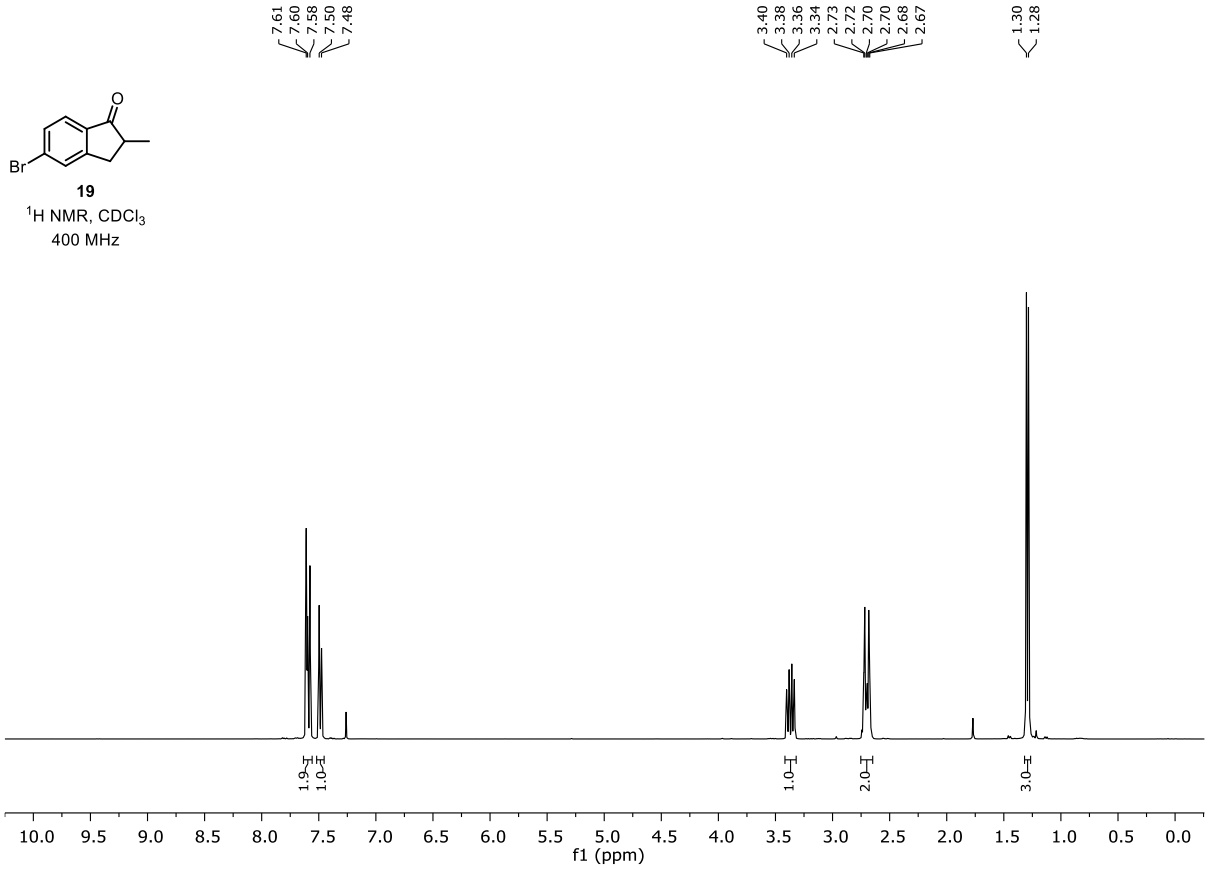
[3] Sheldrick, G. M. (2015). Acta Cryst. A71, 3–8.

[4] Farrugia, L. J. (2012). J. Appl. Cryst. 45, 849–854.

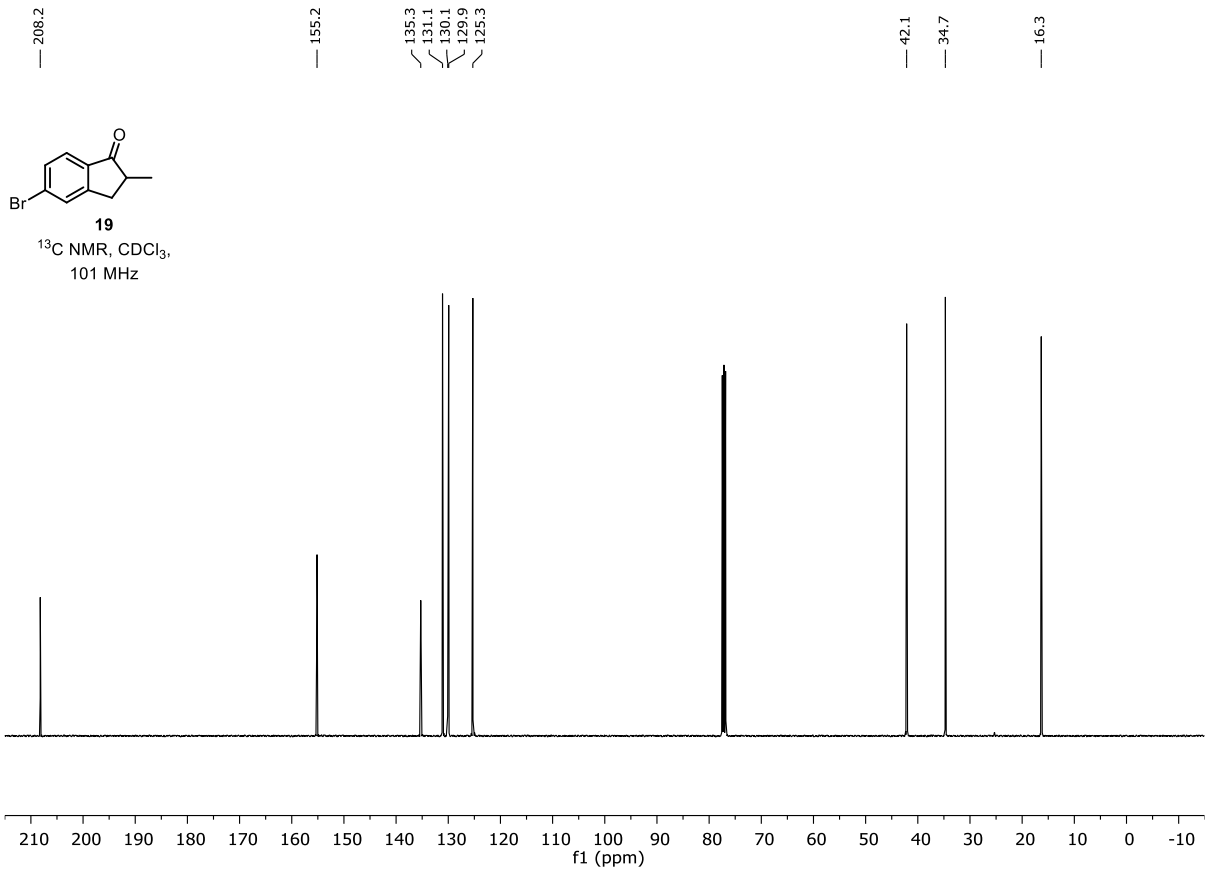
3.2 NMR spectra



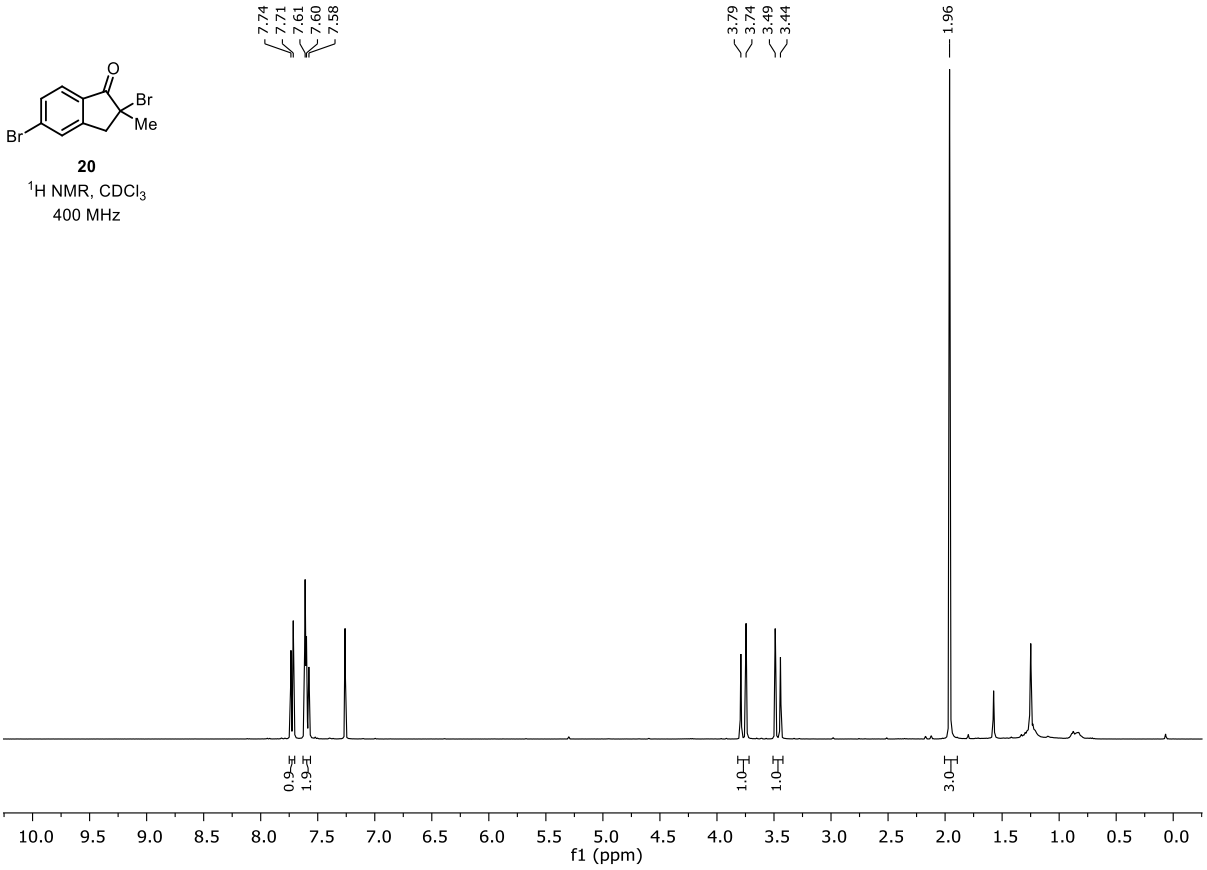




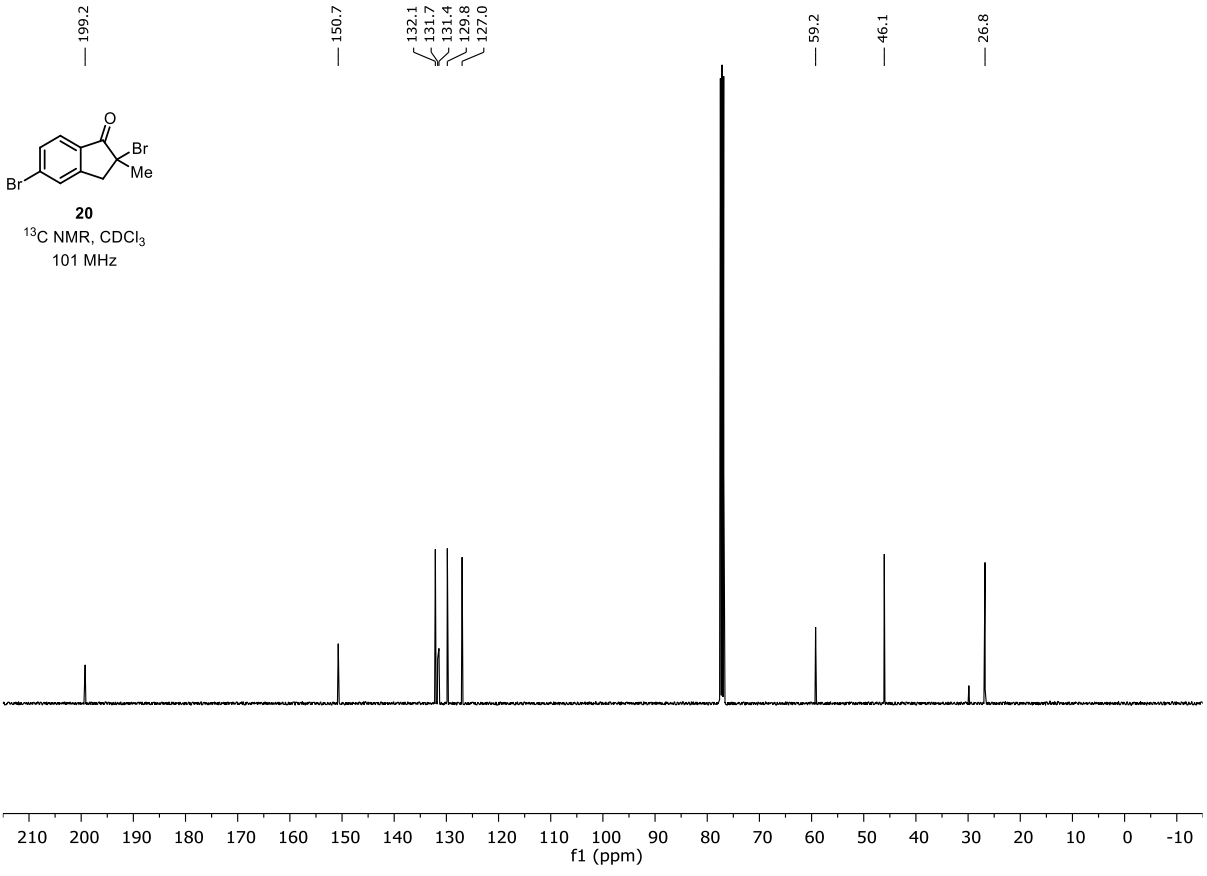
19
^{1}H NMR, $CDCl_3$
400 MHz



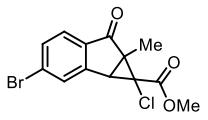
19
^{13}C NMR, $CDCl_3$,
101 MHz



20
^{1}H NMR, $CDCl_3$
400 MHz



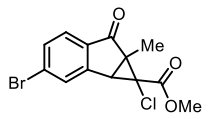
20
^{13}C NMR, $CDCl_3$
101 MHz



21

^{1}H NMR, $CDCl_3$

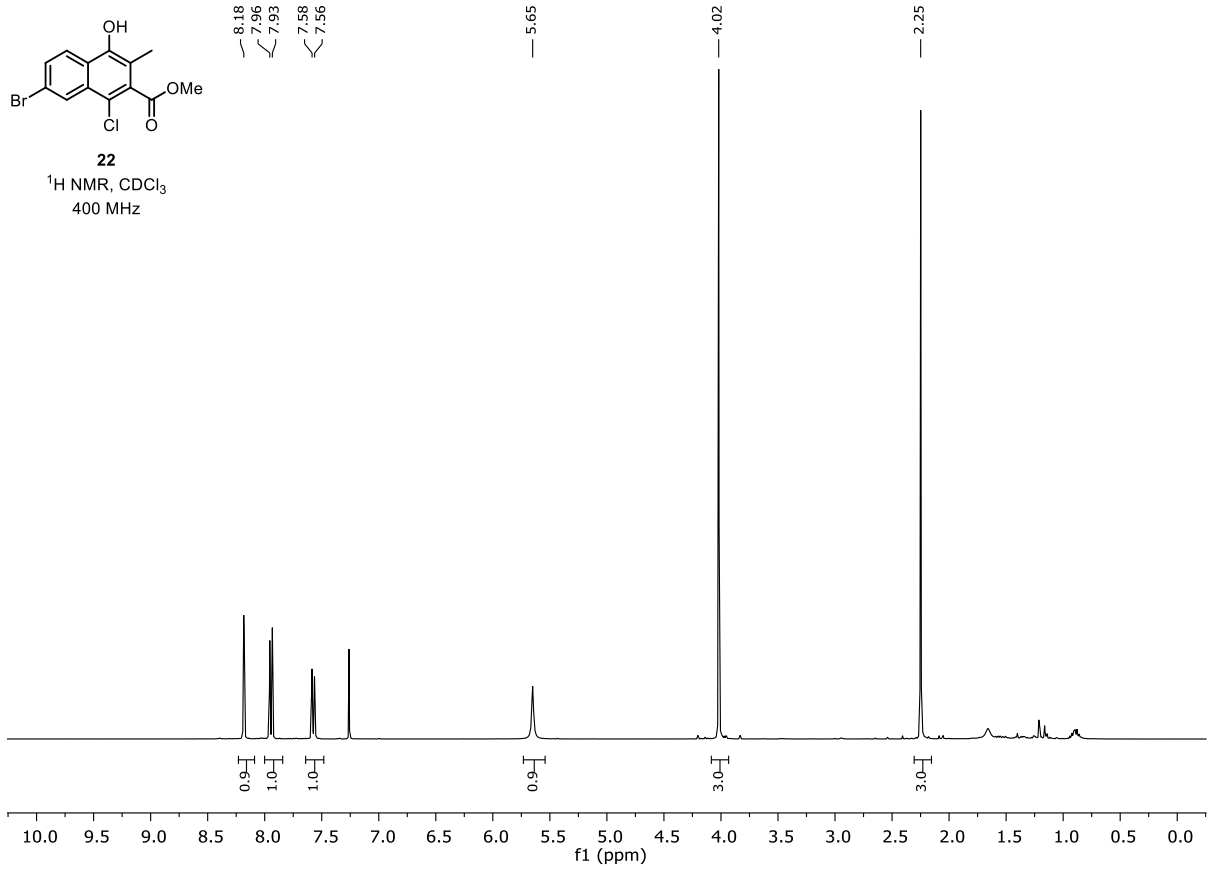
400 MHz

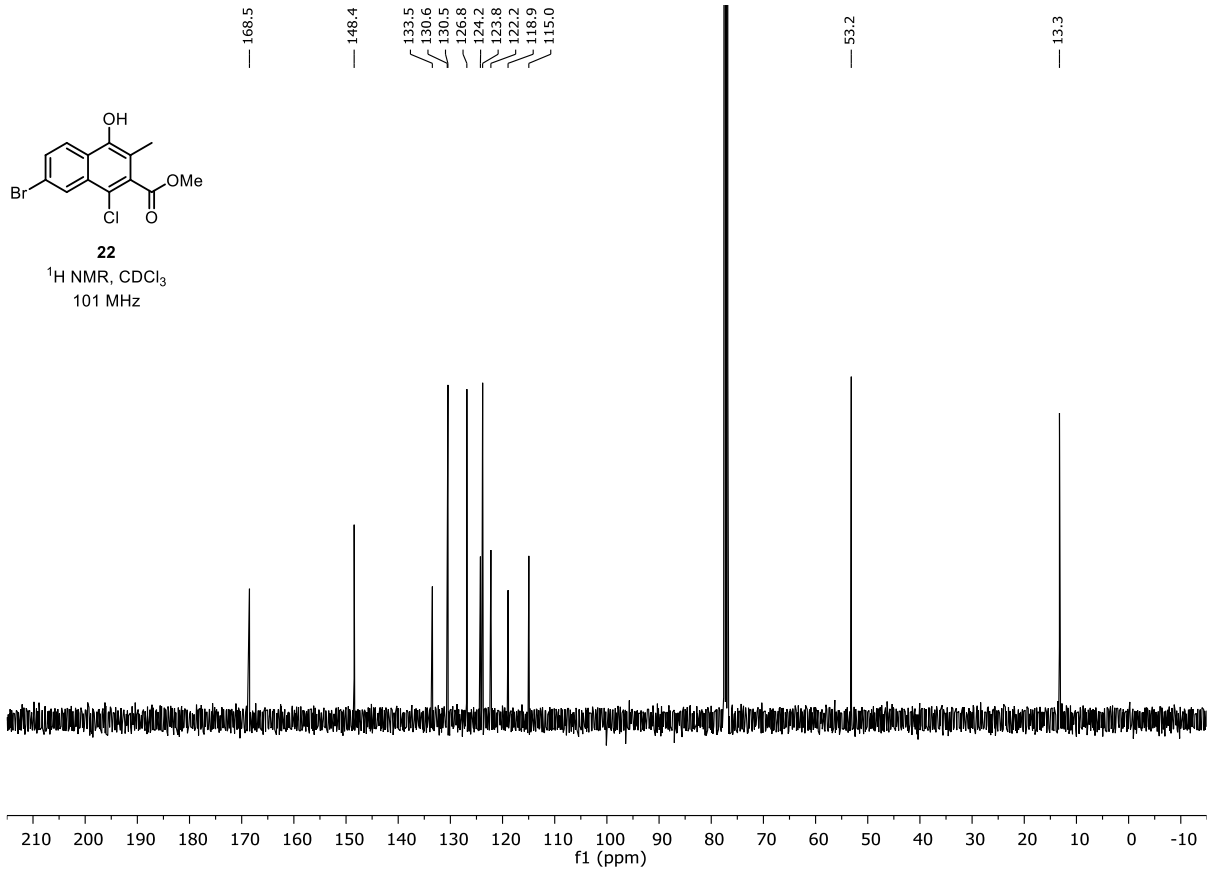


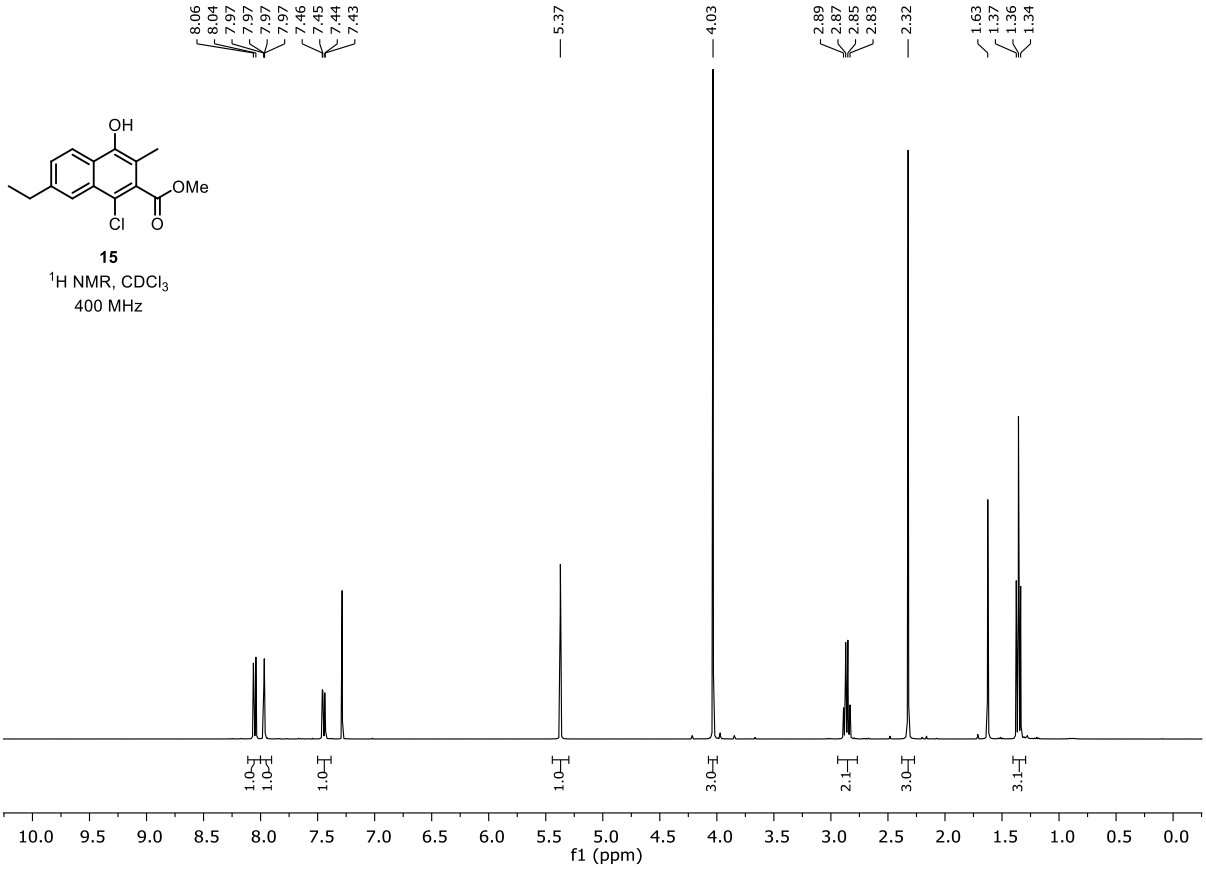
21

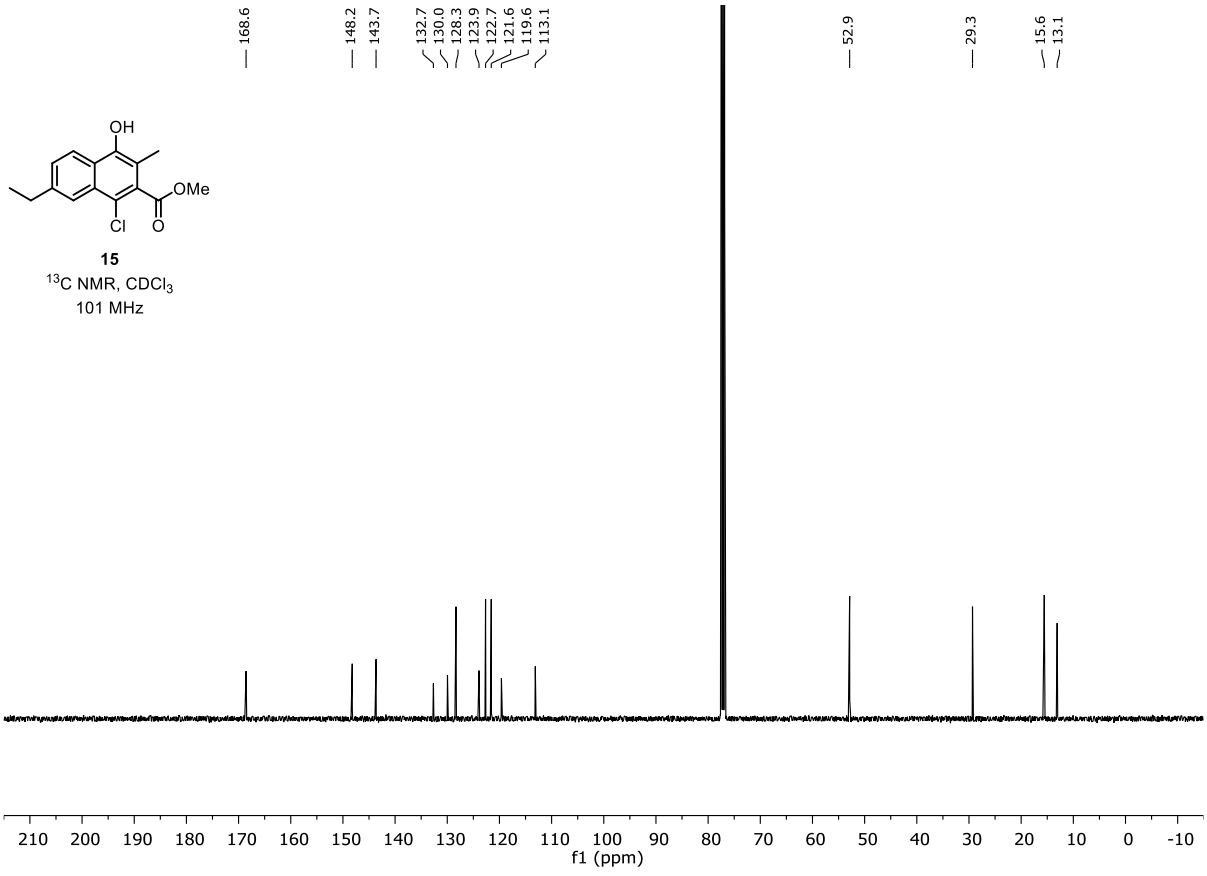
^{13}C NMR, $CDCl_3$

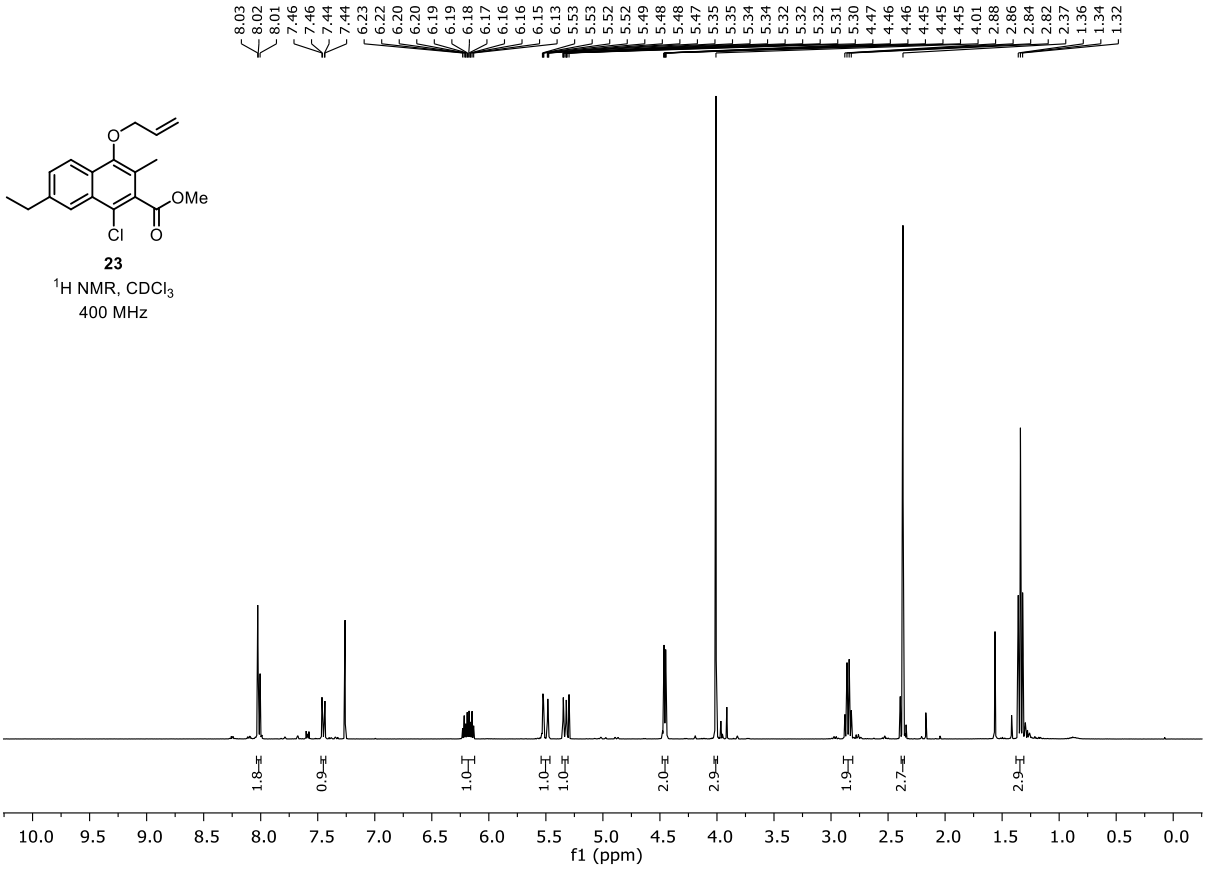
101 MHz


OH
Br
OMe
Cl
O
22
^{1}H NMR, $CDCl_3$
400 MHz
8.18
7.96
7.93
7.58
7.56
5.65
4.02
2.25
0.9
1.0
1.0
0.9
3.0
3.0
f1 (ppm)

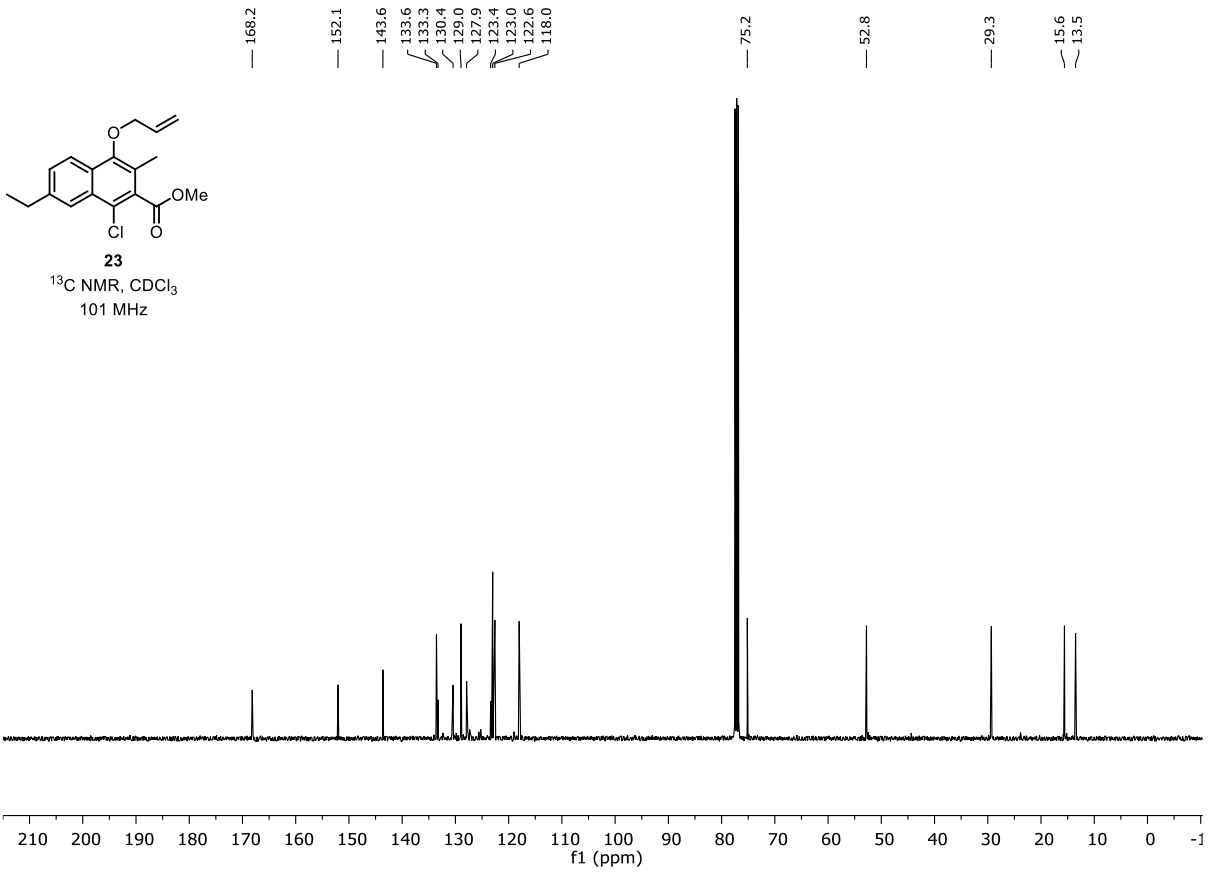

OH
Br
OMe
Cl
O
22
^{1}H NMR, $CDCl_3$
101 MHz
168.5
148.4
133.5
130.6
130.5
126.8
124.2
123.8
122.2
118.9
115.0
53.2
13.3
f1 (ppm)


8.06
8.04
7.97
7.97
7.97
7.97
7.46
7.45
7.44
7.43
5.37
4.03
2.89
2.87
2.85
2.83
2.32
1.63
1.37
1.36
1.34
OH
OMe
Cl
O
15
1H NMR, CDCl3
400 MHz
1.0
1.0
1.0
1.0
3.0
2.1
3.0
3.1
f1 (ppm)

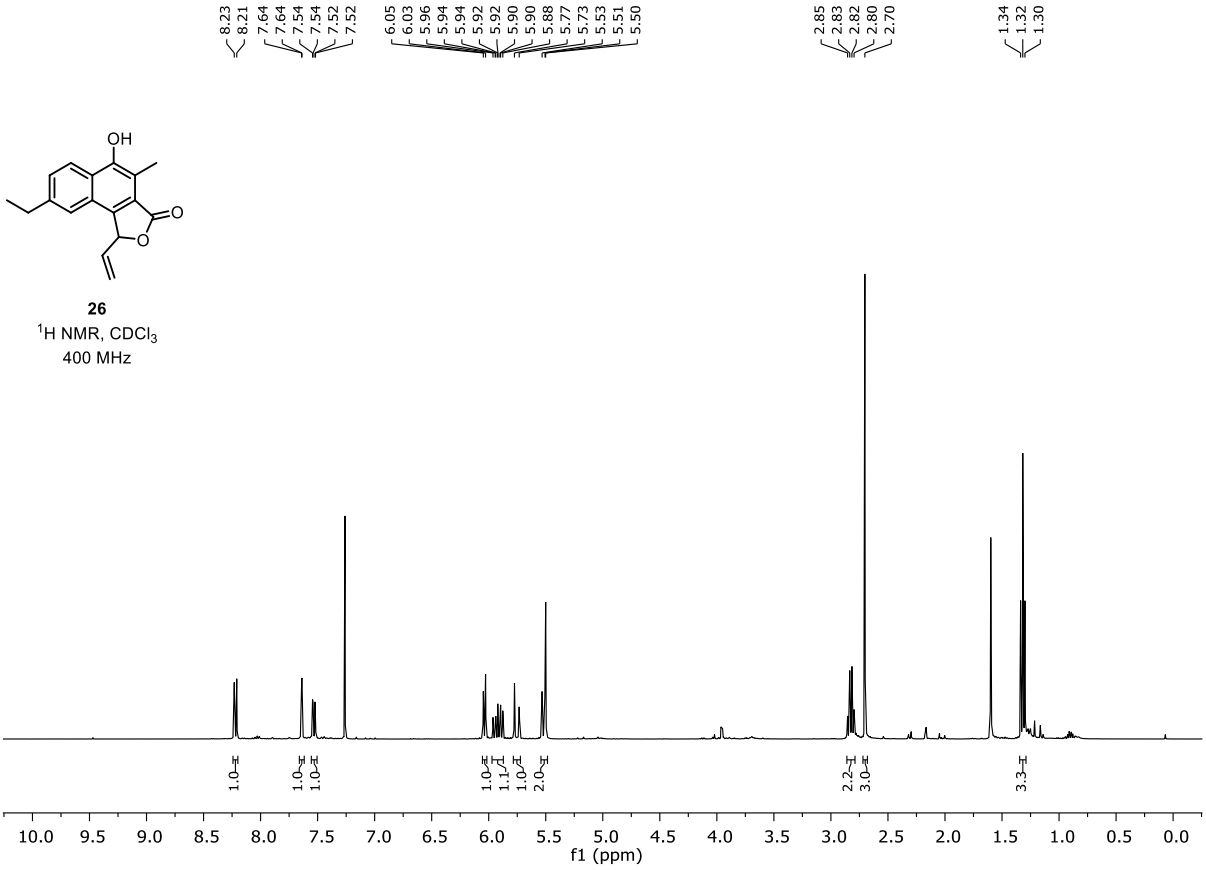

168.6
148.2
143.7
132.7
130.0
128.3
123.9
122.7
121.6
119.6
113.1
52.9
29.3
15.6
13.1
OH
OMe
Cl
O
15
13C NMR, CDCl3
101 MHz
f1 (ppm)



