DISSERTATION ZUR ERLANGUNG DES DOKTORGRADES
DER FAKULTÄT FÜR CHEMIE UND PHARMAZIE
DER LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Studies toward the Total Synthesis of Psammaplysin A and Acid-catalyzed Cycloisomerization of Neopentylic Epoxides

von

Kevin Rafael Sokol

aus München, Deutschland

2020

Erklärung

Diese Dissertation wurde im Sinne von § 7 der Promotionsordnung vom 15. November 2016 von Herrn Prof. Dr. Thomas Magauer betreut.

Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfsmittel erarbeitet.

München, den 26. Juni 2020

_____

Kevin Rafael Sokol

Dissertation eingereicht am:	01.07.2020
1. Gutachter:	Prof. Dr. Thomas Magauer
2. Gutachter:	Prof. Dr. Ronald Micura
Mündliche Prüfung am:	30.07.2020

To my parents

“Questions you cannot answer are usually far better for you
than answers you cannot question.”
– **Yuval Noah Harari, 21 Lessons for the 21st Century**

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

Synthesis of Vicinal Quaternary All-Carbon Centers via Acid-catalyzed Cycloisomerization of Neopentylic Epoxides

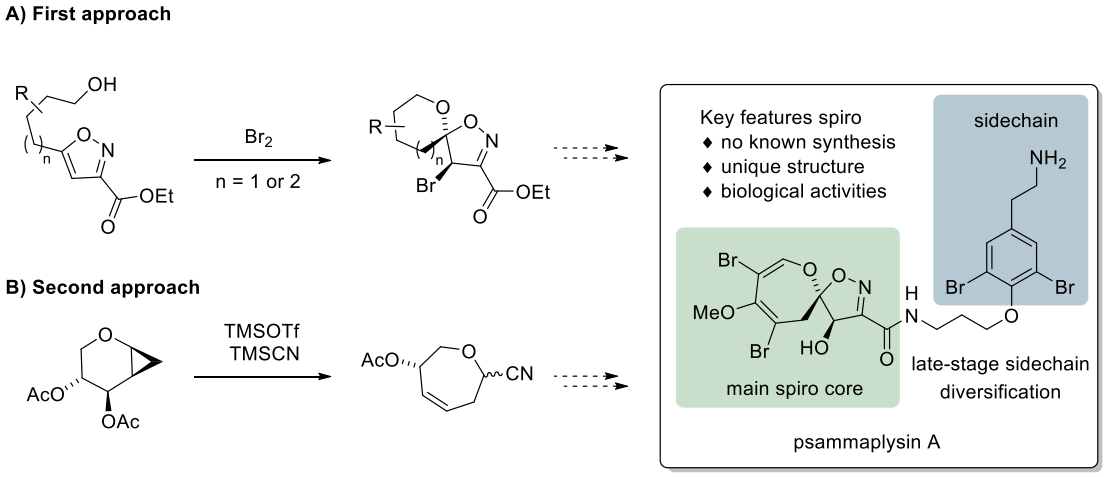
Matthias Schmid[†[a]], Kevin Rafael Sokol[†[a]], Lukas Anton Wein[a], Sofia Torres Venegas[a], Christina Meisenbichler[a], Klaus Wurst[b], Maren Podewitz[b] and Thomas Magauer*[a] *Angew. Chem. Int. Ed.* **2020**, submitted 22. June 2020.

.

Abstract

Part I: Studies toward the Total Synthesis of Psammaplysin A

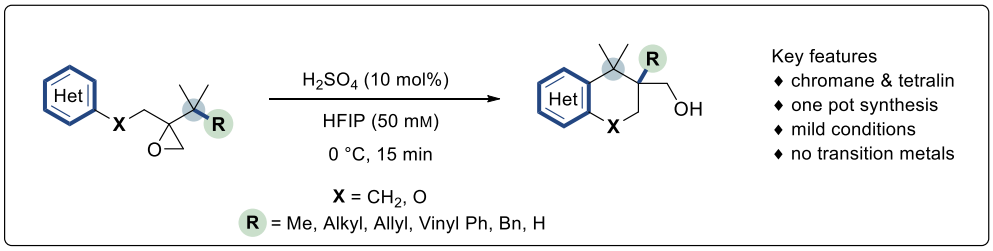
Psammaplysin A is a bromotyrosine alkaloid isolated from the marine sponges *Verongida* and *Dictyoceratida* and shows broad biological activities ranging from antibiotic, antimalarial, anti-HIV to antitumor activities. Apart from its intriguing physiological properties, psammaplysin A possesses an unique and highly-decorated dihydrooxepin which is fused to an isoxazoline via a spiroacetal. Amide linkage to a sidechain derived from bromotyramine ultimately distinguishes psammaplysin A from more than 40 natural congeners. Moreover, this linker was identified to be important for its biological and physiochemical properties. Despite its remarkable bioactivities and fascinating structural features, no total synthesis has been reported to date. By facing this highly challenging target, we envision two main approaches to achieve a modular, scalable and convergent synthetic entry to psammaplysin A.



Our first approach is based on the bromine induced spirocyclization of isoxazoles to provide rapid access to the designed spiroacetal motif of psammaplysin A. Herein, variation of the alkyl chain bearing the terminal alcohol will shine light on the potential and limitations of this cyclization step. In contrast to this, a second strategy will focus on the initial construction of an already functionalized dihydrooxepin moiety. For this purpose, the Ferrier-type ring-expansion of cyclopropanes is investigated to access the seven-membered oxacycle with the desired substitution pattern. With the tetrahydrooxepin in hand, we imagine fast access to different valuable intermediates for the construction of the missing spiro motif.

Part II: Acid-catalyzed Cycloisomerization of Neopentylic Epoxides

In the second part of this thesis, we describe the development of a powerful cycloisomerization reaction of 2,2-disubstituted neopentylic epoxides. Herein, the practical and efficient acid-catalyzed cascade enabled rapid access to highly functionalized tetralins and chromanes featuring vicinal all-carbon quaternary centers. These skeletons are common motifs in natural products and its construction still represents a major challenge for organic chemists.



Due to our mild reaction conditions, several functional groups and electron-rich to -neutral arenes are tolerated. Further investigations by variation of the substitution pattern in the starting material provided detailed insights into migration tendencies and gave access to further tricyclic compounds. In addition, a competing disproportionation pathway of dihydronaphthalene to its corresponding tetralin und naphthalene was discovered, which depend on the stability of the formed cationic intermediates.

Acknowledgements

Already at school, I was enthusiastic about chemistry, especially organic chemistry. This passion has accompanied me throughout my whole studies and ultimately never left me during my PhD time. Nevertheless, my time as a PhD student has certainly been the most interesting, exciting and challenging period of my life and many great people accompanied me on this journey.

Foremost, I would like to thank my supervisor Prof. Dr. Thomas Magauer for giving me the opportunity to conduct my PhD studies in his research group, where I was able to expand my chemistry knowledge under his guidance. I was especially fascinated by Tommy's enthusiasm for chemistry as well for his experience in the field of organic synthesis, which always motivated me to become a better chemist. I am very grateful for working on a challenging and captivating project, where he also gave me the freedom implement my own creativity and ideas to find solutions.

I am very grateful to Prof. Dr. Dirk Trauner for all the support he provided during the first period during my PhD studies at the LMU and for being my first supervisor in my Bachelor's thesis in 2014. His passion for science was highly inspiring and I was able to benefit greatly from getting to experience an excellent learning environment by also being part of the Trauner Group. Also, I want to thank Dr. Johannes Broichhagen for being a good and patient first mentor. His teaching was the foundation for my further chemical career as well as Dr. David Barber, which was also one of my mentors during my time within in the Trauner research group.

Furthermore, I am very thankful to Prof. Dr. Ronald Micura for agreeing to be the second reviewer of this thesis. I would also like to thank Dr. Dorian Didier, Prof. Dr. Lena Daumann, Prof. Dr. Hendrik Zipse and Prof. Dr. Paul Knochel for being on my defense committee.

For assistance with my natural product projects, I would like to thank my colleagues, Dr. Lara Weisheit, Dr. Giandomenico Magagnano, Dr. Gabriele Prina Cerai, Dr. Denis Höfler, Florian Neuruhrer, Constantin Nuber and Julien Monz.

Furthermore, I am especially grateful to Dr. Matthias Schmid, Lukas Wein, Sofia Torres Venegas, and Dr. Maren Podewitz who worked together with me on the acid catalyzed cycloisomerization reaction an interesting project during my Ph.D. thesis.

I would like to thank all past and present members of the Magauer and Trauner groups for the support, good times and for becoming lovely friends.

Within the Magauer lab, I had the great pleasure of working with many excellent scientists and friendly people during my stay in this group. Particularly, Franz-Lucas Haut and Sofia Torres Venegeas, who were my awesome lab mates and always created an inspiring and working friendly atmosphere in Lab 1. I also appreciate Franz-Lucas Haut good taste of music, which was always welcome and often put a smile on my face. Sofia Torres Venegas deserves huge thanks for the

organization for our moving to Innsbruck, as well as for being my “Denkzellen” buddy for almost three years. I would also like to thank Dr. Denis Höfler, the fourth member in lab 1 for working with me on the psammaplysins and have valuable discussions. Furthermore, I would like to thank Christian Steinborn for the funny moments in the lab and Christoph Habiger for our biweekly breakfast. Thanks to Alexander Rode and Ivica Zamarija for interesting discussions about my project. A special thanks goes to Lukas Wein for our weekly running and swimming lesson during the lunch break and for interesting discussions. Julian Feilner for always be patient and helpful advice. I would also like to thank the newest member of the Magauer group Lisa Röder for funny moments.

For proofreading of parts of this dissertation, I want to thank Alexander Rode, Franz-Lucas Haut, Christoph Habiger, Sina Götzfried and Dr. Denis Höfler.

I would also like to thank Raphael Plangger and Katharina Hoppe for being friends outside the laboratory and for showing me the best places in Innsbruck.

My research would not have been possible without the help of the whole analytical department at the LMU Munich. Dr. Werner Spahl and Sonja Kosak are thanked for their work in high-resolution mass spectrometry. Dr. David Stevenson, Claudia Dubler and Petra Keilholz are thanked for their help in the NMR facility. Finally, Dr. Peter Mayer’s work in single crystal X-ray analysis is an irreplaceable asset to the department.

As well for the analytical measurements, which were taken at the organic chemistry department at the LFU Innsbruck. Christina Meisenbichler and Thomas Müller are thanked for their work in high resolution mass spectrometry. Sofia Torres Venegas and Christoph Kreutz are thanked for their help in the NMR facility and Dr. Klaus Wurst’s work in single crystal X-ray analysis.

Lastly, I would like to thank my immediate and extended family, Astrid, Dagmer and Karim Hammerl, Nadja and Joachim Sokol, Leonie, Alina, Olivia and Luyang Xiong and Karin, Robert and Natalie Mayer for their exceptional support and all their love. You have all been such important influences in my life, and I cannot thank you enough for all you have given me.

Additionally, I thank Stefan Gaubatz, Christopher Betz, Anton Hilger, Michael Fuchs and Maximilian Scherrer for their friendship and for many unforgettable moments.

List of Abbreviations

Å	Ångström
°C	degrees Celsius
δ	chemical shift in ppm downfield relative to a standard
Ac	acetyl
Ar	undefined aryl substituent
ATR	attenuated total reflection (IR)
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
Bz	benzoyl
Calcd	calculated
CAM	ceric ammonium molybdate(IV)
cat.	Catalytic
Cbz	carboxybenzyl
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichlor-5,6-dicyano-1,4-benzochinone
DFT	density functional theory
DIBAL-H	diisobutylaluminium hydride
DIPA	*N*,*N*-diisopropylamine
DIPEA	*N*,*N*-diisopropylethylamine (Hünig's base)
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethyl formamide
DMP	Dess−Martin Periodinane
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
ee	enantiomeric excess
EI	electron ionization
equiv	equivalent(s)
Et	ethyl
EtOAc	ethyl acetate
ESI	electrospray ionization

e.g.	*exempli gratia* (for example)
g	gram
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HPLC	high-pressure liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	Hertz
i	*iso*
IC_{50}	half maximal inhibitory concentration
imH	imidazole
IR	infrared spectroscopy
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
LDA	lithium *N*,*N*-diisopropylamide
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
Min	minutes
mL	milliliter
mmol	millimole
MS	molecular sieves
MsCl	mesylsulfonyl chloride
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect correlation spectroscopy
p	*para*
Pd/C	palladium on charcoal
PG	protecting group
Ph	phenyl
Ph.D.	Doctor of Philosophy
ppm	parts per million
Pr	propyl
py	pyridine

R*f*	retardation factor (TLC)
SAM	*S*-adenosyl methionine
T	temperature
t	time
t	*tert*
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-tutyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMDS	tetramethyldisiloxane
TMS	trimethylsilyl
UV	ultraviolet
wt%	weight percent

Table of Contents

PART I

Studies toward the Total Synthesis of Psammaplysin A

1 Introduction

1.1 Natural Products

All compounds produced in living organisms are defined as natural products, ranging from simple molecules to highly complex structures.[1] These molecules have a specific function within the organism and some may be essential for the maintance of the organism. For instance, amino acids, carbohydrates, lipids and nucleic acids are some of the essential molecules for life and called primary metabolites. In contrast, secondary metabolites are often only found in certain organism and not absolutely required for growth and survival. These molecules serve a distinct purpose and have therefore a specialized function in the metabolic process.[2]

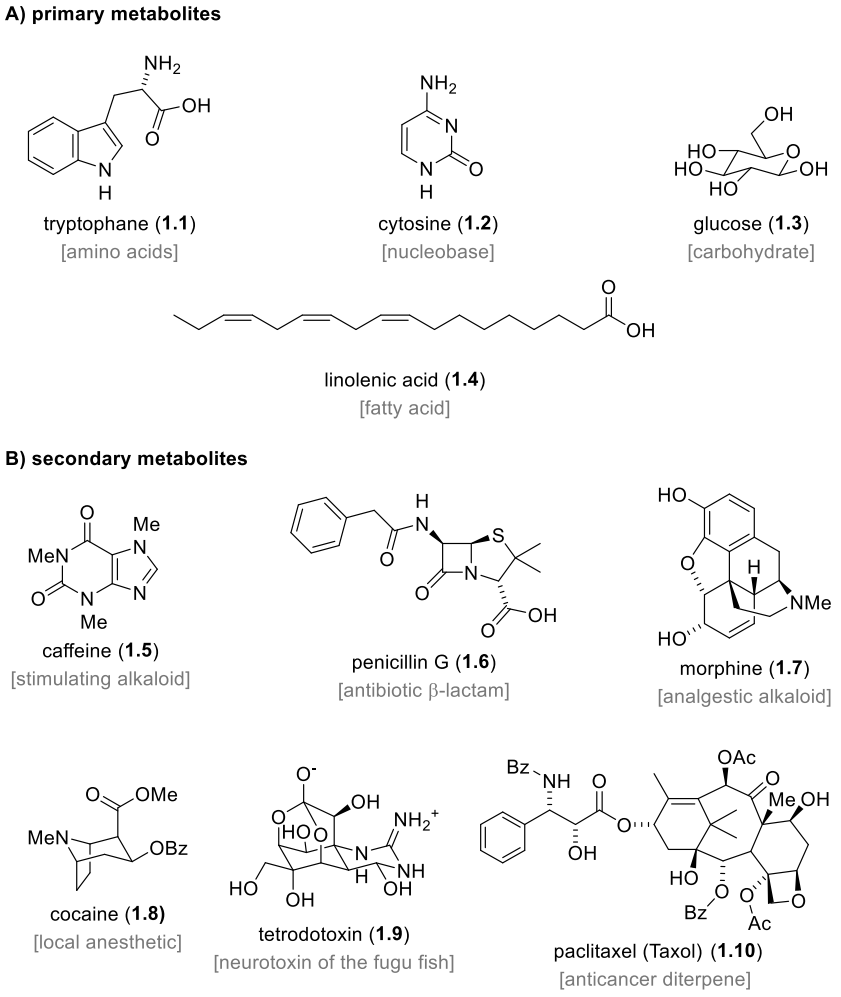


Figure 1: A) Selected primary metabolites. B) Selected secondary metabolites.

In Figure 1 A an example is illustrated for each subclass of primary metabolites. Tryptophan (**1.1**), also abbreviated Trp or W, is in its natural L-form a proteinogenic α-amino acid possessing an aromatic indole framework and a component of more complex structures. Cytosine (**1.2**), also

abbreviated Cyt or C, is one of the four nucleic bases in DNA and RNA, together with adenine (A), guanine (G) and thymine (T) (uracil in RNA). An anomeric junction of these nucleobases to the five-membered sugar pentose (ribose in RNA and deoxyribose in DNA) build the nucleoside. Phosphorylation on the 5'-postion of sugar backbone finally gives the nucleotide. Nucleotides play the central role in metabolism at a fundamental, cellular level and are the buildings blocks for nucleic acids, which contain the genetic information in all organisms. The most abundant monosaccharide is glucose (**1.3**), which naturally occurs as D-glucose and is produced by plants through photosynthesis, in which water and carbon dioxide are converted in a light-dependent reaction to oxygen and glucose. The latter is used as an energy and carbon source by living organisms. However, most of the glucose does not occur in its free form, but is found in polymers and belongs therefore to the class of carbohydrates. Apart from this, linoleic acid (**1.4**) is an omega-3, essential fatty acid, which plays an important role as an ingredient in many seeds and oils.

2600 B.C are the earliest records the use of natural products depicted on clay tablets from Mesopotamia. These display extracts of cypress and myrrh, which were used against diseases and still play a crucial role in traditional medicine for the treatment of coughs, colds and inflammations.[3] Natural products have become part of our culture and traditions, for example almost everyone knows the about the awakening effect of coffee triggered by the secondary metabolite caffeine (**1.5**), a stimulating alkaloid. penicillin G (**1.6**), morphine (**1.7**) or cocaine (**1.8**) are among to natural products that have been extensively applied in the field of traditional medicine. The highly oxidized natural product tetrodotoxin (**1.9**) is a potent neurotoxin of the fugu fish. The structure was eluciaded by Woodward[4] in 1964 and finally fully confirmed by X-ray crystallography in 1970[5]. A further complex natural product is paclitaxel (Taxol) (**1.10**), which has been established for the treatment of breast cancer. Taxol (**1.10**) was initially isolated from the bark of *Taxus brevifolia*. For 1 g Taxol® (**1.10**), the bark of about three fully-grown 100-years-old trees are required. By a current demand of 100 to 200 kg *per annum* and in respect to the low natural abundance, chemical (semi)synthesis turned out as a suitable method to produce sufficient amounts of the natural product.[6]

1.2 Natural Products of Marine Origin

As described in a report by Snader *et al*., around 80% of new approved drugs between 1983 and 1994 are of natural origin, while 62% of approved anticancer drugs are of natural origin or are derived from natural products parents.[7] However, natural based drugs have been identified to be a promising source in the drug discovery in the 1990s high throughput screening, post genomics techniques and combinatorially synthesis gained attention in the development of drugs in

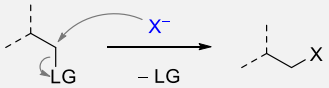
pharmaceutical industry. Thereby, natural products-based drug discovery depends on the identification of novel compounds, especially with novel scaffolds. In a comparative analysis, Kong and coworkers[8] came to the conclusion that marine natural products are superior in terms of bioactivity and scaffolds motives. For example, approximately 1% of the tested marine samples and only approximately 0.1% of the tested terrestrial samples exhibit anti-tumor potential.[9] Further comparison of marine and terrestrial natural products demonstrated that marine organisms exclusively utilized 71% of the molecular scaffolds in the Dictionary of Marine Natural Products.[8] For this reason marine origin natural products are a promising for the discovery of novel medically relevant scaffolds.

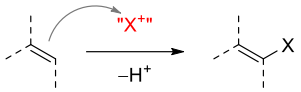
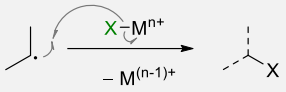
1.3 Halogenated Natural Products of Marine Origin

Interestingly, less than 50 examples of halogenated marine natural products have been reported until 1968. However, the amount was increased to more than 5000 compounds by 2015 and is steadily increasing up to date.[10] This result is attributed to new isolation and cultivation techniques, like marine bioprocessing, and remote submersibles, which are able to access into further depths in the oceans. It is not surprising, that most of the halogenated natural products arise from marine organisms, due to high halide concentration in the oceans compared to a terrestrial environment. Sources of these natural products are organism such as sponges, cyanobacteria, molluscs, sea hares, mussels, bryozoans (moss animals), tunicates, soft corals, symbiotic bacteria, marine phytoplankton, macroalgae, marine bacteria and marine fungi.[11]

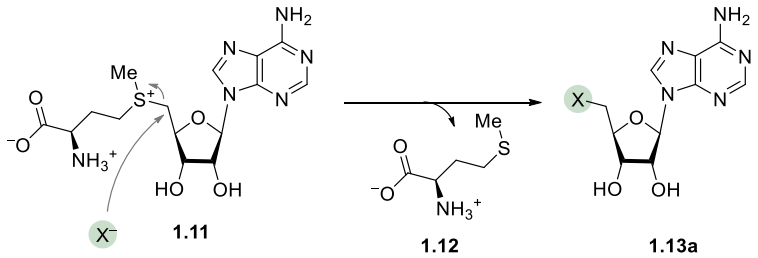
Thus, the exploration of the biosynthesis of those organohalogens is an important research field. In general, there are three different types of halogenases. The classification was carried out according to the chemical nature of active halogen species (Table 1). The primary halogen sources for all halogenases are solvated halide anions.[12]

Table 1: Biohalogenation pathways.

class	C−X bond forming reaction	halogenating agent (enzymes)
nucleophilic		halide X^- (SAM fluorinase, SAM chlorinase, SAM-dependent halide methyl transferase)

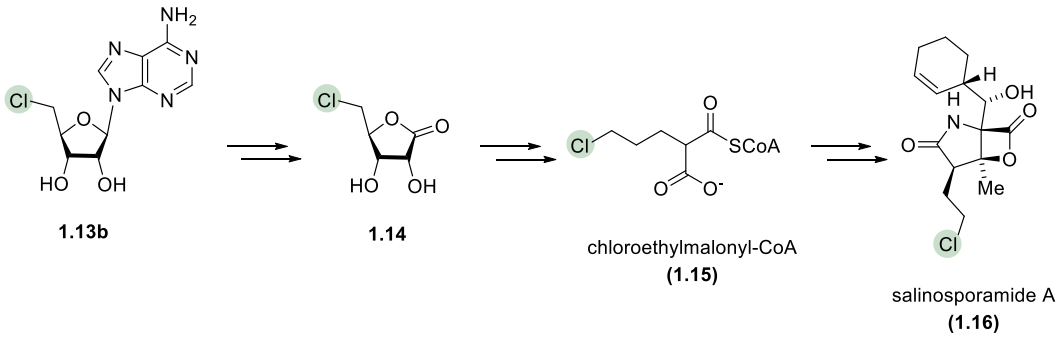
electrophilic		hypohalite XO^- (Haem-dependent Halo-peroxidases, Vanadate-dependent Halo-peroxidases, Flavin-dependent halogenases)
radical		halogenradical $X^{\bullet}$ (Non-haem iron/2-oxoglutarate dependent halogenases)

Halide anions especially, fluoride and chloride, are not known for nucleophilic substitution reaction in water, but a few halogenases are able to use solvated halide anions for nucleophilic substitutions reactions on carbon centers. In all reported cases, SAM (**1.11**) is a decisive factor in this transformation. The α-position of the sulfonium ion is highly electrophilic due to its positive charge on sulfur and the formed thioether is a good leaving group, which make these positions convenient for nucleophilic substitutions.



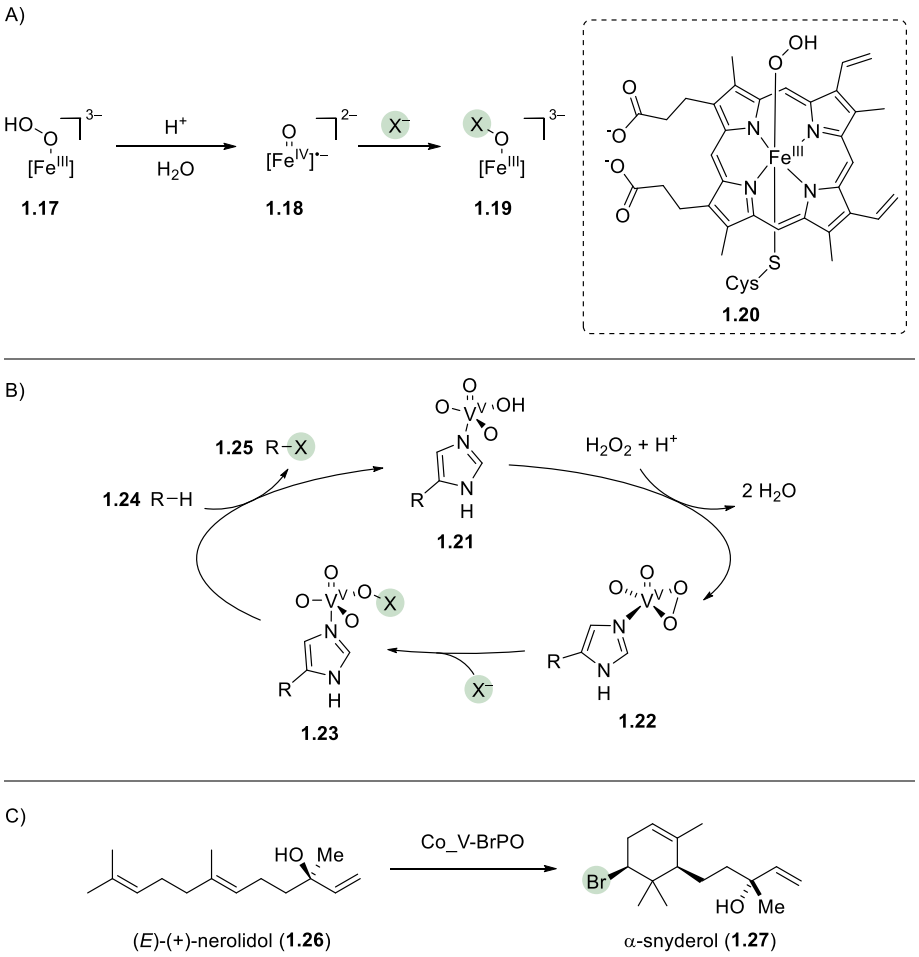
Scheme 1: Nucleophilic halogenation via SAM-dependent halogenases.

While SAM-dependent halide methyl transferases exclusively attack on the terminal methyl group to produce halogenated methane (MeX) others halogenate the adenosine moiety by releasing *L*-methionine (**1.12**), illustrated in Scheme 1. However, these enzymes are only able to incorporate chlorides, bromides and iodides the SAM fluorinase is able to implement fluorides. So far, this is the only native fluorinating enzyme, which has been identified to date. This transformation is impressive, due to the fact that a free fluoride ion is difficult to generate, particular in an aqueous medium. Herein, SAM (**1.11**) is not the cofactor for this S_N2 substitution but serves as a substrate. While the fluorinase accepts chlorides, the structurally related chlorinase accepts chlorides, bromides, and iodides but not fluorides. For instance the formation of 5'-chloro-5'-deoxyadenosine (**1.13b**) is used under physiological conditions to generate chloroethylmalonyl-CoA (**1.15**), which is then incorporated into salinosporamide A (**1.16**).[12-13]



Scheme 2: Biosynthesis of salinosporamide A (**1.16**) involves nucleophilic halogenation via SAM-dependent halogenases.

Compared to the nucleophilic substitution, the electrophilic substitution of halogens is performed on electrophilic systems such as aromatic or alkene systems. The decisive factor is the electrophilicity of the halogen source, which nature achieves by oxidation of halides using oxygen or hydrogen peroxide. As a result of the difference in the electronegativity of oxygen, the halogen possesses a partial positive charge, which then can undergo electrophilic substitution. Under these circumstances, no fluorine can be incorporated, since fluorine has the highest electronegativity. For that reason haem- and vanadium-dependent haloperoxidases and flavin dependent halogenases are not able to incorporate fluorine by using hydrogen peroxide or oxygen in. In the proposed mechanism of the haem-dependent haloperoxidase, the first step is the binding of hydrogen peroxide to the redox active haem factor Fe(III) (**1.17**). In this redox transformation the Fe(III) active center is oxidized to the Fe(IV) species (**1.18**), while hydrogen peroxide is reduced to water. The activated species (**1.19**) now is able to oxidize the halide to the corresponding hypohalous acid (Scheme 3). Due to the missing binding side for organic substrates in these enzymes, a low substrate specificity and regio-/stereoselectivity was observed. The formed hypohalous acid are highly reactive and quickly reacts in an electrophilic substitution or addition with any substrate which is around.[12]

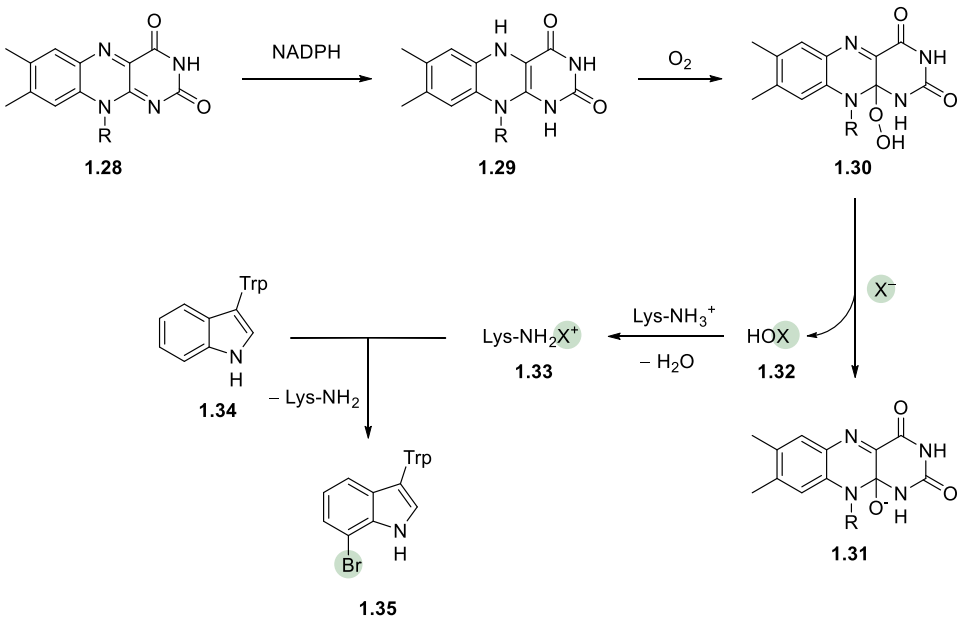


Scheme 3: A) Proposed mechanism of Haem-dependent Halo-peroxidases. B) Proposed catalytic cycle of a vanadium-dependent haloperoxidases (V-HPO). C) Example of selective bromination in the biosynthesis of α-snyderol (**1.27**).

Vanadium-dependent haloperoxidases also utilize hydrogen peroxide, but in contrast to the haem-dependent haloperoxidases, in a catalytic cycle without changing the oxidation state of the metal center, which is illustrated in Scheme 3B. Vanadate (**1.21**) binds to the histidine residue of the corresponding enzyme in the active site. Activation by hydrogen peroxide forming a vanadium(V)-peroxide complex (**1.22**). In the oxidation step the halide is oxidized to the vanadium(V) bounded hypohalous acid (**1.23**). In comparison with the haem-dependent haloperoxidases, the vanadium-dependent analogue exhibit a higher substrate specificity and regio-/stereoselectivity. Therefore, it is assumed that the halogenation species stays at least in close proximity to the enzyme. For example V-BrPOs are involved in the biosynthesis of α-snyderol (**1.27**) by an enantioselective bromination of (*E*)-(+)-nerolidol (**1.26**) which is displayed in Scheme 3C.[14-15]

During the flavin-dependent halogenases (Scheme 4) the flavin cofactor (**1.29**) binds oxygen to form the hydroperoxyflavin intermediate. This step is recognized also for other FAD-dependent monooxygenases. The peroxide species **1.30** is capable of oxidizing the halide anion, which is

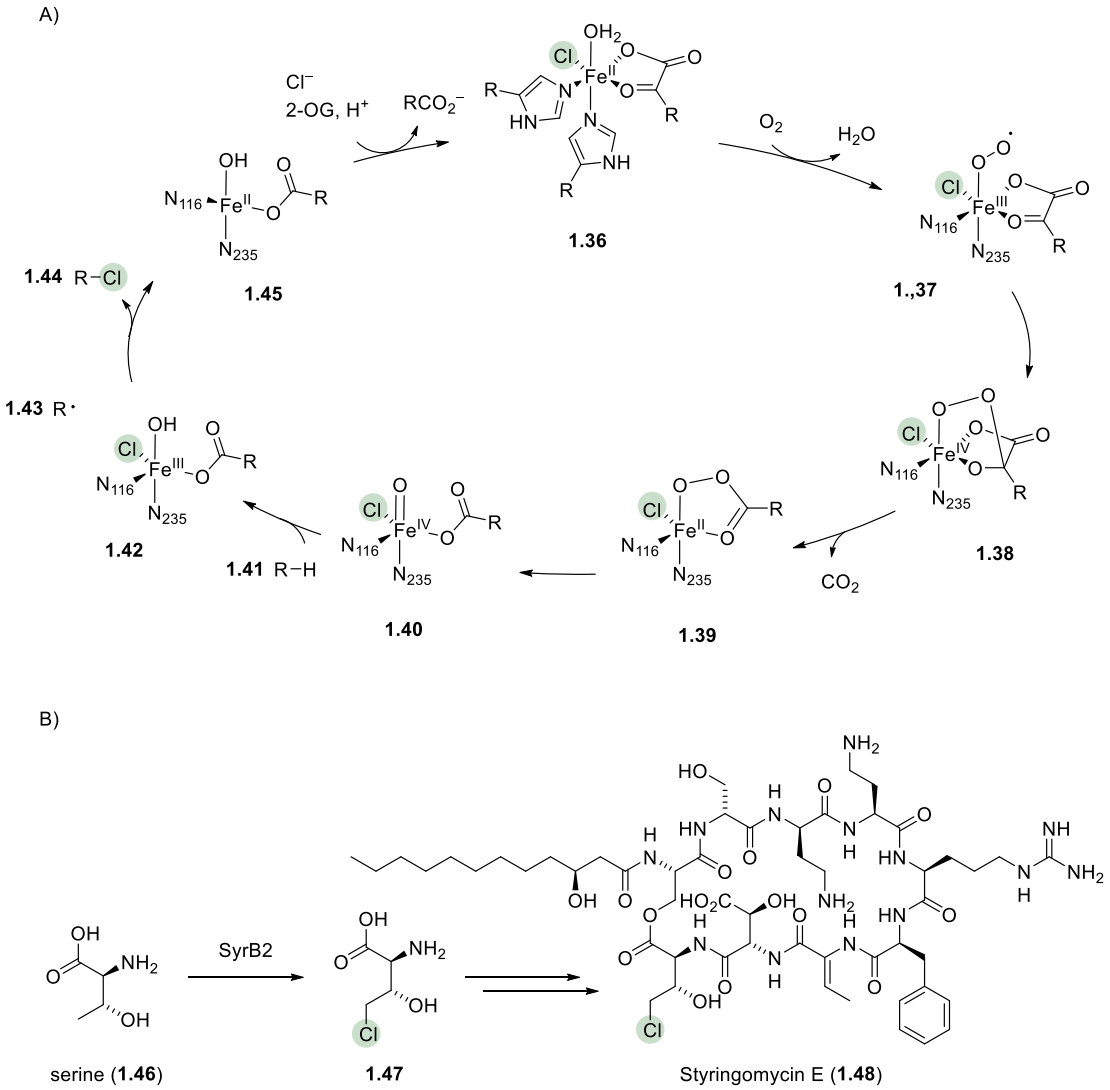
located in proximity to the intermediate. Here the hypohalous acid **1.32** is not released but reacts in a second step active center with the organic substrates which are also bound within the active side. In the proposed mechanism, the hypohalous acid **1.32** is initially bound to a lysine residue, which is transferred to the second active site. The active electrophilic halogenation reagent in this mechanism is a *N*-haloanime **1.33**, which undergoes the desired substitution.[12]



Scheme 4: Electrophilic halogenation via flavin-dependent halogenases within the biosynthesis of bromo tryptophan.

The permanent binding of all substrates, flavin-dependent halogenases show high substrate-, regio- and stereoselective. So for example electrophilic substitution of tryptophan (**1.34**) at the C7-position. However, this proposed mechanism includes several species that can exist in different protonation states, so Scheme 4 only represents a general reaction mechanism.[12]

The third way of the insertion of halogens is the radical pathway via non-haem iron/2-oxoglutarate dependent halogenases, which are restricted to chlorides and bromides. During this process oxygen and 2-oxoglutarate (2-OG) serves as cosubstrates. In the first step, oxygen is bounded to histidine and 2-oxoglutaric acid coordinated iron by the release of water. The oxygen-bound structure is commonly described as Fe(III) superoxido complex, which is then transformed to a peroxy structure. After the oxidative decarboxylation and peracid cleavage, the Fe(IV) oxido species generates the reactive species, which is abstracting a hydrogen atom from an aliphatic carbon atom. The proximity of the formed carbon radical directly allows the recombination with the iron bound chloride forming the desired halogen carbon bond. Regeneration of the active enzyme by addition of chloride and 2-oxoglutarate closes the catalytic cycle catalytic cycle.[12]



Scheme 5: A) Proposed catalytic cycle of a 2-OG-dependent halogenases. B) Biosynthesis of Styringomycin E (**1.48**) from serine (**1.46**).

In general, non-haem iron/2-OG-dependent halogenases halogenate α-amino acids on the aliphatic chain, mainly at a terminal C-atom. For example the halogenase SyrB2 chlorinates selectively the terminal position of *L*-threonine (**1.46**), as depicted in Scheme 5B. This chlorinated amino acid (**1.47**) constitutes the natural product Styringomycin E (**1.48**).[12, 16]

1.4 Bromotyrosine Natural Products

The halogenated aromatic amino acids 3,5-diiodotyrosine was described by Dreschel and coworkers in 1907, as one of first marine natural products. Six years later, the corresponding 3,5-bromotyrosine derivative (**1.49**) was isolated by Morner and coworkers from two coral species. Further secondary metabolites of this class were discovered in 1967, when Sharma and Burkholder

isolated 2,6-dibromo-4-acetamide-4-hydroxy-cyclohexadienone (**1.50**). Since that time, the number of reports on these marine natural products has steadily increased and to date more than 280 second metabolites are known to be biologically active with a variety of biological activities including anti-microbial, anti-cancer, anti-fouling, anti-viral, ATPase regulator, calcium channel modulator, etc.[17]

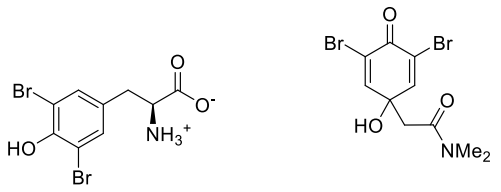


Figure 2: First isolated bromotyrosine natural products.

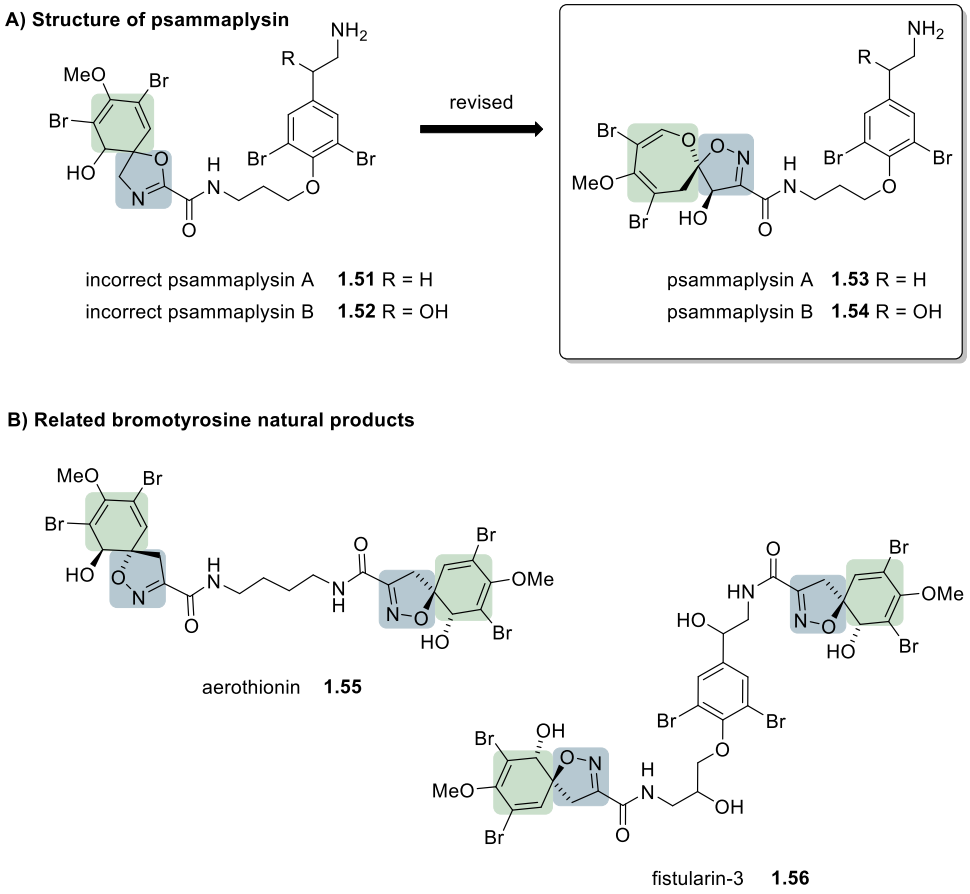
For convenience, the bromotyrosine derivatives are divided into six categories: simple bromotyrosine derivatives, spirocyclohexadienyl-isoxazolines, spirooxepin-isoxazolines, oximes, bastadins, and other structural classes. Simple bromotyrosine derivatives are based on one bromotyrosine with further degradation, reduction, hydroxylation, alkylation or esterification with simple substrates. Spirocyclohexadienyl-isoxazoline bromotyrosine derivatives possess one or two spiro-cyclohexadienyl-isoxazoline motifs, generated in the arene oxide biosynthetic pathway out of bromotyrosine derivatives. Members within this class include one two three bromotyrosine units and further functional groups like histamine. In the oxime class, the amine function of tyrosine is oxidized to an oxime. The geometry of the oxime function was reported to the *E*-configuration in almost every case. Additionally functional groups like histamine, disulfide, cysteine or tyramine are found this class. The bastadins are a series of predominantly macrocyclic bromotyrosine derivatives, which are biogenetically derived from four bromotyrosines by the oxidative phenolic coupling of two tyramine–tyrosine units connected through an amide bond. The outstanding feature of the last class is the spirooxepin-isoxazoline motif. However, there are also members of bromo tyrosine derived products, which do not fit in any of the already mentioned classes.

1.5 Spiro Isoxazoline Dihydrooxepin Family of Natural Products

1.5.1 Spiro Isolation of Isoxazoline Dihydrooxepin Natural Products

The first isolated members of the isoxazoline-oxepin spiro family of natural products were psammaplysin A (**1.53**) and B (**1.54**), which have been discovered in 1883 by Kashman and co-workers from a marine sponge *Psammaplysilla purpurea* (order *Verongida*).[18] Additionally, they

isolated the known natural products aerothionin (**1.55**)[19] and fistularin-3 (**1.56**)[20]. Based on the spectroscopic data of psammaplysin A (**1.53**) and B (**1.54**) and in comparison to the spirocyclic ring motif present in aerothionin (**1.55**) and fistularin-3 (**1.56**), Kashman and coworkers predict an incorrect structure of psammaplysin A (**1.51**) and B (**1.52**), respectively (see Scheme 6).



Scheme 6: A) Previously incorrect assignment of psammaplysin structures and the revised structures. B) Related other bromotyrosine derived natural products.

In 1985, psammaplysin A (**1.53**) and B (**1.54**) were isolated by Clary and coworkers. By the mean of 2D-NMR-spectroscopy (^{13}C–^{13}C-connectivity plot) and single-crystal X-ray crystallography, they succeeded in identifying a novel spirocyclic dihydrooxepin-isoxazoline structure of psammaplysin A. Although Clardy was able to obtain crystals of psammaplysin A acetamide by acetylation of psammaplysin A (**1.53**), the resolution was not refined enough to determine the absolute stereochemistry, but the relative stereochemistry.[21] In 2012, Motti and coworkers isolated several compounds, which belong to the psammaplysin family including psammaplysin A (**1.53**). Based on 2D-NOESY data, no interaction between the protons attached to the C5 and H7 was observed. Therefore, they assigned the stereochemistry to 6*R*,7*R*, as for this no NOE interactions between H5 and H7 were visible in the spectrum.[22] In 2015, investigation by Garson and coworkers about the absolute stereochemistry of psammaplysin A (**1.53**) was performed. In their

work, they compared earlier reports using X-Ray crystallographic data[21], NOESY correlation[22], modelling studies[22] and ECD spectra of psammaplysin with the ECD spectra of known bromotyrosine derived spirocyclic hexadienyl-isoxazolines[23-25] of which the absolute configuration is known, like aerothionin (**1.55**). Furthermore, this stereochemistry was also supported by time-dependent density functional theory ECD calculations and NMR analysis of methoxyphenylacetic ester.[26]

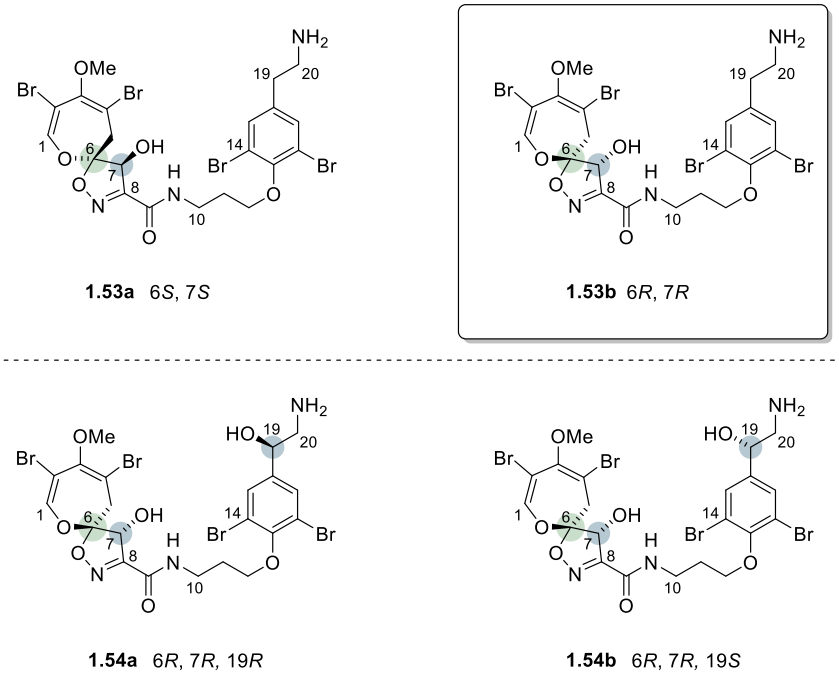


Figure 3: All possible stereoconfigurations of psammaplysin A (**1.53**) and B (**1.54**).

Some members of the natural product family possess an additional C19 stereocenter. Chiral HPLC purification of psammaplysin B acetamide revealed two compounds, each possessing a negative optical rotation and therefore suggesting the presence of diastereomers differing in configuration at the C19 position. Additional hydrolysis afforded carbamate, which showed an optical rotation close to zero. This also indicate a racemic mixture, but enantioselective HPLC failed to distinguish two enantiomers. Further investigation using methoxyphenylacetic esters also failed due to hydrolysis of the ester.[27] Therefore, the racemic nature of this product was not verified. Certainly, it is worthy to note, that the benzylic positions are known for isomerization during preparation and/or purification isomerization can be occur. ^{1}H-NMR signals of psammaplysin B (**1.54**) and its derivatives did not indicate diastereomers. Enantioselective HPLC studies on psammaplysin B (**1.53**) revealed only a single broadened peak, which does not guarantee the presence of a single diastereomer.[26]

In 2019, for the first time Hou-Wen and coworkers reported the isolation of frondoplysin A (**1.55**). Their X-ray crystallographic analysis data revealed the absolute configuration of frondoplysin A (**1.55**) as 6*R*,7*R* configuration in the spirooxepin-isoxazoline ring system and additionally the benzylic hydroxy moiety as 19*R*.

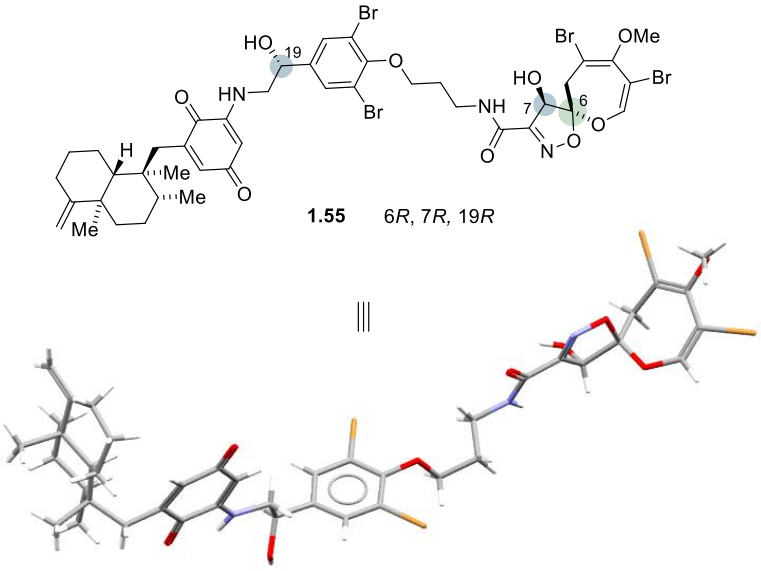
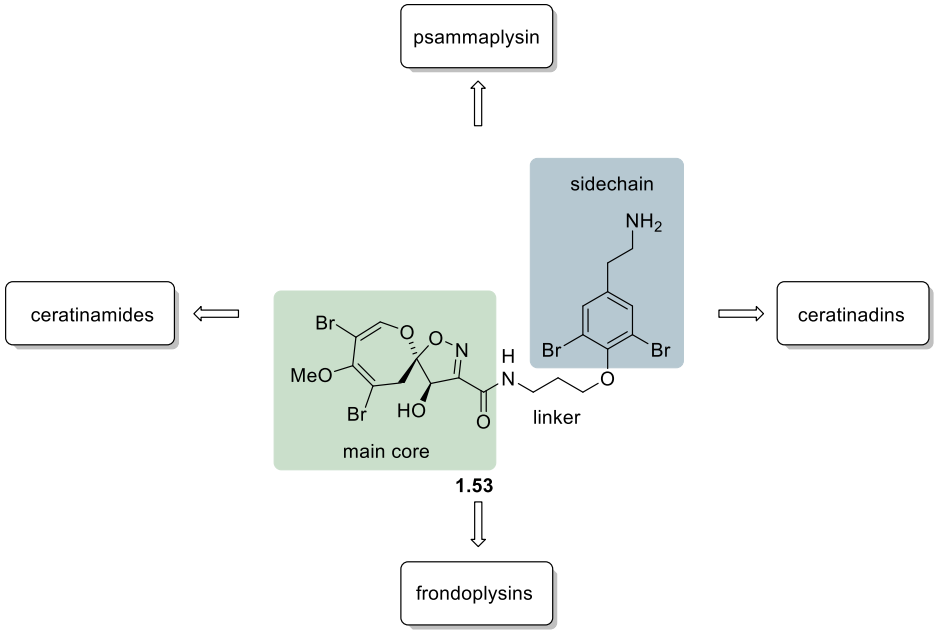


Figure 4: Structure of frondoplysin A and its crystal structure.

All isolated members within the spirooxepin isoxazoline family of natural products show a negative optical rotation. Obviously, it is assumed that all share the same absolute configuration and the biosynthetic pathway of this spiro ring system.[27-30]

1.5.2 Classes of Isoxazoline Dihydrooxepin Natural Products



Scheme 7: Framework of isoxazoline dihydrooxepin spiro natural products and their different classes.

The unique spiro-oxepin-isoxazoline ring structure is a common motif in the four different natural classes of psammaplysin, ceratinamides, ceratinadins and frondoplysins. To date, 43 natural products were mainly isolated with this particular backbone (36 psammaplysin[18, 21-22, 27-28, 30-35], three ceratinamides[28, 36], two ceratinadins[37] and two frondoplysins[38]) isolated and characterized.

1.5.2.1 Psammaplysin Family of Natural Products

Since the first isolation in 1983, 36 derivatives of the psammaplysin family have been identified so far. The class of psammaplysin have been reported over the last decade and describes as followed (psammaplysin A (**1.53**)[18, 21-22, 27-28, 31-32, 34-36], B (**1.54**)[18, 21-22, 27-28, 31-32], C (**1.56**)[31-32], D (**1.57**)[27, 34], E (**1.58**)[27, 32, 34-36], hydroxy-E (**1.59**)[27], F (**1.60**)[32, 37], G (**1.61**)[30], H (**1.62**)[39], I (**1.62**) – J (**1.63**)[22], K – hydroxy-W (**1.64** – **1.84**)[27], X (**1.85**) – Y (**1.87**)[28] and Z (**1.88**) and hydroxy-Z (**1.89**)[35]). These compounds have been mainly isolated from the orders *Verongida* (*genera Aplysinella, Psammaplysinella, Pseudoceratina, and Suberea*)[21-22, 27-29, 31-32, 34-37] and *Dictyoceratida* (*genera Hyatella sp.*[30] and *Dysidea frondosa*[38]) and characterized via NMR, mass spectroscopy and optical rotation.

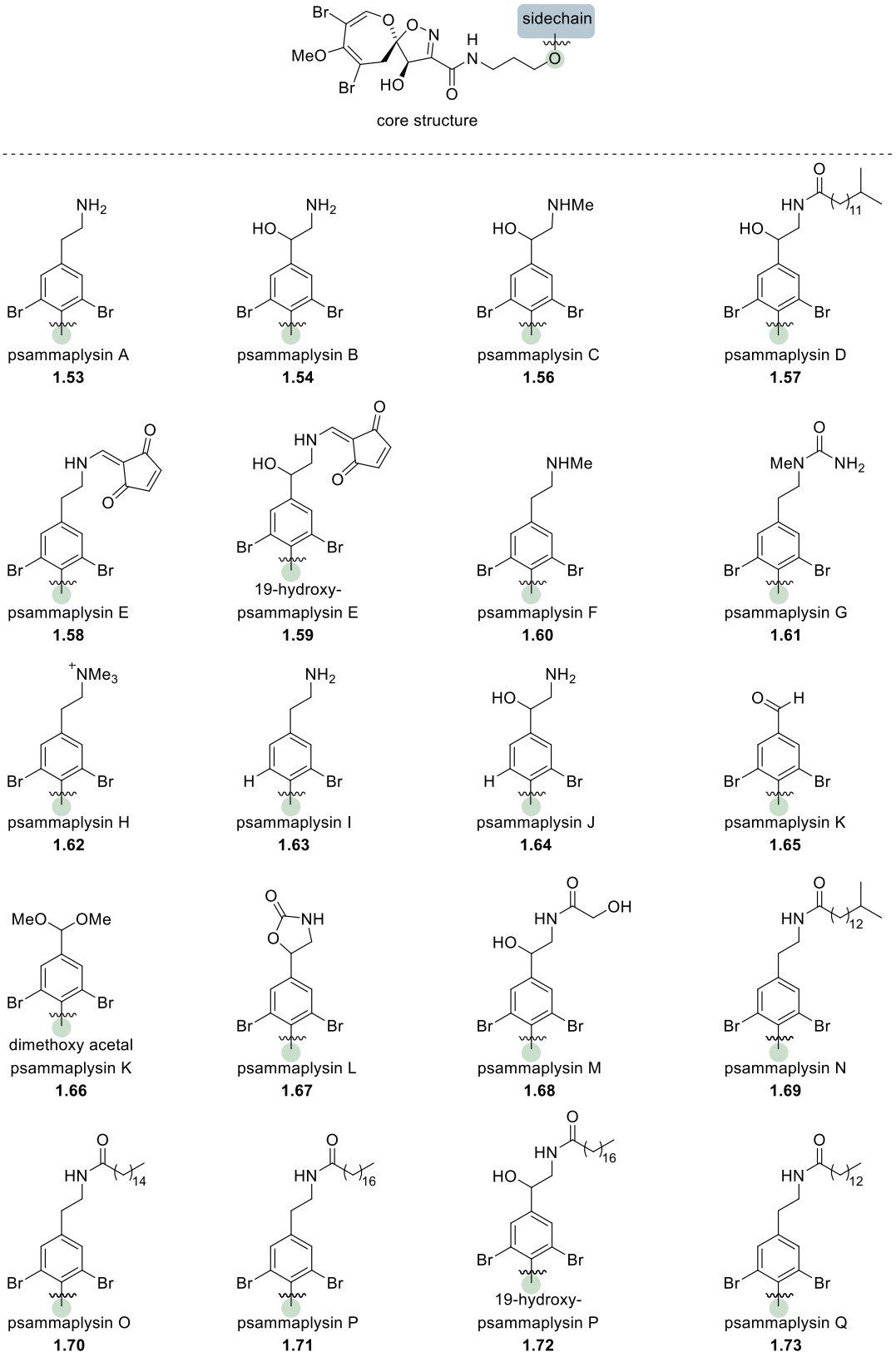


Figure 5: Chemical structures of the different psammaplysin derivatives (part 1).

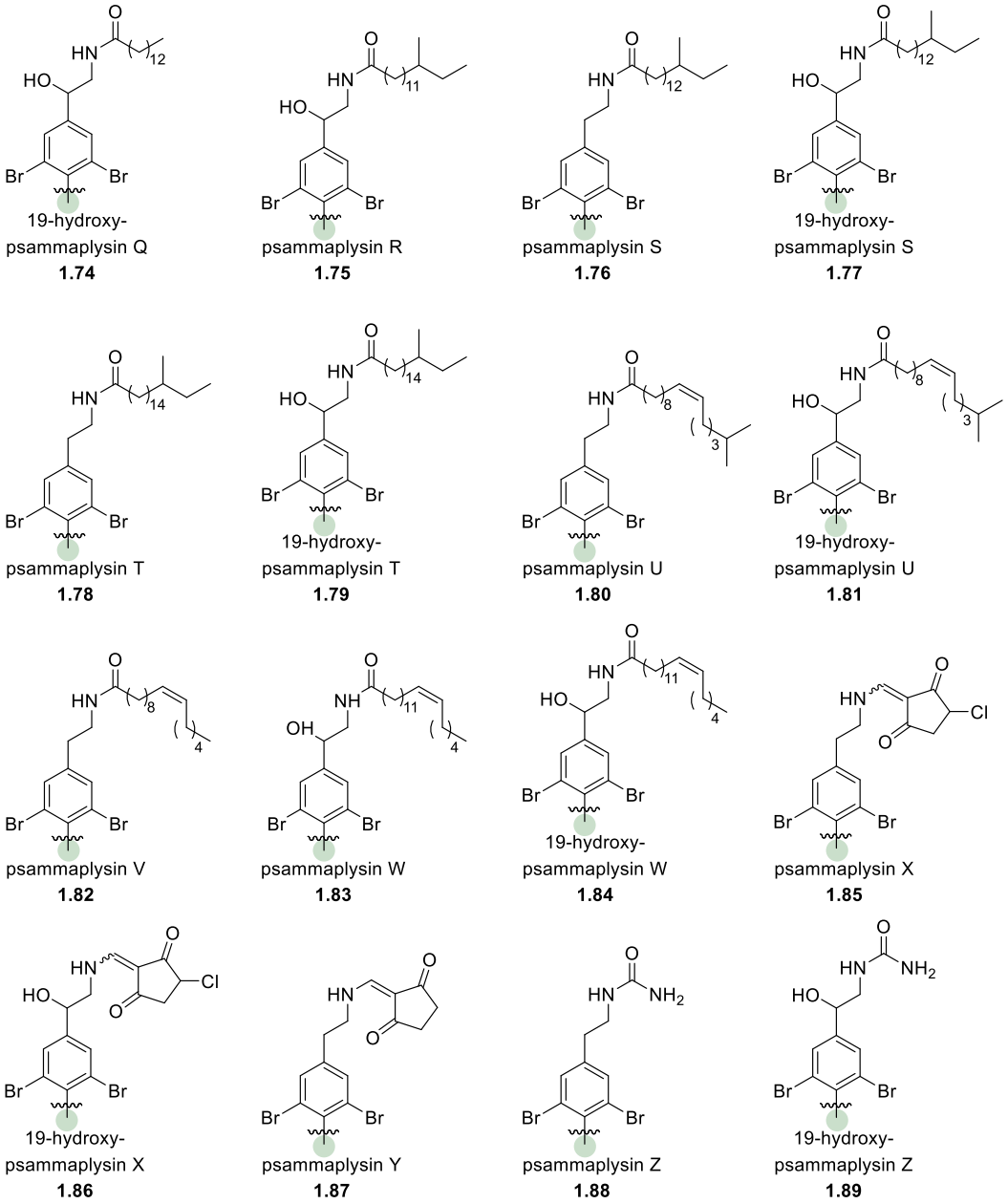


Figure 6: Chemical structures of the different psammaplysin derivatives (part 2).

The modification of the different members are mainly located at the terminal ethylamine residue (C19 and C20 positions) of the moloka'iamine subunit, except for psammaplysin I (**1.63**) and J (**1.64**), in which each have a mono-brominated aromatic ring.[22] Furthermore, psammaplysin K (**1.65**) and dimethoxy acetal K (**1.66**), exhibit a benzaldehyde moiety or a dimethoxy acetal, respectively.[27] While the benzylic position has either a hydroxy or an aliphatic residue, amines, substituted amines, amides (mainly coupled fatty acids), ureas, cyclic carbamates and enamines are substitutions at the C20 position [18, 21-22, 27-28, 30-35]

The compounds were evaluated towards their biological activities and demonstrated multiple effects such as cytotoxicity, anti-malarial, anti-viral, anti-fouling, anti-microbial, and anti-oxidant activity. Psammaplysins A (**1.53**) and B (**1.54**) displayed anti-bacterial *in vitro* activity against gram positive bacteria and Escherichia coli (*E. Coli)* and cell growth inhibition in human colon tumor cell-line colorectal carcinoma cells (HCT116) (IC_{50} = 6.0 µg/mL), psammaplysin C (**1.56**) pronounced cytotoxic effect and reduced IC_{50} values to 3.0 µg/mL.[18, 31] Further psammaplysin A (**1.53**) displayed cytotoxicity against triple-negative breast cancer (MDA-MB-231) (IC_{50} = 3.9 µM) and cervical carcinoma (HeLa) (IC_{50} = 8.5 µM) cell lines.[35]

Psammaplysin D (**1.57**) was found to be highly active against human immunodeficiency virus (HIV-1) at concentration of 0.1 µM.[34] Psammaplysin E (**1.58**) inhibited the cell growth of human colon adenocarcinoma (LoVo) (IC_{50} = 5.0 µg/mL)[34], oral epidermoid carcinoma (KB) (IC_{50} = 5.0 µg/mL)[34], MDA-MB-231 (IC_{50} = 0.21-0.29 µM)[35, 40] and HeLa (IC_{50} = 2.19-3.7 µM)[35, 40] cancer cell lines and revealed moderate immunosuppressive activity[34-35]. Hydroxy-psammaplysin E (**1.59**) displayed a moderate antimalarial activity against the 3D7 drug-sensitive strain of *P. falciparum* with an IC_{50} value of 6.4 µM.[27] Furthermore, psammaplysin F (**1.60**) inhibited up to 80% of four bacterial strains at a concentration of 50 µM[33] and showed antiplasmodial activity in 3D7 and Dd2 strains of *P. falciparum* with IC_{50} values of 0.87 µM and 1.4 µM, respectively.[30] When comparing drug-resistant (K1) and drug-sensitive (FCR3) strains of *P. falciparum*, psammaplysin F (**1.60**) was active in low concentration (IC_{50} values of 3.77 and 2.45 µg/mL), but without a significantly observed selectivity towards the R1 strain.[37] Recently, psammaplysin F (**1.60**) was identified to regulate the synthesis of stress granules in MCF7, HeLa and MCF7MDR cells. The combination with bortezomib and sorafenib led to an enhanced effect of cell viability inhibition.[41] Psammaplysin G (**1.61**) showed an inhibition of 98% the in Dd2 cell strain of *P. falciparum* at a concentration of 40 µM.[30] Similarly, psammaplysin H (**1.62**) possesses potent antiplasmodial potency in the 3D7 strain (IC_{50} = 0.41 µM) and was also selective towards the 3D7 strain with a selectivity index (SI) of >97%.[29] Psammaplysins X (**1.85**) and Y (**1.87**) and 19-hydroxy-psammaplysin X (**1.86**) showed potent cytotoxicity against six cancer cell lines (HCT-15 , PC-3 ACHN MDA-MB-231 NUGC-3 NCI-H23) with a GI_{50} values down to concentrations of 0.8 µM.[28] Psammaplysin Z (**1.88**) and 19-hydroxy-psammaplysin (**1.89**) demonstrated low efficiency against MDA-MB-231 and HeLa cancer cells with IC_{50} values ranging from concentration of 13.2 to 22.2 µM. However, in cytotoxic studies in colon carcinoma HCT-116, both substances reduced the cell growth to 50% at a concentration of 8.2 and 7.0 µM.[35]

Lee and coworkers reported the spirooxepin-isoxazoline ring moiety as a crucial factor of the cytotoxic activity. Their investigation on the molok'iamines (**1.90**), ceratinamines (**1.92**) and their corresponding hydroxy derivatives (**1.91** and **1.93**), revealed no cytotoxic activity in human cancer

lines (HCT-15 , PC-3 ACHN MDA-MB-231 NUGC-3 NCI-H23) of the used compounds in concentrations up to 70 µM.[28] Shaala and coworkers confirmed these results in further investigations.[42]

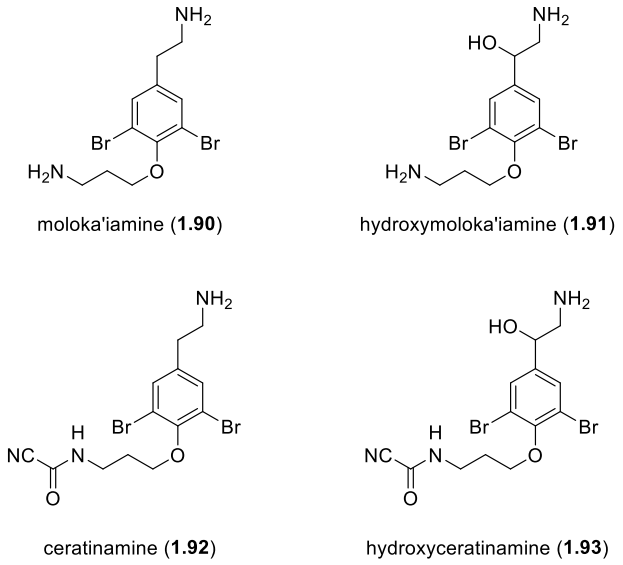


Figure 7: General structure of the side chain of psammaplysin members.

However, the potency of the pharmaceutical activity of these spirooxepin-isoxazoline natural products mainly depends on the bromotyramine moiety. In particular, the substitution pattern of the terminal amine. For example, psammaplysin E (**1.59**) (terminal 2-(methylene)cyclopent-4-ene-1,3-dione moiety) displayed a higher potency to inhibit cell growth as psammaplysin A (**1.53**) (free terminal amine) against MDA-MB-231 and HeLa cancer cells lower than 0.20 µM. Moreover, psammaplysin Z (**1.88**) and 19-hydroxy-psammaplysin Z (**1.89**) showed an even significant lower activity against these cells lines caused by the presence of the terminal urea moiety in both compounds.[35] However, psammaplysin D (**1.57**) with its 12-methyl myristic acid sidechain as a further example demonstrated a lack in activity (GI_{50} > 10 µM) based to the high lipophilic character of the compound compared to psammaplysin A (**1.53**) possessing the free amine.

1.5.2.2 Ceratinamides Family of Natural Products

Ceratinamides A (**1.94**) and B (**1.96**) were isolated from marine sponge *Pseudoceratina purpurea* collected from the Hachijo-jima in 1996 by Fusetani and coworkers.[36] Hydroxy ceratinamide A (**1.95**) was obtained from the micronesian subarea marine sponge (order *Verongida*, family *Aplysinellidae*) by Lee and coworkers in 2013.[28] Almost two years later ceratinamide A (**1.94**) and hydroxy-ceratinamide A (**1.95**) were extracted by El Sayed and coworkers.[40] Isolation of ceratinamides was always described with the isolation of known members of the psammaplysin

family. Therefore, the main structural motif is represented as the formamide functionality[28] within the sidechain. However, ceratinamide B (**1.96**) contains as only member a fatty acid amid group.[28, 36]

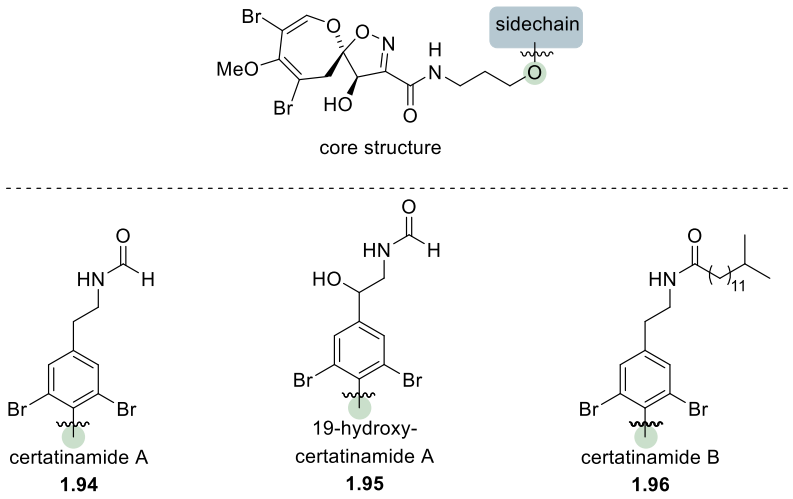


Figure 8: Members within the ceratinamide family.

Ceratinamides A (**1.94**) and B (**1.96**) exhibit antifouling activity through the inhibition of the metamorphosis and settlement of the barnacle *B. amphitrite* ranging from ED_{50} to 0.10 and 2.4 mg/mL and a low cytotoxic effect against P33 cancer cells with IC_{50} values with a concentration of more than 10 µM.[36] So far hydroxy-ceratinamide A (**1.95**) has not been evaluated for its biological activity yet.

1.5.2.3 Ceratinadins Family of Natural Products

In 2018, two new bromotyrosine alkaloids, named ceratinadins E (1.97) and F (1.98), were extracted from an Okinawan marine sponge Pseudoceratina sp. in Okinawa by Kubota and coworkers together with psammaplysin A (1.53) and F (1.60). The characteristic feature of ceratinadin family is the repetitive moloka'iamine motifs in the sidechain. The Absolute configuration was assigned to 6R,7R isomer by the means of NMR and ECD spectroscopy the comparison with already isolated and characterized psammaplysin A (1.53).[37]

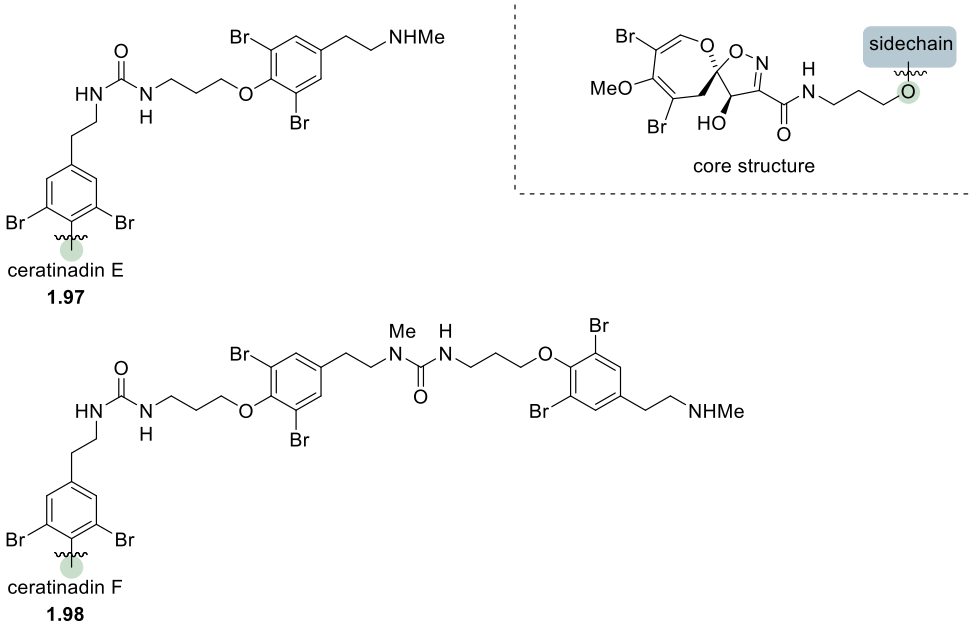


Figure 9: Structure of ceratinadin E (**1.97**) and F (**1.98**) Members within the ceratinadin family.

In vitro studies of ceratinadin E (**1.97**) and F (**1.98**) were conducted in drug-resistant (K1) and drug-sensitive (FCR3) strains of *Plasmodium falciparum* to evaluate antimalarial activity. It was found that ceratinadin E (**1.97**) requires almost half of the concentration in the drug-sensitive as drug-resistant in the drug- resistant strains. Conversely, ceratinadin F (**1.98**) did not show any significant antimalarial activity.[37]

1.5.2.4 Frondoplysins Family of Natural Products

Two frondoplysins derivatives were described by Hou-Wen and coworkers, isolated from the sponge *Dysidea frondosa* (no. XD1506A) from the South China Sea.[38] This was also the first time the absolute configuration of this class of natural products was fully determined by X-ray crystallography and validated the proposed 6*R*,7*R* isomer. The characteristic feature of the frondoplysin derived products is their avarone and neoavarone motif in the side chain.

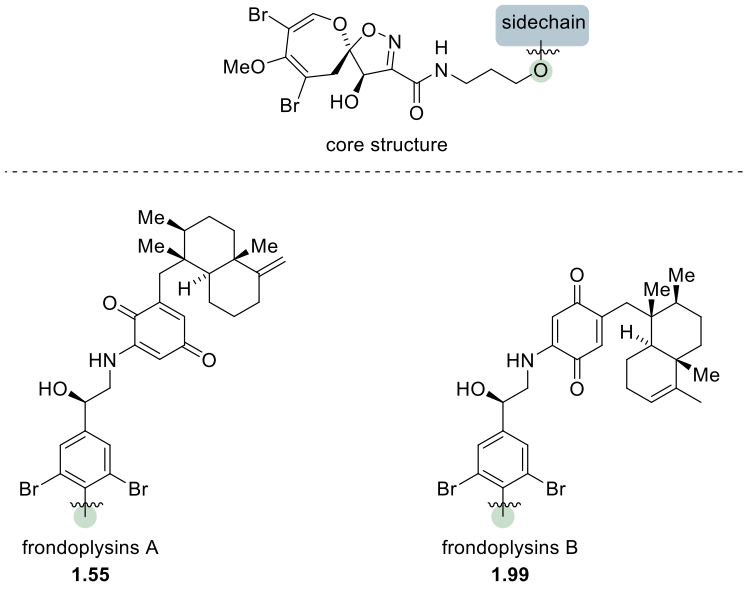


Figure 10: Structures of frondoplysin A (**1.55**) and B (**1.99**).

Frondoplysin A (**1.55**) was found to be a potent inhibitor of the targeting protein-tyrosine phosphatase 1B (PTP1B) with an (IC_{50} = 0.39 µM) while frondoplysin B (**1.99**) demonstrated a lower activity (IC_{50} = 0.65 µM).[38] Moreover, frondoplysin A revealed a higher inhibitory activity compared to thiazolidinediones (IC_{50} of 5.0 µM)[43] and similar reducing properties as benzofurane and benzothiophene biphenyls (IC_{50} = 0.36 µM)[44]. An enzymatic kinetic study outlined that **1.55** acts as a mixed PTP1B inhibitor, but the mode of action is still unknown. Additionally, it displayed significant higher antioxidant activity compared to vitamin C in the zebrafish model, but cytotoxic effects were not observed. [38]

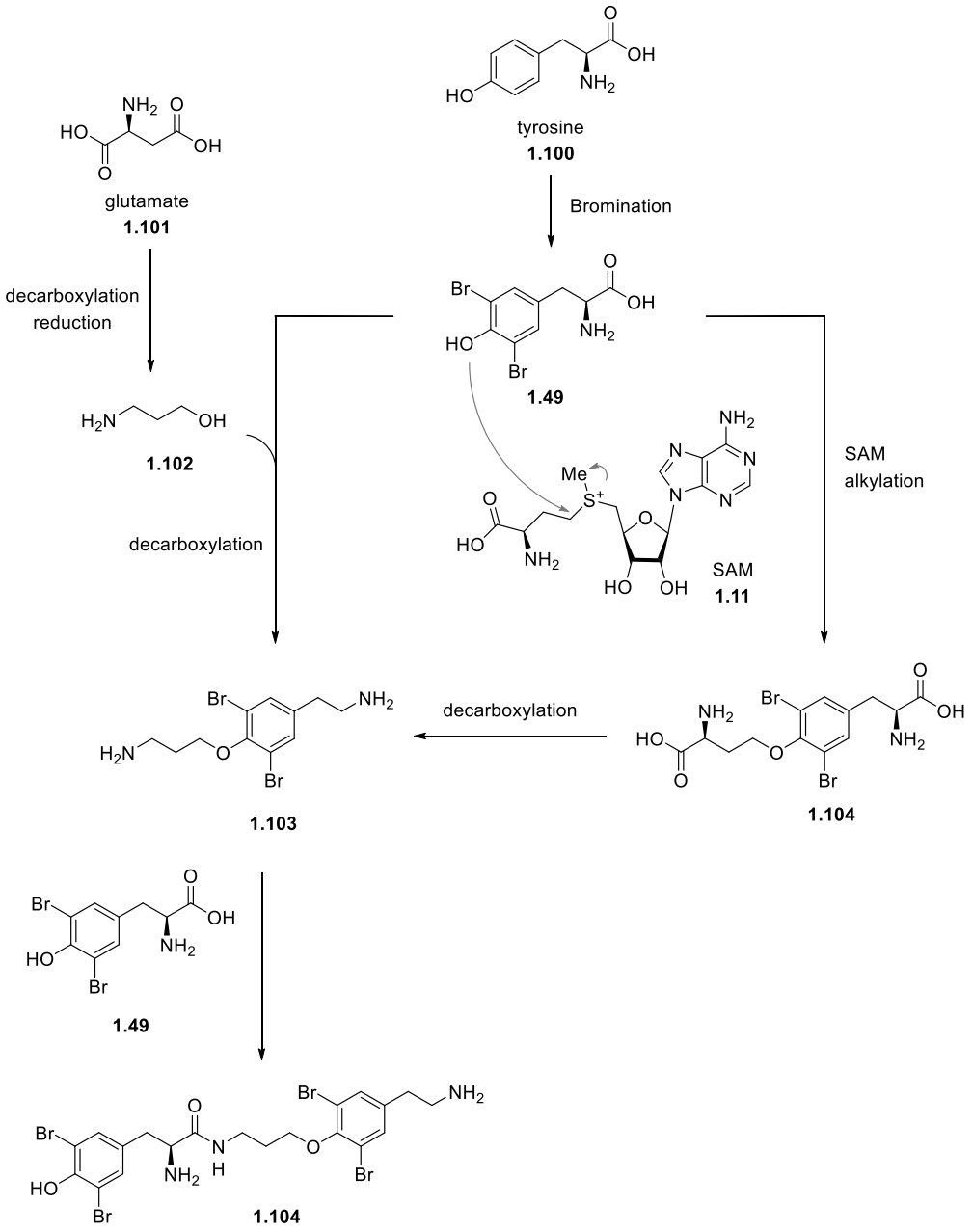
1.5.3 Biosynthesis of Bromotyrosine derived Natural Products

The spirooxepin-isoxazoline family of natural products feature are derived from bromotyrosine and include members such as aerothionin, fistularin and further analogues. These natural products were mainly isolated from marine sponges of the order *Verongida*.[14, 45] The spirooxepin-isoxazoline is a unique structure and is rarely found in natural products.

The biosynthesis of oximinotyrosine derived natural products are widely unexplored based on their extreme difficult investigation of secondary metabolites from marine sponges, which are always associated with microorganism. Today, two different proposed mechanism are available as reported by Rogers[46] in 2007 and by Lindel[45] in 2010 are discussed in the following sections.

1.5.3.1 Proposed Biosynthesis of Bromotyrosine Natural Products

The biosynthesis, the bromination of tyrosine (**1.100**) is catalyzed by the bromooxiperoxidase, a vanadium-dependent haloperoxidases (compare chapter 1.3 Halogenated Natural Products) to generate the bromo tyrosine buildings block **1.49** for further modifications.[38, 46]



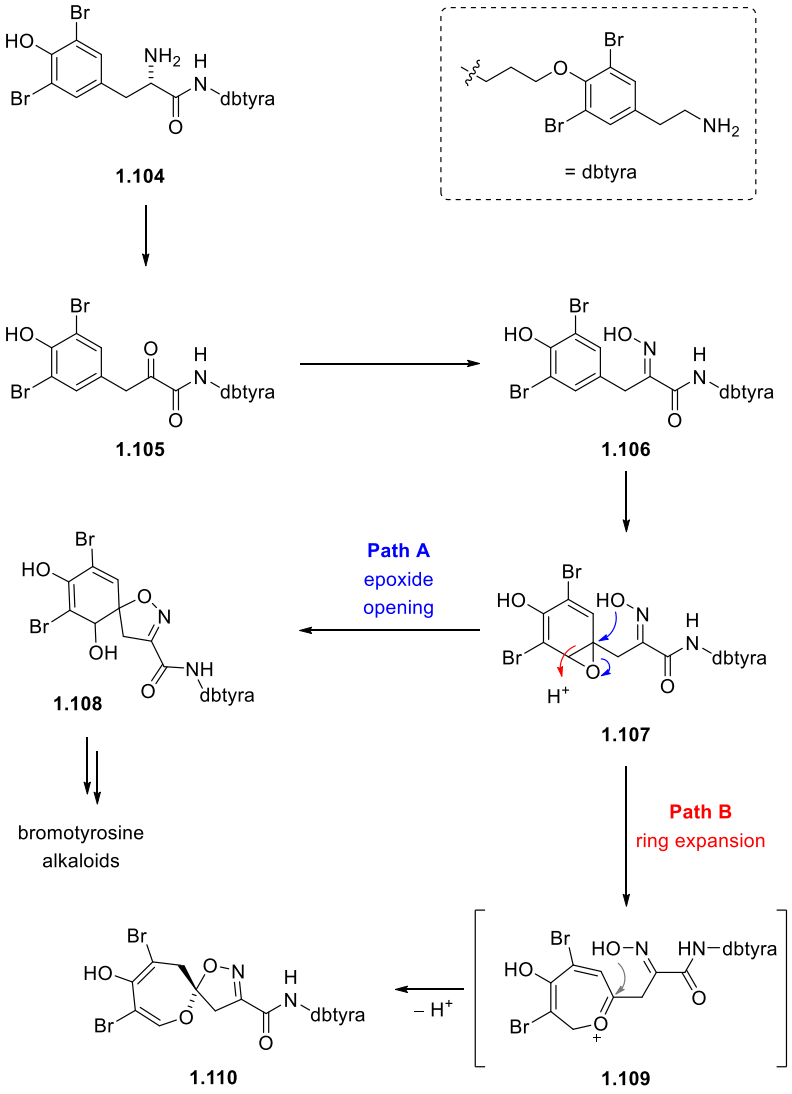
Scheme 8: Proposed biosynthesis of isoxazoline oxepin natural products (part 1).

The *O*-alkylation of phenol **1.49** is still not fully understood. The currently accepted mechanism includes either SAM (**1.11**) or glutamate (**1.101**) as candidates for the linker chain formation. SAM as cofactor is known for alkylation, in which carboxylic acid **1.104** is generated. Dual decarboxylation afforded the moloka'iamine (**1.103**).[46] Another proposed biosynthesis starts with

the degradation of glutamate (**1.101**) to generate the propanol linker **1.102**, which then is connected by etherification to the phenol **1.49** and subsequent decarboxylation afforded moloka'iamine (**1.103**).[38] Finally, amide formation with a second bromotyrosine **1.49** affords the common intermediate for both proposed biosynthesis pathways.[38, 46]

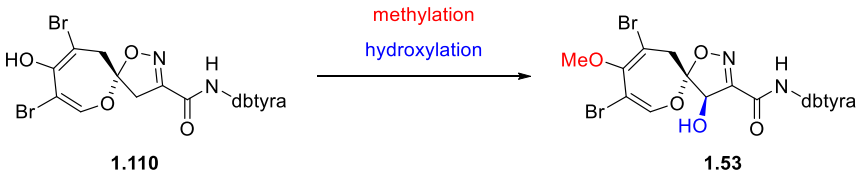
1.5.3.2 Proposed Ring-Expansion Mechanism by Roll

The first proposed biosynthesis was reported by Roll in 1985.[21] In the first steps, the amine **1.104** is oxidized to an oxime **1.106**, which can be also found in already mentioned other marine natural products. Based on the experimentally demonstrated biosynthesis of aranotin published by Neuss *et al*.[47] and Brannon *et al*.[48], Roll postulated an arene oxide intermediate **1.107**, which then underwent a ring-expansion to afford the desired oxepin-isoxazoline spiro structure **1.110**. For this step, a concerted or cationic mechanism is plausible. With this proposed biosynthesis, also the biosynthesis of further spiro marine natural products might be explained by a S_N2 like opening of the arene oxide **1.107**.



Scheme 9: Proposed biosynthesis of isoxazoline-oxepin natural products by Roll (part 2).

The illustrated mechanism in Scheme 9 was also referenced by Jiao and coworkers in 2019 for the biosynthesis of frondoplysin A (**1.55**) and B (**1.99**).[38] Methylation by the cosubstrate SAM finally generated the enol ether motif and a following diastereoselective oxidation generates the hydroxy-isoxazoline structure.[38] Another pathway was suggested with already methylated dibromotyrosine **1.104** as starting material, which followed the same mechanism as described above.[49]

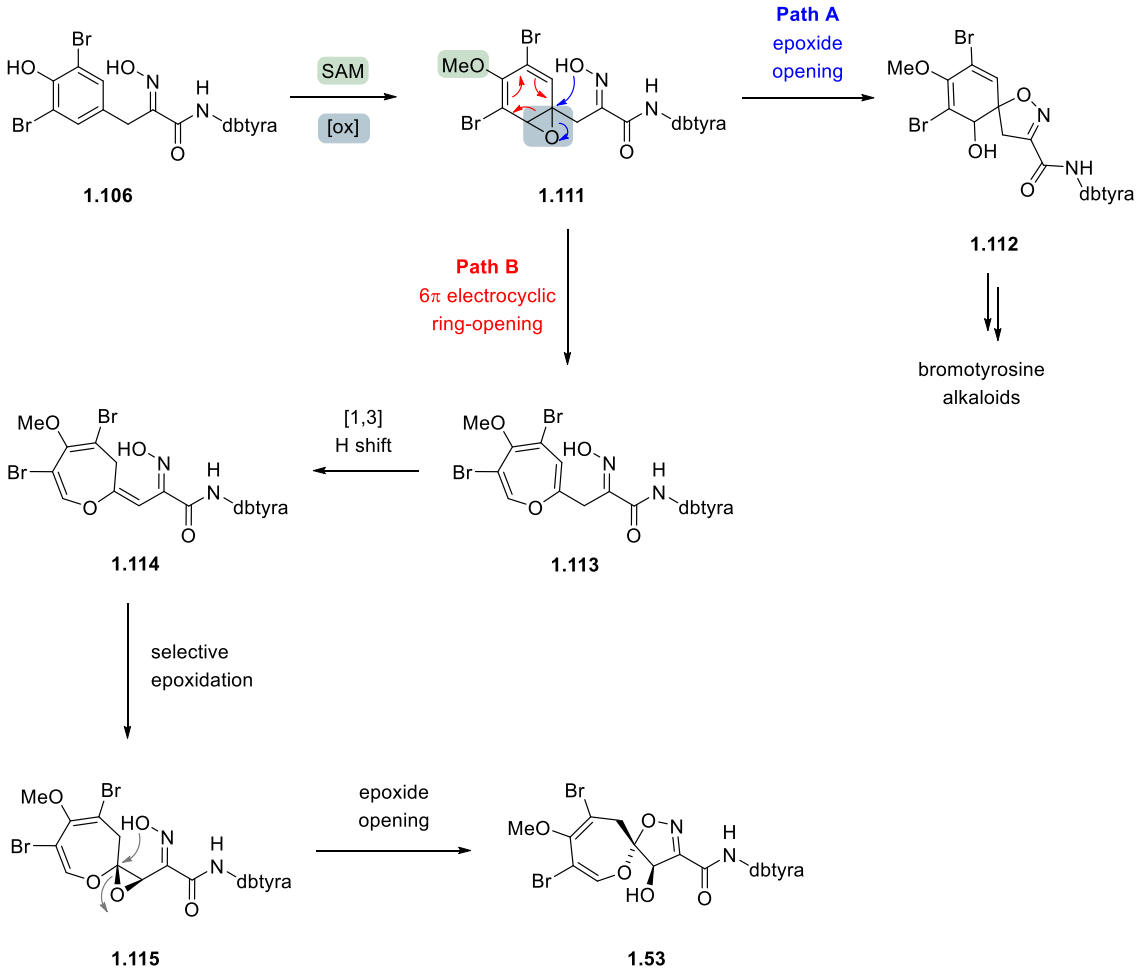


Scheme 10: Final modification of isoxazoline-oxepin natural products.

1.5.3.3 Proposed Ring-Expansion Mechanism by Lindel

Lindel proposed a similar biosynthesis as Roll, however, formation of the spiro is built in a different way.[45] In the first step, phenol **1.104** is methylated via SAM dependent methylase. The epoxidation is achieved by a monooxygenase (possible a cytochrome P450[50]) providing the arene oxide **1.111**. Subsequently, the latter can undergo either an oxime mediated ring-opening to the spiro-cyclohexadiene system (**1.112**) (Scheme 11, blue arrows), as already described by Roll or a 6π disrotatory electrocyclic ring-opening to the oxepin **1.113** (Scheme 11, red arrows). The spiro-cyclohexadiene precursor **1.112**, which is present in natural products like fistularins and areothions can additionally act as a building block for further bromotyrosine natural products. In the case of the oxepin a 1,3-hydride shift induces isomerization to the conjugated oxime **1.114**, followed by a second oxidation to provide the asymmetric epoxide **1.115**. In the final step, the epoxide opening by the oxime generates the spiro **1.53**, already including the hydroxy-isoxazoline. Nevertheless, Lindel also mentioned that there could be also a direct pathway from oxime **1.106**.[49, 51]

In 2017, Karuso and coworkers isolated several bromotyrosine alkaloids including an enantiomer of a known carboxylic acid. This report suggested an enantiodivergent step in the biosynthesis of bromotyrosine alkaloids resulting in an increased structural diversity. However, this step occurs during arene oxide **1.111** formation. The enantiotopic epoxidation is an interesting enantiodivergent desymmetrization that leads to enantiomers of natural products, which might be produced by different species.[52]

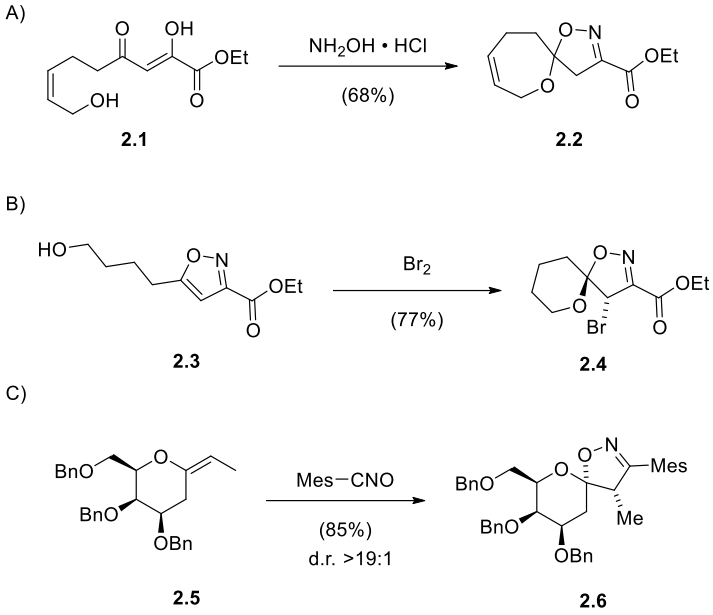


Scheme 11: Proposed biosynthesis of isoxazoline-oxepin natural products by Lindel (part 2).

2 Previous Efforts toward the Synthesis of Psammaplysin A

While there are many total synthesis of spiro[4;5]-cyclohexadiene isoxazoline containing natural products[45], there are only few model substrates for spiro[4;6]-cycloheptadiene isoxazoline core motif. Despite their promising biological activity, there are no published syntheses of any member of the hydroxy-isoxazoline-dihydrooxepin natural products to date. Due to the lack of naturally occurring material, a concise synthesis will be necessary to establish a comprehensive biological evaluation of the psammaplysins and shine light on structure–activity relationships by the investigation of fully synthetic analogs.

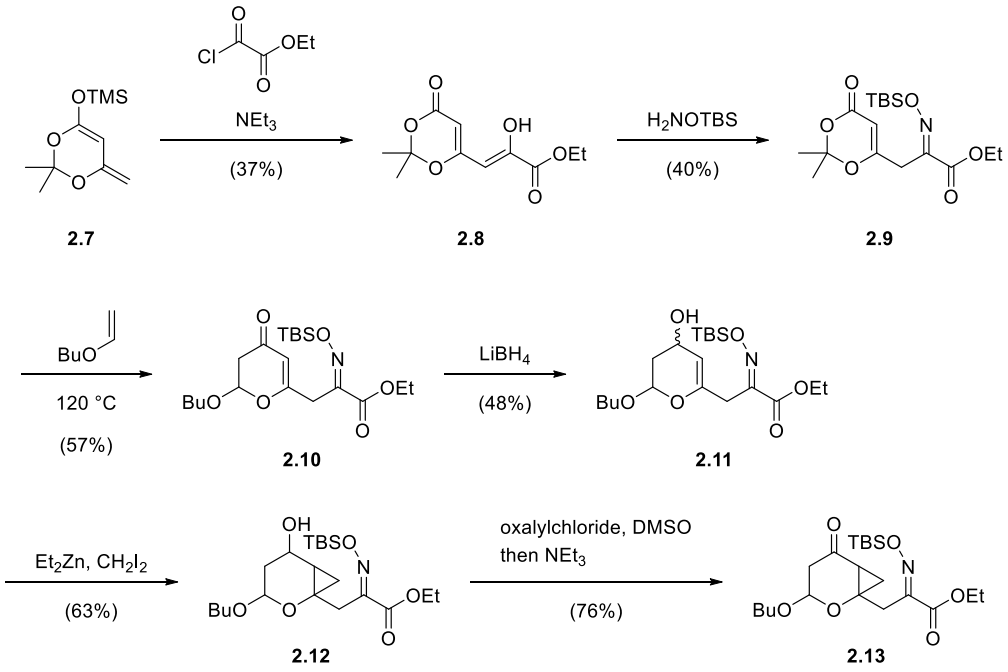
Mioskowski reported the first approach for spiro[4;6]-cycloheptadiene isoxazoline synthesis by the condensation of hydroxylamine onto the more electron deficient ketone and direct spiro cyclization.[53] Although a single example of a low functionalized [4;6] spiro **2.2** exist in this report (Scheme 12 A), Lindel describes this methodology as the most promising model study towards isoxazoline-oxepin natural products.[45]



Scheme 12: A) Spiro isoxazoline ring formation via condensation. B) Spiro isoxazoline ring formation via bromonium cyclization. C) Spiro isoxazoline ring formation via [1,3]-dipolar cycloaddition.

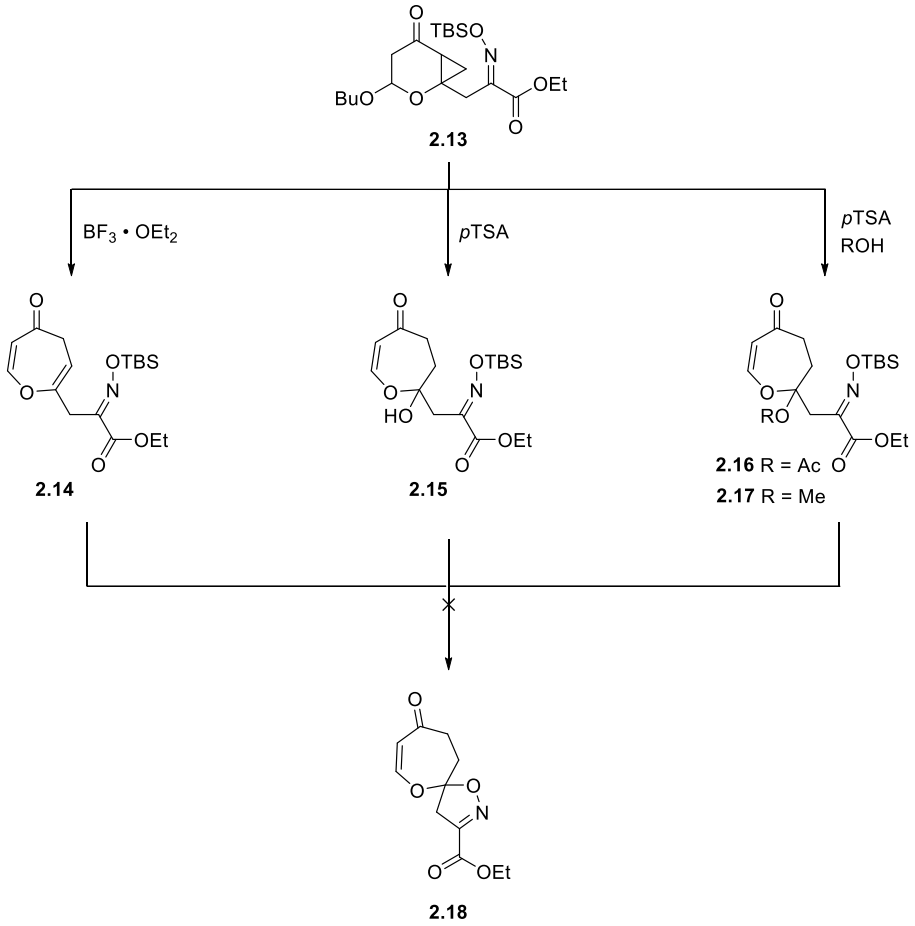
Hamme and coworkers demonstrated a spirocyclation via an electrophilic bromination step. Intramolecular opening of the bromonium by primary alcohols or carboxylic acids afforded the desired spiro product. Nevertheless, they reported only the formation of five- and six-membered spiro-isoxazolines (Scheme 12 B).[54] In the work of Lieberknecht and coworkers the utility of [1,3]-dipolar cycloaddition reactions to synthesize spiro isoxazoline starting from a terminal enol ether **2.5** was described.[55]

In 2015, a dissertation towards the total synthesis of psammaplysin was provided by the Vanderwal group.[56] Their basic strategy was the installation of a donor acceptor cyclopropane and its ring-expansion to directly build up the [4;6] spiro moiety. The addition of silyl enol ether **2.7** to acid chloride afforded in enol **2.8**, which was then condensed with *tert*-butyldimethylsilyl protected hydroxylamine. Thermal ketene formation and trapping *n*-butyl vinyl ether yielded the pyranone **2.10**. In their work, they also demonstrated that the direct cyclopropanation of dihydropyrone **2.10** was not possible. However, a three step sequence including reduction (lithium borohydride), cyclopropanation (Simmons−Smith), and oxidation (Swern) allowed them to access the desired cyclopropane **2.13**.



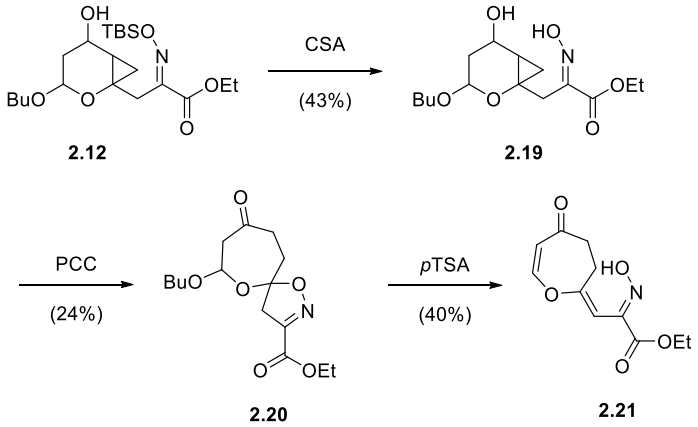
Scheme 13: Synthesis towards the psammaplysin family starting from silyl ketene acetal **2.7** to access cyclopropane **2.13**.

However, ketone **2.13** did not undergo the desired spiro cyclization, while addition of Lewis acid resulted in the formation of hydrooxepin **2.14**, Brønsted acids formed hemiacetal **2.15** and acetal **2.16** or **2.17**, depending on the solvent.



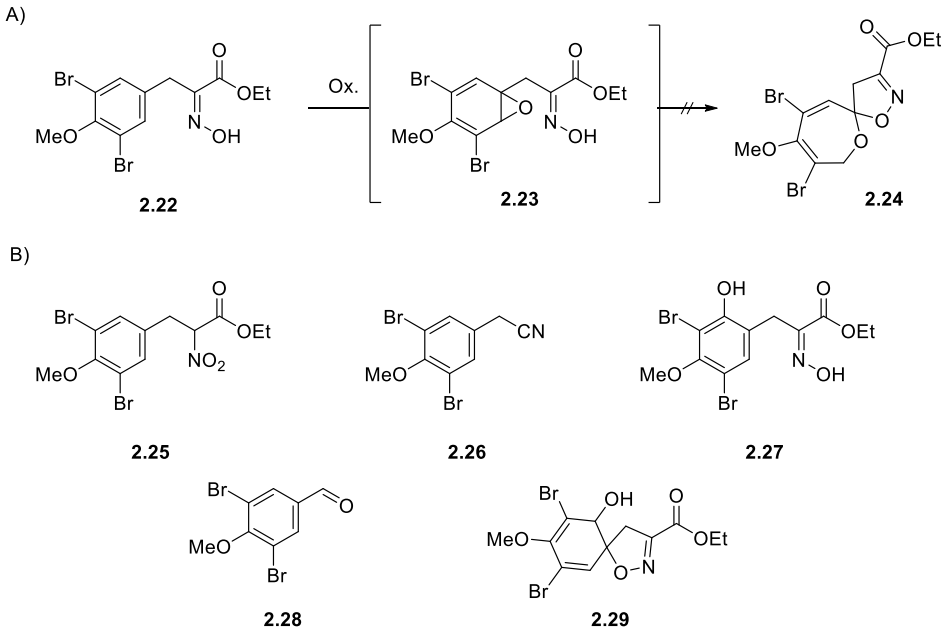
Scheme 14: Attempted synthesis of spiro **2.18** from dihydropyrone **2.13**.

Although, this thesis demonstrated the successful synthesis of the spiro **2.20** from alcohol **2.12**, the obtained hydrooxepin moiety was still lacking in the correct substitution pattern. Formation of the enone motif under acidic conditions resulted in the undesired opening of the spiro residue, which evidenced the acid lability of this spiro motif.



Scheme 15: Synthesis of spiro **2.20** and undesired subsequent side reaction.

An attempted bio-inspired oxidation of the aromatic core was reported by Clardy to directly access the seven-membered ring.[49] However, oxidation of the aromatic core is performed on simple benzene or anisole derivatives with short reactions times to prevent undesired side reactions. Although, reactions were run for up to 37 days only low yields were obtained of the oxidized products **2.25** to **2.29**. A low yielding biomimetic synthesis of areothionin **2.29** was accomplished by this method, showing that in general an oxidation of the aromatic ring is possible, but further oxidation studies are required to develop better methods to generate the necessary arene oxide, which might gave the desired spirocycles.

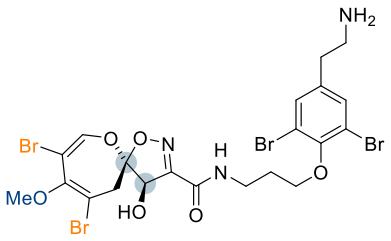


Scheme 16: A) Planned oxidation of the aromatic ring to access spirohydrooxepin. B) Isolated products of different oxidations protocols.

3 Results and Discussion

3.1 Retrosynthetic Analysis of Psammaplysin A

Even almost 40 years after the first isolation of psammaplysin A (**3.1**)[18], there are only two synthetic studies known (Clardy[49], Vanderwal[56]). This already indicates that the synthesis of this structural motif represents a great challenge for synthetic chemists. Furthermore, the spirocyclic nature of the natural product brings in sterical hindrance which could cause reactivity issues for planned synthetic (post)-modifications.[57-58]

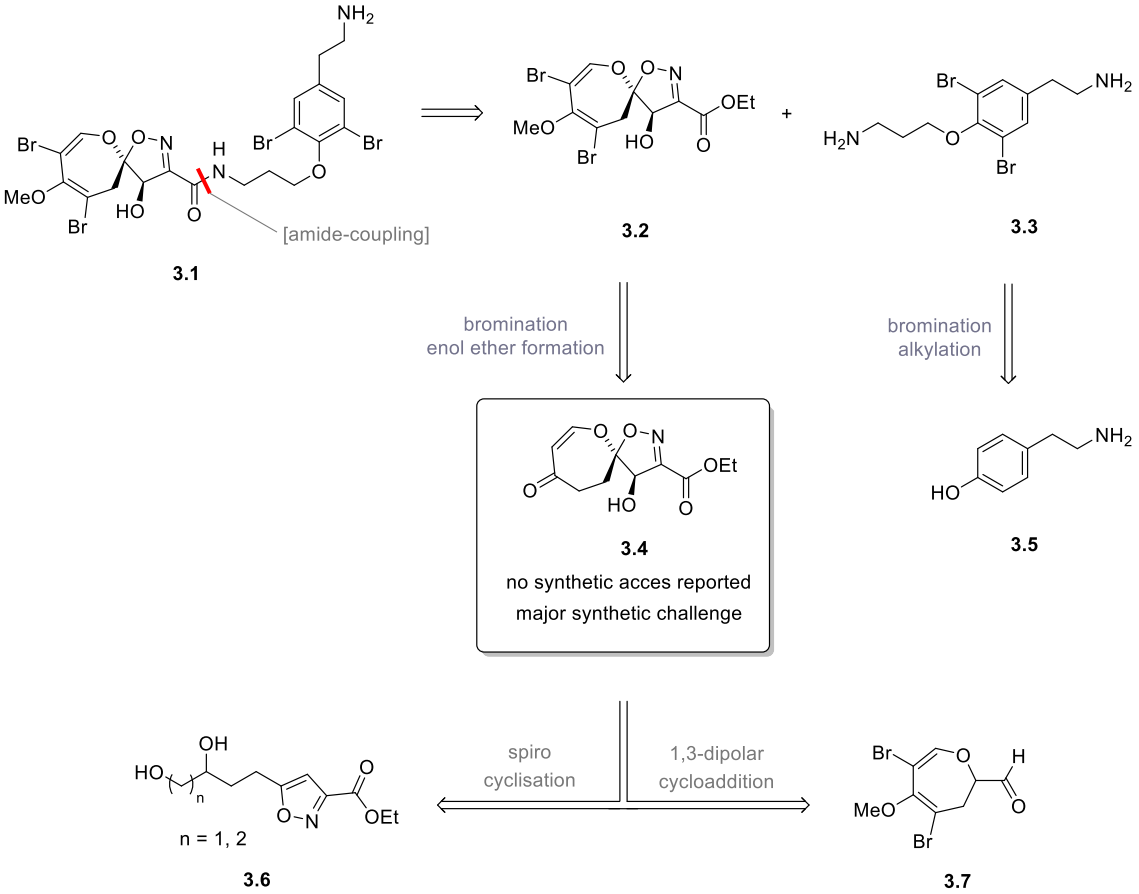


psammaplysin A (**3.1**)

Figure 11: Structure of psammaplysin A (**3.1**)

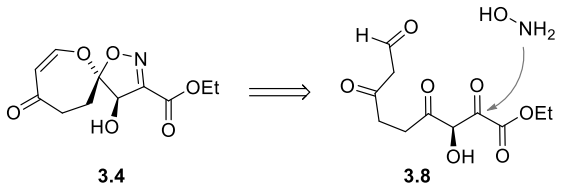
Psammaplysin A (**3.1**) has two vicinal stereocenters, one can be classified as a spiro acetal and the other as a secondary alcohol within the isoxazoline structure. Another prominent feature is the 1,3-dibromo-2-methoxy substitution pattern on the dihydrooxepin motif. This dense substitution pattern on the seven-membered ring significantly increases the difficulty of the synthesis. Furthermore, this particular dihydrooxepin includes a bis-enolether system, which is known to hydrolyze easily.[59] The surprising stability of the brominated enol ethers is based on electron withdrawing groups at the β-position as demonstrated in pioneering work of Schwarte *et al.*.[60] Isoxazoline structure is the second ring structure of the spiro and itself a common structure in chemistry. However, syntheses of spiroisoxazolines are limited to few methods. Furthermore, acetal spiro center in psammaplysin was expected to open up under acidic conditions. This opening of the isoxazoline motif was demonstrated by studies toward the synthesis of psammaplysin.[56] Finally bis-brominated tyramine derivative is linked to the scaffold via an amide bond.

To realize a convergent synthetic entry for the psammaplysin family, the retrosynthetic disconnection of the amide bond will allow late-stage diversification to access different members of bromotyrosine natural products. Additionally, this strategy will allow rapid entry to synthetic analogs of **3.1** to shine light on their structure-activity-relationships. Herein, the amine **3.3** will be easily accessible from tyramine **3.5** within a few steps via bromination, modification of the phenethylamine functionality and phenol coupling with the propane linker.[49, 61]



Scheme 17: Retrosynthetic analysis of psammaplysin A (**3.1**).

In contrast to this, the highly oxidized spiro-dihydrooxepin-isoxazoline ring structure **3.2** displays a unique heterocyclic skeleton for which we envisioned a stepwise bromination with final enol ether formation. This strategy was also successfully applied on related compounds by Guy and coworkers.[62] Our first approach commenced with the linear substituted isoxazoline **3.6**, which might give access to spiro **3.4** after spiro cyclization with the primary alcohol. The second approach already included a substituted dihydrooxepin aldehyde **3.7**. After enol formation or elimination to the terminal double bond, [1,3]-dipolar cycloaddition with a nitrile oxide would afford our key intermediate **3.4**.



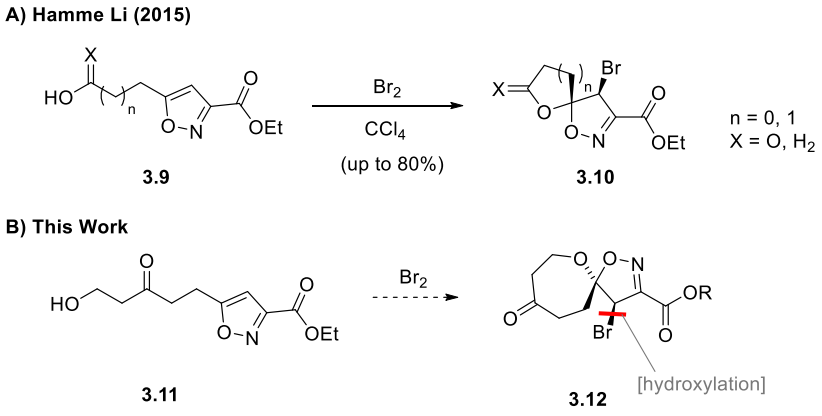
Scheme 18: Condensation disconnections of spiro **3.4** to linear pentacarbonyl **3.8**.

A further retrosynthetic disconnection of spiro **3.4** to linear pentacarbonyl **3.8** envisioned by a series of condensation reactions with hydroxylamine is illustrated in Scheme 18. However, this disconnection may not be practical in the forward sensesense as it requires a 1,2,4,7,9-pentacarbonyl moiety as a key structural feature of the psammaplysins.

3.2 First-Generation Approach: Spiro Cyclization

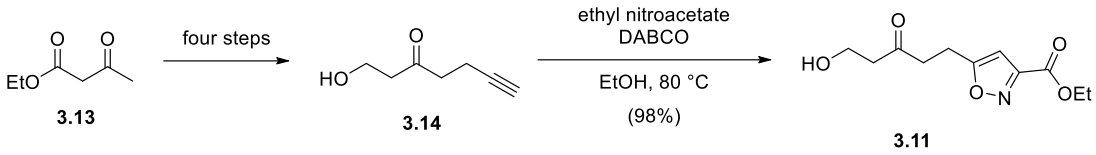
3.2.1 Bromo Spiro-Cyclization to the [6;4] Spiro System

Our initial survey through the literature revealed a methodology of Hamme Li and coworkers, which relied on a highly efficient oxidative spirocyclization via dearomatization of linear isoxazole **3.9**.[54] However, their report was limited to aliphatic and primary alcohols as well carboxylic acids to afford [5;4] and [4;4] spiro systems **3.10**. By enhancing this strategy, we imagine to directly access the desired [6;4] spiro system **3.12** bearing the ketone functionality on the oxepin moiety.



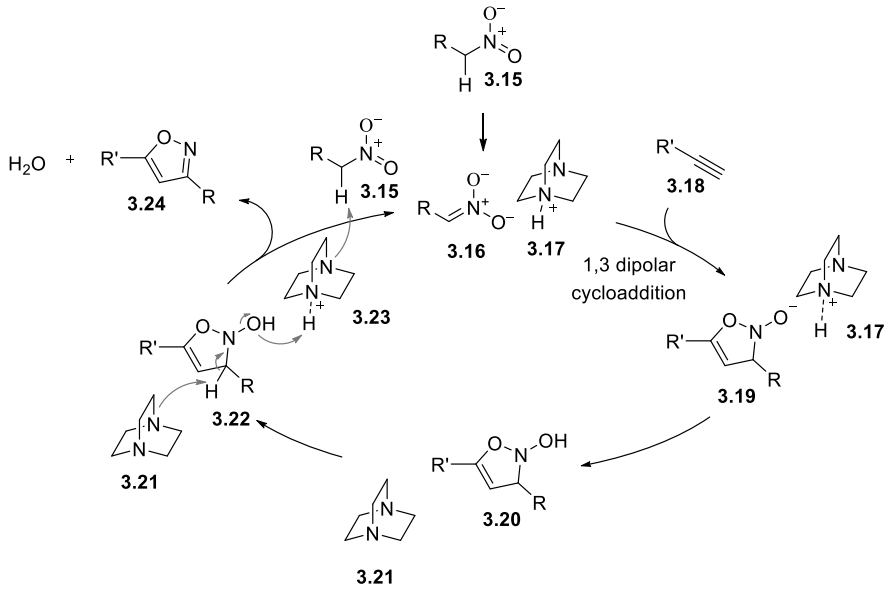
Scheme 19: A) Spiro cyclization of isoxazole **3.9**. B) Planned synthesis of spiro **3.11** from isoxazole **3.11**.

For the synthesis of cyclization precursor **3.11**, commercially available acetoacetate **3.13** was converted into alkyne **3.14** in four steps. Finally, DABCO-catalyzed [1,3]-dipolar cycloaddition of alkyne **3.14** with ethyl nitro acetate afforded the desired isoxazole **3.11** in excellent yield.[63-64]



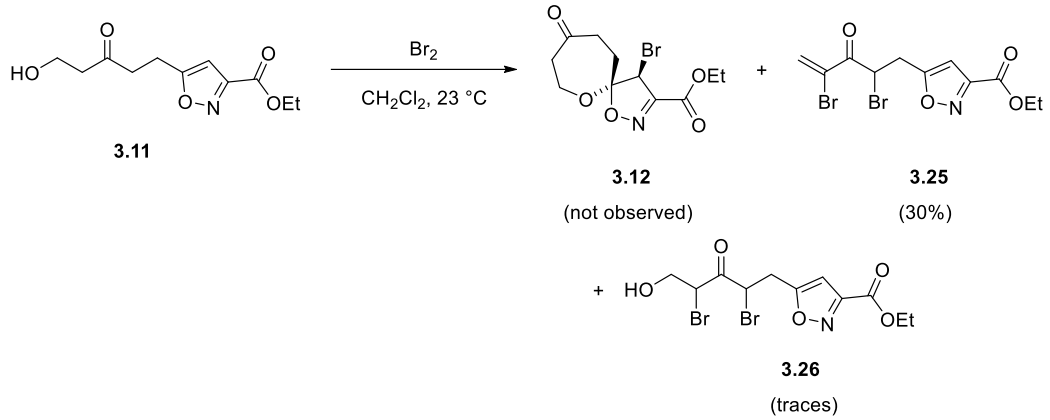
Scheme 20: Synthesis of isoxazole **3.11** from acetoacetate **3.13**.

The proposed mechanism[64] of this DABCO-catalyzed (10-20 mol%) [1,3]-dipolar cycloaddition is illustrated in Scheme 21. Nitro compound **3.15** enters the catalytic cyclic via deprotonation of the α-acidic nitro position by DABCO to unmask its [1,3]-dipolar character. In polar protic solvents like ethanol both ions exist as single ions. Dipole **3.16** undergoes the [3+2]-cycloaddition with alkyne **3.18** to form five-membered cycle **3.19**. **3.20** is generated by the protonation by the protonated DBACO species **3.17**. Deprotonation protonation sequence of **3.20** catalyzed by DABCO **2.21** afforded isoxazole **3.24**, water and the free DABCO **2.21**. DABCO **2.21** reenter the catalytic cycle by deprotonation of the next nitro compound **3.15**.[64-65]



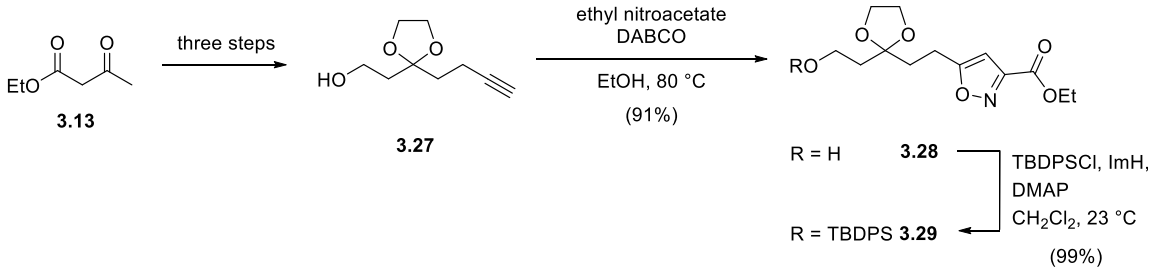
Scheme 21: Proposed mechanism for the DABCO catalyst [1,3]-dipolar cycloaddition with nitro compounds.

Unfortunately, linear precursor **3.11** did not undergo the desired bromo-cyclization. However, α-bromination was observed as the major side reaction. By the formation of hydrogen bromide, primary alcohol is substituted by bromide and directly eliminate to the corresponding enone system (Scheme 22).



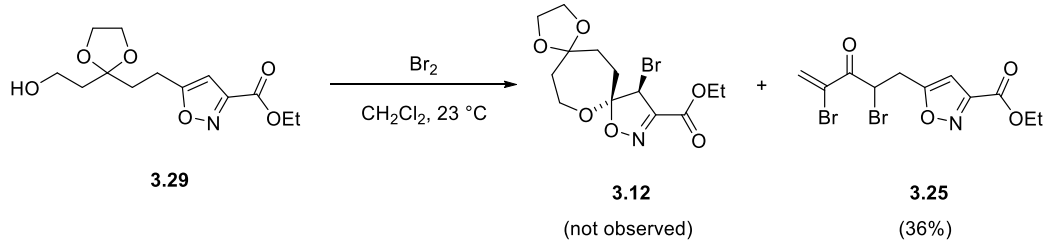
Scheme 22: Attempted synthesis of **3.12** and isolated ketone **3.25**.

To avoid α-bromination in the cyclization step, the ketone moiety was protected as its corresponding acetal. For this purpose, alkyne **3.27** was subjected to the previously used reaction conditions to yield isoxazole **3.28** in excellent yield (Scheme 23).



Scheme 23: Synthesis of acetal protected isoxazole **3.28** and **3.29**.

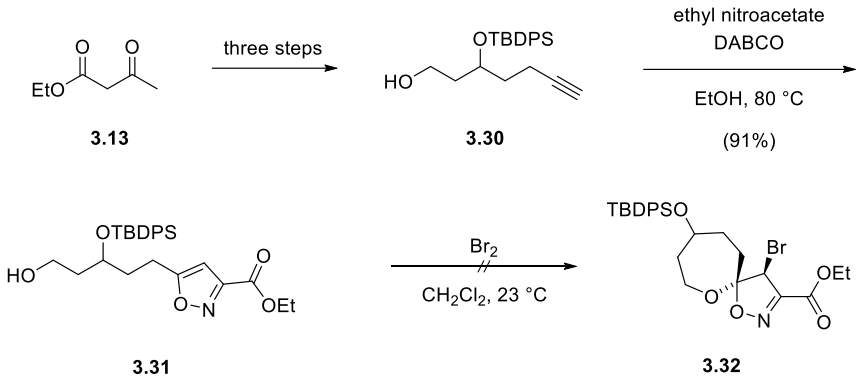
Unfortunately, acetal **3.29** turned out to be unstable upon exposure to bromine in dichloromethane leading again to bromoketone **3.25**, presumably via initial deprotection of the ketone moiety followed by alpha-bromination.



Scheme 24: Attempted synthesis of spiro **3.12** and isolated ketone **3.25**.

For this reason, reduction of ketone and subsequent protection with stable *tert*-butyldiphenylsilyl group was chosen. Starting from acetoacetate **3.13**, primary alcohol **3.30** was accessed by sodium borohydride reduction, *tert*-tutyldiphenylsilyl protection and diisobutylaluminium hydride

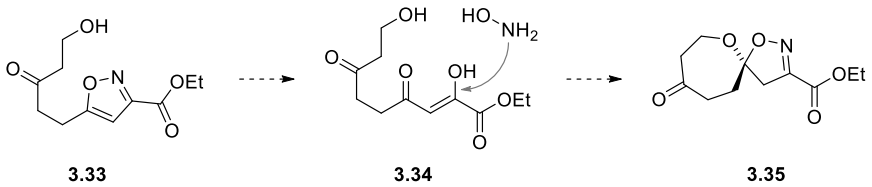
reduction. [1,3]-dipolar cycloaddition delivered isoxazole **3.31** in 91% yield. However, even up to 25 equivalents of bromine still showed no conversion toward any cyclized products.



Scheme 25: Attempted synthesis of spiro **3.32**.

3.2.2 Isoxazole Reduction to 1,3-Diketone

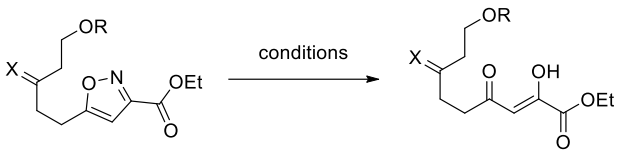
With isoxazole **3.33** in hand, we envisioned to directly reduce the isoxazole motif to the corresponding diketone **3.34**. In our envisioned synthetic route, spiro **3.35** can be constructed by series of condensations with hydroxylamine and diketone **3.34**. The chemoselective condensation of hydroxylamine onto the more electron-deficient ketone with the formation of similar seven-membered ring systems was reported by Smietana and coworkers.[53]



Scheme 26: Planned synthetic route towards spiro **3.35**.

However, reduction of isoxazoles bearing an ester at the group on 3-position to the corresponding 1,3-ketone are mainly known in literature. Nevertheless many conditions are known for aliphatic-substituted isoxazole at the 3-position.[66-68] Conditions on substrate **3.11**, **3.28** and **3.29** resulted in no reaction except for condition with molybdenum hexacarbonyl at 90 °C (Table 2, entry 9) affording a complex reaction mixture.

Table 2: Screening for reduction of isoxazole **3.36**–**3.38**.



R = H; X = O **3.11**
R = H; X = -OCH_2CH_2O- **3.28**
R = TBS X = -OCH_2CH_2O- **3.29**

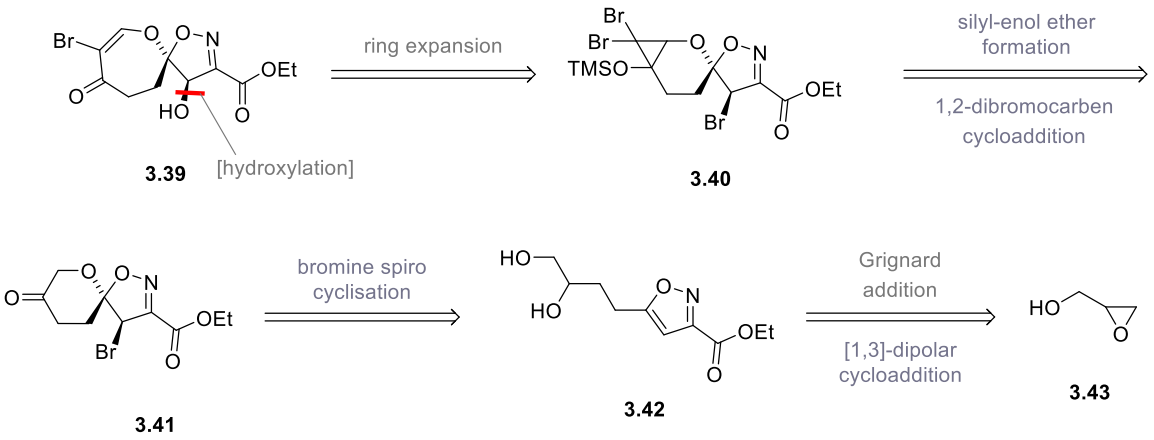
R = H; X = O **3.36**
R = H; X = -OCH_2CH_2O- **3.37**
R = TBS X = -OCH_2CH_2O- **3.38**

entry	X	R	conditions	solvent	result
1	O	H	Raney Nickel, H_2	MeOH	no reaction
2	O	H	Raney Nickel, H_2	EtOH	no reaction
3	O	H	Raney Nickel, H_2, AcOH	EtOH	no reaction
3	-OCH_2CH_2O-	H	Raney Nickel, H_2	MeOH	no reaction
4	-OCH_2CH_2O-	H	Raney Nickel, H_2,	EtOH	no reaction
5	-OCH_2CH_2O-	H	Raney Nickel, H_2, AcOH	MeOH	no reaction
6	-OCH_2CH_2O-	TBS	Raney Nickel, H_2, AcOH	MeOH	no reaction
7	OTBDPS	H	Raney Nickel, H_2	EtOH	no reaction
8	OTBDPS	H	Raney Nickel, H_2, AcOH	MeOH	no reaction
9	OTBDPS	H	$Mo(CO)_6$, 90 °C	MeCN	complex mixture

With these results in hands, this approach was not continued, as an alternative synthetic access would include multistep synthesis with several protection and deprotection steps.

3.2.3 Bromo Spiro-Cyclization and Ring-Expansion

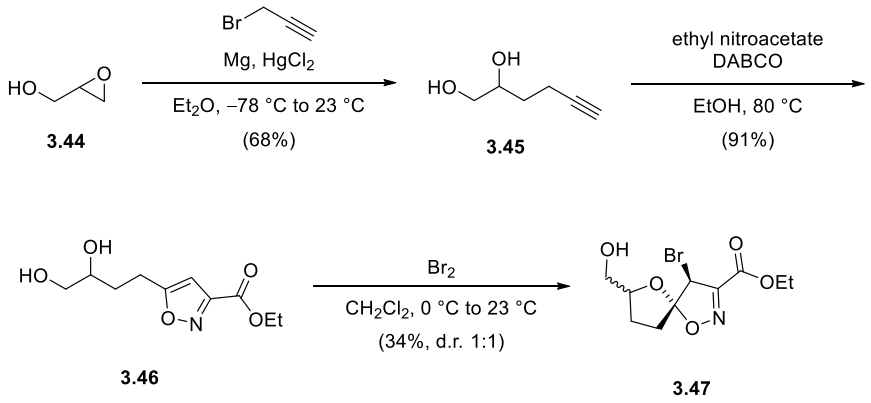
Spiro cyclization to afford the seven-membered ring was not accessible under our previous conditions. Therefore, we designed a ring-expansion strategy to access the key-motif from six-membered ring systems, which are fused to a cyclopropane.



Scheme 27: Retrosynthetic analysis of spiro **3.39** based on a ring-expansion of cyclopropane **3.40**.

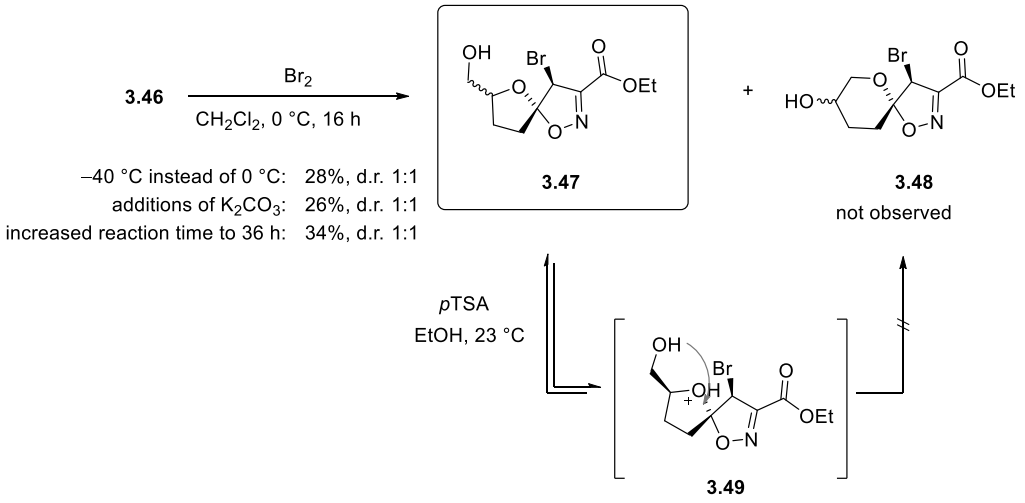
Advantage of this retrosynthetic route would the direct installation of the first bromine in enone **3.39** by the opening the dibromocyclopropane **3.40**. Bromoform is a well-known precursor for the synthesis of dibromocarbenes, reacts with silyl protected enol ether to generate the cyclopropane.[69] Regioselective conditions for silyl enol protection were described by Wanner[70] from pyranons. Isoxazole **3.42** can undergo the already mentioned bromo induced spiro-cyclization with the more reactive primary alcohol and subsequent oxidation of the secondary alcohol and could be tracked back to commercially available glycidol **3.43**.

Our new synthetic route commenced with the conversion of glycidol **3.43** into diol **3.45** upon treatment with propargylmagnesium bromide in the presence of catalytic amounts of mercury chloride to avoid allene formation.[71-72] Subsequent [1,3]-dipolar cycloaddition with ethyl nitro acetate gave the desired isoxazole **3.46** in excellent yield. Initial attempts for the oxidative spirocyclization delivered only the undesired [4;4]-spiro motif as mixture of two diastereomers, which could be separated via HPLC.



Scheme 28: Synthesis of spiro **3.47** as diastereomeric mixture from glycidol **3.44**.

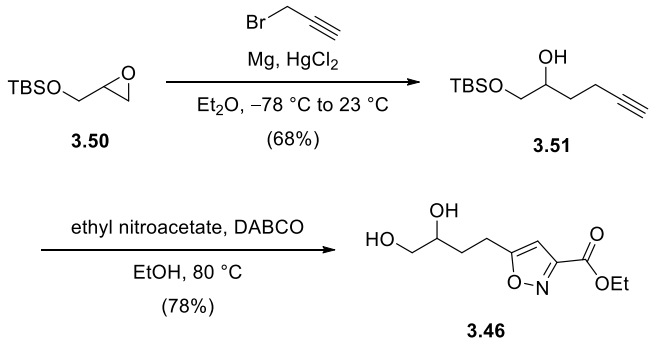
Primary and secondary alcohols only slightly differ in their reactivity and nucleophilicity. Further aspects like ring size and steric hindrance should also influence the outcome of this reaction. However, exclusively formation of the five-membered ring was observed. The 5-*exo-tet* cyclization is more favored compared to the 6-*exo-tet* cyclization for kinetic reasons.[73] Comparing the formation of five- and six-membered ring systems, the smaller ring is formed more rapidly. The strain engendered in reaching the transition state leading to a six-membered ring is higher than compared to five-member rings, although the six-membered ring is the thermodynamic more stable product.[73-74] Efforts to tune the thermodynamic or kinetic parameters by varying the nucleophilic character, temperatures and reaction times did not improve the reaction outcome. Nevertheless, attempt to shift the reaction to the 6-*exo-tet* cyclization were unsuccessful.



Scheme 29: Attempted synthesis of spiro **3.48** under modified conditions or transacetalization.

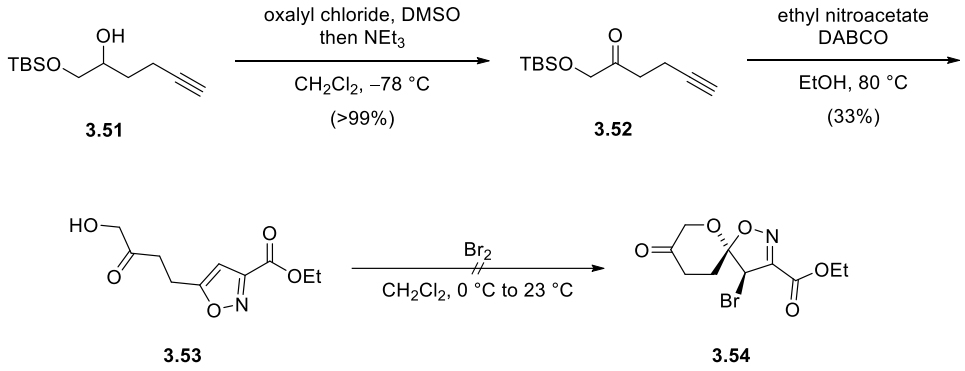
Opening of the spiro acetal was observed under acidic conditions on similar spiro systems.[56] By the addition of *p*-toluenesulfonic acid to **3.47** in ethanol, we aimed to shift the equilibrium to the more thermodynamic product. However, we only recovered our starting material. For that reason,

we envisioned to use protecting group to achieve the desired reactivity to access the six-membered ring system. Starting with *tert*-butyldimethylsilyl-protected glycidol **3.50**, we synthesized alkyne **3.51** in good yield. Surprisingly, *tert*-butyldimethylsilyl-group was not stable under the DABCO catalyzed [1,3]-dipolar cycloaddition conditions, yielding diol **3.46** in 78% yield.



Scheme 30: Synthesis of diol **3.46**.

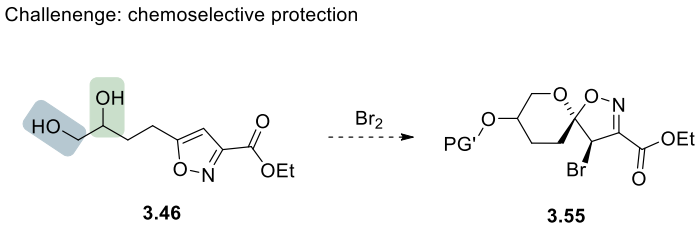
Based on this result, oxidation of alcohol **3.51** under Swern conditions quantitatively afforded ketone **3.51**, which readily underwent the [1,3]-dipolar cycloaddition with ethyl nitroactetae to yield isoxazole **3.53** in only moderate yield. However, addition of bromine to a solution of isoxazole **3.53** in dichloromethane resulted in a complex reaction mixture without any detection of spiro compound **3.54**.



Scheme 31: Synthesis of isoxazole **3.53** and attempted synthesis of bromide **3.54**.

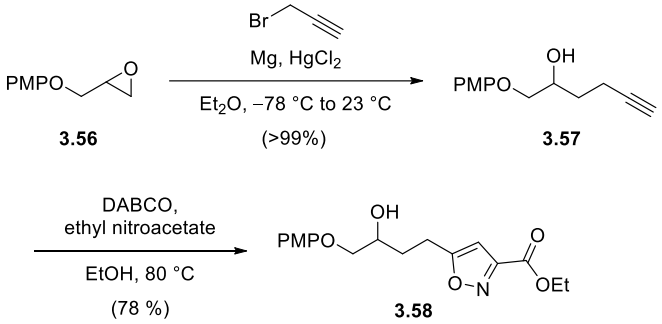
Due to the observed previous reaction outcome with ketones and protected ketones, we went one step back to diol **3.46** that we had used before. Although the five-membered ring was the only product observed, we aimed to use the protecting group chemistry to force the system to form the six-membered ring system. Commercially available protected glycidol **3.56** including the *p*-methoxy phenol protecting group on the primary alcohol was found to be an excellent substrate for our synthesis. Removal of the *p*-methoxy phenol under oxidative conditions tolerated a variety

of further functionalization of the secondary alcohol and was expected to not cleaved in the DABCO catalyzed [1,3]-dipolar cycloaddition.



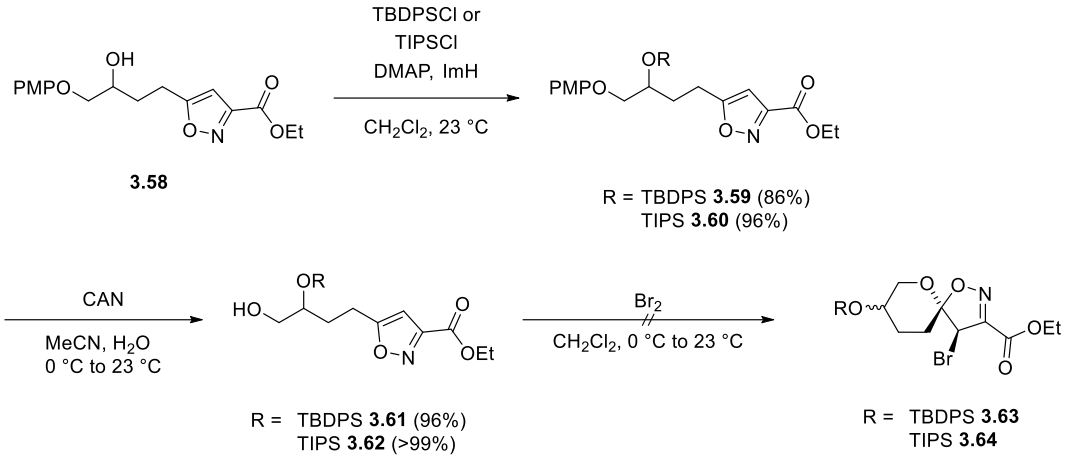
Scheme 32: Orthogonal protecting group approach to afford spiro **3.55**.

Grignard addition under already used conditions with *p*-methoxy phenol-protected glycidol **3.56** afforded alcohol **3.57** in excellent yield. Subsequent [1,3]-dipolar cycloaddition yielded isoxazole **3.57** in 78% yield.



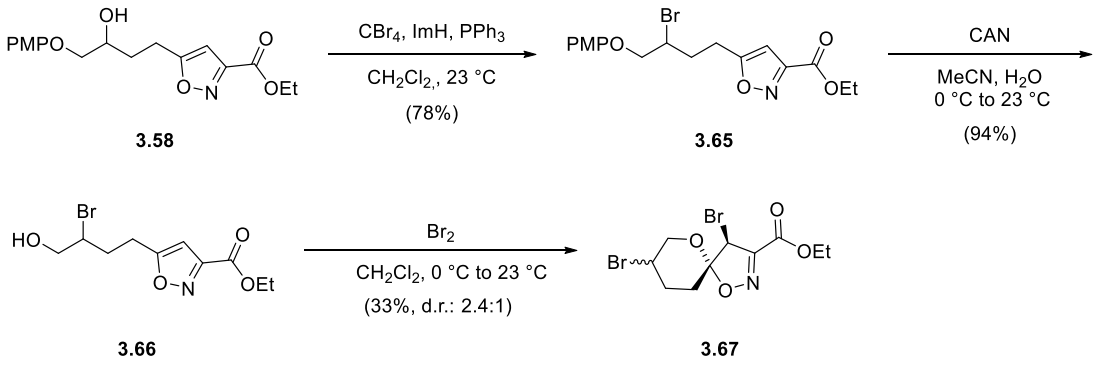
Scheme 33: Synthesis of isoxazole **3.58**

Acetyl protection was found to be problematic due to the migration of the acetyl group in oxidative cleavage step yielding a mixture of protected primary and secondary alcohols. Therefore, triisopropylsilyl- as well *tert*-tutyldiphenylsilyl-protecting groups were investigated to mask the secondary alcohol **3.58**. Oxidative cleavage of phenol ether worked afforded primary alcohol **3.61** and **3.62** in 96% and almost quantitative yield, respectively. However, no spiro cyclization was observed upon exposure to bromine and only starting material was recovered. These results might be explained by the bulky silyl protection groups leading to steric hindrance in the transition state.



Scheme 34: Attempted synthesis of spiro **3.63** and **3.64**.

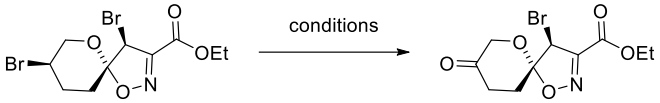
Exposure of the alcohol **3.58** to Apple conditions afforded afforded bromide **3.65** in good yields. Removal of the paramethoxy phenyl afford yielded bromohydrin **3.66** in excellent yield without the observation of any epoxide formation. Interestingly, bromide **3.67** underwent the bromine induced spirocyclidsation in acceptable yield (33%).



Scheme 35: Synthesis of spiro **3.67** as a mixture of diastereomers.

We envisioned to selectively oxidize the more accessible bromide under Kornblum conditions.[75] While low temperatures (entry 1, Table 3) showed no reaction, higher temperatures (entry 2 to 4, Table 3) led to decomposition of the starting material, as well the addition of silver nitrate (entry 5, Table 3).

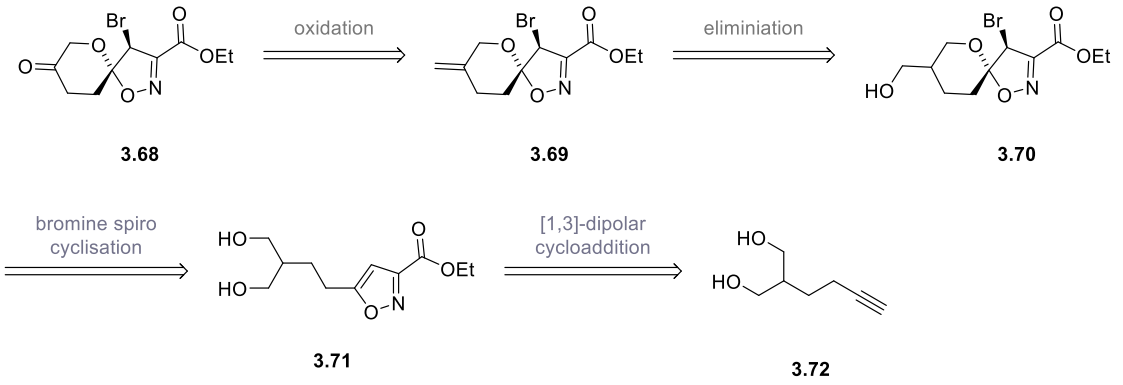
Table 3: Oxidation screening for bromide 3.67.



3.67 **3.68**

entry	conditions	result
1	DMSO, $KHCO_3$, 60 °C, 16 h	no reaction
2	DMSO, $KHCO_3$, 100 °C, 5 h	decomposition
3	DMSO, K_2CO_3, 100 °C, 5 h	decomposition
4	DMSO, TEA, 100 °C, 5 h	decomposition
5	DMSO, $NaHCO_3$, $AgNO_3$, 100 °C, 6 h	decomposition
6	DMSO, Ag_2CO_3, 75 °C, 16 h	no reaction
7	DMSO, Ag_2CO_3, 90 °C, 16 h	complex mixture
8	DMSO, Ag_2CO_3, 100 °C, 16 h	decomposition

With these results in hand, synthesis of ketone **3.68** was found to be highly challenging from **3.58**. Further investigation were focus on the synthesis of diol **3.71** and its further modification for the synthesis ketone **3.69** (Scheme 37)

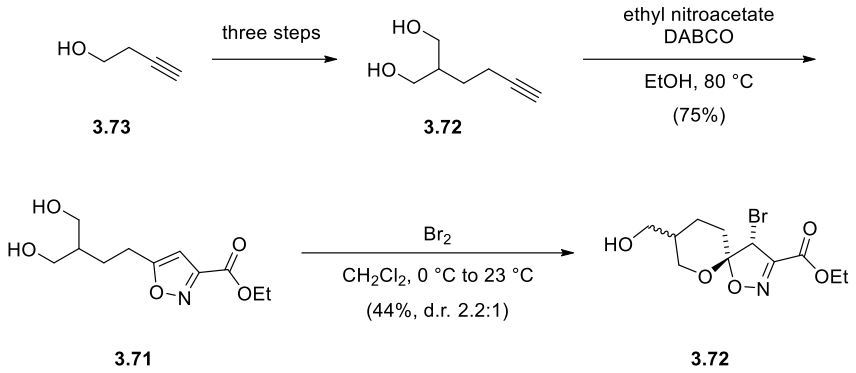


3.68 **3.69** **3.70**

3.71 **3.72**

Scheme 36: Retrosynthetic analysis of ketone **3.70**.

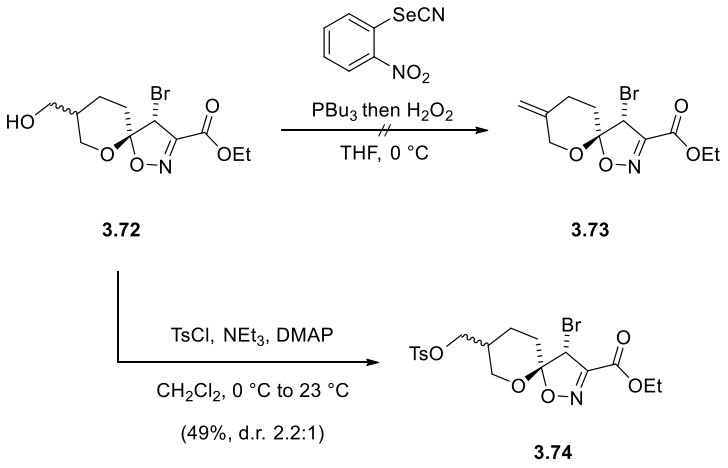
Synthesis of ketone **3.68** would be realized by an elimination/oxidation sequence of alcohol **3.70**, which was tracked back to isoxazole **3.71**. Isoxazole can be finally synthesized via a [1,3]-dipolar cycloaddition with ethyl nitro acetate and alkyne **3.72**.



Scheme 37: Synthesis of spiro **3.72** as diastereomeric mixture.

Starting from alkyne **3.73**, alcohol was converted in to the iodide under Appel conditions. Substitution under basic conditions with diethylmalonate and lithium aluminium reduction gave diol **3.72** in 44% over three steps. Subsequent DABCO catalyzed [1,3]-dipolar cycloaddition afforded isoxazole **3.71** in good yield. Bromine induced spiro cyclization afforded the desired spiro compounds as mixture of diastereomers, which could only be separated by HPLC.

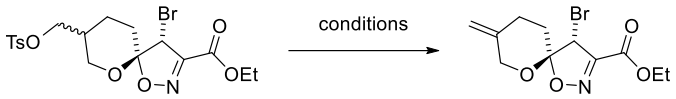
However, classic Criego elimination protocols[76] were not successful and resulted in decomposition. Tosylation of the alcohol afforded an inseperate mixture of diastereomers **3.74**.



Scheme 38: Synthesis of tosyl **3.74** and attempted elimination of alcohol to terminal alkene **3.73**.

Conversion of tosyl **3.74** into the iodide *in situ* and adding a base resulted in complex reaction mixtures (entry 1 and 2, Table 4), while direct elimination showed no reactivity (entry 6−9, Table 4). Interestingly, nucleophilic bases like sodium ethanolate did no undergo nucleophilic substitution of the bromide. Substitution of bromide was a further planned step in our envisioned synthetic route.[77-79]

Table 4: Conditions for the elimination of tosylate **3.75**.

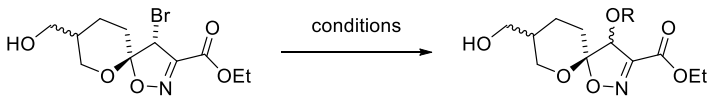


3.75 **3.76**

entry	conditions	result
1	NaI, DMF, 55 °C, then DBU, 80 °C, 3 h	complex mixture
2	NaI, DMF, 55 °C, then DBU, 60 °C, 3 h	complex mixture
3	DBU, DMF, 40 °C, 6 h	no reaction
4	DBU, DMF, 80 °C, 6 h	no reaction
5	DBU, DMF, 100 °C, 6 h	complex mixture
6	KO*t*Bu, DMF, 80 °C, 6 h	no reaction
7	DABCO, DMF, 80 °C, 6 h	no reaction
8	DIPEA, DMF, 80 °C, 6 h	no reaction
9	EtONa, DMF, 80 °C, 6 h	no reaction

Attempted substitution of bromide **3.72** are summarized in Table 5. Bromide **3.72** showed no reaction with silver acetate (entry 1, Table 5) at 60 °C, while higher temperatures gave complex reactions mixtures. Additionally, potassium superoxide led to consumption of the starting material but only a complex mixture without formation of the desired compound was observed.[80] While ketone synthesis and hydroxylation of bromide were found to be challenging, we reconsidered a different synthetic route towards the natural product.

Table 5: Conditions for the substitution reaction of bromide **3.72**

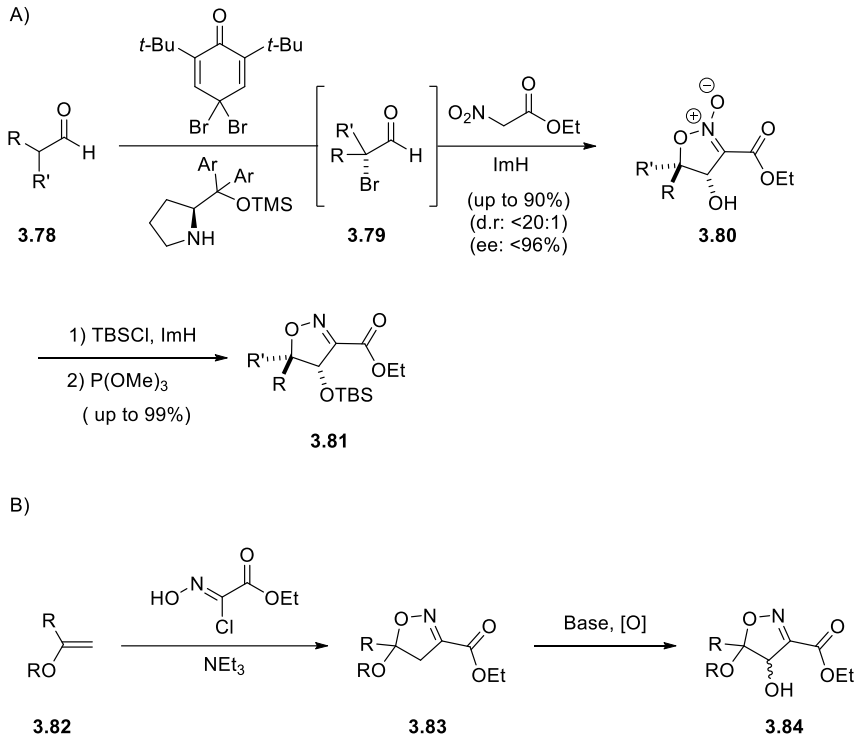


3.72 **3.77**

entry	conditions	R	result
1	AcOAg, AcOH, 60 °C, 4 h	OAc	no reaction
2	AcOAg, AcOH, 100 °C, 4 h	OAc	complex mixture
3	KO_2, 18-crown-6, DMSO, 23 °C, 1 h	OH	complex mixture

3.3 Second Generation: Lactonisation

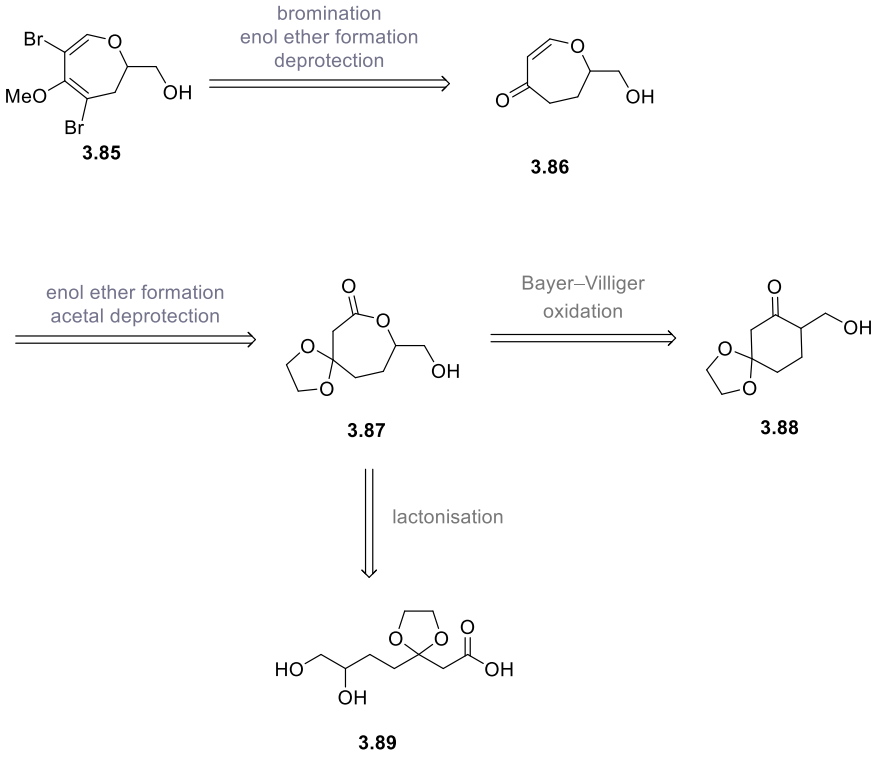
Our previous synthetic studies towards the construction of the spiro scaffold in psammaplysin A (**3.1**) were found to be challenging. In addition, setting the absolute stereochemistry of the spiro center was an unsolved issue. While isoxazolines are well-known building block in synthesis, synthesis of 4-hydroxy-isoxazoline is limited to some reported examples.[81-84] Moreover for the asymmetric synthesis of this particular motif, only few reports exist, which can be basically reduced to two approaches (Scheme 40)[84-88] An enantioselective synthesis of hydroxy-isoxazolines **3.80** was reported by Jørgensen and coworkers[85] starting from aldehyde **3.72** in a pot procedure.



Scheme 39: A) Synthesis of chiral hydroxy-isoxazoline **3.81** by enantioselective bromination and cyclization and reduction. B) Synthesis of isoxazoline **3.83** and hydroxylation.

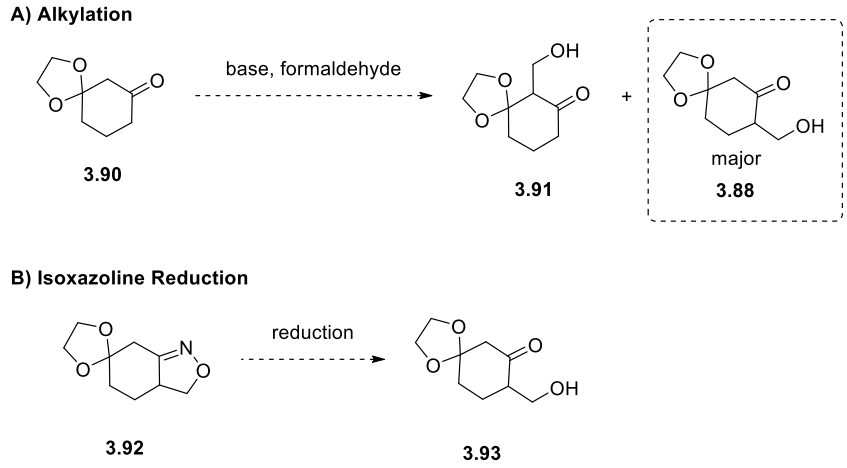
Alternative protocols promoted the elimination of the primary alcohol to the corresponding double bond, which after [1,3]-dipolar cycloaddition with nitrile oxide afforded the desired isoxazoline **3.83**.[89-90] Isoxazoline are acidic enough to be deprotonated and hydroxylated.[88, 91-92]

Although seven-membered ring system are a challenging motif in organic synthesis, we aimed to synthesize the high substituted dihydrooxepin **3.85** with a primary alcohol for further modification, i.e. elimination to the terminal double bond. Substituted dihydrooxepin **3.85** should be synthesized from enone **3.86** by bromination and enol ether formation. Enone **3.86** was envisioned to be synthesized from lactone **3.87** (Scheme 41). For the desired ketone functionality, we considered acetal as a suitable protecting group for our synthetic route. Lactone **3.87** could be either synthesized by Baeyer−Villiger oxidation of ketone **3.88** or by lactonisation of carboxylic acid **3.89**.



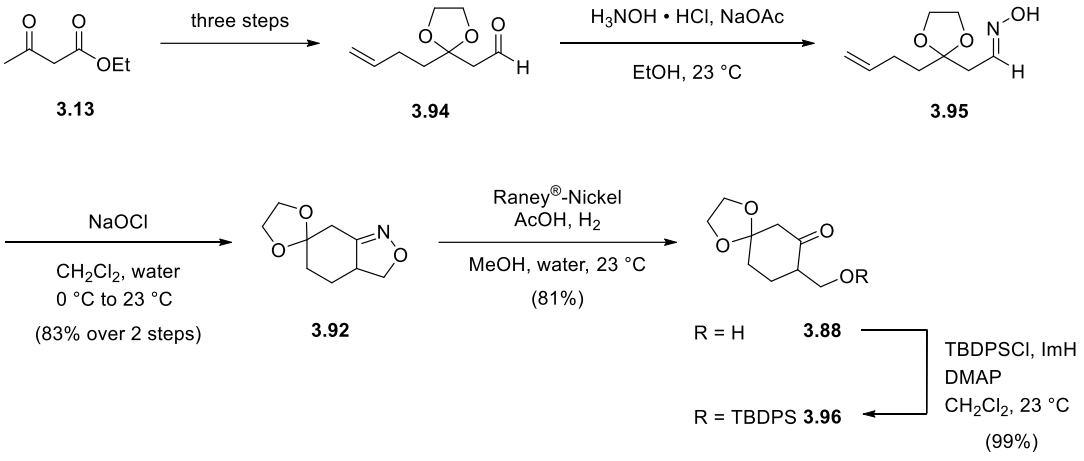
Scheme 40: Retrosynthetic analysis of alcohol **3.85** from ketone **3.88** and carboxylic acid **3.89**.

Baeyer–Villiger oxidation[93-96] is a known protocol for the synthesis of seven-membered lactones, although the was only a single example in literature[97], which possess an acetal functionality in the β-position of the ketone. Simple alkylation of ketone **3.90** would probably form a mixture of the desired regioisomer **3.88** and undesired regioisomer **3.90**. To overcome this regioselectivity issue, we aimed to reduce isoxazoline **3.92** to directly access ketone **3.93** (Scheme 42).



Scheme 41: A) Constructions of ketone **3.91** and **3.88** by alkylation of ketone **3.90**. B) Synthesis of ketone **3.93** by reduction of isoxazoline **3.92**.

Commercially inexpensive acetoacetate **3.90** was converted into literature known aldehyde **3.94** within three steps.[98] Condensation with hydroxylamine afforded intermediate oxime **3.95** which was purified by simple extraction and directly oxidized with sodium hypochlorite forming the reactive nitrile oxide *in situ*. An intramolecular [1,3]-dipolar cycloaddition with the terminal alkene in **3.95** yielded the desired isoxazoline in 83% yield over two steps. Reduction by Raney®-Nickel under hydrogen atmosphere afforded ketone **3.88** in 81% yield.

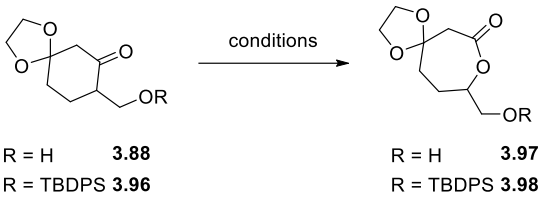


Scheme 42: Synthesis of ketone **3.88** from acetoacetate **3.13**.

Screening of different bases for the Bayer–Villiger oxdiation with *meta*-chloroperbenzoic acid yielded lactone **3.97** in good yields on small scale. However, we were not able to reproduce these results on larger scale for unknown reason. To verify these results, different batches of *meta*-chloroperbenzoic acid, dichloromethane and potassium carbonate were tested. Finally, reaction temperature (entry 10, Table 6) and time (entry 11, Table 6) were increased with no effect on the

conversion. Further tests on cyclohexanone with different batches under these conditions were still successful.

Table 6: Conditions for Baeyer−Villiger Oxidation of ketone **3.88** and **3.96**



R = H **3.88**
R = TBDPS **3.96**

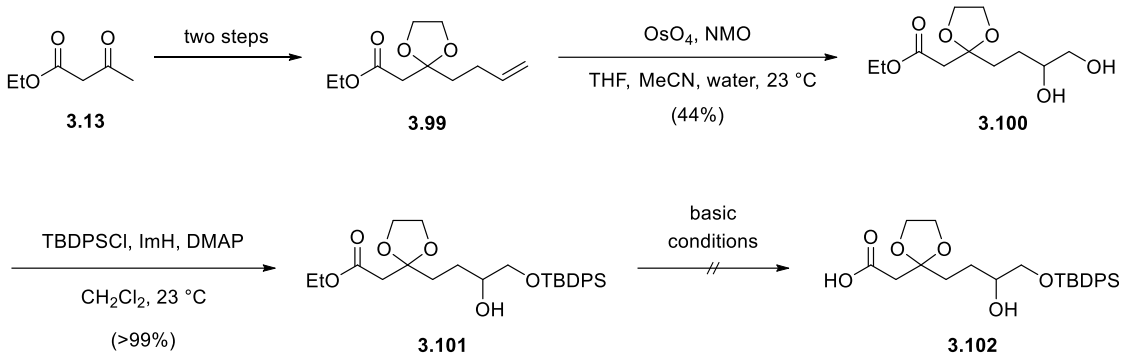
R = H **3.97**
R = TBDPS **3.98**

entry	R	conditions	scale	yield
1	H	*m*-CPBA, CH_2Cl_2, 23 °C, 4 h	0.05 mmol	no conversion
2	H	*m*-CPBA, CH_2Cl_2, Na_2CO_3, 23 °C, 4 h	0.05 mmol	66%
3	H	*m*-CPBA, CH_2Cl_2, Li_2CO_3, 23 °C, 4 h	0.05 mmol	38%
4	H	*m*-CPBA, CH_2Cl_2, K_2CO_3, 23 °C, 4 h	0.05 mmol	93%
5	H	*m*-CPBA, CH_2Cl_2, Cs_2CO_3, 23 °C, 4 h	0.05 mmol	90%
6	H	*m*-CPBA, CH_2Cl_2, NaOAc, 23 °C, 0 °C to4 h	0.05 mmol	no conversion
7	H	*m*-CPBA, CH_2Cl_2, $NaHCO_3$, 0 °C to 23 °C, 4 h	0.05 mmol	no conversion
9	H	*m*-CPBA, CH_2Cl_2, K_2CO_3, 0 °C to 23 °C, 4 h	0.5 mmol	no conversion
10	H	*m*-CPBA, CH_2Cl_2, K_2CO_3, 0 °C to 40 °C, 4 h	0.5 mmol	no conversion
11	H	*m*-CPBA, CH_2Cl_2, K_2CO_3, 0 °C to 40 °C, 24 h	0.5 mmol	no conversion
12	TBDPS	*m*-CPBA, CH_2Cl_2, 23 °C, 4 h	0.05 mmol	no conversion
13	TBDPS	*m*-CPBA, CH_2Cl_2, K_2CO_3, 23 °C, 4 h	0.05 mmol	no conversion

With these results of the Baeyer−Villiger Oxidation this route was found be ineffective for further investigation.

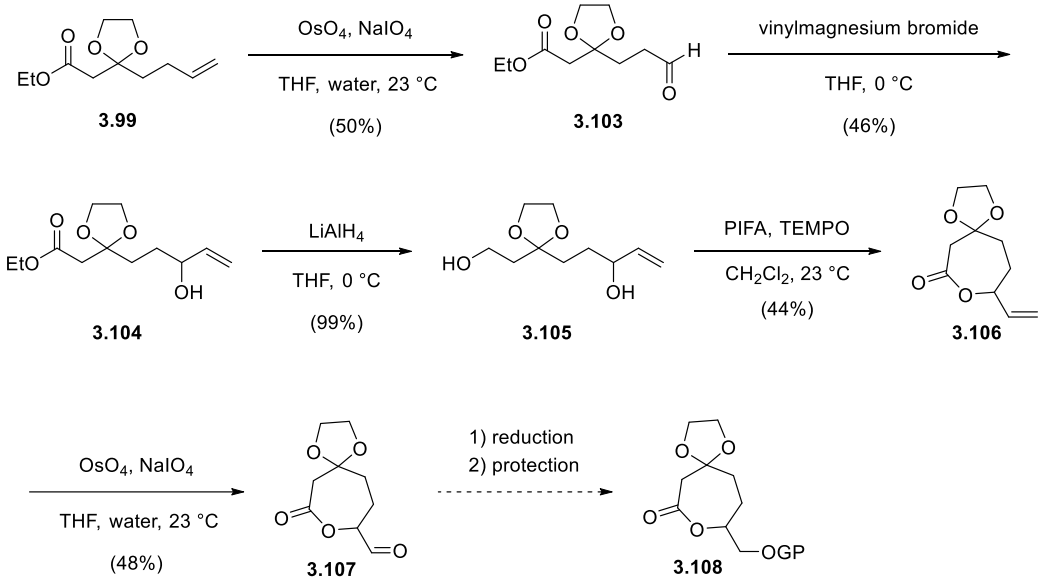
In parallel, lactonisation was under investigation. Starting from acetoacetate **3.13** alkene **3.99** was obtained in two steps.[98] Dihydroxylation afforded diol **3.100** in only moderate yield. *Tert*-butyldiphenylsilyl was chosen as stable protection group for the protection of the primary alcohol.

Hydrolysis of ester **3.101** under different basic conditions resulted either in no reaction, migration or cleavage of the *tert*-tutyldiphenylsilyl group, affording a complex mixture.



Scheme 43: Synthesis of ester **3.101** and attempted hydrolysis.

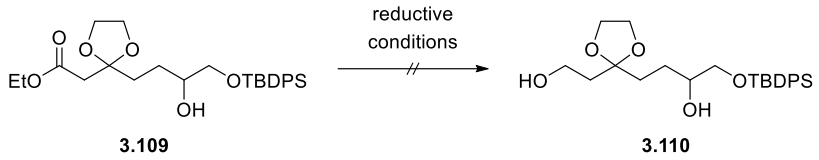
To avoid this undesired isomerization and cleavage, alkene **3.99** was oxidized to aldehyde **3.103** by Lemieux–Johnson oxidation protocol.[99] Slow addition of vinyl magnesium bromide afforded vinyl alcohol **3.103** in acceptable yields. Instead of hydrolysis and subsequent lactonisation, which may require high dilution to avoid dimerization a selective protocol for the formation of seven-membered lactones was found by Ebine and coworkers[100]. Lithium aluminium hydride reduction afforded the desired diol **3.105**, which underwent the desired oxidative lactonisation.



Scheme 44: Synthesis of lactone **3.107** and further modification to access lactone **3.108**.

Alkene **3.106** was also converted under same Lemieux–Johnson oxidation conditions to the corresponding aldehyde **3.107** in acceptable yields. Nevertheless, upscaling of this reaction resulted in lower yields.

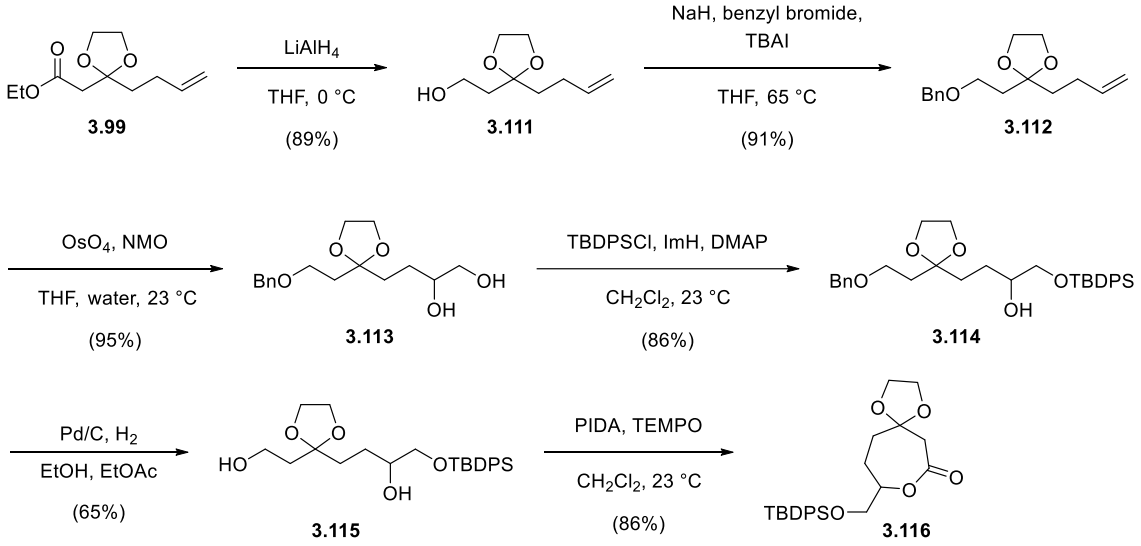
Reduction of ester **3.109** was also found to be problematic and resulted again in complex reaction mixture in which migration or cleavage was observed for the *tert*-tutyldiphenylsilyl group migration or cleavage was observed.



3.109 **3.110**

Scheme 45: Attempted reduction of **3.109**.

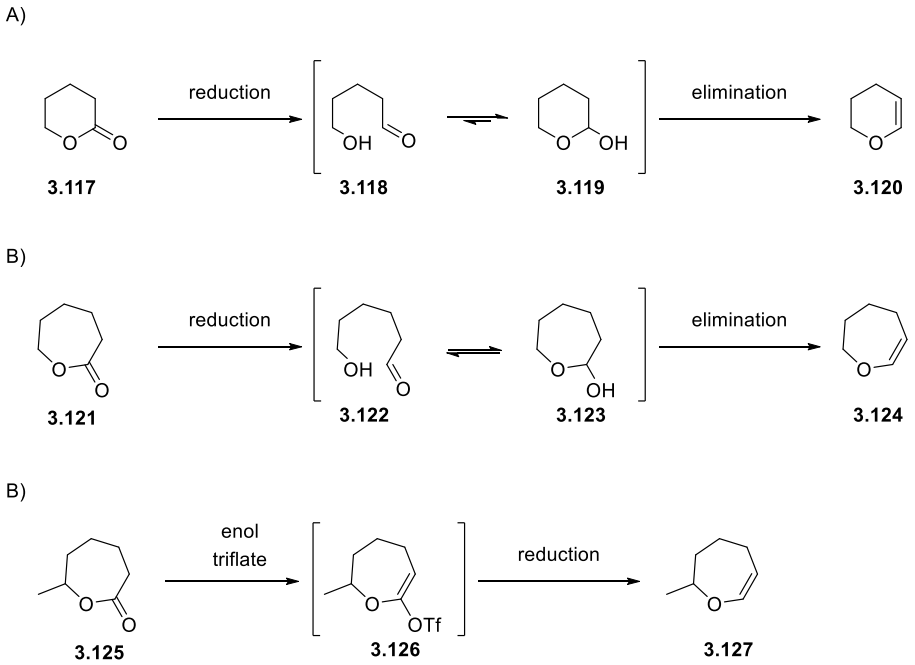
While reductive conditions later in the synthesis proved to be challenging, ester **3.99** was directly reduced on an early stage and alcohol **3.111** was benzyl protected. Dihydroxylation of alkene **3.112** yielded diol **3.113** in 95% yield. Subsequent selective silyl protection of the primary alcohol **3.113** was accomplished in good yield with minor amounts of the bis-protected product. Unfortunately, benzyl deprotection was found to be more challenging. After optimization of the conditions (mixture of ethyl acetate and methanol), alcohol **3.115** was fromed in 65% yield. Lactone **3.116** was finally obtained in good yield under oxidative lactonisation conditions.



3.99 **3.111** **3.112** **3.113** **3.114** **3.115** **3.116**

Scheme 46: Synthesis of lactone **3.116**.

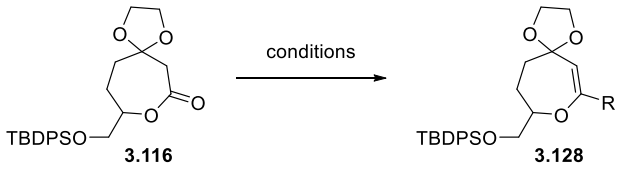
In the literature several protocols for the synthesis of cyclic enol ethers from six-membered lactones are known.[101-103] mainly by reduction and subsequent elimination. For a seven-membered ring system, no reported examples of this transformation are known in the literature, which is mainly due to the fact that seven-membered lactols open more easily into the acyclic chain, which would then lead to several side reactions. For that reasons protocols for seven-membered enol ether formation include enol formation with subsequent reduction.[103-105]



Scheme 47 A) General synthesis of enol ether **3.120** from six membered lactones **3.117**. B) General synthesis of enol ether **3.124** from seven membered lactones **3.121**. C) Alternative synthesis of enol ether **3.127** seven-membered lactones **3.125**.

Attempts of direct enol ether formation resulted in complex products mixtures in which no enol ether formation was observed (entry 1 and 2, Table 7). Triflation of **3.128** was also unsuccessful resulting in complex reaction mixtures (entry 3 to 5, Table 7). Phosphorylation, which were described to be more promising on seven-membered ring systems[106] afforded also complex reaction mixtures.

Table 7: Conditions for enol ether formation of lactone **3.116.**



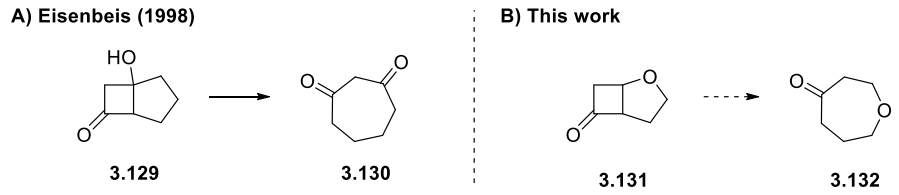
entry	conditions	R	result
1	DIBAL-H, CH_2Cl_2, −78 °C, 20 min then MsCl, NEt_3, 45 °C, 1 h	H	decomposition
2	DIBAL-H, CH_2Cl_2, −78 °C, 20 min then MsCl, NEt_3, DCE, 75 °C, 10 min	H	decomposition
3	LiHMDS, Comins reagent, THF, −78 °C to 23 °C, 2 h	OTf	complex mixture

4	NaHMDS, Comins reagent, THF, −78 °C to 23 °C, 2 h	OTf	complex mixture
5	LDA, Comins reagent, THF, −78 °C to 23 °C, 2 h	OTf	complex mixture
6	LDA, $(PhO)_2P(O)Cl$, THF, −78 °C to 23 °C, 2 h	$P(O)(OPh)_2$	complex mixture

Attempts to access this enol ether were unsuccessful and demonstrate the complexity of the enol ether formation from seven-membered lactones.

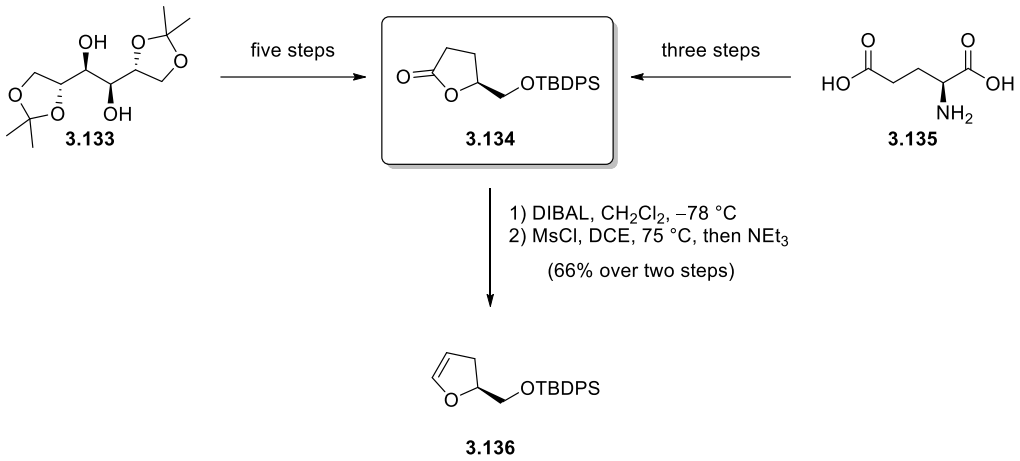
3.4 Third-Generation: Cyclobutane Ring-Expansion

Previous efforts required multi-step synthesis to install the desired substitution pattern before closing the seven-membered ring. In our third generation approach we envisioned to directly access the seven-membered ring system with subsequent modification of the substitution pattern. Inspired by the ring-expansion of cyclobutane **3.129** to the corresponding seven membered-ring systems **3.130**[107], we envisioned to use this ring-expansion on a modified compound **3.131**, for which the tertiary alcohol is replaced by a ether functionality affording the desired oxepanone **3.132**.



Scheme 48: A) Literature known synthesis of diketone **3.130**. B) Planned synthesis of ketone **3.132**.

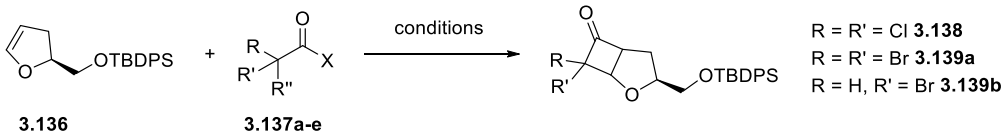
Starting our synthesis with lactone **3.134** was the first limiting factor. Although synthesis from glutamate **3.135** was possible within three steps, this route included complicated work-up protocols and was plagued by varying yields. Therefore, we opted for a slightly longer route that began with acetonide **3.133**. Cyclic enol ether **3.136** was obtained by diisobutylaluminium hydride reduction and subsequent mesylation and elimination. Up to 66% yields were obtained by increasing the deactivation time for the silica used in the flash column chromatography (up to 24 h), while shorter deactivations times resulted in significant lower yields due to decomposition pathways.



Scheme 49: Two different synthetic entries for gamma-lactone **3.135** and its conversion to 2,3-dihydrofuran **3.136**.

Preparation of dichloroketene by reduction of the trichloro acetyl **3.137a** with zinc copper couple (entry 1−6, Table 8) gave only trace amounts of the desired cyclobutane. Generation of dichloroketene via dichloroacetyl chloride **3.137b** afforded cyclobutane **3.318** after short improved reaction conditions in quantitative yield. Attempts to access brominated cyclobutanone (entry 10 to 13, Table 8) were unsuccessful and only traces of the desired product were detected,

Table 8: Screening for ketene formation and [2+2]-cycloaddition

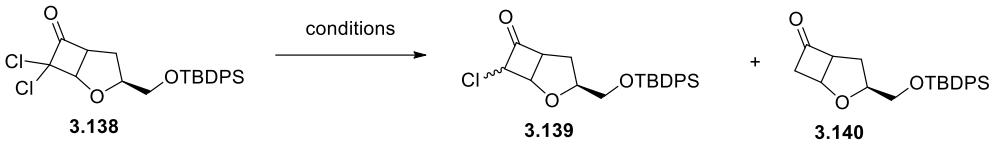


entry	R	R‘	R“	X	conditions	result
1	Cl	Cl	Cl	Cl	Zn/Cu, Et_2O, 23 °C, 4 h	no reaction
2	Cl	Cl	Cl	Cl	Zn/Cu, TMSCl, Et_2O, 23 °C, 4 h	no reaction
3	Cl	Cl	Cl	Cl	Zn/Cu, $POCl_3$, Et_2O, 23 °C, 4 h	traces
4	Cl	Cl	Cl	Cl	Zn/Cu, $POCl_3$, *n*-hexane, 23 °C, 4 h	traces
5	Cl	Cl	Cl	Cl	Zn/Cu, $POCl_3$, *n*-hexane, 65 °C, 4 h	no reaction
6	Cl	Cl	Cl	Cl	Zn/Cu, acid chloride freshly distilled, *n*-hexane, 65 °C, 4 h	traces
7	Cl	Cl	H	Cl	NEt_3, Et_2O, 23 °C, 1 h	traces
8	Cl	Cl	H	Cl	NEt_3, hexane, 68 °C, 1 h	**3.138** (66%)

9	Cl	Cl	H	Cl	NEt_3, hexane, 68 °C, 15 min	**3.138** >99%, d.r. 4.6/1
10	Br	Br	Br	Br	Zn/Cu, Et_2O, 23 °C, 1 h	no reaction
11	Br	Br	H	Br	NEt_3, hexane, 68 °C, 15 min	traces
12	Br	H	H	Br	NEt_3, hexane, 68 °C, 15 min	traces
13	Br	Br	Br	OTMS	PPh_3, toluene, 110 °C, 8 h	traces

With dichlorobutane in hand, same conditions for the desired ring-expansion were screened. In all cases, we either observed only (partial) dehalogenation and/or complex product mixtures were formed.

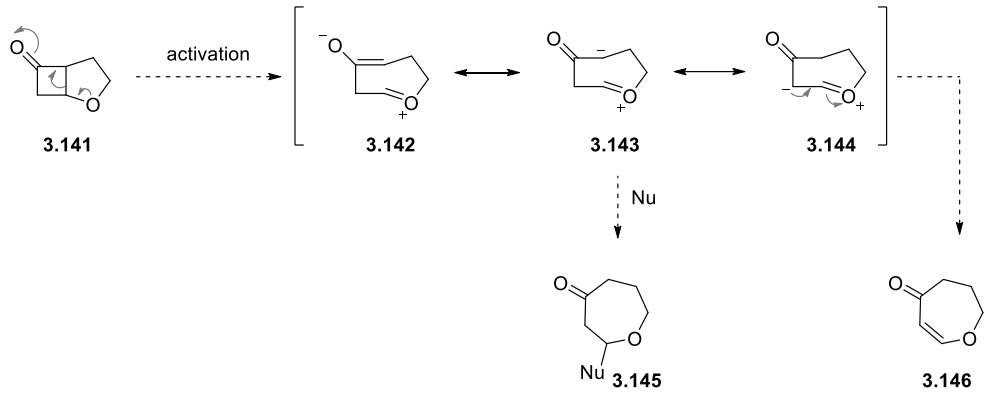
Table 9: Conditions for attempted ring-expansion



3.138 **3.139** **3.140**

entry	**conditions**	**result**
1	Zn, NH_4Cl, MeOH	**3.140** (28%), **3.139** (7%)
2	Zn, AcOH	complex mixture
3	Zn, AcOH, MeOH	complex mixture
4	SmI_2, MeOH, THF	complex mixture

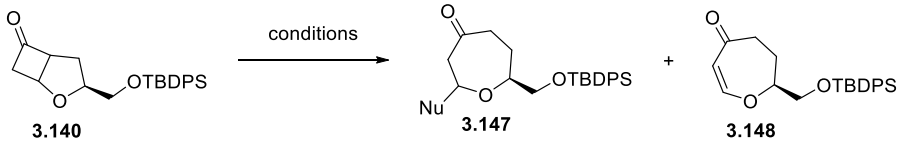
The driving force of the reported ring-expansion in Scheme 49, is beside the strain release of the four membered ring system the formation of the carbonyl functionality. Further investigations to activate the carbonyl in the cyclobutane **3.140** or increased temperatures to overcome the activation barrier may also induce the desired ring-expansion.



Scheme 50: Proposed mechanism for the ring-expansion of cyclobutane **3.141** to access seven-membered oxacycles.

Our proposed ring-expansion would start with the activation of carbonyl **3.141**, which opens to a seven-membered cycle forming a zwitterionic species, which after tautomerization leads to the formation of enone **3.146** or can be trapped by a nucleophile to afford oxepanone **3.145**.

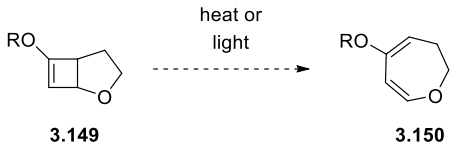
Table 10: Conditions for ring expansion of cyclobutane **3.140.**



entry	conditions	results
1	sulfolane, 23 °C to 180 °C	no reaction
2	AcOH, sulfolane, 23 °C to 180 °C	no reaction
3	TEA, sulfolane, 23 °C to 180 °C	no reaction
4	DMAP, sulfolane, 23 °C to 180 °C	no reaction
5	$AcONH_4$, sulfolane, 23 °C to 180 °C	no reaction
6	AcOH, 23 °C to 120 °C	no reaction
7	TFA, sulfolane, 23 °C to 120 °C	no reaction
8	*p*TSA, sulfolane, 23 °C to 120 °C	no reaction
9	TMSOTf, CH_2Cl_2, −20 °C then water	no reaction
10	TMSOTf, CH_2Cl_2, –20 °C then MeOH	no reaction
11	$BF_3{\cdot}OEt_2$, CH_2Cl_2, –20 °C to 23 °C	no reaction

12	TESH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –20 °C to 23 °C	no reaction
13	TESH, TMSOTf, CH_2Cl_2, –20 °C to 23 °C	no reaction
14	TESH, TMSOTf, MeCN, –20 °C to 23 °C	no reaction
15	TMSOTf, CH_2Cl_2, –20 °C then water	no reaction

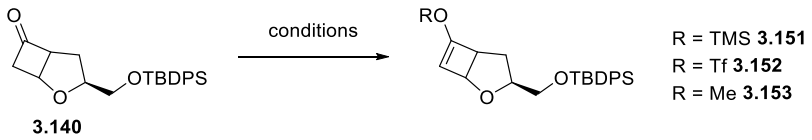
In all cases even under harsh reaction with Lewis or Brønsted acids no desired reactivity was observed, only partial cleavage of the protecting group took place. With this attempted ring-expansion we turned our further investigation towards a retro [2+2]-approach, in which cyclobutane **3.149** would significantly increases the ring strain to push the system to the desired seven-membered ring-expansion. Especially, if the methoxy group can be installed, this would give a fast access to the desired dihydrooxepin motif.



Scheme 51: Planned synthesis of dihydrooxepin **3.150**.

However, formation of the desired enol ether formation was not observed under any tested conditions (entry 1 to 6, Table 11). Only orthoester (entry 7, Table 11) under acidic conditions showed conversion, but resulted in a complex reaction mixture.

Table 11: Reaction conditions for the enol ether formation.



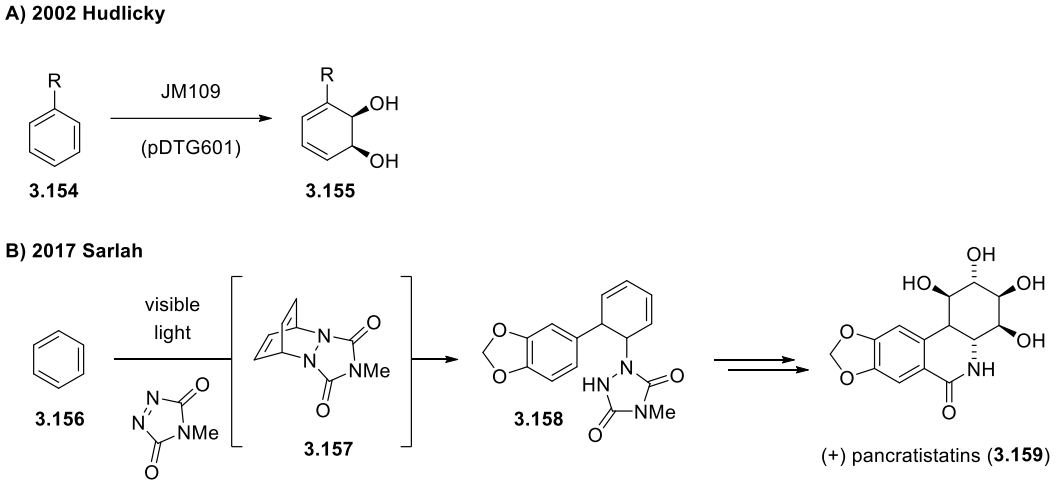
entry	conditions	R	result
1	LiHMDS, TMSOTf, THF, –78 °C to 23 °C, 2 h	TMS	no reaction
2	KHMDS, TMSOTf, THF, –78 °C to rt, 2 h	TMS	no reaction
3	LDA, TMSOTf, THF, –78 °C to rt, 2 h	TMS	no reaction
4	NEt_3, TMSOTf, THF, –78 °C to rt, 2 h	TMS	no reaction
5	NEt_3, TMSCl, NaI, MeCN, –78 °C to 23 °C, 4 h	TMS	no reaction

6	LDA, Comins reagent, –78 °C to 23 °C	Tf	no reaction
7	*p*TSA, $HC(OMe)_3$, MeOH, 65 °C	Me	complex mixture

Since silyl enol formation, triflation or enol ether formation failed for our system **3.140** (Table 11), we turned our efforts to a bioinspired synthesis of toward the synthesis of psammaplysin A (**3.1**).

3.5 Fourth-Generation: Bioinspired Synthesis

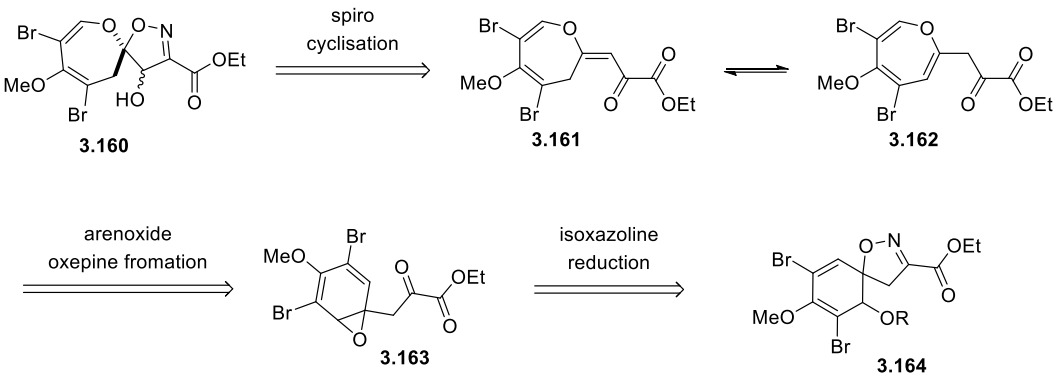
The oxidation dearomatization of aromatic systems displays a challenging hurdle for organic chemists to access functionalized cyclohexadienes. However, in recent years different groups have demonstrated the possibility directly oxidation of the aromatic framework. Already in 2002 Hudlicky and coworkers reported an enzymatic oxidation of simple aromatic structures **3.154** to the corresponding diols.[108] In 2017, Sarlah and coworkers published a total synthesis of (+)-pancratistatins (**3.159**) from benzene **3.156** employing an enantioselective, dearomative trans-carboamination.[109] Although, there are several oxidation protocols described in the literature,[110-112] these reactions are mainly limited to simple substituted aromatic systems.



Scheme 52: A) Enzymatic oxidation of simple aromatic systems **3.156**. B) Photochemical oxidation of benzene **3.156** and further modification toward (+)-pancratistatins (**3.159**).

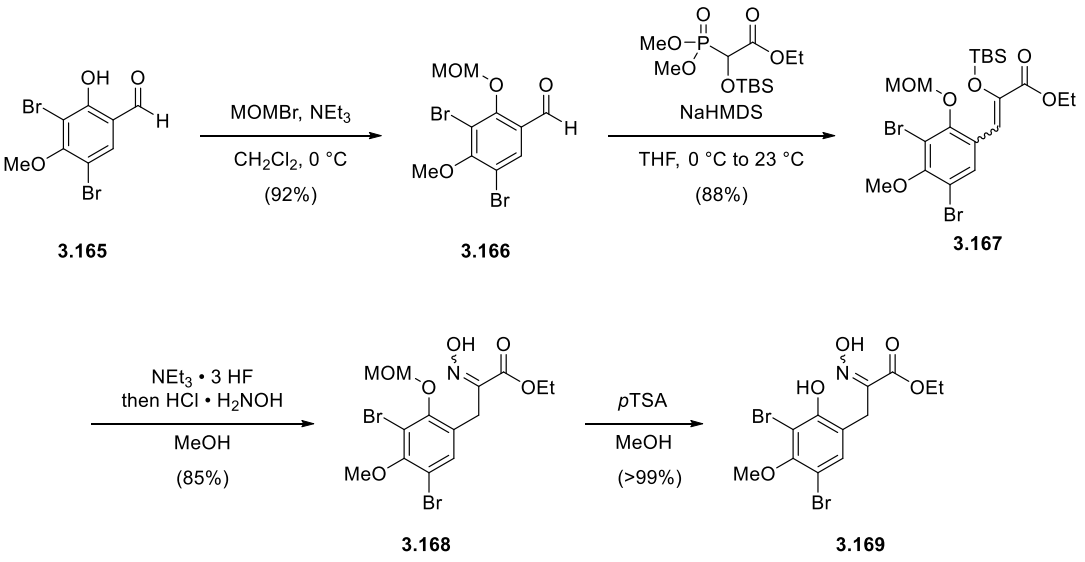
For that reason we envisioned a more bioinspired synthesis. In our synthetic route oxepin **3.162** should be in in equilibrium with enone **3.162**, which is a suitable precursor for selective epoxidation, condensation with hydroxylamine and finally cyclization. Key-intermediate would be the arene oxide **3.163**. While direct epoxidation of the aromatic core was envision to be

problematic, we envisioned to synthesize spiro **3.164**. Reduction of the nitron-oxygen bond would afford a tertiary alcohol, which can undergo the epoxide formation.



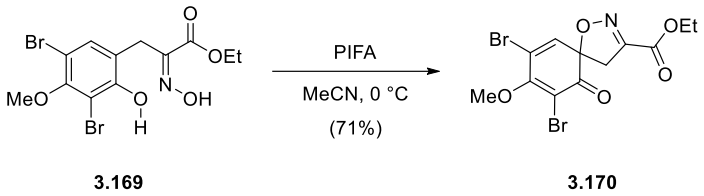
Scheme 53: Retrosynthetic analysis of spiro **3.160** from spiro **3.164**.

Methoxymethyl acetal protection of phenol **3.165** followed by Wittig-olefination gave the desired enol ether **3.167** in good yield as a mixture of (*E*)- and (*Z*)-isomers. *Tert*-butyldimethylsilyl-cleavage afforded a ketone, which was directly converted into oxime in a one-pot procedure in good yield without the need of flash column chromatography. Treatment with *p*-toluenesulfonic acid in methanol gave the desired phenol **3.169** in quantitative yield.



Scheme 54: Synthesis of oxime **3.169** from aldehyde **3.165**.

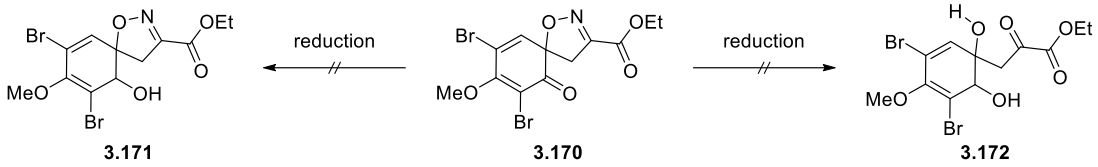
After a short screening including different hypervalent iodine reagents or electrochemistry, (bis(trifluoroacetoxy)iodo)benzene (PIFA) in acetonitrile was found to be best reagent for this oxidative cyclization.



3.169 3.170

Scheme 55: Synthesis of spiro **3.170**.

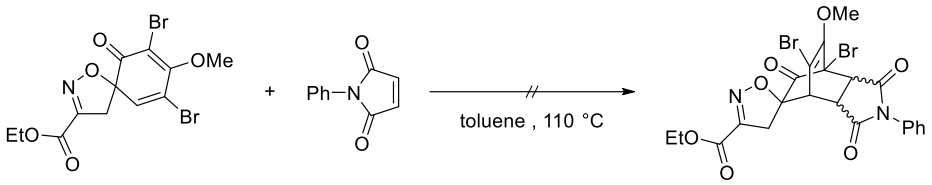
Attempts to reduce the ketone or isoxazoline functionality in **3.170** were unsuccessful and gave only decomposition of the starting material.



3.171 3.170 3.172

Scheme 56: Attempted ketone or isoxazoline reduction of spiro **3.170**.

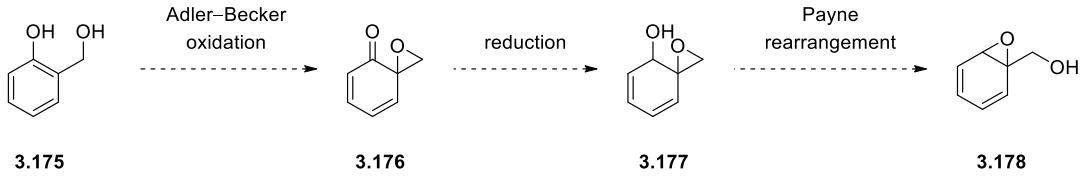
Selective reduction of dienone **3.170** is known to be a challenging transformation.[45] Attempts to mask the diene motif by Diels−Alder reaction with maleimide **3.173** were unsuccessful. While maleimide **3.173** was recovered quantitatively, spiro **3.170** led to complete decomposition pathways.



3.170 3.173 3.174

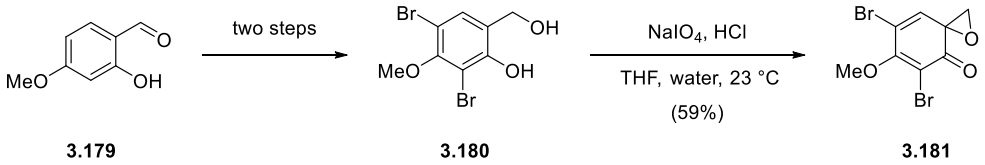
Scheme 57: Attempted Diels−Alder reaction of ketone **3.174** with maleimide **3.173**.

Due to the thermal instability of isoxazoline **3.170**, we turned our attention to a more reliable synthesis. In the Alder−Becker oxidation phenols are oxidized with their benzylic alcohols to epoxide ketones. These fairly unknown reaction has been used for the synthesis of complex natural products (*i.e.* (±)-ovalicin[113] and calicheamicinone[114]). In our case, the highly substituted phenol would undergo oxidation followed by Payne rearrangement[115].



Scheme 58: Synthesis plan involving Alder−Becker oxidation to access arene oxide **3.178** from phenol **3.175**.

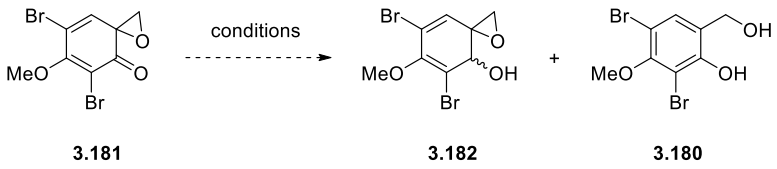
Phenol **3.180** was synthesized in two steps (bromination and reduction) of aldehyde **3.179**. Alder−Becker oxidation afforded epoxide **3.180** in 59% yield. Unfortunately, epoxide **3.180** slow decomposed upon purification on silica and over time.



Scheme 59: Synthesis of epoxide **3.181**.

With epoxide **3.181** in hand, conditions for the selective ketone reduction were investigated. Unfortunately, we found that all reductions conditions favored consecutive rearomatization of the substrate to the benzylic alcohol **3.180**, together with decomposition of the starting material (Table 12).

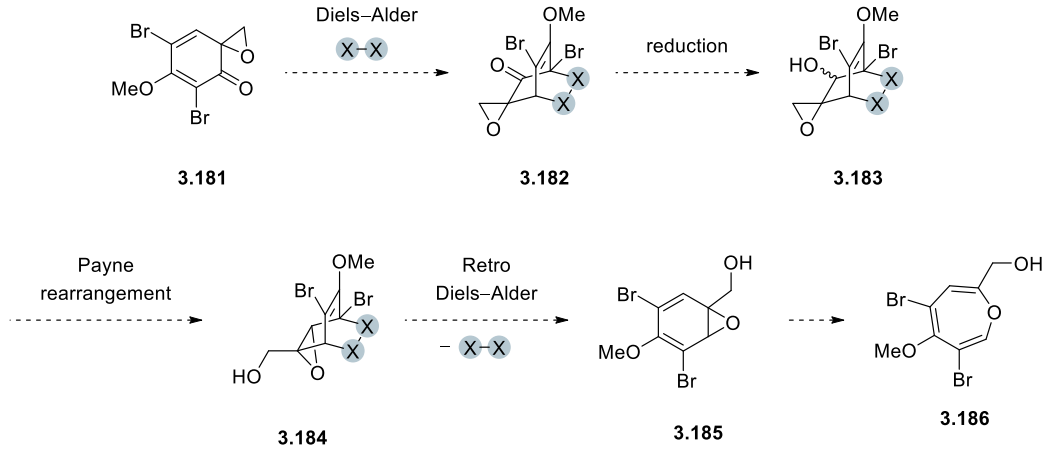
Table 12: Conditions for the reduction of ketone **3.180.**



entry	conditions	result
1	$NaBH_4$, MeOH, 0 °C	**3.180**
2	$NaBH_4$, THF, 0 °C	**3.180**
3	$NaBH_4$, $CeCl_3$, MeOH, 0 °C	**3.180**
4	$LiBH_4$, MeOH, 0 °C	**3.180**
5	$Zn(BH_4)_2$, THF, 0 °C	**3.180**
6	$LiAlH_4$, THF, 0 °C	decomposition

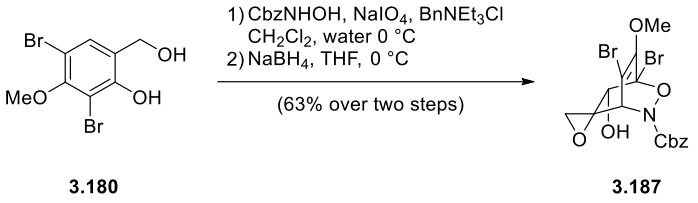
7	DIBAL-H, THF, 0 °C	decomposition
8	DIBAL-H, THF, − 78 °C	decomposition
9	Red-Al, 0 °C	decomposition

Epoxide **3.181** was found to be highly reactive although reduction often resulted in reduction of the epoxide and subsequent aromatization. This undesired behavior was attributed to the high activation of the diene system of compound **3.181**. We hypothesized that blocking the diene of this system could be beneficial to allow further transformations bypassing undesired reaction pathways. Diene **3.181** could eventually be temporary protected by a Diels−Alder reaction with a suitable dienophile of choice. The latter could then undergo retro Diels−Alder in a subsequent step to access the desired oxepin building block (Scheme 61).



Scheme 60: Planned synthesis of oxepin **3.186** from ketone **3.181**.

Inspired by work by Good and coworkers[116] nitrosyloxide reagents were selected first. In a one pot procedure oxidation of the aromatic core and Diels−Alder reaction afforded a ketone intermediate, which was directly reduced to the more stable alcohol **3.187**.

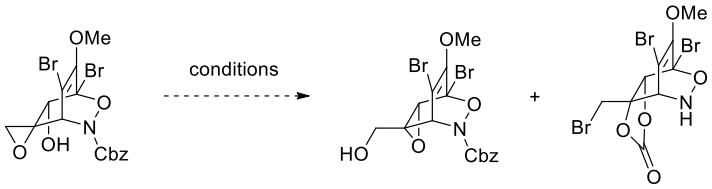


3.180 **3.187**

Scheme 61: Synthesis of alcohol **3.187**.

With alcohol **3.187** in hand, we investigated conditions for for the formation of epoxide **3.188**. At this point the realtive stereochemistry of the alcohol **3.187** was not fully determined. As summarized in Table 13, all conditions investigated to rearrange epoxide **3.187** to desired epoxide **3.188** and gave either decomposition (entry 1, 2) no reaction (entry 3) or addition of solvent to the Cbz (entry 4). Addition of sodium hydride afforded an unexpected crystalline side product 14 (entry 5). After full conversion (more than 56 h) carbonate **3.189** was isolated in 32% yield (entry 6). The carbonate structure was confirmed by X-ray crystallography.

Table 13: Conditions for Payne rearrangement of epoxide **3.187**.

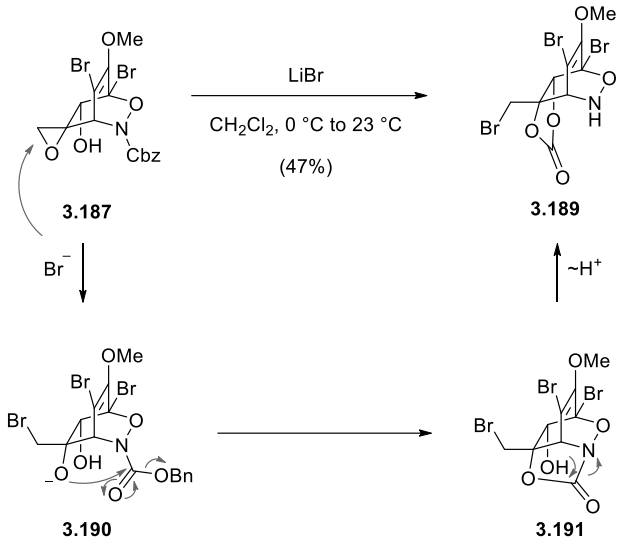


3.187 **3.188** **3.189**

entry	conditions	result
1	$LiHBEt_3$, THF	decomposition
2	KOH powdered, THF	decomposition
3	NaOH (1M), THF, 0 °C	no reaction
4	NaOH (1 M), MeOH	complex mixture
5	NaH, THF, 16 h	traces of **3.188**
6	NaH, THF, 56 h	**3.188** (32%)

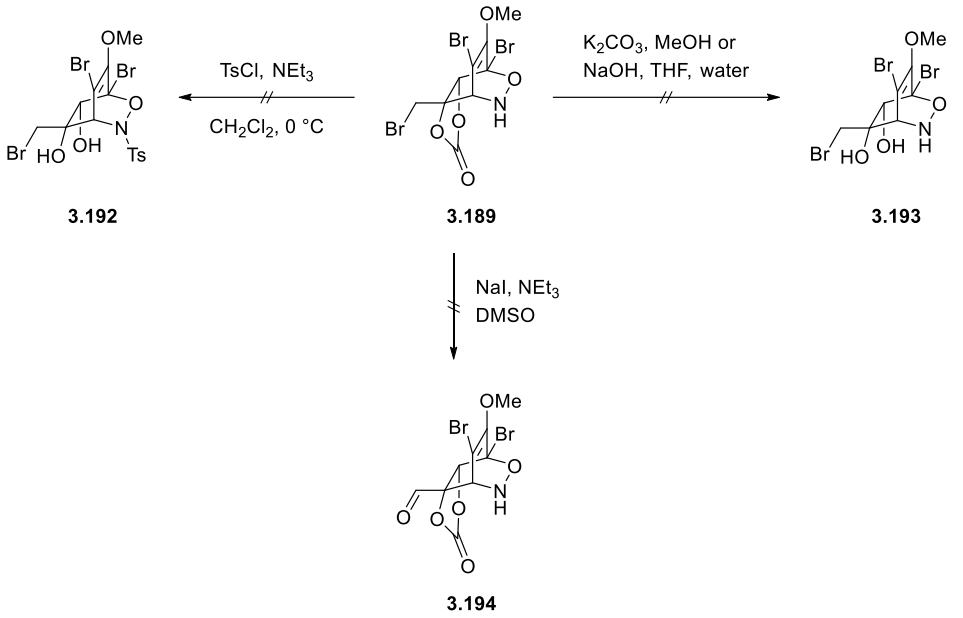
Even if the mechanism for the formation of carbonate **3.188** in presence of sodium hydride is still unclear, useful information about the reactivity of the system was obtained. By the addition of lithium bromide carbonate was obtained in 47% yield. In our proposed reaction mechanism bromide opens the epoxide **3.187**. The resulting alkoxide **3.190** attacks the carabamte motif of the

Cbz group to generate the cyclic carbamate **3.191**. Final step is the attack of the free alcohol in **3.191** to generate the carbonate **3.189** (Scheme 63).



Scheme 62: Proposed mechanism for the synthesis of carbonate **3.189**.

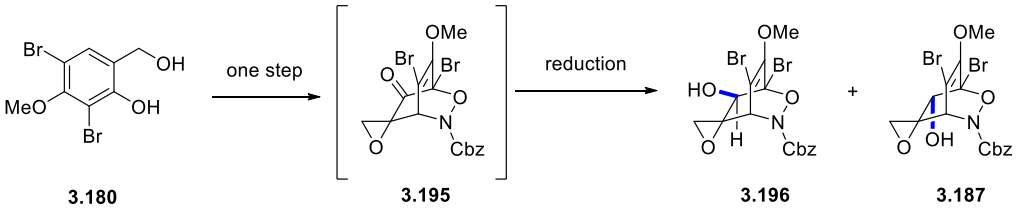
The hydrolysis of the carbonate **3.189** by the use of methanol and potassium carbonate or sodium hydroxide in mixtures of tetrahydrofuran and water resulted in decomposition of the starting material. In all cases, decomposition of the starting material was observed. Modification of the bromide in dimethyl sulfoxide to synthesize the aldehyde resulted in decomposition of the starting material too. While the free NH bond was seen crucial for further modification, attempted tosylation resulted also in decomposition.



Scheme 63: Attempted synthesis of tosyl **3.192**, hydrolysis of carbonate and Kornblum oxidation of bromide **3.189**.

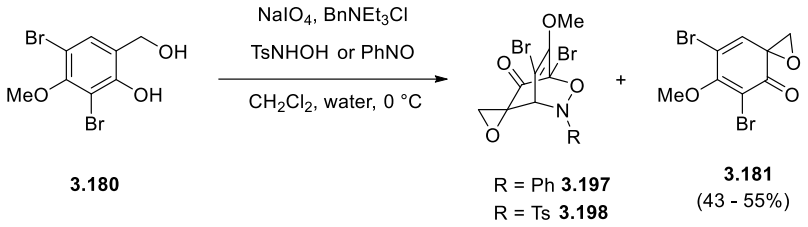
To avoid carbonate formation, reduction of ketone **3.195** would require the other isomer. Conditions for the attempted selective reduction of ketone **3.195** to access the equatorial alcohol are summarized in Table 14.

Table 14: Conditions for the reduction of ketone **3.195**.



entry	conditions	result
1	$LiHBEt_3$, THF, 0 °C	**3.187** (33%)
2	DIBAL-H, THF, 0 °C	decomposition
3	DIBAL-H, THF, −78 °C	decomposition
4	K-Selectride®, THF, 0 °C	complex mixture
5	$LiBH_4$, THF	decomposition
6	Bu_4NBH_4, THF, 0 °C	**3.187** (25%)
7	$NaBH(OAc)_3$,, THF, 0 °C	**3.187** (74%)

While reduction of ketone **3.195** to set the right stereochemistry was unsuccessful and attempted modification of the carbonate **3.189** of carbonate resulted in decomposition, we aimed to use another functional group on the nitrogen. For that reasons other *NO*-reagents, which are suitable for this reactions-cascade were investigated.



3.180

R = Ph **3.197**
R = Ts **3.198**

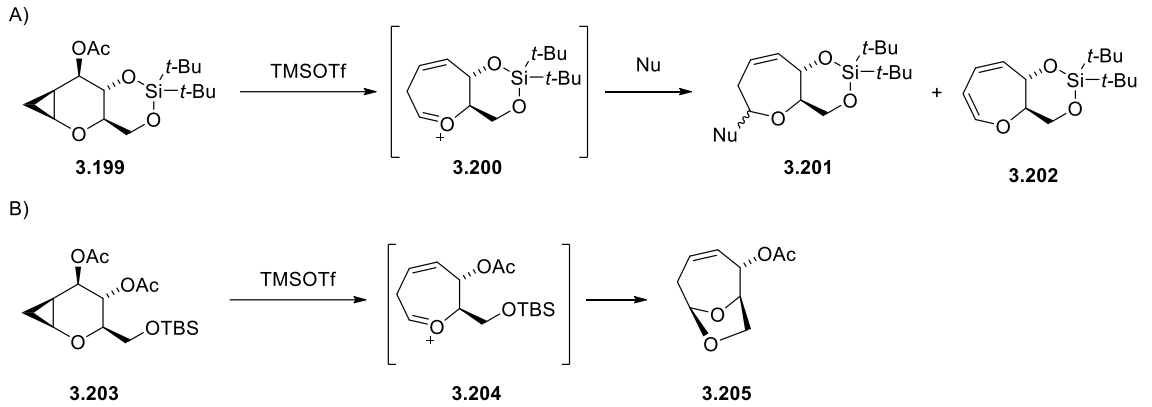
3.181
(43 - 55%)

Scheme 64: Attempted synthesis of ketone **3.197** and **3.198** and isolated ketone **3.181**.

Nitrosobenzene or a tosylated derivative thereof did not undergo the desired Diels−Alder reaction with **3.181**. Modification with nitrosobenzene under high pressure conditions (14 kbar) turned out unsuccessful as well and resulted in a complex mixture. Additionally, a variety of solvents also revealed no desired product formation. However, nitrosobenzene showed almost quantitative yields with cyclohexadiene. Due to its complex synthesis and instable intermediates we turned our attention to a more robust route, which also would allow to work on larger scales.

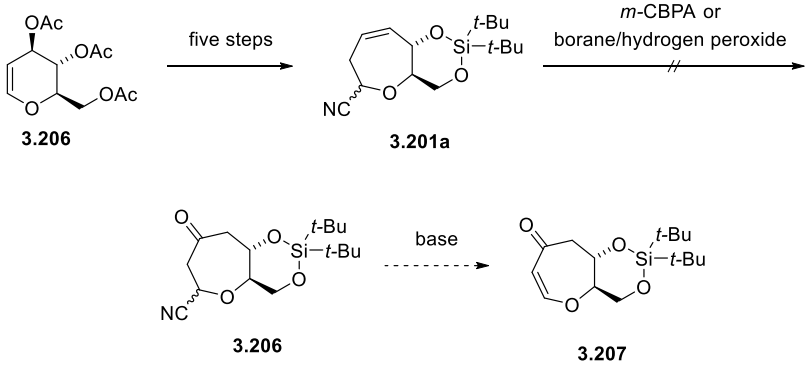
3.6 Fifth-Generation: Cyclopropane Ring-expansion

In early work, Hoberg and coworkers[117] demonstrated a Ferrier type ring-expansion of cyclopropane **3.199**. Activation of cyclopropane **3.199** with TMSOTf afforded oxonium ion **3.200**, which can be trapped by nucleophile to afford **3.201** or undergo elimination to afford dihydrooxepin **3.202**. A change of protecting group yielded a bicyclic derivative **3.205**.



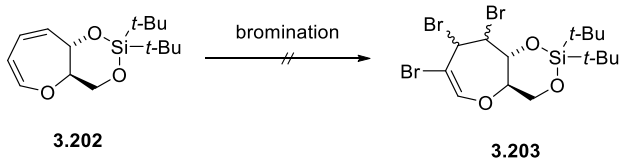
Scheme 65: A) Ring-expansion of access the seven-membered oxacycle **3.201** and **3.202**. B) Ring expansion of acetate **3.203** to bicycle **3.205**.

As a model substrate nitrile **3.201a** was synthesized within five steps. After oxidation of the double bond in nitrile **3.201a** nitrile should be eliminated under basic conditions to afford enone **3.207.** However, attempted oxidation with borane/hydrogen peroxide or *meta*-chloroperbenzoic acid of the double bond were unsuccessful.



Scheme 66: Synthesis of nitrile **3.201a** and attempted synthesis of ketone **3.206**.

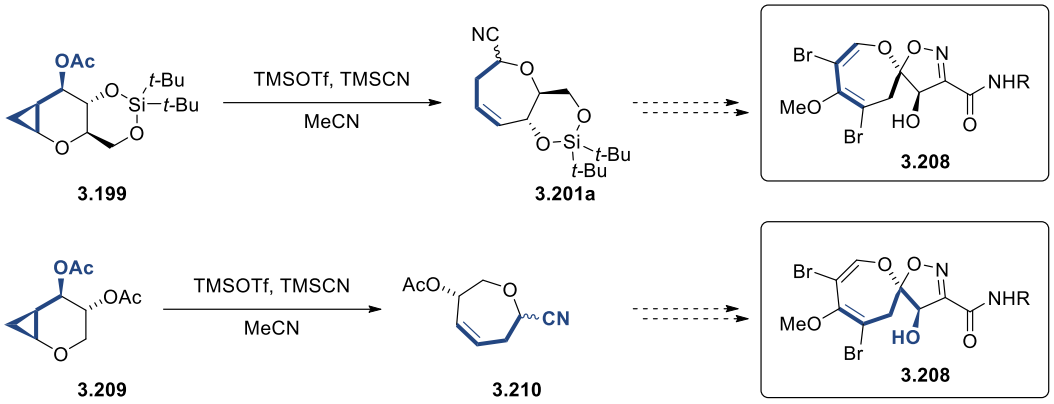
With side product **3.202** bromination was investigated. Although different conditions afforded no brominated products, insight about the reactivity of hydrooxepin **3.202** were obtained.



Scheme 67: Attempted synthesis of bromide **3.203**.

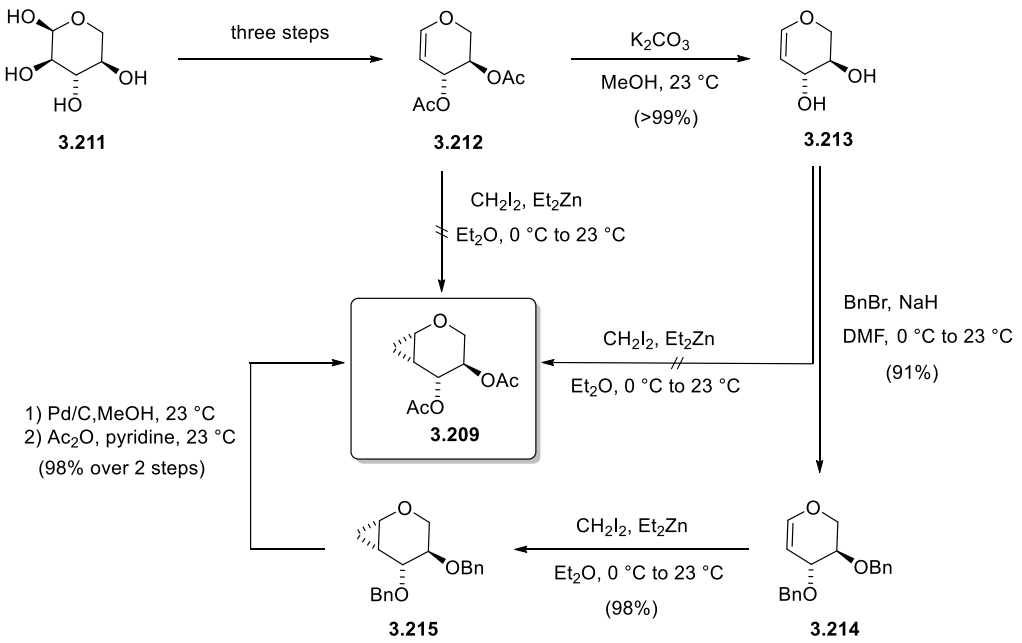
However, the chosen model substrate **3.201a** lacked on the desired substitution pattern, we envisioned an optimized route towards our desired seven-membered ring from cyclopropane **3.209**.

There we envision to synthesize acetate **3.209**. Ring expansion would with same conditions would afford nitrile **3.210**, where nitrile function can be used for the synthesis of the isoxazoline structure present in the core of isoxazoline-dihydrooxepine **3.208**.



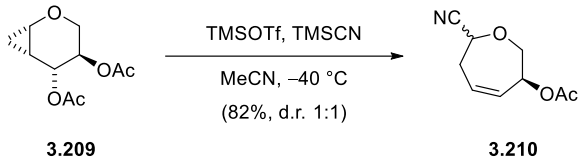
Scheme 68: Ring-expansion strategies to access nitrile **3.201a** and **3.210**.

Starting from inexpensive α-D-xylose **3.211** cyclic enol ether **3.212** was obtained in three steps. Direct Simmons−Smith cyclopropanation of acetate **3.212** showed no reactions. While free alcohol **3.213** gave a complex mixture. Benzyl protected alcohol **3.214** afforded the desired cyclopropane **3.215** in excellent yields as a single diastereomer. Cleavage of the benzyl ether protecting groups was achieved by catalytic hydrogenolysis using palladium on activated charcoal as catalyst. Debenzylation was successful on a 14 mmol scale employing of 10 mol% catalyst. However, running the reaction on 67 mmol scale, only traces of free alcohol were observed. Attempts to improve the yield by increasing the reaction time were also not successful. Finally increasing the amount of palladium up to 20 mol% afforded the desired alcohol by simple filtration over celite in almost quantitative yield. Subsequent acetylation afforded the desired cyclopropane **3.209**.



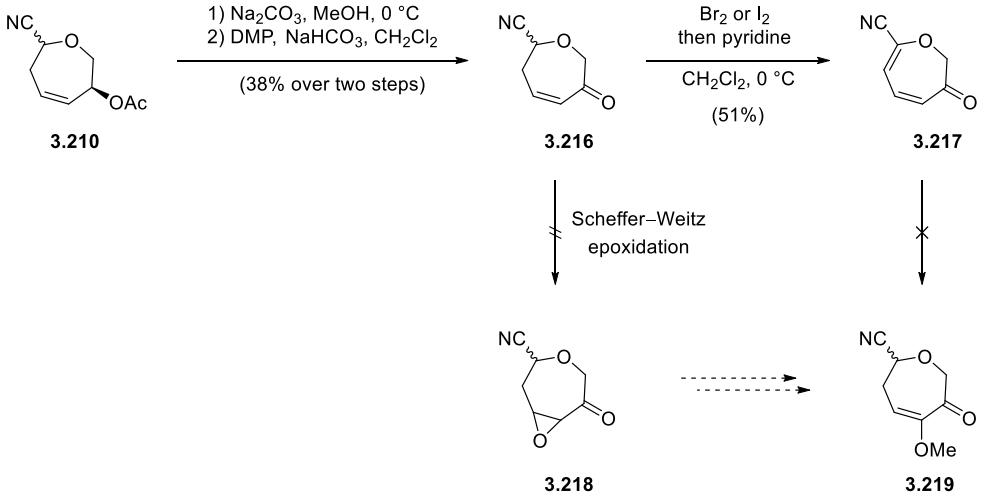
Scheme 69: Synthesis of cyclopropane **3.209**.

Key ring-expansion was successful to afforde the nitrile **3.210** on a 14 mmol scale in 82% , however with no diastereoselectivity. Seperation of the both diastereomers was accomplished by HPLC.



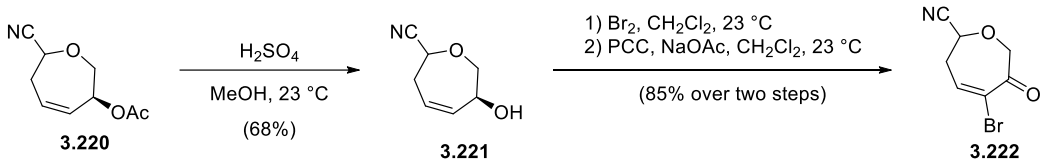
Scheme 70: Synthesis of nitrile **3.210** as a diastereomeric mixture.

Under mild basic conditions acetyl deprotection of **3.210** was successful, but purification was found to be challenging. Several conditions to hydrolyze ester **3.210** were investigated, but using the crude material for the next oxidation step (Dess−Martin oxidation) afforded pure ketone **3.216.** Addition of bromine or iodine to **3.216** showed no desired α-halogenation of the enone system. Halogenation occurred at the the α-position of the nitrile and subsequent elimination took place to generate the nitrile **3.217**. Scheffer−Weitz epoxidations were also problematic with nitrile **3.216**.



Scheme 71: Synthesis of ketone **3.216** and attempted further modification.

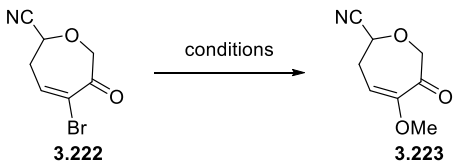
Improved acetate deprotection under acidic conditions delivered alcohol **3.221** as an inseperate mixture of diastereomers. By changing the sequence to bromination of the double and subsequent oxidation ketone **3.222** was obtained in 85% yield over two steps.



Scheme 72: Synthesis of bromide **3.222**.

Attempts for methanol coupling under known protocols [118-120] did only result in no reaction or dehalogenated products. While palladium catalyzed reaction showed insertion into the carbon bromide bond (entry 1 and 4, Table 15) copper catalyzed reaction showed no reaction at all.

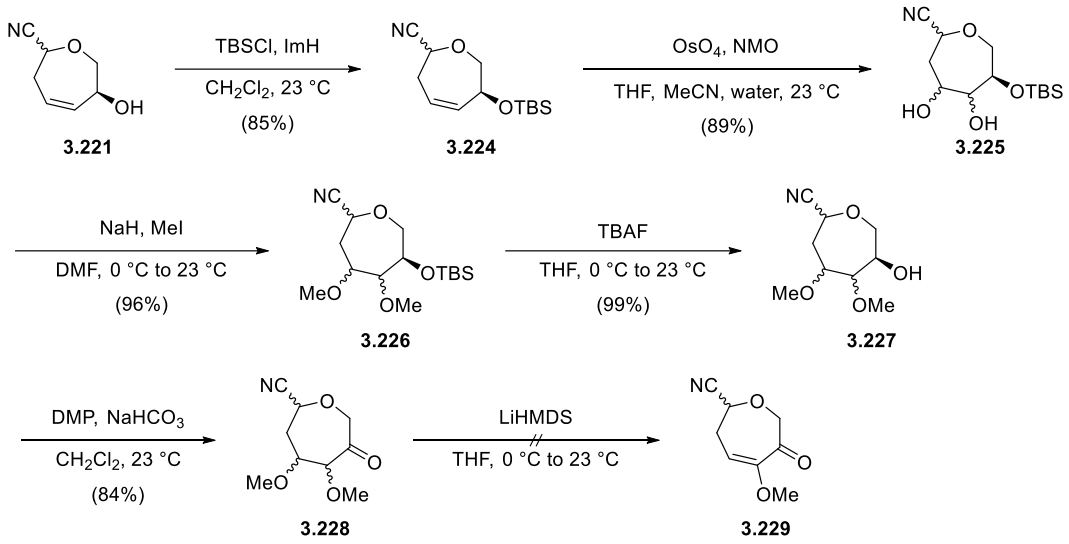
Table 15: Conditions for methoxylation of bromide **3.222.**



entry	conditions	results
1	$KB(OMe)_4$, SPhos, $Pd(MeCN)_2Cl_2$, 1,4-dioxane, 90 °C, 4 h	dehalogenation
2	MeOH, CuI, Me4Phen, Cs_2CO_3, toluene, 80 °C, 24 h	no reaction

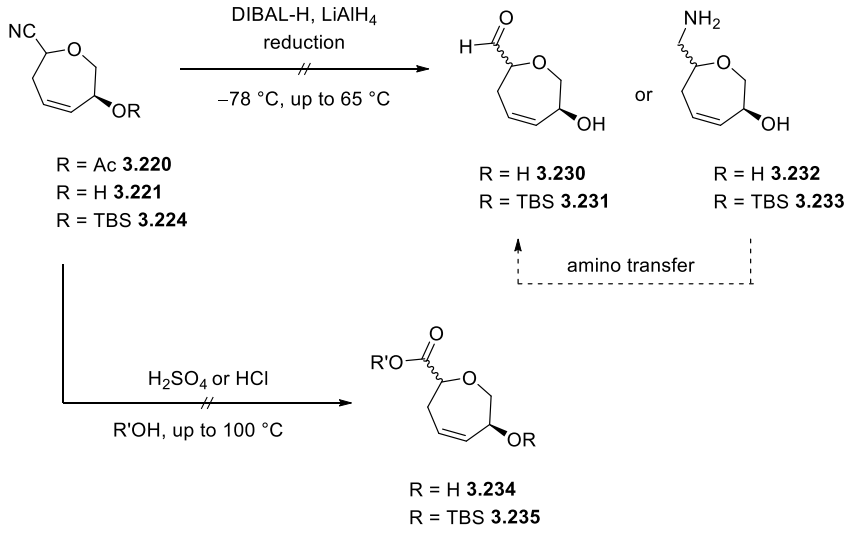
3	MeOH, CuI, Phen, Cs_2CO_3, MeCN, 80 °C, 8 h	no reaction
4	MeOH, BINAP, $Pd(OAc)_2$, Cs_2CO_3, THF, 65 °C, 48 h	dehalogenation

In a second attempt to install of the desired methoxy functionality, we investigated the dihydroxylation of nitrile **3.221**. However, we only obtained a complex mixture of several diastereomers, which were partially separated by HPLC chromatography. Methylation of the mixture of diol **3.225**, *tert*-butyldimethylsilyl deprotection and subsequent Dess−Martin oxidation gave inseperate mixture of diastereomers of ketone **3.228.** Elimination of the β-methoxy under basic conditions to give ketone **3.228** was unsuccessful.



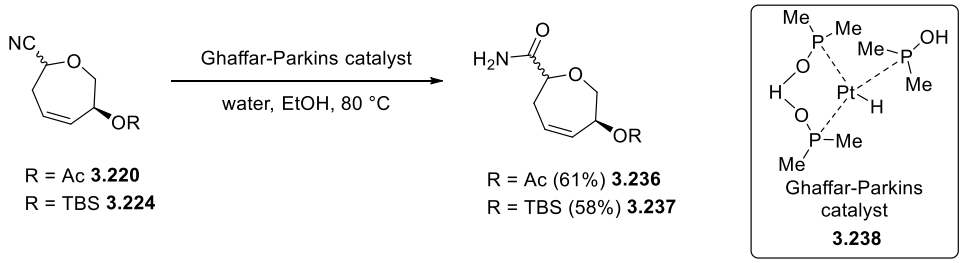
Scheme 73: Synthesis of ketone **3.228** from alcohol **3.221** and attempted synthesis of ketone **3.229**.

In parallel, the modification of the nitrile function was under investigation. Many examples are known in literature for this transformation. Surprisingly, the nitrile function turned out to be stable and showed no reaction under reductive conditions (*i.e.* lithium aluminium hydride or diisobutylaluminium hydride) at low temperatures, while increasing temperatures led to decomposition. Acidic conditions were also not successful for the modification of the nitrile function. The only observed reaction was the cleavage of the acetyl group or silyl group at higher temperatures with partial decomposition.



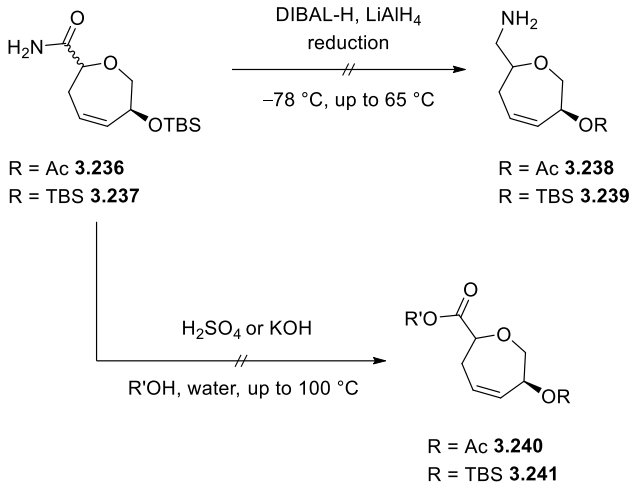
Scheme 74: Attempted synthesis of aldehyde **3.230** and **3.231,** amine **3.232** and **3.233** or ester **3.234** and **3.235**.

Reduction or hydrolysis conditions were found to be problematic for this modification of nitrile. Surprisingly, Ghaffar−Parkins catalyst converted nitrile **3.220** and **3.224** to amide **3.236** and **3.237** in 61% and 58% yield, respectively.



Scheme 75: Synthesis of amide **3.236** and **3.237**.

With amide **3.236** and **3.237** in hand, same conditions already tested for nitriles **3.220** and **3.224** were investigated, with almost similar results. While reduction at low temperatures showed no reaction, higher temperatures afforded complex reactions mixtures. Hydrolysis under acidic or basic conditions was unsuccessful at lower temperatures and resulted also in decomposition at higer temperatures,

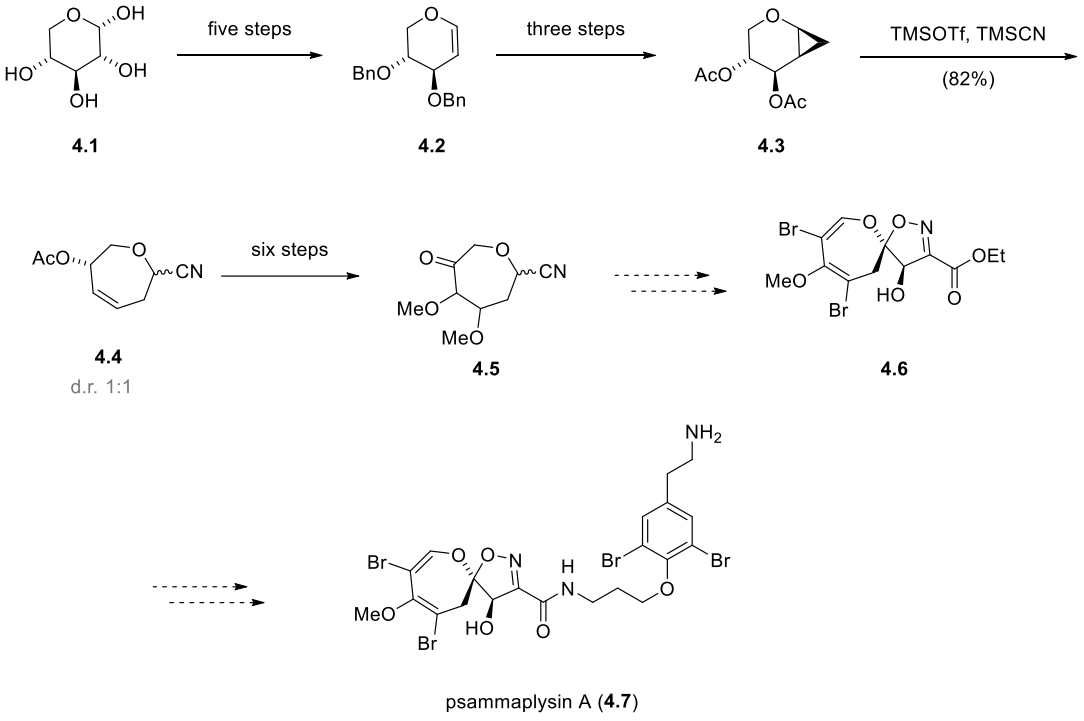


Scheme 76: Attempted synthesis of amine **3.238** and **3.239** or ester **3.240** and **3.241**.

4 Summary and Outlook

Progress toward the total synthesis of psammaplysin A (**4.7**) was reported in this thesis. At first, several spiro isoxazolines were synthesized via a bromine spiro-cyclization. However, direct access to the desired seven-membered-ring framework as well as ring-expansion reactions were found to be challenging. Thus, the synthesis of the seven-membered ring from linear and cyclic precursors was studied in detail. These studies resulted in the development of a ring expansion and versatile route for the synthesis of the seven-membered ring core of psammaplysin A (**4.7**).

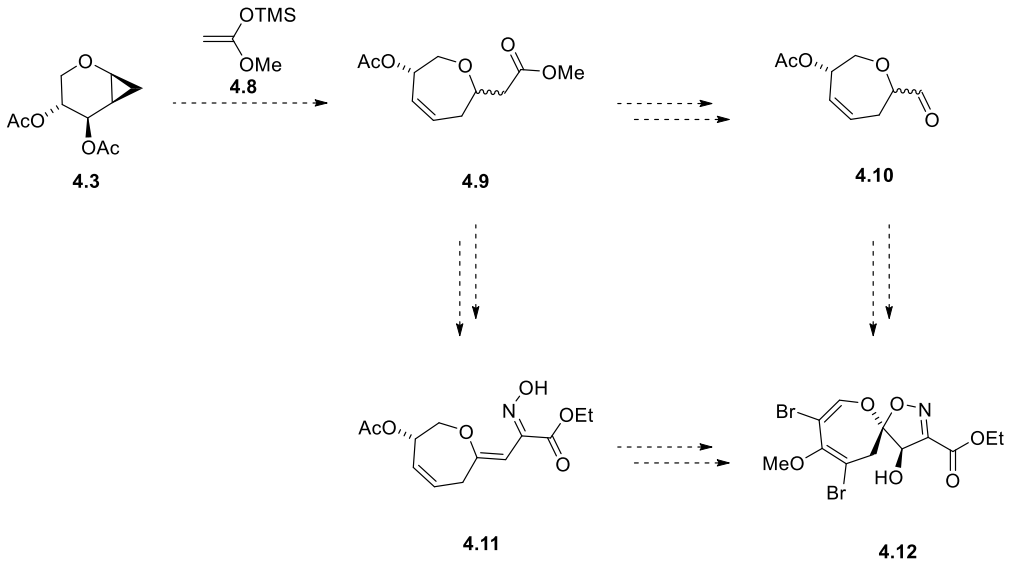
Starting from commercially and inexpensive α-D-xylose (**4.1**), we prepared cyclic enol ether **4.2** within five steps (Scheme 78). Diastereoselective Simmons−Smith cyclopropanation installed the required cyclopropane moiety. Further modifications of the hydroxy-groups afforded acetate **4.3**, as optimal compound for our envisioned Ferrier-type ring expansion.



Scheme 77: Convergent synthesis of the seven-membered ring of psammaplysin A (**4.7**) and nitrile **4.5.**

Activation via trimethyl triflate resulted in the ring-expanded oxacyle **4.4**, which was trapped with trimethylsilyl cyanide to afford nitrile **4.4** as a mixture of two diastereomers (d.r. 1:1) in good yield. With an established route toward the seven-membered ring of the natural product in hand, we extensively investigated modifications towards our target spiro compound **4.6**. The desired methoxy group was successfully installed via dihydroxylation and methylation in **4.5**. Further directions include the elimination of the β-methoxy group, ketone reduction and elimination of the corresponding alcohol. Finally, bromination of the enol ether systems afford the desired subsitution

opattern in psammaplysin A (**4.7**). Spirocyclization can occur via two different pathways. Either elimination to afford terminal alkene, which can undergo a [1,3]-dipolar cycloaddition or selective bromination and Henry reaction to afford the desired hydroxy-isoxazoline structure. In both cases transformation of the nitrile group to the corresponding aldehyde is required. However, nitrile reductions or hydrolysis proved to be challenging. For that reasons an alternative route would include Ferrier type ring-expansion with trimethylsilyl ketene acetal instead of trimethylsilyl nitrile (**4.8**) and cyclopropane **4.3**.



Scheme 78: Alternative route towards key intermediate **4.12** via Ferrier-type ring-expansion to afford ester **4.9** and further modification to aldehyde **4.10** or oxime **4.11**.

Degradation of ester **4.9** would give aldehyde **4.10** as an important structure in our synthesis, which then can be cyclized and further functionalized to our key intermediate **4.12**. Alternatively, ester **4.9** could be converted into oxime **4.11**, which also would be a suitable precursor toward the synthesis of psammaplysin A (**4.7**).

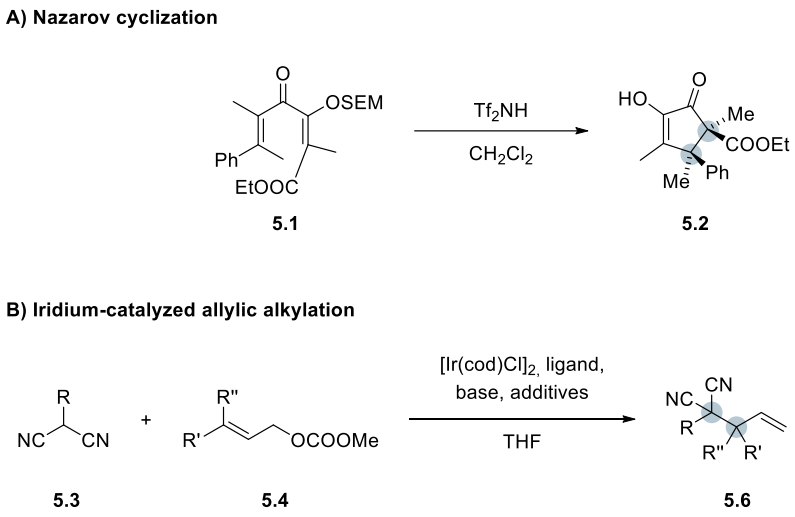
Overall, the pursued strategies presented in this thesis constitute significant progress toward the first total synthesis of psammaplysin A (**4.7**). Further studies on the completion of the total synthesis of psammaplysin A are currently under investigation in the Magauer laboratories.

PART II

Acid-catalyzed Cycloisomerization of Neopentylic Epoxides

5 Introduction

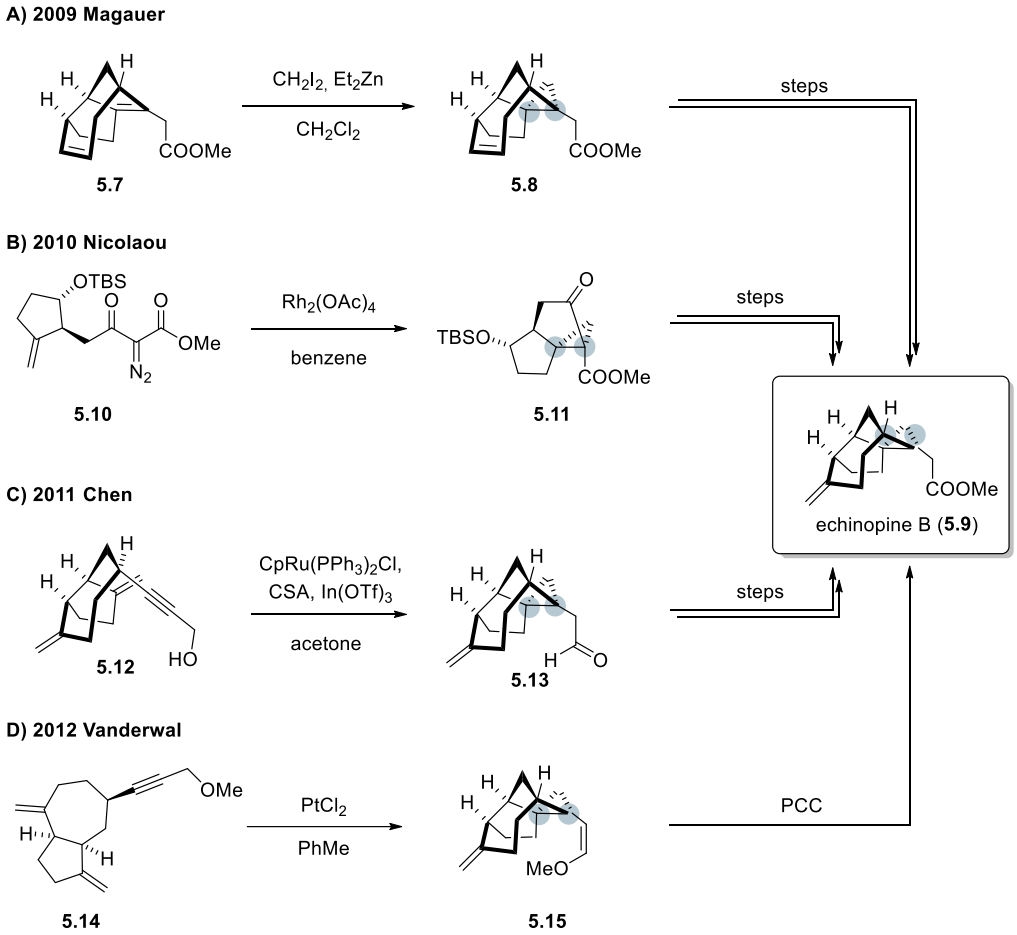
One element of structure that unexceptionally increases the difficulty of a chemical synthesis is the presence of all-carbon quaternary center. The difficulty to synthesize such centers arises from the steric hindrance imposed by the four attached carbons and the limited number of carbon-carbon bond-forming reactions that reliably assemble quaternary carbons. Despite the tremendous development within the last decades such as alkylation, radical reaction, photochemical reaction, pericyclic reaction, and many others their synthetic efficiency is hampered by the scope limitations and deficiency in enantioselective control.[121-122] The challenge is exacerbated further when two all-carbon quaternary stereocenter are adjacent. Despite the remarkable advances that have been made in the formation of all-carbon quaternary stereocenters, the construction of such these motif remains a significant challenge. Previously, a number of methods have been developed to directly synthesize vicinal all-carbon quaternary centers, including Nazarov cyclization[123] or iridium-catalyzed alkylation[124] just to name a few.[125-126]



Scheme 79: A) Nazarov cyclization of ketone **5.1** to afford enone **5.2** containing vicinal all-carbon quaternary center. B) Iridium-catalyzed allylic alkylation of malononitrile derivative **5.3** with allylic carbonate **5.4** to afford bis-nitrile **5.6** containing vicinal all-carbon quaternary center.

Echinopine B (**5.9**), a sesquiterpenes is isolated from the root of the plant *Echinops spinosus*.[127] With its novel structure bearing a vicinal all carbon highly strained cyclopropane, several groups developed different strategies for the formation of this highly challenging structure motif. The first total synthesis was accomplished by Magauer and coworkers in 2009, in which they confirmed also the proposed structure.[128] In their approach, regioselective cyclopropanation of ester **5.7** using a modified Furukawa–Simmons–Smith's reagent afforded the tetracyclic intermediate, which bears the desired cyclopropane with the vicinal all quaternary carbon center. Additionally, they accomplished the synthesis of this cyclopropane **5.8** by Corey–Chaykovsky cyclopropanation.

Several subsequent transformations delivered the natural product. One year later Nicolaou and coworkers reported the second total synthesis.[129] In their key step diazo ester **5.10** reacts with rhodium acetate to generate an carbenoid, which subsequently undergo an intramolecular cyclopropanation.



Scheme 80: A) Magauer's synthesis of echinopine B (**5.9**) with key intermediate **5.8**. B) Nicolaou's synthesis of echinopine B (**5.9**) with key intermediate **5.13**. C) Chen's synthesis of echinopine B (**5.9**) with key intermediate **5.13**. D) Vanderwal synthesis of echinopine B (**5.9**) with key intermediate **5.15.**

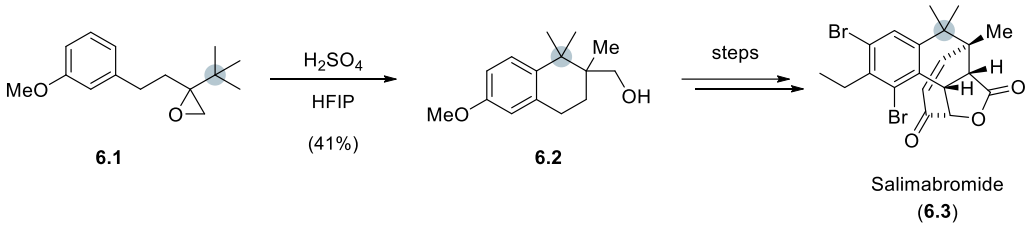
In 2011, Chen and coworkers reported another total synthesis.[130] The key reaction in this bioinspired synthesis is an ruthenium-catalyzed redox bicycloisomerization of enynol **5.12**. The synthesis was completed by oxidation of aldehyde **5.13** and subsequent methylation. Vanderwal and coworkers reported a concise total synthesis of echinopine B (**5.9**) in 2012. In their key step platinum(II) chloride-catalyzed enyne cycloisomerization, bicycle **5.14** was converted into enol ether **5.15** which afforded echinopine B (**5.9**) after pyridinium chlorochromate oxidation.

Although current methods give access to the desired vicinal all carbon quaternary centers, these often are only working with specific substrates, conditions or include multistep procedures.

Especially, benzylic positions are challenging and often resulted in low yielding multistep transformation. To address these issues, novel protocols are required.[131-132]

6 Previous Efforts

The accomplished total synthesis of salimabromide (**6.3**), included an elegant step for the synthesis of vicinal all carbon quaternary centers via an acid-catalytic cycloisomerization of 2,2-disubstituted neopentylic epoxide **6.1**. This powerful reaction afforded tetrahydronaphthalene **6.2** in a single step via a Wagner−Meerwein rearrangement and subsequent Friedel−Crafts alkylation in moderate 41% yield from linear precursors under mild conditions.[133]



Scheme 81: Key-step in the total synthesis of salimabromide (**6.3**) by cycloisomerization of linear epoxide **6.1** to afford teralin **6.2**.

However, the scope and limitation of this powerful ring-formation were not available at this stage of the project. For that reasons further investigations and optimization for this rearrangement/cyclization reaction cascade of 2,2-disubstituted neopentylic epoxides were initiated.

7 Results and Discussion

Reprinted from submitted manuscript Matthias Schmid[†[a]], Kevin Rafael Sokol[†[a]], Lukas Anton Wein[a], Sofia Torres Venegas[a], Christina Meisenbichler[a], Klaus Wurst[b], Maren Podewitz[b] and Thomas Magauer*[a]

COMMUNICATION WILEY-VCH

Synthesis of Vicinal Quaternary All-Carbon Centers via Acid-catalyzed Cycloisomerization of Neopentylic Epoxides

Matthias Schmid[†][a], Kevin Rafael Sokol[†][a], Lukas Anton Wein[a], Sofia Torres Venegas[a], Christina Meisenbichler[a], Klaus Wurst[b], Maren Podewitz[b] and Thomas Magauer*[a]

a. Dr. Matthias Schmid, Kevin Rafael Sokol, Lukas Anton Wein, Sofia Torres Venegas, Christina Meisenbichler and Prof. Dr. Thomas Magauer
Institute of Organic Chemistry and Center for Molecular Biosciences
Leopold-Franzens-University Innsbruck
Innrain 80–82, 6020 Innsbruck, Austria
E-mail: thomas.magauer@uibk.ac.at

b. Dr. Maren Podewitz and Dr. Klaus Wurst
Institute of General, Inorganic and Theoretical Chemistry and Center for Molecular Biosciences
Innrain 80–82, 6020 Innsbruck, Austria

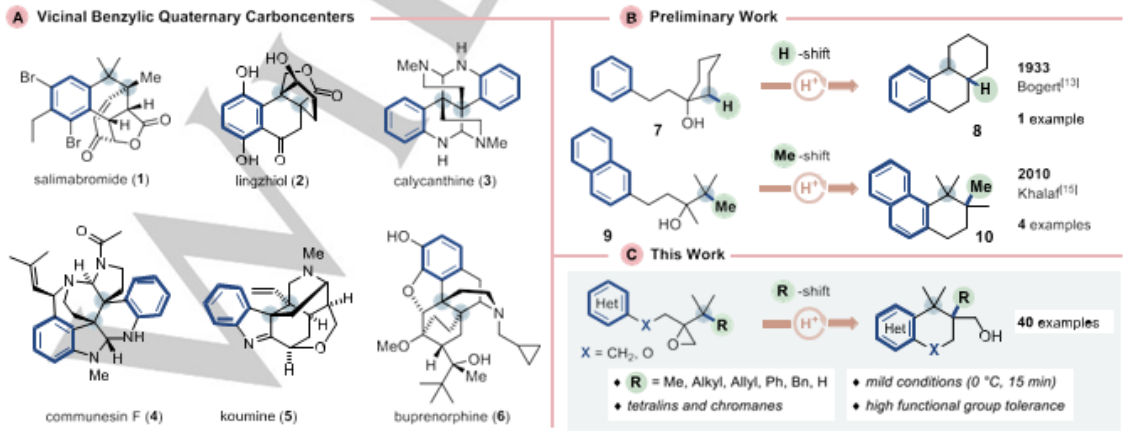
† These authors contributed equally

Supporting information for this article is given via a link at the end of the document.

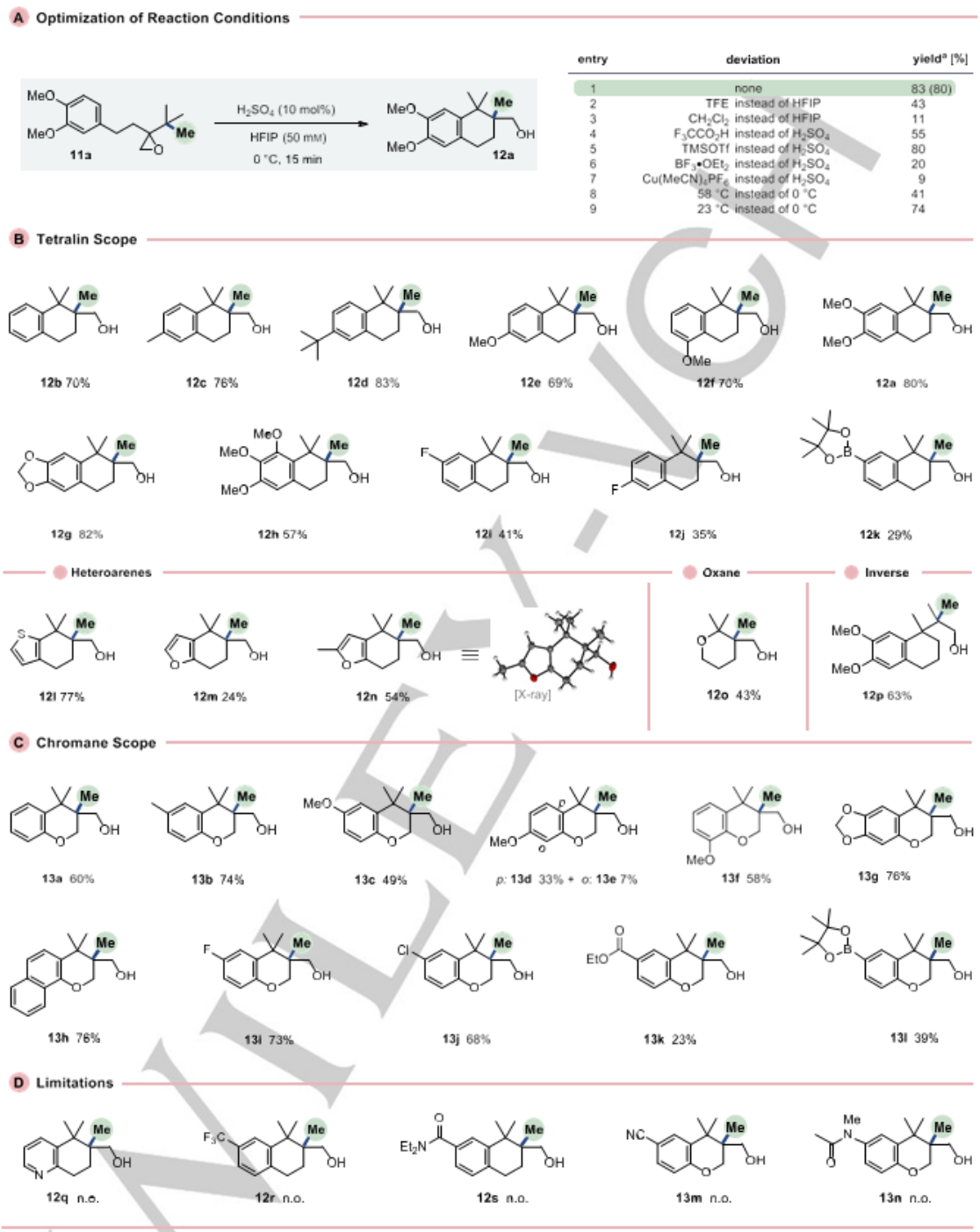
Abstract: Vicinal quaternary carbon centers, a common structural unit in natural products, represent a major challenge for synthetic chemists. Here, we report our studies on the development of a catalytic cycloisomerization of 2,2-disubstituted neopentylic epoxides to produce highly substituted tetralins and chromanes. Termination of the sequence occurs via Friedel–Crafts type alkylation of the remote (hetero)arene linker. The transformation is efficiently promoted by sulfuric acid and proceeds best in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as solvent. Variation of the substitution pattern provided detailed insights into migration tendencies and revealed a competing disproportionation pathway of dihydronaphthalenes at ambient temperature.

Vicinal quaternary carbon centers are present in many bioactive natural products (e.g. salimabromide (**1**),[1] lingzhiol (**2**),[2] calycanthine (**3**),[3] communesin F (**4**),[4] koumine (**5**)[5]) and pharmaceuticals such as buprenorphine (**6**)[6] (Scheme 1A). The presence of these structural units were reported to increase structural rigidity allowing for a tighter binding to their molecular target in many cases and greater selectivity than more flexible congeners.[7] In nature, all-carbon quaternary centers are, for instance, accessible via reactions that proceed via carbocation intermediates.[8,9] For the construction in the chemical laboratory, a well-assorted toolbox has been established in the past.[9,10] However, synthetic challenges remain as multistep procedures that are accompanied by low-yielding transformations are often required.[11]

In the context of the synthesis of salimabromide (**1**), we were investigating methods to efficiently construct the fully substituted tetrahydronaphthalene core.[12] We found that ring-formation and installation of the two crucial vicinal quaternary carbon centers was possible in a single step by employing a powerful cycloisomerization reaction of a 2,2-disubstituted neopentylic epoxide. This chemistry was inspired by the seminal report of Bogert and Cook in 1933 (Scheme 1B).[13,14] In this work, a tandem hydride migration/Friedel–Crafts type cyclization of the tertiary alcohol **7** enabled the synthesis of octahydrophenanthrene system **8**. In 2010, Khalaf extended the rearrangement-cyclization cascade by resorting to acyclic tertiary alcohols such as **9** to enable installation of two vicinal *gem*-dimethyl groups.[15] Unfortunately, both of these reports were strictly limited to a few unfunctionalized hydrocarbon frameworks. Herein, we disclose the synthesis of vicinal all-carbon quaternary centers by the consecutive 1,2-rearrangement/cyclization of 2,2-disubstituted neopentylic epoxides under mild conditions (Scheme 1C).



Scheme 1. A) Natural products and pharmaceuticals featuring vicinal all-carbon quaternary centers. **B)** Preliminary work by Bogert[13] and Khalaf[15] **C)** Concept of this work.



Scheme 2. A) Optimization of the cycloisomerization. B) Scope for tetralins. C) Scope for chromanes. D) Selected limitations. Migrated sigma bond highlighted in bold blue. [a] ^{1}H NMR yields with 2,3,5,6-tetrachloronitrobenzene as the internal standard and isolated yields in parentheses. n.o. = not observed.

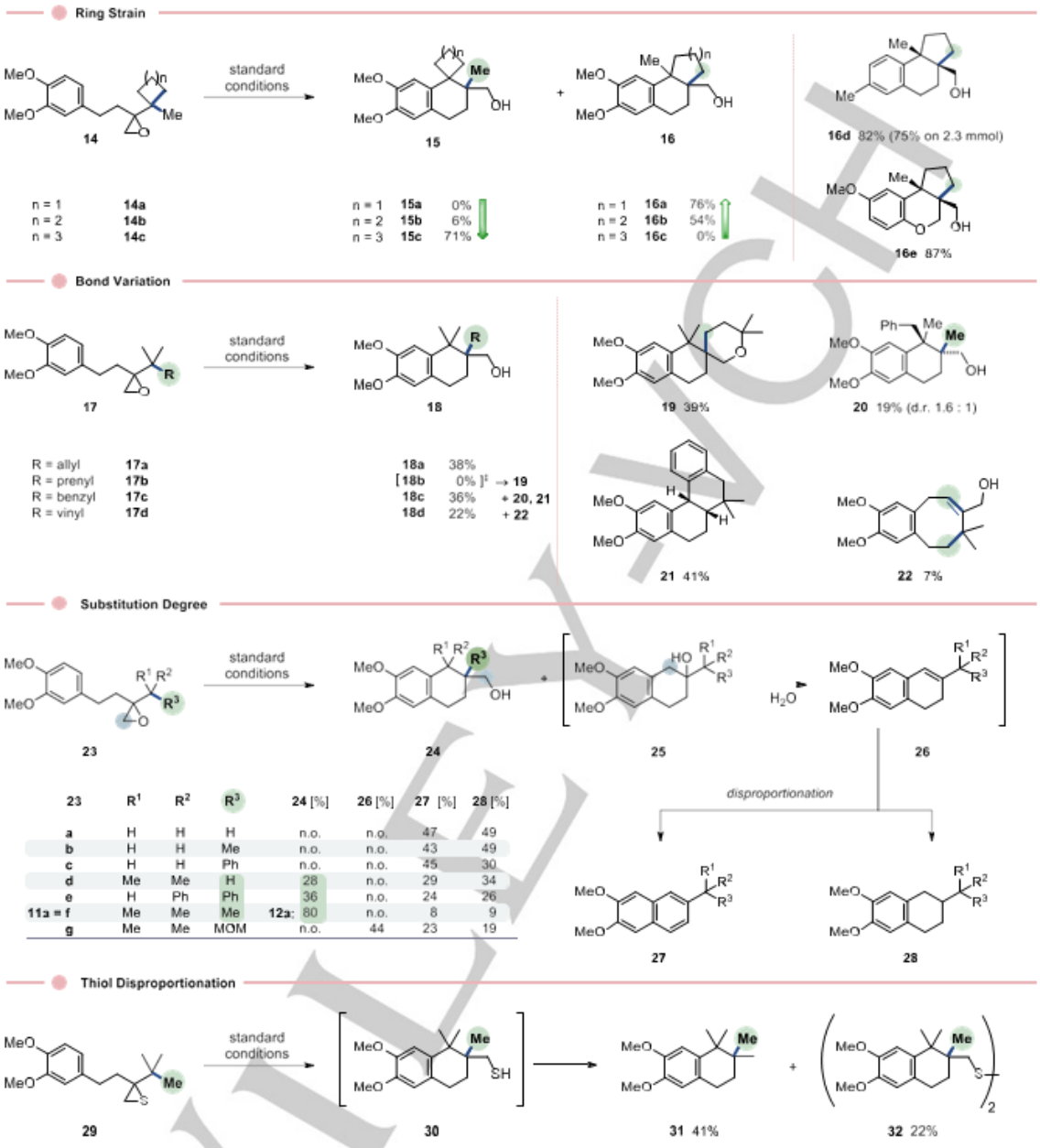
Selective migration of various alkyl residues was achieved by exploiting ring strain, carbon-carbon bond strengths and carbocation stabilities. This allowed for the synthesis of a library of polyfunctionalized tetralin and chromane systems.

For the initial optimization of the reaction conditions, we employed the readily available, electron-rich arene **11a**. We were pleased to find that the cycloisomerization proceeded most efficiently in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP)[16] at 0 °C and sulfuric acid (10 mol%) as catalyst, affording the tetralin **12a** in 83% yield within 15 minutes. The use of alternative solvents, Brønstedt or Lewis acids were found to be inferior and led to significant reduced yields (entries 2–6).[17] Higher temperatures (23 °C, entry 7; 58 °C, entry 8) were less effective for this transformation, leading to complex mixtures of uncyclized byproducts. With the optimized conditions in hand, the scope of the cycloisomerization was investigated in more detail. As a first parameter, we studied different aromatic residues as nucleophilic component for the Friedel–Crafts termination step. Activating methyl and *tert*-butyl substituents provide yields up to 83% (**12c**, **12d**). Methoxy substituted tetralins were obtained in virtual identical yield as the unsubstituted tetralin **12b**, with only little influence of the substitution pattern (69% for **12e**, 70% for **12f**). Noteworthy, **12e** was previously synthesized by the same cascade under non-optimized conditions in only 43% yield.[12] Remarkably, a fully methylated pyrogallol derived epoxide formed the corresponding tetralin **12h** in only 57% yield. We believe that this results from the trajectory of the approaching arene which leads to severe steric interaction between the outer methoxy groups and the tertiary carbocation unit. As expected, substrates with deactivating substituents delivered the corresponding tetralins in only low yields or completely shut down the reaction (compare Scheme 2D, limitations). The fluorinated tetralins **12i** and **12j** were formed in 35 and 41% yield, respectively. Pinacolon boronate **12k** was formed in 29%, which represents a valuable building block for further derivatizations via Suzuki–Miyaura cross-coupling reactions. Electron-rich, non-basic heterocycles also proved to be compatible with the reaction conditions. For a thiophene substrate, efficient alkylation took place to afford the annealed 6/5-system **12l** in 77% yield. The furans **12m** and **12n** were formed in lower yields under the reaction conditions probably due to competing hydrolysis or polymerization.[18] We were pleased to see that the methodology is not only limited to aromatic nucleophiles: oxane **12o** was formed in 43% from the corresponding primary alcohol. Interestingly, even for this relatively small nucleophile no oxolane formation was observed. This underpinned our assumption that the formation of a less-strained six-membered ring must be one of the major driving forces of the cascade (*vide infra*). This hypothesis was also experimentally supported by product **12p**, which was formed from a distal epoxide via a formally inverse methyl migration along the alkyl chain. The non-rearranged 7/6-system was not observed under these conditions.

Having investigated the conversion of a panel of variously substituted (hetero)arenes to afford tetralins, we proceeded to vary the carbon chain connecting the epoxide and (hetero)arene. By replacement of the ethylene linker with an oxymethylene unit, we envisioned to access heterocyclic chromane systems. We were pleased to see that a series of these readily available phenyl ethers delivered the highly substituted chromanes (**13a–l**) in medium to good yields. For all substrates investigated, a competing hydride shift to form a stabilized phenoxycarbocation ion was not observed. Electron-rich phenyl as well as naphthyl ethers underwent the cascade reaction in up to 76% yield. Similarly substituted chromanes were generated in only slightly reduced yields when compared to the corresponding tetralin analogues. An exception was the methoxy derivative **13d**, which was formed in only 33% together with 7% of its *ortho*-regioisomer **13e**. Interestingly, we observed an unexpected effect of the substitution pattern of methoxyphenols, affording the highest yield (58%) for the *ortho*-substituted derivative **13f**. The *p*-fluoro and chloro-phenyl ethers delivered the corresponding chromanes **13i** and **13j** in 73% and 68% yield, respectively. From substrates carrying electron-withdrawing groups (CO_2Et, Bpin) only small amounts of the corresponding chromanes were isolated (23% for **13k**, 39% for **13l**). In these cases, the phenyl ether proved to be less stable leading to the isolation of free phenols in substantial amounts. Electron-poor (hetero)arene turned out to be incompatible not only for the formation of tetralins, but also for chromane systems. The 2,3-substituted pyridine **12q** was not observed even in the presence of excess acid and prolonged reaction times. A trifluoromethyl groups (**12r**), amide (**12s**) or nitrile (**13m**) prevented the final cyclization and gave mostly complex mixtures of uncyclized elimination products. To our surprise, the protected aniline derivative **13n** was not accessible either and only afforded a complex mixture.

To better understand the reaction sequence, we studied the migration tendencies of different alkyl residues. For this purpose, we replaced the *tert*-butyl group attached to the epoxide with different aliphatic rings (ring-size = 4, 5, 6). Highly strained methyl-cyclobutyl epoxide **14a** underwent exclusively ring-expansion/alkyl migration, affording *cis*-benzohydrindane **16a** in 76% yield. The same behavior was observed for the formation of tetralin **16d** (82%) and chromane **16e** (87%). The less-strained cyclopentyl derivative **14b** afforded both *cis*-benzodecaline **16b** and spirane **15b** as an inseparable mixture (9:1 ratio), still preferring the ring expanded product **16b** in 54% yield. Cyclohexyl derivatives **14c** exclusively formed the spirane **15c** (71%) with no detectable amounts of the 7/6/6-expansion product **16c**.

In an effort to investigate the requirements for successful 1,2-migration, we further modified the *tert*-butyl group and replaced one of the three methyl groups with an allyl, prenyl, benzyl and a vinyl group. Epoxide **17a** afforded the allyl migrated tetralin **18a** in 38% yield as the major product. A preferential migration of the weaker allylic bond was also observed for the prenyl substrate (**17b**). For this particular case, we observed protonation of the remote double bond of **18b** and subsequent spiroxane formation with the neopentylic alcohol (39% for **19**). Similar migration was observed for the benzyl group giving **18c** in 36% yield. The competing methyl migration was also observed for this substrate leading to the formation of **20** as a mixture of diastereomers (d.r. 1.6:1) in 19% yield. Careful analysis of the product mixture revealed the unusual 6/6/6/6-product **21** (hexahydro benzo[c]phenanthrene) as the major product (41%). Despite the stronger sp^2-sp^3 bond (*t*-Bu-vinyl = 97.8kcalmol^{-1}, *t*-Bu-methyl = 87.5kcalmol^{-1})[19], the migration of a vinyl group was also observed to afford tetralin **18d** in 22% together with a complex product mixture. The eight-membered product **22** was isolated as the only by-product in 7% yield, originating from at least two alkyl migration steps.[20]

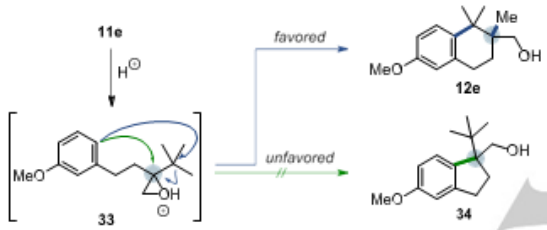


Scheme 3. Variation of the tetrasubstituted carbon atoms.

To investigate the requirements for successful migratory cycloisomerization, we varied the substitution degree of the terminal alkyl carbon starting with a methyl group (**23a**, $R^1 = R^2 = R^3 = H$). As expected, no cycloisomerization was observed for this epoxide, but the disproportionated naphthalene **27a** (47%) and tetralin **28a** (49%) were obtained in nearly quantitative combined yield. The same results were observed for substrates carrying an ethyl (**23b**) or a benzyl (**23c**) group. When an *iso*-propyl group was present, naphthalene **27d** (29%) and tetralin **28d** (34%) still prevailed. However, a 1,2-hydride shift was also observed to afford the cycloisomerized tetralin **24d** in 28% yield. Diphenylmethyl derivative **23e** afforded the corresponding products in similar yields. Surprisingly, in this case only phenyl migration with low diastereoselective control (**23e**, 36%, d.r. 1.9:1) was observed. Epoxide **11a**, that was used for the optimization delivered the disproportionated naphthalene **27f** (8%) and tetralin

28f (9%) under the reaction conditions. For the methoxymethyl group in substrate **23g** we exclusively observed direct alkylation leading to a mixture of dihydronaphthalene **26g** and its disproportionation products – the corresponding naphthalene **27g** and tetralin **28g**.[20] Fast disproportionation was not only observed for dihydronaphthalenes but also for cycloisomerized neopentylic thiol **30**. The use of thiirane **29** directly gave a mixture of desulfurized tetralin **31** (41%) and the corresponding disulfide **32** (22%).[21] While the disproportionation of thiols to disulfides and hydrogen is a common reaction,[22] the formation of a hydrocarbon and a disulfide is unprecedented to the best of our knowledge. Finally, we also screened a panel of chiral Lewis and Brønsted acid catalysts employing substrates **11a** and **17d**. Unfortunately, we did not observe any asymmetric induction so far (see Supporting Information for screening).

Noteworthy, for all substrates investigated no five- or seven-membered ring systems were observed. This result was also supported by DFT calculations with the ωB97X-D/6-311G(d,p)/SMD(F_3CCH_2OH) employing **11e.**



Scheme 4. Reaction outcome of the protonated epoxide.

We found that the formation of the six-membered ring (**12e**) *via* the corresponding sigma complex is thermodynamically favored over the formation of the five-membered ring (**34**), presumably because of geometrical constraints (see Supporting Information for details). Whether the formation of the five-membered rings is kinetically hindered or undergo fast interconversion remains to be investigated.

In conclusion, we reported a powerful cycloisomerization reaction of 2,2-disubstituted neopentylic epoxides. The reaction does not require transition metal catalysts and proceeds under mild conditions in HFIP as the solvent. Variation of the terminating nucleophile enabled rapid access to functionalized chromanes and tetralins featuring vicinal all-carbon quaternary centers. The use of cycloalkyl moieties allowed for the formation of tricyclic ring systems in one step. Analysis of the byproducts revealed a fast disproportionation of dihydronaphthalenes to naphthalenes and tetralins.

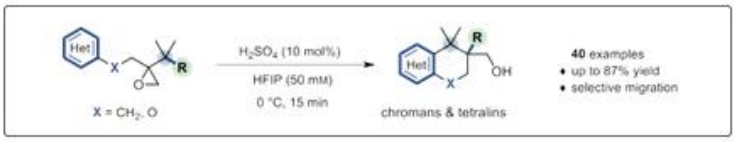
Acknowledgements

T.M. acknowledges the European Research Council under the European Union's Horizon 2020 research and innovation program (grant agreement No 714049) and the Center for Molecular Biosciences (CMBI). M.S. gratefully acknowledges financial support from the German Academic Scholarship Foundation and the German National Academy of Sciences Leopoldina. L. A. Wein and S. Torres Venegas gratefully acknowledge financial support by the Tyrolean Science Fund TWF (F.16642/5-2019 to L.A.W. and UNI-0404/2354 to S.T.V). M. P. would like to thank the Austrian Science Fund FWF (M-2005).

Keywords: rearrangements • epoxides • tetralin • chromane • carbocation chemistry

1 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.
2 Y.-M. Yan, J. Ai, L. L. Zhou, A. C. K. Chung, R. Li, J. Nie, P. Fang, X.-L. Wang, J. Luo, Q. Hu et al., *Org. Lett.* **2013**, *15*, 5488.
3 G. R. Eccles, *Proc. Amer. Pharm. Assoc.* **1888**, 382.
4 H. Hayashi, H. Matsumoto, K. Akiyama, *Biosci. Biotechnol. Biochem.* **2004**, *68*, 753.
[5] C.-T. Liu, Q.-W. Wang, C.-H. Wang, J. *Am. Chem. Soc.* **1981**, *103*, 4634.
6 R. C. Heel, R. N. Brogden, T. M. Speight, G. *S. Avery, Drugs* **1979**, *17*, 81.
7 J. I. Juncosa, M. Hansen, L. A. Bonner, J. P. Cueva, R. Maglathlin, J. D. McCorvy, D. Marona-Lewicka, M. A. Lill, D. E. Nichols, *ACS Chem. Neurosci.* **2013**, *4*, 96.
8 E. A. Peterson, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11943.
9 W. S. Johnson, *Angew. Chem. Int. Ed.* **1976**, *15*, 9.
10 a) H. Zheng, Y. Wang, C. Xu, X. Xu, L. Lin, X. Liu, X. Feng, *Nat. Commun.* **2018**, *9*, 1; b) R. Long, J. Huang, J. Gong, Z. Yang, *Nat. Prod. Rep.* **2015**, *32*, 1584; c) K. W. Quasdorf, L. E. Overman, *Nature* **2014**, *516*, 181; d) M. Büschleb, S. Dorich, S. Hanessian, D. Tao, K. B. Schenthal, L. E. Overman, *Angew. Chem. Int. Ed.* **2016**, *55*, 4156.
[11] F. Schneider, K. Samarin, S. Zanella, T. Gaich, *Science* **2020**, *367*, 676.
[12] a) M. Schmid, A. S. Grossmann, P. Mayer, T. Müller, T. Magauer, *Tetrahedron* **2019**, *75*, 3195; b) M. Schmid, A. S. Grossmann, K. Wurst, T. Magauer, *J. Am. Chem. Soc.* **2018**, *140*, 8444.
[13] M. T. Bogert, Science (*New York, N.Y.*) **1933**, *77*, 289.
[14] J. W. Cook, C. L. Hewett, *J. Chem. Soc.* **1933**, 1098.
[15] A. A. Khalaf, H. A. Albar, K. O. El-Fouty, *Indian J. Chem.; Sect. B: Org. Chem. Incl. Med. Chem.* **2010**, *49B*, 203.
[16] I. Colomer, A. E. R. Chamberlain, M. B. Haughey, T. J. Donohoe, *Nat. Rev. Chem.* **2017**, *1*, 88.
[17] For a full optimization table, see Supporting Information.
[18] In the case of **12n** the corresponding hydrolyzed diketone was isolated in 11% yield.
[19] S. J. Blanksby, G. B. Ellison, *Accounts of chemical research* **2003**, *36*, 255.
[20] For a proposed reaction mechanism, see Supporting Information.
[21] The combined yield was increased to 92% by employing TMSOTf instead of H_2SO_4.
[22] J. Choi, N. M. Yoon, *J. Org. Chem.* **1995**, *60*, 3266.

Entry for the Table of Contents



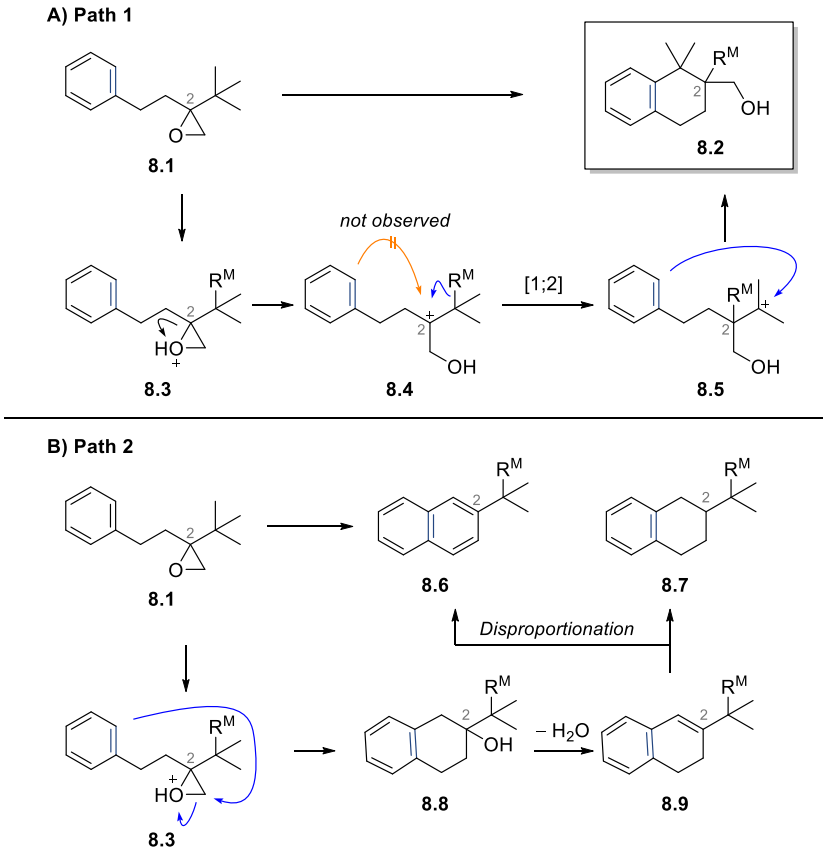
A powerful cycloisomerization cascade reaction of neopentylic epoxides was developed. Acid catalyzed epoxide opening promotes a consecutive Wagner–Meerwein shift/Friedel–Craft type alkylation sequence. This enabled rapid access to functionalized tetralin and chromane scaffolds featuring vicinal all-carbon quaternary centers.

Institute and/or researcher Twitter usernames: @MagauerGroup, @M_Schmid_Chem

8 Conclusion and Further Directions

Intensive optimization of the cycloisomerization of 2,2-disubstituted neopentylic epoxides revealed the highest yields for substituted tetralins at 0 °C in HFIP as solvent in catalytic amount of sulfuric acid. Thereby, a competing disproportionation pathway of dihydronaphthalen was discovered.

Mechanistically, we suggest that the reaction proceeds through protonation of epoxide **8.1**. Subsequently opening of protonated epoxide **8.3** generated the tertiary cation **8.4**. While empirical data showed no evidence of the trapping of this cationic species, we assume that the Wagner−Meerwein shift is favored or the nucleophilic intramolecular attack is repressed by steric hindrance or an unfavoured transition state. After the [1,2] shift tertiary cation **8.5** is formed and terminated the reaction cascade by an intramolecular Friedel−Craft alkylation to afford tetralin **8.2**. This was also supported by DFT calculations.



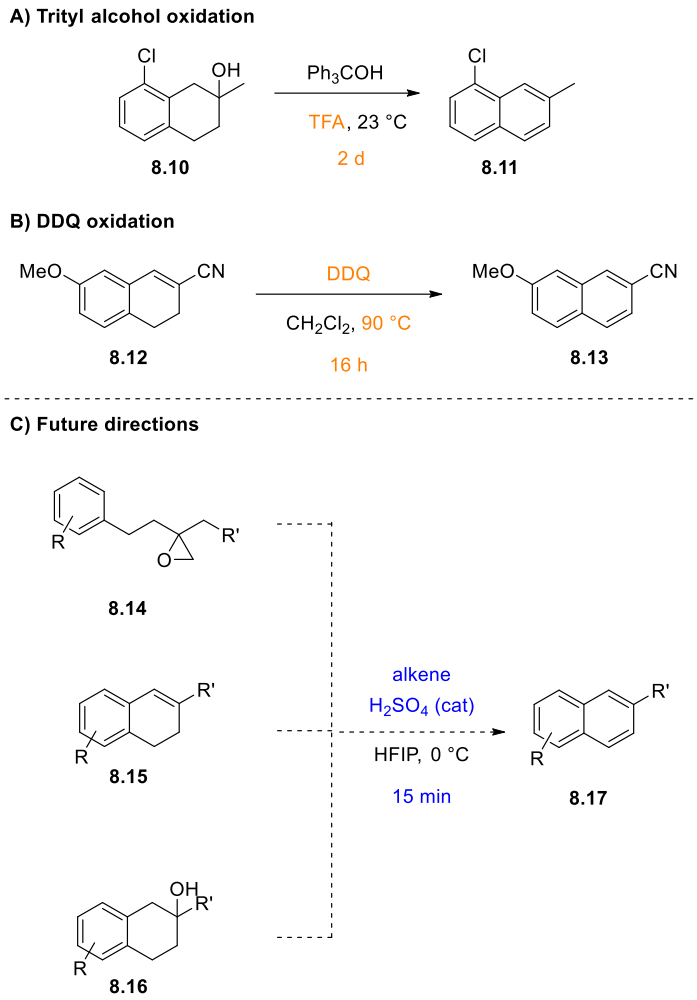
Scheme 82: A) Proposed reaction pathway for the cycloisomerization of epoxide **8.1** to alcohols **8.2**. B) Proposed reaction pathway for side reaction of epoxides to naphthalene **8.6** and tetralin **8.7**.

In the competitive pathway protonated epoxide **8.3**, undergoes nucleophilic attack by less substituted carbon center by an intramolecular nucleophile in a *6-exo-tet* fashion generating a

tertiary alcohol **8.8** Under acidic conditions elimination occurs to hydronaphthalene **8.9** which undergoes a disproportion reaction to naphthalene **8.6** and tetralin **8.7**.

This work was mainly focused on the synthesis of tetralin derivatives. The mild reaction conditions tolerated a variety of functional groups, like ethers, alkyls, boronic esters, esters and halides as well several different nucleophiles like electron rich to electron neutral aromatic system, hetereoarenes and other nucleophiles like alcohols. Furthermore, chromanones, bearing vicinal quaternary all carbon centers were able to be prepared by this methodology. Modification of the *tert*-butyl group by replacing one of the three methyl groups also gave insight in the migrations tendencies and showed limitation for this cascade reaction. These results were finally used for ring-expansions to access tricyclic compounds.

Nevertheless, this work also demonstrated that less-substituted epoxides exclusively delivered naphthalene **8.6** and tetralin **8.7** in excellent yields. Although there are only a few examples for the synthesis of functionalized naphthalene at the two position from similar starting material, these require often harsh reaction conditions such as long reactions times, strong acidic conditions or toxic reagents such as DDQ.[134-136]



Scheme 83: A) Literature synthesis of naphthalene **8.11** from tertiary alcohols **8.10**. B) Current synthesis naphthalene **8.13** from alkene **8.12**. C) Future work on the synthesis of naphthalene **8.15** from epoxide **8.14**.

With our results in hand, we envision to further expand this methodology for the synthesis of naphthalenes **8.17** from epoxides **8.14**, hydronaphthelenes **8.15** and tertiary alcohols **8.16** by the addition of strained alkene, which undergo the observed disproportionation.

Experimental Part

9 Experimental Section

9.1 General Experimental Details

General Working Methods

All reactions were performed in glassware fitted with rubber septa under a positive pressure of argon, unless otherwise noted. All glassware was dried in an oven at 130 °C prior to use. Air- and moisture-sensitive liquids were transferred via syringe or stainless-steel cannula through rubber septa. Solids were added under inert gas or were dissolved in appropriate solvents. High pressure reactions were conducted in a miniclave steel apparatus from *BÜCHI AG*. Low temperature-reactions were carried out in a Dewar vessel filled with a cooling agent: acetone/dry ice (−78 °C), H_2O/ice (0 °C). Reaction temperatures above 23 °C were conducted in a heated oil bath. The reactions were magnetically stirred and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC), using glass 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 basic potassium permanganate solution ($KMnO_4$), aqueous acidic ceric ammonium molybdate solution (CAM), or an aqueous acidic *p*-anisaldehyde solution and were developed by heating with a heat gun. Flash-column chromatography on silica gel was performed as described by Still *et al.*,[159] employing silica gel (60 Å, 40–63 µm, *Merck KGaA*). Flash column chromatography on silica gel using triethylamine pretreated silica gel was performed by preparing the silica gel slurry with triethylamine (7.5% v/v in corresponding eluent mixture) and flushing the column with the eluent prior to loading the compound on the column. The yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) pure material.

Solvents and Reagents

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone prior to use. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), diisopropylamine (DIPA) and *N*,*N*-diisopropylethylamine (DIPEA) were distilled under nitrogen atmosphere from calcium hydride prior to use. Benzene (PhH), Chlorobenzene (PhCl), toluene (PhMe), 1,4-dioxane, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile (MeCN), ethanol (EtOH) 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, Acros Organics, Alfa Aesar, Strem Chemicals, TCI Europe, carbolution, ABCR*) and were used as received. Solvents for extraction, crystallization and flash column chromatography on silica gel were purchased in technical grade and distilled under reduced pressure prior to use.

Lithium chloride and lithium bromide were dried at 100 °C under vacuum (0.1 mmHg) for 12 h and stored in a drying oven at 130 °C (760 mmHg); the hot, dried solid was flame dried under vacuum (0.1 mmHg) for 4–5 min immediately prior to use. 4 Å molecular sieves were washed (methanol, acetone, dichloromethane) and then dried at 100 °C under vacuum (0.1 mmHg) for 12 h and stored in a drying oven at 130 °C (760 mmHg); the molecular sieves were flame dried under vacuum (0.1 mmHg) for 4–5 min immediately prior to use. The molarity of *n*-butyllithium solutions was determined by titration against diphenylacetic acid as an indicator (average of three determinations).[160]

NMR Spectroscopy

NMR spectra were measured on a *Bruker* Avance III HD 800 MHz spectrometer equipped with a CryoProbeTM, *Bruker* Avance III HD 400 MHz spectrometer equipped with a CryoProbeTM, *Bruker* AXR300, *Varian* VXR400 S and *Bruker* AMX600 spectrometers operating at 800 MHz, 400 MHz, 300 MHz, 400 MHz and 600 MHz for proton nuclei (200 MHz, 100 MHz, 75 MHz, 100 MHz, 150 MHz for carbon nuclei), respectively. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, $CDHCl_2$: δ 5.32, C_6HD_5: 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, CD_2Cl_2: δ 54.00, C_6D_6: 128.06, acetone-d_6: 29.84). ^{1}H NMR spectroscopic data are reported as follows: Chemical shift in ppm (multiplicity, coupling constants *J* (Hz), integration intensity, assigned proton) (e.g. "5.21 (t, $^3J_{9/8}$ = 7.3 Hz, 1H, H-9)"). The multiplicities are abbreviated with s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), p (pentet), se (sextet), h (heptet) 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. Protons of diastereotopic methylene groups are reported as H-Xa and H-Xb, where H-Xa is the more downfield shifted proton. The nomenclature is arbitrarily and does not correspond to the spin system. Furthermore, the numbering of the proton and carbon atoms does not correspond to the IUPAC nomenclature. ^{13}C NMR spectroscopic data are reported as follows: Chemical shift in ppm (assigned carbon) (e.g. "159.22 (C-21)"). In cases were resonances overlap or cannot be unambiguously assigned to a single proton or carbon atom, multiple assignments are listed (e.g. the ^{13}C NMR assignment "18.29 (C-16, C-17), 17.84 (C-16, C-17)" indicates that the resonance at 18.29 is either C-16 or C-17). In addition to ^{1}H and ^{13}C NMR measurements, 2D NMR techniques such as homonuclear correlation spectroscopy (COSY), 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. All raw FID files were processed and the spectra analyzed using the program *MestReNova 9.0.1* from *Mestrelab Research S. L.*

Mass Spectrometry

All mass spectra were measured by the analytic section of the Department of Chemistry, *Ludwig-Maximilians-Universität München*. Mass spectra were recorded on the following spectrometers (ionisation mode in brackets): MAT 95 (EI) and MAT 90 (ESI) from *Thermo Finnigan gmbH.* Mass spectra were recorded in high-resolution. The method used is reported at the relevant section of the experimental section.

IR Spectroscopy

IR spectra were recorded on a *PerkinElmer* Spectrum BX II FT-IR system. Data are represented in frequency of absorption (cm^{-1}).

Optical Rotation

Optical rotation values were recorded on a *PerkinElmer 241* or *Anton Paar MCP 200* polarimeter. The specific rotation is calculated as follows:

$$[\alpha]_{\lambda}^{\varphi} = \frac{\alpha}{\beta \cdot d}$$

α: recorded optical rotation

β: concentration of the analyte in 10 mg/mL

d: length of the cuvette in dm

φ: measuring temperature in °C

λ: wave length in nm

The respective concentration and the solvent are denoted in the analytical part of the experimental description.

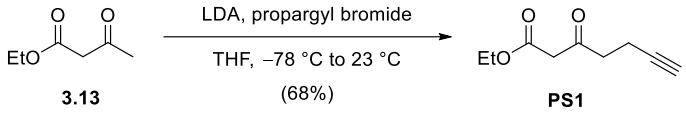
Melting Point Ranges

Melting point ranges were measured on a B-540 melting point apparatus from *BÜCHI Labortechnik AG* and are uncorrected.

9.2 Experimental Procedures, X-Ray Crystallographic and Spectroscopic data

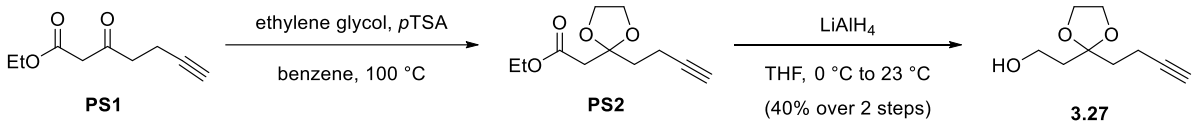
9.2.1 Supporting Information for Chapter I

9.2.1.1 Experimental procedures



Synthesis of alkyne **PS1**: To a solution of diisopropylamine (15.5 mL, 110 mmol, 2.20 equiv) in tetrahydrofuran (200 mL) was added a solution of *n*-butyllithium (2.44 M in hexanes, 42.0 mL, 105 mmol, 2.10 equiv) at −78 °C. After 10 min, ethyl acetoacetate (**3.13**) (6.32 mL, 49.9 mmol, 1 equiv) was added dropwise at −78 °C. After complete addition, the reaction mixture was slowly allowed to warm to 0 °C and stirring for 1 h before a solution of propargyl bromide (80% in toluene, 5.68 mL, 59.9 mmol, 1.20 equiv) was added at 0 °C. After complete addition, the resulting yellow reaction mixture was allowed to warm to 23 °C. After 1 h, saturated aqueous ammonium chloride solution (200 mL) was added to quench excess of base. The reaction mixture was extracted with ethyl acetate (3×100 mL), the combined organic phases were washed with water (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 carefully concentrated (>200 mbar, 42 °C) to afford alkyne **PS1** (5.69 g, 33.8 mmol, 68%) as a yellow oil, which was pure enough to use without further purification.

All analytical data were in agreement with the literature. [137]

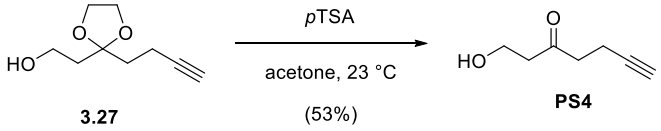


Synthesis of alcohol **3.27**: To a solution of alkyne **PS1** (5.69 g, 33.8 mmol, 1 equiv) in benzene (100 mL) in a dean-stark trap apparatus. Ethylene glycol (3.77 mL, 67.6 mmol, 2.00 equiv) and *p*-toluene sulfonic acid monohydrate (644 mg, 3.38 mmol, 10.0 mol%) were added and the reaction mixture was heat to 100 C. After 16 h, the reaction mixture was allowed to cool to 23 C and acid was neutralized with saturated aqueous sodium hydrogen carbonate solution (100 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3×100 mL) and the combined organic phases were washed with water (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 to afford acetal **PS2** as a pale yellow oil, which was pure enough without further purification.

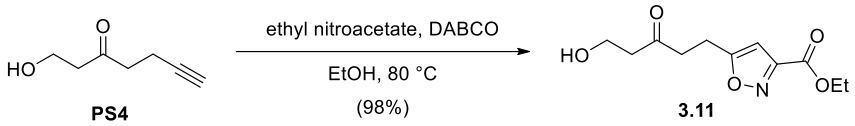
The acetal **PS2** was dissolved in tetrahydrofuran (50 mL) and added dropwise to a suspension of lithium aluminum hydride (2.56 g, 67.6 mmol, 2.00 equiv) in tetrahydrofuran (100 mL) at 0 °C. After 2 h stirring at 0 °C, excess of lithium aluminum hydride was quenched carefully by the dropwise addition ethyl acetate (100 mL) at 0 °C and saturated aqueous solution of sodium potassium tartrate (100 mL). After phase separation (around 4 h), the phases were separated and the aqueous phase was extracted with ethyl acetate (3×100 mL) and the combined organic phases were washed with water (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 to yield alcohol **3.27** (2.32 g, 13.5 mmol, 40% over two steps) a pale yellow oil.

All analytical data were in agreement with the literature.[137]



Synthesis of ketone **PS4**: To a solution of acetal **3.27** (1.00 g, 5.88 mmol, 1 equiv) in acetone (16 mL) was added *p*-toluenesulfonic acid monohydrate (279 mg, 1.47 mmol, 25.0 mol%) at 23 °C. After 16 h, the reaction mixture was diluted with water (20 mL) and diethyl ether (20 mL). The organic phases were separated, the aqueous phase extracted with diethyl ether (3×30 mL), the combined organic phases were washed with saturated aqueous sodium hydrogen carbonate solution (30 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 (50% ethyl acetate in *n*-hexane) to afford ketone **PS4** (392 mg, 3.11 mmol, 53%) as a colorless oil.

All analytical data were in agreement with the literature. [137]



Synthesis of isoxazole **3.11**: To a solution of alkyne **PS4** (380 mg, 3.01 mmol, 1 equiv) in ethanol (5 mL) was added DABCO (33.8 mg, 301 µmol, 10.0 mol%) and ethyl nitroacetate (836 µL, 7.53 mmol, 2.50 equiv) and the resulting yellow solution was heated to 80 °C. After 2 d, the reaction mixture was allowed to cool to 23 °C and the solution was concentrated. The crude product was purified by flash column chromatography on silica gel (1% methanol in dichloromethane) to afford isoxazole **3.11** (709 mg, 2.94 mmol, 98%) as a yellow oil.

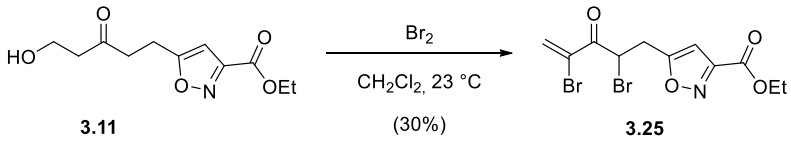
TLC (80% ethyl acetate in hexane): R_f: 0.26 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (t, *J* = 1.0 Hz, 1H), 4.40 (qt, *J* = 7.1, 2.0 Hz, 2H), 3.87 (tt, *J* = 5.4, 1.8 Hz, 2H), 3.24 – 3.05 (m, 2H), 2.91 (t, *J* = 7.2 Hz, 2H), 2.69 (td, *J* = 5.5, 2.4 Hz, 2H), 2.19 (s, 1H), 1.39 (tt, *J* = 7.1, 1.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.3, 173.8, 160.1, 156.6, 102.2, 62.3, 57.8, 44.7, 40.2, 20.6, 14.2.

HRMS (ESI): calcd. for $C_{11}H_{16}NO_5$ $[M+H]^+$: 242.1023 ; found: 242.0935.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3429, 2983, 2940, 2904, 1712, 1593, 1556, 1460, 1424, 1388, 1219, 1099, 1019, 929, 859, 833, 779.



Synthesis of enone **3.25**: To a solution of alcohol **3.11** (25.0 mg, 104 µmol, 1 equiv) in dichloromethane (2 mL) was added bromine (53.4 µL, 1.04 mmol, 10.00 equiv) at 0 °C. The resulting brown solution was slowly allowed to warm to 23 °C. After 16 h, excess of bromine was quenched with saturated aqueous thiosulfate solution (10 mL) and the phases were separated. The aqueous phase was extracted with dichloromethane (3×5 mL), the combined phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a yellow solid. The crude product was purified by flash column chromatography on silica gel (3% methanol in dichloromethane) to afford enone **3.25** (11.8 mg, 31.1 µmol, 30%) as pale yellow oil. Analytical data were provides by Dr. Lara Weisheit.

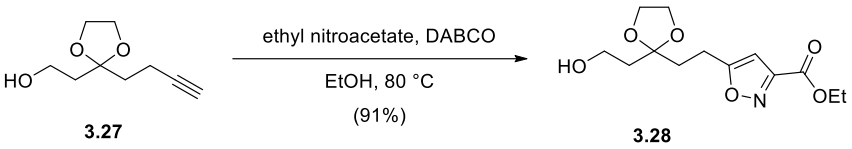
TLC (20% ethyl acetate in *n*-hexane): R_f: 0.23 (UV, CAM)

^{1}H NMR (800 MHz, $CDCl_3$) δ 6.98 (d, *J* = 2.8 Hz, 1H), 6.59 (t, *J* = 0.8 Hz, 1H), 6.48 (d, *J* = 2.7 Hz, 1H), 5.32 (dd, *J* = 7.8, 6.7 Hz, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 3.69 (ddd, *J* = 15.9, 6.7, 0.8 Hz, 1H), 3.57 – 3.50 (m, 1H), 1.42 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (201 MHz, $CDCl_3$) δ 186.7, 169.9, 159.9, 156.8, 131.6, 126.9, 104.3, 62.5, 40.6, 31.2, 14.3.

HRMS (ESI): calcd. for $C_{11}H_{12}{}^{79}Br_2NO_4$ $[M+H]^+$: 379.9128.; found: 379.9134.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2980, 1731, 1599, 1462, 1421, 1225, 1100, 1021, 941, 835, 780.



3.27 **3.28**

Synthesis of isoxazole **3.28**: To a solution of alcohol **3.27** (1.00 g, 5.88 mmol, 1 equiv) in ethanol (12 mL) was added DABCO (65.9 mg, 588 µmol, 10.0 mol%) and ethyl nitroacetate (1.43 mL, 12.9 mmol, 2.20 equiv). The resulting yellow solution was heated to 80 °C. After 3 d, the yellow reaction mixture was allowed to cool to 23 °C and was concentrated. The crude product was purified by flash column chromatography on silica gel (2% methanol in dichloromethane) to afford isoxazole **3.28** (1.53 g, 5.35 mmol, 91%) as a colorless oil.

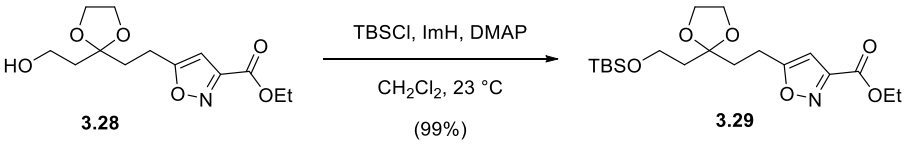
TLC (2% methanol in dichloromethane): R_f: 0.19 (UV, CAM)

^{1}H NMR (599 MHz, $CDCl_3$) δ 6.42 (t, *J* = 0.9 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.06 – 4.02 (m, 2H), 4.02 – 3.98 (m, 2H), 3.77 (q, *J* = 5.1 Hz, 2H), 2.95 – 2.81 (m, 2H), 2.54 (s, 1H), 2.17 – 2.07 (m, 2H), 1.97 – 1.88 (m, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 175.0, 160.3, 156.6, 111.0, 101.6, 65.2, 62.2, 58.8, 38.6, 34.7, 21.4, 14.3.

HRMS (ESI): calcd. for $C_{13}H_{20}O_6N$ $[M+H]^+$: 286.1285 ; found: 286.1289.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3440, 2959, 2889, 1729, 1593, 1460, 1425, 1390, 1367, 1212, 1132, 1102, 1023, 949, 897, 834, 779.



Synthesis of isoxazole **3.29**: To a solution of alcohol **3.28** (150 mg, 526 µmol, 1 equiv) in dichloromethane (3 mL)) was added imidazole (43.0 mg, 631 µmol, 1.2 equiv), DMAP (6.4 mg, 52.6 µmol, 10.0 mol%) and *tert*-butyldimethylsilyl chloride (83.2 mg, 552 µmol, 1.05 equiv) were added in sequence. After 16 h, the reaction mixture was diluted with dichloromethane (10 mL) and water (10 mL) to hydrolyze unreacted *tert*-butyldimethylsilyl chloride. The phases were seperated and the aqueous phase was extracted with dichloromethane (3×10 mL), the combined organic phases were dried over sodium sulfate, the dried solution was filtered and concentrated. The crude product flash column chromatography on silica gel (25% diethyl ether in petrol ether) to afford isoxazole **3.29** (208 mg, 522 mmol, 99%) as a colorless oil.

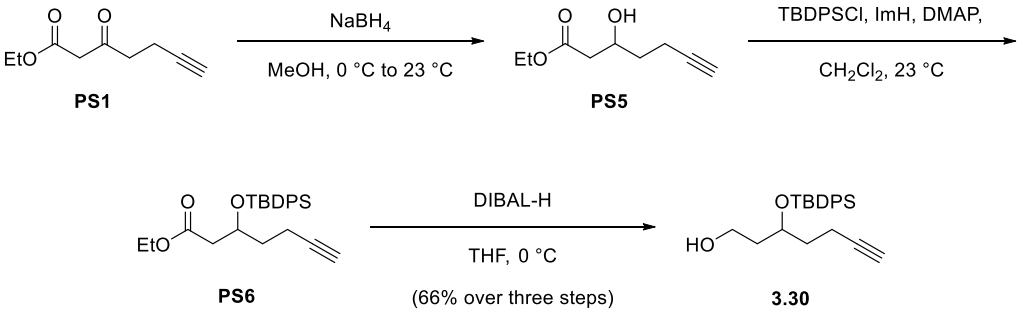
TLC (10% ethyl acetate in cyclohexane): R_f: 0.19 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (d, *J* = 1.0 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.94 (s, 4H), 3.72 (t, *J* = 6.6 Hz, 2H), 2.95 – 2.85 (m, 2H), 2.16 – 2.06 (m, 2H), 1.87 (t, *J* = 6.6 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 160.4, 156.5, 109.8, 101.4, 65.1, 62.1, 59.1, 40.0, 35.2, 26.0, 21.4, 18.4, 14.3, -5.3, -5.4.

HRMS (ESI): calcd. for $C_{19}H_{33}NNaO_6Si$ $[M+Na]^+$: 422.1969; found: 422.1948.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2955, 2930, 2884, 2857, 1732, 1594, 1463, 1425, 1390, 1362, 1251, 1213, 1160, 1098, 1056, 1025, 949, 836, 777.



Synthesis of alkyne **3.30**: To a solution of ketone **PS1** (500 mg, 2.97 mmol, 1 equiv) in methanol (14 mL) was added sodium borohydride (169 mg, 4.46 mmol, 1.50 equiv) at 0 °C and the reaction mixture was allowed to warm to 23 °C. After 30 min, the reaction mixture was diluted with diethyl

ether (20 mL) and sat aqueous ammonium chloride solution (20 mL) was added to quench excess of sodium borohydride. The organic phases were separated and the aqueous phase extracted with diethyl ether (3×30 mL). The combined organic phases were dried over sodium sulfate, the dried solution was filtered and concentrated. The alcohol **PS5** was pure enough to use without further purification.

To a solution of crude alcohol **PS5** (506 mg, 2.97 mmol, 1 equiv) in dichloromethane (14 mL) was added DMAP (36.3 mg, 297 µmol, 10.0 mol%), imidazole (303 mg, 4.46 mmol, 1.50 equiv) and *tert*-butyl(chloro)diphenylsilane (801 µL, 3.12 mmol, 1.05 equiv) in sequence and the resulting mixture was stirred at 23 °C. After 16 h, the mixture was diluted with water (50 mL) to hydrolyze unreacted *tert*-butyl(chloro)diphenylsilane and the aqueous phase was extracted with dichloromethane (3×50 mL). The combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a colorless oil. The crude ester **PS6** was used without further purification in the next step.

To a solution of ester **PS6** in dichloromethane (28 mL) was added a solution of diisobutyl aluminum hydride (1.00 M in toluene, 5.94 mL, 5.94 mmol, 2.00 equiv) at 0 °C. After 1 h, the reaction mixture was allowed to warm to 23 °C. Excess of hydride was quenched by the addition of ethyl acetate (50 mL) und saturated aqueous potassium sodium tartrate solution (50 mL) was added. After 2 h, phases were seperated, the aqueous phase was extracted with diethyl ether (3×30 mL). The combined organic phases 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 (10% diethyl ether in hexane) to afford alkyne **3.30** (720 mg, 2.00 mmol, 66% over three steps) as a colorless oil.

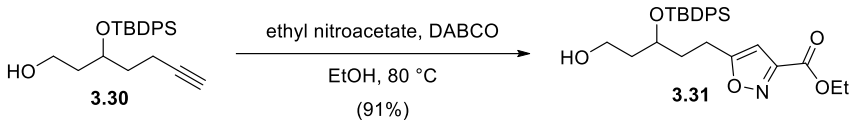
TLC (20% ethyl acetate in hexane): R_f: 0.30 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.63 (m, 4H), 7.49 – 7.34 (m, 6H), 4.11 – 4.00 (m, 1H), 3.68 (q, *J* = 8.8, 6.6 Hz, 1H), 3.62 (t, *J* = 5.2 Hz, 1H), 2.14 (tdd, *J* = 7.2, 2.7, 1.4 Hz, 2H), 1.83 (t, *J* = 2.7 Hz, 1H), 1.81 – 1.72 (m, 3H), 1.72 – 1.64 (m, 1H), 1.07 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.1, 136.1, 133.9, 133.9, 130.0, 130.0, 127.8, 127.8, 84.0, 70.8, 68.5, 59.7, 38.1, 35.3, 27.2, 19.5, 14.5.

HRMS (ESI): calcd. for $C_{13}H_{20}O_6N$ $[M+H]^+$: 286.1285 ; found: 286.1289.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3305, 2931, 2889, 2857, 1472, 1463, 1427, 1390, 1362, 1259, 1189, 1158, 1104, 1090, 1027, 1006, 997, 937, 909, 821, 739, 696.



Synthesis of isoxazole **3.31**: To a solution of diol alkyne **3.30** (324 mg, 884 µmol, 1 equiv) in ethanol (3.0 mL) was added DABCO (9.90 mg, 88.4 µmol, 10.0 mol%) and ethyl nitroacetate (196 µL, 1.77 mmol, 2.00 equiv) and the resulting yellow solution was heated to 80 °C. After 2 d, the reaction mixture was allowed to cool to 23 °C and the solution was concentrated. The crude product was purified by flash column chromatography on silica gel (1% methanol in dichloromethane) to afford isoxazole **3.31** (388 mg, 806 µmol, 91%) as a pale yellow oil.

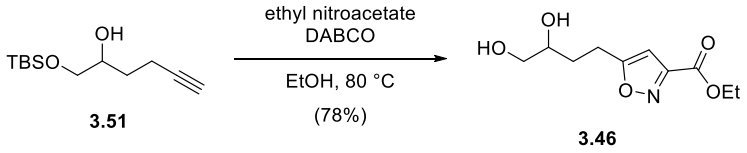
TLC (1% methanol in dichloromethane): R_f: 0.27 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.56 (m, 4H), 7.42 – 7.27 (m, 6H), 6.08 (d, *J* = 0.9 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.94 (p, *J* = 5.6 Hz, 1H), 3.61 (dp, *J* = 15.7, 5.5 Hz, 2H), 2.75 – 2.58 (m, 2H), 1.92 – 1.60 (m, 4H), 1.42 (s, 1H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.00 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 160.3, 156.4, 136.0, 136.0, 133.8, 133.6, 130.1, 130.1, 127.9, 127.9, 101.5, 70.4, 62.2, 59.6, 38.3, 34.2, 27.2, 22.4, 19.5, 14.3.

HRMS (EI): calcd. for $C_{27}H_{36}NO_5Si$ $[M+H]^+$: 482.2357; found: 482.2364.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3478, 2932, 2858, 1797, 1732, 1591, 1462, 1427, 1390, 1212, 1104, 1023, 822, 779, 741, 703, 612.



Synthesis of isoxazole **3.46**: To a solution of alkyne **3.51** (100 mg, 441 µmol, 1 equiv) in ethanol (1.0 mL) was added DABCO (4.95 mg, 44.2 µmol, 10.0 mol%) and ethyl nitroacetate (98.1 µL, 883 µmol, 2.00 equiv) and the resulting yellow solution was heated to 80 °C. After 2 d, the reaction mixture was allowed to cool to 23 °C and the solution was concentrated. The crude product was purified by flash column chromatography silica gel (4% methanol in dichloromethane) to afford isoxazole **3.46** (78.9 mg, 344 µmol, 78%) as a colorless oil.

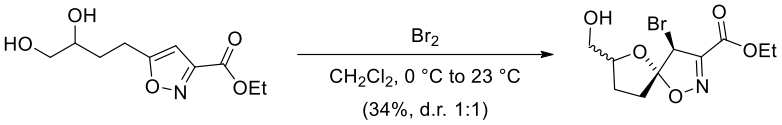
TLC (40% ethyl acetate in cyclohexane): R_f: 0.07 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 – 6.31 (m, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.77 – 3.68 (m, 1H), 3.65 (dd, *J* = 11.1, 3.1 Hz, 1H), 3.47 (dd, *J* = 11.1, 7.3 Hz, 1H), 3.07 – 2.83 (m, 4H), 1.88 – 1.75 (m, 2H), 1.38 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.17, 160.3, 156.5, 101.9, 70.9, 66.6, 62.3, 30.6, 23.1, 14.2.

HRMS (ESI): calcd. for $C_{10}H_{16}O_5N$ $[M+H]^+$: 230.1023; found: 230.1025.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3410, 2936, 1733, 1593, 1462, 1213, 1100, 1023, 835, 780.



3.46 **3.47**

Synthesis of spiro **3.47**: To a solution of alcohol **3.46** (100 mg, 436 µmol, 1 equiv) in dichloromethane (4.4 mL) was added bromine (112 µL, 2.18 mmol, 5.00 equiv) at 0 °C. The resulting brown solution was slowly allowed to warm to 23 °C. After 16 h, excess of bromine was quenched with saturated aqueous thiosulfate solution (15 mL) and the phases were separated. The aqueous phase was extracted with dichloromethane (3×5 mL), the combined phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a yellow solid. The crude product was purified by flash column chromatography silica gel (3% methanol in dichloromethane) to afford a mixture of diastereomers of spiro **3.47** (34.2 mg, 149 µmol, 34%, d.r. 1:1) as pale yellow oil.

A small sample was purified by HPLC chromatography (40% ethyl acetate in *n*-hexane grading to 50% ethyl acetate in *n*-hexane in 30 min) to isolate two diastereomers as a colorless oil.

less polar diastereomer

TLC (3% methanol in dichloromethane): R_f: 0.14 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (s, 1H), 4.52 (dddd, *J* = 8.2, 6.0, 5.2, 3.1 Hz, 1H), 4.46 – 4.34 (m, 2H), 3.75 (dd, *J* = 12.0, 3.1 Hz, 1H), 3.58 (dd, *J* = 12.0, 5.2 Hz, 1H), 2.60 (ddd, *J* = 14.1, 10.3, 8.6 Hz, 1H), 2.49 (ddd, *J* = 14.1, 8.6, 4.3 Hz, 1H), 2.28 (dq, *J* = 12.6, 8.5 Hz, 1H), 1.94 (dddd, *J* = 12.6, 10.4, 6.0, 4.3 Hz, 1H), 1.62 (s, 1H), 1.39 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 153.3, 120.0, 82.9, 64.6, 62.7, 47.2, 33.0, 25.3, 14.2.

HRMS (ESI): calcd. for $C_{10}H_{15}{}^{79}BrNO_5$ $[M+H]^+$: 308.0128; found: 308.0130.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3433, 2937, 1727, 1569, 1462, 1406, 1381, 1329, 1256, 1212, 1179, 1114, 1066, 1015, 919, 782, 757.

more polar diastereomer

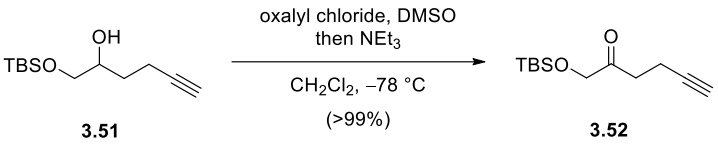
TLC (3% methanol in dichloromethane): R_f: 0.14 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (s, 1H), 4.56 – 4.48 (m, 1H), 4.46 – 4.35 (m, 2H), 3.73 (dd, *J* = 12.2, 2.9 Hz, 1H), 3.58 (dd, *J* = 12.2, 5.3 Hz, 1H), 2.65 – 2.45 (m, 2H), 2.26 – 2.04 (m, 2H), 2.00 – 1.85 (m, 1H), 1.39 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 153.0, 119.7, 84.7, 65.0, 62.7, 47.0, 34.7, 25.1, 14.2.

HRMS (ESI): calcd. for $C_{10}H_{15}{}^{79}BrNO_5$ $[M+H]^+$: 308.0128; found: 308.0130.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3457, 2983, 2937, 1727, 1569, 1458, 1405, 1381, 1328, 1258, 1210, 1174, 1121, 1096, 1068, 1016, 969, 921, 903, 840, 783, 759, 728.



3.51 **3.52**

Synthesis of ketone **3.52**: To a solution of oxalyl chloride (3.00 mL, 6.00 mmol, 3.00 equiv) in dichloromethane (9.0 mL) was added a solution of dimethyl sulfoxide (1.00 M in dichloromethane, 10.0 mL, 10.0 mmol, 5.00 equiv) at −78 °C. After 15 min, a solution of alcohol **3.51** (1.00 M in dichloromethane, 2.00 mL, 2.00 mmol, 1 equiv) was added dropwise and the resulting solution was stirred at −78 °C. After further 30 min, triethylamine (2.78 mL, 20.0 mmol, 10.0 equiv) was added at −78 °C and the temperature was kept for 15 min before the reaction mixture was slowly allowed to warm to 23 °C. After 1 h, the mixture was diluted with puffer-solution (pH = 7). The phases were separated and the aqueous solution was extracted with diethyl ether (3×40 mL). The combined organic phases 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 (10% diethyl ether in *n*-hexane) to afford ketone **3.52** (453 mg, 2.00 mmol, >99%) as a yellow oil.

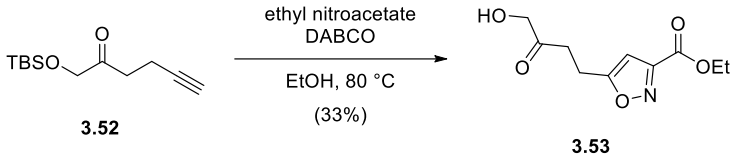
TLC (10% ethyl acetate in cyclohexane): R_f: 0.63 ($KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (s, 2H), 2.77 (dd, *J* = 7.6, 6.9 Hz, 2H), 2.56 – 2.37 (m, 2H), 1.94 (t, *J* = 2.7 Hz, 1H), 0.93 (s, 9H), 0.09 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.1, 83.2, 69.5, 68.8, 37.6, 25.9, 18.4, 12.7, -5.4.

HRMS (EI): calcd. for $C_8H_{13}O_2Si$ $[M\text{-}t\text{-}Bu]^{-+}$: 169.0679; found: 169.0678.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3313, 2954, 2930, 2888, 2858, 1723, 1472, 1464, 1434, 1406, 1390, 1362, 1254, 1157, 1103, 1081, 1006, 939, 835, 816, 777, 736, 669.



3.52 **3.53**

Synthesis of isoxazole **3.53**: To a solution of diol **3.52** (100 mg, 442 µmol, 1 equiv) in ethanol (1.0 mL) was added DABCO (4.95 mg, 44.2 µmol, 10.0 mol%) and ethyl nitroacetate (98.1 µL, 883 µmol, 2.00 equiv) and the resulting yellow solution was heated to 80 °C. After 2 d, the reaction mixture was allowed to cool to 23 °C and the solution was concentrated. The crude product was purified by flash column chromatography on silica gel (1% methanol in dichloromethane) to afford isoxazole **3.53** (33.3 mg, 147 µmol, 33%) as a pale yellow oil.

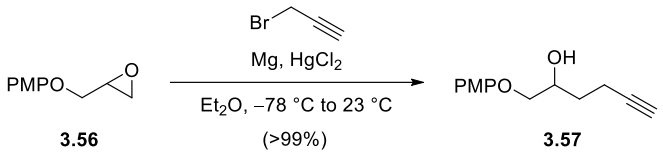
TLC (50% ethyl acetate in cyclohexane): R_f: 0.21 (UV, CAM)

^{1}H NMR (599 MHz, $CDCl_3$) δ 6.44 (t, *J* = 0.9 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.28 (t, *J* = 0.8 Hz, 2H), 3.17 (td, *J* = 7.2, 0.9 Hz, 2H), 2.87 (tt, *J* = 7.3, 0.8 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 207.2, 173.2, 160.0, 156.7, 102.3, 68.3, 62.3, 35.5, 20.5, 14.2.

HRMS (EI): calcd. for $C_8H_{11}NO_3$ $[M\text{-}HOCH_2C(O)]^{-+}$: 169.0733; found: 169.0732.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3451, 339, 2985, 2915, 1724, 1594, 1461, 1425, 1391, 1367, 1211, 1103, 1070, 1019, 933, 860, 835, 780.



Synthesis of alkyne **3.57**: To a suspension of magnesium turnings (1.08 g, 44.4 mmol, 8.00 equiv) and mercury chloride (90.4 mg, 333 µmol, 6.00 mol%) in diethyl ether (30 mL) was added one grain of iodine. The orange solution was stirred for 30 min at 23 °C, before a solution of propargyl bromide (80%wt in toluene, 1.67 mL, 19.4 mmol, 3.50 equiv) in diethyl ether (13.0 mL) was added dropwise over 30 min. The exothermic reaction was particularly cooled with an ice bath. After complete addition, the reaction mixture was stirred for 1 h at 23 °C, before the black reaction mixture was added dropwise to a solution of epoxide **3.56** (1.00 g, 5.55 mmol, 1 equiv) in diethyl ether (100 mL) at −78 °C over 1 h. After complete addition, the grey suspension was slowly allowed to warm to 23 °C. After 3 h, ethyl acetate (50 mL) was added to quench excess of the Grignard reagent at 0 °C and saturated aqueous ammonium chloride solution was added (100 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3×40 mL). The combined organic phases were dried over sodium sulfate and the filtrate was concentrated to give a yellow oil. The crude product was purified by flash column chromatography on silica gel (30% ethyl acetate in *n*-hexane) to afford alkyne **3.57** (1.22 g, 5.55 mmol, >99%) as a colorless solid.

TLC (20% ethyl acetate in hexane): R_f: 0.08 (UV, CAM)

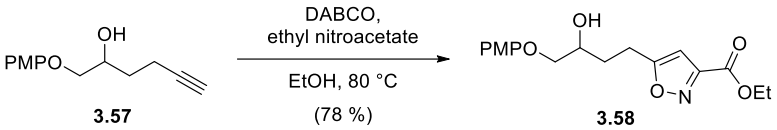
mp: 82.5 – 83.2 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 – 6.73 (m, 4H), 4.14 (dddd, *J* = 9.8, 5.8, 2.7, 0.9 Hz, 1H), 3.96 (dd, *J* = 9.3, 3.3 Hz, 1H), 3.82 (dd, *J* = 9.3, 7.2 Hz, 1H), 3.77 (s, 3H), 2.47 – 2.37 (m, 3H), 1.99 (t, *J* = 2.7 Hz, 1H), 1.79 (td, *J* = 7.4, 5.9 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 152.8, 115.7, 114.8, 83.9, 72.8, 69.1, 69.0, 55.9, 31.9, 14.9.

HRMS (EI): calcd. for $C_{13}H_{16}O_3$ $[M]^{\cdot+}$: 220.1094; found: 220.1093.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3418, 3290, 2937, 1515, 1455, 1338, 1290, 1243, 1179, 1105, 1043, 878, 826, 745, 628.



3.57 **3.58**

Synthesis of isoxazole **3.58**: To a solution of alkyne **3.57** (250 mg, 1.13 mmol, 1 equiv) in ethanol (2.0 mL) was added DABCO (12.7 mg, 113 µmol, 10.0 mol%) and ethyl nitroacetate (139 µL, 1.25 mmol, 1.10 equiv) and the resulting yellow solution was heated to 80 °C. After 4 d, the reaction mixture was allowed to cool to 23 °C and the solution was concentrated. The crude product was purified by flash column chromatography on silica gel (30% ethyl acetate in hexane) to afford isoxazole **3.58** (299 mg, 881 µmol, 78%) as a colorless solid.

TLC (20% ethyl acetate in cyclohexane): R_f: 0.08 (UV, CAM)

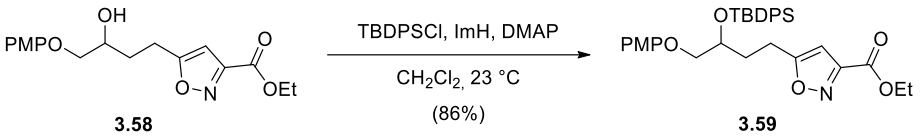
mp: 61.4 – 64.2 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 4H), 6.46 (t, *J* = 0.8 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 4.05 – 3.94 (m, 1H), 3.93 (dd, *J* = 9.3, 3.3 Hz, 1H), 3.81 (dd, *J* = 9.3, 7.1 Hz, 1H), 3.76 (s, 3H), 3.15 – 2.92 (m, 2H), 2.50 (d, *J* = 4.0 Hz, 1H), 1.96 (tdd, *J* = 8.6, 5.2, 3.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 160.3, 156.6, 154.4, 152.6, 115.7, 114.9, 102.0, 72.7, 69.1, 62.2, 55.9, 30.8, 23.0, 14.3.

HRMS (ESI): calcd. for $C_{17}H_{25}N_2O_6$ $[M+NH_4]^+$: 353.1707; found: 353.1707.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3451, 3137, 2934, 2836, 1732, 1593, 1508, 1462, 1390, 1230, 1182, 1105, 1030, 928, 826, 780, 748.



3.58 **3.59**

Synthesis of isoxazole **3.59**: To a solution of alcohol **3.58** (150 mg, 447 µmol, 1 equiv) in dichloromethane (1 mL) was added DMAP (5.46 mg, 44.7 µmol, 10 mol%), imidazole (45.7 mg, 671 µmol, 1.50 equiv) and *tert*-butyl(chloro)diphenylsilane (174 µL, 671 µmol, 1.50 equiv) in sequence and the resulting mixture was stirred at 23 °C. After 16 h, the reaction mixture was diluted with water (5 mL) to hydrolyze unreacted *tert*-butyl(chloro)diphenylsilane. The aqueous phase was extracted with dichloromethane (3×5 mL), the combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a colorless oil. The

crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in *n*-hexane) to afford isoxazole **3.59** (222 mg, 386 µmol, 86%) as a colorless oil.

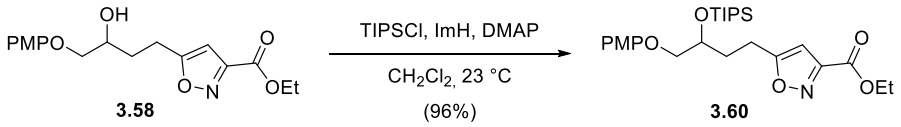
TLC (10% ethyl acetate in *n*-hexane): R_f: 0.14 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.62 (m, 4H), 7.49 – 7.29 (m, 6H), 6.78 – 6.69 (m, 2H), 6.61 – 6.53 (m, 2H), 6.24 (s, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.08 (p, *J* = 5.6 Hz, 1H), 3.84 (dd, *J* = 9.6, 5.1 Hz, 1H), 3.75 (m, 4H), 2.89 (hept, *J* = 7.9 Hz, 2H), 2.08 – 1.96 (m, 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.08 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 175.3, 160.3, 156.4, 154.0, 152.6, 136.0, 133.8, 133.5, 130.1, 129.9, 128.0, 127.8, 115.3, 114.7, 101.6, 71.1, 70.4, 62.2, 55.9, 32.0, 27.2, 22.3, 19.5, 14.3.

HRMS (ESI): calcd. for $C_{33}H_{43}O_6N_2Si$ $[M+NH_4]^+$: 591.2885; found: 591.2883.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3136, 3071, 3048, 2932, 2858, 1730, 1592, 1507, 1462, 1428, 1390, 1363, 1303, 1230, 1210, 1181, 1030, 997, 934, 822, 778, 740, 701, 689.



Synthesis of isoxazole **3.61**: To a solution of alcohol **3.58** (70.0 mg, 209 µmol, 1 equiv) in dichloromethane (420 µL) was added DMAP (2.55 mg, 20.9 µmol, 10.0 mol%), imidazole (21.3 mg, 313 µmol, 1.50 equiv) and *triiso*-propylsilyl chloride (53.5 µL, 250 µmol, 1.20 equiv) in sequence and the resulting mixture was stirred at 23 °C. After 16 h, the mixture was diluted with water (5 mL) to hydrolyze unreacted *triiso*-propylsilyl chloride and the aqueous phase was extracted with dichloromethane (3×5 mL) and the combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a colorless oil. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in *n*-hexane) to afford isoxazole **3.60** (98.5 mg, 200 µmol, 96%) as a colorless oil.

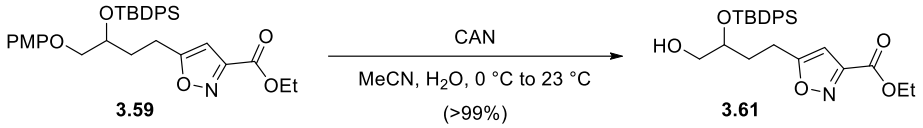
TLC (15% ethyl acetate in *n*-hexane): R_f: 0.34 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 – 6.77 (m, 4H), 6.43 (s, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.27 (t, *J* = 5.6 Hz, 1H), 3.94 (dd, *J* = 9.3, 5.3 Hz, 1H), 3.77 (s, 4H), 2.98 (dt, *J* = 8.5, 6.4 Hz, 2H), 2.16 – 2.02 (m, 2H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.07 (d, *J* = 5.3 Hz, 21H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 175.6, 160.3, 156.5, 154.1, 152.8, 115.4, 114.8, 101.6, 71.6, 69.8, 62.2, 55.9, 32.5, 21.9, 18.3, 14.3, 12.7.

HRMS (EI): calcd. for $C_{26}H_{41}NO_6Si$ $[M]^{\cdot+}$:491.2698; found: 491.2691.

IR (ATR, neat) $\tilde{\nu}_{max}$:2942, 2866, 1731, 1594, 1508, 1462, 1389, 1366, 1302, 1230, 1211, 1181, 1125, 1105, 1036, 1014, 921, 883, 824, 778, 736, 680.



Synthesis of alcohol **3.61**: To a solution of isoxazole **3.59** (19.0 mg, 33.1 µmol, 1 equiv) in acetonitrile (800 µL) and water (200 µL) was added ammonium cerium(IV) nitrate (39.9 mg, 72.9 µmol, 2.20 equiv) in one portion at 0 °C and the resulting orange mixture was slowly allowed to warm to 23 °C. After 1 h, the reaction mixture was diluted with diethyl ether (10 mL) and water (10 mL) and the phases were separated and the aqueous phase was extracted with diethyl ether (3×5 mL). The combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a yellow oil. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexane) to afford alcohol **3.61** (15.6 mg, 33.1 µmol, >99%) as a yellow oil.

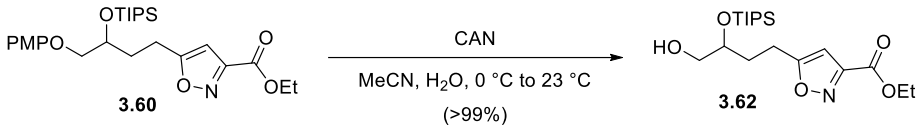
TLC (20% ethyl acetate in cyclohexane): R_f: 0.13 (UV, CAM)

^{1}H NMR (599 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 4H), 7.48 – 7.41 (m, 2H), 7.42 – 7.36 (m, 4H), 6.18 (d, *J* = 0.9 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 3.86 – 3.79 (m, 1H), 3.61 – 3.47 (m, 2H), 2.82 – 2.70 (m, 2H), 1.97 – 1.82 (m, 2H), 1.70 (dd, *J* = 7.0, 5.7 Hz, 1H), 1.41 (t, *J* = 7.2 Hz, 3H), 1.08 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 175.0, 160.3, 156.4, 135.9, 135.8, 133.7, 133.3, 130.2, 130.2, 128.0, 101.5, 72.8, 65.8, 62.2, 31.3, 27.2, 22.6, 19.5, 14.3.

HRMS (ESI): calcd. for $C_{26}H_{34}NO_5Si$ $[M+H]^+$: 468.2201; found: 468.2210.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3459, 3072, 3050, 2931, 2893, 2858, 1732, 1591, 1472, 1462, 1428, 1390, 1363, 1303, 1244, 1212, 1160, 1105, 1055, 1023, 998, 937, 862, 822, 779, 741, 702.



Synthesis of alcohol **3.62**: To a solution of isoxazole (15.0 mg, 30.5 µmol, 1 equiv) in acetonitrile (800 µL) and water (200 µL) was added ammonium cerium(IV) nitrate (36.8 mg, 67.1 µmol, 2.20 equiv) in one portion at 0 °C and the resulting orange mixture was slowly allowed to warm to 23 °C. After 1 h, the mixture was diluted with diethyl ether (10 mL) and water (10 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3×5 mL). The combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a yellow oil. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in *n*-hexane) to afford alcohol **3.62** (14.9 mg, 30.5 µmol, >99%) as a yellow oil.

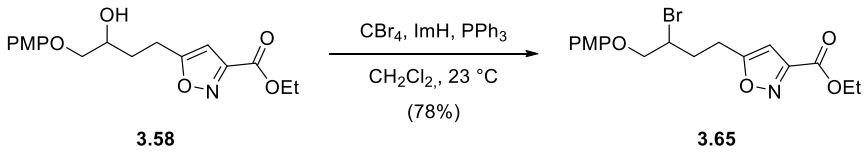
TLC (20% ethyl acetate in cyclohexane): R_f: 0.31 (UV, CAM)

^{1}H NMR (599 MHz, $CDCl_3$) δ 6.42 (d, *J* = 0.8 Hz, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 3.98 (dt, *J* = 6.3, 4.5 Hz, 1H), 3.67 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.59 (dd, *J* = 11.2, 3.9 Hz, 1H), 2.90 (dq, *J* = 15.8, 9.5 Hz, 2H), 2.06 (ddt, *J* = 12.9, 9.9, 6.4 Hz, 1H), 1.99 (dtd, *J* = 15.4, 5.8, 5.0, 3.5 Hz, 1H), 1.81 (s, 1H), 1.41 (td, *J* = 7.3, 2.0 Hz, 3H), 1.27 – 0.99 (m, 21H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 175.2, 160.3, 156.5, 101.6, 71.6, 65.5, 62.2, 31.7, 22.5, 18.2, 14.3, 12.6.

HRMS (ESI): calcd. for $C_{19}H_{36}NO_5Si$ $[M+H]^+$: 386.2357; found: 386.2351.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3475, 2925, 2857, 1732, 1595, 1461, 1380, 1245, 1214, 1091, 1017, 891, 780.



Synthesis of bromide **3.65**: To a solution of alcohol **3.65** (50.0 mg, 149 µmol, 1 equiv) in dichloromethane (1.0 mL) was added imidazole (13.2 mg, 194 µmol, 1.30 equiv), triphenylphosine (43.0 mg, 164 µmol, 1.10 equiv) and carbon tetrabromide (59.3 mg, 179 µmol, 1.20 equiv) at 0 °C and the resulting reaction mixture was allowed to warm to 23 °C. After 3 h, a saturated aqueous solution of thiosulfate (5 mL) was added to quench unreacted triphenylphosphine and the aqueous phase was extracted with dichloromethane (3×5 mL). The combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a pale

yellow oil. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexane) to afford bromide **3.65** (46.2 mg, 116 µmol, 78%) as a colorless oil.

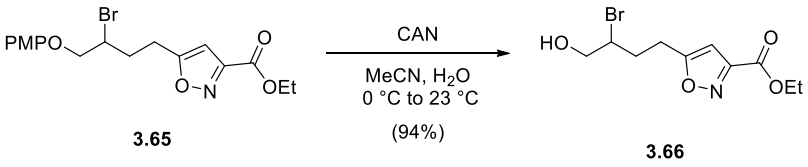
TLC (25% ethyl acetate in cyclohexane): R_f: 0.35 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 4H), 6.48 (s, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 4.31 – 4.20 (m, 1H), 4.24 – 4.13 (m, 1H), 4.15 – 4.04 (m, 1H), 3.77 (s, 3H), 3.16 (ddd, *J* = 14.9, 9.0, 5.1 Hz, 1H), 3.04 (ddd, *J* = 15.8, 9.0, 7.1 Hz, 1H), 2.54 (dddd, *J* = 14.6, 9.0, 7.1, 3.2 Hz, 1H), 2.24 (dtd, *J* = 14.5, 9.2, 5.1 Hz, 1H), 1.41 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 160.2, 156.6, 154.7, 152.2, 116.1, 114.9, 102.3, 72.6, 62.3, 55.9, 50.0, 33.0, 24.9, 14.3.

HRMS (EI): calcd. for $C_{17}H_{20}O_5N^{79}Br$ $[M]^{\cdot+}$: 397.0519; found: 397.0506.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2925, 2853, 1731, 1654, 1594, 1507, 1461, 1389, 1287, 1228, 1106, 1025, 928, 826, 780, 752.



Synthesis of alcohol **3.66**: To a solution of bromide **3.65** (48.5 mg, 122 µmol, 1 equiv) in acetonitrile (800 µL) and water (200 µL) was added ammonium cerium(IV) nitrate (147 mg, 268 µmol, 2.20 equiv) at 0 °C. After 20 min, the orange solution was allowed to warm to 23 °C. After 2 h, the solution was diluted with diethyl ether (10 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3×5 mL) and the combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a yellow oil. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in *n*-hexane) to afford alcohol **3.66** (33.4 mg, 114 µmol, 94%) as a yellow oil.

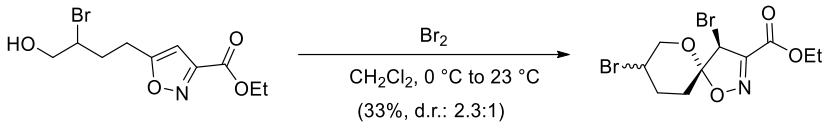
TLC (40% ethyl acetate in cyclohexane): R_f: 0.32 (UV, CAM)

^{1}H NMR (599 MHz, $CDCl_3$) δ 6.60 – 6.31 (s, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.17 – 3.96 (m, 1H), 3.84 (t, *J* = 5.0 Hz, 2H), 3.12 (ddd, *J* = 15.7, 8.8, 5.1 Hz, 1H), 3.01 (dt, *J* = 15.9, 8.1 Hz, 1H), 2.33 (dddd, *J* = 14.4, 8.6, 7.3, 3.6 Hz, 1H), 2.21 (dtd, *J* = 18.6, 9.0, 4.5 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.6, 160.1, 156.6, 102.4, 67.1, 62.3, 56.9, 32.5, 25.0, 14.3.

HRMS (EI): calcd. for $C_{10}H_{14}O_4N^{79}Br$ $[M]^{+}$: 291.0106; found: 291.0097.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3434, 3138, 2934, 1731, 1594, 1462, 1428, 1390, 1366, 1213, 1103, 1021, 933, 860, 835, 780.



3.66 **3.67**

Synthesis of spiro **3.67**: To a solution of alcohol **3.66** (100 mg, 342 µmol, 1 equiv) in dichloromethane (4.4 mL) was added bromine (112 µL, 2.18 mmol, 5.00 equiv) at 0 °C. The resulting brown solution was slowly allowed to warm to 23 °C. After 16 h, excess of bromine was quenched by the addition of saturated aqueous thiosulfate solution (15 mL) and the phases were separated and the aqueous phase was extracted with dichloromethane (3×5mL). The combined phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a yellow solid. The crude product was purified by flash column chromatography on silica gel (3% methanol in dichloromethane) to afford spiro **3.67** (42.5 mg, 115 µmol, 34%, d.r. 2.3:1) as pale yellow oil.

An analytical sample was purified by HPLC chromatography (40% ethyl acetate in *n*-hexane grading to 50% ethyl acetate in *n*-hexane in 30 min) to isolate both diastereomers.

less polar diastereomer

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

^{1}H NMR (599 MHz, $CDCl_3$) δ 4.87 (d, *J* = 0.5 Hz, 1H), 4.49 – 4.29 (m, 2H), 4.16 – 3.98 (m, 2H), 3.92 – 3.80 (m, 1H), 2.43 (dddd, *J* = 14.0, 12.2, 4.1, 2.4 Hz, 2H), 2.38 – 2.30 (m, 1H), 2.12 – 2.03 (m, 1H), 1.40 (td, *J* = 7.2, 0.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 158.7, 154.0, 108.8, 67.9, 62.9, 50.4, 42.4, 32.2, 31.1, 14.2.

HRMS (EI): calcd. for $C_{10}H_{12}{}^{79}BrNO_4$ $[M\text{-}Br]^+$: 290.0022; found: 289.9813.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2983, 2938, 2869, 1730, 1578, 1440, 1405, 1380, 1369, 1349, 1334, 1311, 1286, 1248, 1224, 1182, 1126, 1110, 1100, 1060, 1016, 1002, 956, 918, 882, 860, 841, 798, 775, 732, 701.

more polar diastereomer

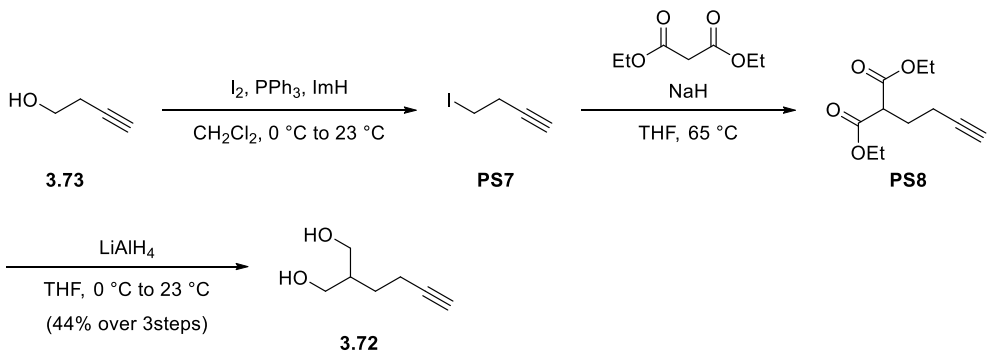
TLC (10% ethyl acetate in cyclohexane): R_f: 0.25 (UV, CAM)

^{1}H NMR (599 MHz, $CDCl_3$) δ 5.01 (s, 1H), 4.44 – 4.33 (m, 4H), 3.90 – 3.73 (m, 1H), 2.59 – 2.34 (m, 2H), 2.34 – 2.05 (m, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 158.7, 154.3, 109.6, 68.8, 62.8, 50.5, 46.4, 29.0, 25.4, 14.2.

HRMS (EI): calcd. for $C_{10}H_{12}{}^{79}BrNO_4$ $[M\text{-}Br]^+$: 290.0022; found: 289.9813.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2983, 2938, 2869, 1730, 1578, 1440, 1405, 1380, 1369, 1349, 1334, 1311, 1286, 1248, 1224, 1182, 1126, 1110, 1100, 1060, 1016, 1002, 956, 918, 882, 860, 841, 798, 775, 732, 701.



Synthesis of diol **3.72**: To a solution of alcohol **3.73** (1.75 g, 25.0 mmol, 1 equiv), imidazole (2.04 g, 30.0 mmol, 1.20 equiv) and triphenylphosphine (7.21 g, 27.5 mmol, 1.10 equiv) in dichloromethane (40 mL) was added iodine (8.25 g, 32.5 mmol, 1.30 equiv) at 0 °C. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 1 h, the reaction mixture was diluted with pentane (200 mL) and excess of iodine was quenched by the addition of saturated aqueous thiosulfate solution and the organic phase was washed with water (2×100 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 residue was dissolved in dichloromethane (1 mL), filtered over a plug of silica, washed with pentane (2×40 mL) and the filtrate was concentrated to iodide **PS7** as give a colorless oil, which was pure enough to use without further purification.

To a suspension of diethylmalonate (4.22 mL, 27.5 mmol, 1.10 equiv) and sodium hydride (60% in mineral oil, 1.10 g, 27.5 mmol, 1.10 equiv) in tetrahydrofuran (65 mL) was added a solution of iodide **PS7** in tetrahydrofuran (25 mL). The reaction mixture was heat to 65 °C. After 16 h, the

reaction mixture was allowed to cool to 23 °C and diluted with diethyl ether (100 mL). Excess of base was quenched by saturated aqueous solution of ammonium chloride (200 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3×100 mL), the combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a pale yellow oil, which was used without further purification.

To a suspension of lithium aluminum hydride (7.58 g, 200 mmol, 8.00 equiv) in tetrahydrofuran (200 mL) was added dropwise a solution of crude alkyne **PS8** in tetrahydrofuran (25 mL) at 0 °C. After 2 h, excess of lithium aluminum hydride was quenched carefully by dropwise addition of ethyl acetate (200 mL) at 0 °C and saturated aqueous sodium potassium tartrate solution (100 mL) was added. After phase separation (approximately 8 h), the phases were separated and the aqueous phase was extracted with ethyl acetate (3×200 mL) and the combined organic phases were washed 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 to give a pale yellow oil. The crude product was purified by flash column chromatography on silica gel (7% methanol in dichloromethane) to afford diol **3.72** (1.41 g, 11.0 mmol, 44% over 3 steps) as a pale yellow oil.

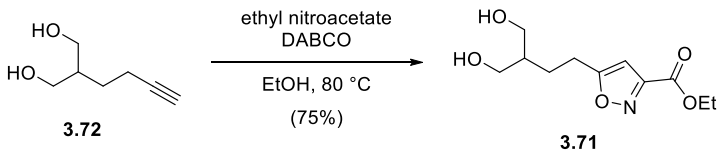
TLC (7% methanol in dichloromethane): R_f: 0.23 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (dd, *J* = 10.9, 4.0 Hz, 2H), 3.62 (dd, *J* = 10.8, 6.8 Hz, 2H), 3.43 (s, 2H), 2.24 (td, *J* = 7.2, 2.6 Hz, 2H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.85 (ddp, *J* = 10.2, 6.9, 3.5 Hz, 1H), 1.51 (q, *J* = 7.1 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 84.1, 69.0, 64.7, 41.0, 26.5, 16.3.

HRMS (ESI): calcd. for $C_7H_{12}NaO_2$ $[M+Na]^+$: 151.0730; found: 151.0729.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3301, 2937, 2884, 1430, 1051, 983, 940.



Synthesis of isoxazole **3.71**: To a solution of diol **3.72** (1.00 g, 7.81 mmol, 1 equiv) in ethanol (13 mL) was added DABCO (87.6 mg, 781 µmol, 10.0 mol%) and ethyl nitroacetate (2.43 mL, 21.9 mmol, 2.80 equiv) and the resulting yellow solution was heat to 80 °C. After 3 d, the reaction mixture was allowed to cool to 23 °C and the solution was concentrated. The crude product was

purified by flash column chromatography on silica gel (5% methanol in dichloromethane) to yield isoxazole **3.71** (1.43 g, 5.88 mmol, 75%) as a colorless solid.

Crystals were good enough for X-Ray analysis

TLC (4% methanol in dichloromethane): R_f: 0.14 (UV, CAM)

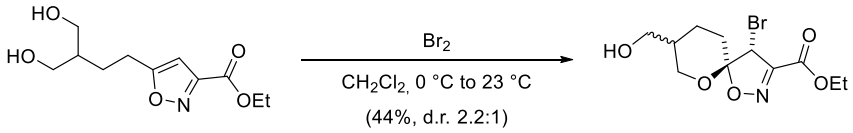
mp: 64.1 – 64.4 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (s, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 3.83 (dd, *J* = 10.6, 3.2 Hz, 2H), 3.71 (dd, *J* = 10.7, 5.6 Hz, 2H), 2.93 – 2.84 (m, 2H), 1.77 (t, *J* = 6.4 Hz, 3H), 1.40 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 175.2, 160.3, 156.5, 101.8, 65.4, 62.3, 41.3, 25.6, 24.6, 14.3.

HRMS (ESI): calcd. for $C_{11}H_{18}NO_5$ $[M+H]^+$: 244.1179; found: 244.1181.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3881, 2933, 2884, 1731, 1592, 1462, 1427, 1391, 1366, 1462, 1427, 1391, 1366, 1300, 1210, 1102, 1022, 1103, 1022, 931, 860, 834.



3.71 **3.72**

Synthesis of spiro **3.72**: To a solution of diol **3.71** (100 mg, 441 µmol, 1 equiv) in dichloromethane (400 µL) was added a solution of bromine (1.00 M in dichloromethane, 4.11 mL, 4.11 mmol, 10.0 equiv) dropwise at 0 °C. The resulting red-brown solution was stirred for 1 h at 0 °C, before it was allowed to warm to 23 °C. After 6 h, excess of bromine was quenched by the addition of saturated aqueous thiosulfate solution (5 mL). The phases were separated and the aqueous solution was extracted with dichloromethane (3×10 mL). The combined organic phases were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (2% methanol in dichloromethane) to afford spiro **3.72** (58.6 mg, 182 µmol, 44%, d.r. 2.2:1) as a colorless oil.

An analytical sample was purified by HPLC chromatography (40% ethyl acetate in *n*-hexane grading to 50% ethyl acetate in *n*-hexane in 30 min) to isolate both diasteromers.

less polar diastereomer

TLC (3% methanol in dichloromethane): R_f: 0.17 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (s, 1H), 4.40 (qd, *J* = 7.1, 3.7 Hz, 2H), 3.86 (ddd, *J* = 11.3, 4.9, 1.9 Hz, 1H), 3.77 (t, *J* = 11.3 Hz, 1H), 3.59 (dd, *J* = 10.7, 5.5 Hz, 1H), 3.51 (dd, *J* = 10.7, 7.3 Hz, 1H), 2.42 – 2.29 (m, 1H), 2.02 – 1.84 (m, 3H), 1.74 – 1.59 (m, 1H), 1.39 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 153.9, 110.1, 66.7, 64.4, 62.7, 50.8, 37.2, 29.9, 23.0, 14.2.

HRMS (ESI): calcd. for $C_{11}H_{17}BrNO_5$ $[M+H]^+$: 322.0285; found: 322.0287.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3436, 2936, 1729, 1575, 1467, 1450, 1380, 1349, 1334, 1250, 1226, 1124, 1079, 1054, 1011, 920, 881, 856, 787, 765, 679.

more polar diastereomer

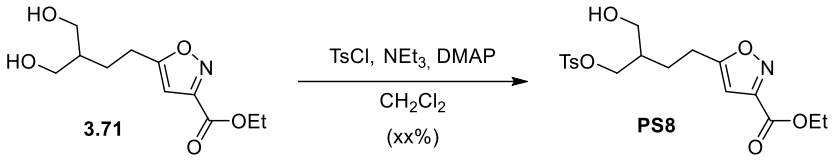
TLC (3% methanol in dichloromethane): R_f: 0.17 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (s, 1H), 4.40 (qd, *J* = 7.1, 3.3 Hz, 2H), 4.18 (dd, *J* = 11.8, 3.2 Hz, 1H), 3.88 – 3.79 (m, 1H), 3.76 – 3.69 (m, 2H), 2.20 – 2.09 (m, 2H), 2.09 – 2.00 (m, 1H), 1.93 – 1.78 (m, 1H), 1.55 (s, 1H), 1.39 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 153.9, 110.4, 64.4, 62.7, 62.2, 50.6, 34.6, 26.1, 21.0, 14.2.

HRMS (ESI): calcd. for $C_{11}H_{17}BrNO_5$ $[M+H]^+$: 322.0285; found: 322.0287.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3440, 2979, 2939, 2876, 1729, 1729, 1574, 1469, 1405, 1381, 1335, 1256, 1231, 1193, 1131, 1077, 1013, 941, 921, 880, 787, 763.



Synthesis of tosyl **PS8**: To a solution of diol **3.71** (100 mg, 441 µmol, 1 equiv) in dichloromethane (4.1 mL) was added pyridine (40.0 µL, 493 µmol, 1.20 equiv), DMAP (5.02 mg, 41.1 µmol, 10 mol%) and *p*-toluenesulfonyl chloride (78.4 mg, 441 µmol, 1.00 equiv) in sequence at 0 °C. The pale yellow solution was stirred for 15 min at 0 °C before the mixture was allowed to warm to 23 °C. After 16 h, the mixture was diluted with aqueous hydrogen chloride solution (1.0 M, 10 mL) and the aqueous phase was extracted with dichloromethane (3×10 mL). The combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a colorless oil. The crude product was purified by flash column

chromatography on silica gel (3% methanol in dichloromethane) to afford, tosyl **PS8** (129 mg, 325 µmol, 79%) as a colorless solid.

TLC (1% methanol in dichloromethane): R_f: 0.17 (UV, CAM)

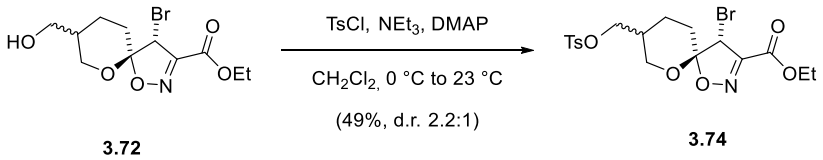
mp: 74.3 – 75.5 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.74 (m, 2H), 7.39 – 7.32 (m, 2H), 6.39 (s, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.16 – 4.04 (m, 2H), 3.71 – 3.56 (m, 2H), 2.85 – 2.75 (m, 2H), 2.44 (s, 3H), 1.93 – 1.66 (m, 4H), 1.40 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 160.1, 156.5, 145.3, 132.8, 130.1, 128.0, 101.9, 69.7, 62.3, 61.4, 39.8, 25.3, 24.2, 21.8, 14.3.

HRMS (ESI): calcd. for $C_{18}H_{23}NNaO_7S$ $[M+Na]^+$: 420.1087; found: 420.1094.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3450, 2933, 1731, 1596, 1494, 1462, 1426, 1390, 1356, 1306, 1292, 1243, 1211, 1189, 1174, 1097, 1019, 964, 939, 832, 814, 779, 706, 687, 666.



3.72 **3.74**

Synthesis of tosyl **3.74**: To a solution of alcohol **3.72** (11.4 mg, 31.8 µmol, 1 equiv) in dichloromethane (300 µL) was added triethylamine (5.31 µL, 38.2 µmol, 1.20 equiv), DMAP (3.89 mg, 3.18 µmol, 10 mol%) and *p*-toluenesulfonyl chloride (7.29 mg, 38.2 µmol, 1.00 equiv) in sequence at 0 °C. The pale yellow solution was stirred for 15 min at 0 °C, before the mixture was allowed to warm to 23 °C. After 16 h, the reaction mixture was diluted with aqueous hydrogen chloride (1.0 M, 10 mL) and the aqueous phase was extracted with dichloromethane (3×10 mL). The combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a colorless oil. The crude product was purified by flash column chromatography on silica gel (100% dichloromethane) to afford tosyl **3.74** (7.50 mg, 0.157 µmol, 49%, d.r. 2.2:1) as a colorless oil.

major diastereomer

TLC (25% ethyl acetate in cyclohexane): R_f: 0.29 (UV, CAM)

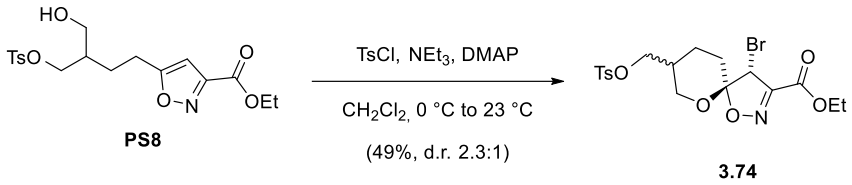
mp: 78.1 – 88.1 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 7.9, 0.7 Hz, 2H), 4.85 (s, 1H), 4.39 (qd, *J* = 7.1, 3.7 Hz, 2H), 4.20 – 4.07 (m, 1H), 3.93 (dd, *J* = 10.0, 5.5 Hz, 1H), 3.80 (dd, *J* = 10.0, 7.7 Hz, 1H), 3.73 (ddd, *J* = 11.3, 4.8, 1.9 Hz, 1H), 3.64 (t, *J* = 11.4 Hz, 1H), 2.46 (s, 3H), 2.36 – 2.29 (m, 1H), 2.20 – 2.06 (m, 1H), 1.96 – 1.83 (m, 1H), 1.68 – 1.58 (m, 1H), 1.38 (t, *J* = 7.1 Hz, 3H).

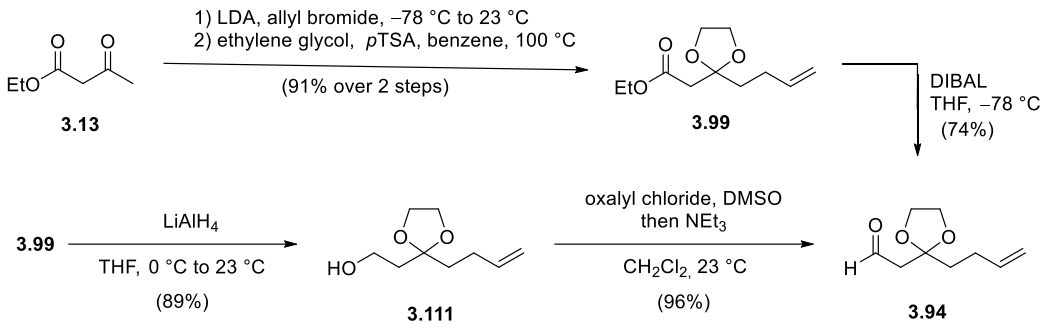
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 153.9, 145.3, 132.7, 130.2, 128.0, 109.6, 70.6, 65.5, 62.7, 50.6, 34.3, 29.5, 22.6, 21.8, 14.2.

zHRMS (ESI): calcd. for $C_{18}H_{23}{}^{79}BrNO_7S$ $[M+H]^+$: 476.0373; found: 476.0370.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2923, 2852, 1731, 1595, 1492, 1454, 1373, 1305, 1189, 1173, 1155, 1082, 1008, 919, 813, 780, 714, 698.



Alternative synthesis of spiro **3.74**: To a solution of tosyl **PS8** (47.0 mg, 118 µmol, 1 equiv) in dichloromethane (120 µL) was added bromine (1.00 M in dichloromethane, 1.18 mL, 1.18 mmol, 10.0 equiv) dropwise at 0 °C. The resulting red-brown solution was stirred for 1 h at 0 °C, before it was allowed to warm to 23 °C. After 6 h, excess of bromine was quenched by the addition of saturated aqueous thiosulfate solution (5 mL). The phases were separated and the aqueous solution was extracted with dichloromethane (3×10 mL). The combined organic phases were dried over magnesium 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 (20% ethyl acetate in hexane) to afford spiro **3.74** (25.3 mg, 44.9 µmol, 45%, d.r. 2.3:1) as a colorless oil.



Synthesis of acetal **3.99**: To a solution of diisopropylamine (31.0 mL, 220 mmol, 2.20 equiv) in tetrahydrofuran (220 mL, 1.00 M) was added *n*-butyllithium (2.50 M in *n*-hexane, 83.9 mL, 210 mmol, 2.10 equiv) at −78 °C. After 10 min, ethyl acetoacetate (**3.13**) (12.6 mL, 99.9 mmol, 1 equiv) was added dropwise at −78 °C. After complete addition, the reaction mixture was slowly allowed to warm to 0 °C. After stirring for 1 h at 0 °C, allyl bromide (10.4 mL, 120 mmol, 1.20 equiv) was added at 0 °C and the resulting yellow reaction mixture was allowed to warm to 23 °C. After 1 h, saturated aqueous ammonium chloride solution (200 mL) was added to quench excess of base. The reaction mixture was extracted with ethyl acetate (3×100 mL), and the combined organic phases were washed with water (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 carefully concentrated (200 mbar, 42 °C) to give an orange oil, which was pure enough to use without further purification. The orange residue was dissolved in benzene (100 mL) and ethylene glycol (16.8 mL, 300 mmol, 3.00 equiv) and to the solution was added *p*-toluenesulfonic acid monohydrate (1.90 g, 9.99 mmol, 10.0 mol%) and the reaction mixture was heat to 100 °C in a Dean–Stark apparatus. After 16 h, the reaction mixture was allowed to cool to 23 °C and the acid was neutralized with saturated aqueous sodium hydrogen carbonate solution (200 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3×100 mL) and the combined organic phases were washed with water (100 mL) and saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate and the dried solution was concentrated to afford acetal **3.99** (19.5 g, 91.0 mmol, 91%) as a pale yellow oil, which was pure enough to use without further purification.

All analytical data were in agreement with the literature.[138]

Synthesis of alcohol **3.111**: To a suspension of lithium aluminum hydride (816 mg, 21.5 mmol, 2.00 equiv) in tetrahydrofuran (100 mL) was added dropwise a solution of acetal **3.99** (500 mM in tetrahydrofuran, 21.5 mL, 10.8 mmol, 1 equiv) at 0 °C. After 2 h, excess of lithium aluminum hydride was quenched carefully by addition of ethyl acetate dropwise at 0 °C. A saturated aqueous sodium potassium tartrate solution (200 mL) and ethyl acetate (200 mL) were added and the grey suspension was stirred vigorously. After 4 h, the phases were separated and the aqueous phase was

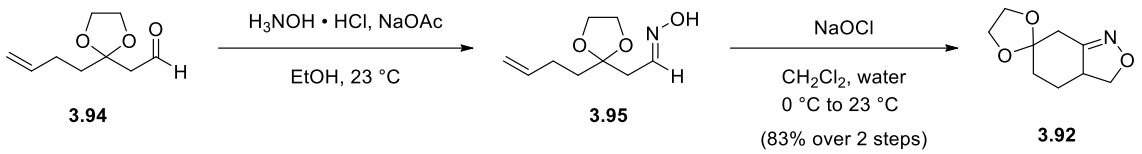
extracted with ethyl acetate (3×100 mL) and the combined organic phases were washed with water (100 mL) and saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate and the dried solution was concentrated to give a yellow oil. The crude product was purified by flash column chromatography on silica gel (2% methanol in dichloromethane) to yield alcohol **3.111** (1.66 g, 9.62 mmol, 89%) as a pale yellow oil.

All analytical data were in agreement with the literature.[138]

Synthesis of aldehyde **3.94**: To a solution of oxalyl chloride (2.00 M in dichloromethane, 9.40 mL, 18.8 mmol, 2.00 equiv) in dichloromethane (90.0 mL) was added a solution of dimethyl sulfoxide (1.00 M in dichloromethane, 37.6 mL, 37.6 mmol, 4.00 equiv) at −78 °C. After 15 min, a solution of alcohol **3.111** (1.00 M in dichloromethane, 9.40 mL, 9.40 mmol, 1 equiv) was added dropwise and the resulting solution was stirred at −78 °C. After further 30 min, triethylamine (13.0 mL, 94.0 mmol, 10.0 equiv) was added at −78 ° C and the temperature was kept for 15 min before the reaction mixture was slowly allowed to warm to 23 °C. After 1 h, the mixture was diluted with water (150 mL). The phases were separated and the aqueous solution was extracted with diethyl ether (3×100 mL). The combined organic phases 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 (100% dichloromethane) to afford aldehyde **3.111** (1.54 mg, 9.02 mmol, 96%) as a pale yellow oil.

All analytical data were in agreement with the literature.[98]

Improved synthesis of aldehyde **3.94** from ester **3.99**: To a solution of ester **3.99** (1.00 g, 4.67 mmol, 1 equiv) in toluene (20 mL) was added diisobutylaluminium hydride (1.00 M in toluene, 9.33 mL, 9.33 mmol, 2.00 equiv) dropwise at −78 °C. After 3 h, methanol (420 µL) was added at −78 °C dropwise. The reaction mixture was stirred for 30 min, before aqueous hydrogen chloride solution (1.00 M, 10 mL) was added at −78 °C and the cloudy suspension was allowed to warm to 23 C. The reaction mixture was diluted with ethyl acetate (30 mL) and water (100 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3×30 mL), the combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a yellow oil. The crude product was purified by flash column chromatography on silica gel (100% dichloromethane) to yield aldehyde **3.94** (590 mg, 3.47 mmol, 74%) as a pale yellow oil.



3.94 **3.95** **3.92**

Synthesis of isoxazoline **3.92**: To a solution of aldehyde **3.94** (590 mg, 3.47 mmol, 1 equiv) in ethanol (6.9 mL) was added sodium acetate (569 mg, 6.93 mmol, 2.00 equiv) and hydroxylamine hydrochloride (631 mg, 5.20 mmol, 1.50 equiv). After 16 h, the pale yellow solution was filtered and the filtrate was concentrated. The residue was diluted with ethyl acetate (25 mL). The organic phase was washed with water (3×20 mL) and saturated aqueous sodium hydrogen carbonate solution (20 mL), the washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give crude oxime **3.95**, which was used without further purification.

To a solution of crude oxime **3.95** in dichloromethane (6.9 mL) was added a solution of sodium hypochlorite (5% in water, 6.82 mL, 5.55 mmol, 1.60 equiv) at 0 °C and the reaction mixture was allowed to warm to 23 °C. After 4 h, excess of hypochlorite was quenched by the addition of aqueous sodium thiosulfate solution (1.0 M, 20 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3×20 mL). The combined organic phases 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 (3% methanol in dichloromethane) to afford isoxazoline **3.92** (541 mg, 2.95 mmol, 85%) as a colorless solid.

TLC (25% ethyl acetate in cyclohexane): R_f: 0.10 (CAM)

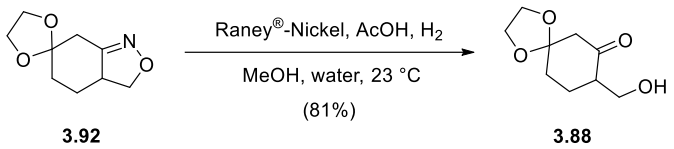
mp: 100.2 – 104.1°C

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (dd, *J* = 10.4, 8.0 Hz, 1H), 4.06 – 3.91 (m, 4H), 3.81 (dd, *J* = 10.4, 8.0 Hz, 1H), 3.18 (dddd, *J* = 15.3, 10.4, 7.6, 3.1 Hz, 1H), 2.87 (dd, *J* = 14.2, 2.5 Hz, 1H), 2.39 (dd, *J* = 14.2, 1.6 Hz, 1H), 2.07 (ddt, *J* = 13.0, 6.7, 3.4 Hz, 1H), 1.91 – 1.71 (m, 2H), 1.69 – 1.53 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 108.7, 73.7, 65.1, 64.8, 47.4, 35.1, 34.1, 27.5.

HRMS (ESI): calcd. for $C_9H_{14}NO_3$ $[M+H]^+$: 184.0968; found: 184.0966.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2955, 2884, 1726, 1629, 1473, 1443, 1422, 1353, 1336, 1296, 1268, 1241, 1207, 1145, 1110, 1085, 1044, 1006, 971, 951, 921, 893, 856, 833, 803, 780, 733, 689.



3.92 **3.88**

Synthesis of alcohol **3.88**: To a solution of isoxazoline **3.92** (540 mg, 2.95 mmol, 1 equiv) in methanol (25 mL) and water (5 mL) was added acetic acid (506 µL, 8.84 mmol, 3.00 equiv) and Raney®-Nickel (25.3 mg, 2.95 µmol, 10.0 mol%) and the black reaction mixture was purged for 20 min with hydrogen. After 16 h, Celite® was added and the reaction mixture was filtered over a plug of Celite® and the plug was washed with dichloromethane (3×10 mL). The filtrate was washed with saturated aqueous sodium hydrogen carbonate solution (30 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3×10 mL) dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a yellow oil. The crude product was purified by flash column chromatography on silica gel (5% methanol in dichloromethane) to afford alcohol **3.88** (421 mg, 2.26 mmol, 77%) as a colorless solid.

