DISSERTATION ZUR ERLANGUNG DES DOKTORGRADES

DER FAKULTÄT FÜR CHEMIE UND PHARMAZIE

DER LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

A Modular Synthesis of Tetracyclic Meroterpenoid Antibiotics

–

Towards the Total Synthesis of Cornexistin

von

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aus Ebersberg, Deutschland

2018

Erklärung

Diese Dissertation wurde im Sinn von § 7 der Promotionsordnung vom 28. November 2011 von Herrn Prof. Dr. Thomas Magauer betreut.

Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfsmittel erarbeitet.

München, den 09.10.2018

……..……..

Raphael Wildermuth

Dissertation eingereicht am:	09.10.2018
1. Gutachter:	Prof. Dr. Thomas Magauer
2. Gutachter:	Prof. Dr. Franz Bracher
Mündliche Prüfung am:	21.11.2018

– To my Family –

for their Love and Support

Science means constantly walking a tightrope between blind faith and curiosity; between expertise and creativity; between bias and openness; between experience and epiphany; between ambition and passion; and between arrogance and conviction - in short, between an old today and a new tomorrow.

(Heinrich Rohrer)

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

"A Negishi cross-coupling reaction enables the total synthesis of (+)-stachyflin."

F.-L. Haut, K. Speck, **R. Wildermuth**, K. Möller, P. Mayer, T. Magauer, *Tetrahedron Lett.* **2018**, *74*, 3348–3357.

"9-Membered Carbocycles: Strategies and Tactics for their Synthesis"

T. Huber[†], **R. E. Wildermuth**[†], T. Magauer, *Chem. Eur. J.* **2018**, *24*, 12107–12120.

"A Modular Synthesis of Tetracyclic Meroterpenoid Antibiotics."

R. Wildermuth, K. Speck, F.-L. Haut, P. Mayer, B. Karge, M. Brönstrup, T. Magauer, *Nat. Commun.* **2017**, 8, 2083.

This work was highlighted in *Org. Chem. Highlights*:
https://www.organic-chemistry.org/Highlights/2018/20August.shtm

"Convergent Assembly of the Tetracyclic Meroterpenoid (–)-Cyclosmenospongine via a Non-Biomimetic Polyene Cyclization."

K. Speck, **R. Wildermuth,** T. Magauer, *Angew. Chem. Int. Ed.* **2016**, *55*, 14131–14135.

"Gold(I)-Catalyzed Enyne Cyclizations: Studies Towards the Total Synthesis of (+)-Aureol**.**"

R. Wildermuth, K. Speck, T. Magauer, *Synthesis* **2016**, *48*, 1814–1824.

([†] = shared authorship)

Parts of this work have been presented at scientific conferences.

Boehringer Ingelheim MedChem PhD Course

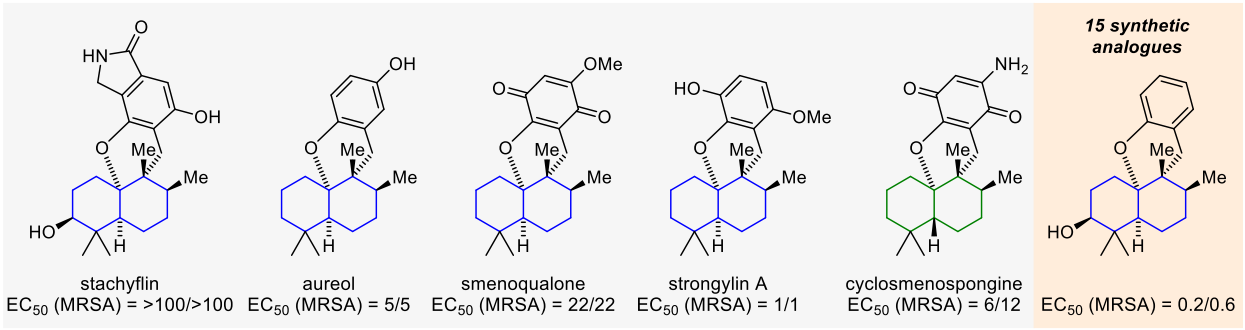
A modular synthesis of tetracyclic meroterpenoid antibiotics (oral presentation). *Biberach*, *Germany*, *2018.*

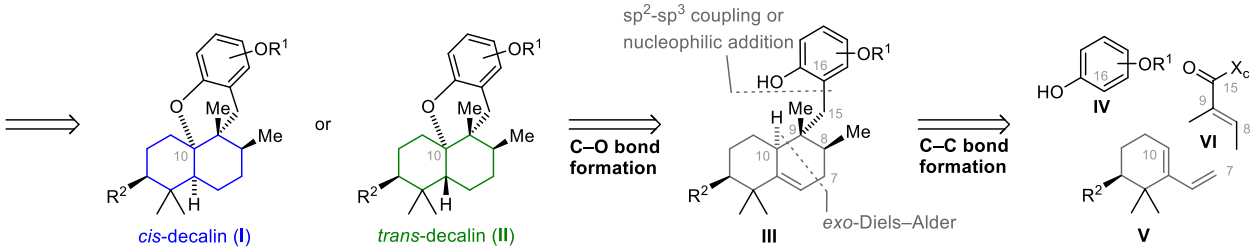
1st Alpine Winter Conference on Medicinal and Synthetic Chemistry

A modular synthesis of tetracyclic meroterpenoid antibiotics (poster). *St.* Anton, *Austria*, *2018.*

ABSTRACT

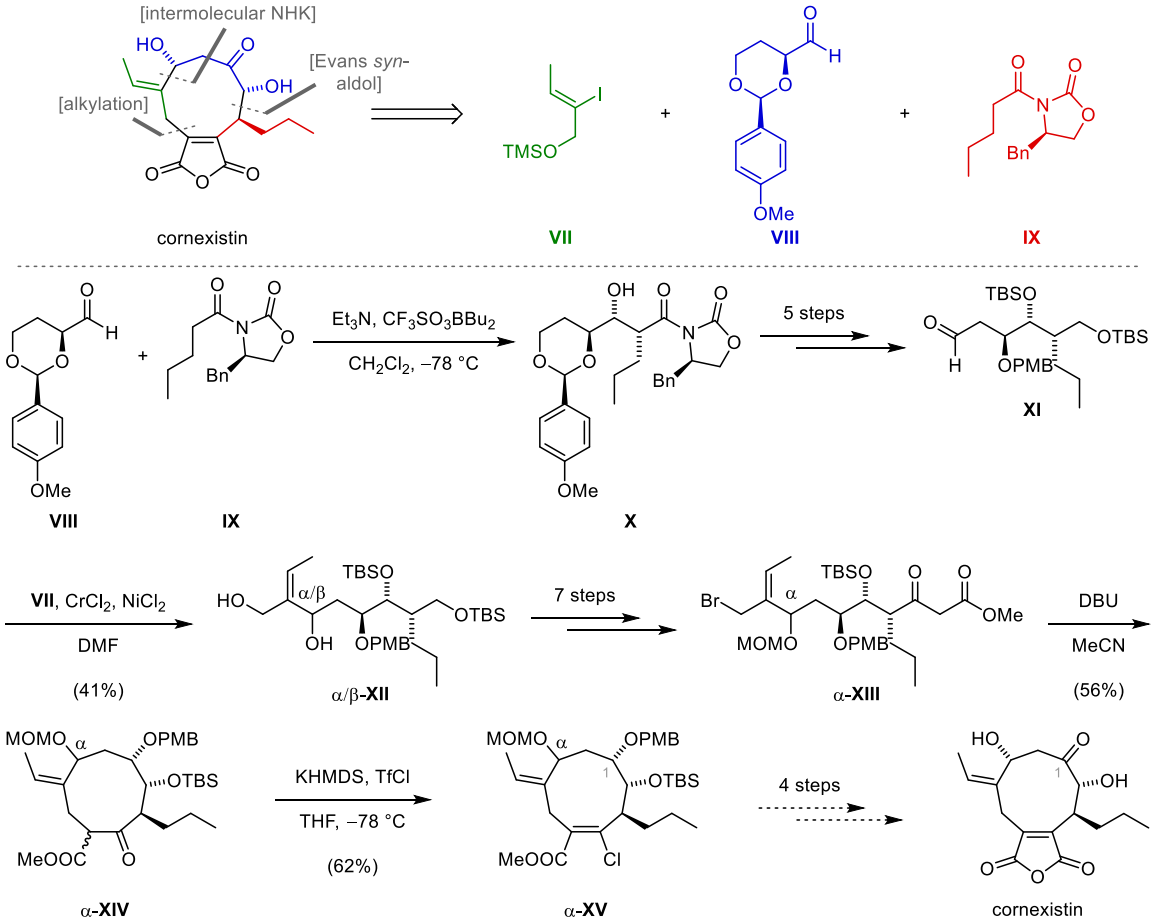
Part I: A synthetic platform for the total synthesis of the structurally related tetracyclic meroterpenoids stachyflin, aureol, smenoqualone, strongylin A, and cyclosmenospongine was developed. Our synthetic strategy employed an auxiliary-controlled Diels–Alder reaction between **V** and **VI** to enable the enantioselective construction of the decalin subunit, which is connected to variously substituted arenes (**IV**) by either carbonyl addition chemistry or sterically demanding sp^2–sp^3 cross-coupling reactions. The selective installation of either the *cis*- or *trans*-decalin **I** or **II** stereochemistry was accomplished by an acid-mediated cyclization/isomerization reaction. This highly modular synthetic platform enabled the synthesis of each of these natural products and 15 non-natural derivatives. Biological profiling reveals that strongylin A and a simplified derivative had potent antibiotic activity against methicillin-resistant *Staphylococcus aureus*.