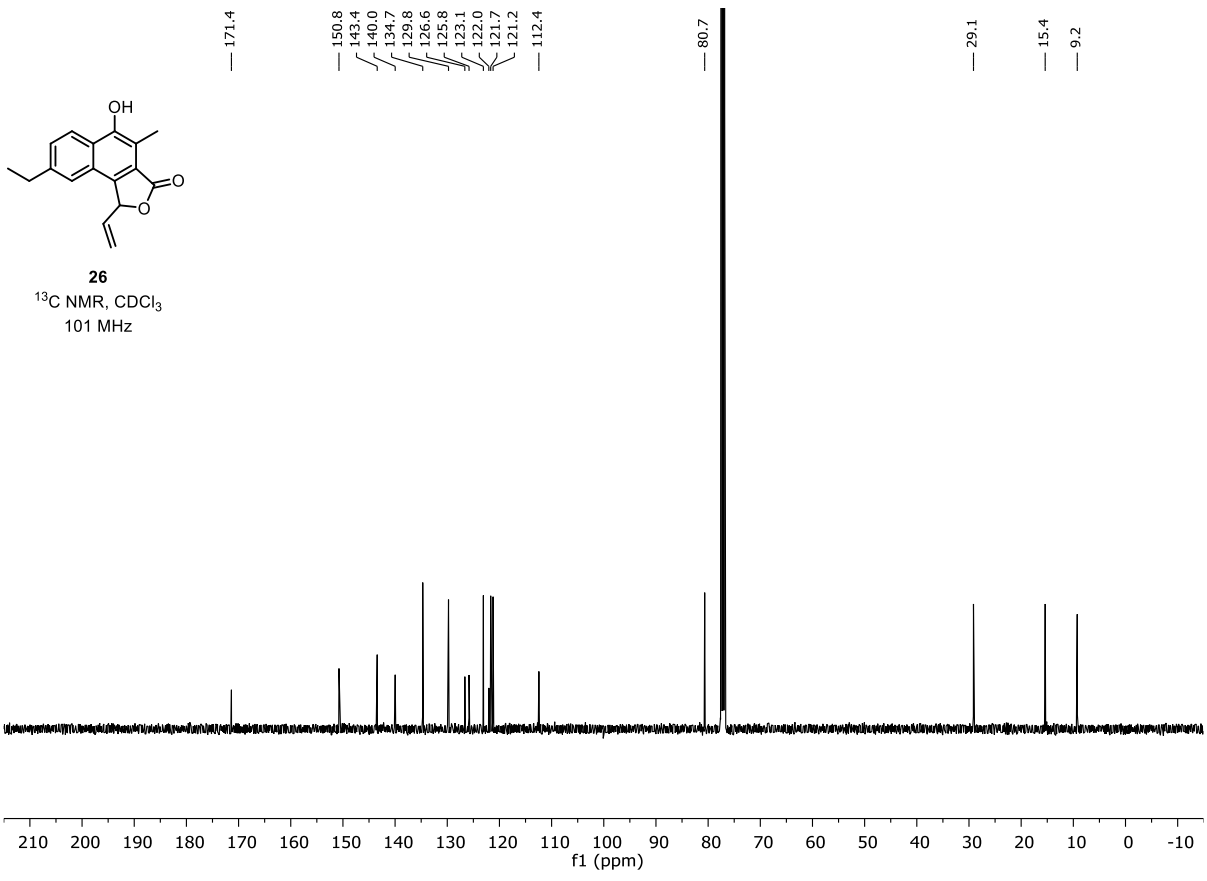
23
^{1}H NMR, $CDCl_3$
400 MHz



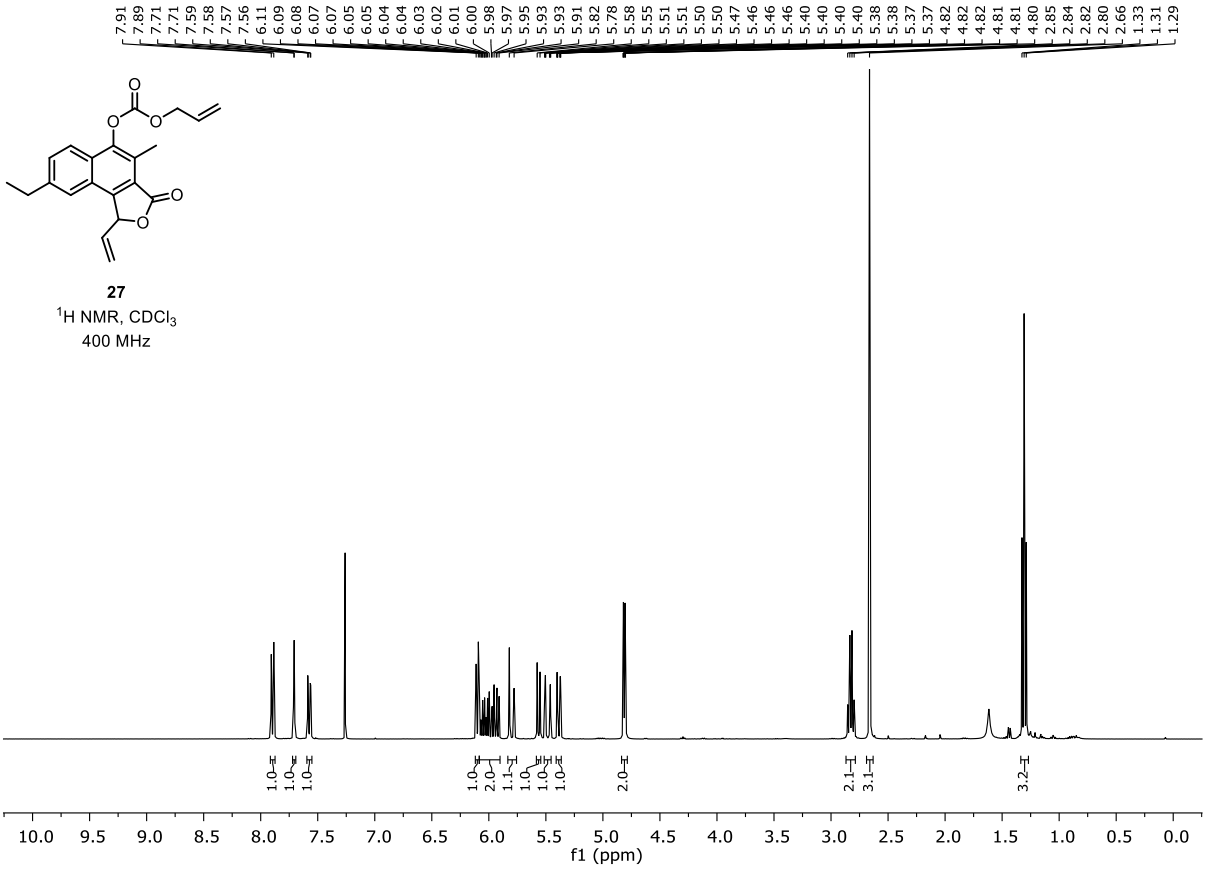
23
^{13}C NMR, $CDCl_3$
101 MHz



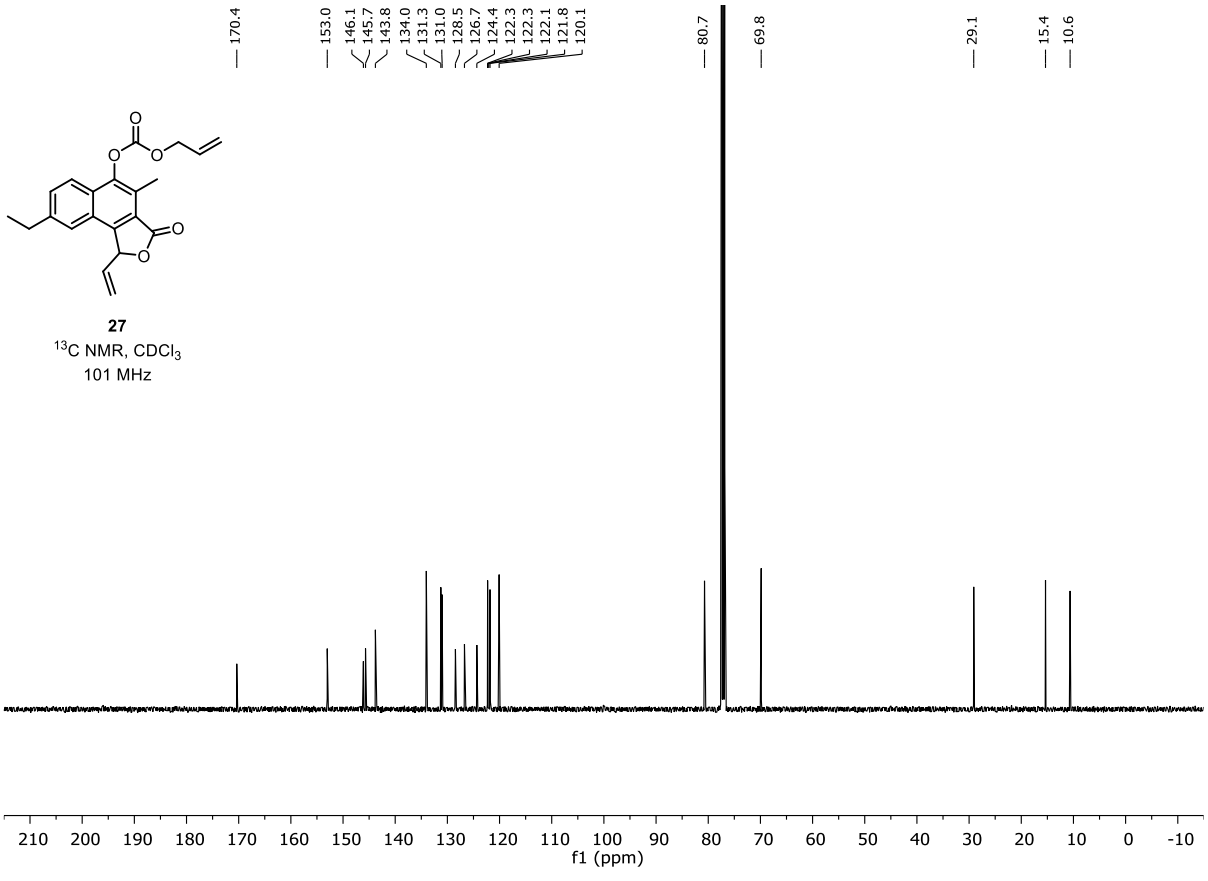
26
^{1}H NMR, $CDCl_3$
400 MHz



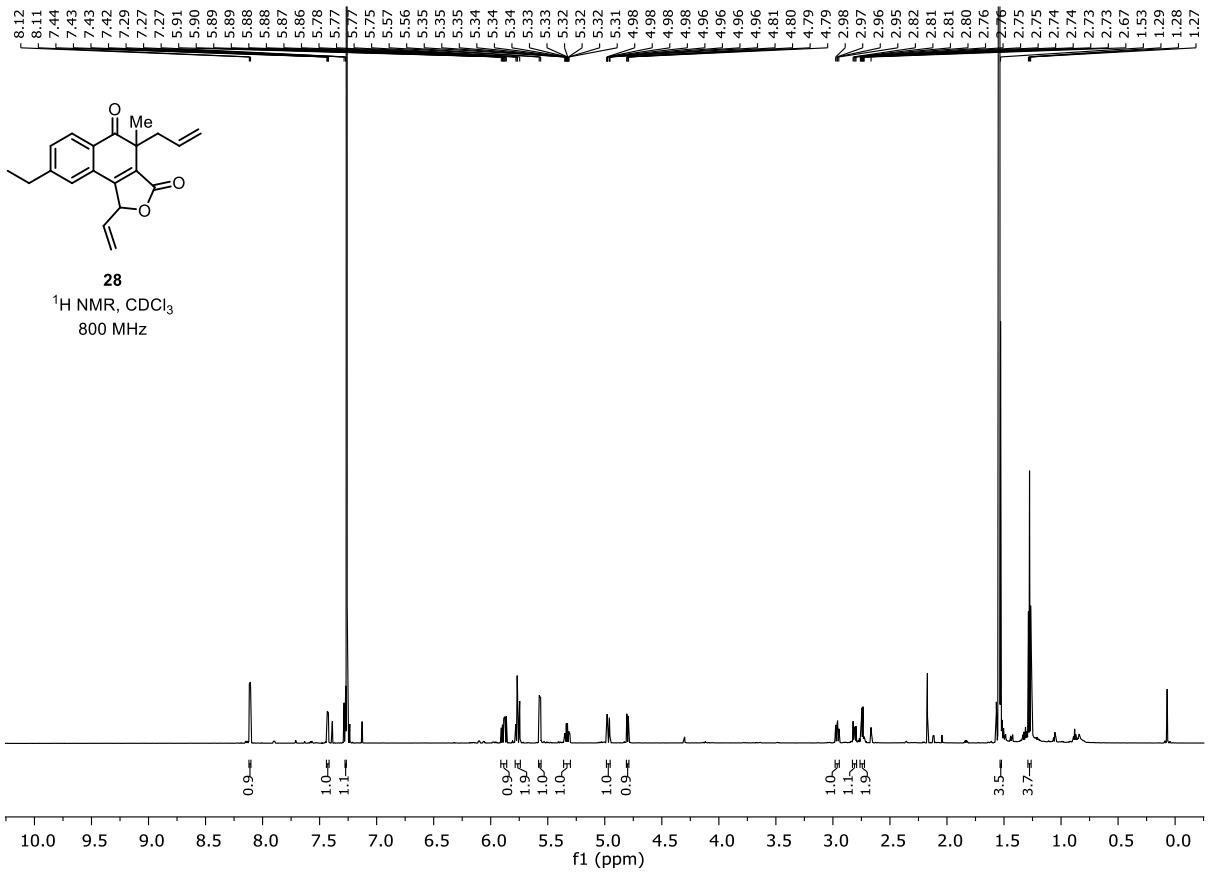
26
^{13}C NMR, $CDCl_3$
101 MHz

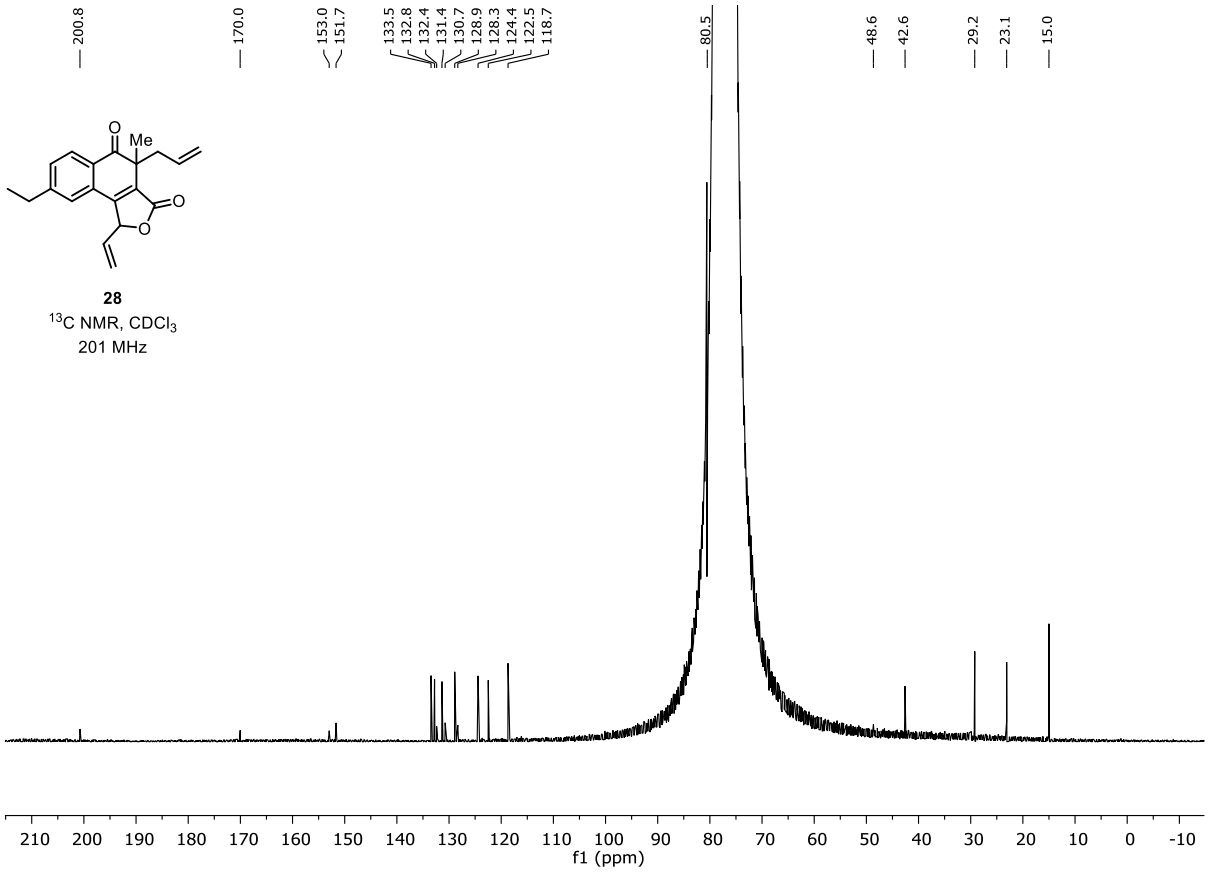


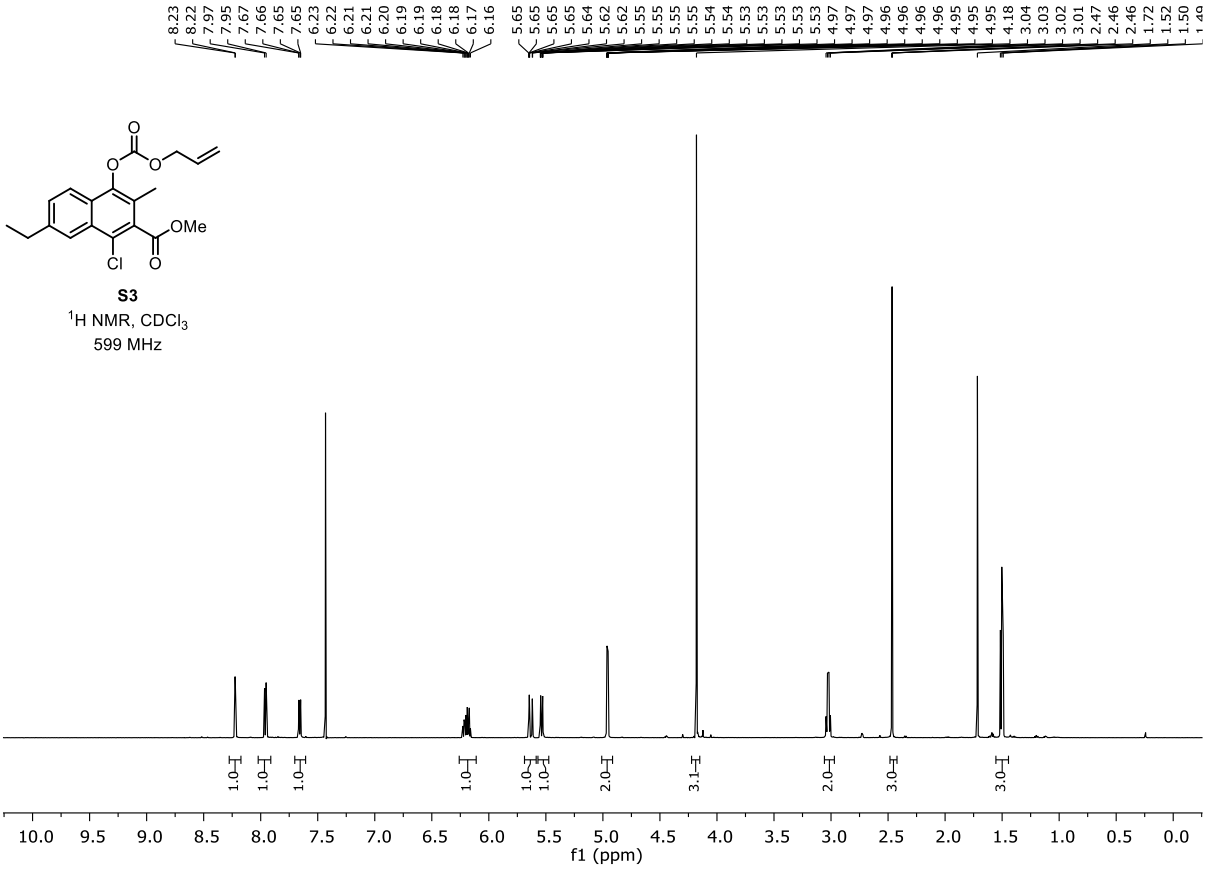
27
^{1}H NMR, $CDCl_3$
400 MHz

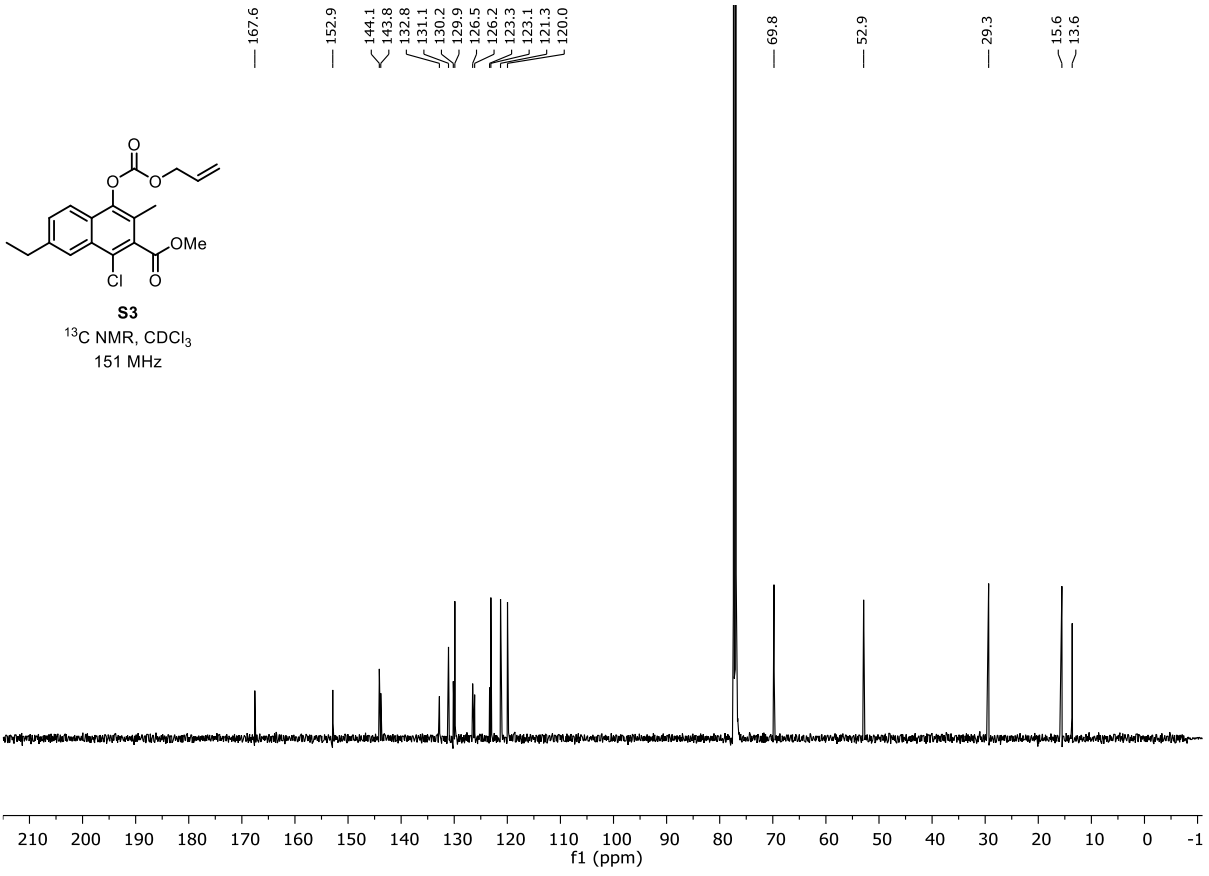


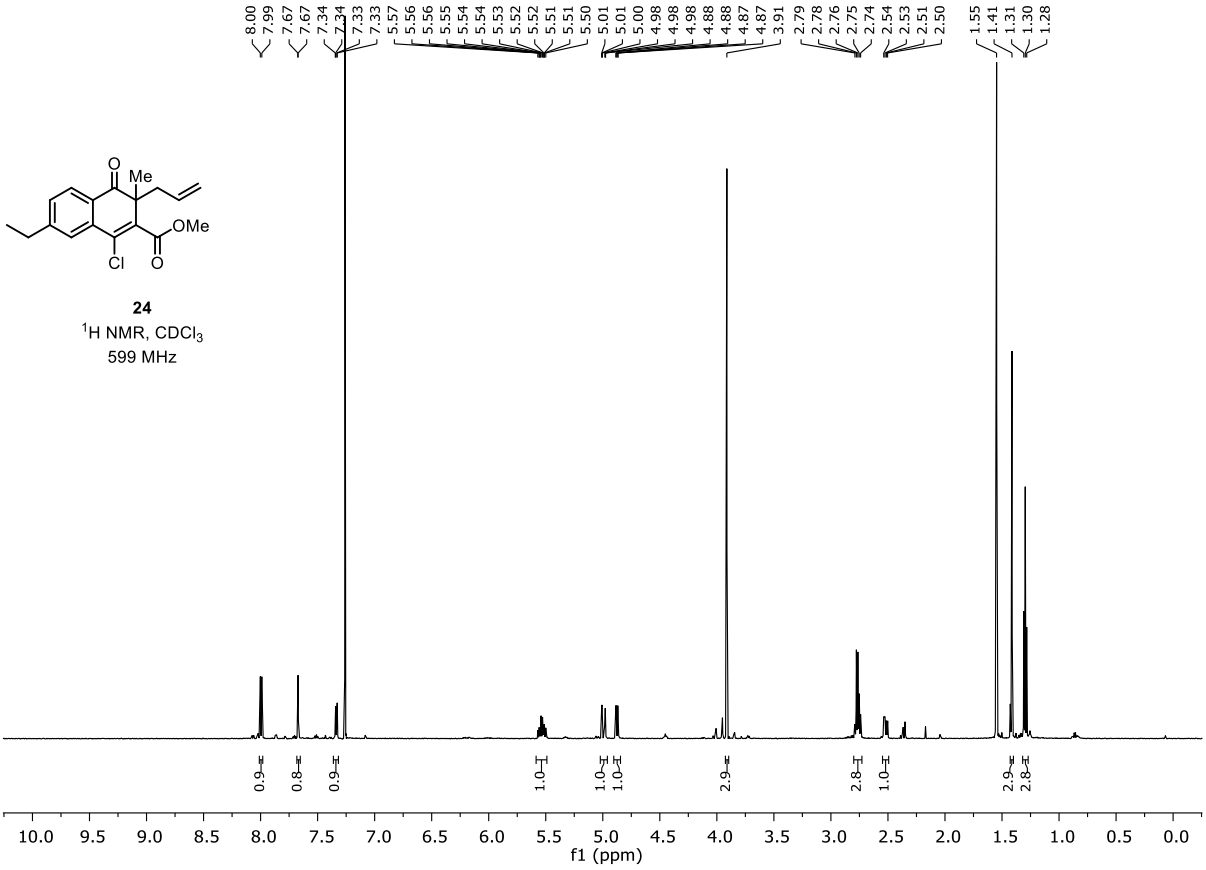
27
^{13}C NMR, $CDCl_3$
101 MHz


8.12 8.11 7.44 7.43 7.43 7.42 7.29 7.27 7.27 5.91 5.90 5.89 5.89 5.88 5.88 5.87 5.86 5.78 5.77 5.77 5.75 5.57 5.56 5.35 5.35 5.35 5.34 5.34 5.34 5.33 5.32 5.32 5.32 5.31 4.98 4.98 4.98 4.98 4.96 4.96 4.96 4.96 4.81 4.80 4.79 4.79 2.98 2.97 2.96 2.95 2.82 2.81 2.81 2.80 2.76 2.76 2.75 2.75 2.74 2.74 2.73 2.67 1.53 1.29 1.28 1.27
Me
O
O
O
28
^{1}H NMR, CDCl$_3$
800 MHz
0.9 1.0 1.1 0.9 1.9 1.0 1.0 1.0 0.9 1.0 1.1 1.9 3.5 3.7
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

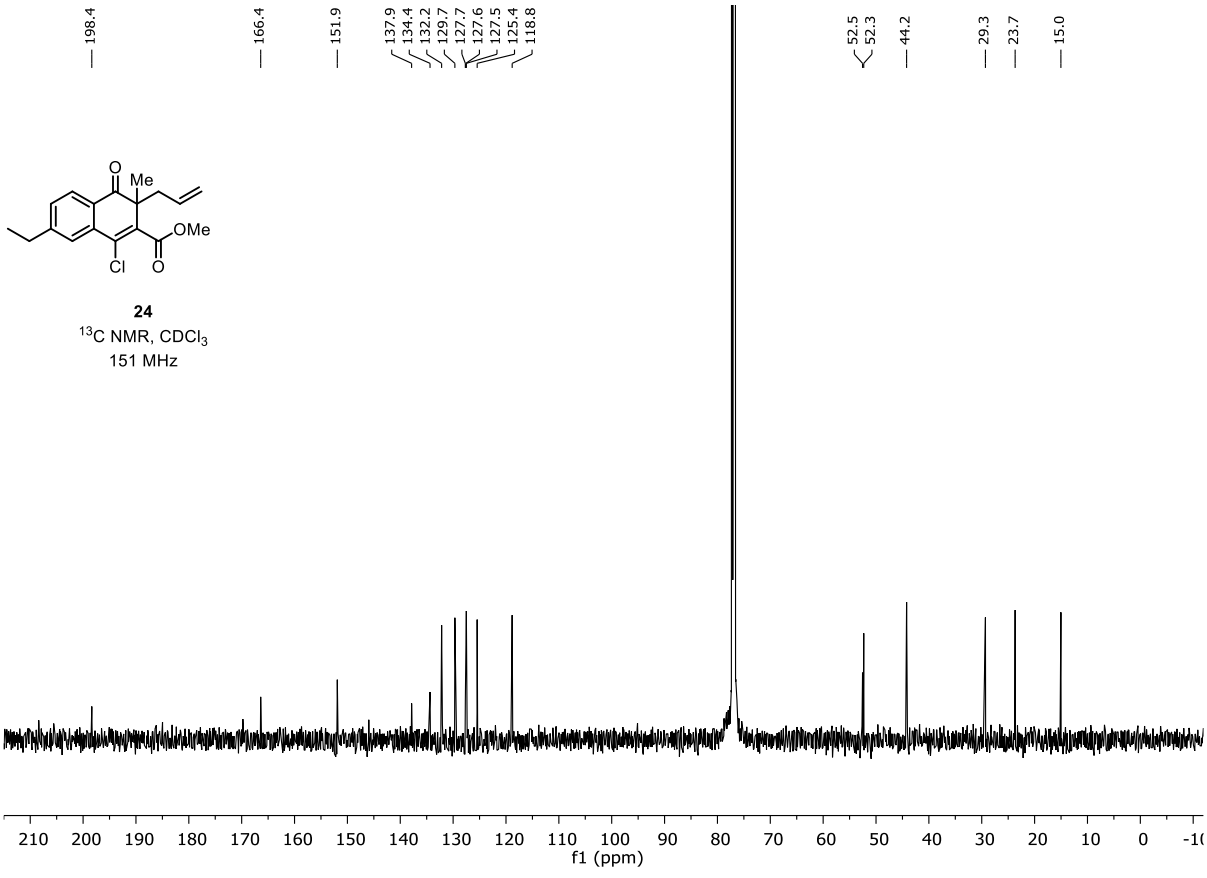

200.8 170.0 153.0 151.7 133.5 132.8 132.4 131.4 130.7 128.9 128.3 124.4 122.5 118.7 80.5 48.6 42.6 29.2 23.1 15.0
Me
O
O
O
28
^{13}C NMR, CDCl$_3$
201 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


S3
1H NMR, CDCl3
599 MHz
f1 (ppm)

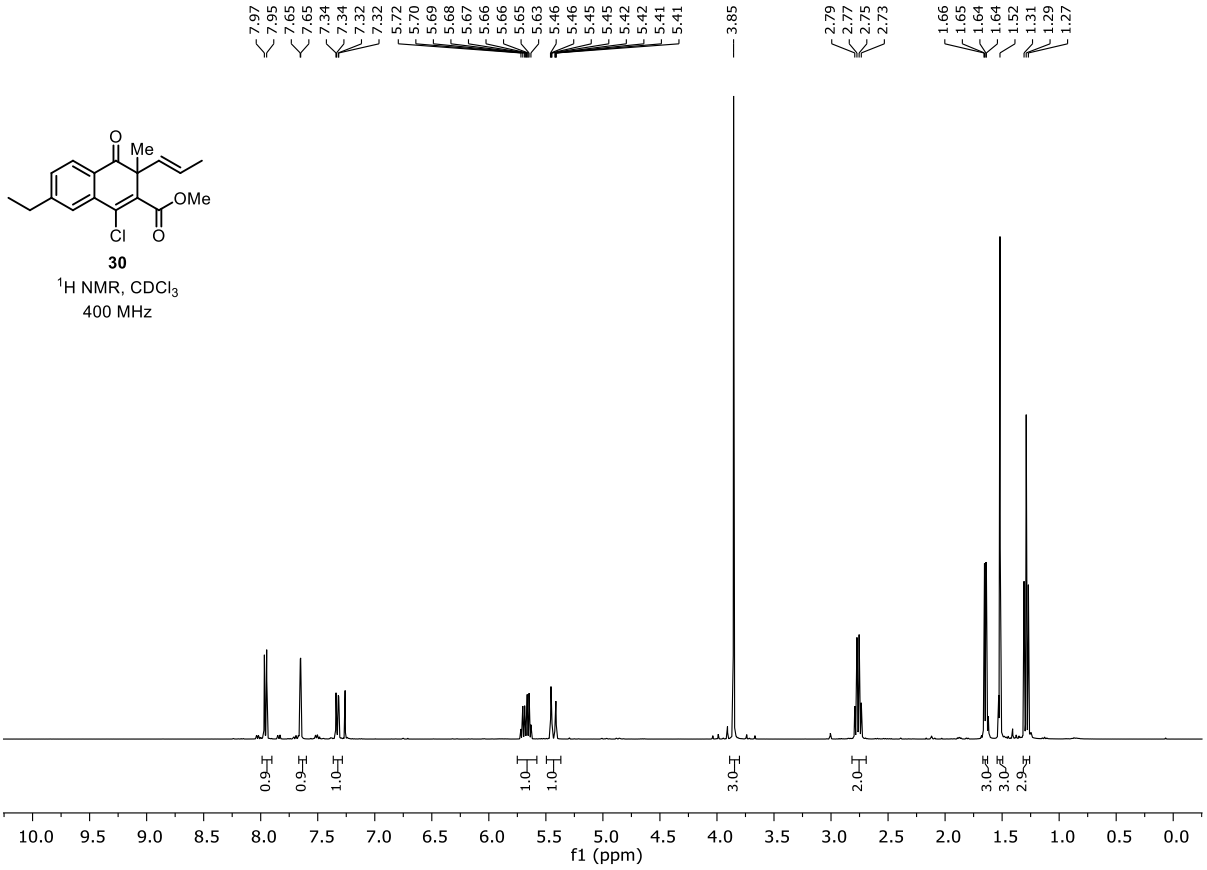

S3
13C NMR, CDCl3
151 MHz
f1 (ppm)

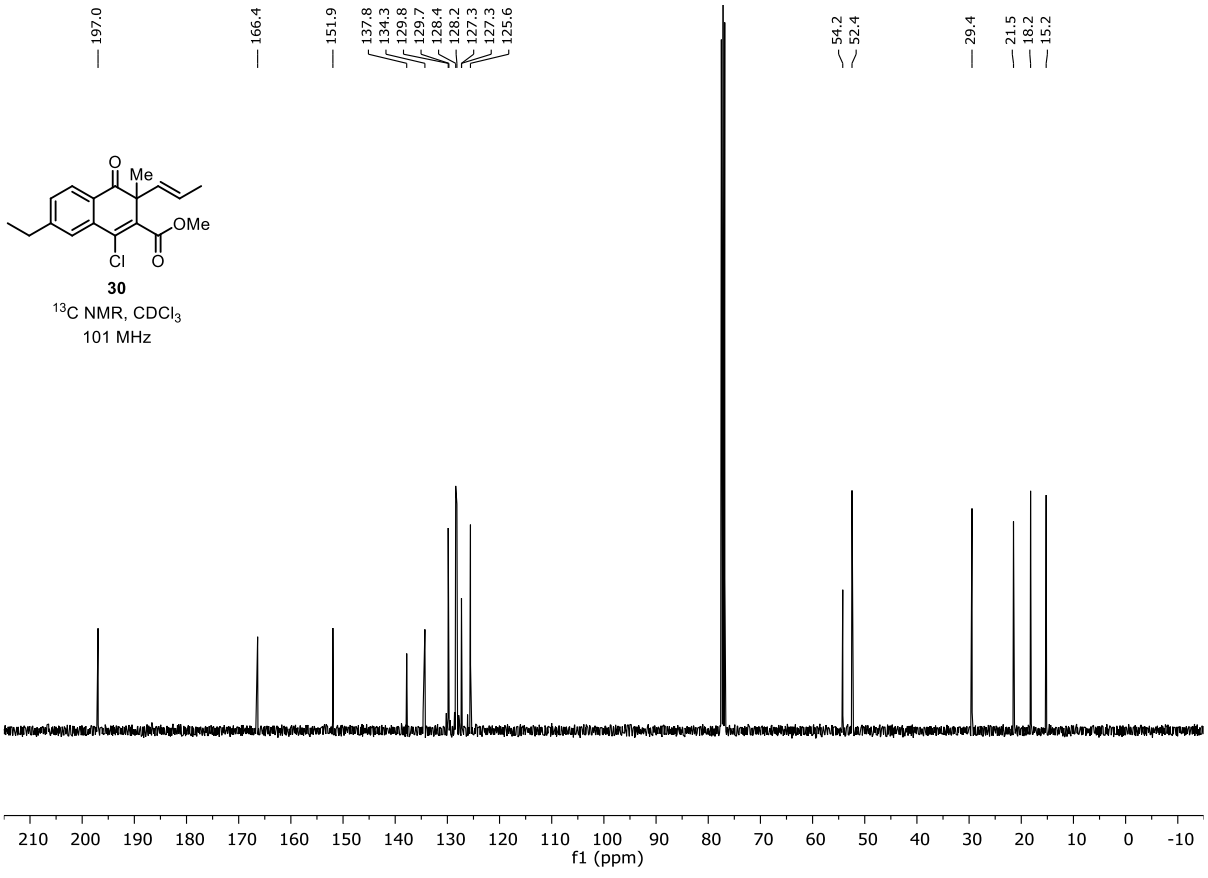


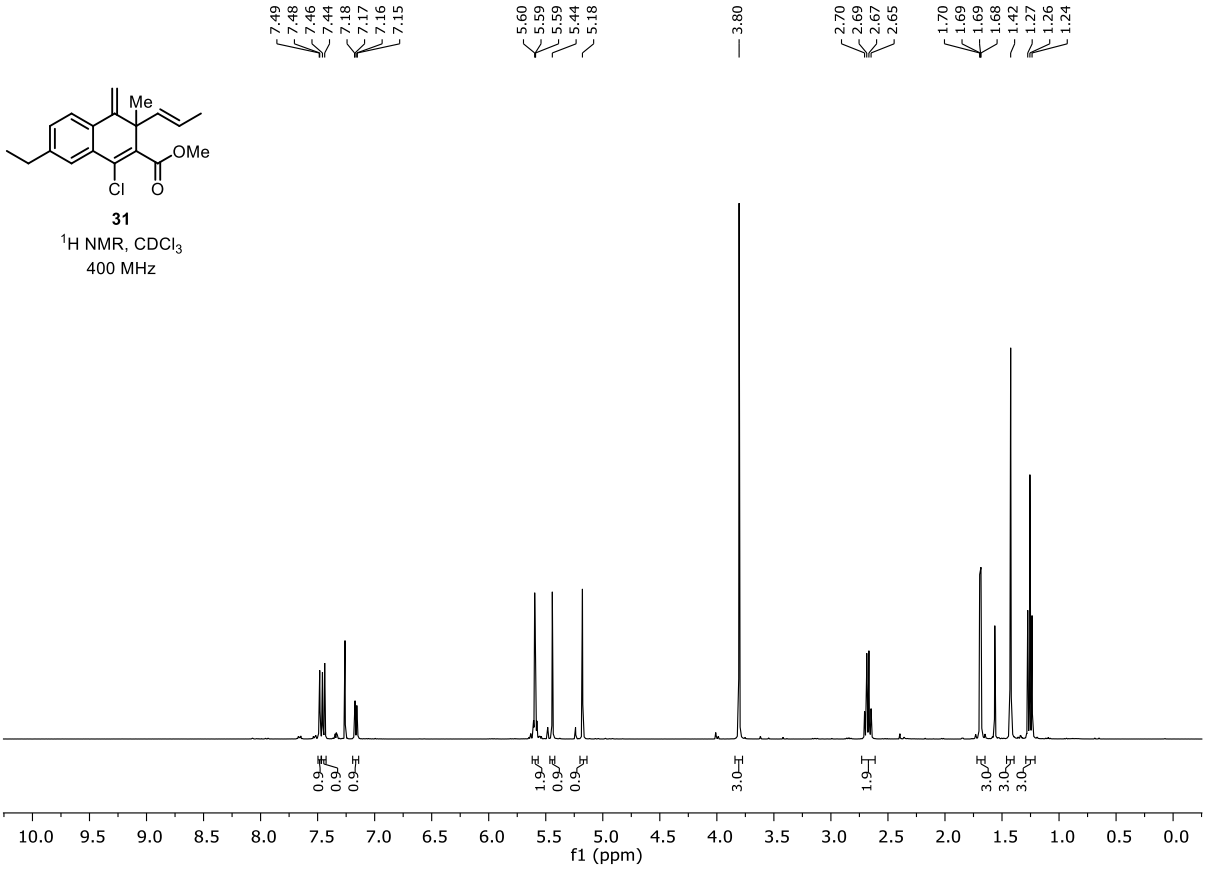
24
^{1}H NMR, $CDCl_3$
599 MHz



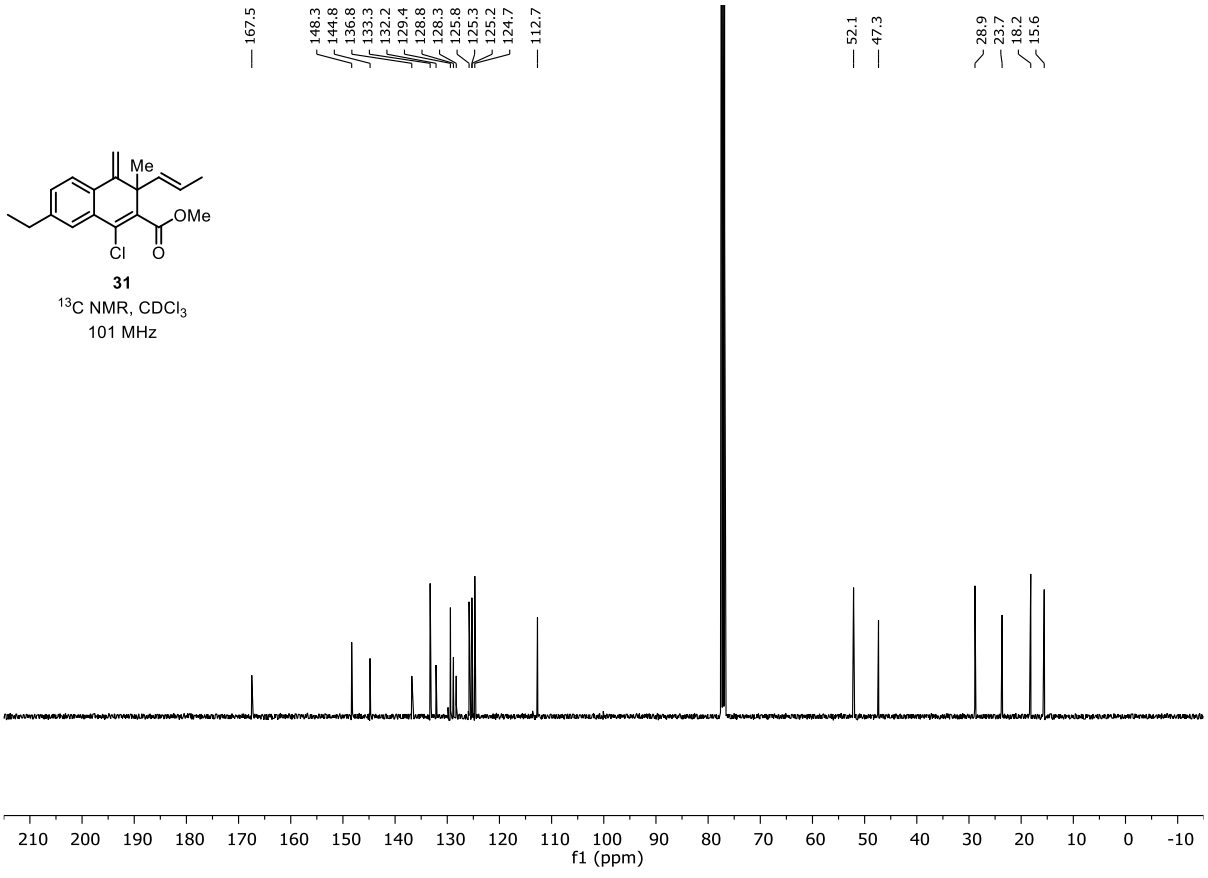
24
^{13}C NMR, $CDCl_3$
151 MHz


7.97
7.95
7.65
7.65
7.34
7.34
7.32
7.32
5.72
5.70
5.69
5.68
5.67
5.66
5.66
5.65
5.63
5.46
5.46
5.45
5.45
5.42
5.42
5.41
5.41
3.85
2.79
2.77
2.75
2.73
1.66
1.65
1.64
1.64
1.52
1.31
1.29
1.27
O
Me
OMe
Cl
O
30
1H NMR, CDCl3
400 MHz
0.9
0.9
1.0
1.0
1.0
3.0
2.0
3.0
3.0
2.9
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

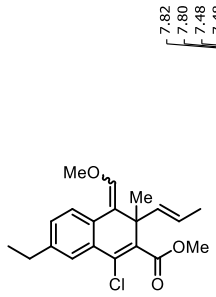

197.0
166.4
151.9
137.8
134.3
129.8
129.7
128.4
128.2
127.3
127.3
125.6
54.2
52.4
29.4
21.5
18.2
15.2
O
Me
OMe
Cl
O
30
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



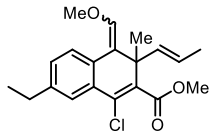
31
^{1}H NMR, $CDCl_3$
400 MHz



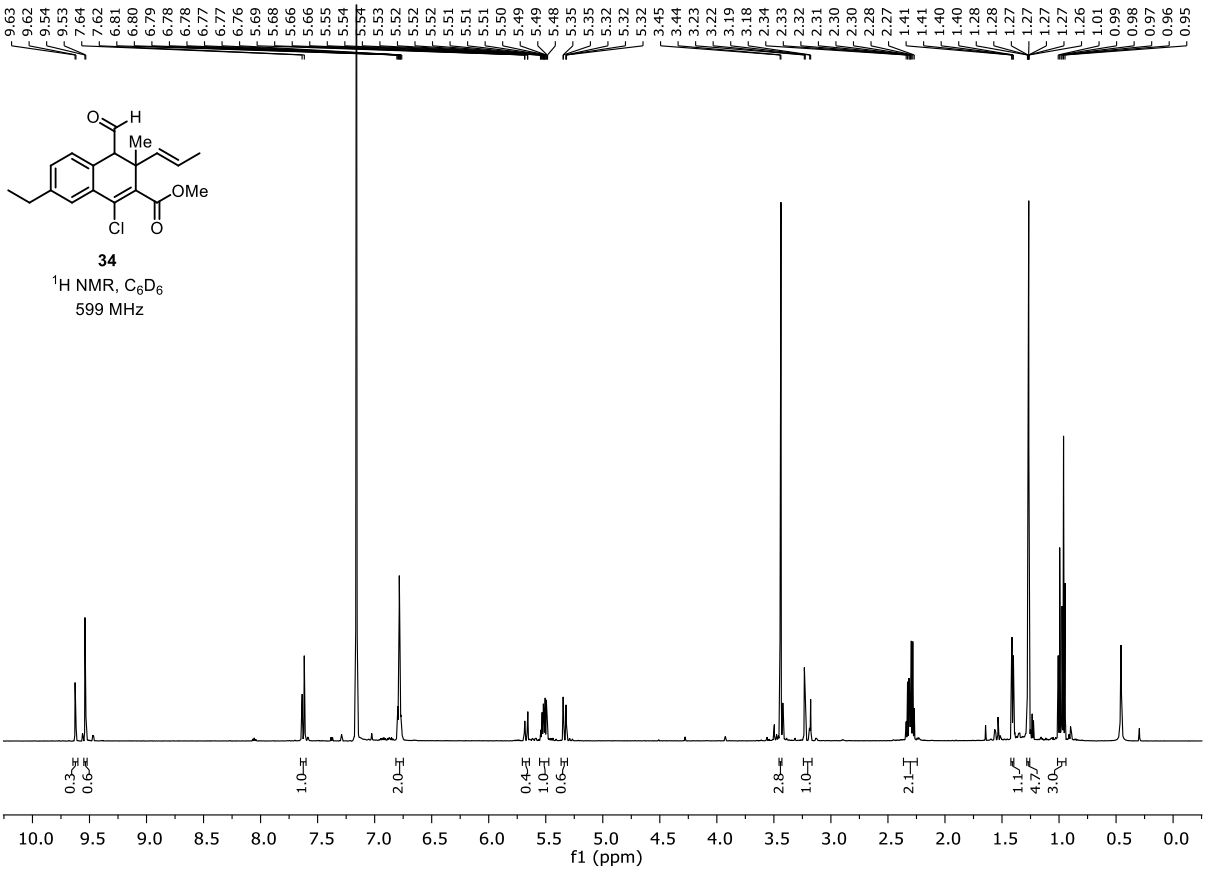
31
^{13}C NMR, $CDCl_3$
101 MHz

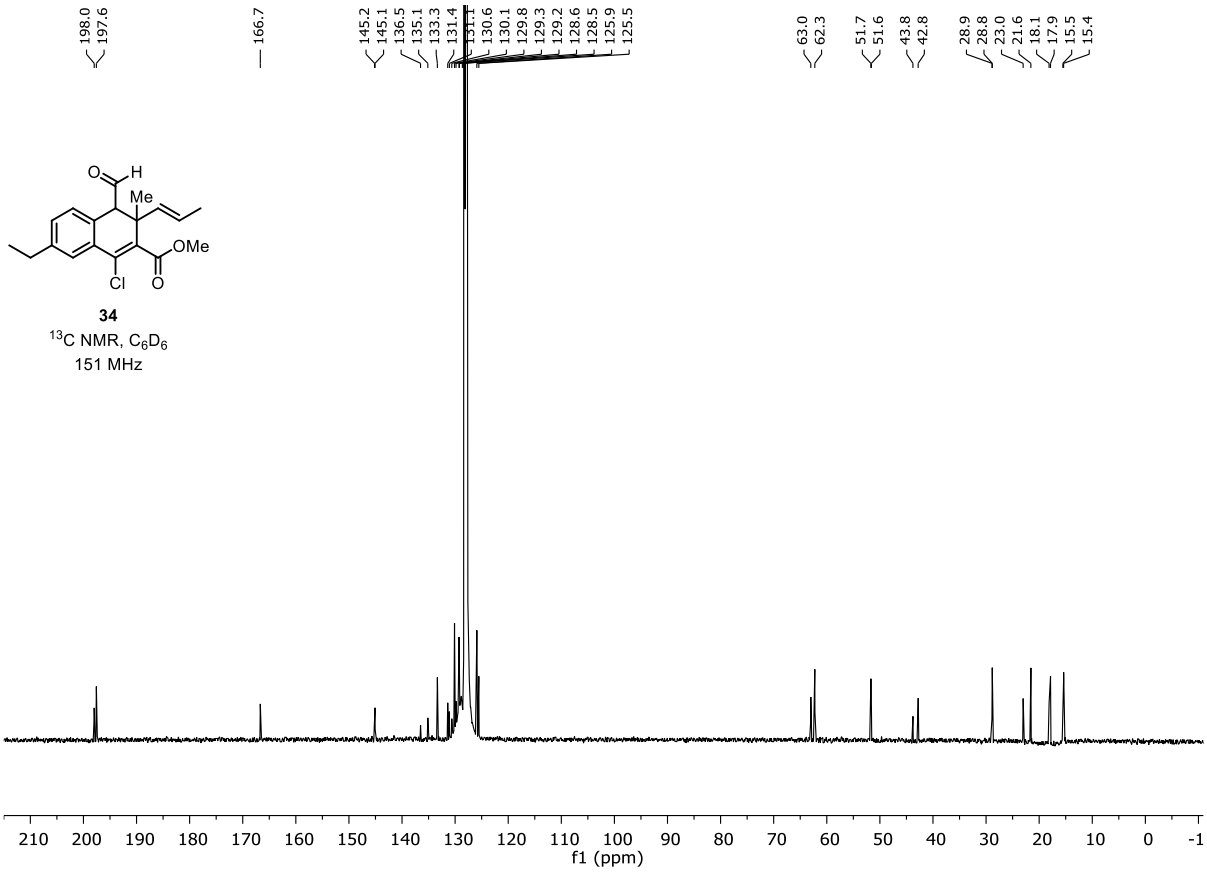


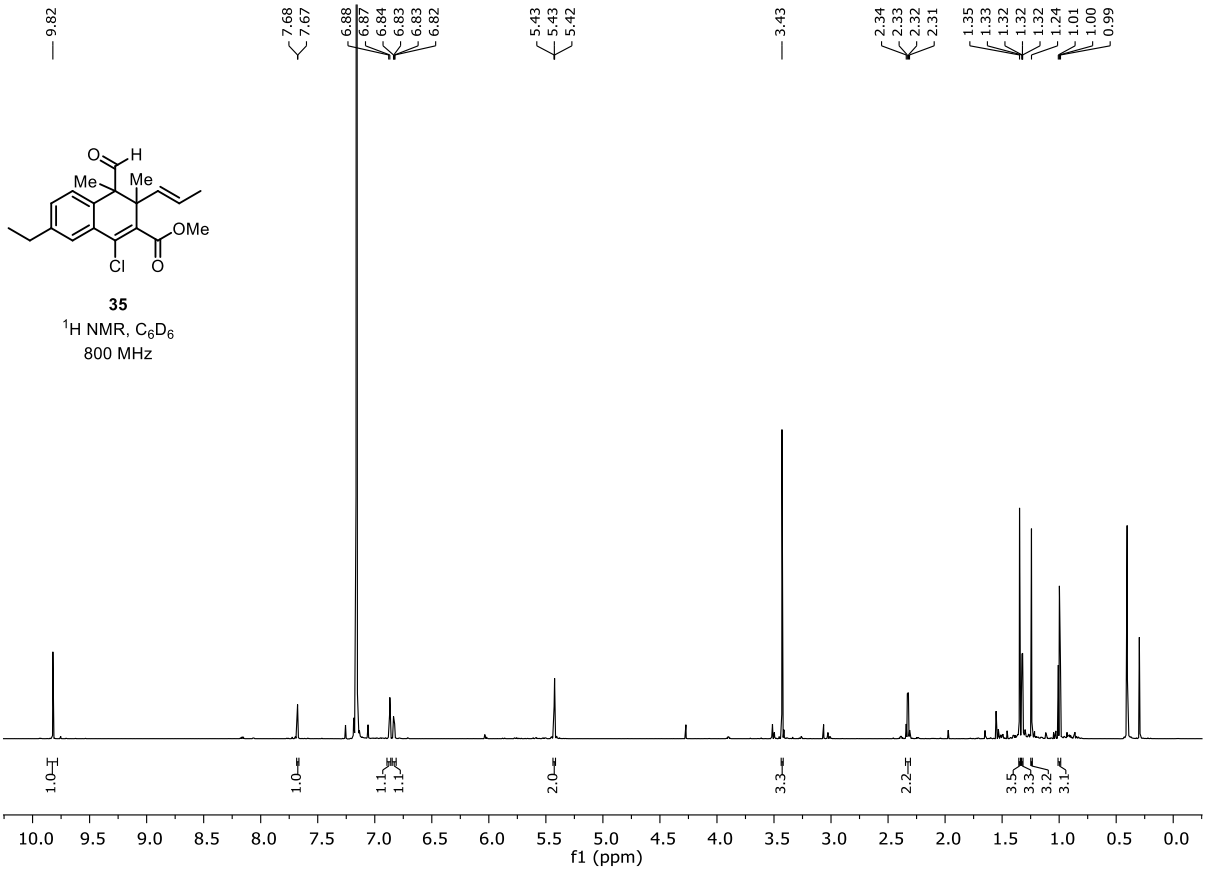
S4
^{1}H NMR, $CDCl_3$
400 MHz



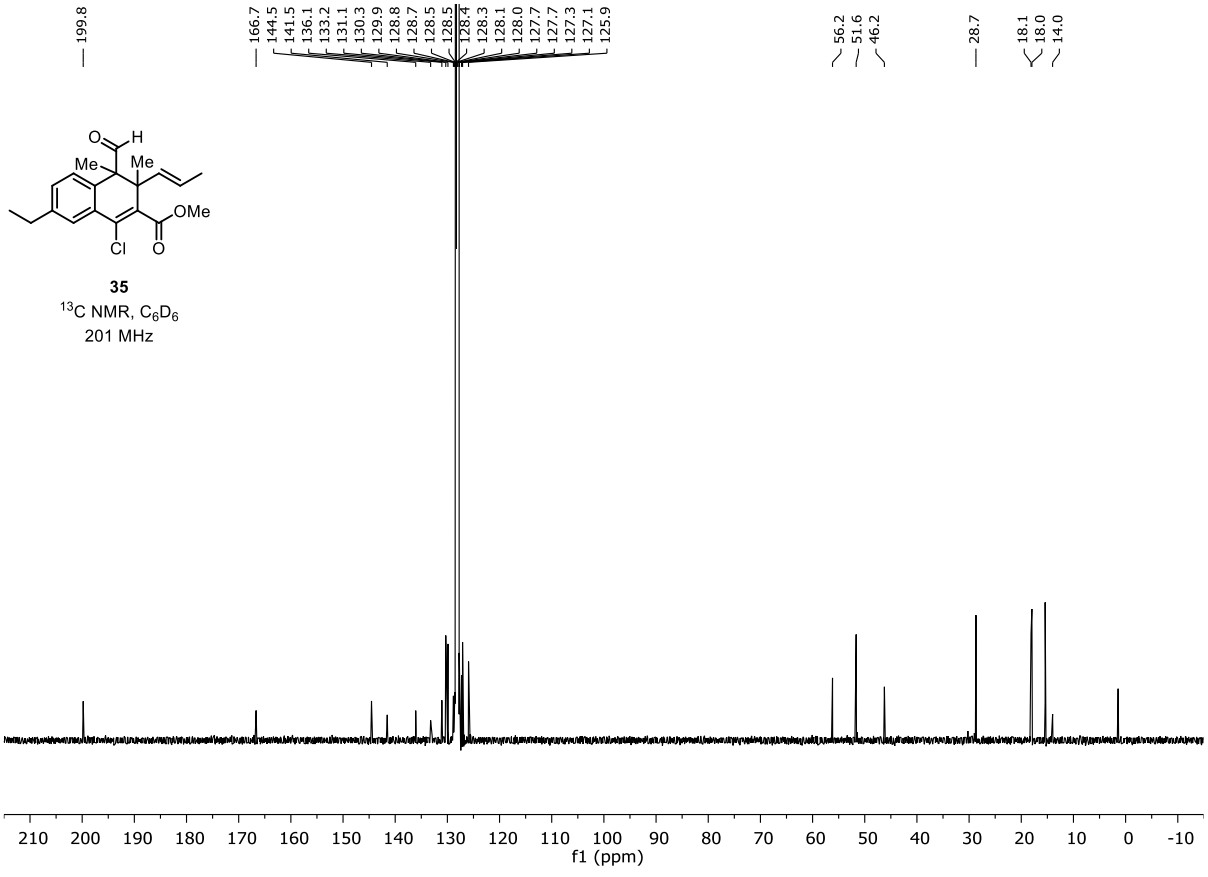
S4
^{13}C NMR, $CDCl_3$
101 MHz


9.63 9.62 9.54 9.53 7.64 7.62 6.81 6.80 6.79 6.78 6.78 6.77 6.77 6.76 5.69 5.68 5.66 5.66 5.55 5.54 5.54 5.53 5.52 5.52 5.52 5.51 5.51 5.51 5.50 5.49 5.49 5.48 5.35 5.35 5.32 5.32 5.32 3.45 3.44 3.23 3.22 3.19 3.18 2.34 2.33 2.32 2.31 2.30 2.30 2.28 2.27 1.41 1.41 1.40 1.40 1.28 1.28 1.27 1.27 1.27 1.27 1.26 1.01 0.99 0.98 0.97 0.96 0.95
O H
Me
OMe
Cl O
34
1H NMR, C6D6
599 MHz
0.3 0.6 1.0 2.0 0.4 1.0 0.6 2.8 1.0 2.1 1.1 4.7 3.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