TLC (5% methanol in dichloromethane): R_f: 0.14 (CAM)

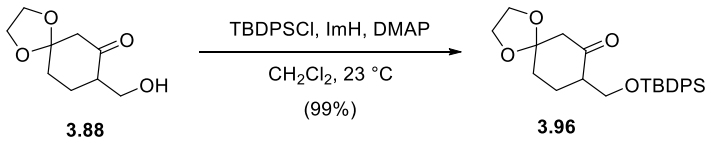
mp: 64.1 – 67.3 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 – 3.90 (m, 4H), 3.77 (dd, *J* = 11.6, 7.2 Hz, 1H), 3.64 (d, *J* = 11.7 Hz, 1H), 2.66 (dd, *J* = 13.8, 1.1 Hz, 1H), 2.58 (ddd, *J* = 13.8, 1.9, 1.1 Hz, 2H), 2.48 (dtdd, *J* = 10.1, 7.1, 4.0, 1.1 Hz, 1H), 2.01 – 1.95 (m, 2H), 1.94 – 1.85 (m, 1H), 1.61 (tt, *J* = 13.1, 8.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.8, 110.3, 65.0, 64.8, 62.3, 51.9, 51.2, 34.2, 23.5.

HRMS (ESI): calcd. for $C_9H_{14}NaO_4$ $[M+Na]^+$: 209.0784; found:209.0795.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3467, 2953, 2882, 1707, 1443, 1415, 1355, 1296, 1238, 1193, 1165, 1081, 1032, 997, 946, 919, 865, 789, 707.



3.88 **3.96**

Synthesis of ketone **3.96**: To a solution of alcohol **3.88** (150 mg, 806 µmol, 1 equiv) in dichloromethane (4 mL) was added DMAP (9.84 mg, 80.6 µmol, 10.0 mol%), imidazole (82.3 mg, 1.21 µmol, 1.50 equiv) and *tert*-butyl(chloro)diphenylsilane (217 µL, 846 µmol, 1.05 equiv) in sequence and the resulting mixture was stirred at 23 °C. After 16 h, the mixture was diluted with water (10 mL) to hydrolyze unreacted *tert*-butyl(chloro)diphenylsilane. The aqueous phase was

extracted with dichloromethane (3×10 mL), the combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a colorless oil. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexane) to afford ketone **3.96** (340 mg, 801 µmol, 99%) as a colorless solid.

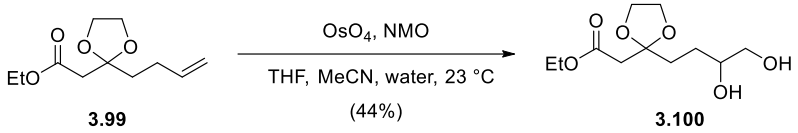
TLC (15% ethyl acetate in hexane): R_f: 0.14 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dt, *J* = 7.9, 1.5 Hz, 4H), 7.39 (tt, *J* = 8.0, 5.8 Hz, 6H), 4.05 (dd, *J* = 10.5, 4.8 Hz, 1H), 4.00 – 3.90 (m, 4H), 3.69 (dd, *J* = 10.5, 7.8 Hz, 1H), 2.65 – 2.45 (m, 3H), 2.29 (ddt, *J* = 13.3, 6.0, 4.4 Hz, 1H), 2.06 – 1.88 (m, 2H), 1.69 – 1.54 (m, 1H), 1.05 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.1, 135.7, 135.7, 133.7, 133.6, 129.8, 127.8, 110.4, 64.9, 64.8, 63.0, 51.7, 51.6, 34.1, 27.0, 24.4, 19.4.

HRMS (ESI): calcd. for $C_{25}H_{32}NaO_4Si$ $[M+Na]^+$: 447.1962; found: 447.1955.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3070, 3048, 2956, 2931, 2885, 2857, 1715, 1589, 1472, 1428, 1390, 1358, 1308, 1242, 1195, 1111, 1090, 1007, 947, 824, 741, 613, 505.



3.99 **3.100**

Synthesis of diol **3.100**: To a solution of acetal **3.99** (1.08 g, 4.12 mmol, 1 equiv) in water (5 mL), tetrahydrofuran (5 mL), and acetonitrile (5 mL) was added osmium tetroxide (4% in water, 650 µL, 82.3 µmol, 2 mol%) and *N*-methylmorpholine *N*-oxide (627 mg, 5.35 mmol, 1.30 equiv) at 23 °C. After 16 h, the brown reaction mixture was diluted with ethyl acetate (20 mL), water (10 mL) and saturated aqueous thiosulfate solution (1 mL) to quench excess of *N*-oxide. The phases were separated and the aqueous phase was extracted with ethyl acetate (3×20 mL), the combined organic phases were dried over sodium sulfate and the dried solution was filtered and the filtrate was concentrated to give a black oil. The crude product was purified by flash column chromatography on silica gel (5% methanol in dichloromethane) to yield diol **3.100** (175 mg, 0.81 mmol, 85%) as a yellow oil.

TLC (7% methanol in dichloromethane): R_f: 0.20 (CAM)

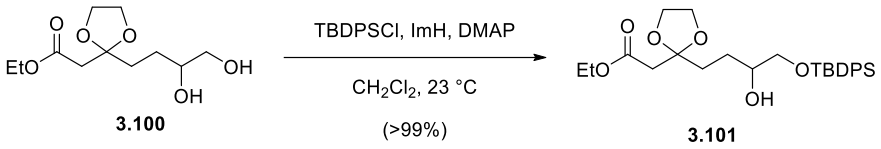
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (q, *J* = 7.1 Hz, 2H), 4.05 – 3.94 (m, 4H), 3.69 (tdd, *J* = 7.7, 5.0, 3.2 Hz, 1H), 3.62 (dd, *J* = 11.1, 3.2 Hz, 1H), 3.44 (dd, *J* = 11.1, 7.3 Hz, 1H), 2.65 (s, 2H), 2.60

– 2.51 (m, 2H), 1.97 (qdd, *J* = 14.3, 9.0, 6.5 Hz, 2H), 1.57 (dddd, *J* = 10.6, 7.6, 5.7, 4.0 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 109.32, 7.12, 66.8, 65.2, 65.2, 60.8, 42.6, 33.6, 27.1, 14.3.

HRMS (ESI): calcd. for $C_{11}H_{20}NaO_6$ $[M+Na]^+$: 271.1152; found: 271.1144.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3413, 2937, 2893, 1730, 1447, 1371, 1306, 1218, 1033, 951, 883.



3.100 **3.101**

Synthesis of ester **3.101**: To a solution of diol **3.100** (170 mg, 685 µmol, 1 equiv) in dichloromethane (3.4 mL) was added DMAP (8.37 mg, 68.5 µmol, 10.0 mol%), imidazole (55.9 mg, 822 µmol, 1.20 equiv) and *tert*-Butyl(chloro)diphenylsilane (176 µL, 685 µmol, 1.00 equiv) in sequence and the resulting mixture was stirred at 23 °C. After 16 h, the mixture was diluted with water (5 mL) to hydrolyze unreacted *tert*-Butyl(chloro)diphenylsilane. The aqueous phase was extracted with dichloromethane (3×5 mL), the combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a colorless oil. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexane) to afford ester **3.103** (332 mg, 682 µmol, ≥99%) as a colorless oil.

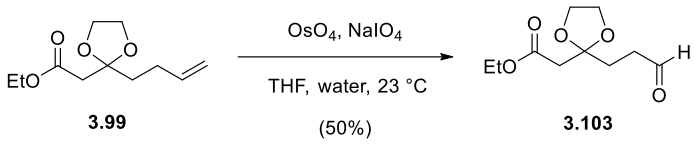
TLC (25% ethyl acetate in cyclohexane): R_f: 0.16 (UV, CAM)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 – 7.63 (m, 4H), 7.41 (dt, *J* = 27.4, 7.4 Hz, 6H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.02 – 3.89 (m, 4H), 3.72 (q, *J* = 7.4, 5.6 Hz, 1H), 3.65 (dd, *J* = 10.2, 3.7 Hz, 1H), 3.50 (dd, *J* = 10.1, 7.2 Hz, 1H), 2.63 (s, 2H), 2.59 (d, *J* = 3.8 Hz, 1H), 2.00 (ddd, *J* = 15.3, 9.5, 6.6 Hz, 1H), 1.89 – 1.80 (m, 1H), 1.54 (q, *J* = 8.2 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.5, 135.7, 135.7, 133.3, 133.3, 129.9, 127.9, 109.4, 72.0, 68.1, 65.3, 65.3, 60.7, 42.9, 33.8, 27.0, 26.9, 19.4, 14.3.

HRMS (ESI): calcd. for $C_{27}H_{38}NaO_6Si$ $[M+Na]^+$: 509.2330; found: 509.2321.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3520, 3070, 2957, 2931, 2894, 2858, 1735, 1473, 1428, 1370, 1224, 1112, 1037, 824, 742, 704.



Synthesis of aldehyde **3.103**: To a solution of alkene **3.99** (522 mg, 2.44 mmol, 1 equiv) in tetrahydrofuran (10 mL) and water (5 mL) was added a solution of osmium tetroxide (4% in water, 760 µL, 97.5 µmol, 4.00 mol%) and sodium periodate (1.30 g, 6.09 mmol, 2.50 equiv) at 23 °C. After 16 h, the brown reaction mixture was diluted with ethyl acetate (20 mL), water (10 mL) and saturated aqueous thiosulfate solution (1 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (3×30 mL), the combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a black oil. The crude product was purified by flash column chromatography on silica gel (5% methanol in dichloromethane) to yield aldehyde **3.103** (264 mg, 1.22 mmol, 50%) as a pale yellow oil.

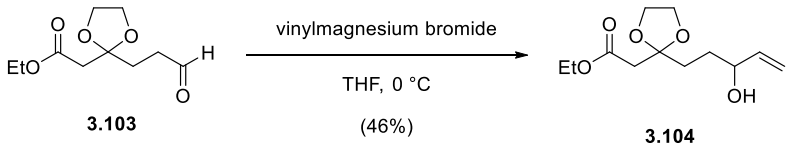
TLC (40% ethyl acetate in cyclohexane): R_f: 0.23 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (t, *J* = 2.1 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.02 – 3.96 (m, 2H), 3.95 – 3.90 (m, 2H), 2.64 (s, 2H), 2.46 (tdd, *J* = 7.0, 2.1, 0.7 Hz, 2H), 2.29 (td, *J* = 6.9, 0.7 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.9, 169.3, 108.5, 65.3, 60.8, 43.1, 38.1, 30.6, 14.3.

HRMS (ESI): calcd. for $C_{10}H_{16}NaO_5$ $[M+Na]^+$: 239.0890; found: 239.0886.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2981, 2897, 2730, 1724, 1442, 1370, 1215, 1112, 1035, 970, 951.



Synthesis of alcohol **3.104**: To a solution of aldehyde **3.103** (95.5 mg, 442 µmol, 1 equiv) in tetrahydrofuran (6.0 mL) was added a solution of vinyl magnesium bromide (1.00 M in tetrahydrofuran, 442 µL, 442 µmol, 1.00 equiv) dropwise at −78 °C and the reaction mixture was slowly allowed to warm to 23 °C. After 1 h, the reaction mixture was diluted with diethyl ether (10 mL) and saturated aqueous ammonium chloride solution (20 mL) to quench excess of the Grignard reagent. The phases were separated and the aqueous phase was extracted with diethyl ether (3×20 mL). The combined organic phases were dried over sodium sulfate and the filtrate was

concentrated. The crude product was purified by flash column chromatography (40% ethyl acetate in hexane) to afford alcohol **3.105** (49.6 mg, 203 µmol, 46%) as a pale yellow oil.

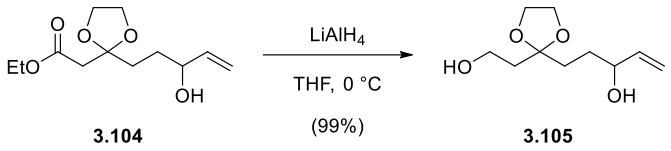
TLC (50% ethyl acetate in cyclohexane): R_f: 0.21 (CAM)

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.85 (ddd, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.23 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.10 (dt, *J* = 10.4, 1.4 Hz, 1H), 4.18 – 4.06 (m, 3H), 4.05 – 3.92 (m, 4H), 2.65 (s, 2H), 2.05 – 1.99 (m, 1H), 2.01 – 1.86 (m, 2H), 1.74 – 1.59 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.6, 141.0, 114.9, 109.4, 72.9, 65.2, 60.7, 42.8, 33.4, 30.9, 14.3.

HRMS (ESI): calcd. for $C_{12}H_{20}NaO_5$ $[M+Na]^+$: 267.1203; found: 267.1199.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3514, 2979, 2963, 2940, 2897, 1733, 1431, 1371, 1303, 1241, 1097, 1056, 1036, 949.



3.104 **3.105**

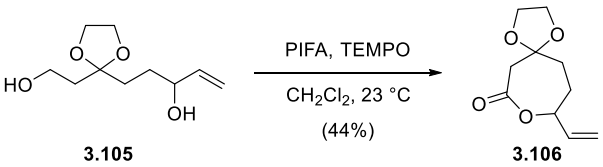
Synthesis of diol **3.105**: To a suspension of lithium aluminum hydride (14.0 mg, 370 µmol, 2.00 equiv) in tetrahydrofuran (740 µL) was added a solution of ester **3.104** (500 mM in tetrahydrofuran, 370 µL, 185 µmol, 1 equiv) dropwise at 0 °C. The resulting reaction mixture was allowed to warm to 23 °C. After 1 h, excess of lithium aluminum hydride was quenched by the dropwise addition of ethyl acetate (10 mL) at 0 °C. The reaction mixture was diluted with saturated aqueous sodium potassium tartrate solution (10 mL). After 1 h, the phases were separated and the aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic phases 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% methanol in dichloromethane) to yield diol **3.105** (37.0 mg, 183 µmol, 99%) as a pale yellow oil.

TLC (5% methanol in dichloromethane): R_f: 0.14 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (ddd, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.23 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.11 (dt, *J* = 10.5, 1.4 Hz, 1H), 4.11 (q, *J* = 6.3 Hz, 1H), 4.03 – 3.95 (m, 4H), 3.73 (d, *J* = 6.2 Hz, 2H), 2.73 (s, 1H), 2.06 (s, 1H), 1.93 (dd, *J* = 6.0, 5.1 Hz, 2H), 1.85 – 1.58 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 115.0, 112.1, 72.9, 65.0, 58.9, 38.4, 32.8, 31.1.

HRMS (ESI): calcd. for $C_{12}H_{20}NaO_5$ $[M+Na]^+$: 267.1203; found: 267.1199.



3.105 **3.106**

Synthesis of lactone **3.106**: To a solution of diol **3.105** (17 mg, 82µmol, 1 equiv) in dichloromethane (0.80 mL) was added (diacetoxyiodo)benzene (58 mg, 0.18 mmol, 2.2 equiv) and TEMPO (1.3 mg, 8.2 µmol, 10 mol%) at 23 °C. After 16 h, the reaction mixture was diluted with saturated aqueous hydrogen carbonate solution (3 mL) and saturated aqueous thiosulfate solution (3 mL) to quench excess of hypervalent iodine. The phases were separated and the aqueous phase was extracted with dichloromethane (3×5 mL). The combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give an orange oil. The crude product was purified by flash column chromatography on silica gel (1% methanol in dichloromethane) to afford lactone **3.106** (7.2 mg, 36 µmol, 44%) as a colorless oil.

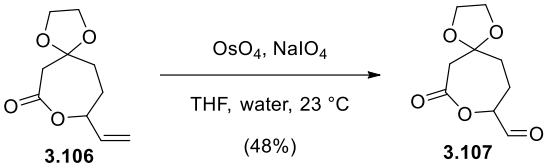
TLC (1% methanol in dichloromethane): R_f: 0.17 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (ddd, *J* = 17.2, 10.6, 5.7 Hz, 1H), 5.38 (dt, *J* = 17.2, 1.3 Hz, 1H), 5.21 (dt, *J* = 10.6, 1.2 Hz, 1H), 4.83 (ddt, *J* = 7.0, 5.7, 1.8 Hz, 1H), 4.16 – 4.06 (m, 1H), 4.05 – 3.92 (m, 3H), 3.11 (d, *J* = 13.8 Hz, 1H), 2.90 (dd, *J* = 13.9, 1.9 Hz, 1H), 2.09 – 1.91 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 136.3, 116.6, 105.5, 80.0, 65.3, 64.8, 44.9, 38.1, 31.0.

HRMS (ESI): calcd. for $C_{10}H_{14}NaO_4$ $[M+Na]^+$: 221.0784; found: 221.0787.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2893, 1733, 1433, 1242, 1077, 1018, 948



3.106 **3.107**

Synthesis of aldehyde **3.111**: To a solution of alkene **3.106** (13 mg, 66 µmol, 1 equiv) in tetrahydrofuran (5.0 mL) and water (2.5 mL) was added a solution of osmium tetroxide (4% in water, 4.3 µL, 3.3 µmol, 4.0 mol%) and sodium periodate (35 mg, 17 µmol, 2.5 equiv) at 23 °C. After 16 h, the brown reaction mixture was diluted with ethyl acetate (10 mL), water (5 mL) and saturated aqueous thiosulfate solution (1 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a black oil. The

crude product was purified by flash column chromatography on silica gel (1% methanol in dichloromethane) to yield aldehyde **3.107** (6.3 mg, 31 mmol, 48%) as a pale yellow oil.

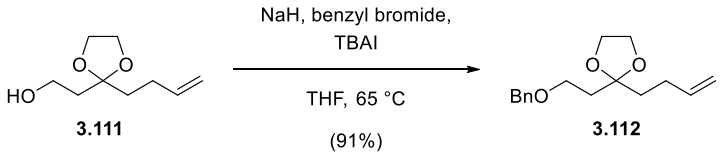
TLC (1% methanol in dichloromethane): R_f: 0.08 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 4.61 (d, *J* = 9.1 Hz, 1H), 4.15 – 4.03 (m, 1H), 4.09 – 3.94 (m, 3H), 3.06 (d, *J* = 14.0 Hz, 1H), 2.95 (dd, *J* = 14.0, 2.2 Hz, 1H), 2.41 – 2.25 (m, 2H), 2.09 – 1.91 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4, 168.0, 105.3, 82.7, 65.4, 64.9, 44.8, 37.9, 26.2.

HRMS (ESI): calcd. for $C_9H_{12}NaO_5$ $[M+Na]^+$: 223.0577; found: 223.0571.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2981, 2897, 2730, 1724, 1442, 1370 1215, 1112, 1036, 970, 951.



Synthesis of alkene **3.112**: To a solution of alcohol **3.111** (1.60 g, 9.29 mmol, 1 equiv) in tetrahydrofuran (40 mL) was added sodium hydride (60% in mineral oil, 446 mg, 11.1 mmol, 1.20 equiv). The resulting mixture was stirred for 15 min, before benzyl bromide (1.21 mL, 10.2 mmol, 1.10 equiv) and tetrabutylammonium iodide (343 mg, 929 µmol, 10.0 mol%equiv) were added in sequence and the resulting reaction mixture was heat to 65 °C. After 16 h, the reaction mixture was allowed to cool to 23 °C and excess of base was quenched by the addition of saturated aqueous ammonium chloride solution (100 mL) and the reaction mixture was diluted with diethyl ether (70 mL). The phases were separated and the aqueous phases was extracted with diethyl ether (3×70 mL). The combined organic phases were dried over sodium sulfate and the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography (7% ethyl acetate in cyclohexane) to yield alkene **3.112** (2.21 g, 8.41 mmol, 91%) as a yellow oil.

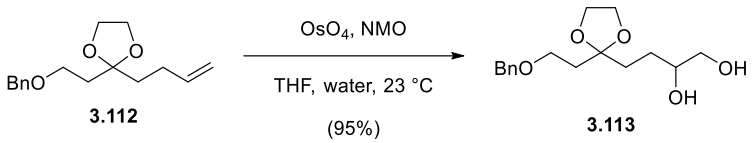
TLC (20% ethyl acetate in cyclohexane): R_f: 0.30 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.24 (m, 5H), 5.82 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.06 – 4.89 (m, 2H), 4.50 (s, 2H), 3.97 – 3.87 (m, 4H), 3.59 (t, *J* = 7.1 Hz, 2H), 2.15 (dtt, *J* = 9.5, 6.4, 1.5 Hz, 2H), 2.01 (t, *J* = 7.1 Hz, 2H), 1.79 – 1.68 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6, 138.6, 128.5, 127.8, 127.7, 114.4, 110.5, 73.2, 66.4, 65.1, 37.2, 37.0, 28.2.

HRMS (ESI): calcd. for $C_{16}H_{22}NaO_3$ $[M+Na]^+$: 285.1461; found: 185.1459.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3066, 3029, 2953, 2877, 1716, 1641, 1496, 1478, 1453, 1366, 1305, 1208, 1152, 1098, 1063, 996, 947, 909, 736.



3.112 **3.113**

Synthesis of diol 3.113: To a solution of alkene **3.11**2 (1.08 g, 4.12 mmol, 1 equiv) in a mixture of water (5 mL), tetrahydrofuran (5 mL) and acetonitrile (5 mL) was added osmium tetroxide (4% in water, 650 µL, 82.3 µmol, 2.00 mol%) and *N*-methylmorpholine *N*-oxide (627 mg, 5.35 mmol, 1.30 equiv) at 23 °C. After 16 h, the brown reaction mixture was diluted with ethyl acetate (20 mL), water (10 mL) and saturated aqueous thiosulfate solution (1 mL) to quench excess of *N*-oxide. The phases were separated and the aqueous phase was extracted with ethyl acetate (3×20 mL), the combined organic phases were dried over sodium sulfate and the filtrate was concentrated to give a black oil. The crude product was purified by flash column chromatography (5% methanol in dichloromethane) to yield diol **3.113** (1.16 g, 4.12 mmol, 95%) as a yellow oil.

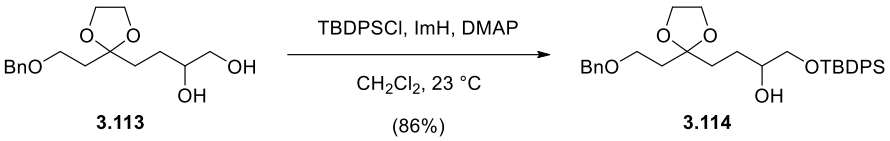
TLC (5% methanol in dichloromethane): R_f: 0.14 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 5H), 4.49 (s, 2H), 3.94 (p, *J* = 1.9 Hz, 4H), 3.67 (dt, *J* = 7.6, 3.7 Hz, 1H), 3.58 (t, *J* = 6.9 Hz, 3H), 3.42 (ddd, *J* = 11.1, 7.1, 4.1 Hz, 1H), 2.62 (d, *J* = 4.2 Hz, 1H), 1.99 (t, *J* = 6.9 Hz, 2H), 1.93 (d, *J* = 6.1 Hz, 1H), 1.89 – 1.72 (m, 2H), 1.62 – 1.47 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 128.6, 127.9, 127.8, 110.7, 73.3, 72.3, 67.0, 66.4, 65.0, 65.0, 36.9, 33.6, 27.4.

HRMS (ESI): calcd. for $C_{16}H_{24}NaO_5$ $[M+Na]^+$: 319.1516; found: 319.1508.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3412, 2956, 2876, 1454, 1368, 1209, 1072, 949, 898, 740, 699.



3.113 **3.114**

Synthesis of **3.114**: To a solution of alcohol **3.113** (274 mg, 925 µmol, 1 equiv) in dichloromethane (4.6 mL) was added DMAP (11.3 mg, 92.5 µmol, 10.0 mol%), imidazole (75.5 mg, 1.11 mmol, 1.20 equiv) and *tert*-butyl(chloro)diphenylsilane (237 µL, 925 µmol, 1.00 equiv) in sequence and the resulting mixture was stirred at 23 °C. After 16 h, the reaction mixture was diluted with water (5 mL) to hydrolyze unreacted *tert*-butyl(chloro)diphenylsilane. The aqueous phase was extracted with dichloromethane (3×5 mL), the combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a colorless oil. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexane) to afford acetal **3.114** (425 mg, 795 µmol, 86%) as a colorless oil.

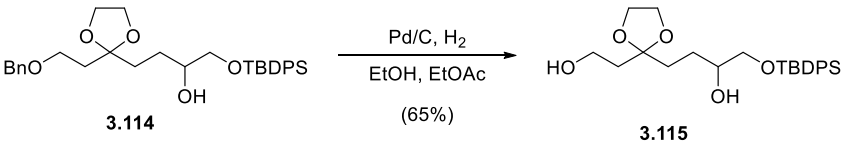
TLC (25% ethyl acetate in cyclohexane): R_f: 0.26 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dq, *J* = 6.4, 1.7 Hz, 4H), 7.47 – 7.35 (m, 6H), 7.34 – 7.21 (m, 5H), 4.47 (s, 2H), 3.90 (s, 4H), 3.69 (qd, *J* = 6.8, 3.7 Hz, 1H), 3.62 (dd, *J* = 10.0, 3.6 Hz, 1H), 3.55 (t, *J* = 7.1 Hz, 2H), 3.52 – 3.43 (m, 2H), 1.97 (t, *J* = 7.1 Hz, 2H), 1.88 – 1.78 (m, 1H), 1.70 – 1.59 (m, 1H), 1.56 – 1.46 (m, 1H), 1.21 (t, *J* = 7.0 Hz, 1H), 1.06 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5, 135.7, 135.7, 133.4, 133.3, 129.9, 128.5, 127.9, 127.8, 127.7, 110.6, 73.2, 72.1, 68.1, 66.4, 65.0, 65.0, 37.1, 33.6, 27.0, 19.4, 15.4.

HRMS (ESI): calcd. for $C_{32}H_{42}NaO_5Si$ $[M+Na]^+$: 557.2694; found: 557.2679.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3466, 3071, 2956, 2930, 2858, 1472, 1428, 1364, 1112, 823, 741, 702.



3.114 **3.115**

Synthesis of diol **3.115**: To a solution of acetal **3.114** (260 mg, 486 µmol, 1 equiv) in a mixture of ethanol (4.9 mL) and ethyl acetate (4.0 mL) was added palladium (10.0% wt on charcoal, 51.7 mg, 48.6 µmol, 10.0 mol%) and the black reaction mixture was purged with hydrogen gas for 20 min. After 8 h under hydrogen atmosphere, Celite® was added and the reaction mixture was filtered over a pad of Celite®, the pad was washed with dichloromethane (3×10 mL) and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexane) to afford diol **3.116** (141 mg, 317 µmol, 65%) as a colorless oil.

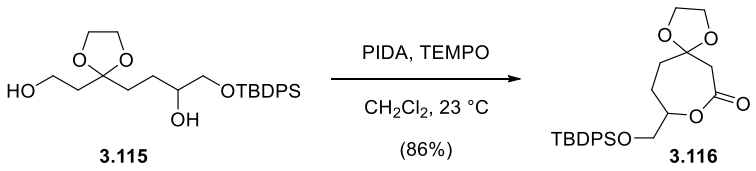
TLC (5% methanol in dichloromethane): R_f: 0.27 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dt, *J* = 8.0, 1.5 Hz, 4H), 7.49 – 7.34 (m, 6H), 4.03 – 3.97 (m, 2H), 3.97 – 3.90 (m, 2H), 3.73 (t, *J* = 5.7 Hz, 3H), 3.64 (dd, *J* = 10.1, 3.6 Hz, 1H), 3.50 (dd, *J* = 10.1, 7.3 Hz, 1H), 2.70 (s, 1H), 2.59 (s, 1H), 1.92 – 1.87 (m, 2H), 1.87 – 1.80 (m, 1H), 1.65 (ddd, *J* = 14.0, 9.2, 7.6 Hz, 1H), 1.48 (ddd, *J* = 8.9, 7.7, 5.9 Hz, 2H), 1.07 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 135.7, 133.3, 133.3, 130.0, 127.9, 112.2, 72.0, 68.1, 65.0, 65.0, 59.0, 38.3, 33.1, 27.1, 27.0, 19.4.

HRMS (ESI): calcd. for $C_{25}H_{36}NaO_5Si$ $[M+Na]^+$: 467.2224; found: 467.2218.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3406, 3070, 2955, 2930, 2889, 2857, 1472, 1428, 1391, 1361, 1112, 1077, 948, 823, 741.



Synthesis of lactone **3.116**: To a solution of diol **3.115** (124 mg, 279 µmol, 1 equiv) in dichloromethane (2.8 mL) was added (diacetoxyiodo)benzene (198 mg, 614 µmol, 2.20 equiv) and TEMPO (4.36 mg, 27.9 µmol, 10.0 mol%) at 23 °C. After 16 h, the reaction mixture was diluted with saturated aqueous hydrogen carbonate solution (5 mL) and saturated aqueous thiosulfate solution (5 mL) to quench excess of hypervalent iodine. The phases were separated and the aqueous phase was extracted with dichloromethane (3×5 mL). The combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give an orange oil. The crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in petrol ether) to afford lactone **3.116** (106 mg, 241 µmol, 86%) as a colorless oil.

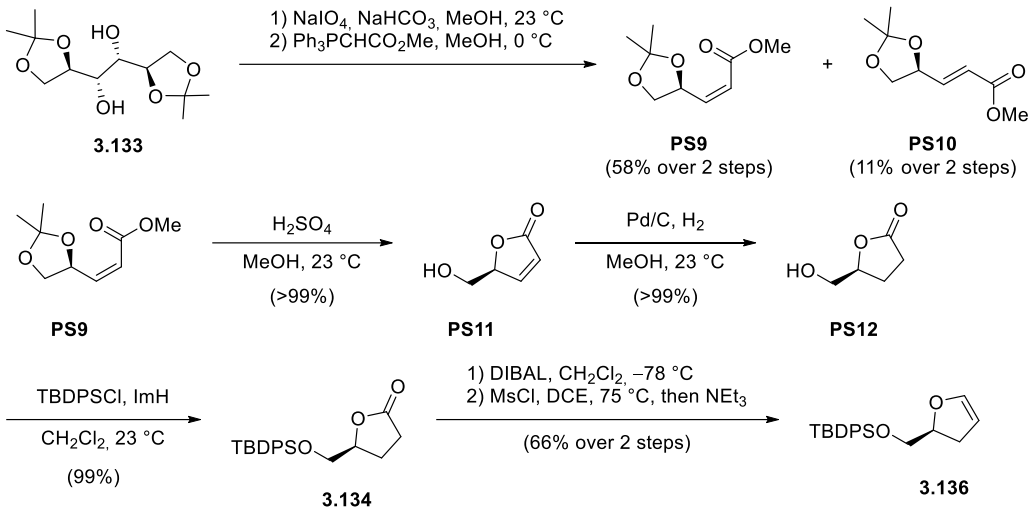
TLC (25% ethyl acetate in cyclohexane): R_f: 0.20 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dt, *J* = 8.0, 1.6 Hz, 4H), 7.49 – 7.35 (m, 6H), 4.38 – 4.24 (m, 1H), 4.14 – 4.07 (m, 1H), 4.04 – 3.92 (m, 3H), 3.84 (dd, *J* = 10.5, 5.4 Hz, 1H), 3.61 (dd, *J* = 10.5, 6.9 Hz, 1H), 3.01 (d, *J* = 13.7 Hz, 1H), 2.84 (dd, *J* = 13.7, 2.3 Hz, 1H), 2.20 – 2.09 (m, 1H), 2.06 – 1.95 (m, 1H), 1.91 (dd, *J* = 13.5, 3.8 Hz, 1H), 1.87 – 1.75 (m, 1H), 1.07 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 135.7, 135.7, 133.2, 133.2, 130.0, 130.0, 128.0, 127.9, 105.7, 79.8, 65.7, 65.2, 64.7, 44.6, 38.1, 27.1, 27.0, 19.4.

HRMS (ESI): calcd. for $C_{25}H_{32}NaO_5Si$ $[M+Na]^+$: 463.1911; found: 463.1898.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3071, 2931, 1890, 1857, 1737, 1589, 1472, 1428, 1361, 1287, 1242, 1112, 1075, 1028, 1008, 946, 823, 799, 742, 703, 612, 505.



Synthesis of enol ether **3.134**: To a solution of 1,2,5,6-di-*O*-isopropylidene-*D*-mannitol (**3.133**) (10.0 g, 38.1 mmol, 1 equiv) in dichloromethane (100 mL) was added saturated aqueous sodium hydrogen carbonate solution (10 mL) and sodium periodate (16.3 g, 76.3 mmol, 2.00 equiv). After 2 h, the reaction mixture was filtered over Celite® to remove any salts. To the filtrate was added methyl 2-(triphenyl-l5-phosphaneylidene)acetate (38.5 g, 115 mmol, 1.50 equiv) at 0 °C. After 1 h, the reaction mixture was concentrated and dissolved in 30% diethyl ether in cyclohexane (400 mL). Precipitating triphenylphosphine oxide was removed by filtration and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica (10% diethyl ether in pentane) to afford the desired (*Z*)-alkene **PS9** (8.29 g, 44.5 mmol, 58% over two steps) and (*E*)-alkene **PS10** (1.62, 8.72 mmol, 11% over two steps).

All analytical data were in agreement with the literature[139]

To a solution of (*Z*)-alkene **PS9** (8.29 g, 44.5 mmol, 1 equiv) in methanol (45 mL) was added sulfuric acid (95%, 119 µL, 2.23 mmol, 5.00 mol%) at 23 °C. After 2 h, the reaction mixture was concentrated and purified by flash column chromatography on silica (3% methanol in dichloromethane) to afford alcohol **PS11** (5.08 g, 44.5 mmol, >99%) as a colorless oil.

All analytical data were in agreement with the literature[139]

To a solution of alcohol **PS11** (5.08 g, 44.5 mmol, 1 equiv) in methanol (450 mL) was added palladium on charcoal (10% wt, 4.74 g, 4.45 mmol, 10 mol%) and the reaction mixture was sparged

with hydrogen for 20 min. After 16 h, under hydrogen atmosphere, Celite® was added and the reaction mixture was filtered over Celite® to give crude alcohol **PS12** (5.16 g, 44.5 mmol, >99%) as a colorless oil, which was pure enough without further purification.

All analytical data were in agreement with the literature[140]

To a solution of alcohol **PS12** (5.16 g, 44.5 mmol, 1.0 equiv) in dichloromethane (450 mL) was added imidazole (3.64 g, 53.4 mmol, 1.20 equiv) and *tert*-butyl(chloro)diphenylsilane (11.6 mL, 44.5 mmol, 1.00 equiv) in sequence and the resulting mixture was stirred at 23 °C. After 16 h, the mixture was diluted with water (500 mL) to hydrolyze unreacted *tert*-butyl(chloro)diphenylsilane and the aqueous solution was extracted with dichloromethane (3×100 mL) and the combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a colorless oil. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexane) to afford lactone **3.134** (15.6 g, 44.0 mmol, 99%) as a colorless solid.

All analytical data were in agreement with the literature.[141]

To a solution of lactone **3.134** (3.13 g, 8.83 mmol, 1 equiv) in dichloromethane (88 mL) was added a solution of diisobutylaluminium hydride (1.00 M in dichloromethane, 17.7 mL, 17.7 mmol, 2.00 equiv) dropwise at −78 °C. After 1 h, methanol (21 mL) and aqueous hydrogen chloride (1.0 M, 44 mL) were added in sequence at −78 °C and the reaction mixture was allowed to warm to 23 °C and diluted with saturated aqueous ammonium chloride solution (100 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3×50 mL). The combined organic phases were dried over sodium sulfate, the dried solution was filtered over Celite® and the filtrate was concentrated to give a pale yellow oil. The crude lactole was dissolved in dichloroethane (88 mL) and mesylchloride (2.06 mL, 26.5 mmol, 3.00 equiv) was added in one portion. The clear solution was stirred for 3 min at 23 °C before it was heated in a pre-warmed oil bath to 75 °C. After 3 min, triethylamine (9.20 mL, 66.2 mmol, 7.50 equiv) was added at 75 °C. After 3 min, the reaction mixture was allowed to cool to 23 °C, diluted with saturated aqueous sodium hydrogen carbonate solution (100 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3×50 mL), the combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a brown oil. The crude product was purified by flash column chromatography on deactivated silica gel (at least 16 h of deactivation) (2% diethyl ether in pentane with 1% triethylamine) to afford the desired enol ether **3.136** (1.97 g, 5.82 mmol, 66%) as a pale yellow oil.

TLC (10% ethyl acetate in cyclohexane): R_f: 0.42 (UV, CAM)

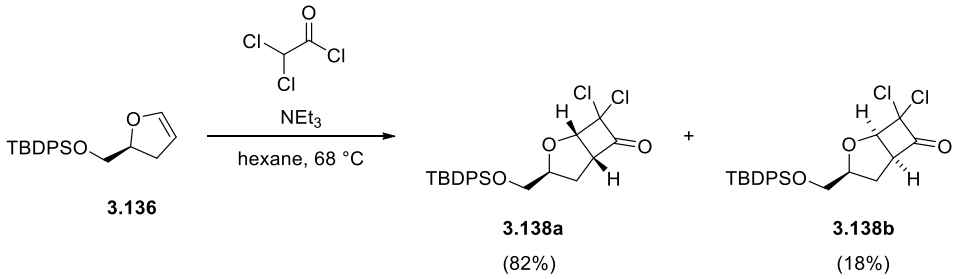
^{1}H NMR (400 MHz, Benzene-d_6) δ 7.86 – 7.72 (m, 4H), 7.27 – 7.18 (m, 6H), 6.17 (q, *J* = 2.4 Hz, 1H), 4.62 (q, *J* = 2.5 Hz, 1H), 4.60 – 4.49 (m, 1H), 3.76 – 3.59 (m, 2H), 2.39 – 2.19 (m, 2H), 1.18 (s, 9H).

^{13}C NMR (101 MHz, C_6D_6) δ 145.8, 136.1, 134.1, 130.0, 128.3, 98.9, 81.5, 66.3, 31.3, 27.1, 19.6.

HRMS (ESI): calcd. for $C_{21}H_{27}O_2Si$ $[M+H]^+$: 339.1775; found: 339.1772.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3071, 3050, 2956, 2930, 2858, 1472, 1428, 1390, 1361, 1188, 1111, 1051, 998, 976, 937, 823, 740, 702.

$[\boldsymbol{\alpha}]_{\boldsymbol{20}}^{\boldsymbol{D}}$ = +52.6 (c = 1.00 in dichloromethane)



Synthesis of cyclobutane **3.138a** and **3.138b**: To a solution of enol ether **3.136** (1.96 g, 5.80 mmol, 1 equiv) in *n*-hexane (30.0 mL) was added 2,2-dichloroacetyl chloride (669 µL, 6.96 mmol, 1.20 equiv) and the cloudy reaction mixture was heat to 68 °C. After 20 min, triethylamine (1.00 mL, 7.54 mmol, 1.30 equiv) was added dropwise at 68 °C. After 15 min, the brown suspension was allowed to cool to 23 °C. The reaction mixture was diluted with *n*-pentane (30 mL) and saturated aqueous hydrogen carbonate solution (30 mL) was added in sequence. The phases were separated and the aqueous phase was extracted with pentane (3×30 mL), the combined organic phases were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (20% diethyl ether in *n*-pentane) to afford cyclobutane **3.138a** (2.13 g, 4.74 mmol, 82%) as a colorless oil and cyclobutane **3.138b** (469 mg, 1.04 mmol, 18%) as a colorless oil.

less polar diastereomer

TLC (10% ethyl acetate in cyclohexane): R_f: 0.37 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (ddd, *J* = 8.1, 4.4, 1.6 Hz, 4H), 7.47 – 7.34 (m, 6H), 4.89 (d, *J* = 5.9 Hz, 1H), 4.39 – 4.18 (m, 2H), 3.83 (dd, *J* = 11.2, 3.9 Hz, 1H), 3.74 (dd, *J* = 11.2, 3.9 Hz, 1H), 2.40 – 2.26 (m, 1H), 2.06 (dt, *J* = 12.9, 9.7 Hz, 1H), 1.06 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.3, 135.8, 135.7, 133.3, 133.2, 130.0, 130.0, 127.9, 127.9, 87.8, 83.3, 82.7, 64.7, 62.2, 31.1, 27.00, 19.4.

HRMS (ESI): calcd. for $C_{23}H_{26}Cl_2NaO_3Si$ $[M+Na]^+$: 471.0920; found: 471.0909.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3071, 2932, 2858, 1809, 1472, 1428, 1110, 996, 823, 742, 703.

$[\boldsymbol{\alpha}]_{\boldsymbol{20}}^{\boldsymbol{D}}$ = +8.80 (c = 0.228 in dichloromethane)

more polar diastereomer

TLC (10% ethyl acetate in cyclohexane): R_f: 0.26 (UV, CAM)

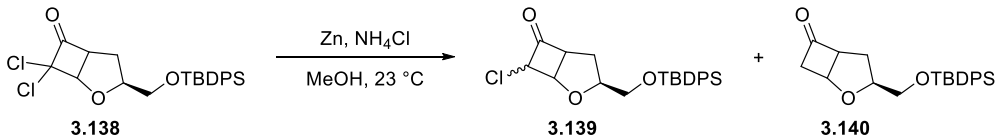
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.59 (m, 6H), 7.51 – 7.33 (m, 9H), 4.78 (d, *J* = 5.7 Hz, 1H), 4.41 (tt, *J* = 7.3, 4.9 Hz, 1H), 4.35 – 4.17 (m, 1H), 3.69 (d, *J* = 4.9 Hz, 2H), 2.39 (ddd, *J* = 13.3, 7.1, 3.6 Hz, 1H), 2.27 (ddd, *J* = 13.2, 10.7, 7.4 Hz, 1H), 1.04 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 135.6, 135.6, 133.2, 133.0, 129.8, 129.8, 127.8, 127.8, 86.1, 83.2, 64.7, 61.3, 30.5, 26.7, 19.2.

HRMS (ESI): calcd. for $C_{23}H_{26}Cl_2NaO_3Si$ $[M+Na]^+$: 471.0920; found: 471.0909.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3072, 2934, 2856, 1810, 1472, 1428, 1110, 996, 823, 742, 703.

$[\boldsymbol{\alpha}]_{\boldsymbol{20}}^{\boldsymbol{D}}$ = +16.0 (c = 0.500 in dichloromethane)



3.138 **3.139** (7%) **3.140** (28%)

Synthesis of cyclobutane **3.140**: To a solution of a diastereomeric mixture of butanone **3.138** (211 mg, 469 µmol, 1 equiv) in methanol (4.70 mL) was added zinc (307 mg, 4.69 mmol, 10.0 equiv) and ammonium chloride (201 mg, 3.76 mmol, 8.00 equiv) in sequence at 23 °C. After 16 h, the reaction mixture was filtered over Celite® and concentrated to a volume of approximately 1 mL and the crude product was purified by flash column chromatography on silica gel (30% diethyl ether in pentane) to afford cyclobutane **3.140** (50.2 mg, 132 µmol, 28%, d.r. 1.8:1) as a colorless oil and chloride **3.139** (14.2 mg, 34.3 µmol, 7%) as a colorless oil.

major diastereomer of **3.140**

TLC (20% ethyl acetate in cyclohexane): R_f: 0.21 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.61 (m, 4H), 7.49 – 7.33 (m, 6H), 4.94 – 4.84 (m, 1H), 4.82 (dd, *J* = 5.2, 4.0 Hz, 1H), 4.36 (tt, *J* = 7.3, 5.0 Hz, 1H), 3.93 – 3.82 (m, 1H), 3.81 – 3.73 (m, 1H), 3.71 (dd, *J* = 7.0, 5.0 Hz, 2H), 2.37 (ddd, *J* = 12.9, 7.2, 2.9 Hz, 1H), 2.29 – 2.14 (m, 1H), 1.05 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.0, 135.8, 133.3, 129.8, 127.8, 85.4, 74.7, 65.0, 62.8, 61.4, 31.1, 26.9, 19.3.

HRMS (ESI): calcd. for $C_{23}H_{28}NaO_3Si$ $[M+Na]^+$: 403,1700; found: 403.1699.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3071, 2931, 2858, 1801, 1650, 1611, 1472, 1428, 1389, 1253, 1112, 997, 823, 741, 703.

Mono chloro cyclobutane

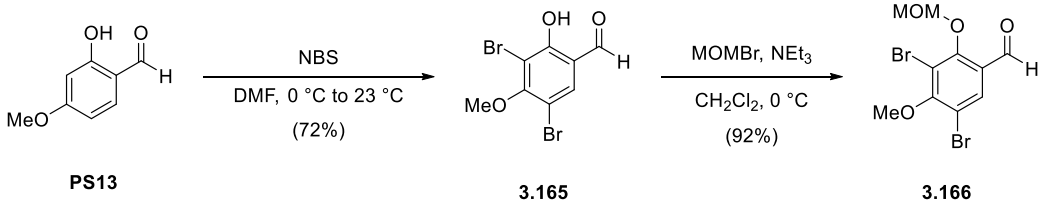
TLC (20% ethyl acetate in cyclohexane): R_f: 0.32 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.59 (m, 4H), 7.49 – 7.33 (m, 6H), 5.04 (t, *J* = 5.8 Hz, 1H), 4.84 (dd, *J* = 6.1, 4.6 Hz, 1H), 4.23 (ddt, *J* = 9.7, 5.8, 4.0 Hz, 1H), 3.95 (dddd, *J* = 9.3, 6.0, 4.6, 1.1 Hz, 1H), 3.83 (dd, *J* = 11.0, 4.2 Hz, 1H), 3.77 (dd, *J* = 11.0, 3.9 Hz, 1H), 2.34 (ddt, *J* = 12.6, 5.7, 1.0 Hz, 1H), 2.03 (dt, *J* = 12.6, 9.4 Hz, 1H), 1.06 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 205.2, 135.8, 135.7, 133.4, 133.4, 129.9, 129.9, 127.9, 127.9, 81.9, 74.1, 65.1, 64.0, 63.1, 32.1, 27.0, 19.4.

HRMS (ESI): calcd. for $C_{23}H_{27}ClNaO_3Si$ $[M+Na]^+$: 437.1310; found: 437.1310.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3071, 2930, 2858, 1794, 1472, 1428, 1390, 1213, 1105, 992, 935, 823, 742, 703.



PS13 **3.165** **3.166**

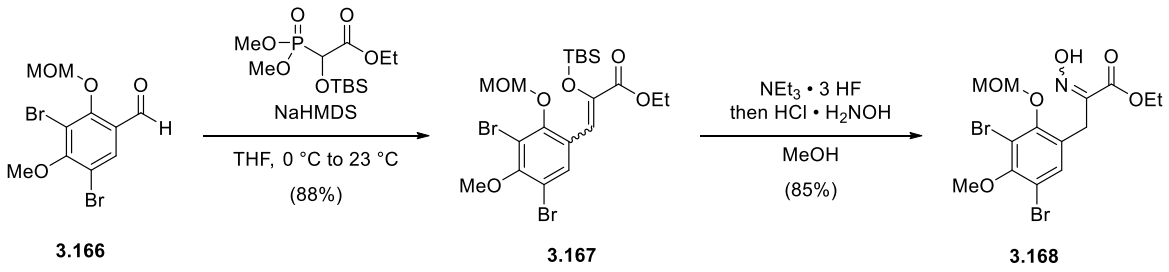
Synthesis of aldehyde **3.166**: To a solution of aldehyde **PS13** (1.10 g, 7.23 mmol, 1 equiv) in dimethylformamide (2 mL) was added a solution of *N*-bromosuccinimide (2.00 M in

dimethylformamide, 7.95 mL, 15.9 mmol, 2.20 equiv) dropwise at 0 °C. The resulting mixture was stirred 10 min at 0 °C, before it was allowed to warm to 23 °C. After 30 min, the reaction mixture was diluted with diethyl ether (50 mL) and the organic phase was washed with water (2x20 mL), sodium thiosulfate (2x20 mL) to quench excess of *N*-bromosuccinimide and the washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate concentrated to give a brown solid. The crude products was recrystallized (50% diethyl ether in cyclohexane) to afford aldehyde **3.165** (1.61 g, 5.19 mmol, 72%) as colorless needles.

All analytical data were in agreement with the literature.[142]

To a solution of aldehyde **3.165** (668 mg, 2.16 mmol, 1 equiv) in tetrahydrofuran (7.2 mL) was added triethylamine (480 µL, 3.45 mmol, 1.60 equiv) and bromo(methoxy)methane (293 µL, 323 mmol, 1.50 equiv) at 0 °C and the reaction mixture was allowed to warm to 23 °C. After 5 h, the reaction mixture was diluted with diethyl ether (50 mL) and the organic phase was washed with water (3×10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% diethyl ether in *n*-pentane) to afford aldehyde **3.166** (704 mg, 1.99 mmol, 92%) as a colorless solid.

All analytical data were in agreement with the literature.[142]



Synthesis of ester **3.168**: To a solution of ethyl 2-((tert-butyldimethylsilyl)oxy)-2-(dimethoxyphosphoryl)acetate (974 mg, 2.98 mmol, 1.50 equiv) was added a solution of sodium bis(trimethylsilyl)amide (1.00 M in tetrahydrofuran, 2.98 mL, 2.98 mmol, 1.50 equiv) dropwise at 0 °C. After 20 min, a solution of aldehyde **3.166** (200 mM in tetrahydrofuran, 9.94 mL, 1.99 mmol, 1 equiv) was added at 0 °C and after complete addition the reaction was allowed to warm to 23 °C. After 5 h diethyl ether (50 mL) and saturated aqueous solution of ammonium chloride solution (30 mL) was added to quench excess of base and the phases were separated. The aqueous phase was extracted with diethyl ether (3×50 mL), the combined phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a pale yellow oil. The crude product was purified by flash column chromatography on silica gel (5% diethyl ether in *n*-pentane)

to afford a mixture of (*Z*)- and (*E*)-silyl ether **3.167** (978 mg, 1.76 mmol, 88%, *E*/*Z* = 1.6:1.0) as a pale yellow oil, which was used in the next step without further purification.

To a solution of crude alkene **3.167** (831 mg, 1.50 mmol, 1 equiv) in methanol (10 mL) was added triethylamine trihydrofluoride (290 µL, 1.80 mmol, 1.20 equiv). After 1 h, hydroxylamine hydrochloride (208 mg, 3.00 mmol, 2.00 equiv) was added at 23 °C. After 8 h, the reaction mixture was diluted with ethyl acetate (60 mL) and the organic phase was washed with water (3×30 mL) and saturated aqueous solution of sodium hydrogen carbonate (30 mL), the washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to afford ester **3.169** (581 mg, 1.28 mmol, 85%) as a colorless solid, which was pure enough to use without further purification.

TLC (20% ethyl acetate in cyclohexane): R_f: 0.14 (UV, CAM)

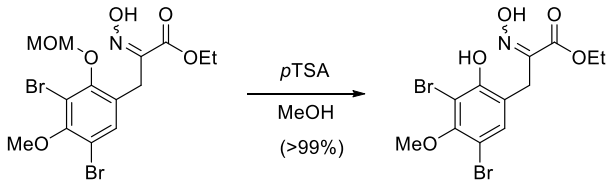
mp: 104.6 – 112.1 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 7.23 (s, 1H), 5.14 (s, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.06 (s, 2H), 3.86 (s, 3H), 3.65 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 154.0, 153.5, 150.6, 131.8, 128.5, 114.7, 113.2, 100.0, 62.3, 60.7, 58.3, 25.4, 14.2.

HRMS (ESI): calcd. for $C_{14}H_{17}{}^{79}Br^{81}BrNNaO_6$ $[M+Na]^+$: 477.9294; found: 477.9264.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3295, 2981, 2939, 2874, 2846, 1722, 1466, 1426, 1403, 1374, 1300, 1208, 1151, 1086, 1045, 1023, 975, 920.



3.168 **3.169**

Synthesis of phenol **3.169**: To a solution of oxime **3.168** (535 mg, 1.18 mmol, 1 equiv) in methanol (12 mL) was added *p*-toluenesulfonic acid monohydrate (2.20 mg, 11.8 µmol, 1.00 mol%). After 16 h, the mixture was concentrated and the residue was diluted with ethyl acetate (40 mL). The organic phase was washed with water (30 mL), saturated aqueous sodium hydrogen carbonate solution (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 to

afford phenol **3.169** (4.83 mg, 1.18 mmol, >99%) as an orange solid, which was pure enough to use without further purification.

TLC (20% ethyl acetate in cyclohexane): R_f: 0.11 (UV, CAM)

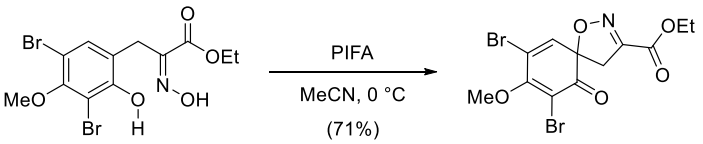
mp: 95.4 – 96.8 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.42 (s, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.90 (s, 2H), 3.84 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 153.9, 151.8, 149.8, 133.7, 119.6, 107.8, 107.6, 63.0, 60.7, 25.6, 14.1.

HRMS (ESI): calcd. for $C_{12}H_{14}{}^{79}Br^{81}BrNO_5$ $[M+Na]^+$: 411.9213; found: 411.9211.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3285, 2983, 2936, 1721, 1593, 1466, 1433, 1394, 1299, 1233, 1201, 1153, 1114, 1056, 1016, 966, 908, 851, 780, 760, 728.



3.169 **3.170**

Synthesis of spiro **3.170**: To a solution of phenol **3.169** (200 mg, 487 µmol, 1 equiv) in acetonitrile (5 mL) was added (bis(trifluoroacetoxy)iodo)benzene (251 mg, 584 µmol, 1.20 equiv) at 0 °C. After 1 h, the reaction mixture was allowed to warm to 23 °C and the solution was diluted with dichloromethane (15 mL) and saturated aqueous thiosulfate (10 mL) to quench excess of hypervalent iodine, saturated aqueous sodium hydrogen carbonate (10 mL) and water (10 mL). The organic phase was separated and the aqueous phase was extracted with dichloromethane (3×20 mL), the combined organic phases 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 (30% diethyl ether in *n*-pentane) to afford spiro **3.170** (414 mg, 344 µmol, 71%) as an orange solid.

TLC (20% ethyl acetate in cyclohexane): R_f: 0.07 (UV, CAM)

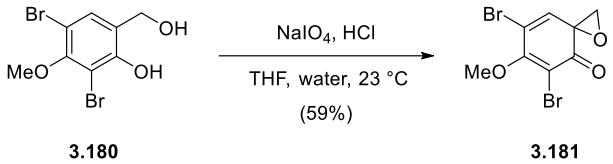
mp: 124.6 – 126.8 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (s, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 4.17 (s, 3H), 3.61 (d, *J* = 17.8 Hz, 1H), 3.29 (d, *J* = 17.9 Hz, 1H), 1.37 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 188.9, 163.3, 159.4, 150.3, 136.2, 120.9, 106.9, 86.9, 62.8, 62.3, 44.7, 14.2.

HRMS (ESI): calcd. for $C_{12}H_{13}{}^{79}Br^{81}Br\ NNaO_6$ $[M+Na+H_2O]^+$: 449.8981; found: 449.8778.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3059, 2983, 2942, 1721, 1681, 1602, 1546, 1446, 1379, 1326, 1289, 1289, 1238, 1129, 991, 947, 900, 831, 776, 741.



3.180 **3.181**

Synthesis of epoxide **3.181**: To a solution of phenol **3.180** (50.0 mg, 160 µmol, 1 equiv) in tetrahydrofuran (1 mL) and aqueous hydrogen chloride (1.0 M, 0.10 mL) was added a aqueous solution of hydrogen chloride (1.0 M, 0.70 mL) and sodium periodate (500 mM in water, 2.56 mL, 1.28 mmol, 8.00 equiv) at 23 C. After 1 ×The crude product was purified by flash column chromatography (40% diethyl ether in pentane) to yield epoxide **3.181** (29.5 mg, 81.0 µmol, 59%) as an orange solid.

NOTE: compound was found to be instable on silica gel, high temperature and decomposed over time (weeks)

TLC (20% ethyl acetate in cyclohexane): R_f: 0.26 (UV, CAM)

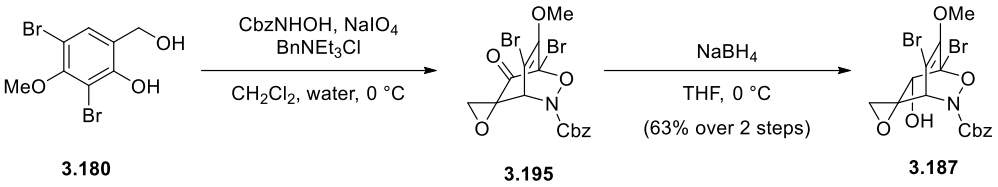
mp: >48.6 °C (decomposition)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (s, 1H), 4.13 (s, 3H), 3.43 (d, *J* = 8.0 Hz, 1H), 3.26 (d, *J* = 7.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 187.2, 164.5, 138.3, 119.9, 110.9, 61.9, 59.3, 57.6.

HRMS (ESI): no mass was obtained for this compound.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3521, 3088, 3062, 3029, 3002, 2944, 1760, 1706, 1655, 1626, 1568, 1475, 1402, 1383, 1285, 1246, 1195, 1093, 1053, 975, 935, 899, 790, 738, 700.



3.180 **3.195** **3.187**

Synthesis of epoxide **3.187**: To a solution of sodium periodate (1.06 g, 4.97 mmol, 3.10 equiv) in water (16 mL) was added a solution of phenol **3.180** (500 mg, 1.60 mmol, 1 equiv) and *N*-benzyl-*N*,*N*,*N*-triethylammonium chloride (37.0 mg, 0.160 mmol, 10.0 mol%) in dichloromethane (12 mL) at 0 °C. After 1 h, a solution of benzyl hydroxycarbamate (466 mg, 2.80 mmol, 1.70 equiv) in dichloromethane (8.5 mL) was added over 2 h via syringe pump, maintaining the reaction temperature at 0 °C. After complete addition, the reaction was stirred for 1.5 h at 0 °C, before the phases were separated and the aqueous phase was extracted with dichloromethane (3×20 mL). The combined organic phases were washed with sat aqueous sodium chloride solution (20 mL), the washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated (Note: the rotary evaporation water bath was maintained at temperature below 20 °C). The crude product was purified via flash chromatography on silica gel (gradient 10% to 50% of EtOAc in *n*-pentane). The solvent was removed under reduced pressure, mantaining the temperature below 20 °C. (Note complete concentration lead to complete decomposition) The material was directly used in the next step.

To a solution of crude epoxide **3.195** in tetrahydrofuran (16 mL) was added molecular sieves (4 Å, 1 g) and sodium borohydride (20.0 mg, 529 µmol, 0.33 equiv) at 0 °C. After 1 h, the reaction mixture was diluted with sat aqueous ammonium chloride solution (20 mL) and dichloromethane (20 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3×20 mL), the combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography (40% diethyl ether in pentane) to yield epoxide **3.187** (482 mg, 1.01 mmol, 63%) as a yellow oil.

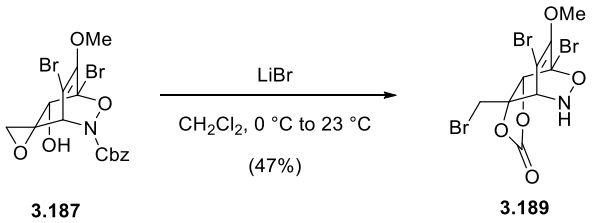
TLC (20% ethyl acetate in cyclohexane): R_f: 0.19 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.31 (m, 5H), 5.31 – 5.16 (m, 2H), 4.45 (s, 1H), 3.88 (s, 3H), 3.82 (s, 1H), 3.21 (d, *J* = 4.4 Hz, 1H), 2.99 (d, *J* = 4.3 Hz, 1H), 2.83 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 151.6, 135.1, 128.8, 128.7, 95.8, 93.3, 70.4, 69.2, 65.8, 61.4, 60.5, 56.5, 52.4.

HRMS (ESI): calcd. for $C_{16}H_{15}{}^{79}Br^{81}BrNNaO_6$ $[M+Na]^+$: 499.9138; found: 499.9043.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3459, 2928, 2852, 1726, 1633, 1534, 1498, 1455, 1386, 1279, 1231, 1150, 1043, 964, 775, 699.



3.187 **3.189**

Synthesis of carbonate **3.189**: To a solution of epoxide **3.187** (99.2 mg, 0.208 mmol, 1 equiv) was added lithium bromide (90.4 mg, 1.04 mmol, 5.0 equiv.) in dichloromethane (1.0 mL) at 0 °C. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 1 h, the reaction mixture was diluted with water (5 mL) and ethyl acetate (5 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (3×5 mL), the combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography (25% ethyl acetate in *n*-pentane) to yield carbonate **3.189** (53.8 mg, 120 µmol, 47%) as a colorless solid.

Crystals obtained by Dr. Gabriele Prina Cerai were good enough for X-ray analysis.

TLC (20% ethyl acetate in cyclohexane): R_f: 0.11 (CAM)

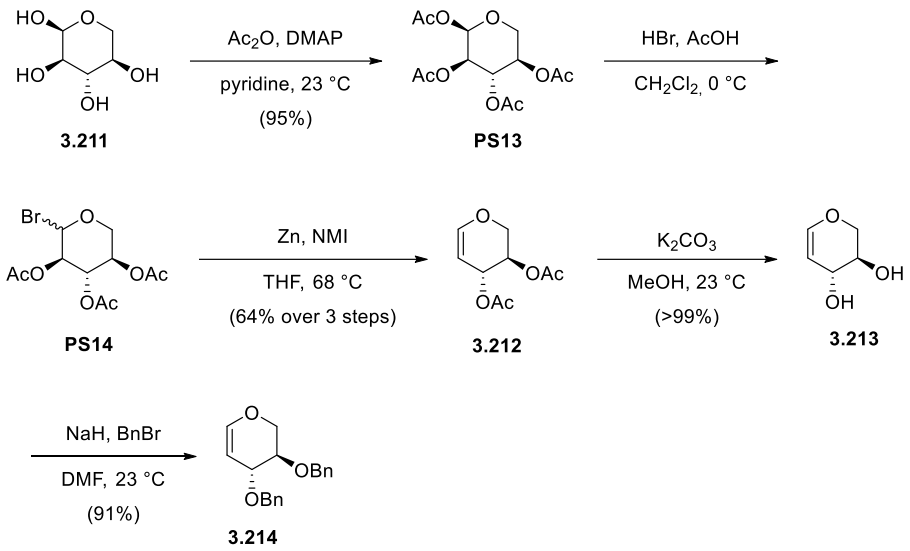
mp: 126.4 – 134.3 °C (decomposition)

^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 6.14 (s, 1H), 4.48 (s, 1H), 4.24 (s, 1H), 4.07 (s, 3H), 3.77 (s, 1H), 3.55 (d, J = 12.0 Hz, 1H).

^{13}C NMR (101 MHz, Methylene Chloride-d_2) δ 151.9, 150.4, 92.7, 89.1, 81.2, 80.8, 65.13, 61.9, 34.9.

HRMS (ESI): calcd. for $C_9H_8{}^{79}Br_2{}^{81}BrNNaO_5$ $[M+Na]^+$: 471.7824; found: 471.7847.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3228, 2971, 1794, 1626, 1452, 1425, 1401, 1356, 1258, 1163, 1103, 1062, 987, 903, 823, 790, 764, 747.



Synthesis of enol ether **3.214**: To a solution of α-D-xylose (**3.211**) (25.0 g, 167 mmol, 1 equiv) in pyridine (120 mL) was added DMAP (12.0 g, 16.7 mmol, 10 mol%) and acetic anhydride (120 mL, 1.30 mol, 8.00 equiv) in sequence at 0 °C and the resulting yellow mixture was allowed to warm to 23 °C. After 16 h, the reaction mixture was diluted with ethyl acetate (500 mL) and washed with water (200 mL), saturated sodium bicarbonate solution (5x200 mL), aqueous hydrochloric acid (1.00 M, 5×200 mL), water (200 mL) and 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 to give a yellow oil (50.3 g, 158 mmol, 95%) (50.8 g, 160 mmol, 96%), which was pure enough and used without further purification.

All analytical data matches with the literature.[143]

Traces of water were removed by co-evaporation with toluene and **PS13** was dissolved in dichloromethane (300 mL). A solution of hydrogen bromide in acetic acid (150 mL, 790 mmol, 5.00 equiv) was added dropwise over 1 h at 0 °C. After complete addition, the reaction mixture was stirred for further 5 min at 0 °C, before the orange reaction mixture was diluted with dichloromethane (150 mL) and ice cold water (300°mL). The phases were separated, the aqueous phase was extracted with dichloromethane (3×150 mL) and the combined organic phases were washed with saturated sodium bicarbonate solution (250 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a colorless liquid. Traces of water were removed by co-evaporation with toluene. The crude bromide **PS13** was directly used in the next step without further purification.

To a suspension of zinc (61.9 g, 947 mmol, 6.00 equiv) in tetrahydrofuran (750 mL) was added 1-methylimidazole (12.7 mL, 160 mmol, 1.01 equiv). After 15 min, a solution of crude bromide **PS13** in tetrahydrofuran (350 mL) was added and the reaction mixture was heated to 68 °C. After

1 h, the reaction mixture was filtered through Celite® and the filtrate was concentrated. The crude product was purified by flash column chromatography (40% diethyl ether in *n*-pentane) to give the cyclic enol ether **3.212** as a pale yellow oil (20.3 g, 10.0 mmol, 64% over 2 steps).

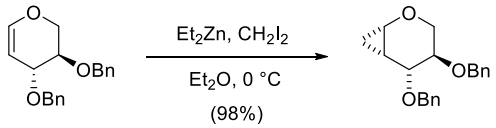
All analytical data matches with the literature.[143]

To a solution of bis-acetate **3.212** (20.2 g, 101 mmol, 1 equiv) in methanol (500 mL) was added potassium carbonate (8.38 g, 60.6 mmol, 60.0 mol%) at 23 °C. After 2 h, the reaction mixture was concentrated and the residue was purified by flash column chromatography (10% methanol in dichloromethane) to yield diol **3.213** as a yellow oil (11.7 g, 101 mmol, >99%).

All analytical data matches with the literature.[144]

To a solution of diol **3.213** (10.2 g, 87.8 mmol, 1 equiv) in *N*,*N*-dimethyl formamide (400 mL), was added sodium hydride (12.0 g, 307 mmol, 3.50 equiv) at 0 °C. After 30 min, benzyl bromide (35.4 mL, 299 mmol, 3.40 equiv) was added dropwise. After complete addition, the reaction mixture was allowed to warm to 23 °C. After 2 h, the brownish reaction mixture was diluted with dichloromethane (100 mL) and the excess of sodium hydride was quenched by the addition of water (1.00 L). The aqueous phase was extracted with dichloromethane (3×150 mL). The combined organic phases were washed with aqueous lithium chloride solution (1.00 M, 200 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give an orange oil. The crude product was purified by flash column chromatography (15% diethyl ether in *n*-pentane) to yield the enol ether **3.214** as a slightly orange oil (23.7 g, 79.9 mmol, 91%).

All analytical data matches with the literature.[144]



3.214 **3.215**

Synthesis of cyclopropane **3.215**: To a solution of enol ether **3.214** (20.0 g, 1.00 equiv, 67.4 mmol) in diethyl ether (450 mL) was added a solution of diethyl zinc (1.00 M in hexane, 47.5 mL, 47.5 mmol, 3.00 equiv) and diiodomethane (3.83 mL, 47.5 mmol, 3.00 equiv) in sequence at 0 °C. After 3 h, the excess of diethyl zinc was quenched by the addition of saturated ammonium chloride solution (100 mL) at 0 °C. The phases were separated and the aqueous phase was extracted with diethyl ether (3×100 mL). The combined organic phases were washed with 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 to give an orange oil. The crude product was purified by flash column chromatography (10% diethyl ether in *n*-pentane) to yield cyclopropane **3.215** (20.6 g, 66.2 mmol, 98%) as a pale yellow oil.

TLC (10% ethyl acetate in cyclohexane) R_f: 0.23 (UV, CAM)

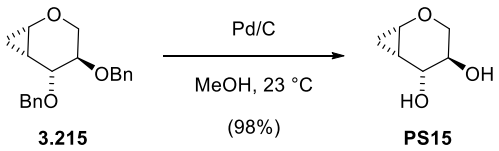
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.23 (m, 10H), 4.83 (d, *J* = 11.8 Hz, 1H), 4.73 (d, *J* = 11.7 Hz, 1H), 4.65 (d, *J* = 11.7 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.08 (t, *J* = 7.2 Hz, 1H), 3.77 (ddd, *J* = 6.8, 5.6, 3.1 Hz, 1H), 3.62 (dd, *J* = 10.7, 4.1 Hz, 1H), 3.39 (ddd, *J* = 10.9, 7.1, 4.1 Hz, 1H), 3.17 (t, *J* = 10.6 Hz, 1H), 1.37 (dq, *J* = 9.9, 7.1 Hz, 1H), 0.81 – 0.70 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8, 138.6, 128.5, 127.9, 127.8, 127.8, 127.7, 77.9, 77.4, 72.9, 70.5, 66.5, 55.8, 15.8, 11.8.

HMRS (ESI) calcd. for $C_{20}H_{22}NaO_9$ $[M+Na]^+$: 333.1461; found 333.1454

IR (ATR, neat) $\tilde{\nu}_{max}$: 3028, 2863, 1496, 1454, 1373, 1317, 1214, 1182, 1154, 1073, 1028, 994, 911, 858, 735, 698, 607, 456.

$[\boldsymbol{\alpha}]_{\boldsymbol{20}}^{\boldsymbol{D}}$ = −46.4 (c = 0.300 in chloroform)



3.215 **PS15**

Synthesis of diol **PS15**: To a solution of cyclopropane **3.215** (4.44 g, 14.3 mmol, 1 equiv) in methanol (150 mL) was added palladium (10.0 wt on activated charcoal, 1.50 g, 1.43 mmol, 10.0 mol%) and the reaction mixture was purged with hydrogen gas for 20 min. After 16 h under hydrogen atmosphere, Celite® was added and the black reaction mixture was filtered over Celite®, washed with a mixture of 10% methanol in dichloromethane (3×100 mL) and the filtrate was concentrated. The crude product was purified by column chromatography on silica-gel (8% methanol in dichloromethane) to yield the diol **PS15** (1.82 g, 14.0 mmol, 98%). as a colorless solid.

TLC (10% methanol in dichloromethane) R_f: 0.22 (CAM)

mp: 96.3 – 97.5 °C

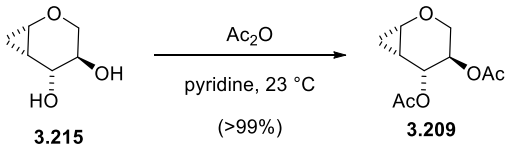
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (dd, *J* = 8.0, 6.9 Hz, 1H), 3.80 – 3.68 (m, 1H), 3.59 (s, 2H), 3.53 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.40 (ddd, *J* = 10.5, 8.0, 4.0 Hz, 1H), 3.17 (t, *J* = 10.5 Hz, 1H), 1.48 – 1.34 (m, 1H), 0.72 (dd, *J* = 8.1, 3.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 72.1, 71.6, 68.6, 55.3, 29.8, 18.6, 11.9.

HMRS (ESI) calcd. for $C_6H_{10}NaO_3$ $[M+Na]^+$: 153.0522; found 153.0519

IR (ATR, neat) $\tilde{\nu}_{max}$: 3403, 3026, 2933, 2865, 1468, 1423, 1388, 1256, 1213, 1162, 1108, 1090, 1061, 1048, 1011, 976, 892, 853, 751, 699, 599.

$[\boldsymbol{\alpha}]_{\boldsymbol{20}}^{\boldsymbol{D}}$ = −82.4 (c = 1.35 in chloroform)



3.215 **3.209**

Synthesis of bis-acetate **3.209**: To a solution of diol **3.215** (1.80 g, 13.9 mmol, 1 equiv) in dichloromethane (15 mL) was added pyridine (5.60 mL, 69.3 mmol, 5.00 equiv), DMAP (169 mg, 1.39 mmol, 10 mol%) and acetic anhydride (5.24 mL, 55.5 mmol, 4.00 equiv) in sequence at 0 °C and the reaction mixture was allowed to warm to 23 °C. After 3 h, the reaction mixture was diluted with ethyl acetate (100 mL) and the organic phase was washed with water (50 mL), saturated aqueous sodium bicarbonate solution (3×50 mL), water (50 mL), aqueous hydrochloric acid (1.0 M, 3×50 mL), water (50 mL) and brine (50 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 (10% diethyl ether in *n*-pentane) to yield acetate **3.209** (2.96 g, 13.8 mmol, quant.) a pale yellow oil.

TLC (5% ethyl acetate in cyclohexane) R_f = 0.31 ($KMnO_4$)

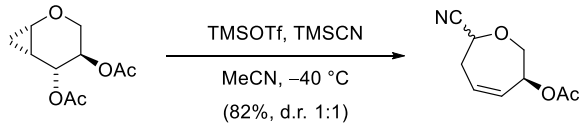
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 – 5.25 (m, 1H), 4.75 (ddd, *J* = 10.5, 8.1, 4.3 Hz, 1H), 3.78 (ddd, *J* = 6.8, 5.6, 3.0 Hz, 1H), 3.63 (dd, *J* = 10.6, 4.3 Hz, 1H), 3.25 (t, *J* = 10.5 Hz, 1H), 2.09 (s, 3H), 2.04 (s, 3H), 1.67 – 1.52 (m, 1H), 0.95 – 0.69 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 170.2, 71.2, 70.0, 65.6, 55.4, 21.3, 21.1, 15.8, 12.3.

HMRS (ESI) calcd. for $C_{10}H_{14}NaO_5$ $[M+Na]^+$: 237.0733; found 273.0729

IR (ATR, neat) $\tilde{\nu}_{max}$: 1732, 1438, 1370, 1227, 1191, 1156, 1075, 1030, 920, 852, 813, 760, 605, 506.

$[\boldsymbol{\alpha}]_{\boldsymbol{20}}^{\boldsymbol{D}}$ = −88.4 (c = 0.700 in chloroform)



3.209 **3.210**

Synthesis of nitrile **3.210**: To a solution of acetate **3.209** (2.94 g, 13.7 mmol, 1.00 equiv) in acetonitrile (68 mL) was added trimethyl-silyl-cyanide (9.20 mL, 69.0 mmol, 5.00 equiv) in one portion and trimethyl-silyl-triflate (740 µL, 4.10 mmol, 30.0 mol%) dropwise at −40 °C. After 2.5 h, excess of Lewis acid was quenched by the addition of saturated aqueous sodium hydrogen carbonate solution (50 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3×150 mL), the combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography (40% diethyl ether in *n*-pentane) to give nitrile **3.210** (2.05 g, 11.3 mmol, 82%, d.r. 1:1) as a pale yellow oil.

A analytical sample was purified by HPLC chromatography (5% ethyl acetate in *n*-hexane grading to 25% ethyl acetate in *n*-hexane in 60 min) to separate both diasteromers.

less polar diastereomer

TLC (20% ethyl acetate in cyclohexane) R_f = 0.23 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 – 5.79 (m, 2H), 5.47 – 5.35 (m, 1H), 4.66 (dd, *J* = 8.3, 3.8 Hz, 1H), 4.10 (dd, *J* = 13.0, 2.9 Hz, 1H), 3.85 – 3.69 (m, 1H), 2.84 – 2.62 (m, 2H), 2.09 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 132.7, 127.3, 117.4, 71.8, 69.2, 67.7, 33.8, 21.1.

HMRS (ESI) calcd. for $C_9H_{12}NNaO_3$ $[M+Na]^+$: 204.0631; found 204.0628.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2930, 1735, 1372, 1236, 1108, 1039, 952, 700.

$[\boldsymbol{\alpha}]_{\boldsymbol{20}}^{\boldsymbol{D}}$ = +2.7 (c = 0.85 in dichloromethane)

more polar diastereomer

TLC (20% ethyl acetate in cyclohexane) R_f = 0.22 (CAM)

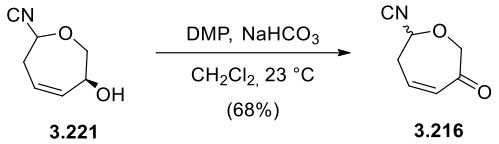
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (dd, *J* = 11.9, 4.1 Hz, 1H), 5.90 – 5.82 (m, 1H), 5.49 – 5.38 (m, 1H), 4.68 (dd, *J* = 6.4, 3.6 Hz, 1H), 4.00 (dd, *J* = 12.6, 7.4 Hz, 1H), 3.80 (dd, *J* = 12.6, 3.1 Hz, 1H), 2.82 – 2.63 (m, 2H), 2.10 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 133.9, 126.5, 117.1, 71.8, 71.5, 68.7 67.3, 34.0, 21.1.

HMRS (ESI) calcd. for $C_9H_{12}NNaO_3$ $[M+Na]^+$: 204.0631; found 204.0628.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2930, 1736, 1372, 1236, 1108, 1039, 952, 700.

$[\boldsymbol{\alpha}]_{\boldsymbol{20}}^{\boldsymbol{D}}$ = +6.6 (c = 1.7 in dichloromethane)



3.221 **3.216**

Synthesis of ketone **3.216**: To a solution of alcohol **3.221** (230 mg, 1.65 mmol, 1 equiv) in dichloromethane (17 mL) was added Dess−Martin periodate (1.75 g, 4.13 mmol, 2.00 equiv) and sodium hydrogen carbonate (417 mg, 4.96 mmol, 3.00 equiv) After 4 h, saturated aqueous thiosulfate (20 mL) and saturated aqueous sodium hydrogen carbonate (20 mL) were added to quench excess of Dess−Martin periodate. The phases were separated and the aqueous phase was extracted with dichloromethane (3×10 mL), the combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by column chromatography (40% diethyl ether in *n*-pentane) to afford ketone **3.216** (155 mg, 1.13 mmol, 68%) as a colorless oil.

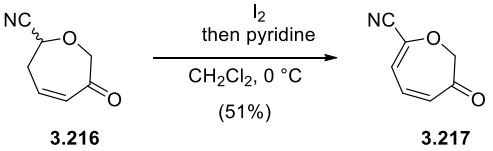
TLC (20% ethyl acetate in cyclohexane): R_f: 0.15 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (ddd, *J* = 12.2, 6.0, 4.1 Hz, 1H), 6.22 – 6.05 (m, 1H), 4.66 (dd, *J* = 9.9, 3.9 Hz, 1H), 4.46 (d, *J* = 18.2 Hz, 1H), 4.33 (d, *J* = 18.1 Hz, 1H), 3.08 (dddd, *J* = 18.7, 9.9, 4.2, 2.4 Hz, 1H), 2.99 – 2.87 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 20010, 139.5, 132.2, 116.7, 76.3, 66.7, 36.9.

HRMS (ESI): calcd. for $C_7H_9NNaO_3$ $[M+H_2O+Na]^+$: 178.0475; found: 178.0461

IR (ATR, neat) $\tilde{\nu}_{max}$: 3482, 2928, 1721, 1663, 1397, 1346, 1277, 1120.



Synthesis of ketone **3.217**: To a solution of nitrile **3.216** (3.0 mg, 22 µmol. 1 equiv) in dichloromethane (0.20 mL) was added iodine (6.7 mg, 26 µmol, 1.2 equiv), DMAP (0.3 mg, 2.2 µmol, 10 mol%) and pyridine (2.6 µL, 33 mmol, 1.5 equiv) at 23 °C. After 24 h, the reaction mixture was concentrated and the crude product was purified by flash column chromatography (30% diethyl ether in pentane) to yield nitrile **3.217** (1.5 mg, 11 µmol, 51%) as a yellow oil.

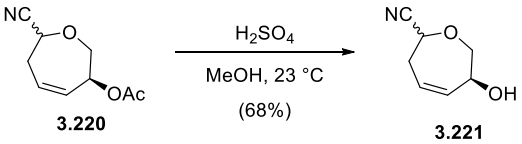
TLC (25% ethyl acetate in cyclohexane): R_f: 0.15 ($KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (dd, *J* = 12.0, 8.0 Hz, 1H), 6.59 (dd, *J* = 11.9, 0.7 Hz, 1H), 6.22 (dd, *J* = 8.0, 0.7 Hz, 1H), 4.59 (d, *J* = 0.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.3, 137.9, 135.6, 134.5, 119.1, 114.4, 78.5.

HRMS (ESI): calcd. for $C_7H_6NO_2$ $[M+H]^+$: 136.0393; found: 136.0219.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2963, 2926, 2850, 1734.



Synthesis of alcohol **3.221**: To a solution of acetate **3.220** (250 mg, 1.40 mmol, 1 equiv) in dichloromethane (6 mL) was added sulfuric acid (80.0 µL, 1.40 mmol, 1.00 equiv) at 23 °C. After 16 h, excess of acid was quenched with saturated sodium bicarbonate solution (10 mL) and the mixture was extracted with dichloromethane (3×10 mL). The combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to afford alcohol **3.221** (160 mg, 930 µmol, 68%, d.r. 1:1) as a pale yellow oil, which was pure enough to use without further purification.

Mixture of diastereomers

TLC (5% methanol in dichloromethane) R_f = 0.25 (CAM)

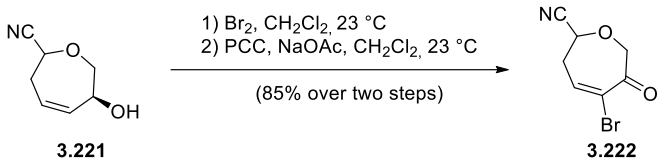
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 – 5.98 (m, 1H), 5.98 – 5.90 (m, 1H), 5.89 – 5.69 (m, 2H), 4.67 (dd, *J* = 6.4, 3.7 Hz, 1H), 4.60 (dd, *J* = 9.3, 3.4 Hz, 1H), 4.49 – 4.31 (m, 2H), 4.09 (ddd, *J* = 12.7,

3.0, 0.7 Hz, 1H), 3.95 (dd, *J* = 12.5, 7.2 Hz, 1H), 3.80 (ddd, *J* = 12.5, 3.0, 0.8 Hz, 1H), 3.73 – 3.60 (m, 1H), 2.85 – 2.57 (m, 4H), 1.92 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 136.7, 124.9, 124.7, 117.8, 117.4, 72.0, 71.5, 70.5, 70.4, 67.9, 67.4, 33.8, 33.7.

HMRS (ESI) calcd. for $C_7H_9NNaO_2$ $[M+Na]^+$: 162.0525; found 162.0525

IR (ATR, neat) $\tilde{\nu}_{max}$: 3406, 2924, 1981, 1426, 1217, 1128, 1047, 934, 878, 755, 703.



3.221 **3.222**

Synthesis of enone **3.222**: A solution of alcohol **3.221** (160 mg, 1.20 mmol, 1 equiv) in dichloromethane (11 mL) was added bromine (77.0µL, 1.50 mmol, 1.30 equiv) at 0 °C and the red-brown reaction mixture was allowed to warm to 23 °C. After 2 h, excess of bromine was quenched by the addition of saturated aqueous sodium sulfite solution (10 mL) and the phases were separated. The aqueous phase was extracted with dichloromethane (3×10 mL). The combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was dissolved in dichloromethane (14 mL) and pyridinium chlorochromate (340 mg, 1.60 mmol, 1.70 equiv), molecular sieves (4.00 g) and anhydrous sodium acetate (78.0 mg, 950 µmol, 1.00 equiv) were added in sequence at 23 °C. After 16 h, the brown reaction mixture was diluted with diethyl ether (10 mL) and the formed precipitate was removed by filtration through a plug of Celite® and the yellow filtrate was concentrated to afford a brown oil. The crude product was purified by flash column chromatography (40% diethyl ether in *n*-pentane) to yield ketone **3.222** (180 mg, 810 µmol, 85% over two steps) as a yellow oil.

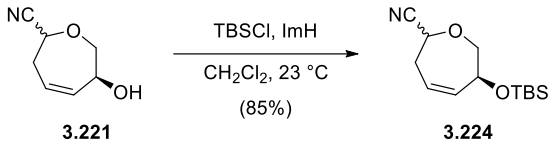
TLC (7% methanol in dichloromethane) R_f: 0.48 (UV, KMnO4)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.19 (dd, *J* = 7.8, 5.6 Hz, 1H), 4.70 (dd, *J* = 10.0, 5.2 Hz, 1H), 4.47 (d, *J* = 7.3 Hz, 2H), 3.09 - 2.87 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.4, 138.5, 127.9, 116.7, 72.6, 64.3, 34.1.

HMRS (ESI) calcd. for $C_7H_6BrNNaO_2$ $[M+Na]^+$: 237.9474; found 237.9470

IR (ATR, neat) $\tilde{\nu}_{max}$: 3506, 2926, 1691, 1604, 1423, 1341, 1188, 1110, 1051, 959, 938, 894, 853, 811, 689, 512, 488.



3.221 **3.224**

Synthesis of nitrile **3.224**: To a solution of alcohol **3.221** (154 mg, 1.11 µmol, 1 equiv) in dichloromethane (10 mL) was added DMAP (13.5 mg, 111 µmol, 10.0 mol%), imidazole (90.4 mg, 1.33 mmol, 1.20 equiv) and *tert*-butyldimethylsilyl chloride (175 mg, 1.16 mmol, 1.05 equiv) in sequence and the resulting mixture was stirred at 23 °C. After 16 h, the mixture was diluted with water (30 mL) to hydrolyze unreacted *tert*-butyldimethylsilyl chloride and the aqueous phase was extracted with dichloromethane (3×10 mL) and the combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a colorless oil. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) to afford nitrile **3.226** (239 mg, 942 µmol, 85%, d.r. 1:1) as a colorless oil.

Mixture of diastereomers

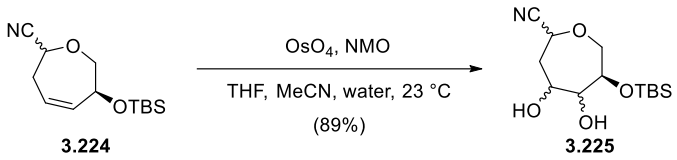
TLC (10% ethyl acetate in cyclohexane): R_f: 0.33 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$**)** δ 5.96 (dtd, *J* = 11.4, 2.8, 1.2 Hz, 1H), 5.86 (dtd, *J* = 11.8, 2.6, 1.2 Hz, 1H), 5.75 – 5.61 (m, 2H), 4.75 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.51 – 4.41 (m, 2H), 4.40 (dd, *J* = 10.2, 2.4 Hz, 1H), 3.92 (ddd, *J* = 12.0, 3.9, 1.2 Hz, 1H), 3.81 (dd, *J* = 12.1, 9.4 Hz, 1H), 3.70 (ddd, *J* = 12.1, 3.9, 1.3 Hz, 1H), 3.42 (dd, *J* = 12.0, 8.8 Hz, 1H), 2.83 – 2.64 (m, 2H), 2.64 – 2.46 (m, 2H), 0.89 (d, *J* = 2.4 Hz, 18H), 0.16 – 0.02 (m, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7, 139.9, 123.6, 122.3, 118.0, 117.0, 74.4, 71.2, 71.1, 70.4, 68.5, 66.1, 35.0, 33.7, 25.9, 18.2, -4.8, -4.7, -4.7, -4.7.

HRMS (ESI): calcd. for $C_{13}H_{23}NNaO_2Si$ $[M+Na]^+$: 276.1390; found: 276.1390.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3037, 2955, 2930, 2886, 2857, 1472, 1426, 1399, 1361, 1323, 1253, 1218, 1090, 1006, 939, 912, 835, 776, 700.



Synthesis of diol **3.225**: To a solution of alkene **3.224** (102 mg, 402 µmol, 1 equiv) in water (2 mL), tetrahydrofuran (2 mL) and acetonitrile (2 mL) was added osmium tetroxide (4% in water, 158 µL, 20.1 µmol, 5.00 mol%) and *N*-methylmorpholine *N*-oxide (61.3 mg, 5.23 µmol, 1.30 equiv). After 16 h, the reaction mixture was diluted with ethyl acetate (15 mL), water (10 mL) and saturated aqueous thiosulfate solution (1 mL) to quench excess of *N*-oxide. The phases were separated and the aqueous phase was extracted with ethyl acetate (3×15 mL), the combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a black oil. The crude product was purified by flash column chromatography (5% methanol in dichloromethane) to yield diol **3.226** (103 mg, 359 µmol, 89% (mixture of several diols)) as a yellow oil.

The two major diastereomers are characterized

More polar diastereomer

TLC (25% ethyl acetate in cyclohexane): R_f: 0.07 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (dd, *J* = 8.3, 5.8 Hz, 1H), 4.18 (t, *J* = 9.0 Hz, 1H), 4.06 – 3.98 (m, 1H), 3.83 – 3.77 (m, 1H), 3.73 (dd, *J* = 4.8, 1.9 Hz, 2H), 2.90 (d, *J* = 9.1 Hz, 1H), 2.79 (d, *J* = 6.4 Hz, 1H), 2.58 (ddd, *J* = 15.0, 8.4, 5.8 Hz, 1H), 2.10 (ddd, *J* = 15.0, 8.4, 2.2 Hz, 1H), 0.91 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 118.6, 74.6, 73.3, 70.7, 67.3, 64.3, 34.9, 25.8, 18.1, -4.6, -4.9.

HRMS (ESI): calcd. for $C_{13}H_{25}NNaO_4Si$ $[M+Na]^+$: 310.1445; found: 310.1438.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3397, 2955, 2930, 2895, 2858, 1768, 1471, 1253, 1107, 1045, 893, 838, 780, 671.

Less polar diastereomer

TLC (25% ethyl acetate in cyclohexane): R_f: 0.07 (CAM) 3 MeOH

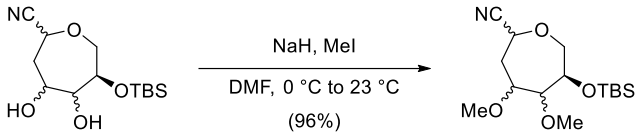
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (dd, *J* = 10.9, 4.3 Hz, 1H), 4.28 (dt, *J* = 6.6, 2.4 Hz, 1H), 3.91 (td, *J* = 8.2, 4.3 Hz, 1H), 3.82 (dd, *J* = 12.7, 4.3 Hz, 1H), 3.68 – 3.56 (m, 2H), 2.64 – 2.56 (m, 1H),

2.43 (d, *J* = 8.2 Hz, 1H), 2.35 (ddd, *J* = 15.1, 6.6, 4.2 Hz, 1H), 2.19 (ddd, *J* = 15.1, 10.9, 2.3 Hz, 1H), 0.90 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 118.7, 77.3, 71.4, 69.0, 68.0, 62.9, 35.0, 25.8, 18.1, -4.3, -4.7.

HRMS (ESI): calcd. for $C_{13}H_{25}NNaO_4Si$ $[M+Na]^+$: 310.1445; found: 310.1438.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3459, 2953, 2930, 2887, 2858, 1658, 1471, 1391, 1361, 1255, 1099, 1006, 871, 837, 778.



3.225 **3.226**

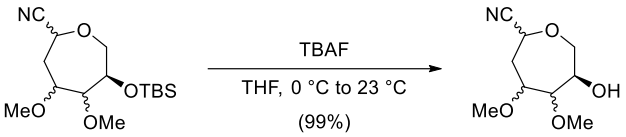
Synthesis of nitrile **3.226**: To a solution of nitrile **3.225** (103 mg, 359 µmol, 1 equiv) in dimethyl formamide (6 mL) was added sodium hydride (60% in mineral oil, 31.5 mg, 788 µmol, 2.2 equiv,) at 0 °C and the reaction mixture was allowed to warm to 23 °C. After 30 min, the yellow reaction mixture was cooled to 0 °C and methyl iodide (98.6 µL, 1.58 mmol, 4.40 equiv) was added dropwise at 0 °C and the reaction mixture was allowed to warm to 23 °C. After 16 h, the reaction mixture was diluted with diethyl ether (20 mL) and saturated aqueous solution of ammonium chloride (20 mL) to quench excess of base. The phases were separated and the aqueous phase was extracted with diethyl ether (3×10 mL). The combined organic phases were washed with water (20 mL), aqueous lithium chloride (1.0 M, 10 ml) and 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 to give a yellow oil. The crude product was purified by flash column chromatography (30% diethyl ether in petrol ether) to yield nitrile **3.226** (108 mg, 343 µmol, 96%) as a colorless oil.

Complex mixture of several diastereomers was only characterized by TLC, HRMS and IR and used without further purification.

TLC (25% ethyl acetate in cyclohexane): R_f: 0.42 (CAM)

HRMS (ESI): calcd. for $C_{15}H_{29}NNaO_4Si$ $[M+Na]^+$: 338.1758; found: 338.1755.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2954, 2930, 2895, 2895, 2857, 1464, 1361, 1254, 1100, 1025, 836, 778.



3.226 **3.227**

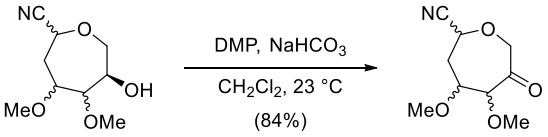
Synthesis of alcohol **3.227**: To a solution of a mixture of nitrile **3.226** (11 mg, 34 µmol, 1 equiv) in tetrahydrofuran (300 µL) was added tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 41 µL, 1.2 equiv) at 0 °C and the clear reaction mixture was allowed to warm to 23 °C. After 4 h, the mixture was diluted with ethyl acetate (5 mL) and water (5 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3×5 mL), the combined phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give a clear oil. The residue was dissolved in dichloromethane and filtered over a plug of silica to remove any salts and the filtrate was concentrated to yield a mixture of diastereomers of alcohol **3.227** (6.8 mg, 34 µmol, 99%) as colorless oil.

Complex mixture of several diastereomers was only characterized by TLC, HRMS and IR and used without further purification.

TLC (25% ethyl acetate in cyclohexane): R_f: 0.12 (UV, CAM)

HRMS (ESI): calcd. for $C_9H_{15}NNaO_4$ $[M+Na]^+$: 224.0893; found: 224.0888.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3456, 2925, 2855, 1734, 1463, 1249, 1194, 1098, 835.



3.227 **3.228**

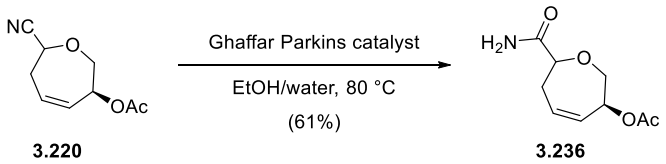
Synthesis of ketone **3.228**: To a solution of alcohol **3.227** (6.6 mg, 33 µmol, 1 equiv) in dichloromethane (0.33 mL) was added Dess−Martin periodate (28 mg, 66 µmol, 2.0 equiv) and sodium hydrogen carbonate (8.3 mg, 98 µmol, 3.0 equiv) After 4 h, the reaction mixture was diluted with dichloromethane (3 mL), saturated aqueous thiosulfate (1 mL) and saturated aqueous sodium hydrogen carbonate (1 mL) were added to quench excess of Dess−Martin periodate. The phases were separated and the aqueous phase was extracted with dichloromethane (3×5 mL), the combined organic phases were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The crude product was purified by column chromatography (40% diethyl ether in *n*-pentane) to afford mixture of diastereomers of ketone **3.228** (5.5 mg, 28 µmol, 84%) as a pale yellow oil.

Complex mixture of several diastereomers was only characterized by TLC, HRMS and IR and used without further purification.

TLC (25% ethyl acetate in cyclohexane): R_f: 0.18 (CAM)

HRMS (ESI): calcd. for $C_9H_{13}NNaO_4$ $[M+Na]^+$: 222.0737; found: 222.0734.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2960, 2930, 2874, 2856, 1732, 1462, 1244, 1099.



3.220 **3.236**

Synthesis of amide **3.236**: To a solution of nitrile (210 mg, 1.16 mmol, 1 equiv) in ethanol (4 mL) and water (1 mL) was added Ghaffar−Parkins Catalyst (49.8 mg, 116 µmol, 10.0 mol%) and the resulting mixture was heated to 80 °C. After 24 h, no further conversion was observed and the reaction mixture was allowed to cool to 23 °C and the solution was concentrated. The crude product was purified by flash column chromatography on silica gel (2% methanol in dichloromethane (100 mL) grading to 4% methanol in dichloromethane (200 mL)) to yield a mixture of diastereomers of amide **3.236** (140 mg, 703 µmol, 0.81 mmol, 61%) as a colorless solid and recovered starting material **3.220** (79.8 mg, 441 µmol, 38%).

Mixture of diastereomers

TLC (5% methanol in dichloromethane): R_f: 0.26 (UV, CAM)

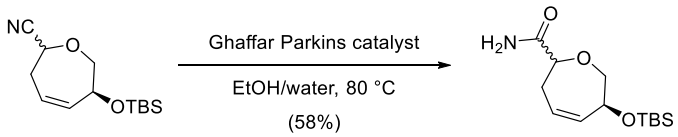
mp: 82.5 – 94.3 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (s, 1H), 6.65 (s, 1H), 6.21 (d, *J* = 16.4 Hz, 2H), 5.98 – 5.83 (m, 2H), 5.78 (dddt, *J* = 11.6, 5.9, 2.0, 0.8 Hz, 1H), 5.71 (dtd, *J* = 11.7, 2.9, 1.1 Hz, 1H), 5.51 – 5.43 (m, 1H), 5.32 – 5.25 (m, 1H), 4.14 (ddd, *J* = 13.6, 3.2, 1.2 Hz, 1H), 4.10 – 4.03 (m, 2H), 4.00 (dd, *J* = 10.7, 2.3 Hz, 1H), 3.81 (dd, *J* = 13.6, 1.9 Hz, 1H), 3.53 (dd, *J* = 11.7, 8.8 Hz, 1H), 2.89 – 2.75 (m, 2H), 2.66 – 2.54 (m, 1H), 2.43 (dddt, *J* = 17.0, 10.7, 3.6, 2.5 Hz, 1H), 2.07 (s, 3H), 2.06 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 174.1, 170.4, 170.1, 132.5, 131.7, 128.2, 127.9, 80.5, 80.1, 72.3, 72.3, 70.5, 70.3, 32.8, 32.0, 21.2, 21.1.

HRMS (ESI): calcd. for $C_9H_{13}NNaO_4$ $[M+Na]^+$: 222.0737; found: 222.0733.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3463, 3340, 2928, 1730, 1675, 1585, 1370, 1231, 1143, 1113, 1034, 954, 868.



3.224 **3.237**

Synthesis of amide **3.237**: To a solution of nitrile **3.224** (20 mg, 79 mmol, 1 equiv) in ethanol (800 µL) and water (200 µL) was added Ghaffar-Parkins Catalyst (6.8 mg, 16 µmol, 10.0 mol%) and the resulting mixture was heat to 80 °C. After 16 h, the reaction mixture was allowed to cool to 23 °C and the solution was concentrated. The crude product was purified by flash column chromatography on silica gel (30% ethyl acetate in *n*-pentane) to yield a mixture of diastereomers of amide **3.237** (140 mg, 703 µmol, 0.81 mmol, 61%) as a colorless solid and recovered starting material **3.224** (13 mg, 46 µmol, 58%).

Mixture of diastereomers

TLC (25% ethyl acetate in cyclohexane): R_f: 0.09 (CAM)

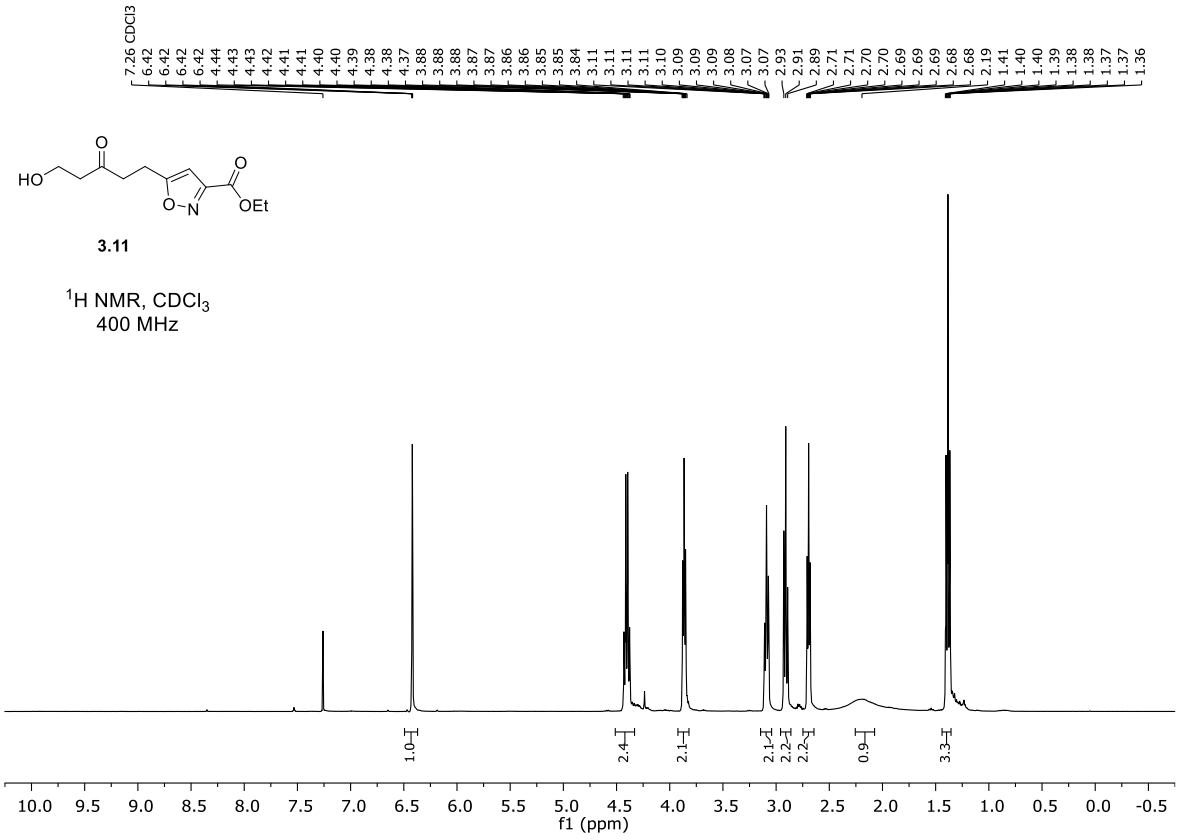
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (s, 1H), 5.89 – 5.50 (m, 6H), 4.46 (ddt, *J* = 9.7, 4.1, 1.9 Hz, 1H), 4.33 (ddd, *J* = 24.4, 7.4, 4.2 Hz, 1H), 4.03 – 3.75 (m, 4H), 3.38 (dd, *J* = 11.6, 9.7 Hz, 1H), 2.91 – 2.57 (m, 3H), 2.35 (dddd, *J* = 15.9, 10.7, 4.2, 2.1 Hz, 2H), 0.90 (d, *J* = 2.2 Hz, 18H), 0.28 – -0.10 (m, 12H).

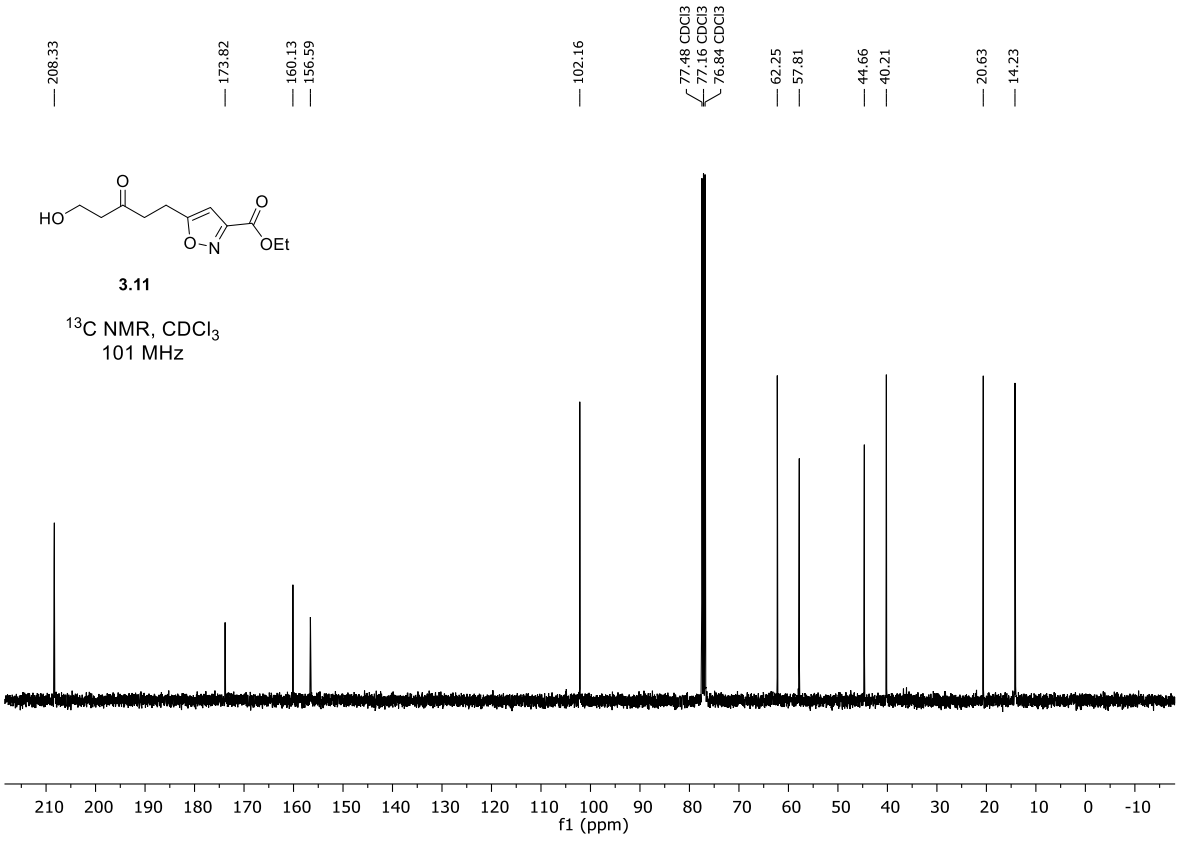
^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 174.2, 139.1, 133.2, 126.8, 125.4, 80.5, 79.8, 76.1, 74.6, 71.6, 71.3, 70.5, 33.6, 29.8, 29.5, 25.9, 25.9, 18.3, 18.3, -4.5, -4.7, -4.7, -4.7.

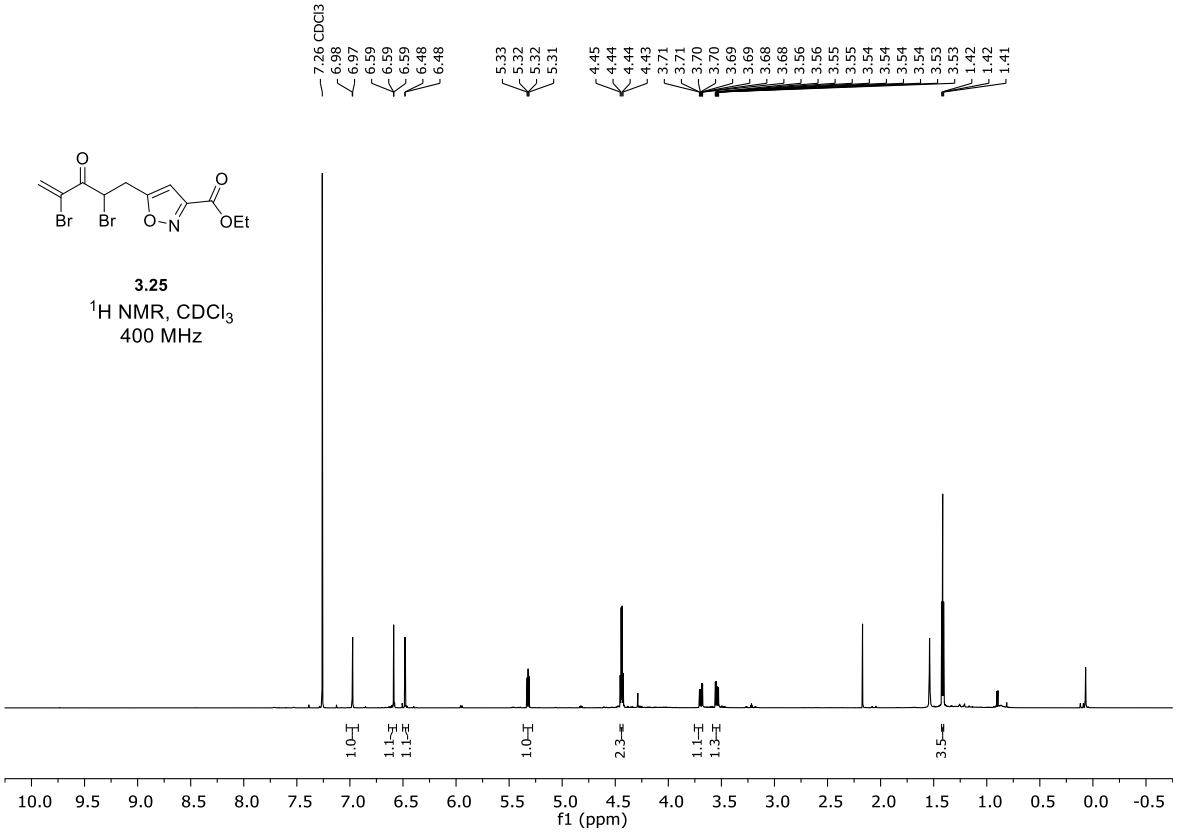
HRMS (ESI): calcd. for $C_{13}H_{25}NNaO_3Si$ $[M+Na]^+$: 294.1496; found: 294.1488.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3479, 3317, 3030, 2955, 2929, 2891, 2891, 2857, 1685, 1590, 1471, 1399, 1329, 1253, 1095, 904, 837, 777.

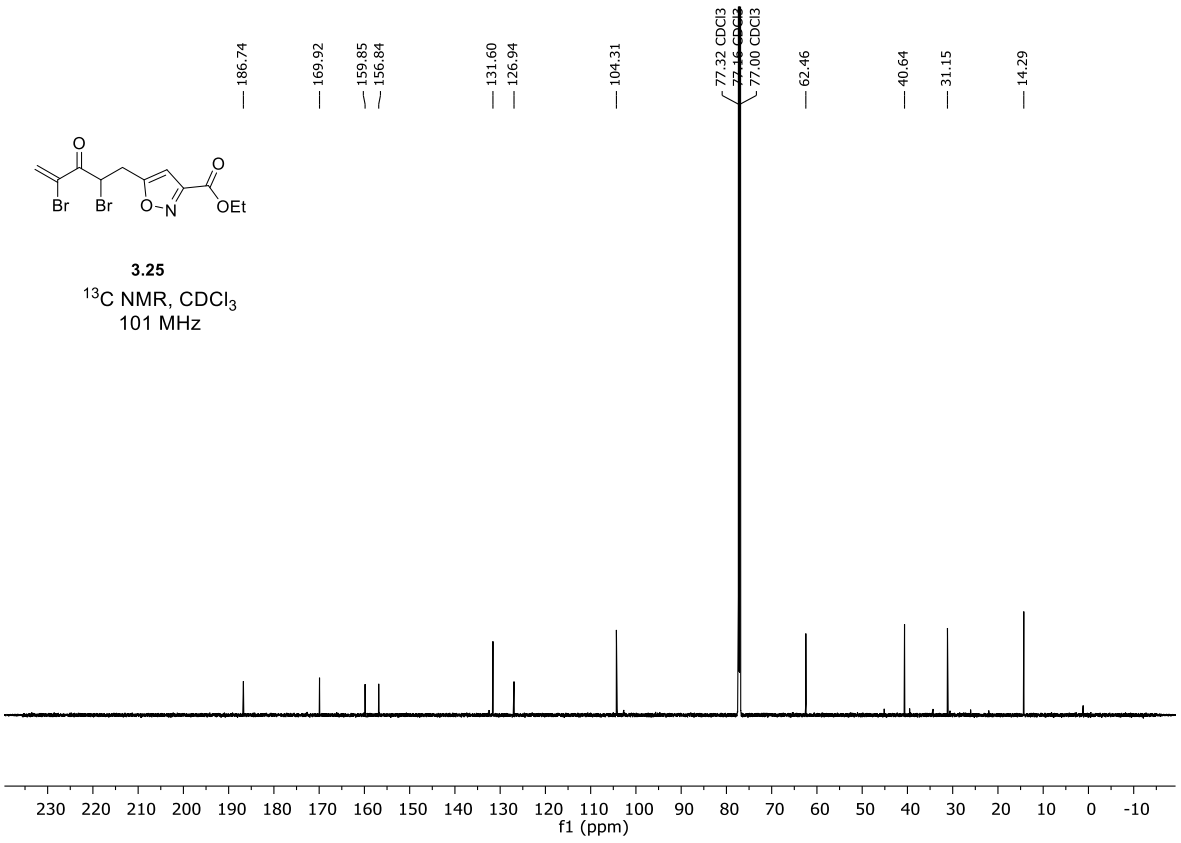
9.2.1.2 NMR Spectra



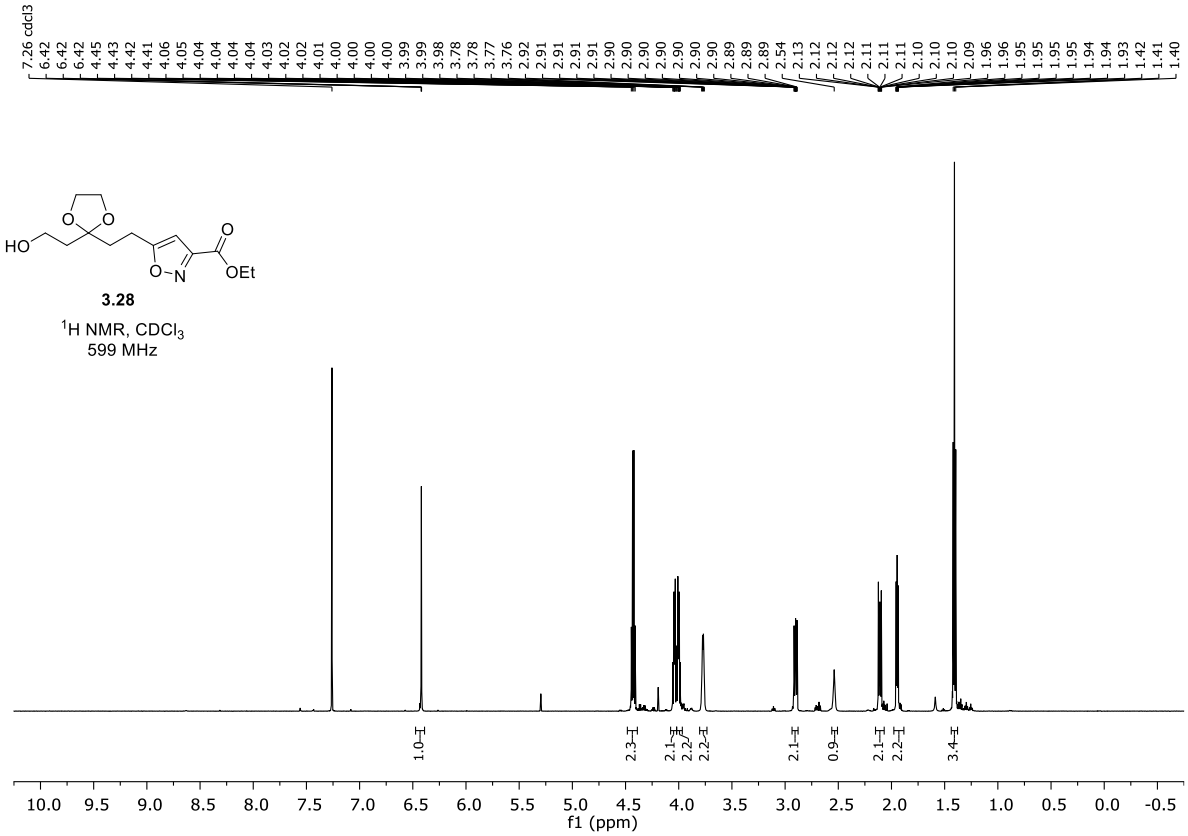


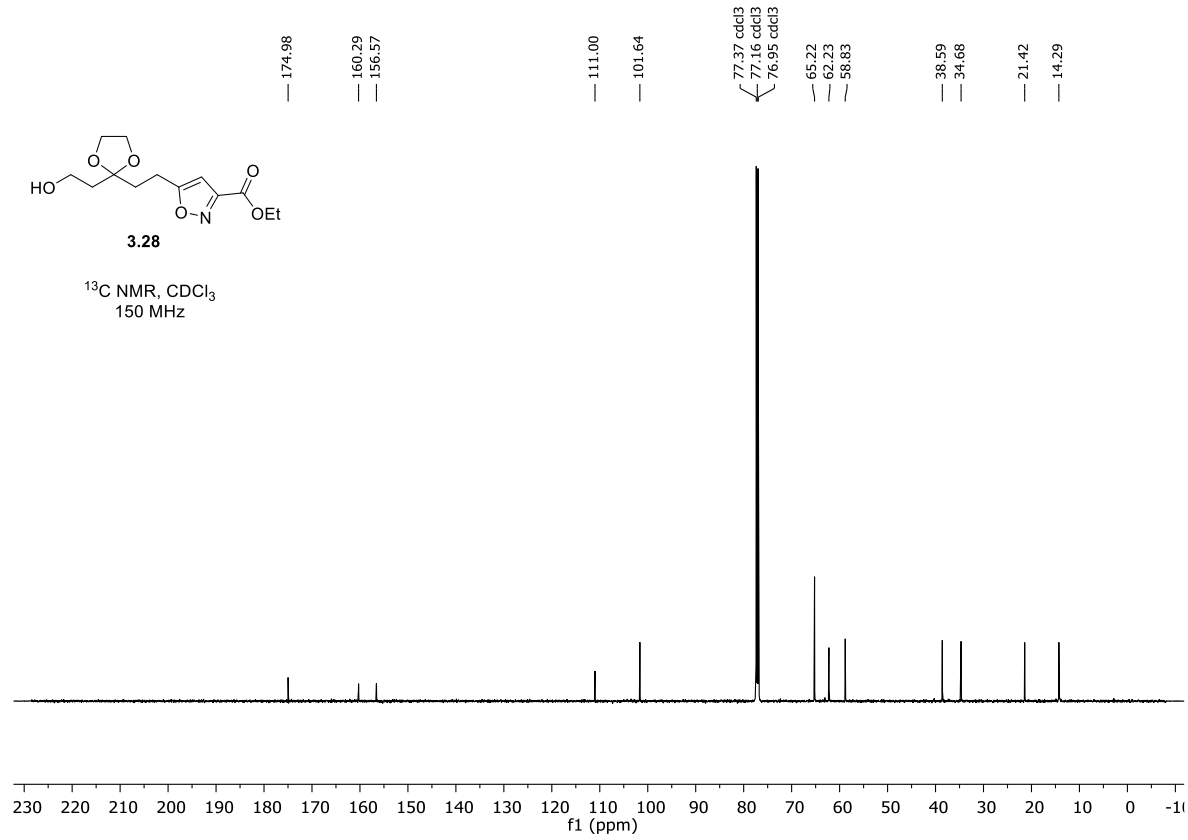


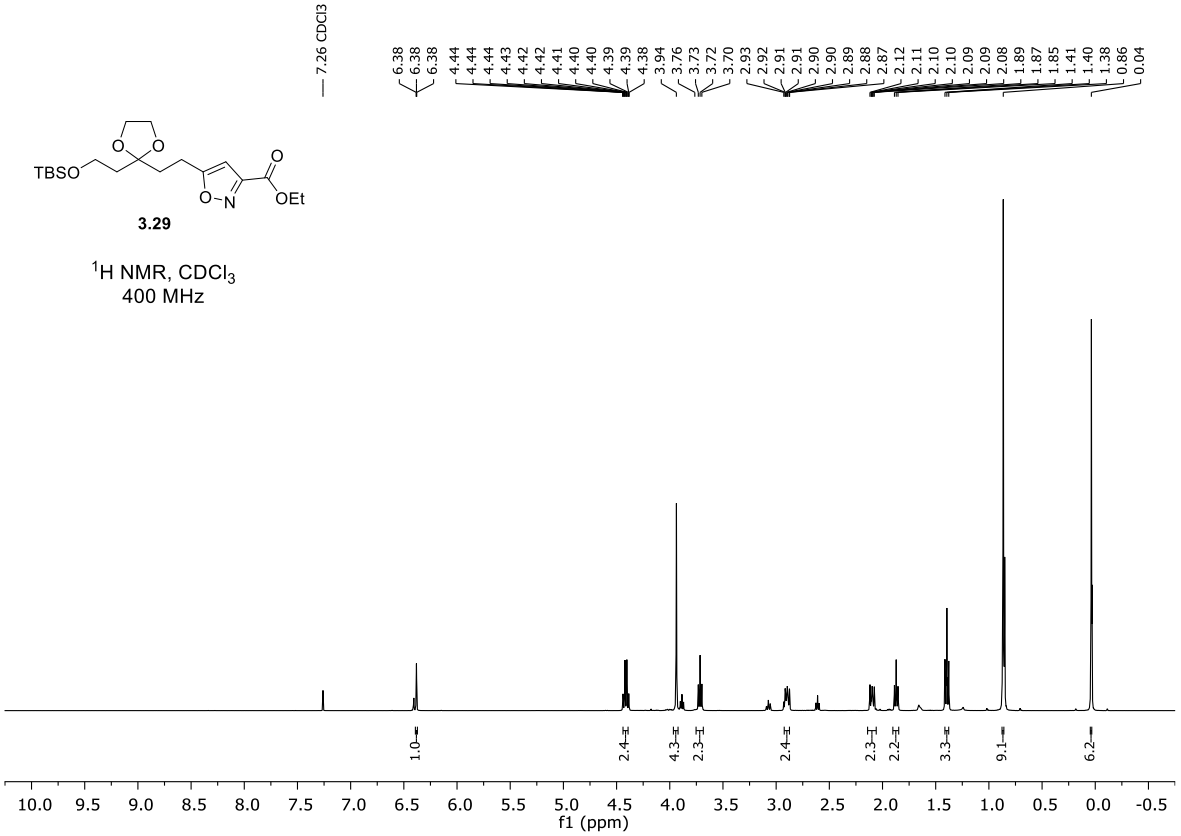
3.25
^{1}H NMR, $CDCl_3$
400 MHz

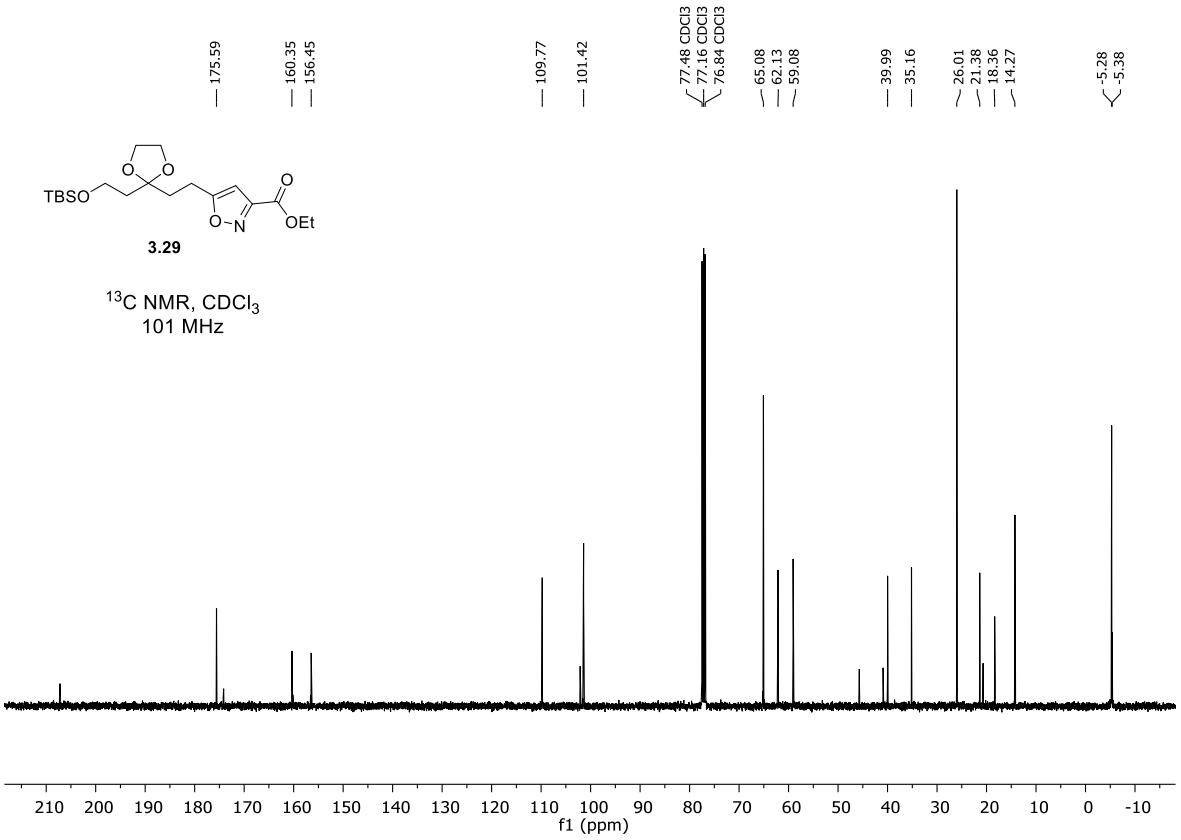


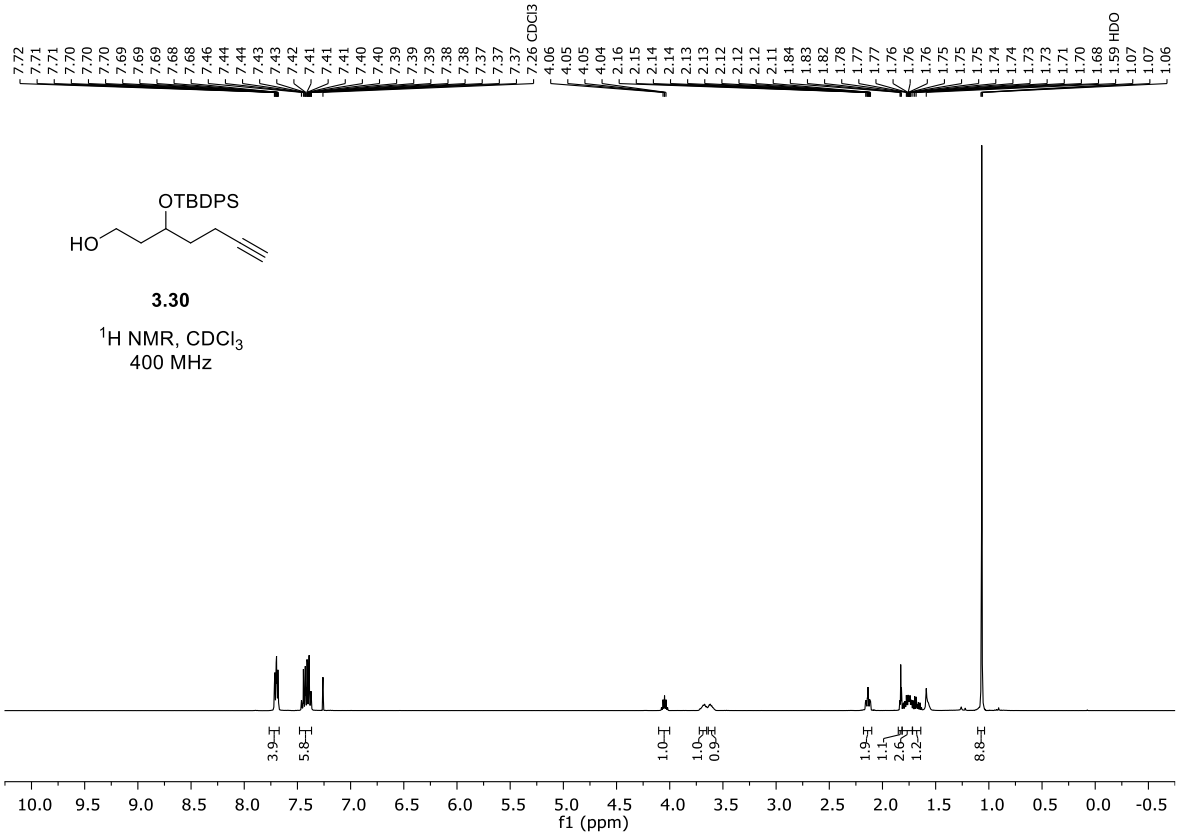
3.25
^{13}C NMR, $CDCl_3$
101 MHz

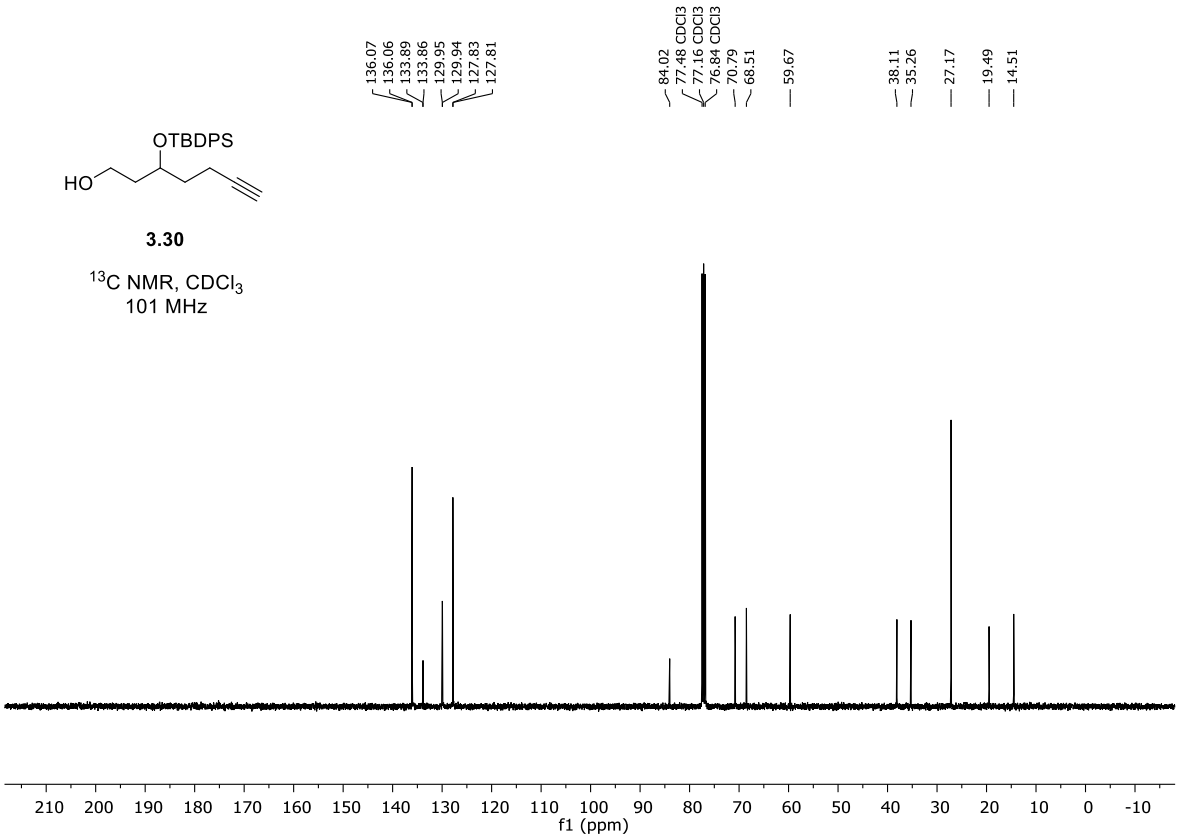

7.26 cdcl3
HO
O
O
O
O
N
OEt
3.28
1H NMR, CDCl3
599 MHz
1.0
2.3
2.1
2.2
2.2
2.1
0.9
2.1
2.2
3.4
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

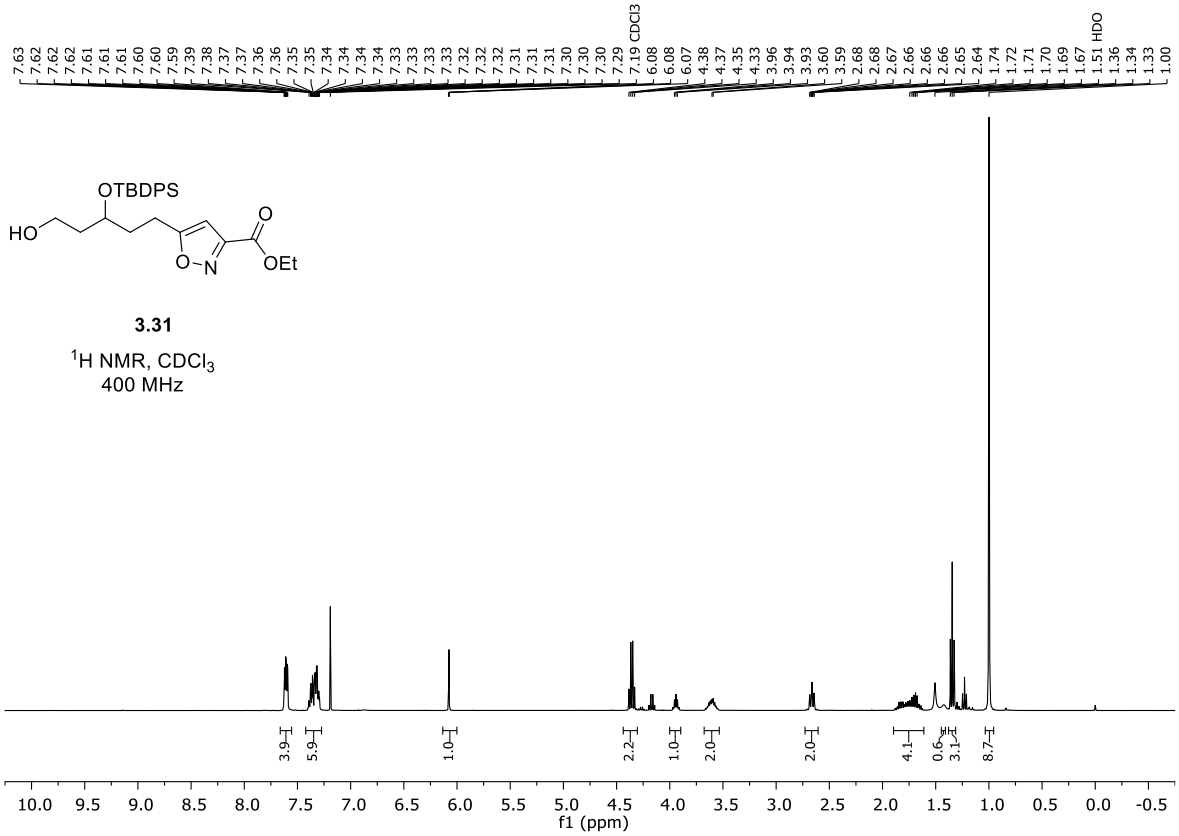

174.98
160.29
156.57
111.00
101.64
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
65.22
62.23
58.83
38.59
34.68
21.42
14.29
HO
O
O
O
O
N
OEt
3.28
13C NMR, CDCl3
150 MHz
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

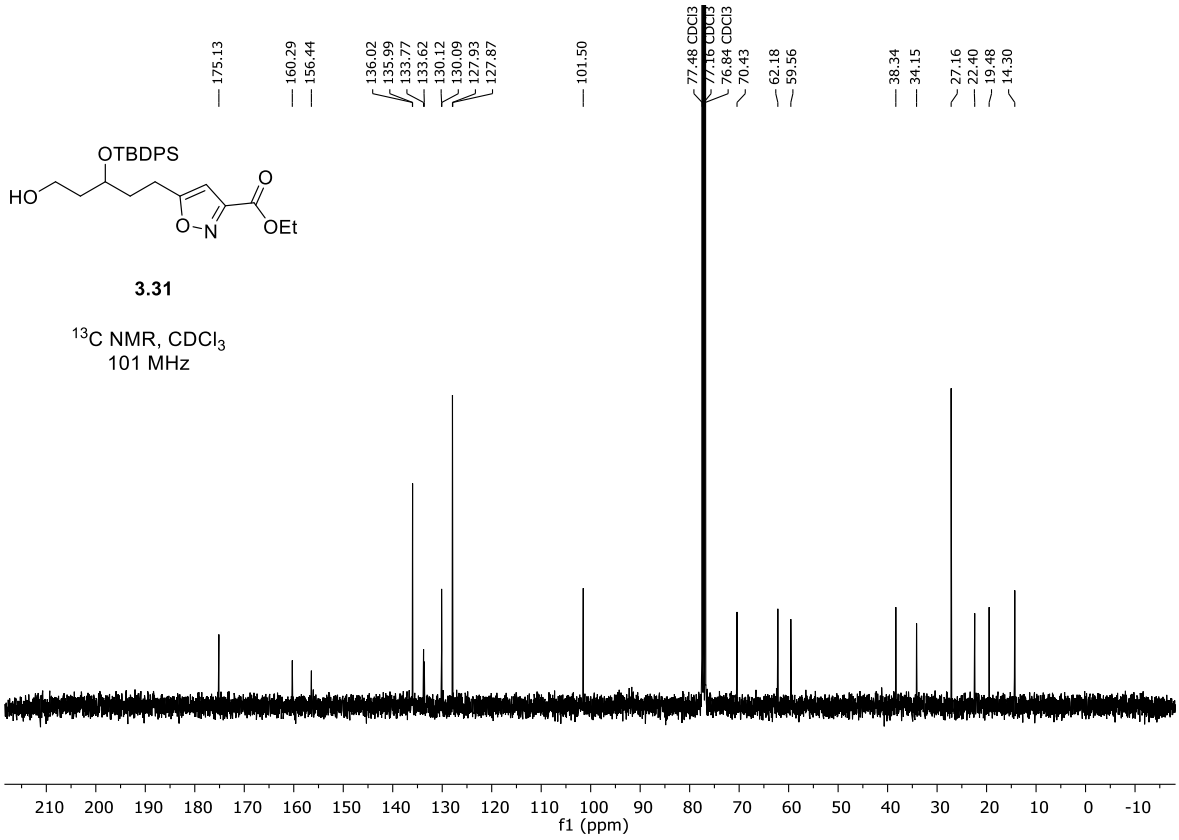

7.26 CDCl3
6.38
6.38
6.38
4.44
4.44
4.44
4.43
4.42
4.42
4.41
4.40
4.40
4.39
4.39
4.38
3.94
3.76
3.73
3.72
3.70
2.93
2.92
2.91
2.91
2.90
2.90
2.89
2.88
2.87
2.12
2.11
2.10
2.10
2.09
2.09
2.08
1.89
1.87
1.85
1.41
1.40
1.38
0.86
0.04
TBSO
O
O
O
N
O
OEt
3.29
1H NMR, CDCl3
400 MHz
1.0
2.4
4.3
2.3
2.4
2.3
2.2
3.3
9.1
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 -0.5
f1 (ppm)

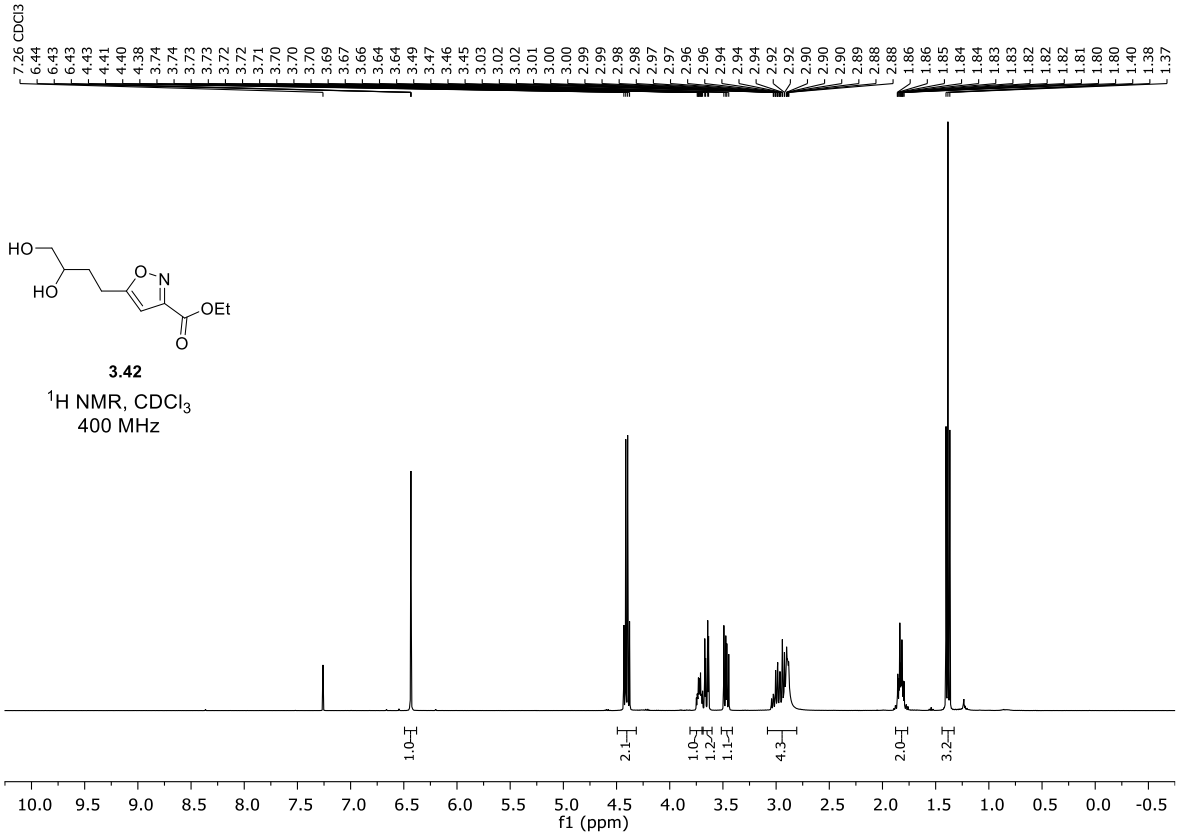

175.59
160.35
156.45
109.77
101.42
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
65.08
62.13
59.08
39.99
35.16
26.01
21.38
18.36
14.27
-5.28
-5.38
TBSO
O
O
O
N
O
OEt
3.29
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

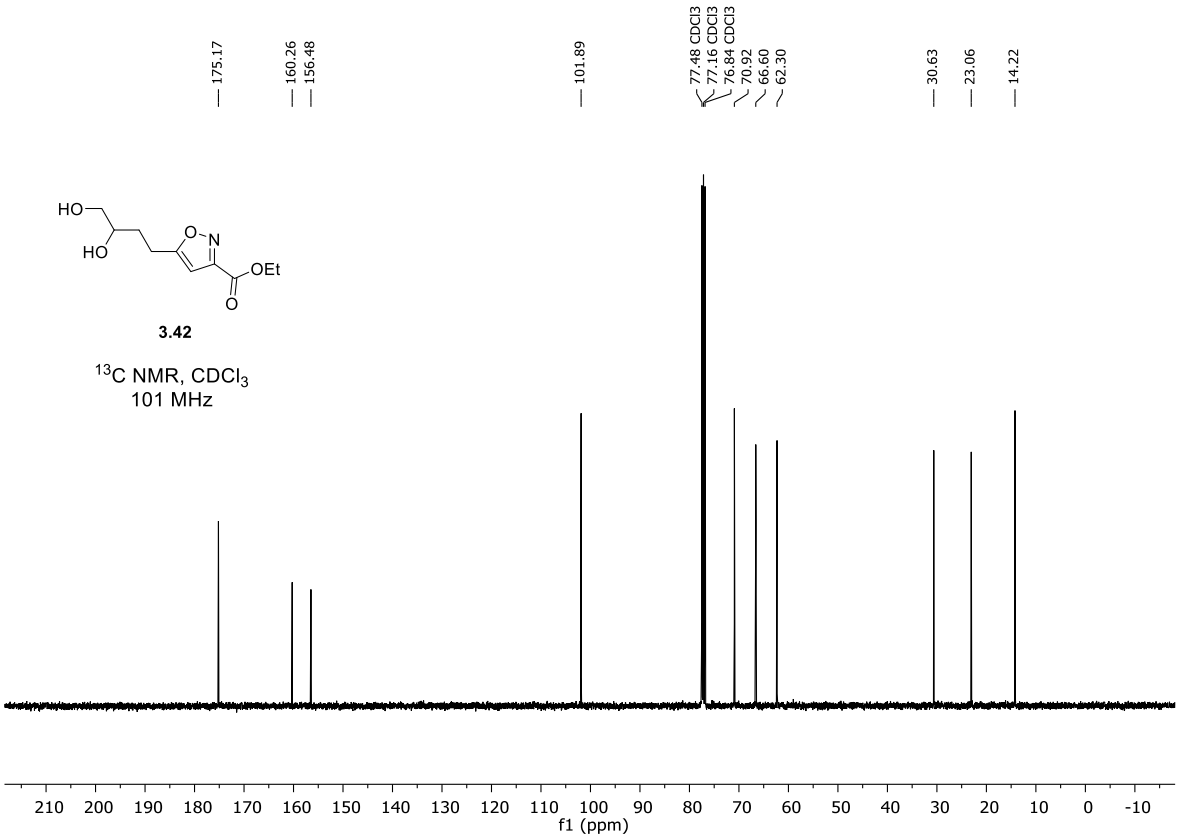

7.72 7.71 7.71 7.70 7.70 7.70 7.69 7.69 7.69 7.68 7.68 7.46 7.44 7.44 7.43 7.43 7.42 7.41 7.41 7.41 7.40 7.40 7.39 7.39 7.39 7.38 7.38 7.37 7.37 7.37 7.26 CDCl3
4.06 4.05 4.05 4.04 2.16 2.15 2.14 2.14 2.13 2.13 2.12 2.12 2.12 2.11 1.84 1.83 1.82 1.78 1.77 1.77 1.76 1.76 1.76 1.75 1.75 1.75 1.74 1.74 1.73 1.73 1.71 1.70 1.68 1.59 HDO 1.07 1.07 1.06
OTBDPS
HO
3.30
1H NMR, CDCl3
400 MHz
3.9 5.8 1.0 1.0 0.9 1.9 1.1 2.6 1.2 8.8
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 -0.5
f1 (ppm)

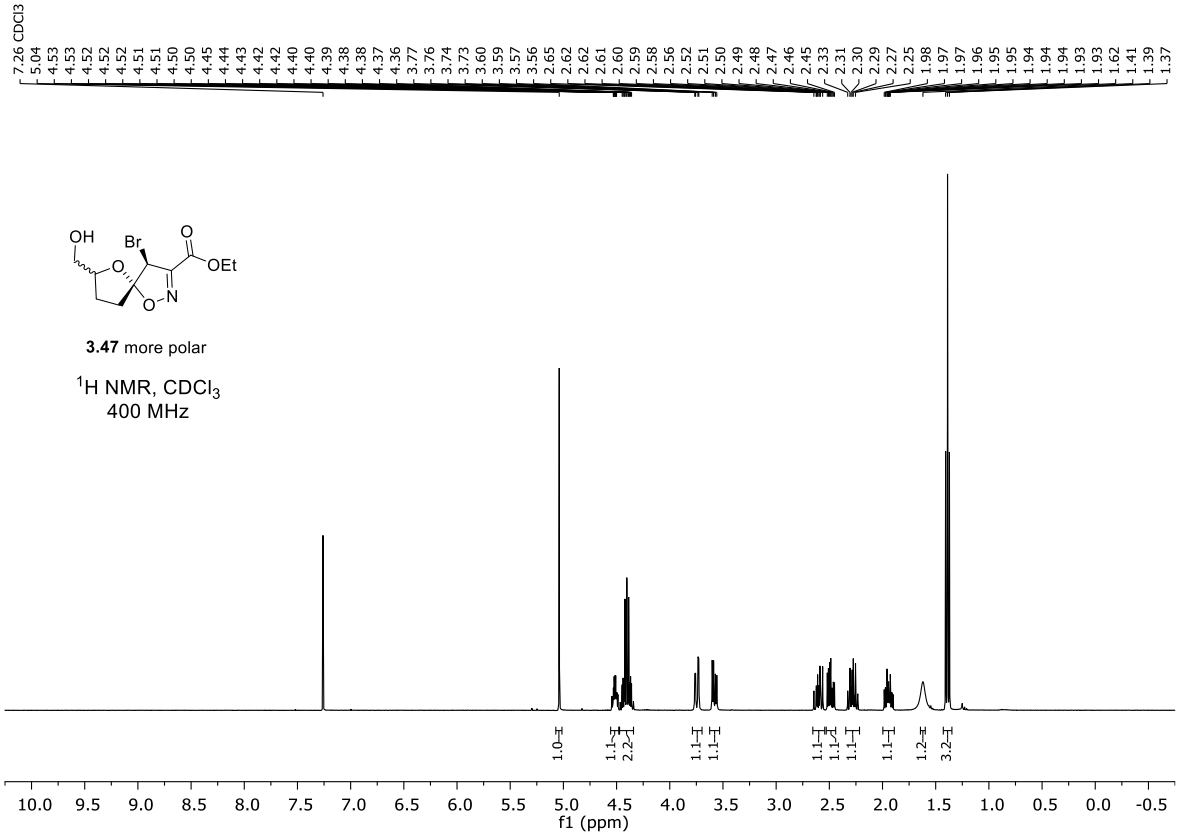

136.07 136.06 133.89 133.86 129.95 129.94 127.83 127.81
84.02 77.48 CDCl3 77.16 CDCl3 76.84 CDCl3 70.79 68.51 59.67
38.11 35.26 27.17 19.49 14.51
OTBDPS
HO
3.30
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

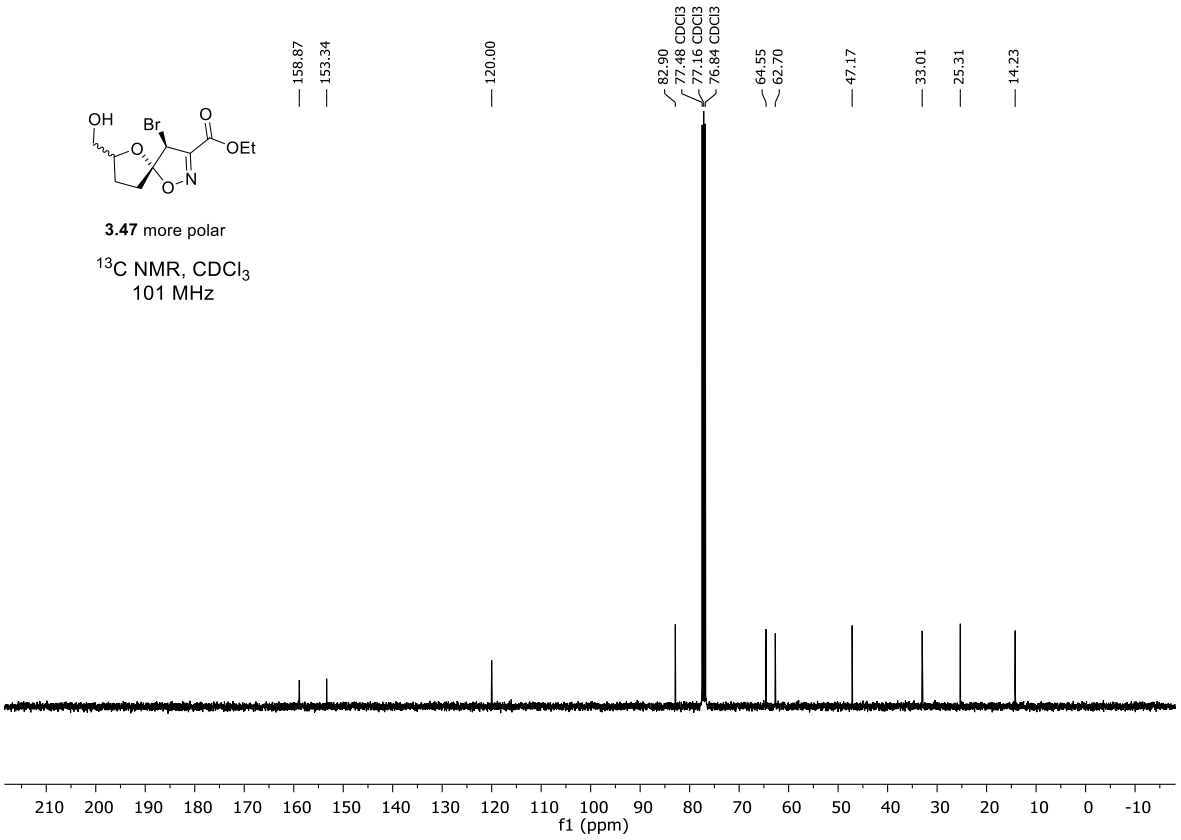

7.63 7.62 7.62 7.62 7.61 7.61 7.61 7.60 7.60 7.59 7.39 7.38 7.37 7.37 7.36 7.36 7.35 7.35 7.34 7.34 7.34 7.34 7.33 7.33 7.33 7.33 7.32 7.32 7.32 7.31 7.31 7.31 7.30 7.30 7.30 7.29 7.19 CDCl3 6.08 6.08 6.07 4.38 4.37 4.35 4.33 3.96 3.94 3.93 3.60 3.59 2.68 2.68 2.67 2.66 2.66 2.66 2.65 2.64 1.74 1.72 1.71 1.70 1.69 1.67 1.51 HDO 1.36 1.34 1.33 1.00
OTBDPS
HO
O
O
N
OEt
3.31
1H NMR, CDCl3
400 MHz
3.9 5.9 1.0 2.2 1.0 2.0 2.0 4.1 0.6 3.1 8.7
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 -0.5
f1 (ppm)

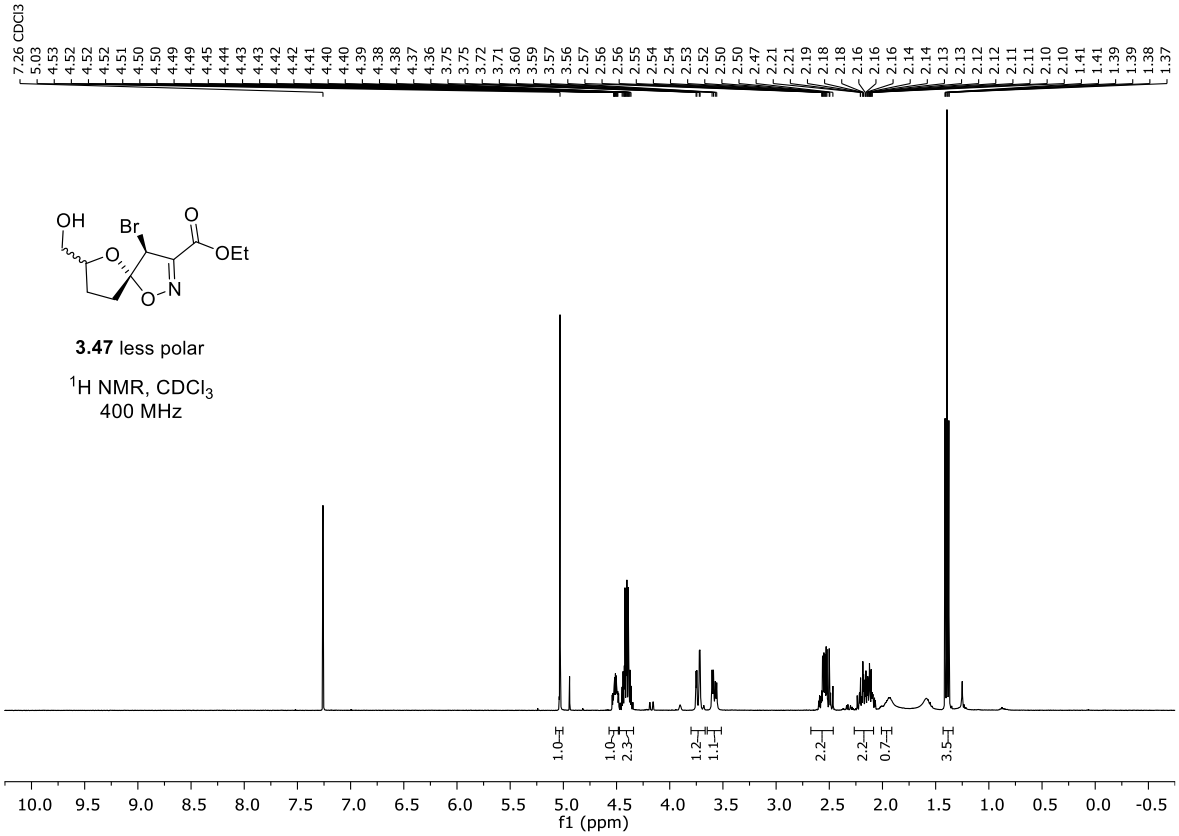

175.13 160.29 156.44 136.02 135.99 133.77 133.62 130.12 130.09 127.93 127.87 101.50 77.48 CDCl3 77.16 CDCl3 76.84 CDCl3 70.43 62.18 59.56 38.34 34.15 27.16 22.40 19.48 14.30
OTBDPS
HO
O
O
N
OEt
3.31
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

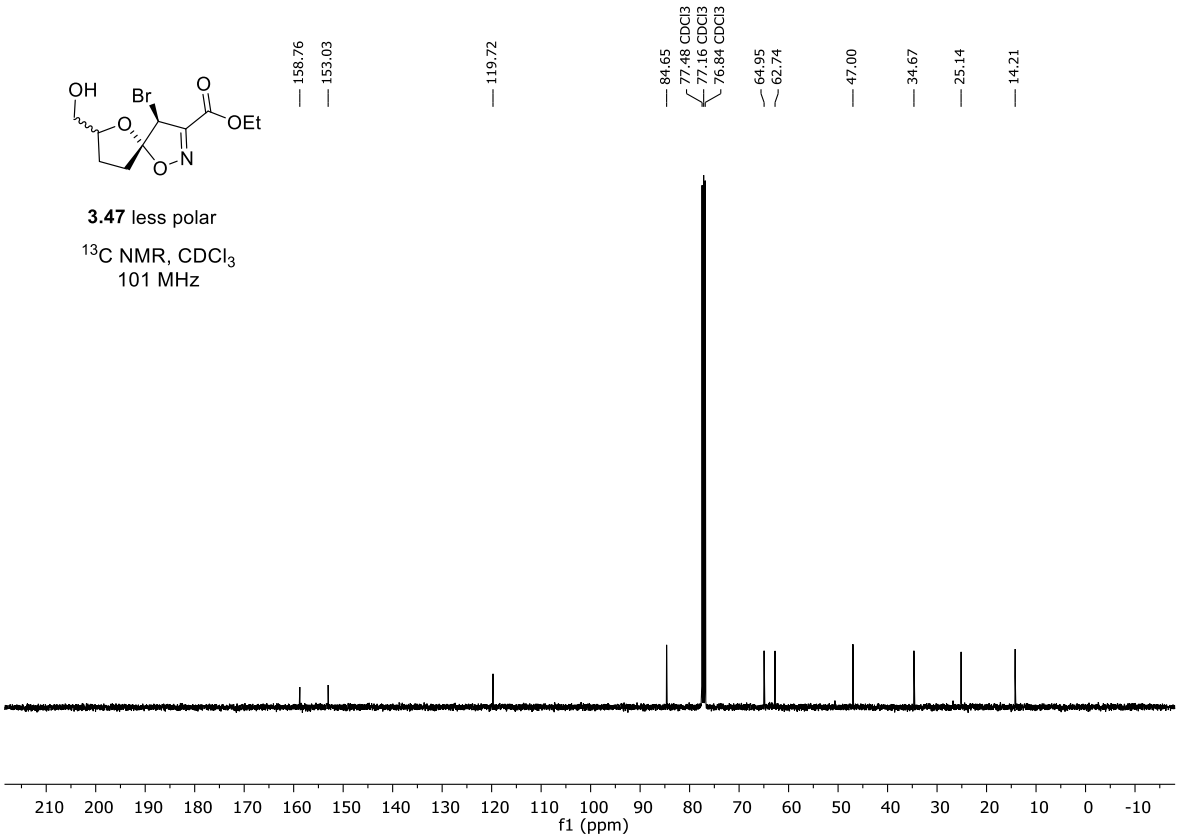

7.26 CDCl3
HO
HO
O
N
OEt
O
3.42
1H NMR, CDCl3
400 MHz
1.0
2.1
1.0
1.2
1.1
4.3
2.0
3.2
f1 (ppm)

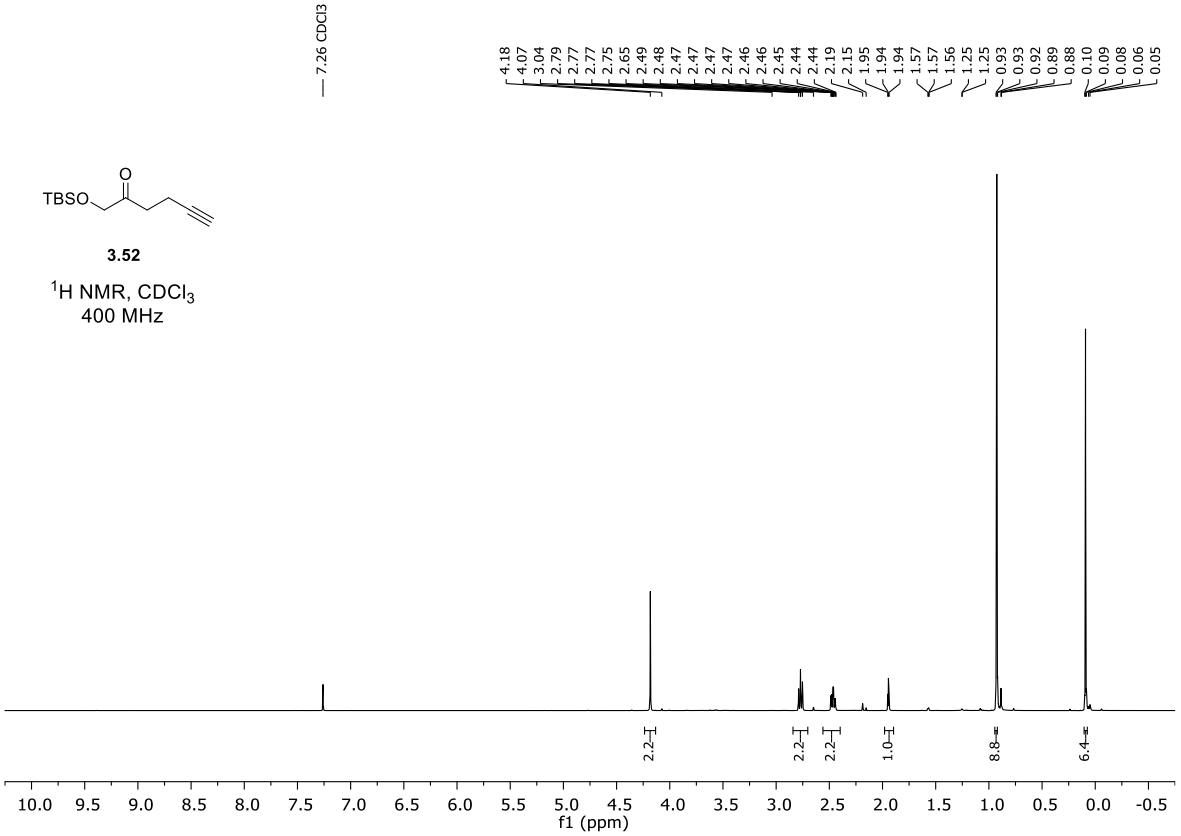

175.17
160.26
156.48
101.89
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
70.92
66.60
62.30
30.63
23.06
14.22
HO
HO
O
N
OEt
O
3.42
13C NMR, CDCl3
101 MHz
f1 (ppm)

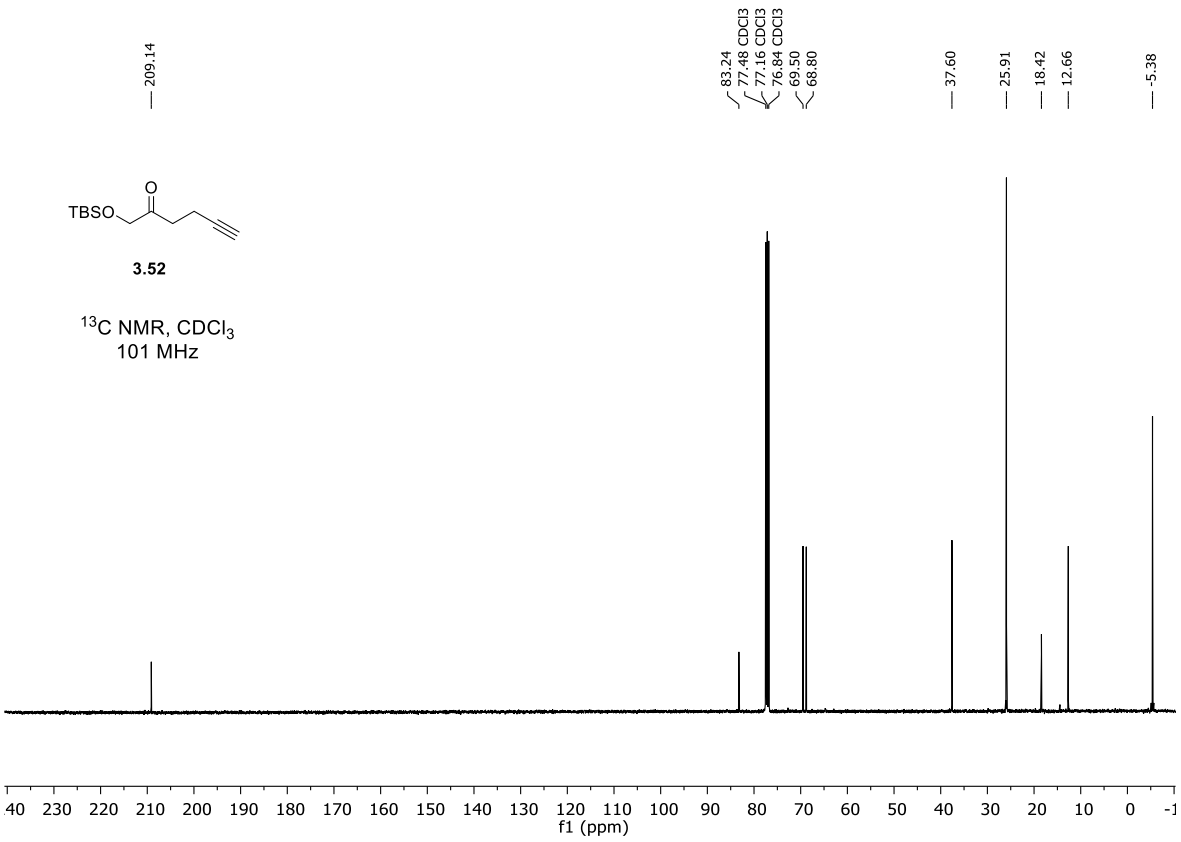

7.26 CDCl3
5.04
4.53
4.52
4.52
4.52
4.51
4.51
4.50
4.50
4.45
4.44
4.43
4.42
4.42
4.40
4.40
4.39
4.38
4.38
4.37
4.36
3.77
3.76
3.74
3.73
3.60
3.59
3.57
3.56
2.65
2.62
2.62
2.61
2.60
2.59
2.58
2.56
2.52
2.51
2.50
2.49
2.48
2.47
2.46
2.45
2.33
2.31
2.30
2.29
2.27
2.25
1.98
1.97
1.97
1.96
1.95
1.95
1.94
1.94
1.94
1.93
1.93
1.62
1.41
1.39
1.37
OH
Br
O
OEt
O
N
O
3.47 more polar
1H NMR, CDCl3
400 MHz
1.0
1.1
2.2
1.1
1.1
1.1
1.1
1.1
1.1
1.2
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 -0.5
f1 (ppm)

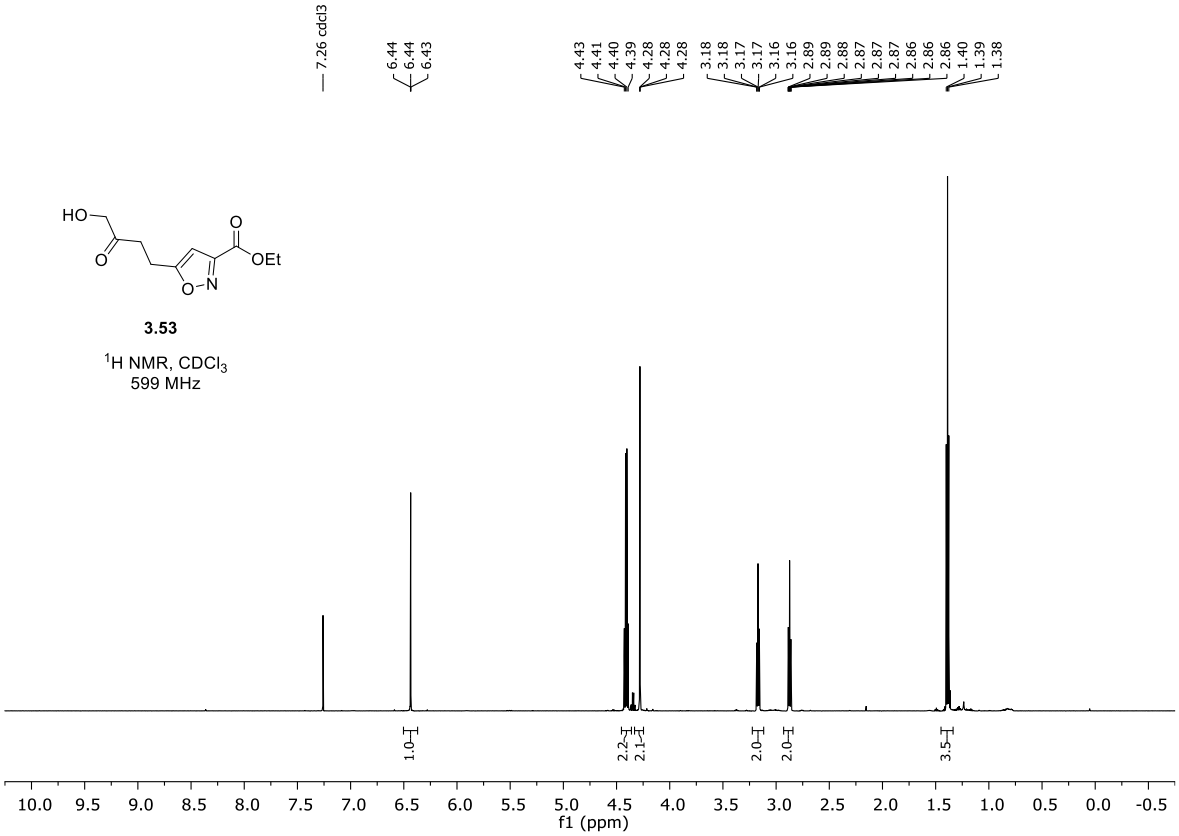

158.87
153.34
120.00
82.90
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
64.55
62.70
47.17
33.01
25.31
14.23
OH
Br
O
OEt
O
N
O
3.47 more polar
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

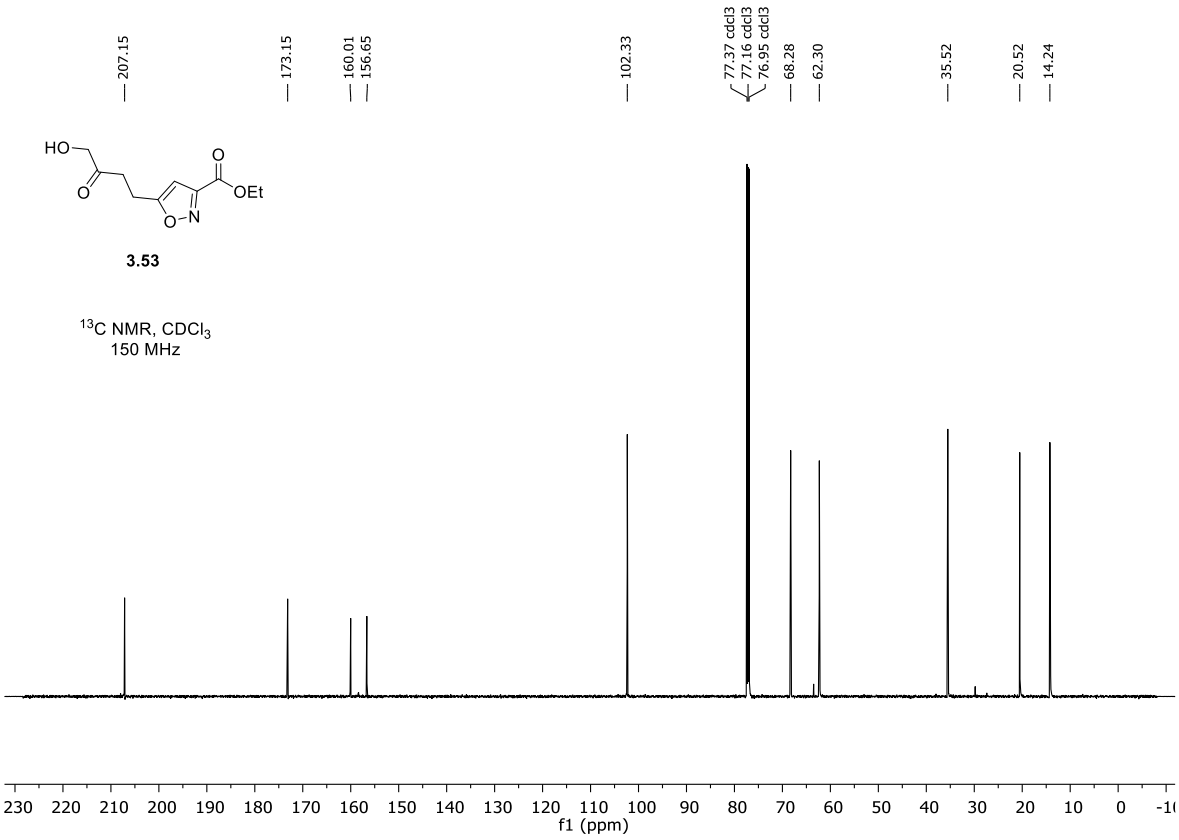

7.26 CDCl3
OH
Br
O
OEt
O
N
3.47 less polar
1H NMR, CDCl3
400 MHz
1.0
1.0
2.3
1.2
1.1
2.2
2.2
0.7
3.5
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

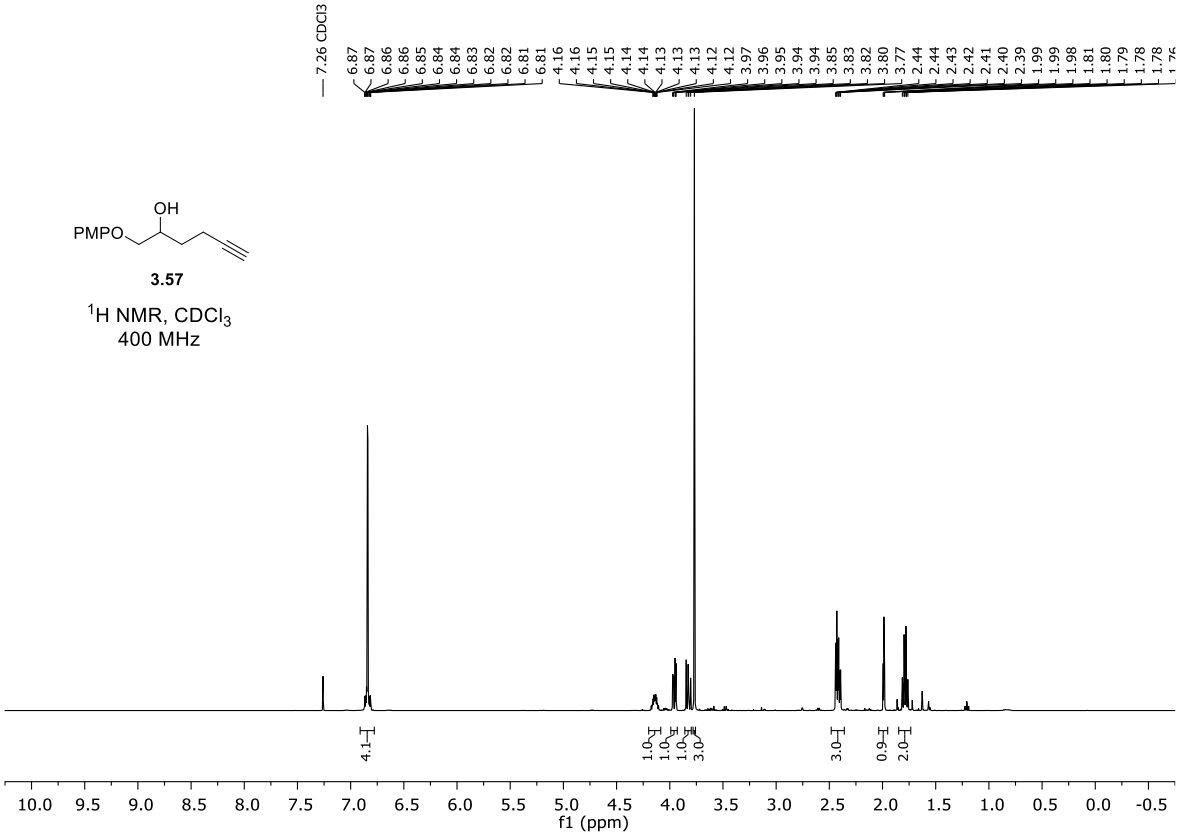

158.76
153.03
119.72
84.65
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
64.95
62.74
47.00
34.67
25.14
14.21
OH
Br
O
OEt
O
N
3.47 less polar
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.26 CDCl3
4.18
4.07
3.04
2.79
2.77
2.77
2.75
2.65
2.49
2.48
2.47
2.47
2.47
2.47
2.46
2.46
2.45
2.44
2.44
2.19
2.15
1.95
1.94
1.94
1.57
1.57
1.56
1.25
1.25
0.93
0.93
0.92
0.89
0.88
0.10
0.09
0.08
0.06
0.05
TBSO
O
3.52
1H NMR, CDCl3
400 MHz
2.2
2.2
2.2
1.0
8.8
6.4
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 -0.5
f1 (ppm)


209.14
83.24
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
69.50
68.80
37.60
25.91
18.42
12.66
-5.38
TBSO
O
3.52
13C NMR, CDCl3
101 MHz
40 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

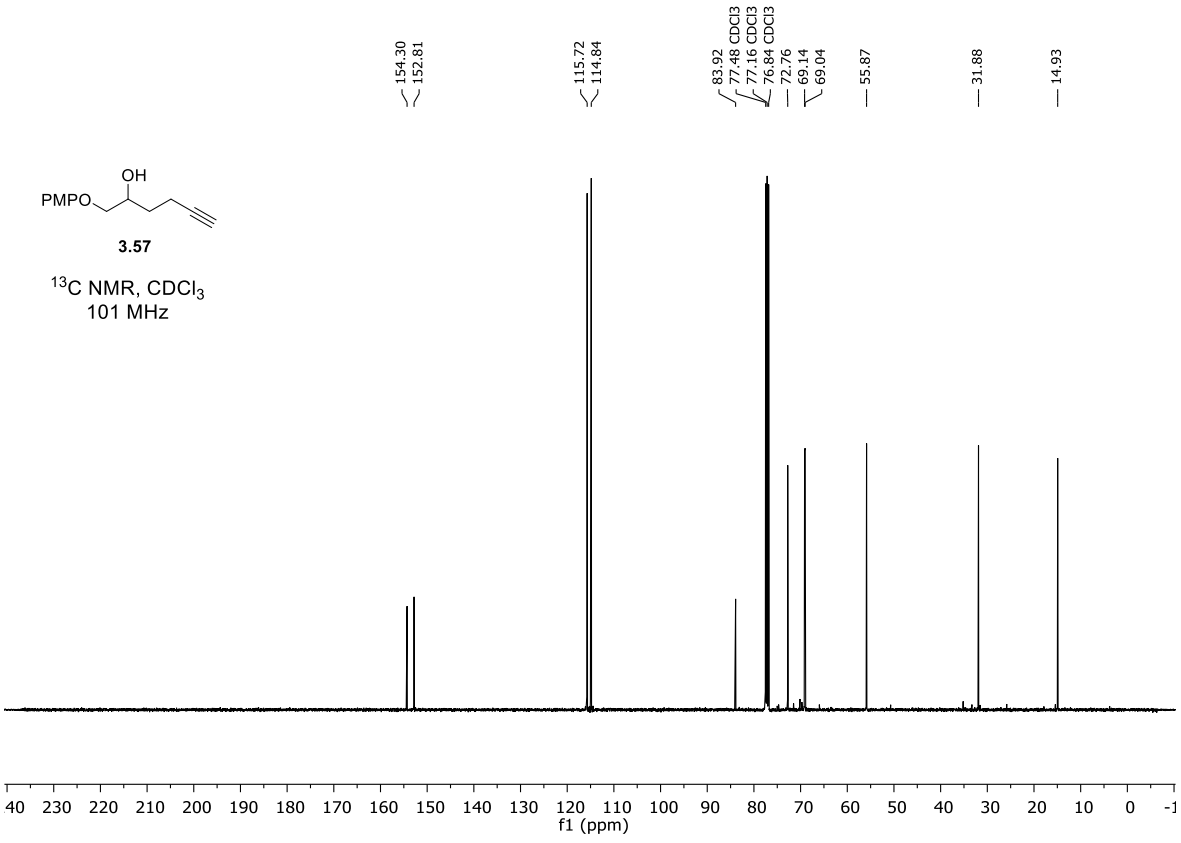

7.26 cdcl3
6.44
6.44
6.43
4.43
4.41
4.40
4.39
4.28
4.28
4.28
3.18
3.18
3.17
3.17
3.16
3.16
2.89
2.89
2.88
2.87
2.87
2.87
2.86
2.86
2.86
1.40
1.39
1.38
HO
O
O
OEt
O
N
3.53
1H NMR, CDCl3
599 MHz
1.0
2.2
2.1
2.0
2.0
3.5
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


207.15
173.15
160.01
156.65
102.33
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
68.28
62.30
35.52
20.52
14.24
HO
O
O
OEt
O
N
3.53
13C NMR, CDCl3
150 MHz
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



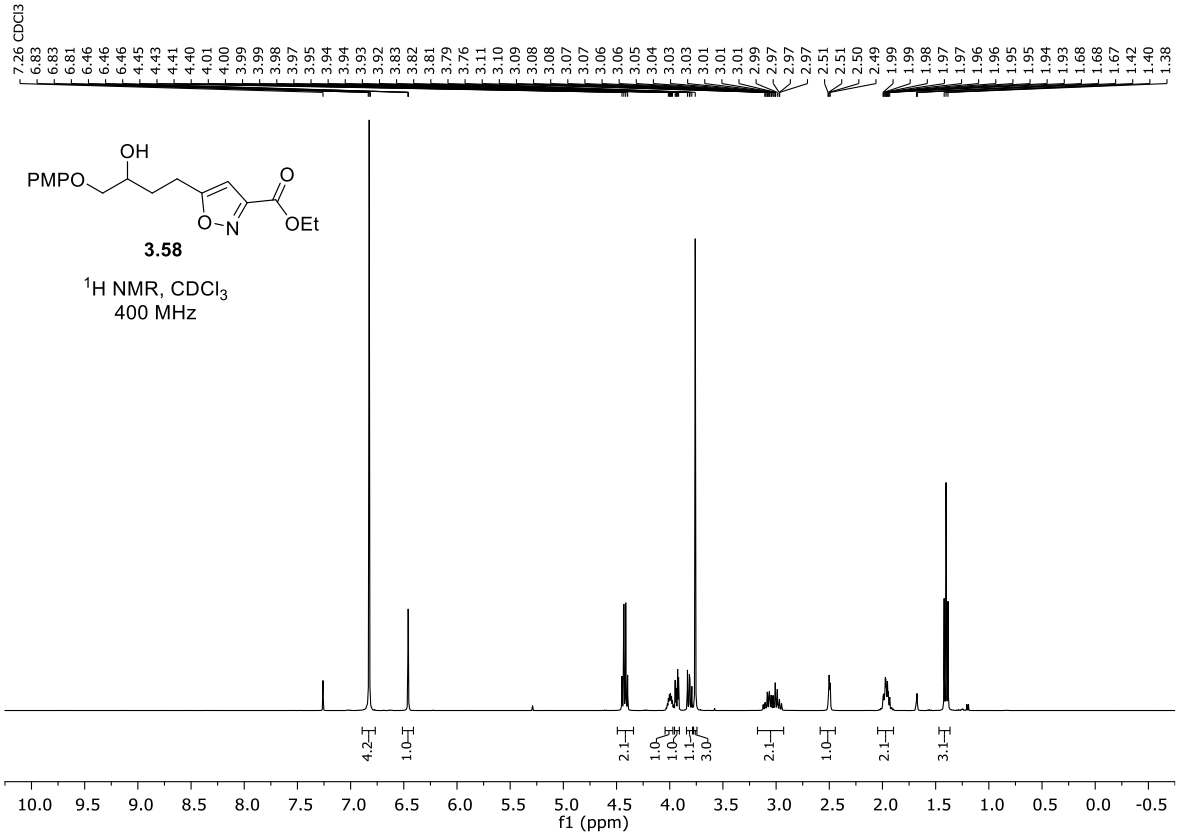
3.57

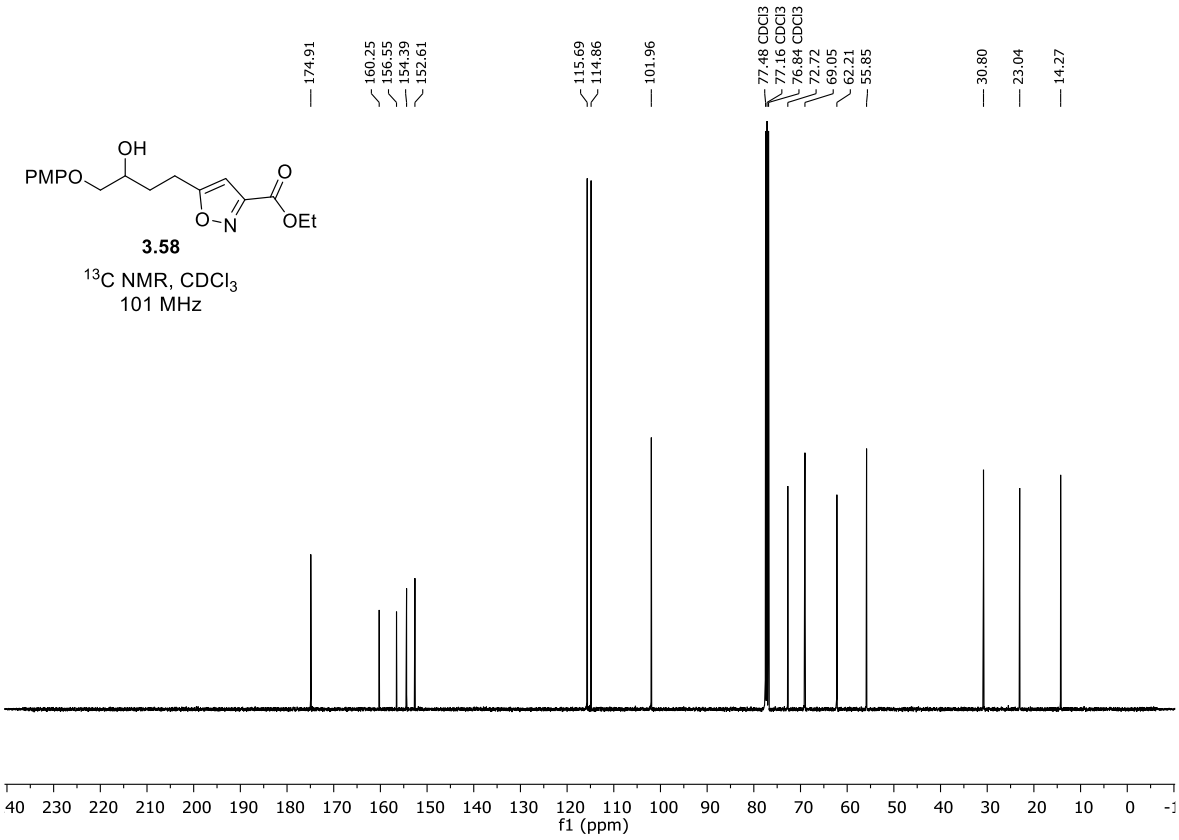
^{1}H NMR, $CDCl_3$
400 MHz

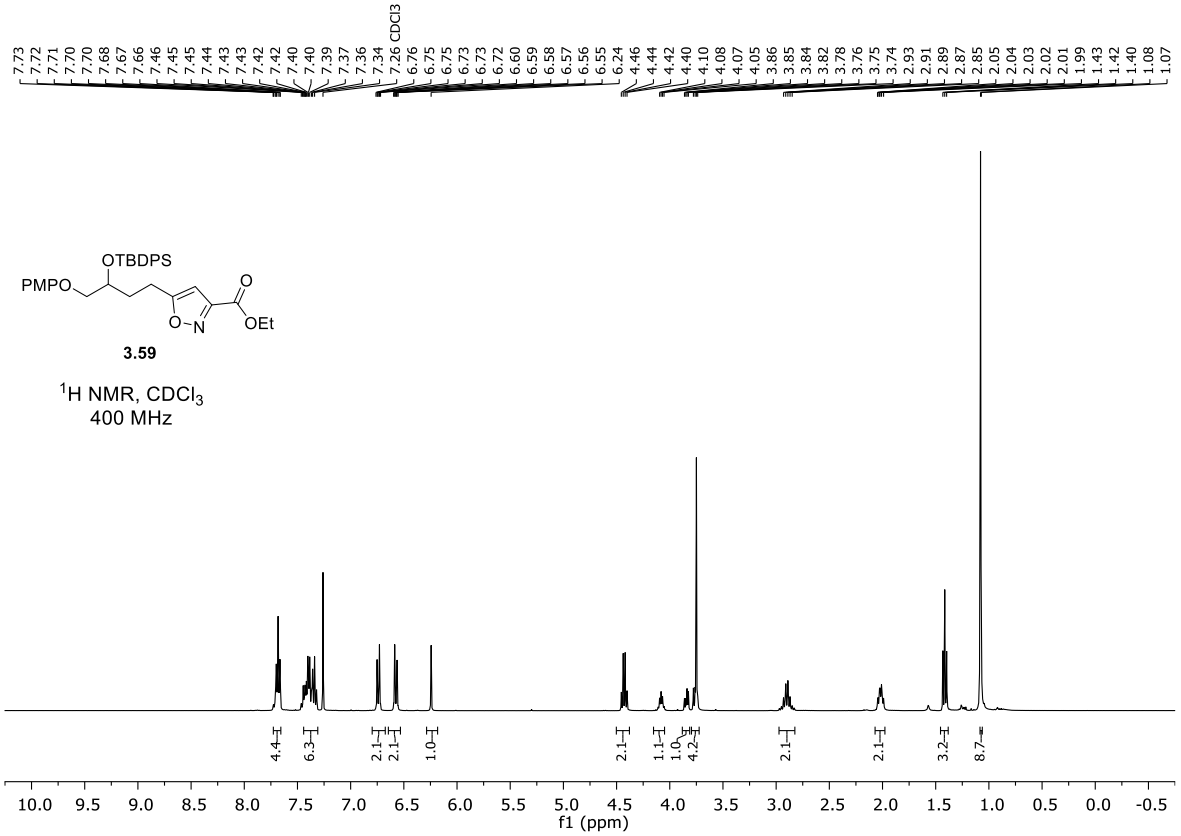


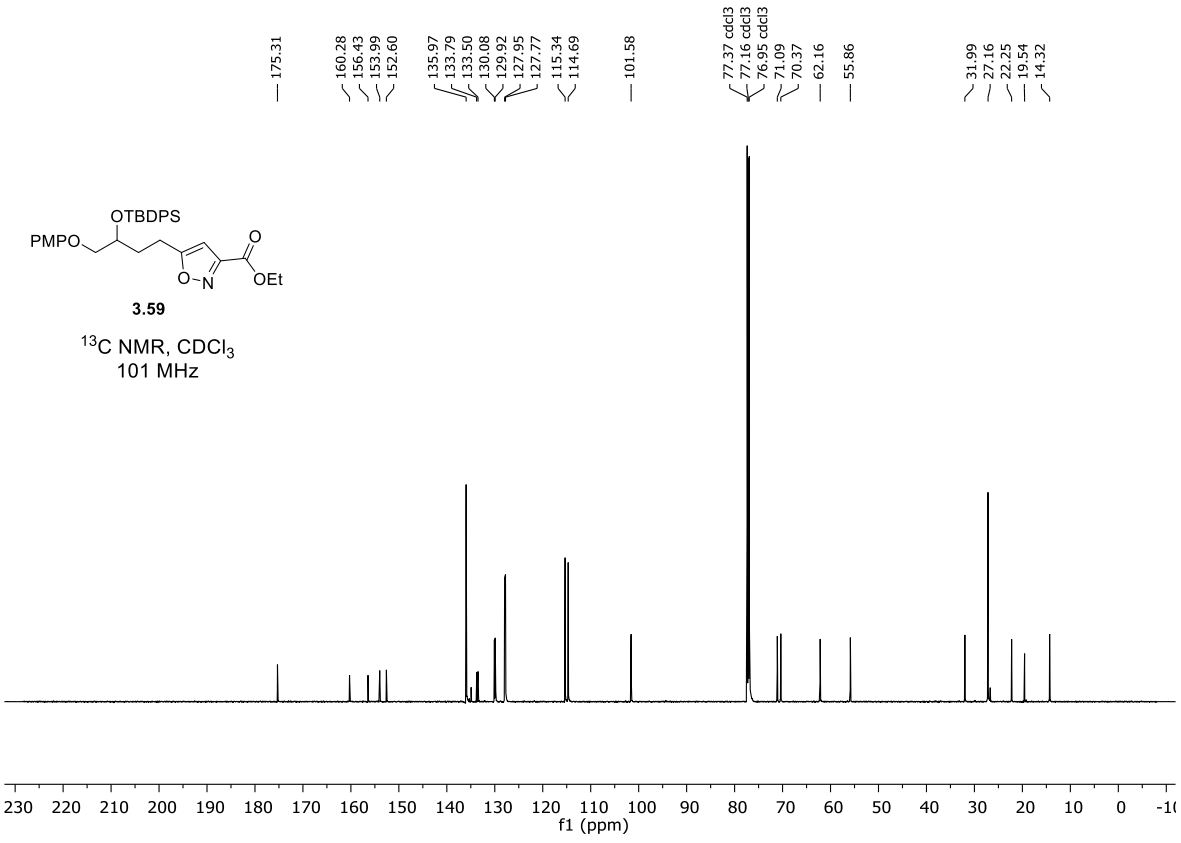
3.57

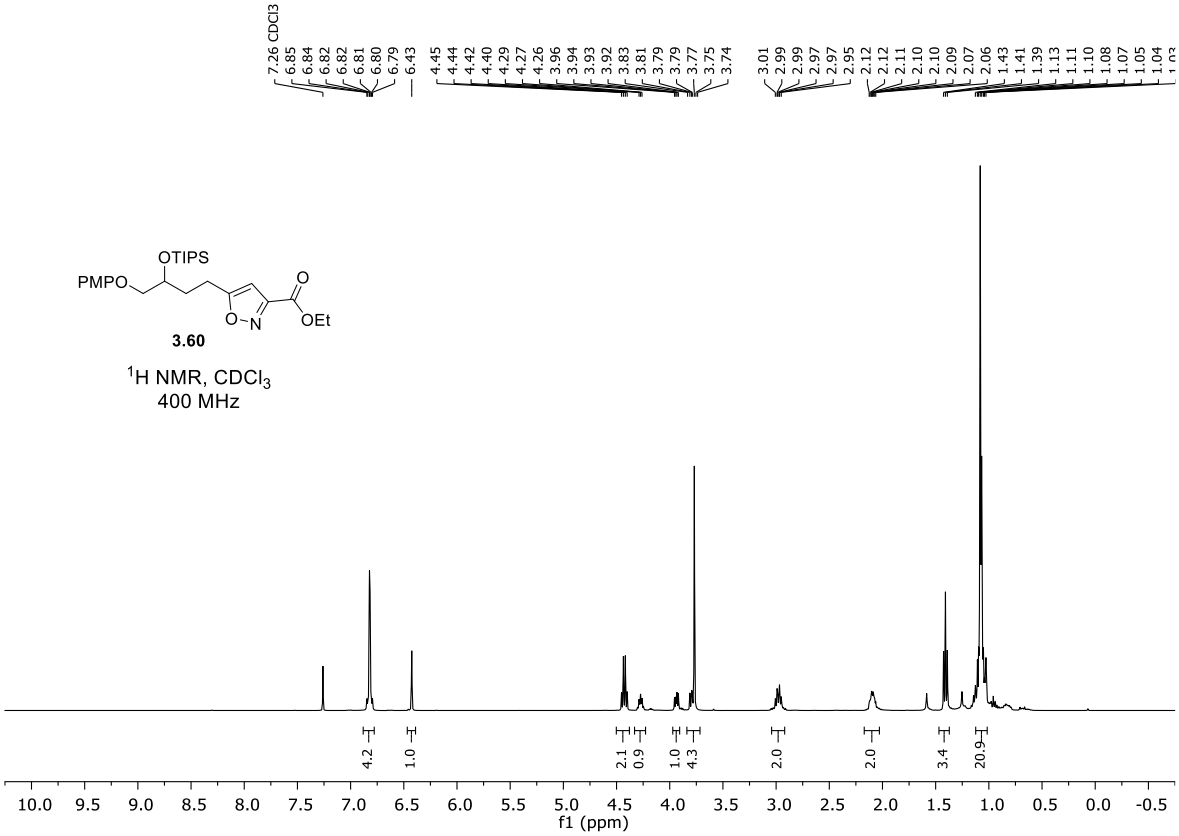
^{13}C NMR, $CDCl_3$
101 MHz

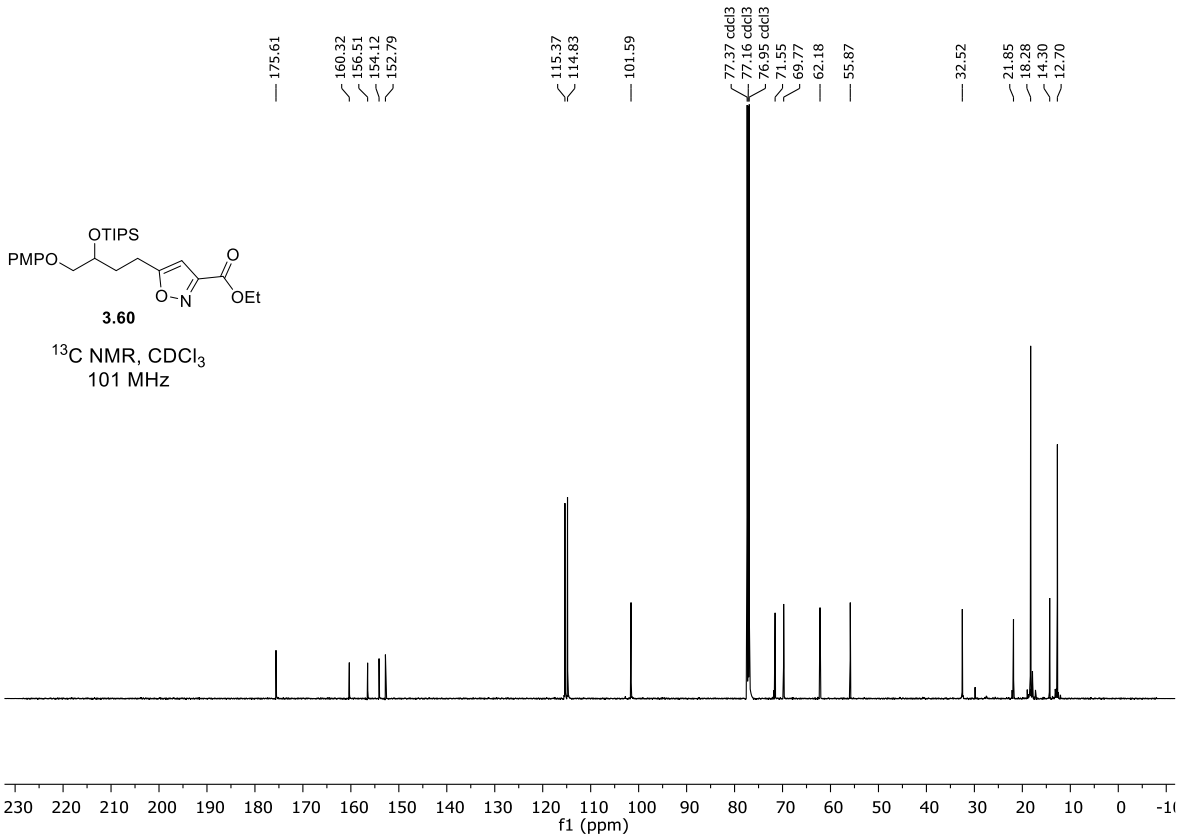

7.26 CDCl3
OH
PMPO
O
OEt
O
N
3.58
1H NMR, CDCl3
400 MHz
4.2
1.0
2.1
1.0
1.0
1.1
3.0
2.1
1.0
2.1
3.1
f1 (ppm)

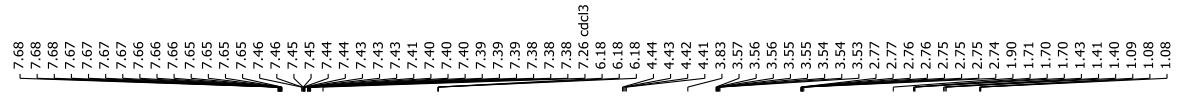

174.91
160.25
156.55
154.39
152.61
115.69
114.86
101.96
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
72.72
69.05
62.21
55.85
30.80
23.04
14.27
OH
PMPO
O
OEt
O
N
3.58
13C NMR, CDCl3
101 MHz
f1 (ppm)

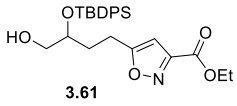

7.73 7.72 7.71 7.70 7.70 7.68 7.67 7.66 7.46 7.45 7.45 7.44 7.43 7.43 7.42 7.42 7.40 7.40 7.39 7.37 7.36 7.34 7.26 CDCl3 6.76 6.75 6.75 6.73 6.73 6.72 6.60 6.59 6.58 6.57 6.56 6.55 6.24 4.46 4.44 4.42 4.40 4.10 4.08 4.07 4.05 3.86 3.85 3.84 3.82 3.78 3.76 3.75 3.74 2.93 2.91 2.89 2.87 2.85 2.05 2.04 2.03 2.02 2.01 1.99 1.43 1.42 1.40 1.08 1.07
OTBDPS
PMPO
O
O
N
OEt
3.59
1H NMR, CDCl3
400 MHz
4.4 6.3 2.1 2.1 1.0 2.1 1.1 1.0 4.2 2.1 2.1 3.2 8.7
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 -0.5
f1 (ppm)


175.31
160.28 156.43 153.99 152.60
135.97 133.79 133.50 130.08 129.92 127.95 127.77 115.34 114.69
101.58
77.37 cdcl3 77.16 cdcl3 76.95 cdcl3 71.09 70.37 62.16 55.86
31.99 27.16 22.25 19.54 14.32
OTBDPS
PMPO
O
O
N
OEt
3.59
13C NMR, CDCl3
101 MHz
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.26 CDCl3
6.85
6.84
6.82
6.82
6.81
6.80
6.79
6.43
4.45
4.44
4.42
4.40
4.29
4.27
4.26
3.96
3.94
3.93
3.92
3.83
3.81
3.79
3.79
3.77
3.75
3.74
3.01
2.99
2.99
2.97
2.97
2.95
2.12
2.12
2.11
2.10
2.10
2.09
2.07
2.06
1.43
1.41
1.39
1.13
1.11
1.10
1.08
1.07
1.05
1.04
OTIPS
PMPO
O
O
N
OEt
3.60
1H NMR, CDCl3
400 MHz
4.2
1.0
2.1
0.9
1.0
4.3
2.0
2.0
3.4
20.9
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 -0.5
f1 (ppm)

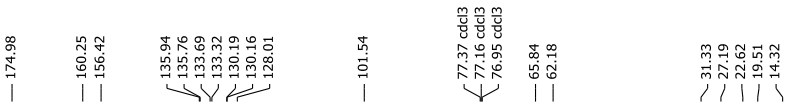

175.61
160.32
156.51
154.12
152.79
115.37
114.83
101.59
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
71.55
69.77
62.18
55.87
32.52
21.85
18.28
14.30
12.70
OTIPS
PMPO
O
O
N
OEt
3.60
13C NMR, CDCl3
101 MHz
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

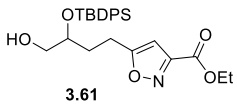




3.61

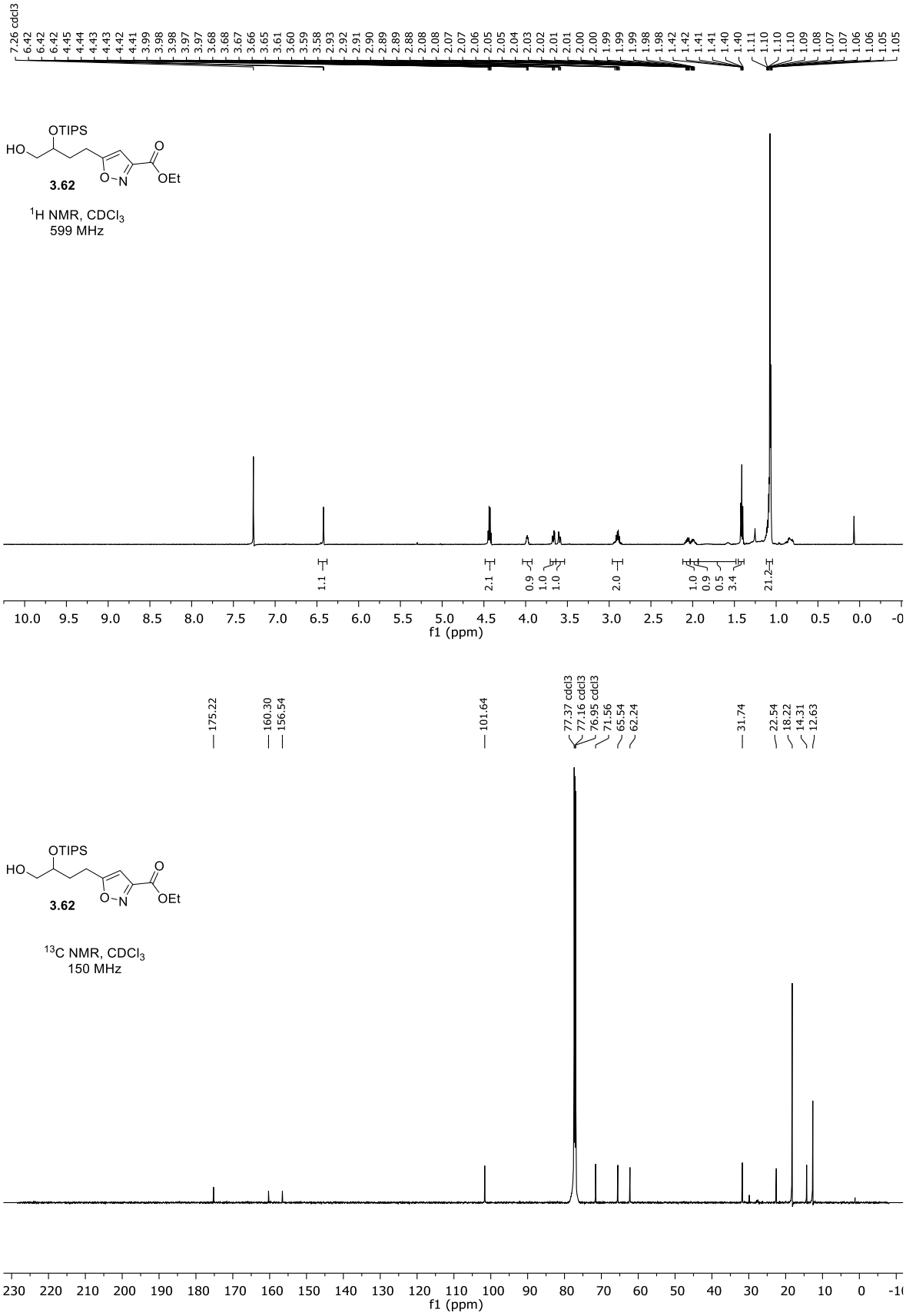
^{1}H NMR, $CDCl_3$
599 MHz

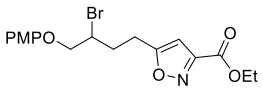




3.61

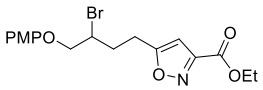
^{13}C NMR, $CDCl_3$
150 MHz


7.26 cdcl3
6.42 6.42 6.42 4.45 4.44 4.43 4.43 4.42 4.41 3.99 3.98 3.98 3.97 3.97 3.68 3.68 3.67 3.66 3.65 3.61 3.60 3.59 3.58 2.93 2.92 2.91 2.90 2.89 2.89 2.88 2.08 2.08 2.07 2.07 2.06 2.05 2.05 2.04 2.03 2.02 2.01 2.01 2.00 2.00 1.99 1.99 1.98 1.98 1.42 1.42 1.41 1.41 1.40 1.40 1.11 1.10 1.10 1.10 1.09 1.08 1.07 1.07 1.06 1.06 1.05 1.05
OTIPS
HO
O
OEt
O
N
3.62
1H NMR, CDCl3
599 MHz
1.1
2.1
0.9
1.0
1.0
2.0
1.0
0.9
0.5
3.4
21.2
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)
175.22
160.30
156.54
101.64
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
71.56
65.54
62.24
31.74
22.54
18.22
14.31
12.63
OTIPS
HO
O
OEt
O
N
3.62
13C NMR, CDCl3
150 MHz
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



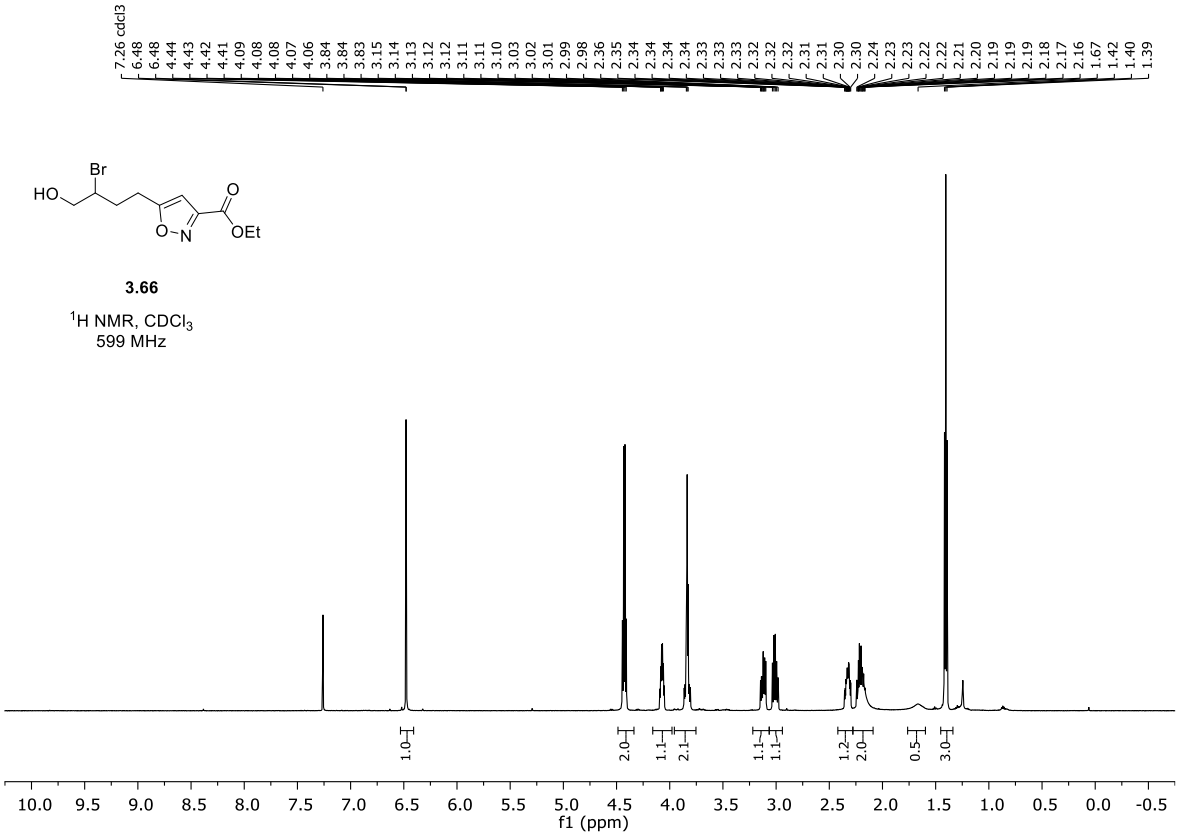
3.65

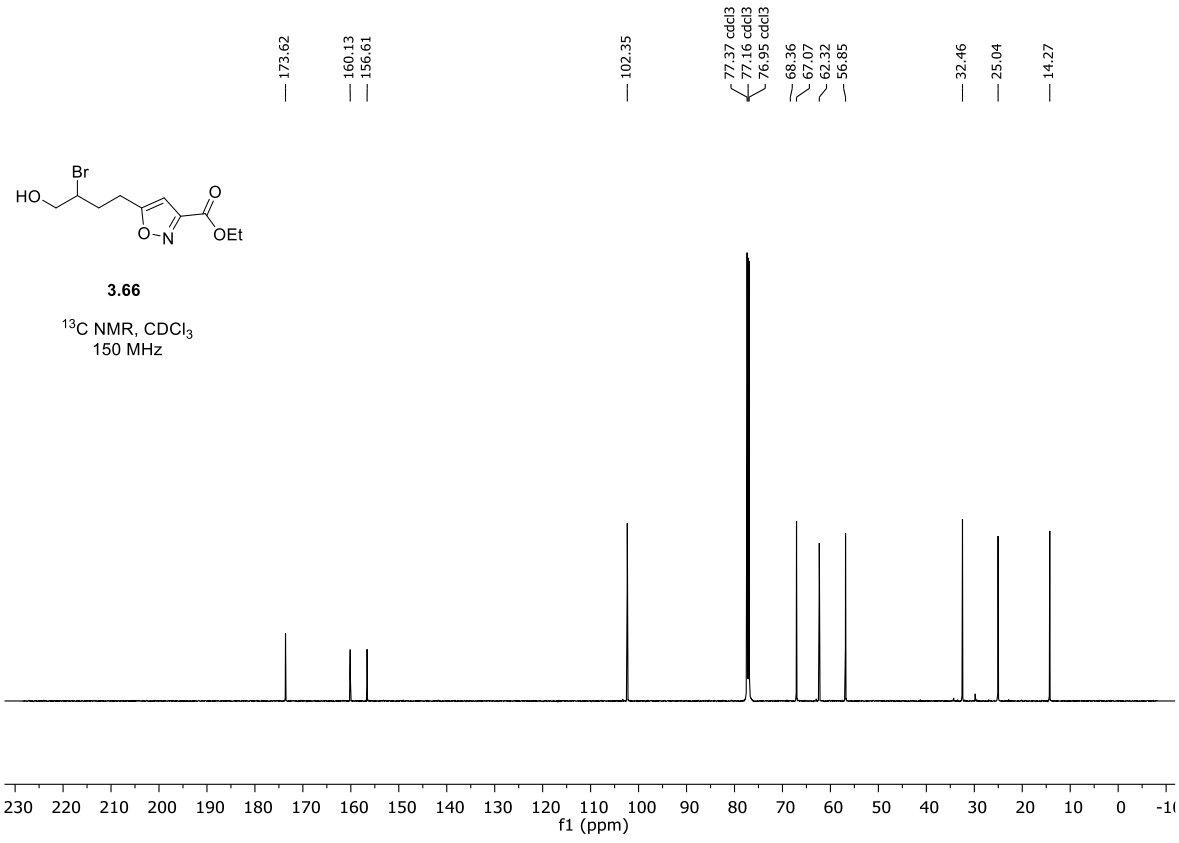
^{1}H NMR, $CDCl_3$
400 MHz

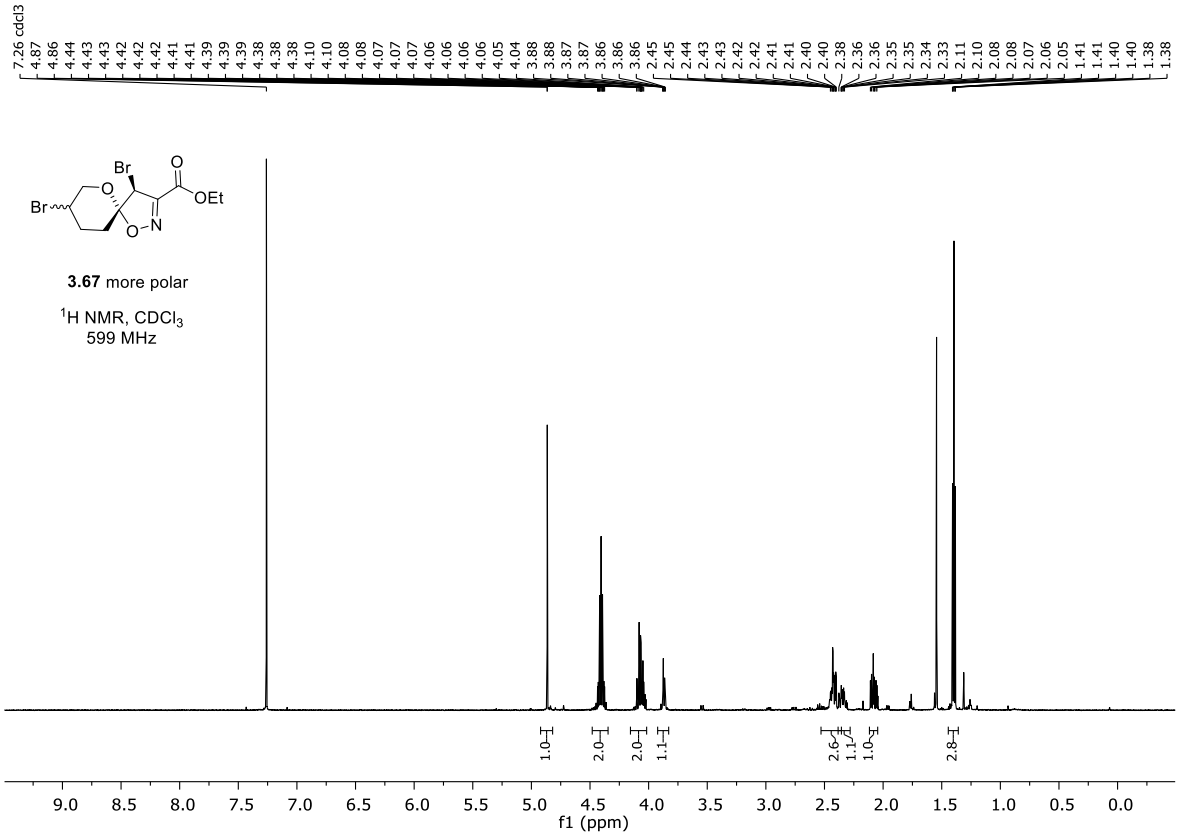


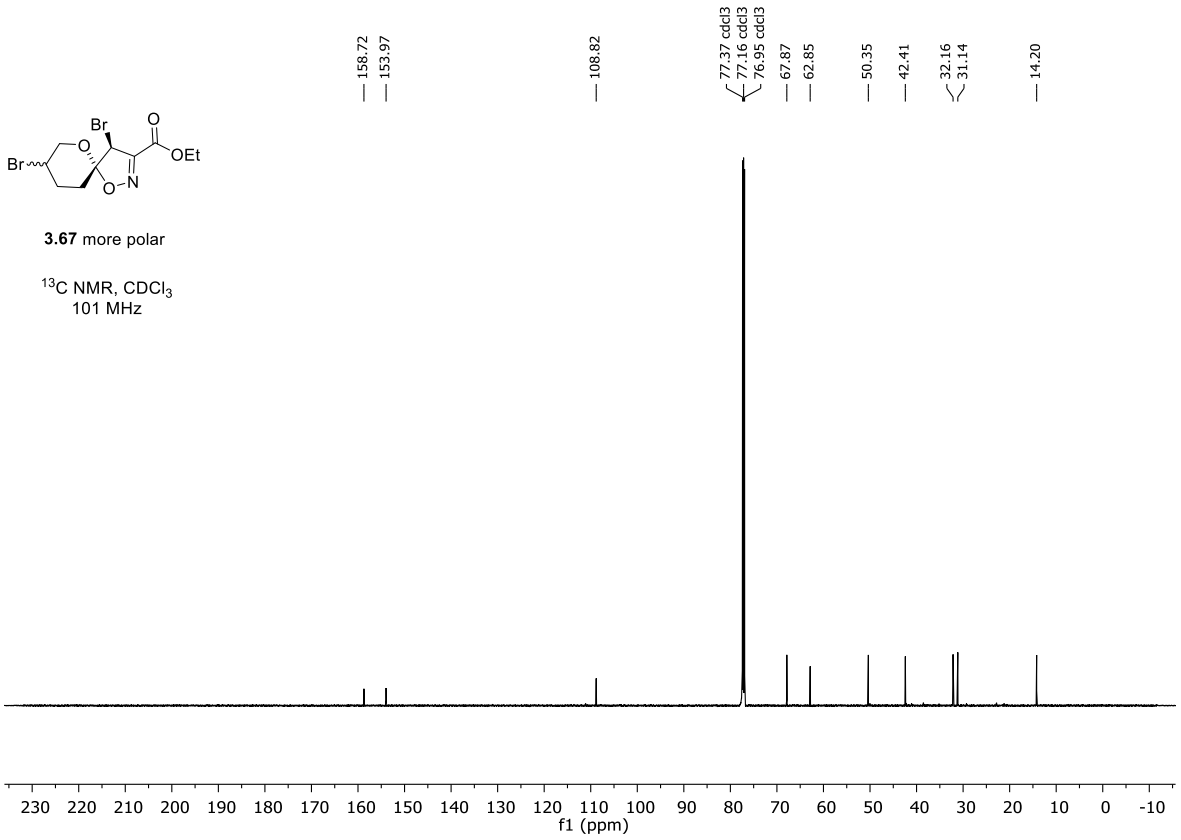
3.65

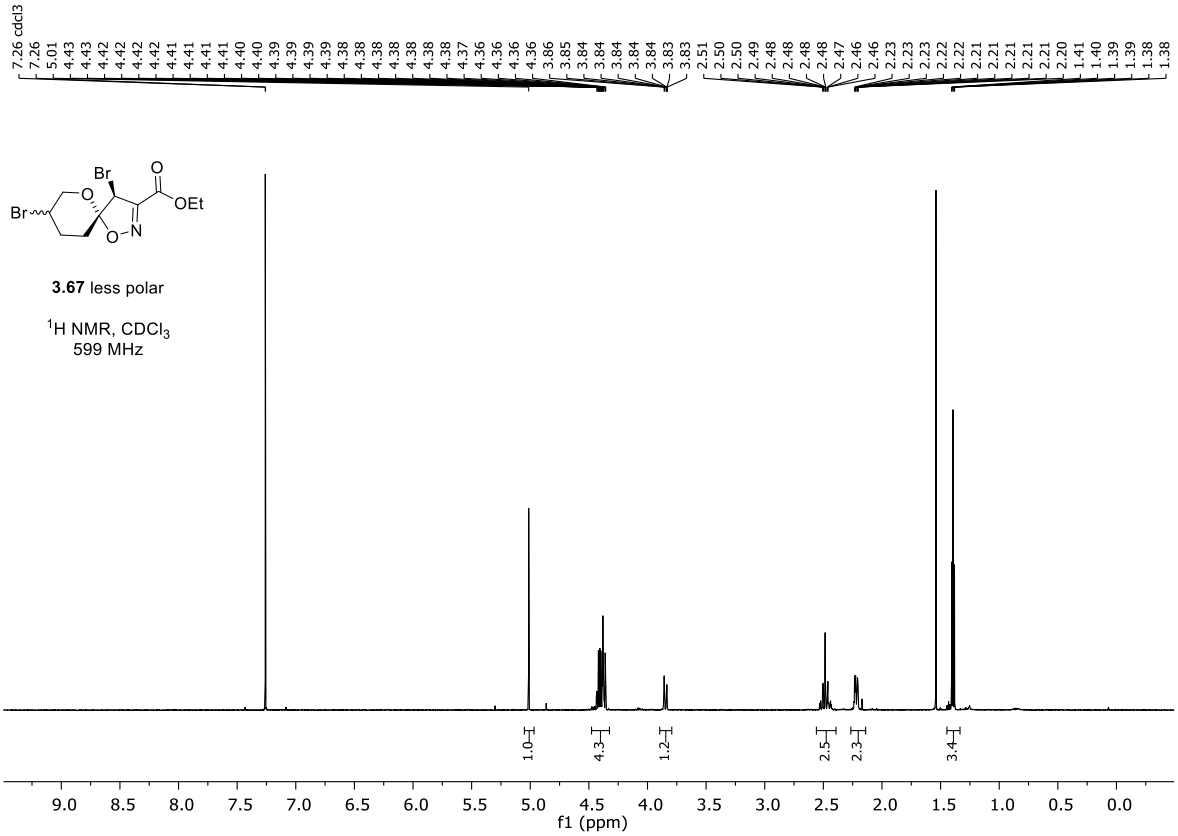
^{13}C NMR, $CDCl_3$
101 MHz

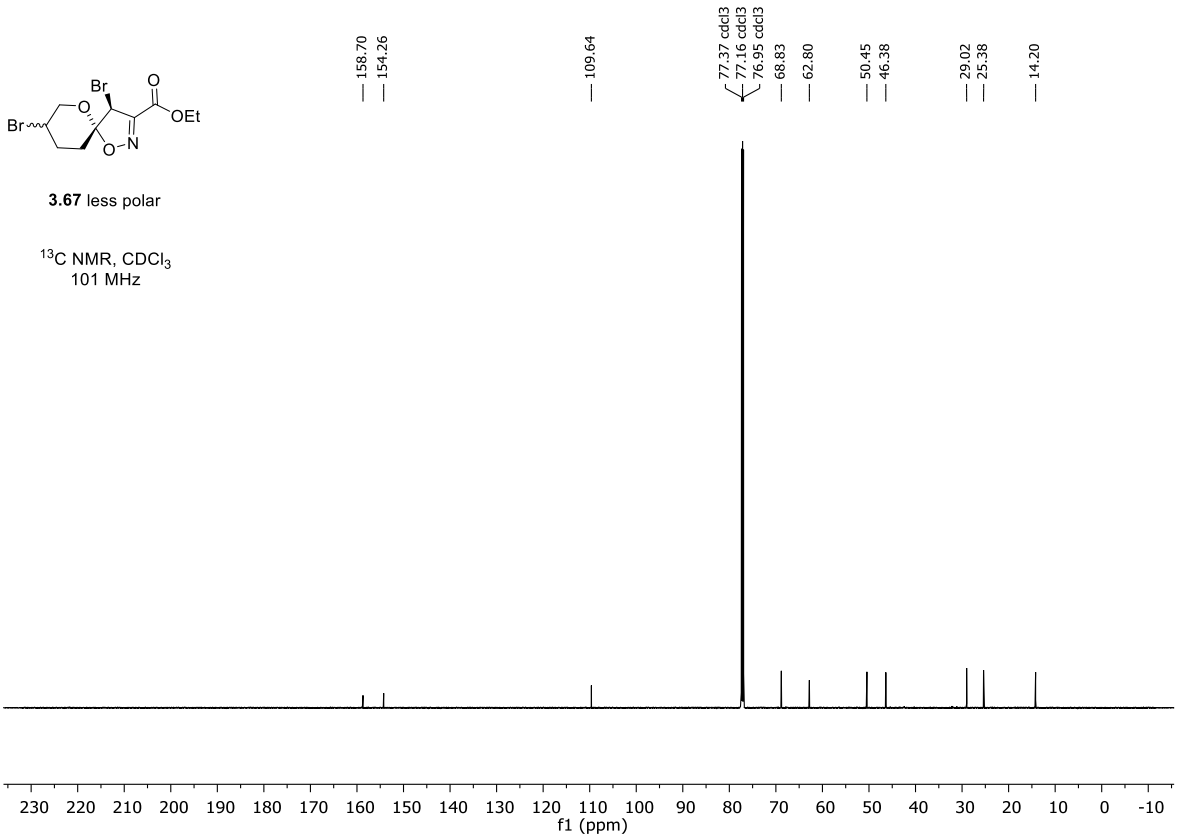

7.26 cdcl3
6.48
6.48
4.44
4.43
4.42
4.41
4.09
4.08
4.08
4.07
4.06
3.84
3.84
3.83
3.15
3.14
3.13
3.12
3.12
3.11
3.11
3.10
3.03
3.02
3.01
2.99
2.98
2.36
2.35
2.34
2.34
2.34
2.33
2.33
2.32
2.32
2.32
2.31
2.31
2.30
2.30
2.24
2.23
2.23
2.22
2.22
2.21
2.20
2.19
2.19
2.19
2.18
2.17
2.16
1.67
1.42
1.40
1.39
Br
HO
O
O
N
OEt
3.66
1H NMR, CDCl3
599 MHz
1.0
2.0
1.1
2.1
1.1
1.1
1.2
2.0
0.5
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 -0.5
f1 (ppm)

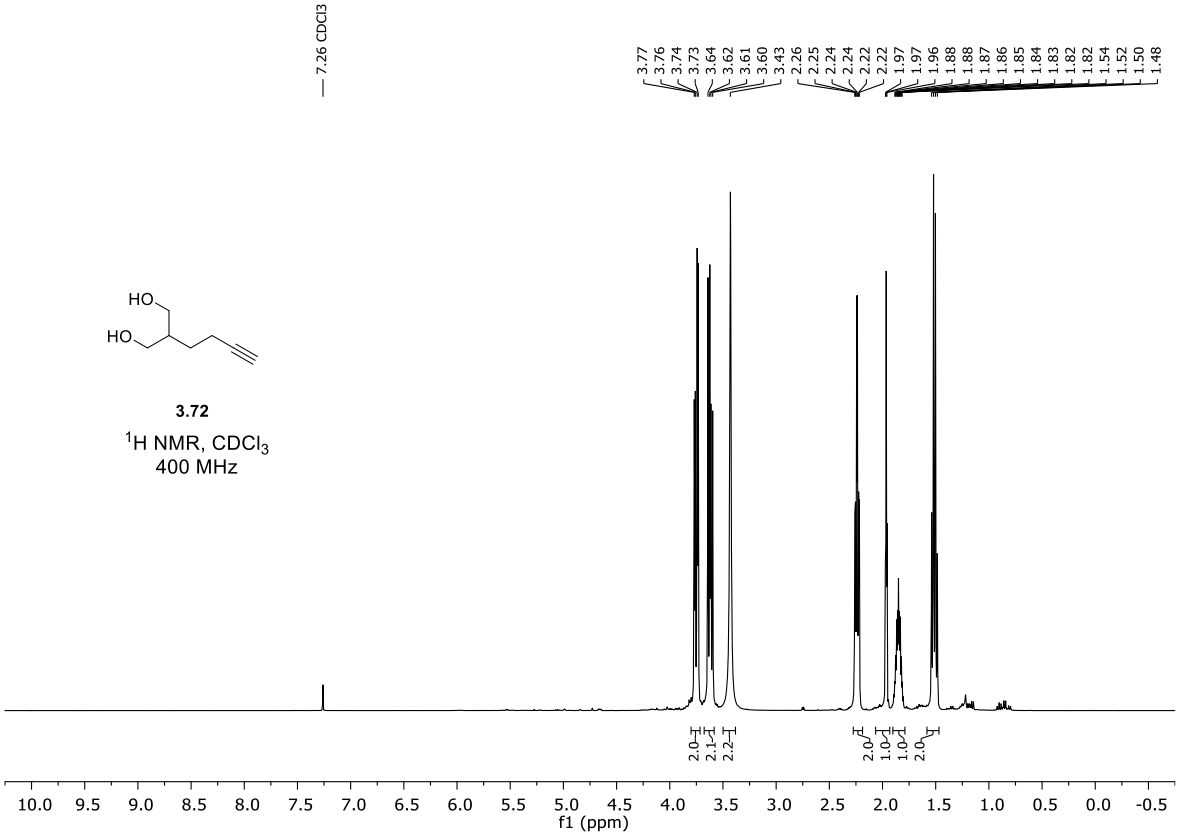

173.62
160.13
156.61
102.35
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
68.36
67.07
62.32
56.85
32.46
25.04
14.27
Br
HO
O
O
N
OEt
3.66
13C NMR, CDCl3
150 MHz
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)


7.26 cdcl3
4.87 4.86 4.44 4.43 4.43 4.42 4.42 4.42 4.41 4.41 4.39 4.39 4.39 4.38 4.38 4.38 4.10 4.10 4.08 4.08 4.07 4.07 4.07 4.06 4.06 4.06 4.06 4.05 4.04 3.88 3.88 3.87 3.87 3.86 3.86 3.86 2.45 2.45 2.44 2.43 2.43 2.42 2.42 2.41 2.41 2.40 2.40 2.38 2.36 2.36 2.35 2.35 2.34 2.33 2.11 2.10 2.08 2.08 2.07 2.06 2.05 1.41 1.41 1.40 1.40 1.38 1.38
Br
O
OEt
Br
O
N
O
3.67 more polar
1H NMR, CDCl3
599 MHz
1.0
2.0
2.0
1.1
2.6
1.1
1.0
2.8
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)


158.72
153.97
108.82
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
67.87
62.85
50.35
42.41
32.16
31.14
14.20
Br
O
OEt
Br
O
N
O
3.67 more polar
13C NMR, CDCl3
101 MHz
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

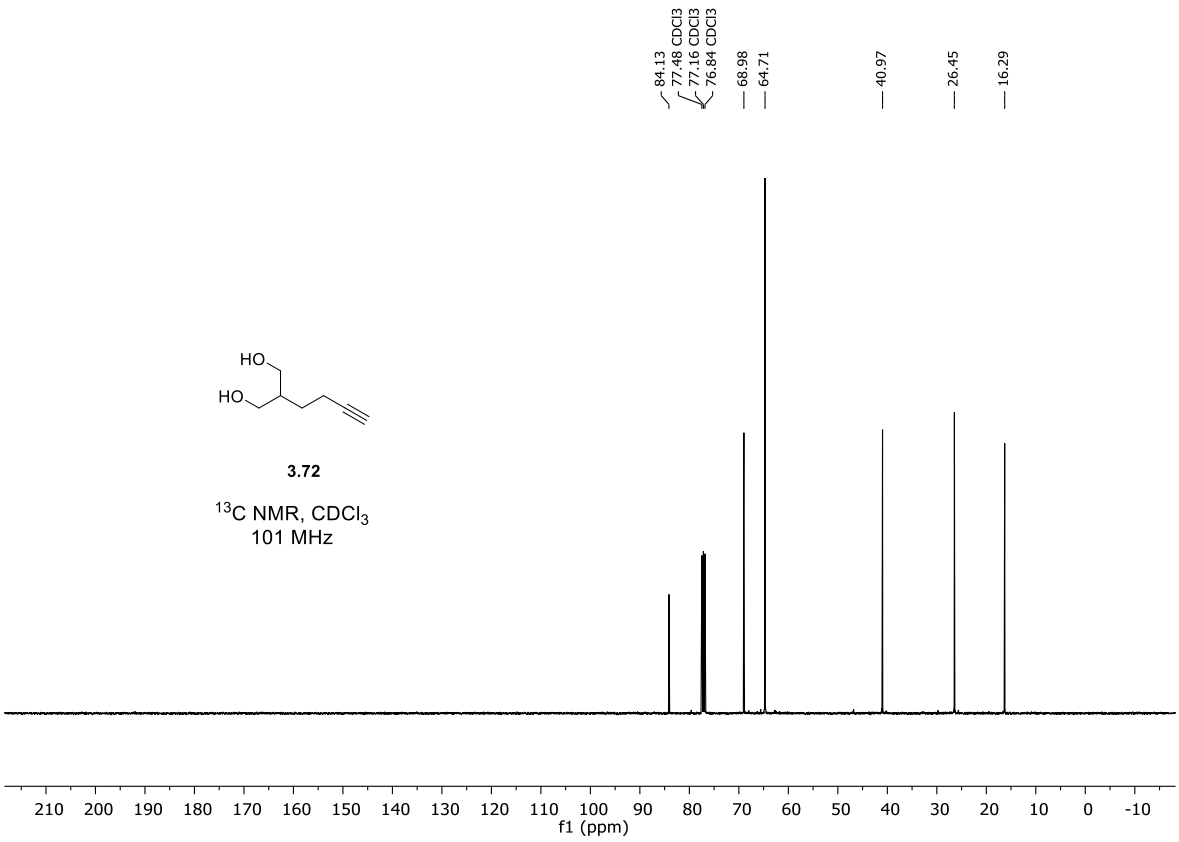

7.26 cdcl3
7.26 5.01 4.43 4.43 4.42 4.42 4.42 4.42 4.41 4.41 4.41 4.40 4.40 4.39 4.39 4.39 4.38 4.38 4.38 4.38 4.38 4.38 4.37 4.36 4.36 4.36 4.36 3.86 3.85 3.84 3.84 3.84 3.84 3.84 3.83 3.83 2.51 2.50 2.50 2.49 2.48 2.48 2.48 2.48 2.47 2.46 2.46 2.23 2.23 2.22 2.22 2.21 2.21 2.21 2.21 2.20 1.41 1.40 1.39 1.39 1.38 1.38
Br
O
OEt
Br
O
N
O
3.67 less polar
1H NMR, CDCl3
599 MHz
1.0
4.3
1.2
2.5
2.3
3.4
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)


158.70
154.26
109.64
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
68.83
62.80
50.45
46.38
29.02
25.38
14.20
Br
O
OEt
Br
O
N
O
3.67 less polar
13C NMR, CDCl3
101 MHz
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



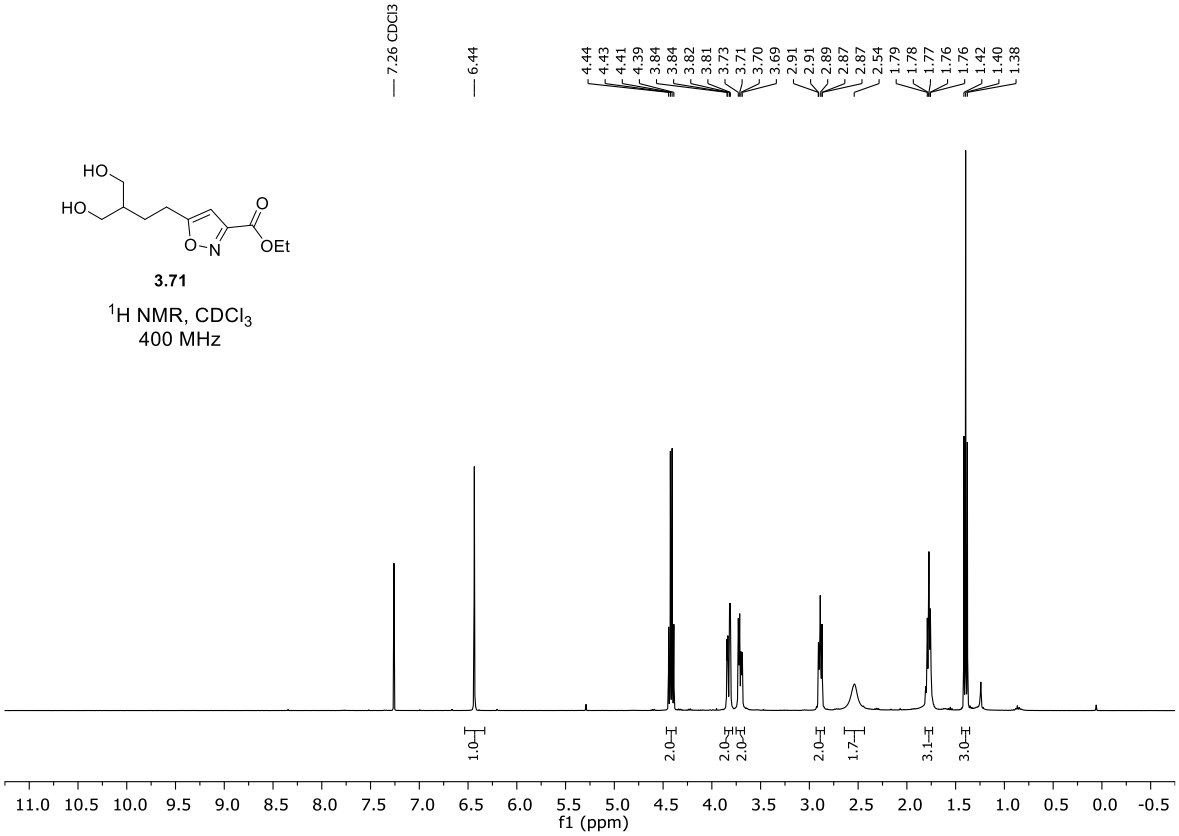
3.72

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



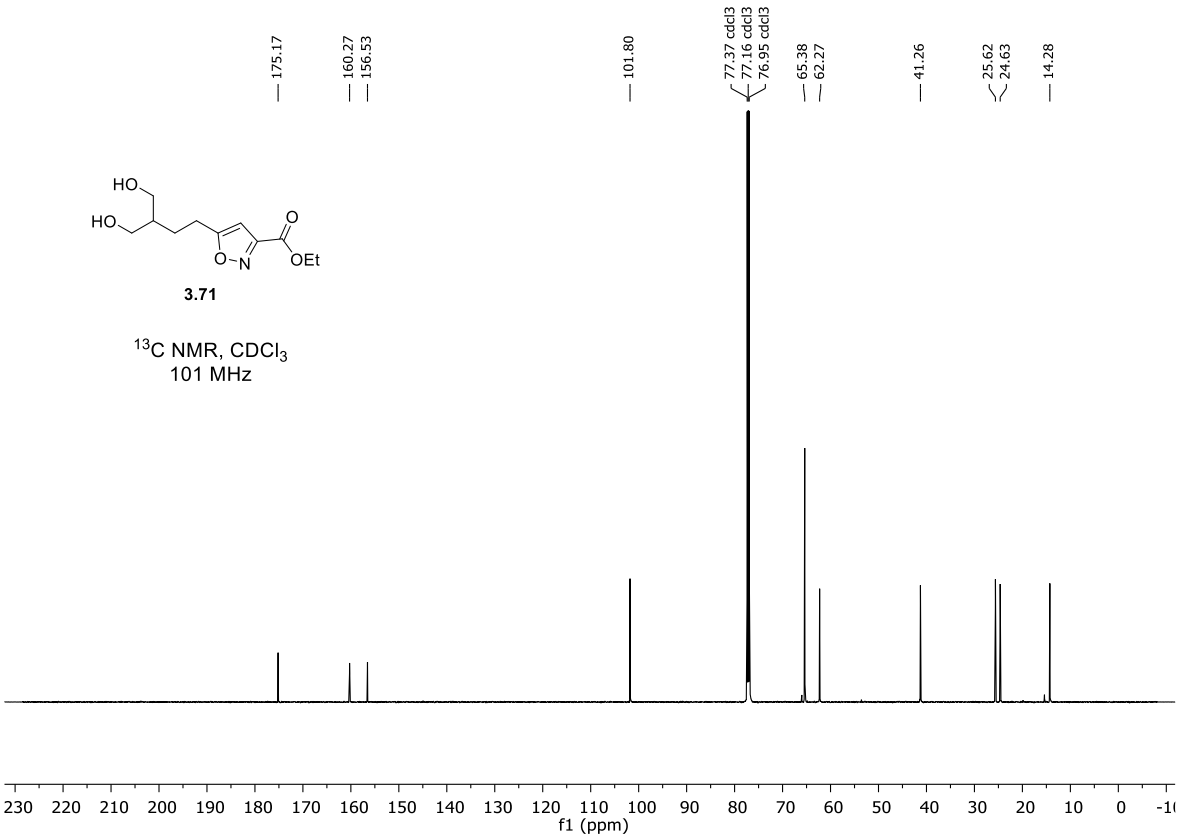
3.72

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



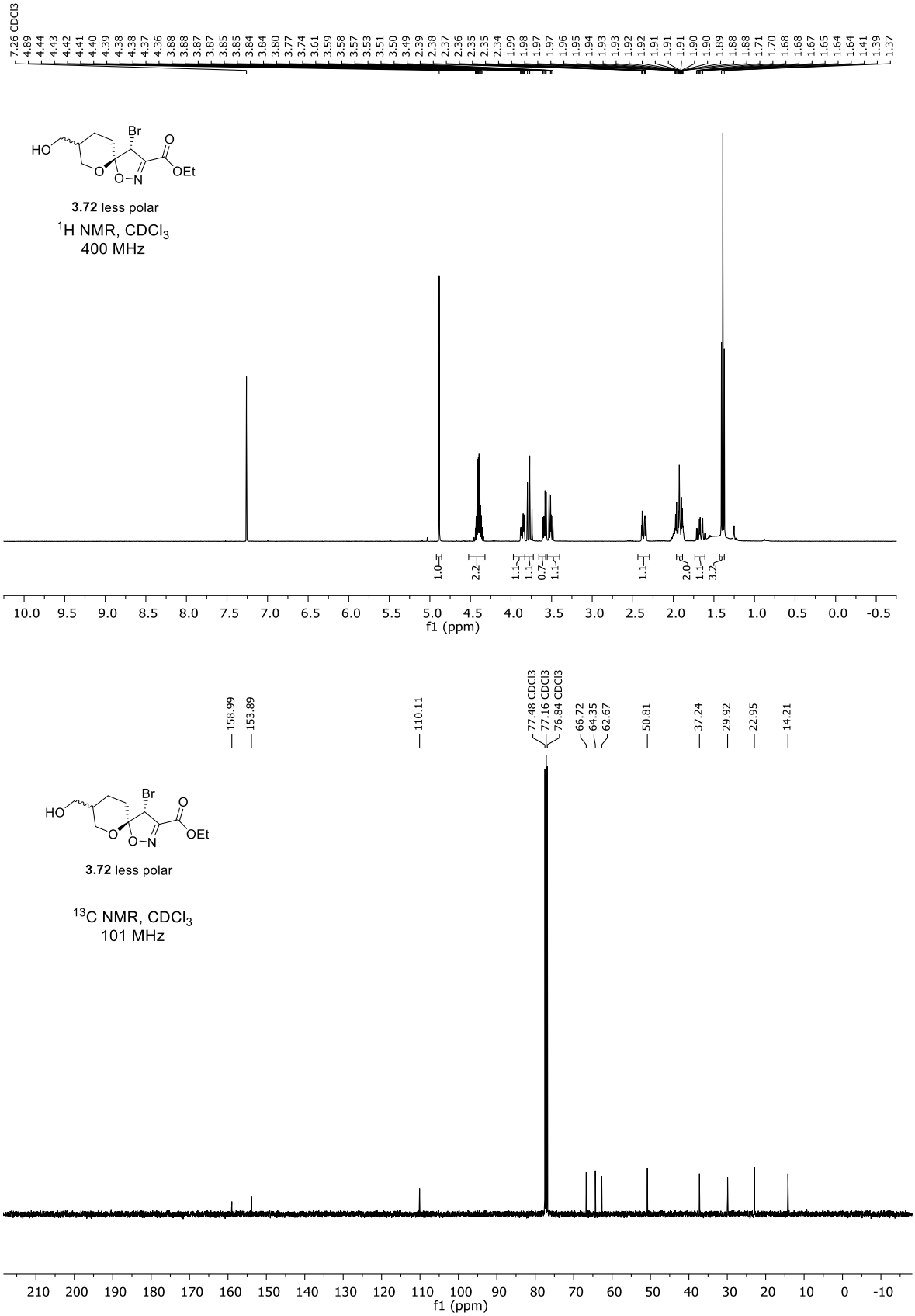
3.71

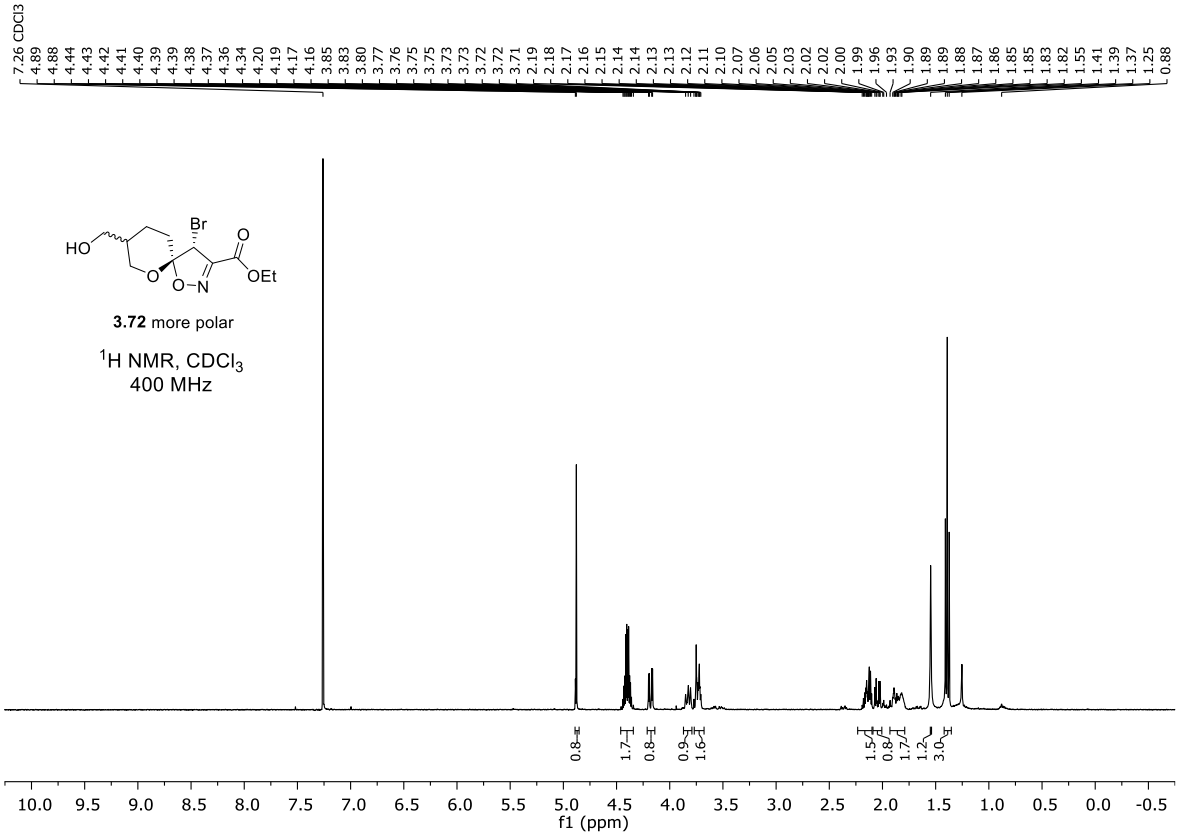
^{1}H NMR, $CDCl_3$
400 MHz



3.71

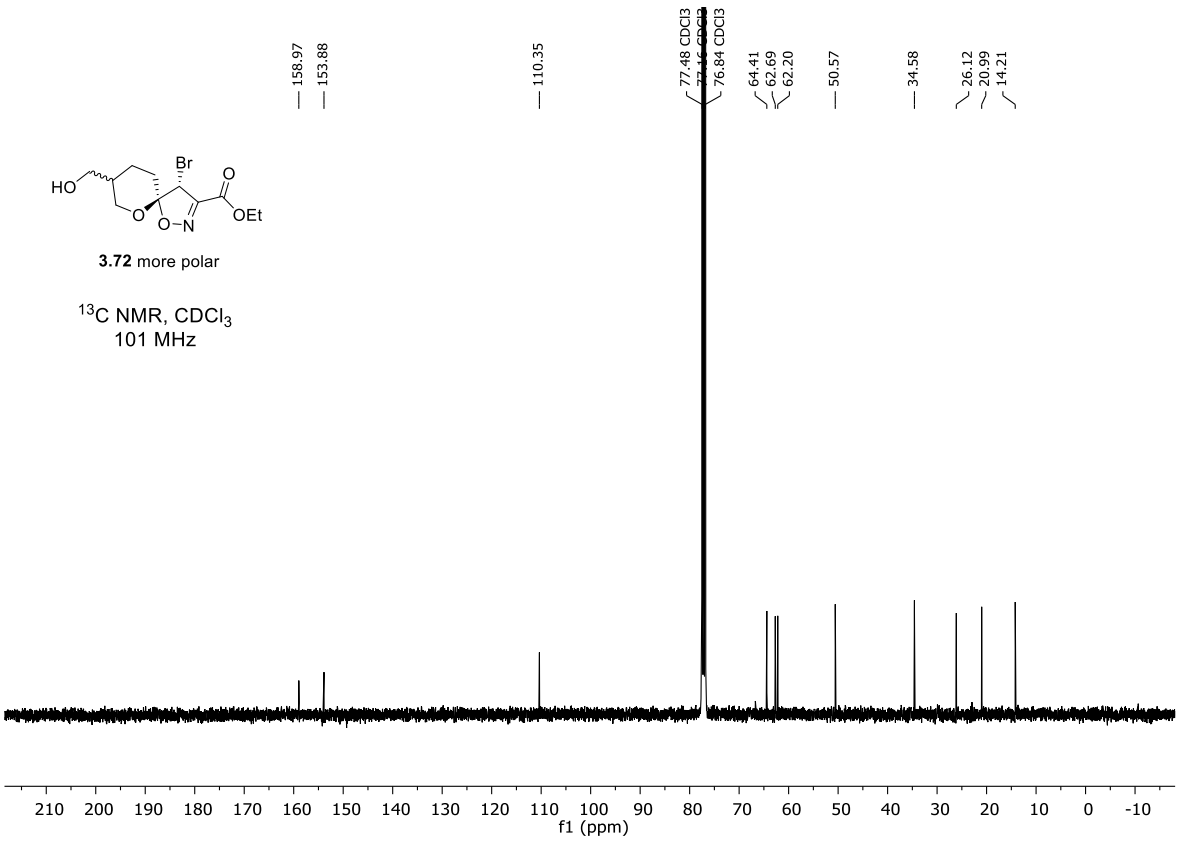
^{13}C NMR, $CDCl_3$
101 MHz


7.26 CDCl3
4.89 4.44 4.43 4.42 4.41 4.40 4.39 4.38 4.38 4.37 4.36 3.88 3.88 3.87 3.87 3.85 3.85 3.84 3.84 3.80 3.77 3.74 3.61 3.59 3.58 3.57 3.53 3.51 3.50 3.49 2.39 2.38 2.37 2.36 2.35 2.35 2.34 1.99 1.98 1.97 1.97 1.96 1.95 1.94 1.93 1.93 1.92 1.92 1.91 1.91 1.91 1.90 1.90 1.89 1.88 1.88 1.71 1.70 1.68 1.68 1.67 1.65 1.64 1.64 1.41 1.39 1.37
HO
Br
O
O
O–N
OEt
3.72 less polar
1H NMR, CDCl3
400 MHz
1.0 2.2 1.1 1.1 0.7 1.1 1.1 2.0 1.1 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 -0.5
f1 (ppm)
158.99
153.89
110.11
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
66.72
64.35
62.67
50.81
37.24
29.92
22.95
14.21
HO
Br
O
O
O–N
OEt
3.72 less polar
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)



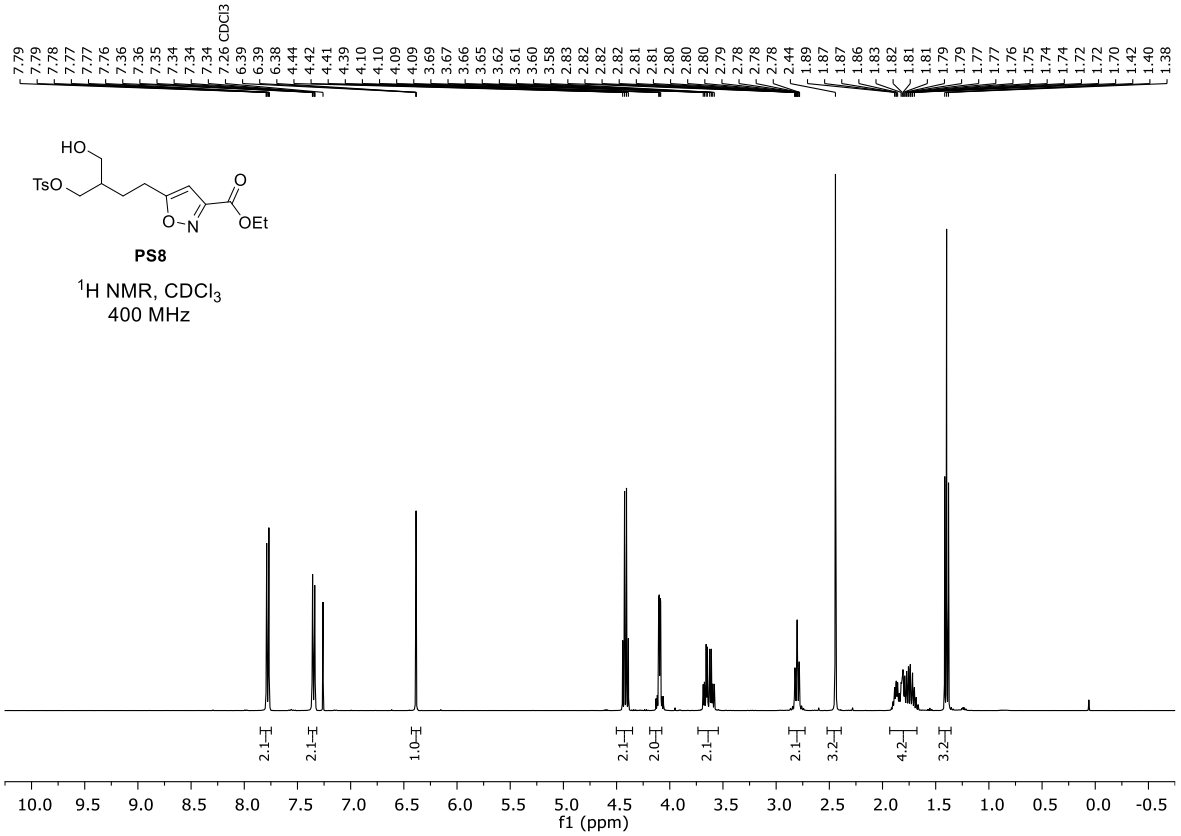
3.72 more polar

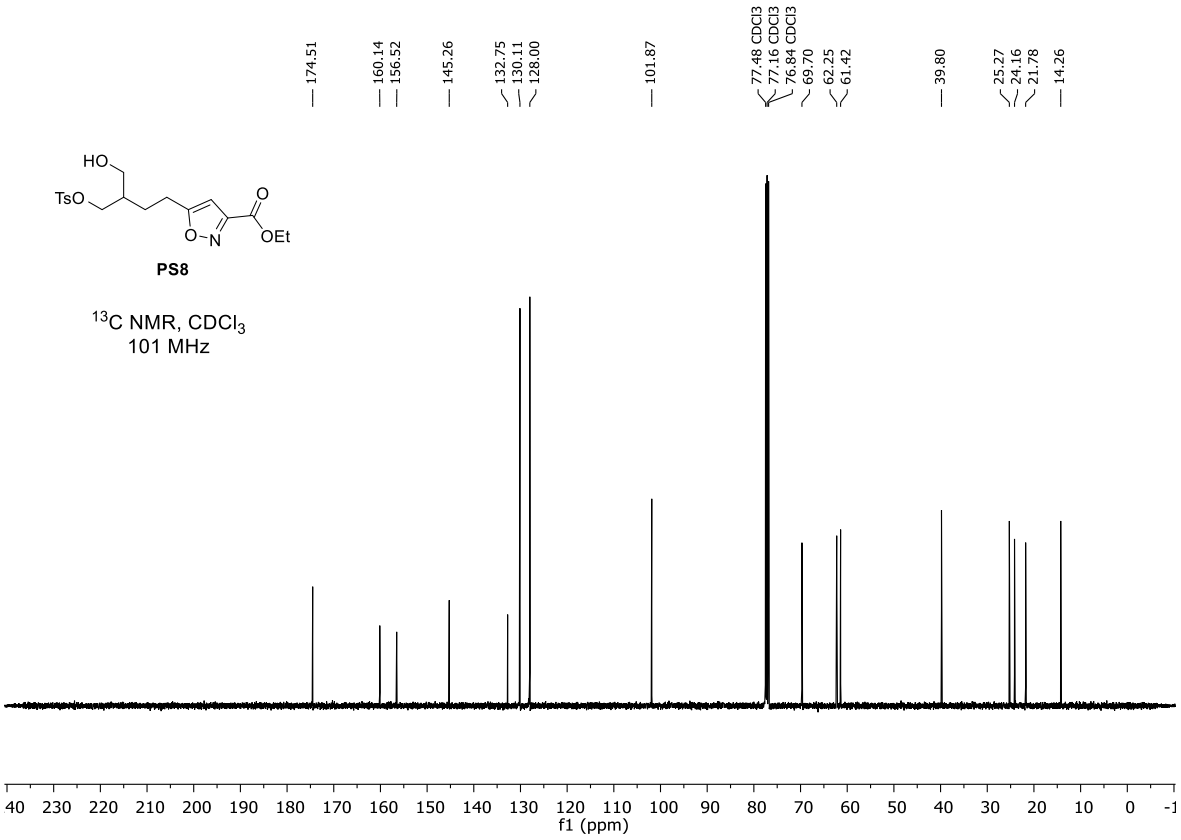
^{1}H NMR, $CDCl_3$
400 MHz

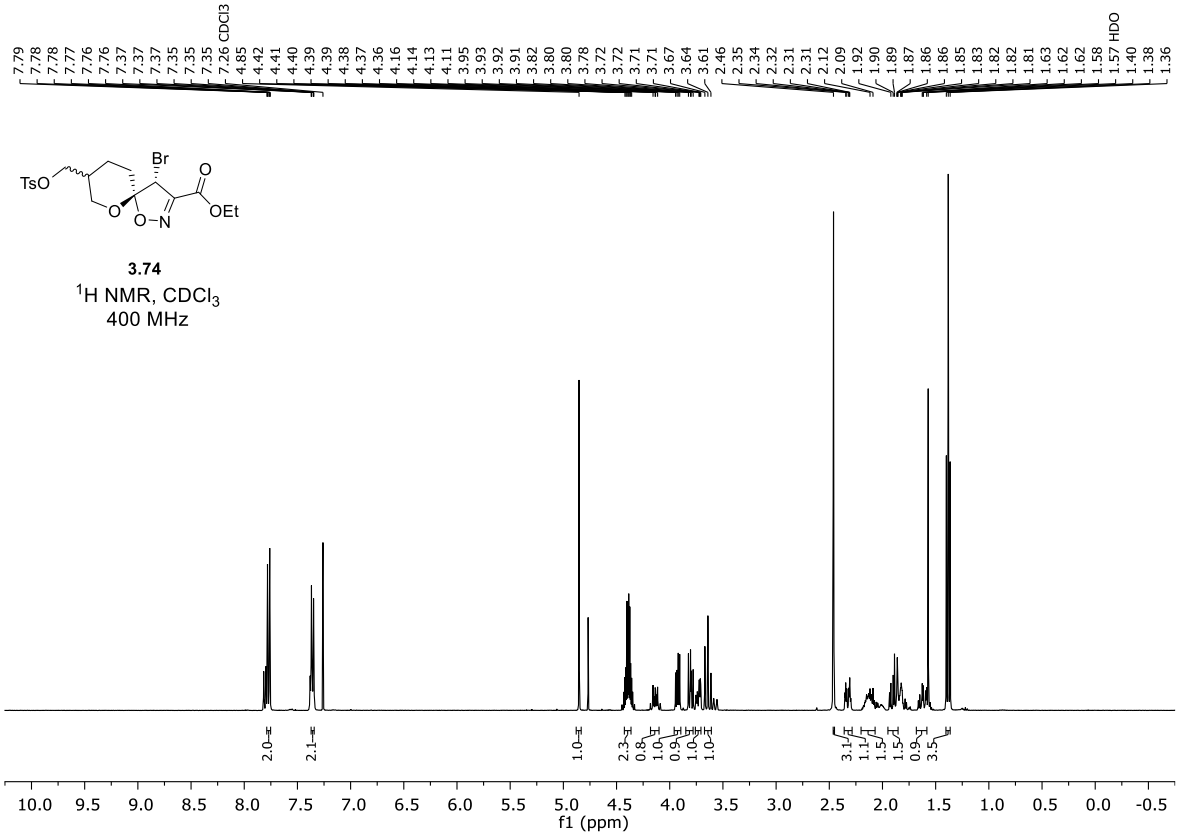


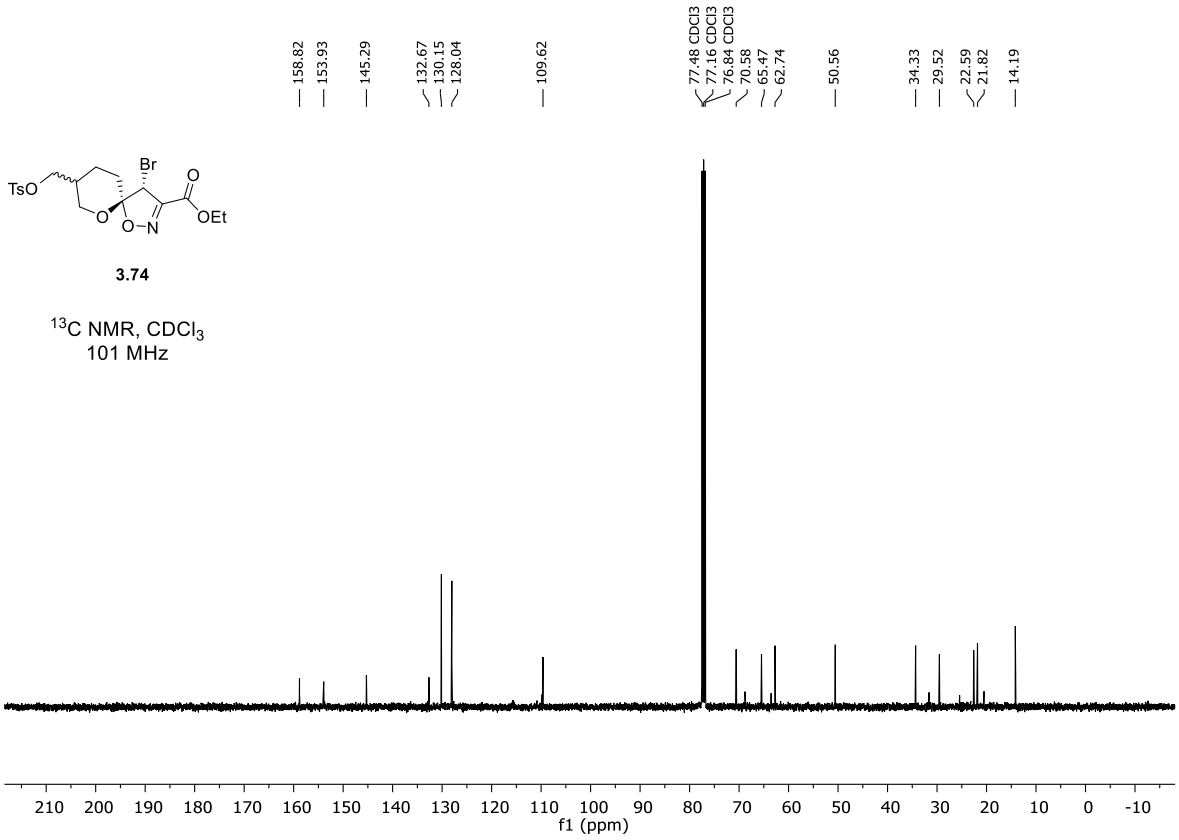
3.72 more polar

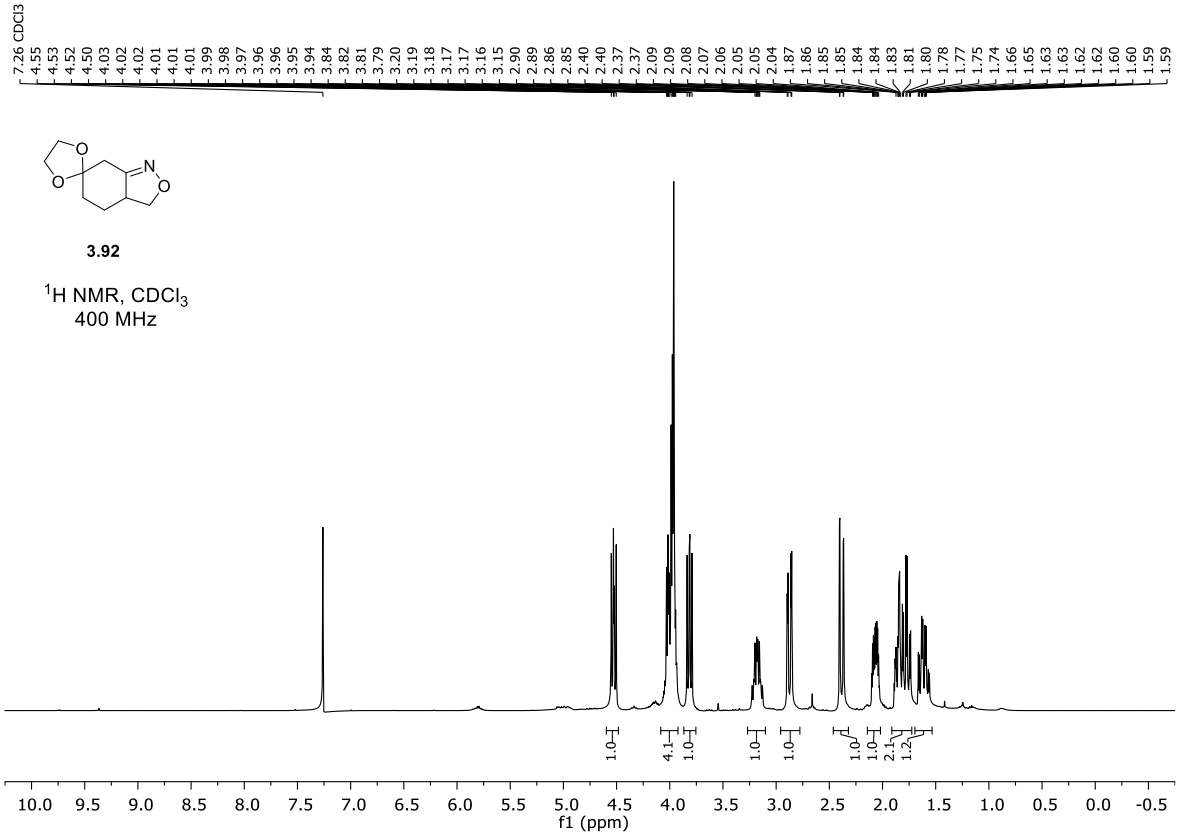
^{13}C NMR, $CDCl_3$
101 MHz

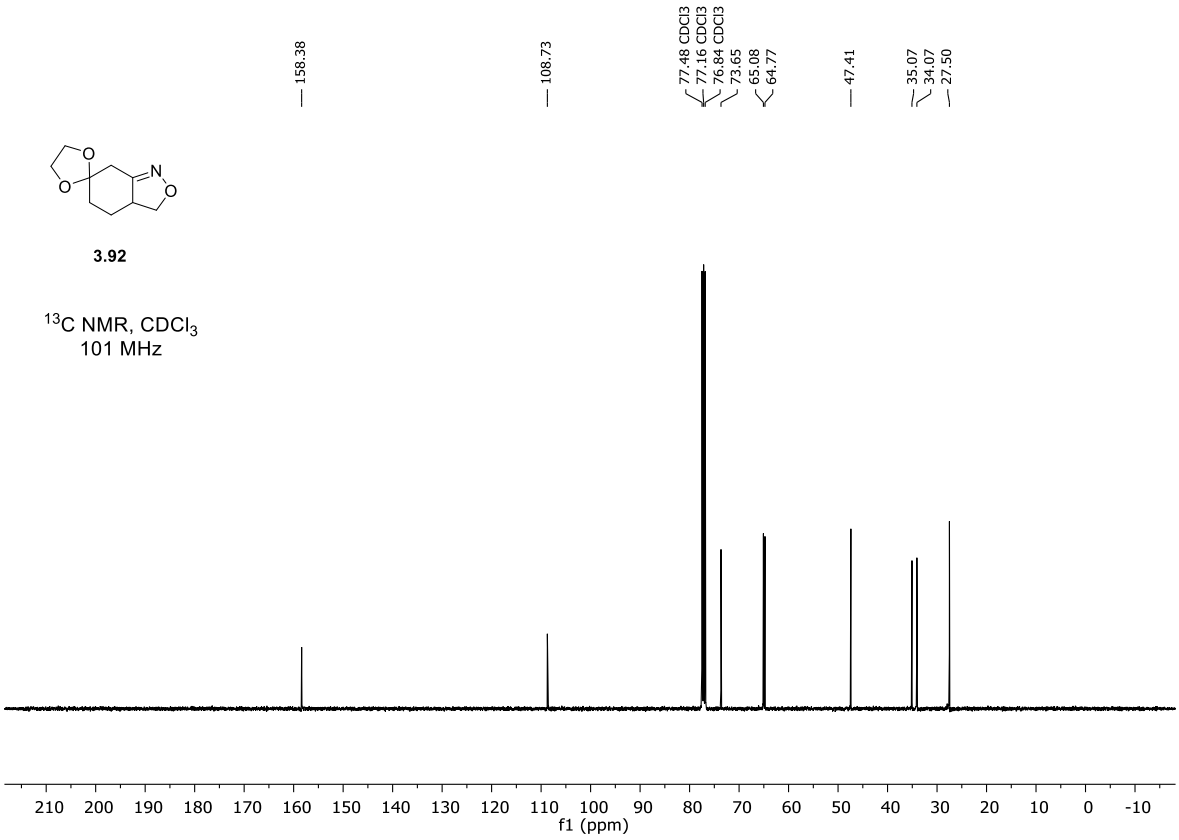

7.79 7.79 7.78 7.77 7.77 7.76 7.36 7.36 7.35 7.34 7.34 7.34 7.26 CDCl3 6.39 6.39 6.38 4.44 4.42 4.41 4.39 4.10 4.10 4.09 4.09 3.69 3.67 3.66 3.65 3.62 3.61 3.60 3.58 2.83 2.82 2.82 2.82 2.81 2.81 2.80 2.80 2.80 2.79 2.78 2.78 2.78 2.44 1.89 1.87 1.87 1.86 1.83 1.82 1.81 1.81 1.79 1.79 1.77 1.77 1.76 1.75 1.74 1.74 1.72 1.72 1.70 1.42 1.40 1.38
HO
TsO
O
O
N
OEt
PS8
1H NMR, CDCl3
400 MHz
2.1 2.1 1.0 2.1 2.0 2.1 2.1 3.2 4.2 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 -0.5
f1 (ppm)

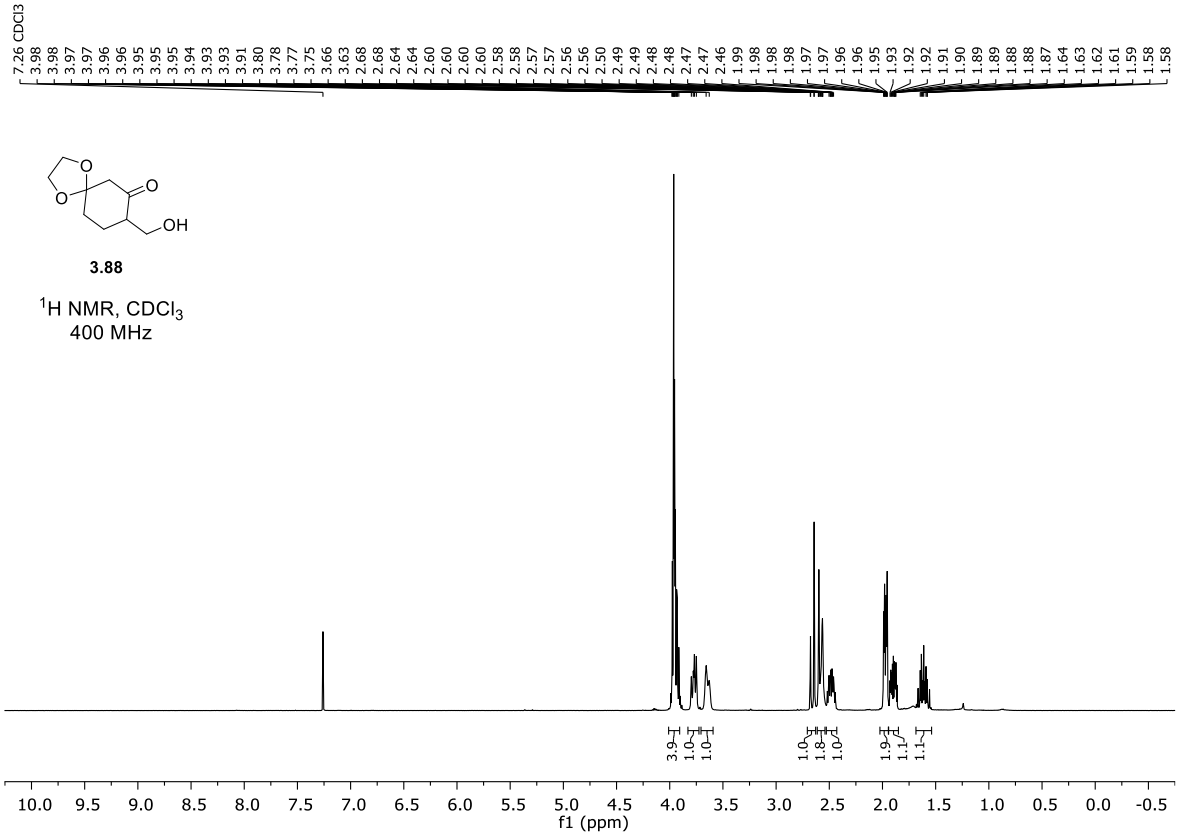

174.51
160.14
156.52
145.26
132.75
130.11
128.00
101.87
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
69.70
62.25
61.42
39.80
25.27
24.16
21.78
14.26
HO
TsO
O
O
N
OEt
PS8
13C NMR, CDCl3
101 MHz
40 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

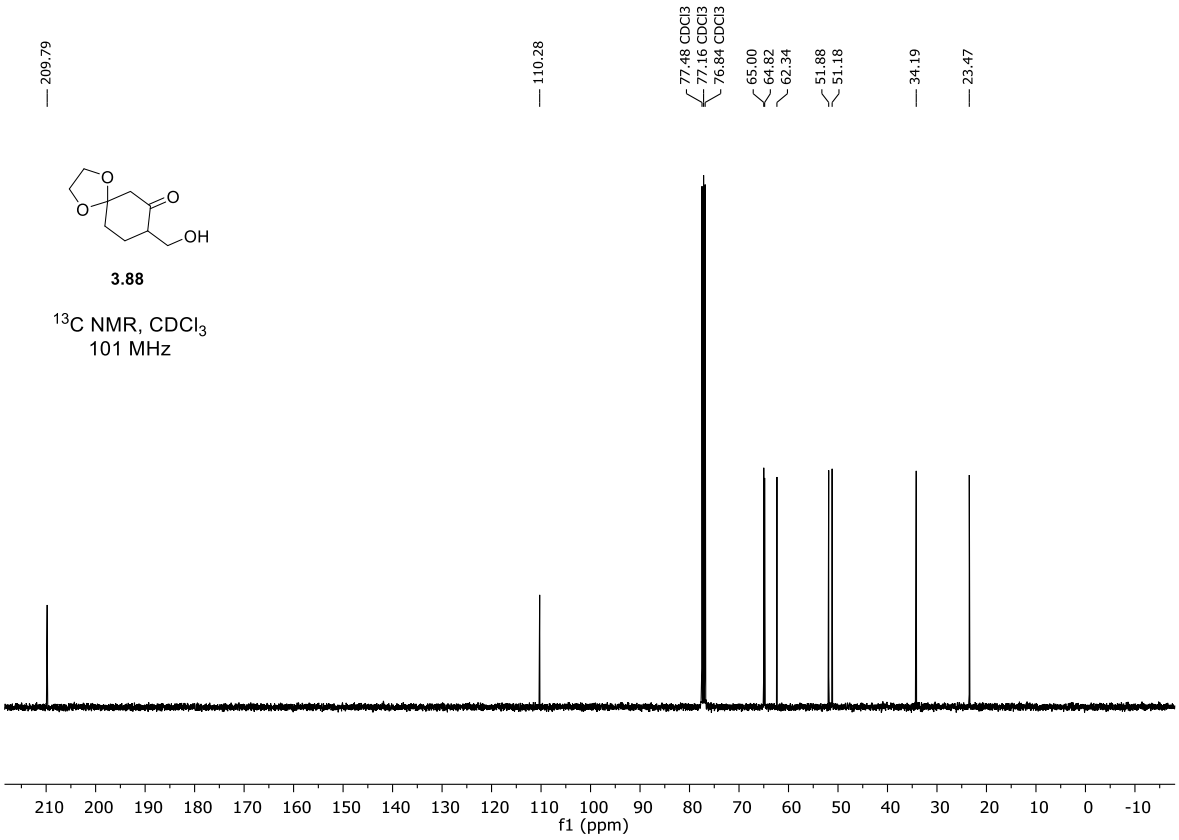

7.79 7.78 7.78 7.77 7.76 7.76 7.37 7.37 7.37 7.35 7.35 7.35 7.26 CDCl3 4.85 4.42 4.41 4.40 4.39 4.39 4.38 4.37 4.36 4.16 4.14 4.13 4.11 3.95 3.93 3.92 3.91 3.82 3.80 3.80 3.78 3.72 3.72 3.71 3.71 3.67 3.64 3.61 2.46 2.35 2.34 2.32 2.31 2.12 2.09 1.92 1.90 1.89 1.87 1.86 1.86 1.85 1.83 1.82 1.82 1.81 1.63 1.62 1.62 1.58 1.57 HDO 1.40 1.38 1.36
TsO
Br
O
O
O
O–N
OEt
3.74
1H NMR, CDCl3
400 MHz
2.0 2.1 1.0 2.3 0.8 1.0 0.9 1.0 1.0 3.1 1.1 1.5 1.5 0.9 3.5
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 -0.5
f1 (ppm)

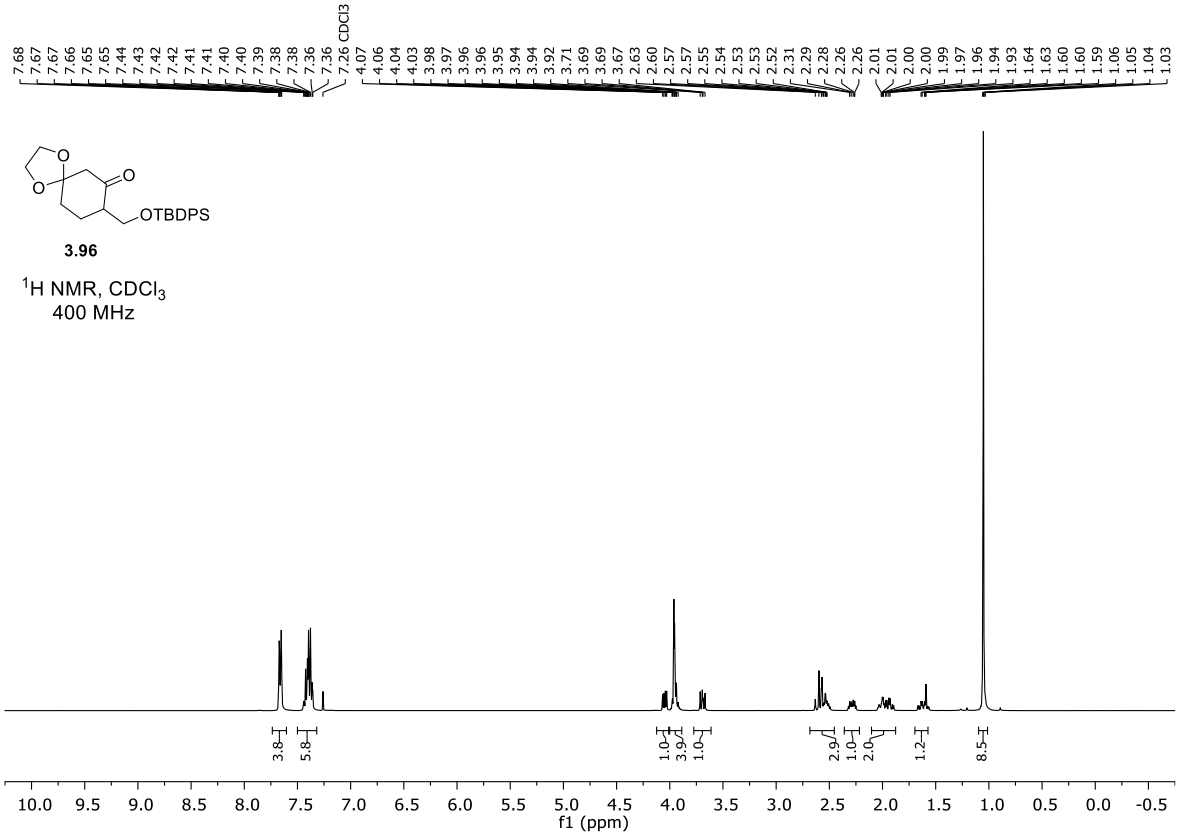

158.82 153.93 145.29 132.67 130.15 128.04 109.62 77.48 CDCl3 77.16 CDCl3 76.84 CDCl3 70.58 65.47 62.74 50.56 34.33 29.52 22.59 21.82 14.19
TsO
Br
O
O
O
O–N
OEt
3.74
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

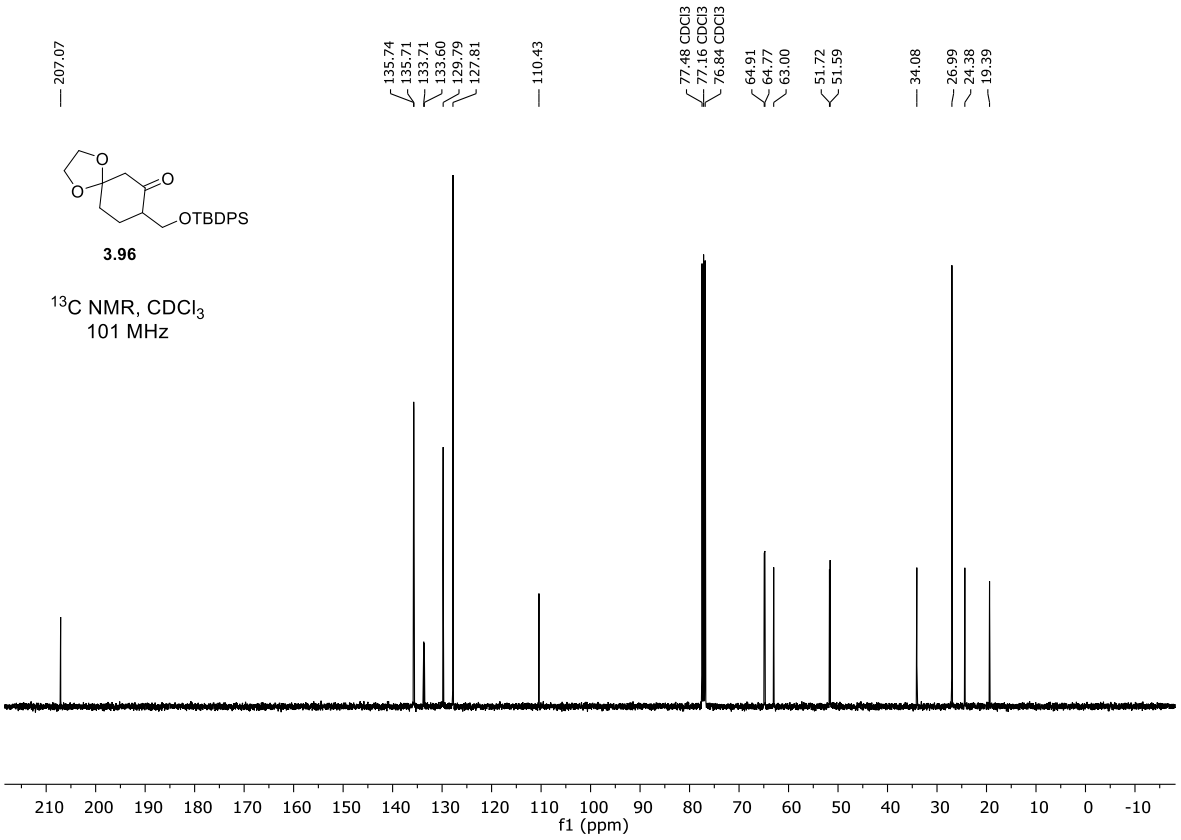

7.26 CDCl3
4.55 4.53 4.52 4.50 4.03 4.02 4.02 4.01 4.01 4.01 3.99 3.98 3.97 3.96 3.96 3.95 3.94 3.84 3.82 3.81 3.79 3.20 3.19 3.18 3.17 3.17 3.16 3.15 2.90 2.89 2.86 2.85 2.40 2.40 2.37 2.37 2.09 2.09 2.08 2.07 2.06 2.05 2.05 2.04 1.87 1.86 1.85 1.85 1.84 1.84 1.83 1.81 1.80 1.78 1.77 1.75 1.74 1.66 1.65 1.63 1.63 1.62 1.62 1.60 1.60 1.59 1.59
O
O
N
O
3.92
1H NMR, CDCl3
400 MHz
1.0 4.1 1.0 1.0 1.0 1.0 1.0 2.1 1.2
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 -0.5
f1 (ppm)

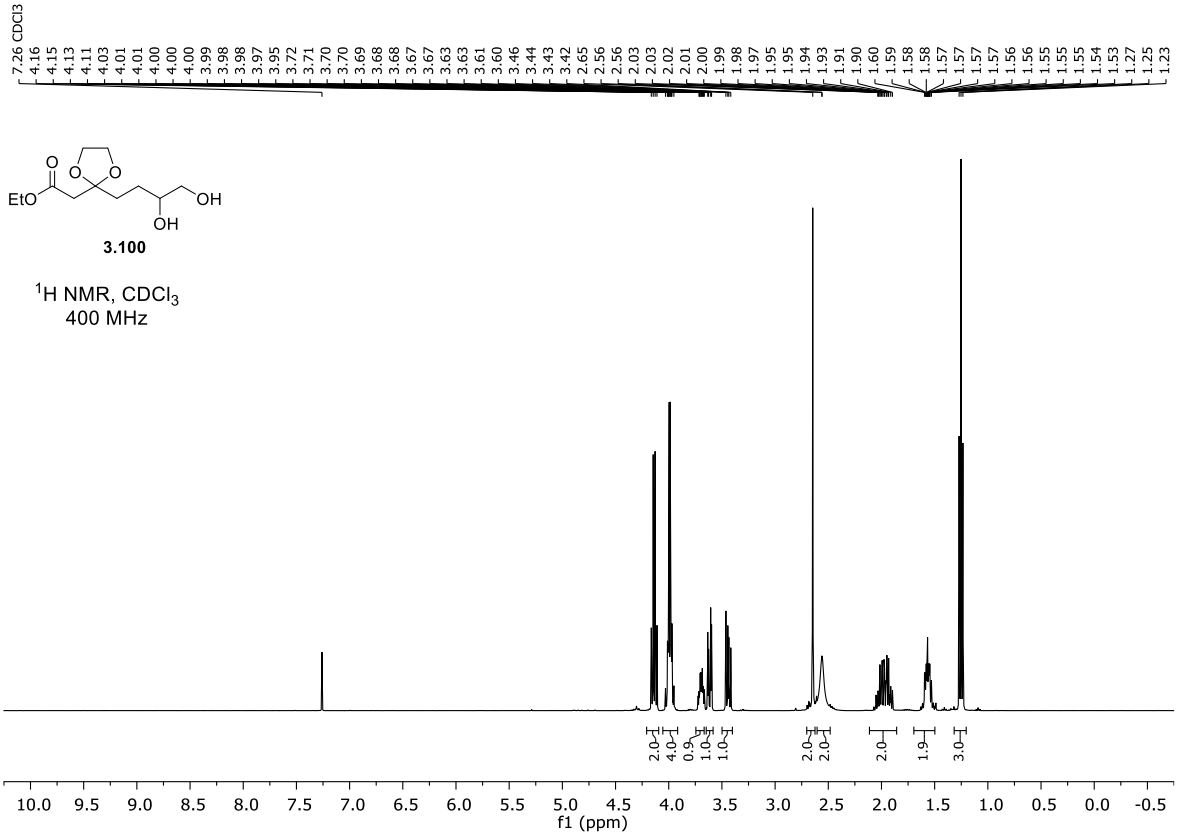

158.38
108.73
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
73.65
65.08
64.77
47.41
35.07
34.07
27.50
O
O
N
O
3.92
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

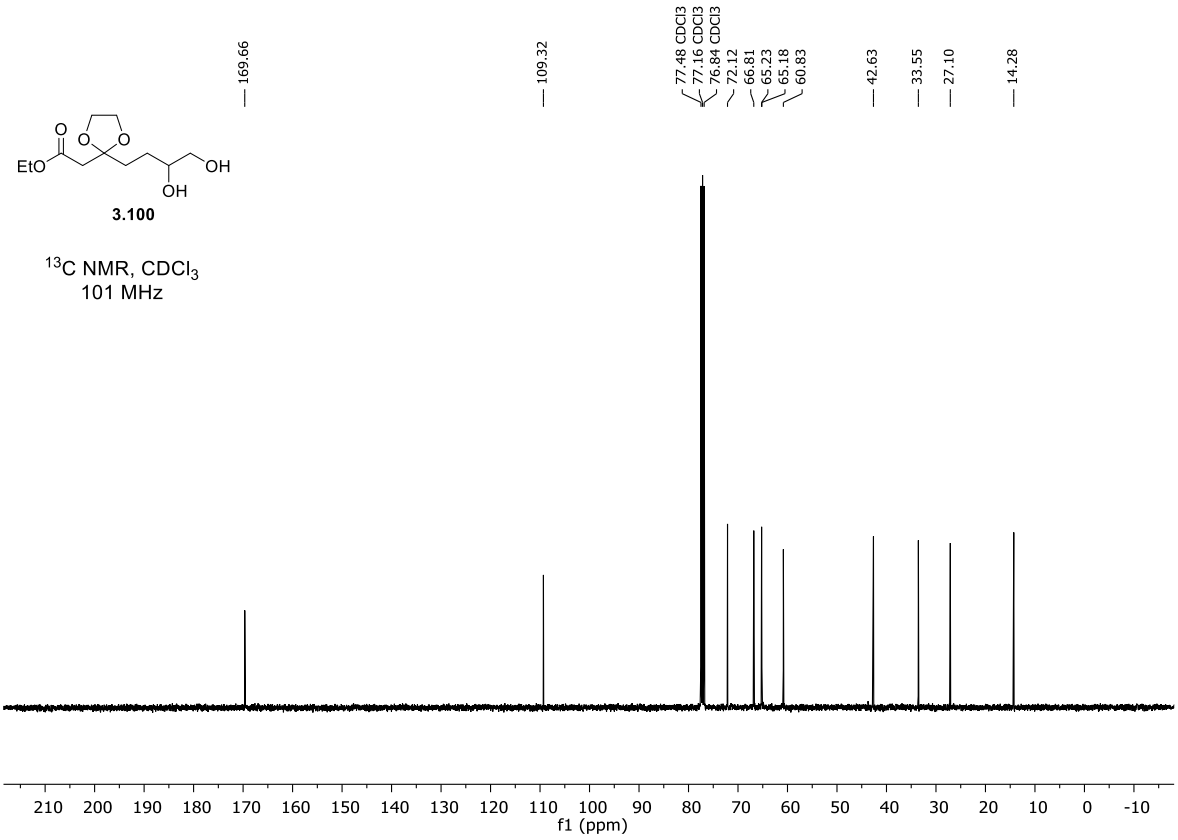

7.26 CDCl3
3.98 3.98 3.97 3.97 3.96 3.96 3.95 3.95 3.94 3.93 3.93 3.91 3.80 3.78 3.77 3.75 3.66 3.63 2.68 2.68 2.64 2.64 2.60 2.60 2.60 2.60 2.58 2.58 2.57 2.57 2.56 2.56 2.50 2.49 2.49 2.48 2.48 2.47 2.47 2.46 1.99 1.98 1.98 1.98 1.97 1.97 1.96 1.96 1.95 1.93 1.92 1.92 1.91 1.90 1.89 1.89 1.88 1.88 1.87 1.64 1.63 1.62 1.61 1.59 1.58 1.58
O
O
O
OH
3.88
1H NMR, CDCl3
400 MHz
3.9
1.0
1.0
1.0
1.8
1.0
1.9
1.1
1.1
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 -0.5
f1 (ppm)

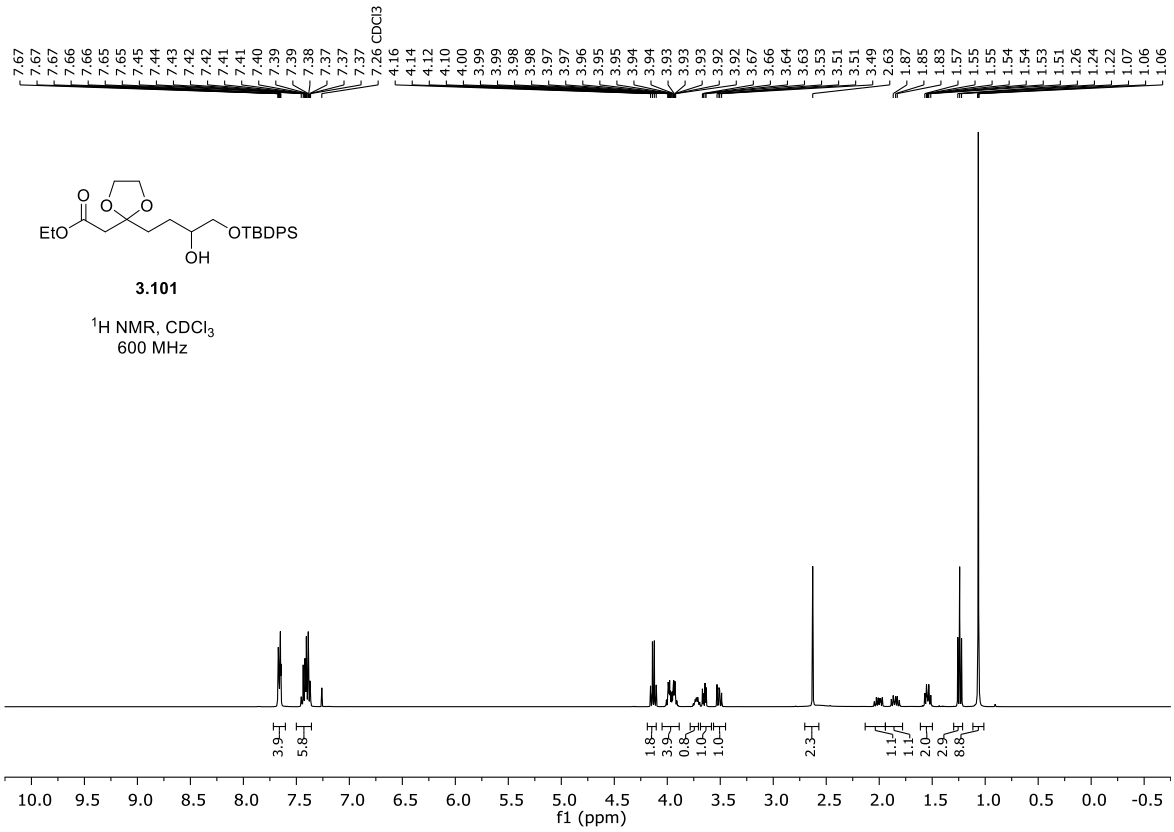

209.79
110.28
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
65.00
64.82
62.34
51.88
51.18
34.19
23.47
O
O
O
OH
3.88
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

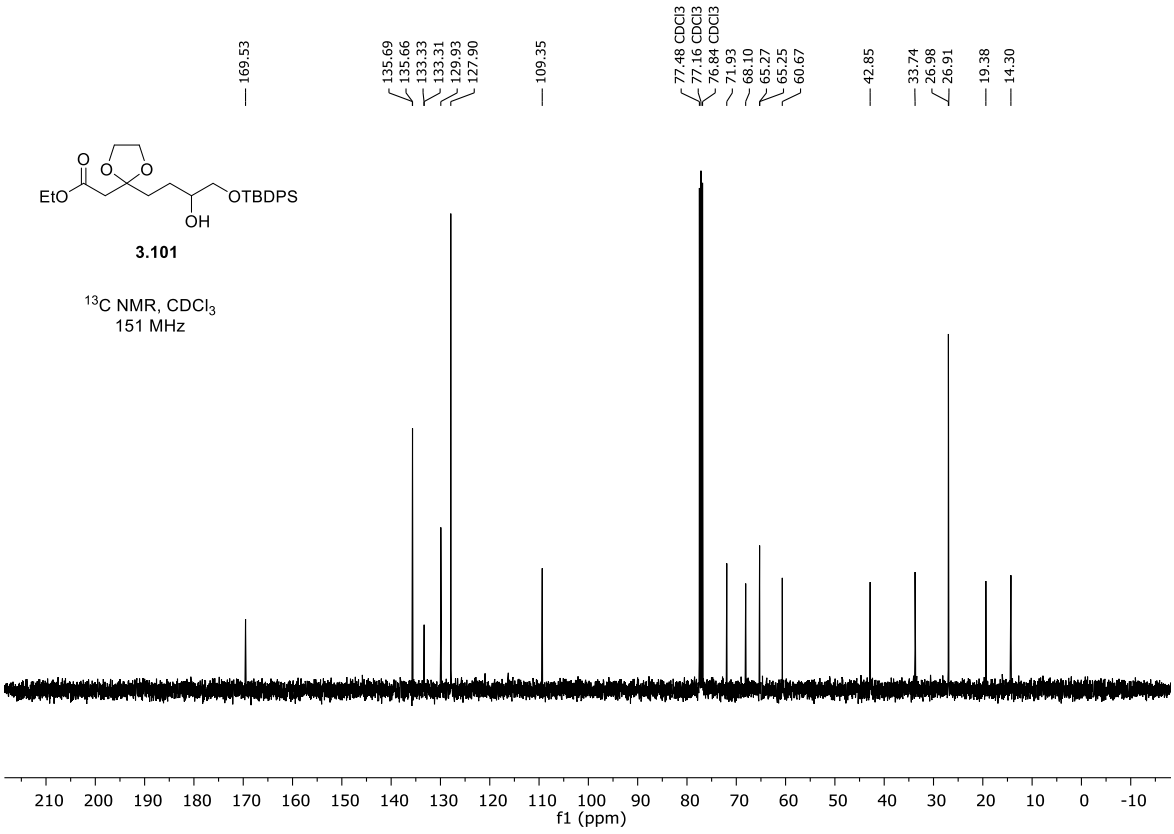

7.68 7.67 7.67 7.66 7.65 7.65 7.44 7.43 7.42 7.42 7.41 7.41 7.40 7.40 7.39 7.38 7.38 7.36 7.36 7.26 CDCl3
4.07 4.06 4.04 4.03 3.98 3.97 3.96 3.96 3.95 3.94 3.94 3.92 3.71 3.69 3.69 3.67 2.63 2.60 2.57 2.57 2.55 2.54 2.53 2.53 2.52 2.31 2.29 2.28 2.26 2.26 2.01 2.01 2.00 2.00 1.99 1.97 1.96 1.94 1.93 1.64 1.63 1.60 1.60 1.59 1.06 1.05 1.04 1.03
O
O
O
OTBDPS
3.96
1H NMR, CDCl3
400 MHz
3.8 5.8 1.0 3.9 1.0 2.9 1.0 2.0 1.2 8.5
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 -0.5
f1 (ppm)

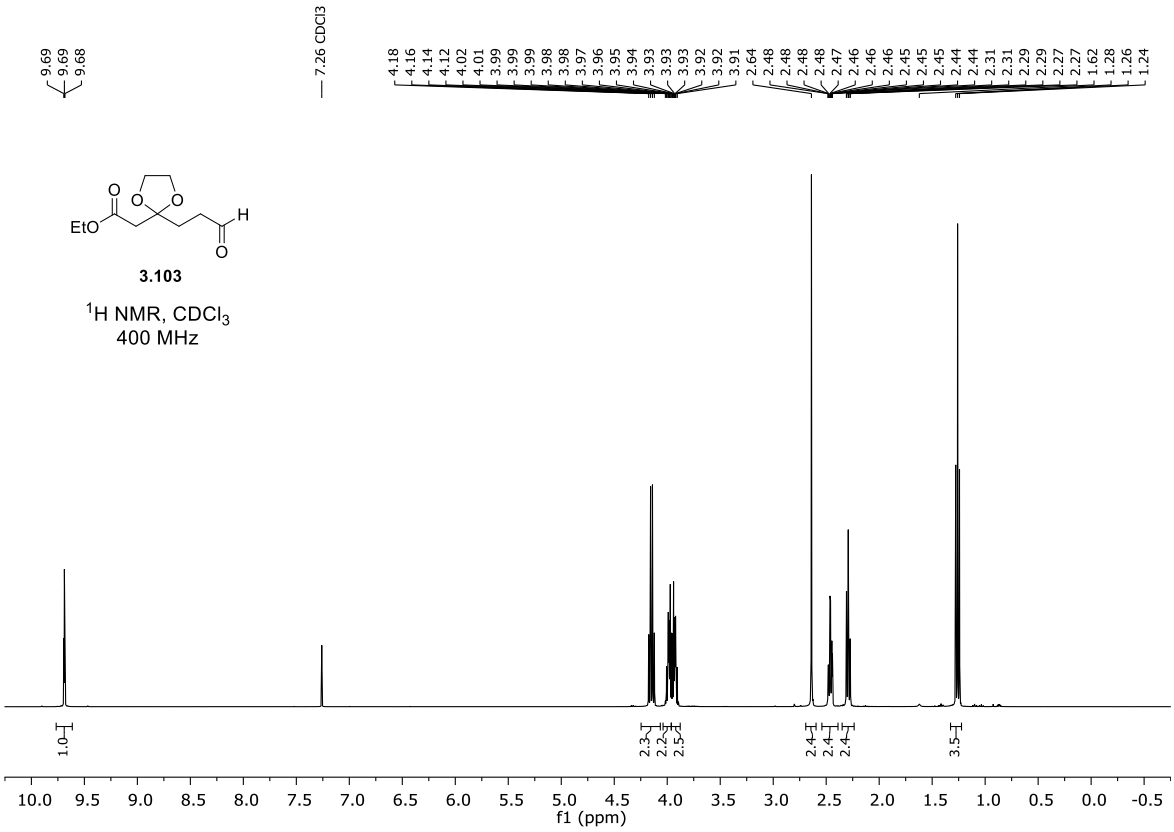

207.07
135.74 135.71 133.71 133.60 129.79 127.81
110.43
77.48 CDCl3 77.16 CDCl3 76.84 CDCl3
64.91 64.77 63.00
51.72 51.59
34.08
26.99 24.38 19.39
O
O
O
OTBDPS
3.96
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

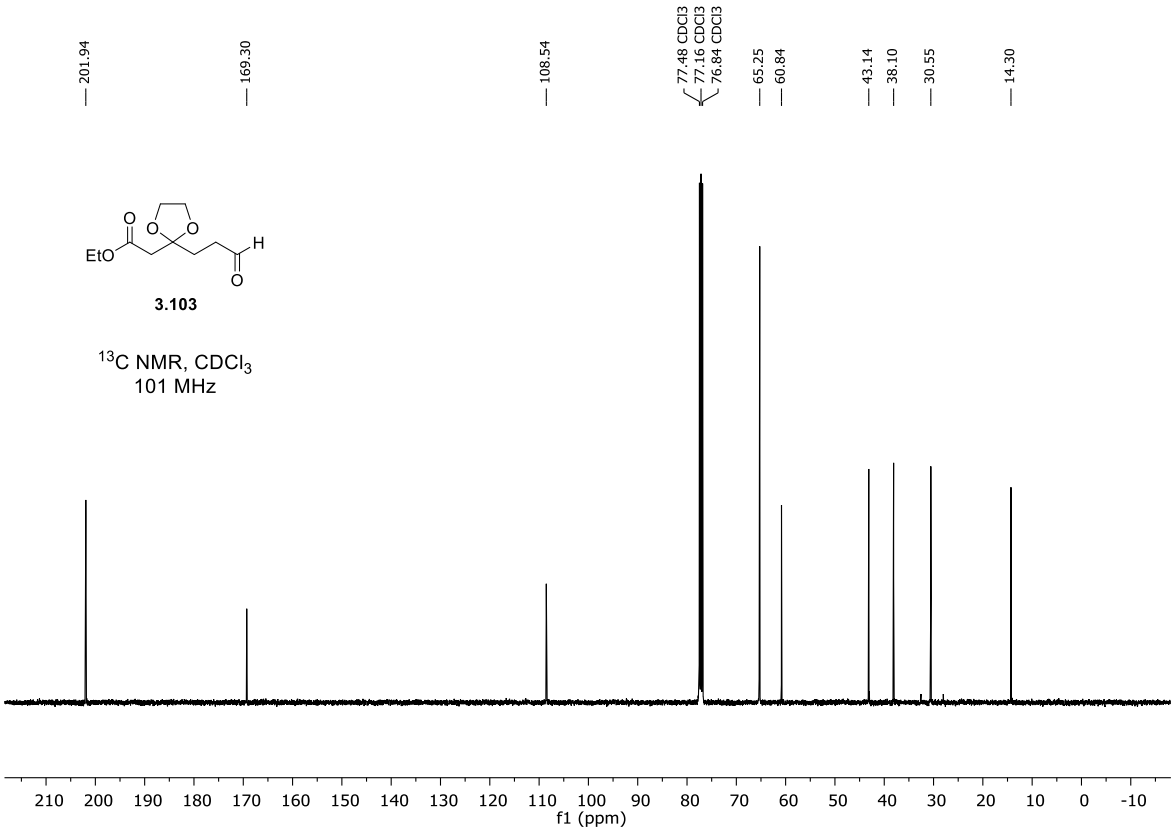

7.26 CDCl3
4.16 4.15 4.13 4.11 4.03 4.01 4.01 4.00 4.00 4.00 3.99 3.98 3.98 3.97 3.95 3.72 3.71 3.70 3.70 3.69 3.68 3.68 3.67 3.67 3.63 3.63 3.61 3.60 3.46 3.44 3.43 3.42 2.65 2.56 2.56 2.03 2.03 2.02 2.01 2.00 1.99 1.98 1.97 1.95 1.95 1.94 1.93 1.91 1.90 1.60 1.59 1.58 1.58 1.57 1.57 1.57 1.57 1.56 1.56 1.55 1.55 1.55 1.54 1.53 1.27 1.25 1.23
EtO
O
O
O
OH
OH
3.100
1H NMR, CDCl3
400 MHz
2.0 4.0 0.9 1.0 1.0 2.0 2.0 2.0 1.9 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 -0.5
f1 (ppm)

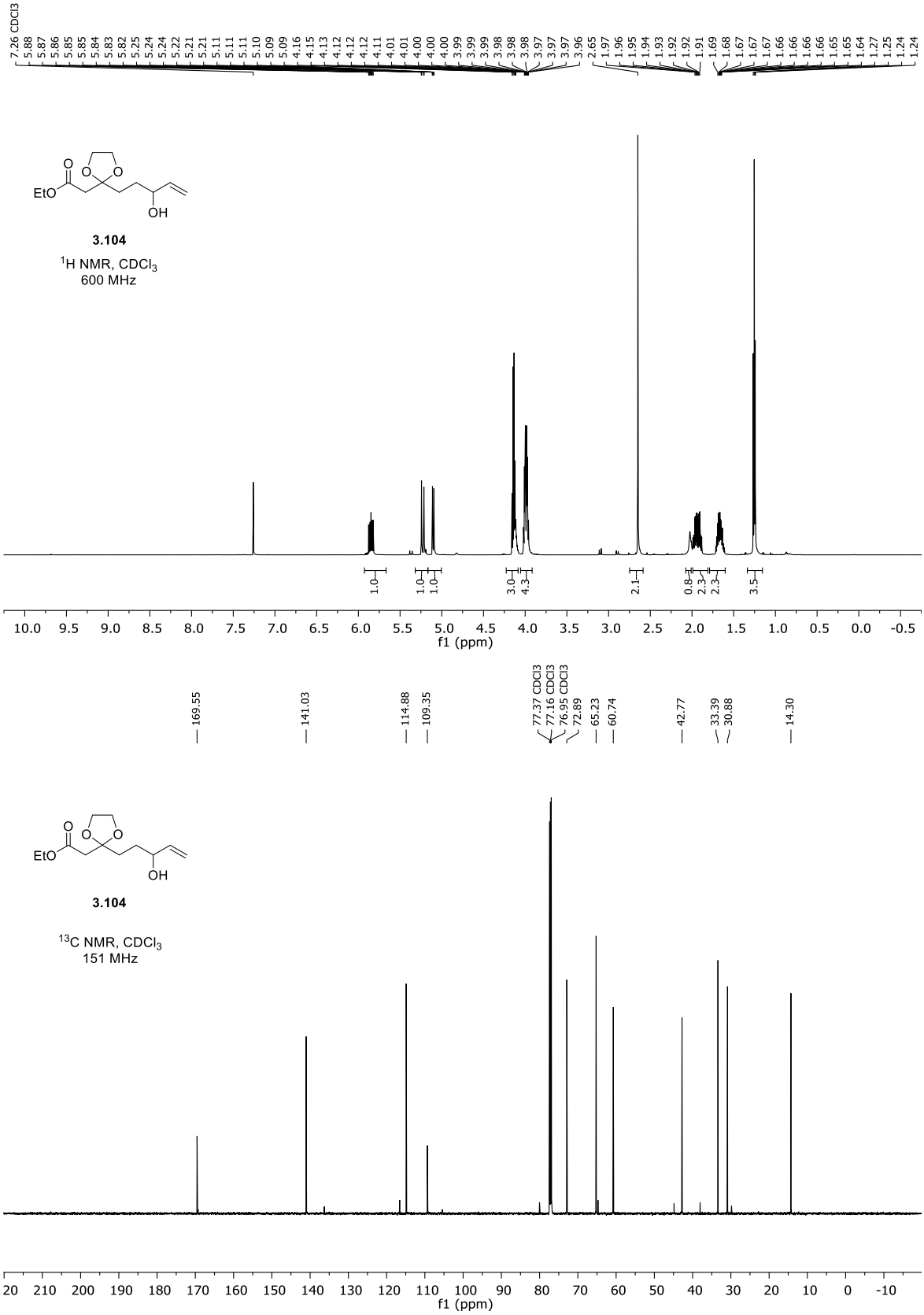

169.66
109.32
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
72.12
66.81
65.23
65.18
60.83
42.63
33.55
27.10
14.28
EtO
O
O
O
OH
OH
3.100
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

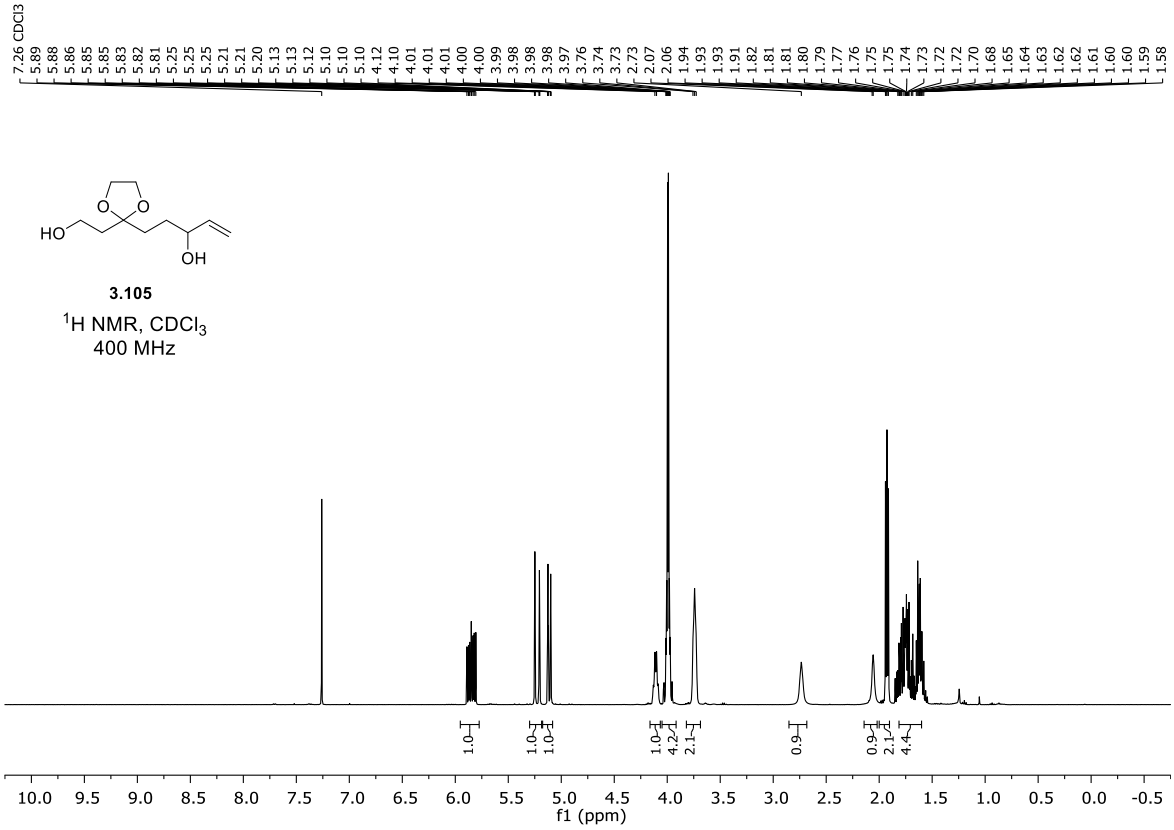

7.67 7.67 7.67 7.66 7.66 7.65 7.65 7.45 7.44 7.43 7.42 7.42 7.41 7.41 7.40 7.39 7.39 7.38 7.37 7.37 7.37 7.26 CDCl3
4.16 4.14 4.12 4.10 4.00 3.99 3.99 3.98 3.98 3.97 3.97 3.96 3.95 3.95 3.94 3.94 3.93 3.93 3.93 3.92 3.92 3.67 3.66 3.64 3.63 3.53 3.51 3.51 3.49 2.63 1.87 1.85 1.83 1.57 1.55 1.55 1.54 1.54 1.53 1.51 1.26 1.24 1.22 1.07 1.06 1.06
O
O
O
EtO
OTBDPS
OH
3.101
1H NMR, CDCl3
600 MHz
3.9 5.8 1.8 3.9 0.8 1.0 1.0 2.3 1.1 1.1 2.0 2.9 8.8 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 -0.5
f1 (ppm)


169.53
135.69 135.66 133.33 133.31 129.93 127.90
109.35
77.48 CDCl3 77.16 CDCl3 76.84 CDCl3 71.93 68.10 65.27 65.25 60.67
42.85
33.74 26.98 26.91
19.38
14.30
O
O
O
EtO
OTBDPS
OH
3.101
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 -10
f1 (ppm)


9.69
9.69
9.68
7.26 CDCl3
4.18
4.16
4.14
4.12
4.02
4.01
3.99
3.99
3.99
3.98
3.98
3.97
3.96
3.95
3.94
3.93
3.93
3.93
3.92
3.92
3.91
2.64
2.48
2.48
2.48
2.48
2.47
2.46
2.46
2.46
2.45
2.45
2.45
2.44
2.44
2.31
2.31
2.29
2.29
2.27
2.27
1.62
1.28
1.26
1.24
EtO
H
3.103
1H NMR, CDCl3
400 MHz
1.0
2.3
2.2
2.5
2.4
2.4
2.4
3.5
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 -0.5
f1 (ppm)

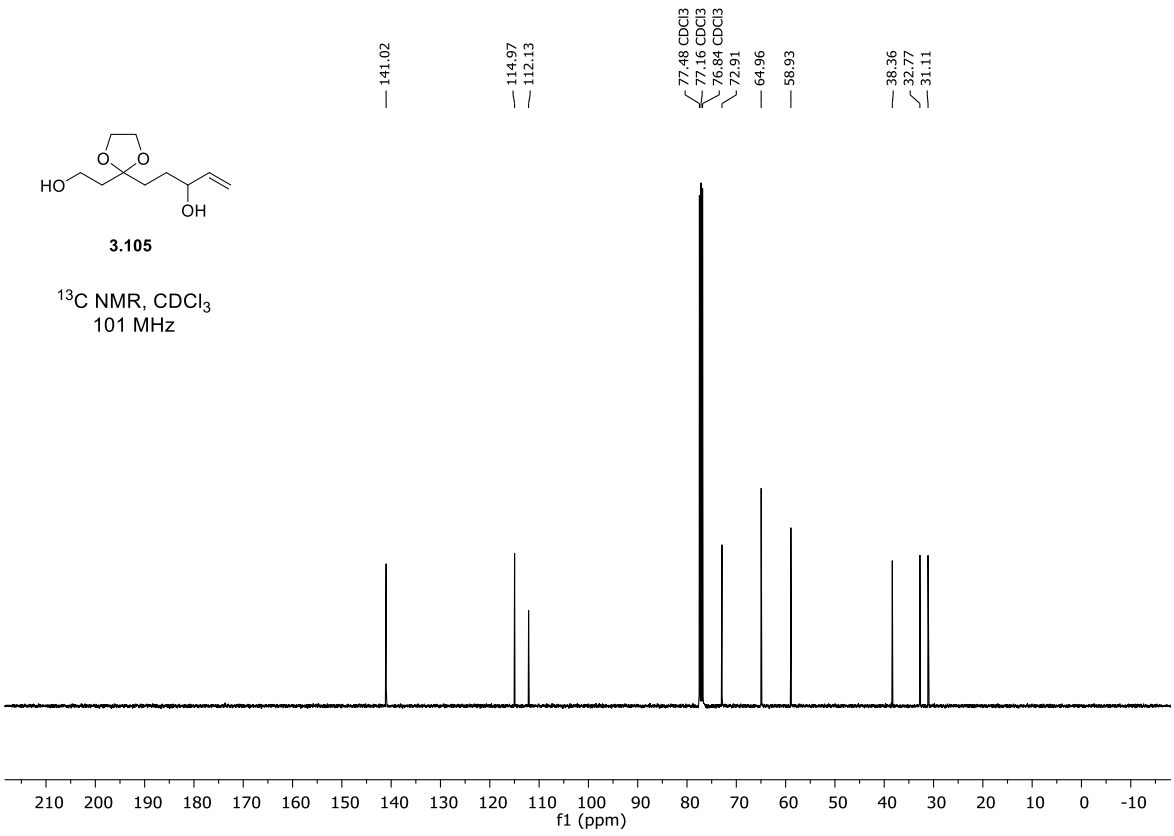

201.94
169.30
108.54
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
65.25
60.84
43.14
38.10
30.55
14.30
EtO
H
3.103
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.26 CDCl3
5.88 5.87 5.86 5.85 5.85 5.84 5.83 5.82 5.25 5.24 5.24 5.22 5.21 5.21 5.11 5.11 5.11 5.10 5.09 5.09 4.16 4.15 4.13 4.12 4.12 4.12 4.11 4.01 4.01 4.00 4.00 4.00 3.99 3.99 3.99 3.98 3.98 3.98 3.97 3.97 3.97 3.96 2.65 1.97 1.96 1.95 1.94 1.93 1.92 1.92 1.91 1.69 1.68 1.67 1.67 1.67 1.66 1.66 1.66 1.66 1.65 1.65 1.64 1.27 1.25 1.24 1.24
EtO
O
O
O
OH
3.104
1H NMR, CDCl3
600 MHz
1.0 1.0 1.0 3.0 4.3 2.1 0.8 2.3 2.3 3.5
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 -0.5
f1 (ppm)
169.55 141.03 114.88 109.35 77.37 CDCl3 77.16 CDCl3 76.95 CDCl3 72.89 65.23 60.74 42.77 33.39 30.88 14.30
EtO
O
O
O
OH
3.104
13C NMR, CDCl3
151 MHz
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



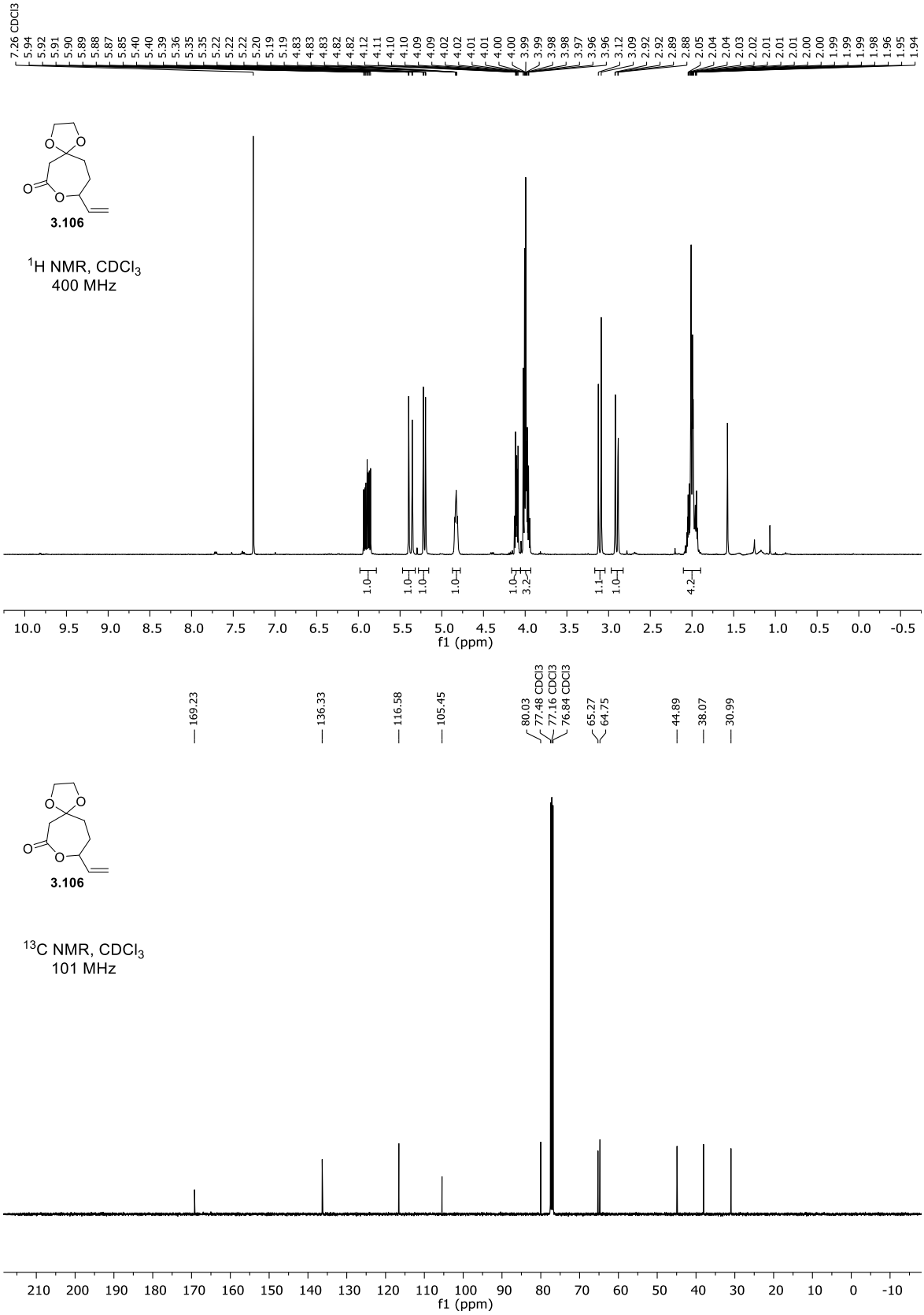
3.105

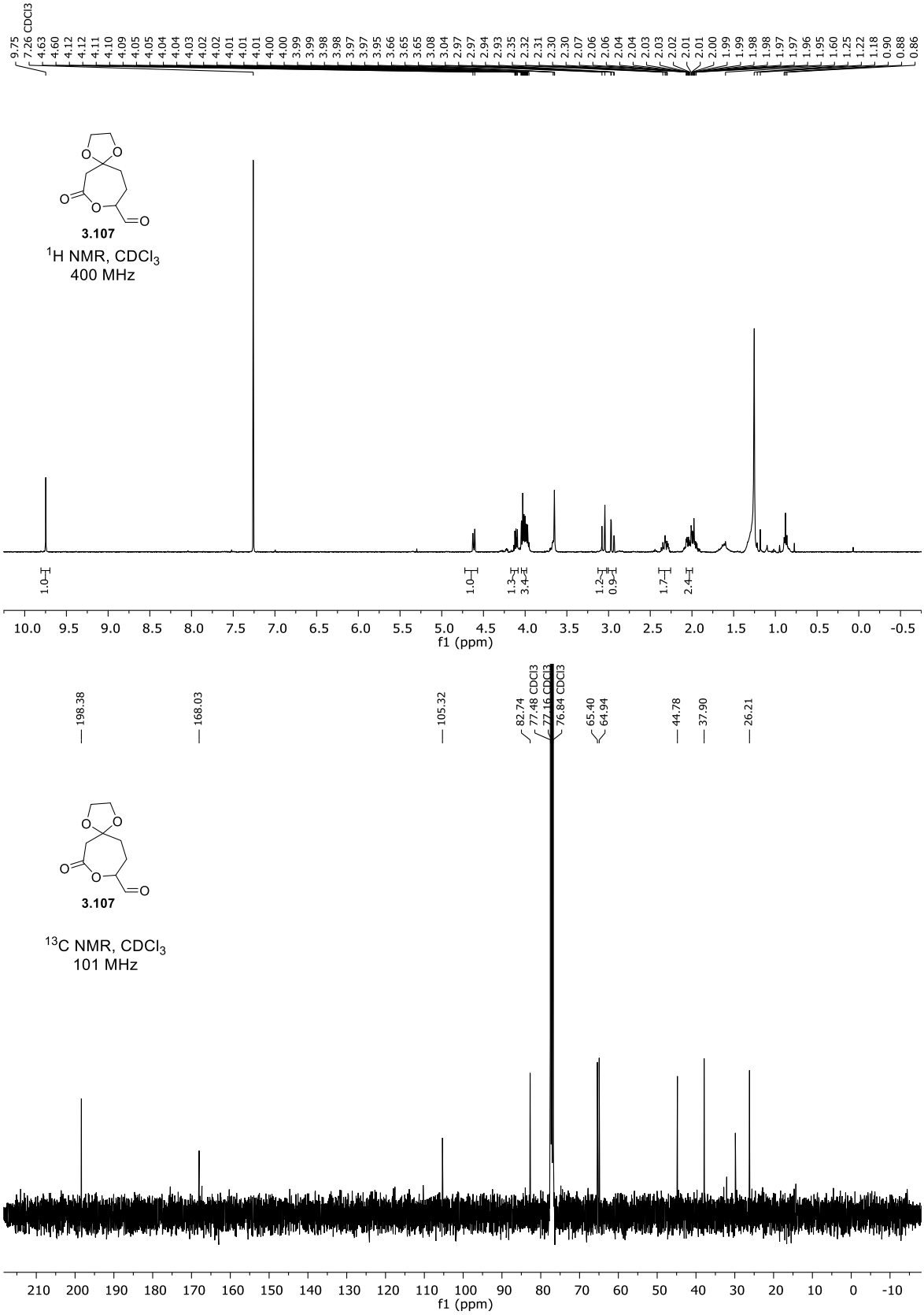
^{1}H NMR, $CDCl_3$
400 MHz

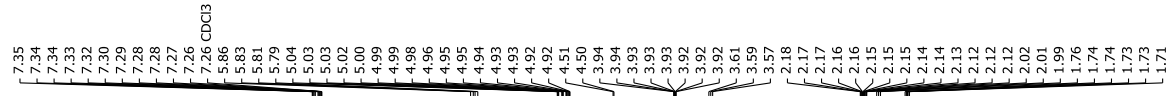


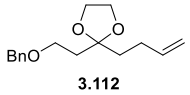
3.105

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


7.26 CDCl3
5.94 5.92 5.91 5.90 5.89 5.88 5.87 5.85 5.40 5.40 5.39 5.36 5.35 5.35 5.22 5.22 5.22 5.20 5.19 5.19 4.83 4.83 4.83 4.82 4.82 4.12 4.11 4.10 4.10 4.09 4.09 4.02 4.02 4.01 4.01 4.00 4.00 3.99 3.99 3.98 3.98 3.97 3.96 3.96 3.12 3.09 2.92 2.92 2.89 2.88 2.05 2.04 2.04 2.03 2.02 2.01 2.01 2.01 2.00 2.00 1.99 1.99 1.99 1.98 1.96 1.95 1.94
3.106
1H NMR, CDCl3
400 MHz
1.0 1.0 1.0 1.0 1.0 3.2 1.1 1.0 4.2
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 -0.5
f1 (ppm)
169.23 136.33 116.58 105.45 80.03 77.48 CDCl3 77.16 CDCl3 76.84 CDCl3 65.27 64.75 44.89 38.07 30.99
3.106
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)

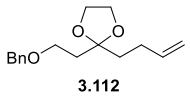

9.75
7.26 CDCl3
4.63
4.60
4.12
4.12
4.11
4.10
4.09
4.05
4.05
4.04
4.04
4.03
4.02
4.02
4.01
4.01
4.01
4.00
4.00
3.99
3.99
3.98
3.98
3.97
3.97
3.95
3.66
3.65
3.65
3.08
3.04
2.97
2.97
2.94
2.93
2.35
2.32
2.31
2.30
2.30
2.07
2.06
2.06
2.04
2.04
2.03
2.03
2.02
2.01
2.01
2.00
1.99
1.99
1.98
1.98
1.97
1.97
1.96
1.95
1.60
1.25
1.22
1.18
0.90
0.88
0.86
3.107
1H NMR, CDCl3
400 MHz
1.0
1.0
1.3
3.4
1.2
0.9
1.7
2.4
f1 (ppm)
198.38
168.03
105.32
82.74
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
65.40
64.94
44.78
37.90
26.21
3.107
13C NMR, CDCl3
101 MHz
f1 (ppm)





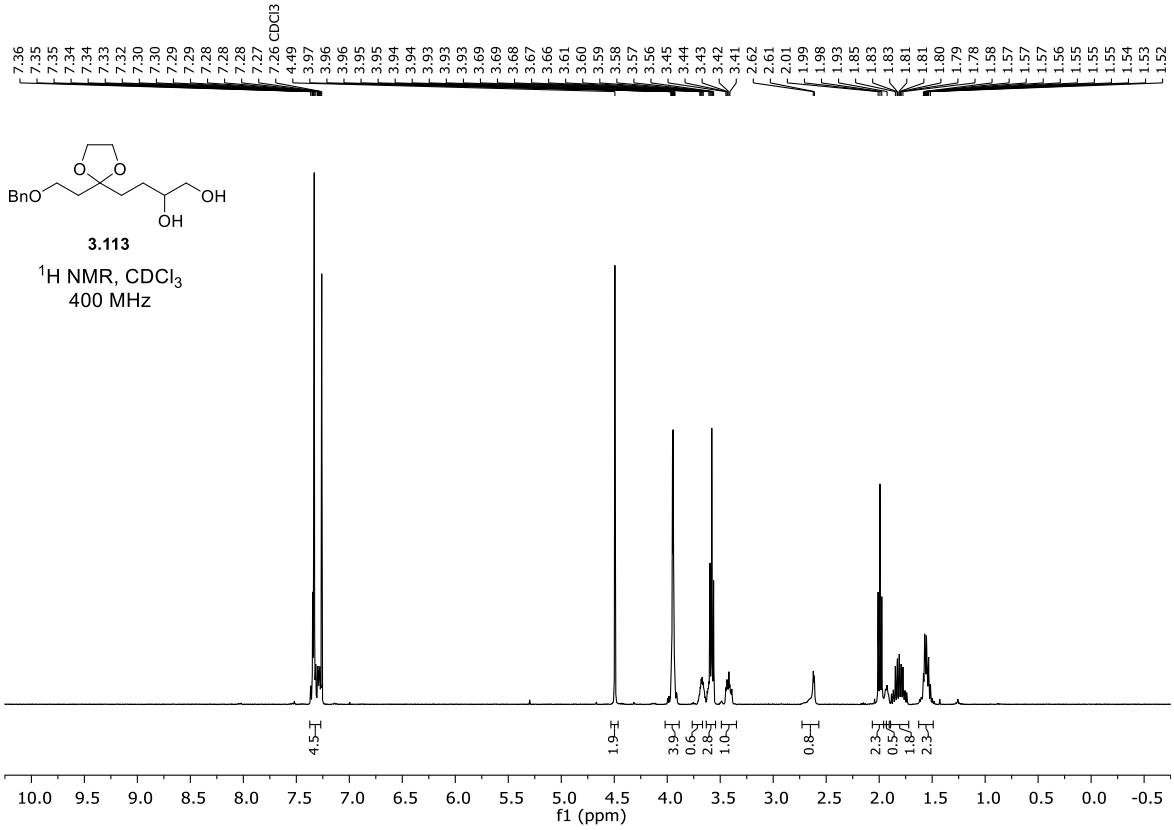
3.112

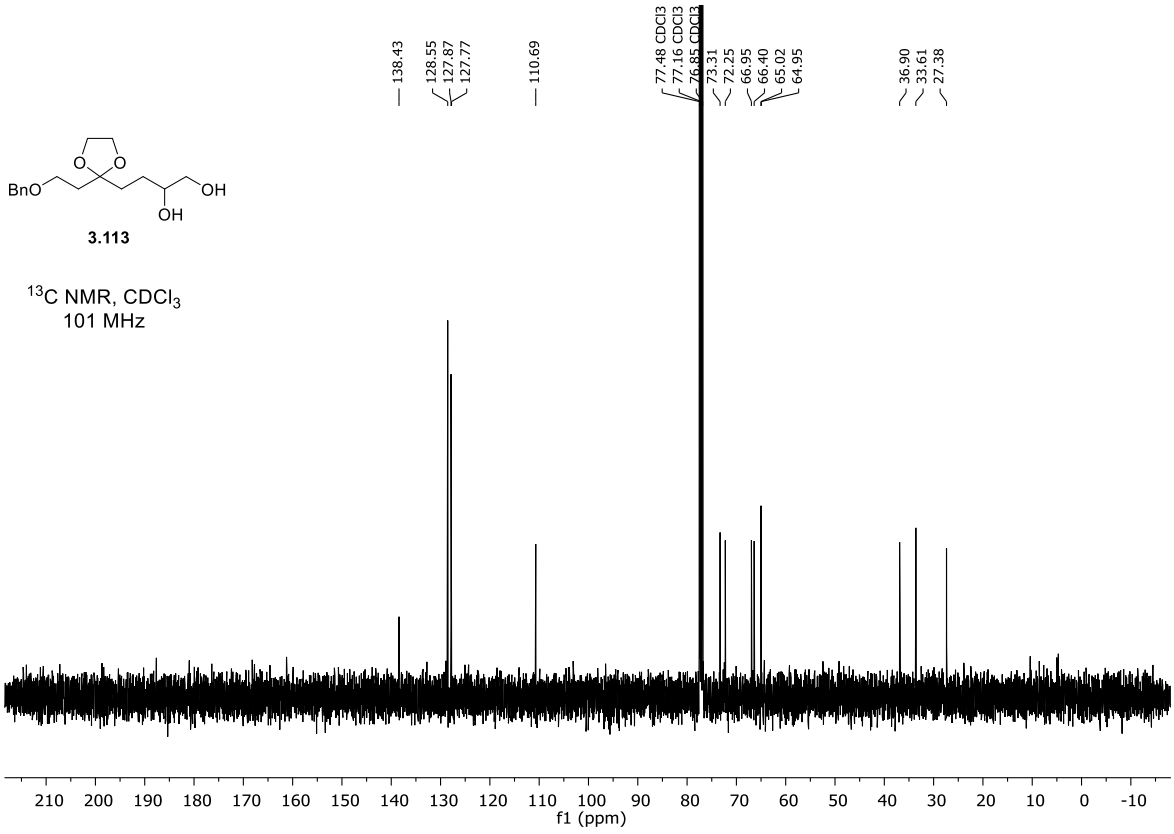
^{1}H NMR, $CDCl_3$
400 MHz

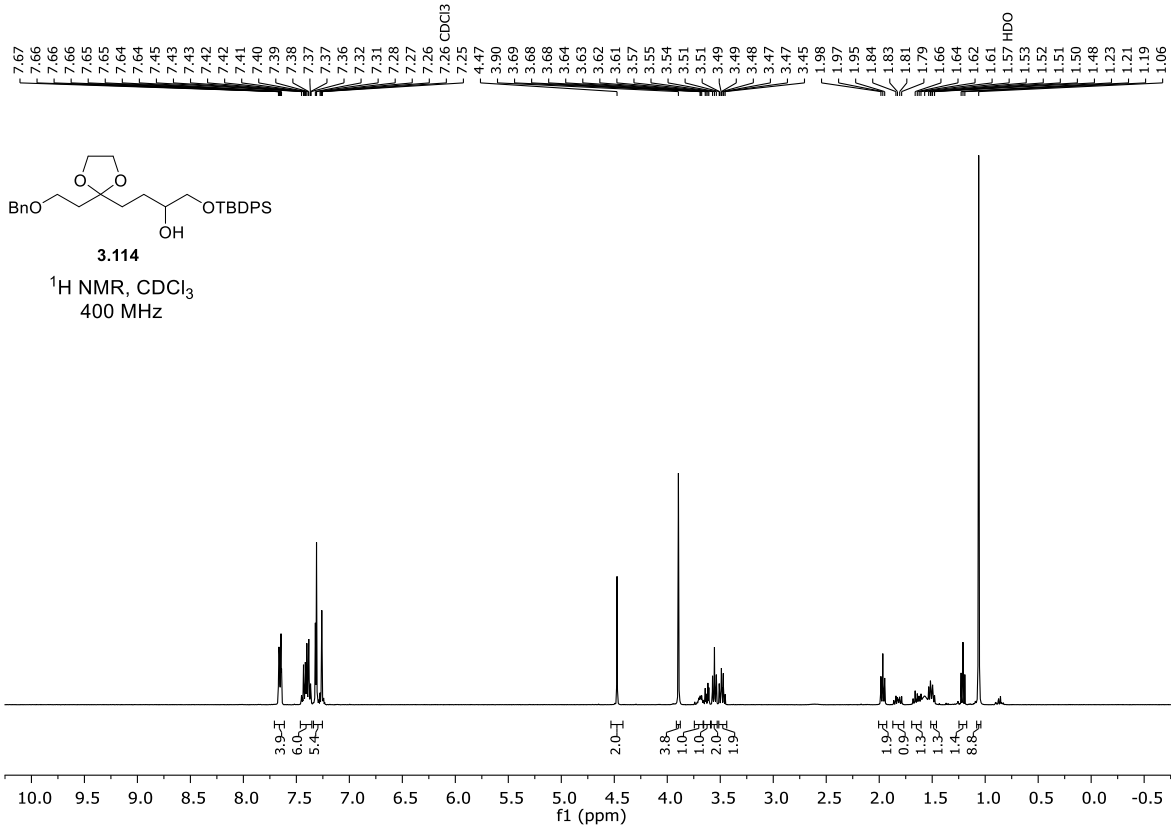


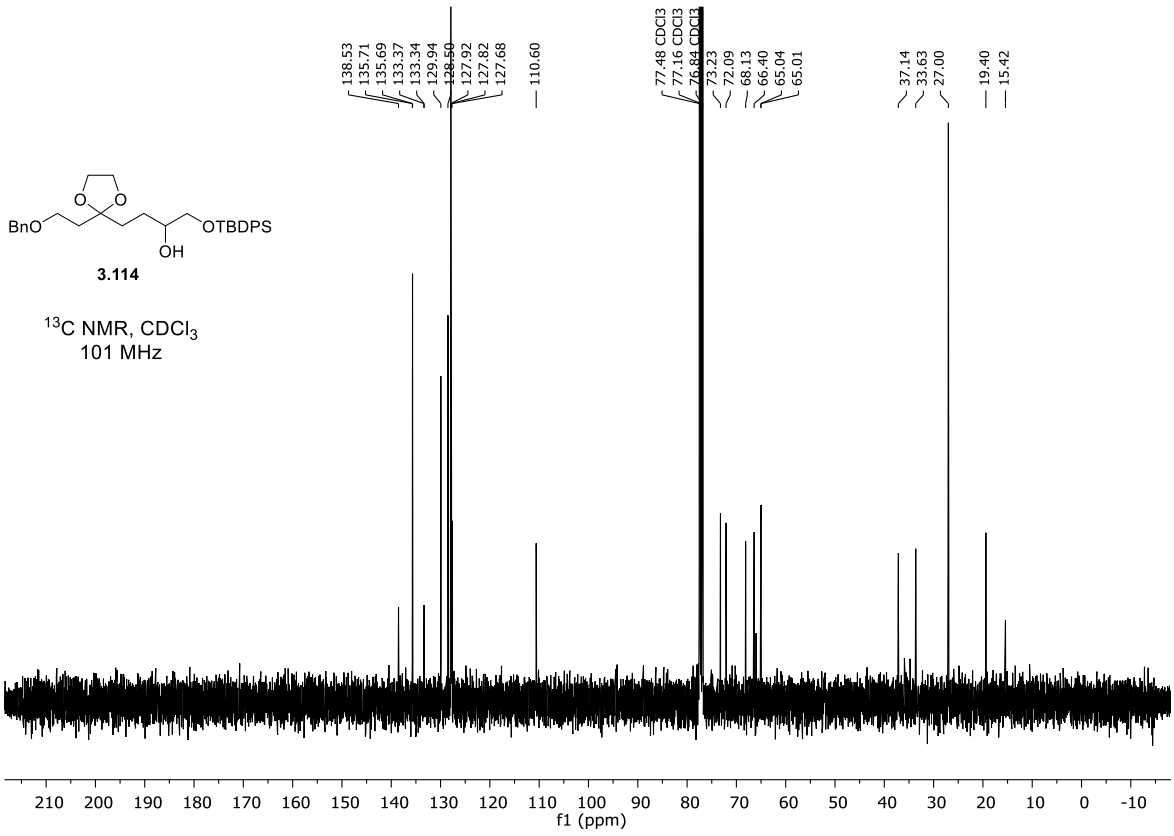
3.112

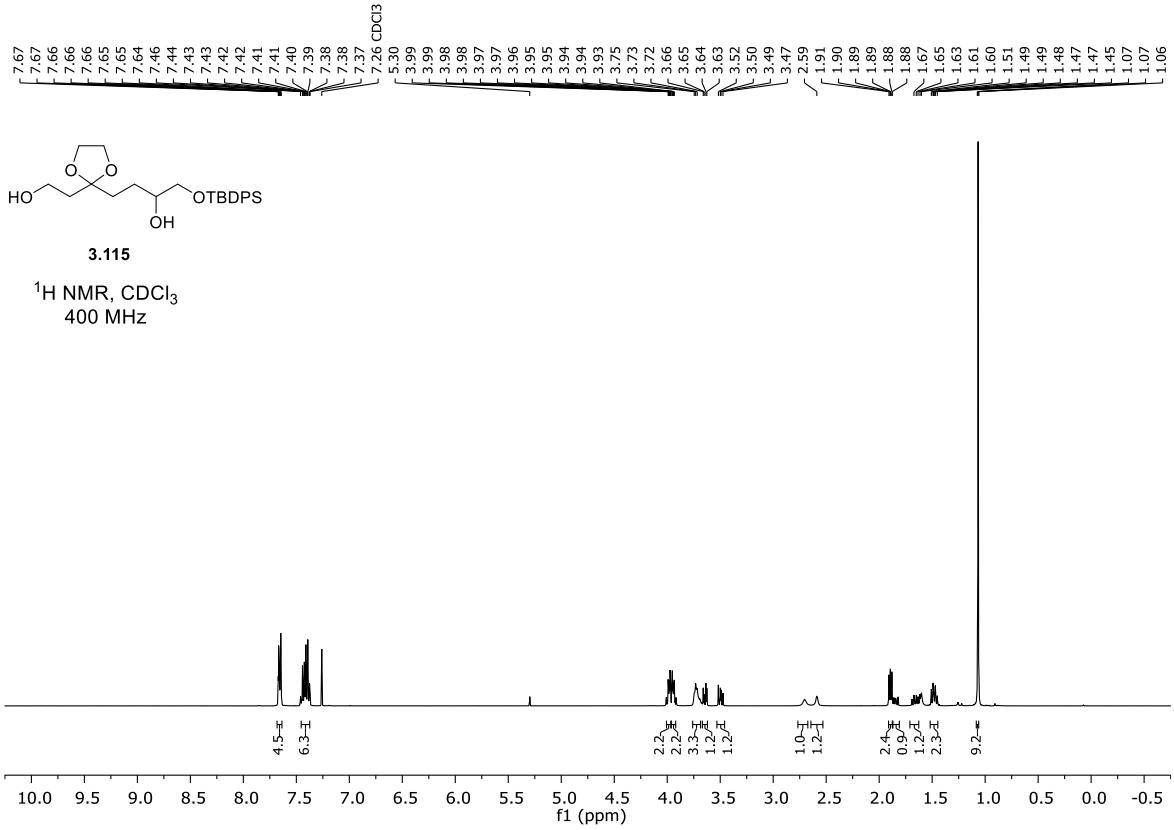
^{13}C NMR, $CDCl_3$
101 MHz

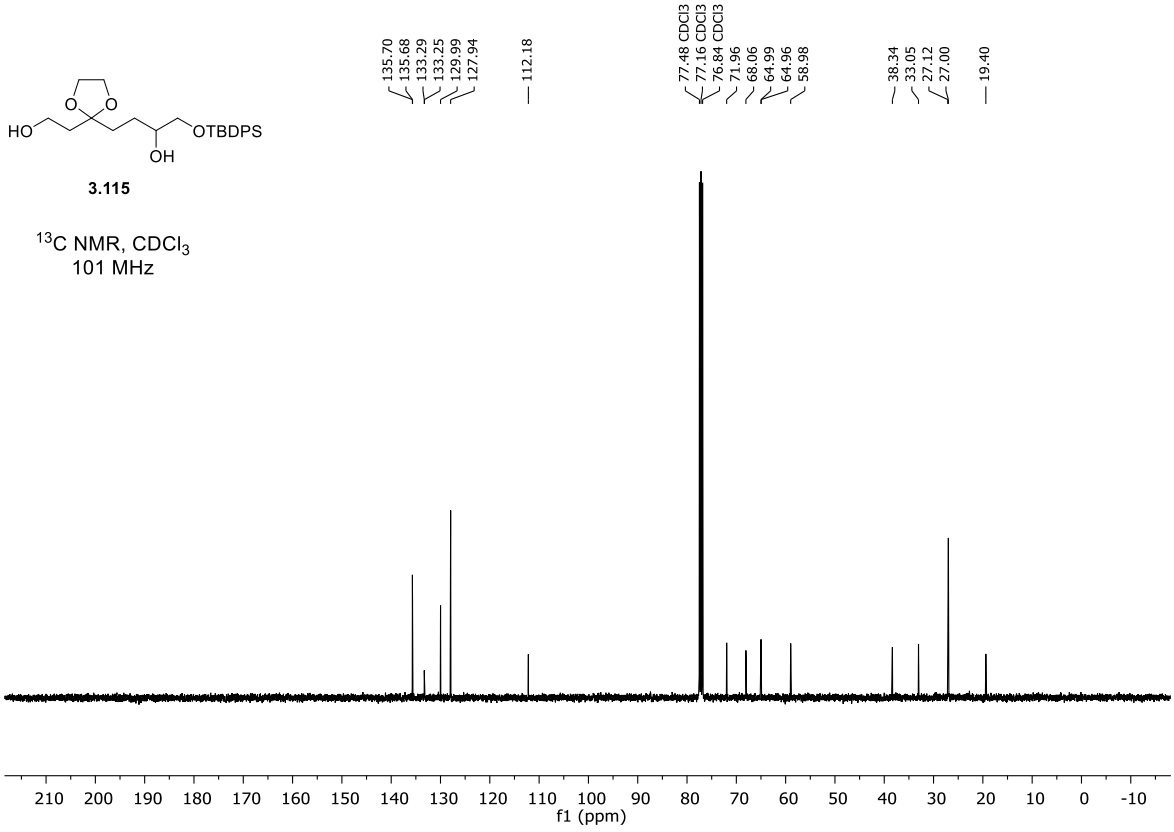

7.36 7.35 7.35 7.34 7.34 7.33 7.32 7.30 7.30 7.29 7.29 7.28 7.28 7.28 7.27 7.26 CDCl3 4.49 3.97 3.96 3.96 3.95 3.95 3.94 3.94 3.93 3.93 3.69 3.69 3.68 3.67 3.66 3.61 3.60 3.59 3.58 3.57 3.56 3.45 3.44 3.43 3.42 3.41 2.62 2.61 2.01 1.99 1.98 1.93 1.85 1.83 1.83 1.81 1.81 1.80 1.79 1.78 1.58 1.57 1.57 1.57 1.56 1.55 1.55 1.55 1.54 1.53 1.52
BnO
OH
OH
3.113
1H NMR, CDCl3
400 MHz
4.5
1.9
3.9
0.6
2.8
1.0
0.8
2.3
0.5
1.8
2.3
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 -0.5
f1 (ppm)

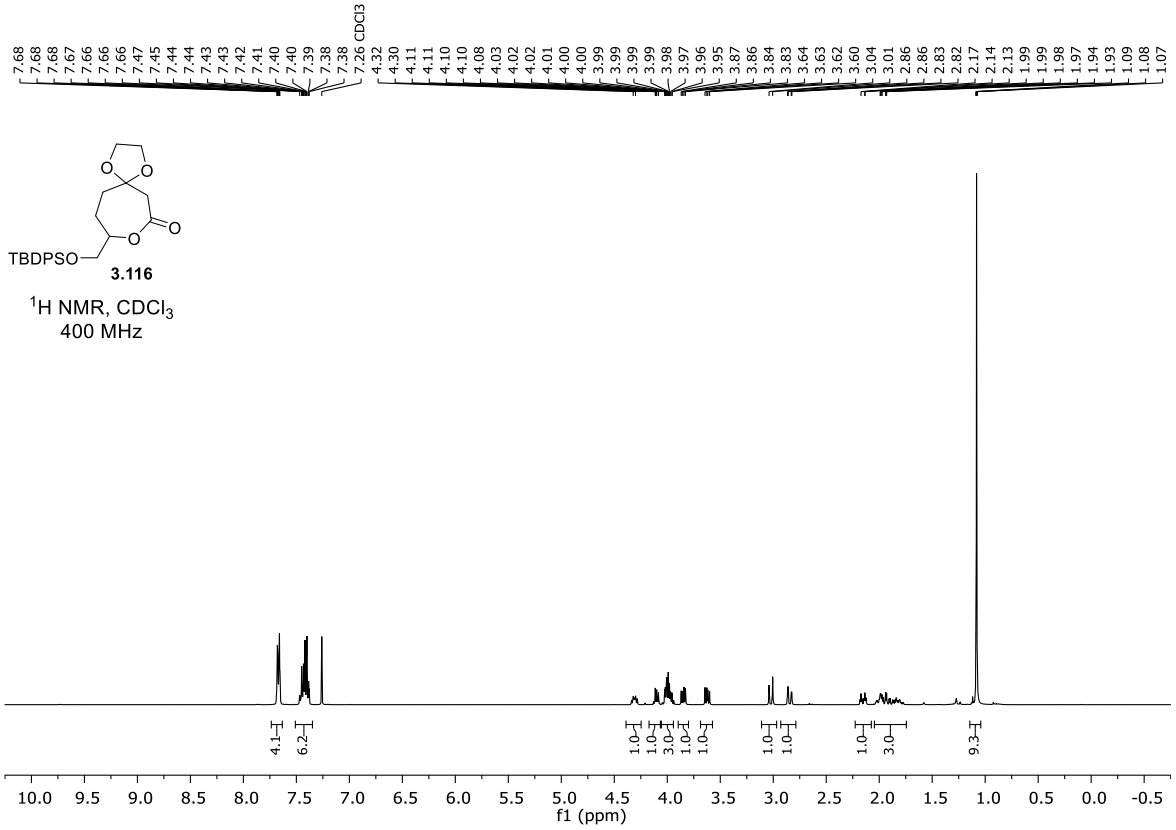

138.43
128.55
127.87
127.77
110.69
77.48 CDCl3
77.16 CDCl3
76.85 CDCl3
73.31
72.25
66.95
66.40
65.02
64.95
36.90
33.61
27.38
BnO
OH
OH
3.113
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

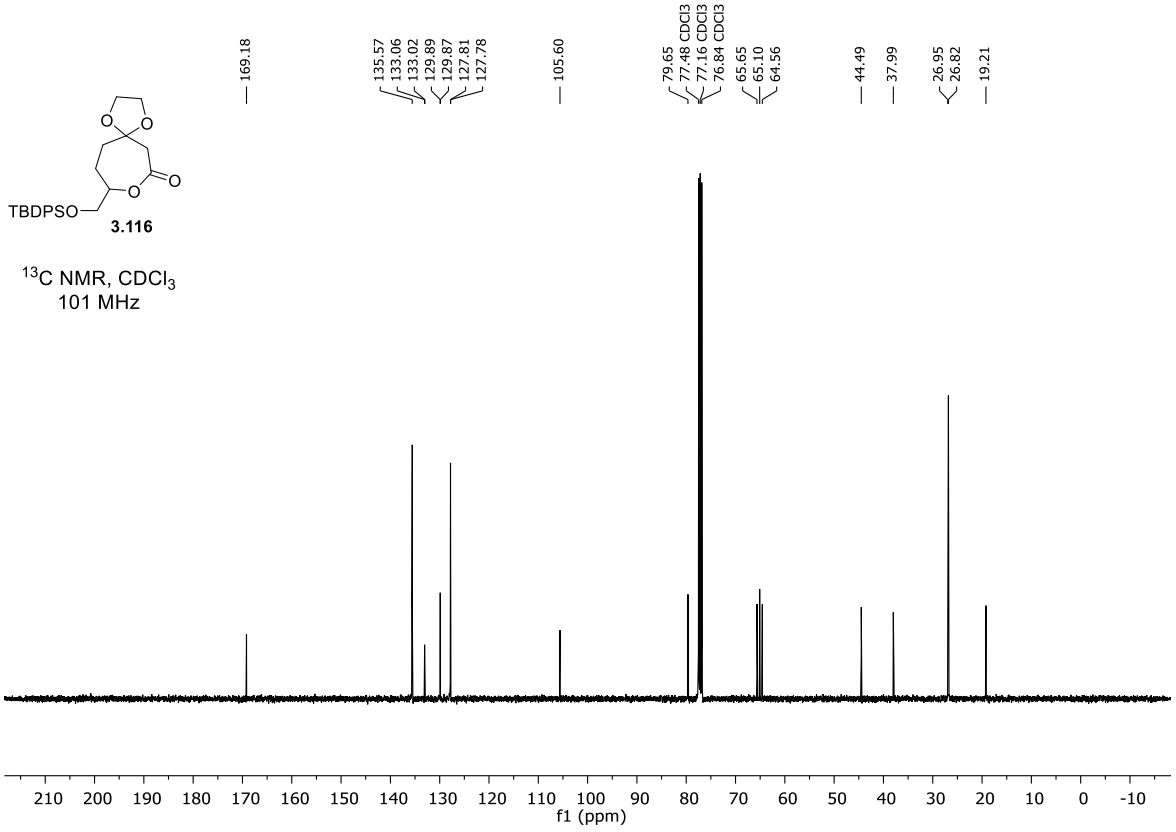

7.67 7.66 7.66 7.66 7.65 7.65 7.64 7.64 7.45 7.43 7.43 7.42 7.42 7.41 7.40 7.39 7.38 7.37 7.37 7.36 7.32 7.31 7.28 7.27 7.26 7.26 CDCl3 7.25
4.47 3.90 3.69 3.68 3.68 3.64 3.63 3.62 3.61 3.57 3.55 3.54 3.51 3.51 3.49 3.49 3.48 3.47 3.47 3.45
1.98 1.97 1.95 1.84 1.83 1.81 1.79 1.66 1.64 1.62 1.61 1.57 HDO 1.53 1.52 1.51 1.50 1.48 1.23 1.21 1.19 1.06
BnO
OTBDPS
OH
3.114
1H NMR, CDCl3
400 MHz
3.9 6.0 5.4 2.0 3.8 1.0 1.0 2.0 1.9 1.9 0.9 1.3 1.3 1.4 8.8
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 -0.5
f1 (ppm)

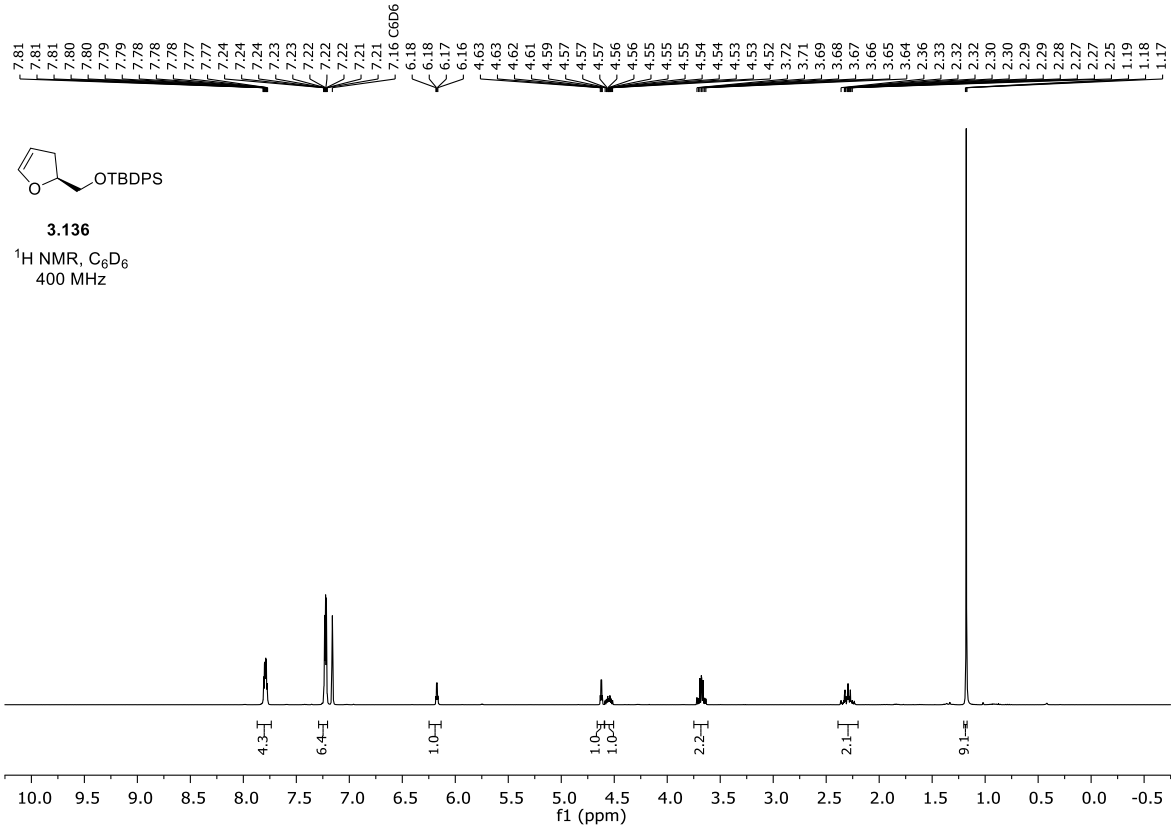

138.53 135.71 135.69 133.37 133.34 129.94 128.50 127.92 127.82 127.68 110.60
77.48 CDCl3 77.16 CDCl3 76.84 CDCl3 73.23 72.09 68.13 66.40 65.04 65.01
37.14 33.63 27.00 19.40 15.42
BnO
OTBDPS
OH
3.114
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

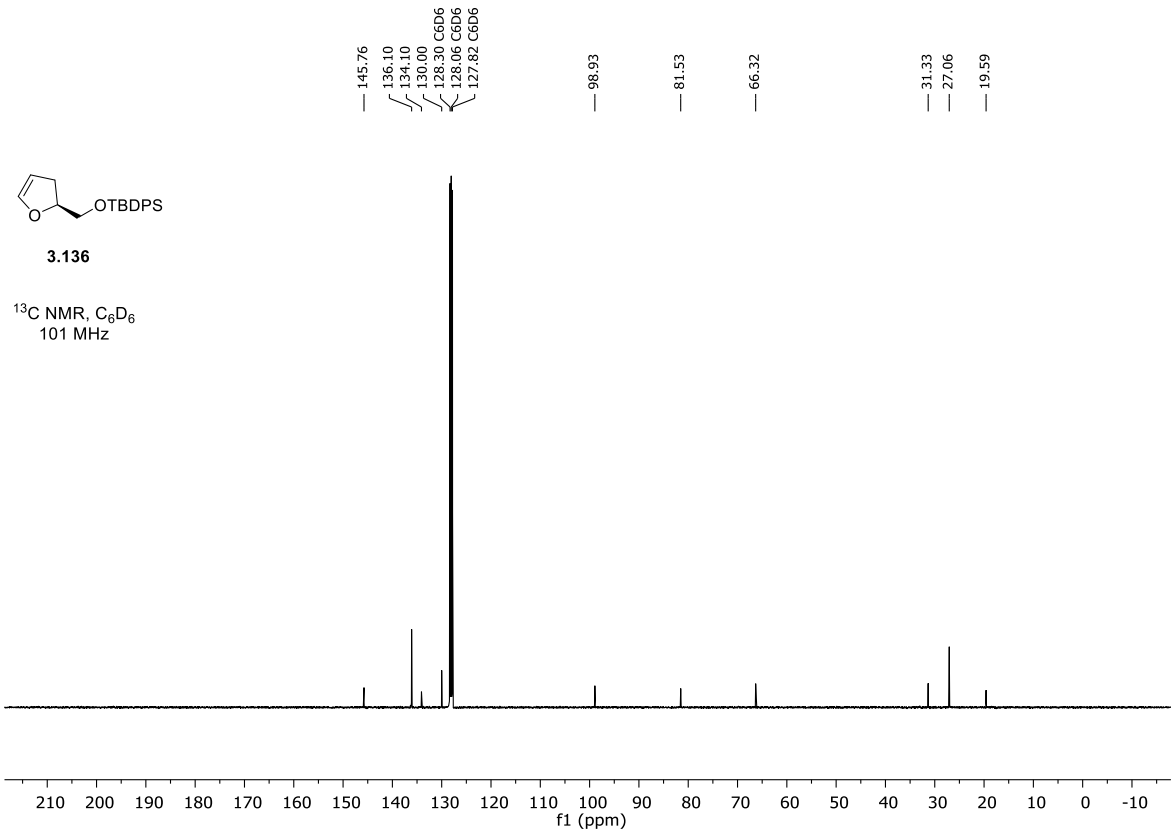

HO
OTBDPS
OH
3.115
1H NMR, CDCl3
400 MHz
f1 (ppm)