The effective concentrations (EC_{50} values) that inhibited the growth of two MRSA strains (DSM 11822/RKI 11-02670) are given in µM.

Part II: In the second part of this thesis, the development of a synthetic route towards the total synthesis of cornexistin is described. Retrosynthetically, the complex nine-membered ring can be dissected into three building blocks **VII**, **VIII** and **IX**. Starting with the construction of the eastern part of cornexistin, **VIII** and **IX** were reacted in a *syn*-Evans-aldol reaction and **X** was further transformed into aldehyde **XI**. At this stage, the third building block **VII** was introduced via an intermolecular NHK reaction giving two diastereoisomers α-**XII** and β-**XII**. The cyclization precursor α-**XIII** was synthesized seven in seven linear steps. An exhaustive screen of reactions conditions revealed the formation of the nine-membered carbocycle α-**XIV** by treatment with DBU in acetonitrile. Upon treatment of α-**XIV** with triflic chloride, chloride α-**XV** was formed instead of the desired enoltriflate. The former is envisioned to undergo should undergo palladium catalyzed carbonylation reaction to form the anhydride moiety of the natural product. Global deprotection and oxidation state adjustment at C-1 would lead to the first total synthesis of cornexistin.



ACKNOWLEDGMENTS

After almost four years, an incredible Ph.D. journey comes to an end and this would not have been possible without the help and support of many people.

First of all, I would like to thank Thomas Magauer for giving me the opportunity to conduct my thesis under his supervision and for entrusting me to finally finish the challenging and stimulating project, which he initially began himself. His confidence in the success of my projects and his unbreakable optimism gave me the occasionally needed motivation to succeed. This, in combination with your extraordinary group made the past four years an exciting PhD experience.

Furthermore, I want to express my gratitude to Dirk Trauner. It was a unique experience to be part of your group and to benefit from your truly inspiring passion for science and your encyclopedic chemical knowledge. I want to thank for your continuous and generous support of the Magauer group, the amazing ski-trips to Saalfelden (although I never saw the "black mamba" live on the slopes) and the unforgettable Christmas parties.

Moreover, I would like to thank Prof. Dr. Franz Bracher, Prof. Dr. Konstantin Karaghiosoff, Prof. Dr. Lena Daumann, Dr. Dorian Didier and Dr. Henry Dube for their suggestions and comments regarding this thesis and being part of my defense committee.

I want to thank Dr. Ben Marsh, Lara Weisheit, Sofia Torrey Venegas and Franz-Lucas Haut for thoroughly proofreading this thesis and improving its quality through their invaluable advice.

Special thanks goes to Team Aureol, Dr. Klaus Speck, for the excellent collaboration and my first master student Franz-Lucas Haut for his dedication he put into our project. Moreover, I want to thank Dave Barber for the great collaboration. I also want to thank my second master student, Christian Steinborn ("Groß C") for his great work and the unlimited supply of candy. Also, all of my hard-working and very motivated students: Johann Degraaf and Kim Saskia Mühlfenzl (Kimmi). It has been a joy to supervise and work with them.

I would especially like to thank my labmates throughout my time in Munich, Dr. Johannes Feierfeil for keeping "Zucht und Ordnung" on our side of the IR Lab, Franz-Lucas Haut who introduced me to finest Berlin-Techno tunes, Sofia Torres Venegas (Shanaynay) and Dr. Ben Marsh. You four made my time in the IR Lab to an unforgettable experience.

Moreover, I would like to thank all of the past and present group members of both the Trauner and Magauer group who made this Ph.D. so unforgettable. I thank Dr. Johannes Feierfeil and Dr. Klaus Speck for suffering through countless burpees with me to train for the Xletics challenges, and rocking them even under miserable weather conditions. Also thank to my new labmates of Lab2 in Innsbruck, Lara Weisheit for being such a cheerful and talkative (sometimes a little bit annoying) benchpartner and

co-driver on our trips from Munich to Innsbruck, Alexander Rode for his exotic music selection and last but not least Christian Steinborn.

Special thanks to Dr. Cedric Hugelshofer, Dr. Teresa Preuhs, Dr. Adriana Grossmann, Dr. Tatjana Huber, Aylin Hirschvogel, Christoph Habiger, Kevin Sokol, Ivica Zamarija, Alexander Rode, Matthias Schmid, Julian Feilner, Lukas Wein and Gabriele Prina Cerai for providing such an amazing and cheerful work environment and providing endless advice.

Moreover, I thank the permanent staff Dr. Martin Sumser, Aleksandra Sarman Grilic, Heike Traub, Carrie Louis, Luis de la Osa de la Rosa, Mariia Palchyk, Gerhard Scherzer (Chemotechnician), Inge Gander and Astrid Weber for keeping the lab running and helping with organizational issues.

I also want to thank all the people at the CCB in Innsbruck, who made our moving and the start in the new environment as smooth as possible. Here I really want to thank Sofia (*Secretary for Innsbruck Relocation Services*) for organizing the smooth moving from Munich to Innsbruck. (I am really sorry for the chair…)

Thanks to the staff from the analytical department of the LMU for their excellent support: Dr. Manfred Spahl, Sonja Kosak and Carola Draxler for mass spectroscopic data, Dr. David Stephenson, Claudia Dubler and Petra Keilholz for NMR data and especially Dr. Peter Mayer for the exceptional single crystal X-ray analysis. At the Leopold-Franzens-Universität Innsbruck, I want to thank ass. Prof. Christoph Kreutz for keeping the NMR machines running and Dr. Thomas Müller for mass spectroscopic data.

Special thanks goes to my wonderful girlfriend Isabelle and to my dear friends Philipp, Otto and Chris who supported and endured me throughout the good and the bad times of this journey.

Thanks to the person who lit the flame of chemistry in me, my chemistry teacher in school, Mr. Herbert Lipsky.

Last but not least, I want to thank my mom, my dad, my sister and my grandmother for all of their love and support. Thanks mom and dad for everything, without you this would not have been possible. I really appreciate everything you have done for me during my whole life and I cannot thank you enough.

LIST OF ABBREVIATIONS

Ac	acetyl
AIBN	azoisobutyronitrile
Ar	undefined aryl substituent
9-BBN	9-borobicyclo[3.3.1]nonane
Bn	benzyl
br	broad (NMR spectroscopy, IR spectroscopy)
B.C.	before christ
BDSB	bromodiethylsulfonium bromopentachloroantimonat
Bu	butyl
calc.	calculated
CCDC	Cambridge Crystallographic Data Centre
COD	1,5-cylcooctadiene
COSY	homonuclear correlation spectroscopy
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
d	doublet (NMR spectroscopy)
d.r.	diastereomeric ratio
DCTMB	1,4-dicyanotetramethyl-benzene
DDQ	2,3-dichloro-4,5-dicyano-1,3-benzoquinone
DIBAL-H	diisobutylaluminum hydride
DIPA	*N*,*N*-diisopropylamine
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMAPP	dimethylallyl pyrophosphate
^{3,4}DMB	3,4-dimethoxybenzyl
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMPU	*N*,*N*'-dimethylpropyleneurea
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino) ethane
dppf	1,1´-bis(diphenylphosphino) ferrocene
ee	enantiomeric excess
EI	electron impact ionization (mass spectrometry)
equiv	equivalent(s)
ESI	electron spray ionization (mass spectrometry)
Et	ethyl
FTIR	Fourier-transform infrared spectroscopy
g	gram(s)
h	hour(s)
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HSQC	heteronuclear single quantum coherence
Hz	Hertz (frequency)
i-	*iso* (isomer)
IC_{50}	half maximal inhibitory concentration
im	imidazole
IMes	1,3-bis(mesityl)imidazole-2-ylidene
IPP	isopentenyl pyrophosphate
IPr	1,3-bis(2,6-diisopropylphenyl) imidazole-2-ylidene
IR	infrared
IUPAC	International Union of Pure and Applied Chemistry
JohnPhos	(2-biphenyl)di-*tert*-butyl-phosphine