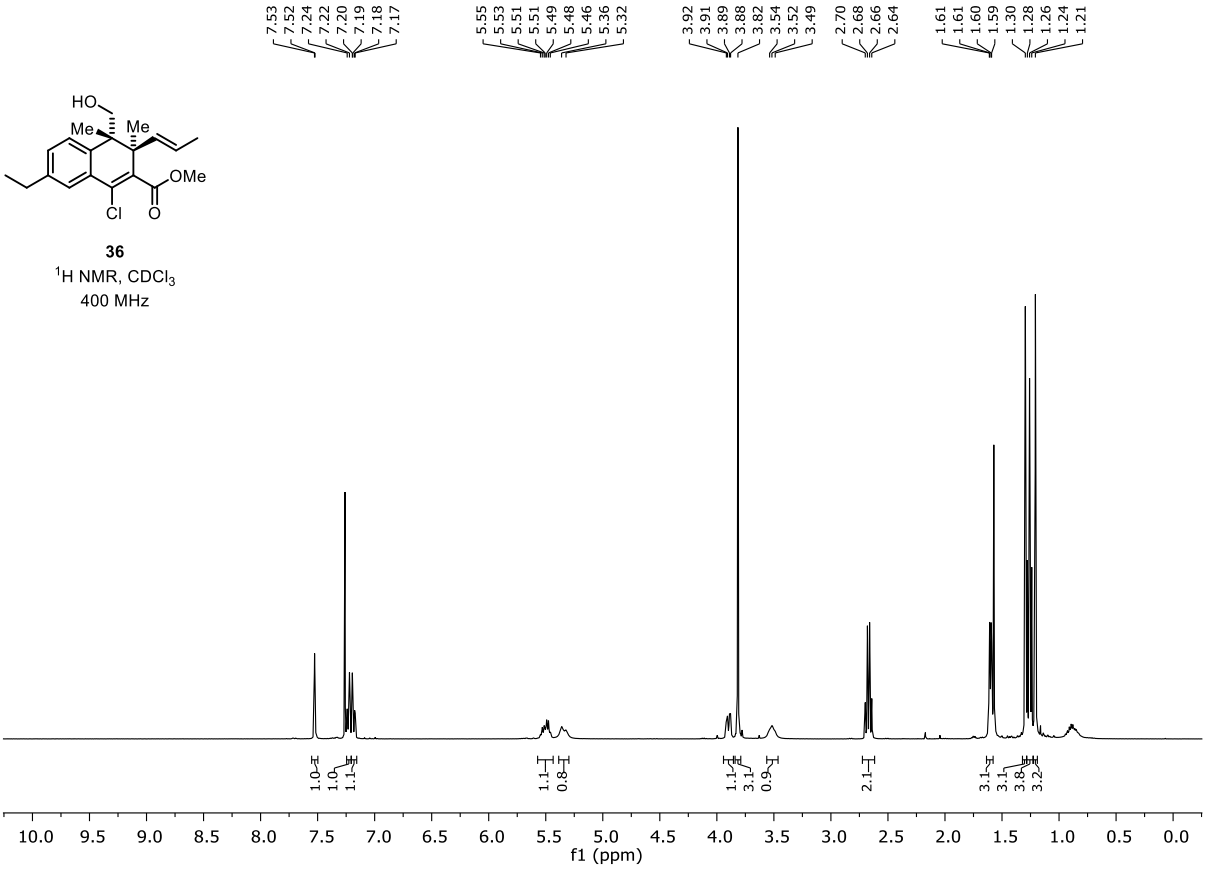

198.0 197.6 166.7 145.2 145.1 136.5 135.1 133.3 131.4 131.1 130.6 130.1 129.8 129.3 129.2 128.6 128.5 125.9 125.5 63.0 62.3 51.7 51.6 43.8 42.8 28.9 28.8 23.0 21.6 18.1 17.9 15.5 15.4
O H
Me
OMe
Cl O
34
13C NMR, C6D6
151 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)



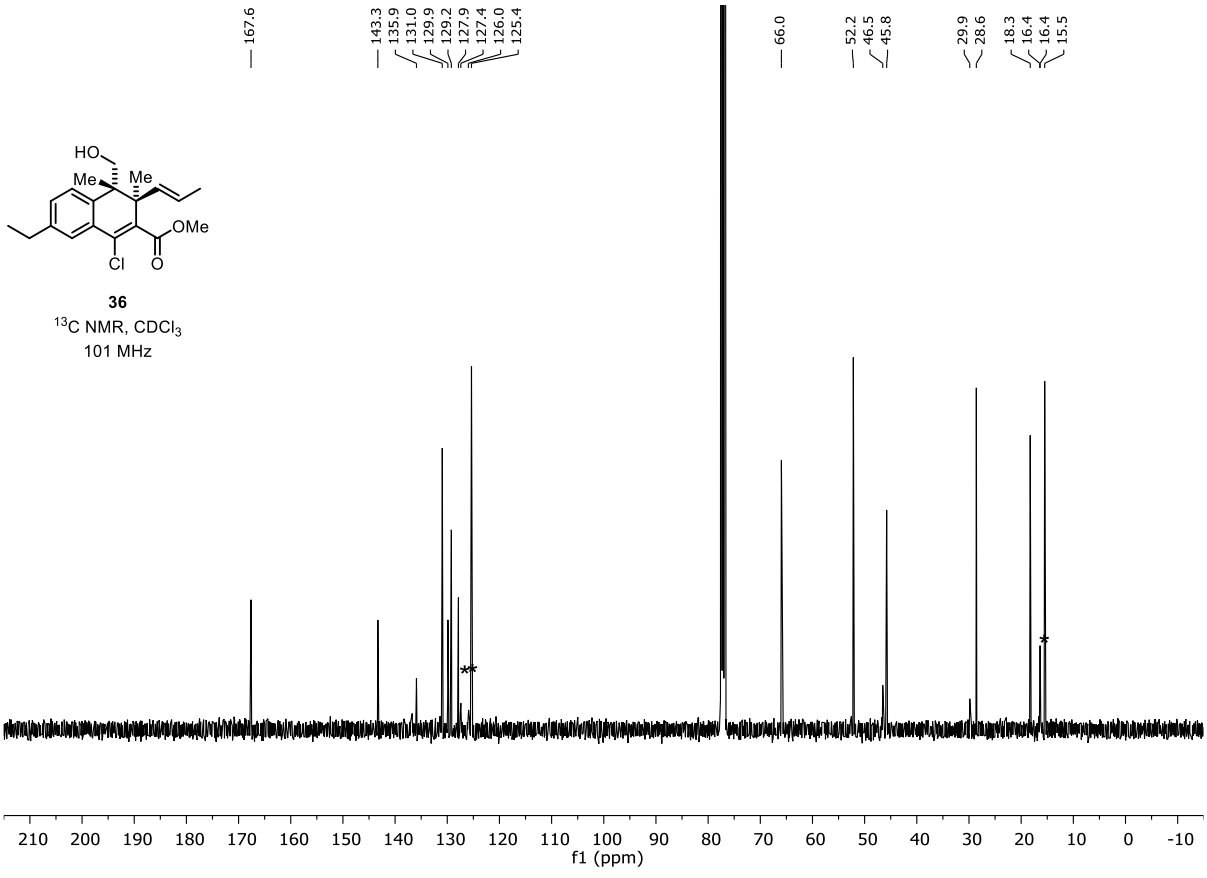
35
^{1}H NMR, C_6D_6
800 MHz



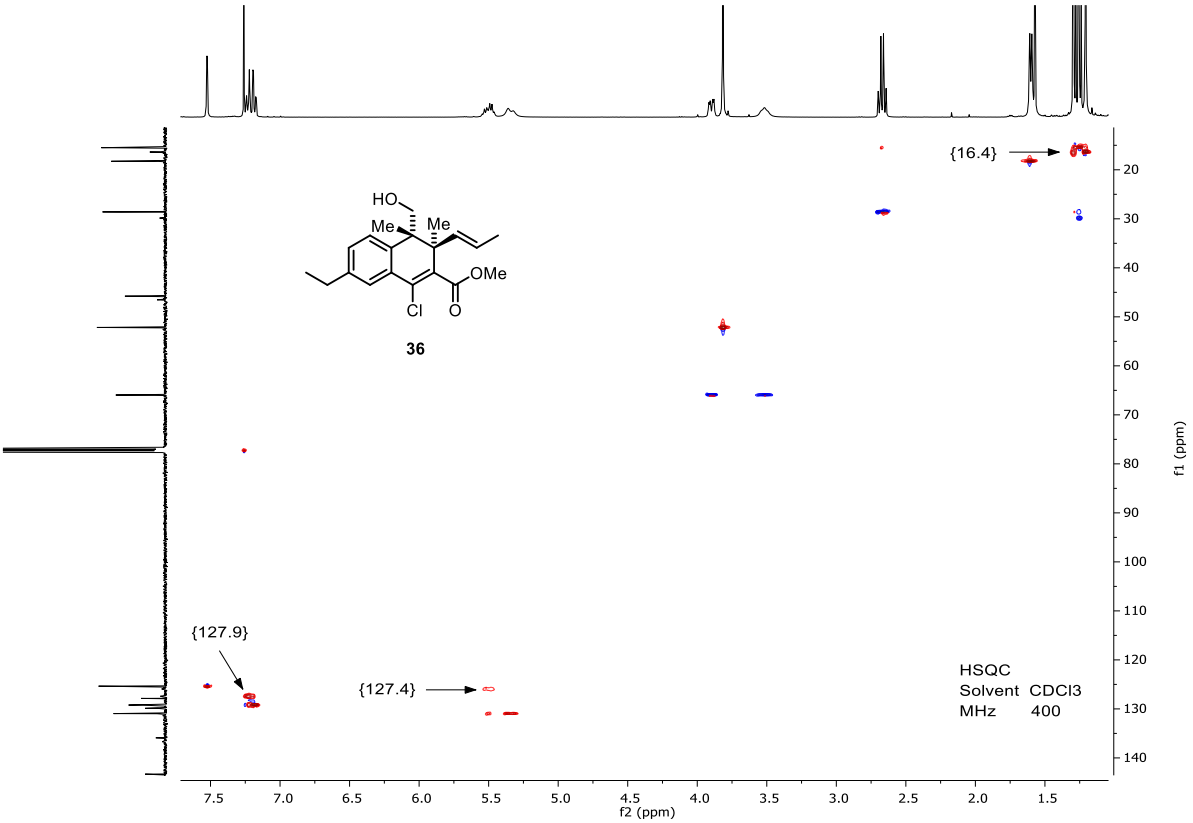
35
^{13}C NMR, C_6D_6
201 MHz

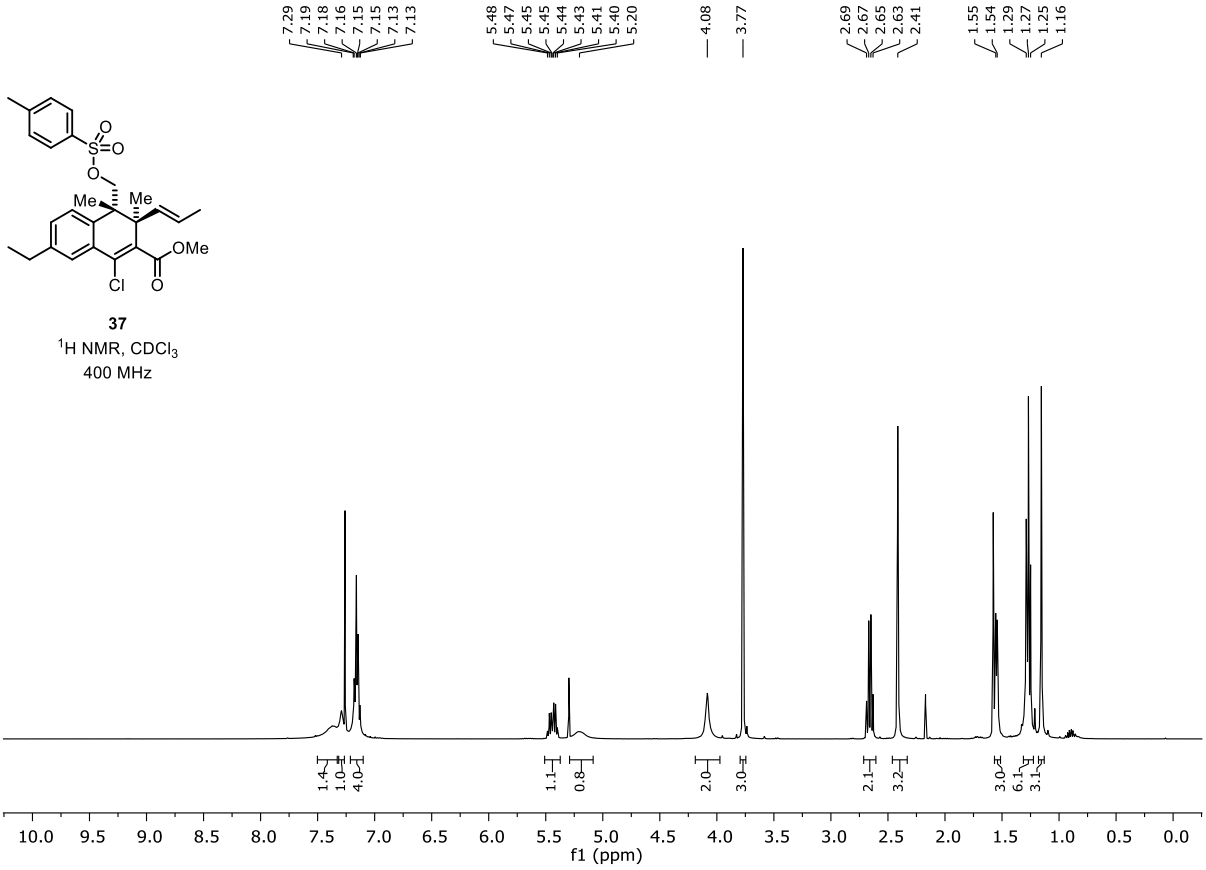


36
^{1}H NMR, $CDCl_3$
400 MHz

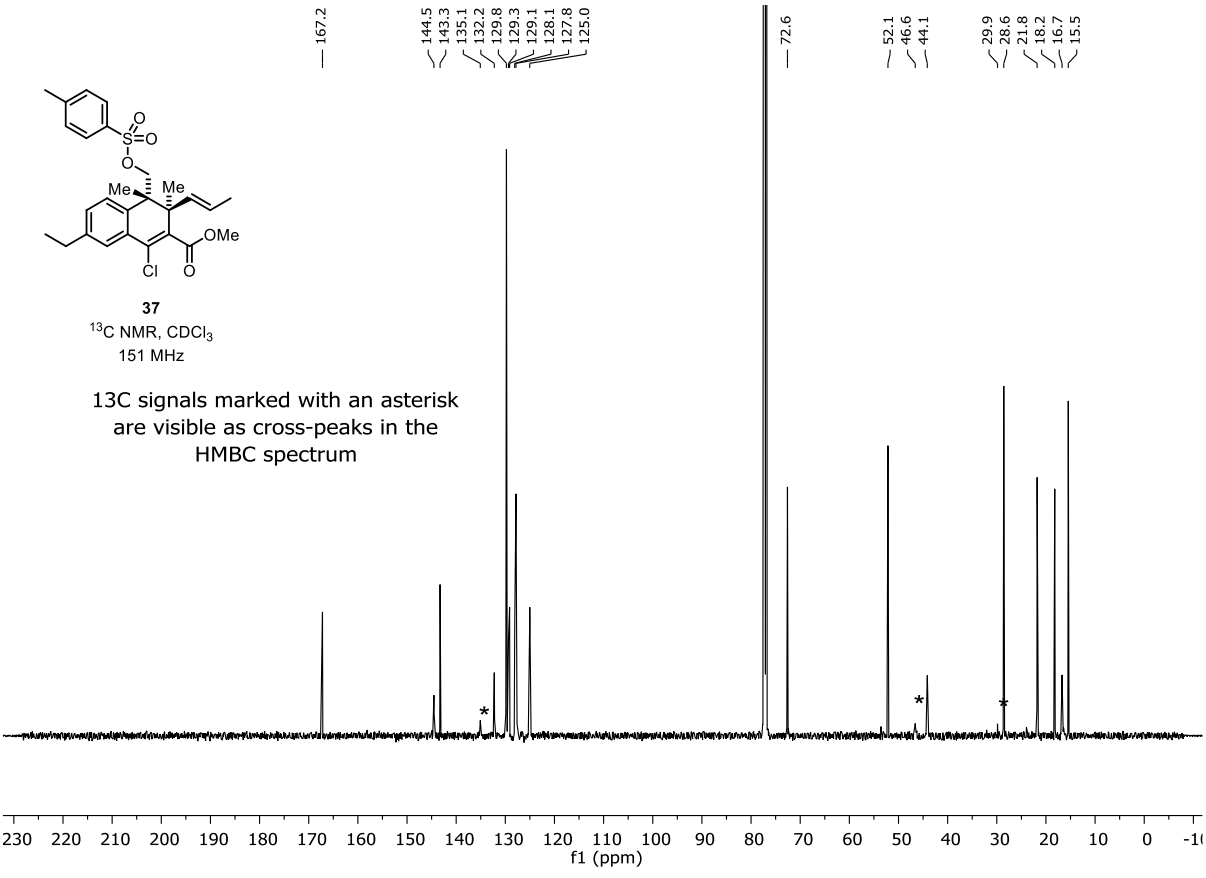


36
^{13}C NMR, $CDCl_3$
101 MHz


HO
Me
Me
OMe
Cl
O
36
{16.4}
{127.9}
{127.4}
HSQC
Solvent CDCl3
MHz 400
f2 (ppm)
f1 (ppm)

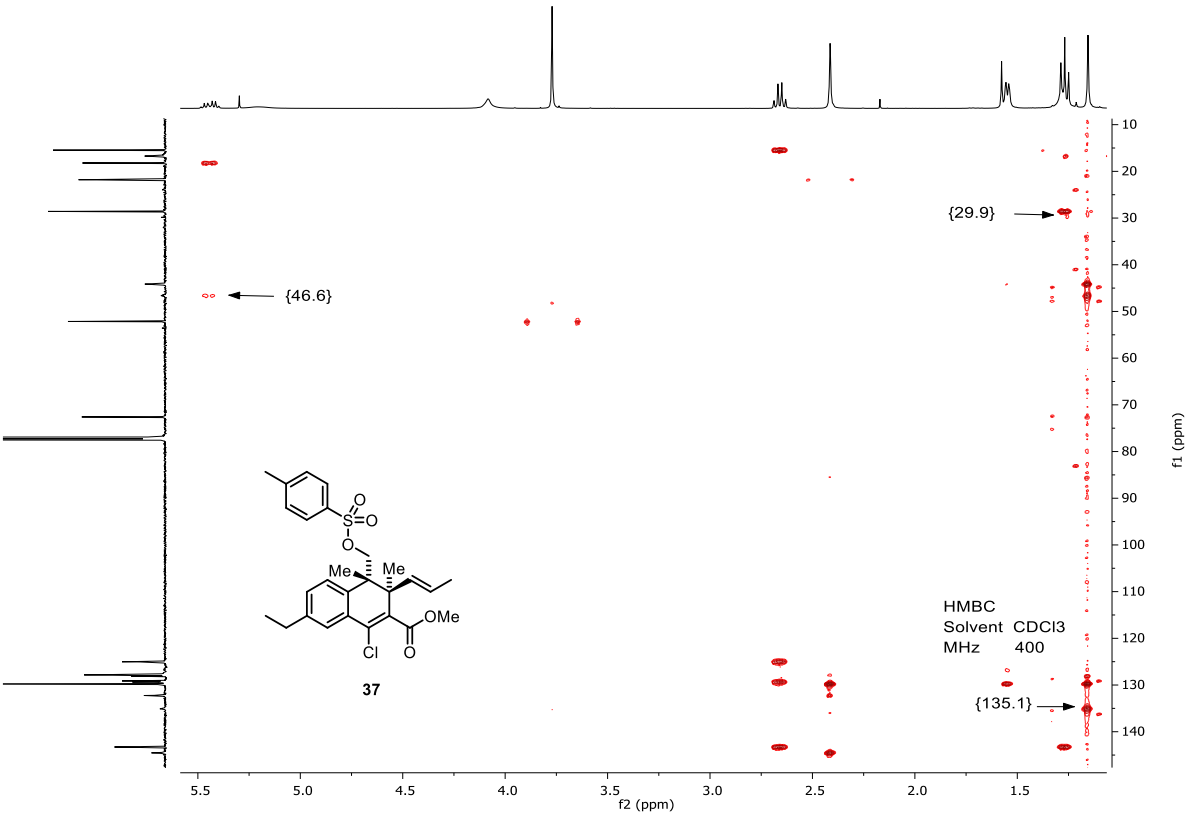


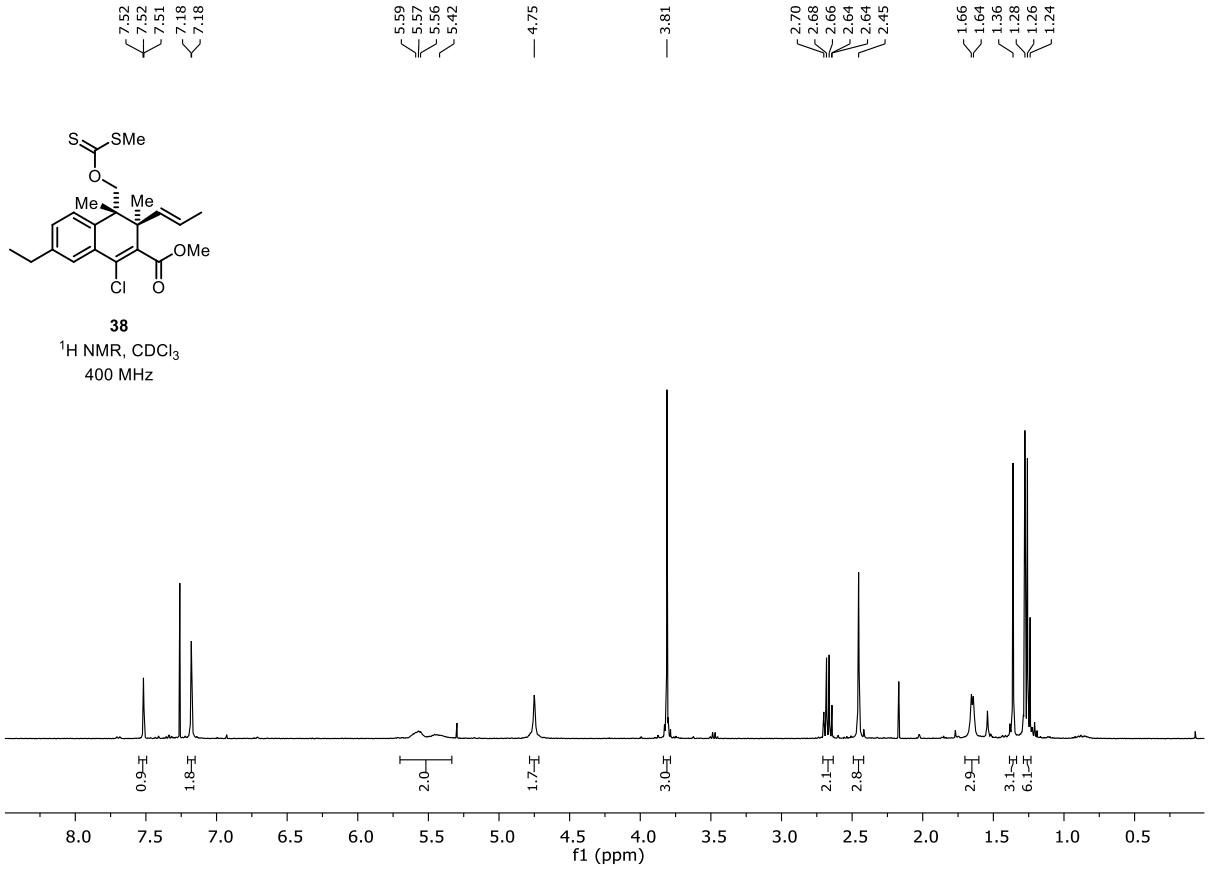
37
^{1}H NMR, $CDCl_3$
400 MHz



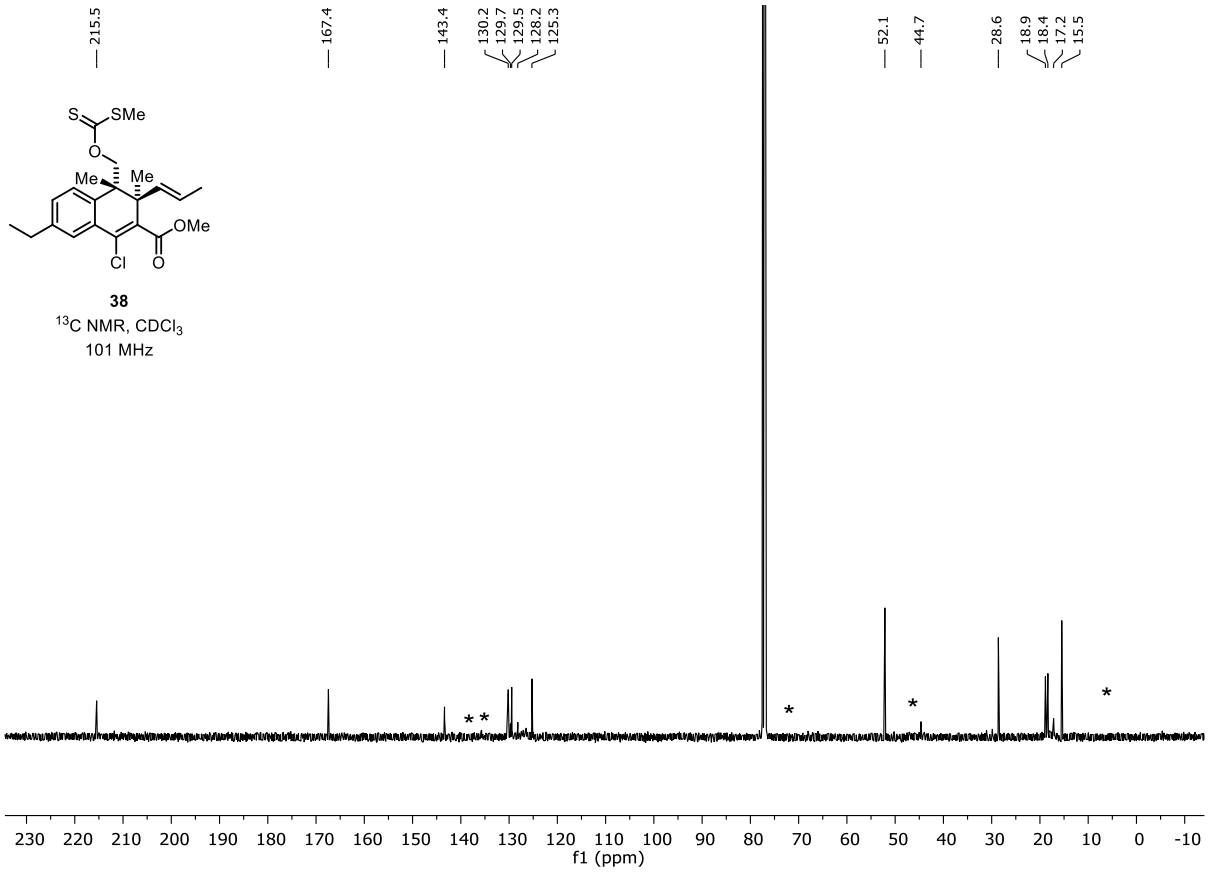
37
^{13}C NMR, $CDCl_3$
151 MHz

13C signals marked with an asterisk are visible as cross-peaks in the HMBC spectrum

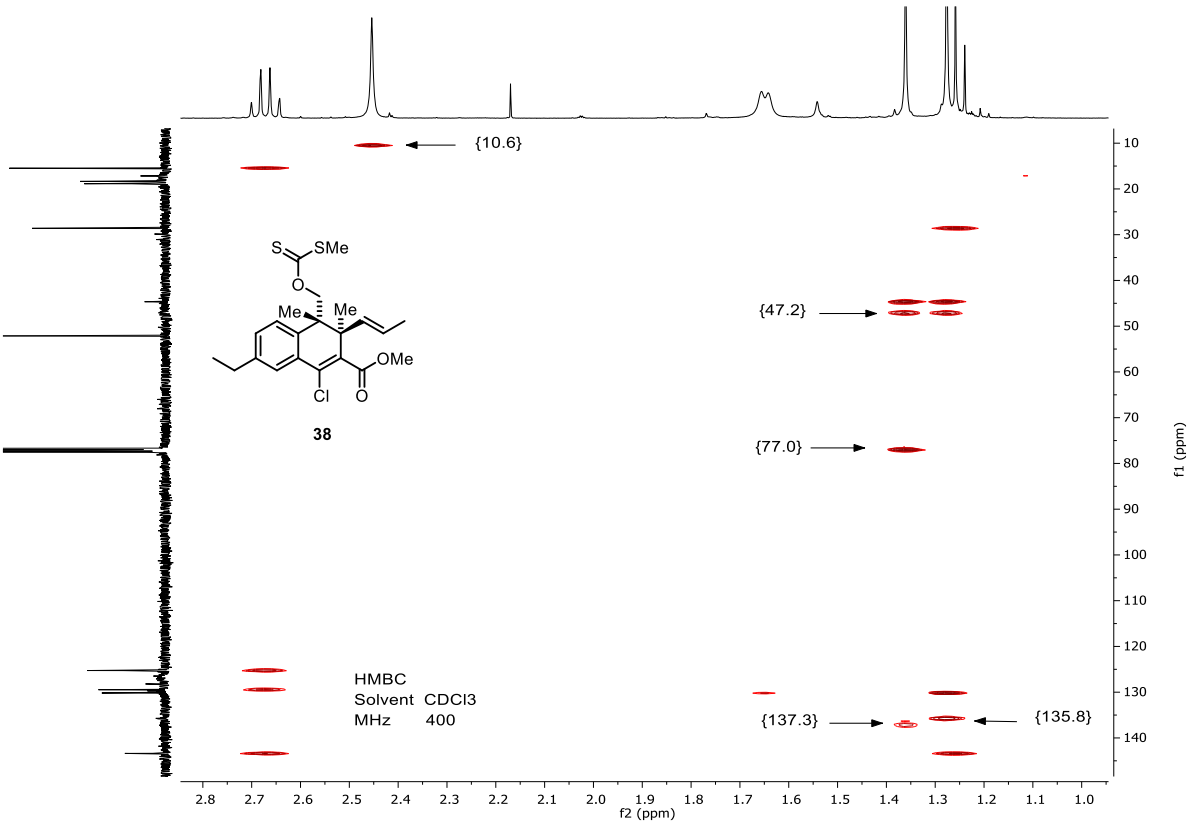

{29.9}
{46.6}
{135.1}
HMBC
Solvent CDCl3
MHz 400
Me
Me
OMe
Cl
O
S
O
O
37
f2 (ppm)
f1 (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
10
20
30
40
50
60
70
80
90
100
110
120
130
140

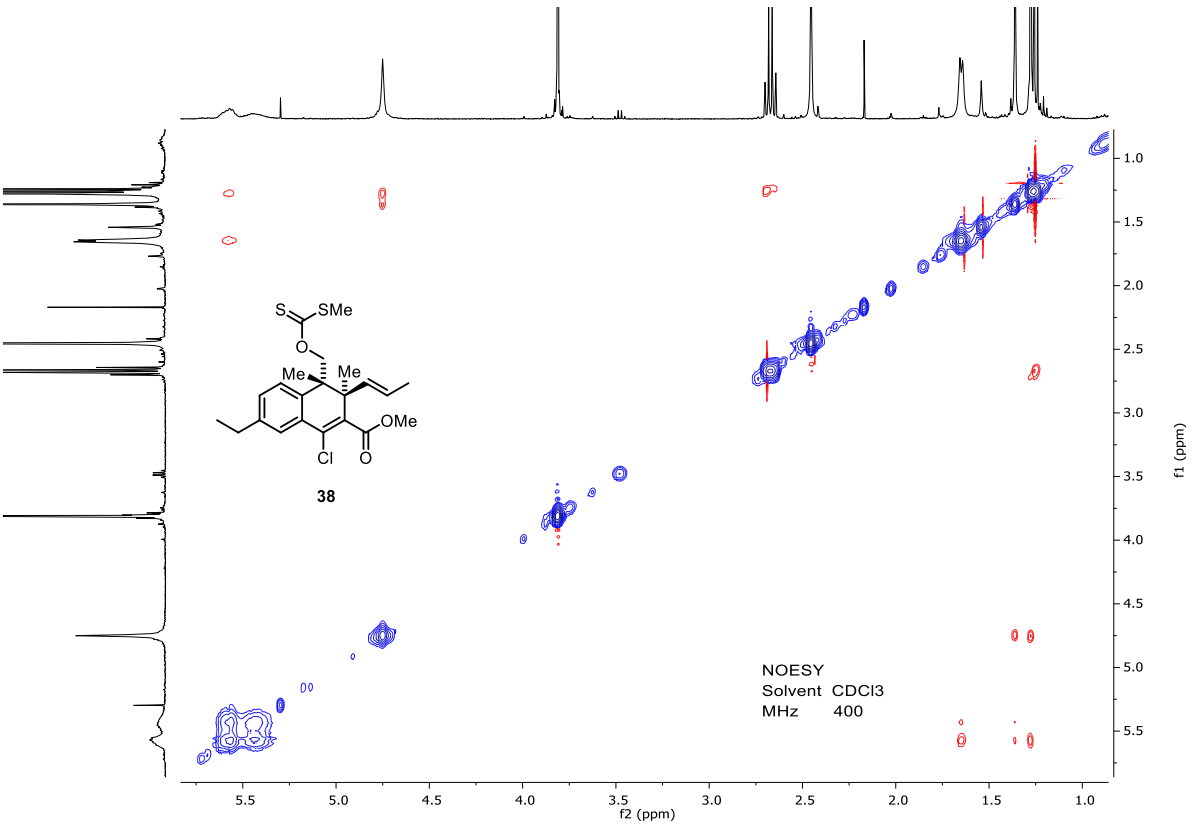


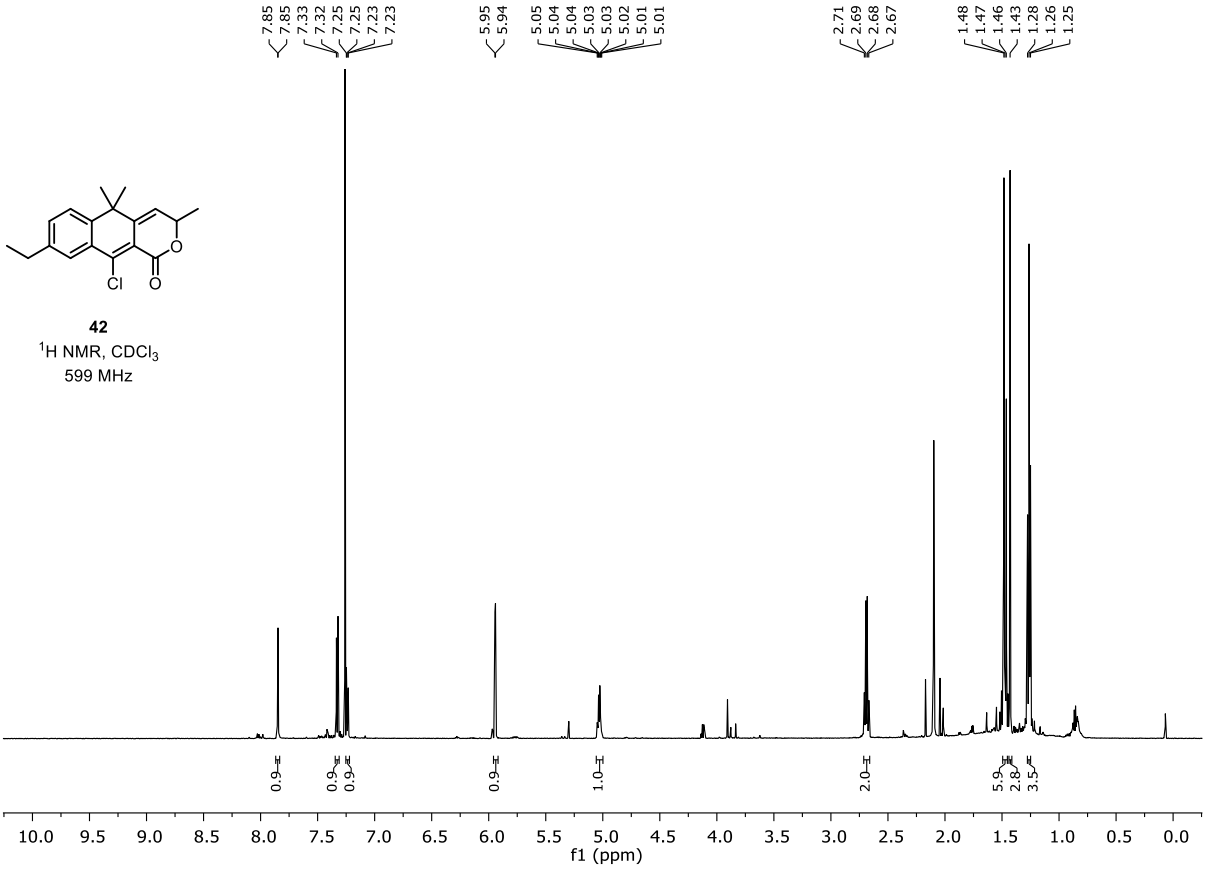
38
^{1}H NMR, $CDCl_3$
400 MHz



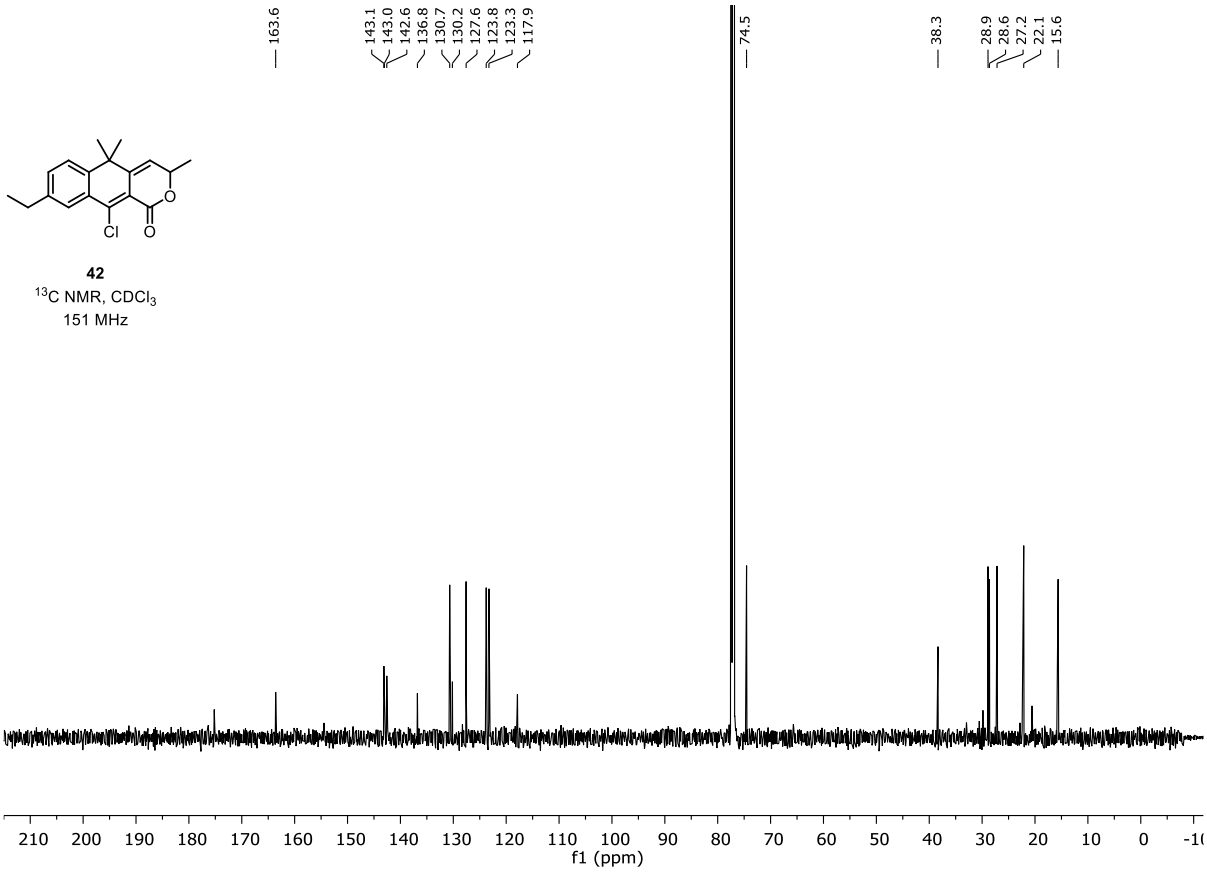
38
^{13}C NMR, $CDCl_3$
101 MHz


{10.6}
{47.2}
{77.0}
{137.3}
{135.8}
HMBC
Solvent CDCl3
MHz 400
38
f2 (ppm)
f1 (ppm)

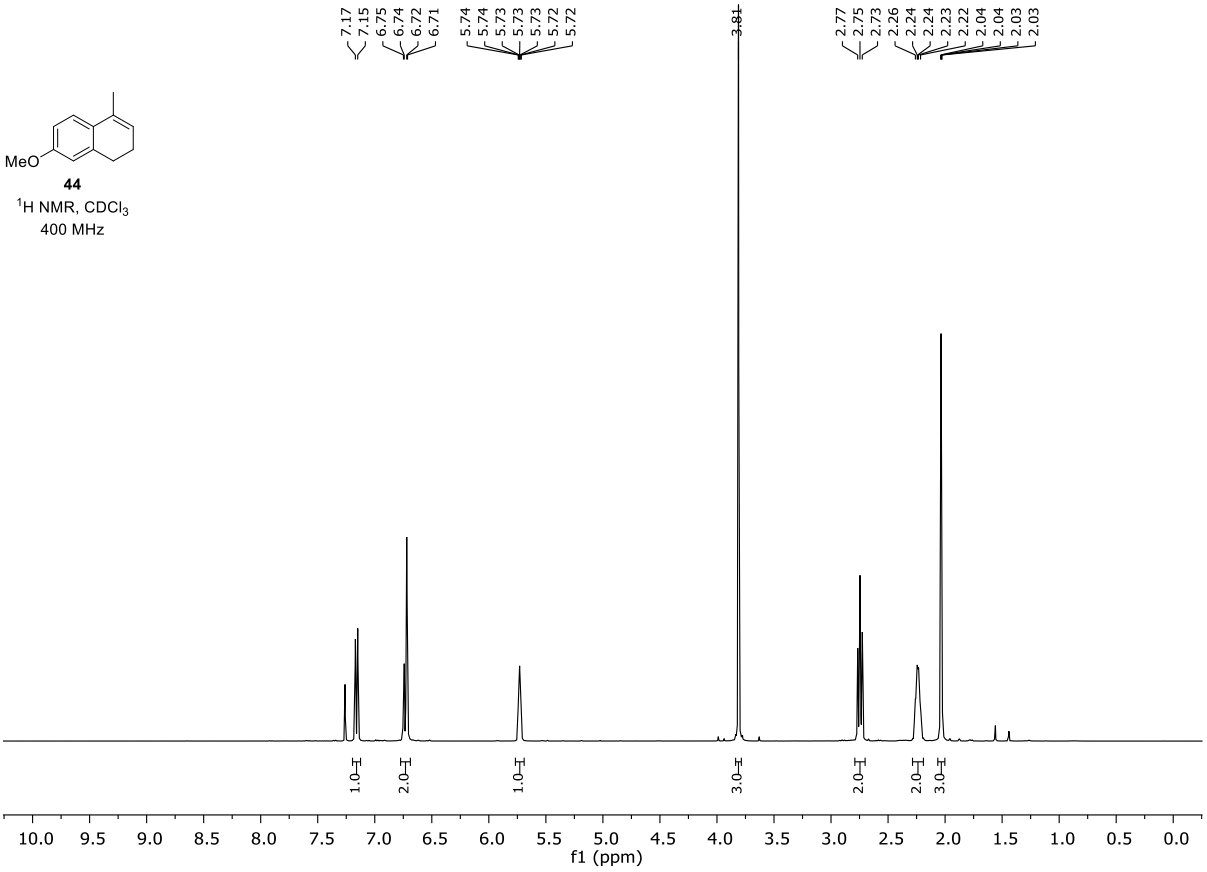

NOESY
Solvent CDCl3
MHz 400
38
f2 (ppm)
f1 (ppm)