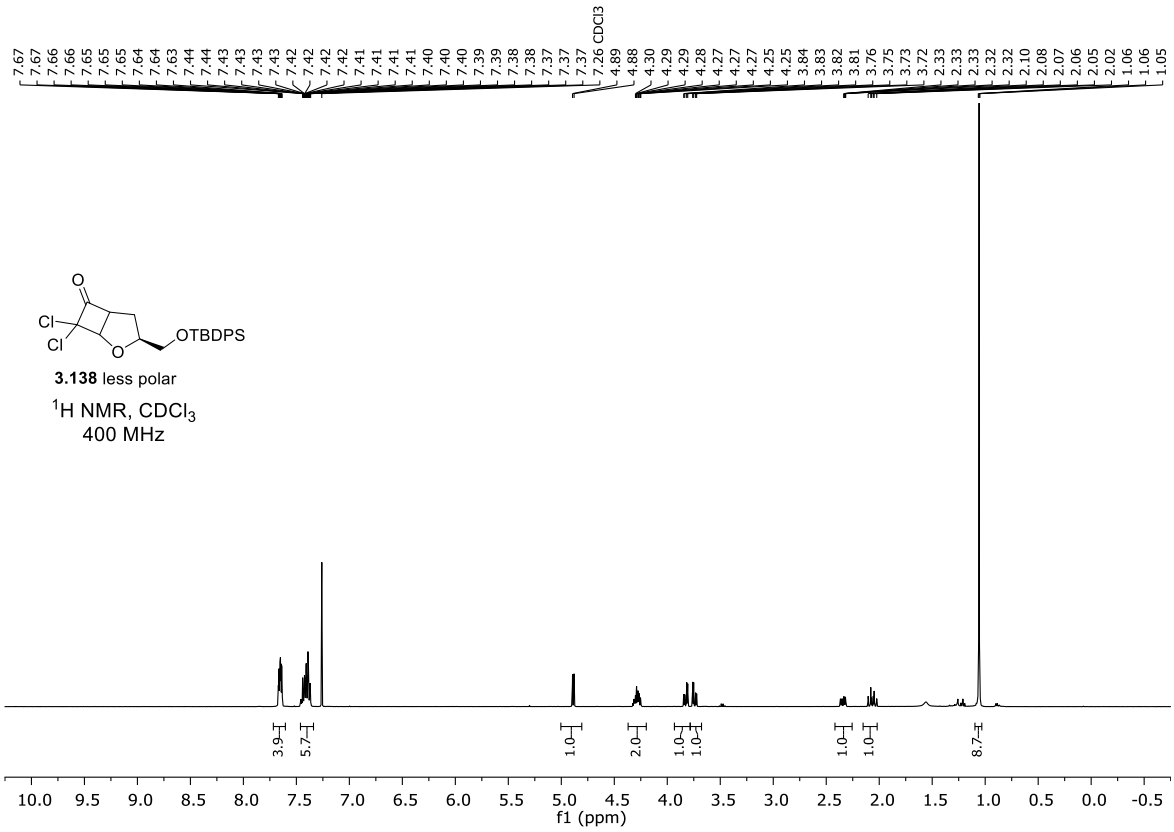

HO
OTBDPS
OH
3.115
13C NMR, CDCl3
101 MHz
f1 (ppm)

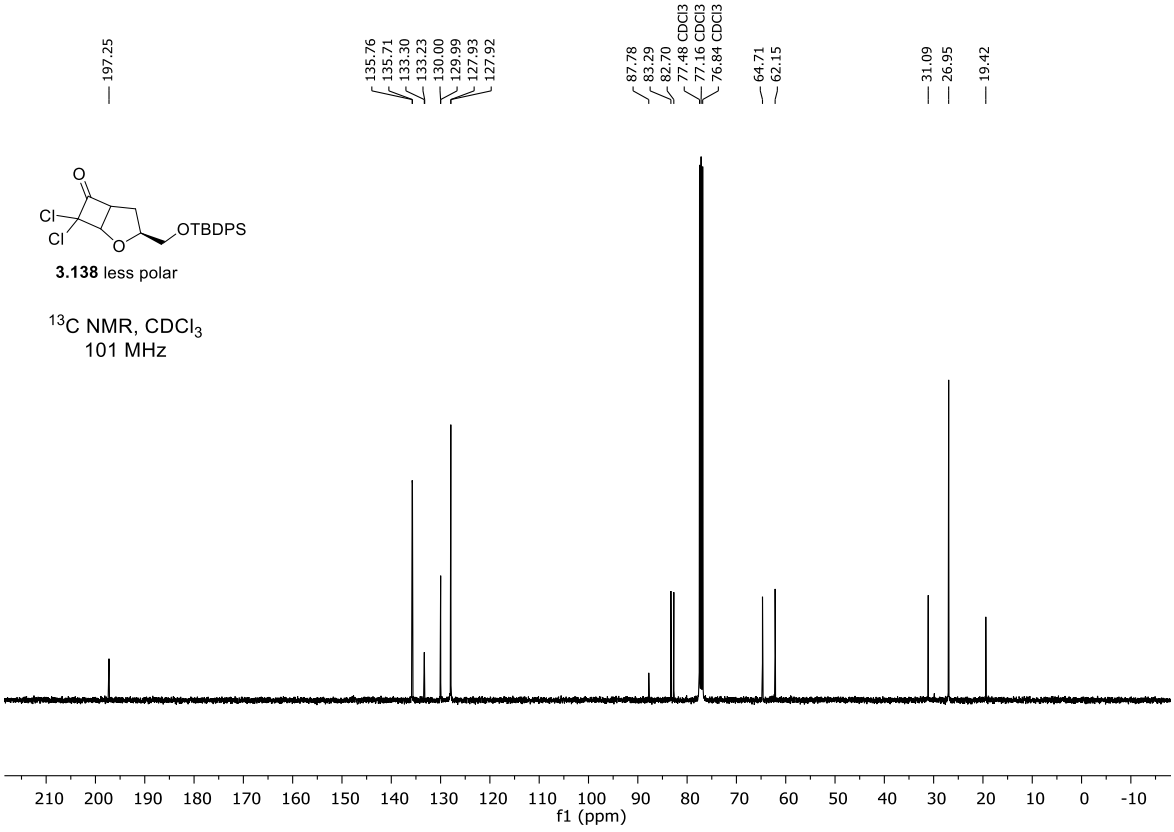

TBDPSO
3.116
^{1}H NMR, CDCl$_3$
400 MHz
f1 (ppm)

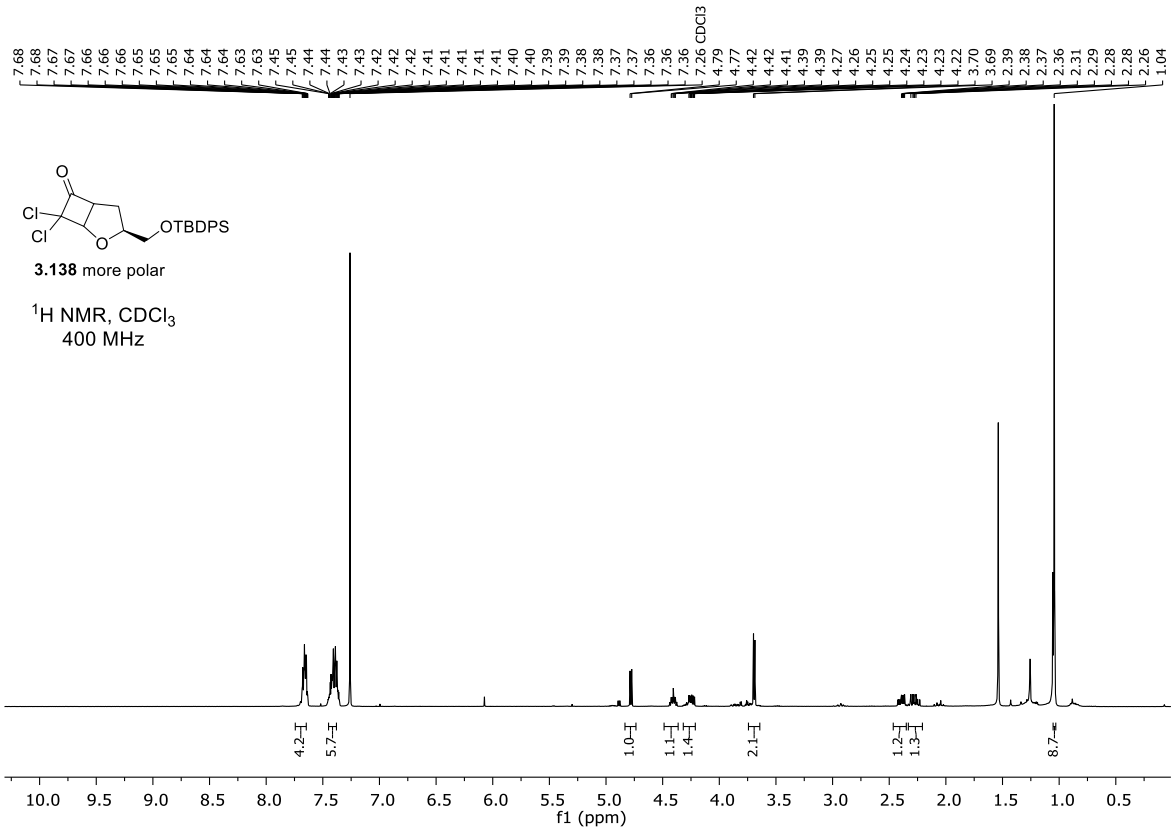

TBDPSO
3.116
^{13}C NMR, CDCl$_3$
101 MHz
f1 (ppm)

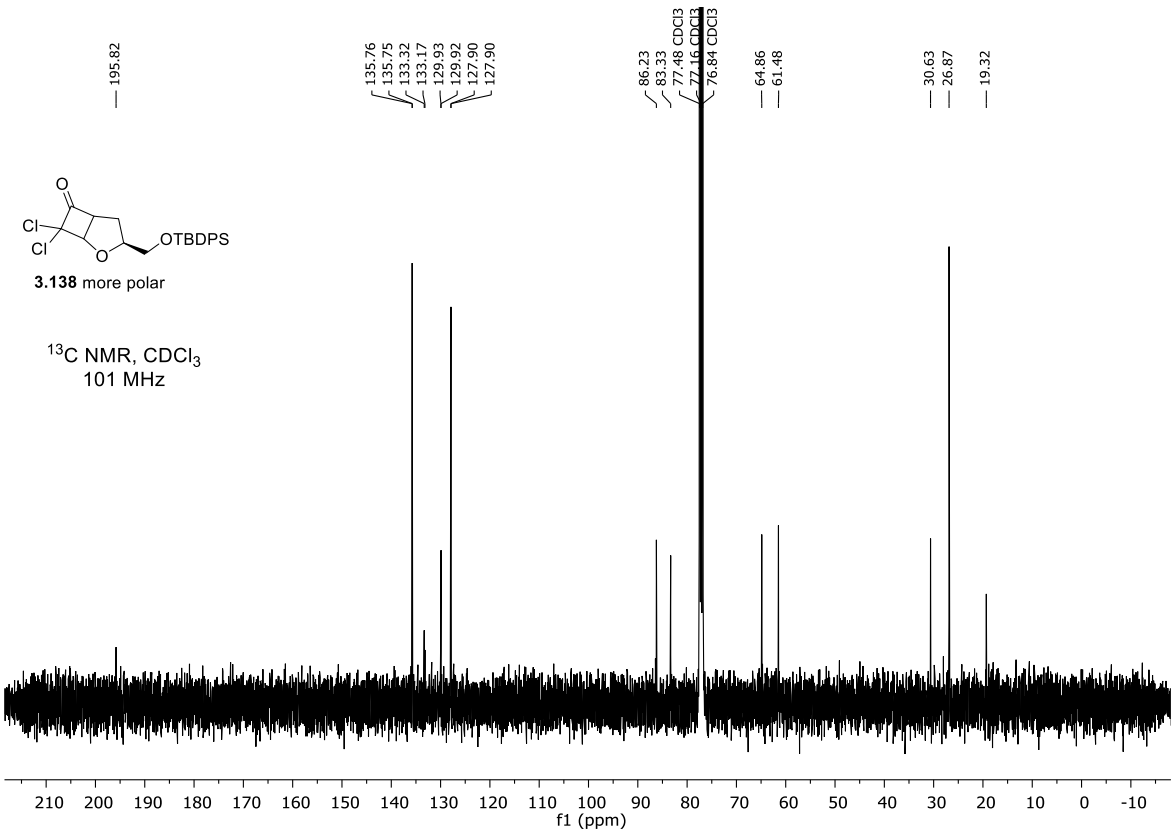

7.81 7.81 7.81 7.80 7.80 7.79 7.79 7.78 7.78 7.78 7.77 7.77 7.24 7.24 7.23 7.22 7.22 7.22 7.21 7.16 C6D6 6.18 6.18 6.17 6.16 4.63 4.63 4.62 4.61 4.59 4.57 4.57 4.57 4.56 4.56 4.55 4.55 4.55 4.54 4.54 4.53 4.53 4.52 3.72 3.71 3.69 3.68 3.67 3.66 3.65 3.64 2.36 2.33 2.32 2.32 2.30 2.30 2.29 2.29 2.28 2.27 2.27 2.25 1.19 1.18 1.17
OTBDPS
3.136
1H NMR, C6D6
400 MHz
4.3 6.4 1.0 1.0 1.0 2.2 2.1 9.1
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 -0.5
f1 (ppm)

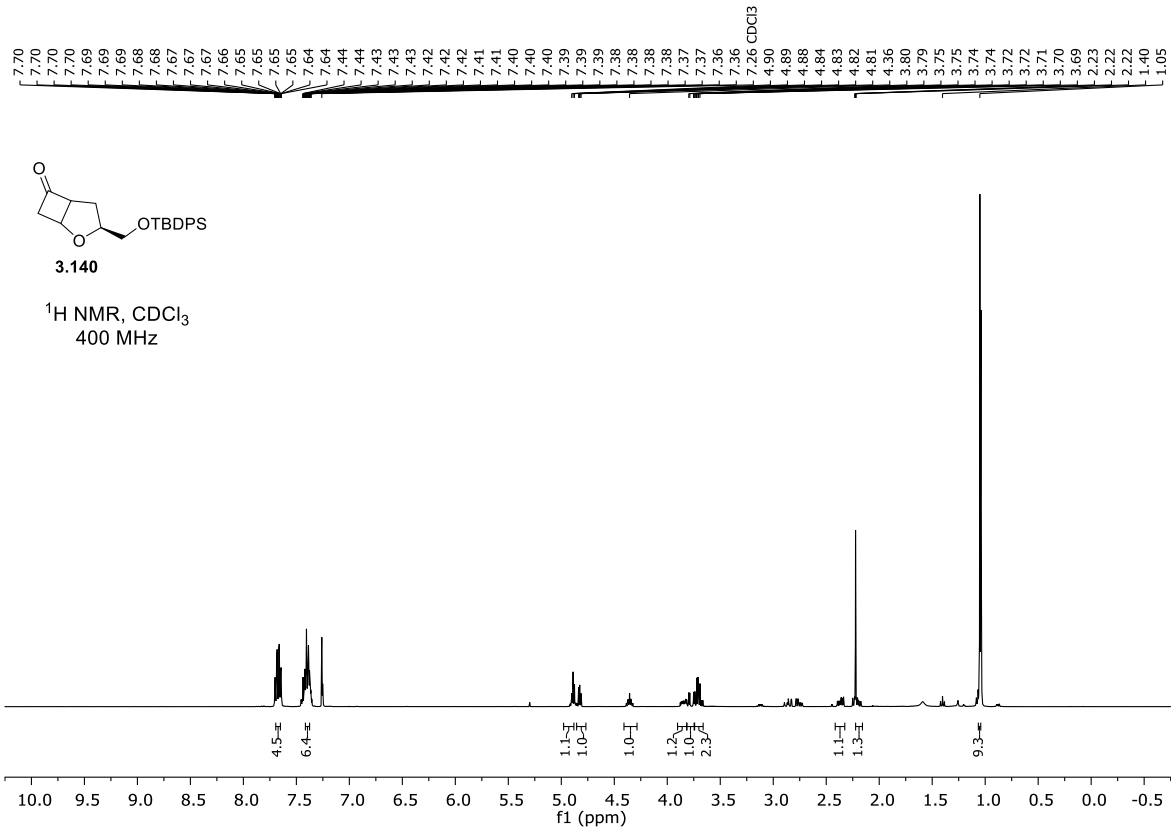

145.76 136.10 134.10 130.00 128.30 C6D6 128.06 C6D6 127.82 C6D6 98.93 81.53 66.32 31.33 27.06 19.59
OTBDPS
3.136
13C NMR, C6D6
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

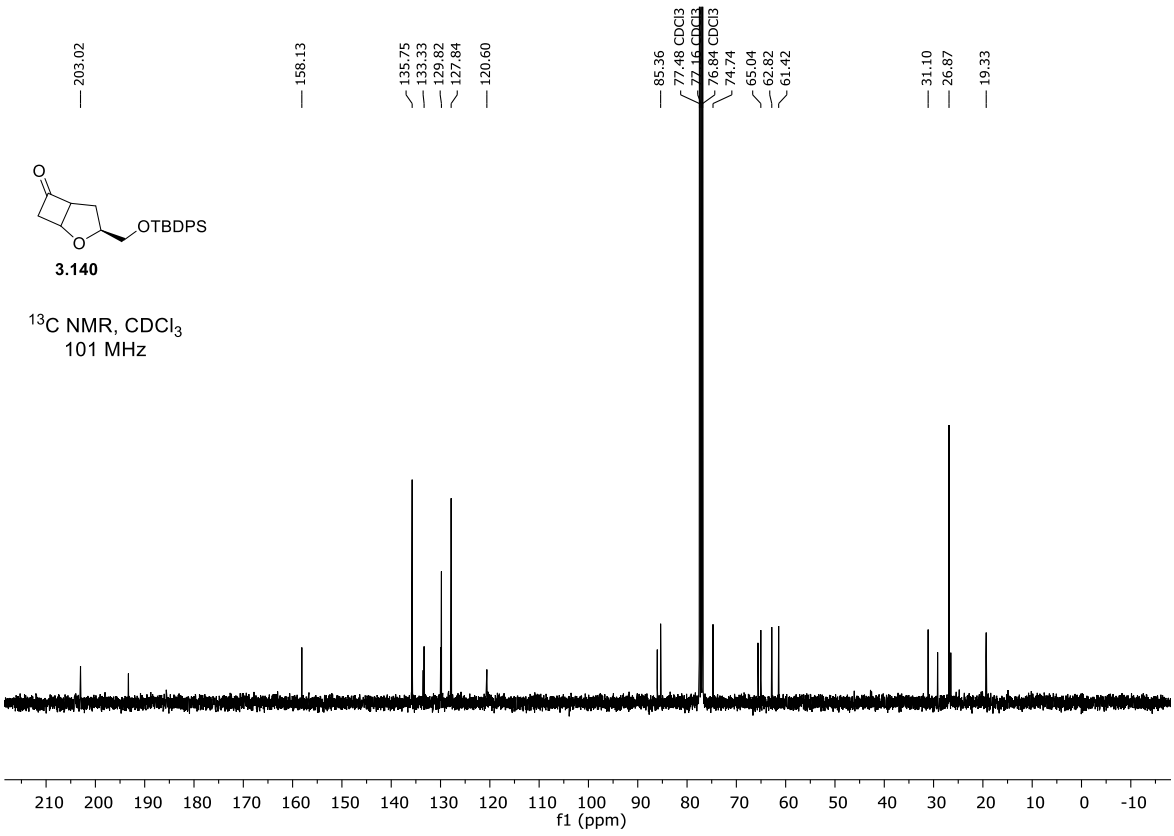

7.26 CDCl3
OTBDPS
Cl
Cl
O
3.138 less polar
1H NMR, CDCl3
400 MHz
3.9
5.7
1.0
2.0
1.0
1.0
1.0
1.0
8.7
f1 (ppm)

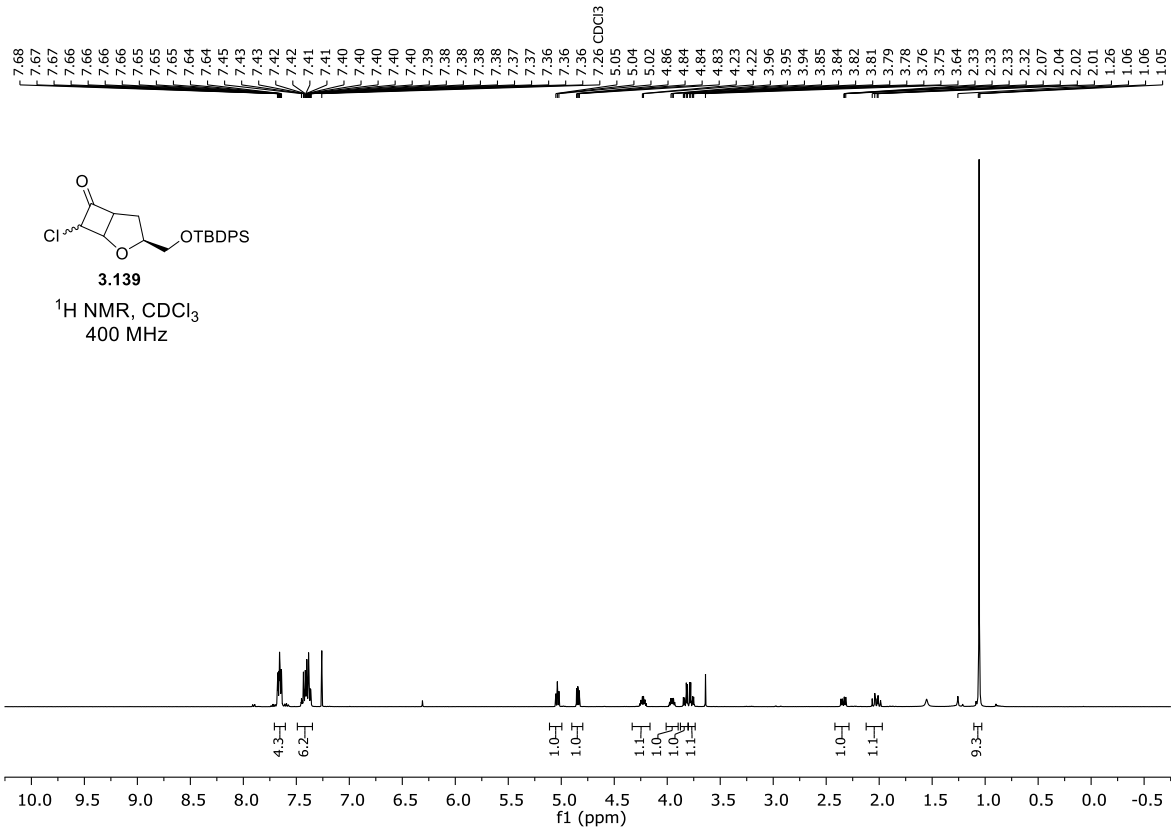

197.25
135.76
135.71
133.30
133.23
130.00
129.99
127.93
127.92
87.78
83.29
82.70
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
64.71
62.15
31.09
26.95
19.42
OTBDPS
Cl
Cl
O
3.138 less polar
13C NMR, CDCl3
101 MHz
f1 (ppm)

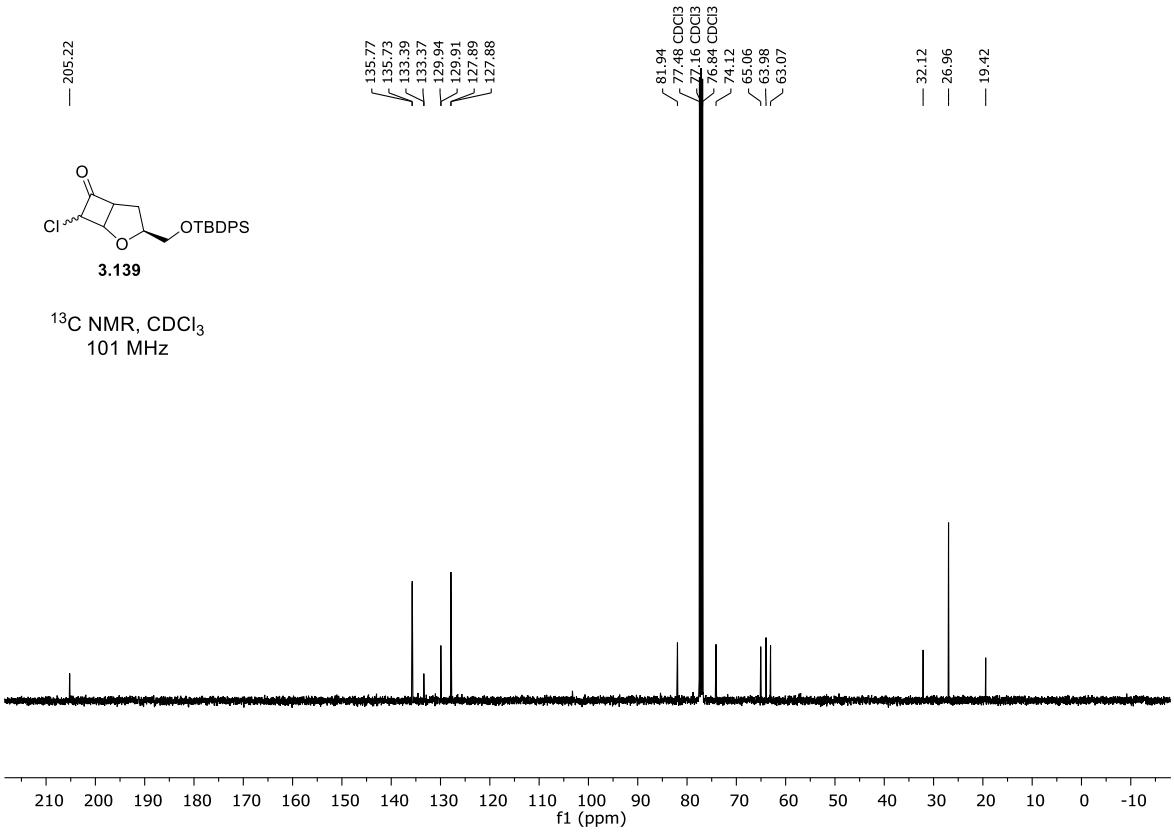

7.68 7.68 7.67 7.67 7.66 7.66 7.66 7.65 7.65 7.65 7.64 7.64 7.64 7.63 7.63 7.45 7.45 7.44 7.44 7.43 7.43 7.42 7.42 7.42 7.41 7.41 7.41 7.41 7.40 7.40 7.39 7.39 7.38 7.38 7.37 7.37 7.36 7.36 7.36 7.26 CDCl3 4.79 4.77 4.42 4.42 4.41 4.39 4.39 4.27 4.26 4.25 4.25 4.24 4.23 4.23 4.22 3.70 3.69 2.39 2.38 2.37 2.36 2.31 2.29 2.28 2.28 2.26 1.04
O
Cl
Cl
O
OTBDPS
3.138 more polar
1H NMR, CDCl3
400 MHz
4.2 5.7 1.0 1.1 1.4 2.1 1.2 1.3 8.7
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
f1 (ppm)

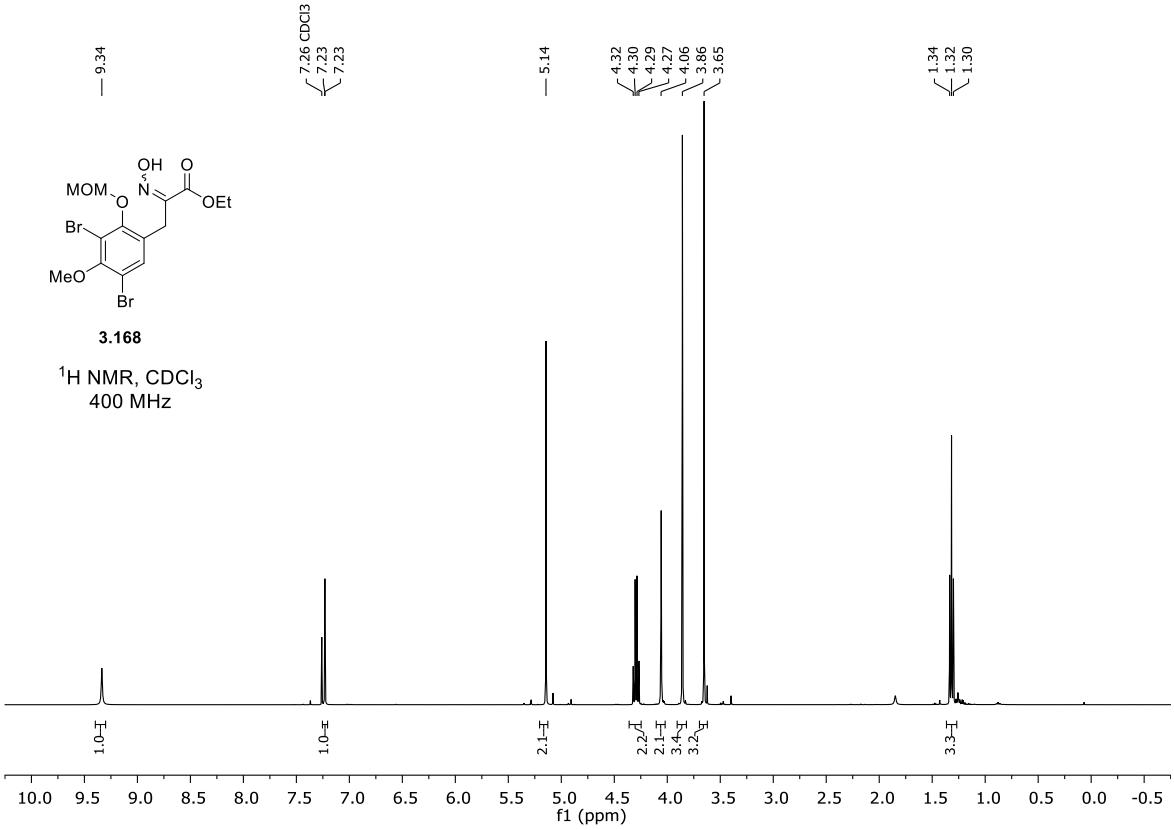

195.82
135.76 135.75 133.32 133.17 129.93 129.92 127.90 127.90
86.23 83.33 77.48 CDCl3 77.16 CDCl3 76.84 CDCl3
64.86 61.48
30.63 26.87 19.32
O
Cl
Cl
O
OTBDPS
3.138 more polar
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.26 CDCl3
OTBDPS
3.140
1H NMR, CDCl3
400 MHz
f1 (ppm)


203.02
158.13
135.75
133.33
129.82
127.84
120.60
85.36
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
74.74
65.04
62.82
61.42
31.10
26.87
19.33
OTBDPS
3.140
13C NMR, CDCl3
101 MHz
f1 (ppm)

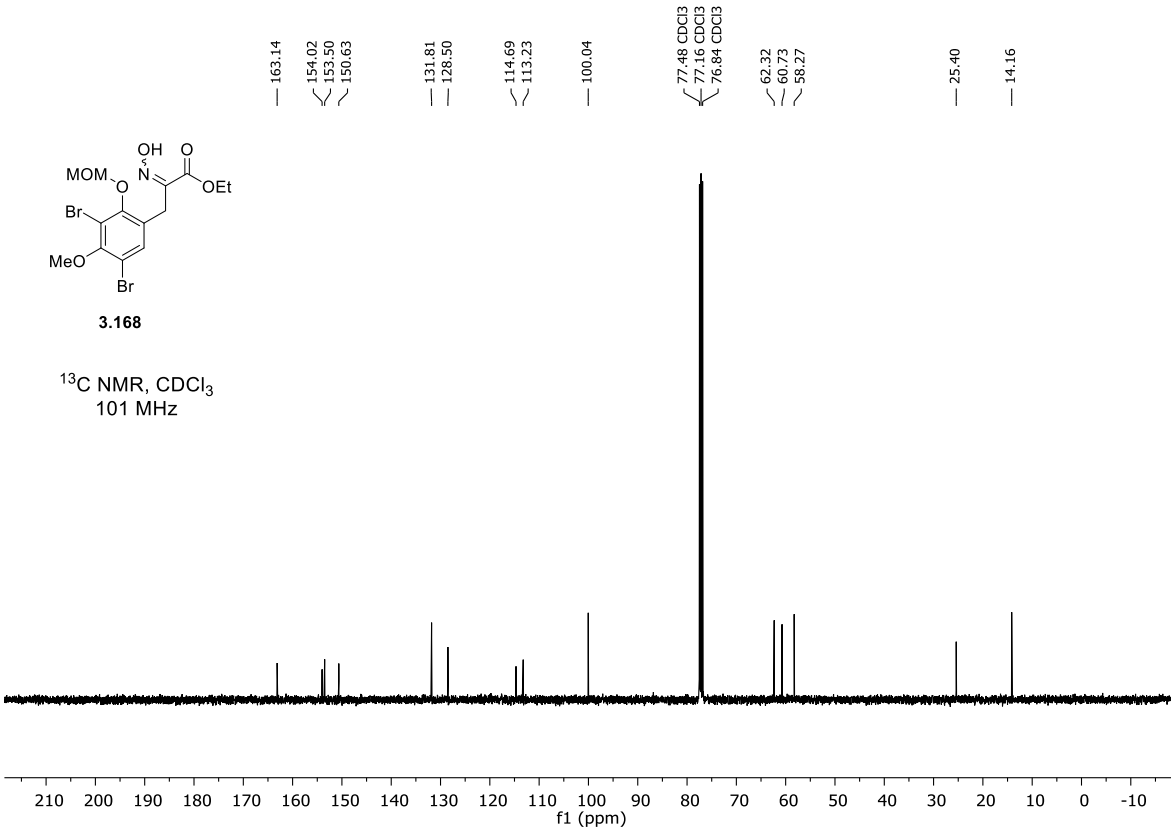

7.68 7.67 7.67 7.66 7.66 7.66 7.66 7.65 7.65 7.65 7.64 7.64 7.45 7.43 7.43 7.42 7.42 7.41 7.41 7.40 7.40 7.40 7.40 7.40 7.39 7.38 7.38 7.38 7.37 7.37 7.36 7.36 7.36 7.26 CDCl3 5.05 5.04 5.02 4.86 4.84 4.84 4.83 4.23 4.22 3.96 3.95 3.94 3.85 3.84 3.82 3.81 3.79 3.78 3.76 3.75 3.64 2.33 2.33 2.33 2.32 2.07 2.04 2.02 2.01 1.26 1.06 1.06 1.05
O
Cl
O
OTBDPS
3.139
1H NMR, CDCl3
400 MHz
4.3 6.2 1.0 1.0 1.1 1.0 1.0 1.1 1.0 1.1 9.3
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 -0.5
f1 (ppm)


205.22
135.77 135.73 133.39 133.37 129.94 129.91 127.89 127.88
81.94 77.48 CDCl3 77.16 CDCl3 76.84 CDCl3 74.12 65.06 63.98 63.07
32.12 26.96 19.42
O
Cl
O
OTBDPS
3.139
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)



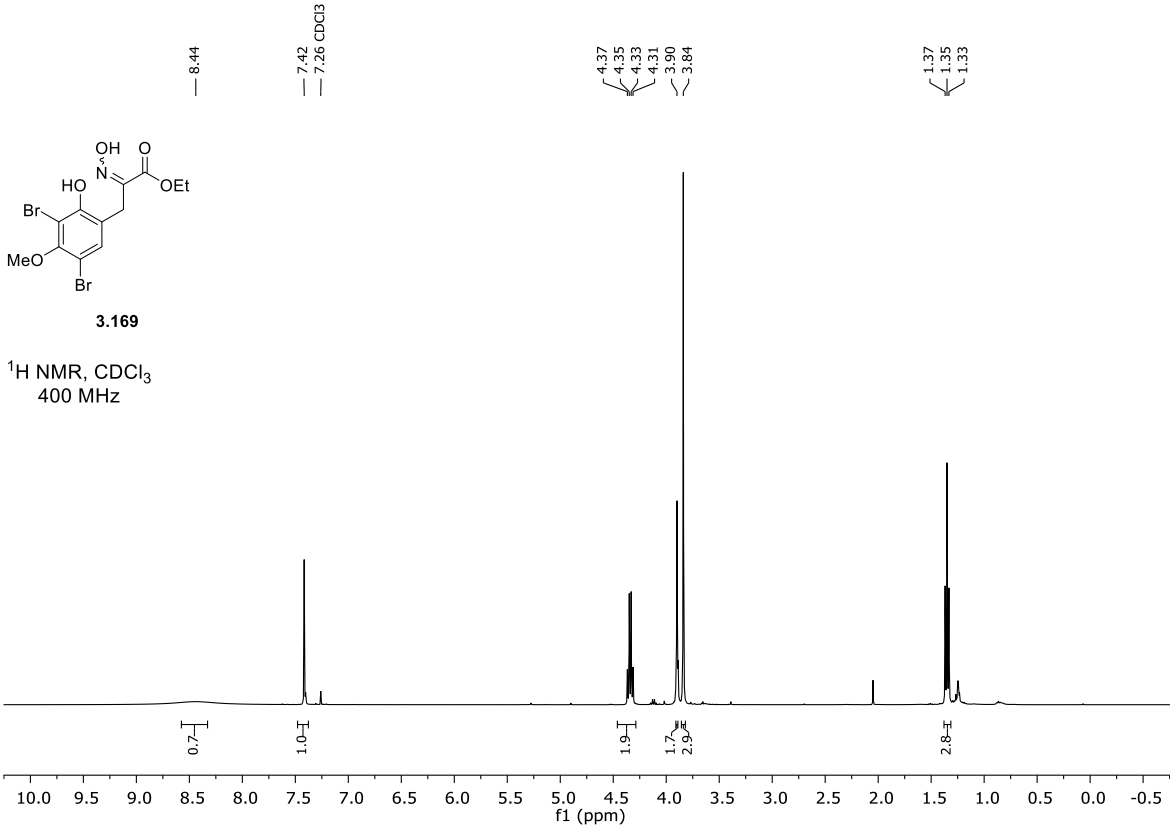
3.168

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



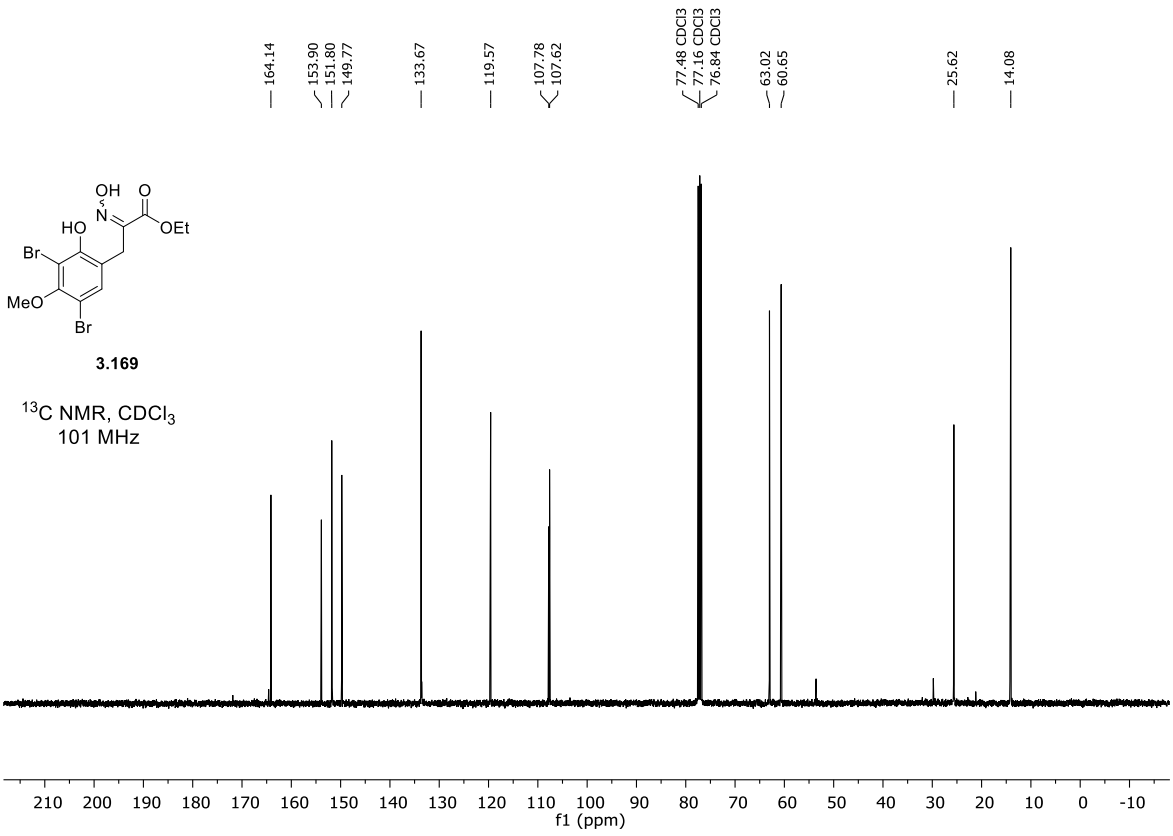
3.168

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



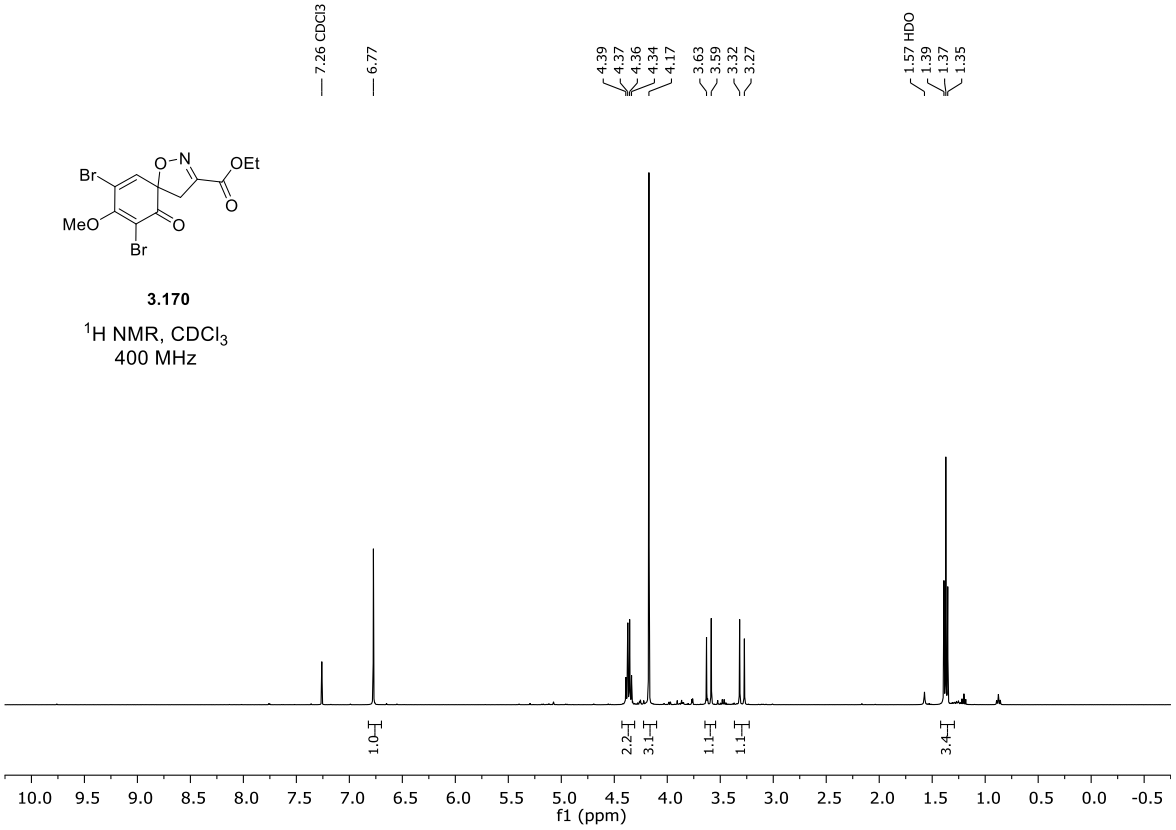
3.169

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



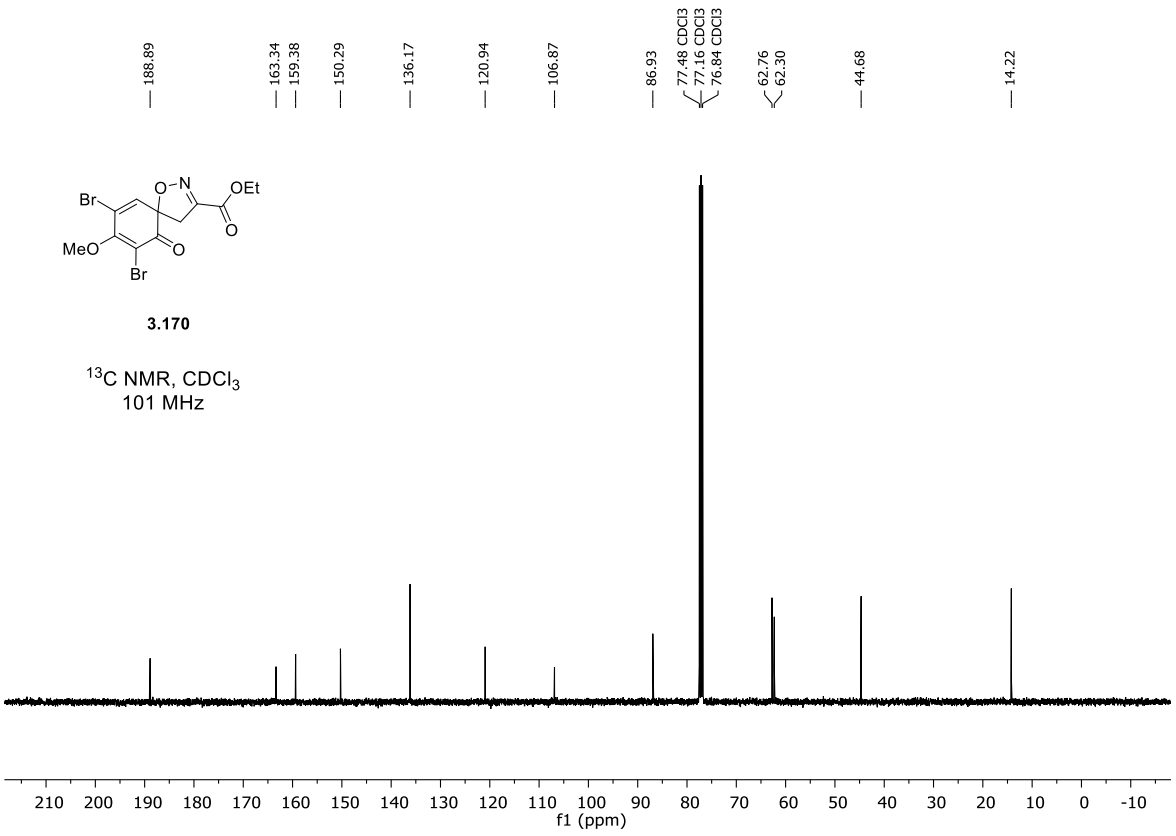
3.169

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



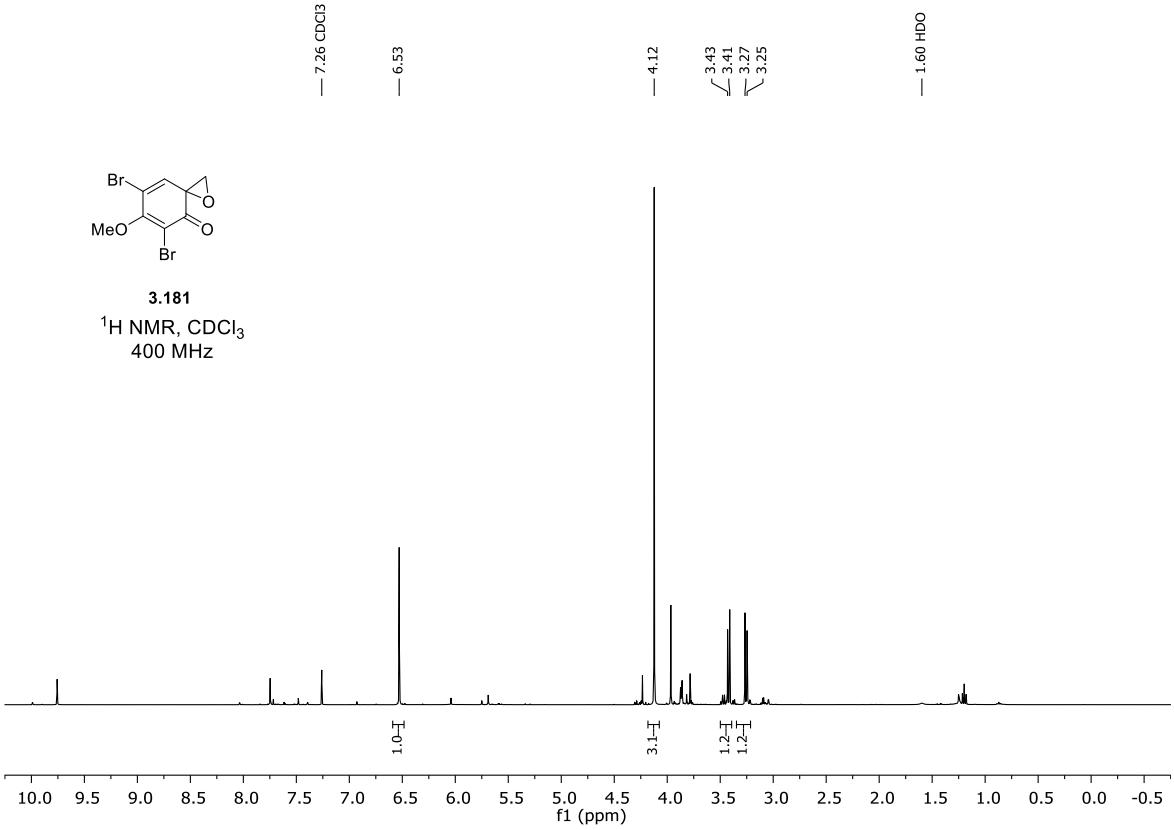
3.170

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



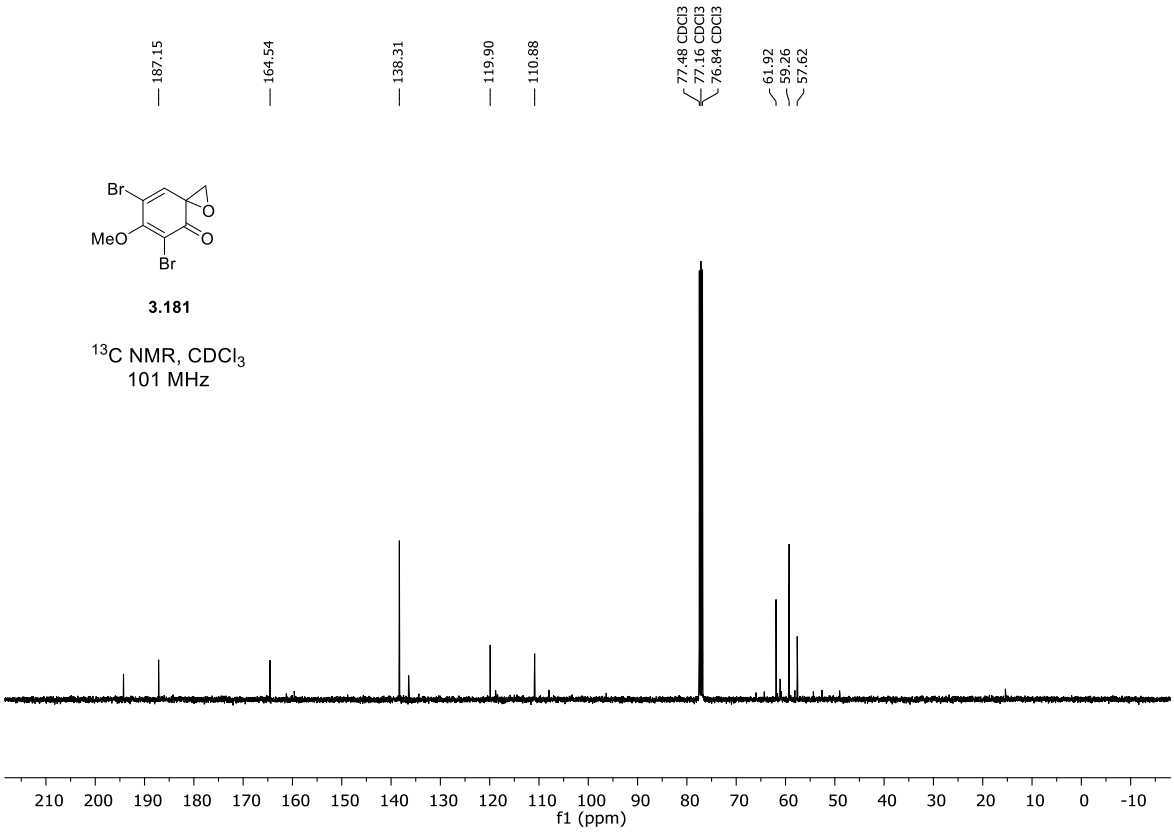
3.170

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



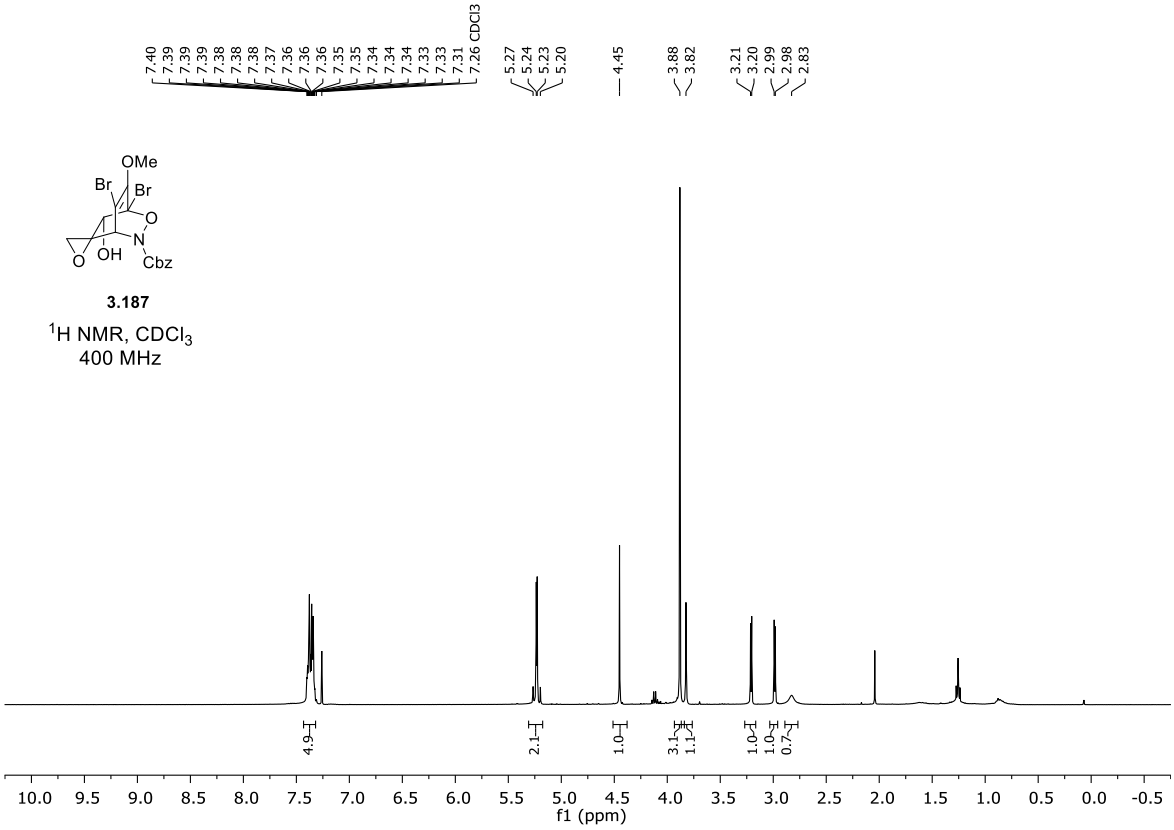
3.181

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



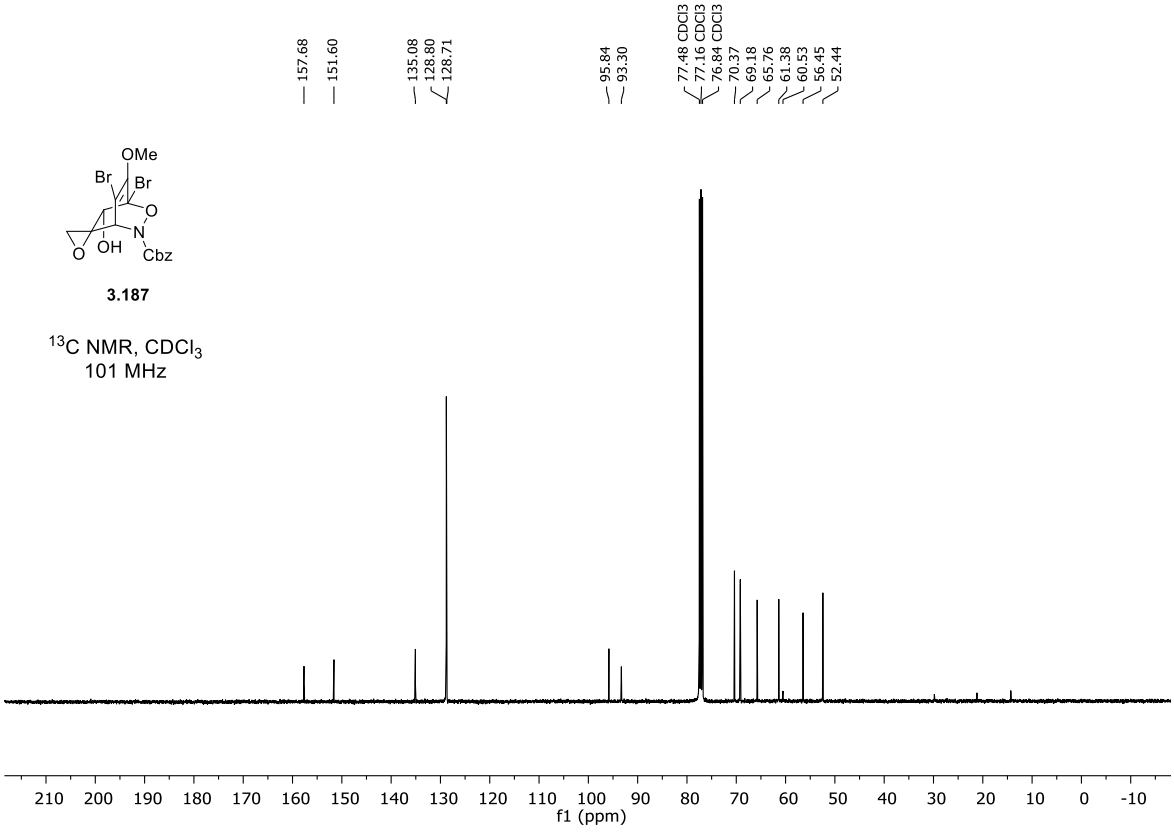
3.181

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



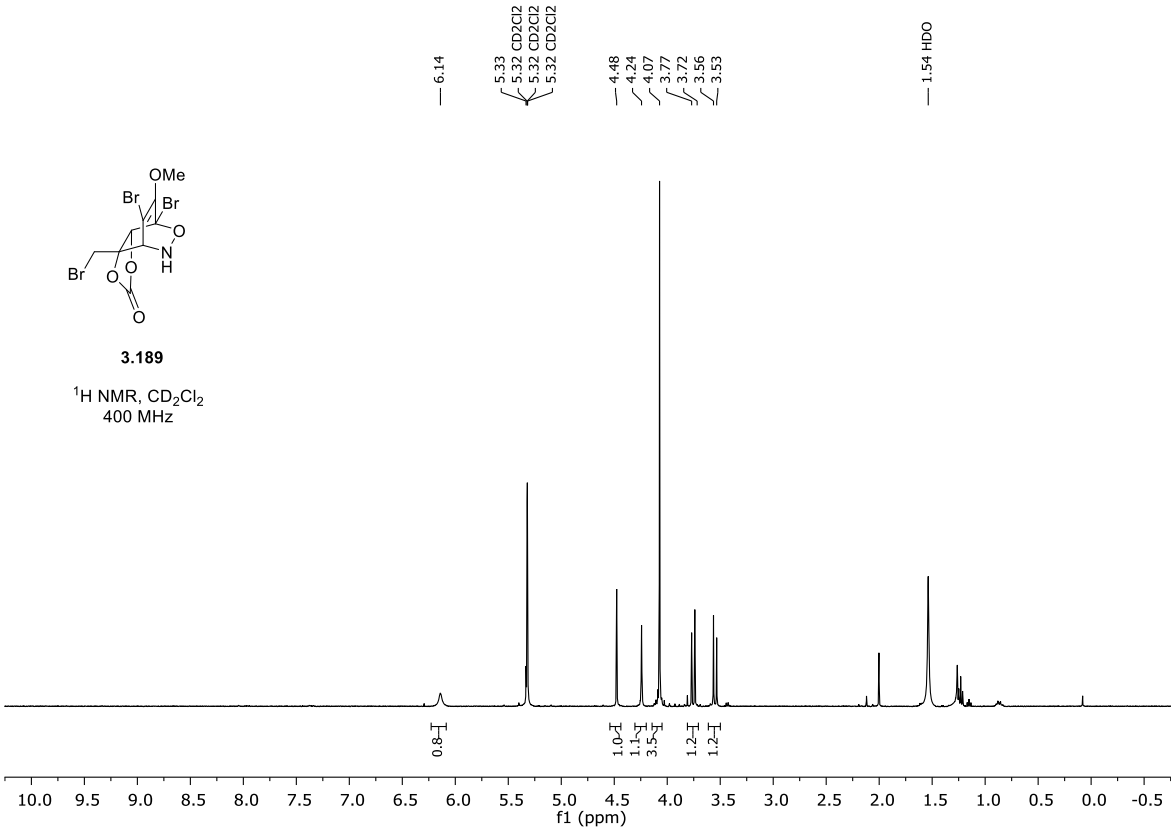
3.187

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



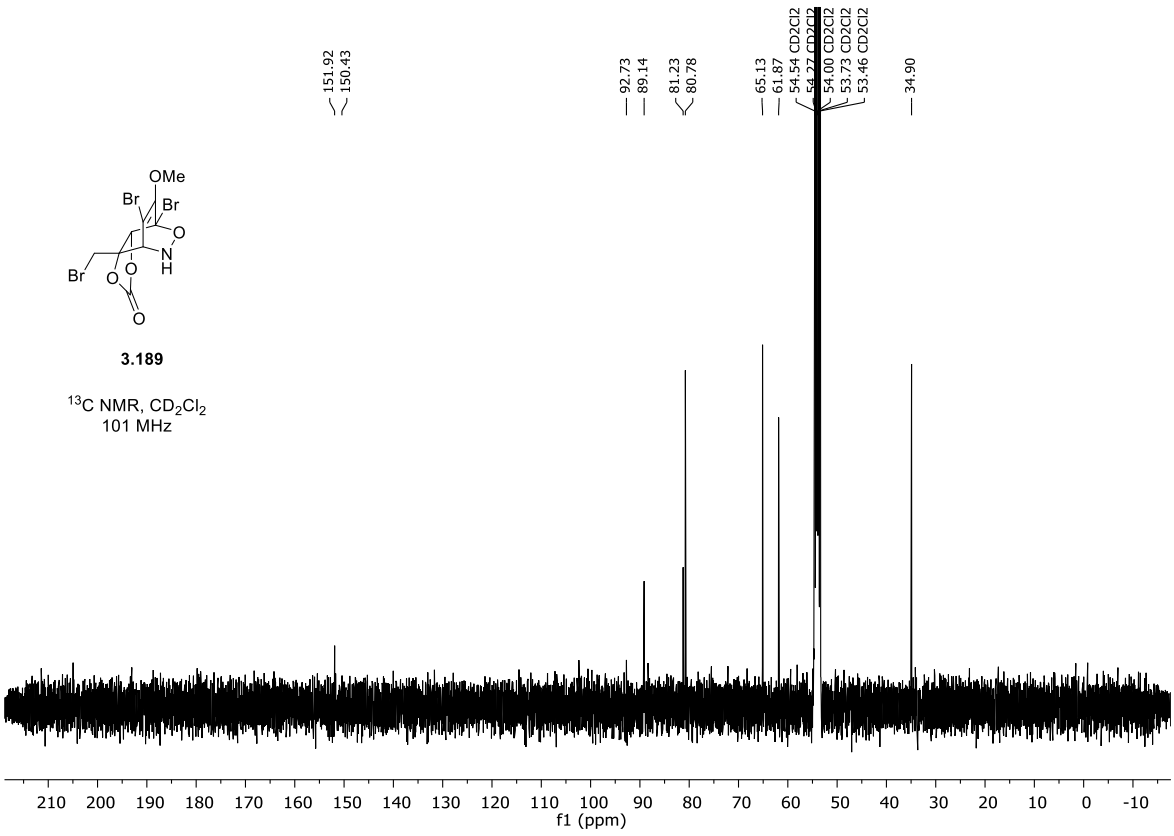
3.187

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



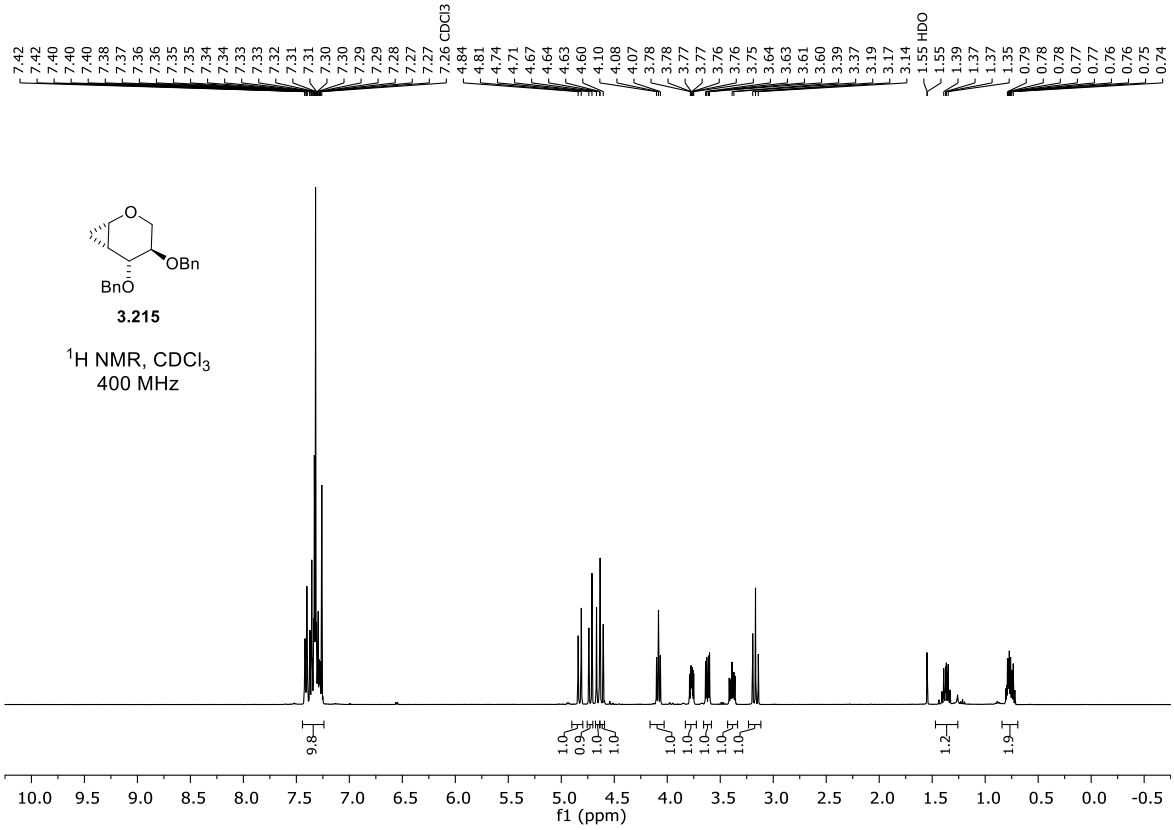
3.189

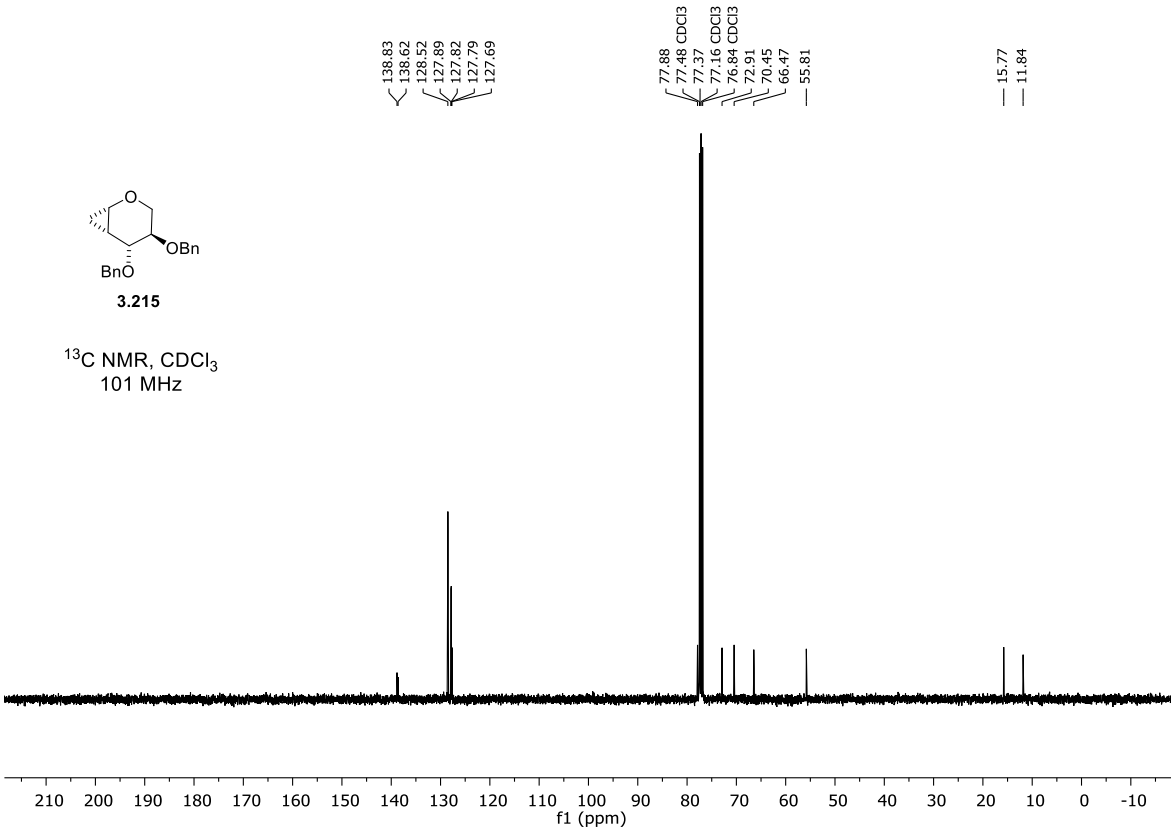
^{1}H NMR, CD_2Cl_2
400 MHz

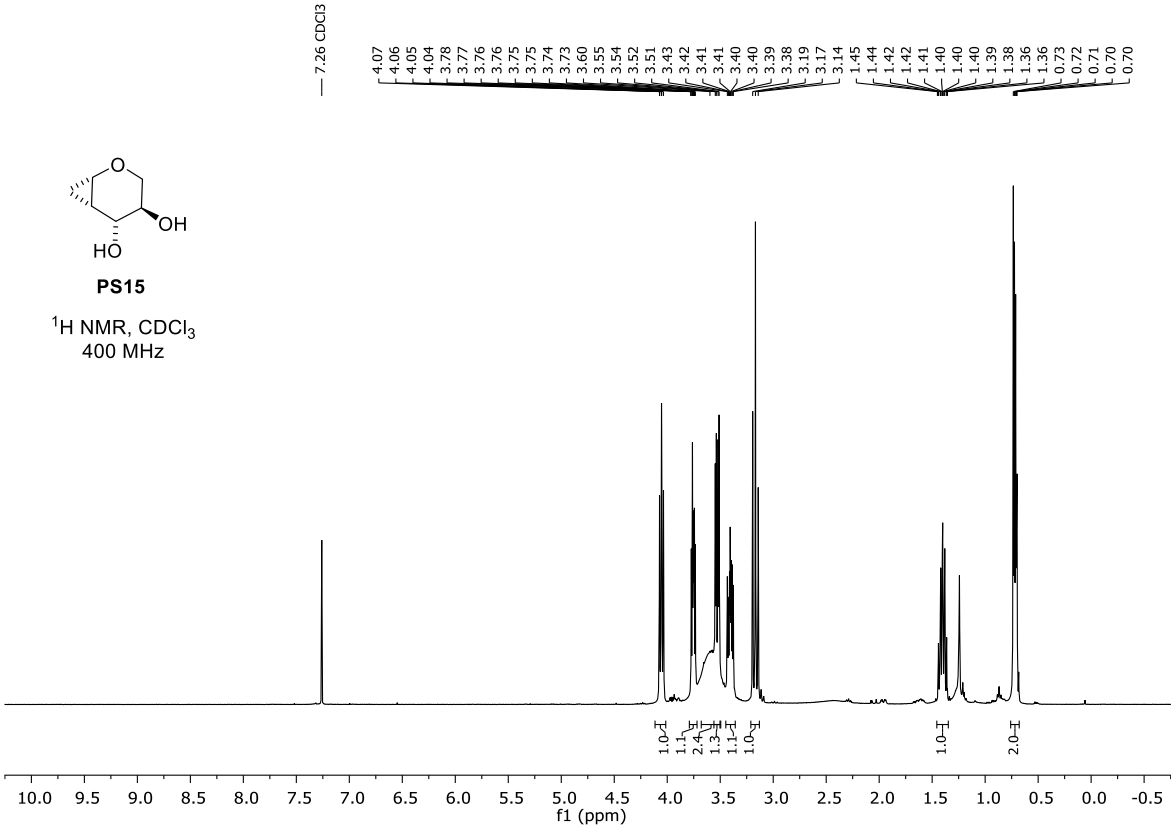


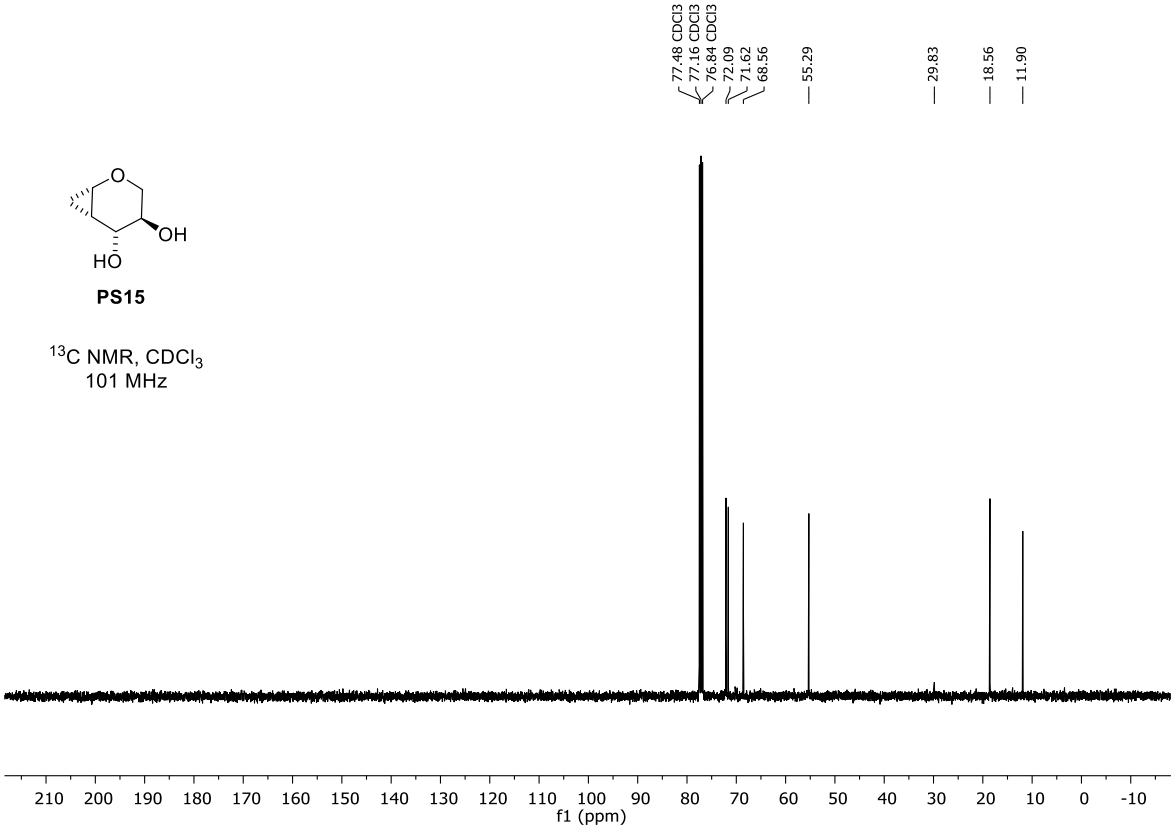
3.189

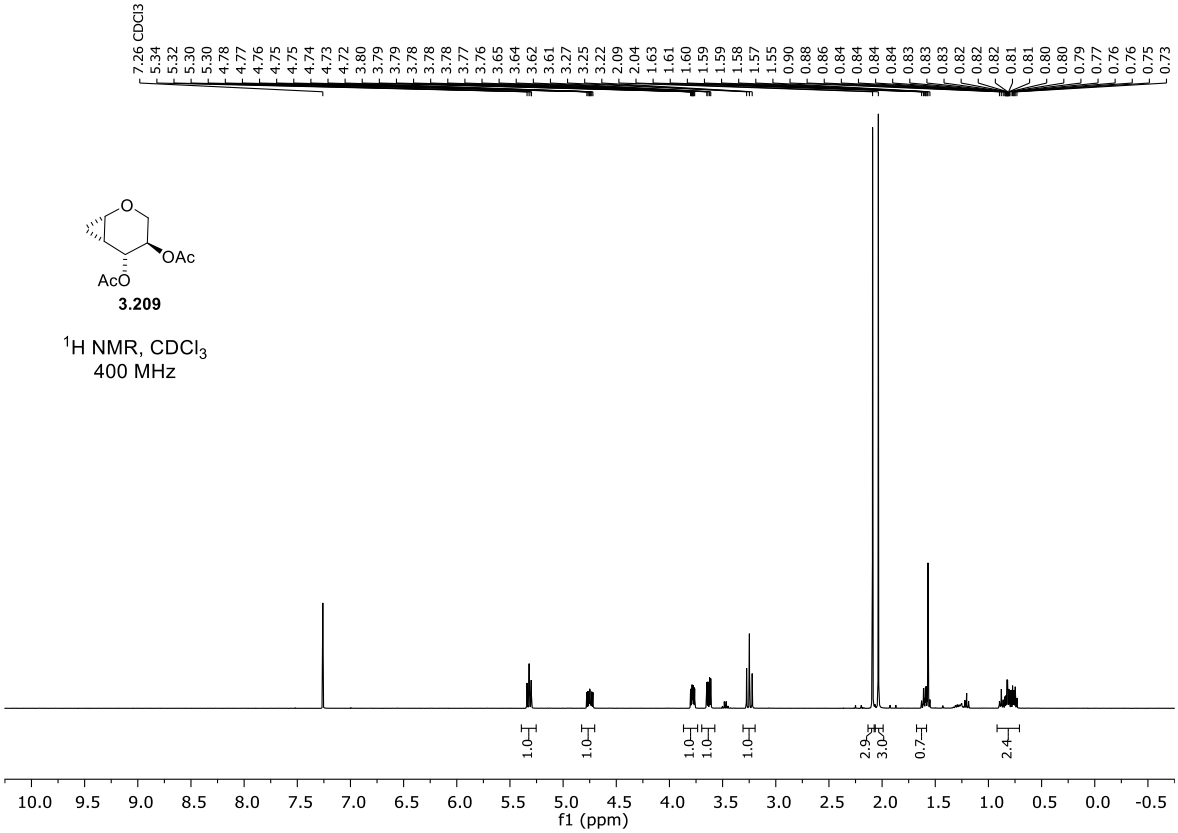
^{13}C NMR, CD_2Cl_2
101 MHz

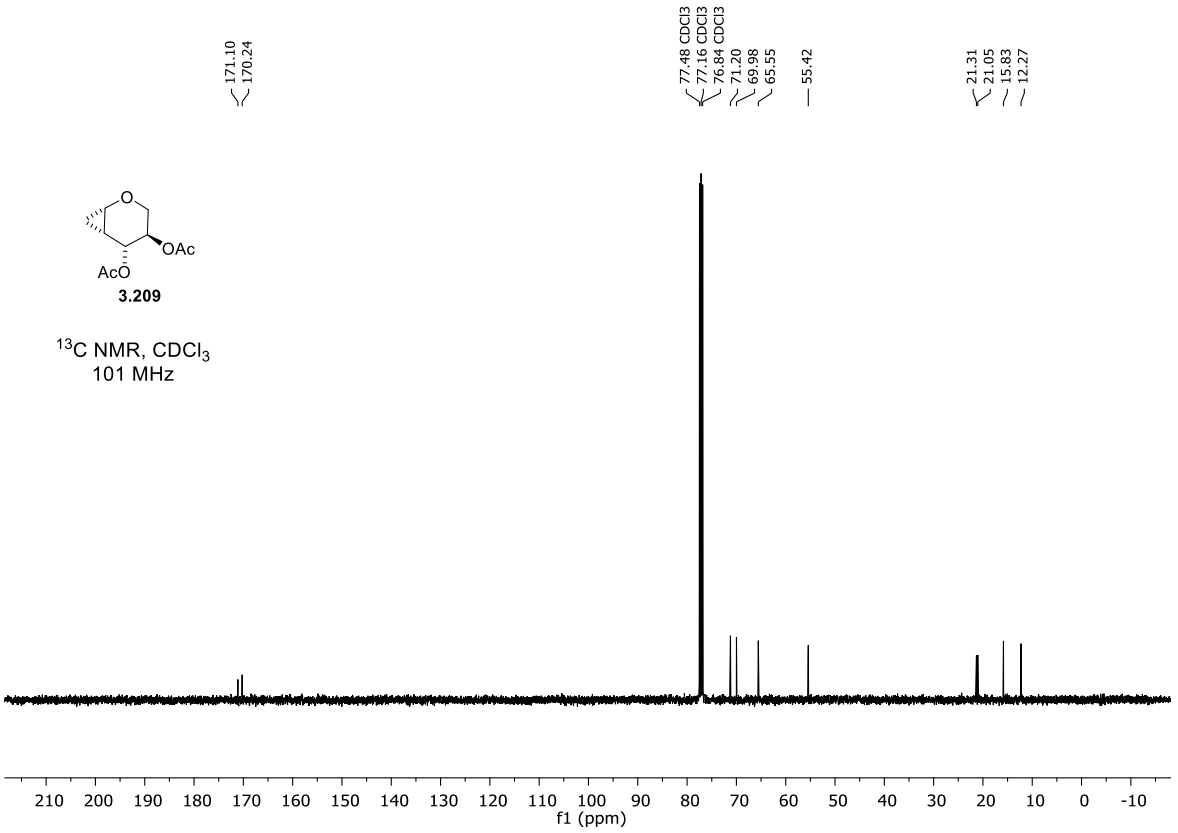

7.42 7.42 7.40 7.40 7.40 7.38 7.37 7.36 7.36 7.35 7.35 7.34 7.34 7.33 7.33 7.32 7.31 7.31 7.30 7.30 7.29 7.29 7.28 7.27 7.27 7.26 CDCl3
4.84 4.81 4.74 4.71 4.67 4.64 4.63 4.60 4.10 4.08 4.07 3.78 3.78 3.77 3.77 3.76 3.76 3.75 3.64 3.63 3.61 3.60 3.39 3.37 3.19 3.17 3.14
1.55 HDO 1.55 1.39 1.37 1.37 1.35 0.79 0.78 0.78 0.77 0.77 0.76 0.76 0.75 0.74
O
OBn
BnO
3.215
1H NMR, CDCl3
400 MHz
9.8
1.0 0.9 1.0 1.0
1.0 1.0 1.0 1.0 1.0
1.2
1.9
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 -0.5
f1 (ppm)

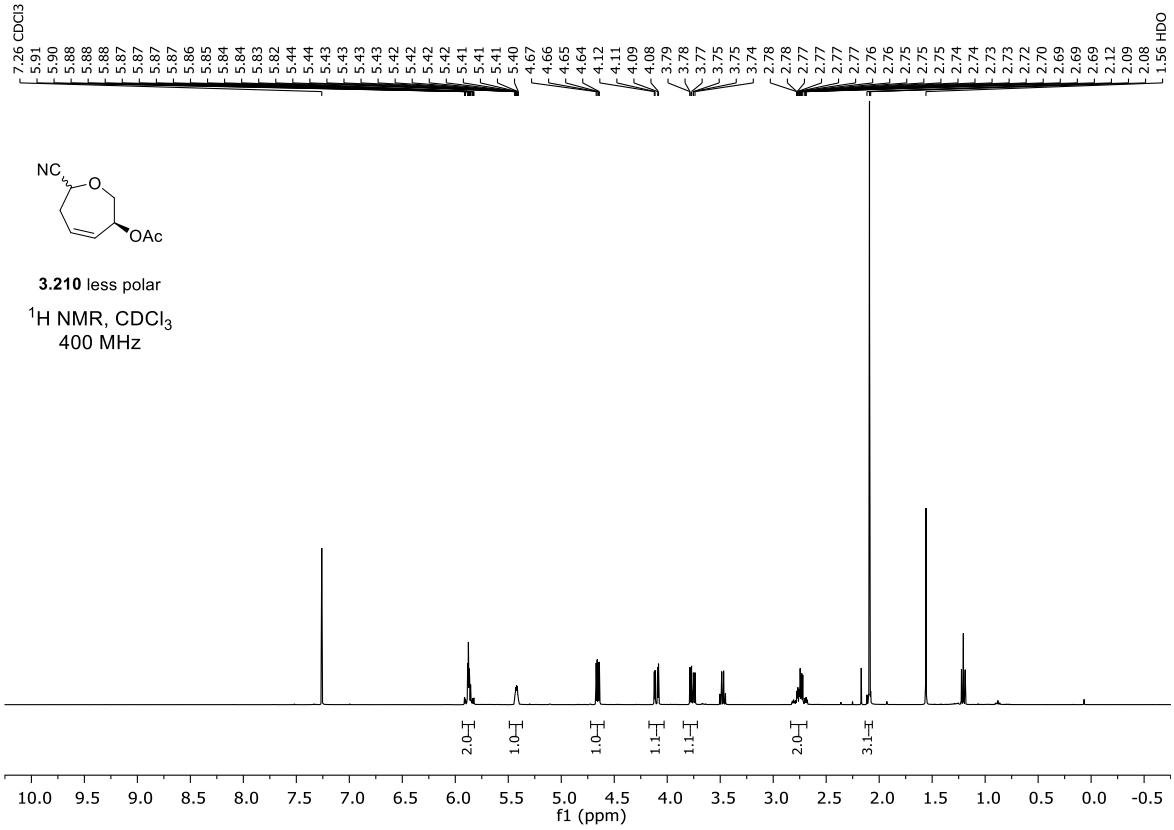

138.83 138.62 128.52 127.89 127.82 127.79 127.69
77.88 77.48 CDCl3 77.37 77.16 CDCl3 76.84 CDCl3 72.91 70.45 66.47 55.81
15.77 11.84
O
OBn
BnO
3.215
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

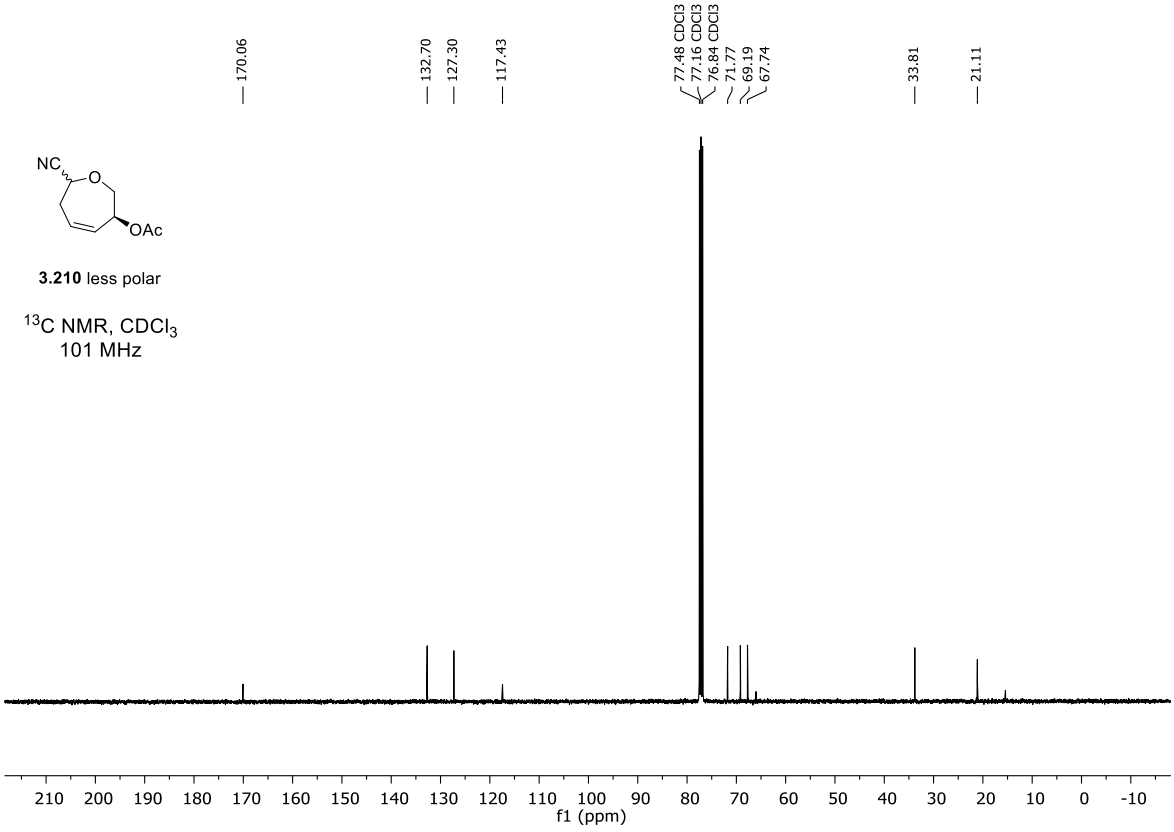

7.26 CDCl3
4.07
4.06
4.05
4.04
3.78
3.77
3.76
3.76
3.75
3.75
3.74
3.73
3.60
3.55
3.54
3.52
3.51
3.43
3.42
3.41
3.41
3.40
3.40
3.39
3.38
3.19
3.17
3.14
1.45
1.44
1.42
1.42
1.41
1.40
1.40
1.40
1.39
1.38
1.36
1.36
0.73
0.72
0.71
0.70
0.70
0.70
O
OH
HO
PS15
1H NMR, CDCl3
400 MHz
1.0
1.1
2.4
1.3
1.1
1.0
1.0
2.0
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 -0.5
f1 (ppm)

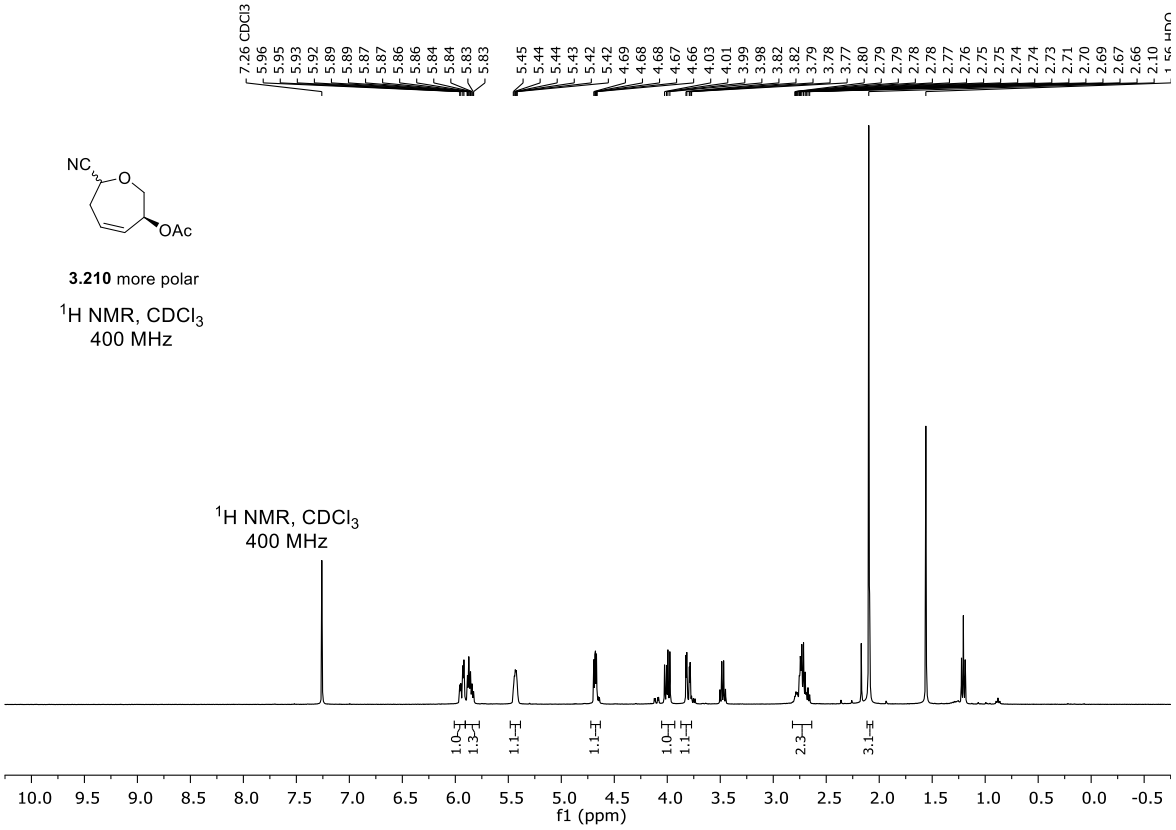

77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
72.09
71.62
68.56
55.29
29.83
18.56
11.90
O
OH
HO
PS15
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

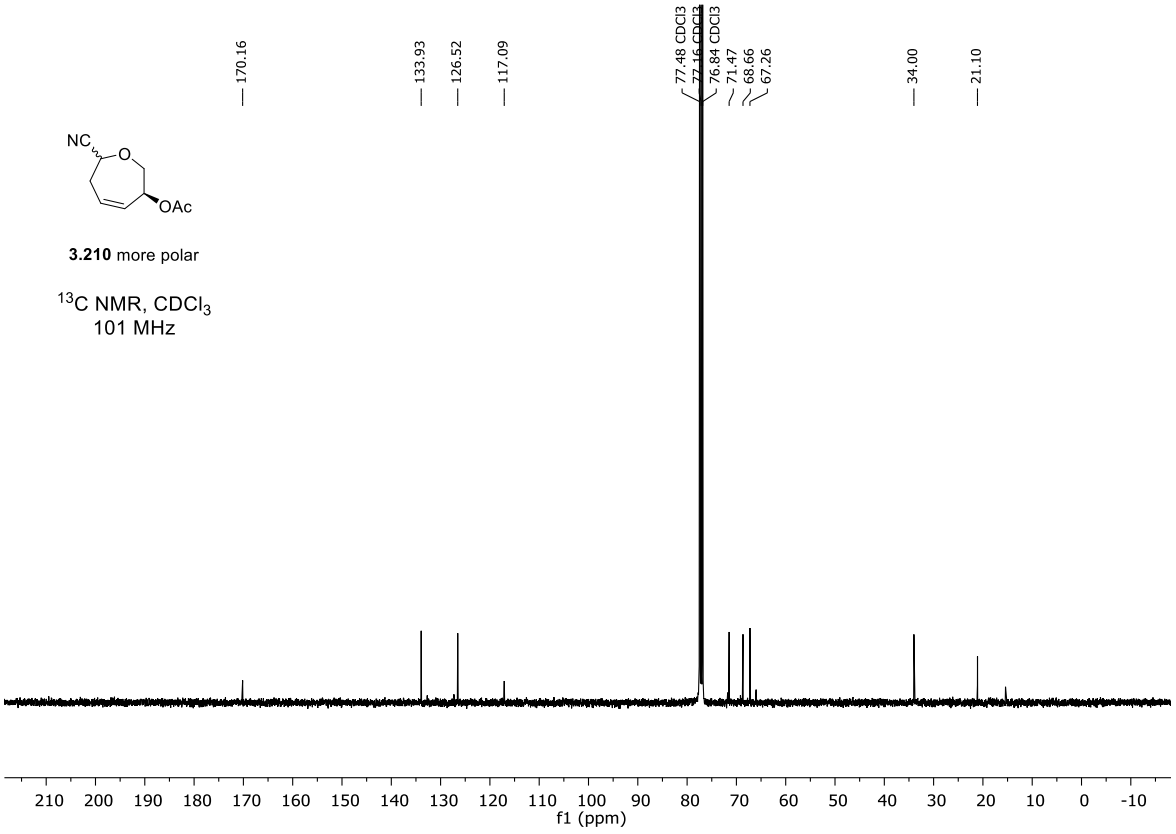

7.26 CDCl3
5.34 5.32 5.30 5.30 4.78 4.77 4.76 4.75 4.75 4.74 4.73 4.72 3.80 3.79 3.79 3.78 3.78 3.78 3.77 3.76 3.65 3.64 3.62 3.61 3.27 3.25 3.22 2.09 2.04 1.63 1.61 1.60 1.59 1.59 1.58 1.57 1.55 0.90 0.88 0.86 0.84 0.84 0.84 0.84 0.83 0.83 0.83 0.82 0.82 0.82 0.81 0.81 0.80 0.80 0.79 0.77 0.76 0.76 0.75 0.73
OAc
AcO
3.209
1H NMR, CDCl3
400 MHz
1.0 1.0 1.0 1.0 1.0 2.9 3.0 0.7 2.4
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 -0.5
f1 (ppm)

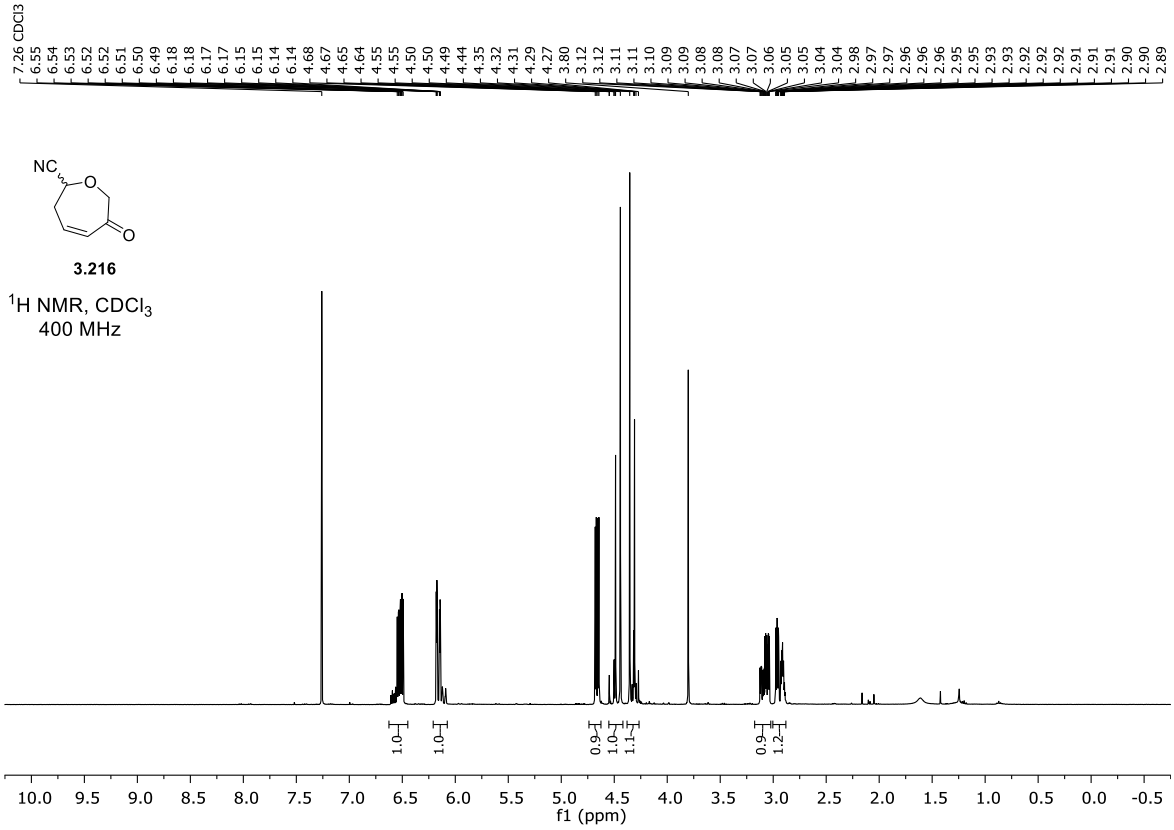

171.10
170.24
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
71.20
69.98
65.55
55.42
21.31
21.05
15.83
12.27
OAc
AcO
3.209
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

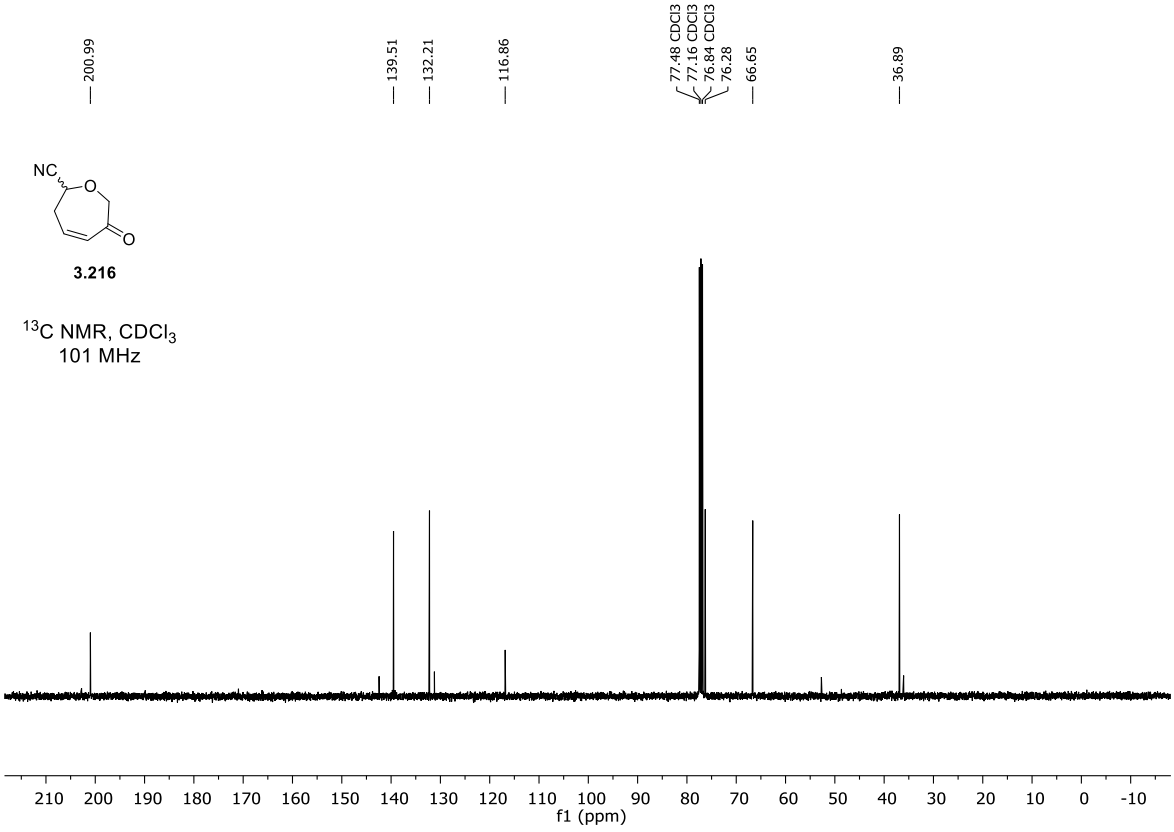

7.26 CDCl3
1.56 HDO
NC
O
OAc
3.210 less polar
1H NMR, CDCl3
400 MHz
2.0
1.0
1.0
1.1
1.1
2.0
3.1
f1 (ppm)

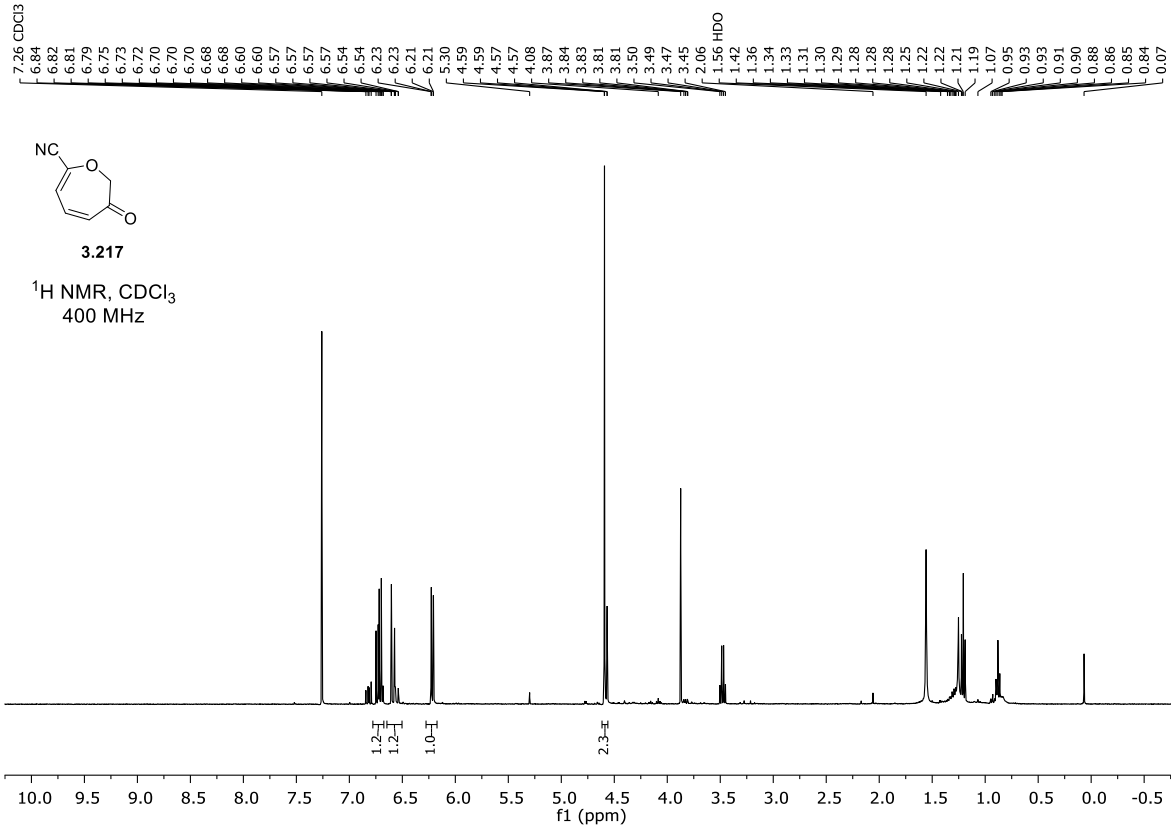

170.06
132.70
127.30
117.43
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
71.77
69.19
67.74
33.81
21.11
NC
O
OAc
3.210 less polar
13C NMR, CDCl3
101 MHz
f1 (ppm)

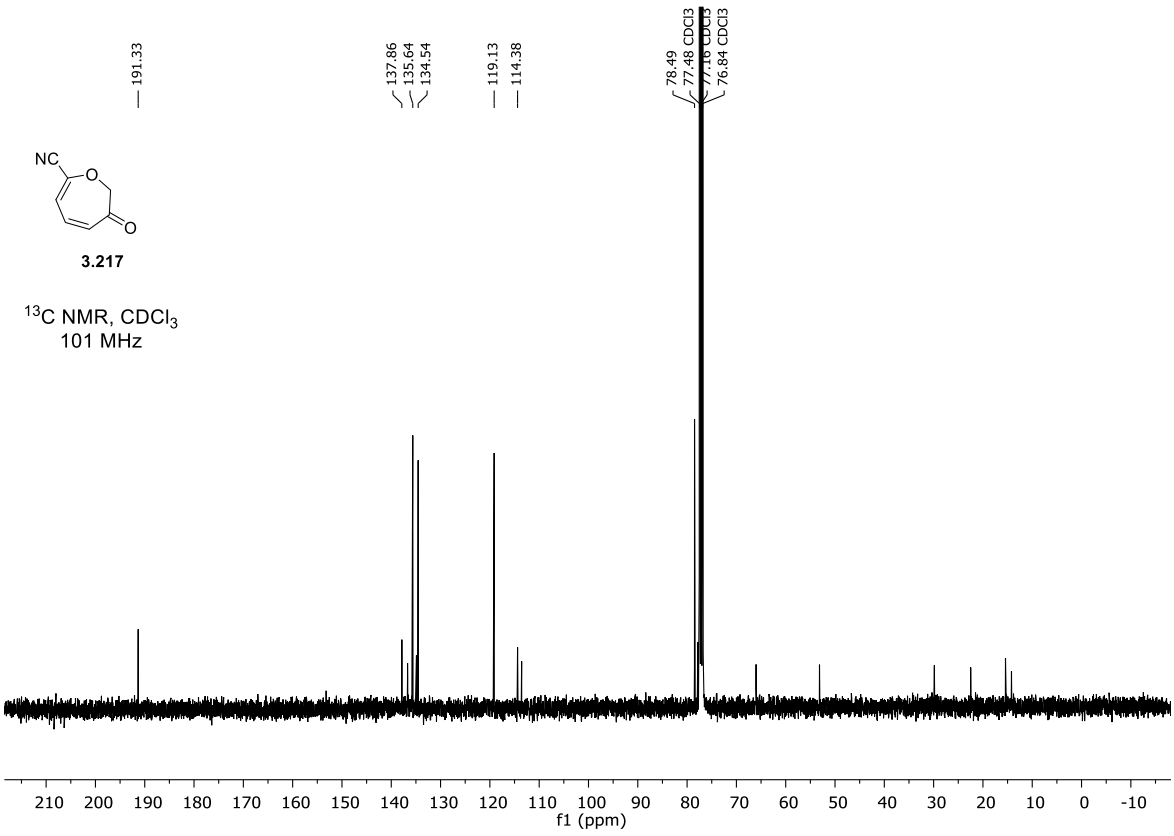

7.26 CDCl3
NC
O
OAc
3.210 more polar
1H NMR, CDCl3
400 MHz
1H NMR, CDCl3
400 MHz
1.0
1.3
1.1
1.1
1.0
1.1
2.3
3.1
f1 (ppm)

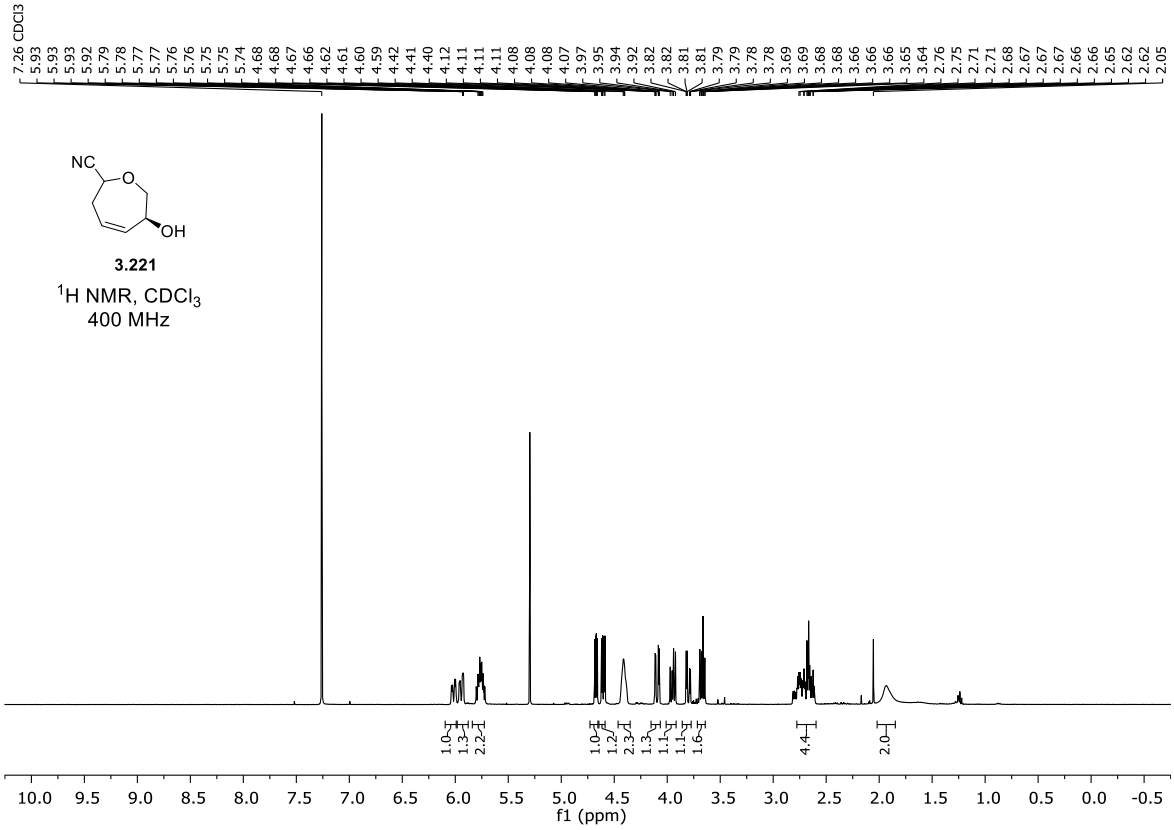

170.16
133.93
126.52
117.09
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
71.47
68.66
67.26
34.00
21.10
NC
O
OAc
3.210 more polar
13C NMR, CDCl3
101 MHz
f1 (ppm)

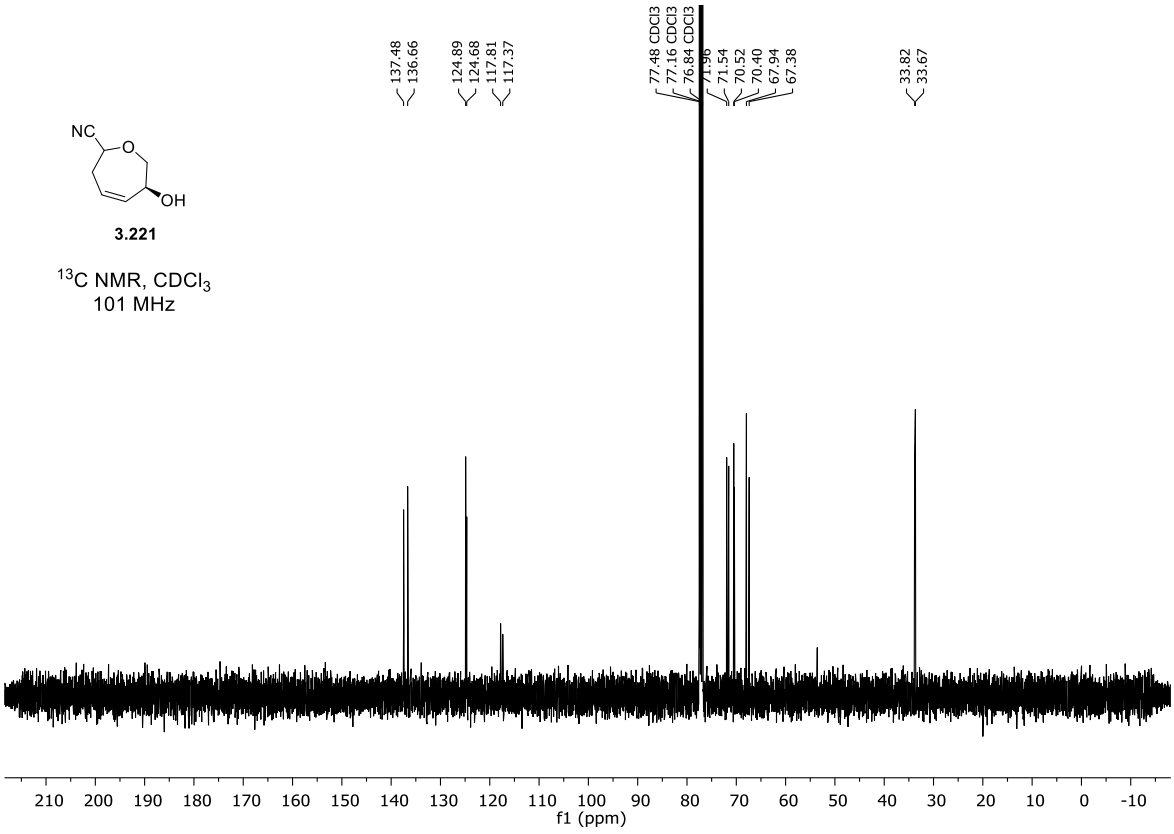

7.26 CDCl3
NC
O
O
3.216
1H NMR, CDCl3
400 MHz
1.0
1.0
0.9
1.0
1.1
0.9
1.2
f1 (ppm)

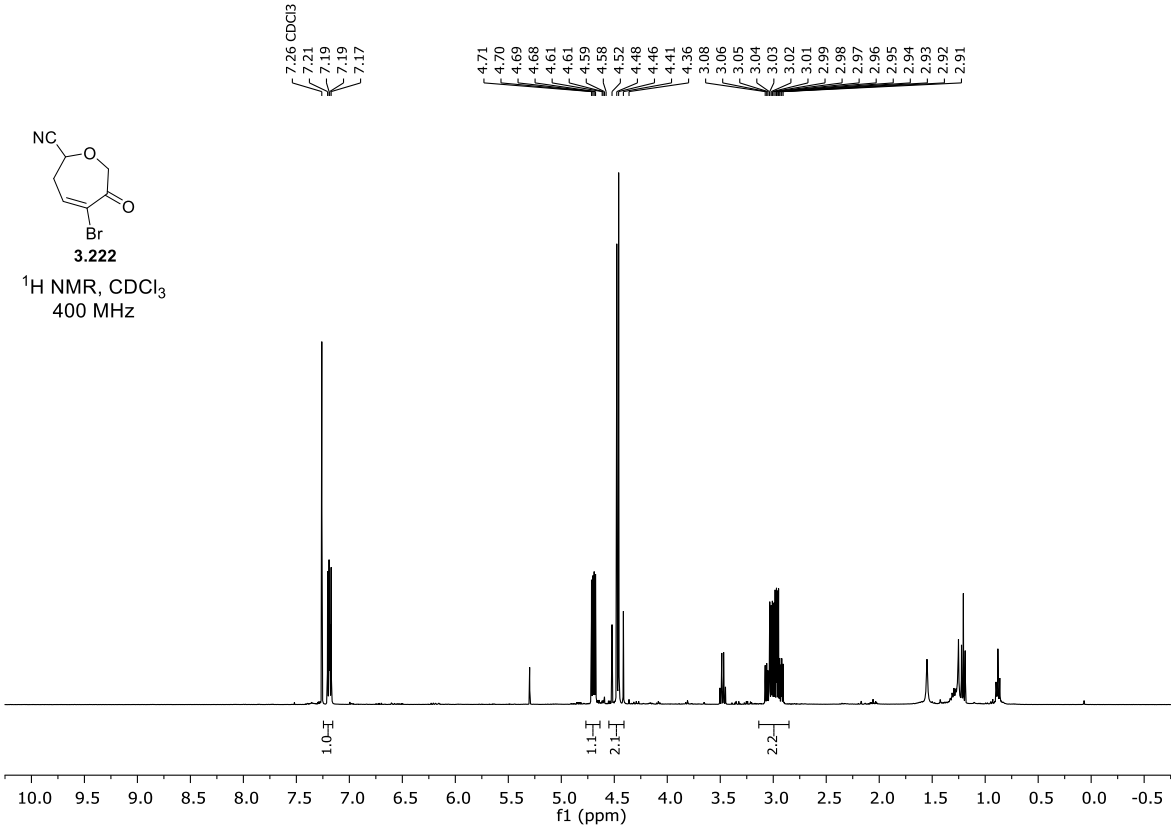

200.99
139.51
132.21
116.86
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
76.28
66.65
36.89
NC
O
O
3.216
13C NMR, CDCl3
101 MHz
f1 (ppm)

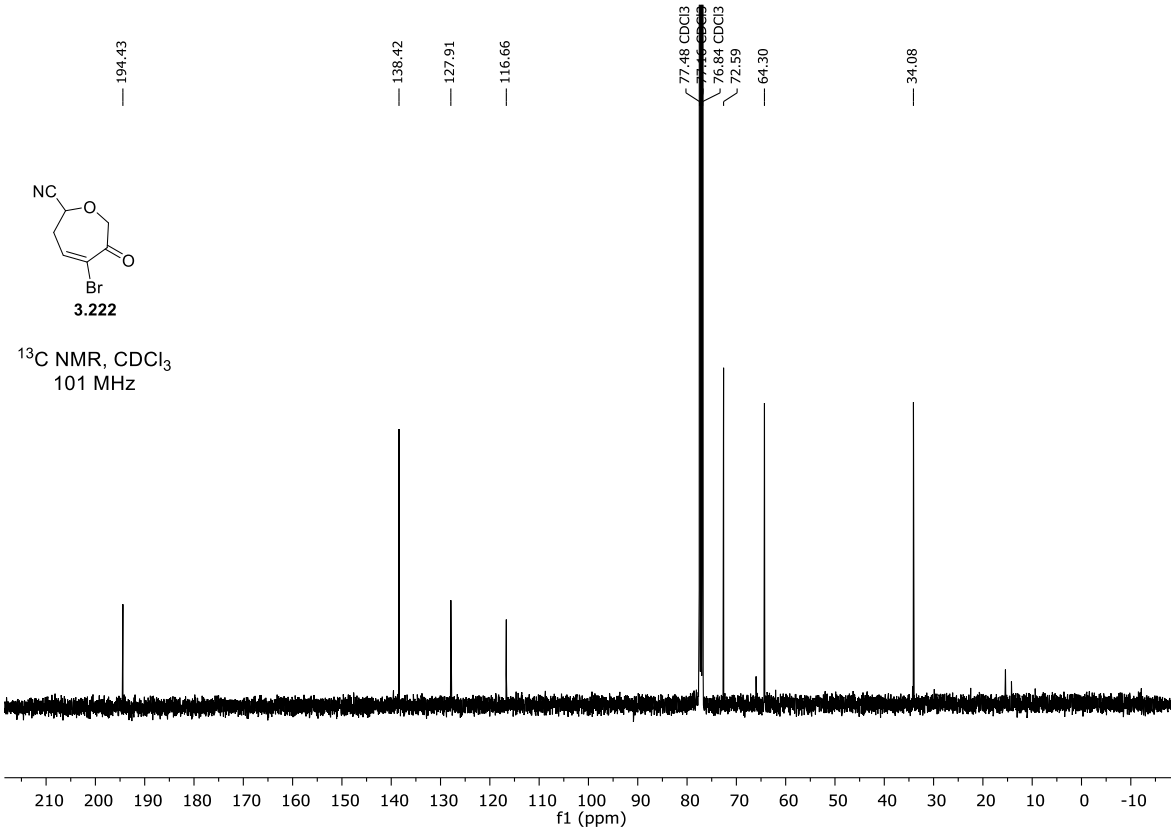

7.26 CDCl3
1.56 HDO
NC
O
O
3.217
1H NMR, CDCl3
400 MHz
1.2
1.2
1.0
2.3
f1 (ppm)

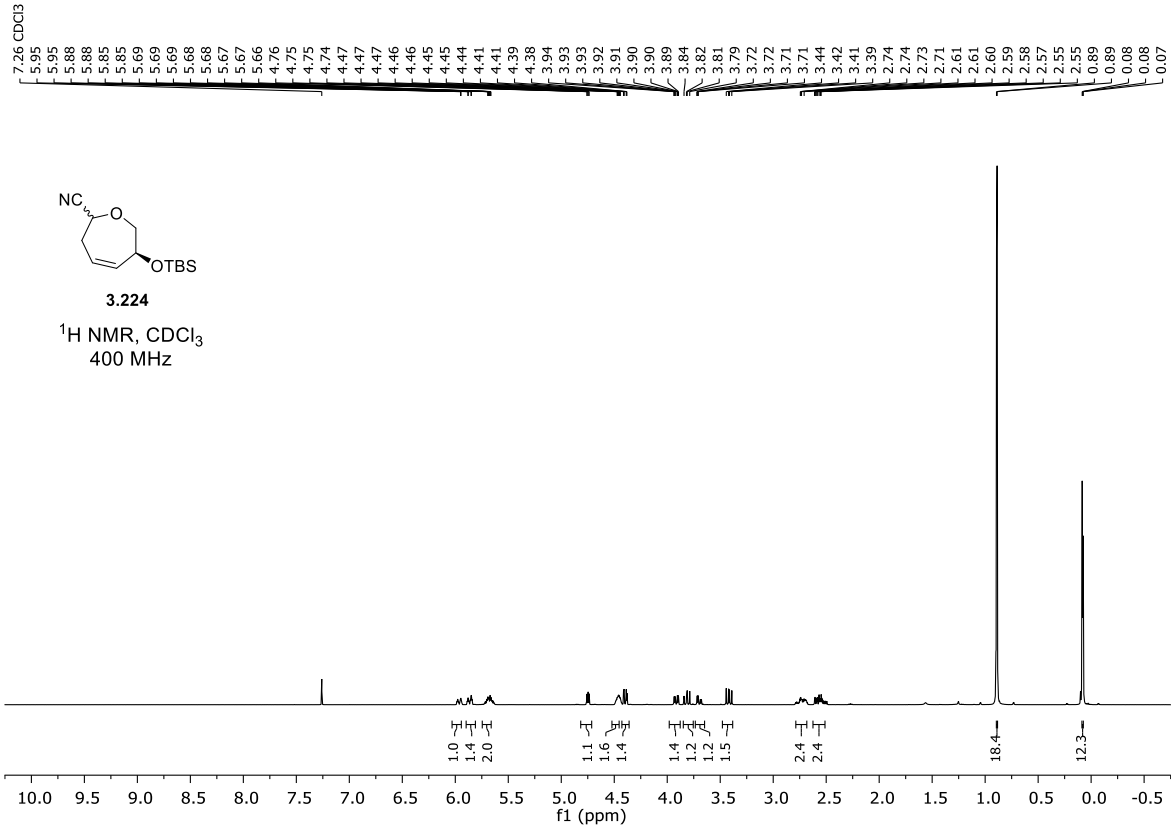

191.33
137.86
135.64
134.54
119.13
114.38
78.49
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
NC
O
O
3.217
13C NMR, CDCl3
101 MHz
f1 (ppm)

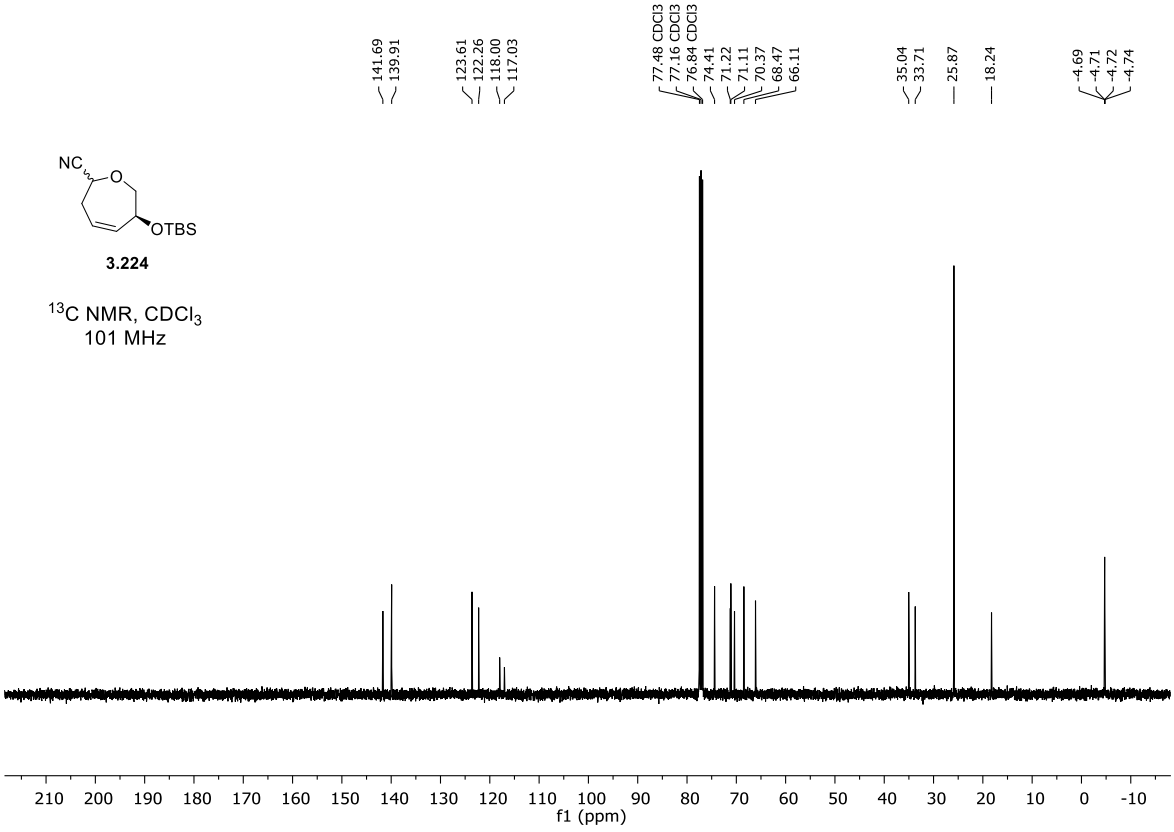

7.26 CDCl3
NC
O
OH
3.221
1H NMR, CDCl3
400 MHz
f1 (ppm)

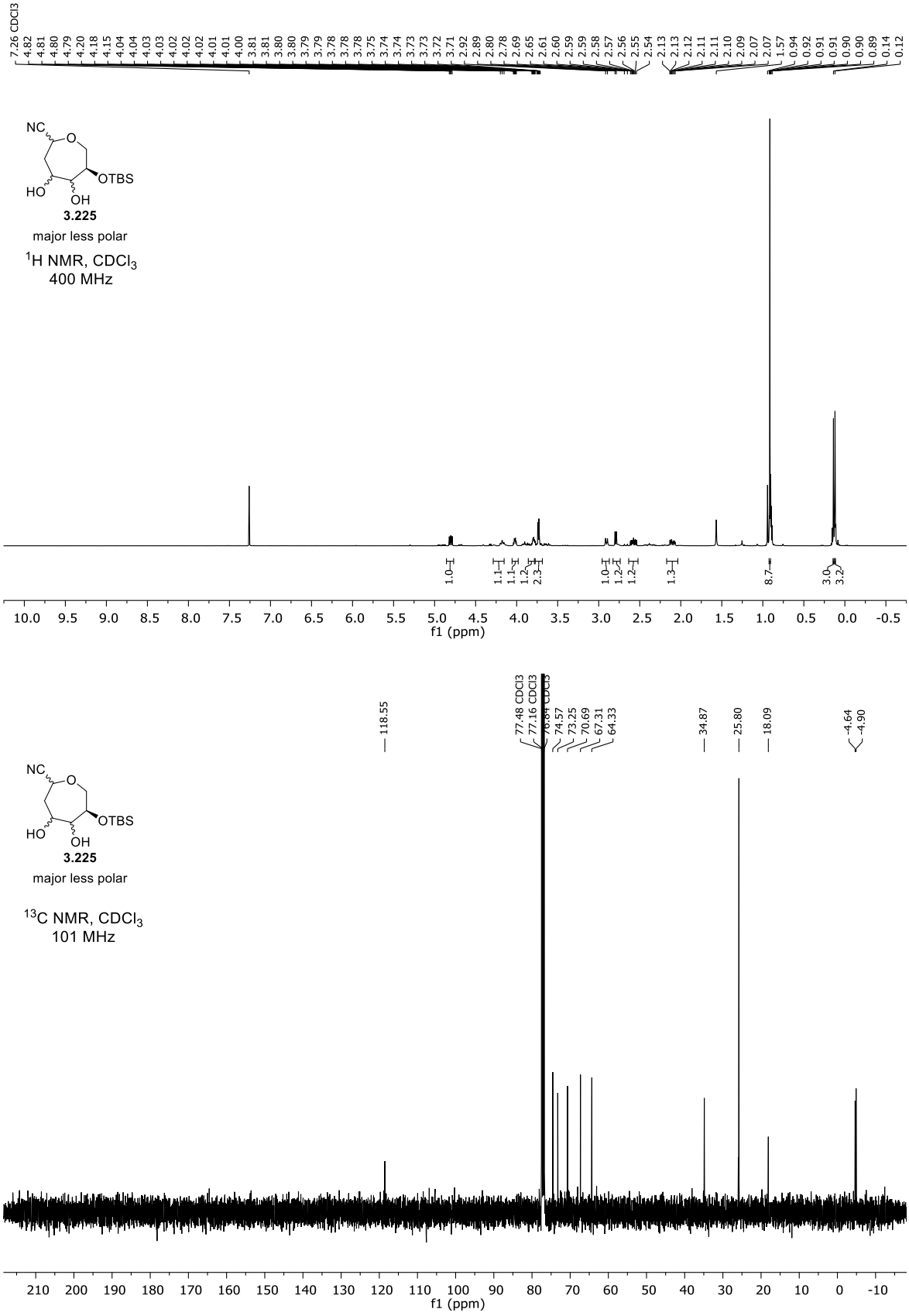

137.48
136.66
124.89
124.68
117.81
117.37
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
71.96
71.54
70.52
70.40
67.94
67.38
33.82
33.67
NC
O
OH
3.221
13C NMR, CDCl3
101 MHz
f1 (ppm)

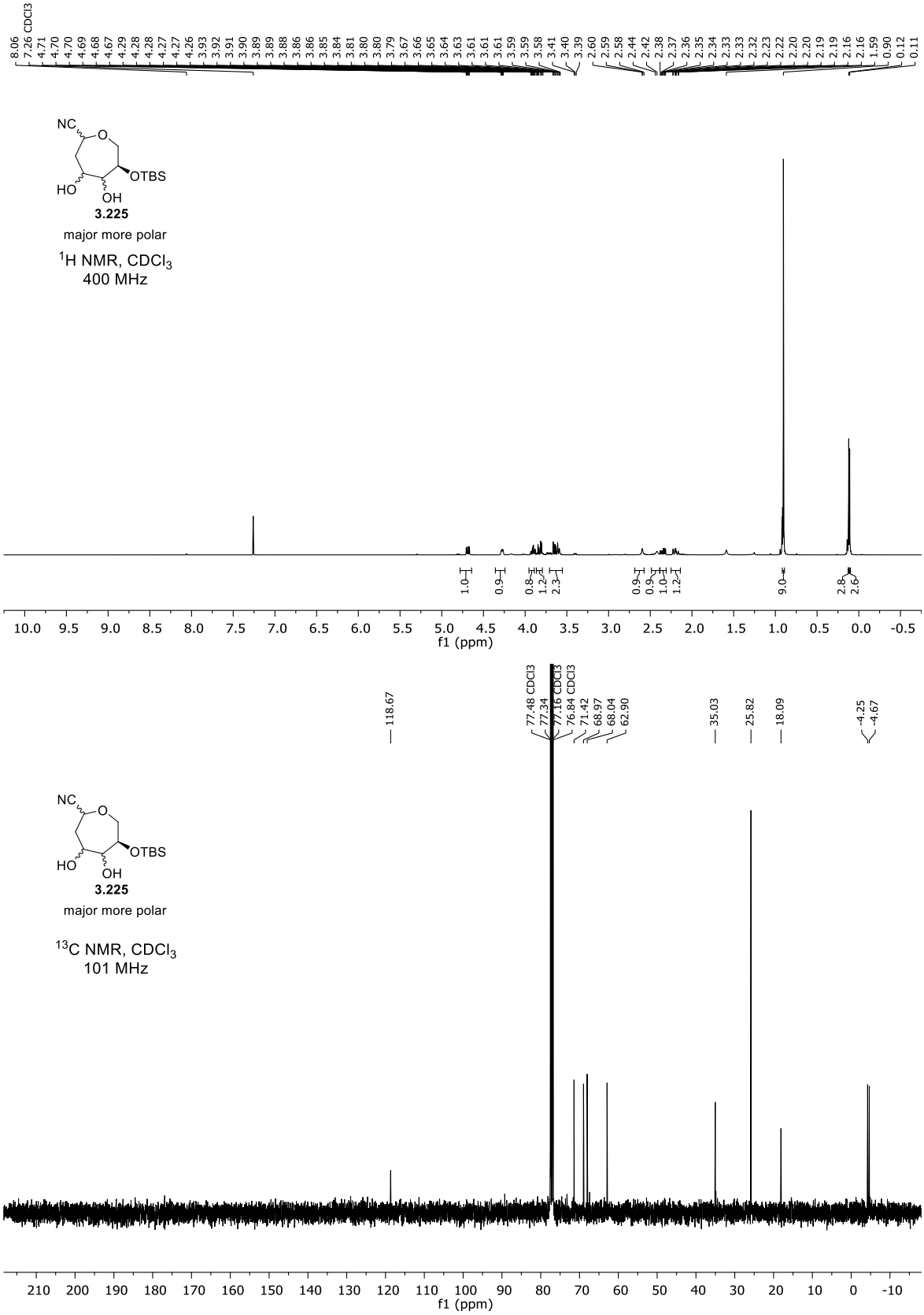

7.26 CDCl3
7.21
7.19
7.19
7.17
4.71
4.70
4.69
4.68
4.61
4.61
4.59
4.58
4.52
4.48
4.46
4.41
4.36
3.08
3.06
3.05
3.04
3.03
3.02
3.01
2.99
2.98
2.97
2.96
2.95
2.94
2.93
2.92
2.91
NC
O
O
Br
3.222
1H NMR, CDCl3
400 MHz
1.0
1.1
2.1
2.2
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

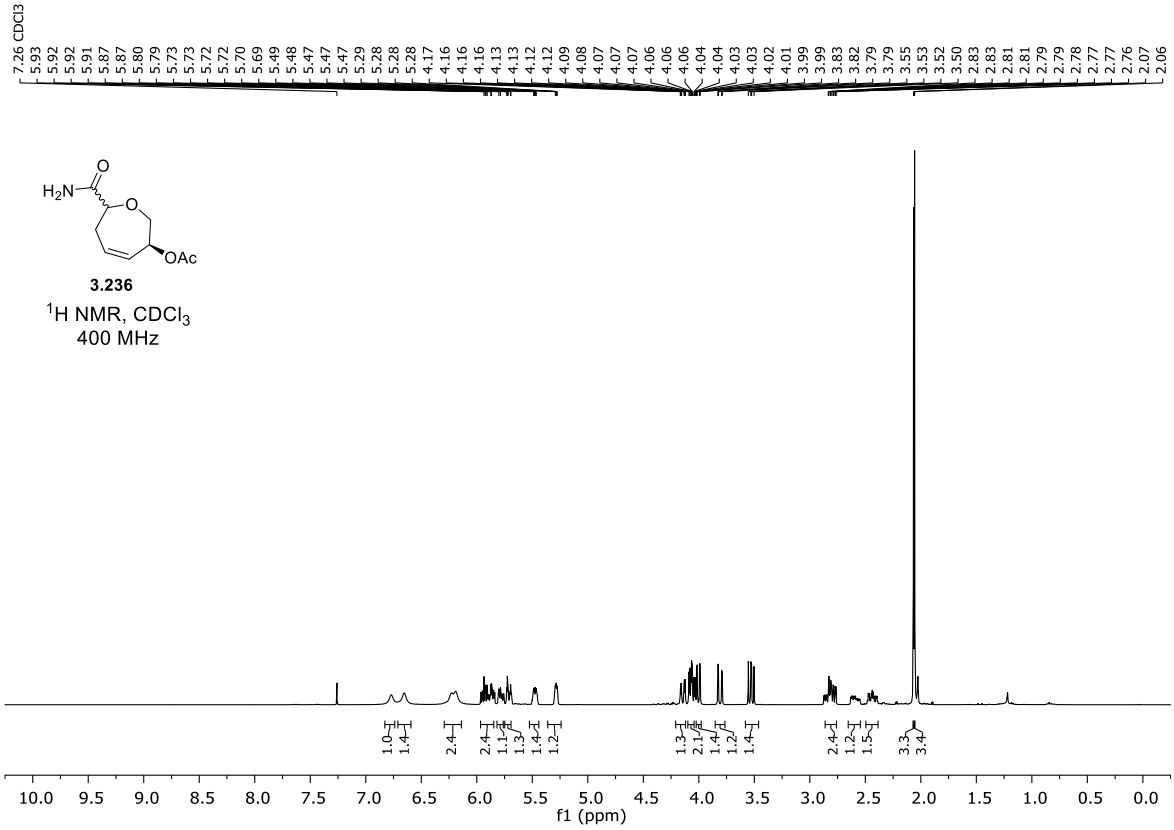

194.43
138.42
127.91
116.66
77.48 CDCl3
76.84 CDCl3
72.59
64.30
34.08
NC
O
O
Br
3.222
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

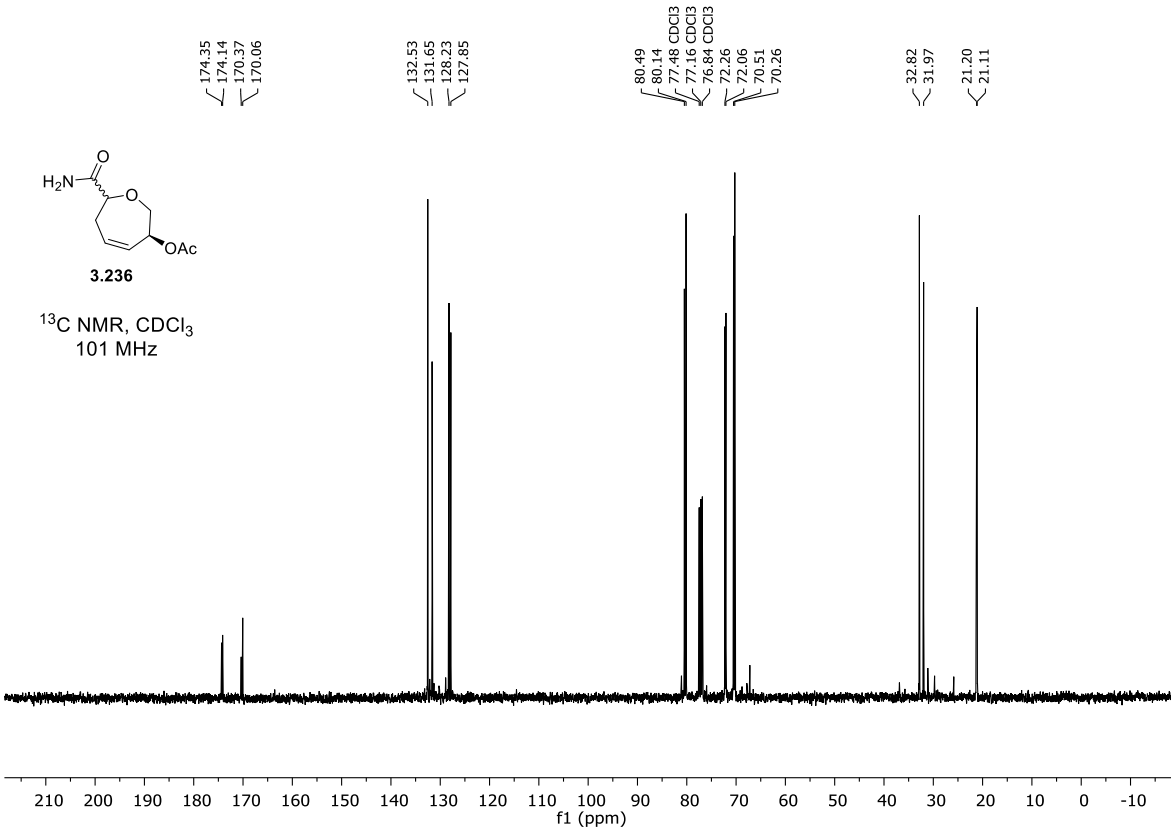

7.26 CDCl3
NC
O
OTBS
3.224
1H NMR, CDCl3
400 MHz
1.0
1.4
2.0
1.1
1.6
1.4
1.4
1.2
1.2
1.5
2.4
2.4
18.4
12.3
f1 (ppm)

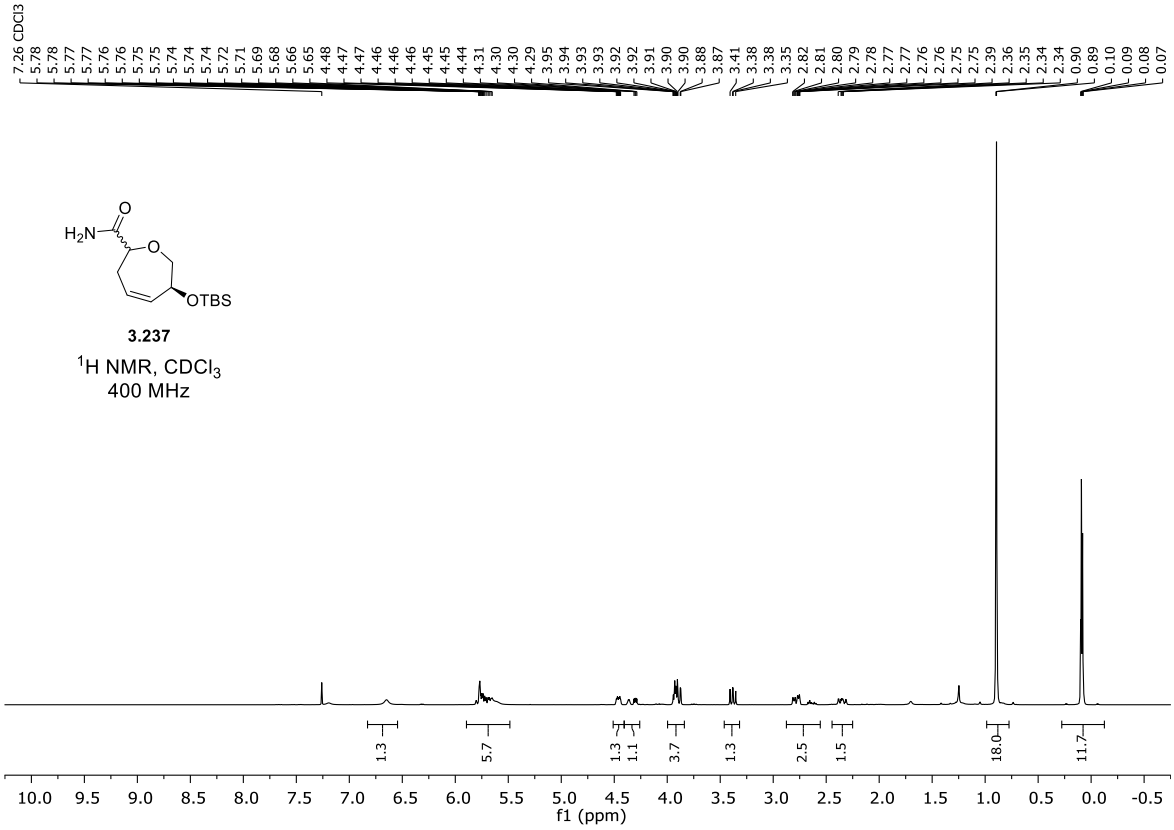

141.69
139.91
123.61
122.26
118.00
117.03
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
74.41
71.22
71.11
70.37
68.47
66.11
35.04
33.71
25.87
18.24
-4.69
-4.71
-4.72
-4.74
NC
O
OTBS
3.224
13C NMR, CDCl3
101 MHz
f1 (ppm)

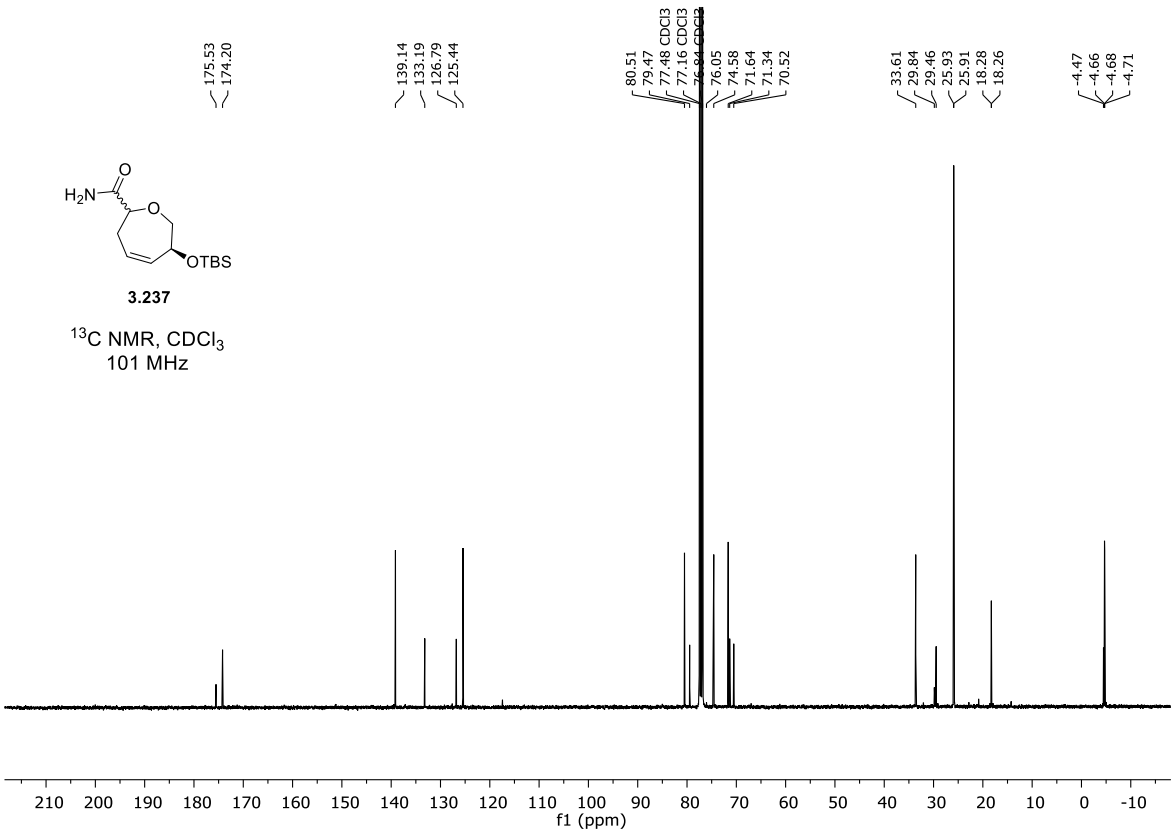

7.26 CDCl3
4.82 4.81 4.80 4.79 4.20 4.18 4.15 4.04 4.04 4.03 4.03 4.02 4.02 4.02 4.01 4.01 4.00 3.81 3.81 3.80 3.80 3.79 3.79 3.78 3.78 3.78 3.75 3.74 3.74 3.73 3.73 3.72 3.71 2.92 2.89 2.80 2.78 2.69 2.65 2.61 2.60 2.59 2.59 2.58 2.57 2.56 2.55 2.54 2.13 2.13 2.12 2.11 2.11 2.10 2.09 2.07 2.07 1.57 0.94 0.92 0.91 0.91 0.90 0.90 0.89 0.14 0.12
NC
O
OTBS
HO
OH
3.225
major less polar
1H NMR, CDCl3
400 MHz
1.0 1.1 1.1 1.2 2.3 1.0 1.2 1.2 1.3 8.7 3.0 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 -0.5
f1 (ppm)
118.55
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
74.57
73.25
70.69
67.31
64.33
34.87
25.80
18.09
-4.64
-4.90
NC
O
OTBS
HO
OH
3.225
major less polar
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)


8.06
7.26 CDCl3
4.71
4.70
4.70
4.69
4.68
4.67
4.29
4.28
4.28
4.27
4.27
4.26
3.93
3.92
3.91
3.90
3.89
3.89
3.88
3.86
3.86
3.85
3.84
3.81
3.80
3.80
3.79
3.67
3.66
3.65
3.64
3.63
3.61
3.61
3.61
3.59
3.59
3.58
3.41
3.40
3.39
2.60
2.59
2.58
2.44
2.42
2.38
2.37
2.36
2.35
2.34
2.33
2.32
2.23
2.22
2.20
2.20
2.19
2.19
2.16
2.16
1.59
0.90
0.12
0.11
NC
O
OTBS
HO
OH
3.225
major more polar
1H NMR, CDCl3
400 MHz
1.0
0.9
0.8
1.2
2.3
0.9
0.9
1.0
1.2
9.0
2.8
2.6
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 -0.5
f1 (ppm)
118.67
77.48 CDCl3
77.34
77.16 CDCl3
76.84 CDCl3
71.42
68.97
68.04
62.90
35.03
25.82
18.09
-4.25
-4.67
NC
O
OTBS
HO
OH
3.225
major more polar
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)


7.26 CDCl3
5.93 5.92 5.92 5.91 5.87 5.87 5.80 5.79 5.73 5.73 5.72 5.72 5.70 5.69 5.49 5.48 5.47 5.47 5.47 5.29 5.28 5.28 5.28 4.17 4.16 4.16 4.16 4.13 4.13 4.12 4.12 4.09 4.08 4.07 4.07 4.07 4.06 4.06 4.06 4.06 4.04 4.04 4.03 4.03 4.02 4.01 3.99 3.99 3.83 3.82 3.79 3.79 3.55 3.53 3.52 3.50 2.83 2.83 2.81 2.81 2.79 2.79 2.78 2.77 2.77 2.76 2.07 2.06
H2N
O
O
OAc
3.236
1H NMR, CDCl3
400 MHz
1.0 1.4 2.4 2.4 1.1 1.3 1.4 1.2 1.3 2.1 1.4 1.2 1.4 2.4 1.2 1.5 3.3 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)


174.35 174.14 170.37 170.06
132.53 131.65 128.23 127.85
80.49 80.14 77.48 CDCl3 77.16 CDCl3 76.84 CDCl3 72.26 72.06 70.51 70.26
32.82 31.97
21.20 21.11
H2N
O
O
OAc
3.236
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)


7.26 CDCl3
5.78 5.78 5.77 5.77 5.76 5.76 5.75 5.75 5.74 5.74 5.74 5.72 5.71 5.69 5.68 5.66 5.65 4.48 4.47 4.47 4.46 4.46 4.46 4.45 4.45 4.44 4.31 4.30 4.30 4.29 3.95 3.94 3.93 3.93 3.92 3.92 3.91 3.90 3.90 3.88 3.87 3.41 3.38 3.38 3.35 2.82 2.81 2.80 2.79 2.78 2.77 2.77 2.76 2.76 2.75 2.75 2.39 2.36 2.35 2.34 2.34 0.90 0.89 0.10 0.09 0.08 0.07
H2N
O
O
OTBS
3.237
1H NMR, CDCl3
400 MHz
1.3
5.7
1.3
1.1
3.7
1.3
2.5
1.5
18.0
11.7
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 -0.5
f1 (ppm)


175.53
174.20
139.14
133.19
126.79
125.44
80.51
79.47
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
76.05
74.58
71.64
71.34
70.52
33.61
29.84
29.46
25.93
25.91
18.28
18.26
-4.47
-4.66
-4.68
-4.71
H2N
O
O
OTBS
3.237
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)

9.2.1.3 X-ray

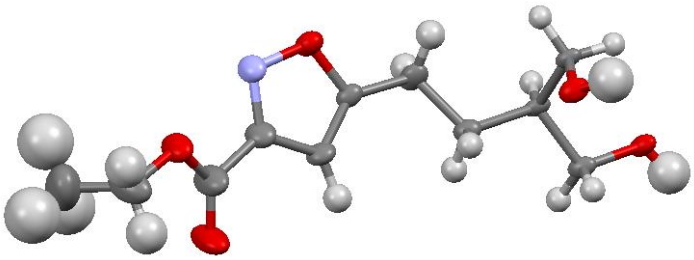


Table 1. Crystal data and structure refinement for diol **3.71**.

Empirical formula	$C_{11}H_{17}NO_5$
Formula weight	243.25
Temperature	100.(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	'P 1 21/c 1'
Unit cell dimensions	a = 21.183(2) Å α= 90°.
	b = 4.8334(5) Å β= 90.932(4)°.
	c = 11.5364(12) Å γ = 90°.
Volume	1181.0(2) $Å^3$
Z	4
Density (calculated)	1.368 Mg/m^3
Absorption coefficient	9.735 mm^{-1}
F(000)	192
Crystal size	0.100 × 0.080 × 0.020 mm^3
Theta range for data collection	3.533–25.026°.
Index ranges	-9<=h<=9, -10<=k<=10, -14<=l<=14

Reflections collected	7700
Independent reflections	22069 [R(int) = 0.0346]
Completeness to theta =	25.242° 100.0 %
Absorption correction	Multi-Scan
Max. and min. transmission	0.850 and 0.971
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1720 / 25 / 192
Goodness-of-fit on F^2	0.1566
Final R indices [I>2sigma(I)]	R1 = 0.01566, wR2 = 0.0450
R indices (all data)	R1 = 0.0685, wR2 = 0.0464
Extinction coefficient	0.001
Largest diff. peak and hole	0.412 and -0.214 e.$Å^{-3}$

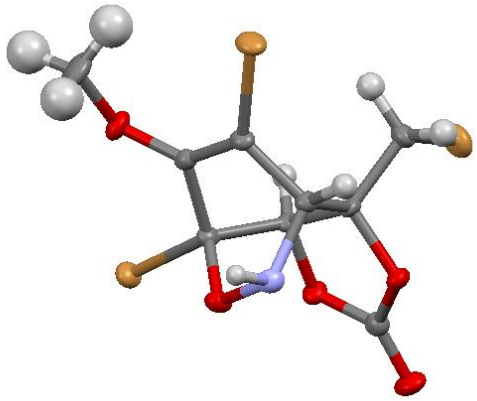


Table 2. Crystal data and structure refinement for carbonate **3.193**.

Empirical formula	$C_9H_8Br_3NO_5$
Formula weight	449.89
Temperature	183(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1 (no. 2)
Unit cell dimensions	a = 7.4190(6) Å α= 69.739(2)°.
	b = 8.2699(7) Å β= 71.601(2)°.
	c = 11.4278(9) Å γ = 79.748(2)°.
Volume	622.28(9) $Å^3$
Z	2
Density (calculated)	2.401 Mg/m^3
Absorption coefficient	9.735 mm^{-1}
F(000)	428
Crystal size	0.080 x 0.060 x 0.040 mm^3
Theta range for data collection	2.633 to 26.088°.
Index ranges	-9<=h<=9, -10<=k<=10, -14<=l<=14

Reflections collected	17066
Independent reflections	2476 [R(int) = 0.0346]
Completeness to theta =	25.242° 100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.724 and 0.527
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2476 / 1 / 168
Goodness-of-fit on F^2	1.035
Final R indices [I>2sigma(I)]	R1 = 0.0195, wR2 = 0.0450
R indices (all data)	R1 = 0.0232, wR2 = 0.0464
Extinction coefficient	0.0085(6)
Largest diff. peak and hole	0.658 and -0.462 e.$Å^{-3}$

9.2.2 Supporting Information for Chapter II

9.2.2.1 General procedures

General Procedure 1 – Aldol condensation

To a solution of aldehyde (1 equiv) in ethanol (1.0 M) was added methylketone (1.00–1.50 equiv) and finely grinded barium hydroxide monohydrate (0.15 equiv, prepared by drying barium hydroxide octahydrate at 200 °C for 3 h) and the suspension was heated at 90 °C. After full conversion of the aldehyde as judged by thin layer chromatography (2–4 h), the colored reaction mixture (often yellowish-orange-red) was allowed to cool to 23 °C, concentrated under reduced pressure, diluted with ethyl acetate/diethylether and filtered over a pad of Celite®. The filtrate was concentrated under reduced pressure to give crude enone, which was used in the next step without further purification.

General Procedure 2 – Enone reduction

a) H_2/Pd

To a solution of crude enone (1 equiv) in ethyl acetate (0.1 M) was added palladium on charcoal (10% palladium on activated charcoal, 1.0–10 mol% Pd) and the resulting black suspension was sparged with hydrogen gas for 20 min. Stirring under hydrogen atmosphere was continued until full conversion as judged by thin layer chromatography. After 2–16 h Celite® was added and the mixture was filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel to yield the saturated ketone.

b) Mg/MeOH

To solution of crude enone in methanol (0.2 M) were added magnesium turnings (2–4 equiv) at (–30 – +23 °C). The suspension was stirred in a water or cooling bath until most metal was dissolved. Conversion was controlled by thin layer chromatography. If necessary, more magnesium turnings were added. Upon full conversion, the reaction was warmed up to ambient temperature and neutralized by addition of saturated aqueous ammonium chloride solution. The mixture was extracted with ethyl acetate (3×). The organic phases were combined, washes with saturated aqueous sodium chloride solution, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel to afford the saturated ketone.

General Procedure 3 – Corey–Chaykovsky epoxidation

A suspension of sodium hydride (60% in mineral oil, 1.50–2.00 equiv) in dimethyl sulfoxide (1.00 M) was heated to 70 °C for 1.5 h (Attention: strong hydrogen evolution!) until a clear solution was formed (sometimes greenish). The basic solution was allowed to cool down to 23 °C and diluted 1:1 with tetrahydrofuran. After cooling the solution to 0 °C, a solution of trimethylsulfonium iodide (1.50–2.00 equiv, 1.0 M in dimethyl sulfoxide) was added dropwise. After 5 min, a solution of the ketone (1 equiv, 1.0 M in tetrahydrofuran) was added dropwise at 0 °C and the resulting reaction mixture was allowed to warm up to 23 °C. After 3 h, the mixture was diluted 3:1 with diethylether and excess base was quenched by addition of water. The aqueous layer was extracted with diethylether (3×), washed with water and twice with concentrated aqueous sodium chloride solution. The solution was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography on silica gel.

General Procedure 4 – Phenol alkylation

In a pressure tube was added potassium carbonate (1.10 equiv) and α-bromo ketone (1.00 equiv) to a solution of phenol (1 equiv, 0.10 M in acetone). The resulting mixture was heated at 70 °C for 16 h. The resulting reaction mixture was concentrated under reduced pressure and diluted with ethyl acetate and water. The aqueous phase was extracted with ethyl acetate (3×) and the combined organic layers were dried with sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford crude phenyl alkyl ether. The crude product was purified by flash column chromatography on silica gel to give the desired compound.

General procedure 5 – Cycloisomerization

To a solution of epoxide (0.200 mmol, 1 equiv) in hexafluoroisopropanol (4 mL, 0.05 M) was added a solution of sulfuric acid in hexafluoroisopropanol (0.040 mL, 0.500 M, 10 mol%) at 0 °C under vigorous stirring. After 15 min, potassium carbonate (1 equiv) was added and the mixture was stirred for further 5 min before the mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel. (Note: The solvent is prone for strong foaming during evaporation!).

9.2.2.2 Optimization of key step

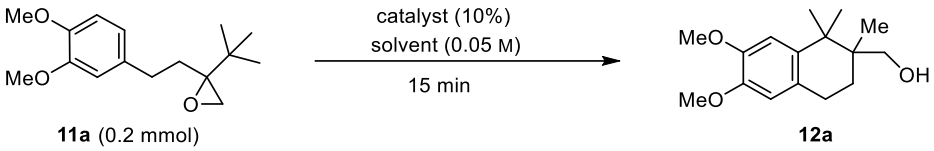


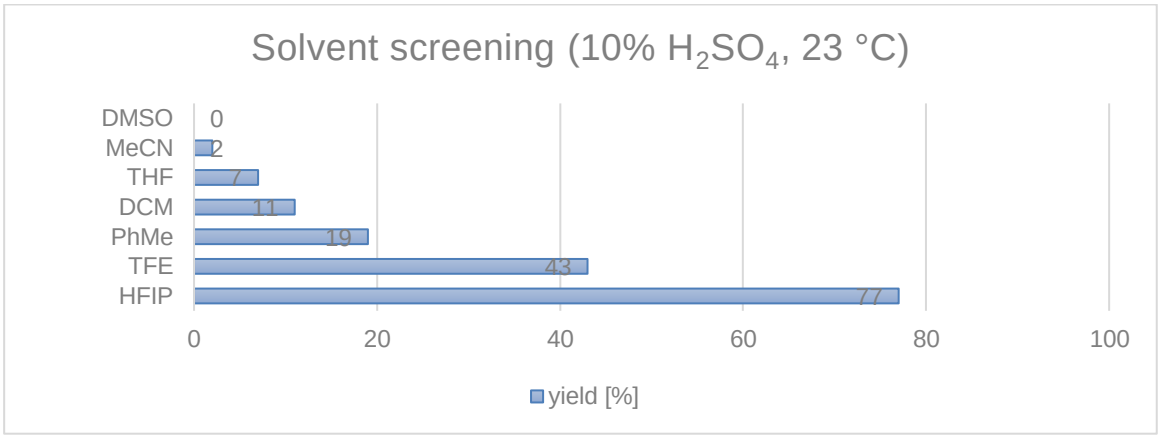
Table S16: Optimization of reaction conditions for conversion of **11a** to **12a**

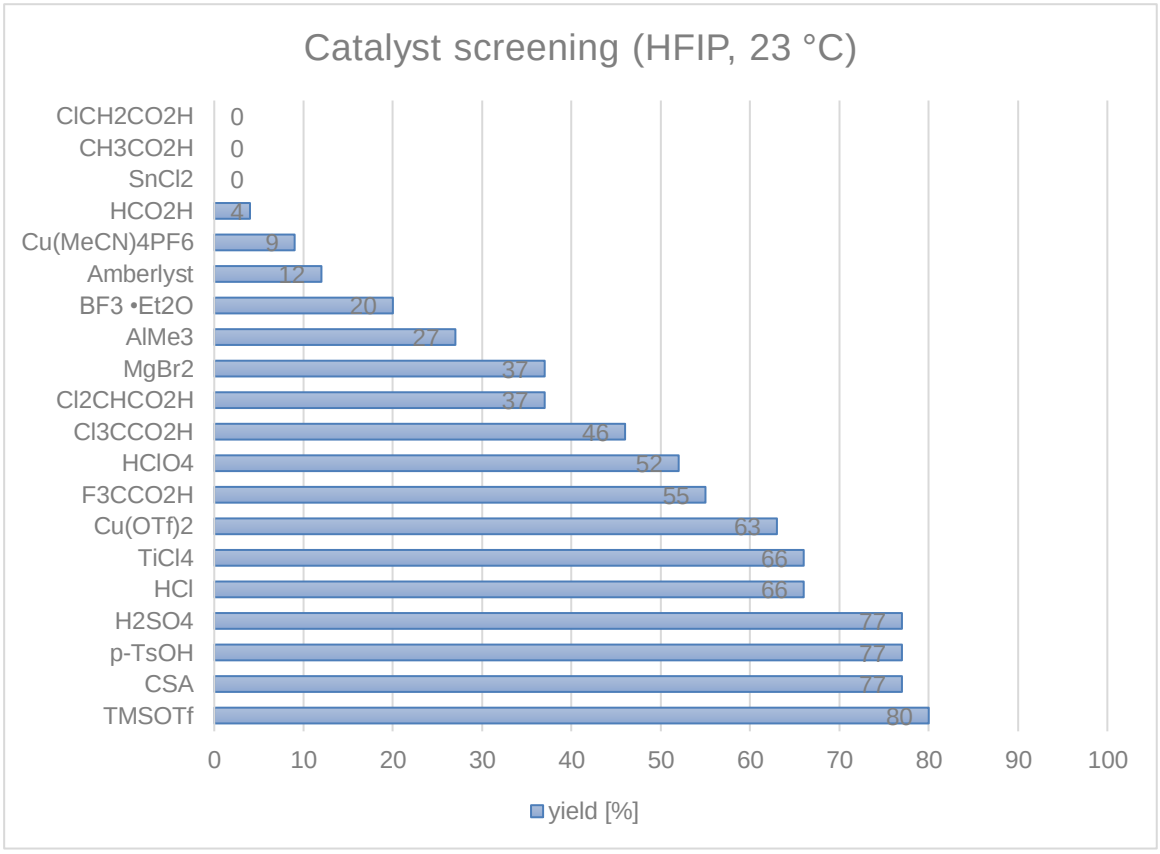
Entry	solvent	catalyst	temperature	yield [%]*	comments
1	HFIP	H_2SO_4	23 °C	77	
2	TFE	H_2SO_4	23 °C	43	
3	MeCN	H_2SO_4	23 °C	2	
4	PhMe	H_2SO_4	23 °C	19	emulsion
5	THF	H_2SO_4	23 °C	7	
6	DCM	H_2SO_4	23 °C	11	
7	DMSO	H_2SO_4	23 °C	n.d.	
8	HFIP	CSA	23 °C	77	
9	HFIP	*p*-TsOH	23 °C	77	
10	HFIP	Amberlyst® 15	23 °C	12	slow conversion
11	HFIP	$HClO_4$ (60%)	23 °C	52	
12	HFIP	HCl (37%)	23 °C	66	
13	HFIP	CH_3CO_2H	23 °C	0	
14	HFIP	HCO_2H	23 °C	4	
15	HFIP	$ClCH_2CO_2H$	23 °C	0	
16	HFIP	Cl_2CHCO_2H	23 °C	37	
17	HFIP	Cl_3CCO_2H	23 °C	46	
18	HFIP	F_3CCO_2H	23 °C	55	
19	HFIP	$Cu(OTf)_2$	23 °C	63	

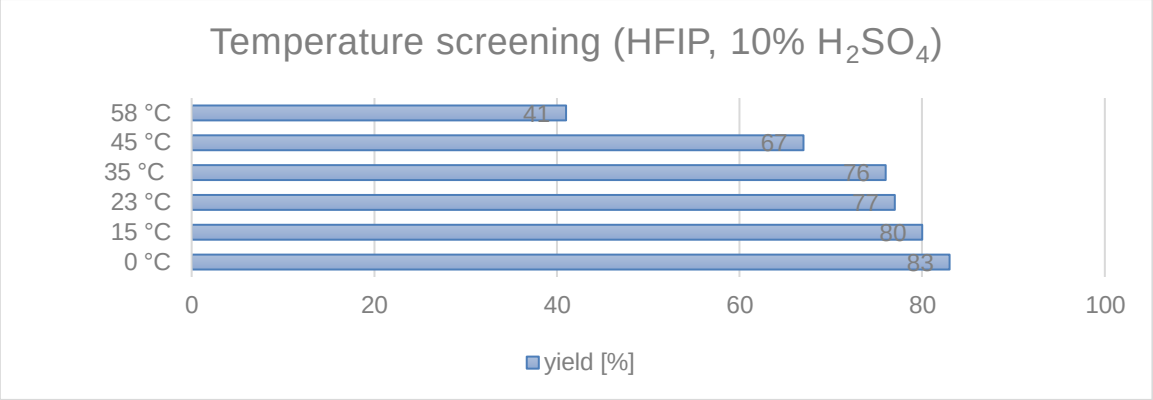
20	HFIP	$TiCl_4$	23 °C	66	
21	HFIP	$BF_3 \bullet Et_2O$	23 °C	20	
22	HFIP	$AlMe_3$	23 °C	27	
23	HFIP	$SnCl_2$	23 °C	n.d.	
24	HFIP	$MgBr_2$	23 °C	37	poor solubility of catalyst
25	HFIP	$Cu(MeCN)_4PF_6$	23 °C	9	
26	HFIP	TMSOTf	23 °C	80	copolar byproduct
27	HFIP	H_2SO_4	58 °C	41	
28	HFIP	H_2SO_4	45 °C	67	
29	HFIP	H_2SO_4	35 °C	76	
30	HFIP	H_2SO_4	15 °C	80	
31	HFIP	H_2SO_4	0 °C	83	

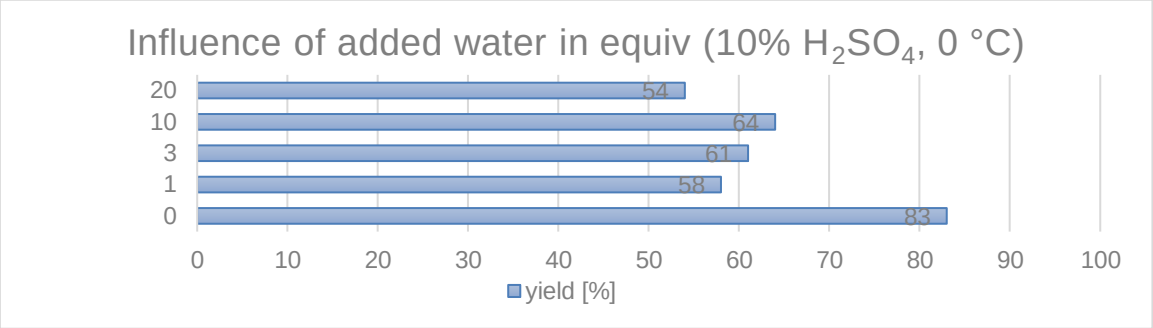
*yield determined by ^{1}H-NMR using 2,3,5,6-tetrachloronitrobenzene as internal standard. HFIP = 1,1,1,3,3,3-hexafluoroisopropanol, TFE = 1,1,1-trifluoroethanol, THF = tetrahydrofuran, DCM = dichloromethane, DMSO = dimethyl sulfoxide, CSA = camphorsulfonic acid.

9.2.2.3 Graphical yield representation of screening

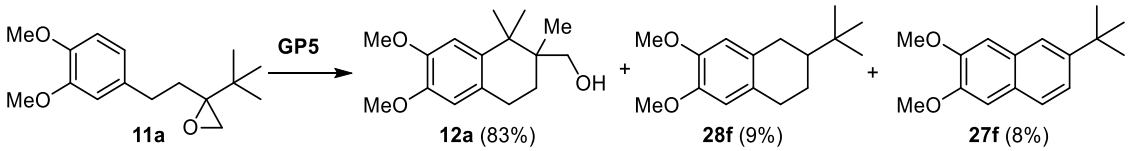








9.2.2.4 Full analysis of byproduct formation for 11a under optimized conditions



(6,7-dimethoxy-1,1,2-trimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (**12a**) was prepared according to **GP5** from **11a** (0.200 mmol, 1 equiv) in 80% yield as a colorless oil (42.4 mg). Flash column chromatography on silica gel (20% ethyl acetate in cyclohexane). All less polar fractions were collected, combined and purified by high pressure liquid chromatography on silica gel (1% ethyl acetate in hexane) to afford tetralin **28f** (4.2 mg, 9%) and naphthalene **27f** (3.9 mg, 8%) as both colorless solids.

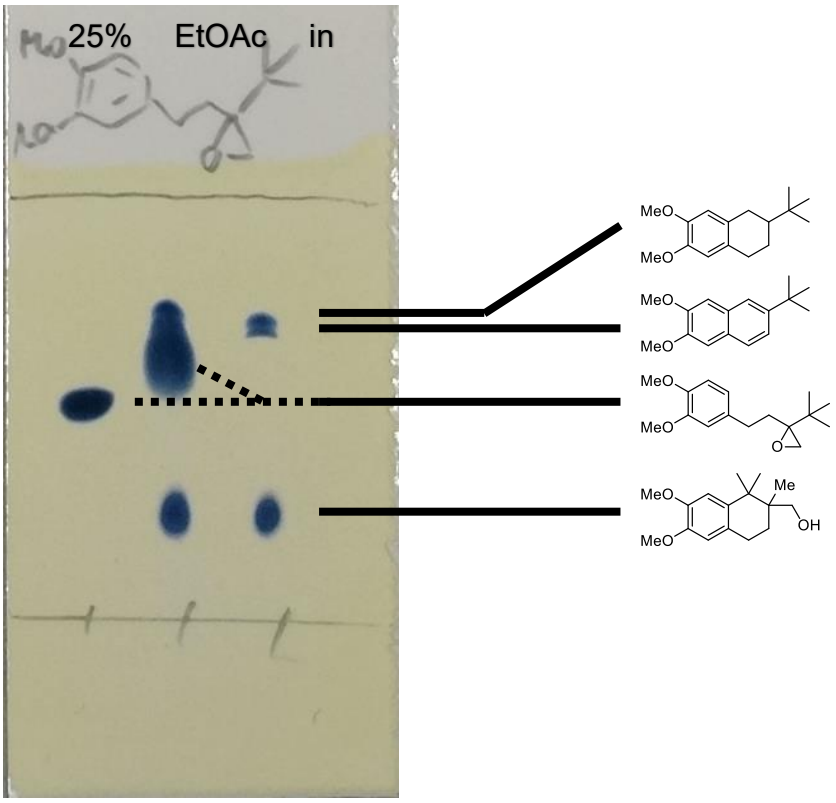
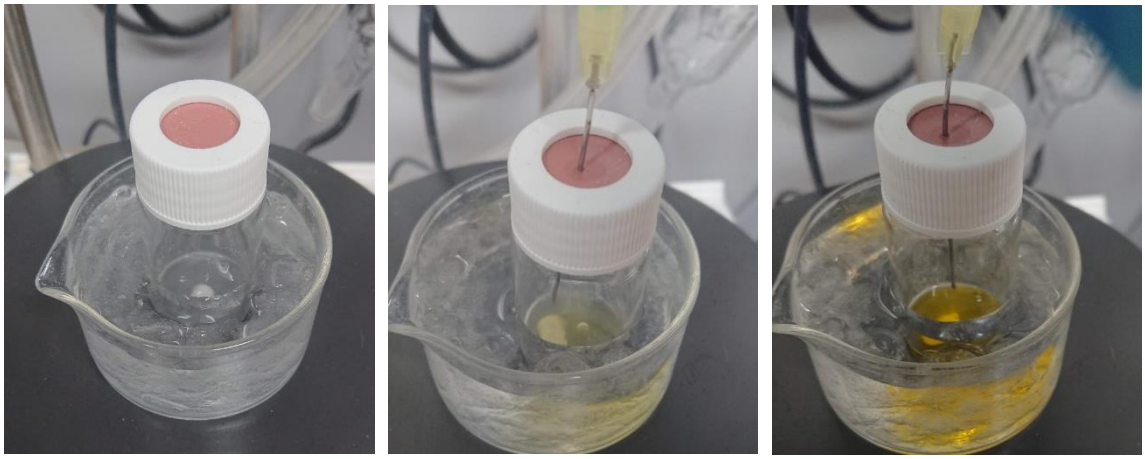
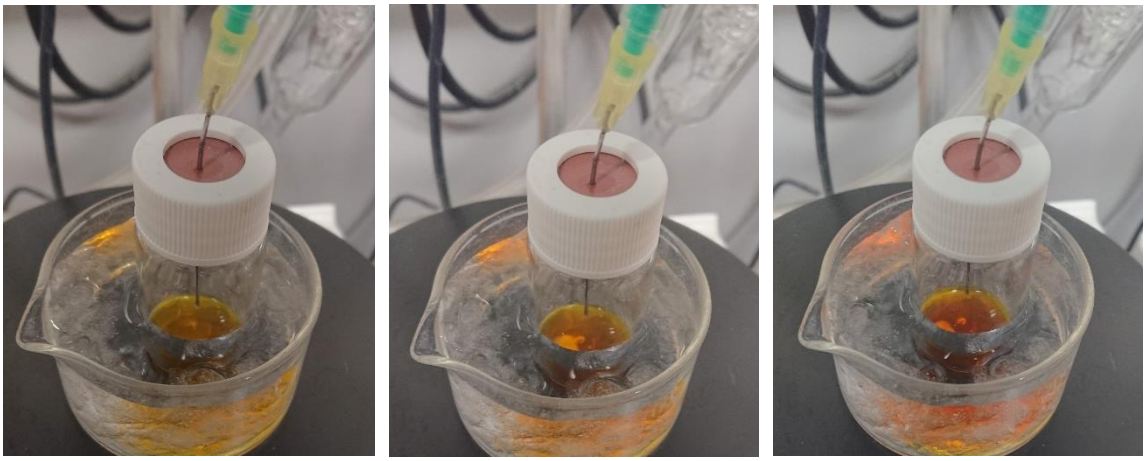


Figure S12: Thin layer chromatography on silica gel of crude reaction mixture after 10 minutes (mobile phase: 25% ethyl acetate in cyclohexane). Note: R_f values distorted due to direct spotting from HFIP solution. Visualized by staining with ceric ammonium molybdate and subsequent heating.

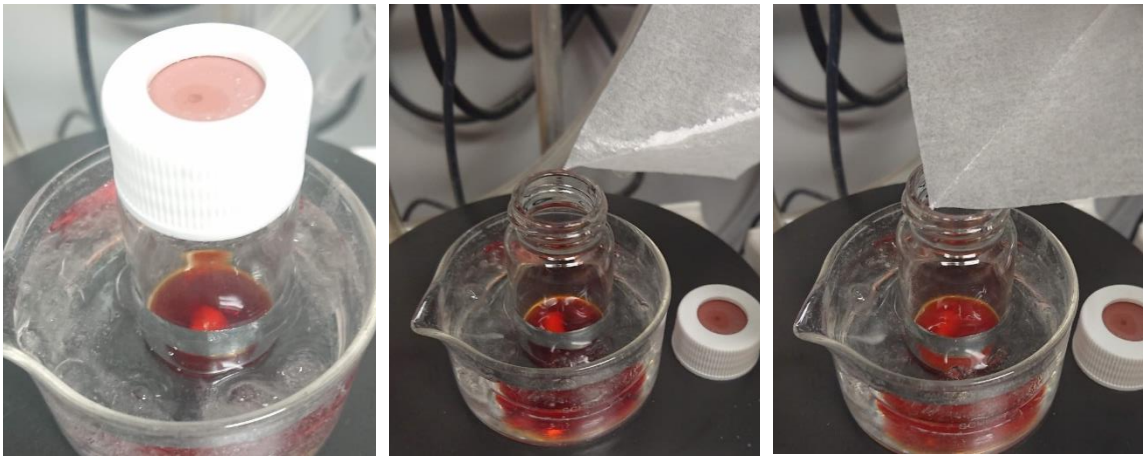
9.2.2.5 Pictural guide of reaction of substrate 11a.



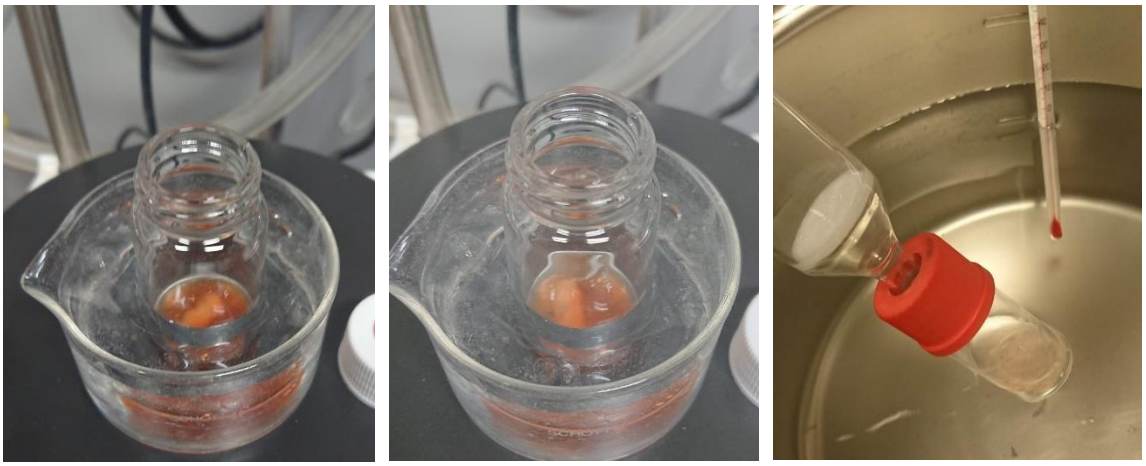
Left: **11a** dissolved in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) at 0 °C. **Center**: Color change after first drop of added sulfuric acid solution. **Right**: Intensive coloring after addition of second drop.



Left: Color change to orange during addition of approximately 20 µL sulfuric acid solution. **Center**: Color change after addition of approximately 30 µL. **Right**: Color after complete addition (40 µL)



Left: Color of reaction mixture after 10 min, reaction control by TLC. **Center**: Addition of potassium carbonate after full conversion (15 min). **Right**: Color after complete addition of potassium carbonate



Right: Color of reaction mixture after 1 min stirring with potassium carbonate. **Center**: Color after stirring with potassium carbonate for 5 min. **Right**: Removal of solvent (42 °C, 400 mbar) – color fades almost entirely to become a colorless to pale yellow oil (solid salts at the bottom)

(6,7-dimethoxy-1,1,2-trimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (**12a**):

TLC (25% ethyl acetate in hexanes): R_f: 0.21 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (s, 1H), 6.51 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.56 (d, *J* = 10.9 Hz, 1H), 3.53 (d, *J* = 10.9 Hz, 1H), 2.80 – 2.64 (m, 2H), 1.80 (dt, *J* = 13.6, 6.2 Hz, 1H), 1.71 (ddd, *J* = 13.5, 8.3, 6.5 Hz, 1H), 1.50 (s, 1H), 1.23 (s, 3H), 1.20 (s, 3H), 0.98 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4, 146.9, 137.9, 127.6, 111.2, 110.1, 67.4, 56.2, 55.8, 39.1, 39.0, 27.8, 27.4, 25.9, 25.4, 19.0.

IR (ATR, neat) $\tilde{\nu}_{max}$ 3506 (br *m*), 2965 (*s*), 2934 (*s*), 2848 (*w*), 1610 (*m*), 1508 (*s*), 1462 (*s*), 1400 (*m*), 1363 (*w*), 1352 (*w*), 1327 (*w*), 1250 (*s*), 1206 (*s*), 1185 (*w*), 1156 (*s*), 1137 (*s*), 1105 (*w*), 1074 (*s*), 1023 (*s*), 975 (*m*), 911 (*m*), 857 (*s*), 832 (*m*), 794 (*m*), 730 (*s*), 646 (*w*), 571 (*w*), 543 (*w*), 489 (*w*), 439 (*w*).

HRMS (ESI) calcd for $C_{16}H_{25}O_3$ $[M+H]^+$: 265.1798; found: 265.1789

2-(*tert*-butyl)-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene (**28f**):

TLC (5% ethyl acetate in cyclohexane): R_f: 0.12 (UV, CAM)

mp: 100.8 -103.1 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (s, 1H), 6.58 (s, 1H), 3.84 (s, 6H), 2.84 – 2.63 (m, 3H), 2.56 – 2.42 (m, 1H), 1.98 (ddq, *J* = 12.2, 4.8, 2.3 Hz, 1H), 1.43 (tdd, *J* = 12.0, 4.9, 2.1 Hz, 1H), 1.36 – 1.24 (m, 1H), 0.94 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1, 147.0, 129.4, 128.9, 112.3, 111.6, 56.1, 56.0, 45.1, 32.6, 30.7, 30.4, 27.4, 24.9.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2954 (*s*), 1609 (*w*), 1517 (*s*), 1464 (*m*), 1394 (*w*), 1364 (*w*), 1268 (*m*), 1238 (*m*), 1215 (*m*), 1118 (*m*), 1030 (*w*), 847 (*w*).

HRMS (ESI): calcd for $C_{16}H_{25}O_2$ $[M+H]^+$: 249.1849; found: 249.1861.

6-(tert-butyl)-2,3-dimethoxynaphthalene (**27f**):

TLC (5% ethyl acetate in cyclohexane): R_f: 0.10 (UV, CAM)

mp: 124.2 – 127.3 °C

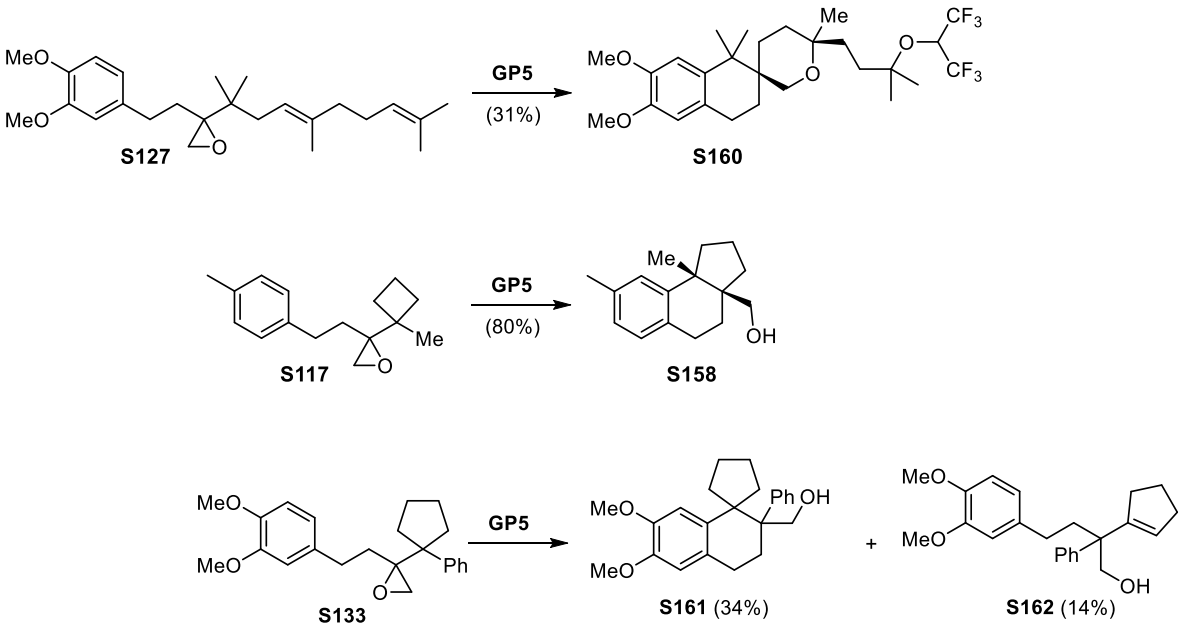
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 5.3, 3.2 Hz, 2H), 7.43 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.12 (s, 1H), 7.09 (s, 1H), 4.00 (s, 3H), 3.99 (s, 3H), 1.40 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6, 149.2, 147.1, 129.2, 127.3, 126.2, 123.1, 121.8, 106.7, 106.1, 55.99, 55.97, 34.8, 31.5.

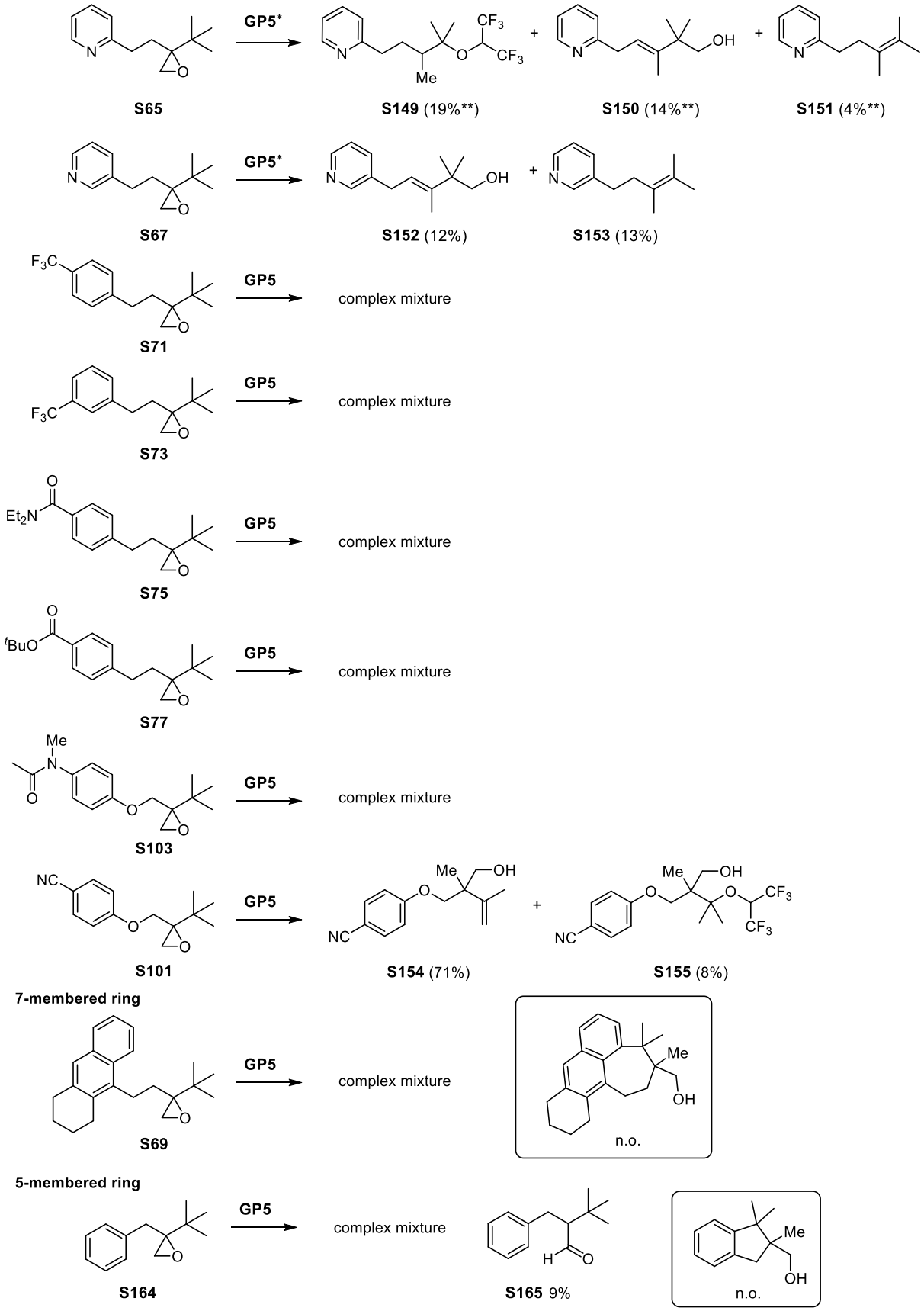
IR (ATR, neat) $\tilde{\nu}_{max}$: 2959 (*s*), 2863 (*w*), 1606 (*w*), 1515 (*m*), 1495 (*w*), 1465 (*w*), 1261 (*w*), 1243 (*w*), 1195 (*w*), 1167 (*w*), 1134 (*w*), 1006 (*w*), 856 (*w*).

HRMS (ESI): calcd for $C_{16}H_{21}O_2$ $[M+H]^+$: 245.1536; found: 245.1529.

9.2.2.6 Additional products



9.2.2.7 Limitations



*110% H_2SO_4 instead of 10%, **^{1}H NMR yields

9.2.2.8 Discussion of mechanism and byproduct formation

The investigation of the presented scope on the cycloisomerization of 2,2-disubsituted neopentylic epoxides led us to following conclusions and assumptions in respect to the reactivity of the substrates towards two main pathways that diverge into several possible reactions.

1) **Pathway 1 (see Scheme)**: The epoxide **S1** first gets protonated towards **S2** by the catalyst and opens by heterolytic cleavage of the C-O bond towards the tertiary carbon, forming a tertiary carbenium ion **S3**. This cation can theoretically be attacked by the distal nucleophile forming a five-membered cycle. However, we could not observe any trapping products of this proposed tertiary cation **S3** – even if the sterically challenging *tert*-butyl group of the investigated scope is replaced by a small methyl group (see substrate **23a –** proposed intermediate **S7**). Replacing the arene nucleophile with a less demanding primary alcohol in substrate **S54** did not lead to the observation of a rearranged oxolane product (see proposed intermediate **S8**). Possible effects that might explain these observations can be summarized in following statements:
    a. The alkyl shift from the adjacent center is very quick (**S3** to **S4**), and the positive charge prefers the terminal position. However, substrate **S63**, which underwent inverse migration speaks against a terminal preference of the positive charge. A charge stabilization after migration by the generated hydroxygroup is unlikely due to the small ringsize (n = 4). In this case, a corresponding product from **S54** via **S9** should have been observed.
    b. The formation of the sigma-complex towards a 5-membered ring is reversible and thermodynamically unfavorable. DFT calculations support this thesis, however, the difference between the 6-membered sigma-complex and the 5-membered sigma-complex lies in the range of only 5 till 6 kcal mol^{-1} (see calculations).
    c. Another probable reason might be the possibility that the opening of **S2** toward **S3** is highly reversible and favors the formation of opened **S3** only if a subsequent migration can form the terminal cation **S4**, which undergoes a kinetically fast cyclization towards a six-membered cycle. This is unlikely, as related epoxides (e.g. 2,3-oxidosqualene) in polyene cyclizations easily undergo cyclization from a tertiary position.
    d. The formation of the sigma-complex towards a 5-membered ring is kinetically unfavorable and slow. While it is commonly accepted that cyclizations prefer 6-membered transition states, we were surprised to not detect any traces of indane systems at all. However, a tremendous kinetic difference between the 6 and 5-membered cyclic system is very likely to be the most important argument for the observed product compositions. This argument is underpinned by observations regarding the alternative pathway 2 (see underneath). Proposed intermediate **S15** underwent intramolecular cyclization towards the fluorene structure **S163** in only 5%, preferring the bimolecular disproportionation in at least 75% despite the low concentration (0.05 M), while proposed intermediate **S14** exclusively cyclized to form the *cis*-decaline core of **21**. This is also in accordance with the classic Boger–Cook rearrangement forming a less-stabilized secondary carbo-cation from a tertiary one before cyclization.

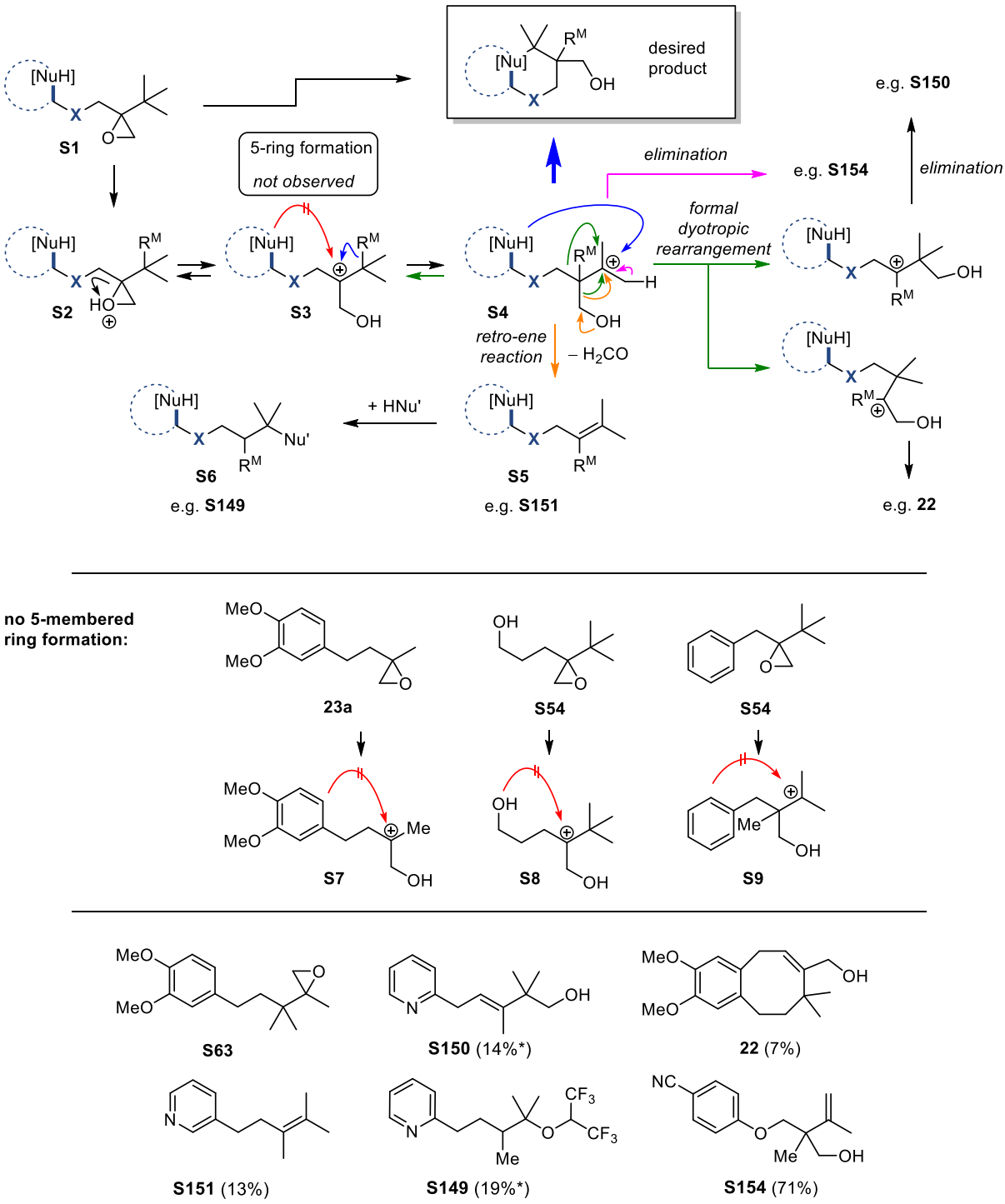
    After migration, the terminal cation can undergo now several pathways. In case of an available intramolecular nucleophile, the investigated molecules exclusively formed 6-membered cycles as in the desired products. Attempts to generate 5 or 7-membered ring systems failed in our hands (see limitations). If no 6-membered cycle can be

formed due to the lack of an appropriate nucleophile like with electron-poor arene moieties or the wrong placement (other ring sizes), it will react preferably according to following possibilities.

i. **Further rearrangements** (**formally dyotropic**): By another alkyl-shift of the just formed adjacent quaternary carbon center, the positive charge migrates to its previous position – all three different possibilities are possible (1) the hydroxymethyl group (2) The just migrated alkyl group, or (3) The residue connected to the arene.
    1. In case of the hydroxylmethyl group, a tertiary cation is formed that can eliminate to form a trisubstituted double bond as observed for pyridine substrate **S65**, what delivered product **S150** in low yield.
    2. Most probably, the just migrated alkyl group is also likely to move, what would nullify the first migration. An elimination product, equivalent to the direct elimination without any migrations, could not be identified for any substrate but is likely to occur.
    3. For vinyl substrate **17d**, we propose that after initial vinyl migration, the subsequent phenethyl-migration affords an allylic cation that leads to the observed 8-membered cycle of **22** (see proposed mechanism in the experimental part).

ii. By a formal **retro-ene reaction**, the molecule **S4** cleaves off formaldehyde to form a tetra substituted double bond (e.g. **S151**). This new nucleophilic moiety can further add nucleophiles like the solvent under the acidic conditions (e.g. **S149**).

iii. **Direct elimination**: Besides the formal dyotropic rearranged products, phenyl ether **S101** delivered the eliminated product **S154** in 71%.



Scheme S84. Pathway 1 – discussion of mechanism and byproduct formation.

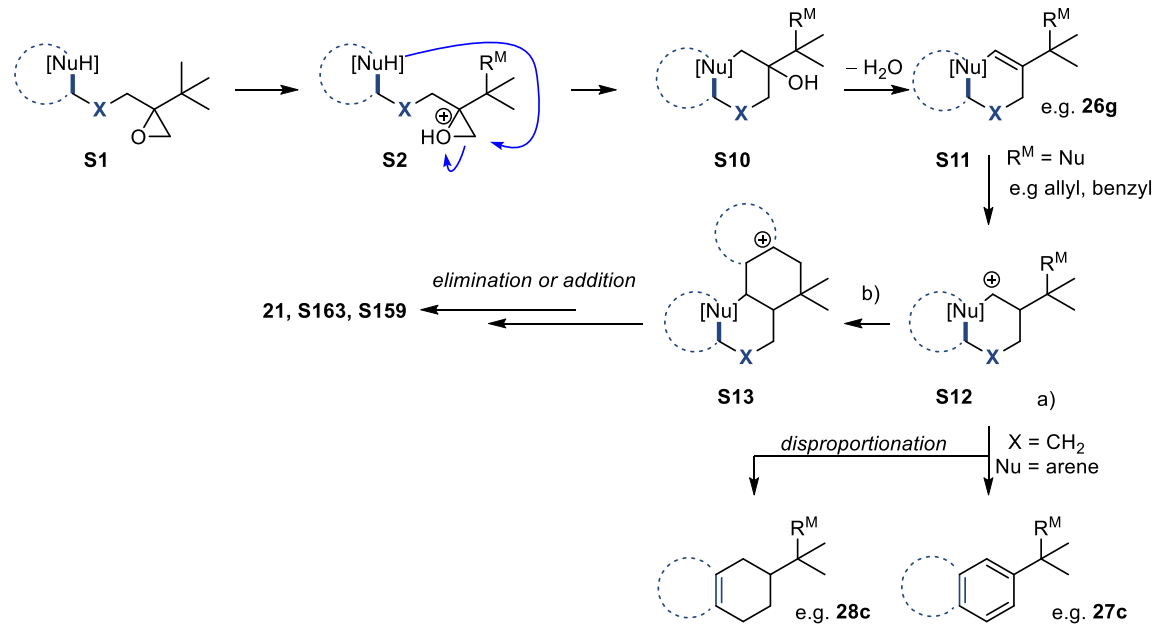
2) **Pathway 2 (see Scheme)**: Intact epoxide **S2** can be intramolecularly attacked on the less substituted methylene carbon in a *6-exo-tet* fashion. In case of an aromatic nucleophile, the tertiary homobenzylic alcohol (**S10**) thus formed, will eliminate under the acidic reaction conditions to form a benzylic double bond **S11** (dihydronaphthalene or 2*H*-chromene, e.g.

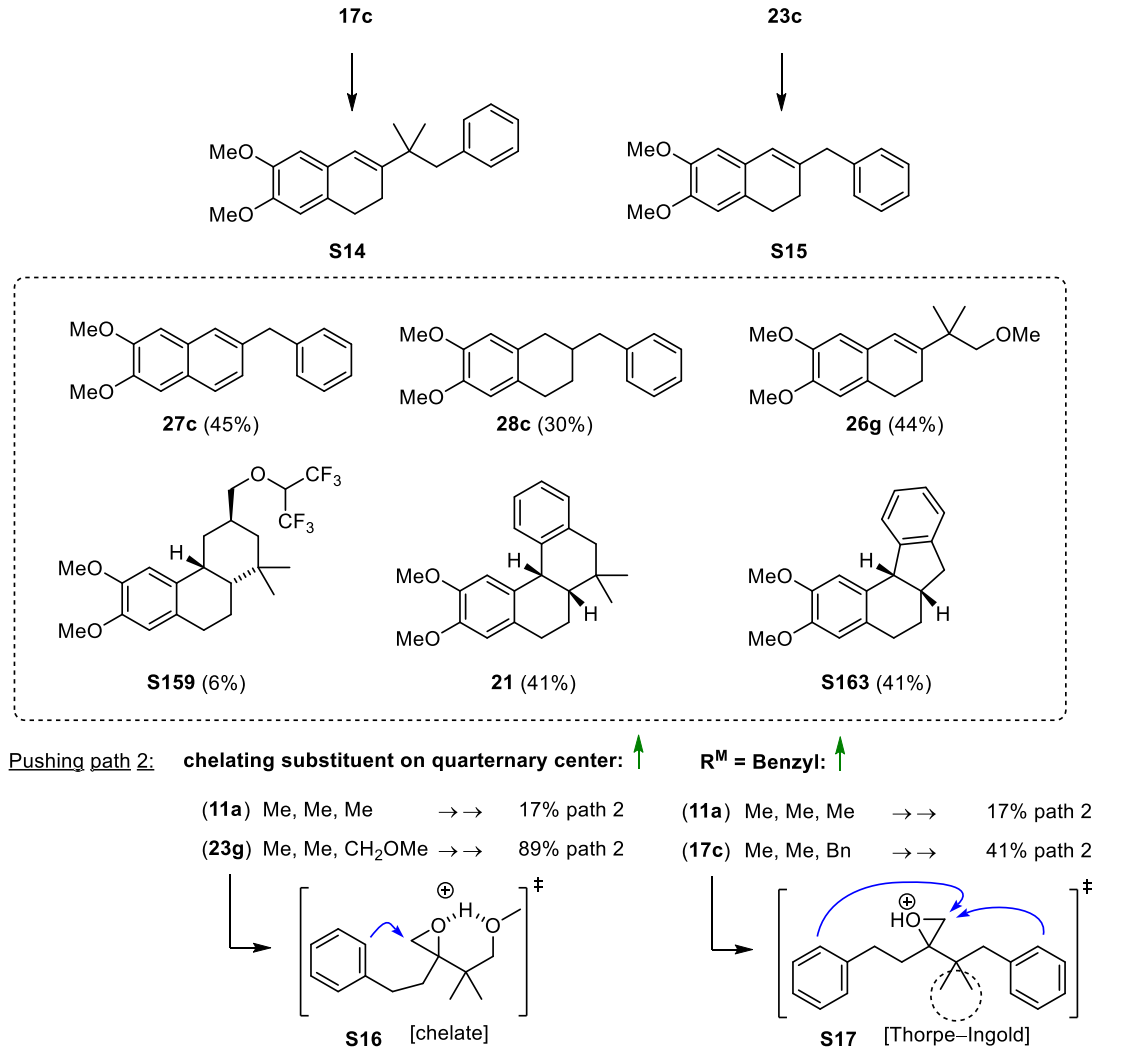
26g). Due to its nucleophilicity, this double bond is prone to protonation– but inversed to form a benzylic cation **S12**, which can undergo further reactions.

a. If no intramolecular nucleophile is available, the cation can react with nucleophiles intermolecularly. The solvent is a nucleophile but addition is reversible due to the high stabilization of the benzylic cation. An appropriate nucleophile might be the electronrich arene core of another product or substrate molecule. However, we did not observe a corresponding intermolecular Friedel-Crafts type alkylation of this tertiary center, probably due to its high sterically hindrance. However, it can react in a different way with another molecule of itself – by disproportionation. Hexafluoroisopropanol has proven in our case to be a very potent solvent for the disproportionation of the occurring electron-rich dihydronaphthalenes towards naphthalenes (e.g. **27c**) and tetralins (e.g. **28c**). Such an intermolecular hydride abstraction happens very quickly and was complete in most cases within 15 minutes at 0 °C – despite the low concentration (0.05 M). Therefore, we reason that hexafluoroisopropanol might be a unique solvent for other ionic reductions employing even stronger hydride donors like silanes or Hantzsch esters, too.
b. In the case of a further distal intramolecular nucleophile another ringclosure is possible (**S13**). In this context, especially substrates **17c** and **23c** are very interesting to compare. Both form related dihydronaphthalenes as intermediates (**S14** and **S15**). One with a phenylethyl group (**S15**), the other one with a benzylgroup (**S15**). Both can undergo with these sidechains subsequent ring closure reactions. However, while we could isolate annealed **21** in 41%, proposed **S15** underwent the second ring alkylation in only 5% (**S163**), preferring the intermolecular disproportion towards the naphthalene **27c** (45%) and tetralin **28c** (30%). The main difference is that the phenethyl group enables the closure to a 6-membered cycle, **S15** needs to form a five-membered cycle. This is an impressive example that the intramolecular Friedel-Crafts alkylation towards five-membered cycles is kinetically highly disfavored, enabling more than 95% of the proposed dihydronapthalene to undergo the intermolecular disproportionation even at concentrations of < 0.05 M.

Pathway 2 can be pushed by chelating substituents on the quaternary carbon center what was observed with substrate **23g** bearing a methoxymethyl group that can stabilize the protonated intact epoxide (see **S16**). Noteworthy, In the case of already discussed substrate **17c** bearing the benzyl group as substituent on the quaternary center we observed the mentioned product **21** in 41% yield. In this special case, the second arene core doubles the chances of a direct arene alkylation according to pathway 2, even further reinforced by the Thorpe–Ingold effect of the *gem*-dimethyl group (see **S17**). Replacing the quaternary carbon adjacent to the epoxide with less substituted carbons also increases the probability of path 2 due to less steric hindrance, less inductive stabilization of the tertiary carbenium ion and of course, by impediment of rearrangements according to pathway 1.

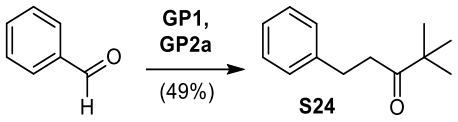
In hexafluoroisopropanol at 0 °C, an expected Meinwald-rearrangement is in the case of most substrates strongly suppressed and renders a rarely observed minor side reaction, while corresponding aldehydes were observed in other solvents systems more prominently.





Scheme S85: Pathway 2 – discussion of mechanism and byproduct formation.

9.2.2.9 Substrate syntheses



4,4-dimethyl-1-phenylpentan-3-one (**S24**) was prepared according to **GP1** (t = 2 h) from benzaldehyde (10.7 mmol, 1 equiv) and pinacolone (1.5 equiv) and **GP2a** (1% Pd, t = 16 h) in 49% yield as a colorless solid. Purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane).

TLC (20% ethyl acetate in cyclohexane): R_f: 0.43 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 – 7.27 (m, 2H), 7.22 – 7.15 (m, 3H), 2.88 (ddd, *J* = 8.0, 6.6, 1.7 Hz, 2H), 2.80 (ddd, *J* = 8.7, 6.7, 1.7 Hz, 2H), 1.11 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 215.1, 141.8, 128.6, 128.5, 126.2, 44.2, 38.6, 30.3, 26.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3027 (*w*), 2967 (*m*), 2869 (*w*), 1704 (*s*), 1604 (*w*), 1496 (*w*), 1477 (*w*), 1454 (*w*), 1394 (*w*), 1366 (*w*), 1084 (*w*), 1070 (*w*), 1030 (*w*), 983 (*w*), 746 (*w*), 699 (*m*).

HRMS (ESI) calcd for $C_{13}H_{18}ONa$ $[M+Na]^+$: 213.1256; found: 213.1247

2-(*tert*-butyl)-2-phenethyloxirane (**S25**) was prepared according to **GP3** (1.6 equiv NaH, 1.6 equiv Me_3SI) from **S24** (2.1 mmol, 1 equiv) in 87% yield as a colorless oil. Purified by flash column chromatography on silica gel (100% *n*-pentane).

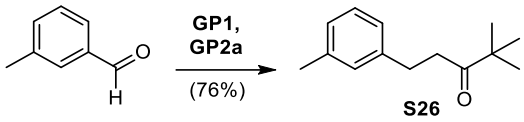
TLC (2% diethyl ether in *n*-pentane) R_f 0.30 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 2H), 7.23 – 7.10 (m, 3H), 2.78 (dd, *J* = 4.3, 0.7 Hz, 1H), 2.68 (d, *J* = 4.2 Hz, 1H), 2.57 (ddd, *J* = 13.5, 11.6, 5.1 Hz, 1H), 2.46 (ddd, *J* = 13.5, 11.7, 5.8 Hz, 1H), 2.14 (ddd, *J* = 14.6, 11.6, 5.8 Hz, 1H), 2.06 – 1.95 (m, 1H), 0.97 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4, 128.6, 128.4, 126.0, 63.5, 48.1, 34.1, 31.6, 30.8, 26.2.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3060 (*w*), 3027 (*m*), 2959 (*s*), 2872 (*m*), 1603 (*w*), 1497 (*m*), 1481 (*m*), 1454 (*m*), 1394 (*w*), 1364 (*m*), 1210 (*w*), 1145 (*w*), 1125 (*w*),1032 (*w*), 935 (*w*), 908 (*w*), 839 (*w*), 751 (*m*), 700 (*s*).

HRMS (ESI) calcd for $C_{14}H_{20}ONa$ $[M+Na]^+$: 227.1412; found: 227.1395



4,4-dimethyl-1-(*m*-tolyl)pentan-3-one (**S26**) was prepared according to **GP1** (t = 3 h) from 3-methylbenzaldehyde (10 mmol, 1 equiv) and pinacolone (1.5 equiv) and **GP2a** (1% Pd, t = 16 h) in 76% yield as a colorless solid. Purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane).

TLC (5% ethyl acetate in cyclohexanes): R_f: 0.33 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.7 Hz, 1H), 7.02 – 6.95 (m, 3H), 2.89 – 2.73 (m, 4H), 2.33 (s, 3H), 1.12 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.2, 141.7, 138.2, 129.3, 128.5, 126.9, 125.5, 44.2, 38.7, 30.2, 26.5, 21.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2966 (*m*), 2932 (*w*) 2907 (*w*), 2869 (*w*), 1705 (*s*), 1609 (*w*), 1477 (*m*), 1463 (*w*), 1408 (*w*), 1394 (*w*), 1365 (*m*), 1294 (*w*), 1094 (*m*), 1078 (*w*), 1041 (*w*), 982 (*m*), 778 (*m*), 700 (*m*).

HRMS (ESI) calcd for $C_{14}H_{21}O$ $[M+H]^+$: 205.1587; found: 205.1590

2-(*tert*-butyl)-2-(3-methylphenethyl)oxirane (**S27**) was prepared according to **GP3** (1.6 equiv NaH, 1.5 equiv Me_3SI) from **S26** (2.9 mmol, 1 equiv) in 92% yield as a colorless oil. Purified by flash column chromatography on silica gel (1% ethyl acetate in cyclohexane).

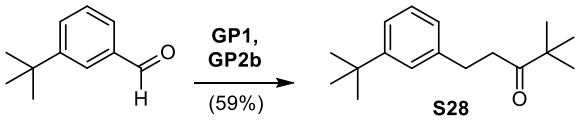
TLC (2% diethyl ether in *n*-pentane) R_f 0.30 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.7 Hz, 1H), 7.07 – 6.85 (m, 3H), 2.78 (dd, *J* = 4.2, 0.7 Hz, 1H), 2.67 (d, *J* = 4.2 Hz, 1H), 2.53 (ddd, *J* = 13.4, 11.7, 5.1 Hz, 1H), 2.42 (ddd, *J* = 13.4, 11.8, 5.7 Hz, 1H), 2.33 (s, 3H), 2.12 (ddd, *J* = 14.6, 11.7, 5.7 Hz, 1H), 2.00 (ddd, *J* = 14.6, 11.7, 5.1 Hz, 1H), 0.97 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3, 138.1, 129.3, 128.5, 126.7, 125.4, 63.5, 48.1, 34.1, 31.7, 30.7, 26.2, 21.5.

IR (ATR, neat) $\tilde{\nu}_{max}$:3013 (*w*), 2958 (*s*), 2871 (*m*), 1706 (*m*), 1609 (*m*), 1590 (*w*), 1480 (*m*), 1464 (*m*), 1394 (*m*), 1364 (*w*), 1144 (*w*), 1124 (*w*), 1042 (*w*), 983 (*w*), 937 (*w*), 914 (*m*), 838 (*m*), 781 (*s*), 701 (*s*).

HRMS (ESI) calcd for $C_{15}H_{22}ONa$ $[M+Na]^+$:241.1569; found: 241.1550



1-(3-(*tert*-butyl)phenyl)-4,4-dimethylpentan-3-one (**S28**) was prepared according to **GP1** (t = 3 h) from *3*-(*tert*-butyl)benzaldehyde (4.0 mmol, 1 equiv) and pinacolone (1.5 equiv) and **GP2b** (4 equiv Mg, T = –30 °C, t = 4 h) in 59% yield as a colorless solid. Purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane).

TLC (20% ethyl acetate in cyclohexanes) R_f: 0.36 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.18 (m, 3H), 7.04 – 6.95 (m, 1H), 2.91 – 2.84 (m, 2H), 2.79 (m, 2H), 1.31 (s, 9H), 1.11 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.1, 151.3, 141.2, 128.1, 125.4, 123.0, 44.1, 38.7, 34.6, 31.4, 30.5, 26.3.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2963 (*s*), 2905 (*w*), 2869 (*w*), 1706 (*s*), 1605 (*w*), 1489 (*w*), 1477 (*m*), 1464 (*w*), 1393 (*w*), 1365 (*m*), 1273 (*w*), 1203 (*w*), 1078 (*m*), 982 (*w*), 793 (*w*), 706 (*w*).

HRMS (ESI) calcd for $C_{17}H_{26}ONa$ $[M+Na]^+$: 269.1882; found: 269.1859

2-(*tert*-butyl)-2-(3-(*tert*-butyl)phenethyl)oxirane (**S29**) was prepared according to **GP3** (1.6 equiv NaH, 1.5 equiv Me_3SI) from **S28** (0.9 mmol; 1 equiv) in 81% yield as a colorless oil. Purified by flash column chromatography on silica gel (1% diethyl ether in *n*-pentane).

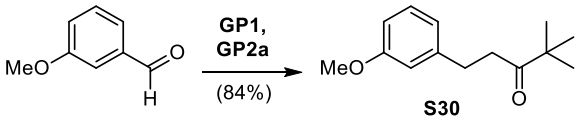
TLC (1% diethyl ether in *n*-pentane) R_f = 0.33 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.24 (q, *J* = 1.7 Hz, 1H), 7.05 (ddd, *J* = 5.6, 3.9, 1.9 Hz, 1H), 2.82 (dd, *J* = 4.1, 0.7 Hz, 1H), 2.73 (d, *J* = 4.2 Hz, 1H), 2.61 (ddd, *J* = 13.5, 11.6, 5.0 Hz, 1H), 2.51 (ddd, *J* = 13.4, 11.8, 5.8 Hz, 1H), 2.19 (ddd, *J* = 14.6, 11.7, 5.8 Hz, 1H), 2.12 – 2.00 (m, 1H), 1.36 (s, 9H), 1.02 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4, 141.9, 128.2, 125.5, 125.5, 123.0, 63.5, 48.1, 34.1, 31.7, 31.5, 31.0, 26.2.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2961 (*s*), 2870 (*m*), 1707 (*m*), 1605 (*w*), 1478 (*m*), 1393 (*w*), 1364 (*m*), 1273 (*w*), 1203 (*w*), 1078 (*w*), 981 (*w*), 907 (*w*), 839 (*w*), 792 (*w*), 706 (*m*).

HRMS (ESI): calcd for $C_{18}H_{28}ONa$ $[M+Na]^+$: 283.2038; found: 283.2030.



S30

1-(3-methoxyphenyl)-4,4-dimethylpentan-3-one (**S30**) was prepared according to **GP1** (t = 2 h) from 3-methoxybenzaldehyde (5 mmol, 1 equiv) and pinacolone (1.5 equiv) and **GP2a** (1% Pd, t = 15 h) in 84% yield as a colorless oil. Purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane).

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*).

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

2-(*tert*-butyl)-2-(3-methoxyphenethyl)oxirane (**S31**) was prepared according to **GP3** (1.6 equiv NaH, 1.5 equiv Me_3SI) from **S30** (3.0 mmol, 1 equiv) in 96% yield as a colorless oil. Purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane).

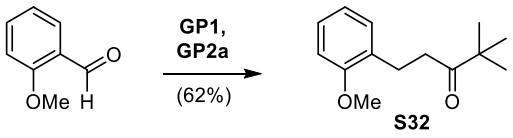
TLC (20% ethyl acetate in hexanes): R_f: 0.57 (CAM)

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



1-(2-methoxyphenyl)-4,4-dimethylpentan-3-one (**S32**) was prepared according to **GP1** (t = 3 h) from 2-anisaldehyde (6.0 mmol, 1 equiv) and pinacolone (1.5 equiv) and **GP2b** (4.5 equiv Mg, T = –30 °C, t = 4 h) in 62% yield as a colorless oil. Purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane).

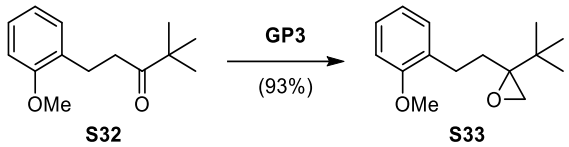
TLC (20% ethyl acetate in cyclohexane) R_f = 0.40 (UV)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (ddd, *J* = 8.1, 7.4, 1.8 Hz, 1H), 7.14 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.94 – 6.74 (m, 2H), 3.82 (s, 3H), 2.86 (tt, *J* = 7.3, 2.0 Hz, 2H), 2.80 – 2.69 (m, 2H), 1.11 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.8, 157.6, 130.3, 130.0, 127.5, 120.6, 110.3, 55.3, 44.3, 36.8, 26.5, 25.6.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2966 (*m*), 2908 (*w*), 2871 (*w*), 2836 (*w*), 1703 (s), 1601 (*w*), 1588 (*w*), 1494 (*m*), 1477 (*m*), 1465 (*m*), 1439 (*m*), 1365 (*w*), 1288 (*w*), 1243 (*s)*, 1161 (*w*), 1112 (*w*), 1079 (*m*), 1052 (*w*), 1033 (*m*), 984 (*w*), 753 (*m*).

HRMS (ESI): calcd for $C_{14}H_{21}O_2$ $[M+H]^+$: 221.1541; found: 221.1534.



S32 **S33**

2-(tert-butyl)-2-(2-methoxyphenethyl)oxirane (**S33**) was prepared according to **GP3** (1.6 equiv NaH, 1.5 equiv Me_3SI) from **S32** (4 mmol, 1 equiv) in 93% yield as a colorless oil. Purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane).

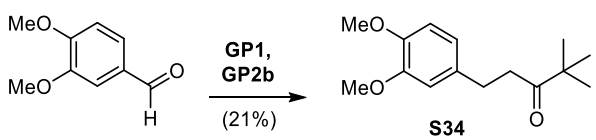
TLC (10% ethyl acetate in cyclohexane) R_f = 0.48

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (ddd, *J* = 8.2, 7.5, 1.8 Hz, 1H), 7.13 (dd, *J* = 7.4, 1.8 Hz, 1H), 6.88 (td, *J* = 7.4, 1.1 Hz, 1H), 6.84 (dd, *J* = 8.2, 1.1 Hz, 1H), 3.82 (s, 3H), 2.78 (d, *J* = 4.3 Hz, 1H), 2.71 (d, *J* = 4.3 Hz, 1H), 2.53 (dd, *J* = 9.4, 7.6 Hz, 2H), 2.13 (ddd, *J* = 14.4, 9.5, 7.7 Hz, 1H), 2.00 – 1.83 (m, 1H), 0.98 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6, 130.7, 129.8, 127.2, 120.6, 110.4, 63.8, 55.3, 48.3, 34.1, 30.1, 26.2, 25.7.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2958 (*m*), 2872 (*w*), 2835 (*w*), 1601 (*w*), 1587 (*w*), 1493 (*m*), 1464 (*m*), 1439 (*w*), 1364 (*w*), 1290 (*w*), 1241 (*s*), 1183 (*m*), 1115 (*w*), 1033 (*m*), 928 (*m*), 896 (*w*), 831 (*w*), 800 (*w*), 751 (*s*).

HRMS (ESI): calcd for $C_{15}H_{23}O_2$ $[M+H]^+$: 235.1698; found: 235.1691.



S34

4,4-dimethyl-1-(3,4-dimethoxyphenyl)pentan-3-one (**S34**) was prepared according to **GP1** (t = 3.5 h) from 3,4-dimethoxybenzaldehyde (120 mmol, 1 equiv) and pinacolone (1.5 equiv) and **GP2b** (4 equiv Mg, T = 23 °C, t = 6 h) in 21% yield as a colorless solid. Purified by flash column chromatography on silica gel (20% ethyl acetate in *n*-pentane).

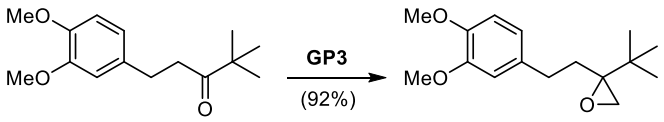
TLC (25% ethyl acetate in hexanes) R_f: 0.38 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 – 6.76 (m, 1H), 6.74 – 6.70 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.86 – 2.73 (m, 4H), 1.10 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.2, 148.9, 147.5, 134.4, 120.3, 112.0, 111.4, 56.1, 56.0, 44.2, 38.8, 29.9, 26.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2963 (*s*), 2935 (*w*), 2907 (*w*), 2870 (*w*), 2834 (*w*), 1703 (*s*), 1607 (*w*), 1590 (*m*), 1515 (*s*), 1464 (*s*), 1418 (*m*), 1394 (*m*), 1365 (*m*), 1261 (*s*), 1238 (*s*), 1191 (*w*), 1154 (*s*), 1140 (*s*), 1080 (*m*), 1029 (*s*), 983 (*m*), 937 (*w*), 890 (*w*), 846 (*w*), 809 (*m*),763 (*m*), 706 (*w*), 634 (*w*), 597 (*w*), 549 (*w*), 481 (*w*), 461 (*w*), 422 (*w*), 411 (*w*).

HRMS (ESI) calcd for $C_{15}H_{22}NaO_3$ $[M+Na]^+$: 273.1461; found: 273.1433.



S34 **11a**

2-(*tert*-butyl)-2-(3,4-dimethoxyphenethyl)oxirane (**11a**) was prepared according to **GP3** (1.6 equiv NaH, 1.5 equiv Me_3SI) from **S34** (24.7 mmol, 1 equiv) in 92% yield as a colorless oil. Purified by flash column chromatography on silica gel (10% ethyl acetate in *n*-pentane).

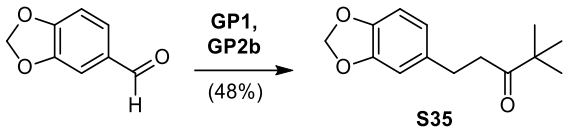
TLC (25% ethyl acetate in cyclohexane): R_f: 0.39 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (d, *J* = 7.9 Hz, 1H), 6.74 – 6.69 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.77 (dd, *J* = 4.2, 0.8 Hz, 1H), 2.67 (d, *J* = 4.2 Hz, 1H), 2.55 – 2.36 (m, 2H), 2.12 (ddd, *J* = 14.6, 11.5, 5.9 Hz, 1H), 2.04 – 1.95 (m, 1H), 0.97 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 147.4, 135.0, 120.1, 111.8, 111.4, 63.5, 56.1, 48.1, 34.1, 31.8, 30.3, 26.2.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2957 (*s*), 2872 (*w*), 2834 (*w*), 1590 (*w*), 1515 (*s*), 1464 (*s*), 1418 (*w*), 1394 (*w*), 1364 (*w*), 1343 (*w*), 1262 (*s*), 1237 (*s*), 1190 (*w*), 1157 (*s*), 1141 (*s*), 1030 (*s*), 921 (*w*), 895 (*w*), 851 (*s*), 808 (*w*), 766 (*w*), 666 (*w*), 620 (*w*), 598 (*w*), 564 (*w*), 523 (*w*), 476 (*w*), 465 (*w*), 421 (*w*).

HRMS (ESI) calcd for $C_{16}H_{24}NaO_3$ $[M+Na]^+$: 287.1618; found: 287.1614.



1-(benzo[*d*][1,3]dioxol-5-yl)-4,4-dimethylpentan-3-one (**S35**) was prepared according to **GP1** (t = 3 h) from piperonal (3.7 mmol, 1 equiv) and pinacolone (1.5 equiv) and **GP2b** (4 equiv Mg, T = –30 °C, t = 4 h) in 48% yield as a colorless solid. Purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane).

TLC (20% ethyl acetate in cyclohexanes): R_f: 0.33 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (d, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 1.7 Hz, 1H), 6.63 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.91 (s, 2H), 2.84 – 2.69 (m, 4H), 1.10 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.9, 147.6, 145.7, 135.4, 121.1, 108.9, 108.2, 100.8, 44.1, 38.7, 29.8, 26.3.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2967 (*w*), 2904 (*w*), 2873 (*w*), 1702 (*m*), 1608 (*w*), 1503 (*m*), 1488 (*s*), 1441 (*m*), 1365 (*m*), 1242 (*s*), 1189 (*m*), 1097 (*m*), 1077 (*m*), 1037 (*s*), 982 (*m*), 929 (*m*), 861 (*w*), 809 (*m*).

HRMS (ESI): calcd for $C_{14}H_{18}O_3Na$ $[M+Na]^+$: 257.1154; found: 257.1139

5-(2-(2-(*tert*-butyl)oxiran-2-yl)ethyl)benzo[*d*][1,3]dioxole (**S36**) was prepared according to **GP3** (1.6 equiv NaH, 1.5 equiv Me_3SI) from **S35** (1.75 mmol, 1 equiv) in 82% yield as a colorless oil. Purified by flash column chromatography on silica gel (10% diethyl ether in *n*-pentane).

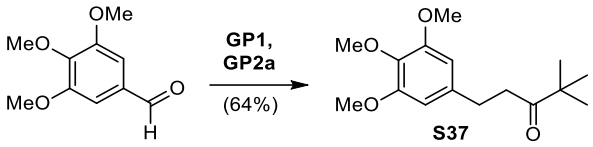
TLC (10% diethyl ether in *n*-pentane) R_f: 0.55 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 1.7 Hz, 1H), 6.62 (dt, *J* = 7.8, 1.1 Hz, 1H), 5.91 (s, 2H), 2.76 (dd, *J* = 4.1, 0.8 Hz, 1H), 2.64 (d, *J* = 4.2 Hz, 1H), 2.48 (ddd, *J* = 13.6, 11.5, 5.2 Hz, 1H), 2.38 (ddd, *J* = 13.6, 11.5, 5.8 Hz, 1H), 2.08 (ddd, *J* = 14.6, 11.5, 5.8 Hz, 1H), 1.96 (ddd, *J* = 14.5, 11.5, 5.2 Hz, 1H), 0.96 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 145.8, 136.2, 121.1, 108.9, 108.3, 100.9, 63.4, 48.1, 34.1, 31.8, 30.5, 26.2.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3051 (*w*), 3016 (*w*), 2959 (*s*), 2928 (*m*), 2872 (*m*), 1608 (*w*), 1503 (*m*), 1491 (*s*), 1443 (*m*), 1364 (*w*), 1245 (*s*), 1189 (*w*), 1097 (*m*), 1040 (*m*), 937 (*m*), 856 (*w*), 782 (*w*), 701 (*w*).

HRMS (ESI) calcd for $C_{15}H_{20}O_3Na$ [M+Na]$^+$: 271.1310; found: 271.1296



4,4-dimethyl-1-(3,4,5-dimethoxyphenyl)pentan-3-one (**S37**) was prepared according to **GP1** (t = 3 h) from 3,4,5-trimethoxybenzaldehyde (7.8 mmol, 1 equiv) and pinacolone (1.5 equiv) and **GP2a** (1% Pd, t = 15 h) in 64% yield as a colorless solid. Purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane).

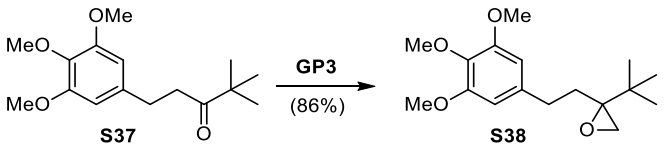
TLC (25% ethyl acetate in hexanes) R_f: 0.32 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (s, 2H), 3.84 (s, 6H), 3.81 (s, 3H), 2.85 – 2.75 (m, 4H), 1.12 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.0, 153.3, 137.6, 136.4 105.5, 61.0, 56.2, 44.3, 38.7, 30.7, 26.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2964 (*s*), 2838 (*w*), 1703 (*s*), 1589 (*s*), 1508 (*s*), 1458 (*s*), 1421 (*s*), 1365 (*m*), 1343 (*m*), 1286 (*w*), 1238 (*s*), 1183 (*w*), 1125 (*s*), 1081 (*s*), 1043 (*w*), 1010 (*s*), 938 (*w*), 895 (*w*), 825 (*m*), 776 (*w*), 745 (*w*), 665 (*w*), 565 (*w*), 528 (*w*).

HRMS (ESI) calcd for $C_{16}H_{24}NaO_4$ [M+Na]$^+$: 303.1567; found: 303.1561.



2-(*tert*-butyl)-2-(3,4,5-trimethoxyphenethyl)oxirane (**S38**) was prepared according to **GP3** (1.6 equiv NaH, 1.5 equiv Me_3SI) from **S37** (4.0 mmol, 1 equiv) in 86% yield as a colorless oil. Purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane).

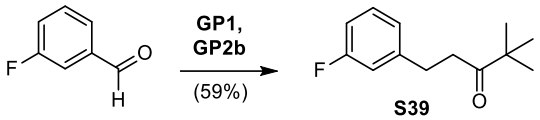
TLC (25% ethyl acetate in hexanes): R_f: 0.36 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (s, 2H), 3.85 (s, 6H), 3.82 (s, 3H), 2.78 (dd, *J* = 4.2, 0.8 Hz, 1H), 2.66 (d, *J* = 4.2 Hz, 1H), 2.55 – 2.35 (m, 2H), 2.12 (ddd, *J* = 14.6, 11.5, 5.9 Hz, 1H), 2.01 (ddd, *J* = 14.5, 11.5, 5.1 Hz, 1H), 0.98 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3, 138.1, 136.3, 105.3, 63.5, 61.0, 56.2, 48.1, 34.1, 31.6, 31.1, 26.2.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2957 (*s*), 2873 (*w*), 2837 (*w*), 1589 (*s*), 1507 (*s*), 1458 (*s*), 1420 (*s*), 1394 (*w*), 1364 (*w*), 1331 (*m*), 1283 (*w*), 1237 (*s*), 1183 (*w*), 1124 (*s*), 1045 (*w*), 1011 (*s*), 976 (*w*), 926 (*w*), 897 (*w*), 825 (*m*), 780 (*w*), 751 (*w*), 701 (*w*), 625 (*w*), 603 (*w*), 527 (*w*).

HRMS (ESI) calcd for $C_{17}H_{26}NaO_4$ $[M+Na]^+$: 317.1723; found: 317.1719.



1-(3-fluorophenyl)-4,4-dimethylpentan-3-one (**S39**) was prepared according to **GP1** (t = 3 h) from 3-fluorobenzaldehyde (6.6 mmol, 1 equiv) and pinacolone (1.5 equiv) and **GP2b** (4 equiv Mg, T = –30 °C, t = 4 h) in 59% yield as a colorless solid. Purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane).

TLC (1% diethyl ether in n-pentante) R_f 0.43 (UV, $KMnO_4$, Anis)

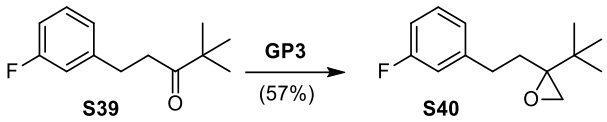
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.17 (m, 1H), 6.98 – 6.94 (m, 1H), 6.91 – 6.82 (m, 2H), 2.92 – 2.84 (m, 2H), 2.83 – 2.75 (m, 2H), 1.11 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.7, 163.0 (d, *J* = 245.6 Hz), 144.3 (d, *J* = 7.6 Hz), 130.0 (d, *J* = 8.5 Hz), 124.2 (d, *J* = 2.7 Hz), 115.4 (d, *J* = 21.0 Hz), 113.0 (d, *J* = 21.1 Hz), 44.2, 38.2, 29.9, 26.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -113.65 (d, *J* = 8.9 Hz).

IR (ATR, neat) $\tilde{\nu}_{max}$: 2954 (*m*), 2920 (*s*), 2871 (*m*), 2853 (*w*), 2359 (*w*), 2337 (*w*), 2238 (*w*), 2195 (*w*), 2143 (*w*), 2116 (*w*), 2005 (*w*), 1976 (*w*), 1707 (*m*), 1462 (*w*), 1378 (*w*), 1084 (*w*), 741(*w*), 701 (*w*).

HRMS (ESI) calcd for $C_{13}H_{17}OFNa$ $[M+Na]^+$: 231.1161; found: 231.1143.



2-(*tert*-butyl)-2-(3-fluorophenethyl)oxirane (**S40**) was prepared according to **GP3** (1.6 equiv NaH, 1.5 equiv Me_3SI) from **S39** (1.2 mmol, 1 equiv) in 57% yield as a colorless oil. Purified by flash column chromatography on silica gel (1% diethyl ether in *n*-pentane).

TLC (1% diethyl ether in *n*-pentane) R_f: 0.40 (UV, $KMnO_4$)

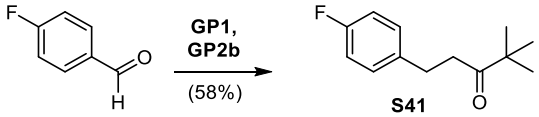
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.18 (m, 1H), 6.98 – 6.93 (m, 1H), 6.91 – 6.83 (m, 2H), 2.78 (d, *J* = 4.1, 1H), 2.64 (d, *J* = 4.1 Hz, 1H), 2.51 (m, 2H), 2.26 – 1.90 (m, 2H), 0.97 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1 (d, *J* = 245.5 Hz), 144.9 (d, *J* = 7.2 Hz), 129.9 (d, *J* = 8.1 Hz), 124.1 (d, *J* = 2.6 Hz), 115.3 (d, *J* = 21.0 Hz), 112.9 (d, *J* = 21.1 Hz), 63.4, 48.1, 34.1, 31.2, 30.4, 26.2.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -113.71.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2956 (*m*), 2924 (*s*), 2854 (*m*), 1738 (*w*), 1596 (*w*), 1458 (*w*), 1376 (*w*), 1261 (*w*), 1222 (*w*), 1182 (*w*), 1171 (*w*), 1098 (*w*), 1051 (*w*), 1031 (*w*), 781 (*w*).

HRMS (ESI): calcd for $C_{14}H_{19}FONa$ $[M+Na]^+$: 245.1318; found: 245.1297.



1-(4-fluorophenyl)-4,4-dimethylpentan-3-one (**S41**) was prepared according to **GP1** (t = 3 h) from 4-fluorobenzaldehyde (10.0 mmol, 1 equiv) and pinacolone (1.5 equiv) and **GP2b** (4 equiv Mg, T = –30 °C, t = 4 h) in 58% yield as a colorless oil. Purified by flash column chromatography on silica gel (10% diethyl ether in *n*-pentane).

TLC (10% diethyl ether in *n*-pentane) R_f = 0.52 (UV, $KMnO_4$)

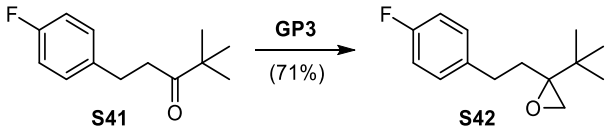
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.09 (m, 2H), 6.95 (t, *J* = 8.8 Hz, 2H), 2.89 – 2.81 (m, 2H), 2.80 – 2.70 (m, 2H), 1.09 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.9, 161.5 (d, *J* = 243.4 Hz), 137.3 (d, *J* = 3.4 Hz), 129.9 (d, *J* = 7.9 Hz), 115.3 (d, *J* = 21.1 Hz), 44.2, 38.6, 29.4, 26.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ -117.48 (t, *J* = 6.9 Hz).

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2969 (w), 2935 (w), 2909 (w), 2872 (w), 1705 (m), 1602 (w), 1510 (s), 1478 (w), 1366 (w), 1222 (m), 1158 (w), 1096 (w), 1077 (w), 982 (w), 830 (m).

HRMS (ESI): calcd for $C_{13}H_{17}FONa$ $[M+Na]^+$: 231.1161; found: 231.1151.



4-fluoro-2-(3-methylphenethyl)oxirane (**S42**) was prepared according to **GP3** (1.6 equiv NaH, 1.5 equiv Me_3SI) from **S41** (2.9 mmol, 1 equiv) in 71% yield as a yellow oil. Purified by flash column chromatography on silica gel (5% diethyl ether in *n*-pentane).

TLC (5% diethyl ether in *n*-pentane) R_f = 0.37 (UV, $KMnO_4$)

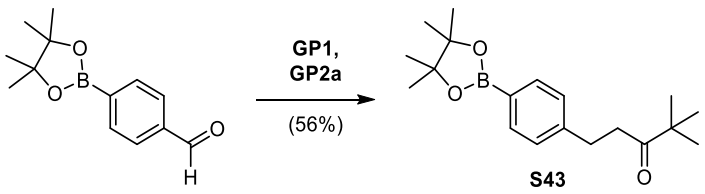
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.08 (m, 2H), 7.02 – 6.87 (m, 2H), 2.78 (d, *J* = 4.2, 1H), 2.65 (d, *J* = 4.1 Hz, 1H), 2.59 – 2.28 (m, 2H), 2.19 – 1.87 (m, 2H), 0.97 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4 (d, *J* = 243.4 Hz), 137.9 (d, *J* = 3.1 Hz), 129.7 (d, *J* = 7.4 Hz), 115.3 (d, *J* = 21.1 Hz), 63.4, 48.0, 34.1, 31.7, 29.9, 26.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ -117.70 (t, *J* = 5.3 Hz).

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2966 (m), 2912 (w), 2873 (w), 1706 (w), 1602 (w), 1510 (s), 1479 (w), 1465 (w), 1394 (w), 1365 (w), 1222 (m), 1158 (w), 1095 (w), 1076 (w), 830 (m).

HRMS (ESI): calcd for $C_{14}H_{19}FONa$ $[M+Na]^+$: 245.1318; found: 245.1307.



4,4-dimethyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-3-one (**S43**) was prepared according to **GP1** (t = 3 h) from 4-formylphenylboronic acid pinacol ester (4 mmol, 1 equiv) and pinacolone (1.5 equiv) and **GP2a** in methanol instead of ethyl acetate (1% Pd, t = 6 h) in 56% yield

as a colorless oil. Purified by flash column chromatography on silica gel (10% diethyl ether in *n*-pentane).

TLC (5% diethyl ether in *n*-pentane) R_f =0.25 (UV, $KMnO_4$)

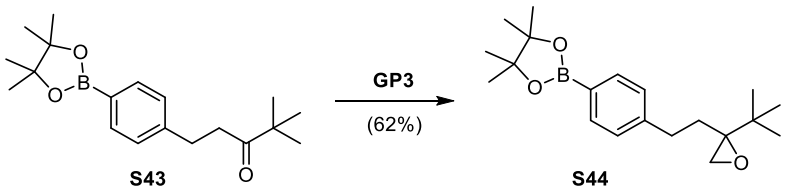
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 2.93 – 2.84 (m, 2H), 2.82 – 2.75 (m, 2H), 1.33 (s, 12H), 1.10 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.9, 145.2, 135.1, 128.0, 83.8, 44.2, 38.4, 30.4, 26.5, 25.0.

^{11}B NMR (128 MHz, $CDCl_3$) δ 31.4.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2975 (*m*), 2932 (*w*), 2871 (*w*), 1706 (*m*), 1612(*w*), 1519(*w*), 1478 (*w*), 1399 (*m*), 1360 (*s*), 1321 (*m*), 1272(*w*), 1214 (*w*), 1145 (*m*), 1090 (*m*), 1022(*w*), 981 (*w*), 963 (*w*), 860 (*w*), 828 (*w*).

HRMS (ESI): calcd for $C_{19}H_{33}BO_3N$ $[M+NH_4]^+$: 334,2554; found: 334.2550.



5-(2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxiran-2-yl)ethyl)benzo[*d*][1,3]dioxole (**S44**) was prepared according to **GP3** (2 equiv NaH, 1.9 equiv Me_3SI) from **S43** (1.75 mmol, 1 equiv) in 62% yield as a colorless oil. Purified by flash column chromatography on silica gel (10% diethyl ether in *n*-pentane).

TLC (5% diethyl ether in *n*-pentane) R_f : 0.25 ($KMnO_4$)

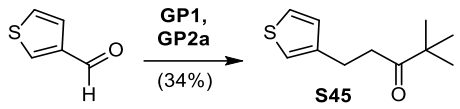
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 2.77 (dd, *J* = 4.1, 0.8 Hz, 1H), 2.66 (d, *J* = 4.2 Hz, 1H), 2.61 – 2.36 (m, 2H), 2.20 – 1.88 (m, 2H), 1.33 (s, 12H), 0.96 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.8, 135.1, 128.0, 127.9, 83.8, 63.5, 48.1, 34.1, 31.4, 31.0, 26.2, 25.0.

^{11}B NMR (128 MHz, $CDCl_3$) δ 31.00.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2965 (*m*), 2927 (*m*), 1780 (*w*), 1706 (*w*), 1612 (*w*), 1465 (*w*), 1398 (*w*), 1361 (*s*), 1321 (*w*), 1272 (*w*), 1214 (*w*), 1145 (*m*), 1090 (*m*), 1022 (*w*), 963 (*w*), 860 (*w*), 827 (*w*).

HRMS (ESI): calcd for $C_{20}H_{31}BO_3Na$ $[M+Na]^+$: 353.2264; found: 353.2241.



4,4-dimethyl-1-(thiophen-3-yl)pentan-3-one (**S45**) was prepared according to **GP1** (t = 2 h) from thiophene-3-carbaldehyde (8.9 mmol, 1 equiv) and pinacolone (1.5 equiv) and **GP2a** (0.5% Pd, t = 16 h) in 34% yield as a colorless solid. Purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane).

TLC (10% ethyl acetate in hexanes): Rf: 0.42 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 4.9, 3.0 Hz, 1H), 6.96 – 6.91 (m, 2H), 2.93 – 2.87 (m, 2H), 2.82 – 2.76 (m, 2H), 1.11 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.0, 141.9, 128.3, 125.6, 120.6, 44.2, 37.7, 26.4, 24.6.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2967 (*s*), 2933 (*w*), 2906 (*w*), 2870 (*w*), 1703 (*vs*), 1537 (*w*), 1477 (*s*), 1464 (*w*), 1445 (*w*), 1409 (*m*), 1394 (*m*), 1465 (*s*), 1288 (*w*), 1225 (*w*), 1154 (*w*), 1079 (*s*), 1042 (*w*), 982 (*m*), 936 (*w*), 899 (*w*), 854 (*w*), 831 (*w*), 7785 (*s*), 670 (*m*), 636 (*m*), 599 (*w*), 553 (*m*).

HRMS (ESI) calcd for $C_{11}H_{16}NaOS$ $[M+Na]^+$: 219.0814; found: 219.0801.

2-(*tert*-butyl)-2-(2-(thiophen-3-yl)ethyl)oxirane (**S46**) was prepared according to **GP3** (1.6 equiv NaH, 1.5 equiv Me_3SI) from **S45** (0.8 mmol, 1 equiv) in 81% yield as a colorless oil. Purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes).

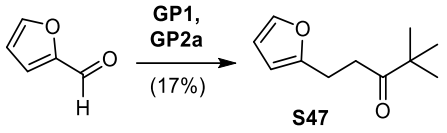
TLC (10% ethyl acetate in hexanes): R_f: 0.44 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.23 (m, 1H), 6.94 (s, 1H), 6.94 – 6.93 (m, 1H), 2.77 (dd, *J* = 4.1, 0.7 Hz, 1H), 2.64 (d, *J* = 4.2 Hz, 1H), 2.62 – 2.54 (m, 1H), 2.54 – 2.45 (m, 1H), 2.16 (ddd, *J* = 14.6, 11.1, 6.0 Hz, 1H), 2.04 (dddd, *J* = 14.5, 11.2, 5.3, 0.8 Hz, 1H), 0.97 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6, 128.3, 125.5, 120.1, 63.4, 48.1, 34.1, 30.4, 26.2, 25.1.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3101 (*w*), 3052 (*w*), 2960 (*s*), 2871 (*m*), 1536 (*w*), 1480 (*m*), 1466 (*w*), 1410 (*w*), 1394 (*w*), 1364 (*m*), 1344 (*w*), 1210 (*w*), 1146 (*w*), 1125 (*w*), 1103 (*w*), 1080 (*w*), 1041 (*w*) 1007 (*w*), 923 (*m*), 895 (*w*), 860 (*m*), 833 (*m*), 775 (*s*), 745 (*w*), 685 (*w*), 651 (*w*), 622 (*w*), 598 (*m*), 578 (*w*), 525 (*w*), 500 (*w*), 485 (*w*), 467 (*w*), 456 (*w*), 445 (*w*), 427 (*w*), 417 (*w*), 406 (*w*).

HRMS (ESI) calcd for $C_{12}H_{19}OS$ $[M+H]^+$: 211.1151; found: 211.1145.



1-(furan-2-yl)-4,4-dimethylpentan-3-one (**S47**) was prepared according to **GP1** (t = 2 h) from furfural (10 mmol, 1 equiv) and pinacolone (1.5 equiv) and **GP2a** (0.5% Pd, t = 16 h) in 17% yield as a colorless oil. Purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane).

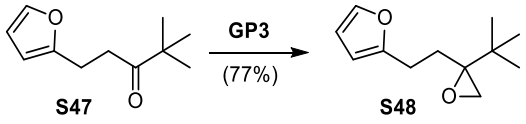
TLC (10% ethyl acetate in hexanes): R_f: 0.41 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.26 (dd, *J* = 3.1, 1.9 Hz, 1H), 5.98 (dq, *J* = 3.2, 0.8 Hz, 1H), 2.90 (ddt, *J* = 8.4, 6.0, 1.3 Hz, 2H), 2.86 – 2.79 (m, 2H), 1.13 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.6, 155.2, 141.1, 110.3, 105.3, 44.3, 35.1, 26.5, 22.6.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2969 (*s*), 2934 (*w*), 2910 (*w*), 2871 (*w*), 1706 (*vs*), 1597 (*w*), 1508 (*m*), 1478 (*s*), 1466 (*w*), 142 (*w*), 1412 (*w*), 1394 (*w*), 1365 (*s*), 1296 (*w*), 122 (*w*), 1149 (*m*), 1084 (*s*), 1074 (*s*), 1043 (*w*), 1009 (*s*), 953 (*m*), 922 (*m*), 898 (*w*), 885 (*m*), 851 (*w*), 803 (*m*), 729 (*s*), 687 (*w*), 600 (*m*), 587 (*w*), 470 (*w*), 418 (*w*).

HRMS (ESI) calcd for $C_{11}H_{16}NaO_2$ $[M+Na]^+$: 203.1043; found: 203.1028.



2-(2-(2-(*tert*-butyl)oxiran-2-yl)ethyl)furan (**S48**) was prepared according to **GP3** (1.6 equiv NaH, 1.5 equiv Me_3SI) from **S47** (0.5 mmol, 1 equiv) in 77% yield as a colorless oil. Purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes).

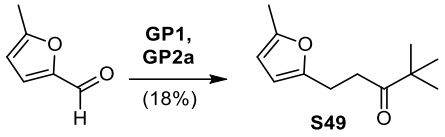
TLC (10% ethyl acetate in hexanes): R_f: 0.43 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.27 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.98 (dq, *J* = 2.9, 0.9 Hz, 1H), 2.76 (d, *J* = 4.1 Hz, 1H), 2.59 (d, *J* = 4.1 Hz, 1H), 2.64 – 2.54 (m, 1H), 2.53 – 2.44 (m, 1H), 2.18 (ddd, *J* = 14.6, 10.5, 6.1 Hz, 1H), 2.12 – 2.02 (m, 1H), 0.97 (s, 9H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 141.0, 110.3, 104.8, 63.1, 48.0, 34.1, 27.8, 26.1, 23.1.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3117 (*w*), 3055 (*w*), 2962 (*s*), 2873 (*m*), 1597 (*w*), 1508 (*m*), 1480 (*m*), 1467 (*w*), 1450 (*w*), 1394 (*w*), 1365 (*m*), 1346 (*w*), 1258 (*w*), 1212 (*w*), 1147 (*m*), 1126 (*w*), 1103 (*w*), 1078 (*w*), 1040 (*w*), 1006 (*m*), 926 (*m*), 885 (*w*), 839 (*w*), 800 (*m*), 727 (*s*), 644 (*w*), 599 (*m*), 549 (*w*), 526 (*w*), 457 (*w*), 445 (*w*), 418 (*w*).

HRMS (ESI) calcd for $C_{12}H_{19}O_2$ $[M+H]^+$: 195.1380; found: 195.1375.



S49

4,4-dimethyl-1-(5-methylfuran-2-yl)pentan-3-one (**S49**) was prepared according to **GP1** (t = 2 h) from 5-methylfuran-2-carbaldehyde (5 mmol, 1 equiv) and pinacolone (1.5 equiv) and **GP2a** (2% Pd, t = 24 h) in 18% yield as a colorless oil. Purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane).

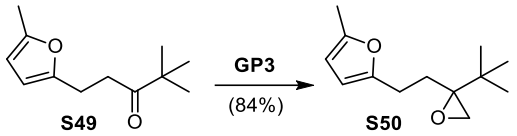
TLC (10% ethyl acetate in cyclohexane): R_f: 0.26 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.84 (d, *J* = 3.1 Hz, 1H), 5.82 (d, *J* = 3.1 Hz, 1H), 2.88 – 2.75 (m, 4H), 2.23 (s, 3H), 1.13 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 214.7, 153.3, 150.6, 106.0, 105.8, 44.3, 35.3, 26.5, 22.7, 13.6.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2967 (*m*), 2923 (*w*), 2871 (*w*), 1706 (*s*), 1618 (*w*), 1570 (*m*), 1478 (*m*), 1465 (*w*), 1438 (*w*), 1412 (*w*), 1394 (*m*), 1366 (*w*), 1295 (*w*), 1219 (*m*), 1147 (*w*), 1080 (*s*), 1019 (*s*), 983 (*w*), 957 (*m*), 934 (*w*), 905 (*w*), 851 (*w*), 780 (*s*), 700 (*w*), 653 (*w*), 622 (*w*), 566 (*w*), 499 (*w*), 484 (*w*), 426 (*w*), 409 (*w*).

HRMS (ESI): calcd for $C_{12}H_{19}O_2$ $[M+H]^+$: 195.1380; found: 195.1376.



2-(2-(2-(*tert*-butyl)oxiran-2-yl)ethyl)-5-methylfuran (**S50**) was prepared according to **GP3** (1.6 equiv NaH, 1.5 equiv Me_3SI) from **S49** (0.5 mmol, 1 equiv) in 84% yield as a colorless oil. Purified by flash column chromatography on silica gel (1% ethyl acetate in cyclohexane grading to 5% ethyl acetate in cyclohexane).

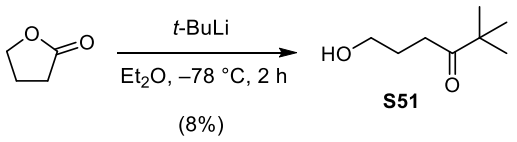
TLC (10% ethyl acetate in cyclohexane): R_f: 0.31 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.84 (d, *J* = 3.3 Hz, 1H), 5.83 (d, *J* = 3.3 Hz, 1H), 2.75 (d, *J* = 4.1 Hz, 1H), 2.59 (d, *J* = 4.1 Hz, 1H), 2.57 – 2.49 (m, 1H), 2.47 – 2.38 (m, 1H), 2.24 (s, 3H), 2.20 – 2.12 (m, 1H), 2.09 – 2.00 (m, 1H), 0.97 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 154.1, 150.4, 105.9, 105.4, 63.1, 48.0, 34.1, 27.9, 26.1, 23.1, 13.6.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3054 (*w*), 2960 (*s*), 2873 (*w*), 1617 (*w*), 1570 (*m*), 1480 (*m*), 1466 (*w*), 1451 (*w*), 1394 (*w*), 1365 (*m*), 1293 (*w*), 1256 (*w*), 1218 (*s*), 1146 (*w*), 1125 (*w*), 1020 (*s*), 996 (*w*), 939 (*m*), 894 (*w*), 837 (*w*), 812 (*w*), 778 (*s*), 670 (*w*), 623 (*w*), 548 (*w*), 526 (*w*).

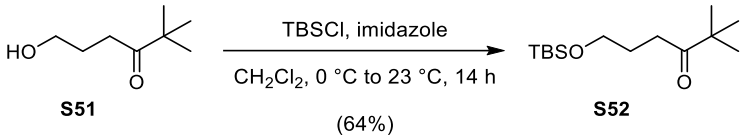
HRMS (ESI): calcd for $C_{13}H_{21}O_2$ $[M+H]^+$: 209.1536; found: 209.1533.



6-hydroxy-2,2-dimethylhexan-3-one (**S51**):

To a solution of γ-butyrolactone (2.61 mL, 34 mmol, 1 eq) in diethyl ether (75 mL) was dropwise added a solution of *t*-butyl lithium (1.60 M in *n*-hexane, 23.4 mL, 37.4 mmol, 1.1 equiv) at –78 °C. After 2 h excess base was quenched by addition of saturated aqueous ammonium chloride solution (50 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 100 mL). The combined organic layers were dried over anhydrous magnesium 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 *n*-pentane) to yield alcohol **S51** (408 mg, 2.83 mmol, 8%) as a colorless oil.

The analytical data were in full agreement with those reported in the literature.[145]



6-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylhexan-3-one (**S52**):

A solution of primary alcohol **S51** (408 mg, 2.83 mmol, 1 equiv) in dichloromethane (10 mL) was treated with imidazole (241 mg, 3.54 mmol, 1.25 equiv) and *t*-butyldimethylsilyl chloride (469 mg, 3.11 mmol, 1.10 equiv) sequentially in one portion at 0 °C. The mixture was slowly warmed to 23 °C. After 14 h saturated aqueous sodium bicarbonate solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (2×15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% diethyl ether in *n*-pentane) to yield silylether **S52** (467 mg, 1.81 mmol, 64%) as a colorless liquid.

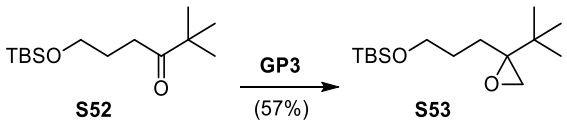
TLC (5% diethyl ether in *n*-pentane): R_f: 0.37 (CAM)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.59 (t, *J* = 6.1 Hz, 2H), 2.56 (t, *J* = 7.2 Hz, 2H), 1.75 (tt, *J* = 7.2, 6.1 Hz, 2H), 1.13 (s, 9H), 0.88 (s, 9H), 0.03 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 216.1, 62.3, 44.3, 32.8, 27.1, 26.6, 26.1, 18.4, –5.2.

IR (ATR, neat): $\tilde{\nu}$ = 2955 (*m*), 2930 (*m*), 2858 (*w*), 1707 (*s*), 1473 (*w*), 1390 (*w*), 1363 (*w*), 1254 (*m*), 1090 (*s*), 1005 (*w*), 958 (*m*), 833 (*s*), 774 (*s*), 734 (*w*).

HRMS (ESI): calcd for $C_{14}H_{30}NaO_2Si$ $[M+Na]^+$: 281.1907; found: 281.1895.



***tert*-butyl(3-(2-(*tert*-butyl)oxiran-2-yl)propoxy)dimethylsilane** (**S53**) was prepared according to **GP3** (2.0 equiv NaH, 1.9 equiv Me_3SI) from **S52** (1.64 mmol, 1 equiv) in 57% yield as a colorless oil. Purified by flash column chromatography on silica gel (5% diethyl ether in *n*-pentane).

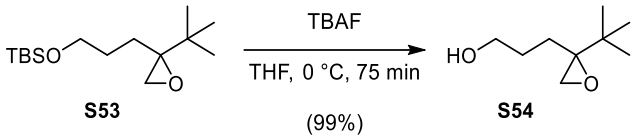
TLC (5% diethyl ether in *n*-pentane): R_f: 0.39 (CAM)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.58 (qt, *J* = 10.1, 6.3 Hz, 2H), 2.72 (d, *J* = 4.3 Hz, 1H), 2.55 (d, *J* = 4.3 Hz, 1H), 1.89 (ddd, *J* = 14.5, 10.2, 6.3 Hz, 1H), 1.70 (ddd, *J* = 14.5, 10.4, 5.6 Hz, 1H), 1.49 – 1.35 (m, 2H), 0.94 (s, 9H), 0.89 (s, 9H), 0.04 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 63.5, 63.4, 48.1, 34.1, 27.9, 26.2, 26.1, 26.0, 18.5, –5.1, –5.2.

IR (ATR, neat): $\tilde{\nu}$ = 2956 (*m*), 2929 (*m*), 2858 (*w*), 1472 (*w*), 1392 (*w*), 1363 (*w*), 1254 (*m*), 1208 (*w*), 1100 (*s*), 1006 (*w*), 969 (*w*), 939 (*w*), 835 (*s*), 775 (*s*).

HRMS (ESI): calcd for $C_{15}H_{33}O_2Si$ $[M+H]^+$: 273.2244; found: 273.2252.



3-(2-(*tert*-butyl)oxiran-2-yl)propan-1-ol (**S54**):

A solution of silylether **S53** (136 mg, 0.500 mmol, 1 equiv) in tetrahydrofuran (5 mL) was treated with a solution of tetra-*n*-butylammonium fluoride (1.00 M in tetrahydrofuran, 0.750 mL, 0.750 mmol, 1.50 equiv) at 0 °C. After 30 min further tetra-*n*-butylammonium fluoride solution in tetrahydrofuran (1.00 M, 0.250 mL, 0.250 mmol, 0.50 equiv) was added. After 45 min aqueous phosphate buffer solution (5 mL, pH=7) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (4 × 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (50% ethyl acetate in *n*-pentane) to yield primary alcohol **S54** (78.0 mg, 0.493 mmol, 99%) as pale yellow oil.

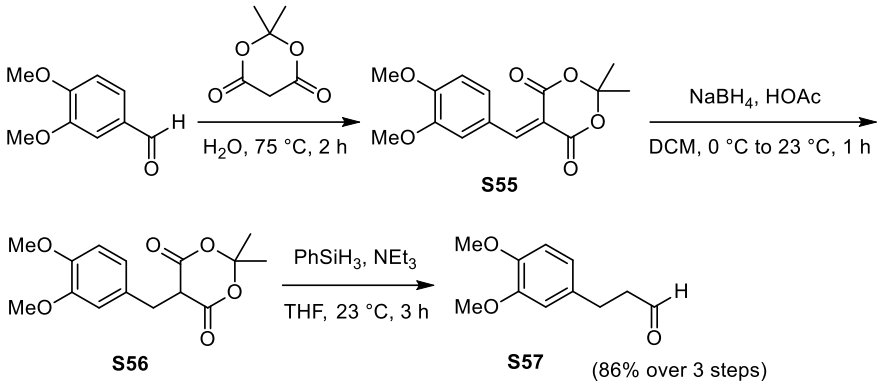
TLC (30% ethyl acetate in *n*-pentane): R_f: 0.39 (CAM)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.60 (t, *J* = 6.2 Hz, 2H), 2.75 (dd, *J* = 4.1, 0.8 Hz, 1H), 2.59 (d, *J* = 4.1 Hz, 1H), 1.99 – 1.76 (m, 3H), 1.48 (dddd, *J* = 12.9, 8.8, 6.3, 3.1 Hz, 2H), 0.95 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 63.6, 63.3, 48.2, 34.1, 27.5, 26.2, 26.2.

IR (ATR, neat): $\tilde{\nu}$ = 3384 (*m, br*), 2957 (*s*), 2873 (*m*), 1481 (*m*), 1394 (*m*), 1364 (*m*), 1211 (*w*), 1131 (*w*), 1059 (*s*), 1024 (*m*), 937 (*m*), 821 (*m*).

HRMS (LTP): calcd for $C_9H_{19}O_2$ $[M+H]^+$: 159.1380; found: 159.1388.



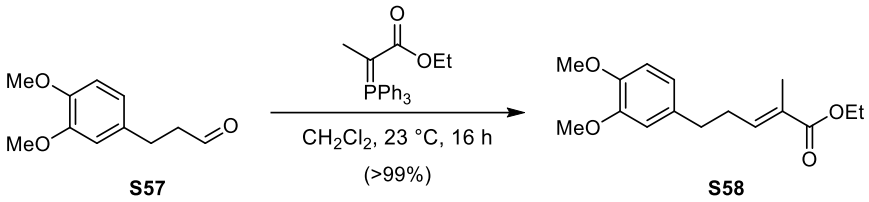
3-(3,4-dimethoxyphenyl)-propanal (**S57**):

To a solution of Meldrum's acid (1.00 g, 6.94 mmol, 1 equiv) in water (25 mL) was added 3,4-dimethoxybenzaldehyde (1.27 g, 7.63 mmol, 1.10 equiv). The mixture was stirred at 75 °C for 2 h. The suspension was cooled down to 0 °C and the yellow precipitate (**S55**) was filtered and washed with cold water (50 mL) and cyclohexane (50 mL).

The crude solid (1.86 g, 6.36 mmol, 1 equiv) was dissolved in a mixture of dichloromethane (50 mL) and acetic acid (7 mL) at 0 °C. Sodium borohydride (480 mg, 12.7 mmol, 2.00 equiv) was added portionwise at 0 °C. The reaction mixture was allowed to reach 23 °C and stirred for 1 h. By careful addition of saturated aqueous sodium bicarbonate solution (50 mL) excess reductant was quenched. The mixture was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over magnesium sulfate. The solution was filtered and the filtrate was concentrated under reduced pressure to afford the crude product **S56** (1.8 g).

The crude product (1.8 g, approx. 6.1 mmol, 1 equiv) was dissolved in tetrahydrofuran (40 mL). Triethylamine (1.7 mL, 12 mmol, 2.0 equiv) and phenylsilane (2.3 mL, 18 mmol, 3.0 equiv) were added to the solution and the reaction mixture was stirred for 3 h at 23 °C. Excess silane was quenched by addition of water (6 mL) and stirring for 15 min. The reaction mixture was diluted with diethyl ether (200 mL) and washed with water (2 × 100 mL) and saturated aqueous sodium chloride solution (100 mL). The organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and purified by flash column chromatography on silica gel to afford 3-(3,4-dimethoxyphenyl)-propanal (**S57**) (1.16 g, 86% over 3 steps) as a colorless oil.

The analytical data were in full agreement with those reported in the literature.[146]



Ethyl (*E*)-5-(3,4-dimethoxyphenyl)-2-methylpent-2-enoate (**S58**):

To a solution of aldehyde **S57** (2.03 g, 10.5 mmol, 1 equiv) in dichloromethane (52 mL, 0.20 M) was added ethyl 2-(triphenyl-l5-phosphaneylidene)propanoate (7.58 g, 20.9 mmol, 2.00 equiv) at 23 °C and the resulting pale yellow solution was stirred at 23 C. After 16 h the mixture was concentrated and the yellow solid was purified by flash column chromatography (30% diethyl ether in petrol ether) to yield ester **S58** (2.92 g, 10.5 mmol, >99%) as a colorless oil.

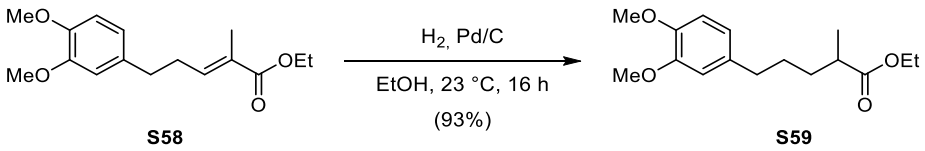
TLC (15% ethyl acetate in cyclohexane): R_f: 0.15 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 – 6.76 (m, 2H), 6.76 – 6.67 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 2.70 (dd, *J* = 8.6, 6.8 Hz, 2H), 2.54 – 2.41 (m, 2H), 1.82 – 1.72 (m, 3H), 1.29 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 149.0, 147.5, 141.1, 134.0, 128.6, 120.3, 111.9, 111.4, 60.6, 56.1, 56.0, 34.5, 30.9, 14.4, 12.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2935 (*m*), 2834 (*m*), 1707 (*s*), 1649 (*w*), 1591 (*w*), 1516 (*s*), 1464 (*m*), 1418 (*m*), 1367 (*w*), 1262 (*s*), 1240 (*s*), 1156 (*m*), 1141 (*m*), 1112 (*m*), 1078 (*m*), 1030 (*m*), 807 (*w*), 764 (*w*).

HRMS (ESI): calcd for $C_{16}H_{22}NaO_4$ $[M+Na]^+$: 301.1410; found: 301.1390.



Ethyl 5-(3,4-dimethoxyphenyl)-2-methylpentanoate (**S59**)

To a solution of ester **S58** (2.91 g, 10.5 mmol, 1 equiv) in ethanol (105 mL, 0.10 M) was added palladium on charcoal (10% palladium on activated charcoal, 1.11 g, 1.05 mmol, 10 mol%) and the resulting black suspension was sparged with hydrogen gas for 20 min and stirring under hydrogen atmosphere was continued until full conversion. After 16 h Celite® was added and the mixture was filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure and the crude

product was purified by flash column chromatography on silica gel (30% diethyl ether in petrol ether) to yield ester **S59** (2.73 g, 10.5 mmol, 93%) as a colorless oil.

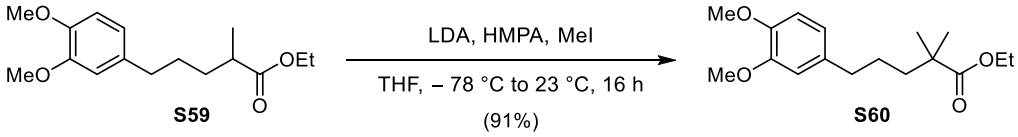
TLC (20% ethyl acetate in cyclohexane): R_f: 0.31 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 – 6.76 (m, 1H), 6.72 – 6.66 (m, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.59 – 2.52 (m, 2H), 2.49 – 2.38 (m, 1H), 1.77 – 1.65 (m, 1H), 1.65 – 1.55 (m, 2H), 1.52 – 1.39 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 148.9, 147.3, 135.0, 120.3, 111.9, 111.3, 60.3, 56.1, 56.0, 40.0, 35.5, 33.5, 29.4, 17.3, 14.4.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2938 (*m*), 2859 (*m*), 2835 (*m*), 1730 (*s*), 1590 (*w*), 1516 (*s*), 1464 (*m*), 1418 (*m*), 1377 (*w*), 1260 (*m*), 1238 (*m*), 1189 (*m*), 1156 (*m*), 1156 (*m*). 1030 (*m*), 808 (*w*), 764 (*w*).

HRMS (ESI): calcd for $C_{16}H_{24}NaO_4$ $[M+Na]^+$: 303.1567; found: 303.1548.



Ethyl 5-(3,4-dimethoxyphenyl)-2,2-dimethylpentanoate (S60)

To a solution of *N*,*N*′-diisopropylamine (1.26 mL, 8.92 mmol, 5.00 equiv) in tetrahydrofuran (18 mL, 0.50 M) was added *n*-butyllithium (2.10 M in hexanes, 4.08 mL, 8.56 mmol, 4.80 equiv) dropwise at –78°C. The mixture was warmed to 0 °C. Hexamethylphosphoramide (3.10 mL, 17.8 mmol, 10.0 equiv) was added dropwise and the solution was stirred for 30 min at 0 °C before a solution of ester **S59** (500 mg, 1.78 mmol, 1 equiv) in tetrahydrofuran (1.8 mL, 1.0 M) was added dropwise at 0 °C. After 60 min, the mixture was cooled to –78 °C and iodomethane (781 µL, 12.5 mmol, 7.00 equiv) was added dropwise. The reaction mixture was allowed to warm to 23 °C. After 16 h, excess of iodomethane was removed by distillation under reduced pressure (200 mbar). The solution was diluted with diethyl ether (30 mL) and aqueous hydrochloric acid (2.0 M, 50 mL) was added to quench excess of. The layers were separated and the aqueous layer was extracted with diethyl ether (3×40 mL). The combined organic layers were washed with water and saturated aqueous sodium chloride solution and dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel (30% diethyl ether in petrol ether) to yield ester **S60** (478 mg, 1.62 mmol, 91%) as a colorless oil.

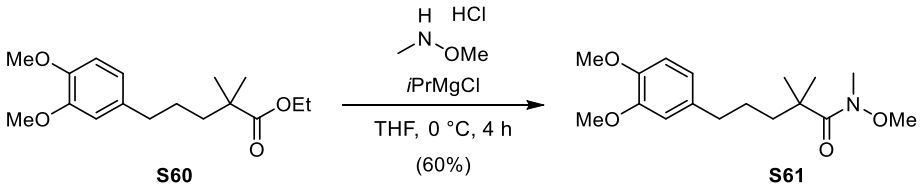
TLC (20% ethyl acetate in cyclohexane): R_f: 0.29 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, *J* = 7.9 Hz, 1H), 6.73 – 6.66 (m, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.53 (td, *J* = 5.6, 4.3, 2.4 Hz, 2H), 1.61 – 1.49 (m, 4H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.15 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.1, 148.9, 147.3, 135.1, 120.3, 111.9, 111.3, 60.3, 56.1, 56.0, 42.2, 40.4, 36.0, 27.1, 25.3, 14.4.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2938 (*m*), 2872 (*m*) 1725 (*s*), 1590 (*w*), 1516 (*s*), 1465 (*m*), 1417 (*w*), 1386 (*w*), 1366 (*w*), 1261 (*m*), 1237 (*m*), 1176 (*m*), 1141 (*m*), 1030 (*m*), 764 (*w*).

HRMS (ESI): calcd for $C_{17}H_{26}NaO_4$ $[M+Na]^+$: 317.1723; found: 317.1703.



5-(3,4-dimethoxyphenyl)-N-methoxy-N,2,2-trimethylpentanamide (**S61**)

To a solution of ester **S60** (471 mg, 1.60 mmol, 1 equiv) and *N*,*O*-dimethylhydroxylamine hydrochloride (780 mg, 8.00 mmol, 5.00 equiv) in tetrahydrofuran (16 mL, 0.10 M) was added isopropylmagnesium chloride (2.00 M in tetrahydrofuran, 7.20 mL, 14.4 mmol, 9.00 equiv) dropwise at 0 °C. After 4 h the mixture was diluted with diethyl ether (20 mL) and excess of base was quenched with saturated aqueous ammonium chloride solution (40 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3×20mL). The combined organic layers were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel (60% diethyl ether in petrol ether) to yield Weinreb amide **S61** (298 mg, 962 µmol, 60%) as a pale yellow oil and starting material **S60** (160 mg, 543 µmol, 34%).

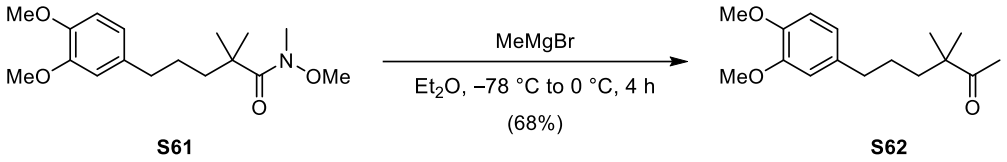
TLC (20% ethyl acetate in cyclohexane): R_f: 0.10 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 – 6.74 (m, 1H), 6.73 – 6.67 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.59 (s, 3H), 3.15 (s, 3H), 2.54 (t, *J* = 7.3 Hz, 2H), 1.68 – 1.60 (m, 2H), 1.60 – 1.50 (m, 2H), 1.21 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.8, 148.9, 147.2, 135.2, 120.4, 111.9, 111.3, 60.5, 56.1, 56.0, 43.2, 39.6, 36.0, 33.9, 27.0, 25.7.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2934 (*s*), 2835(*m*), 1644(*s*), 1590 (*w*), 1515 (*s*), 1464 (*m*), 1417 (*m*), 1386 (*w*), 1355 (*m*), 1261 (*m*), 1236 (*m*), 1156 (*m*), 1030 (*m*), 944 (*m*), 808 (*w*), 763 (*w*),

HRMS (ESI): calcd for $C_{17}H_{27}NNaO_4$ $[M+Na]^+$: 332.1832; found: 332.1812.



S61 **S62**

6-(3,4-dimethoxyphenyl)-3,3-dimethylhexan-2-one (S62)

To a solution of Weinreb amide **S61** (250 mg, 808 µmol, 1 equiv) in diethyl ether (8.0 mL, 0.10 M) was added a methylmagnesium bromide solution (1.00 M in tetrahydrofuran, 1.62 mL, 1.62 mmol, 2.00 equiv) dropwise at –78°C and after complete addition the reaction mixture was allowed to warm up to 0 °C. After 4 h excess of base was quenched by the addition of aqueous hydrogen chloride solution (1.0 M, 20 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3×20mL). The combined organic layers dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel chromatography (30% diethyl ether in petrol ether) to yield ketone **S62** (148 mg, 560 µmol, 68%) as a yellow oil.

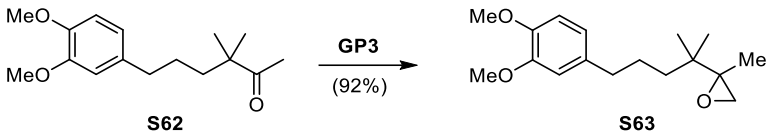
TLC (20% ethyl acetate in cyclohexane): R_f: 0.23 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, *J* = 7.9 Hz, 1H), 6.72 – 6.63 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 2.52 (t, *J* = 7.1 Hz, 2H), 2.05 (s, 3H), 1.57 – 1.40 (m, 4H), 1.09 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.1, 148.9, 147.3, 134.8, 120.3, 111.8, 111.3, 56.0, 55.9, 47.8, 39.5, 36.0, 26.8, 25.1, 24.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2936 (*s*), 2861 (*m*), 1703 (*s*), 1590 (*w*), 1516 (*w*), 1464 (*m*), 1417 (*m*), 1354 (*w*), 1261 (*m*), 1237 (*m*), 1141 (*m*), 1030 (*m*).

HRMS (ESI): calcd for $C_{16}H_{24}NaO_3$ $[M+Na]^+$: 287.1618; found: 287.1601.



S62 S63

2-(5-(3,4-dimethoxyphenyl)-2-methylpentan-2-yl)-2-methyloxirane (S63) was prepared according to **GP3** (2.0 equiv NaH, 2.0 equiv Me_3SI) from **S62** (548 µmol, 1 equiv) in 92% yield as a pale yellow oil. Purified by flash column chromatography on silica gel (30% diethyl ether in petrol ether).

TLC (20% ethyl acetate in cyclohexane): R_f: 0.29 (UV, CAM)

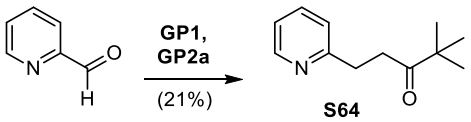
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.37 (m, 2H), 7.32 (ddd, *J* = 7.9, 6.8, 1.2 Hz, 2H), 7.26 – 7.17 (m, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 6.55 – 6.45 (m, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 2.97 (dd, *J* = 4.3, 0.7 Hz, 1H), 2.77 (d, *J* = 4.3 Hz, 1H), 2.32 (ddd, *J* = 13.7, 11.3, 5.2 Hz, 1H), 2.21 (ddd, *J* = 13.7, 11.3, 6.0 Hz, 1H), 1.86 (ddd, *J* = 14.8, 11.3, 6.0 Hz, 1H), 1.74 (ddd, *J* = 14.8, 11.3, 5.3 Hz, 1H), 1.34 (s, 3H), 1.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 147.2, 135.3, 120.3, 111.9, 111.3, 61.3, 56.1, 56.0, 51.3, 39.5, 36.4, 36.1, 26.4, 23.6, 23.5, 18.7.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2938 (*s*), 1590 (*w*), 1515 (*s*), 1464 (*m*), 1378 (*w*), 1261 (*m*), 1237 (*m*), 1141 (*m*), 1030 (*m*), 806 (*w*).

HRMS (ESI): calcd for $C_{17}H_{26}NaO_3$ $[M+Na]^+$: 301.1774; found: 301.1756.

9.2.2.10 Unsuccessful substrates



S64

4,4-dimethyl-1-(pyridin-2-yl)pentan-3-one (**S64**) was prepared according to **GP1** (t = 4 h) from pyridine-2-carbaldehyde (5 mmol, 1 equiv) and pinacolone (1.5 equiv) and **GP2a** (1% Pd, t = 5 h) in 21% yield as a colorless oil. Purified by flash column chromatography on silica gel (25% ethyl acetate in cyclohexane grading to 50% ethyl acetate in cyclohexane).

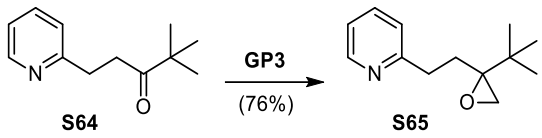
TLC (50% ethyl acetate in cyclohexane): R_f: 0.43 ($KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.48 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.54 (td, *J* = 7.7, 1.8 Hz, 1H), 7.16 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.06 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 3.04 – 2.95 (m, 4H), 1.10 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 215.2, 161.1, 149.3, 136.4, 123.4, 121.2, 44.2, 36.1, 32.2, 26.5.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2967 (*m*), 2907 (*w*), 2871 (*w*), 1702 (*s*), 1591 (*m*), 1569 (*w*), 1475 (*s*), 1435 (*m*), 1394 (*w*), 1365 (*m*), 1295 (*w*), 1224 (*w*), 1147 (*w*), 1078 (*m*), 1050 (*w*), 985 (*m*), 828 (*w*), 788 (*w*), 756 (*s*), 628 (*w*), 599 (*w*), 557 (*w*), 512 (*w*), 462 (*w*).

HRMS (ESI): calcd for $C_{12}H_{18}NO$ $[M+H]^+$: 192.1383; found: 192.1382.



2-(2-(2-(tert-butyl)oxiran-2-yl)ethyl)pyridine (**S65**) was prepared according to **GP3** (1.6 equiv NaH, 1.5 equiv Me_3SI) from **S64** (1.0 mmol, 1 equiv) in 76% yield as a colorless oil. Purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane grading to 25% ethyl acetate in cyclohexane).

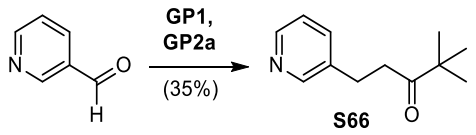
TLC (50% ethyl acetate in cyclohexane): R_f: 0.50 ($KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (dd, *J* = 4.9, 1.2 Hz, 1H), 7.55 (td, *J* = 7.7, 1.9 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.07 (ddd, *J* = 7.7, 4.9, 1.1 Hz, 1H), 2.74 (d, *J* = 4.2 Hz, 1H), 2.73 – 2.57 (m, 2H), 2.64 (d, *J* = 4.1 Hz, 1H), 2.27 (ddd, *J* = 14.6, 10.9, 6.0 Hz, 1H), 2.12 (ddd, *J* = 14.6, 10.9, 5.6 Hz, 1H), 0.94 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 162.0, 149.3, 136.5, 122.9, 121.1, 63.4, 47.9, 34.1, 33.1, 29.4, 26.1.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3052 (*w*), 3008 (*w*), 2961 (*s*), 2872 (*w*), 1593 (*s*), 1569 (*m*), 1474 (*s*), 1434 (*s*), 1394 (*w*), 1364 (*m*), 1316 (*w*), 1291 (*w*), 1257 (*w*), 1211 (*w*), 1147 (*m*), 1126 (*w*), 1095 (*w*), 1051 (*w*), 992 (*m*), 932 (*w*), 896 (*m*), 829 (*m*), 794 (*w*), 769 (*s*), 749 (*s*), 670 (*w*), 627 (*w*), 591 (*w*), 554 (*m*), 516 (*m*).

HRMS (ESI): calcd for $C_{13}H_{20}NO$ $[M+H]^+$: 206.1539; found: 206.1526.



4,4-dimethyl-1-(pyridin-3-yl)pentan-3-one (**S66**) was prepared according to **GP1** (t = 4 h) from pyridine-3-carbaldehyde (5.0 mmol, 1 equiv) and pinacolone (1.5 equiv) and **GP2a** (2% Pd, t = 5 h)

in 35% yield as a colorless oil. Purified by flash column chromatography on silica gel (25% ethyl acetate in cyclohexane grading to 50% ethyl acetate in cyclohexane).

TLC (50% ethyl acetate in cyclohexane): R_f: 0.33 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.46 (d, *J* = 2.3 Hz, 1H), 8.44 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.51 (dt, *J* = 7.8, 2.0 Hz, 1H), 7.19 (dd, *J* = 7.8, 4.8 Hz, 1H), 2.92 – 2.86 (m, 2H), 2.83 – 2.77 (m, 2H), 1.10 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 214.3, 150.0, 147.7, 137.0, 136.1, 123.4, 44.2, 38.0, 27.2, 26.4.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3030 (*w*), 2967 (*s*), 2933 (*w*), 2908 (*w*), 2870 (*w*), 1702 (*s*), 1592 (*w*), 1575 (*w*), 1478 (*s*), 1445 (*w*), 1423 (*m*), 1395 (*w*), 1366 (*m*), 1294 (*w*), 1224 (*w*), 1191 (*w*), 1158 (*w*), 1125 (*w*), 1105 (*w*), 1078 (*s*), 1044 (*w*), 1026 (*m*), 982 (*m*), 939 (*w*), 867 (*w*), 826 (*w*), 802 (*m*), 756 (*w*), 714 (*s*), 631 (*m*), 596 (*w*), 553 (*w*), 505 (*w*), 455 (*w*).

HRMS (ESI): calcd for $C_{12}H_{18}NO$ $[M+H]^+$: 192.1383; found: 192.1279.

3-(2-(2-(*tert*-butyl)oxiran-2-yl)ethyl)pyridine (**S67**) was prepared according to **GP3** (1.6 equiv NaH, 1.5 equiv Me_3SI) from **S66** (0.50 mmol, 1 equiv) in 89% yield as yellowish oil. Purified by flash column chromatography on silica gel (25% ethyl acetate in cyclohexane grading to 50% ethyl acetate in cyclohexane).

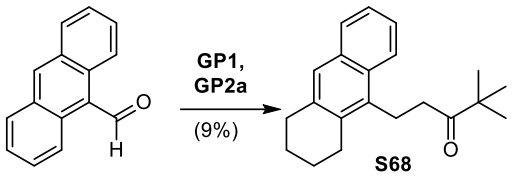
TLC (50% ethyl acetate in cyclohexane): R_f: 0.36 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.45 – 8.41 (m, 1H), 7.49 (ddd, *J* = 7.8, 2.4, 1.6 Hz, 1H), 7.19 (ddd, *J* = 7.7, 4.7, 0.9 Hz, 1H), 2.79 (d, *J* = 4.2 Hz, 1H), 2.65 (d, *J* = 4.1 Hz, 1H), 2.60 – 2.40 (m, 2H), 2.17 – 1.94 (m, 2H), 0.96 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 150.0, 147.6, 137.5, 135.9, 123.5, 63.3, 48.0, 34.1, 31.1, 27.8, 26.1.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3051 (*w*), 3027 (*w*), 2960 (*s*), 2872 (*m*), 1704 (*w*), 1591 (*w*), 1575 (*m*), 1479 (*s*), 1423 (*s*), 1395 (*w*), 1365 (*m*), 1291 (*w*), 1257 (*w*), 1210 (*w*), 1194 (*w*), 1146 (*w*), 1126 (*w*), 1103 (*w*), 1079 (*w*), 1027 (*m*), 978 (*w*), 930 (*w*), 895 (*w*), 843 (*w*), 827 (*m*), 801 (*m*), 751 (*w*), 715 (*s*), 676 (*w*), 630 (*w*), 587 (*w*), 553 (*w*), 526 (*w*).

HRMS (ESI): calcd for $C_{13}H_{20}NO$ $[M+H]^+$: 206.1539; found: 206.1536.



4,4-dimethyl-1-(1,2,3,4-tetrahydroanthracen-9-yl)pentan-3-one (**S68**) was prepared according to **GP1** (t = 2 h) from anthracene-9-carbaldehyde (10 mmol, 1 equiv) and pinacolone (1.5 equiv) and **GP2a** (2% Pd, t = 36 h) in 9% yield as a pale yellow solid. Purified by flash column chromatography on silica gel (1% ethyl acetate in cyclohexane grading to 5% ethyl acetate in cyclohexane grading to 10% ethyl acetate in cyclohexane). Note: very difficult separation from byproducts.

TLC (10% ethyl acetate in hexanes): R_f: 0.46 (CAM)

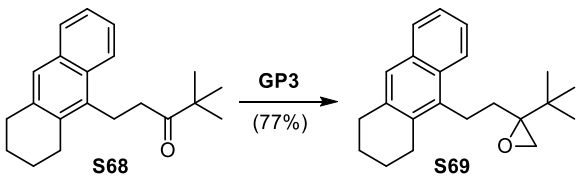
mp: 66.0 – 67.9 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.5 Hz, 1H), 7.74 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.48 (s, 1H), 7.45 – 7.36 (m, 2H), 3.37 – 3.28 (m, 2H), 2.99 (t, *J* = 6.1 Hz, 2H), 2.93 (t, *J* = 6.5 Hz, 2H), 2.80 – 2.73 (m, 2H), 1.97 – 1.88 (m, 2H), 1.88 – 1.80 (m, 2H), 1.17 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.69, 136.4, 134.6, 133.6, 132.4, 130.5, 128.1, 126.1, 125.4, 124.9, 123.2, 44.4, 36.6, 31.0, 27.1, 26.5, 23.8, 22.9, 22.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3063 (*w*), 2965 (*w*), 2930 (*s*), 2866 (*m*), 2835 (*w*), 1703 (*s*), 1595 (*w*), 1566 (*w*), 1500 (*m*), 1476 (*s*), 1434 (*w*), 1409 (*w*), 1393 (*w*), 1365 (*w*), 1327 (*w*), 1316 (*w*), 1291 (*w*), 1252 (*w*), 1234 (*w*), 1168 (*w*), 1078 (*s*), 1023 (*w*), 979 (*m*), 949 (*w*), 911 (*m*), 874 (*m*), 847 (*m*), 824 (*w*), 773 (*w*), 745 (*s*), 673 (*w*), 650 (*w*), 638 (*w*), 606 (*w*), 553 (*w*), 470 (*w*), 447 (*w*), 421 (*w*), 413 (*w*).

HRMS (ESI) calcd for $C_{21}H_{26}NaO$ $[M+Na]^+$: 317.1876; found: 317.1834.



2-(*tert*-butyl)-2-(2-(1,2,3,4-tetrahydroanthracen-9-yl)ethyl)oxirane (**S69**) was prepared according to **GP3** (1.6 equiv NaH, 1.5 equiv Me_3SI) from **S68** (0.5 mmol, 1 equiv) in 77% yield as a colorless solid. Purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane grading to 10% ethyl acetate in cyclohexane).

TLC (10% ethyl acetate in hexanes): Rf: 0.50 (CAM)

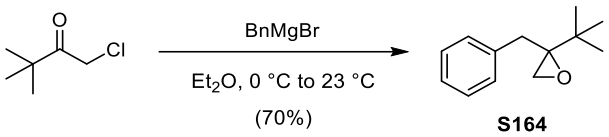
mp: 109.0 – 112.7 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.73 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.47 (s, 1H), 7.44 (ddd, *J* = 8.5, 6.8, 1.6 Hz, 1H), 7.39 (ddd, *J* = 7.9, 6.7, 1.3 Hz, 1H), 3.06 – 2.96 (m, 3H), 2.96 – 2.84 (m, 5H), 2.12 (ddd, *J* = 14.9, 12.5, 5.6 Hz, 1H), 2.05 – 1.98 (m, 1H), 1.98 – 1.89 (m, 2H), 1.89 – 1.81 (m, 2H), 1.01 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.3, 135.1, 133.4, 132.4, 130.6, 128.0, 125.9, 125.3, 124.8, 123.4, 63.8, 48.1, 34.2, 31.0, 29.1, 27.0, 26.2, 23.9, 23.0, 22.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3051 (w), 1956 (w), 2930 (s), 2869 (m), 2834 (w), 1704 (w), 1594 (w), 1567 (w), 1500 (w), 1476 (m), 1449 (w), 1434 (w), 1393 (w), 1363 (m), 1342 (w), 1327 (w), 1316 (w), 1252 (w), 1234 (w), 1210 (w), 1176 (w9, 1145 (w), 1124 (w), 1102 (w), 1077 (w), 1058 (w), 1028 (w), 1002 (w), 973 (w), 938 (w), 911 (w), 874 (w), 844 8m), 825 (w), 806 (w9, 778 (w9, 744 (s), 706 (w), 582 (w), 658 (w), 639 (w), 596 (w), 559 (w), 524 (w), 483 (w), 455 (w).

HRMS (ESI) calcd for $C_{22}H_{28}NaO$ $[M+Na]^+$: 331.2032; found: 331.2023.



S164

2-benzyl-2-(*tert*-butyl)oxirane (S164) To a solution of 1-chloro-3,3-dimethylbutan-2-one (1.01 mL, 7.43 mmol, 1 equiv) in diethyl ether (14.8 mL) was added a solution of benzylmagnesium bromide (1.00 M in tetrahydrofuran, 9.66 mL, 9.66 mmol 1.30 equiv.) at 0 °C and the reaction mixture was slowly allowed to warm to 23 °C. After 5 h the mixture was cooled to 0 °C and excess of Grignard reagent was quenched by addition of saturated aqueous ammonium chloride solution. x 25 mL) and the combined organic were dried over sodium sulfate, filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% diethyl ether in *n*-pentane) to afforded epoxide **S164** (988 mg, 5.19 mmol, 70%) as a pale yellow oil.

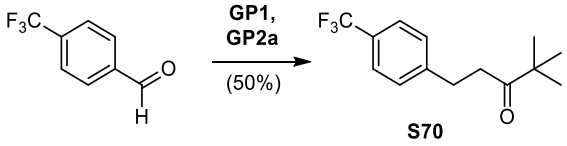
TLC (10% ethyl acetate in cyclohexane): R_f: 0.50 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.10 (m, 5H), 3.05 (s, 2H), 2.59 (d, *J* = 4.4 Hz, 1H), 2.01 (d, *J* = 4.5 Hz, 1H), 1.03 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.0, 130.5, 128.1, 126.4, 63.6, 47.6, 35.8, 34.1, 26.4.

HRMS (ESI): calcd for $C_{13}H_{18}NaO$ $[M+Na]^+$: 213.1250; found: 213.1241.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3028 (*m*), 2961 (*s*), 2872 (*m*), 1480 (*m*), 1454 (*m*), 1394 (*m*), 1365 (*m*), 1311 (*m*), 1202 (*w*), 1119 (*m*), 1078 (*w*), 1031 (*m*), 971 (*m*), 899 (*m*), 816 (*m*), 755 (*m*), 698 (*s*), 658 (*m*).



S70

4,4-dimethyl-1-(4-(trifluoromethyl)phenyl)pentan-3-one (**S70**) was prepared according to **GP1** (t = 2 h) from 4-trifluoromethyl benzaldehyde (25 mmol, 1 equiv) and pinacolone (1.5 equiv) and **GP2b** (4 equiv Mg, T = 0 °C, t = 3 h) in 50% yield as a colorless oil. Purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane).

TLC (5% diethyl ether in *n*–pentane): R_f: 0.46 (UV, CAM)

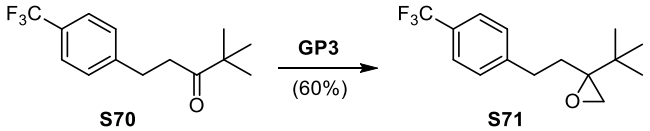
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 2.93 (t, J = 7.4 Hz, 2H), 2.81 (ddd, J = 8.0, 7.0, 1.0 Hz, 2H), 1.11 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 214.5, 145.9, 128.9, 128.6 (q, J = 32.3 Hz), 125.5 (q, J = 3.8 Hz), 124.4 (q, J = 271.8 Hz), 44.2, 38.1, 29.9, 26.5.

^{19}F NMR (376 MHz, Chloroform-d) δ -62.37.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2970 (w,br), 1704 (m), 1618 (w), 1479 (w), 1418 (w), 1367 (w), 1322 (s), 1162 (m), 1120 (s), 1066 (s), 1018 (m), 982 (w), 832 (m), 735 (w) cm^{-1}.

HRMS (ESI): calcd for $C_{14}H_{18}F_3O$ $[M+H]^+$: 259.1304; found: 259.1304.



S70 **S71**

2-(*tert*-butyl)-2-(4-(trifluoromethyl)phenethyl)oxirane (**S71**) was prepared according to **GP3** (2.0 equiv NaH, 1.9 equiv Me_3SI) from **S70** (1.50 mmol, 1 equiv) in 60% yield as a colorless oil. Purified by flash column chromatography on silica gel (5% diethyl ether in *n*-pentane).

TLC (5% diethyl ether in *n*-pentane) R_f: 0.48 (UV, CAM)

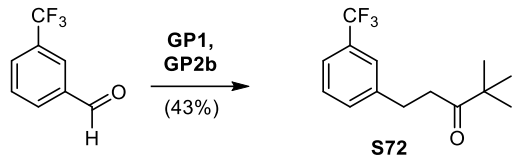
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (d, J = 7.7 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H), 2.61 (dd, J = 4.1, 0.8 Hz, 1H), 2.46 (d, J = 4.1 Hz, 1H), 2.45 – 2.26 (m, 2H), 2.03 – 1.79 (m, 2H), 0.79 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 146.5, 128.8, 128.4 (q, J = 32.3 Hz), 125.5 (q, J = 3.8 Hz), 124.5 (q, J = 271.9 Hz), 63.3, 48.0, 34.1, 31.2, 30.5, 26.1.

^{19}F NMR (376 MHz, Chloroform-d) δ -62.33.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2963 (*br w*), 1619 (*w*), 1481 (*w*), 1417 (*w*), 1365 (*w*), 1324 (*s*), 1163 (*m*), 1122 (*s*), 1068 (*s*), 1019 (*w*), 932 (*w*), 836 (*w*).

HRMS (ESI) calcd for $C_{15}H_{19}F_3O_2Na$ $[M+Na]^{\cdot}$: 295.1280; found: 295.1274.



S72

1-(3-trifluoromethylphenyl)-4,4-dimethylpentan-3-one (**S72**) was prepared according to **GP1** (t = 3 h) from 3-trifluoromethylbenzaldehyde (5.0 mmol, 1 equiv) and pinacolone (1.5 equiv) and **GP2b** (4 equiv Mg, T = –30 °C, t = 4 h) in 43% yield as a yellow oil. Purified by flash column chromatography on silica gel (10% diethyl ether in *n*-pentane).

TLC (10% diethyl ether in *n*-pentane) R_f: 0.41 (UV, $KMnO_4$)

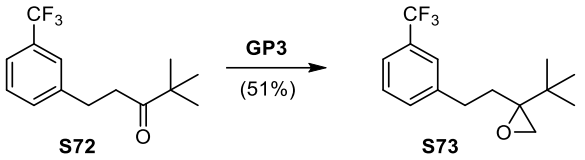
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.34 (m, 4H), 2.99 – 2.89 (m, 2H), 2.87 – 2.72 (m, 2H), 1.11 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 214.5, 142.6, 132.1, 130.9 (d, *J* = 32.2 Hz), 129.0, 125.2 (d, *J* = 3.3 Hz), 124.3 (d, *J* = 271.9 Hz), 123.1 (d, *J* = 3.4 Hz), 44.2, 38.2, 29.9, 26.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.60.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2970 (w), 2909 (*w*), 2873 (*w*), 1705 (*m*), 1478 (*w*), 1450 (*w*), 1329 (*s*), 1200 (*w*), 1163 (*m*), 1123 (*s*), 1098 (*w*), 1074 (*m*), 983 (*w*), 802 (*w*), 703 (*w*).

HRMS (ESI): calcd for $C_{14}H_{17}F_3ONa$ $[M+Na]^+$: 281.1129; found: 281.1119.



3-trifluoromethyl-2-(3-methylphenethyl)oxirane (**S73**) was prepared according to **GP3** (3.0 equiv NaH, 2.7 equiv Me_3SI) from **S72** (1.5 mmol, 1 equiv) in 51% yield as a yellow oil. Purified by flash column chromatography on silica gel (5% diethyl ether in *n*-pentane).

TLC (10% diethyl ether in *n*-pentane) R_f 0.55 (UV, $KMnO_4$)

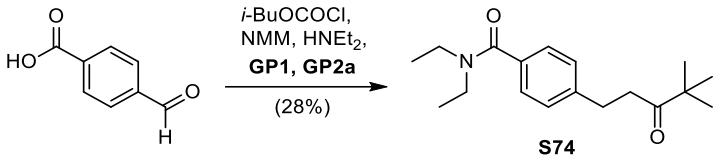
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.41 (m, 2H), 7.41 – 7.31 (m, 2H), 2.80 (d, *J* = 4.1 Hz, 1H), 2.65 (d, *J* = 4.1 Hz, 1H), 2.63 – 2.44 (m, 2H), 2.24 – 1.92 (m, 2H), 0.98 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 131.9, 131.1, 130.9 (d, J = 31.9 Hz), 129.0, 125.1 (q, J = 3.4 Hz), 124.37 (q, J= 271.87 Hz), 122.9 (q, *J* = 3.6 Hz), 63.3, 48.1, 34.1, 31.3, 30.5, 26.1.

^{19}F NMR (282 MHz, $CDCl_3$) δ -62.57.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2970 (*w*), 2911 (*w*), 2874 (*w*), 1705 (*m*), 1616 (*w*), 1479 (*w*), 1450 (*w*), 1330 (*s*), 1199 (*w*), 1330 (*s*), 1199 (*w*), 1164 (*m*), 1125 (*s*), 1098 (*w*), 1074 (*m*), 983 (*w*), 802 (*w*), 703 (*w*).

HRMS (ESI): calcd for $C_{15}H_{19}F_3ONa$ $[M+Na]^+$: 295.1286; found: 295.1273.



4-(4,4-dimethyl-3-oxopentyl)-N,N-diethylbenzamide (**S74**) A solution of 4-carboxy benzaldehyde (3.00 g, 20.0 mmol, 1 equiv) in dichloromethane (40 mL) was treated with *N*-methyl morpholine (3.03 g, 30.0 mmol, 1.50 equiv) and *iso*-butyl chlorocarbonate (3.55 g, 26.0 mmol, 1.3 equiv) at –15 °C. The mixture stirred for 30 min before the cooling bath was removed. After 1 h diethylamine (3.10 mL, 30.0 mmol, 1.50 equiv) was added dropwise at –15 °C. After 4.5 h aqueous hydrogen chloride solution (1 M, 30 mL) was added and the layers were separated. The organic layer was washed with aqueous hydrogen chloride solution (1 M, 2×30 mL) and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude amide was subjected to **GP1** (t = 2.5 h, 1.5 equiv pinacolone) and **GP2b** (4 equiv Mg, T = 0 °C, t = 4 h) to yield **S74** in 28% yield as a colorless oil. Purified by flash

column chromatography on silica gel (10% ethyl acetate in cyclohexane grading to 40% ethyl acetate in cyclohexane).

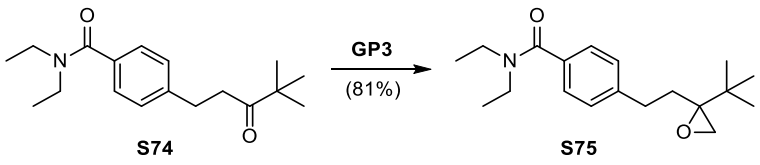
TLC (30% ethyl acetate in *n*-pentane): R_f: 0.19 (UV, $KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 – 7.26 (m, 2H), 7.22 – 7.17 (m, 2H), 3.51 (s, 2H), 3.38 – 3.13 (m, 2H), 2.96 – 2.84 (m, 2H), 2.82 – 2.73 (m, 2H), 1.31 – 1.11 (m, 6H), 1.10 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 214.8, 171.5, 142.9, 135.1, 128.6, 126.7, 44.2, 43.6 (*br*), 39.4 (*br*), 38.4, 30.0, 26.5, 14.3 (*br*), 13.1 (*br*).

IR (ATR, neat) $\tilde{\nu}_{max}$: 2969 (*br m*), 1703 (*m*), 1627 (*s*), 1512 (*w*), 1474 (*m*), 1425 (*s*), 1365 (*m*), 1315 (*m*), 1286 (*m*), 1221 (*w*), 1094 (*m*), 1079 (*m*), 983 (*w*), 835 (*m*), 790 (*w*), 761 (*w*).

HRMS (ESI): calcd for $C_{18}H_{27}NO_2Na$ $[M+Na]^+$: 312.1934; found: 312.1926.



4-(2-(2-(tert-butyl)oxiran-2-yl)ethyl)-N,N-diethylbenzamide (**S75**) was prepared according to **GP3** (2.0 equiv NaH, 1.9 equiv Me_3SI) from **S74** (1.50 mmol, 1 equiv) in 81% yield as a colorless oil. Purified by flash column chromatography on silica gel (35% ethyl acetate in *n*-pentane).

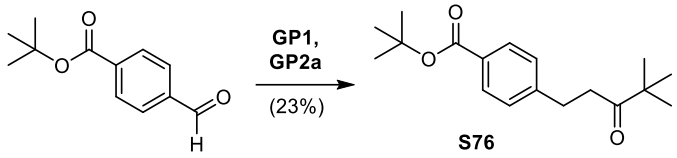
TLC (5% ethyl acetate in *n*-pentane) R_f: 0.24 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 – 7.26 (m, 2H), 7.21 – 7.16 (m, 2H), 3.61 – 3.42 (m, 2H), 3.27 (s, 2H), 2.77 (dd, J = 4.1, 0.7 Hz, 1H), 2.65 (d, J = 4.1 Hz, 1H), 2.52 (dddd, J = 39.6, 13.6, 11.4, 5.5 Hz, 2H), 2.05 (dddd, J = 45.7, 14.7, 11.4, 5.5 Hz, 2H), 1.29 – 1.17 (m, 3H), 1.17 – 1.09 (m, 3H), 0.96 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 171.5, 143.5, 135.0, 128.4, 126.6, 63.4, 48.1, 43.4, 39.3, 34.1, 31.3, 30.5, 26.2, 14.4, 13.0.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2967 (*br m*), 2873 (*w*), 1630 (*s*), 1458 (*m*), 1425 (*m*), 1381 (*w*), 1364 (*w*), 1315 (*w*), 1286 (*m*), 1220 (*w*), 1094 (*m*), 940 (*w*), 835 (*m*).

HRMS (ESI) calcd for $C_{19}H_{29}NO_2Na$ $[M+Na]^+$: 326.2091; found: 326.2083.



***tert*-butyl 4-(4,4-dimethyl-3-oxopentyl)benzoate** (**S76**) was prepared according to **GP1** (t = 3 h) from *t*-butyl 4-formylbenzoate (10 mmol, 1 equiv) and pinacolone (1.5 equiv) and **GP2a** (1% Pd, t = 16 h) in 23% yield as a colorless solid. Purified by flash column chromatography on silica gel (10% ethyl acetate in petrol ether).

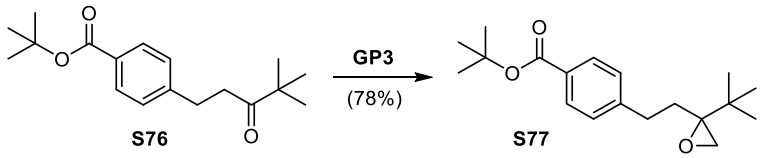
TLC (10% ethyl acetate in petrol ether) R_f 0.21 (UV, $KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 2.92 (t, *J* = 7.4 Hz, 2H), 2.80 (ddd, *J* = 8.1, 6.9, 1.0 Hz, 2H), 1.58 (s, 9H), 1.10 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.6, 165.9, 146.7, 130.1, 129.8, 128.4, 80.9, 44.2, 38.2, 30.1, 28.4, 26.5.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2971 (*m*), 2933 (*w*), 2871 (*w*), 1709 (*s*), 1612 (*w*), 1367 (*m*), 1292 (*s*), 1255 (*w*), 1167(*m*), 1115 (*m*), 1078 (*w*).

HRMS (ESI): calcd for $C_{18}H_{26}O_3Na$ $[M+Na]^+$: 313.1780; found: 313.1761.



***tert*-butyl 4-(2-(2-(tert-butyl)oxiran-2-yl)ethyl)benzoate** (**S77**) was prepared according to **GP3** (3.0 equiv NaH, 2.9 equiv Me_3SI) from **S76** (1.5 mmol, 1 equiv) in 78% yield as a yellow oil. Purified by flash column chromatography on silica gel (10% ethyl acetate in petrol ether).

TLC (5% ethyl acetate in petrol ether) R_f 0.45 (UV, CAM)

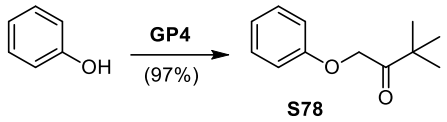
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.87 (m, 2H), 7.24 – 7.17 (m, 2H), 2.78 (dd, *J* = 4.1, 0.8 Hz, 1H), 2.65 (d, *J* = 4.2 Hz, 1H), 2.63 – 2.56 (m, 1H), 2.50 (ddd, *J* = 13.7, 11.4, 6.0 Hz, 1H), 2.12 (ddd, *J* = 14.6, 11.3, 6.0 Hz, 1H), 2.01 (ddd, *J* = 14.6, 11.4, 5.3 Hz, 1H), 1.58 (s, 9H), 0.96 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 147.3, 129.9, 129.8, 128.3, 80.9, 63.4, 48.1, 34.1, 31.2, 30.7, 28.4, 26.2.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2970 (*m*), 2935 (*m*), 2872 (*w*), 1711 (*s*), 1611 (*w*), 1478 (*w*), 1458 (*w*), 1393 (*w*), 1367 (*w*), 1309 (*s*), 1292 (*w*), 1255 (*w*), 1167 (*s*), 1116 (*m*), 1020 (*w*), 851 (*w*), 769 (*w*).

HRMS (ESI): calcd for $C_{19}H_{28}O_3Na$ $[M+Na]^+$: 327.1931; found: 327.1919.

9.2.2.11 Chromanes



3,3-dimethyl-1-phenoxybutan-2-one (**S78**) was prepared according to **GP4** from phenol (1.4 mmol, 1 equiv) and 1-bromo-3,3-dimethylbutan-2-one (1.0 equiv) in 97% yield as a colorless oil. Purified by flash column chromatography on silica gel (20% diethyl ether in petrol ether).

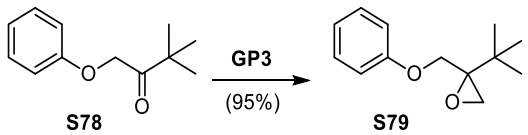
TLC (10% ethyl acetate in cyclohexane): R_f: 0.35 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.15 (m, 2H), 6.91 (tt, *J* = 7.4, 1.0 Hz, 1H), 6.86 – 6.76 (m, 2H), 4.80 (s, 2H), 1.19 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.6, 158.2, 129.6, 121.6, 114.8, 69.0, 43.3, 26.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3065 (*w*), 3042 (*w*), 2967 (*s*), 2873 (*m*), 1723 (*s*), 1599 (*s*), 1589 (*m*), 1495 (*s*), 1432 (*m*), 1396 (*w*), 1368 (*w*), 1308 (*w*), 1226 (*s*), 1174 (*w*), 1107 (*w*), 1079 (*w*), 1049 (*m*), 988 (*m*), 880 (*w*), 753 (*m*), 690 (*m*).

HRMS (ESI): calcd for $C_{12}H_{16}NaO_2$ $[M+Na]^+$: 215.1043; found: 215.1042.



2-(*tert*-butyl)-2-(phenoxymethyl)oxirane (**S79**) was prepared according to **GP3** (2.0 equiv NaH, 2.0 equiv Me_3SI) from **S78** (1.2 mmol, 1 equiv) in 95% yield as a pale yellow oil. Purified by flash column chromatography on silica gel (10% diethyl ether in *n*-pentane).

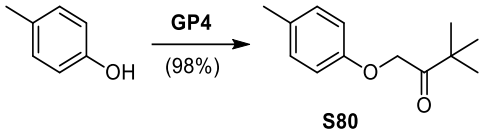
TLC (10% ethyl acetate in cyclohexane): R_f: 0.47 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.15 (m, 2H), 6.90 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.87 – 6.82 (m, 2H), 4.24 (d, *J* = 10.8 Hz, 1H), 3.96 (d, *J* = 10.8 Hz, 1H), 2.82 (s, 2H), 1.00 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 129.6, 121.25, 114.8, 68.4, 62.5, 48.5, 32.9, 26.3.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3064 (*w*), 2962 (*s*), 2874 (*m*), 1599 (*s*), 1588 (*m*), 1496 (*m*), 1397 (*m*), 1366 (*w*), 1300 (*w*), 1242 (*s*), 1167 (*m*), 1078 (*w*), 1046 (*m*), 940 (*w*), 902 (*w*), 831 (*w*), 787 (*w*), 752 (*m*), 691 (*m*).

HRMS (ESI): calcd for $C_{13}H_{18}NaO_2$ $[M+Na]^+$: 229.1199; found: 229.1199.



S80

3,3-dimethyl-1-(*p*-tolyloxy)butan-2-one (**S80**) was prepared according to **GP4** from *p*-cresol (1.4 mmol, 1 equiv) and 1-bromo-3,3-dimethylbutan-2-one (1.0 equiv) in 98% yield as a colorless solid. Purified by flash column chromatography on silica gel (10% diethyl ether in petrol ether).

TLC (10% ethyl acetate in cyclohexane): R_f: 0.33 (UV, CAM)

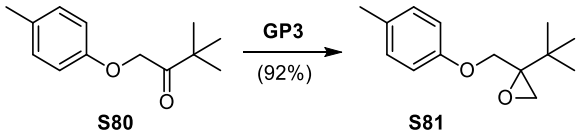
mp: 44.1 – 44.3 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 – 7.03 (m, 2H), 6.84 – 6.73 (m, 2H), 4.83 (s, 2H), 2.28 (s, 3H), 1.24 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.8, 156.1, 130.9, 130.1, 114.7, 69.3, 43.3, 26.5, 20.6.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3031 (*w*), 2966 (*m*), 2872 (*m*), 1725 (*s*), 1613 (*w*), 1587 (*w*), 1510 (*s*), 1478 (*m*), 1367 (*w*), 1299 (*w*), 1229 (*w*), 1178 (*m*), 1112 (*w*), 1048 (*m*), 991 (*m*), 817 (*w*).

HRMS (ESI): calcd for $C_{13}H_{18}NaO_2$ $[M+Na]^+$: 229.1199; found: 229.1194.



S80 **S81**

2-(*tert*-butyl)-2-((*p*-tolyloxy)methyl)oxirane (**S81**) was prepared according to **GP3** (2.0 equiv NaH, 2.0 equiv Me_3SI) from **S80** (1.3 mmol, 1 equiv) in 92% yield as a colorless solid. Purified by flash column chromatography on silica gel (10% diethyl ether in *n*-pentane).

TLC (10% ethyl acetate in cyclohexane): R_f: 0.35 (UV, CAM)

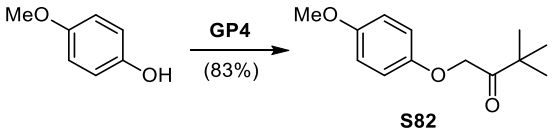
mp: 48.5 – 50.4 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.02 (m, 2H), 6.84 – 6.75 (m, 2H), 4.27 (d, *J* = 10.8 Hz, 1H), 3.98 (d, *J* = 10.8 Hz, 1H), 2.87 (s, 2H), 2.28 (s, 3H), 1.05 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 130.4, 130.0, 114.6, 68.6, 62.6, 48.5, 32.9, 26.4, 20.6.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2961 (*s*), 2873 (*m*), 1614 (*w*), 1512 (*s*), 1480 (*w*), 1397 (*w*), 1366 (*w*), 1290 (*w*), 1243 (*m*), 1168 (*w*), 1047 (*m*), 1040 (*w*), 817 (*w*).

HRMS (ESI): calcd for $C_{14}H_{20}NaO_2$ $[M+Na]^+$: 243.1356; found: 243.1355.



S82

1-(4-methoxyphenoxy)-3,3-dimethylbutan-2-one (**S82**) was prepared according to **GP4** from 4-methoxyphenol (1.4 mmol, 1 equiv) and 1-bromo-3,3-dimethylbutan-2-one (1.0 equiv) in 83% yield as a colorless oil. Purified by flash column chromatography on silica gel (30% diethyl ether in *n*-pentane).

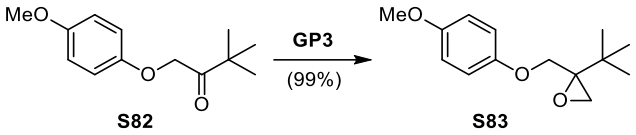
TLC (10% ethyl acetate in cyclohexane): R_f: 0.19 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 – 6.77 (m, 4H), 4.81 (s, 2H), 3.76 (s, 3H), 1.24 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 210.0, 154.5, 152.5, 116.1, 114.8, 70.1, 55.8, 43.3, 26.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2965 (*m*), 2909 (*m*), 2835 (*w*), 1723 (*s*), 1506 (*s*), 1478 (*m*), 1506 (*s*), 1478 (*w*), 1465 (*w*), 1368 (*w*), 1223 (s), 1181 (*w*), 1108 (*w*), 1048 (*m*), 991 (*m*), 825 (*m*), 720 (*w*).

HRMS (ESI): calcd for $C_{13}H_{19}O_3$ $[M+H]^+$: 223.1329; found: 223.1327.



S82 **S83**

2-(*tert*-butyl)-2-((4-methoxyphenoxy)methyl)oxirane (**S83**) was prepared according to **GP3** (2.0 equiv NaH, 2.0 equiv Me_3SI) from **S82** (1.2 mmol, 1 equiv) in 99% yield as a colorless solid. Purified by flash column chromatography on silica gel (15% diethyl ether in *n*-pentane).

TLC (10% ethyl acetate in cyclohexane): R_f: 0.29 (UV, CAM)

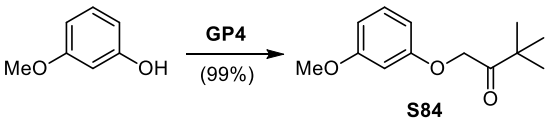
mp: 53.5 – 54.3 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 – 6.78 (m, 4H), 4.24 (d, *J* = 10.8 Hz, 1H), 3.97 (d, *J* = 10.7 Hz, 1H), 3.76 (s, 3H), 2.92 – 2.80 (m, 2H), 1.05 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 153.1, 115.8, 114.8, 69.2, 62.6, 55.9, 48.5, 32.9, 26.4.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2961 (*w*), 2834 (*m*), 1508 (*s*), 1465 (*m*), 1398 (*w*), 1366 (*w*), 1230 (*s*), 1180 (*w*), 1107 (*w*), 1046 (*m*), 940 (*w*), 825 (*m*), 751 (*w*).

HRMS (ESI): calcd for $C_{14}H_{20}NaO_3$ $[M+Na]^+$: 259,1305; found: 259.1303.



S84

1-(3-methoxyphenoxy)-3,3-dimethylbutan-2-one (**S84**) was prepared according to **GP4** from 4-methoxyphenol (1.4 mmol, 1 equiv) and 1-bromo-3,3-dimethylbutan-2-one (1.0 equiv) in 99% yield as a colorless oil. Purified by flash column chromatography on silica gel (20% diethyl ether in *n*-pentane).

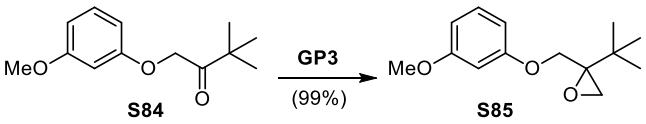
TLC (10% ethyl acetate in cyclohexane): R_f: 0.21 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.07 (m, 1H), 6.52 (ddd, *J* = 8.3, 2.4, 0.9 Hz, 1H), 6.48 – 6.40 (m, 2H), 4.83 (s, 2H), 3.76 (s, 3H), 1.23 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.4, 160.9, 159.3, 130.0, 107.2, 106.6, 101.4, 68.90, 55.3, 43.2, 26.4.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2965 (*m*), 2873 (*m*), 2837 (*m*), 1723 (*s*), 1593 (*s*), 1491 (*s*), 1457 (*m*), 1437 (*m*), 1396 (*m*), 1368 (*w*), 1334 (*w*), 1283 (*m*), 1263 (*m*), 1199 (*m*), 1156 (*s*), 1124 (*w*), 1102 (*w*), 1049 (*m*), 999 (*m*), 990 (*m*), 931 (*m*), 833 (*m*), 761 (*m*), 685 (*m*).

HRMS (ESI): calcd for $C_{13}H_{18}NaO_3$ $[M+Na]^+$: 245.1148; found: 245.1144.



S84 **S85**

2-(*tert*-butyl)-2-((3-methoxyphenoxy)methyl)oxirane (**S85**) was prepared according to **GP3** (2.0 equiv NaH, 2.0 equiv Me_3SI) from **S84** (1.2 mmol, 1 equiv) in 99% yield as a pale yellow oil. Purified by flash column chromatography on silica gel (10% diethyl ether in *n*-pentane).

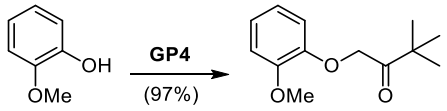
TLC (10% ethyl acetate in cyclohexane): R_f: 0.33 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, *J* = 8.2 Hz, 1H), 6.56 – 6.42 (m, 3H), 4.28 (d, *J* = 10.8 Hz, 1H), 3.99 (d, *J* = 10.8 Hz, 1H), 3.79 (s, 3H), 2.87 (s, 2H), 1.05 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 160.0, 130.0, 106.9, 106.8, 101.3, 68.5, 62.5, 55.4, 48.5, 32.9, 26.3.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2961 (*s*), 2875 (*m*), 2836 (*w)*, 1594 (*s*), 1492 (*s*), 1398 (*m*), 1366 (*w*), 1334 (*w*), 1285 (*m*), 1265 (*m*), 1201 (*m*), 1149 (*s*), 1082 (*w*), 1049 (*m*), 936 (*w*), 835 (*w*), 762 (*w*), 686 (*w*).

HRMS (ESI): calcd for $C_{14}H_{20}NaO_3$ $[M+Na]^+$: 259,1305; found: 259.1303.



S86

1-(2-methoxyphenoxy)-3,3-dimethylbutan-2-one (**S86**) was prepared according to **GP4** from 4-methoxyphenol (1.4 mmol, 1 equiv) and 1-bromo-3,3-dimethylbutan-2-one (1.0 equiv) in 97% yield as a colorless solid. Purified by flash column chromatography on silica gel (20% diethyl ether in *n*-pentane).

TLC (10% ethyl acetate in cyclohexane): R_f: 0.21 (UV, CAM)

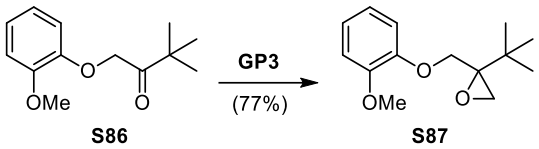
mp: 65.9 - 72.8 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 – 6.80 (m, 3H), 6.73 (dd, *J* = 7.9, 1.5 Hz, 1H), 4.93 (s, 2H), 3.86 (s, 3H), 1.22 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.4, 149.8, 147.7, 122.3, 120.8, 114.4, 112.2, 70.1, 56.0, 43.1, 26.4.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3074 (*w*), 2983 (*m*), 2961 (*s*), 2931 (*m*), 2868 (*m*), 2840 (*m*), 1714 (*s*), 1591 (*m*), 1502 (*s*), 1477 (*m*), 1457 (*m*), 1427 (*m*), 1396 (*m)*, 1368 (*m*), 1331 (*m*), 1294 (*m*), 1273 (*s*), 1244 (*s*), 1217 (*m*), 1179 (*m*), 1132 (*m*), 1094 (*m*), 1057 (*m*), 1045 (*m*), 1027 (*m*), 988 (*s*), 963 (*s*), 782 (*m*), 747 (*m*).

HRMS (ESI): calcd for $C_{13}H_{18}NaO_3$ $[M+Na]^+$: 245.1148; found: 245.1147.



S86 **S87**

2-(*tert*-butyl)-2-((2-methoxyphenoxy)methyl)oxirane (**S87**) was prepared according to **GP3** (2.0 equiv NaH, 2.0 equiv Me_3SI) from **S86** (1.2 mmol, 1 equiv) in 77% yield as a pale yellow solid. Purified by flash column chromatography on silica gel (10% diethyl ether in *n*-pentane).

TLC (10% ethyl acetate in cyclohexane): R_f: 0.29 (UV, CAM)

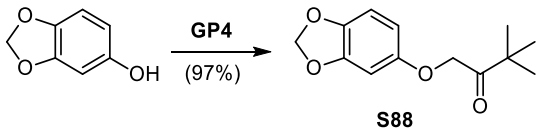
mp: 49.5 - 51.2 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 – 6.82 (m, 4H), 4.36 (dd, *J* = 11.1, 0.7 Hz, 1H), 4.08 (d, *J* = 11.1 Hz, 1H), 3.84 (s, 3H), 2.97 (d, *J* = 4.7 Hz, 1H), 2.86 (d, *J* = 4.7 Hz, 1H), 1.06 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.0, 148.7, 121.8, 121.0, 114.5, 112.3, 69.5, 62.7, 56.1, 48.3, 32.9, 26.3.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3064 (*w*), 2960 (*s*), 2874 (*m*), 2835 (*m*), 1593 (*m*), 1505 (*s*), 1455 (*m*), 1398 (*w*), 1455 (*w*), 1398 (*w*), 1366 (*w*), 1330 (*w*), 1252 (*s*), 1224 (*m*), 1179 (*m*), 1122 (*m*), 1029 (*m*), 940 (*w*), 904 (*w*), 831 (*w*), 742 (*w*).

HRMS (ESI): calcd for $C_{14}H_{20}NaO_3$ $[M+Na]^+$: 259.1305; found: 259.1302.



S88

1-(benzo[*d*][1,3]dioxol-5-yloxy)-3,3-dimethylbutan-2-one (**S88**) was prepared according to **GP4** from sesamol (1.4 mmol, 1 equiv) and 1-bromo-3,3-dimethylbutan-2-one (1.0 equiv) in 97% yield as a colorless oil. Purified by flash column chromatography on silica gel (18% diethyl ether in petrol ether).

TLC (10% ethyl acetate in cyclohexane): R_f: 0.22 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (d, *J* = 8.5 Hz, 1H), 6.51 (d, *J* = 2.6 Hz, 1H), 6.28 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.91 (s, 2H), 4.79 (s, 2H), 1.23 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.7, 153.8, 148.5, 142.4, 108.0, 106.2, 101.4, 98.7, 70.2, 43.3, 26.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2967 (*m*), 2905 (*m*), 1722 (*s*), 1630 (*w*), 1502 (*m*), 1484 (*s*), 1396 (*w*), 1367 (*w*), 1243 (*w*), 1182 (*s*), 1142 (*w*), 1077 (*m*), 1035 (*s*), 990 (*s*), 937 (*m*), 837 (*w*), 815 (*m*), 782 (*m*), 747 (*w*), 713 (*w*), 612 (*w*).

HRMS (ESI): calcd for $C_{13}H_{16}NaO_4$ $[M+Na]^+$: 259.0941; found: 259.0924.

S88 **S89**

5-((2-(*tert*-butyl)oxiran-2-yl)methoxy)benzo[*d*][1,3]dioxole (**S89**) was prepared according to **GP3** (2.0 equiv NaH, 2.0 equiv Me_3SI) from **S88** (1.1 mmol, 1 equiv) in 97% yield as a pale yellow oil. Purified by flash column chromatography on silica gel (15% diethyl ether in *n*-pentane).

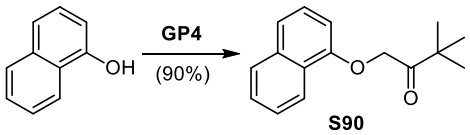
TLC (10% ethyl acetate in cyclohexane): R_f: 0.34 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (d, *J* = 8.5 Hz, 1H), 6.49 (d, *J* = 2.5 Hz, 1H), 6.31 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.91 (s, 2H), 4.21 (d, *J* = 10.8 Hz, 1H), 3.94 (d, *J* = 10.8 Hz, 1H), 2.86 (s, 2H), 1.04 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 148.4, 142.0, 108.0, 106.0, 101.3, 98.5, 69.5, 62.5, 48.5, 32.9, 26.3.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2963 (*m*), 2876 (*m*), 1712 (*w*), 1631 (*w*), 1608 (*w*), 1503 (*m*), 1487 (*s*), 1397 (*w*), 1366 (*w*), 1270 (*w*), 1242 (*w*), 1186 (*s*), 1134 (*m*), 1102 (*m*), 1037 (*m*), 939(*w*), 839 (*w*), 816 (*w*).

HRMS (ESI): calcd for $C_{14}H_{18}NaO_4$ $[M+Na]^+$: 273.1097; found: 273.1094.



S90

3,3-dimethyl-1-(naphthalen-1-yloxy)butan-2-one (**S90**) was prepared according to **GP4** from 1-naphthol (1.5 mmol, 1 equiv) and 1-bromo-3,3-dimethylbutan-2-one (1.0 equiv) in 90% yield as a colorless solid. Purified by flash column chromatography on silica gel (10% diethyl ether in *n*-pentane).

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

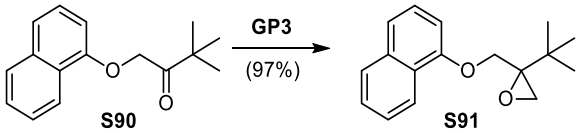
mp: 54.1 – 55.7 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 – 8.35 (m, 1H), 7.87 – 7.78 (m, 1H), 7.57 – 7.43 (m, 3H), 7.40 – 7.30 (m, 1H), 6.66 (dd, *J* = 7.7, 0.9 Hz, 1H), 5.04 (s, 2H), 1.30 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.4, 154.0, 134.71, 127.51, 126.68, 125.81, 125.60, 125.57, 122.35, 121.27, 105.14, 69.46, 43.38, 26.48.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3053 (*w*), 2967 (*m*), 1725 (*s*), 1597 (*w*), 1581 (*m*), 1509 (*m*), 1464 (*m*), 1397 (*s*), 1367 (*w*), 1273 (*w*), 1234 (*m*), 1124 (*w*), 1087 (*w*), 1059 (*m*), 989 (*w*), 791 (*w*), 771 (*m*).

HRMS (ESI): calcd for $C_{16}H_{18}NaO_2$ $[M+Na]^+$: 265,1199; found: 265.1192.



2-(*tert*-butyl)-2-((naphthalen-1-yloxy)methyl)oxirane (**S91**) was prepared according to **GP3** (2.0 equiv NaH, 2.0 equiv Me_3SI) from **S90** (1.3 mmol, 1 equiv) in 97% yield as a colorless oil. Purified by flash column chromatography on silica gel (10% diethyl ether in *n*-pentane).

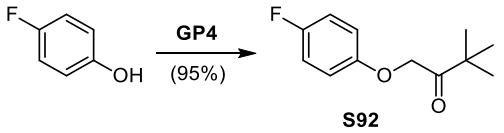
TLC: (10% ethyl acetate in cyclohexane): R_f: 0.40 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.21 (m, 1H), 7.88 – 7.79 (m, 1H), 7.56 – 7.43 (m, 3H), 7.38 (dd, *J* = 8.3, 7.5 Hz, 1H), 6.81 (dd, *J* = 7.5, 1.0 Hz, 1H), 4.51 (d, *J* = 10.6 Hz, 1H), 4.16 (d, *J* = 10.6 Hz, 1H), 3.05 – 2.93 (m, 2H), 1.15 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 134.6, 127.6, 126.6, 125.9, 125.7, 125.4, 122.2, 120.7, 104.8, 69.0, 62.6, 48.8, 32.9, 26.4.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3055 (*m*), 2961 (*s*), 2873 (*m*), 1595 (*m*), 1580 (*s*), 1509 (*m*), 1479 (*m*), 1462 (*m*), 1394 (*s*), 1365 (*m*), 1267 (*s*), 1239 (*s*), 1214 (*w*), 1178 (*w*), 1156 (*m*), 1099 (*s*), 1069 (*m*), 1020 (*m*), 1001 (*m*), 940 (*w*), 790 (*m*), 769 (*m*), 572 (*m*).

HRMS (ESI) calcd for $C_{17}H_{20}NaO_2$ $[M+Na]^+$: 279,1356; found: 279,1354.



S92

1-(4-fluorophenoxy)-3,3-dimethylbutan-2-one (**S92**) was prepared according to **GP4** from 4-fluorophenol (1.4 mmol, 1 equiv) and 1-bromo-3,3-dimethylbutan-2-one (1.0 equiv) in 95% yield as a colorless oil. Purified by flash column chromatography on silica gel (15% diethyl ether in *n*-pentane).

TLC (10% ethyl acetate in cyclohexane): R_f: 0.27 (UV, CAM)

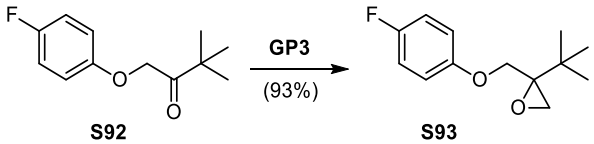
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 – 6.92 (m, 2H), 6.88 – 6.79 (m, 2H), 4.83 (s, 2H), 1.24 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.6, 157.8 (d, *J* = 239.3 Hz), 154.4 (d, *J* = 2.2 Hz), 116.1 (d, *J* = 4.8 Hz), 116.0 (d, *J* = 10.2 Hz), 69.8, 43.3, 26.5.

^{19}F NMR (282 MHz, $CDCl_3$) δ -122.95.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2968 (*m*), 1723 (*s*), 1505 (*s*), 1479 (*m*), 1368 (*w*), 1297 (*m*), 1208 (*m*), 1098 (*w*), 1048 (*m*), 991 (*m*), 827 (*m*), 800 (*w*), 727 (*w*).

HRMS (ESI): calcd for $C_{12}H_{16}FO_2$ $[M+H]^+$: 211.1129; found: 211.1122.



S92 **S93**

2-(*tert*-butyl)-2-((4-fluorophenoxy)methyl)oxirane (**S93**) was prepared according to **GP3** (2.0 equiv NaH, 2.0 equiv Me_3SI) from **S92** (1.2 mmol, 1 equiv) in 93% yield as a colorless solid. Purified by flash column chromatography on silica gel (10% diethyl ether in *n*-pentane).

TLC (10% ethyl acetate in cyclohexane): R_f: 0.38 (UV, CAM)

mp: 35.2 – 38.0 °C

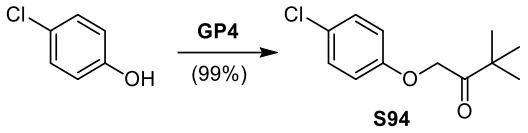
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 – 6.91 (m, 2H), 6.88 – 6.78 (m, 2H), 4.24 (d, *J* = 10.8 Hz, 1H), 4.00 (d, *J* = 10.8 Hz, 1H), 2.87 (s, 2H), 1.05 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6 (d, *J* = 238.6 Hz), 155.0 (d, *J* = 2.1 Hz), 116.0 (d, *J* = 19.2 Hz), 115.8 (d, *J* = 4.0 Hz), 69.1, 62.5, 48.4, 32.9, 26.3.

^{19}F NMR (282 MHz, $CDCl_3$) δ -123.63.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2964 (*m*), 2877 (*w*), 1507 (*s*), 1480 (*m)*, 1397 (*w*), 1366 (*w*), 1248 (*m*), 1208 (*s*), 1097 (*w*), 1045 (*m*), 940 (*w*), 828 (*m*), 767 (*w*).

HRMS (ESI): calcd for $C_{13}H_{17}FNaO_2$ $[M+Na]^+$: 247,1105; found: 247.1104.



S94

1-(4-chlorophenoxy)-3,3-dimethylbutan-2-one (**S94**) was prepared according to **GP4** from 4-chlorophenol (1.4 mmol, 1 equiv) and 1-bromo-3,3-dimethylbutan-2-one (1.0 equiv) in 99% yield as a colorless solid. Purified by flash column chromatography on silica gel (18% diethyl ether in *n*-pentane).

TLC (5% ethyl acetate in cyclohexane): R_f: 0.15 (UV, CAM)

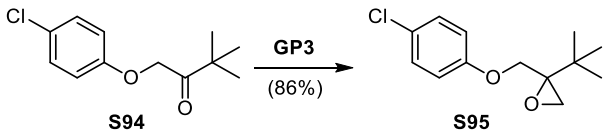
mp: 60.9 – 63.1 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.18 (m, 2H), 6.83 – 6.75 (m, 2H), 4.84 (s, 2H), 1.24 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.3, 156.8, 129.5, 126.6, 116.2, 69.2, 43.3, 26.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2968 (*m*), 1723 (*s*), 1594 (*w*), 1491 (*s*), 1368 (*w*), 1304 (*w*), 1233 (*m*), 1172 (*w*), 1093 (*w*), 1047 (*m*), 991 (*m*), 823 (*w*).

HRMS (ESI): calcd for $C_{12}H_{15}ClNaO_2$ $[M+Na]^+$: 249.0653; found: 249.0652.



S94 **S95**

2-(*tert*-butyl)-2-((4-chlorophenoxy)methyl)oxirane (**S95**) was prepared according to **GP3** (2.0 equiv NaH, 2.0 equiv Me_3SI) from **S94** (0.9 mmol, 1 equiv) in 86% yield as a colorless solid. Purified by flash column chromatography on silica gel (10% diethyl ether in petrol ether).

TLC (10% ethyl acetate in cyclohexane): R_f: 0.45 (UV, CAM)

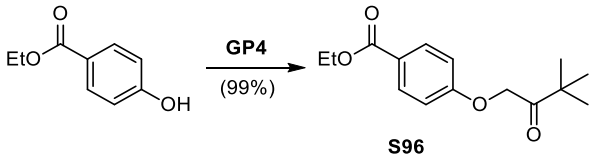
mp: 57.3 – 58.1 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.18 (m, 2H), 6.86 – 6.77 (m, 2H), 4.24 (d, *J* = 10.8 Hz, 1H), 4.01 (d, *J* = 10.8 Hz, 1H), 2.91 – 2.82 (m, 2H), 1.04 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 129.5, 126.1, 116.1, 68.7, 62.5, 48.4, 32.9, 26.3.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3063 (*w*), 2965 (*m*), 2874 (*m*), 1728 (*w*), 1597 (*w*), 1582 (*w*), 1492 (*s*), 1397 (*w*), 1365 (*w*), 1286 (*w*), 1244 (*s*), 1167 (*w*), 1093 (*w*), 1044 (*w*), 938 (*w*), 824 (*m*).

HRMS (ESI): calcd for $C_{13}H_{17}ClNaO_2$ $[M+Na]^+$: 263,0809; found: 263,0809.



S96

ethyl 4-(3,3-dimethyl-2-oxobutoxy)benzoate (**S96**) was prepared according to **GP4** from ethyl 4-hydroxybenzoate (1.5 mmol, 1 equiv) and 1-bromo-3,3-dimethylbutan-2-one (1.0 equiv) in 99% yield as a colorless solid. Purified by flash column chromatography on silica gel (15% diethyl ether in *n*-pentane).

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

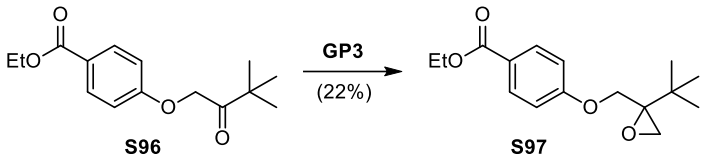
mp: 47.8 - 50.0 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.95 (m, 2H), 6.91 – 6.83 (m, 2H), 4.93 (s, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.26 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.9, 166.3, 161.8, 131.7, 123.9, 114.3, 68.7, 60.8, 43.3, 26.5, 14.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2971 (*m*), 1709 (*s*), 1605 (*s*), 1583 (*w*), 1510 (*m*), 1478 (*w*), 1419 (*m*), 1393 (*w*), 1367 (*m*), 1315 (*w*), 1274 (*s*), 1238 (*s*), 1169 (*s*), 1105 (*s*), 1047 (*m*), 1019 (*w*), 991 (*m*), 848 (*w*), 770 (*m*), 696 (*w*).

HRMS (ESI): calcd for $C_{15}H_{21}O_4$ $[M+H]^+$: 265,1434; found: 265,1434.



S96 S97

ethyl 4-((2-(*tert*-butyl)oxiran-2-yl)methoxy)benzoate (**S97**) was prepared according to **GP3** (2.0 equiv NaH, 2.0 equiv Me_3SI) from **S96** (1.5 mmol, 1 equiv) in 22% yield as a pale yellow oil. Purified by flash column chromatography on silica gel (15% diethyl ether in petrol ether).

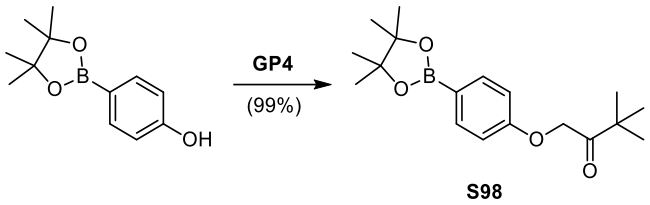
TLC (10% ethyl acetate in cyclohexane): R_f: 0.31 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.90 (m, 2H), 6.97 – 6.83 (m, 2H), 4.40 – 4.24 (m, 3H), 4.09 (d, *J* = 10.9 Hz, 1H), 2.88 (q, *J* = 4.6 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 162.4, 131.7, 123.5, 114.3, 68.5, 62.4, 60.8, 48.4, 32.9, 26.3, 14.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2964 (*m*), 1712 (*s*), 1606 (*s*), 1581 (*w*), 1510 (*m*), 1479 (*w*), 1421 (*w*), 1396 (*w*), 1367 (*w*), 1276 (*s*), 1252 (*s*), 1167 (*m*), 1104 (*m*), 1041 (*w*), 848 (*w*), 771 (*m*), 696 (*w*).

HRMS (ESI): calcd for $C_{16}H_{23}O_4$ $[M+H]^+$: 279,1591; found: 279.1590.



S98

3,3-dimethyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)butan-2-one (**S98**) was prepared according to **GP4** from 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (1.5 mmol, 1 equiv) and 1-bromo-3,3-dimethylbutan-2-one (1.0 equiv) in 99% yield as a colorless solid. Purified by flash column chromatography on silica gel (10% diethyl ether in *n*-pentane).

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

mp: 110.2 – 112.1 °C

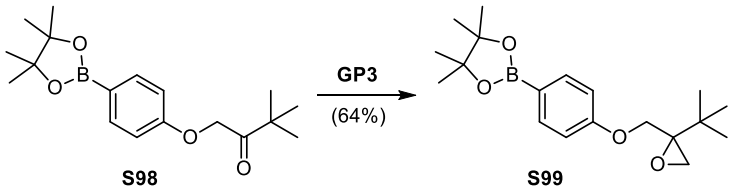
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.63 (m, 2H), 6.98 – 6.75 (m, 2H), 4.88 (s, 2H), 1.32 (s, 12H), 1.24 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.3, 160.7, 136.7, 114.1, 83.7, 68.7, 43.3, 26.5, 25.0.

^{11}B NMR (128 MHz, $CDCl_3$) δ 30.60.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2975 (*m*), 1725 (*s*), 1603 (*s*), 1572 (*w*), 1515 (*w*), 1478 (*w*), 1396 (*m*), 1358 (*s*), 1320 (*m*), 1233 (*m*), 1143 (*s*), 1088 (*m*), 1047 (*m*), 990 (*m*), 963 (*m*), 860 (*m*), 831 (*m*), 735 (*m*).

HRMS (EI): calcd for $C_{18}H_{27}BO_4$ $[M+Na]^+$: 341.1895; found: 341.1892.



2-(4-((2-(*tert*-butyl)oxiran-2-yl)methoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**S99**) was prepared according to **GP3** (2.0 equiv NaH, 2.0 equiv Me_3SI) from **S98** (1.3 mmol, 1 equiv) in 64% yield as colorless needles. Purified by flash column chromatography on silica gel (15% diethyl ether in *n*-pentane).

TLC (10% ethyl acetate in cyclohexane): R_f: 0.34 (UV, CAM)

mp: 79.5 – 81.1 °C

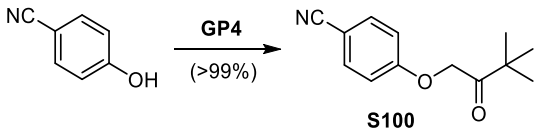
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.64 (m, 2H), 6.98 – 6.77 (m, 2H), 4.31 (d, *J* = 10.8 Hz, 1H), 4.03 (d, *J* = 10.8 Hz, 1H), 2.87 (s, 2H), 1.33 (s, 12H), 1.05 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3, 136.6, 114.1, 83.7, 68.3, 62.5, 48.5, 32.9, 26.4, 25.0.

^{11}B NMR (128 MHz, $CDCl_3$) δ 31.63.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2975 (*m*), 1604 (*s*), 1571 (*w*), 1514 (*w*), 1480 (*m*), 1396 (*m*), 1358 (*s*), 1319 (*m*), 1275 (*m*), 1244 (*m*), 1143 (*m*), 1091 (*m*), 1042 (*m*), 963 (*w*), 860 (*w*), 834 (*m*), 736 (*w*).

HRMS (EI): calcd for $C_{19}H_{29}BO_4$ $[M+Na]^+$: 355.2051; found: 355.2049.



4-(3,3-dimethyl-2-oxobutoxy)benzonitrile (**S100**) was prepared according to **GP4** from 4-hydroxybenzonitrile (1.5 mmol, 1 equiv) and 1-bromo-3,3-dimethylbutan-2-one (1.0 equiv) in

>99% yield as a colorless solid. Purified by flash column chromatography on silica gel (15% diethyl ether in petrol ether).

TLC (20% ethyl acetate in cyclohexane): R_f: 0.19 (UV, CAM)

mp: 85.9 – 87.4 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62 – 7.54 (m, 2H), 6.94 – 6.85 (m, 2H), 4.94 (s, 2H), 1.26 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.4, 161.4, 134.2, 119.1, 115.5, 105.0, 68.6, 43.4, 26.4.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2969, 2871, 2224, 1722, 1605, 1576, 1508, 1479, 1434, 1369, 1310, 1242, 1174, 1046, 992, 834 cm^{-1}.

HRMS (ESI): calcd for $C_{13}H_{15}NNaO_2$ $[M+Na]^+$: 240,0995; found: 240,0993.

4-((2-(tert-butyl)oxiran-2-yl)methoxy)benzonitrile (**S101**) was prepared according to **GP3** (1.6 equiv NaH, 1.6 equiv Me_3SI) from **S100** (2.1 mmol, 1 equiv) in 84% yield as a colorless oil. Purified by flash column chromatography on silica gel (15% diethyl ether in petrol ether).

TLC (20% ethyl acetate in cyclohexane): R_f: 0.21 (UV, CAM)

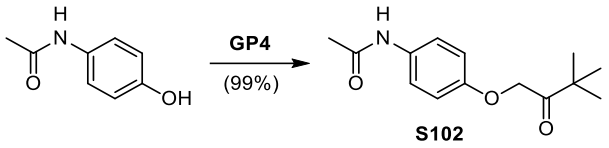
mp: 57.7 – 60.8 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 – 7.50 (m, 2H), 7.02 – 6.89 (m, 2H), 4.30 (d, *J* = 11.0 Hz, 1H), 4.12 (d, *J* = 10.9 Hz, 1H), 2.89 (d, *J* = 4.6 Hz, 1H), 2.84 (d, *J* = 4.5 Hz, 1H), 1.05 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.98, 134.1, 119.2, 115.5, 104.6, 68.6, 62.3, 48.3, 32.9, 26.3.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3069, 2964, 2874, 2225, 1605, 1575, 1509, 1481, 1398, 1367, 1301, 1258, 1172, 1113, 1040, 1018, 942, 836 cm^{-1}.

HRMS (ESI): calcd for $C_{14}H_{17}NNaO_2$ $[M+Na]^+$: 254,1151; found: 254,1150.



***N*-(4-(3,3-dimethyl-2-oxobutoxy)phenyl)acetamide** (**S102**) was prepared according to **GP4** from *N*-(4-hydroxyphenyl)acetamide (1.4 mmol, 1 equiv) and 1-bromo-3,3-dimethylbutan-2-one (1.0 equiv) in 99% yield as a colorless solid. Purified by flash column chromatography on silica gel (10% diethyl ether in *n*-pentane).

TLC (10% ethyl acetate in cyclohexane): R_f: 0.30 (UV, CAM)

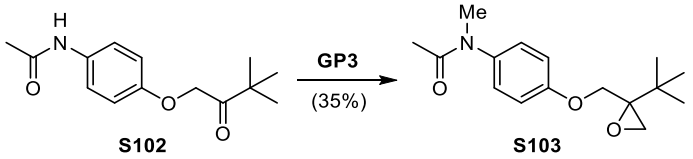
mp: 123.2 – 124.4

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.39 – 7.30 (m, 2H), 6.84 – 6.68 (m, 2H), 4.83 (s, 2H), 2.09 (s, 3H), 1.23 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 210.0, 168.7, 154.8, 132.1, 121.9, 115.1, 69.3, 43.3, 26.5, 24.3.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3304 (br *m*), 3134 (*w*), 3070 (*w*), 2968 (*m*), 1720 (*m*), 1663 (*m*), 1605 (*m*), 1541 (*m*), 1509 (*s*), 1479 (*m*), 1433 (*m*), 1410 (*m*), 1369 (*m*), 1307 (*m*), 1280 (*m*), 1228 (*m*), 1175 (*m*), 1114 (*w*), 1048 (*m*), 993 (*m*), 829 (*m*).

HRMS (ESI): calcd for $C_{14}H_{19}NNaO_3$ $[M+H]^+$: 272.1257; found: 272.1243.



***N*-(4-((2-(tert-butyl)oxiran-2-yl)methoxy)phenyl)-*N*-methylacetamide** (**S103**) was prepared according to **GP3** (2.0 equiv NaH, 2.0 equiv Me_3SI) from **S102** (1.2 mmol, 1 equiv) in 35% yield as a pale yellow oil. Purified by flash column chromatography on silica gel (40% diethyl ether in *n*-pentane).

TLC (30% ethyl acetate in cyclohexane): R_f: 0.07 (UV, CAM)

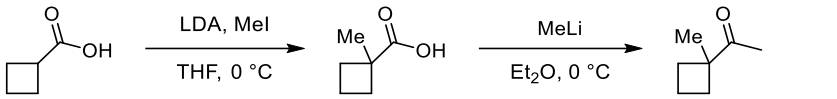
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 – 7.00 (m, 2H), 6.93 – 6.85 (m, 2H), 4.27 (d, *J* = 10.8 Hz, 1H), 4.03 (d, *J* = 10.8 Hz, 1H), 3.19 (s, 3H), 2.90 – 2.81 (m, 2H), 1.82 (s, 3H), 1.04 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 158.0, 137.8, 128.2, 115.7, 68.6, 62.5, 48.4, 37.4, 32.7, 26.3, 22.4.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2965 (*m*), 2927 (*m*), 1726 (*w*), 1660 (*s*), 1512 (*s*), 1380 (*m*), 1299 (*m*), 1245 (*m*), 1143 (*w*), 1045 (*w*), 883 (*w*).

HRMS (ESI): calcd for $C_{16}H_{24}NO_3$ $[M+H]^+$: 278.1751; found: 278.1732.

9.2.2.12 Substrates for alkyl migrations.



S104 **S105** (73% over 2 steps)

Two step alkylation procedure:

1-methylcyclobutane-1-carboxylic acid (**S104**): To a solution of diisopropylamine (10.7 mL, 75.3 mmol, 2.40 equiv) in tetrahydrofuran (90 mL) was added *n-butyllithium (2.5 M in hexanes, 30.1 mL, 75.3 mmol,* 2.40 equiv.) dropwise at 0 °C. The resulting pale yellow solution was stirred at 0 °C. After 15 min a solution of cyclobutanecarboxylic acid (3.00 mL, 31.4 mmol, 1 equiv.) in tetrahydrofuran (10 mL, 3.1 M) was added dropwise at 0 °C. After 15 min methyl iodide (1.96 mL, 31.4 mmol, 1.00 equiv) was added at 0 °C and the pale yellow reaction mixture was slowly allowed to warm up to 23 °C. After 3 d the yellow solution was cooled to 0 °C and excess of base was quenched by addition of aqueous hydrochloric acid (3.00 M, 300 mL), the aqueous layer was extracted with diethyl ether (4 × 250 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (250 mL), dried over sodium sulfate and the filtrate was concentrated under reduced pressure to give an orange oil (3.58 g, 31.4 mmol, quant.), which was used without further purification.

1-(1-methylcyclobutyl)ethan-1-one (**S105**)**:** To an orange solution of crude 1-methylcyclobutane-1-carboxylic acid (3.58 g, 31.4 mmol, 1 equiv.) in diethyl ether (100 mL, 300 mM) was added methyl lithium (1.60 M in diethyl ether, 39.2 mL, 62.7 mmol, 2.00 equiv) dropwise at 0 °C over 3 h (syringe pump 13.1 mL/h). After 8 h the cloudy pale yellow reaction mixture was poured into queous hydrochloric acid (6 M, 200 mL) at 0 °C to quench excess of lithium reagent. The resulting mixture was extracted with diethyl ether (3 × 50 mL) and the combined organic layers were washed with water (50 mL) and saturated aqueous sodium hydrogen carbonate solution (2 × 50 mL). The washed solution was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel (10% diethyl ether in *n*-pentane) to afford the desired ketone **S105** (2.58 g, 23.0 mmol, 73% over two steps) as a colorless to pale yellow oil.

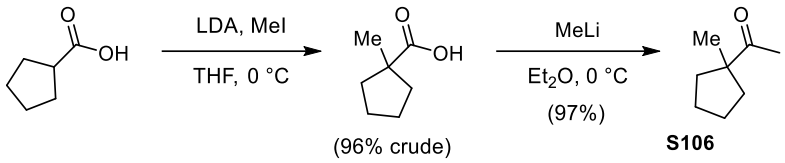
TLC (15% ethyl acetate in cyclohexane): R_f: 0.38 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 – 2.30 (m, 2H), 2.05 (s, 3H), 1.98 – 1.86 (m, 1H), 1.77 – 1.65 (m, 3H), 1.34 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.8, 50.2, 30.3, 24.0, 23.7, 14.4.

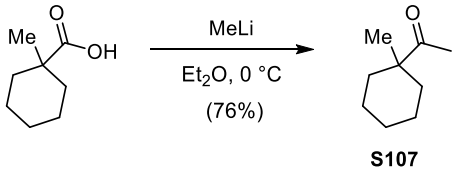
HRMS (ESI): calcd for $C_7H_{13}O$ $[M+H]^+$: 113.0961; found: 113.0965.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2959 (*s*), 2870 (*m*), 1703 (*s*), 1456 (*m*), 1432 (*m*), 1354 (*w*), 1296 (*w*), 1243 (*w*), 1119 (*m*), 964 (*w*).



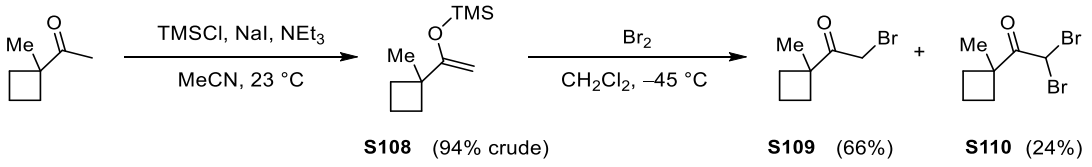
1-(1-methylcyclopentyl)ethan-1-one (**S106**) was prepared from cyclopentanecarboxylic acid (40 mmol, 1 equiv) according to the two step alkylation procedure of 1-(1-methylcyclobutyl)ethan-1-one (**S105**).

The analytical data were in full agreement with those reported in the literature.[147]



1-(1-methylcyclohexyl)ethan-1-one (**S107**) was prepared from 1-methylcyclohexane-1-carboxylic acid (5 mmol, 1 equiv) according to the alkylation procedure of 1-(1-methylcyclobutyl)ethan-1-one (**S105**).

The analytical data were in full agreement with those reported in the literature.[147]



trimethyl((1-(1-methylcyclobutyl)vinyl)oxy)silane (**S108**): To a solution of 1-(1-methylcyclobutyl)ethan-1-one (**S105**) (2.24 g, 20.0 mmol, 1 equiv) and oven dried (110 °C, 2 h) sodium iodide (3.59 g, 24.0 mmol, 1.20 equiv) in acetonitrile (30 mL, 0.67 M) was added triethylamine (4.18 mL, 30.0 mmol, 1.50 equiv) and trimethylsilyl chloride (3.04 mL, 24.0 mmol, 1.20 equiv) in sequence at 23 °C. After 16 h the mixture was diluted with pentane (30 mL) and saturated aqueous ammonium chloride solution (30 mL) was added to quench excess of trimethylsilyl chloride. The aqueous layer was extracted with pentane (3 × 20 mL) and the

combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The combined organic layers were dried over magnesium sulfate, filtered and the filtrate was concentrated under reduced pressure to give crude trimethylsilyl ether **S108** as a colorless oil (3.45 g, 18.7 mmol, 94%), which was used without further purification.

2-bromo-1-(1-methylcyclobutyl)ethan-1-one (**S109**): To a solution of crude trimethylsilyl ether **S108** (3.45 g, 18.7 mmol, 1 equiv) in dichloromethane (120 mL, 0.156 M) was added a solution of bromine (1.06 mL, 20.6 mmol, 1.10 equiv.) in dichloromethane (41.2 mL, 0.500 M) dropwise at –40 °C. After 5 min the brown solution was allowed to warm up to 23 °C and after further 15 min saturated aqueous thiosulfate solution (20 mL) and water (20 mL) were added to quench excess of bromine. The layers were separated and the pale yellow solution was extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried over magnesium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a yellow oil. Purification of the crude product by flash column chromatography on silica gel (150 g silica gel, 10% diethyl ether in *n*-pentane) afforded desired bromoketone **S109** (2.35 g, 12.3 mmol, 66%) as a pale yellow oil and bisbromoketone **S110** (1.21 g, 4.48 mmol, 24%) as yellow needles.

TLC (15% ethyl acetate in cyclohexane): R_f: 0.49 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (s, 2H), 2.49 (tdd, *J* = 9.4, 6.9, 2.8 Hz, 2H), 2.09 – 1.94 (m, 1H), 1.91 – 1.73 (m, 3H), 1.47 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 205.0, 49.3, 31.1, 31.0, 23.9, 14.9.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2960 (*s*), 2870 (*m*), 1718 (*s*), 1456 (*m*), 1393 (*w*), 1298 (*w*), 1247 (*w*), 1052 (*m*), 1017 (*m*).

HRMS (ESI): calcd for $C_7H_{11}{}^{79}BrNaO$ $[M+Na]^+$: 212.9885; found: 212.9891.

2,2-dibromo-1-(1-methylcyclobutyl)ethan-1-one (**S110**):

TLC (15% ethyl acetate in cyclohexane): R_f: 0.54 (UV, CAM)

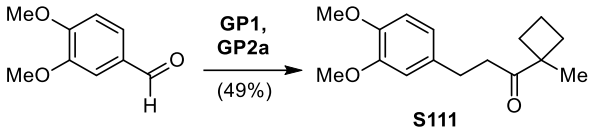
mp: 53.8 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (s, 1H), 2.65 – 2.52 (m, 2H), 2.11 – 1.97 (m, 1H), 1.95 – 1.78 (m, 3H), 1.56 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.2, 48.4, 38.0, 31.7, 24.4, 15.0.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2961 (*m*), 2870 (*m*), 1720 (*s*), 1454 (*m*), 1378 (*w*), 1292 (*m*), 1246 (*m*), 1154 (*m*), 1046 (*m*), 1003 (*m*), 767 (*m*).

HRMS (LTP): calcd for $C_7H_{14}{}^{79}Br_2NO$ $[M+NH_4]^+$: 285.9437; found: 285.9446.



S111

3-(3,4-dimethoxyphenyl)-1-(1-methylcyclobutyl)propan-1-one (**S111**) was prepared according to **GP1** (t = 3 h) from 3,4-dimethoxybenzaldehyde (2.0 mmol, 1 equiv) and 1-(1-methylcyclobutyl)ethan-1-one (**S105**) (1.3 equiv) and **GP2a** (1% Pd, t = 16 h) in 49% yield as a colorless solid. Purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane).

TLC (20% ethyl acetate in cyclohexane): R_f: 0.29 (UV, CAM)

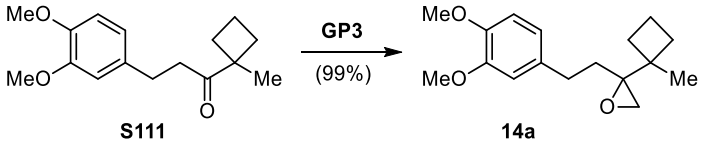
mp: 40.4 – 41.9 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, *J* = 8.7 Hz, 1H), 6.72 (dd, *J* = 6.4, 2.0 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.85 (t, *J* = 7.5 Hz, 2H), 2.72 – 2.65 (m, 2H), 2.32 (tdd, *J* = 9.5, 7.3, 3.3 Hz, 2H), 1.98 – 1.86 (m, 1H), 1.77 – 1.63 (m, 3H), 1.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 213.8, 149.0, 147.5, 134.4, 120.3, 111.9, 111.4, 56.1, 56.0, 49.9, 38.4, 30.3, 29.8, 23.7, 14.6.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2955 (*s*), 2935 (*s*), 2868 (*m*), 2834 (*m*), 1702 (*s*), 1590 (*m*), 1516 (*s*), 1463 (*m*), 1418 (*m*), 1356 (*w*), 1262 (*s*), 1238 (*s*), 1155 (*m*), 1141 (*m*), 1073 (*w*), 1030 (*m*).