HMDS	hexamethyldisilazide
LBA	Lewis acid assisted chiral Brønsted acid protonation
LDA	lithium *N*,*N*-diisopropylamide
L_n	ligand(s)
m	medium (IR spectroscopy)
m	multiplet (NMR spectroscopy)
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
min	minute(s)
mL	milliliter
mmol	millimole
MS	mass spectrometry
MsCl	methanesulfonyl chloride
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect correlation spectroscopy
Nu	nucleophile
p	*para* (isomer)
Ph	phenyl
PIFA	phenyliodine bis(trifluoroacetate)
pin	pinacol
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
p-TsOH	*para*-toluenesulfonic acid
q	quartet (NMR spectroscopy)
R	undefined substituent
R_f	retardation factor
s	strong (IR spectroscopy)
s	singlet (NMR spectroscopy)
SPhos	2-dicyclohexylphospino-2´,6´-dimethoxybiphenyl
T	temperature
t	triplet (NMR spectroscopy)
t-	(*tert*-) tertiary (isomer)
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl
w	weak (IR spectroscopy)
XPhos	2-dicyclohexylphosphino-2´,4´,6´-triisopropylbiphenyl

TABLE OF CONTENTS

THEORETICAL SECTION

PART I:

A MODULAR SYNTHESIS OF TETRACYCLIC MEROTERPENOID ANTIBIOTICS

1.1 Introduction

1.1.1 Antibiotics

The discovery and production of antibiotics (from ancient Greek αντιβιοτικά, *antibiotiká*) belongs to mankind greatest achievements, revolutionizing medicine in the 20th century. Since the discovery of penicillin by Alexander Fleming in 1928, a variety of antibiotics has been developed (Figure 1). In the last decades, the world's supply of antibiotics has been weakened by bacteria evolving resistance to these drugs.[1] This is favored due to the ever-increasing prescription against nonbacterial infections and unregulated use, both applying a selective pressure on bacteria to build resistance to those drugs.[2] The growing resistance of bacteria against antibiotics can be explained by Charles Darwin's quote: "Survival of the fittest".

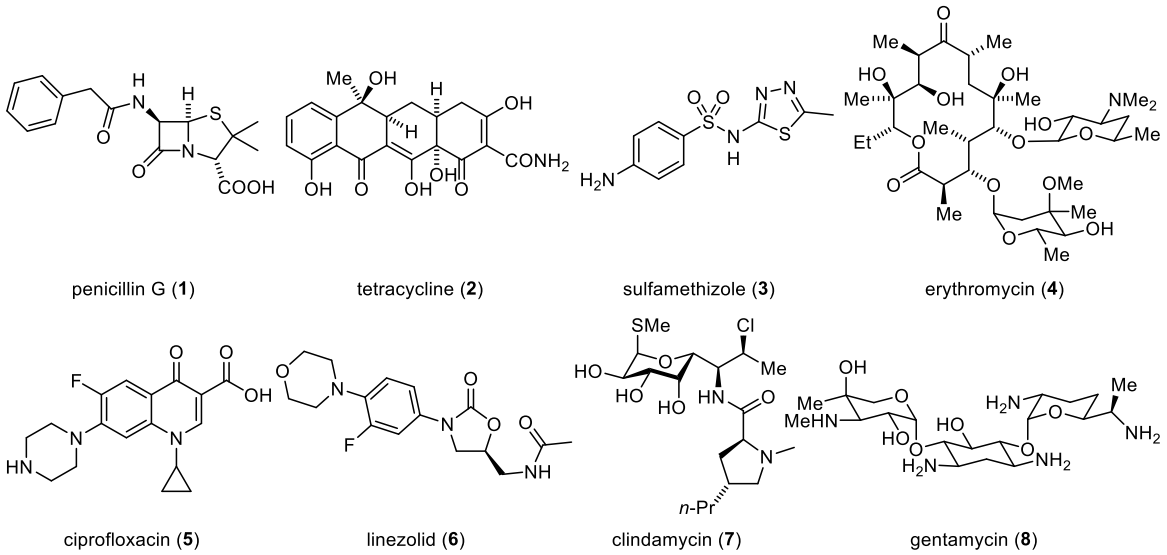


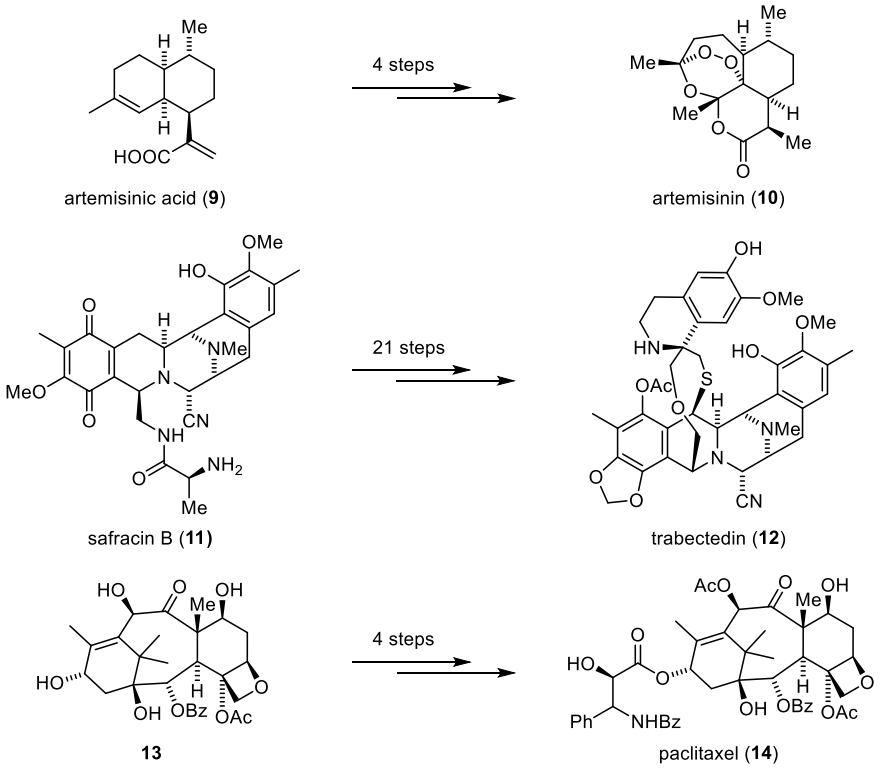
Figure 1 | Selected antibiotics from the modern era.

Antibiotics in bacteria cells can affect their target by inhibition of the cell wall synthesis, protein synthesis, and DNA/RNA synthesis.[3] Bacteria that survive antibiotic-induced death form the next generation of bacteria through cell division and the mechanisms of resistance are shared by horizontal gene transfer.[4] Those resistance mechanisms can be divided in three general groups: limited permeability of the cell membrane and efflux pumps by the drug, mutation of the binding site and more efficient

[1] For a review see: S. E. Rossiter, M. H. Fletcher, W. M. Wuest, *Chem. Rev.* **2017**, *117*, 12415−12474.
[2] a) H. C. Neu, *Science* **1992**, 257, 1064−1073. b) B. Spellberg, D. N. Gilbert, *Clin. Infect. Dis.* **2014**, *59*, 71−75. c) V. K. Viswanathan, *Gut Microbes* **2014**, *5*, 3−4.
[3] a) C. Walsh, C. *Antibiotics: Actions, Origins, Resistance*; ASM Press: Washington, DC, **2003**. b) C. Walsh, T. A. Wencewicz, *Antibiotics: Challenges, Mechanisms, Opportunities*; ASM Press: Washington, DC, **2016**.
[4] T. S. Crofts, A. J. Gasparrini, G. Dantas, *Nat. Rev. Microbiol.* **2017**, *15*, 422−434.

degradation of the drug in the cell.[5] In this course, natural products have often been the foundation for the development of new antibiotics for example tetracycline (**2**), erythromycin (**4**) and clindamycin (**7**). The antibiotics sulfamethizole, (**3**) ciprofloxacin (**5**) and linezolid (**6**) in Figure 1 are fully synthetic drugs and, compared to the natural product derived antibiotics, lack in structural diversity and complexity.

To overcome resistant pathogens, the discovery and development of new generations of antibiotics is greater than ever. Scientist from natural products isolation, total synthesis and medicinal chemists need to continue their efforts finding new targets and developing new classes of antibiotics. The synthesis of natural products on industrial scale is mostly achieved by semisynthesis. Isolation of the target or intermediates from nature or microbial fermentation reactors followed by synthetic modifications has allowed the development of highly complex drugs that could be produced at reasonable costs. Recent examples are the synthesis of artemisinin (**10**) from the fermentation product artemisinic acid (**9**) (Sanofi), trabectedin (**12**) from safracin B (**11**) (Pharma Mar) or paclitaxel (**14**) from **13**, an isolate from European yew needles (Bristol-Myers Squibb) (Scheme 1).[6]



Scheme 1 | Industrial semisynthesis of natural products.