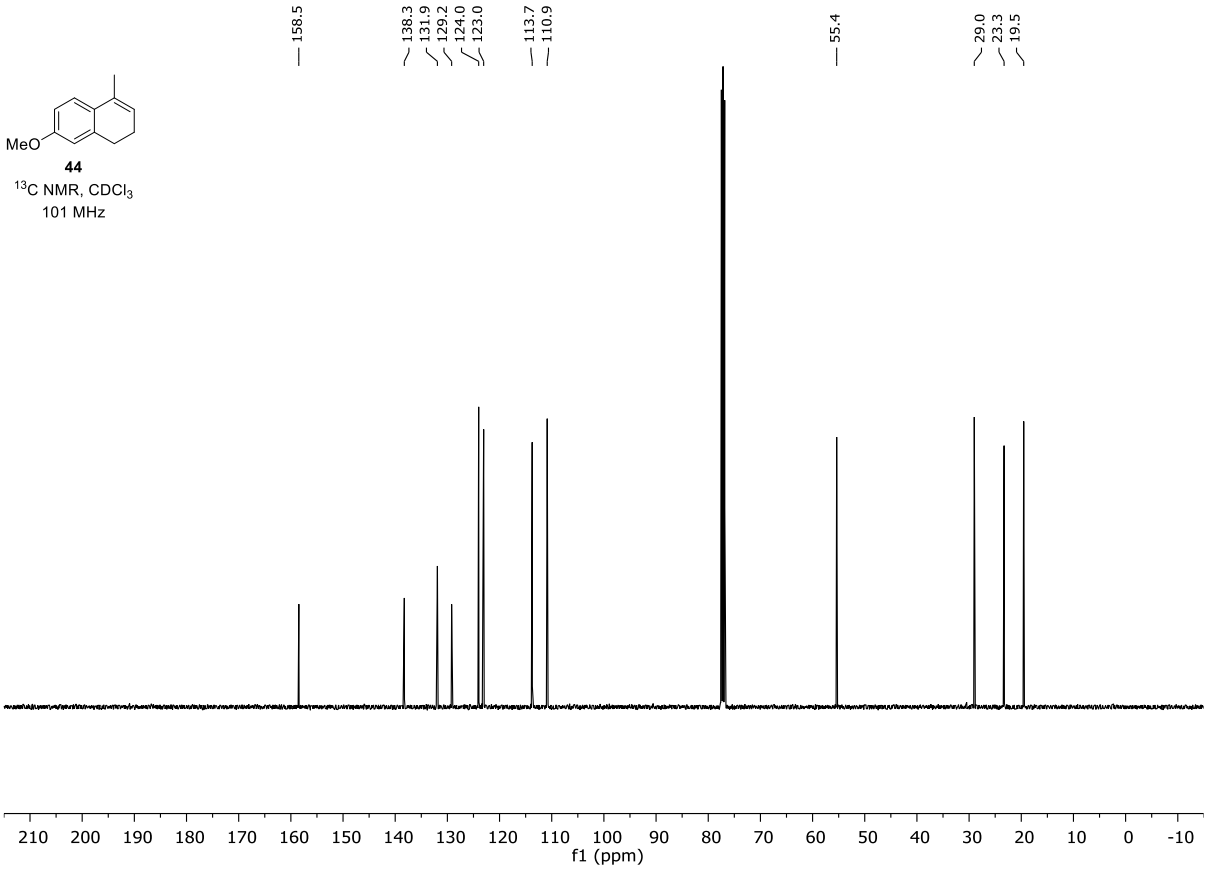


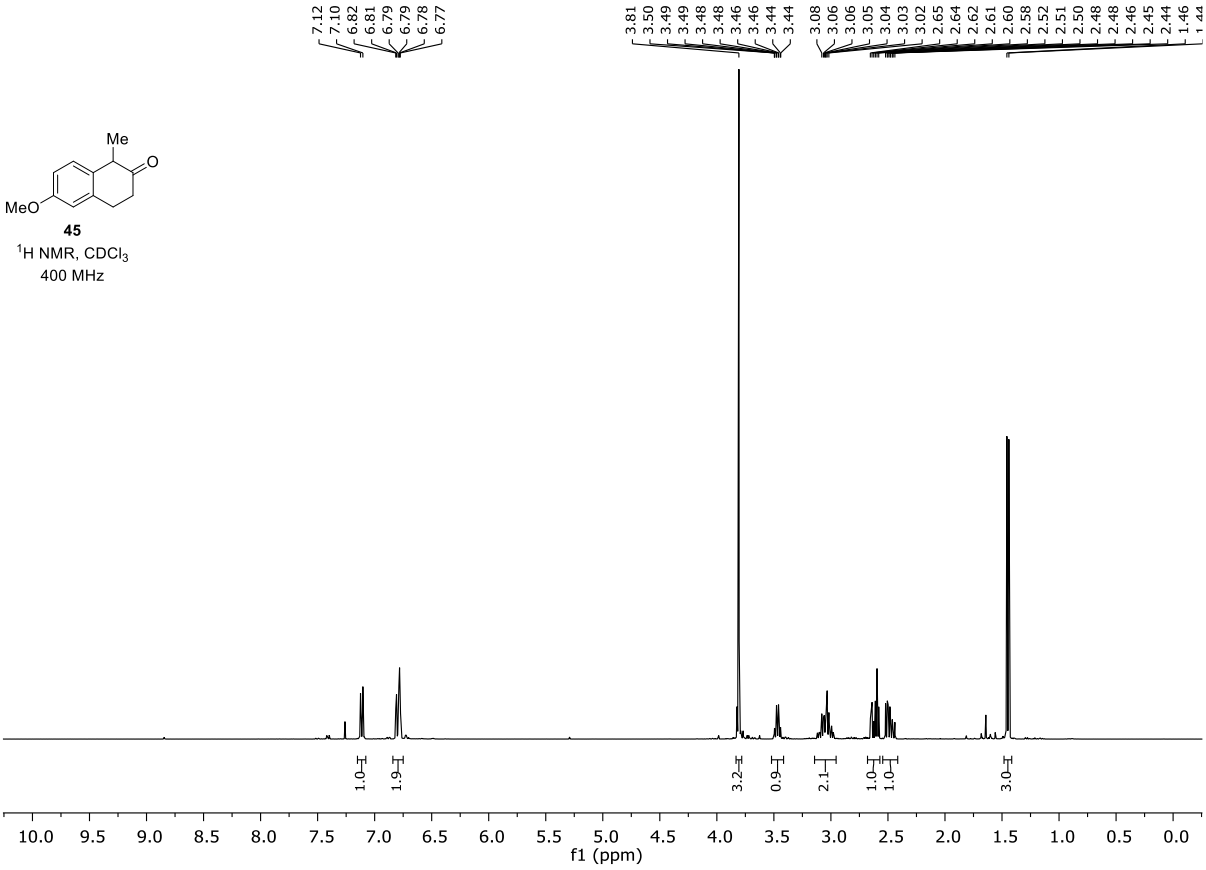
42
^{1}H NMR, $CDCl_3$
599 MHz

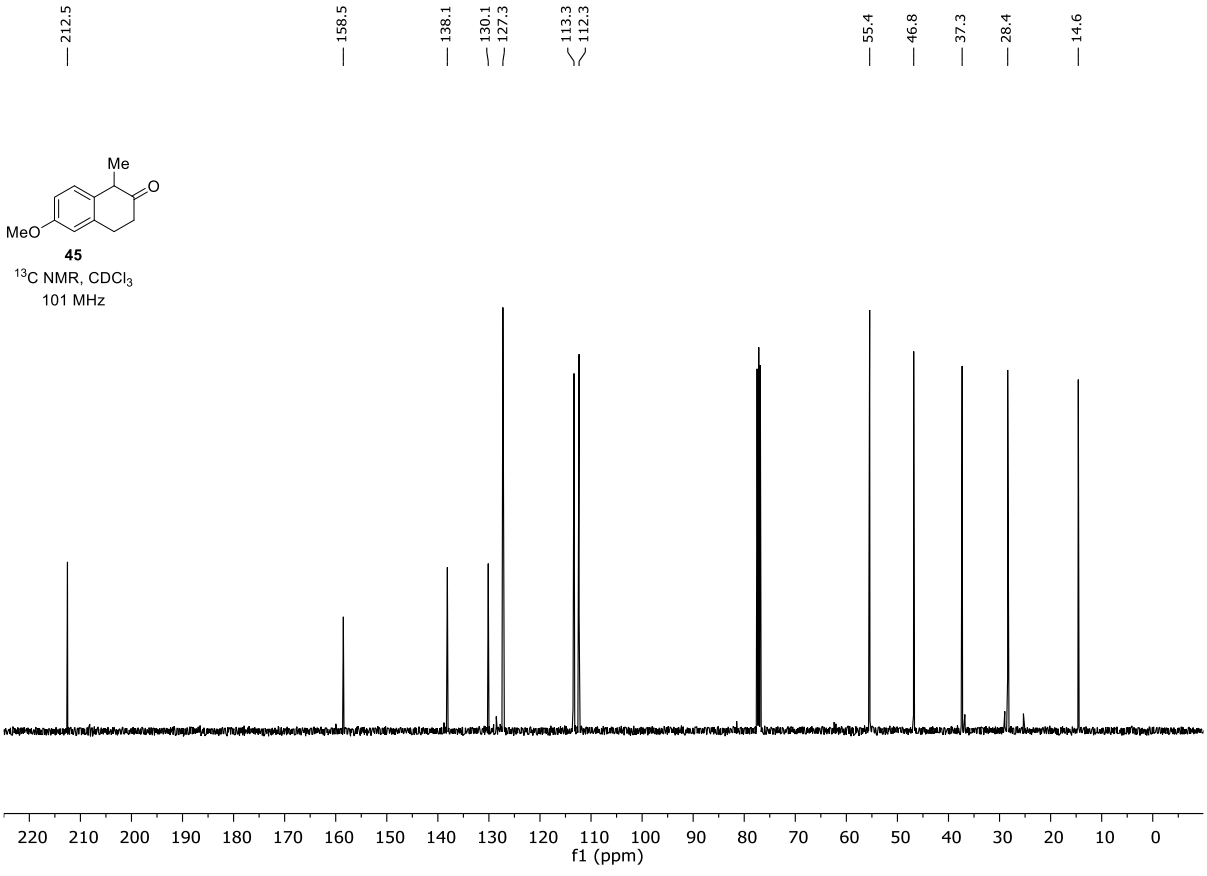


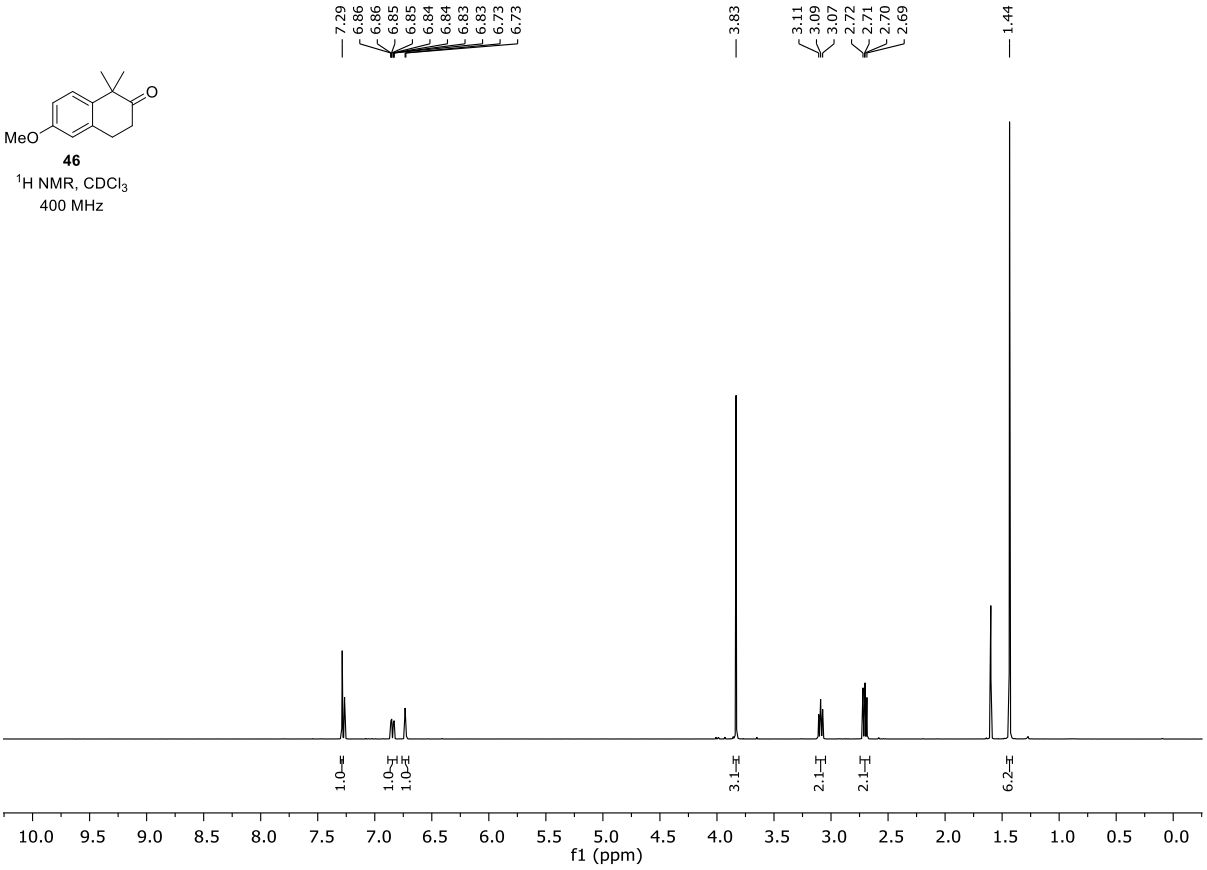
42
^{13}C NMR, $CDCl_3$
151 MHz

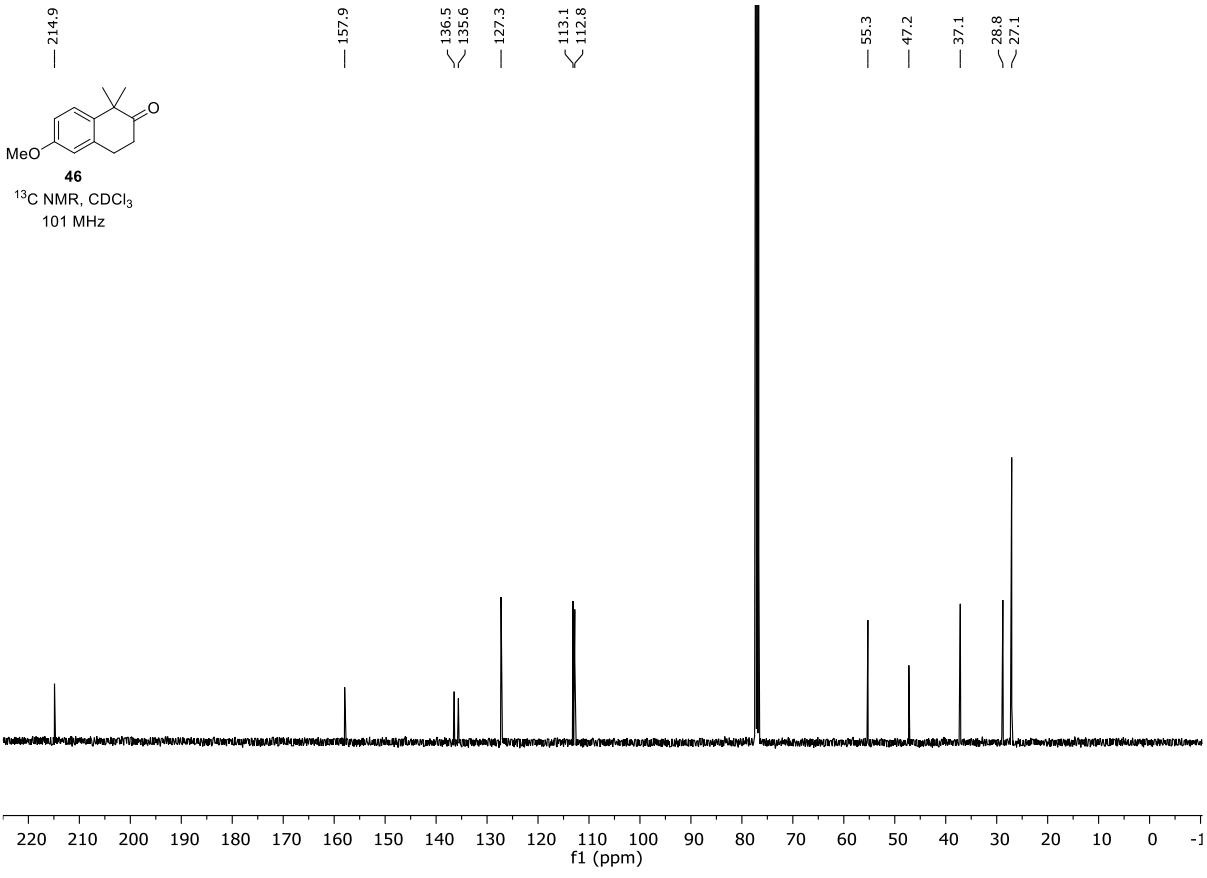

MeO
44
1H NMR, CDCl3
400 MHz
7.17
7.15
6.75
6.74
6.72
6.71
5.74
5.74
5.73
5.73
5.73
5.72
5.72
3.81
2.77
2.75
2.73
2.26
2.24
2.24
2.23
2.22
2.04
2.04
2.03
2.03
1.0
2.0
1.0
3.0
2.0
2.0
3.0
f1 (ppm)

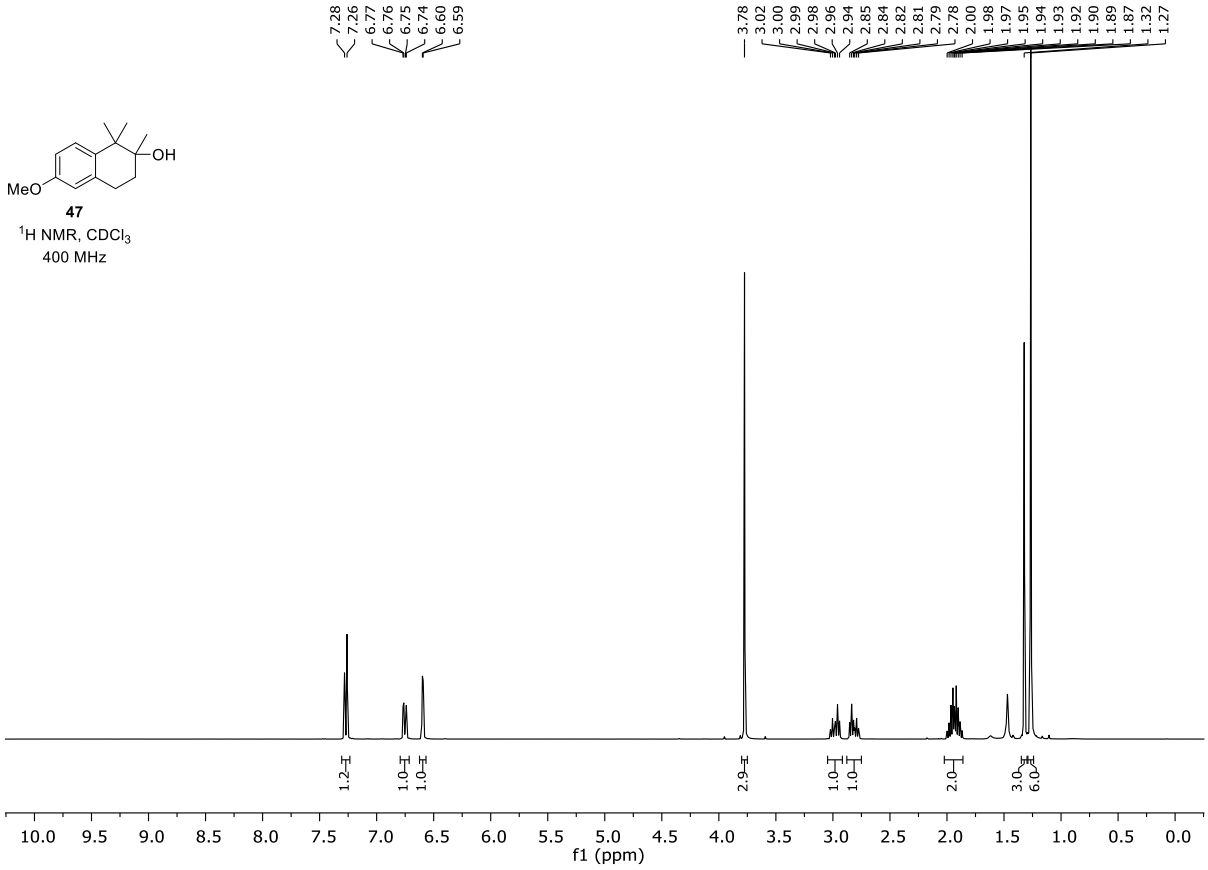

MeO
44
13C NMR, CDCl3
101 MHz
158.5
138.3
131.9
129.2
124.0
123.0
113.7
110.9
55.4
29.0
23.3
19.5
f1 (ppm)

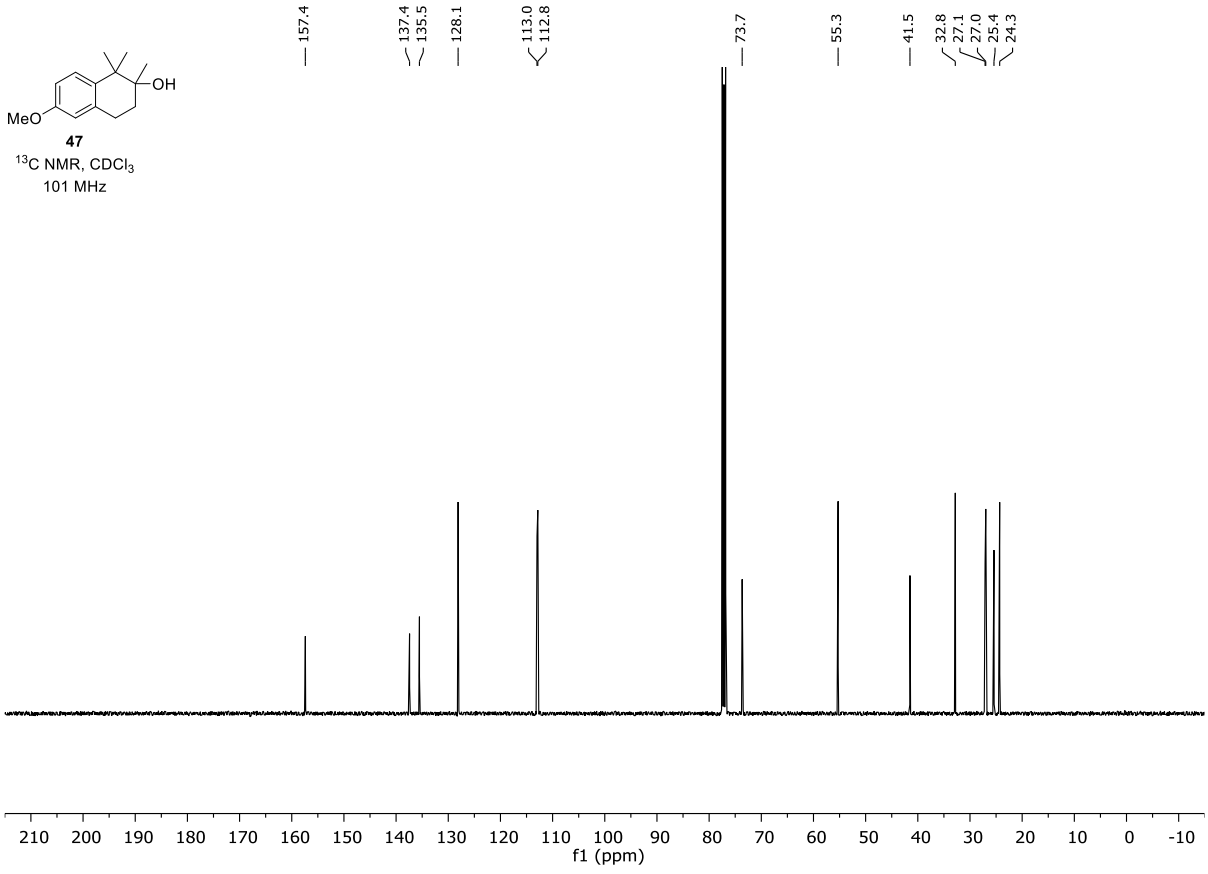

7.12
7.10
6.82
6.81
6.79
6.79
6.78
6.77
3.81
3.50
3.49
3.49
3.48
3.48
3.46
3.46
3.44
3.44
3.08
3.06
3.06
3.05
3.04
3.03
3.02
2.65
2.64
2.62
2.61
2.60
2.58
2.52
2.51
2.50
2.48
2.48
2.46
2.45
2.44
1.46
1.44
Me
O
MeO
45
^{1}H NMR, $CDCl_3$
400 MHz
1.0
1.9
3.2
0.9
2.1
1.0
1.0
3.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

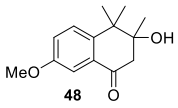

212.5
158.5
138.1
130.1
127.3
113.3
112.3
55.4
46.8
37.3
28.4
14.6
Me
O
MeO
45
^{13}C NMR, $CDCl_3$
101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.29
6.86
6.86
6.85
6.85
6.84
6.84
6.83
6.83
6.73
6.73
3.83
3.11
3.09
3.07
2.72
2.71
2.70
2.69
1.44
MeO
O
46
1H NMR, CDCl3
400 MHz
1.0
1.0
1.0
3.1
2.1
2.1
6.2
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

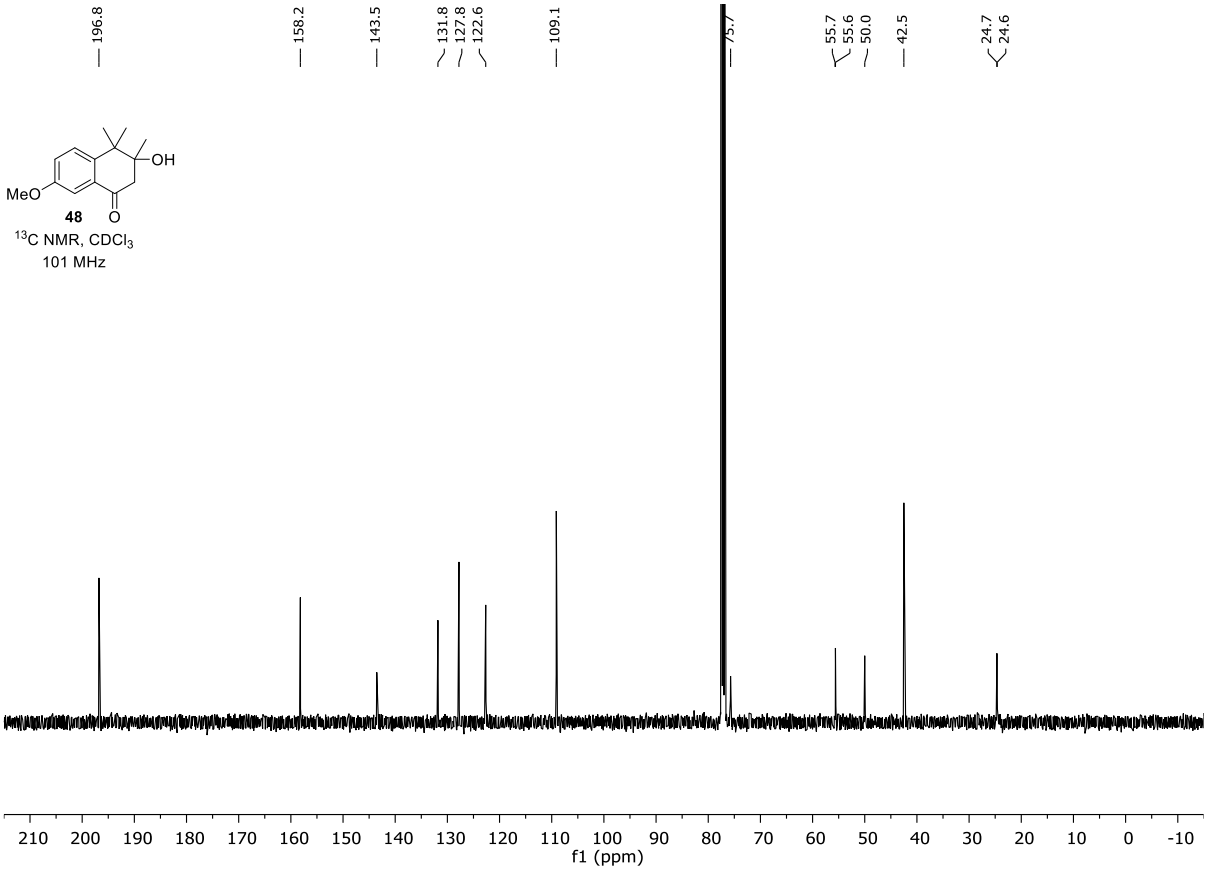

214.9
157.9
136.5
135.6
127.3
113.1
112.8
55.3
47.2
37.1
28.8
27.1
MeO
O
46
13C NMR, CDCl3
101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.28
7.26
6.77
6.76
6.75
6.74
6.60
6.59
3.78
3.02
3.00
2.99
2.98
2.96
2.94
2.85
2.84
2.82
2.81
2.79
2.78
2.00
1.98
1.97
1.95
1.94
1.93
1.92
1.90
1.89
1.87
1.32
1.27
OH
MeO
47
1H NMR, CDCl3
400 MHz
1.2
1.0
1.0
2.9
1.0
1.0
2.0
3.0
6.0
f1 (ppm)

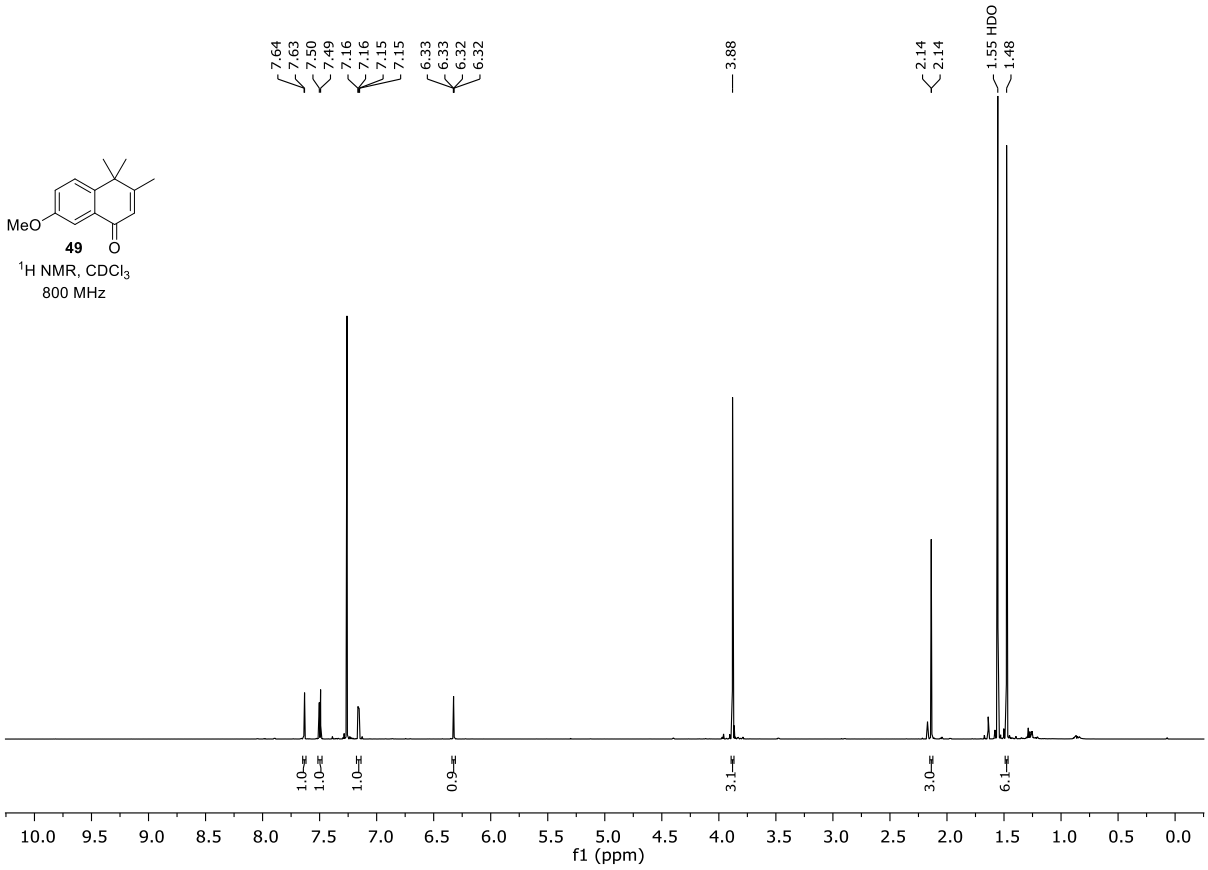

157.4
137.4
135.5
128.1
113.0
112.8
73.7
55.3
41.5
32.8
27.1
27.0
25.4
24.3
OH
MeO
47
13C NMR, CDCl3
101 MHz
f1 (ppm)

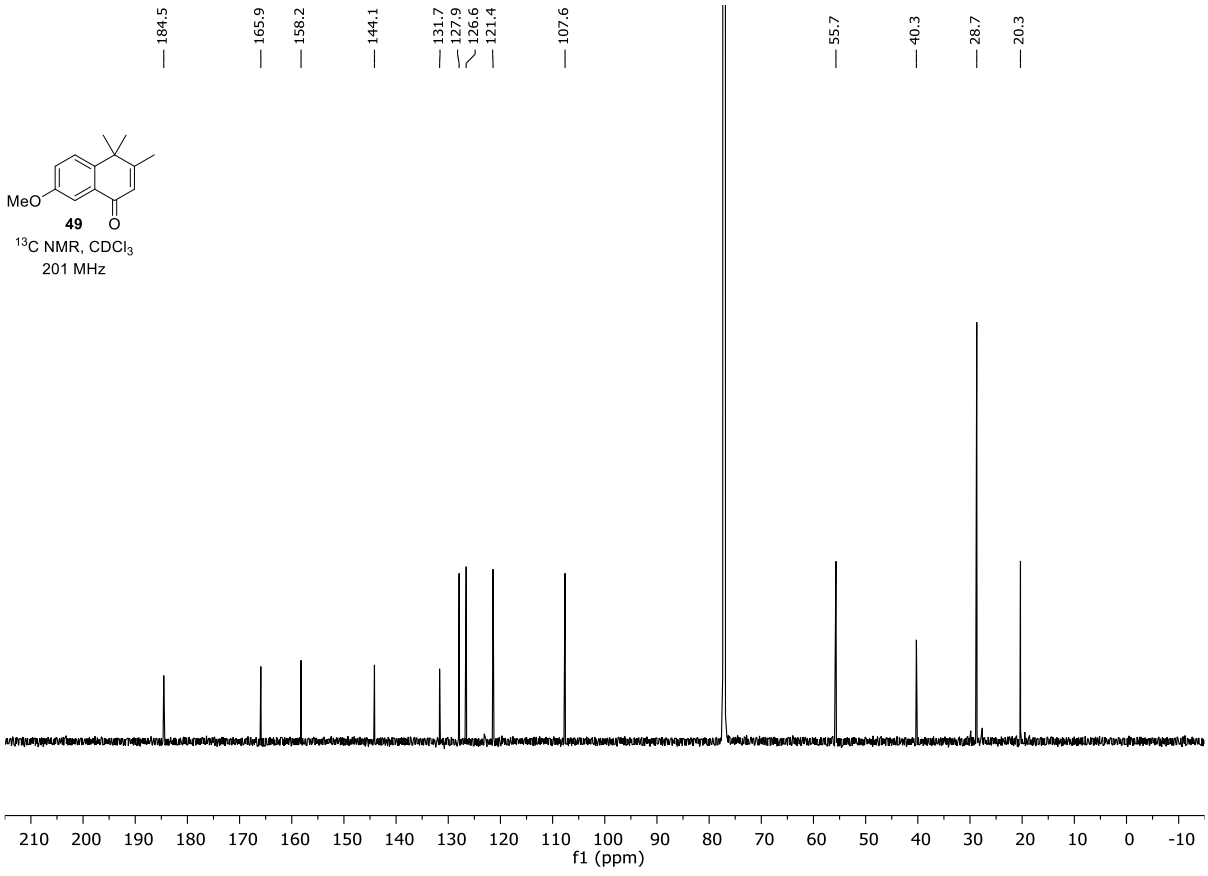


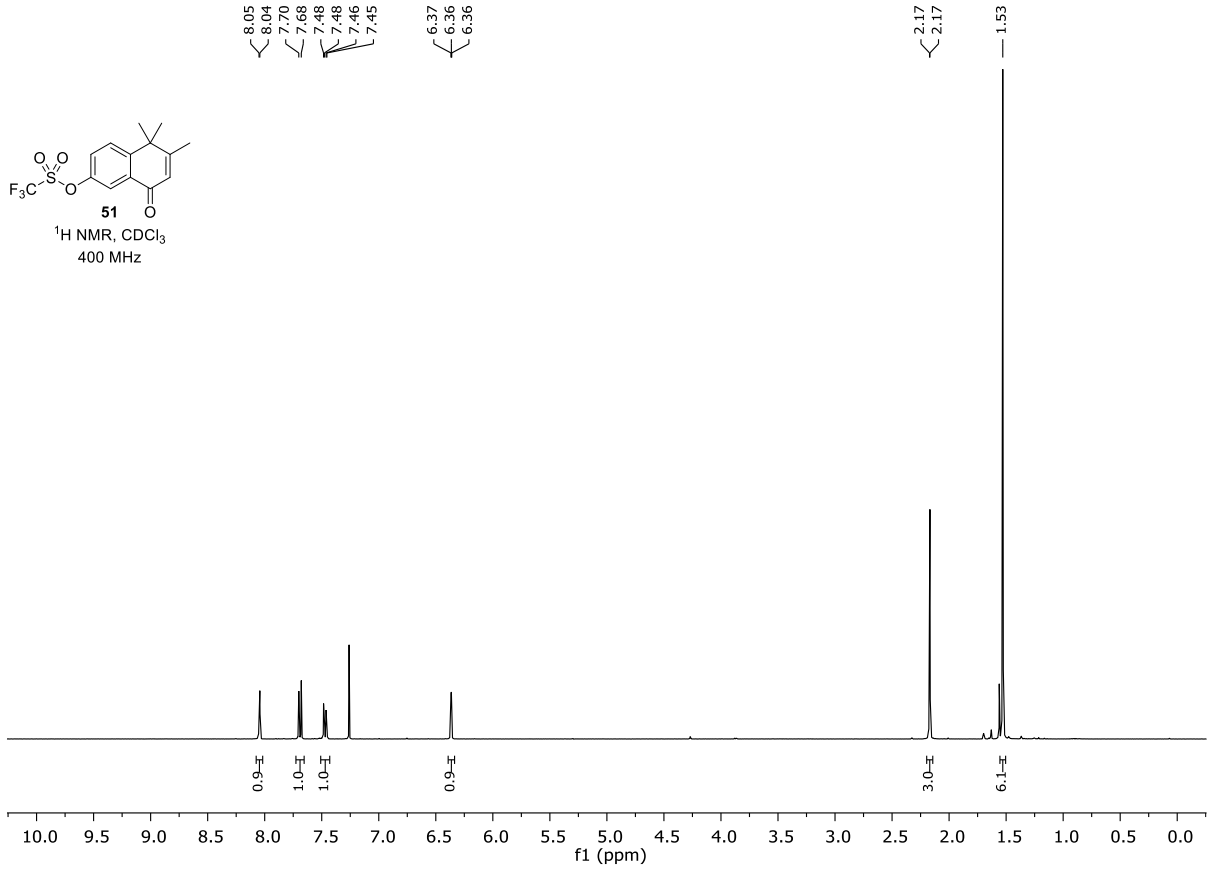
^{1}H NMR, $CDCl_3$
400 MHz

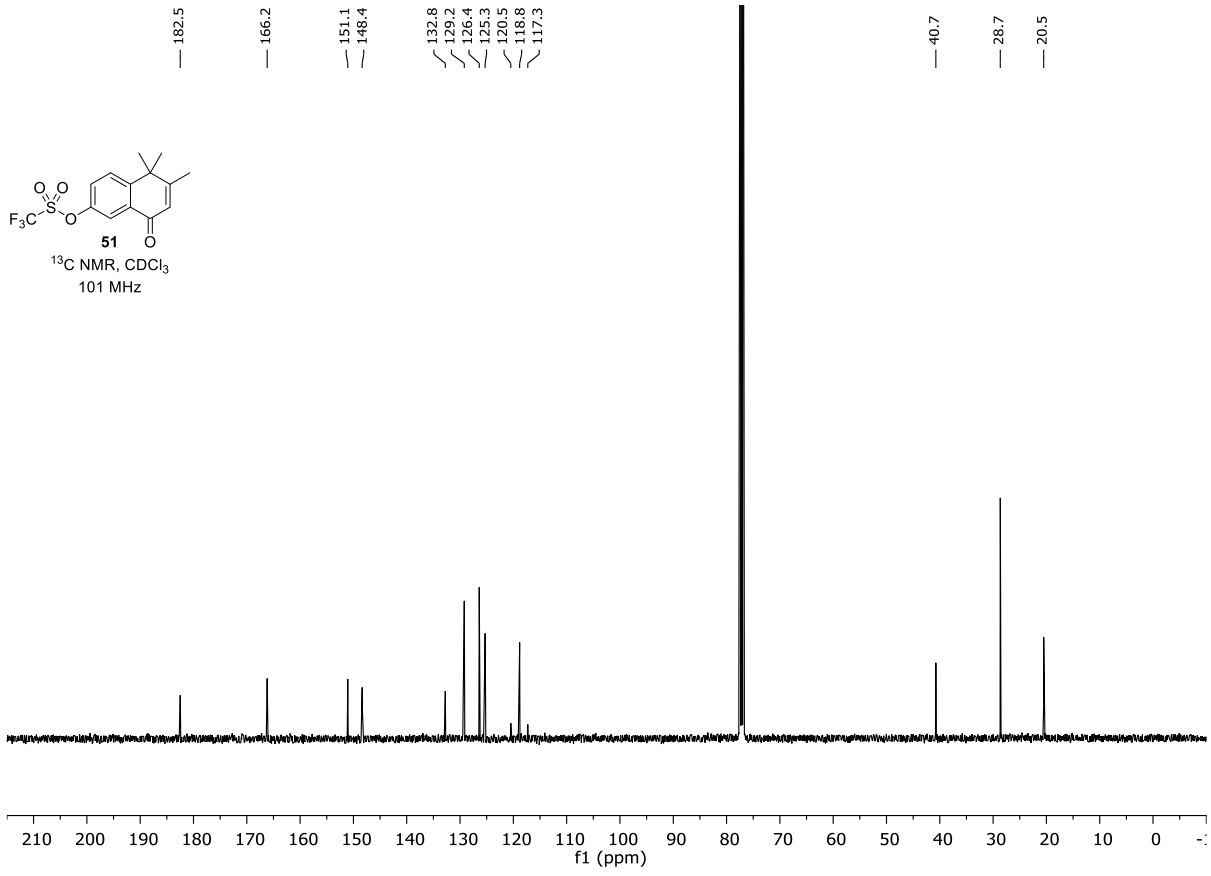


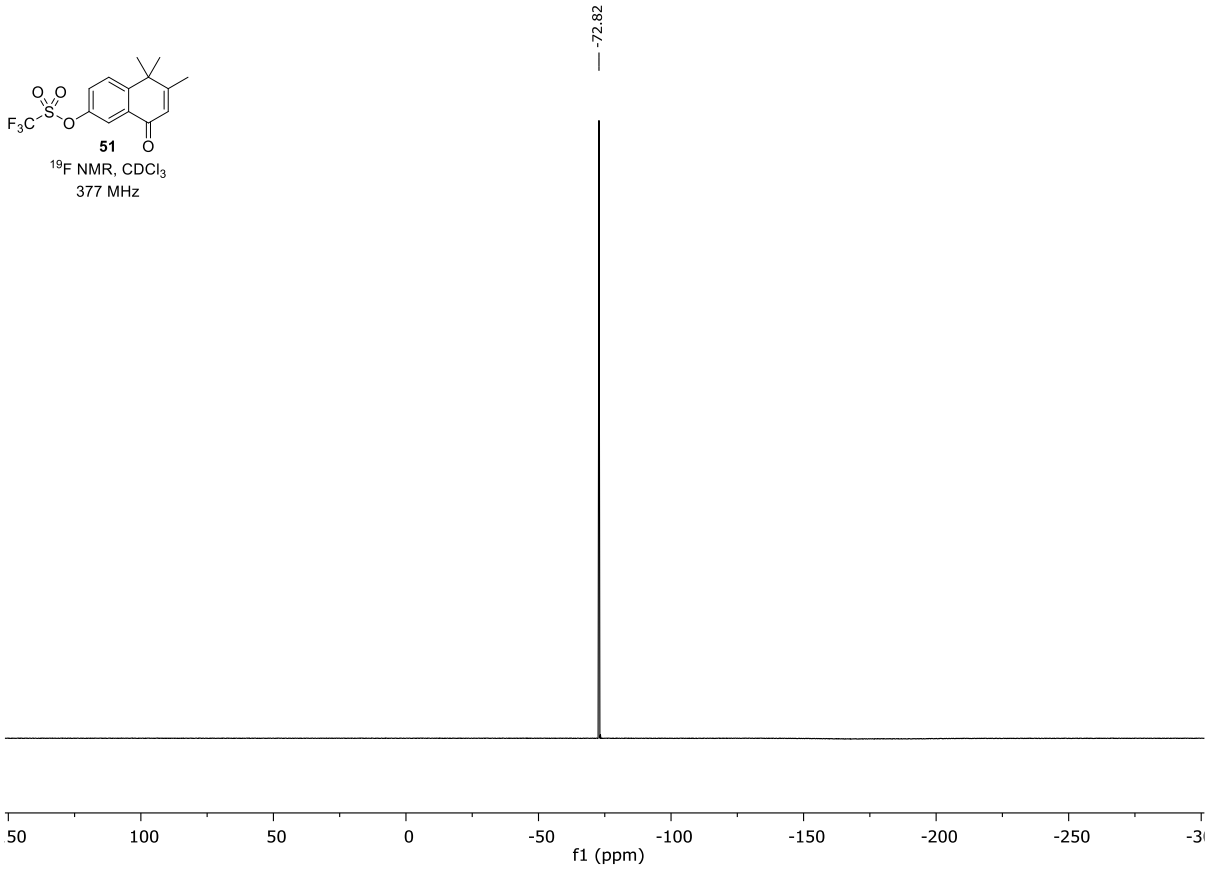
^{13}C NMR, $CDCl_3$
101 MHz

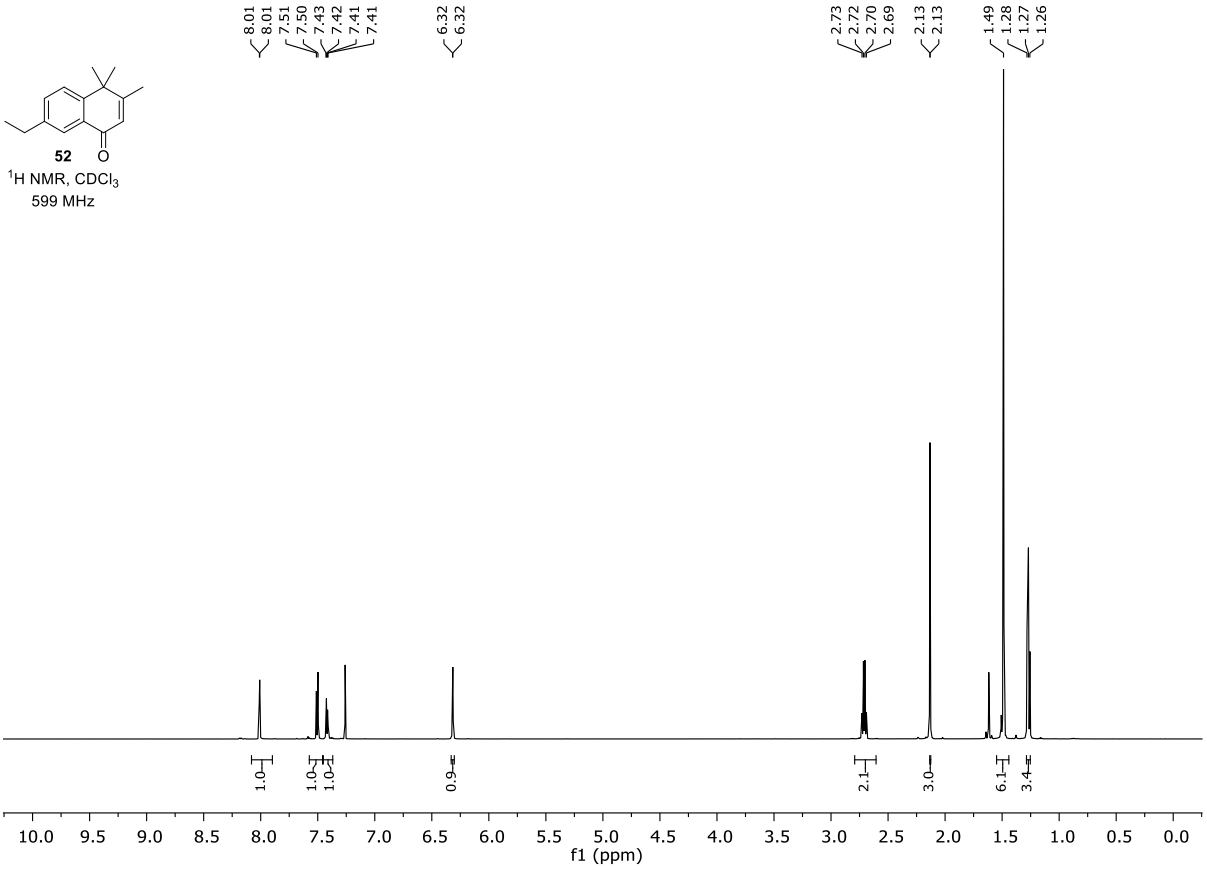

7.64
7.63
7.50
7.49
7.16
7.16
7.15
7.15
6.33
6.33
6.32
6.32
3.88
2.14
2.14
1.55 HDO
1.48
MeO
49
O
1H NMR, CDCl3
800 MHz
1.0
1.0
1.0
0.9
3.1
3.0
6.1
f1 (ppm)

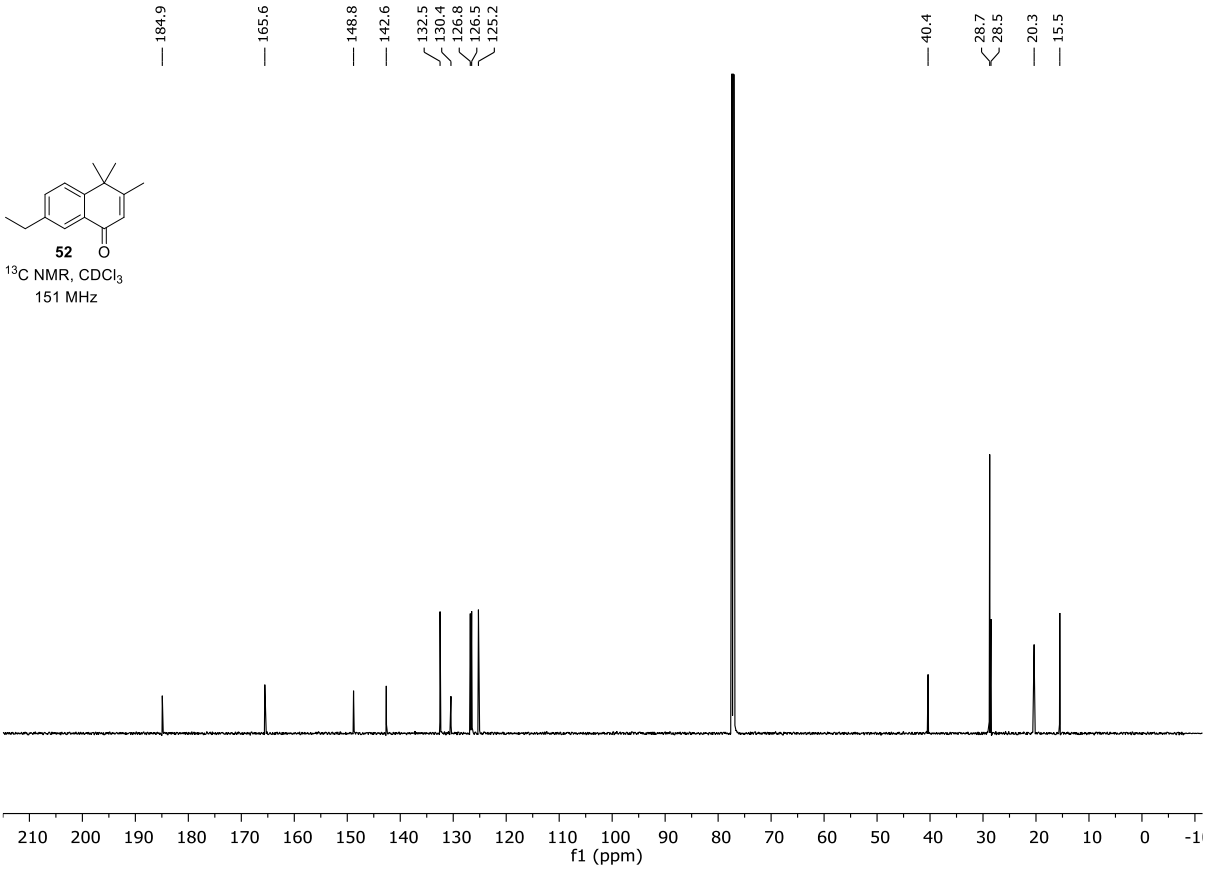

184.5
165.9
158.2
144.1
131.7
127.9
126.6
121.4
107.6
55.7
40.3
28.7
20.3
MeO
49
O
13C NMR, CDCl3
201 MHz
f1 (ppm)