HRMS (ESI): calcd for $C_{16}H_{22}NaO_3$ $[M+Na]^+$: 285.1461; found: 285.1458.



S111 **14a**

2-(3,4-dimethoxyphenethyl)-2-(1-methylcyclobutyl)oxirane (**14a**) was prepared according to **GP3** (2.0 equiv NaH, 2.0 equiv Me_3SI) from **S111** (0.5 mmol, 1 equiv) in 99% yield as a colorless oil. Purified by flash column chromatography on silica gel (20% diethyl ether in *n*-pentane).

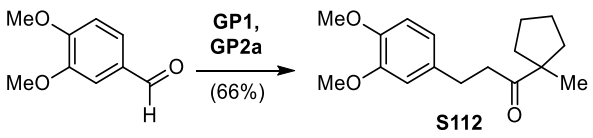
TLC (10% ethyl acetate in cyclohexane): R_f: 0.17 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (d, *J* = 7.9 Hz, 1H), 6.75 – 6.66 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.67 (d, *J* = 4.5 Hz, 1H), 2.59 – 2.40 (m, 3H), 2.23 – 2.12 (m, 1H), 2.05 – 1.79 (m, 4H), 1.71 – 1.59 (m, 2H), 1.31 (s, 3H), 1.26 (dddd, *J* = 8.3, 7.5, 5.6, 2.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 147.4, 135.0, 120.1, 111.8, 111.4, 62.2, 56.1, 56.0, 48.0, 42.0, 31.8, 30.2, 30.0, 27.2, 24.1, 14.6.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2954 (*m*), 2932 (*m*), 2869 (*w*), 1591 (*w)*, 1515 (*s*), 1463 (*m*), 1418 (*w*), 1375 (*w*), 1260 (*s*), 1237 (*m*), 1157 (*m*), 1140 (*m*), 1030 (*m*), 924 (*w*), 849 (*w*), 807 (*w*), 765 (*w*).

HRMS (ESI): calcd for $C_{17}H_{24}NaO_3$ $[M+Na]^+$: 299.1618; found: 299.1609.



3-(3,4-dimethoxyphenyl)-1-(1-methylcyclopentyl)propan-1-one (**S112**) was prepared according to **GP1** (t = 2 h) from 3,4-dimethoxybenzaldehyde (2.0 mmol, 1 equiv) and 1-(1-methylcyclopentyl)ethan-1-one (**S106**) (1.5 equiv) and **GP2a** (1% Pd, t = 16 h) in 66% yield as a colorless solid. Purified by flash column chromatography on silica gel (20% diethyl ether in petrol ether).

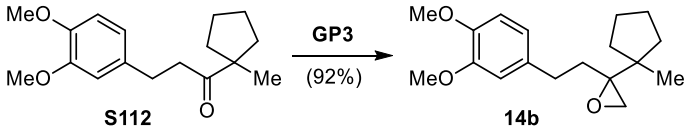
TLC (20% ethyl acetate in cyclohexane): R_f: 0.32 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, *J* = 8.7 Hz, 1H), 6.75 – 6.67 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 2.84 (ddd, *J* = 7.8, 6.6, 1.7 Hz, 2H), 2.80 – 2.69 (m, 2H), 2.03 – 1.88 (m, 2H), 1.70 – 1.49 (m, 4H), 1.36 (dddd, *J* = 12.4, 6.7, 3.0, 1.5 Hz, 2H), 1.15 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.2, 149.0, 147.4, 134.4, 120.3, 112.0, 111.5, 56.0, 56.0, 56.00, 39.7, 36.3, 30.1, 25.2, 24.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2955 (*s*), 2870 (*m*), 2834 (*m*), 1700 (*s*), 1590 (*m*), 1515 (*s*), 1463 (*m*), 1418 (*m*), 1354 (*w*), 1261 (*s*), 1237 (*s*), 1155 (*m*), 1030 (*m*), 807 (*w*), 763 (*w*).

HRMS (ESI): calcd for $C_{17}H_{24}NaO_3$ $[M+Na]^+$: 299.1618; found: 299.1616.



2-(3,4-dimethoxyphenethyl)-2-(1-methylcyclopentyl)oxirane (**14b**) was prepared according to **GP3** (2.0 equiv NaH, 2.0 equiv Me_3SI) from **S112** (1.2 mmol, 1 equiv) in 92% yield as a colorless oil. Purified by flash column chromatography on silica gel (20% diethyl ether in petrol ether).

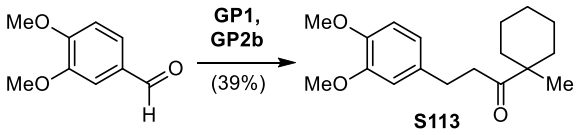
TLC (20% ethyl acetate in cyclohexane): R_f: 0.42 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (d, *J* = 7.9 Hz, 1H), 6.74 – 6.68 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.70 (d, *J* = 4.3 Hz, 1H), 2.62 (dd, *J* = 4.2, 0.7 Hz, 1H), 2.53 (ddd, *J* = 13.6, 11.6, 5.1 Hz, 1H), 2.42 (ddd, *J* = 13.6, 11.6, 5.8 Hz, 1H), 2.14 (ddd, *J* = 14.6, 11.6, 5.8 Hz, 1H), 2.01 (ddd, *J* = 14.6, 11.6, 5.1 Hz, 1H), 1.76 – 1.47 (m, 6H), 1.43 – 1.33 (m, 1H), 1.16 – 1.08 (m, 1H), 1.07 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 147.3, 135.0, 120.1, 111.8, 111.4, 62.8, 56.1, 56.0, 48.8, 46.3, 35.5, 43.0, 32.7, 30.2, 24.8, 24.5, 24.2.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2955 (*s*), 2870 (*m*), 2833 (*m*), 1591 (*w*), 1515 (*s*), 1463 (*m*), 1418 (*m*), 1261 (*m*), 1236 (*m*), 1156 (*m*), 1031 (*m*), 807 (*w*), 766 (*w*).

HRMS (ESI): calcd for $C_{18}H_{26}NaO_3$ $[M+Na]^+$: 313.1774; found: 313.1760.



3-(3,4-dimethoxyphenyl)-1-(1-methylcyclohexyl)propan-1-one (**S113**) was prepared according to **GP1** (t = 4 h) from 3,4-dimethoxybenzaldehyde (3.0 mmol, 1 equiv) and 1-(1-methylcyclohexyl)ethan-1-one (**S107**) (1.0 equiv) and **GP2b** (4 equiv Mg, T = 23 °C, t = 4 h) in 39% yield as a colorless solid. Purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane).

TLC (25% ethyl acetate in cyclohexane): R_f: 0.26 (UV, CAM)

mp: 86.7 – 88.6 °C

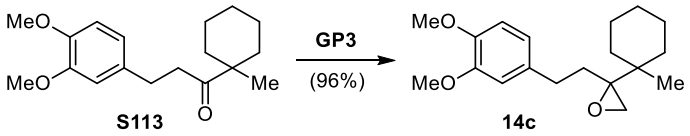
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 – 6.74 (m, 1H), 6.74 – 6.69 (m, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 2.87 – 2.78 (m, 2H), 2.74 (ddd, *J* = 8.5, 6.7, 1.6 Hz, 2H), 1.97 – 1.86 (m, 2H), 1.58 – 1.47 (m, 2H), 1.46 – 1.36 (m, 1H), 1.35 – 1.19 (m, 5H), 0.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.9, 148.9, 147.4, 134.5, 120.3, 112.0, 111.4, 56.0, 55.9, 48.2, 38.8, 34.7, 29.7, 25.9, 24.7, 23.0.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3014 (*w*), 2915 (*s*), 2855 (*m*), 1693 (*s*), 1604 (*w*), 1590 (*m*), 1513 (*s*), 1466 (*w*), 1452 (*s*), 1414 (*m)*, 1381 (*w*), 1361 (*w*), 1348 (*w*), 1336 (*w*), 1298 (*w*), 1252 (*w*), 1231 (*s*), 1197 (*w*), 1169 (*w*), 1153 (*s*), 1143 (*w*), 1132 (*w*), 1069 (*m*), 1028 (*s*), 995 (*m*), 978 (*w*), 941 (*w*),

885 (*w*), 856 (*w*), 806 (*s*), 792 (*w*), 769 *M*), 758 (*m*), 704 (*w*), 646 (*w*), 630 (*w*), 598 (*w*), 549 (*m*), 520 (*w*), 480 (*w*), 410 (*w*).

HRMS (ESI) calcd for $C_{18}H_{26}NaO_3$ $[M+Na]^+$: 313.1774; found: 313.1765.



S113 14c

2-(3,4-dimethoxyphenethyl)-2-(1-methylcyclohexyl)oxirane (**14c**) was prepared according to **GP3** (1.6 equiv NaH, 1.5 equiv Me_3SI) from **S113** (1.0 mmol, 1 equiv) in 96% yield as a colorless oil. Purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane).

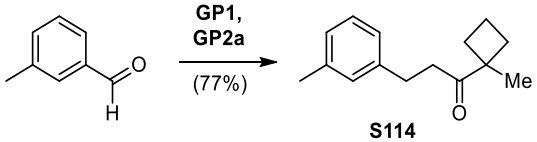
TLC (25% ethyl acetate in cyclohexane): R_f: 0.28 (UV, CAM)

^{1}H NMR (400 MHz, CDCl3) δ 6.78 (d, *J* = 7.9 Hz, 1H), 6.73 – 6.66 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 2.80 (dd, *J* = 4.1, 0.7 Hz, 1H), 2.63 (d, *J* = 4.2 Hz, 1H), 2.49 (ddd, *J* = 13.6, 11.4, 5.2 Hz, 1H), 2.41 (ddd, *J* = 13.6, 11.4, 5.9 Hz, 1H), 2.10 (ddd, *J* = 14.6, 11.4, 5.9 Hz, 1H), 1.99 (ddd, *J* = 14.6, 11.4, 5.2 Hz, 1H), 1.62 – 1.29 (m, 8H), 1.25 – 1.05 (m, 2H), 1.00 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 147.2, 135.0, 120.0, 111.8, 111.4, 64.2, 56.0, 55.9, 47.4, 36.3, 32.9, 32.0, 31.5, 30.2, 26.2, 22.0, 22.0, 20.2.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2928 (*s*), 2858 (*m*), 2834 (*w*), 1607 (*w*), 1590 (*w*), 1514 (*s*), 1463 (*s*), 1449 (*s*), 1417 (*m*), 1378 (*w*), 1344 (*w*), 1258 (*s*), 1235 (*s*), 1191 (*w*), 1155 (*s*), 1139 (*s*), 1096 (*w*), 1029 (*s*), 970 (*w*), 921 (*w*), 886 (*w*), 850 (*m*), 805 (*m*); 765 (*m*), 675 (*w*), 632 (*w*), 596 (*w*), 547 (*w*), 514 (*w*), 469 (*w*).

HRMS (ESI) calcd for $C_{19}H_{28}NaO_3$ $[M+Na]^+$: 327.1931; found: 327.1926.



S114

1-(1-methylcyclobutyl)-3-(*m*-tolyl)propan-1-one (**S114**) was prepared according to **GP1** (t = 3 h) from 2-methylbenzaldehyde (5.0 mmol, 1 equiv) and 1-(1-methylcyclobutyl)ethan-1-one (**S105**) (1.5 equiv) and **GP2a** (10% Pd, t = 16 h) in 77% yield as a colorless oil. Purified by flash column chromatography on silica gel (10% diethyl ether in petrol ether).

TLC (10% ethyl acetate in cyclohexane): R_f: 0.39 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.13 (m, 1H), 7.05 – 6.95 (m, 3H), 2.91 – 2.80 (m, 2H), 2.77 – 2.65 (m, 2H), 2.42 – 2.27 (m, 5H), 2.04 – 1.86 (m, 1H), 1.80 – 1.64 (m, 3H), 1.33 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 213.8, 141.6, 138.2, 129.3, 128.5, 126.9, 125.5, 49.9, 38.2, 30.3, 30.1, 23.7, 21.5, 14.6.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2957 (*s*), 2868 (*m*), 1703 (*s*), 1609 (*w*), 1455 (*m*), 1357 (*w*), 1071 (*m*), 780 (*w*), 700 (*w*).

HRMS (ESI): calcd for $C_{15}H_{20}NaO$ $[M+Na]^+$: 239.1406; found: 239.1405.

S114 **S115**

2-(3-methylphenethyl)-2-(1-methylcyclobutyl)oxirane (**S115**) was prepared according to **GP3** (2.0 equiv NaH, 2.0 equiv Me_3SI) from **S114** (3.2 mmol, 1 equiv) in 88% yield as a colorless oil. Purified by flash column chromatography on silica gel (4% diethyl ether in petrol ether).

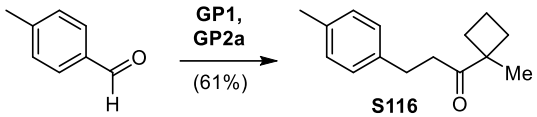
TLC (10% ethyl acetate in cyclohexane): R_f: 0.51 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.14 (m, 1H), 7.06 – 6.94 (m, 3H), 2.69 (d, *J* = 4.5 Hz, 1H), 2.63 – 2.43 (m, 3H), 2.34 (s, 3H), 2.26 – 2.13 (m, 1H), 2.06 – 1.81 (m, 4H), 1.73 – 1.57 (m, 2H), 1.32 (s, 3H), 1.27 (ddt, *J* = 5.6, 2.6, 1.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3, 138.1, 129.2, 128.5, 126.7, 125.4, 62.2, 48.0, 42.0, 31.7, 30.5, 30.0, 27.2, 24.1, 21.5, 14.6.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2954 (*s*), 2927 (*s*), 2868 (*m*), 1609 (*m*), 1590 (*w*), 1488 (*m*), 2456 (*m*), 1375 (*m*), 1246 (*w*), 1170 (*w*), 1091 (*w*), 1037 (*w*), 941 (*w*), 917 (*w*), 781 (*m*), 699 (*m*).

HRMS (ESI): calcd for $C_{16}H_{22}NaO$ $[M+Na]^+$: 253.1563; found: 253,1561.



1-(1-methylcyclobutyl)-3-(p-tolyl)propan-1-one (**S116**) was prepared according to **GP1** (t = 3 h) from 3-methylbenzaldehyde (10.1 mmol, 1 equiv) and 1-(1-methylcyclobutyl)ethan-1-one (**S105**) (1.5 equiv) and **GP2a** (10% Pd, t = 16 h) in 61% yield as a colorless oil. Purified by flash column chromatography on silica gel (10% diethyl ether in petrol ether).

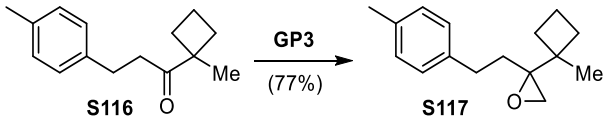
TLC (10% ethyl acetate in cyclohexane): R_f: 0.45 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 4H), 2.85 (dd, *J* = 8.3, 6.9 Hz, 2H), 2.75 – 2.61 (m, 2H), 2.42 – 2.24 (m, 5H), 2.04 – 1.85 (m, 1H), 1.79 – 1.63 (m, 3H), 1.32 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 213.8, 138.6, 135.7, 129.7, 128.4, 49.9, 38.3, 30.3, 29.7, 23.7, 21.1, 14.6.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2956 (*s*), 2929 (*s*), 2867 (*m*), 1703 (*s*), 1515 (*m*), 1454 (*m*), 1356 (*w*), 1072 (*m*), 993 (*w*), 810 (*m*).

HRMS (ESI): calcd for $C_{15}H_{20}NaO$ $[M+Na]^+$: 239,1406; found: 239,1403.



2-(1-methylcyclobutyl)-2-(4-methylphenethyl)oxirane (**S117**) was prepared according to **GP3** (2.0 equiv NaH, 2.0 equiv Me_3SI) from **S116** (11.4 mmol, 1 equiv) in 77% yield as a colorless oil. Purified by flash column chromatography on silica gel (4% diethyl ether in petrol ether).

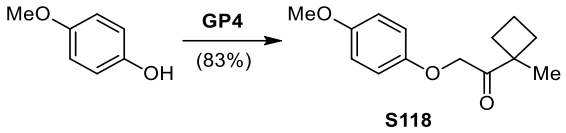
TLC (5% ethyl acetate in cyclohexane): R_f: 0.35 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.00 (m, 4H), 2.68 (d, *J* = 4.5 Hz, 1H), 2.61 – 2.40 (m, 3H), 2.31 (s, 3H), 2.22 – 2.10 (m, 1H), 2.06 – 1.91 (m, 3H), 1.91 – 1.78 (m, 1H), 1.72 – 1.59 (m, 2H), 1.30 (s, 3H), 1.27 – 1.22 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.2, 135.5, 129.2, 128.3, 62.3, 48.0, 43.0, 31.7, 30.1, 30.0, 27.2, 24.1, 21.1, 14.6.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2955 (*s*), 2928 (*s*), 2868 (*m*), 1515 (*m*), 1455 (*w*), 1375 (*w*), 810 (*w*).

HRMS (ESI): calcd for $C_{16}H_{22}NaO$ $[M+Na]^+$: 253,1563; found: 253,1557.



S118

3-(4-methoxyphenyl)-1-(1-methylcyclobutyl)propan-1-one (**S118**) was prepared according to **GP4** from 4-methoxyphenol (8.9 mmol, 1 equiv) and 2-bromo-1-(1-methylcyclobutyl)ethan-1-one (**S109**) (1.1 equiv) in 83% yield as a yellow oil. Purified by flash column chromatography on silica gel (10% diethyl ether in *n*-pentane).

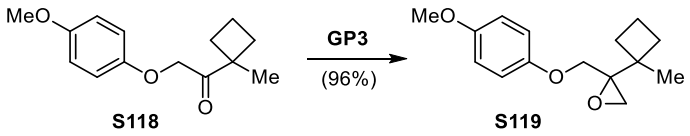
TLC (20% ethyl acetate in cyclohexane): R_f: 0.22 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 – 6.77 (m, 4H), 4.70 (s, 2H), 3.76 (s, 3H), 2.50 (tdd, *J* = 9.3, 7.4, 3.1 Hz, 2H), 2.10 – 1.96 (m, 1H), 1.90 – 1.74 (m, 3H), 1.49 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5, 154.5, 152.4, 115.9, 114.8, 70.5, 55.8, 48.6, 30.8, 23.5, 15.2.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2956 (*m*), 2835 (*w*), 1721 (*m*), 1508 (*s*), 1438 (*w*), 1230 (*m*), 1108 (*w*), 1036 (*w*), 825 (*w*).

HRMS (ESI): calcd for $C_{14}H_{18}NaO_3$ $[M+Na]^+$: 257,1148; found: 257,1146.



S118 **S119**

2-((4-methoxyphenoxy)methyl)-2-(1-methylcyclobutyl)oxirane (**S119**) was prepared according to **GP3** (2.0 equiv NaH, 2.0 equiv Me_3SI) from **S118** (7.3 mmol, 1 equiv) in 96% yield as a pale yellow oil. Purified by flash column chromatography on silica gel (15% diethyl ether in petrol ether).

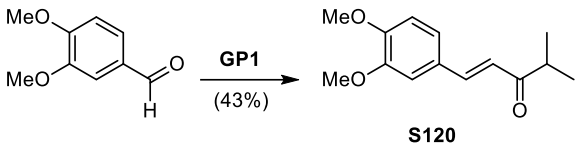
TLC (15% ethyl acetate in cyclohexane): R_f: 0.42 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 – 6.75 (m, 4H), 4.15 (d, *J* = 10.9 Hz, 1H), 3.96 (d, *J* = 11.0 Hz, 1H), 3.76 (s, 3H), 2.85 (d, *J* = 4.7 Hz, 1H), 2.62 (d, *J* = 4.7 Hz, 1H), 2.35 – 2.19 (m, 1H), 2.08 – 1.87 (m, 2H), 1.70 (dddd, *J* = 10.1, 9.2, 4.8, 2.6 Hz, 2H), 1.38 (s, 3H), 1.35 – 1.26 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1, 153.2, 115.7, 114.7, 69.0, 61.5, 55.9, 47.4, 40.3, 30.3, 27.4, 23.9, 15.2.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2932 (*m*), 2870 (*m*), 1508 (*s*), 1464 (*w*), 1230 (*s*), 1181 (*w*), 1107 (*w*), 1043 (*m*), 945 (*w*), 825 (*m*), 748 (*w*).

HRMS (ESI): calcd for $C_{15}H_{20}NaO_3$ $[M+Na]^+$: 271.1305; found: 271.1303.



S120

(*E*)-1-(3,4-dimethoxyphenyl)-4-methylpent-1-en-3-one (**S120**) was prepared according to **GP1** (t = 3 h) from 3,4-dimethoxybenzaldehyde (30.0 mmol, 1 equiv) and 3-methyl-2-butanone (1.0 equiv) in 43% yield as a yellow highly viscous oil. Purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane grading to 25% ethyl acetate in cyclohexane).

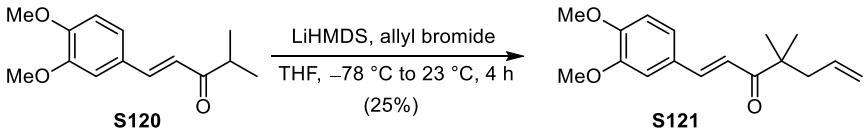
TLC (25% ethyl acetate in cyclohexane): R_f: 0.25 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55 (d, *J* = 16.0 Hz, 1H), 7.14 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.08 (d, *J* = 2.0 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.68 (d, *J* = 16.0 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 2.94 (hept, *J* = 6.9 Hz, 1H), 1.18 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 204.0, 151.4, 149.4, 142.6, 127.8, 123.1, 122.7, 111.2, 109.9, 56.1, 56.1, 39.1, 18.8.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2966 (*m*), 2933 (*w*), 2871 (*w*), 2837 (*w*), 1683 (*w*), 1656 (*w*), 1594 (*s*), 1580 (*m*), 1510 (*s*), 1463 (*m*), 1421 (*w*), 1382 (*w*), 1338 (*w*), 1302 (*w*), 1260 (*s*), 1231 (*m*), 1203 (*m*), 1161 (*m*), 1139 (*s*), 1097 (*w*), 1056 (*s*), 1024 (*s*), 984 (*w*), 845 (*w*), 807 (*w*), 768 (*w*), 746 (*w*), 604 (*w*), 566 (*w*), 484 (*w*).

HRMS (ESI): calcd for $C_{14}H_{19}O_3$ $[M+H]^+$: 235.1329; found: 235.1323.



S120 **S121**

(*E*)-1-(3,4-dimethoxyphenyl)-4,4-dimethylhepta-1,6-dien-3-one (**S121**):

To a solution of (*E*)-1-(3,4-dimethoxyphenyl)-4-methylpent-1-en-3-one (**S120**) (234 mg, 1.00 mmol, 1 equiv) in tetrahydrofuran (2 mL) at – 78 °C was added lithium bis(trimethylsilyl)amide (1.40 mL, 1.40 mmol, 1.40 equiv, 1.0 M in tetrahydrofuran) dropwise via syringe over a period of 30 seconds. A yellow solution was formed that was stirred at –78 °C for 10 min and then warmed to 0 °C. The red solution was cooled to –78 °C . Allyl bromide

(121 µL, 1.40 mmol, 1.40 equiv) was added. After 5 min the solution was allowed to warm to 23 °C and stirred for 4 h. Excess base was quenched by addition of saturated aqueous ammonium chloride solution (5 mL). The mixture 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 under reduced pressure and purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane grading to 25% ethyl acetate in cyclohexane) to yield the title compound **S121** (67.9 mg, 25%) as a pale yellow oil.

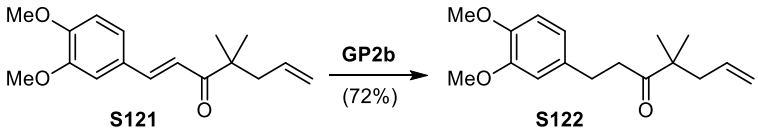
TLC (25% ethyl acetate in cyclohexane): R_f: 0.37 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62 (d, *J* = 15.5 Hz, 1H), 7.16 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.06 (d, *J* = 2.0 Hz, 1H), 6.96 (d, *J* = 15.4 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 5.76 – 5.64 (m, 1H), 5.07 – 5.03 (m, 1H), 5.01 (t, *J* = 1.2 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 2.35 (dt, *J* = 7.4, 1.2 Hz, 2H), 1.20 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 203.4, 151.3, 149.3, 143.2, 134.3, 128.0, 122.8, 118.8, 118.0, 111.2, 110.3, 56.1, 46.6, 44.1, 24.2.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3075 (*w*), 2964 (*m*), 2934 (*w*), 2837 (*w*), 1675 (*m*), 1639 (*w*), 1592 (*s*), 1578 (*s*), 1509 (*s*), 1463 (*s*), 1441 (*m*), 1420 (*m*), 1385 (*w*), 1365 (*w*), 1338 (*w*), 1306 (*w*), 1255 (*s*), 1234 (*s*), 1196 (*w*), 1160 (*s*), 1138 (*s*), 1089 (*m*), 1044 (*s*), 1023 (*s*), 1006 (*m*), 984 (*s*), 916 (*m*), 873 (*w*), 843 (*w*), 806 (*m*), 767 (*w*), 728 (*w*), 672 (*w*), 642 (*w*), 615 (*w*), 583 (*w*), 553 (*m*), 509 (*w*), 485 (*w*), 461 (*w*), 421 (*w*).

HRMS (ESI): calcd for $C_{17}H_{23}O_3$ $[M+H]^+$: 275.1642; found: 275.1635.



1-(3,4-dimethoxyphenyl)-4,4-dimethylhept-6-en-3-one (**S122**) was prepared according to **GP2b** (4 equiv Mg, T = 23 °C, t = 4.5 h) from **S121** (0.7 mmol, 1 equiv) in 72% yield as a colorless oil. Purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane grading to 10% ethyl acetate in cyclohexane).

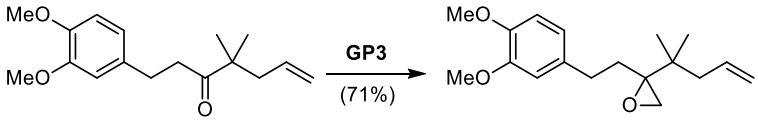
TLC (25% ethyl acetate in cyclohexane): R_f: 0.49 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.82 – 6.74 (m, 1H), 6.74 – 6.67 (m, 2H), 5.63 (ddt, *J* = 16.5, 10.5, 7.4 Hz, 1H), 5.12 – 4.93 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 2.85 – 2.79 (m, 2H), 2.78 – 2.69 (m, 2H), 2.23 (d, *J* = 7.3 Hz, 2H), 1.08 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 214.3, 149.0, 147.4, 134.3, 134.2, 120.3, 118.0, 112.0, 111.4, 56.0, 56.0, 47.6, 44.1, 39.5, 29.7, 24.1.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3073 (*w*), 2964 (*m*), 2933 (*m*), 2834 (*w*), 1702 (*s*), 1639 (*w*), 1607 (*w*), 1590 (*w*), 1514 (*s*), 1464 (*m*), 1451 (*m*), 1417 (*w*), 1386 (*w*), 1365 (*w*), 1258 (*s*), 1235 (*s*), 1191 (*w*), 1154 (*s*), 1140 (*s*), 1088 (*w*), 1067 (*w*), 1028 (*s*), 995 (*m*), 916 (*m*), 848 (*w*), 805 (*m*), 762 (*m*), 634 (*w*), 597 (*w*), 548 (*w*), 477 (*w*), 463 (*w*), 421 (*w*).

HRMS (ESI): calcd for $C_{17}H_{24}NaO_3$ $[M+Na]^+$: 299.1618; found: 299.1612.



S122 **17a**

2-(3,4-dimethoxyphenethyl)-2-(2-methylpent-4-en-2-yl)oxirane (**17a**) was prepared according to **GP3** (1.6 equiv NaH, 1.5 equiv Me_3SI) from **S122** (0.9 mmol, 1 equiv) in 71% yield as a colorless oil. Purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane grading to 10% ethyl acetate in cyclohexane).

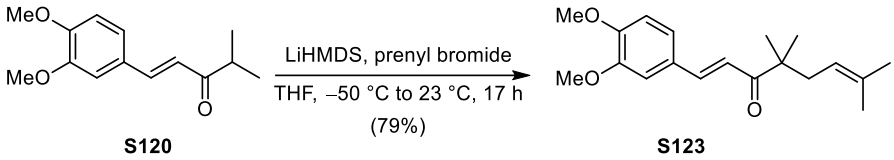
TLC (25% ethyl acetate in cyclohexane): R_f: 0.59 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.79 (d, *J* = 8.0 Hz, 1H), 6.74 – 6.68 (m, 2H), 5.82 (ddt, *J* = 16.6, 10.5, 7.4 Hz, 1H), 5.08 – 4.99 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.75 (d, *J* = 4.1 Hz, 1H), 2.66 (d, *J* = 4.1 Hz, 1H), 2.49 (ddd, *J* = 13.5, 11.4, 5.2 Hz, 1H), 2.39 (ddd, *J* = 13.5, 11.5, 5.9 Hz, 1H), 2.20 – 1.99 (m, 4H), 0.95 (s, 3H), 0.89 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 149.0, 147.4, 135.1, 134.9, 120.1, 117.3, 111.8, 111.4, 62.8, 56.1, 56.0, 47.6, 43.7, 37.1, 31.5, 30.1, 23.6, 23.1.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3072 (*w*), 2962 (*m*), 2935 (*m*), 2834 (*w*), 1638 (*w*), 1607 (*w*), 1590 (*w*), 1514 (*s*), 1464 (*m*), 1417 (*w*), 1385 (*w*), 1365 (*w*), 1343 (*w*), 1258 (*s*), 1235 (*s*), 1192 (*w*), 1156 (*s*), 1139 (*s*), 1029 (*s*), 996 (*w*), 913 (*m*), 850 (*w*), 805 (*m*), 765 (*m*), 702 (*w*), 643 (*w*), 614 (*w*), 563 (*w*), 538 (*w*), 463 (*w*).

HRMS (ESI): calcd for $C_{18}H_{26}NaO_3$ $[M+Na]^+$: 313.1774; found: 313.1752.



S120 **S123**

(*E*)-1-(3,4-dimethoxyphenyl)-4,4,7-trimethylocta-1,6-dien-3-one (**S123**):

A solution of lithium hexamethyldisilazide (1.00 M in tetrahydrofuran, 3.00 mmol, 3.00 mL, 1.50 equiv) was diluted with tetrahydrofuran (40 mL) and cooled to –50 °C. A solution of enone **S120** (469 mg, 2.00 mmol, 1 equiv) in tetrahydrofuran (10 mL) was added dropwise, whereupon the color of the mixture turned intense red. After 90 min prenyl bromide (1.16 mL, 10.0 mmol, 5.00 equiv) was added dropwise. After 15 min the cooling bath was removed and stirring was continued. After 15 h saturated aqueous sodium bicarbonate solution (40 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 80 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% diethyl ether in *n*-pentane) to yield α-tertiary ketone **S123** (475 mg, 1.57 mmol, 79%) as yellow oil.

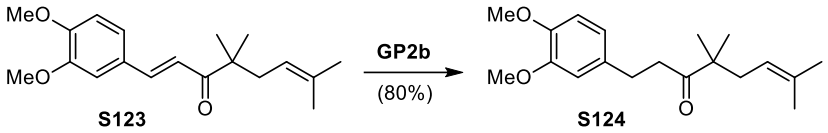
TLC (20% diethyl ether in *n*-pentane): R_f: 0.27 (UV, CAM)

^{1}H-NMR (400 MHz, $CDCl_3$): 7.62 (d, *J* = 15.5 Hz, 1H), 7.17 (ddd, *J* = 8.3, 2.0, 0.6 Hz, 1H), 7.06 (d, *J* = 2.0 Hz, 1H), 6.97 (d, *J* = 15.5 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 5.04 (tp, *J* = 7.5, 1.4 Hz, 1H), 3.93 (d, *J* = 0.8 Hz, 3H), 3.91 (d, *J* = 1.0 Hz, 3H), 2.31 (dt, *J* = 7.7, 1.2 Hz, 2H), 1.67 (d, *J* = 1.3 Hz, 3H), 1.60 (d, *J* = 1.4 Hz, 3H), 1.19 (d, *J* = 0.7 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 204.0, 151.2, 149.3, 142.8, 134.2, 128.1, 122.8, 120.0, 119.1, 111.2, 110.4, 56.1, 56.1, 47.3, 38.2, 26.1, 24.3, 18.1.

IR (ATR, neat): $\tilde{\nu}_{max}$ = 2965 (*w*), 2930 (br *w*), 1677 (*w*), 1594 (*m*), 1511 (*s*), 1465 (*w*), 1421 (*w*), 1384 (*w*), 1339 (*w*), 1309 (*w*), 1261 (*s*), 1161 (*w*), 1139 (*m*), 1063 (*s*), 1025 (*m*), 984 (*w*), 843 (*w*), 807 (*w*), 767 (*w*).

HRMS (ESI): calcd for $C_{19}H_{27}O_3$ $[M+H]^+$: 303.1955; found: 303.1938.



1-(3,4-dimethoxyphenyl)-4,4,7-trimethyloct-6-en-3-one (**S124**) was prepared according to **GP2b** (4 equiv Mg, T = 23 °C, t = 5 h) from **S123** (1.6 mmol, 1 equiv) in 80% yield as a colorless oil. Purified by flash column chromatography on silica gel (20% diethyl ether in *n*-pentane).

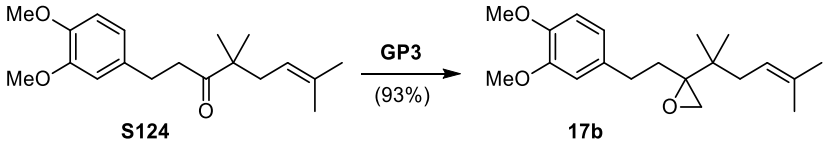
TLC (20% diethyl ether in *n*-pentane): R_f: 0.22 (UV, CAM)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.78 (d, *J* = 8.6 Hz, 1H), 6.73 – 6.69 (m, 2H), 4.92 (ddq, *J* = 8.9, 5.8, 1.4 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.81 (ddd, *J* = 7.7, 6.5, 1.8 Hz, 2H), 2.76 – 2.68 (m, 2H), 2.22 – 2.14 (m, 2H), 1.67 (q, *J* = 1.3 Hz, 3H), 1.58 (d, *J* = 1.4 Hz, 3H), 1.07 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.9, 149.0, 147.4, 134.5, 134.3, 120.3, 119.8, 112.0, 111.4, 56.1, 56.0, 48.2, 39.5, 38.2, 29.7, 26.1, 24.1, 18.0.

IR (ATR, neat): $\tilde{\nu}_{max}$ = 2964 (*m*), 2929 (br *m*), 1702 (*s*), 1591 (*w*), 1515 (*s*), 1465 (*m*), 1418 (*w*), 1384 (*w*), 1364 (*w*), 1261 (*s*), 1237 (*s*), 1155 (*m*), 1140 (*m*), 1071 (*w*), 1030 (*s*), 988 (*w*), 851 (*w*), 807 (*w*), 763 (*w*).

HRMS (ESI): calcd for $C_{19}H_{29}O_3$ $[M+H]^+$: 305.2111; found: 305.2108.



2-(3,4-dimethoxyphenethyl)-2-(2,5-dimethylhex-4-en-2-yl)oxirane (**17b**) was prepared according to **GP3** (2.0 equiv NaH, 1.9 equiv Me_3SI) from **S124** (1.1 mmol, 1 equiv) in 93% yield as a colorless oil. Purified by flash column chromatography on silica gel (20% diethyl ether in *n*-pentane).

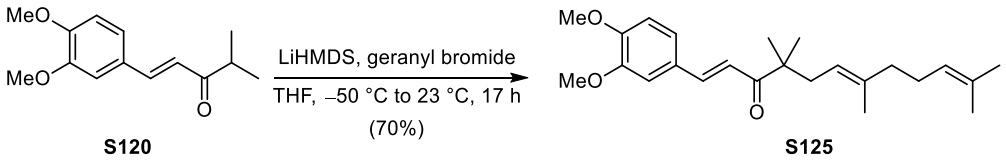
TLC (20% diethyl ether in *n*-pentane): R_f: 0.27 (UV, CAM)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.79 (d, *J* = 7.9 Hz, 1H), 6.76 – 6.67 (m, 2H), 5.18 (tdq, J = 7.2, 2.8, 1.4 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.76 (dd, *J* = 4.1, 0.8 Hz, 1H), 2.66 (d, *J* = 4.2 Hz, 1H), 2.50 (ddd, *J* = 13.6, 11.4, 5.2 Hz, 1H), 2.39 (ddd, *J* = 13.5, 11.4, 5.9 Hz, 1H), 2.17 – 1.96 (m, 4H), 1.72 (q, *J* = 1.3 Hz, 3H), 1.60 (d, *J* = 1.4 Hz, 3H), 0.94 (s, 3H), 0.87 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 147.3, 135.0, 133.3, 120.6, 120.1, 111.9, 111.4, 63.0, 56.1, 56.0, 47.8, 37.8, 37.4, 31.6, 30.2, 26.2, 23.6, 23.1, 18.1.

IR (ATR, neat): $\tilde{\nu}_{max}$ = 2963 (*m*), 2932 (br *m*), 1590 (*w*), 1515 (*s*), 1464 (*m*), 1418 (*m*), 1384 (*w*), 1260 (*s*), 1237 (*s*), 1156 (*m*), 1140 (*m*), 1030 (*s*), 921 (*w*), 850 (*w*), 807 (*w*), 765 (*w*) cm^{-1}.

HRMS (ESI): calcd for $C_{20}H_{31}O_3$ $[M+H]^+$: 319.2268; found: 319.2264.



S120 **S125**

(1*E*,6*E*)-1-(3,4-dimethoxyphenyl)-4,4,7,11-tetramethyldodeca-1,6,10-trien-3-one (**S125**):

A solution of lithium hexamethyldisilazide (1.00 M in tetrahydrofuran, 2.25 mmol, 2.25 mL, 1.50 equiv) was diluted with tetrahydrofuran (30 mL) and cooled to –50 °C. Enone **S120** (351 mg, 1.50 mmol, 1 equiv) in tetrahydrofuran (7.5 mL) was added dropwise, whereupon the color of the mixture turned intense red. After 1 h geranyl bromide (1.49 mL, 7.50 mmol, 5.00 equiv) was added dropwise. After 10 min the cooling bath was removed and stirring was continued. After 16 h saturated aqueous sodium bicarbonate solution (30 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% diethyl ether in *n*-pentane) to yield α-tertiary ketone **S125** (387 mg, 1.04 mmol, 70%) as yellow oil.

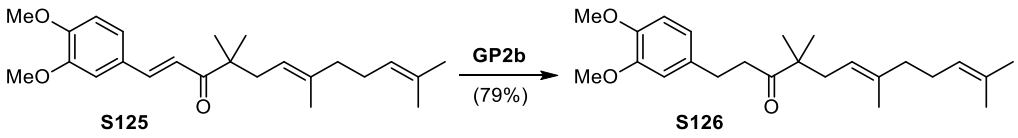
TLC (20% ethyl acetate in *n*-pentane): R_f: 0.53 (UV, CAM)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 15.5 Hz, 1H), 7.17 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.06 (d, *J* = 2.0 Hz, 1H), 6.97 (d, *J* = 15.5 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 5.05 (ddddd, *J* = 9.7, 6.8, 5.4, 2.8, 1.4 Hz, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 2.32 (d, *J* = 7.5 Hz, 2H), 2.01 (dq, *J* = 13.4, 7.1 Hz, 4H), 1.65 (d, *J* = 1.4 Hz, 3H), 1.60 (d, *J* = 1.4 Hz, 3H), 1.56 (d, *J* = 1.4 Hz, 3H), 1.19 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 204.0, 151.2, 149.3, 142.8, 137.8, 131.5, 128.2, 124.4, 122.8, 120.0, 119.1, 111.3, 110.4, 56.1, 56.1, 47.4, 40.1, 38.0, 26.8, 25.8, 24.2, 17.8, 16.4.

IR (ATR, neat): $\tilde{\nu}_{max}$ = 2963 (*m*), 2920 (br *m*), 1677 (*m*), 1593 (*s*), 1510 (*s*), 1464 (*m*), 1420 (*m*), 1384 (*w*), 1308 (*w*), 1258 (*s*), 1160 (*m*), 1138 (*s*), 1060 (*s*), 1025 (*s*), 983 (*m*), 842 (*w*), 805 (*m*), 766 (*w*), 556 (*w*) cm^{-1}.

HRMS (ESI): calcd for $C_{24}H_{34}NaO_3$ $[M+Na]^+$: 393.2400; found: 393.2395.



(*E*)-1-(3,4-dimethoxyphenyl)-4,4,7,11-tetramethyldodeca-6,10-dien-3-one (**S126**) was prepared according to **GP2b** (4 equiv Mg, T = 23 °C, t = 4.5 h) from **S125** (1.0 mmol, 1 equiv) in 79% yield as a colorless oil. Purified by flash column chromatography on silica gel (20% diethyl ether in *n*-pentane).

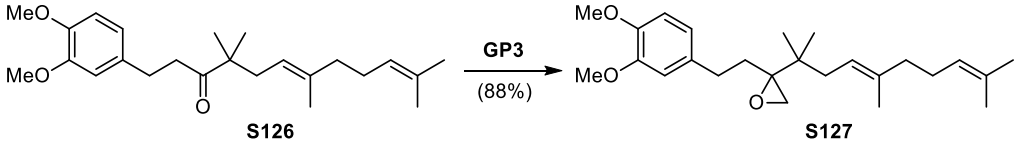
TLC (20% diethyl ether in *n*-pentane): R_f: 0.35 (UV, CAM)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.81 – 6.69 (m, 3H), 5.05 (ddp, *J* = 6.9, 5.7, 1.4 Hz, 1H), 4.96 (tq, *J* = 7.5, 1.3 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 2.87 – 2.68 (m, 4H), 2.23 – 2.14 (m, 2H), 2.10 – 1.92 (m, 4H), 1.66 (q, *J* = 1.3 Hz, 3H), 1.58 (d, *J* = 1.3 Hz, 3H), 1.57 (d, *J* = 1.4 Hz, 3H), 1.07 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.9, 149.0, 147.4, 137.9, 134.5, 131.6, 124.3, 120.3, 119.8, 112.0, 111.4, 56.1, 56.0, 48.2, 40.1, 39.5, 38.0, 29.8, 26.7, 25.8, 24.1, 17.8, 16.3.

IR (ATR, neat): $\tilde{\nu}_{max}$ = 2929 (br *m*), 1702 (*s*), 1590 (*w*), 1515 (*s*), 1464 (*m*), 1418 (*m*), 1384 (*w*), 1363 (*w*), 1260 (*s*), 1236 (*s*), 1154 (*m*), 1140 (*m*), 1069 (*w*), 1030 (*s*), 849 (*w*), 805 (*m*), 763 (*m*), 637 (*w*), 551 (*w*).

HRMS (ESI): calcd for $C_{24}H_{36}NaO_3$ $[M+Na]^+$: 395.2557; found: 395.2556.



(*E*)-2-(3,4-dimethoxyphenethyl)-2-(2,5,9-trimethyldeca-4,8-dien-2-yl)oxirane (**S127**) was prepared according to **GP3** (1.6 equiv NaH, 1.5 equiv Me_3SI) from **S126** (0.70 mmol, 1 equiv) in 88% yield as a pale yellow oil. Purified by flash column chromatography on silica gel (20% diethyl ether in *n*-pentane).

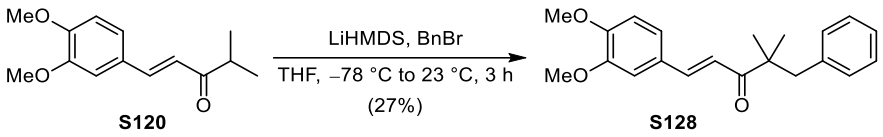
TLC (20% diethyl ether in *n*-pentane): R_f: 0.26 (UV, CAM)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.79 (d, *J* = 7.9 Hz, 1H), 6.76 – 6.67 (m, 2H), 5.19 (tq, *J* = 7.4, 1.3 Hz, 1H), 5.08 (tp, *J* = 6.9, 1.5 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.79 – 2.72 (m, 1H), 2.66 (d, *J* = 4.2 Hz, 1H), 2.50 (ddd, *J* = 13.5, 11.4, 5.2 Hz, 1H), 2.39 (ddd, *J* = 13.5, 11.5, 5.9 Hz, 1H), 2.13 – 1.99 (m, 8H), 1.67 (d, *J* = 1.4 Hz, 3H), 1.60 (dd, *J* = 3.1, 1.4 Hz, 6H), 0.95 (s, 3H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 147.3, 136.9, 135.0, 131.5, 124.5, 120.7, 120.1, 111.9, 111.4, 63.0, 56.1, 56.0, 47.9, 40.2, 37.9, 37.2, 31.6, 30.2, 26.8, 25.9, 23.7, 22.8, 17.8, 16.3.

IR (ATR, neat): $\tilde{\nu}_{max}$ = 2963 (br *m*), 2931 (*w*), 1591 (*w*), 1515 (*s*), 1464 (*m*), 1418 (*m*), 1384 (*w*), 1260 (*s*), 1237 (*s*), 1157 (*m*), 1140 (*m*), 1031 (*m*), 806 (*w*), 766 (*w*).

HRMS (ESI): calcd for $C_{25}H_{38}NaO_3$ $[M+Na]^+$: 409.2713; found: 409.2709.



S120 **S128**

(*E*)-1-(3,4-dimethoxyphenyl)-4,4-dimethyl-5-phenylpent-1-en-3-one (S128):

To a solution of **S120** (234 mg, 1.00 mmol, 1 equiv) in tetrahydrofuran (2 mL) at – 78 °C was added lithium bis(trimethylsilyl)amide (1.40 mL, 1.0 M in tetrahydrofuran 1.40 mmol, 1.40 equiv) dropwise via syringe over a period of 30 seconds. A yellow solution formed, that was stirred at – 78 °C for 10 min and then warmed to 0 °C. The resulted red solution was cooled to –78 °C again. Benzyl bromide (167 µL, 1.40 mmol, 1.40 equiv) was added and stirring was continued at –78 °C for 5 min. The solution was allowed to warm to 23 °C and stirred for 3 h. By addition of saturated aqueous ammonium chloride solution (5 mL) excess base was quenched. The mixture 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 solution was filtered and the filtrate was concentrated under reduced pressure and purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane to 25% ethyl acetate in cyclohexane) to yield compound **S128** (87.0 mg, 27%) as a pale yellow oil.

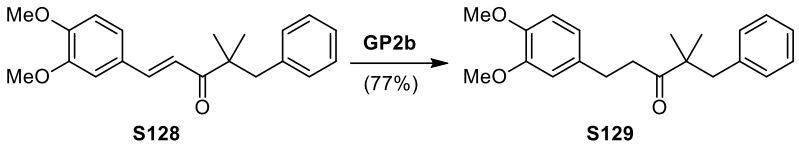
TLC (25% ethyl acetate in cyclohexane): R_f: 0.38 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (d, *J* = 15.4 Hz, 1H), 7.25 – 7.14 (m, 4H), 7.14 – 7.09 (m, 2H), 7.05 (d, *J* = 2.0 Hz, 1H), 6.98 (d, *J* = 15.4 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 2.92 (s, 2H), 1.21 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 203.4, 151.3, 149.2, 143.1, 137.9, 130.4, 128.0, 127.9, 126.4, 122.9, 119.2, 111.2, 110.3, 56.0, 47.7, 45.5, 24.4.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3061 (*w*), 3026 (*w*), 2964 (*m*), 2933 (*w*), 2868 (*w*), 2837 (*w*), 1674 (*m*), 1591 (*s*), 1578 (*s*), 1509 (*s*), 1463 (*m*), 1453 (*m*), 1441 (*m*), 1420 (*m*), 1385 (*w*), 1365 (*w*), 1338 (*w*), 1305 (*w*), 1256 (*s*), 1233 (*s*), 1196 (*w*), 1160 (*m*), 1137 (*s*), 1076 (*m*), 1054 (*s*), 1022 (*s*), 1004 (*m*), 983 (*m*), 942 (*w*), 913 (*w*), 844 (*w*), 806 (*m*), 767 (*w*), 751 (*m*), 733 (*m*), 701 (*s*), 647 (*w*), 615 (*w*), 574 (*w*), 553 (*m*), 505 (*w*), 476 (*w*), 421 (*w*).

HRMS (ESI): calcd for $C_{21}H_{25}O_3$ $[M+H]^+$: 325.1798; found: 325.1792.



S128 **S129**

5-(3,4-dimethoxyphenyl)-2,2-dimethyl-1-phenylpentan-3-one (**S129**) was prepared according to **GP2b** (4 equiv Mg, T = 23 °C, t = 2 h) from **S128** (1.0 mmol, 1 equiv) in 77% yield as a colorless solid. Purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane grading to 10% ethyl acetate in cyclohexane).

TLC (25% ethyl acetate in cyclohexane): R_f: 0.53 (CAM)

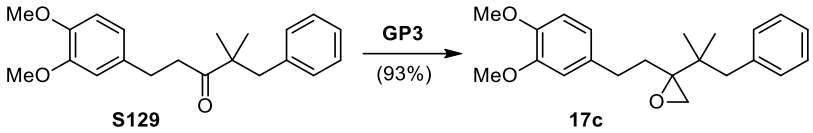
mp: 45.3 – 47.0 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37 – 7.26 (m, 3H), 7.15 – 7.07 (m, 2H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.78 – 6.71 (m, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 2.92 – 2.80 (m, 4H), 2.79 – 2.65 (m, 2H), 1.18 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 214.7, 148.9, 147.4, 137.9, 134.2, 130.3, 128.1, 126.4, 120.3, 112.0, 111.4, 56.0, 55.9, 48.5, 45.8, 40.6, 29.5, 24.3.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3061 (*w*), 3027 (*w*), 2962 (*m*), 2933 (*m*), 2833 (*w*), 1700 (*s*), 1605 (*w*), 1590 (*w*), 1514 (*s*), 1464 (*m*), 1452 (*m*), 1418 (*w*), 1387 (*w*), 1364 (*w*), 1260 (*s*), 1235 (*s*), 1190 (*w*), 1154 (*m*), 1140 (*m*), 1077 (*w*), 1028 (*s*), 991 (*w*), 941 (*w*), 889 (*w*), 849 (*w*), 805 (*w*), 763 (*w*), 746 (*m*), 703 (*s*), 633 (*w*), 610 (*w*), 597 (*w*), 548 (*w*), 523 (*w*), 480 (*w*).

HRMS (ESI): calcd for $C_{21}H_{26}NaO_3$ $[M+Na]^+$: 349.1774; found: 349.1766.



2-(3,4-dimethoxyphenethyl)-2-(2-methyl-1-phenylpropan-2-yl)oxirane (**17c**) was prepared according to **GP3** (1.6 equiv NaH, 1.5 equiv Me_3SI) from **S129** (0.8 mmol, 1 equiv) in 93% yield as a colorless oil. Purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane).

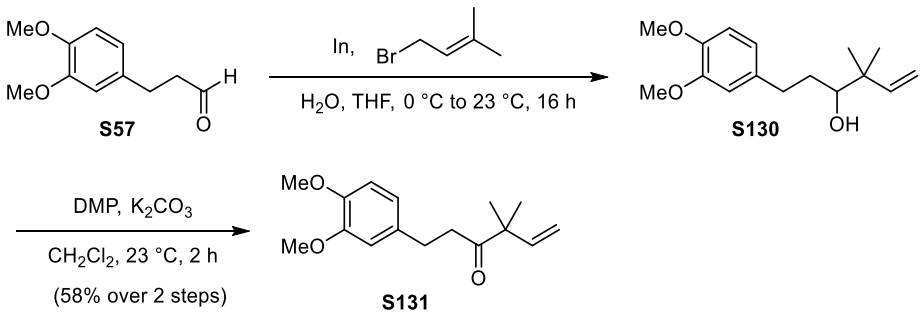
TLC (25% ethyl acetate in cyclohexane): R_f: 0.58 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 – 7.18 (m, 3H), 7.15 – 7.10 (m, 2H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.75 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.72 (d, *J* = 2.0 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.80 – 2.74 (m, 1H), 2.69 – 2.60 (m, 3H), 2.53 (ddd, *J* = 13.5, 11.3, 5.4 Hz, 1H), 2.44 (ddd, *J* = 13.4, 11.4, 5.9 Hz, 1H), 2.26 – 2.17 (m, 1H), 2.17 – 2.08 (m, 1H), 0.96 (s, 3H), 0.84 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 149.0, 147.4, 138.5, 134.8, 130.8, 127.9, 126.2, 120.2, 111.9, 111.5, 63.0, 56.1, 56.0, 48.1, 44.8, 38.2, 31.9, 30.2, 23.6, 22.4.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3058 (*w*), 3027 (*w*), 2959 (*w*), 2935 (*m*), 2873 (*w*), 2834 (*w*), 1604 (*w*), 1590 (*w*), 1514 (*s*), 1464 (*m*), 1453 (*m*), 1418 (*w*), 1386 (*w*), 1364 (*w*), 1343 (*w*), 1259 (*s*), 1235 (*s*), 1192 (*w*), 1155 (*m*), 1139 (*m*), 1071 (*w*), 1028 (*s*), 910 (*m*), 850 (*w*), 806 (*m*), 765 (*w*), 729 (*s*), 702 (*s*), 646 (*w*), 631 (*w*), 610 (*w*), 562 (*w*), 548 (*w*), 509 (*w*), 467 (*w*).

HRMS (ESI): calcd for $C_{22}H_{28}NaO_3$ $[M+Na]^+$: 363.1931; found: 363.1903.



1-(3,4-dimethoxyphenyl)-4,4-dimethylhex-5-en-3-one (**S131**):

Prenyl bromide (0.89 mL, 7.7 mmol, 3.0 equiv) was added dropwise to a stirred suspension of 3-(3,4-dimethoxyphenyl)-propanal (**S57**) (500 mg, 2.57 mmol, 1 equiv) and indium (590 mg, 5.15 mmol, 2.00 equiv) in a mixture of water (3.2 mL) and tetrahydrofuran (3.2 mL) at 0 °C. The reaction mixture was allowed to warm to 23 °C. After 16 h, aqueous hydrochloric acid (1.0 M) was

added untill the white emulsion clearified and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution and dried over sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to afford the crude alcohol **S130** that was used without further purification.

To a solution of the crude alcohol (approx. 2.6 mmol, 1 equiv) in dichloromethane (13 mL) was added potassium carbonate (0.71 g, 5.2 mmol, 2.0 equiv) and Dess–Martin periodinane (2.2 g, 5.2 mmol, 2.0 equiv) at 23 °C. The mixture was stirred for 2 h. The suspension was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) afforded ketone **S131** (391 mg, 58% over 2 steps) as a colorless oil.

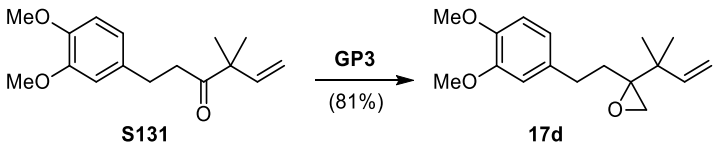
TLC (25% ethyl acetate in cyclohexane): R_f: 0.26 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 – 6.74 (m, 1H), 6.71 – 6.65 (m, 2H), 5.91 – 5.79 (m, 1H), 5.11 (s, 1H), 5.08 (dd, *J* = 6.2, 0.9 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 2.82 – 2.70 (m, 4H), 1.18 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.2, 148.9, 147.4, 142.4, 134.1, 120.3, 114.4, 111.9, 111.3, 56.0, 55.9, 50.8, 39.6, 29.8, 23.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2969 (*m*), 2934 (*m*), 2834 (*w*), 1706 (*s*), 1635 (*w*), 1607 (*w*), 1590 (*w*), 1514 (*s*), 1464 (*m*), 1416 (*m*), 1378 (*w*), 1363 (*w*), 1259 (*s*), 1235 (*s*) ,1191 (*w*), 1135 (*s*), 1074 (*s*), 1028 (*s*), 919 (*m*), 846 (*w*), 807 (*m*), 762 (*m*), 700 (*m*); 681 (*w*), 635 (*w*), 595 (*w*), 549 (*w*), 497 (*s*).

HRMS (ESI) calcd for $C_{16}H_{22}NaO_3$ $[M+Na]^+$: 285.1461; found: 285.1453



S131 17d

2-(3,4-dimethoxyphenethyl)-2-(2-methylbut-3-en-2-yl)oxirane (**17d**) was prepared according to **GP3** (1.6 equiv NaH, 1.6 equiv Me_3SI) from **S131** (1.0 mmol, 1 equiv) in 81% yield as a colorless oil. Purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane).

TLC (25% ethyl acetate in cyclohexane): R_f: 0.28 (CAM)

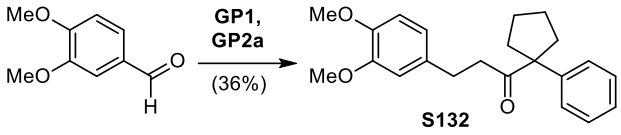
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, *J* = 7.9 Hz, 1H), 6.71 – 6.66 (m, 2H), 5.94 – 5.83 (m, 1H), 5.06 – 5.03 (m, 1H), 5.01 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 2.74 (d, *J* = 4.2 Hz, 1H), 2.65 (d, *J* =

4.3 Hz, 1H), 2.47 (ddd, *J* = 13.6, 11.4, 5.3 Hz, 1H), 2.38 (ddd, *J* = 13.6, 11.4, 5.9 Hz, 1H), 2.07 (ddd, *J* = 14.6, 11.4, 5.9 Hz, 1H), 1.96 (ddd, *J* = 14.7, 11.4, 5.3 Hz, 1H), 1.05 (s, 3H), 1.03 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 147.2, 144.7, 134.7, 120.0, 112.5, 111.7, 111.3, 62.6, 55.9, 55.9, 47.6, 40.2, 31.9, 30.1, 23.4, 22.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3080 (*w*), 3057 (*w*), 2965 (*m*), 2935 (*m*), 2873 (*w*), 2833 (*w*), 1637 (*w*), 1607 (*w*), 1590 (*w*), 1513 (*s*), 1463 (*m*), 1416 (*m*), 1379 (*w*), 1347 (*w*), 1259 (*s*), 1234 (*s*), 1191 (*w*), 1156 (*s*), 1139 (*s*), 1029 (*s*), 914 (*s*), 850 (*w*), 836 (*w*), 807 (*m*), 765 (*m*), 695 (*w*), 657 (*w*), 619 (*w*), 598 (*w*), 575 (*w*), 546 (*w*), 505 (*w*), 461 (*w*).

HRMS (ESI) calcd for $C_{17}H_{25}O_3$ $[M+H]^+$: 277.1798; found: 277.1792.



S132

3-(3,4-dimethoxyphenyl)-1-(1-phenylcyclopentyl)propan-1-one (**S132**) was prepared according to **GP1** (t = 4 h) from 3,4-dimethoxybenzaldehyde (2.0 mmol, 1 equiv) and 1-(1-phenylcyclopentyl)ethan-1-one (1.0 equiv) and **GP2a** (1% Pd, t = 16 h) in 36% yield as a colorless solid. Purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane).

TLC (25% ethyl acetate in cyclohexane): R_f: 0.29 (UV, CAM)

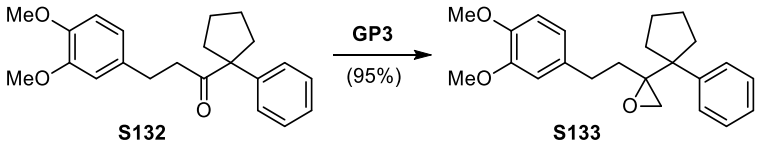
mp: 47.5 – 49.0°C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 2H), 7.24 – 7.17 (m, 3H), 6.69 (d, *J* = 8.1 Hz, 1H), 6.53 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.49 (d, *J* = 2.0 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 2.66 (t, *J* = 7.4 Hz, 2H), 2.52 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 2H), 2.48 – 2.38 (m, 2H), 1.93 – 1.82 (m, 2H), 1.72 – 1.54 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 210.5, 148.8, 147.3, 142.8, 134.0, 128.7, 127.1, 126.9, 120.2, 111.7, 111.2, 65.5, 56.0, 55.9, 39.7, 34.5, 30.3, 23.8.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2951 (*s*), 2871 (*w*), 2833 (*w*), 1702 (*s*), 1591 (*m*), 1514 (*s*), 1493 (*w*), 1463 (*w*), 1448 (*m*), 1417 (*w*), 1349 (*w*), 1259 (*s*), 1235 (*s*), 1190 (*w*), 1153 (*s*), 1138 (*s*), 1083 (*w*), 1065 (*w*), 1028 (*s*), 969 (*w*), 940 (*w*), 909 (*w*), 850 (*w*), 804 (*m*), 760 (*s*), 700 (*s*), 633 (*w*), 594 (*w*), 548 (*m*), 461 (*w*).

HRMS (ESI) calcd for $C_{22}H_{26}NaO_3$ $[M+Na]^+$: 361.1774; found: 361.1765.



2-(3,4-dimethoxyphenethyl)-2-(1-phenylcyclopentyl)oxirane (**S133**) was prepared according to **GP3** (1.6 equiv NaH, 1.5 equiv Me_3SI) from **S132** (0.5 mmol, 1 equiv) in 95% yield as a colorless oil. Purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane).

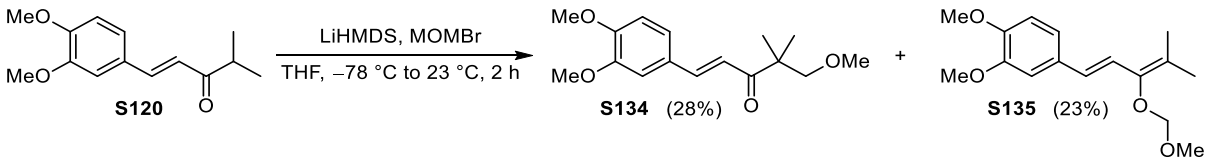
TLC (25% ethyl acetate in cyclohexane): R_f: 0.32 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 4H), 7.25 – 7.18 (m, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.53 – 6.46 (m, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.02 (d, *J* = 4.3 Hz, 1H), 2.84 (d, *J* = 4.3 Hz, 1H), 2.33 (ddd, *J* = 13.6, 10.2, 6.1 Hz, 1H), 2.26 – 2.12 (m, 2H), 1.94 (dt, *J* = 13.3, 8.8 Hz, 1H), 1.88 – 1.58 (m, 7H), 1.43 (dtt, *J* = 12.4, 9.7, 7.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8, 147.1, 145.8, 134.6, 128.3, 127.2, 126.2, 119.9, 111.6, 111.2, 62.9, 55.9, 55.8, 55.2, 49.9, 34.8, 33.3, 32.5, 30.0, 23.5, 23.3.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2951 (*s*), 2872 (*w*), 2833 (*w*), 1591 (*m*), 1513 (*s*), 1494 (*w*), 1452 (*s*), 1417 (*m*), 1331 (*w*), 1258 (*s*), 1234 (*s*), 1191 (*w*), 1155 (*s*), 1139 (*s*), 1028 (*s*), 972 (*w*), 910 (*m*), 848 (*m*), 806 (*m*), 759 (*s*), 734 (*w*), 700 (*s*), 641 (*w*), 598 (*w*), 543 (*m*), 486 (*w*).

HRMS (ESI) calcd for $C_{23}H_{28}NaO_3$ $[M+Na]^+$: 375.1931; found: 375.1929.



(*E*)-1-(3,4-dimethoxyphenyl)-5-methoxy-4,4-dimethylpent-1-en-3-one (**S134**)

To a solution of enone **S120** (234 mg, 1.00 mmol, 1 equiv) in tetrahydrofuran (2 mL) at – 78 °C was added lithium bis(trimethylsilyl)amide (1 M in THF, 1.40 mL, 1.40 mmol, 1.40 equiv) dropwise via syringe over a period of 30 seconds. A yellow solution was formed that was stirred at –78 °C for 10 min and then warmed to 0 °C. The now red solution was cooled to –78 °C again. Methoxymethyl bromide (114 µL, 1.40 mmol, 1.40 equiv) was added and stirring at –78 °C was continued for 5 min. The solution was stirred at 23 °C for 3 h. By addition of saturated aqueous ammonium chloride solution (5 mL) excess base was quenched. The mixture 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 and filtered. The filtrate was concentrated under reduced pressure and purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane grading to 25% ethyl acetate in cyclohexane) to yield compound **S134** (79.0 mg, 28%) as a pale yellow oil that solidified upon storage. Additionally, enol ether **S135** (64.0 mg, 23%) was obtained as a pale yellow oil.

Analytical data of **S134**:

TLC (25% ethyl acetate in cyclohexane): R_f: 0.40 (CAM)

mp: 49.5 – 52.0 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (d, *J* = 15.5 Hz, 1H), 7.14 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.04 (d, *J* = 2.0 Hz, 1H), 6.97 (d, *J* = 15.5 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.45 (s, 2H), 3.31 (s, 3H), 1.20 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 202.6, 151.2, 149.2, 143.1, 128.0, 122.8, 119.0, 111.1, 110.3, 79.5, 59.5, 56.0 (2C), 47.7, 22.0.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2966 (*w*), 2931 (*m*), 2873 (*w*), 2836 (*m*), 1678 (*m*), 1591 (*s*), 1578 (*s*), 1509 (*s*), 1462 (*m*), 1442 (*m*) 1420 (*m*), 1393 (*w*), 1364 (*w*), 1338 (*w*), 1308 (*w*), 1256 (*s*), 1233 (*s*), 1199 (*w*), 1160 (*m*), 1138 (*s*), 1107 (*s*), 1065 (*s*), 1021 (*s*), 983 (*s*), 963 (*m*), 927 (*w*), 845 (*w*), 807 (*m*), 767 (*m*), 728 (*w*), 647 (*w*), 607 (*w*), 555 (*w*), 513 (*w*), 487 (*w*), 462 (*w*), 431 (*w*), 415 (*w*) cm^{-1}.

HRMS (ESI): calcd for $C_{16}H_{22}NaO_4$ $[M+Na]^+$: 301.1410; found: 301.1404.

Analytical data of **S135**:

TLC (25% ethyl acetate in cyclohexane): R_f: 0.50 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.97 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.78 (d, *J* = 15.7 Hz, 1H), 6.62 (d, *J* = 15.7 Hz, 1H), 4.85 (s, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.58 (s, 3H), 1.87 (s, 3H), 1.86 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 149.2, 148.8, 146.4, 130.8, 127.1, 122.8, 119.6, 119.4, 111.4, 109.1, 97.9, 57.5, 56.0, 55.9, 19.2, 19.0.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3054 (*w*), 2994 (*w*), 2932 (*m*), 2907 (*m*), 2835 (*w*), 1637 (*w*), 1599 (*w*), 1580 (*w*), 1510 (*s*), 1463 (*m*), 1441 (*m*), 1417 (*w*), 1383 (*w*), 1332 (*w*), 1294 (*w*), 1251 (*s*), 1228 (*s*), 1196 (*w*), 1156 (*s*), 1137 (*s*), 1108 (*m*), 1071 (*s*), 1025 (*s*), 991 (*s*), 963 (*s*), 924 (*m*), 902 (*w*),

864 (*w*), 837 (*w*), 803 (*m*), 765 (*w*), 728 (*w*), 684 (*w*), 612 (*w*), 591 (*w*), 562 (*w*), 534 (*w*), 474 (*w*), 441 (*w*).

HRMS (ESI): calcd for $C_{16}H_{22}NaO_4$ $[M+Na]^+$: 301.1410; found: 301.1406.

S134 **S136**

5-(3,4-dimethoxyphenyl)-1-methoxy-2,2-dimethylpentan-3-one (**S136**) was prepared according to **GP2b** (4 equiv Mg, T = 23 °C, t = 4.5 h) from **S134** (0.6 mmol, 1 equiv) in 64% yield as a colorless solid. Purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane grading to 25% ethyl acetate in cyclohexane).

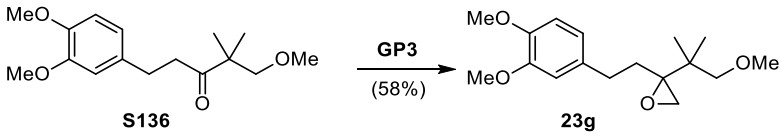
TLC (25% ethyl acetate in cyclohexane): R_f: 0.49 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.78 – 6.73 (m, 1H), 6.72 – 6.66 (m, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.33 (s, 2H), 3.25 (s, 3H), 2.83 – 2.73 (m, 4H), 1.07 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 213.3, 148.8, 147.3, 134.4, 120.2, 111.9, 111.3, 79.7, 59.2, 55.9, 55.8, 48.4, 39.7, 29.3, 21.9.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2963 (*w*), 2932 (*m*), 2874 (*w*), 2834 (*w*), 1704 (*s*), 1607 (*w*), 1590 (*w*), 1514 (*s*), 1463 (*m*), 1418 (*w*), 1394 (*w*), 1363 (*w*), 1258 (*s*), 1235 (*s*), 1195 (*w*), 1141 (*s*), 1107 (*s*), 1075 (*m*), 1027 (*s*), 981 (*w*), 961 (*w*), 928 (*w*), 890 (*w*), 850 (*w*), 803 (*m*), 763 (*m*), 710 (*w*), 636 (*w*), 597 (*w*), 550 (*w*), 462 (*w*), 416 (*w*) cm^{-1}.

HRMS (ESI): calcd for $C_{16}H_{24}NaO_4$ $[M+Na]^+$: 303.1567; found: 303.1559.



S136 **23g**

2-(3,4-dimethoxyphenethyl)-2-(1-methoxy-2-methylpropan-2-yl)oxirane (**23g**) was prepared according to **GP3** (1.6 equiv NaH, 1.5 equiv Me_3SI) from **S136** (0.40 mmol, 1 equiv) in 58% yield as a colorless oil. Purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane).

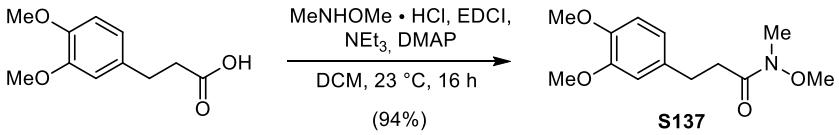
TLC (25% ethyl acetate in cyclohexane): R_f: 0.52 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.77 (d, *J* = 7.9 Hz, 1H), 6.72 – 6.68 (m, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.30 (s, 3H), 3.17 (q, *J* = 9.2 Hz, 2H), 2.79 (d, *J* = 4.2 Hz, 1H), 2.67 (d, *J* = 4.2 Hz, 1H), 2.48 (ddd, *J* = 13.6, 11.4, 5.2 Hz, 1H), 2.40 (ddd, *J* = 13.6, 11.4, 5.8 Hz, 1H), 2.11 (ddd, *J* = 14.5, 11.4, 5.9 Hz, 1H), 1.97 (ddd, *J* = 14.5, 11.4, 5.2 Hz, 1H), 0.97 (s, 3H), 0.91 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 148.9, 147.2, 134.9, 120.1, 111.8, 111.4, 79.4, 61.7, 59.2, 56.0, 55.9, 48.3, 38.4, 31.8, 29.9, 21.4, 21.4.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2958 (*w*), 2934 (*m*), 2873 (*w*), 2833 (*w*), 1607 (*w*), 1590 (*w*), 1514 (*s*), 1463 (*m*), 1417 (*w*), 1396 (*w*), 1364 (*w*), 1347 (*w*), 1259 (*s*), 1235 (*s*), 1201 (*w*), 1156 (*s*), 1139 (*s*), 1104 (*s*), 1028 (*s*), 963 (*w*), 947 (*w*), 921 (*w*), 849 (*w*), 806 (*m*), 765 (*m*), 622 (*w*), 599 (*w*), 588 (*w*), 560 (*w*), 521 (*w*), 465 (*w*), 421 (*w*), 413 (*w*) cm^{-1}.

HRMS (ESI): calcd for $C_{17}H_{26}NaO_3$ $[M+Na]^+$: 317.1723; found: 317.1699.



S137

3-(3,4-dimethoxyphenyl)-*N*-methoxy-*N*-methylpropanamide (**S137**)

To a solution of 3-(3,4-dimethoxyphenyl)propanoic acid (2.50 g, 11.9 mmol, 1 equiv) in dichloromethane (60 mL, 0.20 M) was added triethylamine (1.81 mL, 13.1 mmol, 1.10 equiv), 4-dimethylaminopyridine (145 mg, 1.19 mmol, 0.100 equiv.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (2.51 g, 13.1 mmol, 1.10 equiv) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.39 g, 14.3 mmol, 1.20 equiv.) in sequence and the pale yellow solution was stirred at 23 °C. After 16 h aqueous hydrochloric acid (1 M, 60 mL) was added to neutralize excess of base. The aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over sodium sulfate and concentrated under reduced pressure to give a pale yellow oil. The crude product was purified by flash column chromatography on silica gel (50% diethyl ether in petrol ether) to afford amide **S137** (2.82 g, 11.1 mmol, 94%) as a colorless oil.

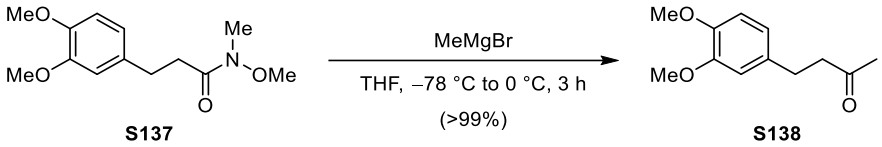
TLC (40% ethyl acetate in cyclohexane): R_f: 0.09 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 – 6.71 (m, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.59 (s, 3H), 3.16 (s, 3H), 2.89 (dd, *J* = 8.7, 6.8 Hz, 2H), 2.71 (t, *J* = 7.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 148.9, 147.5, 134.1, 120.3, 112.0, 111.4, 61.3, 56.0, 55.9, 34.1, 32.3, 30.4.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2936 (*m*), 2834 (*m*), 1657 (*s*), 1590 (*m*), 1514 (*s*), 1450 (*m*), 1416 (*s*), 1383 (*m*), 1330 (*w*), 1259 (*s*), 1233 (*s*), 1139 (*s*), 1026 (*s*), 989 (*w*), 852 (*m*), 763 (*m*).

HRMS (ESI): calcd for $C_{13}H_{20}NO_4$ $[M+H]^+$: 254.1387; found: 254.1385.



S137 **S138**

4-(3,4-dimethoxyphenyl)butan-2-one (**S138**)

To a solution of amide **S137** (253 mg, 1.00 mmol, 1 equiv) in tetrahydrofuran (10 mL, 0.10 M) was added a methylmagnesium bromide solution (1.00 M in diethyl ether, 2.00 mL, 2.00 mmol 2.00 equiv.) at –78 °C dropwise. After 5 min the mixture was allowed to warm up to 0 °C and after 3x 25 mL), the combined organic were dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (50% diethyl ether in petrol ether) to afford ketone **S138** (208 mg, 1.00 mmol, >99%) as a colorless solid.**TLC** (30% ethyl acetate in cyclohexane): R_f: 0.21 (UV, CAM)

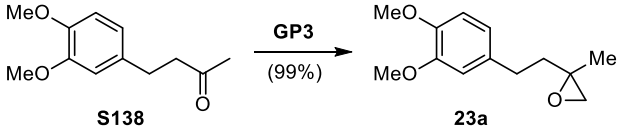
mp: 54.6 – 56.3 °C

^{1}H NMR (400 MHz, CDCl3) δ 6.78 (d, *J* = 8.6 Hz, 1H), 6.71 (dq, *J* = 4.3, 1.9 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.88 – 2.79 (m, 2H), 2.78 – 2.70 (m, 2H), 2.13 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.2, 149.0, 147.5, 133.8, 120.2, 111.8, 111.4, 56.1, 56.0, 45.6, 30.3, 29.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2936 (*m*), 2835 (*m*), 1713 (*s*), 1590 (*m*), 1515 (*s*), 1464 (*m*), 1419 (*m*), 1363 (*m*), 1259 (*s*), 1235 (*m*), 1155 (*m*), 1028 (*m*), 804 (*w*), 755 (*w*).

HRMS (LTP): calcd for $C_{12}H_{17}O_3$ $[M+H]^+$: 209,1172; found: 209,1180.



S138 **23a**

2-(3,4-dimethoxyphenethyl)-2-methyloxirane (**23a**) was prepared according to **GP3** (2.0 equiv NaH, 2.0 equiv Me_3SI) from **S138** (0.9 mmol, 1 equiv) in 99% yield as a colorless solid. Purified by flash column chromatography on silica gel (40% diethyl ether in *n*-pentane).

TLC (10% ethyl acetate in cyclohexane): R_f: 0.08 (UV, CAM)

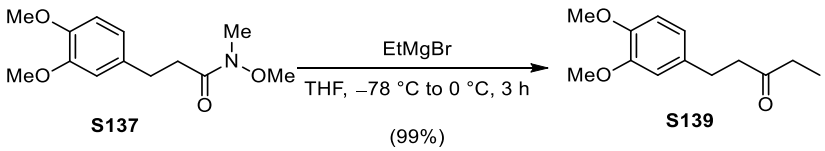
mp: 41.5 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 – 6.76 (m, 1H), 6.75 – 6.67 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.70 – 2.63 (m, 2H), 2.63 – 2.60 (m, 1H), 2.58 (dd, *J* = 4.8, 0.7 Hz, 1H), 1.95 – 1.77 (m, 2H), 1.37 (d, *J* = 0.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 147.4, 134.4, 120.2, 111.7, 111.4, 56.8, 56.1, 56.0, 54.1, 38.9, 31.1, 21.1.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3037 (*w*), 2934 (*m*), 2834 (*m*), 1590 *(w*), 1515 (*s*), 1464 (*m*), 1418 (*m*), 1389 (*w*), 1262 (*m*), 1236 (*m*), 1156 (*m*), 1142 (*m*), 1073 (*w*), 1029 (*m*), 900 (*w*), 806 (*w*), 765 (*w*).

HRMS (LTB): calcd for $C_{13}H_{19}O_3$ $[M+H]^+$: 223,1329; found: 223.1339.



1-(3,4-dimethoxyphenyl)pentan-3-one (**S139**):

To a solution of Weinreb amide **S137** (253 mg, 1.00 mmol, 1 equiv.) in tetrahydrofuran (10 mL, 0.10 M) was added ethylmagnesium bromide solution (2.00 M in diethyl ether, 1.00 mL, 2.00 mmol 2.00 equiv.) at –78 °C dropwise. After 5 min the mixture was allowed to warm up to 0 °C and stirred for 3x 25 mL), the combined organic were dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (50% diethyl ether in petrol ether) to afford ketone **S139** (222 mg, 1.00 mmol, >99%) as a colorless oil.

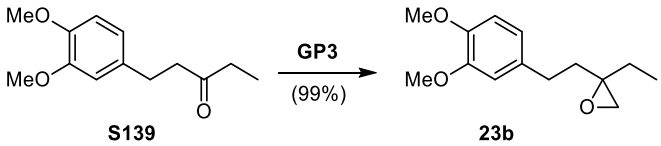
TLC (30% ethyl acetate in cyclohexane): R_f: 0.33 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 – 6.76 (m, 1H), 6.73 – 6.69 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.85 (dd, *J* = 8.2, 6.8 Hz, 2H), 2.75 – 2.66 (m, 2H), 2.40 (q, *J* = 7.3 Hz, 2H), 1.04 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 211.0, 149.0, 147.5, 134.0, 120.2, 111.9, 111.4, 56.0, 56.0, 44.3, 36.4, 29.7, 7.9.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2936 (*m*), 2835 (*m*), 1712 (*s*), 1590 (*w*), 1515 (*s*), 1463 (*m*), 1418 (*m*), 1364 (*w*), 1260 (*s*), 1236 (*m*), 1155 (*m*), 1028 (*m*), 807 (*w*), 764 (*w*).

HRMS (LTB): calcd for $C_{13}H_{19}O_3$ $[M+H]^+$: 223.1329; found: 223.1334.



S139 **23b**

2-(3,4-dimethoxyphenethyl)-2-ethyloxirane (**23b**) was prepared according to **GP3** (2.0 equiv NaH, 2.0 equiv Me_3SI) from **S139** (1.0 mmol, 1 equiv) in 99% yield as a colorless oil. Purified by flash column chromatography on silica gel (30% diethyl ether in *n*-pentane).

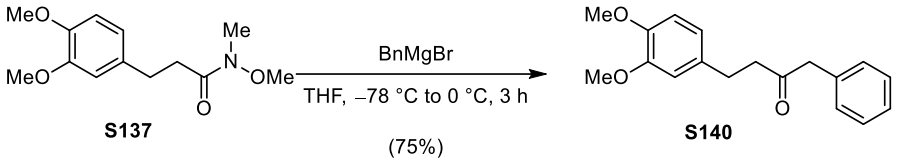
TLC (10% ethyl acetate in cyclohexane): R_f: 0.11 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 – 6.76 (m, 1H), 6.74 – 6.68 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.67 – 2.56 (m, 4H), 1.99 – 1.79 (m, 2H), 1.77 – 1.56 (m, 2H), 0.96 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 147.4, 134.5, 120.1, 111.7, 111.4, 60.0, 56.1, 56.0, 52.3, 36.1, 30.7, 27.3, 9.1.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2937 (*m*), 2835 (*s*), 1590 (*w*), 1515 (*s*), 1464 (*m*), 1418 (*w*), 1261 (*m*), 1236 (*m*), 1156 (*m*), 1141 (*m*), 1029 (*m*), 902 (*w*), 807 (*w*), 765 (*w*).

HRMS (LTB): calcd for $C_{14}H_{21}O_3$ $[M+H]^+$: 237.1485; found: 237.1497.



4-(3,4-dimethoxyphenyl)-1-phenylbutan-2-one (**S140**)

To a solution of amide **S137** (1.00 g, 3.95 mmol, 1 equiv.) in tetrahydrofuran (40 mL, 0.10 M) was added a benzylmagnesium bromide (1.00 M in tetrahydrofuran, 3.95 mL, 7.90 mmol 2.00 equiv.) dropwise at –78 °C. After 5 min the mixture was allowed to warm up to 0 °C and after 3x 50 mL), the combined organic layers were dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (40% diethyl ether in petrol ether) to afford ketone **S140** (845 mg, 2.97 mmol, 75%) as a colorless oil.

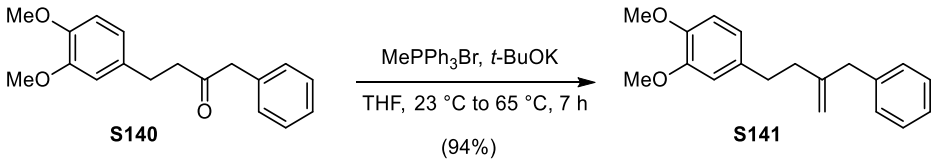
TLC (25% ethyl acetate in cyclohexane): R_f: 0.31 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.22 (m, 3H), 7.18 – 7.13 (m, 2H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.69 – 6.61 (m, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.66 (s, 2H), 2.85 – 2.79 (m, 2H), 2.78 – 2.72 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.7, 149.0, 147.5, 134.2, 133.7, 129.5, 128.9, 127.2, 120.2, 111.8, 111.4, 56.1, 55.9, 50.6, 43.9, 29.6.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3030 (*w*), 3000 (*w*), 2935 (*m*), 2834 (*m*), 1713 (*s*), 1590 (*m*), 1515 (*s*), 1454 (*m*), 1418 (*m*), 1360 (*w*), 1261 (*s*), 1236 (*m*), 1142 (*m*), 1082 (*m*), 1029 (*m*), 806 (*w*), 763 (*w*), 700 (*m*).

HRMS (ESI): calcd for $C_{18}H_{20}NaO_3$ $[M+Na]^+$: 307.1305; found: 307.1285.



4-(3-benzylbut-3-en-1-yl)-1,2-dimethoxybenzene (**S141**)

To a solution of methyltriphenylphosphonium bromide (2.68 g, 7.50 mmol, 5.00 equiv) in tetrahydrofuran (7.5 mL, 1.0 M) was added potassium *tert*-butoxide (842 mg, 7.50 mmol, 5.00 equiv) and the resulting orange solution was stirred at 23 °C. After 2 h a solution of ketone **S140** (427 mg, 1.50 mmol, 1 equiv) in tetrahydrofuran (3.0 mL, 0.50 M) was added at 23 °C. After

1 h the mixture was filtered over a pad of silica and concentrated to give a red oil. The crude product was purified by flash column chromatography on deactivated silica gel (1% triethylamine and 20% diethyl ether in petrol ether) to afford alkene **S141** (394 mg, 1.39 mmol, 93%) as a colorless oil.

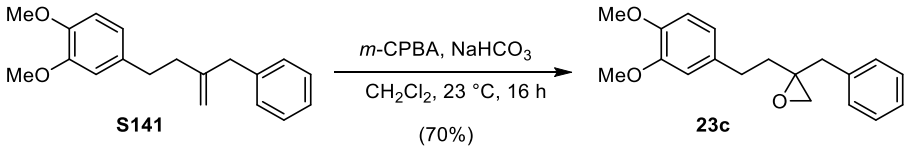
TLC (20% ethyl acetate in cyclohexane): R_f: 0.32 (UV, CAM)

^{1}H NMR (400 MHz, CDCl3) δ 7.37 – 7.25 (m, 2H), 7.25 – 7.16 (m, 3H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.72 – 6.63 (m, 2H), 4.89 (s, 1H), 4.82 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.38 (s, 2H), 2.78 – 2.62 (m, 2H), 2.28 (dd, *J* = 8.9, 7.2 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 148.6, 147.3, 139.8, 134.8, 129.1, 128.4, 126.2, 120.2, 111.8, 111.7, 111.3, 56.0, 55.9, 43.5, 37.4, 34.0.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3061 (*w*), 3025 (*m*), 2998 (*m*), 2933 (*m*), 2833 (*m*), 1644 (*m*), 1590 (*m*), 1514 (*s*), 1495 (*m*), 1463 (*m*), 1452 (*m*), 1417 (*m*), 1332 (*w*), 1260 (*s*), 1235 (*s*), 1191 (*m*), 1154 (*m*), 1075 (*m*), 1030 (*m*), 893 (*m*), 805 (*m*), 764 (*w*), 734 (*m*), 700 (*m*).

HRMS (ESI): calcd for $C_{19}H_{22}NaO_2$ $[M+Na]^+$: 305.1512; found: 305.1493.



To a suspension of alkene **S141** (390 mg, 1.38 mmol, 1 equiv.) and sodium bicarbonate (348 mg, 4.14 mmol, 3.00 equiv.) in dichloromethane (14 mL, 0.10 M) was added *m*-chloroperoxybenzoic acid (~70% wt., 681 mg, 2.76 mmol, 2.00 equiv) at 0 °C and the resulting pale yellow solution was slowly allowed to warm up to 23 °C. After 16 h the mixture was diluted with saturated aqueous sodium bicarbonate (10 mL) and saturated aqueous thiosulfate solution (10 mL) to quench excess of *m*-chloroperoxybenzoic acid. The aqueous layer was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a yellow oil. The crude product was purified by flash column chromatography on silica gel (20% diethyl ether in petrol ether) to afford epoxide **23c** (286 mg, 0.960 mmol, 70%) as a colorless oil.

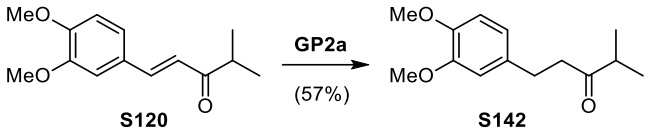
TLC (20% ethyl acetate in cyclohexane): R_f: 0.25 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.19 (m, 5H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.70 – 6.61 (m, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 2.98 (d, *J* = 14.4 Hz, 1H), 2.90 (d, *J* = 14.3 Hz, 1H), 2.69 – 2.57 (m, 4H), 1.94 – 1.74 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 147.4, 137.0, 134.3, 129.8, 128.5, 126.8, 120.2, 111.7, 111.4, 59.6, 56.1, 56.0, 52.1, 41.1, 36.0, 30.7.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3028 (*m*), 2999 (*m*), 2932 (*m*), 2834 (*m*), 1724 (*m*), 1590 (*m*), 1514 (*s*), 1453 (*m*), 1418 (*m*), 1322 (*w*), 1260 (*s*), 1235 (*s*), 1155 (*m*), 1076 (*w*), 1028 (*m*), 921 (*w*), 852 (*w*), 805 (*m*), 764 (*m*), 703 (*m*).

HRMS (ESI): calcd for $C_{19}H_{22}NaO_3$ $[M+Na]^+$: 321.1461; found: 321.1445.



S120 S142

1-(3,4-dimethoxyphenyl)-4-methylpentan-3-one (**S142**) was prepared accoriding to **GP2a** (10% Pd, t = 16 h) from **S120** (1.7 mmol, 1 equiv) in 57% yield as a colorless oil. Purified by flash column chromatography on silica gel (10% diethyl ether in petrol ether).

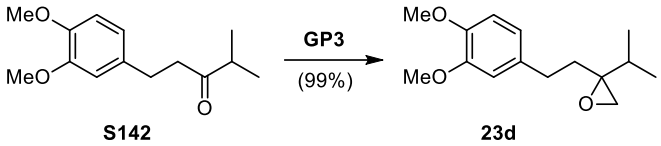
TLC (20% ethyl acetate in cyclohexane): R_f: 0.23 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 – 6.73 (m, 1H), 6.73 – 6.67 (m, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 2.83 (ddd, *J* = 8.2, 6.9, 1.8 Hz, 2H), 2.74 (ddd, *J* = 8.4, 7.1, 1.7 Hz, 2H), 2.55 (p, *J* = 6.9 Hz, 1H), 1.07 (s, 3H), 1.05 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.0, 149.0, 147.4, 134.1, 120.2, 111.9, 111.4, 56.0, 55.9, 42.3, 41.2, 29.6, 18.2.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2968 (*s*), 2933 (*s*), 2835 (*m*), 1709 (*s*), 1590 (*w*), 1516 (*s*), 1465 (*m*), 1418 (*w*), 1363 (*w*), 1261 (*s*), 1237 (*m*), 1156 (*m*), 1140 (*m*), 1073 (*w*), 1029 (*m*), 805 (*w*), 764 (*w*).

HRMS (LTP): calcd for $C_{14}H_{21}O_3$ $[M+H]^+$: 237.1485; found: 237.1493.



S142 23d

2-(3,4-dimethoxyphenethyl)-2-isopropyloxirane (**23d**) was prepared according to **GP3** (2.0 equiv NaH, 2.0 equiv Me_3SI) from **S142** (1.0 mmol, 1 equiv) in 99% yield as a colorless oil. Purified by flash column chromatography on silica gel (20% diethyl ether in *n*-pentane).

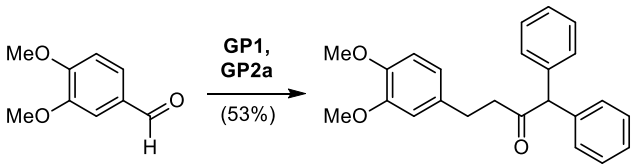
TLC (10% ethyl acetate in cyclohexane): R_f: 0.17 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 – 6.77 (m, 1H), 6.74 – 6.68 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.67 – 2.60 (m, 2H), 2.60 – 2.46 (m, 2H), 2.01 – 1.88 (m, 2H), 1.79 (p, *J* = 6.9 Hz, 1H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 147.3, 134.7, 120.1, 111.8, 111.4, 62.4, 56.1, 56.0, 50.6, 33.2, 32.5, 30.2, 18.4, 18.0.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2960 (*s*), 2834 (*m*), 1590 (*m*), 1515 (*s*), 1464 (*m*), 1418 (*s*), 1261 (*s*), 1236 (*m*), 1156 (*m*), 1141 (*m*), 1030 (*m*), 930 (*w*), 863 (*w*), 808 (*w*), 766 (*w*).

HRMS (LTB): calcd for $C_{15}H_{23}O_3$ $[M+H]^+$: 251.1642; found: 251.1651.



S143

4-(3,4-dimethoxyphenyl)-1,1-diphenylbutan-2-one (**S143**) was prepared according to **GP1** (t = 3 h) from 3,4-dimethoxybenzaldehyde (3.0 mmol, 1 equiv) and 1,1-diphenylpropan-2-one (1.1 equiv) and **GP2a** (10% Pd, t = 16 h) in 53% yield as a colorless oil. Purified by flash column chromatography on silica gel (10% diethyl ether in petrol ether).

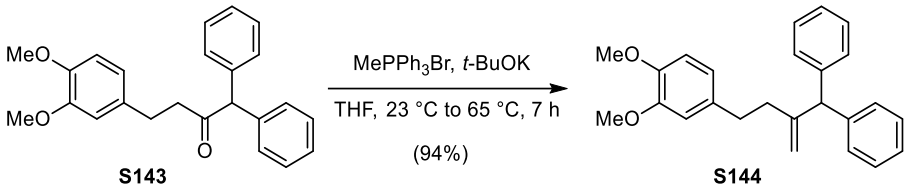
TLC (25% ethyl acetate in cyclohexane): R_f: 0.27 (UV, CAM)

^{1}H NMR (400 MHz, CDCl3) δ 7.39 – 7.20 (m, 6H), 7.21 – 7.12 (m, 4H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.67 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.62 (d, *J* = 2.0 Hz, 1H), 5.05 (s, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 2.87 (s, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.9, 149.0, 147.5, 138.3, 133.6, 129.1, 128.8, 127.3, 120.4, 111.9, 111.4, 64.6, 56.1, 55.9, 44.7, 29.9.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3059 (*w*), 3026 (*w*), 3001 (*m*), 2931 (*m*), 2834 (*m*), 1717 (*s*), 1591 (*m*), 1515 (*s*), 1495 (*m*), 1452 (*m*), 1418 (*m*), 1358 (*w*), 1262 (*s*), 1237 (*m*), 1154 (*m*), 1080 (*w*), 1029 (*m*), 748 (*w*), 701 (*m*).

HRMS (ESI): calcd for $C_{24}H_{24}NaO_3$ $[M+Na]^+$: 383.1618; found: 383.1599.



S143 **S144**

(4-(3,4-dimethoxyphenyl)-2-methylenebutane-1,1-diyl)dibenzene (**S144**):

To a solution of methyltriphenylphosphonium bromide (1.34 g, 3.75 mmol, 5.00 equiv) in tetrahydrofuran (3.75 mL, 1.00 M) was added potassium *t*-butoxide (420 mg, 3.75 mmol, 5.00 equiv) and the resulting orange solution was stirred at 23 °C. After 2 h a solution of ketone **S143** (270 mg, 0.749 mmol, 1 equiv) in tetrahydrofuran (1.5 mL, 0.50 M) was added dropwise and the resulting solution was stirred at 65 °C. After 5 h the mixture was filtered over a pad of silica and concentrated to give a red oil. The crude product was purified by flash column chromatography on deactivated silica gel (1% triethylamine and 20% diethyl ether in petrol ether) to afford alkene **S144** (252 mg, 0.703 mmol, 94%) as a colorless solid.

TLC (15% ethyl acetate in cyclohexane): R_f: 0.31 (UV, CAM)

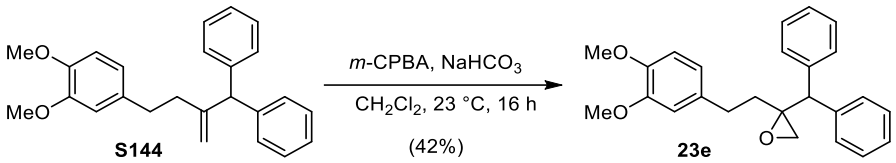
mp: 65.5 - 71.1 °C

^{1}H NMR (400 MHz, CDCl3) δ 7.31 – 7.26 (m, 3H), 7.23 – 7.10 (m, 7H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.71 – 6.60 (m, 2H), 5.14 (s, 1H), 4.73 (s, 1H), 4.55 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 2.82 – 2.65 (m, 2H), 2.45 – 2.27 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5, 148.9, 147.3, 142.4, 134.7, 129.5, 128.4, 126.5, 120.4, 114.3, 111.9, 111.3, 57.8, 56.1, 55.9, 38.1, 34.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3060 (*m*), 3025 (*m*), 2933 (*m*), 2834 (*m*), 1592 (*m*), 1515 (*s*), 1493 (*m*), 1417 (*m*), 1261 (*m*), 1237 (*m*), 1155 (*m*), 1030 (*m*), 758 (*m*), 701 (*m*).

HRMS (ESI): calcd for $C_{25}H_{27}O_2$ $[M+H]^+$: 359.2006; found: 359.1999.



2-benzhydryl-2-(3,4-dimethoxyphenethyl)oxirane (**23e**):

To a suspension of alkene **S144** (229 mg, 0.639 mmol, 1 equiv.) and sodium bicarbonate (80.5 mg, 0.958 mmol, 1.50 equiv.) in dichloromethane (6.4 mL, 0.10 M) was added *m*-chloroperoxybenzoic acid (~70% wt., 205 mg, 0.805 mmol, 1.30 equiv) at 0 °C and the resulting pale yellow solution was slowly allowed to warm up to 23 °C. After 16 h the mixture was diluted with saturated aqueous sodium bicarbonate (10 mL) and saturated aqueous thiosulfate solution (10 mL) to quench excess of *m*-chloroperoxybenzoic acid. The aqueous layer was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a yellow oil. The crude product was purified by flash column chromatography on silica gel (20% diethyl ether in petrol ether) to afford epoxide **23e** (99.5 mg, 0.639 mmol, 42%) as a colorless oil.

TLC (20% ethyl acetate in cyclohexane): R_f: 0.30 (UV, CAM)

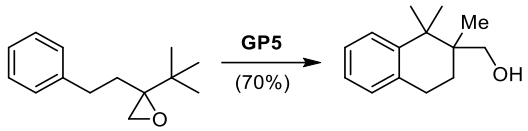
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.20 (m, 10H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.75 – 6.56 (m, 2H), 4.37 (s, 1H), 3.91 – 3.88 (m, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.68 (d, *J* = 10.3 Hz, 1H), 2.59 (d, *J* = 4.7 Hz, 1H), 2.26 (dd, *J* = 4.6, 0.8 Hz, 1H), 2.20 – 2.08 (m, 1H), 1.91 (ddd, *J* = 14.3, 9.0, 7.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 147.4, 140.5, 140.2, 134.1, 129.7, 129.6, 128.5, 128.3, 126.9, 126.8, 120.2, 111.7, 111.3, 60.5, 56.1, 55.9, 54.1, 49.0, 36.1, 31.0.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3026 (*m*), 2928 (*s*), 2850 (*m*), 1726 (*m*), 1590 (*m*), 1515 (*s*), 1452 (*m*), 1261 (*m*), 1237 (*m*), 1156 (*m*), 1030 (*m*), 703 (*m*).

HRMS (ESI): calcd for $C_{25}H_{26}NaO_3$ $[M+Na]^+$: 397.1774; found: 397.1765.

9.2.2.13 Epoxide Rearrangements



S25 12b

(1,1,2-trimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (**12b**) was prepared according to GP5 from **S25** (0.200 mmol, 1 equiv) in 70% yield as a colorless oil (28.4 mg). Purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane).

TLC (20% diethyl ether in *n*-pentane) R_f 0.30 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.15 (tdd, *J* = 7.8, 1.8, 0.9 Hz, 1H), 7.09 (td, *J* = 7.2, 1.4 Hz, 1H), 7.07 – 7.03 (m, 1H), 3.59 (d, *J* = 10.8 Hz, 1H), 3.55 (d, *J* = 10.8 Hz, 1H), 2.90 – 2.74 (m, 2H), 1.83 (dt, *J* = 13.7, 6.3 Hz, 1H), 1.74 (ddd, *J* = 13.6, 8.3, 6.7 Hz, 1H), 1.32 (s, 1H), 1.26 (s, 3H), 1.23 (s, 3H), 1.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.0, 135.2, 128.8, 126.8, 126.0, 125.2, 67.3, 39.2, 39.1, 27.7, 27.0, 26.2, 25.2, 19.0.

HRMS (ESI) calcd for $C_{14}H_{20}ONa$ $[M+Na]^+$: 227.1412; found: 227.1396

IR (ATR, neat) $\tilde{\nu}_{max}$: 3405 (br), 3055 (w), 3026 (w), 2967 (s), 2929 (s), 1490 (m), 1460 (m), 1446 (w), 1365 (w), 1244 (w), 1084 (m), 1036 (m), 942 (w), 760 (m), 722 (w), 703 (w).

S27 12c

(1,1,2,6-tetramethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (**12c**) was prepared according to **GP5** from **S27** (0.200 mmol, 1 equiv) in 76% yield as a colorless oil (33.0 mg). Purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane).

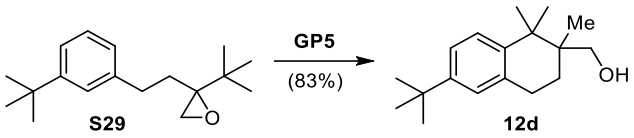
TLC (10% ethyl acetate in cyclohexane) R_f 0.21 (UV, CAM)

^{1}H NMR (400 MHz, CDCl3) δ 7.24 (d, *J* = 8.1 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.88 (s, 1H), 3.58 (d, *J* = 10.8 Hz, 1H), 3.54 (d, *J* = 10.9 Hz, 1H), 2.87 – 2.65 (m, 2H), 2.29 (s, 3H), 1.82 (dt, *J* = 13.6, 6.3 Hz, 1H), 1.73 (dd, *J* = 13.6, 6.6 Hz, 1H), 1.33 (s, 1H), 1.25 (s, 3H), 1.22 (s, 3H), 1.00 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2, 135.2, 134.7, 129.5, 127.1, 126.8, 67.5, 39.2, 39.0, 27.9, 27.2, 26.2, 25.4, 20.9, 19.1.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3371 (br), 2969 (s), 2925 (s), 1614 (w), 1499 (m), 1459 (m), 1434 (w), 1388 (w), 1365 (w), 1291 (w), 1232 (w), 1160 (w), 1024 (m), 1004 (w), 873 (w), 814 (w).

HRMS (ESI) calcd for $C_{15}H_{22}ONa$ $[M+Na]^+$: 241.1569; found: 241.1551



S29 12d

(6-(tert-butyl)-1,1,2-trimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (**12d**) was prepared according to **GP5** from **S29** (0.200 mmol, 1 equiv) in 83% yield as a colorless oil (43.0 mg). Purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane).

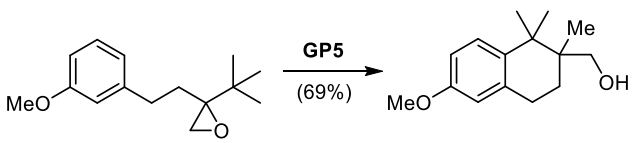
TLC (30% diethyl ether in *n*-pentane) R_f 0.19 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 1H), 7.17 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.06 – 6.99 (m, 1H), 3.56 (d, *J* = 1.1 Hz, 2H), 2.80 (q, *J* = 7.4, 6.4 Hz, 2H), 1.82 (dt, *J* = 13.7, 6.2 Hz, 1H), 1.74 (ddd, *J* = 13.6, 8.3, 6.6 Hz, 1H), 1.31 (s, 9H), 1.25 (s, 3H), 1.22 (s, 3H), 1.00 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.8, 143.0, 134.6, 126.5, 125.6, 123.3, 67.5, 39.2, 38.9, 34.2, 31.5, 27.9, 27.4, 26.5, 25.3, 19.1.

IR (ATR, neat) $\tilde{\nu}_{max}$: 1500 (*w*), 1461 (*m*), 1407 (*w*), 1392 (*w*), 1363 (*m*), 1299 (*w*), 1271 (*w*), 1128 (*w*), 1069 (*w*), 1024 (*m*), 1004 (*w*), 883 (*w*), 822 (*w*), 753 (*w*), 713 (*w*), 681 (*w*).

HRMS (ESI): calcd for $C_{18}H_{28}ONa$ $[M+Na]^+$: 283.2038; found: 283.2018



S31 12e

(6-methoxy-1,1,2-trimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (**12e**) was prepared according to **GP5** from **S31** (0.200 mmol, 1 equiv) in 69% yield as a colorless solid (32.3 mg). Purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane).

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

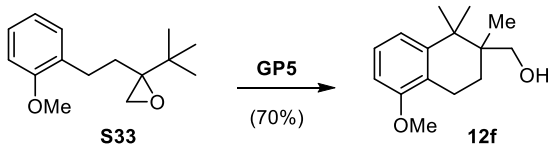
mp: 80.5 – 81.4 °C

^{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*).

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



(2-methoxy-1,1,2-trimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (**12f**) was prepared according to **GP5** from **S33** (0.200 mmol, 1 equiv) in 70% yield as a colorless oil (32.8 mg). Purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane).

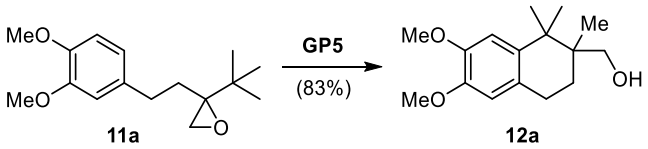
TLC (20% ethyl acetate in cyclohexane) R_f = 0.45 (CAM, UV)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.08 (m, 1H), 6.98 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.67 (d, *J* = 1.0 Hz, 1H), 3.82 (s, 3H), 3.55 (s, 2H), 2.73 – 2.59 (m, 2H), 1.82 (dt, *J* = 13.8, 6.3 Hz, 1H), 1.71 (ddd, *J* = 13.7, 8.0, 6.9 Hz, 1H), 1.25 (s, 3H), 1.23 (s, 4H), 0.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 147.4, 126.4, 124.6, 119.0, 106.4, 77.2, 67.5, 55.4, 39.3, 38.8, 27.7, 26.6, 25.4, 20.2, 19.0.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3387 (br), 2968 (m), 2936 (m), 1769 (w), 1580 (m), 1459 (s), 1435 (m), 1365 (w), 1349 (w), 1311 (w), 1255 (s), 1169 (w), 1061 (s), 1022 (m), 943 (w), 850 (w), 779 (m), 745 (w), 716 (w).

HRMS (ESI): calcd for $C_{15}H_{22}O_2Na$ $[M+Na]^+$: 257.1518; found: 257.1509



(6,7-dimethoxy-1,1,2-trimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (**12a**) was prepared according to **GP5** from **11a** (0.200 mmol, 1 equiv) in 83% yield as a colorless oil (44.0 mg). Purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane).

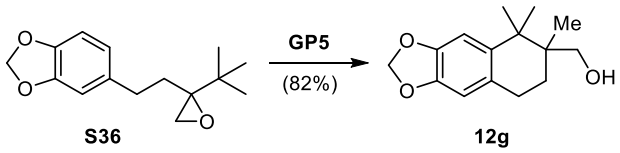
TLC (25% ethyl acetate in hexanes): R_f: 0.21 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (s, 1H), 6.51 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.56 (d, *J* = 10.9 Hz, 1H), 3.53 (d, *J* = 10.9 Hz, 1H), 2.80 – 2.64 (m, 2H), 1.80 (dt, *J* = 13.6, 6.2 Hz, 1H), 1.71 (ddd, *J* = 13.5, 8.3, 6.5 Hz, 1H), 1.50 (s, 1H), 1.23 (s, 3H), 1.20 (s, 3H), 0.98 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4, 146.9, 137.9, 127.6, 111.2, 110.1, 67.4, 56.2, 55.8, 39.1, 39.0, 27.8, 27.4, 25.9, 25.4, 19.0.

IR (ATR, neat) $\tilde{\nu}_{max}$ 3506 (br *m*), 2965 (*s*), 2934 (*s*), 2848 (*w*), 1610 (*m*), 1508 (*s*), 1462 (*s*), 1400 (*m*), 1363 (*w*), 1352 (*w*), 1327 (*w*), 1250 (*s*), 1206 (*s*), 1185 (*w*), 1156 (*s*), 1137 (*s*), 1105 (*w*), 1074 (*s*), 1023 (*s*), 975 (*m*), 911 (*m*), 857 (*s*), 832 (*m*), 794 (*m*), 730 (*s*), 646 (*w*), 571 (*w*), 543 (*w*), 489 (*w*), 439 (*w*).

HRMS (ESI) calcd for $C_{16}H_{25}O_3$ $[M+H]^+$: 265.1798; found: 265.1789.



(5,5,6-trimethyl-5,6,7,8-tetrahydronaphtho[2,3-d][1,3]dioxol-6-yl)methanol (**12g**) was prepared according to **GP5** from **S36** (0.200 mmol, 1 equiv) in 82% yield as a colorless oil (40.7 mg). Purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane).

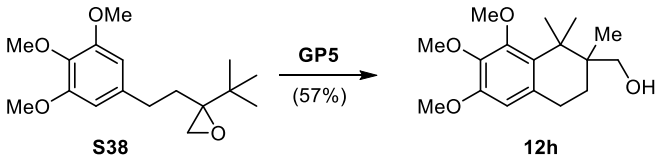
TLC (20% ethyl acetate in cyclohexane) R_f 0.25 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (s, 1H), 6.50 (s, 1H), 5.88 (s, 2H), 3.55 (d, J= 10.8 Hz, 1H), 3.54 (d, J = 10.8 Hz, 1H), 2.82 – 2.58 (m, 2H), 1.78 (dt, *J* = 13.6, 6.2 Hz, 1H), 1.69 (ddd, *J* = 13.6, 8.3, 6.5 Hz, 1H), 1.21 (s, 3H), 1.18 (s, 3H), 0.98 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.2, 145.3, 139.1, 128.5, 108.2, 106.7, 100.7, 67.4, 39.4, 39.1, 27.9, 27.3, 26.5, 25.5, 19.1.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3385 (*br*), 2968(*m*), 1504 (*m*), 1484 (*s*), 1369 (*w*), 1237 (*s*), 1110 (*w*), 1039 (*s*), 939 (*m*), 861 (*m*), 842 (*w*).

HRMS (ESI): calcd for $C_{15}H_{20}O_3Na$ $[M+Na]^+$: 271.1310; found: 271.1292



(6,7,8-trimethoxy-1,1,2-trimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (**12h**) was prepared according to **GP5** from **S38** (0.200 mmol, 1 equiv) in 57% yield as a colorless oil (33.8 mg). Purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane).

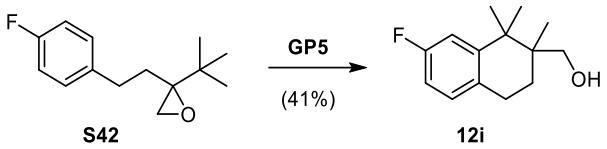
TLC (20% ethyl acetate in hexanes): R_f: 0.21 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (d, *J* = 0.9 Hz, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.58 (s, 2H), 2.89 – 2.41 (m, 2H), 1.78 – 1.61 (m, 2H), 1.31 (s, 3H), 1.45 (s, 1H), 1.30 (s, 3H), 0.98 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 151.2, 141.2, 132.0, 131.3, 107.1, 67.0, 60.7, 60.5, 55.8, 40.4, 39.3, 27.4, 27.2, 24.9, 23.1, 18.9.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3441 (*br m*), 2968 (*m*), 2936 (*s*), 2851 (*w*), 1597 (*m*), 1573 (*w*), 1488 (*s*), 1463 (*m*), 1447 (*m*), 1431 (*w*), 1397 (*s*), 1348 (*m*), 1338 (*m*), 1326 (*m*), 1244 (*m*), 1194 (*m*), 1022 (*s*), 974 (*w*), 936 (*w*), 859 (*w*), 831 (*w*), 794 (*w*).

HRMS (ESI): calcd for $C_{17}H_{26}O_4Na$ $[M+Na]^+$: 317.1729; found: 317.1713.



S42 12i

(7-fluoro-1,1,2-trimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (**12i**) was prepared according to **GP5** from **S42** (0.200 mmol, 1 equiv) in 41% yield as a colorless oil (18.4 mg). Purified by flash column chromatography on silica gel (10% diethyl ether in *n*-pentane).

TLC (10% diethyl ether in *n*-pentane) R_f 0.35 (UV, $KMnO_4$)

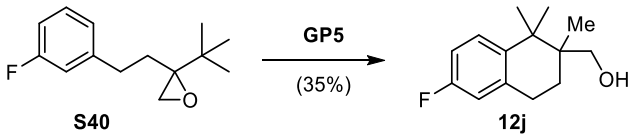
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 – 6.94 (m, 2H), 6.78 (td, *J* = 8.3, 2.7 Hz, 1H), 3.65 – 3.38 (m, 2H), 2.76 (m, 2H), 1.93 – 1.63 (m, 2H), 1.23 (s, 3H), 1.21 (s, 3H), 0.99 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 161.6 (d, *J* = 241.0 Hz), 148.4 (d, *J* = 4.3 Hz), 130.8 , 130.2 (d, *J* = 8.5 Hz), 113.2 (d, *J* = 21.0 Hz), 112.5 (d, *J* = 21.2 Hz), 67.4, 39.6, 39.0, 27.7, 27.2, 25.6, 25.3, 19.1.

^{19}F NMR (282 MHz, $CDCl_3$) δ -117.31 (dt, *J* = 12.8, 7.1 Hz).

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3378 (*br m*), 2971 (*s*), 2933 (*s*), 1613 (*m*), 1587 (*m*), 1499 (*s*), 1480 (*m*), 1436 (*w*), 1411 (*w*), 1367 (*w*), 1252 (*m*), 1190 (*w*), 1023 (*m*), 945 (*w*), 867 (*w*), 816 (*w*).

HRMS (ESI): calcd for $C_{14}H_{19}FONa$ $[M+Na]^+$: 245.1318; found: 245.1304



S40 12j

(6-fluoro-1,1,2-trimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (12j) was prepared according to **GP5** from **S40** (0.200 mmol, 1 equiv) in 35% yield as a colorless oil (15.7 mg). Purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane).

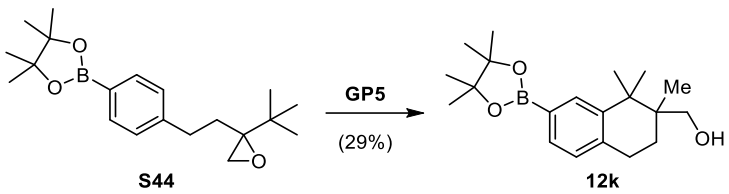
TLC (10% diethyl ether in *n*-pentane): R_f: 0.35 (UV, $KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 1H), 6.89 – 6.78 (m, 1H), 6.77 – 6.69 (m, 1H), 3.57 (d, *J* = 10.9 Hz, 1H), 3.52 (d, *J* = 10.8 Hz, 1H), 2.87 – 2.70 (m, 2H), 1.82 (dt, *J* = 13.7, 6.3 Hz, 1H), 1.78 – 1.65 (m, 1H), 1.23 (s, 3H), 1.21 (s, 3H), 0.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6 (d, *J* = 243.4 Hz), 141.8 (d, *J* = 3.0 Hz), 137.6 (d, *J* = 7.2 Hz), 128.5 (d, *J* = 8.0 Hz), 114.7 (d, *J* = 20.2 Hz), 113.2 (d, *J* = 20.6 Hz), 67.3, 39.2, 39.0, 27.9, 27.0, 26.4, 25.5, 19.1.

.**IR** (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3371 (*br m*), 2970 (*m*), 2941 (*m*), 2882 (*w*), 1612 (*m*), 1589 (*w*),1495 (*s*), 1461 (*m*), 1434 (*w*), 1420 (*w*), 1366 (*w*), 1247 (*m*), 1150 (*w*), 1127 (*w*), 11025 (*m*), 1005 (*m*), 862 (*m*), 813 (*w*).

HRMS (ESI): calcd for $C_{14}H_{19}FONa$ $[M+Na]^+$: 245.1318; found: 245.1297.



S44 12k

(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,1,2-trimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (**12k**) was prepared according to **GP5** from **S44** (0.200 mmol, 1 equiv) in 29% yield as a colorless oil (19.3 mg). Purified by flash column chromatography on silica gel (20% diethyl ether in *n*-pentane).

TLC (15% diethyl ether in *n*-pentane) R_f =0.25 ($KMnO_4$)

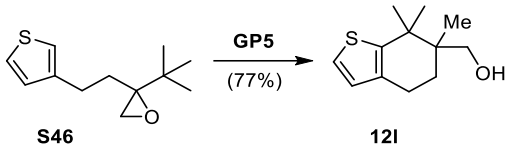
^{1}H NMR (400 MHz, CDCl3) δ 7.78 (s, 1H), 7.52 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 3.55 (q, *J* = 10.9 Hz, 3H), 2.83 (q, *J* = 7.3, 6.5 Hz, 2H), 1.82 (dt, *J* = 12.7, 6.3 Hz, 1H), 1.78 – 1.67 (m, 1H), 1.33 (s, 12H), 1.28 (s, 3H), 1.27 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 145.3, 138.8, 133.4, 131.6, 128.3, 83.5, 67.3, 39.2, 27.6, 26.9, 26.5, 25.1, 24.9, 19.0.

^{11}B NMR (128 MHz, CDCl3) δ 31.77.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3469 (*br*), 2974 (*m*), 2926 (*m*), 1609 (*w*), 1460 (*w*). 1390 (*m*), 1361 (*s*), 1315 (*w*), 1273 (*w*), 1228 (*w*), 1146 (*m*), 1100 (*w*), 1026 (*w*), 964 (*w*), 874 (*w*), 851 (*w*), 827 (*w*).

HRMS (ESI): calcd for $C_{20}H_{31}BO_3Na$ $[M+Na]^+$: 353.2264; found: 353.2249



S46 **12l**

(6,7,7-trimethyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-6-yl)methanol (**12l**) was prepared according to **GP5** from **S46** (0.200 mmol, 1 equiv) in 77% yield as a pale yellow oil (31.2 mg). Purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane).

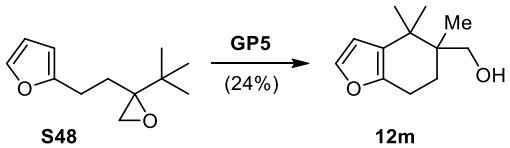
TLC (10% ethyl acetate in hexanes): R_f: 0.19 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 5.1 Hz, 1H), 6.68 (d, *J* = 5.1 Hz, 1H), 3.58 (d, *J* = 5.2 Hz, 2H), 2.64 – 2.59 (m, 2H), 1.82 (dt, *J* = 13.6, 6.2 Hz, 1H), 1.71 (dt, *J* = 13.8, 7.0 Hz, 1H), 1.32 (s, 3H), 1.27 (s, 3H), 1.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.0, 133.6, 127.2, 122.0, 67.5, 40.3, 39.3, 28.8, 28.1, 27.0, 22.7, 18.5.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3375 (br *s*), 2964 (*s*), 2934 (*s*), 1456 (*s*), 1365 (*m*), 1337 (*w*), 1321 (*w*), 1242 (*m*), 1192 (*w*), 1167 (*w*), 1116 (*w*), 1029 (*s*), 968 (*m*), 885 (*w*), 828 (*m*), 789 (*w*), 711 (*s*), 692 (*m*), 637 (*m*), 556 (*m*).

HRMS (ESI) calcd for $C_{12}H_{19}OS$ $[M+H]^+$: 211.1151; found: 211.1146.



S48 **12m**

(4,4,5-trimethyl-4,5,6,7-tetrahydrobenzofuran-5-yl)methanol (**12m**) was prepared according to **GP5** from **S48** (0.200 mmol, 1 equiv) in 24% yield as a colorless oil (9.3 mg). Purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane).

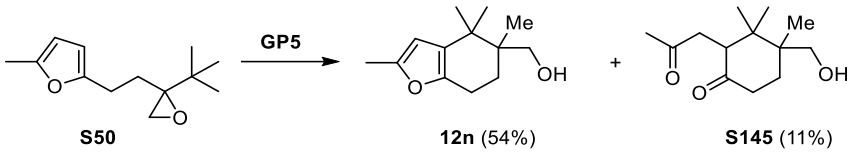
TLC (10% ethyl acetate in hexanes): R_f: 0.17 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (dt, *J* = 1.8, 0.9 Hz, 1H), 6.22 (d, *J* = 1.9 Hz, 1H), 3.56 (d, *J* = 10.8 Hz, 1H), 3.52 (d, *J* = 10.8 Hz, 1H), 2.60 – 2.53 (m, 2H), 1.84 (dt, *J* = 13.6, 6.2 Hz, 1H), 1.76 – 1.68 (m, 1H), 1.55 (s, 1H), 1.13 (s, 3H), 1.08 (s, 3H), 0.96 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4, 140.8, 126.2, 108.6, 67.4, 39.9, 35.8, 28.1, 26.2, 24.5, 20.3, 18.1.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3407 (br *s*), 2965 (*s*), 2936 (*m*), 2877 (*w*), 1632 (*w*), 1508 (*w*), 1458 (*m*), 1365 (*w*), 1338 (*w*), 1219 (*w*), 1192 (*w*), 1170 (*w*), 1134 (*m*), 1096 (*w*), 1058 (*s*), 1026 (*s*), 963 (*w*), 939 (*w*), 894 (*w*), 807 (*w*), 728 (*m*), 696 (*m*), 671 (*w*), 632 (*w*), 601 (*w*), 537 (*w*), 502 (*w*), 491 (*w*); 471 (*w*), 448 (*w*).

HRMS (ESI) calcd for $C_{12}H_{19}O_2$ $[M+H]^+$: 195.1380; found: 195.1375.



(2,4,4,5-tetramethyl-4,5,6,7-tetrahydrobenzofuran-5-yl)methanol (**12n**) was prepared according to **GP5** from **S50** (0.200 mmol, 1 equiv) in 54% yield as a colorless oil, that slowly crystallized upon storage (22.3 mg). Besides, hydrolyzed furan **S145** (5.0 mg, 11%) was isolated as a colorless oil. Purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane grading to 25% ethyl acetate in cyclohexane).

Analytical data of **12n**:

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

mp: 48.2 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.80 (s, 1H), 3.54 (d, *J* = 5.3 Hz, 2H), 2.60 – 2.45 (m, 2H), 2.24 (s, 3H), 1.80 (dt, *J* = 13.4, 6.2 Hz, 1H), 1.74 – 1.64 (m, 1H), 1.28 (t, *J* = 5.5 Hz, 1H), 1.10 (s, 3H), 1.05 (s, 3H), 0.94 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 150.3, 146.4, 126.9, 104.4, 67.5, 39.8, 35.8, 28.2, 26.1, 24.5, 20.2, 18.2, 13.8.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3384 (*m*), 2963 (*m*), 2924 (*m*), 2880 (*w*), 1640 (*w*), 1618 (*w*), 1583 (*w*), 1456 (*m*), 1381 (*m*), 1364 (*w*), 1340 (*w*), 1272 (*w*), 1254 (*w*), 1218 (*m*), 1193 (*m*), 1177 (*w*), 1140 (*w*), 1099 (*w*), 1065 (*m*), 1024 (*s*), 1001 (*m*), 950 (*m*), 907 (*w*), 890 (*w*), 792 (*m*), 756 (*w*), 703 (*w*), 687 (*w*), 672 (*w*), 620 (*w*), 586 (*w*), 514 (*w*), 463 (*w*).

HRMS (ESI): calcd for $C_{13}H_{21}O_2$ $[M+H]^+$: 209.1536; found: 209.1532.

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

Analytical data of **S145**:

TLC (25% ethyl acetate in cyclohexane): R_f: 0.05 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.66 (d, *J* = 10.8 Hz, 1H), 3.53 (d, *J* = 10.8 Hz, 1H), 3.29 (dd, *J* = 9.8, 2.7 Hz, 1H), 2.99 (dd, *J* = 17.2, 9.7 Hz, 1H), 2.61 – 2.49 (m, 1H), 2.30 (dt, *J* = 14.0, 3.9 Hz, 1H), 2.23 (s, 3H), 2.13 (dd, *J* = 17.2, 2.7 Hz, 1H), 1.85 (dd, *J* = 3.5, 1.5 Hz, 1H), 1.82 (d, *J* = 3.6 Hz, 1H), 1.36 (s, 1H), 1.33 (s, 3H), 0.97 (s, 3H), 0.76 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 211.5, 208.1, 69.2, 52.1, 43.4, 41.0, 37.8, 37.3, 32.6, 30.7, 23.1, 19.2, 17.4.

2D-NMR in appendix

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3449 (*m*), 2969 (*m*), 2882 (*w*), 1706 (*s*), 1460 (*w*), 1427 (*w*), 1356 (*m*), 1321 (*w*), 1266 (*w*), 1233 (*w*), 1177 (*w*), 1143 (*w*), 1032 (*m*), 1004 (*w*), 975 (*w*), 917 (*w*), 895 (*w*), 873 (*w*), 783 (*w*), 762 (*w*), 714 (*w*), 653 (*w*), 621 (*w*), 565 (*w*), 523 (*w*), 482 (*w*), 454 (*w*), 420 (*w*) cm^{-1}.

HRMS (ESI): calcd for $C_{13}H_{22}NaO_3$ $[M+Na]^+$: 249.1461; found: 249.1457.

S54 **12o**

(2,2,3-trimethyltetrahydro-2H-pyran-3-yl)methanol (**12o**) was prepared according to **GP5** from **S54** (0.200 mmol, 1 equiv) in 43% yield as a pale yellow oil (13.6 mg). Purified by flash column chromatography on silica gel (33% ethyl acetate in *n*-pentane).

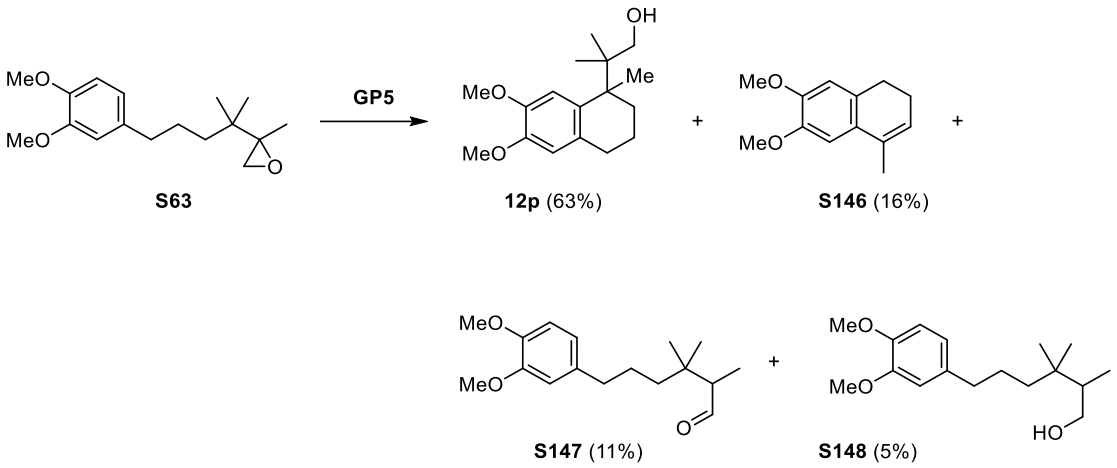
TLC (40% ethyl acetate in *n*-pentane): R_f: 0.28 (CAM)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.75 (d, J = 10.8 Hz, 1H), 3.72 – 3.64 (m, 2H), 3.50 (d, J = 10.9 Hz, 1H), 2.17 – 1.92 (m, 1H), 1.88 – 1.79 (m, 1H), 1.68 – 1.63 (m, 1H), 1.57 – 1.50 (m, 2H), 1.23 (s, 3H), 1.20 (s, 3H), 0.86 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 69.3, 61.4, 39.1, 29.8, 28.5, 23.3, 23.0, 22.6, 20.5.

IR (ATR, neat): $\tilde{\nu}$ = 3430 (br *m*), 2927 (*s*), 2859 (*s*), 1731 (*w*), 1456 (*m*), 1366 (*m*), 1219 (*w*), 1201 (*w*), 1159 (*w*), 1117 (*w*), 1085 (*s*), 1025 (*s*), 963 (*w*), 864 (*w*), 822 (*w*), 777 (*w*).

HRMS (ESI): calcd for $C_9H_{19}O_2$ $[M+H]^+$: 159.1380; found: 159.1376.



2-(6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methylpropan-1-ol (**12p**) was prepared according to **GP5** from **S63** (0.200 mmol, 1 equiv) in 63% yield as a colorless oil (34.8 mg). Further products: **S146** (6.7 mg, 16%, colorless solid), **S147** (6.2 mg, 11%, colorless oil) and **S148** (2.9 mg, 5%, colorless oil). Purified by flash column chromatography on silica gel (1% ethyl acetate in cyclohexane grading to 25% ethyl acetate in cyclohexane).

TLC (20% ethyl acetate in cyclohexane): R_f: 0.12 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.53 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.47 – 3.36 (m, 2H), 2.63 – 2.52 (m, 2H), 1.96 (td, *J* = 13.1, 3.6 Hz, 1H), 1.86 (ddt, *J* = 12.0, 9.3, 4.0 Hz, 1H), 1.56 (dddd, *J* = 13.5, 5.4, 3.1, 1.3 Hz, 1H), 1.47 (tddd, *J* = 12.6, 9.6, 6.0, 3.2 Hz, 1H), 1.32 (s, 3H), 1.13 (s, 1H), 1.04 (s, 3H), 0.95 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.8, 146.4, 134.5, 132.1, 113.0, 111.7, 69.9, 56.1, 55.8, 43.0, 41.9, 35.8, 31.6, 26.1, 21.7, 21.7.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3461 (br *m*), 2938 (*s*), 1609 (*w*), 1511 (*s*), 1464 (*m*), 1398 (*w*), 1341 (*w*), 1255 (*m*), 1216 (*m*), 1115 (*w*), 1029 (*w*).

HRMS (ESI): calcd for $C_{17}H_{26}NaO_3$ $[M+Na]^+$: 301.1774; found: 301.1755.

6,7-dimethoxy-4-methyl-1,2-dihydronaphthalene (**S146**):

TLC (20% ethyl acetate in cyclohexane): R_f: 0.35 (UV, CAM)

mp: 61.2 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 1H), 6.70 (d, *J* = 0.9 Hz, 1H), 5.75 (ddt, *J* = 4.5, 3.0, 1.5 Hz, 1H), 3.89 (s, 3H), 3.89 (s, 3H), 2.76 – 2.60 (m, 2H), 2.22 (dddd, *J* = 9.5, 6.2, 4.5, 1.9 Hz, 2H), 2.04 (q, *J* = 1.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 147.3, 131.9, 129.2, 128.9, 123.5, 111.5, 107.6, 56.4, 56.2, 28.2, 23.5, 19.6.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2936 (*m*), 2829 (*m*), 1602 (*w*), 1511 (*s*), 1464 (*m*), 1365 (*w*), 1327 (*w*), 1265 (*m*), 1218 (*m*), 1194 (*m*), 1145 (*s*), 1057 (*m*), 863 (*w*).

HRMS (ESI): calcd for $C_{13}H_{17}O_2$ $[M+H]^+$: 205.1223; found: 205.1214.

6-(3,4-dimethoxyphenyl)-2,3,3-trimethylhexanal (**S147**):

TLC (20% ethyl acetate in cyclohexane): R_f: 0.24 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (d, *J* = 3.0 Hz, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 6.74 – 6.67 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 2.57 – 2.48 (m, 2H), 2.25 (qd, *J* = 6.9, 3.0 Hz, 1H), 1.67 – 1.47 (m, 2H), 1.44 – 1.22 (m, 2H), 1.01 (s, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.95 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.5, 149.0, 147.3, 135.1, 120.3, 111.8, 111.4, 56.1, 56.0, 54.0, 40.6, 36.3, 35.6, 26.0, 25.2, 25.0, 9.0.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2937 (*s*), 1718 (*s*), 1590 (*w*), 1515 (*s*), 1464 (*m*), 1260 (*m*), 1236 (*m*), 1142 (*m*), 1030 (*m*).

HRMS (ESI): calcd for $C_{17}H_{26}NaO_3$ $[M+Na]^+$: 301.1774; found: 301.1757.

6-(3,4-dimethoxyphenyl)-2,3,3-trimethylhexan-1-ol (**S148**):

TLC (20% ethyl acetate in cyclohexane): R_f: 0.06 (UV, CAM)

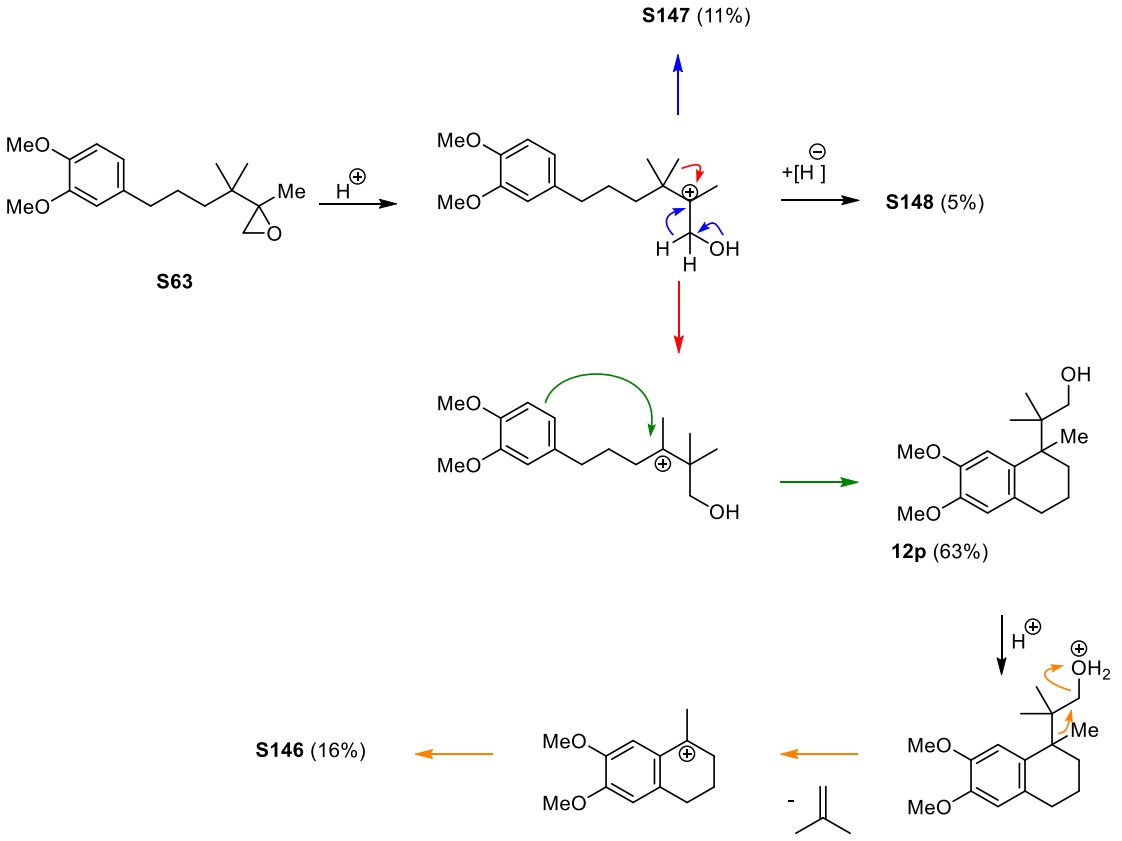
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 – 6.76 (m, 1H), 6.71 (d, *J* = 7.3 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.79 (dd, *J* = 10.4, 3.7 Hz, 1H), 3.32 (dd, *J* = 10.4, 8.9 Hz, 1H), 2.52 (t, *J* = 7.7 Hz, 2H), 1.65 – 1.40 (m, 4H), 1.32 (ddd, *J* = 13.5, 10.4, 6.4 Hz, 1H), 1.21 (ddd, *J* = 13.5, 10.0, 7.0 Hz, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.85 (s, 3H), 0.82 (s, 3H).

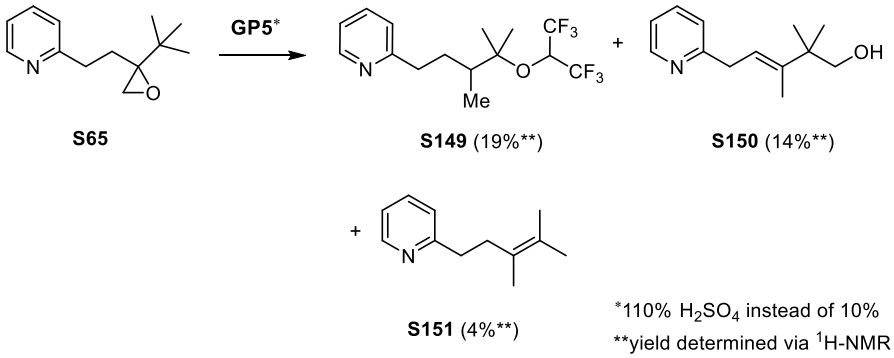
^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8, 147.1, 135.4, 120.1, 111.7, 111.2, 65.1, 55.9, 55.9, 43.4, 40.5, 36.4, 34.5, 25.9, 24.9, 24.8, 12.0.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3507 (br *m*), 2937 (*s*), 1591 (*w*), 1515 (*s*), 1464 (*m*), 1417 (*m*), 1261 (*m*), 1235 (*m*), 1142 (*m*), 1029 (*m*), 805 (*w*).

HRMS (ESI): calcd for $C_{17}H_{28}NaO_3$ $[M+Na]^+$: 303.1931; found: 303.1931.

Proposed reaction mechanism:





No reaction of epoxide **S65** was observed under the conditions of **GP5**.

By increasing the catalyst amount to 110% sulfuric acid under otherwise identical conditions to **GP5**, three main products (**S149**, **S150**, **S151**) could be isolated. Yields were determined via ^{1}H-NMR using 1,2,4,5-tetrachloro-3-nitrobenzene (15.6 mg) as internal standard. Purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane grading to 50% ethyl acetate in cyclohexane).

Analytical data of **S149**:

TLC (50% ethyl acetate in cyclohexane): R_f: 0.58 ($KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.54 – 8.50 (m, 1H), 7.62 – 7.56 (m, 1H), 7.16 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.12 – 7.07 (m, 1H), 4.27 (hept, *J* = 6.0 Hz, 1H), 2.94 (ddd, *J* = 13.7, 10.5, 5.2 Hz, 1H), 2.69 (ddd, *J* = 13.7, 10.0, 6.6 Hz, 1H), 2.12 – 2.02 (m, 1H), 1.70 – 1.61 (m, 1H), 1.49 – 1.38 (m, 1H), 1.17 (s, 6H), 1.02 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 162.4, 149.4, 136.5, 122.9, 121.2, 84.4, 69.6, 43.2, 37.0, 31.7, 22.8, 22.4, 14.4.

2D-NMR in appendix (HSQC, HMBC)

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2977 (*w*), 1591 (*w*), 1570 (*w*), 1474 (*w*), 1435 (*w*), 1396 (*w*), 1356 (*w*), 1285 (*m*), 1258 (*w*), 1221 (*m*), 1190 (*s*), 1126 (*m*), 1099 (*m*), 1051 (*w*), 951 (*w*), 889 (*w*), 750 (*w*), 686 (*w*).

HRMS (ESI): calcd for $C_{15}H_{20}F_6NO$ $[M+H]^+$: 344.1444; found: 344.1419.

Analytical data of **S150:**

TLC (50% ethyl acetate in cyclohexane): R_f: 0.12 ($KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 – 8.47 (m, 1H), 7.62 – 7.56 (m, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.13 – 7.07 (m, 1H), 5.65 – 5.57 (m, 1H), 3.62 (d, *J* = 7.3 Hz, 2H), 3.39 (s, 2H), 1.67 (s, 3H), 1.18 – 1.15 (m, 1H), 1.09 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 160.9, 149.4, 141.1, 136.6, 122.9, 122.6, 121.3, 69.8, 42.0, 36.9, 23.9, 12.9.

2D-NMR in appendix (HSQC, HMBC, COSY)

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3365 (*m*), 3304 (*m*), 2962 (*s*), 2923 (*m*), 2871 (*m*), 1593 (*s*), 1569 (*m*), 1475 (*s*), 1435 (*s*), 1376 (*w*), 1284 (*w*), 1222 (*w*), 1191 (*w*), 1150 (*w*), 1051 (*s*), 1003 (*w*), 892 (*w*), 758 (*m*), 634 (*w*), 609 (*w*), 601 (*w*), 586 (*w*), 547 (*w*).

HRMS (ESI): calcd for $C_{13}H_{20}NO$ $[M+H]^+$: 206.1539; found: 206.1526.

Analytical data of **S151**

TLC (50% ethyl acetate in cyclohexane): R_f: 0.68 ($KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.54 – 8.50 (m, 1H), 7.59 – 7.54 (m, 1H), 7.13 – 7.06 (m, 2H), 2.85 – 2.79 (m, 2H), 2.47 – 2.39 (m, 2H), 1.70 – 1.67 (m, 3H), 1.63 (s, 3H), 1.58 – 1.54 (m, 3H).

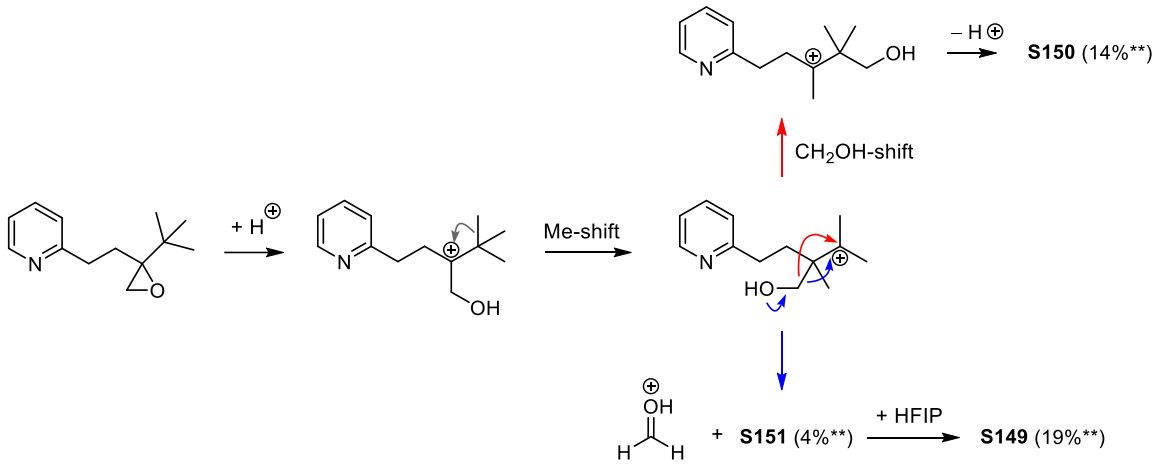
^{13}C NMR (101 MHz, $CDCl_3$) δ: 162.4, 149.4, 136.3, 126.8, 125.3, 123.0, 121.0, 37.2, 35.2, 20.7, 20.2, 18.5.

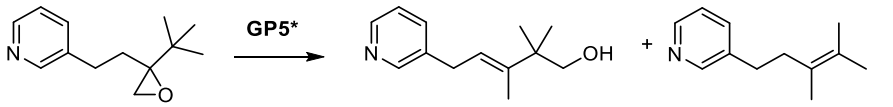
2D-NMR in appendix (HSQC, HMBC, COSY)

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3064 (*w*), 3007 (*w*), 2960 (*m*), 2920 (*s*), 2862 (*m*), 1589 (*s*), 1569 (*m*), 1473 (*s*), 1434 (*s*), 1373 (*w*), 1307 (*w*), 1217 (*w*), 1182 (*w*), 1149 (*w*), 1118 (*w*), 1084 (*w*), 1050 (*w*), 994 (*w*), 889 (*w*), 748 (*s*), 606 (*w*), 551 (*w*), 508 (*w*).

HRMS (ESI): calcd for $C_{12}H_{18}N$ $[M+H]^+$: 176.1434; found: 176.1423.

Proposed reaction mechanism for formation of **S149**, **S150** and **S151**.





S67 **S152** (12%) **S153** (13%)

*110% H_2SO_4 instead of 10%

No reaction of epoxide **S67** was observed under the conditions of **GP5**.

By increasing the catalyst amount to 110% sulfuric acid under otherwise identical conditions to **GP5**, two main products **S152** (12%, 5.0 mg) and **S153** (13%, 4.7 mg) could be isolated. Purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane grading to 50% ethyl acetate in cyclohexane).

Analytical data of **S152:**

TLC (50% ethyl acetate in cyclohexane): R_f: 0.15 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.46 – 8.41 (m, 2H), 7.52 – 7.43 (m, 1H), 7.21 (ddd, *J* = 7.8, 4.8, 0.9 Hz, 1H), 5.47 (td, *J* = 7.1, 1.4 Hz, 1H), 3.44 (s, 2H), 3.41 (d, *J* = 7.1 Hz, 2H), 1.72 (q, *J* = 1.0 Hz, 3H), 1.07 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 150.0, 147.6, 141.3, 136.9, 135.8, 123.6, 123.1, 70.0, 41.9, 31.8, 24.0, 13.0.

2D-NMR in appendix (HSQC, HMBC, COSY)

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3325 (*m*), 2961 (*s*), 2870 (*m*), 1654 (*w*), 1577 (*w*), 1478 (*m*), 1423 (*s*), 1376 (*w*), 1283 (*w*), 1256 (*w*), 1219 (*w*), 1190 (*m*), 1125 (*w*), 1100 (*w*), 1050 (*s*), 1029 (*m*), 890 (*w*), 798 (*w*), 713 (*s*), 686 (*w*), 637 (*w*), 584 (*w*), 452 (*w*).

HRMS (ESI): calcd for $C_{13}H_{20}NO$ $[M+H]^+$: 206.1539; found: 206.1536.

Analytical data of **S153**

TLC (50% ethyl acetate in cyclohexane): R_f: 0.69 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.44 – 8.40 (m, 2H), 7.47 (dt, *J* = 7.8, 2.0 Hz, 1H), 7.18 (ddd, *J* = 7.7, 4.8, 0.9 Hz, 1H), 2.65 (dd, *J* = 8.9, 6.7 Hz, 2H), 2.31 (dd, *J* = 9.0, 6.8 Hz, 2H), 1.67 (d, *J* = 1.1 Hz, 3H), 1.63 (s, 3H), 1.50 (d, *J* = 1.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 150.1, 147.3, 137.8, 136.0, 126.1, 125.8, 123.3, 36.4, 31.7, 20.7, 20.1, 18.6.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3026 (*w*), 2990 (*w*), 2959 (*w*), 2921 (*s*), 2861 (*m*), 1575 (*w*), 1478 (*m*), 1447 (*w*), 1422 (*s*), 1373 (*w*), 1193 (*w*), 1176 (*w*), 1154 (*w*), 1127 (*w*), 1096 (*w*), 1027 (*m*), 889 (*w*), 833 (*w*), 796 (*m*), 713 (*s*), 631 (*w*), 602 (*w*), 435 (*w*).

HRMS (ESI): calcd for $C_{12}H_{18}N$ $[M+H]^+$: 176.1434; found: 176.1432.

S164 **S165**

2-benzyl-3,3-dimethylbutanal (S165) was prepared according to **GP5** from **S164** (0.200 mmol, 1 equiv) in 9% yield as a colorless oil (3.4 mg). Purified by flash column chromatography on silica gel (15% diethyl ether in *n*-pentane – approx. 70% purity achieved) and by high pressure liquid chromatography (1% ethyl acetate in *n*-hexane)

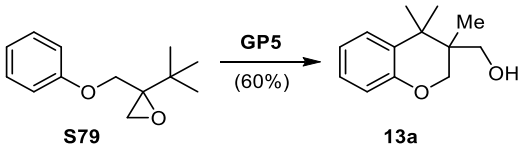
TLC (10% ethyl acetate in cyclohexane): R_f: 0.43 (UV, CAM)

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.76 (d, *J* = 2.6 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 2H), 3.03 (dd, *J* = 14.1, 11.1 Hz, 1H), 2.88 – 2.79 (m, 1H), 2.52 – 2.37 (m, 1H), 1.09 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 205.6, 140.6, 129.0, 128.7, 126.3, 63.9, 34.1, 31.2, 28.2.

HRMS (ESI): calcd for $C_{13}H_{18}NaO$ $[M+Na]^+$: 213.1250; found: 213.1241.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3028 (*w*), 2961 (*s*), 2926 (*s*), 2854 (*m*), 1724 (*s*), 1497 (*w*), 1497 (*w*), 1455 (*w*), 1369 (*w*), 699 (*w*).



(3,4,4-trimethylchroman-3-yl)methanol (**13a**) was prepared according to **GP5** from **S79** (0.200 mmol, 1 equiv) in 60% yield as a colorless oil (24.6 mg). Purified by flash column chromatography on silica gel (15% ethyl acetate in cyclohexane).

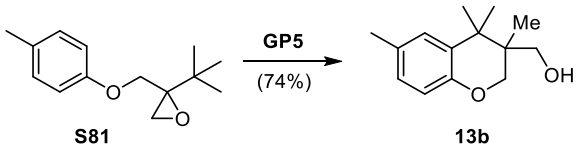
TLC (20% ethyl acetate in cyclohexane): R_f: 0.24 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.08 (ddd, *J* = 8.3, 7.2, 1.6 Hz, 1H), 6.90 (td, *J* = 7.5, 1.4 Hz, 1H), 6.78 (dd, *J* = 8.1, 1.4 Hz, 1H), 4.11 (d, *J* = 11.1 Hz, 1H), 3.90 (d, *J* = 11.1 Hz, 1H), 3.62 (d, *J* = 11.0 Hz, 1H), 3.48 (d, *J* = 11.0 Hz, 1H), 1.68 (s, 1H), 1.27 (s, 3H), 1.22 (s, 3H), 0.98 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6, 131.6, 127.4, 127.1, 121.0, 116.7, 67.5, 65.0, 39.0, 36.5, 29.3, 23.2, 14.6.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3449 (br *m*), 3031 (*w*), 2970 (*s*), 2883 (*m*), 1600 (*m*), 1580 (*m*), 1490 (*s*), 1448 (*m*), 1366 (*w*), 1300 (*m*), 1276 (*m*), 1226 (*s*), 1164 (*w*), 1088 (*w*), 1050 (*m*), 753 (*m*).

HRMS (ESI): calcd for $C_{13}H_{18}NaO_2$ $[M+Na]^+$: 229.1199; found: 229.1199.



(3,4,4,7-tetramethylchroman-3-yl)methanol (**13b**) was prepared according to **GP5** from **S81** (0.200 mmol, 1 equiv) in 74% yield as a colorless oil (32.7 mg). Purified by flash column chromatography on silica gel (10% ethyl acetate in petrol ether).

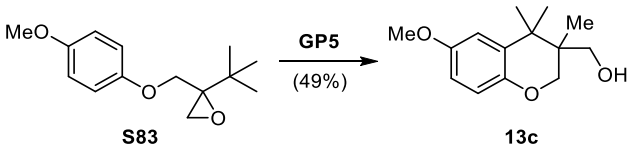
TLC (20% ethyl acetate in cyclohexane): R_f: 0.18 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 2.1 Hz, 1H), 6.93 – 6.85 (m, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 4.07 (d, *J* = 11.0 Hz, 1H), 3.87 (d, *J* = 11.1 Hz, 1H), 3.62 (d, *J* = 11.0 Hz, 1H), 3.47 (d, *J* = 11.2 Hz, 1H), 2.27 (s, 3H), 1.62 (s, 1H), 1.26 (s, 3H), 1.21 (s, 3H), 1.00 – 0.93 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3, 131.3, 130.1, 127.8, 127.7, 116.4, 67.6, 65.1, 39.1, 36.5, 29.3, 23.1, 21.0, 14.6.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3433 (br *m*), 3025 (*w*), 2969 (*s*), 2883 (*m*), 1499 (*s*), 1463 (*m*), 1406 (*w*), 1279 (*m*), 1230 (*m*), 1106 (*w*), 1084 (*w*), 1029 (*m*), 814 (*m*), 786 (*w*).

HRMS (ESI): calcd for $C_{14}H_{20}NaO_2$ $[M+Na]^+$: 243.1356; found: 243.1350.



S83 **13c**

(7-methoxy-3,4,4-trimethylchroman-3-yl)methanol (**13c**) was prepared according to **GP5** from **S83** (0.200 mmol, 1 equiv) in 49% yield as a colorless oil (23.3 mg). Purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane).

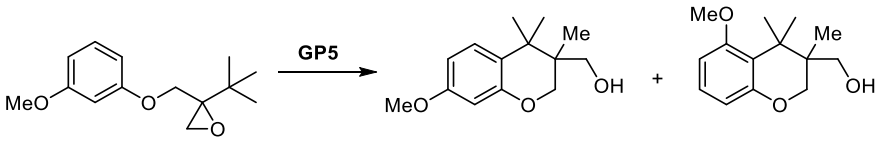
TLC (20% ethyl acetate in cyclohexane): R_f: 0.22 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (d, *J* = 2.9 Hz, 1H), 6.74 – 6.64 (m, 2H), 4.05 (d, *J* = 11.1 Hz, 1H), 3.86 (d, *J* = 11.1 Hz, 1H), 3.76 (s, 3H), 3.61 (d, *J* = 11.0 Hz, 1H), 3.46 (d, *J* = 11.0 Hz, 1H), 1.73 (s, 1H), 1.26 (s, 3H), 1.21 (s, 3H), 0.96 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9, 147.6, 132.6, 117.0, 112.9, 112.5, 67.6, 65.0, 55.8, 39.0, 36.9, 29.2, 23.1, 14.6.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3484 (br *m*), 2970 (*s*), 2834 (*m*), 1499 (*s*), 1418 (*w*), 1274 (*m*), 1201 (*m*), 1179 (*m*), 1049 (*m*).

HRMS (ESI): calcd for $C_{14}H_{20}NaO_3$ $[M+Na]^+$: 259.1305; found: 259.1302.



S85 **13d** (33%) **13e** (7%)

(6-methoxy-3,4,4-trimethylchroman-3-yl)methanol (**13d**) was prepared according to **GP5** from **S85** (0.200 mmol, 1 equiv) in 31% yield as a colorless oil (14.7 mg). Purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane). Additionally, regioisomer **13e** was isolated in 7% yield as a colorless oil (3.3 mg)

TLC (20% ethyl acetate in cyclohexane): R_f: 0.15 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.7 Hz, 1H), 6.50 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.33 (d, *J* = 2.6 Hz, 1H), 4.09 (d, *J* = 11.1 Hz, 1H), 3.90 (d, *J* = 11.2 Hz, 1H), 3.75 (s, 3H), 3.61 (d, *J* = 11.3 Hz, 1H), 3.47 (d, *J* = 11.0 Hz, 1H), 1.55 (s, 1H), 1.24 (s, 3H), 1.19 (s, 3H), 0.96 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 154.4, 128.0, 123.9, 108.1, 101.1, 67.8, 64.9, 55.4, 39.0, 36.1, 29.2, 23.3, 14.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3433 (br *m*), 2967 (*s*), 2835 (*m*), 1617 (*m*), 1582 (*m*), 1503 (*s*), 1464 (*m*), 1440 (*m*), 1418 (*m*), 1396 (*w*), 1316 (*w*), 1285 (*m*), 1249 (*m*), 1194 (*m*), 1167 (*m*), 1149 (*s*), 1088 (*m*), 1030 (*s*), 936 (*w*), 833 (*m*), 802 (*w*), 727 (*w*).

HRMS (ESI): calcd for $C_{14}H_{20}NaO_3$ $[M+Na]^+$: 259,1305; found: 259.1303.

(5-methoxy-3,4,4-trimethylchroman-3-yl)methanol (**13e**)

TLC (20% ethyl acetate in cyclohexane): R_f: 0.23 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (t, *J* = 8.2 Hz, 1H), 6.46 (d, *J* = 8.2 Hz, 2H), 4.02 (d, *J* = 10.8 Hz, 1H), 3.80 (d, *J* = 10.8 Hz, 1H), 3.80 (s, 3H), 3.67 (d, *J* = 11.1 Hz, 1H), 3.47 (d, *J* = 11.1 Hz, 1H), 1.51 – 1.44 (m, 1H), 1.33 (s, 3H), 1.31 (s, 3H), 0.95 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 155.7, 127.2, 119.8, 110.3, 104.3, 67.3, 64.9, 55.3, 40.5, 36.9, 24.5, 20.6, 14.0.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3437 (br *m*) 2972 (*s*), 2934 (*s*), 1603 (*m*), 1583 (*m*), 1472 (*m*), 1438 (*m*), 1308 (*m*), 1251 (*s*), 1139 (*m*), 1109 (*m*), 1080 (*m*), 1032 (*m*), 786 (*m*), 730 (*w*).

HRMS (ESI): calcd for $C_{14}H_{20}NaO_3$ $[M+Na]^+$: 259,1305; found: 259.1292.

S87 **13f**

(6-methoxy-3,4,4-trimethylchroman-3-yl)methanol (**13f**) was prepared according to **GP5** from **S87** (0.200 mmol, 1 equiv) in 58% yield as a colorless oil (27.6 mg). Purified by flash column chromatography on silica gel (25% ethyl acetate in cyclohexane).

TLC (20% ethyl acetate in cyclohexane): R_f: 0.19 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 – 6.80 (m, 2H), 6.70 (dd, *J* = 6.8, 2.7 Hz, 1H), 4.20 (d, *J* = 11.1 Hz, 1H), 4.00 – 3.90 (m, 1H), 3.85 (s, 3H), 3.63 (d, *J* = 11.2 Hz, 1H), 3.46 (d, *J* = 11.1 Hz, 1H), 1.73 (s, 1H), 1.26 (s, 3H), 1.21 (s, 3H), 0.98 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.0, 143.0, 132.4, 120.4, 119.2, 108.6, 67.9, 64.8, 55.9, 38.9, 36.6, 29.2, 23.2, 14.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3488 (br *m*), 2969 (*s*), 2835 (*m*), 1583 (*m*), 1477 (*s*), 1439 (*m*), 1328 (*w*), 1260 (*s*), 1223 (*m*), 1177 (*w*), 1116 (*w*), 1058 (*s*), 1032 (*m*), 779 (*w*), 733 (*m*).

HRMS (ESI): calcd for $C_{14}H_{20}NaO_3$ $[M+Na]^+$: 259.1305; found: 259.1298.

S89 **13g**

(7,8,8-trimethyl-7,8-dihydro-6*H*-[1,3]dioxolo[4,5-*g*]chromen-7-yl)methanol (**13g**) was prepared according to **GP5** from **S89** (0.200 mmol, 1 equiv) in 76% yield as a pale yellow oil (38.1 mg). Purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane).

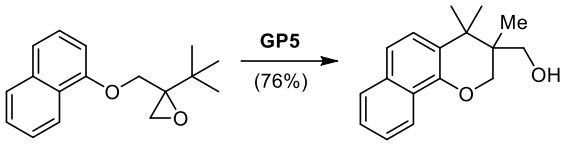
TLC (20% ethyl acetate in cyclohexane): R_f: 0.17 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (s, 1H), 6.31 (s, 1H), 5.86 (q, *J* = 1.4 Hz, 2H), 4.03 (d, *J* = 11.0 Hz, 1H), 3.83 (d, *J* = 11.0, 1H), 3.61 (d, *J* = 11.2 Hz, 1H), 3.45 (d, *J* = 11.0 Hz, 1H), 1.57 (s, 1H), 1.22 (s, 3H), 1.16 (s, 3H), 0.95 (d, *J* = 0.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.3, 146.2, 142.1, 123.3, 106.1, 101.0, 98.2, 67.7, 65.0, 38.9, 36.7, 29.3, 23.4, 14.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3455 (br *m*), 2970 (*s*), 2883 (*m*), 1630 (*w*), 1503 (*m*), 1483 (*s*), 1427 (*m*), 1346 (*w*), 1246 (*m*), 1166 (*s*), 1129 (*m*), 1038 (*m*), 938 (*w*), 834 (*w*).

HRMS (ESI): calcd for $C_{14}H_{18}NaO_4$ $[M+Na]^+$: 273.1097; found: 273.1096.



S91 **13h**

(3,4,4-trimethyl-3,4-dihydro-2*H*-benzo[*h*]chromen-3-yl)methanol (**13h**) was prepared according to **GP5** from **S91** (0.200 mmol, 1 equiv) in 76% yield as a colorless oil (39.1 mg). Purified by flash column chromatography on silica gel (10% ethyl acetate in petrol ether).

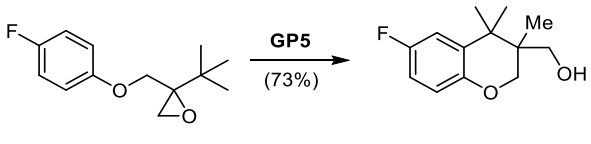
TLC: (20% ethyl acetate in cyclohexane): R_f: 0.24 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.15 (m, 1H), 7.77 – 7.70 (m, 1H), 7.47 – 7.40 (m, 2H), 7.40 – 7.33 (m, 2H), 4.32 (d, *J* = 11.0 Hz, 1H), 4.05 (d, *J* = 11.0 Hz, 1H), 3.69 (d, *J* = 11.0 Hz, 1H), 3.52 (d, *J* = 11.1 Hz, 1H), 1.55 (s, 1H), 1.34 (s, 3H), 1.28 (s, 3H), 1.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.5, 132.9, 127.3, 126.0, 125.4, 125.1, 125.0, 124.8, 122.1, 120.4, 68.0, 65.1, 39.1, 36.6, 29.1, 23.2, 14.6.

IR (ATR, neat): 3441 (br *m*), 3055 (*w*), 2970 (*s*), 2885 (*m*), 1596 (*w*), 1574 (*m*), 1507 (*m*), 1471 (*m*), 1430 (*m*), 1394 (*m*), 1367 (*m*), 1350 (*m*), 1283 (*m*), 1222 (*m*), 1207 (*w*), 1155 (*w*), 1094 (*m*), 1019 (*m*), 806 (*m*), 748 (*w*), 735 (*w*), 677 (*w*).

HRMS (ESI) calcd for $C_{17}H_{20}NaO_2$ $[M+Na]^+$: 279,1356; found: 279,1354.



S93 **13i**

(6-fluoro-3,4,4-trimethylchroman-3-yl)methanol (**13i**) was prepared according to **GP5** from **S93** (0.200 mmol, 1 equiv) in 73% yield as a colorless oil (32.9 mg). Purified by flash column chromatography on silica gel (15% ethyl acetate in petrol ether).

TLC (20% ethyl acetate in cyclohexane): R_f: 0.19 (UV, CAM)

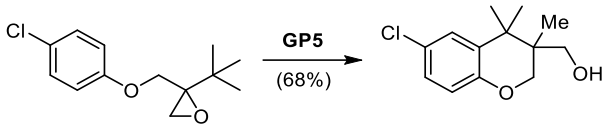
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 – 6.87 (m, 1H), 6.77 (ddd, *J* = 8.9, 7.7, 3.0 Hz, 1H), 6.71 (dd, *J* = 8.9, 5.1 Hz, 1H), 4.08 (d, *J* = 11.1 Hz, 1H), 3.86 (d, *J* = 11.2 Hz, 1H), 3.58 (d, *J* = 11.0 Hz, 1H), 3.47 (d, *J* = 11.0 Hz, 1H), 1.72 (s, 1H), 1.25 (s, 3H), 1.20 (s, 3H), 0.96 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5 (d, *J* = 237.3 Hz), 149.5 (d, *J* = 1.9 Hz), 133.0 (d, *J* = 6.3 Hz), 117.5 (d, *J* = 8.1 Hz), 113.9 (d, *J* = 23.2 Hz), 113.4 (d, *J* = 23.1 Hz), 67.7, 64.9, 38.8, 36.9, 29.15, 23.1, 14.5.

^{19}F NMR (282 MHz, $CDCl_3$) δ –123.30.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3435 (br *m*), 2971 (*m*), 1494 (*s*), 1417 (*m*), 1262 (*m*), 1177 (*m*), 1031 (*m*), 940 (*w*), 867 (*w*), 813 (*w*), 789 (*w*), 724 (*w*).

HRMS (ESI): calcd for $C_{13}H_{17}FNaO_2$ $[M+Na]^+$: 247.1105; found: 247.1103.



S95 **13j**

(6-chloro-3,4,4-trimethylchroman-3-yl)methanol (**13j**) was prepared according to **GP5** from **S95** (0.200 mmol, 1 equiv) in 68% yield as a colorless oil (32.9 mg). Purified by flash column chromatography on silica gel (20% ethyl acetate in petrol ether).

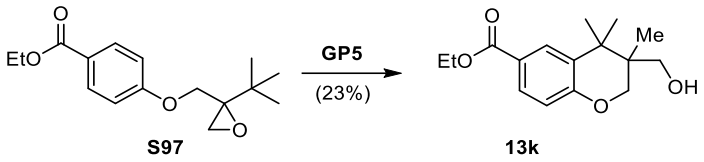
TLC (20% ethyl acetate in cyclohexane): R_f: 0.29 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 2.6 Hz, 1H), 7.02 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.71 (d, *J* = 8.6 Hz, 1H), 4.10 (d, *J* = 11.1 Hz, 1H), 3.88 (d, *J* = 11.1 Hz, 1H), 3.57 (d, *J* = 11.0 Hz, 1H), 3.48 (d, *J* = 11.0 Hz, 1H), 1.54 (s, 1H), 1.26 (s, 3H), 1.21 (s, 3H), 0.97 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1, 133.2, 127.1, 127.0, 125.6, 118.0, 67.6, 64.7, 38.7, 36.7, 29.0, 23.0, 14.4.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3411 (br *m*), 2972 (*s*), 2885 (*m*), 1572 (*w*), 1486 (*s*), 1402 (*m*), 1266 (*s*), 1227 (*m*), 1158 (*w*), 1104 (*m*), 1028 (*s*), 877 (*m*), 816 (*m*), 789 (*m*), 736 (*m*), 703 (*m*).

HRMS (ESI): calcd for $C_{13}H_{17}ClNaO_2$ $[M+Na]^+$: 263.0809; found: 263.0808.



ethyl 3-(hydroxymethyl)-3,4,4-trimethylchromane-6-carboxylate (**13k**) was prepared according to **GP5** from **S97** (0.200 mmol, 1 equiv) in 23% yield as a colorless oil (12.6 mg). Purified by flash column chromatography on silica gel (20% ethyl acetate in petrol ether).

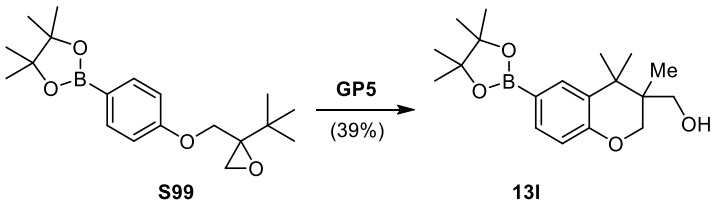
TLC (20% ethyl acetate in cyclohexane): R_f: 0.17 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 2.1 Hz, 1H), 7.77 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 4.18 (d, *J* = 11.1 Hz, 1H), 3.94 (d, *J* = 11.1 Hz, 1H), 3.62 – 3.43 (m, 2H), 1.60 (s, 1H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.29 (s, 3H), 1.26 (s, 3H), 0.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 157.7, 131.5, 129.7, 128.9, 123.3, 116.7, 67.9, 64.7, 60.8, 38.9, 36.6, 28.9, 23.2, 14.6, 14.6.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3457 (br m), 2973 (*m*), 1710 (*s*), 1609 (*m*), 1578 (*m*), 1496 (*m*), 1465 (*m*), 1391 (*m*), 1367 (*m*), 1291 (*m*), 1253 (*s*), 1172 (*m*), 1106 (*m*), 1028 (*s*), 915 (*w*), 836 (*w*), 770 (*m*), 738 (*w*), 626 (*w*).

HRMS (ESI): calcd for $C_{16}H_{23}O_4$ $[M+H]^+$: 279.1591; found: 279.1576.



(3,4,4-trimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)chroman-3-yl)methanol (**13l**) was prepared according to **GP5** from **S99** (0.200 mmol, 1 equiv) in 39% yield as a colorless oil (25.7 mg). Purified by flash column chromatography on silica gel (10% ethyl acetate in petrol ether – approx. 80% purity achieved) and by high pressure liquid chromatography (0.1% *i*-propanol in *n*-hexane grading to 2% *i*-propanol in *n*-hexane)

TLC (20% ethyl acetate in cyclohexane): R_f: 0.19 (UV, CAM)

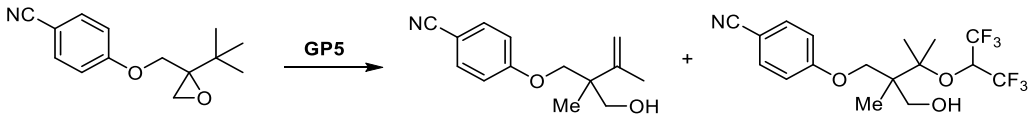
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 1.6 Hz, 1H), 7.54 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 4.13 (d, *J* = 11.0 Hz, 1H), 3.91 (d, *J* = 11.1 Hz, 1H), 3.58 (d, *J* = 10.9 Hz, 1H), 3.47 (d, *J* = 11.0 Hz, 1H), 1.73 (s, 1H), 1.33 (s, 12H), 1.28 (s, 3H), 1.26 (s, 3H), 0.97 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 136.6, 134.5, 134.0, 130.9, 116.2, 83.6, 67.6, 64.8, 39.0, 36.5, 29.0, 25.0, 23.1, 14.6.

^{11}B NMR (128 MHz, $CDCl_3$) δ 30.13.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3477 (br *m*), 2975 (*s*), 2928 (*m*), 1606 (*m*), 1572 (*w*), 1466 (*m*), 1371 (*m*), 1352 (*s*), 1315 (*m*), 1272 (*m*), 1237 (*m*), 1145 (*m*), 1097 (*m*), 1035 (*m*), 964 (*w*), 856 (*w*), 683 (*w*).

HRMS (ESI): calcd for $C_{19}H_{29}BO_4$ $[M+Na]^+$: 355.2051; found: 355.2030.



S101 **S154** (71%) **S155** (8%)

Exposing of **S101** (0.200 mmol, 1 equiv) to the conditions of the **GP5** led to the formation of alkene **S154** (33.0 mg, 71%) and alcohol **S155** (3.9 mg, 8%). Purified by high pressure liquid chromatography on silica gel (15% ethyl acetate in hexane grading to 25% ethyl acetate in hexane over 30 min).

4-((2-(hydroxymethyl)-2,3-dimethylbut-3-en-1-yl)oxy)benzonitrile (**S154**)

TLC (20% ethyl acetate in cyclohexane): R_f: 0.09 (UV, CAM)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 – 7.53 (m, 2H), 7.02 – 6.94 (m, 2H), 5.05 (p, *J* = 1.3 Hz, 1H), 4.87 (t, *J* = 0.9 Hz, 1H), 4.06 (d, *J* = 8.9 Hz, 1H), 3.99 (d, *J* = 8.9 Hz, 1H), 3.68 (d, *J* = 6.1 Hz, 2H), 1.81 (dd, *J* = 1.5, 0.7 Hz, 3H), 1.59 (s, 1H), 1.19 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 146.0, 134.1, 119.3, 115.4, 113.2, 104.3, 72.1, 66.1, 45.1, 20.1, 19.2.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3503 (*br m*), 2972 (*m*), 2943 (*m*), 2887 (*m*), 1605 (*s*), 1509 (*s*), 1469 (*w*), 1303 (*m*), 1259 (*s*), 1172 (*m*), 1024 (*m*), 897 (*m*), 835 (*m*).

HRMS (ESI): calcd for $C_{14}H_{17}NNaO_2$ $[M+Na]^+$: 254.1151; found: 254.1142.

4-(3-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-(hydroxymethyl)-2,3-dimethylbutoxy)benzonitrile (**S155**)

TLC (20% ethyl acetate in cyclohexane): R_f: 0.10 (UV, CAM)

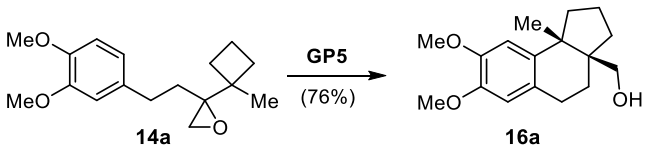
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 – 7.52 (m, 2H), 7.00 – 6.92 (m, 2H), 4.35 (p, *J* = 5.7 Hz, 1H), 4.19 (d, *J* = 9.3 Hz, 1H), 4.06 (d, *J* = 9.4 Hz, 1H), 3.89 (dd, *J* = 11.6, 4.9 Hz, 1H), 3.71 (dd, *J* = 11.6, 7.4 Hz, 1H), 1.98 (dd, *J* = 7.4, 5.0 Hz, 1H), 1.36 (s, 3H), 1.34 (s, 3H), 1.08 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.1, 134.2, 121.6 (q, *J* = 284.6 Hz), 119.3, 115.4, 104.4, 86.3, 70.1, 69.0 (hept, *J* = 32.2 Hz), 65.4, 46.4, 22.2, 21.9, 16.3.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -72.79 (d, *J* = 5.8 Hz).

IR (ATR, neat) $\tilde{\nu}_{max}$: 3492 (*br m*), 2981 (*m*), 2951 (*m*), 2919 (*m*), 1606 (*s*), 1510 (*s*), 1474 (*s*), 1356 (*m*), 1284 (*s*), 1259 (*s*), 1228 (*s*), 1191 (*s*), 1173 (*s*), 1124 (*m*), 1099 (*m*), 1030 (*w*), 885 (*m*), 834 (*m*), 686 (*m*).

HRMS (ESI): calcd for $C_{17}H_{19}F_6NNaO_3$ $[M+Na]^+$: 422.1161; found: 422.1146.



(7,8-dimethoxy-9b-methyl-1,2,3,9b-tetrahydrocyclopenta[*c*]chromen-3a(4*H*)-yl)methanol (**16a**) was prepared according to **GP5** from **14a** (0.200 mmol, 1 equiv) in 76% yield as a colorless oil (42.1 mg). Purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane).

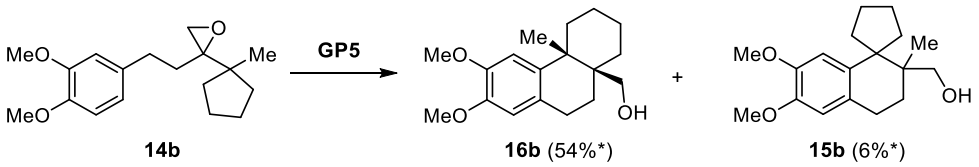
TLC (20% ethyl acetate in cyclohexane): R_f: 0.13 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H), 6.52 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.66 – 3.53 (m, 2H), 2.83 – 2.61 (m, 2H), 2.07 – 1.99 (m, 1H), 1.88 – 1.58 (m, 6H), 1.56 – 1.39 (m, 2H), 1.22 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5, 146.9, 136.8, 127.7, 111.1, 110.5, 67.6, 56.2, 55.8, 47.1, 47.1, 42.6, 32.6, 26.3, 26.0, 24.0, 21.1.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3502 (br *m*), 2952 (*s*), 2932 (*s*), 2872 (*m*), 2851 (*m*), 1610 (*m*), 1510 (*s*), 1463 (*m*), 1399 (*w*), 1399 (*w*), 1374 (*w*), 1353 (*w*), 1311 (*w*), 1257 (*s*), 1232 (*m*), 1211 (*m*), 1146 (*m*), 1129 (*m*), 1087 (*m*), 1072 (*m*), 1030 (*m*), 987 (*m*), 859 (*m*), 731 (*m*).

HRMS (ESI): calcd for $C_{17}H_{24}NaO_3$ $[M+Na]^+$: 299.1618; found: 299.1604.



14b **16b** (54%*) **15b** (6%*)

Exposing of **14b** (0.200 mmol, 1 equiv) to the conditions of the **GP5** led to the formation of a inseperable mixture of spiran **15b** and benzodecaline **16b** (34.8 mg, 60%, 9:1 ratio). Purified by flash column chromatography on silica gel (30% diethyl ether in petrol ether)

Yields were determined by ^{1}H-NMR

Analytical data of **16b** (major compound)

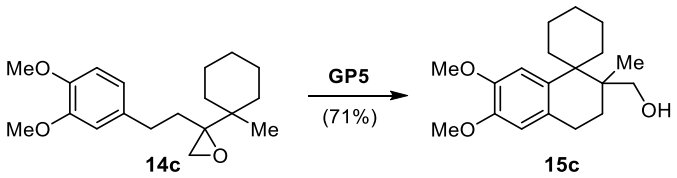
TLC (20% ethyl acetate in cyclohexane): R_f: 0.09 (UV, CAM)

^{1}H NMR (400 MHz, CDCl3) δ 6.75 (s, 1H), 6.54 (s, 1H), 3.84 (s, 6H), 3.73 – 3.53 (m, 2H), 2.94 – 2.64 (m, 2H), 2.17 – 1.93 (m, 1H), 1.95 – 1.79 (m, 1H), 1.72 (dt, *J* = 13.0, 6.0 Hz, 1H), 1.65 – 1.34 (m, 8H), 1.21 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5, 146.9, 137.8, 127.6, 111.5, 109.6, 77.5, 77.2, 76.8, 66.9, 56.2, 55.8, 39.0, 38.7, 29.7 (br, assigned by HSQC), 25.9, 24.8 (br, assigned by HSQC), 22.8, 21.3.

HRMS (ESI): calcd for $C_{18}H_{26}NaO_3$ $[M+Na]^+$: 313.1774; found: 313.1756.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3500 (br *m*), 2931 (*s*), 2858 (*m*), 1609 (*w*), 1513 (*s*), 1465 (*m*), 1446 (*m*), 1399 (*w*), 1351 (*w*), 1251 (*s*), 1222 (*m*), 1205 (*m*), 1161 (*m*), 1075 (*w*), 1018 (*m*), 910 (*w*), 856 (*w*), 785 (*w*), 731 (*w*).



14c **15c**

(6',7'-dimethoxy-2'-methyl-3',4'-dihydro-2'*H*-spiro[cyclohexane-1,1'-naphthalen]-2'-yl)methanol (**15c**) was prepared according to **GP5** from **14c** (0.200 mmol, 1 equiv) in 71% yield as a colorless oil (42.1 mg). Purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane).

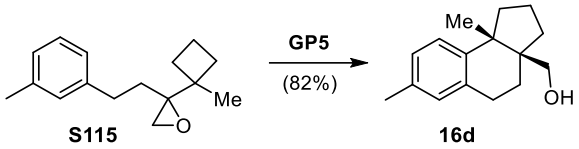
TLC (20% ethyl acetate in cyclohexane) R_f 0.25 (UV, CAM)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 (s, 1H), 6.56 (s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.44 (d, *J* = 10.9 Hz, 1H), 3.35 (d, *J* = 10.9 Hz, 1H), 2.86 – 2.73 (m, 2H), 1.84 (ddd, *J* = 13.7, 8.8, 4.7 Hz, 1H), 1.81 – 1.67 (m, 7H), 1.60 – 1.45 (m, 2H), 1.42 – 1.15 (m, 3H)., 0.98 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 146.6, 145.9, 137.5, 129.0, 112.5, 112.2, 67.6, 56.3, 55.8, 42.5, 42.1, 32.1, 29.5, 26.9, 25.9, 25.8, 24.7, 22.8, 19.7.

HRMS (ESI): calcd for $C_{19}H_{28}NaO_3$ $[M+Na]^+$: 327.1936; found 327.1926

IR (ATR, neat) $\tilde{\nu}_{max}$: 3536 (*br*), 2929 (*s*), 2853 (*m*), 1609 (*w*), 1511 (*s*), 1464 (*m*), 1452 (*m*), 1257 (*m*), 1200 (*m*), 1155 (*w*), 1083 (*m*), 1016 (*m*), 856 (*w*).



S115 **16d**

(7,9b-dimethyl-1,2,3,4,5,9b-hexahydro-3a*H*-cyclopenta[*a*]naphthalen-3a-yl)methanol (**16d**) was prepared according to **GP5** from **S115** (0.200 mmol, 1 equiv) in 82% yield as a colorless oil (37.9 mg). Purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane).

On 2.3 mmol scale product **16d** was afforded in 75% yield (396 mg).

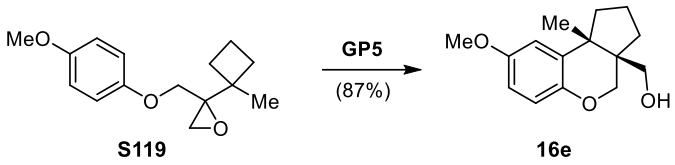
TLC (10% ethyl acetate in cyclohexane): R_f: 0.09 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.1 Hz, 1H), 6.98 (ddq, *J* = 8.2, 2.1, 0.7 Hz, 1H), 6.91 – 6.84 (m, 1H), 3.62 (qd, *J* = 10.7, 5.6 Hz, 2H), 2.82 (ddd, *J* = 17.2, 7.9, 5.8 Hz, 1H), 2.71 (dt, *J* = 17.2, 6.3 Hz, 1H), 2.28 (s, 3H), 2.04 (ddd, *J* = 12.9, 9.1, 5.9 Hz, 1H), 1.92 – 1.73 (m, 4H), 1.72 – 1.60 (m, 2H), 1.57 – 1.46 (m, 2H), 1.23 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1, 135.4, 134.7, 129.4, 127.4, 127.1, 67.6, 47.3, 47.1, 42.9, 33.1, 26.4, 26.3, 23.9, 21.1, 20.9.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3464 (br *w*), 2922 (*s*), 2854 (*s*), 1609 (*w*), 1499 (*m*), 1457 (*w*), 1377 (*w*), 1286 (*w*), 1217 (*m*), 1192 (*w*), 1100 (*w*), 1042 (*w*), 937 (*w*), 817 (*w*).

HRMS (ESI): calcd for $C_{16}H_{22}NaO$ $[M+Na]^+$: 253.1563; found: 253,1562.



((3aS,9bR)-8-methoxy-9b-methyl-1,2,3,9b-tetrahydrocyclopenta[*c*]chromen-3a(4*H*)-yl)methanol (**16e**) was prepared according to **GP5** from **S119** (0.200 mmol, 1 equiv) in 87% yield as a brownish oil (43.0 mg). Purified by flash column chromatography on silica gel (30% diethyl ether in petrol ether).

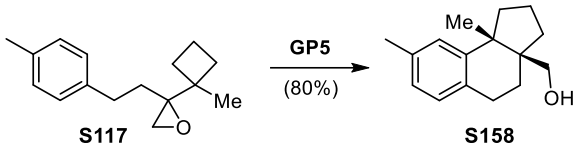
TLC (20% ethyl acetate in cyclohexane): R_f: 0.13 (UV, CAM)

^{1}H NMR (400 MHz, CDCl3) δ 6.79 (d, *J* = 3.0 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.66 (dd, *J* = 8.8, 3.0 Hz, 1H), 4.05 (d, *J* = 11.0 Hz, 1H), 3.78 (d, *J* = 11.1 Hz, 1H), 3.76 (s, 3H), 3.71 (d, *J* = 10.8 Hz, 1H), 3.62 (d, *J* = 10.8 Hz, 1H), 2.11 – 1.98 (m, 1H), 1.97 – 1.65 (m, 4H), 1.64 – 1.49 (m, 2H), 1.27 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 147.7, 132.6, 117.4, 113.1, 112.4, 68.2, 65.6, 55.8, 46.5, 44.7, 43.3, 30.4, 22.7, 21.0.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3439 (br *m*), 2954 (*s*), 2874 (*s*), 1614 (*w*), 1497 (*s*), 1419 (*m*), 1377 (*w*), 1272 (*m*), 1203 (*s*), 1055 (*m*), 1028 (*m*), 811 (*m*).

HRMS (ESI): calcd for $C_{15}H_{20}NaO_3$ $[M+Na]^+$: 271.1305; found: 271.1300.



(8,9b-dimethyl-1,2,3,4,5,9b-hexahydro-3a*H*-cyclopenta[*a*]naphthalen-3a-yl)methanol (**S158**) was prepared according to **GP5** from **S117** (0.200 mmol, 1 equiv) in 80% yield as a colorless oil (36.8 mg). Purified by flash column chromatography on silica gel (20% diethyl ether in petrol ether).

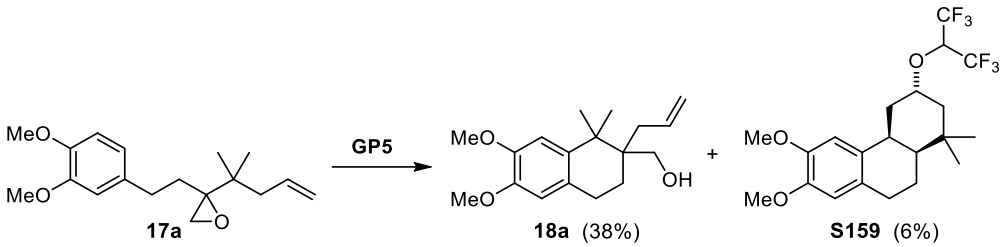
TLC (20% ethyl acetate in cyclohexane): R_f: 0.24 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 1.8 Hz, 1H), 6.96 (d, *J* = 7.7 Hz, 1H), 6.94 – 6.86 (m, 1H), 3.62 (q, *J* = 10.7 Hz, 2H), 2.90 – 2.76 (m, 1H), 2.71 (dt, *J* = 17.0, 6.2 Hz, 1H), 2.30 (t, *J* = 0.7 Hz, 3H), 2.06 (ddd, *J* = 12.8, 9.0, 6.0 Hz, 1H), 1.91 – 1.73 (m, 4H), 1.72 – 1.60 (m, 2H), 1.60 – 1.46 (m, 2H), 1.24 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 135.4, 132.4, 128.8, 128.0, 126.3, 67.6, 47.3, 47.3, 42.9, 33.2, 26.4, 26.0, 23.9, 21.4, 21.1.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3367 (br *m*), 2952 (*s*), 2873 (*m*), 1613 (*w*), 1502 (*w*), 1460 (*w*), 1375 (*w*), 1027 (*w*), 1002 (*w*), 809 (*w*).

HRMS (ESI): calcd for $C_{16}H_{22}NaO$ $[M+Na]^+$: 253,1563; found: 253,1554.



(2-allyl-6,7-dimethoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (**18a**) was prepared according to **GP5** from **17a** (0.200 mmol, 1 equiv) in 38% yield as a colorless oil (22.0 mg). Purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane grading to 30% ethyl acetate in cyclohexane). Byproduct **S159** (5.5 mg, 6%) was isolated as a colorless oil.

Analytical data of **18a**:

TLC (25% ethyl acetate in cyclohexane): R_f: 0.22 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.82 (s, 1H), 6.52 (s, 1H), 6.09 (dddd, *J* = 16.8, 10.0, 8.4, 6.5 Hz, 1H), 5.22 – 5.15 (m, 1H), 5.14 – 5.09 (m, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.74 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.57 (dd, *J* = 11.6, 7.0 Hz, 1H), 2.78 – 2.72 (m, 2H), 2.41 (dd, *J* = 14.0, 8.4 Hz, 1H), 2.11 (dd, *J* = 14.0, 6.5 Hz, 1H), 1.87 (dt, *J* = 13.5, 6.6 Hz, 1H), 1.66 (dt, *J* = 13.8, 7.0 Hz, 1H), 1.45 (dd, *J* = 7.1, 5.3 Hz, 1H), 1.31 (s, 3H), 1.28 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.5, 147.0, 137.9, 137.0, 127.5, 117.6, 111.1, 110.1, 66.5, 56.2, 55.9, 42.1, 40.1, 37.4, 27.7, 26.4, 25.7, 24.8.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3511 (*w*), 3451 (*w*), 2934 (*m*), 2850 (*w*), 1610 (*w*), 1509 (*s*), 1464 (*m*), 1399 (*w*), 1374 (*w*), 1353 (*w*), 1329 (*w*), 1254 (*s*), 1219 (*m*), 1160 (*w*), 1145 (*w*), 1133 (*w*), 1074 (*w*), 1031 (*m*), 984 (*w*), 895 (*w*), 856 (*w*), 796 (*w*), 740 (*w*).

HRMS (ESI): calcd for $C_{18}H_{26}NaO_3$ $[M+Na]^+$: 363.1774; found: 313.1751.

Analytical data of **S159**:

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

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.57 (s, 1H), 6.56 (s, 1H), 4.19 (hept, *J* = 6.0 Hz, 1H), 4.00 – 3.90 (m, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 2.96 (dt, *J* = 13.4, 4.3 Hz, 1H), 2.81 (ddd, *J* = 16.8, 5.9, 1.9 Hz, 1H), 2.70 (ddd, *J* = 17.4, 12.2, 6.5 Hz, 1H), 2.12 – 2.04 (m, 1H), 1.88 – 1.81 (m, 1H), 1.75 – 1.63 (m, 1H), 1.68 – 1.60 (m, 1H), 1.60 – 1.50 (m, 2H), 1.51 – 1.44 (m, 1H), 1.47 – 1.38 (m, 1H), 1.07 (s, 3H), 1.04 (s, 3H).

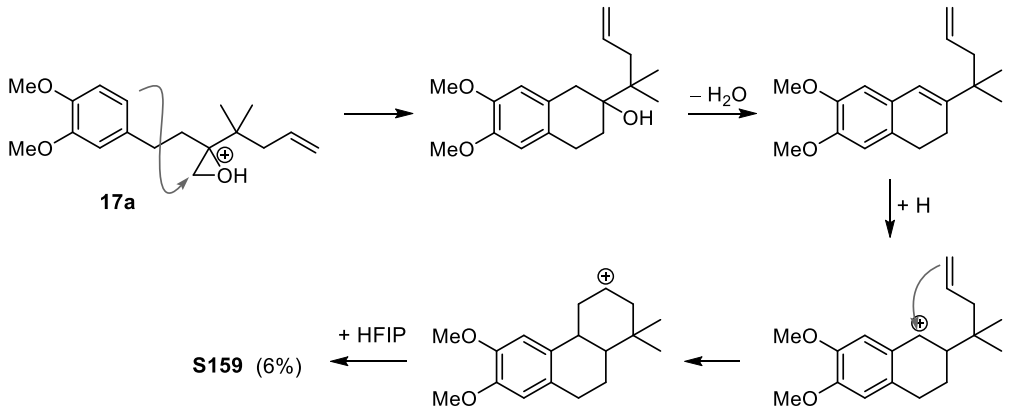
^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.6, 147.4, 132.4, 128.0, 111.8, 111.5, 80.8, 74.1, 56.2, 56.0, 43.3, 39.8, 37.3, 36.0, 34.6, 29.7, 29.7, 28.1, 18.8.

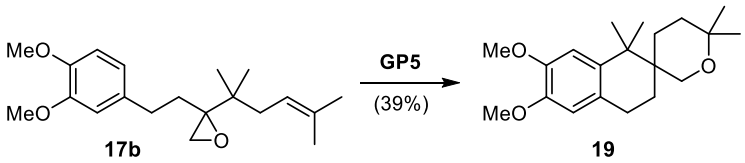
^{19}F NMR (376 MHz, $CDCl_3$) δ -74.04 – -74.22 (m).

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2944 (*m*), 2858 (*w*), 1610 (*w*), 1512 (*m*), 1467 (*w*), 1389 (*w*), 1368 (*w*), 1285 (*m*), 1261 (*m*), 1215 (*s*), 1190 (*s*), 1126 (*m*), 1100 (*m*), 1035 (*w*), 994 (*w*), 944 (*w*), 923 (*w*), 896 (*w*), 871 (*w*), 801 (*w*), 755 (*w*), 739 (*w*), 687 (*w*) cm^{-1}.

HRMS (ESI): calcd for $C_{21}H_{26}F_6NaO_3$ $[M+Na]^+$: 463.1678; found: 463.1643.

Proposed reaction mechanism for **S159** formation:





6,7-dimethoxy-1,1,6',6'-tetramethyl-3,4,5',6'-tetrahydro-1*H*,2'*H*,4'*H*-spiro[naphthalene-2,3'-pyran] (**19**) was prepared according to **GP5** from **17b** (0.200 mmol, 1 equiv) in 39% yield as a colorless oil (24.7 mg). Purified by high pressure liquid chromatography on silica gel (0.1% *i*-propanol in *n*-hexane grading to 1.5% *i*-propanol in *n*-hexane).

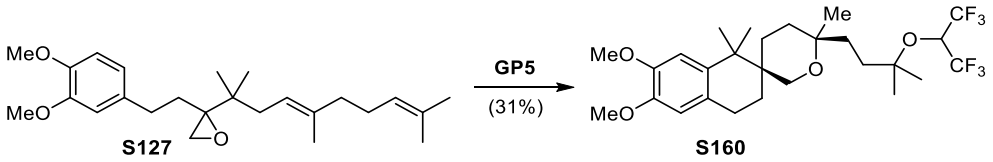
TLC (20% diethyl ether in *n*-pentane): R_f: 0.19 (UV, CAM)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.80 (s, 1H), 6.52 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.75 (d, J = 11.7 Hz, 1H), 3.32 (dd, J = 11.8, 2.4 Hz, 1H), 2.84 – 2.60 (m, 2H), 1.96 (t, J = 6.9 Hz, 2H), 1.80 (dd, J = 13.1, 4.0 Hz, 1H), 1.72 (dd, J = 13.2, 4.0 Hz, 1H), 1.38 – 1.30 (m, 2H), 1.26 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4, 147.0, 137.9, 127.4, 111.3, 110.0, 71.2, 65.2, 56.2, 55.9, 38.9, 36.4, 32.5, 31.2, 26.3, 26.3, 25.3, 23.5, 23.1, 22.3.

IR (ATR, neat): $\tilde{\nu}_{max}$ = 2967 (*s*), 1609 (*w*), 1513 (*s*), 1463 (*m*), 1365 (*w*), 1255 (*s*), 1205 (*m*), 1153 (*m*), 1077 (*m*), 1047 (*m*), 856 (*w*), 798 (*w*) cm^{-1}.

HRMS (ESI): calcd for $C_{20}H_{30}NaO_3$ $[M+Na]^+$: 341.2087 ; found: 341.2072.



6'-(3-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-3-methylbutyl)-6,7-dimethoxy-1,1,6'-trimethyl-3,4,5',6'-tetrahydro-1*H*,2'*H*,4'*H*-spiro[naphthalene-2,3'-pyran] (**S160**) was prepared according to **GP5** from **S127** (0.200 mmol, 1 equiv) in 31% yield as a colorless oil (34.6 mg) as single diastereomer. Purified by high pressure liquid chromatography on silica gel (0.1% *i*-propanol in *n*-hexane grading to 1.5% *i*-propanol in *n*-hexane).

TLC (20% diethyl ether in *n*-pentane): R_f: 0.17 (UV, CAM)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 6.80 (s, 1H), 6.51 (s, 1H), 4.27 (hept, J = 6.0 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.75 (d, J = 11.7 Hz, 1H), 3.31 (dd, J = 11.6, 2.3 Hz, 1H), 2.73 (dt, J = 17.3, 6.4 Hz, 1H), 2.71 – 2.63 (m, 1H), 2.00 – 1.88 (m, 2H), 1.82 (td, J = 13.5, 4.0 Hz, 1H), 1.68 (td, J =

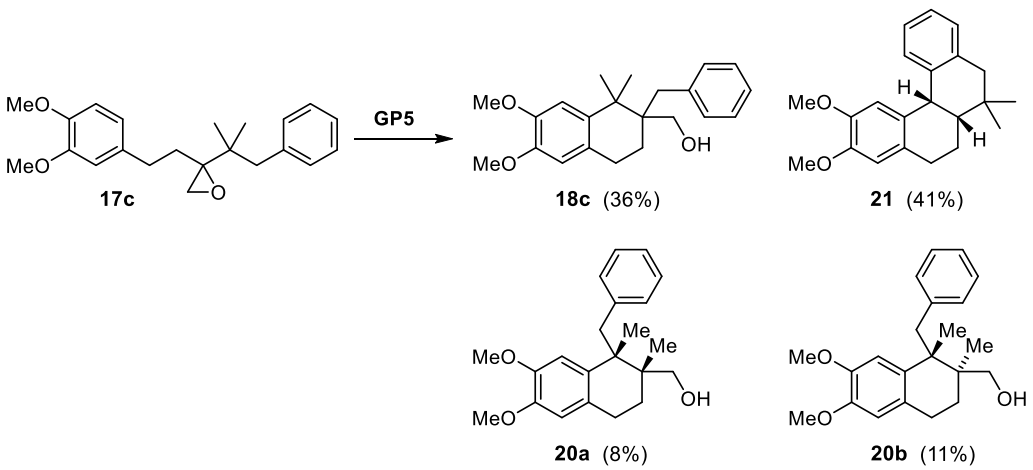
13.4, 4.2 Hz, 1H), 1.46 (d, J = 4.9 Hz, 4H), 1.38 – 1.28 (m, 4H), 1.26 (s, 3H), 1.25 (s, 6H), 1.21 (s, 3H), 1.18 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 147.4, 147.0, 137.9, 127.4, 111.3, 110.0, 81.8, 70.3 – 69.1 (m), 69.6, 65.0, 56.2, 55.9, 44.2, 42.7, 38.9, 36.5, 30.5, 26.4, 26.2, 25.5, 25.4, 25.3, 23.2, 23.1, 20.3, 18.1.

^{19}F-NMR (376 MHz, $CDCl_3$) δ –73.15 (d, *J* = 5.8 Hz).

IR (ATR, neat): $\tilde{\nu}_{max}$ = 2924 (br *m*), 2852 (*w*), 1730 (*w*), 1610 (*w*), 1510 (*m*), 1465 (*w*), 1356 (*m*), 1284 (*s*), 1255 (*s*), 1219 (*s*), 1188 (*s*), 1152 (*m*), 1123 (*m*), 1098 (*m*), 1080 (*s*), 1046 (*m*), 971 (*w*), 890 (*w*), 857 (*w*), 797 (*w*), 730 (*w*), 686 (*m*).

HRMS (ESI): calcd for $C_{28}H_{40}F_6NaO_4$ $[M+Na]^+$: 577.2723; found: 577.2719.



(2-benzyl-6,7-dimethoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (**18c**) was prepared according to **GP5** from **17c** (0.200 mmol, 1 equiv) in 36% yield as a colorless oil (24.4 mg). Further products: **21** (26.2 mg, 41%, colorless solid), **20a** (5.2 mg, 8%, colorless oil) and **20b** (7.5 mg, 11%, colorless oil). Purified by flash column chromatography on silica gel (1% ethyl acetate in cyclohexane grading to 25% ethyl acetate in cyclohexane).

Analytical data of **18c**:

TLC (25% ethyl acetate in cyclohexane): R_f: 0.34 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37 – 7.29 (m, 4H), 7.26 – 7.22 (m, 1H), 6.83 (s, 1H), 6.51 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.82 – 3.77 (m, 1H), 3.46 – 3.38 (m, 1H), 3.03 (d, *J* = 13.1 Hz, 1H), 2.83 – 2.67 (m, 2H), 2.54 (d, *J* = 13.1 Hz, 1H), 1.97 (ddd, *J* = 13.5, 6.0, 4.2 Hz, 1H), 1.68 (ddd, *J* = 13.5, 9.8, 7.1 Hz, 1H), 1.35 (s, 3H), 1.33 (s, 3H), 0.49 (dd, *J* = 9.2, 3.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.4, 147.0, 139.6, 137.6, 130.4, 128.8, 127.8, 126.6, 111.1, 110.2, 65.3, 56.2, 55.8, 43.2, 40.2, 39.8, 29.3, 26.0, 24.7, 24.3.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3530 (*w*), 3026 (*w*), 2933 (*m*), 2850 (*w*), 1609 (*w*), 1509 (*s*), 1463 (*m*), 1452 (*m*), 1491 (*w*), 1357 (*w*), 1325 (*w*), 1252 (*s*), 1207 (*m*), 1182 (*w*), 1153 (*s*), 1079 (*m*), 1065 (*m*), 1028 (*m*), 968 (*w*), 910 (*w*), 858 (*w*), 823 (*w*), 795 (*w*), 767 (*w*), 732 (*s*), 706 (*s*), 646 (*w*), 599 (*w*), 478 (*w*), 415 (*w*).

HRMS (ESI): calcd for $C_{22}H_{28}NaO_3$ $[M+Na]^+$: 363.1931; found: 363.1904.

Analytical data of **21**:

TLC (25% ethyl acetate in cyclohexane): R_f: 0.69 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.19 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.11 – 7.02 (m, 3H), 6.86 (s, 1H), 6.63 (s, 1H), 4.08 – 4.01 (m, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 2.76 (d, *J* = 16.8 Hz, 1H), 2.73 – 2.62 (m, 2H), 2.55 (d, *J* = 16.8 Hz, 1H), 1.93 – 1.85 (m, 1H), 1.79 (dt, *J* = 11.8, 4.1 Hz, 1H), 1.42 – 1.30 (m, 1H), 1.12 (s, 3H), 1.08 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.7, 146.5, 138.0, 135.8, 130.7, 129.5, 129.4, 128.2, 125.8, 125.7, 115.1, 111.9, 56.3, 56.0, 43.9, 40.78, 40.59, 32.31, 29.13, 28.51, 28.06, 20.88.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2930 (*m*), 2866 (*w*), 2835 (*w*), 1608 (*w*), 1510 (*s*), 1489 (*w*), 1462 (*m*), 1450 (*m*), 1405 (*w*), 1385 (*w*), 1365 (*w*), 1356 (*w*), 1338 (*w*), 1276 (*m*), 1236 (*s*), 1226 (*s*), 1193 (*w*), 1158 (*w*), 1138 (*w*), 1115 (*s*), 1097 (*w*), 1076 (*w*), 1027 (*m*), 1009 (*w*), 975 (*w*), 910 (*m*), 880 (*w*), 858 (*w*), 843 (*w*), 811 (*w*), 797 (*w*), 730 (*s*), 702 (*w*), 673 (*w*), 647 (*w*), 622 (*w*), 580 (*w*), 533 (*w*), 501 (*w*), 465 (*w*), 440 (*w*), 412 (*w*).

HRMS (ESI): calcd for $C_{22}H_{26}NaO_2$ $[M+Na]^+$: 345.1825; found: 345.1801.

Analytical data of **20a**:

TLC (25% ethyl acetate in cyclohexane): R_f: 0.24 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.13 – 7.06 (m, 3H), 6.64 – 6.60 (m, 2H), 6.55 (s, 1H), 5.66 (s, 1H), 3.90 (d, *J* = 10.8 Hz, 1H), 3.84 (s, 3H), 3.77 (d, *J* = 10.9 Hz, 1H), 3.27 (s, 3H), 2.87 – 2.80 (m, 3H), 2.72 (d, *J* = 12.5 Hz, 1H), 2.13 – 2.02 (m, 1H), 1.72 – 1.64 (m, 1H), 1.41 – 1.37 (m, 1H), 1.30 (s, 3H), 0.97 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 146.8, 145.5, 139.3, 133.4, 131.7, 127.4, 127.3, 125.9, 112.4, 110.9, 69.4, 55.8, 55.3, 45.0, 43.9, 39.9, 27.3, 25.7, 20.1, 18.7.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3498 (*w*), 3026 (*w*), 2922 (*m*), 2850 (*w*), 1609 (*w*), 1510 (*s*), 1495 (*w*), 1464 (*m*), 1452 (*m*), 1400 (*w*), 1375 (*w*), 1353 (*w*), 1254 (*s*), 1212 (*s*), 1159 (*m*), 1115 (*m*), 1093 (*w*), 1077 (*w*), 1034 (*s*), 974 (*w*), 911 (*w*), 859 (*w*), 798 (*m*), 756 (*w*), 729 (*s*), 702 (*s*), 669 (*w*), 646 (*w*), 547 (*w*), 500 (*w*), 435 (*w*).

HRMS (ESI): calcd for $C_{22}H_{28}NaO_3$ $[M+Na]^+$: 363.1931; found: 363.1905

Analytical data of **20b**:

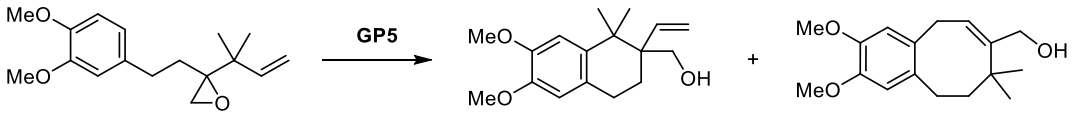
TLC (25% ethyl acetate in cyclohexane): R_f: 0.18 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ:.13 – 7.07 (m, 3H), 6.63 – 6.59 (m, 2H), 6.54 (s, 1H), 5.64 (s, 1H), 3.84 (s, 3H), 3.58 – 3.47 (m, 2H), 3.28 (s, 3H), 2.87 – 2.71 (m, 4H), 2.05 – 1.95 (m, 1H), 1.87 (ddd, *J* = 14.1, 7.0, 2.1 Hz, 1H), 1.25 – 1.21 (m, 1H), 1.19 (s, 3H), 1.18 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 146.8, 145.5, 138.8, 132.9, 131.8, 128.1, 127.4, 125.9, 112.4, 111.0, 66.6, 55.8, 55.3, 45.4, 42.8, 40.5, 26.8, 26.1, 19.8, 19.1.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3542 (*w*), 3514 (*w*), 3025 (*w*), 2930 (*m*), 2850 (*w*), 1609 (*w*), 1513 (*s*), 1495 (*w*), 1464 (*m*), 1453 (*m*), 1417 (*w*), 1400 (*w*), 1353 (*w*), 1331 (*w*), 1254 (*s*), 1211 (*s*), 1151 (*m*), 1107 (*m*), 1077 (*w*), 1029 (*s*), 979 (*w*), 940 (*w*), 909 (*w*), 858 (*w*), 795 (*w*), 755 (*w*), 728 (*m*), 702 (*m*), 669 (*w*), 646 (*w*), 609 (*w*), 548 (*w*), 498 (*w*), 438 (*w*), 421 (*w*).

HRMS (ESI): calcd for $C_{22}H_{28}NaO_3$ $[M+Na]^+$: 363.1931; found: 363.1902.



17d **18d** (22%) **22** (7%)

Exposing of **17d** (0.200 mmol, 1 equiv) to the conditions of **GP5** led to the formation of tetralin **18d** (22%, colorless oil) and cyclooctene **22** (7%*, colorless oil). Purified by high pressure liquid chromatography on silica gel (15% ethyl acetate in *n*-hexane grading to 25% ethyl acetate in *n*-hexane in 30 min).

*yield determined by ^{1}H-NMR

(6,7-dimethoxy-1,2-dimethyl-1-vinyl-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (**18d**)

TLC (25% ethyl acetate in cyclohexane): R_f: 0.19 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 1H), 6.55 (s, 1H), 6.01 (dd, *J* = 17.7, 11.1 Hz, 1H), 5.36 (d, *J* = 11.1 Hz, 1H), 5.22 (d, *J* = 17.9 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.69 (d, *J* = 11.1 Hz, 1H), 3.53 (t, *J* = 10.2 Hz, 1H), 2.86 (ddd, *J* = 17.8, 11.7, 6.4 Hz, 1H), 2.74 (ddd, *J* = 17.2, 6.4, 2.4 Hz, 1H), 2.02 (ddd, *J* = 13.6, 6.5, 2.6 Hz, 1H), 1.87 (td, *J* = 12.5, 6.4 Hz, 1H), 1.58 (s, 1H), 1.27 (s, 3H), 1.16 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.6, 147.3, 141.6, 137.2, 127.5, 116.2, 111.5, 110.1, 63.1, 56.3, 55.9, 46.4, 38.8, 30.5, 25.6, 23.7, 23f.1.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3503 (*w,br*), 2957 (*m*), 1610 (*w*), 1510 (*s*), 1464 (*m*), 1400 (*w*), 1354 (*w*), 1254 (*s*), 1207 (*m*), 1155 (*m*), 1078 (*m*), 1027 (*m*), 967 (*w*), 913 (*w*), 857 (*w*), 797 (*w*).

HRMS (ESI): calcd for $C_{17}H_{24}O_3Na$ $[M+Na]^+$: 299.1623; found: 299.1612.

(*E*)-(2,3-dimethoxy-8,8-dimethyl-5,8,9,10-tetrahydrobenzo[8]annulen-7-yl)methanol (**22**)

TLC (25% ethyl acetate in cyclohexane): R_f: 0.13 (UV, CAM)

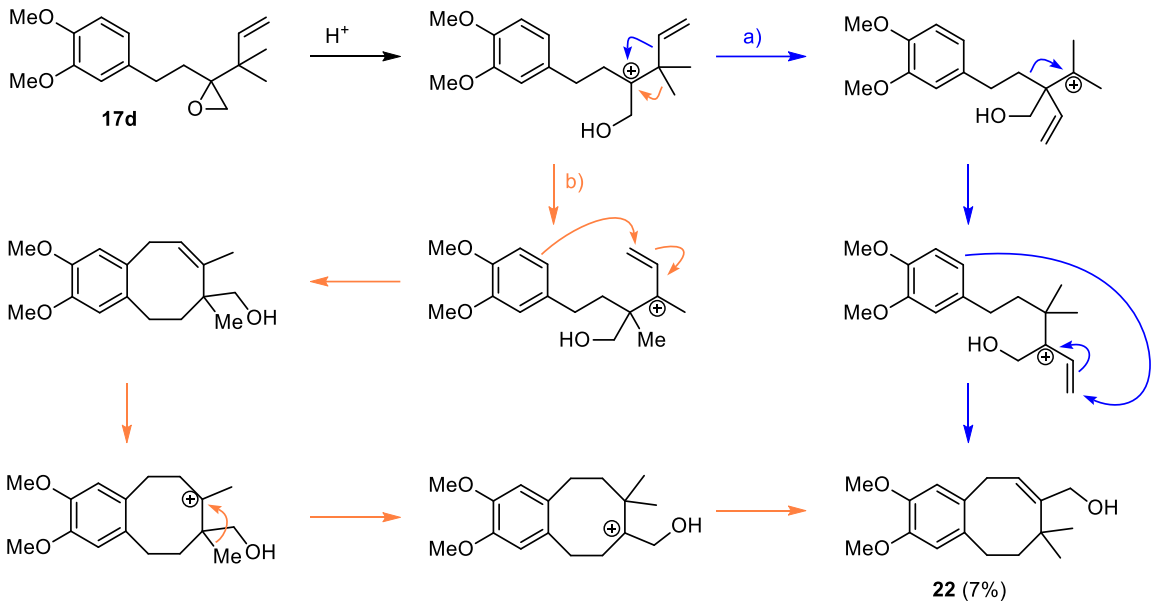
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.66 (s, 1H), 6.61 (s, 1H), 5.78 (tt, *J* = 6.0, 1.3 Hz, 1H), 3.85 (s, 3H), 3.85 (s, 3H), 3.42 (dt, *J* = 6.1, 1.9 Hz, 2H), 3.35 (s, 2H), 2.94 – 2.88 (m, 2H), 2.35 (dddd, *J* = 7.9, 4.8, 3.4, 1.7 Hz, 2H), 1.21 (s, 1H), 1.02 (s, 6H).

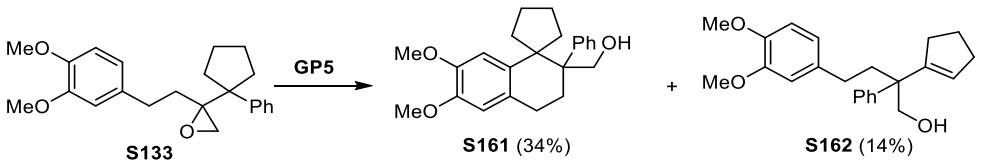
^{13}C NMR (151 MHz, $CDCl_3$) δ 147.3, 146.7, 143.6, 133.5, 132.8, 122.9, 112.4, 112.2, 69.9, 56.2, 56.1, 42.2, 33.2, 31.9, 28.0, 24.3.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$:3493 (*br m*), 2932 (*s*), 1608 (*w*), 1516 (*s*), 1463 (*m*), 1341 (*w*), 1265 (*m*), 1226 (*m*), 1200 (*m*), 1039 (*m*)

HRMS (ESI): calcd for $C_{17}H_{24}O_3Na$ $[M+Na]^+$: 299.1623; found: 299.1608.

Proposed reaction mechanism for formation of **22:**





Exposing of **S133** (0.200 mmol, 1 equiv) to the conditions of the **GP5** led to the formation of **S161** (24.1 mg, 34%, colorless oil) and **S162** (10.1 mg, 14%, colorless oil). Purified by flash column chromatography on silica gel (20% ethyl acetate in petrol ether).

Analytically pure samples of **S161** and **S162** were obtained by normal-phase semi-preparative HPLC purification using 15% ethyl acetate in *n*-hexane as eluent initially, grading to 25% ethyl acetate in *n*-hexane as eluent over 30 min.

Analytical data of **S161**:

TLC (20% ethyl acetate in petrolether) R_f: 0.11 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.5, 1.3 Hz, 2H), 7.40 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.31 – 7.26 (m, 1H), 4.25 (d, *J* = 11.0 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.78 (dd, *J* = 12.3, 9.4 Hz, 1H), 3.08 – 2.93 (m, 1H), 2.90 (dd, *J* = 6.6, 2.4 Hz, 1H), 2.58 (td, *J* = 12.3, 6.6 Hz, 1H), 2.21 – 2.10 (m, 2H), 1.98 (dt, *J* = 13.1, 6.8 Hz, 1H), 1.92 – 1.82 (m, 1H), 1.72 (dt, *J* = 12.8, 7.9 Hz, 1H), 1.51

(dd, *J* = 12.9, 6.7 Hz, 1H), 1.43 (dt, *J* = 12.7, 6.2 Hz, 1H), 1.11 (dd, *J* = 9.8, 3.4 Hz, 1H), 0.64 (dt, *J* = 12.6, 7.1 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 147.2, 146.9, 141.9, 139.4, 129.2, 128.4, 128.2, 127.0, 126.7, 111.2, 110.8, 62.7, 56.1, 55.9, 51.9, 49.3, 41.3, 34.5, 28.0, 27.7, 26.5, 25.5.

2D-NMR in appendix

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3481 (br), 2947 (m), 2868 (m), 1609(w), 1514 (s), 1463 (m), 1369 (w), 1337 (w), 1254 (m), 1239 (w), 1208 (m), 1158 (w), 1096 (w), 1023 (m), 911 (w), 856 (w), 706 (m), 647 (m).

HRMS (ESI): calcd for $C_{23}H_{28}O_3Na$ $[M+Na]^+$: 375.1936; found: 375.1916

Analytical data of **S162**:

TLC (20% ethyl acetate in petrolether) R_f 0.11 (UV, CAM)

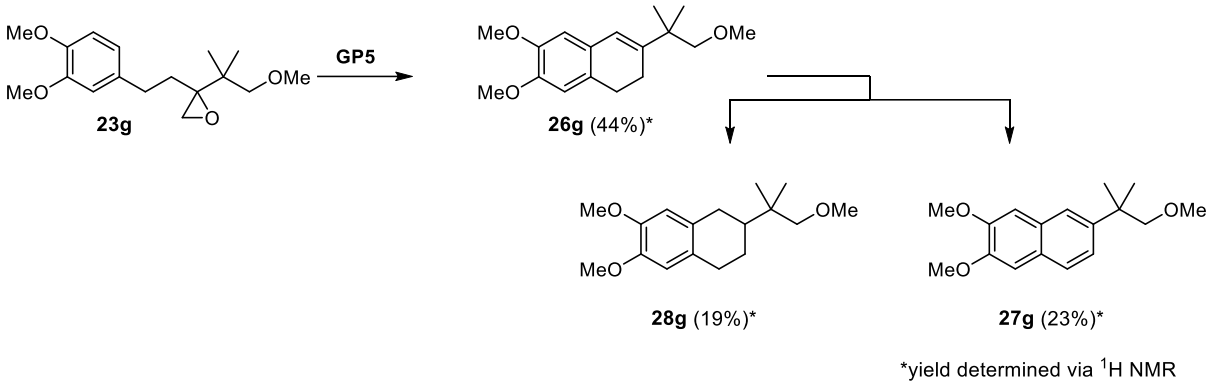
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.33 (t, *J* = 7.6 Hz, 2H), 7.29 – 7.26 (m, 2H), 7.25 – 7.22 (m, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.69 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.67 (d, *J* = 1.9 Hz, 1H), 5.73 (t, *J* = 2.1 Hz, 1H), 4.14 – 3.92 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.43 (ddt, *J* = 7.4, 4.6, 2.3 Hz, 2H), 2.41 – 2.32 (m, 2H), 2.28 (td, *J* = 12.6, 4.7 Hz, 1H), 2.16 – 1.99 (m, 3H), 1.88 – 1.71 (m, 2H), 1.13 (t, *J* = 6.7 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 149.0, 147.3, 147.1, 143.5, 135.7, 128.6, 127.4, 127.3, 126.7, 120.2, 111.9, 111.4, 65.7, 56.1, 56.0, 50.0, 35.9, 32.7, 32.5, 30.5, 23.4.

2D-NMR in appendix

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 3493 (br), 2863 (m), 2845 (m), 1591 (w), 1514 (s), 1495 (w), 1463 (m), 1445 (w), 1417 (w), 1261 (s), 1261 (m), 1155 (m), 1140 (m), 1030(m), 765 (m), 702 (m).

HRMS (ESI): calcd for $C_{23}H_{28}O_3Na$ $[M+Na]^+$: 375.1936; found: 375.1915



Exposing of **23g** (0.200 mmol, 1 equiv) to the conditions of **GP5** led to the formation of tetralin **26g** (44%*, colorless oil), tetraline **28g** (19%, colorless oil) and naphthalene **27g** (23%*, colorless oil). Yields were determined via ^{1}H-NMR using 1,2,4,5-Tetrachloro-3-nitrobenzene (15.8 mg) as internal standard. Analyticaly pure samples were isolated by flash column chromatography on silica gel (1% ethyl acetate in cyclohexane grading to 5% ethyl acetate in cyclohexane).

Analytical data of **26g**:

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

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.65 (s, 1H), 6.61 (s, 1H), 6.23 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.34 (s, 3H), 3.29 (s, 2H), 2.72 – 2.66 (m, 2H), 2.28 – 2.21 (m, 2H), 1.14 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.4, 147.4, 144.9, 127.9, 127.2, 120.7, 111.0, 110.1, 80.8, 59.5, 56.2, 56.1, 40.1, 28.5, 24.2, 24.1.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2958 (*w*), 2932 (*w*), 2871 (*w*), 2829 (*w*), 1606 (*w*), 1512 (*s*), 1462 (*m*), 1450 (*m*), 1406 (*w*), 1391 (*w*), 1359 (*w*), 1337 (*w*), 1322 (*w*), 1303 (*w*), 1277 (*w*), 1256 (*m*), 1234 (*s*), 1213 (*m*), 1193 (*m*), 1166 (*w*), 1152 (*w*), 1125 (*s*), 1106 (*s*), 1062 (*w*), 1030 (*w*), 999 (*m*), 960 (*w*), 915 (*w*), 876 (*m*), 850 (*w*), 825 (*w*), 772 (*w*), 753 (*w*), 732 (*w*), 598 (*w*), 479 (*w*), 433 (*w*), 416 (*w*) cm^{-1}.

HRMS (ESI): calcd for $C_{17}H_{24}NaO_3$ $[M+Na]^+$: 299.1618; found: 299.1596.

Analytical data of **28g**:

TLC (25% ethyl acetate in cyclohexane): R_f: 0.49 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.59 (s, 1H), 6.57 (s, 1H), 3.84 (s, 3H), 3.84 (s, 3H), 3.34 (s, 3H), 3.24 – 3.14 (m, 2H), 2.76 – 2.64 (m, 3H), 2.60 – 2.49 (m, 1H), 1.99 – 1.89 (m, 1H), 1.69 (tdd, *J* = 11.9, 5.0, 2.2 Hz, 1H), 1.39 – 1.27 (m, 1H), 0.96 (s, 3H), 0.91 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.1, 147.0, 129.2, 128.9, 112.3, 111.6, 81.1, 59.5, 56.1, 56.0, 40.9, 36.7, 30.4, 30.3, 24.5, 22.7, 22.0.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2929 (*m*), 2871 (*w*), 2832 (*w*), 1609 (*w*), 1515 (*s*), 1463 (*m*), 1450 (*m*), 1407 (*w*), 1393 (*w*), 1362 (*w*), 1330 (*w*), 1294 (*w*), 1267 (*m*), 1249 (*m*), 1224 (*m*), 1191 (*m*), 1109 (*s*), 1068 (*w*), 1025 (*m*), 1000 (*w*), 972 (*w*), 918 (*w*), 899 (*w*), 847 (*m*), 813 (*w*), 775 (*w*), 740 (*w*), 550 (*w*), 439 (*w*) cm^{-1}.

HRMS (ESI): calcd for $C_{17}H_{26}NaO_3$ $[M+Na]^+$: 301.1774; found: 301.1752

Analytical data of **27g**:

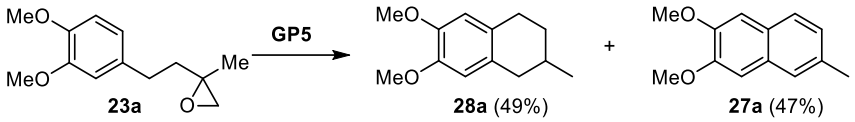
TLC (25% ethyl acetate in cyclohexane): R_f: 0.40 (CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 – 7.62 (m, 2H), 7.41 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.12 (s, 1H), 7.09 (s, 1H), 4.00 (s, 3H), 3.99 (s, 3H), 3.48 (s, 2H), 3.32 (s, 3H), 1.41 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 149.6, 149.3, 143.6, 129.2, 127.6, 126.2, 123.2, 123.1, 106.8, 106.1, 83.1, 59.6, 56.0, 56.0, 39.2, 26.3.

IR (ATR, $CDCl_3$) $\tilde{\nu}_{max}$: 2960 (*w*), 2933 (*w*), 2870 (*w*), 2828 (*w*), 1632 (*w*), 1607 (*w*), 1510 (*s*), 1490 (*s*), 1462 (*m*), 1436 (*m*), 1416 (*m*), 1393 (*w*), 1362 (*w*), 1320 (*w*), 1252 (*s*), 1196 (*s*), 1165 (*s*), 1134 (*s*), 1106 (*s*), 1034 (*w*), 1006 (*s*), 962 (*w*), 916 (*w*), 885 (*m*), 849 (*s*), 831 (*w*), 808 (*w*), 753 (*m*), 731 (*w*), 640 (*w*), 618 (*w*), 506 (*w*), 478 (*m*) cm^{-1}.

HRMS (ESI): calcd for $C_{17}H_{22}NaO_3$ $[M+Na]^+$: 297.1461; found: 297.1440.



Exposing of **23a** (0.200 mmol, 1 equiv) to the conditions of the **GP5** led to the formation of tetraline **28a** (20.1 mg, 49%, colorless oil) and naphthalene **27a** (19.0 mg, 47%, colorless solid). Purified by flash column chromatography on silica gel (5% diethyl ether in petrol ether).

6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydronaphthalene (**28a**):

TLC (10% ethyl acetate in cyclohexane): R_f: 0.26 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (s, 1H), 6.55 (s, 1H), 3.84 (s, 6H), 2.80 – 2.62 (m, 3H), 2.42 – 2.23 (m, 1H), 1.95 – 1.71 (m, 2H), 1.46 – 1.30 (m, 1H), 1.05 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1, 147.1, 128.8, 128.5, 112.0, 111.8, 56.0, 37.8, 31.8, 29.5, 29.0, 22.1.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2994 (*w*), 2948 (*s*), 2910 (*s*), 2832 (*m*), 1610 (*w*), 1516 (*s*), 1454 (*m*), 1407 (*w*), 1351 (*w*), 1326 (*w*), 1288 (*w*), 1268 (*m*), 1247 (*m*), 1230 (*m*), 1212 (*m*), 1116 (*m*), 1027 (*w*), 994 (*w*), 847 (*w*).

HRMS (LTB): calcd for $C_{13}H_{19}O_2$ $[M+H]^+$: 207.1380; found: 207.1386.

2,3-dimethoxy-6-methylnaphthalene (**27a**):

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

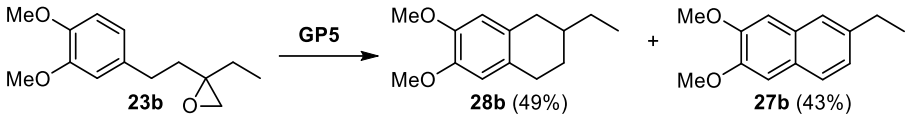
mp: 90.1 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.3 Hz, 1H), 7.47 (s, 1H), 7.18 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.07 (d, *J* = 15.9 Hz, 2H), 3.99 (s, 3H), 3.99 (s, 3H), 2.47 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7, 149.0, 133.8, 129.5, 127.3, 126.5, 126.3, 125.7, 106.3, 106.0, 56.0, 21.7.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2998 (*w*), 2937 (*m*), 1631 (*m*), 1610 (*m*), 1512 (*m*), 1492 (*m*), 1461 (*m*), 1438 (*m*), 1414 (*m*), 1318 (*w*), 1254 (*s*), 1207 (*m*), 1162 (*m*), 1130 (*m*), 1015 (*w*), 856 (*m*), 750 (*w*).

HRMS (LTP): calcd for $C_{13}H_{15}O_2$ $[M+H]^+$: 203.1067; found: 203.1067.



Exposing of **23b** (0.200 mmol, 1 equiv) to the conditions of the **GP5** led to the formation of tetraline **28b** (20.1 mg, 49%, colorless oil) and naphthalene **27b** (19.0 mg, 47%, colorless solid). Purified by flash column chromatography on silica gel (5% diethyl ether in petrol ether).

6,7-dimethoxy-2-ethyl-1,2,3,4-tetrahydronaphthalene (**28b**):

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

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (d, *J* = 2.6 Hz, 2H), 3.84 (s, 6H), 2.84 – 2.68 (m, 3H), 2.41 – 2.27 (m, 1H), 1.99 – 1.85 (m, 1H), 1.66 – 1.53 (m, 1H), 1.45 – 1.28 (m, 3H), 0.98 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1, 147.1, 128.8, 128.8, 112.1, 111.8, 56.0, 36.3, 35.6, 29.5, 29.38, 29.0, 11.7.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2958 (*m*), 2914 (*s*), 2874 (*m*), 2851 (*m*), 1610 (*w*), 1517 (*s*), 1464 (*m*), 1407 (*w*), 1353 (*w*), 1324 (*w*), 1261 (*m*), 1223 (*m*), 1118 (*m*), 1016 (*w*), 847 (*w*).

HRMS (ESI): calcd for $C_{14}H_{21}O_2$ $[M+H]^+$: 221.1536; found: 221.1541.

2,3-dimethoxy-6-ethylnaphthalene (**27b**):

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

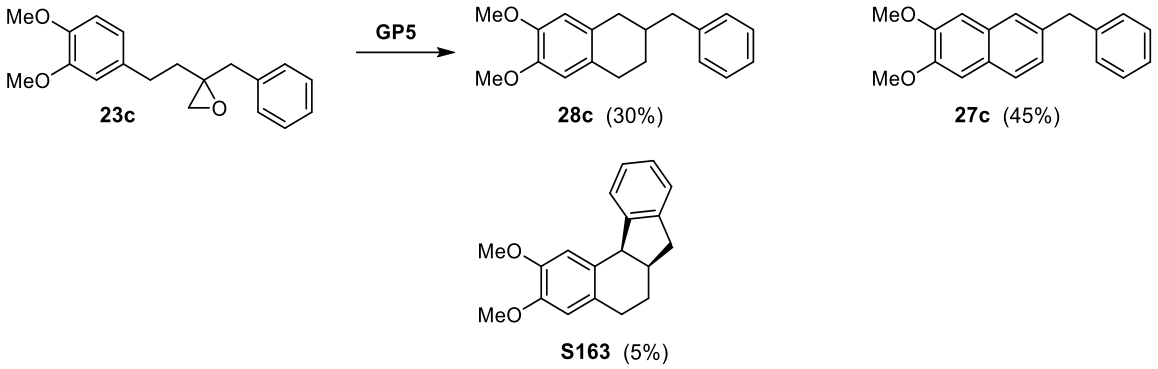
mp: 108.4 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 1H), 7.50 – 7.47 (m, 1H), 7.21 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.09 (d, *J* = 6.8 Hz, 2H), 4.00 (s, 3H), 3.99 (s, 3H), 2.77 (q, *J* = 7.6 Hz, 2H), 1.31 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6, 149.0, 140.3, 129.5, 127.6, 126.4, 125.4, 124.4, 106.3, 106.2, 56.0, 29.1, 15.8.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3052 (*w*), 2998 (*m*), 2962 (*s*), 2931 (*m*), 2851 (*m*), 1631 (*w*), 1609 (*m*), 1578 (*w*), 1512 (*s*), 1492 (*m*), 1461 (*m*), 1437 (*m*), 1421 (*m*), 1407 (*m*), 1318 (*w*), 1255 (*s*), 1206 (*m*), 1163 (*s*), 1130 (*s*), 1031 (*w*), 1005 (*m*), 898 (*w*), 857 (*m*).

HRMS (ESI): calcd for $C_{14}H_{17}O_2$ $[M+H]^+$: 217.1223; found: 217.1218.



Exposing of **23c** (0.200 mmol, 1 equiv) to the conditions of the **GP5** led to the formation of tetraline **28c** (17.1 mg, 30%, colorless oil), naphthalene **27c** (25.0 mg, 45%, colorless solid) and benzofluorene **S163** (2.90 mg, 5%). Purified by HPLC column chromatography on silica gel (2% ethyl acetate in hexane).

2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene (**28c**):

TLC (10% ethyl acetate in cyclohexane): R_f: 0.26 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.25 – 7.19 (m, 3H), 6.58 (s, 1H), 6.53 (s, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 2.83 – 2.57 (m, 5H), 2.48 – 2.33 (m, 1H), 2.11 – 1.98 (m, 1H), 1.98 – 1.88 (m, 1H), 1.52 – 1.34 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1, 147.1, 140.9, 129.3, 128.5, 128.4, 128.3, 126.0, 112.0, 111.7, 56.0, 56.0, 43.1, 36.5, 35.7, 29.5, 28.9.

IR (ATR, neat) $\tilde{\nu}_{max}$:3061 (*w*), 3025 (*m*), 2998 (*m*), 2914 (*s*), 2831 (*m*), 1608 (*m*), 1515 (*s*), 1452 (*m*), 1408 (*w*), 1353 (*m*), 1408 (*m*), 1353 (*m*), 1326 (*m*), 1249 (*m*), 1224 (*m*), 1115 (*s*), 1018 (*m*), 978 (*w*), 924 (*w*), 848 (*m*), 794 (*w*), 749 (*m*), 700 (*m*).

HRMS (ESI): calcd for $C_{19}H_{23}O_2$ $[M+H]^+$: 283.1693; found: 283.1675.

2,3-dimethoxy-6,6a,7,11b-tetrahydro-5*H*-benzo[c]fluorene (**S163**):

TLC (10% ethyl acetate in cyclohexane): R_f: 0.21 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.19 (m, 1H), 7.07 – 7.01 (m, 3H), 6.72 (s, 1H), 6.53 (s, 1H), 3.85 (s, 4H), 3.78 (s, 3H), 3.24 (ddd, *J* = 30.3, 17.5, 7.4 Hz, 2H), 2.72 (d, *J* = 18.0 Hz, 1H), 2.69 – 2.61 (m, 2H), 2.08 (t, *J* = 3.1 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5, 147.2, 142.7, 135.1, 134.1, 129.5, 127.3, 126.5, 126.0, 125.7, 112.3, 110.8, 56.2, 56.0, 39.8, 37.1, 36.8, 29.3, 25.5.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3056 (*w*), 2996 (*m*), 2922 (*s*), 2852 (*m*), 2830 (*m*), 1733 (*w*), 1609 (*w*), 1511 (*s*), 1489 (*m*), 1450 (*m*), 1405 (*w*), 1352 (*w*), 1254 (*m*), 1222 (*m*), 1152 (*w*), 1123 (*m*), 1110 (*m*), 1049 (*w*), 975 (*w*), 846 (*w*), 798 (*w*), 736 (*w*).

HRMS (ESI): calcd for $C_{19}H_{21}O_2$ $[M+H]^+$: 281.1536; found: 281.1519.

6-benzyl-2,3-dimethoxynaphthalene (**27c**):

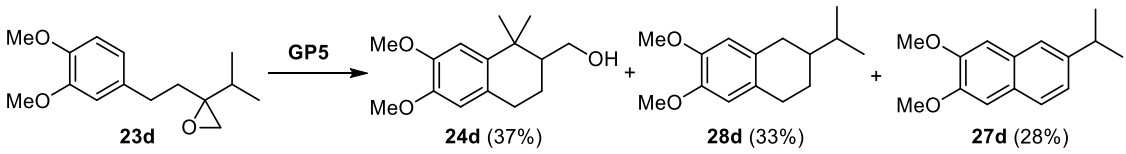
TLC (10% ethyl acetate in cyclohexane): R_f: 0.18 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 1H), 7.50 – 7.46 (m, 1H), 7.34 – 7.27 (m, 2H), 7.26 – 7.16 (m, 4H), 7.10 (s, 1H), 7.07 (s, 1H), 4.12 (s, 2H), 3.99 (s, 3H), 3.98 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7, 149.2, 141.4, 137.1, 129.5, 129.2, 128.6, 127.8, 126.6, 126.2, 126.0, 125.9, 106.3, 106.3, 56.0, 55.9, 42.1.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3057 (*m*), 3000 (*m*), 2933 (*m*), 2828 (*m*), 1631 (*w*), 1609 (*m*), 1511 (*s*), 1490 (*s*), 1462 (*m*), 1436 (*m*), 1419 (*m*), 1253 (s), 1205 (*m*), 1162 (*m*), 1130 (*m*), 1075 (*m*), 1009 (*m*), 855 (*m*), 739 (*m*), 700 (*m*).

HRMS (ESI): calcd for $C_{19}H_{19}O_2$ $[M+H]^+$: 279.1380; found: 279.1361.



(6,7-dimethoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (**24d**) was prepared according to **GP5** from **23d** (0.200 mmol, 1 equiv) in 37% yield as a colorless oil (18.3 mg). Further products: **28d** (15.3 mg, 33%, colorless oil) and **27d** (13.1 mg, 28%, colorless solid). Purified by flash column chromatography on silica gel (5% diethyl ether in petrol ether grading to 25% diethyl ether in petrol ether).

(**6,7-dimethoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methanol** (**24d**):

TLC (20% ethyl acetate in cyclohexane): R_f: 0.09 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (s, 1H), 6.53 (s, 1H), 3.96 (dd, *J* = 10.5, 3.4 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.54 – 3.45 (m, 1H), 2.80 – 2.71 (m, 2H), 2.12 – 2.03 (m, 1H), 1.74 – 1.60 (m, 2H), 1.38 (s, 3H), 1.30 (s, 1H), 1.15 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4, 147.1, 137.9, 128.3, 111.4, 110.0, 63.9, 56.2, 55.9, 47.6, 36.1, 30.7, 29.0, 26.5, 22.3.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3484 (br *m*), 2932 (*s*), 1610 (*w*), 1510 (*s*), 1464 (*m*), 1401 (*w*), 1349 (*w*), 1254 (*s*), 1207 (*m*), 1152 (*m*), 1073 (*m*), 1026 (*m*), 1005 (*m*), 970 (*m*), 860 (*w*), 830 (*w*), 777 (*w*).

HRMS (LTB): calcd for $C_{15}H_{23}O_3$ $[M+H]^+$: 251.1642; found: 251.1644.

2-isopropyl-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene (**28d**):

TLC (10% ethyl acetate in cyclohexane): R_f: 0.24 (UV, CAM)

^{1}H NMR (400 MHz, CDCl3) δ 6.58 (d, *J* = 2.9 Hz, 2H), 3.84 (s, 6H), 2.77 – 2.66 (m, 3H), 2.45 (ddd, *J* = 16.2, 11.3, 1.6 Hz, 1H), 1.99 – 1.83 (m, 1H), 1.66 – 1.52 (m, 1H), 1.52 – 1.42 (m, 1H), 1.43 – 1.29 (m, 1H), 0.96 (dd, *J* = 6.7, 1.8 Hz, 6H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1, 147.0, 129.1, 128.9, 112.2, 111.7, 56.0, 41.1, 32.8, 32.4, 29.6, 27.0, 20.1, 19.8.

IR (ATR, neat) $\tilde{\nu}_{max}$: 2954 (*s*), 2929 (*s*), 2870 (*m*), 1610 (*w*), 1517 (*s*), 1464 (*m*), 1408 (*w*), 1385 (*w*), 1365 (*w*), 1264 (*m*), 1239 (*m*), 1226 (*m*), 1116 (*m*), 1018 (*w*), 847 (*w*).

HRMS (LTB): calcd for $C_{15}H_{23}O_2$ $[M+H]^+$: 235.1693; found: 235.1693.

6-isopropyl-2,3-dimethoxynaphthalene (**27d**):

TLC (10% ethyl acetate in cyclohexane): R_f: 0.21 (UV, CAM)

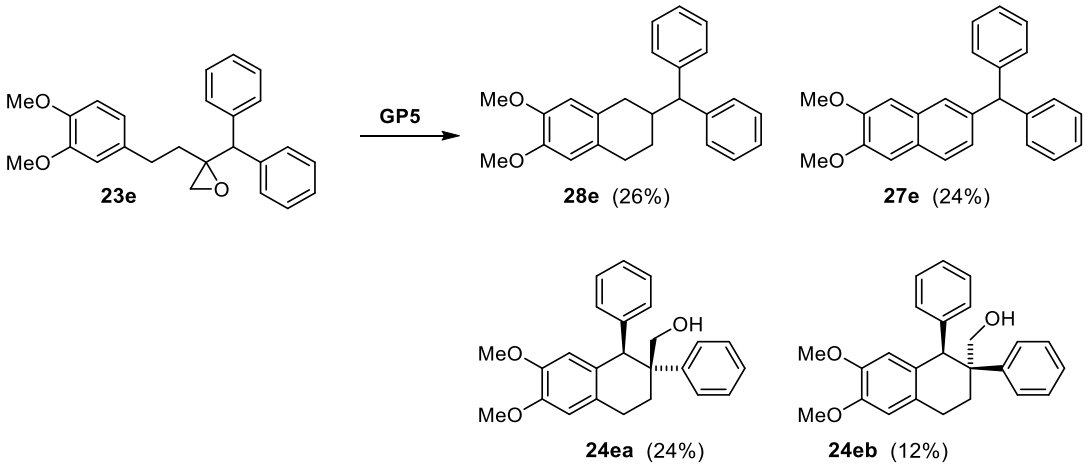
mp: 108.8 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 1H), 7.51 (d, *J* = 1.8 Hz, 1H), 7.24 (d, *J* = 1.8 Hz, 1H), 7.10 (s, 2H), 4.00 (s, 3H), 3.99 (s, 3H), 3.03 (hept, *J* = 6.9 Hz, 1H), 1.33 (d, *J* = 6.9 Hz, 6H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6, 149.1, 144.9, 129.5, 127.7, 126.4, 124.1, 122.9, 106.3, 106.3, 56.0, 56.0, 34.3, 24.2.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3057 (*w*), 2998 (*w*), 2958 (*s*), 2925 (*m*), 2866 (*w*), 1609 (*m*), 1514 (*m*), 1493 (*m*), 1455 (*m*), 1409 (*w*), 1302 (*w*), 1256 (*s*), 1214 (*w*), 1195 (*w*), 1164 (*m*), 1147 (*m*), 1127 (*m*), 1005 (*m*), 897 (*w*), 855 (*m*).

HRMS (ESI): calcd for $C_{15}H_{19}O_2$ $[M+H]^+$: 231.1380; found: 231.1375.



(6,7-dimethoxy-1,2-diphenyl-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (**24ea**) was prepared according to **GP5** from **23e** (0.200 mmol, 1 equiv) in 24% yield as a colorless oil (17.6 mg). Further products: **24eb** (12.2 mg, 12%, colorless oil), **28e** (18.3 mg, 26%, colorless oil) and **27e** (16.9 mg, 24%, colorless oil). Purified by flash column chromatography on silica gel (1% ethyl acetate in cyclohexane grading to 25% ethyl acetate in cyclohexane).

2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene (**28e**):

TLC (10% ethyl acetate in cyclohexane): R_f: 0.19 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 8H), 7.22 – 7.15 (m, 2H), 6.58 (s, 1H), 6.44 (s, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.63 (d, *J* = 10.8 Hz, 1H), 2.72 (dd, *J* = 8.4, 4.5 Hz, 2H), 2.67 – 2.56 (m, 2H), 2.35 (dd, *J* = 17.2, 10.8 Hz, 1H), 1.87 (ddt, *J* = 11.1, 4.7, 2.3 Hz, 1H), 1.37 (ddt, *J* = 13.1, 10.7, 8.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2, 147.1, 144.3, 144.2, 128.7, 128.7, 128.4, 128.3, 128.2, 128.2, 126.3 (2x), 112.1, 111.6, 58.6, 56.0, 56.0, 38.3, 35.1, 28.9, 28.3.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3059 (*w*), 3025 (*m*), 2998 (*w*), 2931 (*m*), 2832 (*m*), 1608 (*w*), 1516 (*s*), 1493 (*m*), 1463 (*m*), 1450 (*m*), 1408 (*w*), 1353 (*w*), 1250 (*m*), 1217 (*m*), 1117 (*m*), 1020 (*w*), 977 (*w*), 853 (*w*), 809 (*w*), 747 (*w*), 705 (*w*).

HRMS (ESI): calcd for $C_{25}H_{26}NaO_2$ $[M+Na]^+$: 381.1825; found: 381.1823.

6-benzyl-2,3-dimethoxynaphthalene (**27e**):

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

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.4 Hz, 1H), 7.35 – 7.27 (m, 5H), 7.27 – 7.19 (m, 2H), 7.19 – 7.14 (m, 5H), 7.10 (s, 1H), 7.01 (s, 1H), 5.68 (s, 1H), 3.99 (s, 3H), 3.95 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7, 149.5, 144.1, 140.1, 129.7, 129.2, 128.5, 127.9, 126.6, 126.5, 126.4, 106.6, 106.2, 57.0, 56.0, 56.0.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3057 (*m*), 3025 (*m*), 3002 (*m*), 2931 (*m*), 1607 (*m*), 1510 (*s*), 1490 (*s*), 1462 (*m*), 1451 (*m*), 1436 (*m*), 1418 (*m*), 1256 (*s*), 1239 (*m*), 1201 (*m*), 1163 (*m*), 1131 (*m*), 1030 (*w*), 1009 (*m*), 898 (*w*), 854 (*m*), 752 (*w*), 701 (*m*).

HRMS (ESI): calcd for $C_{25}H_{22}NaO_2$ $[M+Na]^+$: 377.1512; found: 377.1507.

6,7-dimethoxy-1,2-diphenyl-1,2,3,4-tetrahydronaphthalen-2-ylmethanol (**24ea**):

TLC (20% ethyl acetate in cyclohexane): R_f: 0.10 (UV, CAM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.38 (m, 2H), 7.33 – 7.23 (m, 4H), 7.25 – 7.11 (m, 4H), 6.48 (s, 1H), 6.44 (s, 1H), 4.83 (s, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.52 – 3.45 (m, 1H), 3.29 (dd, *J* = 11.3, 9.6 Hz, 1H), 2.78 (dd, *J* = 17.6, 5.8 Hz, 1H), 2.45 (ddd, *J* = 17.6, 11.9, 6.6 Hz, 1H), 2.04 (ddd, *J* = 13.8, 12.0, 6.2 Hz, 1H), 1.89 (dd, *J* = 13.8, 6.5 Hz, 1H), 1.01 (dd, *J* = 9.6, 3.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5, 147.4, 143.3, 142.4, 130.9, 130.5, 128.5, 128.2, 127.8, 127.7, 126.3, 124.1, 112.7, 110.8, 70.0, 55.8, 55.6, 48.6, 47.1, 25.12, 24.6.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3537 (br *w*), 3057 (*w*), 2924 (*s*), 2852 (*m*), 1739 (*w*), 1609 (*w*), 1512 (*m*), 1464 (*m*), 1359 (*w*), 1257 (*m*), 1229 (*m*), 1114 (*m*), 1033 (*m*), 850 (*w*), 761 (*w*), 701 (*w*).

HRMS (ESI): calcd for $C_{25}H_{26}NaO_3$ $[M+Na]^+$: 397.1774; found: 397.1753.

6,7-dimethoxy-1,2-diphenyl-1,2,3,4-tetrahydronaphthalen-2-ylmethanol (**24eb**):

TLC (20% ethyl acetate in cyclohexane): R_f: 0.07 (UV, CAM)

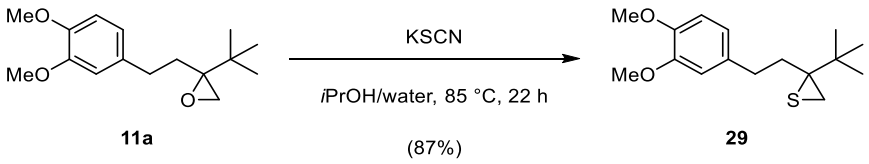
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.11 (m, 5H), 6.95 – 6.85 (m, 3H), 6.73 (s, 1H), 6.54 – 6.48 (m, 2H), 6.35 (s, 1H), 4.20 – 4.11 (m, 1H), 3.96 (s, 1H), 3.90 (s, 4H), 3.70 (s, 3H), 3.18 – 3.01 (m, 2H), 2.42 – 2.29 (m, 1H), 2.16 (dd, *J* = 13.6, 5.5 Hz, 1H), 1.09 (dd, *J* = 10.7, 3.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.8, 147.6, 143.2, 142.8, 130.1, 129.9, 128.5, 127.6, 127.2, 127.0, 126.6, 125.6, 113.1, 111.0, 67.1, 56.0, 55.9, 53.39, 46.9, 25.6, 21.3.

IR (ATR, neat) $\tilde{\nu}_{max}$: 3498 (br *m*), 3059 (*m*), 3025 (*m*), 2934 (*s*), 1724 (*m*), 1608 (*m*), 1511 (*s*), 1451 (*m*), 1405 (*m*), 1330 (*m*), 1260 (*m*), 1232 (*m*), 1115 (*m*), 1032 (*m*), 766 (*m*), 702 (*m*).

HRMS (ESI): calcd for $C_{25}H_{26}NaO_3$ $[M+Na]^+$: 397.1774; found: 397.1753.

9.2.2.14 Thiirane



2-(tert-butyl)-2-(3,4-dimethoxyphenethyl)thiirane (**29**):

To a solution of epoxide **11a** (206 mg, 780 µmol, 1 equiv) in *i*-PrOH (10 mL) was added potassium thiocyanate (682 mg, 7.02 mmol, 9.00 equiv) in water (4 mL). The mixture was heated in a sealed glass vial at 85 °C. After 22 The residue was purified by flash column chromatography (5% diethyl ether in *n*-pentane) to yield thiirane **29** (190 mg, 679 µmol, 87%) as colorless oil.

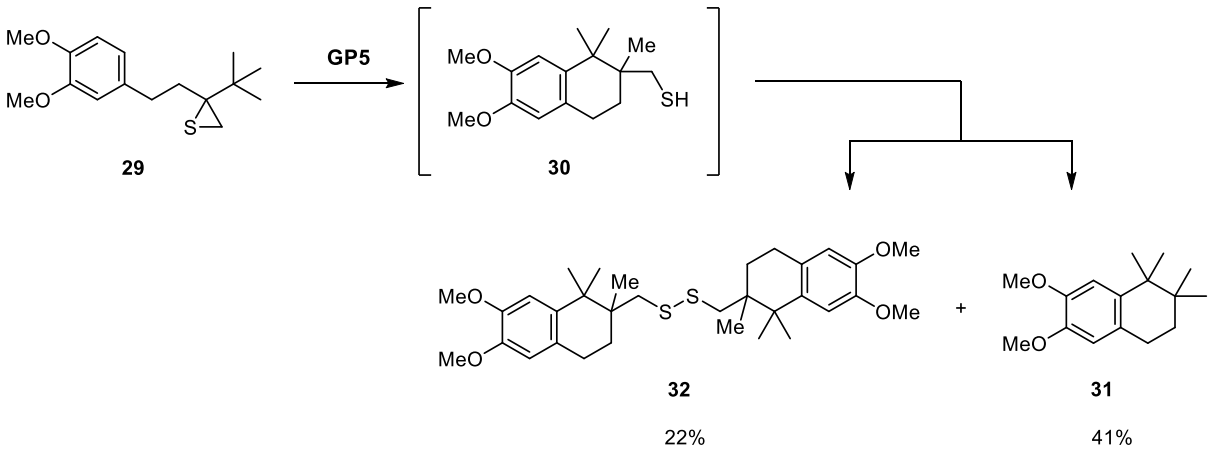
TLC (10% diethyl ether in *n*-pentane) = 0.22 (UV, CAM)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.79 (d, *J* = 8.1 Hz, 1H), 6.71 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.68 (d, *J* = 2.0 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.73 – 2.63 (m, 1H), 2.47 (d, *J* = 1.7 Hz, 1H), 2.46 – 2.37 (m, 1H), 2.36 (d, J = 1.7 Hz, 1H), 2.33 (dd, *J* = 12.0, 4.4 Hz, 1H), 2.10 (ddd, *J* = 14.0, 11.8, 4.2 Hz, 1H), 1.06 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 147.4, 135.0, 120.2, 111.9, 111.4, 58.2, 56.1, 56.0, 35.9, 32.6, 28.6, 28.0.

IR (ATR, neat): $\tilde{\nu}_{max}$ = 2955 (br *m*), 2832 (*w*), 1590 (*w*), 1514 (*s*), 1463 (*m*), 1417 (*m*), 1392 (*w*), 1364 (*w*), 1334 (*w*), 1259 (*s*), 1235 (*s*), 1191 (*w*), 1156 (*s*), 1139 (*s*), 1029 (*s*), 930 (br *w*), 852 (*w*), 805 (*m*).

HRMS (ESI): calcd for $C_{16}H_{24}NaO_2S$ $[M+Na]^+$: 303.1389; found: 303.1375.



Note: Thiol **30** disproportionates to disulfide **32** and tetralin **31** under conditions of **GP5** and is hence not observed.

1,2-bis((6,7-dimethoxy-1,1,2-trimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)methyl)disulfane (**32**) was prepared according to **GP5** from **29** (0.200 mmol, 1 equiv) in 22% yield as a colorless oil (12.1 mg, mixture of diastereomers). Purified by high pressure liquid chromatography on silica gel (0.5% isopropanol in hexane grading to 2.5% isopropanol in hexane). Besides decalin **31** (20.6 mg, 41%) was isolated as a colorless oil.

Note: Usage of trimethylsilyl trifluoromethanesulfonate instead of sulfuric acid resulted in higher yield in this special case: Disulfide **32** (26.3 mg, 47%) and tetraline **31** (22.3 mg, 45%)

Analytical data of **32:**

TLC (10% diethyl ether in *n*-pentane) = 0.08 (UV, CAM)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.80 (d, J = 2.2 Hz, 2H), 6.51 (d, J = 4.5 Hz, 2H), 3.86 (s, 6H), 3.83 (d, J = 4.0 Hz, 6H), 3.10 (d, J = 4.5 Hz, 4H), 2.78 (dddd, J = 15.9, 9.5, 6.5, 3.4 Hz, 2H), 2.66 (dt, J = 17.4, 5.8 Hz, 2H), 1.90 – 1.70 (m, 4H), 1.25 (d, J = 9.1 Hz, 6H), 1.22 (d, J = 5.8 Hz, 6H), 1.06 (d, J = 7.3 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6, 147.1, 137.3, 127.2, 111.2, 110.2, 56.2, 55.9, 49.2, 49.0, 40.6, 40.6, 39.1, 29.9, 28.9, 28.9, 28.1, 25.9, 25.1, 25.0, 20.9, 20.9.

IR (ATR, neat): $\tilde{\nu}_{max}$ = 2967 (*m*), 2926 (*m*), 2849 (*w*), 1610 (*w*), 1509 (*s*), 1462 (*m*), 1400 (*w*), 1373 (*w*), 1353 (*w*), 1327 (*w*), 1253 (*s*), 1232 (*m*), 1206 (*s*), 1181 (*w*), 1151 (*m*), 1122 (*m*), 1102 (*w*), 1075 (*m*), 1038 (*m*), 976 (*w*), 910 (*w*), 856 (*w*), 831 (*w*).

HRMS (ESI): calcd for $C_{32}H_{46}O_4NaS_2$ $[M+Na]^+$: 581.2730; found: 581.2714.

Analytical data of **31:**

TLC (10% diethyl ether in *n*-pentane) = 0.63 (UV, CAM)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.84 (s, 1H), 6.51 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 2.72 (t, J = 6.8 Hz, 2H), 1.65 (t, J = 6.8 Hz, 2H), 1.21 (s, 6H), 0.94 (s, 6H).

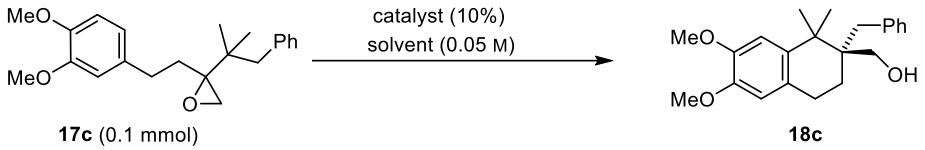
^{13}C NMR (101 MHz, $CDCl_3$) δ 147.3, 146.7, 138.5, 127.3, 111.2, 110.3, 56.2, 55.8, 39.6, 34.6, 33.4, 26.6, 26.3, 24.6.

IR (ATR, neat): $\tilde{\nu}_{max}$ = 2967 (*m*), 2926 (*m*), 2849 (*w*), 1610 (*w*), 1509 (*s*), 1462 (*m*), 1400 (*w*), 1373 (*w*), 1353 (*w*), 1327 (*w*), 1253 (*s*), 1232 (*m*), 1206 (*s*), 1181 (*s*), 1151 (*s*), 1122 (*w*), 1102 (*s*), 1075 (*w*), 1038 (*w*), 976 (*w*), 910 (*w*), 856 (*m*), 831 (*m*).

HRMS (ESI): calcd for $C_{16}H_{24}NaO_2$ [M+Na]+ 271.1669; found: 271.1663.

9.2.2.15 Asymmetric attempts for desymmetrization of epoxide 17c

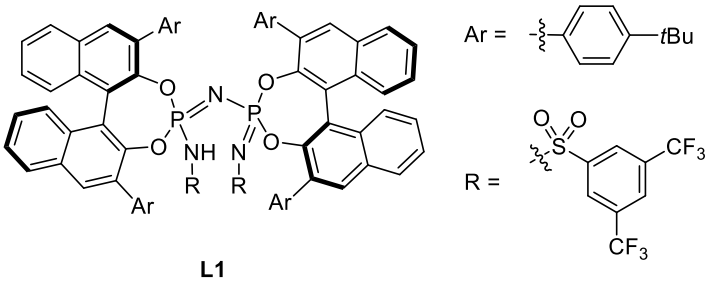
Substrate **17c** was chosen as modell substrate for desymmetrization experiments with chiral catalysts due to expected π-stacking effects of the benzylgroup. Attempts with **11a** are not shown (no ee values were observed for **13a**).



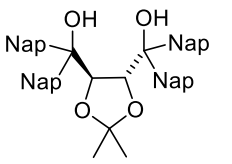
17c (0.1 mmol) **18c**

Table S17: Screening of chiral catalyst for desymmetrization of 17c.

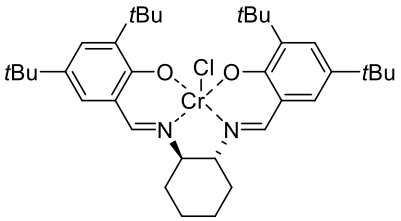
Entry	solvent	**conditions,** reaction time	temperature	yield [%]*	ee
1	HFIP	**L1**, 4 d	0 °C	11	<1
2	PhMe	**L1**, 14 d	23 °C	6	<1
3	PhMe	$TiCl_4$, **L2**, 3 d	23 °C	16	<1
4	PhMe	**L2**, MeLi, then $TiCl_4$, 3 d	23 °C	n.d.	-
5	PhMe	**L3,** 2 d	23 °C	n.d.	-
6	PhMe, THF	**L3,** 2 d	23 °C	n.d.	-
7	PhMe	$Cu(OTf)_2$, **L4**	23 °C	n.d.	-



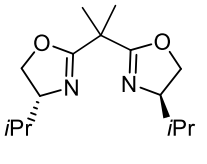
L1



L2



L3



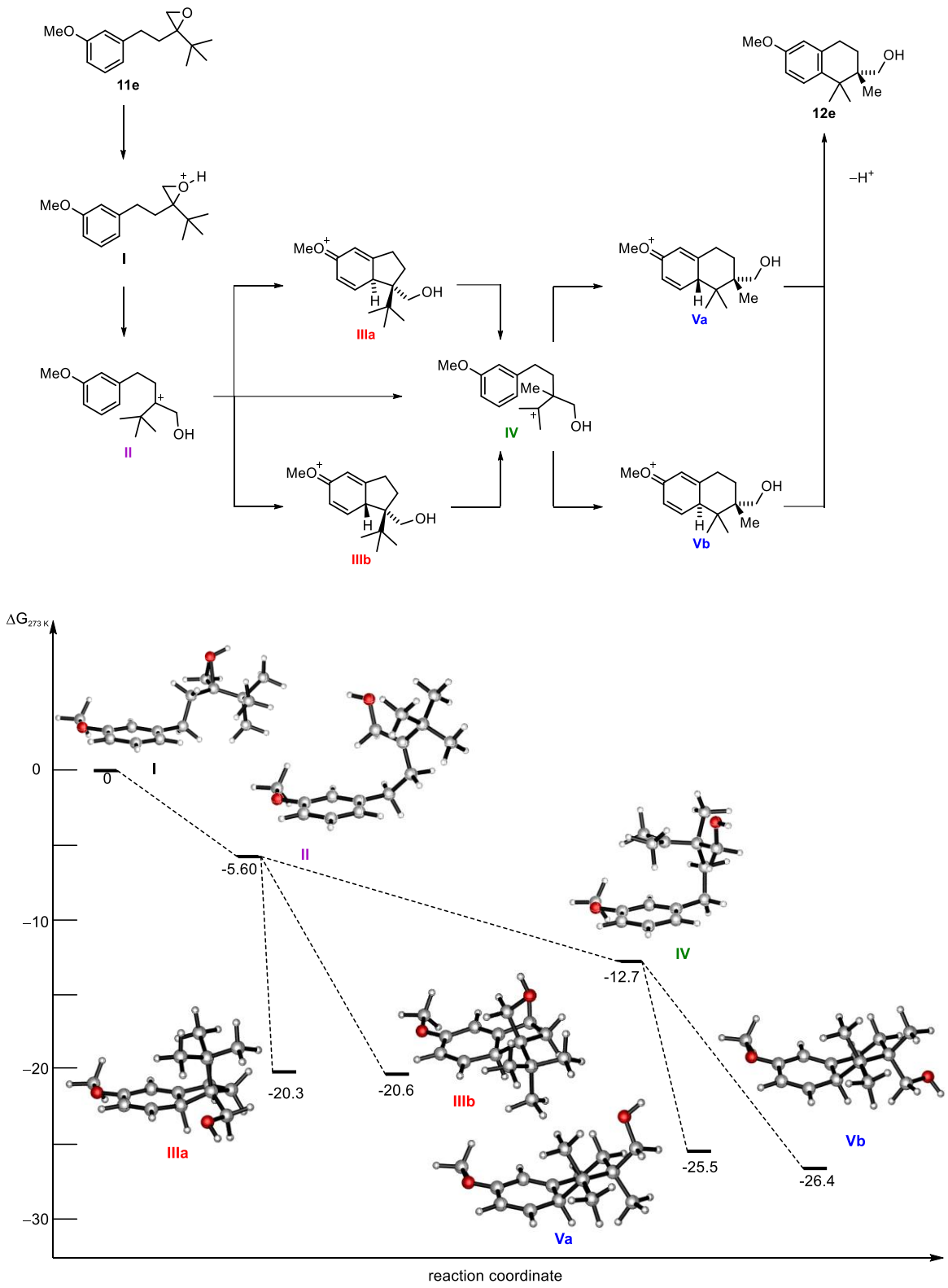
L4

In the shown transformation, starting from racemic epoxide **17c** we investigated if chirality can be induced (Table S2). Therefore asymmetric Brønsted and Lewis acids were employed. Using chiral phosphoric acid **L1**[148] under standard conditions (GP5) led to a slow product formation, but no observable enantiomeric excess (Entry 1). The same result was obtained by switching the solvent to toluene (Entry 2). Unfortunately, most Lewis acids react with the best performing, but Lewis basic solvent 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) to release Brønsted acids. Hence, HFIP is incompatible and a switch to aprotic toluene was inevitable (Entries 3–7). Titanium tetrachloride in combination with **L2** led indeed to product formation, but despite our expectations to no enantiomeric excess (Entry 3).[133] However, by formation of the complex under water free conditions (preform alkoxide in situ with methyl lithium and addition of titanium tetrachloride in sequence) the reactions showed no conversion at all (Entry 4). Neither chromium salen complex **L3**[149] in toluene/toluene–tetrahydrofuran (Entries 5 and 6) nor copper(II) with Box ligand **L4** (Entry 7) were able to catalyze the reaction at all.[150]

9.2.2.16 Computational Details

All calculations were carried out with the Gaussian 16 package* Investigated structures were fully optimized in implicit solvent the ωB97X-D range-separated hybrid functional[151] and 6-311G(d,p) basis set on all atoms. Bulk solvent effects were modelled (implicitly) by SMD polarizable continuum model of Cramer and Truhlar[152] as implemented in Gaussian 16. The internally stored parameters for 2,2,2-trifluoro ethanol (ε = 26.726) were used. All species were calculated considering closed-shell electronic configurations (singlet). The possibility of different conformations was taken into account for all structures. Frequency analyses were carried out with ωB97X-D/6-311G(d,p)/SMD to ensure localized stationary points corresponds to energy minima. Zero-point energy and thermal corrections were calculated using the standard rigid-rotator/harmonic oscillator model to obtain Gibbs energies at 273.15 K, no scaling of the frequencies was applied. Gibbs free energies (ΔG_{273K}) were used for the discussion on the relative stabilities of the considered structures. Cartesian coordinates, electronic energies, entropies, enthalpies and Gibbs free energies of the low energy conformations are given as the Supporting Information.

*Gaussian 16, Revision C.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.



Scheme S3. Energetical overview of proposed intermediates in the Brønsted acid catalyzed cycloisomerization of **11e**, according to a stepwise mechanism including epoxide opening, 1,2-methyl shift and Friedel–Crafts type alkylation, calculated at the SMD(F_3CCH_2OH)/ ωB97X-D/6-311(d+p) level. Free energies are given in kcal mol^{-1}.

We assume that epoxide **11e** is protonated whereupon it opens up to give carbocation **II**. Carbocation **II** can then either undergo a Friedel–Crafts alkylation directly to form the five-

membered σ-complexes **IIIa** and **IIIb** or a 1,2-methyl shift precedes this event. In that case carbocation **IV** is formed which is trapped by the arene to give rise to the six-membered σ-complexes **Va** and **Vb**. As exclusively six-membered products are observed, we assume that the five-membered σ-complexes **IIIa** and **IIIb** are formed only temporary and equilibrate with cation **IV** (which reacts to energetically favored **Va** and **Vb**. Another conceiveable theory is that the ring strain of the corresponding five-membered π-complexes (not shown) is too high and therefore these intermediates are not crossed at all. (Note: Transition states are very hard to predict in these cases, especially in the cage of 1,1,1,3,3,3-hexafluoro-2-propanol and are therefore not calculated.)

Table S3. Energies, enthalpies, Gibbs free energies and entropies of the structures calculated at the SMD/ωB97X-D/6-311G(d+p) level.

Compound	**E_0**	**E_0+ZPE**	**H**	**S**	**G**
	(Hartree)[b]	**(Hartree)[b]**	**(Hartree)[b,c]**	**(cal mol^{-1} K^{-1})**	**(Hartree)[b,c]**
I[a]	-735.623786	-735.267264	-735.251420	134.8	-735.307485
II[a]	-735.628775	-735.275758	-735.259177	137.7	-735.316405
III[a]	-735.642819	-735.288599	-735.272378	133.1	-735.327652
IVa[a]	-735.659722	-735.302406	-735.287268	126.9	-735.339906
IVb[a]	-735.659320	-735.302403	-735.286989	128.3	-735.340240
Va[a]	-735.668080	-735.310300	-735.294960	128.0	-735.348109
Vb[a]	-735.669578	-735.311697	-735.296386	128.1	-735.349561

[a]2,2,2-Trifluoro ethanol (ε = 26.726) as solvent. [b] 1 Hartree = 627.5 kcal mol^{-1}. [c]Thermal corrections at 273.15 K.

Cartesian coordianates of lowest energy structures optimized at the SMD/ωB97X-D/6-311G(d+p) level

Structure I

C	3.998958	-1.24364	-0.44384
C	3.652505	0.04803	-0.0349
C	2.343745	0.321869	0.356911
C	1.381906	-0.69136	0.343529
C	1.73106	-1.97338	-0.06312
C	3.041198	-2.24153	-0.45549
C	-0.04437	-0.37307	0.722987
C	-0.81968	0.112846	-0.51584
C	-2.20824	0.598615	-0.19547
C	-3.33519	-0.37423	0.172059
C	-2.3593	2.025234	0.080666
C	-4.71813	0.14209	-0.25891
C	-3.10752	-1.74726	-0.47292
C	-3.31911	-0.49219	1.710338
C	4.357324	2.287526	0.351664
H	-3.52822	1.631012	-1.54725
H	5.021862	-1.43824	-0.74328
H	2.055062	1.315309	0.67816
H	0.985552	-2.76143	-0.07245
H	3.316737	-3.24144	-0.77103
H	-0.51152	-1.26769	1.137426
H	-0.06491	0.396662	1.499873
H	-0.26645	0.939231	-0.9672
H	-0.87276	-0.68547	-1.25706
H	-3.25334	2.400068	0.562018
H	-1.48134	2.651484	0.166952
H	-5.47559	-0.54234	0.125194
H	-4.96372	1.127338	0.146866
H	-4.83662	0.145856	-1.34735
H	-3.93961	-2.4033	-0.21109
H	-2.19067	-2.22372	-0.12122
H	-3.06709	-1.67428	-1.56273
H	-3.55727	0.46101	2.188056
H	-4.07875	-1.21746	2.008498
H	-2.36013	-0.84022	2.093962
H	5.288992	2.841778	0.260701
H	3.601436	2.74149	-0.29722
H	4.01598	2.322005	1.391222
O	-2.57835	1.654793	-1.34294
O	4.652272	0.960833	-0.05045

Structure II

C	3.130354	-1.16568	-1.17857
C	3.19389	-0.0829	-0.29773
C	2.214509	0.067368	0.683955
C	1.174135	-0.85927	0.79046
C	1.120361	-1.93791	-0.0867
C	2.100411	-2.0822	-1.06595
C	0.121892	-0.67482	1.865205
C	-1.31705	-0.77341	1.356483
C	-1.84733	0.195846	0.389818
C	-3.16113	-0.04492	-0.25664
C	-1.01812	1.366436	0.115629
C	-3.83927	-1.35586	0.15538
C	-4.10238	1.140669	0.098719
C	-2.89397	-0.07946	-1.79168
C	4.341163	1.885211	0.389544
H	3.896639	-1.26699	-1.93751
H	2.245151	0.902701	1.372332
H	0.328154	-2.67415	-0.01065

H	2.059317	-2.92383	-1.74775
H	0.23432	-1.45791	2.619002
H	0.283249	0.269836	2.389556
H	-1.54458	-1.77737	0.985789
H	-2.02439	-0.67088	2.201033
H	-0.68588	1.752215	1.094811
H	-0.09834	0.909317	-0.30849
H	-4.80774	-1.40805	-0.34467
H	-3.26713	-2.23347	-0.15379
H	-4.02103	-1.41136	1.230798
H	-5.0467	0.965053	-0.41997
H	-3.69729	2.097961	-0.21713
H	-4.2999	1.164818	1.172466
H	-0.87635	3.008753	-0.865
H	-2.20597	-0.8882	-2.04694
H	-3.85277	-0.28044	-2.27345
H	-2.501	0.865443	-2.15852
H	5.232038	2.421535	0.070518
H	3.471122	2.543554	0.300628
H	4.460318	1.572566	1.431582
O	-1.55377	2.349507	-0.69935
O	4.230508	0.766036	-0.47468

Structure III

C	-2.5493	1.374447	-0.86098
C	-2.49698	0.171045	-0.15341
C	-1.51957	-0.01252	0.824724
C	-0.59447	1.000524	1.104017
C	-0.68064	2.209669	0.422722
C	-1.65399	2.387367	-0.55875
C	0.517711	0.738098	2.0862
C	1.383554	-0.47393	1.712147
C	1.966909	-0.46704	0.267496
C	0.950239	-0.83936	-0.75871
C	2.665192	0.87361	0.000492
C	0.298439	-2.15397	-0.72323
C	0.710699	-0.01371	-1.93549
C	3.02676	-1.61468	0.191786
C	-3.53747	-1.918	0.321972
H	-3.30673	1.499342	-1.62485
H	-1.47618	-0.93575	1.38901
H	0.019931	3.007145	0.64271
H	-1.71067	3.325646	-1.09811
H	1.139115	1.631236	2.179845
H	0.102382	0.544764	3.079762
H	2.240269	-0.51931	2.388573
H	0.824388	-1.39737	1.871504
H	3.265688	1.11161	0.886187
H	1.926923	1.67211	-0.12832
H	0.893193	-2.76295	-1.42534
H	0.299213	-2.65286	0.241815
H	-0.69964	-2.10489	-1.15983
H	0.117954	-0.51329	-2.69705
H	0.172762	0.885491	-1.59007
H	1.664329	0.36484	-2.31684
H	3.900706	1.604995	-1.30692
H	2.622271	-2.55153	0.573639
H	3.39536	-1.75926	-0.82282
H	3.867389	-1.31315	0.818774
H	-4.38142	-2.47452	-0.07857
H	-2.64177	-2.54422	0.272978
H	-3.73832	-1.64644	1.362513
O	3.486201	0.755874	-1.14531
O	-3.41366	-0.76099	-0.49275

Structure IVa

C	1.83108	-1.65277	0.057535
C	2.663886	-0.48658	0.023909
C	2.160513	0.785551	-0.3482
C	0.853419	0.875423	-0.70304
C	-0.02592	-0.30358	-0.80031
C	0.535717	-1.57056	-0.29967
C	0.070441	2.104155	-1.02384
C	-1.39315	1.62832	-1.13299
C	-1.47936	0.201879	-0.50567
C	-2.4773	-0.605	-1.34669
C	-1.84865	0.250623	1.02997
C	-1.59712	-1.08084	1.760038
C	-1.04181	1.325145	1.77944
C	-3.34313	0.585235	1.184834
C	4.864056	0.370461	0.371666
H	-0.03686	-0.47874	-1.89914
H	2.286982	-2.58128	0.374484
H	2.786126	1.666148	-0.30633
H	-0.10394	-2.44338	-0.31414
H	0.220587	2.846939	-0.23774
H	0.436711	2.554617	-1.9501
H	-1.67444	1.570784	-2.1871
H	-2.08342	2.326653	-0.66248
H	-3.47349	-0.15809	-1.26012
H	-2.175	-0.52324	-2.39892
H	-2.01271	-1.01296	2.769624
H	-2.06691	-1.9177	1.246926
H	-0.52949	-1.28629	1.872272
H	-1.29645	1.280622	2.841344
H	-1.2647	2.337462	1.435444
H	0.036841	1.159208	1.70619
H	-3.6349	1.473836	0.618486
H	-3.97329	-0.24871	0.86767
H	-3.56133	0.780359	2.237883
H	-3.08972	-2.43765	-1.53322
H	5.798981	-0.09863	0.660096
H	4.947191	0.796695	-0.6281
H	4.582466	1.129672	1.101249
O	-2.49087	-1.96523	-0.95295
O	3.89646	-0.69741	0.373425

Structure IVb

C	-2.01592	-1.61967	0.351011
C	-2.86755	-0.4952	0.074489
C	-2.34936	0.732442	-0.40447
C	-1.0131	0.817924	-0.62649
C	-0.10208	-0.33948	-0.50534
C	-0.69823	-1.54633	0.100651
C	-0.22148	2.048166	-0.92349
C	1.246393	1.596984	-0.83598
C	1.252206	0.281753	-0.01337
C	1.043373	0.603372	1.477162
C	2.525367	-0.60434	-0.28693
C	3.785117	0.281126	-0.36255
C	2.759997	-1.63468	0.830214
C	2.406711	-1.35676	-1.62234
C	-5.10765	0.325516	0.087905
H	0.075344	-0.62661	-1.56041
H	-2.4831	-2.51139	0.747262
H	-2.98606	1.598597	-0.51905
H	-0.07052	-2.41241	0.268671
H	-0.47018	2.812624	-0.18221
H	-0.4903	2.463224	-1.898
H	1.630568	1.405173	-1.83988

H	1.881262	2.350562	-0.37395
H	0.924352	-0.33013	2.039124
H	0.108337	1.168528	1.597855
H	4.666953	-0.35942	-0.45435
H	3.767641	0.93965	-1.23408
H	3.890255	0.89075	0.533938
H	3.602871	-2.27508	0.557201
H	1.900365	-2.28743	0.99899
H	3.007949	-1.1437	1.77358
H	1.654685	-2.15054	-1.59177
H	2.171419	-0.68818	-2.45631
H	3.362502	-1.83358	-1.8536
H	1.979787	1.52579	2.900241
H	-6.05616	-0.13377	0.345608
H	-4.9157	1.183777	0.731652
H	-5.09706	0.610182	-0.96402
O	2.131602	1.356343	1.969334
O	-4.12135	-0.69903	0.32949

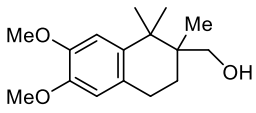
Structure Va

C	2.400638	1.585933	-0.08033
C	2.868036	0.237137	0.031841
C	2.031954	-0.86021	-0.29063
C	0.751671	-0.63863	-0.68973
C	0.170988	0.72634	-0.7475
C	1.130807	1.812591	-0.44951
C	-0.15692	-1.75485	-1.06662
C	-1.44311	-1.69074	-0.23494
C	-2.14388	-0.32377	-0.30862
C	-1.16444	0.834068	0.127313
C	-1.78767	2.215256	-0.12762
C	-0.76759	0.743287	1.609096
C	-3.40524	-0.40208	0.577208
C	-2.67752	-0.08737	-1.7351
C	4.714623	-1.17722	0.569936
H	-0.14903	0.885981	-1.78799
H	3.098266	2.383657	0.137035
H	2.413677	-1.8705	-0.23868
H	0.780946	2.833029	-0.54442
H	0.340359	-2.71669	-0.9374
H	-0.39763	-1.65015	-2.13071
H	-2.13042	-2.46306	-0.59072
H	-1.21529	-1.93443	0.803119
H	-1.20137	3.004721	0.34559
H	-2.78577	2.269067	0.309181
H	-1.87217	2.445378	-1.19184
H	-1.64703	0.850245	2.241664
H	-0.29917	-0.21034	1.859854
H	-0.06323	1.540101	1.860632
H	-3.862	0.589989	0.672524
H	-4.12507	-1.04031	0.049062
H	-3.19583	-0.98164	-2.08928
H	-3.39052	0.739672	-1.76118
H	-1.89312	0.137129	-2.46095
H	-3.9589	-1.06691	2.309005
H	5.721225	-0.96806	0.916406
H	4.173536	-1.76517	1.310834
H	4.743762	-1.68508	-0.3939
O	-3.12441	-0.9489	1.853531
O	4.096991	0.11825	0.4219

Structure Vb

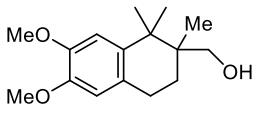
C	-2.44675	1.41742	-0.65723
C	-2.89457	0.13439	-0.20443
C	-1.99677	-0.95323	-0.07101
C	-0.67708	-0.77558	-0.34427
C	-0.12462	0.548303	-0.72511
C	-1.14171	1.609097	-0.90195
C	0.3049	-1.88754	-0.24593
C	1.437189	-1.49826	0.711232
C	2.118791	-0.16626	0.351641
C	1.063	0.996988	0.248715
C	0.462274	1.326245	1.624091
C	1.690639	2.277412	-0.32645
C	2.881958	-0.31022	-0.98065
C	3.15967	0.113033	1.450434
C	-4.76173	-1.17128	0.504835
H	0.344569	0.413002	-1.71107
H	-3.18698	2.195731	-0.786
H	-2.36021	-1.92724	0.226352
H	-0.80458	2.577383	-1.25073
H	-0.18221	-2.80645	0.08163
H	0.719829	-2.0716	-1.24371
H	2.187908	-2.28818	0.704476
H	1.041058	-1.4443	1.728546
H	-0.3266	2.075623	1.527479
H	1.226032	1.745194	2.280514
H	0.031765	0.452754	2.117878
H	2.618939	2.513386	0.195331
H	1.91438	2.192294	-1.39242
H	1.029205	3.134546	-0.18867
H	2.195336	-0.32985	-1.83781
H	3.541109	0.555092	-1.1094
H	2.722079	0.051143	2.448204
H	3.947009	-0.63955	1.380791
H	3.627333	1.093666	1.340339
H	4.220485	-1.50938	-1.7097
H	-5.81257	-0.93667	0.637748
H	-4.63934	-1.94893	-0.24877
H	-4.31548	-1.46659	1.454111
O	3.639296	-1.50657	-0.94842
O	-4.16308	0.057291	0.04233

9.2.2.17 NMR spectra



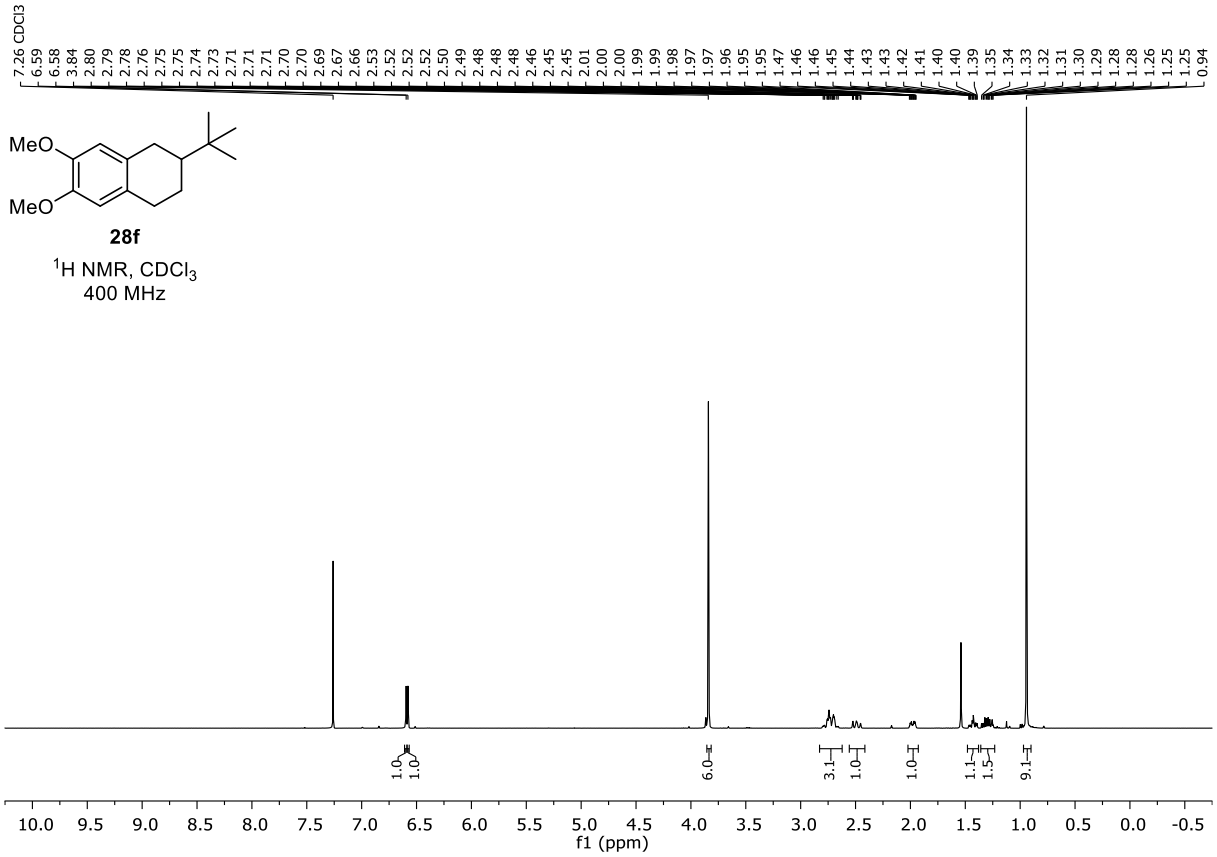
12a

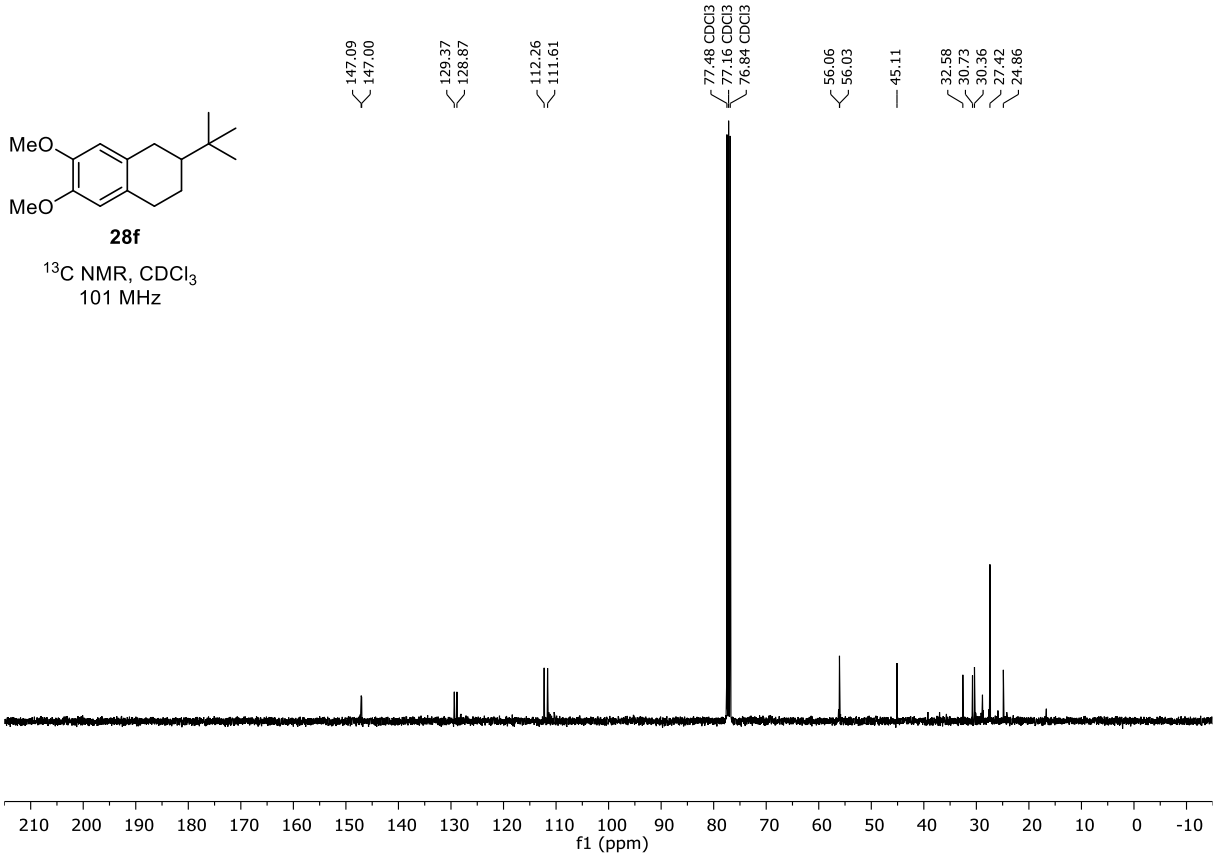
^{1}H NMR, $CDCl_3$
400 MHz

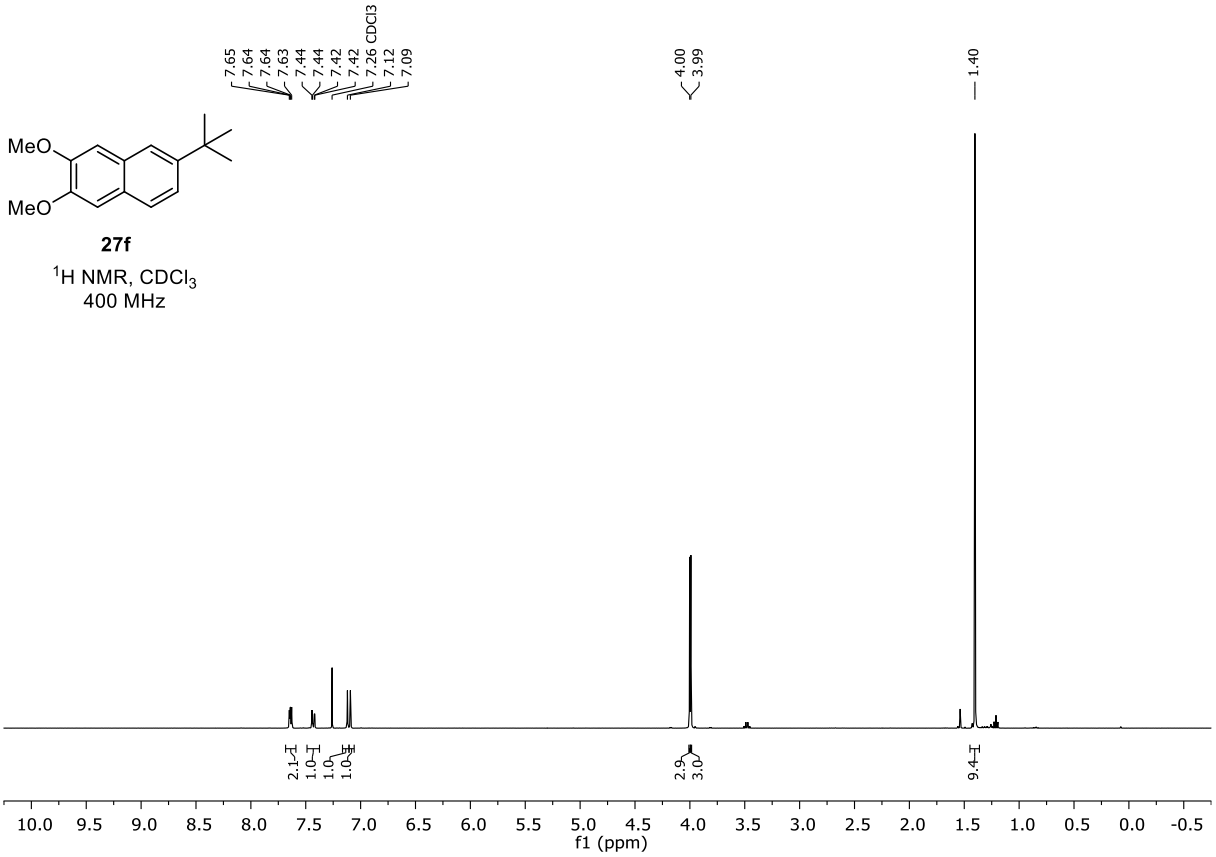


12a

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

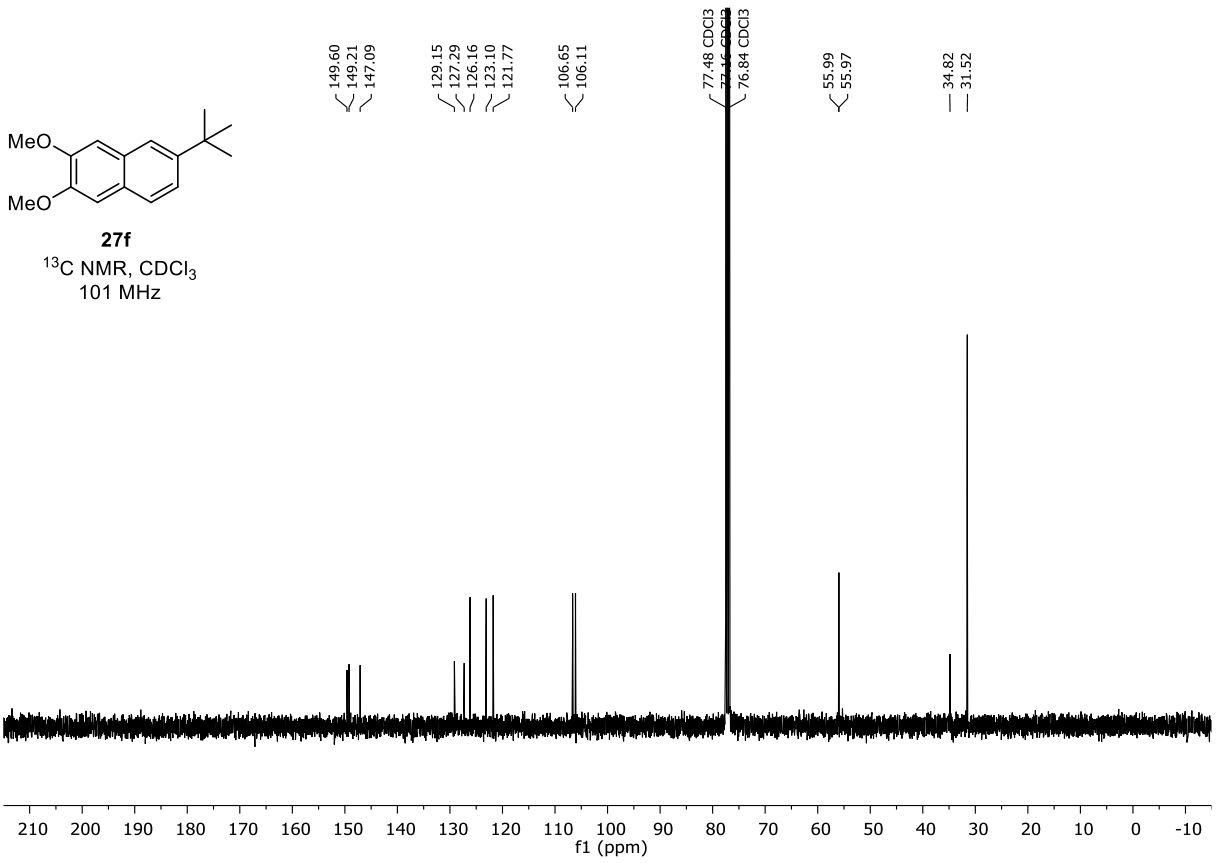

7.26 CDCl3
6.59
6.58
3.84
2.80
2.79
2.78
2.76
2.75
2.75
2.74
2.73
2.71
2.71
2.71
2.70
2.70
2.69
2.67
2.66
2.53
2.52
2.52
2.52
2.50
2.49
2.48
2.48
2.48
2.46
2.45
2.45
2.01
2.00
2.00
1.99
1.99
1.98
1.97
1.97
1.96
1.95
1.95
1.47
1.46
1.46
1.45
1.44
1.43
1.43
1.42
1.41
1.40
1.40
1.39
1.35
1.34
1.33
1.32
1.31
1.30
1.29
1.28
1.28
1.26
1.25
1.25
0.94
MeO
MeO
28f
1H NMR, CDCl3
400 MHz
1.0
1.0
6.0
3.1
1.0
1.0
1.1
1.5
9.1
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 -0.5
f1 (ppm)


147.09
147.00
129.37
128.87
112.26
111.61
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
56.06
56.03
45.11
32.58
30.73
30.36
27.42
24.86
MeO
MeO
28f
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)



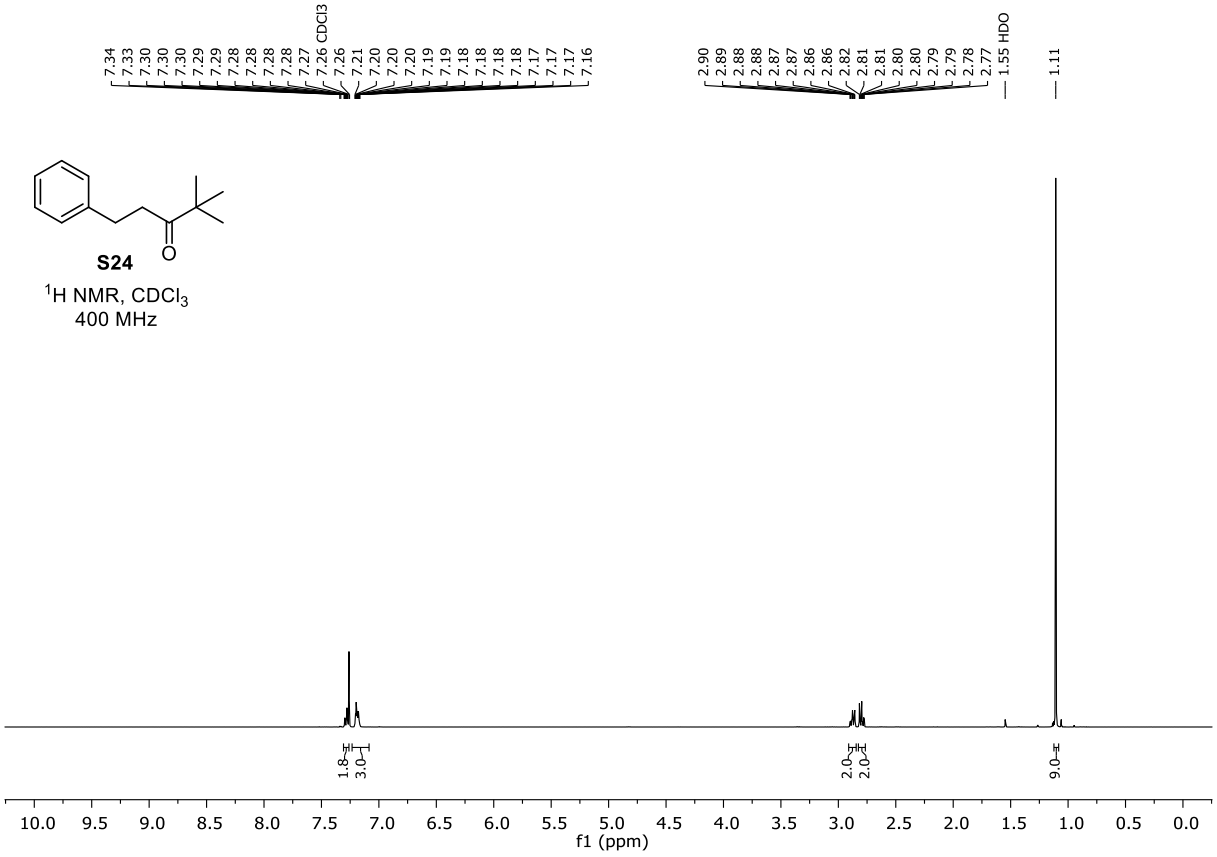
27f

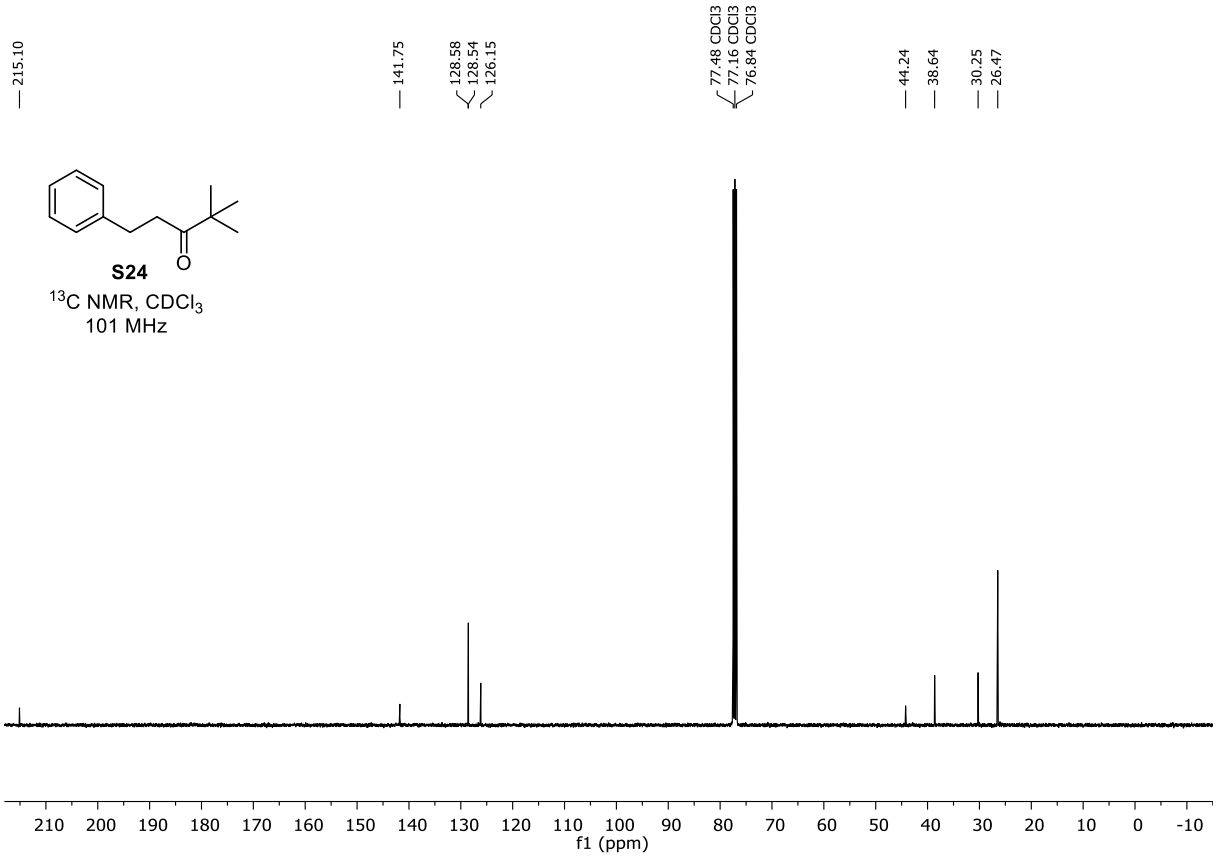
^{1}H NMR, $CDCl_3$
400 MHz

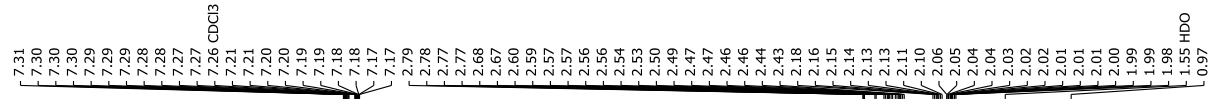


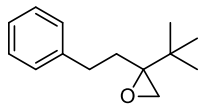
27f

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


7.34
7.33
7.30
7.30
7.30
7.29
7.29
7.28
7.28
7.28
7.28
7.27
7.26 CDCl3
7.26
7.21
7.20
7.20
7.20
7.19
7.19
7.18
7.18
7.18
7.17
7.17
7.17
7.16
2.90
2.89
2.88
2.88
2.87
2.87
2.86
2.86
2.82
2.81
2.81
2.80
2.80
2.79
2.79
2.78
2.77
1.55 HDO
1.11
O
S24
1H NMR, CDCl3
400 MHz
1.8
3.0
2.0
2.0
9.0
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)

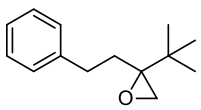

215.10
141.75
128.58
128.54
126.15
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
44.24
38.64
30.25
26.47
O
S24
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)





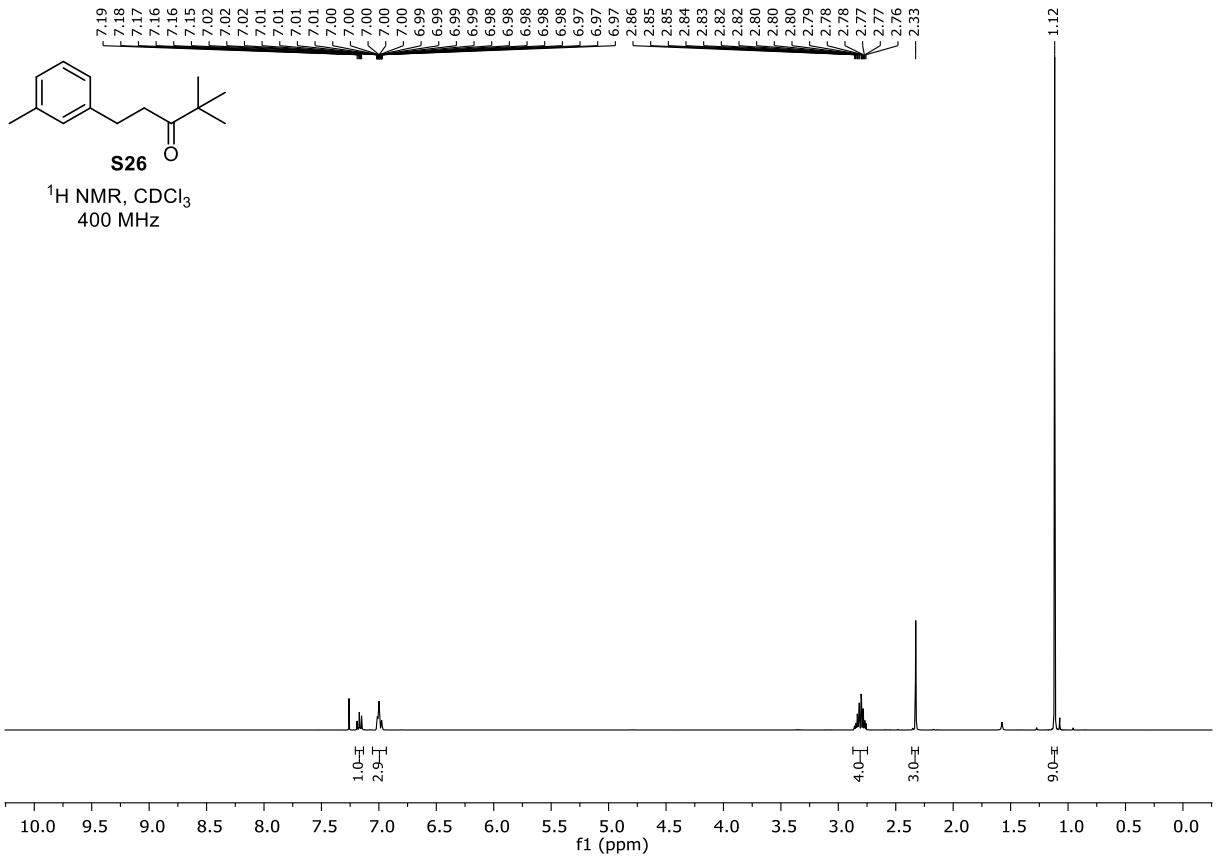
S25

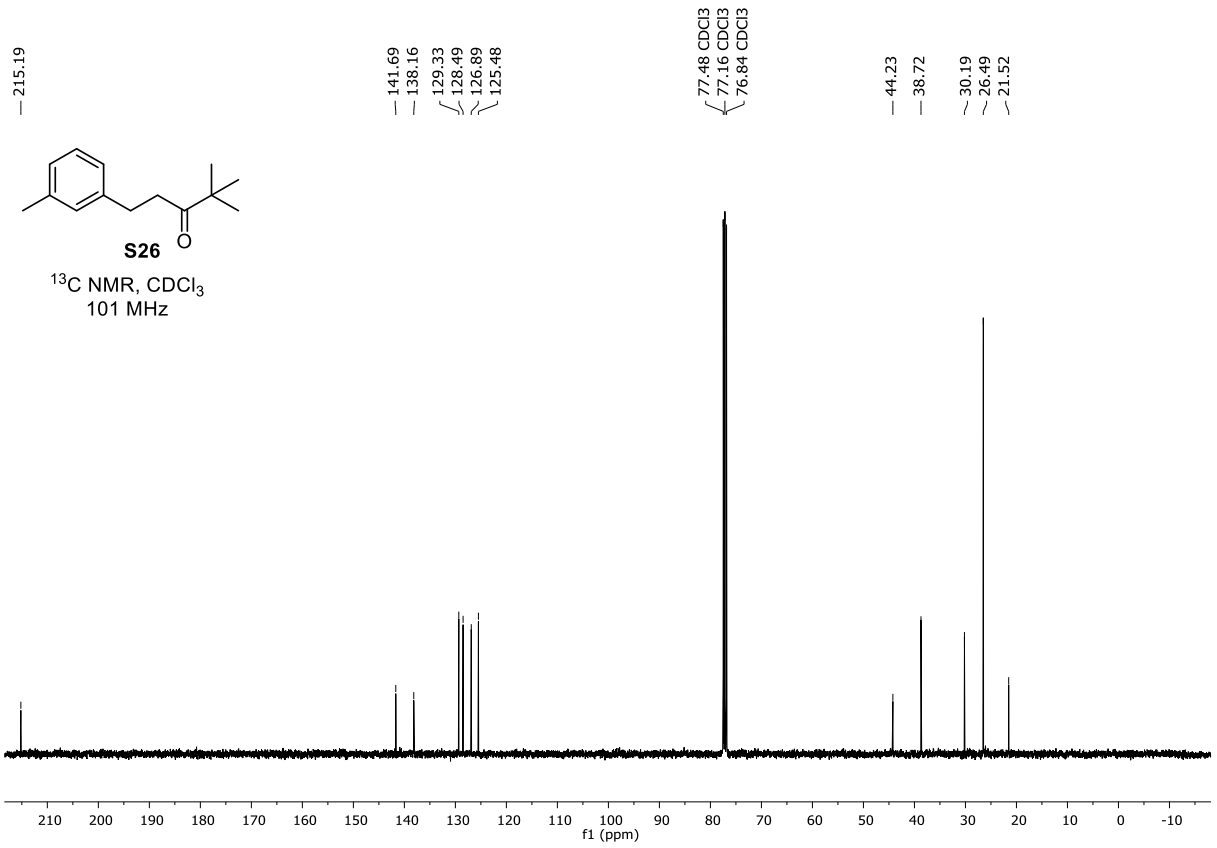
^{1}H NMR, $CDCl_3$
400 MHz

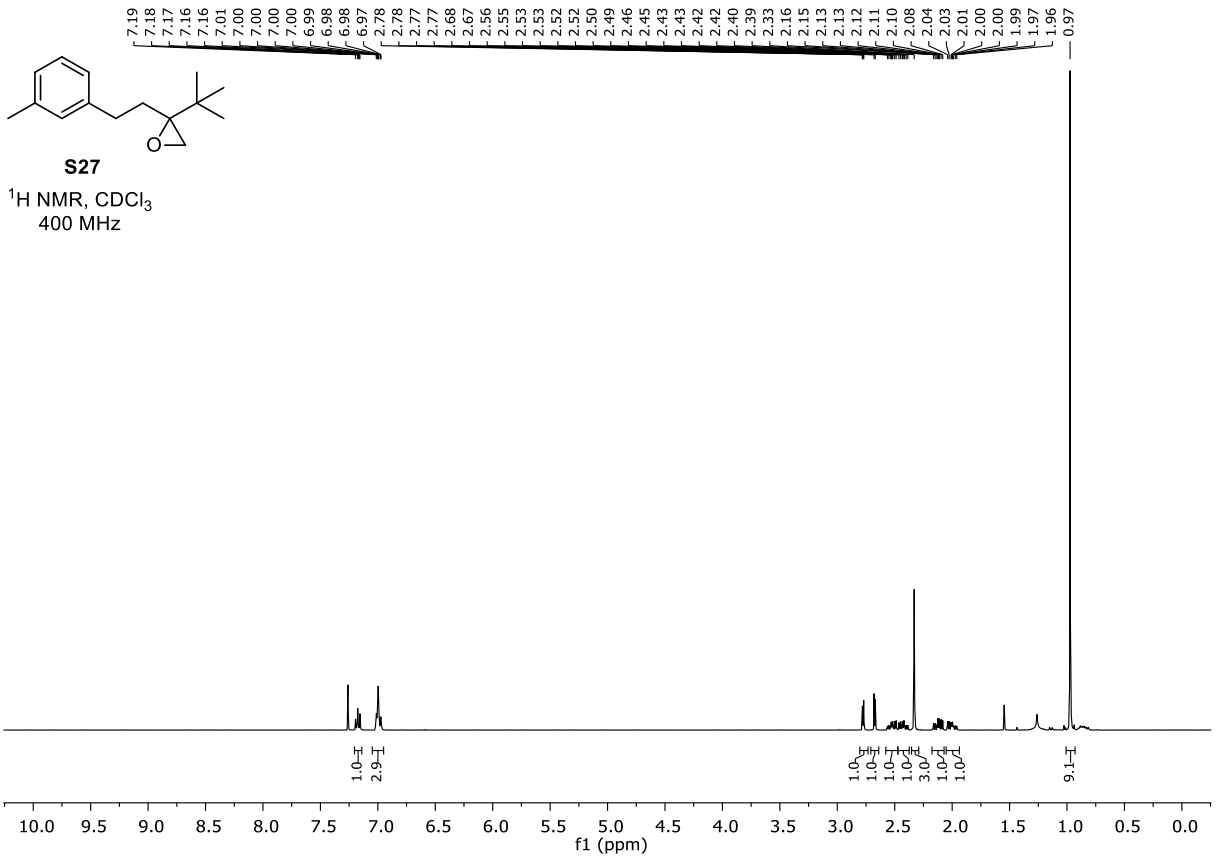


S25

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

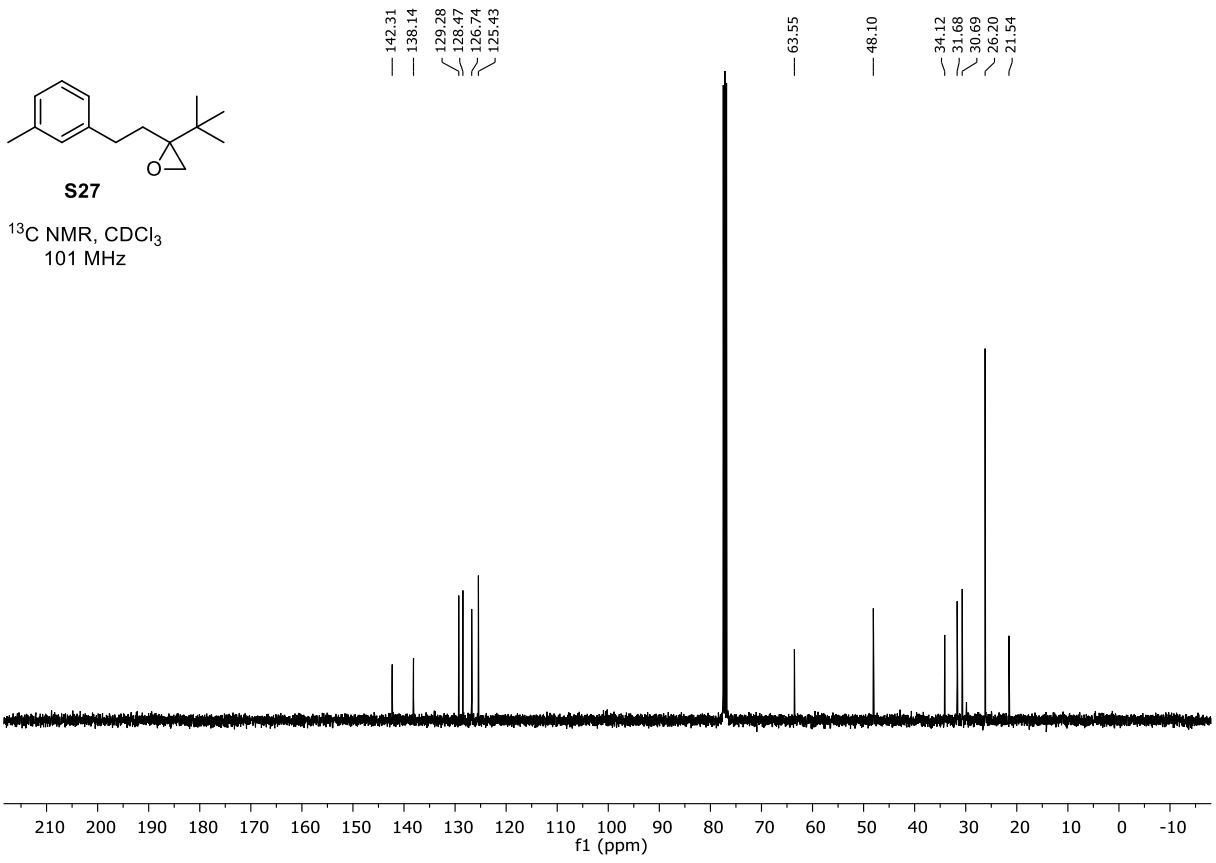

7.19 7.18 7.17 7.16 7.16 7.15 7.02 7.02 7.01 7.01 7.01 7.00 7.00 7.00 7.00 6.99 6.99 6.99 6.98 6.98 6.98 6.98 6.97 6.97 6.97
2.86 2.85 2.85 2.84 2.83 2.82 2.82 2.80 2.80 2.80 2.79 2.78 2.78 2.77 2.77 2.76 2.33
1.12
O
S26
1H NMR, CDCl3
400 MHz
1.0 2.9 4.0 3.0 9.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


215.19
141.69 138.16 129.33 128.49 126.89 125.48
77.48 CDCl3 77.16 CDCl3 76.84 CDCl3
44.23 38.72 30.19 26.49 21.52
O
S26
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)



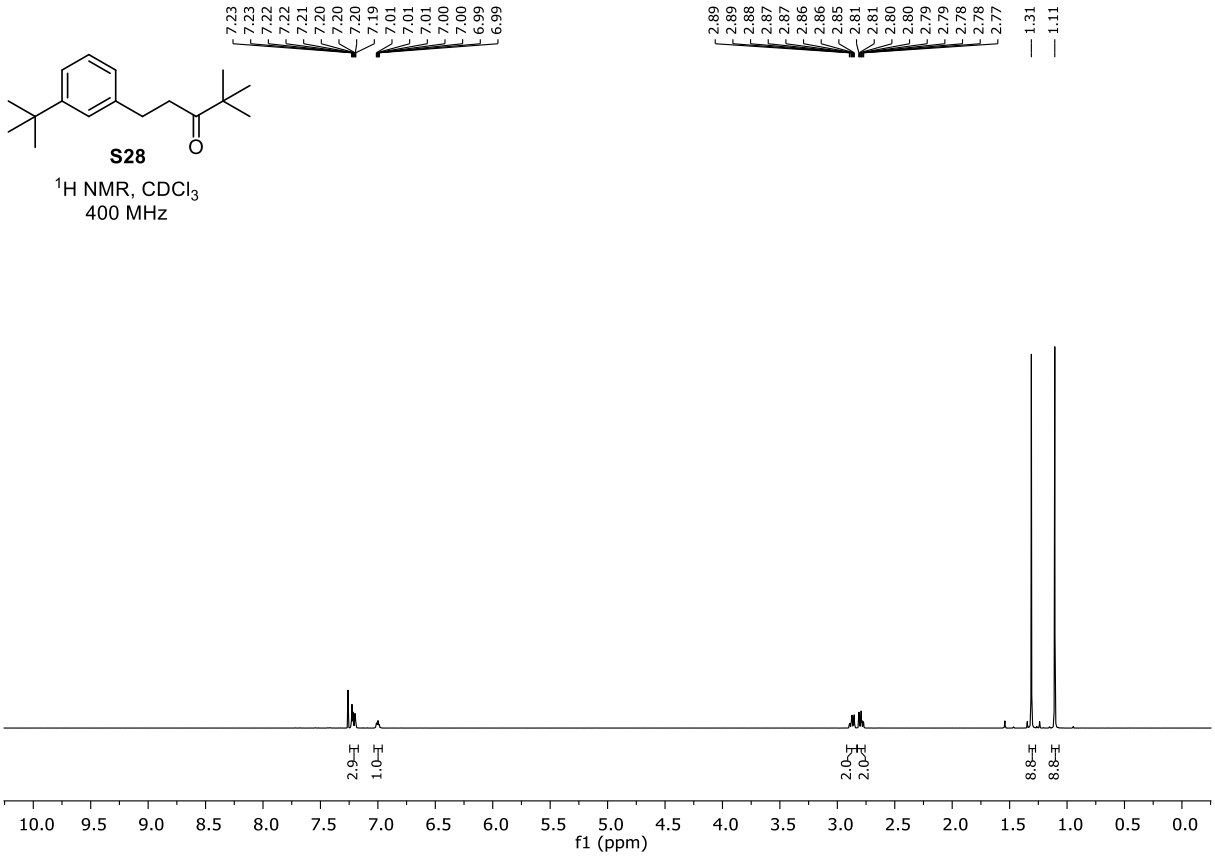
S27

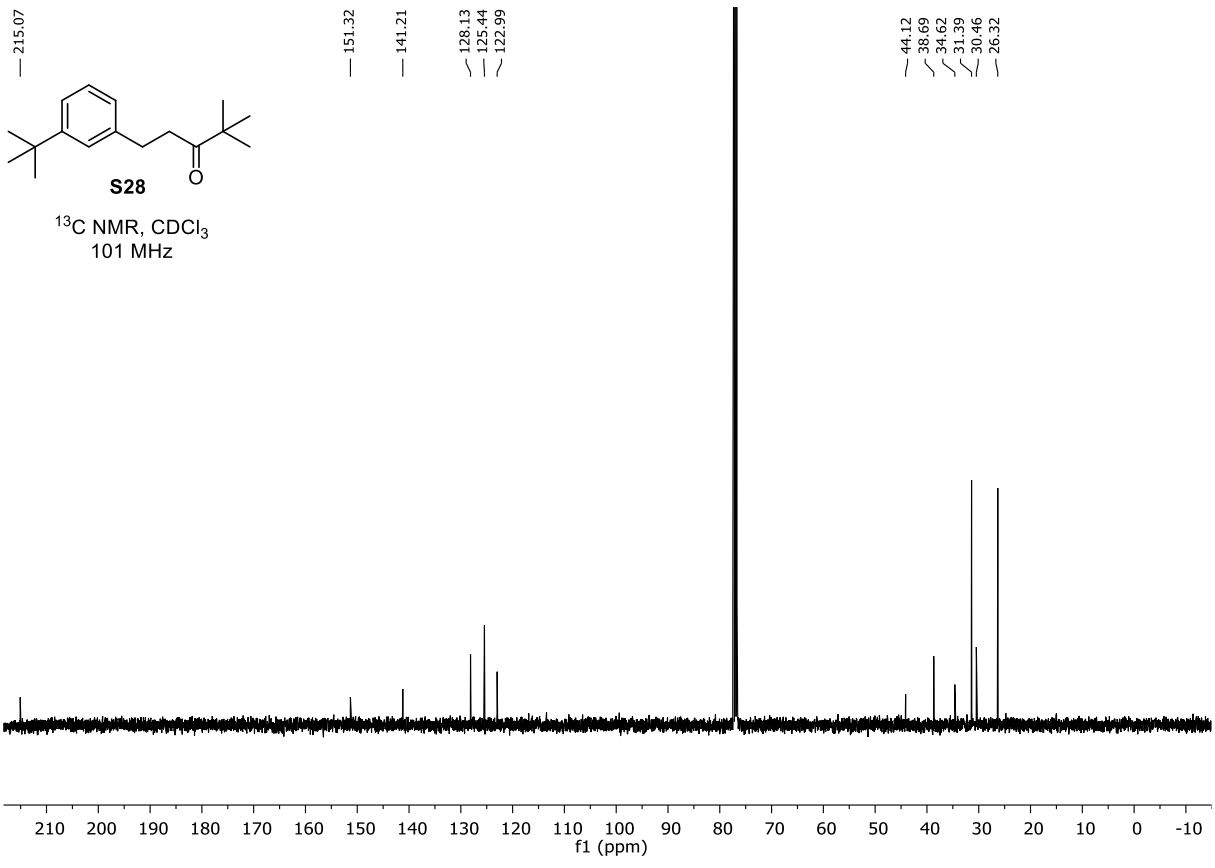
^{1}H NMR, $CDCl_3$
400 MHz

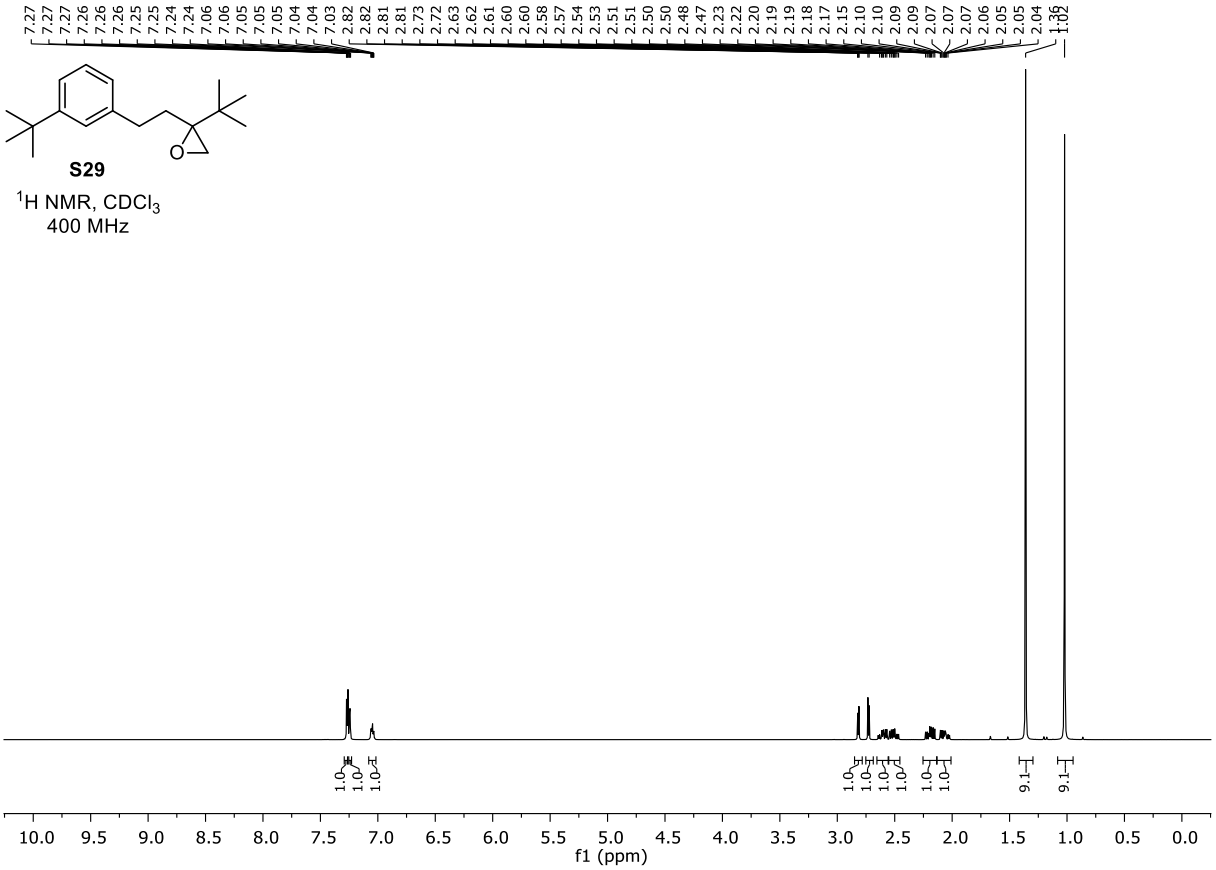


S27

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

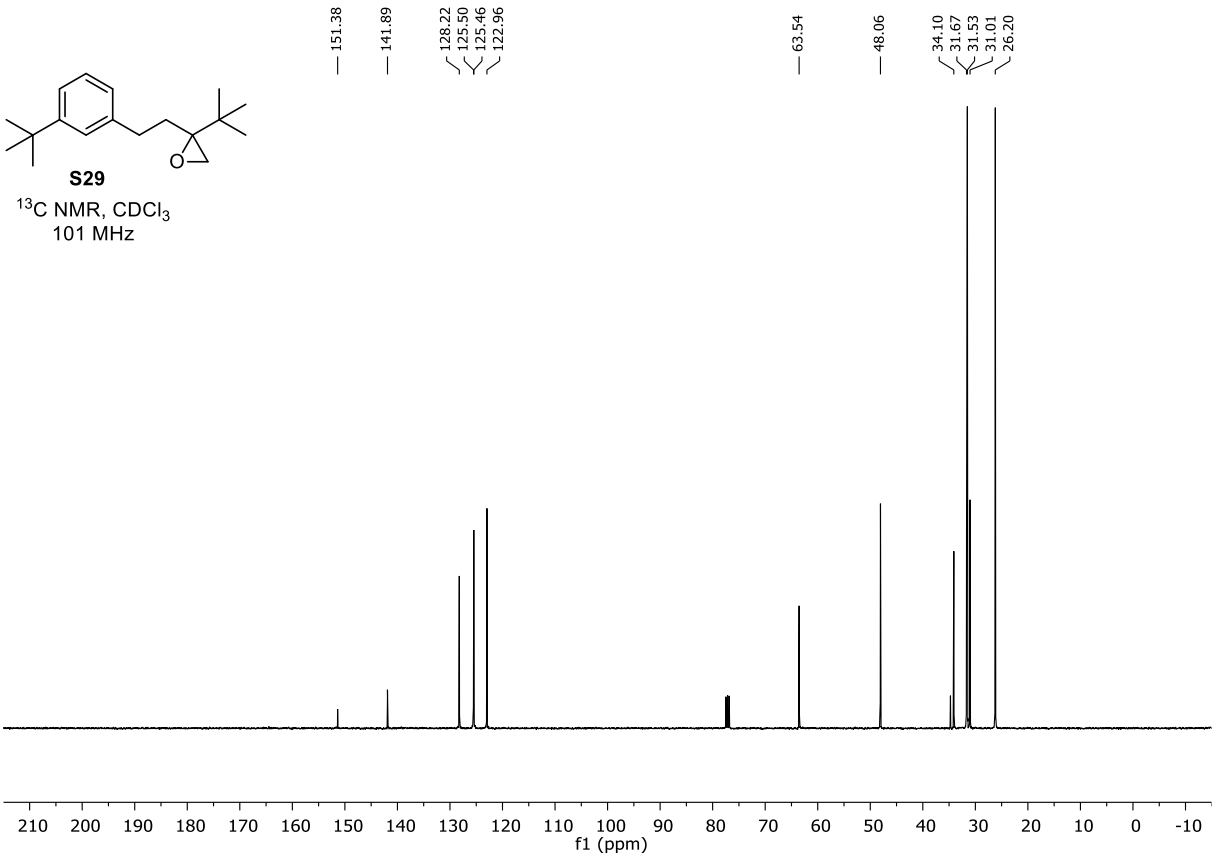

7.23
7.23
7.22
7.22
7.21
7.20
7.20
7.20
7.19
7.01
7.01
7.01
7.00
7.00
6.99
6.99
2.89
2.89
2.88
2.87
2.87
2.86
2.86
2.85
2.81
2.81
2.80
2.80
2.79
2.79
2.78
2.78
2.77
1.31
1.11
O
S28
^{1}H NMR, CDCl$_3$
400 MHz
2.9
1.0
2.0
2.0
8.8
8.8
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


215.07
151.32
141.21
128.13
125.44
122.99
44.12
38.69
34.62
31.39
30.46
26.32
O
S28
^{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)



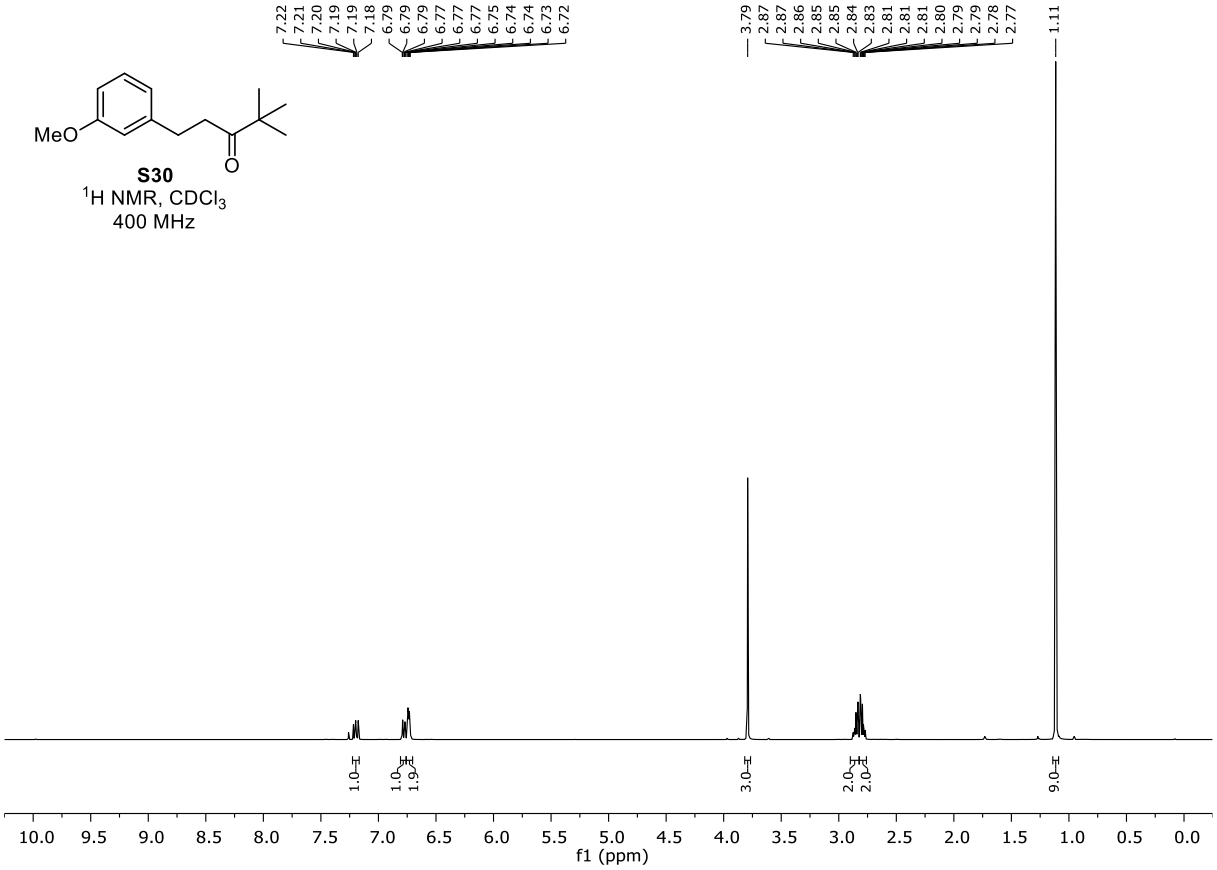
S29

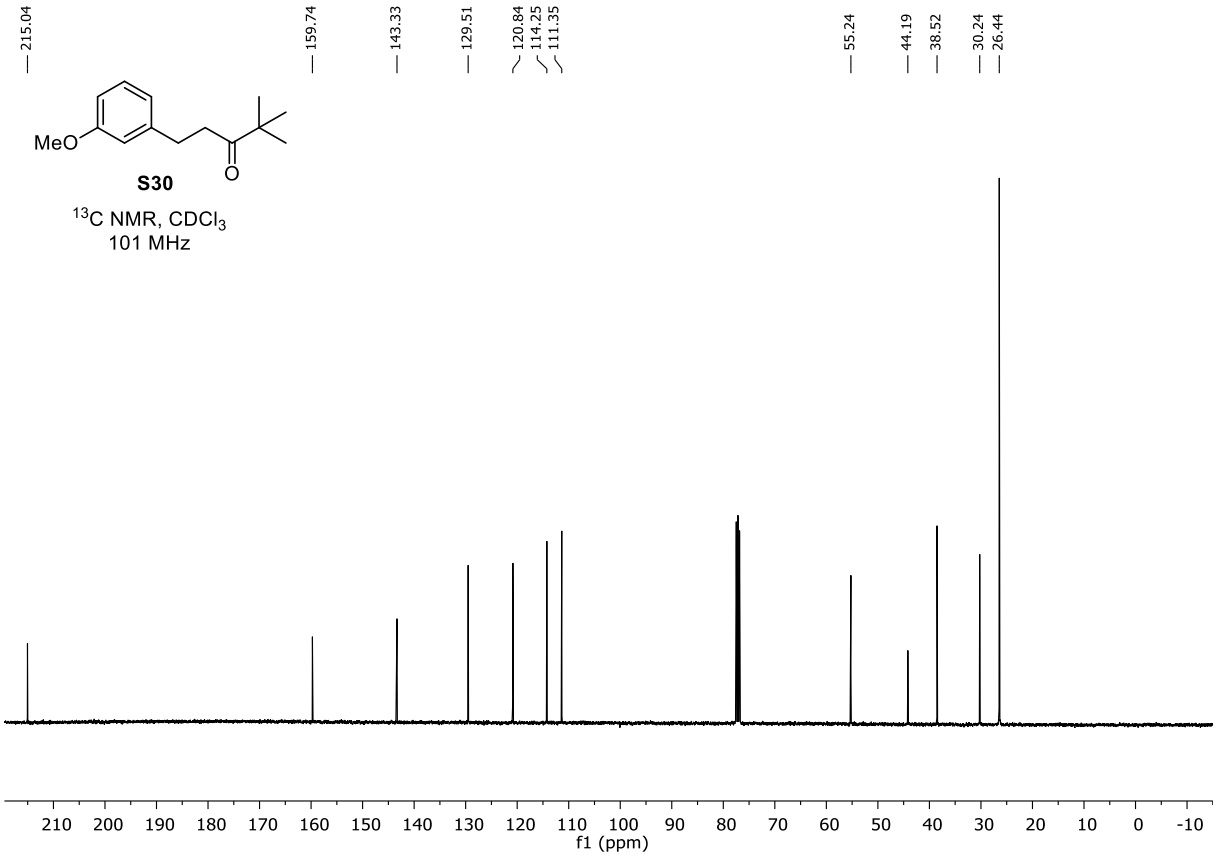
^{1}H NMR, $CDCl_3$
400 MHz

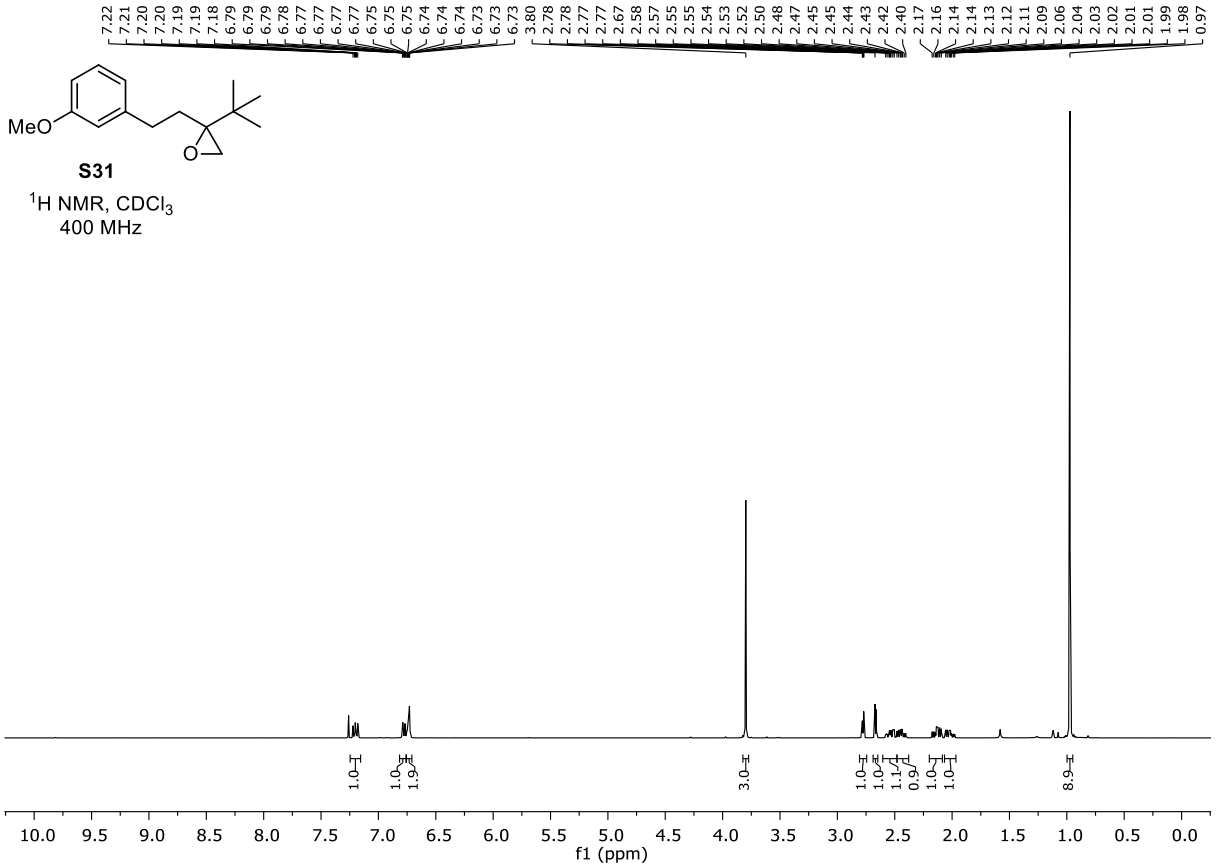


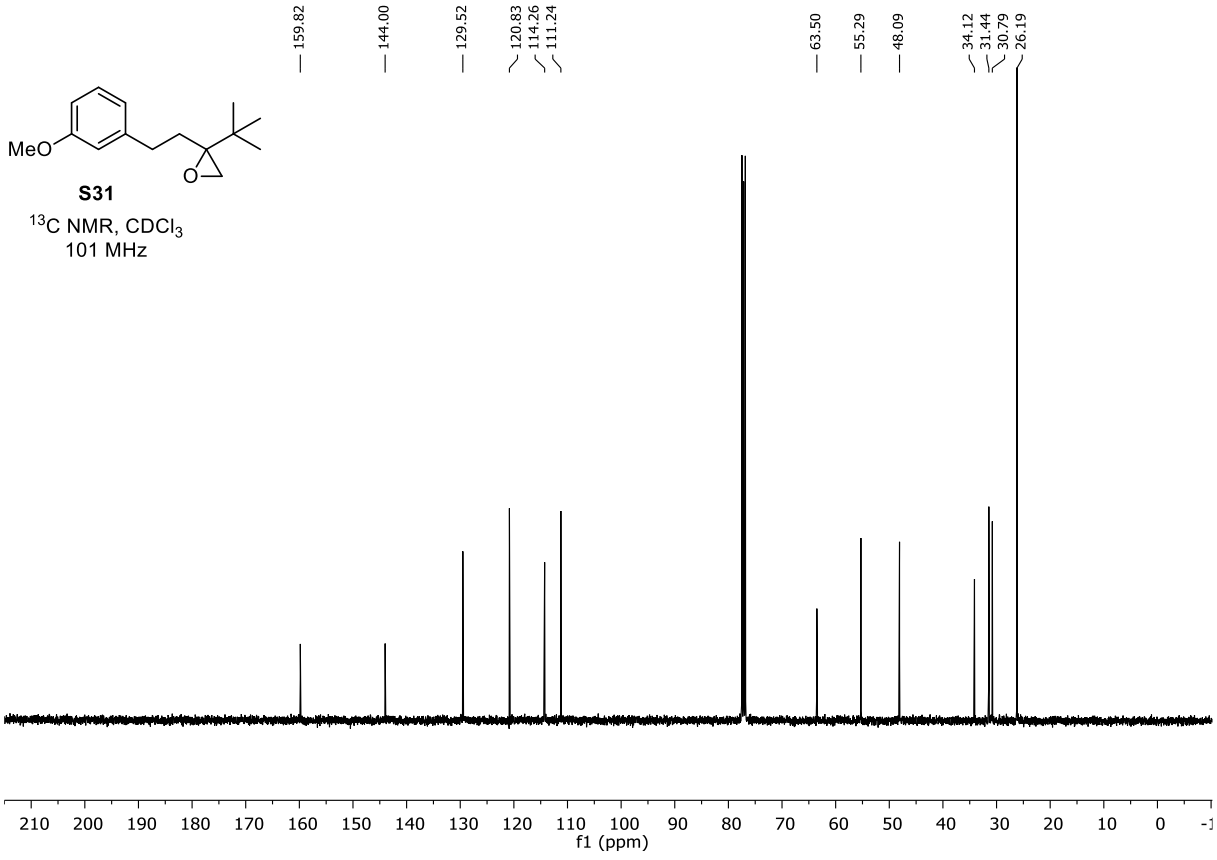
S29

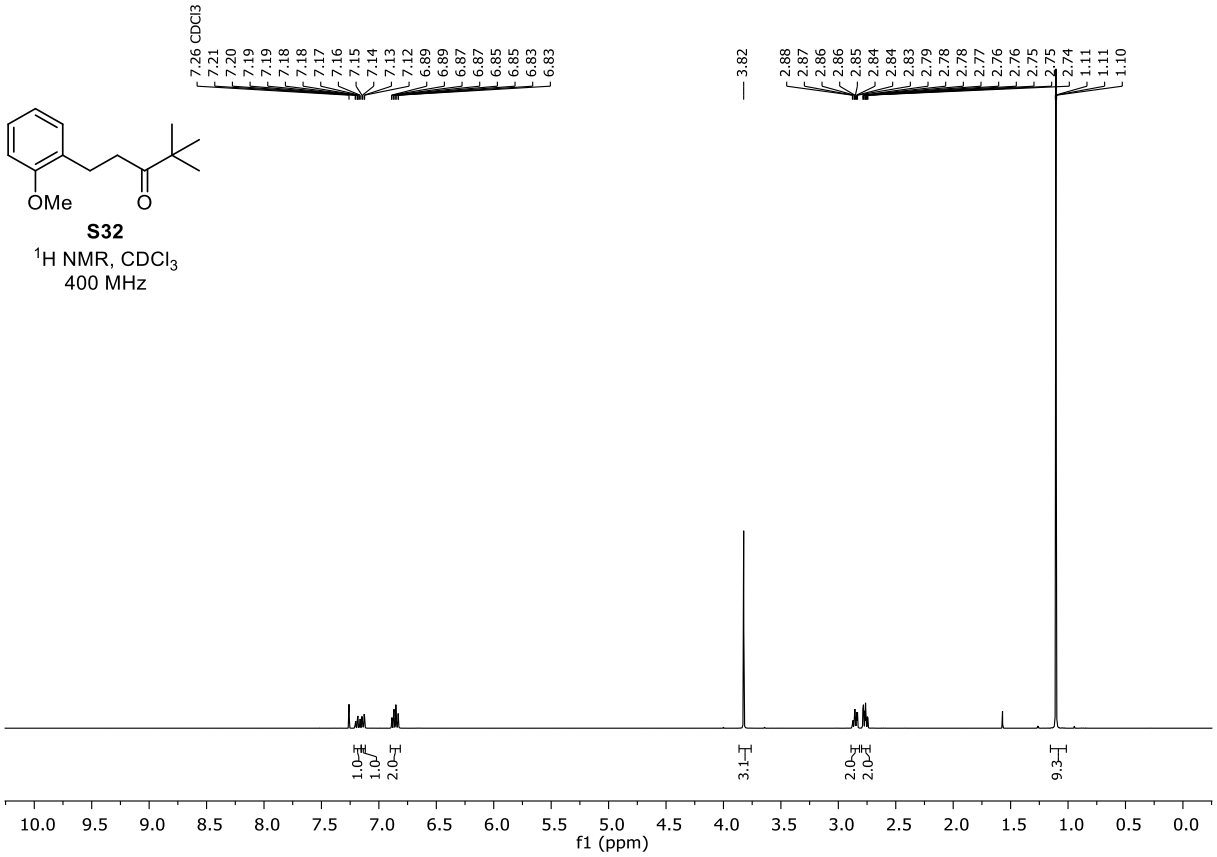
^{13}C NMR, $CDCl_3$
101 MHz


7.22
7.21
7.20
7.19
7.19
7.18
6.79
6.79
6.79
6.77
6.77
6.77
6.75
6.74
6.74
6.73
6.72
3.79
2.87
2.87
2.86
2.85
2.85
2.84
2.83
2.81
2.81
2.81
2.80
2.79
2.79
2.78
2.77
1.11
MeO
O
S30
1H NMR, CDCl3
400 MHz
1.0
1.0
1.9
3.0
2.0
2.0
9.0
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)


215.04
159.74
143.33
129.51
120.84
114.25
111.35
55.24
44.19
38.52
30.24
26.44
MeO
O
S30
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)

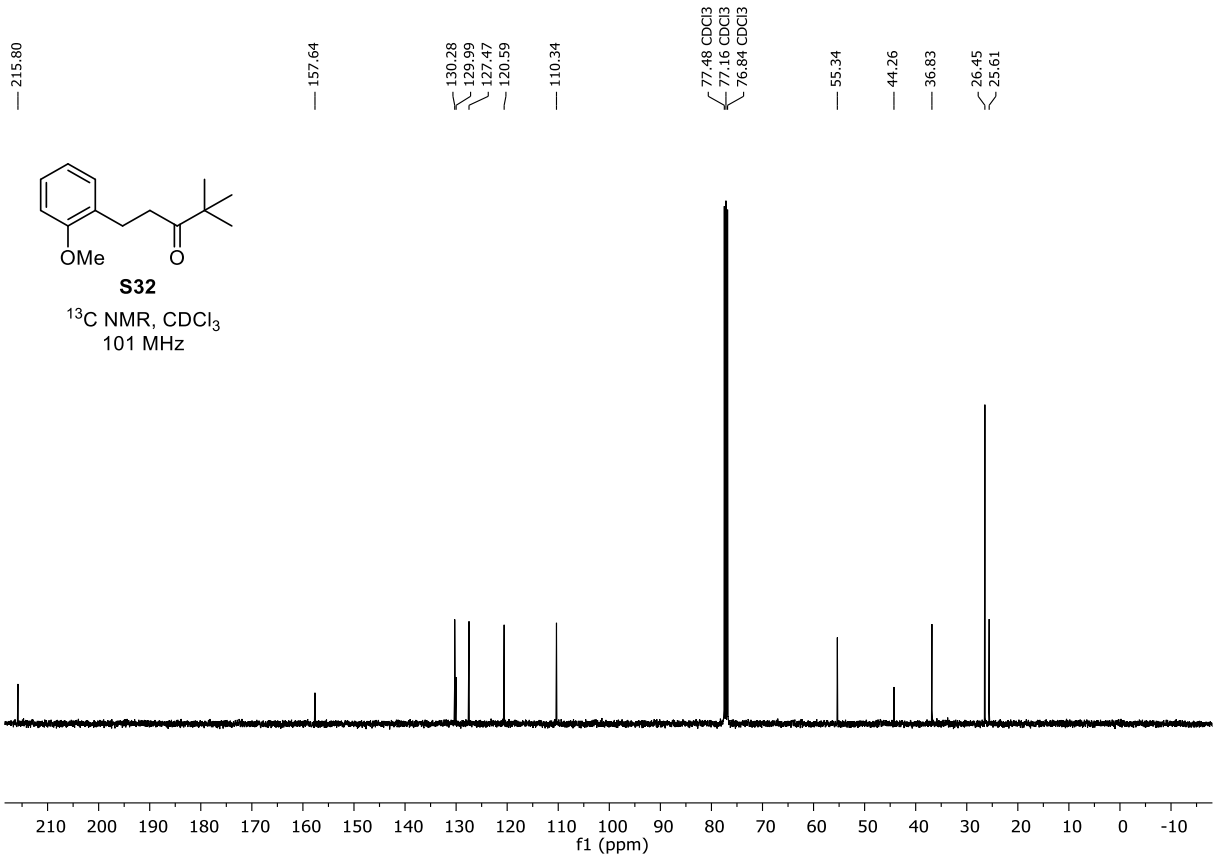

MeO
O
S31
1H NMR, CDCl3
400 MHz
f1 (ppm)


MeO
O
S31
13C NMR, CDCl3
101 MHz
f1 (ppm)



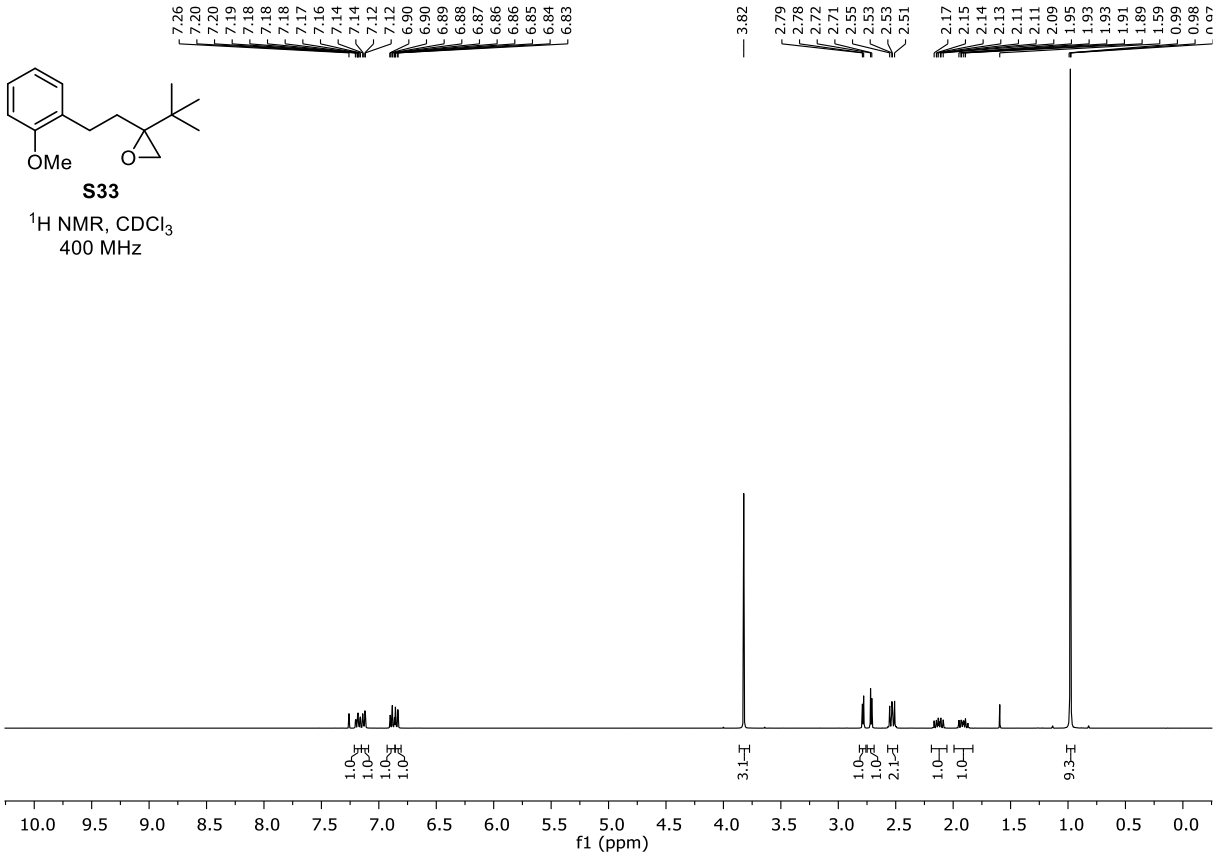
S32

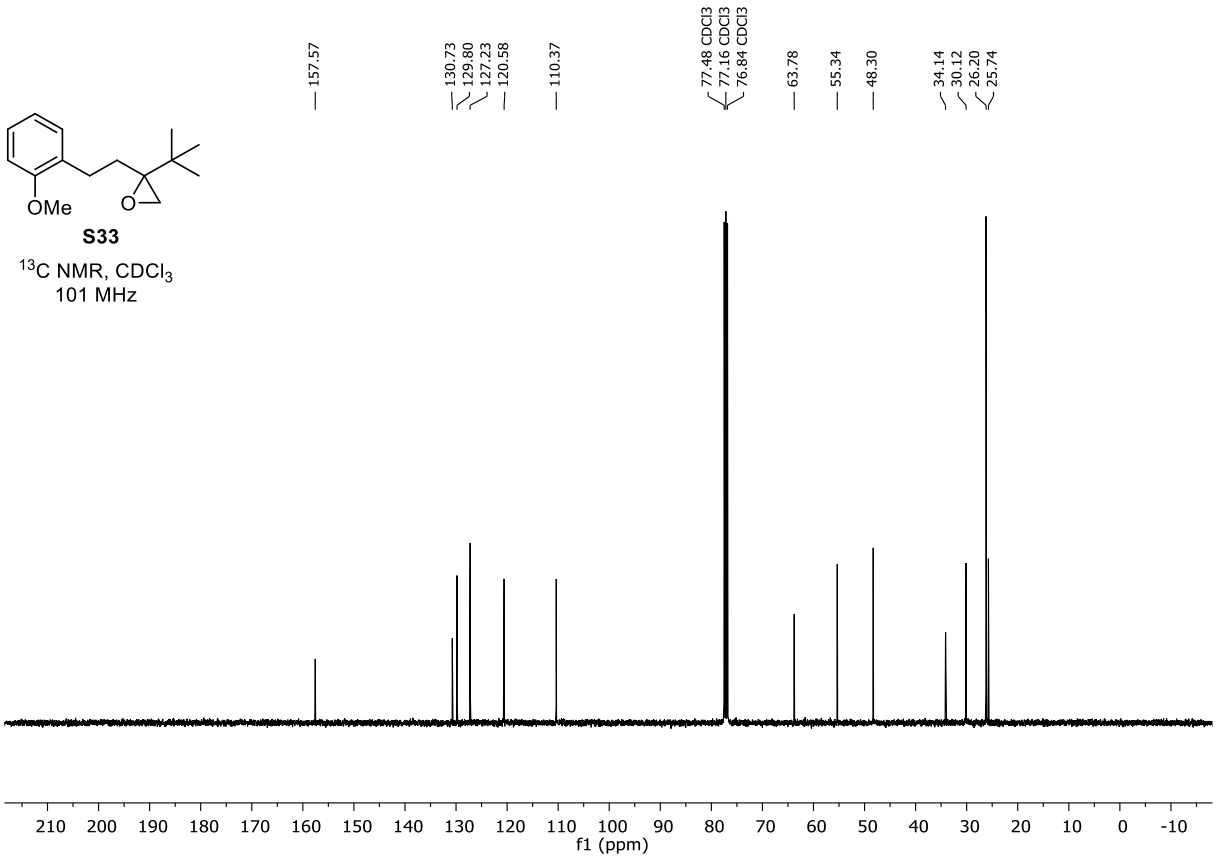
^{1}H NMR, $CDCl_3$
400 MHz

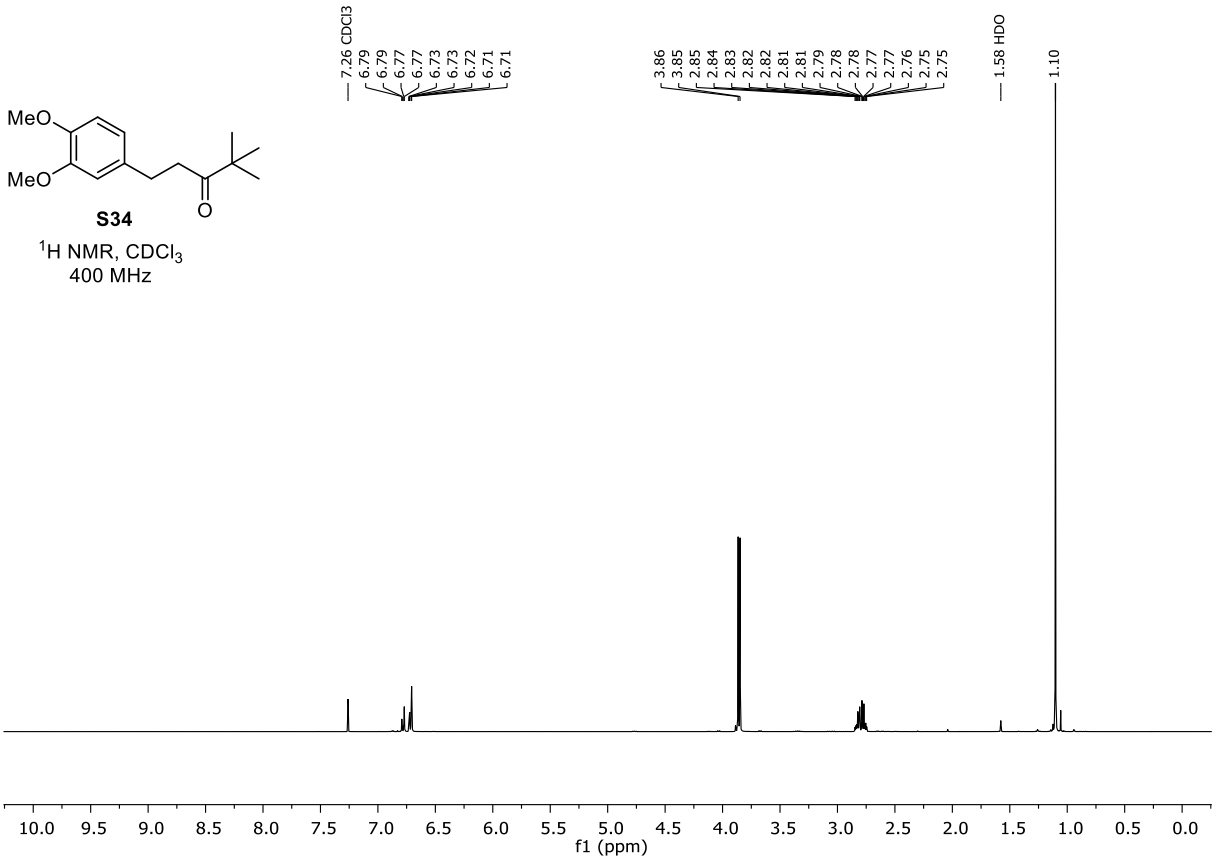


S32

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

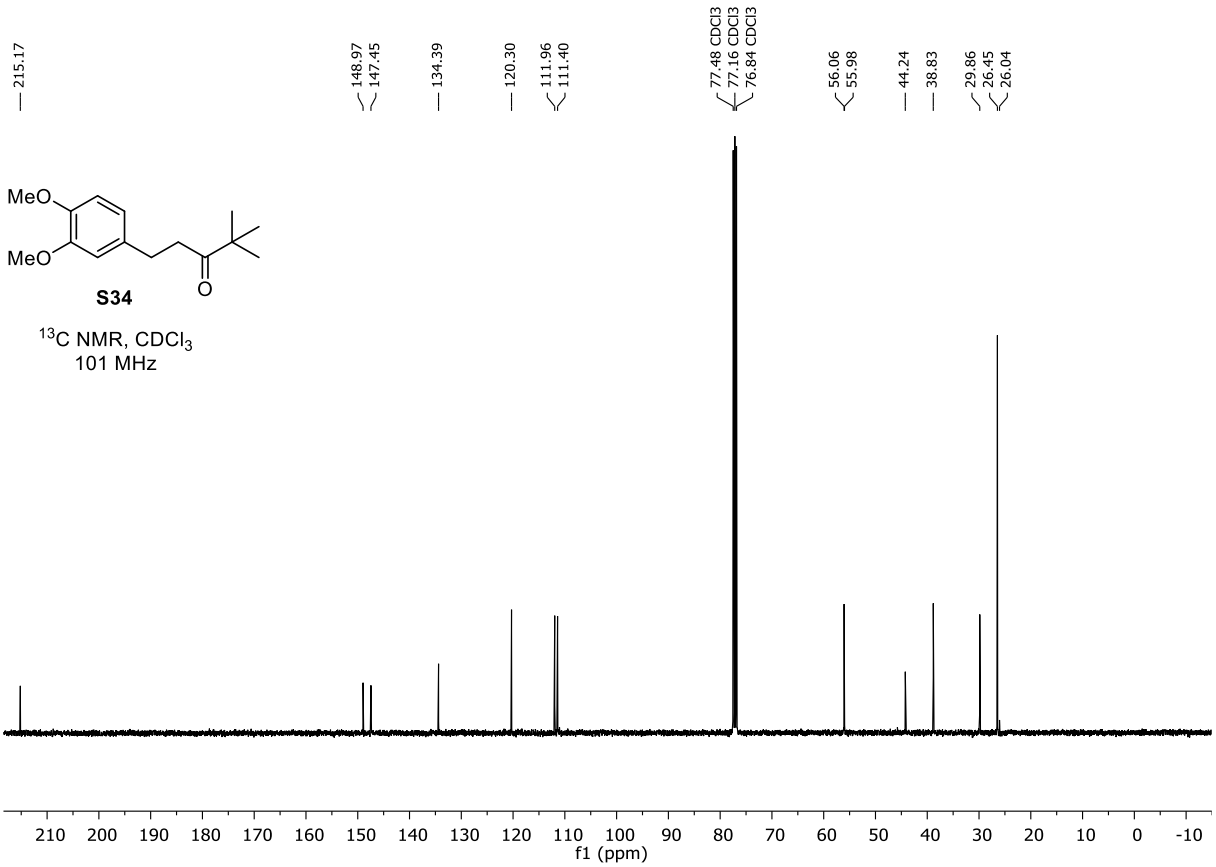

OMe
O
S33
1H NMR, CDCl3
400 MHz
f1 (ppm)


OMe
O
S33
13C NMR, CDCl3
101 MHz
f1 (ppm)