[5] a) J. M. Munita, C. A. Arias, A. R. Unit, A. D. Santiago, *Microb. Spectr.* **2016**, *4*, 1−37. b) J. M. A. Blair, M. A. Webber, A. J. Baylay, D. O. Ogbolu, L. J. V. Piddock, *Nat. Rev. Microbiol.* **2015**, *13*, 42−51. c) K. P. Langton, P. J. F. Henderson, R. B. Herbert, *Nat. Prod. Rep*. **2005**, *22*, 439−451.

[6] a) C. Cuevas et al., *Org. Lett.* **2000**, *2*, 2545−2548. b) C. Cuevas, M. Perez, A. Francesch, C. Fernandez, J. L. Chicharro, P. Gallego, M. Zarzuelo, F. de la Calle, I. Manzanares, International Patent WO 200069862, **2000**. c) J. Turconi, F. Griolet, R. Guevel, G. Oddon, R. Villa, A. Geatti, M. Hvala, K. Rossen, R. Goeller, A. Burgard, *Org. Process Res. Dev.* **2014**, *18*, 417−422. d) J. Dhainaut, A. Dlubala, R. Guevel, A. Medard, G. Oddon, N. Raymond, J. Turconi, International Patent WO 2011026865, **2011**. e) R. A. Holton, International Patent WO 199306079, **1993**. e) E. Ravina, *The Evolution of Drug Discovery: From Traditional Medicines to Modern Drugs*, Wiley-VCH: Weinheim, Germany, **2011**.

Although semisynthetic methods increased over the last decades, there are cases were elaborated substructures or targets cannot be synthesized by this procedure and the remaining option becomes *de novo* total synthesis. Natural products that fit in that category forming the foundation of new antibiotic candidates are for example halichondrin B, epothilone, cryptophycin, PM060184, discodermolide, diazonamide A and ingenol. Those elaborated targets have attracted many synthetic chemistry groups over the last decades.[7]

1.1.2 Strategies for the synthesis of *cis*-decalin systems

The *cis*-decalin system is present in various natural products such as kalihinene X (**15**), nahuoic acid $C_i(B_{ii})$ (**16**), ouabain (**17**), integramycin (**18**), coloradocin (**19**), branimycin (**20**) vinigrol (**21**) or stachyflin (**22**) (Figure 2). The interesting and synthetically challenging structure coupled with a vast of biological activities has led to the development of various new and efficient methods to access *cis*-decalins.[8] In this section, selected methods to synthesize *cis*-decalins by new methodologies or in natural product total synthesis are highlighted in a chronological order.[9]

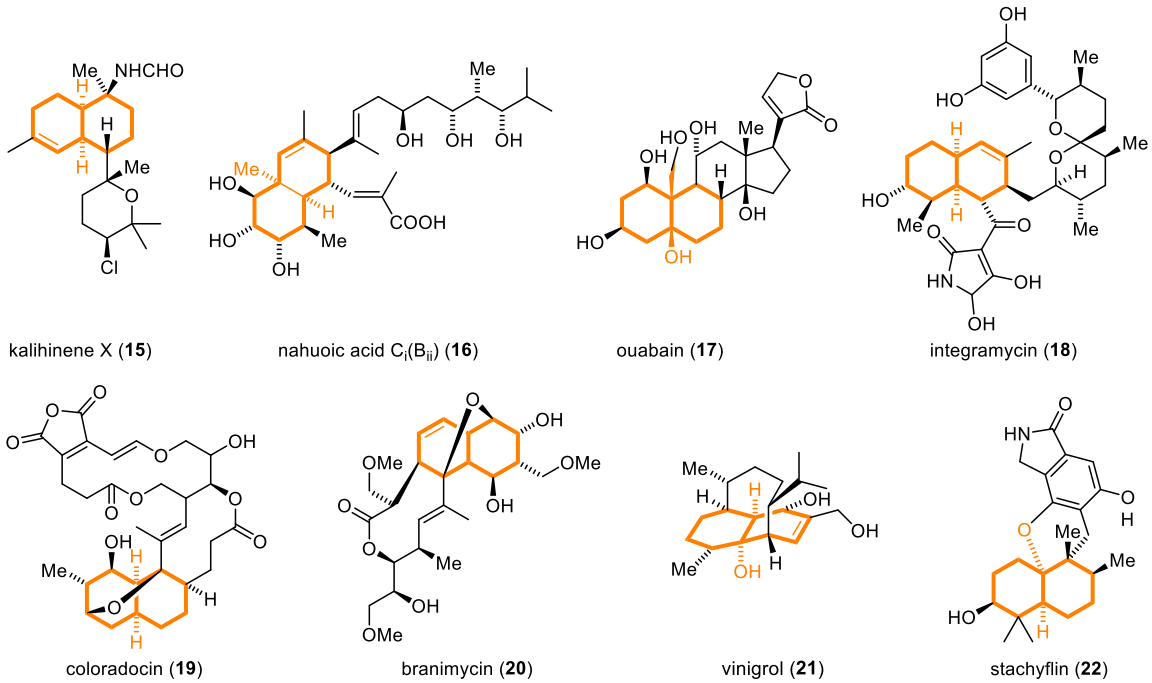
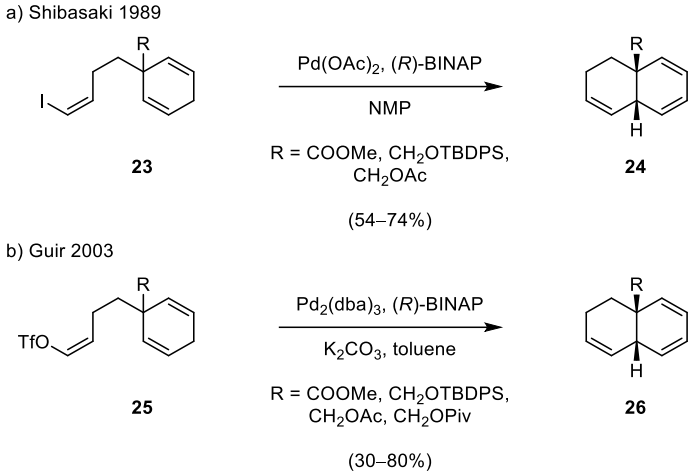


Figure 2 | Selected natural products featuring a *cis*-fused decalin system.

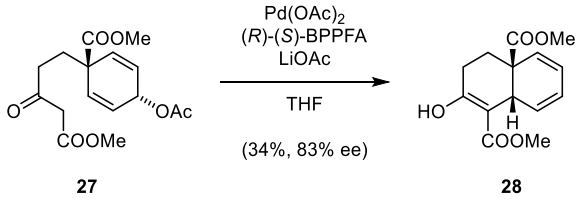
[7] For a review see: T. K. Allred, F. Manoni, P. G. Harran, *Chem. Rev.* **2017**, *117*, 11994−12051.
[8] For a review see: V. Singh, S. R. Iyer, S. Pal, *Tetrahedron* **2005**, *61*, 9197–9231.
[9] For the synthesis of the aureol family of meroterpenoids see: K. Speck (2016) The Total Synthesis of Tetracyclic Meroterpenoid Natural Products – Gold(I)-Catalyzed Cyclizations of 1-Bromo-1,5-Enynes. PhD Thesis. LMU Munich.

One of the first examples for an asymmetric approach to *cis*-decalins was reported in 1989 by Shibasaki[10] in his asymmetric synthesis of **24** via an intramolecular Heck-type cyclization of alkenyl iodide **23** in the presence of a chiral ligand (Scheme 2a).



Scheme 2 | Asymmetric approach towards *cis*-decalin **24** and **26** by a) Shibasaki and b) Guir.

After extensive screening, *cis*-decalin **24** was obtained in 74% yield with an enantiomeric excess of 46%. In 2003, the Guir laboratory further optimized this type of reaction utilizing triflate **25** as cyclization precursor.[11] A wide range of phosphinamine ligands was screened for this reaction showing that palladium complexes formed with BINAP gave **26** (R = COOMe) in 65% yield and 83% ee. Other ligands like ferrocenyloxazoline gave the best results in terms of enantiomeric excess (85%) but low yields (30%) (Scheme 2b).

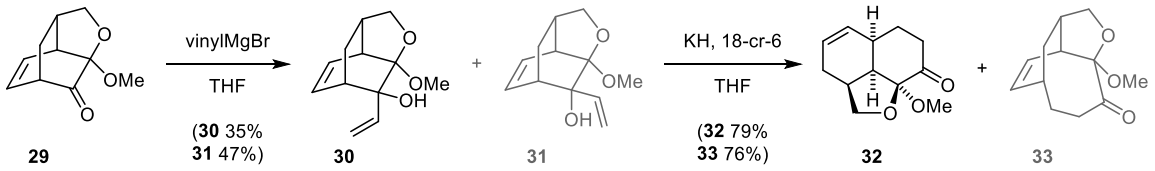


Scheme 3 | Asymmetric synthesis of **28** by Shibasaki.