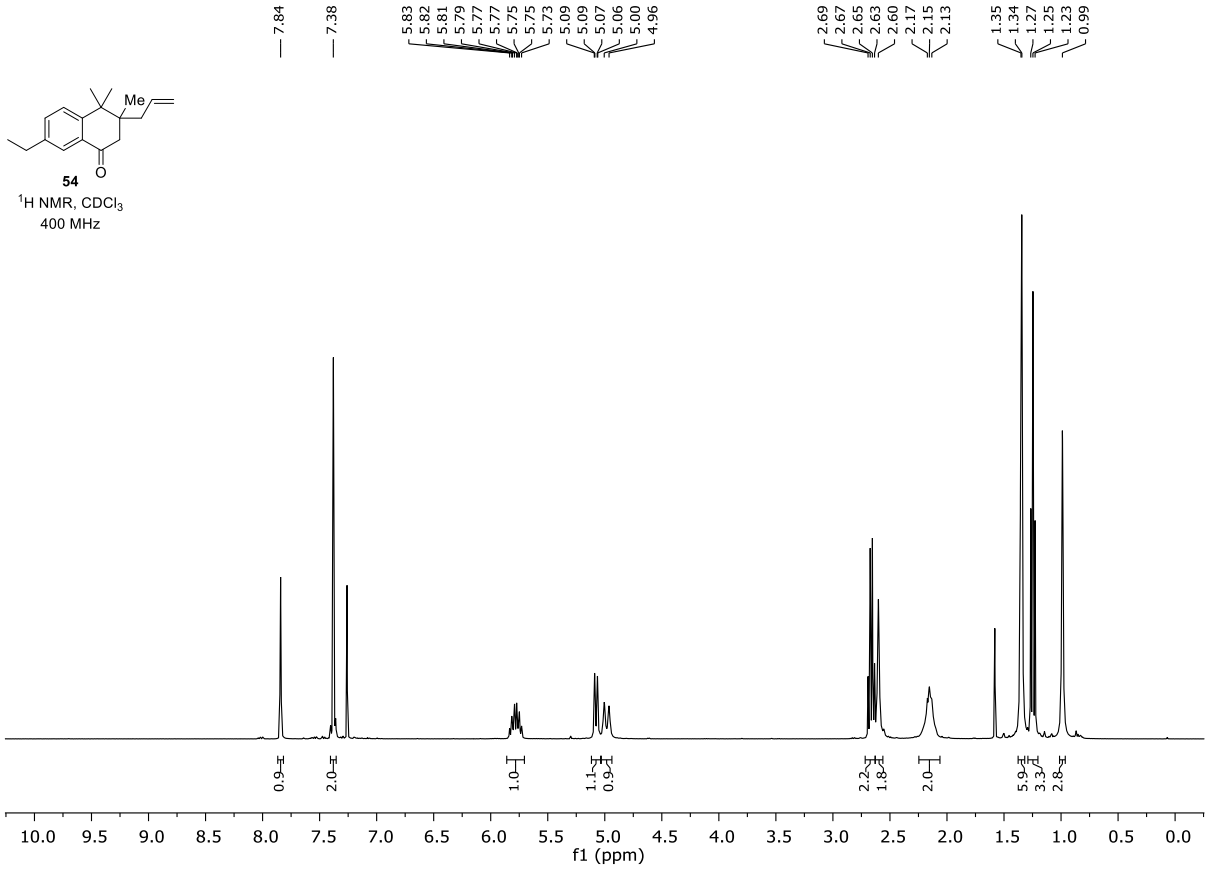

8.05
8.04
7.70
7.68
7.48
7.48
7.46
7.45
6.37
6.36
6.36
2.17
2.17
1.53
51
^{1}H NMR, $CDCl_3$
400 MHz
0.9
1.0
1.0
0.9
3.0
6.1
f1 (ppm)

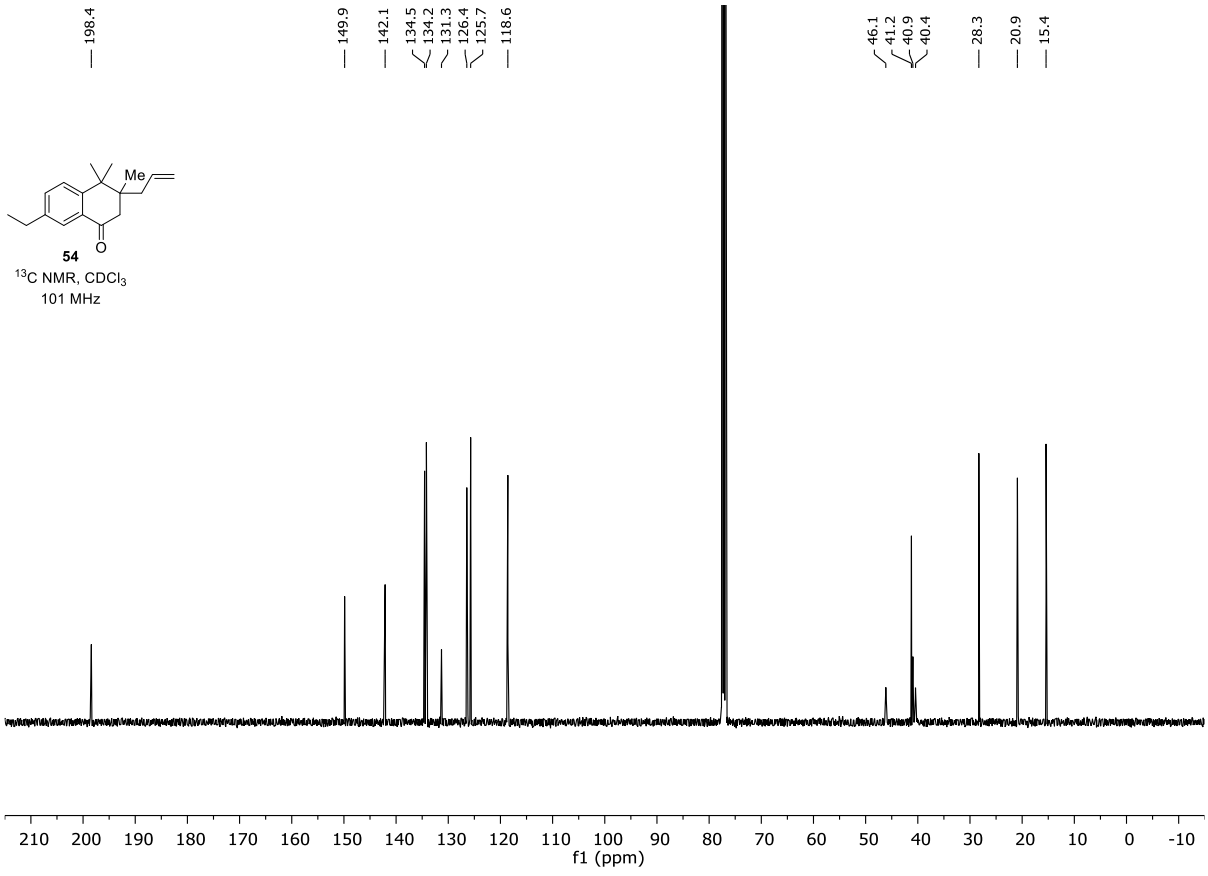

182.5
166.2
151.1
148.4
132.8
129.2
126.4
125.3
120.5
118.8
117.3
40.7
28.7
20.5
51
^{13}C NMR, $CDCl_3$
101 MHz
f1 (ppm)

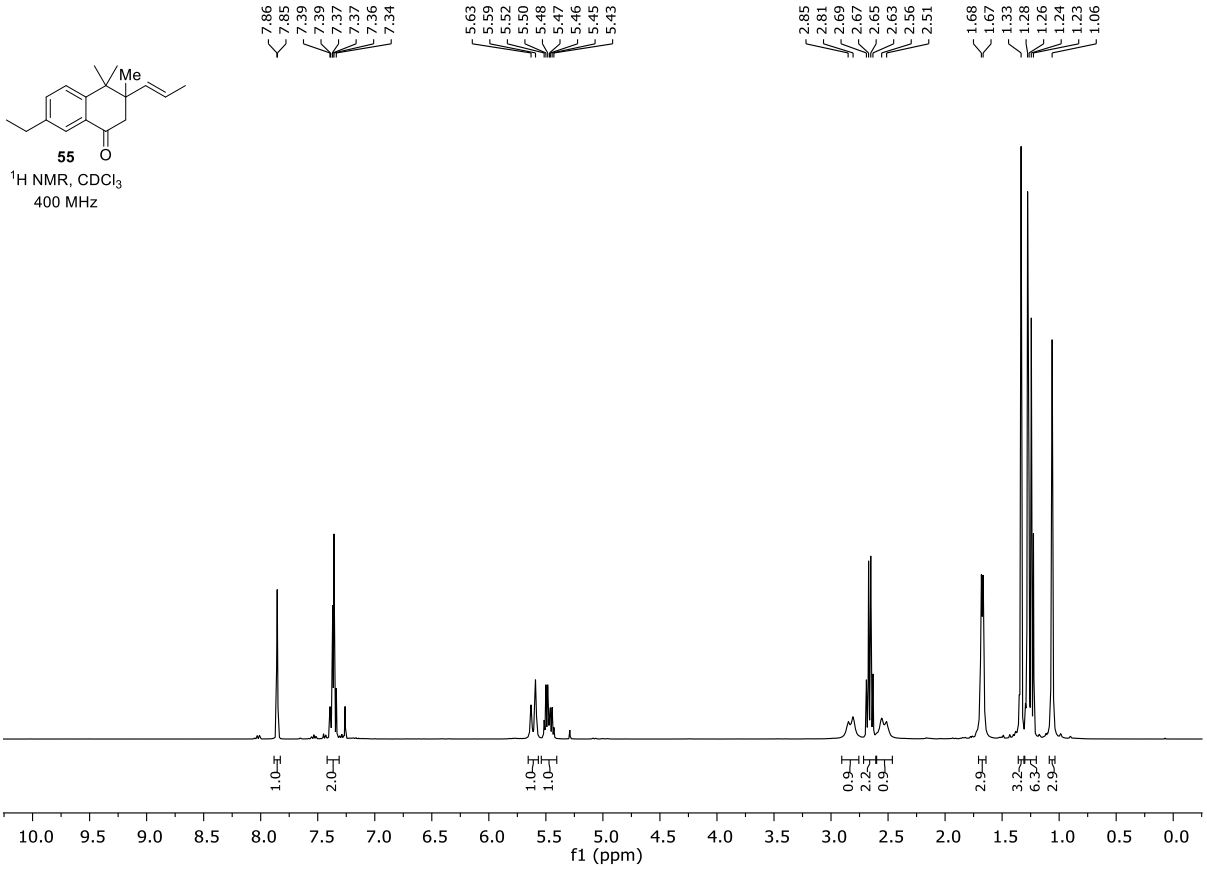

-72.82
51
19F NMR, CDCl3
377 MHz
50
100
50
0
-50
-100
-150
-200
-250
f1 (ppm)

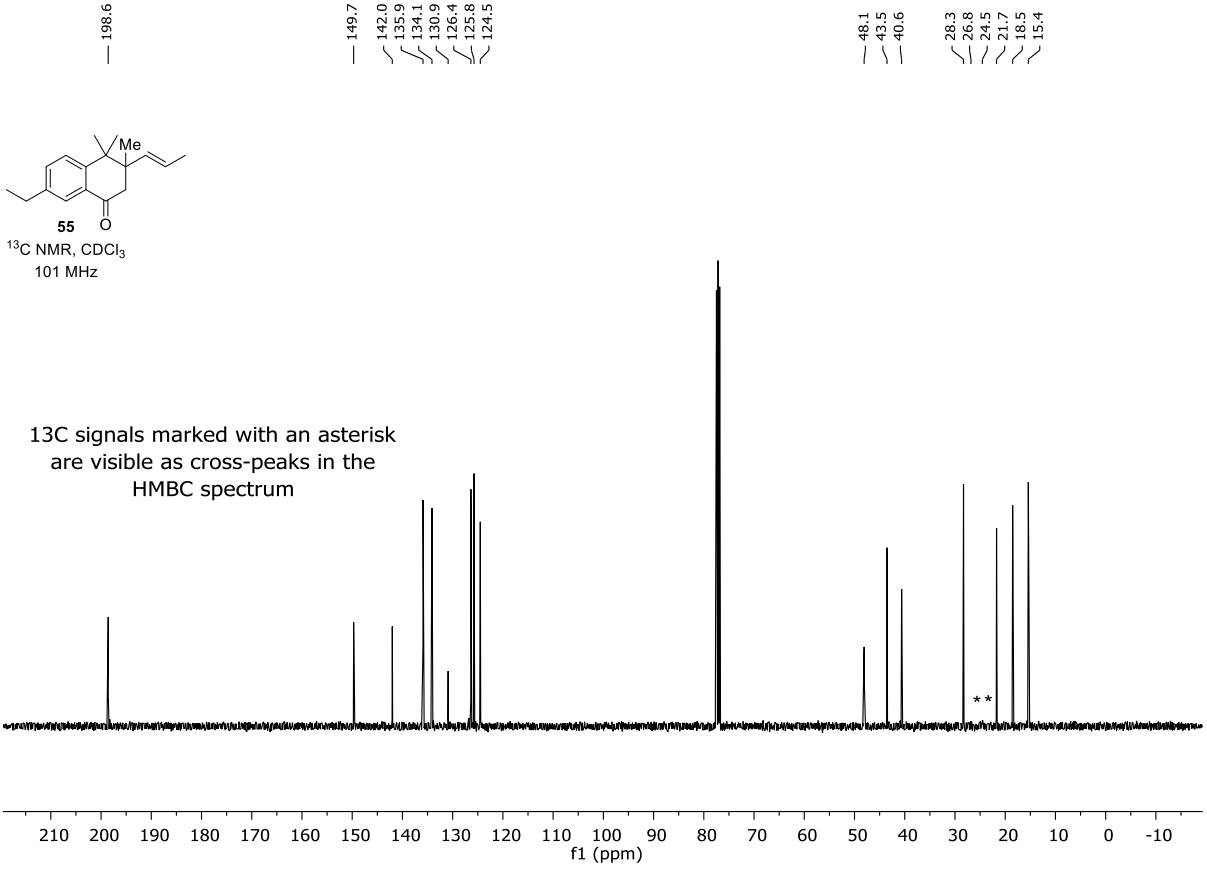

8.01
8.01
7.51
7.50
7.43
7.42
7.41
7.41
6.32
6.32
2.73
2.72
2.70
2.69
2.13
2.13
1.49
1.28
1.27
1.26
52
O
1H NMR, CDCl3
599 MHz
1.0
1.0
1.0
0.9
2.1
3.0
6.1
3.4
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

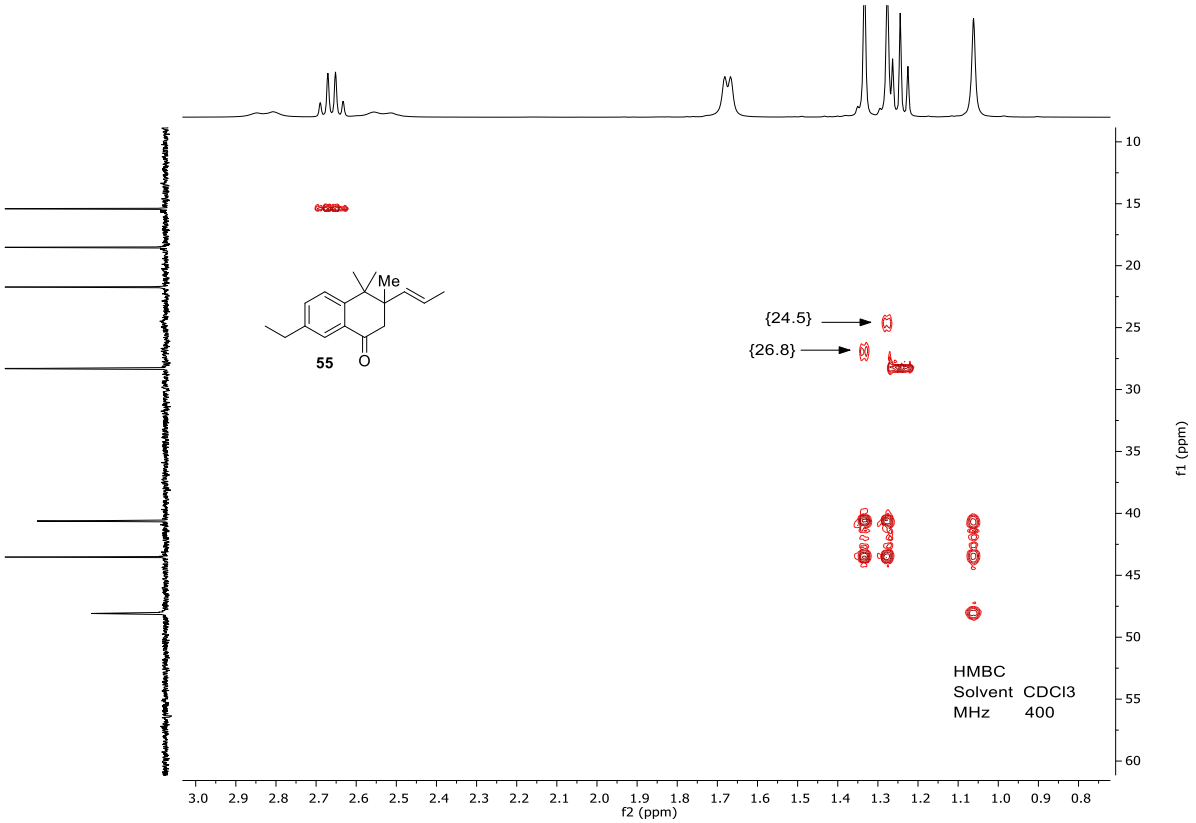

184.9
165.6
148.8
142.6
132.5
130.4
126.8
126.5
125.2
40.4
28.7
28.5
20.3
15.5
52
O
13C NMR, CDCl3
151 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

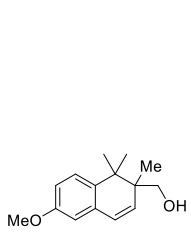

7.84
7.38
5.83
5.82
5.81
5.79
5.77
5.77
5.75
5.75
5.73
5.09
5.09
5.07
5.06
5.00
4.96
2.69
2.67
2.65
2.63
2.60
2.17
2.15
2.13
1.35
1.34
1.27
1.25
1.23
0.99
Me
O
54
^{1}H NMR, $CDCl_3$
400 MHz
0.9
2.0
1.0
1.1
0.9
2.2
1.8
2.0
5.9
3.3
2.8
f1 (ppm)


198.4
149.9
142.1
134.5
134.2
131.3
126.4
125.7
118.6
46.1
41.2
40.9
40.4
28.3
20.9
15.4
Me
O
54
^{13}C NMR, $CDCl_3$
101 MHz
f1 (ppm)

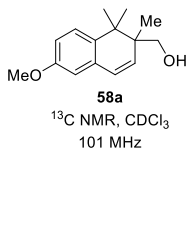

7.86
7.85
7.39
7.39
7.37
7.37
7.36
7.34
5.63
5.59
5.52
5.50
5.48
5.47
5.46
5.45
5.43
2.85
2.81
2.69
2.67
2.65
2.63
2.56
2.51
1.68
1.67
1.33
1.28
1.26
1.24
1.23
1.06
Me
O
55
1H NMR, CDCl3
400 MHz
1.0
2.0
1.0
1.0
0.9
2.2
0.9
2.9
3.2
6.3
2.9
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


198.6
149.7
142.0
135.9
134.1
130.9
126.4
125.8
124.5
48.1
43.5
40.6
28.3
26.8
24.5
21.7
18.5
15.4
Me
O
55
13C NMR, CDCl3
101 MHz
13C signals marked with an asterisk
are visible as cross-peaks in the
HMBC spectrum
* *
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

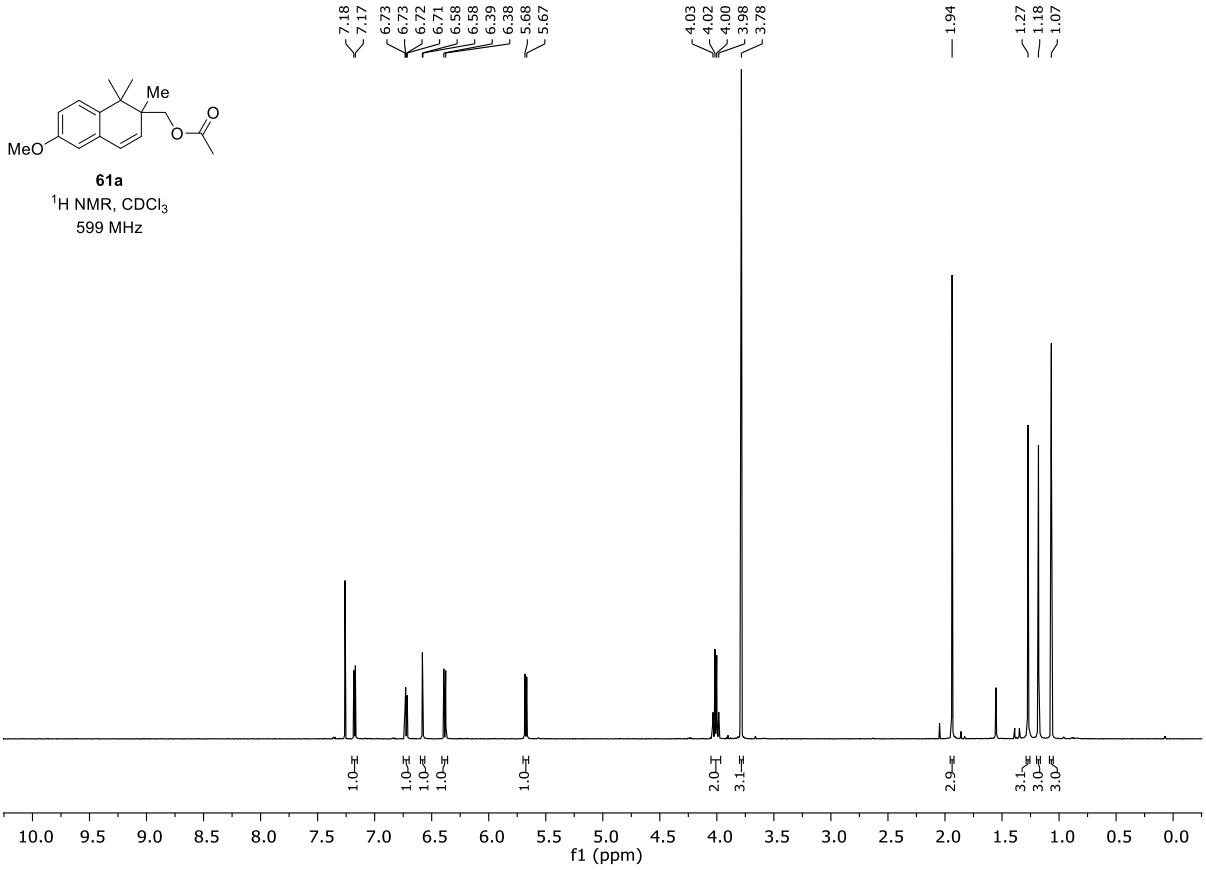

Me
55
O
{24.5}
{26.8}
HMBC
Solvent CDCl3
MHz 400
f2 (ppm)
f1 (ppm)



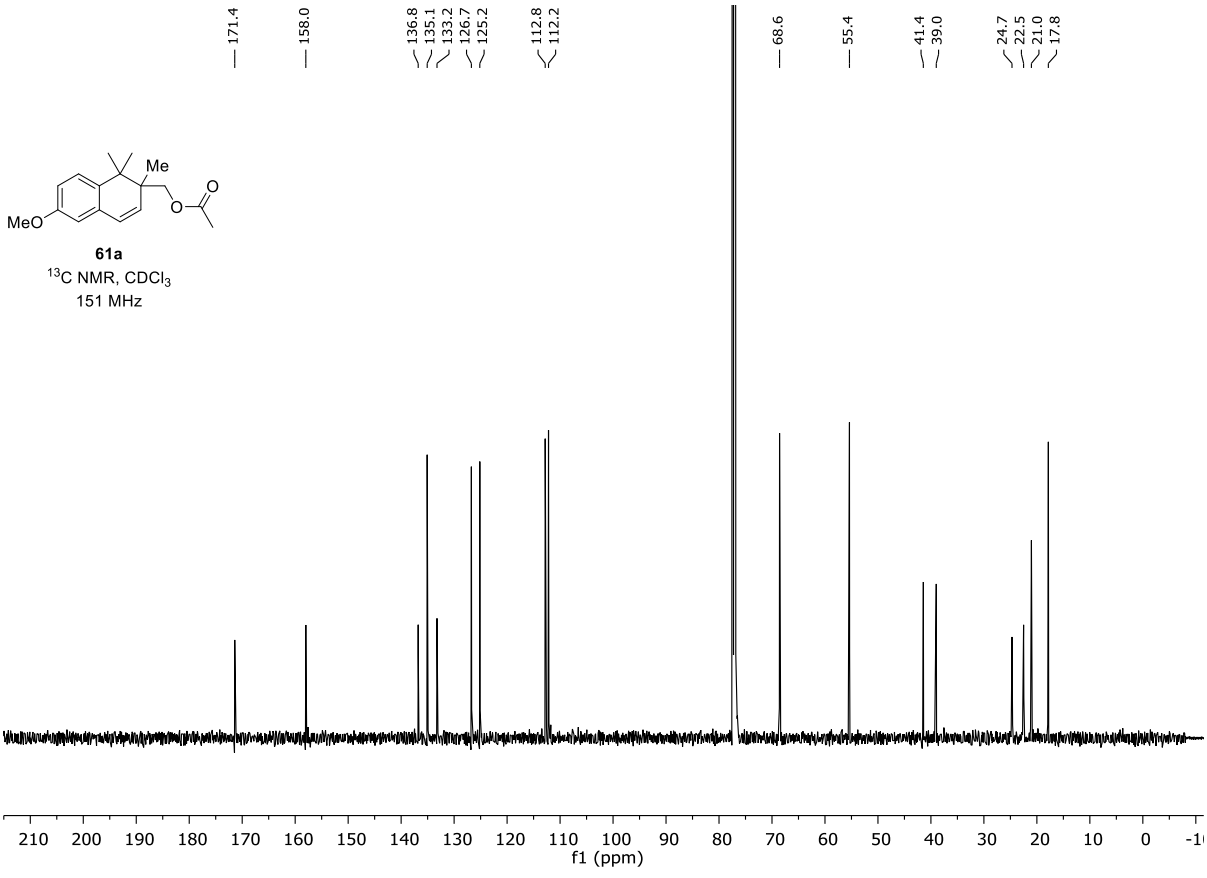
58a
^{1}H NMR, $CDCl_3$
400 MHz



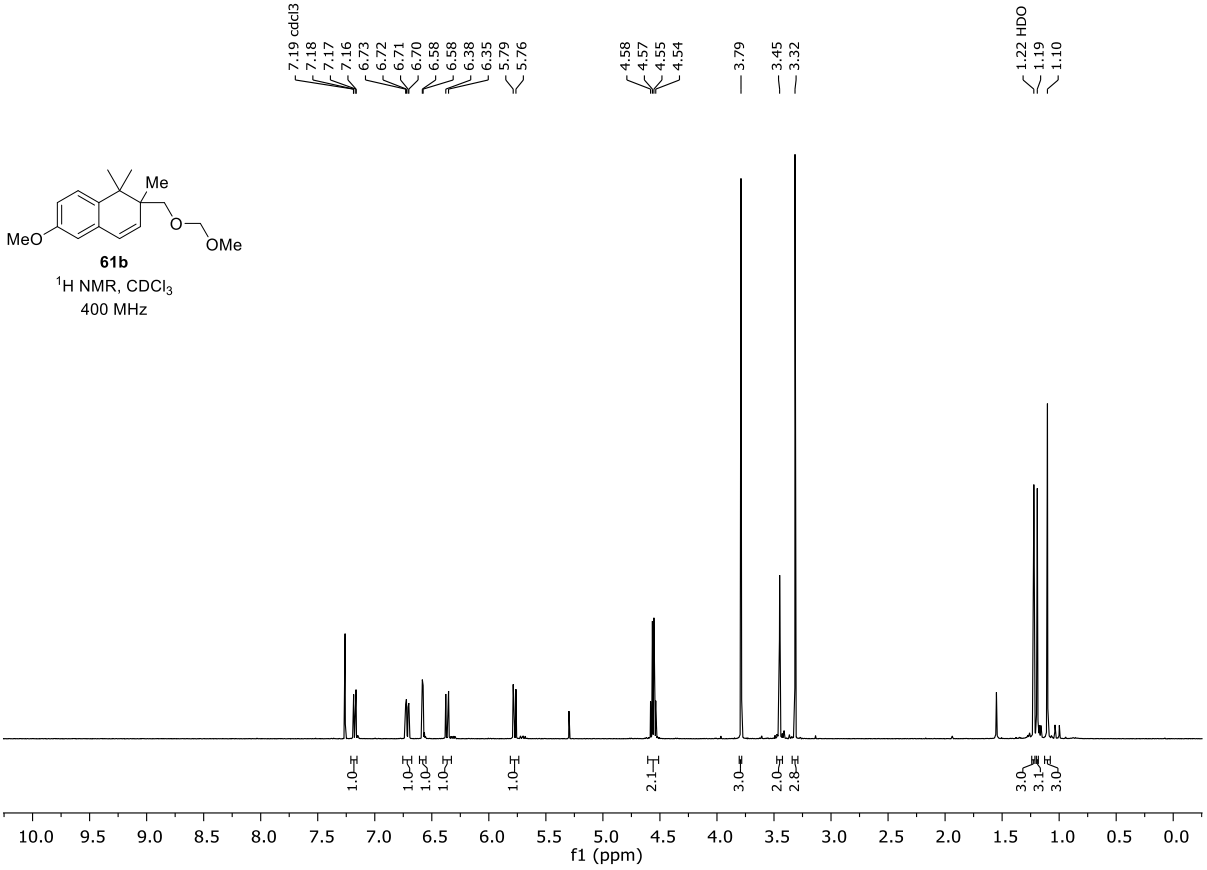
58a
^{13}C NMR, $CDCl_3$
101 MHz

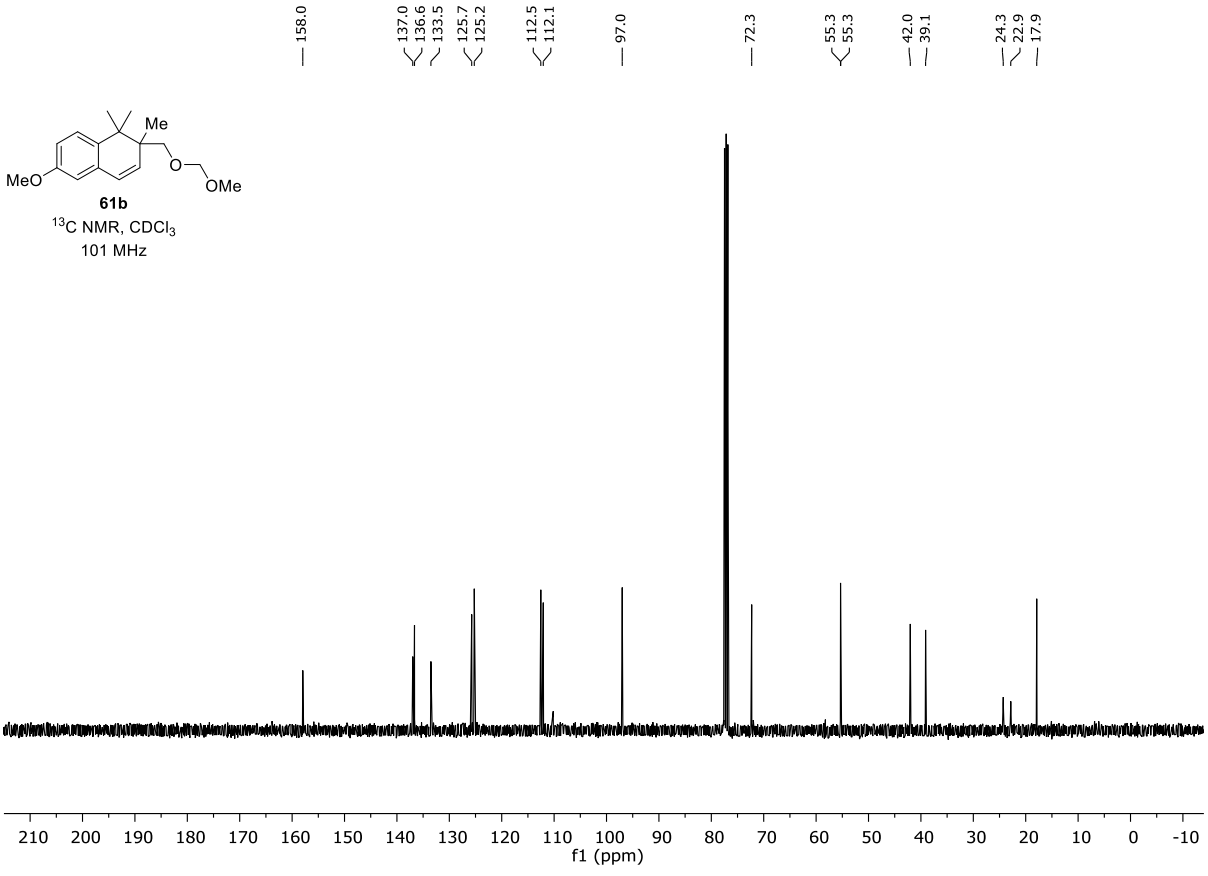


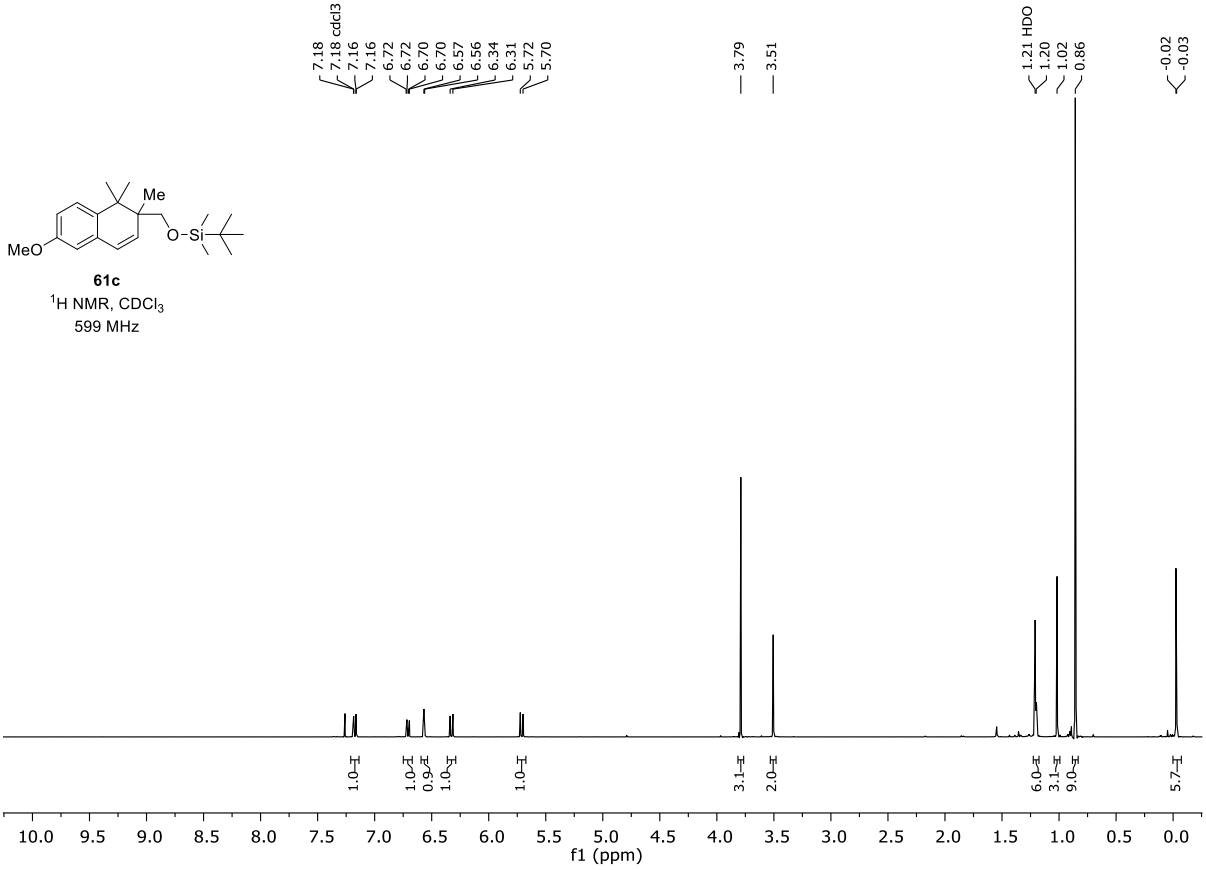
61a
^{1}H NMR, $CDCl_3$
599 MHz

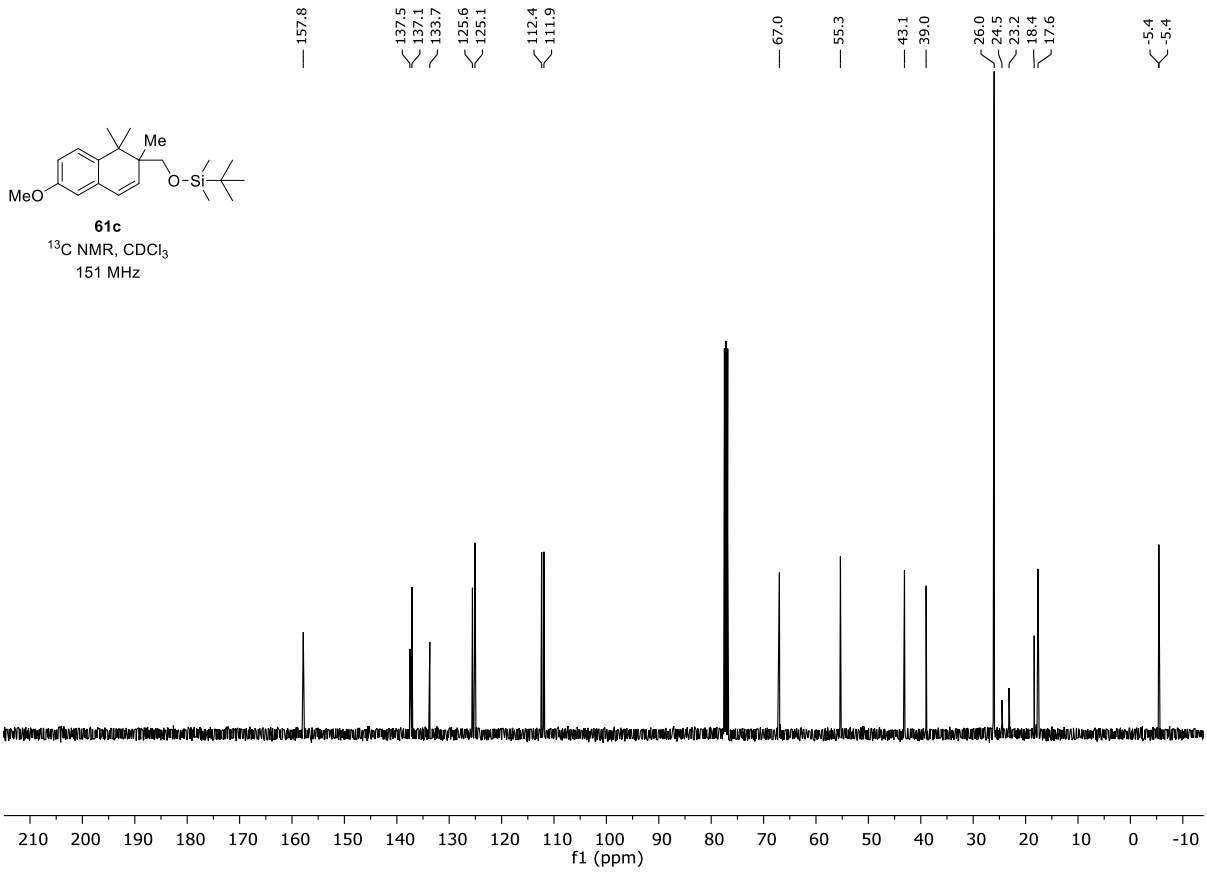


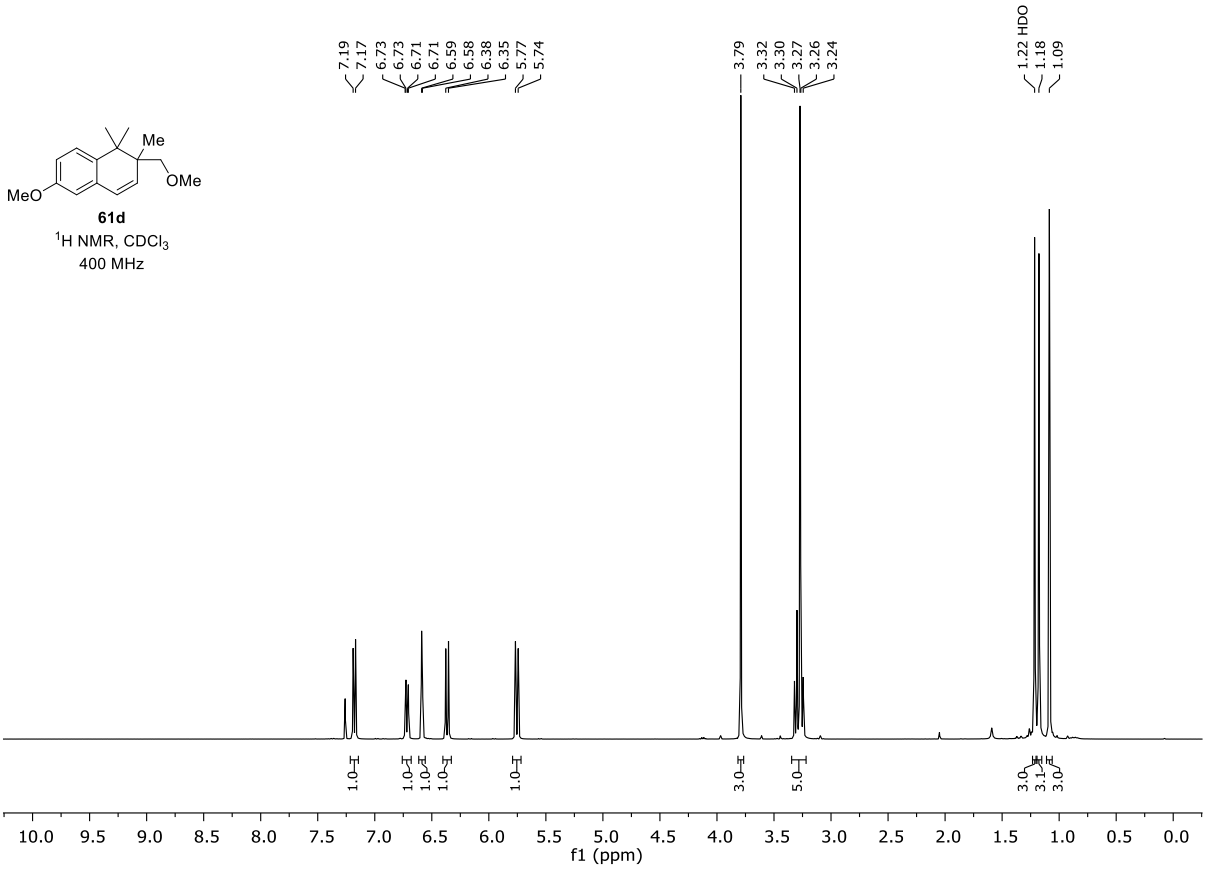
61a
^{13}C NMR, $CDCl_3$
151 MHz

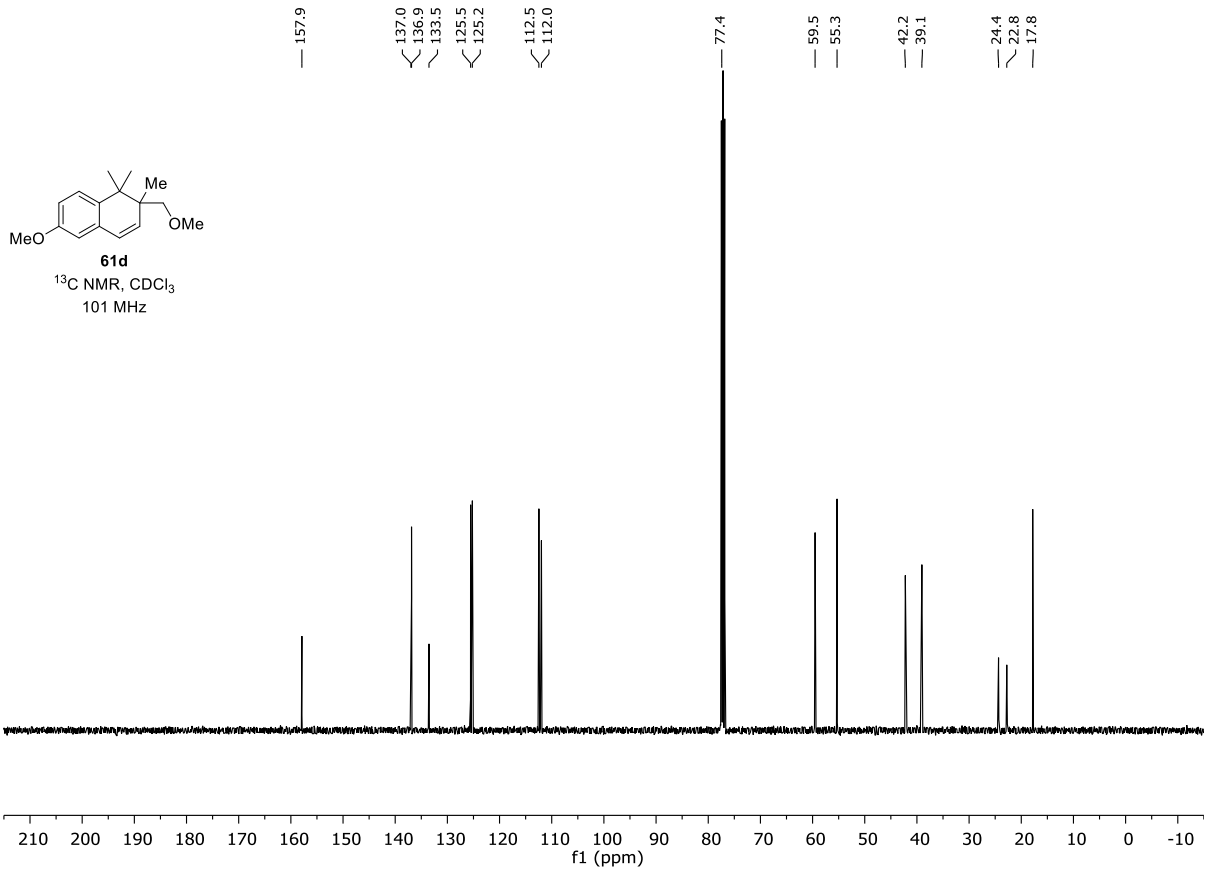

7.19 cdcl3
7.18
7.17
7.16
6.73
6.72
6.71
6.70
6.58
6.58
6.38
6.35
5.79
5.76
4.58
4.57
4.55
4.54
3.79
3.45
3.32
1.22 HDO
1.19
1.10
Me
MeO
O
OMe
61b
1H NMR, CDCl3
400 MHz
1.0
1.0
1.0
1.0
2.1
3.0
2.0
2.8
3.0
3.1
3.0
f1 (ppm)

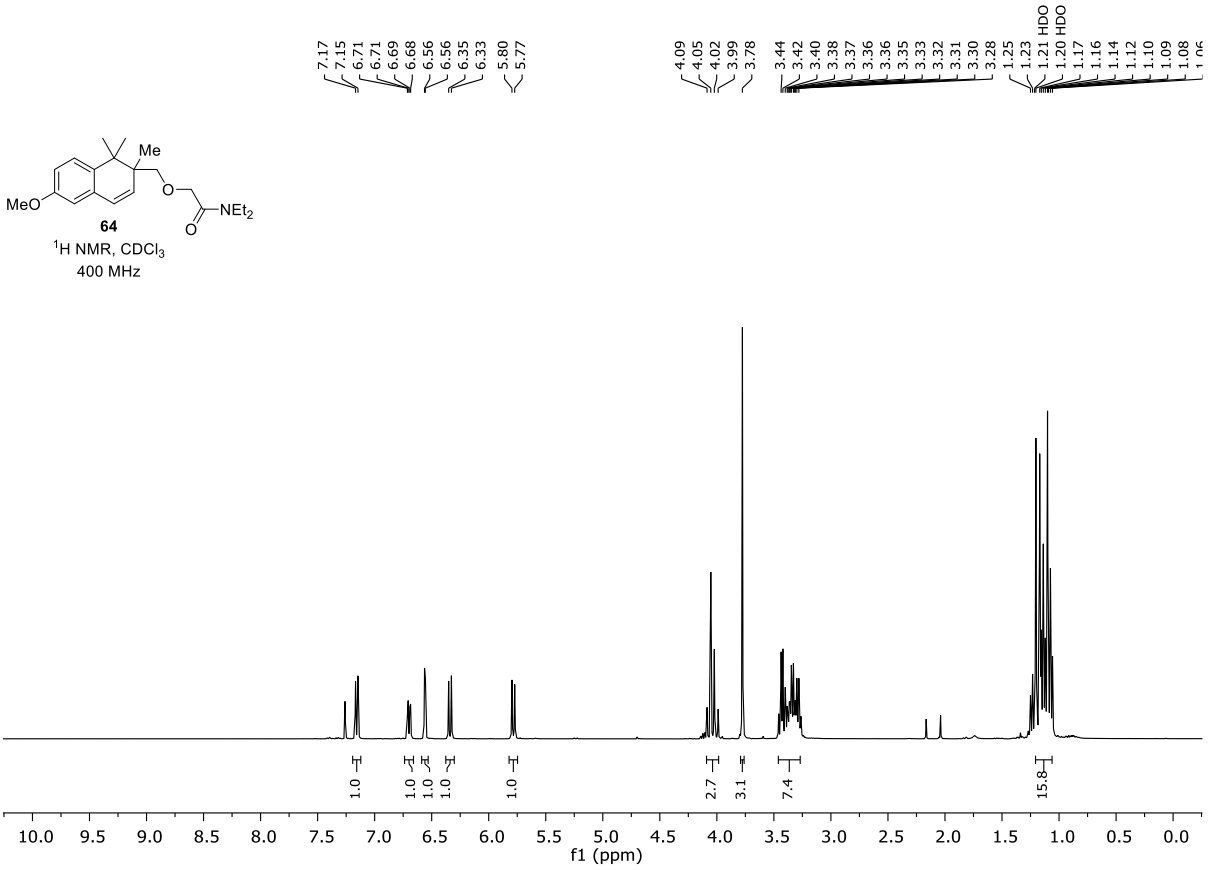

158.0
137.0
136.6
133.5
125.7
125.2
112.5
112.1
97.0
72.3
55.3
55.3
42.0
39.1
24.3
22.9
17.9
Me
MeO
O
OMe
61b
13C NMR, CDCl3
101 MHz
f1 (ppm)