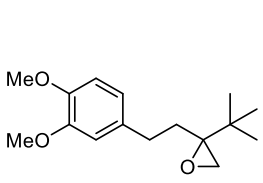
S34

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



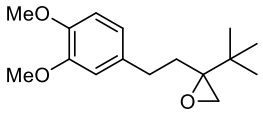
S34

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



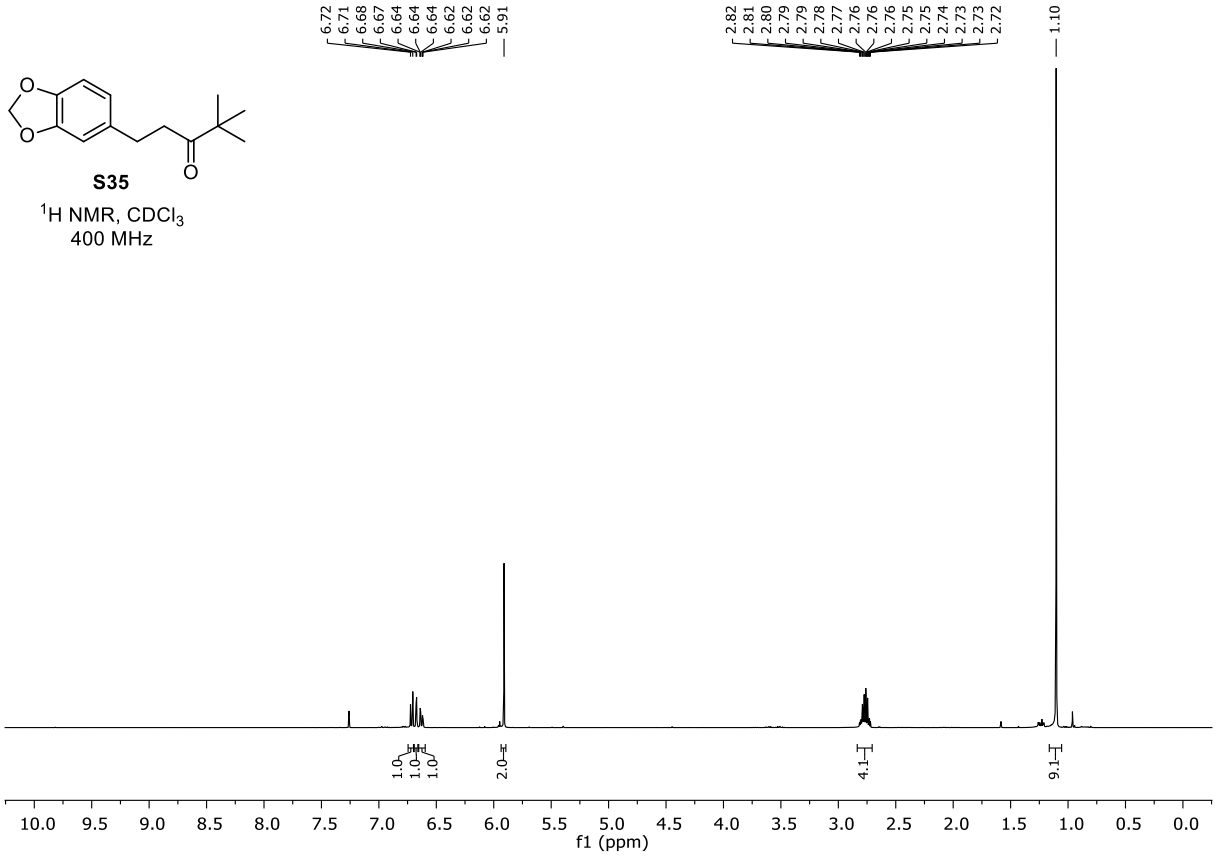
11a

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



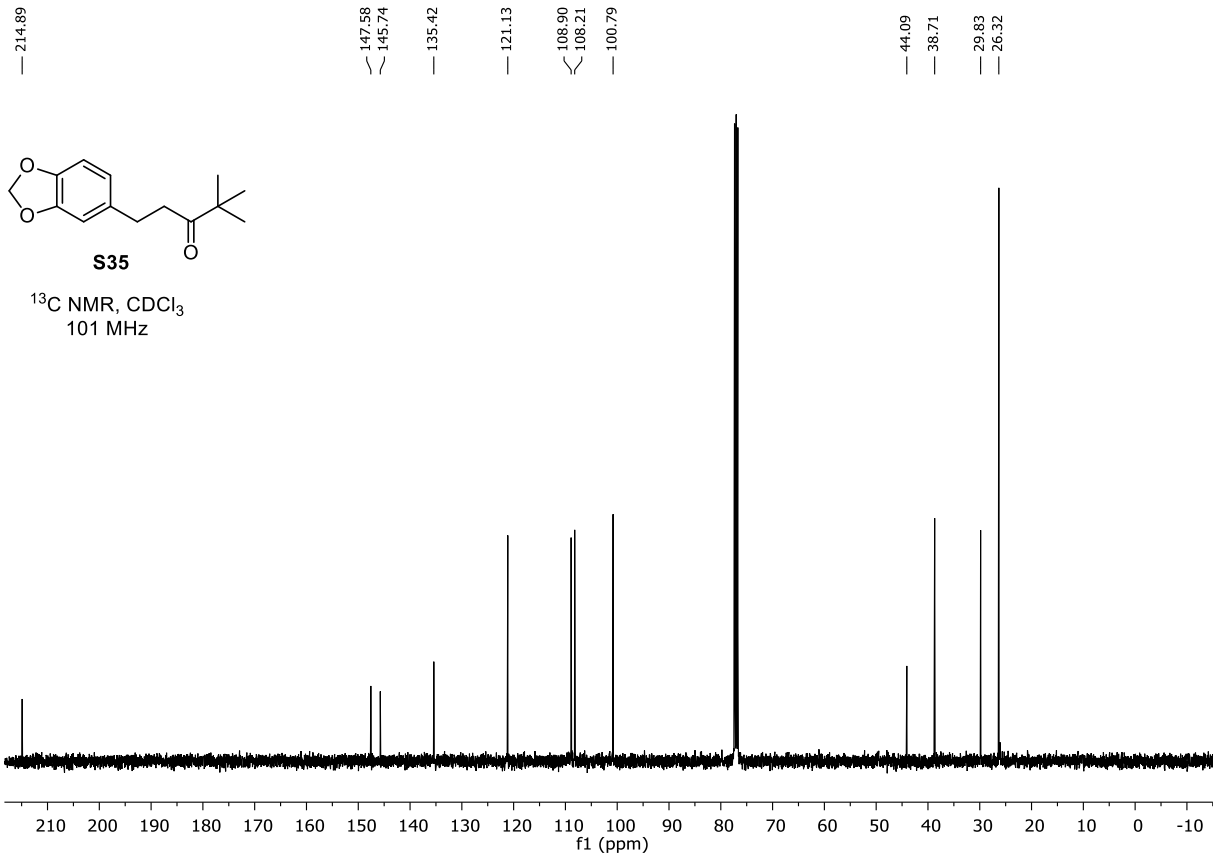
11a

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



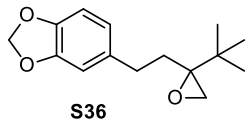
S35

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



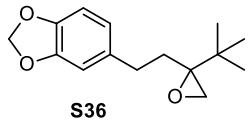
S35

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



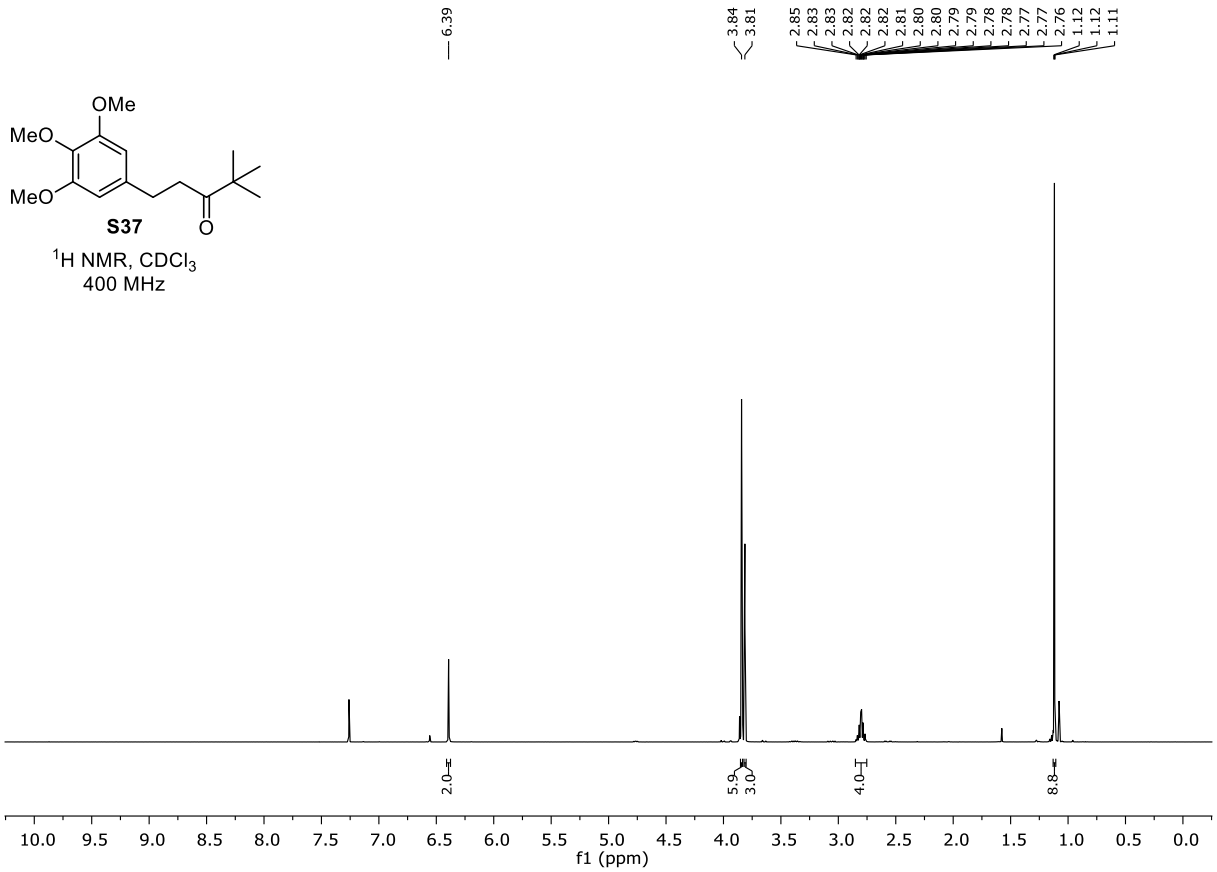
S36

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

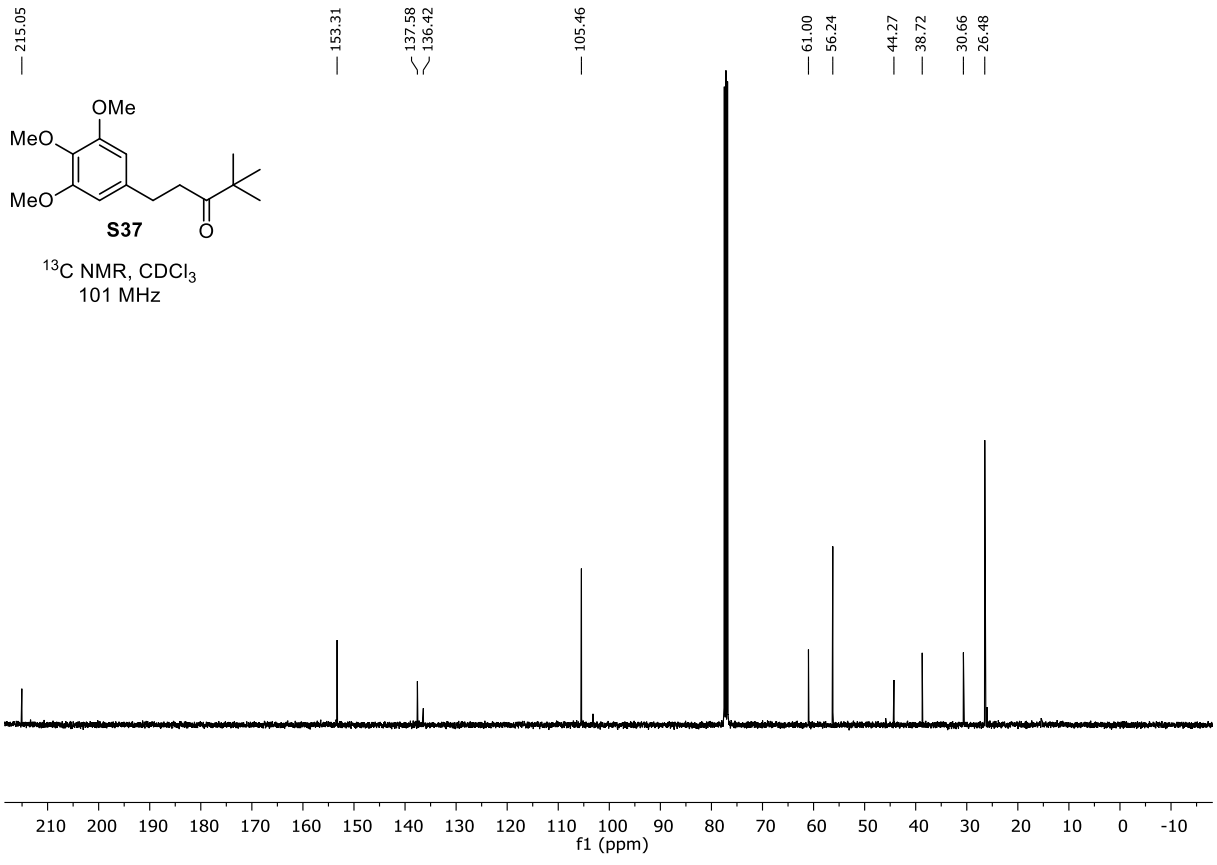


S36

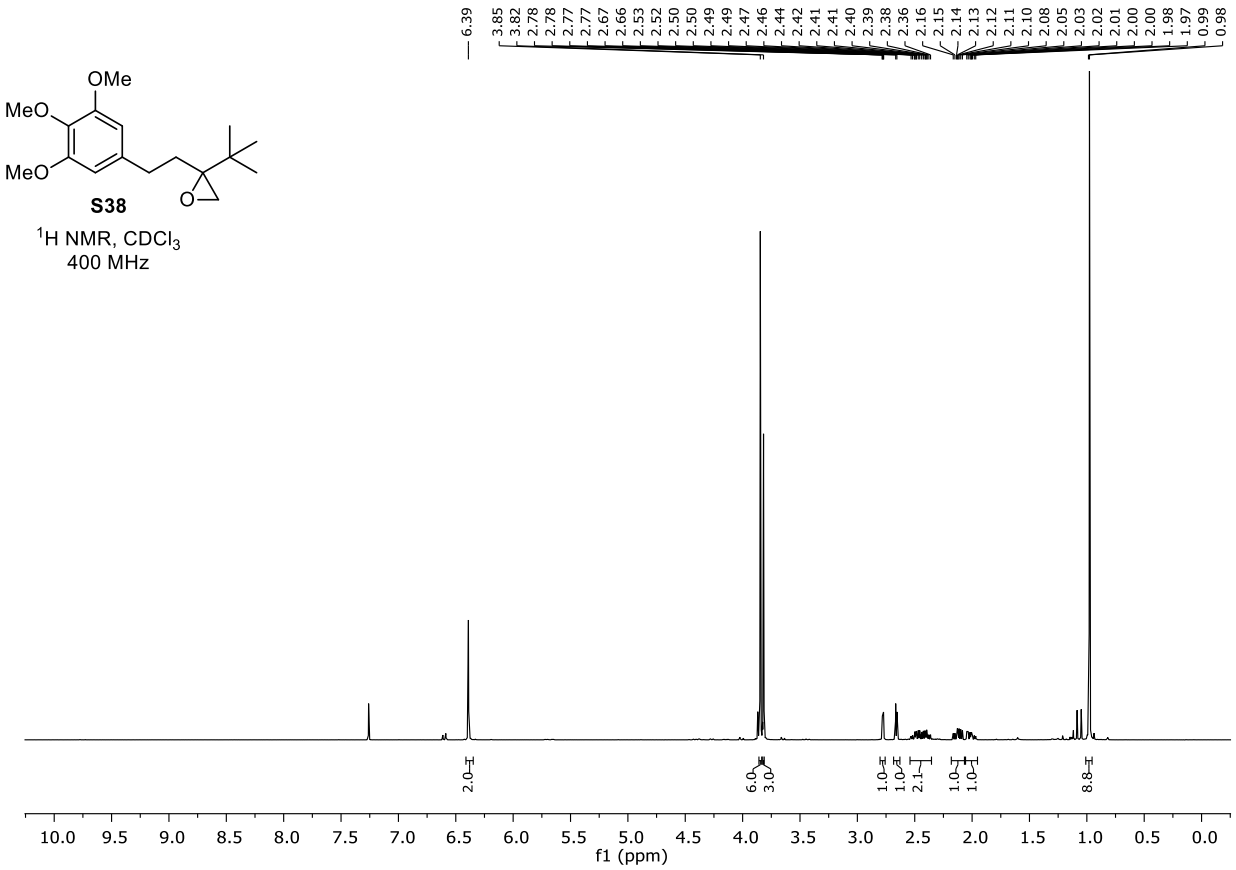
^{13}C NMR, $CDCl_3$
101 MHz

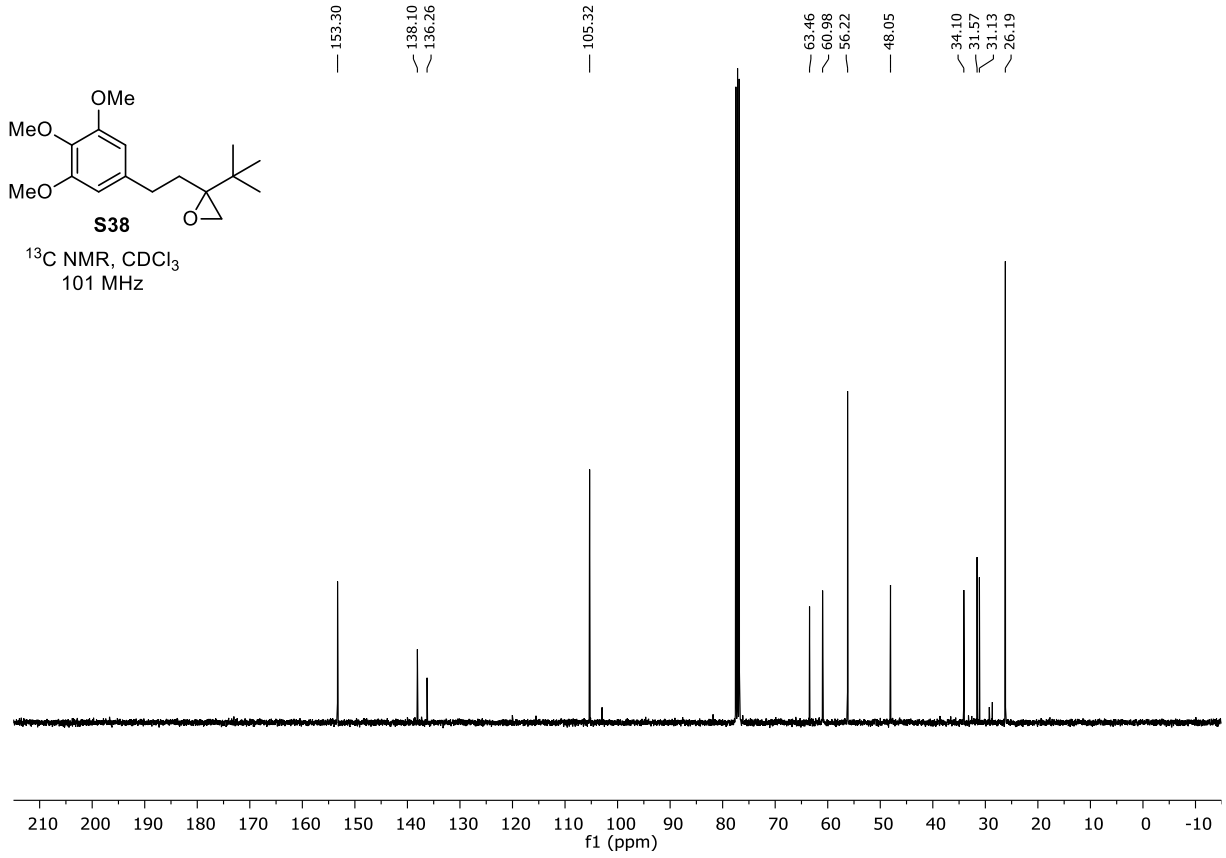


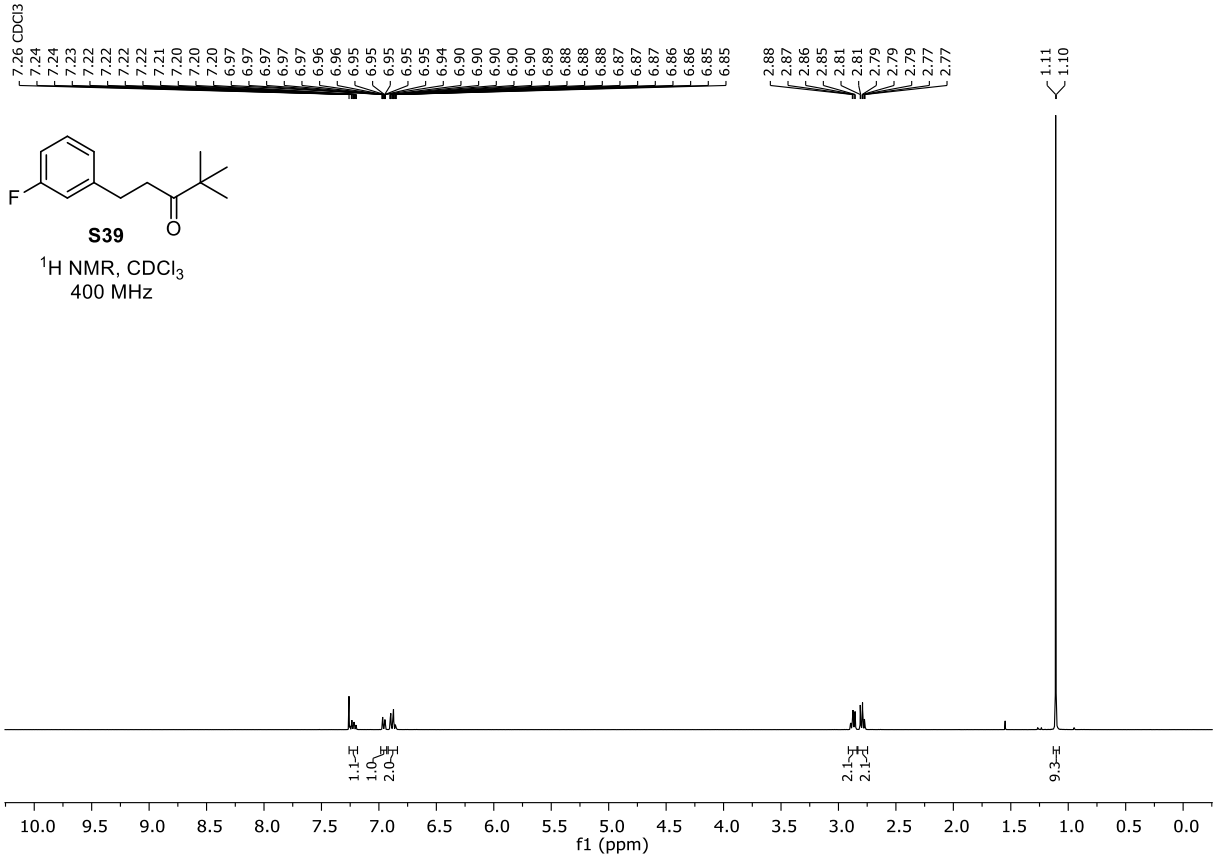
^{1}H NMR, $CDCl_3$
400 MHz

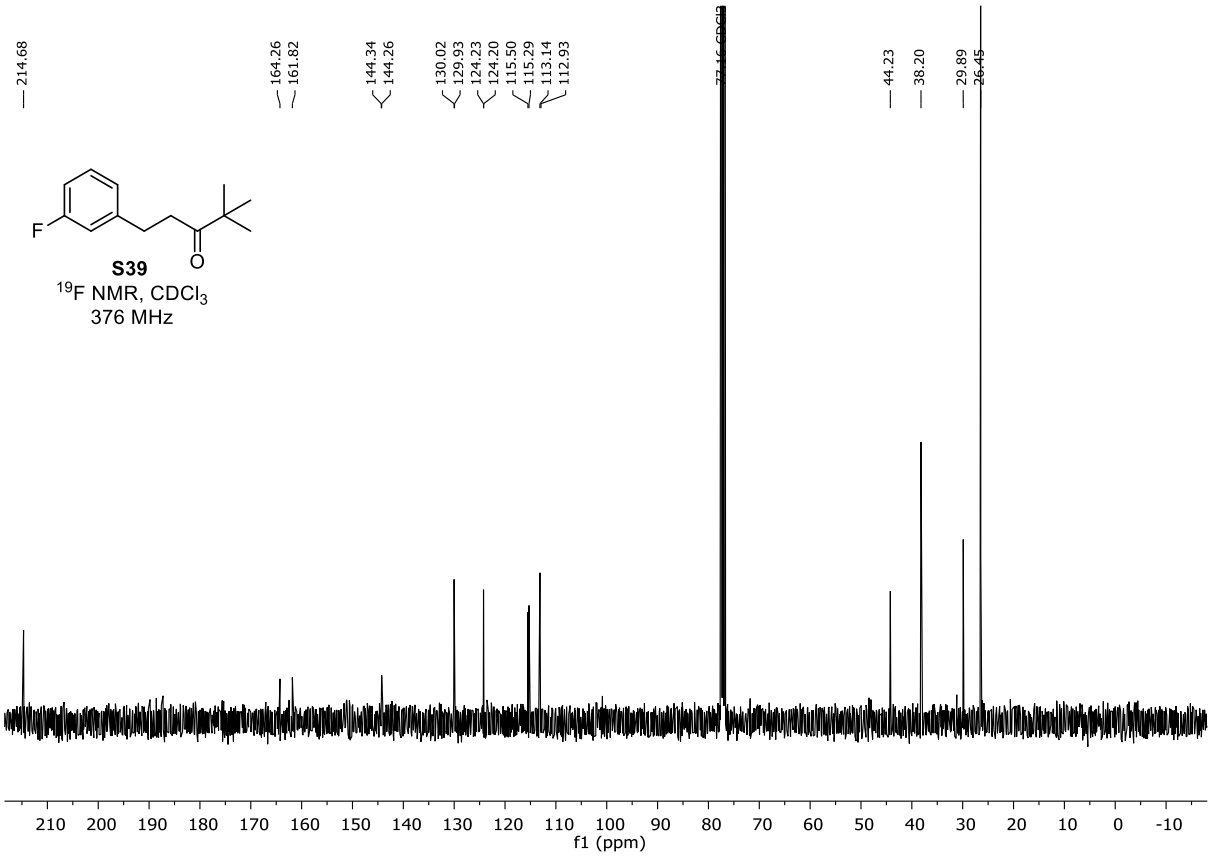


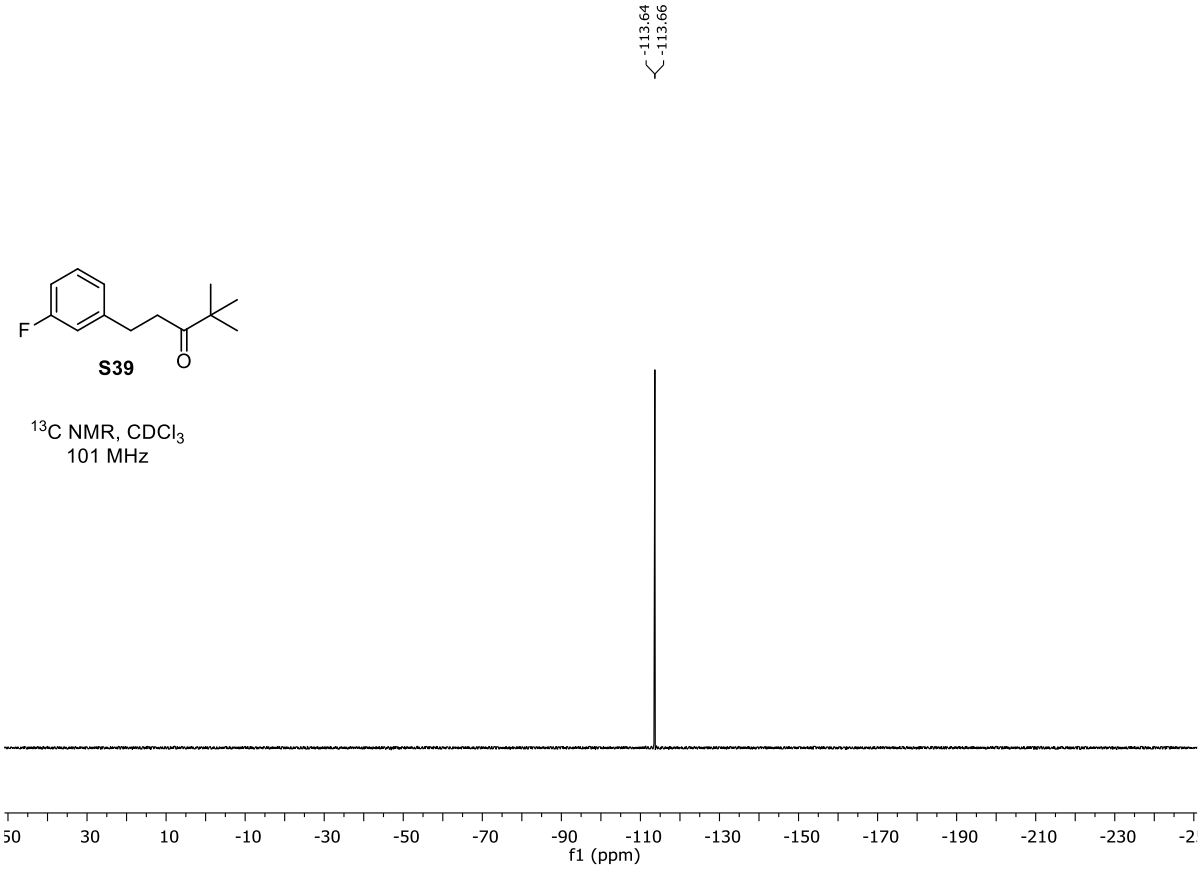
^{13}C NMR, $CDCl_3$
101 MHz

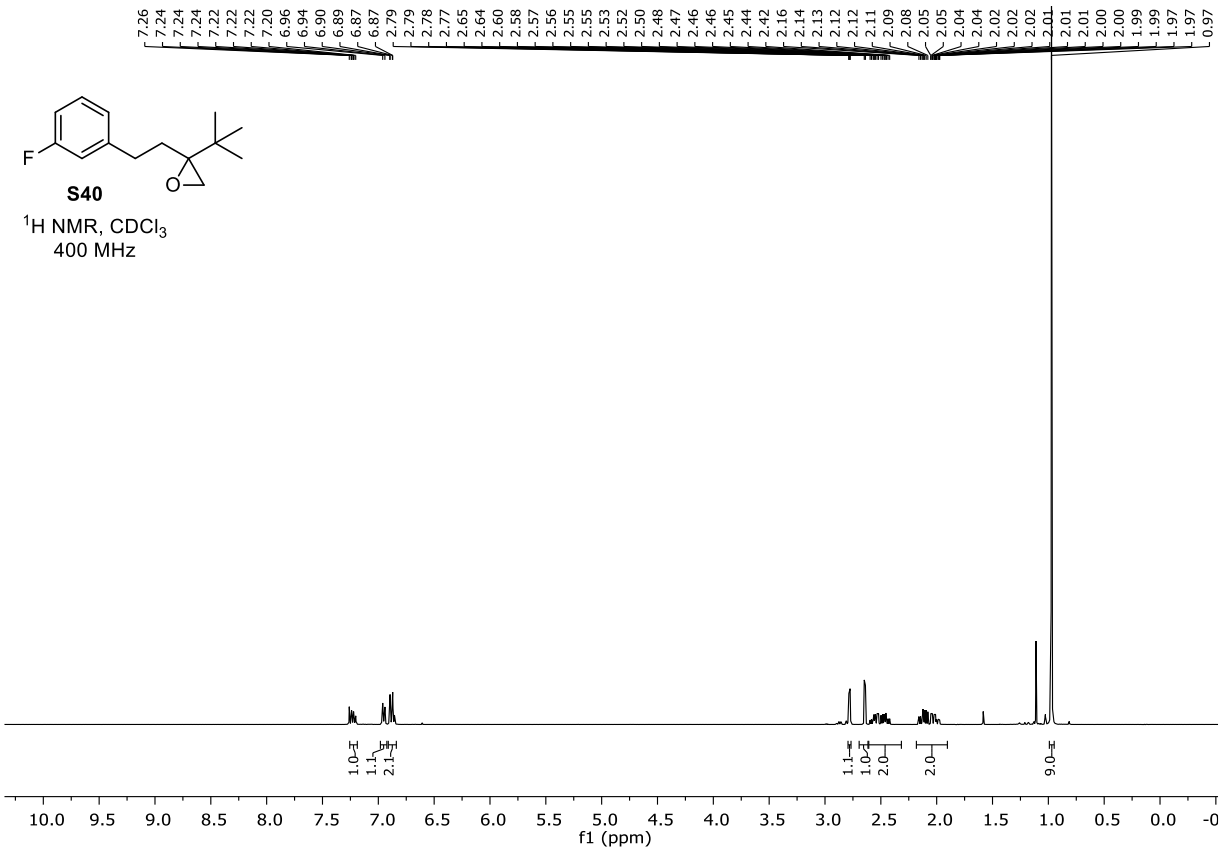

OMe
MeO
MeO
O
S38
^{1}H NMR, CDCl$_3$
400 MHz
6.39
3.85
3.82
2.78
2.78
2.77
2.77
2.67
2.66
2.53
2.52
2.50
2.50
2.49
2.49
2.47
2.46
2.44
2.42
2.41
2.41
2.40
2.39
2.38
2.36
2.16
2.15
2.14
2.13
2.12
2.11
2.10
2.08
2.05
2.03
2.02
2.01
2.00
2.00
1.98
1.97
0.99
0.98
2.0
6.0
3.0
1.0
1.0
2.1
1.0
1.0
8.8
10.0 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)

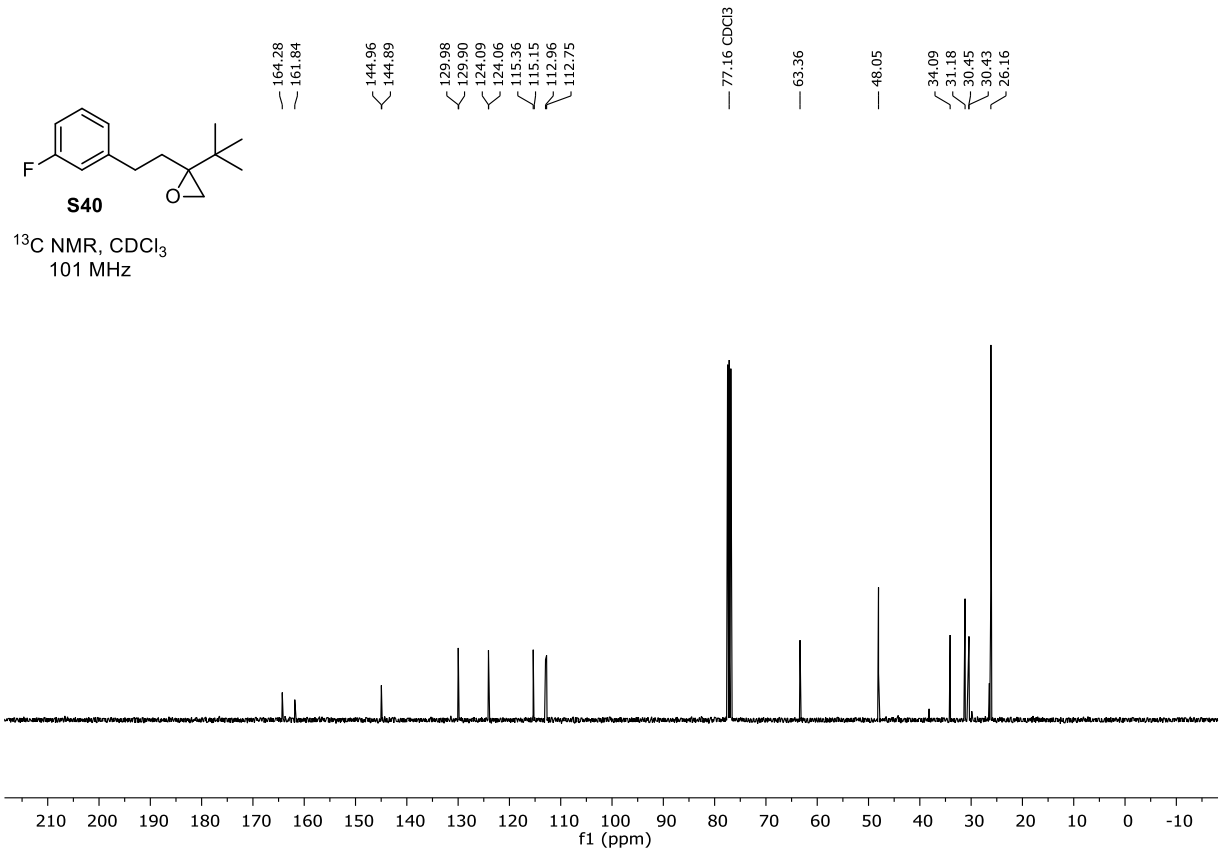

OMe
MeO
MeO
O
S38
^{13}C NMR, CDCl$_3$
101 MHz
153.30
138.10
136.26
105.32
63.46
60.98
56.22
48.05
34.10
31.57
31.13
26.19
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

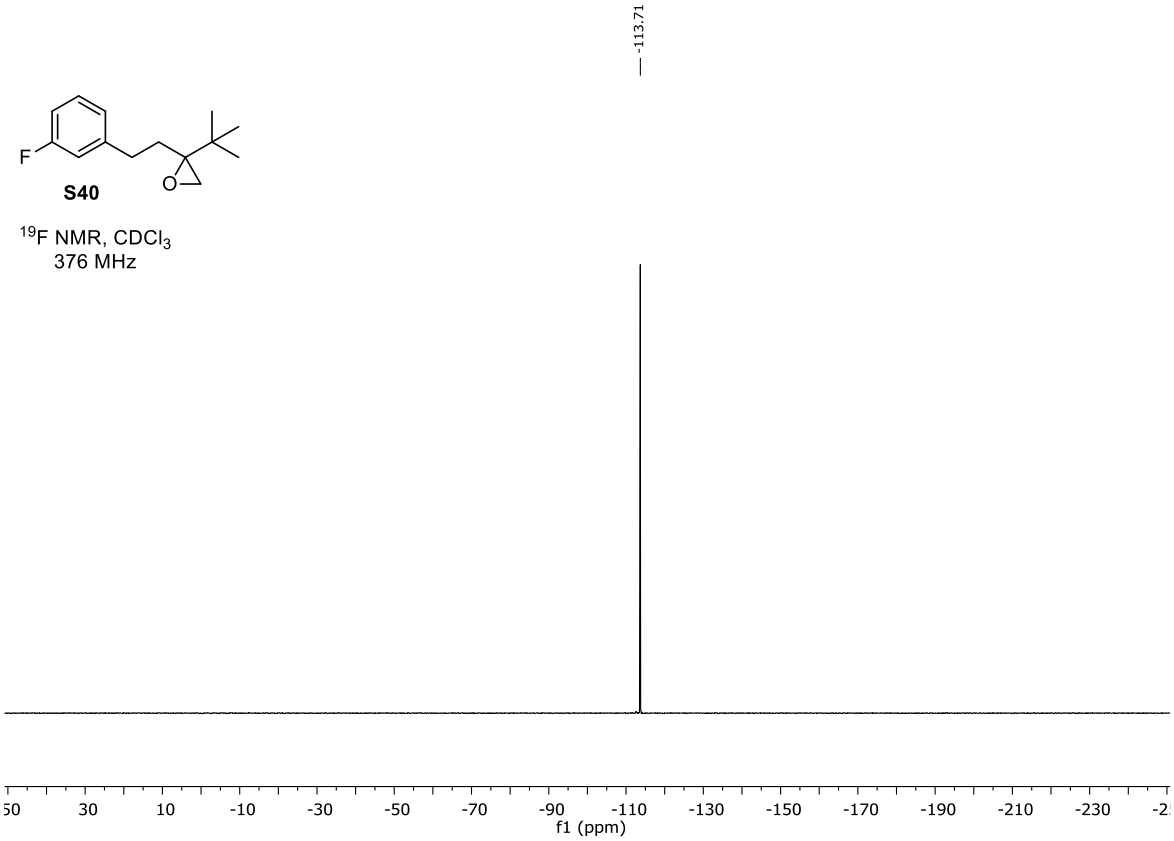

7.26 CDCl3
F
O
S39
1H NMR, CDCl3
400 MHz
f1 (ppm)


F
O
S39
19F NMR, CDCl3
376 MHz
f1 (ppm)


-113.64
-113.66
F
O
S39
^{13}C NMR, $CDCl_3$
101 MHz
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

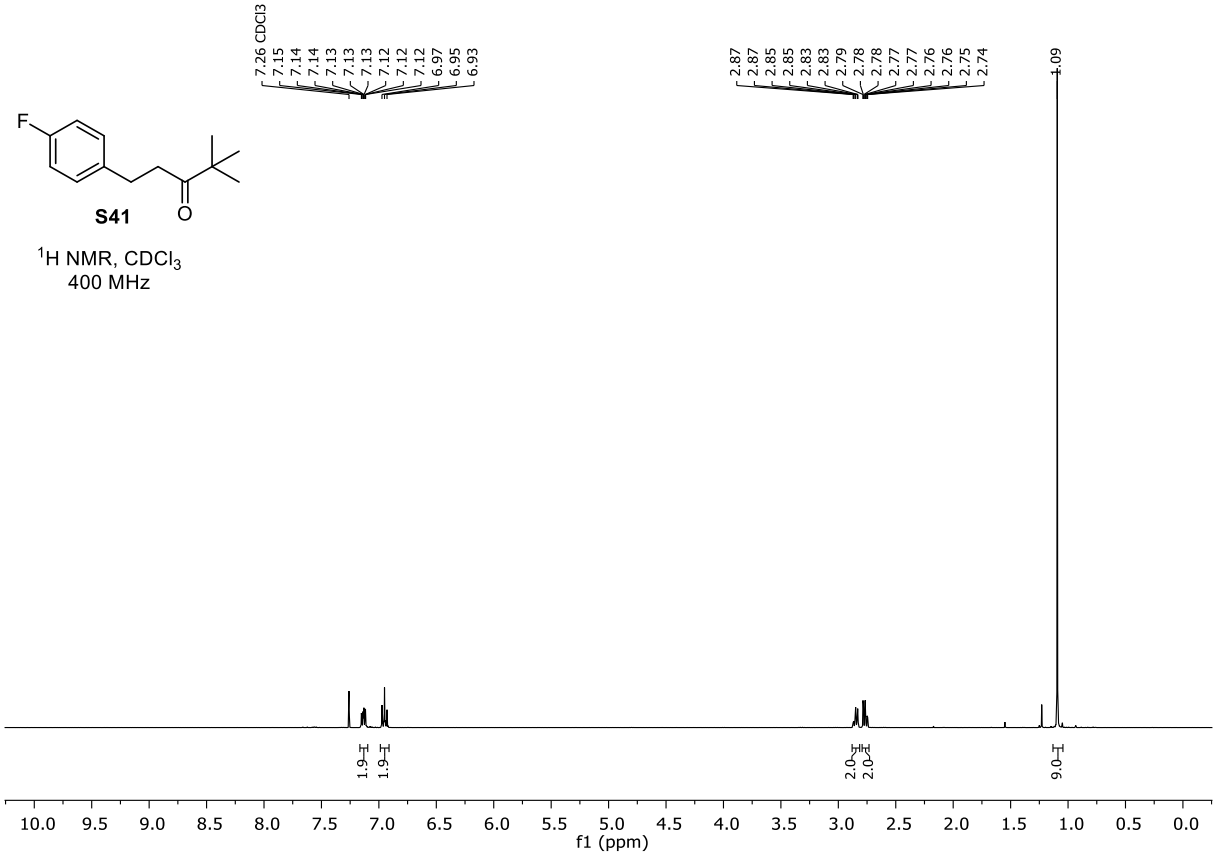

F
O
S40
1H NMR, CDCl3
400 MHz
f1 (ppm)


F
O
S40
13C NMR, CDCl3
101 MHz
f1 (ppm)

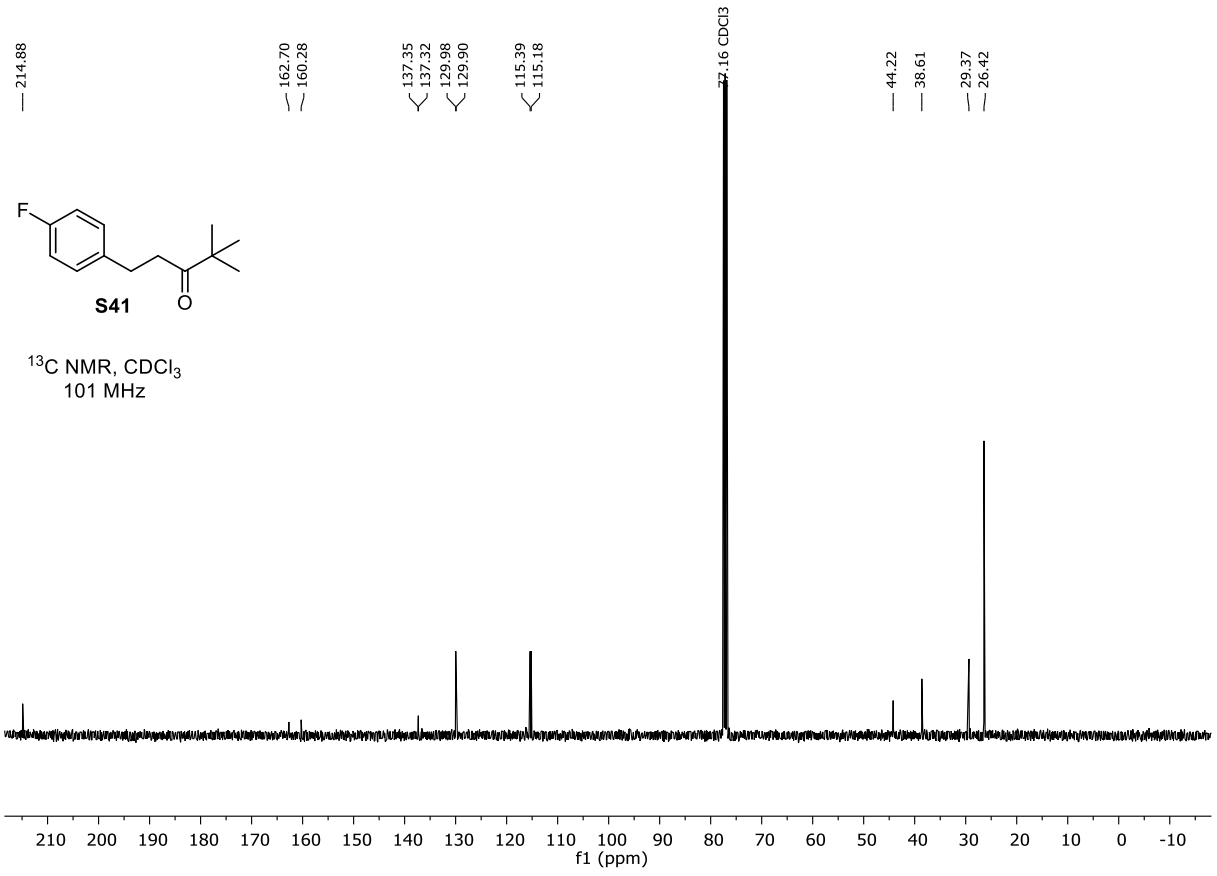


S40

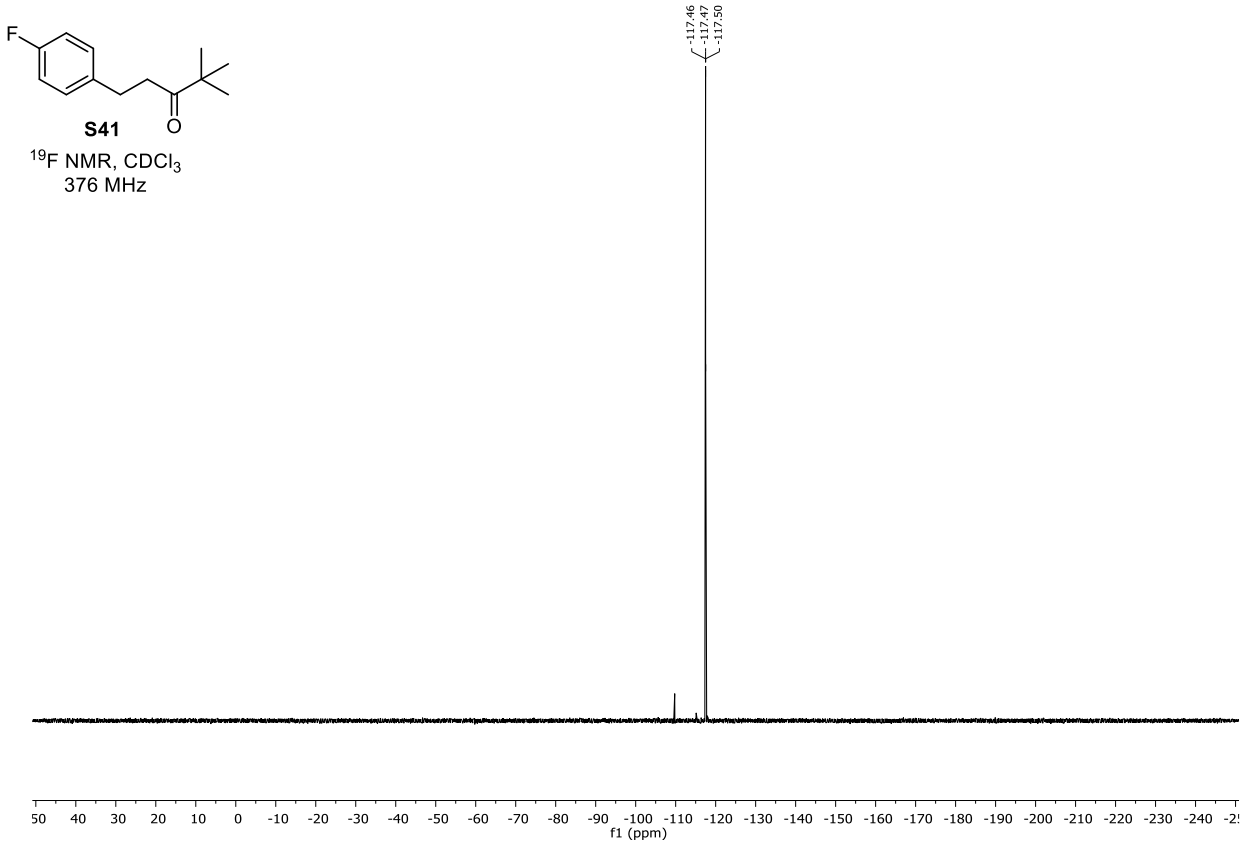
^{19}F NMR, $CDCl_3$
376 MHz

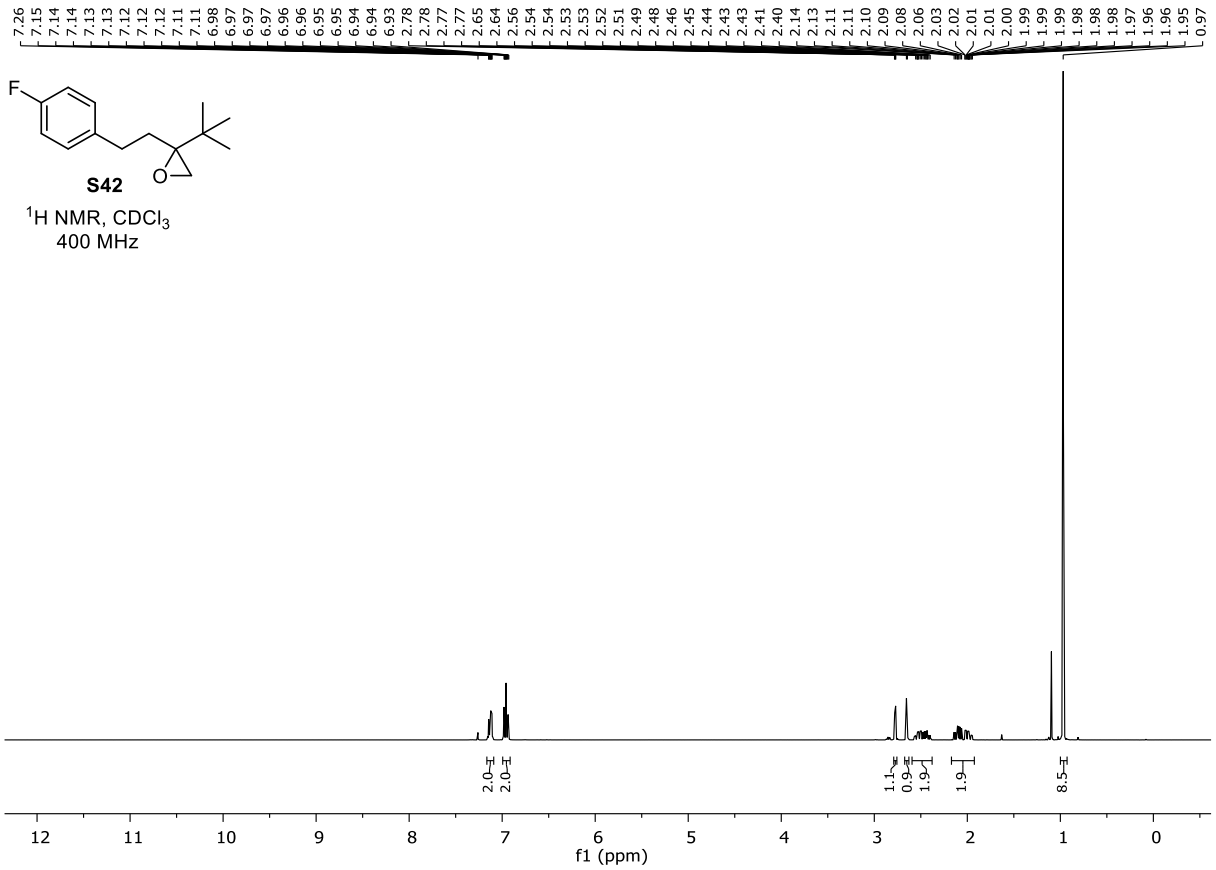


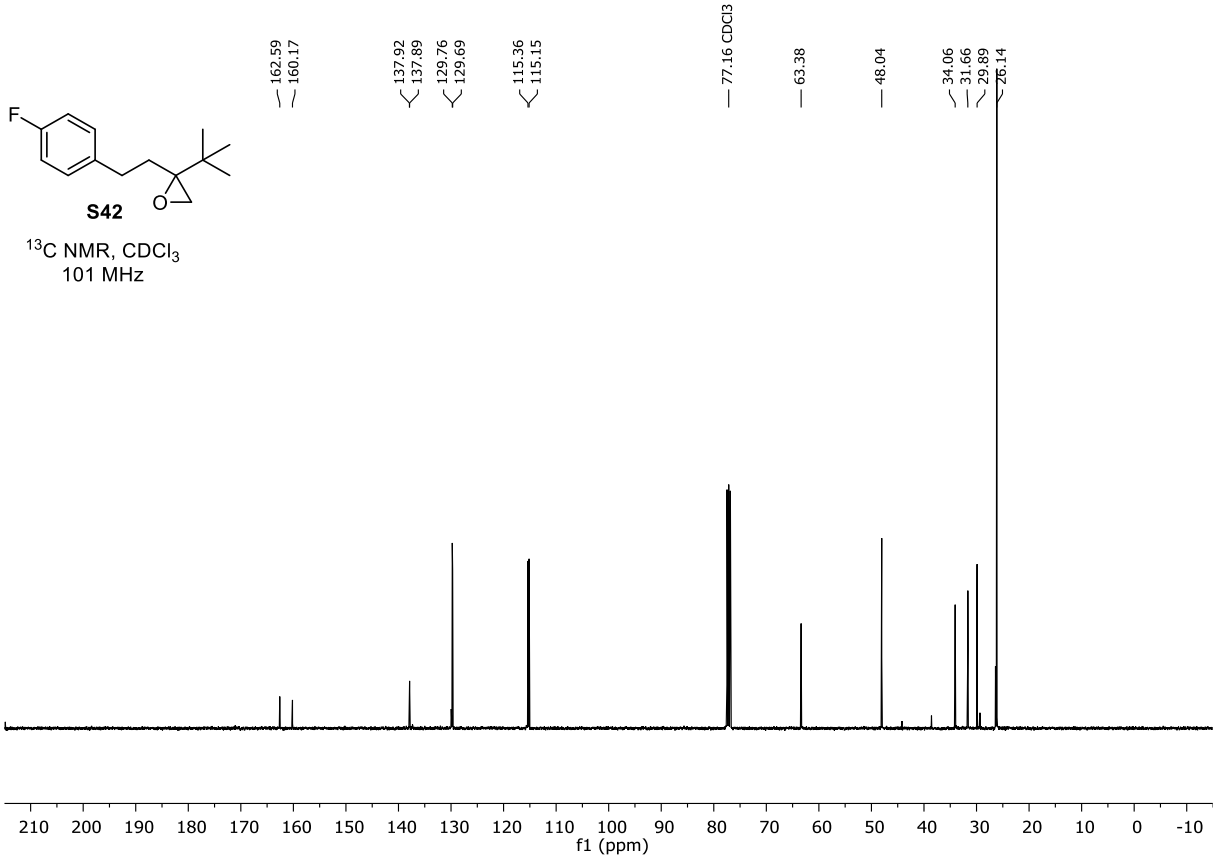
^{1}H NMR, $CDCl_3$
400 MHz

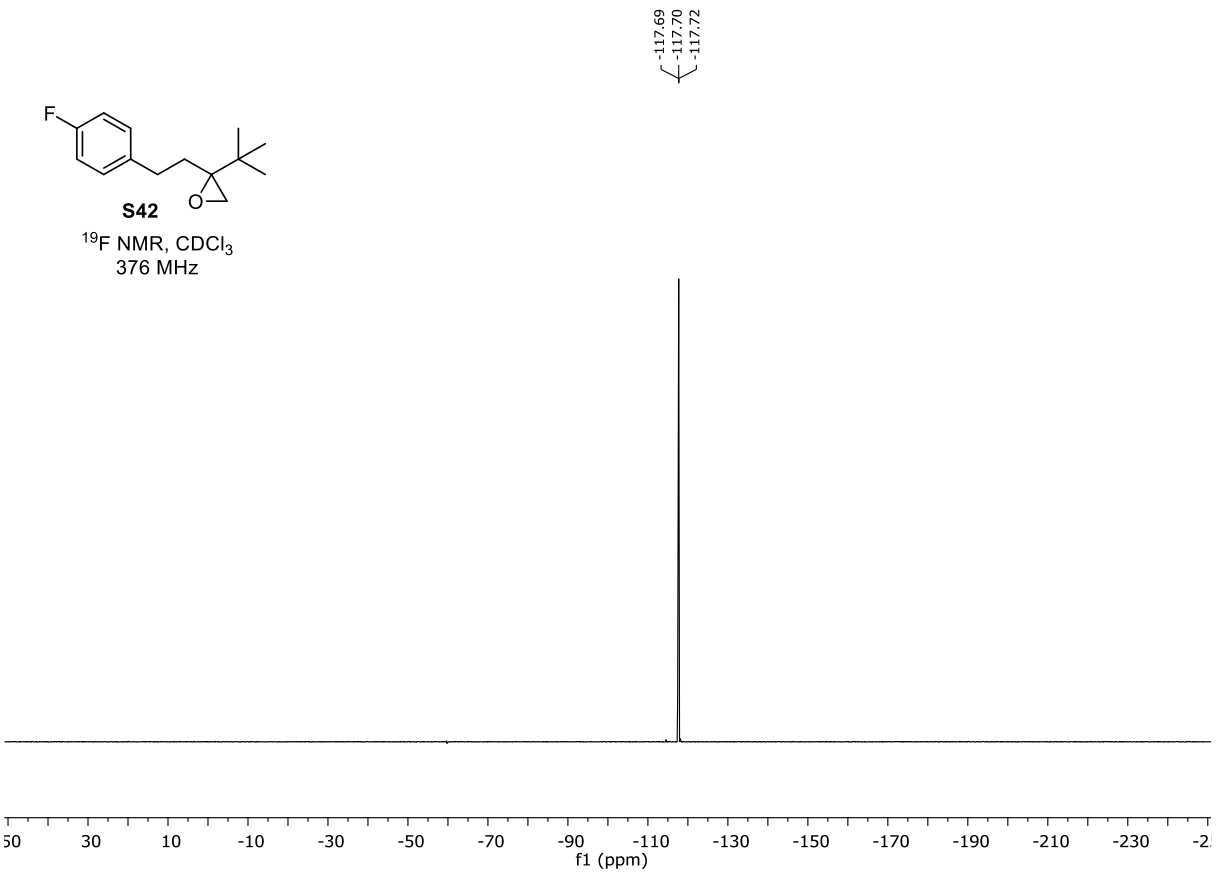


^{13}C NMR, $CDCl_3$
101 MHz


F
O
S41
19F NMR, CDCl3
376 MHz
-117.46
-117.47
-117.50
50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

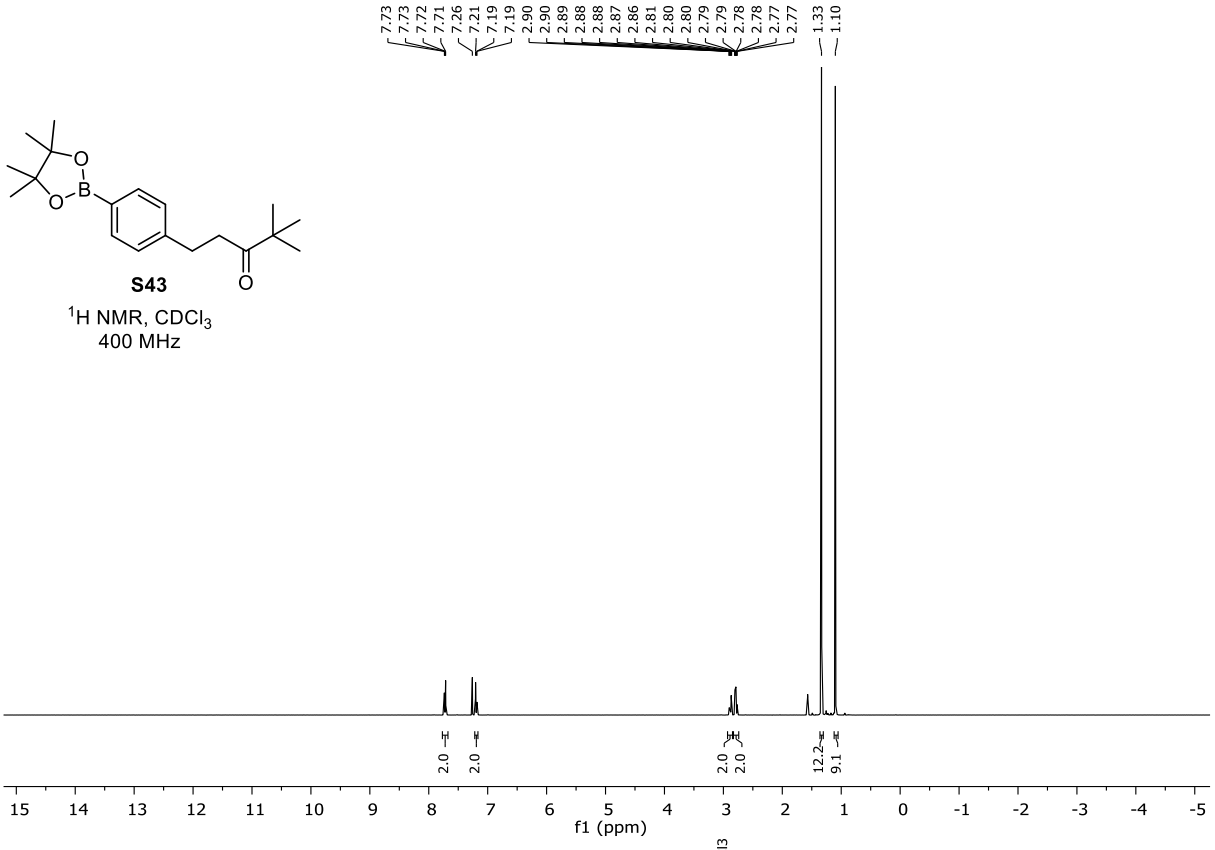

F
O
S42
1H NMR, CDCl3
400 MHz
f1 (ppm)

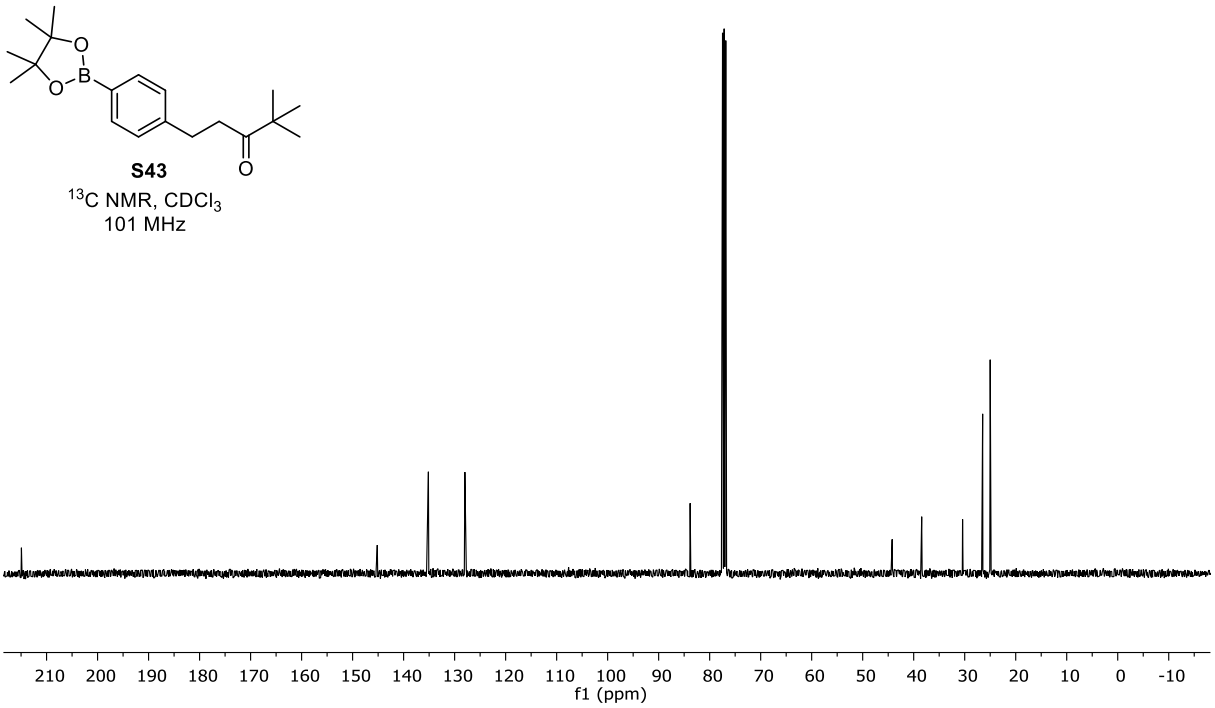

F
O
S42
13C NMR, CDCl3
101 MHz
f1 (ppm)



S42

^{19}F NMR, $CDCl_3$
376 MHz



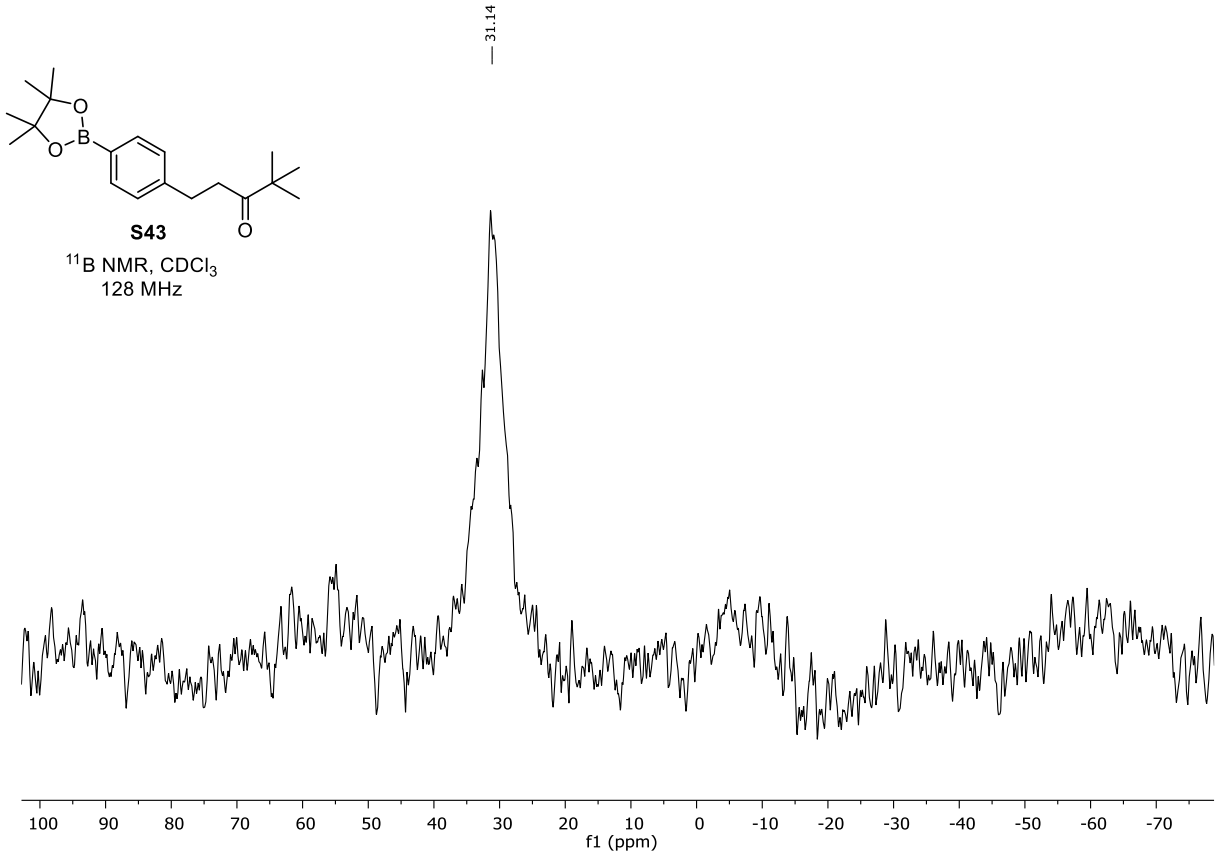


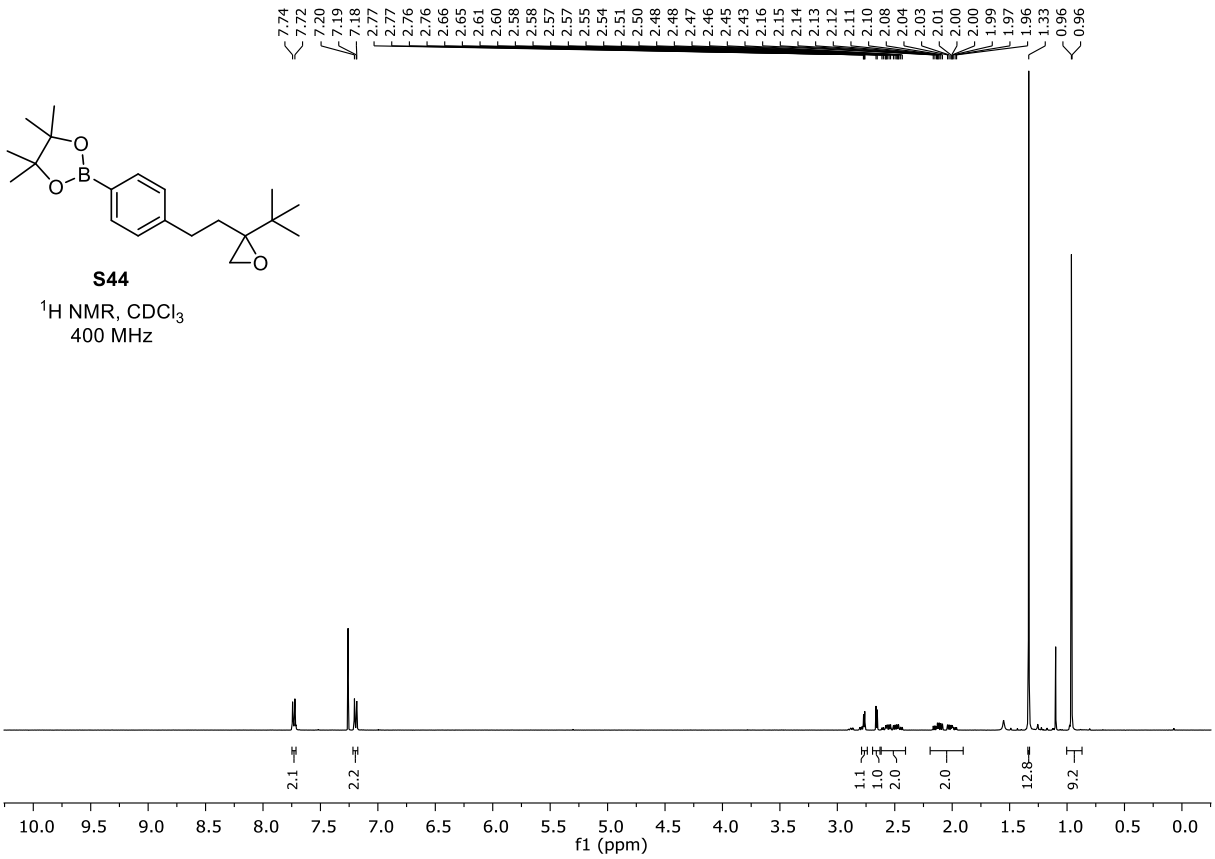
S43

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

S43

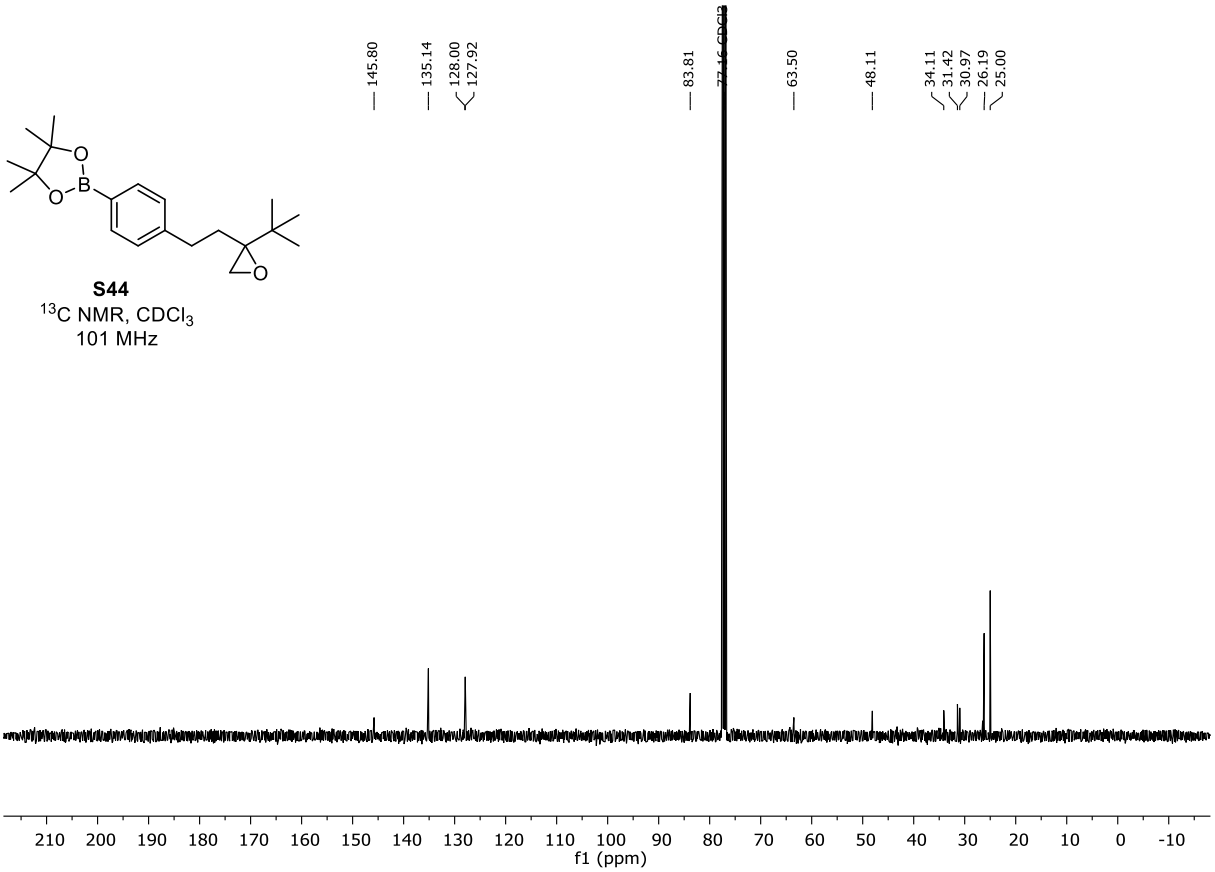
^{13}C NMR, $CDCl_3$
101 MHz


31.14
S43
11B NMR, CDCl3
128 MHz
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70
f1 (ppm)



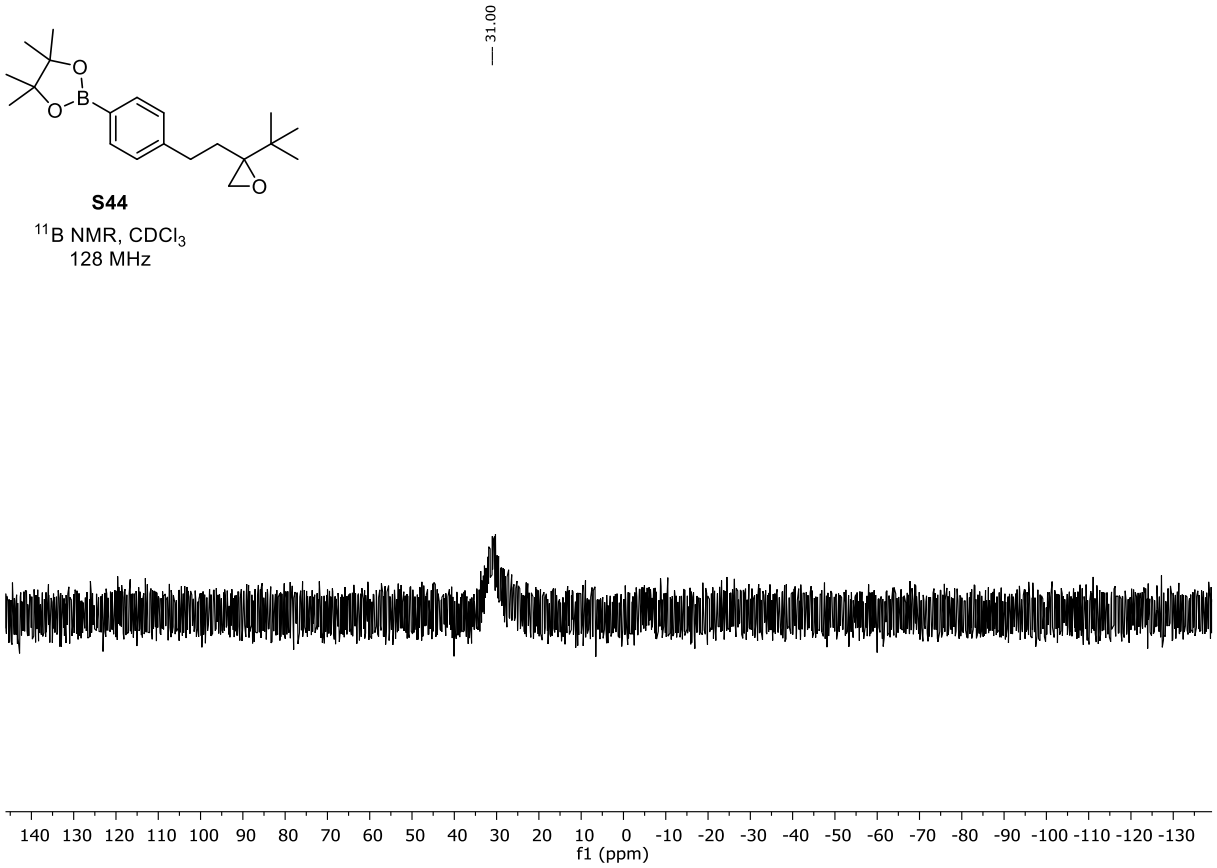
S44

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



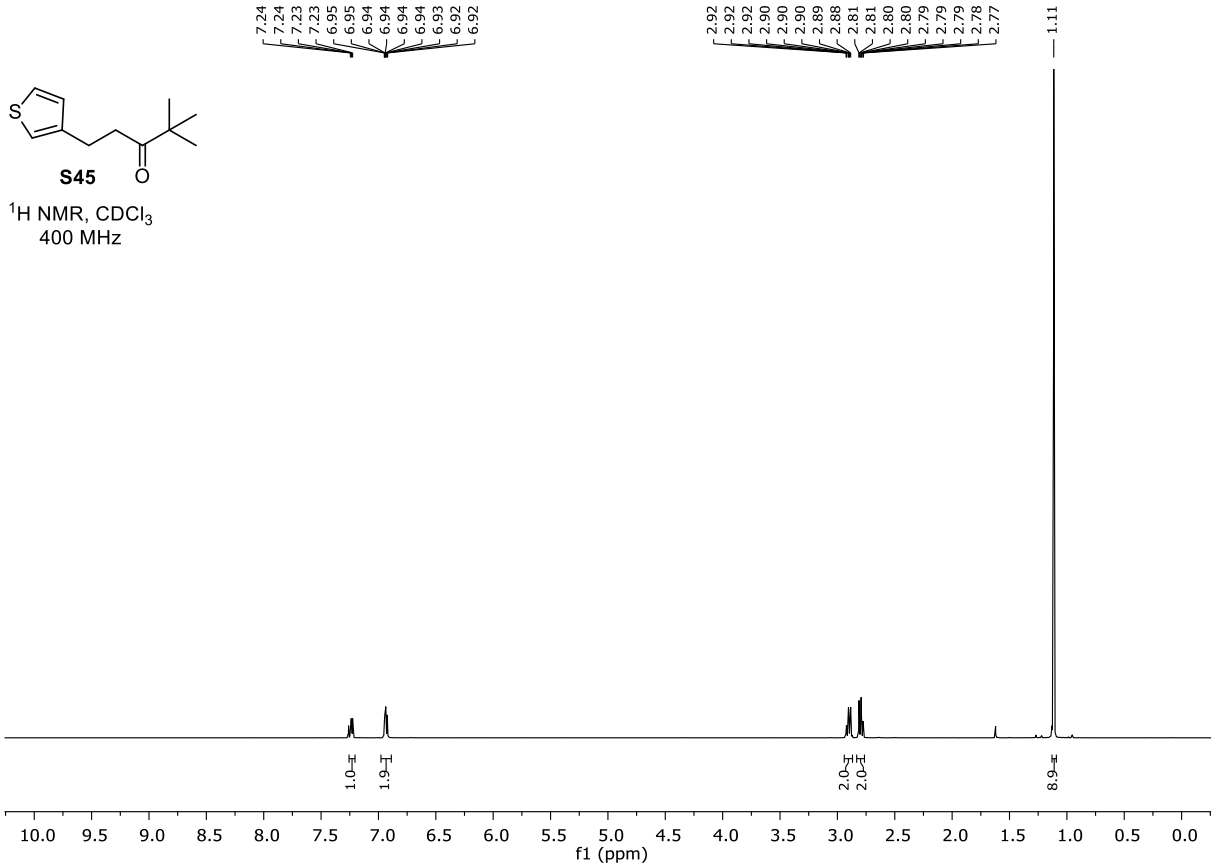
S44

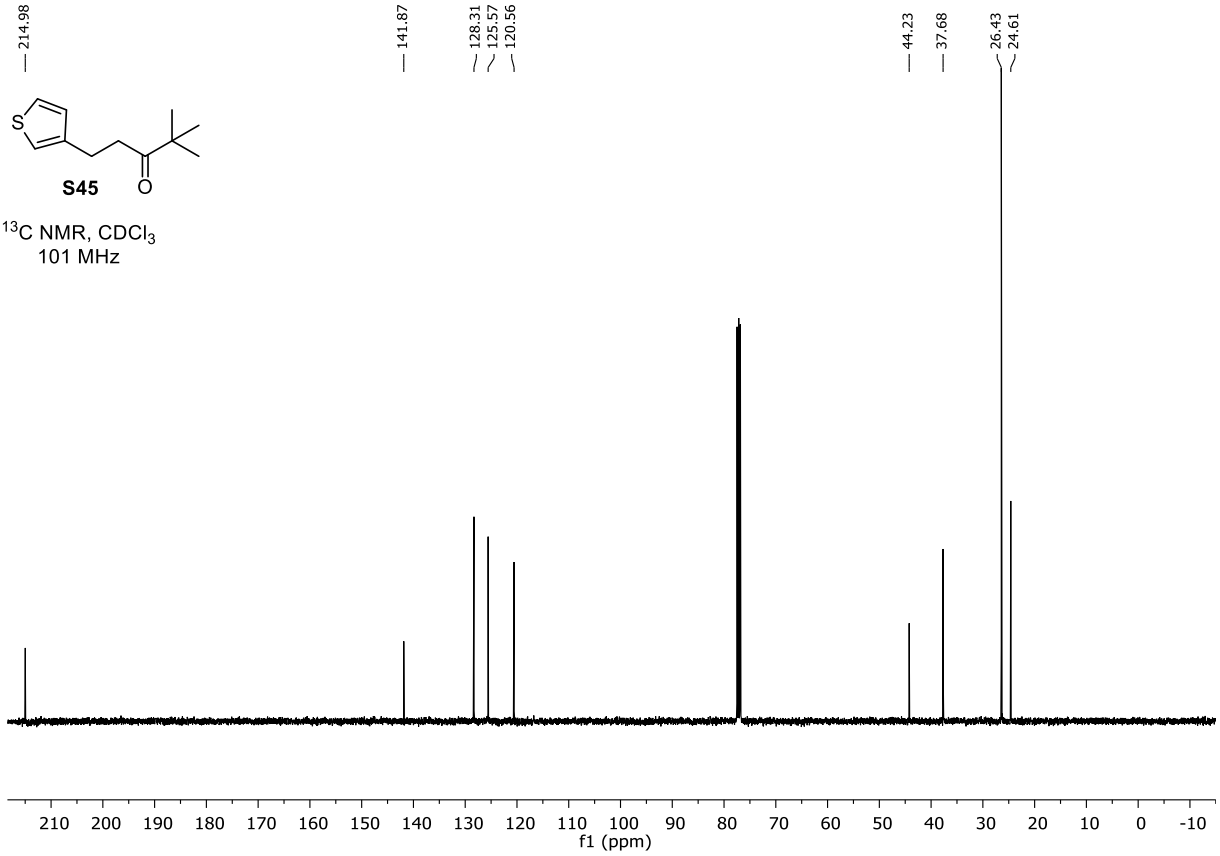
^{13}C NMR, $CDCl_3$
101 MHz

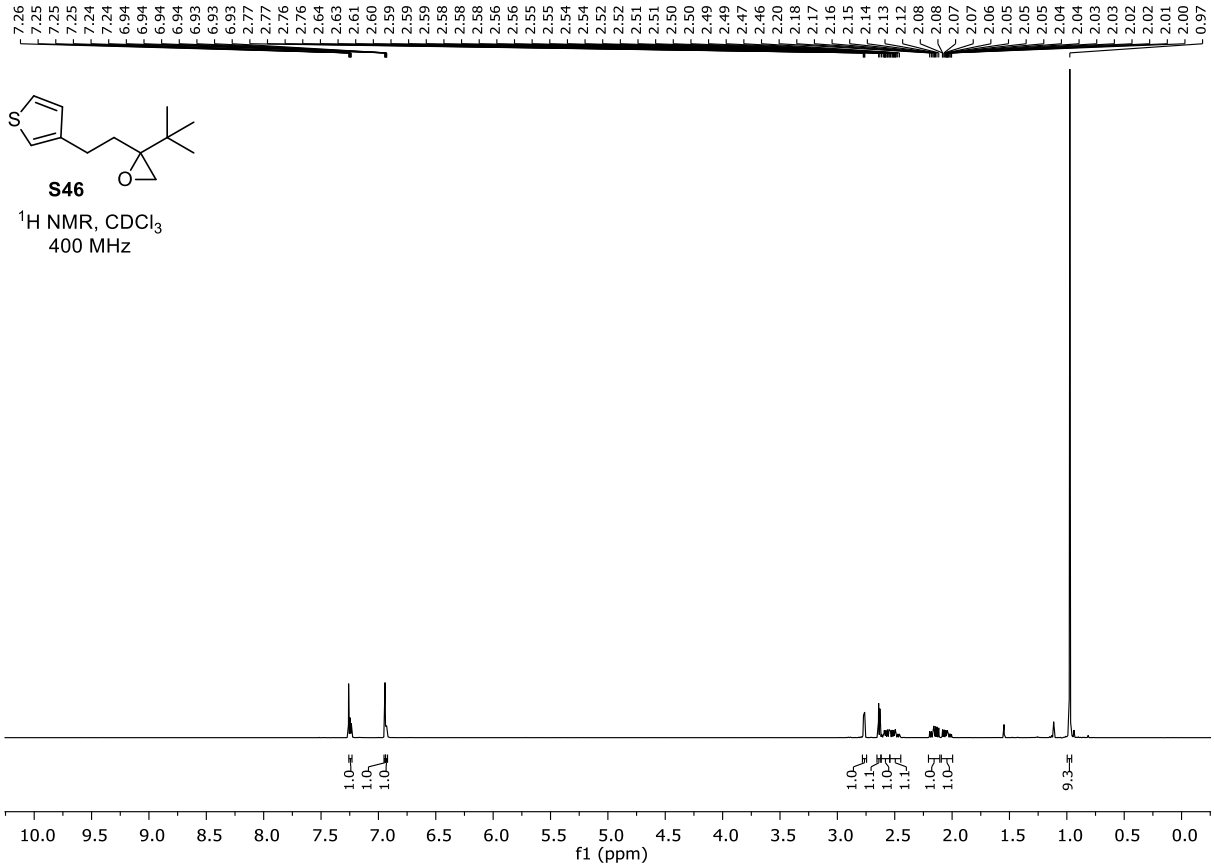


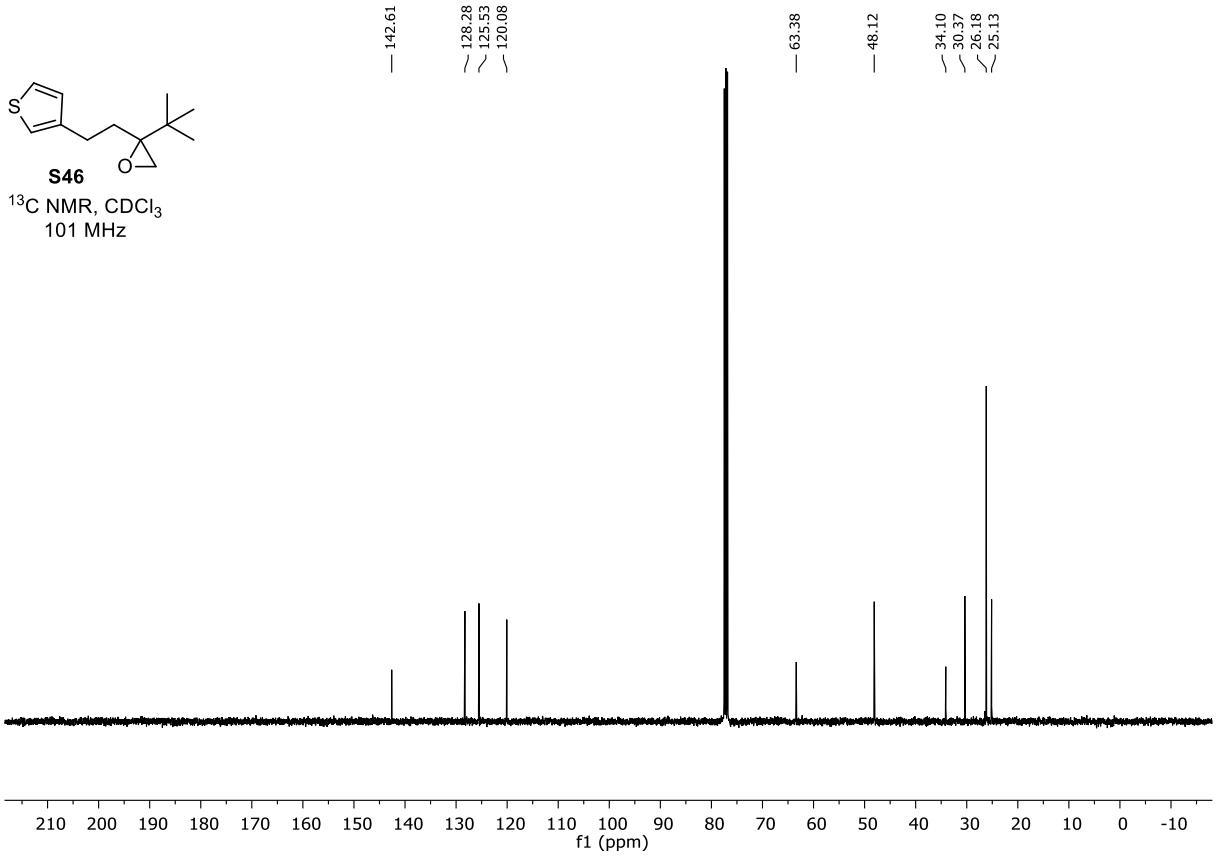
S44

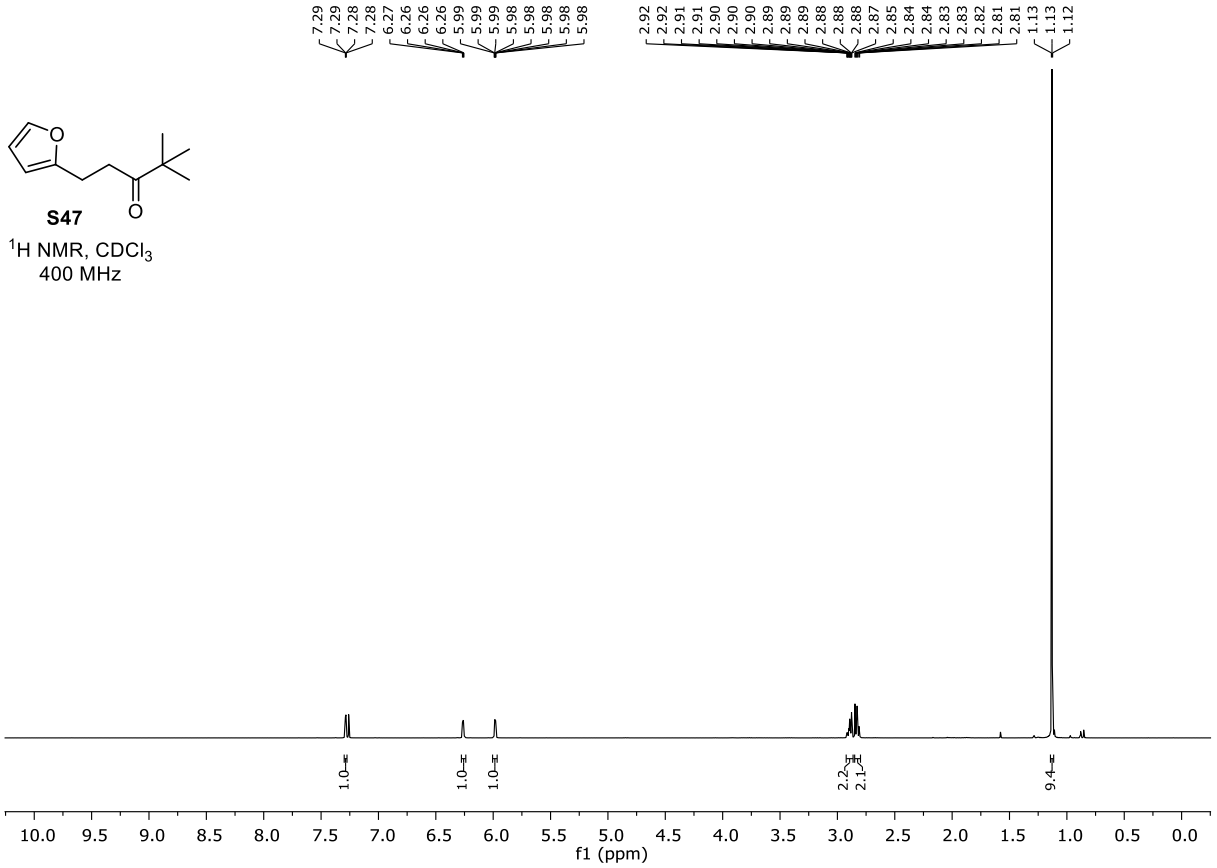
^{11}B NMR, $CDCl_3$
128 MHz

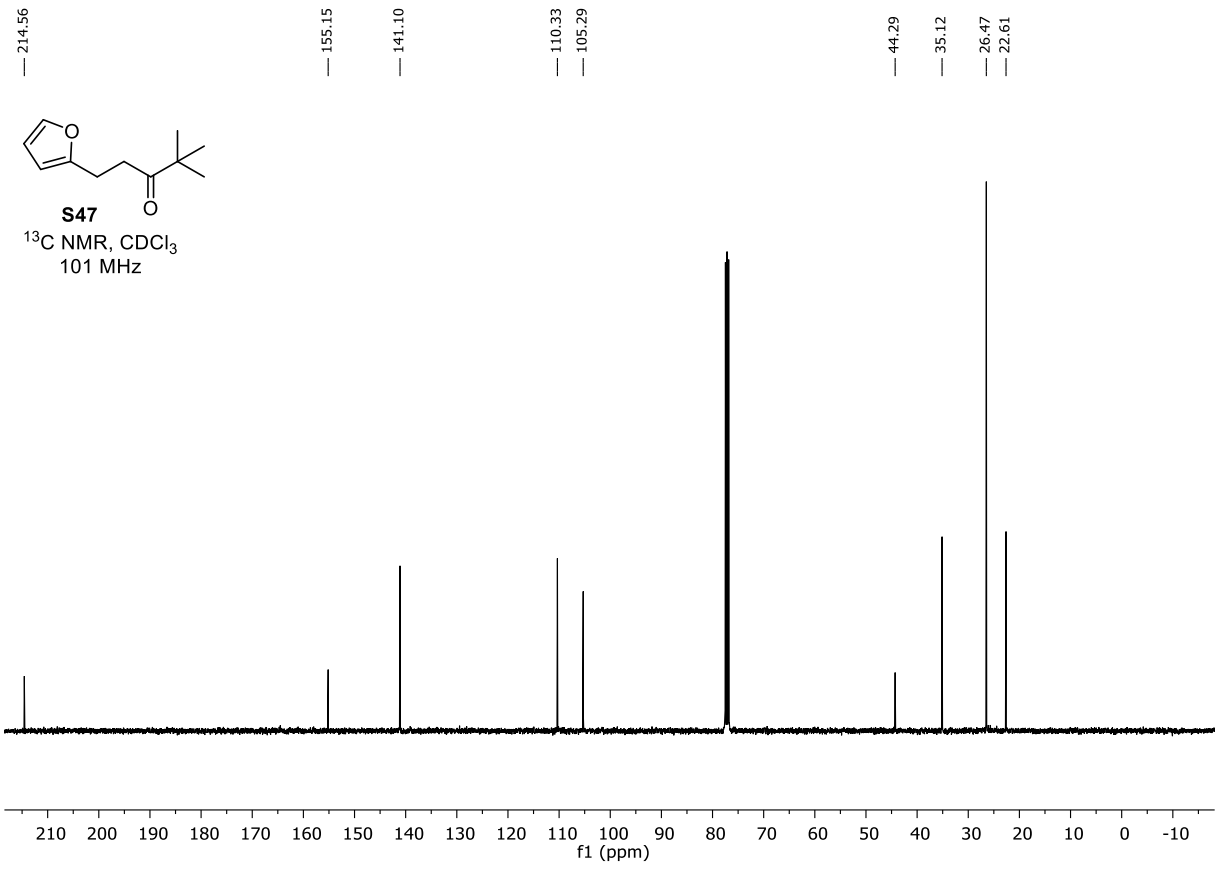

7.24
7.24
7.23
7.23
6.95
6.95
6.94
6.94
6.94
6.94
6.93
6.92
6.92
2.92
2.92
2.92
2.90
2.90
2.90
2.89
2.88
2.81
2.81
2.80
2.80
2.79
2.79
2.79
2.78
2.77
1.11
S
S45
O
1H NMR, CDCl3
400 MHz
1.0
1.9
2.0
2.0
8.9
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

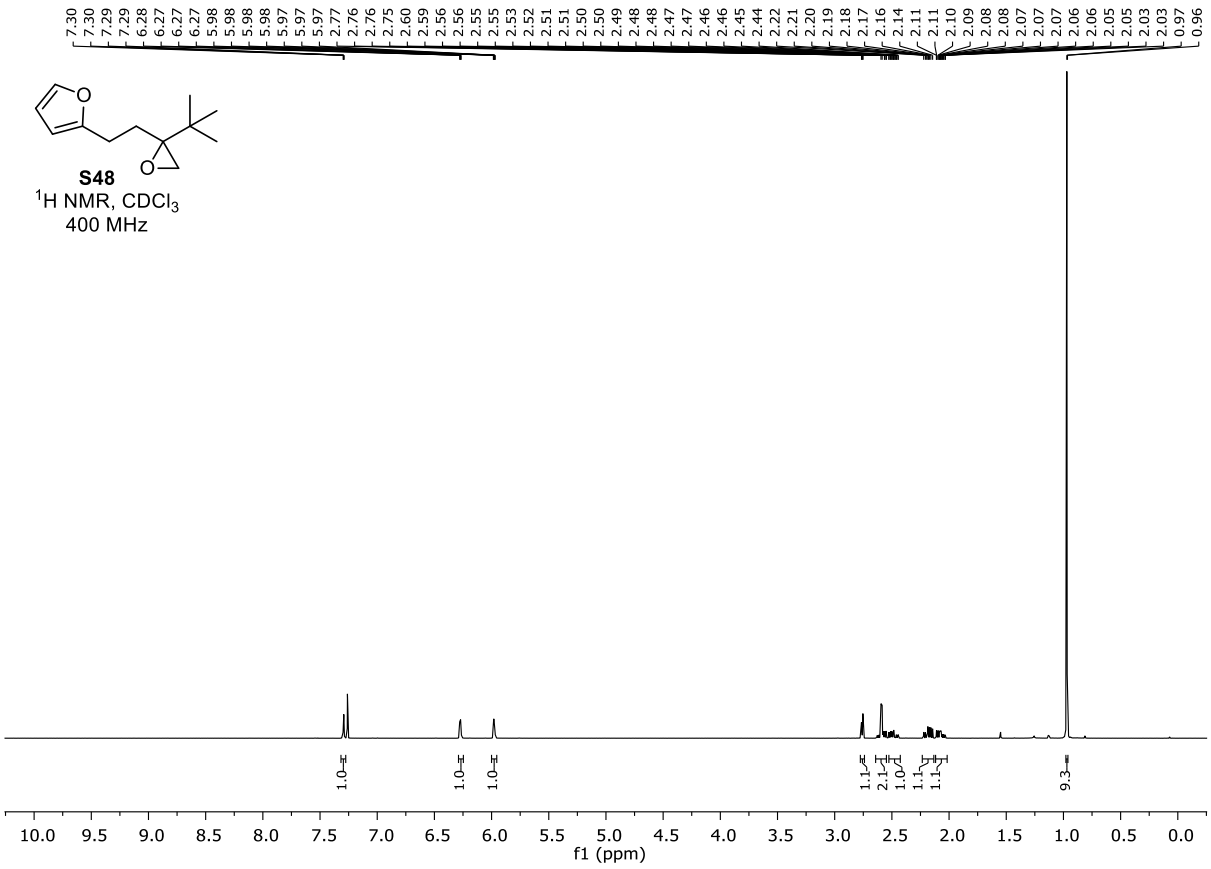

214.98
141.87
128.31
125.57
120.56
44.23
37.68
26.43
24.61
S
S45
O
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

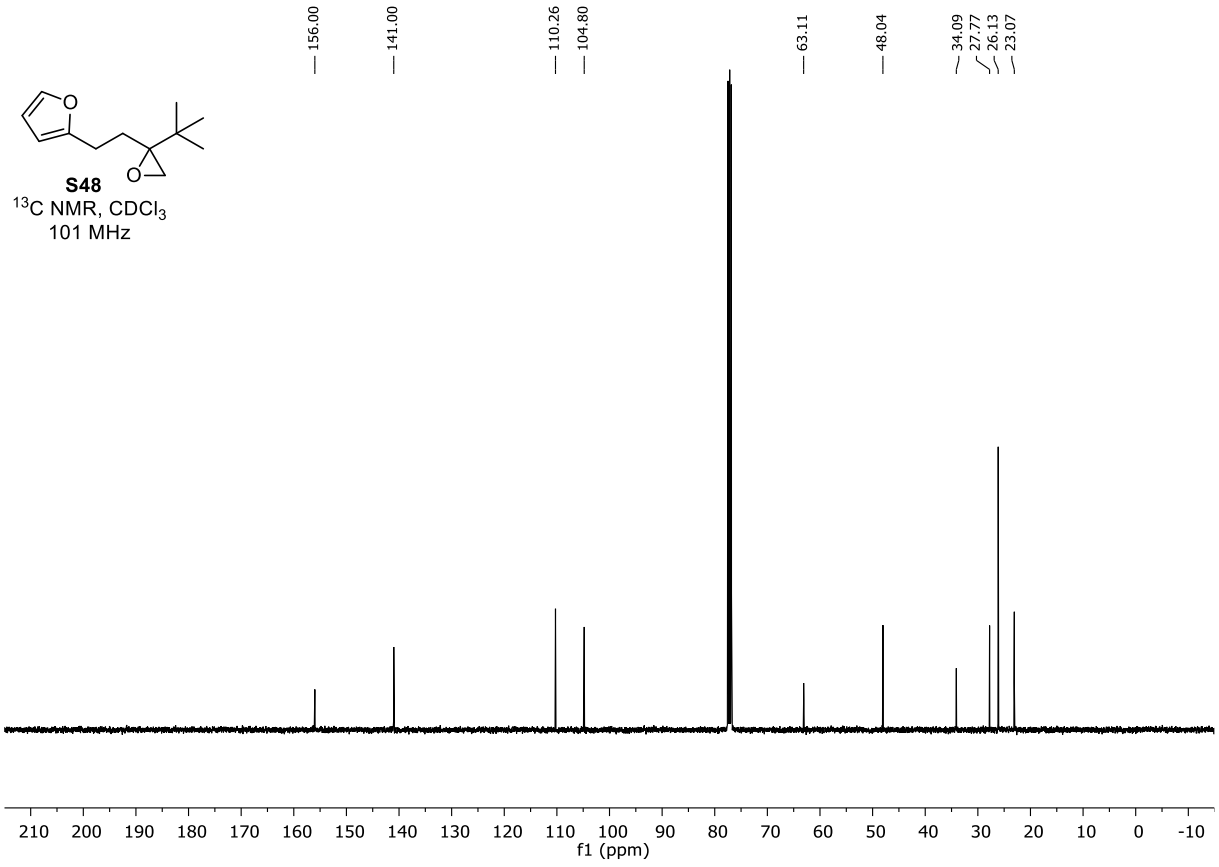

S
O
S46
1H NMR, CDCl3
400 MHz
f1 (ppm)

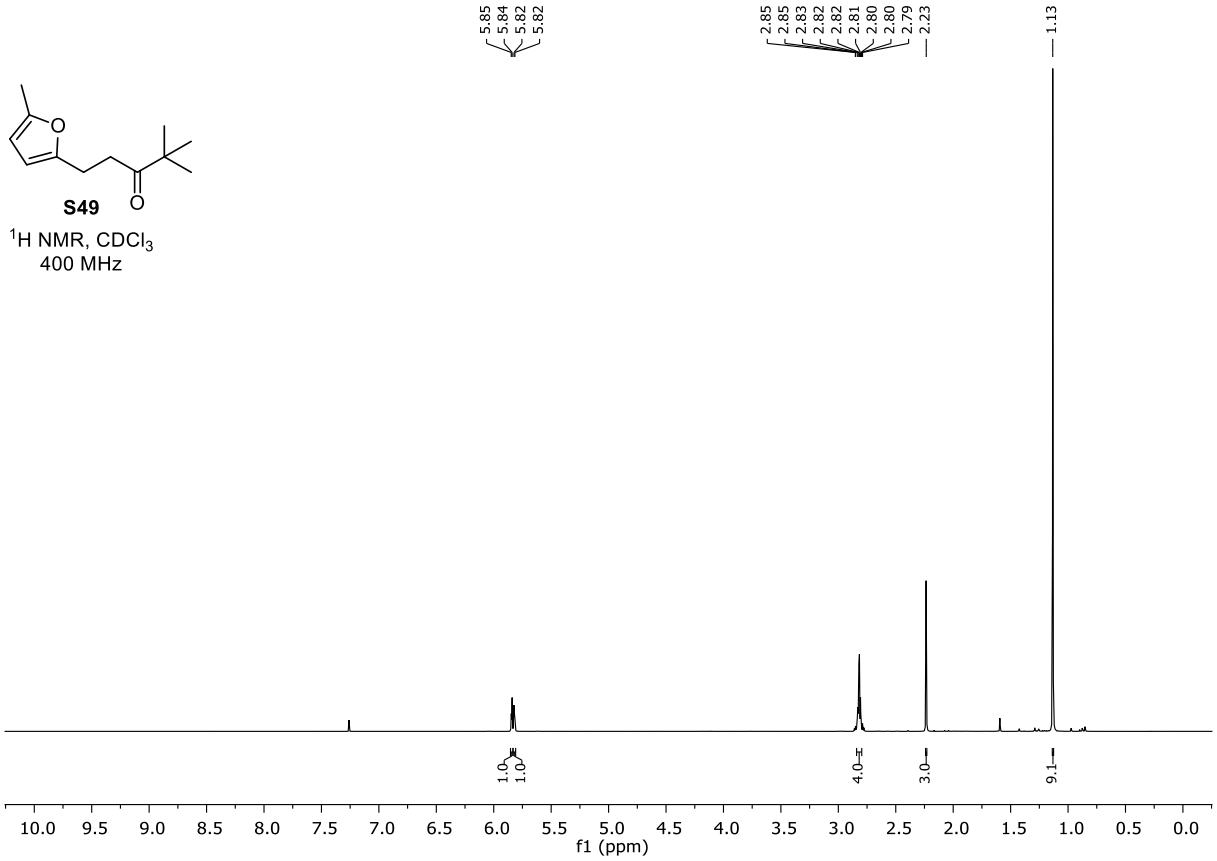

S
O
S46
13C NMR, CDCl3
101 MHz
142.61
128.28
125.53
120.08
63.38
48.12
34.10
30.37
26.18
25.13
f1 (ppm)

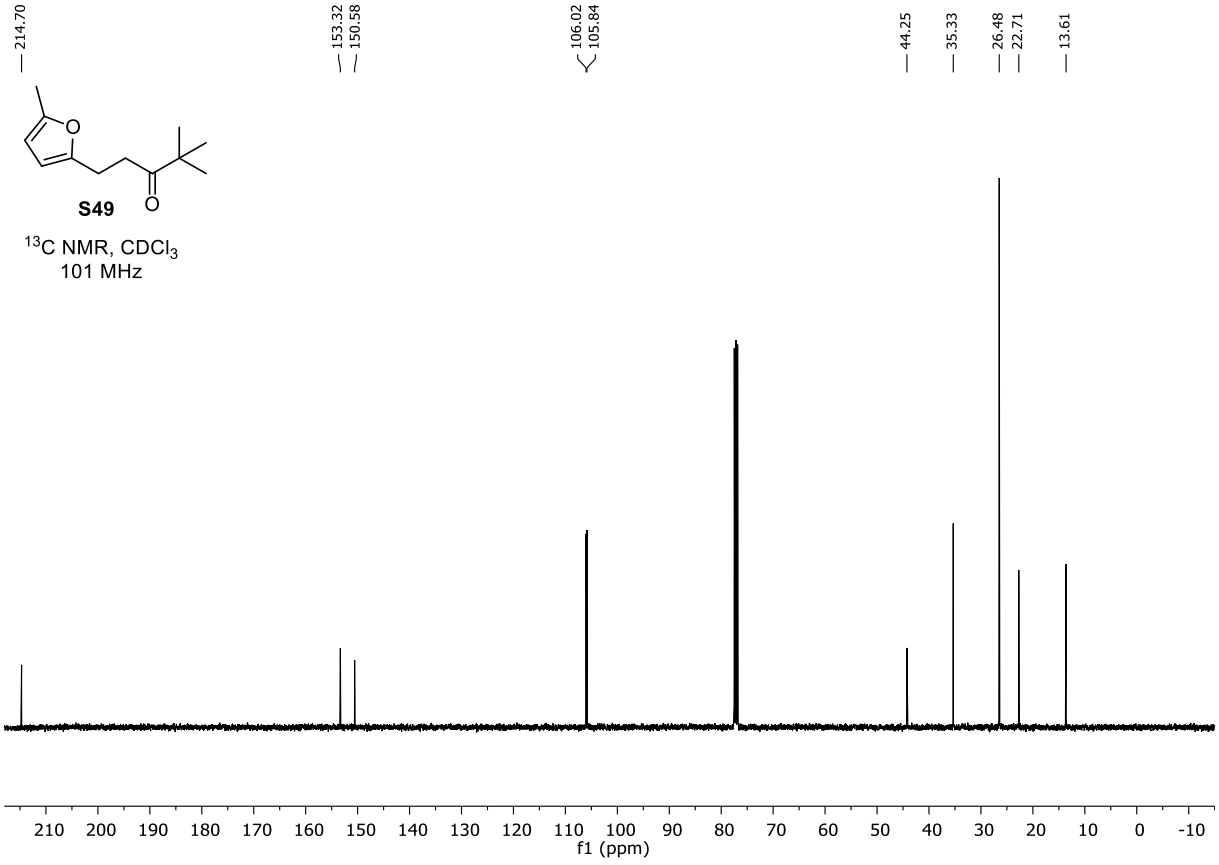

7.29
7.29
7.28
7.28
6.27
6.26
6.26
6.26
5.99
5.99
5.99
5.98
5.98
5.98
5.98
5.98
2.92
2.92
2.91
2.91
2.90
2.90
2.90
2.89
2.89
2.89
2.88
2.88
2.88
2.87
2.85
2.84
2.84
2.83
2.82
2.81
2.81
1.13
1.13
1.12
O
O
S47
1H NMR, CDCl3
400 MHz
1.0
1.0
1.0
2.2
2.1
9.4
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

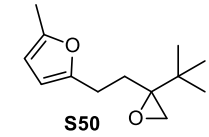

214.56
155.15
141.10
110.33
105.29
44.29
35.12
26.47
22.61
O
O
S47
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.30
7.30
7.29
7.29
6.28
6.27
6.27
6.27
5.98
5.98
5.98
5.97
5.97
5.97
2.77
2.76
2.76
2.75
2.60
2.59
2.56
2.56
2.55
2.55
2.53
2.52
2.51
2.51
2.50
2.50
2.49
2.48
2.48
2.47
2.47
2.46
2.46
2.45
2.44
2.22
2.21
2.20
2.19
2.18
2.17
2.16
2.14
2.11
2.11
2.10
2.09
2.08
2.08
2.07
2.07
2.07
2.06
2.06
2.05
2.05
2.03
0.97
0.96
S48
1H NMR, CDCl3
400 MHz
1.0
1.0
1.0
1.1
2.1
1.0
1.1
1.1
9.3
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)


156.00
141.00
110.26
104.80
63.11
48.04
34.09
27.77
26.13
23.07
S48
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)

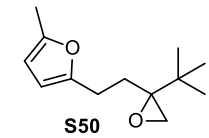

5.85
5.84
5.82
5.82
2.85
2.85
2.83
2.82
2.82
2.81
2.80
2.80
2.79
2.23
1.13
S49
1H NMR, CDCl3
400 MHz
1.0
1.0
4.0
3.0
9.1
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


214.70
153.32
150.58
106.02
105.84
44.25
35.33
26.48
22.71
13.61
S49
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)



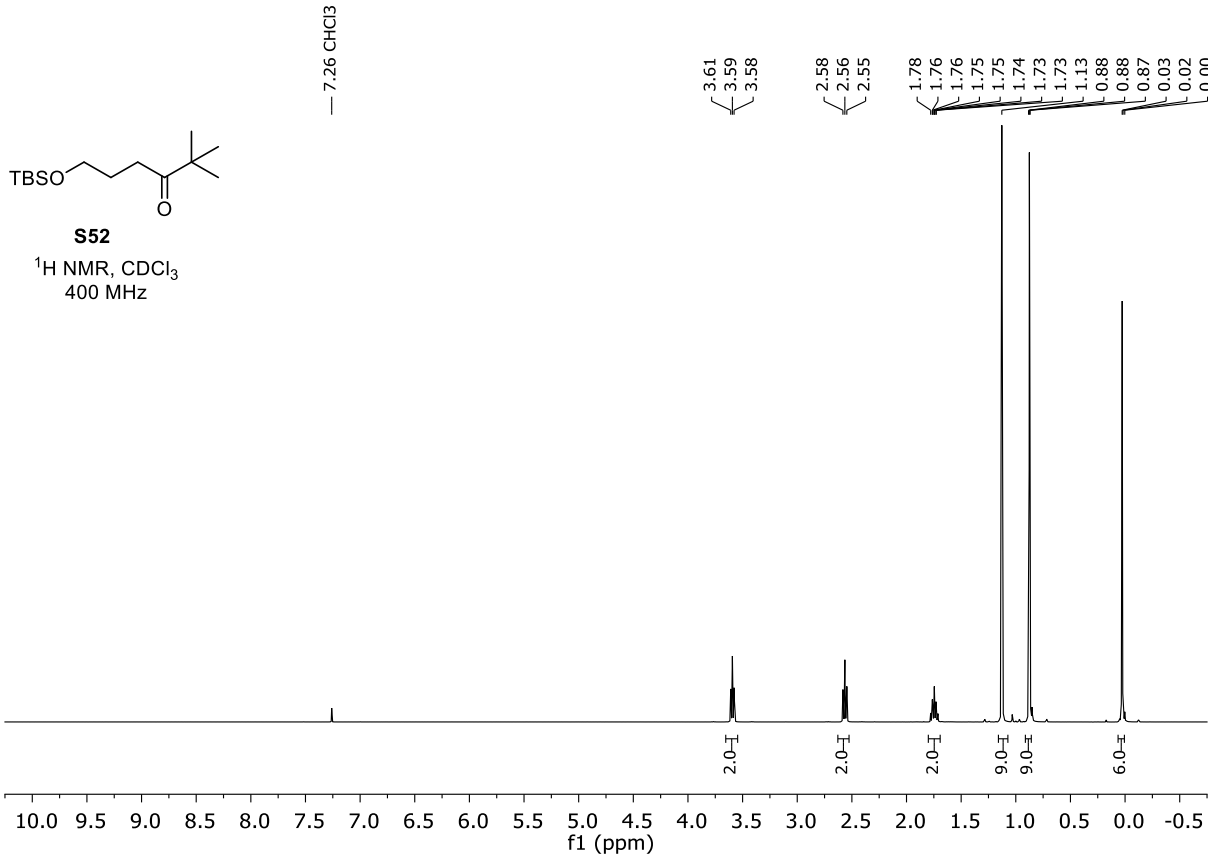
S50

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

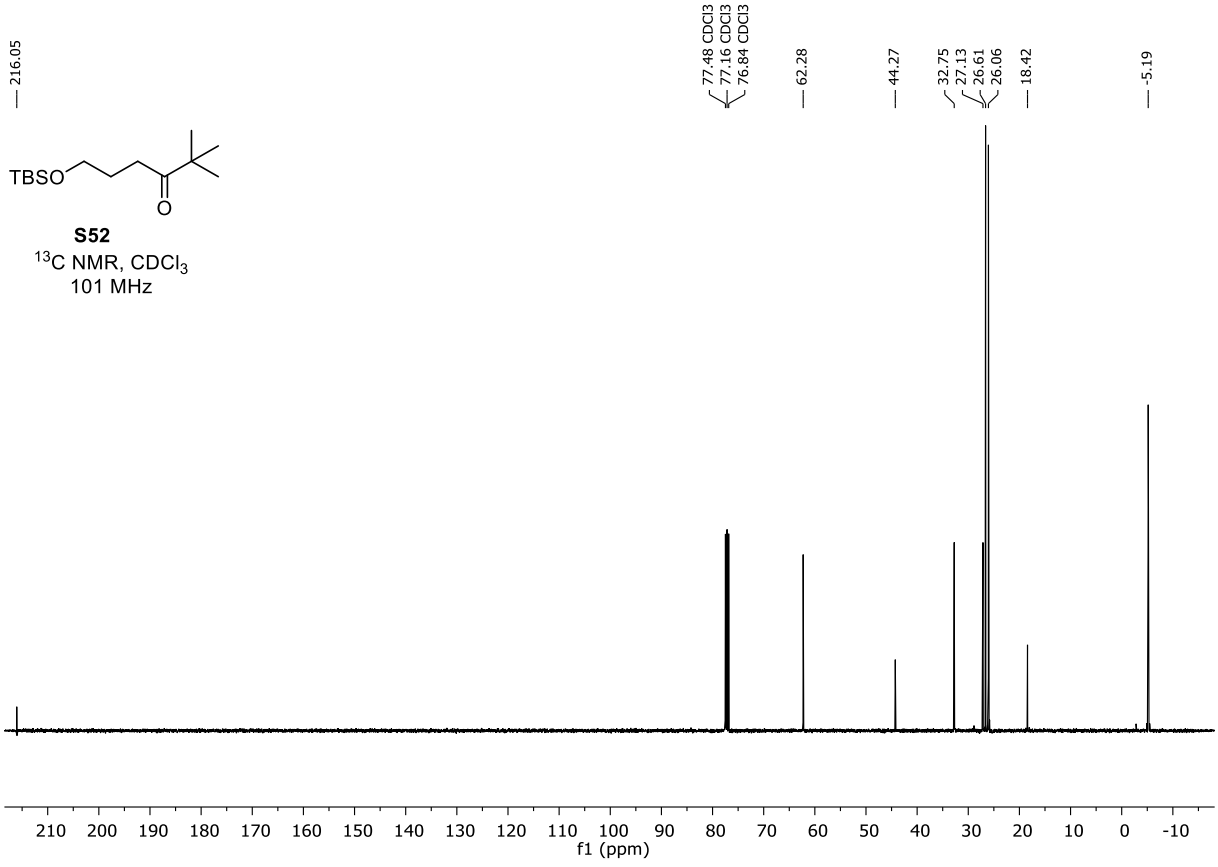


S50

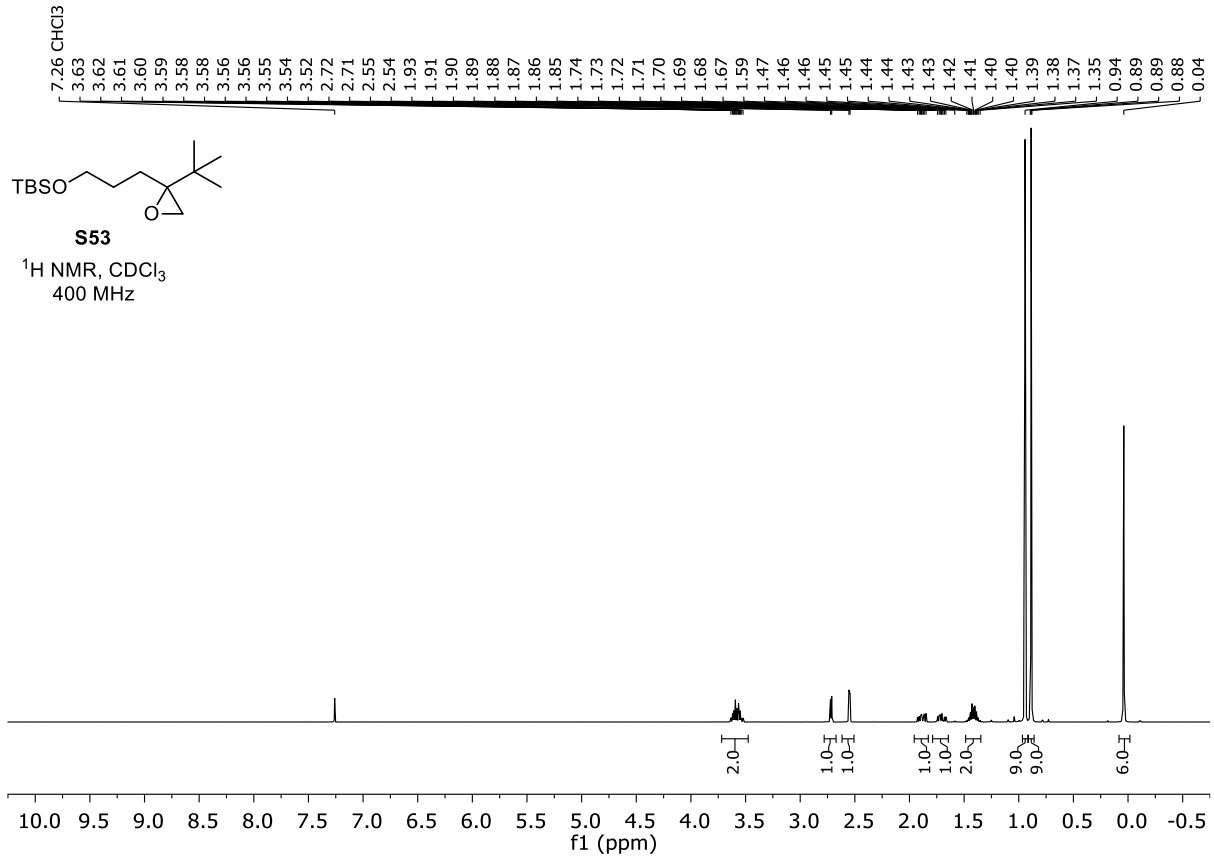
^{13}C NMR, $CDCl_3$
101 MHz



S52
^{1}H NMR, $CDCl_3$
400 MHz

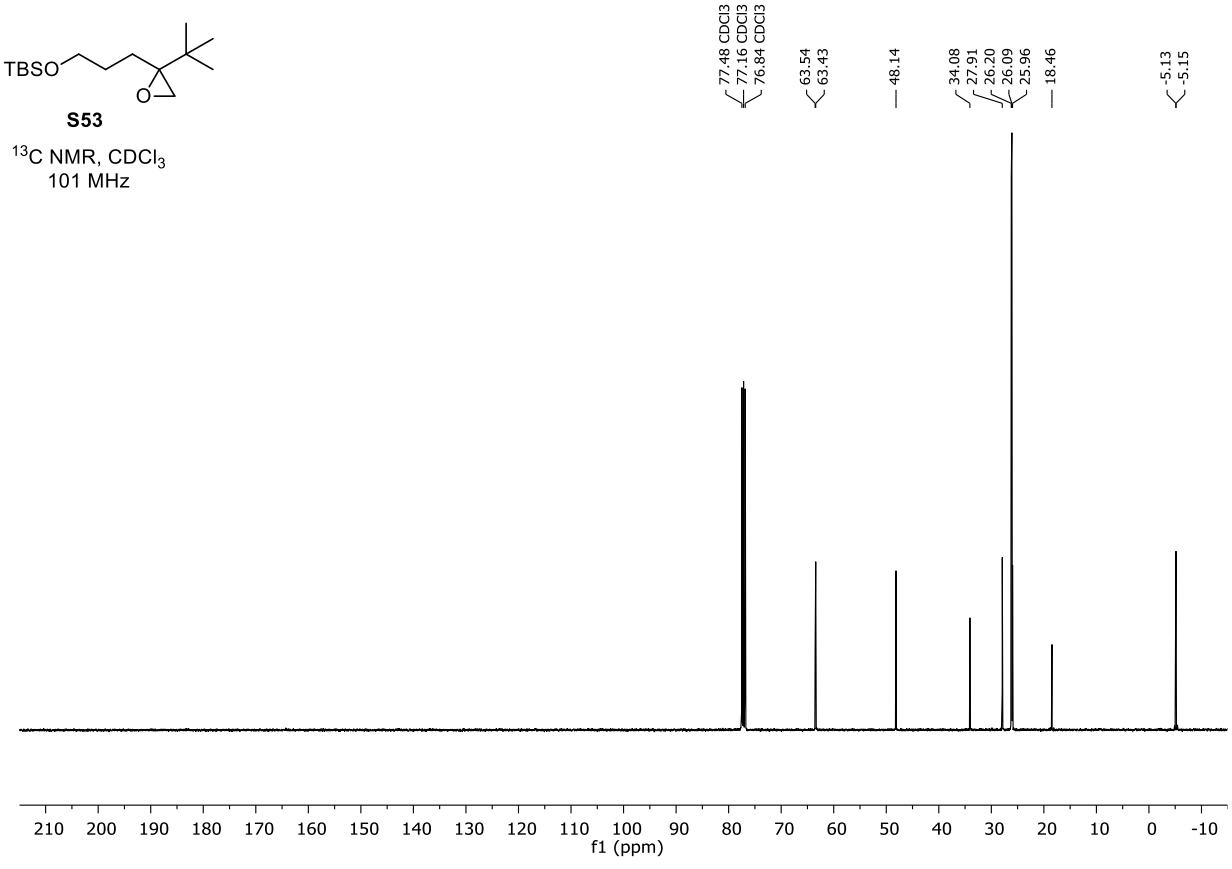


S52
^{13}C NMR, $CDCl_3$
101 MHz



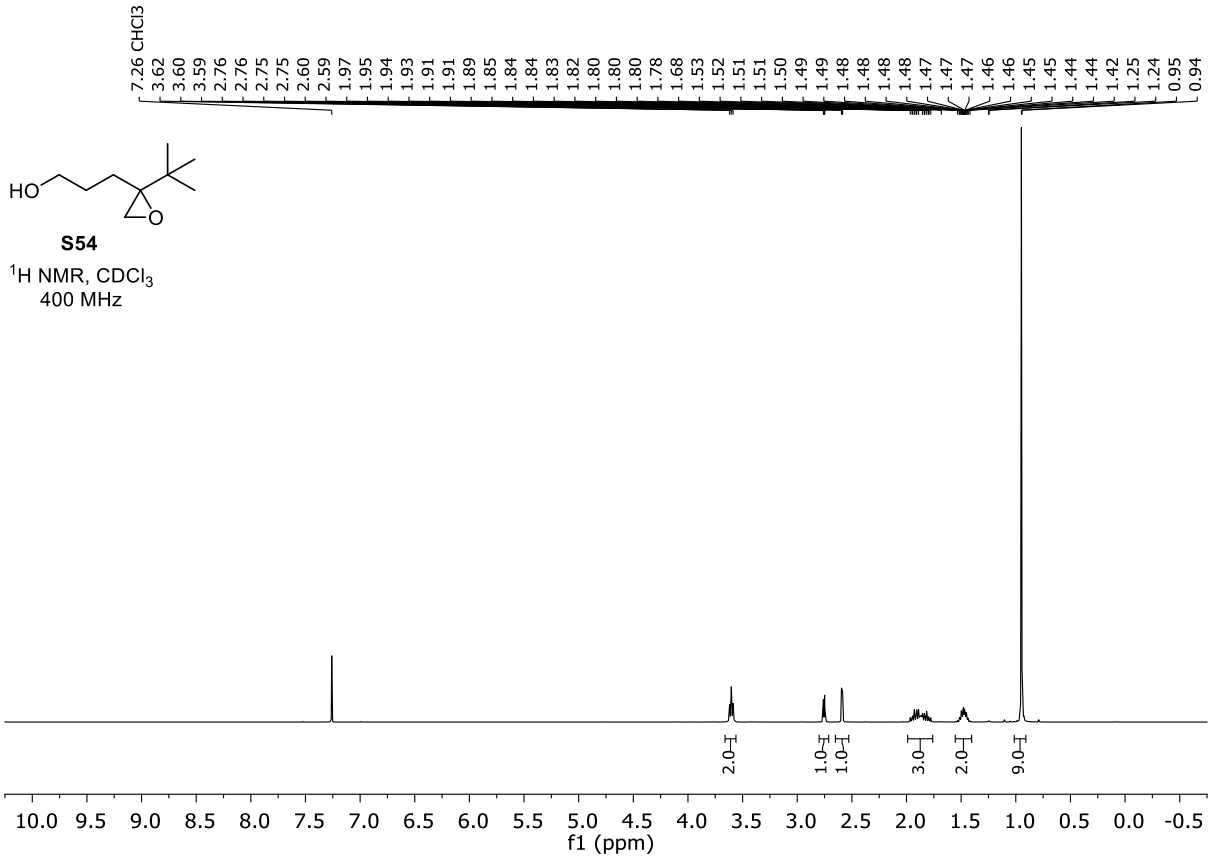
S53

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



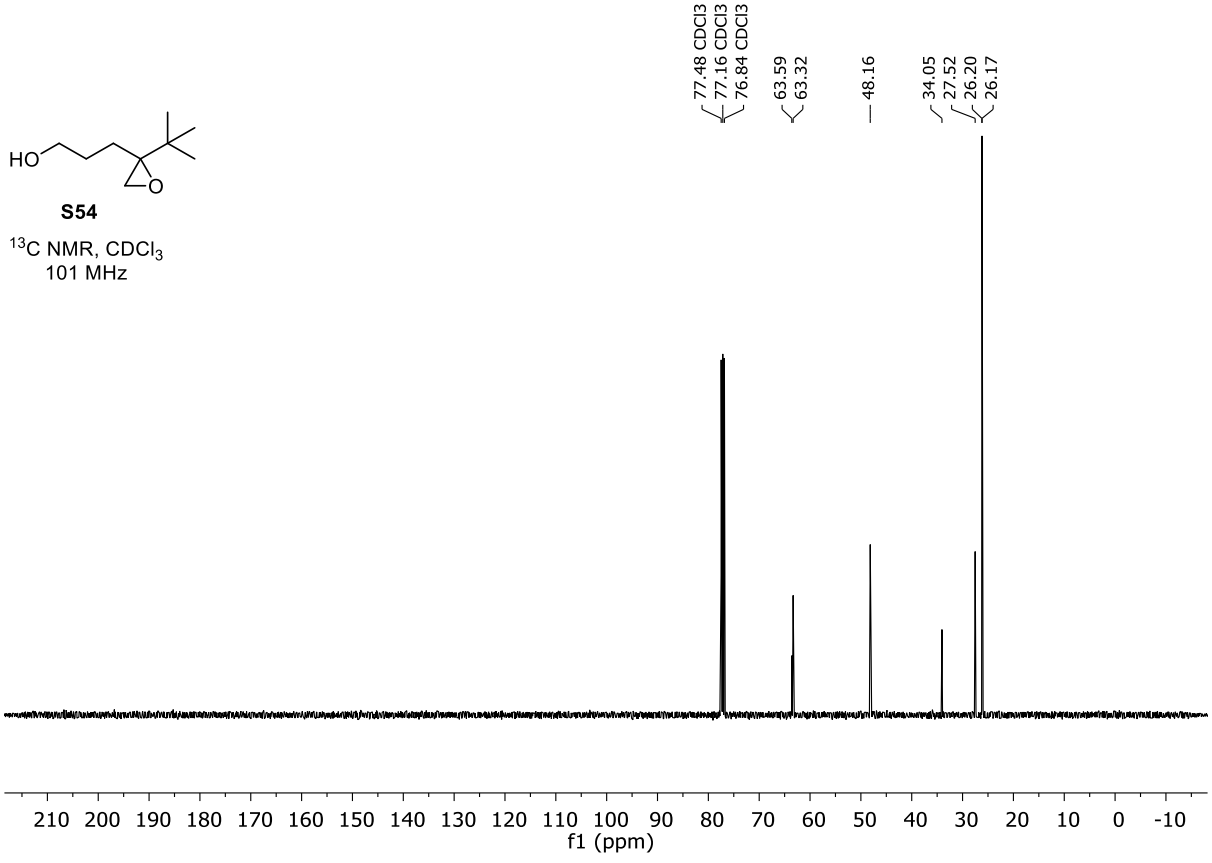
S53

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



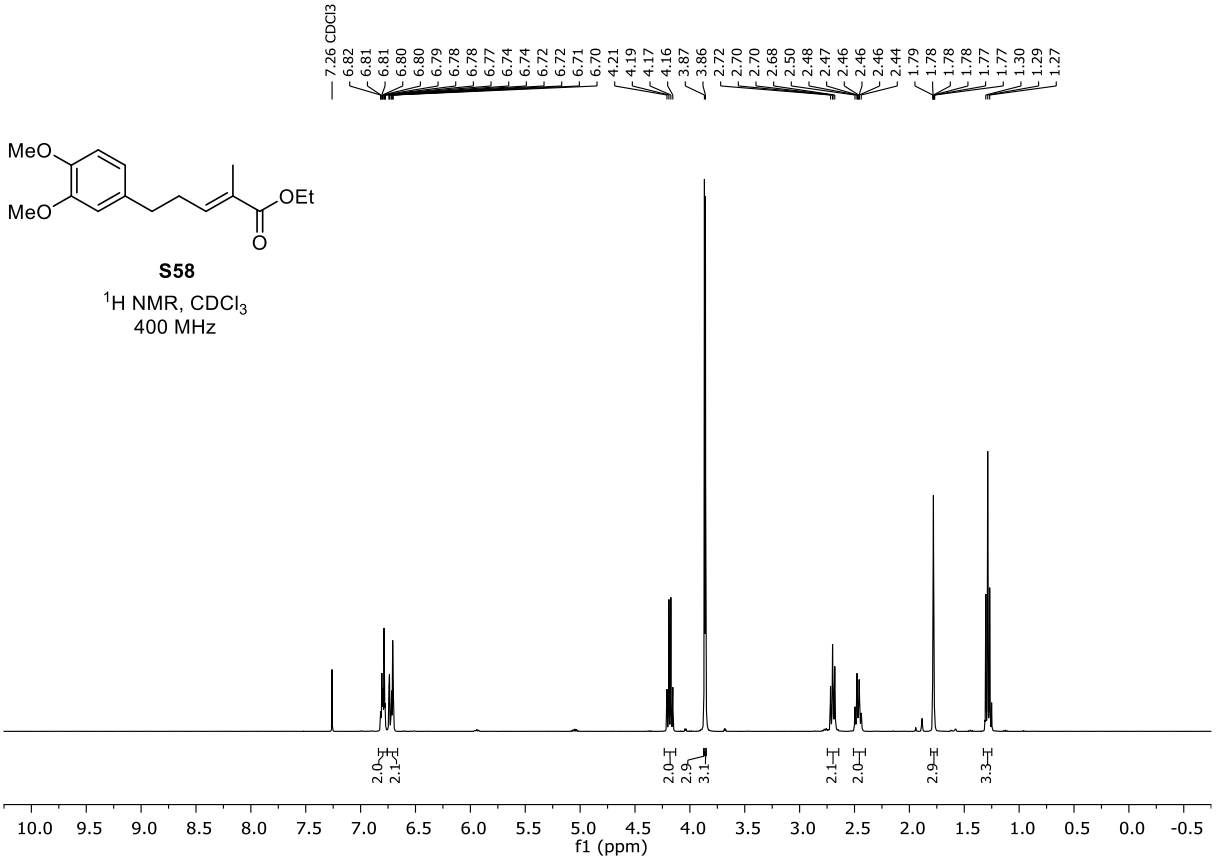
S54

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



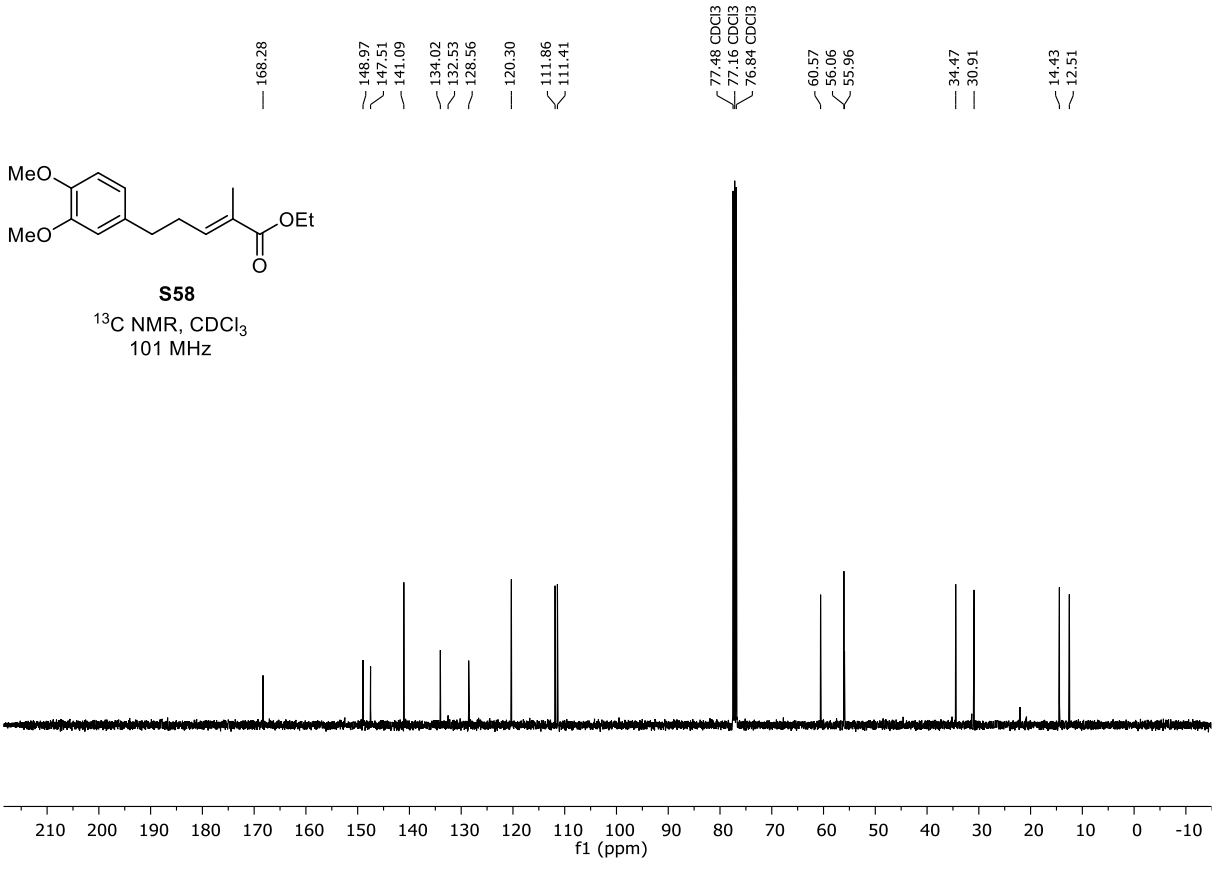
S54

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



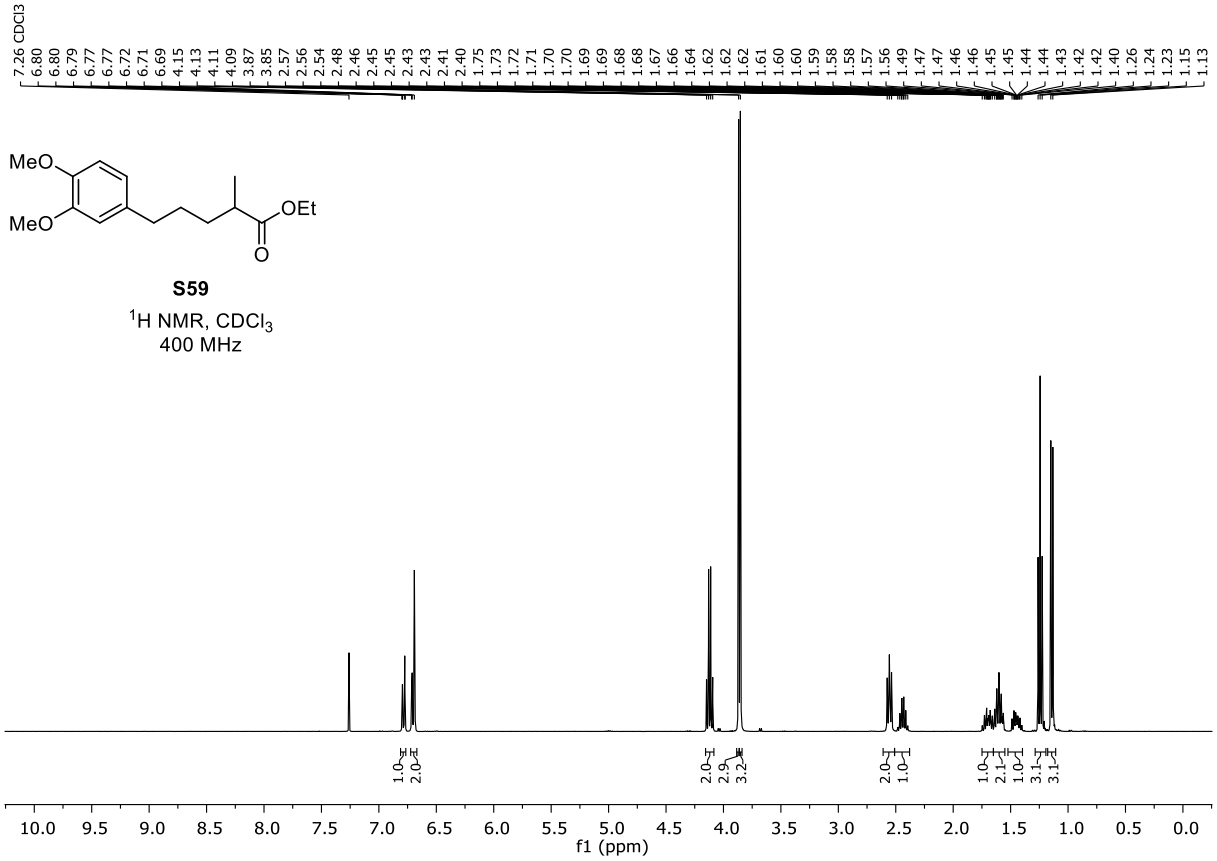
S58

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



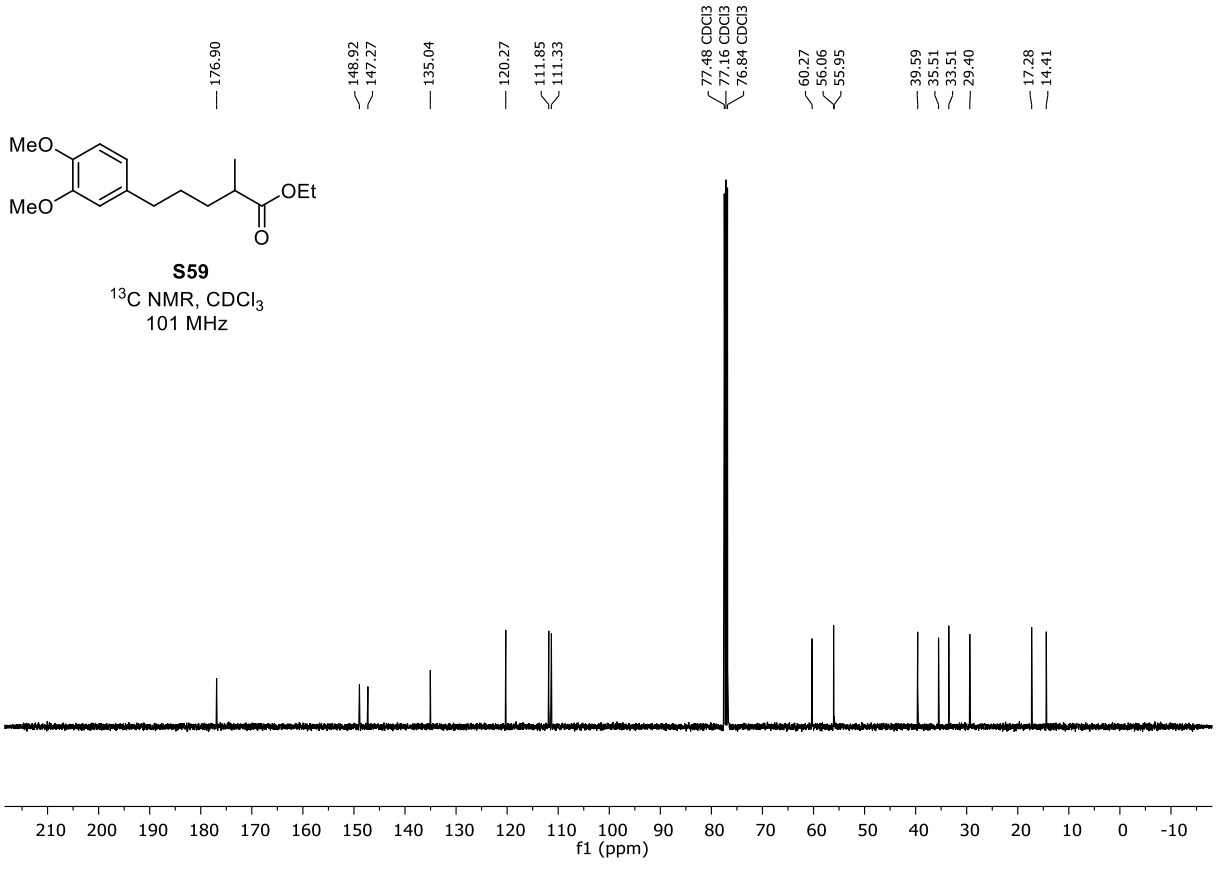
S58

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



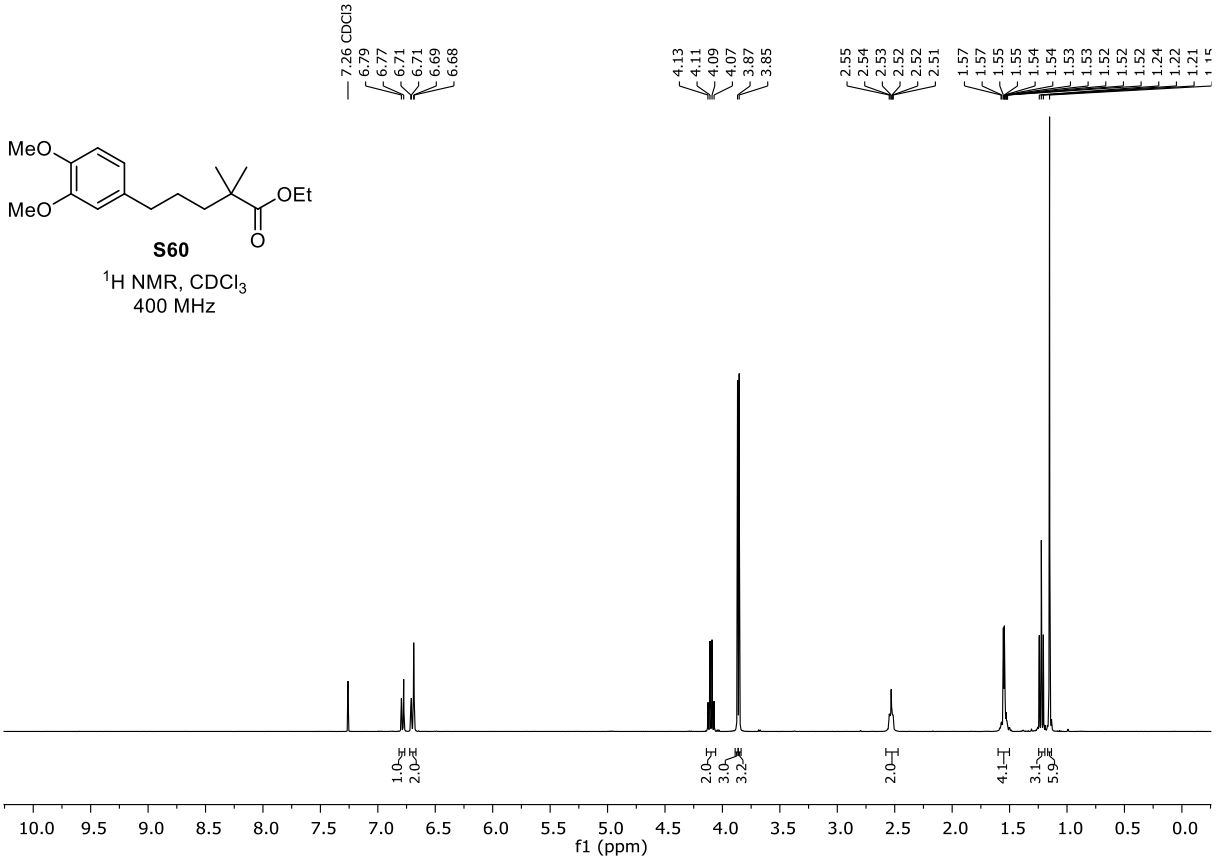
S59

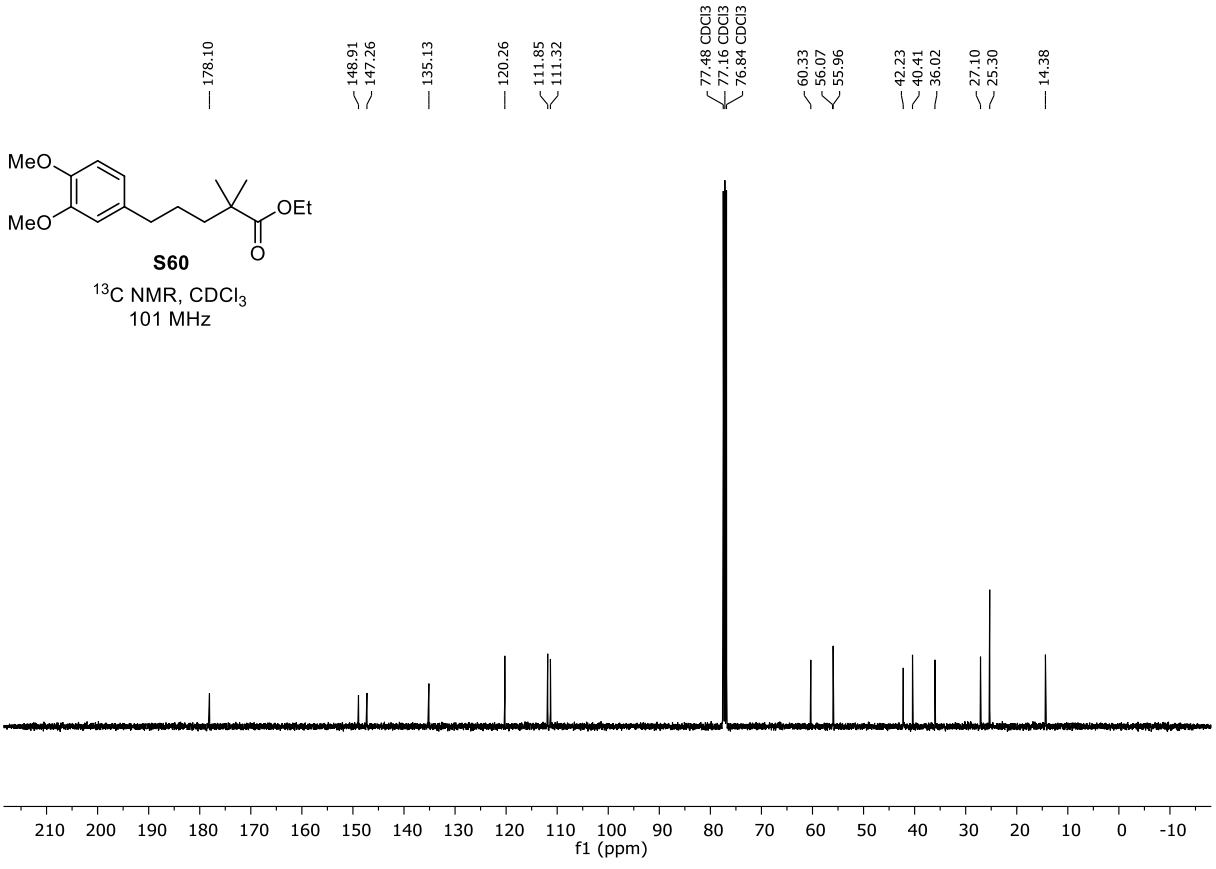
^{1}H NMR, $CDCl_3$
400 MHz

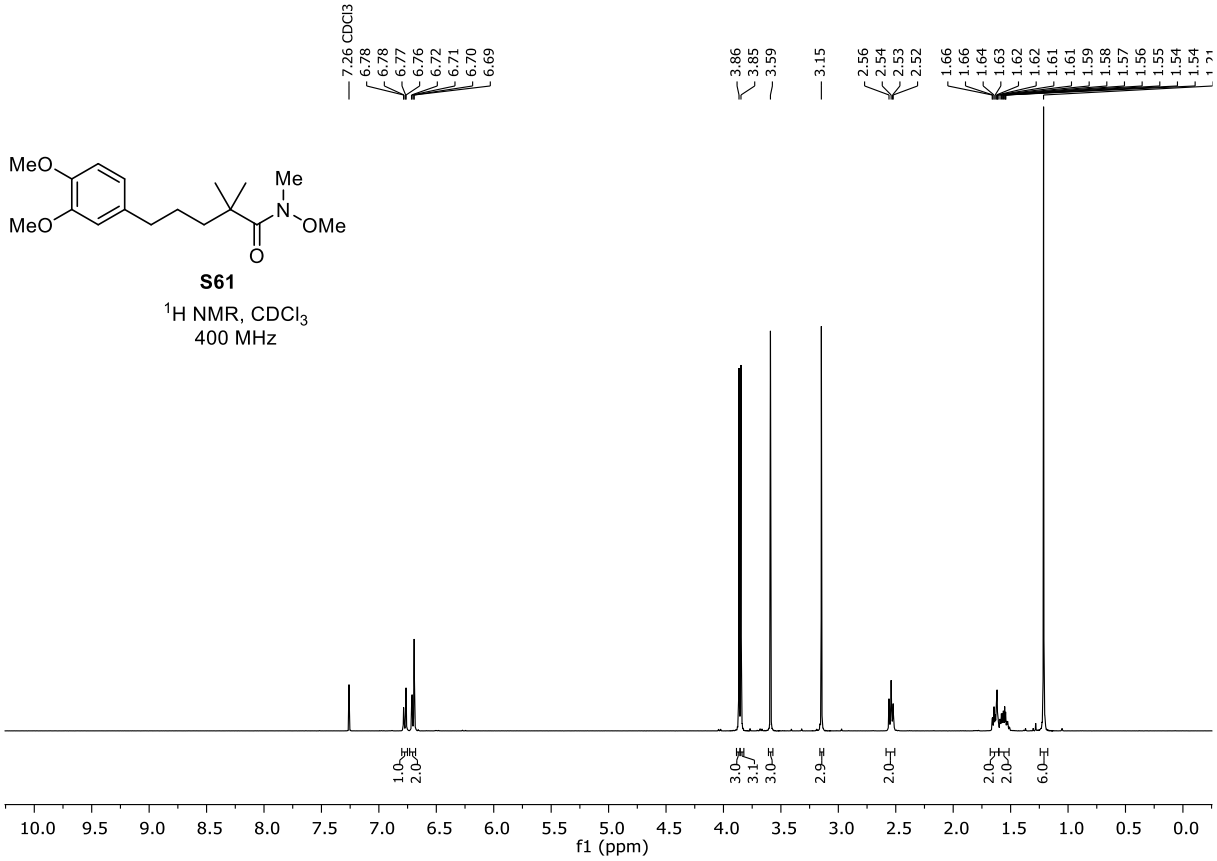


S59

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

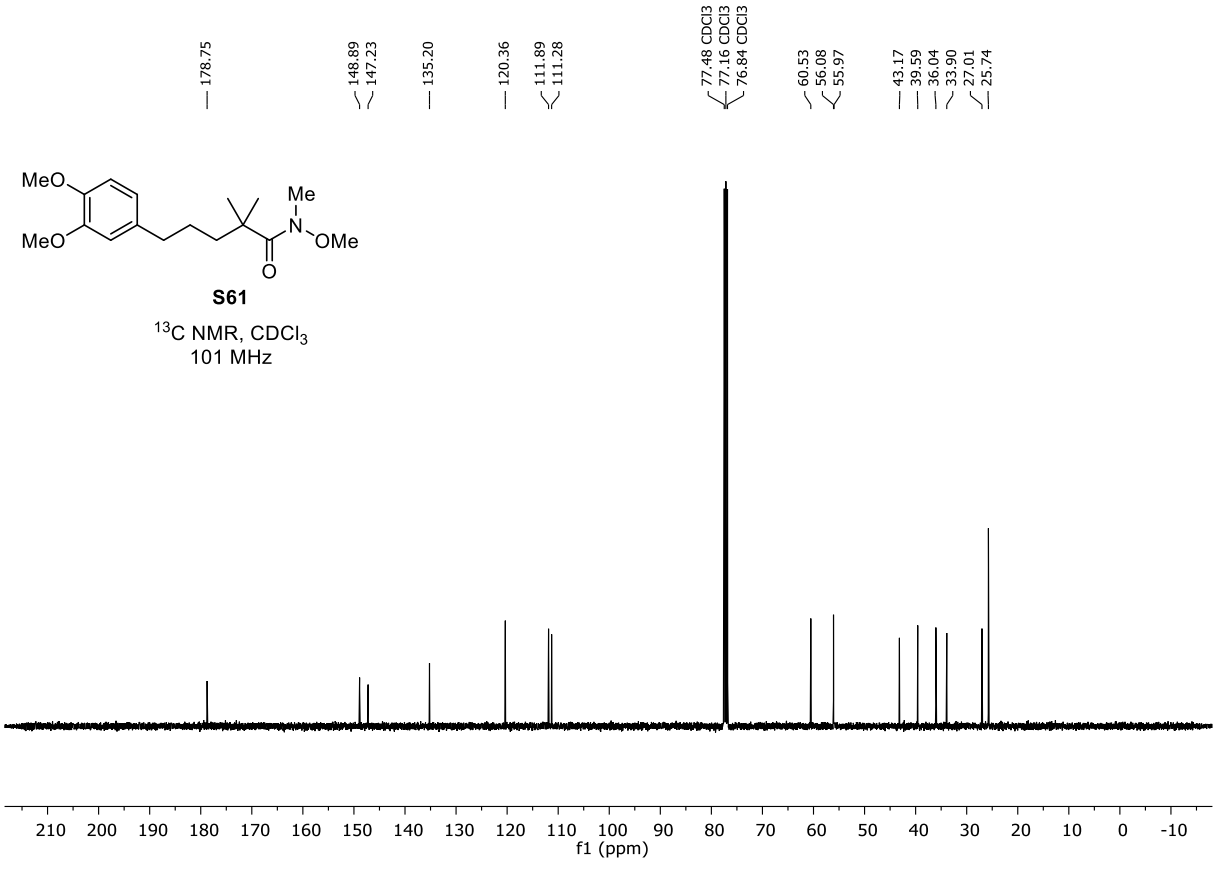

7.26 CDCl3
6.79
6.77
6.71
6.71
6.69
6.68
4.13
4.11
4.09
4.07
3.87
3.85
2.55
2.54
2.53
2.52
2.52
2.51
1.57
1.57
1.55
1.55
1.54
1.54
1.53
1.53
1.52
1.52
1.52
1.24
1.22
1.21
MeO
MeO
OEt
O
S60
1H NMR, CDCl3
400 MHz
1.0
2.0
2.0
3.0
3.2
2.0
4.1
3.1
5.9
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


178.10
148.91
147.26
135.13
120.26
111.85
111.32
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
60.33
56.07
55.96
42.23
40.41
36.02
27.10
25.30
14.38
MeO
MeO
OEt
O
S60
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)



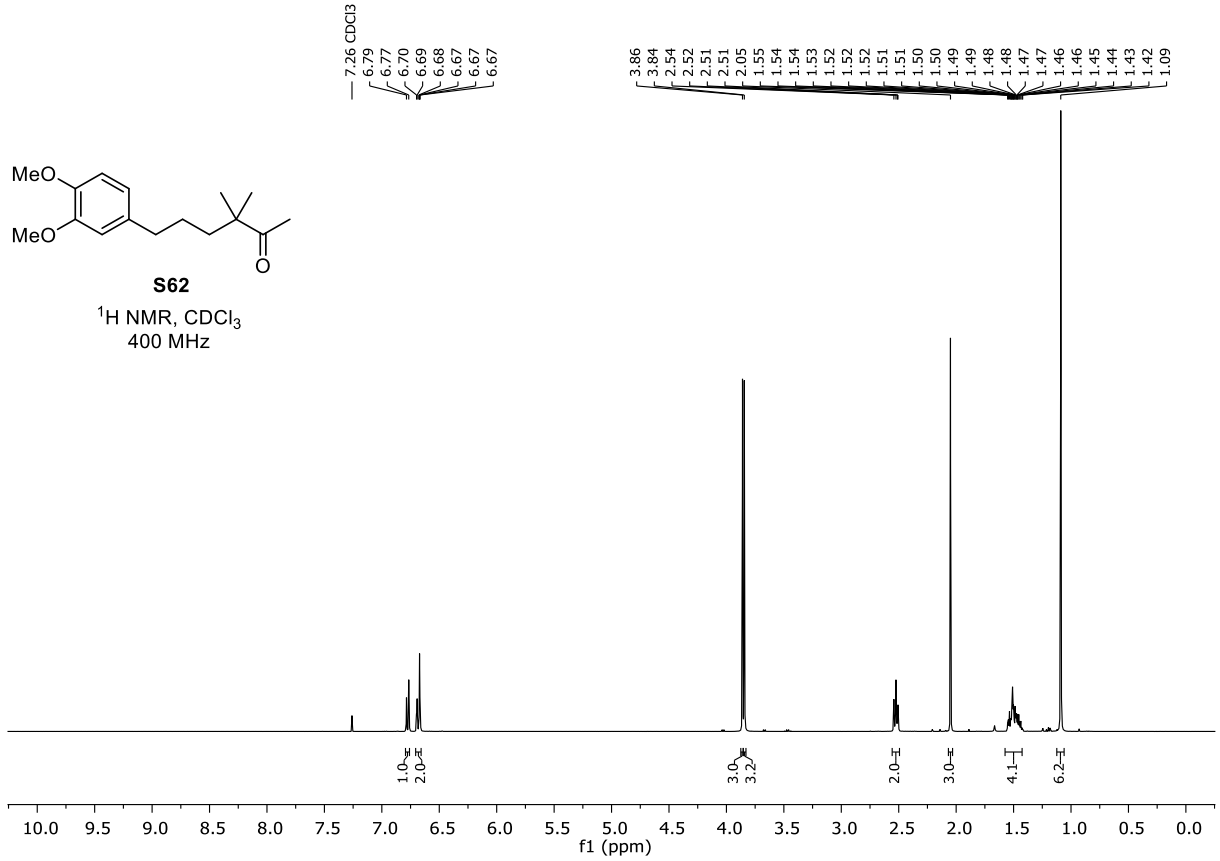
S61

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



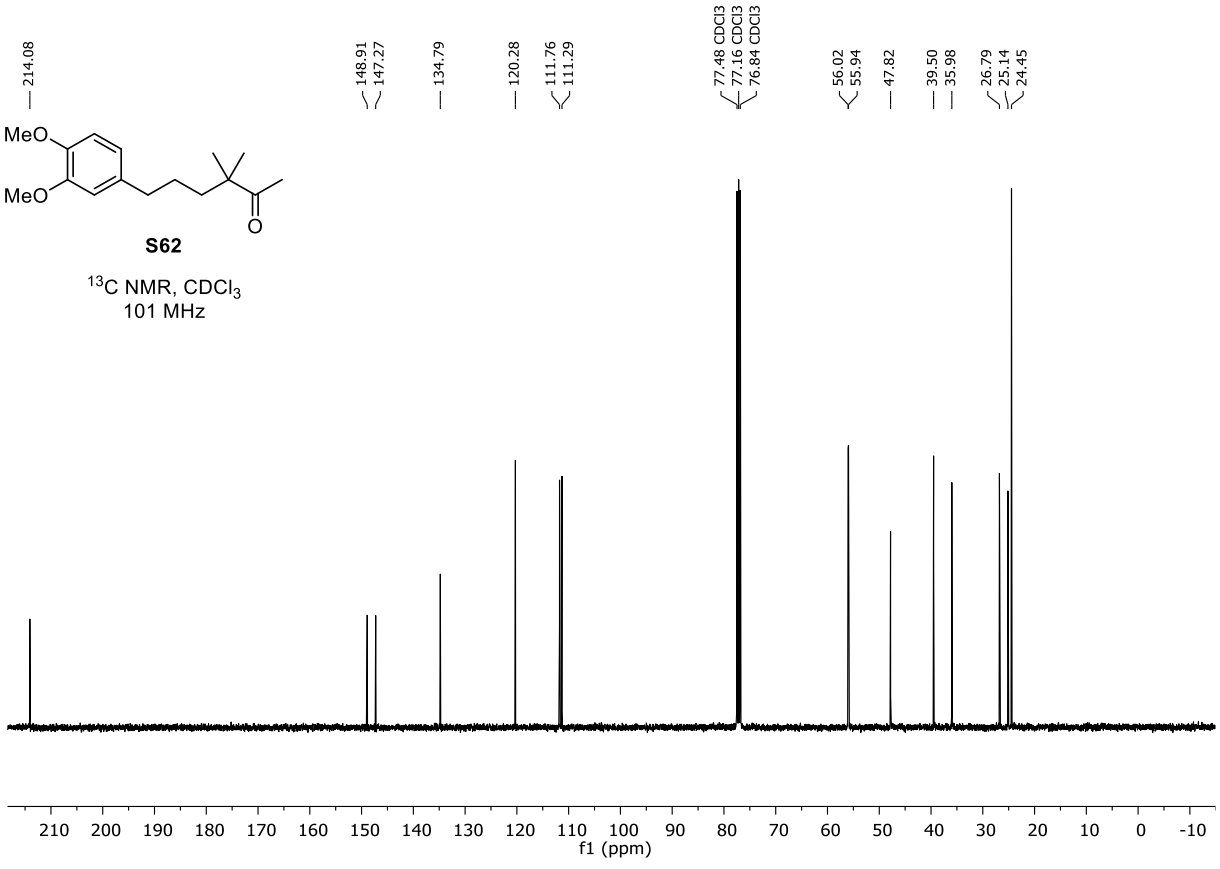
S61

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



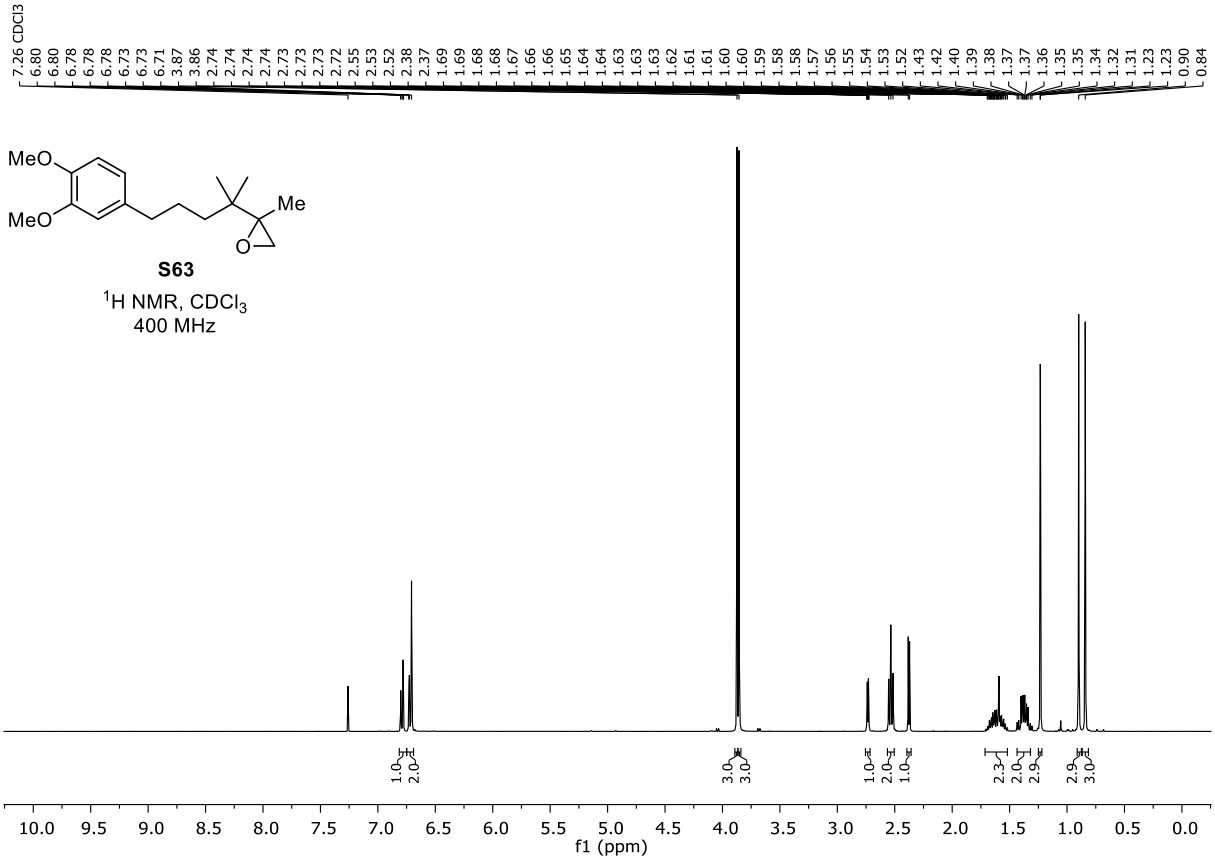
S62

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



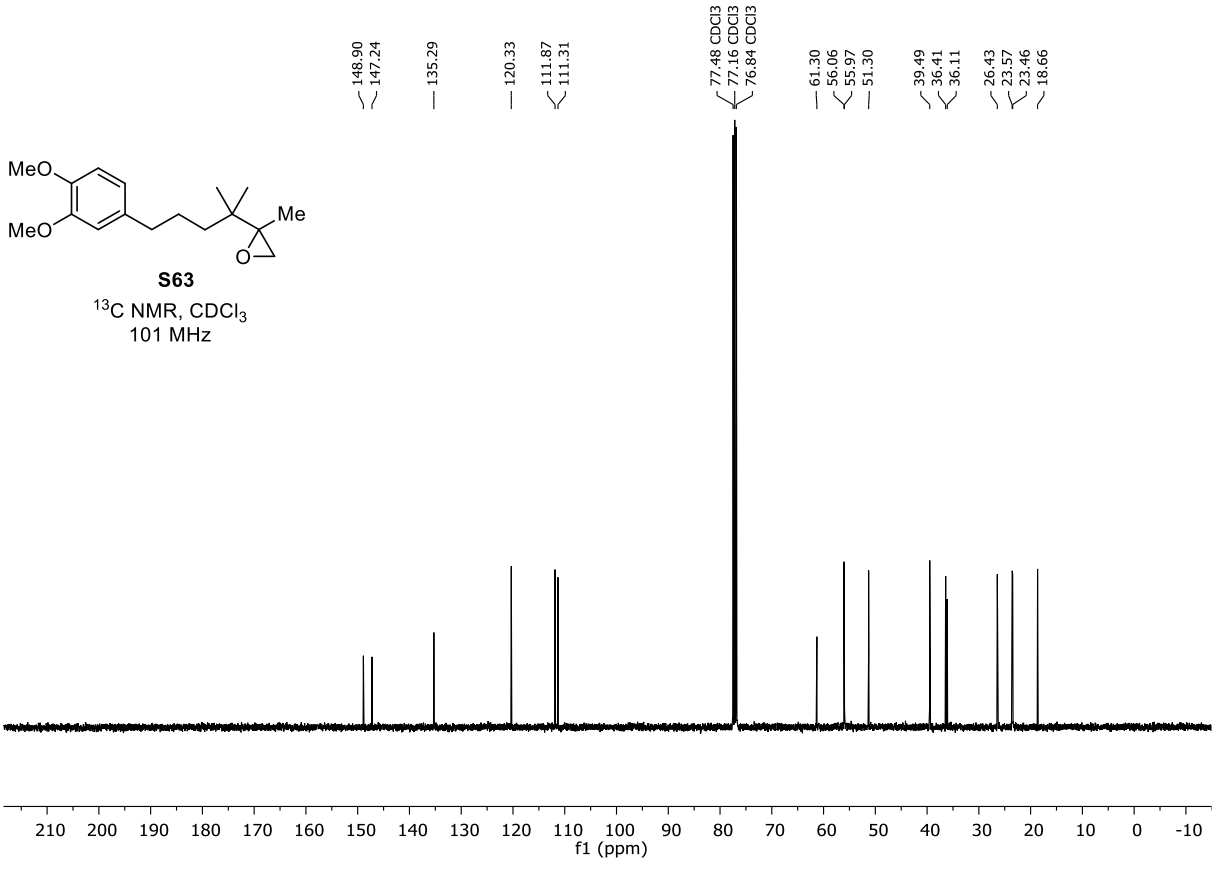
S62

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



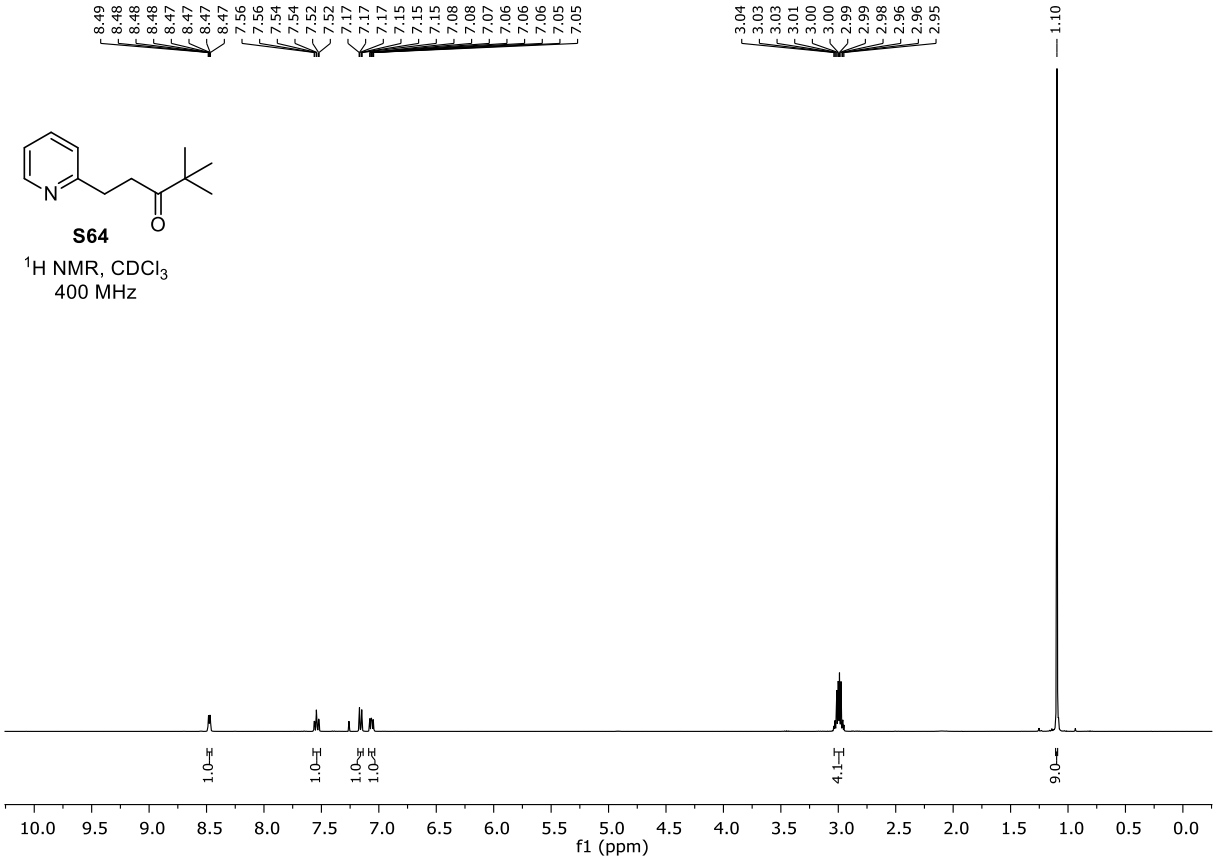
S63

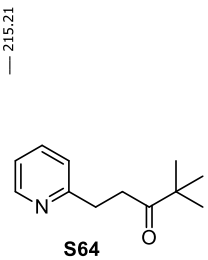
^{1}H NMR, $CDCl_3$
400 MHz



S63

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



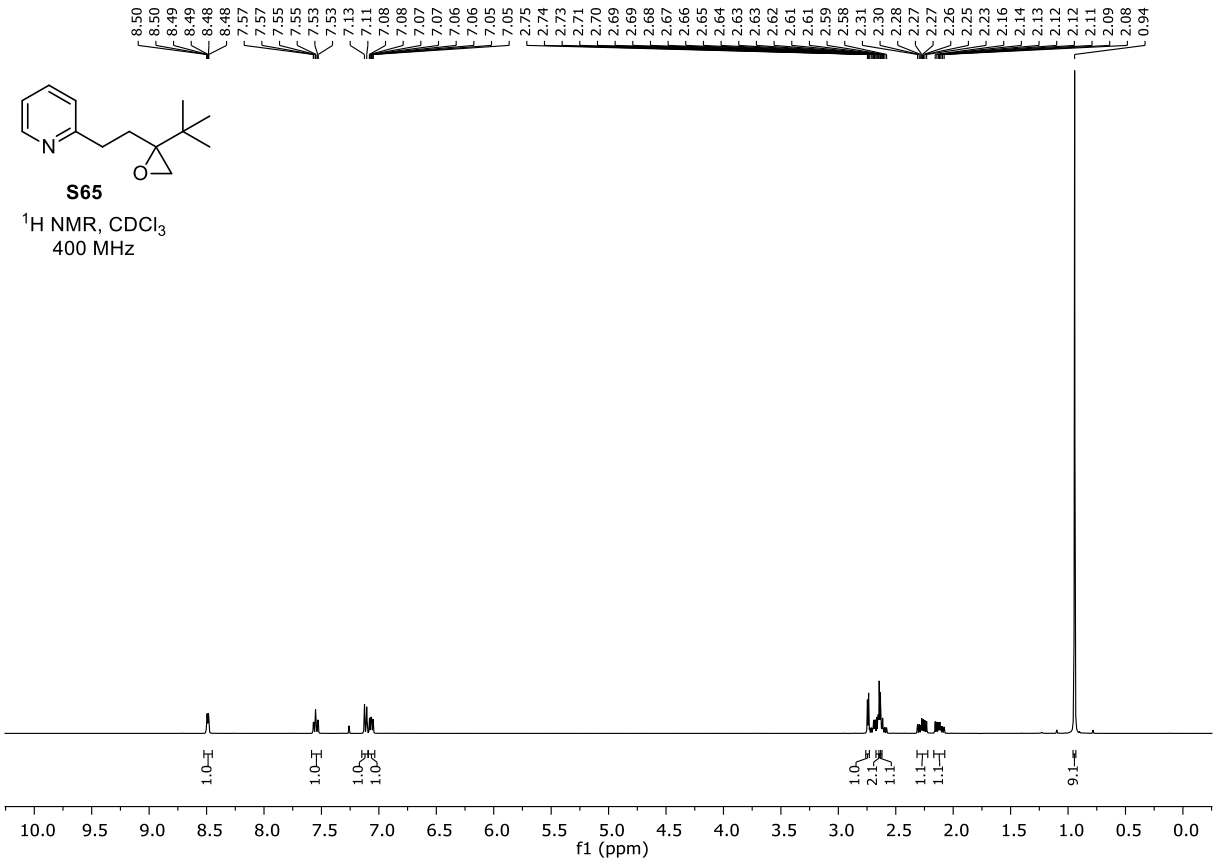


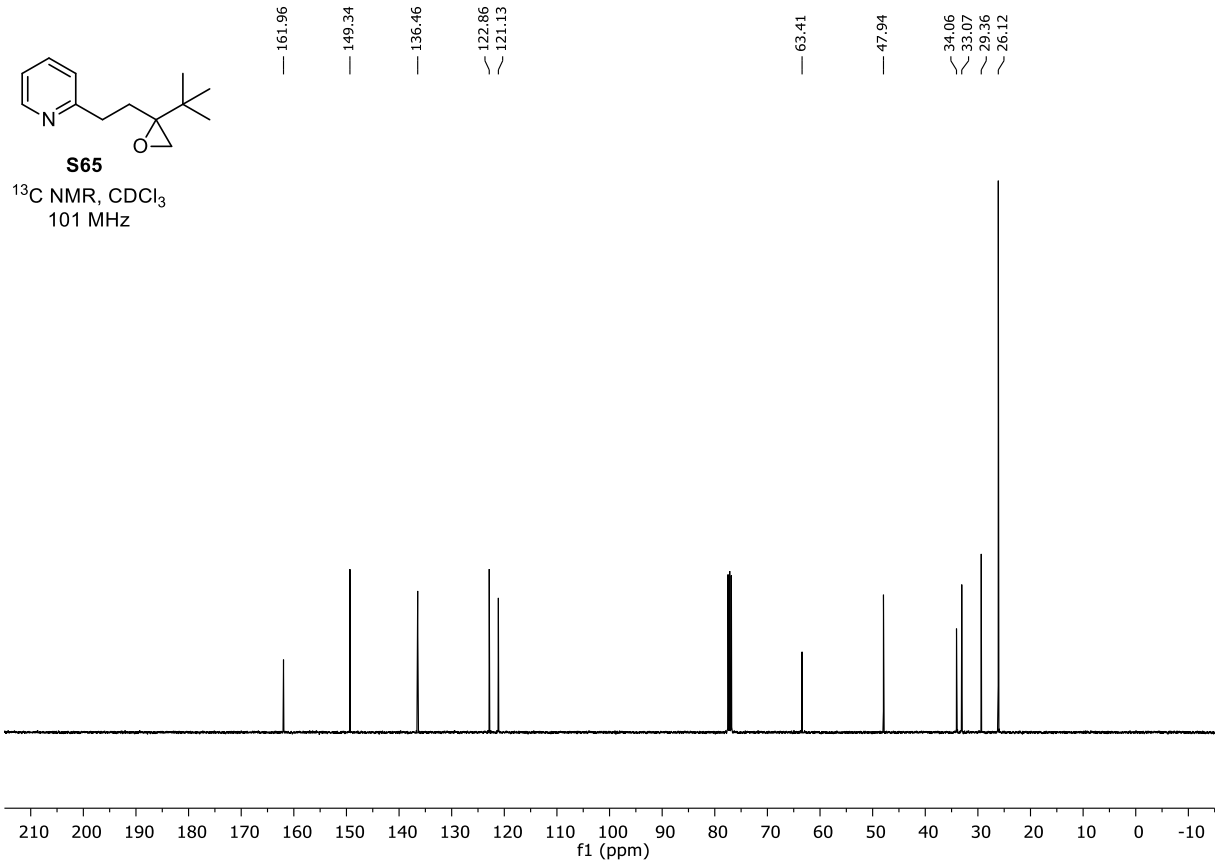
S64

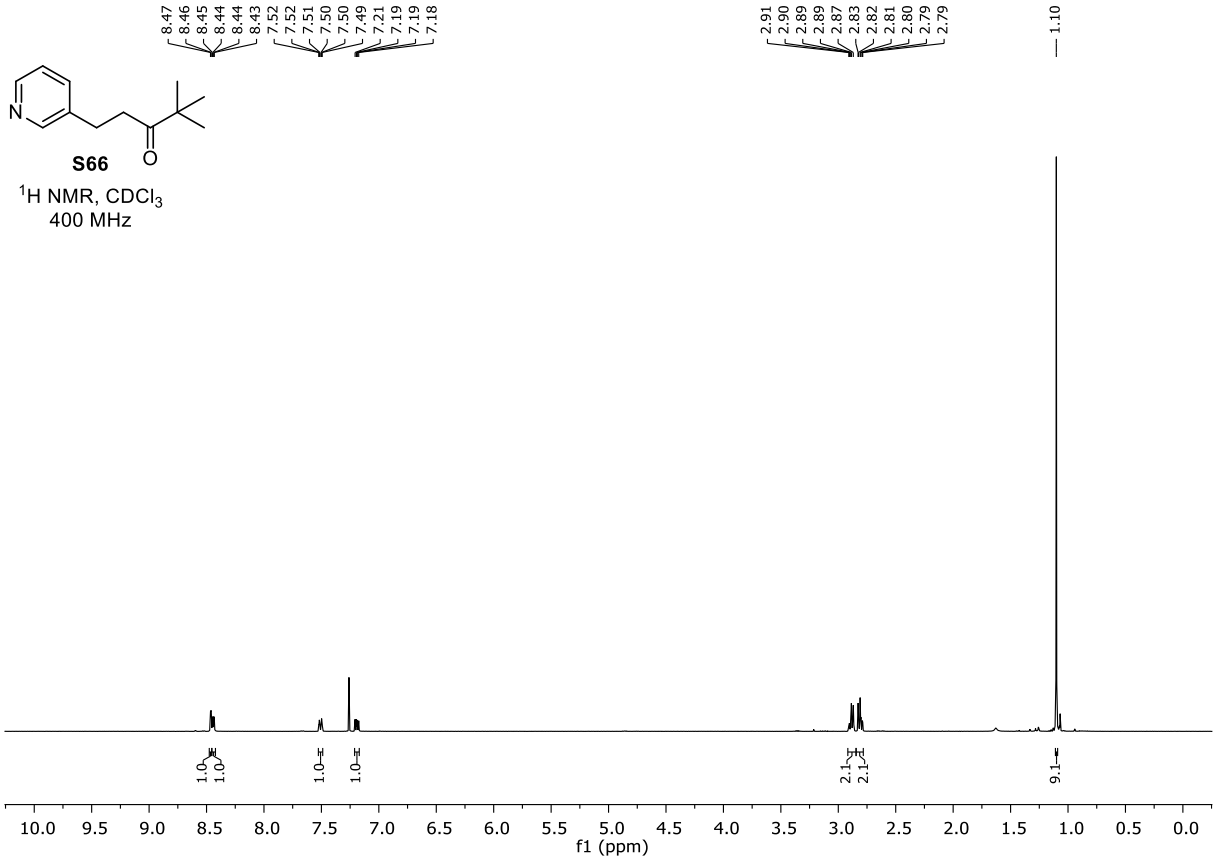
^{1}H NMR, $CDCl_3$
400 MHz

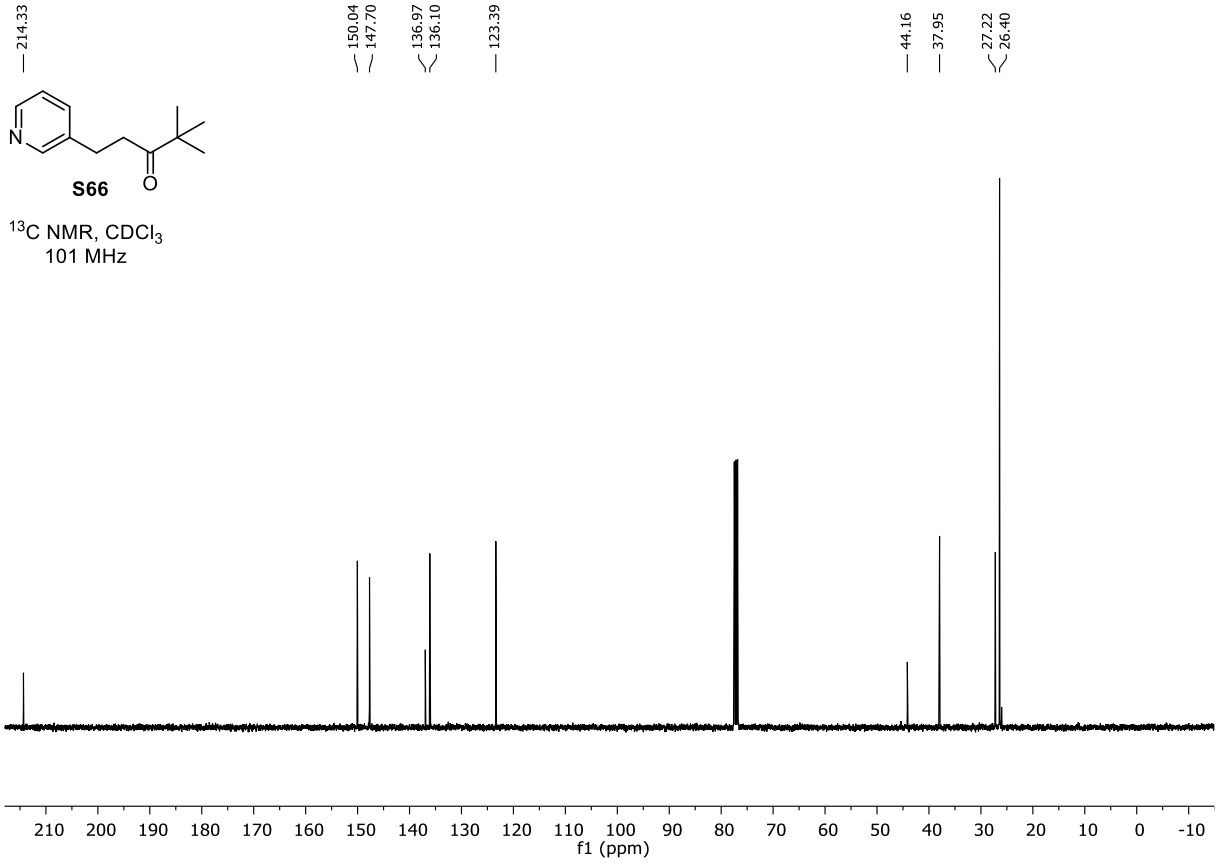
S64

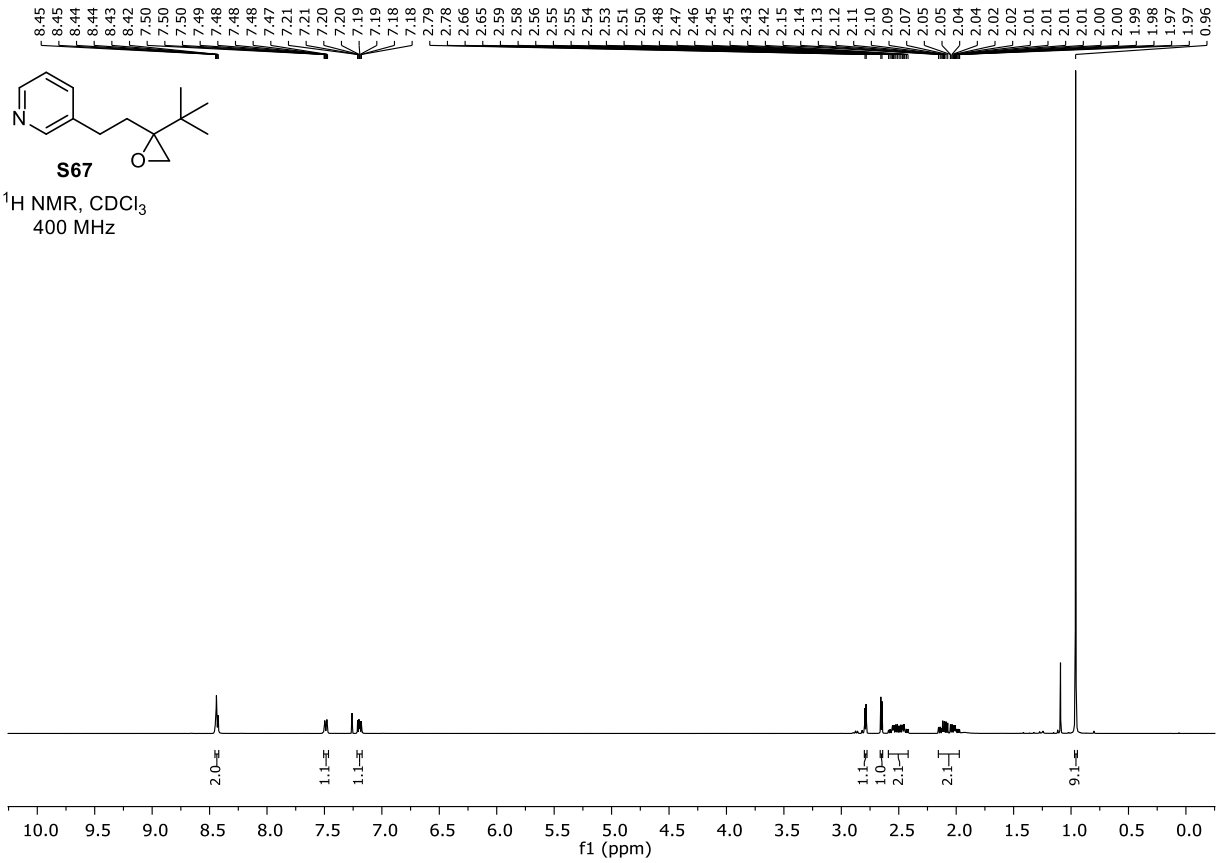
^{13}C NMR, $CDCl_3$
101 MHz

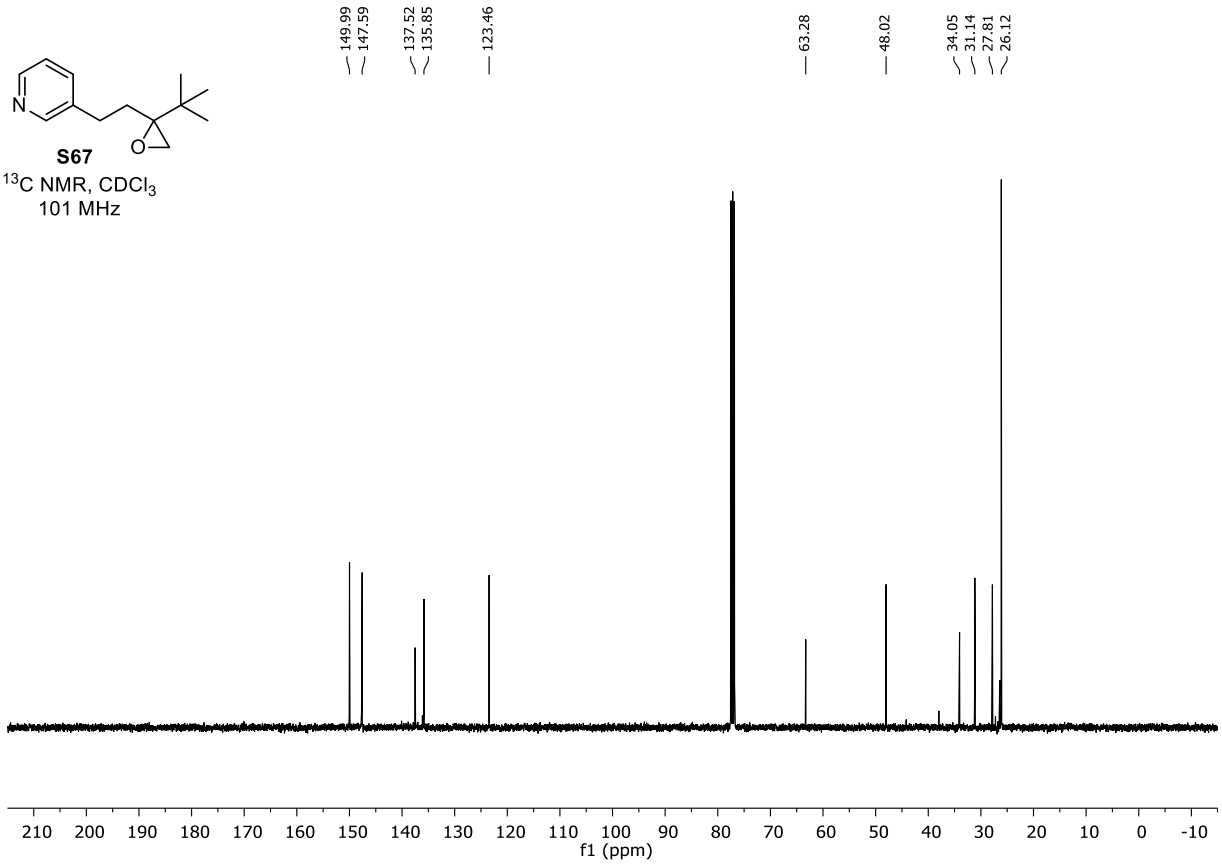

S65
1H NMR, CDCl3
400 MHz
f1 (ppm)

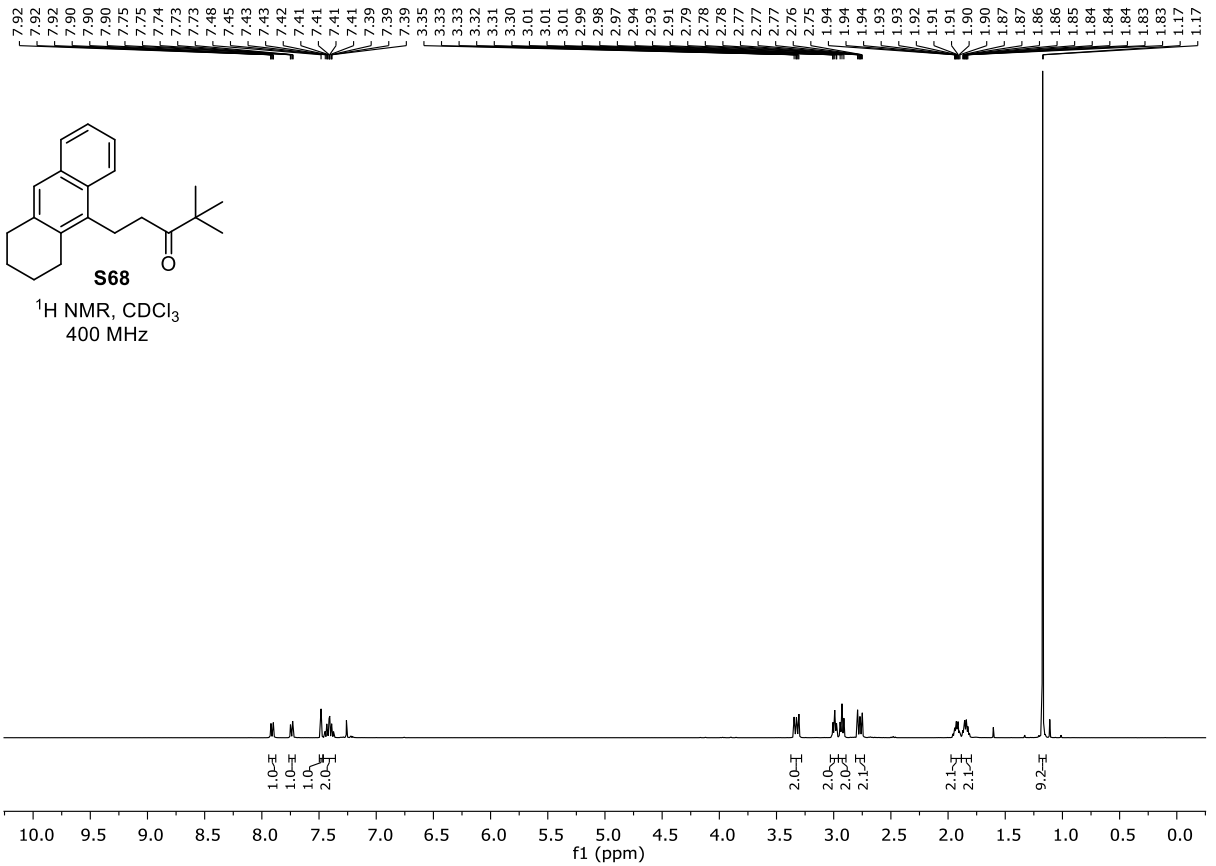

S65
13C NMR, CDCl3
101 MHz
f1 (ppm)

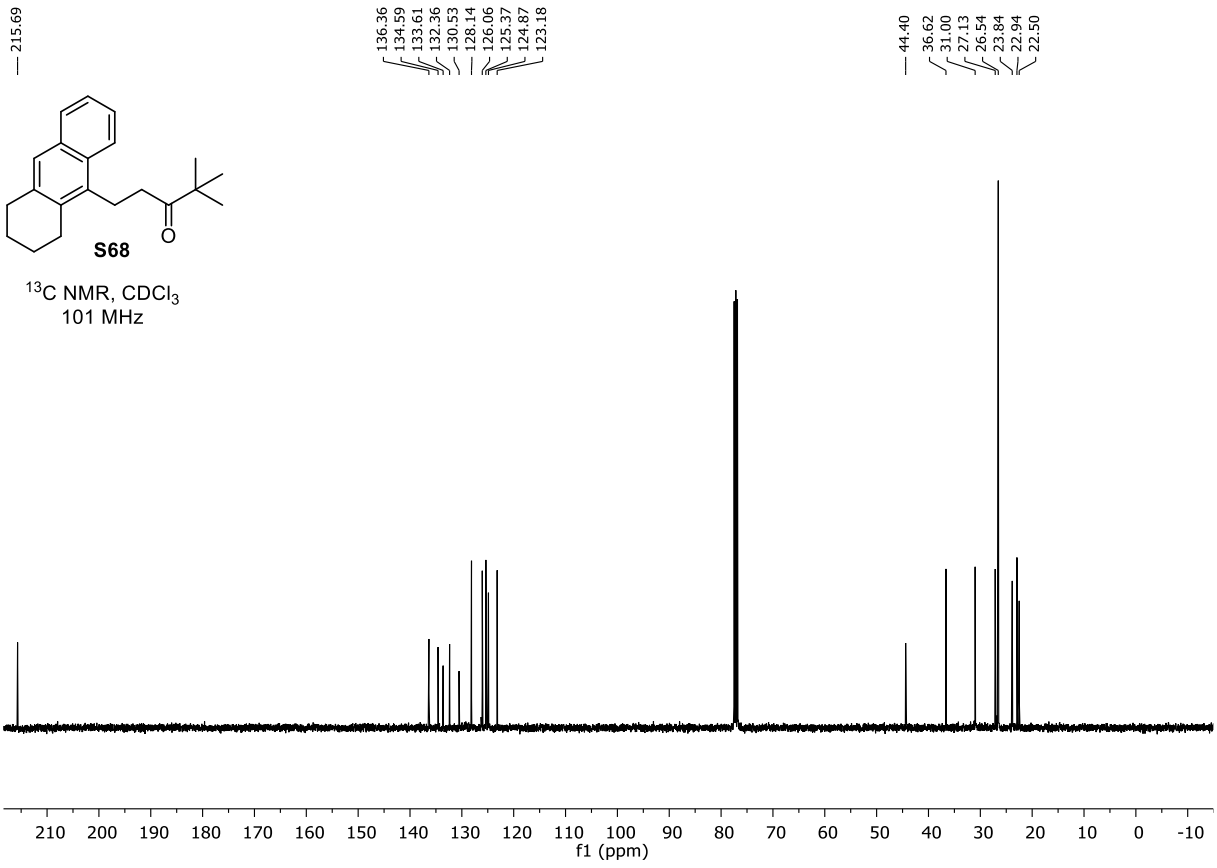

8.47
8.46
8.45
8.44
8.44
8.43
7.52
7.52
7.51
7.50
7.50
7.49
7.21
7.19
7.19
7.18
2.91
2.90
2.89
2.89
2.87
2.83
2.82
2.81
2.80
2.79
2.79
1.10
S66
1H NMR, CDCl3
400 MHz
1.0
1.0
1.0
1.0
2.1
2.1
9.1
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

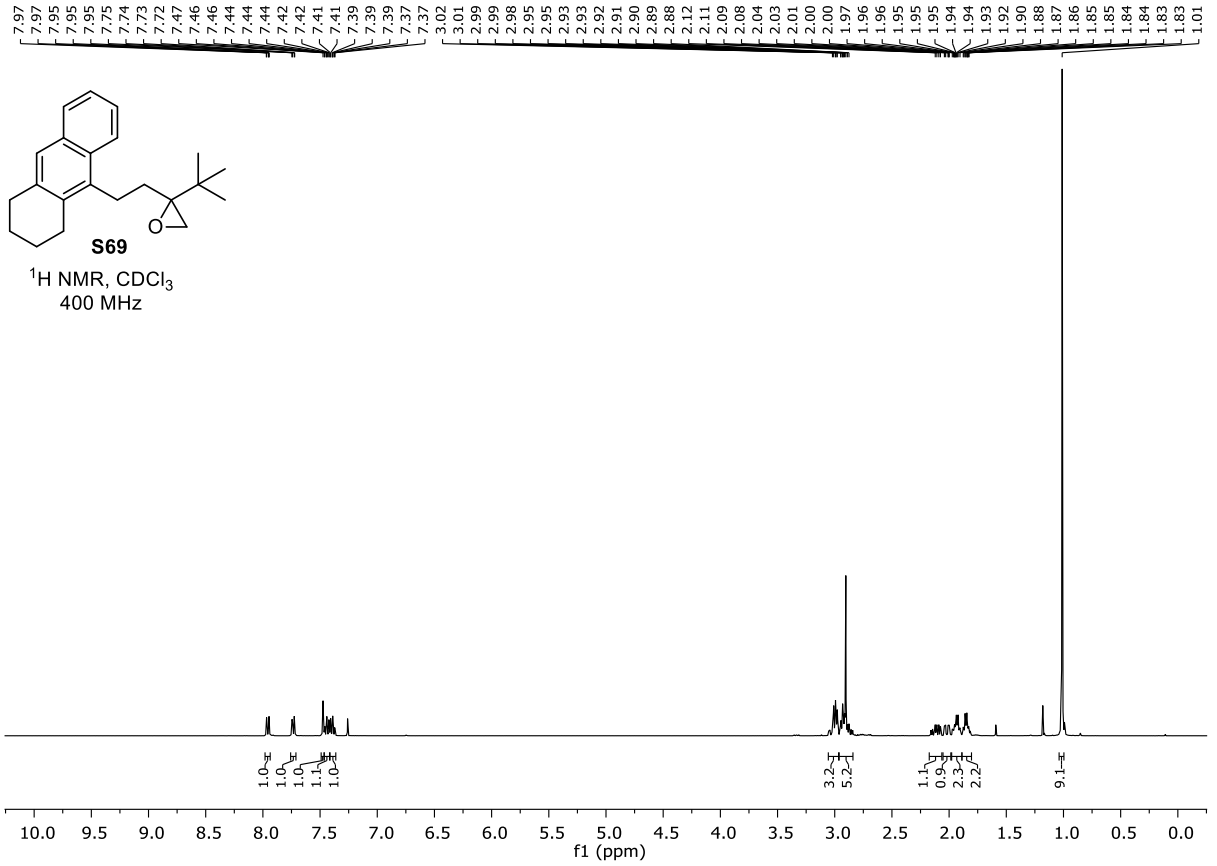

214.33
150.04
147.70
136.97
136.10
123.39
44.16
37.95
27.22
26.40
S66
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

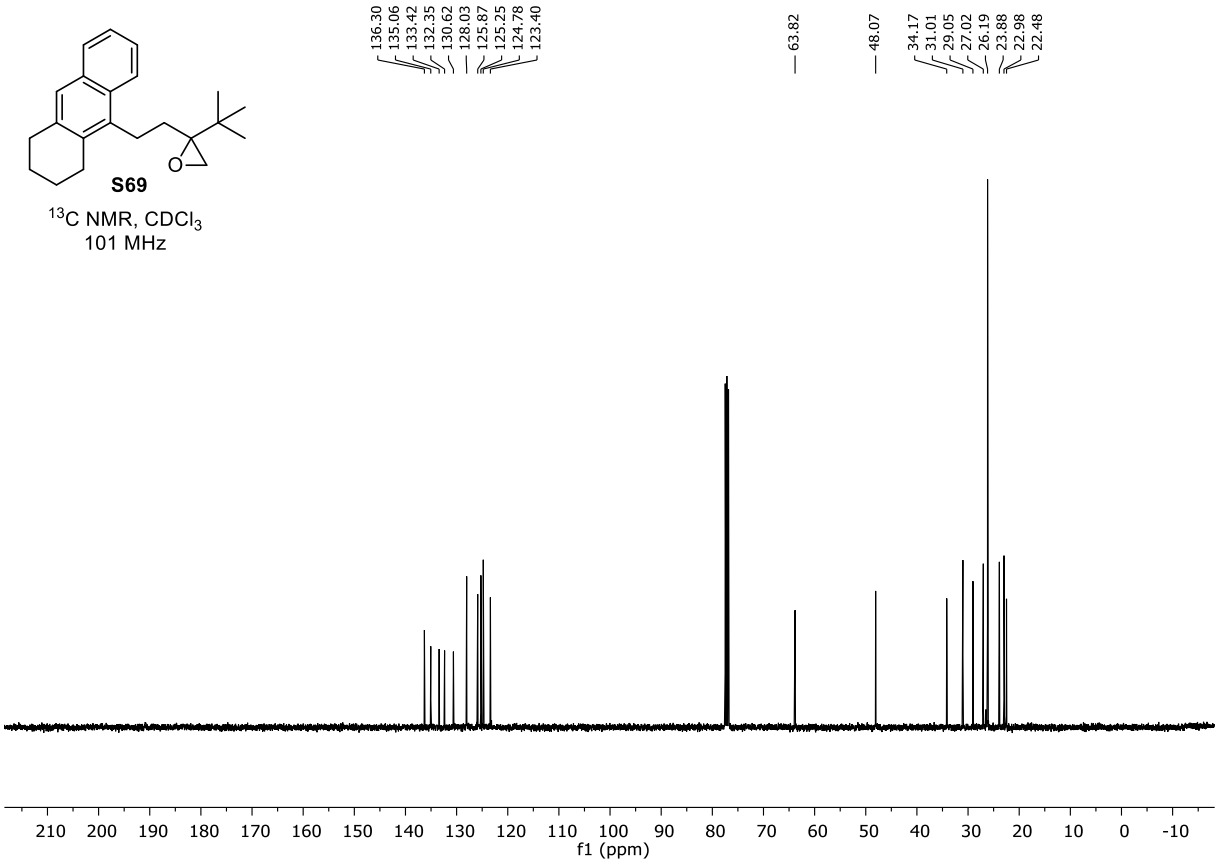

S67
^{1}H NMR, CDCl$_3$
400 MHz
f1 (ppm)

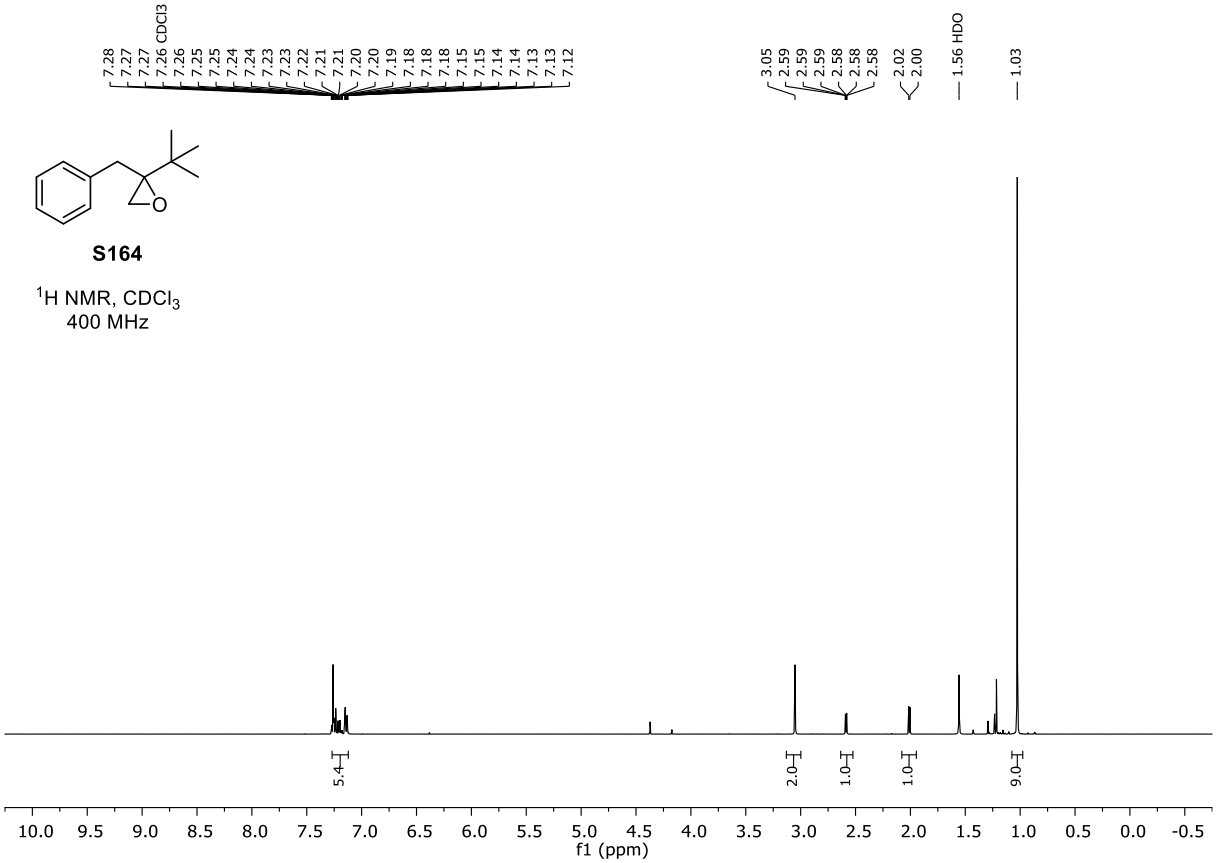

S67
^{13}C NMR, CDCl$_3$
101 MHz
f1 (ppm)


S68
^{1}H NMR, $CDCl_3$
400 MHz
f1 (ppm)


S68
^{13}C NMR, $CDCl_3$
101 MHz
f1 (ppm)

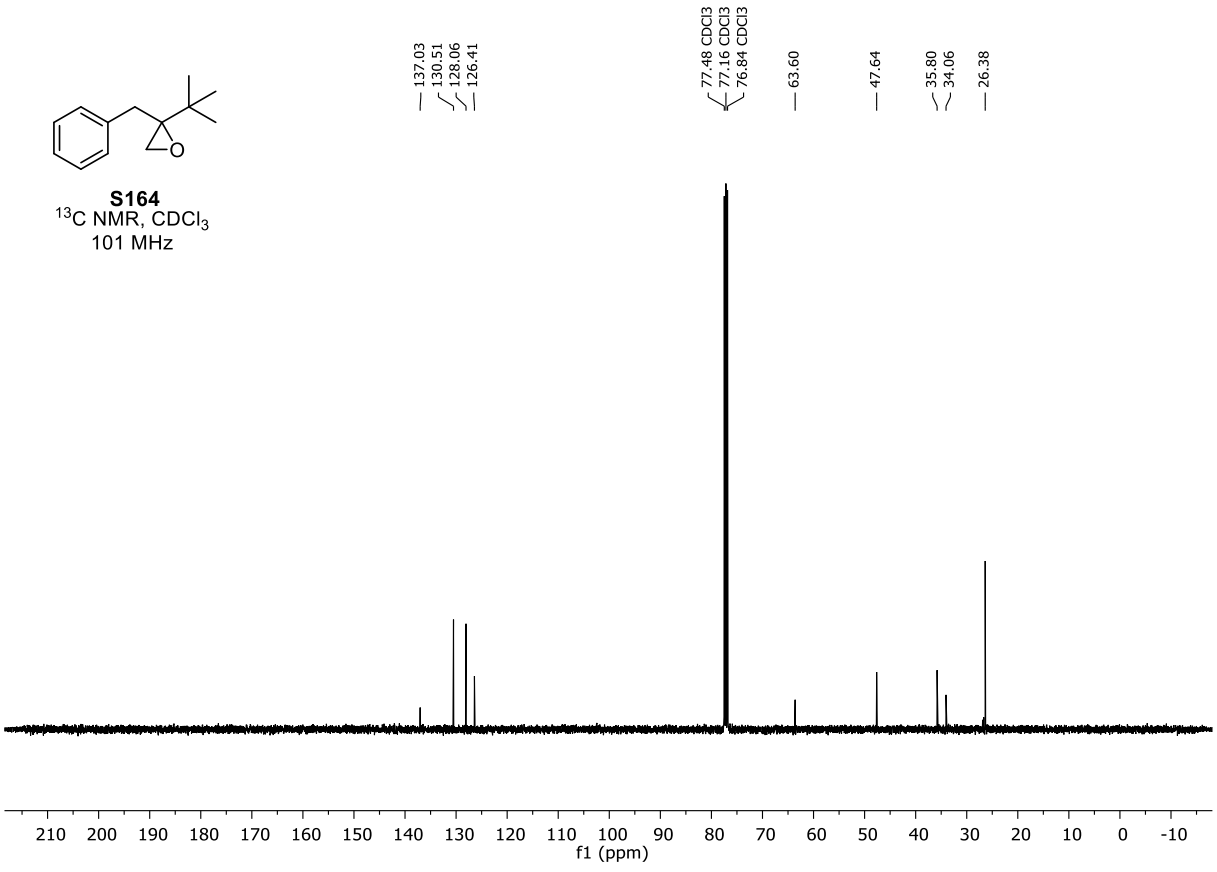

S69
^{1}H NMR, CDCl$_3$
400 MHz
f1 (ppm)


S69
^{13}C NMR, CDCl$_3$
101 MHz
f1 (ppm)



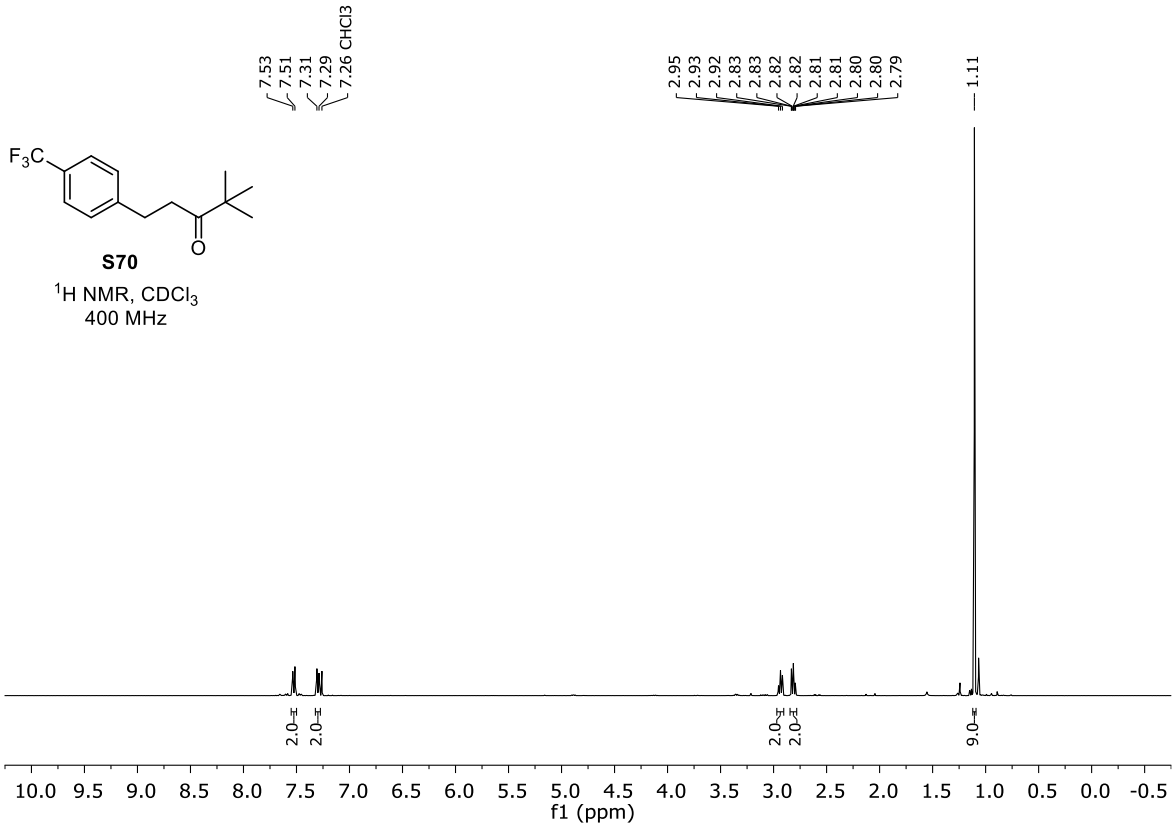
S164

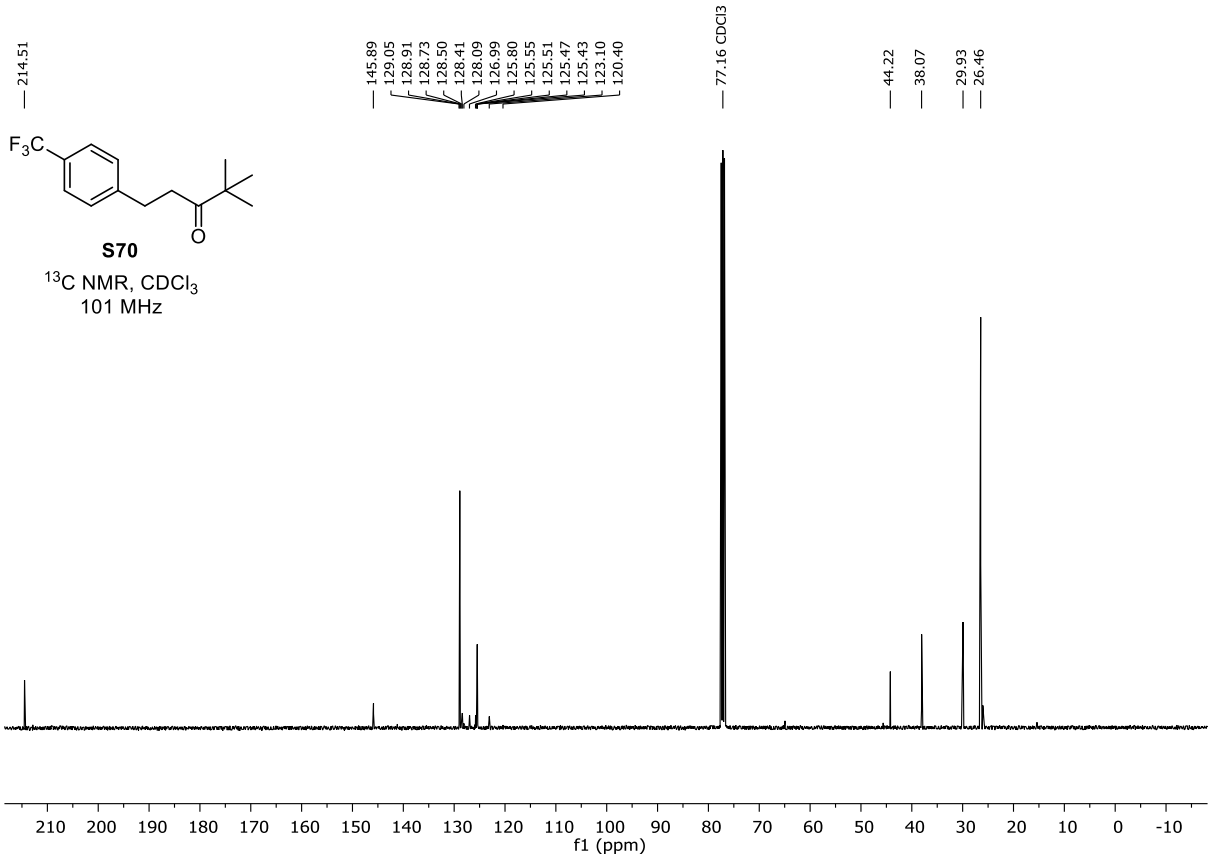
^{1}H NMR, $CDCl_3$
400 MHz

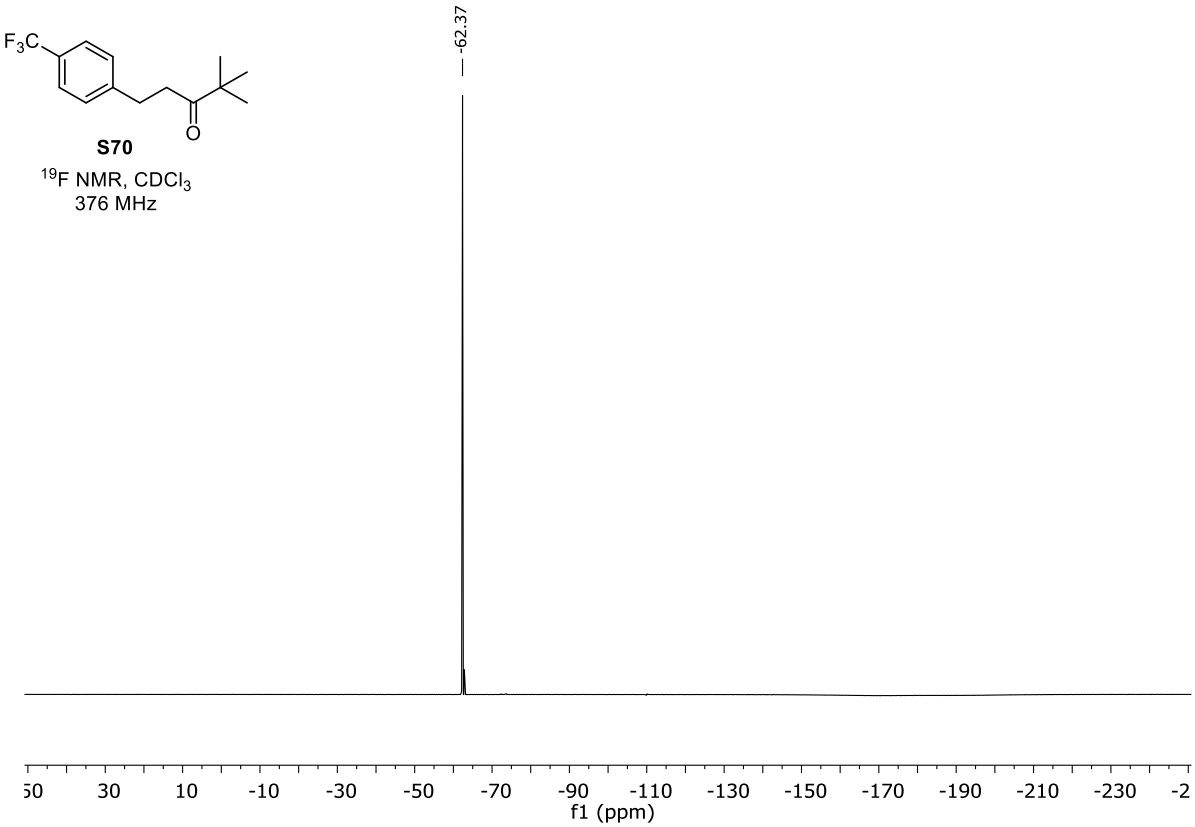


S164

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

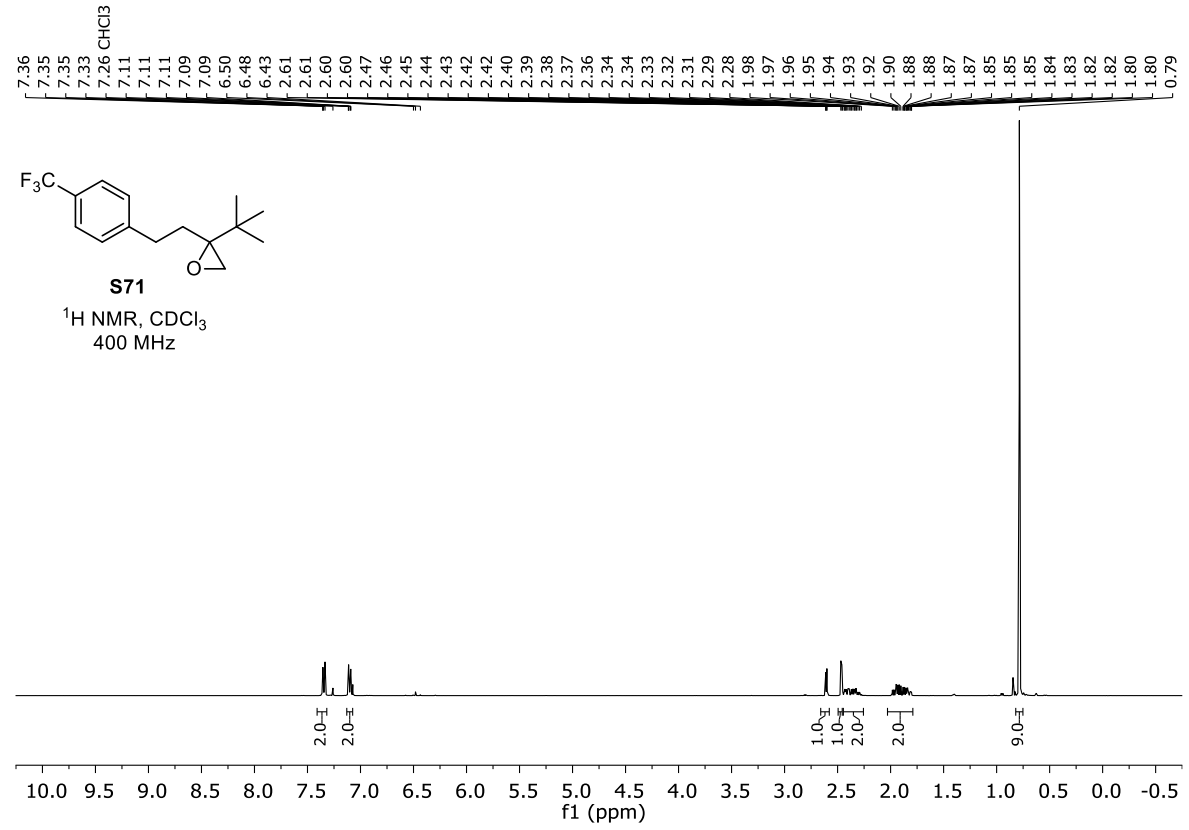

7.53
7.51
7.31
7.29
7.26 CHCl3
2.95
2.93
2.92
2.83
2.83
2.82
2.82
2.81
2.81
2.80
2.80
2.79
1.11
F3C
O
S70
1H NMR, CDCl3
400 MHz
2.0
2.0
2.0
2.0
9.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

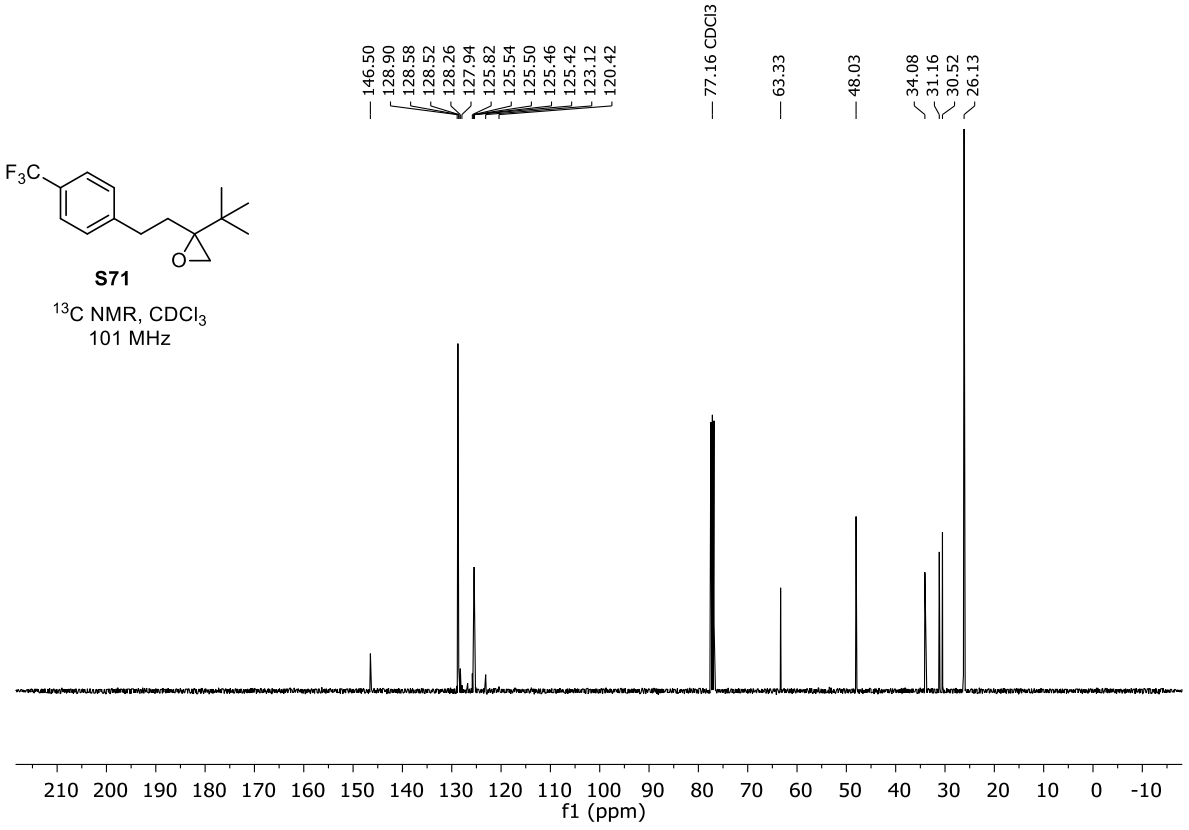

214.51
145.89
129.05
128.91
128.73
128.50
128.41
128.09
126.99
125.80
125.55
125.51
125.47
125.43
123.10
120.40
77.16 CDCl3
44.22
38.07
29.93
26.46
F3C
O
S70
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

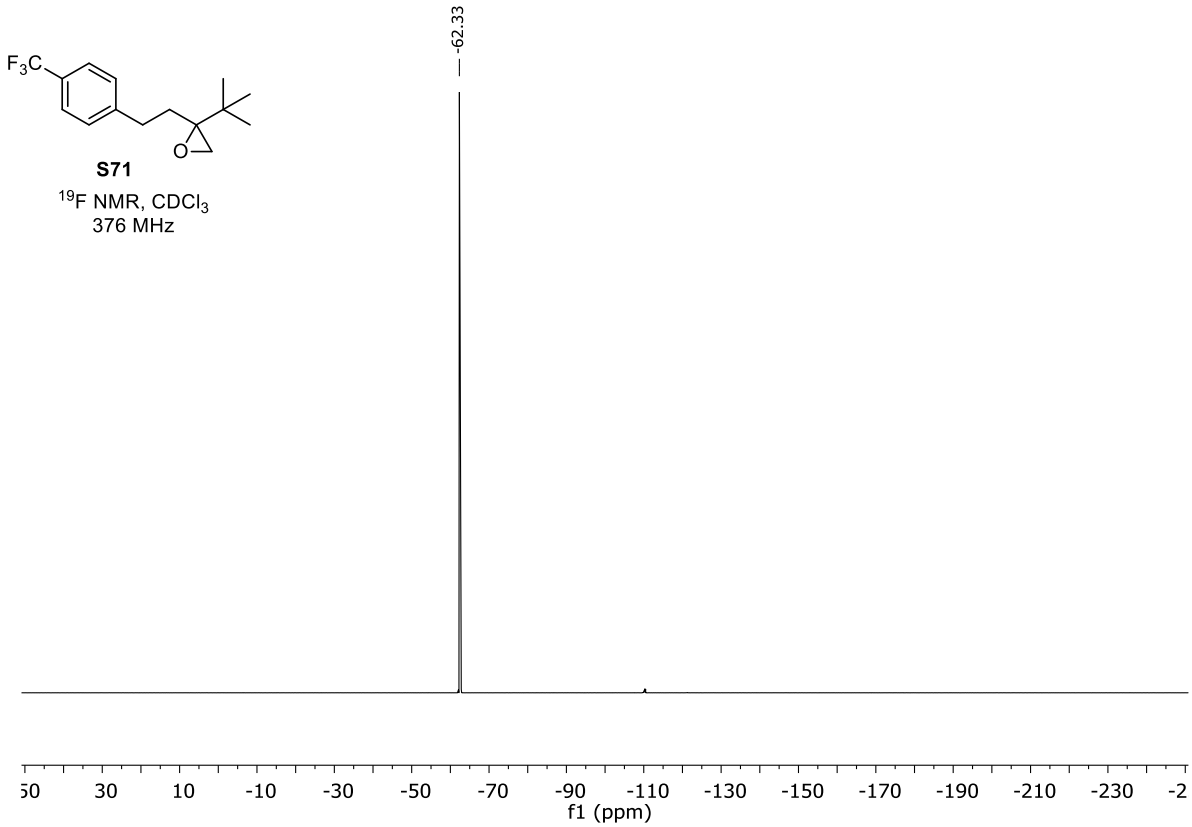


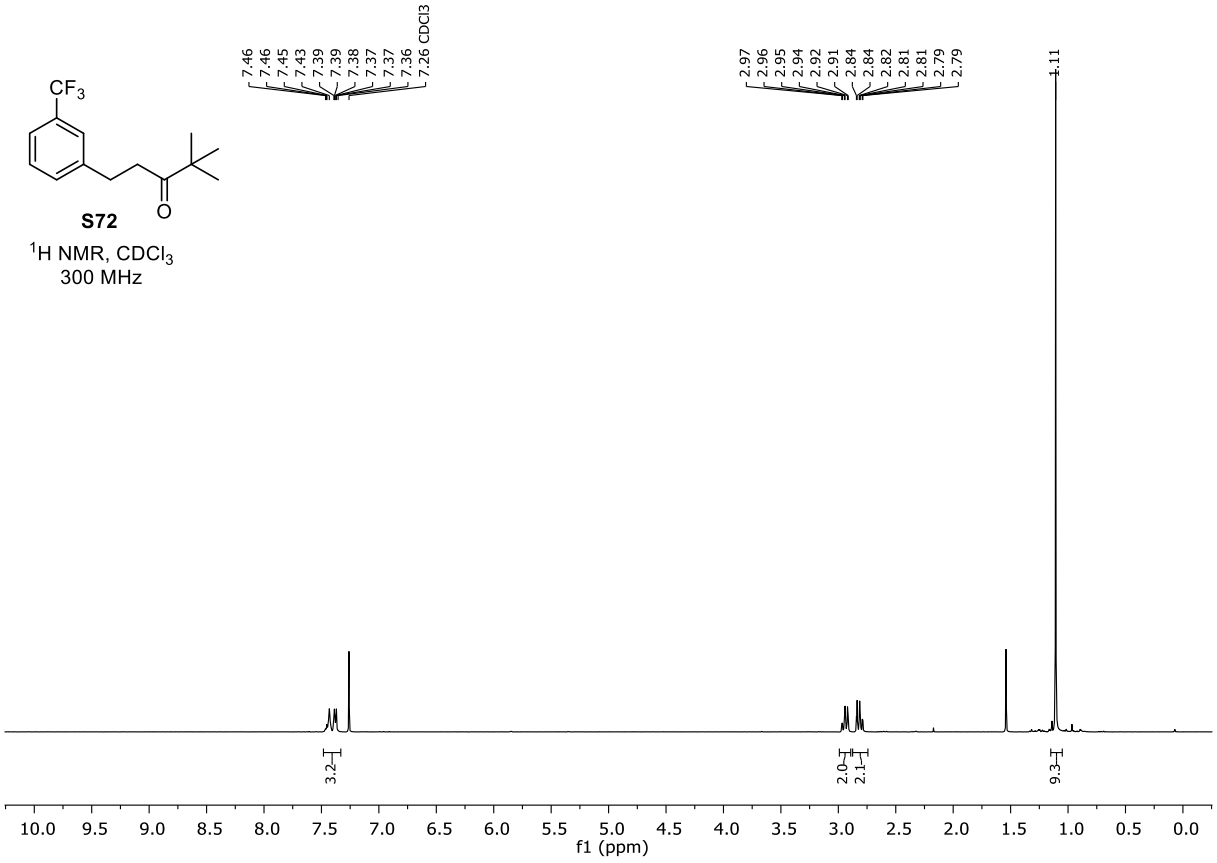
S70

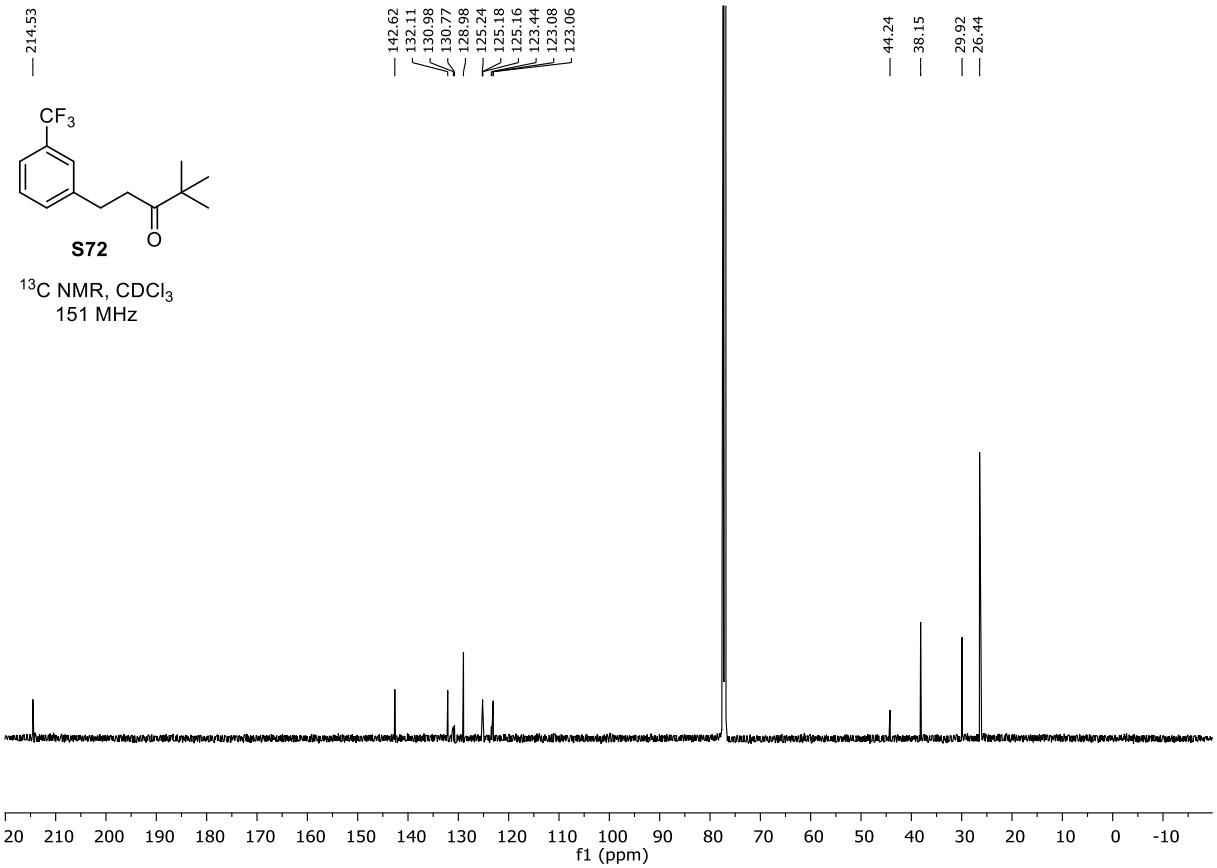
^{19}F NMR, $CDCl_3$
376 MHz

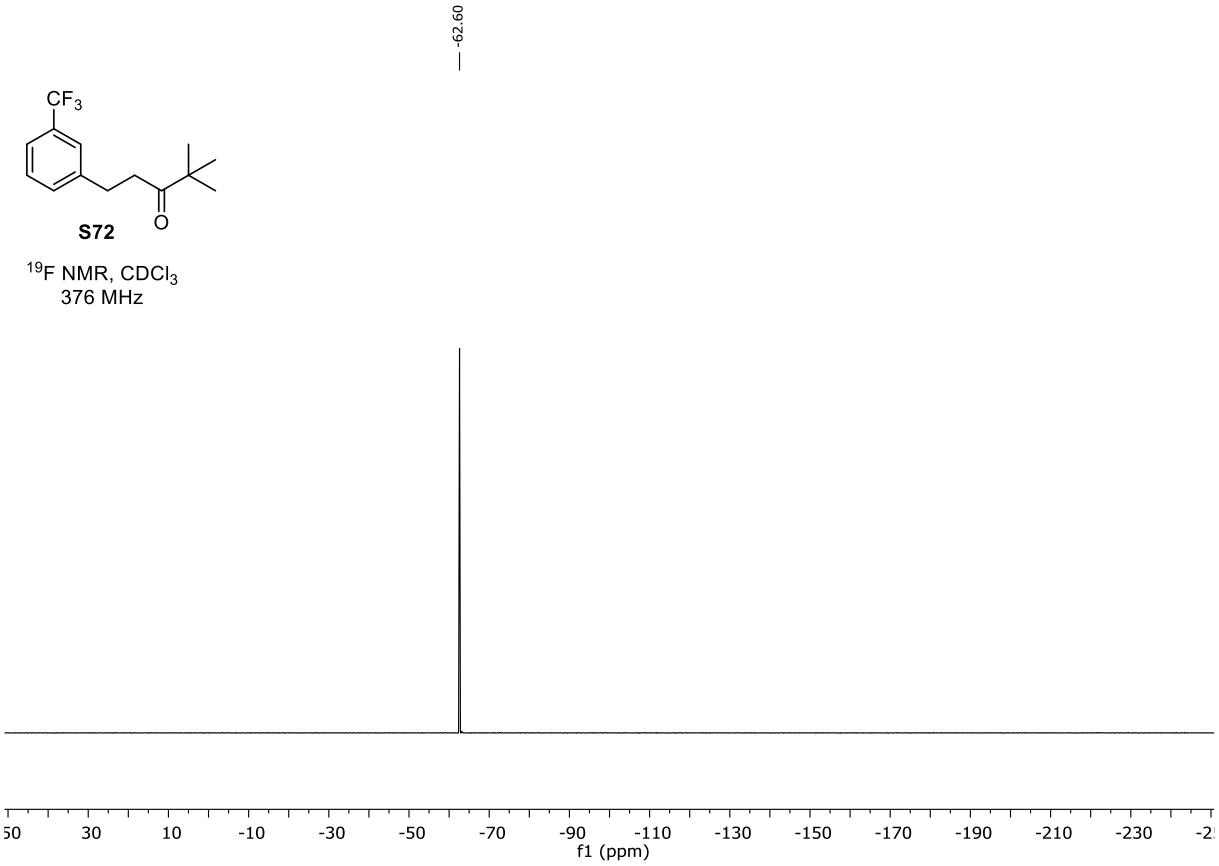

7.36 7.35 7.35 7.33 7.26 CHCl3 7.11 7.11 7.11 7.09 7.09 6.50 6.48 6.43 2.61 2.61 2.60 2.60 2.47 2.46 2.45 2.44 2.43 2.42 2.42 2.40 2.39 2.38 2.37 2.36 2.34 2.34 2.33 2.32 2.31 2.29 2.28 1.98 1.97 1.96 1.95 1.94 1.93 1.92 1.90 1.88 1.88 1.87 1.87 1.85 1.85 1.85 1.84 1.83 1.82 1.82 1.80 1.80 0.79
F3C
O
S71
1H NMR, CDCl3
400 MHz
2.0 2.0 1.0 1.0 2.0 2.0 9.0
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 -0.5
f1 (ppm)

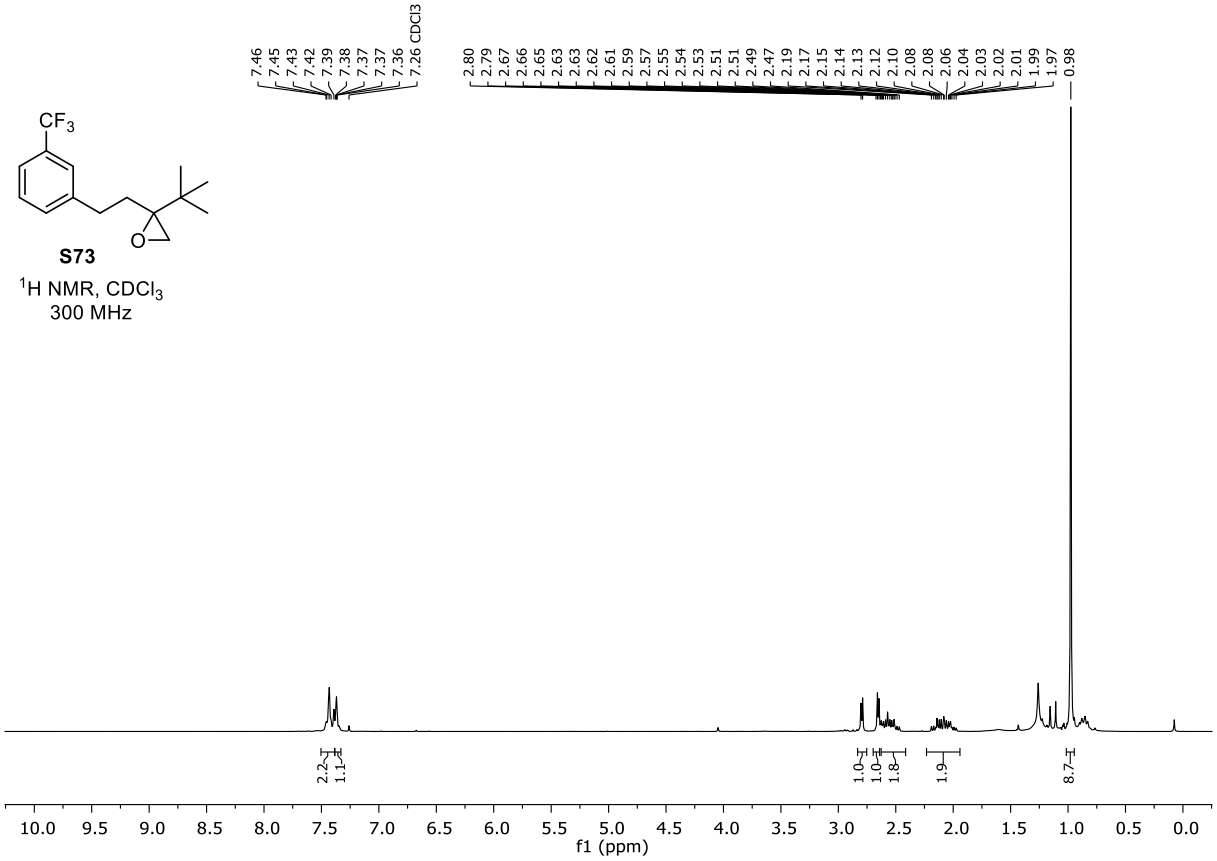

146.50 128.90 128.58 128.52 128.26 127.94 125.82 125.54 125.50 125.46 125.42 123.12 120.42 77.16 CDCl3 63.33 48.03 34.08 31.16 30.52 26.13
F3C
O
S71
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

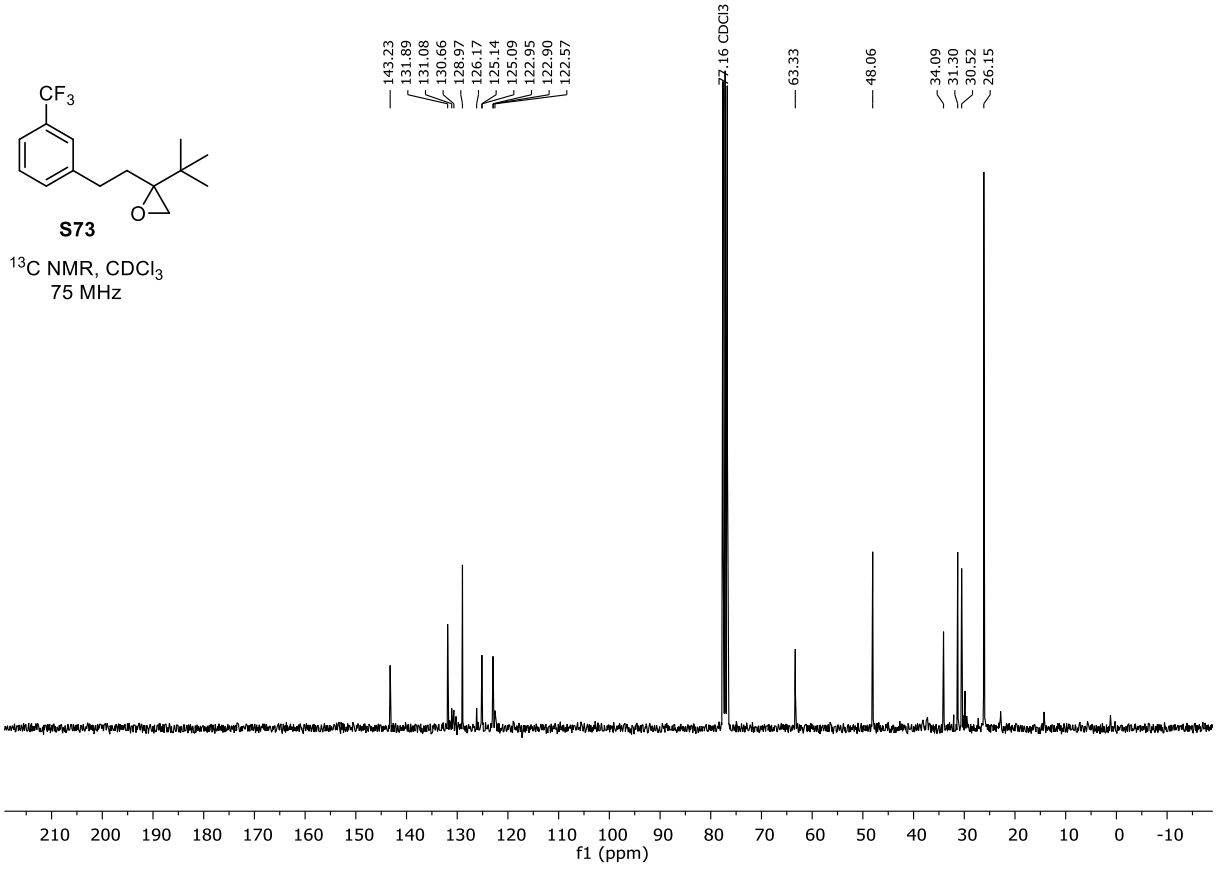

F3C
O
S71
19F NMR, CDCl3
376 MHz
-62.33
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
-2
f1 (ppm)

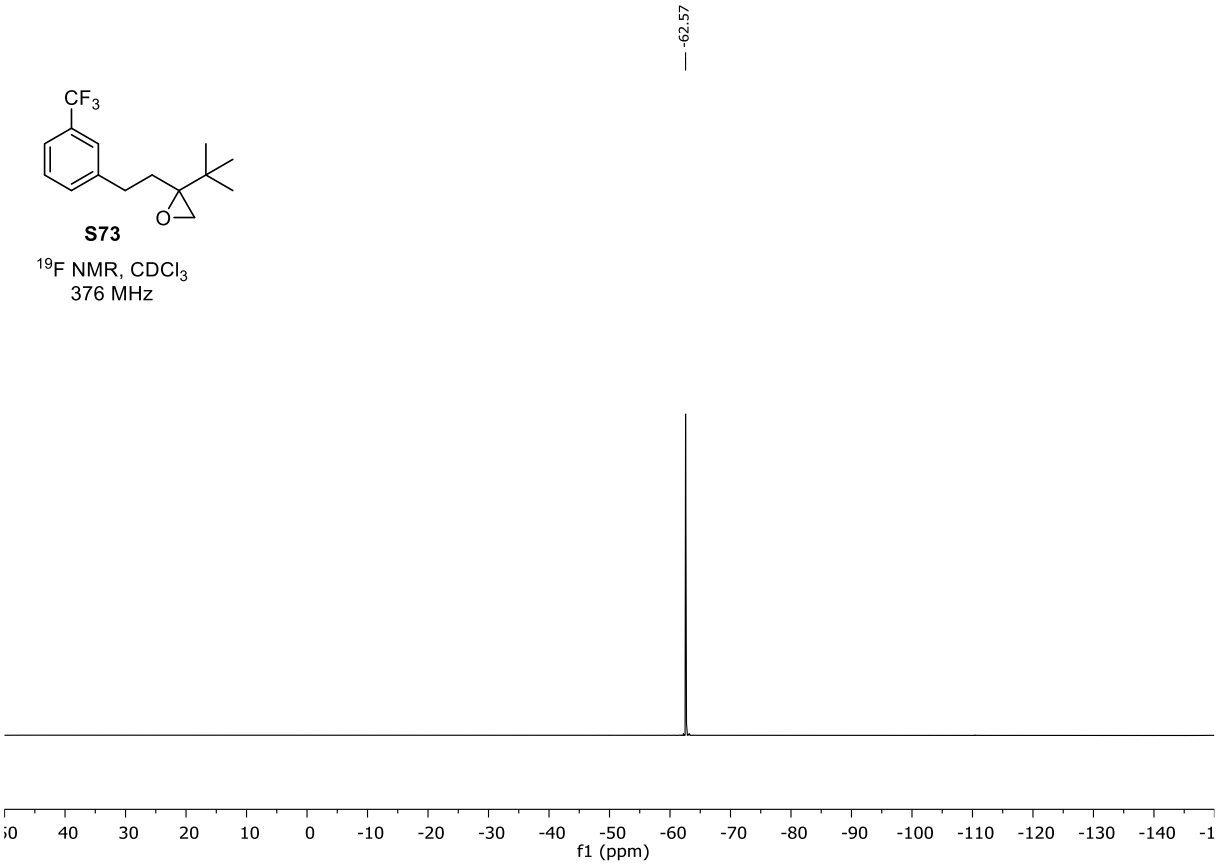

7.46
7.46
7.45
7.43
7.39
7.39
7.38
7.37
7.37
7.36
7.26 CDCl3
2.97
2.96
2.95
2.94
2.92
2.91
2.84
2.84
2.82
2.81
2.81
2.79
2.79
1.11
CF3
O
S72
1H NMR, CDCl3
300 MHz
3.2
2.0
2.1
9.3
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

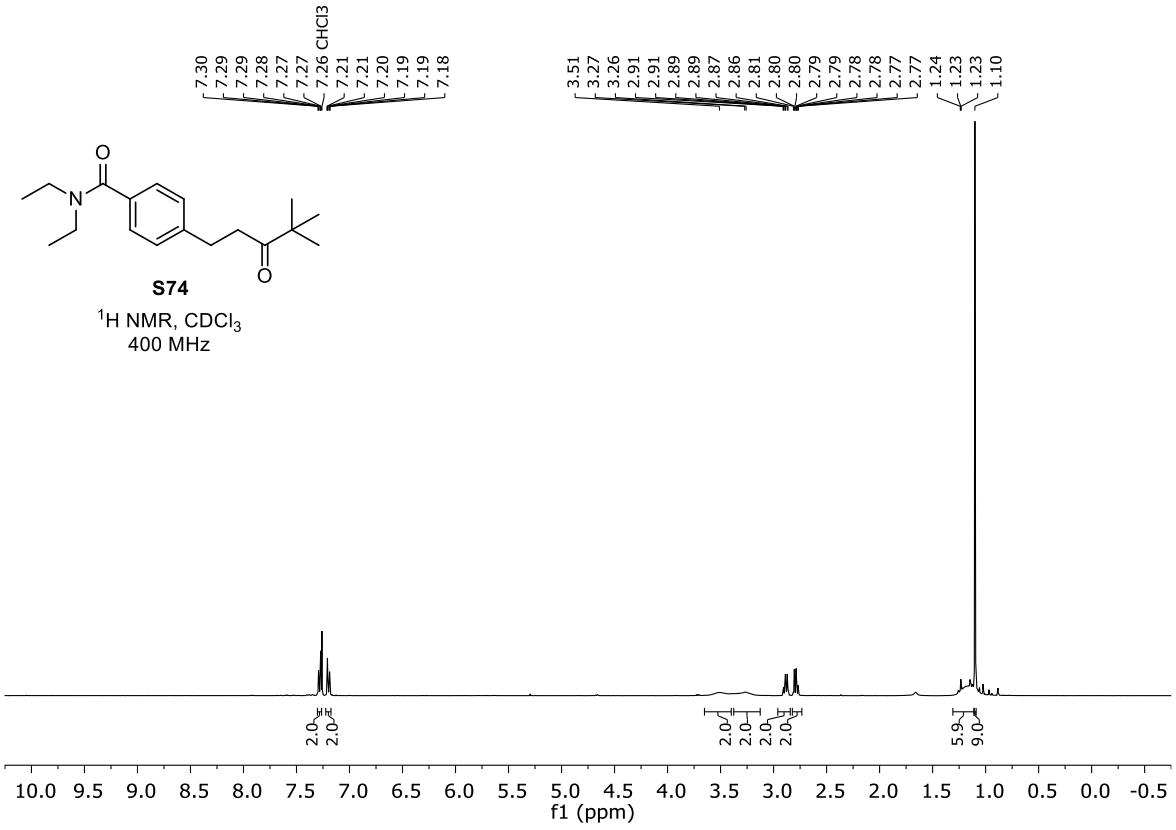

214.53
142.62
132.11
130.98
130.77
128.98
125.24
125.18
125.16
123.44
123.08
123.06
44.24
38.15
29.92
26.44
CF3
O
S72
13C NMR, CDCl3
151 MHz
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


-62.60
CF3
O
S72
19F NMR, CDCl3
376 MHz
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)


CF3
O
S73
1H NMR, CDCl3
300 MHz
7.46
7.45
7.43
7.42
7.39
7.38
7.37
7.37
7.36
7.26 CDCl3
2.80
2.79
2.67
2.66
2.65
2.63
2.63
2.62
2.61
2.59
2.57
2.55
2.54
2.53
2.51
2.51
2.49
2.47
2.19
2.17
2.15
2.14
2.13
2.12
2.10
2.08
2.08
2.06
2.04
2.03
2.02
2.01
1.99
1.97
0.98
2.2
1.1
1.0
1.0
1.8
1.9
8.7
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)

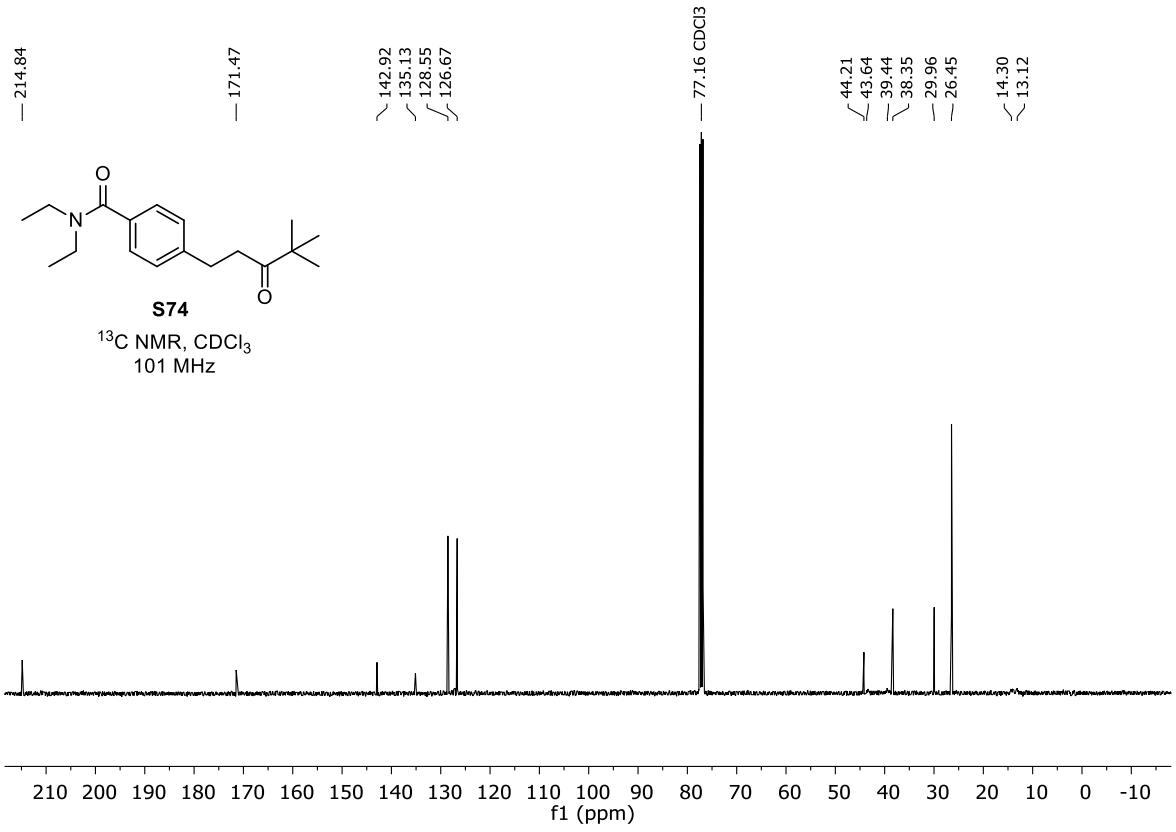

CF3
O
S73
13C NMR, CDCl3
75 MHz
143.23
131.89
131.08
130.66
128.97
126.17
125.14
125.09
122.95
122.90
122.57
77.16 CDCl3
63.33
48.06
34.09
31.30
30.52
26.15
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


-62.57
CF3
O
S73
19F NMR, CDCl3
376 MHz
50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -1
f1 (ppm)



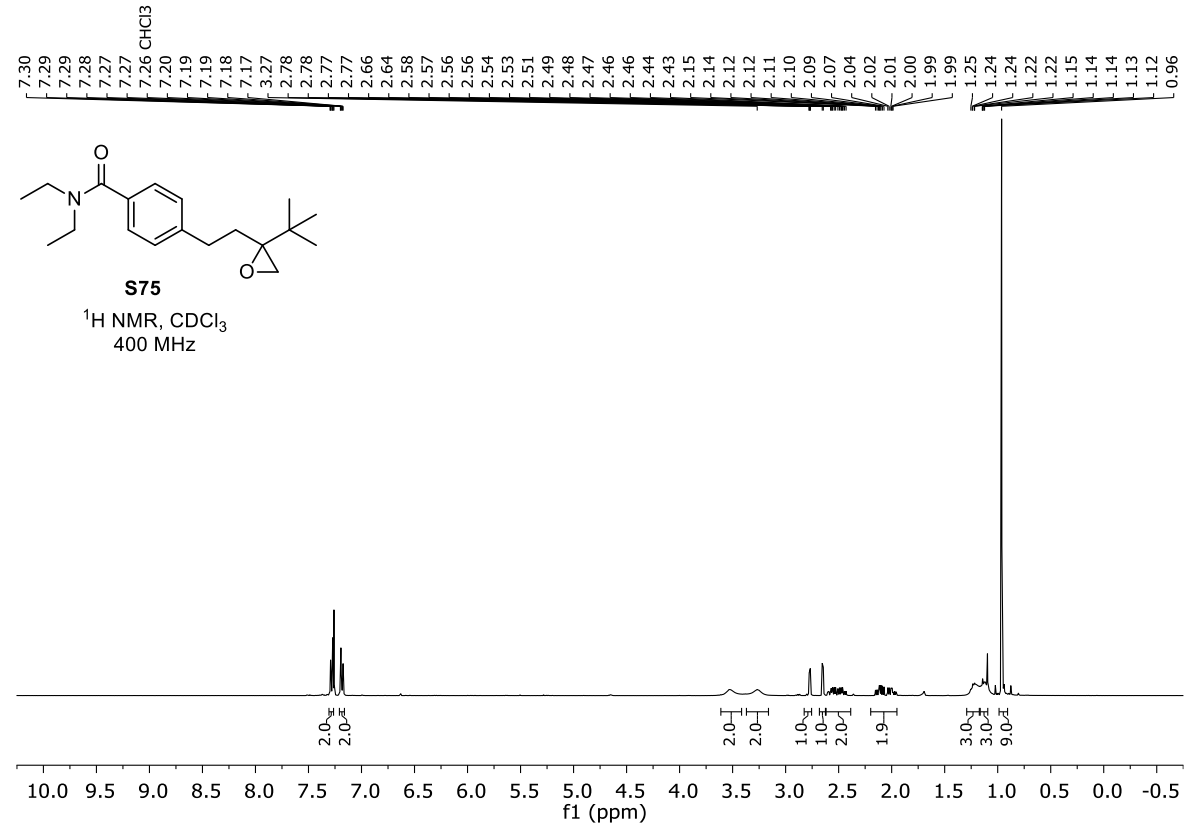
S74

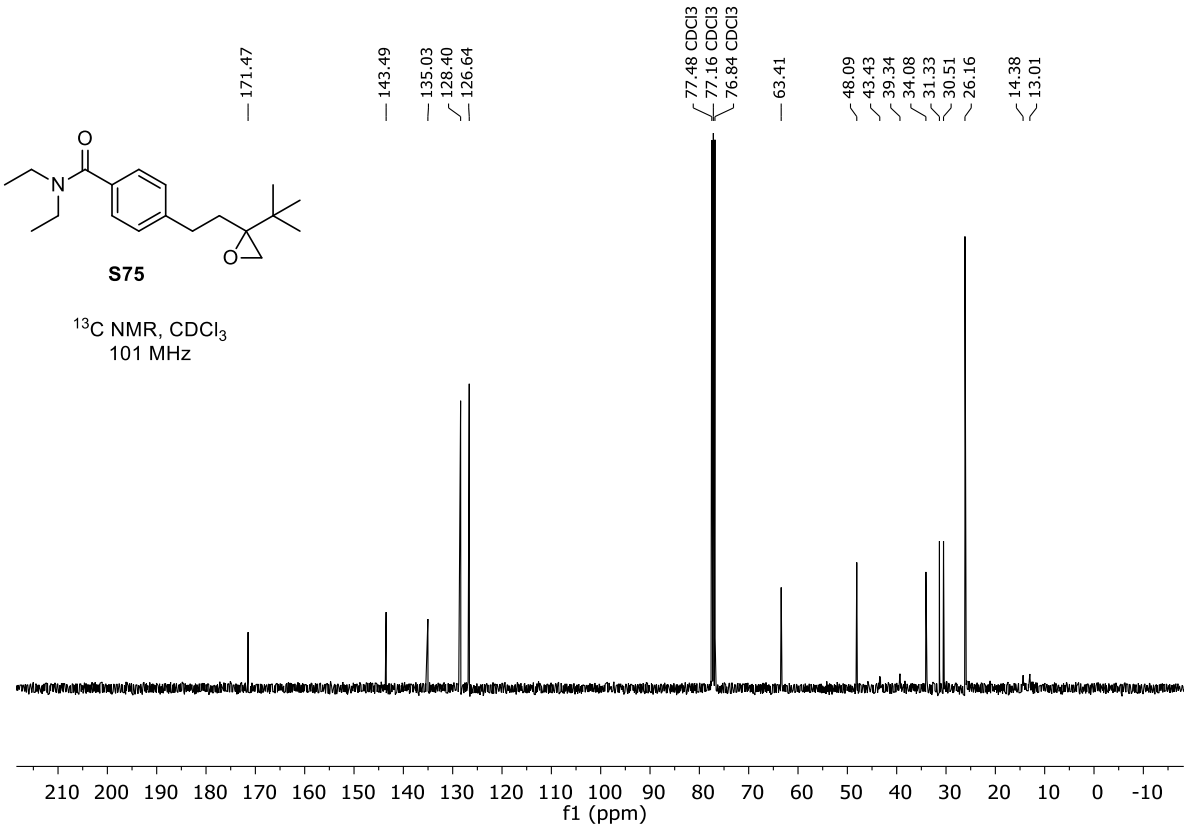
^{1}H NMR, $CDCl_3$
400 MHz

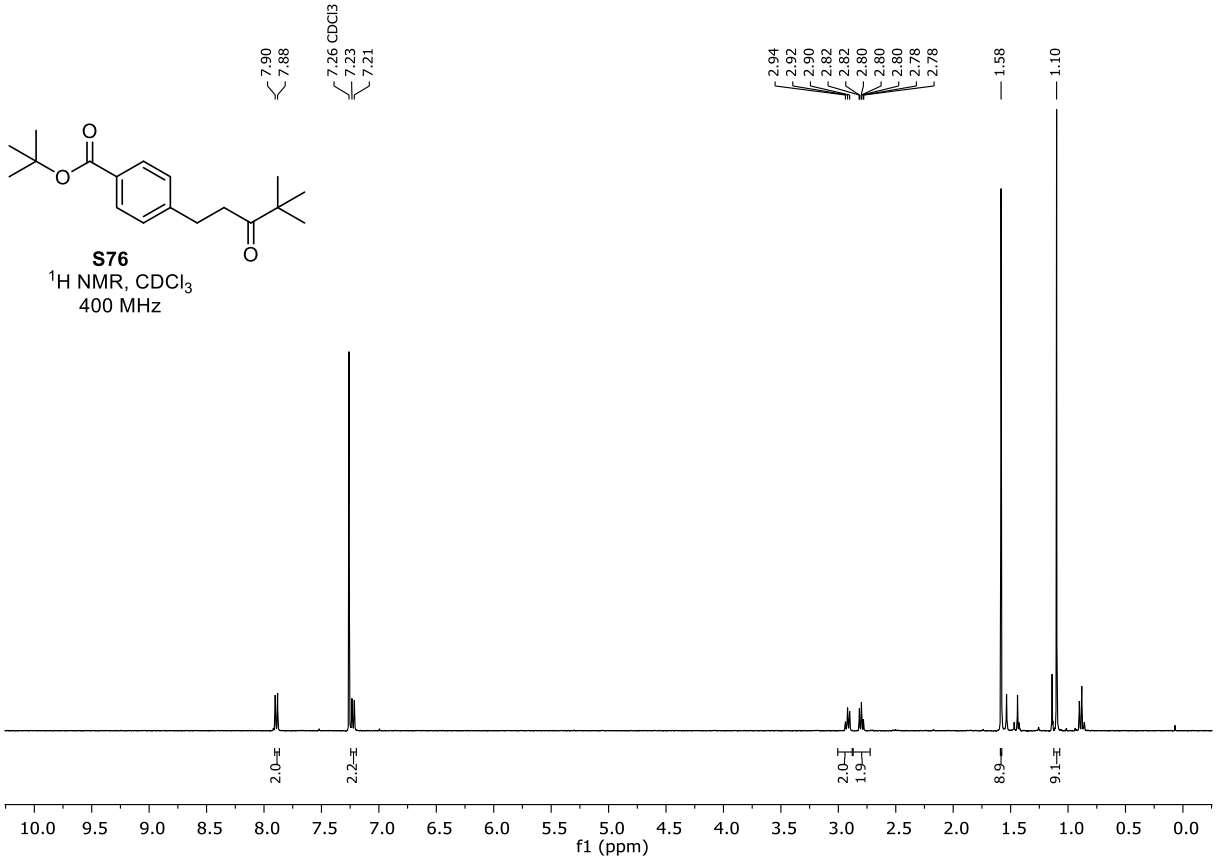


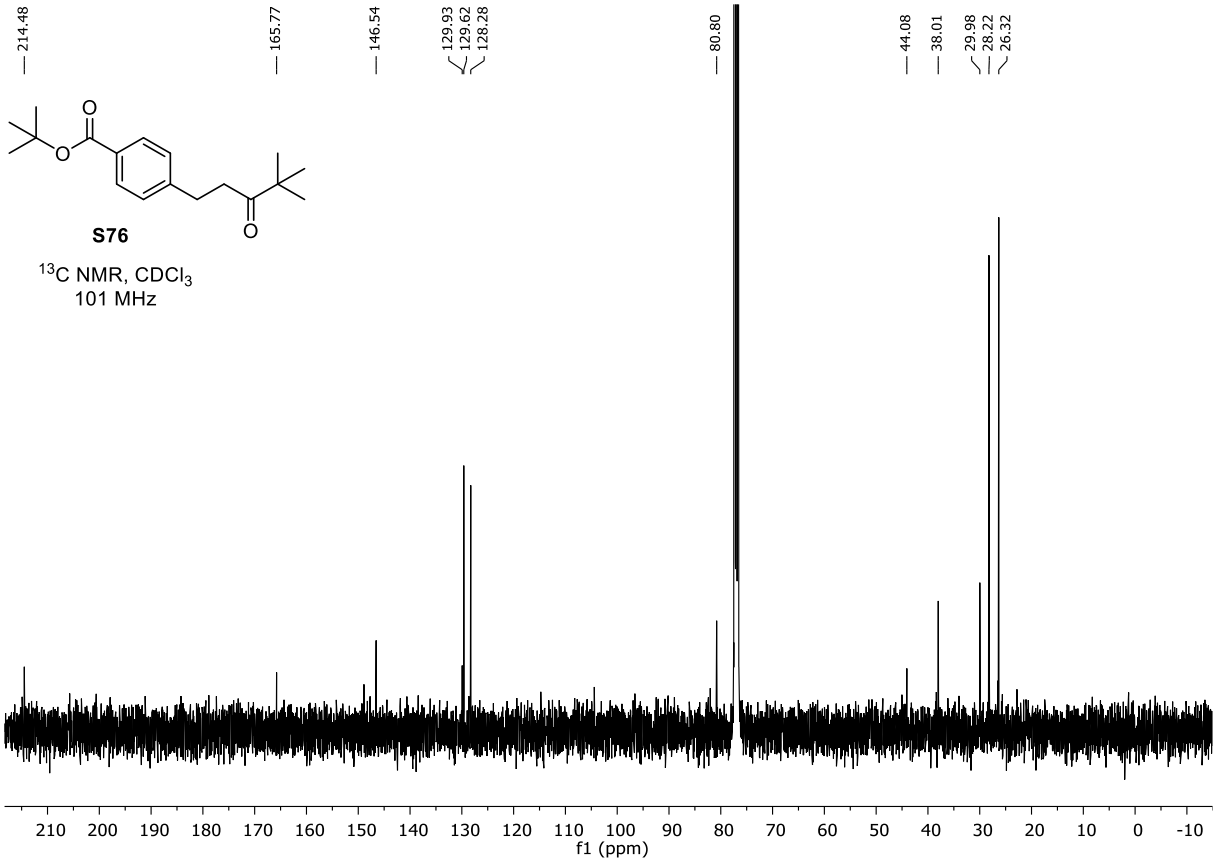
S74

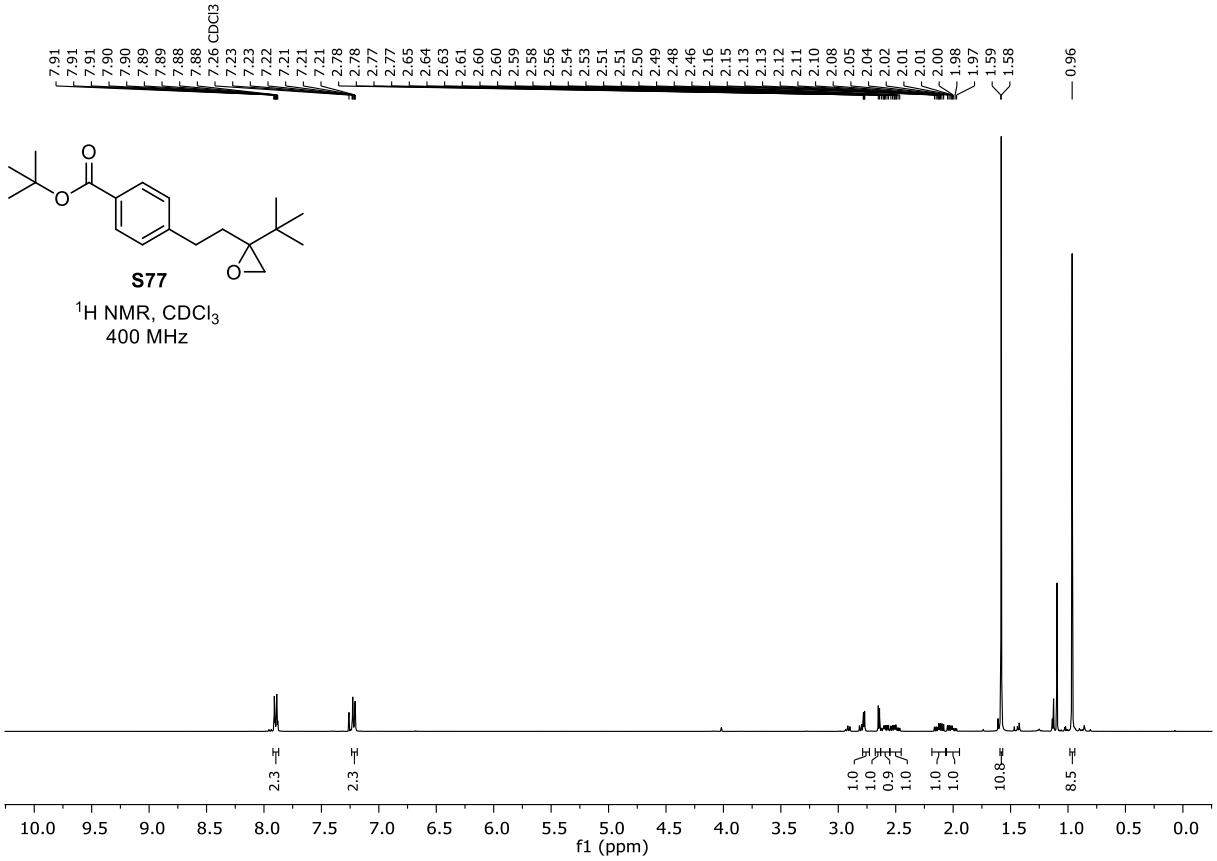
^{13}C NMR, $CDCl_3$
101 MHz

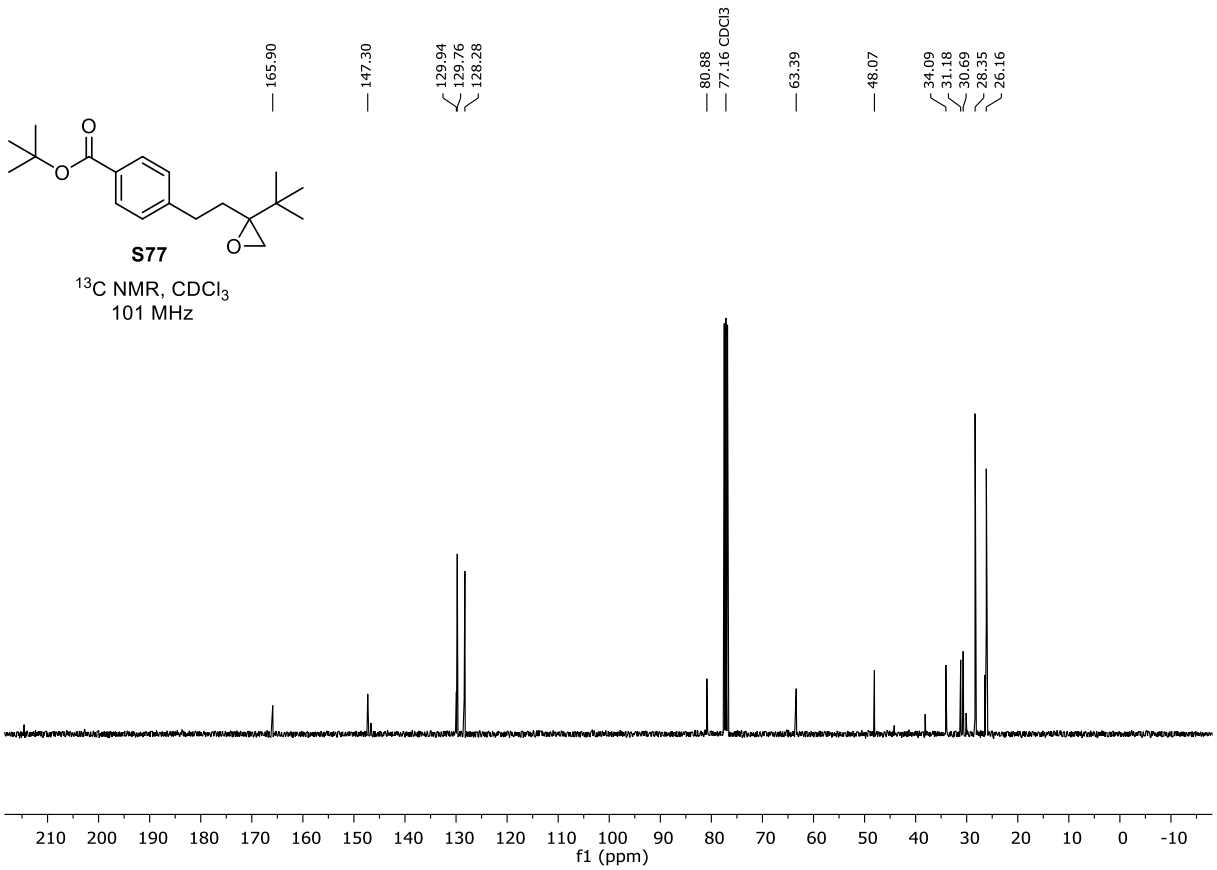

7.30 7.29 7.29 7.28 7.27 7.27 7.26 CHCl3 7.20 7.19 7.19 7.18 7.17 3.27 2.78 2.78 2.77 2.77 2.66 2.64 2.58 2.57 2.56 2.56 2.54 2.53 2.51 2.49 2.48 2.47 2.46 2.46 2.44 2.43 2.15 2.14 2.12 2.12 2.11 2.10 2.09 2.07 2.04 2.02 2.01 2.00 1.99 1.25 1.24 1.24 1.22 1.22 1.15 1.14 1.14 1.13 1.12 0.96
S75
1H NMR, CDCl3
400 MHz
2.0 2.0 2.0 2.0 1.0 1.0 2.0 1.9 3.0 3.0 9.0
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 -0.5
f1 (ppm)

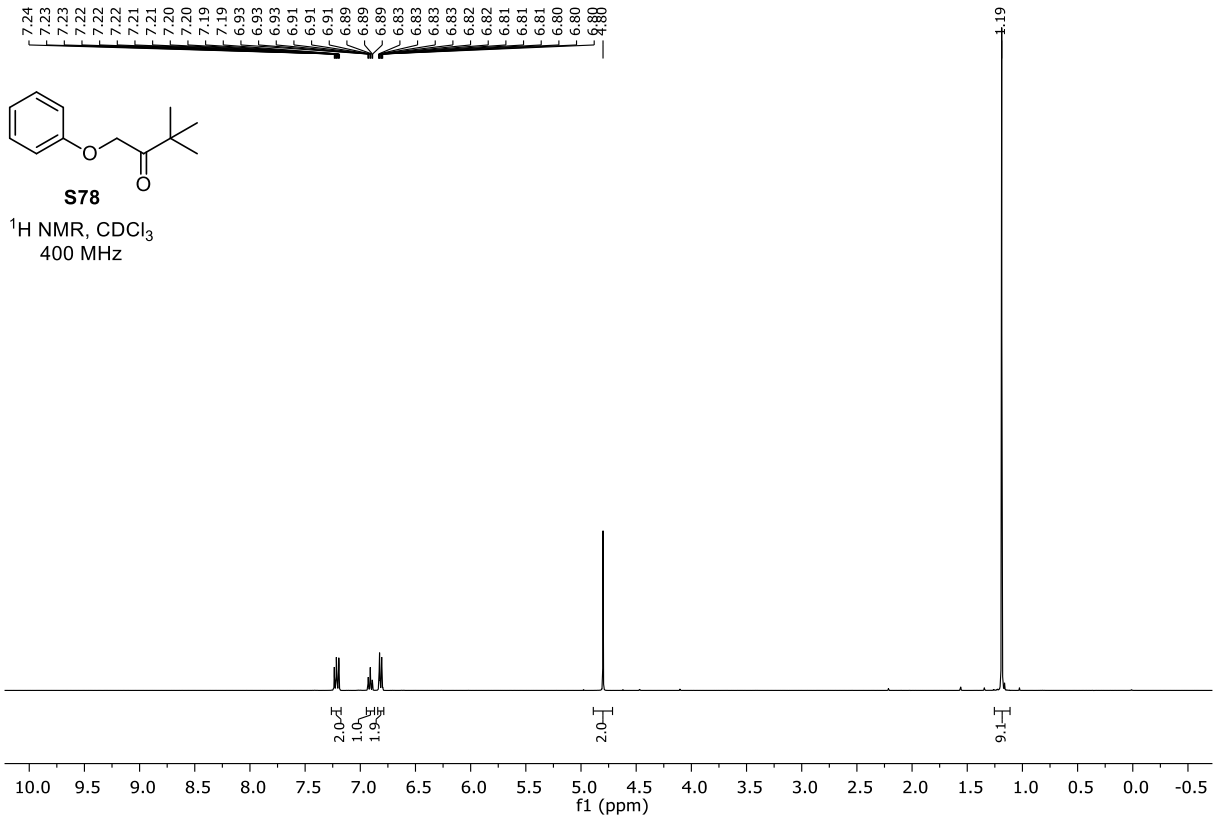

171.47 143.49 135.03 128.40 126.64 77.48 CDCl3 77.16 CDCl3 76.84 CDCl3 63.41 48.09 43.43 39.34 34.08 31.33 30.51 26.16 14.38 13.01
S75
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.90
7.88
7.26 CDCl3
7.23
7.21
2.94
2.92
2.90
2.82
2.82
2.80
2.80
2.80
2.78
2.78
1.58
1.10
S76
1H NMR, CDCl3
400 MHz
2.0
2.2
2.0
1.9
8.9
9.1
f1 (ppm)


214.48
165.77
146.54
129.93
129.62
128.28
80.80
44.08
38.01
29.98
28.22
26.32
S76
13C NMR, CDCl3
101 MHz
f1 (ppm)

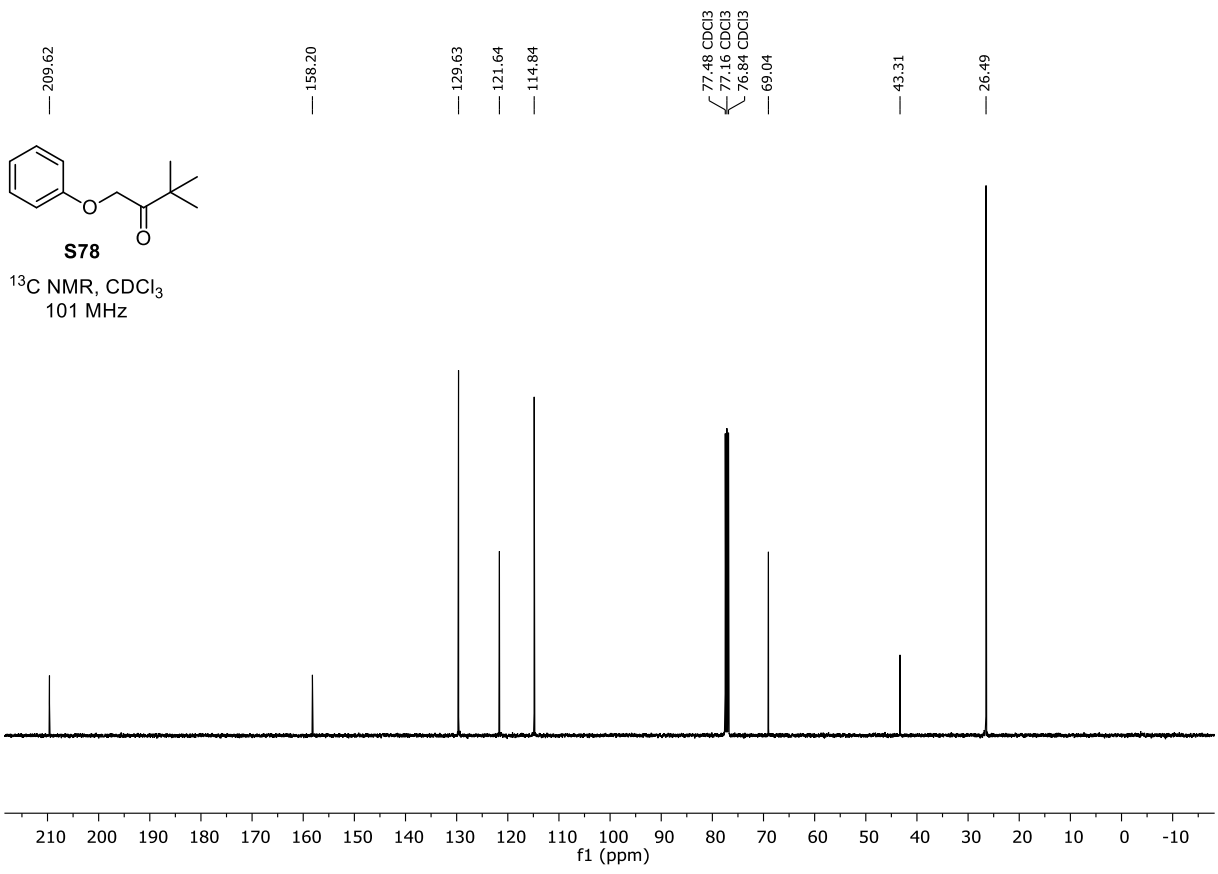

7.91 7.91 7.91 7.90 7.90 7.89 7.89 7.88 7.88 7.26 CDCl3 7.23 7.23 7.22 7.21 7.21 7.21 2.78 2.78 2.77 2.77 2.65 2.64 2.63 2.61 2.60 2.60 2.59 2.58 2.56 2.54 2.53 2.51 2.51 2.50 2.49 2.48 2.46 2.16 2.15 2.13 2.13 2.12 2.11 2.10 2.08 2.05 2.04 2.02 2.01 2.01 2.00 1.98 1.97 1.59 1.58 0.96
S77
1H NMR, CDCl3
400 MHz
2.3 2.3 1.0 1.0 0.9 1.0 1.0 1.0 10.8 8.5
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)


165.90 147.30 129.94 129.76 128.28 80.88 77.16 CDCl3 63.39 48.07 34.09 31.18 30.69 28.35 26.16
S77
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)



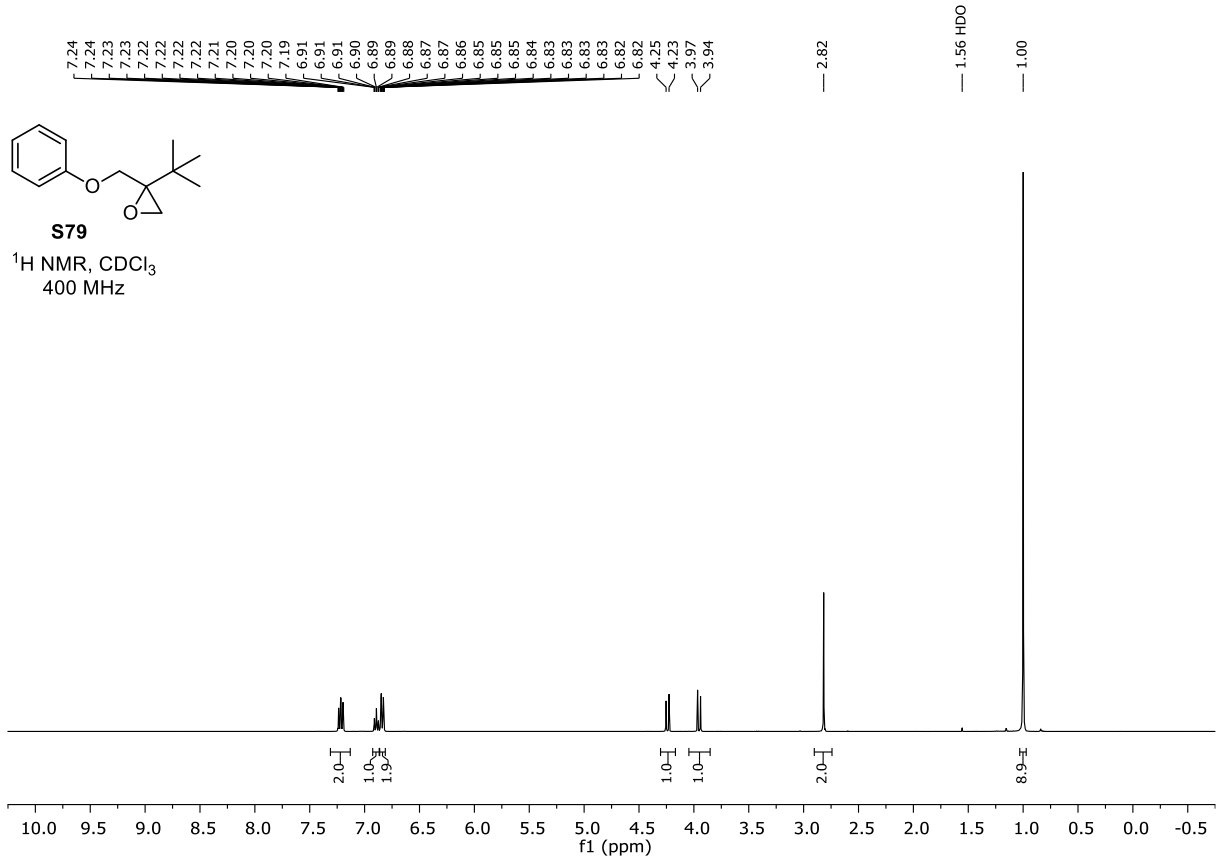
S78

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



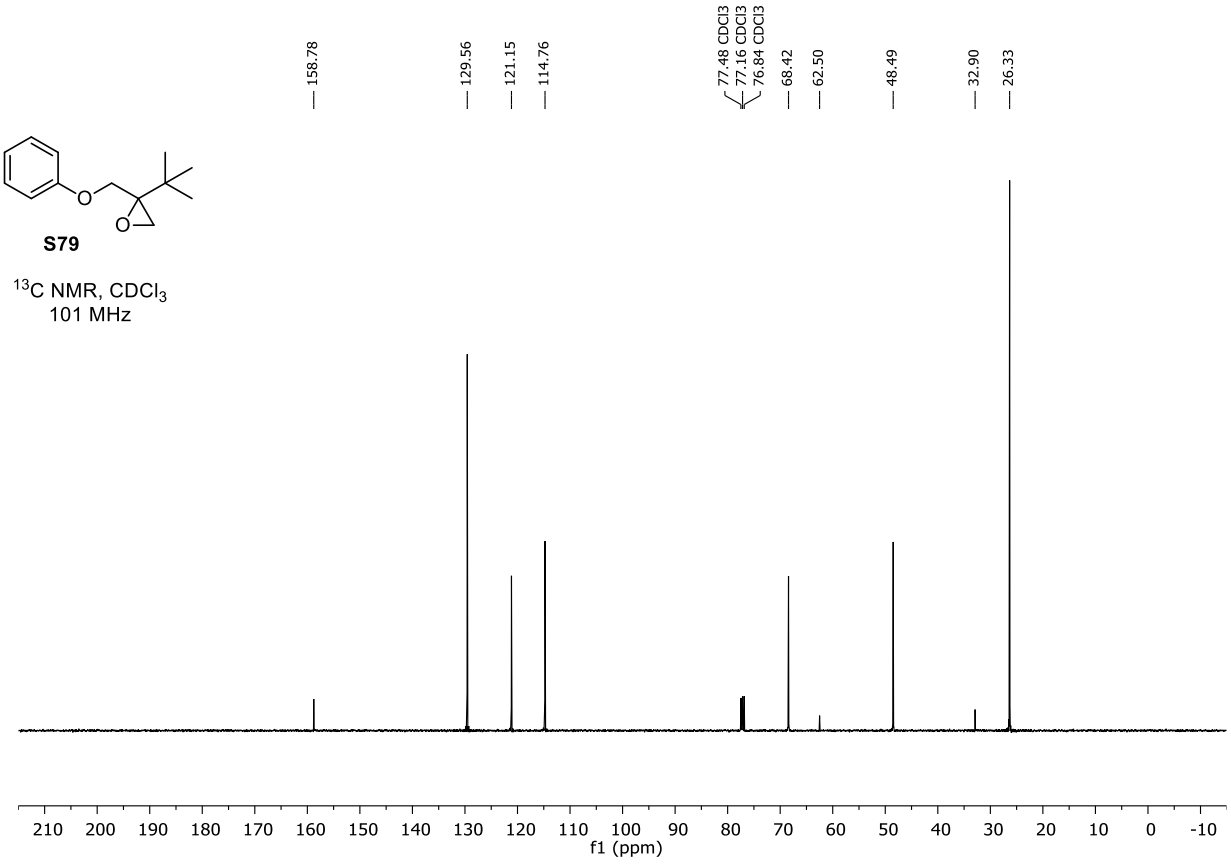
S78

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



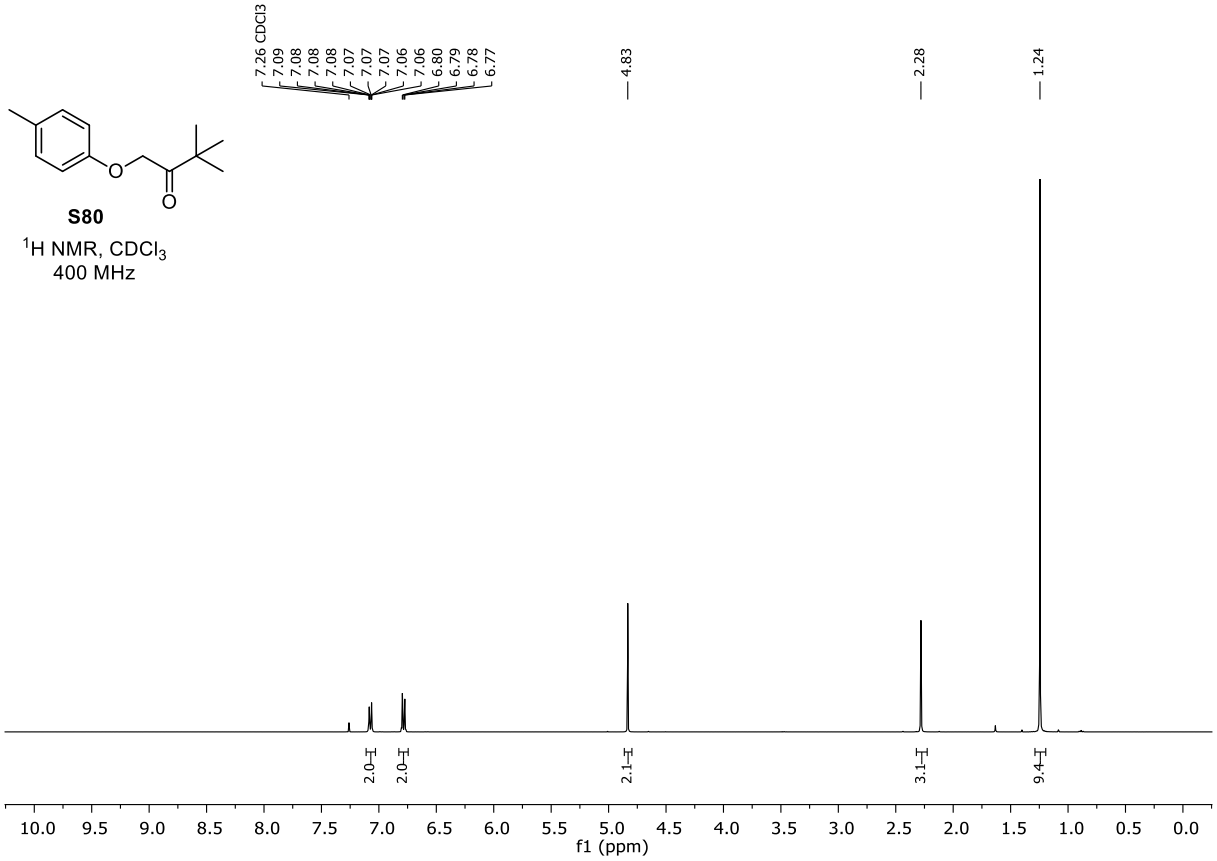
S79

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



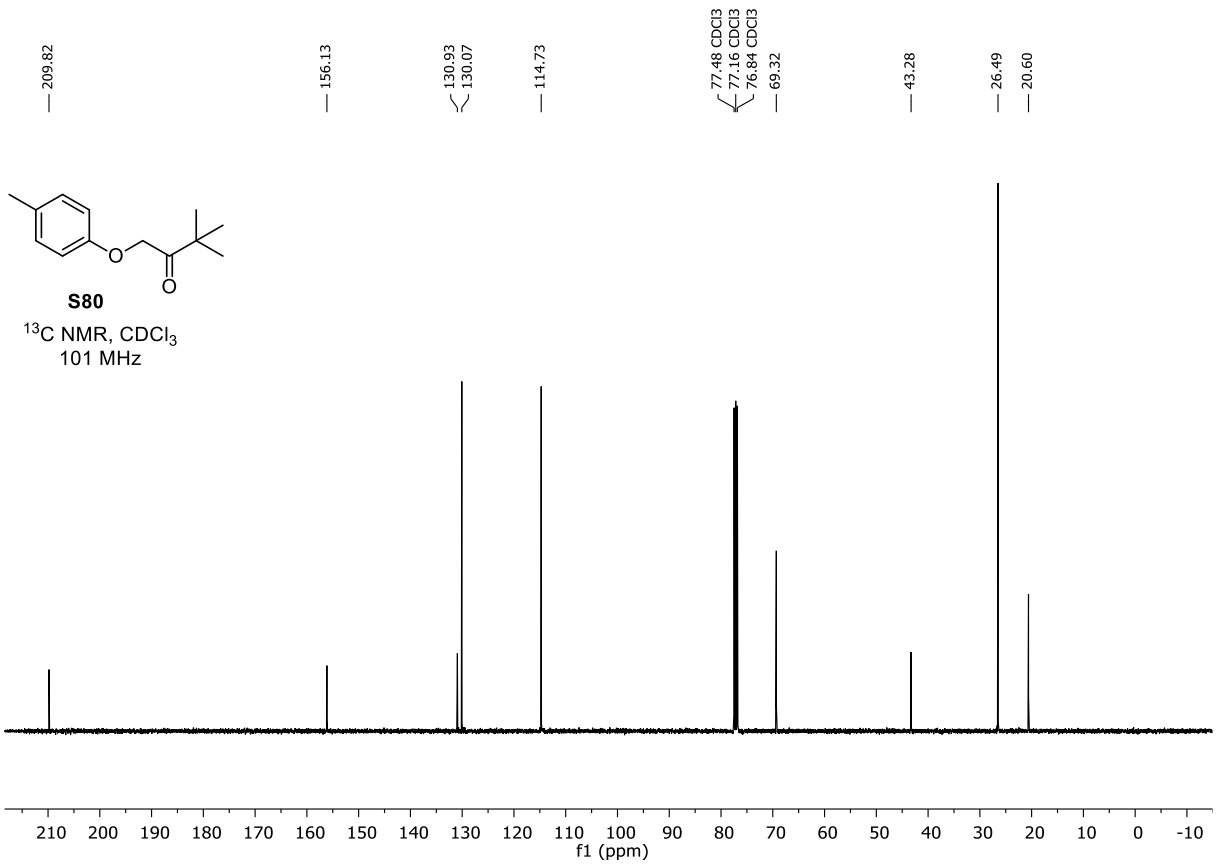
S79

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



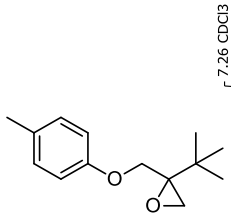
S80

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

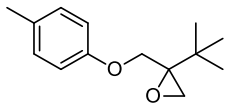


S80

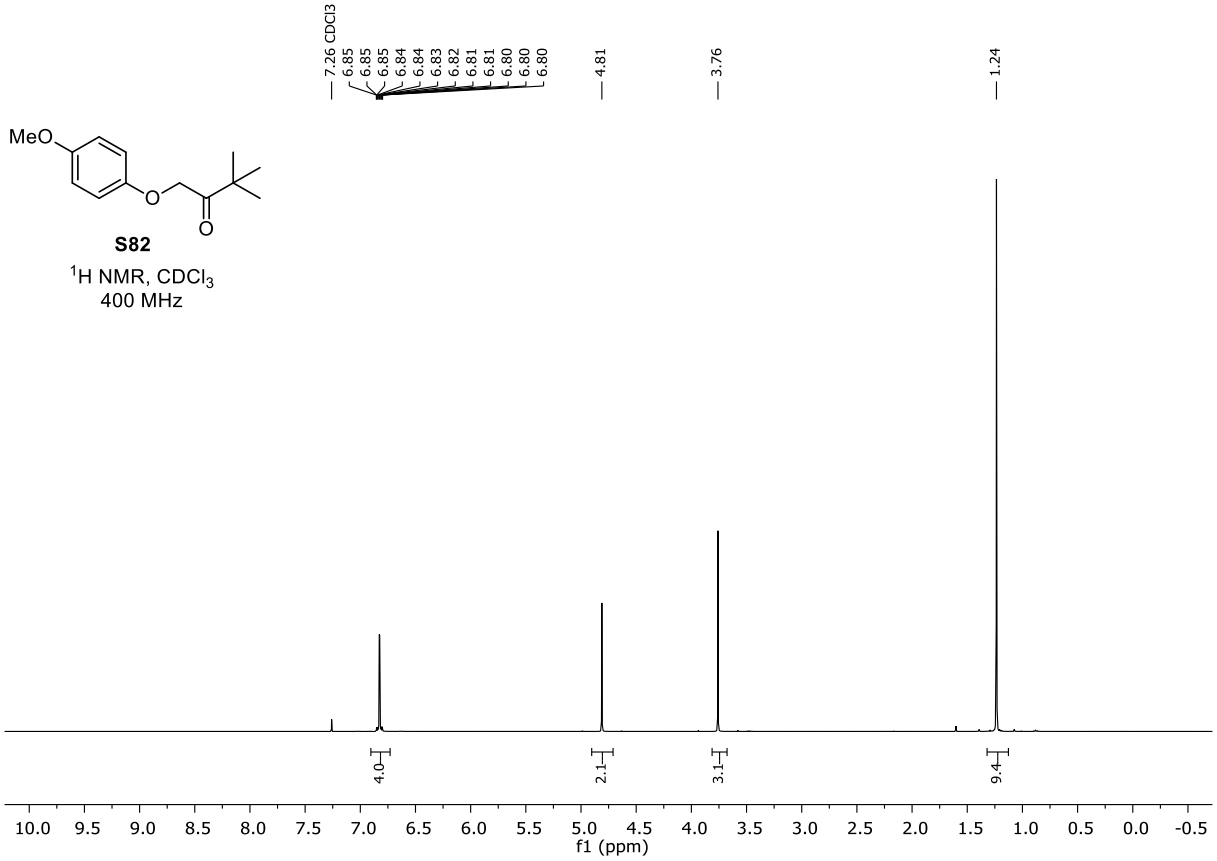
^{13}C NMR, $CDCl_3$
101 MHz



S81
^{1}H NMR, $CDCl_3$
400 MHz

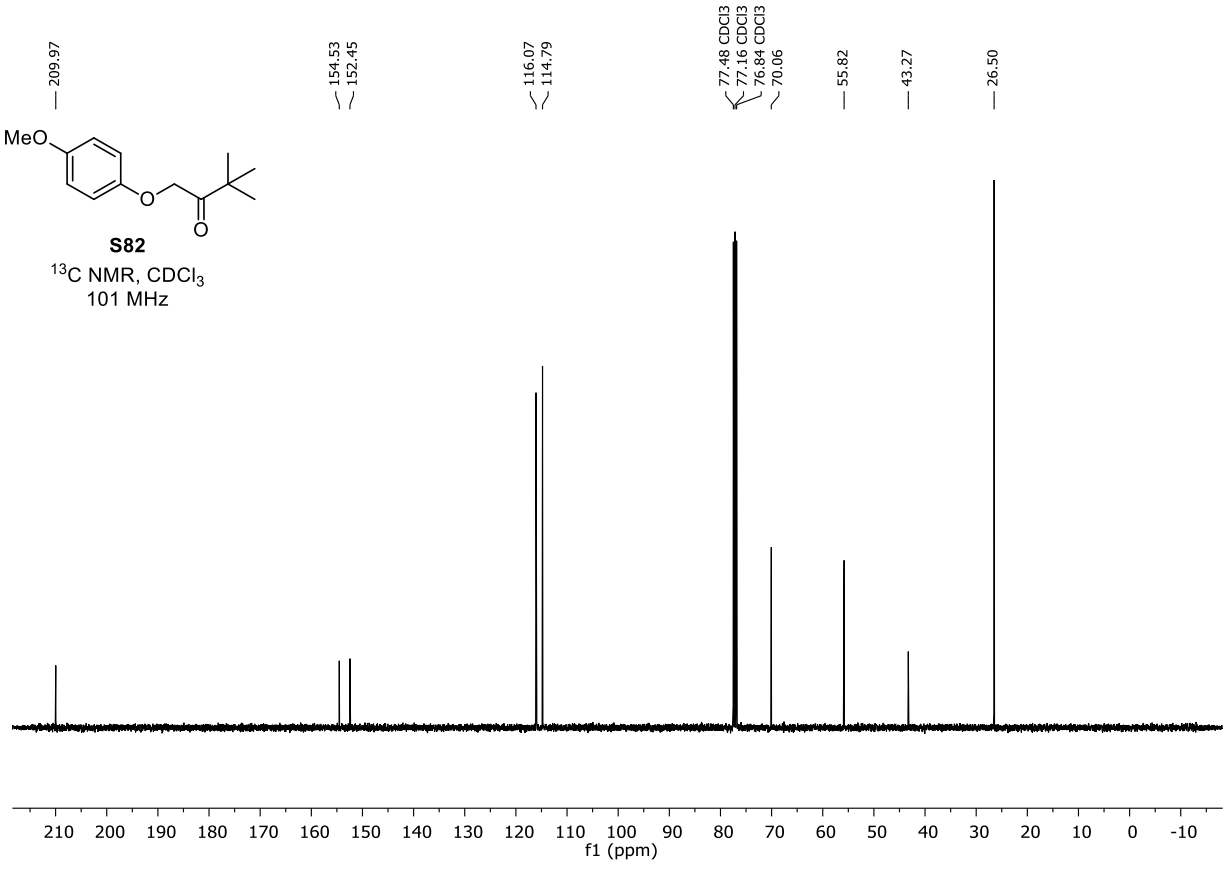


S81
^{13}C NMR, $CDCl_3$
101 MHz



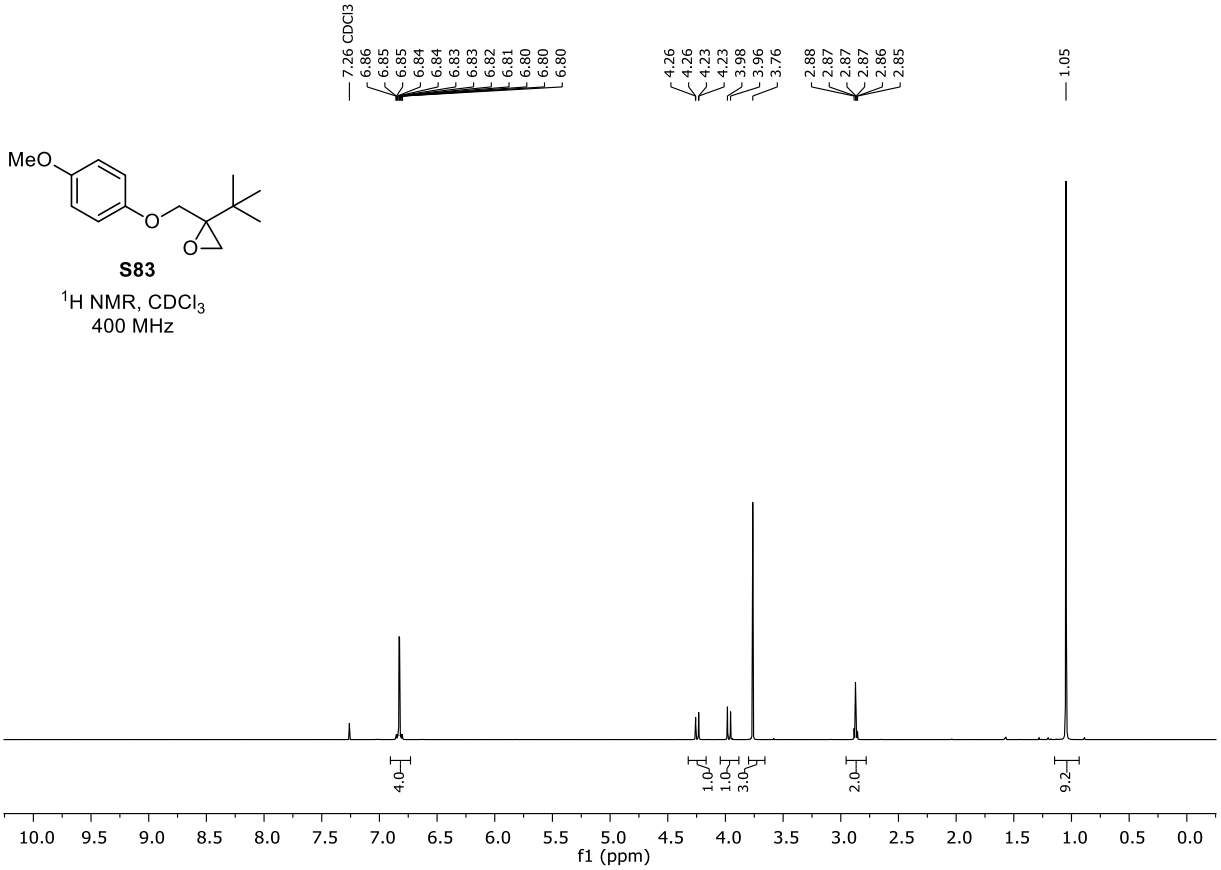
S82

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



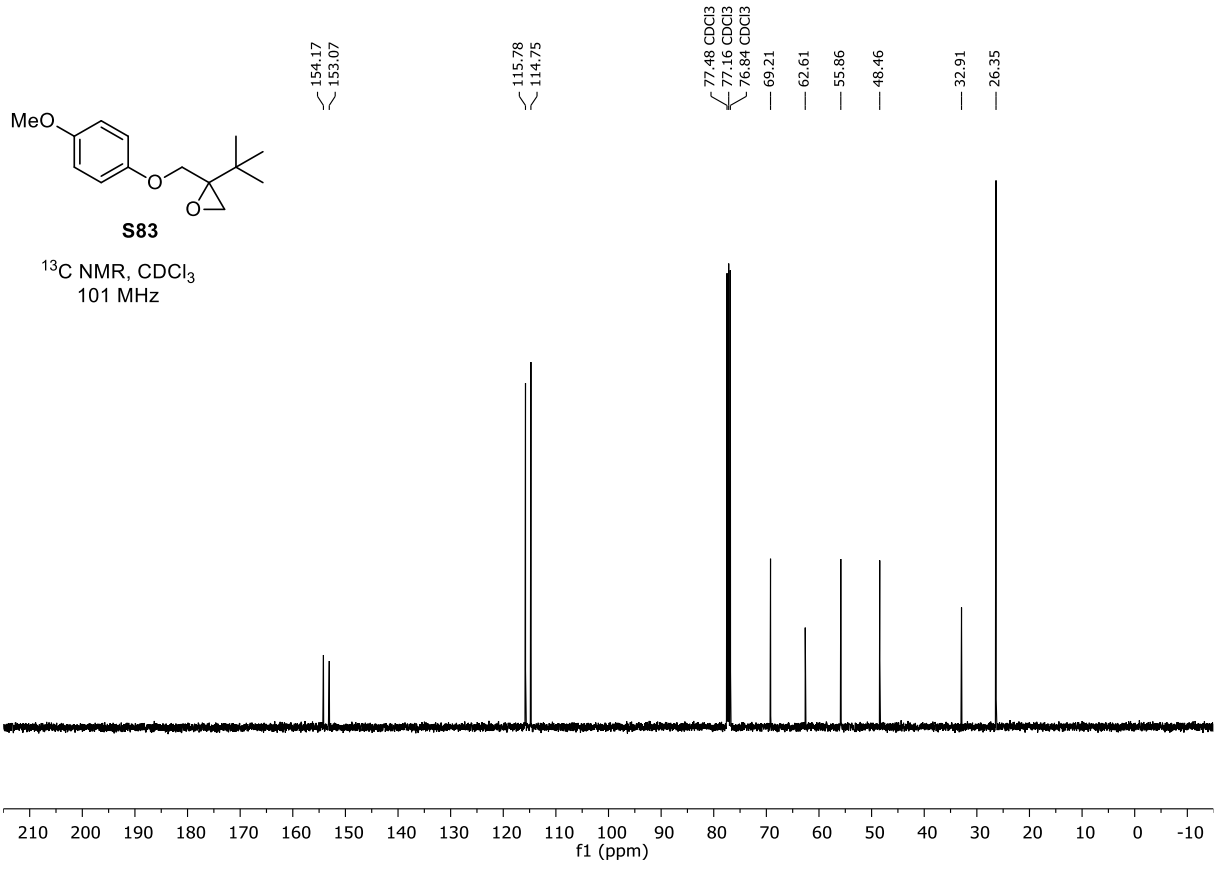
S82

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



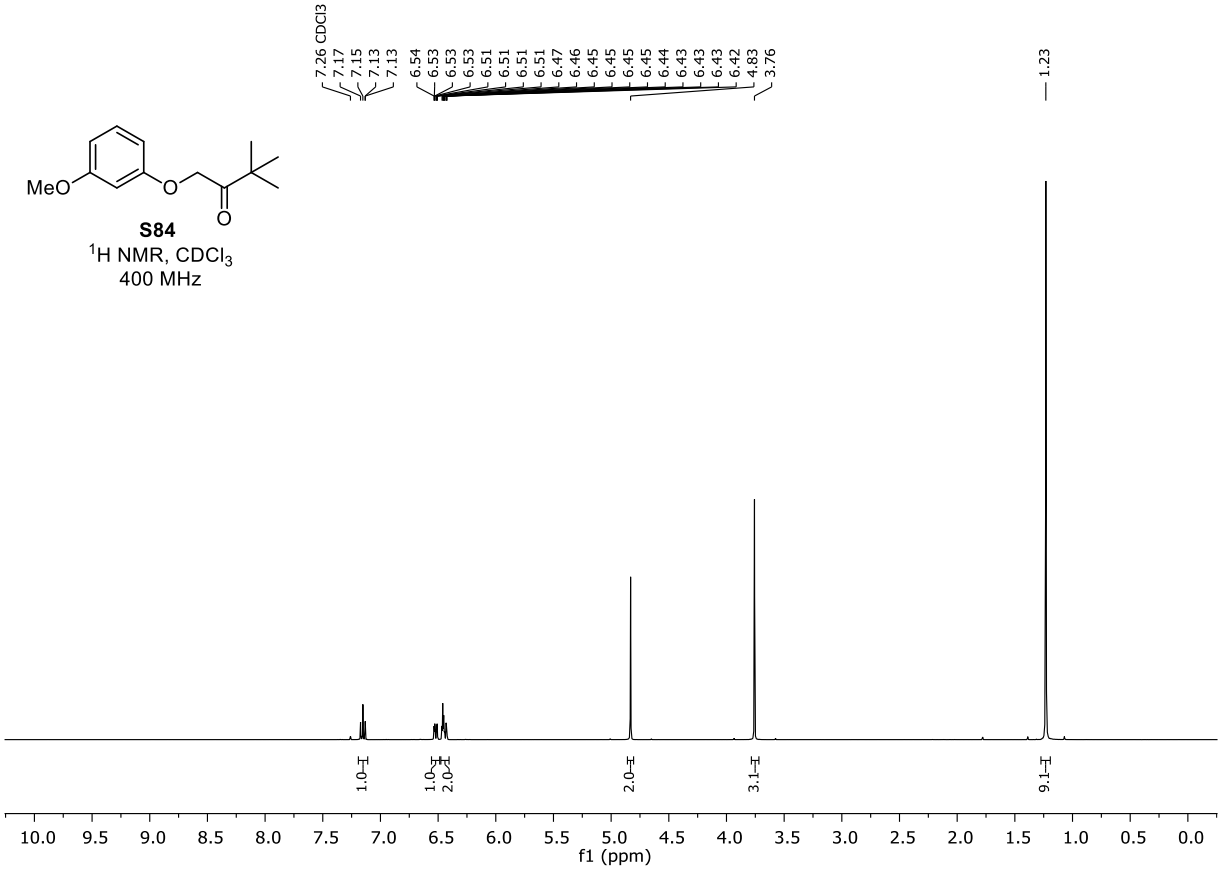
S83

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



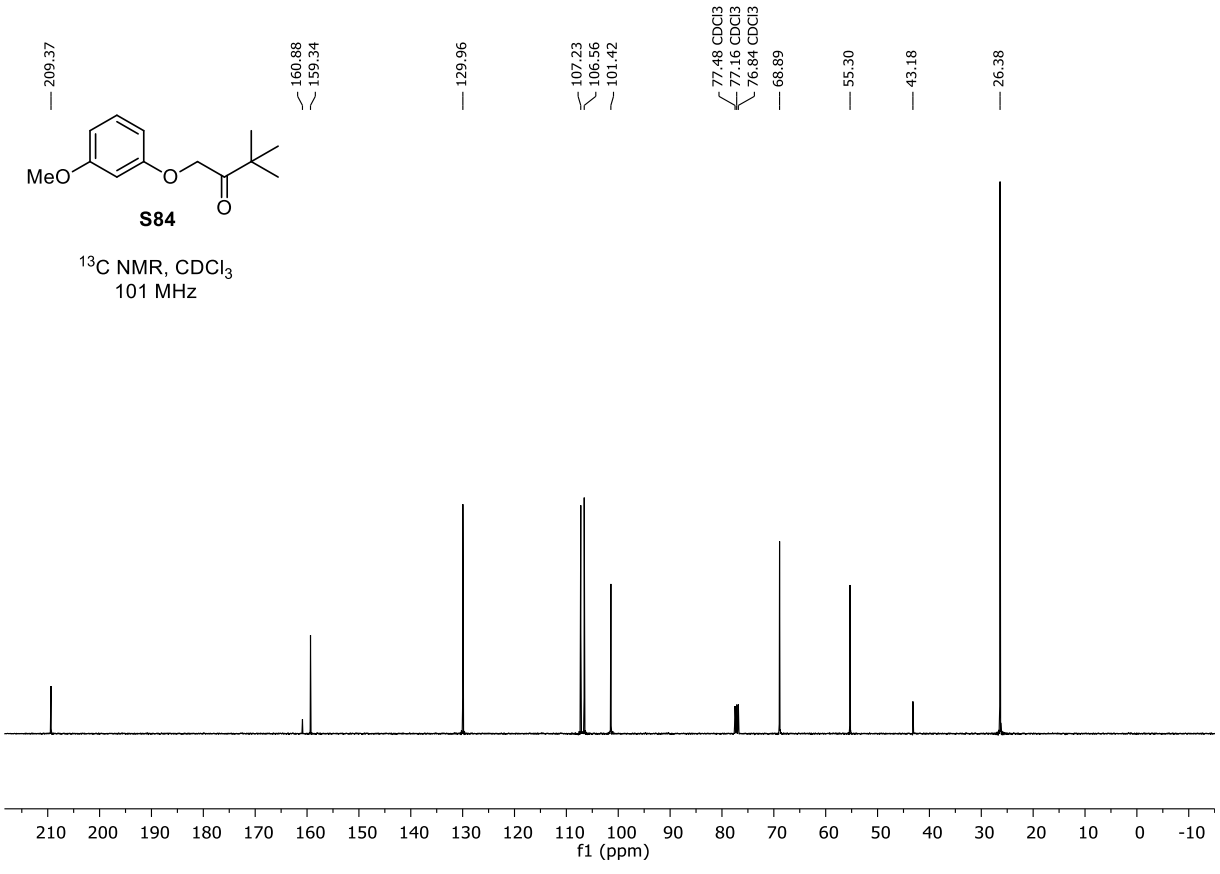
S83

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



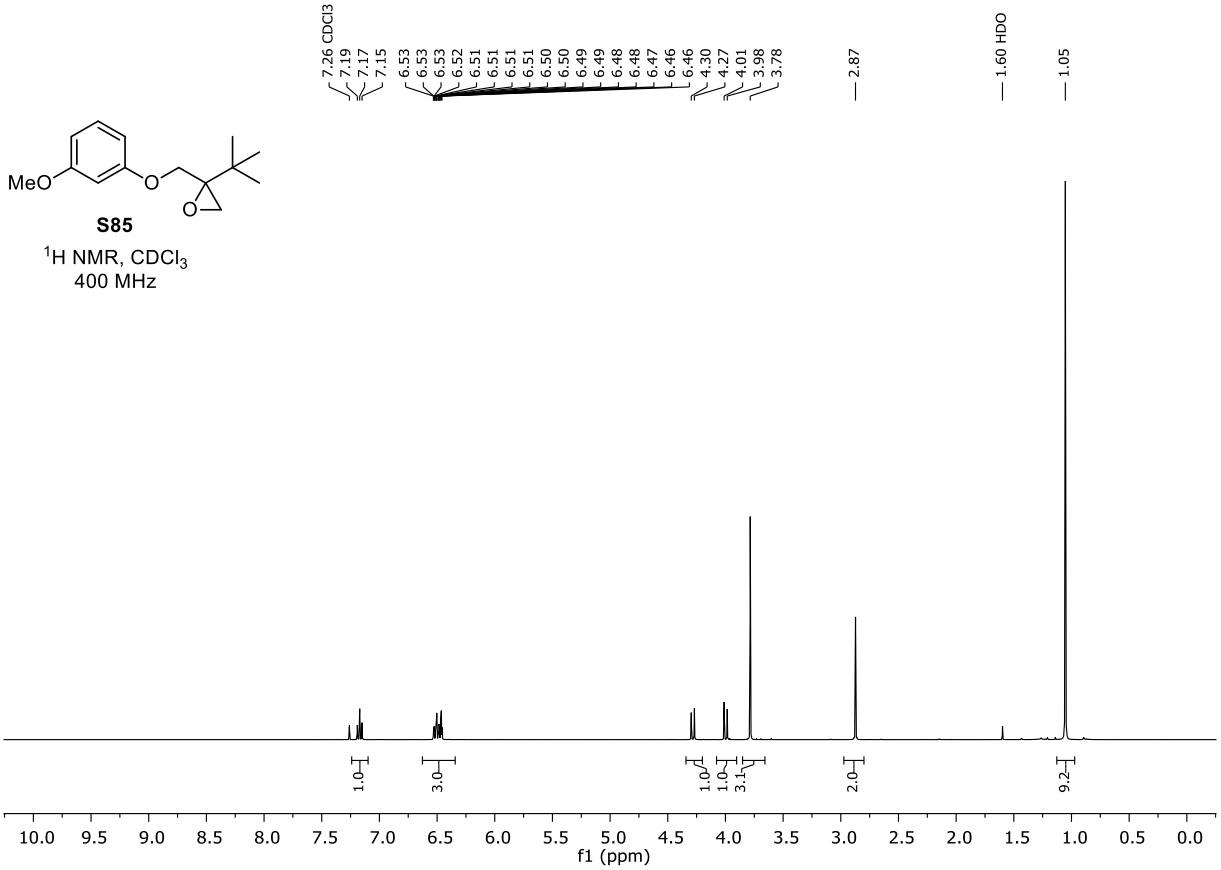
S84

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



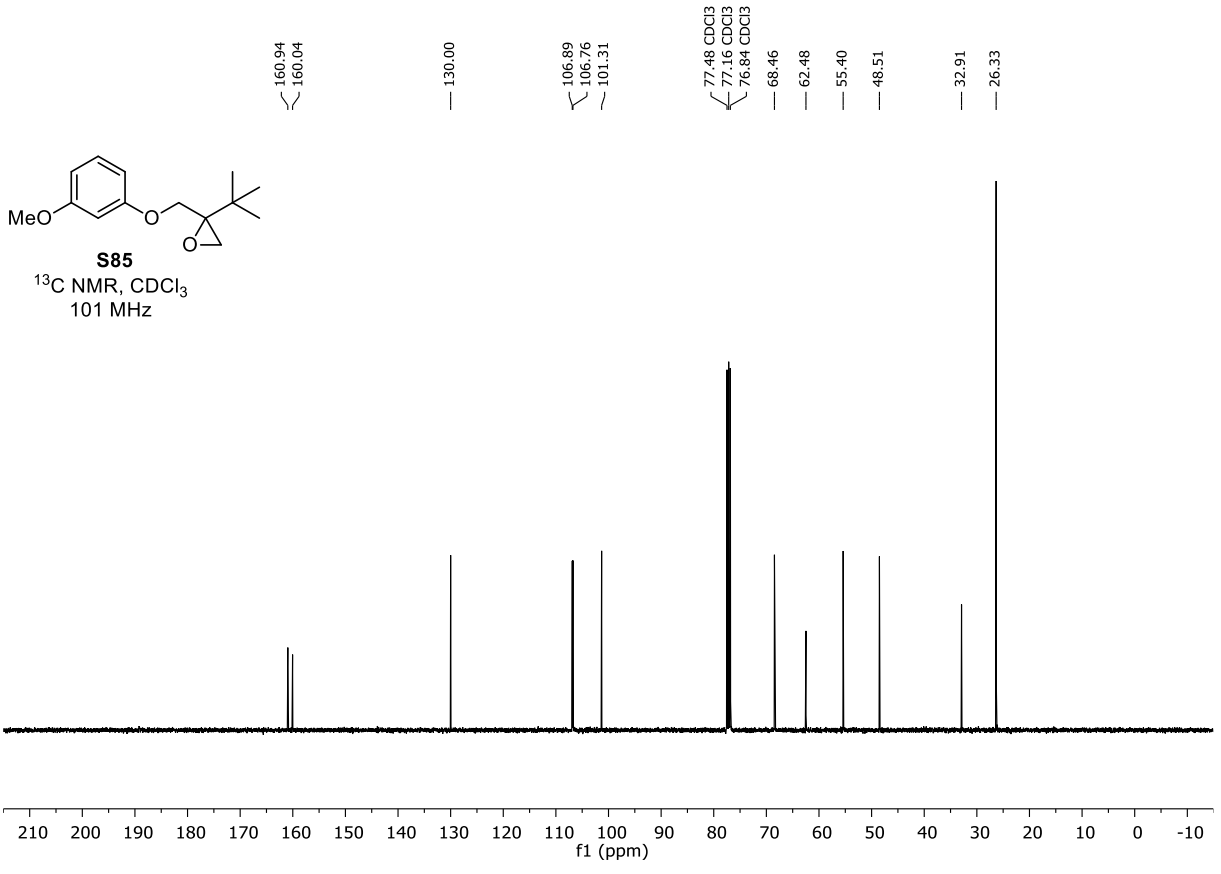
S84

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



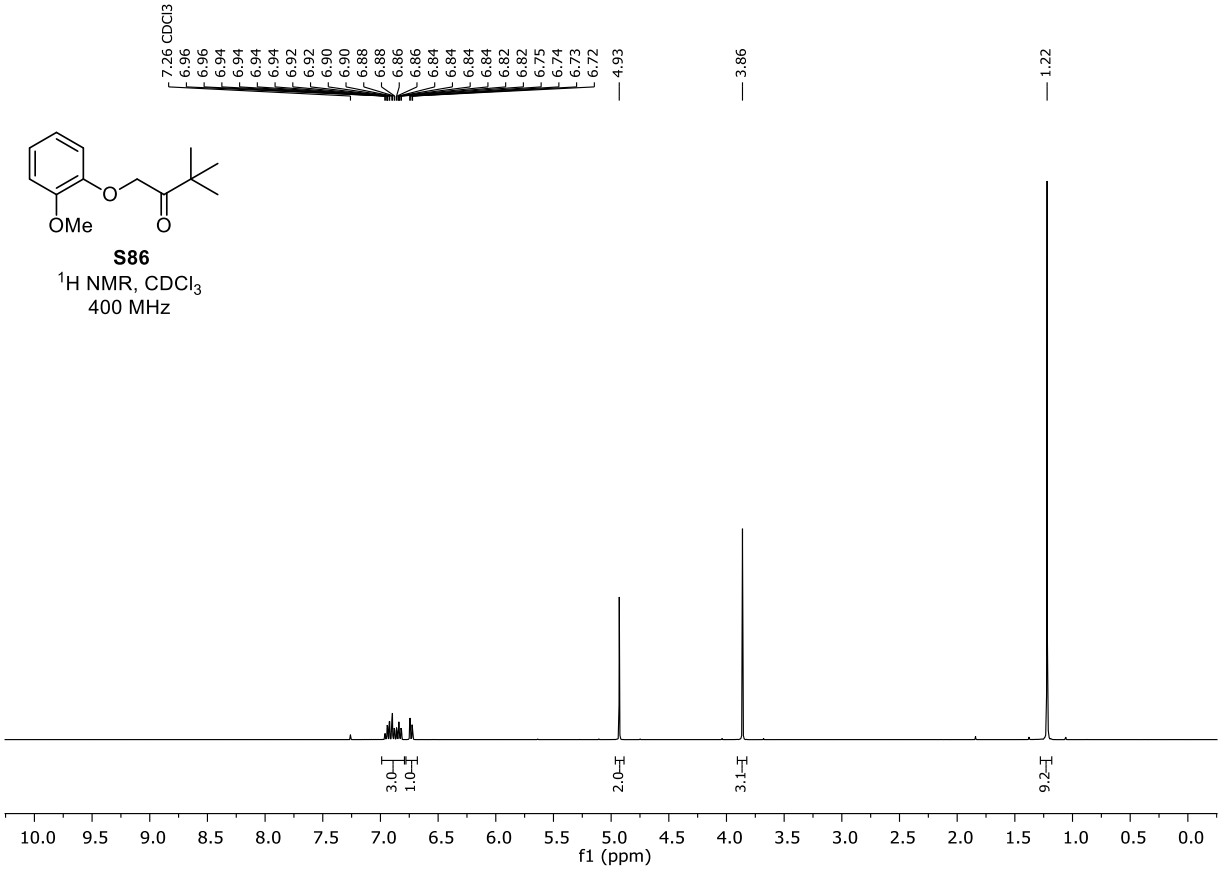
S85

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

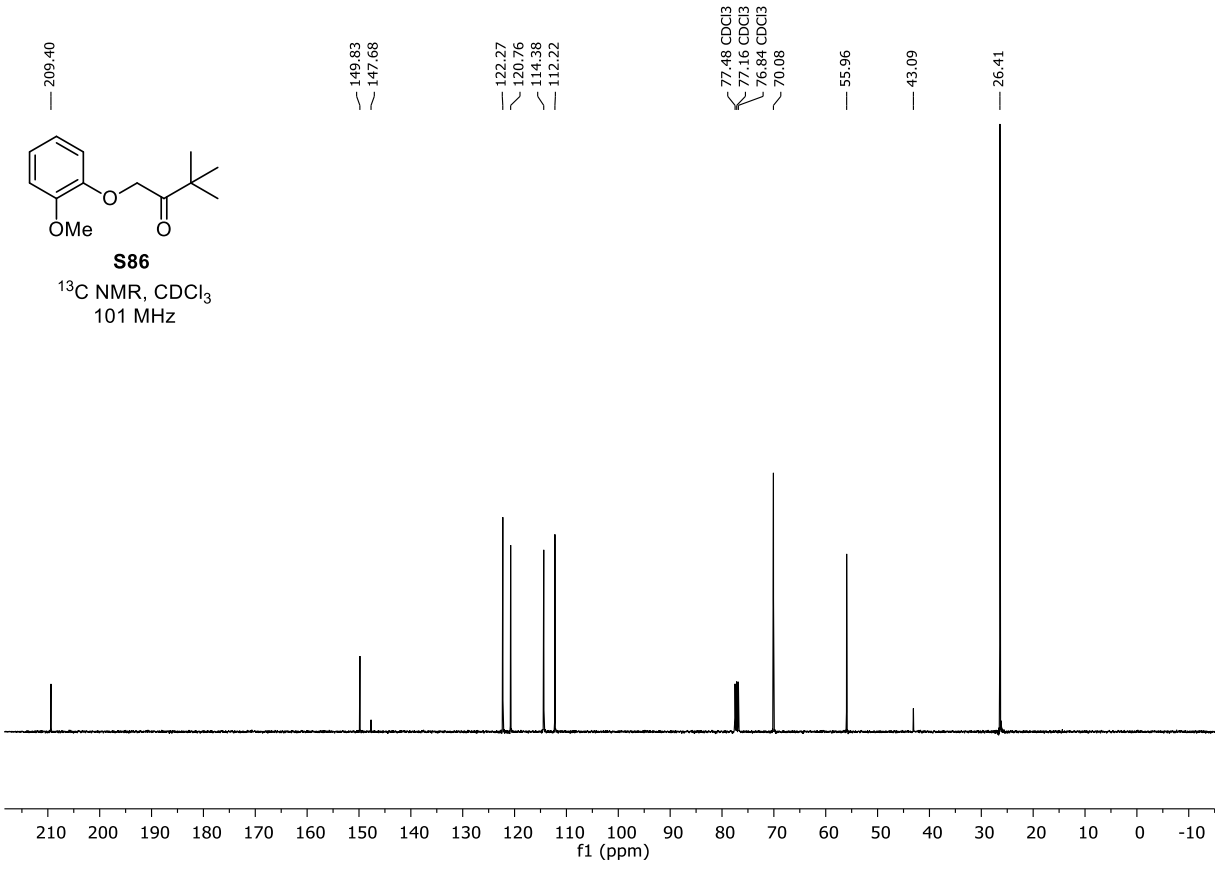


S85

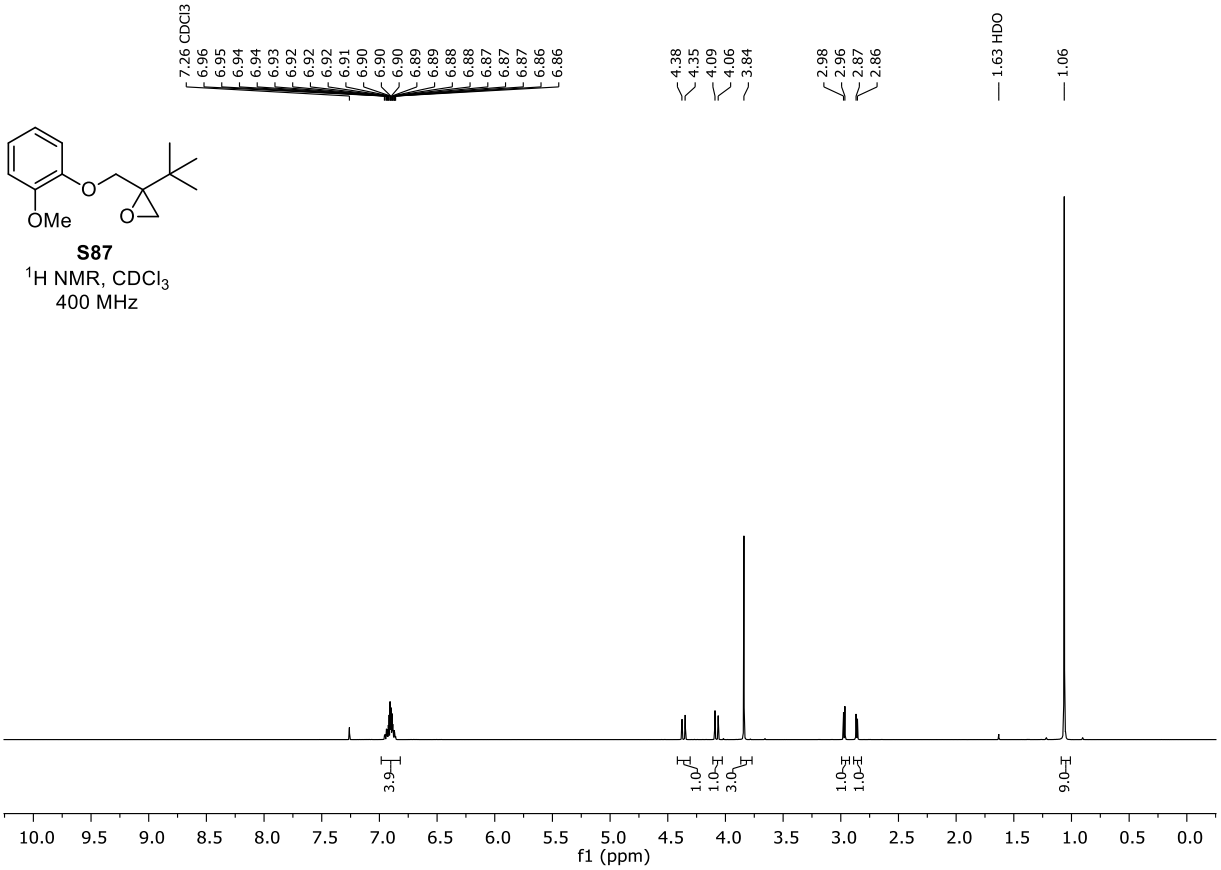
^{13}C NMR, $CDCl_3$
101 MHz



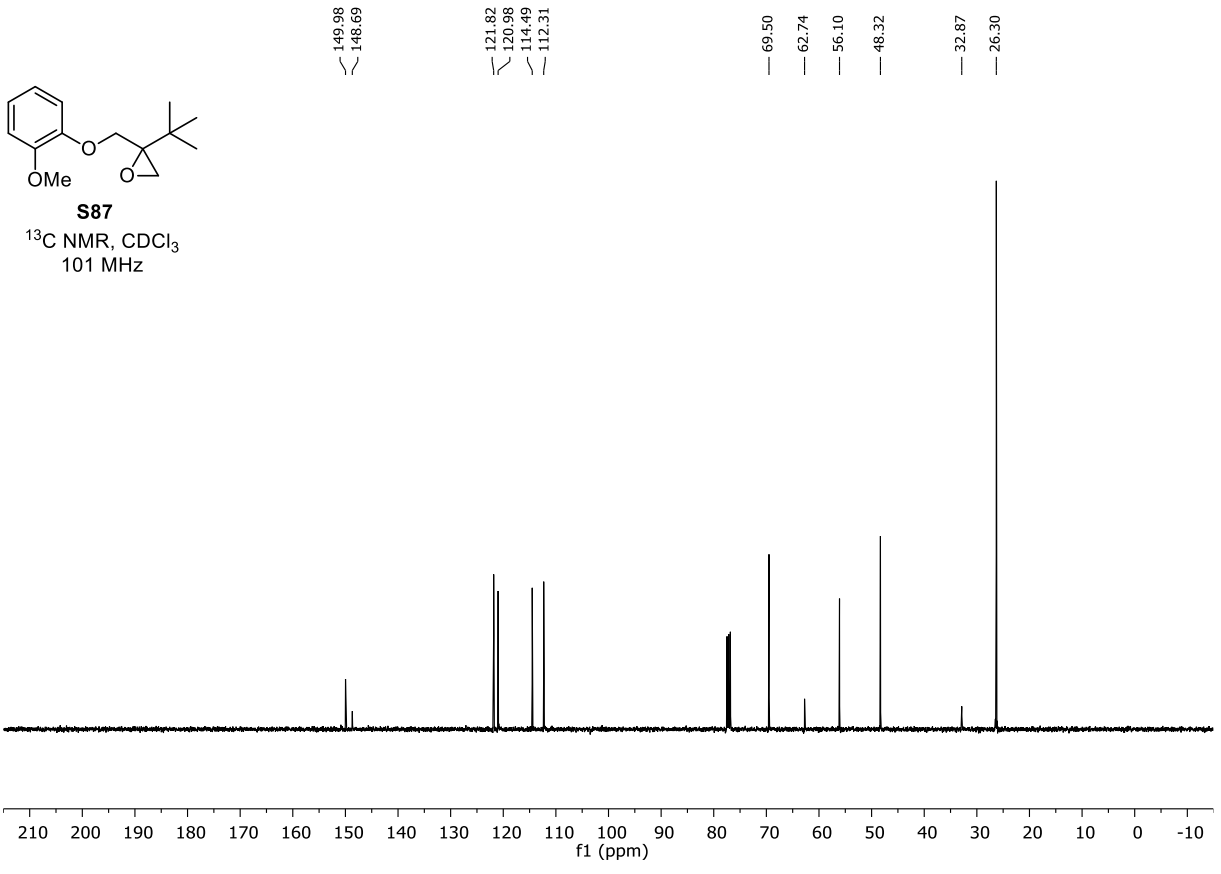
S86
^{1}H NMR, $CDCl_3$
400 MHz



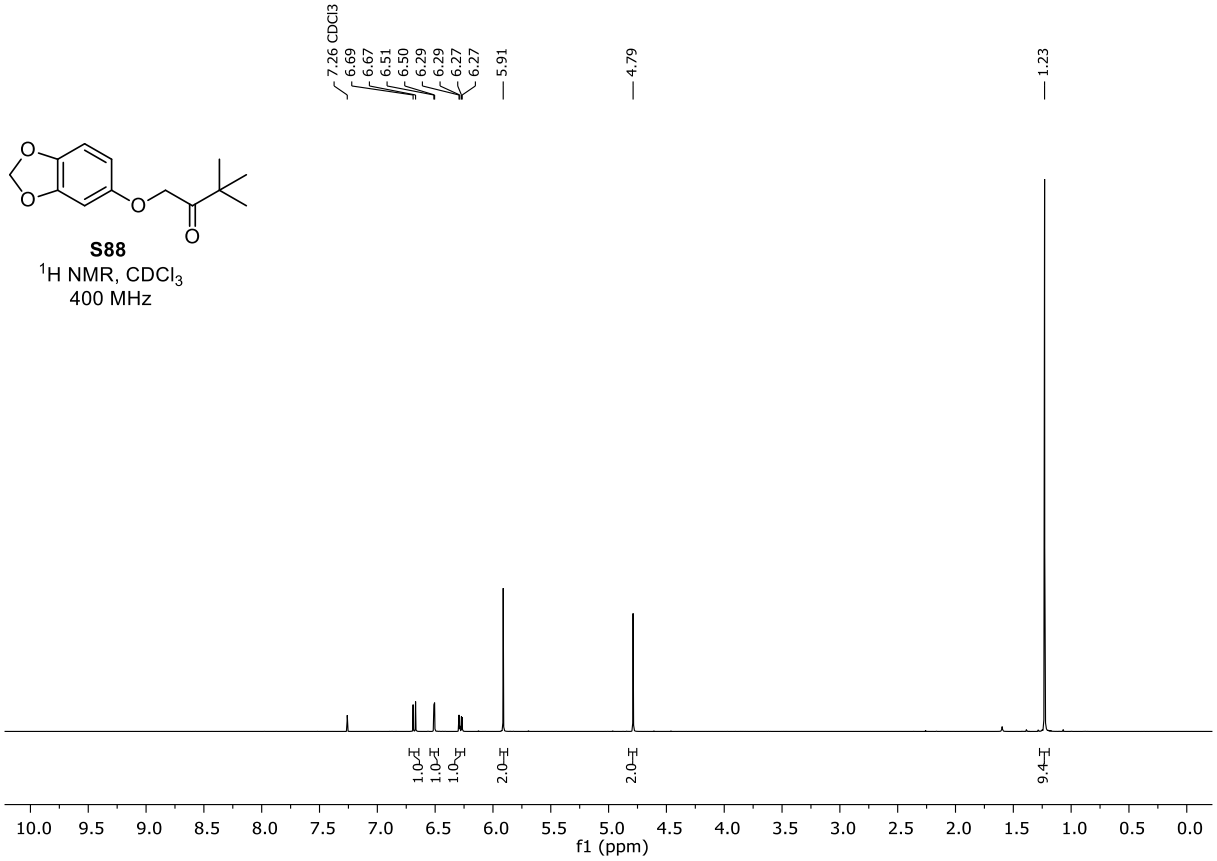
S86
^{13}C NMR, $CDCl_3$
101 MHz



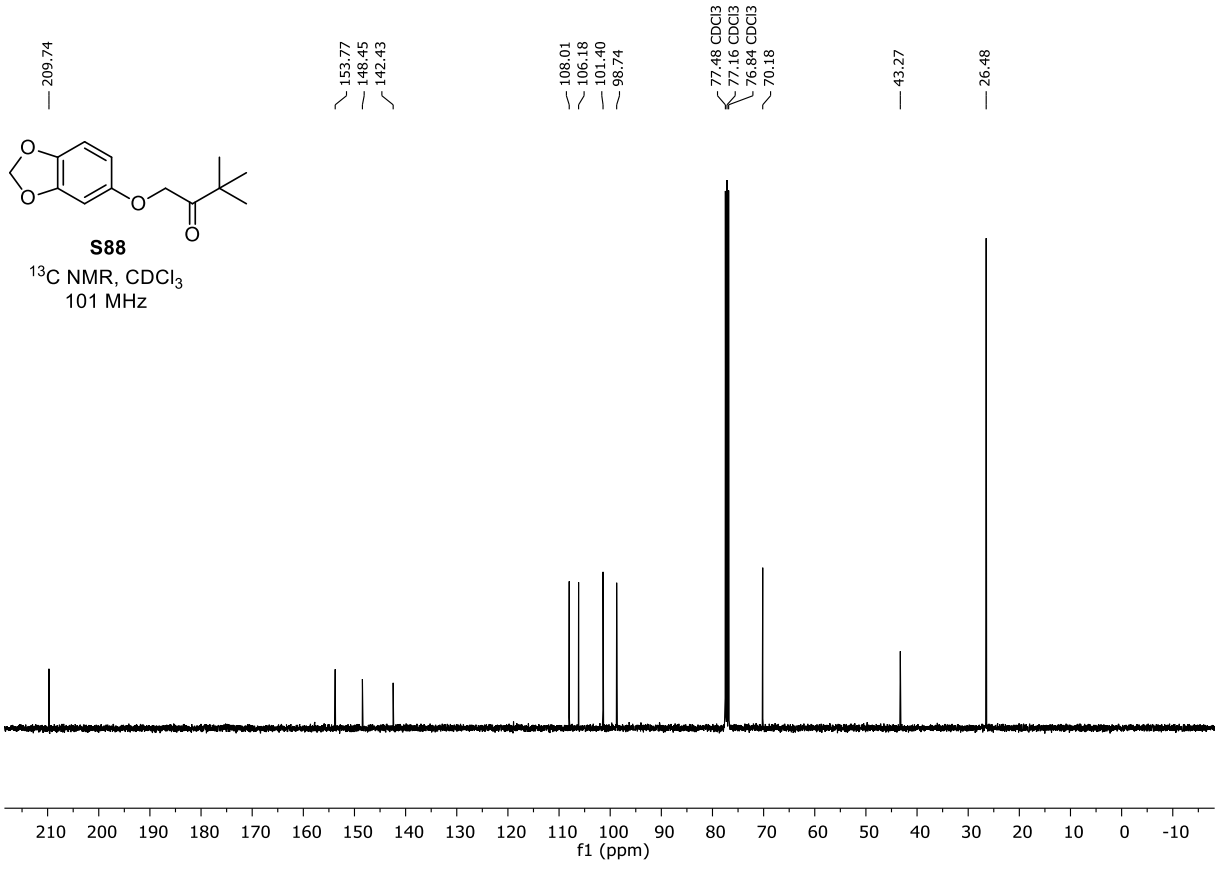
S87
^{1}H NMR, $CDCl_3$
400 MHz



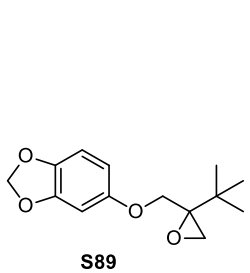
S87
^{13}C NMR, $CDCl_3$
101 MHz



S88
^{1}H NMR, $CDCl_3$
400 MHz

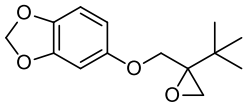


S88
^{13}C NMR, $CDCl_3$
101 MHz



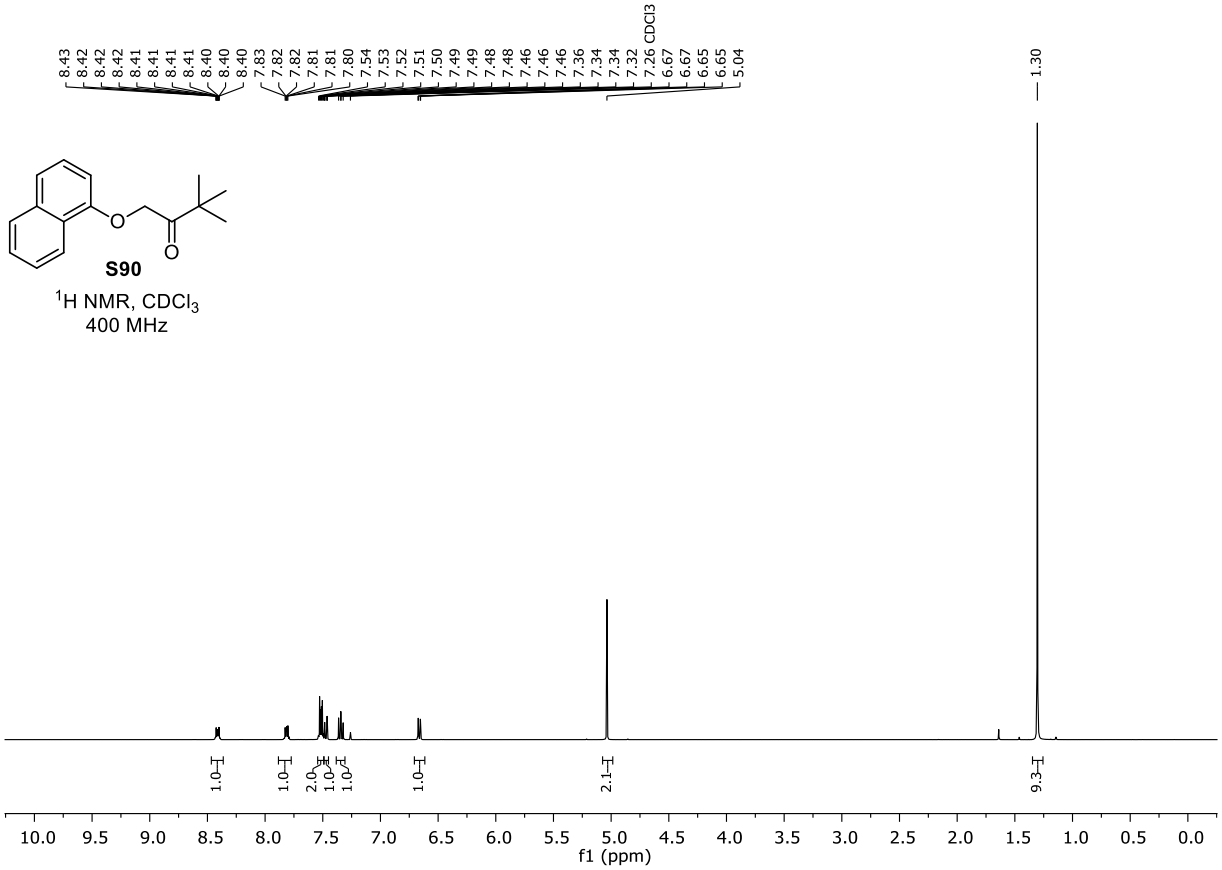
S89

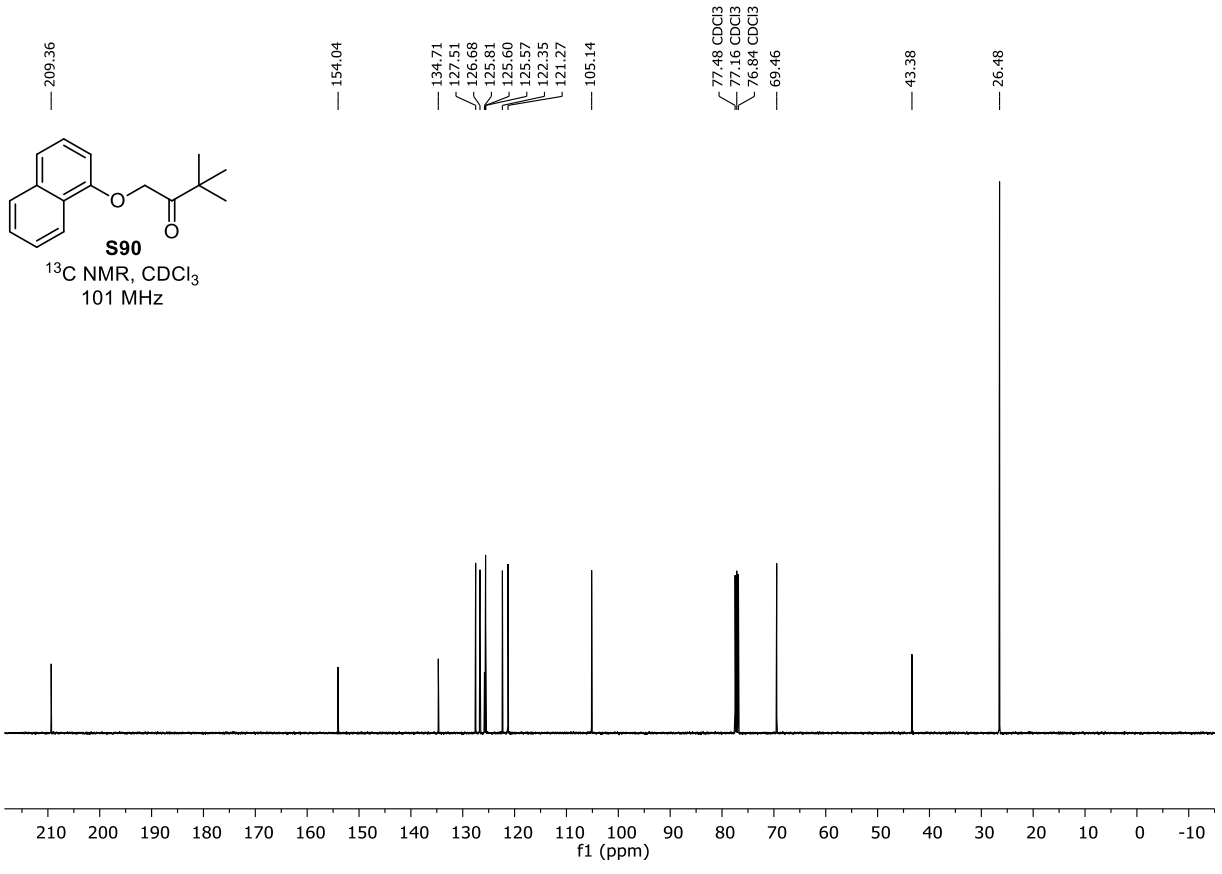
^{1}H NMR, $CDCl_3$
400 MHz

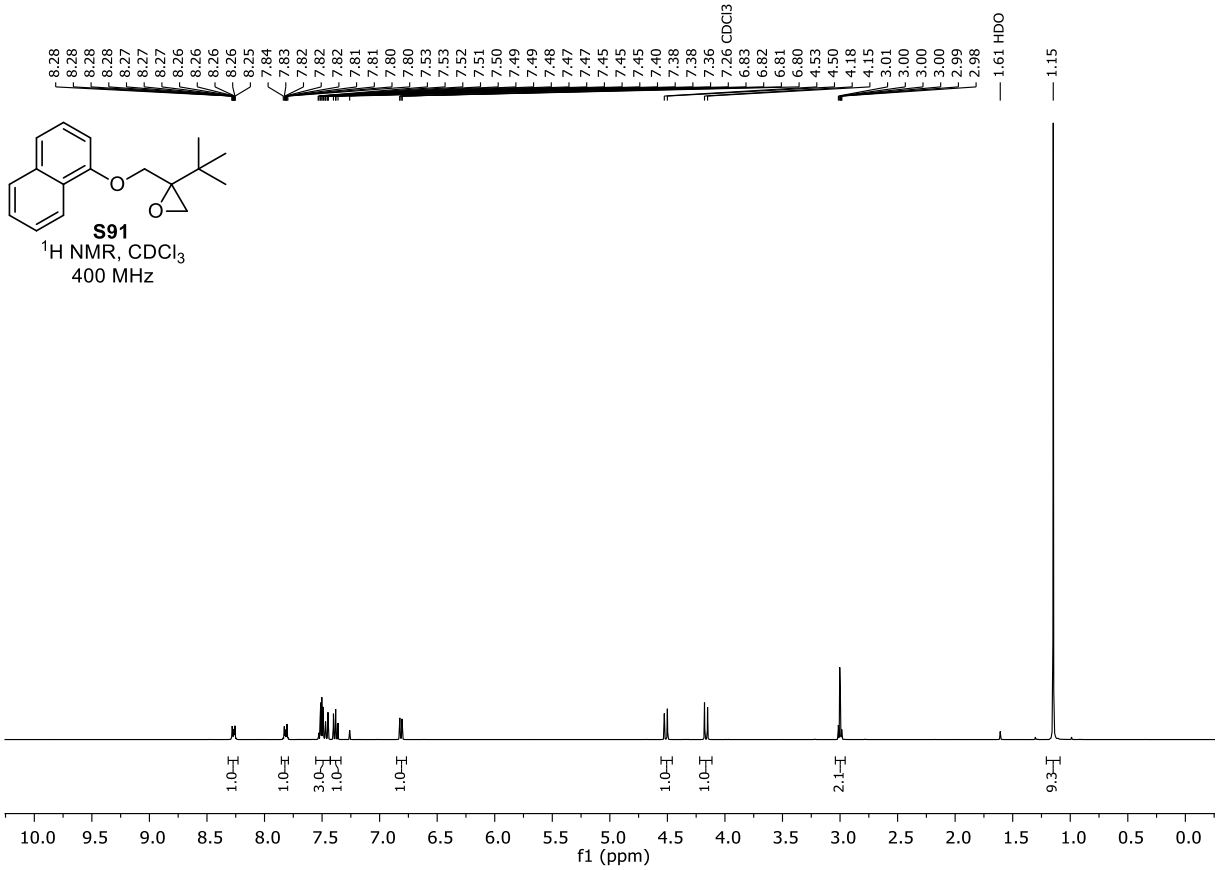


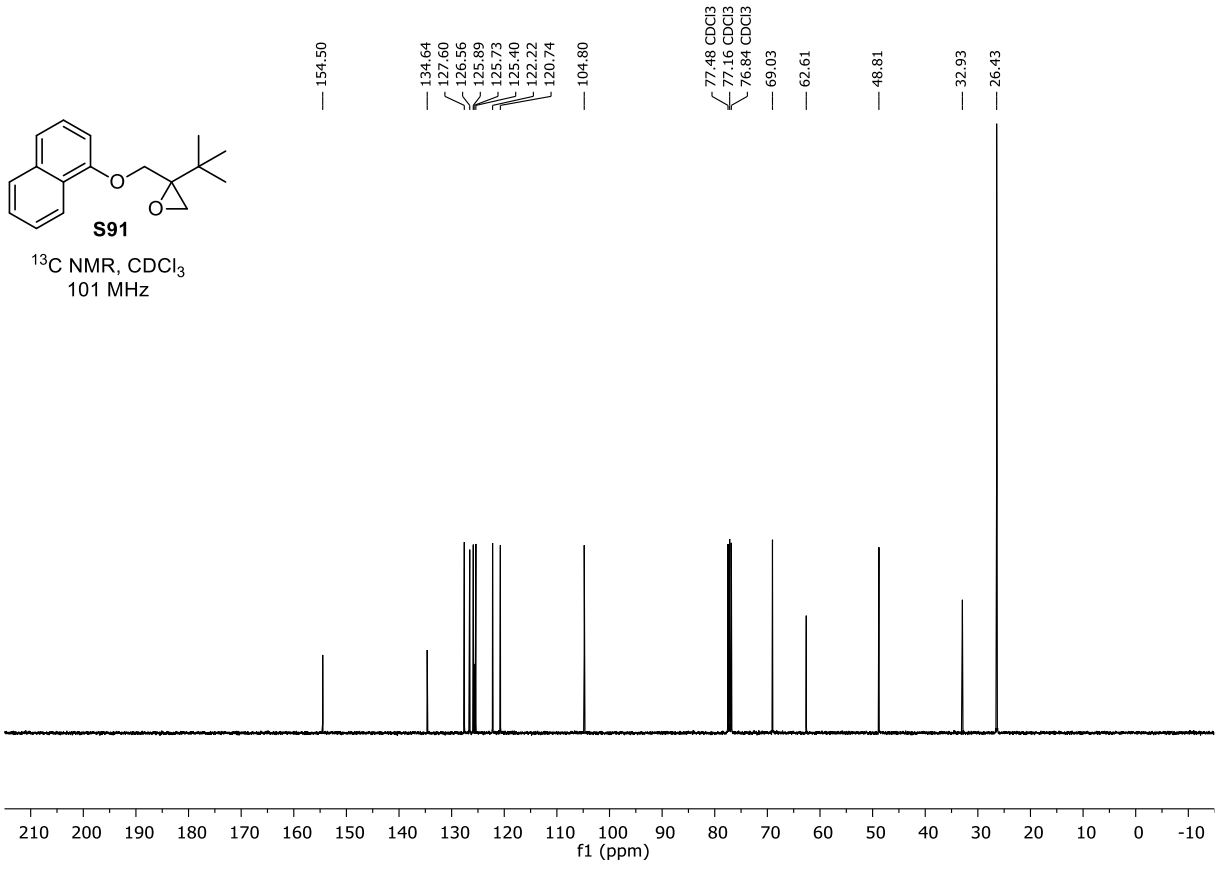
S89

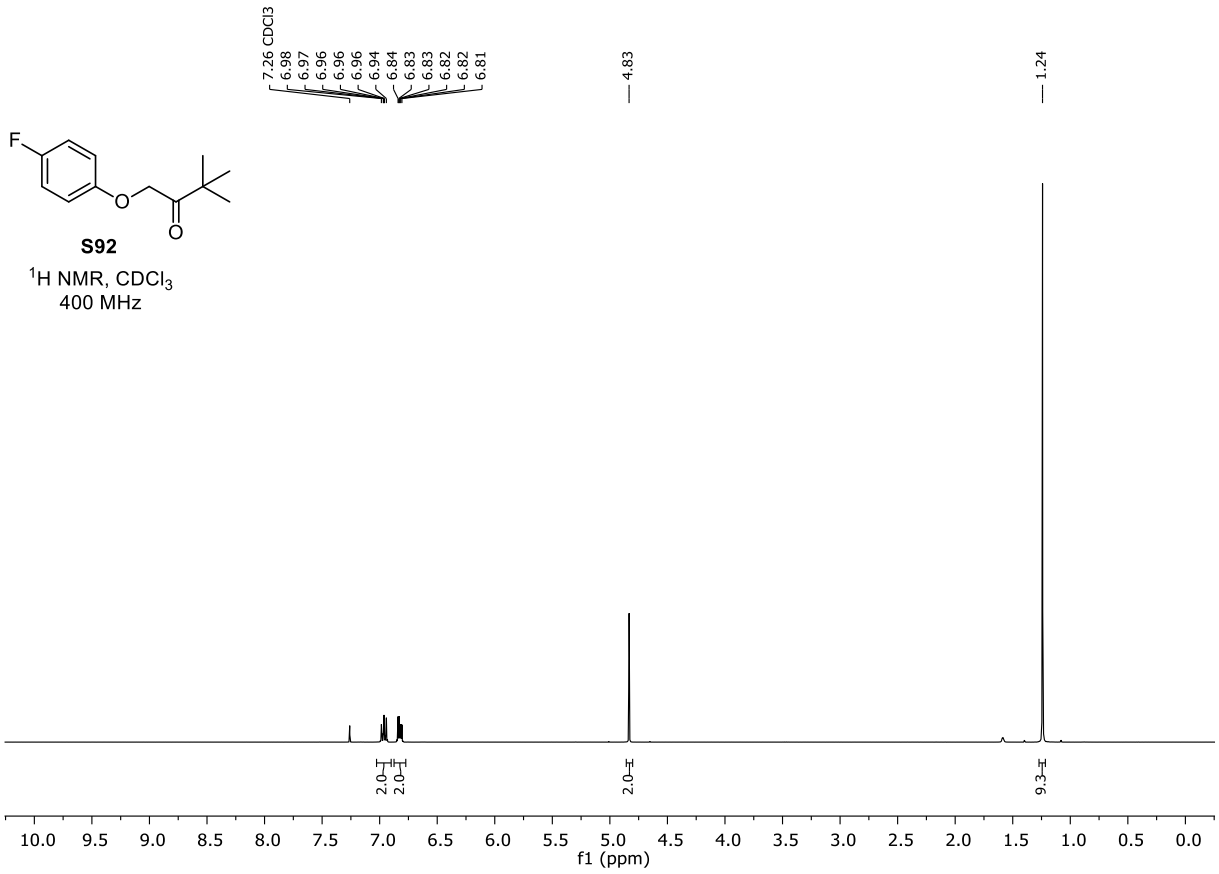
^{13}C NMR, $CDCl_3$
101 MHz


8.43
8.42
8.42
8.42
8.41
8.41
8.41
8.41
8.40
8.40
8.40
7.83
7.82
7.82
7.81
7.81
7.80
7.54
7.53
7.52
7.51
7.50
7.49
7.49
7.48
7.48
7.46
7.46
7.46
7.36
7.34
7.34
7.32
7.26 CDCl3
6.67
6.67
6.65
6.65
5.04
1.30
O
O
S90
1H NMR, CDCl3
400 MHz
1.0
1.0
2.0
1.0
1.0
2.1
9.3
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)