Further developing their asymmetric synthesis of *cis*-decalin systems, the Shibasaki group reported another palladium catalyzed method from prochiral allylic acetate **27**.[12] Treatment of **27** with a complex of palladium(0) (generated from 1 equiv $Pd(OAc)_2$ and 2 *n*-butyl lithium) and a chiral ligand in the presence of base induced the formation of an π-allyl palladium intermediate which then reacts with the

[10] Y. Sato, M. Sodeoka, M. Shibasaki, *J. Org. Chem.* **1989**, *54*, 4738–4739.
[11] D. Kiely, P. J. Guir, *Tetrahedron Lett.* **2003**, *44*, 7377–7380.
[12] T. Takemoto, Y. Nishikimi, M. Sodeoka, M. Shibasaki, *Tetrahedron Lett.* **1992**, *33*, 3531–3532.

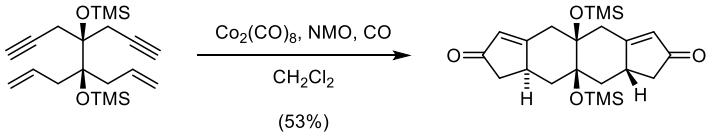
enolate to the highly substituted *cis*-decalin **28**. After optimizing their methodology, **28** was obtained in 34% and 83% ee (Scheme 3). This reaction was later applied in their total synthesis of (+)-vemolepin.[13] In 1996, the group of Liu reported a stereocontrolled synthesis of *cis*-decalin **32** and bicyclo[4.2.2]dec-7-en-4-one **33**.[14] This methodology starts with tricycle **29**, readily available via a two-step procedure from 2-methoxy phenol.[15] Addition of vinylmagnesium bromide to **29** gave a diastereomeric mixture of alcohols **30** and **31** that were separated by column chromatography. Exposure of the minor diastereoisomer **30** to potassium hydride in the presence of 18-crown-six, initiated a [3,3]-sigmatropic rearrangement to afford **32**. Under the same conditions, the major isomer **31** afforded an unexpected [1,3]-sigmatropic rearrangement product **33**.



29 30 31 32 33

Scheme 4 | Stereocontrolled syntheses of *cis*-decalin **32** and bicyclo[4.2.2]dec-7-en-4-one **33**.

A unique formation of *cis*-decalins from a linear precursor via a tandem Pauson–Khand cyclization was reported in 2000 by J. M. Cook and co-workers.[16] Applying the Pauson–Khand protocol to diene-diyne **34** afforded a mixture of *cis*:*trans* decalins (4:1) **35**. To rationalize the preferential formation of the *cis*-decalin system, MM2 calculations were performed to determine the relative energies of the diastereomers. Since calculations showed that the *trans*-decalin was slightly lower in energy than the *cis*-decalin (2.5 kcal/mol), steric interactions in the metallacycle intermediate during the Pauson–Khand reaction are expected to determine product formation in favor of the *cis*-decalin. Although the overall yield of 53% for the formation of **35** is just moderate, the yield of each individual carbon–carbon bond formed in this process was at least 89% (Scheme 5).

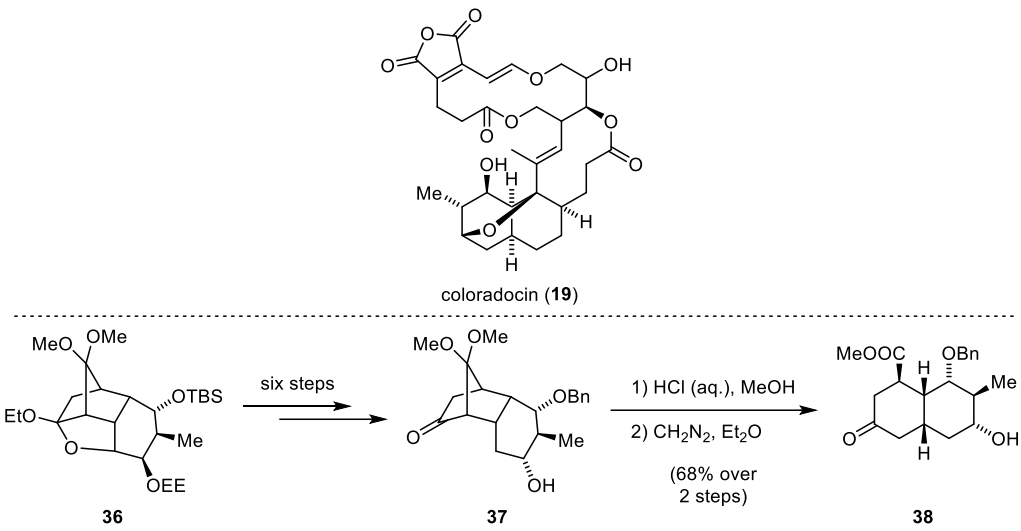


34 35

Scheme 5 | A tandem Pauson–Khand reaction in the construction of tetracycle **35**.

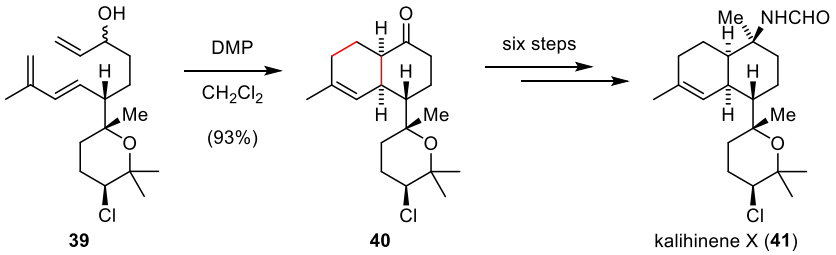
[13] K. Ohrai, K. Kondo, M. Sodeoka, M. Shibasak, *J. Am. Chem. Soc.* **1994**, *116*, 11737–11748.
[14] T. Lee, C. Liao, W. Liu, *Tetrahedron Lett.* **1996**, *37*, 5897–5900.
[15] C. S. Chu, T. H. Lee, C. C. Liao, *Synlett* **1994**, 635–636.
[16] S. G. Van Ornum, M. M. Bruendl, H. Cao, M. Reddy, D. S. Grubisha, D. W. Bennett, J. M. Cook, *J. Org. Chem.* **2000**, *65*, 1957–1971.

Coloradocin (**19**), the most complex natural product of a family of polycyclic antibiotics has been targeted by the group of E. Gössinger (Scheme 6).[17] Starting with **36**, an intermediate from their former synthesis of nodusmicin,[18] a six steps sequence gave access to fragmentation precursor **37**. Treatment of **37** under mild acidic conditions induced fragmentation to a decalinone that is directly esterified to yield the *cis*-decalin core of **38** in good yield.



Scheme 6 | Synthesis of the decalin subunit of coloradocin (**19**).

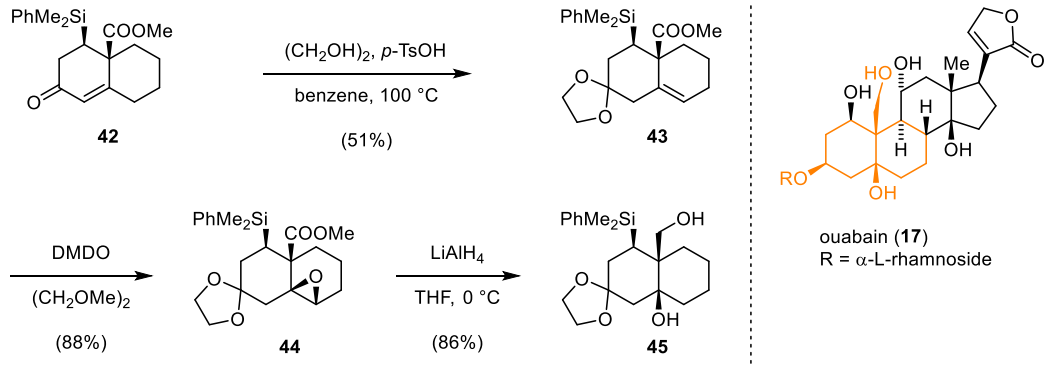
The diterpenoid kalihinene X (**41**) belongs to a family of natural products possessing either a *cis*- or *trans*-decalin system connected to a tetrahydropyran or tetrahydrofuran unit. The first total synthesis of this natural product and determination of the absolute configuration was achieved by H. Mitome in 2002 (Scheme 7).[19] Oxidation of allylic alcohol **39**, itself prepared in eight linear steps, with Dess–Martin periodinane resulted in the formation of a highly reactive *exo*-enone that directly underwent an intramolecular Diels–Alder cycloaddition, selectively forming *cis*-decalin **40**. After this key step, the total synthesis of kalihinene X (**41**) was accomplished in six further steps.



Scheme 7 | Total synthesis of marine diterpenoid kalihinene X (**41**).