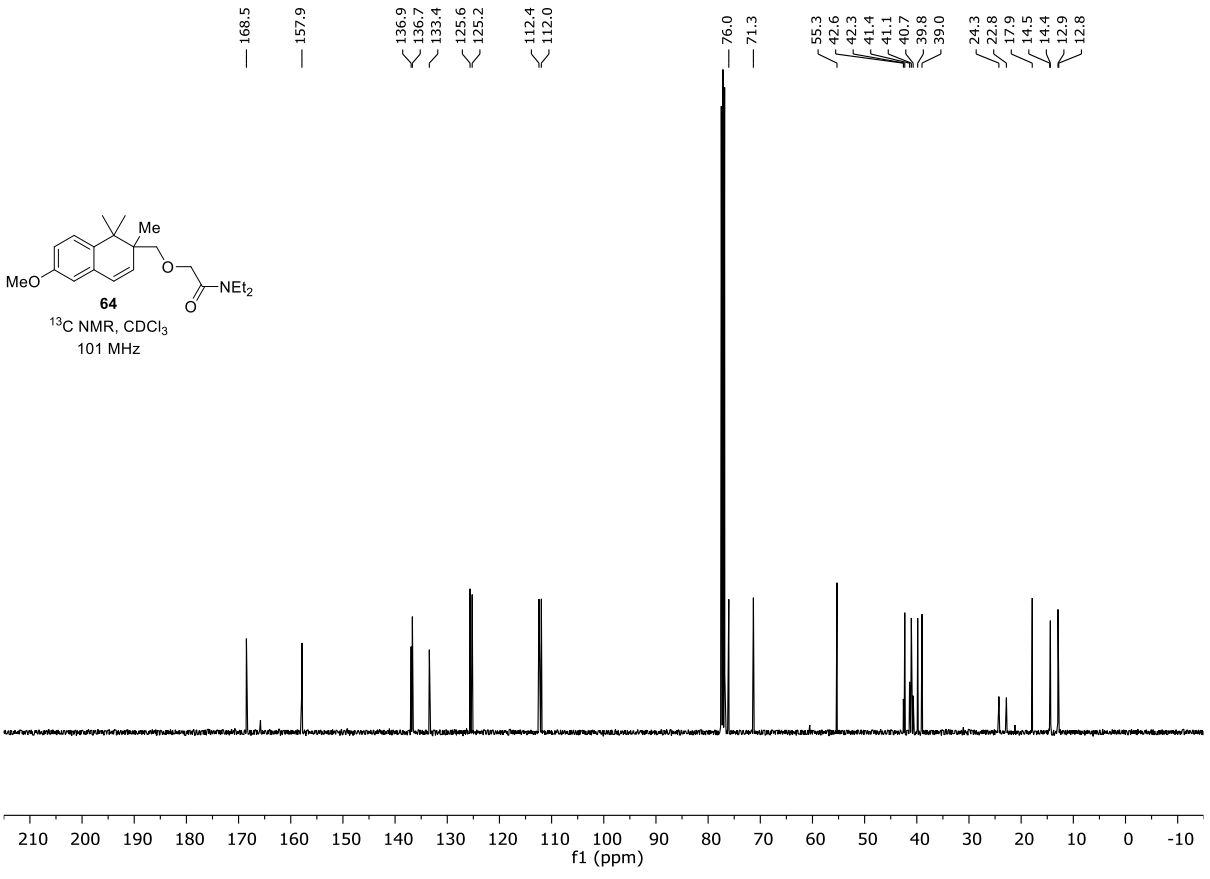

7.18
7.18 cdcl3
7.16
7.16
6.72
6.72
6.70
6.70
6.57
6.56
6.34
6.31
5.72
5.70
3.79
3.51
1.21 HDO
1.20
1.02
0.86
-0.02
-0.03
Me
MeO
O-Si
61c
1H NMR, CDCl3
599 MHz
1.0
1.0
0.9
1.0
1.0
3.1
2.0
6.0
3.1
9.0
5.7
f1 (ppm)

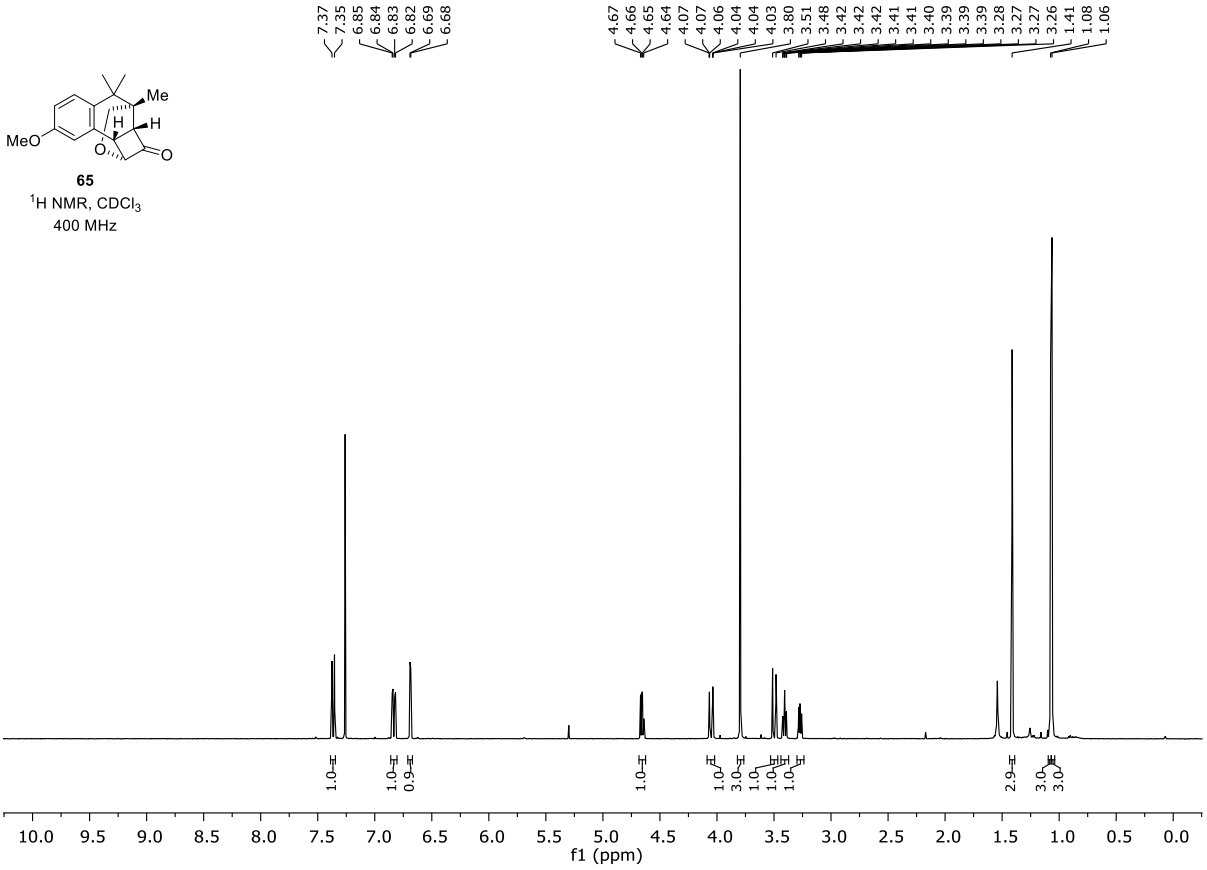

157.8
137.5
137.1
133.7
125.6
125.1
112.4
111.9
67.0
55.3
43.1
39.0
26.0
24.5
23.2
18.4
17.6
-5.4
-5.4
Me
MeO
O-Si
61c
13C NMR, CDCl3
151 MHz
f1 (ppm)

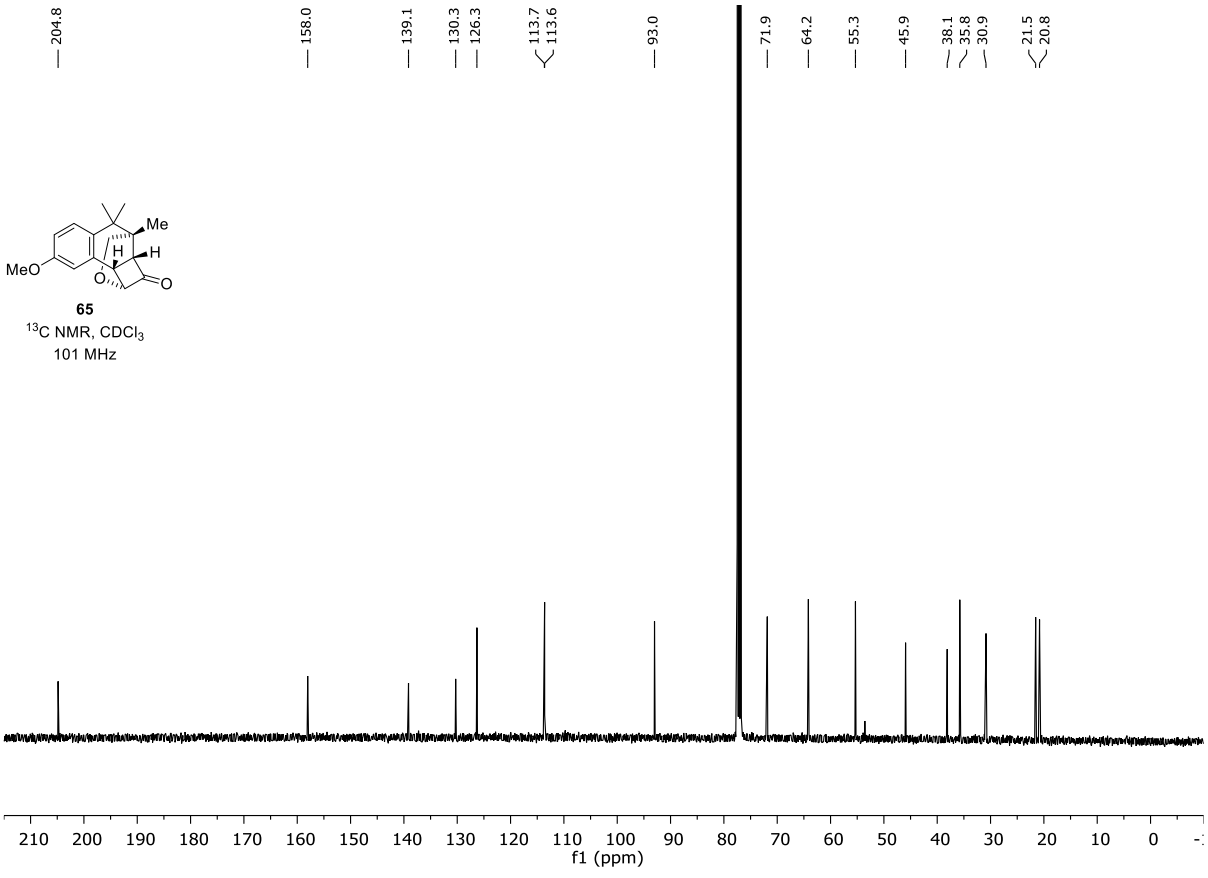

Me
MeO
OMe
61d
1H NMR, CDCl3
400 MHz
7.19
7.17
6.73
6.71
6.59
6.58
6.38
6.35
5.77
5.74
3.79
3.32
3.30
3.27
3.26
3.24
1.22 HDO
1.18
1.09
1.0
1.0
1.0
1.0
1.0
3.0
5.0
3.0
3.1
3.0
f1 (ppm)

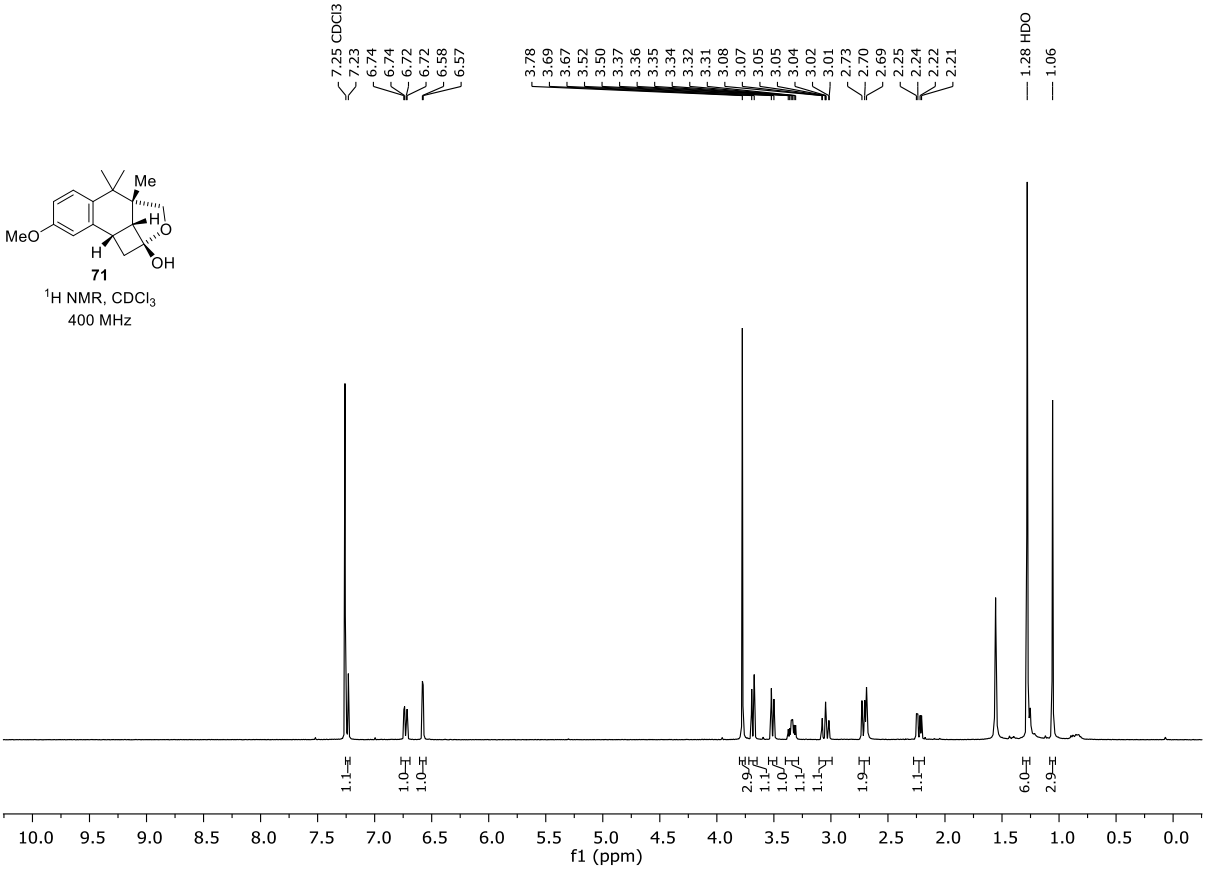

Me
MeO
OMe
61d
13C NMR, CDCl3
101 MHz
157.9
137.0
136.9
133.5
125.5
125.2
112.5
112.0
77.4
59.5
55.3
42.2
39.1
24.4
22.8
17.8
f1 (ppm)

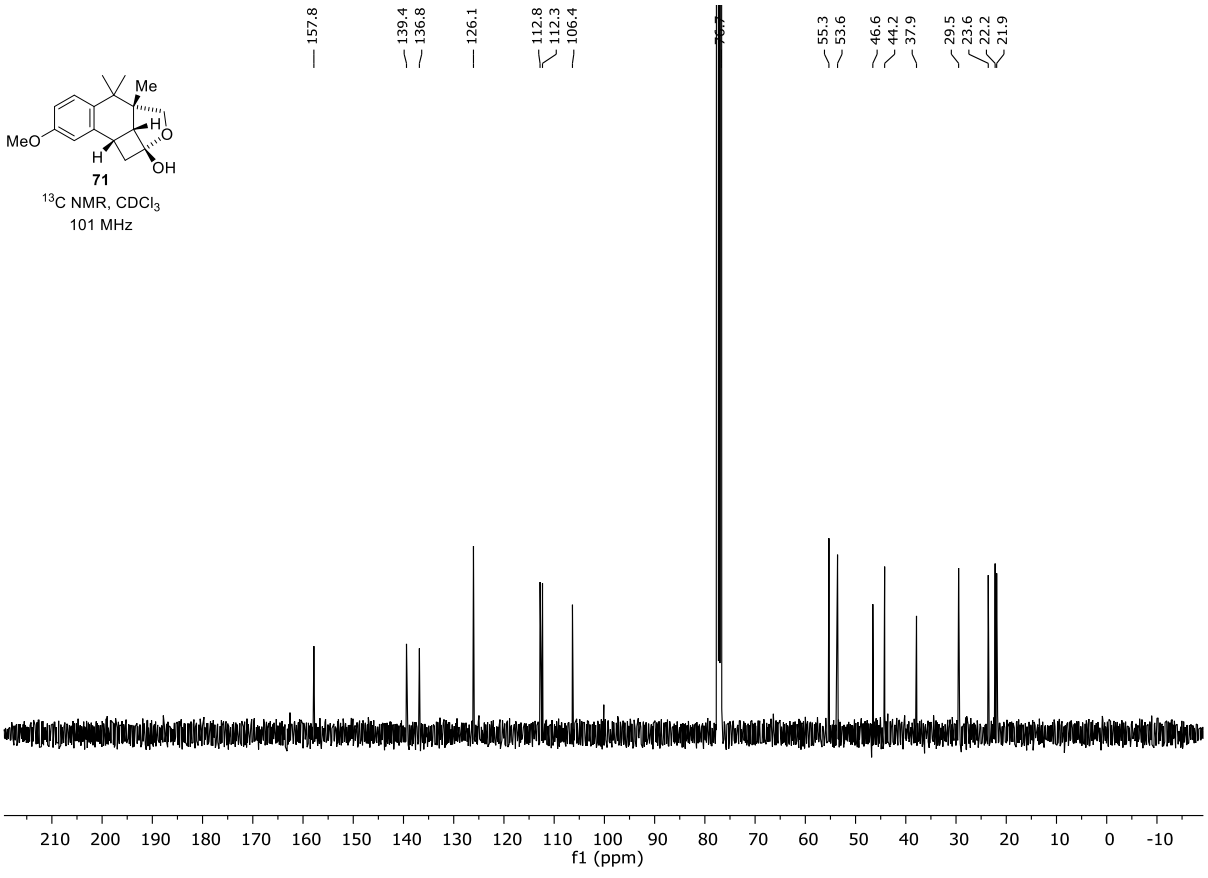

7.17
7.15
6.71
6.71
6.69
6.68
6.56
6.56
6.35
6.33
5.80
5.77
4.09
4.05
4.02
3.99
3.78
3.44
3.42
3.40
3.38
3.37
3.36
3.36
3.35
3.33
3.32
3.31
3.30
3.28
1.25
1.23
1.21 HDO
1.20 HDO
1.17
1.16
1.14
1.12
1.10
1.09
1.08
Me
MeO
O
NEt2
O
64
1H NMR, CDCl3
400 MHz
1.0
1.0
1.0
1.0
1.0
2.7
3.1
7.4
15.8
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

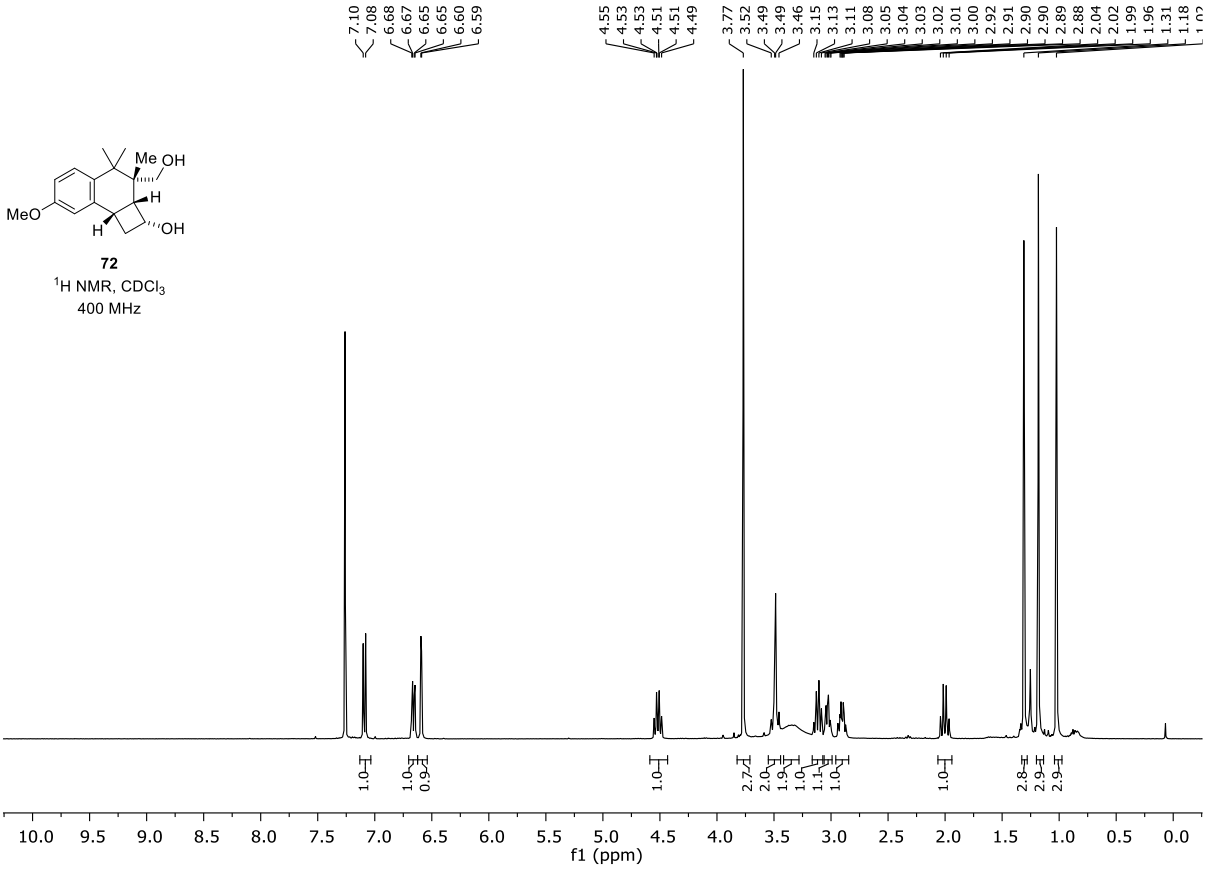

168.5
157.9
136.9
136.7
133.4
125.6
125.2
112.4
112.0
76.0
71.3
55.3
42.6
42.3
41.4
41.1
40.7
39.8
39.0
24.3
22.8
17.9
14.5
14.4
12.9
12.8
Me
MeO
O
NEt2
O
64
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.37
7.35
6.85
6.84
6.83
6.82
6.69
6.68
4.67
4.66
4.65
4.64
4.07
4.07
4.06
4.04
4.04
4.03
3.80
3.51
3.48
3.42
3.42
3.42
3.41
3.40
3.39
3.39
3.39
3.28
3.27
3.27
3.26
1.41
1.08
1.06
Me
H
H
MeO
O
O
65
1H NMR, CDCl3
400 MHz
1.0
1.0
0.9
1.0
1.0
3.0
1.0
1.0
1.0
2.9
3.0
3.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

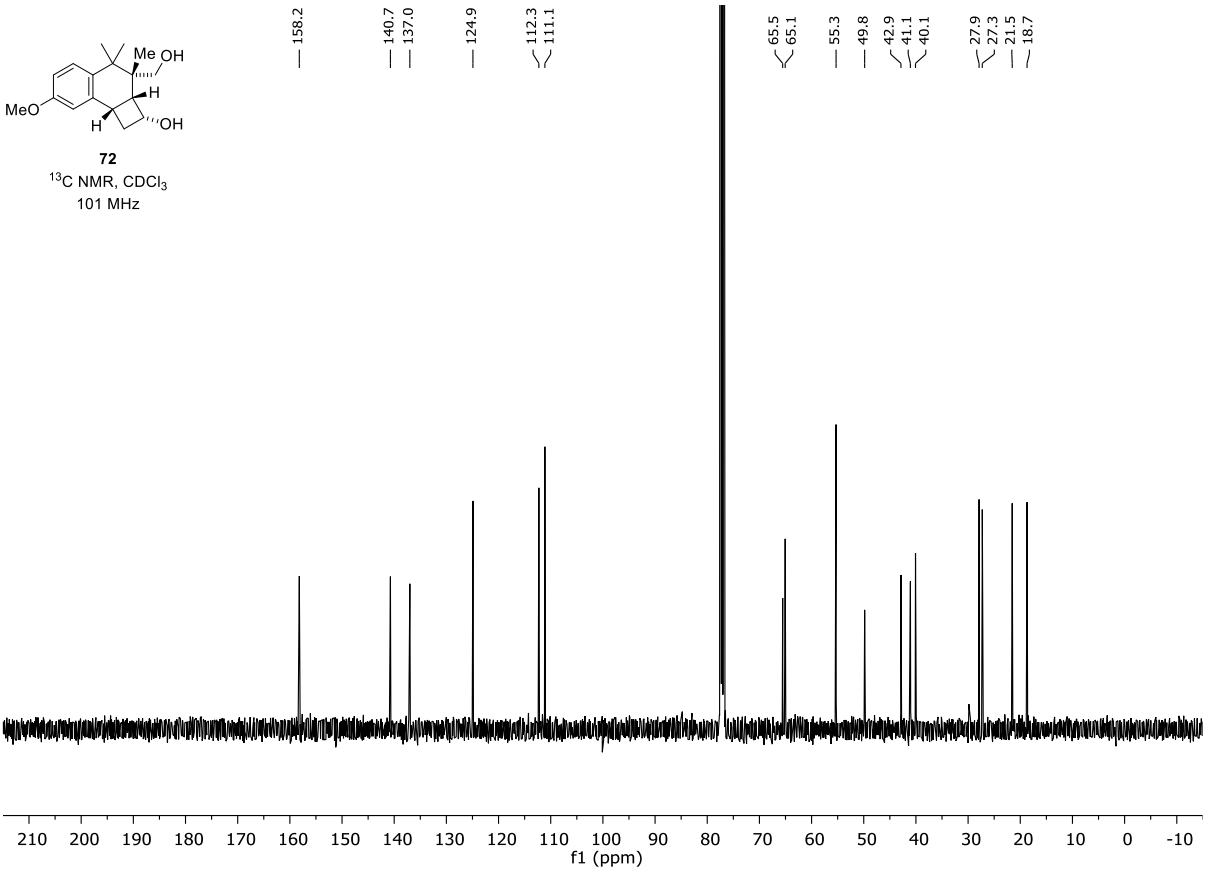

204.8
158.0
139.1
130.3
126.3
113.7
113.6
93.0
71.9
64.2
55.3
45.9
38.1
35.8
30.9
21.5
20.8
Me
H
H
MeO
O
O
65
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.25 CDCl3
7.23
6.74
6.74
6.72
6.72
6.58
6.57
3.78
3.69
3.67
3.52
3.50
3.37
3.36
3.35
3.34
3.32
3.31
3.08
3.07
3.05
3.05
3.04
3.02
3.01
2.73
2.70
2.69
2.25
2.24
2.22
2.21
1.28 HDO
1.06
Me
H
O
MeO
H
OH
71
1H NMR, CDCl3
400 MHz
1.1
1.0
1.0
2.9
1.1
1.0
1.1
1.1
1.9
1.1
6.0
2.9
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

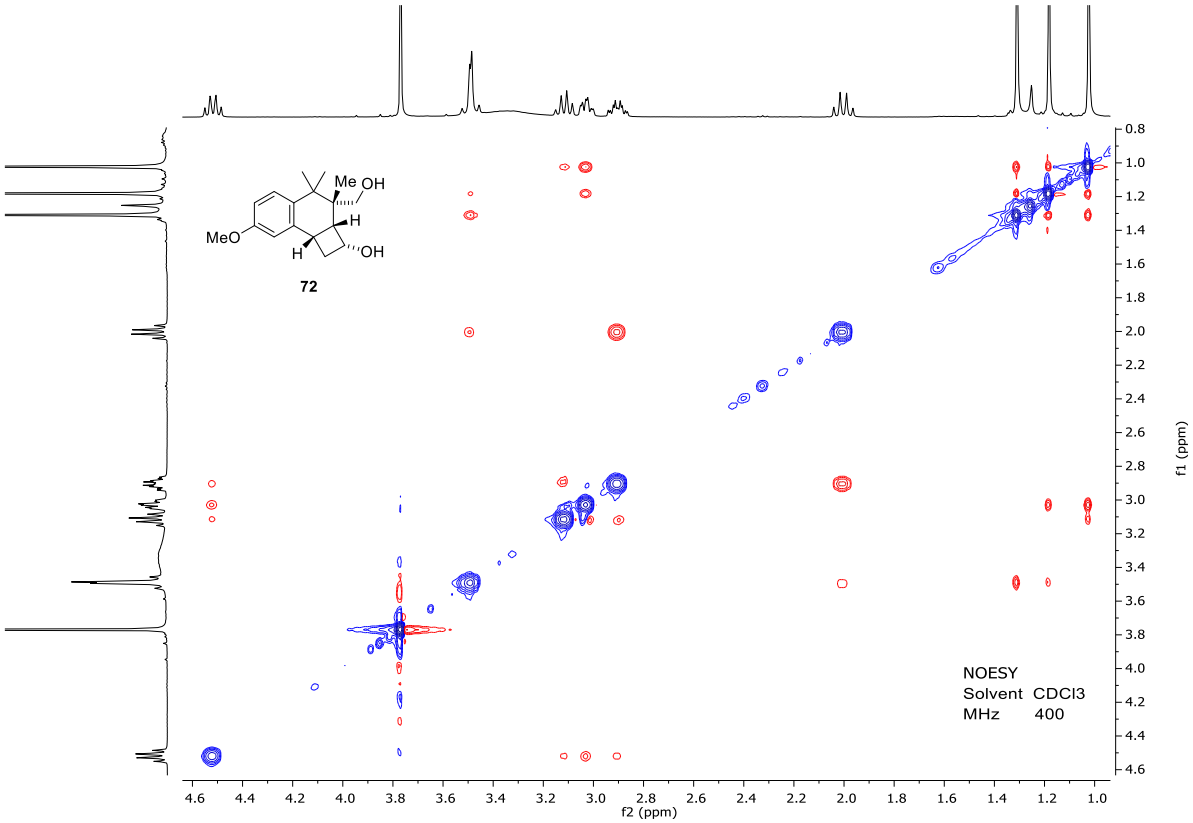

157.8
139.4
136.8
126.1
112.8
112.3
106.4
76.7
55.3
53.6
46.6
44.2
37.9
29.5
23.6
22.2
21.9
Me
H
O
MeO
H
OH
71
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

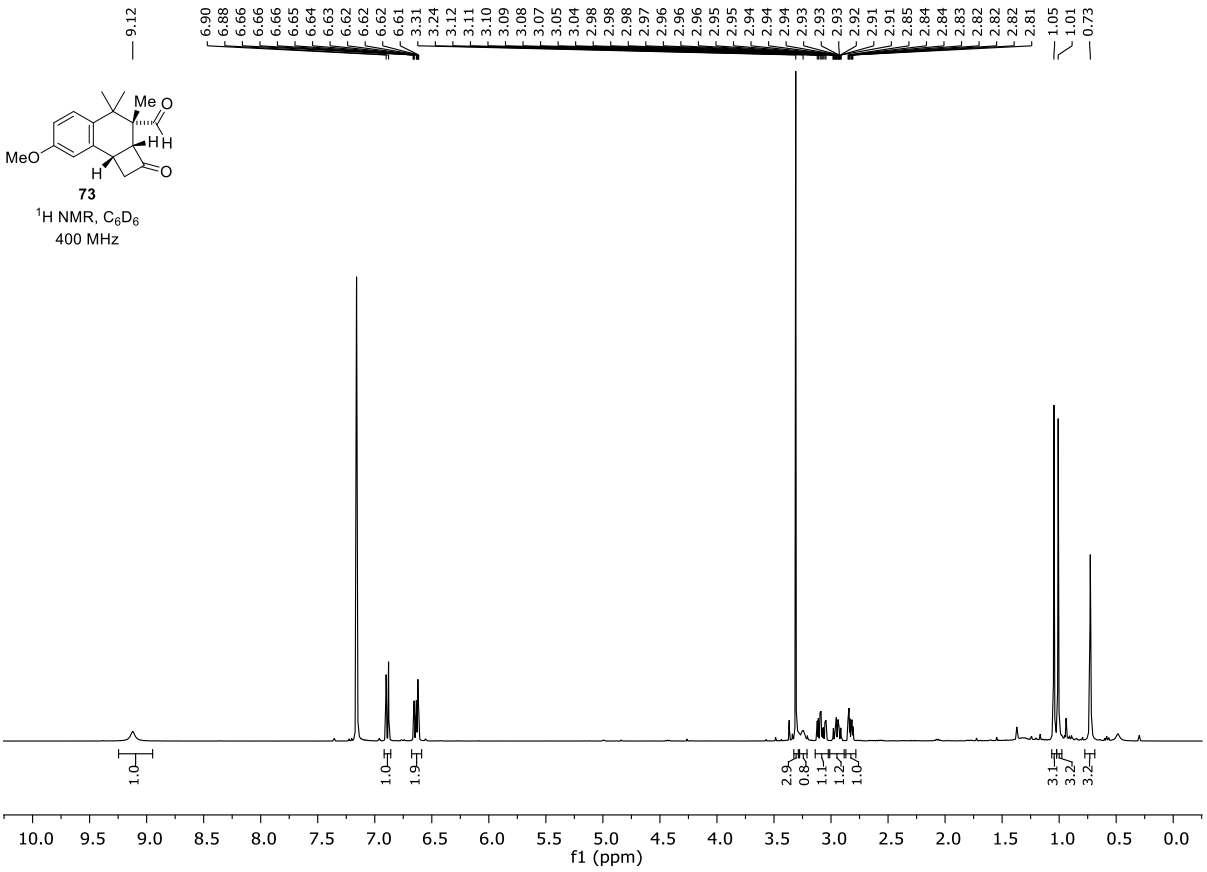


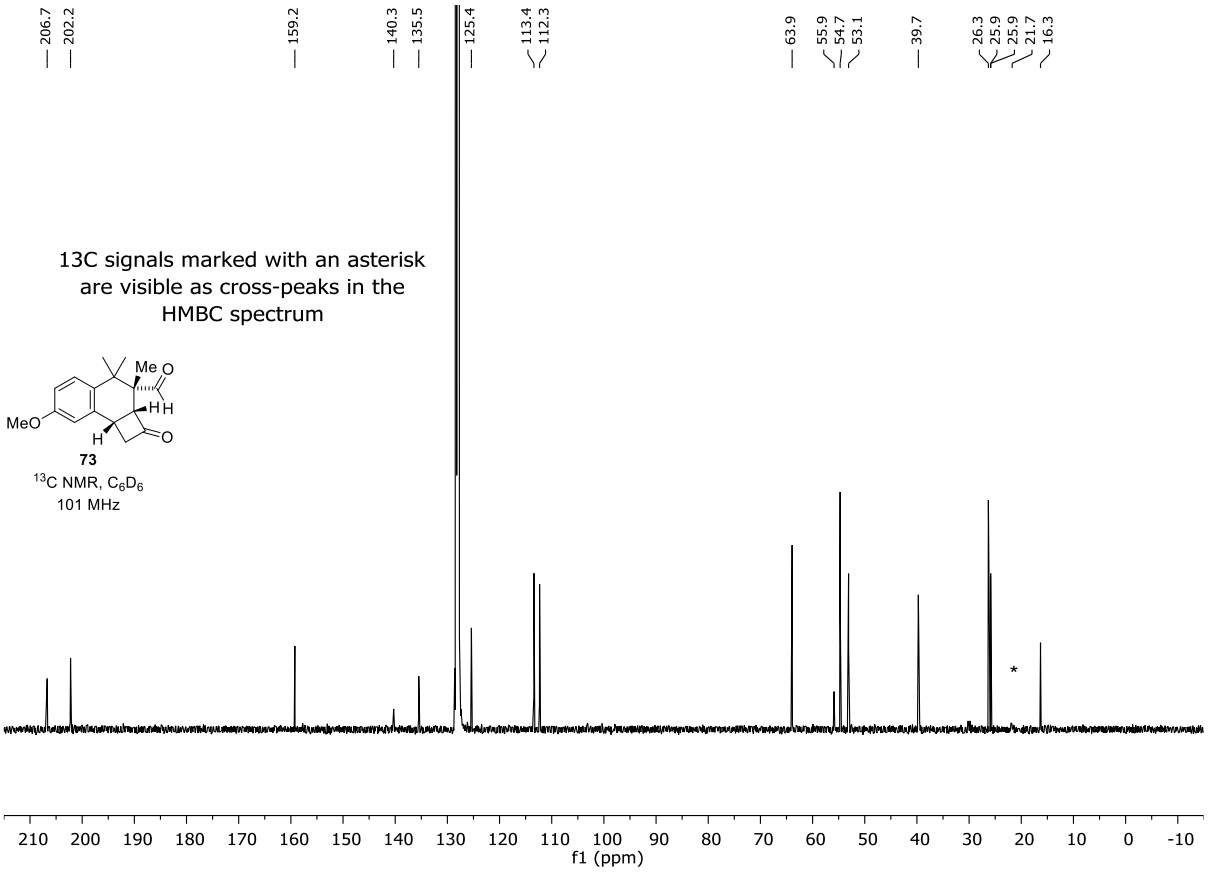
72
^{1}H NMR, $CDCl_3$
400 MHz

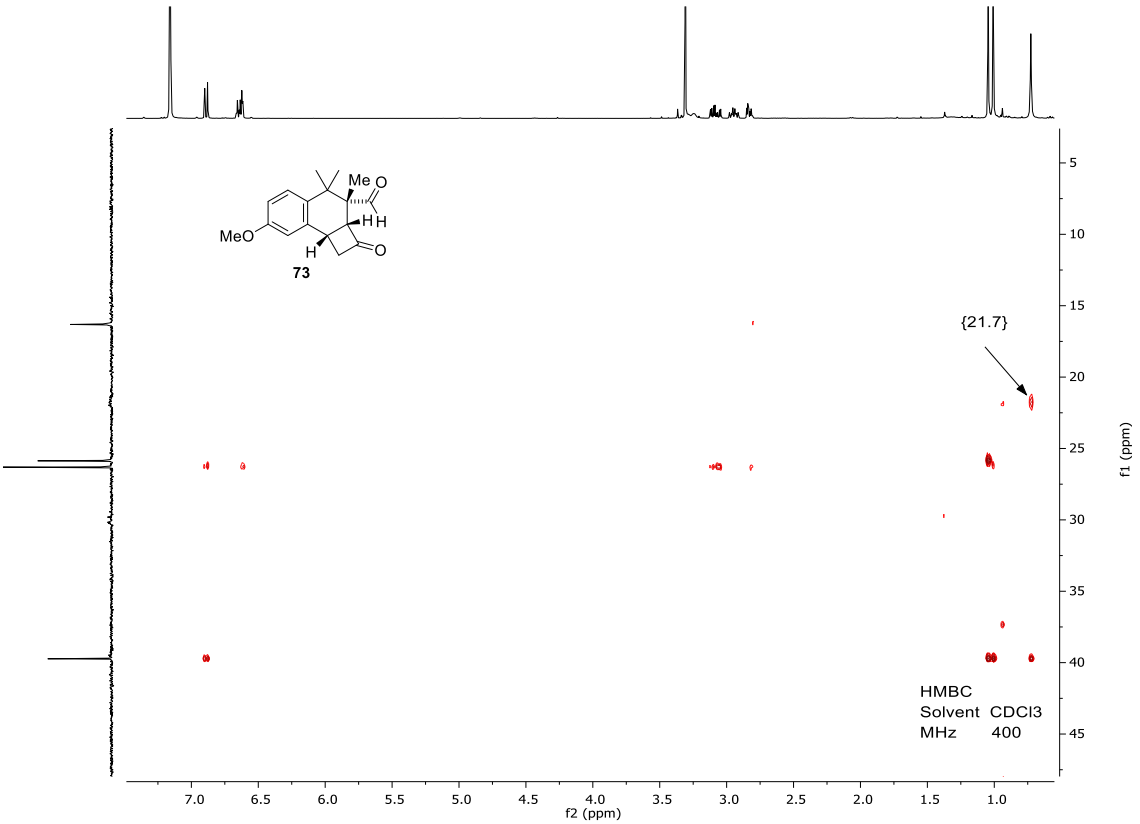


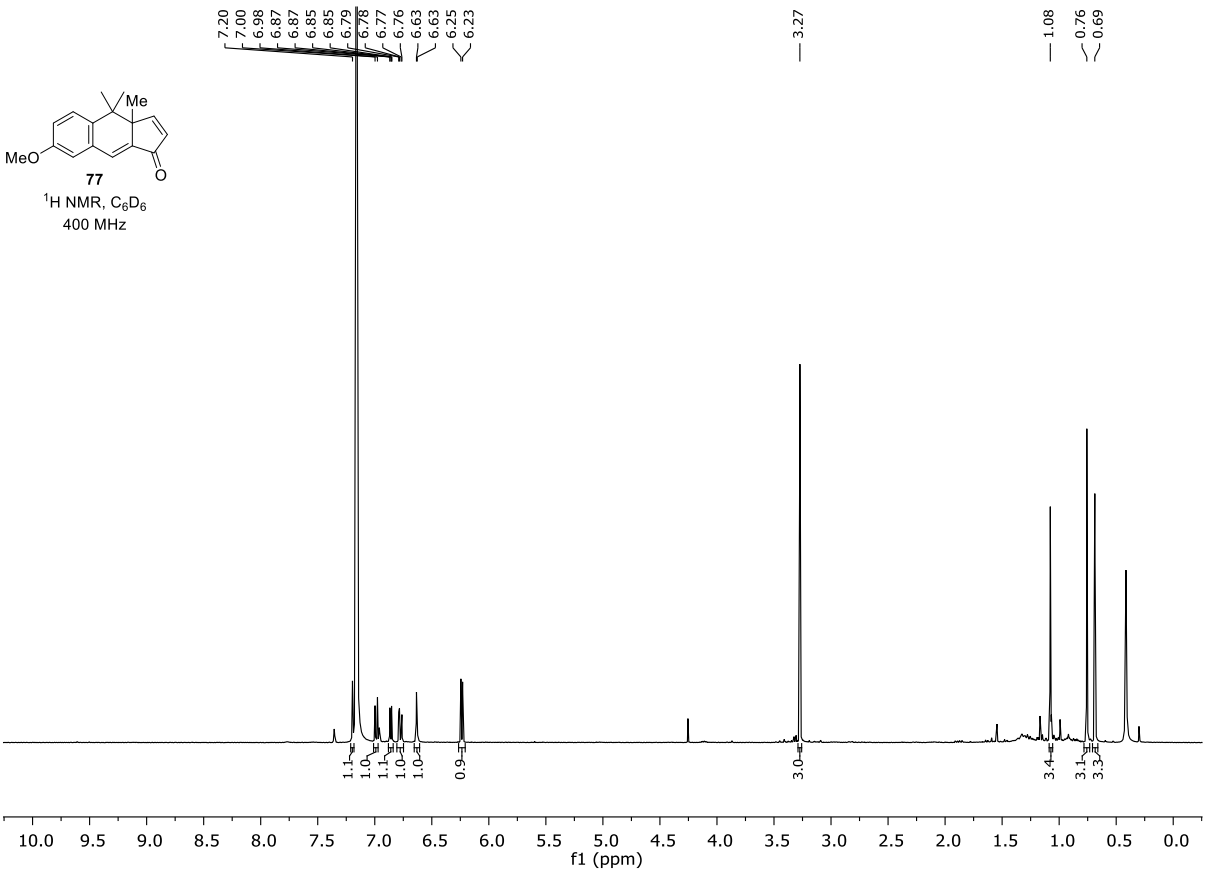
72
^{13}C NMR, $CDCl_3$
101 MHz

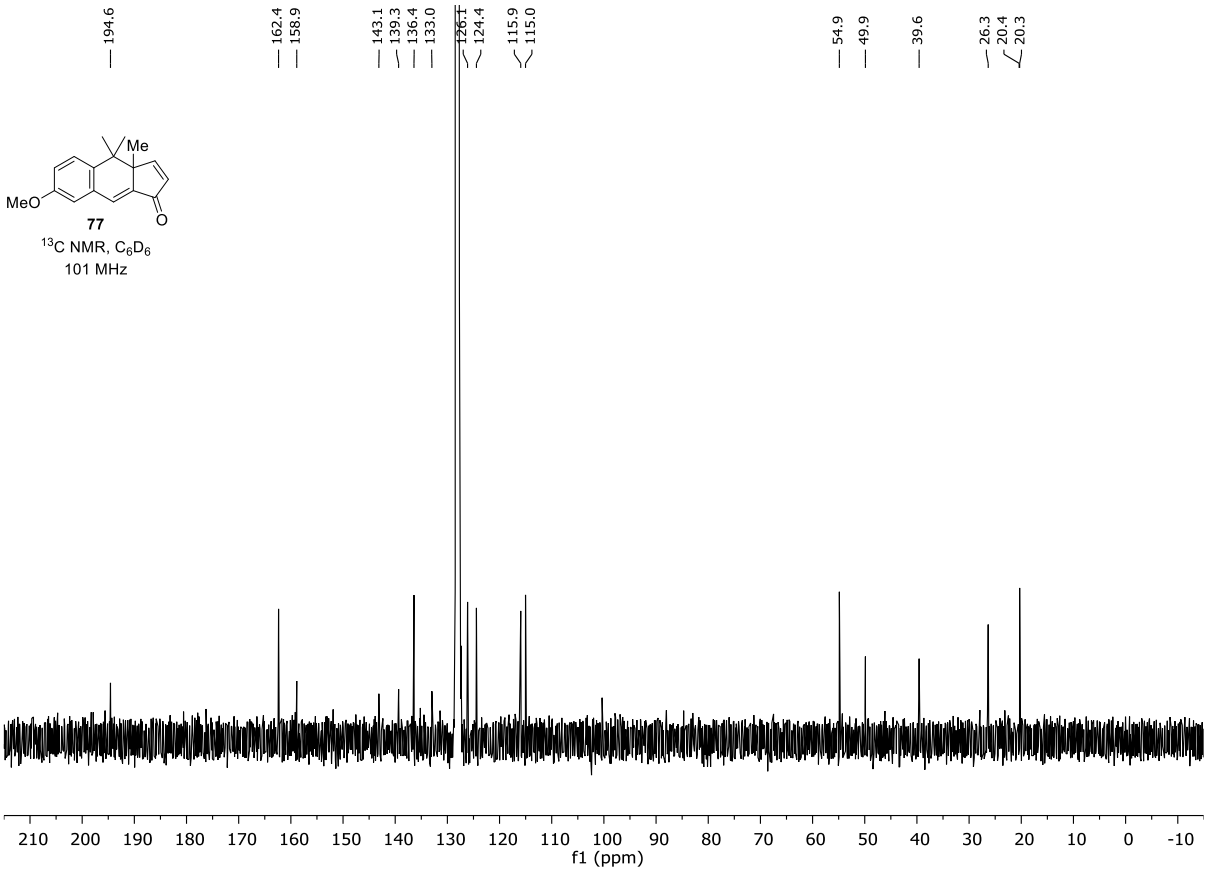

Me OH
H
MeO
H
OH
72
NOESY
Solvent CDCl3
MHz 400
f2 (ppm)
f1 (ppm)

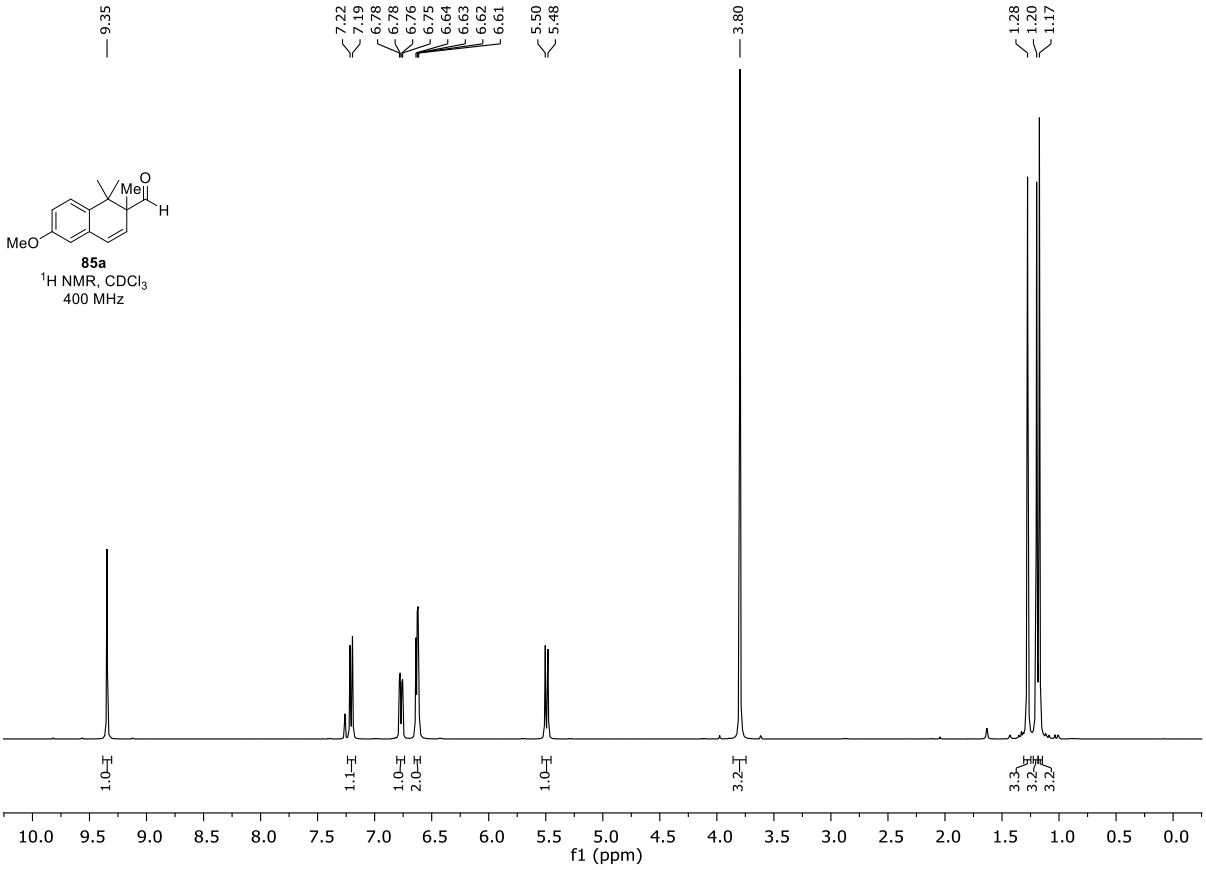

9.12
6.90 6.88 6.66 6.66 6.66 6.65 6.64 6.63 6.62 6.62 6.62 6.61 3.31 3.24 3.12 3.11 3.10 3.09 3.08 3.07 3.05 3.04 2.98 2.98 2.98 2.97 2.96 2.96 2.96 2.95 2.95 2.94 2.94 2.94 2.93 2.93 2.93 2.92 2.91 2.91 2.85 2.84 2.84 2.83 2.82 2.82 2.82 2.81 1.05 1.01 0.73
Me O
H H
MeO
H
O
73
1H NMR, C6D6
400 MHz
1.0 1.0 1.9 2.9 0.8 1.1 1.2 1.0 3.1 3.2 3.2
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