209.36
154.04
134.71
127.51
126.68
125.81
125.60
125.57
122.35
121.27
105.14
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
69.46
43.38
26.48
O
O
S90
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)

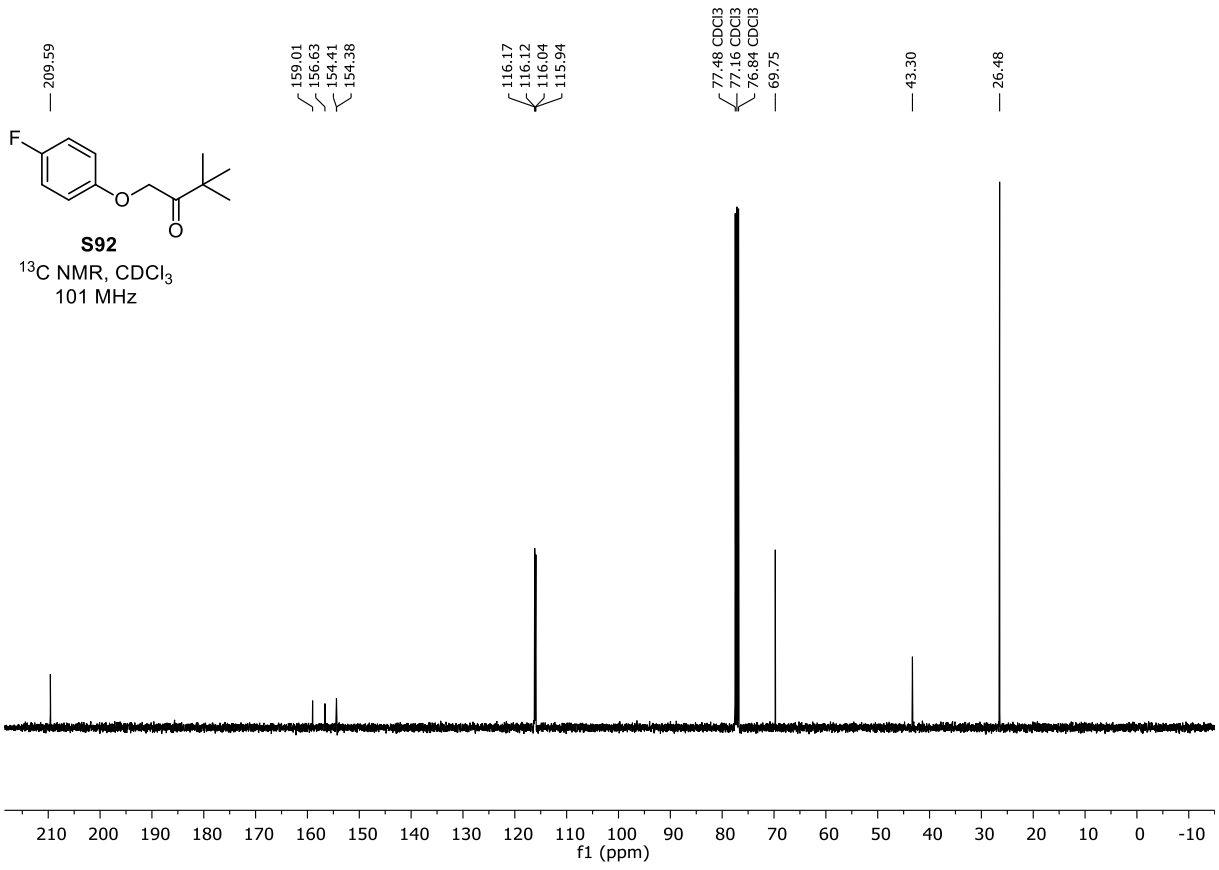

8.28 8.28 8.28 8.28 8.27 8.27 8.26 8.26 8.26 8.26 8.25 7.84 7.83 7.82 7.82 7.82 7.81 7.81 7.80 7.80 7.53 7.53 7.52 7.51 7.50 7.49 7.49 7.48 7.47 7.47 7.45 7.45 7.45 7.40 7.38 7.38 7.36 7.26 CDCl3 6.83 6.82 6.81 6.80 4.53 4.50 4.18 4.15 3.01 3.00 3.00 3.00 2.99 2.98 1.61 HDO 1.15
O
O
S91
^{1}H NMR, CDCl$_3$
400 MHz
1.0 1.0 3.0 1.0 1.0 1.0 1.0 2.1 9.3
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)


154.50 134.64 127.60 126.56 125.89 125.73 125.40 122.22 120.74 104.80 77.48 CDCl3 77.16 CDCl3 76.84 CDCl3 69.03 62.61 48.81 32.93 26.43
O
O
S91
^{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)



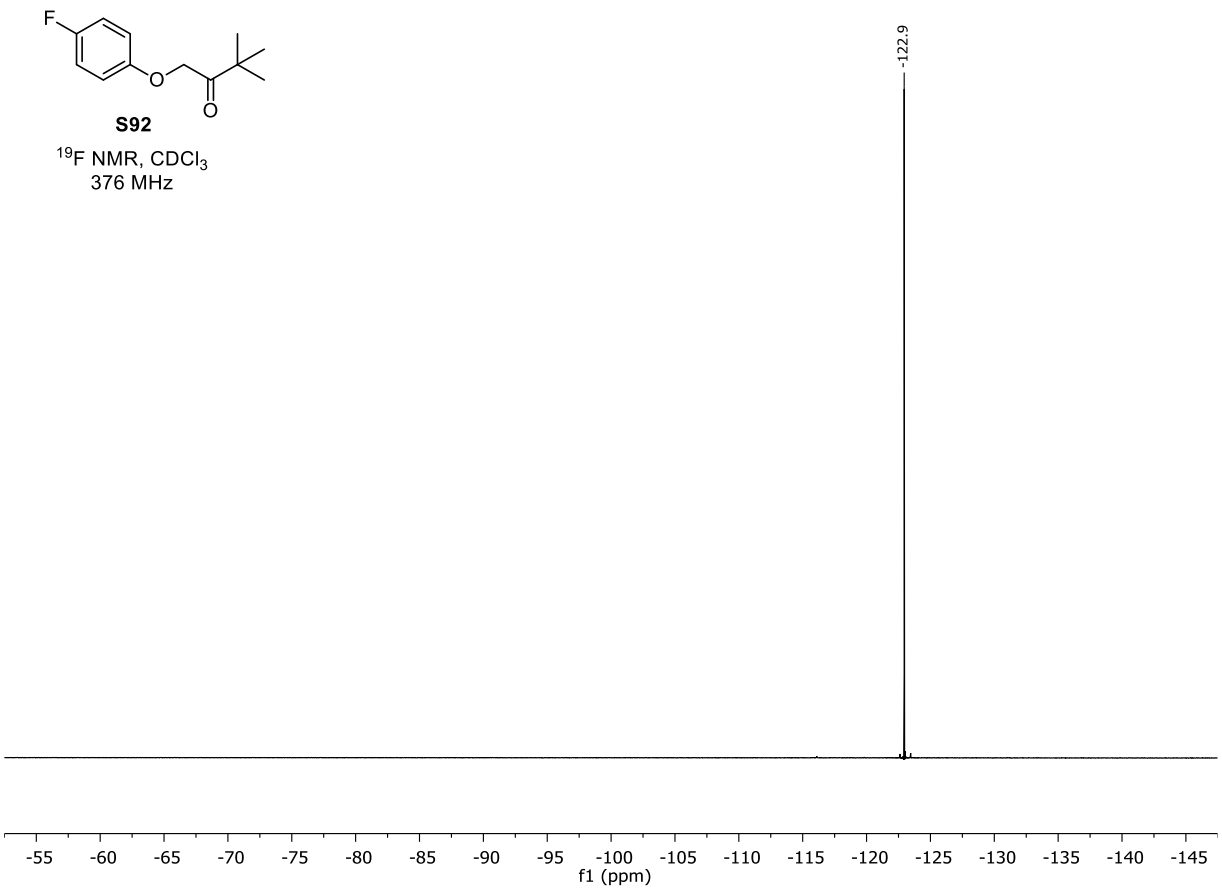
S92

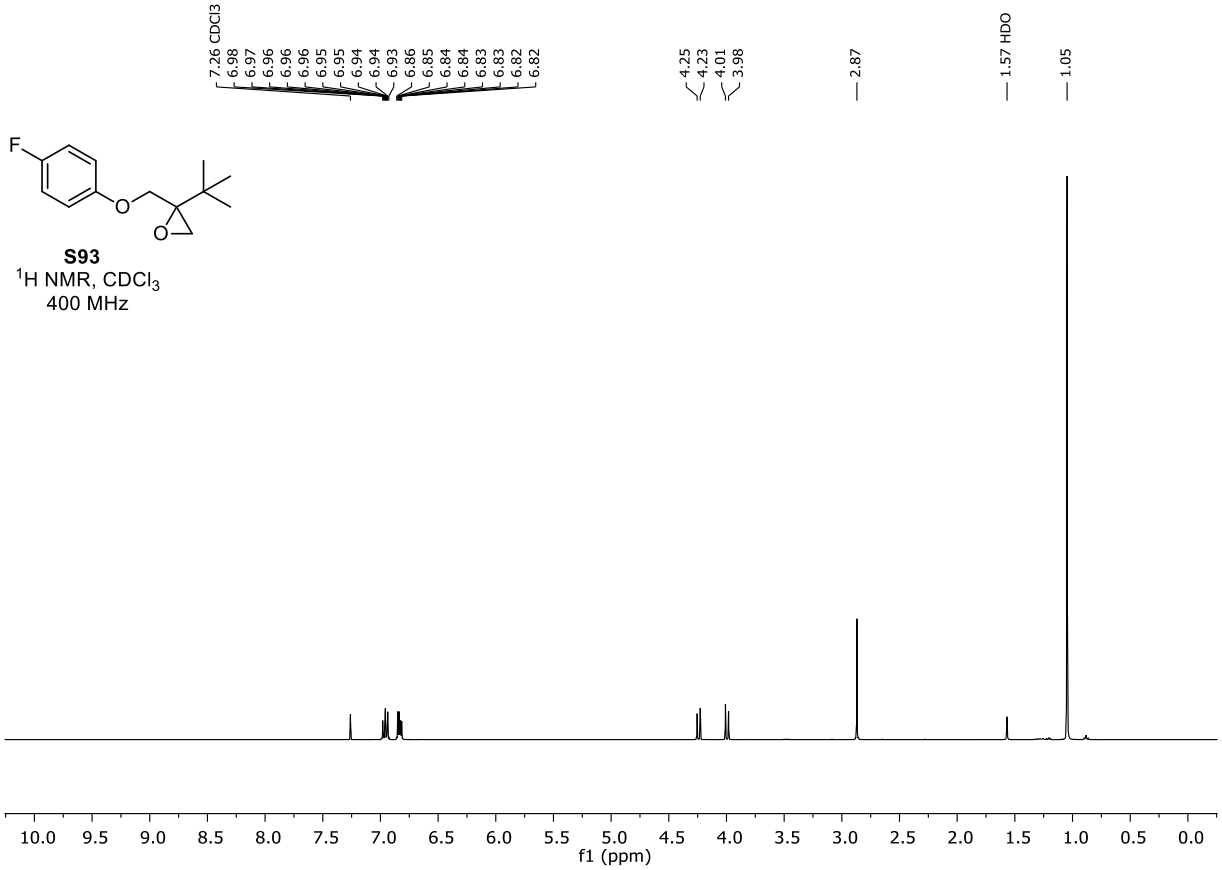
^{1}H NMR, $CDCl_3$
400 MHz



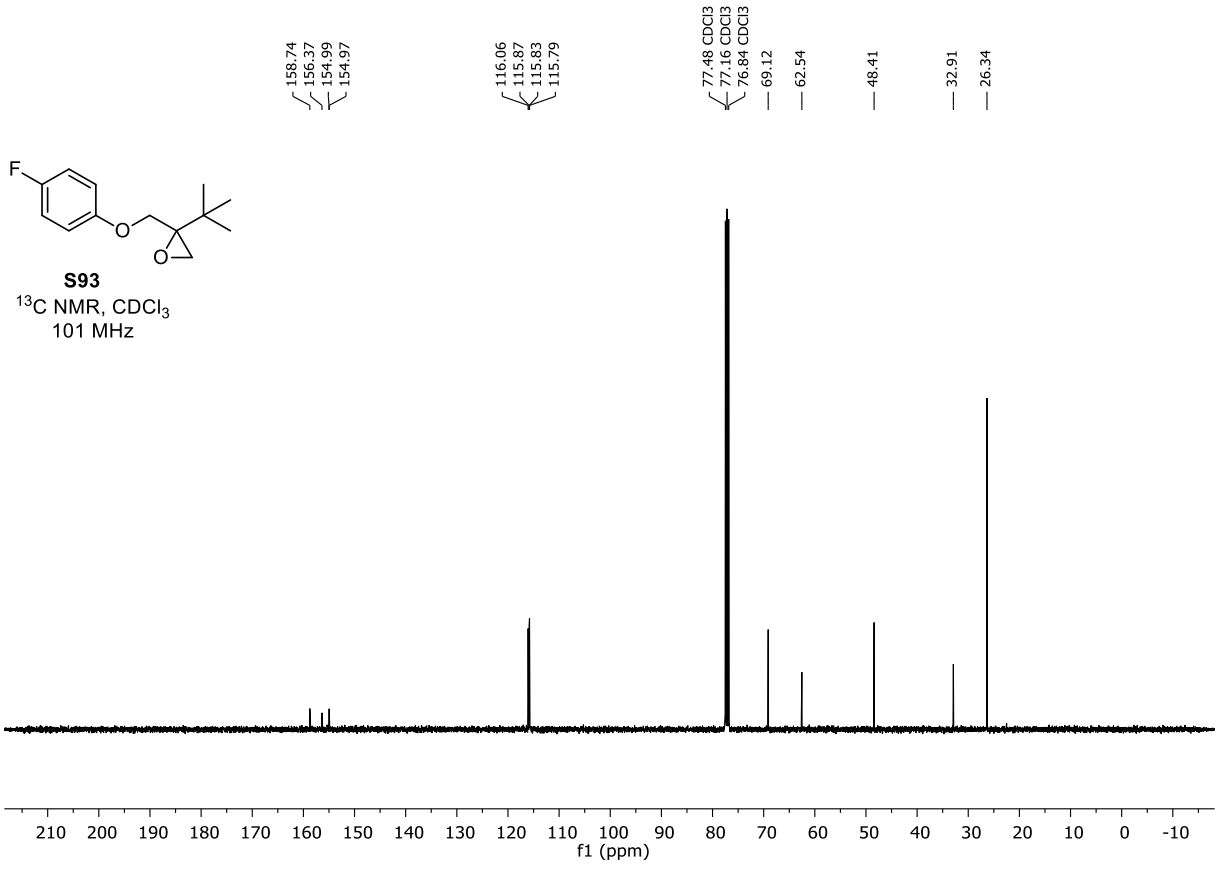
S92

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

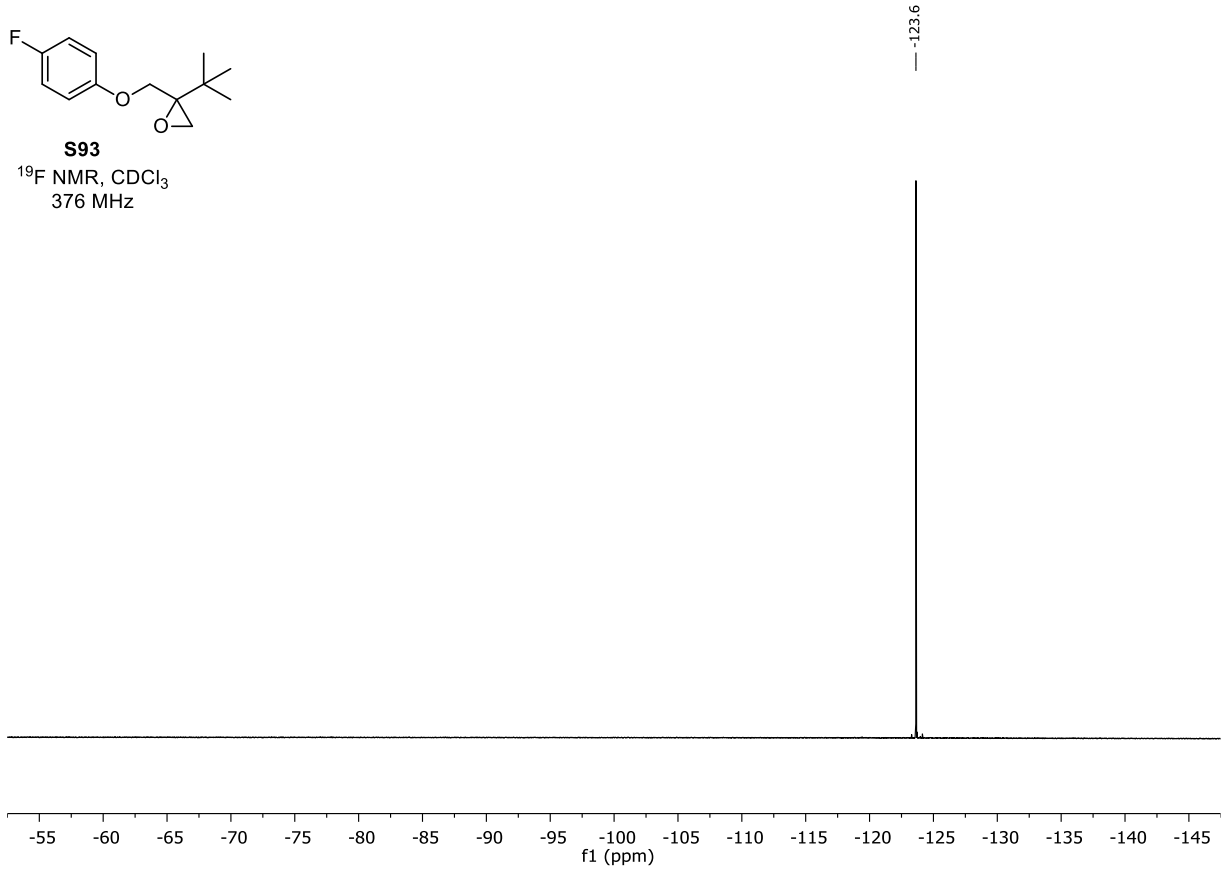

F
O
O
S92
19F NMR, CDCl3
376 MHz
-122.9
-55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145
f1 (ppm)



S93
^{1}H NMR, $CDCl_3$
400 MHz

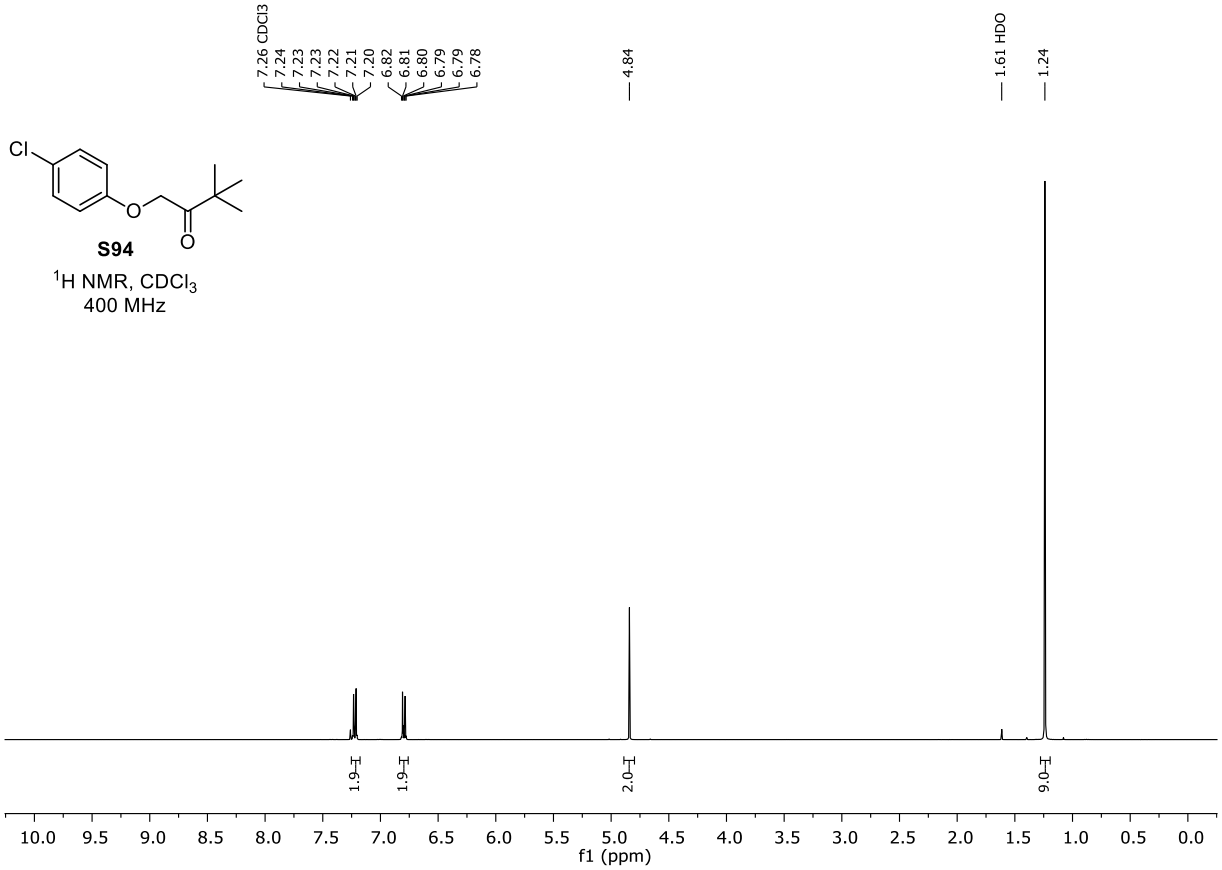


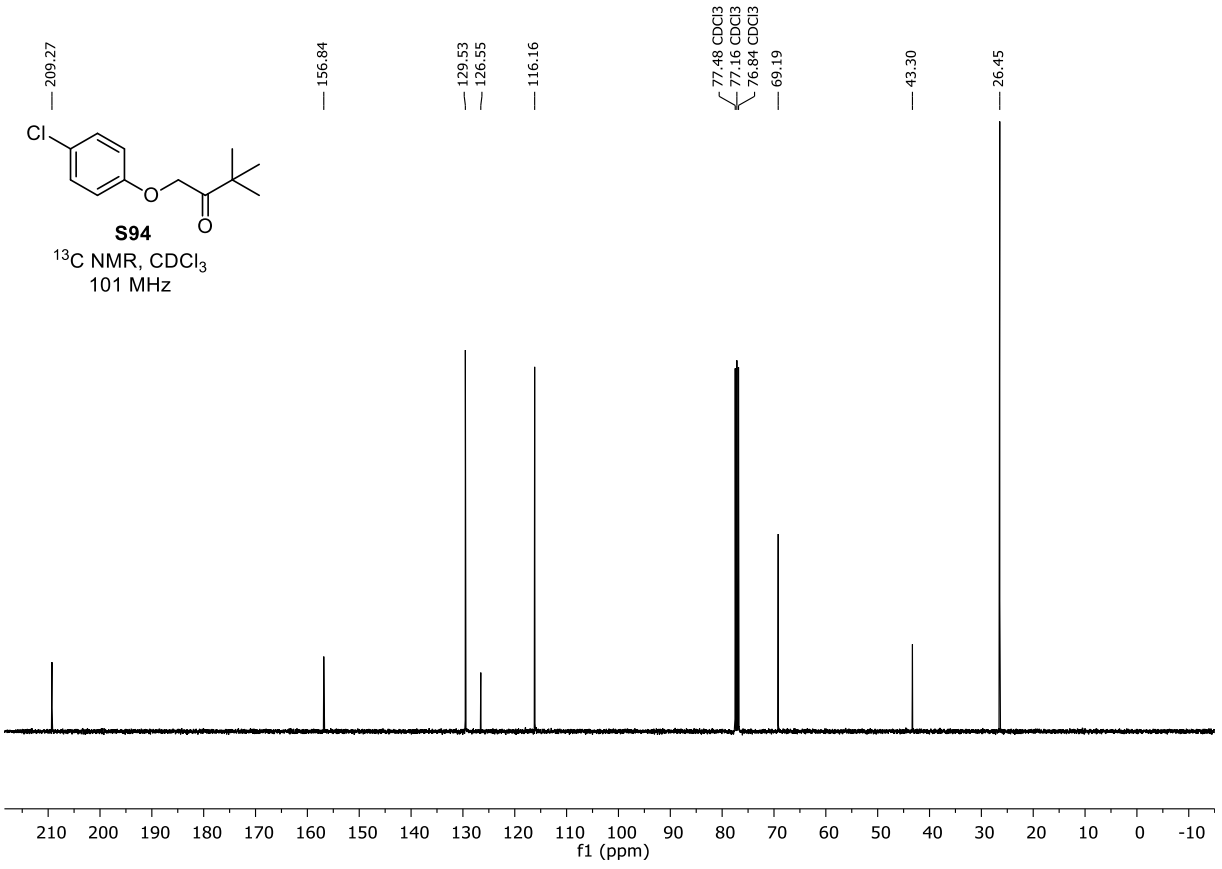
S93
^{13}C NMR, $CDCl_3$
101 MHz

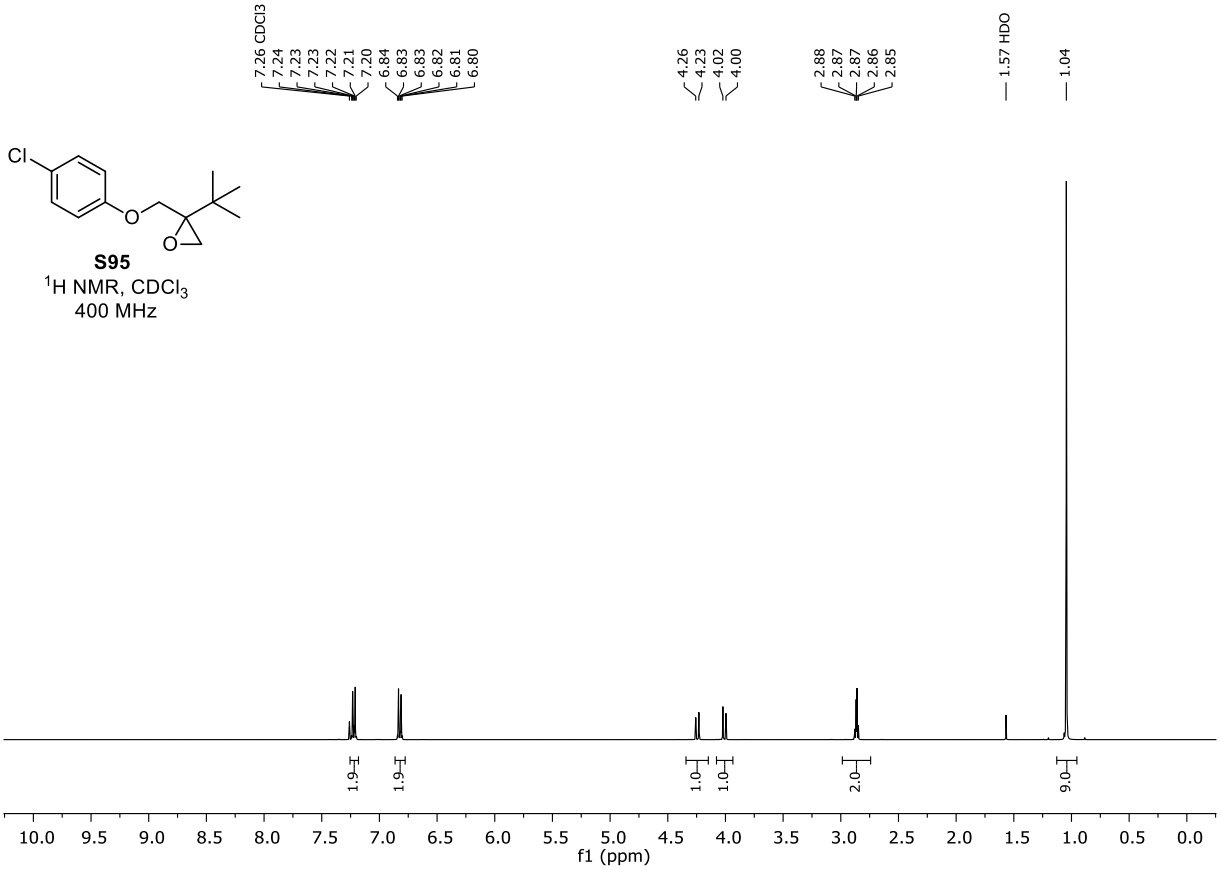


S93

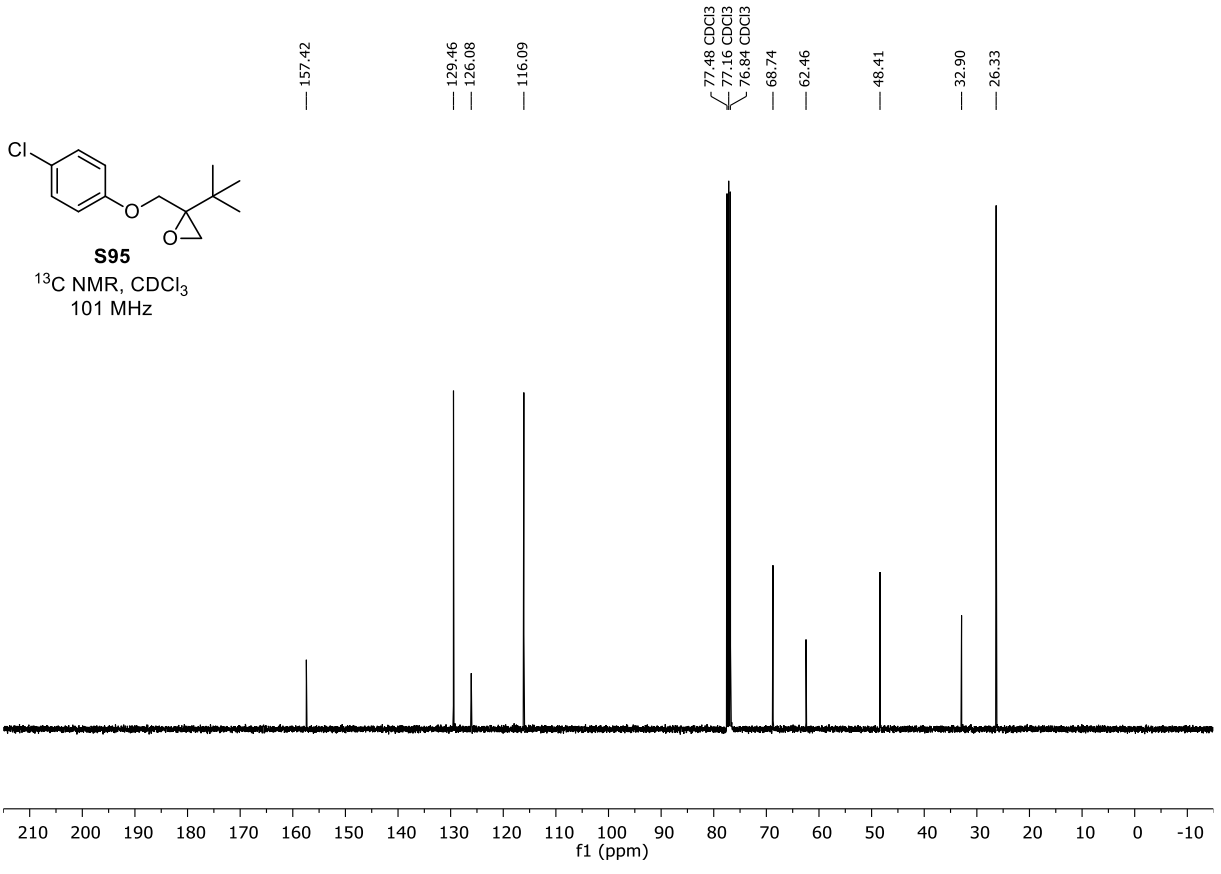
^{19}F NMR, $CDCl_3$
376 MHz


7.26 CDCl3
7.24
7.23
7.23
7.22
7.21
7.20
6.82
6.81
6.80
6.79
6.79
6.78
4.84
1.61 HDO
1.24
Cl
O
O
S94
1H NMR, CDCl3
400 MHz
1.9
1.9
2.0
9.0
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)

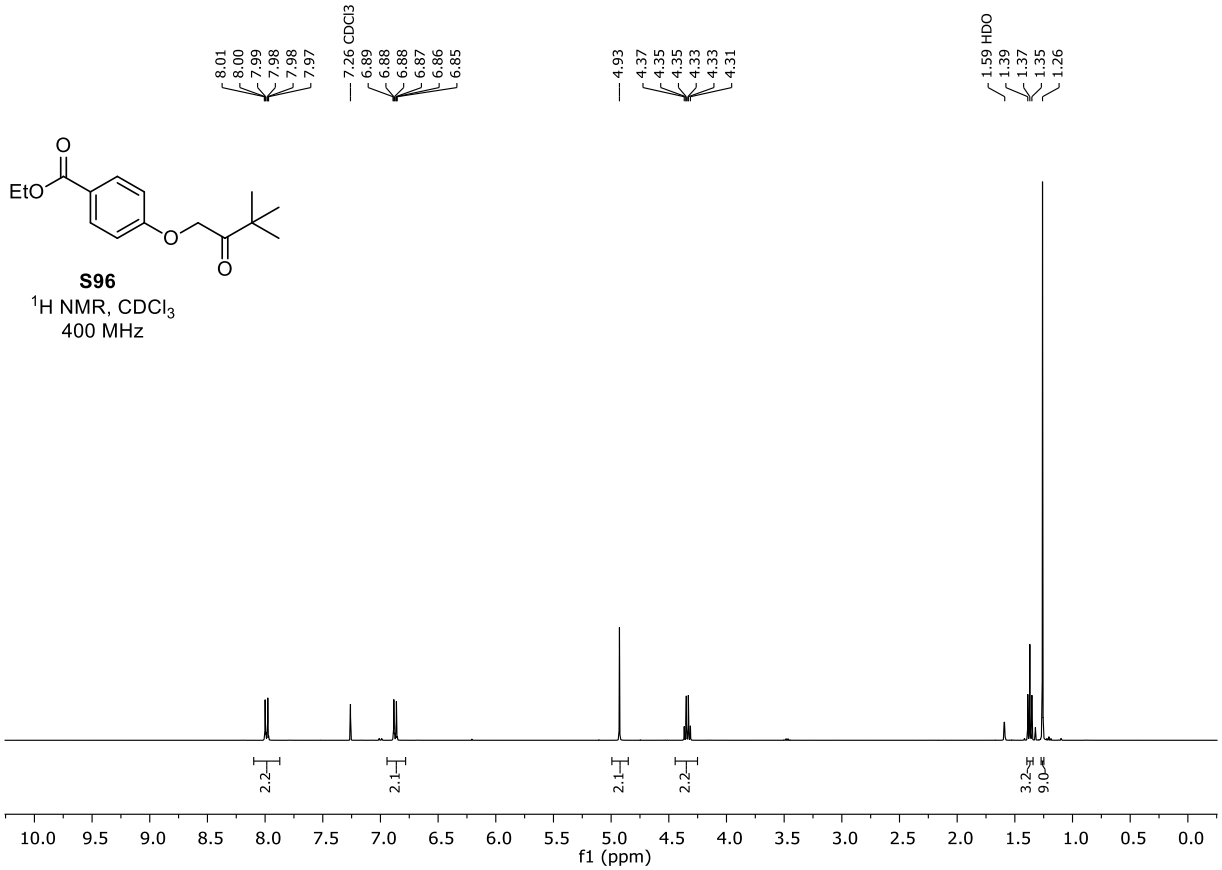

209.27
156.84
129.53
126.55
116.16
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
69.19
43.30
26.45
Cl
O
O
S94
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



S95
^{1}H NMR, $CDCl_3$
400 MHz

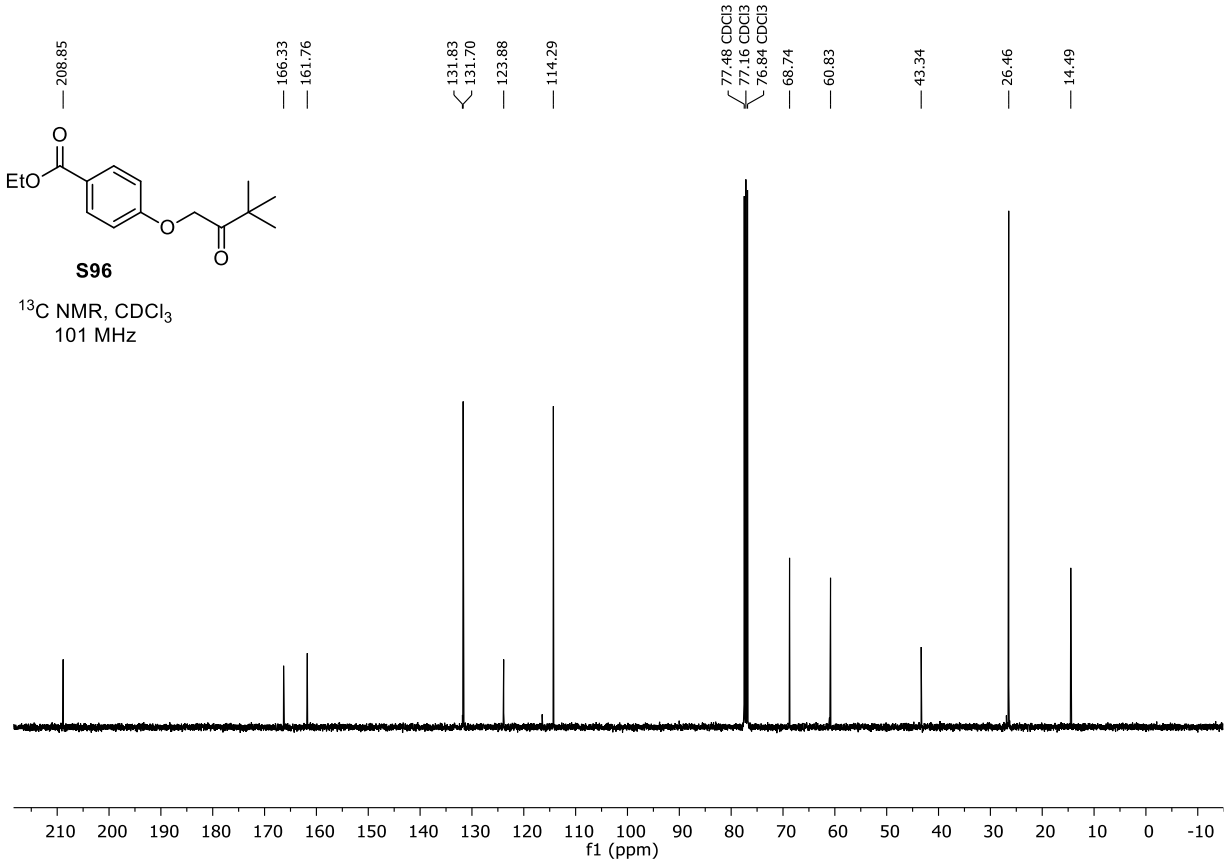


S95
^{13}C NMR, $CDCl_3$
101 MHz



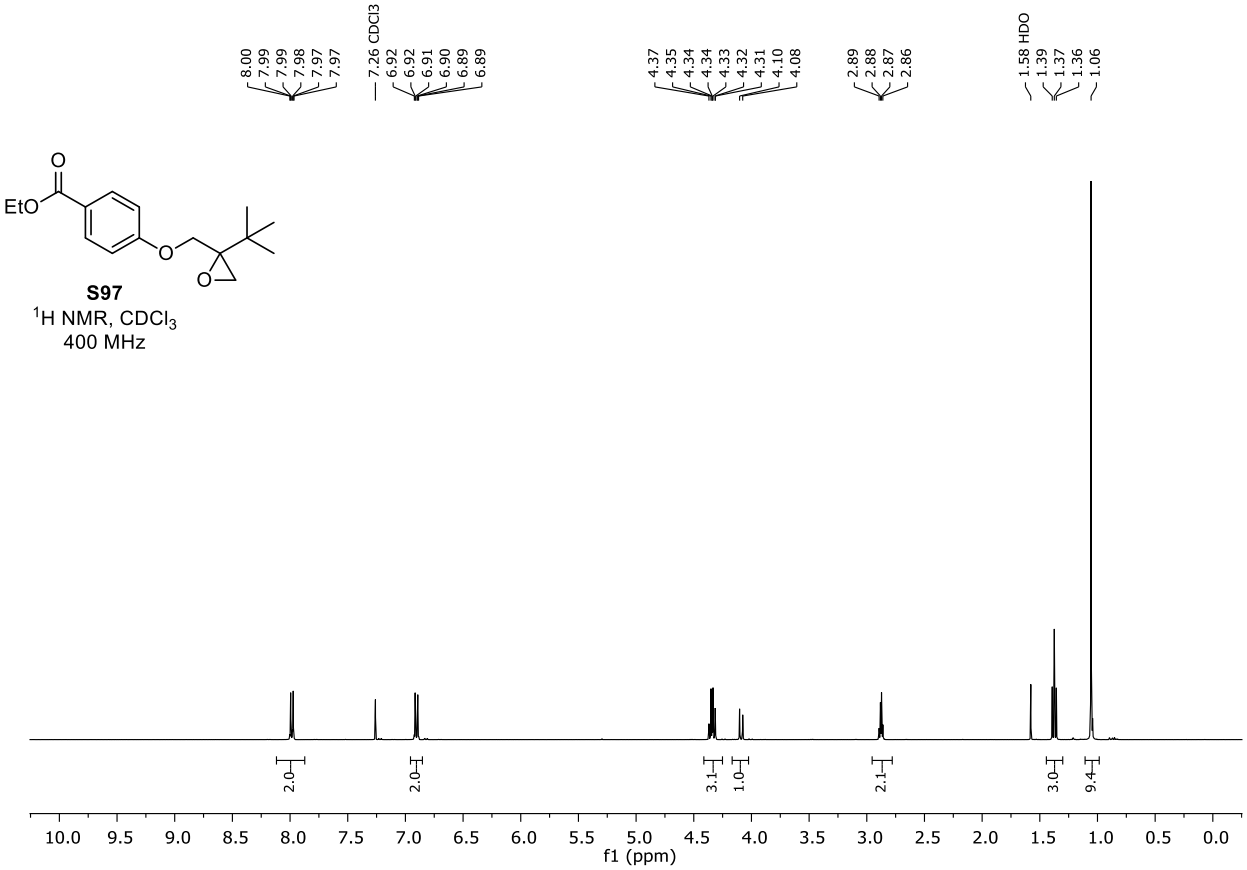
S96

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

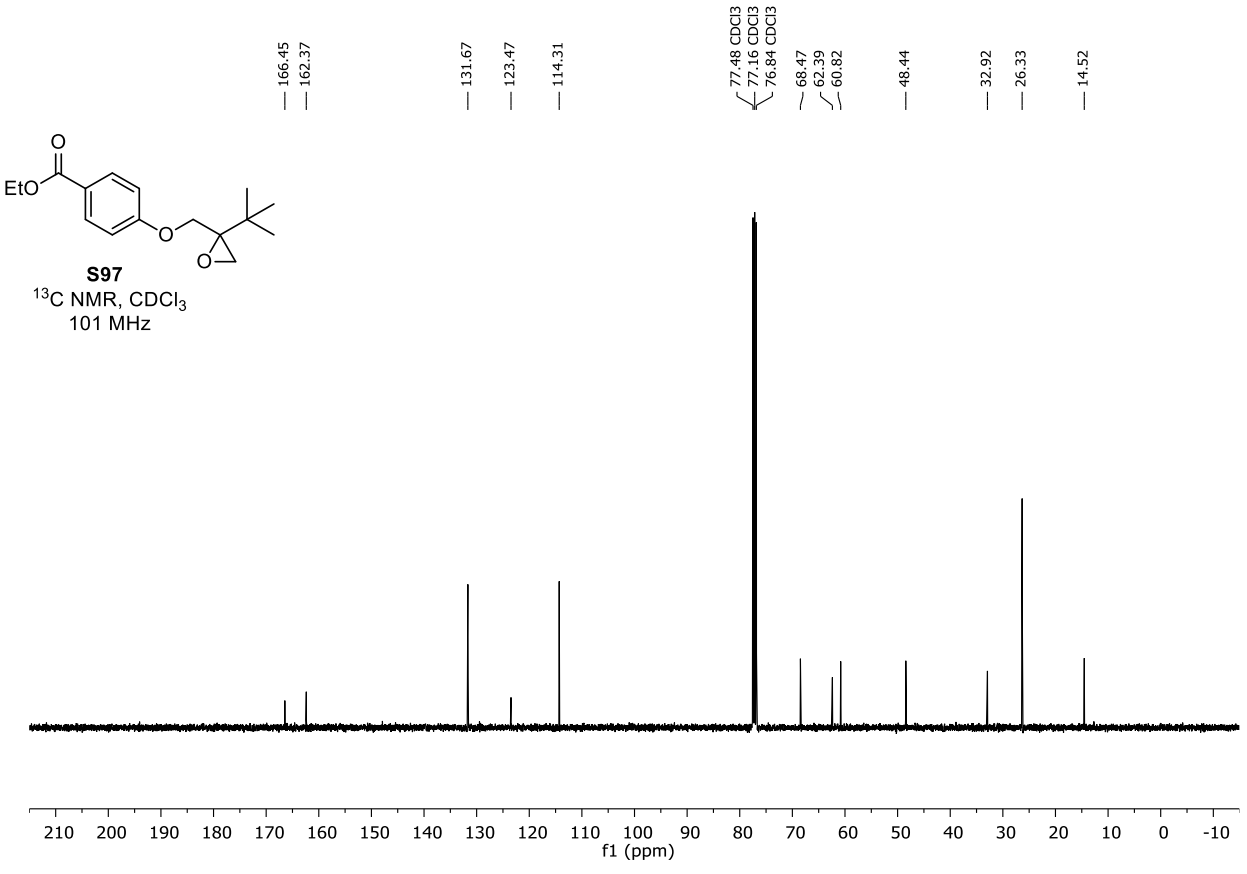


S96

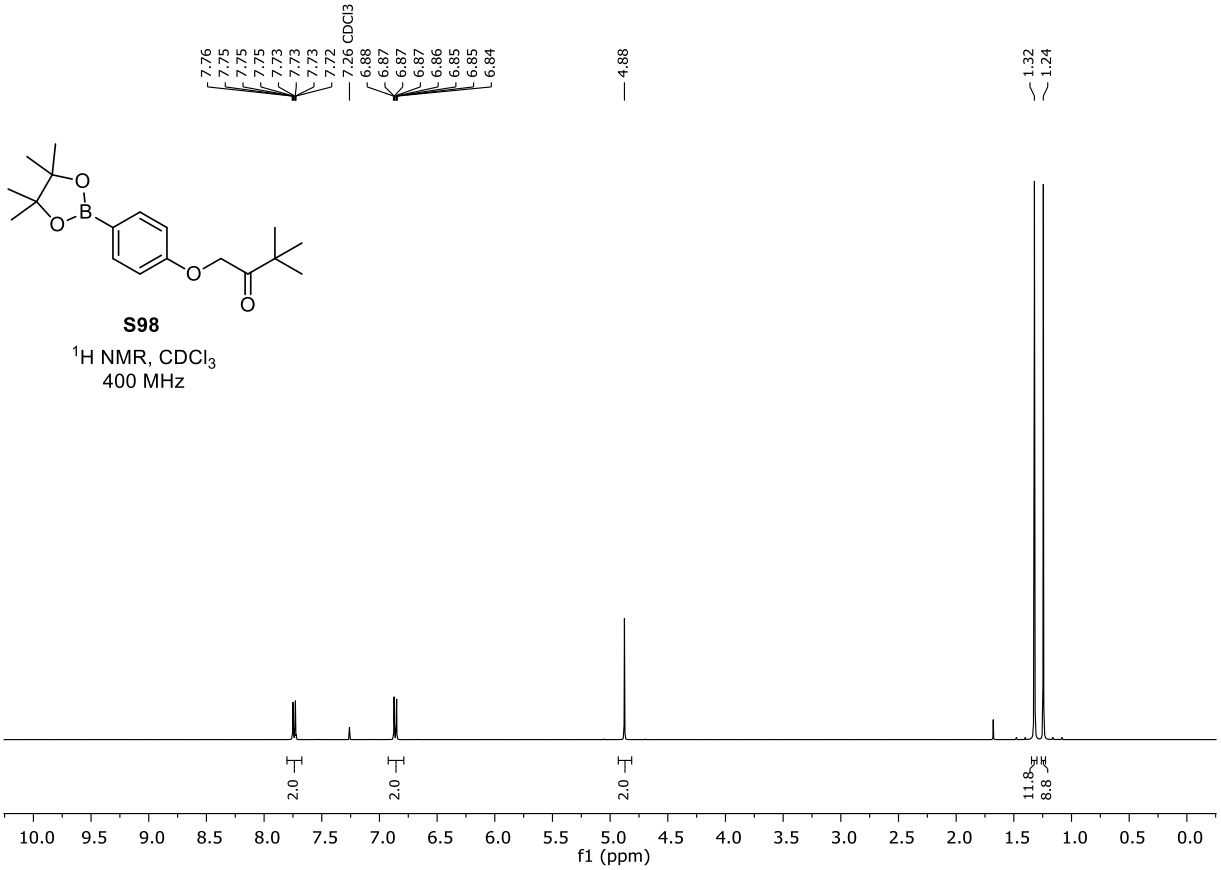
^{13}C NMR, $CDCl_3$
101 MHz



S97
^{1}H NMR, $CDCl_3$
400 MHz

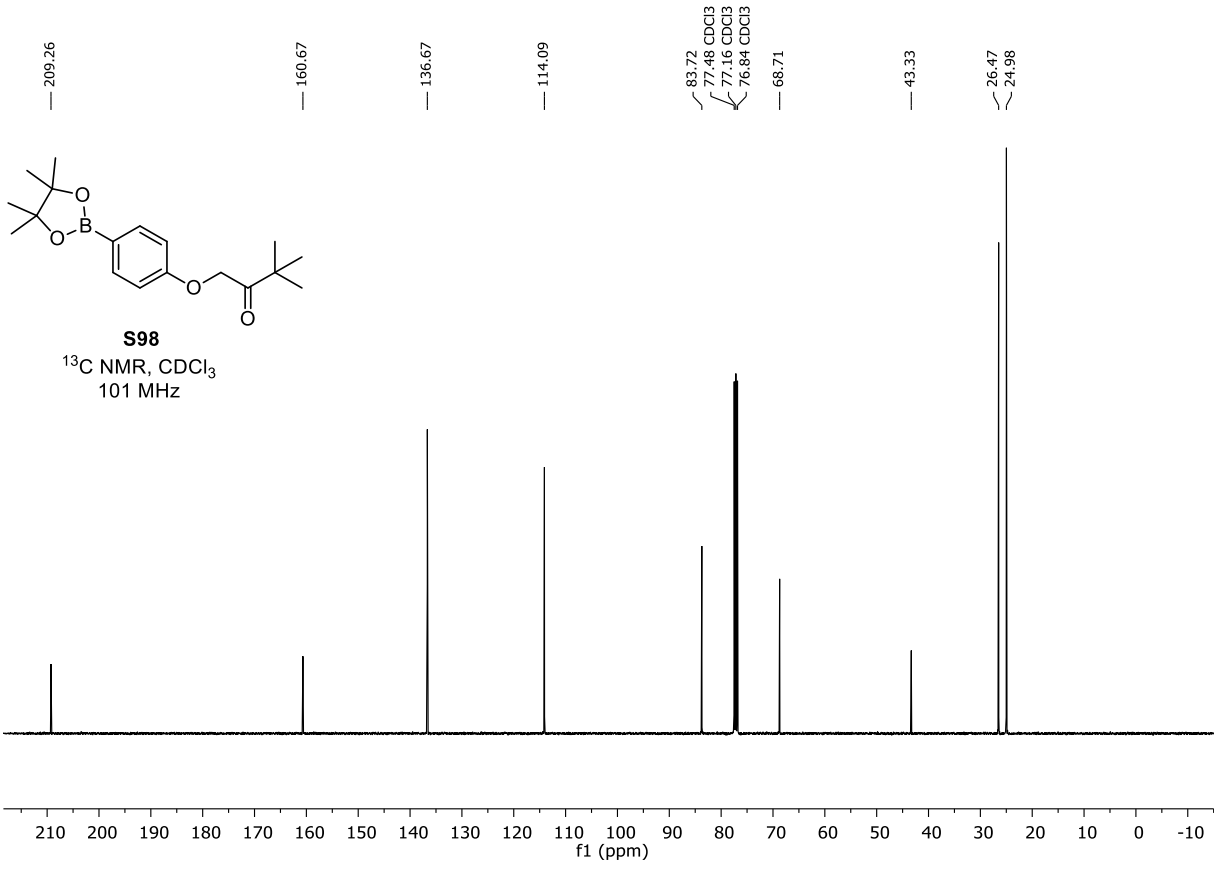


S97
^{13}C NMR, $CDCl_3$
101 MHz



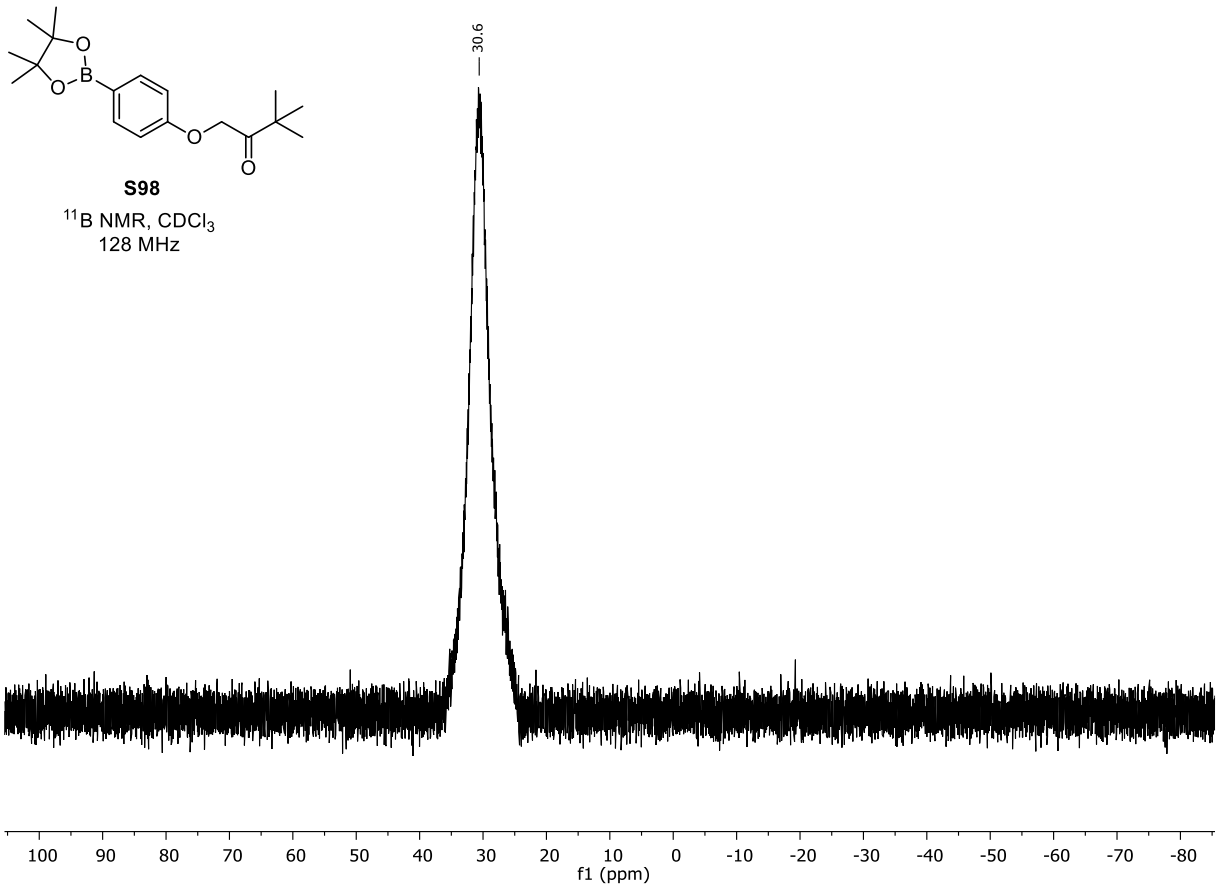
S98

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



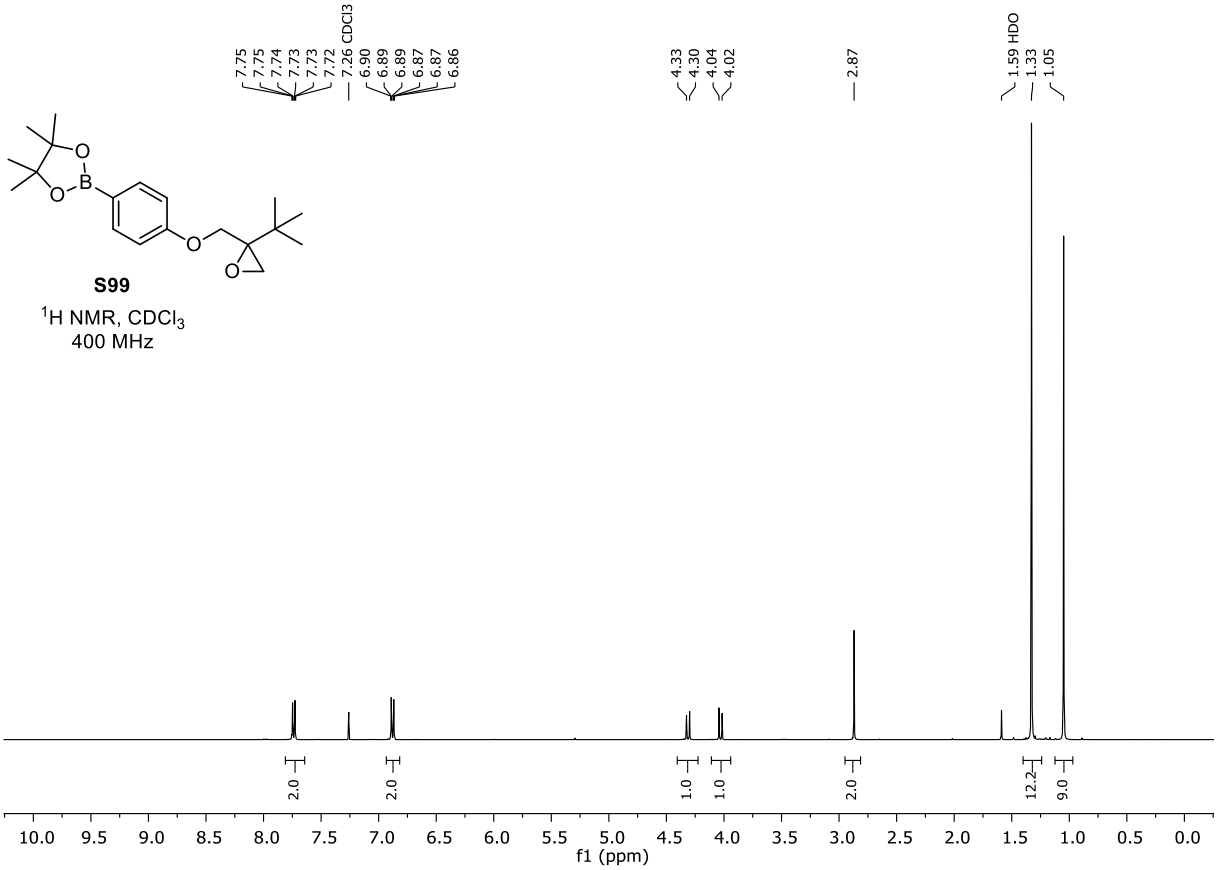
S98

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



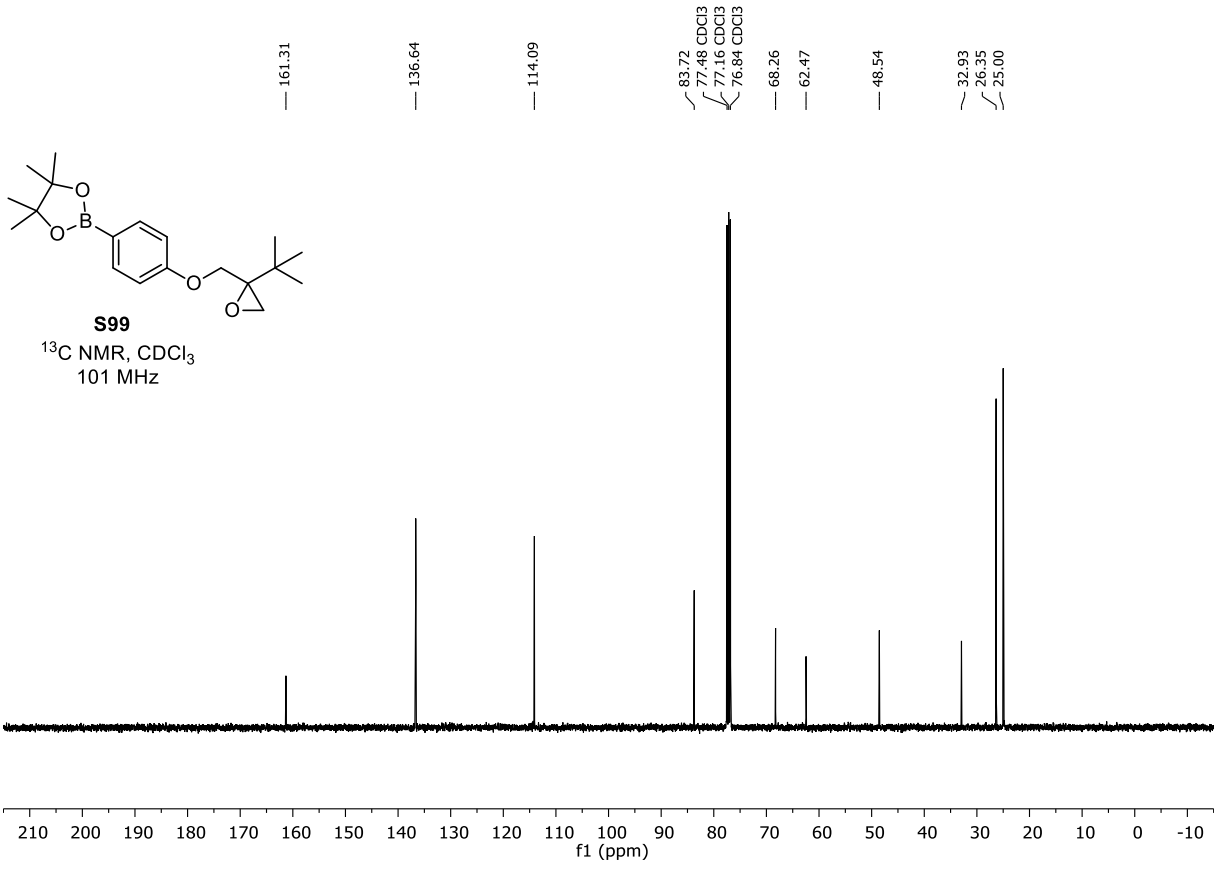
S98

^{11}B NMR, $CDCl_3$
128 MHz



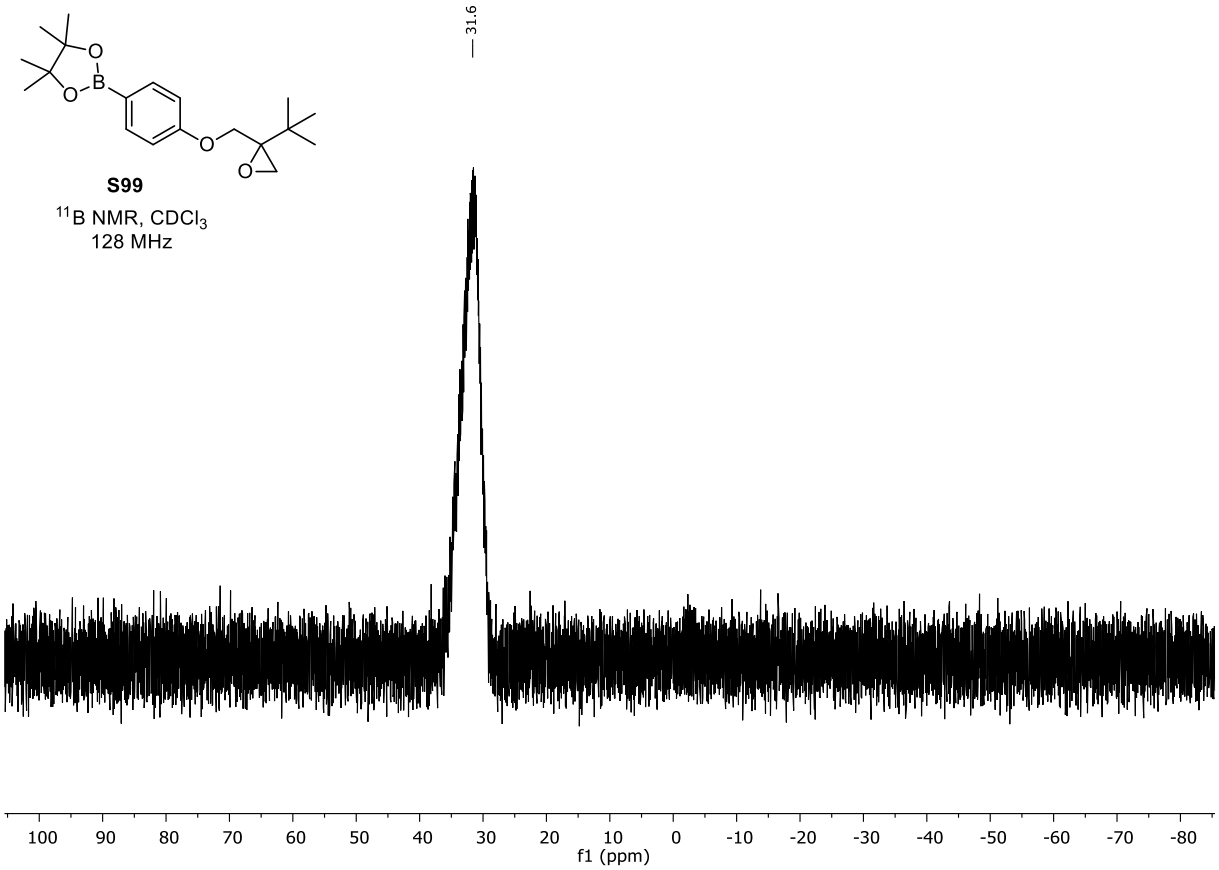
S99

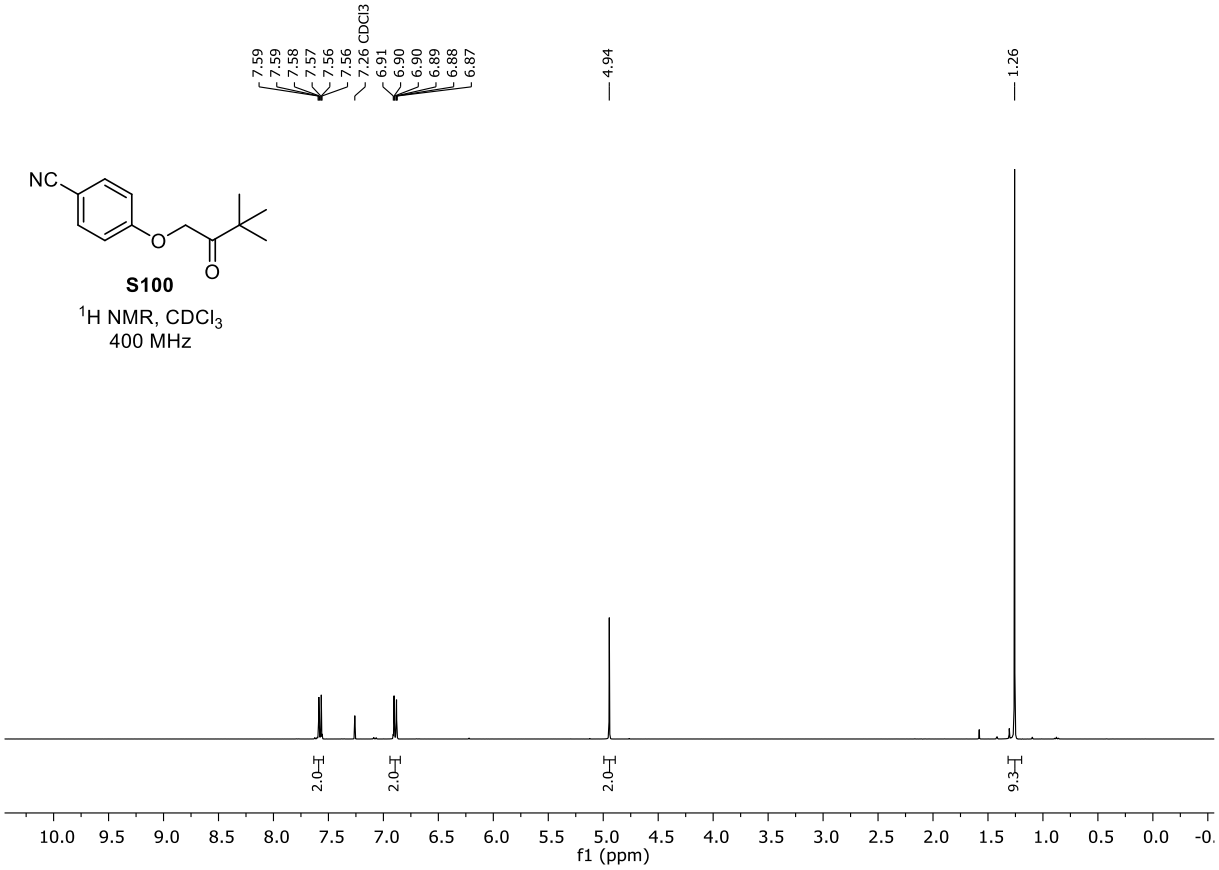
^{1}H NMR, $CDCl_3$
400 MHz



S99

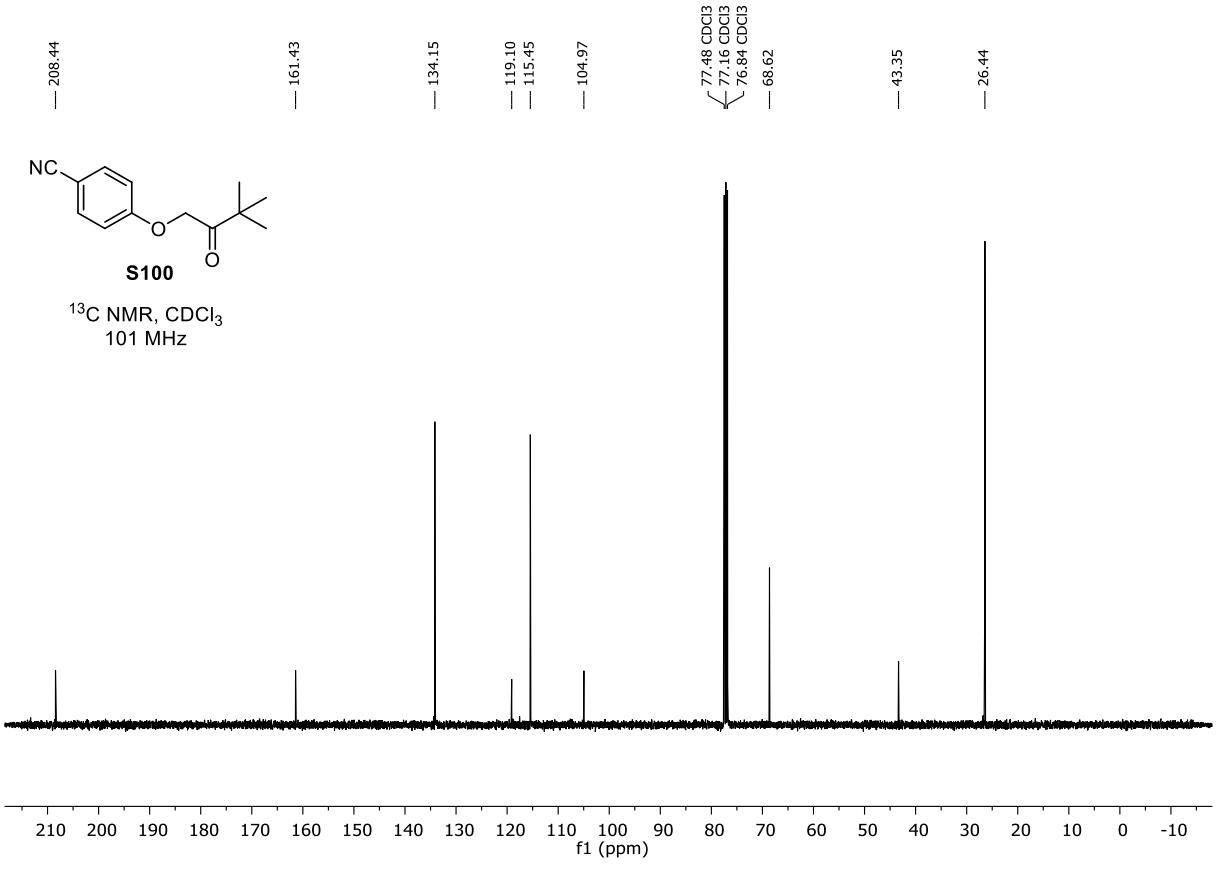
^{13}C NMR, $CDCl_3$
101 MHz


31.6
S99
11B NMR, CDCl3
128 MHz
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80
f1 (ppm)



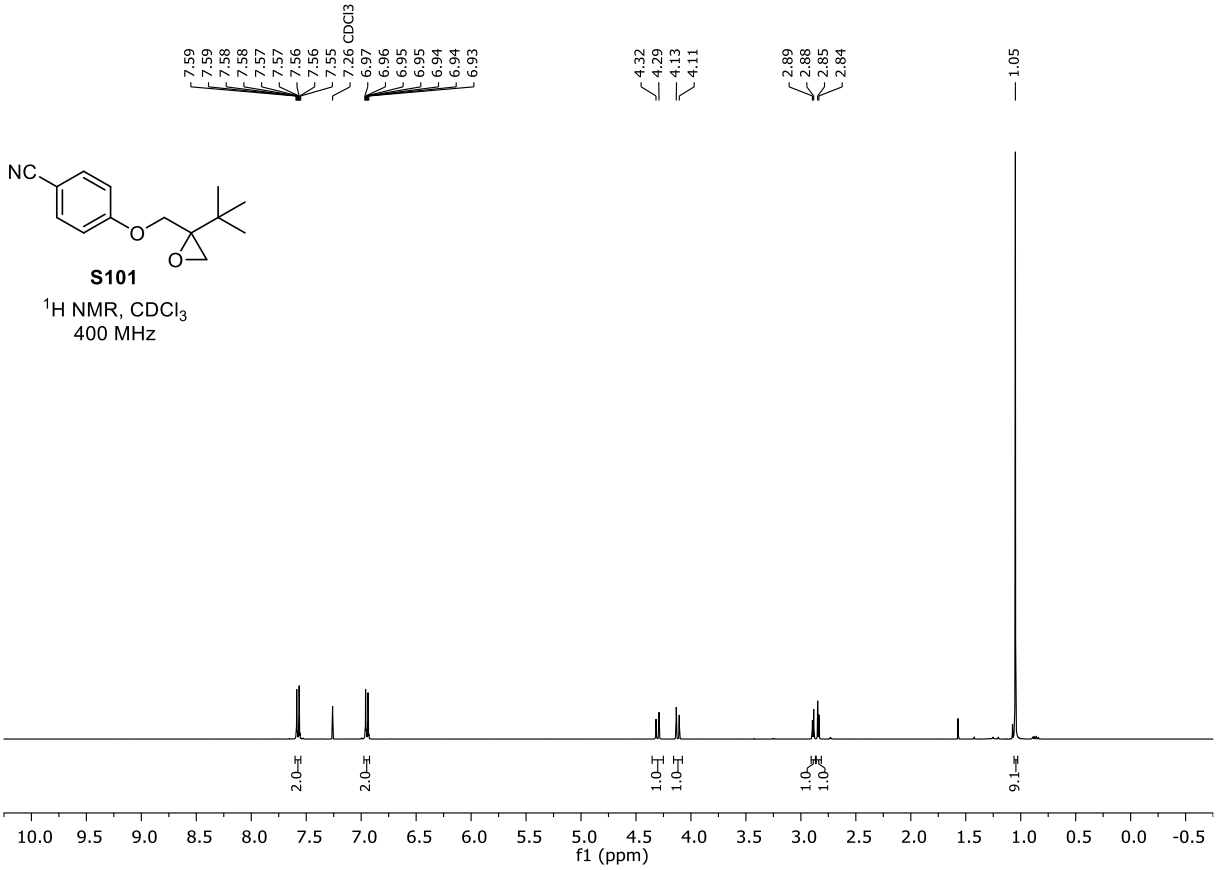
S100

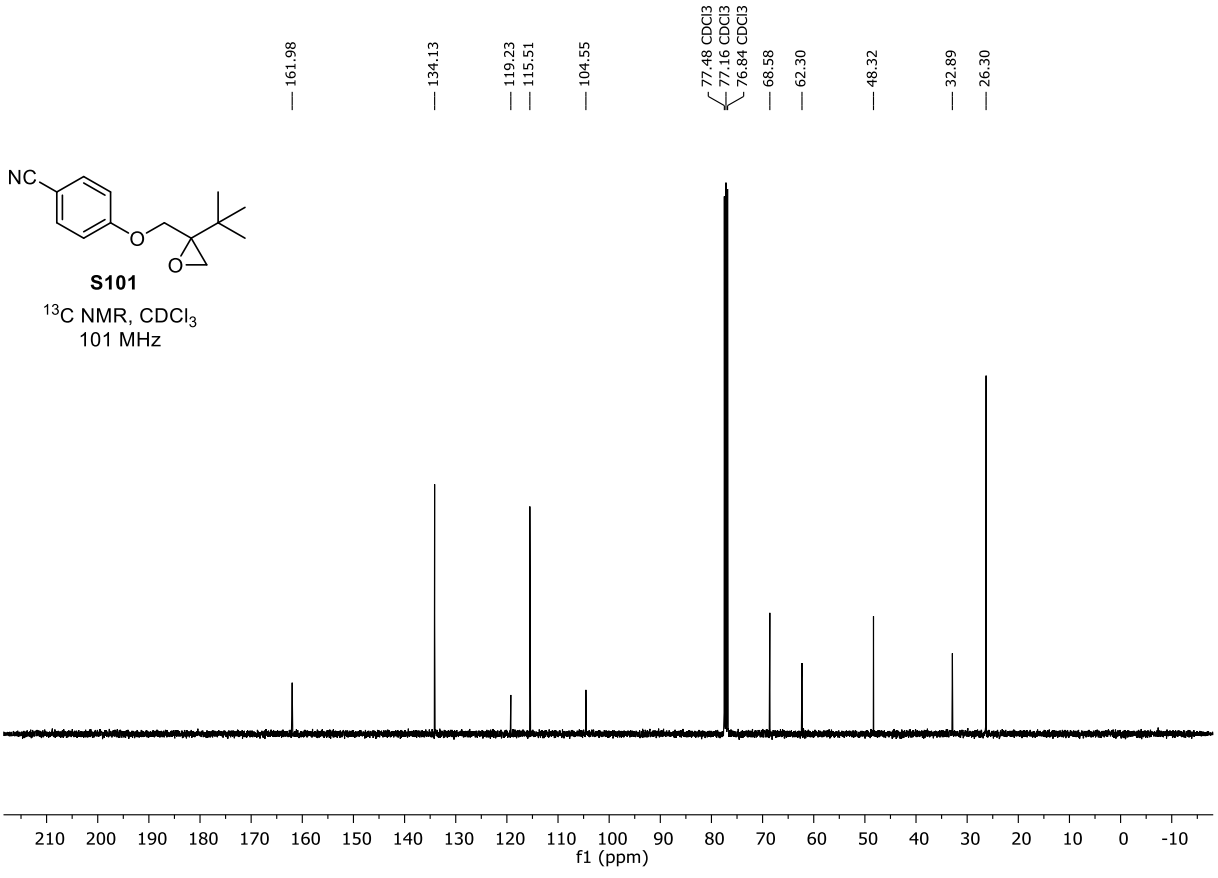
^{1}H NMR, $CDCl_3$
400 MHz

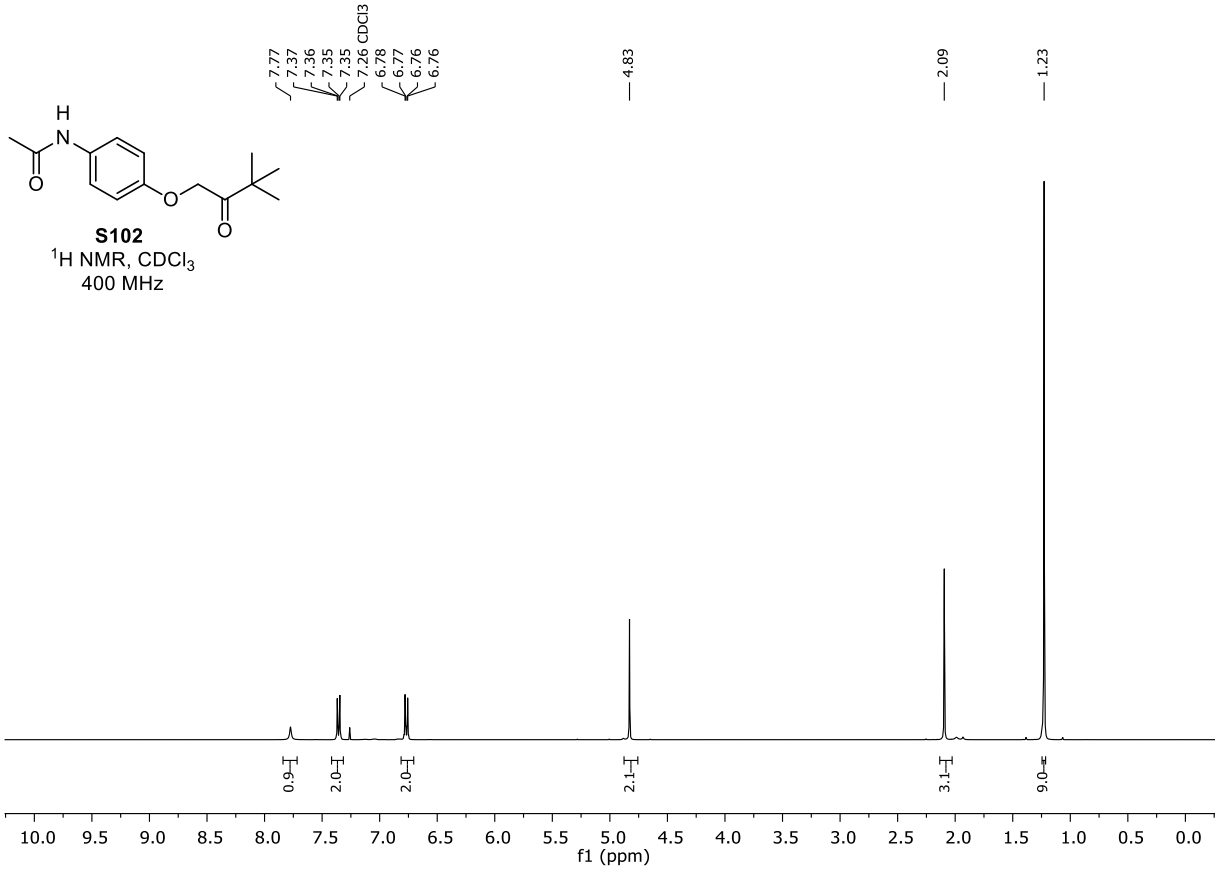


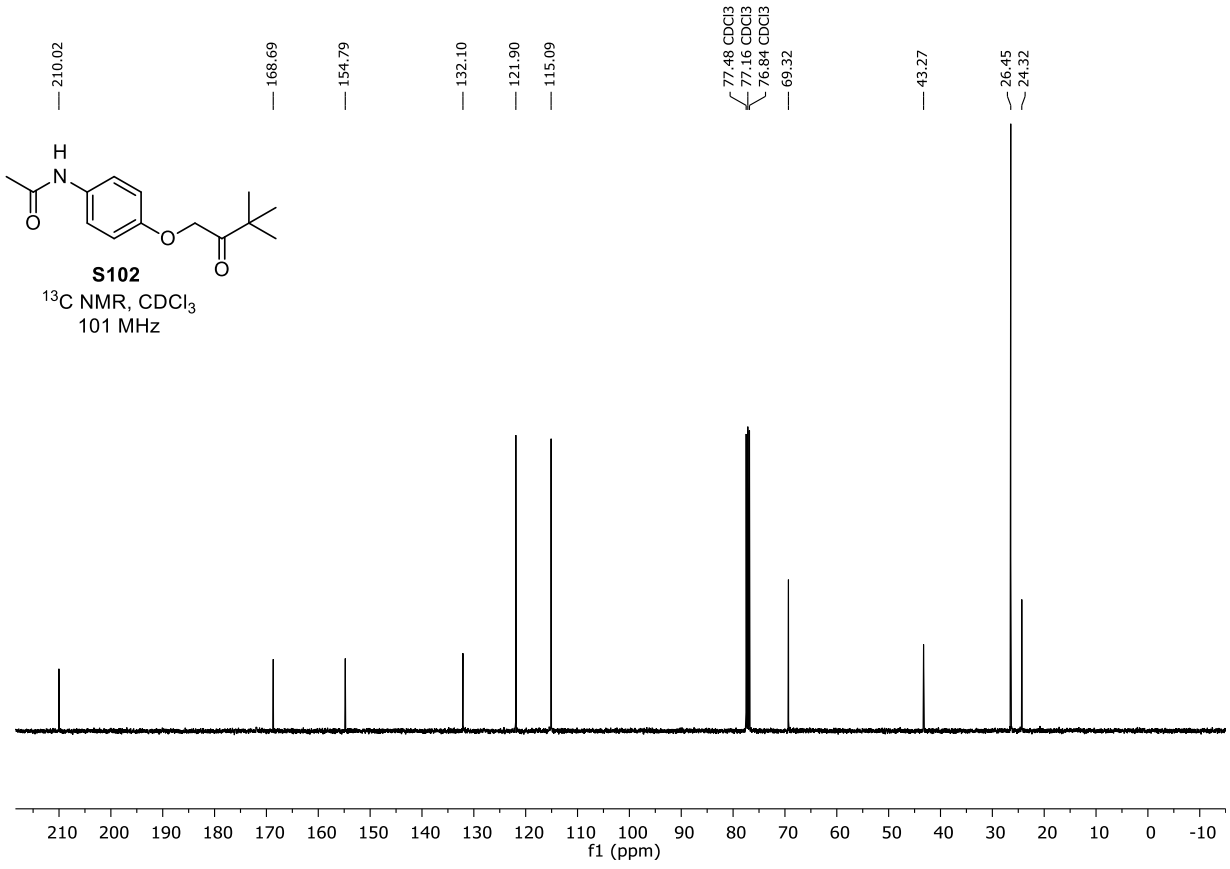
S100

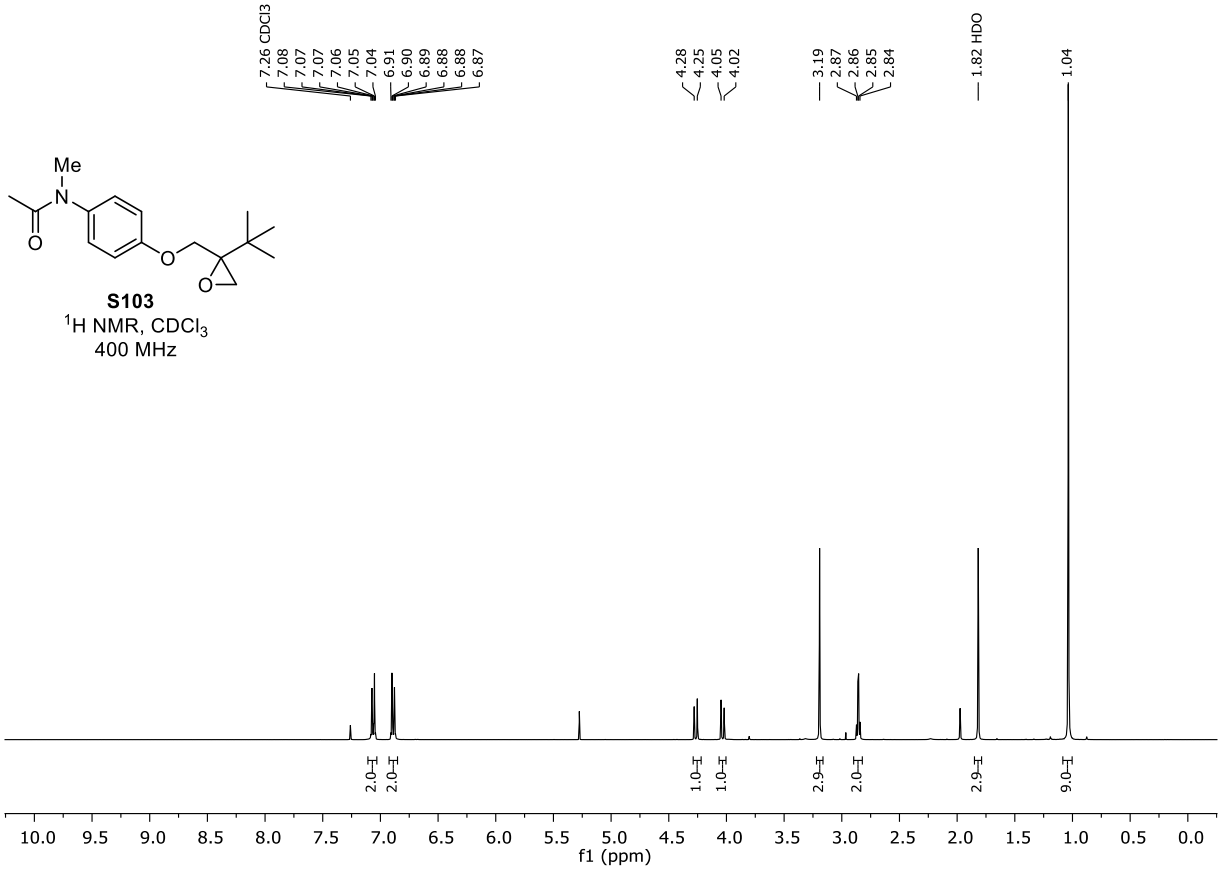
^{13}C NMR, $CDCl_3$
101 MHz


7.59
7.59
7.58
7.58
7.57
7.57
7.56
7.56
7.55
7.26 CDCl3
6.97
6.96
6.95
6.95
6.94
6.94
6.93
4.32
4.29
4.13
4.11
2.89
2.88
2.85
2.84
1.05
NC
O
O
S101
1H NMR, CDCl3
400 MHz
2.0
2.0
1.0
1.0
1.0
1.0
9.1
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 -0.5
f1 (ppm)

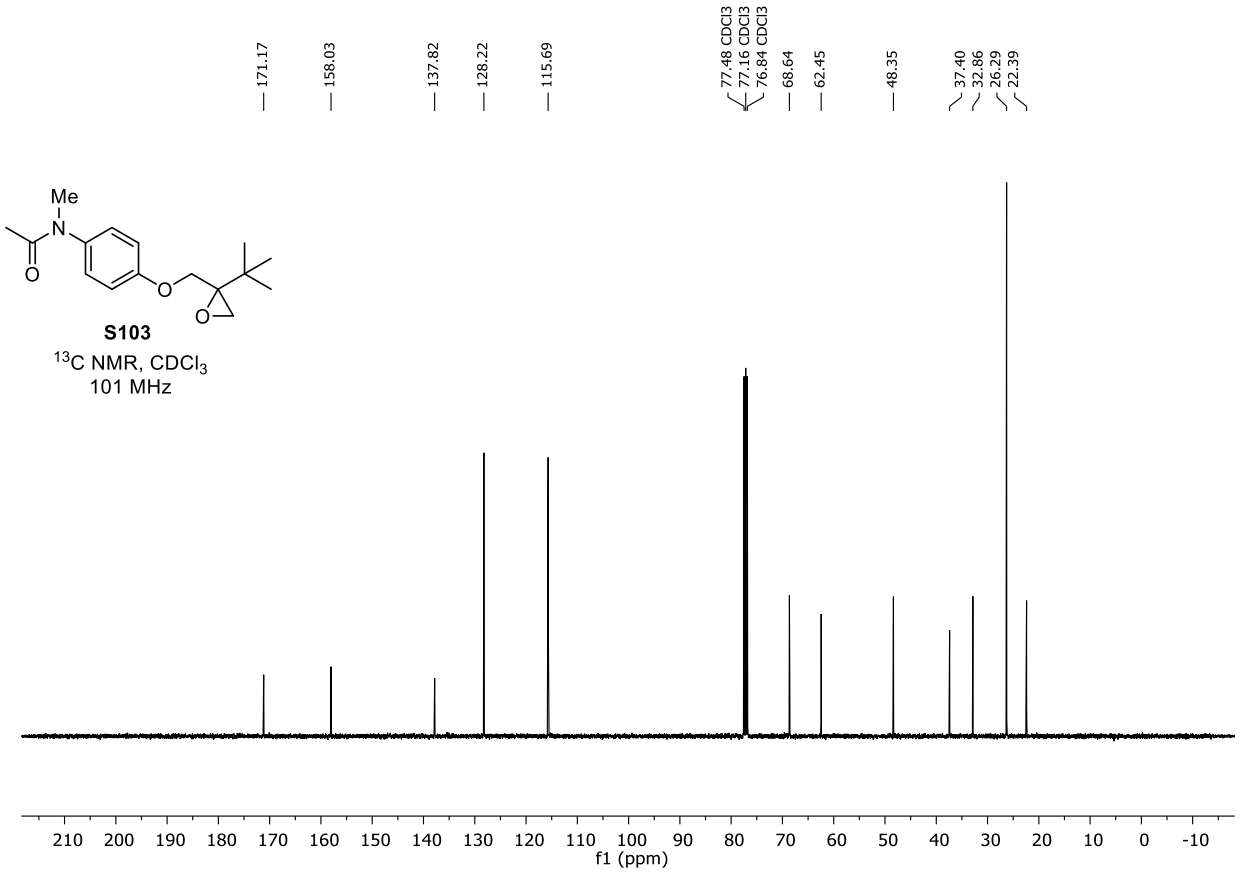

161.98
134.13
119.23
115.51
104.55
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
68.58
62.30
48.32
32.89
26.30
NC
O
O
S101
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.77
7.37
7.36
7.35
7.35
7.26 CDCl3
6.78
6.77
6.76
6.76
4.83
2.09
1.23
S102
1H NMR, CDCl3
400 MHz
0.9
2.0
2.0
2.1
3.1
9.0
f1 (ppm)

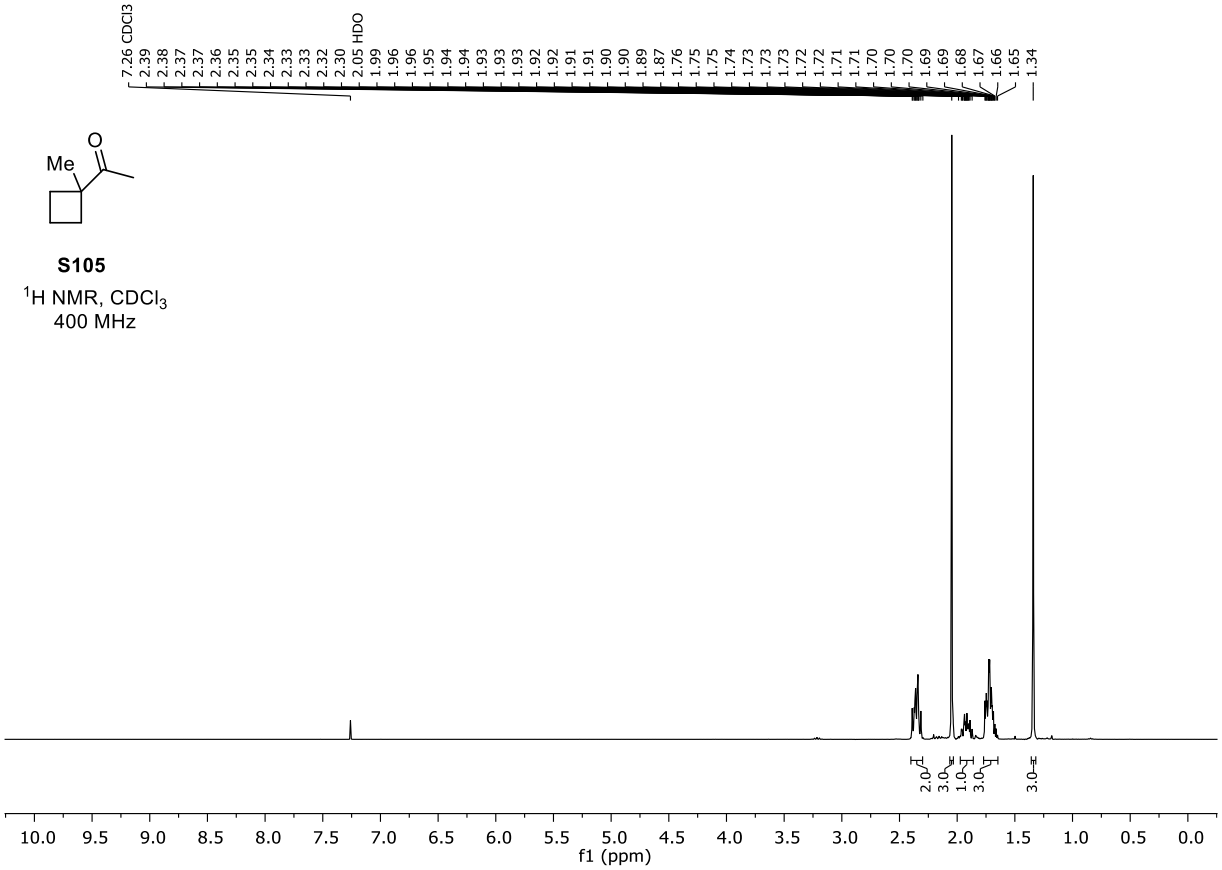

210.02
168.69
154.79
132.10
121.90
115.09
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
69.32
43.27
26.45
24.32
S102
13C NMR, CDCl3
101 MHz
f1 (ppm)



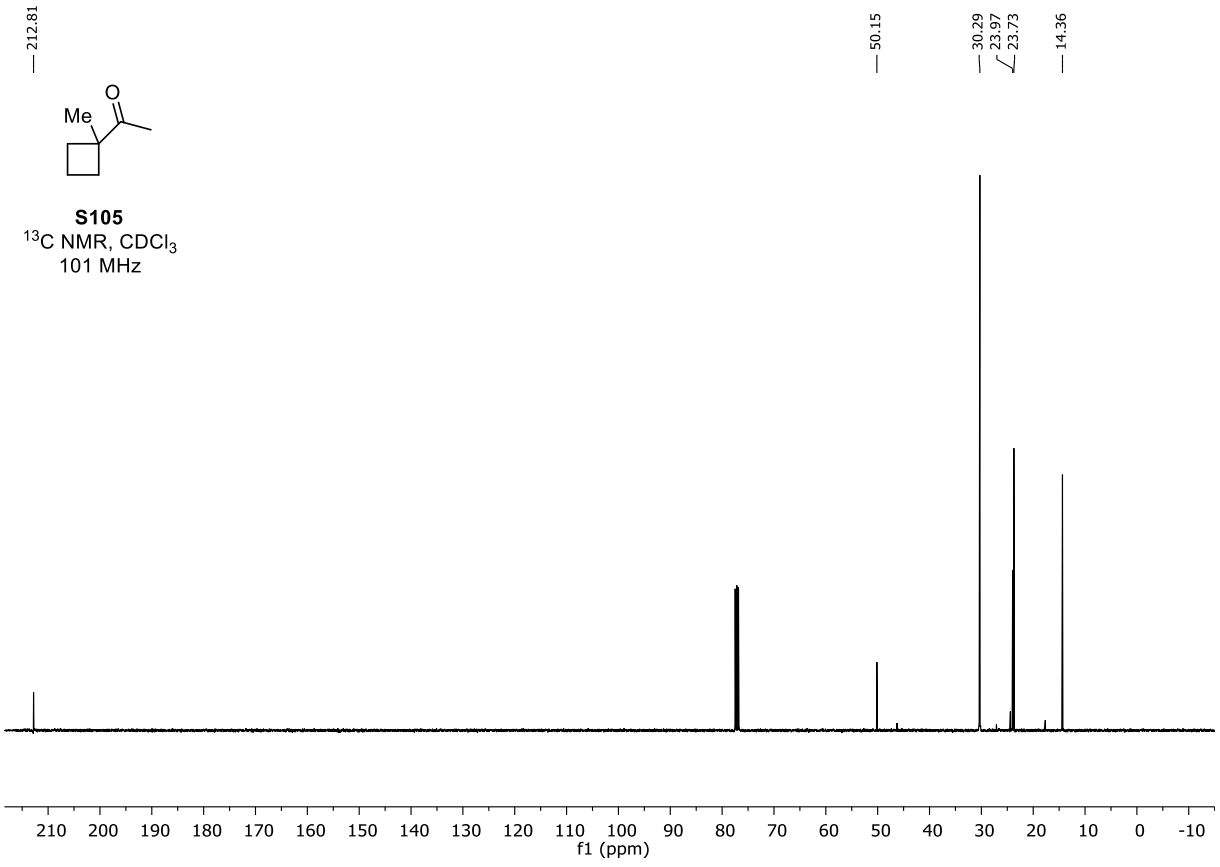
S103
^{1}H NMR, $CDCl_3$
400 MHz



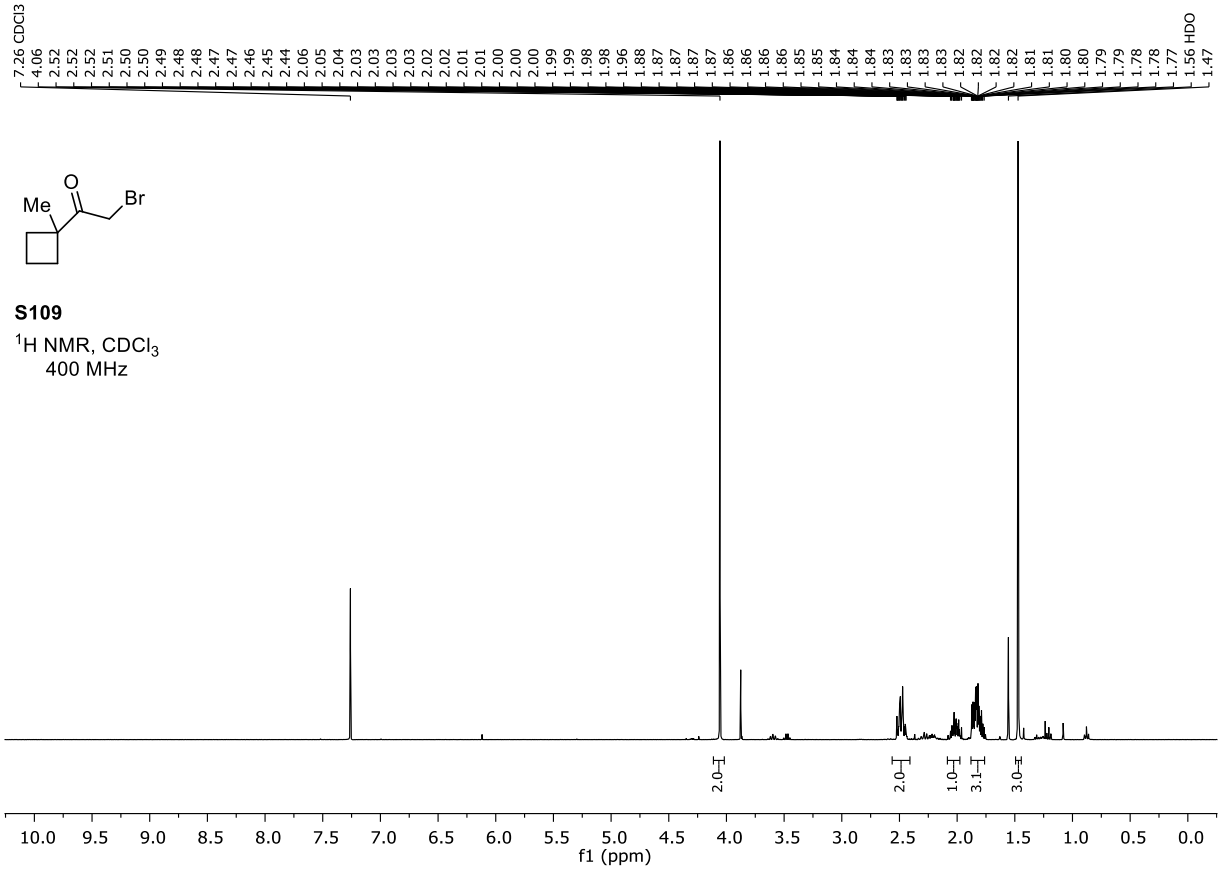
S103
^{13}C NMR, $CDCl_3$
101 MHz



S105
^{1}H NMR, $CDCl_3$
400 MHz

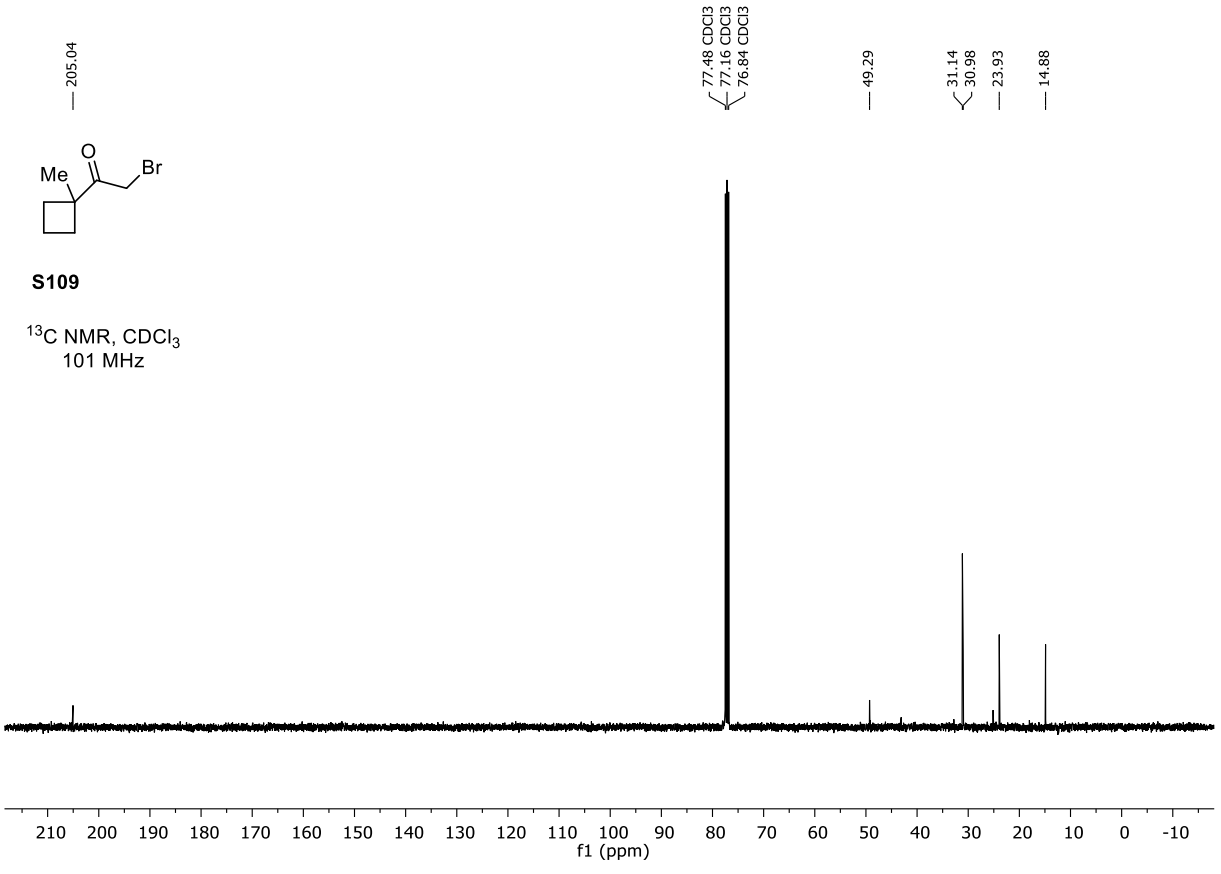


S105
^{13}C NMR, $CDCl_3$
101 MHz



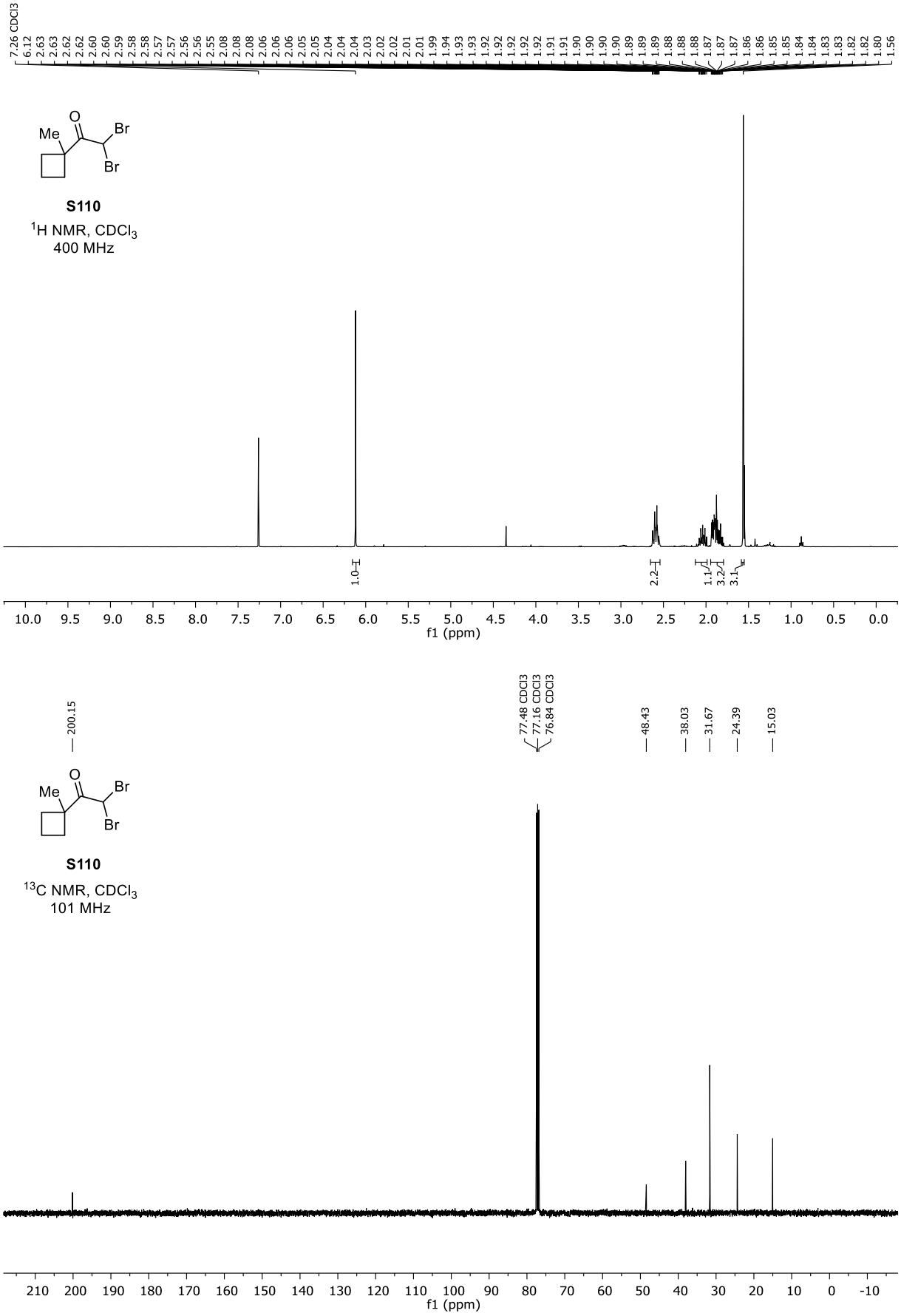
S109

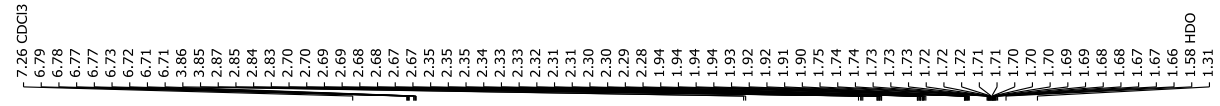
^{1}H NMR, $CDCl_3$
400 MHz

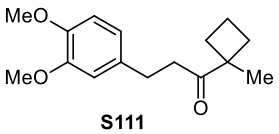


S109

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

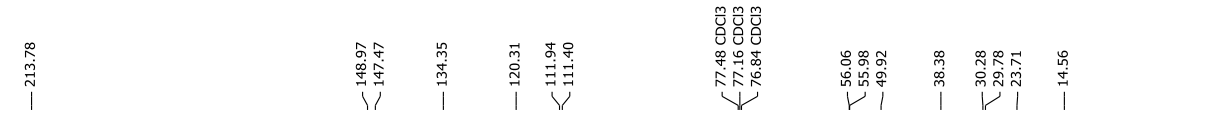

7.26 CDCl3
6.12 2.63 2.63 2.62 2.62 2.60 2.60 2.59 2.58 2.58 2.57 2.57 2.56 2.56 2.55 2.08 2.08 2.06 2.06 2.06 2.05 2.05 2.04 2.04 2.04 2.03 2.02 2.02 2.01 2.01 1.99 1.94 1.93 1.93 1.92 1.92 1.92 1.92 1.91 1.91 1.90 1.90 1.90 1.90 1.89 1.89 1.89 1.88 1.88 1.88 1.87 1.87 1.87 1.86 1.86 1.85 1.85 1.84 1.84 1.83 1.83 1.82 1.82 1.80 1.56
Me
O
Br
Br
S110
1H NMR, CDCl3
400 MHz
1.0
2.2
1.1
3.2
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)
200.15
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
48.43
38.03
31.67
24.39
15.03
Me
O
Br
Br
S110
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)

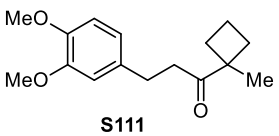




S111

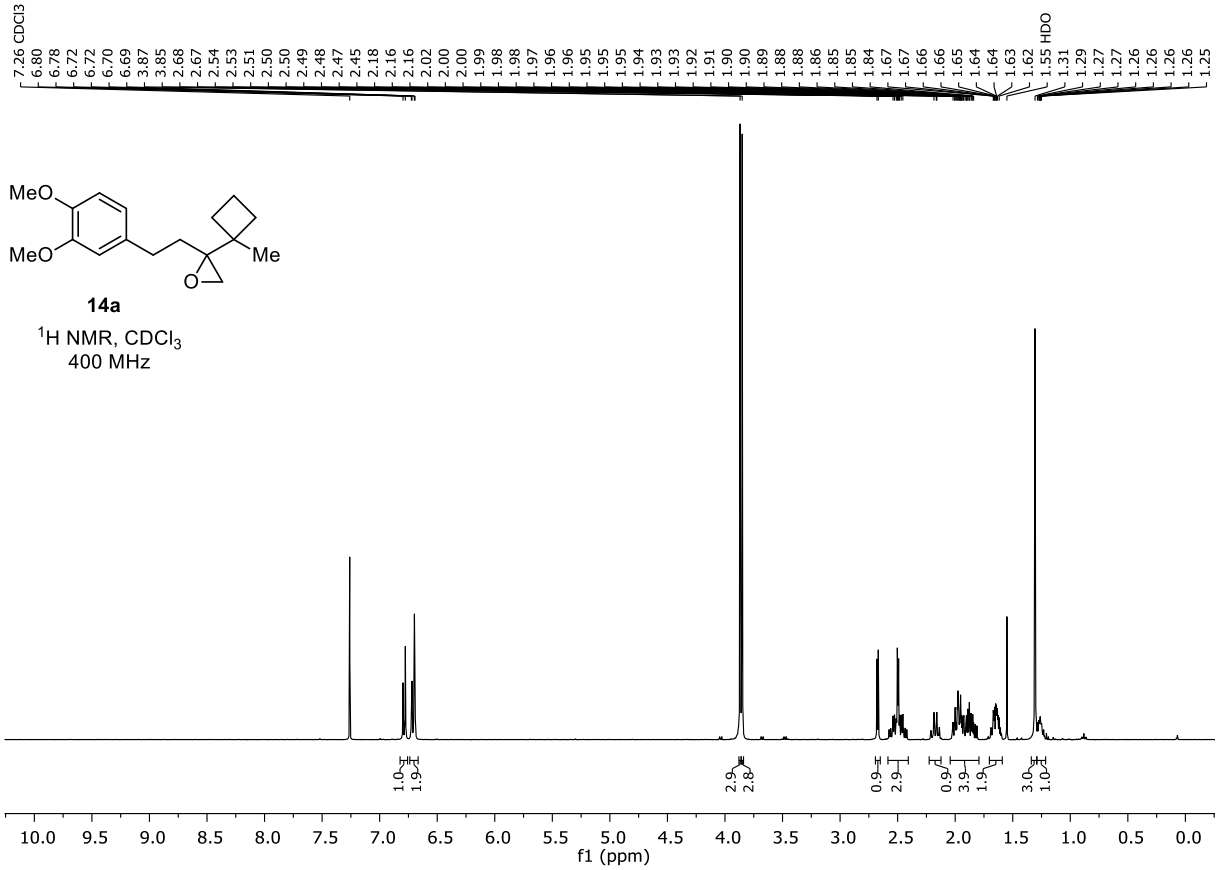
^{1}H NMR, $CDCl_3$
400 MHz

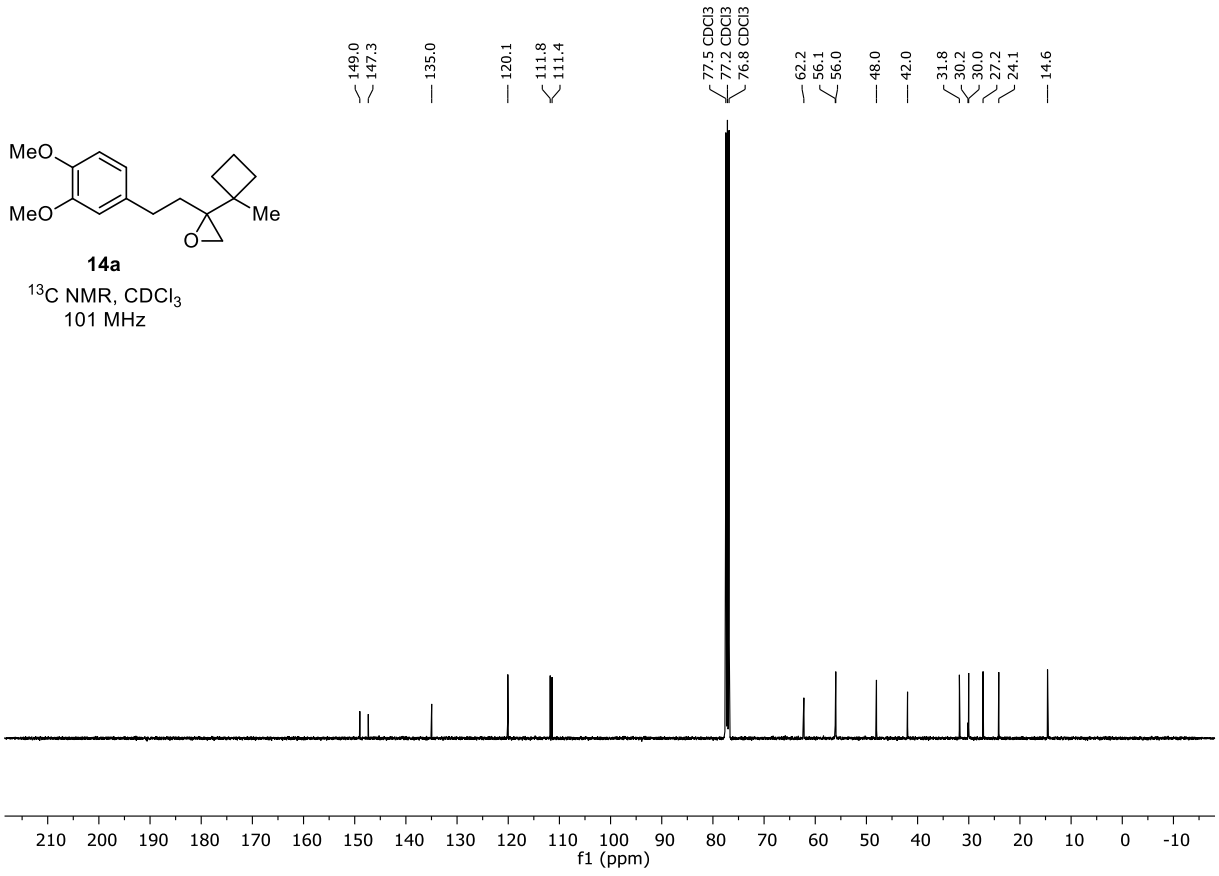


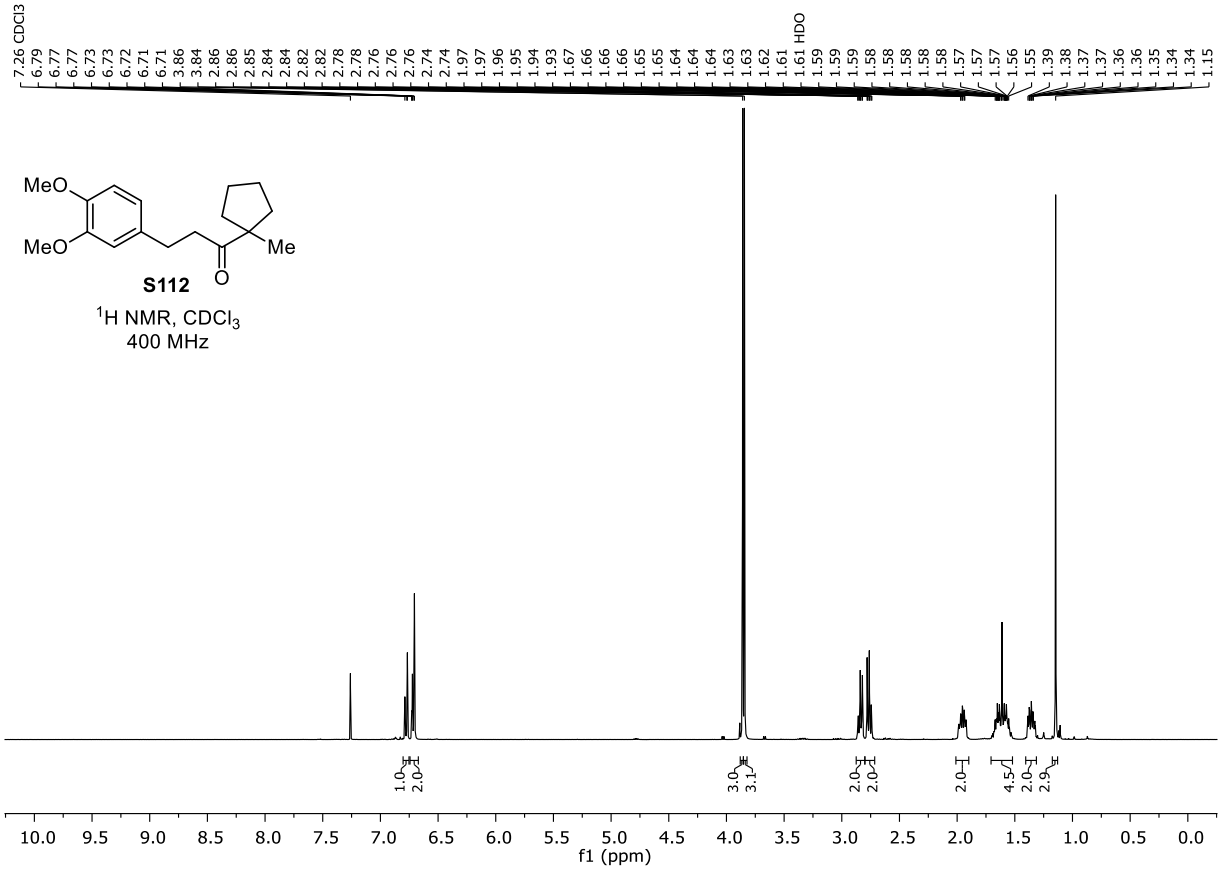


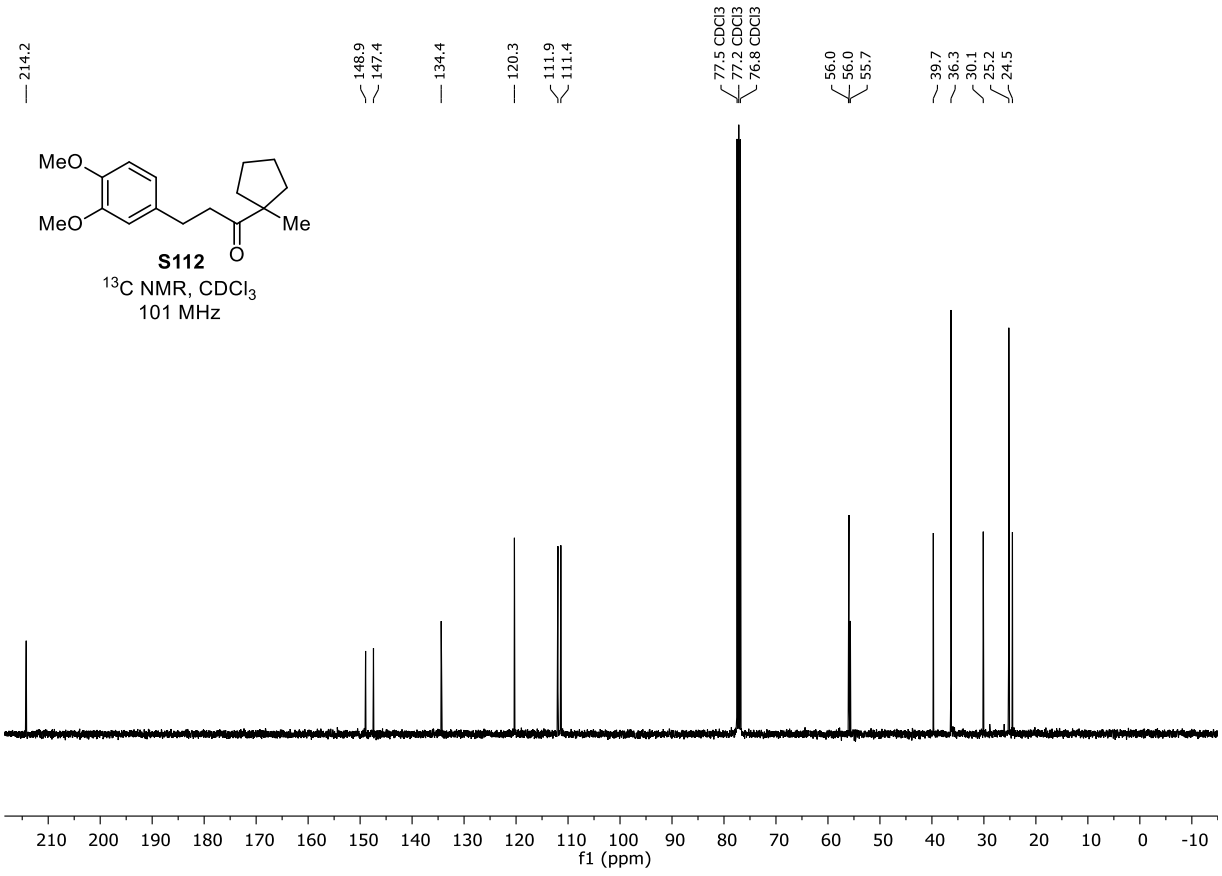
S111

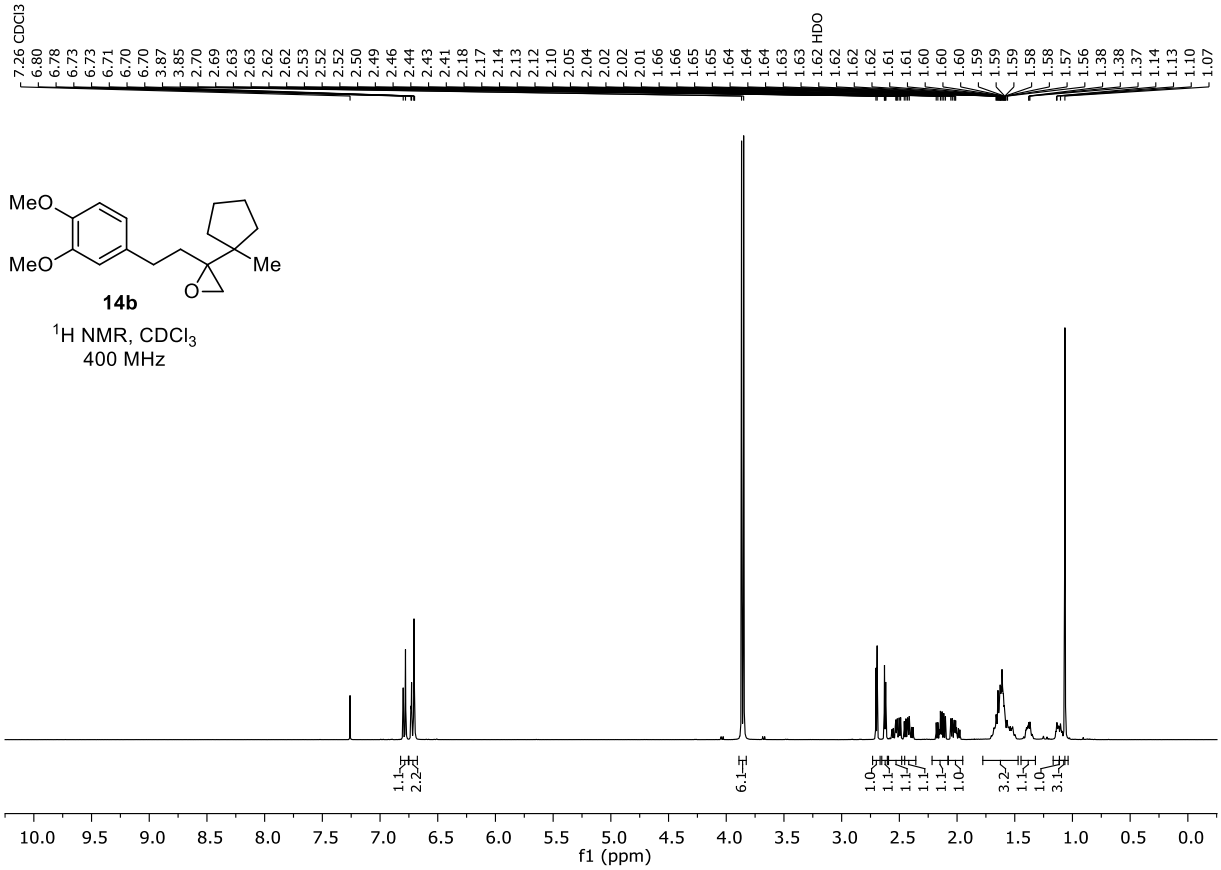
^{13}C NMR, $CDCl_3$
101 MHz

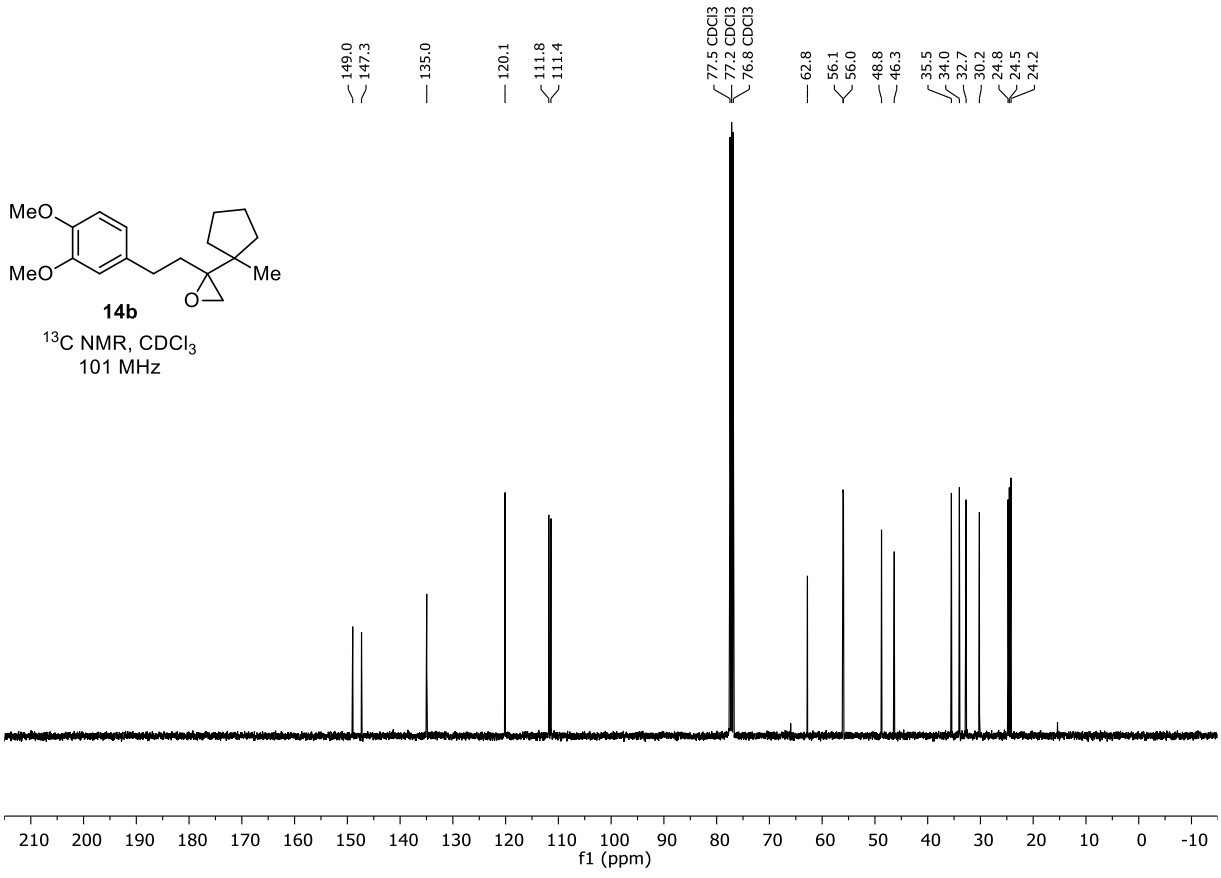

7.26 CDCl3
1.55 HDO
MeO
MeO
Me
O
14a
1H NMR, CDCl3
400 MHz
1.0
1.9
2.9
2.8
0.9
2.9
0.9
3.9
1.9
3.0
1.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

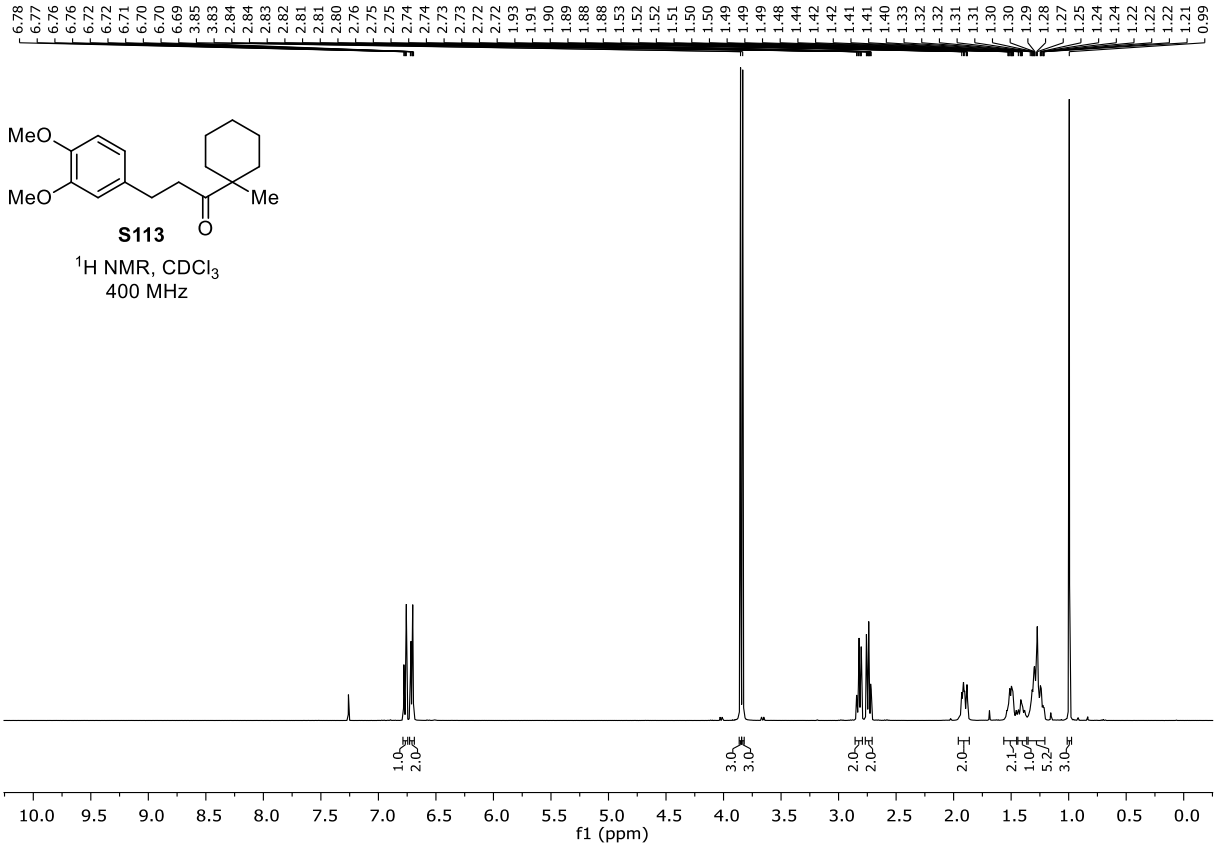

149.0
147.3
135.0
120.1
111.8
111.4
77.5 CDCl3
77.2 CDCl3
76.8 CDCl3
62.2
56.1
56.0
48.0
42.0
31.8
30.2
30.0
27.2
24.1
14.6
MeO
MeO
Me
O
14a
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

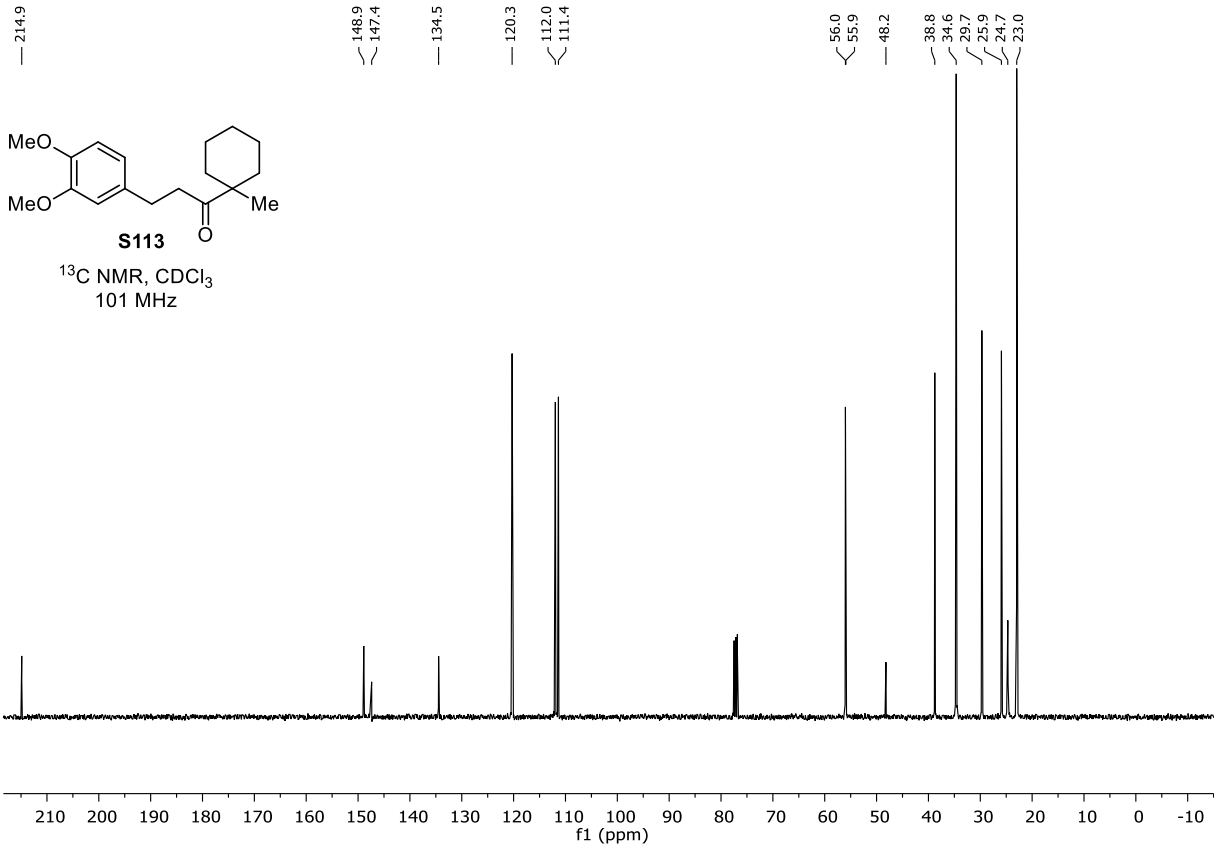

7.26 CDCl3
1.61 HDO
MeO
MeO
Me
O
S112
1H NMR, CDCl3
400 MHz
1.0
2.0
3.0
3.1
2.0
2.0
2.0
4.5
2.0
2.9
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

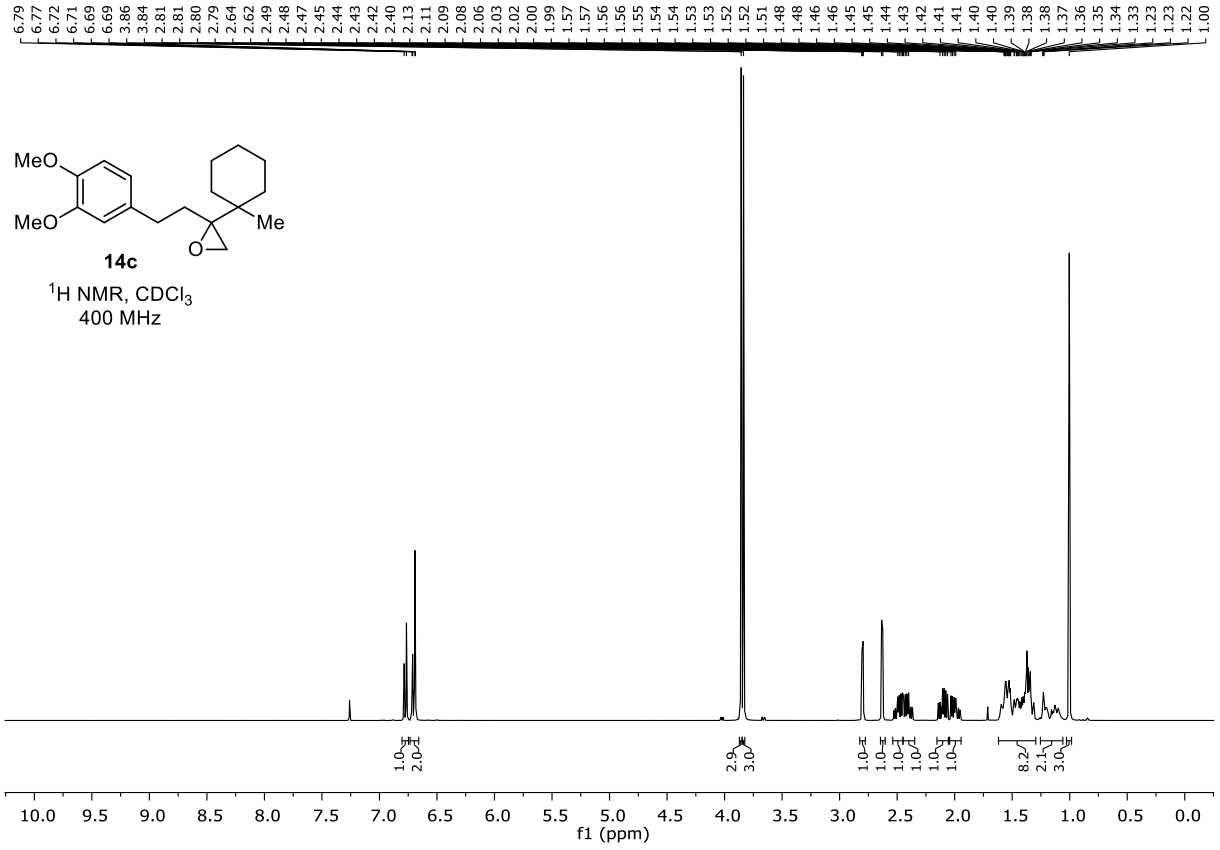

214.2
148.9
147.4
134.4
120.3
111.9
111.4
77.5 CDCl3
77.2 CDCl3
76.8 CDCl3
56.0
56.0
55.7
39.7
36.3
30.1
25.2
24.5
MeO
MeO
Me
O
S112
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

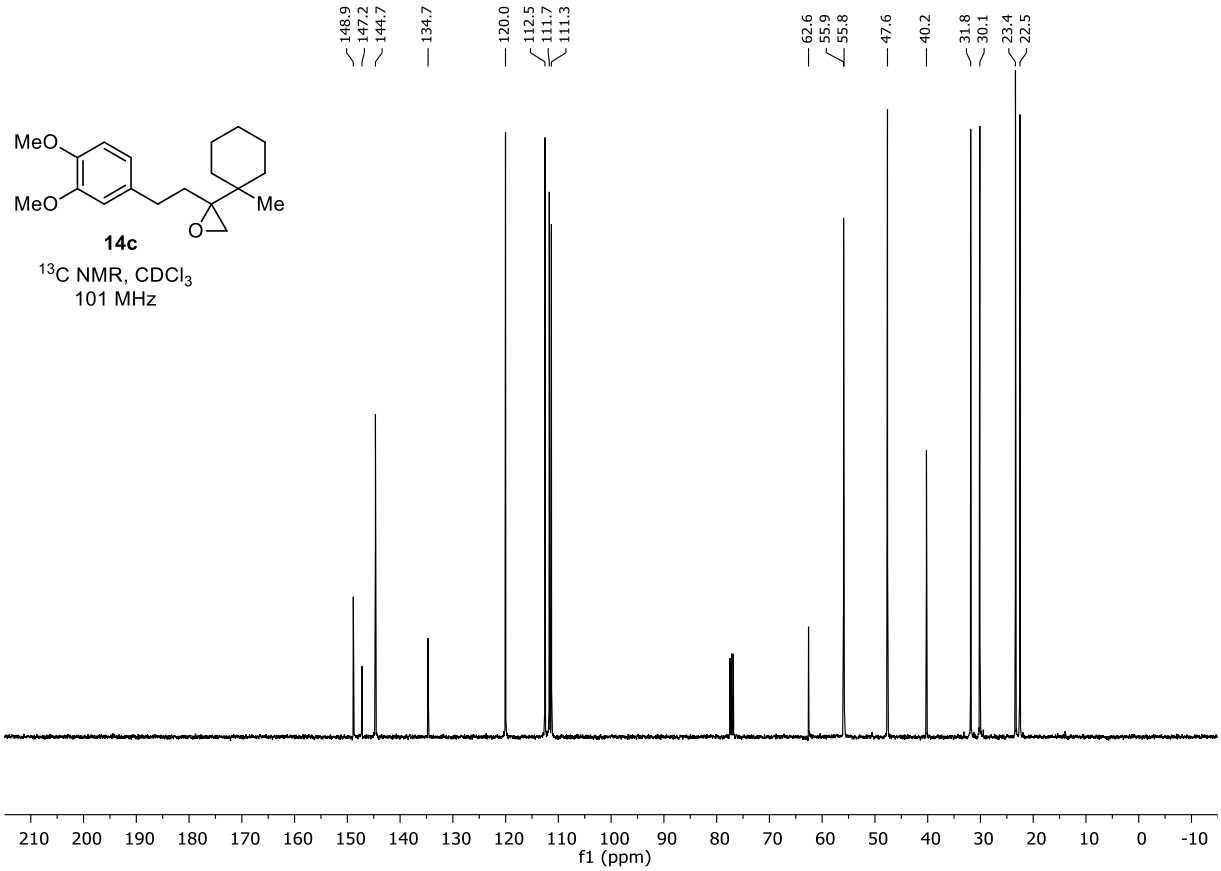

7.26 CDCl3
1.62 HDO
MeO
MeO
Me
O
14b
1H NMR, CDCl3
400 MHz
f1 (ppm)

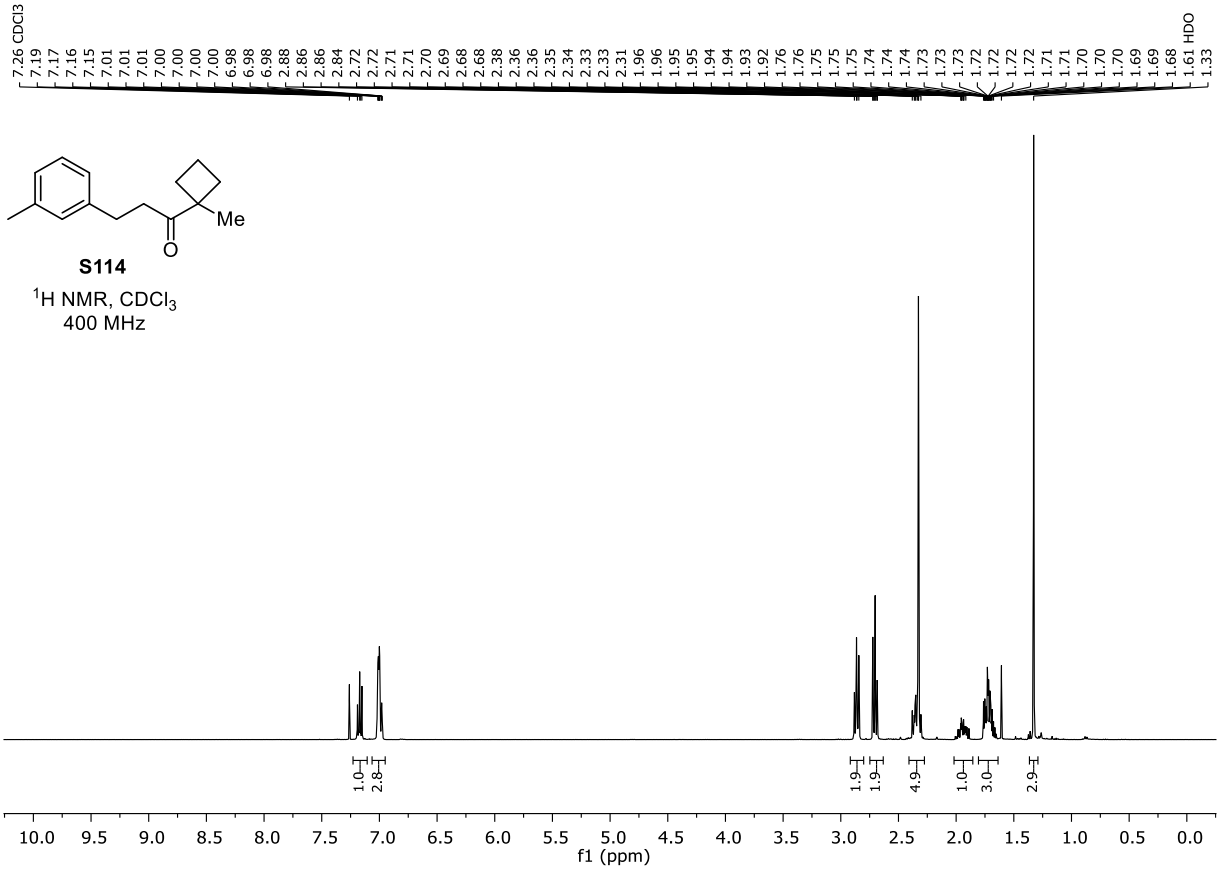

149.0
147.3
135.0
120.1
111.8
111.4
77.5 CDCl3
77.2 CDCl3
76.8 CDCl3
62.8
56.1
56.0
48.8
46.3
35.5
34.0
32.7
30.2
24.8
24.5
24.2
MeO
MeO
Me
O
14b
13C NMR, CDCl3
101 MHz
f1 (ppm)

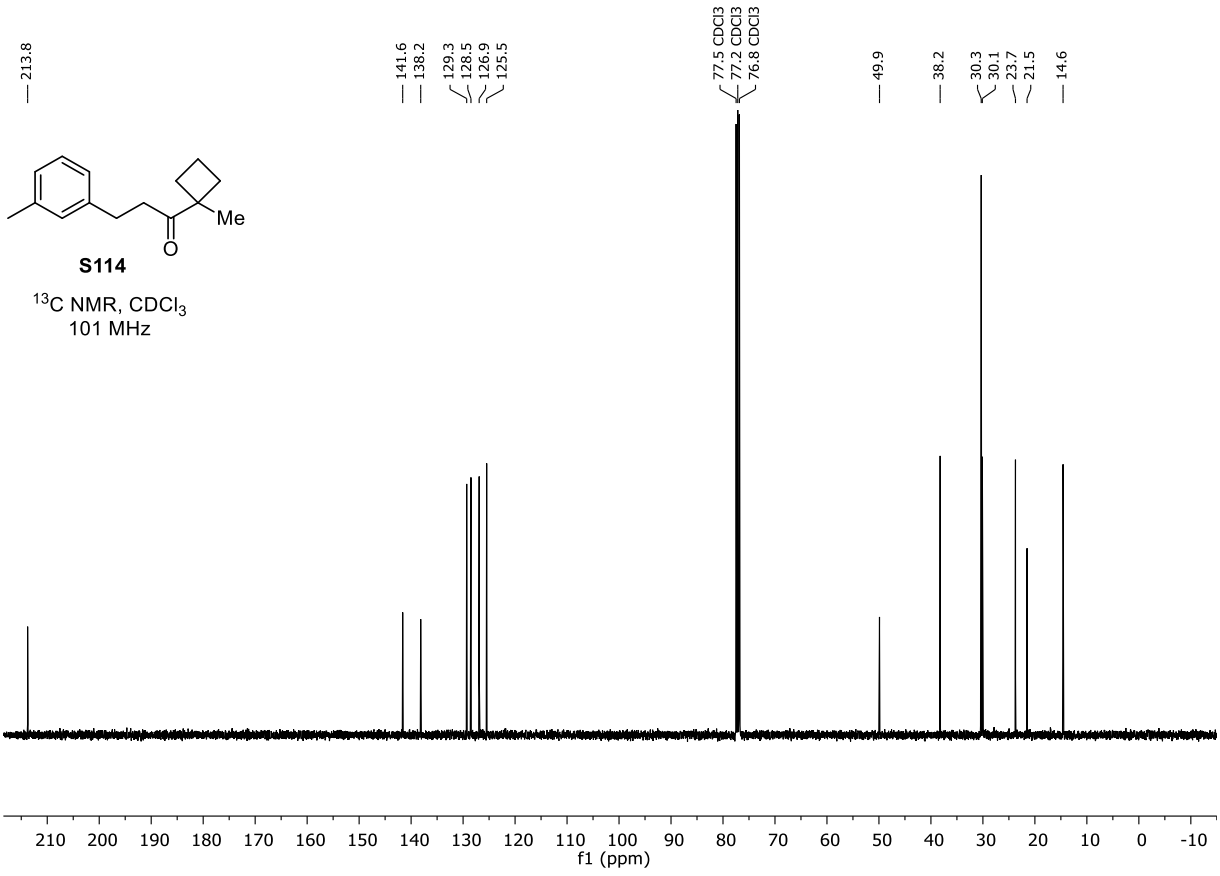

MeO
MeO
Me
O
S113
1H NMR, CDCl3
400 MHz
f1 (ppm)

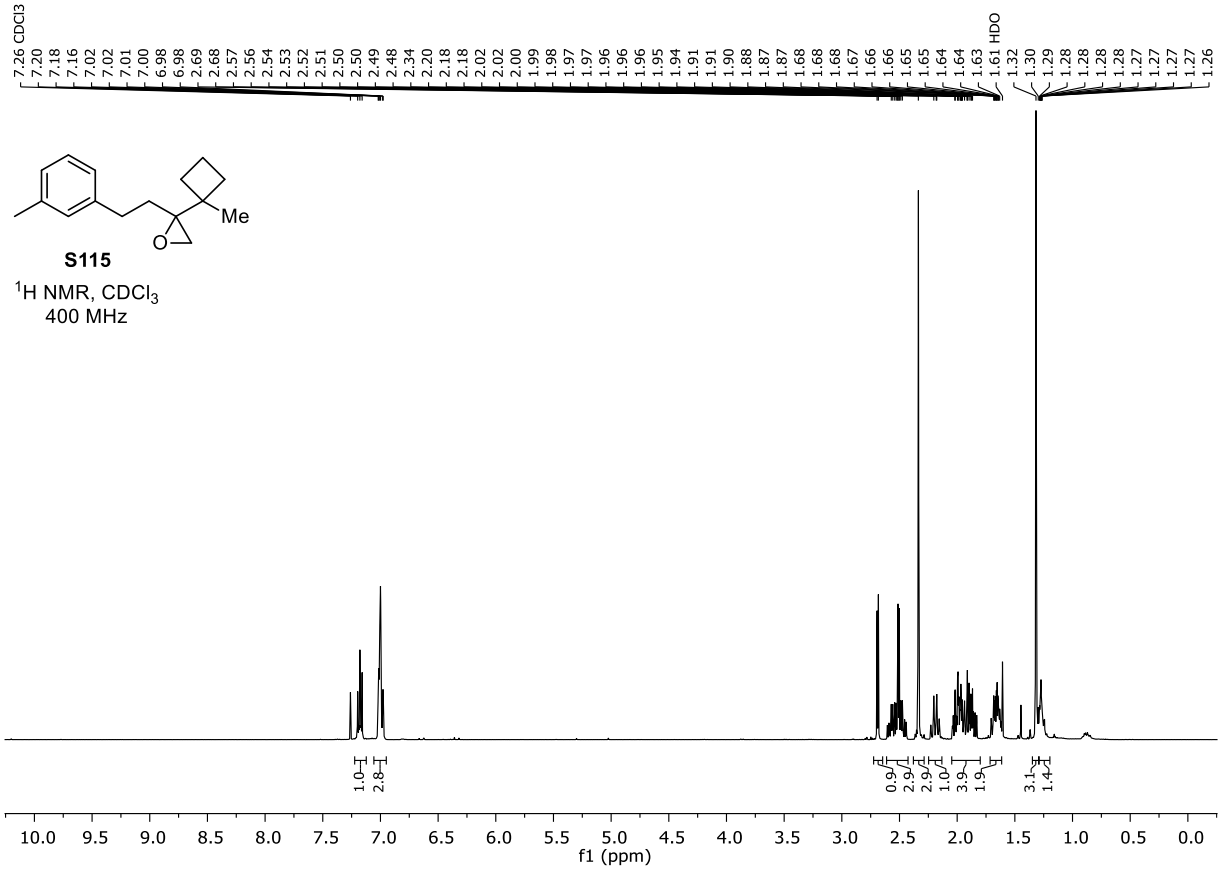

MeO
MeO
Me
O
S113
13C NMR, CDCl3
101 MHz
f1 (ppm)

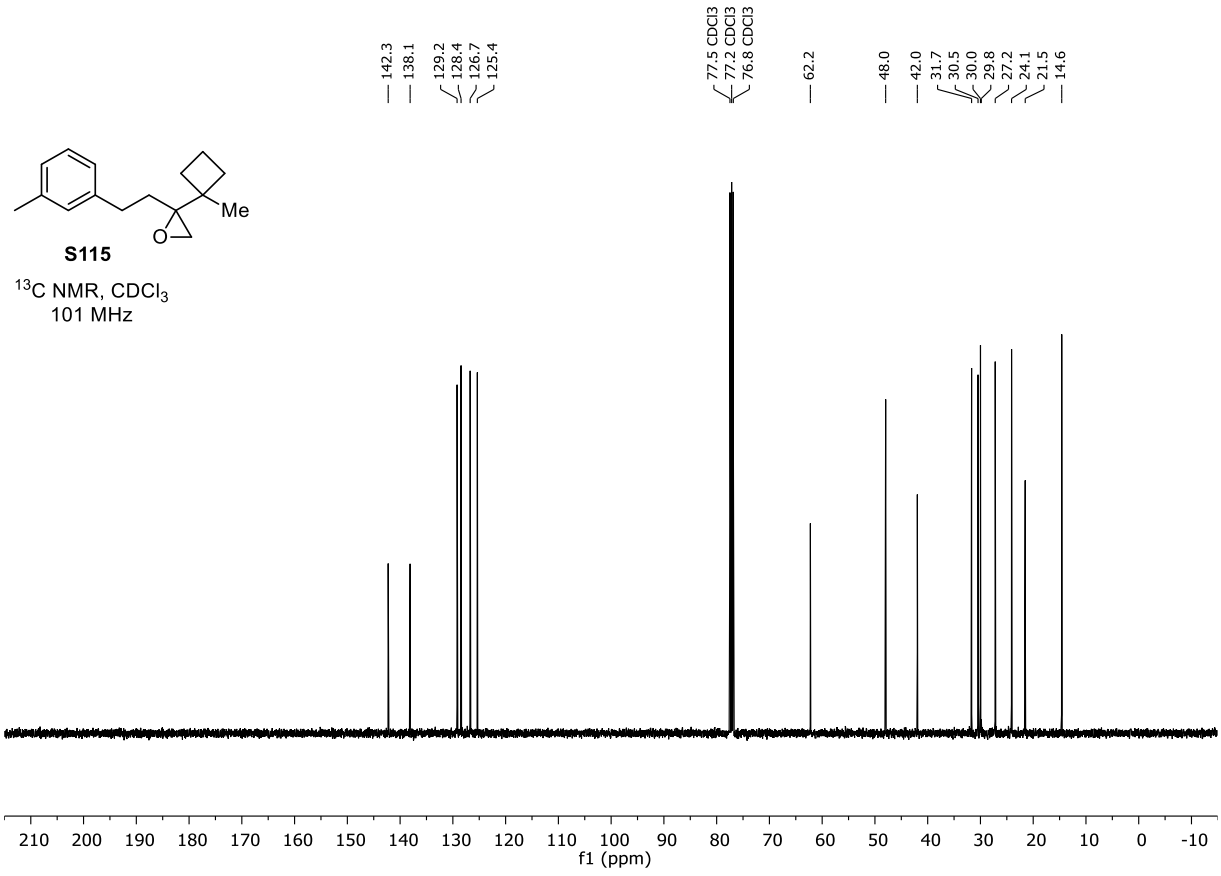

MeO
MeO
Me
O
14c
1H NMR, CDCl3
400 MHz
f1 (ppm)

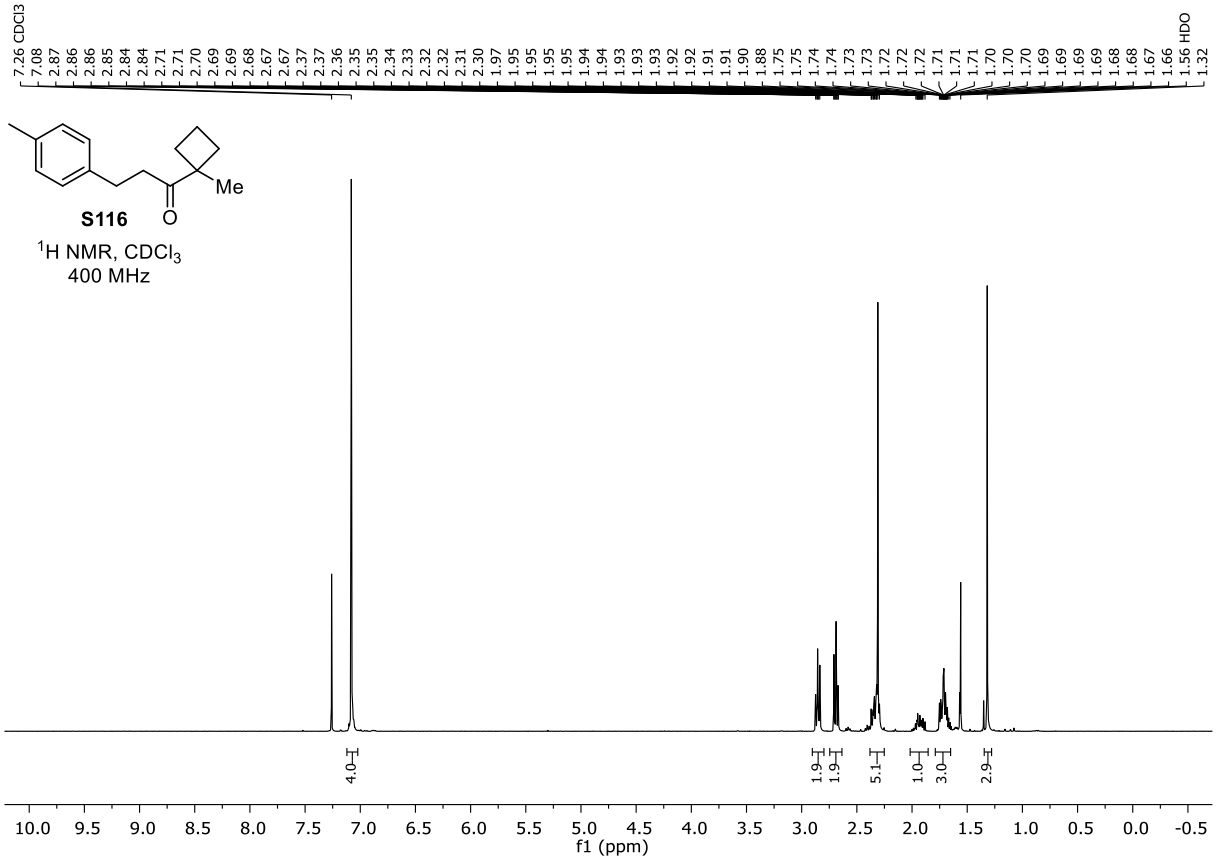

MeO
MeO
Me
O
14c
13C NMR, CDCl3
101 MHz
f1 (ppm)

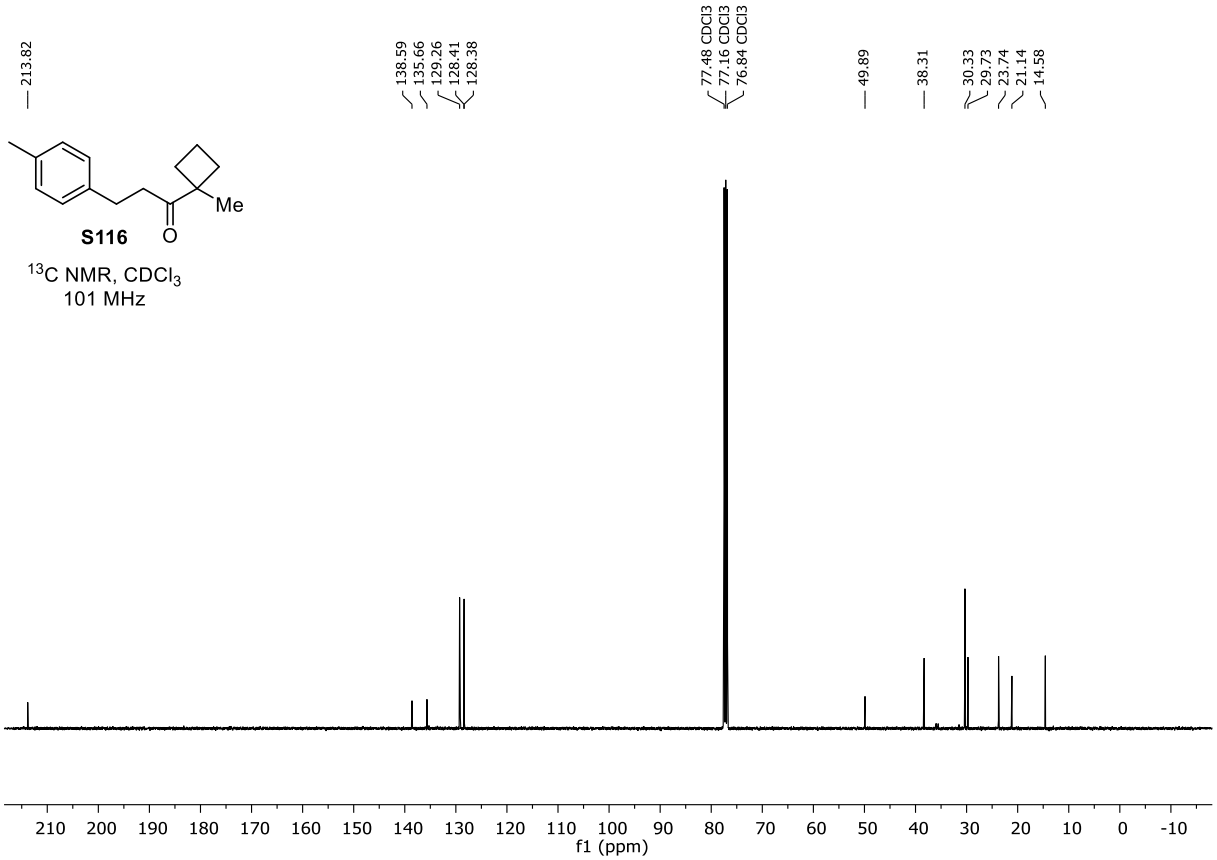

7.26 CDCl3
7.19
7.17
7.16
7.15
7.01
7.01
7.01
7.00
7.00
7.00
7.00
6.98
6.98
6.98
2.88
2.86
2.86
2.84
2.72
2.72
2.71
2.71
2.70
2.69
2.68
2.68
2.38
2.36
2.36
2.35
2.34
2.33
2.33
2.31
1.96
1.96
1.95
1.95
1.94
1.94
1.93
1.92
1.76
1.76
1.75
1.75
1.75
1.74
1.74
1.74
1.73
1.73
1.73
1.72
1.72
1.72
1.72
1.71
1.71
1.70
1.70
1.70
1.69
1.69
1.68
1.61 HDO
1.33
Me
O
S114
1H NMR, CDCl3
400 MHz
1.0
2.8
1.9
1.9
4.9
1.0
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)

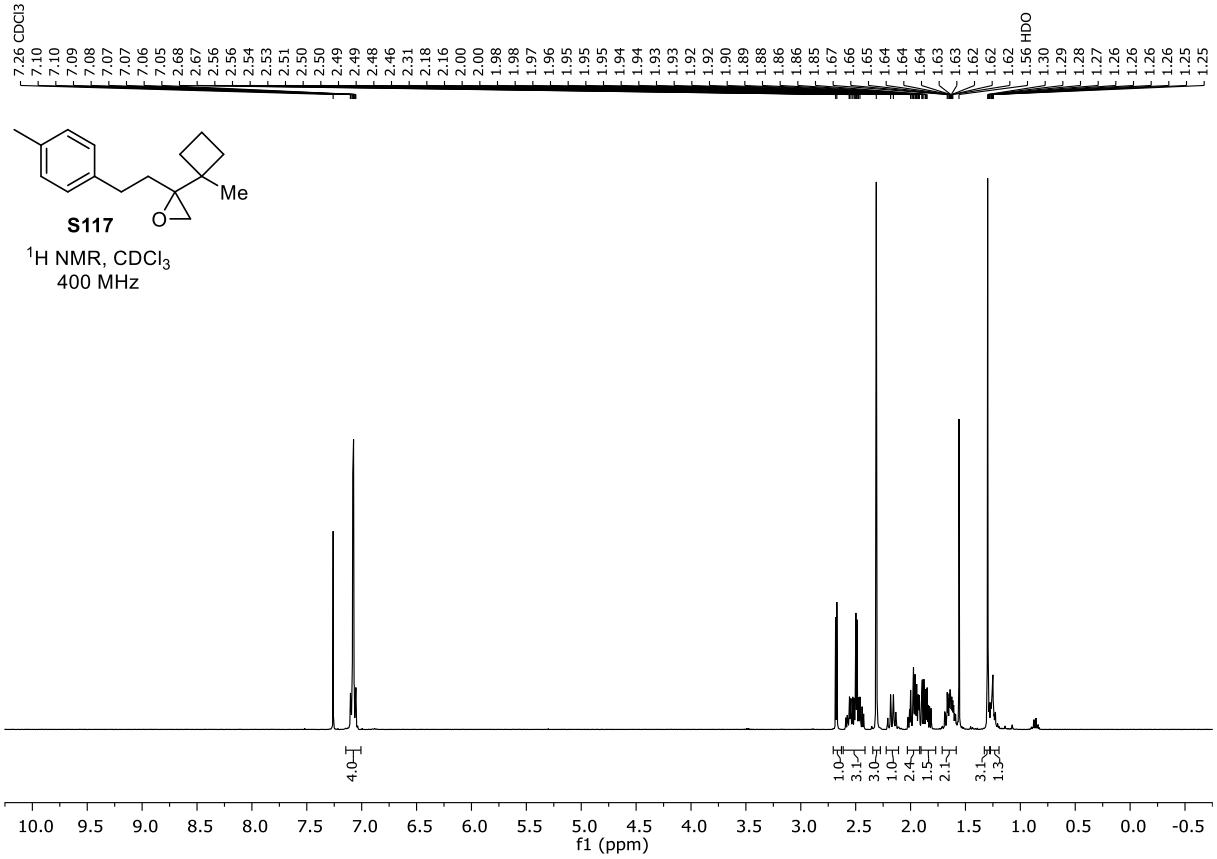

213.8
141.6
138.2
129.3
128.5
126.9
125.5
77.5 CDCl3
77.2 CDCl3
76.8 CDCl3
49.9
38.2
30.3
30.1
23.7
21.5
14.6
Me
O
S114
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

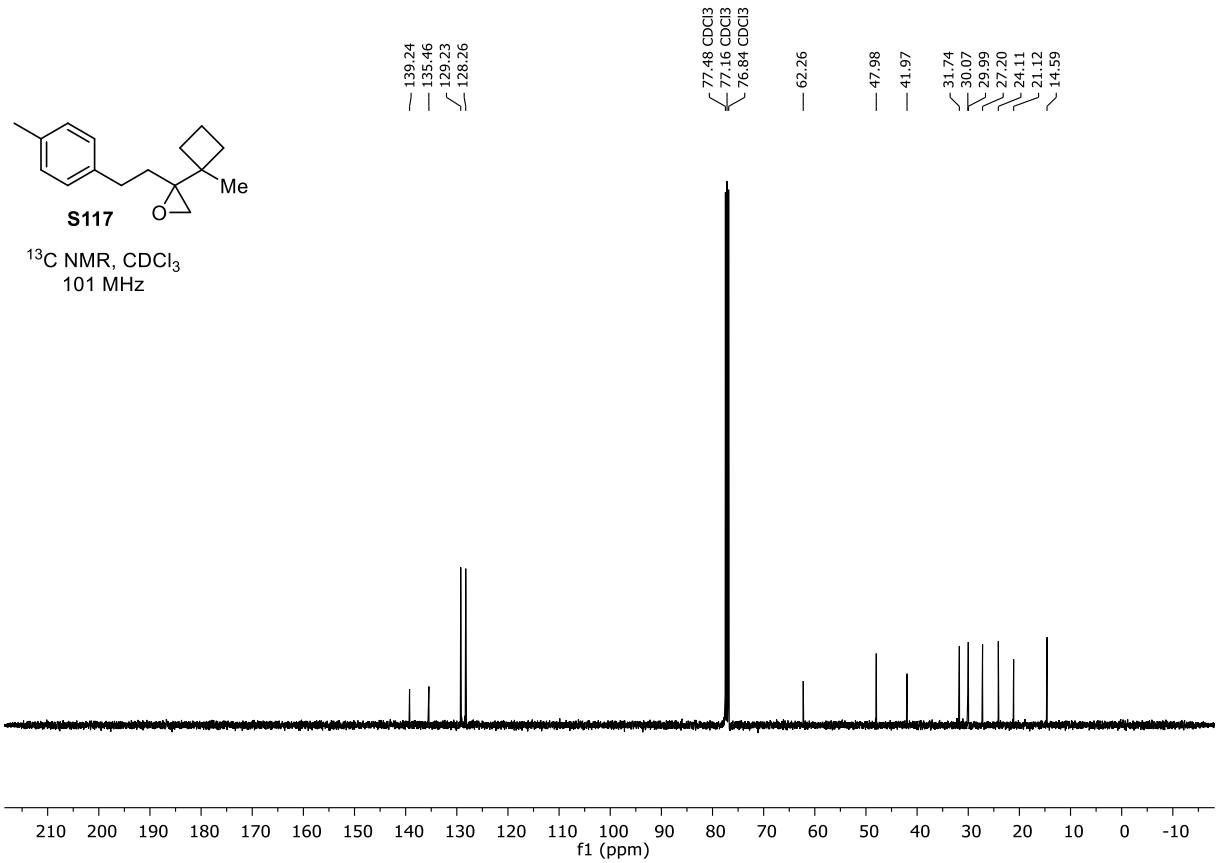

7.26 CDCl3
1.61 HDO
Me
O
S115
1H NMR, CDCl3
400 MHz
1.0
2.8
0.9
2.9
2.9
1.0
3.9
1.9
3.1
1.4
f1 (ppm)

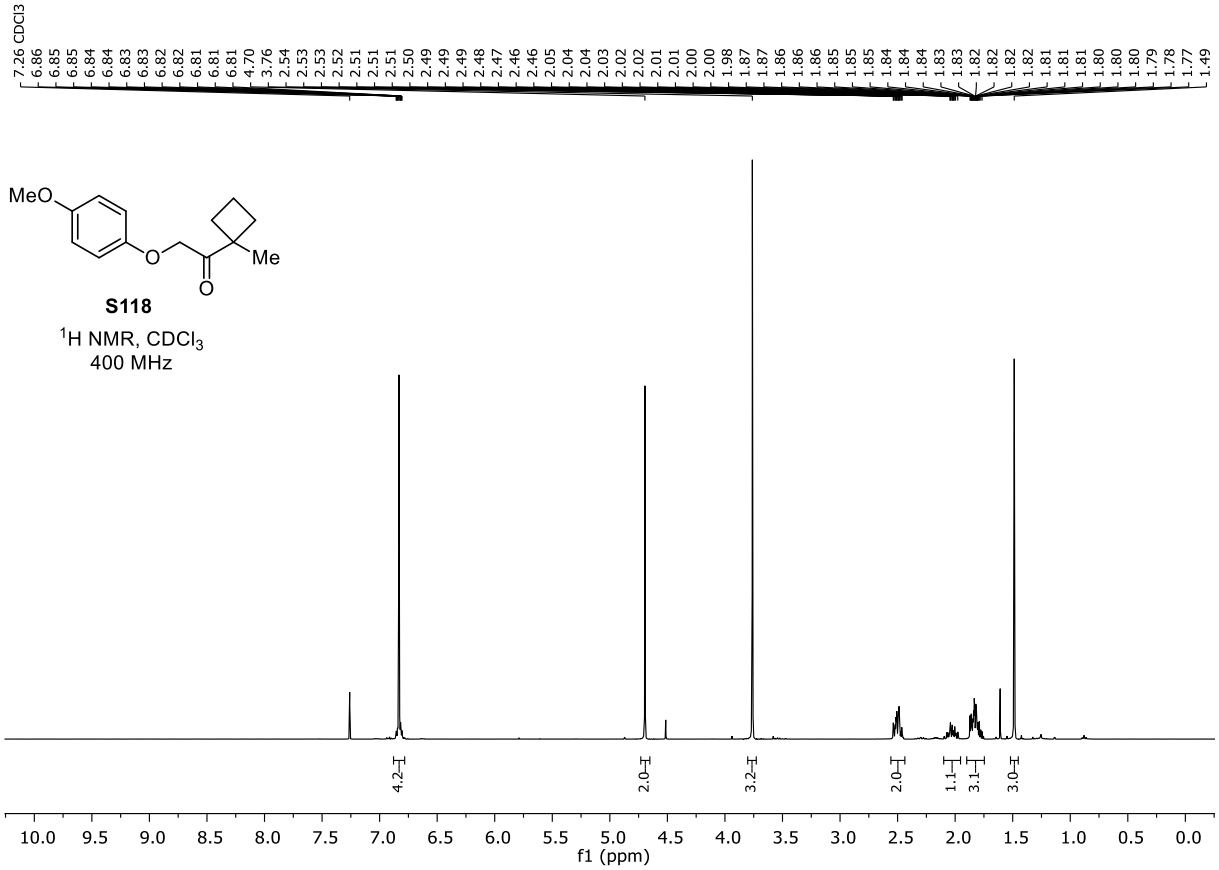

142.3
138.1
129.2
128.4
126.7
125.4
77.5 CDCl3
77.2 CDCl3
76.8 CDCl3
62.2
48.0
42.0
31.7
30.5
30.0
29.8
27.2
24.1
21.5
14.6
Me
O
S115
13C NMR, CDCl3
101 MHz
f1 (ppm)

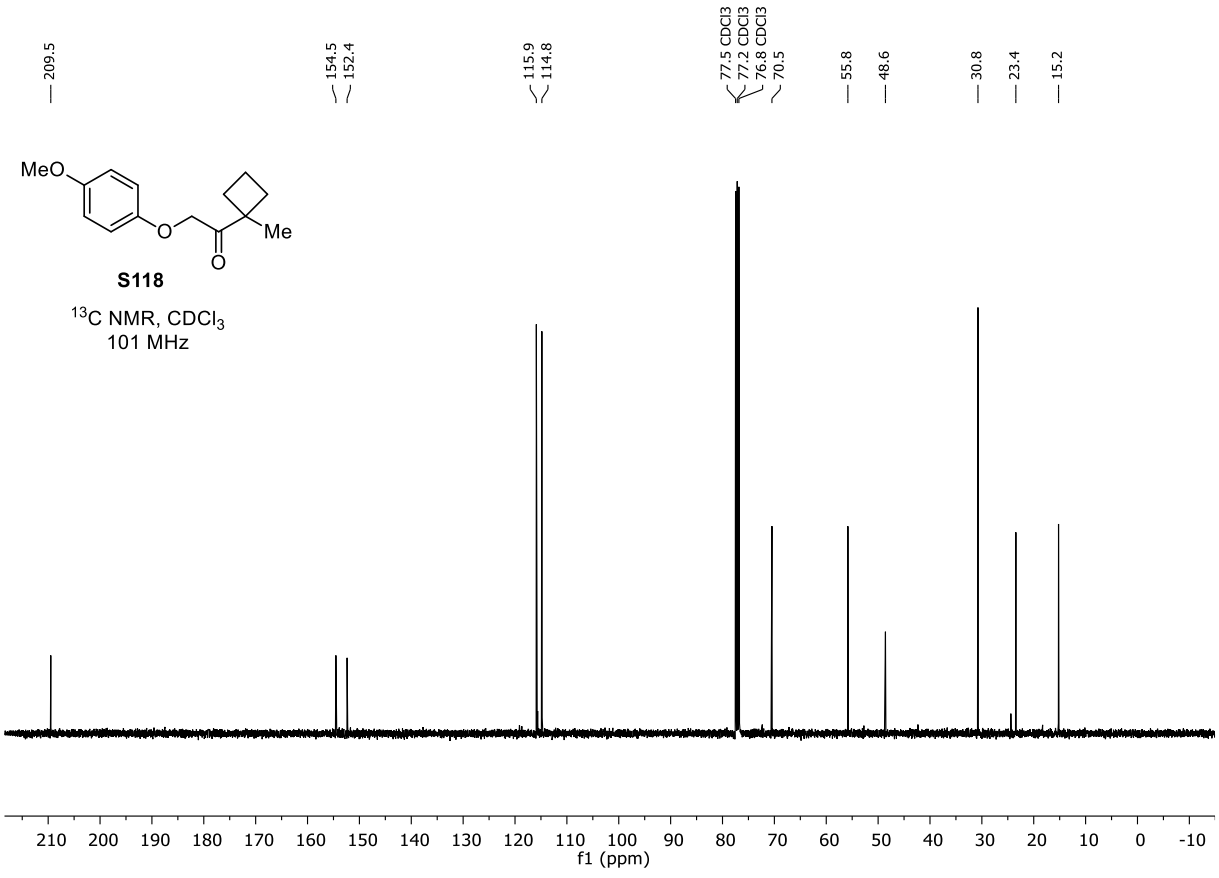

7.26 CDCl3
1.56 HDO
Me
O
S116
1H NMR, CDCl3
400 MHz
4.0
1.9
1.9
5.1
1.0
3.0
2.9
f1 (ppm)

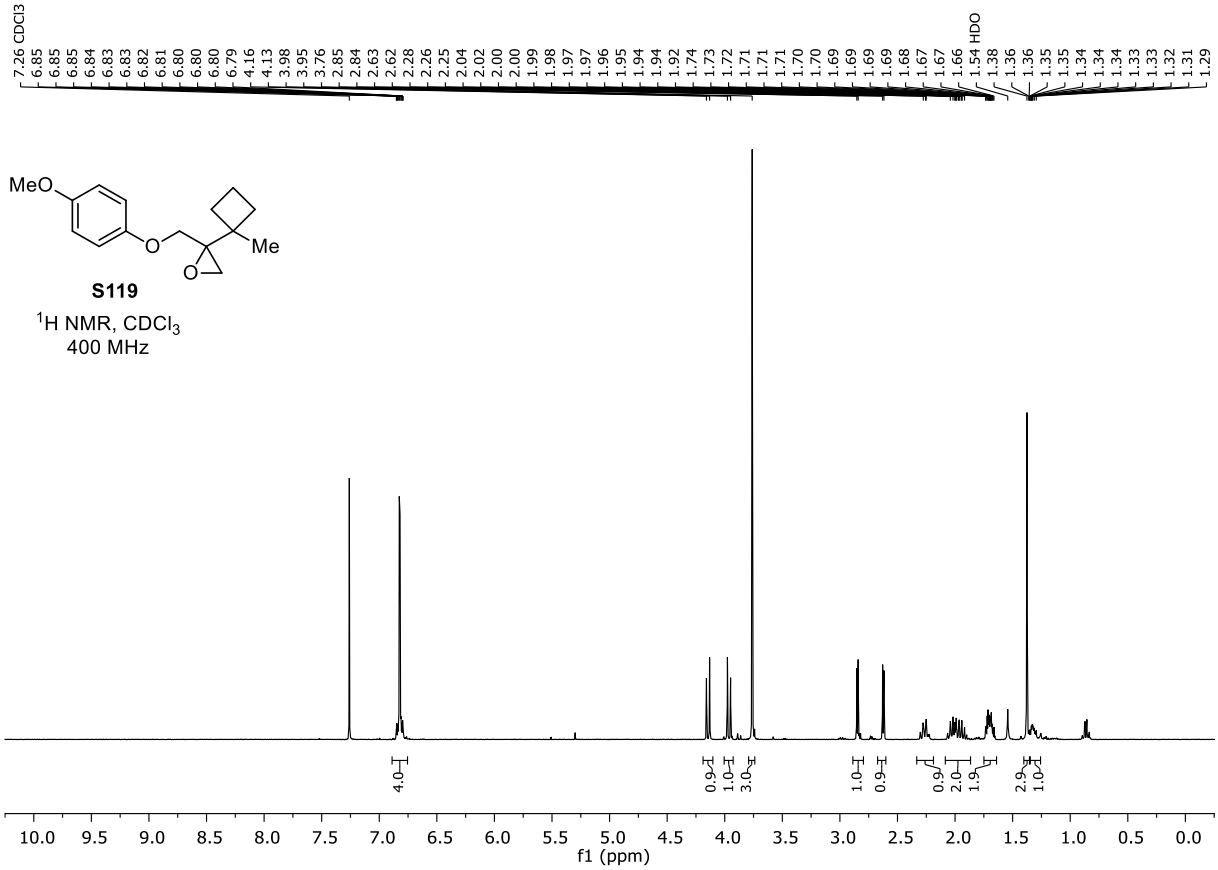

213.82
138.59
135.66
129.26
128.41
128.38
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
49.89
38.31
30.33
29.73
23.74
21.14
14.58
Me
O
S116
13C NMR, CDCl3
101 MHz
f1 (ppm)

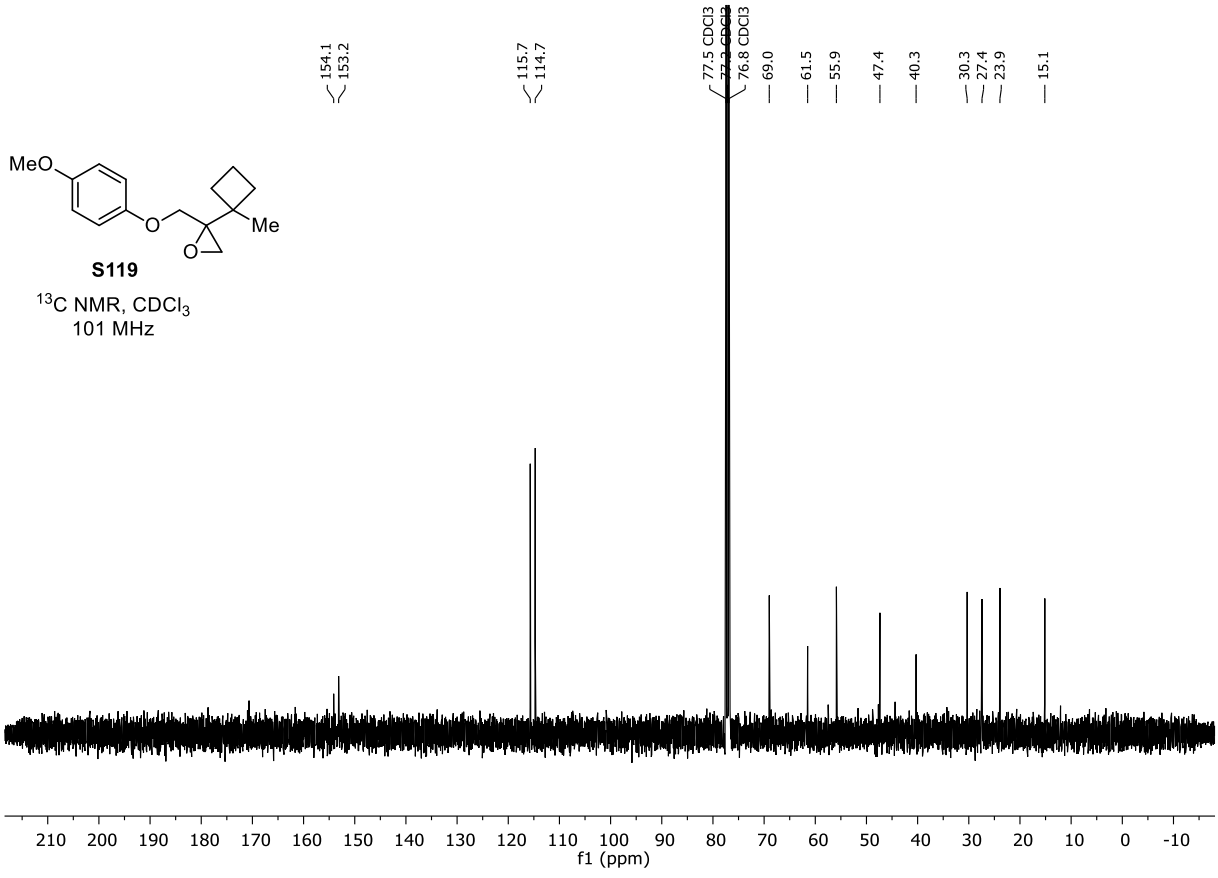

7.26 CDCl3
1.56 HDO
Me
O
S117
1H NMR, CDCl3
400 MHz
4.0
1.0
3.1
3.0
1.0
2.4
1.5
2.1
3.1
1.3
f1 (ppm)

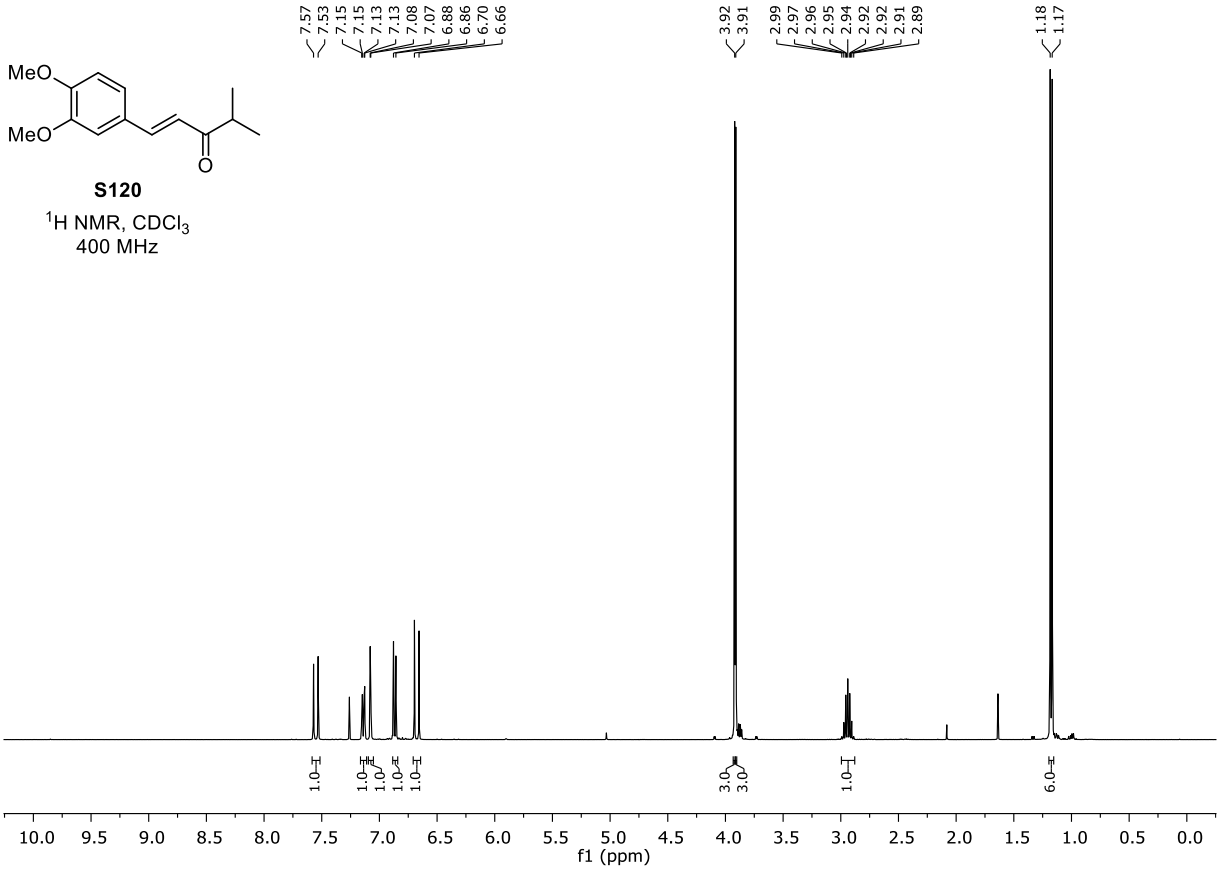

139.24
135.46
129.23
128.26
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.26
47.98
41.97
31.74
30.07
29.99
27.20
24.11
21.12
14.59
Me
O
S117
13C NMR, CDCl3
101 MHz
f1 (ppm)


7.26 CDCl3
6.86 6.85 6.85 6.84 6.84 6.83 6.83 6.82 6.82 6.81 6.81 6.81 4.70 3.76 2.54 2.53 2.53 2.52 2.51 2.51 2.51 2.50 2.49 2.49 2.48 2.47 2.46 2.46 2.05 2.04 2.04 2.03 2.02 2.02 2.01 2.01 2.00 2.00 1.98 1.87 1.87 1.86 1.86 1.86 1.85 1.85 1.85 1.84 1.84 1.84 1.83 1.83 1.82 1.82 1.82 1.82 1.81 1.81 1.81 1.80 1.80 1.80 1.79 1.78 1.77 1.49
MeO
O
Me
O
S118
1H NMR, CDCl3
400 MHz
4.2
2.0
3.2
2.0
1.1
3.1
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)


209.5
154.5
152.4
115.9
114.8
77.5 CDCl3
77.2 CDCl3
76.8 CDCl3
70.5
55.8
48.6
30.8
23.4
15.2
MeO
O
Me
O
S118
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)

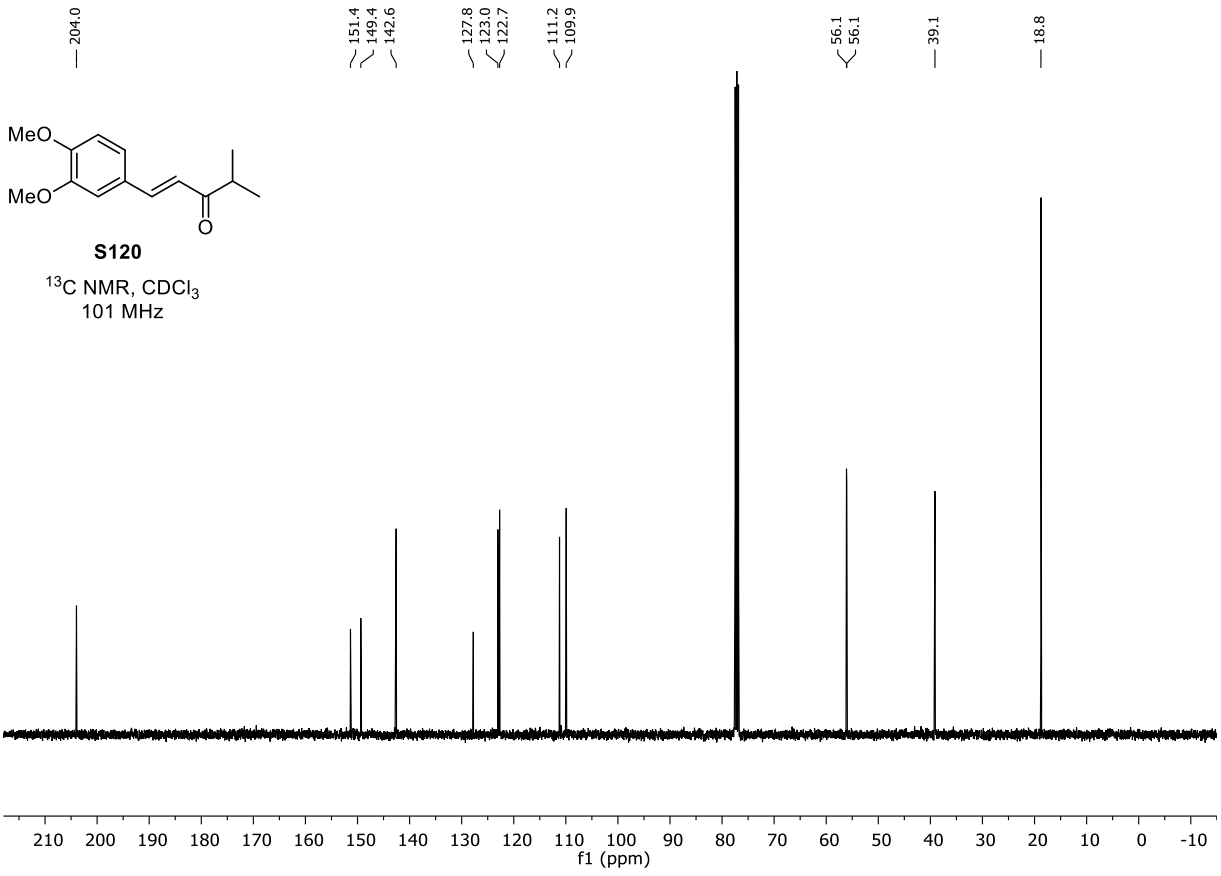

7.26 CDCl3
1.54 HDO
MeO
O
Me
O
S119
1H NMR, CDCl3
400 MHz
4.0
0.9
1.0
3.0
1.0
0.9
0.9
2.0
1.9
2.9
1.0
f1 (ppm)


154.1
153.2
115.7
114.7
77.5 CDCl3
77.2 CDCl3
76.8 CDCl3
69.0
61.5
55.9
47.4
40.3
30.3
27.4
23.9
15.1
MeO
O
Me
O
S119
13C NMR, CDCl3
101 MHz
f1 (ppm)



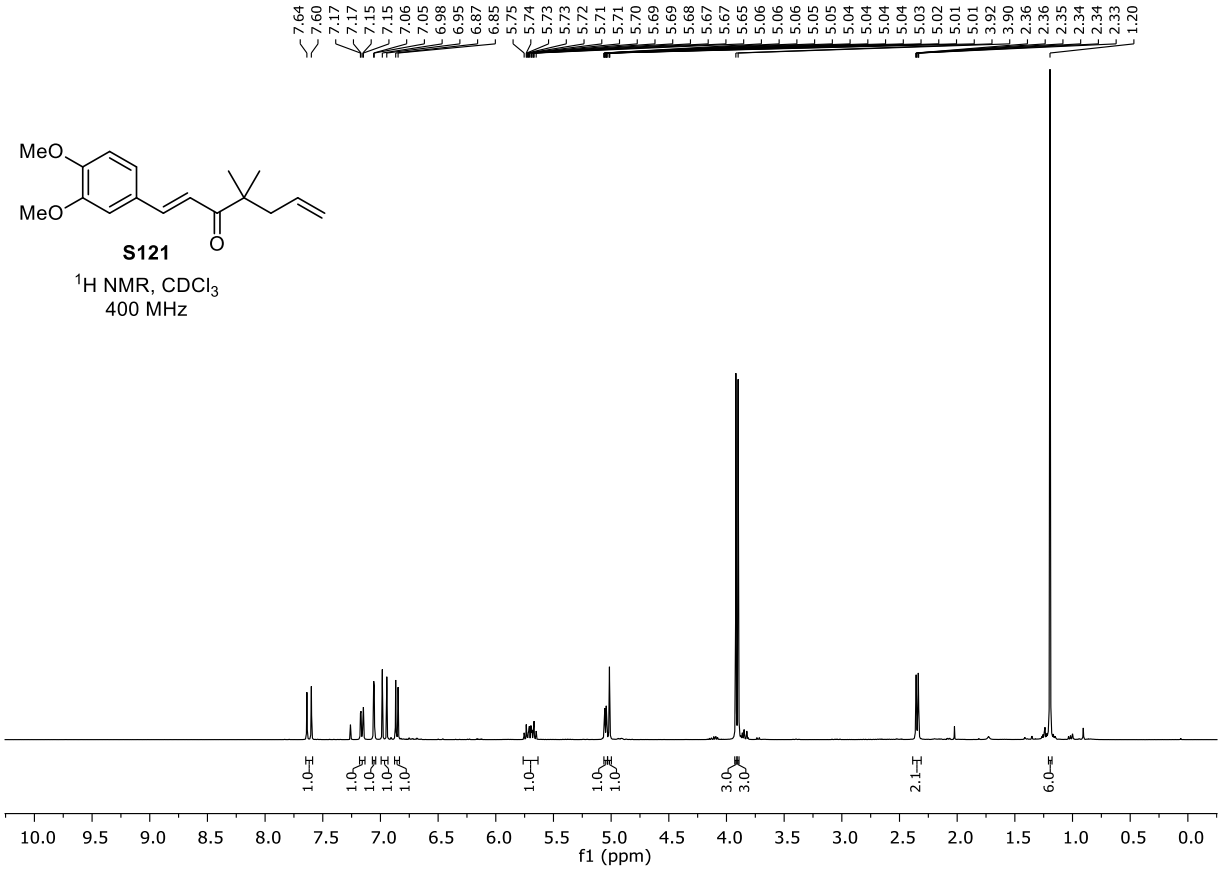
S120

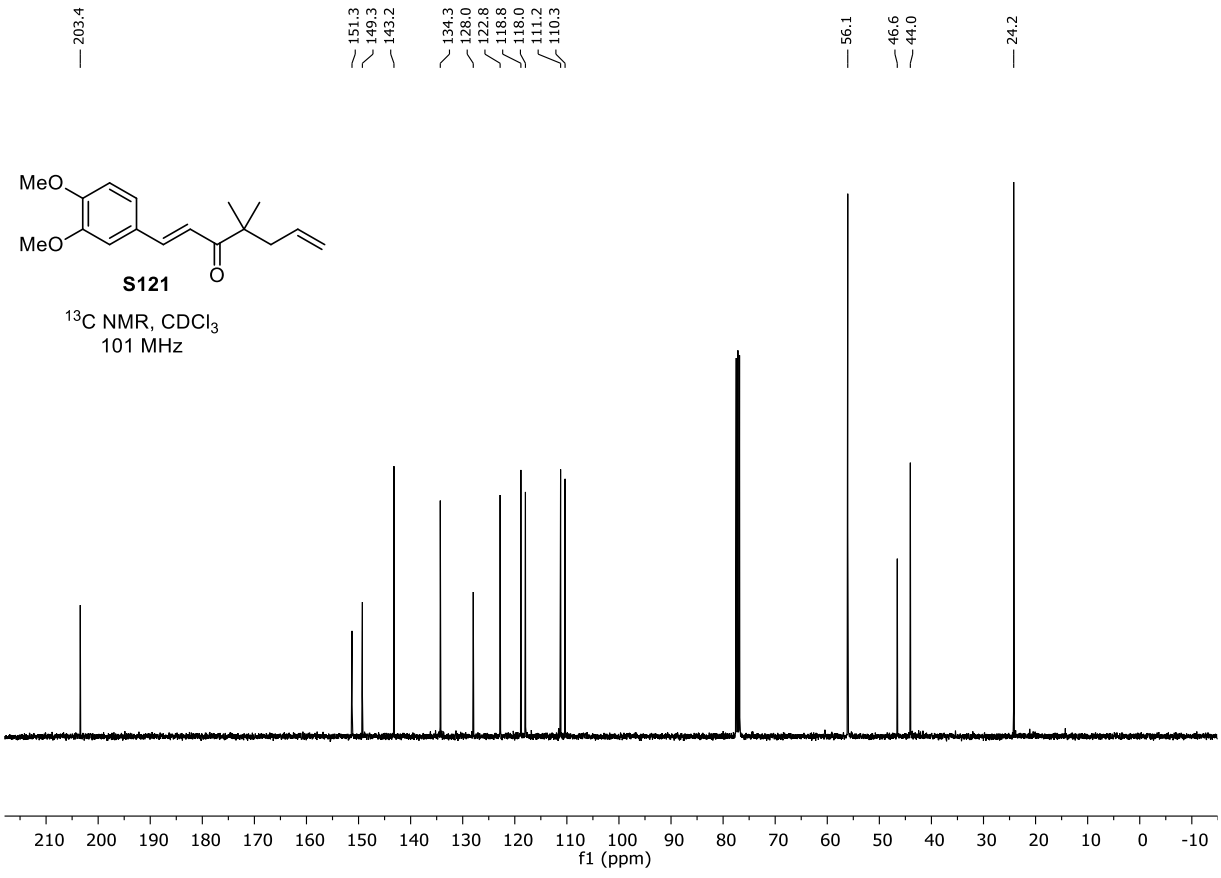
^{1}H NMR, $CDCl_3$
400 MHz

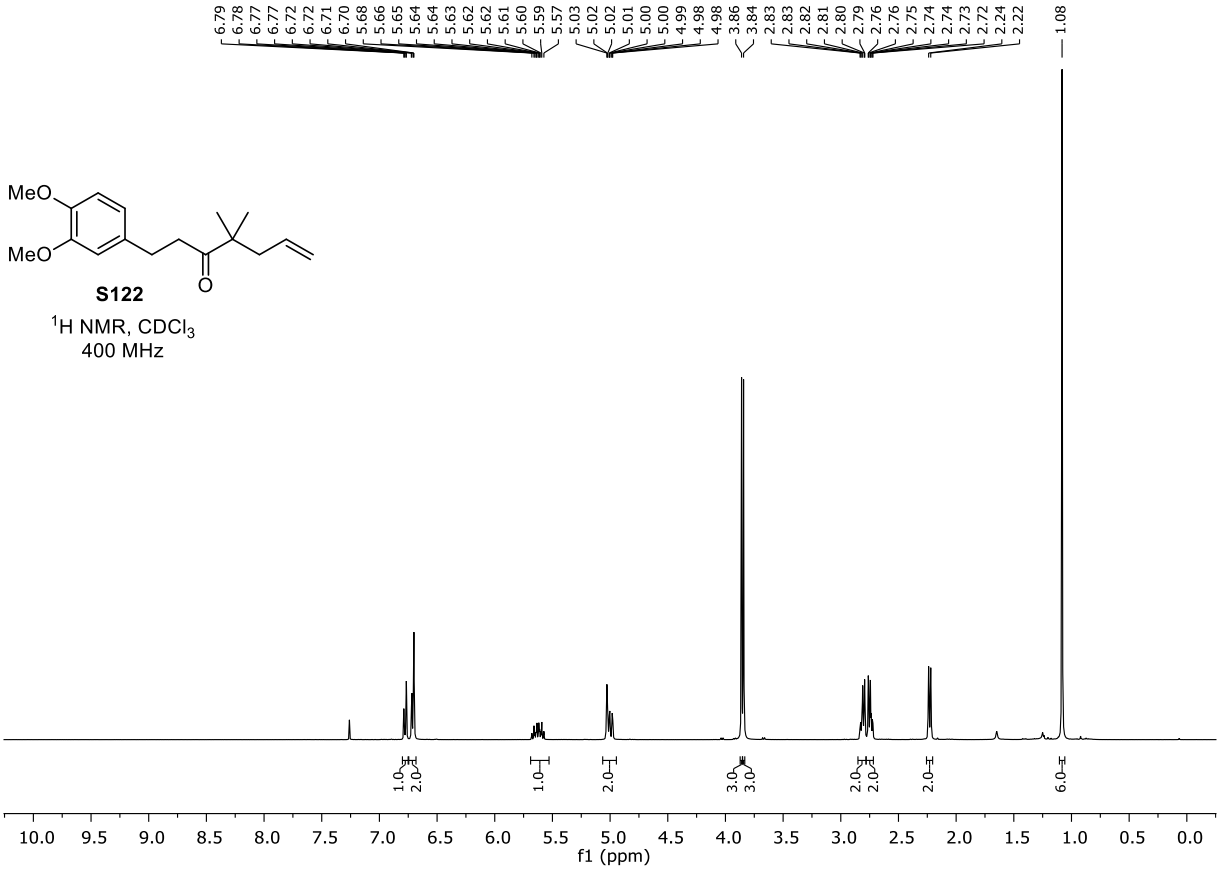


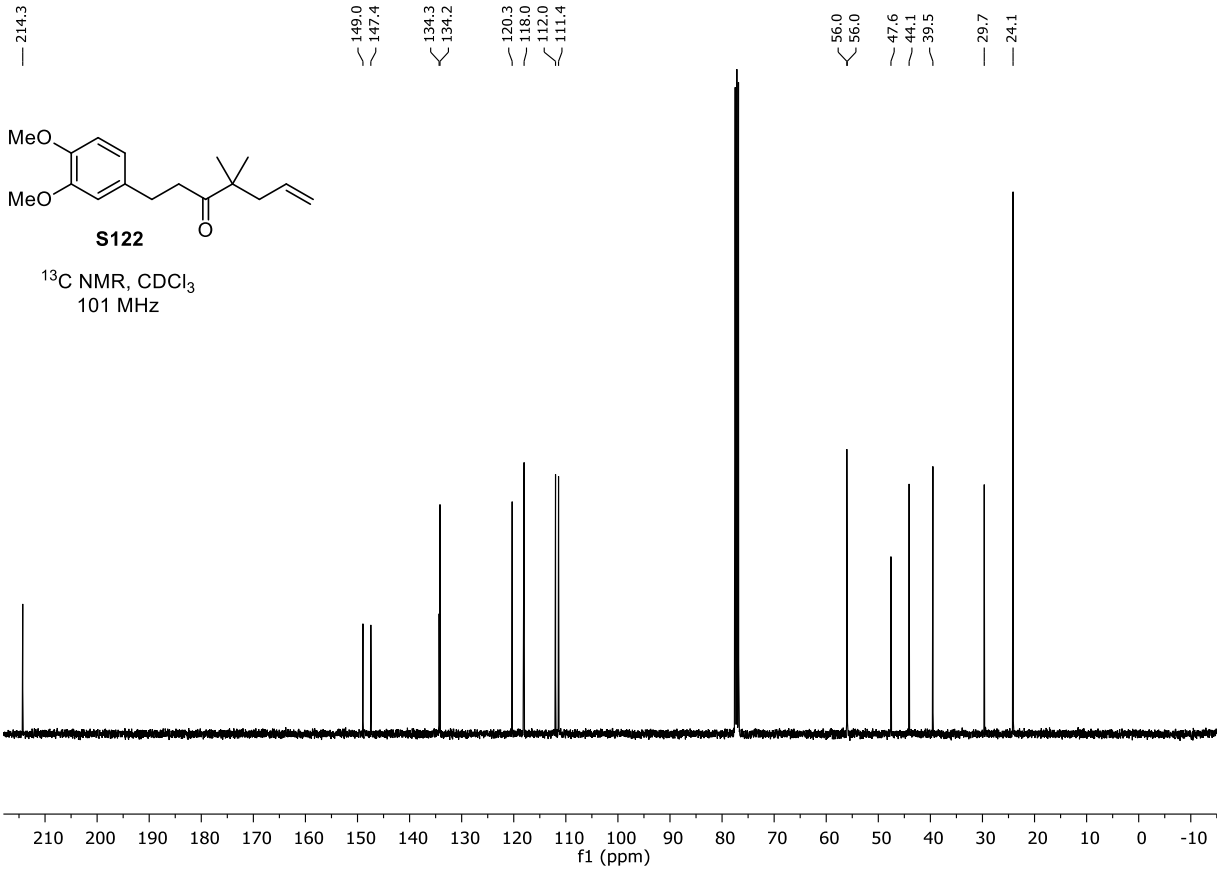
S120

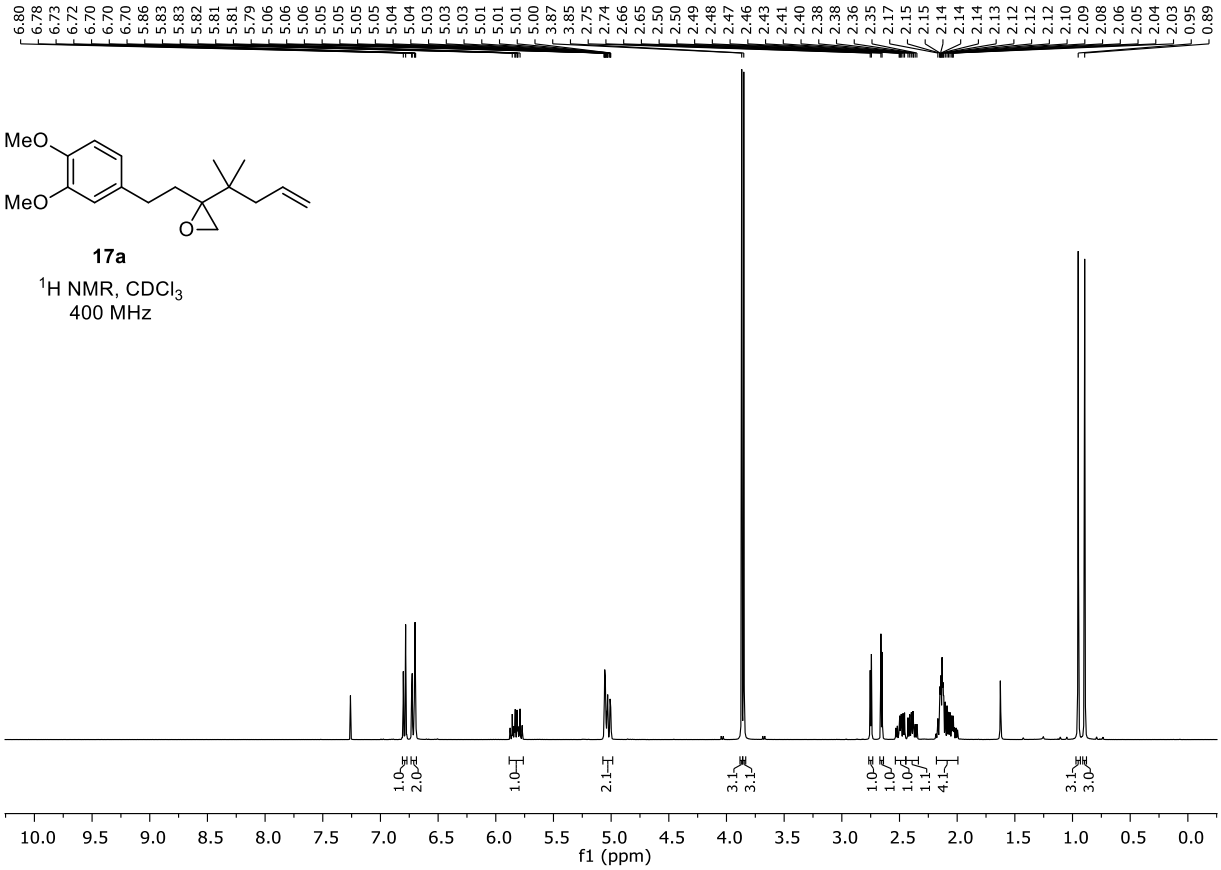
^{13}C NMR, $CDCl_3$
101 MHz

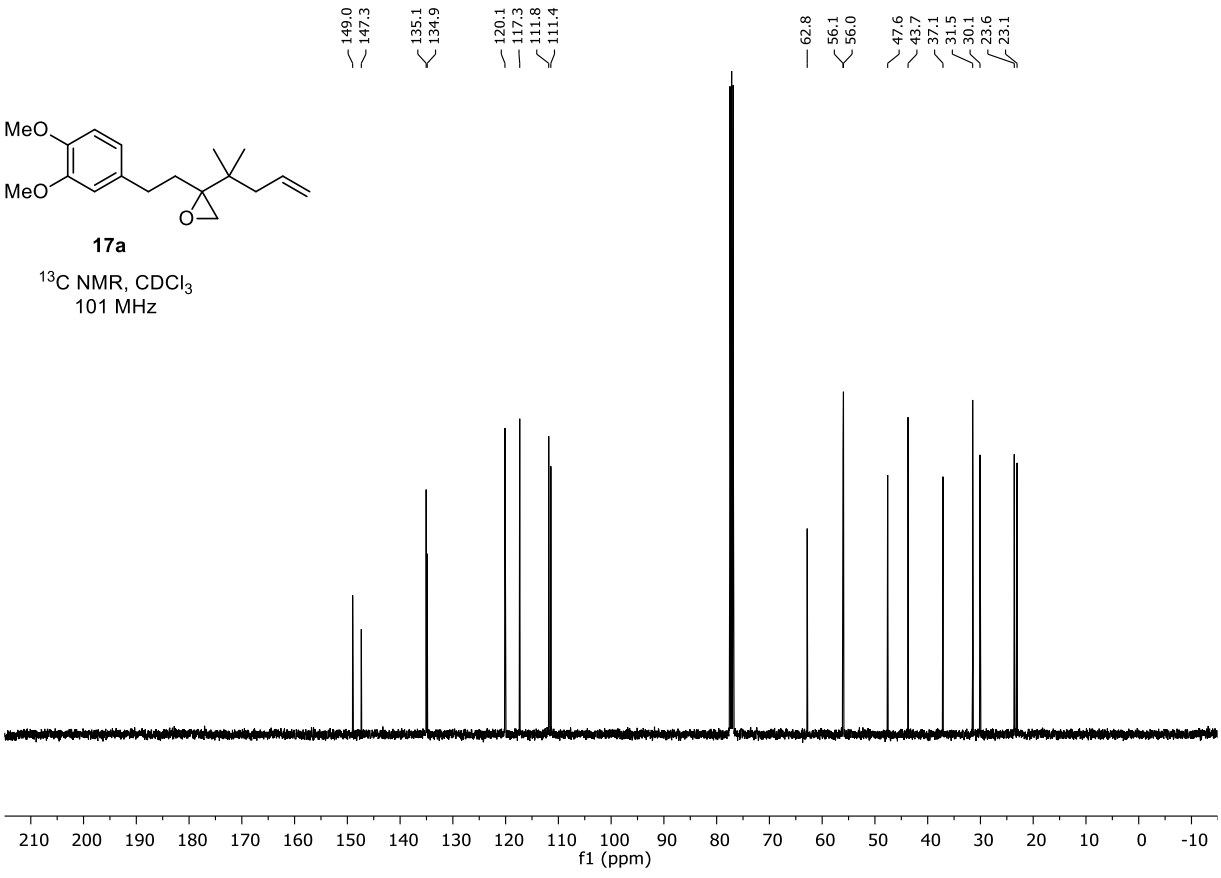

MeO
MeO
O
S121
1H NMR, CDCl3
400 MHz
f1 (ppm)

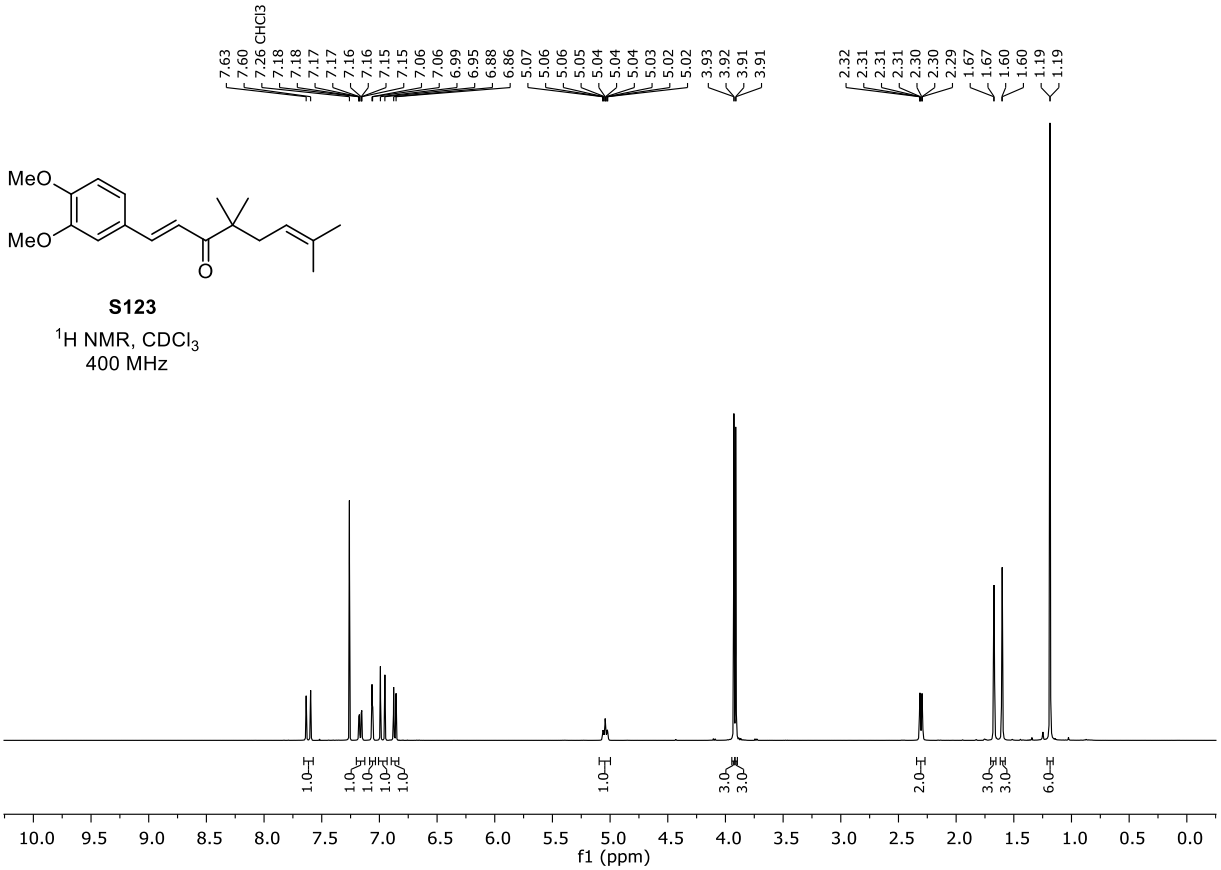

MeO
MeO
O
S121
13C NMR, CDCl3
101 MHz
f1 (ppm)

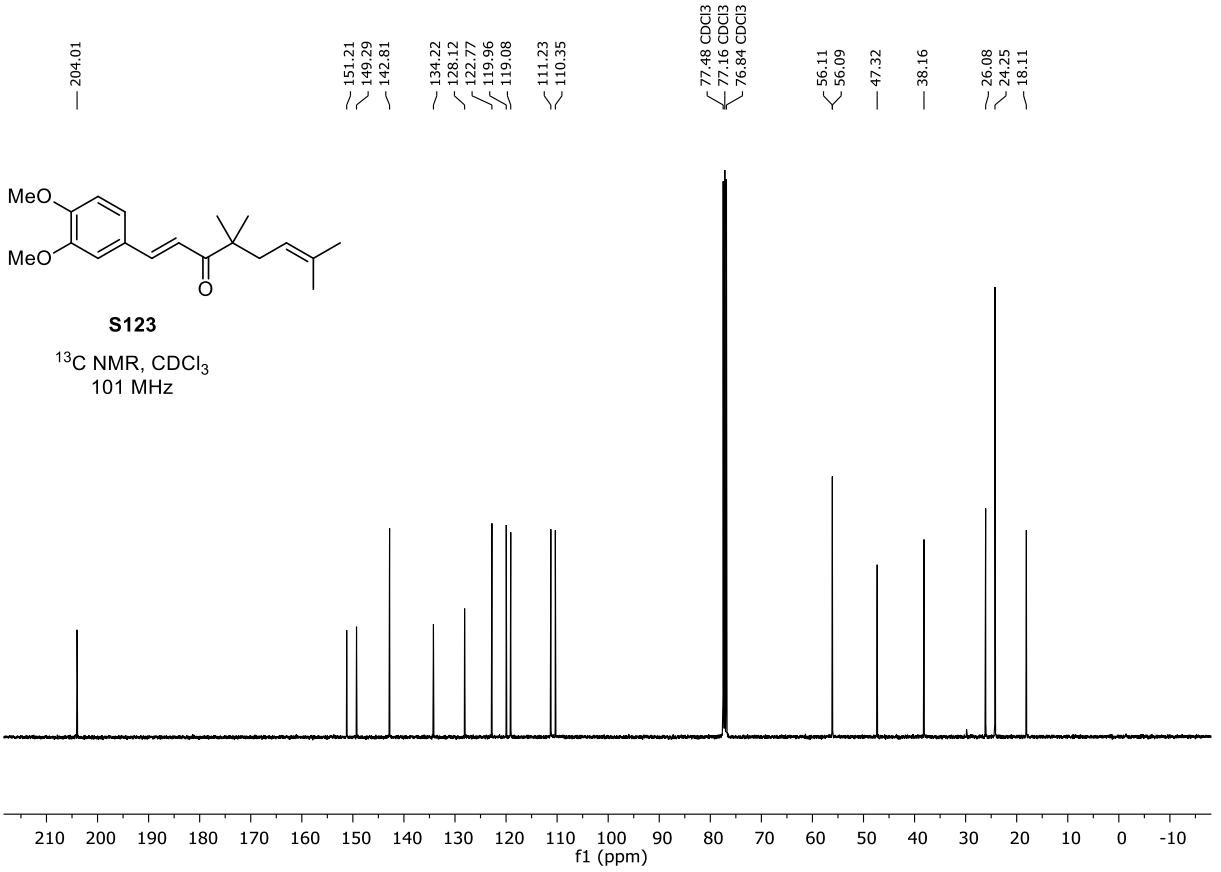

MeO
MeO
O
S122
1H NMR, CDCl3
400 MHz
f1 (ppm)

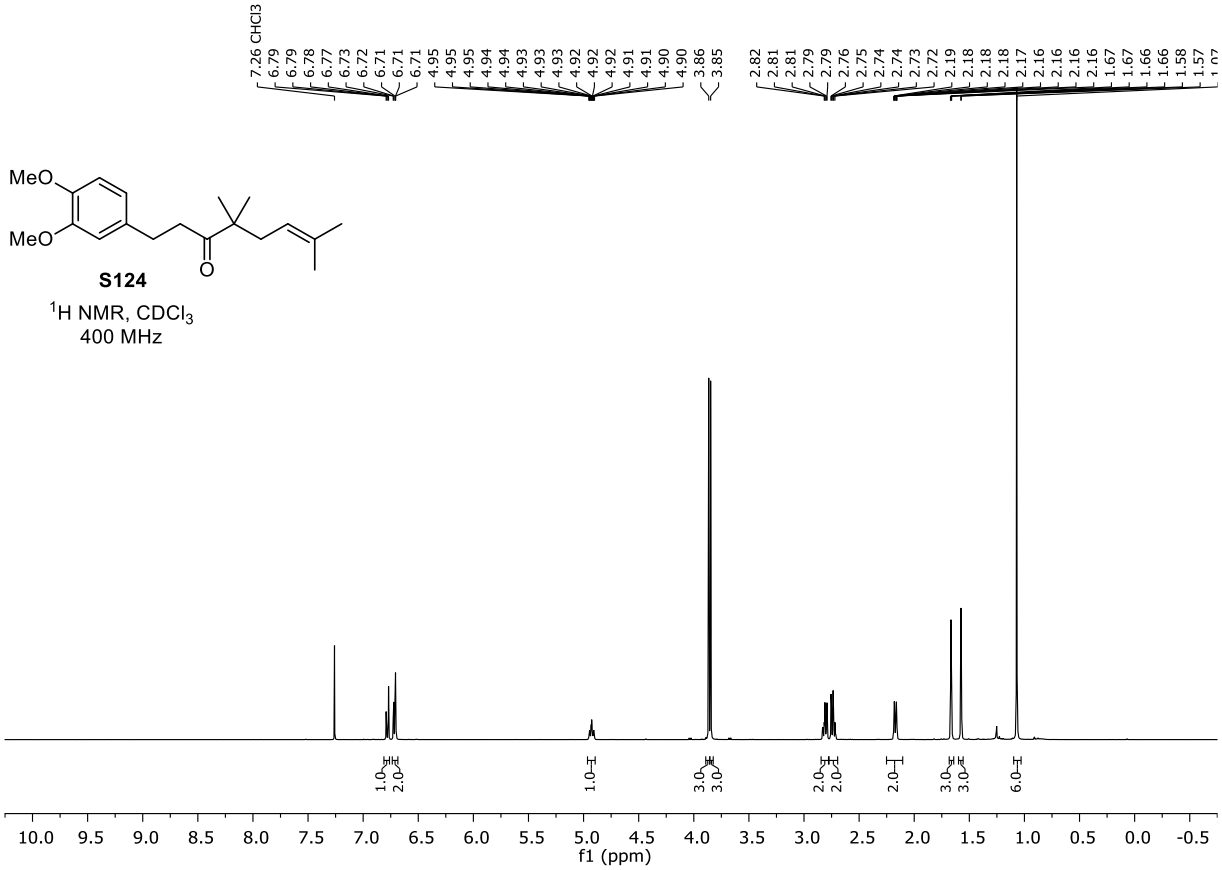

MeO
MeO
O
S122
13C NMR, CDCl3
101 MHz
f1 (ppm)

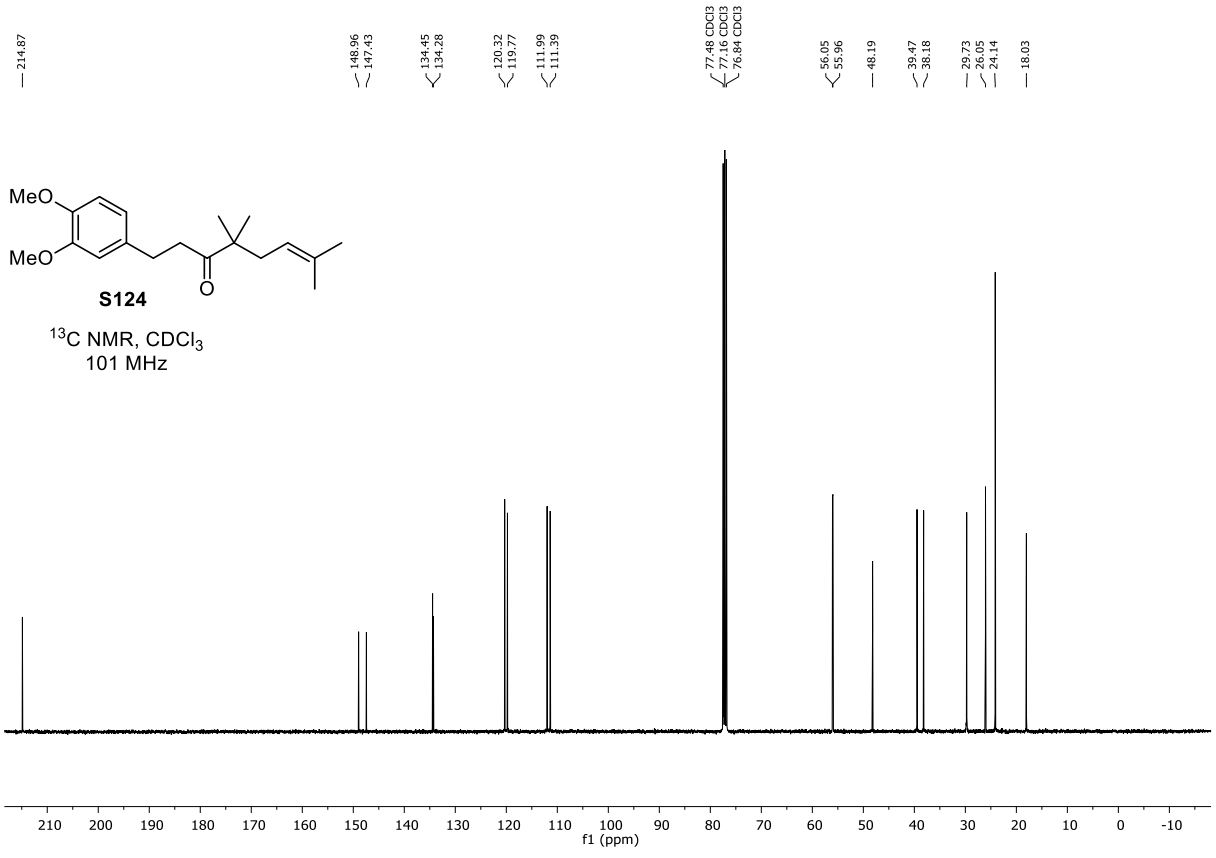

MeO
MeO
O
17a
^{1}H NMR, $CDCl_3$
400 MHz
f1 (ppm)

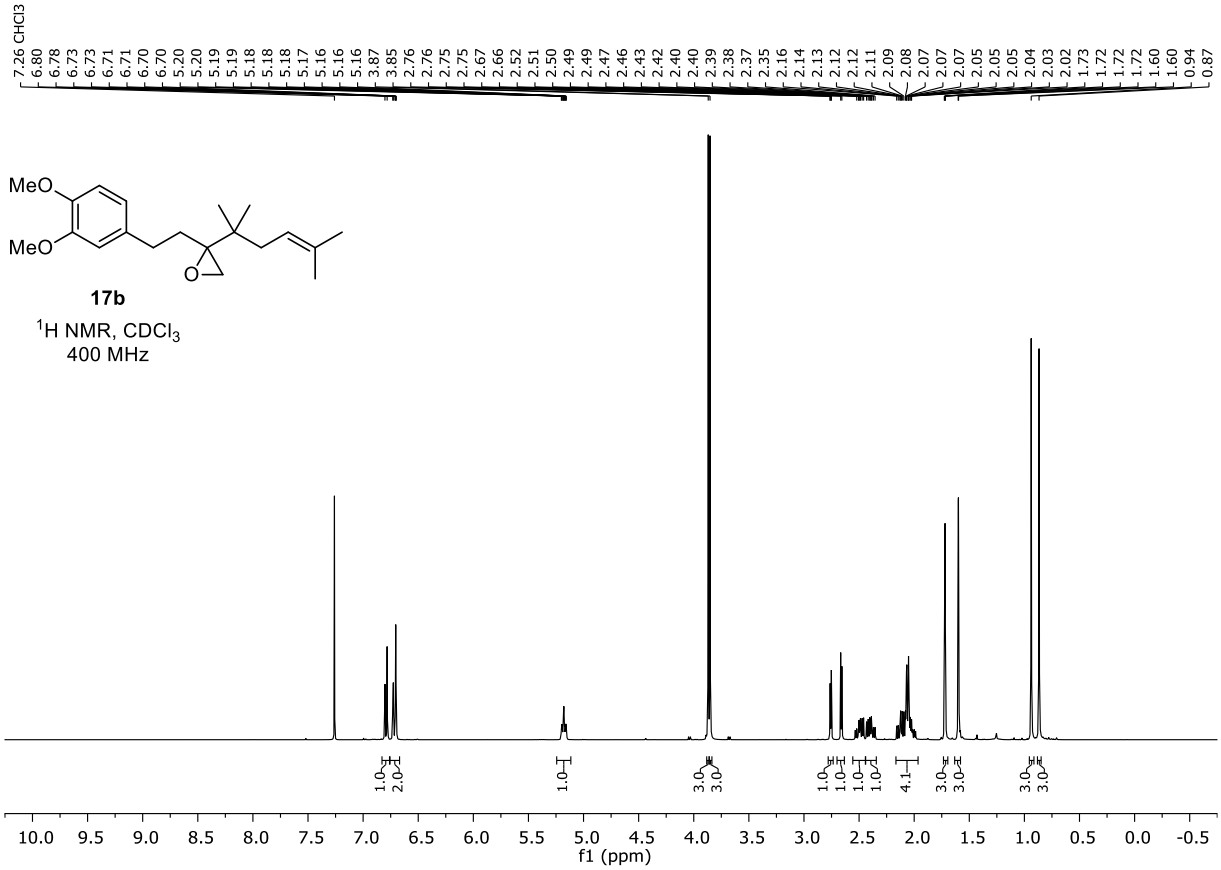

MeO
MeO
O
17a
^{13}C NMR, $CDCl_3$
101 MHz
f1 (ppm)

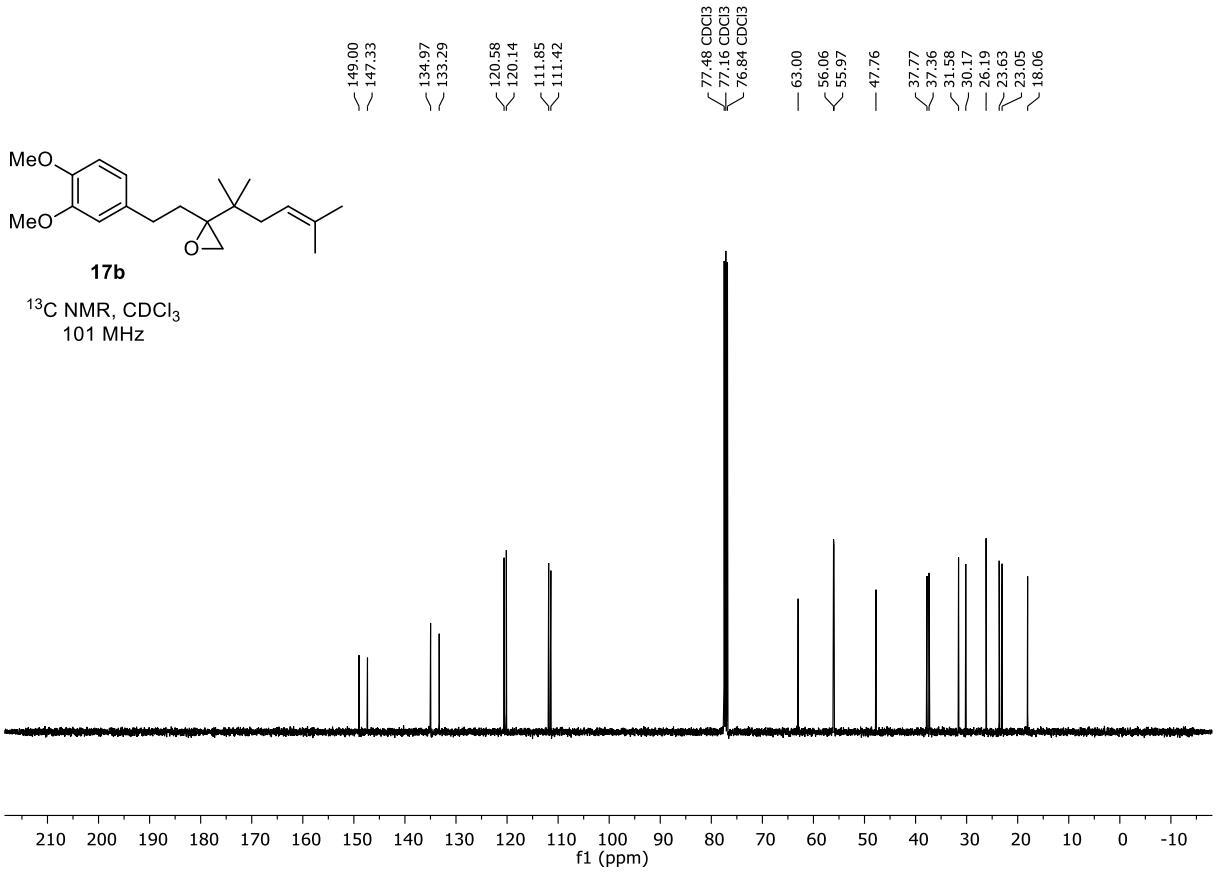

7.63
7.60
7.26 CHCl3
7.18
7.17
7.17
7.16
7.16
7.15
7.15
7.06
7.06
6.99
6.95
6.88
6.86
5.07
5.06
5.06
5.05
5.04
5.04
5.04
5.03
5.02
5.02
3.93
3.92
3.91
3.91
2.32
2.31
2.31
2.31
2.30
2.30
2.29
1.67
1.67
1.60
1.60
1.19
1.19
MeO
MeO
O
S123
1H NMR, CDCl3
400 MHz
1.0
1.0
1.0
1.0
1.0
1.0
3.0
3.0
2.0
3.0
3.0
6.0
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)

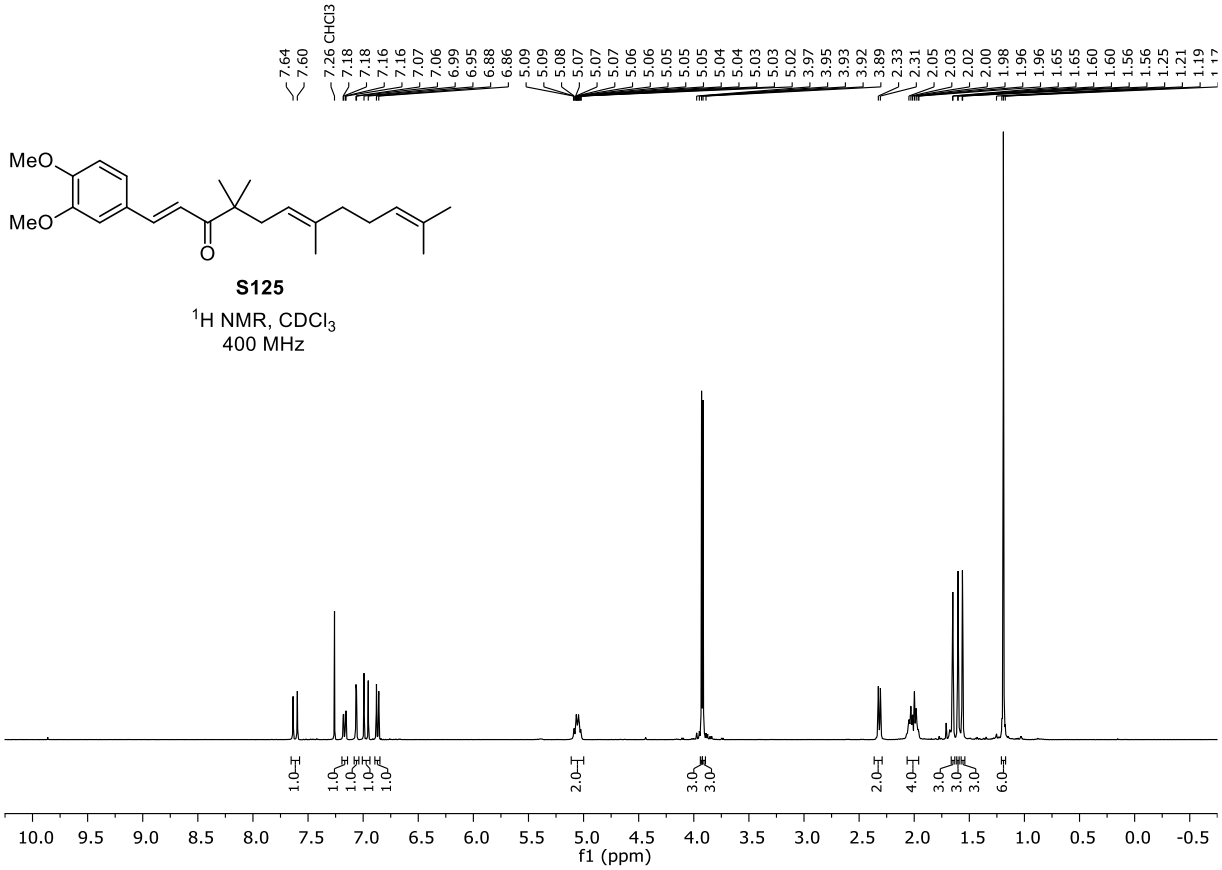

204.01
151.21
149.29
142.81
134.22
128.12
122.77
119.96
119.08
111.23
110.35
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
56.11
56.09
47.32
38.16
26.08
24.25
18.11
MeO
MeO
O
S123
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

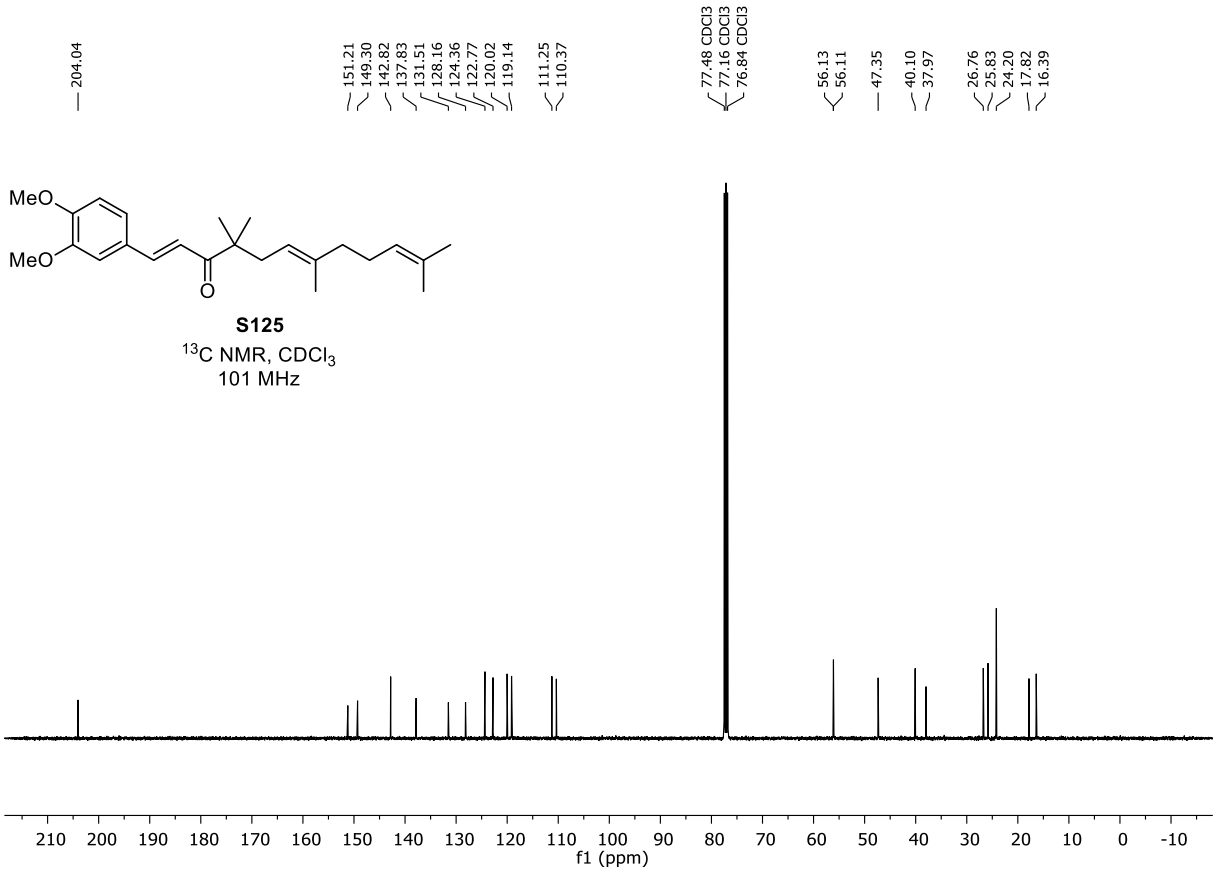

MeO
MeO
O
S124
1H NMR, CDCl3
400 MHz
f1 (ppm)

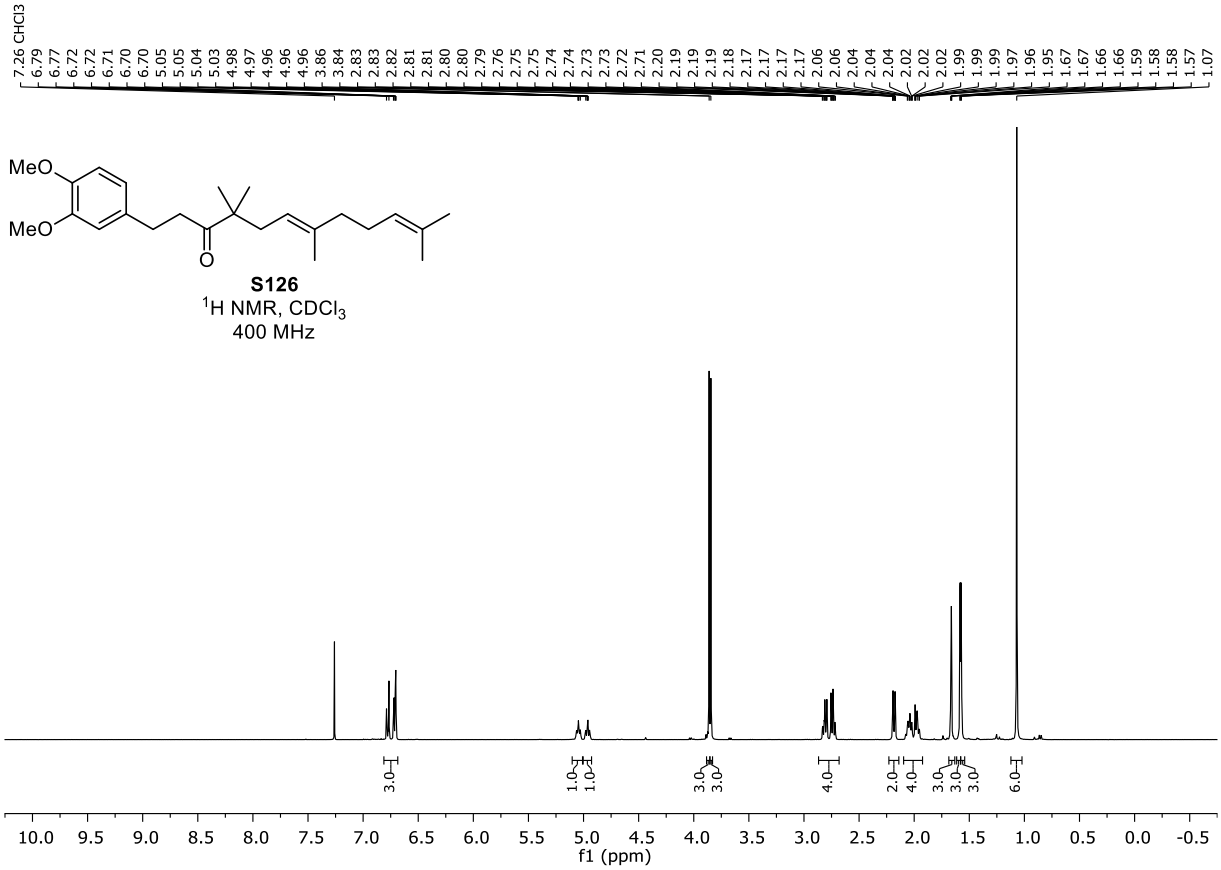

MeO
MeO
O
S124
13C NMR, CDCl3
101 MHz
f1 (ppm)

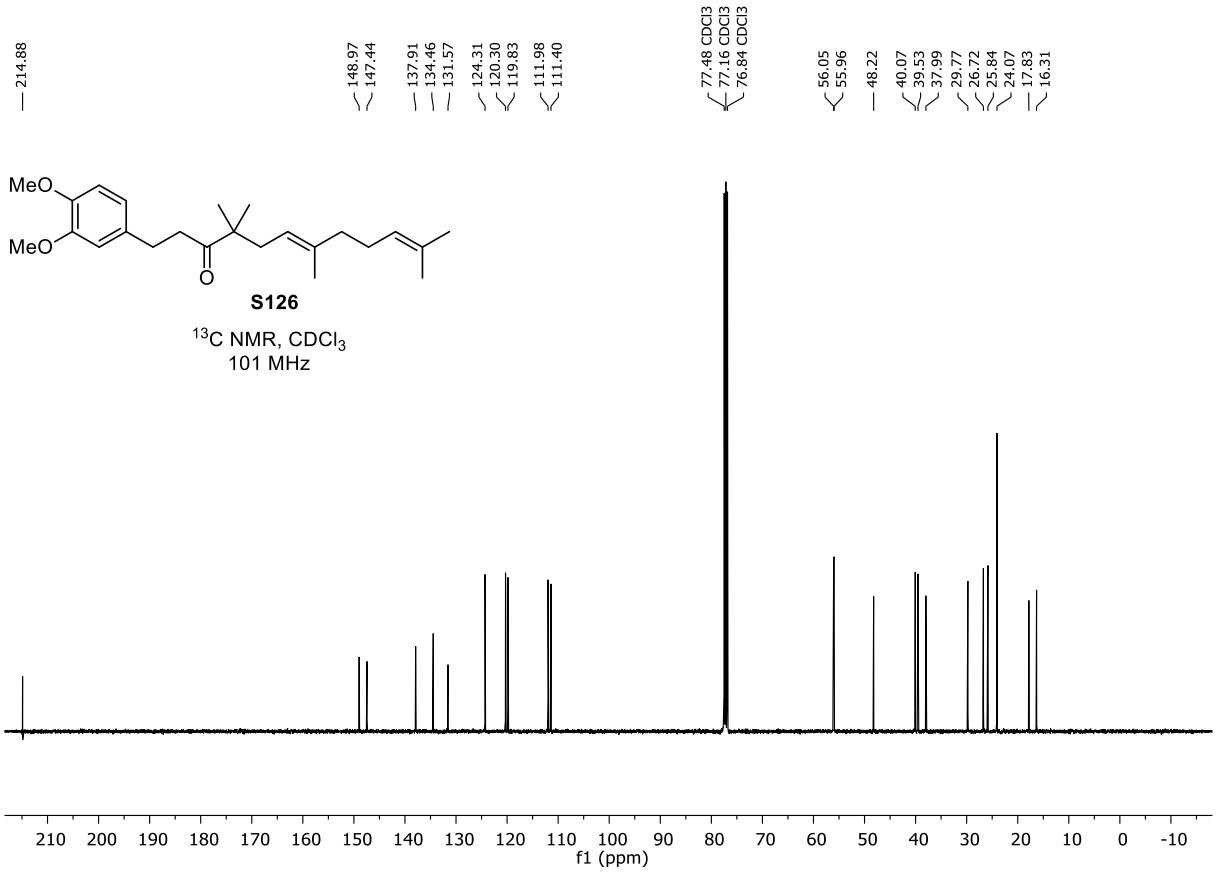

7.26 CHCl3
MeO
MeO
O
17b
1H NMR, CDCl3
400 MHz
f1 (ppm)

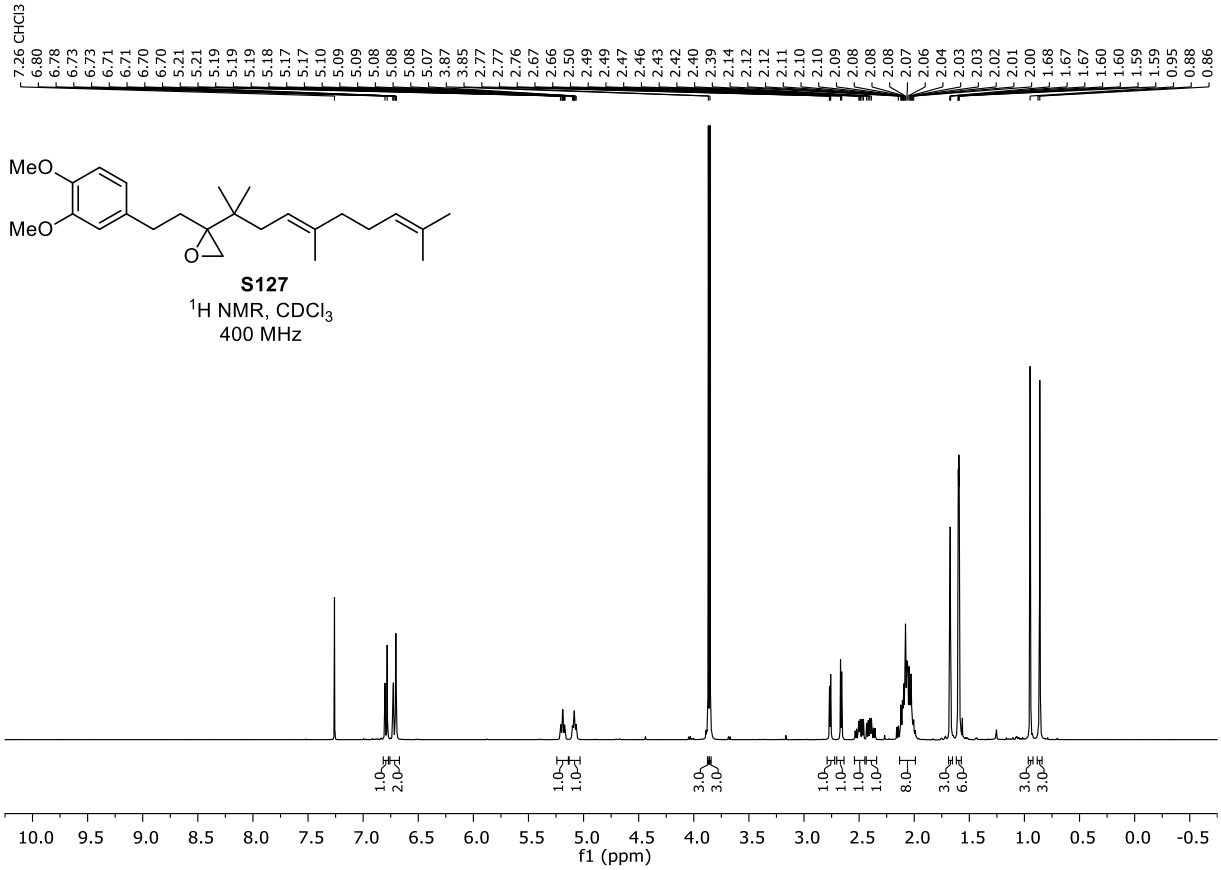

77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
MeO
MeO
O
17b
13C NMR, CDCl3
101 MHz
f1 (ppm)

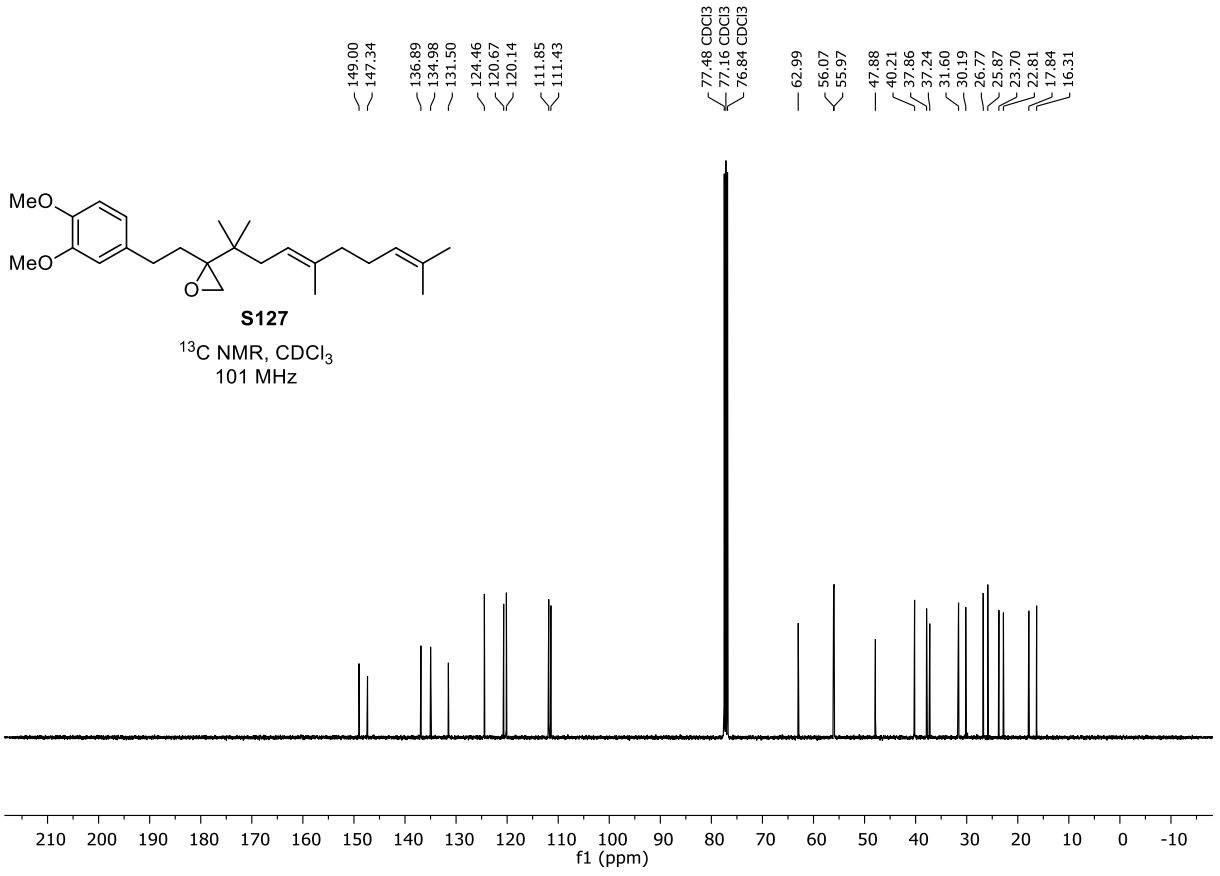

MeO
MeO
O
S125
1H NMR, CDCl3
400 MHz
f1 (ppm)

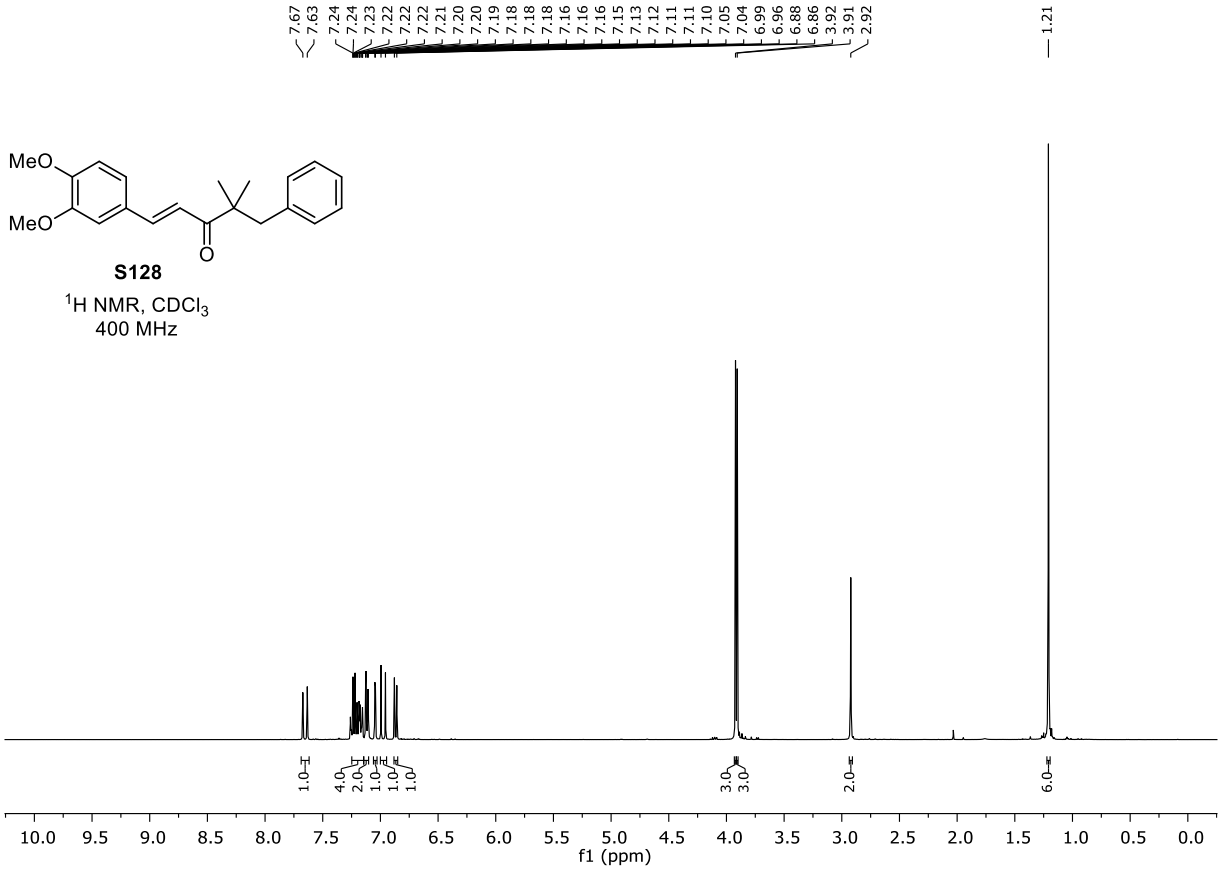

MeO
MeO
O
S125
13C NMR, CDCl3
101 MHz
f1 (ppm)

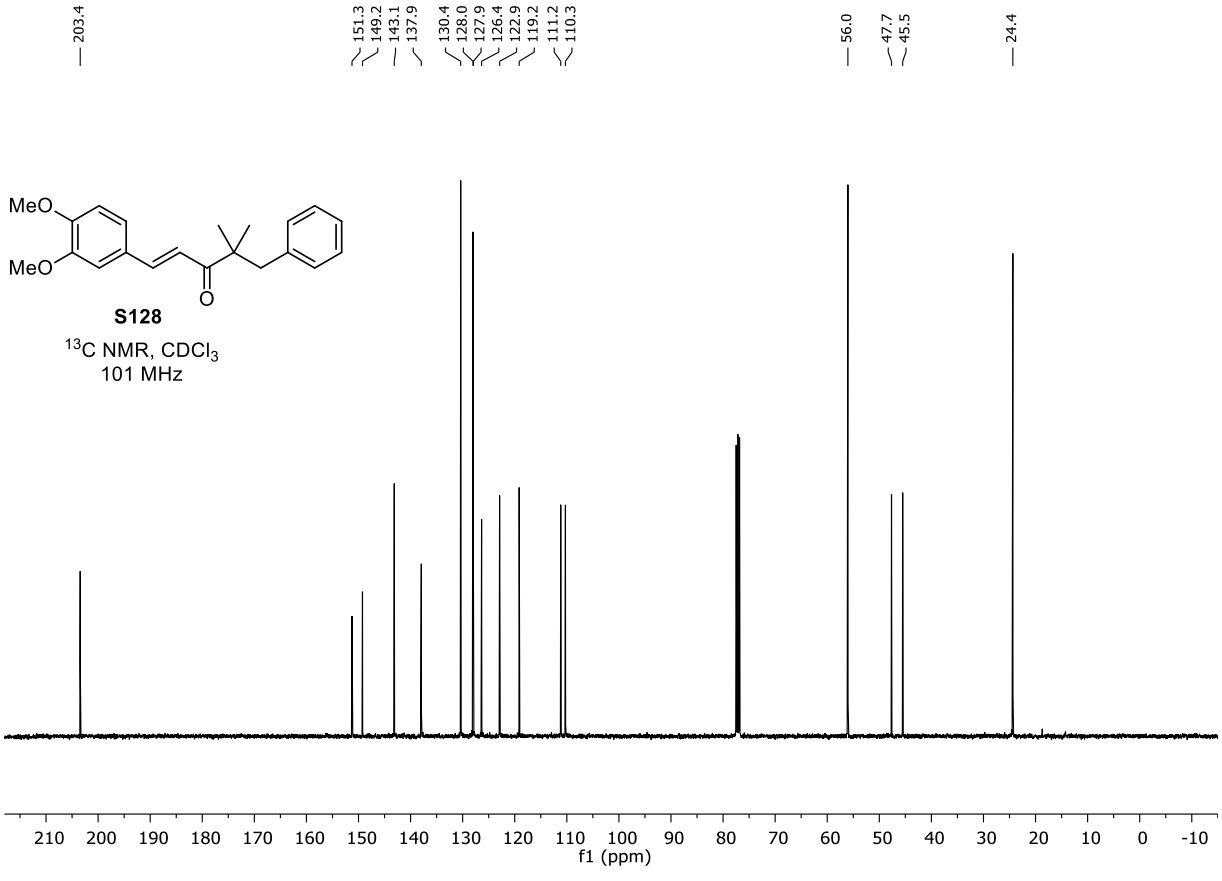

MeO
MeO
O
S126
1H NMR, CDCl3
400 MHz
f1 (ppm)

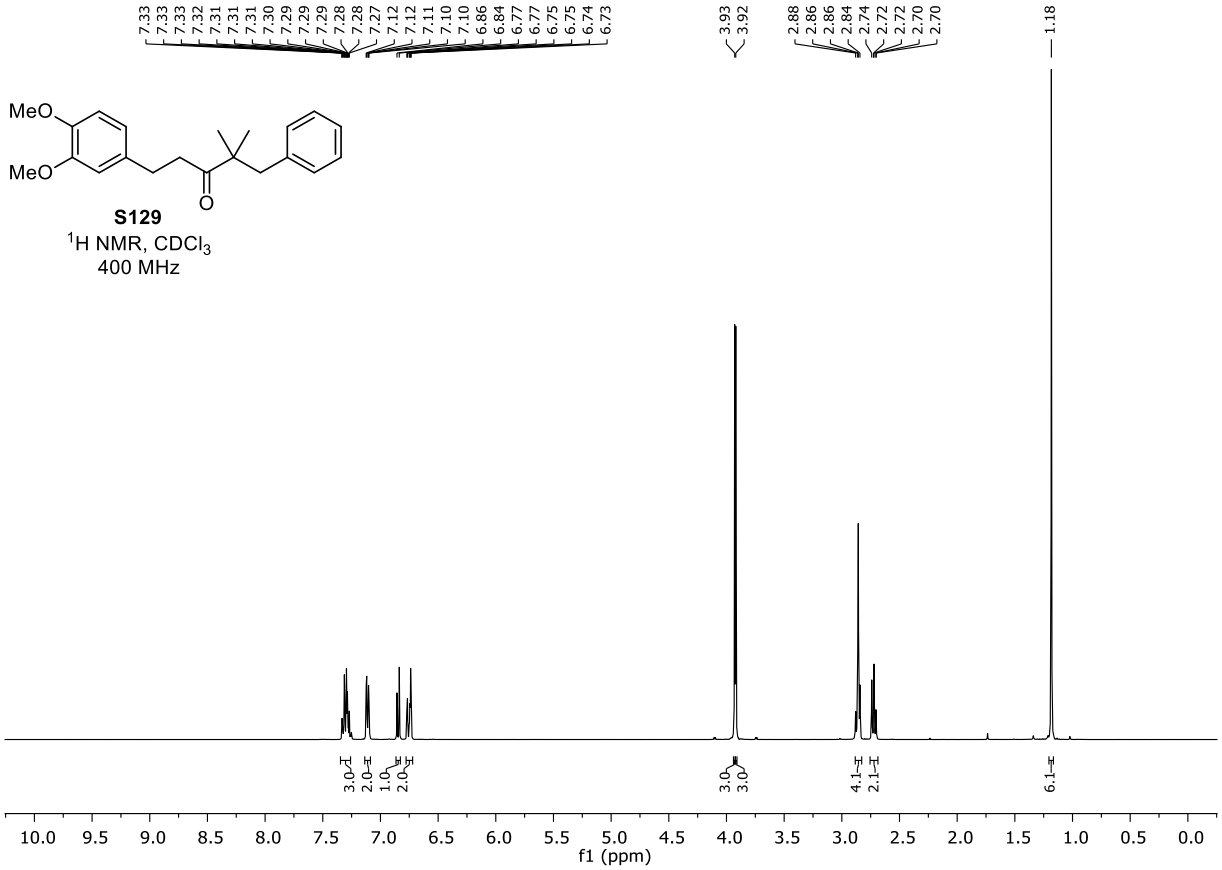

MeO
MeO
O
S126
13C NMR, CDCl3
101 MHz
f1 (ppm)

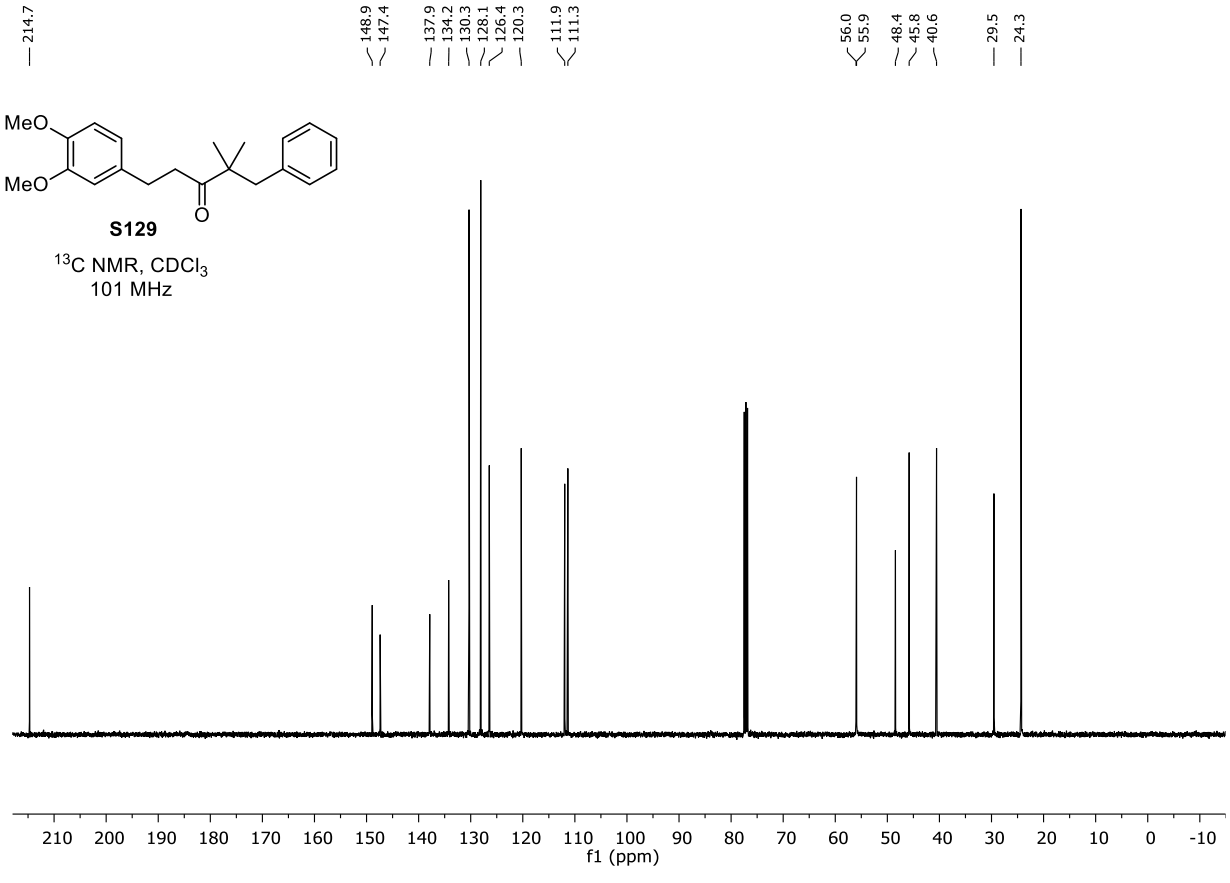

7.26 CHCl3
6.80 6.78 6.73 6.73 6.71 6.71 6.70 6.70 5.21 5.21 5.19 5.19 5.19 5.18 5.17 5.17 5.10 5.09 5.09 5.08 5.08 5.08 5.07 3.87 3.85 2.77 2.77 2.76 2.67 2.66 2.50 2.49 2.49 2.47 2.46 2.43 2.42 2.40 2.39 2.14 2.12 2.12 2.11 2.10 2.10 2.09 2.08 2.08 2.08 2.07 2.06 2.04 2.03 2.03 2.02 2.01 2.00 1.68 1.67 1.67 1.60 1.60 1.59 1.59 0.95 0.88 0.86
MeO
MeO
O
S127
1H NMR, CDCl3
400 MHz
1.0 2.0 1.0 1.0 3.0 3.0 1.0 1.0 1.0 1.0 8.0 3.0 6.0 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 -0.5
f1 (ppm)

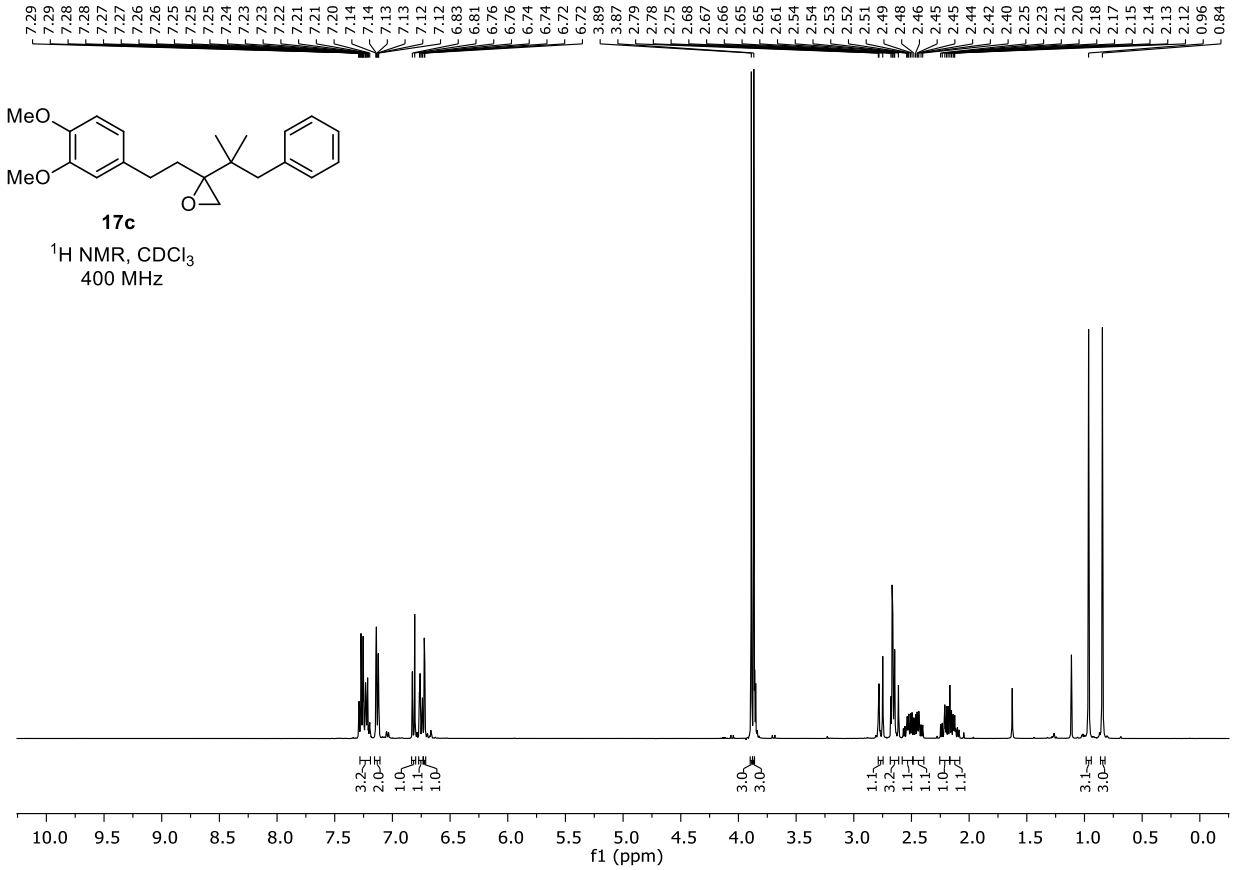

149.00 147.34 136.89 134.98 131.50 124.46 120.67 120.14 111.85 111.43 77.48 CDCl3 77.16 CDCl3 76.84 CDCl3 62.99 56.07 55.97 47.88 40.21 37.86 37.24 31.60 30.19 26.77 25.87 23.70 22.81 17.84 16.31
MeO
MeO
O
S127
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

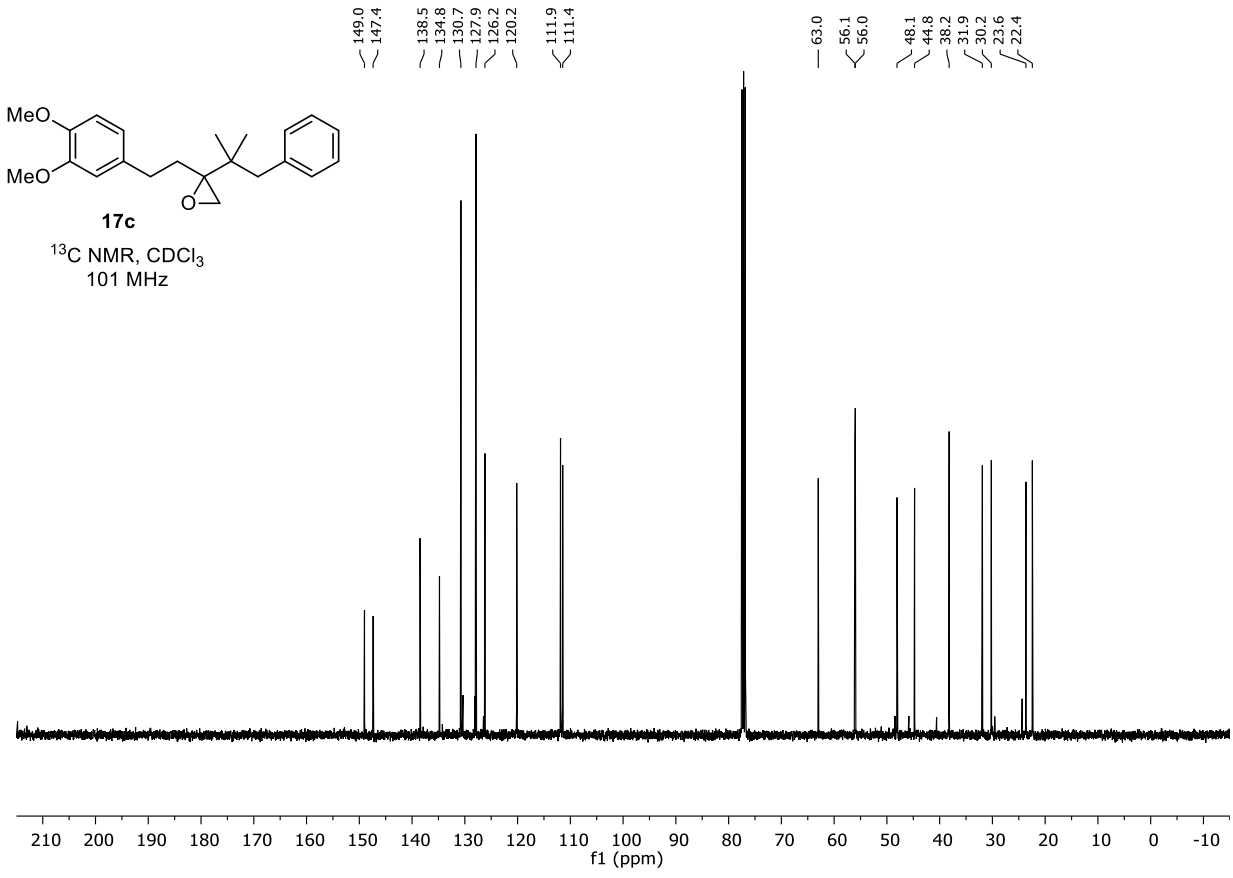

MeO
MeO
O
S128
1H NMR, CDCl3
400 MHz
f1 (ppm)

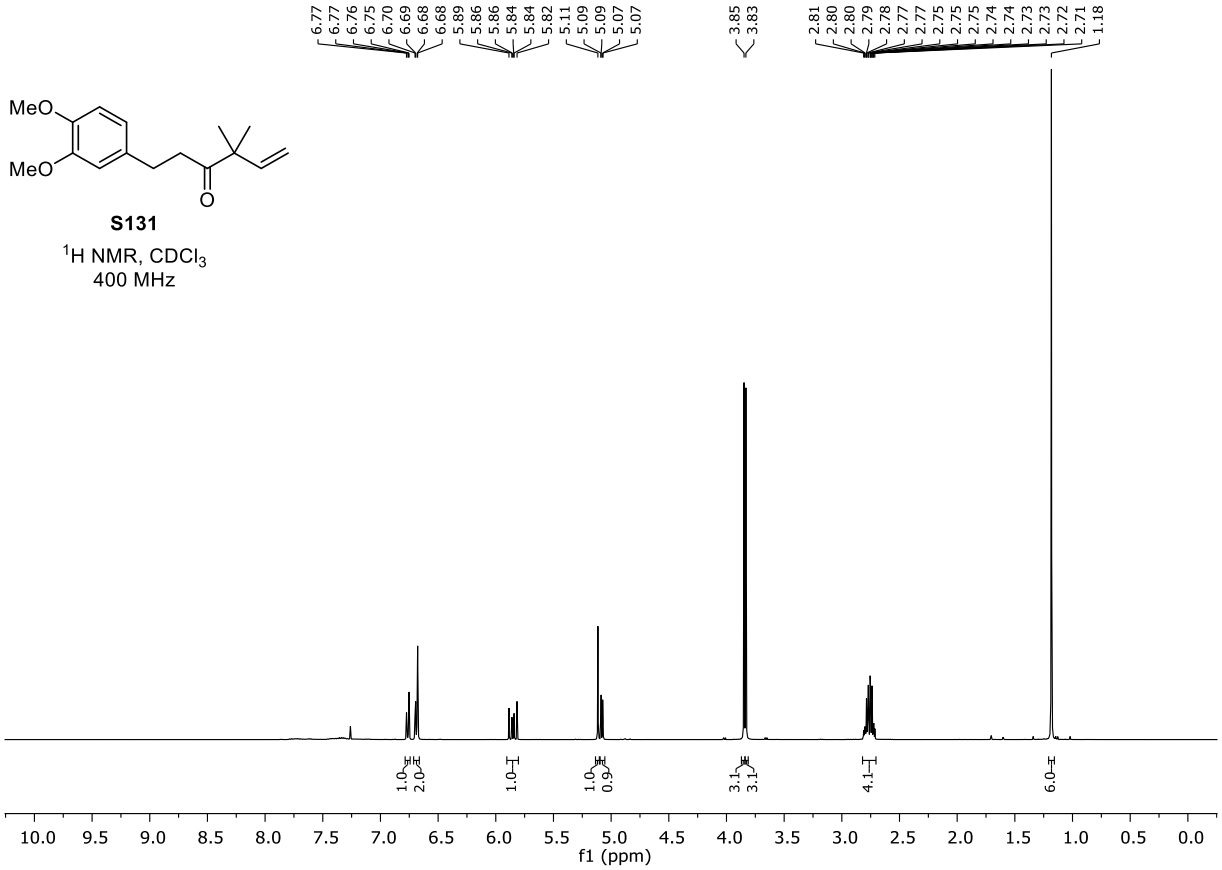

MeO
MeO
O
S128
13C NMR, CDCl3
101 MHz
f1 (ppm)


MeO
MeO
O
S129
1H NMR, CDCl3
400 MHz
f1 (ppm)


MeO
MeO
O
S129
13C NMR, CDCl3
101 MHz
f1 (ppm)

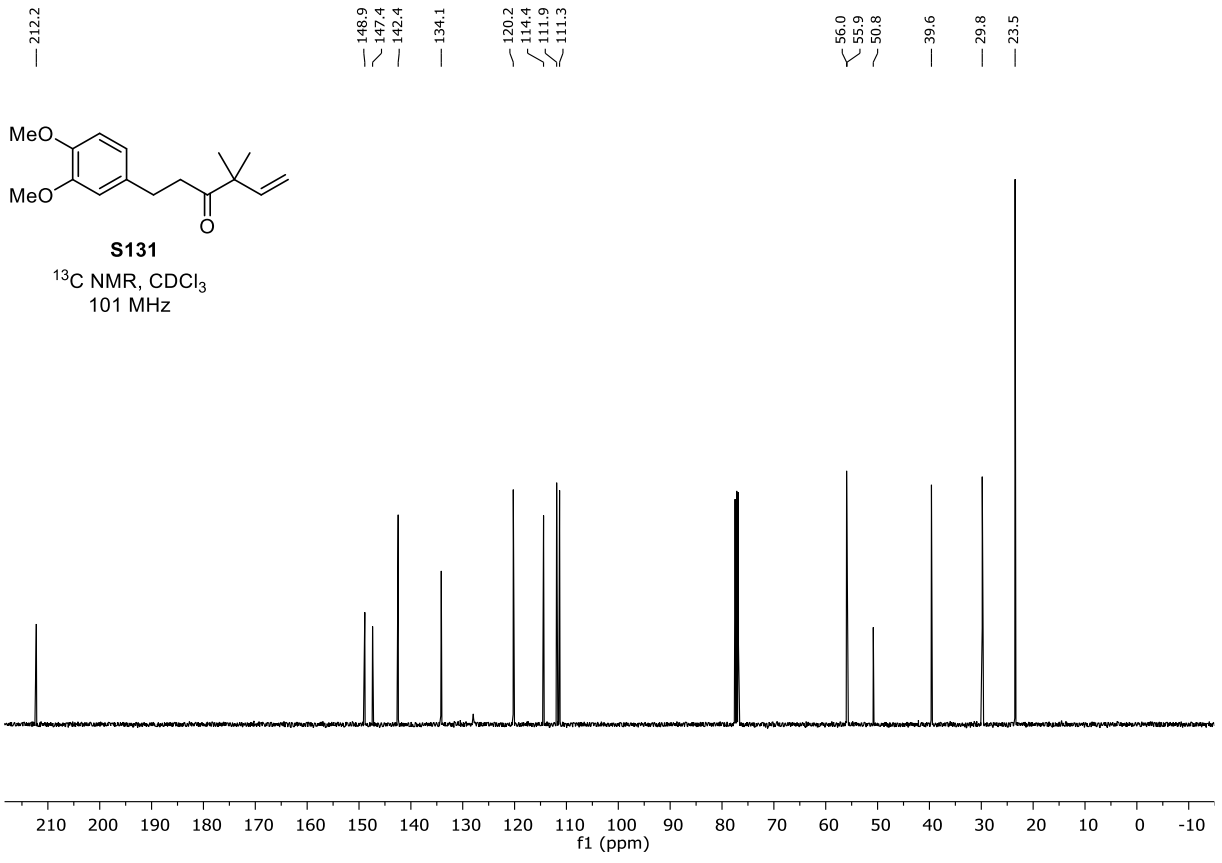

MeO
MeO
O
17c
^{1}H NMR, CDCl$_3$
400 MHz
f1 (ppm)


MeO
MeO
O
17c
^{13}C NMR, CDCl$_3$
101 MHz
f1 (ppm)



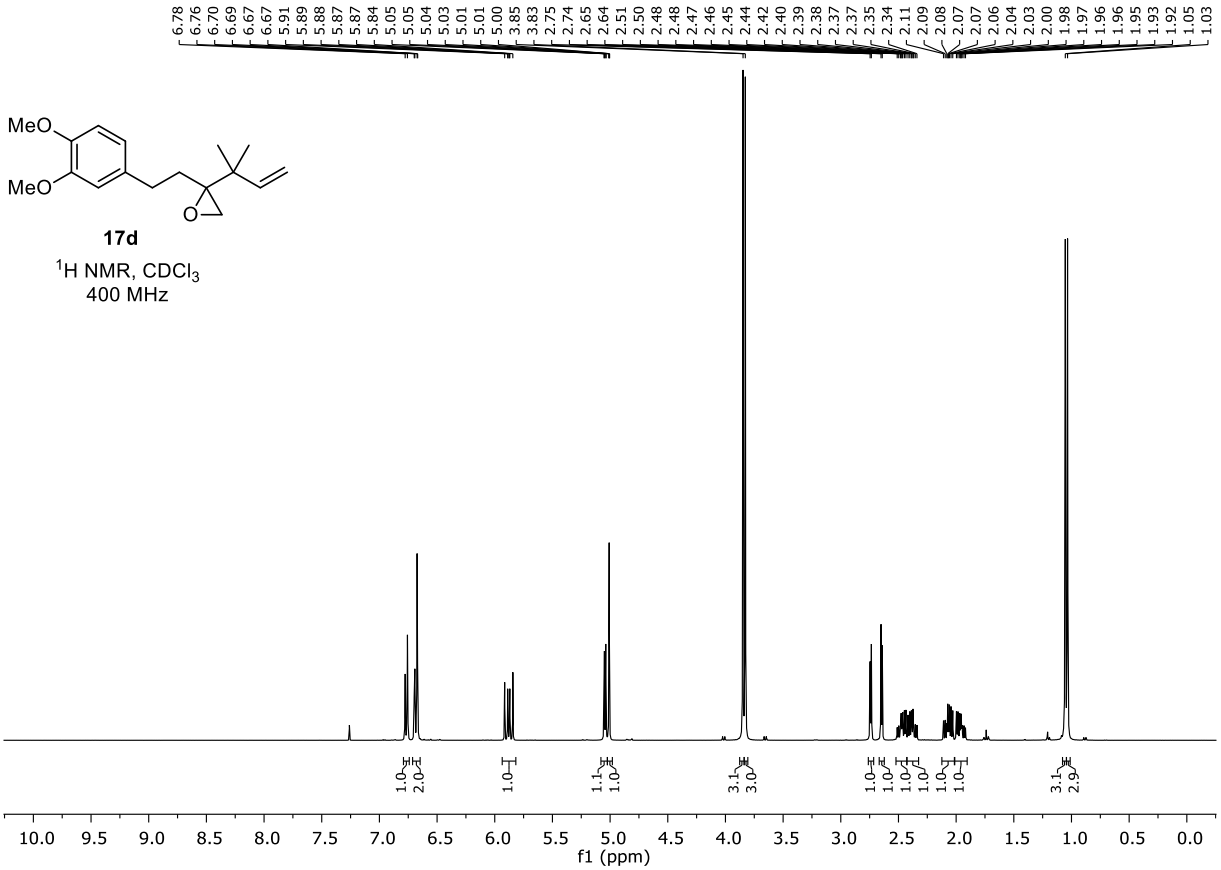
S131

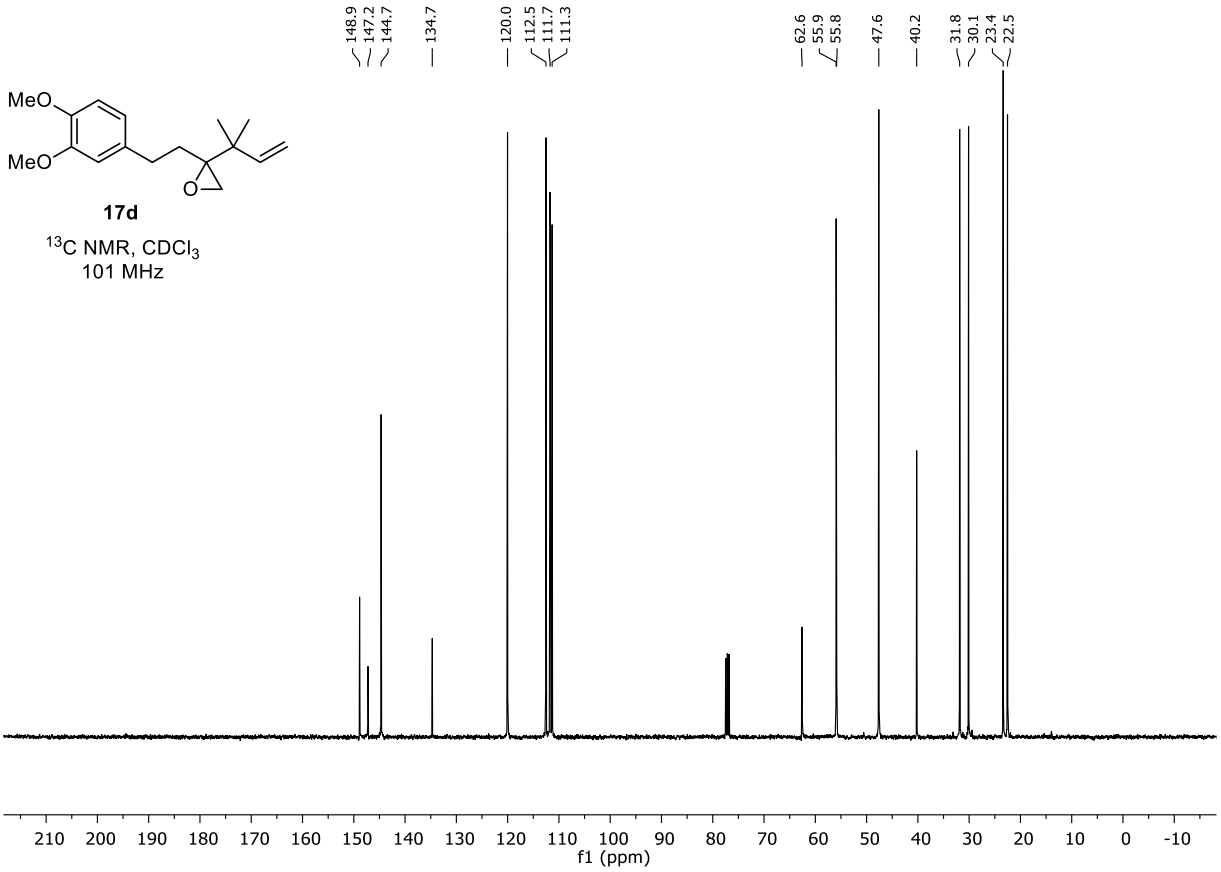
^{1}H NMR, $CDCl_3$
400 MHz

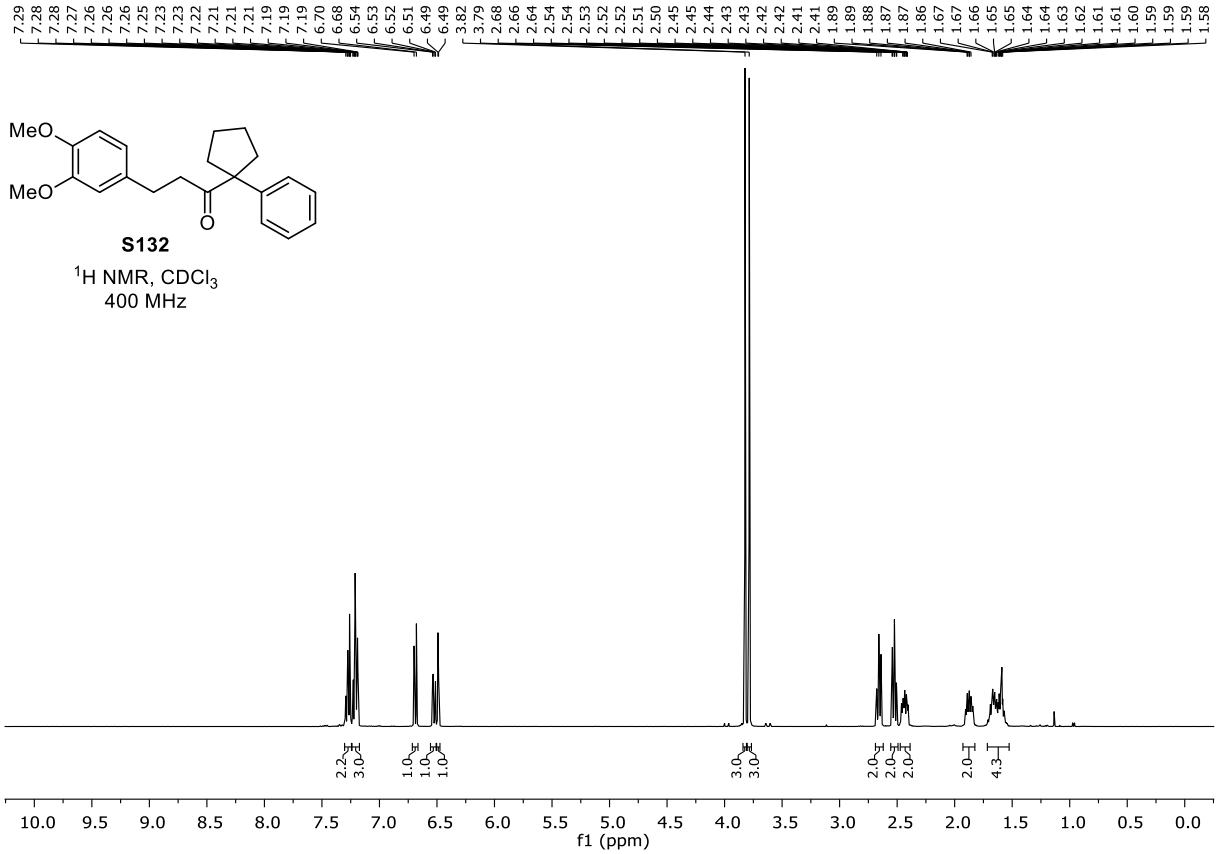


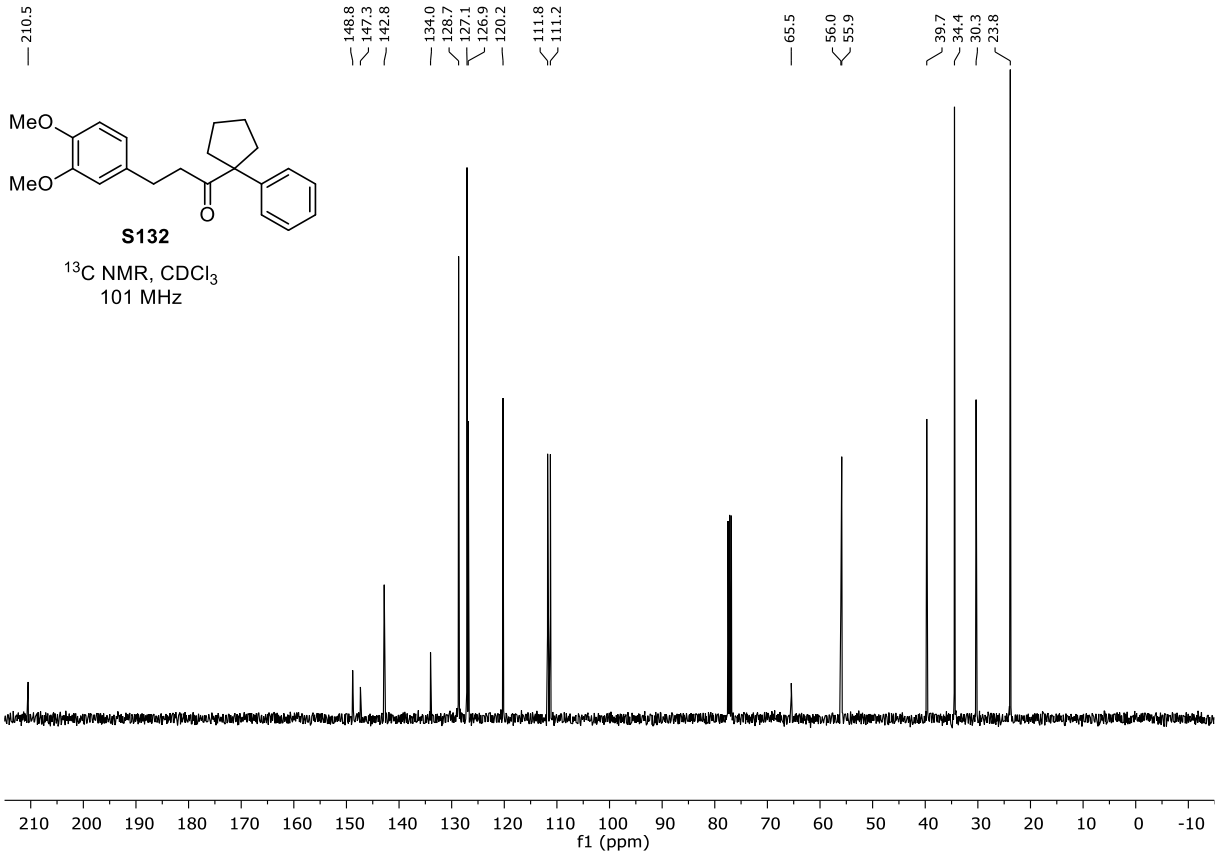
S131

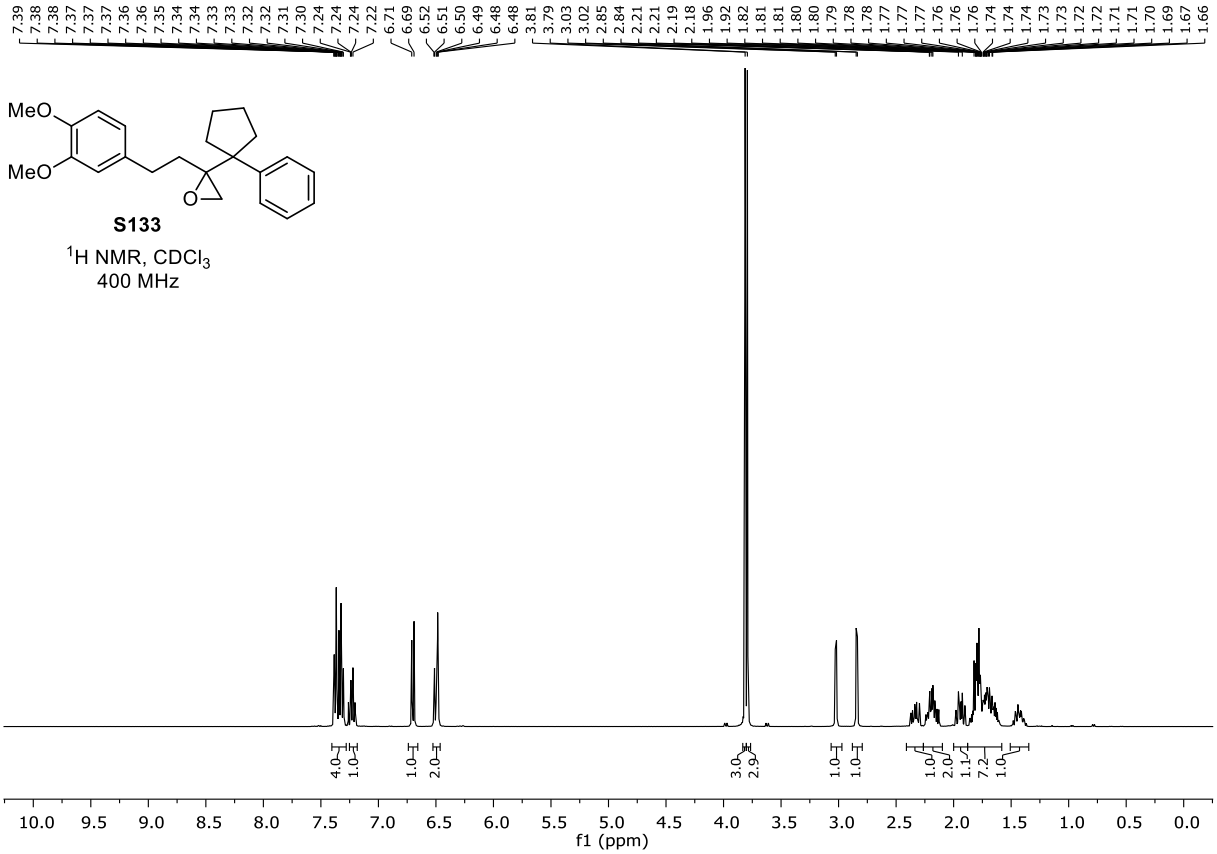
^{13}C NMR, $CDCl_3$
101 MHz

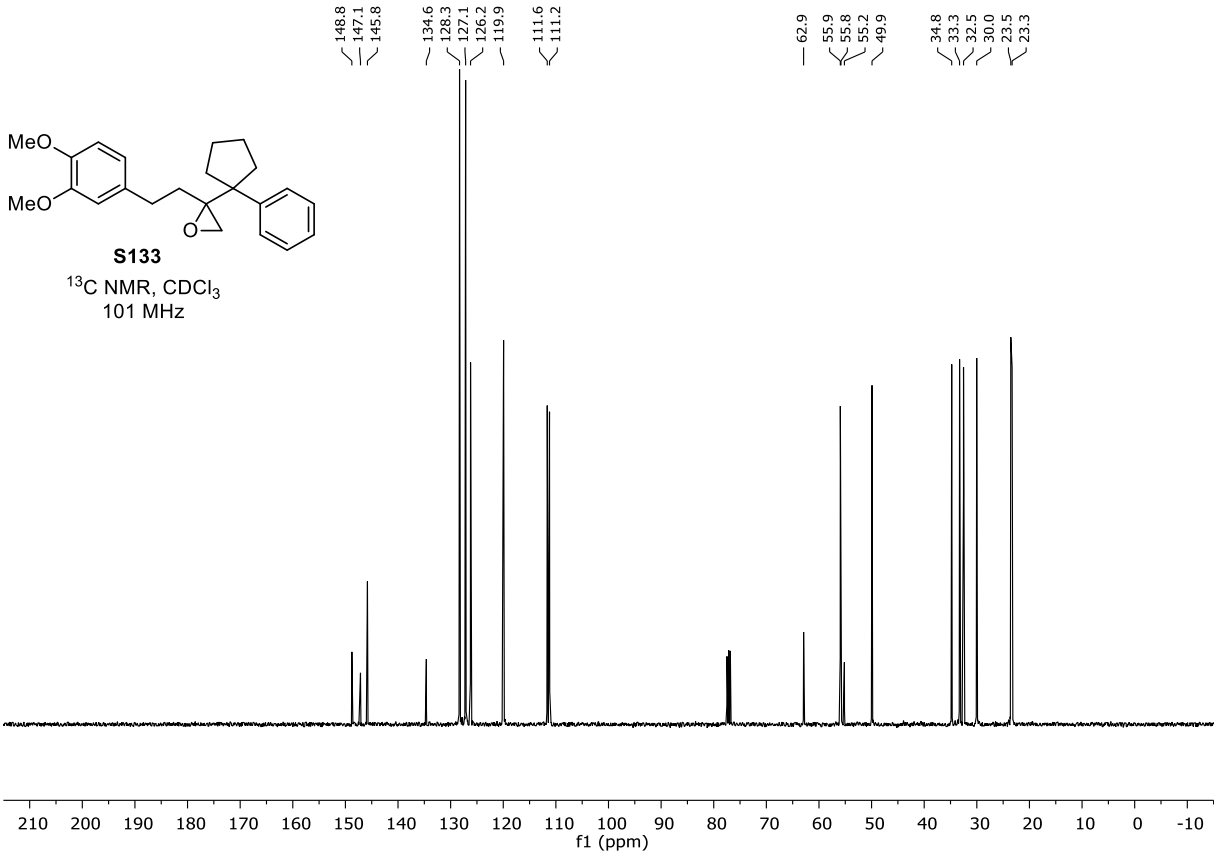

MeO
MeO
O
17d
1H NMR, CDCl3
400 MHz
f1 (ppm)

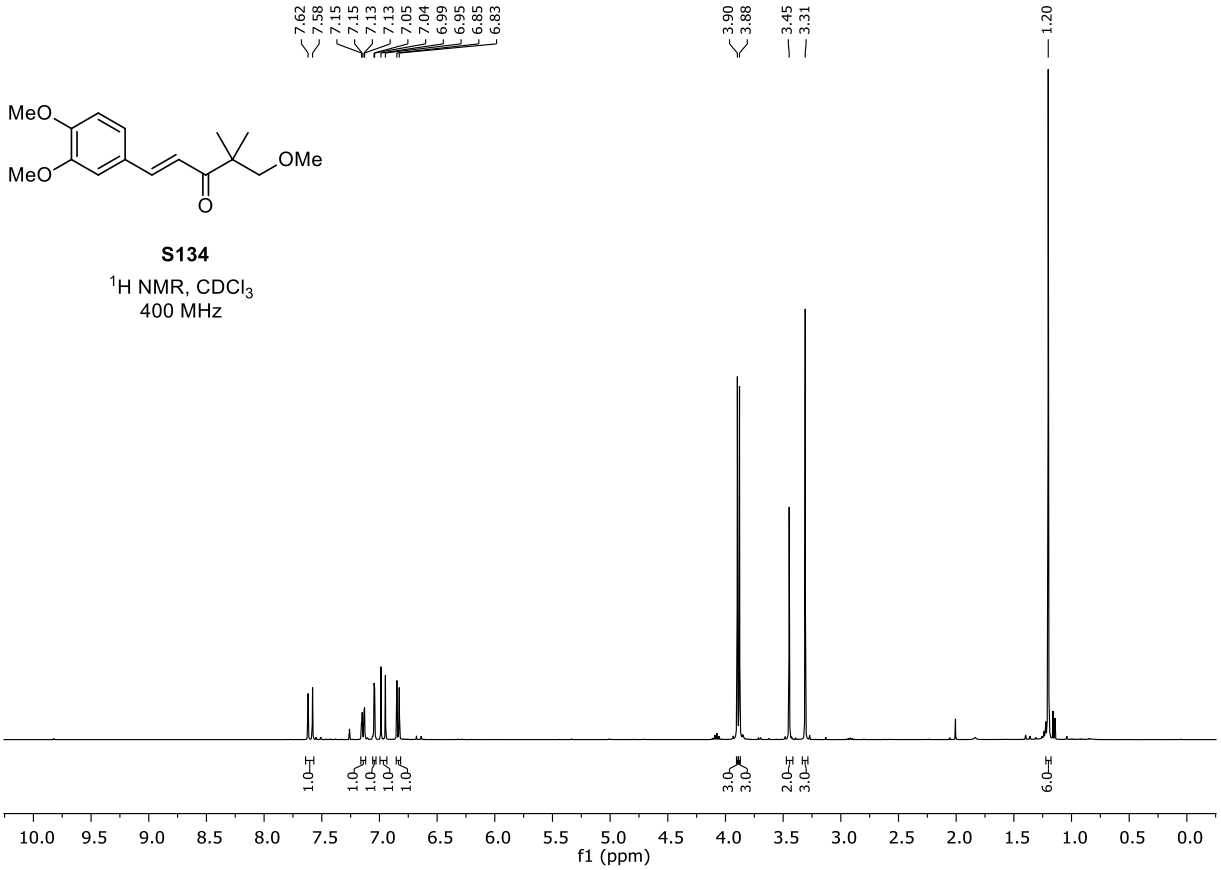

MeO
MeO
O
17d
13C NMR, CDCl3
101 MHz
f1 (ppm)


MeO
MeO
O
S132
^{1}H NMR, $CDCl_3$
400 MHz
f1 (ppm)


MeO
MeO
O
S132
^{13}C NMR, $CDCl_3$
101 MHz
f1 (ppm)

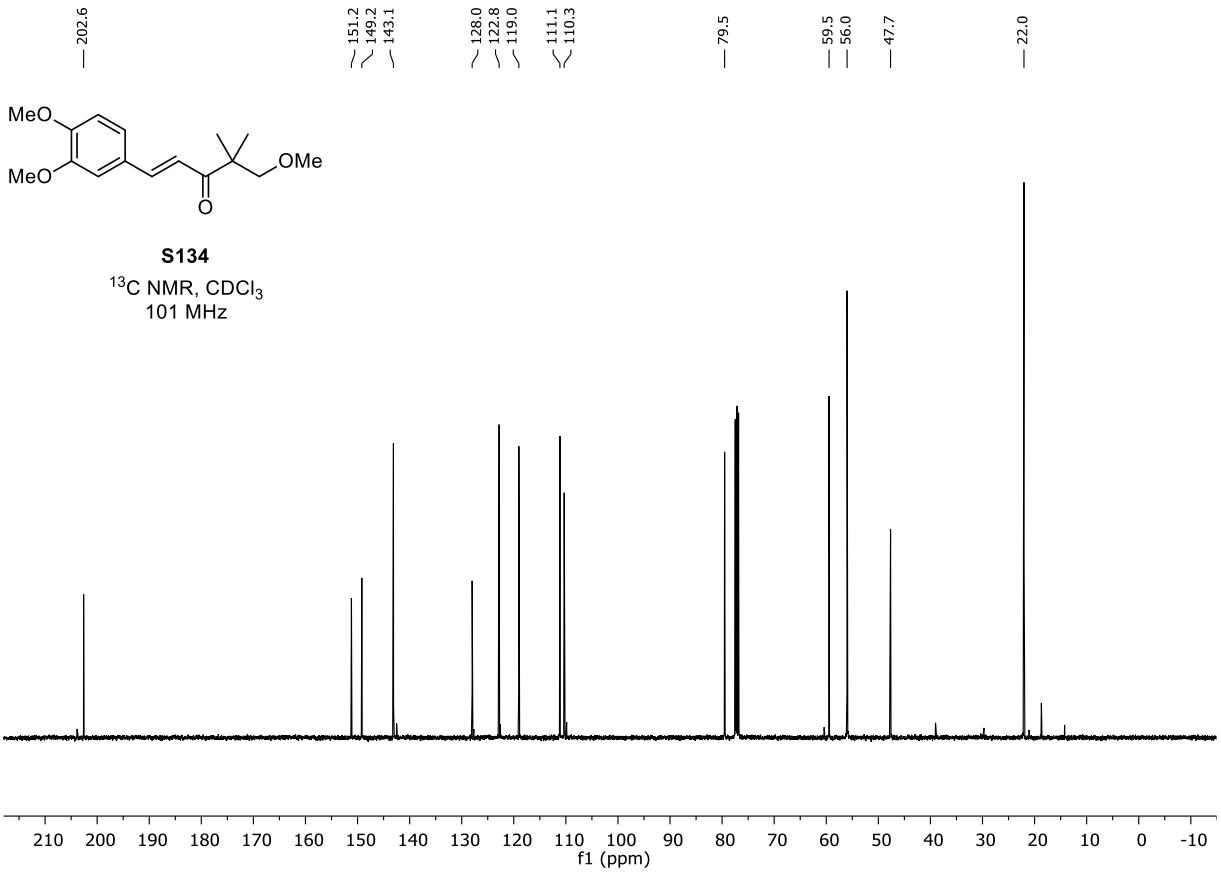

MeO
MeO
O
S133
1H NMR, CDCl3
400 MHz
f1 (ppm)


MeO
MeO
O
S133
13C NMR, CDCl3
101 MHz
f1 (ppm)



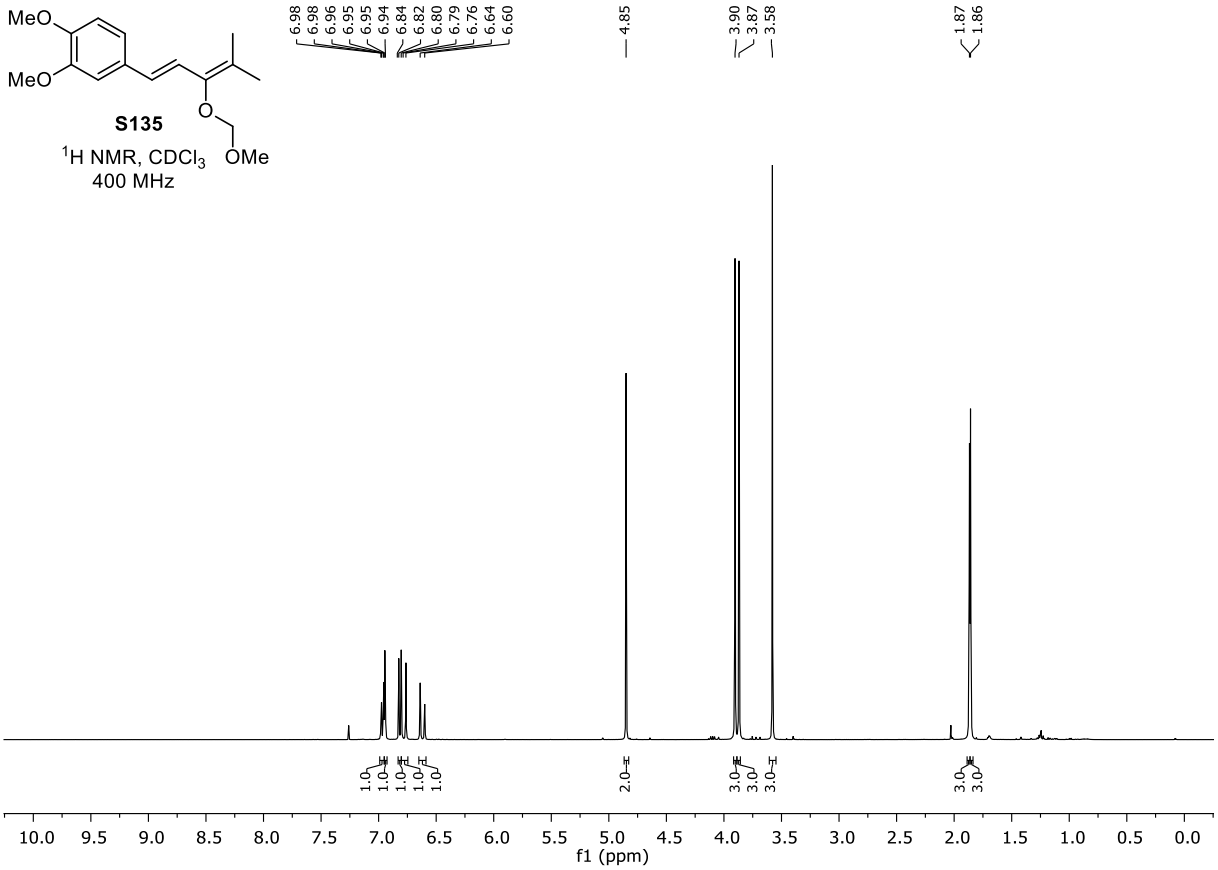
S134

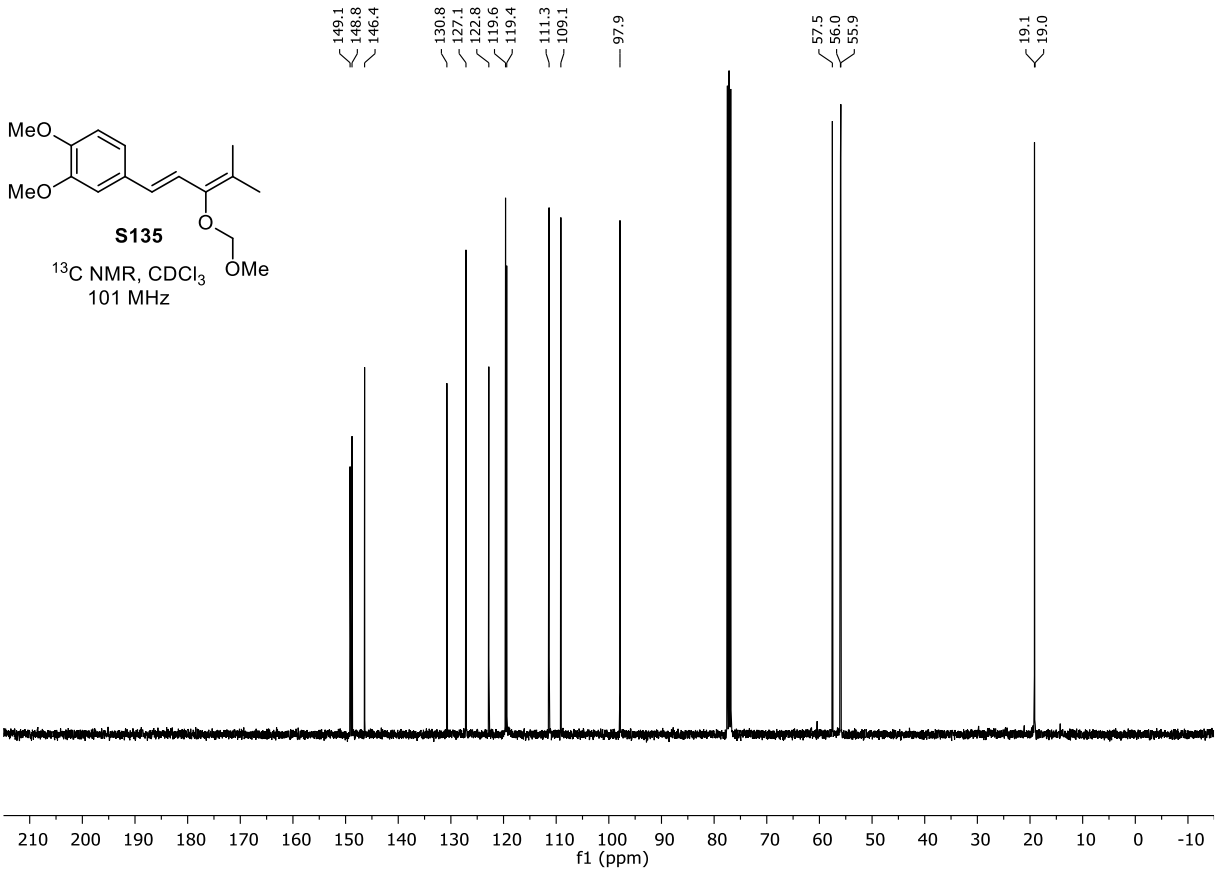
^{1}H NMR, $CDCl_3$
400 MHz

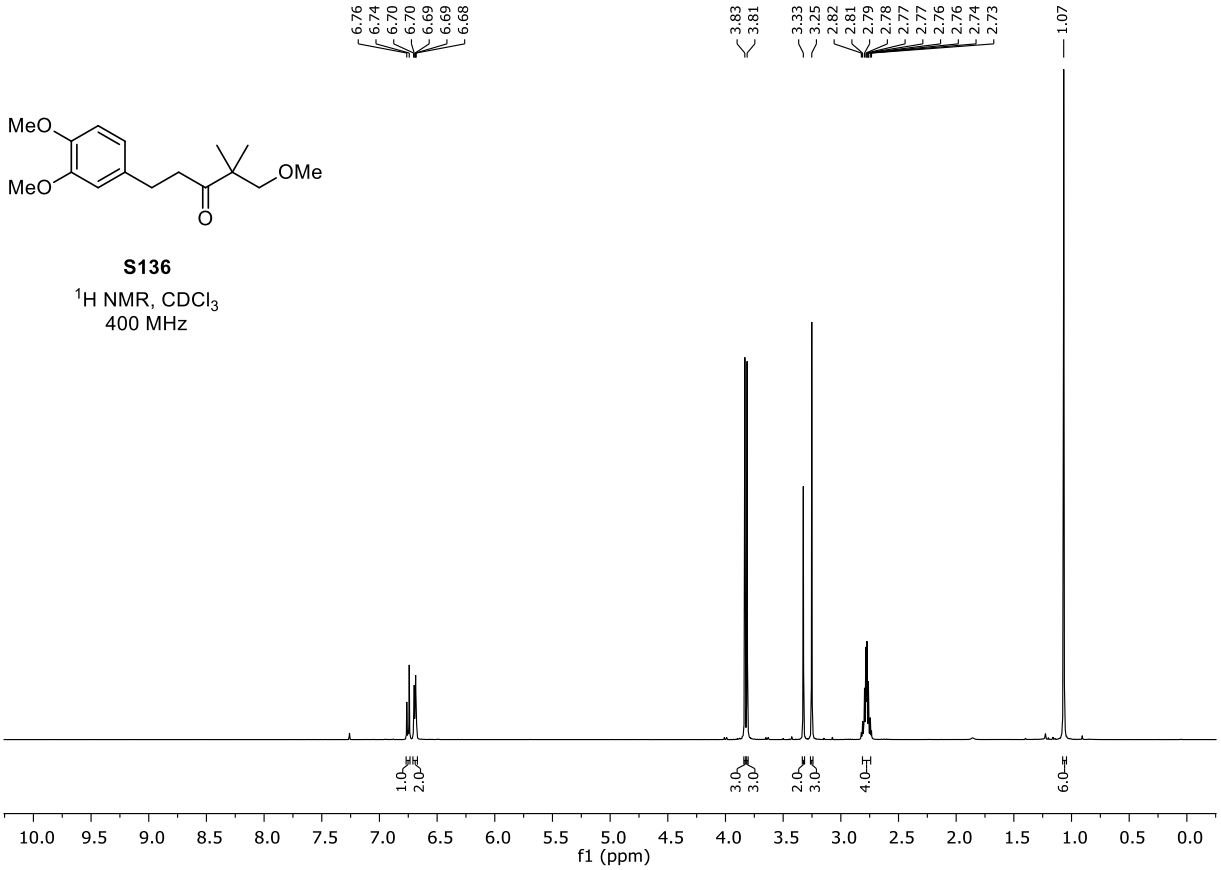


S134

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

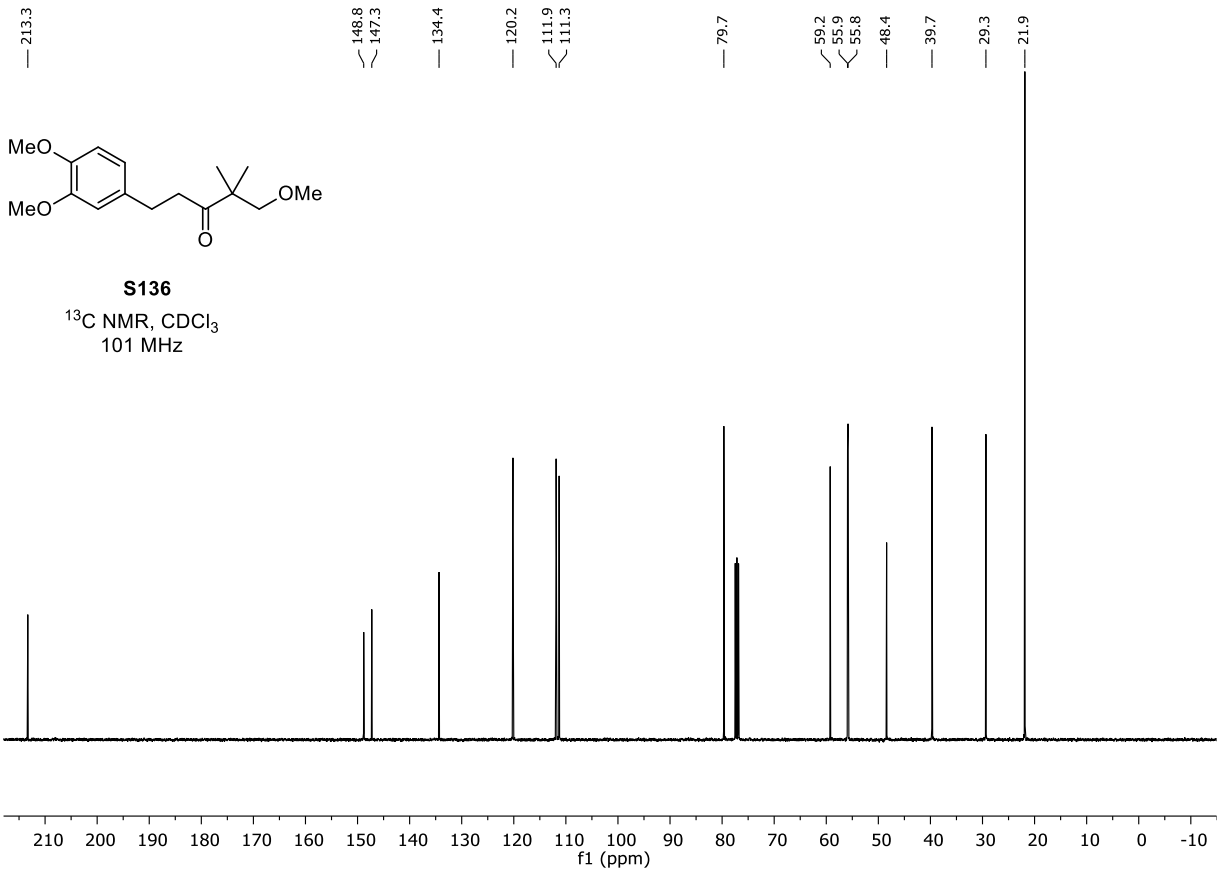

MeO
MeO
O
OMe
S135
^{1}H NMR, $CDCl_3$
400 MHz
6.98
6.98
6.96
6.95
6.95
6.94
6.84
6.82
6.80
6.79
6.76
6.64
6.60
4.85
3.90
3.87
3.58
1.87
1.86
1.0
1.0
1.0
1.0
2.0
3.0
3.0
3.0
3.0
3.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


MeO
MeO
O
OMe
S135
^{13}C NMR, $CDCl_3$
101 MHz
149.1
148.8
146.4
130.8
127.1
122.8
119.6
119.4
111.3
109.1
97.9
57.5
56.0
55.9
19.1
19.0
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)



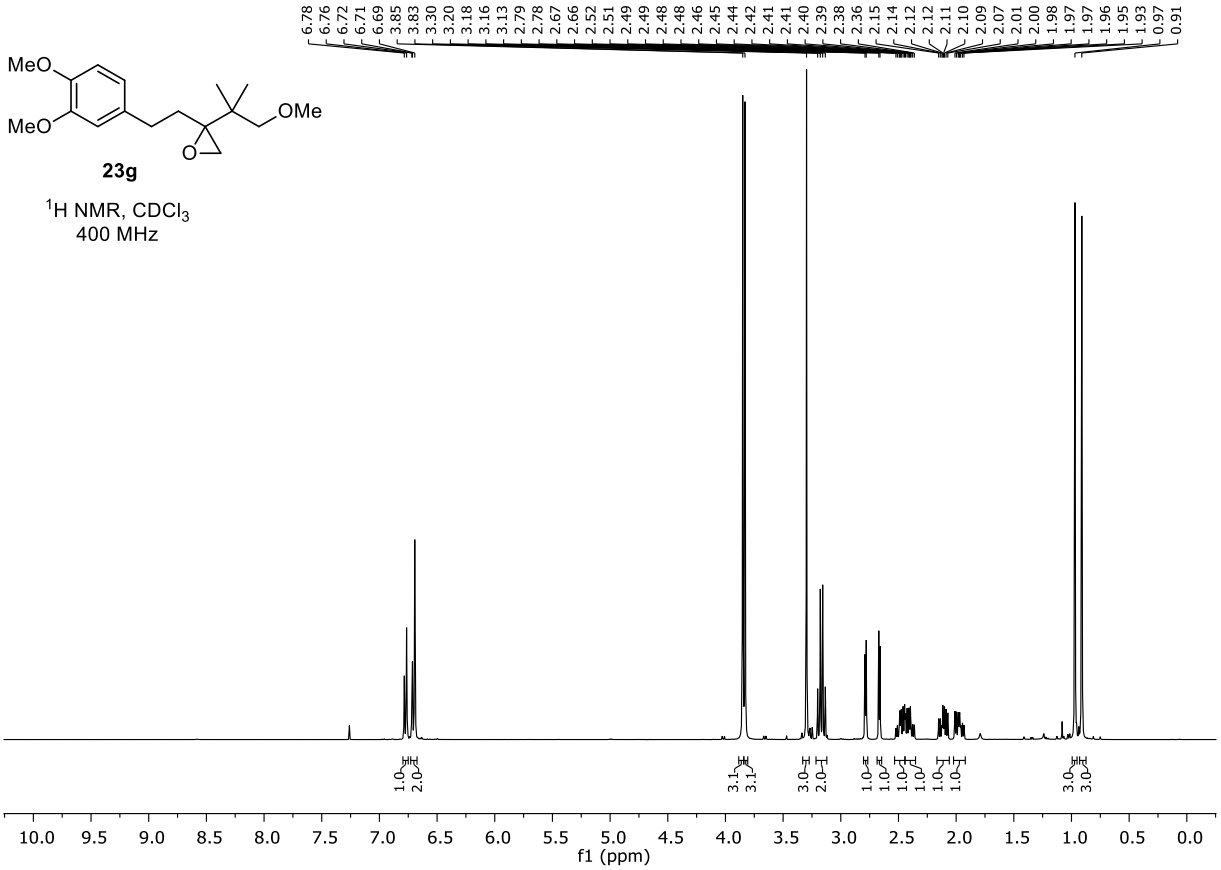
S136

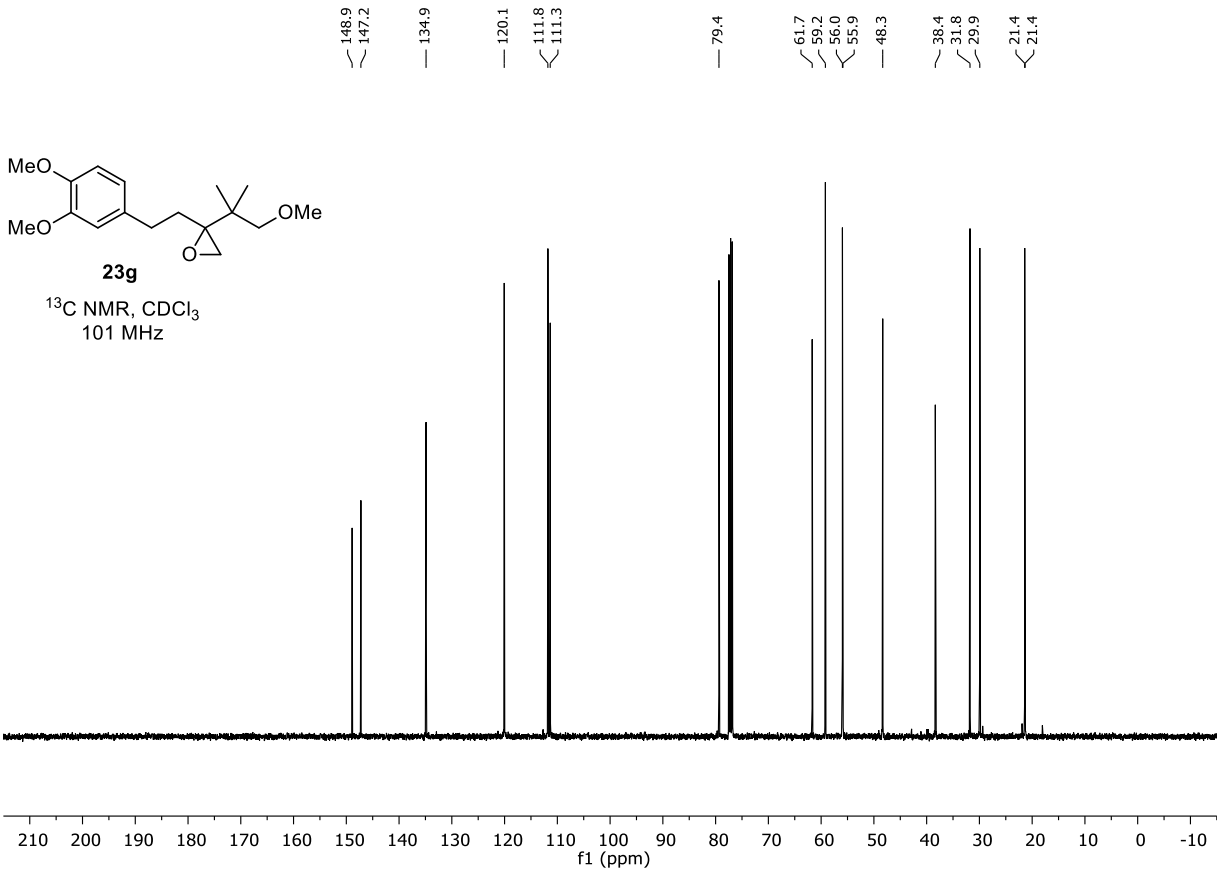
^{1}H NMR, $CDCl_3$
400 MHz

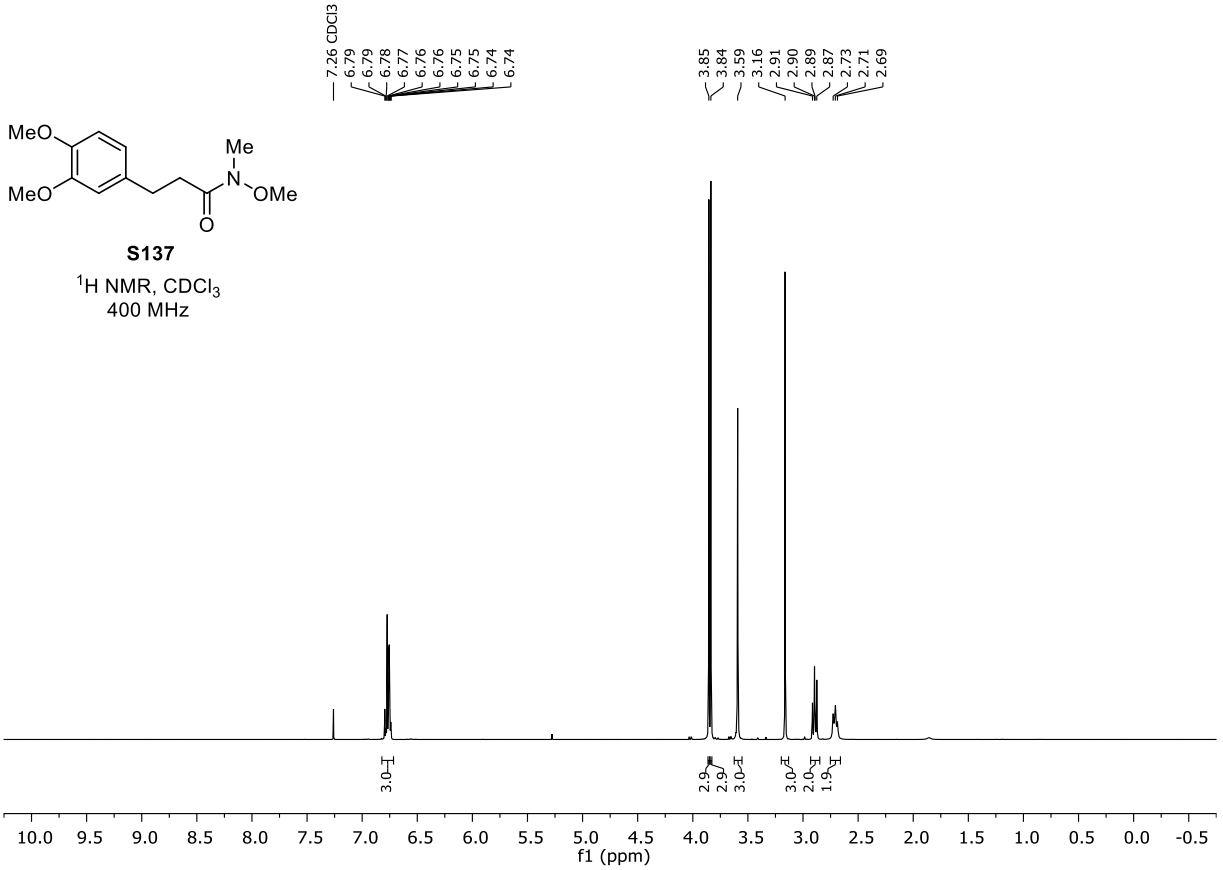


S136

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

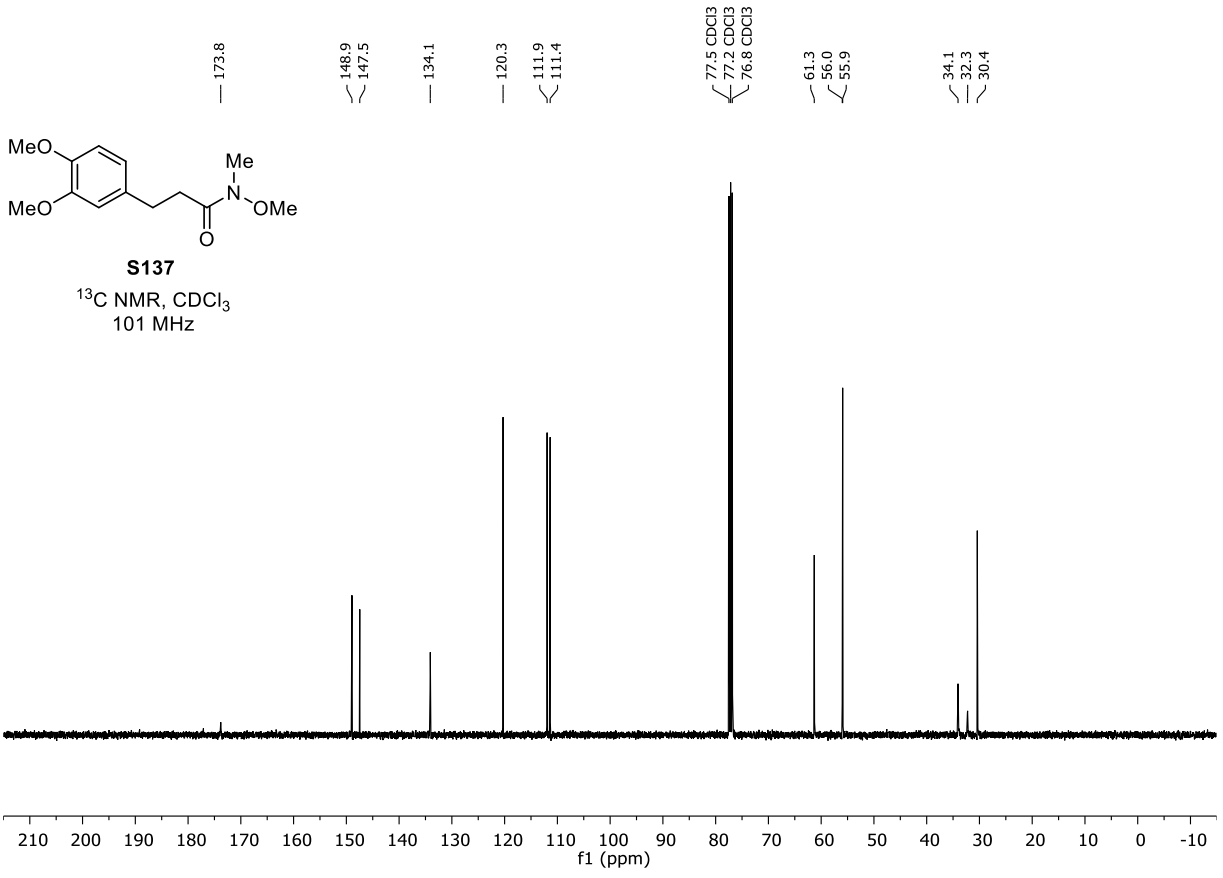

MeO
MeO
OMe
O
23g
^{1}H NMR, CDCl$_3$
400 MHz
f1 (ppm)


MeO
MeO
OMe
O
23g
^{13}C NMR, CDCl$_3$
101 MHz
f1 (ppm)



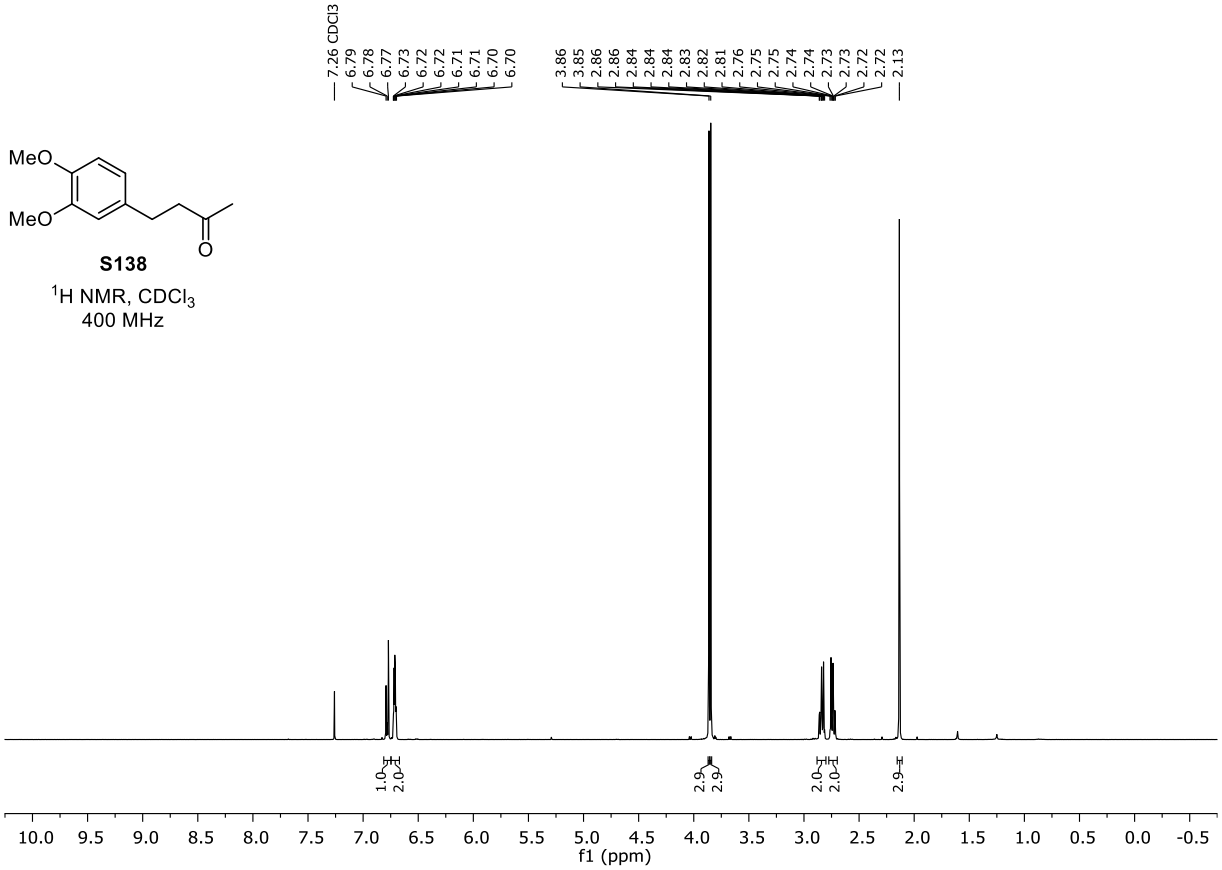
S137

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



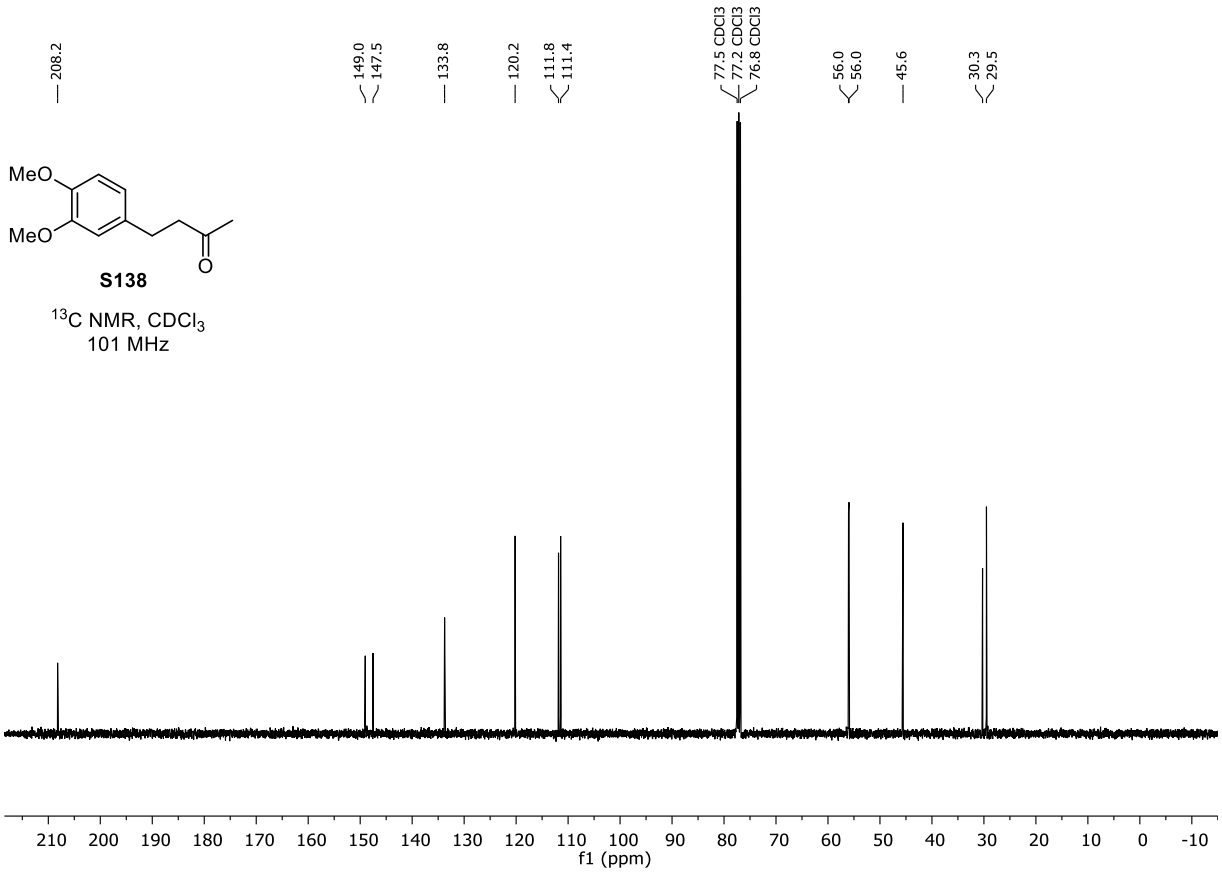
S137

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



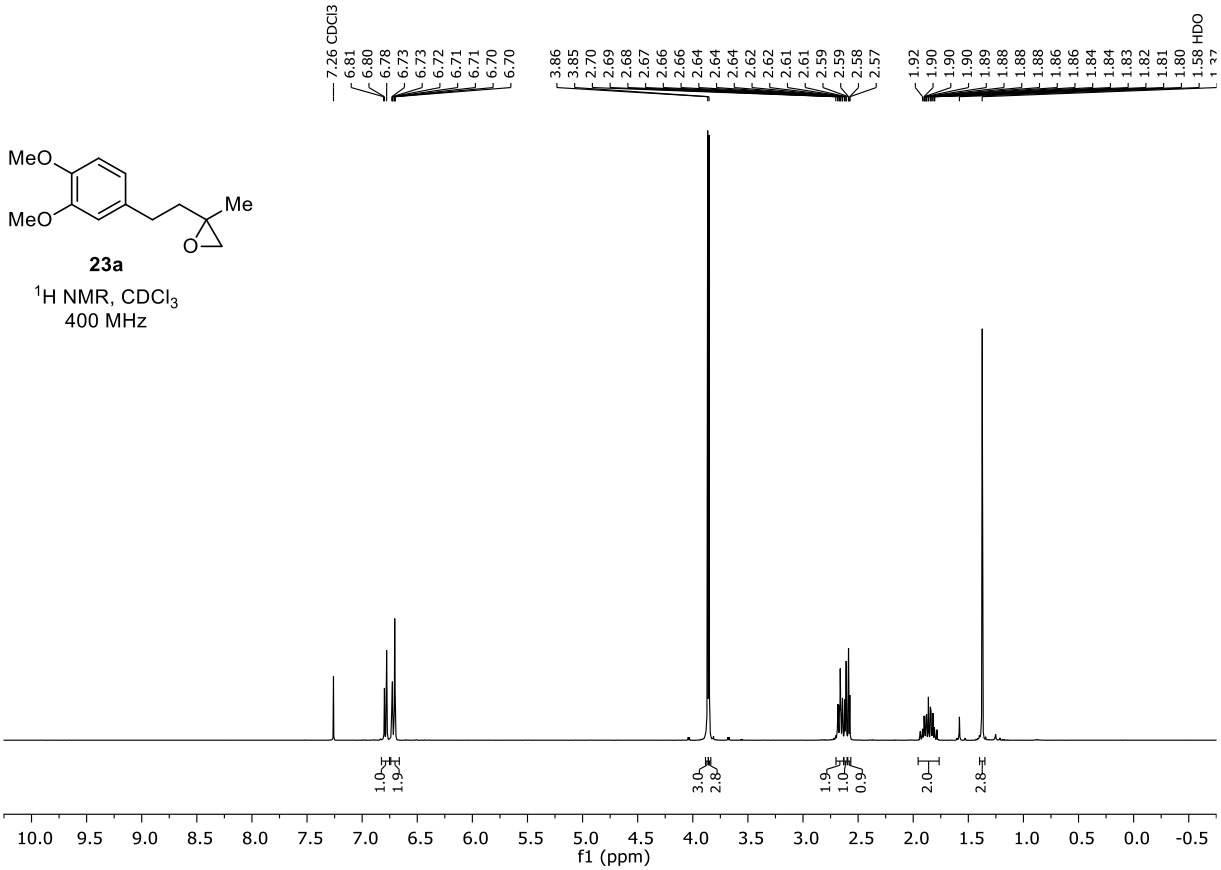
S138

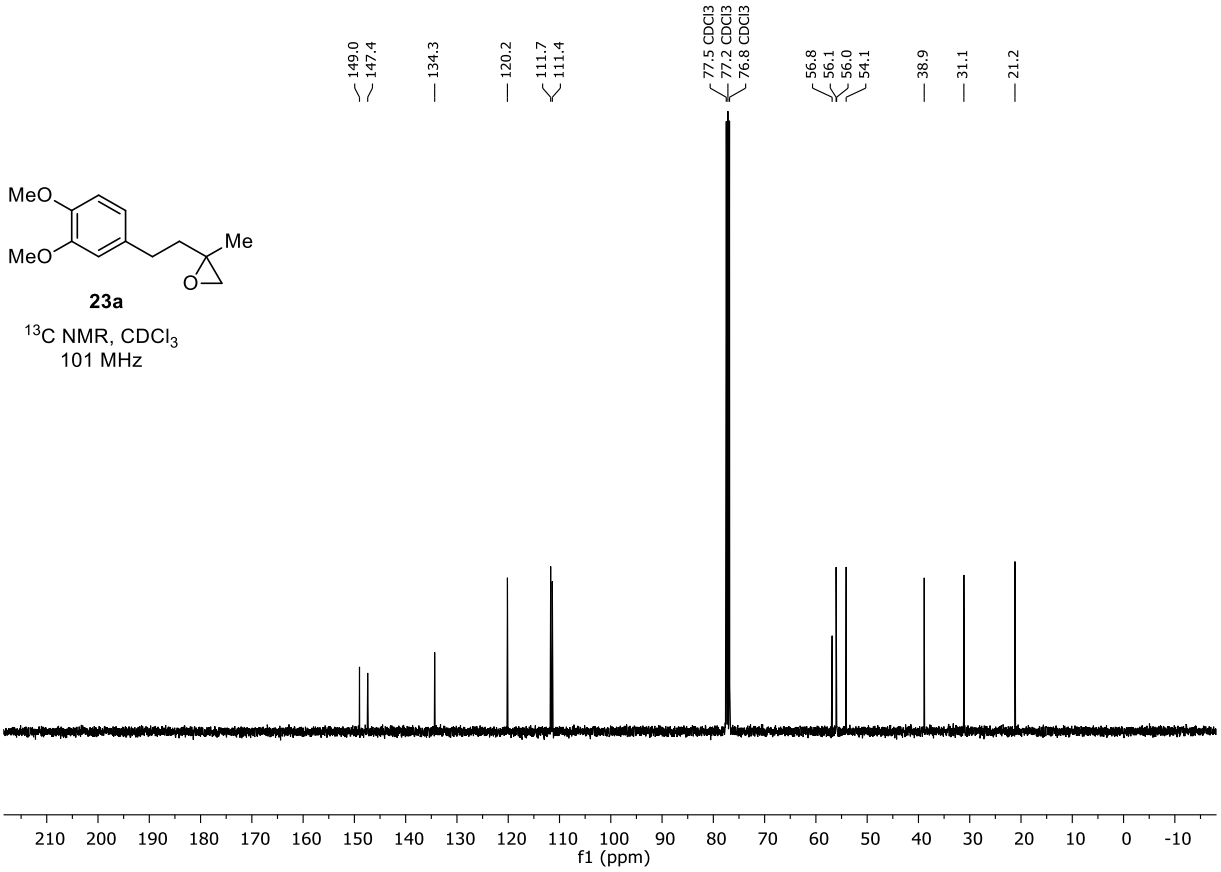
^{1}H NMR, $CDCl_3$
400 MHz

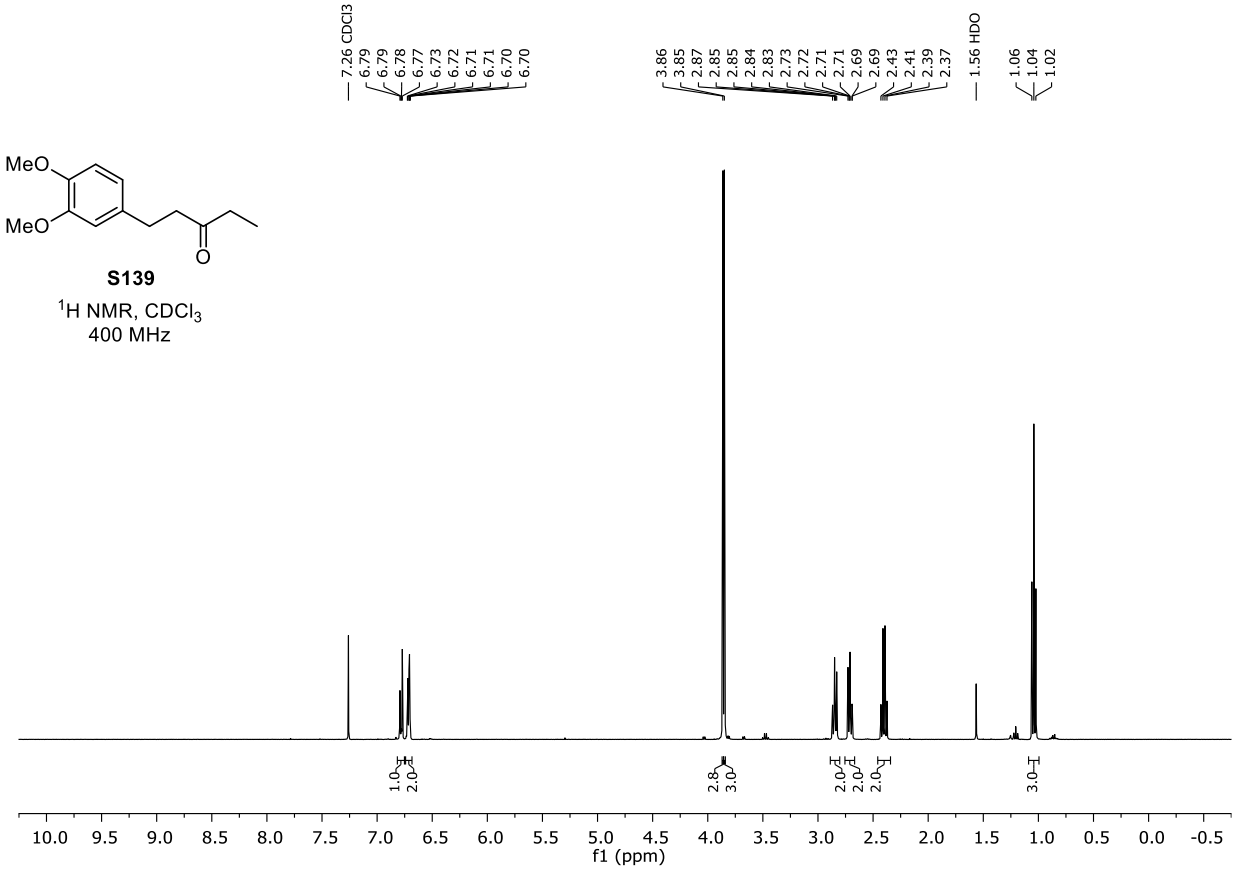


S138

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

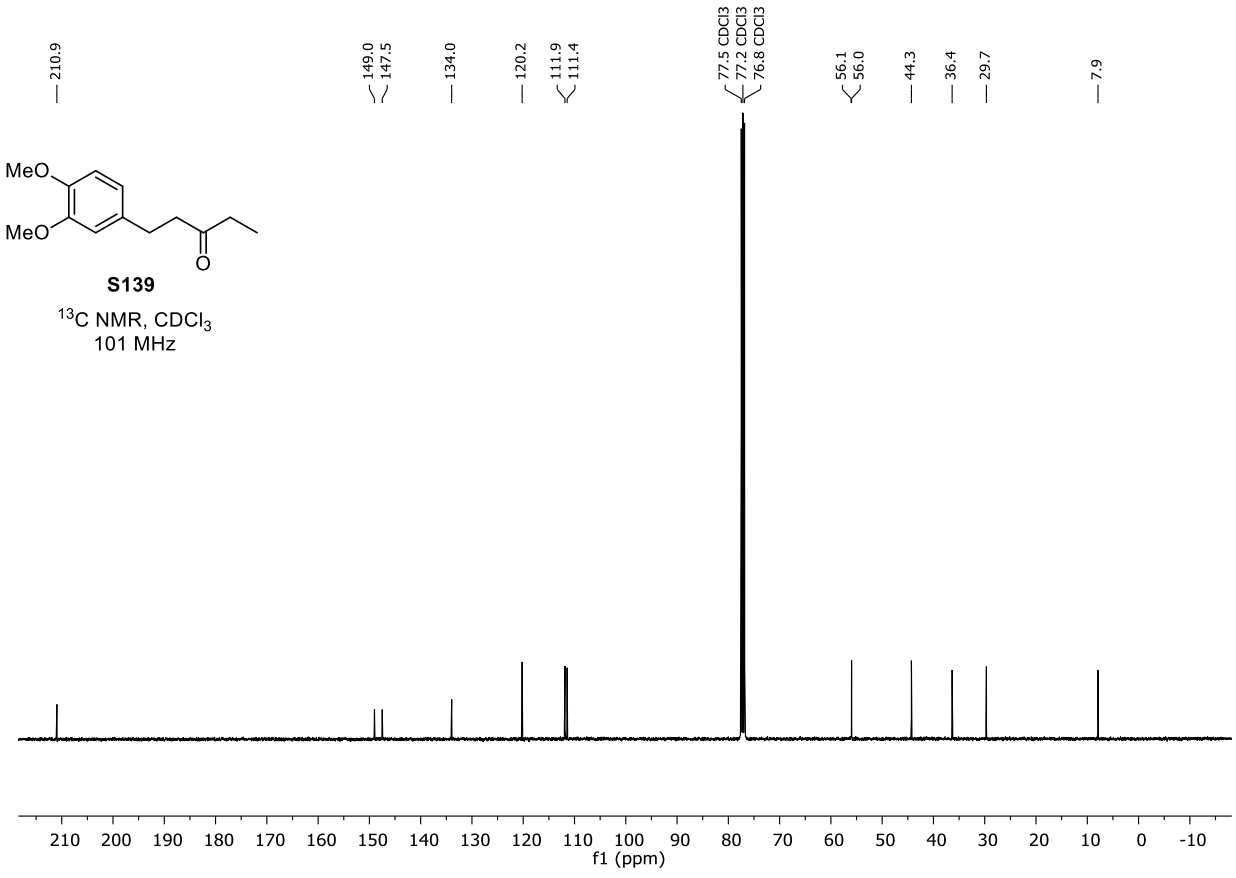

7.26 CDCl3
6.81
6.80
6.78
6.73
6.73
6.72
6.71
6.71
6.70
6.70
3.86
3.85
2.70
2.69
2.68
2.67
2.66
2.66
2.64
2.64
2.64
2.62
2.62
2.61
2.61
2.59
2.59
2.58
2.57
1.92
1.90
1.90
1.90
1.89
1.88
1.88
1.88
1.86
1.86
1.84
1.84
1.83
1.82
1.81
1.80
1.58 HDO
MeO
MeO
Me
O
23a
1H NMR, CDCl3
400 MHz
1.0
1.9
3.0
2.8
1.9
1.0
0.9
2.0
2.8
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 -0.5
f1 (ppm)