[17] E. Gössinger, A. Schwartz, N. Sereinig, *Tetrahedron* **2000**, *56*, 2007–2014.
[18] E. Gössinger, M. Graupe, K. Zimmermann, *Monatsh. Chem.* **1993**, *124*, 965–979.
[19] H. Miyaoka, H. Shida, N. Yamada, H. Mitome, Y. Yamada, *Tetrahedron Lett.* **2002**, *43*, 2227–2230.

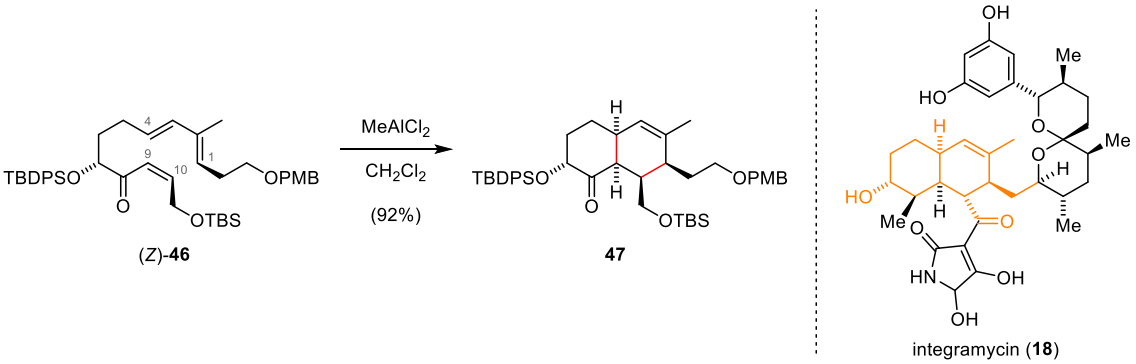
During their development of a synthetic route towards ouabain (**17**), Jung and co-workers synthesized several novel hydroxylated *cis*-decalin derivatives containing the AB-ring system of the target (Scheme 8).[20] Protection of the carbonyl functionality in **42** under migration of the double bond gave alkene **43** that was stereoselectively epoxidized to **44** with 3,3-dimethyldioxirane (DMDO) applying Yang's protocol.[21] Reductive opening of the epoxide with lithium aluminum hydride gave exclusively the desired AB ring system (highlighted in orange) of ouabain (**17**).



Scheme 8 | Synthetic approach to the AB ring system of ouabain (**17**).

In 2005, the group of W. R. Roush accomplished the synthesis of the core fragment **47** of integramycin (**18**) (Scheme 9).[22] Biosynthetically, the decalin core of integramycin (**18**) might arise via an *exo*-selective, intramolecular type I Diels–Alder reaction. Since this would proceed via a sterically disfavored transition state, the group of Roush developed a suitable cyclization precursor for this reaction. First, (*E*)-**46** was synthesized and the intramolecular Diels–Alder reaction was initiated by treatment with methylaluminum dichloride. Contrary to expectations, this resulted selectively in the formation of the *trans*-fused decalin. To investigate the influence of the double bond geometry, triene (*Z*)-**46** was synthesized accordingly. When this cyclization precursor was treated with methylaluminum dichloride at –78 °C, *cis*-fused decalin **47** was formed in 92% yield. Those type of reactions are hypothesized to proceed via a concerted but nonsynchronous transition state. Therefore, bonding between C-1 and C-10 are more advanced than the bonding between C-4 and C-9 and by minimizing steric repulsion of the diene and the dieneophile, the *cis* vs. *trans* ring fusion selectivity is inverted (i.e. (*E*)-**46** leads to the trans- and (*Z*)-**46** leads to the *cis*-decalin).[23]

[20] M. E. Jung, G. Piizzi, *J. Org. Chem.* **2003**, *68*, 2572–2582.
[21] D. Yang, G.-S. Jiao, *Chem. Eur. J.* **2000**, *6*, 3517–3521.
[22] T. A. Dineen, W. R. Roush, *Org. Lett.* **2005**, *7*, 1355–1358.
[23] W. R. Roush, S. M. Peseckis, *J. Am. Chem. Soc.* **1981**, *103*, 6–12.

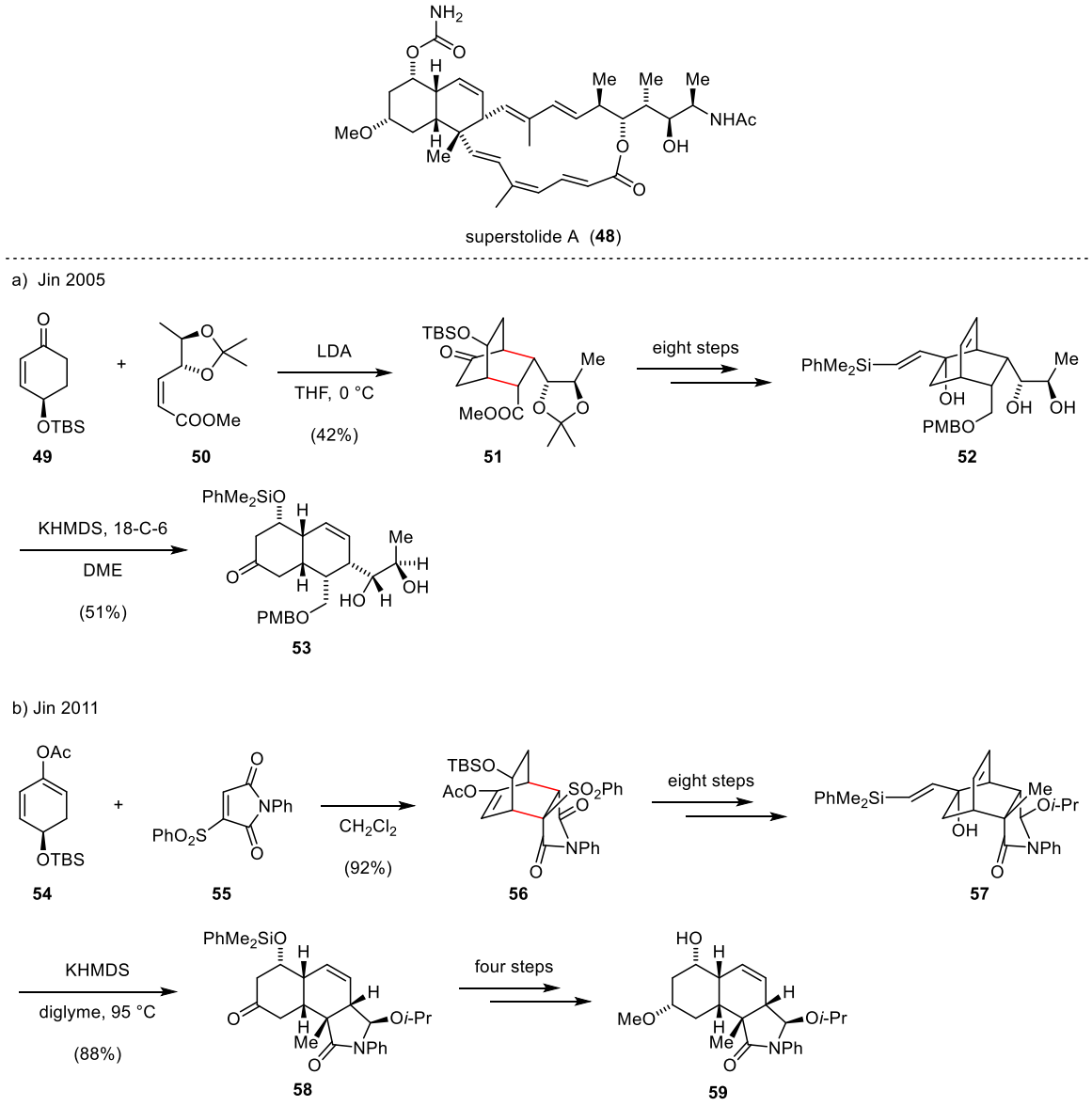


Scheme 9 | A Diels–Alder approach to the core unit **47** of integramycin (**18**).

In 2005, the group of Jin and coworkers reported a convergent strategy for the asymmetric synthesis of the decalin core of the macrolide superstolide A (**48**) (Scheme 10a).[24] Their synthesis of the *cis*-decalin commenced with a double Michael addition sequence between lithium-enolate of **49** and **50** giving just one of eight possible diastereomers. The so obtained tricycle **51** was further converted into **52** in eight steps. The *cis*-decalin system **53** was formed via an anionic oxy-Cope rearrangement of **52** initiated by an excess of potassium bis(trimethylsilyl)amide at elevated temperature.