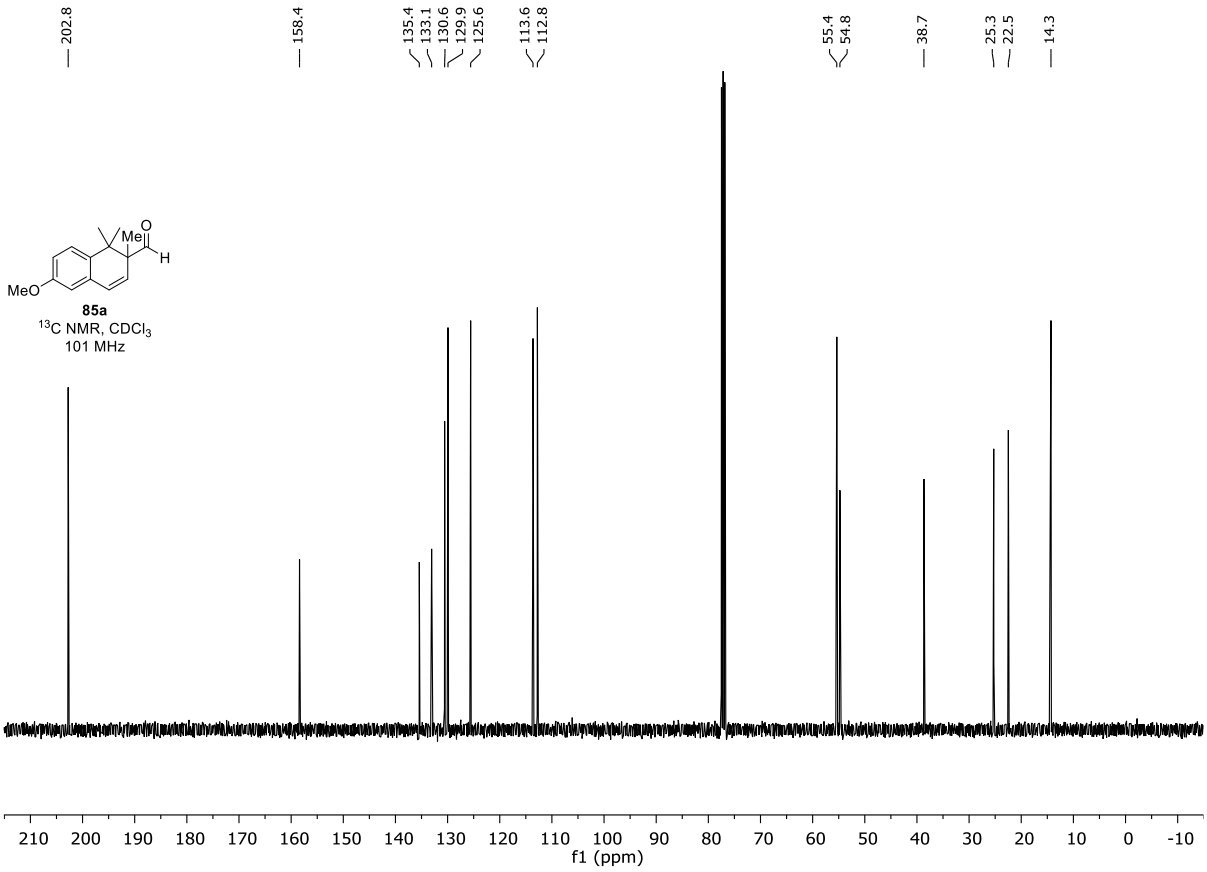

206.7 202.2 159.2 140.3 135.5 125.4 113.4 112.3 63.9 55.9 54.7 53.1 39.7 26.3 25.9 25.9 21.7 16.3
13C signals marked with an asterisk are visible as cross-peaks in the HMBC spectrum
Me O
H H
MeO
H
O
73
13C NMR, C6D6
101 MHz
*
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

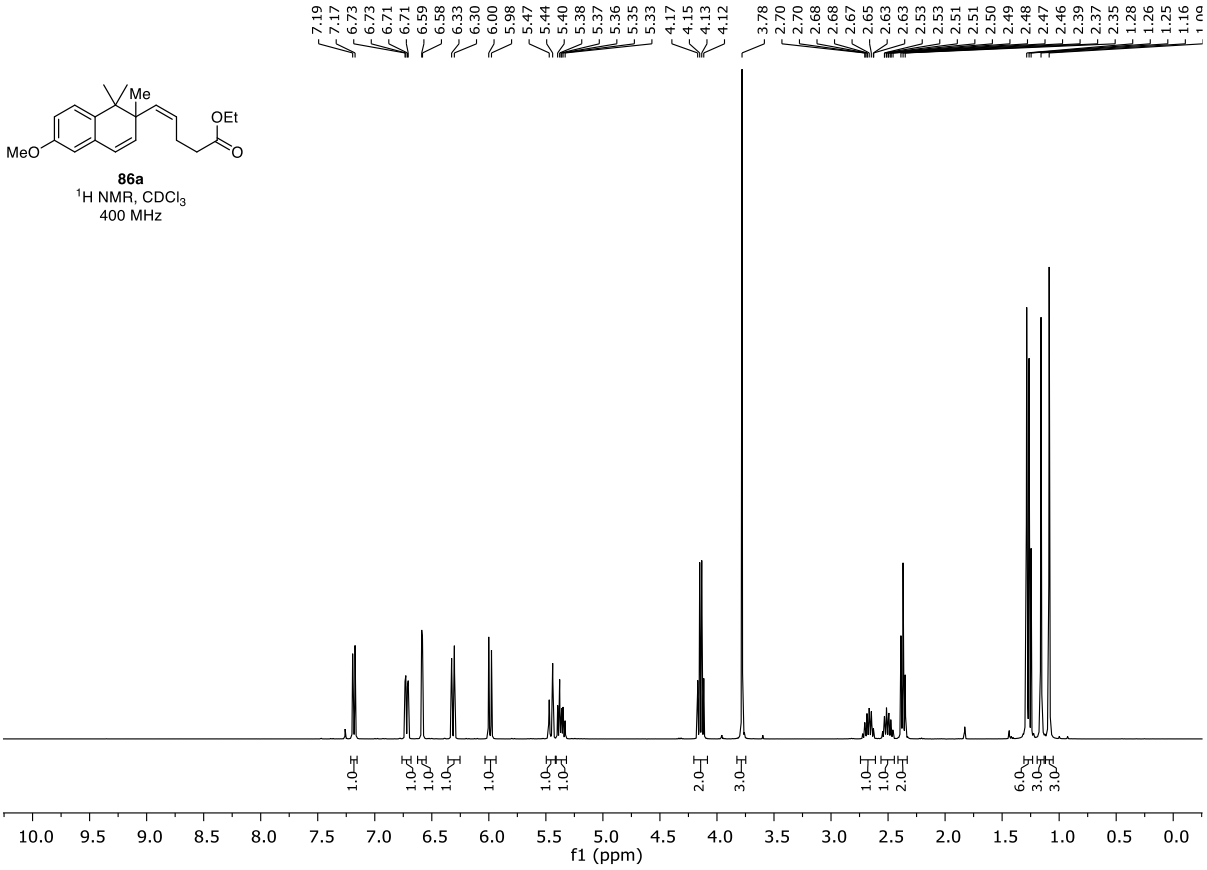

Me
O
H
H
MeO
H
O
73
{21.7}
HMBC
Solvent CDCl3
MHz 400
f2 (ppm)
f1 (ppm)

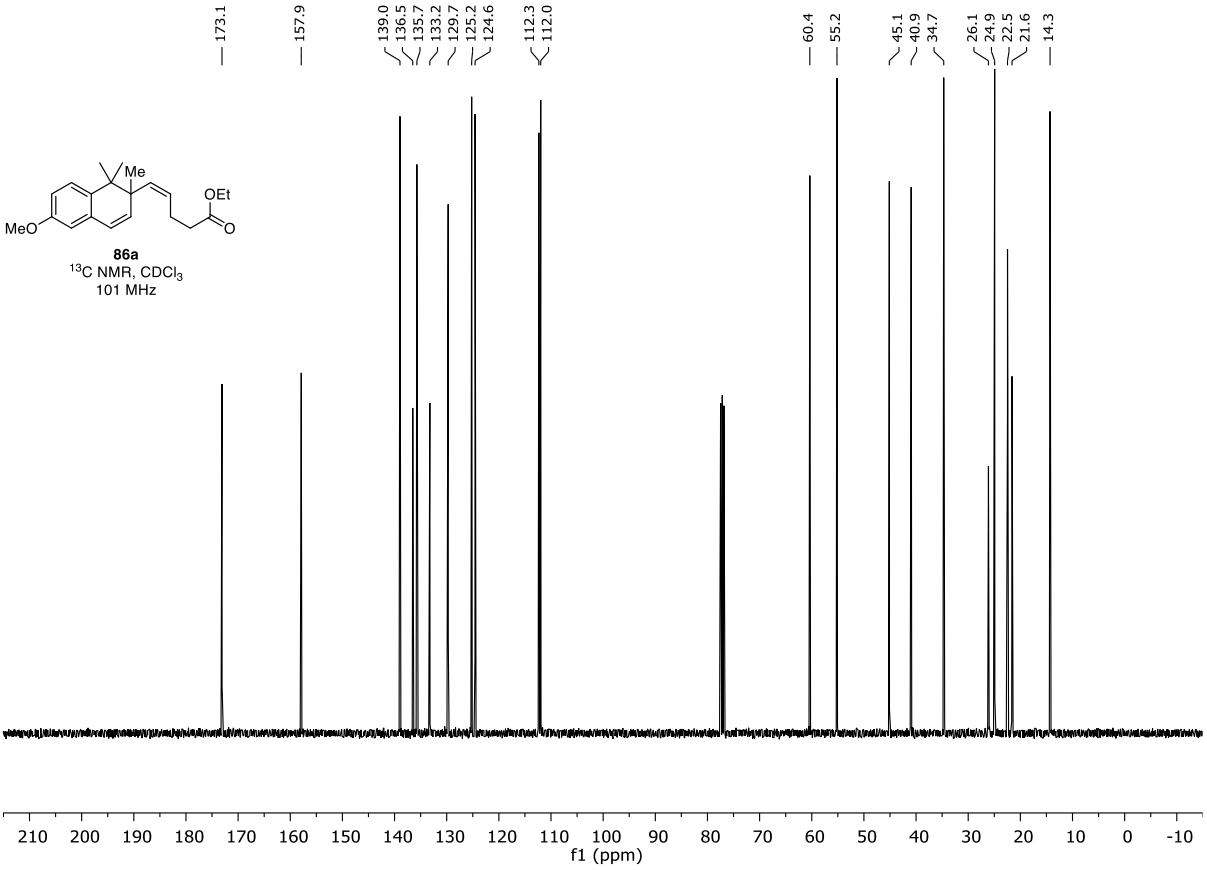

7.20
7.00
6.98
6.87
6.87
6.85
6.85
6.79
6.78
6.77
6.76
6.63
6.63
6.25
6.23
3.27
1.08
0.76
0.69
Me
MeO
O
77
1H NMR, C6D6
400 MHz
1.1
1.0
1.1
1.0
1.0
0.9
3.0
3.4
3.1
3.3
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

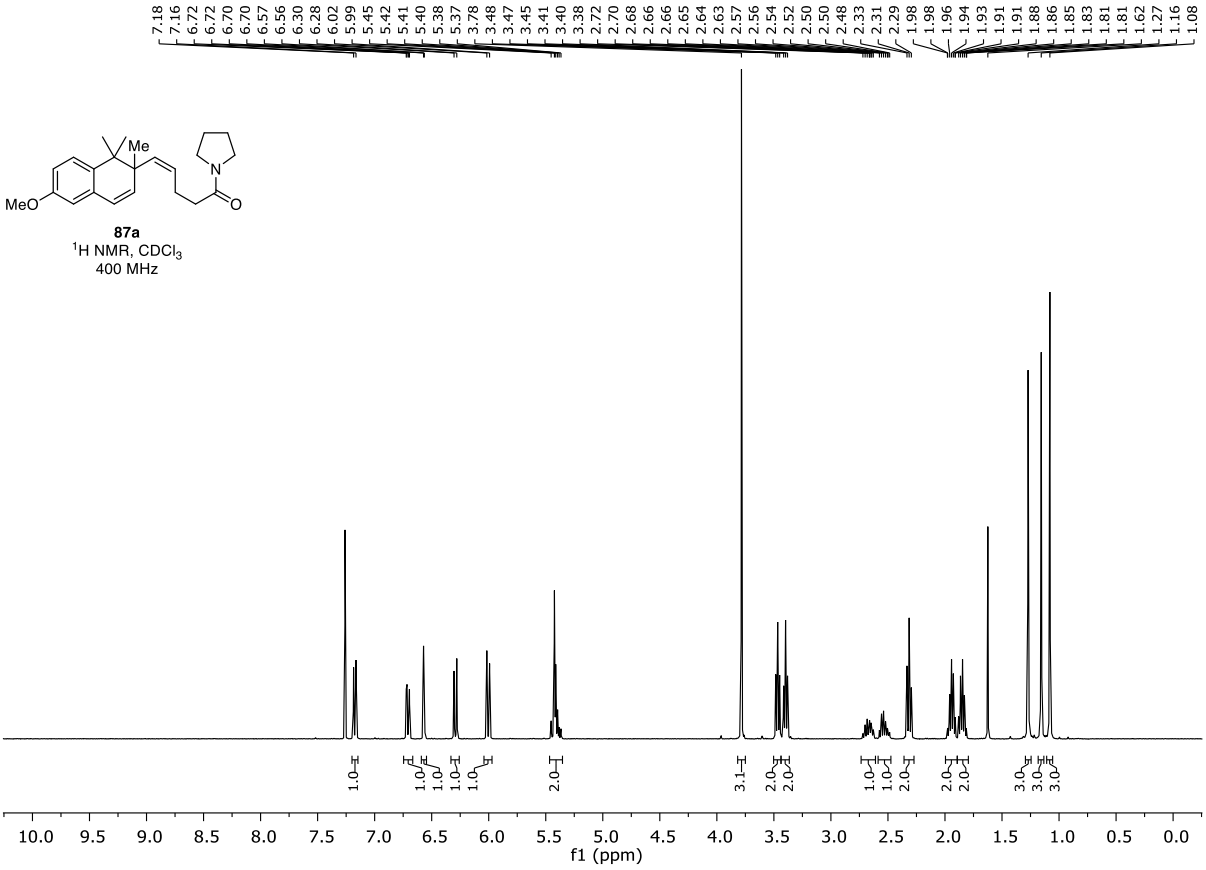

194.6
162.4
158.9
143.1
139.3
136.4
133.0
126.1
124.4
115.9
115.0
54.9
49.9
39.6
26.3
20.4
20.3
Me
MeO
O
77
13C NMR, C6D6
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

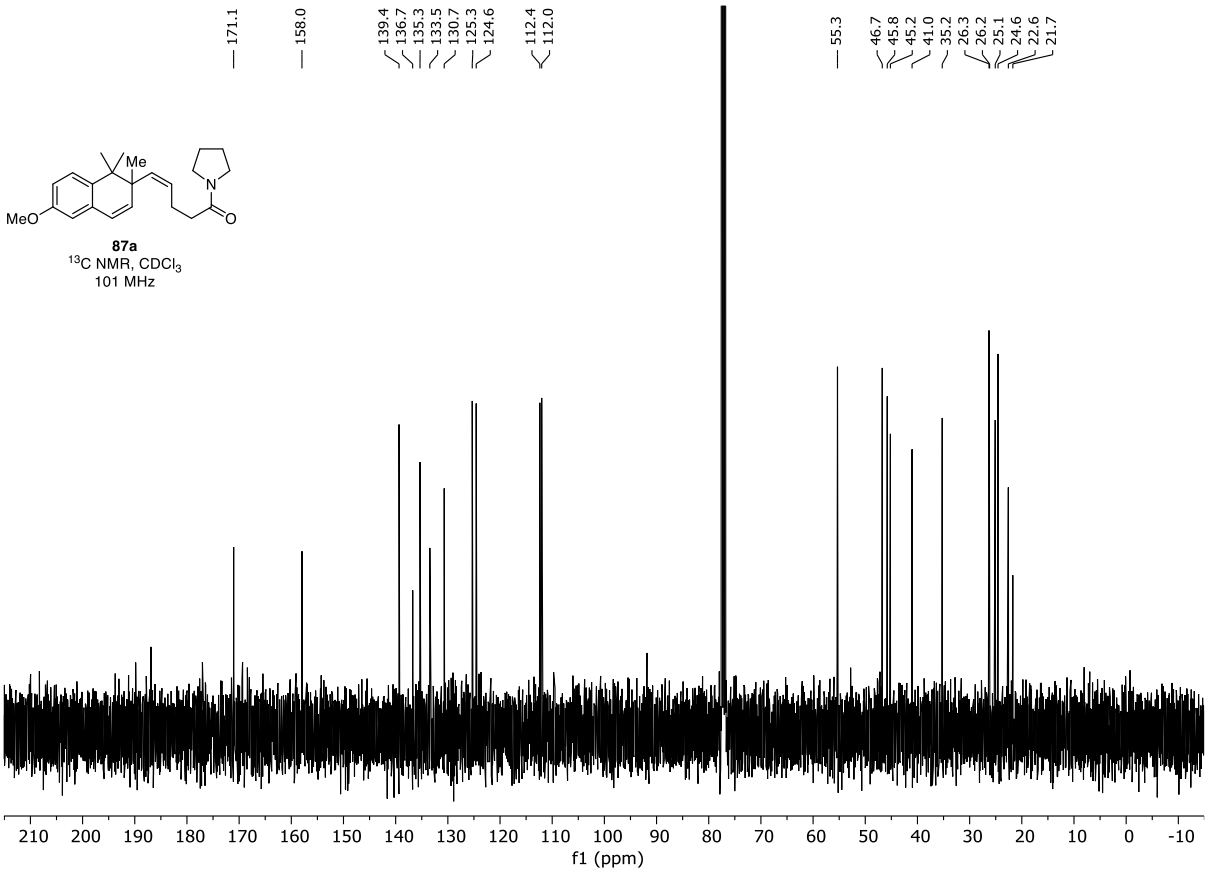

9.35
7.22
7.19
6.78
6.78
6.76
6.75
6.64
6.63
6.62
6.61
5.50
5.48
3.80
1.28
1.20
1.17
Me
O
H
MeO
85a
1H NMR, CDCl3
400 MHz
1.0
1.1
1.0
2.0
1.0
3.2
3.3
3.2
3.2
f1 (ppm)

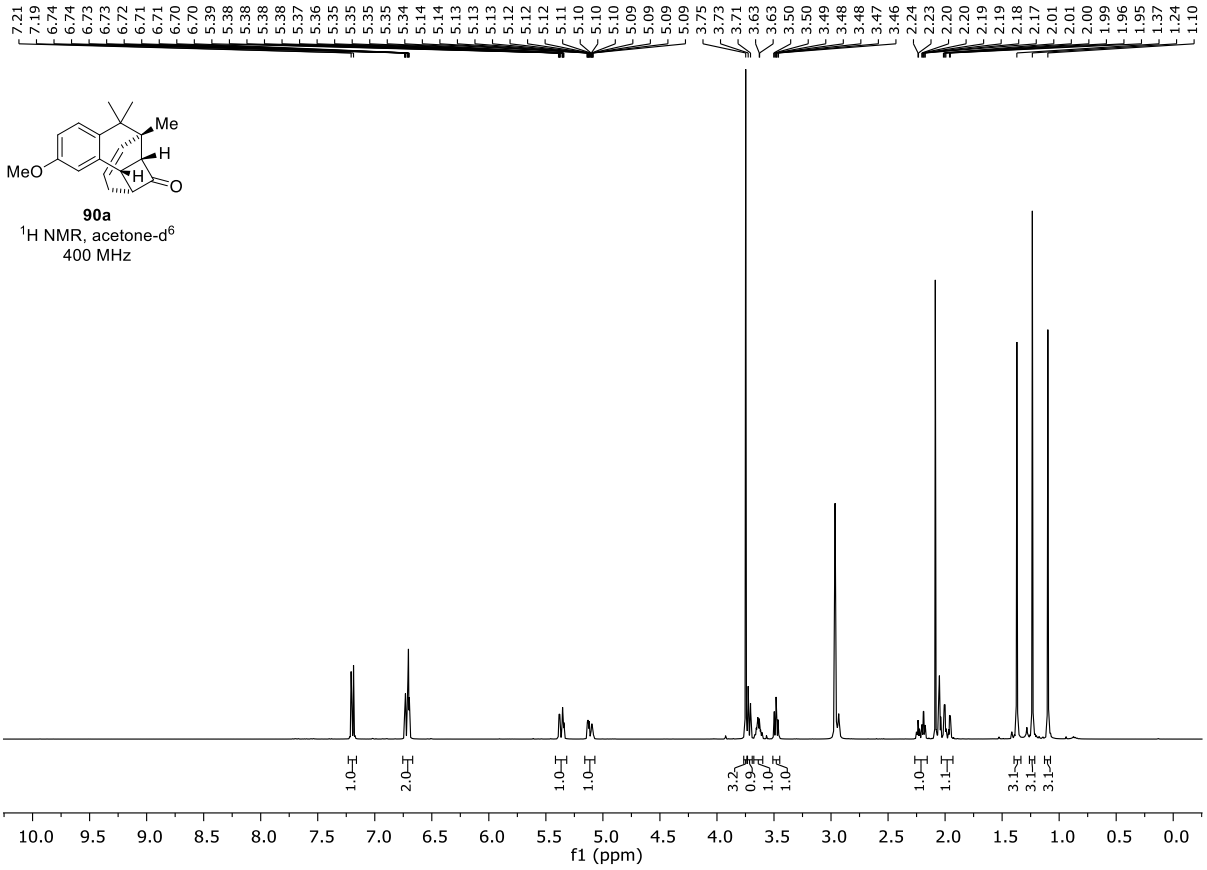

202.8
158.4
135.4
133.1
130.6
129.9
125.6
113.6
112.8
55.4
54.8
38.7
25.3
22.5
14.3
Me
O
H
MeO
85a
13C NMR, CDCl3
101 MHz
f1 (ppm)

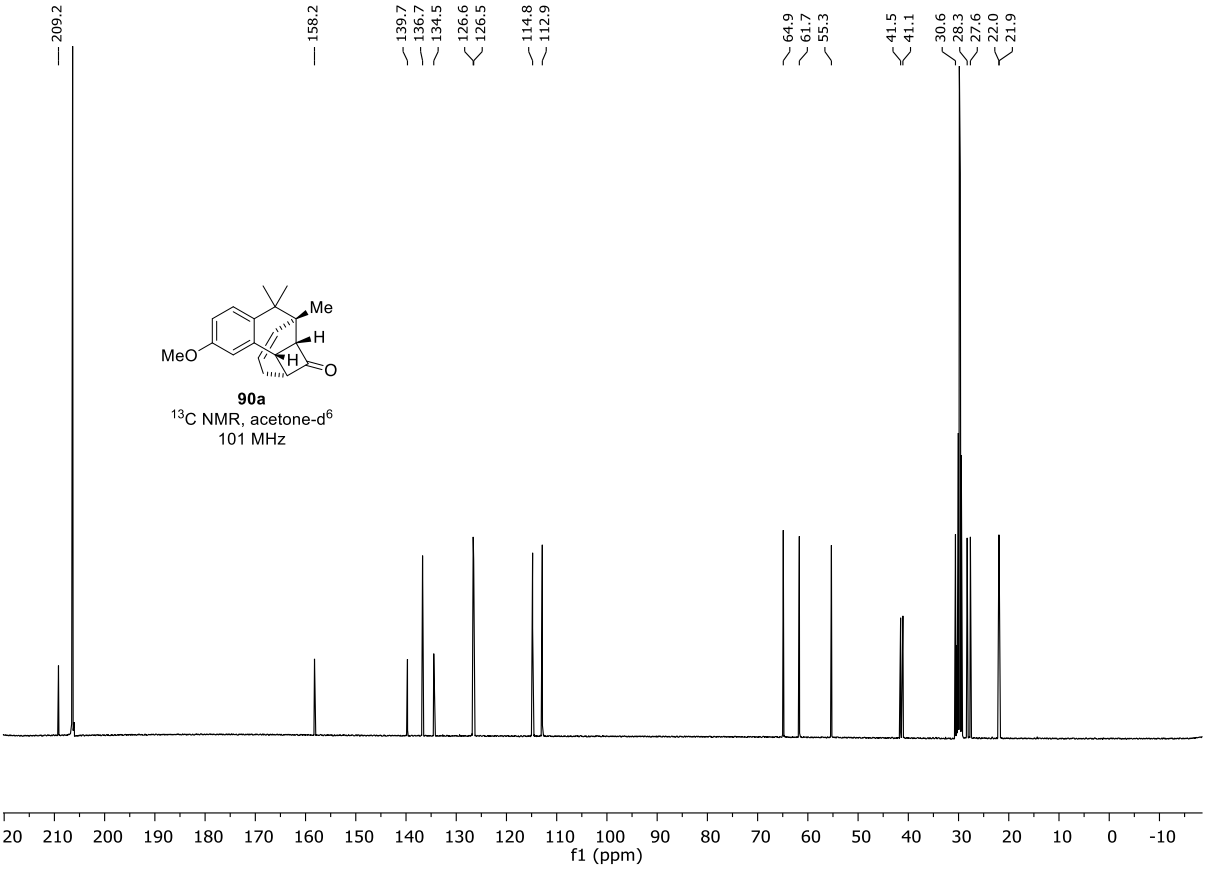

Me
OEt
MeO
O
86a
^{1}H NMR, $CDCl_3$
400 MHz
f1 (ppm)

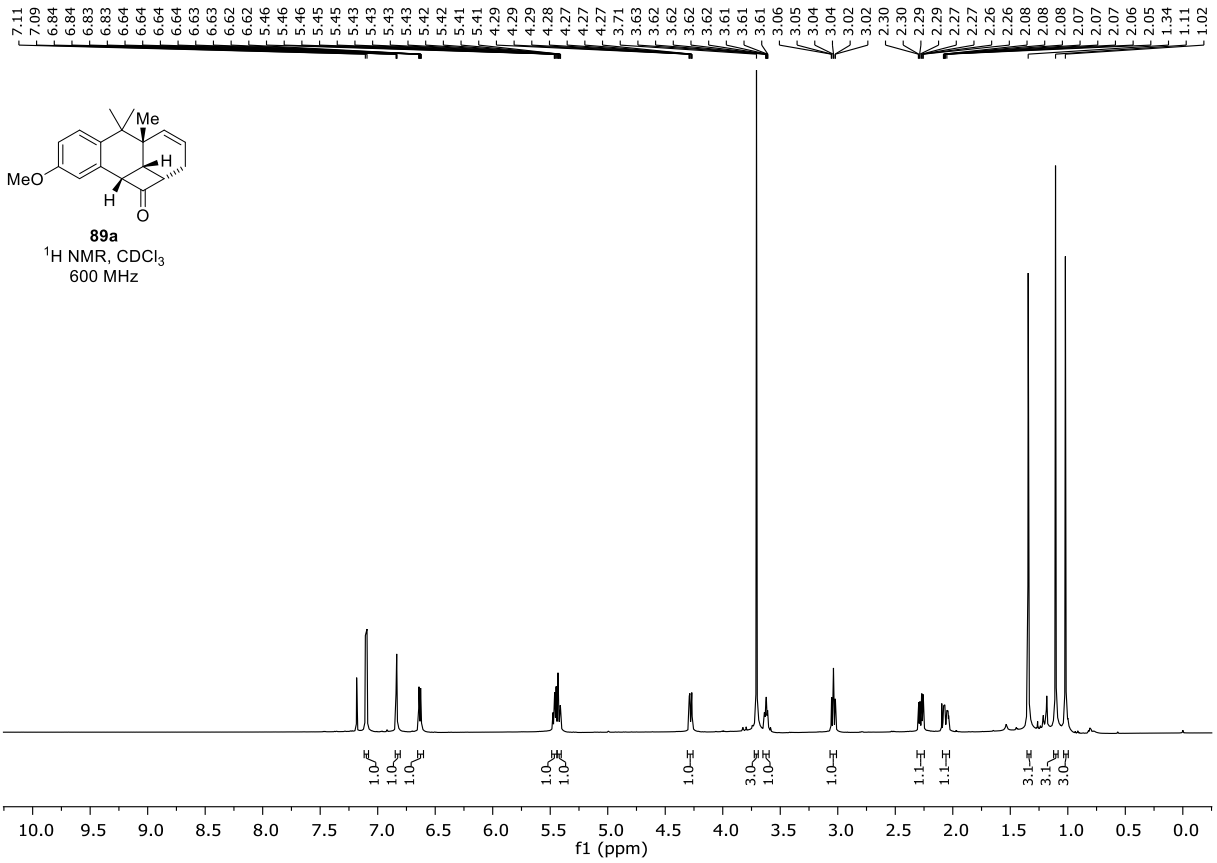

Me
OEt
MeO
O
86a
^{13}C NMR, $CDCl_3$
101 MHz
f1 (ppm)


7.18 7.16 6.72 6.72 6.70 6.70 6.57 6.56 6.30 6.28 6.02 5.99 5.45 5.42 5.41 5.40 5.38 5.37 3.78 3.48 3.47 3.45 3.41 3.40 3.38 2.72 2.70 2.68 2.66 2.66 2.65 2.64 2.63 2.57 2.56 2.54 2.52 2.50 2.50 2.48 2.33 2.31 2.29 1.98 1.98 1.96 1.94 1.93 1.91 1.91 1.88 1.86 1.85 1.83 1.81 1.81 1.62 1.27 1.16 1.08
Me
N
O
MeO
87a
^{1}H NMR, $CDCl_3$
400 MHz
1.0 1.0 1.0 1.0 2.0 3.1 2.0 2.0 1.0 1.0 2.0 2.0 2.0 3.0 3.0 3.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

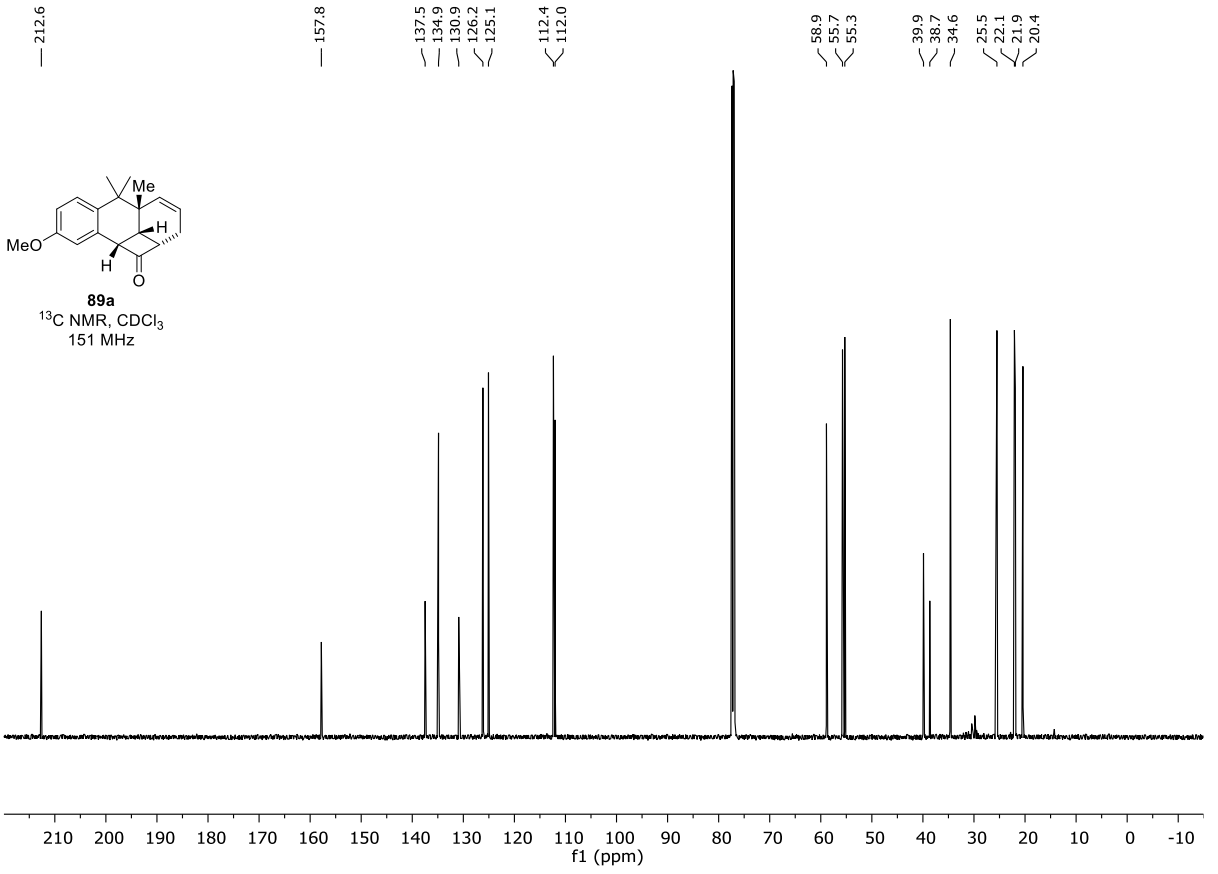

171.1 158.0 139.4 136.7 135.3 133.5 130.7 125.3 124.6 112.4 112.0 55.3 46.7 45.8 45.2 41.0 35.2 26.3 26.2 25.1 24.6 22.6 21.7
Me
N
O
MeO
87a
^{13}C NMR, $CDCl_3$
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me
H
MeO
H
O
90a
1H NMR, acetone-d6
400 MHz
f1 (ppm)

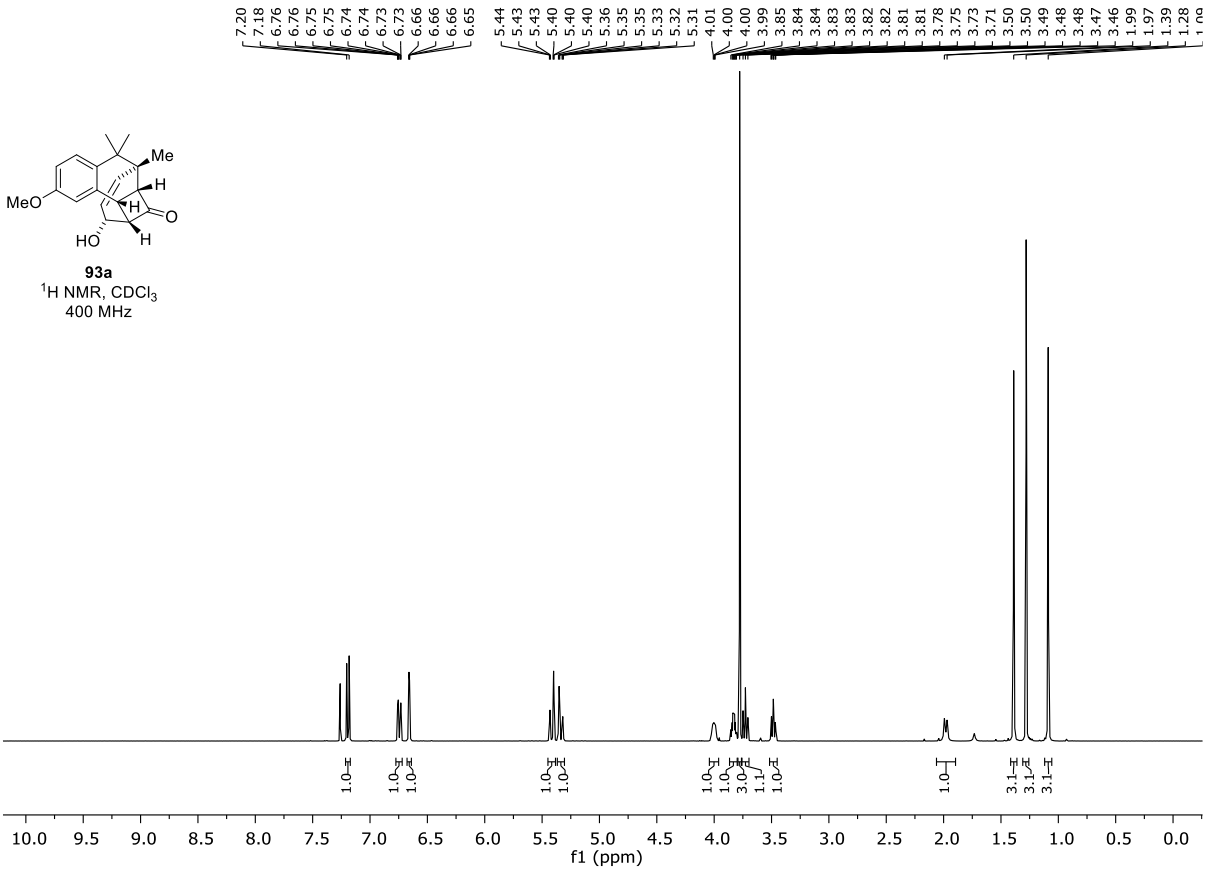

Me
H
MeO
H
O
90a
13C NMR, acetone-d6
101 MHz
f1 (ppm)

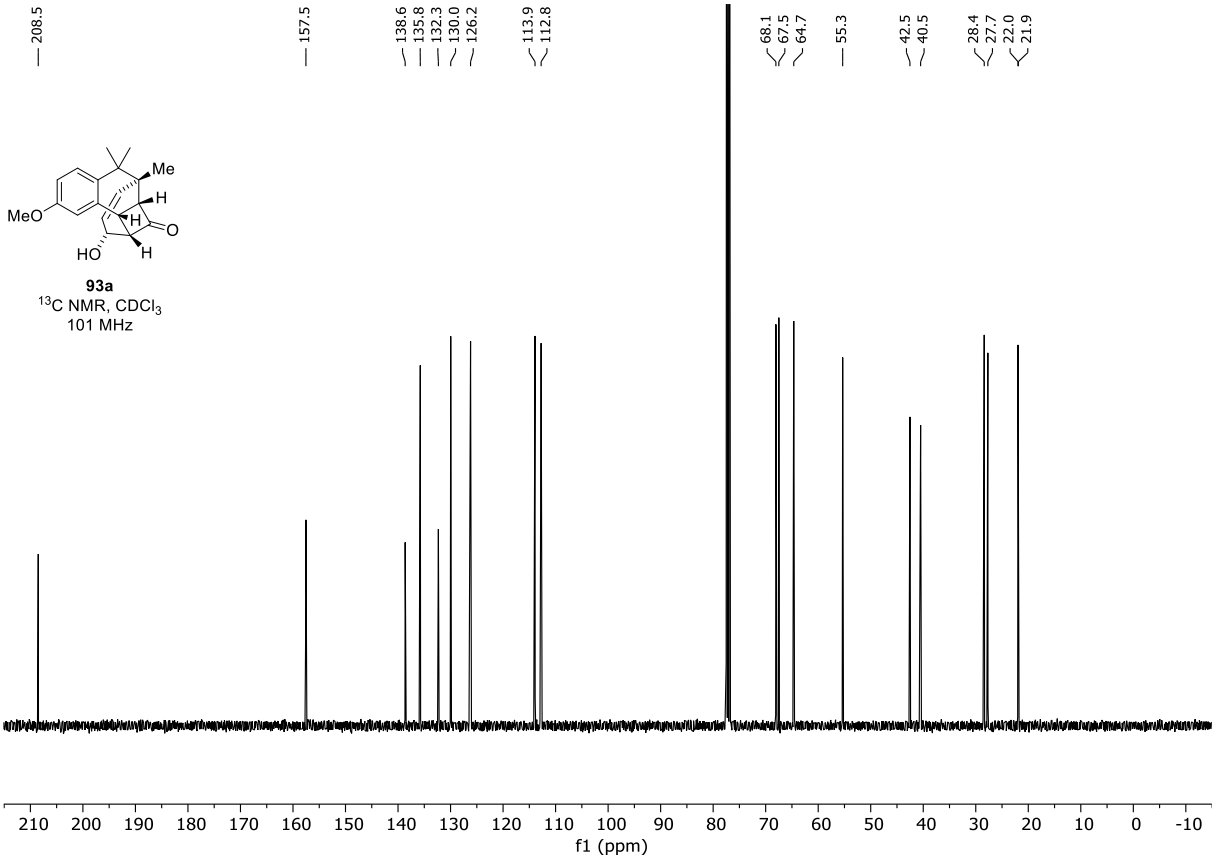


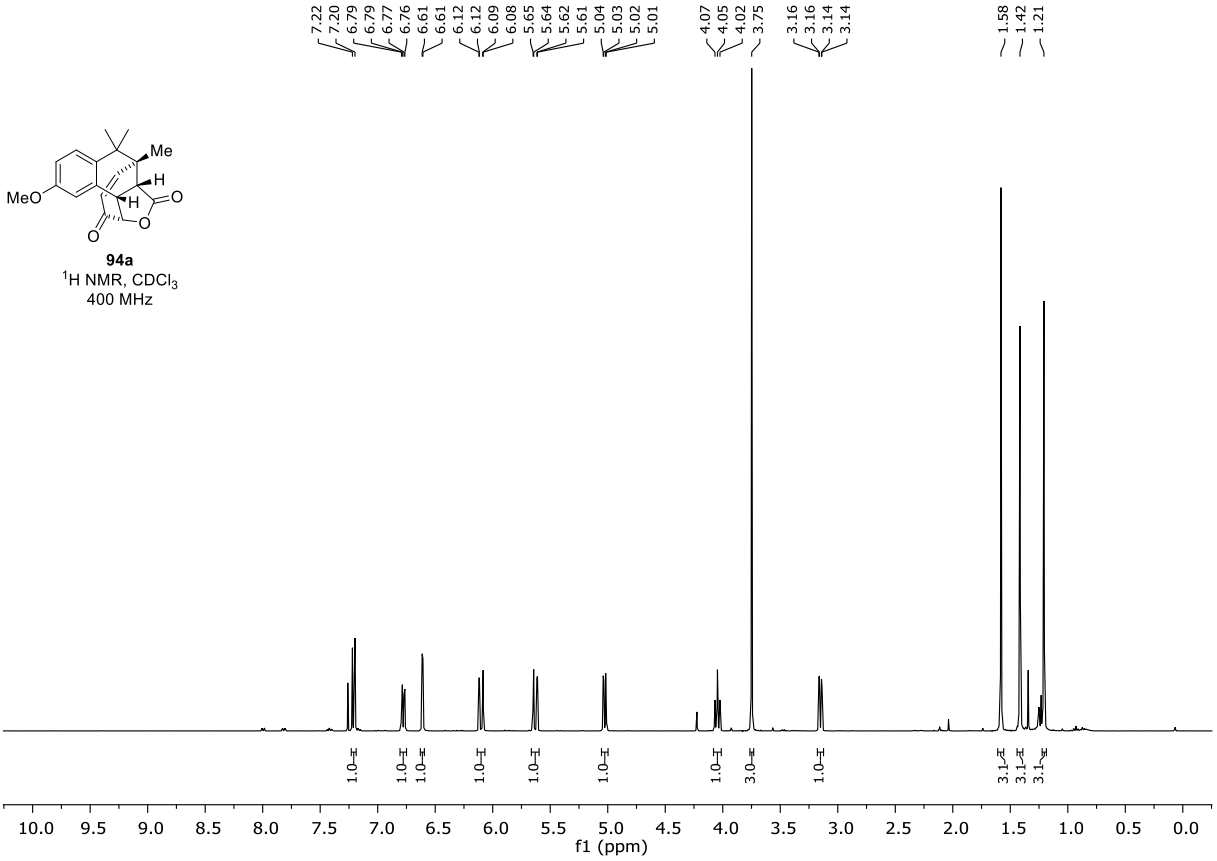
89a
^{1}H NMR, $CDCl_3$
600 MHz

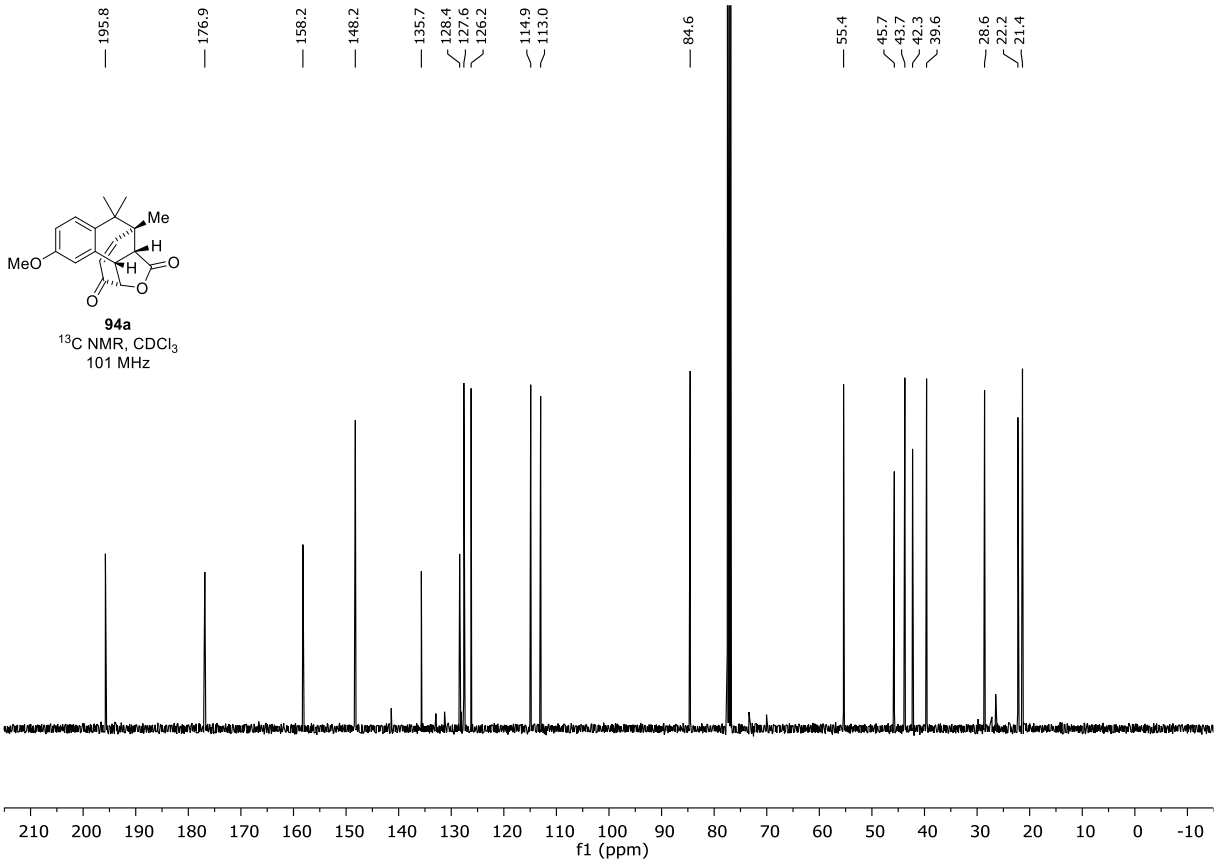


89a
^{13}C NMR, $CDCl_3$
151 MHz


Me
H
MeO
H
O
HO
H
93a
1H NMR, CDCl3
400 MHz
f1 (ppm)


Me
H
MeO
H
O
HO
H
93a
13C NMR, CDCl3
101 MHz
f1 (ppm)