149.0
147.4
134.3
120.2
111.7
111.4
77.5 CDCl3
77.2 CDCl3
76.8 CDCl3
56.8
56.1
56.0
54.1
38.9
31.1
21.2
MeO
MeO
Me
O
23a
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)



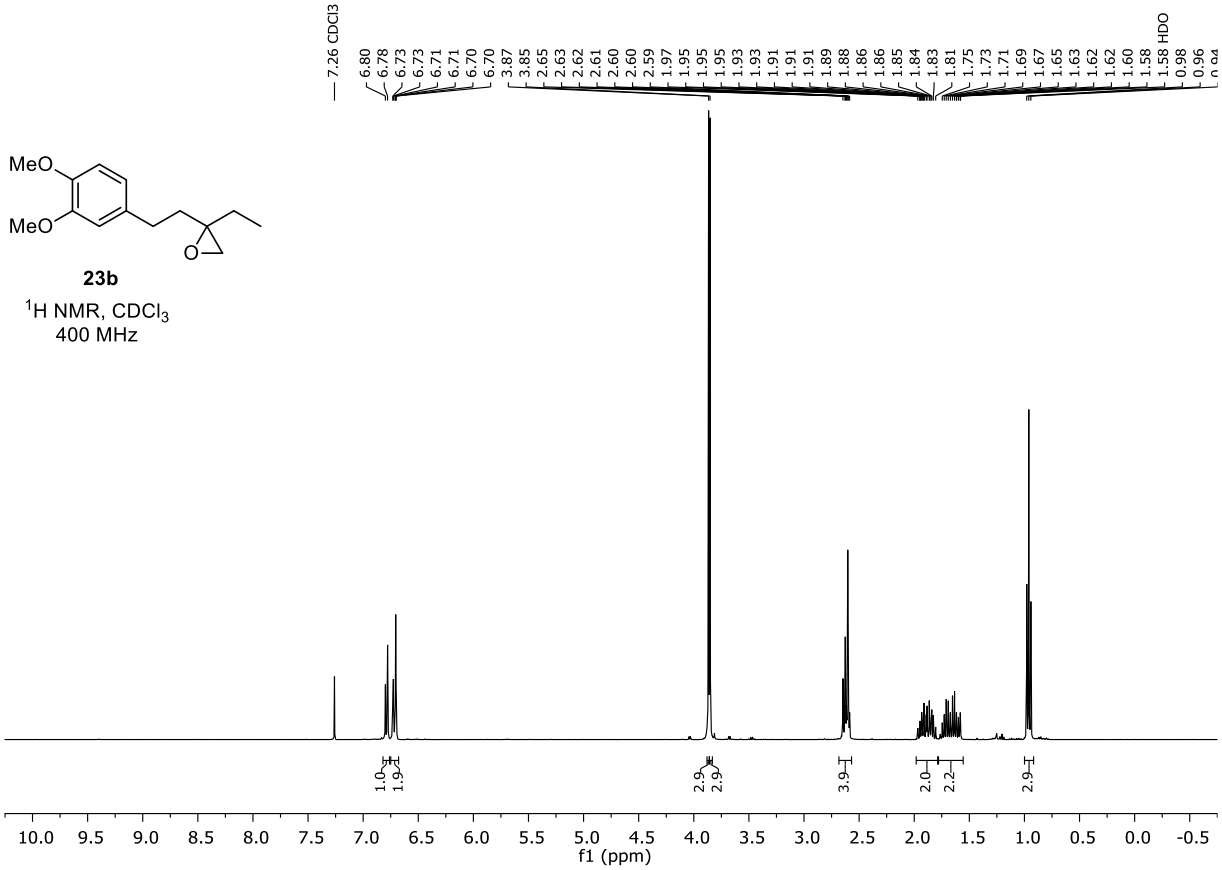
S139

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



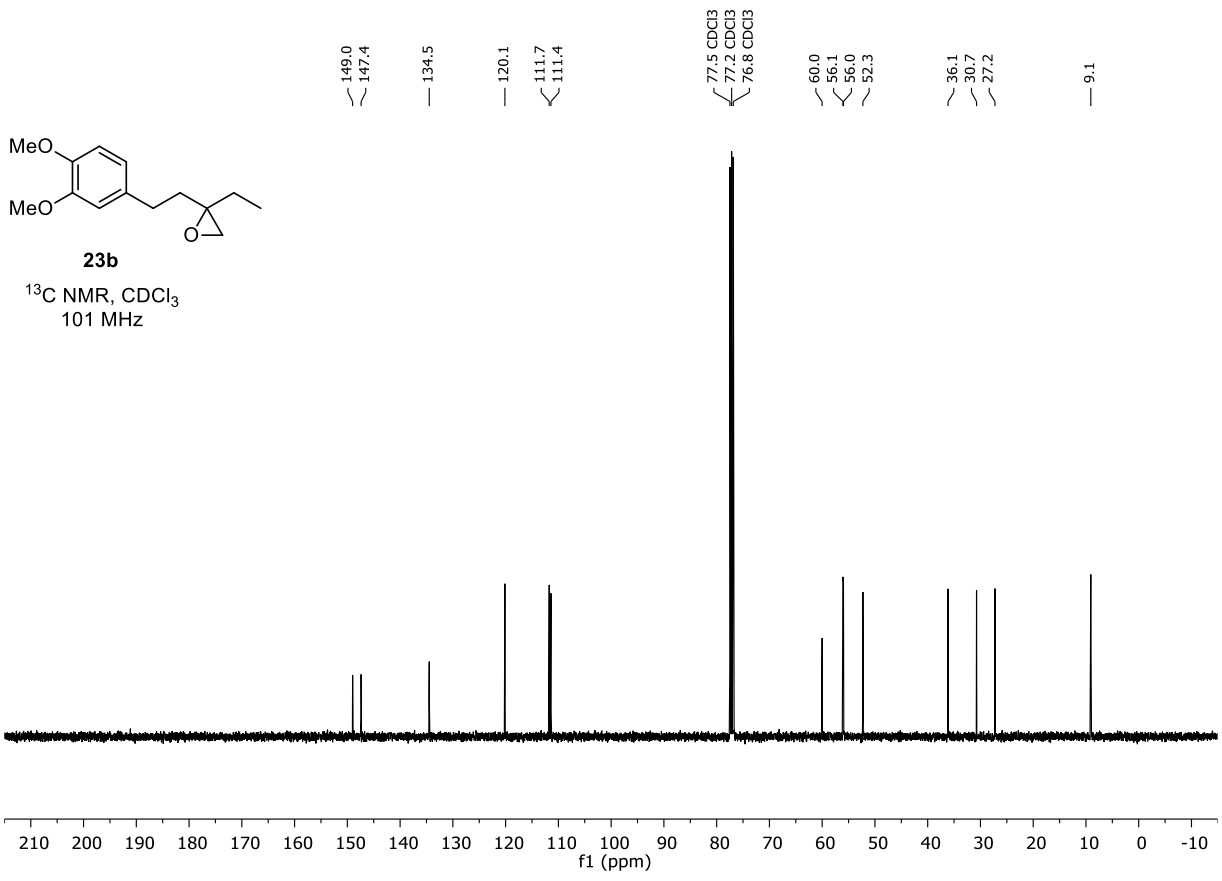
S139

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



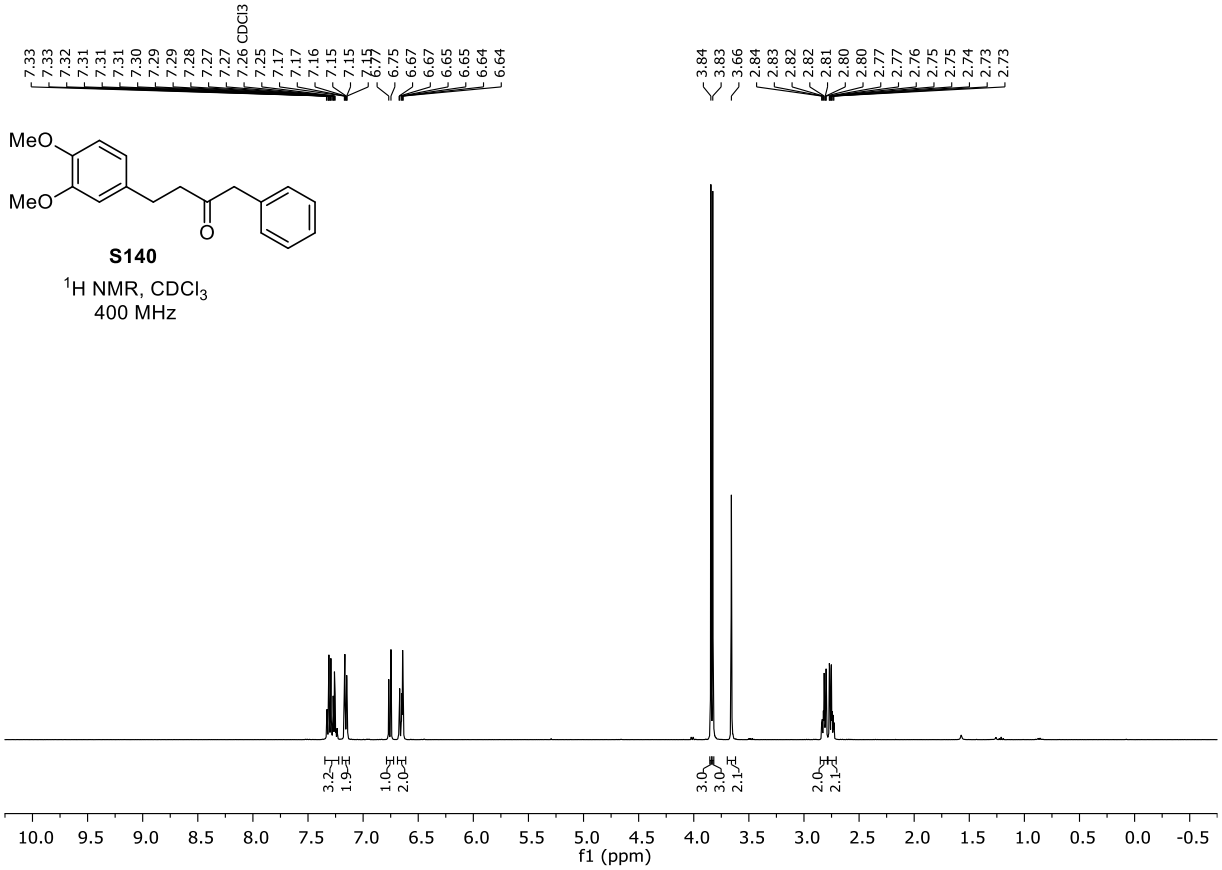
23b

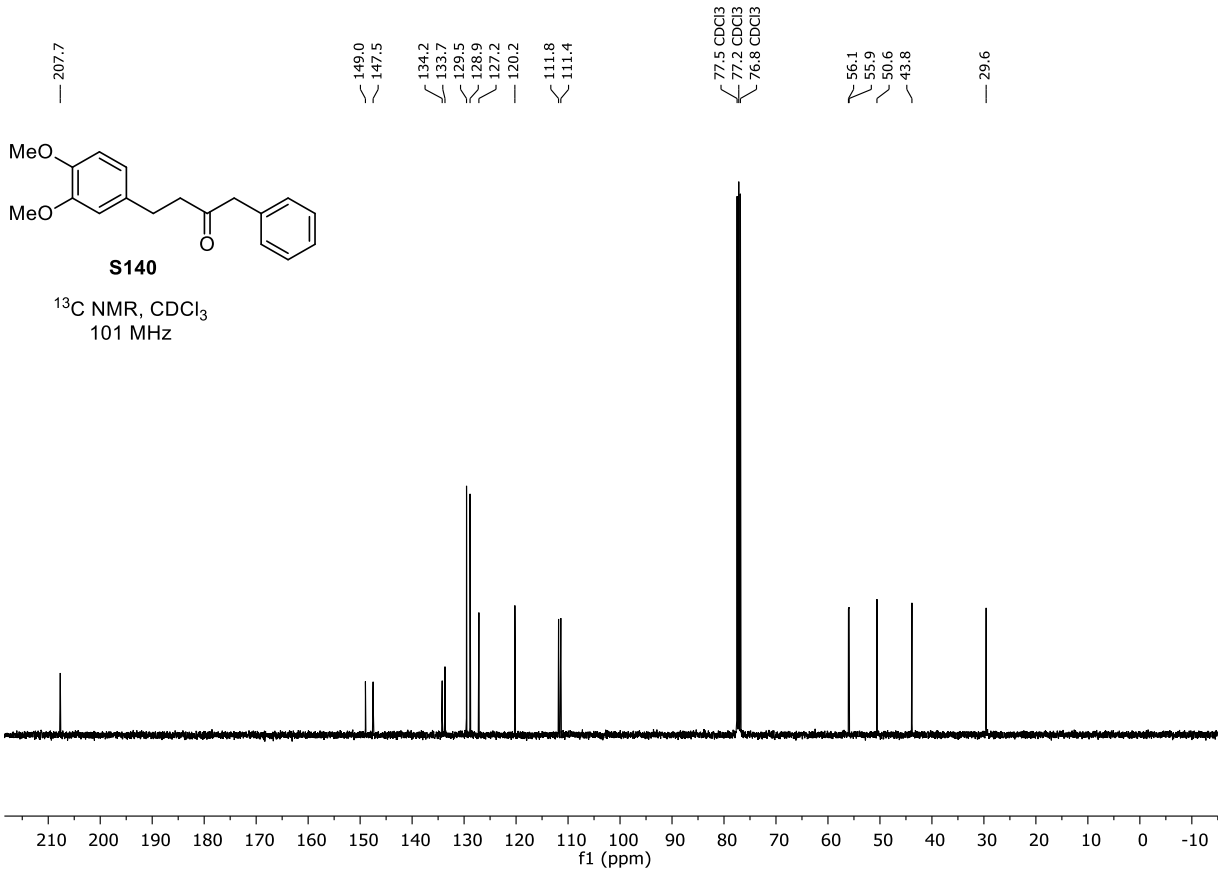
^{1}H NMR, $CDCl_3$
400 MHz

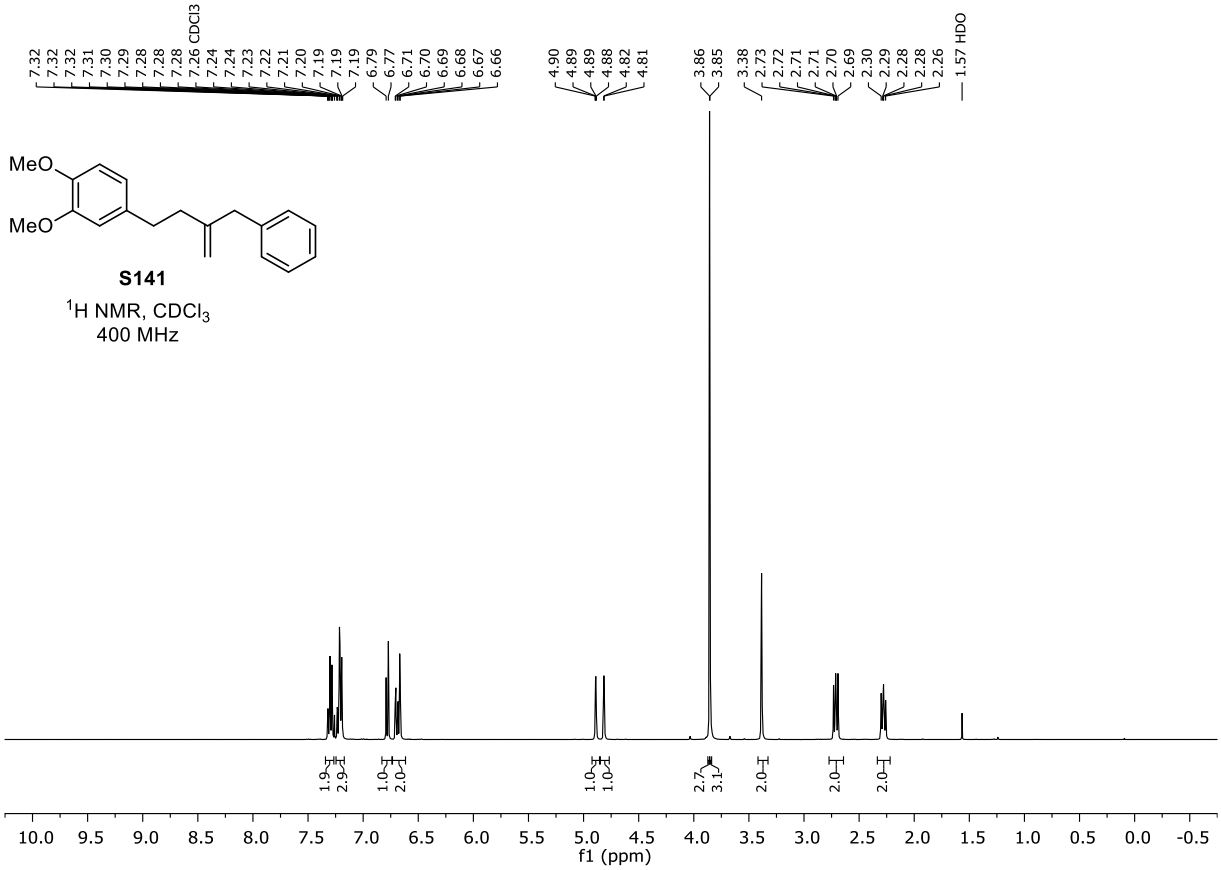


23b

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

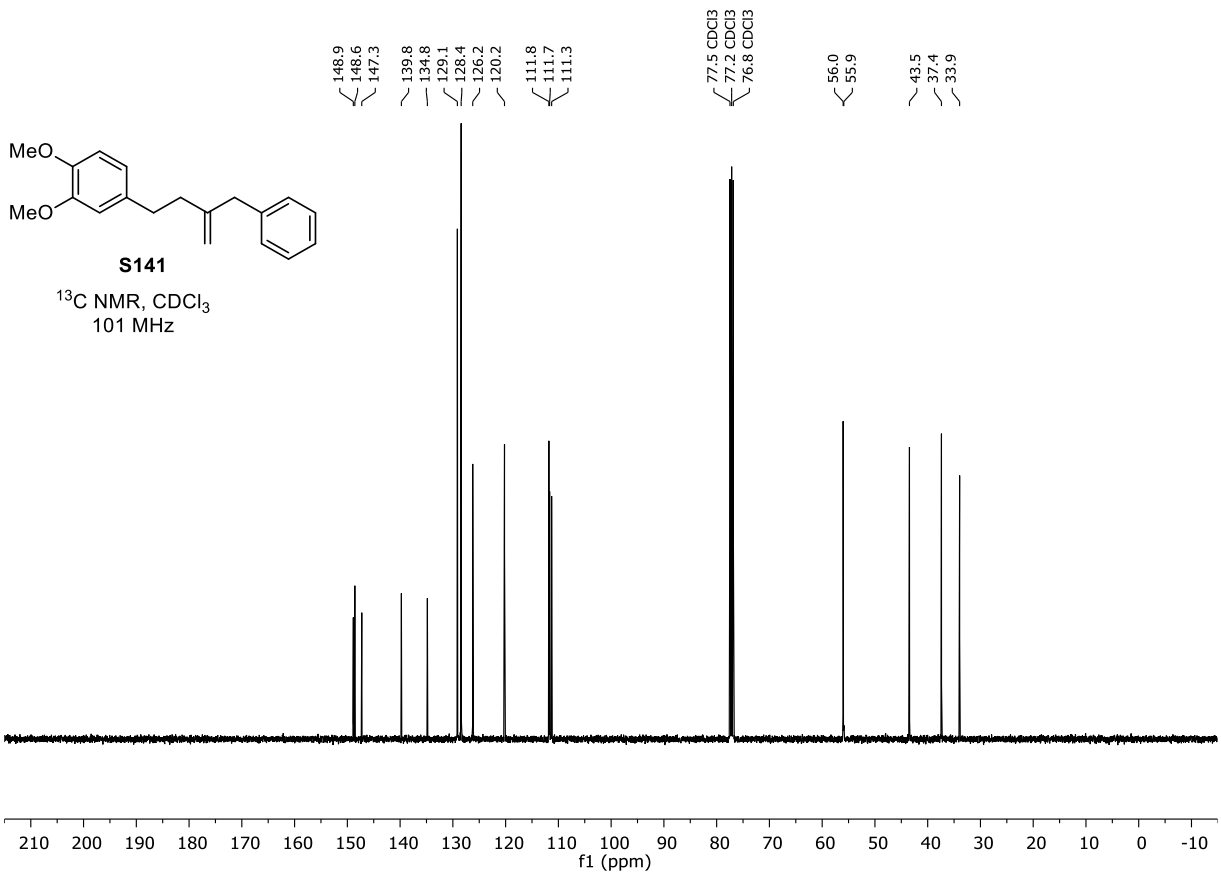

MeO
MeO
O
S140
1H NMR, CDCl3
400 MHz
f1 (ppm)


MeO
MeO
O
S140
13C NMR, CDCl3
101 MHz
f1 (ppm)



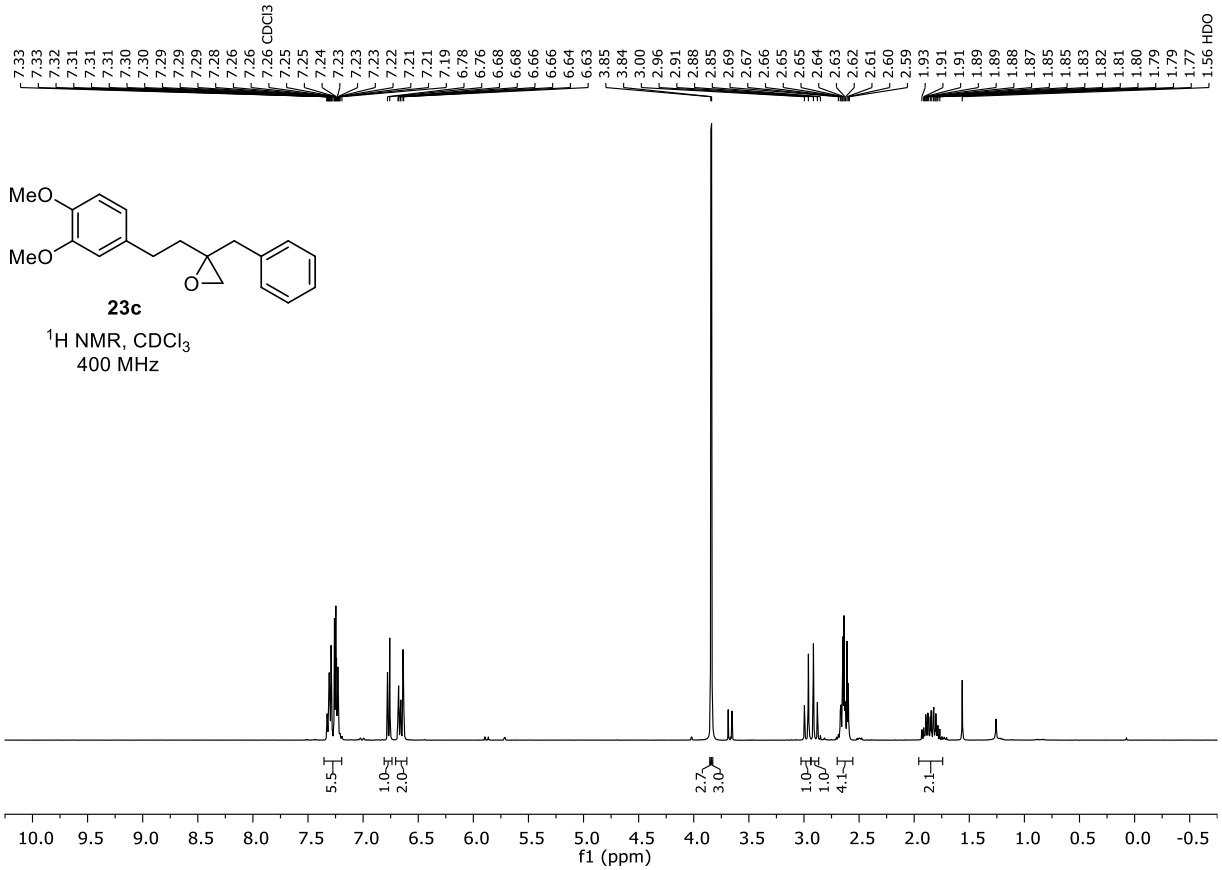
S141

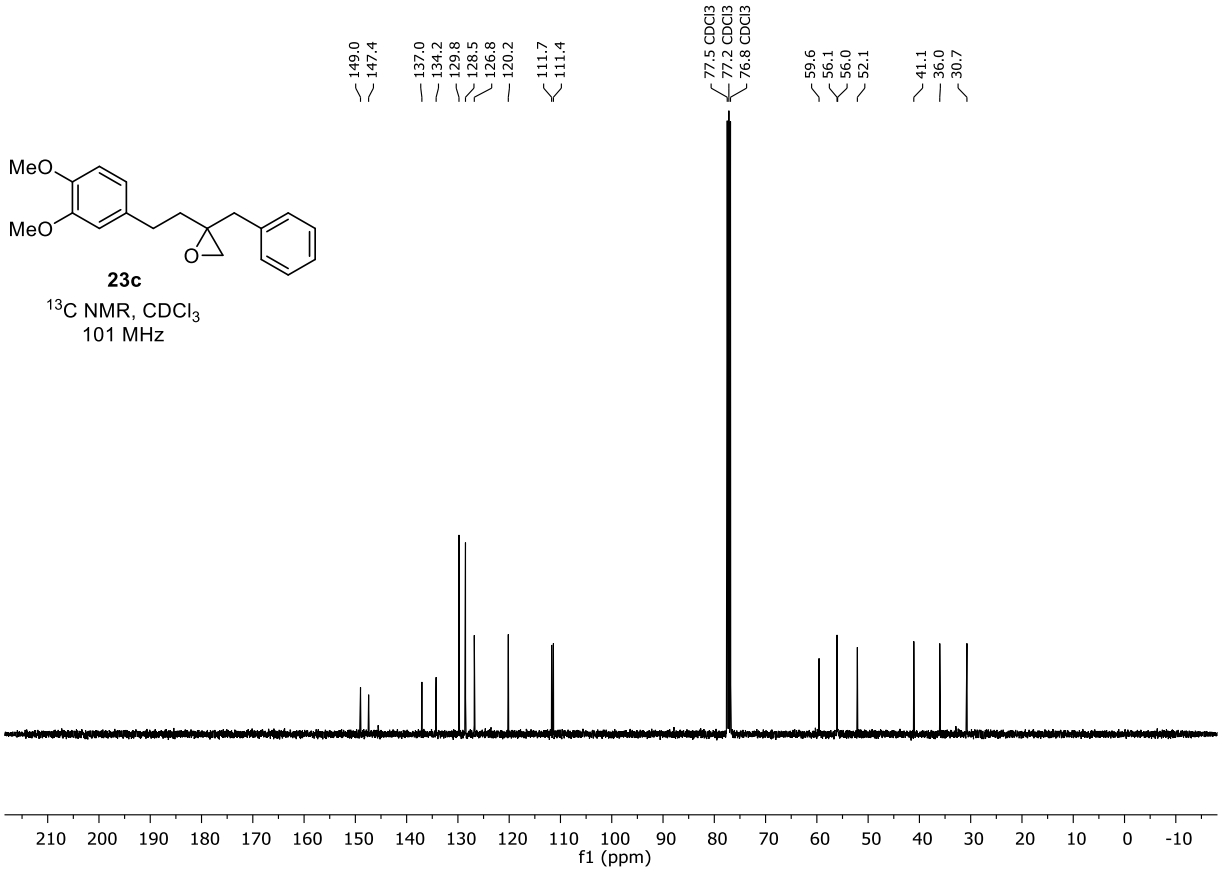
^{1}H NMR, $CDCl_3$
400 MHz

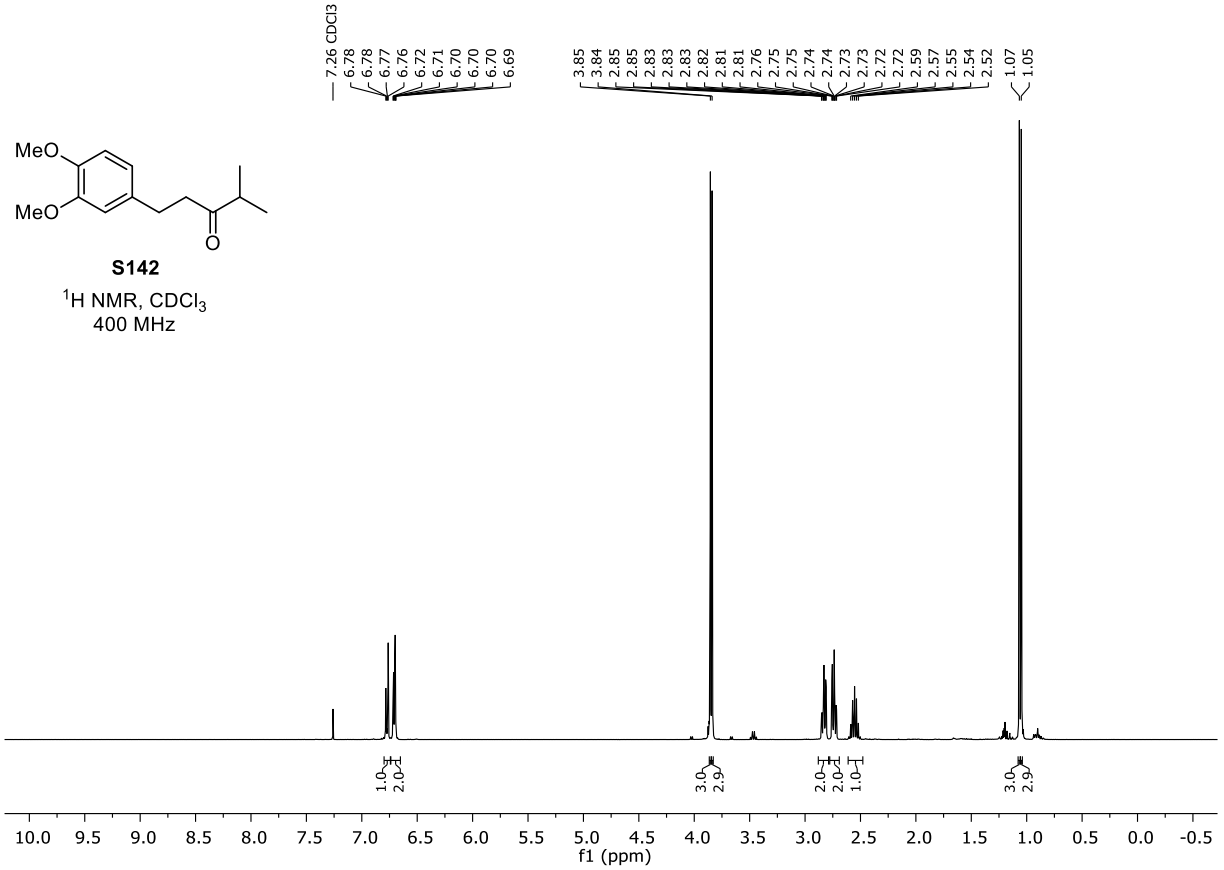


S141

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

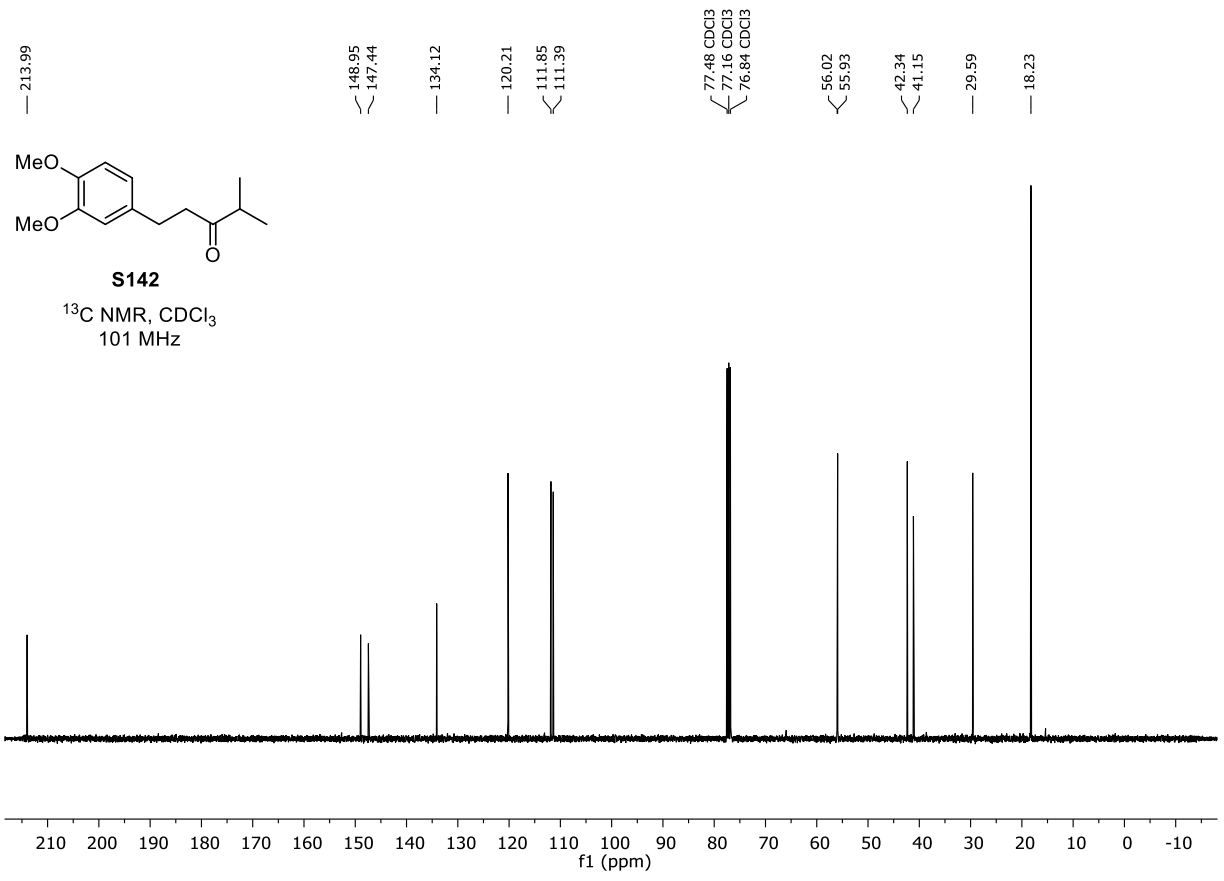

MeO
MeO
O
23c
^{1}H NMR, $CDCl_3$
400 MHz
f1 (ppm)


MeO
MeO
O
23c
^{13}C NMR, $CDCl_3$
101 MHz
f1 (ppm)



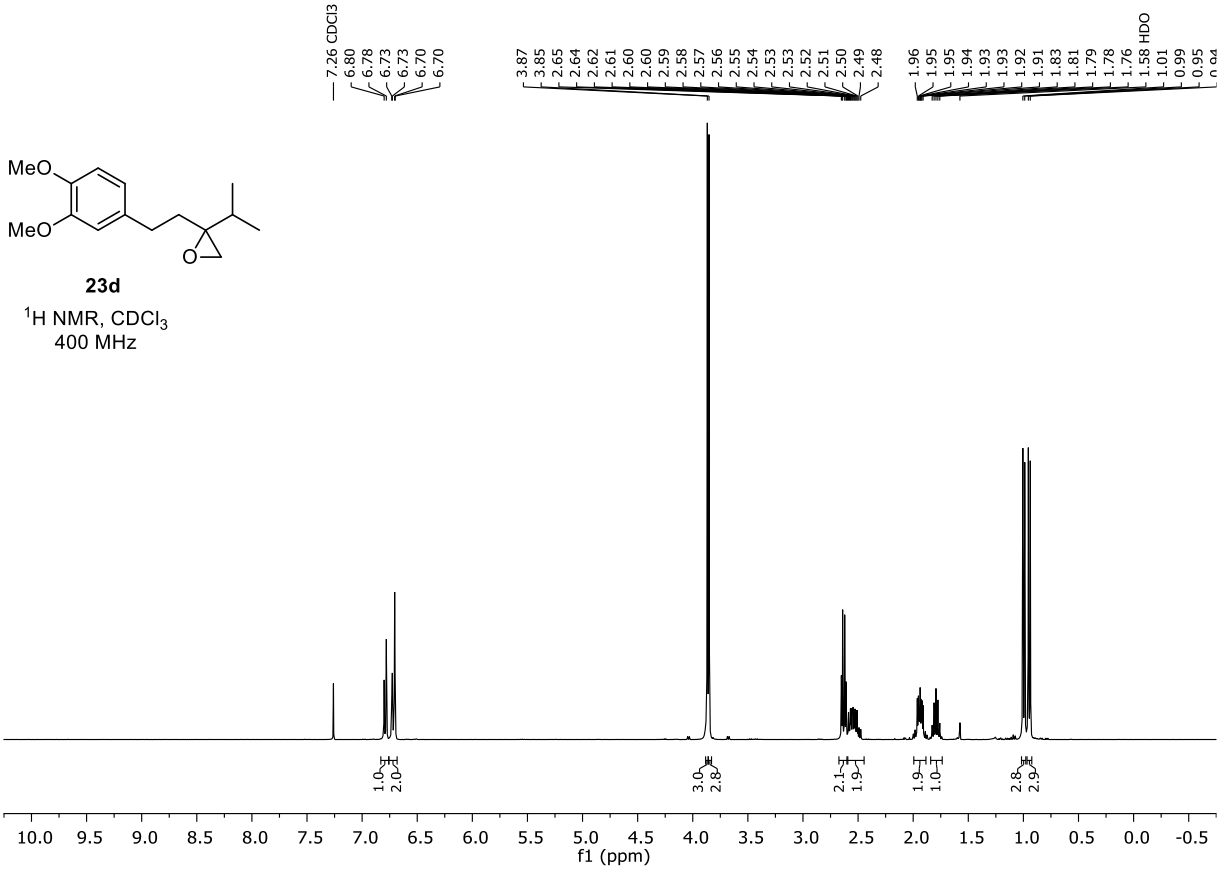
S142

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



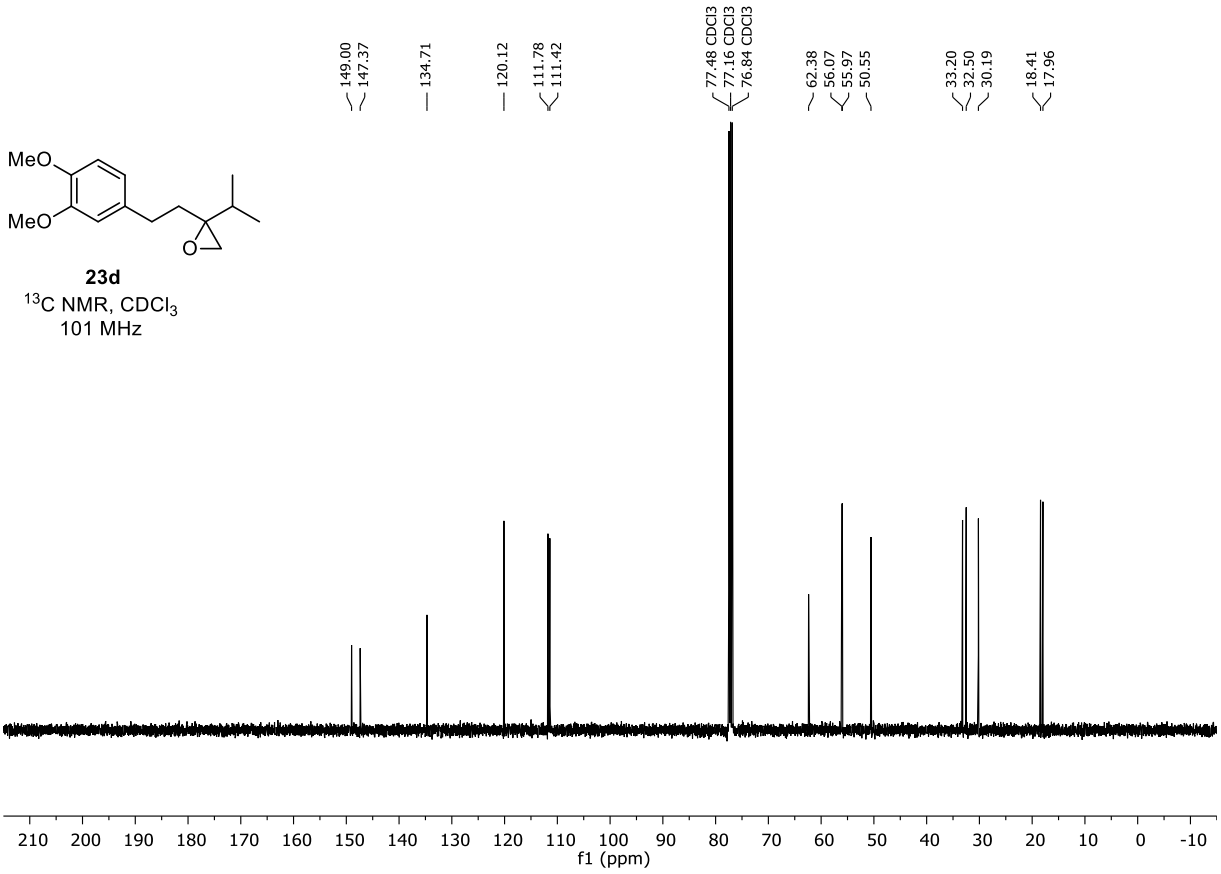
S142

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



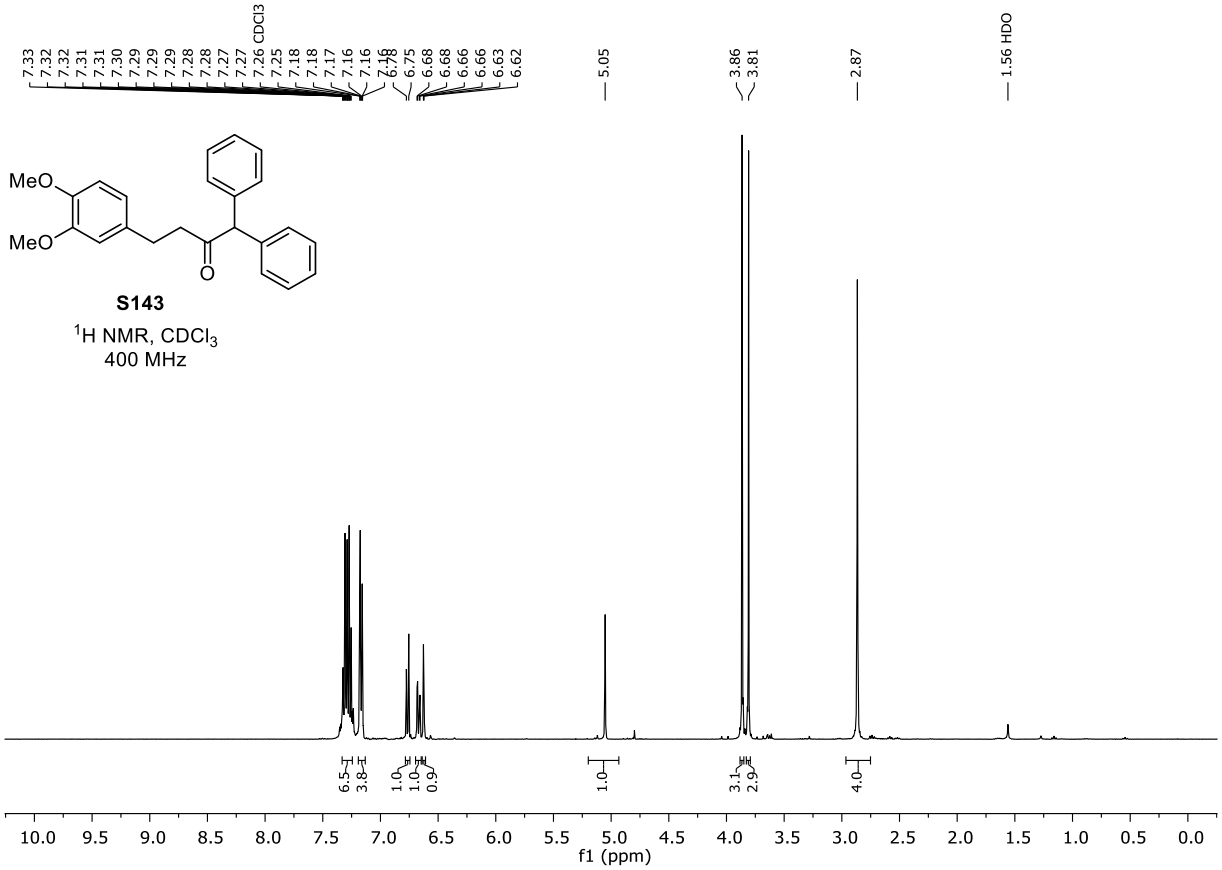
23d

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



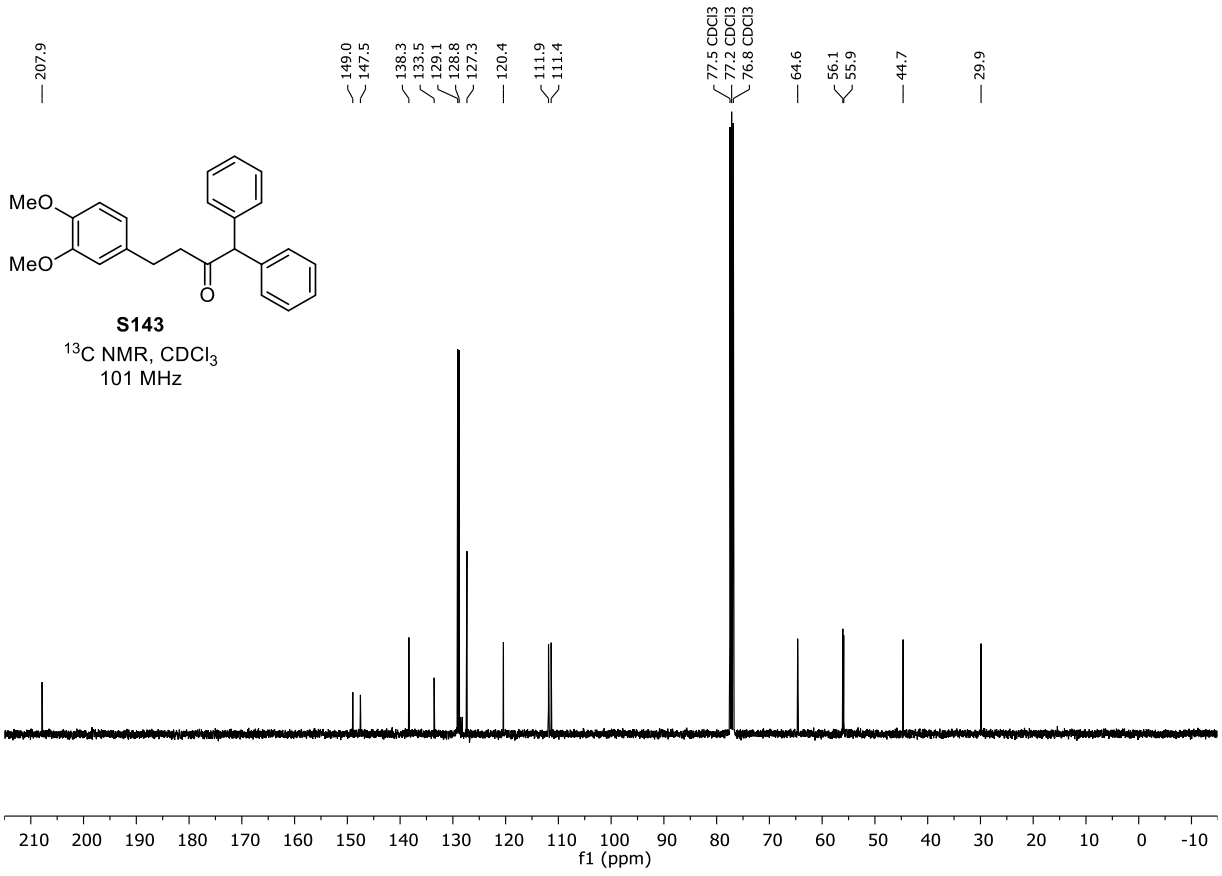
23d

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



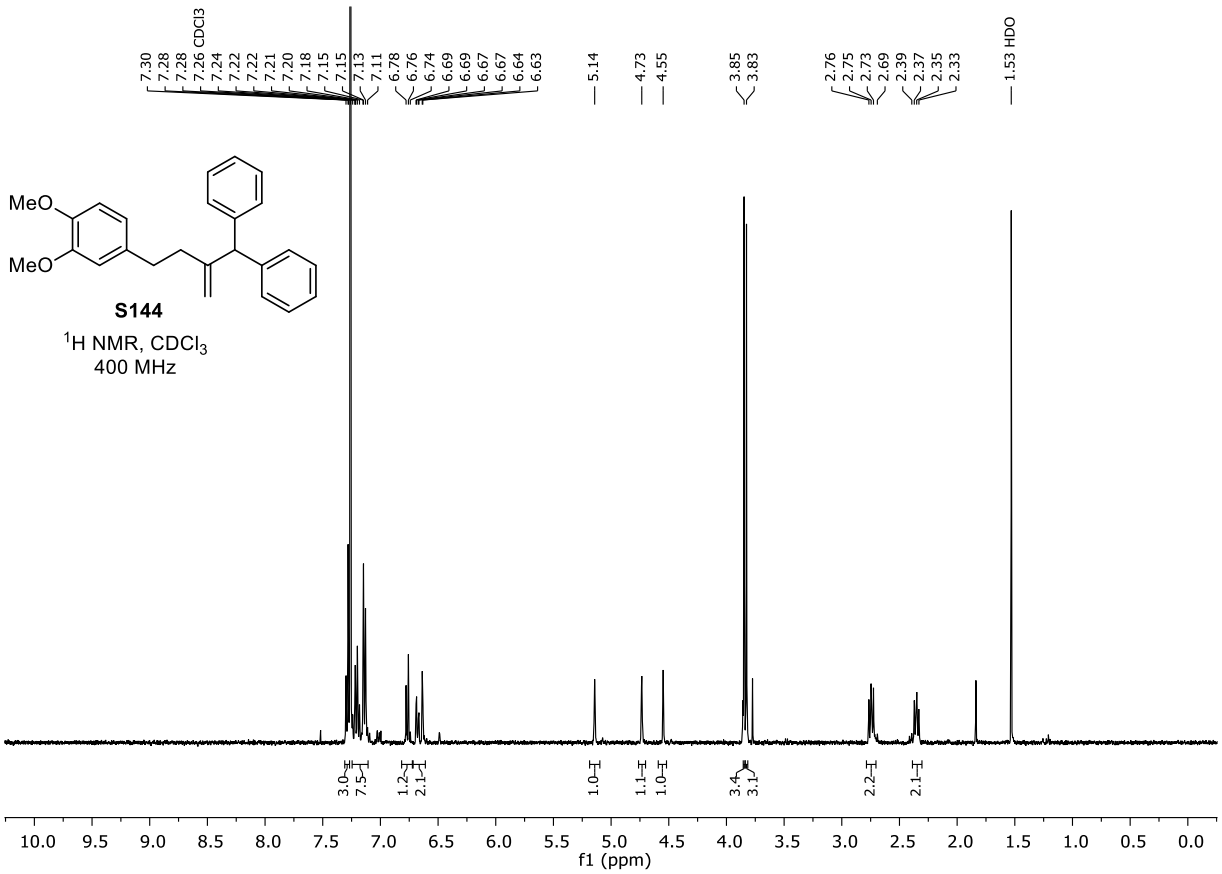
S143

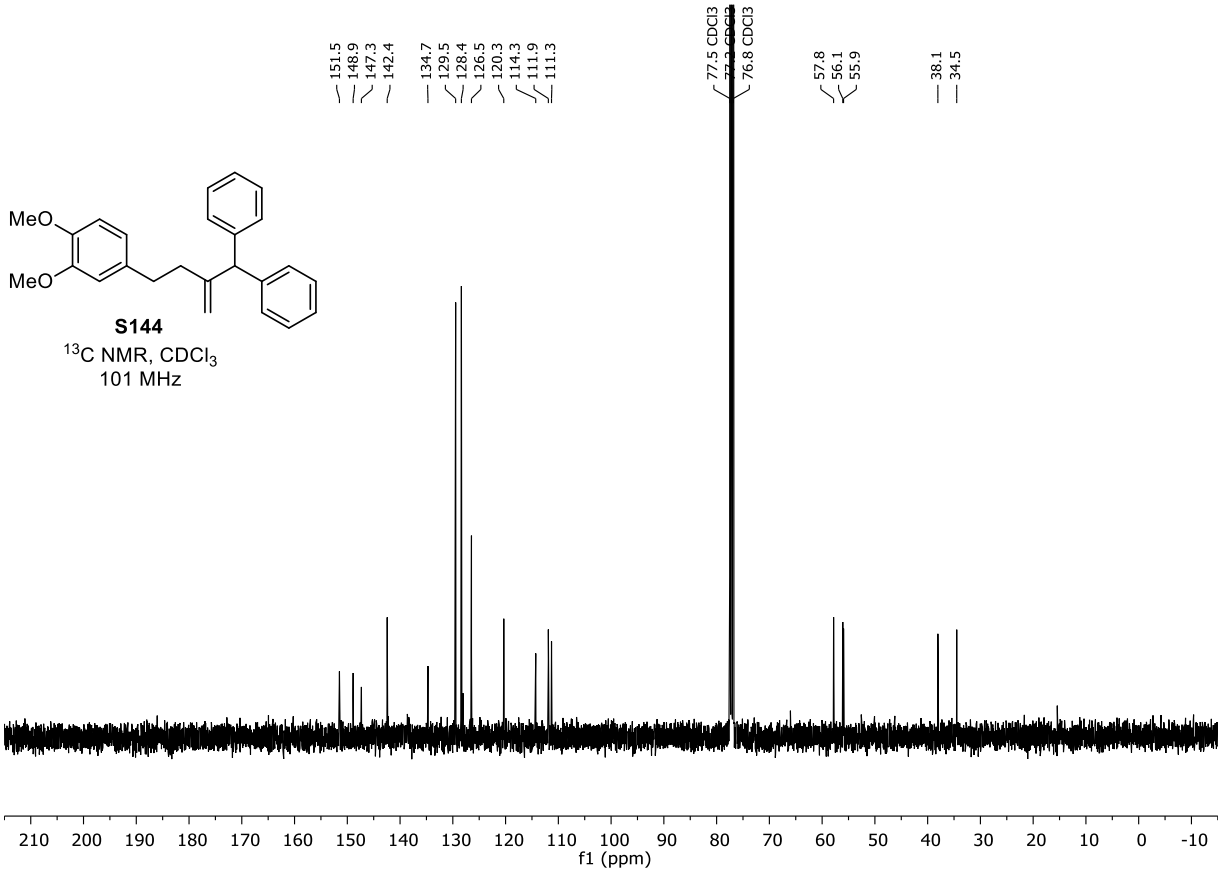
^{1}H NMR, $CDCl_3$
400 MHz

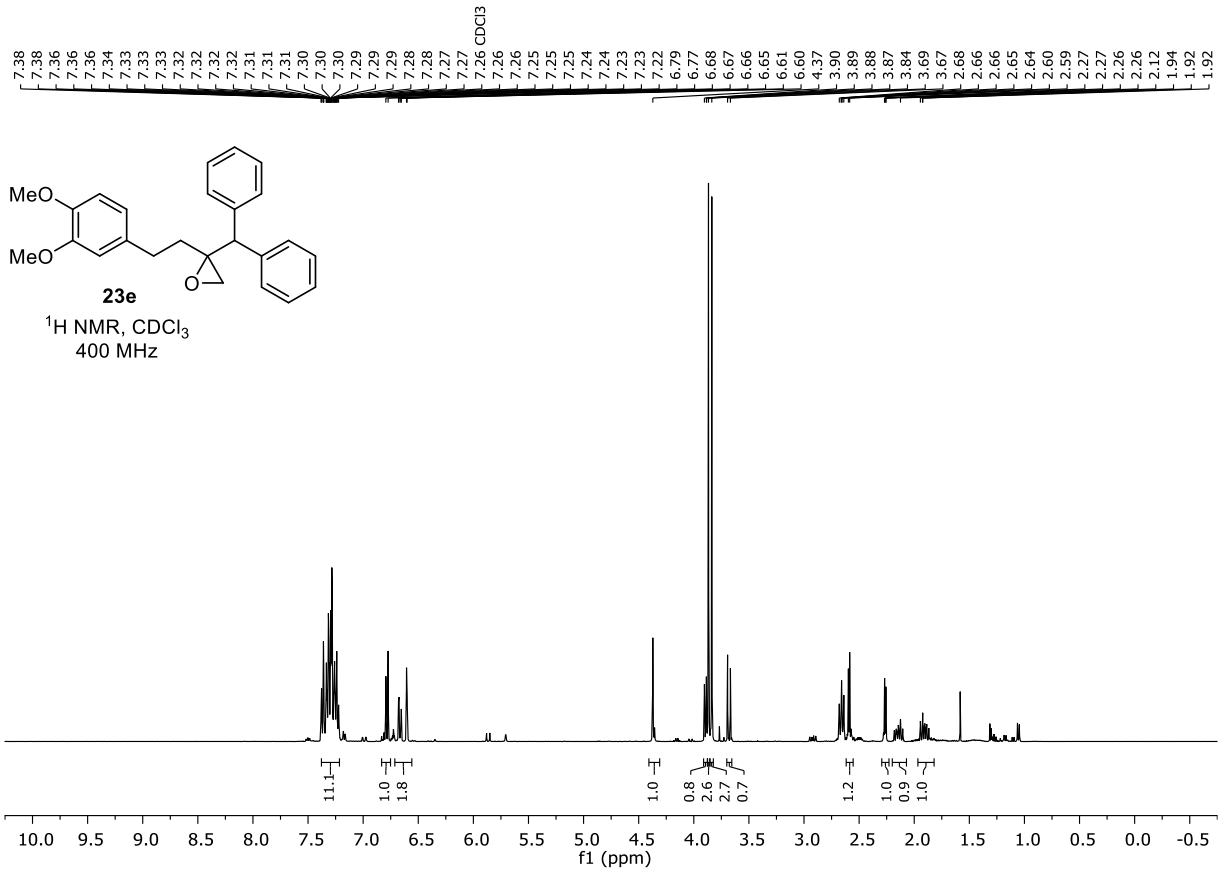


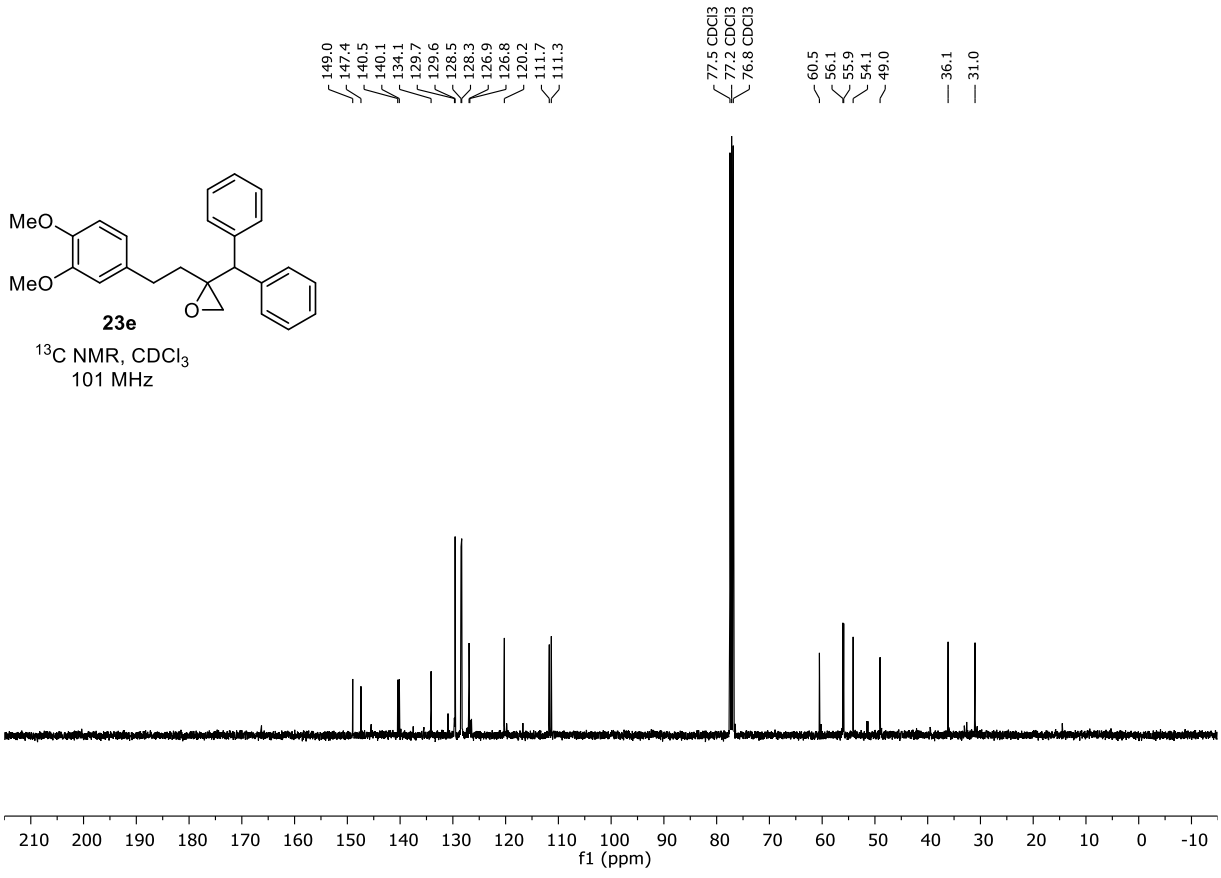
S143

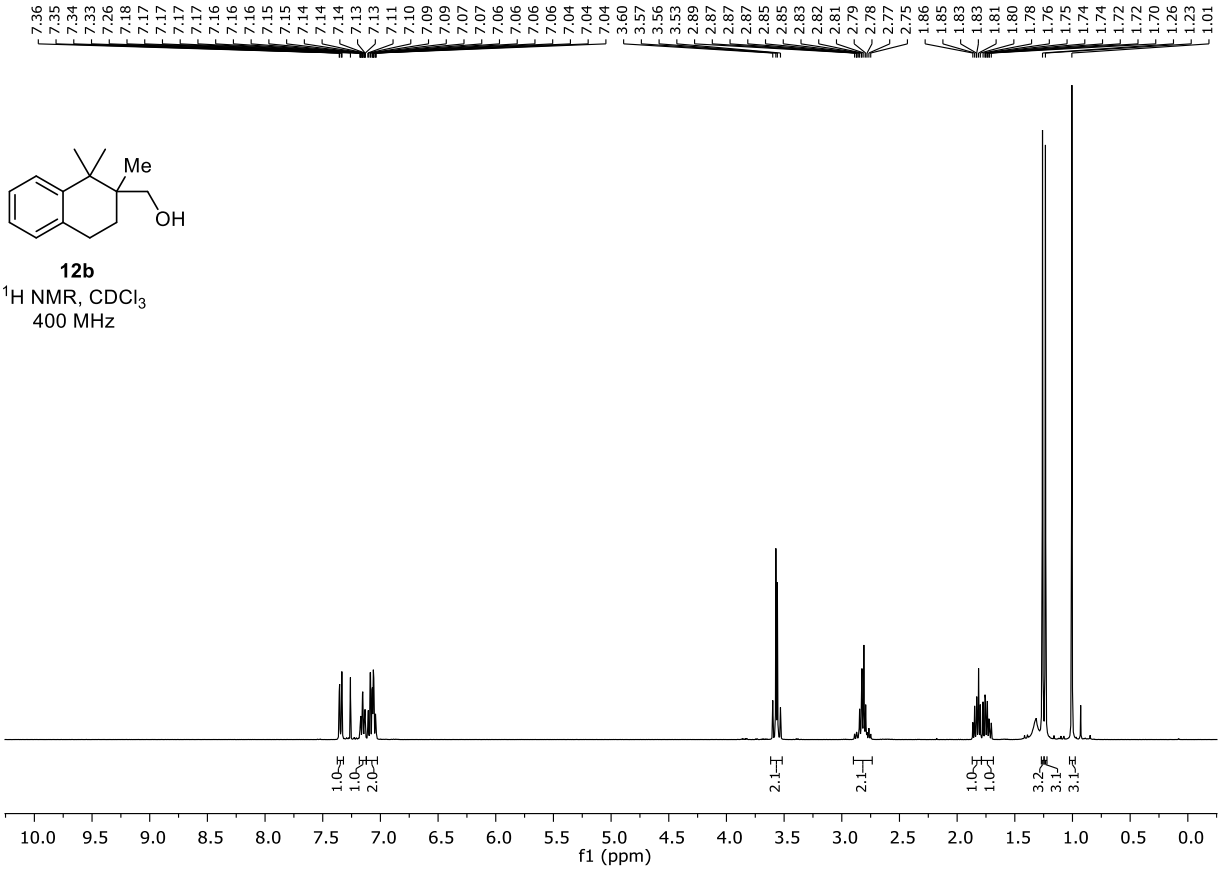
^{13}C NMR, $CDCl_3$
101 MHz

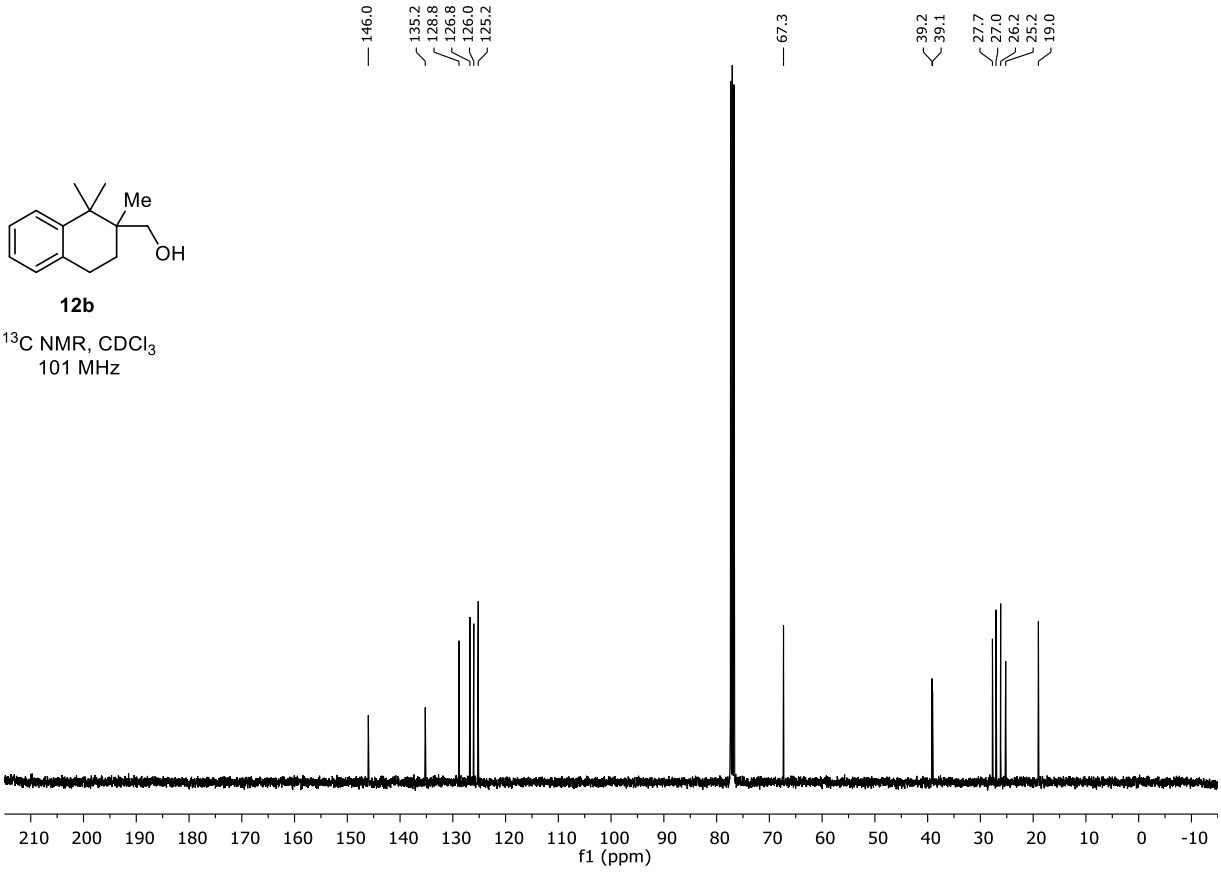

7.30
7.28
7.28
7.26 CDCl3
7.24
7.22
7.22
7.21
7.20
7.18
7.15
7.15
7.13
7.11
6.78
6.76
6.74
6.69
6.69
6.67
6.67
6.64
6.63
5.14
4.73
4.55
3.85
3.83
2.76
2.75
2.73
2.69
2.39
2.37
2.35
2.33
1.53 HDO
MeO
MeO
S144
1H NMR, CDCl3
400 MHz
3.0
7.5
1.2
2.1
1.0
1.1
1.0
3.4
3.1
2.2
2.1
10.0 9.5 9.0 8.5 8.0 7.5 7.0 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)

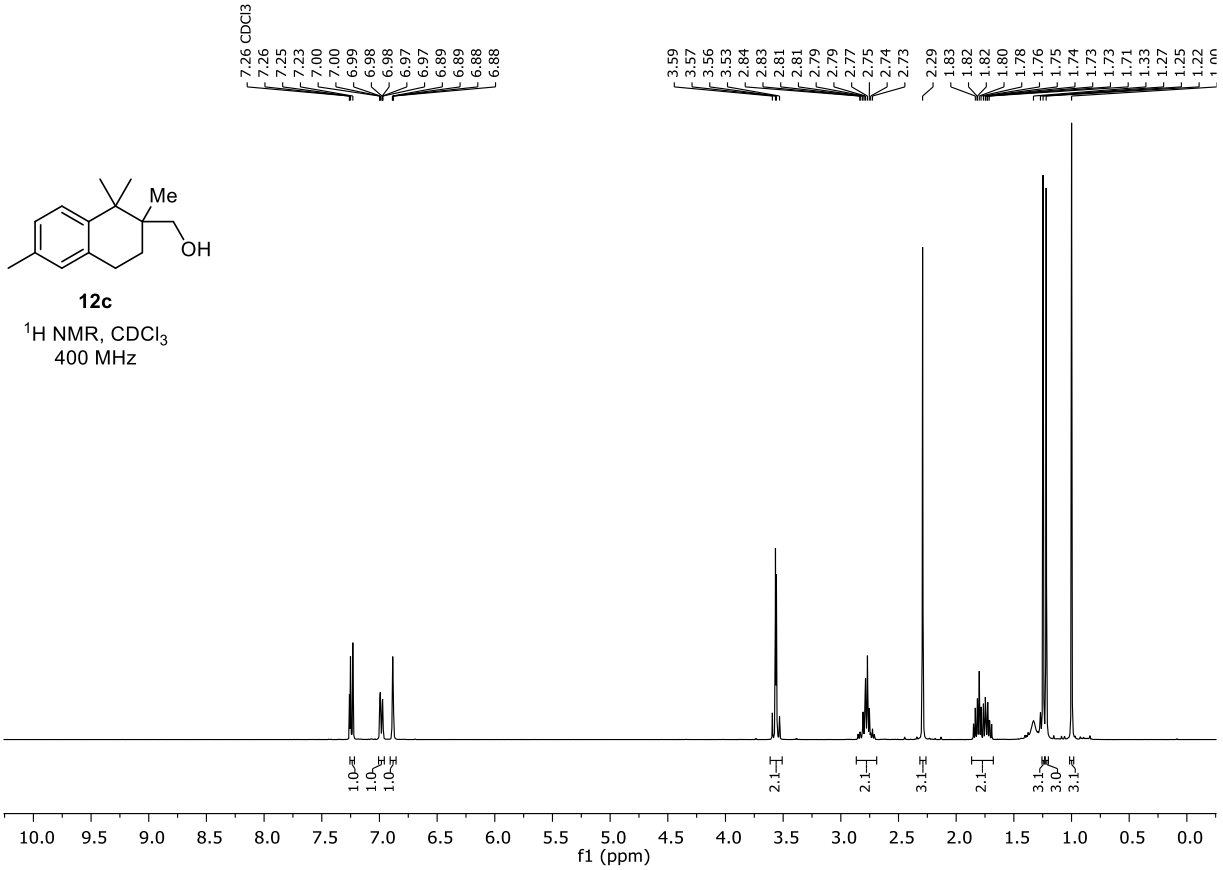

151.5
148.9
147.3
142.4
134.7
129.5
128.4
126.5
120.3
114.3
111.9
111.3
77.5 CDCl3
77.3 CDCl3
76.8 CDCl3
57.8
56.1
55.9
38.1
34.5
MeO
MeO
S144
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


MeO
MeO
O
23e
^{1}H NMR, CDCl$_3$
400 MHz
CDCl3
f1 (ppm)


MeO
MeO
O
23e
^{13}C NMR, CDCl$_3$
101 MHz
77.5 CDCl3
77.2 CDCl3
76.8 CDCl3
f1 (ppm)

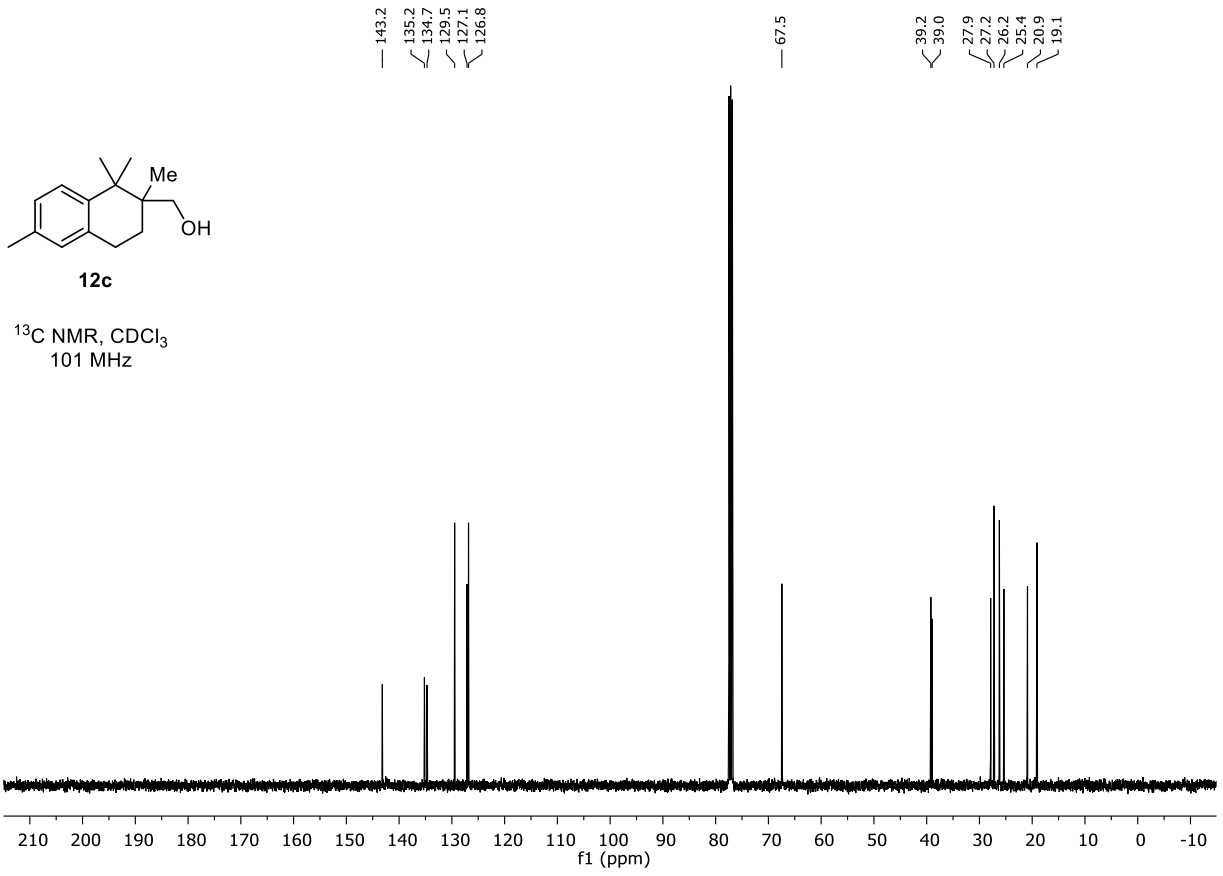

Me
OH
12b
1H NMR, CDCl3
400 MHz
f1 (ppm)


Me
OH
12b
13C NMR, CDCl3
101 MHz
f1 (ppm)



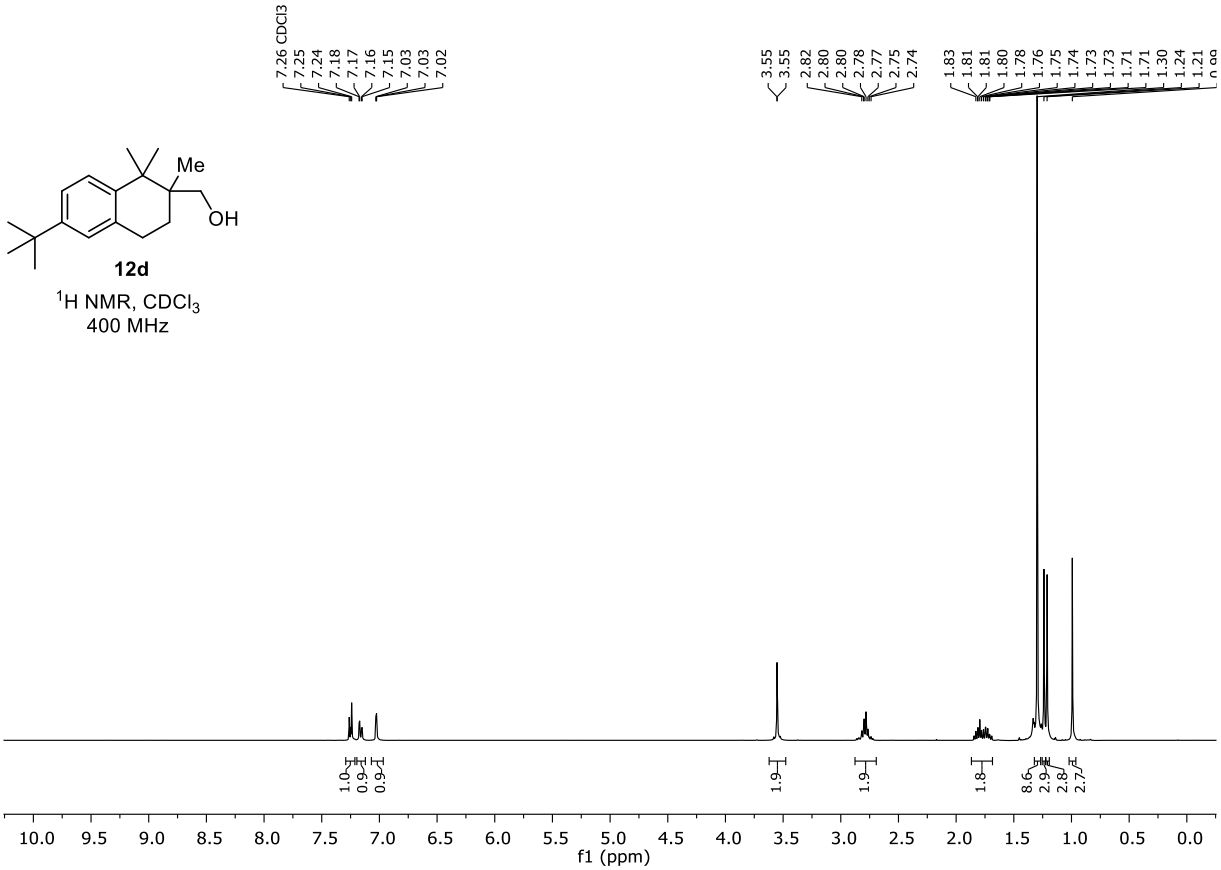
12c

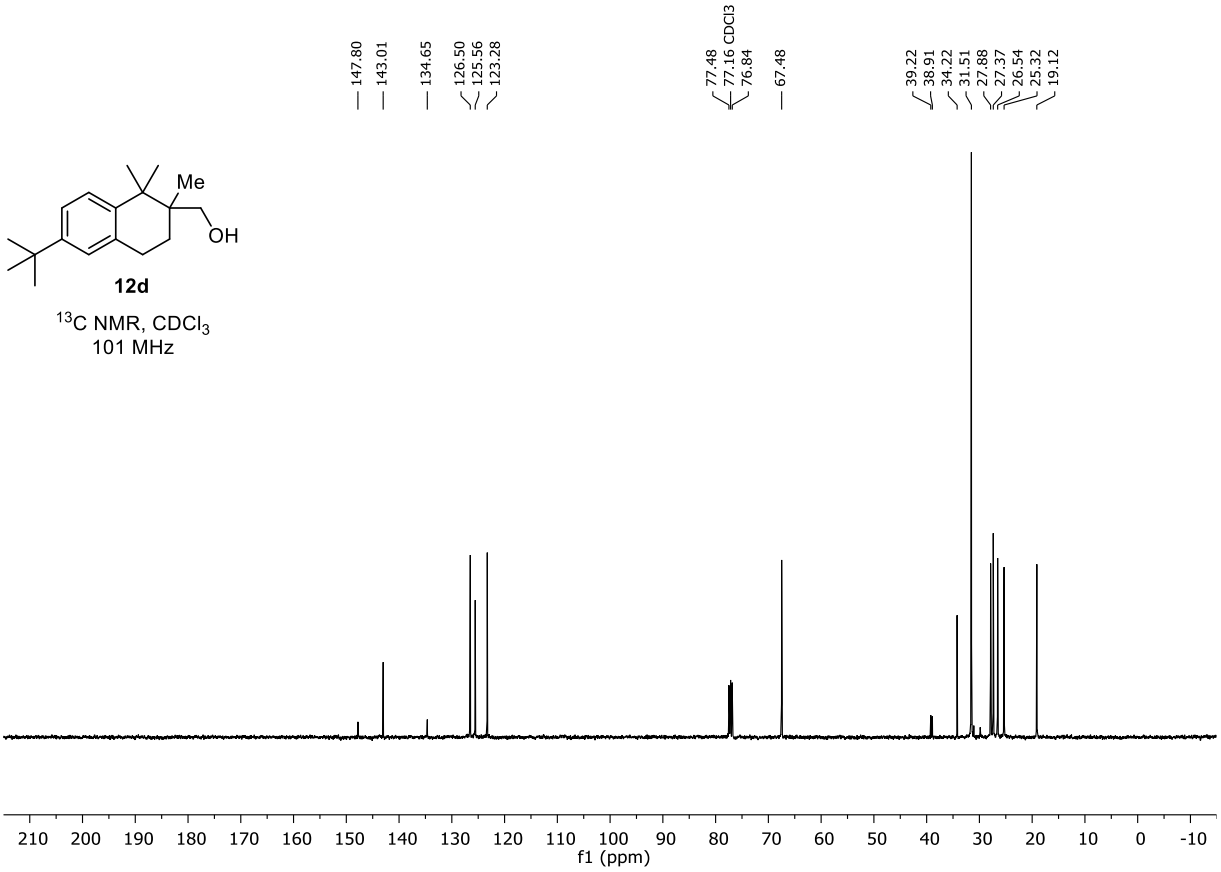
^{1}H NMR, $CDCl_3$
400 MHz

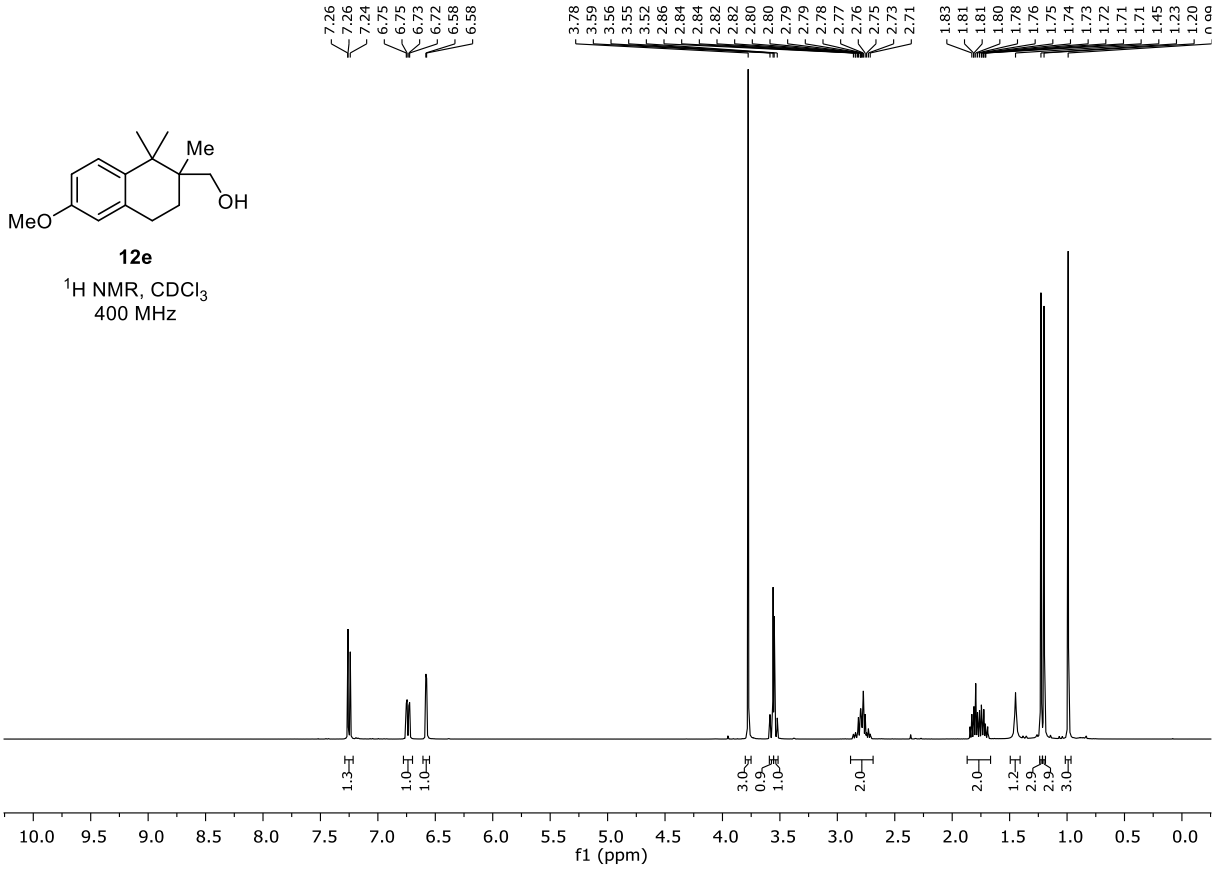


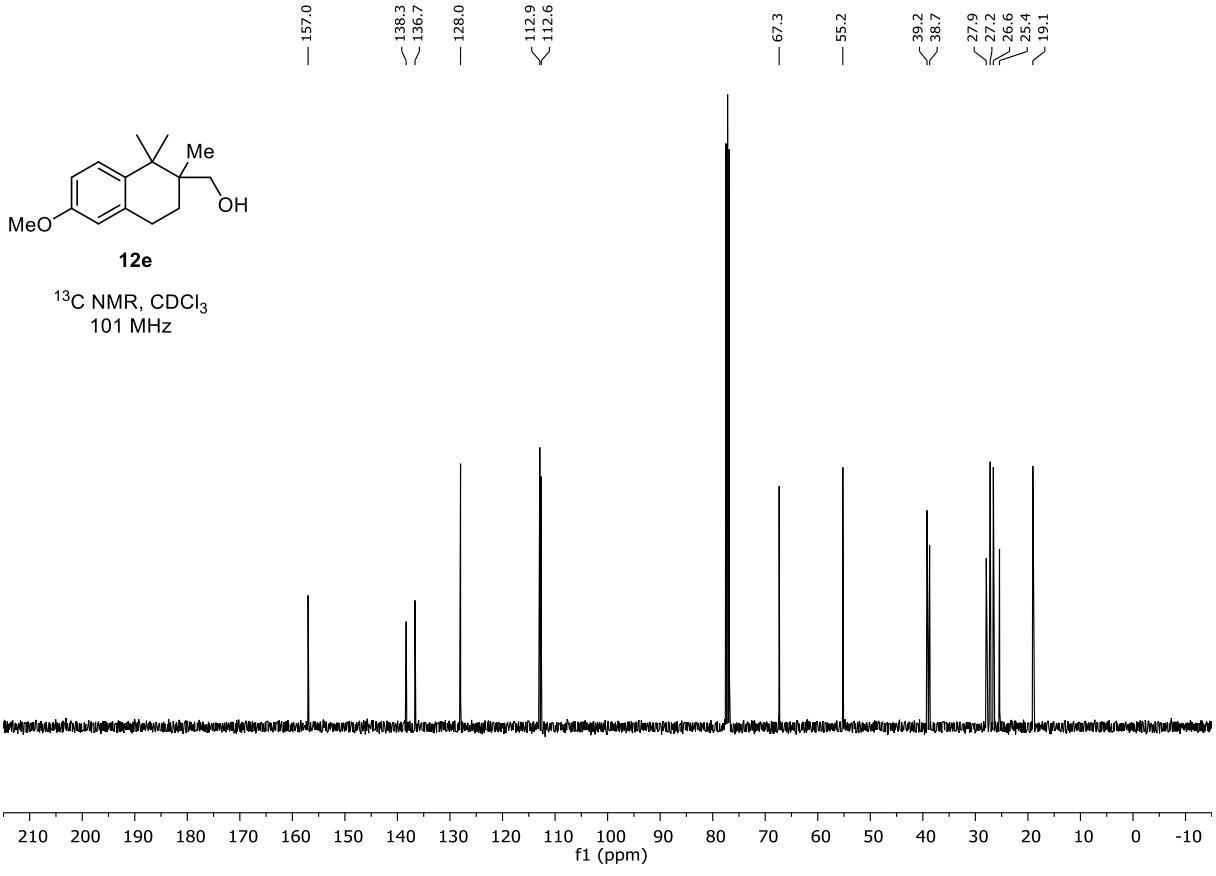
12c

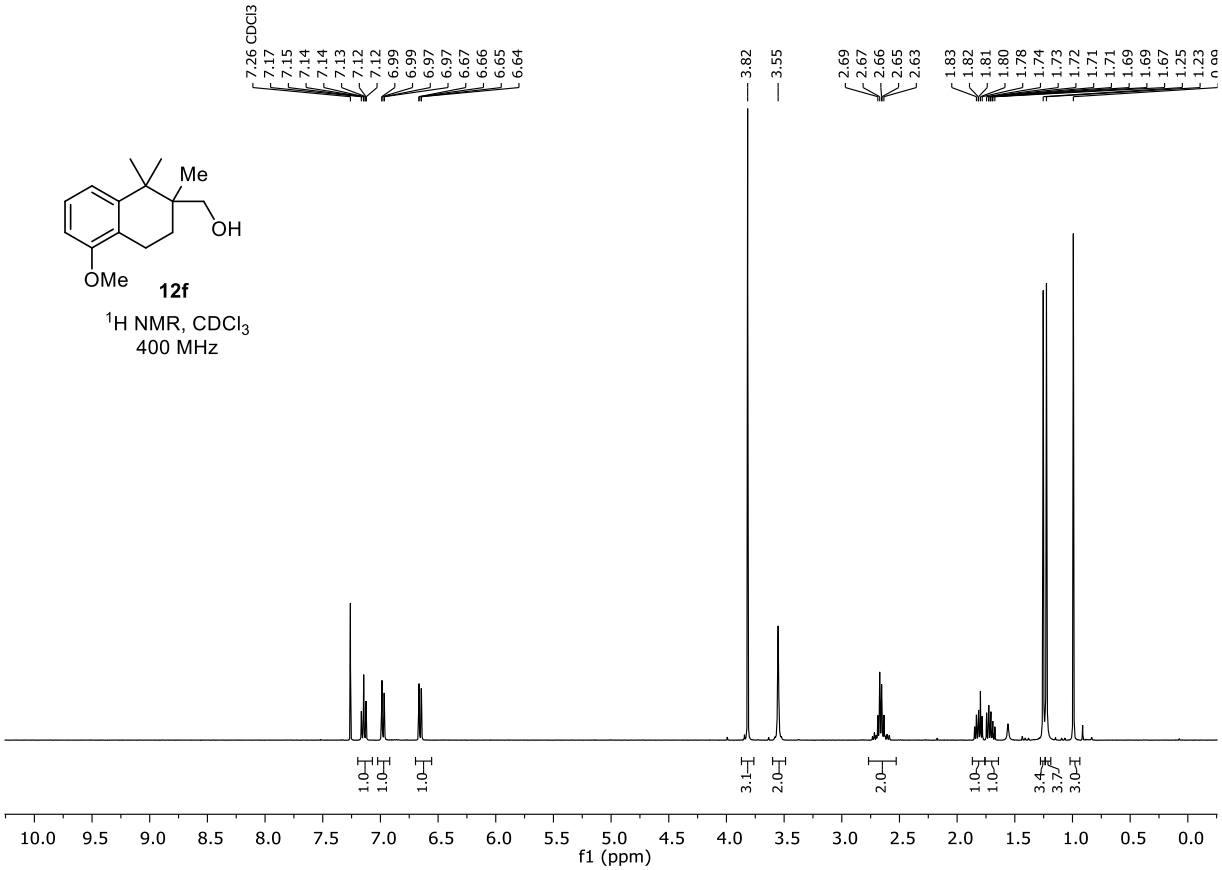
^{13}C NMR, $CDCl_3$
101 MHz

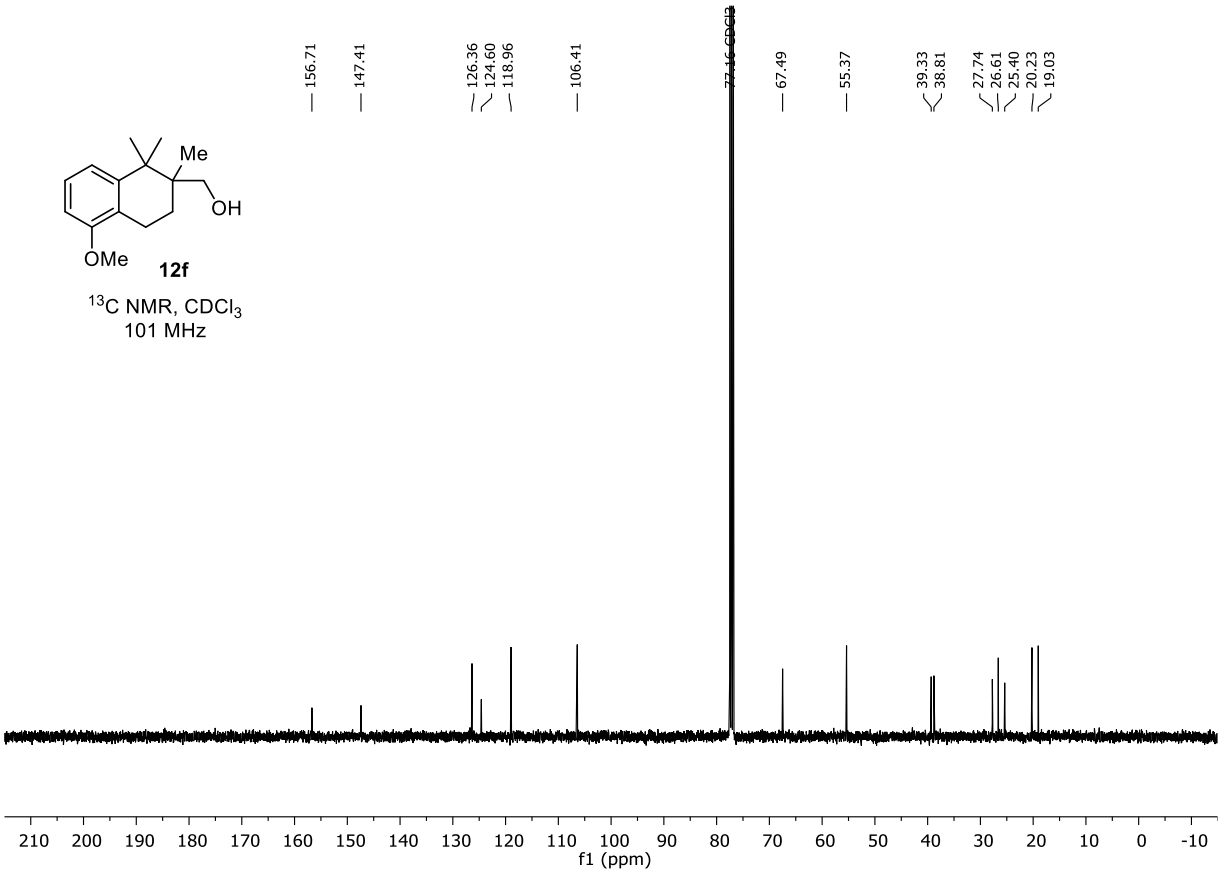

7.26 CDCl3
7.25
7.24
7.18
7.17
7.16
7.15
7.03
7.03
7.02
3.55
3.55
2.82
2.80
2.80
2.78
2.77
2.75
2.74
1.83
1.81
1.81
1.80
1.78
1.76
1.75
1.74
1.73
1.71
1.71
1.30
1.24
1.21
Me
OH
12d
1H NMR, CDCl3
400 MHz
1.0
0.9
0.9
1.9
1.9
1.8
8.6
2.9
2.8
2.7
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

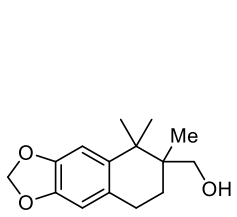

147.80
143.01
134.65
126.50
125.56
123.28
77.48
77.16 CDCl3
76.84
67.48
39.22
38.91
34.22
31.51
27.88
27.37
26.54
25.32
19.12
Me
OH
12d
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me
OH
MeO
12e
1H NMR, CDCl3
400 MHz
f1 (ppm)


Me
OH
MeO
12e
13C NMR, CDCl3
101 MHz
f1 (ppm)

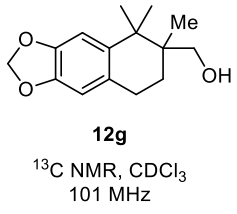

7.26 CDCl3
7.17
7.15
7.14
7.14
7.13
7.12
7.12
6.99
6.99
6.97
6.97
6.67
6.66
6.65
6.64
3.82
3.55
2.69
2.67
2.66
2.65
2.63
1.83
1.82
1.81
1.80
1.78
1.74
1.73
1.72
1.71
1.71
1.69
1.69
1.67
1.25
1.23
Me
OH
OMe
12f
1H NMR, CDCl3
400 MHz
1.0
1.0
1.0
3.1
2.0
2.0
1.0
1.0
3.4
3.7
3.0
10.0 9.5 9.0 8.5 8.0 7.5 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)


156.71
147.41
126.36
124.60
118.96
106.41
77.16 CDCl3
67.49
55.37
39.33
38.81
27.74
26.61
25.40
20.23
19.03
Me
OH
OMe
12f
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)



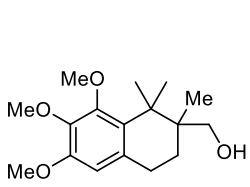
12g

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



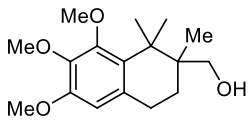
12g

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



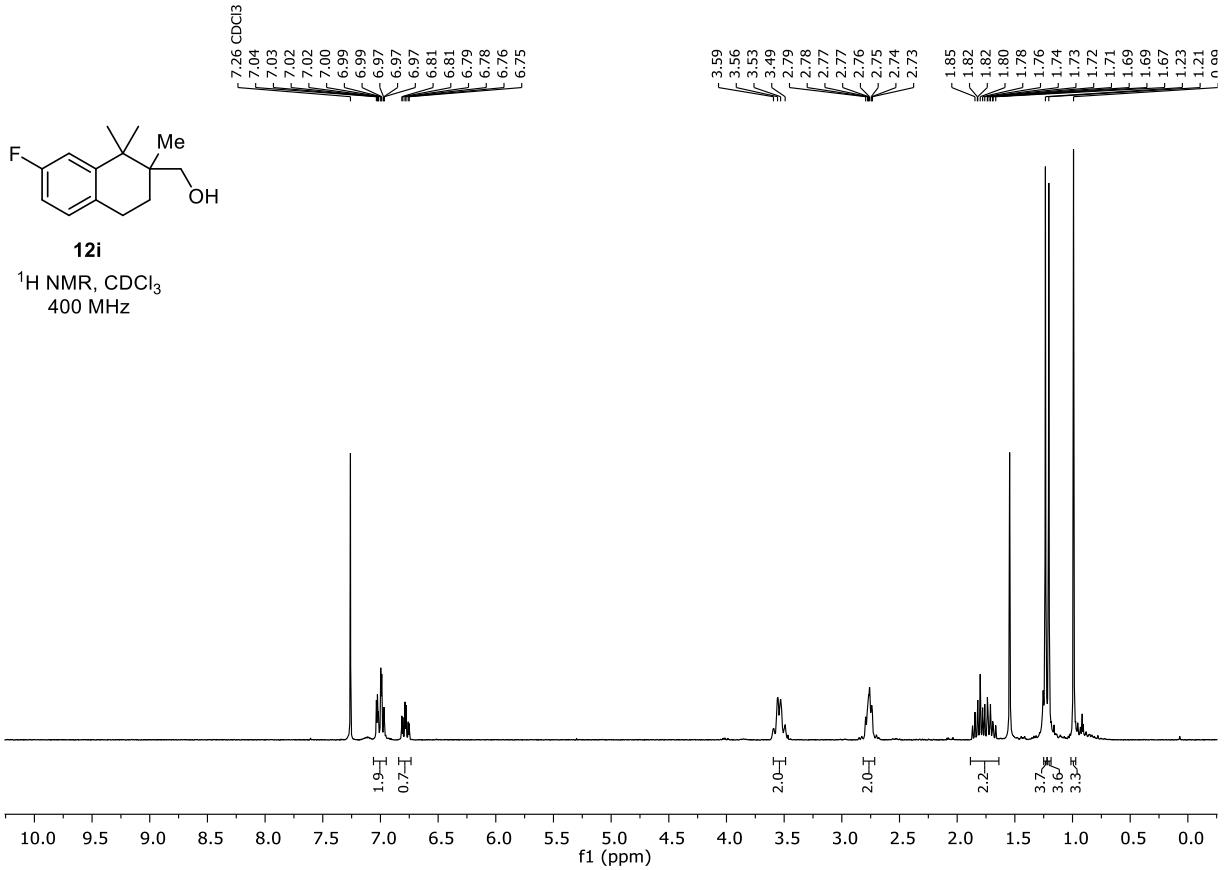
12h

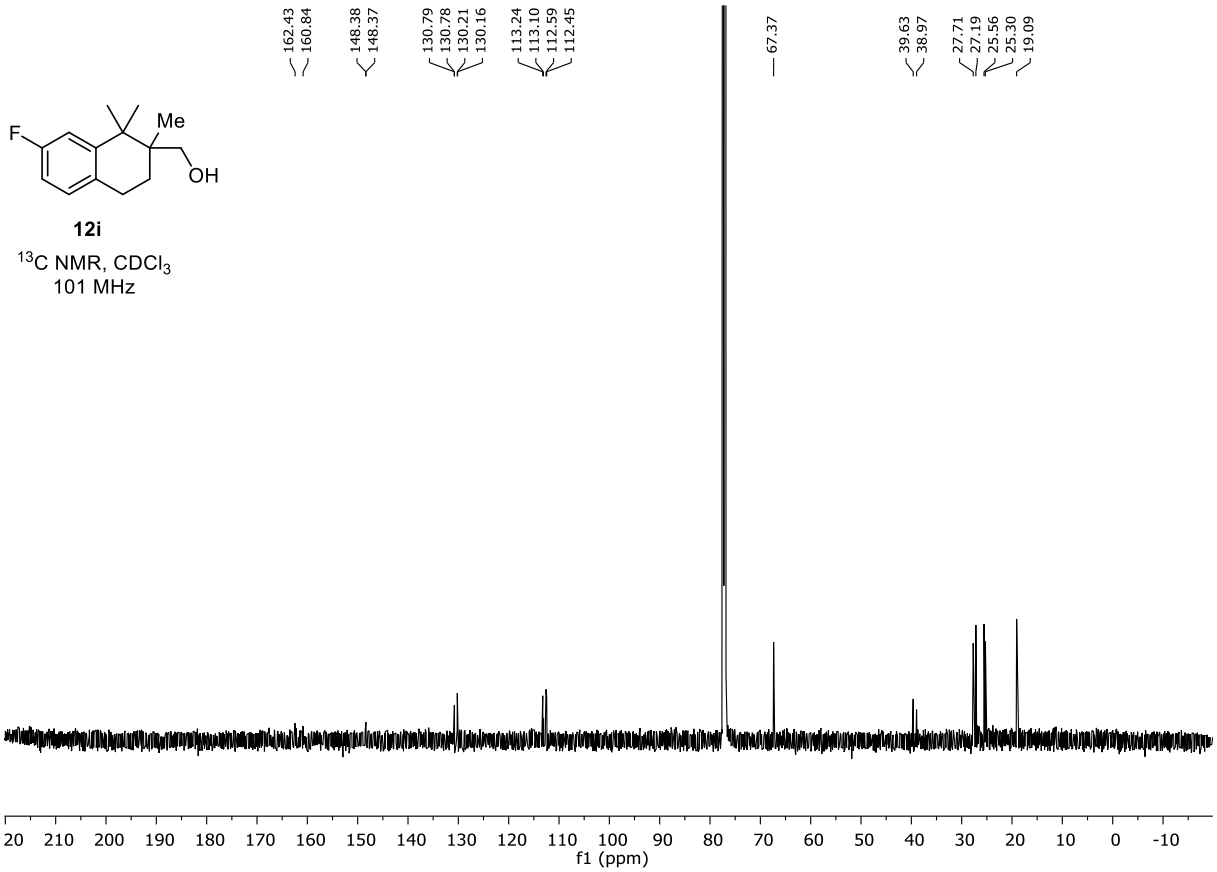
^{1}H NMR, $CDCl_3$
400 MHz

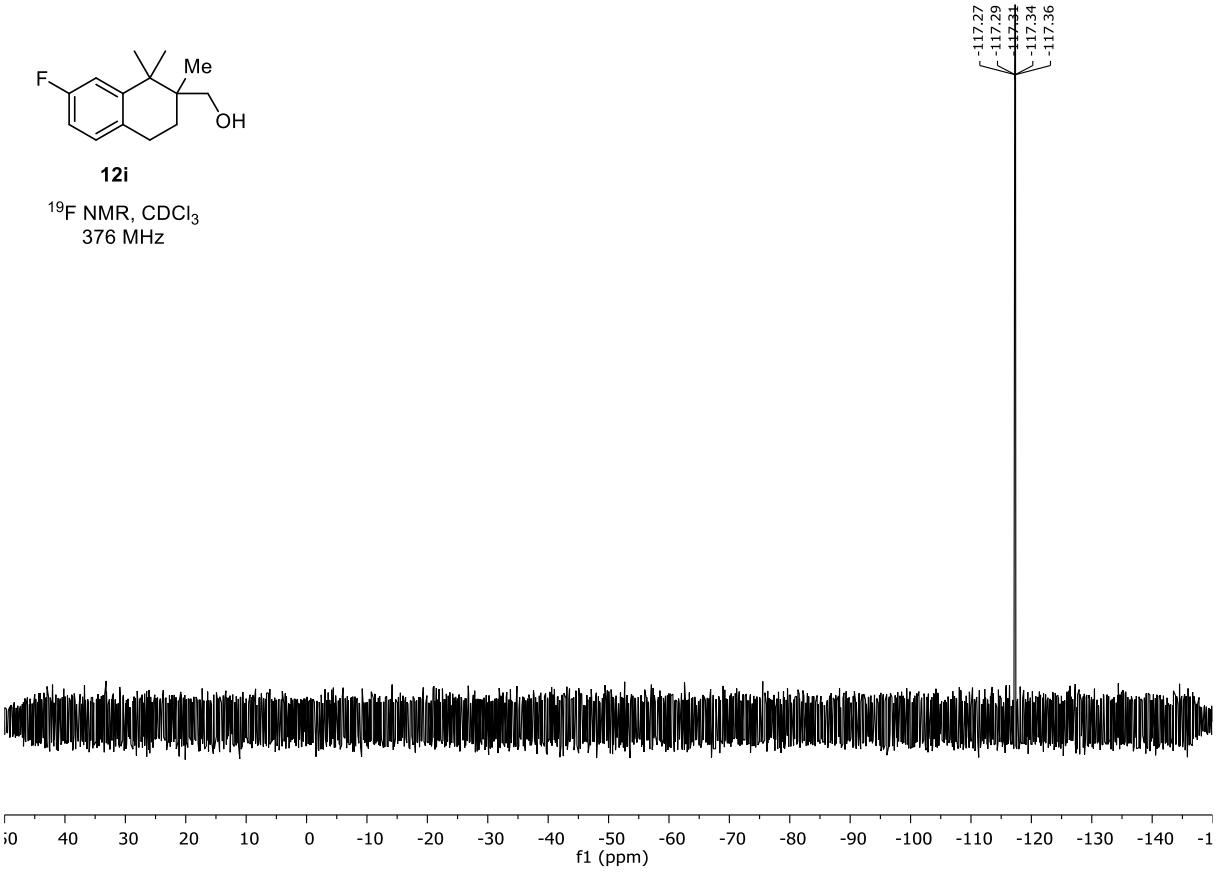


12h

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

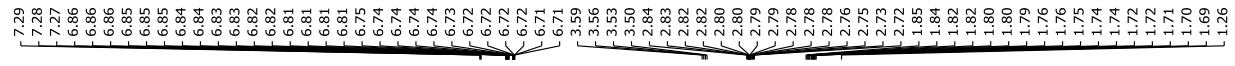

7.26 CDCl3
7.04
7.03
7.02
7.02
7.00
6.99
6.99
6.97
6.97
6.97
6.81
6.81
6.79
6.78
6.76
6.75
3.59
3.56
3.53
3.49
2.79
2.78
2.77
2.77
2.76
2.75
2.74
2.73
1.85
1.82
1.82
1.80
1.78
1.76
1.74
1.73
1.72
1.71
1.69
1.69
1.67
1.23
1.21
F
Me
OH
12i
1H NMR, CDCl3
400 MHz
1.9
0.7
2.0
2.0
2.2
3.7
3.6
3.3
10.0 9.5 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)

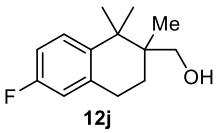

162.43
160.84
148.38
148.37
130.79
130.78
130.21
130.16
113.24
113.10
112.59
112.45
67.37
39.63
38.97
27.71
27.19
25.56
25.30
19.09
F
Me
OH
12i
13C NMR, CDCl3
101 MHz
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



12i

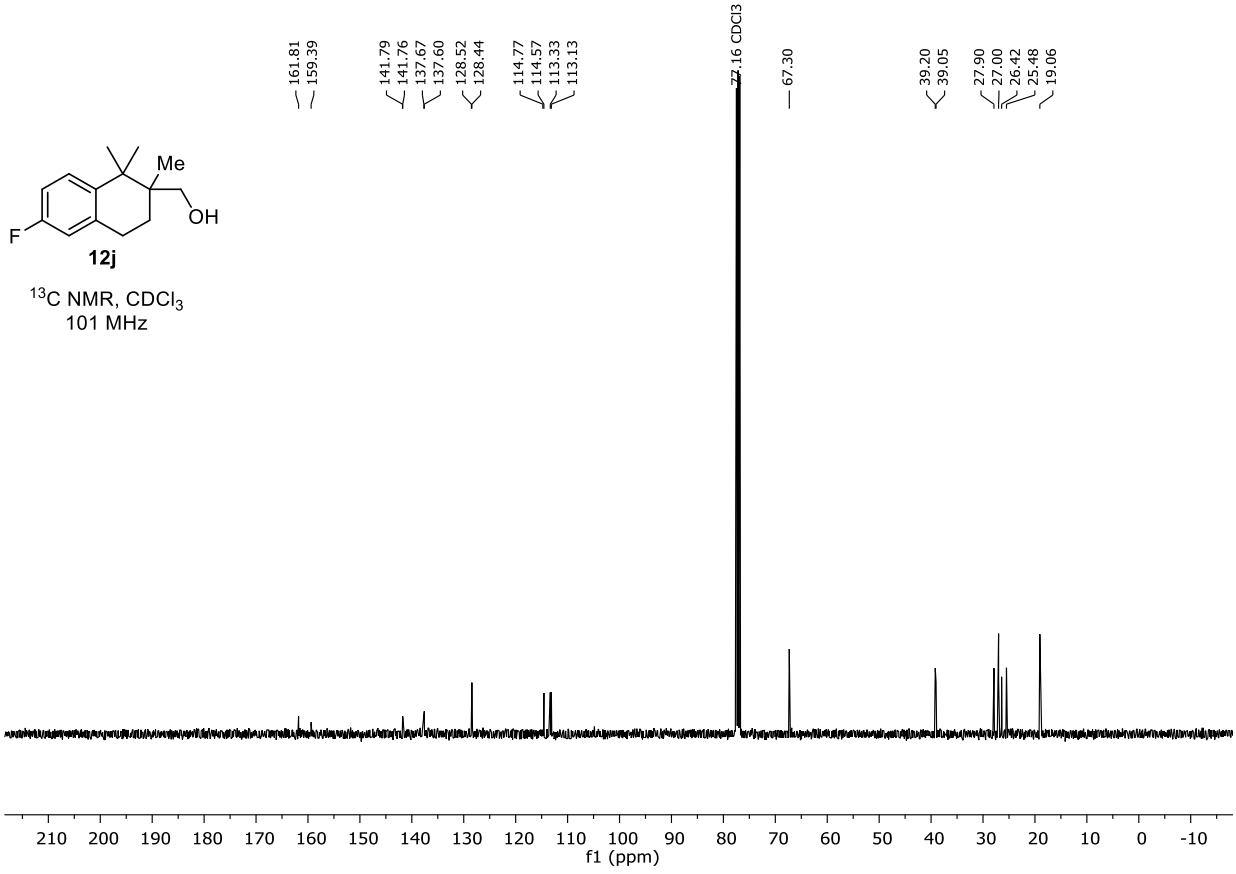
^{19}F NMR, $CDCl_3$
376 MHz





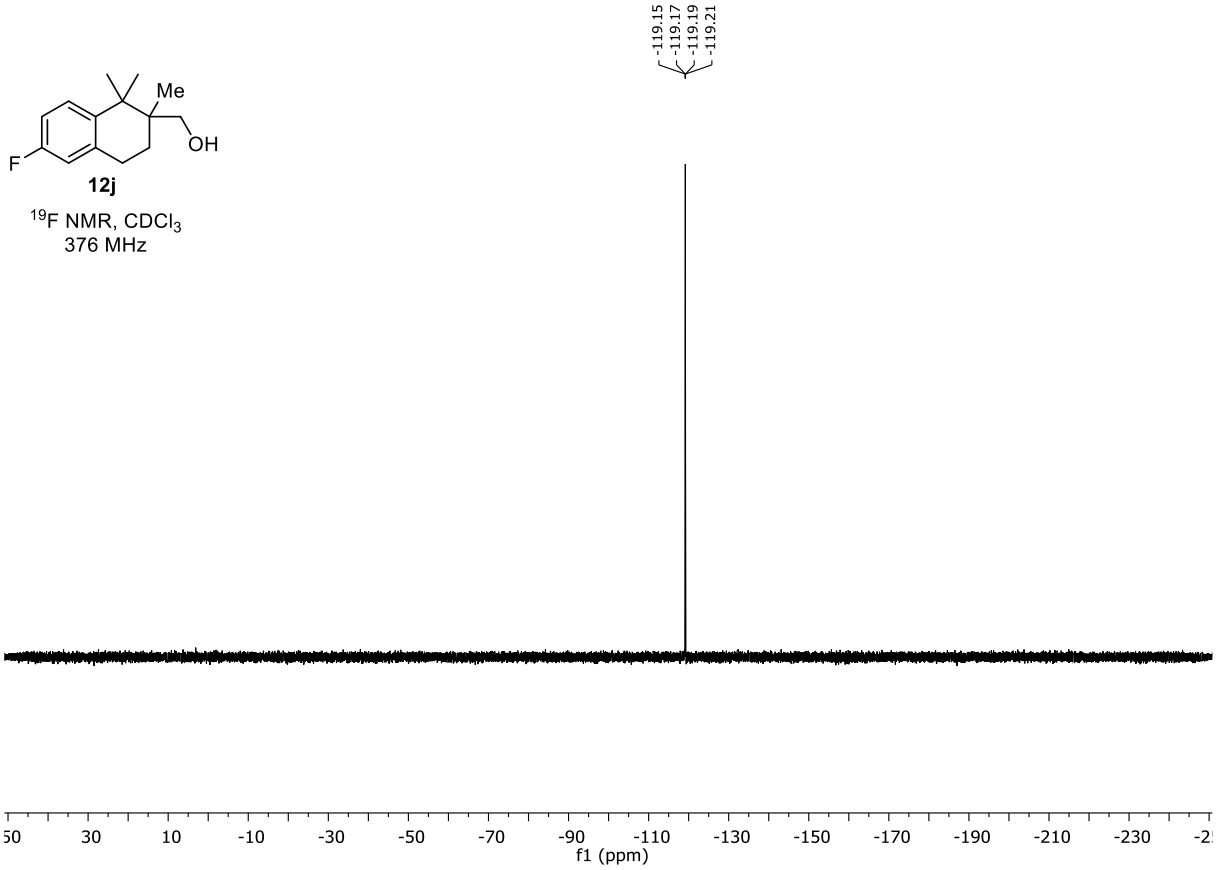
12j

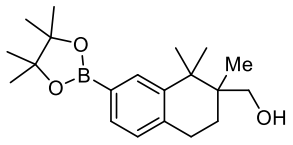
^{1}H NMR, $CDCl_3$
400 MHz



12j

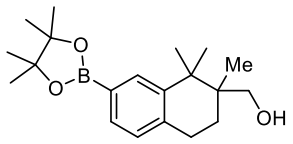
^{13}C NMR, $CDCl_3$
101 MHz


-119.15
-119.17
-119.19
-119.21
Me
OH
F
12j
^{19}F NMR, CDCl$_3$
376 MHz
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)



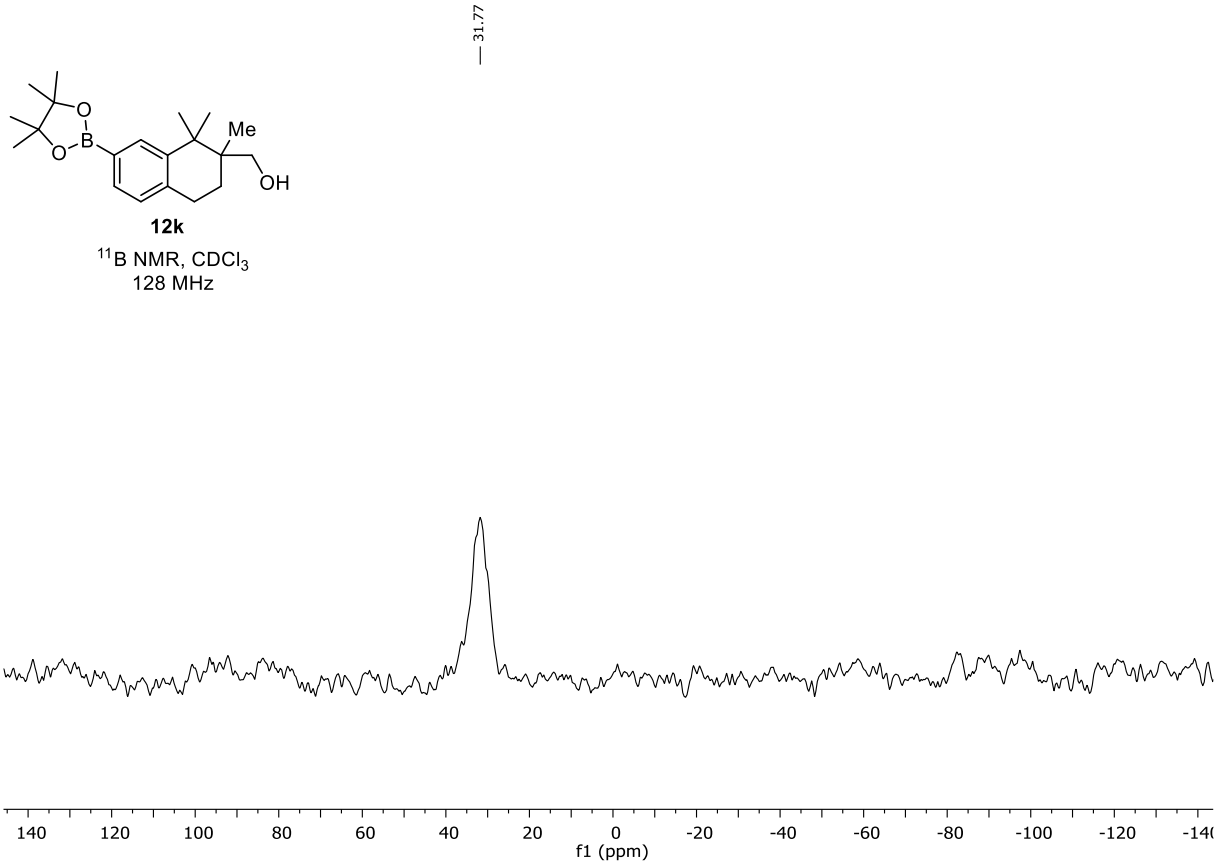
12k

^{1}H NMR, $CDCl_3$
600 MHz



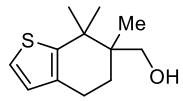
12k

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



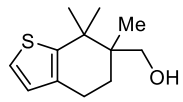
12k

^{11}B NMR, $CDCl_3$
128 MHz



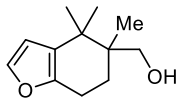
12l

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



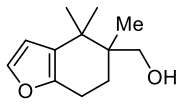
12l

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



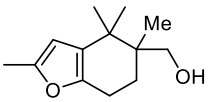
12m

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



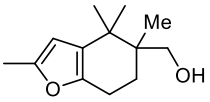
12m

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



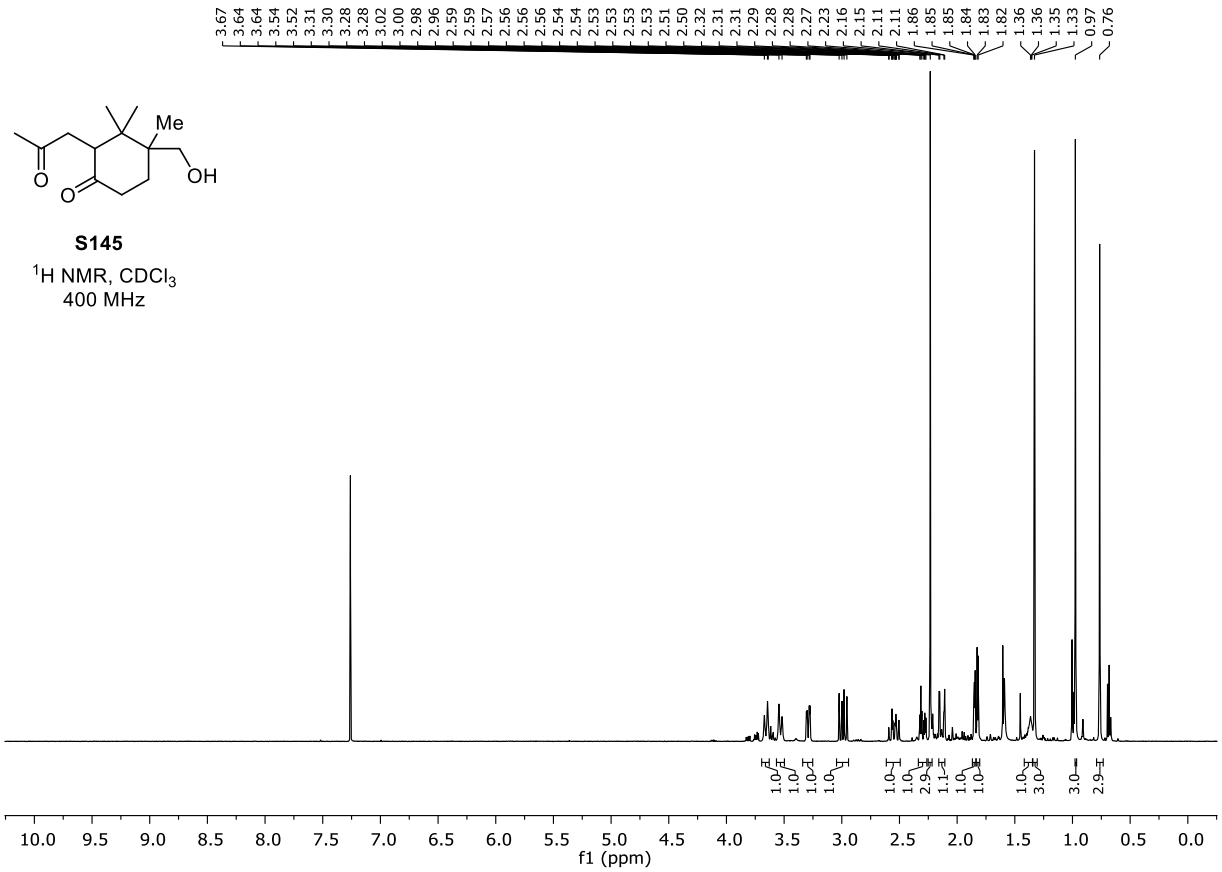
12n

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



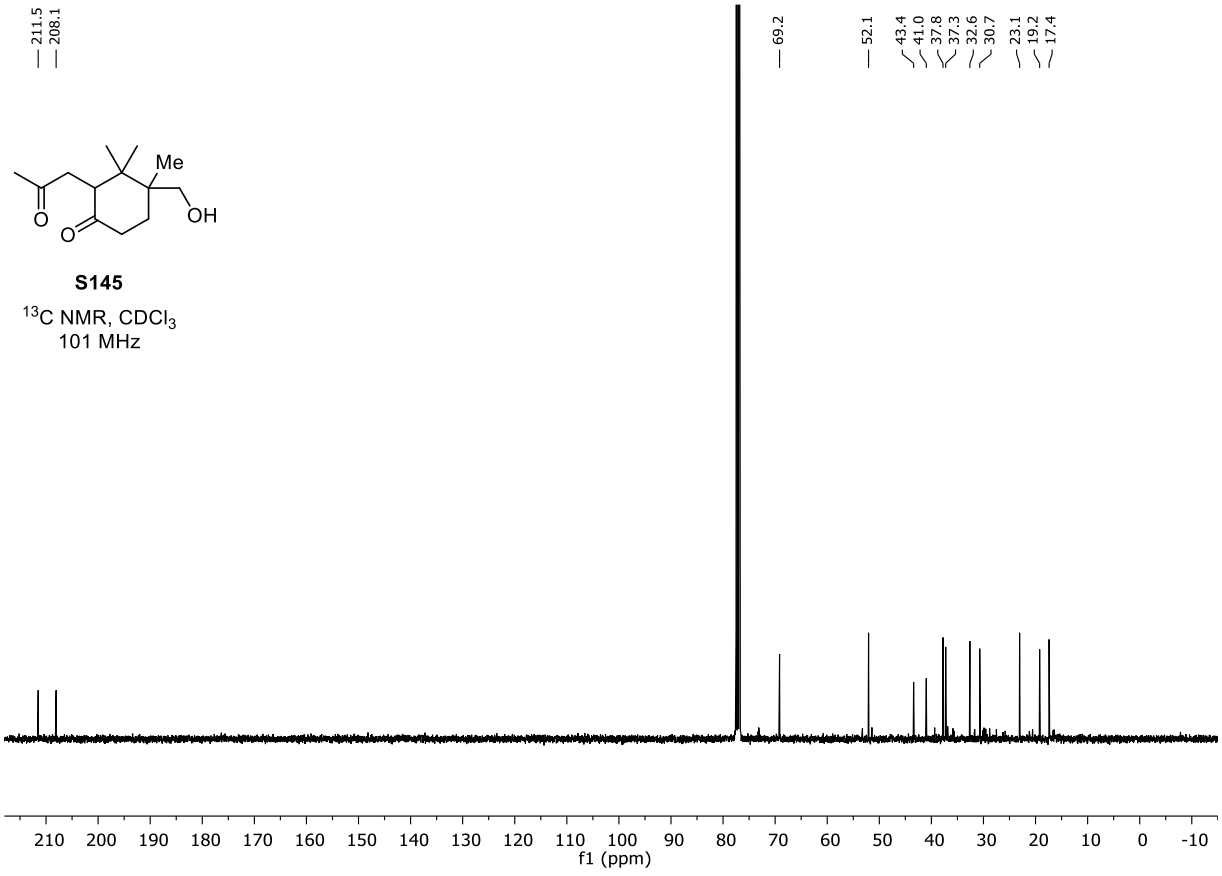
12n

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



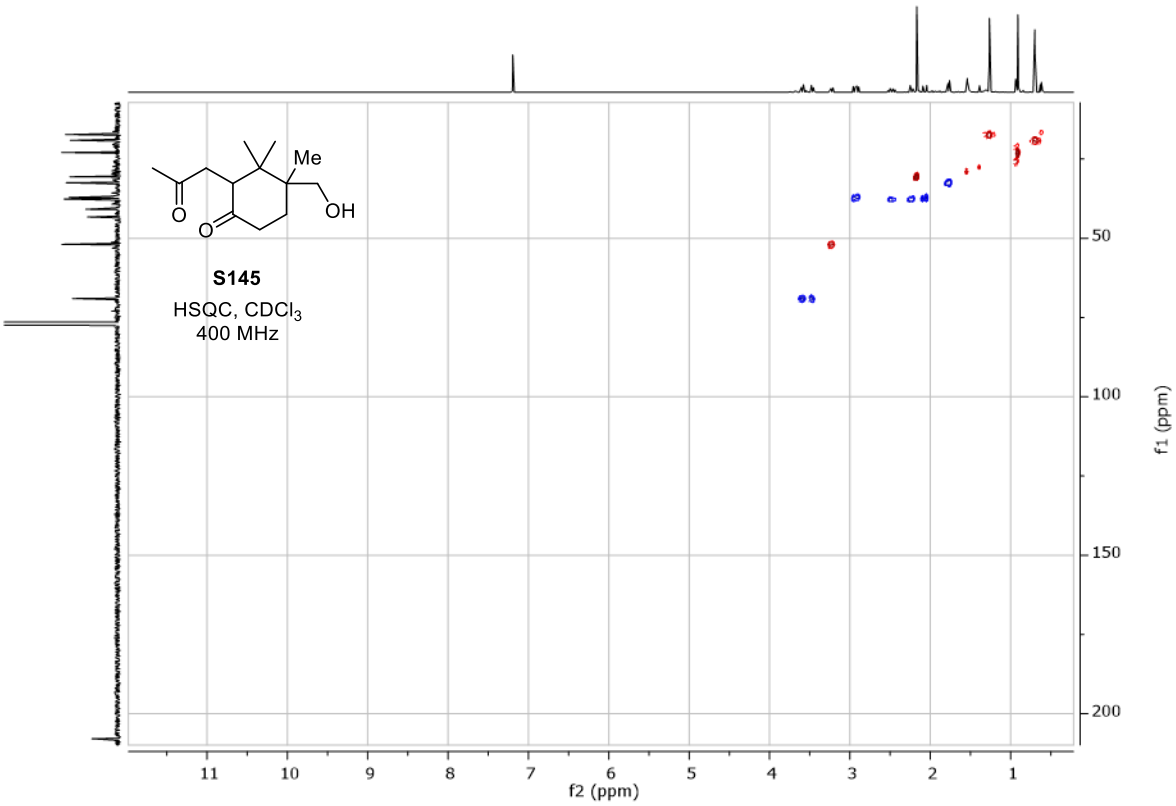
S145

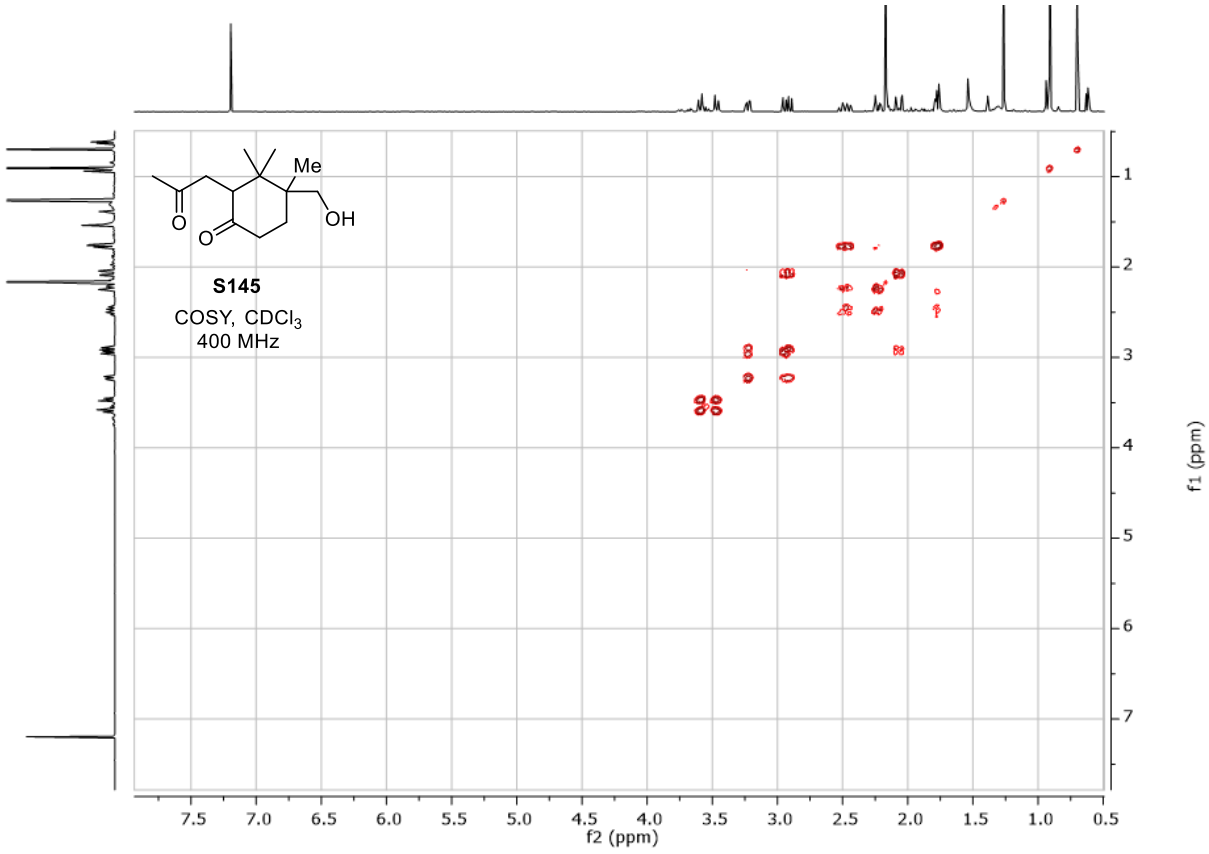
^{1}H NMR, $CDCl_3$
400 MHz

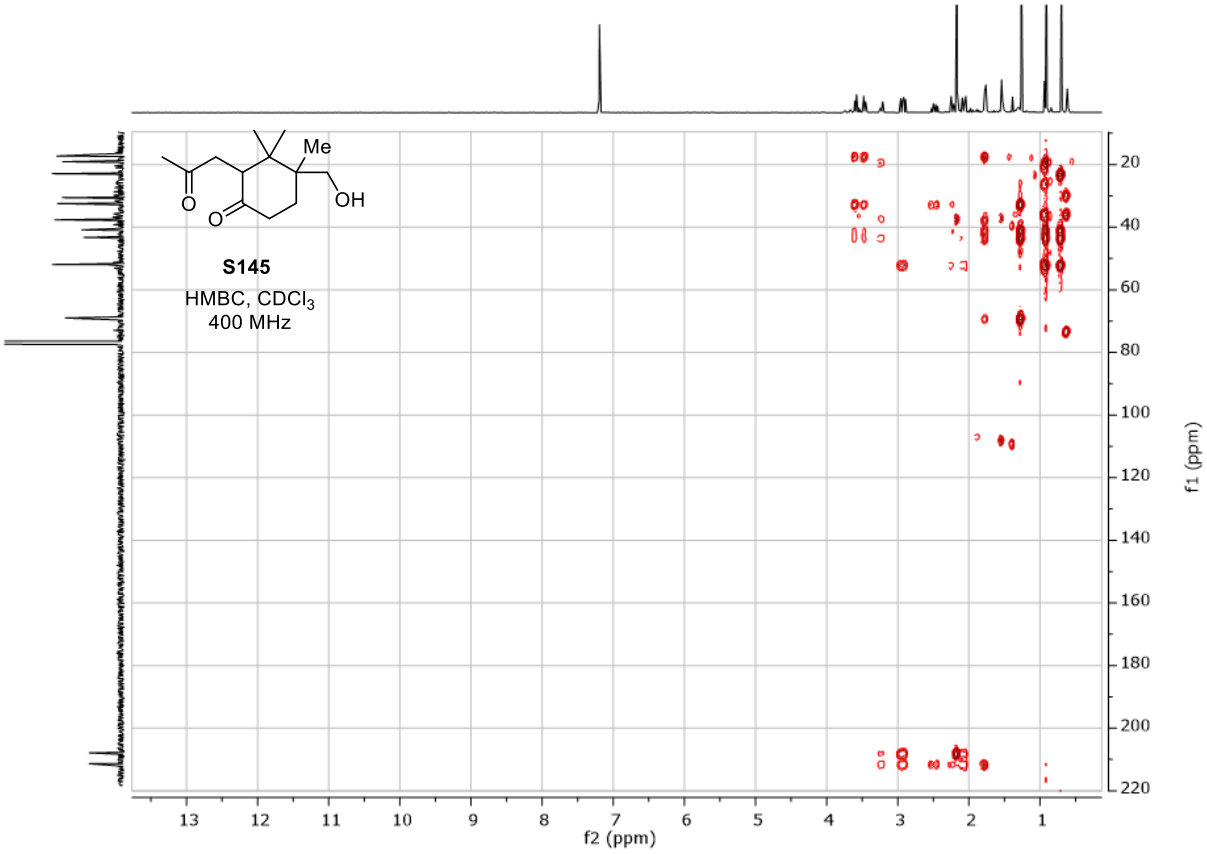


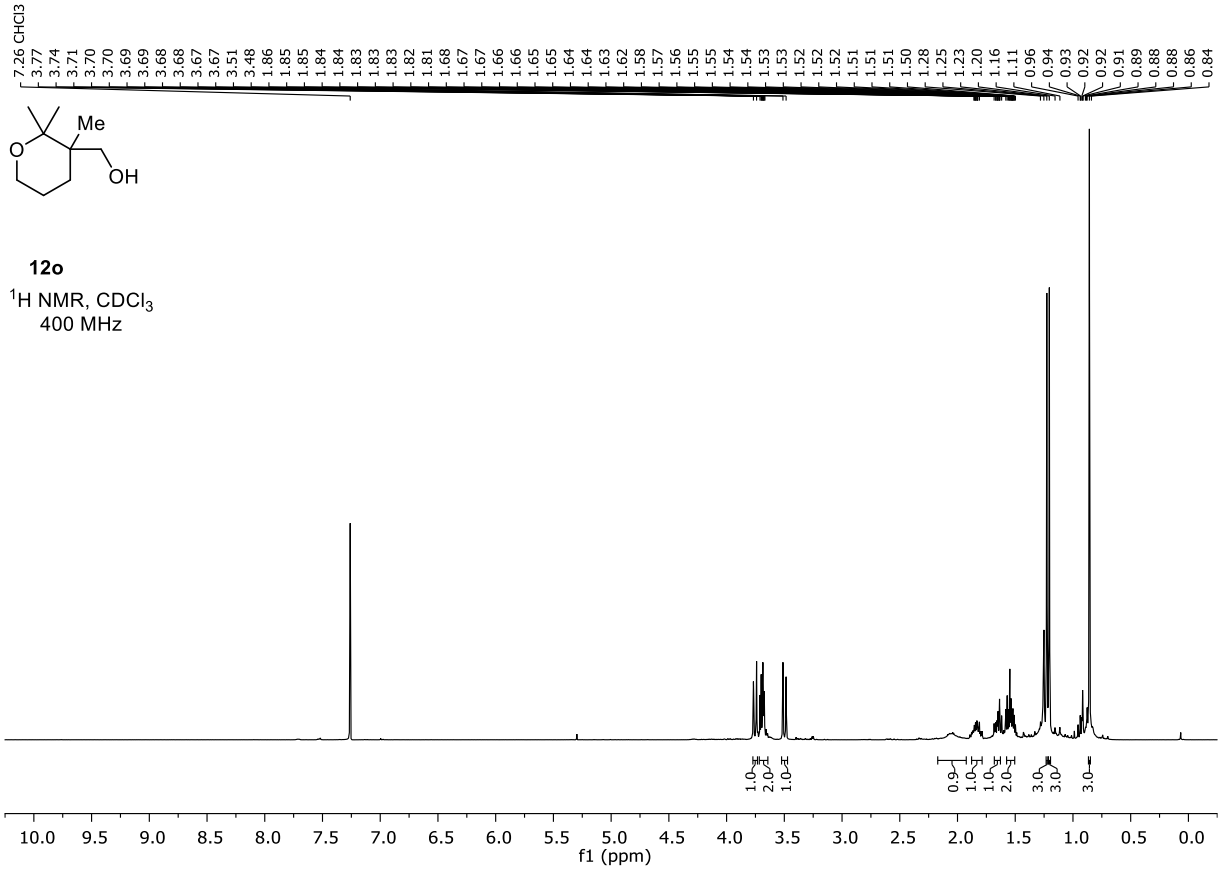
S145

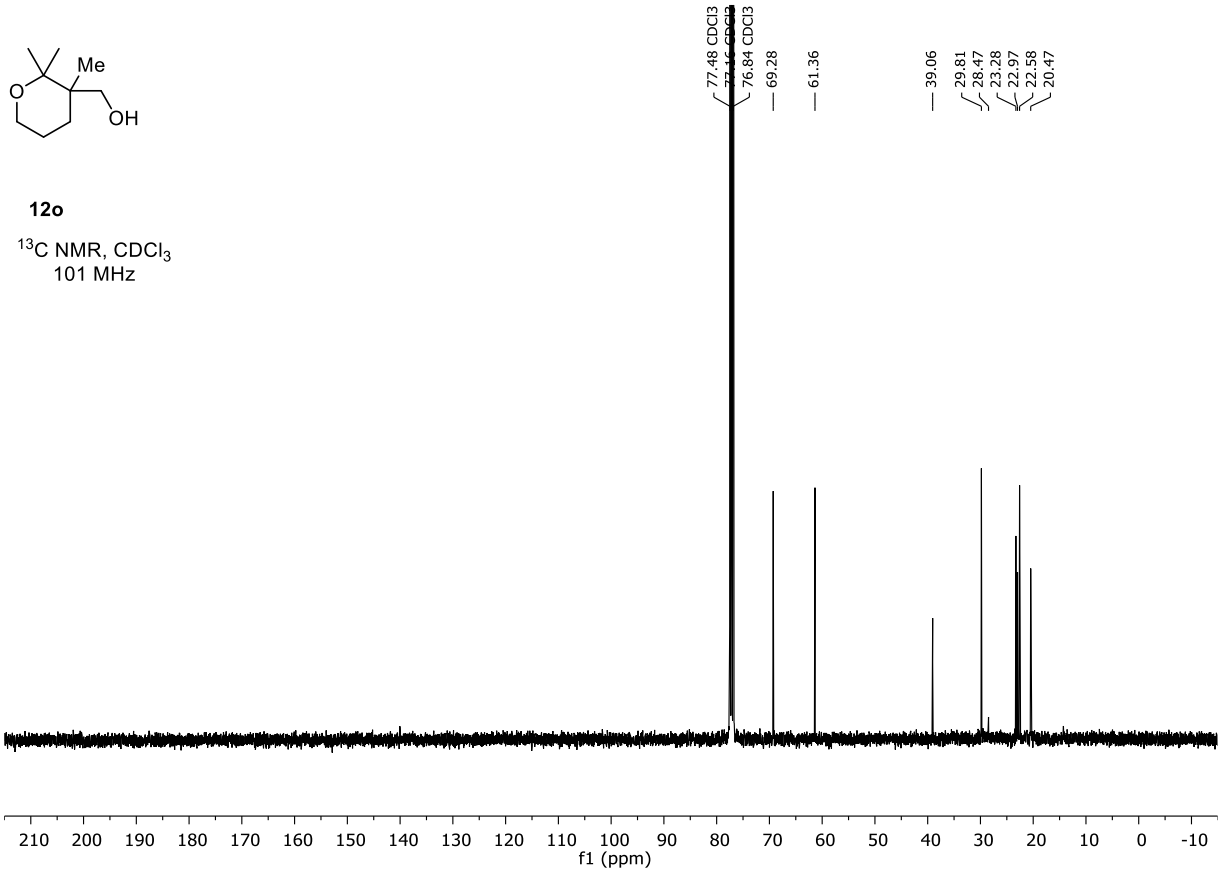
^{13}C NMR, $CDCl_3$
101 MHz

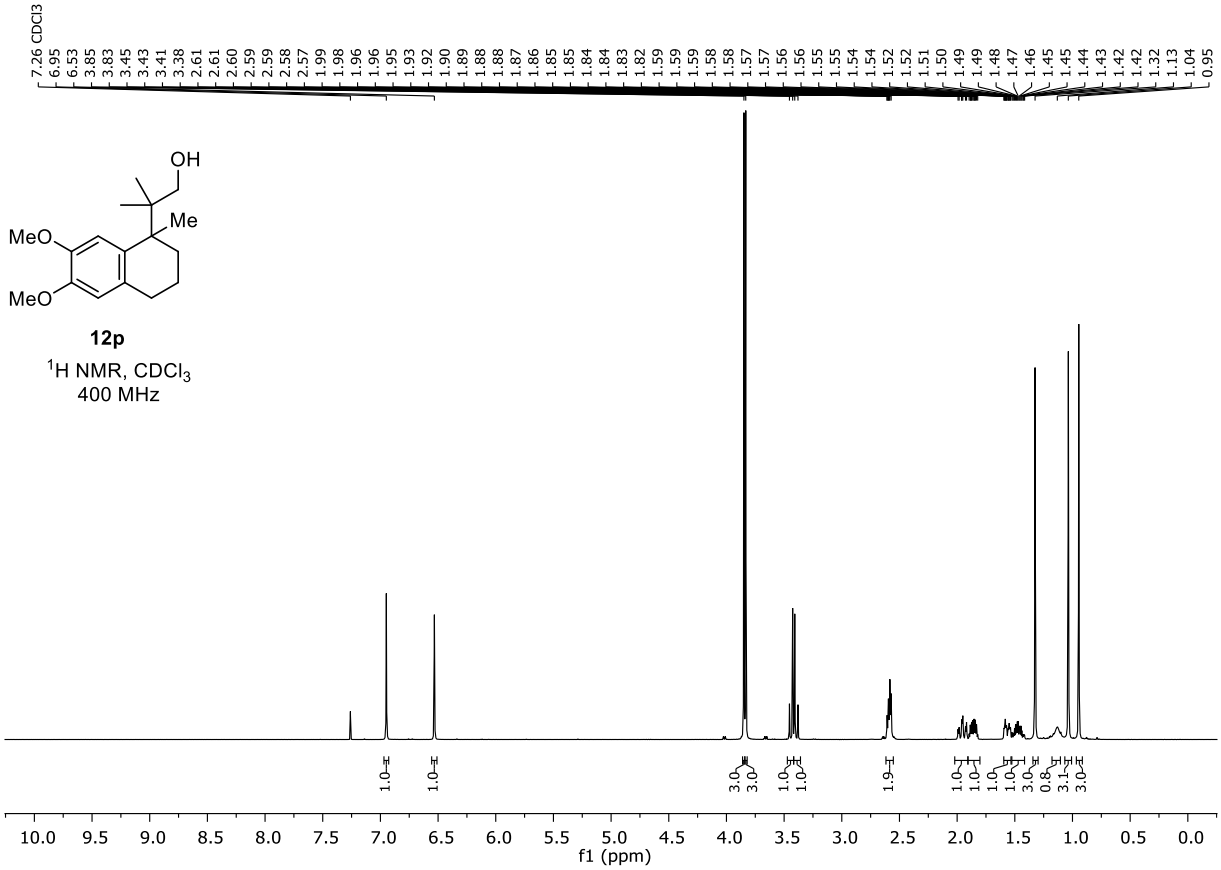

Me
OH
O
O
S145
HSQC, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)


Me
OH
O
O
S145
COSY, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)


Me
OH
O
O
S145
HMBC, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)

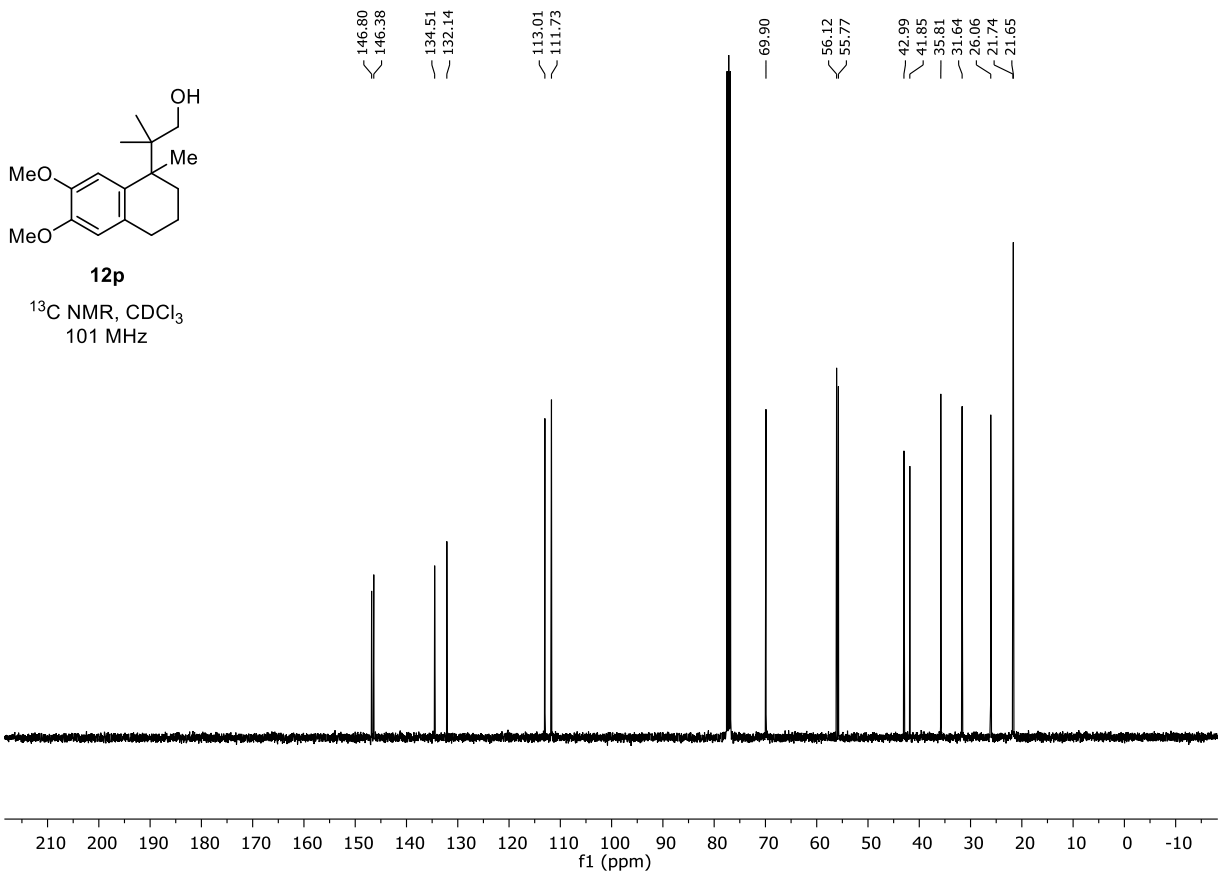

7.26 CHCl3
Me
O
OH
12o
1H NMR, CDCl3
400 MHz
f1 (ppm)


77.48 CDCl3
76.84 CDCl3
69.28
61.36
39.06
29.81
28.47
23.28
22.97
22.58
20.47
Me
O
OH
12o
13C NMR, CDCl3
101 MHz
f1 (ppm)



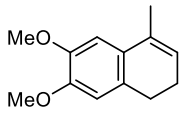
12p

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



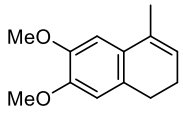
12p

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



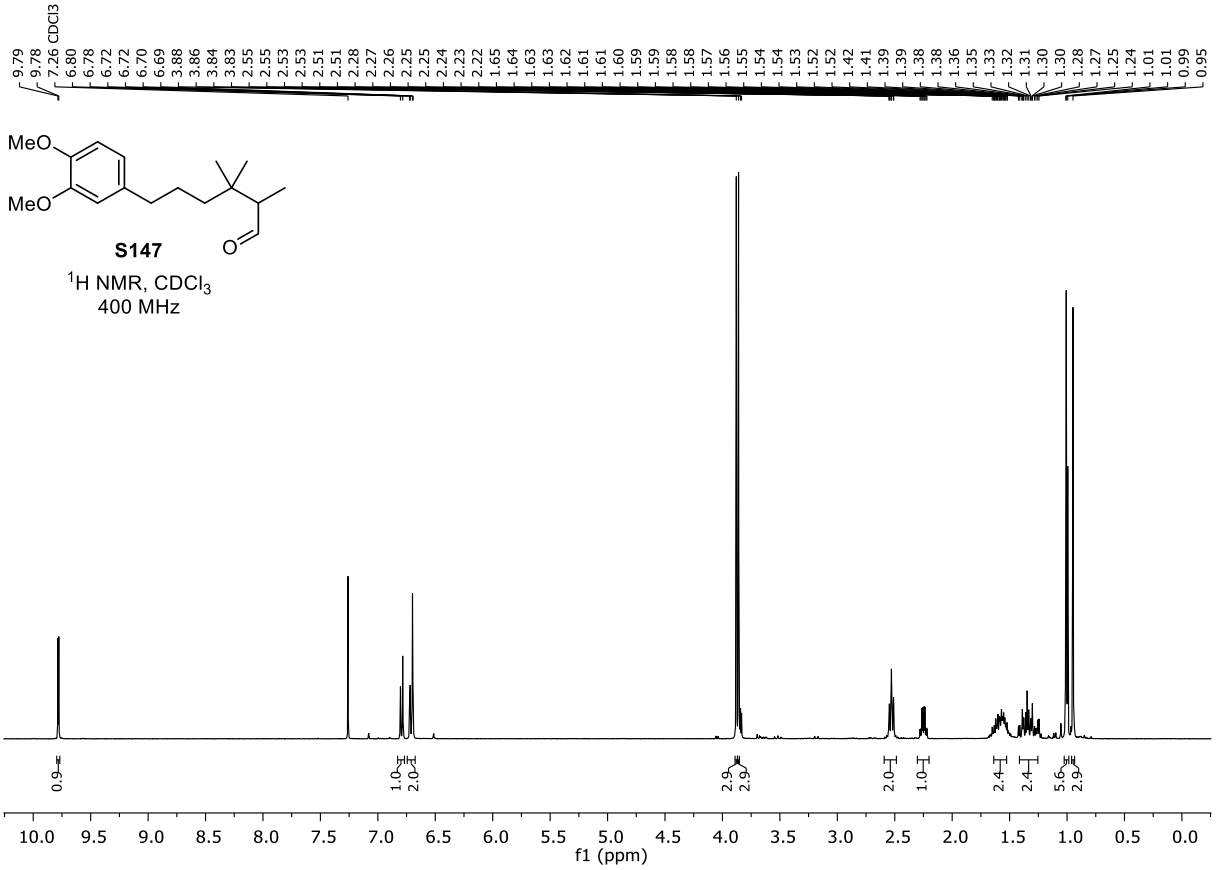
S146

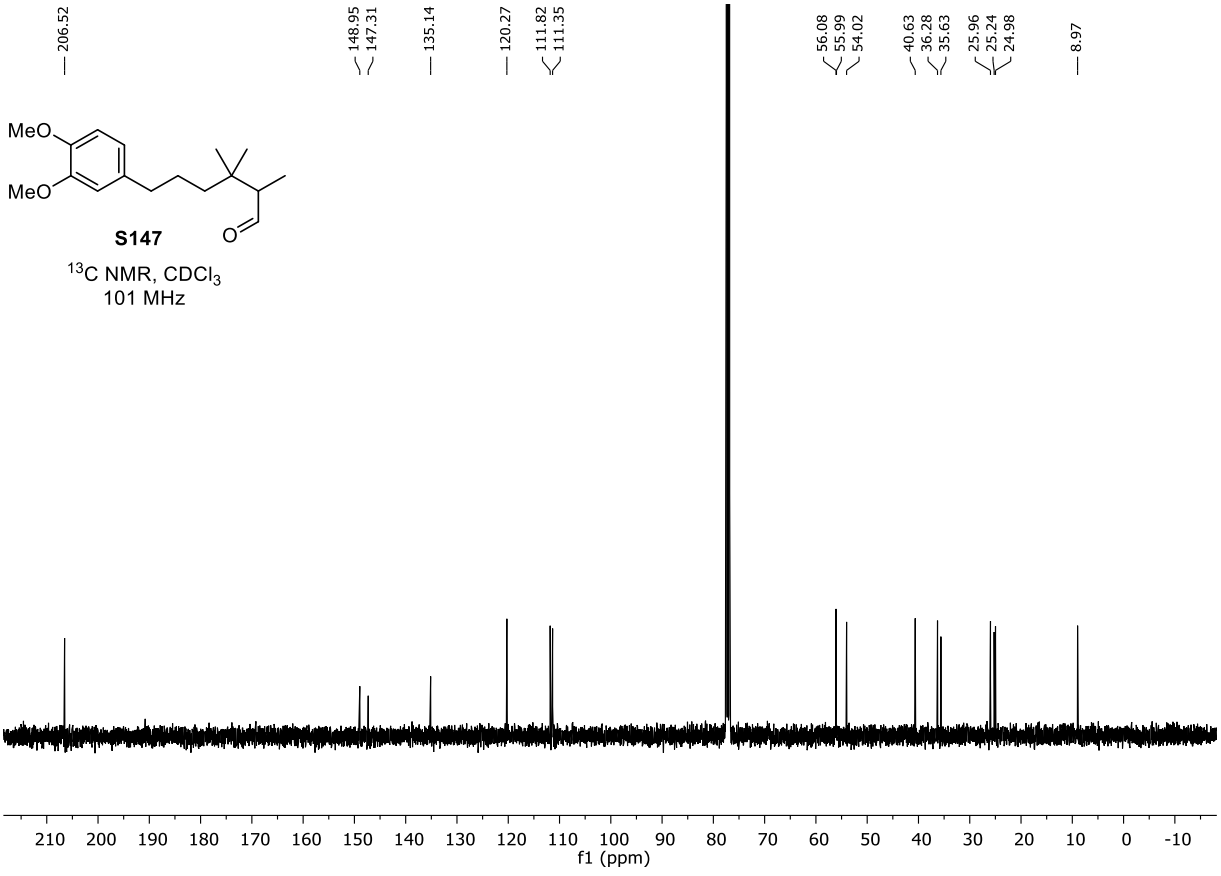
^{1}H NMR, $CDCl_3$
400 MHz

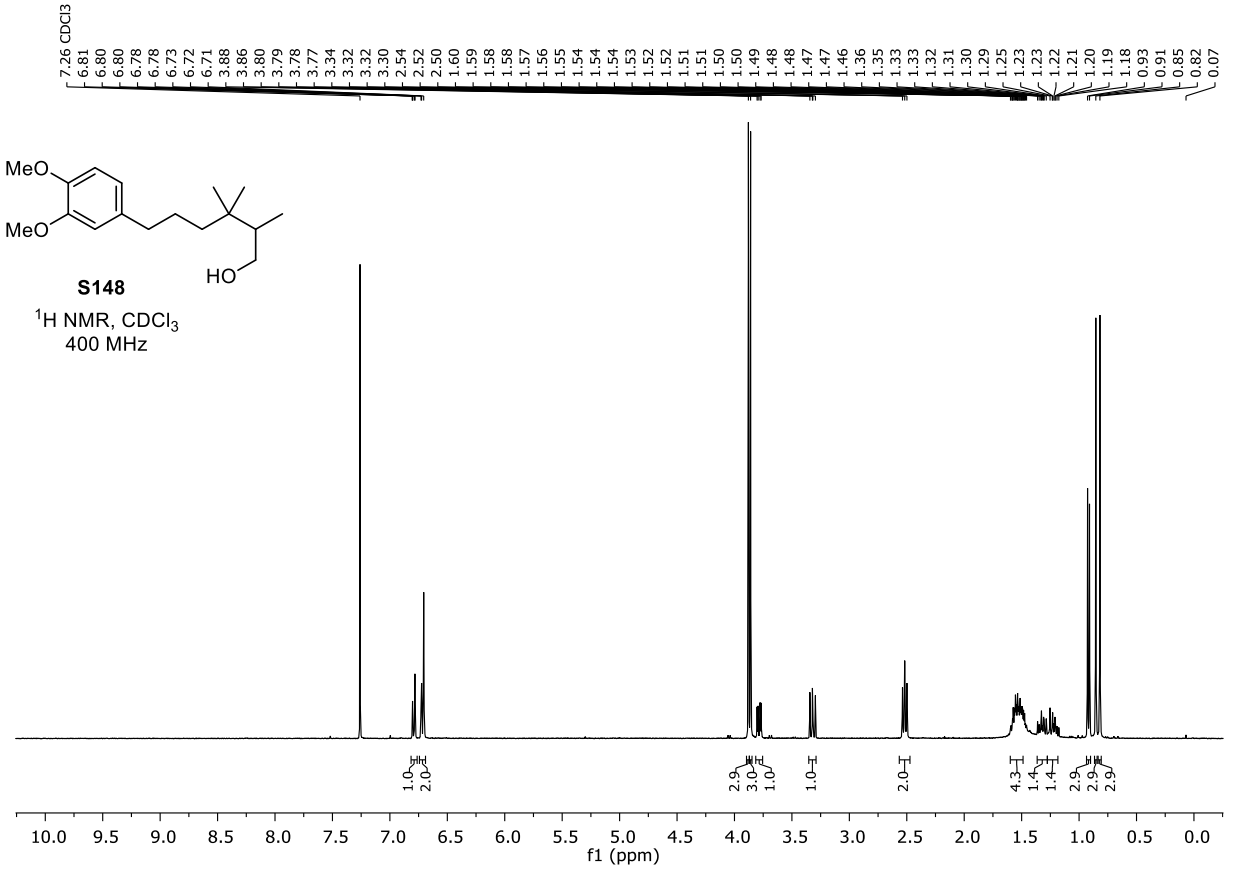


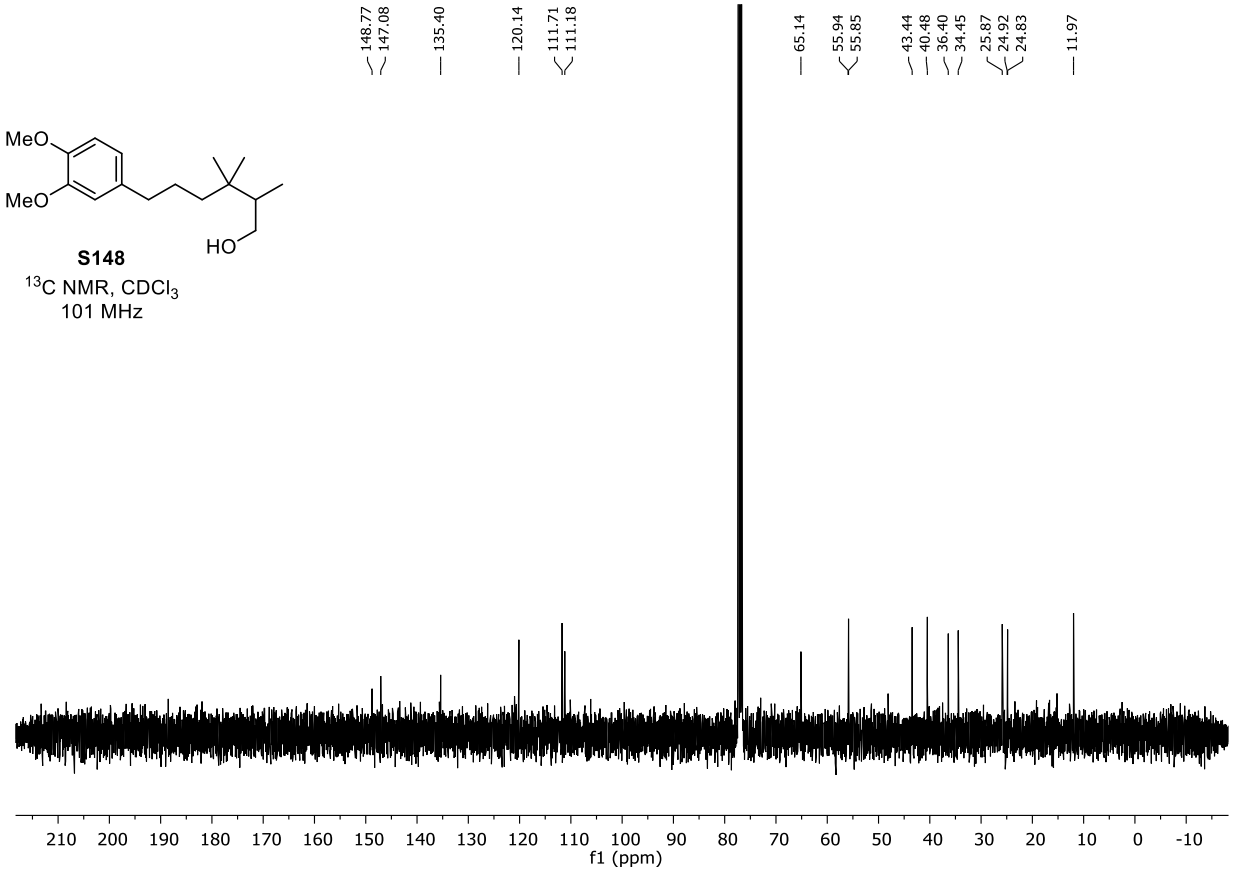
S146

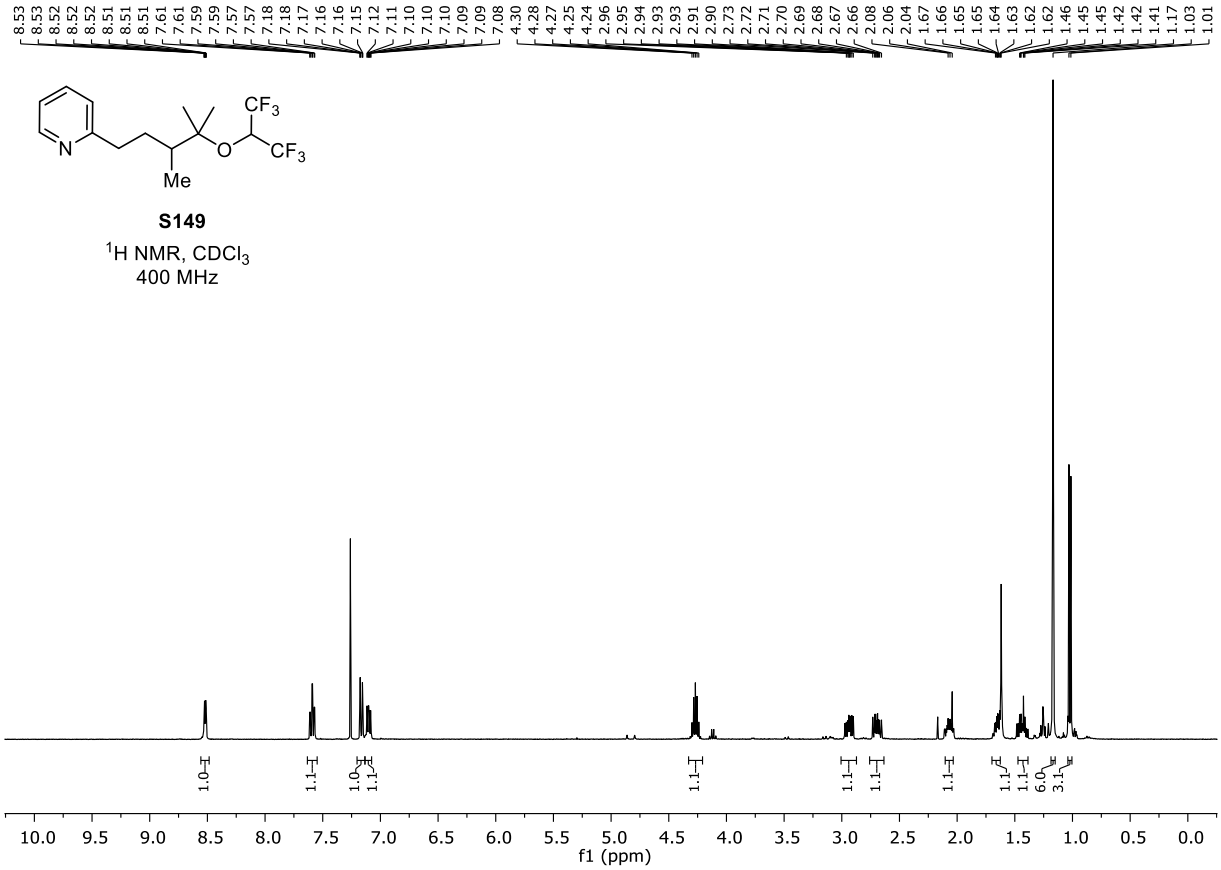
^{13}C NMR, $CDCl_3$
101 MHz

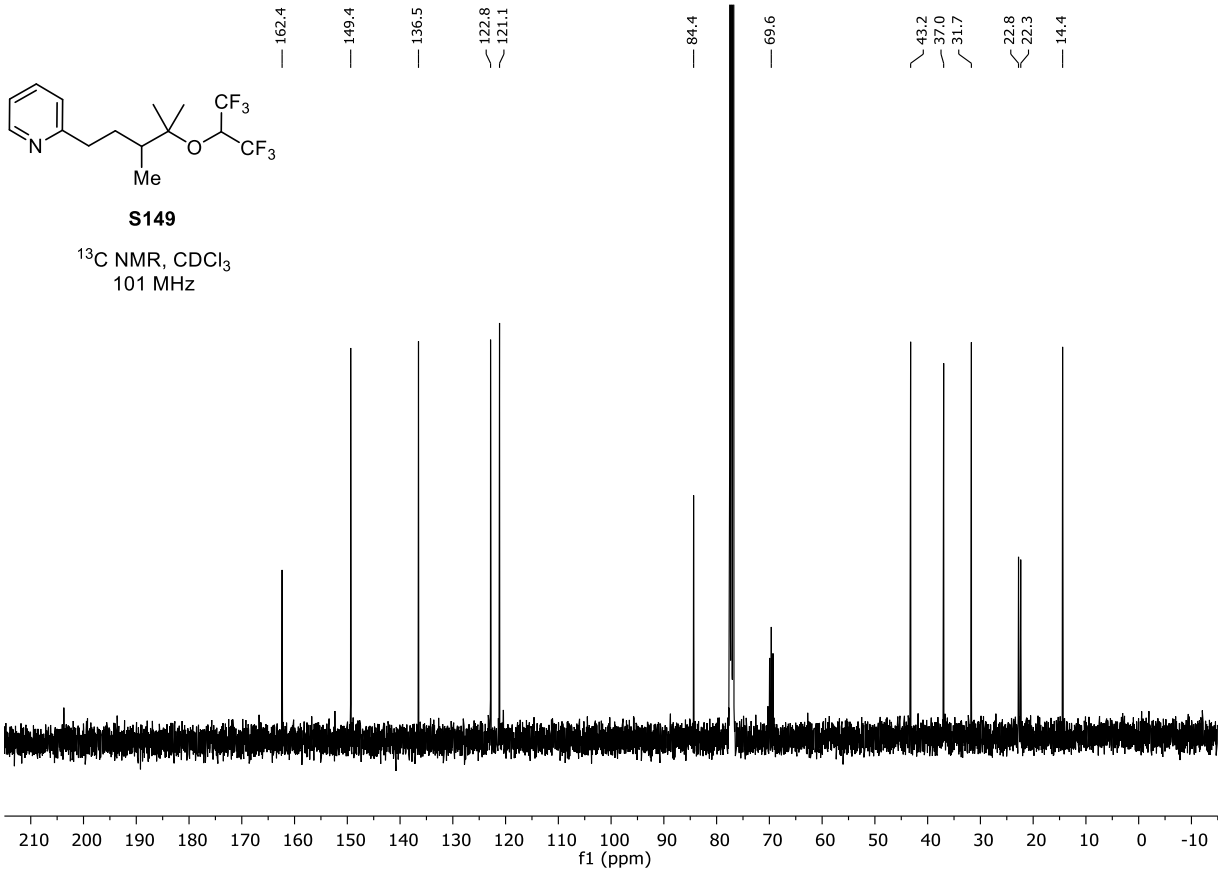

9.79
9.78
7.26 CDCl3
6.80
6.78
6.72
6.72
6.70
6.69
3.88
3.86
3.84
3.83
2.55
2.55
2.53
2.53
2.51
2.51
2.28
2.27
2.26
2.25
2.25
2.24
2.23
2.22
1.65
1.64
1.63
1.63
1.62
1.61
1.61
1.60
1.59
1.59
1.58
1.58
1.57
1.56
1.55
1.54
1.54
1.53
1.52
1.52
1.42
1.41
1.39
1.39
1.38
1.38
1.36
1.35
1.33
1.32
1.31
1.30
1.30
1.28
1.27
1.25
1.24
1.01
1.01
0.99
0.95
MeO
MeO
O
S147
1H NMR, CDCl3
400 MHz
0.9
1.0
2.0
2.9
2.9
2.0
1.0
2.4
2.4
5.6
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)

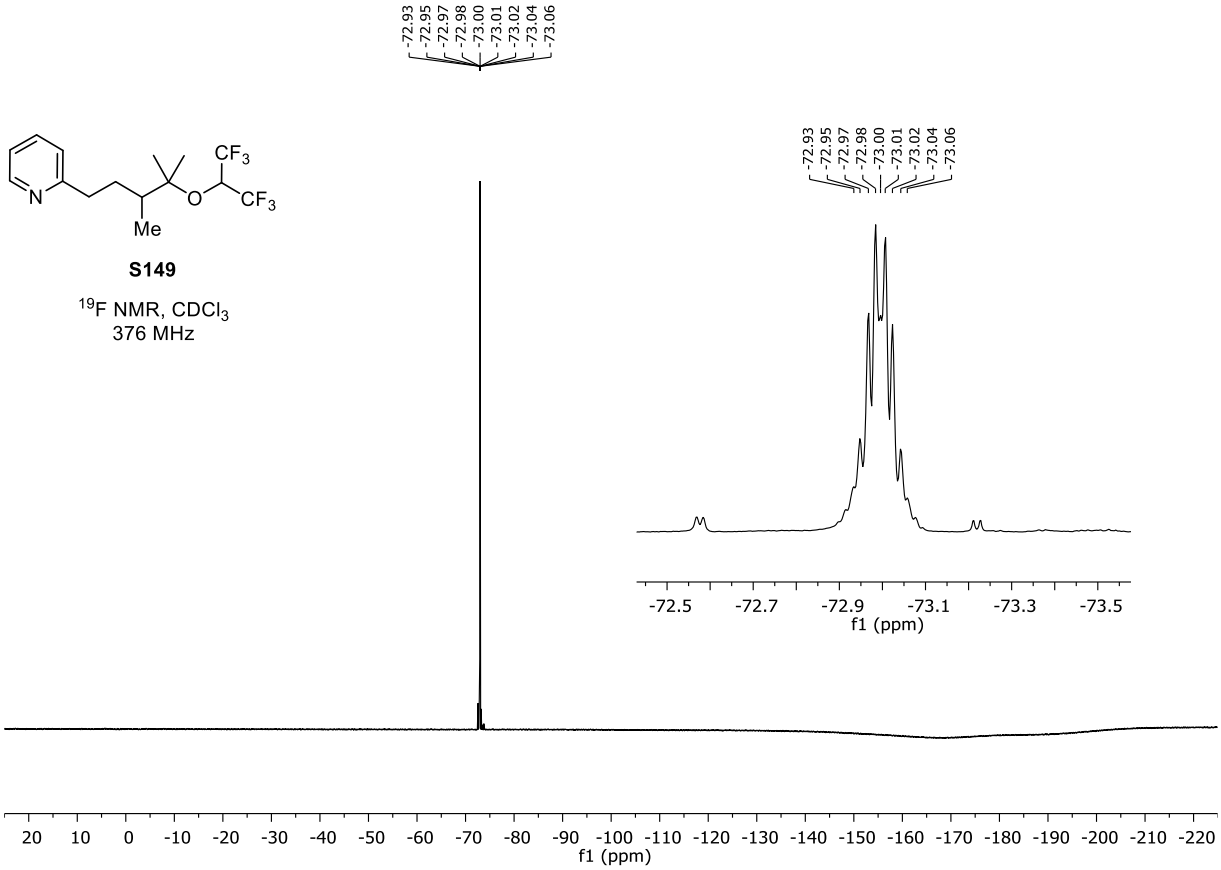

206.52
148.95
147.31
135.14
120.27
111.82
111.35
56.08
55.99
54.02
40.63
36.28
35.63
25.96
25.24
24.98
8.97
MeO
MeO
O
S147
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

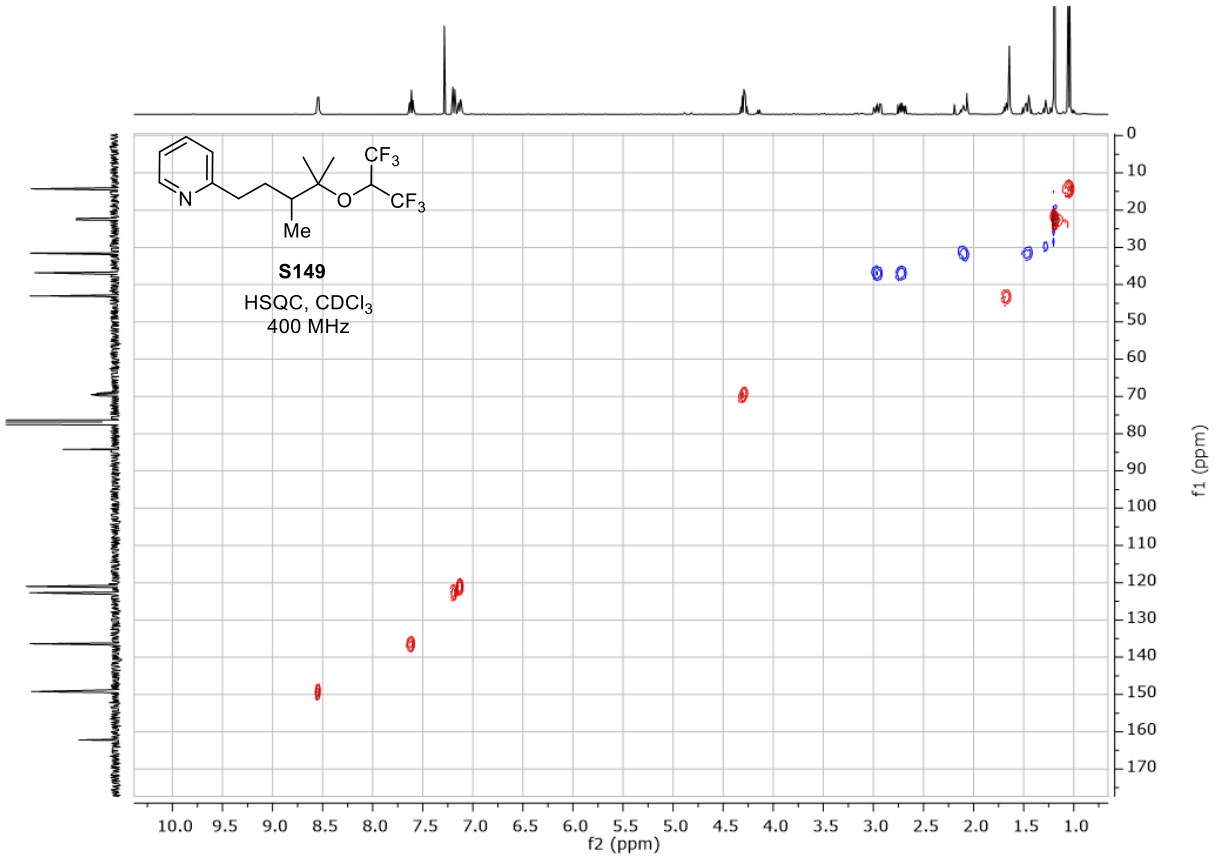

MeO
MeO
HO
S148
1H NMR, CDCl3
400 MHz
f1 (ppm)

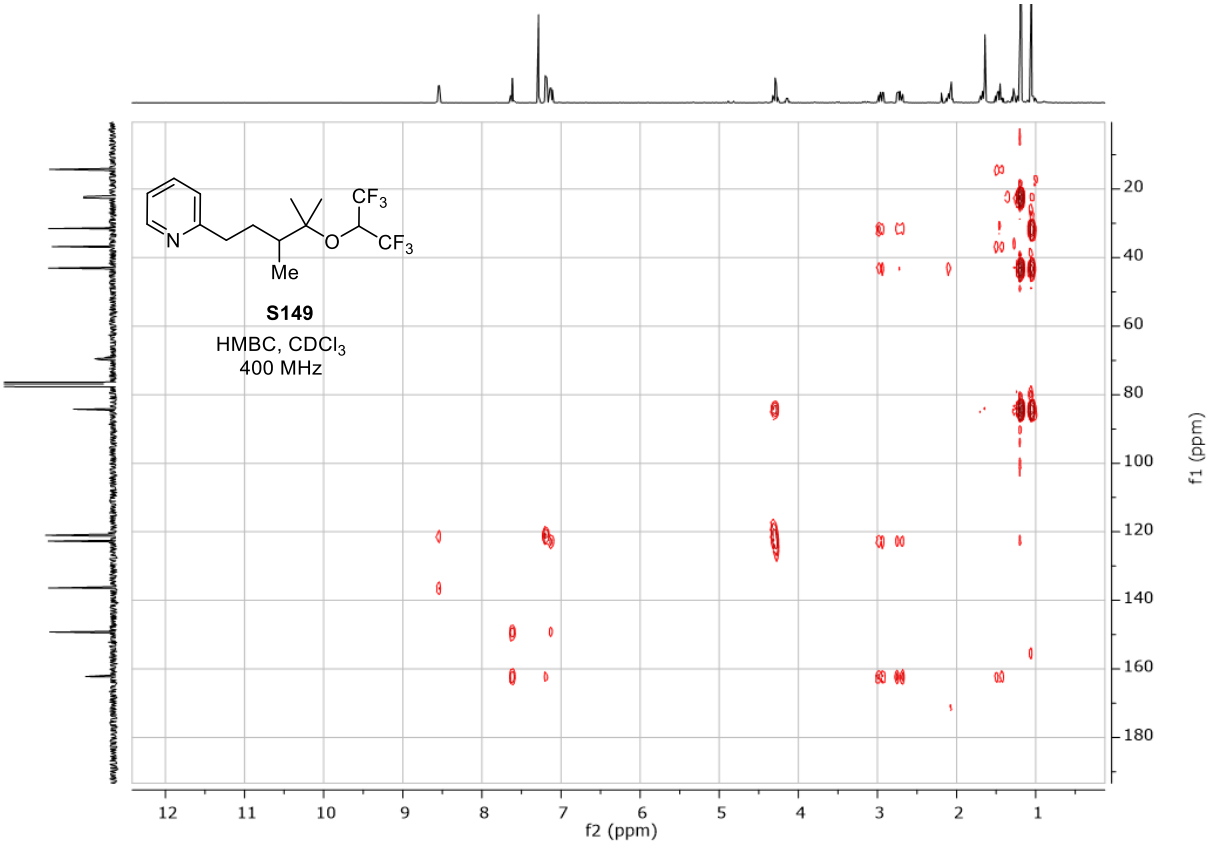

MeO
MeO
HO
S148
13C NMR, CDCl3
101 MHz
f1 (ppm)

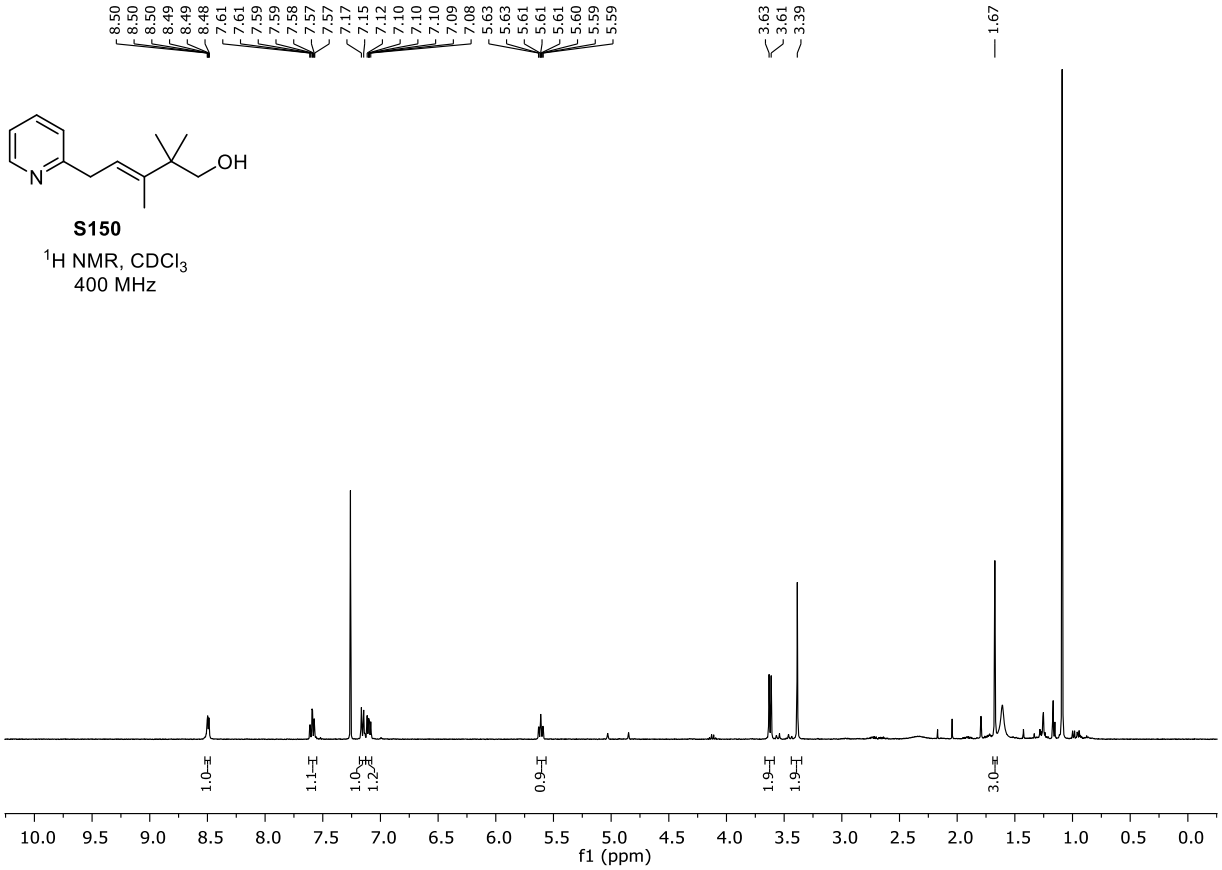

8.53 8.53 8.52 8.52 8.52 8.51 8.51 8.51 7.61 7.61 7.59 7.59 7.57 7.57 7.18 7.17 7.16 7.16 7.15 7.12 7.11 7.10 7.10 7.10 7.09 7.09 7.08
4.30 4.28 4.27 4.25 4.24 2.96 2.95 2.94 2.93 2.93 2.91 2.90 2.73 2.72 2.71 2.70 2.69 2.68 2.67 2.66 2.08 2.06 2.04 1.67 1.66 1.65 1.65 1.64 1.63 1.62 1.62 1.46 1.45 1.45 1.42 1.42 1.41 1.17 1.03 1.01
CF3
CF3
O
N
Me
S149
1H NMR, CDCl3
400 MHz
1.0 1.1 1.0 1.1 1.1 1.1 1.1 1.1 1.1 6.0 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)


162.4 149.4 136.5 122.8 121.1 84.4 69.6 43.2 37.0 31.7 22.8 22.3 14.4
CF3
CF3
O
N
Me
S149
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)


-72.93
-72.95
-72.97
-72.98
-73.00
-73.01
-73.02
-73.04
-73.06
CF3
CF3
O
N
Me
S149
19F NMR, CDCl3
376 MHz
-72.5
-72.7
-72.9
-73.1
-73.3
-73.5
f1 (ppm)
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

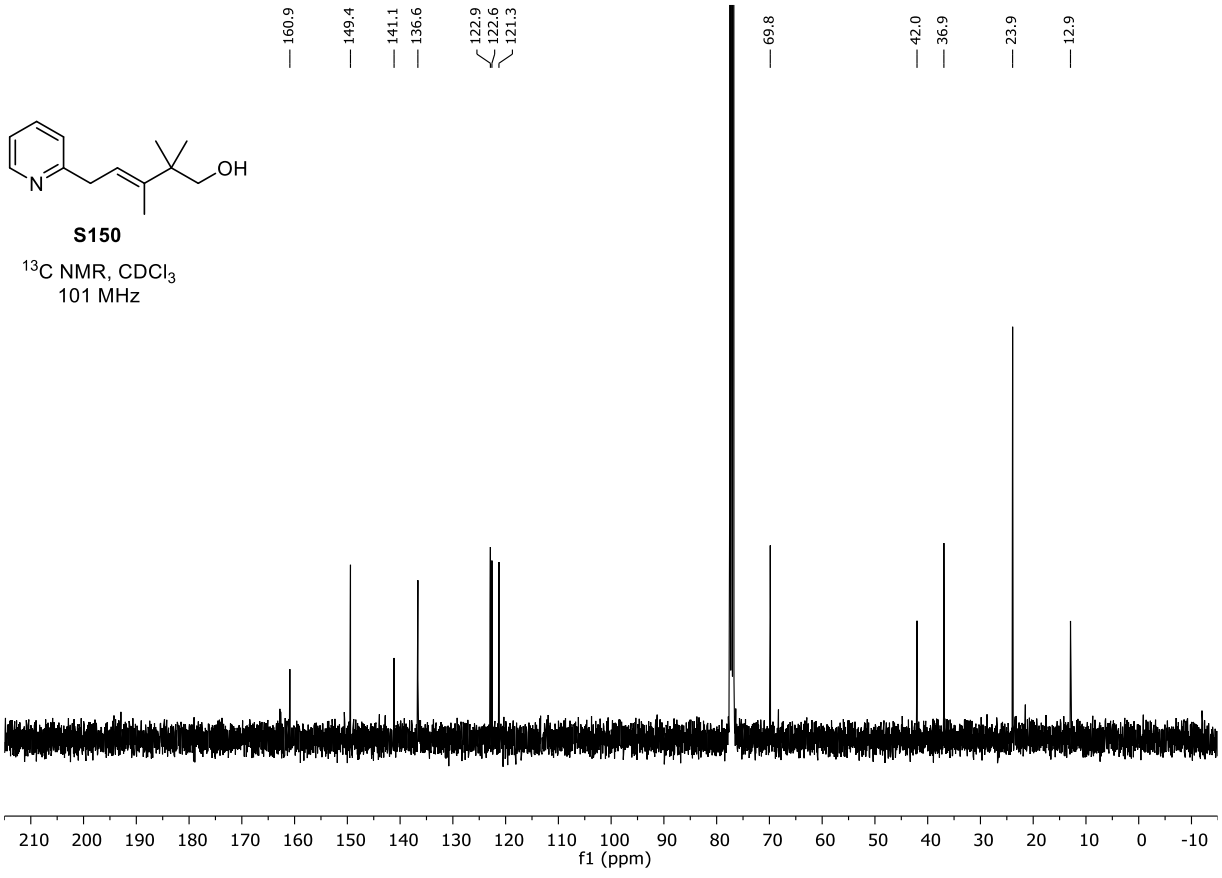

CF3
CF3
O
N
Me
S149
HSQC, CDCl3
400 MHz
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f2 (ppm)
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170
f1 (ppm)


CF3
CF3
N
O
Me
S149
HMBC, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)



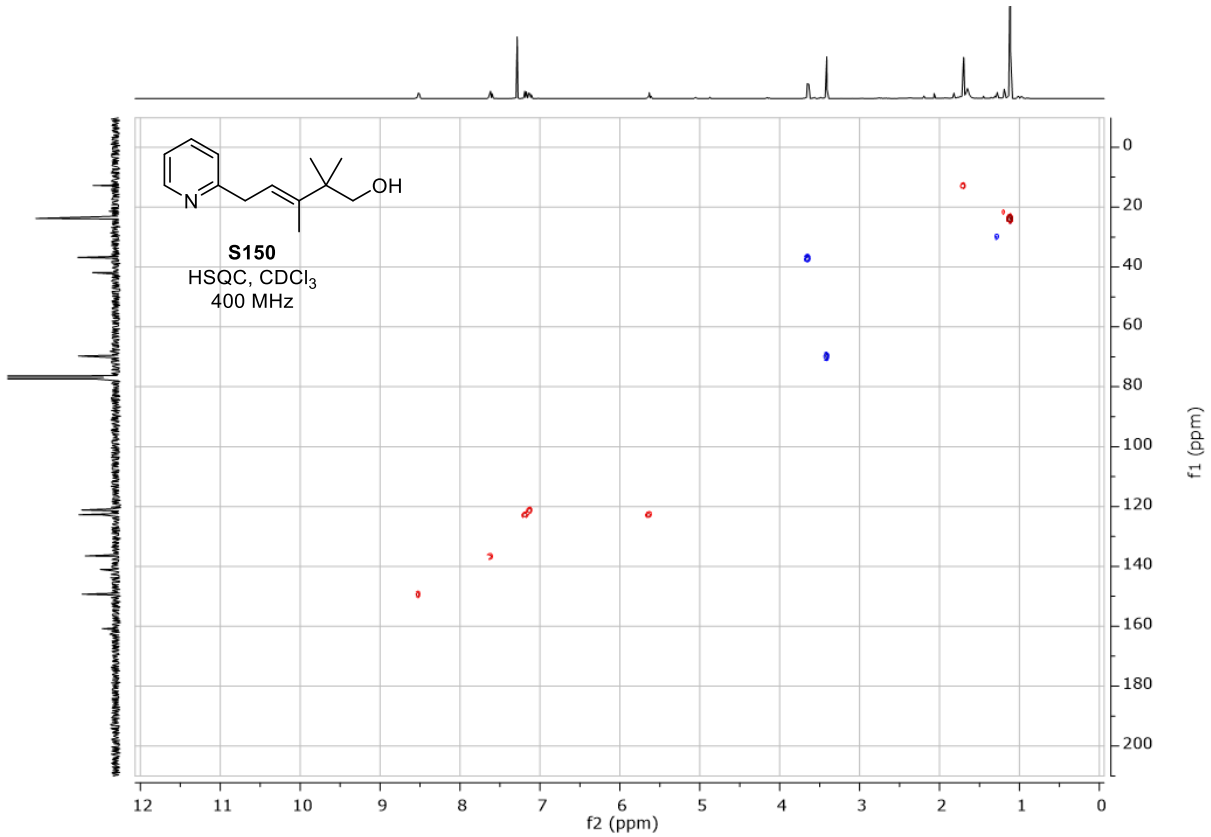
S150

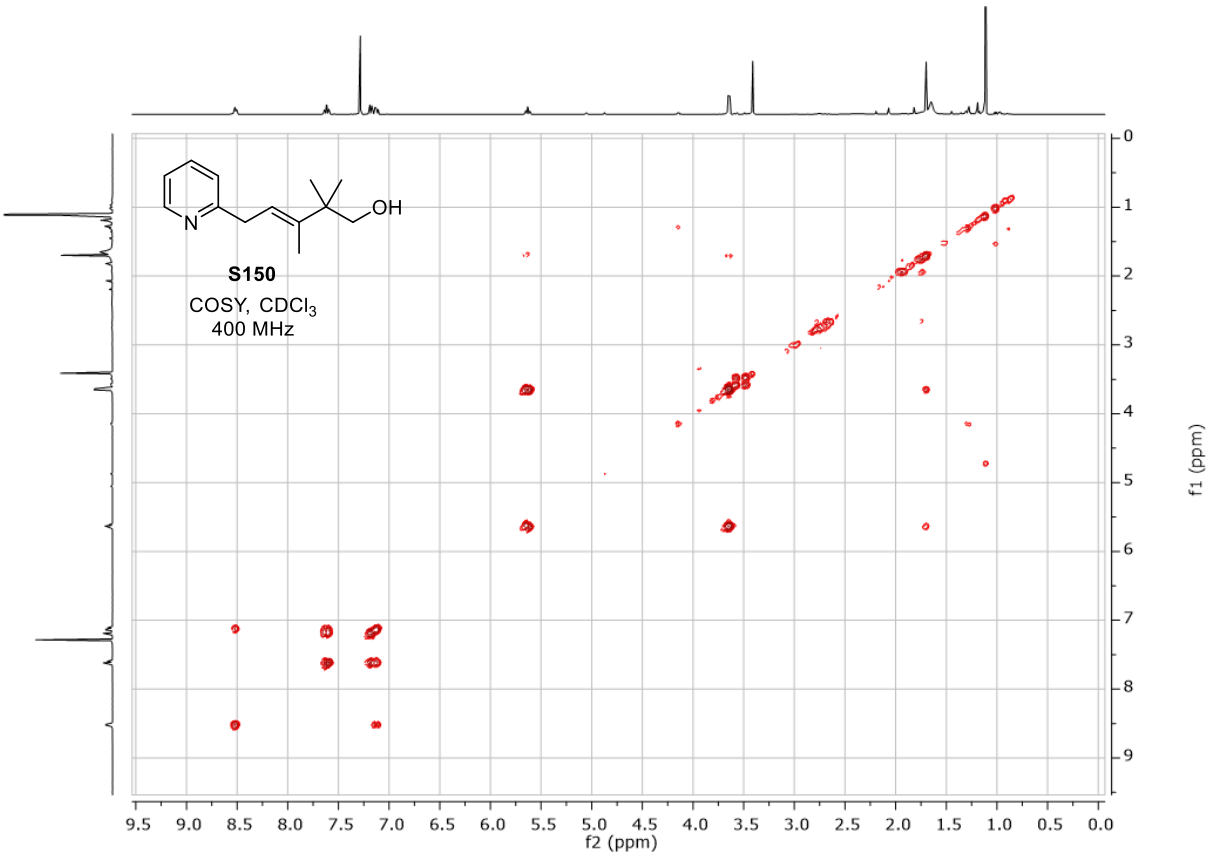
^{1}H NMR, $CDCl_3$
400 MHz

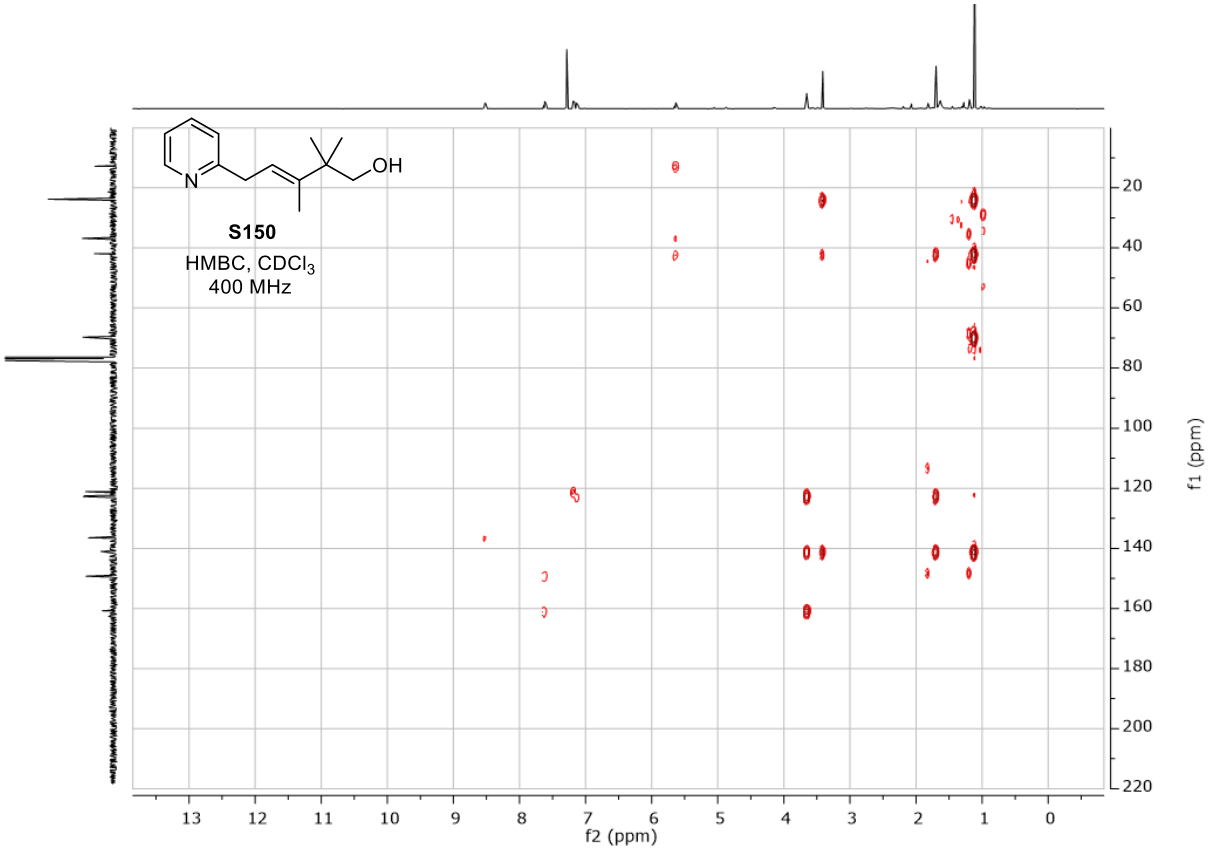


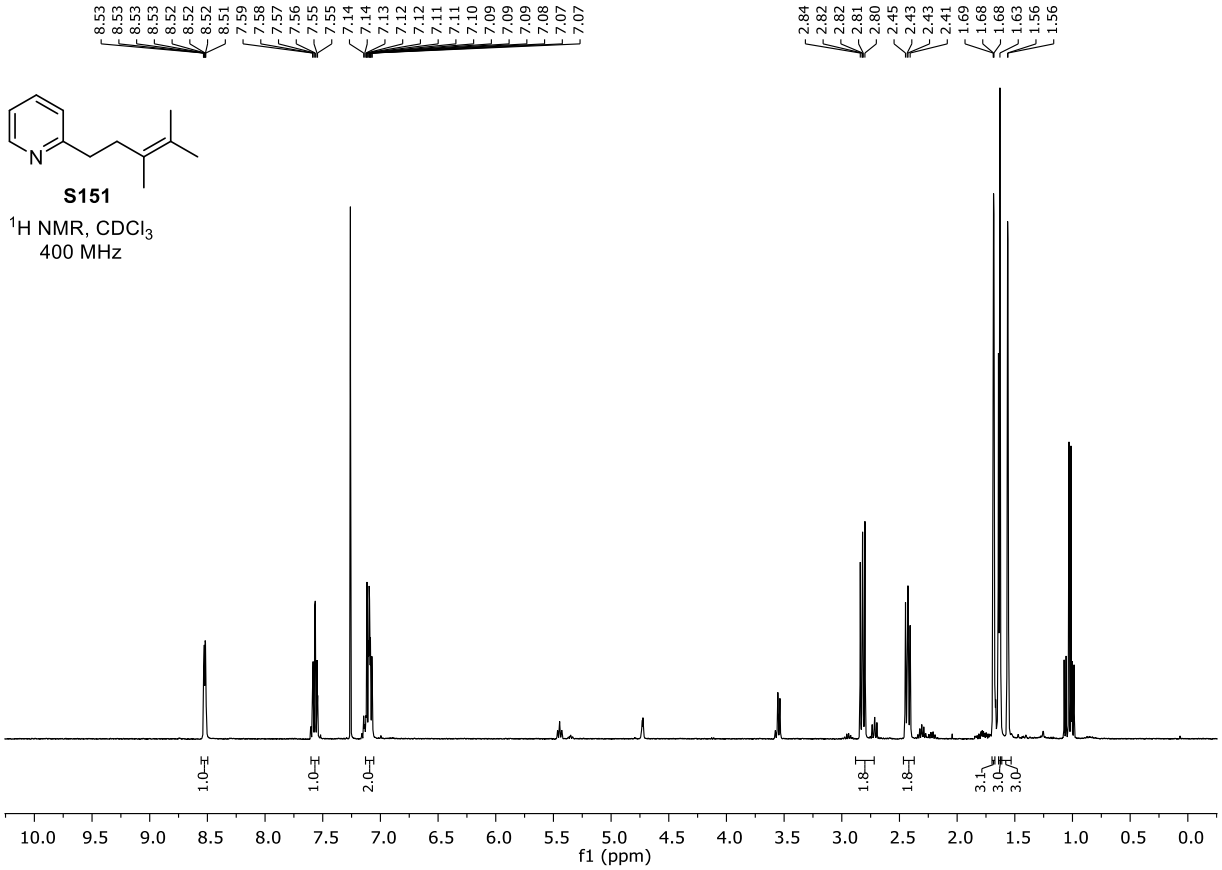
S150

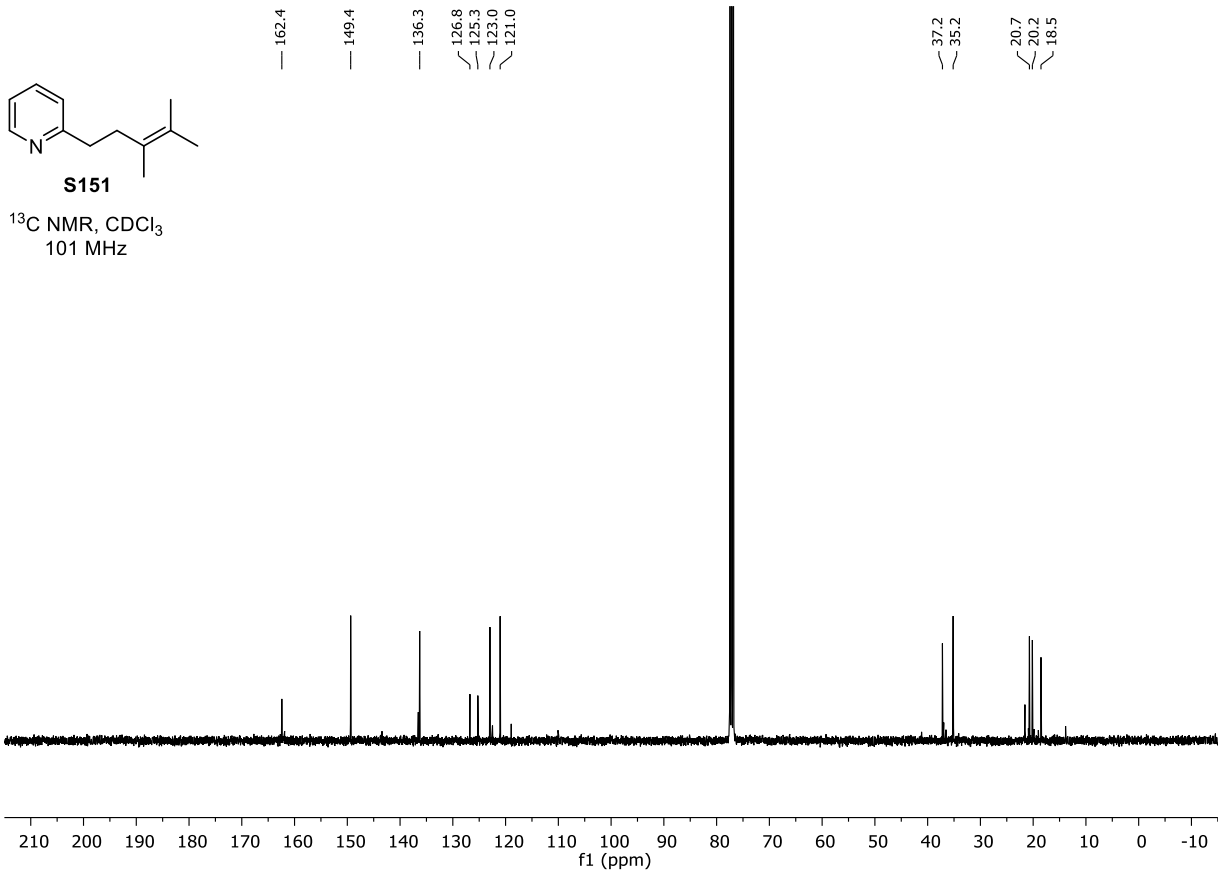
^{13}C NMR, $CDCl_3$
101 MHz

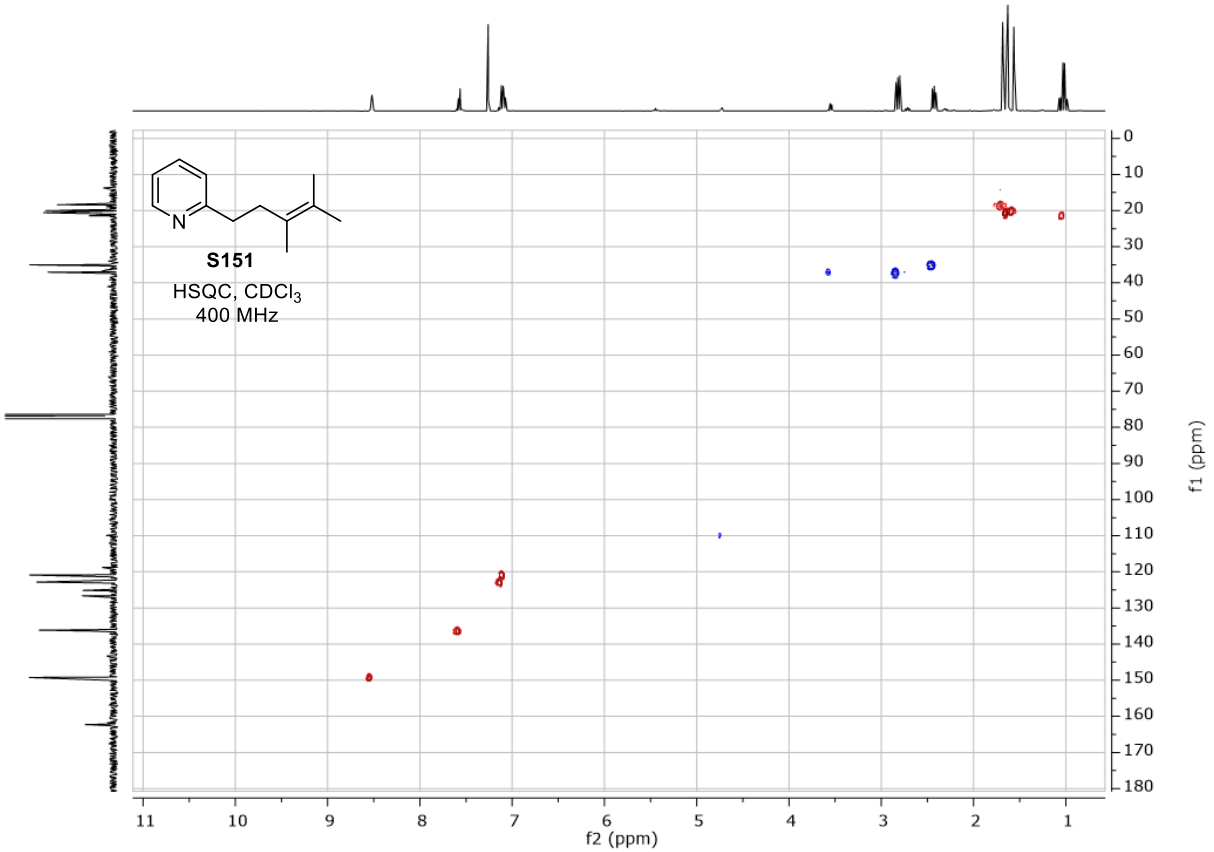

OH
N
S150
HSQC, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)

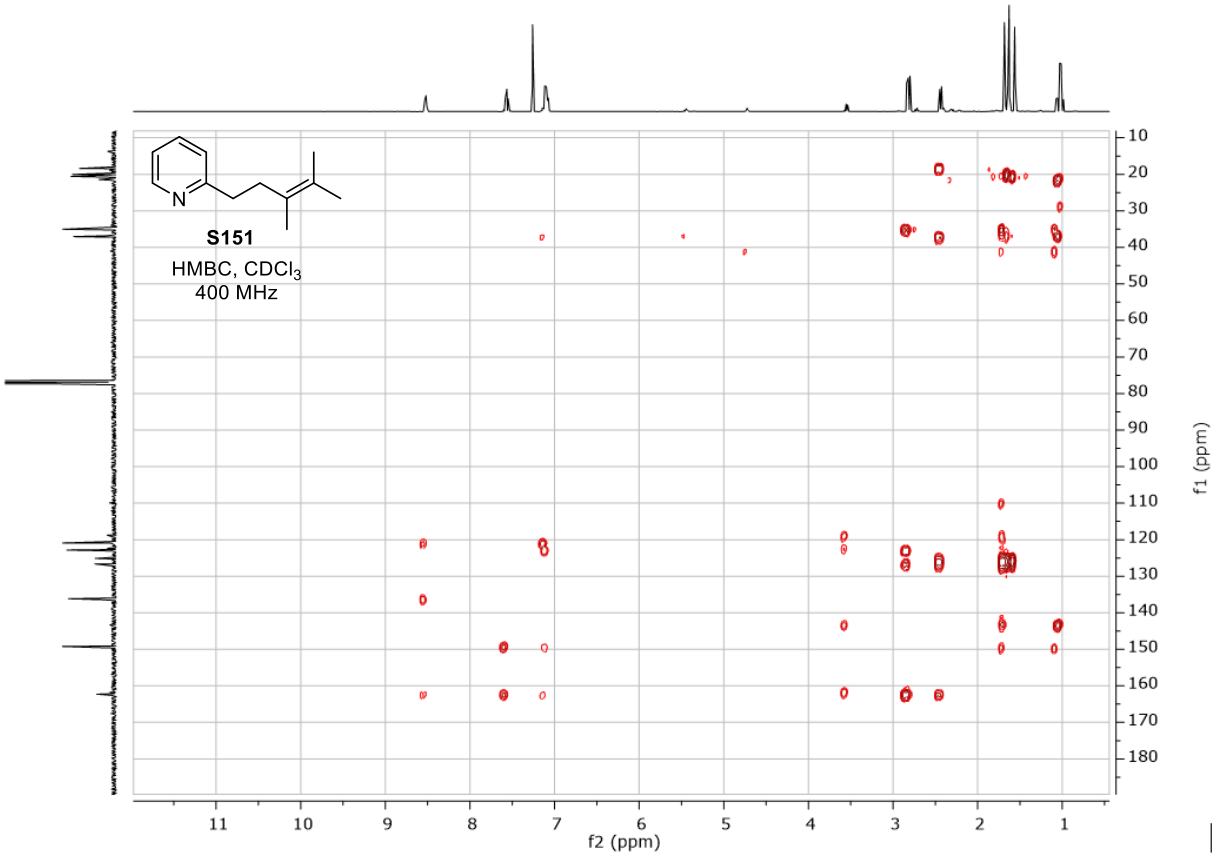

OH
N
S150
COSY, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)

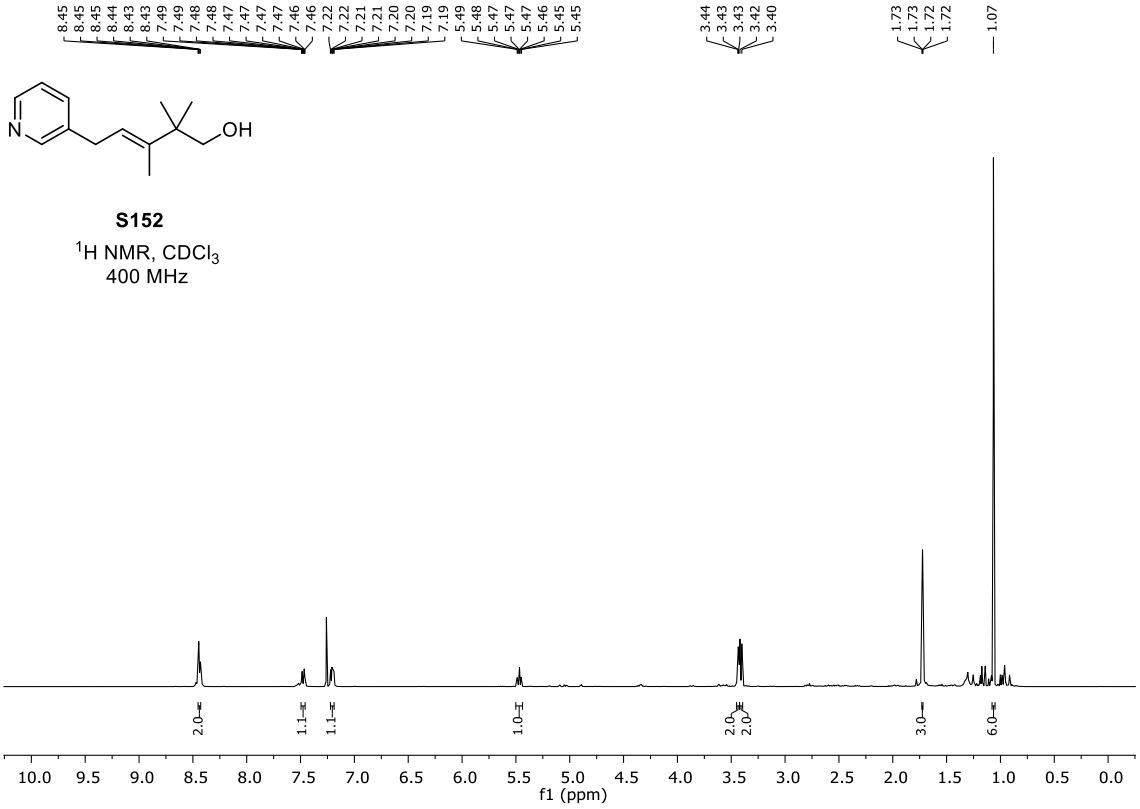

OH
N
S150
HMBC, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)


8.53 8.53 8.53 8.53 8.52 8.52 8.52 8.51 7.59 7.58 7.57 7.56 7.55 7.55 7.55 7.14 7.14 7.13 7.12 7.12 7.11 7.11 7.10 7.09 7.09 7.09 7.08 7.07 7.07
2.84 2.82 2.82 2.81 2.80 2.45 2.43 2.43 2.41 1.69 1.68 1.68 1.63 1.56 1.56
N
S151
^{1}H NMR, $CDCl_3$
400 MHz
1.0 1.0 2.0 1.8 1.8 3.1 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)


162.4 149.4 136.3 126.8 125.3 123.0 121.0 37.2 35.2 20.7 20.2 18.5
N
S151
^{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)

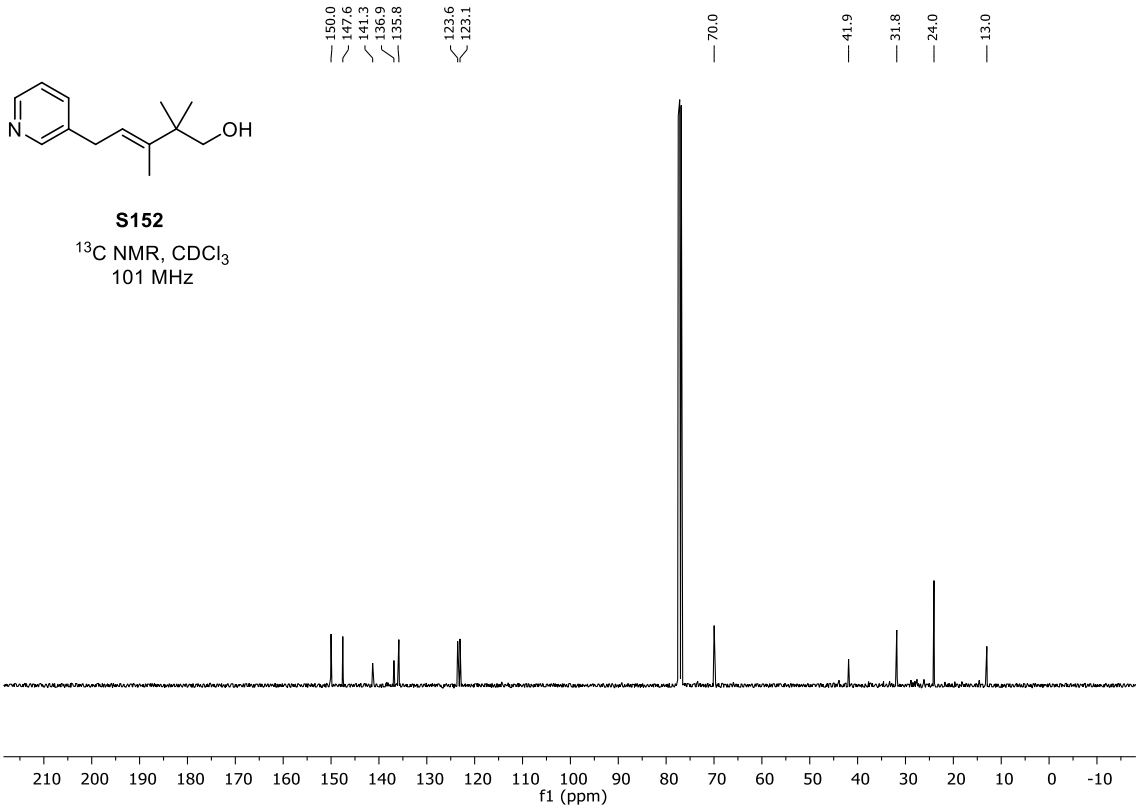

S151
HSQC, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)


S151
HMBC, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)



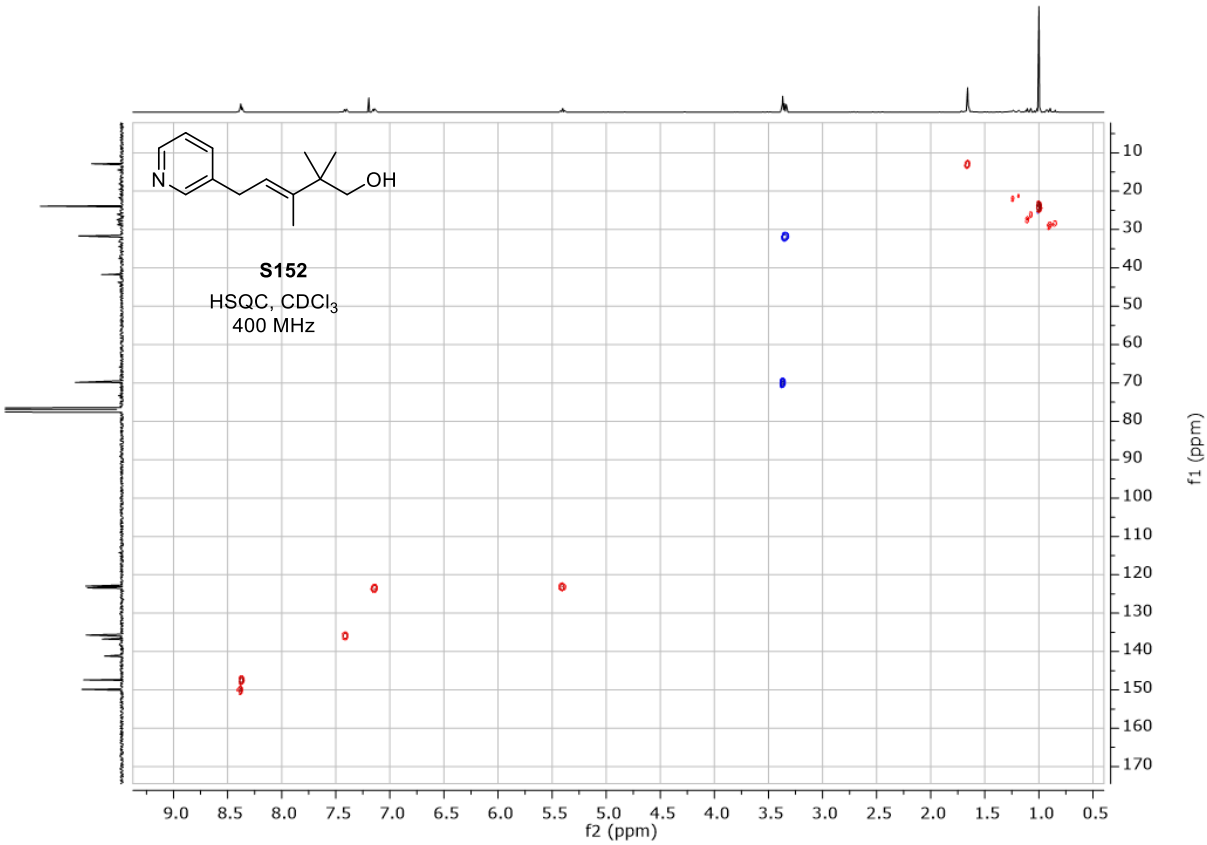
S152

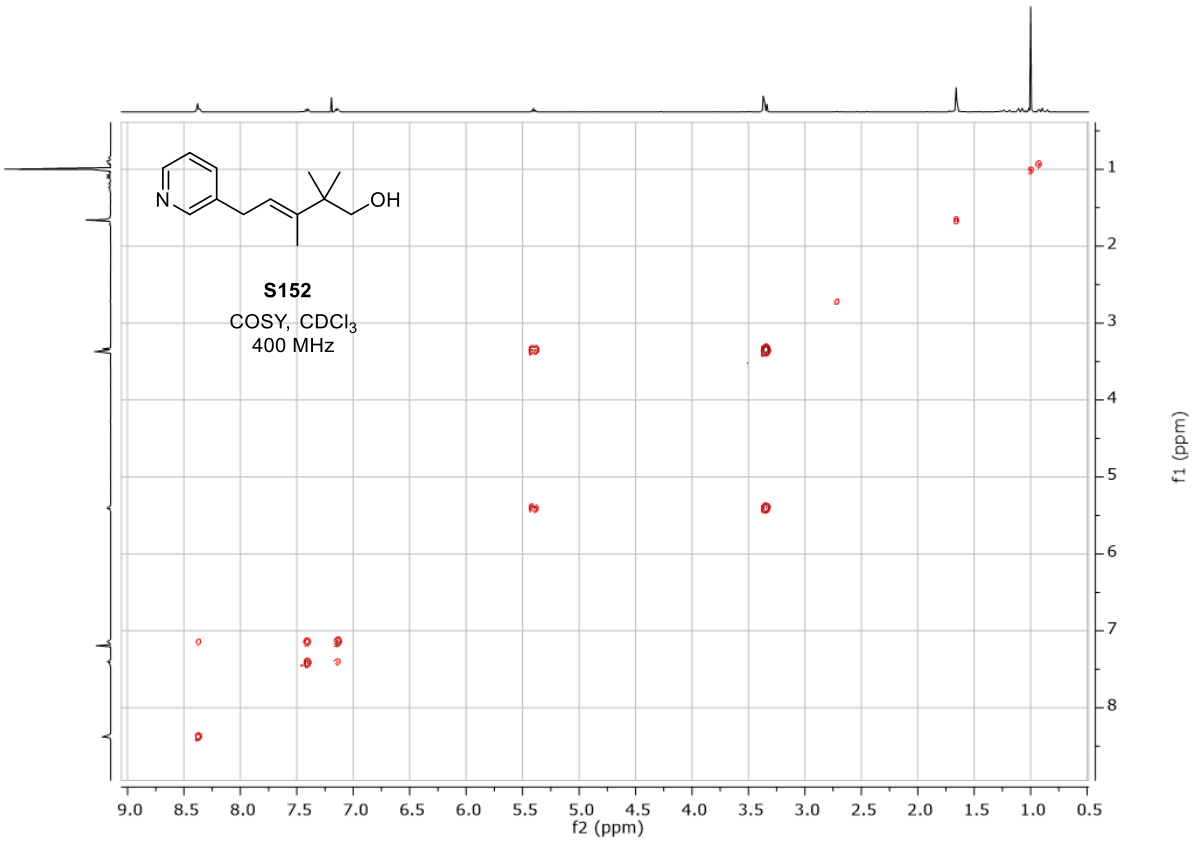
^{1}H NMR, $CDCl_3$
400 MHz

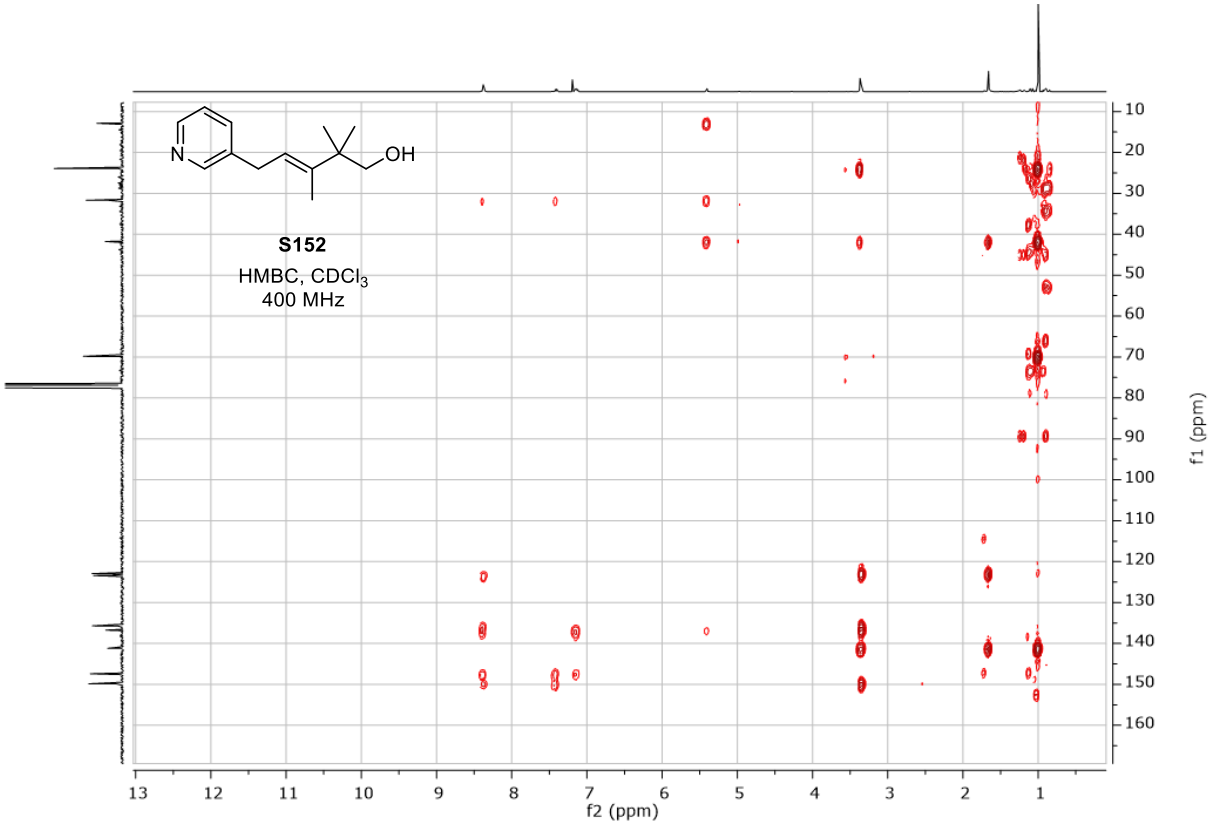


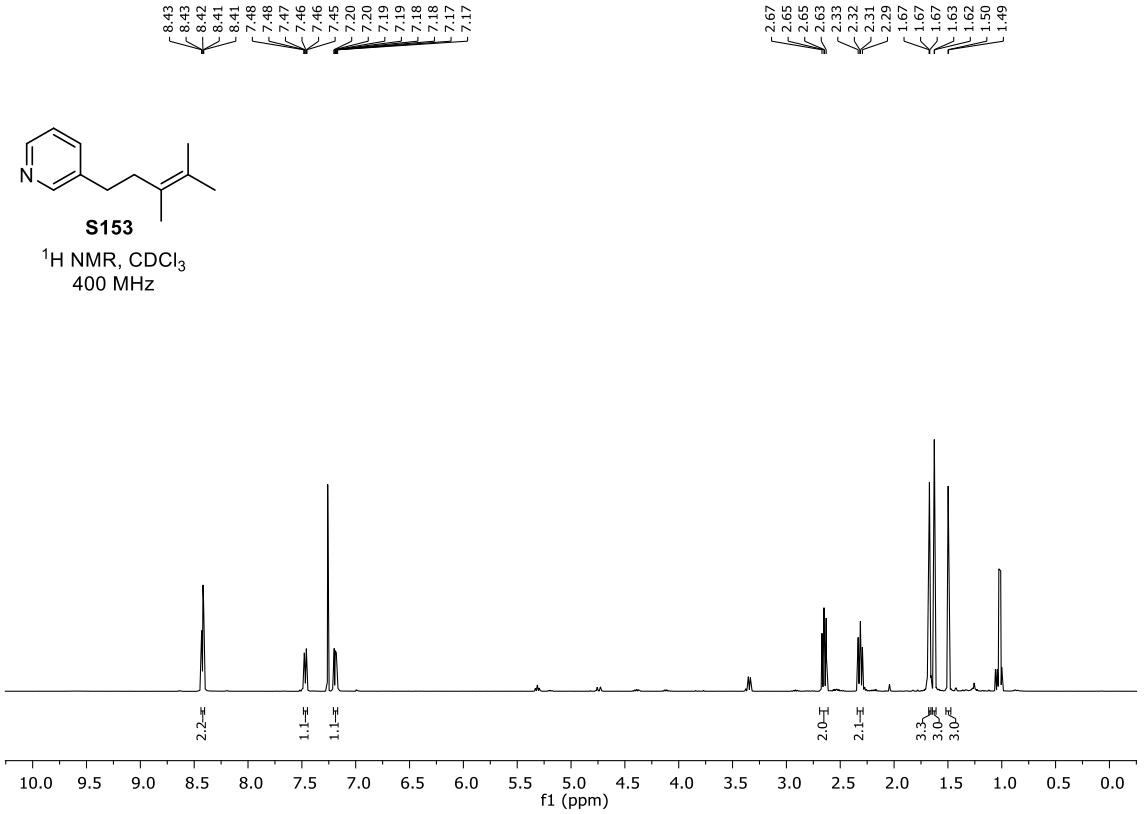
S152

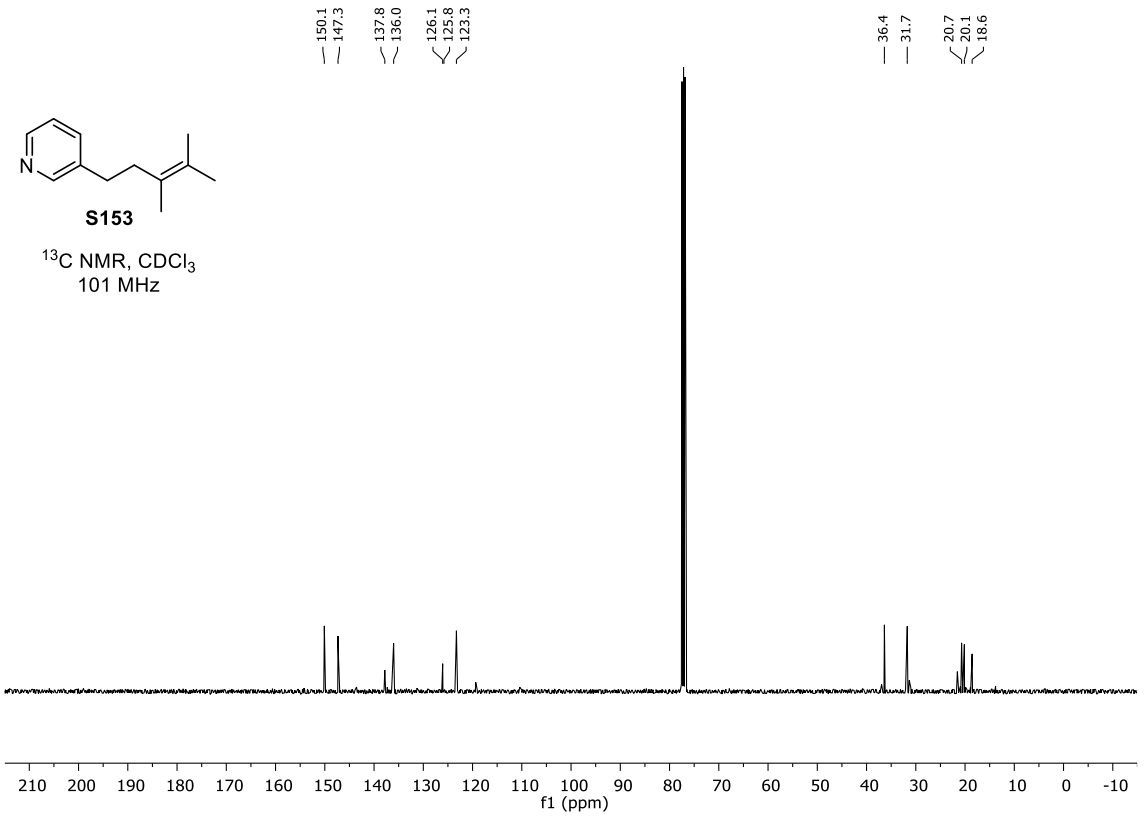
^{13}C NMR, $CDCl_3$
101 MHz

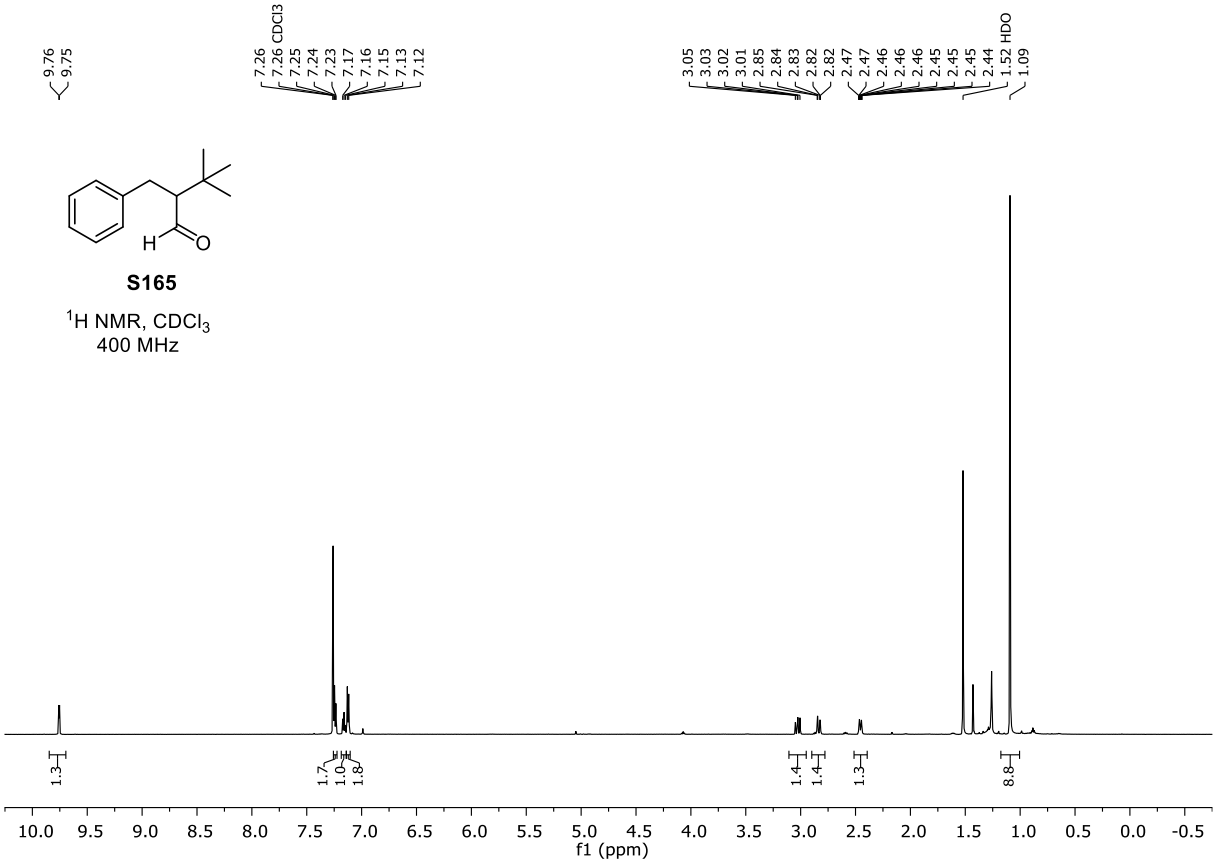

N
OH
S152
HSQC, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)


N
OH
S152
COSY, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)


N
OH
S152
HMBC, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)

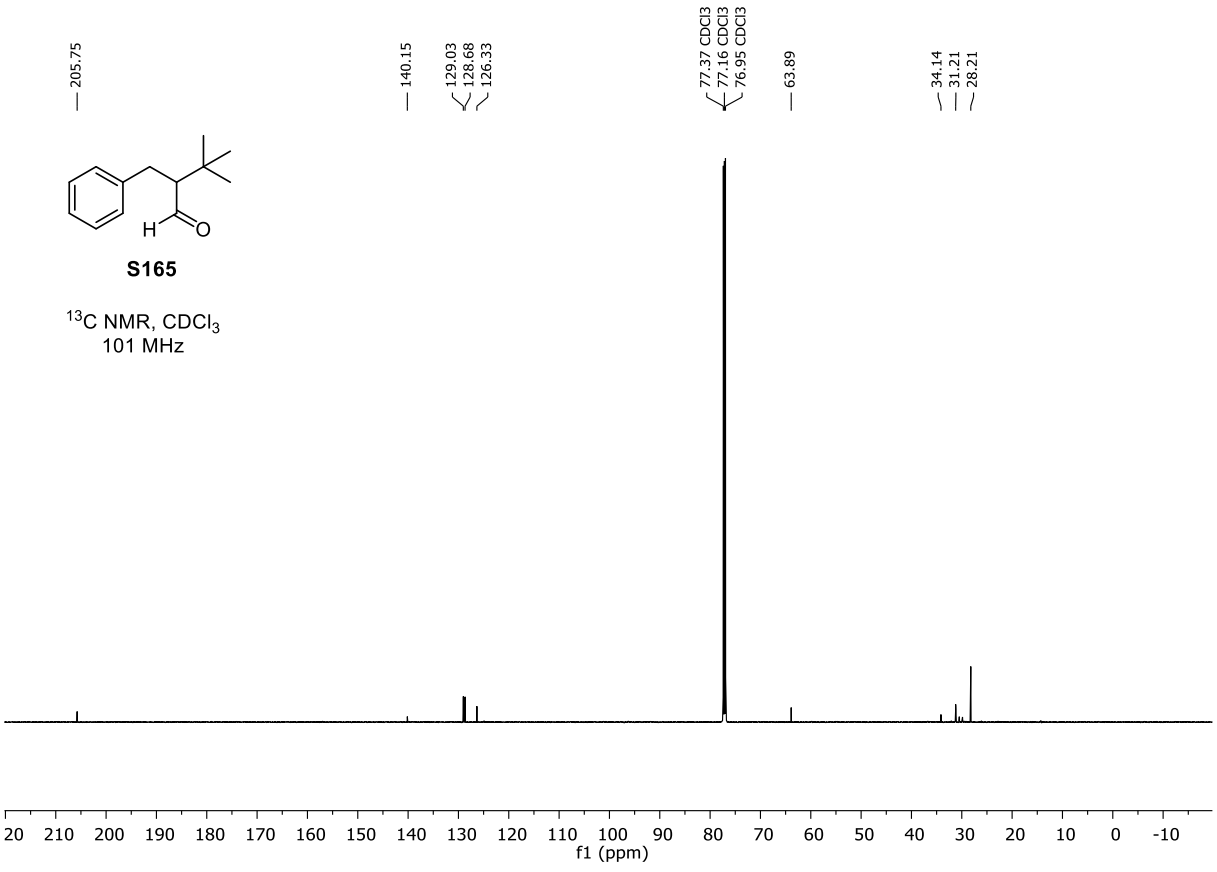

8.43
8.43
8.42
8.41
8.41
7.48
7.48
7.47
7.46
7.46
7.45
7.20
7.20
7.19
7.19
7.18
7.18
7.17
7.17
7.17
2.67
2.65
2.65
2.63
2.33
2.32
2.31
2.29
1.67
1.67
1.67
1.63
1.62
1.50
1.49
N
S153
1H NMR, CDCl3
400 MHz
2.2
1.1
1.1
2.0
2.1
3.3
3.0
3.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


150.1
147.3
137.8
136.0
126.1
125.8
123.3
36.4
31.7
20.7
20.1
18.6
N
S153
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)



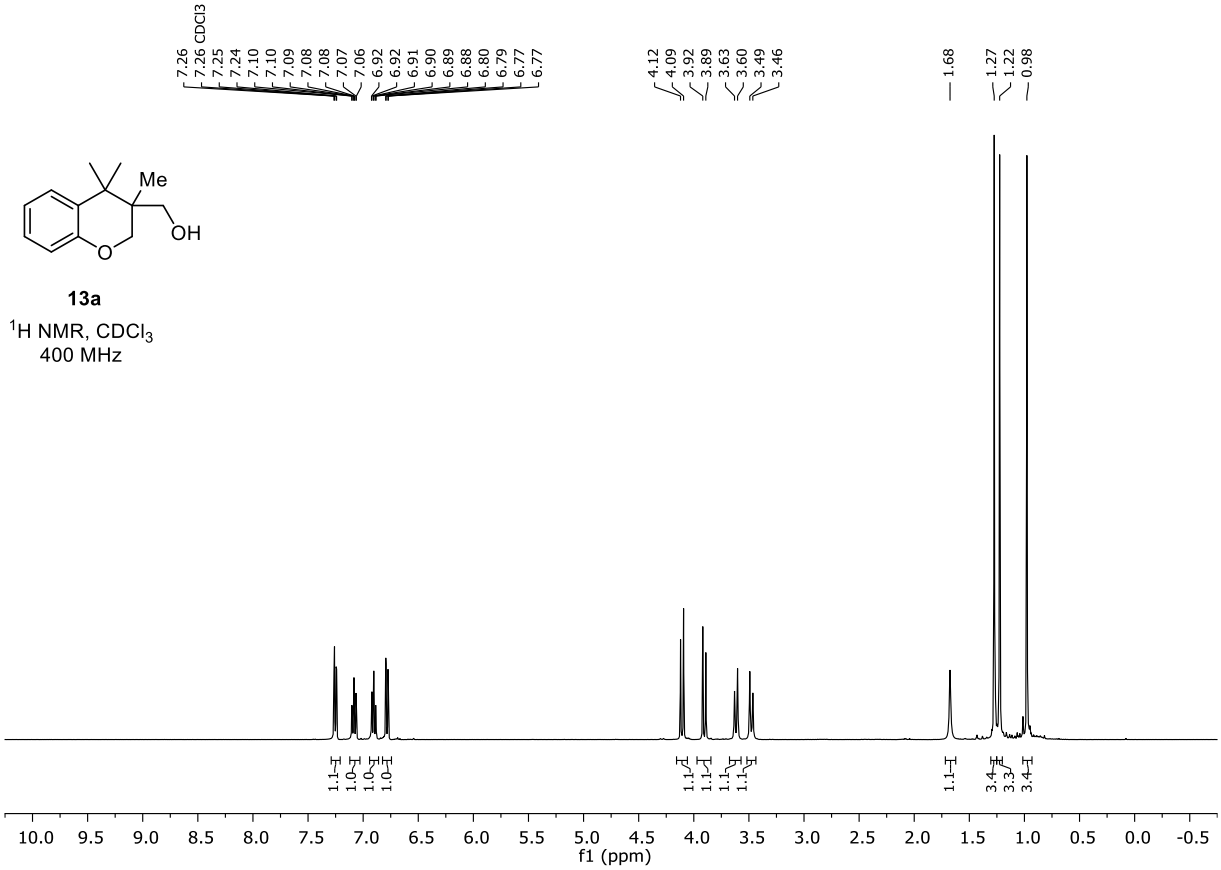
S165

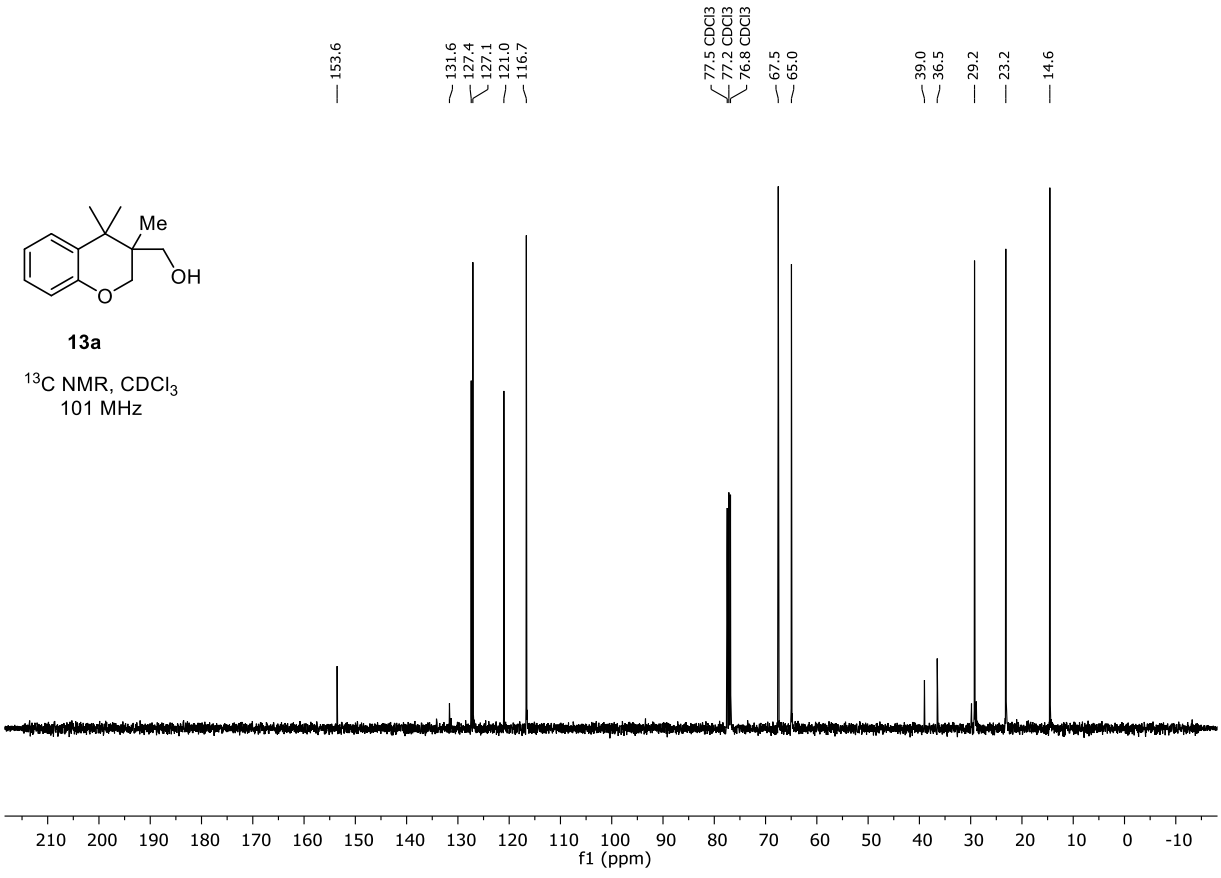
^{1}H NMR, $CDCl_3$
400 MHz

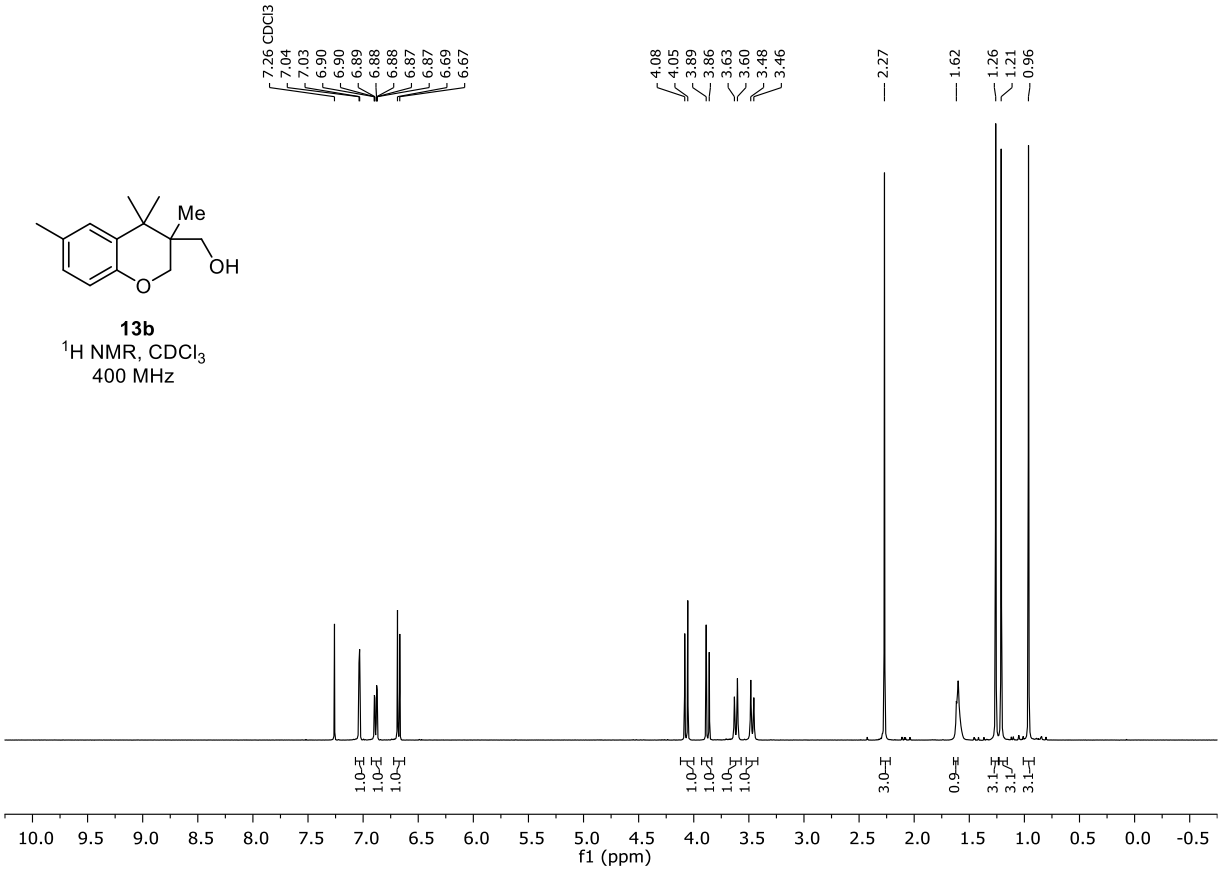


S165

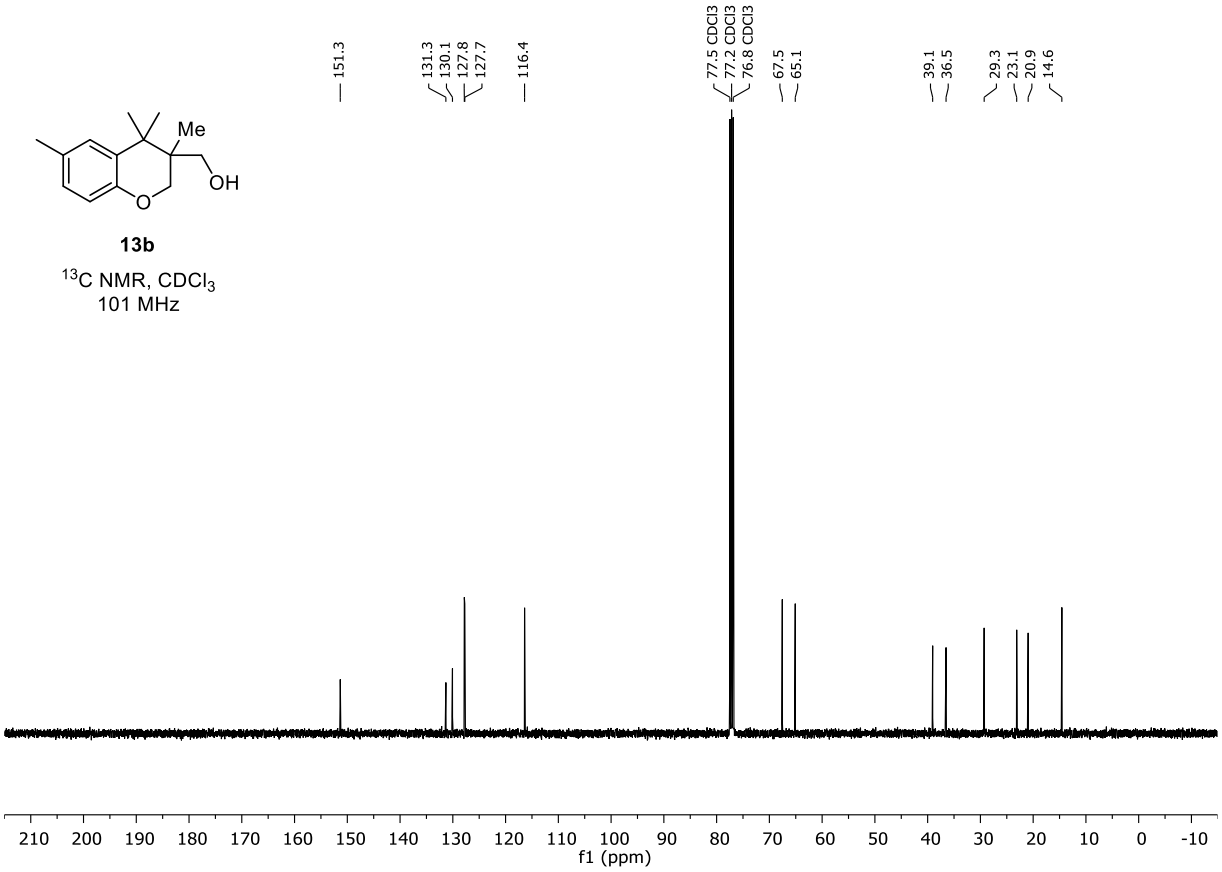
^{13}C NMR, $CDCl_3$
101 MHz


7.26 CDCl3
7.25
7.24
7.10
7.09
7.08
7.08
7.07
7.06
6.92
6.92
6.91
6.90
6.89
6.88
6.80
6.79
6.77
6.77
4.12
4.09
3.92
3.89
3.63
3.60
3.49
3.46
1.68
1.27
1.22
0.98
Me
OH
O
13a
1H NMR, CDCl3
400 MHz
1.1
1.0
1.0
1.0
1.1
1.1
1.1
1.1
1.1
3.4
3.3
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 -0.5
f1 (ppm)

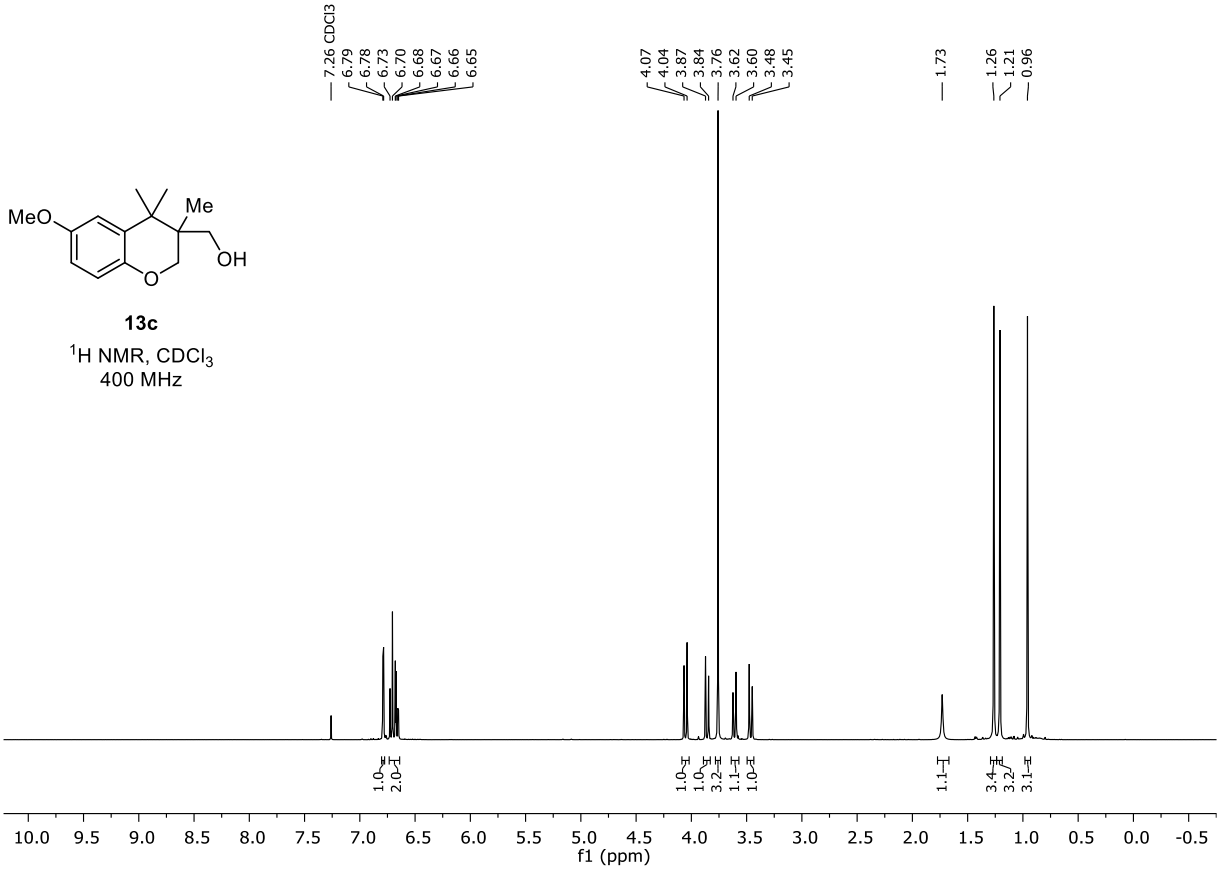

153.6
131.6
127.4
127.1
121.0
116.7
77.5 CDCl3
77.2 CDCl3
76.8 CDCl3
67.5
65.0
39.0
36.5
29.2
23.2
14.6
Me
OH
O
13a
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

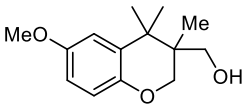


13b
^{1}H NMR, $CDCl_3$
400 MHz



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



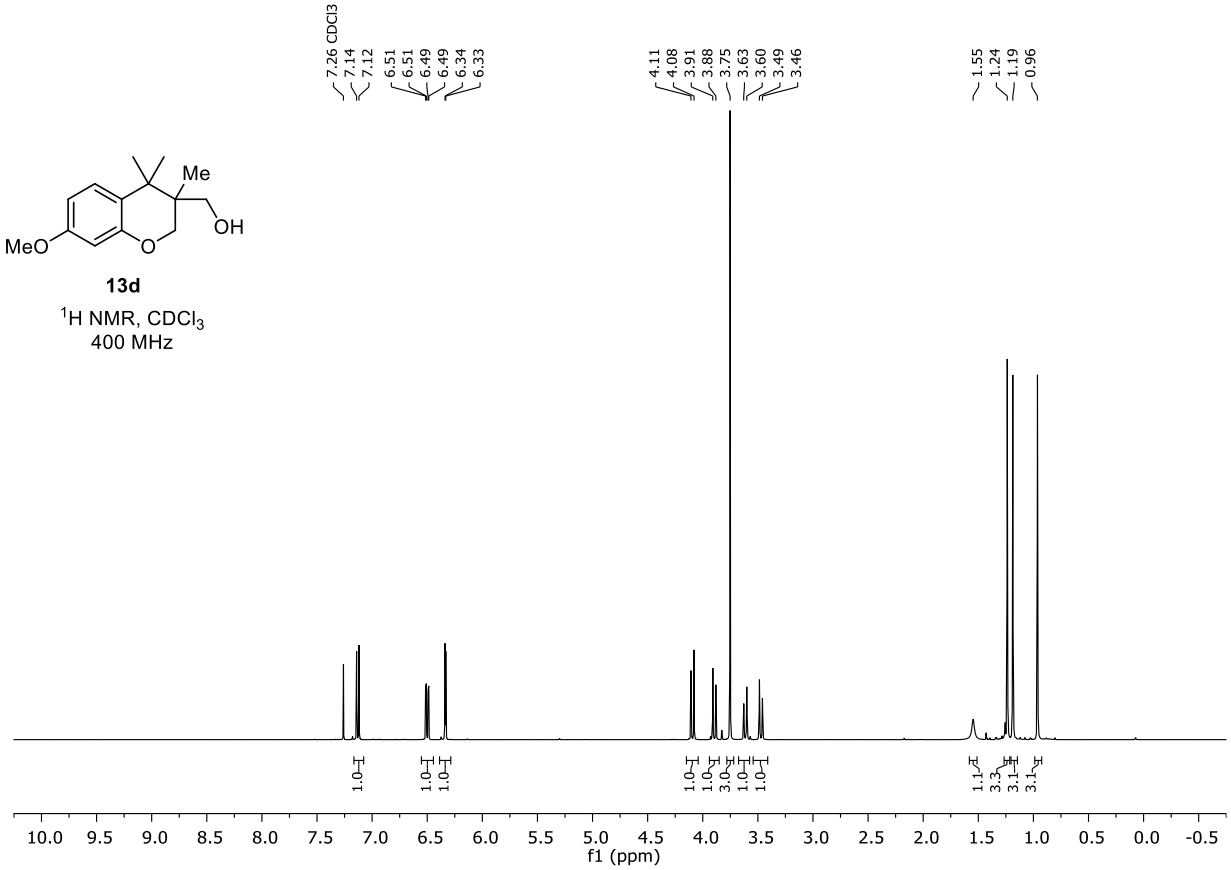


13c

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

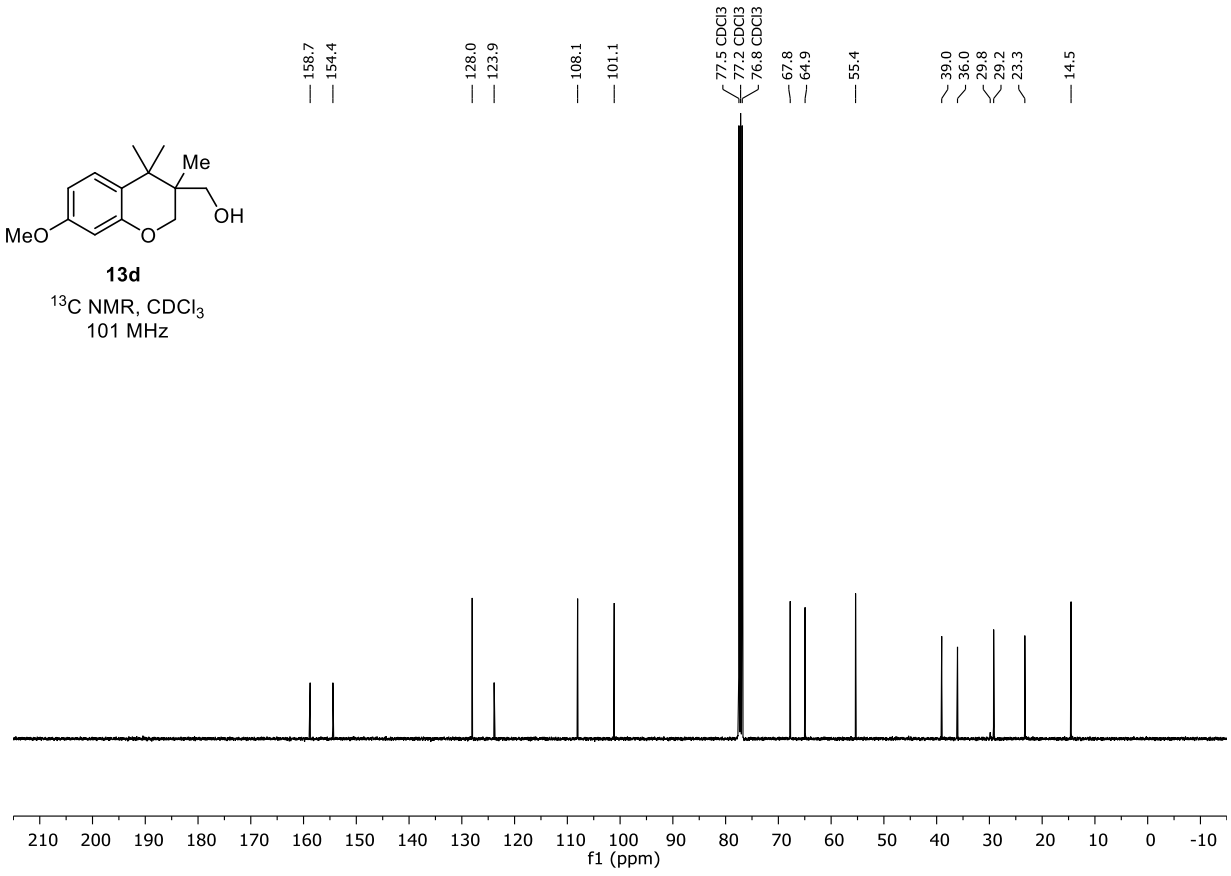
13c

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



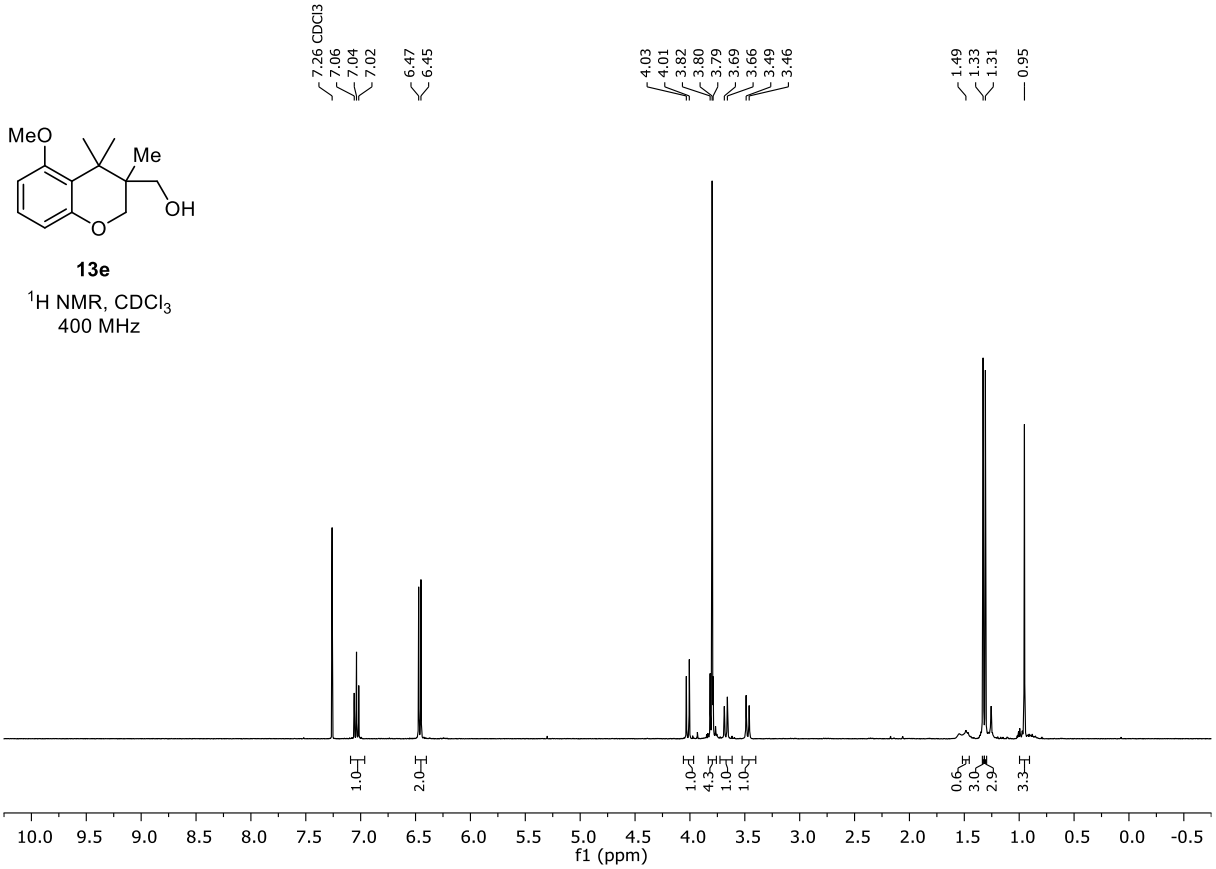
13d

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



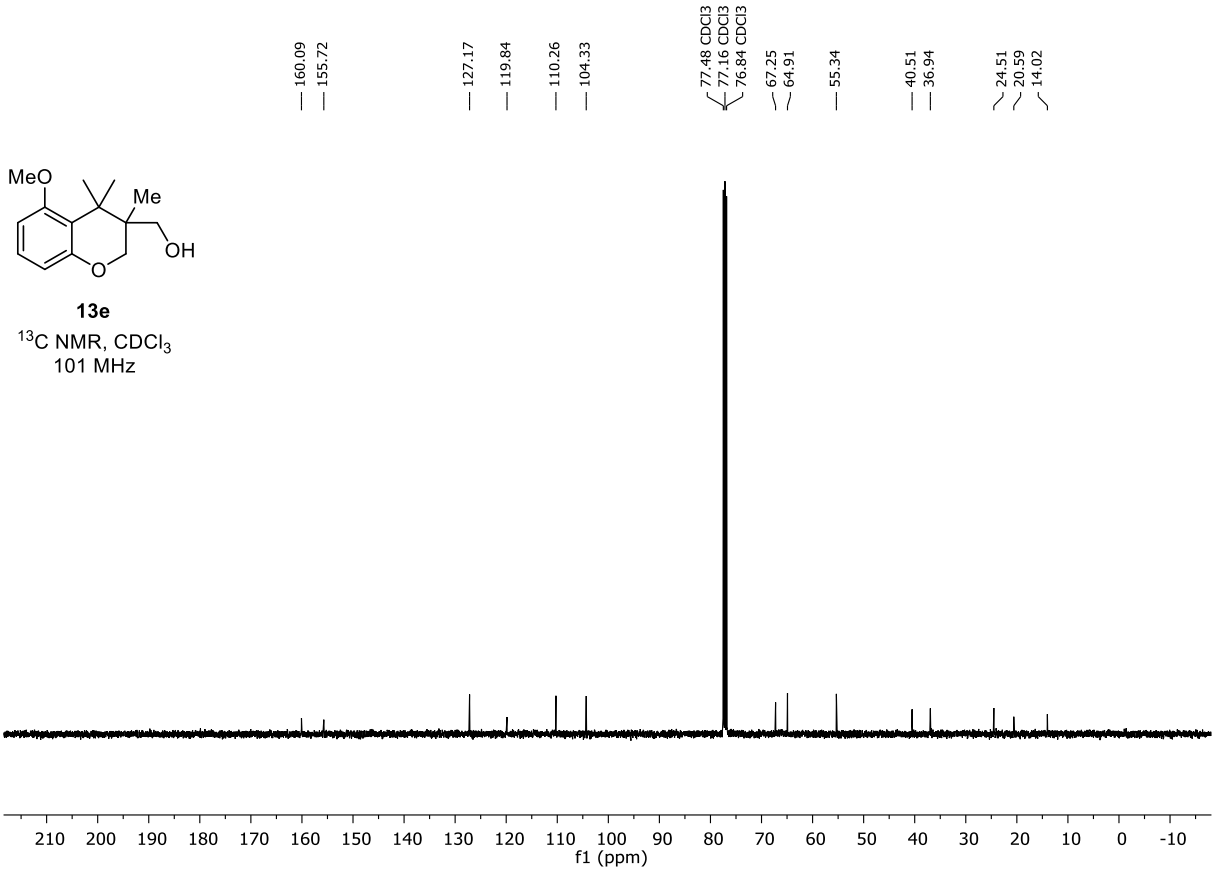
13d

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



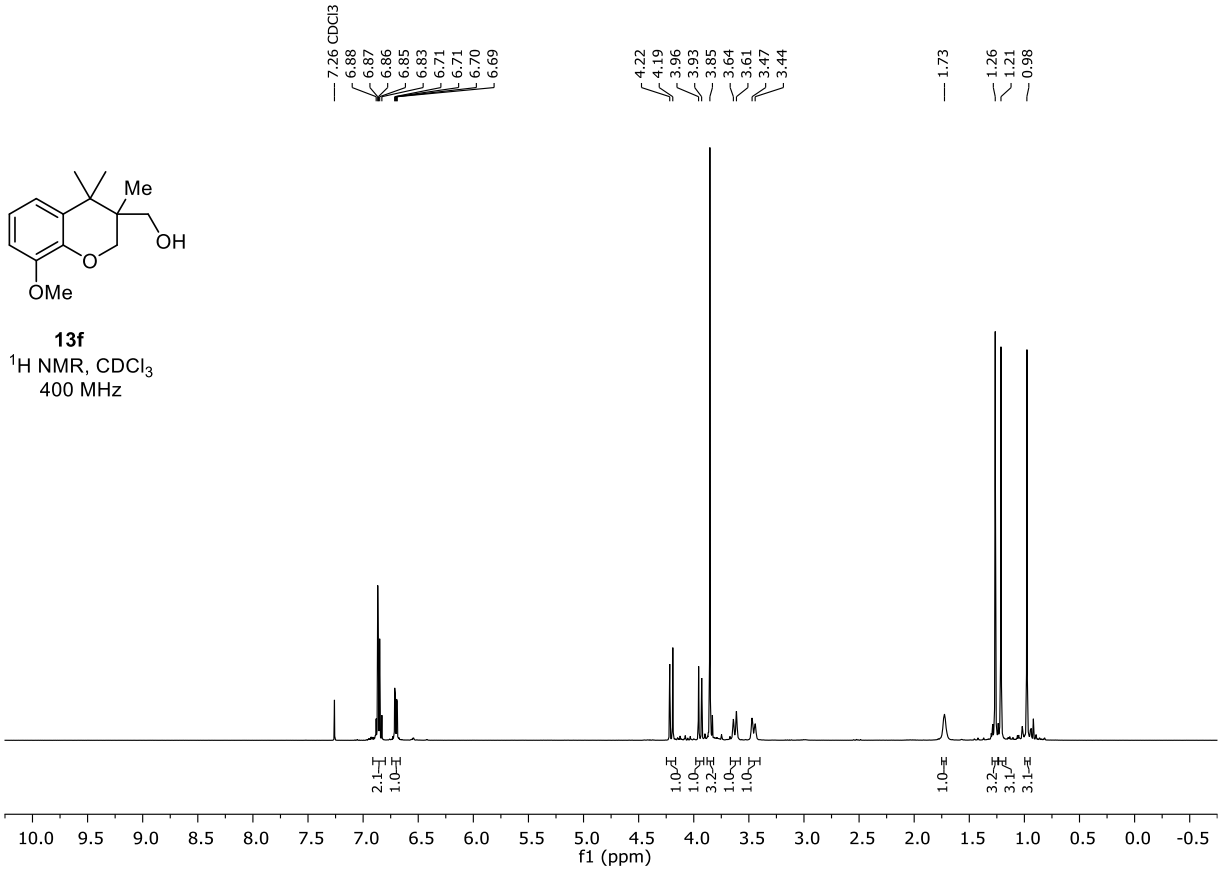
13e

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

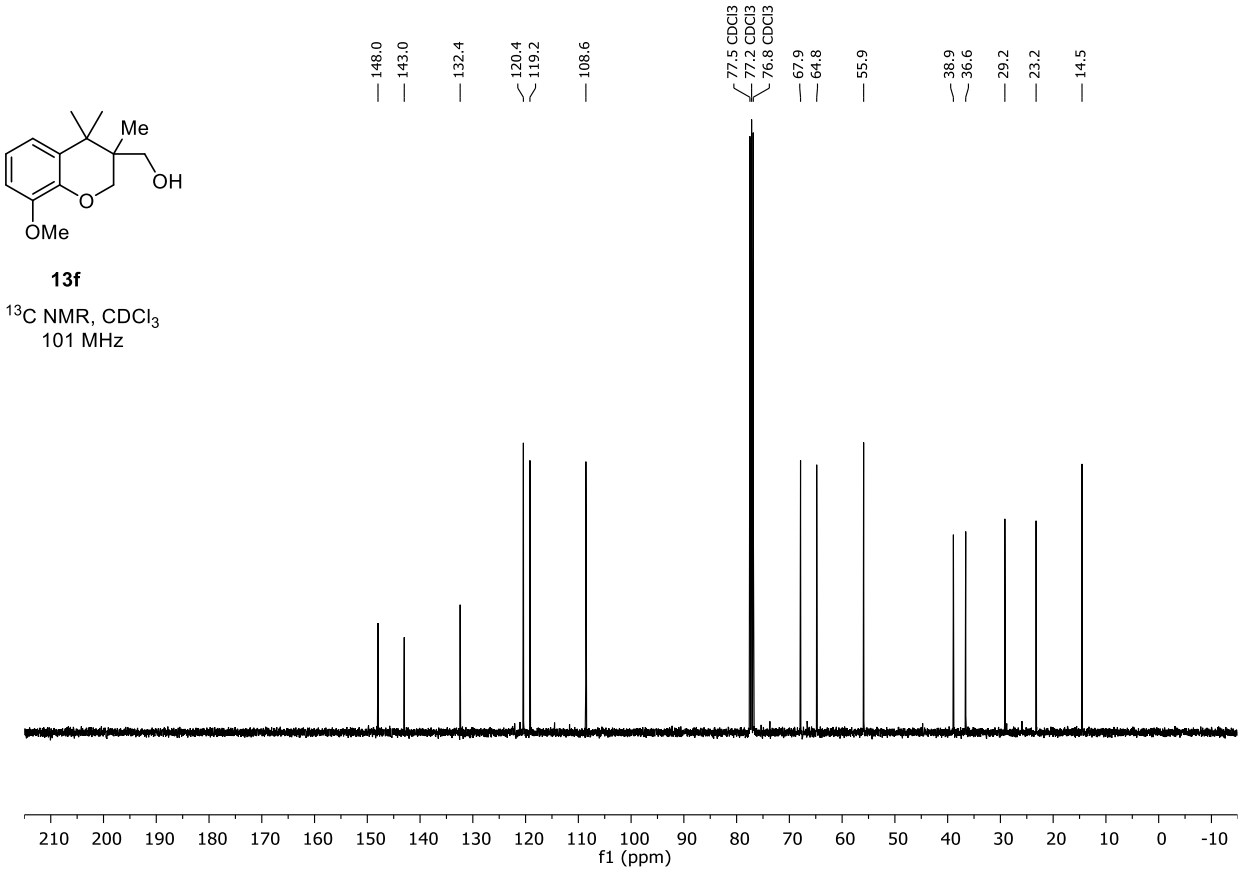


13e

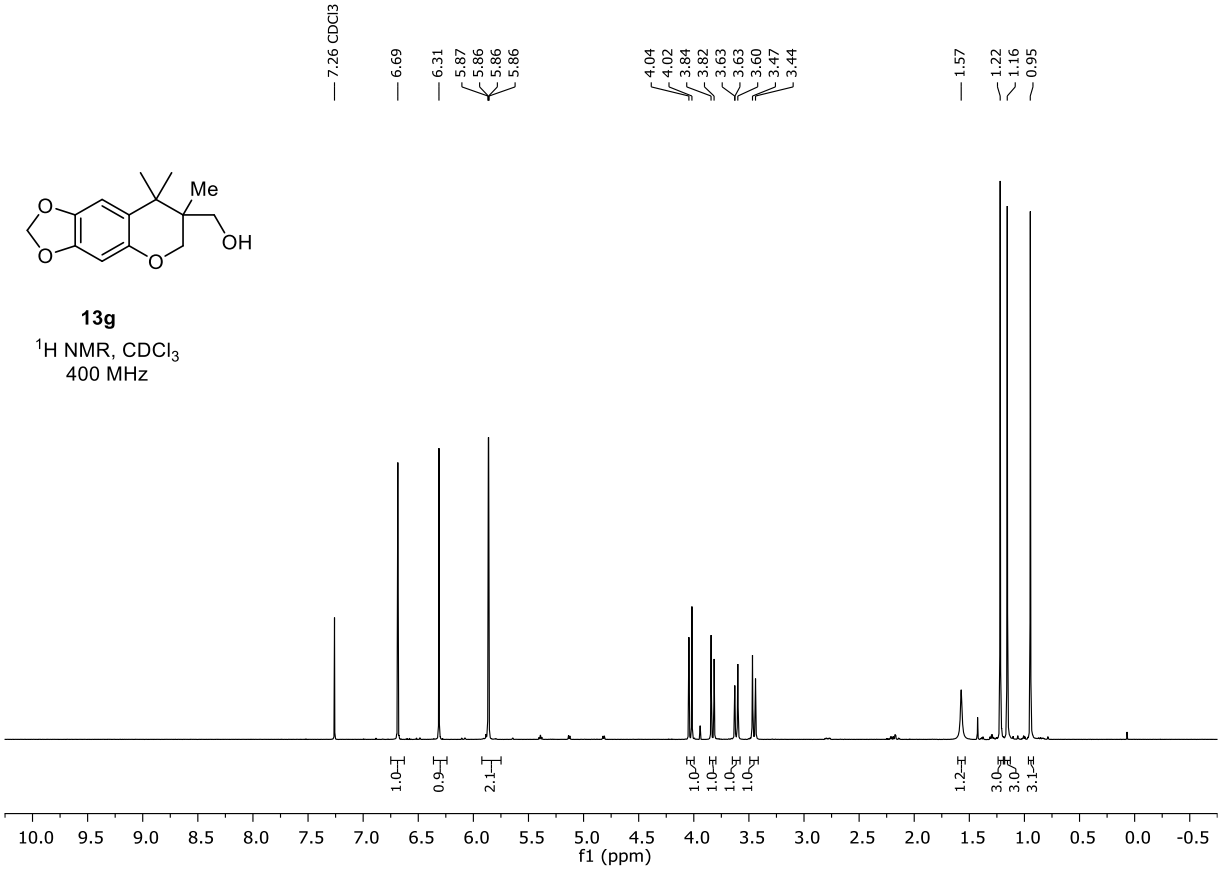
^{13}C NMR, $CDCl_3$
101 MHz



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

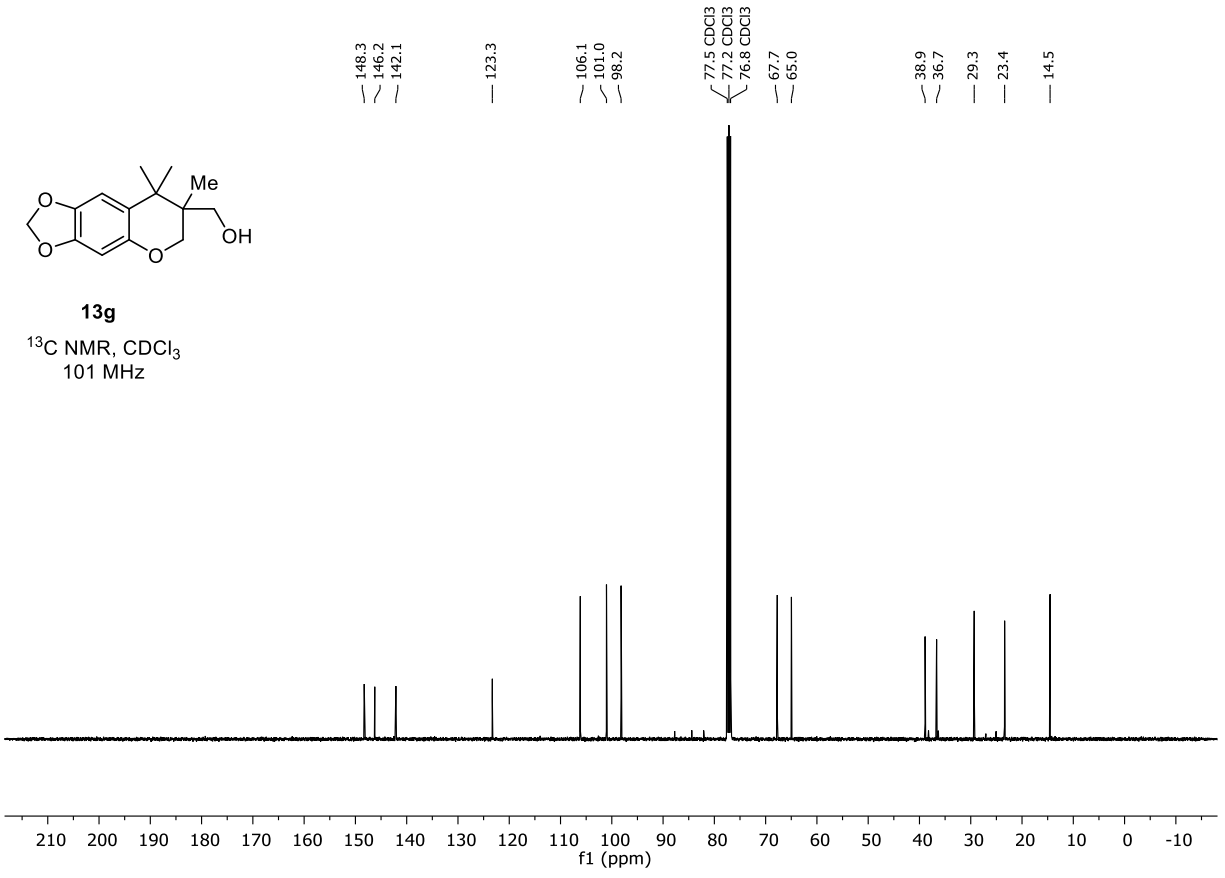


13f
^{13}C NMR, $CDCl_3$
101 MHz



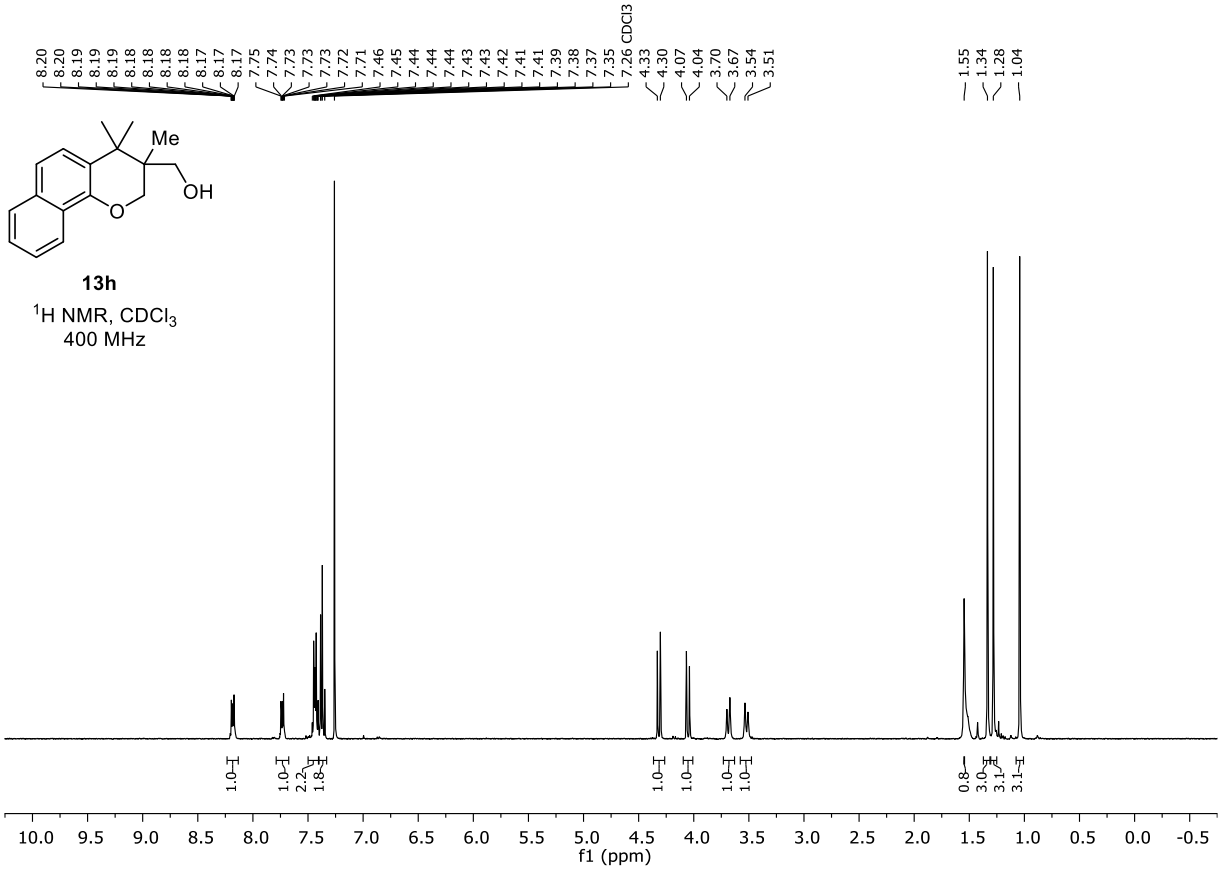
13g

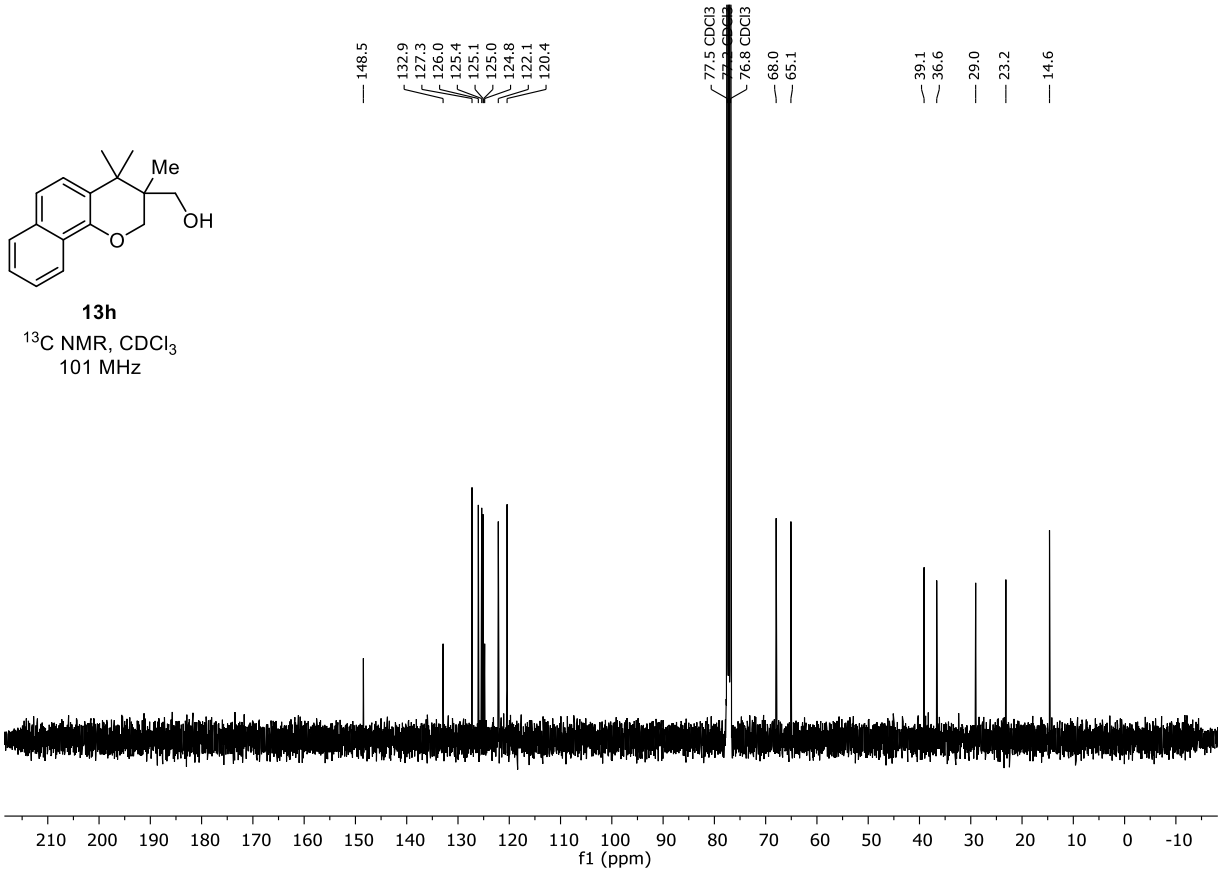
^{1}H NMR, $CDCl_3$
400 MHz

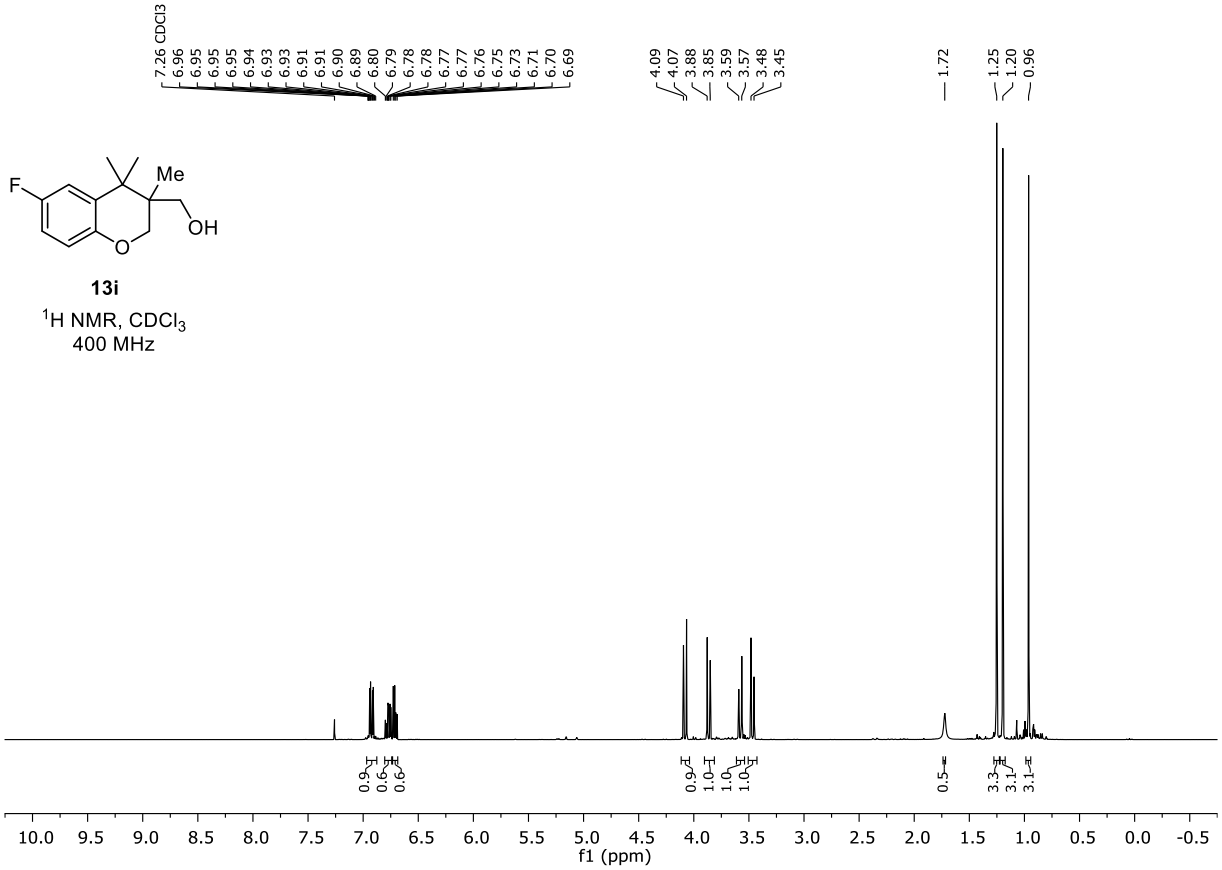


13g

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

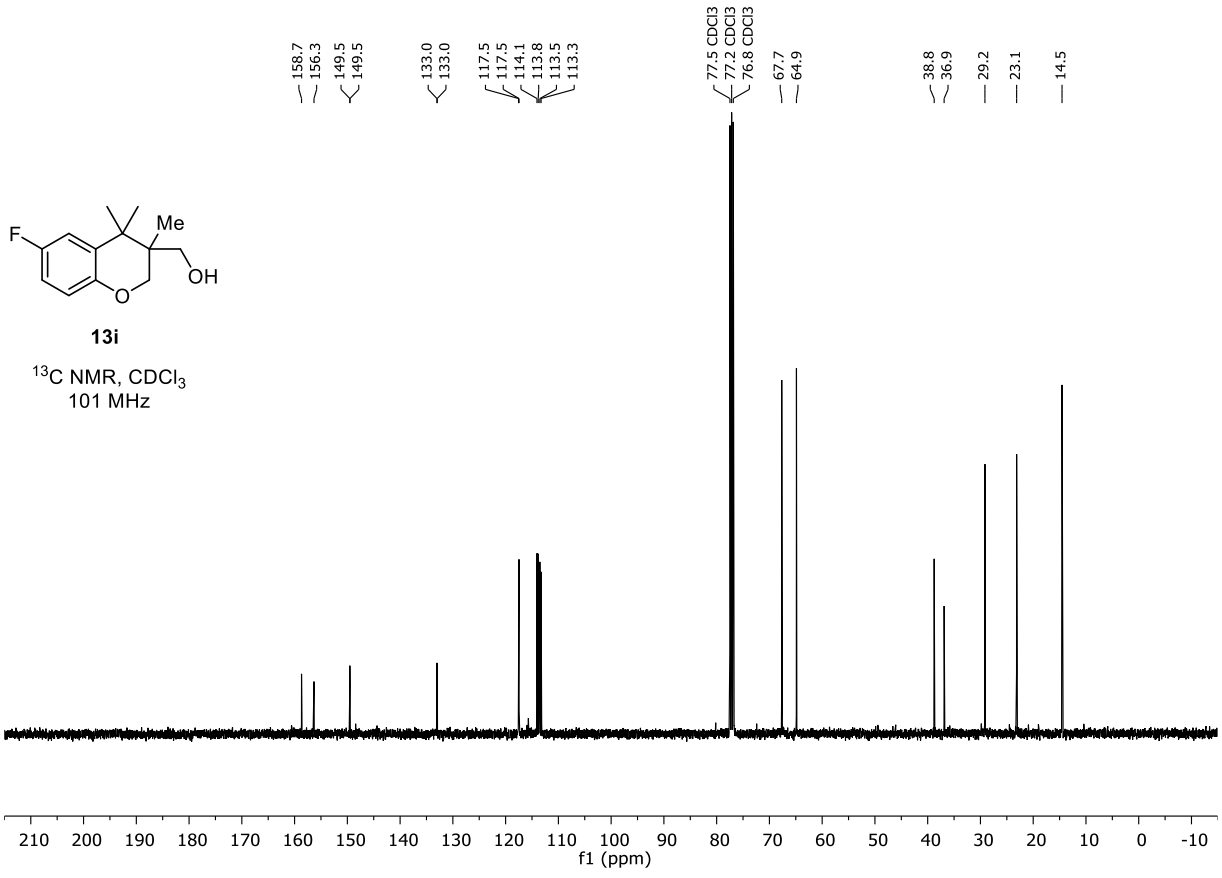

Me
OH
O
13h
1H NMR, CDCl3
400 MHz
f1 (ppm)


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



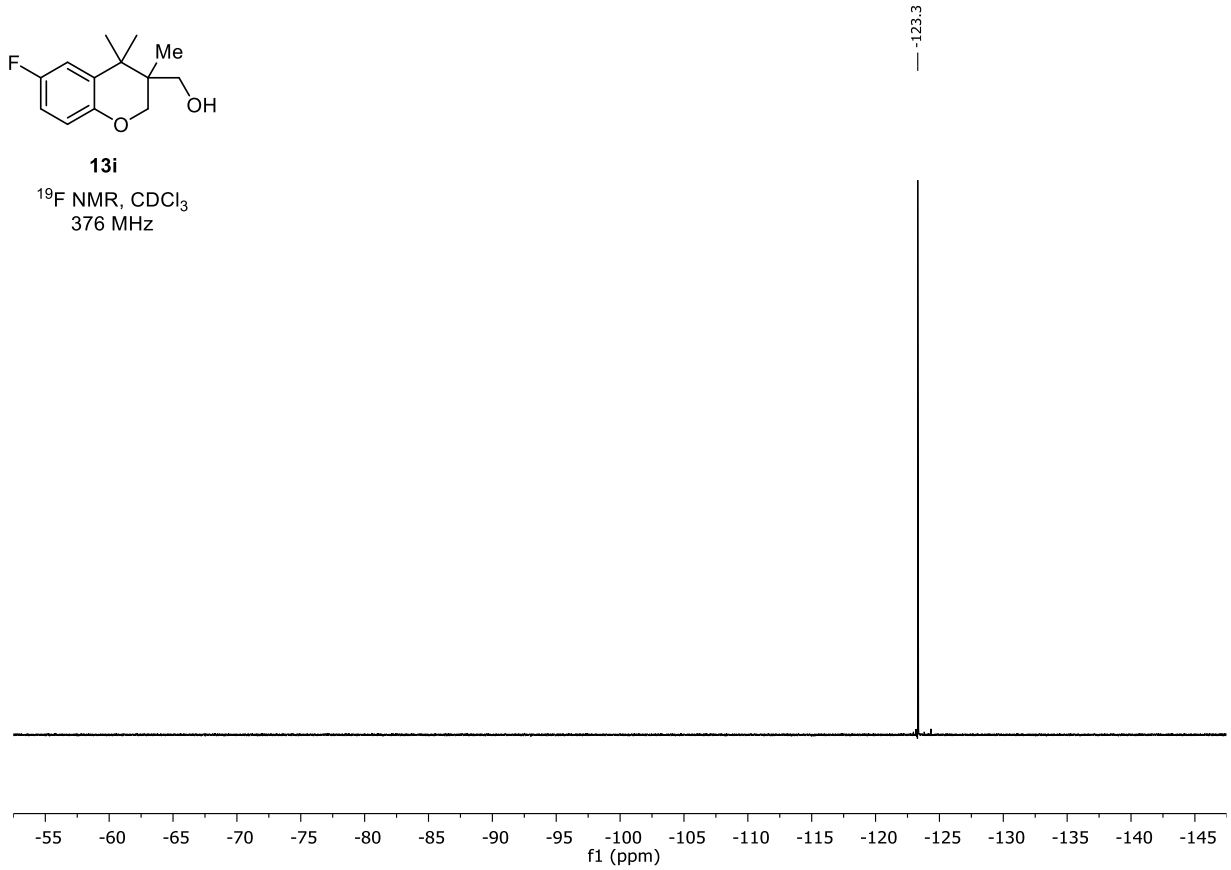
13i

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



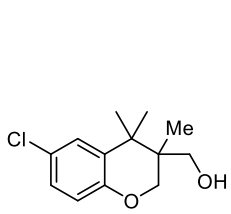
13i

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



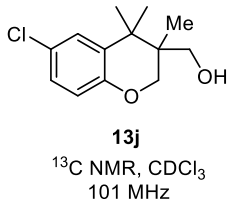
13i

^{19}F NMR, $CDCl_3$
376 MHz



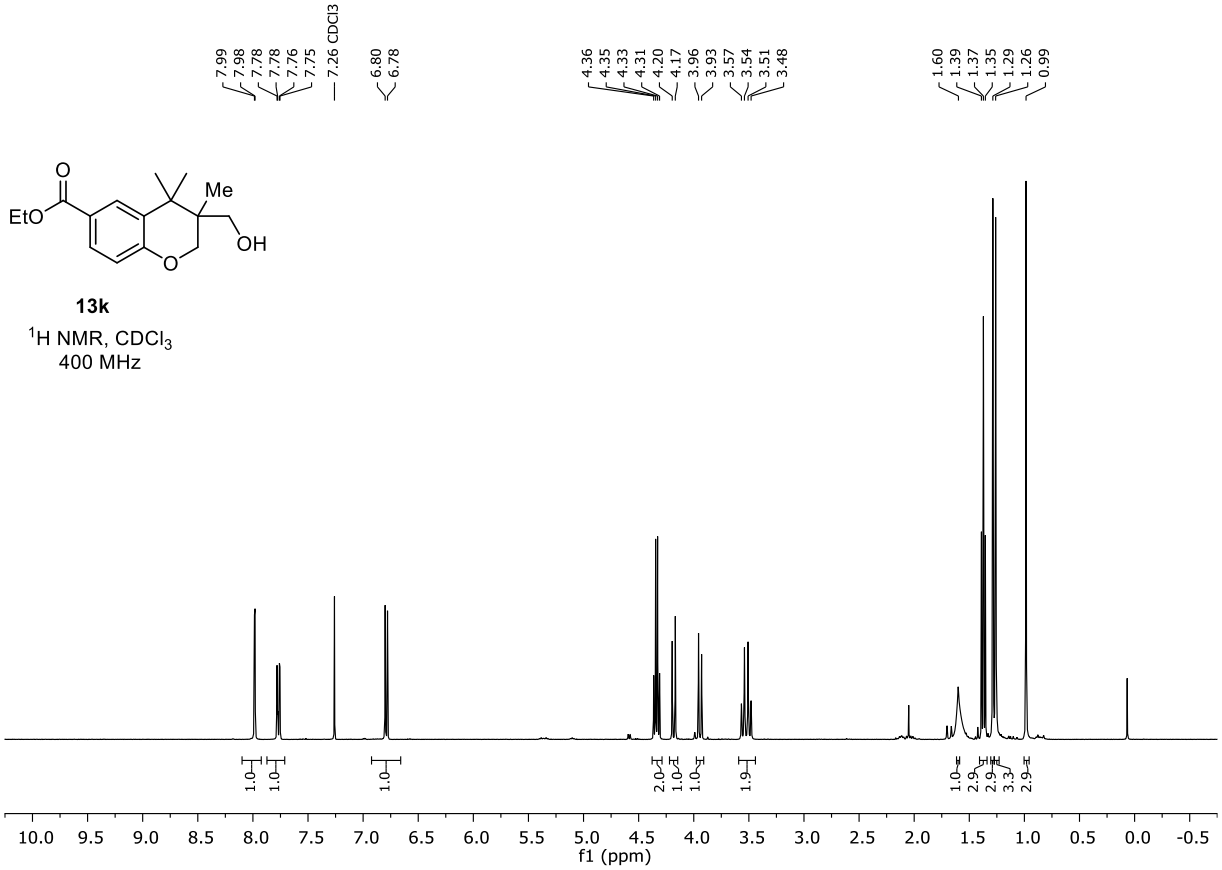
13j

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



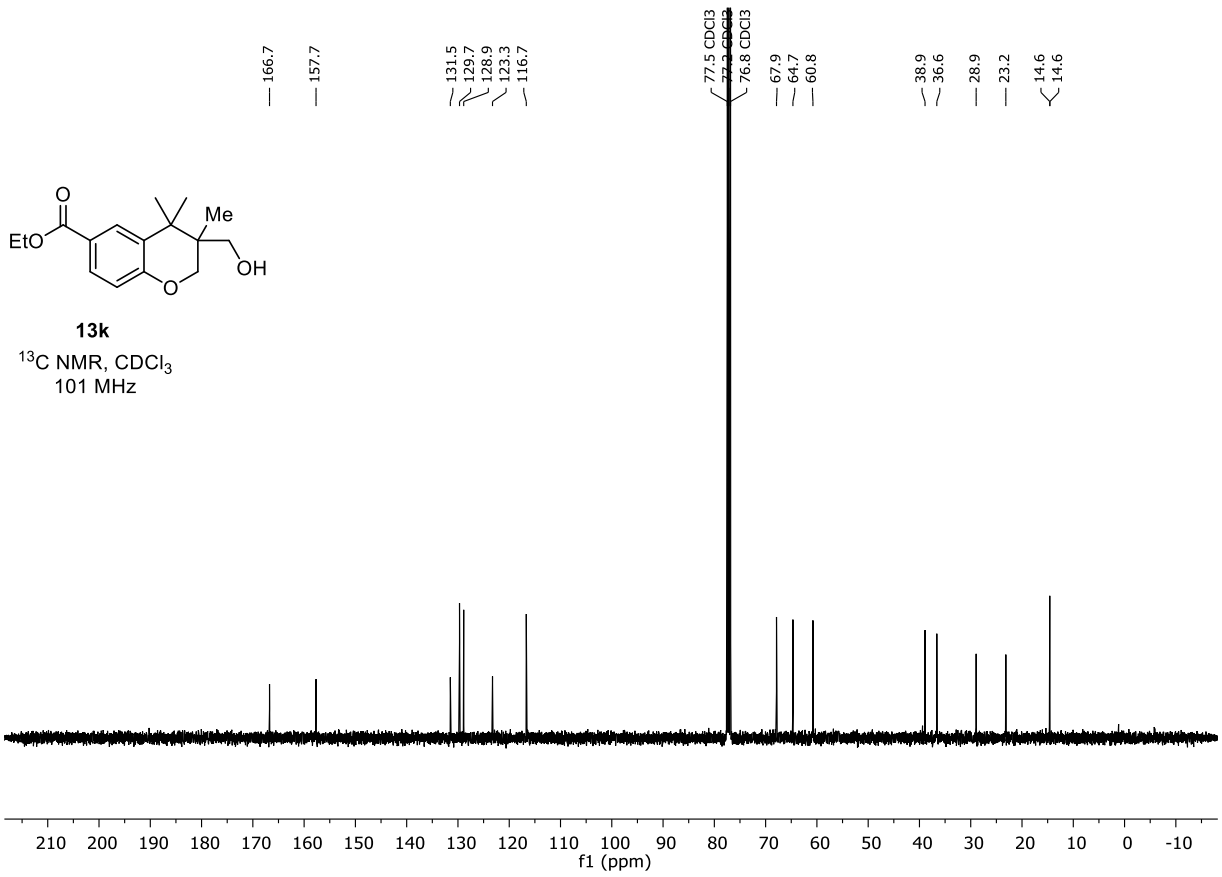
13j

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



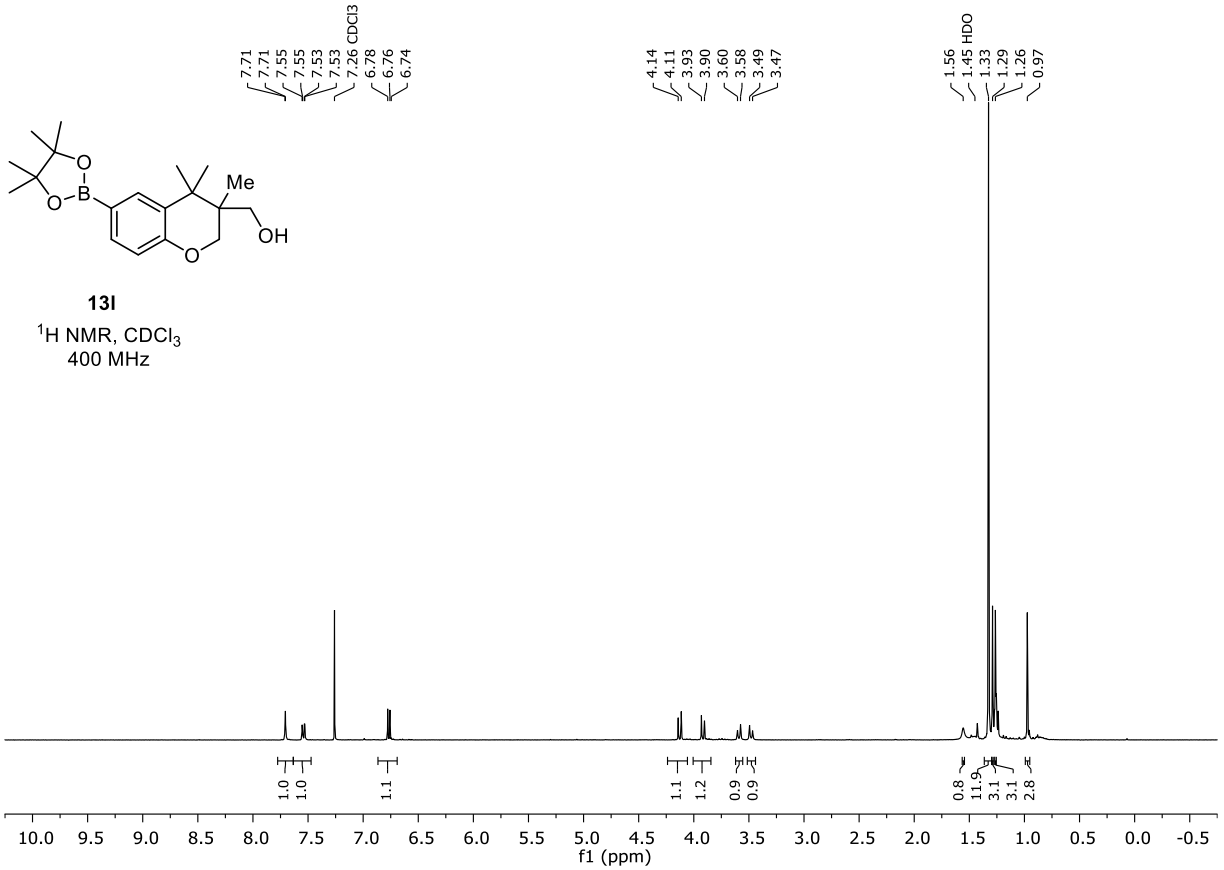
13k

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



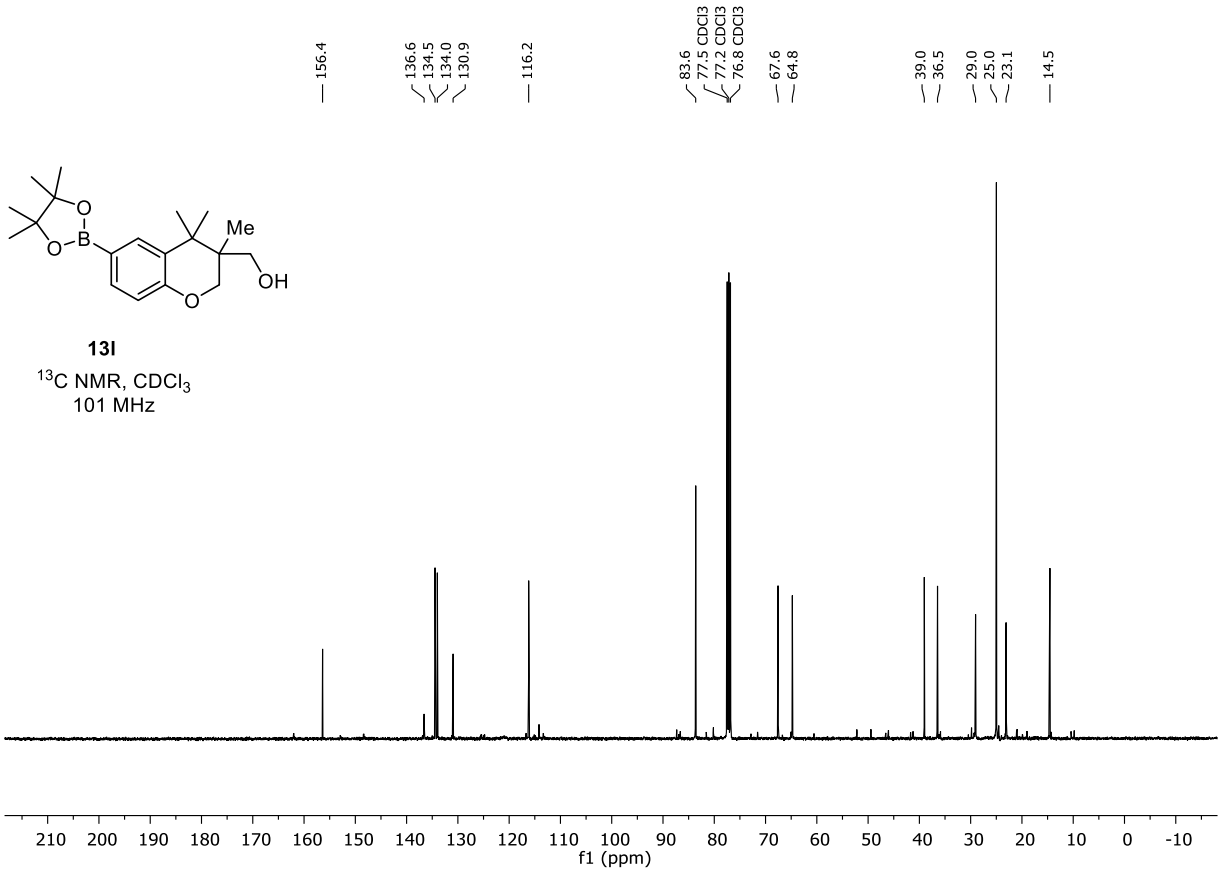
13k

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



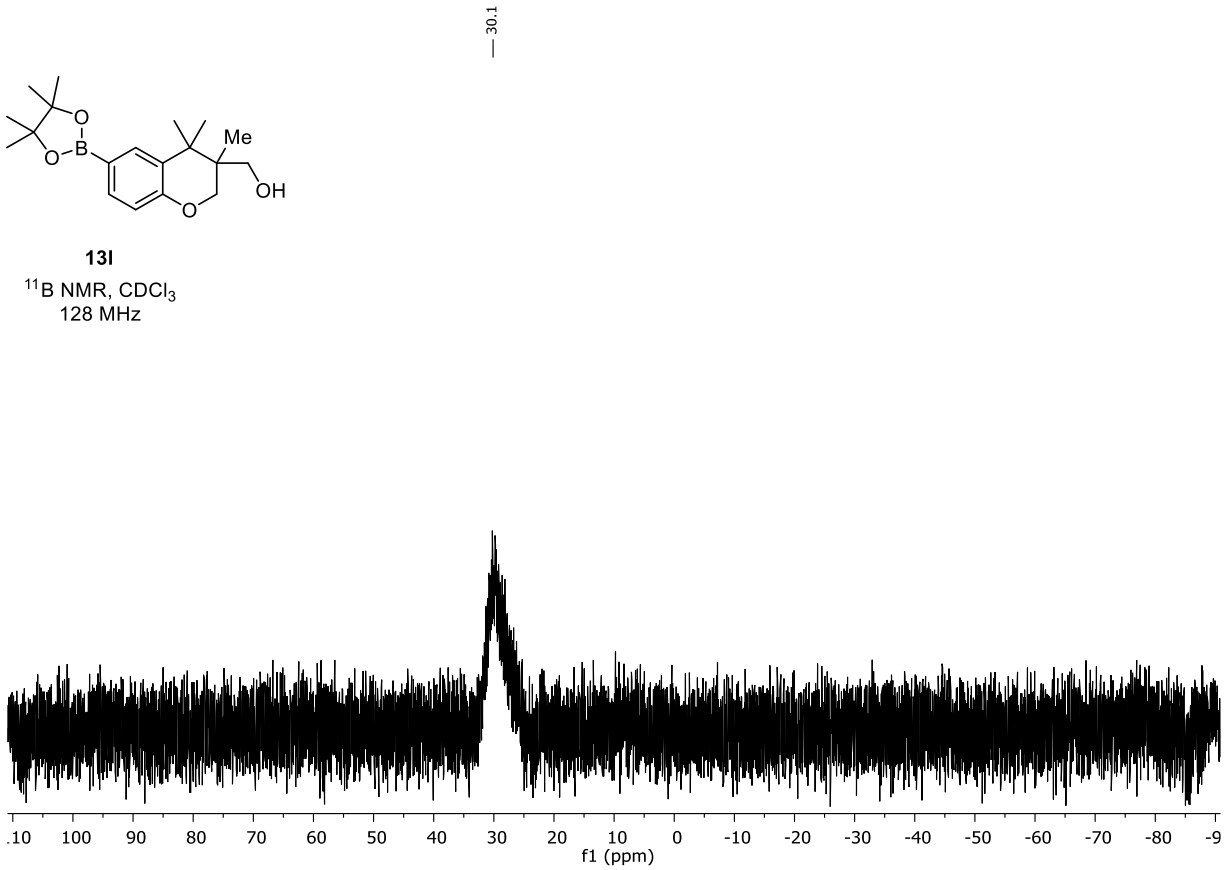
13l

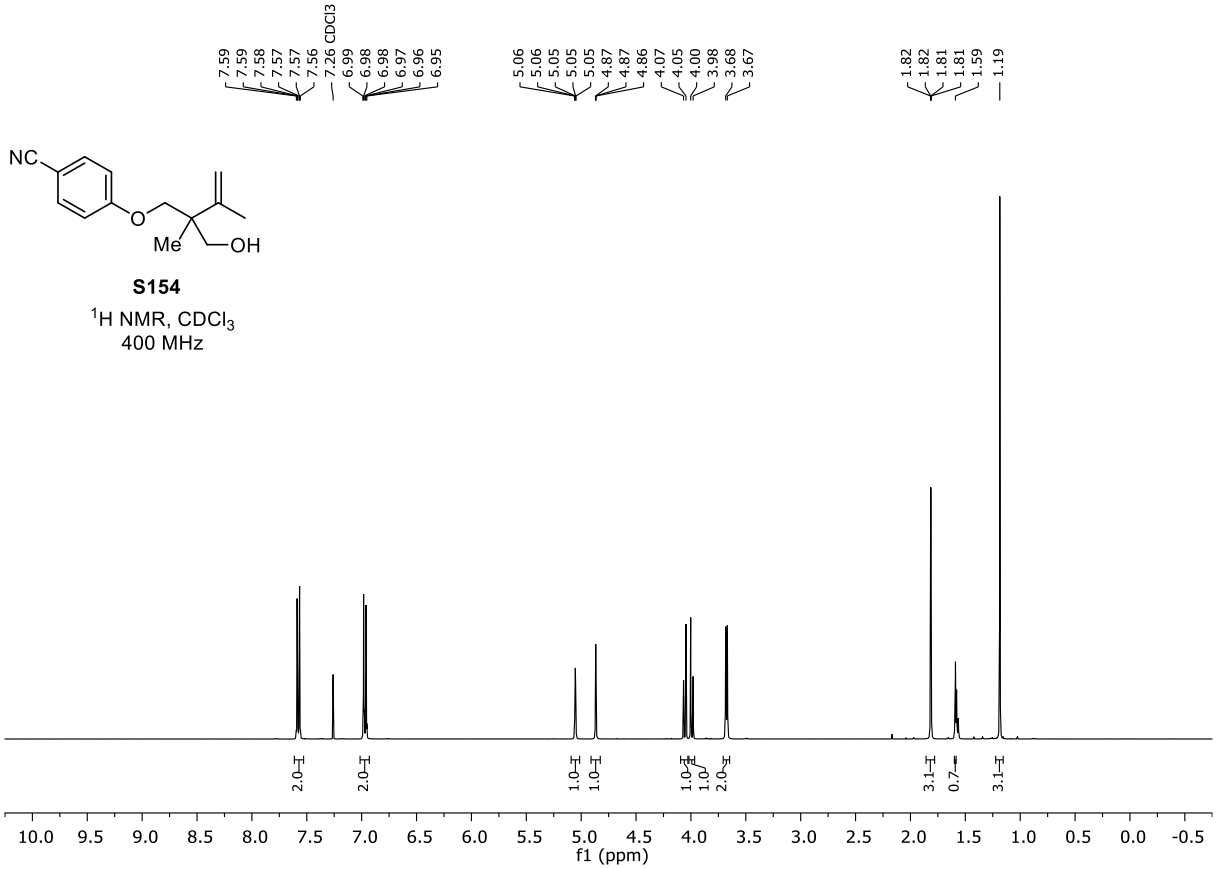
^{1}H NMR, $CDCl_3$
400 MHz



13l

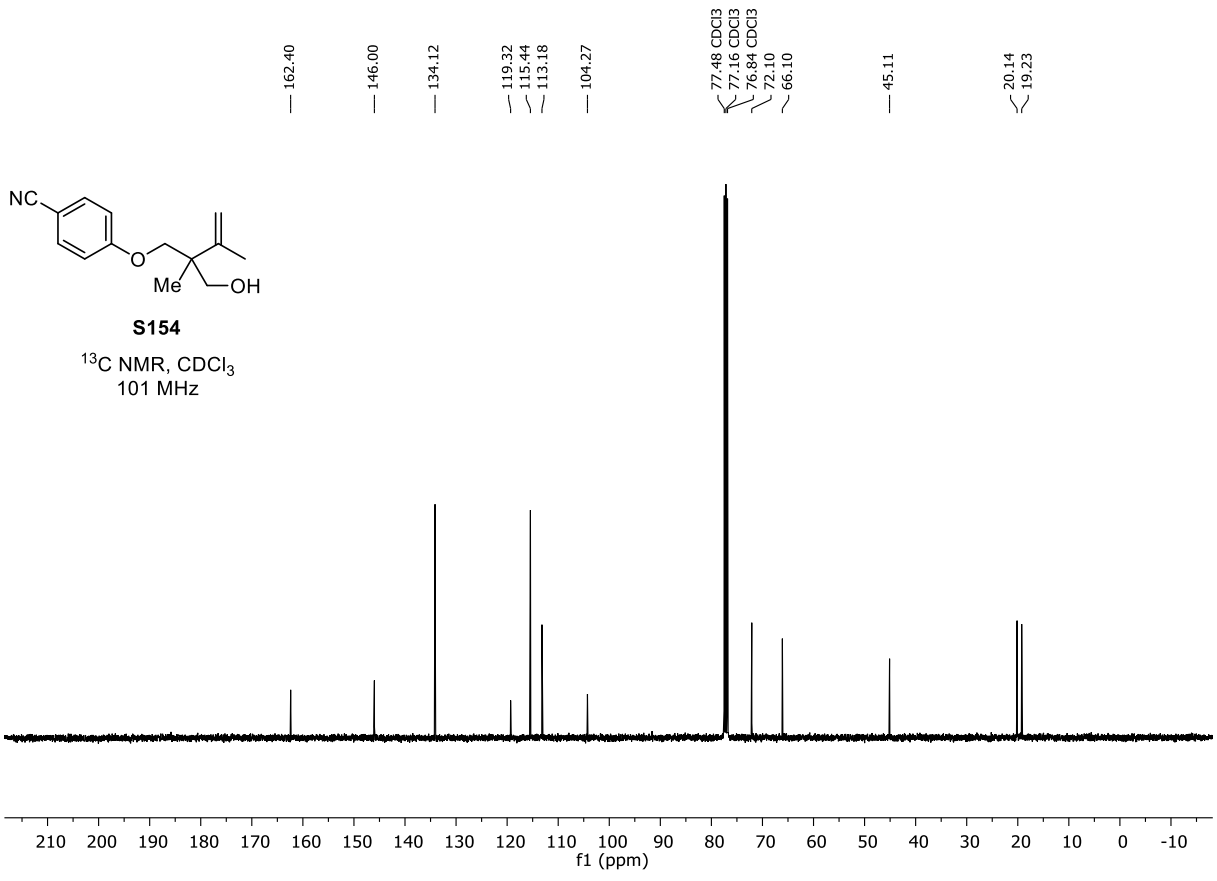
^{13}C NMR, $CDCl_3$
101 MHz


30.1
O
B
O
Me
OH
O
13l
11B NMR, CDCl3
128 MHz
.10 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -9
f1 (ppm)



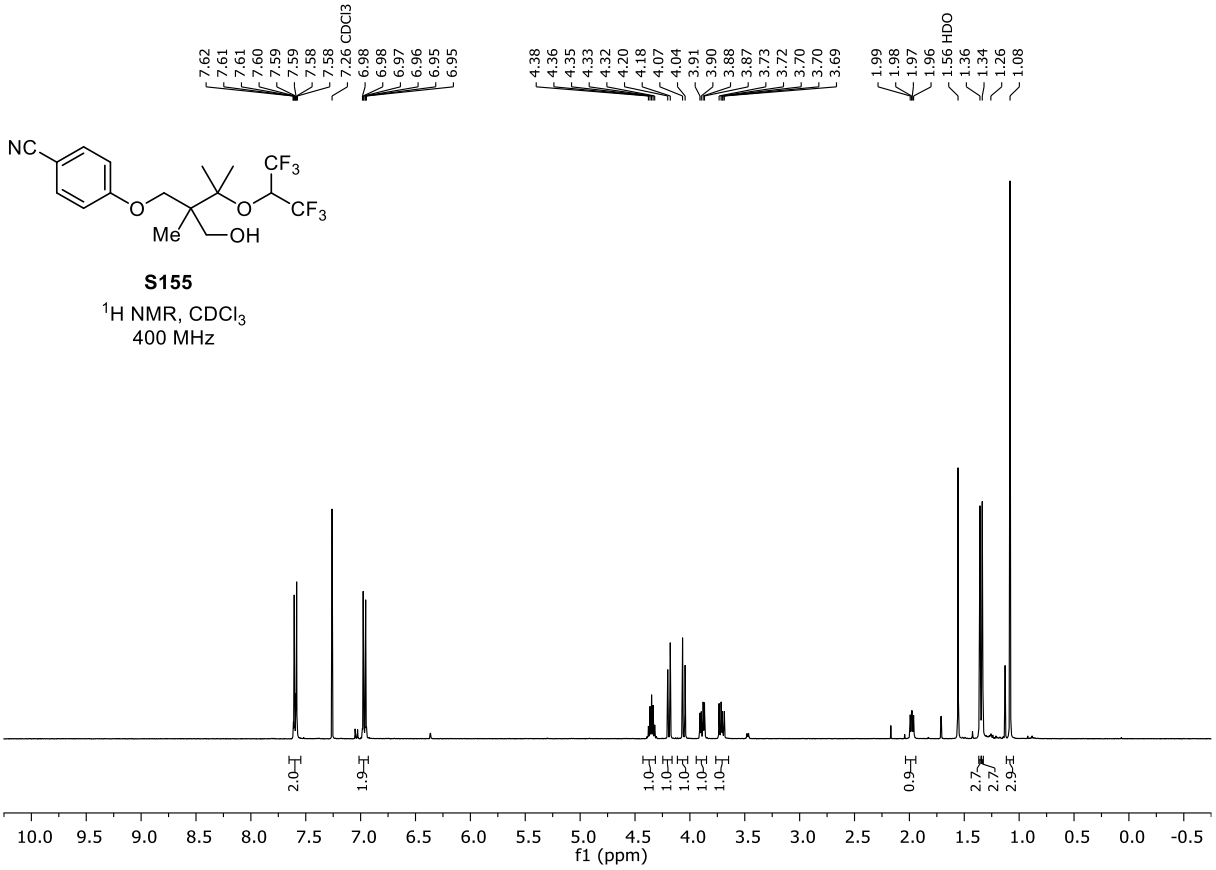
S154

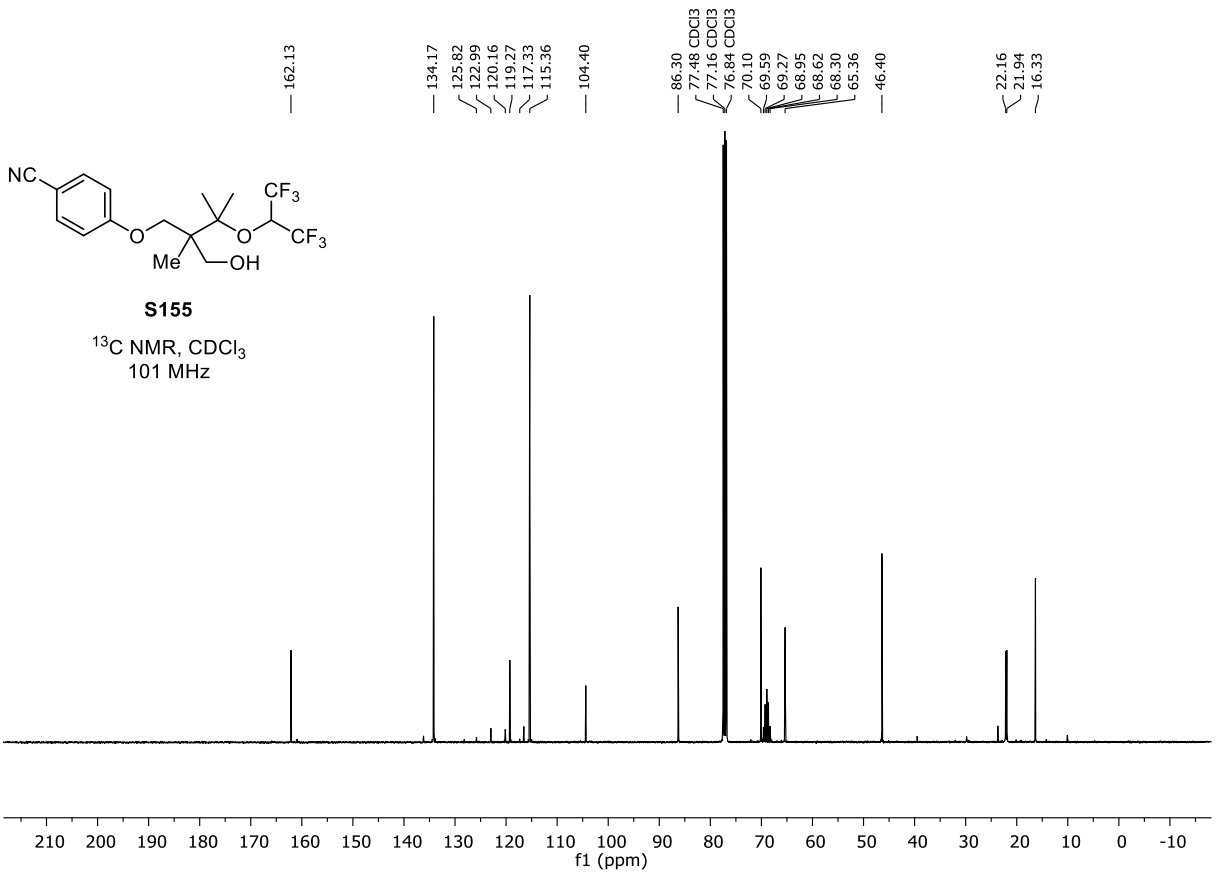
^{1}H NMR, $CDCl_3$
400 MHz

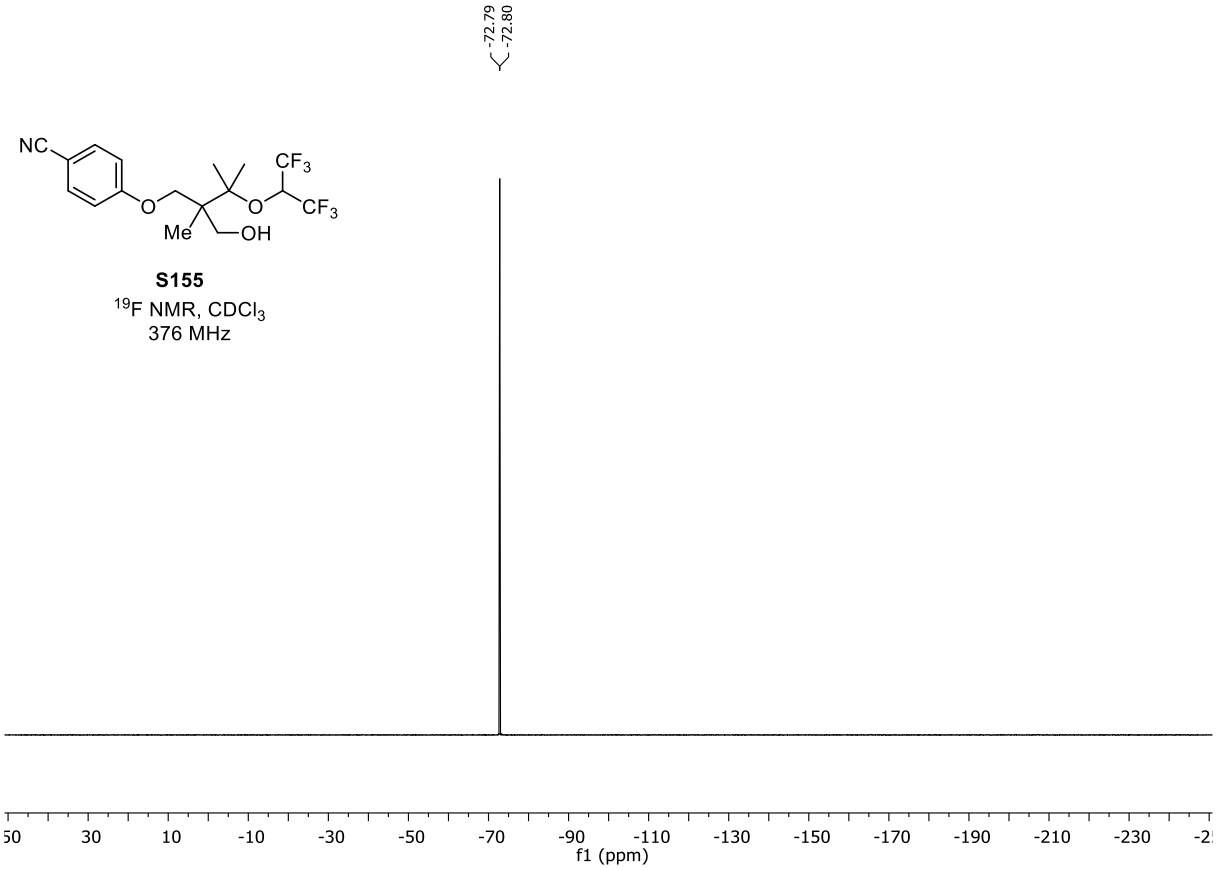


S154

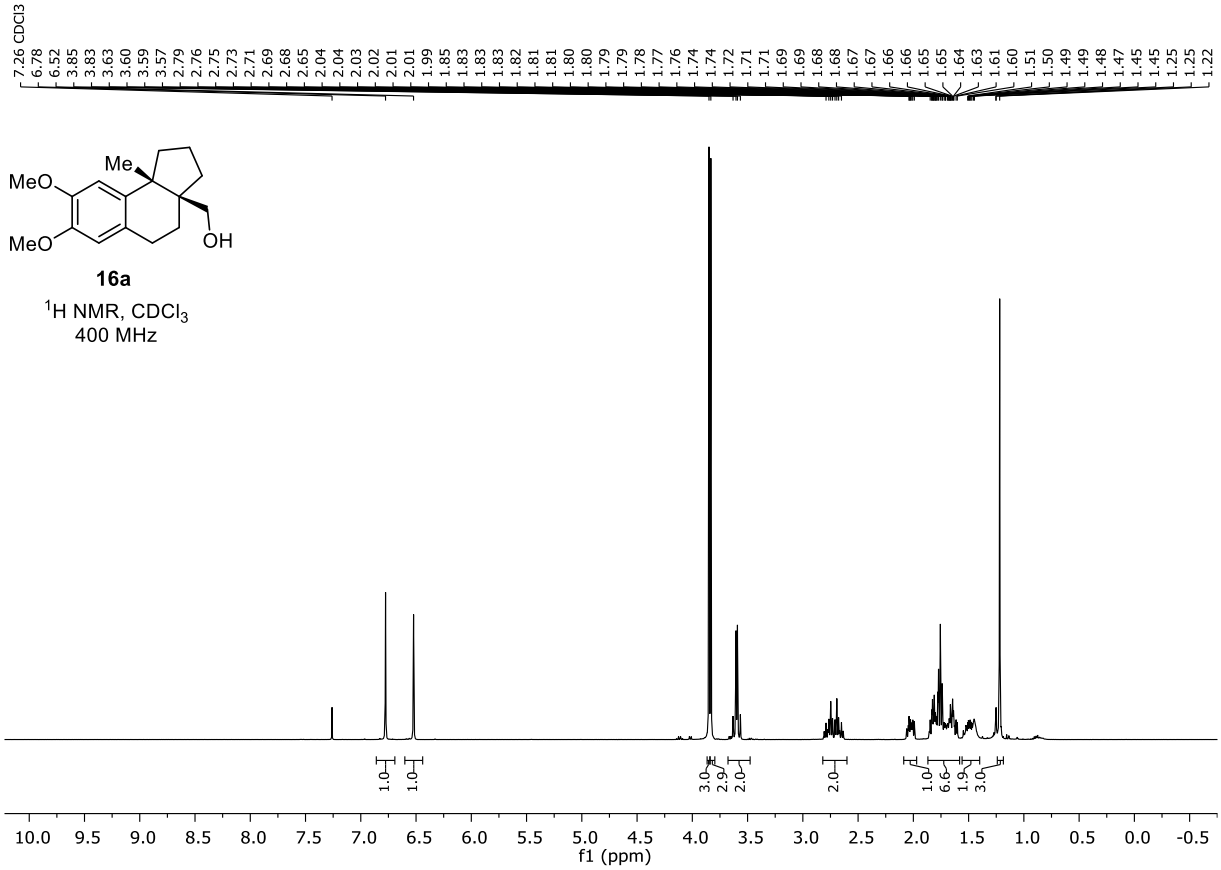
^{13}C NMR, $CDCl_3$
101 MHz

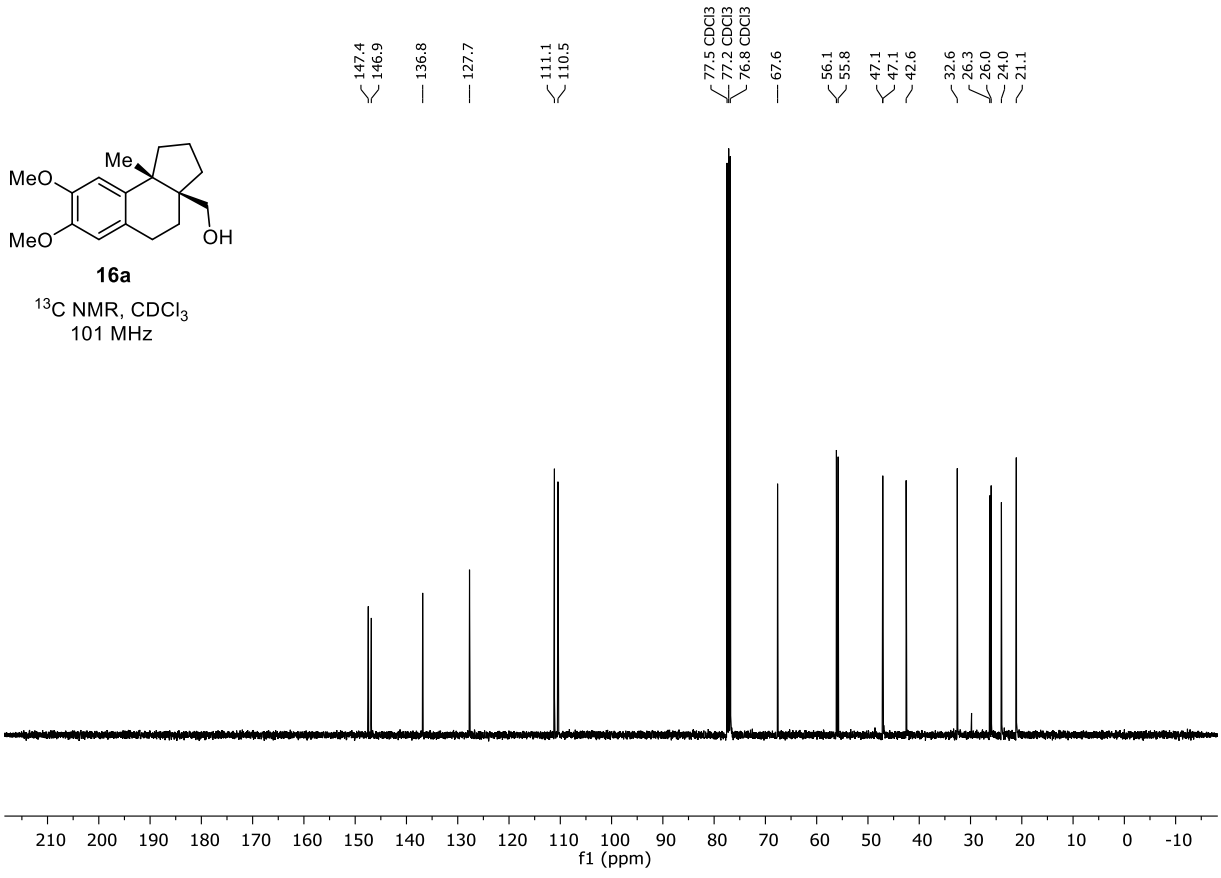

7.62
7.61
7.61
7.60
7.59
7.59
7.58
7.58
7.26 CDCl3
6.98
6.98
6.97
6.96
6.95
6.95
4.38
4.36
4.35
4.33
4.32
4.20
4.18
4.07
4.04
3.91
3.90
3.88
3.87
3.73
3.72
3.70
3.70
3.69
1.99
1.98
1.97
1.96
1.56 HDO
1.36
1.34
1.26
1.08
NC
CF3
O
O
CF3
Me
OH
S155
1H NMR, CDCl3
400 MHz
2.0
1.9
1.0
1.0
1.0
1.0
0.9
2.7
2.7
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 -0.5
f1 (ppm)

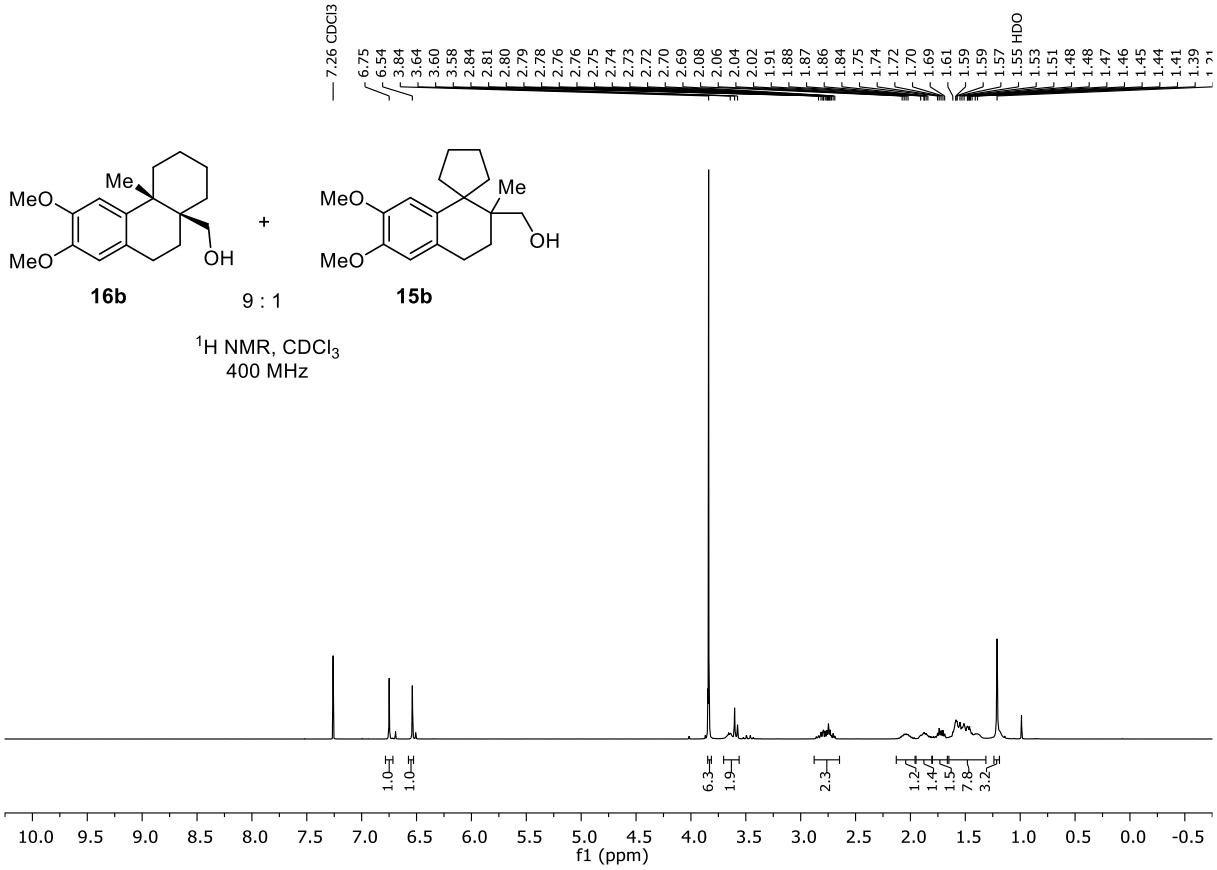

162.13
134.17
125.82
122.99
120.16
119.27
117.33
115.36
104.40
86.30
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
70.10
69.59
69.27
68.95
68.62
68.30
65.36
46.40
22.16
21.94
16.33
NC
CF3
O
O
CF3
Me
OH
S155
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