Six years later, the Jin laboratory reported a new, powerful approach to the *cis*-decalin core of superstolide A (**48**) (Scheme 10b).[25] They investigated a regio, stereo, and facial selective [4+2] cycloaddition between an 1,3-diene with highly activated vinyl sulfones. This new methodology has been applied to access bicyclo[2.2.2]octanone **56** by the reaction of diene **54** and dienophile **55** in excellent yield. The cyclization product was further converted into **57** which underwent an anionic oxy-Cope rearrangement to afford *cis*-decalin **58**. With those two approaches towards the total synthesis of superstolide A (**48**), Jin and coworkers had set the foundation for the total synthesis of truncated superstolide A.[26]

[24] Z. Hua, W. Yu, M. Su, Z. Jin, *Org. Lett.* **2005**, *7*, 1939–1942.
[25] L. Chen, Z. Hua, G. Li, Z. Jin, *Org. Lett.* **2011**, *13*, 3580–3583.
[26] L. Chen, K. B. Riaz A., P. Huang, Z. Jin, *Angew. Chem. Int. Ed.* **2013**, *52*, 3446–344.



Scheme 10 | Construction of the *cis*-declain systems a) **53** and b) **59** via an anionic oxy-Cope rearrangement.

In 1998, branimycin (**20**) was isolated by the Laatsch group from the actinomycetes strain GW 60/1571.[27] Due to its promising antibiotic activity against *Streptomyces viridochromogenes*, the Mulzer group from the university of Vienna became interested in this complex natural product.[28] In their first approach, the *cis*-decalin system was planned be formed by a transannular Diels–Alder reaction (TADA). Based on previous results from the Roush group[29] and supported by DFT calculations, Mulzer and coworkers designed cyclization precursor **60** that should undergo a TADA reaction via the *exo* transition state. Indeed, the TADA reaction could be initiated by refluxing **60** in xylene for 36 h and the

[27] M. Speitling, Dissertation, Universität Gçttingen (Germany), **1998**.
[28] For the full paper of all approaches perused see: V. S. Enev, W. Felzmann, A. Gromov, S. Marchart, J. Mulzer, *Chem. Eur. J.* **2012**, *18*, 9651–9668.
[29] a) W. R. Roush, J. W. Coe, *Tetrahedron Lett.* **1987**, *28*, 931–934. b) J. W. Coe, W. R. Roush, *J. Org. Chem.* **1989**, *54*, 915–930.

desired product **61** was obtained in 80% yield (Scheme 11a).[30] At this stage, this route was abandoned due to more promising results in their group.

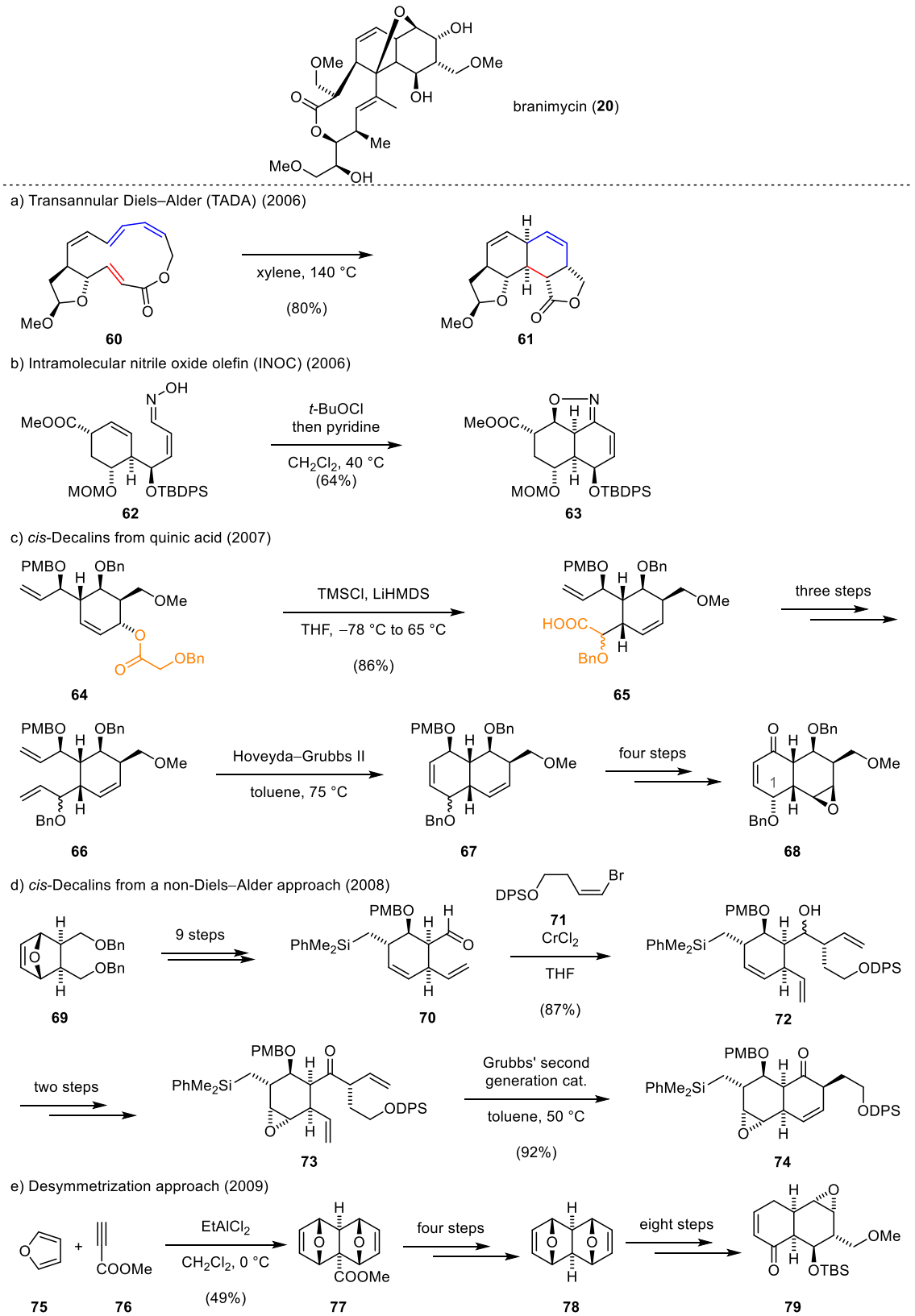
In their second approach, an intramolecular nitrile oxide olefin (INOC) cyclization reaction was applied to form the *cis*-decalin core.[31] This strategy was first tested on a model substrate **62** that was stable towards double bond isomerization. Formation of the nitrile oxide was followed by in situ cycloaddition to yield isoxazoline **63** as a single diastereomer (Scheme 11b).[32] This promising results were then translated to a suitable substrate for the total synthesis of branimycin (**20**). Unfortunately, this substrate was prone to epimerization and the approach was completely discarded.

Another approach started from (–)-quinic acid as cheap (0.98 €/g) chiral building block from which intermediate **64** was synthesized in 17 steps (Scheme 11c).[33] By forming the TMS-enolether in situ, the Claisen–Ireland rearrangement was initiated giving **65** as a mixture of diastereomers for the OBn group. Olefin **65** was further functionalized by esterification, reduction to the aldehyde and Wittig reaction to the ring-closing metathesis precursor **66**. In the course of screening for the optimal conditions, Hoveyda–Grubbs' second generation catalyst gave the desired product **67** in 65% yield. In the following four steps, highly functionalized *cis*-α,β-unsaturated ketone **68** was prepared with all positions functionalized for the synthesis of branimycin (**20**). However, **64** has to be synthesized in a 17 steps sequence and stereocenter at C-1 has to be inverted at some later stage.

Hence, a more direct route still employing a ring-closing metathesis reaction to form one of the decalin rings was developed.[34] In a nine steps desymmetrization sequence, **69** was transformed into **70** employing an enzymatic, enantiotopos-selective acetylation.[35] The side chain containing the second double bond for the ring-closing metathesis reaction was introducted by intermolecular Hiyama–Nozaki–Kishi reaction of aldehyde **70** with allylbromide **71**. In the presence of chromium(II) chloride, a mixture of three diastereomeric alcohols **72** was obtained (only the desired diastereomers are shown in Scheme 11d). After oxidation of the secondary alcohol **72** with Dess–Martin periodinane and epoxidation with *meta*-chloroperoxybenzoic acid, **73** was subjected to ring-closing metathesis conditions giving **74** that was further converted into a highly elaborated intermediate. Those results encouraged the Mulzer group to develop a shorter route to access a decalin intermediate **79** by desymmetrization of diepoxynaphthalene **78**.[36] Starting with a twofold Diels–Alder reaction of methyl propiolate (**76**) and furan (**75**), *cis*-decalin **77** was generated in multigram quantities. Formal decarboxylation of **77** proceeded uneventfully and diepoxynaphthalene **78** was obtained in good overall

[30] J. Mulzer, D. Castagnolo, W. Felzmann, S. Marchart, C. Pilger, V. S. Enev *Chem. Eur. J.* **2006**, *12*, 5992–6001.
[31] For a review see: J. Mulzer in *Organic Synthesis Highlights, Vol. I* (Eds.: J. Mulzer, H. J. Altenbach, M. Braun, K. Krohn, H. U. Reissig), VCH, Weinheim, **1990**, 77.
[32] V. S. Enev, M. Drescher, J. Mulzer, *Tetrahedron* **2007**, *63*, 5930–5939.
[33] S. Marchart, J. Mulzer, V. S. Enev, *Org. Lett.* **2007**, *9*, 813–816.
[34] V. S. Enev, M. Drescher, J. Mulzer, *Org. Lett.* **2008**, *10*, 413–416.
[35] For the first four steps see: a) C. Cinquin, I. Shaper, G. Mandville, R. Bloch, *Synlett*, 339–340. b) K. Takao, H. Yasui, S. Yamamoto, D. Sasaki, S. Kawasaki, G. Watanabe, K. Tadano, *J. Org. Chem.* **2004**, *69*, 8789–8795.
[36] A. Gromov, V. Enev, J. Mulzer, *Org. Lett.* **2009**, *11*, 2884–2886.