7.22
7.20
6.79
6.79
6.77
6.76
6.61
6.61
6.12
6.12
6.09
6.08
5.65
5.64
5.62
5.61
5.04
5.03
5.02
5.01
4.07
4.05
4.02
3.75
3.16
3.16
3.14
3.14
1.58
1.42
1.21
Me
H
H
MeO
O
O
O
94a
1H NMR, CDCl3
400 MHz
1.0
1.0
1.0
1.0
1.0
1.0
1.0
3.0
1.0
3.1
3.1
3.1
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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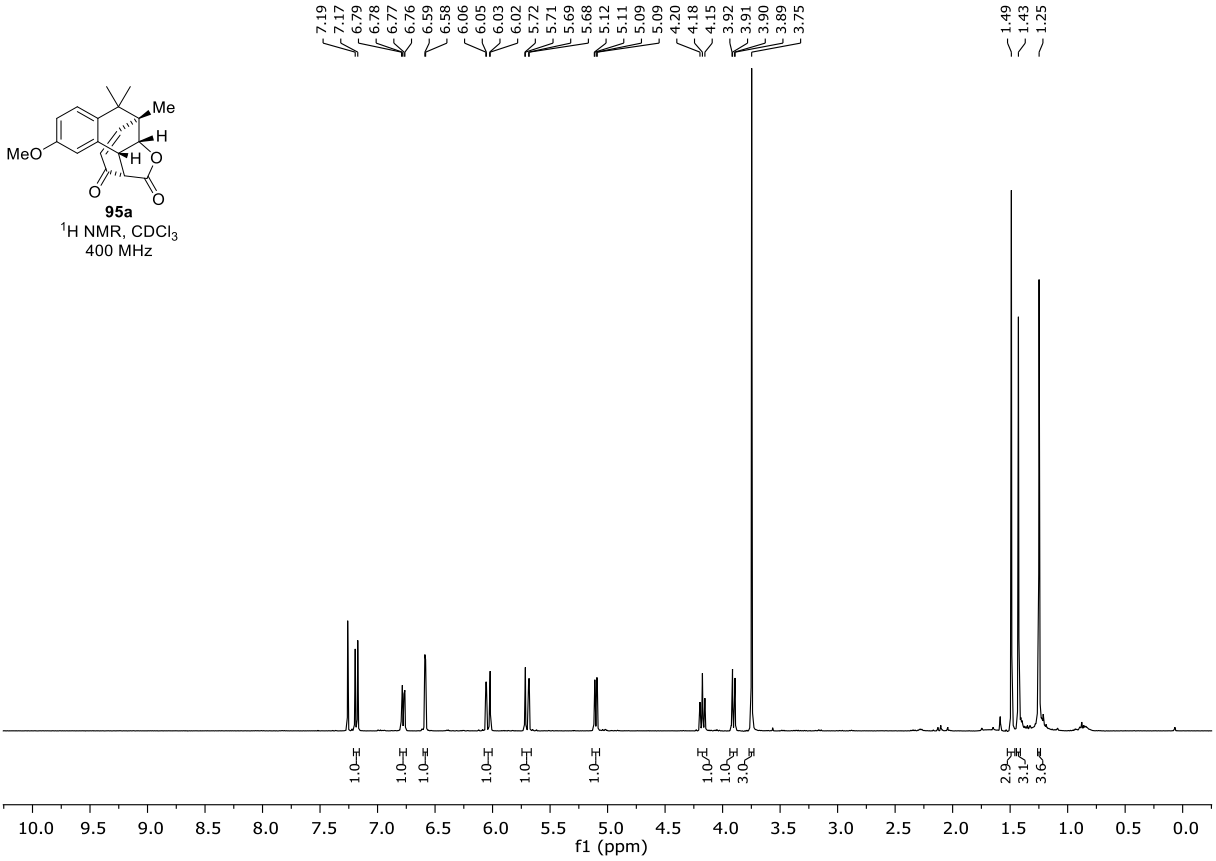
176.9
158.2
148.2
135.7
128.4
127.6
126.2
114.9
113.0
84.6
55.4
45.7
43.7
42.3
39.6
28.6
22.2
21.4
Me
H
H
MeO
O
O
O
94a
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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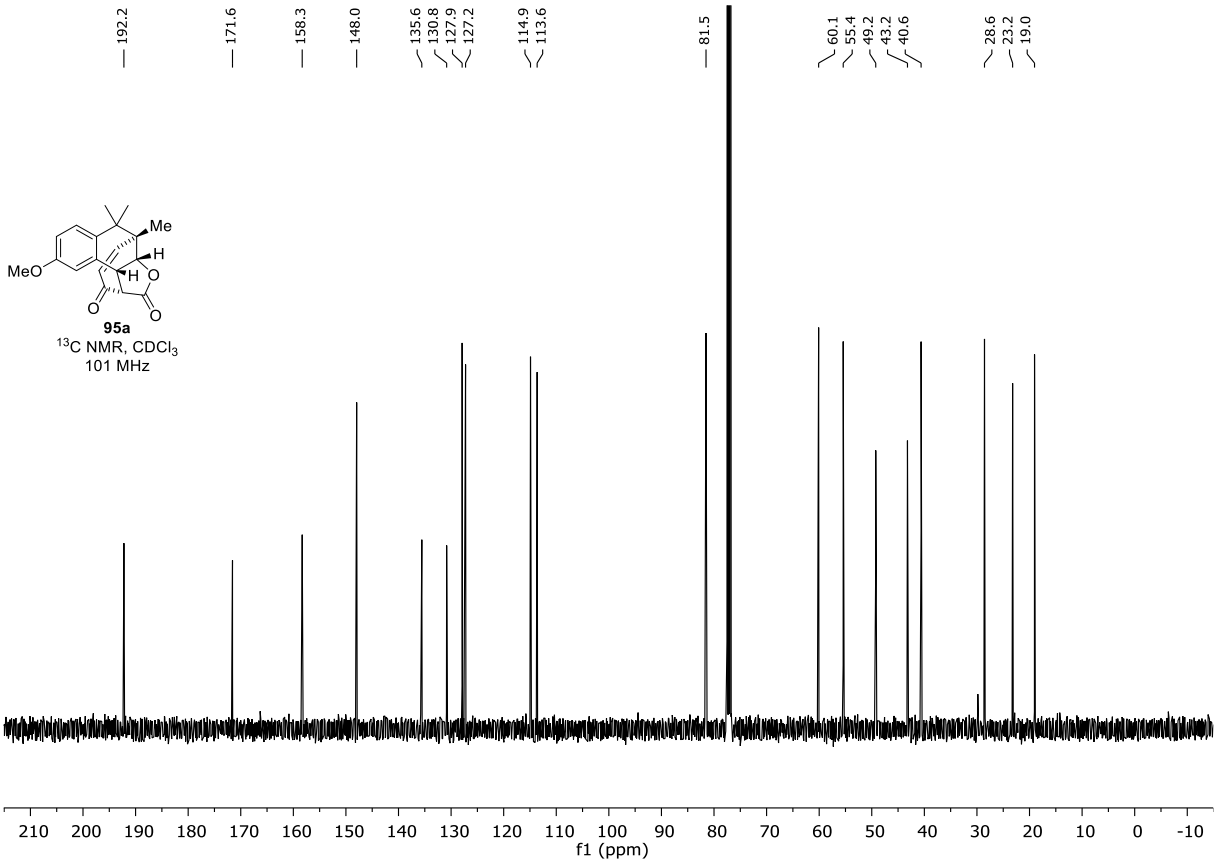
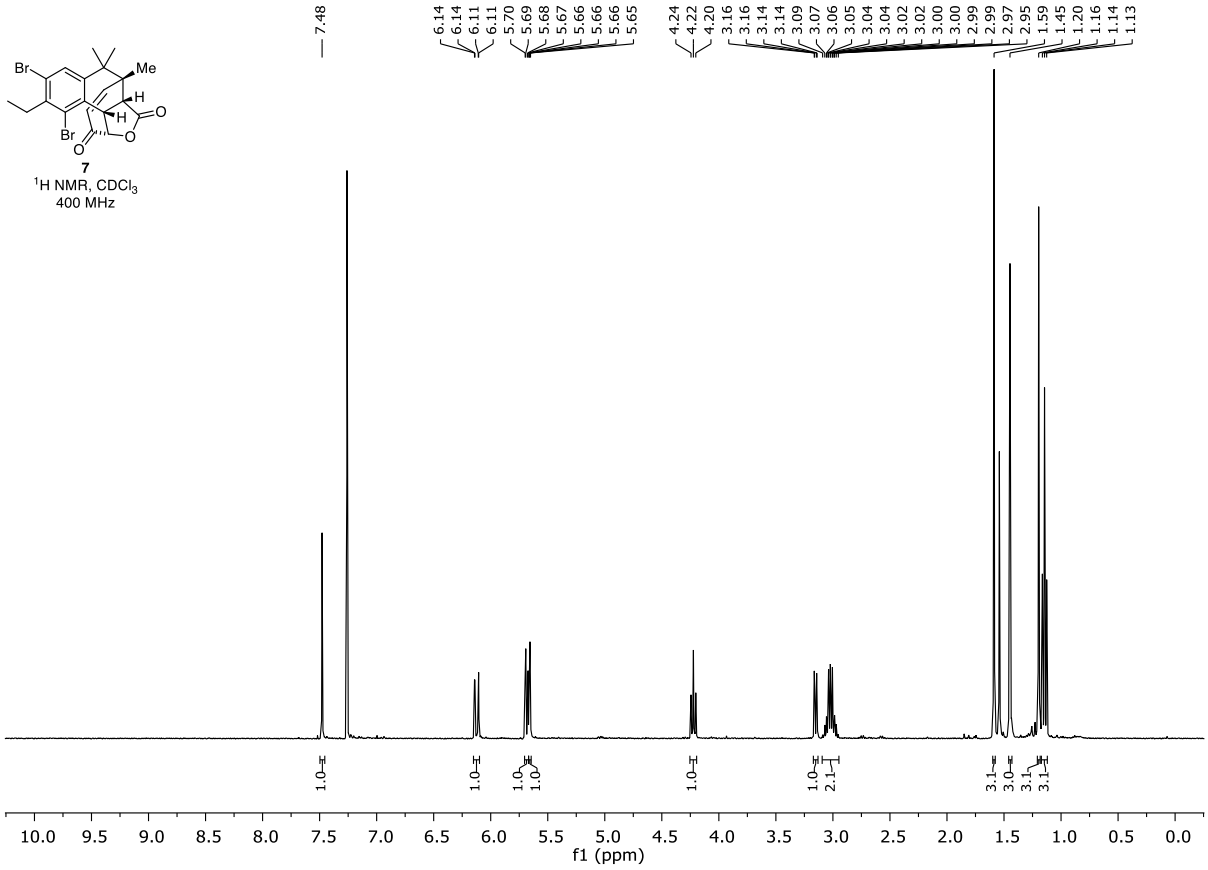
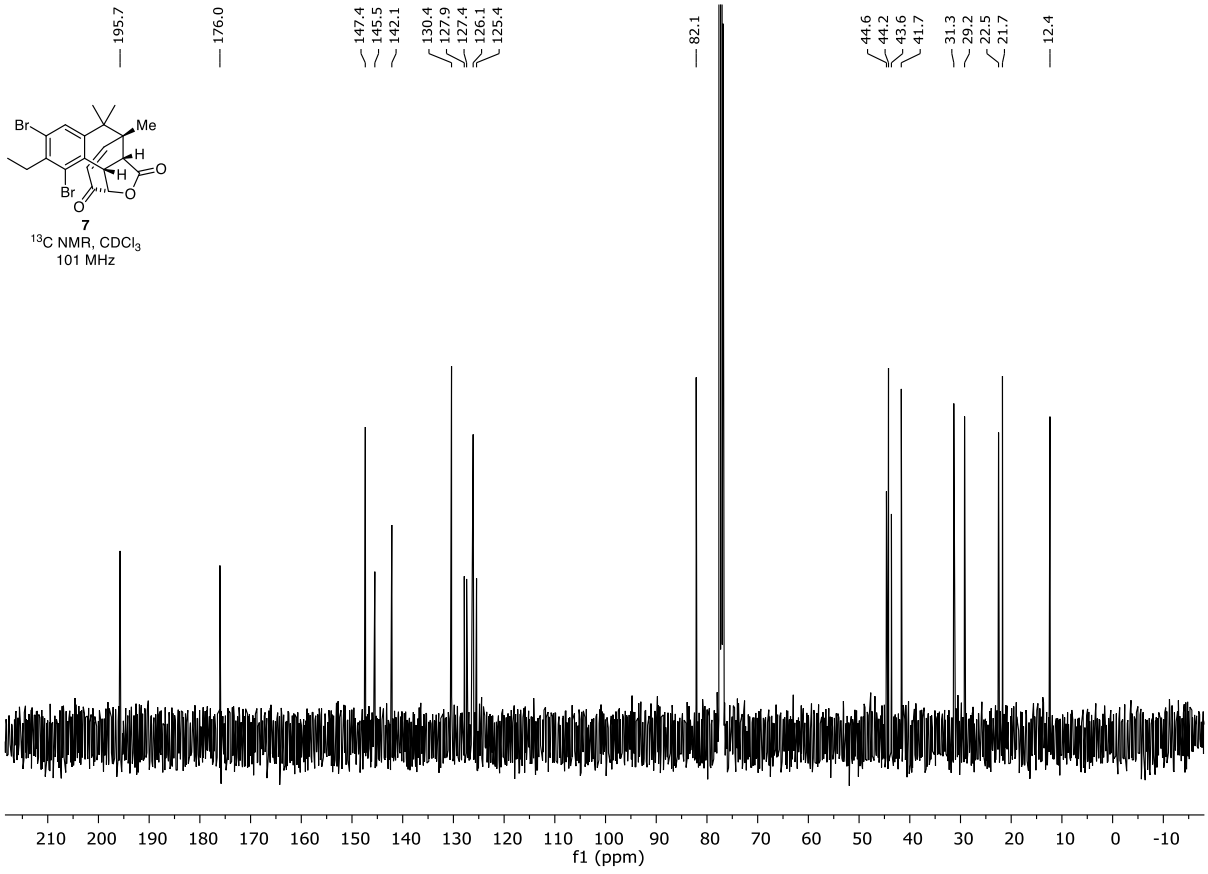
7.17
6.79
6.78
6.77
6.76
6.59
6.58
6.06
6.05
6.03
6.02
5.72
5.71
5.69
5.68
5.12
5.11
5.09
5.09
4.20
4.18
4.15
3.92
3.91
3.90
3.89
3.75
1.49
1.43
1.25
Me
H
MeO
H
O
O
O
95a
1H NMR, CDCl3
400 MHz
1.0
1.0
1.0
1.0
1.0
1.0
1.0
1.0
3.0
2.9
3.1
3.6
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


192.2
171.6
158.3
148.0
135.6
130.8
127.9
127.2
114.9
113.6
81.5
60.1
55.4
49.2
43.2
40.6
28.6
23.2
19.0
Me
H
MeO
H
O
O
O
95a
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

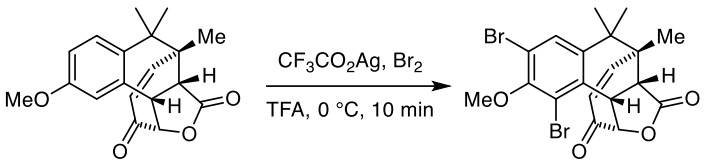

7
^{1}H NMR, $CDCl_3$
400 MHz
f1 (ppm)


7
^{13}C NMR, $CDCl_3$
101 MHz
f1 (ppm)

4 Supporting information to chapter II – 2.3

4.1 General experimental details

Synthesis of methoxysalimabromide (**II.18**)



II.17 **II.18**

To a vigorously stirred solution of lactone **II.17** (8.9 mg, 28 µmol, 1 equiv) and silver(I) trifluoroacetate (19 mg, 85 µmol, 3.0 equiv) in trifluoroacetic acid (0.3 mL) was added bromine (4.3 µL, 85 µmol, 3.0 equiv) at 0 °C. The instantly formed milky suspension was stirred at 0 °C for 10 min. Excess bromine and trifluoroacetic acid was quenched by addition of saturated aqueous sodium bicarbonate solution (10 mL) and saturated aqueous sodium thiosulfate solution (1 mL). The suspension was extracted with dichloromethane (4 × 10 mL). The combined organic layers were dried over sodium sulfate and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (1. Column: 5% ethyl acetate in cyclohexane, 2. Column: 30% dichlormethane in cyclohexane) afforded the title compound **II.18** (8.9 mg, 66%) crystalline colorless solid.

TLC (50% ethyl acetate in cyclohexane): R_f: 0.46 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 6.13 (dd, *J* = 13.1, 1.4 Hz, 1H), 5.68 (dd, *J* = 13.1, 2.0 Hz, 1H), 5.63 (dd, *J* = 8.3, 2.0 Hz, 1H), 4.19 (t, *J* = 8.4 Hz, 1H), 3.84 (s, 3H), 3.15 (dd, *J* = 8.4, 1.4 Hz, 1H), 1.59 (s, 3H), 1.45 (s, 3H), 1.20 (s, 3H).

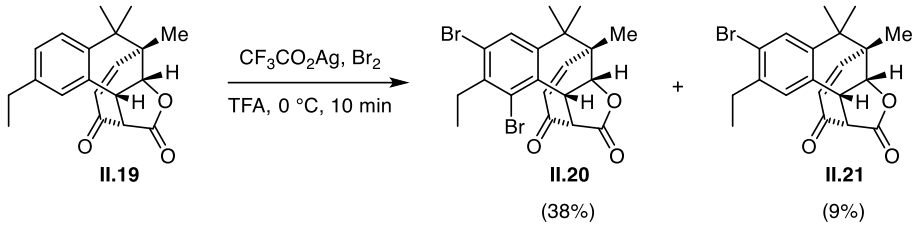
^{13}C NMR (101 MHz, $CDCl_3$) δ 195.63, 175.91, 153.29, 147.28, 143.42, 130.77, 128.91, 126.16, 121.03, 118.50, 81.92, 60.79, 44.70, 43.96, 43.51, 41.12, 29.18, 22.53, 21.70.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2982 (m), 2938 (m), 1785 8s), 1685 (s), 1616 (w), 1538 (w), 1510 (w), 1469 (m), 1423 (w), 1393 (w), 1378 (w), 1324 (w), 1305 (w), 1276 8m), 1233 (w), 1218 (w), 1177 (w), 1159 (m), 1127 (m), 1110 (w), 1069 (w), 1038 (s), 984 (w), 962 (m), 909 (w), 875 (w), 827

(m), 769 (w), 737 (s), 689 (w), 649 (w), 626 (w), 606 (w), 566 (w), 545 (w), 509 (w), 454 (w), 413 (w).

HRMS (ESI): calcd for $C_{19}H_{18}Br^{79}Br^{81}NaO_4$ $[M+Na]^+$: 492.9444 found: 492.9430

Synthesis of isosalimabromide (**II.20**)



To a vigorously stirred solution of lactone **II.19** (30 mg, 97 µmol, 1 equiv) and silver(I) trifluoroacetate (64 mg, 0.29 mmol, 3.0 equiv) in trifluoroacetic acid (0.5 mL) was added bromine (15 µL, 0.29 µmol, 3.0 equiv) at 0 °C. The instantly formed milky suspension was stirred at 0 °C for 10 min. Excess bromine and trifluoroacetic acid was quenched by addition of saturated aqueous sodium bicarbonate solution (15 mL) and saturated aqueous sodium thiosulfate solution (1 mL). The suspension was extracted with dichloromethane (4 × 10 mL). The combined organic layers were dried over sodium sulfate and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane) afforded the title compound **II.20** (17.4 mg, 38%) and the monobrominated compound **II.21** (3.4 mg, 9%) as both crystalline colorless solids.

Analytical data of **II.20**

TLC (50% ethyl acetate in cyclohexane): R_f: 0.56 (CAM)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 (s, 1H), 6.06 (dd, *J* = 13.2, 1.8 Hz, 1H), 5.74 (dd, *J* = 13.2, 1.8 Hz, 1H), 5.07 (dd, *J* = 7.9, 1.8 Hz, 1H), 4.55 (dd, *J* = 8.6, 1.8 Hz, 1H), 4.24 (t, *J* = 8.2 Hz, 1H), 3.08 – 2.95 (m, 2H), 1.51 (s, 3H), 1.46 (s, 3H), 1.24 (s, 3H), 1.14 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.57, 171.35, 147.22, 145.26, 142.28, 130.01, 129.95, 127.93, 127.81, 125.24, 80.89, 57.33, 48.46, 44.43, 42.78, 31.32, 29.18, 23.33, 19.36, 12.34.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2978 (m), 2934 (w), 2875 (w), 1778 (s), 1676 (s), 1618 (w), 1579 (w), 1529 (w), 1463 (w), 1394 (w), 1375 (w), 1355 (w), 1341 (w), 1316 (w), 1259 (w), 1228 (w), 1185 (w),

1163 (m), 1130 (w), 1094 (w), 1064 (w), 1029 (m), 982 (w), 949 (w), 911 (w), 875 (w), 848 (w), 793 (w), 731 (m), 702 (w), 678 (w), 648 (w), 564 (w), 525 (w), 502 (w), 484 (w), 458 (w), 431 (w).

HRMS (ESI): calcd for $C_{20}H_{20}Br^{79}Br^{81}NaO_3$ $[M+Na]^+$: 490.9651 found: 490.9631.

Analytical data of **II.21**

TLC (50% ethyl acetate in cyclohexane): R_f: 0.52 (CAM)

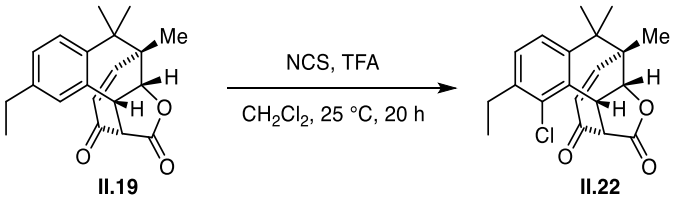
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 6.94 (s, 1H), 6.03 (dd, *J* = 13.2, 1.8 Hz, 1H), 5.71 (dd, *J* = 13.2, 1.7 Hz, 1H), 5.09 (dd, *J* = 8.3, 1.8 Hz, 1H), 4.14 (t, *J* = 8.6 Hz, 1H), 3.90 (dd, *J* = 8.9, 1.7 Hz, 1H), 2.67 (q, *J* = 7.5 Hz, 2H), 1.49 (s, 3H), 1.44 (s, 3H), 1.26 (s, 3H), 1.18 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.01, 171.32, 147.49, 143.02, 142.37, 130.33, 129.99, 129.19, 128.13, 124.57, 81.20, 59.92, 48.97, 43.57, 40.05, 28.93, 28.44, 22.97, 19.04, 14.19.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2966 (m), 2925 (m), 2853 (w), 1776 (s), 1672 (s), 1616 (w), 1482 (w), 1462 (w), 1394 (w), 1374 (w), 1355 (w), 1341 (w), 1318 (w), 1260 (w), 1223 (w), 1204 (w), 1188 (w), 1159 (s), 1128 (w), 1092 (w), 1064 (w), 1022 (s), 950 (w), 908 (s), 872 (w), 855 (w), 845 (w), 809 (m), 729 (s), 686 (w), 648 (w), 616 (w), 553 (w), 524 (w), 498 (w), 452 (w), 406 (w).

HRMS (ESI): calcd for $C_{20}H_{21}Br^{79}NaO_3$ $[M+Na]^+$: 411.0566 found: 490.0560.

Synthesis of isosalimamonochloride (**II.22**)



II.19 **II.22** (25%)

To a suspension of *N*-chlorosuccinimide (17 mg, 0.13 mmol, 2.0 equiv) and lactone **II.19** (20 mg, 64 µmol, 1 equiv) in dichloromethane (0.6 mL) at 0 °C was added trifluoroacetic acid (19 µL, 0.26 mmol, 4.0 equiv). The mixture was stirred for 20 h at 25 °C and excess acid was quenched by addition of saturated aqueous sodium bicarbonate solution (2 mL) and saturated aqueous sodium thiosulfate solution (0.5 mL). The mixture was extracted with dichloromethane (3 × 5 ml). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced

pressure. Purification by flash column chromatography on silica gel (5% ethyl acetate in hexanes) afforded the title compound **II.22** (5.6 mg, 25%) as colorless solid.

TLC (50% ethyl acetate in cyclohexane): R_f: 0.50 (CAM)

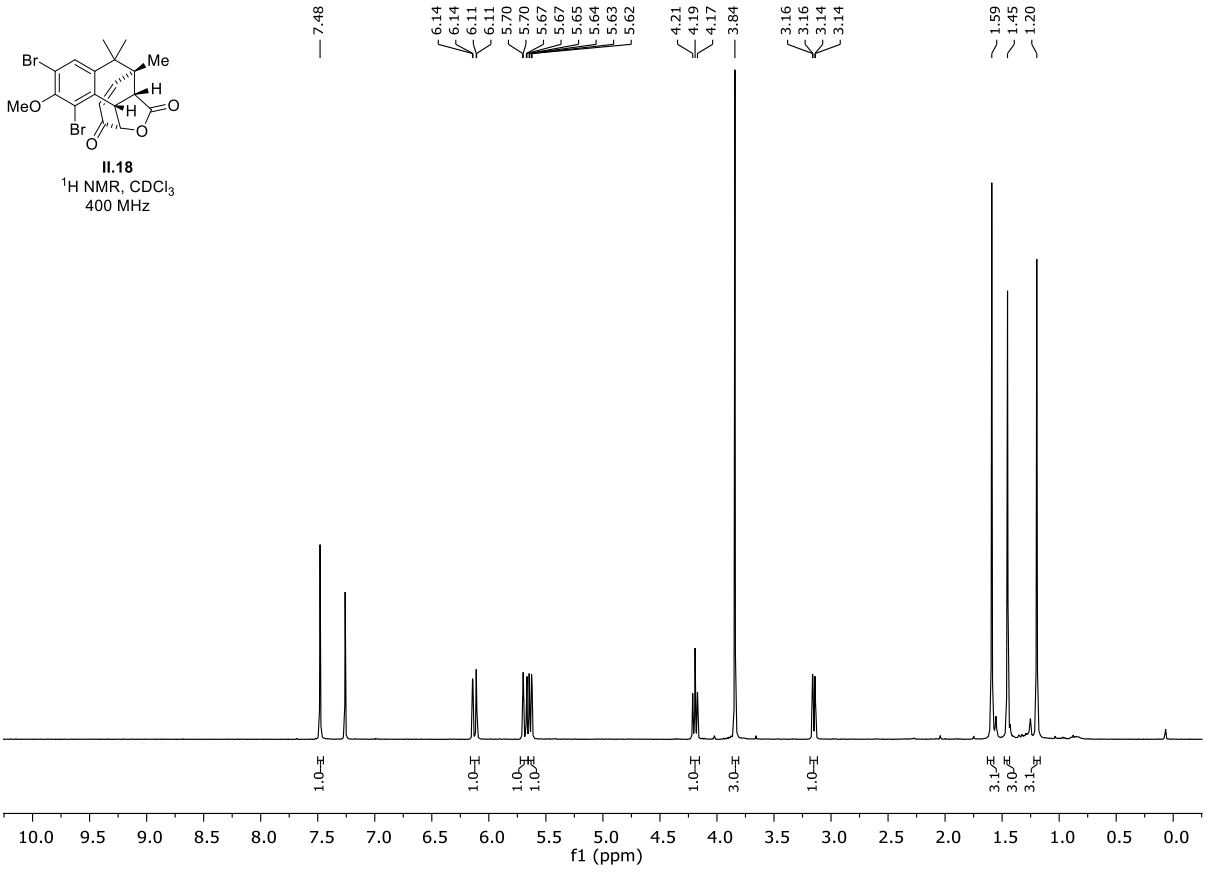
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.3 Hz, 1H), 7.08 (d, *J* = 8.3 Hz, 1H), 5.99 (dd, *J* = 13.2, 1.8 Hz, 1H), 5.65 (dd, *J* = 13.2, 1.7 Hz, 1H), 5.02 (dd, *J* = 8.0, 1.8 Hz, 1H), 4.37 (dd, *J* = 8.5, 1.8 Hz, 1H), 4.22 (t, *J* = 8.3 Hz, 1H), 2.71 – 2.60 (m, 2H), 1.44 (s, 3H), 1.40 (s, 3H), 1.17 (s, 3H), 1.13 (t, *J* = 7.5 Hz, 3H).

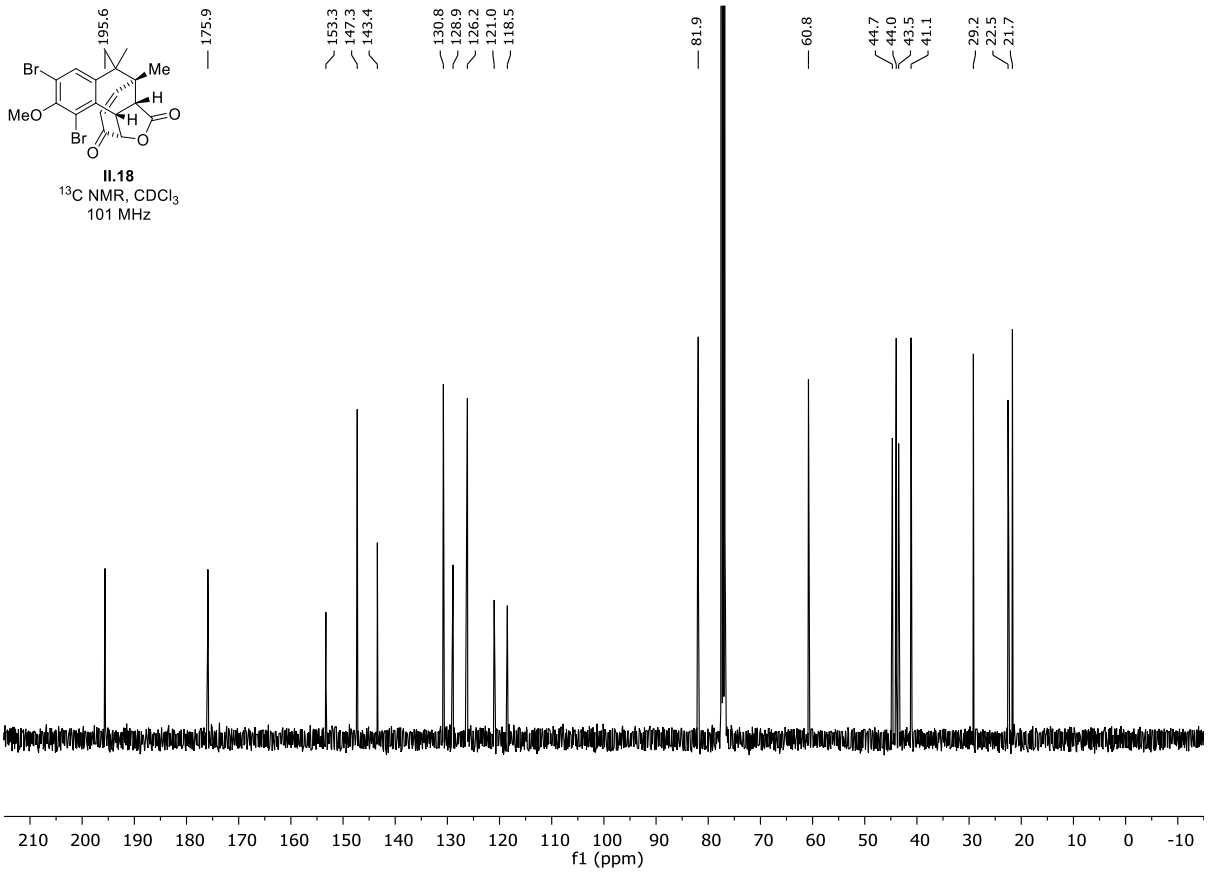
^{13}C NMR (101 MHz, $CDCl_3$) δ 191.94, 171.85, 147.54, 143.53, 141.03, 134.29, 129.59, 128.26, 127.79, 124.52, 81.22, 57.74, 48.60, 44.12, 40.48, 29.09, 27.01, 23.39, 19.32, 13.78.

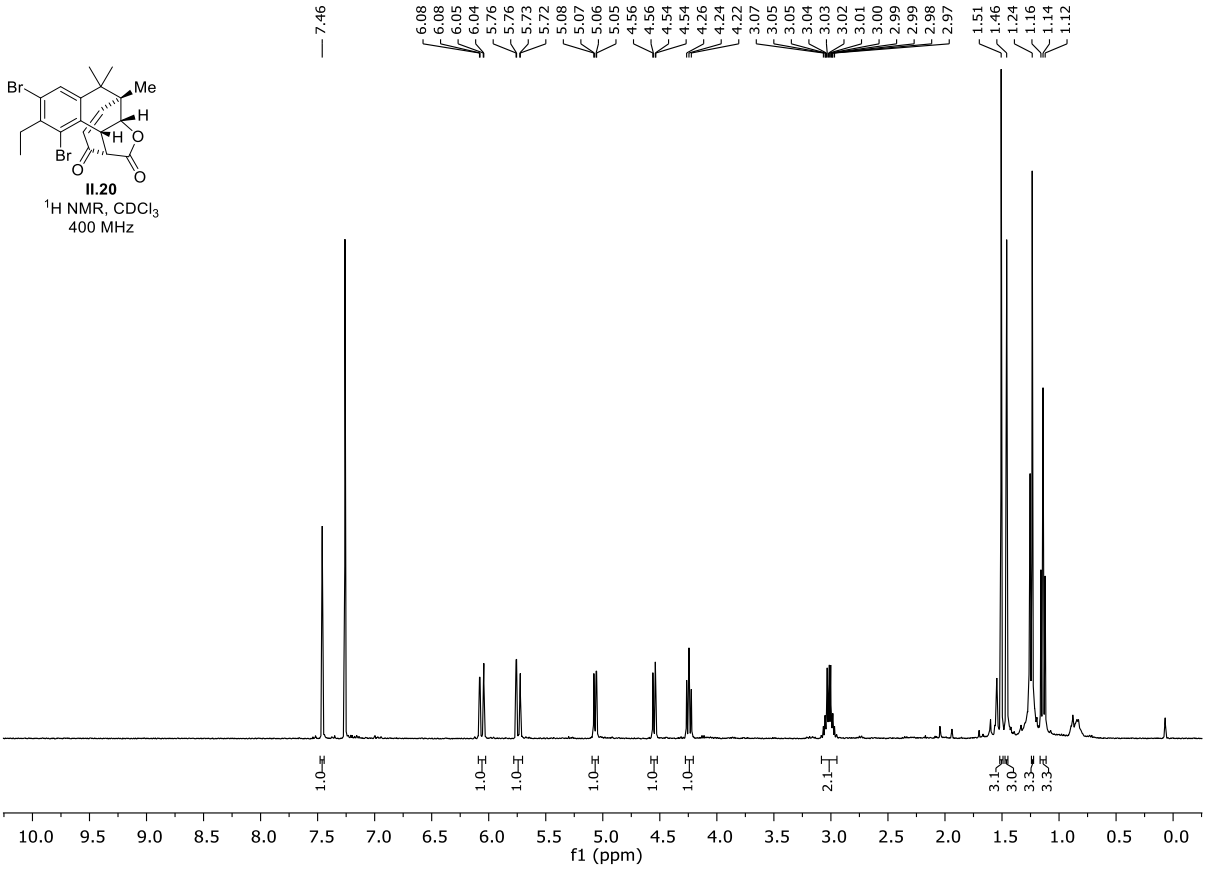
IR (ATR, neat) $\tilde{\nu}_{max}$: 2975 (m), 2925 (m), 1775 (s), 1677 (s), 1618 (w), 1477 (w), 1463 (w), 1404 (w), 1375 (w), 1356 (w), 1340 (w), 1261 (w), 1225 (w), 1184 (m), 1164 (m), 1129 (w), 1095 (w), 1065 (w), 1025 (s), 910 (w), 876 (w), 849 (w), 829 (w), 808 (w), 733 (m), 677 (w), 649 (w), 473 (w), 412 (w),

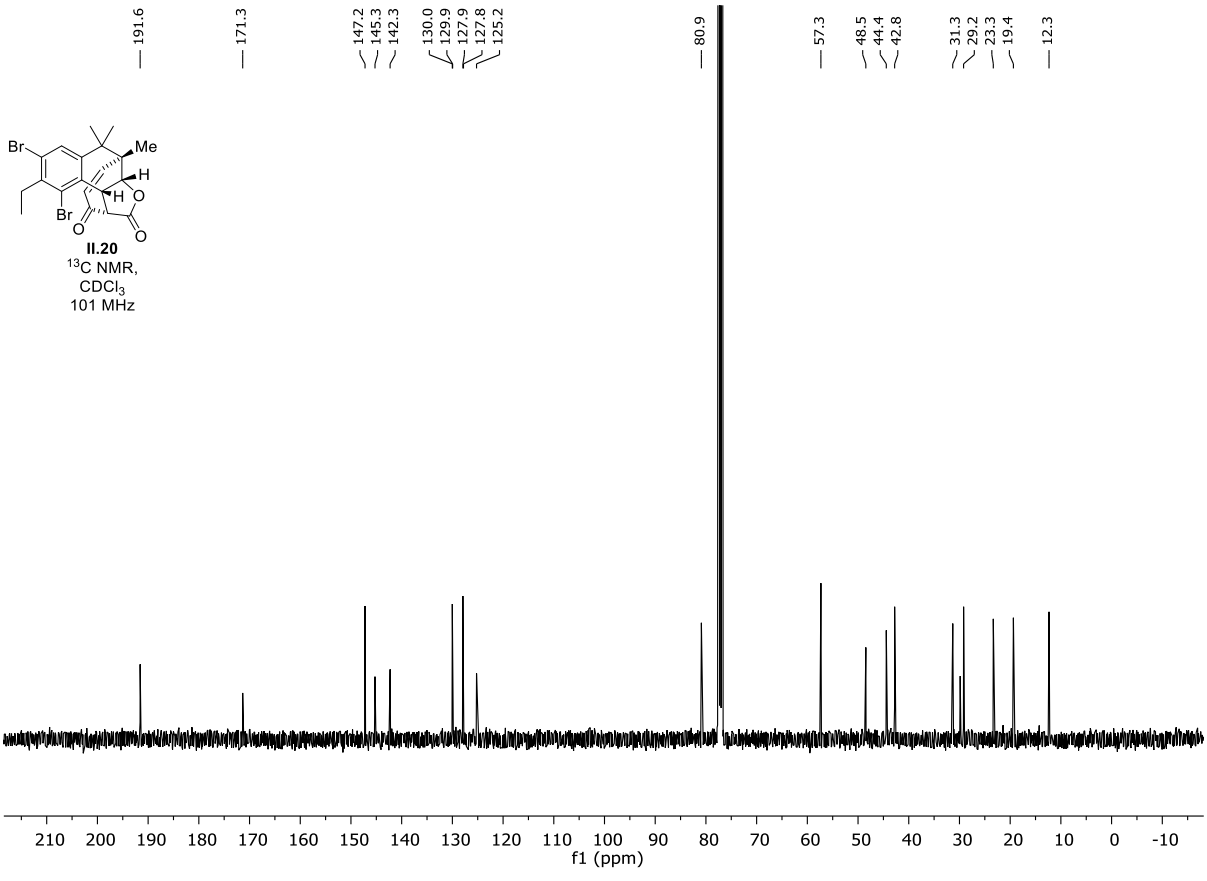
HRMS (ESI): calcd for $C_{20}H_{21}Cl^{35}NaO_3$ $[M+Na]^+$: 369.1071 found: 367.1067.

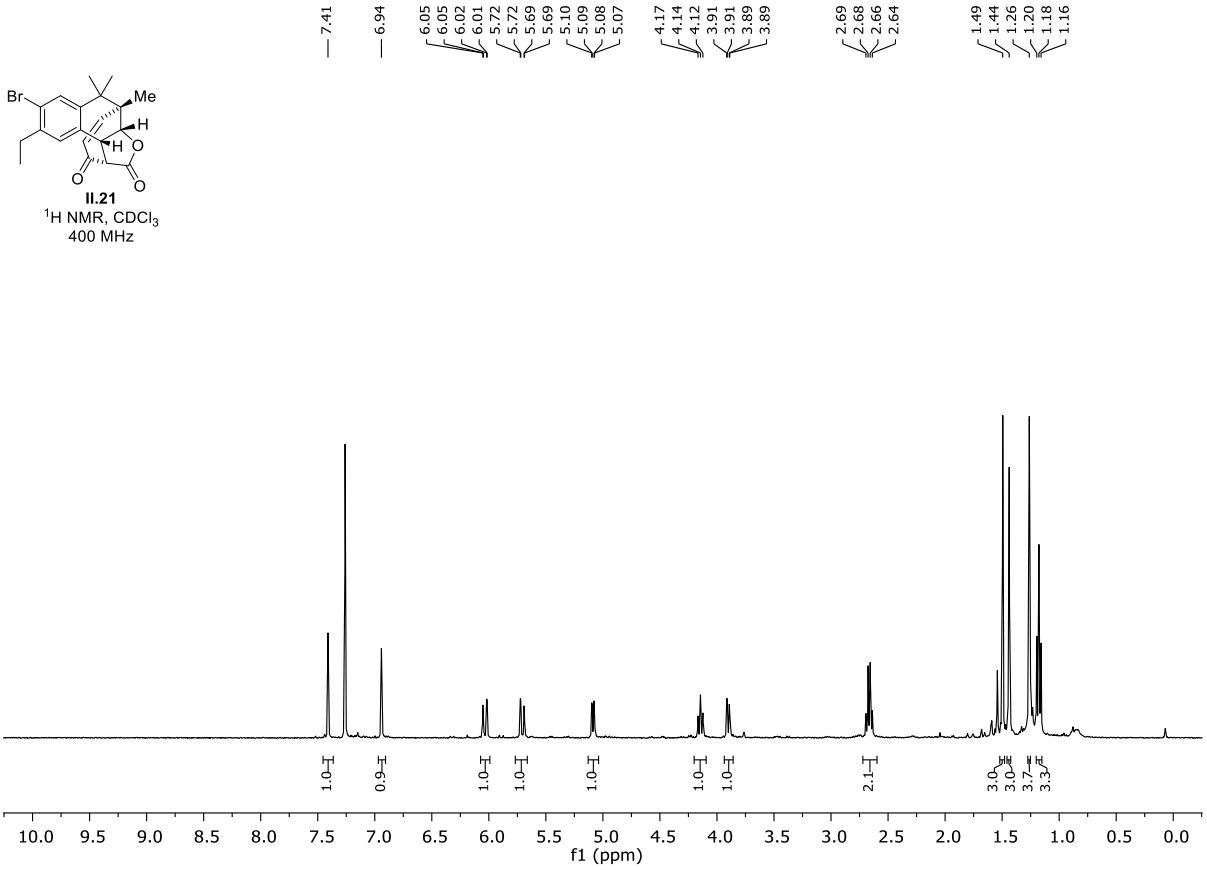
4.2 NMR spectra



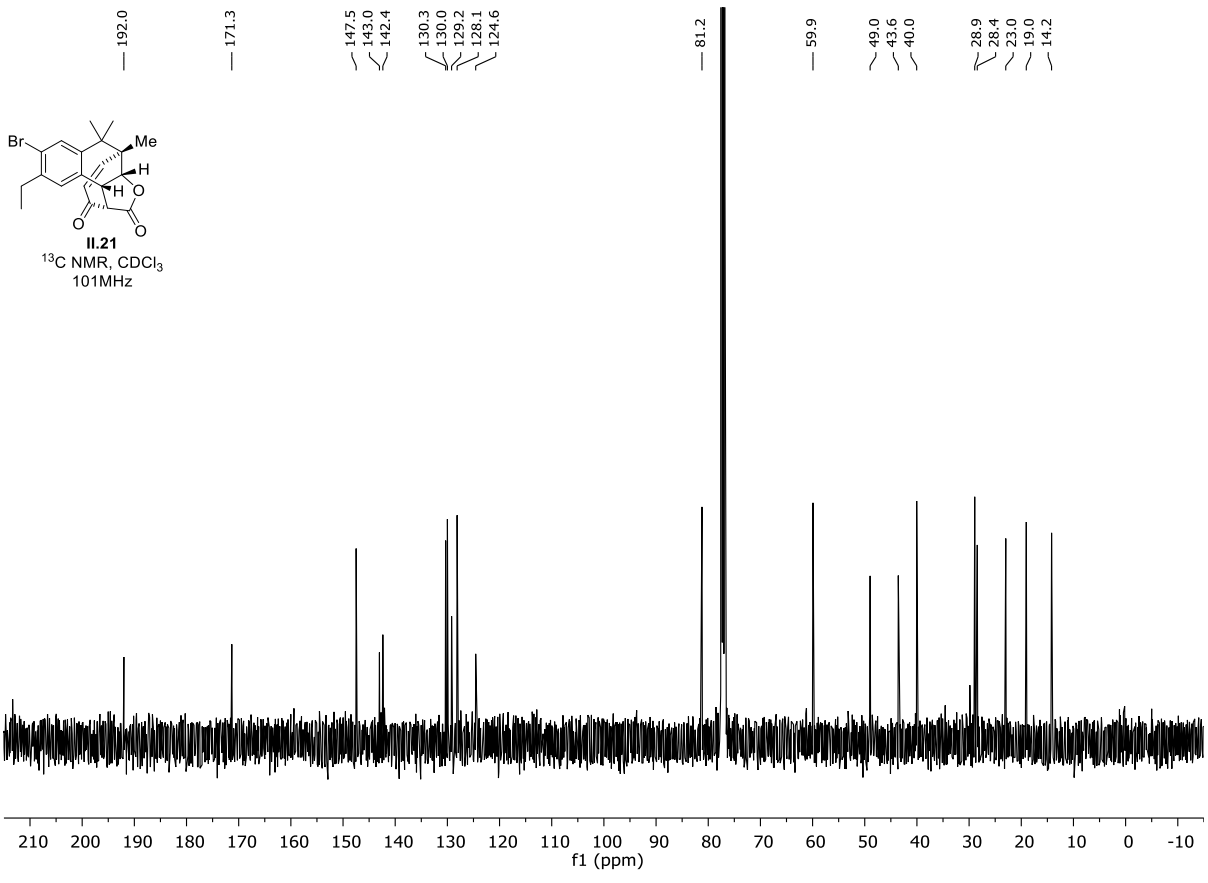



II.20
^{1}H NMR, $CDCl_3$
400 MHz
f1 (ppm)

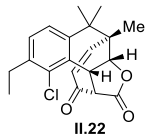

II.20
^{13}C NMR,
$CDCl_3$
101 MHz
f1 (ppm)



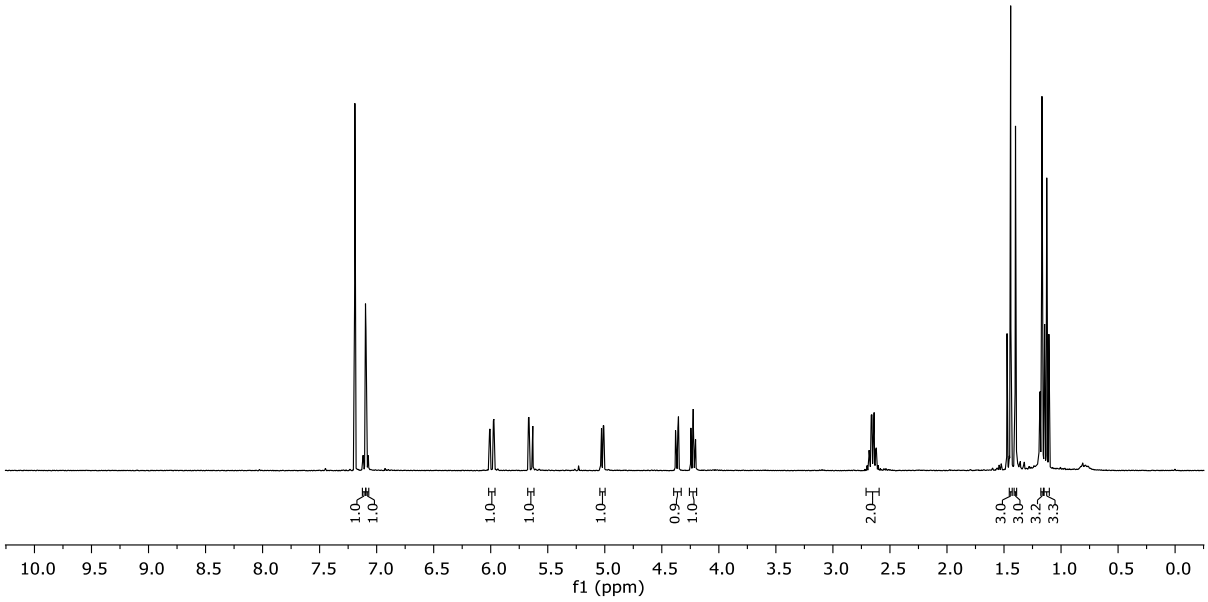
II.21
^{1}H NMR, $CDCl_3$
400 MHz

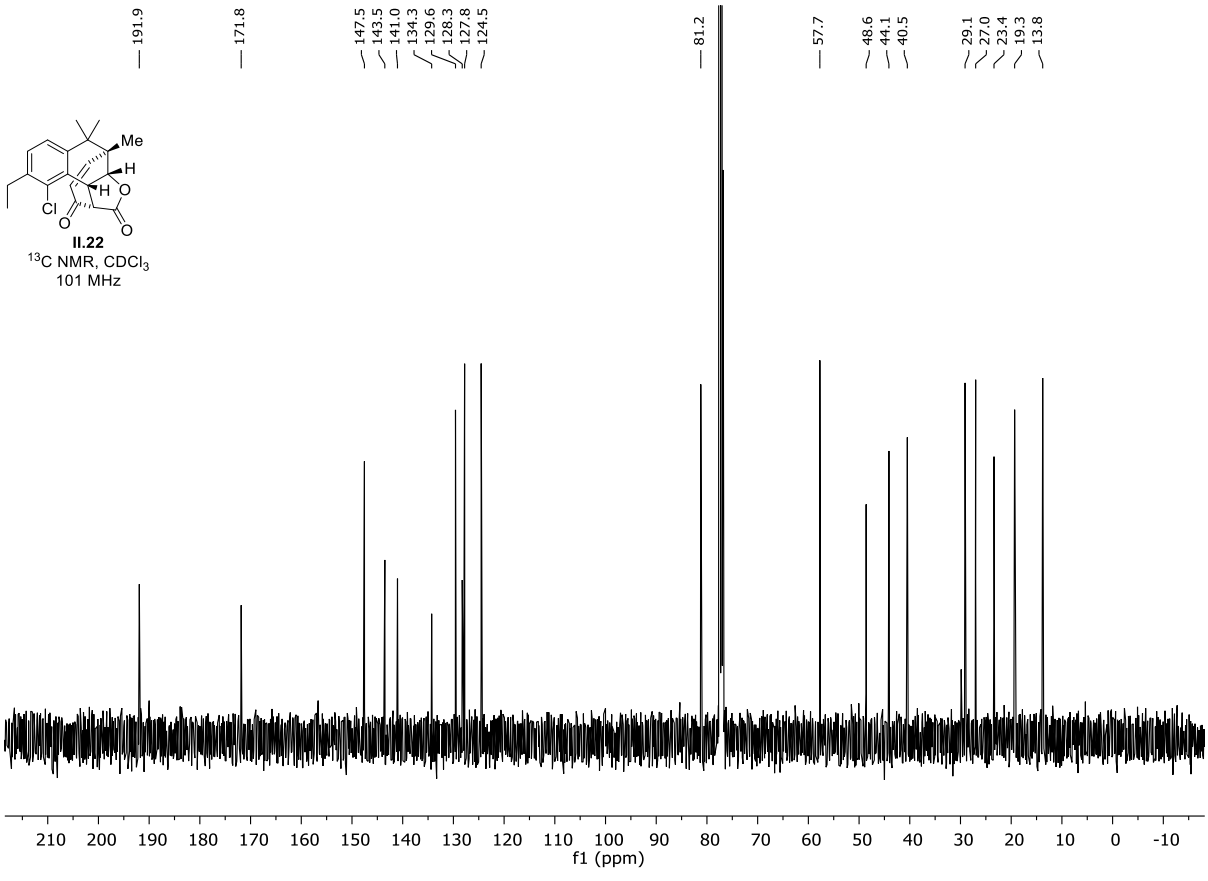


II.21
^{13}C NMR, $CDCl_3$
101MHz



II.22
^{1}H NMR, $CDCl_3$
400 MHz





II.22
^{13}C NMR, $CDCl_3$
101 MHz