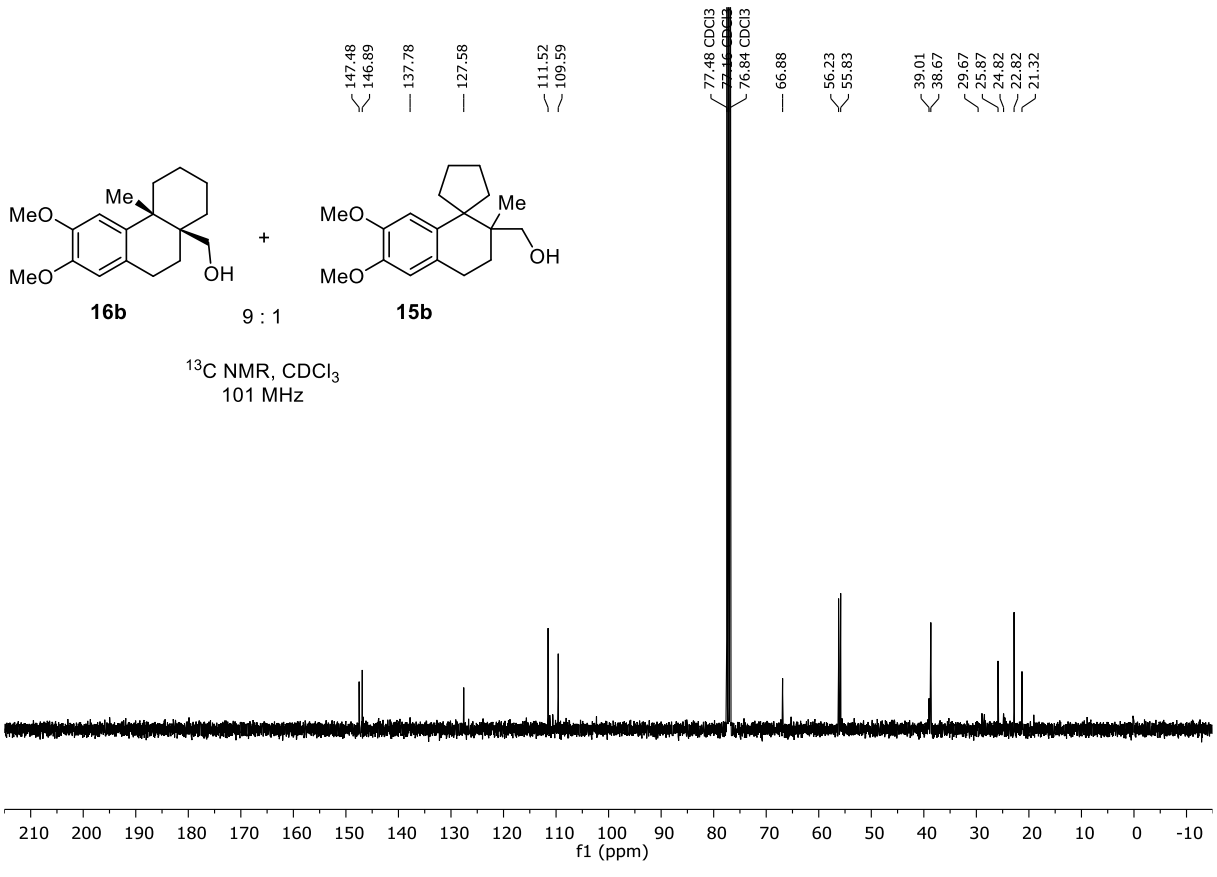


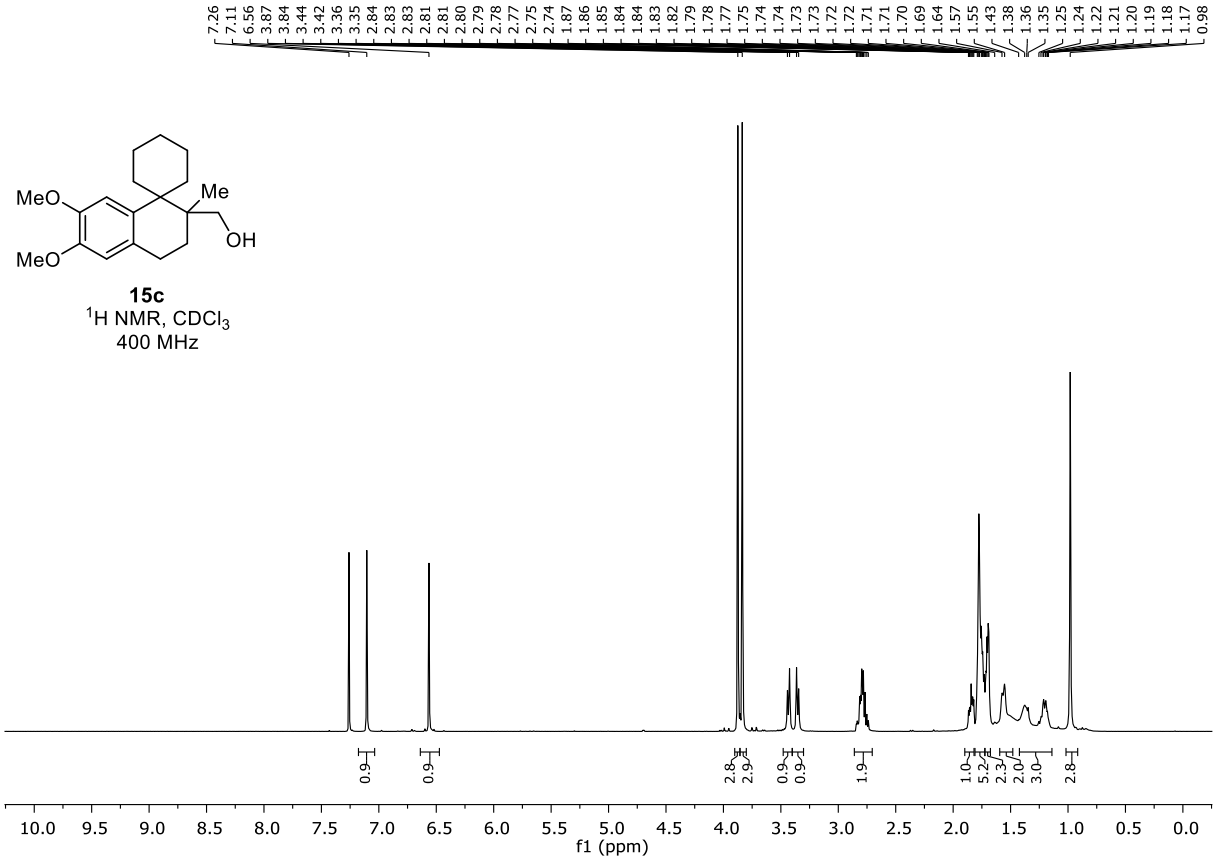
S155
^{19}F NMR, $CDCl_3$
376 MHz


7.26 CDCl3
6.78
6.52
3.85
3.83
3.63
3.60
3.59
3.57
2.79
2.76
2.75
2.73
2.71
2.69
2.68
2.65
2.04
2.04
2.03
2.02
2.01
2.01
1.99
1.85
1.83
1.83
1.83
1.82
1.81
1.81
1.80
1.80
1.79
1.79
1.78
1.77
1.76
1.74
1.74
1.72
1.71
1.71
1.69
1.69
1.68
1.68
1.67
1.67
1.66
1.66
1.65
1.65
1.64
1.63
1.61
1.60
1.51
1.50
1.49
1.49
1.48
1.47
1.45
1.45
1.25
1.25
1.22
Me
MeO
MeO
OH
16a
1H NMR, CDCl3
400 MHz
1.0
1.0
3.0
2.9
2.0
2.0
1.0
6.6
1.9
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 -0.5
f1 (ppm)

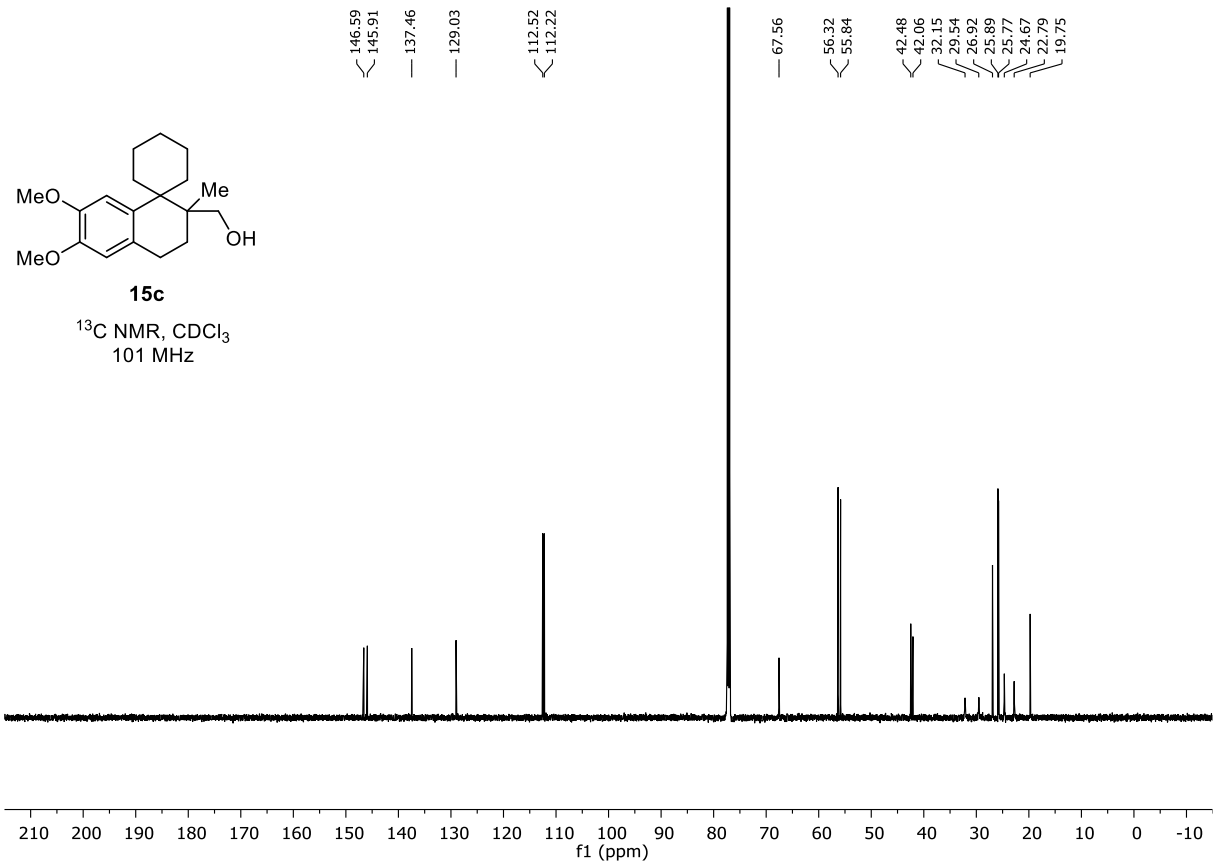

147.4
146.9
136.8
127.7
111.1
110.5
77.5 CDCl3
77.2 CDCl3
76.8 CDCl3
67.6
56.1
55.8
47.1
47.1
42.6
32.6
26.3
26.0
24.0
21.1
Me
MeO
MeO
OH
16a
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.26 CDCl3
6.75
6.54
3.84
3.64
3.60
3.58
2.84
2.81
2.80
2.79
2.78
2.76
2.76
2.75
2.74
2.73
2.72
2.70
2.69
2.08
2.06
2.04
2.02
1.91
1.88
1.87
1.86
1.84
1.75
1.74
1.72
1.70
1.69
1.61
1.59
1.59
1.57
1.55 HDO
1.53
1.51
1.48
1.48
1.47
1.46
1.45
1.44
1.41
1.39
MeO
MeO
Me
OH
16b
9 : 1
15b
1H NMR, CDCl3
400 MHz
1.0
1.0
6.3
1.9
2.3
1.2
1.4
1.5
7.8
3.2
f1 (ppm)

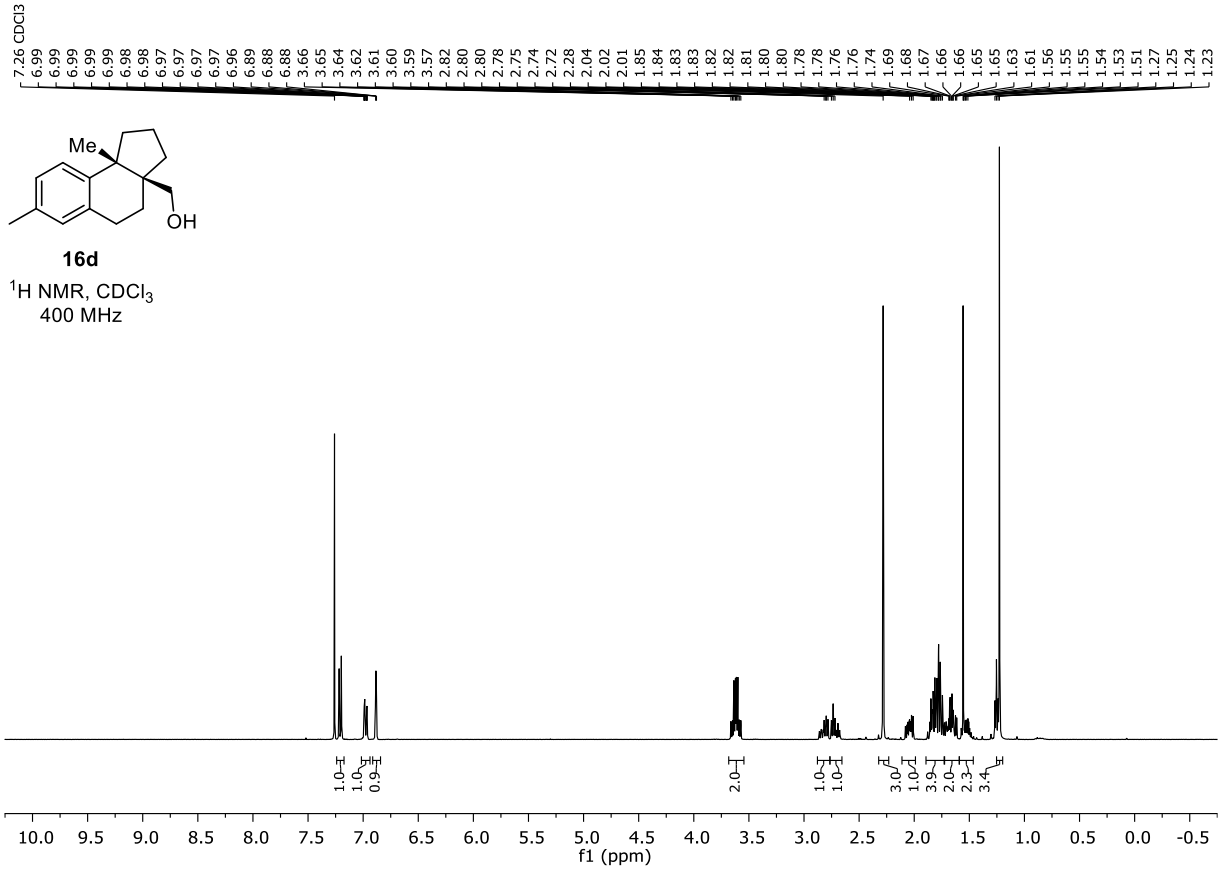

147.48
146.89
137.78
127.58
111.52
109.59
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
66.88
56.23
55.83
39.01
38.67
29.67
25.87
24.82
22.82
21.32
MeO
MeO
Me
OH
16b
9 : 1
15b
13C NMR, CDCl3
101 MHz
f1 (ppm)

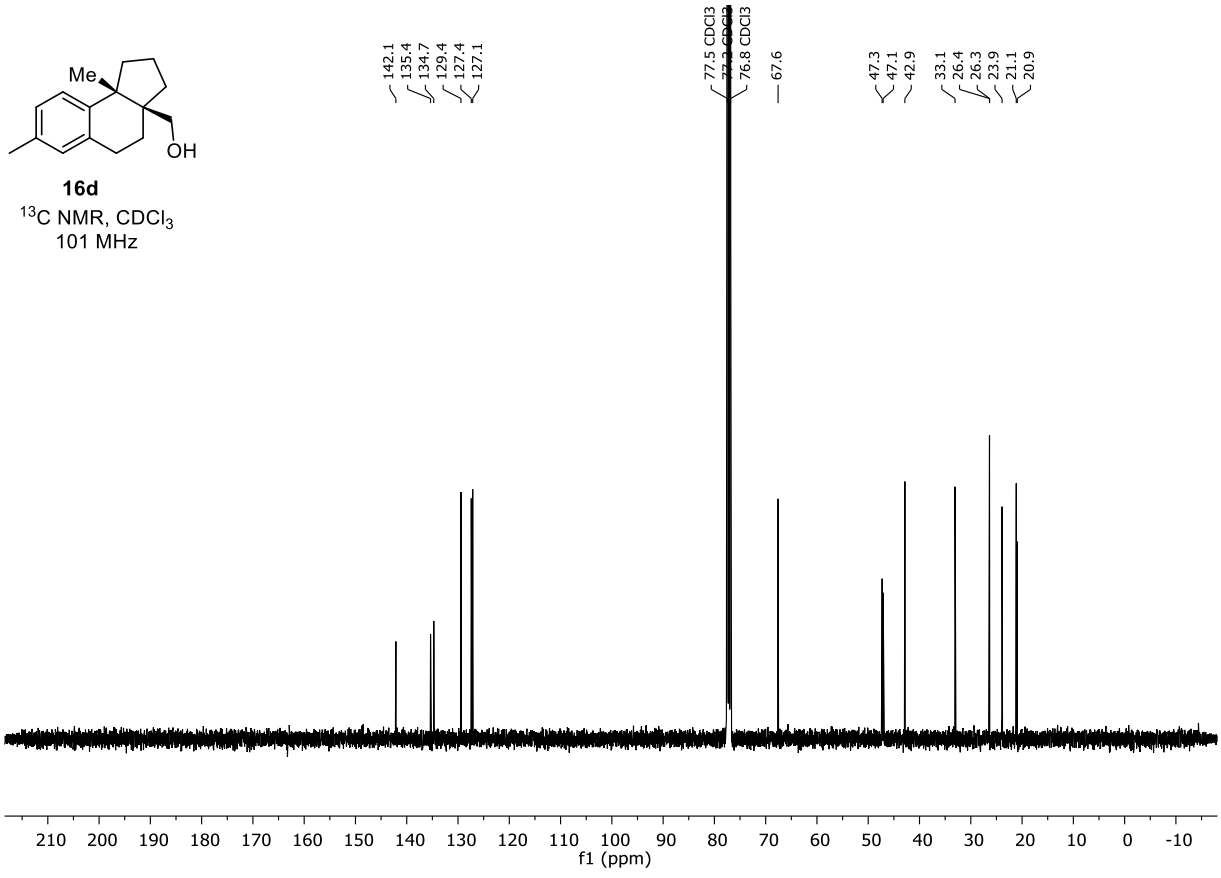


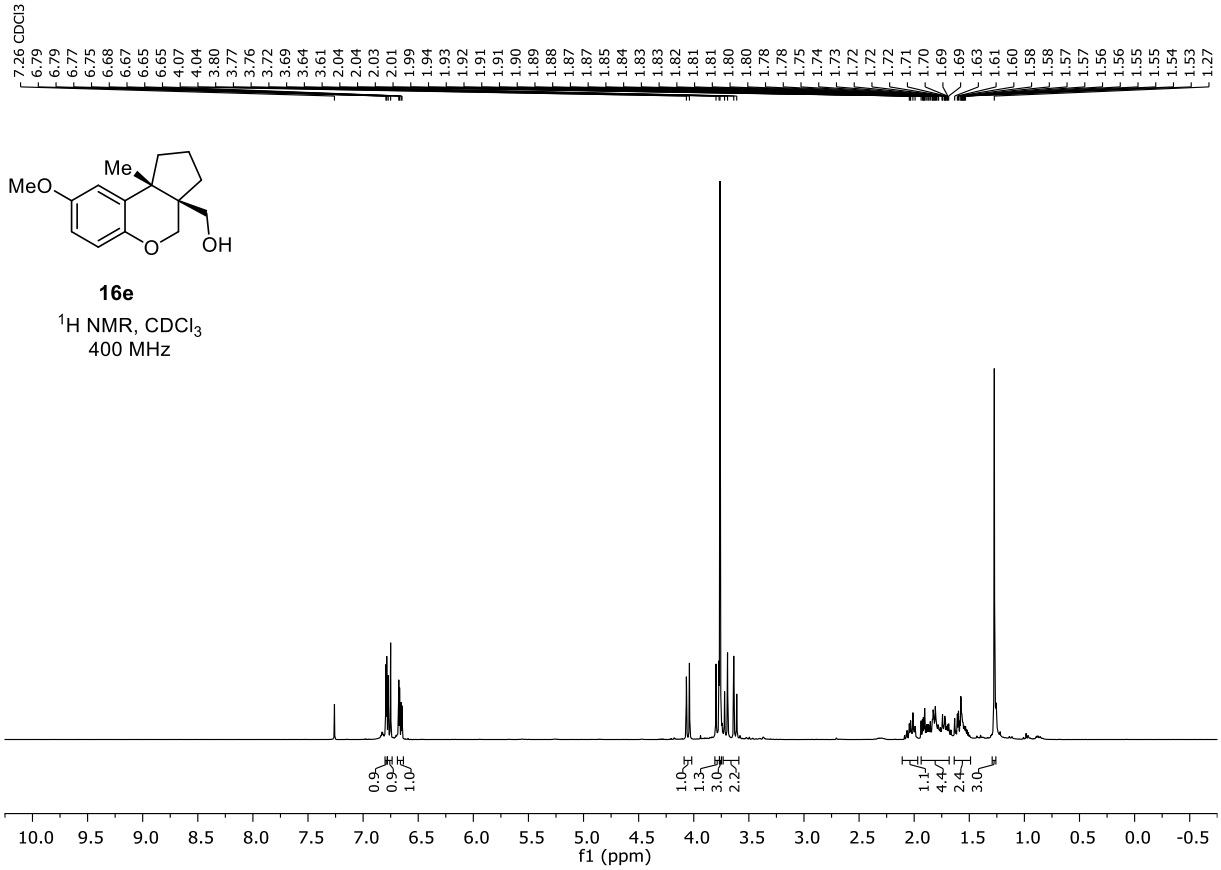
15c
^{1}H NMR, $CDCl_3$
400 MHz



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

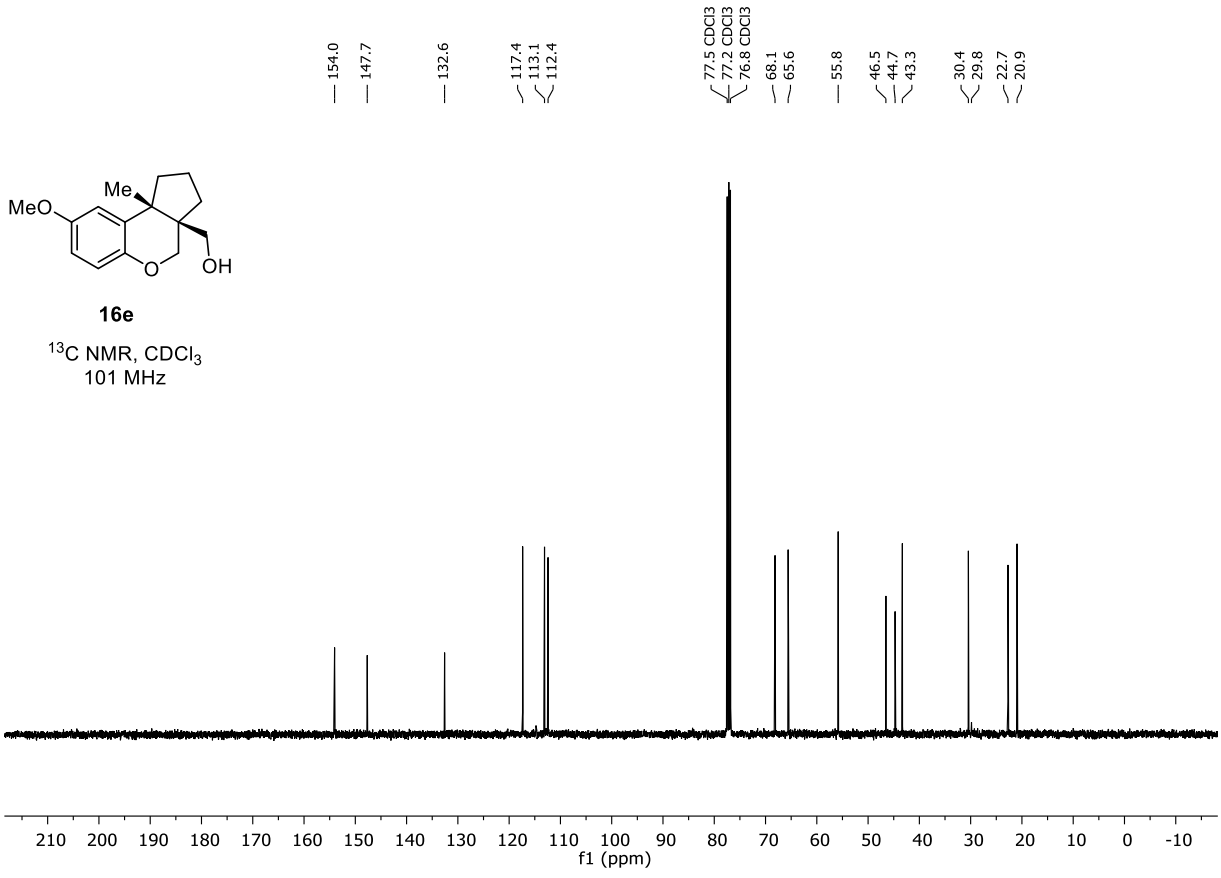

7.26 CDCl3
Me
OH
16d
1H NMR, CDCl3
400 MHz
1.0
1.0
0.9
2.0
1.0
1.0
3.0
1.0
3.9
2.0
2.3
3.4
f1 (ppm)


Me
OH
16d
13C NMR, CDCl3
101 MHz
142.1
135.4
134.7
129.4
127.4
127.1
77.5 CDCl3
77.2 CDCl3
76.8 CDCl3
67.6
47.3
47.1
42.9
33.1
26.4
26.3
23.9
21.1
20.9
f1 (ppm)



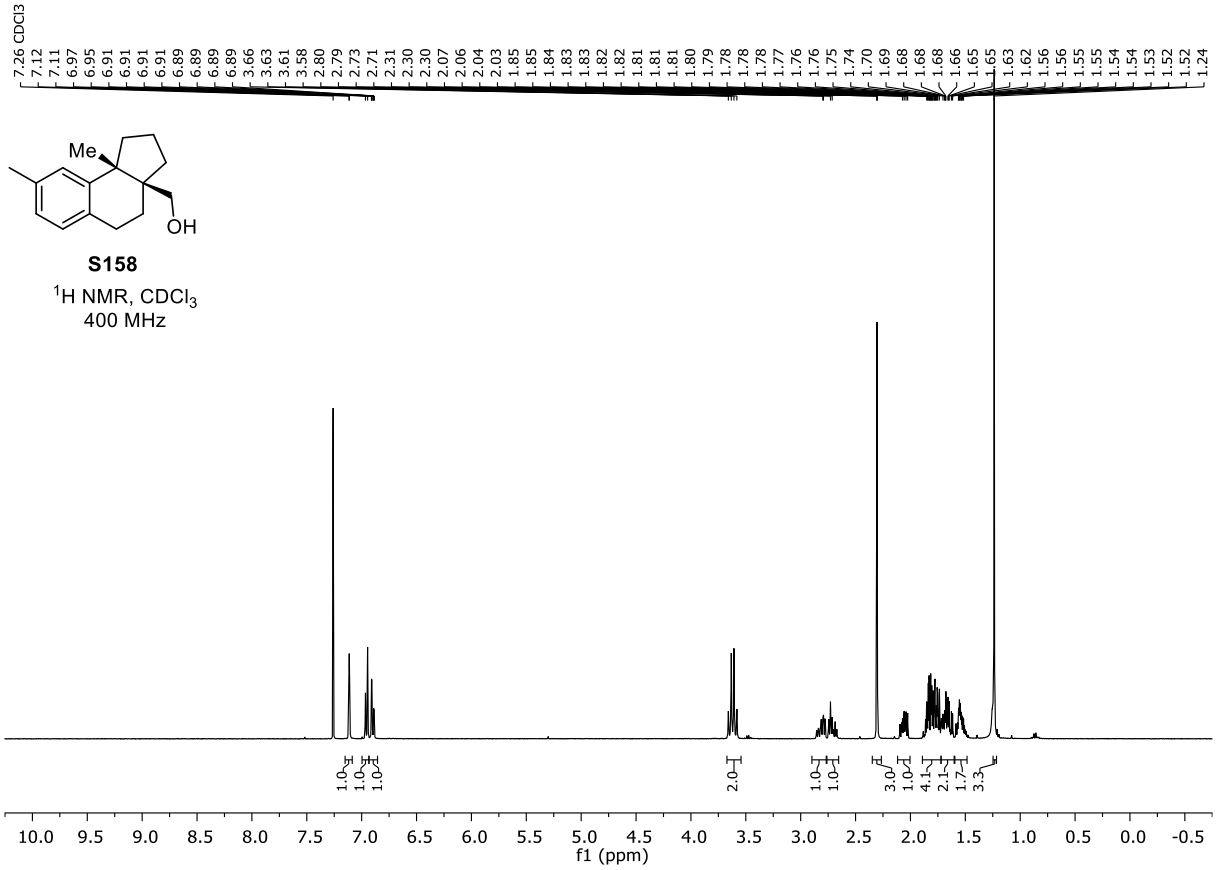
16e

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



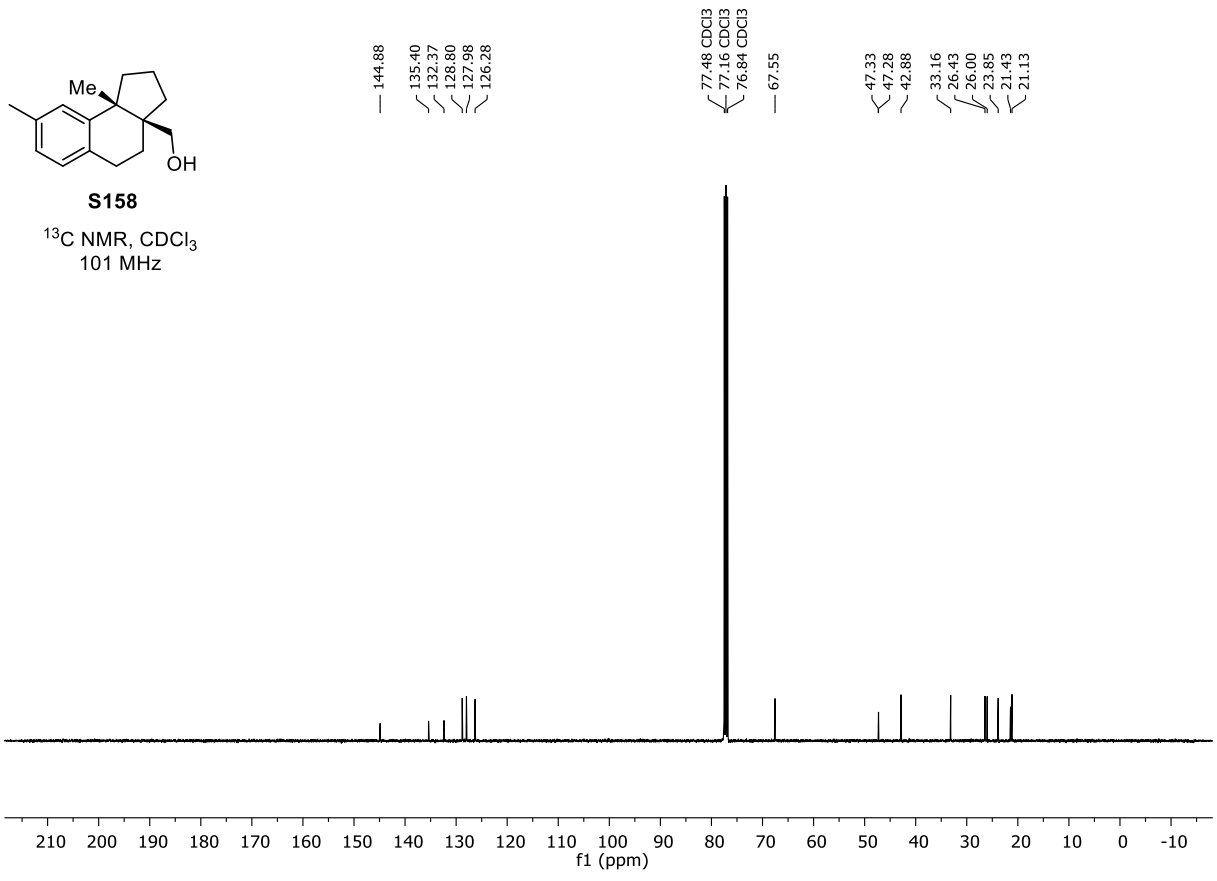
16e

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



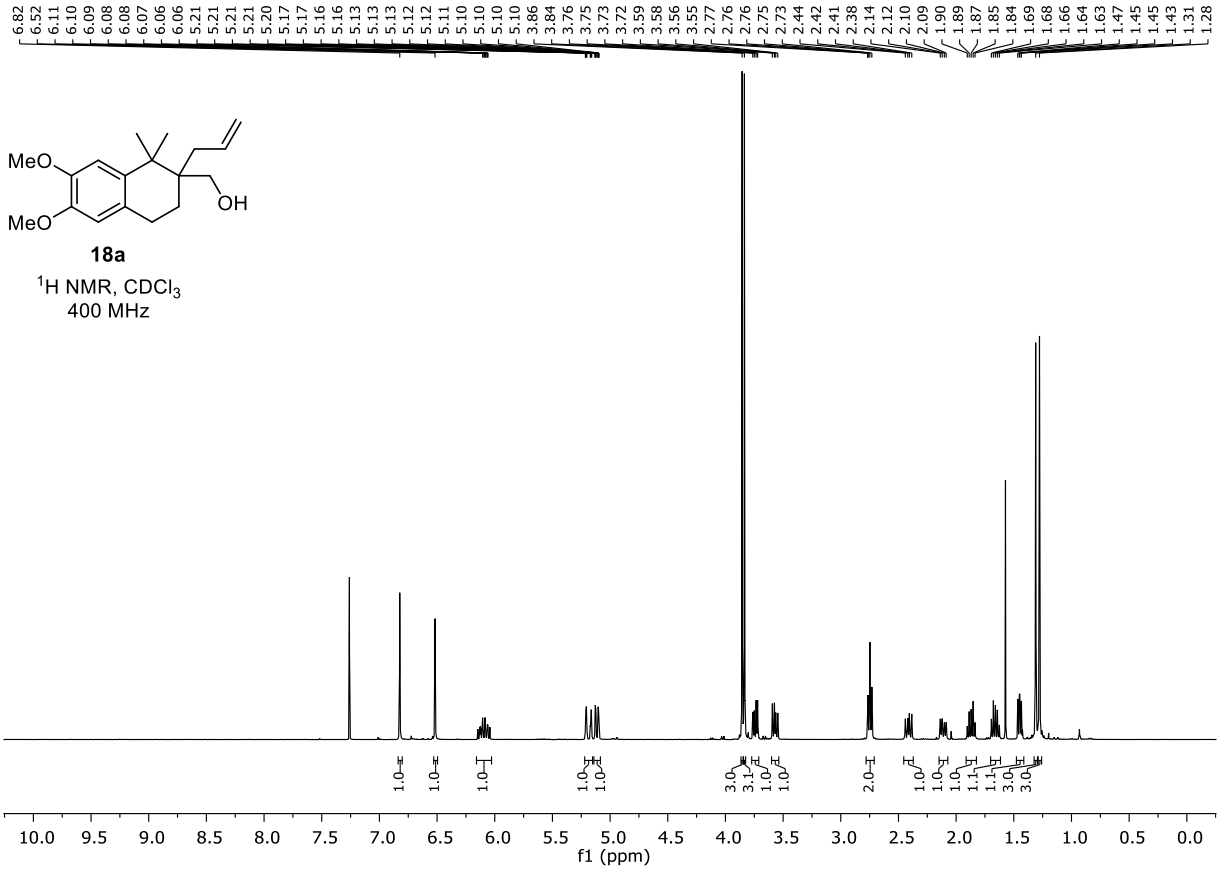
S158

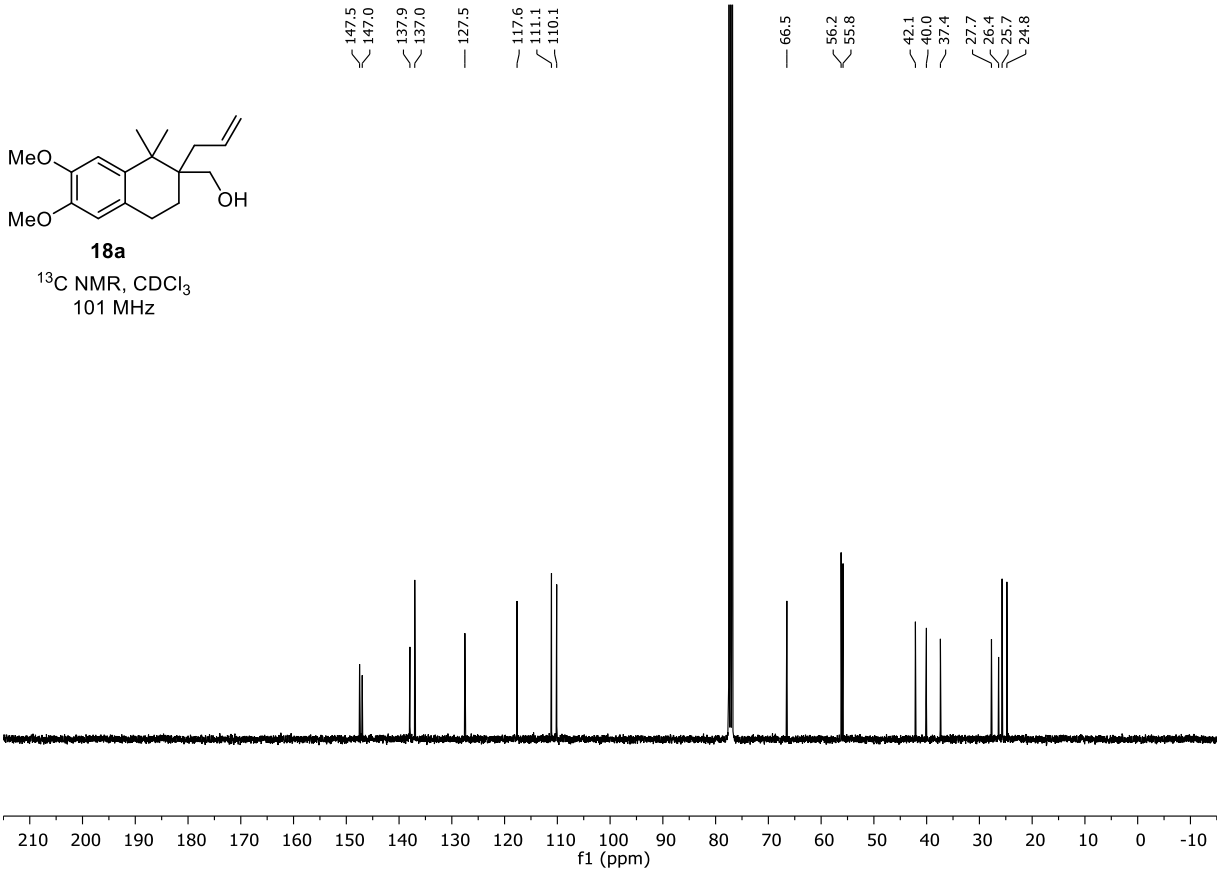
^{1}H NMR, $CDCl_3$
400 MHz

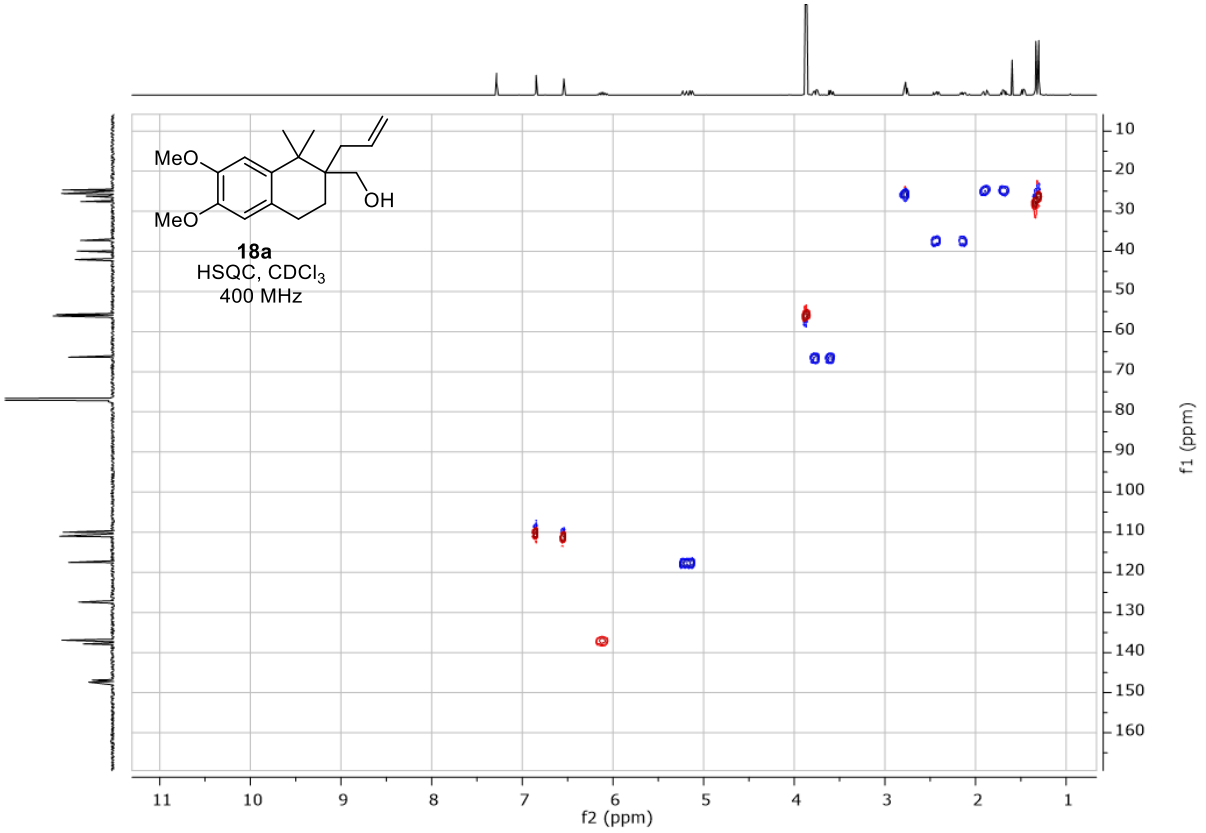


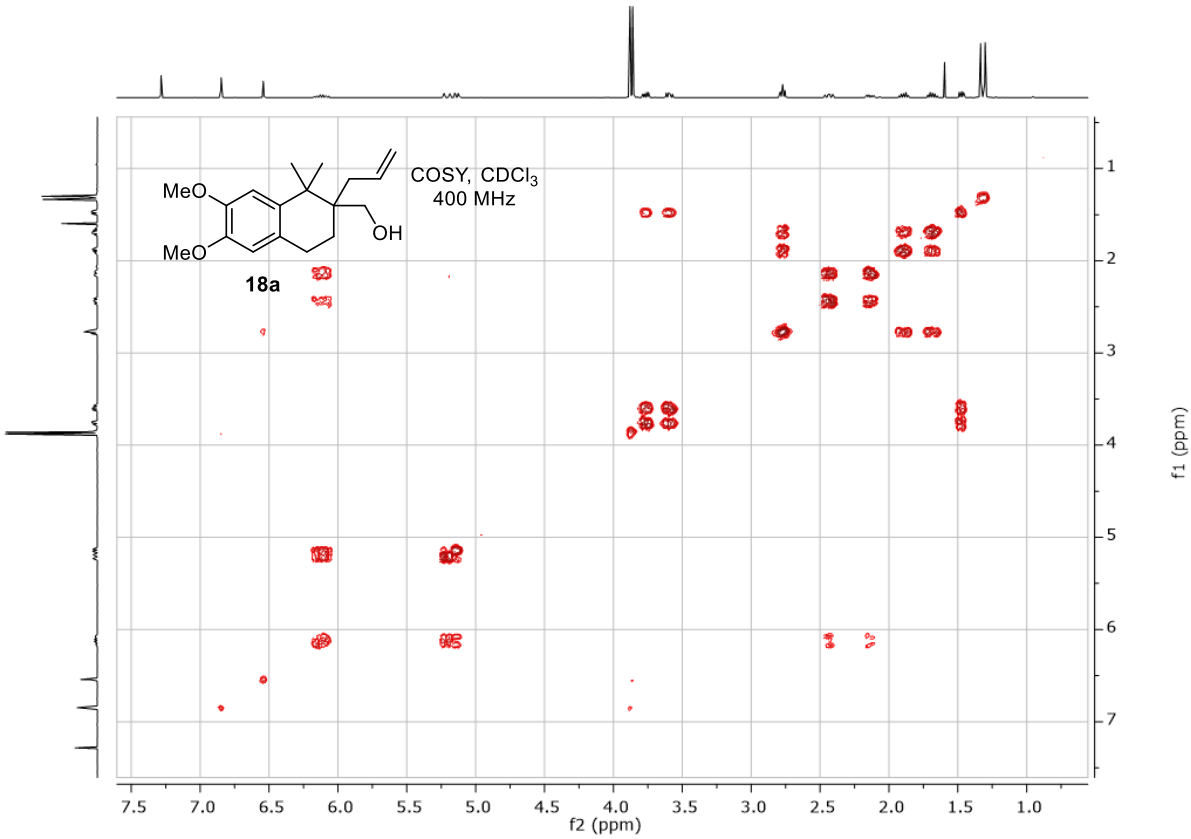
S158

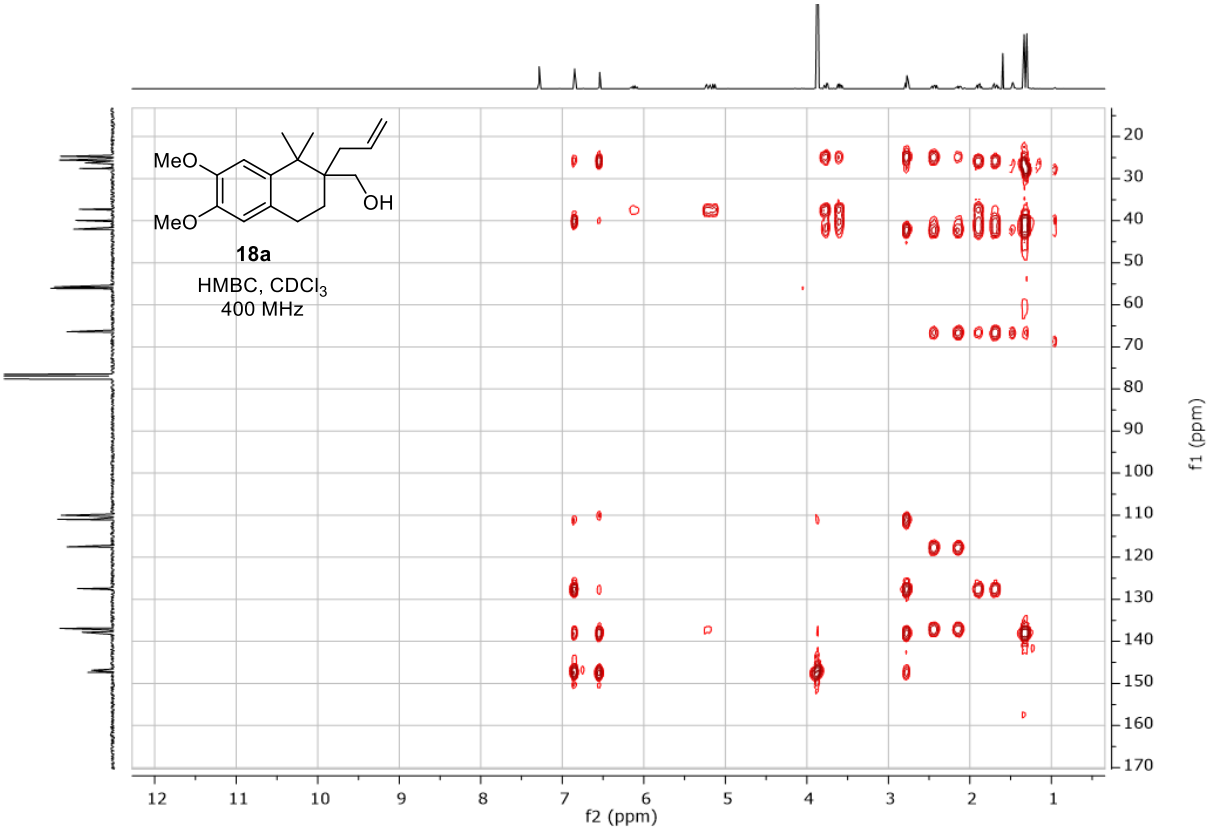
^{13}C NMR, $CDCl_3$
101 MHz

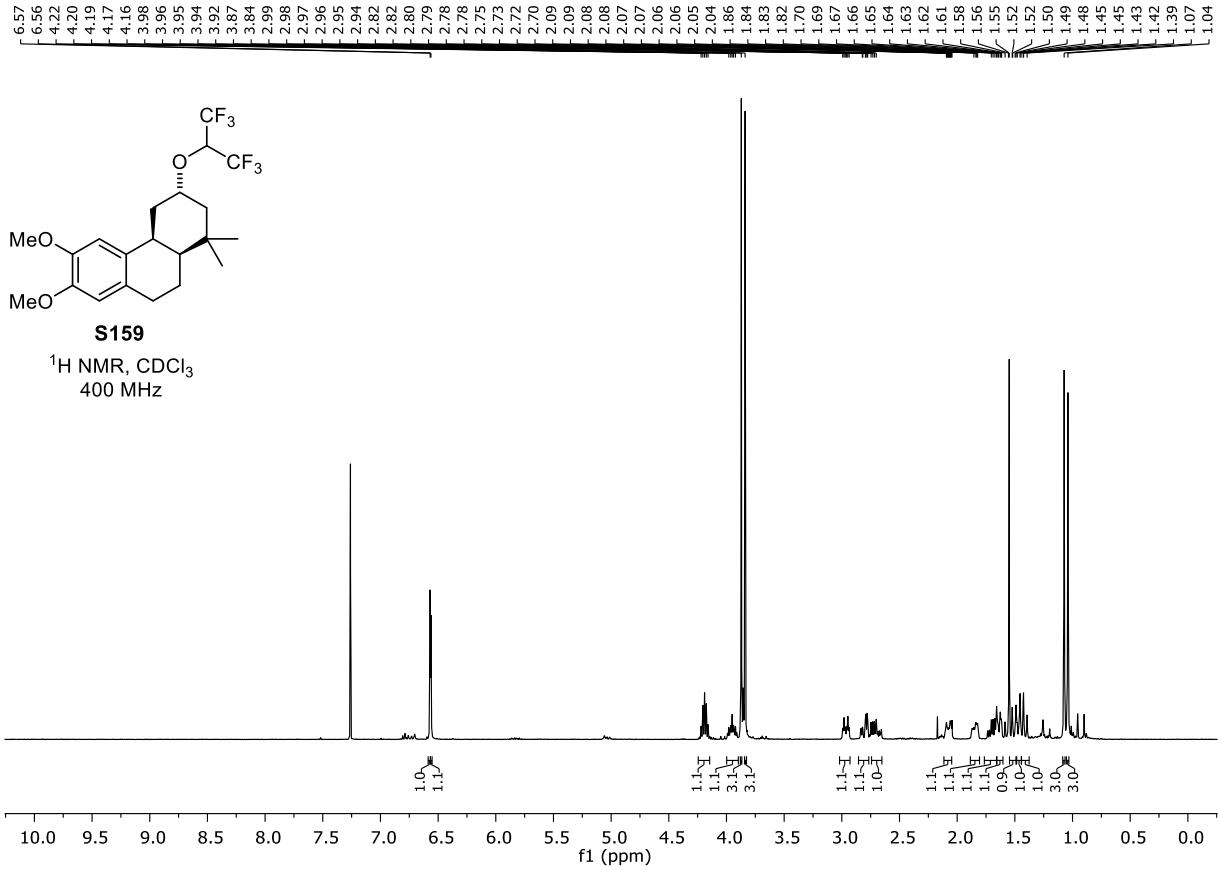

MeO
MeO
OH
18a
1H NMR, CDCl3
400 MHz
f1 (ppm)

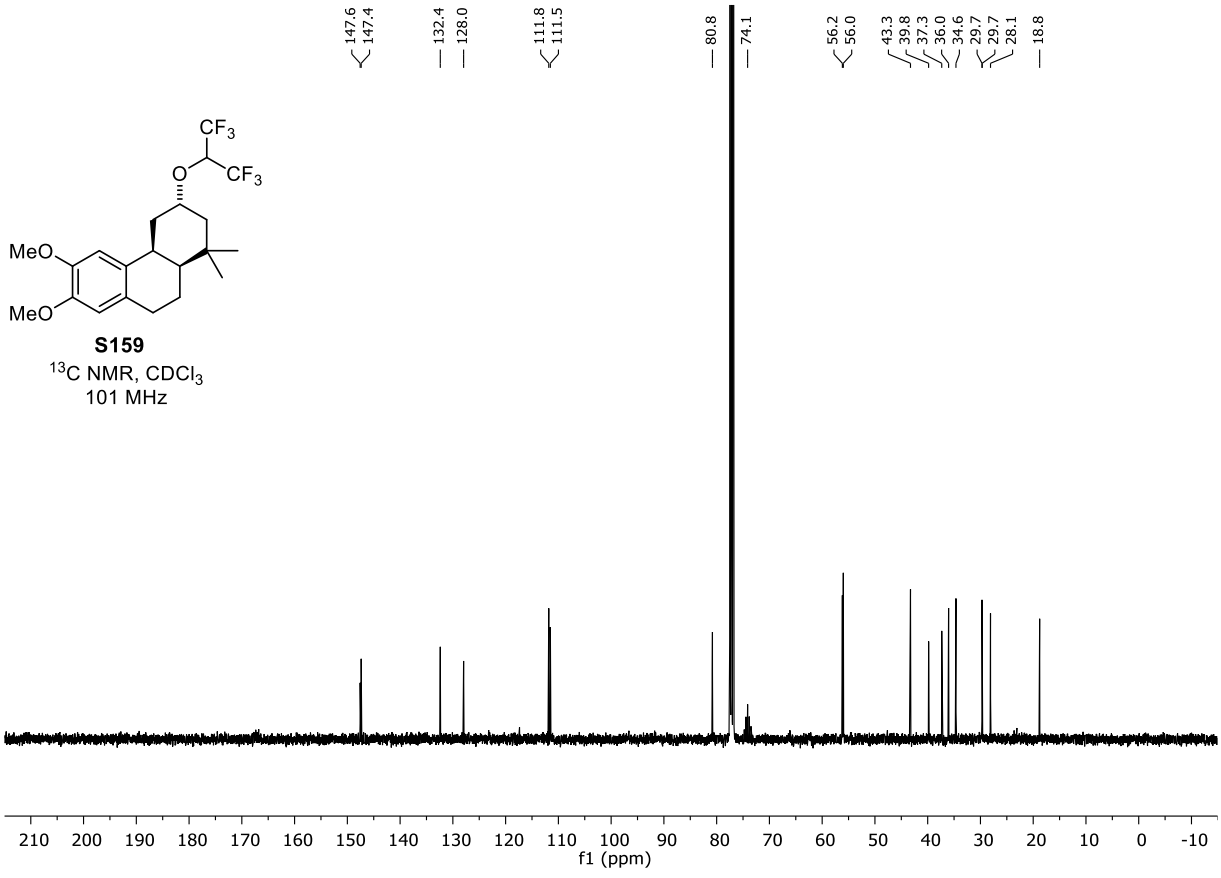

MeO
MeO
OH
18a
13C NMR, CDCl3
101 MHz
f1 (ppm)

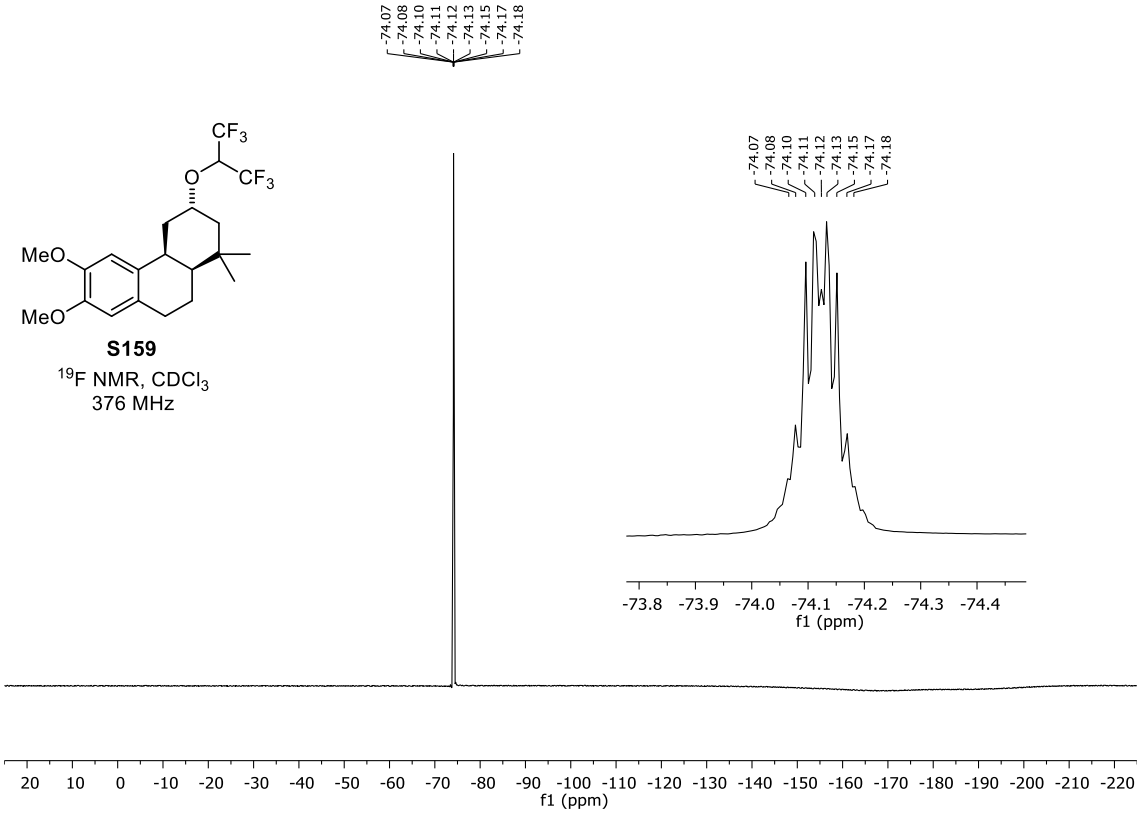

MeO
MeO
OH
18a
HSQC, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)

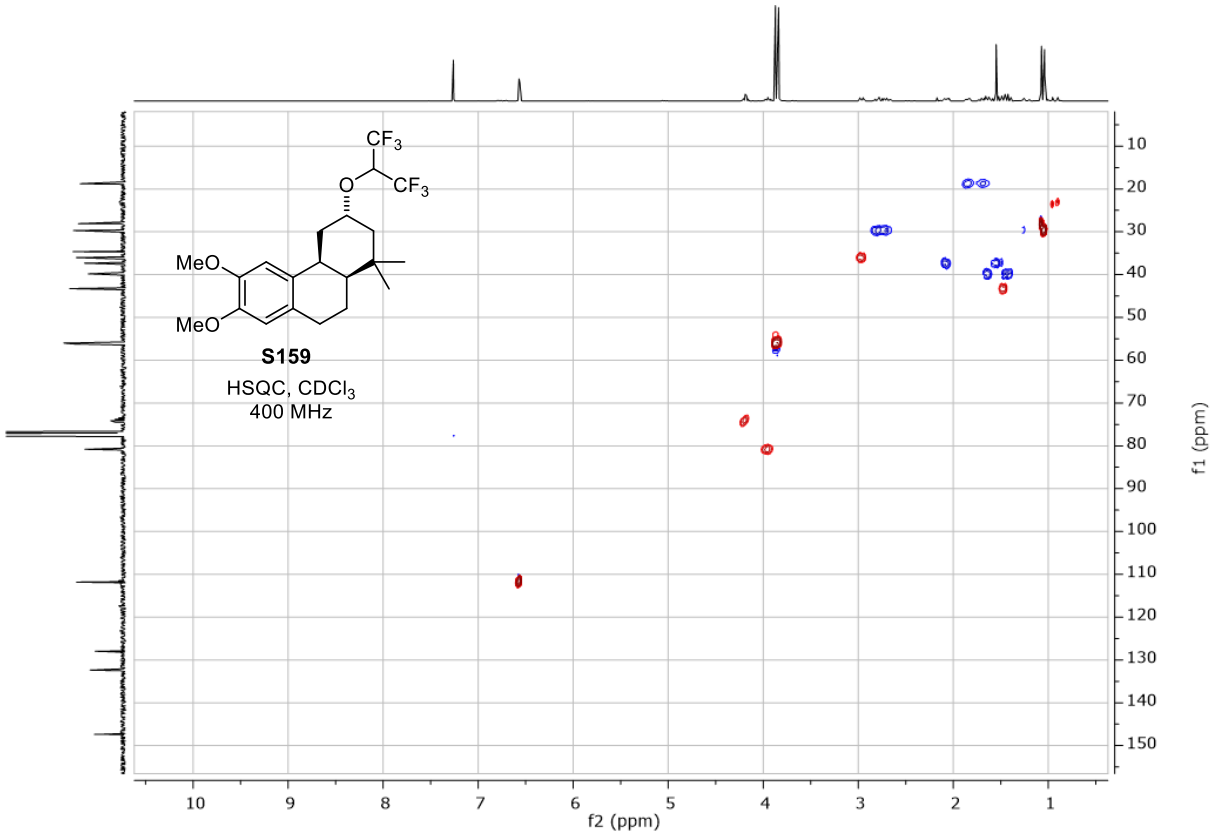

MeO
MeO
OH
18a
COSY, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)

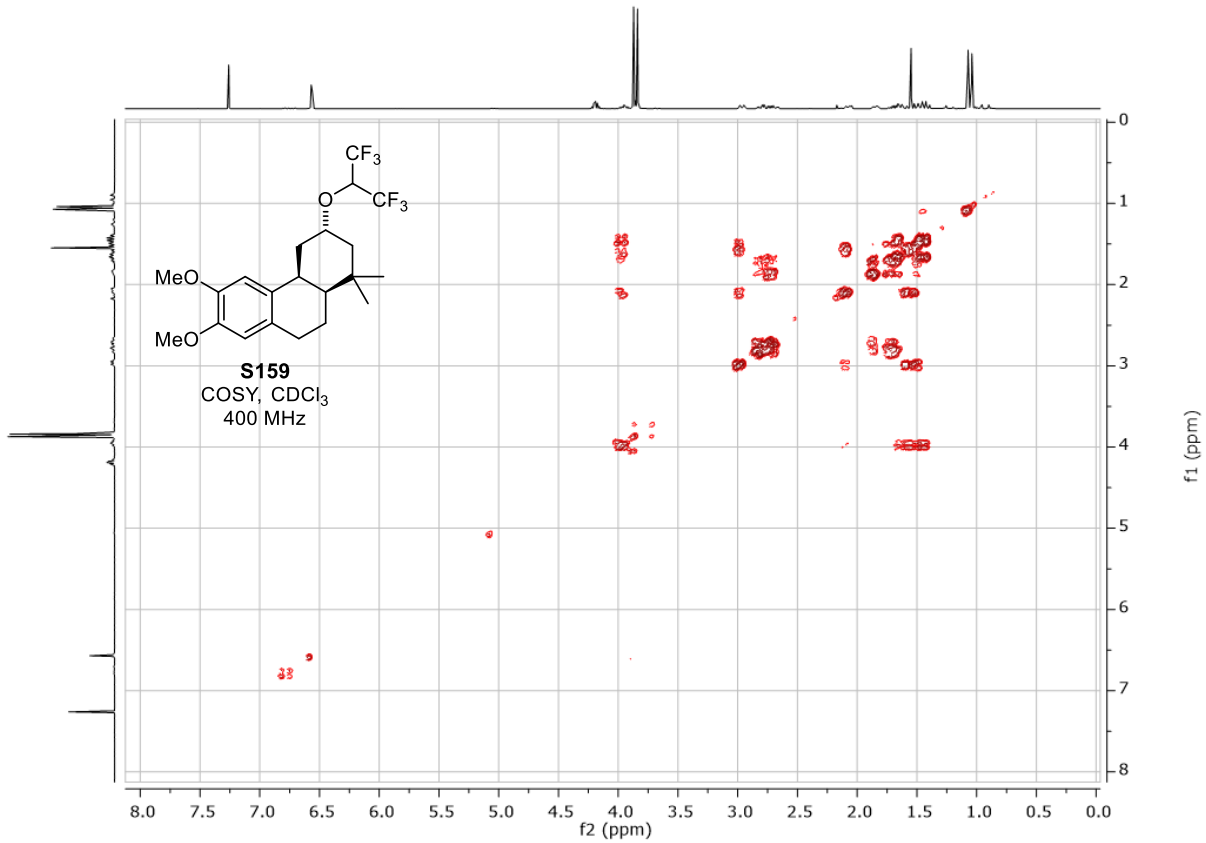

MeO
MeO
OH
18a
HMBC, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)

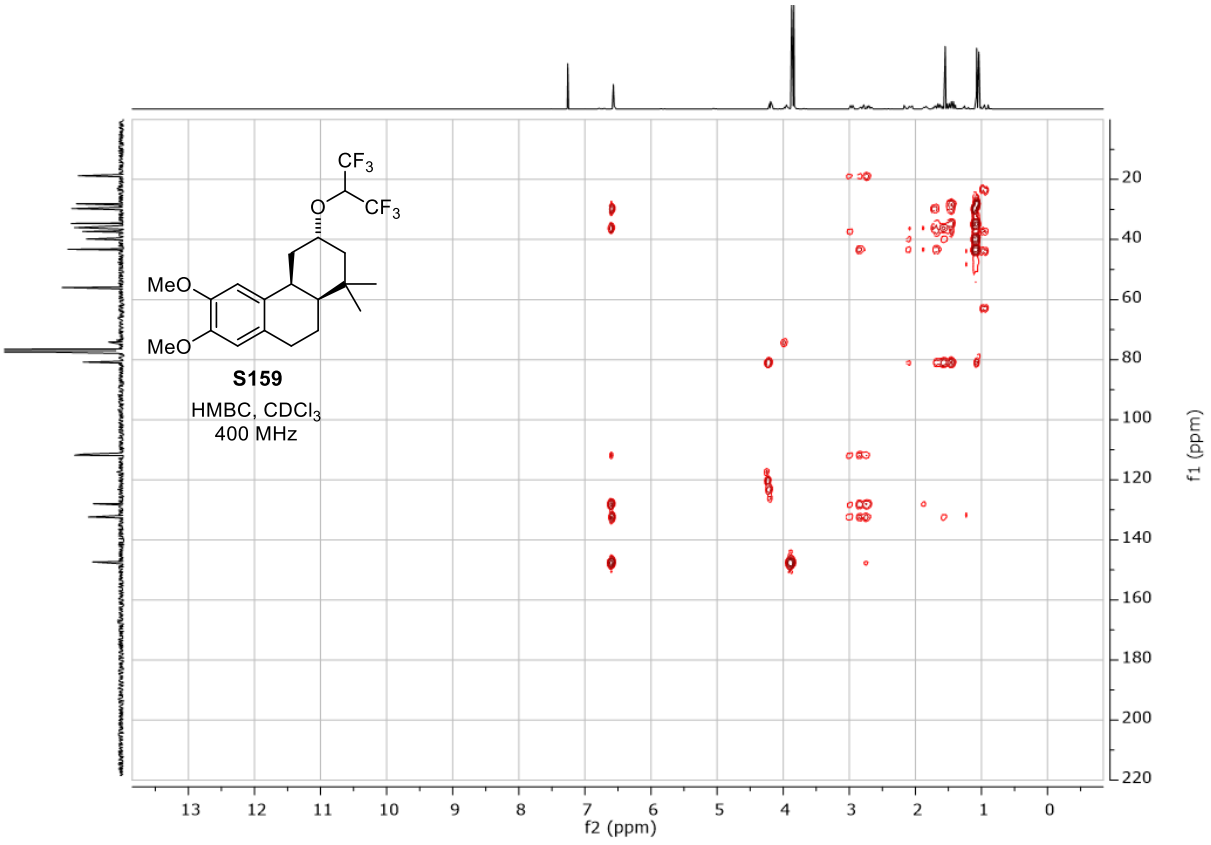

6.57 6.56 4.22 4.20 4.19 4.17 4.16 3.98 3.96 3.95 3.94 3.92 3.87 3.84 2.99 2.98 2.97 2.96 2.95 2.94 2.82 2.82 2.80 2.79 2.78 2.78 2.75 2.73 2.72 2.70 2.09 2.09 2.08 2.08 2.07 2.07 2.06 2.06 2.05 2.04 1.86 1.84 1.83 1.82 1.70 1.69 1.67 1.66 1.65 1.64 1.63 1.62 1.61 1.58 1.56 1.55 1.52 1.52 1.50 1.49 1.48 1.45 1.45 1.43 1.42 1.39 1.07 1.04
CF3
O
CF3
MeO
MeO
S159
1H NMR, CDCl3
400 MHz
1.0 1.1 1.1 1.1 3.1 3.1 1.1 1.1 1.0 1.1 1.1 1.1 0.9 1.0 1.0 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)

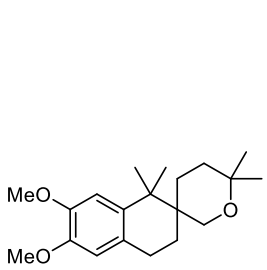

147.6 147.4 132.4 128.0 111.8 111.5 80.8 74.1 56.2 56.0 43.3 39.8 37.3 36.0 34.6 29.7 29.7 28.1 18.8
CF3
O
CF3
MeO
MeO
S159
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


-74.07
-74.08
-74.10
-74.11
-74.12
-74.13
-74.15
-74.17
-74.18
CF3
O
CF3
MeO
MeO
S159
19F NMR, CDCl3
376 MHz
-73.8 -73.9 -74.0 -74.1 -74.2 -74.3 -74.4
f1 (ppm)
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)


CF3
O
CF3
MeO
MeO
S159
HSQC, CDCl3
400 MHz
10 9 8 7 6 5 4 3 2 1
f2 (ppm)
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150
f1 (ppm)

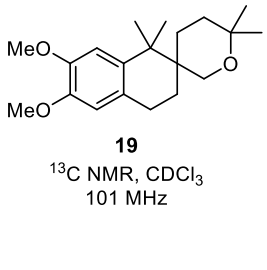

CF3
O
CF3
MeO
MeO
S159
COSY, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)


CF3
O
CF3
MeO
MeO
S159
HMBC, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)



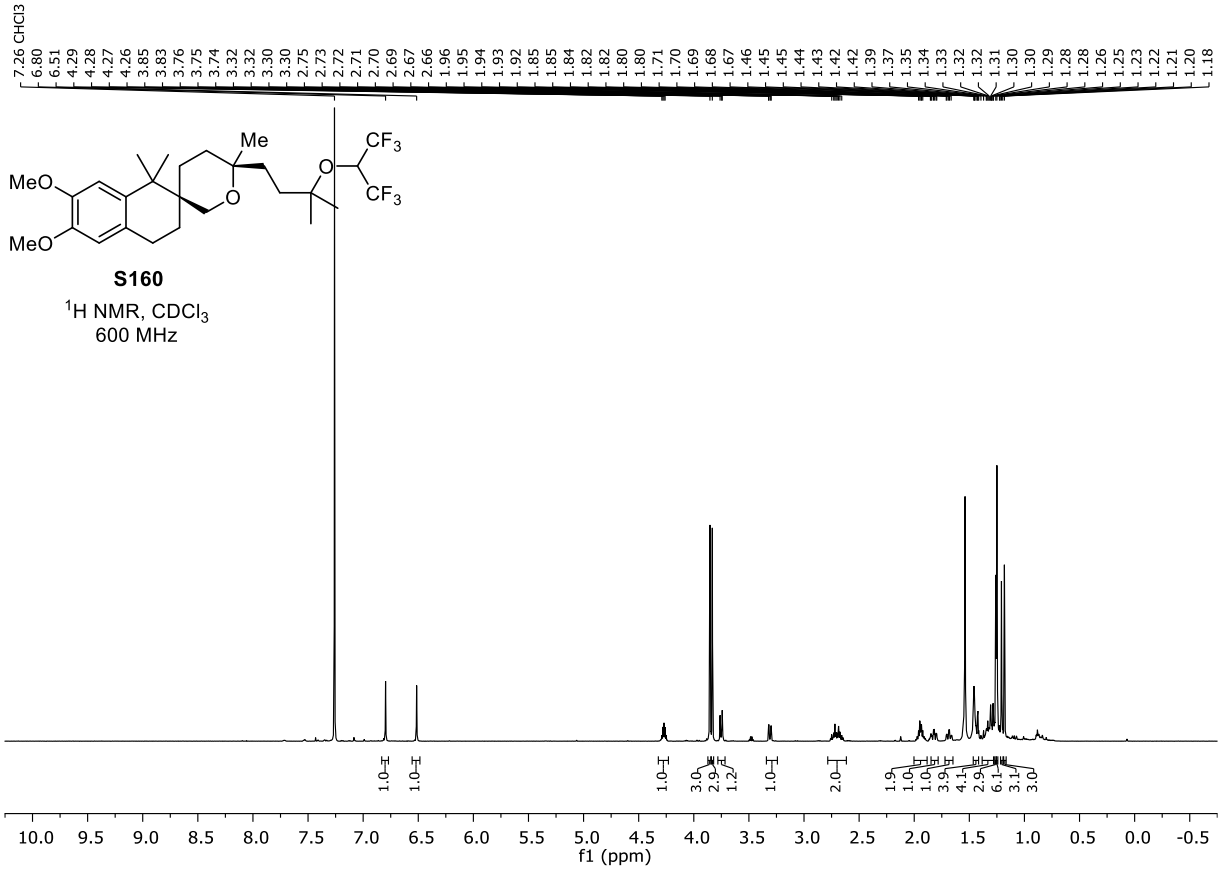
19

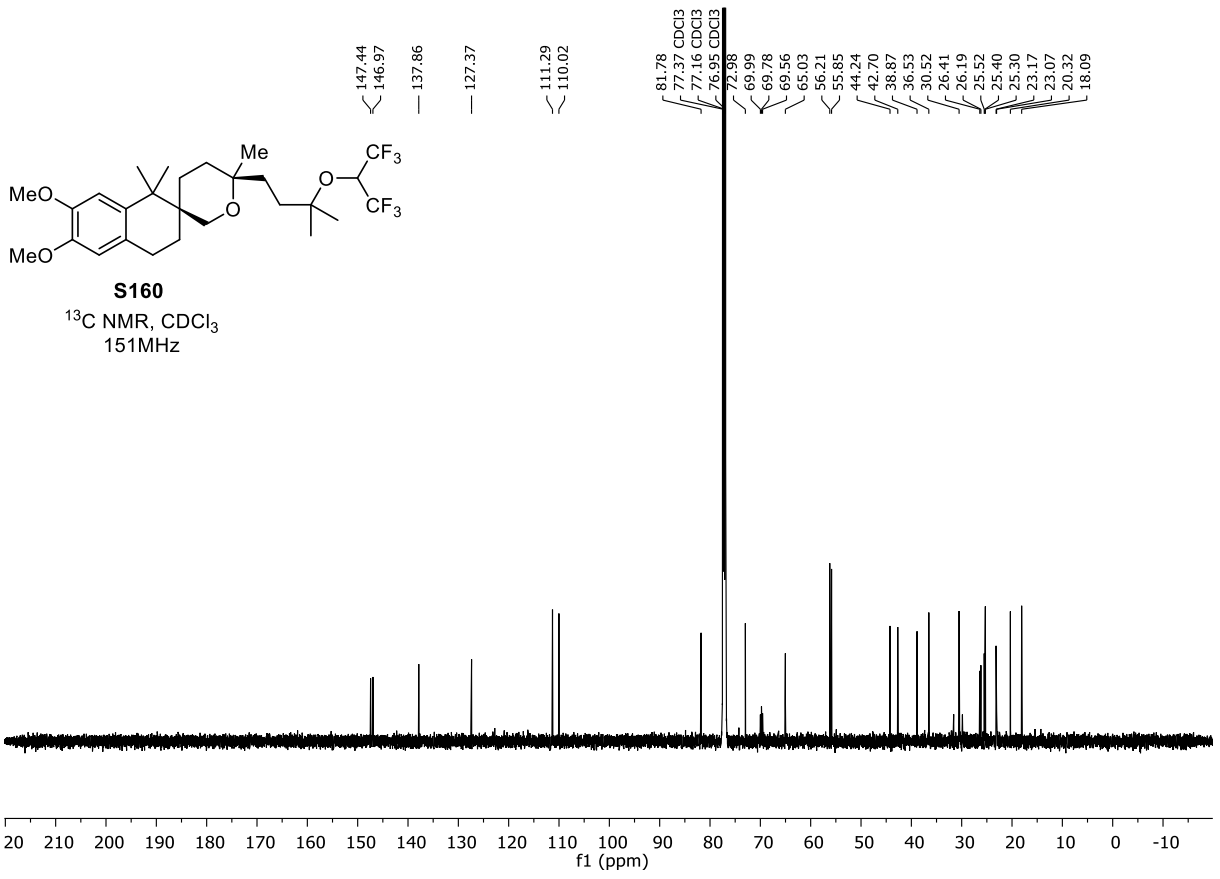
^{1}H NMR, $CDCl_3$
400 MHz

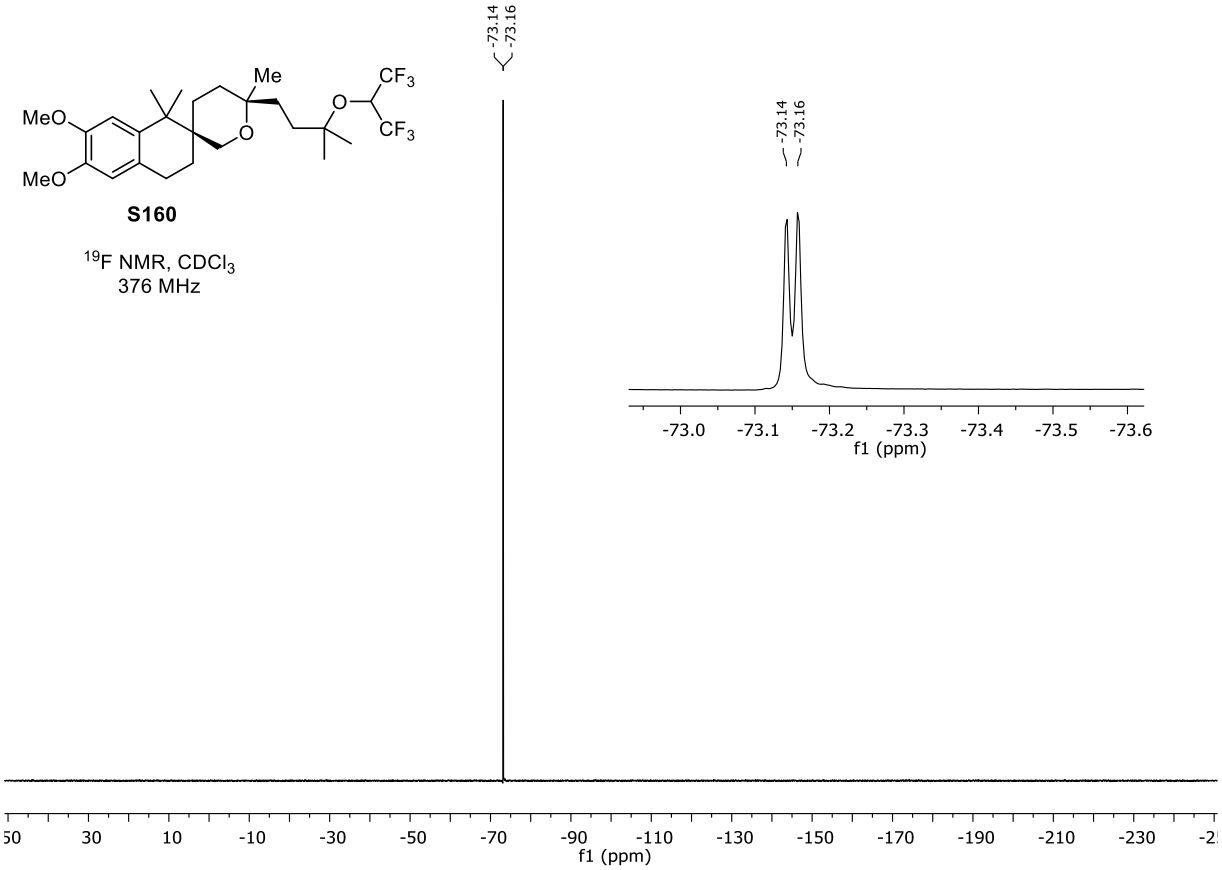


19

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

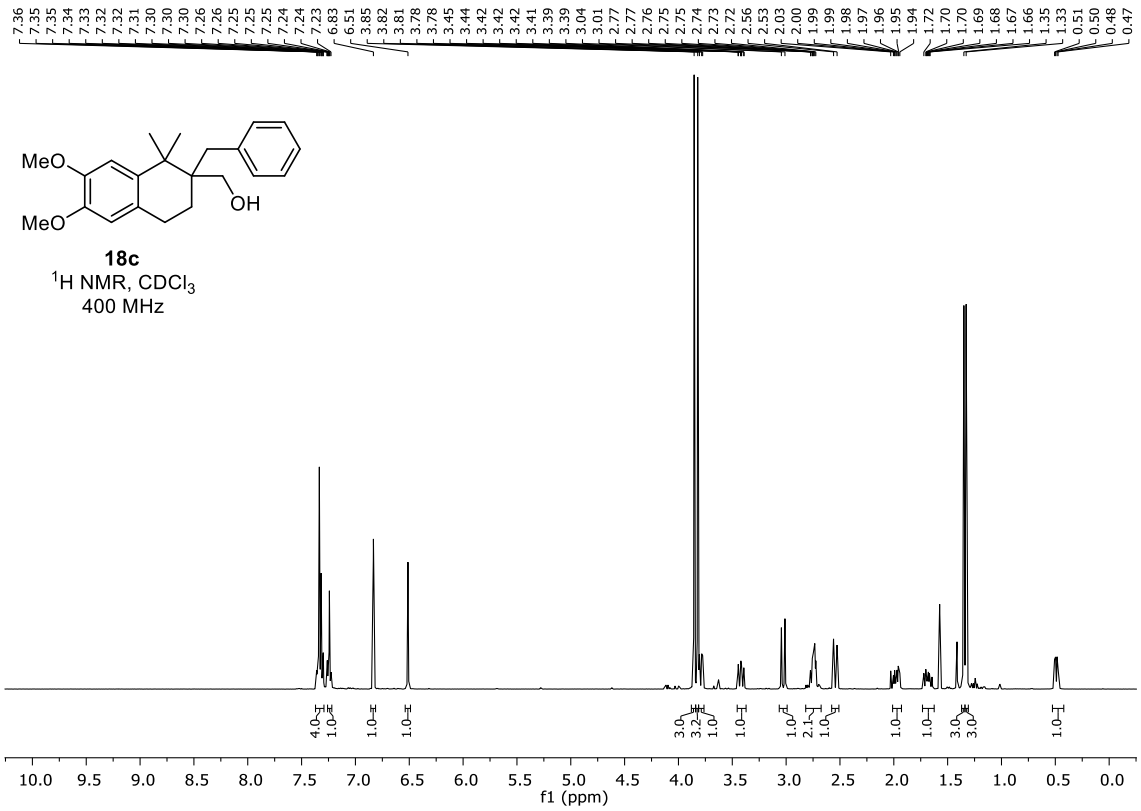

7.26 CHCl3
6.80
6.51
4.29
4.28
4.27
4.26
3.85
3.83
3.76
3.75
3.74
3.32
3.32
3.30
3.30
2.75
2.73
2.72
2.71
2.70
2.69
2.67
2.66
1.96
1.95
1.94
1.93
1.92
1.85
1.85
1.84
1.82
1.82
1.80
1.80
1.71
1.70
1.69
1.68
1.67
1.46
1.45
1.45
1.44
1.43
1.42
1.42
1.39
1.37
1.35
1.34
1.33
1.32
1.32
1.31
1.30
1.30
1.29
1.28
1.28
1.26
1.25
1.23
1.22
1.21
1.20
1.18
Me
CF3
O
MeO
O
CF3
MeO
S160
1H NMR, CDCl3
600 MHz
1.0
1.0
1.0
3.0
2.9
1.2
1.0
2.0
1.9
1.0
1.0
3.9
4.1
2.9
6.1
3.1
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 -0.5
f1 (ppm)

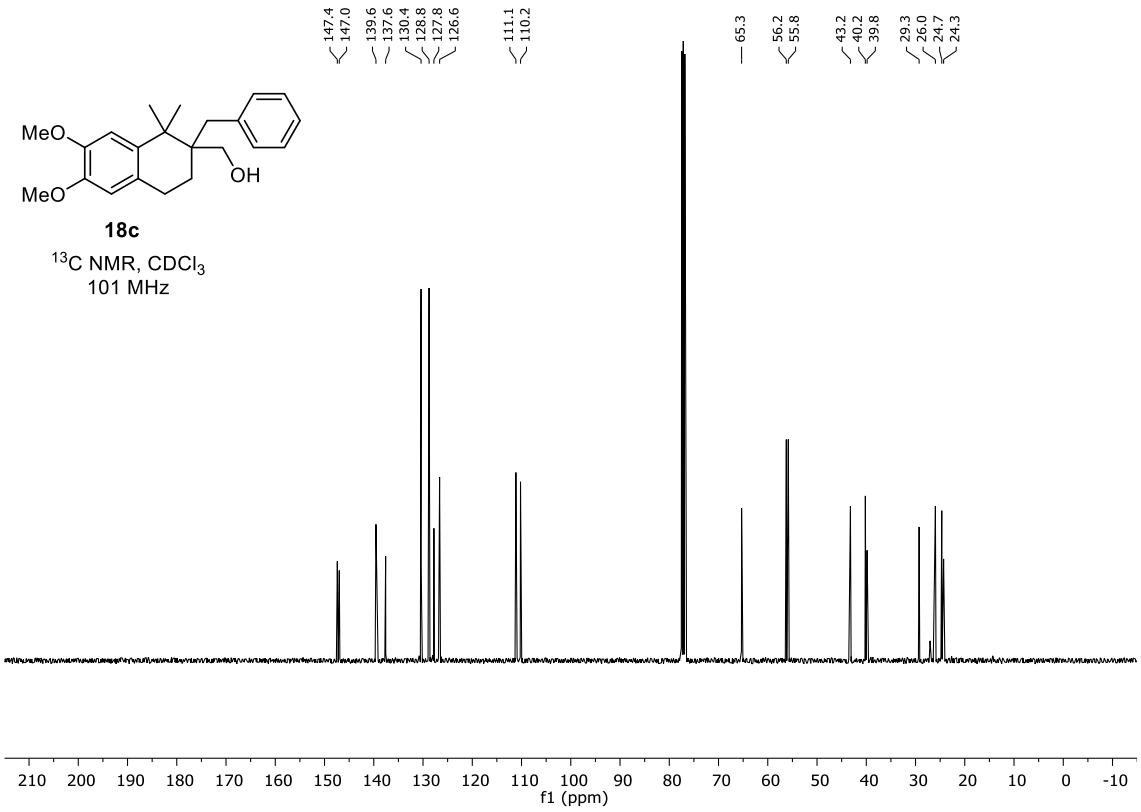

147.44
146.97
137.86
127.37
111.29
110.02
81.78
77.37 CDCl3
77.16 CDCl3
76.95 CDCl3
72.98
69.99
69.78
69.56
65.03
56.21
55.85
44.24
42.70
38.87
36.53
30.52
26.41
26.19
25.52
25.40
25.30
23.17
23.07
20.32
18.09
Me
CF3
O
MeO
O
CF3
MeO
S160
13C NMR, CDCl3
151MHz
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

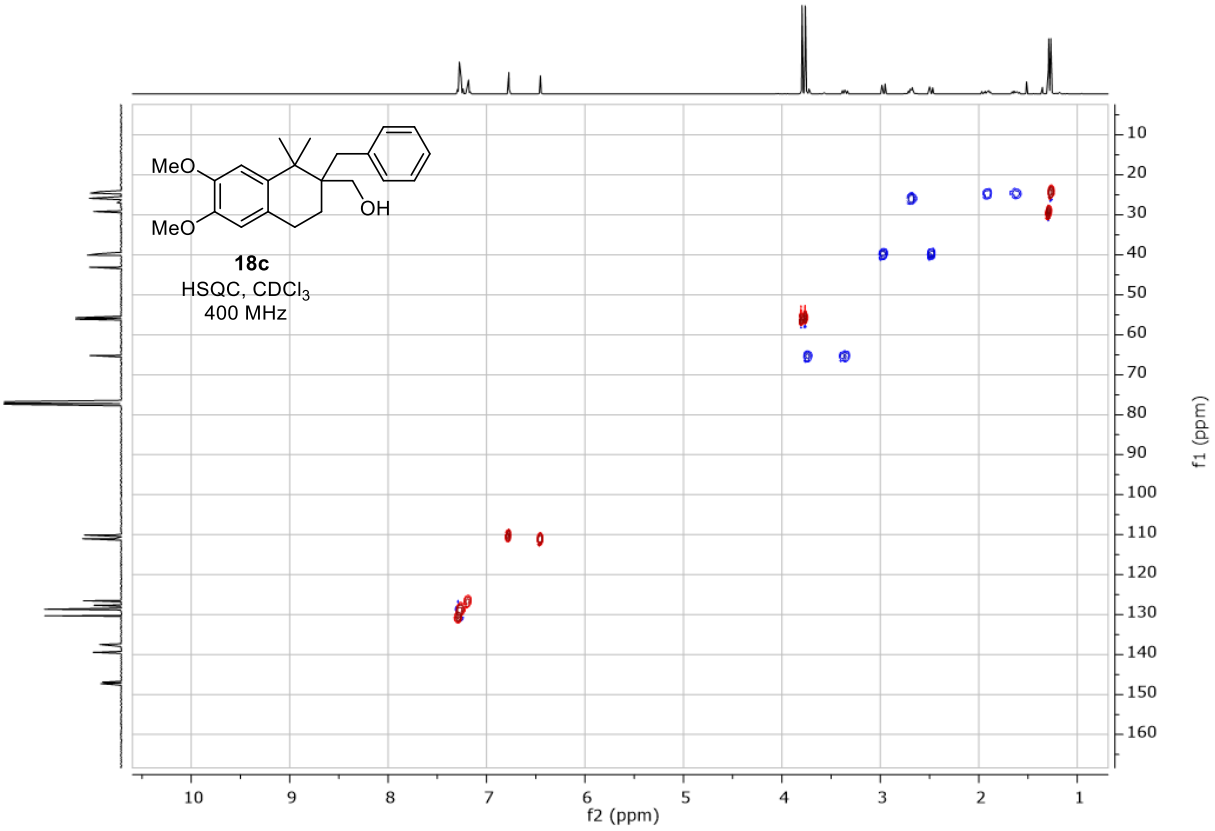


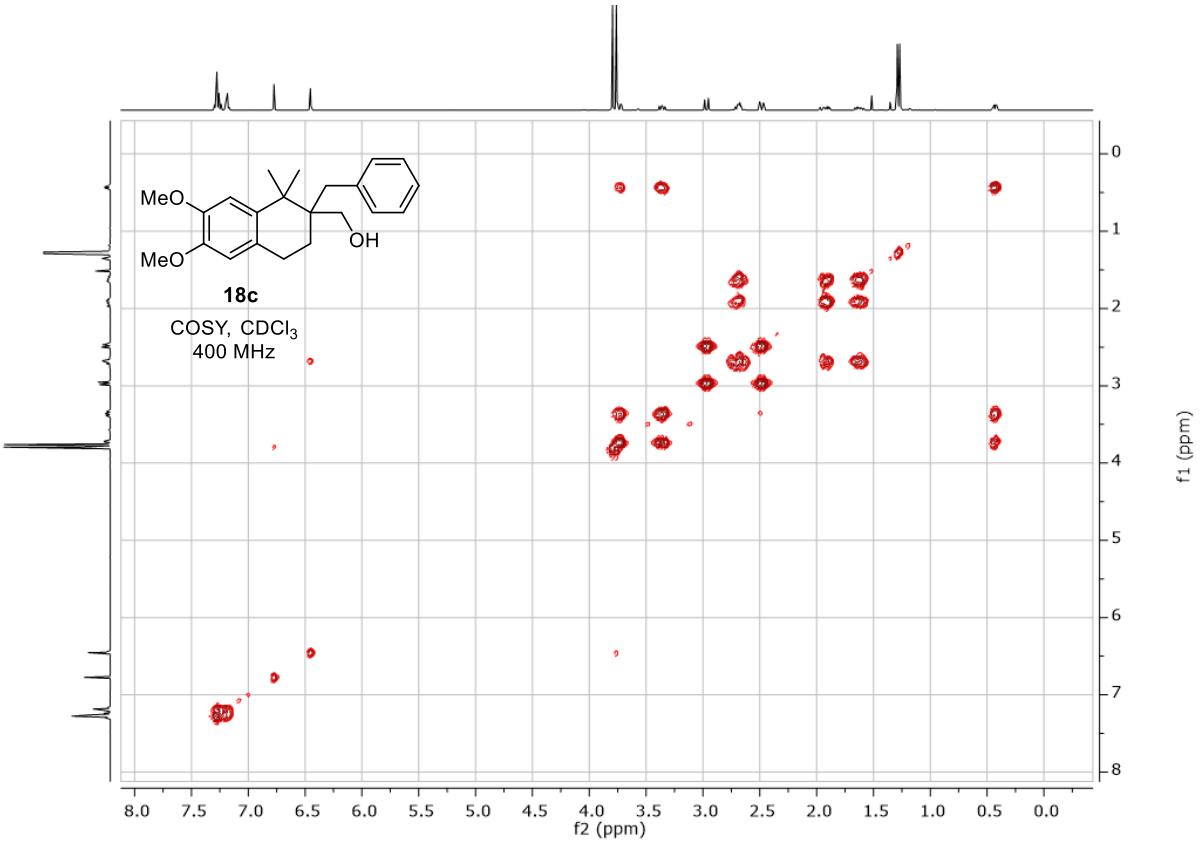
S160

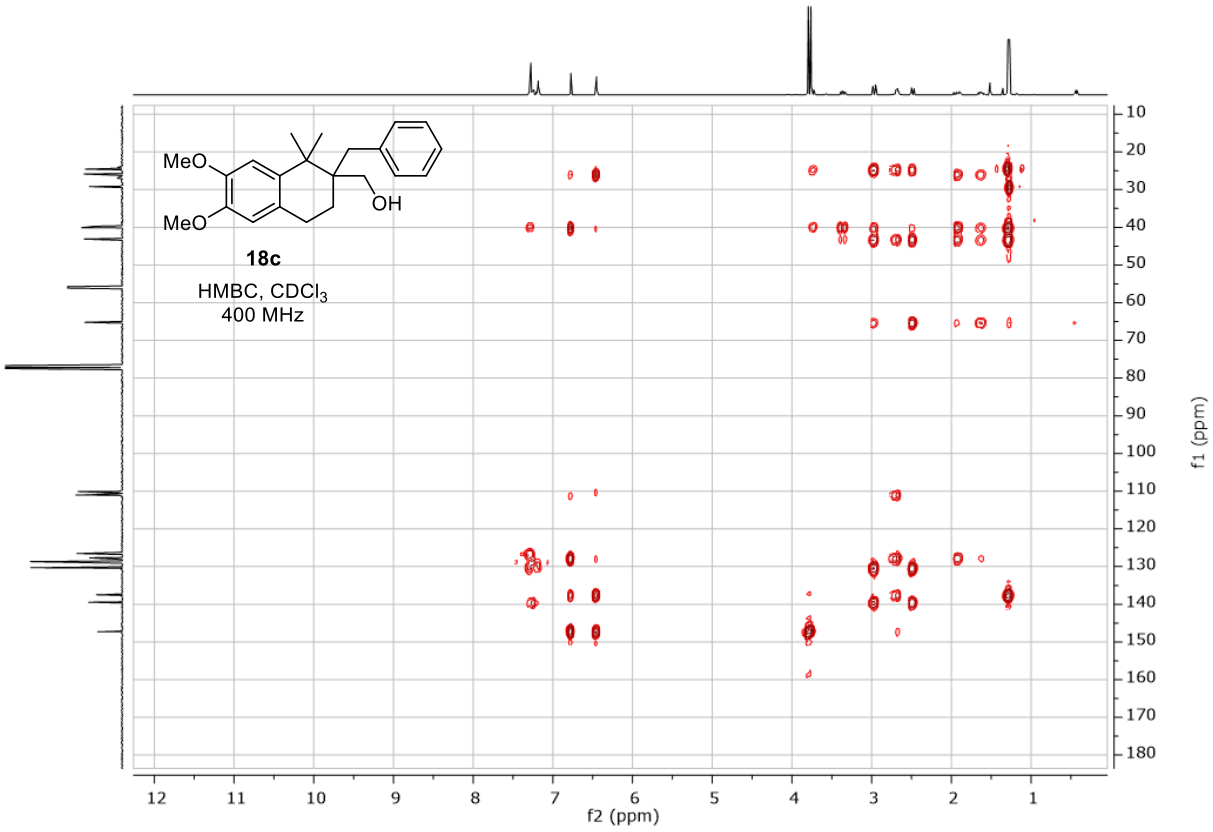
^{19}F NMR, $CDCl_3$
376 MHz

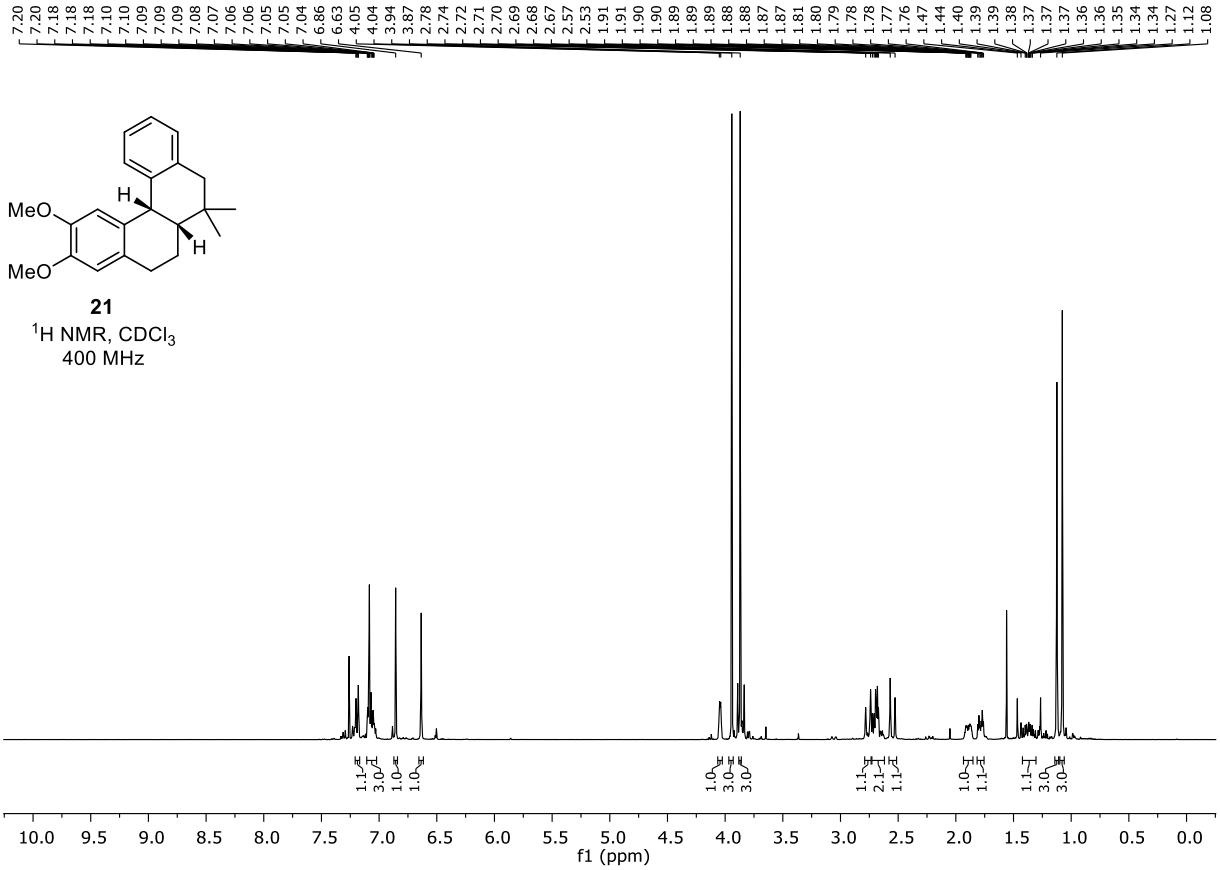

MeO
MeO
OH
18c
1H NMR, CDCl3
400 MHz
f1 (ppm)


MeO
MeO
OH
18c
13C NMR, CDCl3
101 MHz
f1 (ppm)

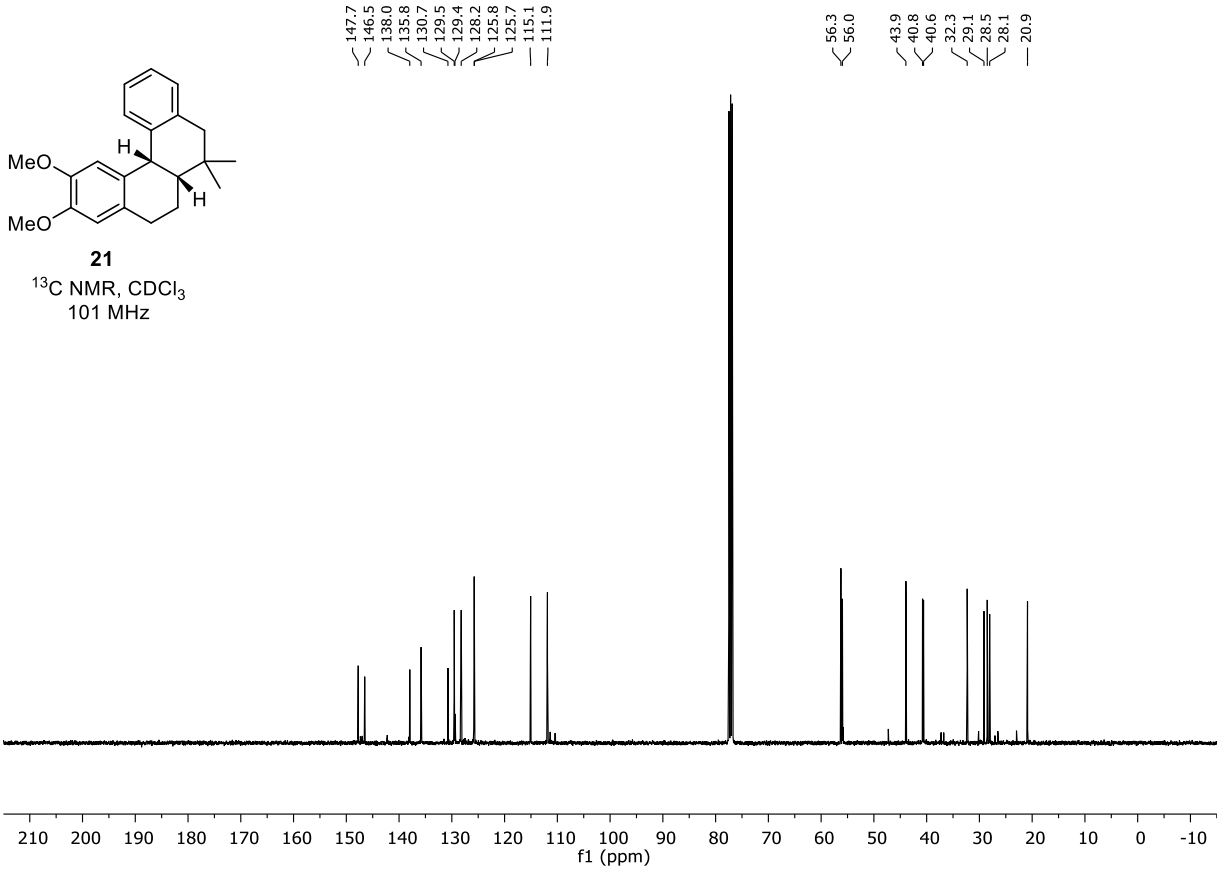

MeO
MeO
OH
18c
HSQC, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)


MeO
MeO
OH
18c
COSY, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)

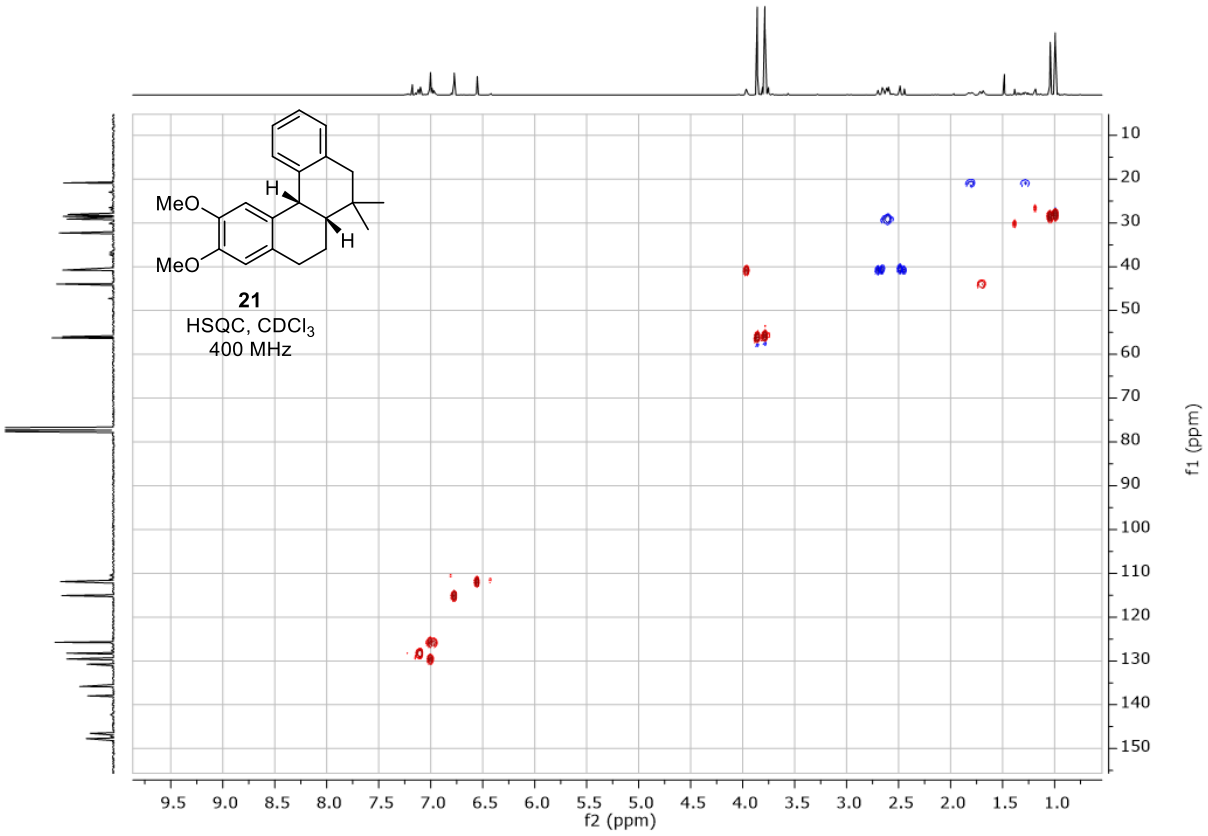

MeO
MeO
OH
18c
HMBC, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)

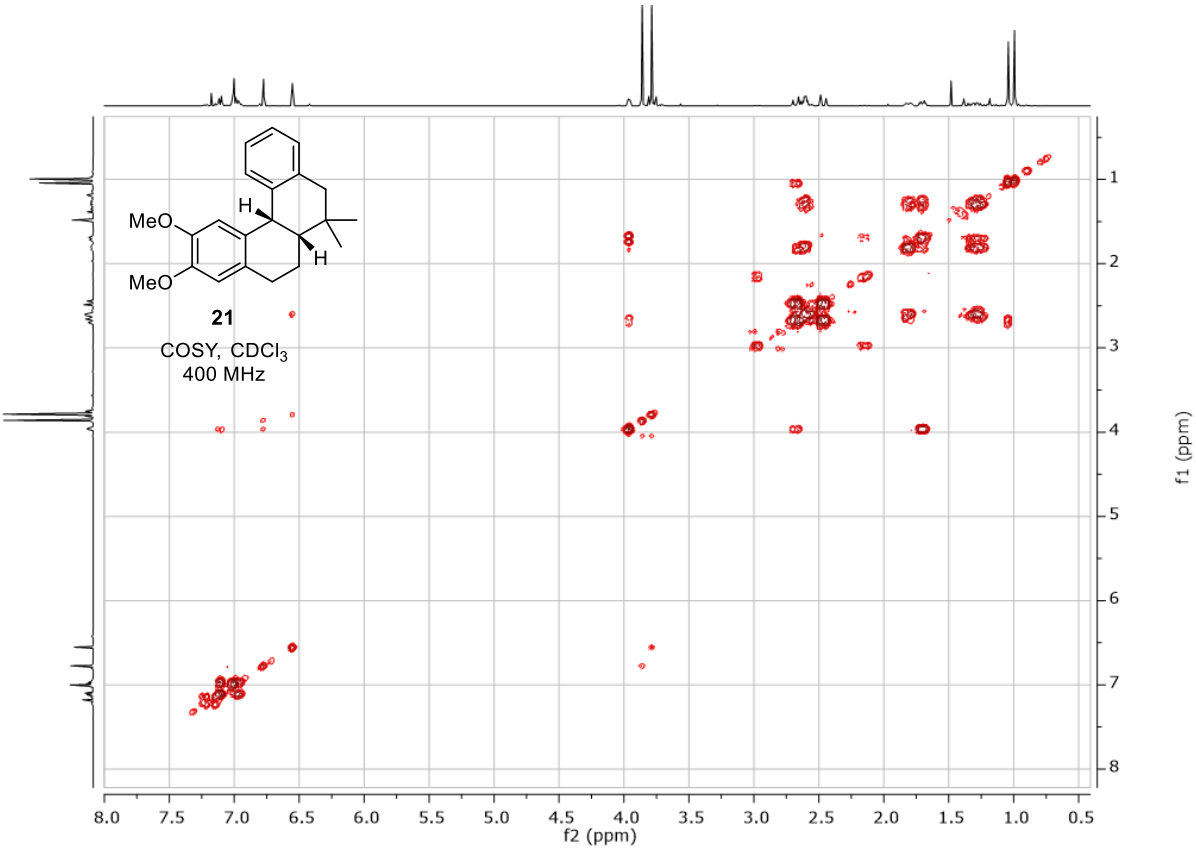


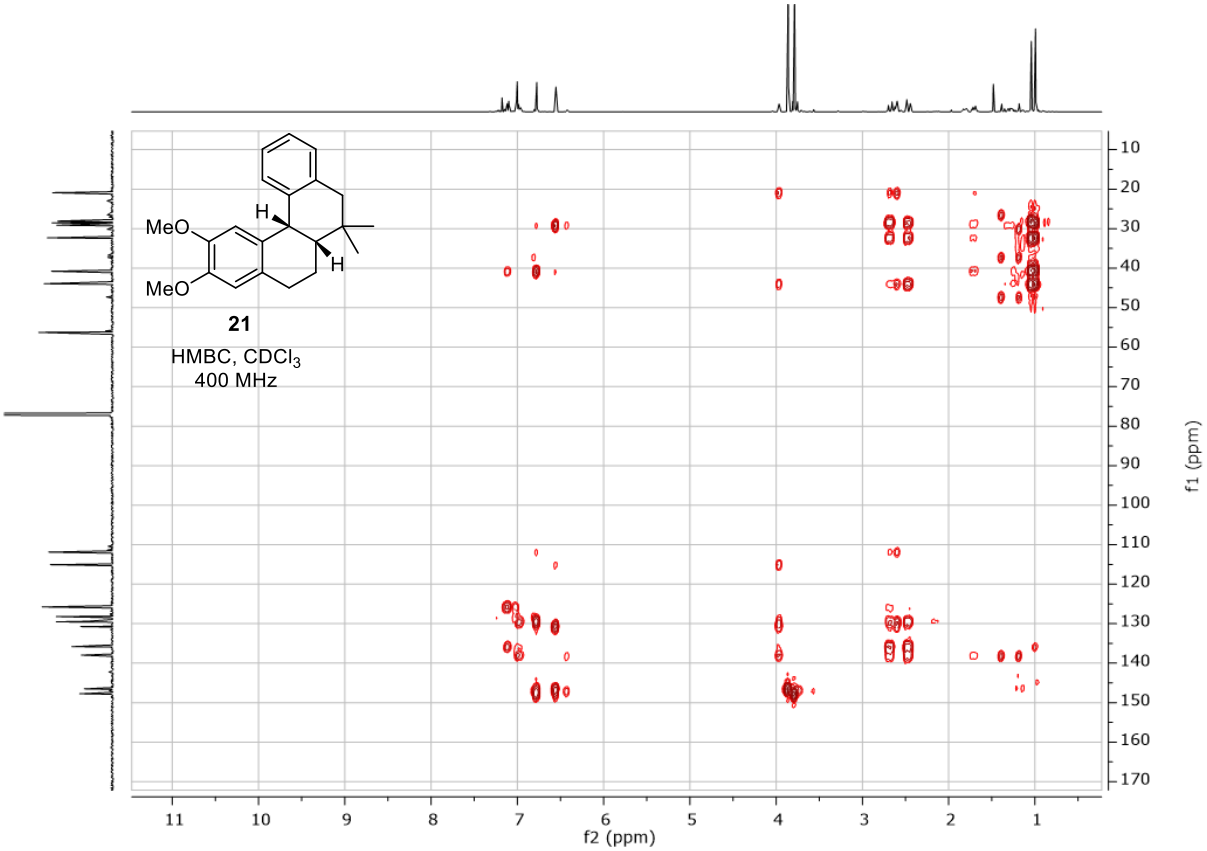
21
^{1}H NMR, $CDCl_3$
400 MHz

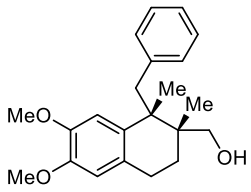


21
^{13}C NMR, $CDCl_3$
101 MHz


MeO
MeO
H
H
21
HSQC, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)

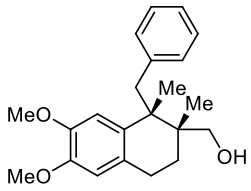

MeO
MeO
H
H
21
COSY, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)


MeO
MeO
H
H
21
HMBC, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)



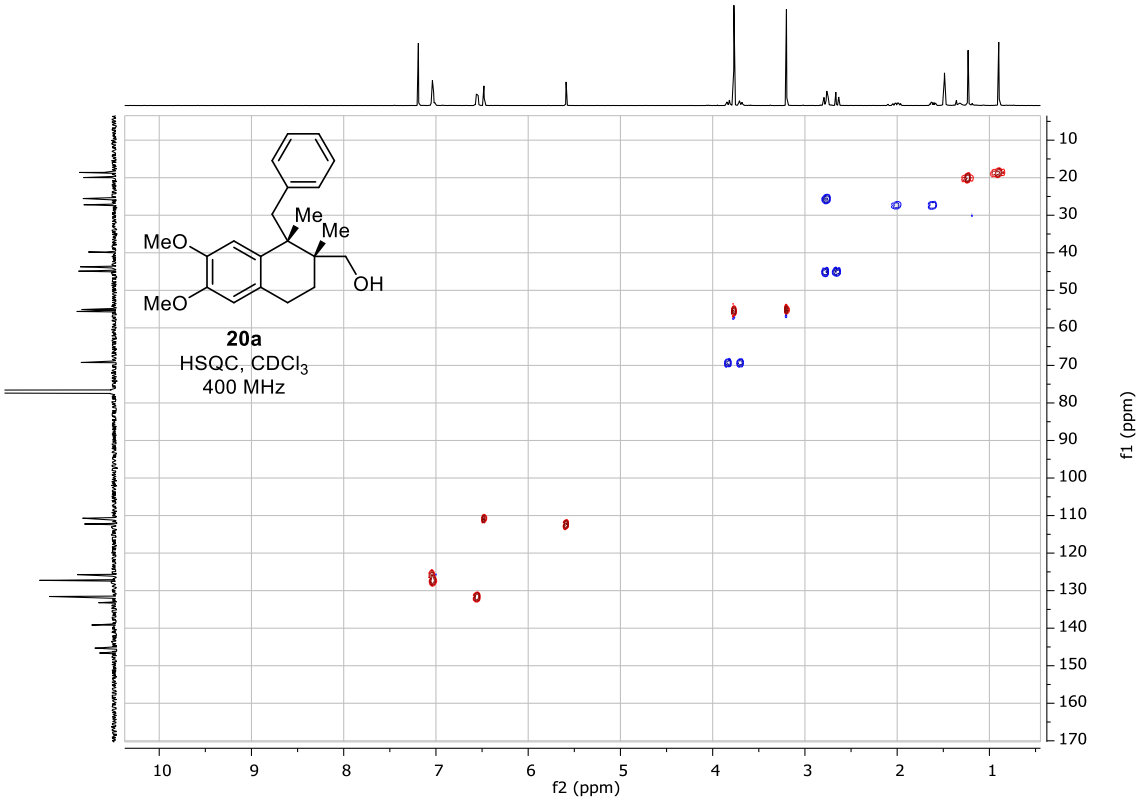
20a

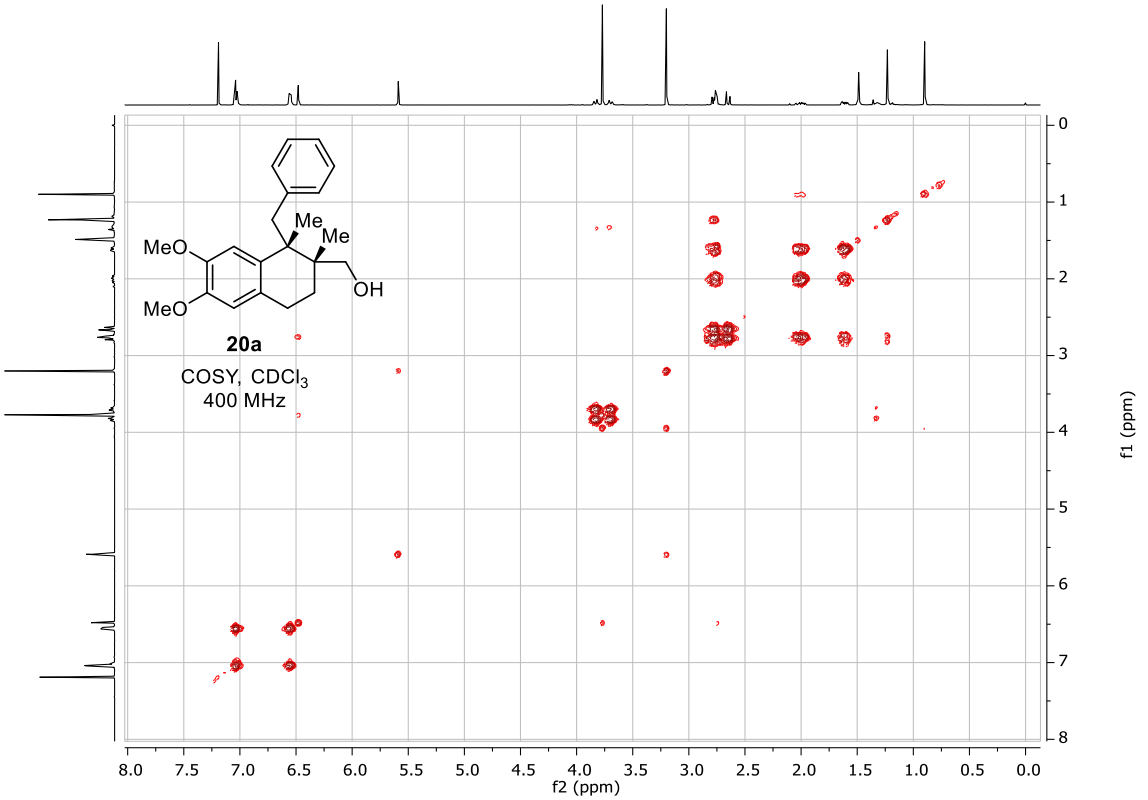
^{1}H NMR, $CDCl_3$
400 MHz

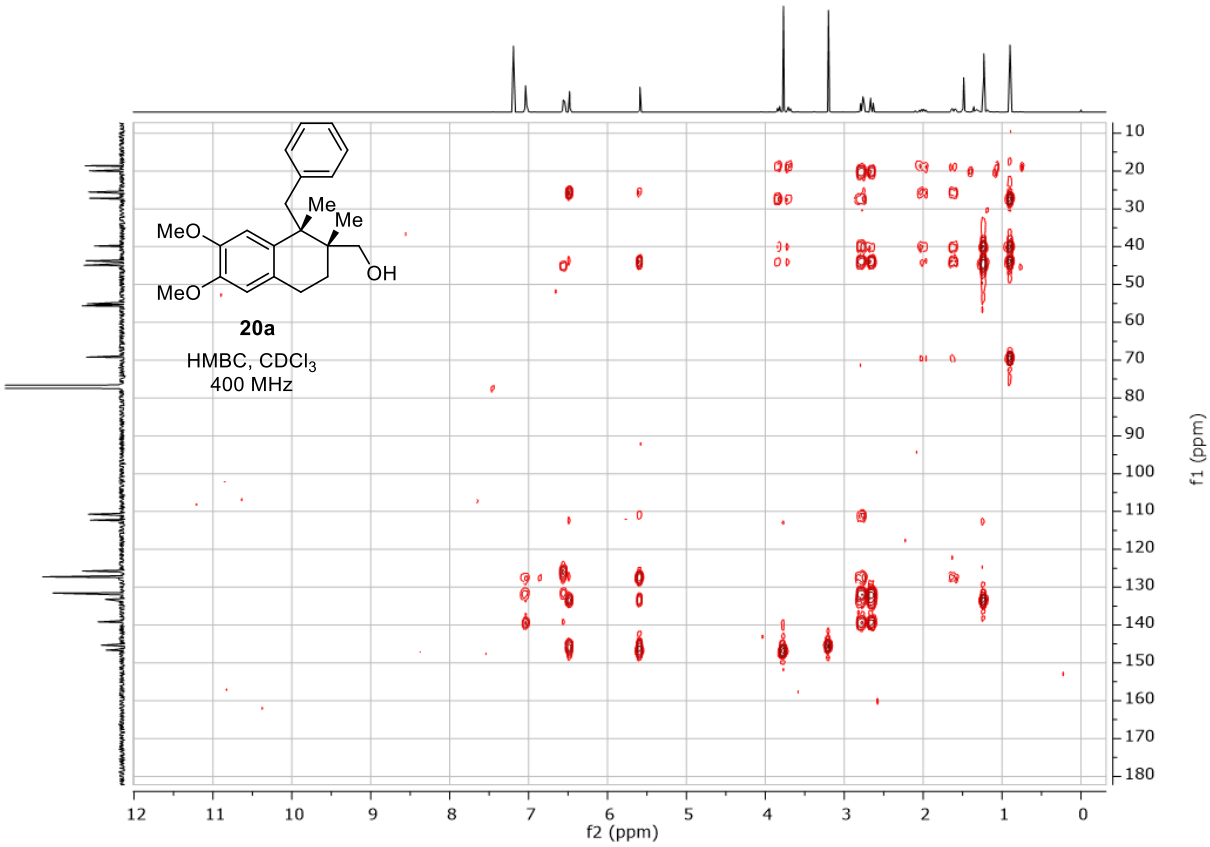


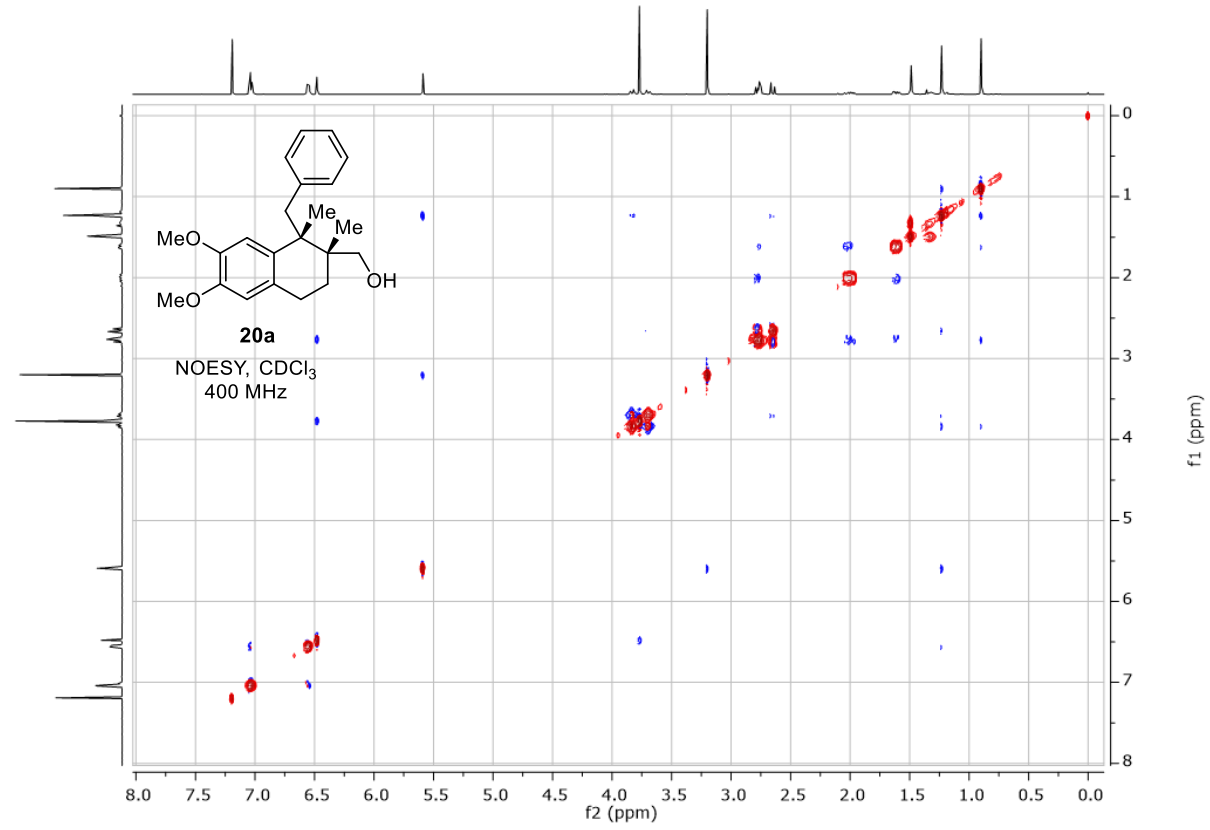
20a

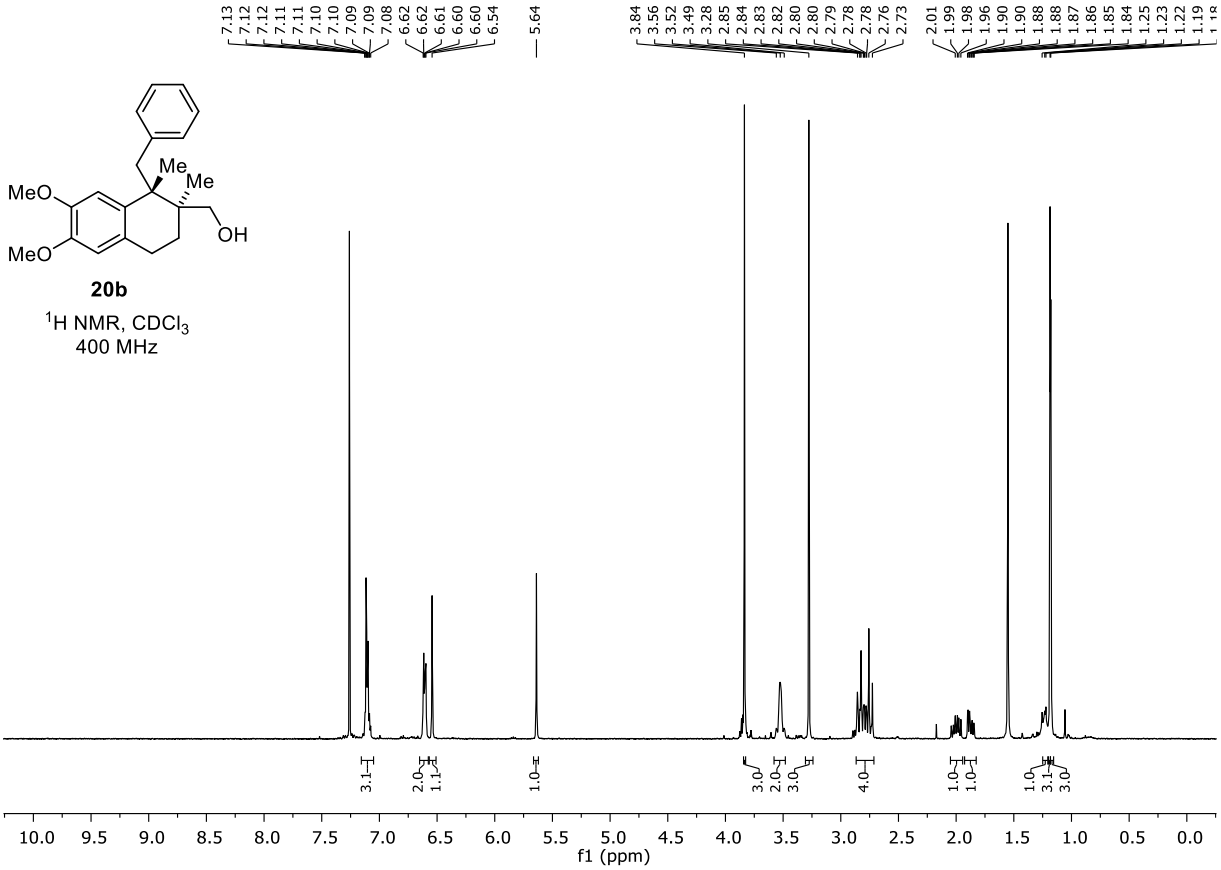
^{13}C NMR, $CDCl_3$
101 MHz

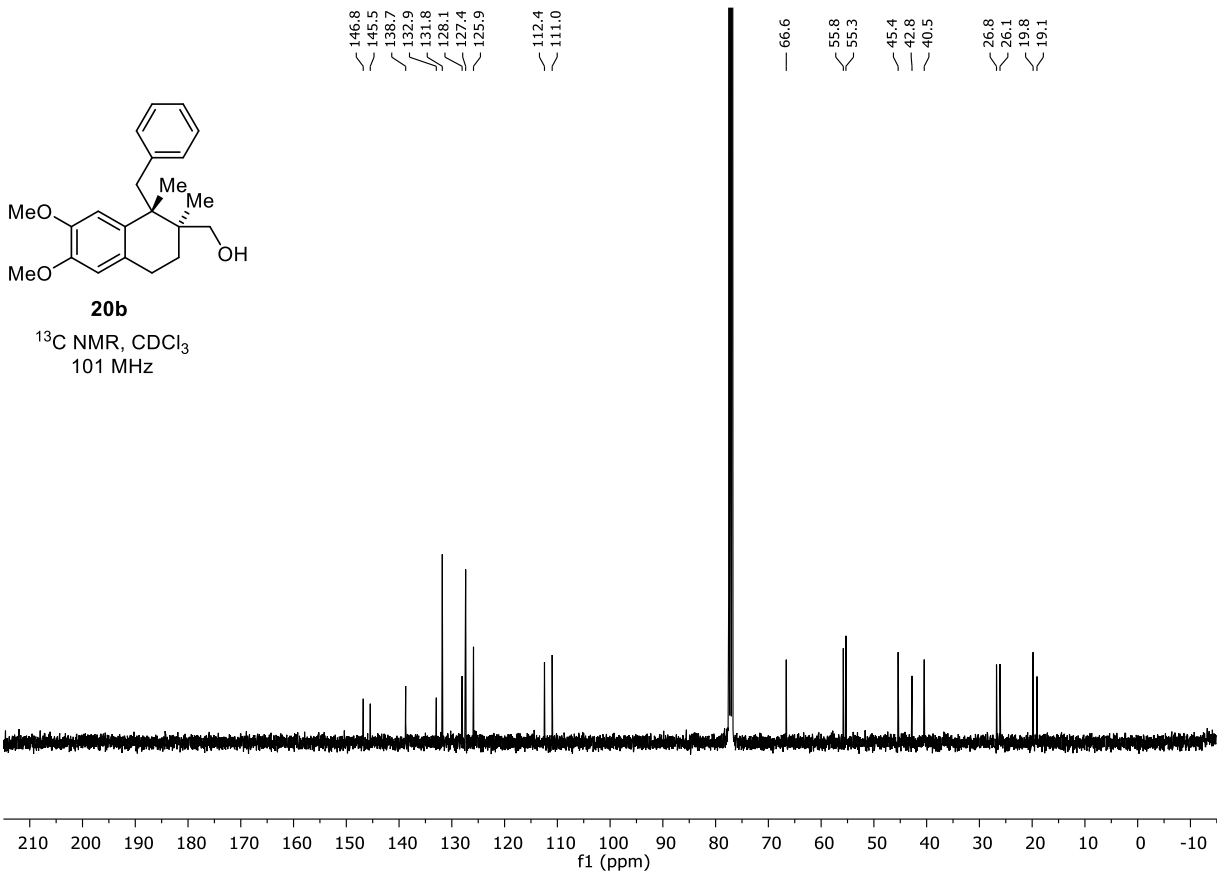

Me
Me
MeO
MeO
OH
20a
HSQC, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)

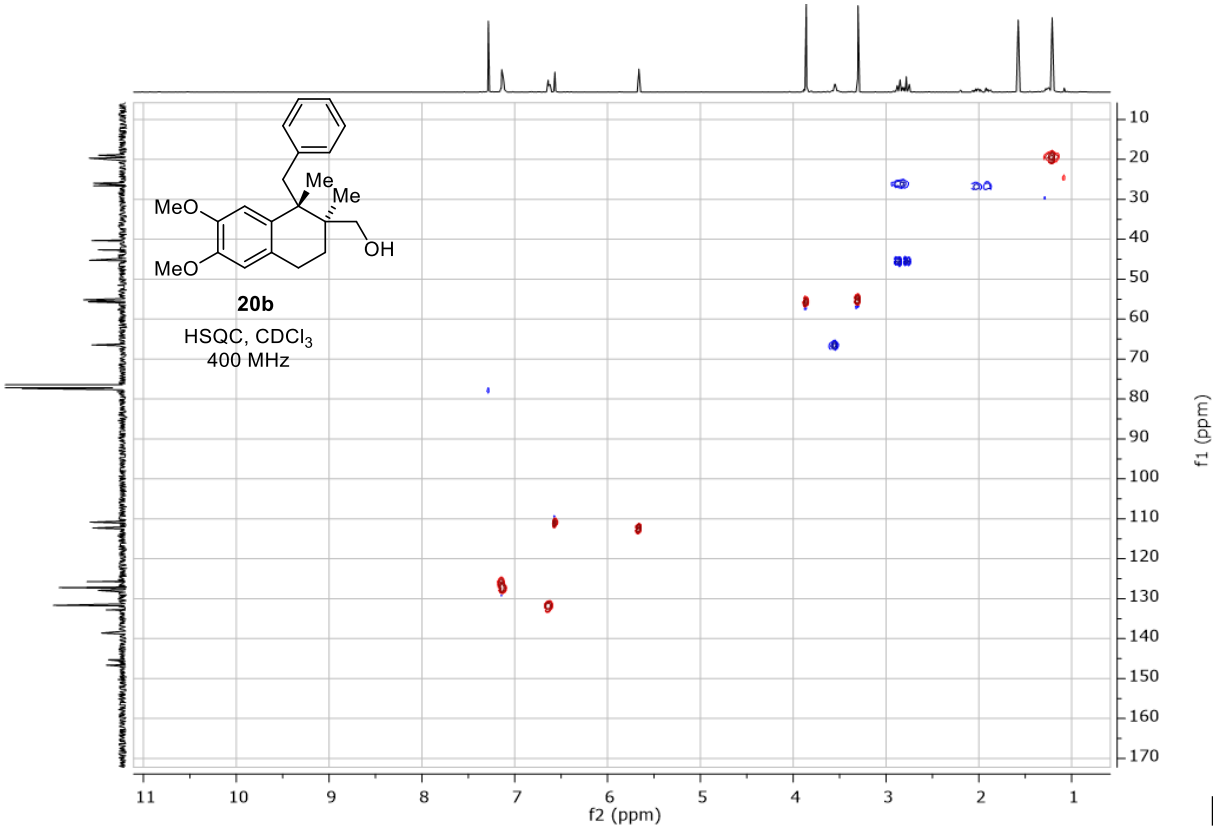

Me
Me
MeO
MeO
OH
20a
COSY, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)

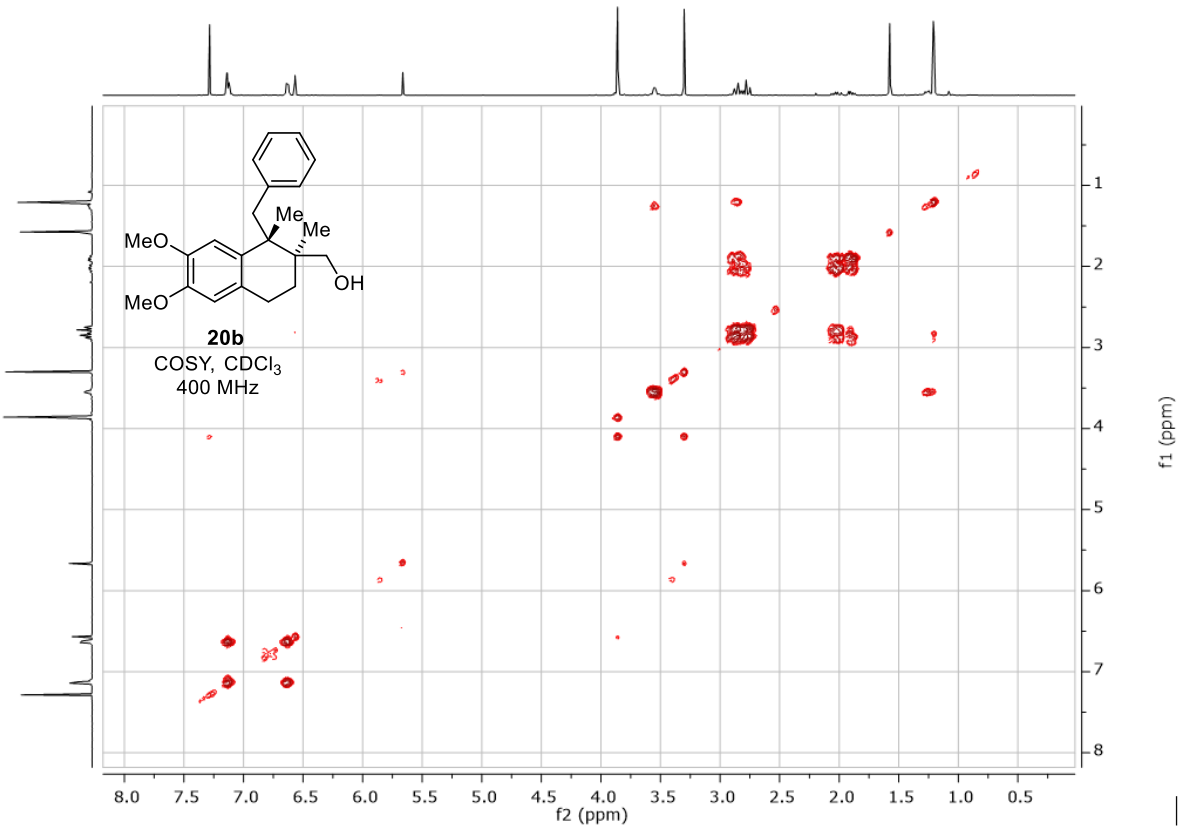

Me
Me
MeO
MeO
OH
20a
HMBC, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)

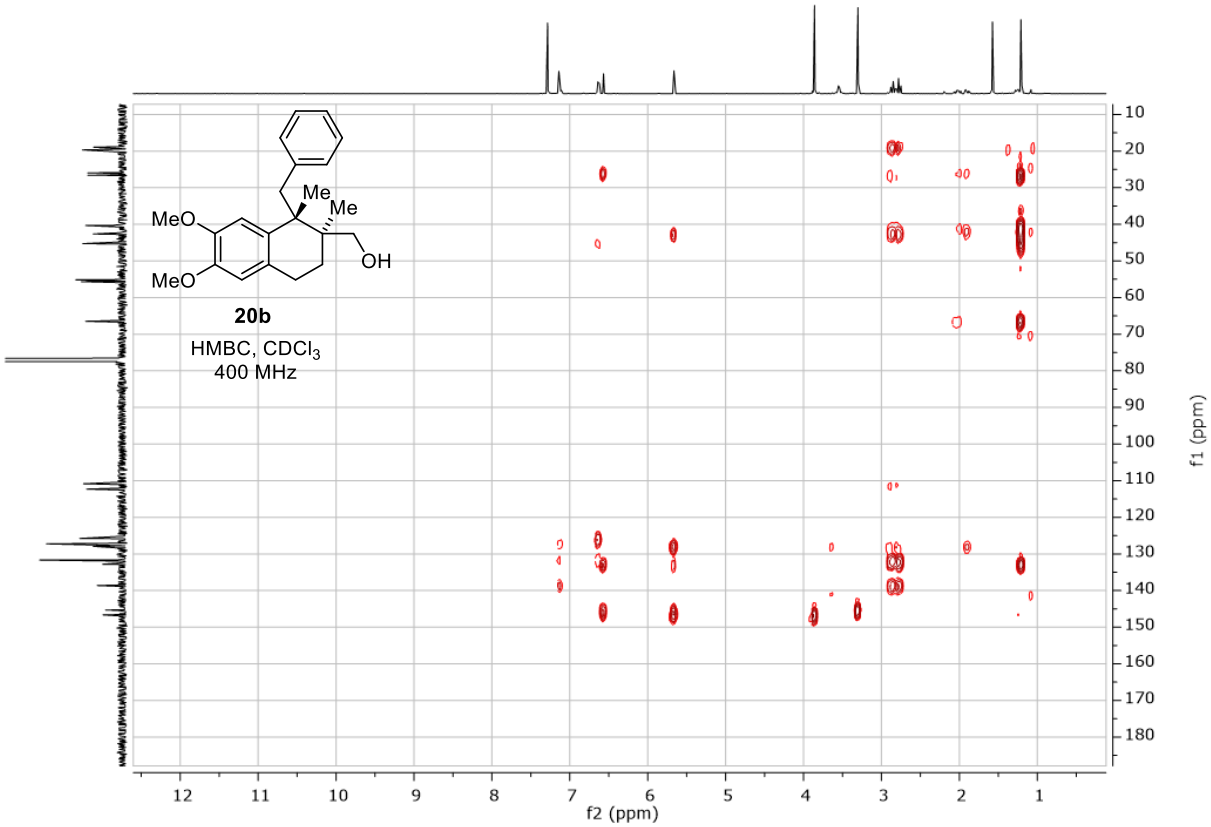

Me
Me
MeO
MeO
OH
20a
NOESY, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)

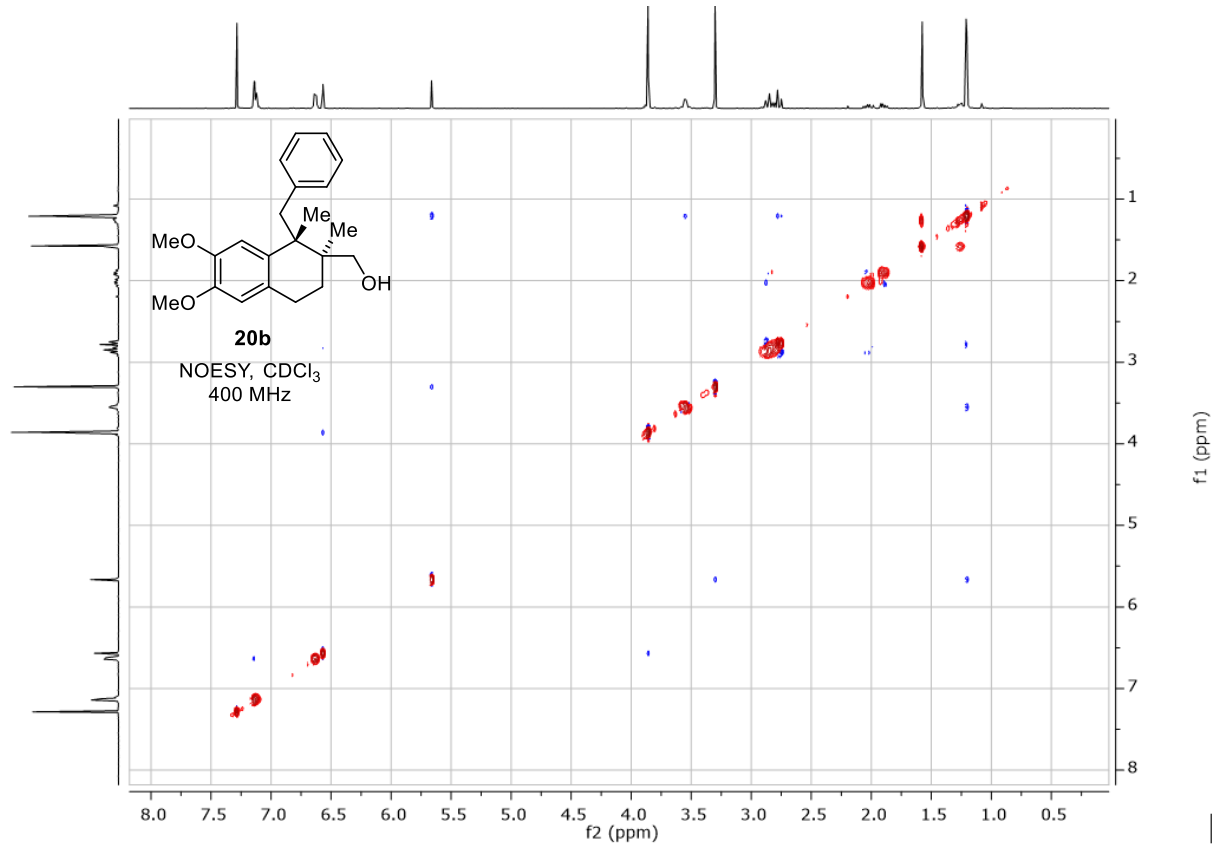

7.13
7.12
7.12
7.11
7.11
7.11
7.10
7.10
7.09
7.09
7.08
6.62
6.62
6.61
6.60
6.60
6.54
5.64
3.84
3.56
3.52
3.49
3.28
2.85
2.84
2.83
2.82
2.80
2.80
2.79
2.78
2.78
2.76
2.73
2.01
1.99
1.98
1.96
1.90
1.90
1.88
1.88
1.87
1.86
1.85
1.84
1.25
1.23
1.22
1.19
Me
Me
MeO
MeO
OH
20b
1H NMR, CDCl3
400 MHz
3.1
2.0
1.1
1.0
3.0
2.0
3.0
4.0
1.0
1.0
1.0
3.1
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)

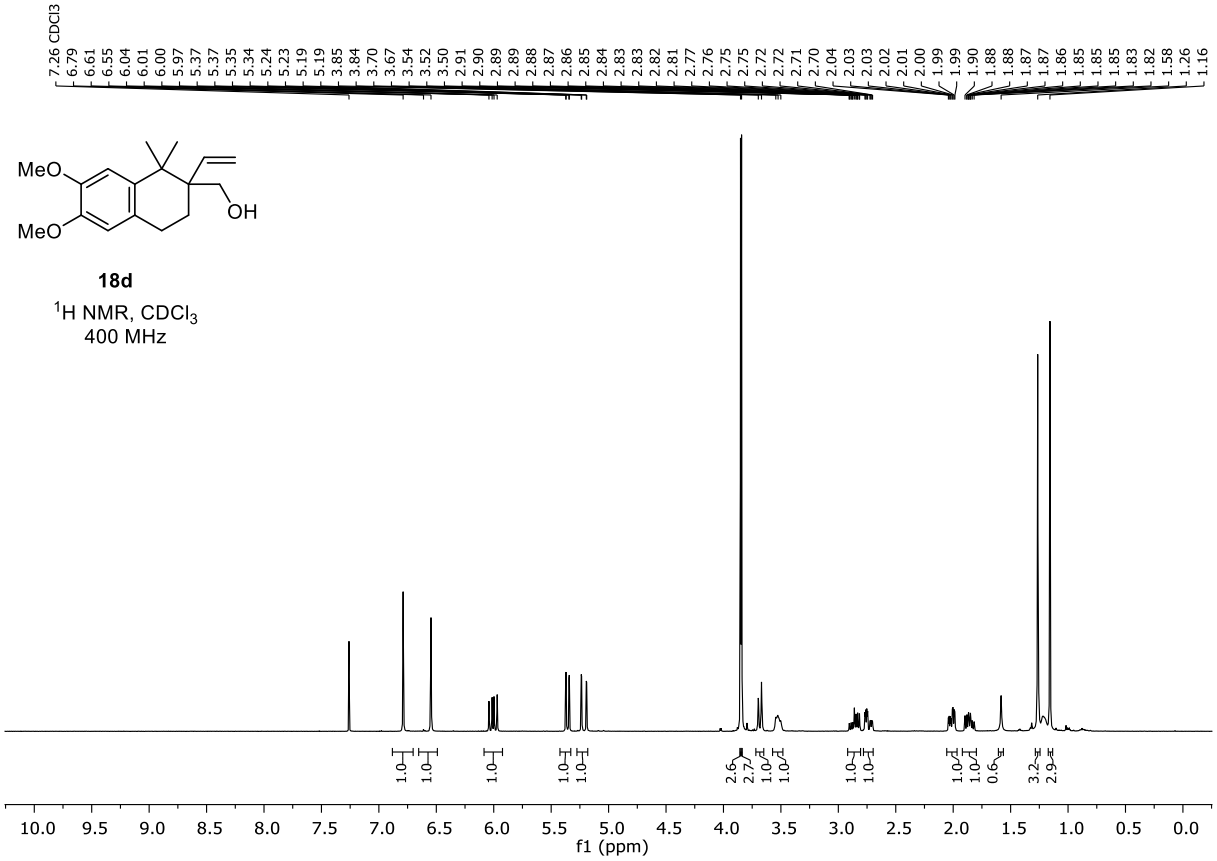

146.8
145.5
138.7
132.9
131.8
128.1
127.4
125.9
112.4
111.0
66.6
55.8
55.3
45.4
42.8
40.5
26.8
26.1
19.8
19.1
Me
Me
MeO
MeO
OH
20b
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

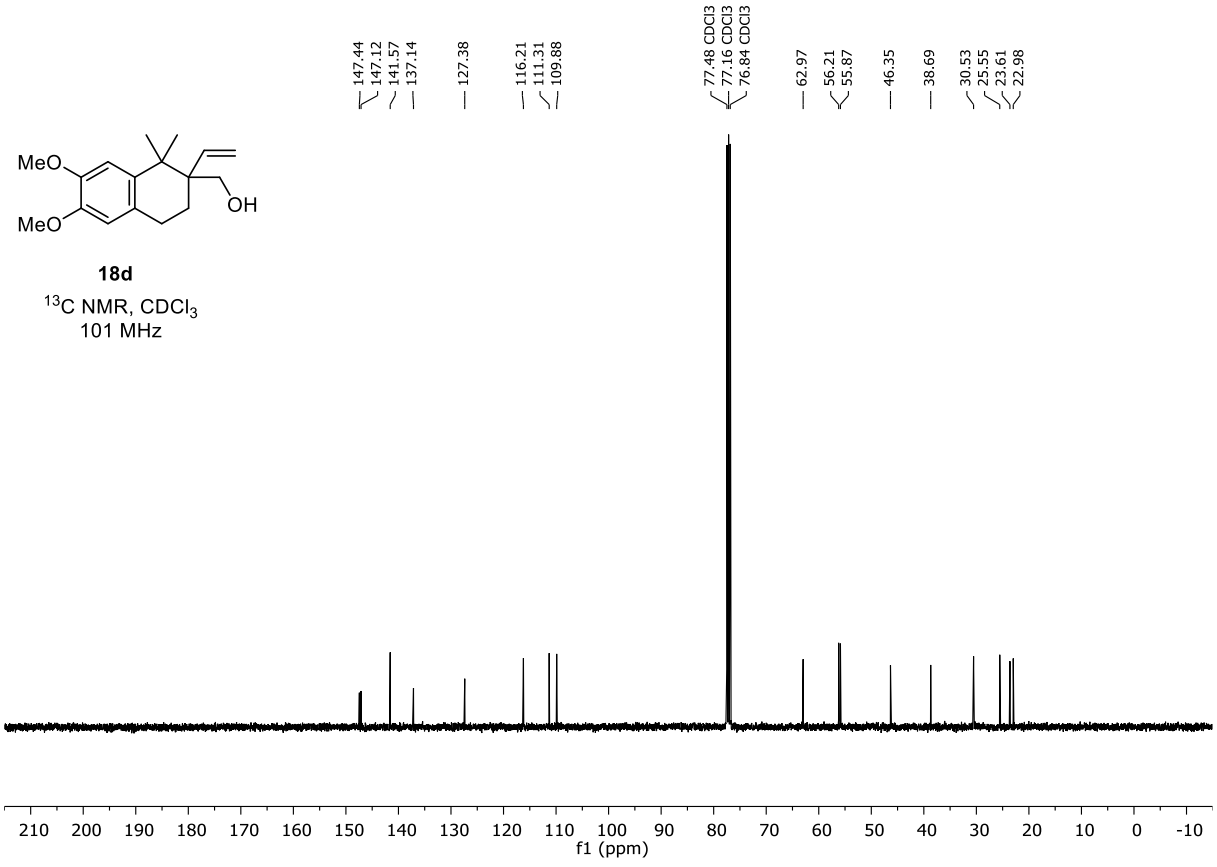

Me
Me
MeO
MeO
OH
20b
HSQC, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)

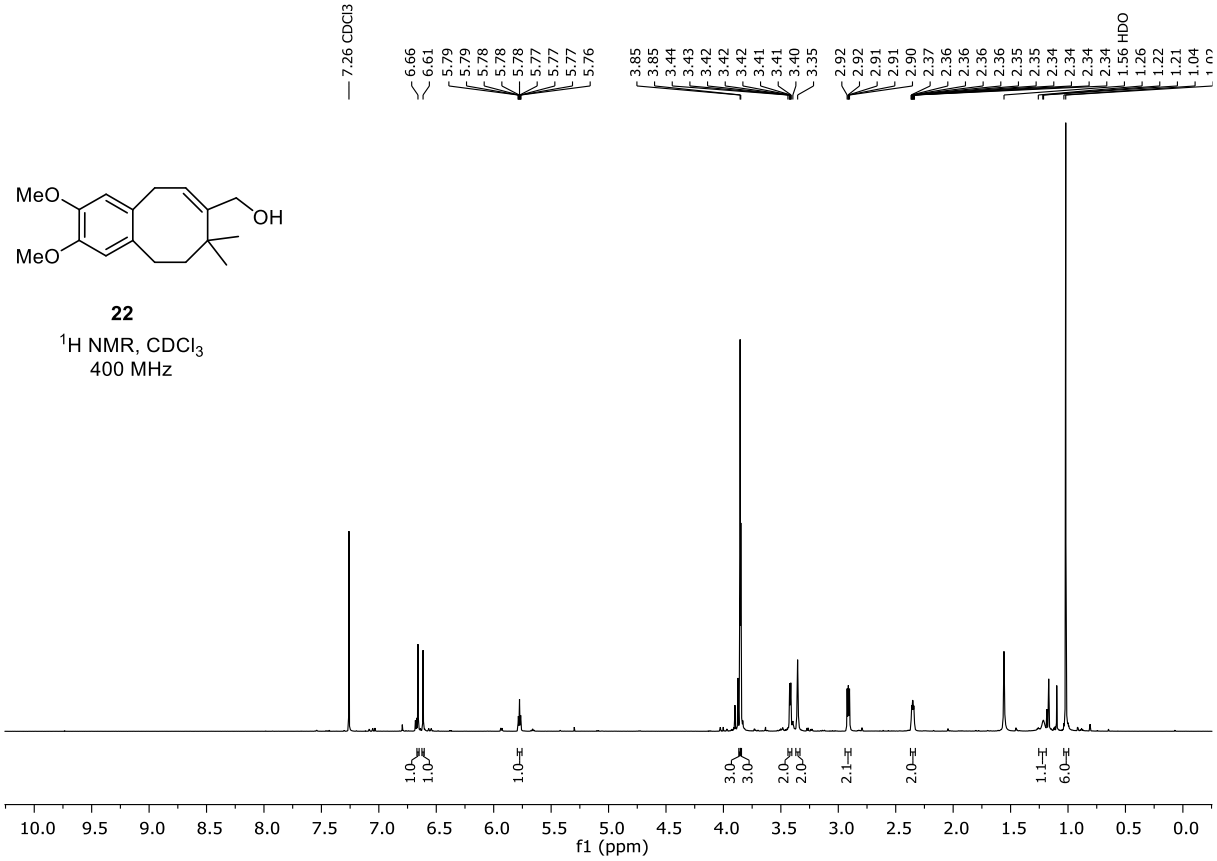

Me
Me
MeO
MeO
OH
20b
COSY, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)


Me
Me
MeO
MeO
OH
20b
HMBC, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)


Me
Me
MeO
MeO
OH
20b
NOESY, CDCl3
400 MHz
f2 (ppm)
f1 (ppm)

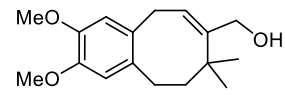

7.26 CDCl3
6.79
6.61
6.55
6.04
6.01
6.00
5.97
5.37
5.37
5.35
5.34
5.24
5.23
5.19
5.19
3.85
3.84
3.70
3.67
3.54
3.52
3.50
2.91
2.90
2.89
2.89
2.88
2.87
2.86
2.85
2.84
2.83
2.83
2.82
2.81
2.77
2.76
2.75
2.75
2.72
2.72
2.71
2.70
2.04
2.03
2.03
2.02
2.01
2.00
1.99
1.99
1.90
1.88
1.88
1.87
1.87
1.86
1.85
1.85
1.85
1.83
1.82
1.58
1.26
1.16
MeO
MeO
OH
18d
1H NMR, CDCl3
400 MHz
1.0
1.0
1.0
1.0
1.0
2.6
2.7
1.0
1.0
1.0
1.0
1.0
1.0
0.6
3.2
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)


147.44
147.12
141.57
137.14
127.38
116.21
111.31
109.88
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.97
56.21
55.87
46.35
38.69
30.53
25.55
23.61
22.98
MeO
MeO
OH
18d
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)



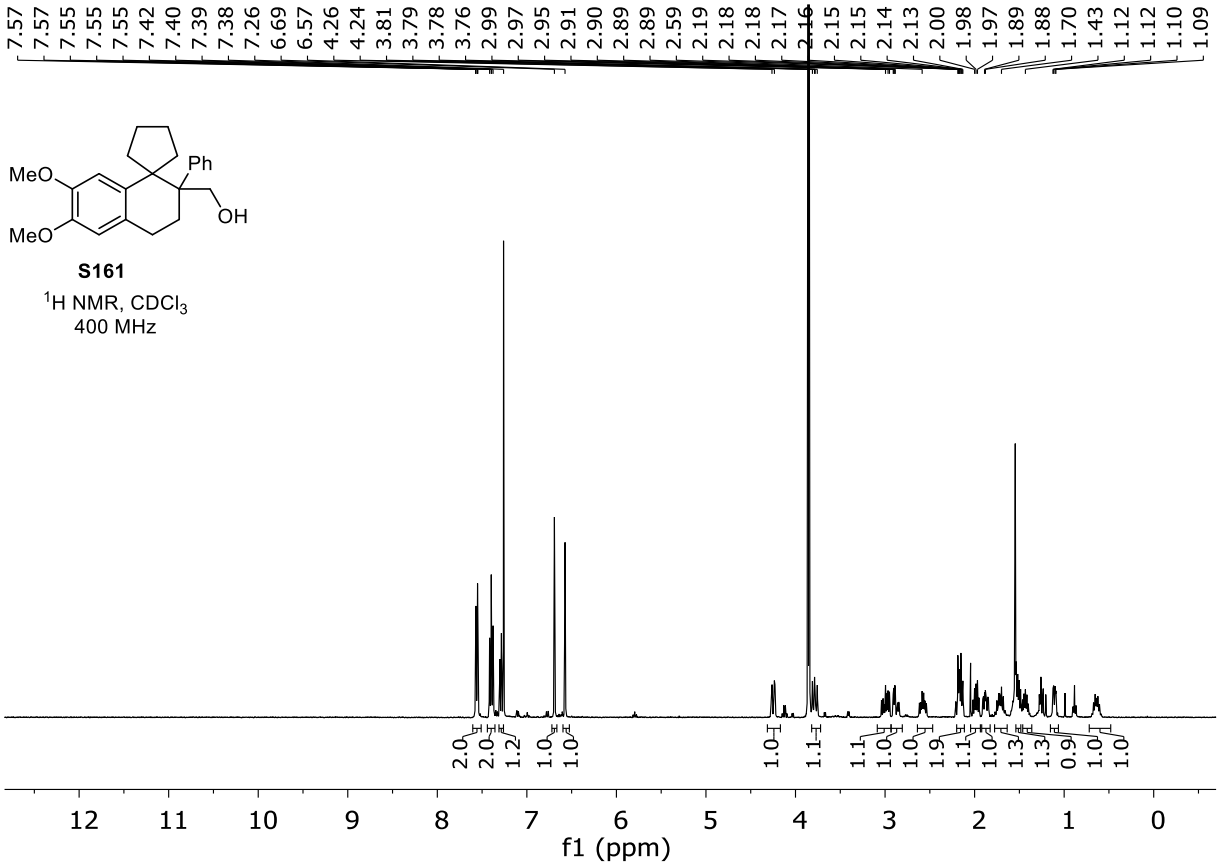
22

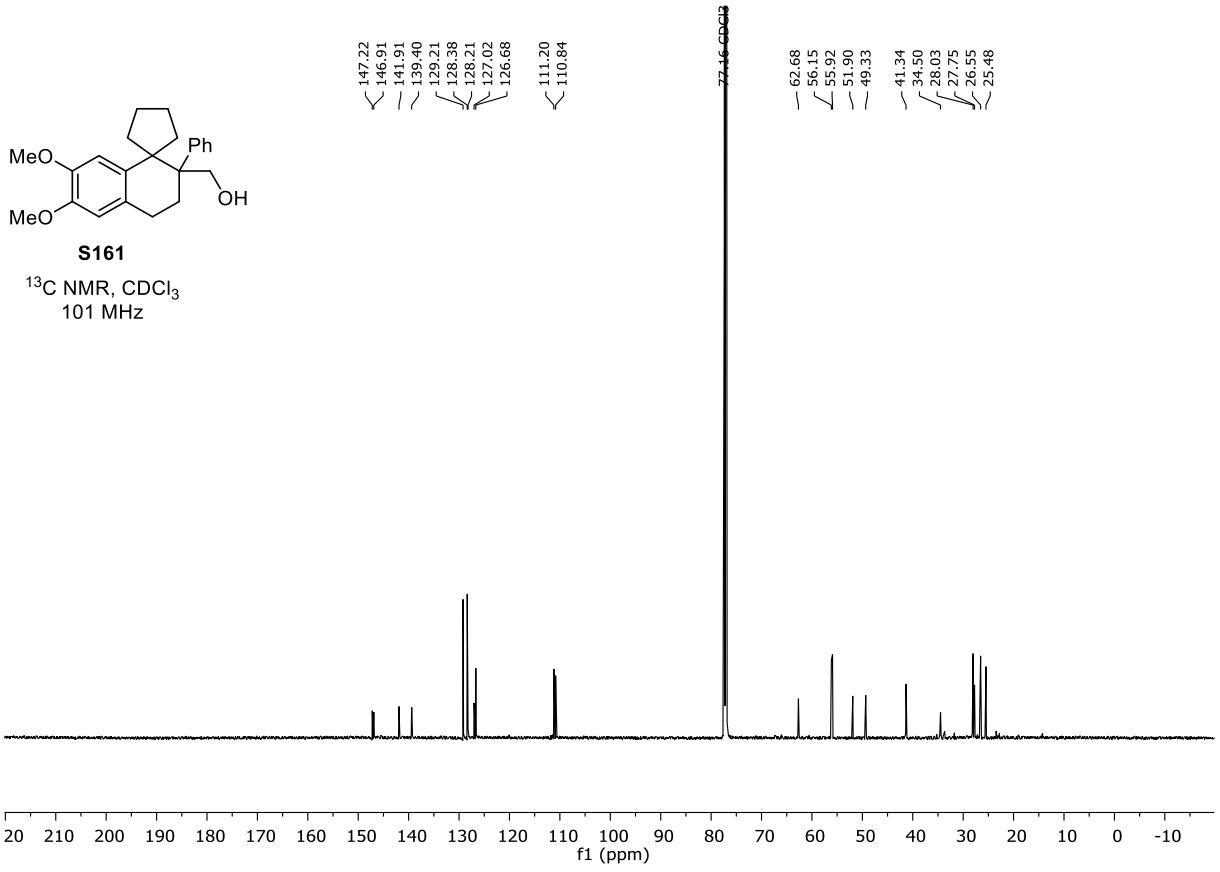
^{1}H NMR, $CDCl_3$
400 MHz

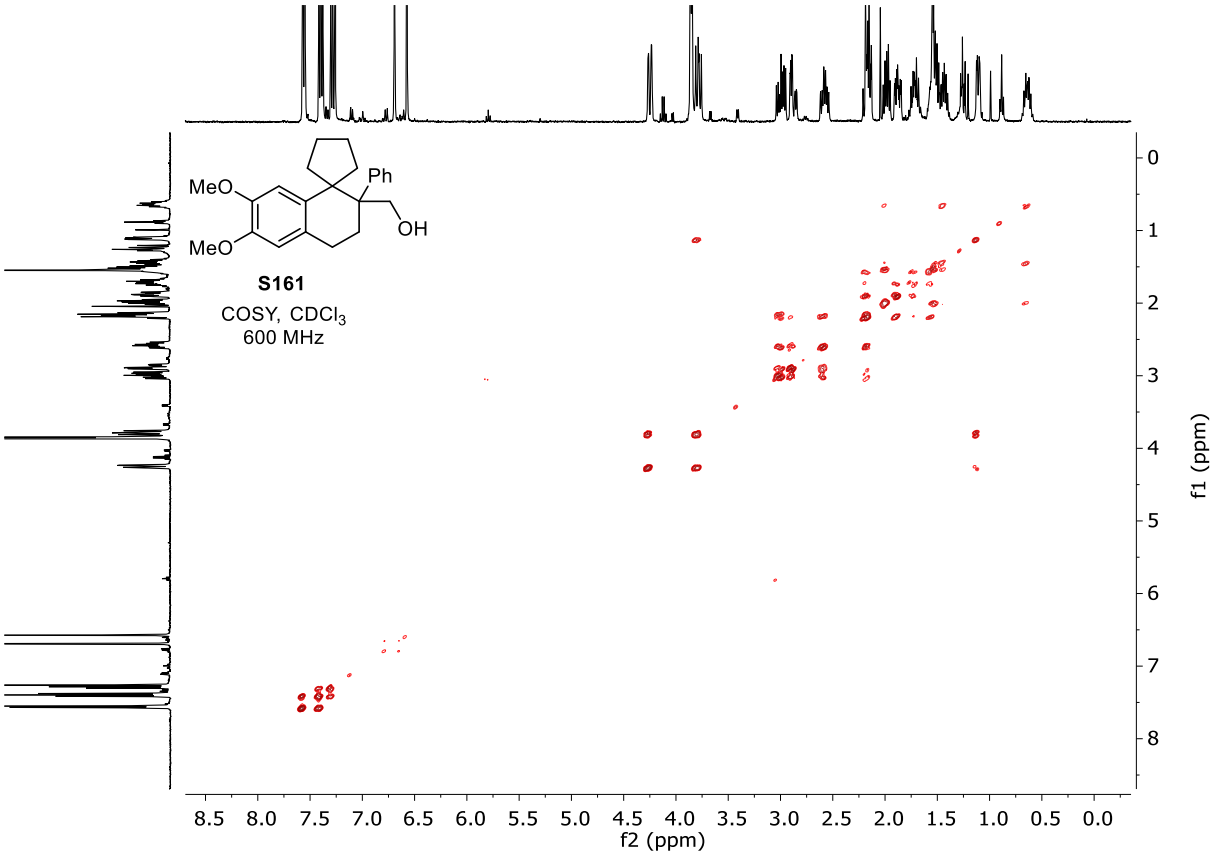


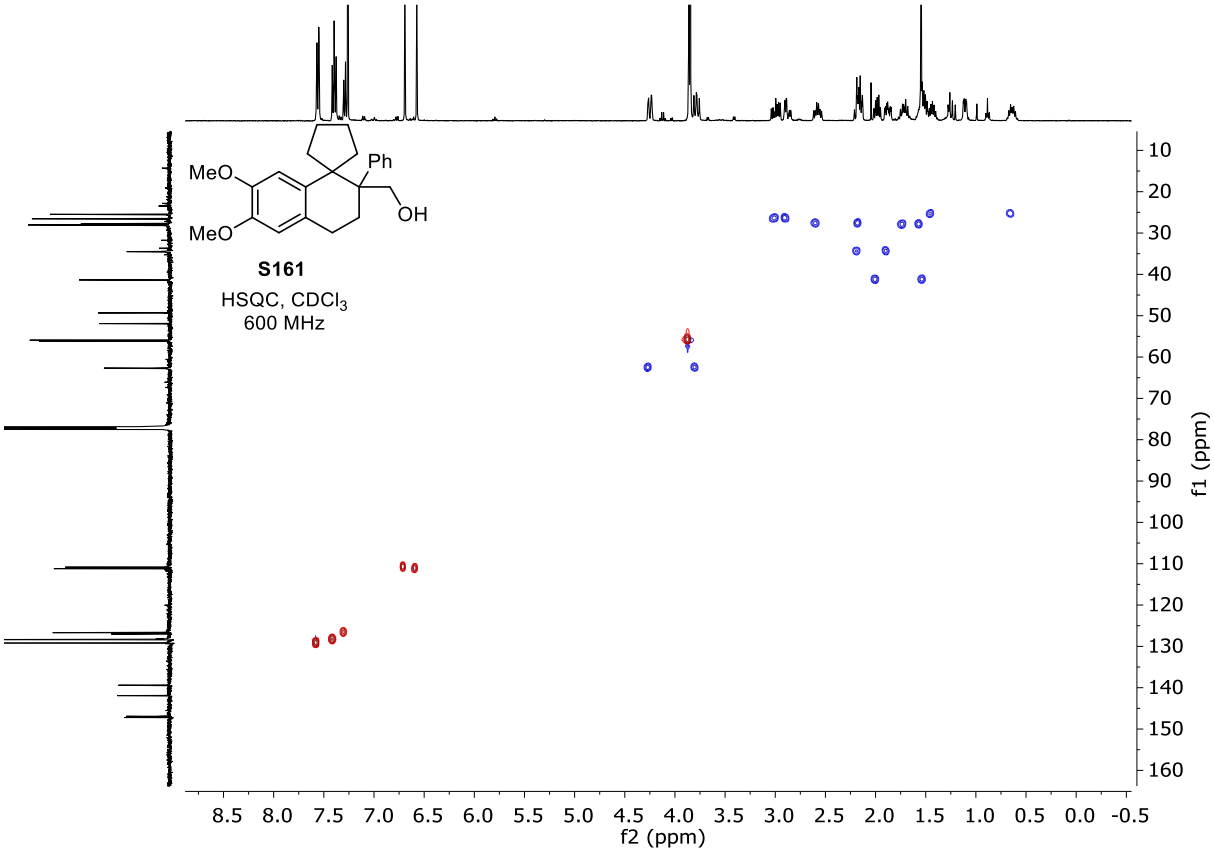
22

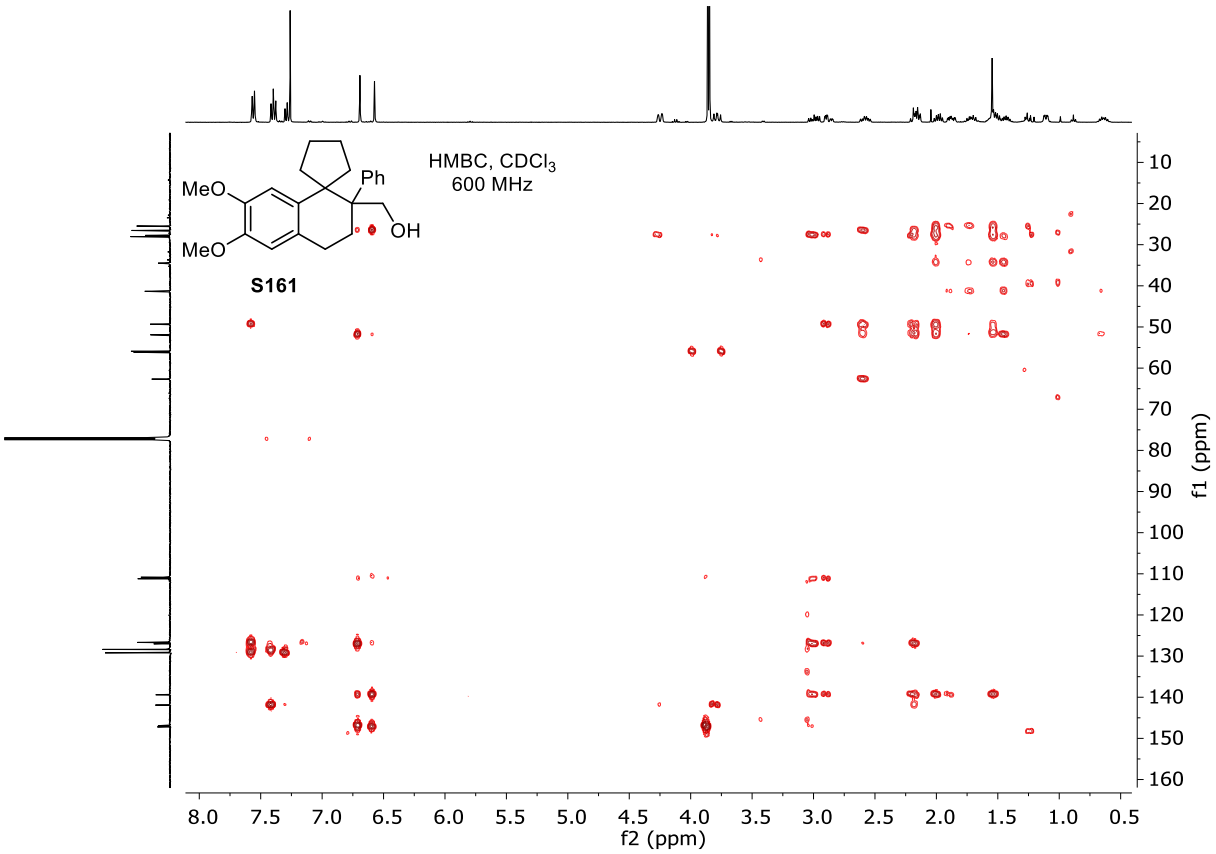
^{13}C NMR, $CDCl_3$
101 MHz

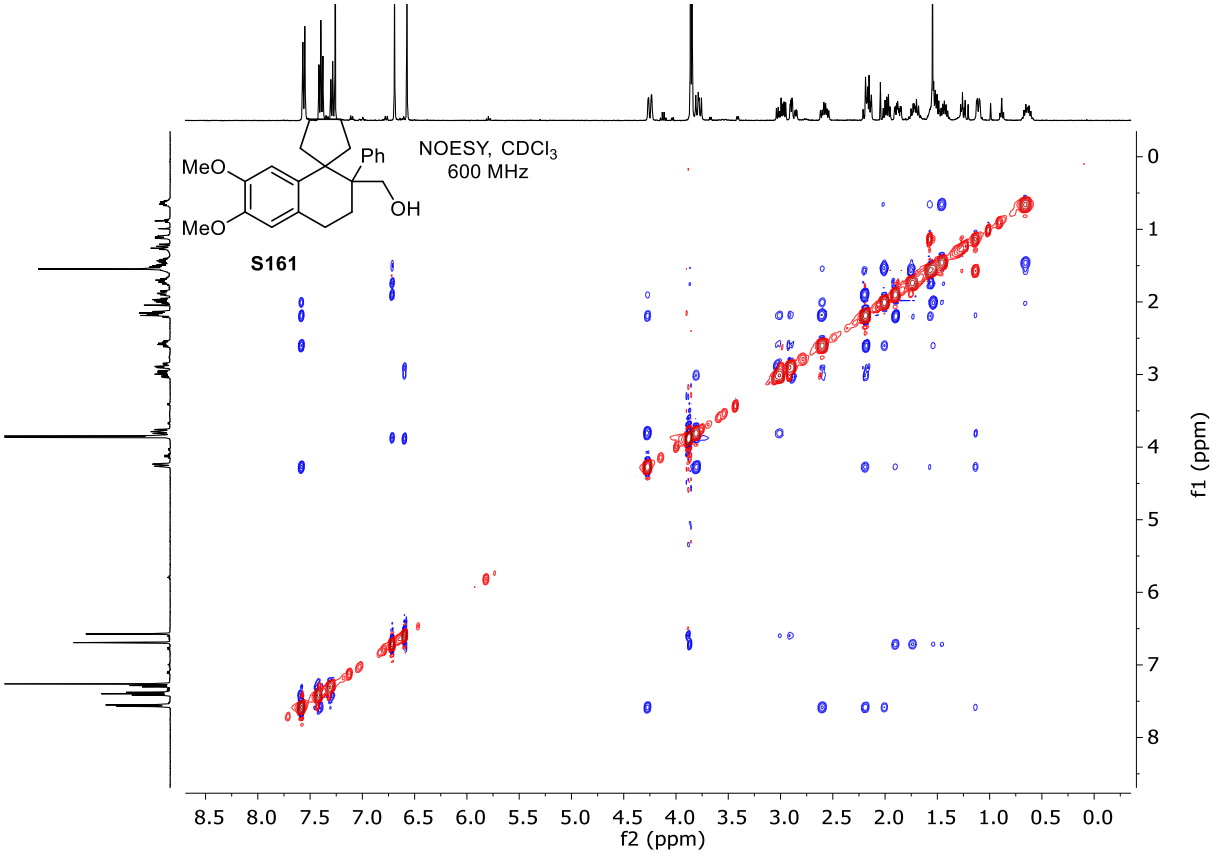

MeO
MeO
Ph
OH
S161
^{1}H NMR, $CDCl_3$
400 MHz
f1 (ppm)

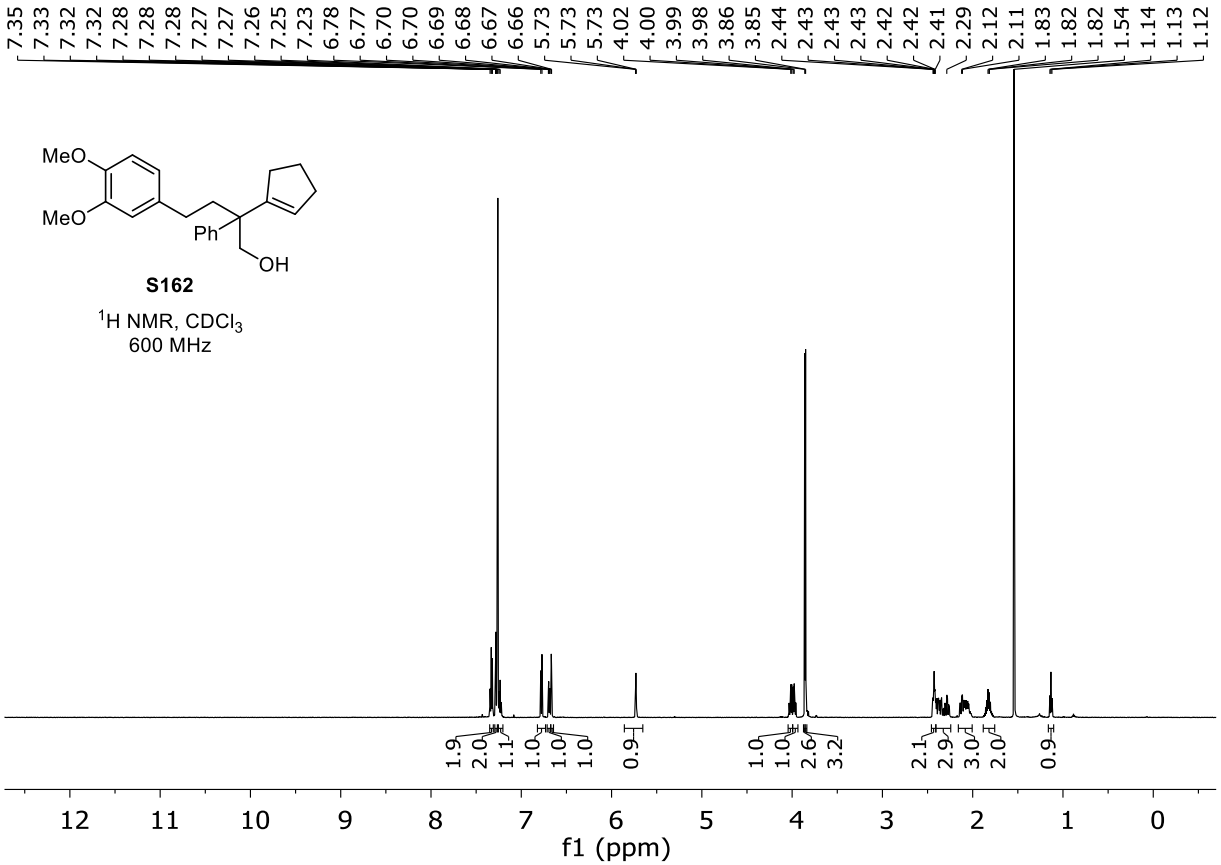

MeO
MeO
Ph
OH
S161
^{13}C NMR, $CDCl_3$
101 MHz
f1 (ppm)

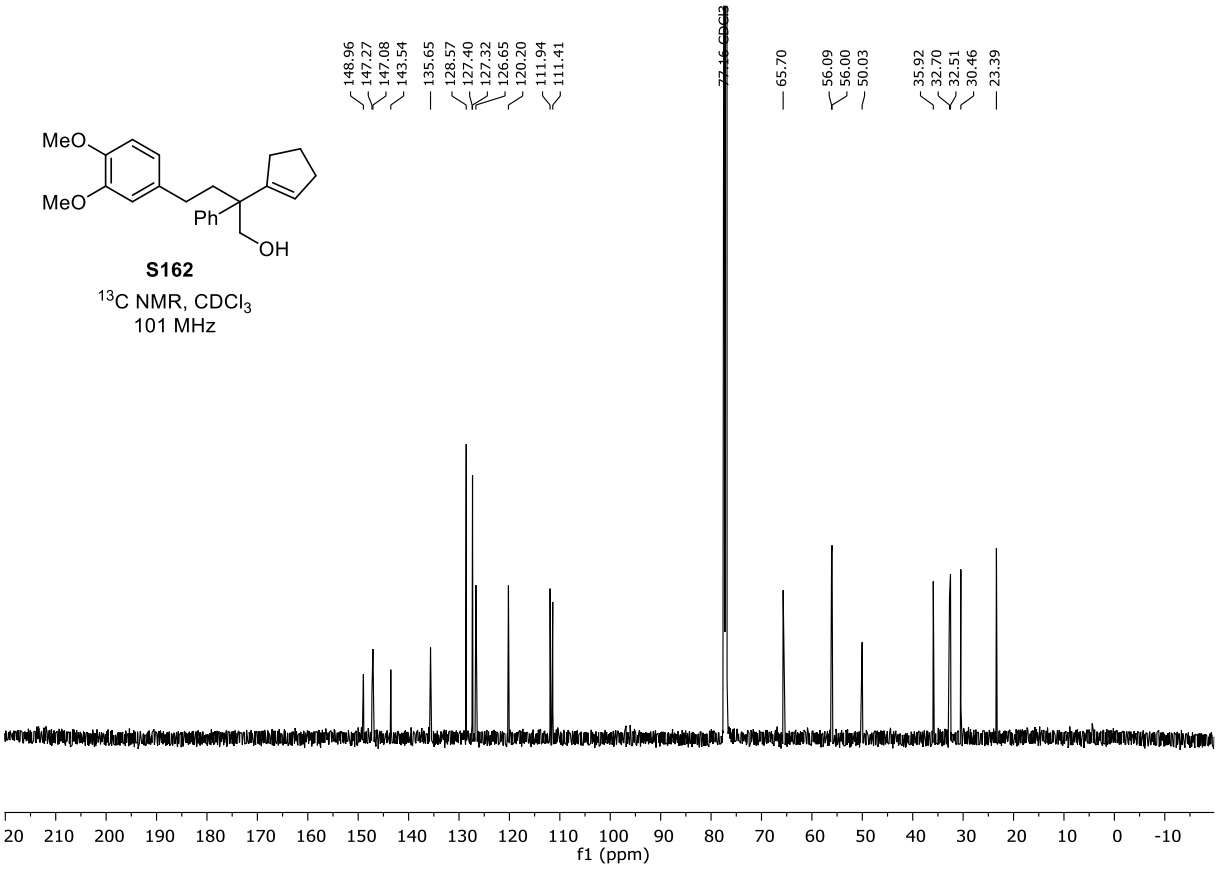

MeO
MeO
Ph
OH
S161
COSY, CDCl3
600 MHz
f2 (ppm)
f1 (ppm)

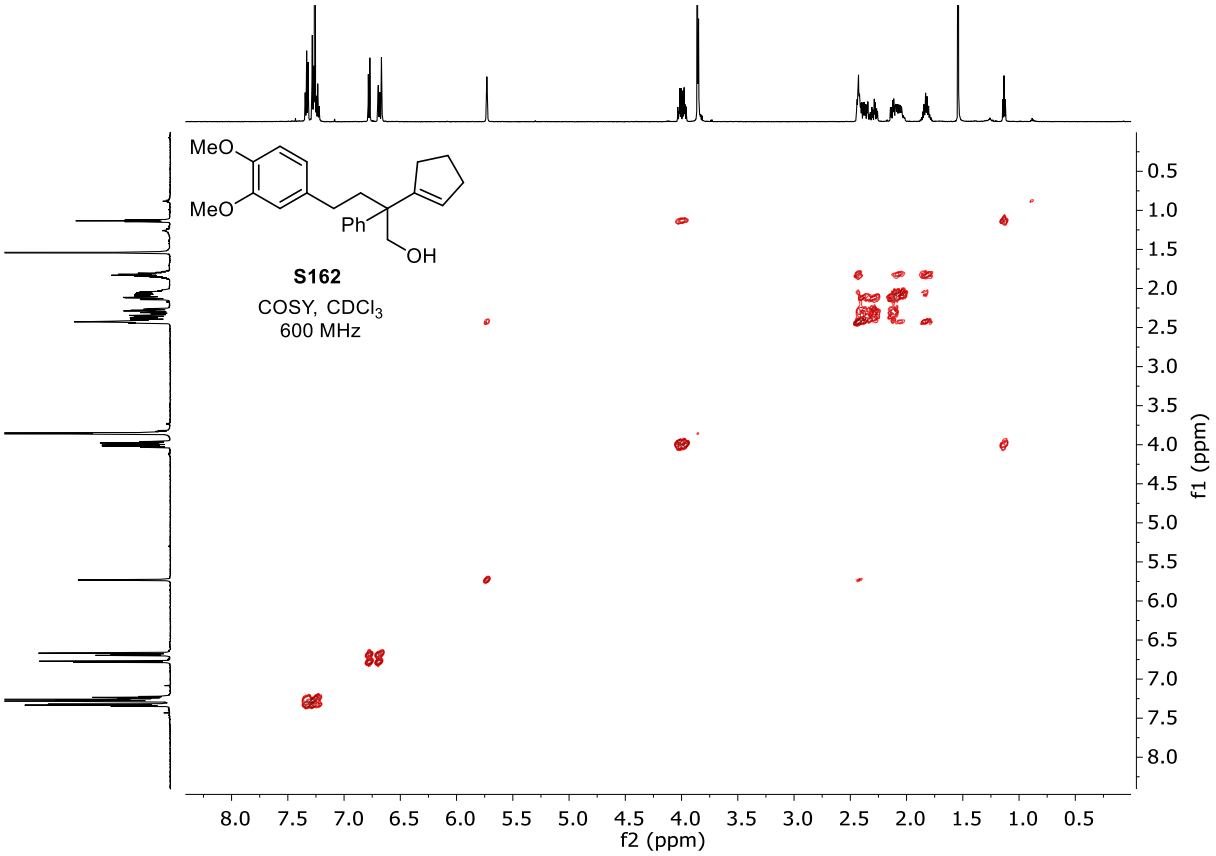

MeO
MeO
Ph
OH
S161
HSQC, CDCl3
600 MHz
f2 (ppm)
f1 (ppm)

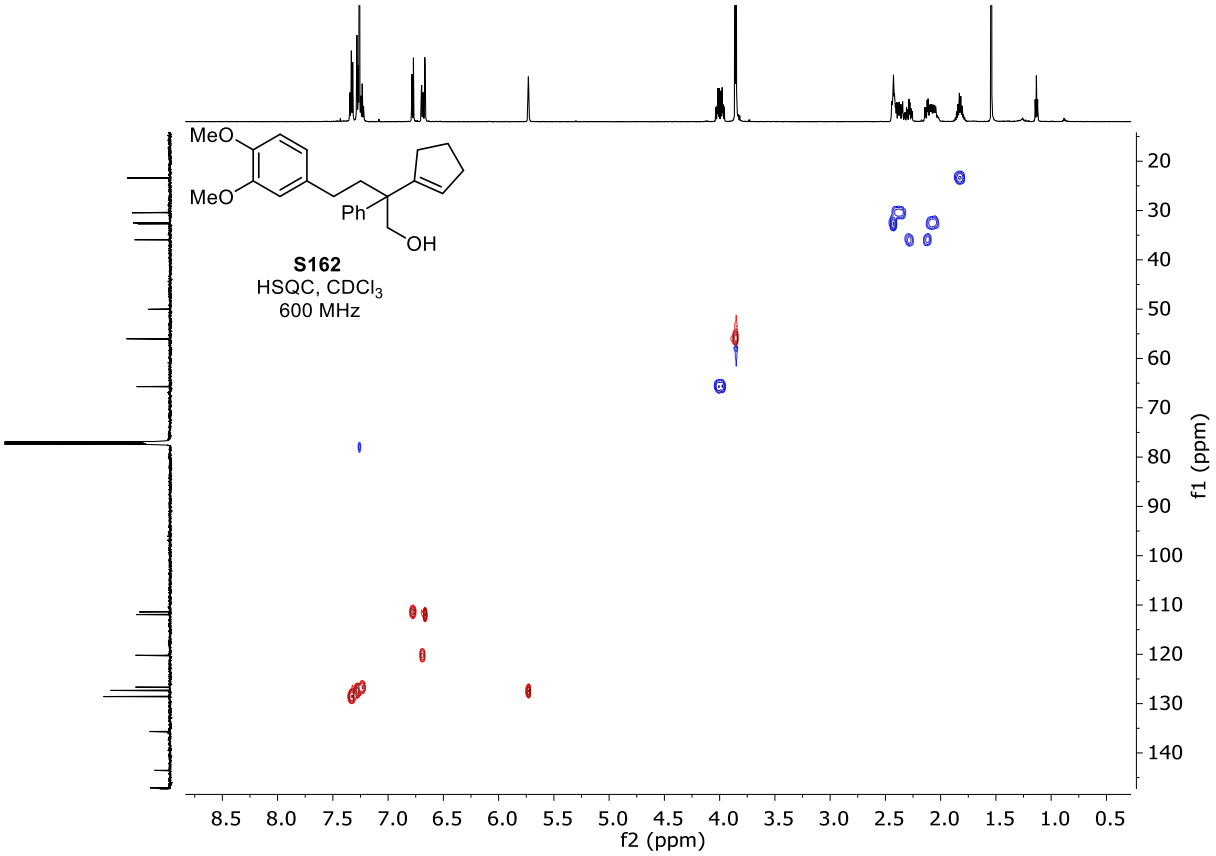

HMBC, CDCl3
600 MHz
MeO
MeO
Ph
OH
S161
f2 (ppm)
f1 (ppm)

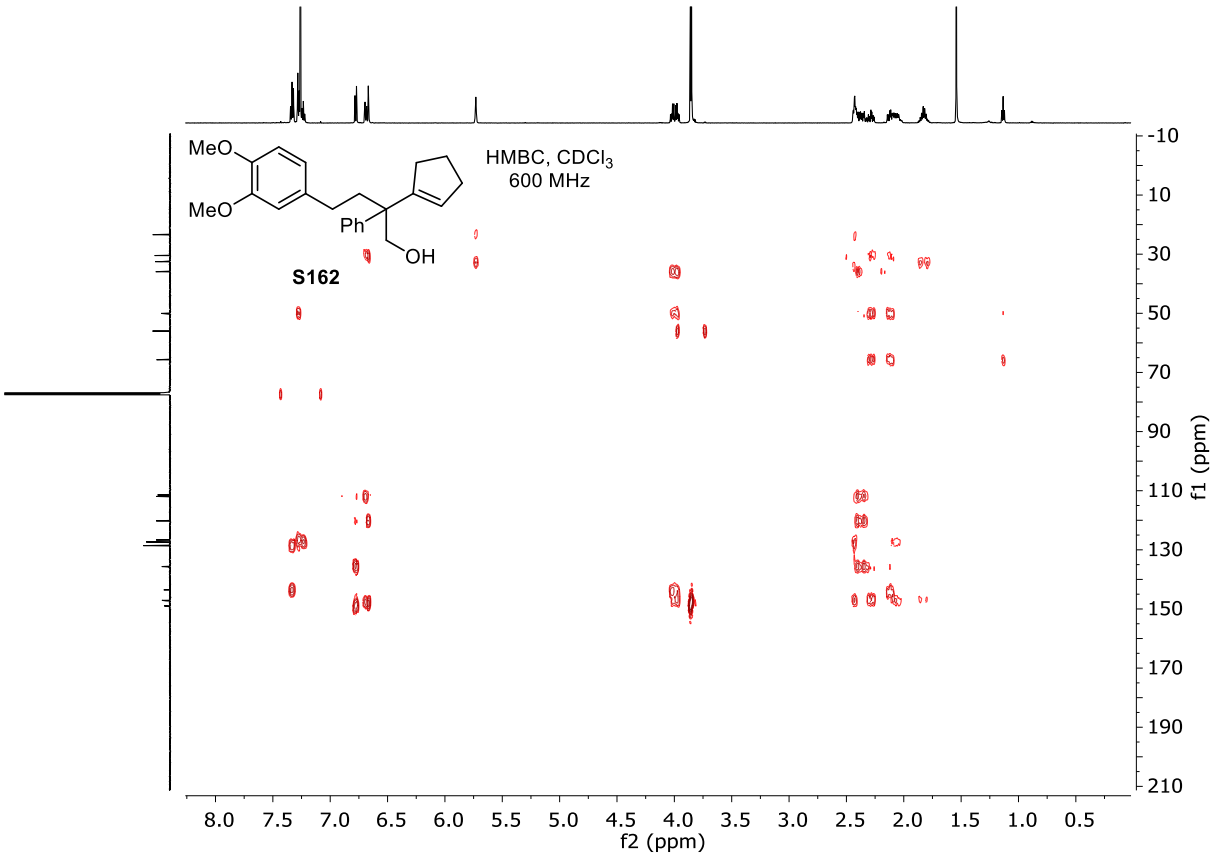

NOESY, CDCl3
600 MHz
MeO
MeO
Ph
OH
S161
f2 (ppm)
f1 (ppm)

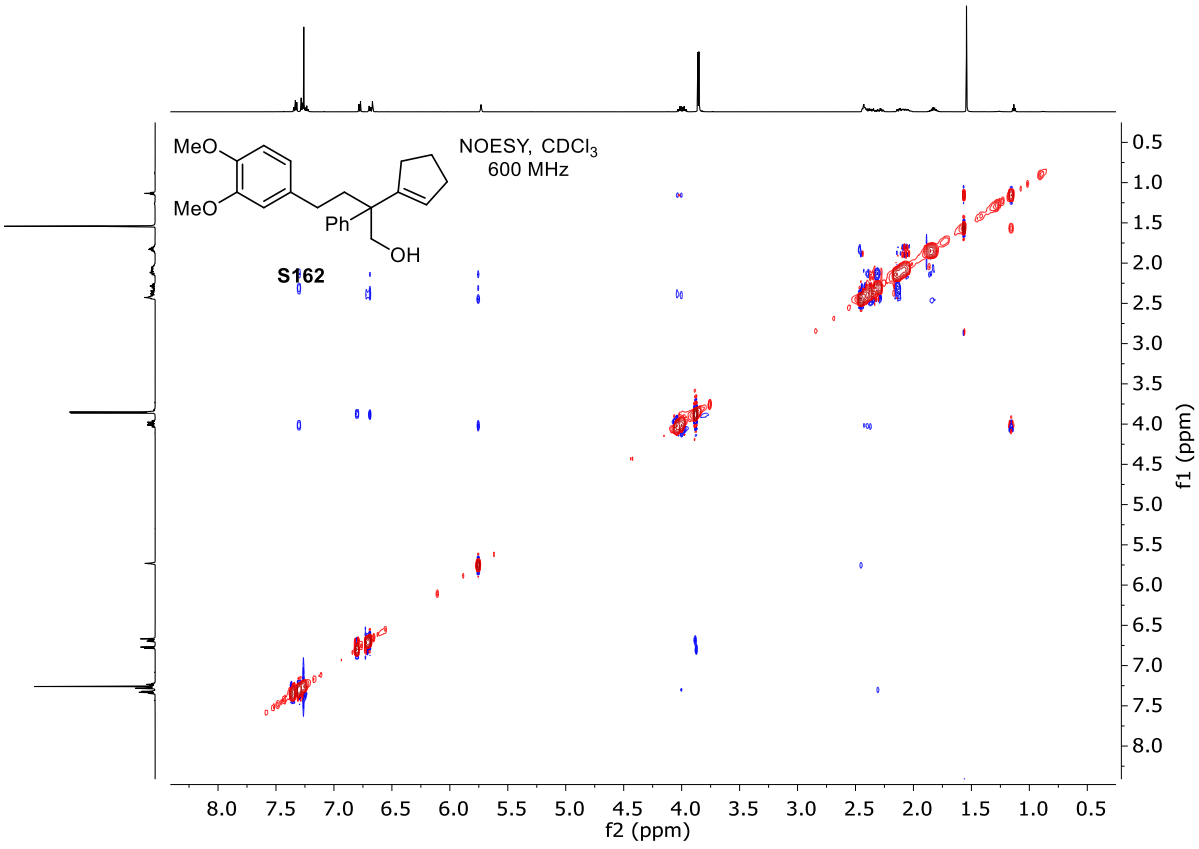

MeO
MeO
Ph
OH
S162
1H NMR, CDCl3
600 MHz
f1 (ppm)

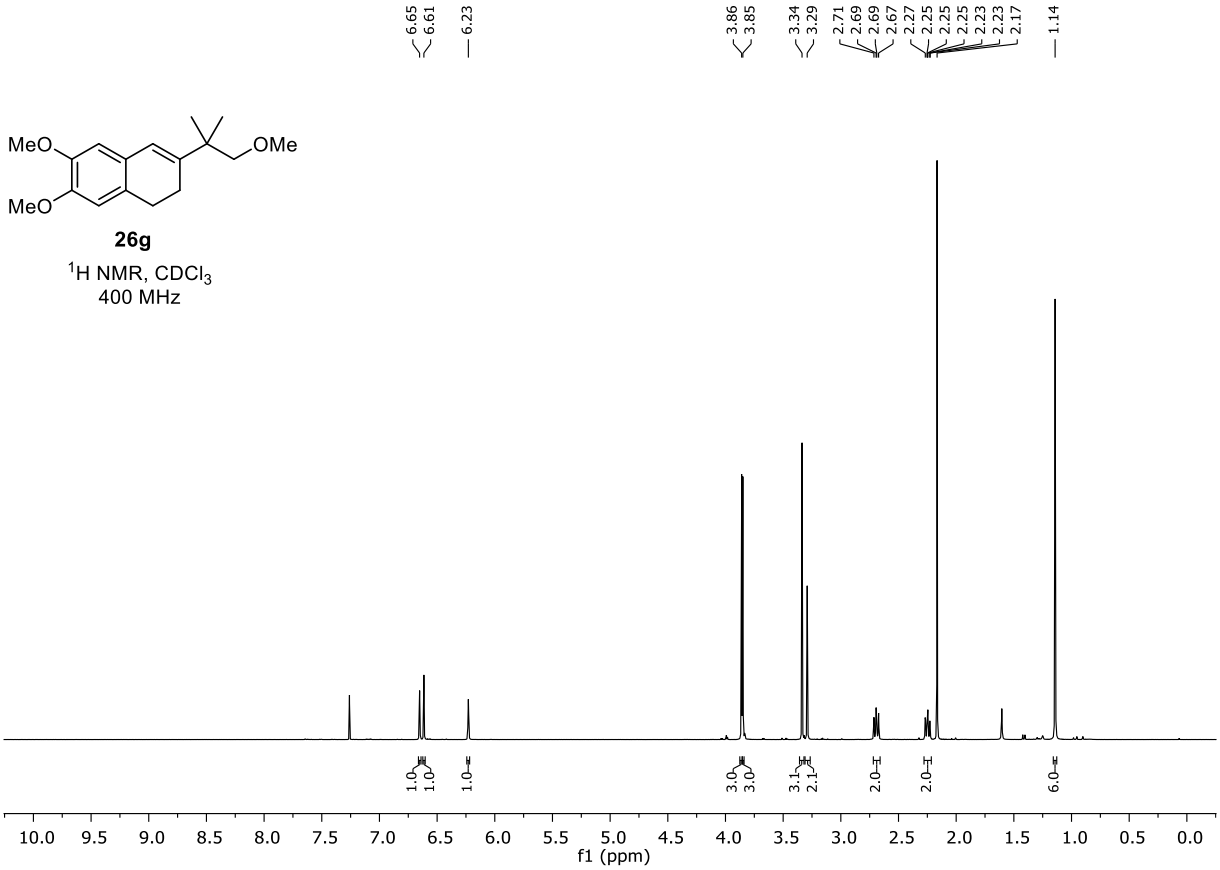

MeO
MeO
Ph
OH
S162
13C NMR, CDCl3
101 MHz
f1 (ppm)


MeO
MeO
Ph
OH
S162
COSY, CDCl3
600 MHz
f2 (ppm)
f1 (ppm)


MeO
MeO
Ph
OH
S162
HSQC, CDCl3
600 MHz
f2 (ppm)
f1 (ppm)

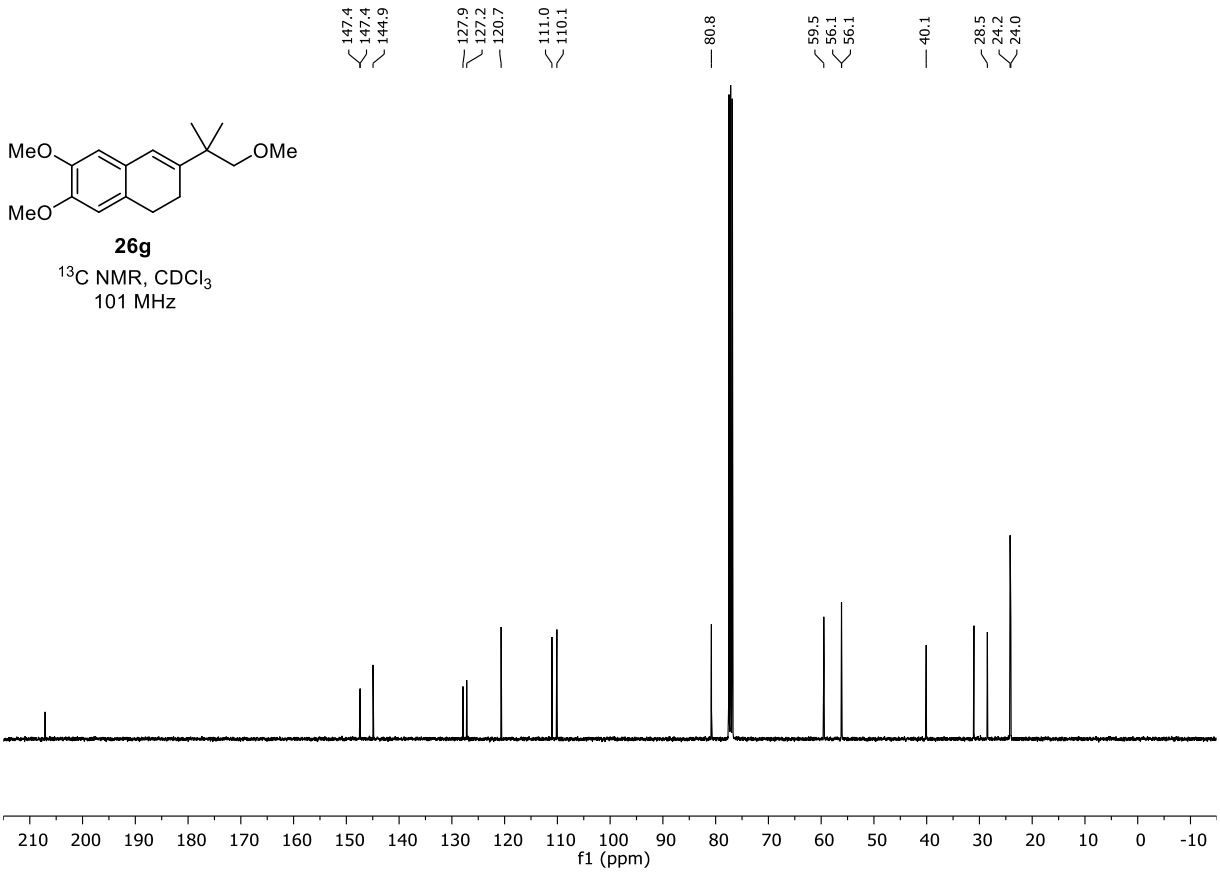

MeO
MeO
Ph
OH
S162
HMBC, CDCl3
600 MHz
f2 (ppm)
f1 (ppm)


MeO
MeO
Ph
OH
S162
NOESY, CDCl3
600 MHz
f2 (ppm)
f1 (ppm)



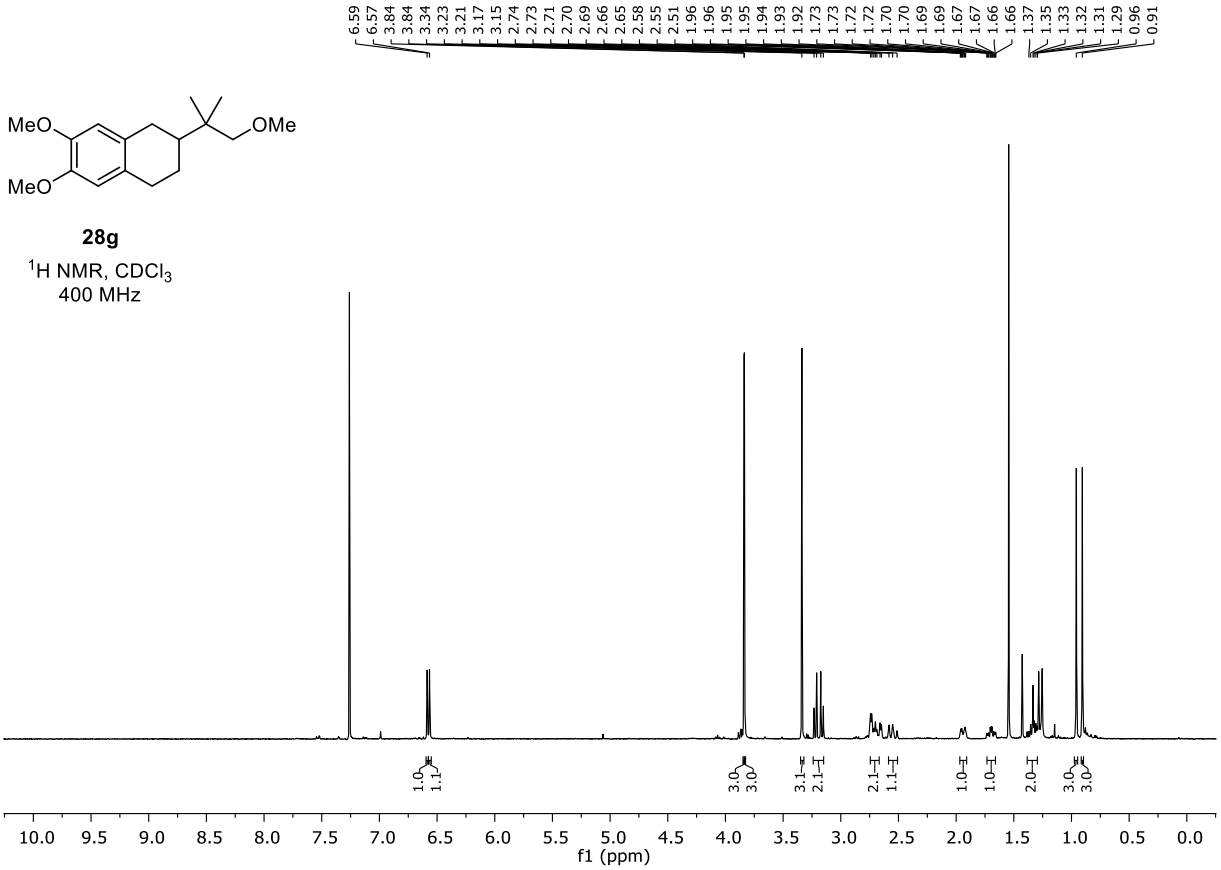
26g

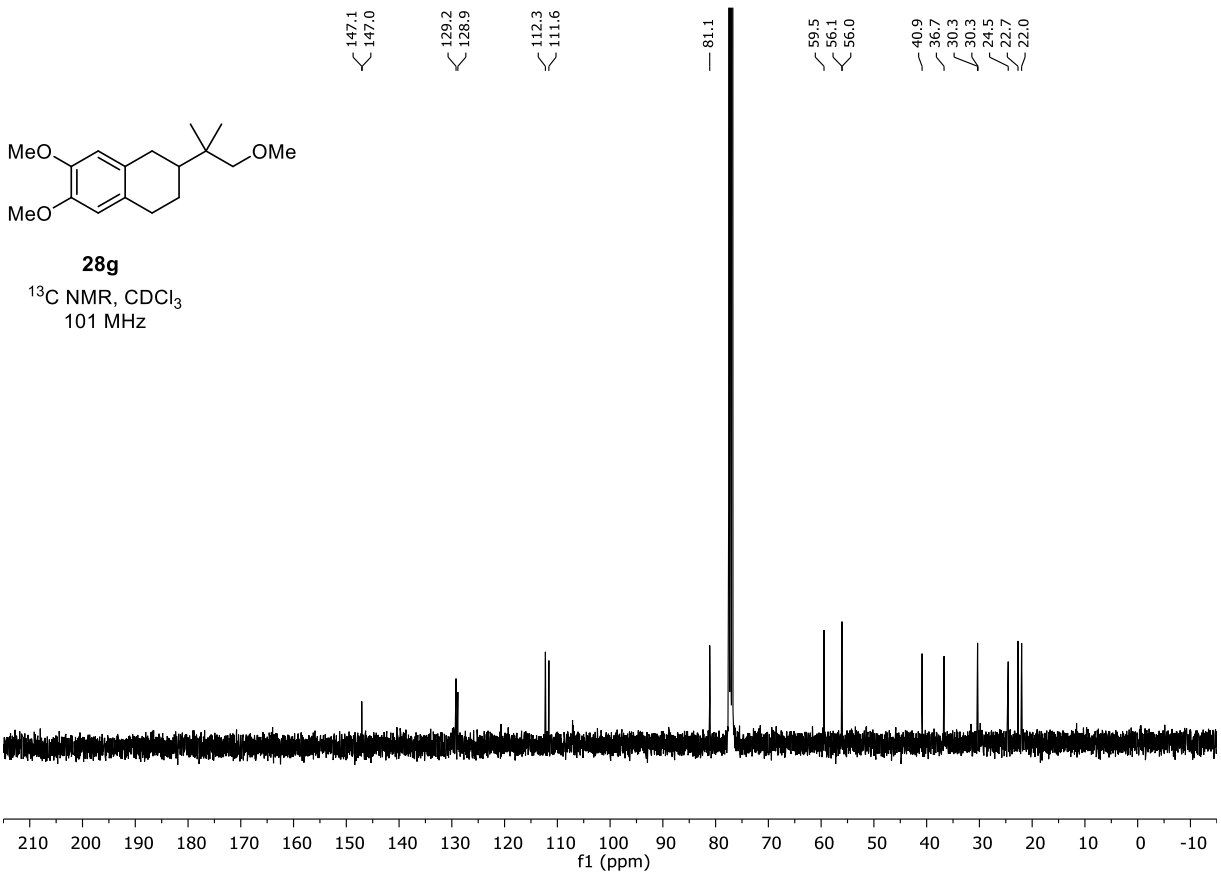
^{1}H NMR, $CDCl_3$
400 MHz

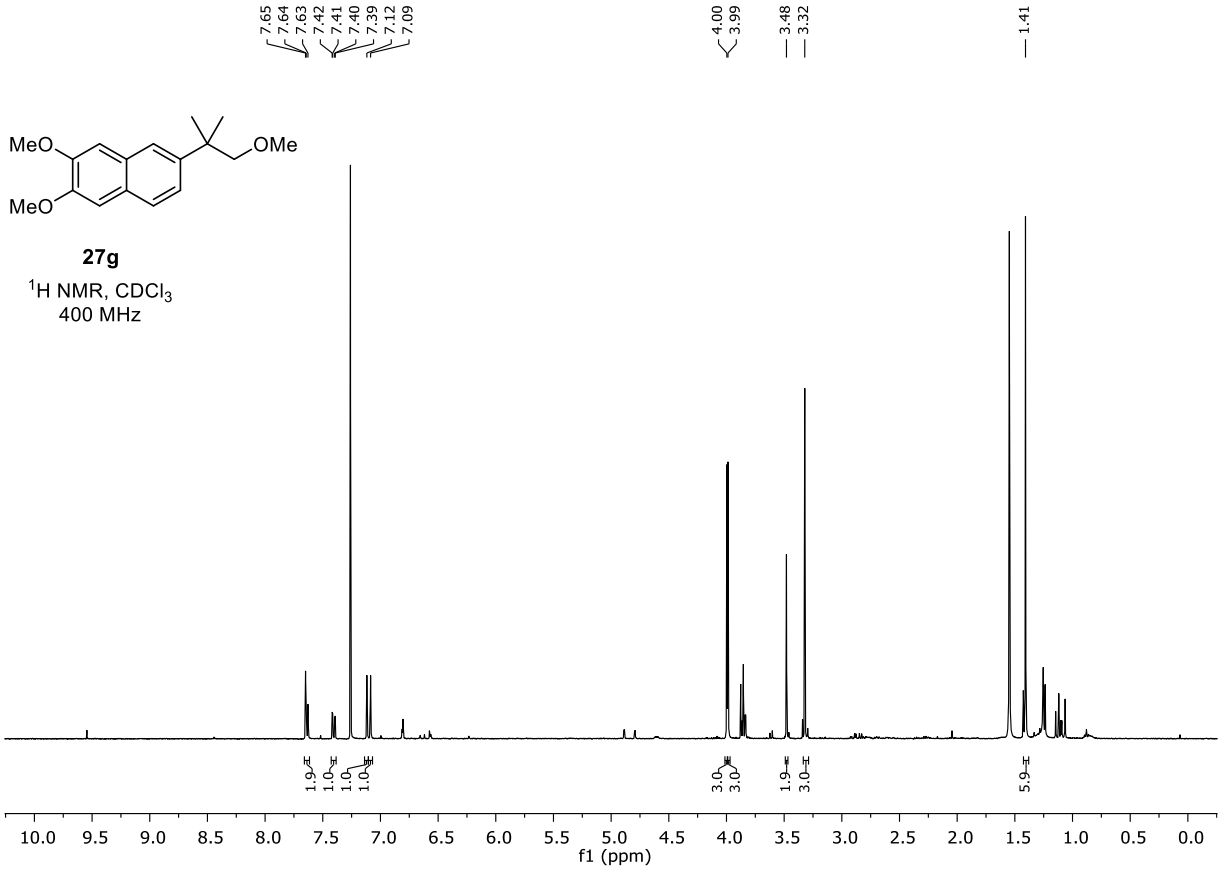


26g

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

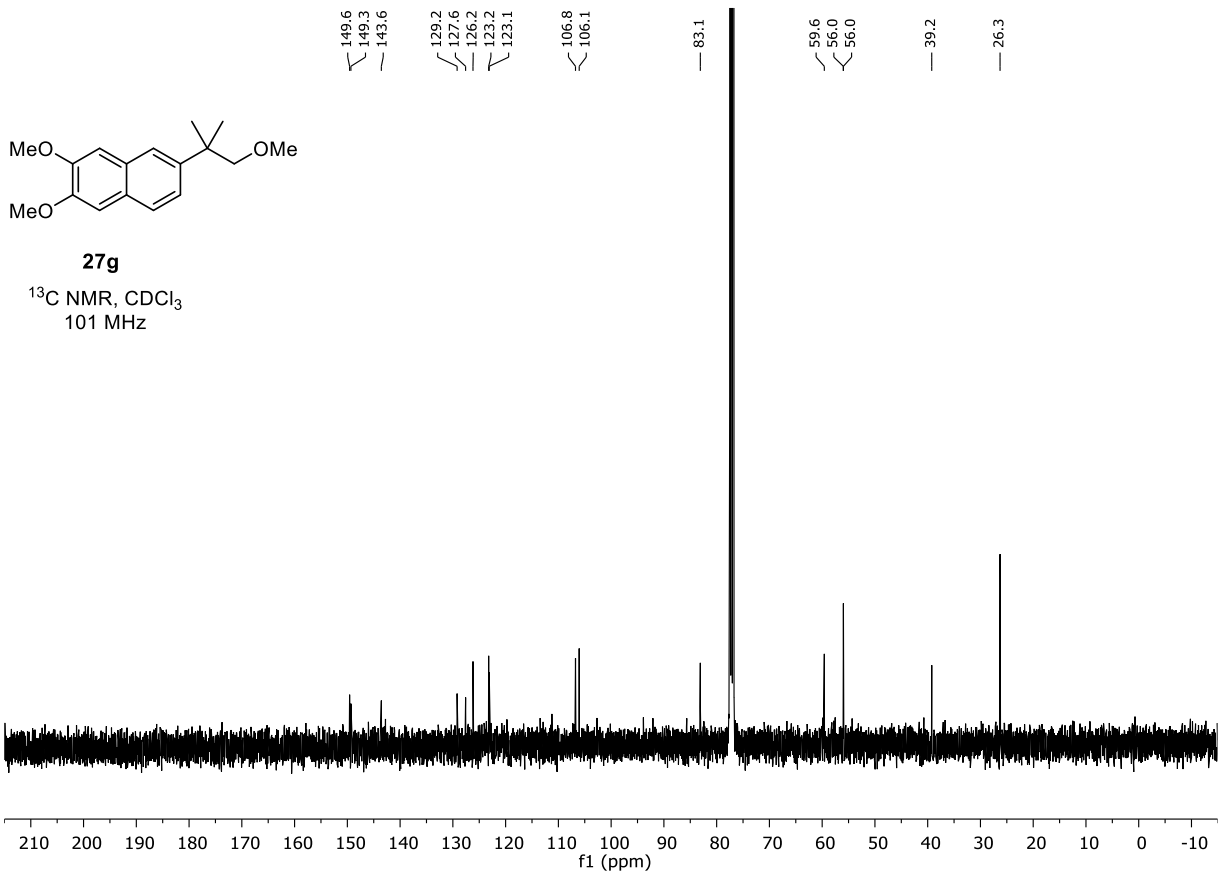

MeO
MeO
OMe
28g
^{1}H NMR, CDCl$_3$
400 MHz
f1 (ppm)


MeO
MeO
OMe
28g
^{13}C NMR, CDCl$_3$
101 MHz
f1 (ppm)



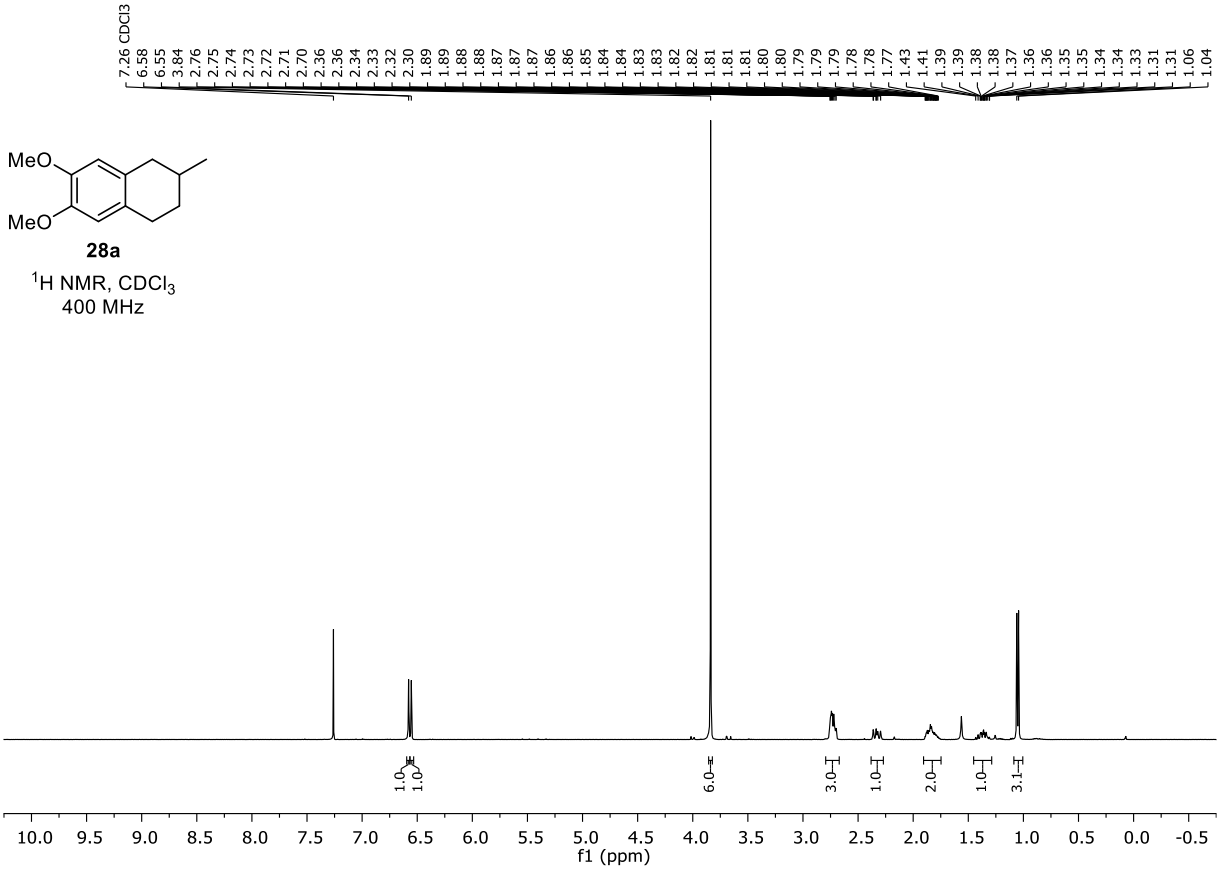
27g

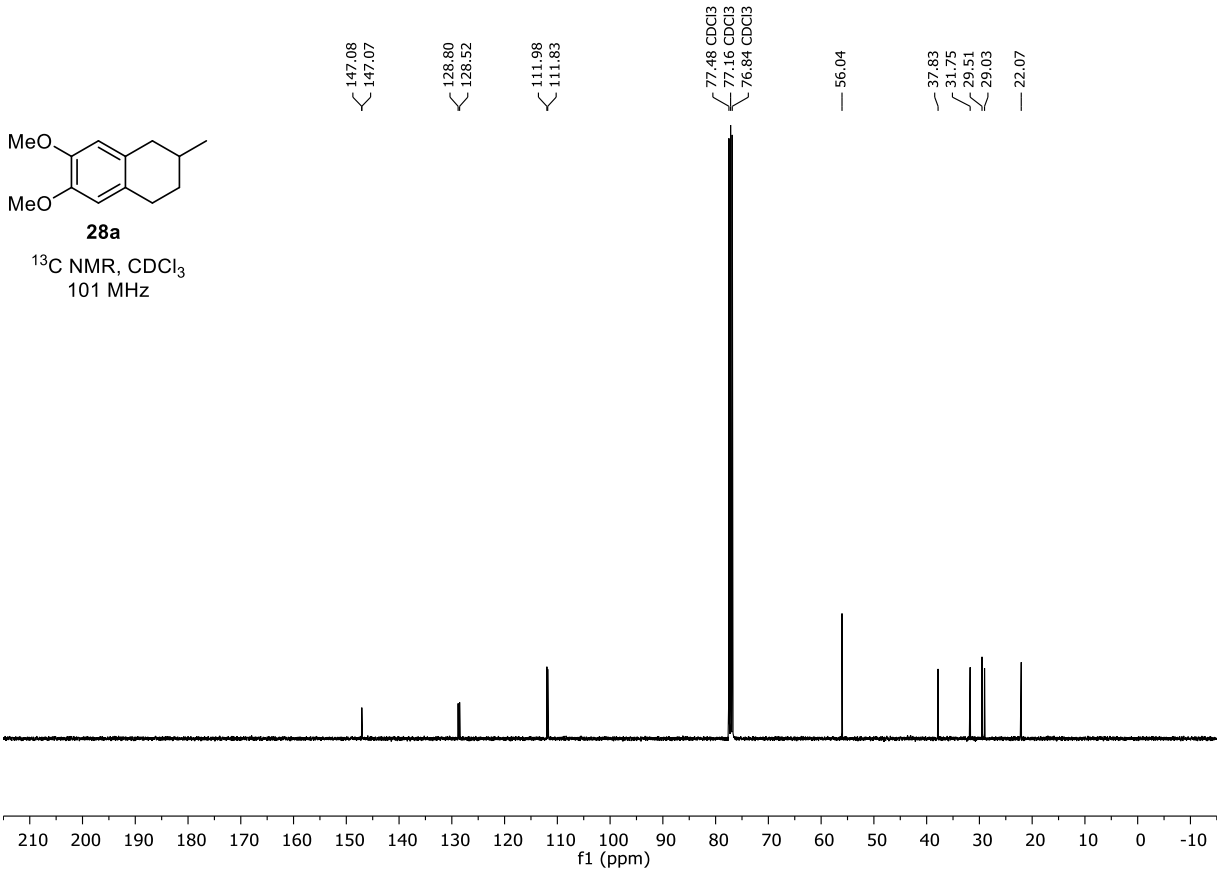
^{1}H NMR, $CDCl_3$
400 MHz

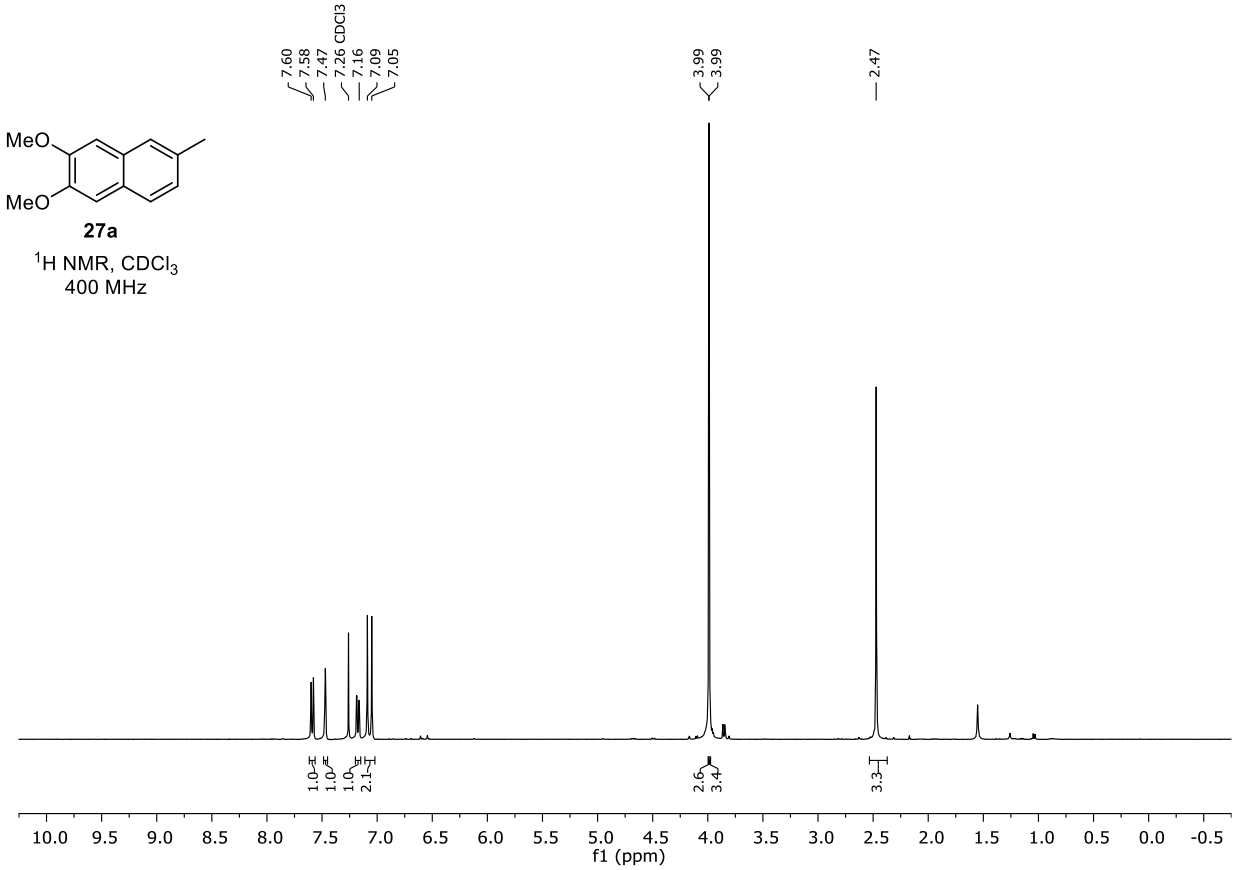


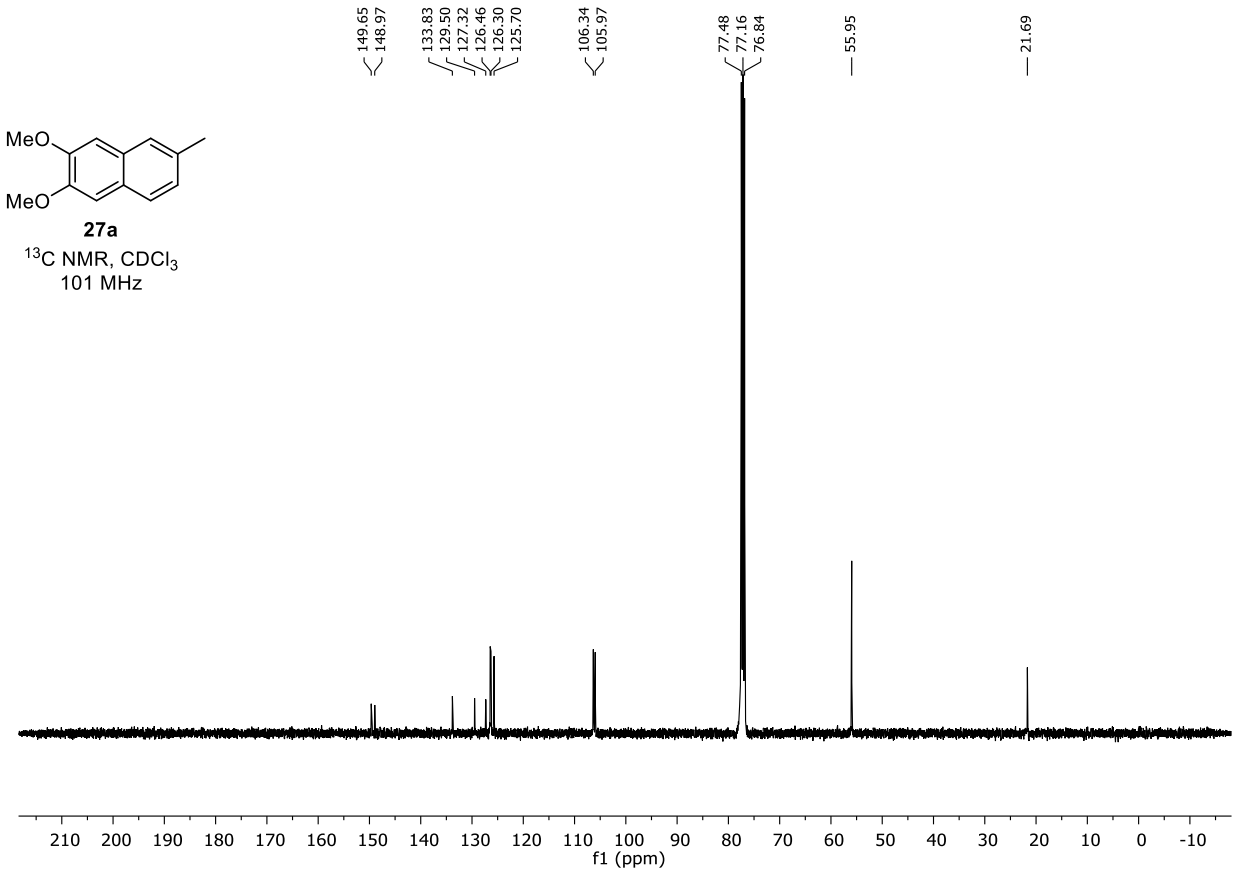
27g

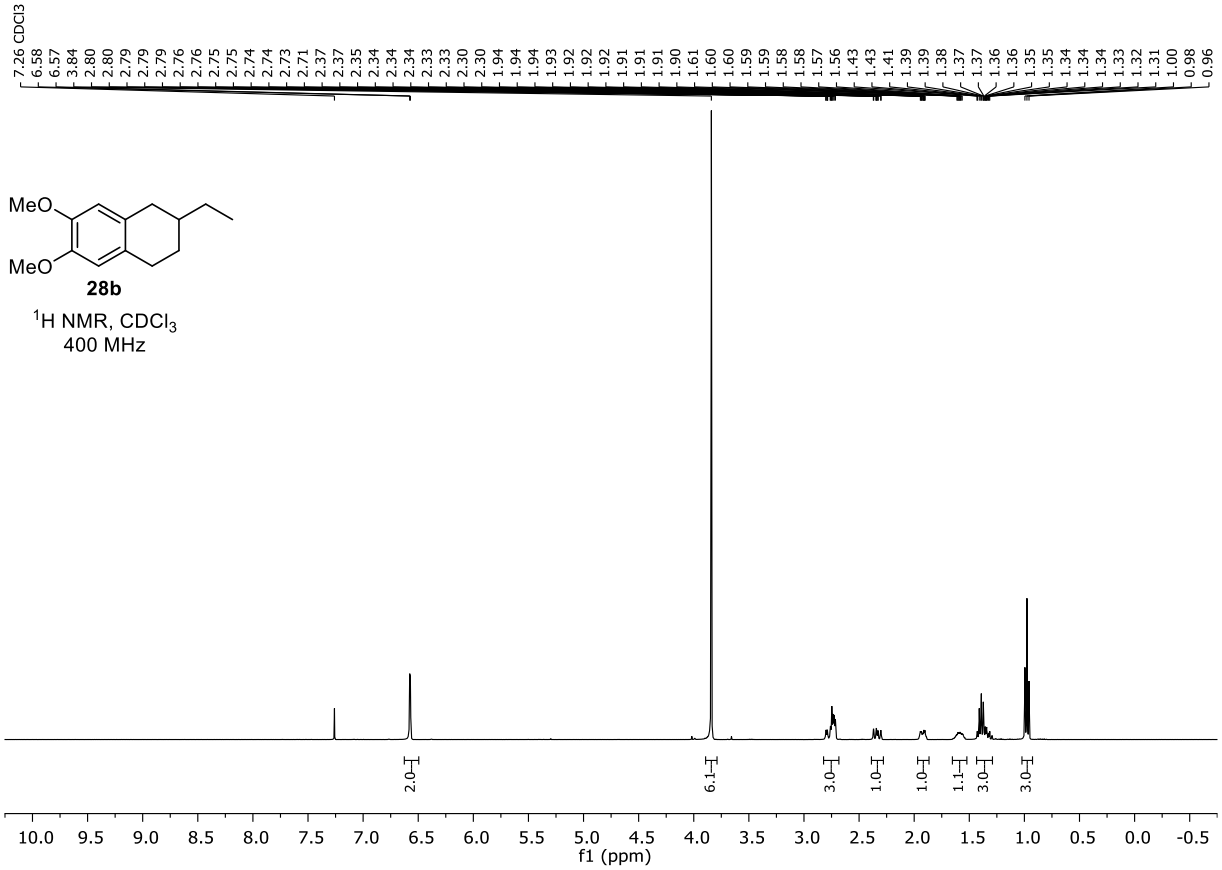
^{13}C NMR, $CDCl_3$
101 MHz

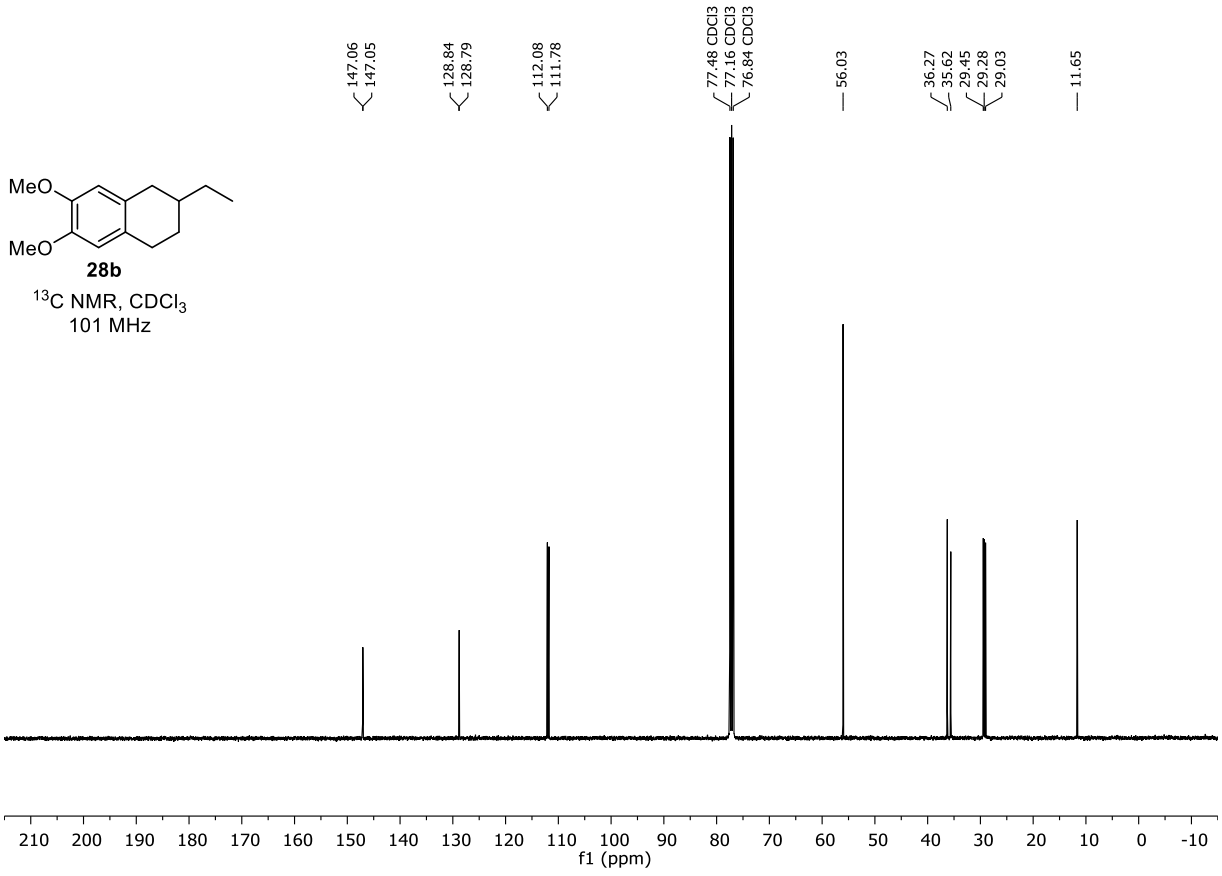

7.26 CDCl3
6.58
6.55
3.84
2.76
2.75
2.74
2.73
2.72
2.71
2.70
2.36
2.36
2.34
2.33
2.32
2.30
1.89
1.89
1.88
1.88
1.87
1.87
1.87
1.86
1.86
1.85
1.84
1.84
1.83
1.83
1.82
1.82
1.81
1.81
1.81
1.80
1.80
1.79
1.79
1.79
1.78
1.78
1.77
1.43
1.41
1.39
1.39
1.38
1.38
1.37
1.36
1.36
1.35
1.35
1.34
1.34
1.33
1.31
1.31
1.06
1.04
MeO
MeO
28a
1H NMR, CDCl3
400 MHz
1.0
1.0
6.0
3.0
1.0
2.0
1.0
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 -0.5
f1 (ppm)

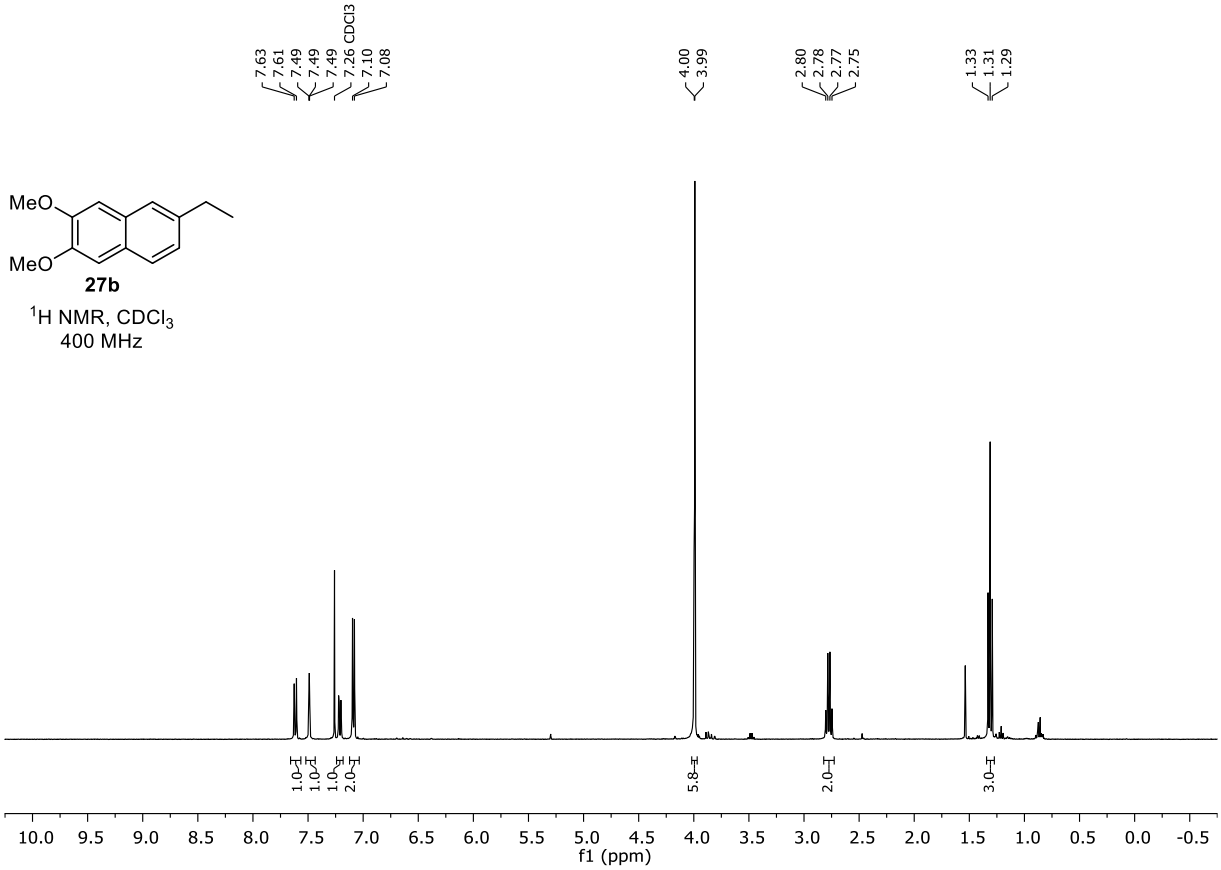

147.08
147.07
128.80
128.52
111.98
111.83
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
56.04
37.83
31.75
29.51
29.03
22.07
MeO
MeO
28a
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

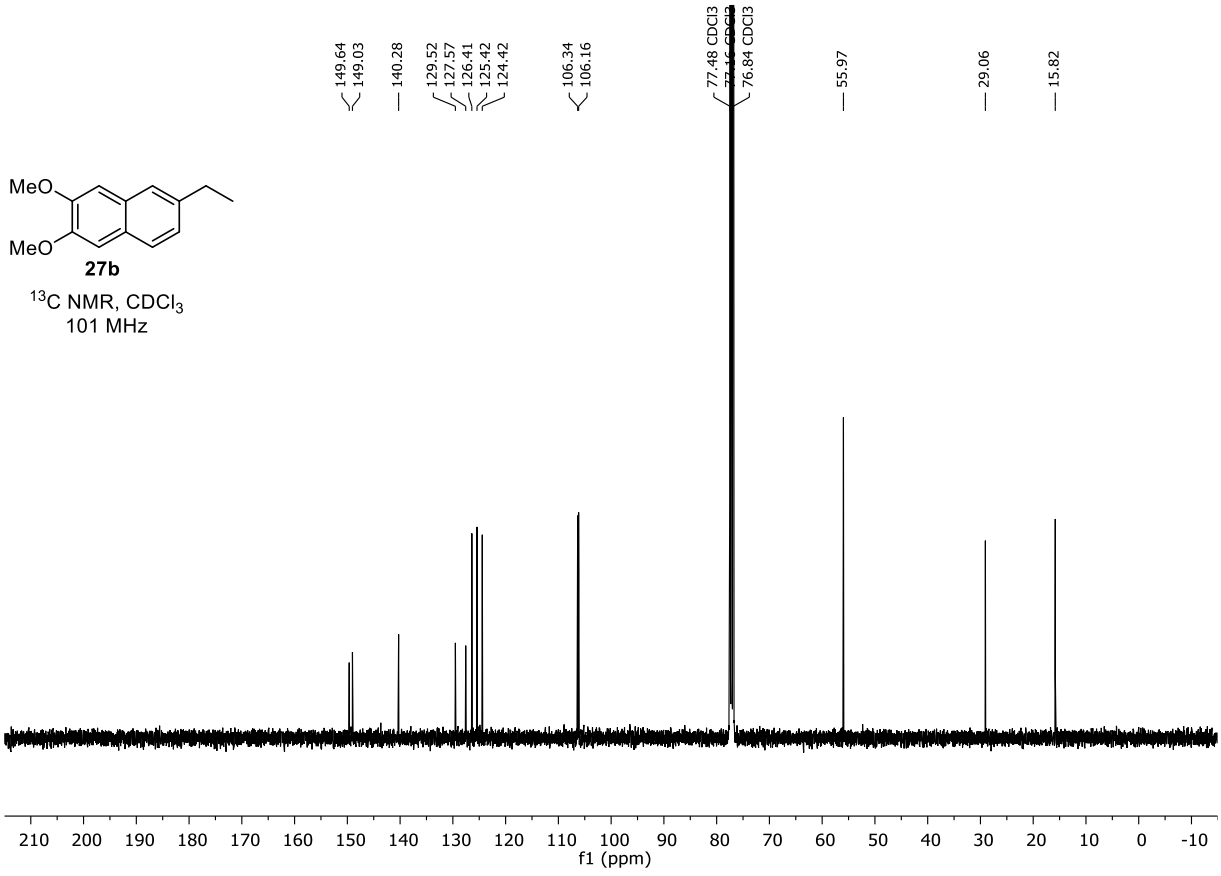

MeO
MeO
27a
1H NMR, CDCl3
400 MHz
7.60
7.58
7.47
7.26 CDCl3
7.16
7.09
7.05
3.99
3.99
2.47
1.0
1.0
1.0
2.1
2.6
3.4
3.3
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

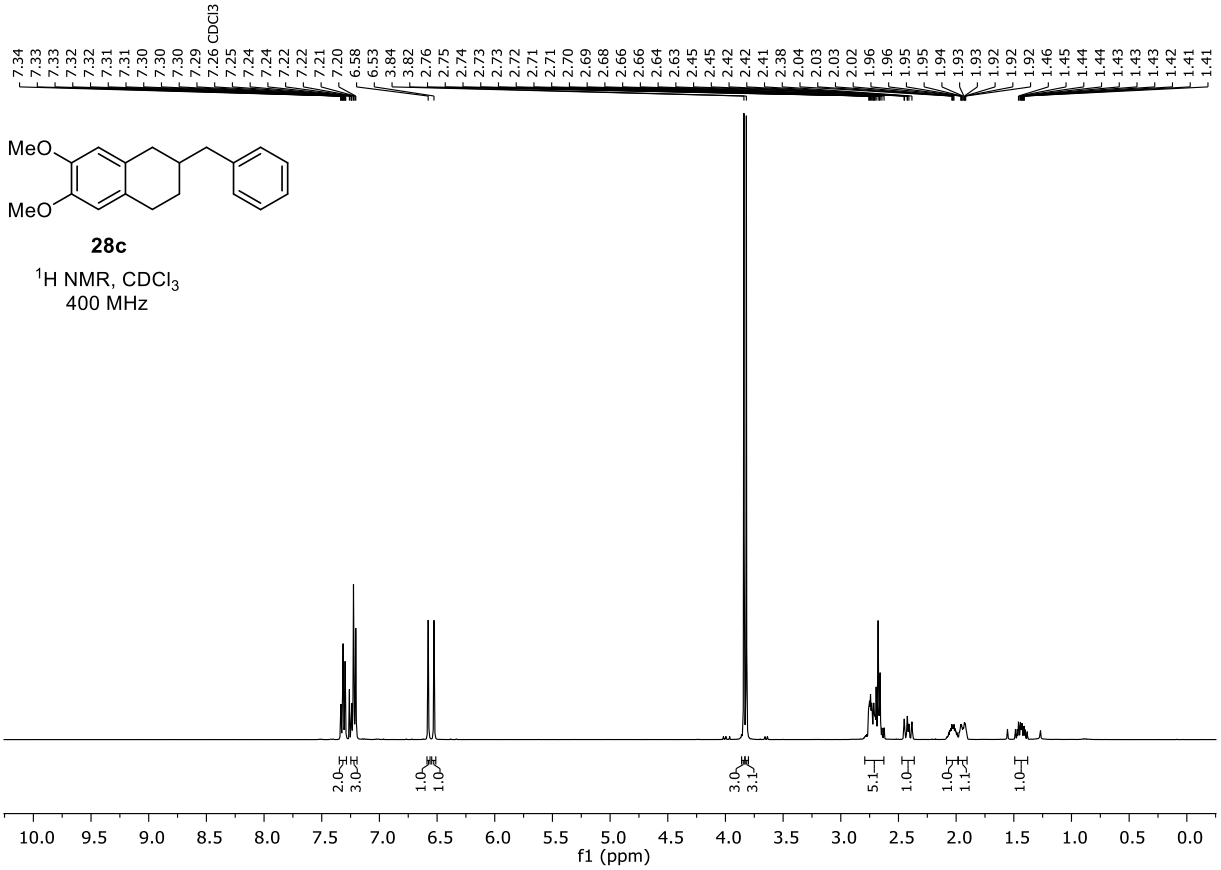

MeO
MeO
27a
13C NMR, CDCl3
101 MHz
149.65
148.97
133.83
129.50
127.32
126.46
126.30
125.70
106.34
105.97
77.48
77.16
76.84
55.95
21.69
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

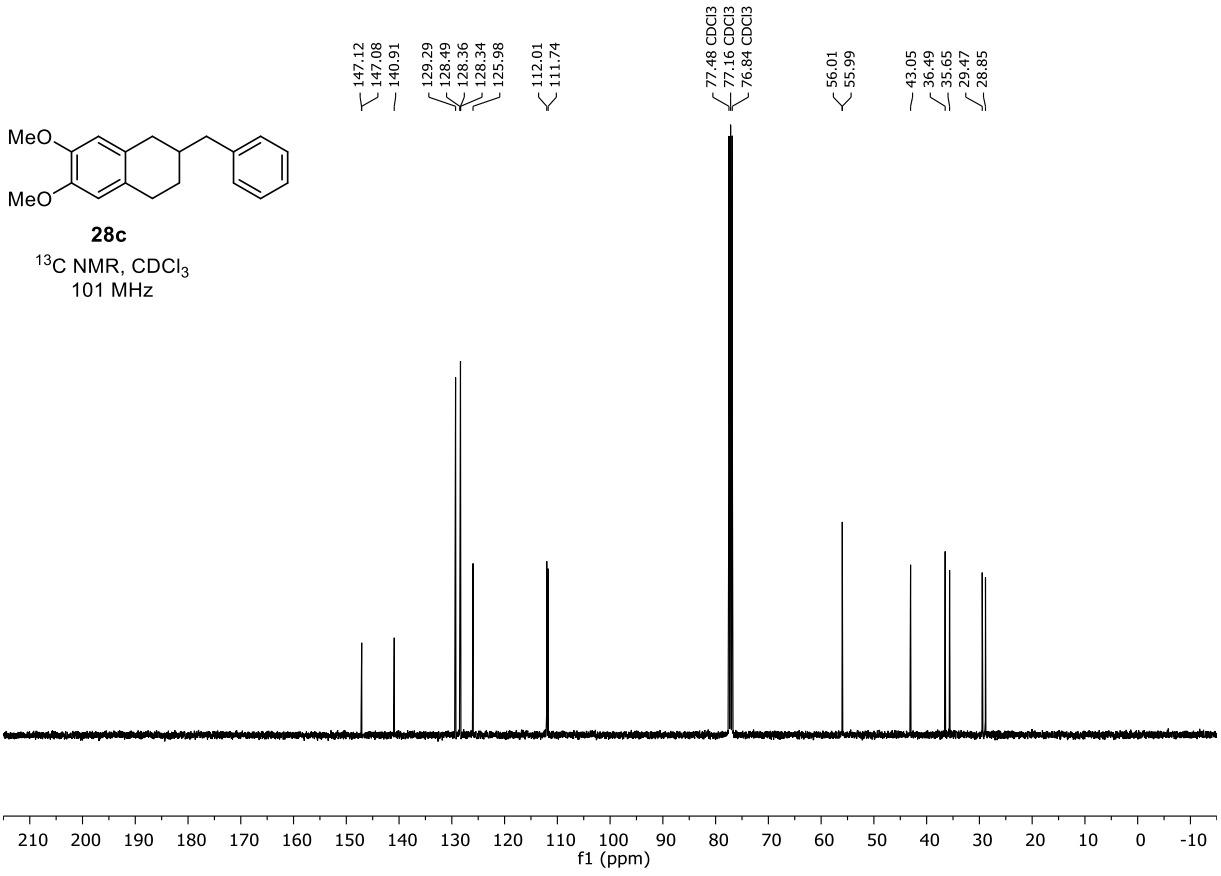

7.26 CDCl3
6.58 6.57 3.84 2.80 2.80 2.79 2.79 2.79 2.76 2.76 2.75 2.75 2.74 2.74 2.73 2.71 2.37 2.37 2.35 2.34 2.34 2.34 2.33 2.33 2.30 2.30 1.94 1.94 1.94 1.93 1.92 1.92 1.92 1.91 1.91 1.91 1.90 1.61 1.60 1.60 1.59 1.59 1.58 1.58 1.57 1.56 1.43 1.43 1.41 1.39 1.39 1.38 1.37 1.37 1.36 1.36 1.35 1.35 1.34 1.34 1.34 1.33 1.32 1.31 1.00 0.98 0.96
MeO
MeO
28b
1H NMR, CDCl3
400 MHz
2.0 6.1 3.0 1.0 1.0 1.1 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 -0.5
f1 (ppm)

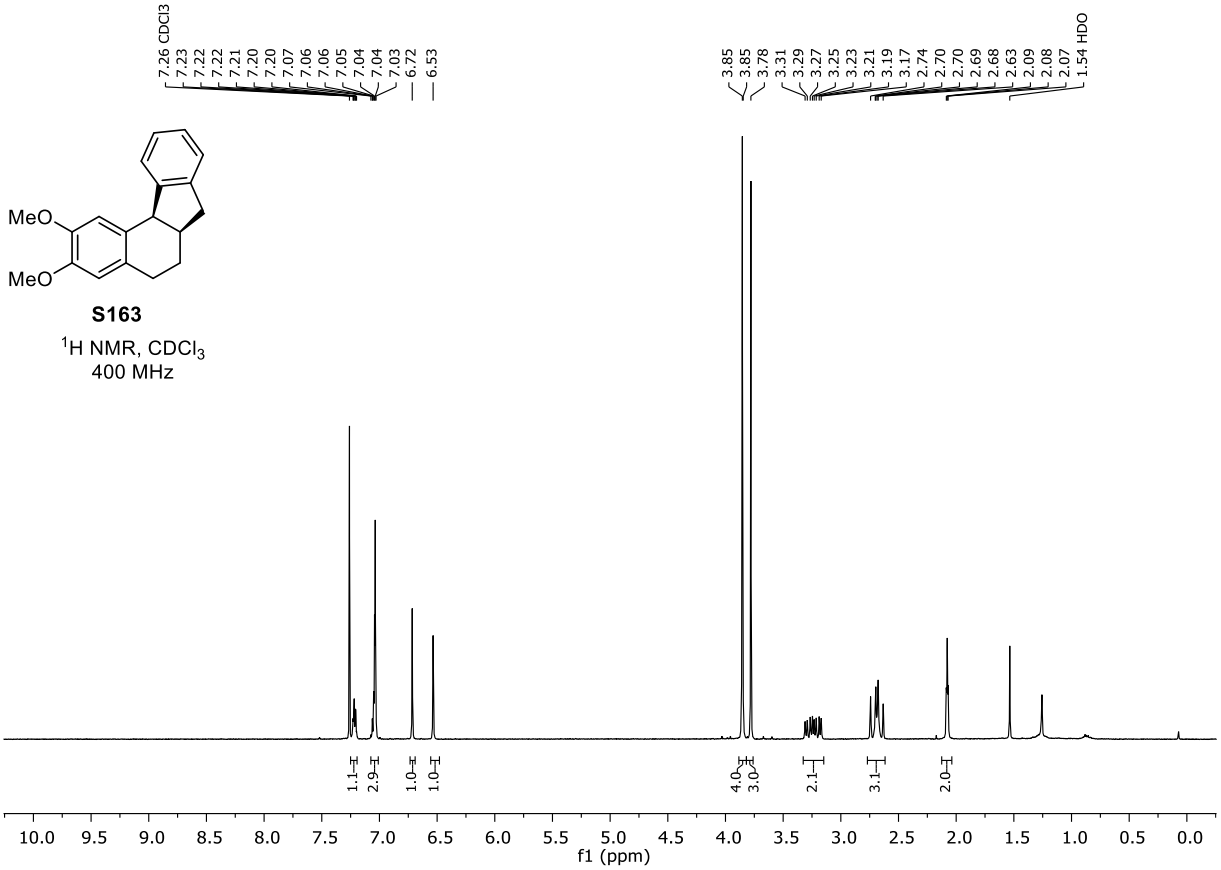

147.06
147.05
128.84
128.79
112.08
111.78
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
56.03
36.27
35.62
29.45
29.28
29.03
11.65
MeO
MeO
28b
13C NMR, CDCl3
101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.63
7.61
7.49
7.49
7.49
7.26 CDCl3
7.10
7.08
4.00
3.99
2.80
2.78
2.77
2.75
1.33
1.31
1.29
MeO
MeO
27b
1H NMR, CDCl3
400 MHz
1.0
1.0
1.0
2.0
5.8
2.0
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 -0.5
f1 (ppm)


149.64
149.03
140.28
129.52
127.57
126.41
125.42
124.42
106.34
106.16
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
55.97
29.06
15.82
MeO
MeO
27b
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)

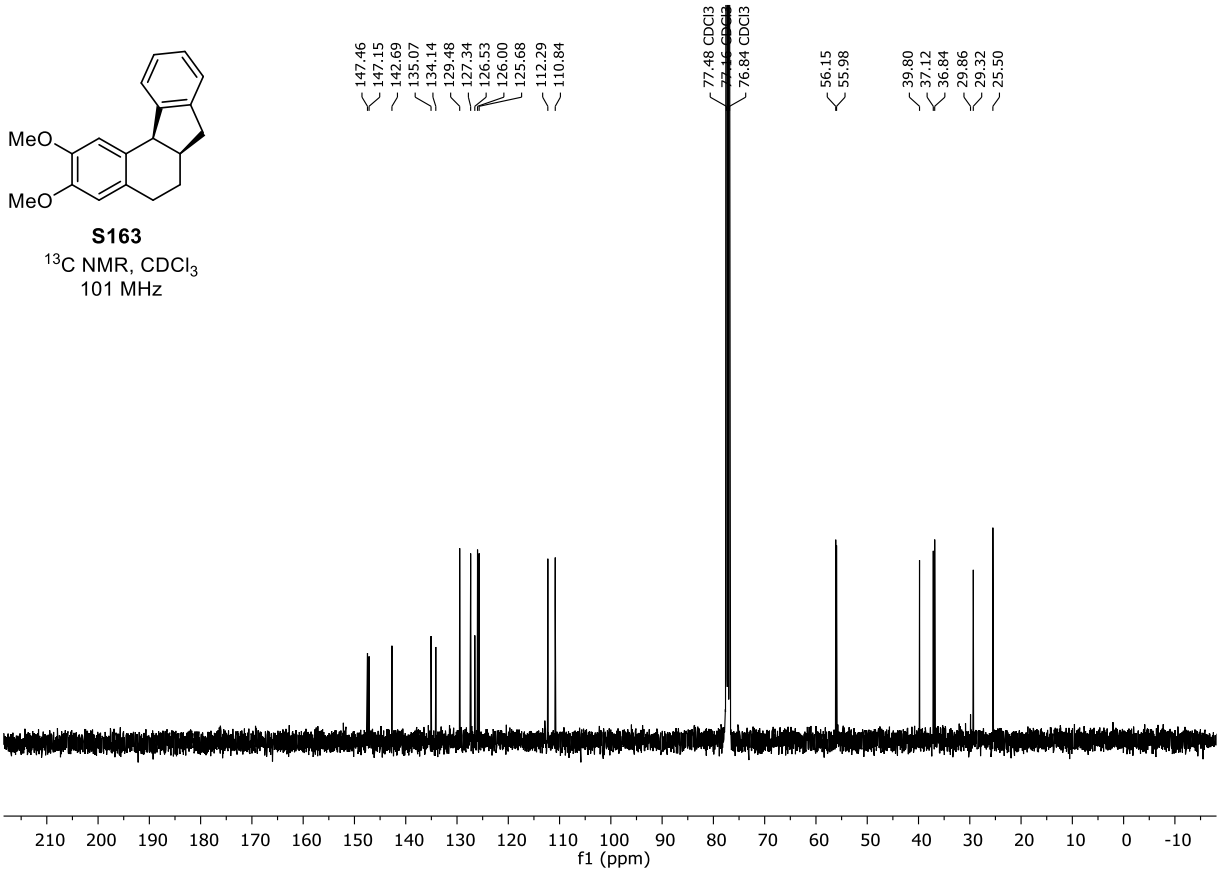

MeO
MeO
28c
^{1}H NMR, CDCl$_3$
400 MHz
f1 (ppm)


MeO
MeO
28c
^{13}C NMR, CDCl$_3$
101 MHz
f1 (ppm)



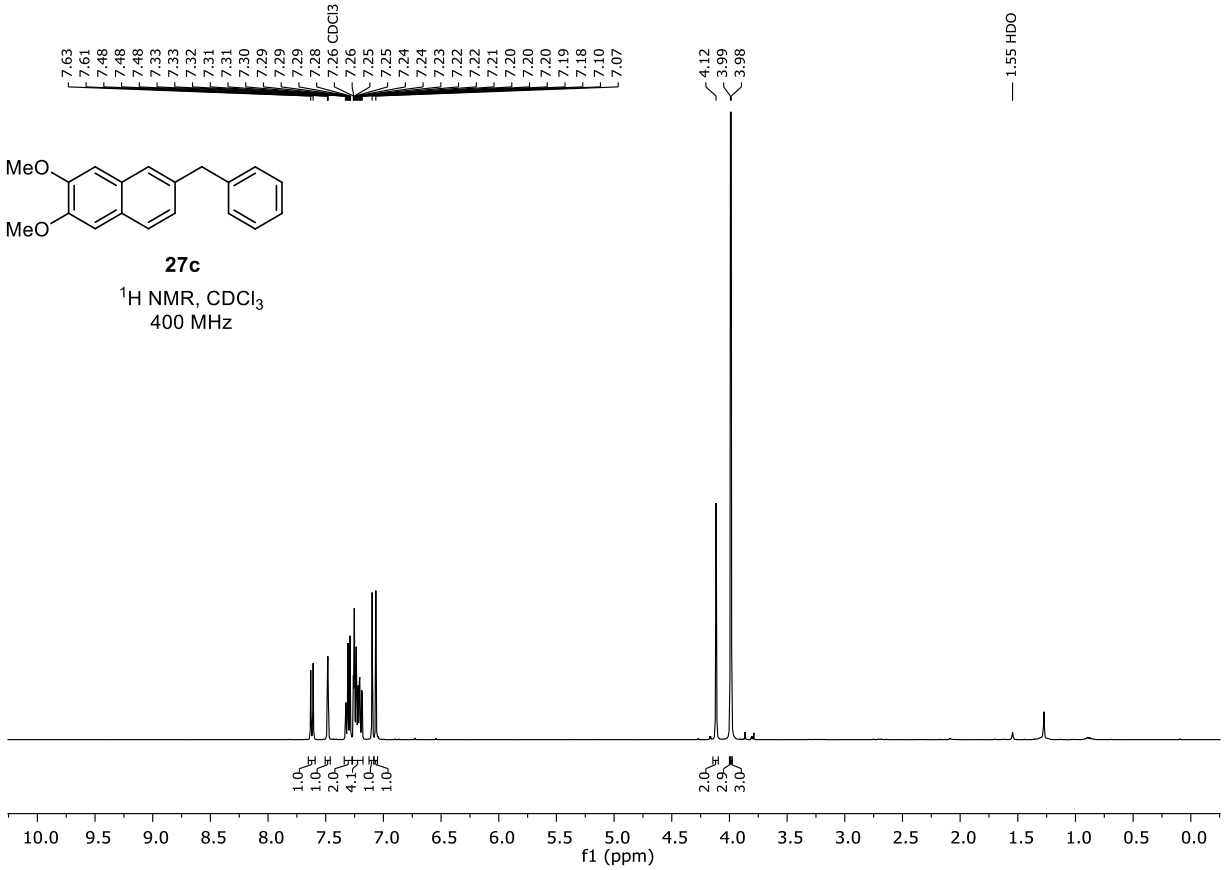
S163

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



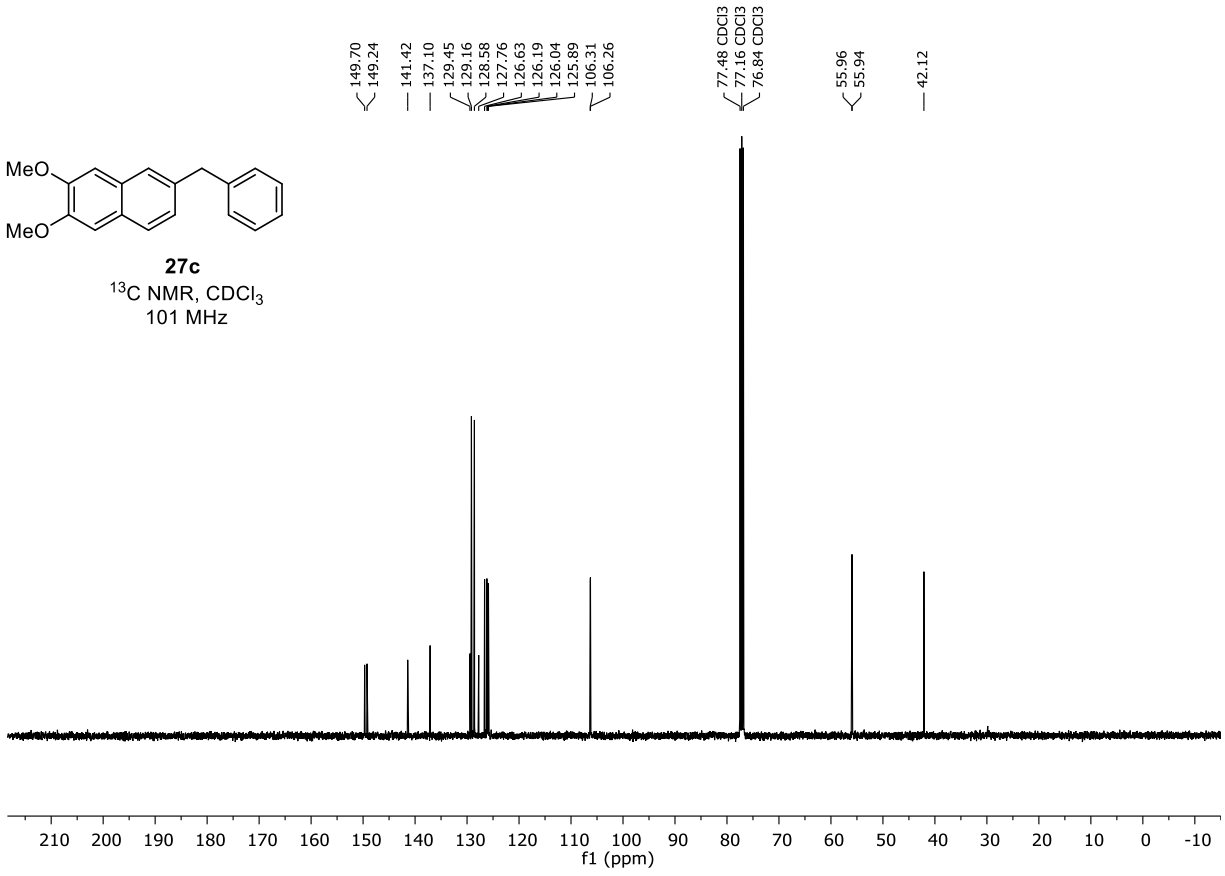
S163

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



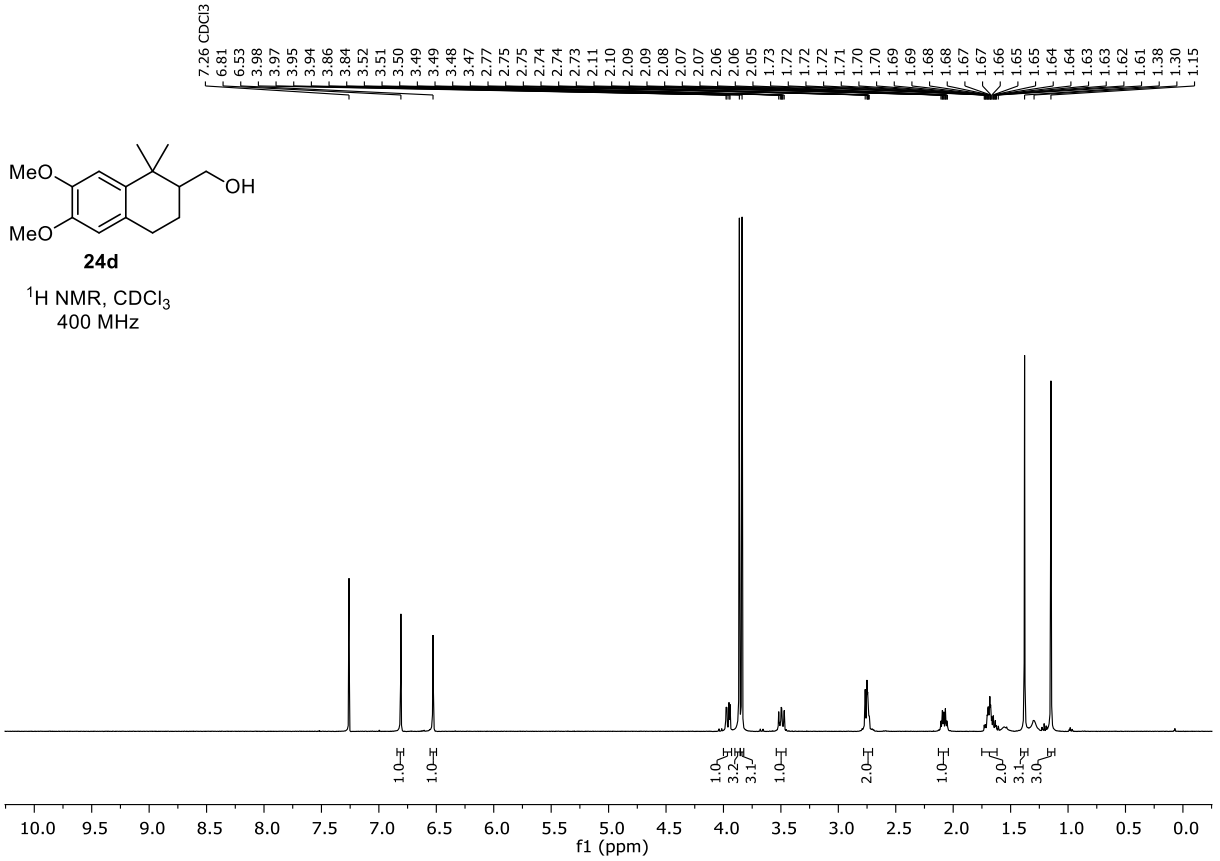
27c

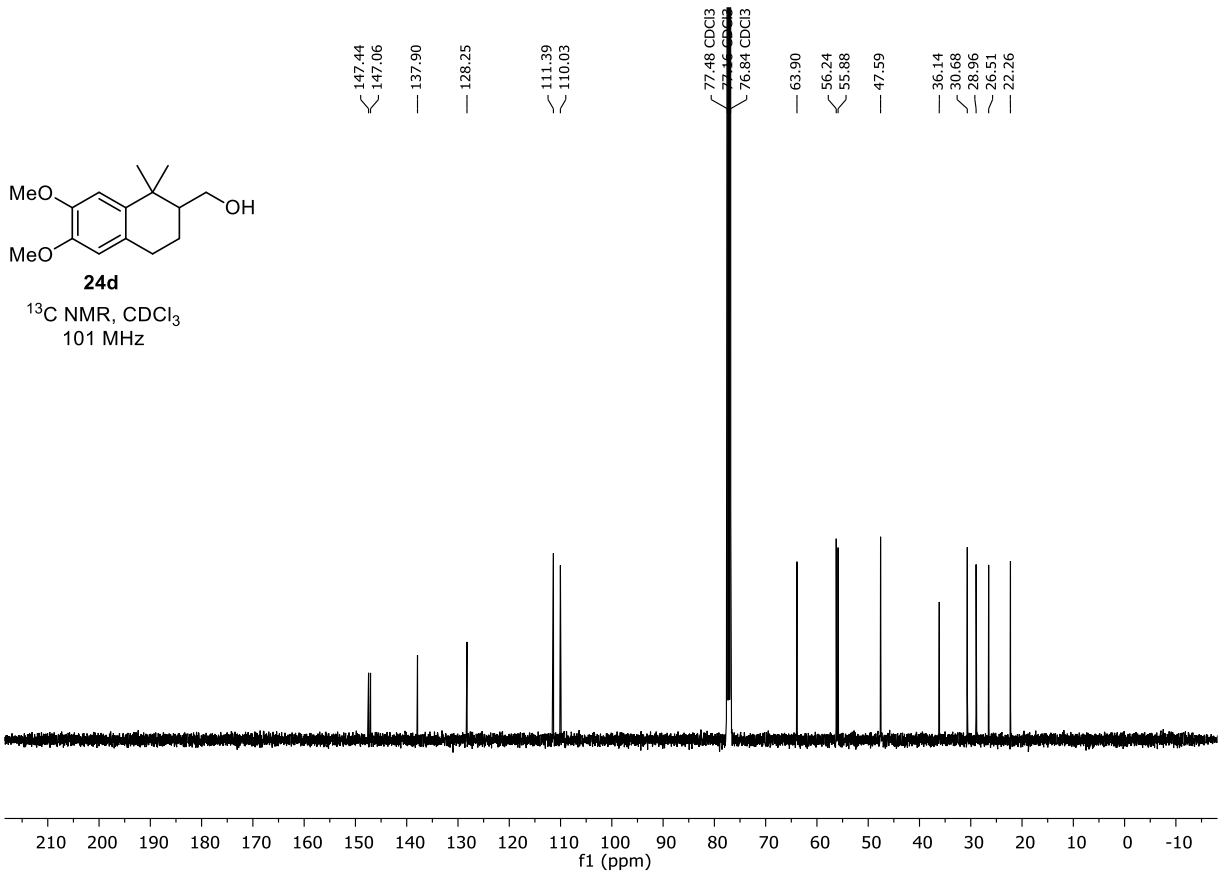
^{1}H NMR, $CDCl_3$
400 MHz

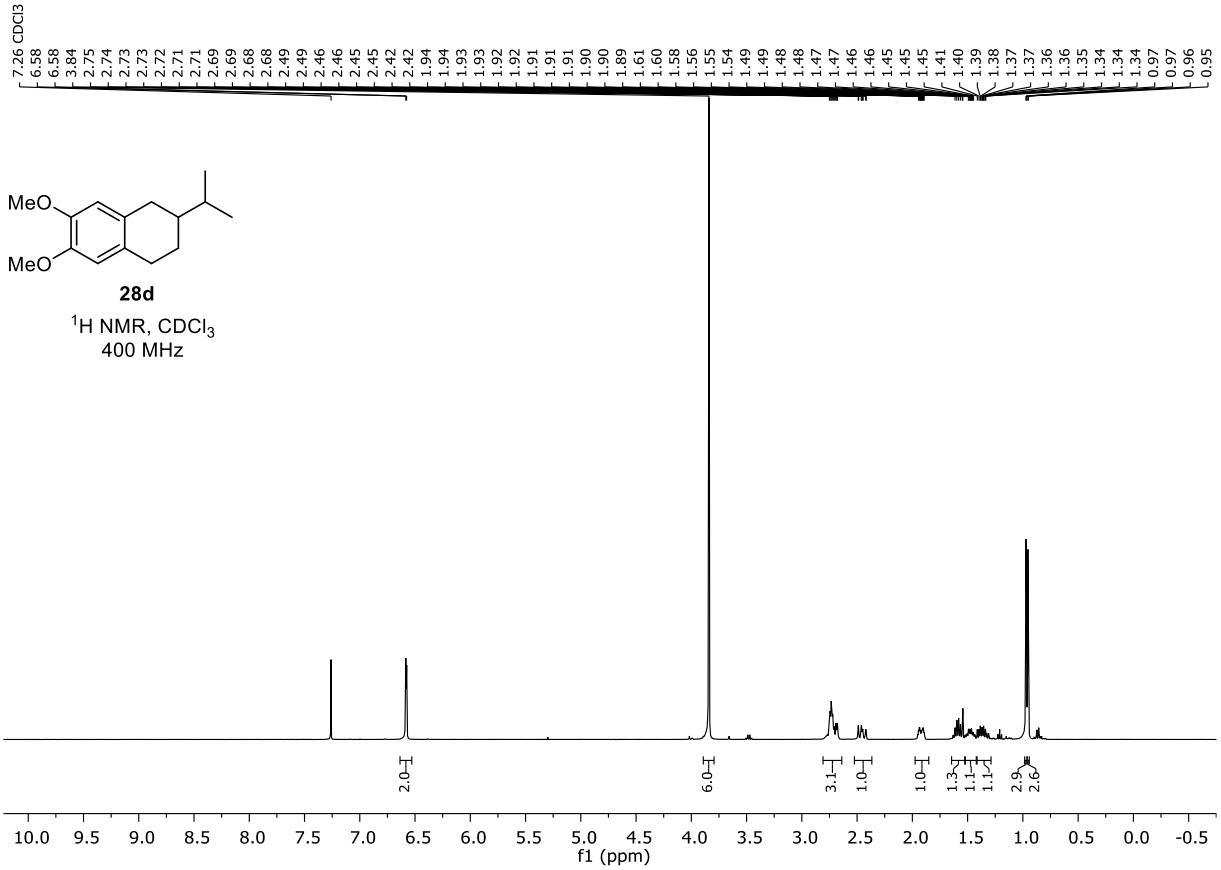


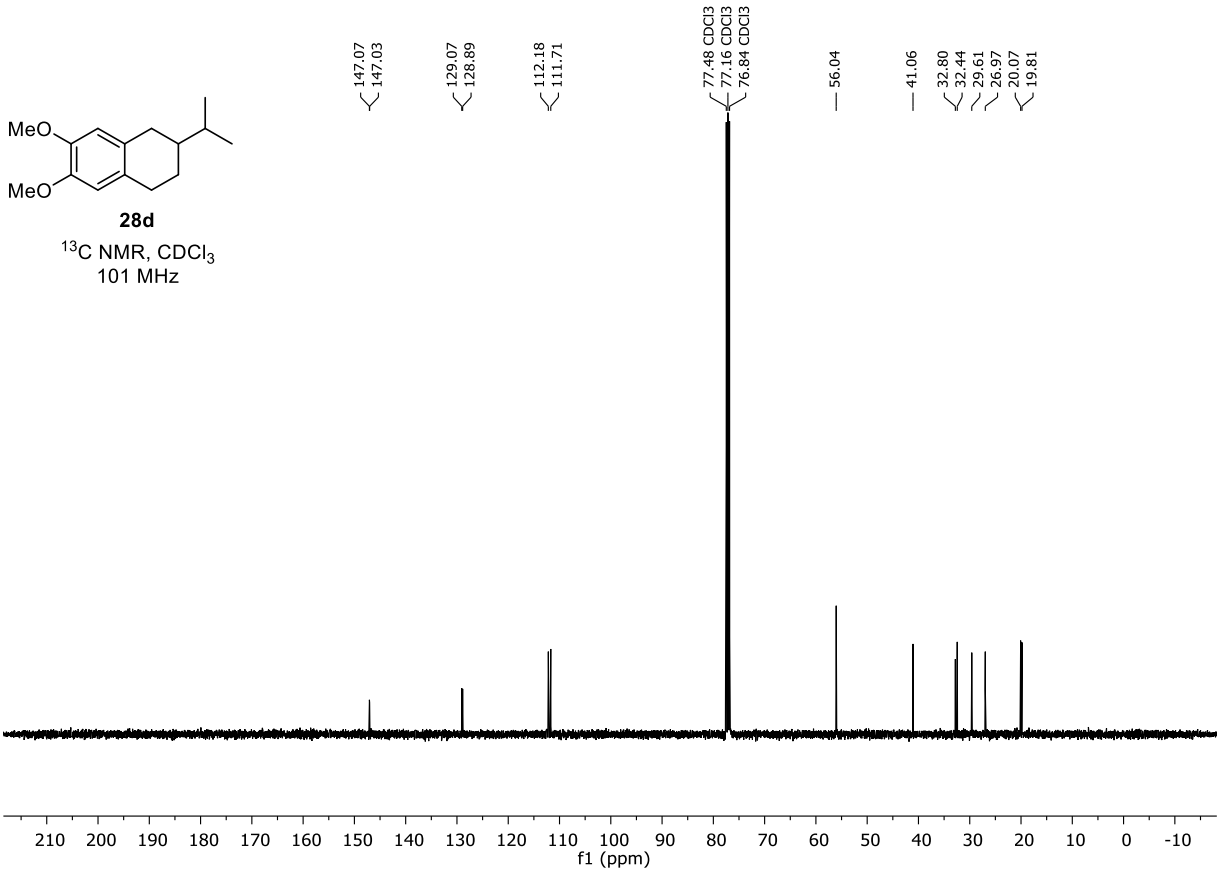
27c

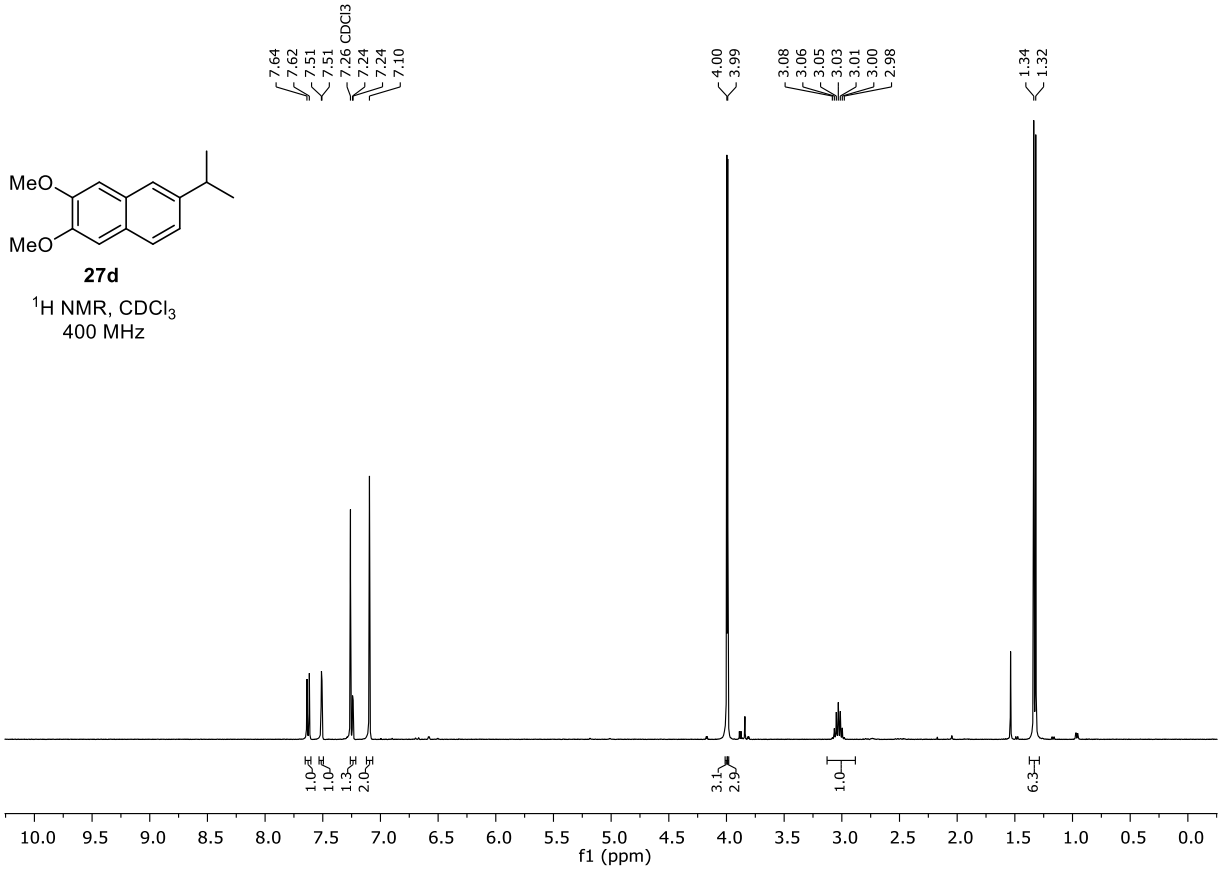
^{13}C NMR, $CDCl_3$
101 MHz


7.26 CDCl3
6.81
6.53
3.98
3.97
3.95
3.94
3.86
3.84
3.52
3.51
3.50
3.49
3.49
3.48
3.47
2.77
2.75
2.75
2.74
2.74
2.73
2.11
2.10
2.09
2.09
2.08
2.07
2.07
2.06
2.06
2.05
1.73
1.72
1.72
1.72
1.71
1.70
1.70
1.69
1.69
1.68
1.68
1.67
1.67
1.66
1.65
1.65
1.64
1.64
1.63
1.62
1.61
1.38
1.30
1.15
MeO
MeO
OH
24d
1H NMR, CDCl3
400 MHz
1.0
1.0
1.0
3.2
3.1
1.0
2.0
1.0
2.0
3.1
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)


147.44
147.06
137.90
128.25
111.39
110.03
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
63.90
56.24
55.88
47.59
36.14
30.68
28.96
26.51
22.26
MeO
MeO
OH
24d
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)

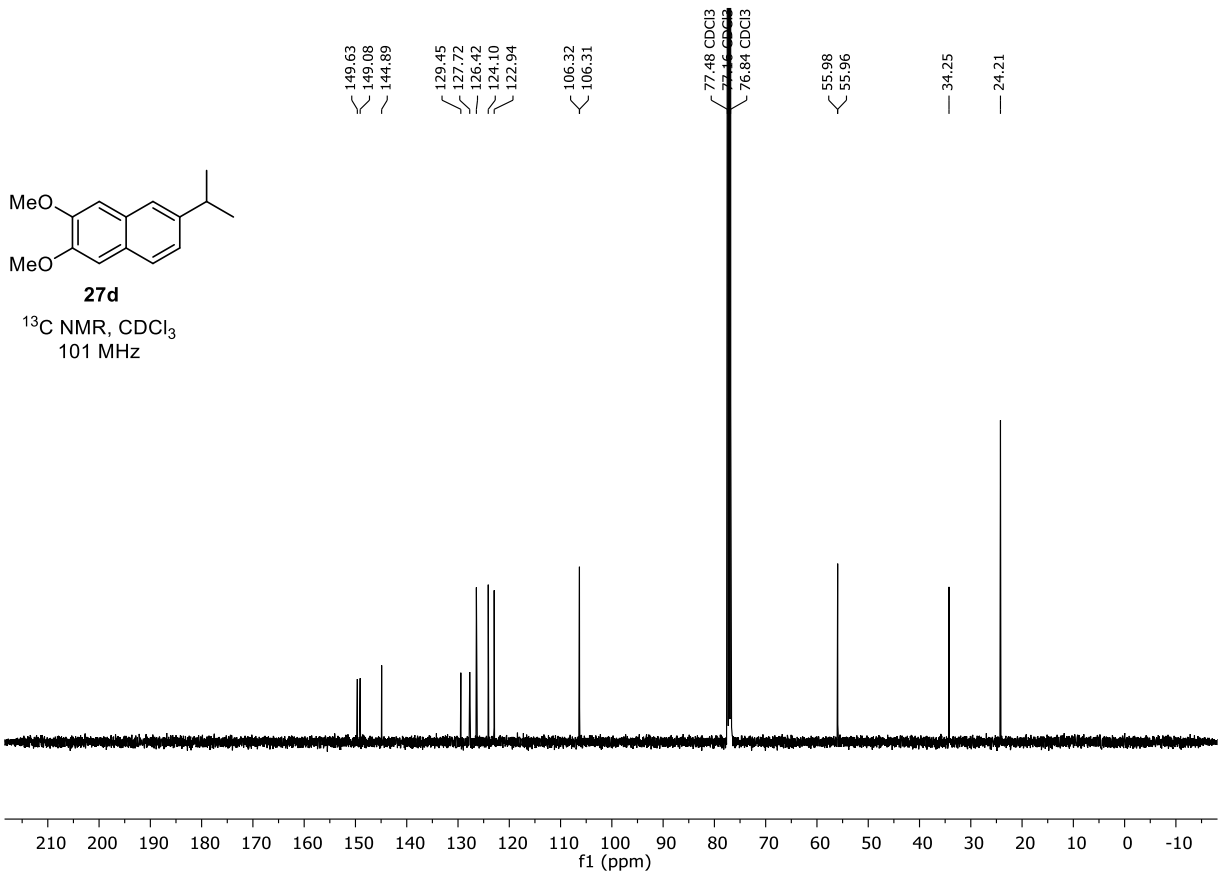

7.26 CDCl3
6.58
6.58
3.84
2.75
2.74
2.73
2.73
2.72
2.71
2.71
2.69
2.69
2.68
2.68
2.49
2.49
2.46
2.46
2.45
2.45
2.42
2.42
1.94
1.94
1.93
1.93
1.92
1.92
1.91
1.91
1.91
1.90
1.90
1.89
1.61
1.60
1.58
1.56
1.55
1.54
1.49
1.49
1.48
1.48
1.47
1.47
1.46
1.46
1.45
1.45
1.45
1.41
1.40
1.39
1.38
1.37
1.37
1.36
1.36
1.35
1.34
1.34
1.34
0.97
0.97
0.96
0.95
MeO
MeO
28d
1H NMR, CDCl3
400 MHz
2.0
6.0
3.1
1.0
1.0
1.3
1.1
1.1
2.9
2.6
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 -0.5
f1 (ppm)


147.07
147.03
129.07
128.89
112.18
111.71
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
56.04
41.06
32.80
32.44
29.61
26.97
20.07
19.81
MeO
MeO
28d
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)



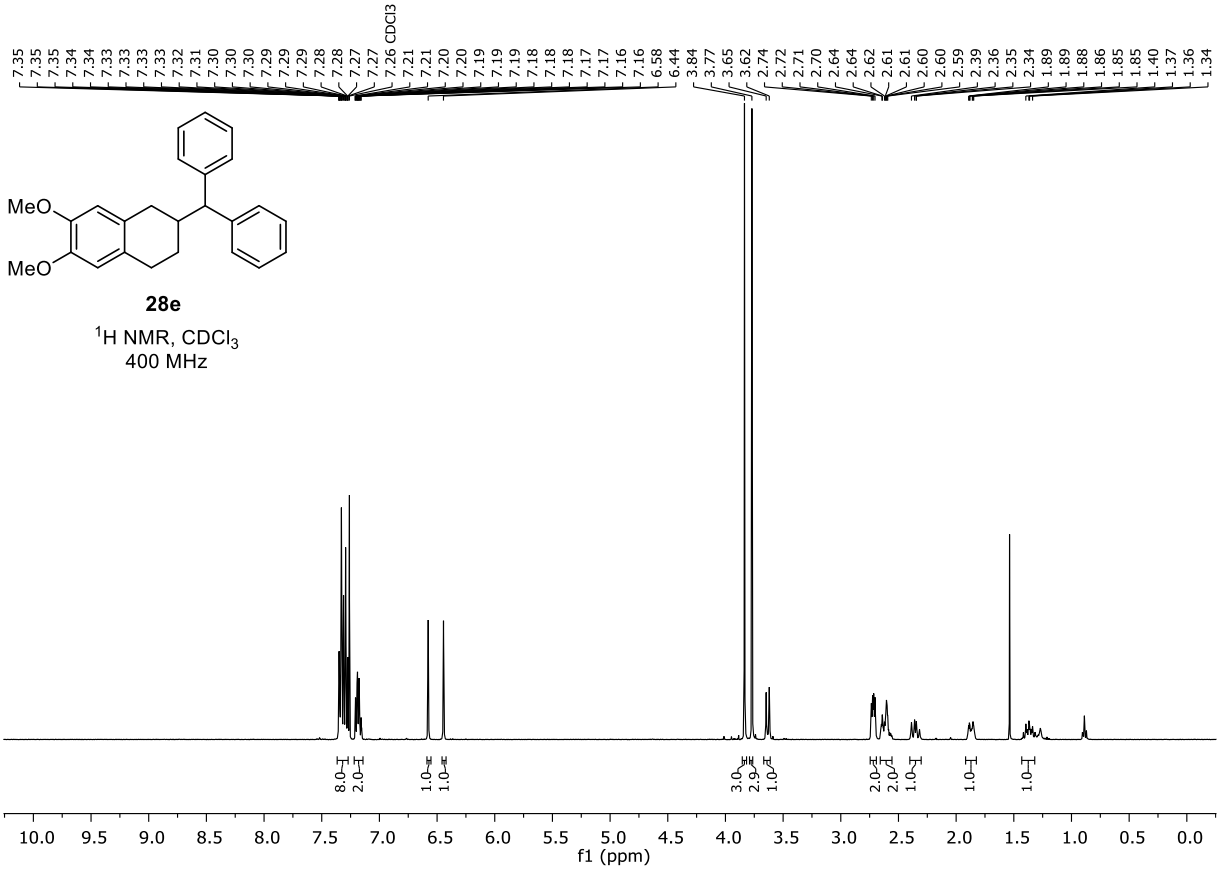
27d

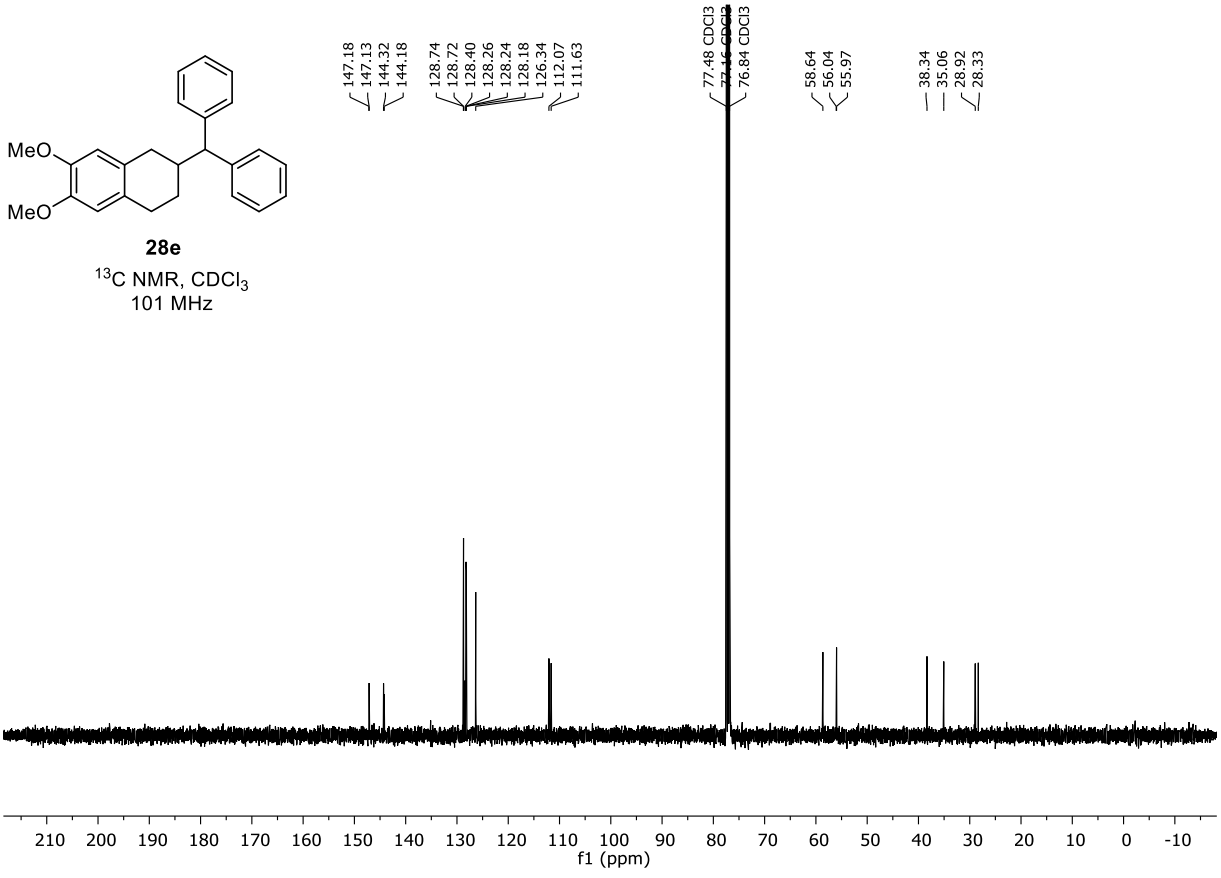
^{1}H NMR, $CDCl_3$
400 MHz

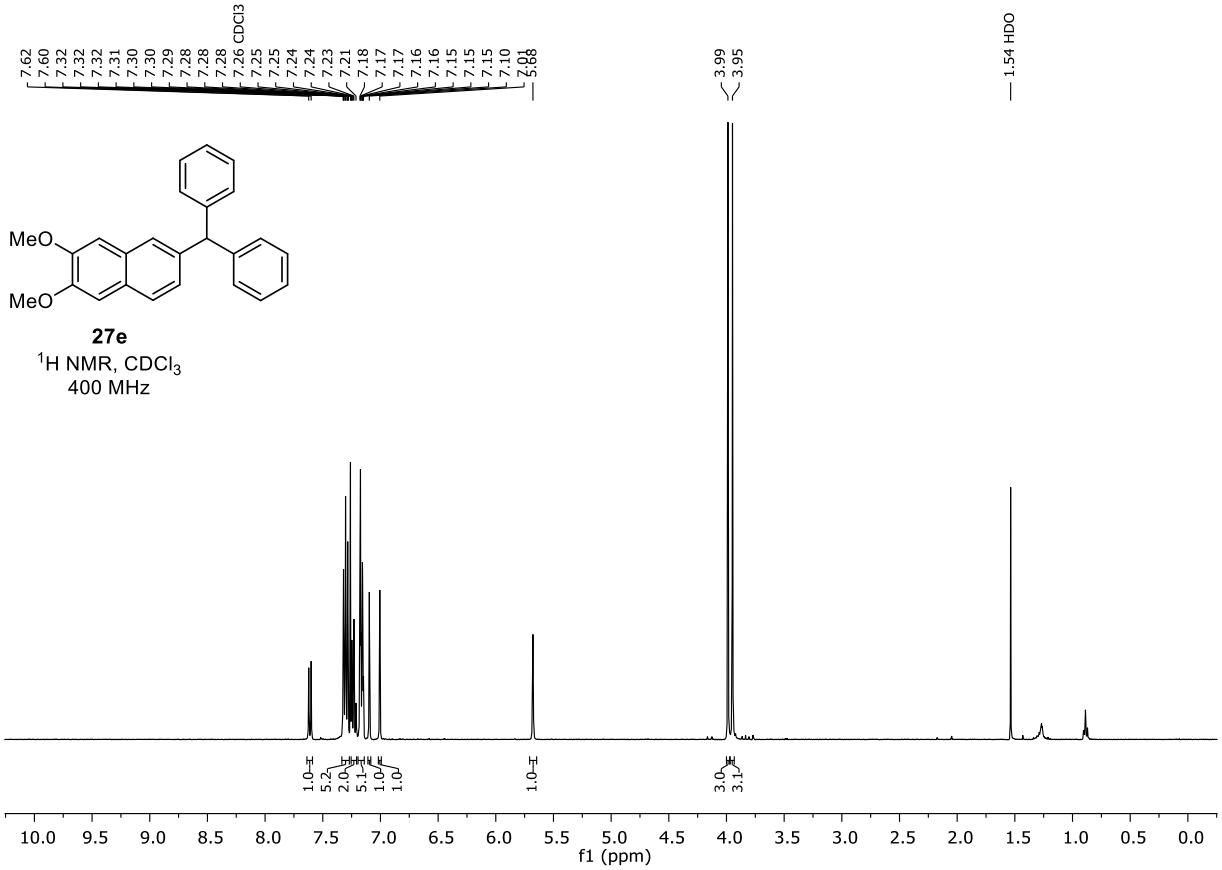


27d

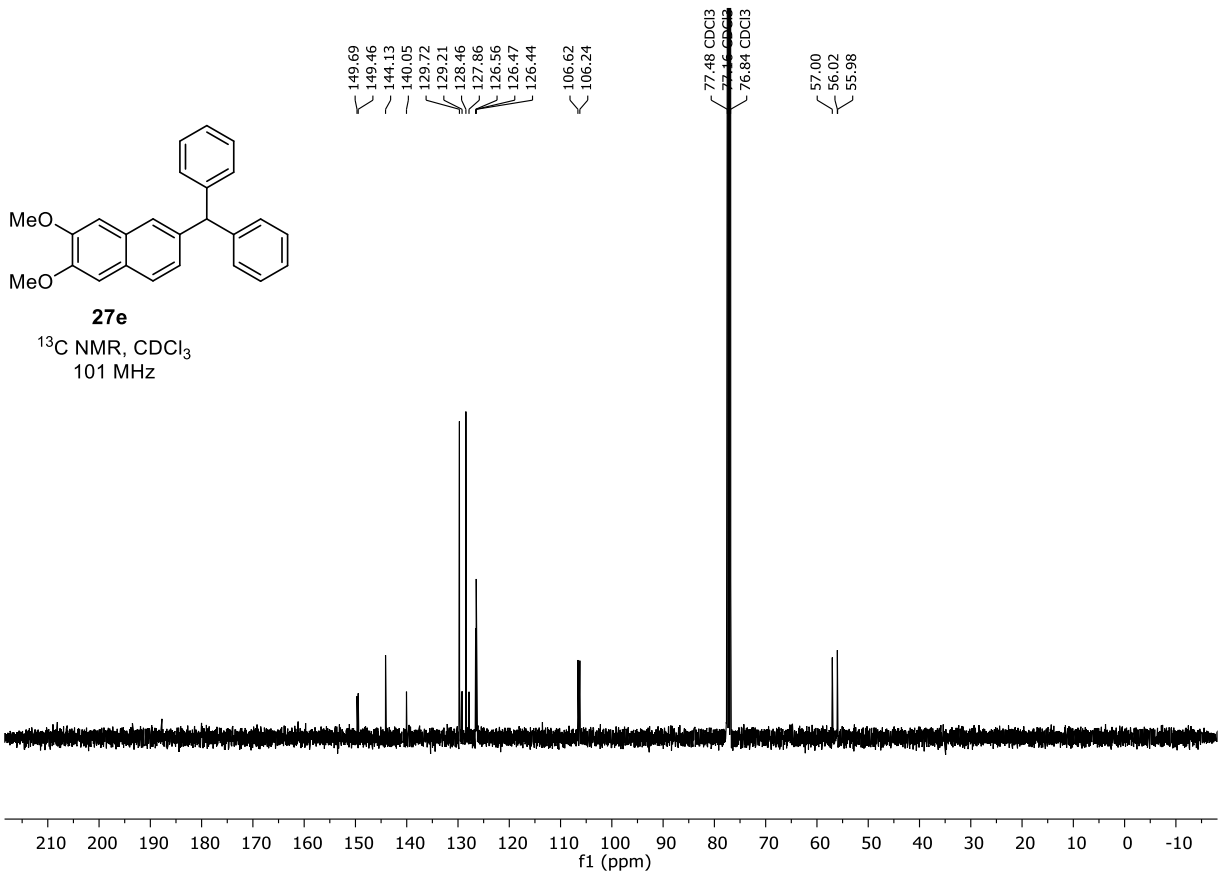
^{13}C NMR, $CDCl_3$
101 MHz


MeO
MeO
28e
1H NMR, CDCl3
400 MHz
f1 (ppm)

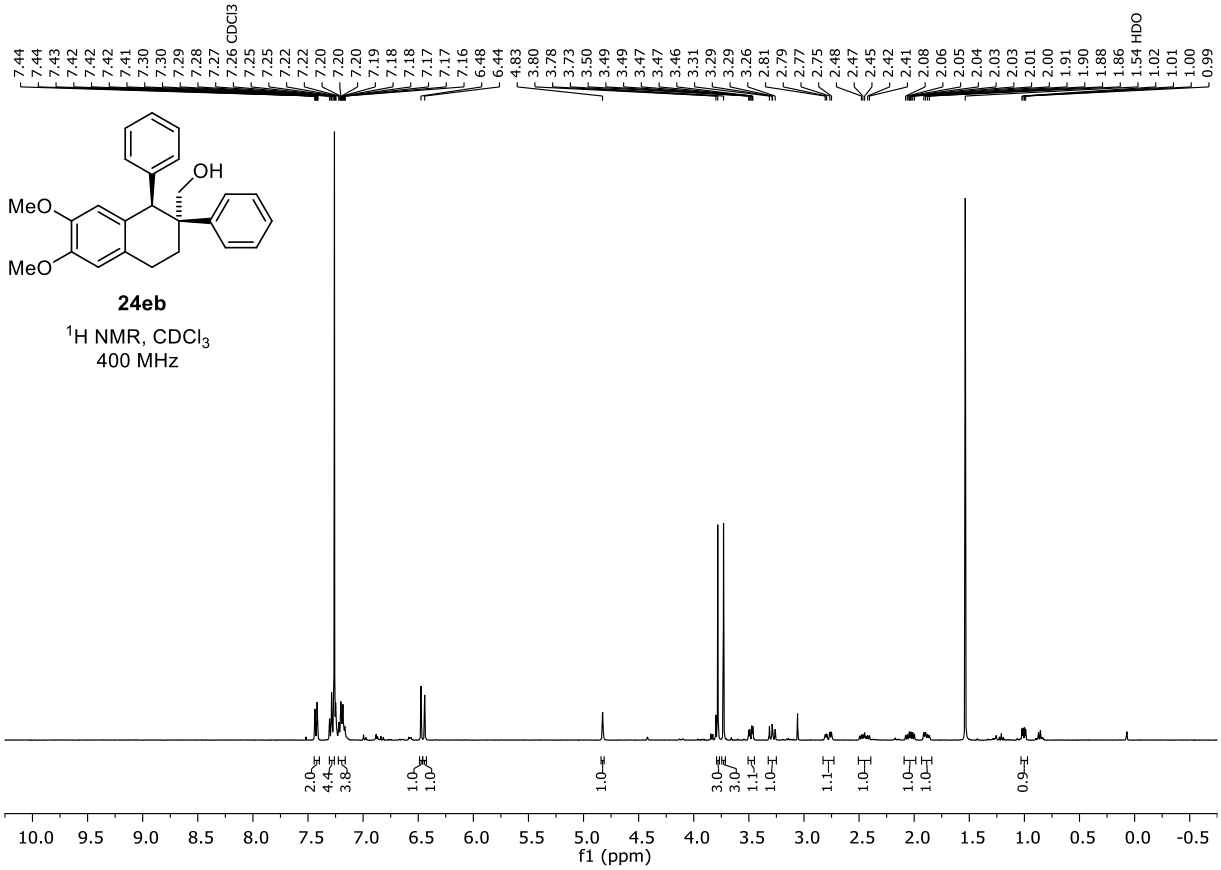

MeO
MeO
28e
13C NMR, CDCl3
101 MHz
f1 (ppm)

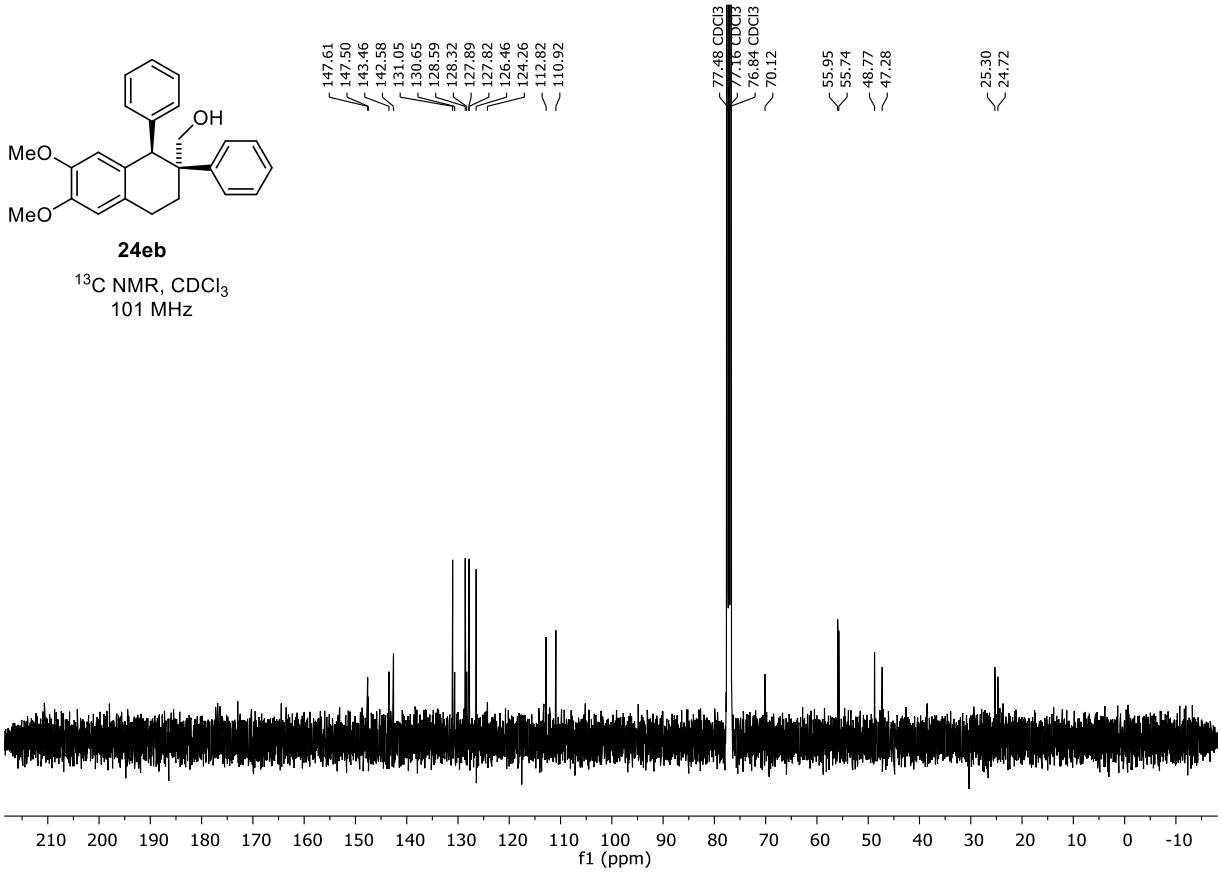


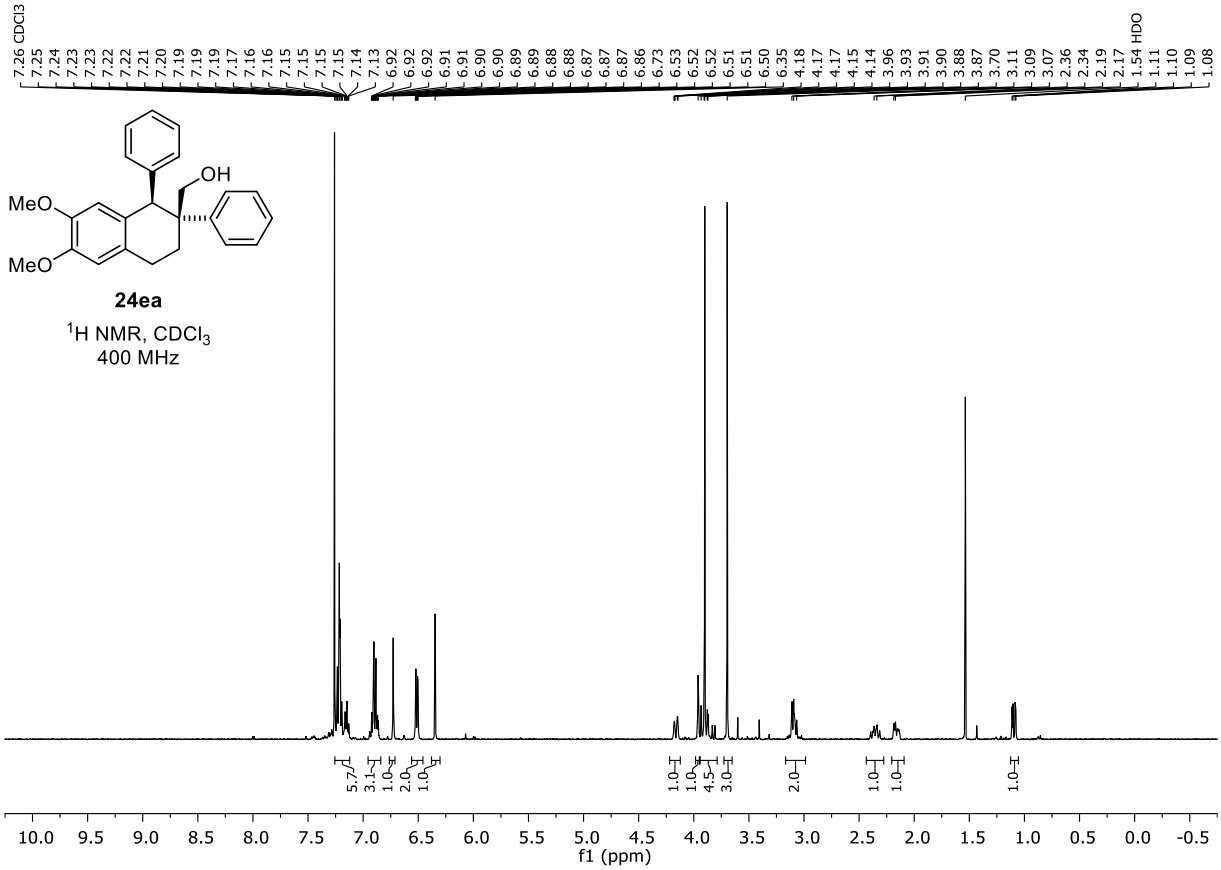
27e
^{1}H NMR, $CDCl_3$
400 MHz

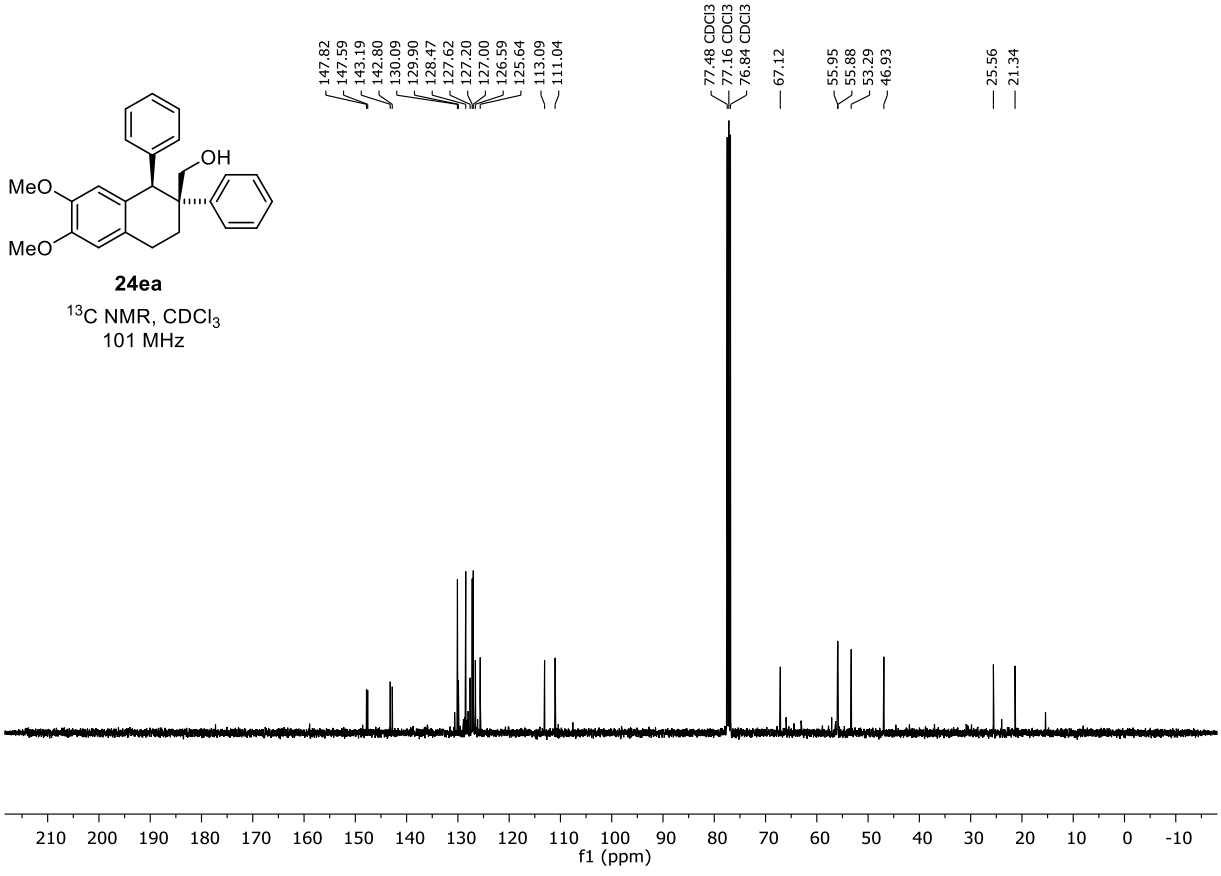


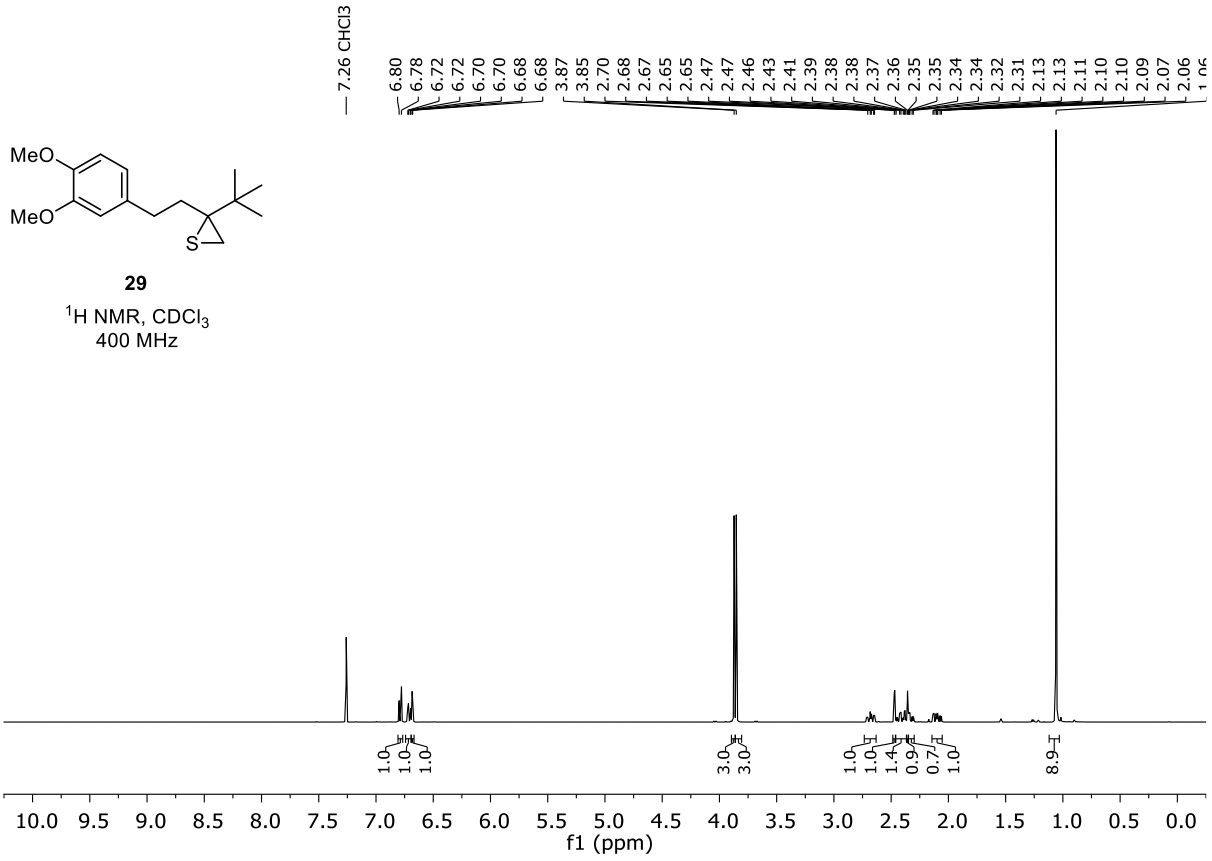
27e
^{13}C NMR, $CDCl_3$
101 MHz


OH
MeO
MeO
24eb
^{1}H NMR, $CDCl_3$
400 MHz
f1 (ppm)


OH
MeO
MeO
24eb
^{13}C NMR, $CDCl_3$
101 MHz
f1 (ppm)

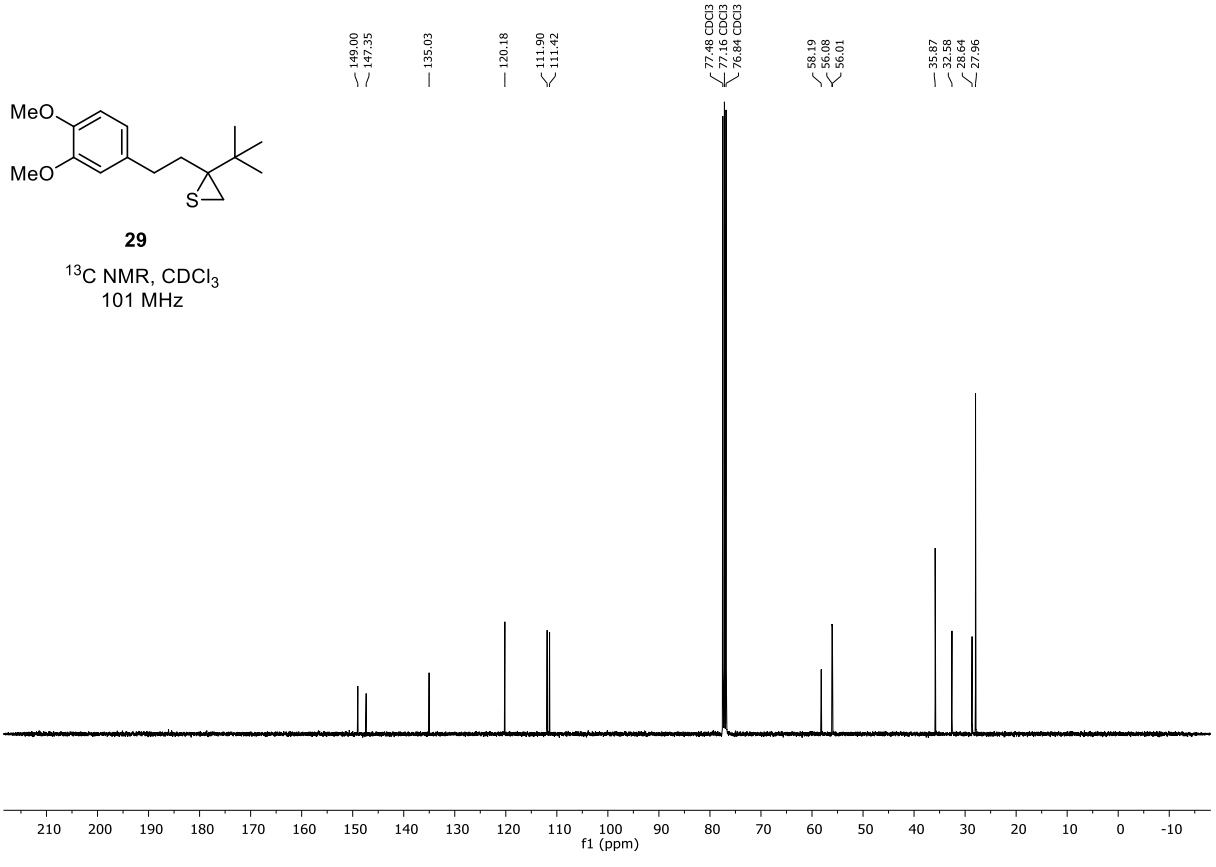

7.26 CDCl3
1.54 HDO
OH
MeO
MeO
24ea
1H NMR, CDCl3
400 MHz
f1 (ppm)


77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
OH
MeO
MeO
24ea
13C NMR, CDCl3
101 MHz
f1 (ppm)



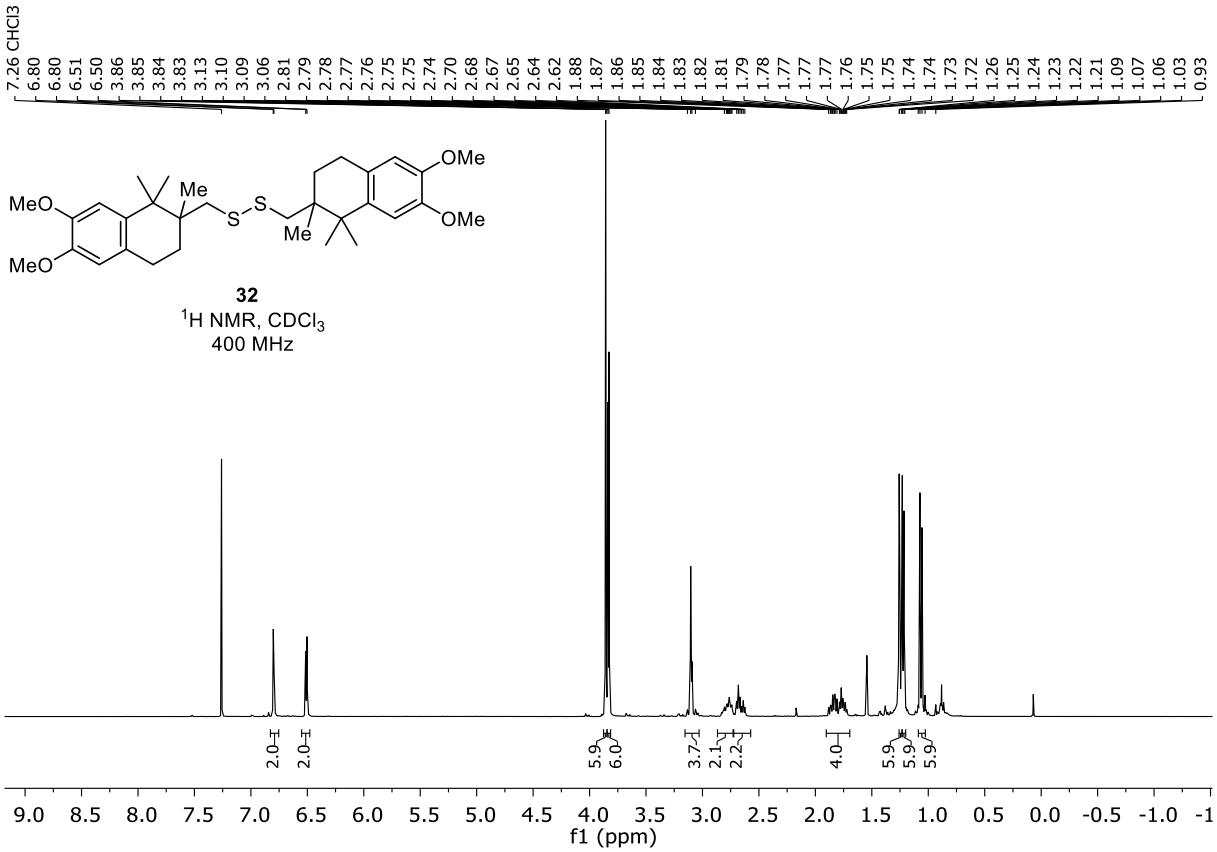
29

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



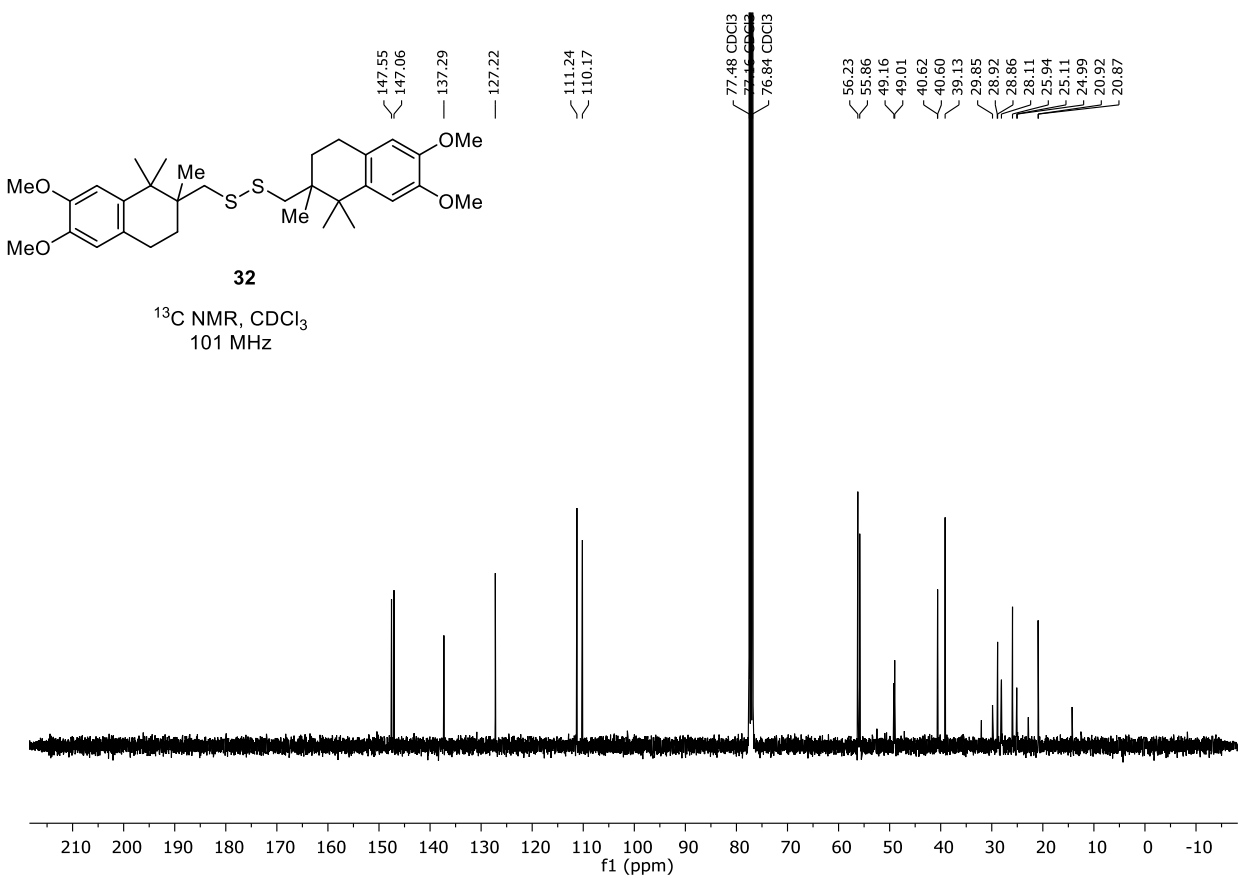
29

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



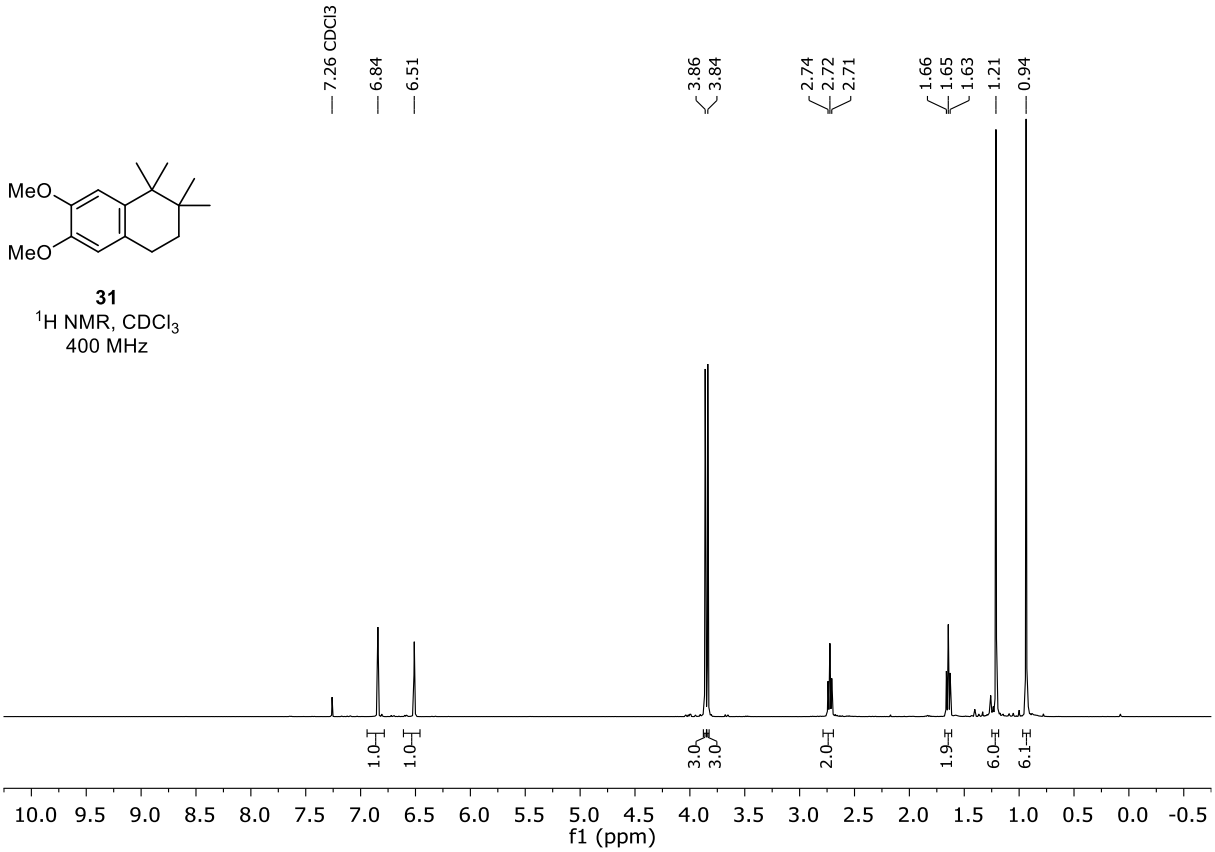
32

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

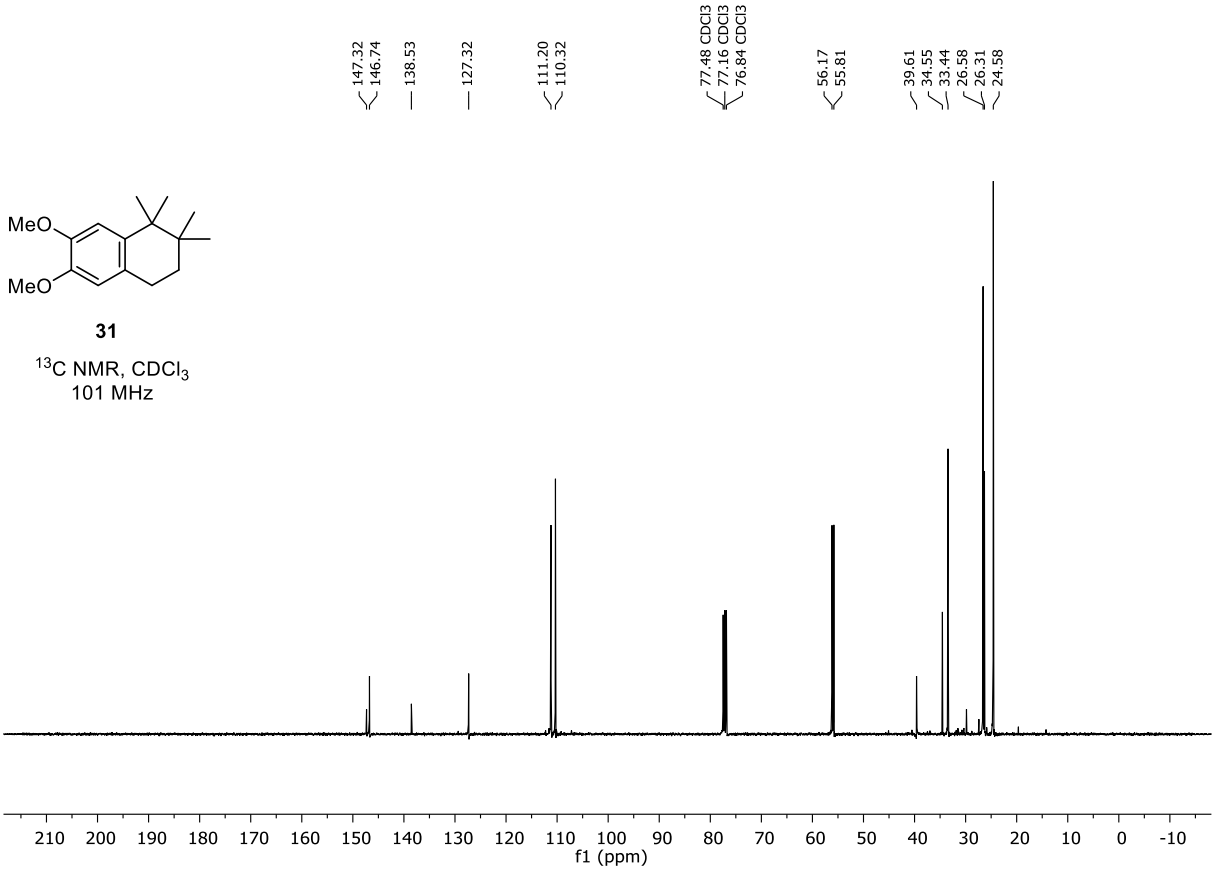


32

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



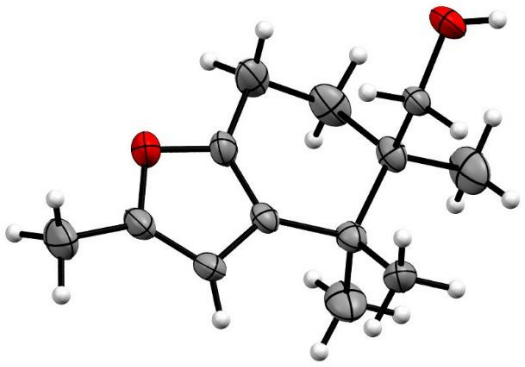
31
^{1}H NMR, $CDCl_3$
400 MHz



31
^{13}C NMR, $CDCl_3$
101 MHz

9.2.2.18 X-ray

Methylfuran (**12n**)



Identification code	mar19-24
Empirical formula	$C_{13}H_{20}O_2$
Formula weight	208.29
Temperature	183(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1 (no. 2)
Unit cell dimensions	a = 8.1230(4) Å α= 73.708(2)°. b = 10.0358(6) Å β= 85.670(2)°. c = 15.3076(9) Å γ = 81.399(2)°.
Volume	1183.57(12) $Å^3$
Z	4
Density (calculated)	1.169 Mg/m^3
Absorption coefficient	0.077 mm^{-1}
F(000)	456
Crystal size	0.180 x 0.120 x 0.060 mm^3
Theta range for data collection	2.133 to 24.998°.
Index ranges	-9 <= h <= 9, -11 <= k <=11, -18 <= l <= 18

Reflections collected	25848
Independent reflections	4169 [R(int) = 0.0332]
Completeness to theta = 24.998°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.977 and 0.962
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4169 / 4 / 290
Goodness-of-fit on F^2	1.031
Final R indices [I>2sigma(I)]	R1 = 0.0421, wR2 = 0.1086
R indices (all data)	R1 = 0.0514, wR2 = 0.1136
Extinction coefficient	0.026(3)
Largest diff. peak and hole	0.273 and -0.190 e.$Å^{-3}$

The structure was deposited in the Cambridge Crystallographic Data Center (CCDC) – deposition number 2010932.

Klicken oder tippen Sie hier, um Text einzugeben.

10 References

[1] Editorial, *Nature Chemical Biology* **2007**, *3*, 351-351.

[2] P. M. Dewick, *Medicinal natural products: a biosynthetic approach*, 3rd edition. ed., Wiley, Chichester, West Sussex, England; New York, NY, USA, **2009**.

[3] M. C. Gordon, J. N. David, *Pure Appl. Chem.* **2005**, *77*, 7-24.

[4] R. B. Woodward, J. Z. Gougoutas, *J. Am. Chem. Soc.* **1964**, *86*, 5030-5030.

[5] A. Furusaki, Y. Tomiie, I. Nitta, *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3332-3341.

[6] D. A. Dias, S. Urban, U. Roessner, *Metabolites* **2012**, *2*.

[7] G. M. Cragg, D. J. Newman, K. M. Snader, *J. Nat. Prod.* **1997**, *60*, 52-60.

[8] D.-X. Kong, Y.-Y. Jiang, H.-Y. Zhang, *Drug Discov. Today* **2010**, *15*, 884-886.

[9] M. H. G. Munro, J. W. Blunt, E. J. Dumdei, S. J. H. Hickford, R. E. Lill, S. Li, C. N. Battershill, A. R. Duckworth, *J. Biotechnol.* **1999**, *70*, 15-25.

[10] W. G. Gribble, *Mar. Drugs* **2015**, *13*.

[11] G. W. Gribble, in *Naturally Occurring Organohalogen Compounds - A Comprehensive Update* (Ed.: G. W. Gribble), Springer Vienna, Vienna, **2010**, pp. 1-1.

[12] H. M. Senn, *Frontiers in Chemistry* **2014**, *2*, 98.

[13] A. S. Eustáquio, R. P. McGlinchey, Y. Liu, C. Hazzard, L. L. Beer, G. Florova, M. M. Alhamadsheh, A. Lechner, A. J. Kale, Y. Kobayashi, K. A. Reynolds, B. S. Moore, *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106*, 12295.

[14] K. Kaur, V. Kumar, A. K. Sharma, G. K. Gupta, *Eur. J. Med. Chem.* **2014**, *77*, 121-133.

[15] J. M. Winter, B. S. Moore, *J. Biol. Chem.* **2009**, *284*, 18577-18581.

[16] L. C. Blasiak, F. H. Vaillancourt, C. T. Walsh, C. L. Drennan, *Nature* **2006**, *440*, 368-371.

[17] J. Peng, J. Li, M. T. Hamann, *Alkaloids Chem Biol* **2005**, *61*, 59-262.

[18] M. Rotem, S. Carmely, Y. Kashman, Y. Loya, *Tetrahedron* **1983**, *39*, 667-676.

[19] K. Moody, R. H. Thomson, E. Fattorusso, L. Minale, G. Sodano, *J. Chem. Soc., Perkin Trans. 1* **1972**, 18-24.

[20] Y. Gopichand, F. J. Schmitz, *Tetrahedron Lett.* **1979**, *20*, 3921-3924.

[21] D. M. Roll, C. W. J. Chang, P. J. Scheuer, G. A. Gray, J. N. Shoolery, G. K. Matsumoto, G. D. Van Duyne, J. Clardy, *J. Am. Chem. Soc.* **1985**, *107*, 2916-2920.

[22] A. D. Wright, P. J. Schupp, J.-P. Schrör, A. Engemann, S. Rohde, D. Kelman, N. de Voogd, A. Carroll, C. A. Motti, *J. Nat. Prod.* **2012**, *75*, 502-506.

[23] J. A. McMillan, I. C. Paul, Y. M. Goo, K. L. Rinehart, W. C. Krueger, L. M. Pschigoda, *Tetrahedron Lett.* **1981**, *22*, 39-42.

[24] P. Ciminiello, V. Costantino, E. Fattorusso, S. Magno, A. Mangoni, M. Pansini, *J. Nat. Prod.* **1994**, *57*, 705-712.

[25] P. Ciminiello, E. Fattorusso, M. Forino, S. Magno, M. Pansini, *Tetrahedron* **1997**, *53*, 6565-6572.

[26] A. Mándi, I. W. Mudianta, T. Kurtán, M. J. Garson, *J. Nat. Prod.* **2015**, *78*, 2051-2056.

[27] I. W. Mudianta, T. Skinner-Adams, K. T. Andrews, R. A. Davis, T. A. Hadi, P. Y. Hayes, M. J. Garson, *J. Nat. Prod.* **2012**, *75*, 2132-2143.

[28] Y.-J. Lee, S. Han, H.-S. Lee, J. S. Kang, J. Yun, C. J. Sim, H. J. Shin, J. S. Lee, *J. Nat. Prod.* **2013**, *76*, 1731-1736.

[29] M. Xu, K. T. Andrews, G. W. Birrell, T. L. Tran, D. Camp, R. A. Davis, R. J. Quinn, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 846-848.

[30] X. Yang, R. A. Davis, M. S. Buchanan, S. Duffy, V. M. Avery, D. Camp, R. J. Quinn, *J. Nat. Prod.* **2010**, *73*, 985-987.

[31] B. R. Copp, C. M. Ireland, L. R. Barrows, *J. Nat. Prod.* **1992**, *55*, 822-823.

[32] S. Liu, X. Fu, F. J. Schmitz, M. Kelly-Borges, *J. Nat. Prod.* **1997**, *60*, 614-615.

[33] D. M. Ramsey, M. Amirul Islam, L. Turnbull, R. A. Davis, C. B. Whitchurch, S. R. McAlpine, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4862-4866.

[34] T. Ichiba, P. J. Scheuer, M. Kelly-Borges, *J. Org. Chem.* **1993**, *58*, 4149-4150.

[35] A. L. Shaala, T. A. D. Youssef, *Biomolecules* **2019**, *9*.

[36] S. Tsukamoto, H. Kato, H. Hirota, N. Fusetani, *Tetrahedron* **1996**, *52*, 8181-8186.

[37] S.-i. Kurimoto, T. Ohno, R. Hokari, A. Ishiyama, M. Iwatsuki, S. Ōmura, J. i. Kobayashi, T. Kubota, *Mar. Drugs* **2018**, *16*.

[38] W.-H. Jiao, J. Li, M.-M. Zhang, J. Cui, Y.-H. Gui, Y. Zhang, J.-Y. Li, K.-C. Liu, H.-W. Lin, *Org. Lett.* **2019**.

[39] X. Xu, W.-H. Hu, P. Y. Zavalij, M. P. Doyle, *Angew. Chem. Int. Ed.* **2011**, *50*, 11152-11155.

[40] L. A. Shaala, D. T. A. Youssef, J. M. Badr, M. Sulaiman, A. Khedr, K. A. El Sayed, *Tetrahedron* **2015**, *71*, 7837-7841.

[41] K. E. Christen, R. A. Davis, D. Kennedy, *Int. J. Biochem. Cell Biol.* **2019**.

[42] J. M. Badr, L. A. Shaala, M. I. Abou-Shoer, M. K. Tawfik, A.-A. M. Habib, *J. Nat. Prod.* **2008**, *71*, 1472-1474.

[43] B. R. Bhattarai, B. Kafle, J.-S. Hwang, D. Khadka, S.-M. Lee, J.-S. Kang, S. W. Ham, I.-O. Han, H. Park, H. Cho, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6161-6165.

[44] M. S. Malamas, J. Sredy, C. Moxham, A. Katz, W. Xu, R. McDevitt, F. O. Adebayo, D. R. Sawicki, L. Seestaller, D. Sullivan, J. R. Taylor, *J. Med. Chem.* **2000**, *43*, 1293-1310.

[45] F. Hentschel, T. Lindel, *Synthesis* **2010**, 181-204.

[46] E. W. Rogers, T. F. Molinski, *J. Nat. Prod.* **2007**, *70*, 1191-1194.

[47] N. Neuss, R. Nagarajan, B. B. Molloy, L. L. Huckstep, *Tetrahedron Lett.* **1968**, *9*, 4467-4471.

[48] D. R. Brannon, J. A. Mabe, B. B. Molloy, W. A. Day, *Biochem. Biophys. Res. Commun.* **1971**, *43*, 588-594.

[49] K. T. Okamoto, J. Clardy, *Tetrahedron Lett.* **1987**, *28*, 4969-4972.

[50] J. E. Stok, S. Chow, E. H. Krenske, C. Farfan Soto, C. Matyas, R. A. Poirier, C. M. Williams, J. J. De Voss, *Chem. Eur. J.* **2016**, *22*, 4408-4412.

[51] K. Ragini, J. Fromont, A. M. Piggott, P. Karuso, *J. Nat. Prod.* **2017**.

[52] Z. Ma, X. Wang, X. Wang, R. A. Rodriguez, C. E. Moore, S. Gao, X. Tan, Y. Ma, A. L. Rheingold, P. S. Baran, C. Chen, *Science* **2014**, *346*, 219.

[53] M. Smietana, V. Gouverneur, C. Mioskowski, *Tetrahedron Lett.* **1999**, *40*, 1291-1294.

[54] P. Das, A. O. Omollo, L. J. Sitole, E. McClendon, E. J. Valente, D. Raucher, L. R. Walker, A. T. Hamme Ii, *Tetrahedron Lett.* **2015**, *56*, 1794-1797.

[55] P. A. Colinas, V. Jäger, A. Lieberknecht, R. D. Bravo, *Tetrahedron Lett.* **2003**, *44*, 1071-1074.

[56] J. S. Carlson, University of California, Irvine (Irvine), **2015**.

[57] K.-H. Hellwich, *Angew. Chem.* **2002**, *114*, 4073-4089.

[58] J. Clayden, N. Greeves, S. Warren, *Organic Chemistry*, OUP Oxford, **2012**.

[59] D. M. Jones, N. F. Wood, *J. Chem. Soc. (Resumed)* **1964**, 5400-5403.

[60] M. Riediker, J. Schwartz, *J. Am. Chem. Soc.* **1982**, *104*, 5842-5844.

[61] N. Ullah, *Z. Naturforsch., B: J. Chem. Sci.* **2009**, *64*, 879-882.

[62] D. C. Harrowven, D. D. Pascoe, I. L. Guy, *Angew. Chem. Int. Ed.* **2007**, *46*, 425-428.

[63] B. Zhu, H. Zhang, S. Pan, C. Wang, J. Ge, J.-S. Lee, S. Q. Yao, *Chem. Eur. J.* **2016**, *22*, 7824-7836.

[64] F. Machetti, L. Cecchi, E. Trogu, F. De Sarlo, *Eur. J. Org. Chem.* **2007**, *2007*, 4352-4359.

[65] L. Cecchi, F. De Sarlo, F. Machetti, *Eur. J. Org. Chem.* **2006**, *2006*, 4852-4860.

[66] J. A. Kenar, *Journal of the J. Am. Oil Chem.' Soc* **2003**, *80*, 1027-1032.

[67] I. V. Sazanovich, A. Balakumar, K. Muthukumaran, E. Hindin, C. Kirmaier, J. R. Diers, J. S. Lindsey, D. F. Bocian, D. Holten, *Inorg. Chem.* **2003**, *42*, 6616-6628.

[68] J. S. Yadav, E. S. Rao, *Synth. Commun.* **1988**, *18*, 2315-2323.

[69] M. R. Sivik, John, Bromoform, **2001**.

[70] K. T. Wanner, *Arch. Pharm.* **1988**, *321*, 81-83.

[71] J. H. Wotiz, *J. Am. Chem. Soc.* **1950**, *72*, 1639-1642.

[72] J. Ramharter, J. Mulzer, *Org. Lett.* **2009**, *11*, 1151-1153.

[73] J. E. Baldwin, *J. Chem. Soc., Chem. Commun.* **1976**, 734-736.

[74] A. L. J. Beckwith, D. M. O'Shea, *Tetrahedron Lett.* **1986**, *27*, 4525-4528.

[75] N. Kornblum, W. J. Jones, G. J. Anderson, *J. Am. Chem. Soc.* **1959**, *81*, 4113-4114.

[76] P. A. Grieco, S. Gilman, M. Nishizawa, *J. Org. Chem.* **1976**, *41*, 1485-1486.

[77] S. Wolff, M. E. Huecas, W. C. Agosta, *J. Org. Chem.* **1982**, *47*, 4358-4359.

[78] R. Kiwus, W. Schwarz, I. Rossnagel, H. Musso, *Chem. Ber.* **1987**, *120*, 435-438.

[79] M. Nomura, Y. Fujihara, *Yukagaku* **1987**, *36*, 515-518.

[80] E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida, C. S. Shiner, *Tetrahedron Lett.* **1975**, *16*, 3183-3186.

[81] R. Noel, V. Gembus, V. Levacher, J. F. Briere, *Org. Biomol. Chem.* **2014**, *12*, 1245-1249.

[82] P. Righi, E. Marotta, A. Landuzzi, G. Rosini, *J. Am. Chem. Soc.* **1996**, *118*, 9446-9447.

[83] W. Schwab, V. Jäger, *Angew. Chem.* **1981**, *93*, 578-579.

[84] E. Marotta, M. Baravelli, L. Maini, P. Righi, G. Rosini, *J. Org. Chem.* **1998**, *63*, 8235-8246.

[85] H. Jiang, P. Elsner, K. L. Jensen, A. Falcicchio, V. Marcos, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2009**, *48*, 6844-6848.

[86] G. Rosini, E. Marotta, P. Righi, J. P. Seerden, *J. Org. Chem.* **1991**, *56*, 6258-6260.

[87] E. Marotta, L. M. Micheloni, N. Scardovi, P. Righi, *Org. Lett.* **2001**, *3*, 727-729.

[88] F. A. Davis, A. Kumar, R. E. Reddy, B. C. Chen, P. A. Wade, S. W. Shah, *J. Org. Chem.* **1993**, *58*, 7591-7593.

[89] S. Sheng, W. Sheng, Q. Hu, H. Qu, M. Cai, *J. Heterocycl. Chem.* **2014**, *51*, 315-321.

[90] Y. I. Kheruze, V. A. Galishev, A. A. Petrov, *Zh. Org. Khim.* **1988**, *24*, 944-949.

[91] R. Annunziata, M. Cinquini, F. Cozzi, L. Raimondi, *Tetrahedron* **1986**, *42*, 2129-2134.

[92] V. Jaeger, D. Schroeter, *Synthesis* **1990**, 556-560.

[93] P. S. Starcher, B. Phillips, *J. Am. Chem. Soc.* **1958**, *80*, 4079-4082.

[94] V. Valerio, D. Petkova, C. Madelaine, N. Maulide, *Chem. Eur. J.* **2013**, *19*, 2606-2610.

[95] M. Inui, A. Nakazaki, S. Kobayashi, *Org. Lett.* **2007**, *9*, 469-472.

[96] A. Corma, M. T. Navarro, L. Nemeth, M. Renz, *Chem. Commun.* **2001**, 2190-2191.

[97] O. N. Zefirova, E. V. Nurieva, V. N. Nuriev, K. A. Potekhin, A. V. Maleev, N. V. Zyk, N. S. Zefirov, *Mendeleev Commun.* **2007**, *17*, 332-334.

[98] S. W. Baldwin, J. D. Wilson, J. Aube, *J. Org. Chem.* **1985**, *50*, 4432-4439.

[99] R. Pappo, J. D. S. Allen, R. U. Lemieux, W. S. Johnson, *J. Org. Chem.* **1956**, *21*, 478-479.

[100] M. Ebine, Y. Suga, H. Fuwa, M. Sasaki, *Org. Biomol. Chem.* **2010**, *8*, 39-42.

[101] K. R. Anderson, S. L. G. Atkinson, T. Fujiwara, M. E. Giles, T. Matsumoto, E. Merifield, J. T. Singleton, T. Saito, T. Sotoguchi, J. A. Tornos, E. L. Way, *Org. Process Res. Dev.* **2010**, *14*, 58-71.

[102] A. Boschi, C. Chiappe, A. De Rubertis, M. F. Ruasse, *J. Org. Chem.* **2000**, *65*, 8470-8477.

[103] J. E. Milne, K. Jarowicki, P. J. Kocienski, *Synlett* **2002**, 607-609.

[104] K. C. Nicolaou, R. Yu, L. Shi, Q. Cai, M. Lu, P. Heretsch, *Org. Lett.* **2013**, *15*, 1994-1997.

[105] T. Wildman, P. J. Kocienski, R. Narquizian, W. G. Whittingham, *Synthesis* **2002**, 393-398.

[106] K. C. Nicolaou, G. Q. Shi, J. L. Gunzner, P. Gärtner, Z. Yang, *J. Am. Chem. Soc.* **1997**, *119*, 5467-5468.

[107] J. A. Ragan, T. W. Makowski, D. J. am Ende, P. J. Clifford, G. R. Young, A. K. Conrad, S. A. Eisenbeis, *Org. Process Res. Dev.* **1998**, *2*, 379-381.

[108] M. A. Endoma, V. P. Bui, J. Hansen, T. Hudlicky, *Org. Process Res. Dev.* **2002**, *6*, 525-532.

[109] L. W. Hernandez, J. Pospech, U. Klöckner, T. W. Bingham, D. Sarlah, *J. Am. Chem. Soc.* **2017**, *139*, 15656-15659.

[110] M. G. Quintana, H. Dalton, *Enzyme Microb. Technol.* **1999**, *24*, 232-236.

[111] J. A. Collins, C. J. Gerry, M. M. Duncan, *Synlett* **2019**, *30*, 2193-2197.

[112] E. H. Southgate, J. Pospech, J. Fu, D. R. Holycross, D. Sarlah, *Nature Chemistry* **2016**, *8*, 922-928.

[113] E. J. Corey, J. P. Dittami, *J. Am. Chem. Soc.* **1985**, *107*, 256-257.

[114] J. N. Haseltine, M. Paz Cabal, N. B. Mantlo, N. Iwasawa, D. S. Yamashita, R. S. Coleman, S. J. Danishefsky, G. K. Schulte, *J. Am. Chem. Soc.* **1991**, *113*, 3850-3866.

[115] G. B. Payne, *J. Org. Chem.* **1962**, *27*, 3819-3822.

[116] S. N. Good, R. J. Sharpe, J. S. Johnson, *J. Am. Chem. Soc.* **2017**, *139*, 12422-12425.

[117] J. O. Hoberg, *J. Org. Chem.* **1997**, *62*, 6615-6618.

[118] T. A. Unzner, A. S. Grossmann, T. Magauer, *Angew. Chem. Int. Ed.* **2016**, *55*, 9763-9767.

[119] R. Kurane, P. Bansode, S. Khanapure, D. Kale, R. Salunkhe, G. Rashinkar, *Catal. Lett.* **2016**, *146*, 2485-2494.

[120] R. A. Altman, A. Shafir, A. Choi, P. A. Lichtor, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 284-286.

[121] C. Li, S. S. Ragab, G. Liu, W. Tang, *Nat. Prod. Rep.* **2020**, *37*, 276-292.

[122] K. W. Quasdorf, L. E. Overman, *Nature* **2014**, *516*, 181-191.

[123] A. Jolit, P. M. Walleser, G. P. A. Yap, M. A. Tius, *Angew. Chem. Int. Ed.* **2014**, *53*, 6180-6183.

[124] J. C. Hethcox, S. E. Shockley, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2018**, *57*, 8664-8667.

[125] R. Long, J. Huang, J. Gong, Z. Yang, *Nat. Prod. Rep.* **2015**, *32*, 1584-1601.

[126] M. Büschleb, S. Dorich, S. Hanessian, D. Tao, K. B. Schenthal, L. E. Overman, *Angew. Chem. Int. Ed.* **2016**, *55*, 4156-4186.

[127] M. Dong, B. Cong, S.-H. Yu, F. Sauriol, C.-H. Huo, Q.-W. Shi, Y.-C. Gu, L. O. Zamir, H. Kiyota, *Org. Lett.* **2008**, *10*, 701-704.

[128] T. Magauer, J. Mulzer, K. Tiefenbacher, *Org. Lett.* **2009**, *11*, 5306-5309.

[129] K. C. Nicolaou, H. Ding, J.-A. Richard, D. Y. K. Chen, *J. Am. Chem. Soc.* **2010**, *132*, 3815-3818.

[130] P. A. Peixoto, J.-A. Richard, R. Severin, D. Y. K. Chen, *Org. Lett.* **2011**, *13*, 5724-5727.

[131] B. Schmalzbauer, D. Menche, *Org. Lett.* **2015**, *17*, 2956-2959.

[132] J. A. Hartsel, D. T. Craft, Q.-H. Chen, M. Ma, P. R. Carlier, *J. Org. Chem.* **2012**, *77*, 3127-3133.

[133] M. Schmid, A. S. Grossmann, K. Wurst, T. Magauer, *J. Am. Chem. Soc.* **2018**, *140*, 8444-8447.

[134] P. Mitra, S. Mandal, S. Chakraborty, D. Mal, *Tetrahedron* **2015**, *71*, 5610-5619.

[135] A. A. Cordi, I. Berque-Bestel, T. Persigand, J.-M. Lacoste, A. Newman-Tancredi, V. Audinot, M. J. Millan, *J. Med. Chem.* **2001**, *44*, 787-805.

[136] W.-G. Lee, A. H. Chan, K. A. Spasov, K. S. Anderson, W. L. Jorgensen, *ACS Med. Chem. Lett.* **2016**, *7*, 1156-1160.

[137] M. Walko, E. Hewitt, S. E. Radford, A. J. Wilson, *RSC Advances* **2019**, *9*, 7610-7614.

[138] S. Pan, S.-Y. Jang, D. Wang, S. S. Liew, Z. Li, J.-S. Lee, S. Q. Yao, *Angew. Chem. Int. Ed.* **2017**, *56*, 11816-11821.

[139] A. K. Ghosh, S. Leshchenko, M. Noetzel, *J. Org. Chem.* **2004**, *69*, 7822-7829.

[140] S. W. Haynes, P. K. Sydor, C. Corre, L. Song, G. L. Challis, *J. Am. Chem. Soc.* **2011**, *133*, 1793-1798.

[141] K. Barral, J. Balzarini, J. Neyts, E. De Clercq, R. C. Hider, M. Camplo, *J. Med. Chem.* **2006**, *49*, 43-50.

[142] T. R. Boehlow, J. J. Harburn, C. D. Spilling, *J. Org. Chem.* **2001**, *66*, 3111-3118.

[143] A. R. Banaag, M. A. Tius, *J. Am. Chem. Soc.* **2007**, *129*, 5328-5329.

[144] B. Wang, D.-C. Xiong, X.-S. Ye, *Org. Lett.* **2015**, *17*, 5698-5701.

[145] J. Eastoe, S. Gold, S. Rogers, P. Wyatt, D. C. Steytler, A. Gurgel, R. K. Heenan, X. Fan, E. J. Beckman, R. M. Enick, *Angew. Chem. Int. Ed.* **2006**, *45*, 3675-3677.

[146] C. G. Frost, B. C. Hartley, *J. Org. Chem.* **2009**, *74*, 3599-3602.

[147] H. Langhals, C. Rüchardt, *Chem. Ber.* **1981**, *114*, 3831-3854.

[148] N. Tsuji, J. L. Kennemur, T. Buyck, S. Lee, S. Prévost, P. S. J. Kaib, D. Bykov, C. Farès, B. List, *Science* **2018**, *359*, 1501.

[149] E. N. Jacobsen, *Acc. Chem. Res.* **2000**, *33*, 421-431.

[150] A. Alexakis, N. Krause, S. Woodward, *Copper-catalyzed asymmetric synthesis*, Wiley-VCH, Weinheim, **2014**.

[151] J.-D. Chai, M. Head-Gordon, *PCCP* **2008**, *10*, 6615-6620.

[152] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B*, **2009**, *113*, 6378-6396.