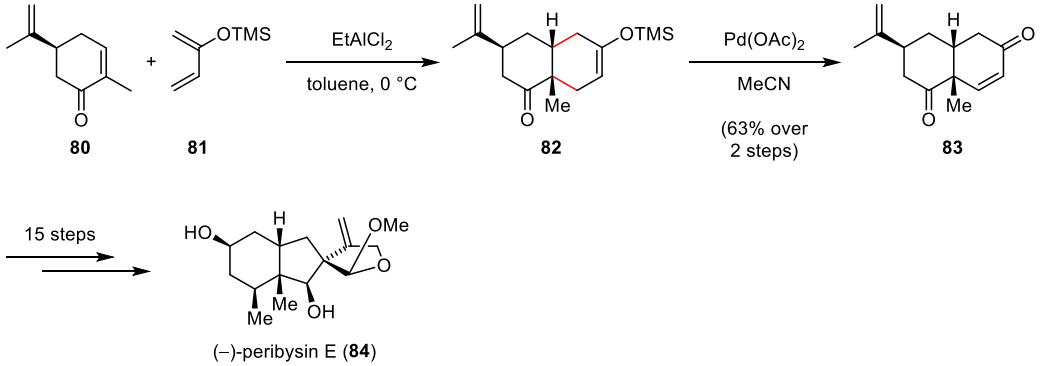
yield (Scheme 11e). Synthesis of intermediate **79** was then accomplished by desymmetrization of **78** via two successive S_N2' reactions and the total synthesis of branimycin (**20**) was accomplished.[37]



Scheme 11 | Novel Approaches to highly substituted *cis*-decalin systems.

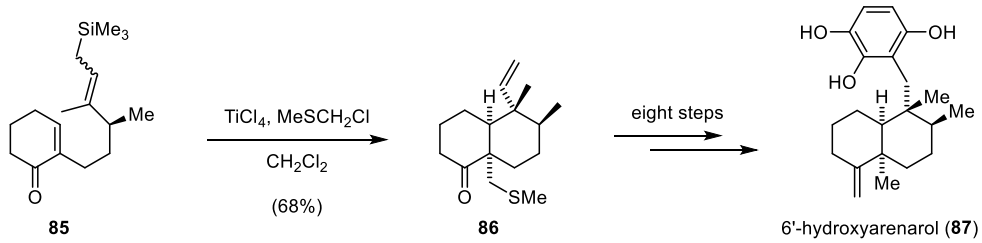
[37] S. Marchart, A. Gromov, J. Mulzer, *Angew. Chem. Int. Ed.* **2010**, *49*, 2050–2053.

In 2008, Danishefsky reported a convergent, stereocontrolled synthesis of the cell adhesion inhibitor peribysin E (**84**) from carvone (**80**).[38] Retrosynthetically, the *cis*-fused six-five carbon skeleton of peribysin E (**84**) should be available from a *cis*-decalin system. In this context, enone **83** was envisioned as suitable intermediate. Its synthesis commenced with a Diels–Alder cycloaddition between commercially available dienophile carvone (**80**) and the diene **81**. The *iso*-prenyl residue of **80** should direct the stereofacial sense of this reaction. As predicted, Lewis acid promoted Diels–Alder reaction between **80** and **81** gave selectively the *cis*-decalin **82** that was directly subjected to Saegusa oxidation affording enone **83** in good overall yield. With this intermediate in hand, Danishefsky and coworker finished the total synthesis of peribysin E (**84**) in 15 further steps (Scheme 12).



Scheme 12 | Total synthesis of peribysin E (**84**).

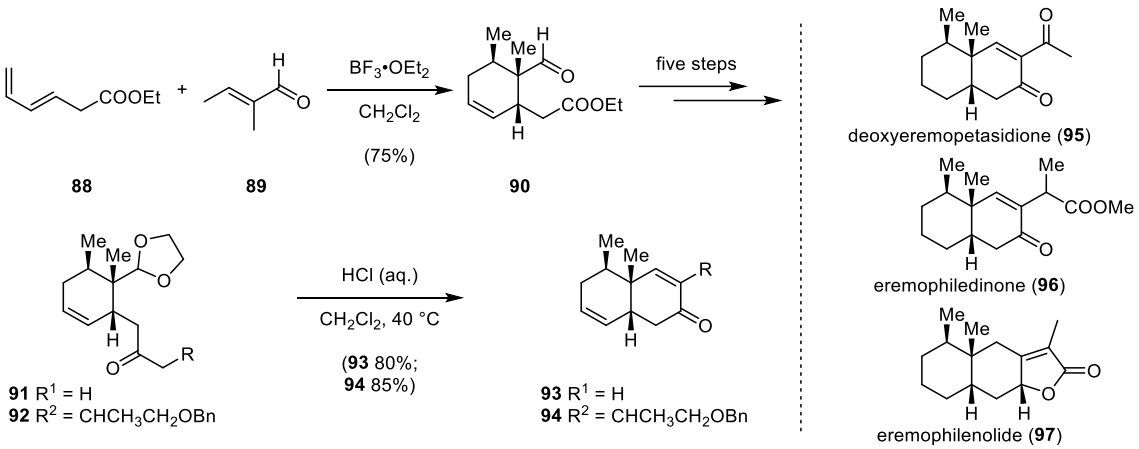
The marine natural product popolohuanone E is believed to be derived by oxidative dimerization of 6′-hydroxyarenarol (**87**). To verify this hypothesis, the group of Anderson targeted **87** by total synthesis in 2008.[39] One of their key transformations was the Lewis acid promoted Hosomi–Sakurai reaction of **85** in the presence of chloromethyl methyl sulfide forming *cis*-decalin **86** as a single diastereomer. The target molecule **87** was obtained after eight steps, but the envisioned dimerization proved to be more challenging than anticipated.



Scheme 13 | Synthesis of 6′-hydroxyarenarol (**87**).

[38] A. R. Angeles, S. P. Waters, S. J. Danishefsky, *J. Am. Chem. Soc.* **2008**, *130*, 13765–13770.
[39] R. H. Munday, R. M. Denton, J. C. Anderson, *J. Org. Chem.* **2008**, *73*, 8033–8038.

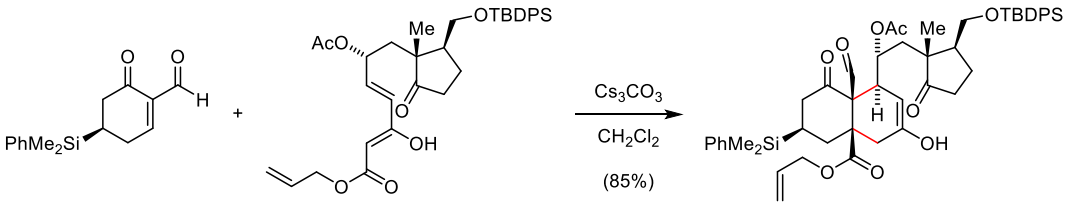
In their course of synthesizing the natural products eremophilenolide (**97**), eremophiledinone (**96**) and deoxyeremopetasidione (**95**), the Das laboratory developed a new and efficient route to construct their common structural feature, a *cis*-fused decalin system.[40] Starting with a highly stereoselective, Lewis acid mediated Diels–Alder cycloaddition between diene **88** and commercially available tiglic aldehyde (**89**), olefin **90** was obtained in very good yield. After five steps, the precursor **91** (or **92**) for the second key transformation was obtained. By treating **91** (or **92**) with aqueous hydrochloric acid (6 M), an intramolecular aldol condensation was initiated forming the *cis*-fused decalin system **93** (or **94**). With those two building blocks in hand, the target natural products **95–97** were successfully synthesized (Scheme 14).



Scheme 14 | A new route to eremophilanes: synthesis of eremophilenolide (**97**), eremophiledinone (**96**) and deoxyeremopetasidione (**95**).

For the first total synthesis of the cardioactive glycoside ouabain (**17**), isolated from the bark of the African ouabio tree (*Acokanthera ouabio*) by Arnaud 1888,[41] the group of Deslongchamps applied an earlier developed methodology for steroid synthesis.[42] The construction of *cis*-decalin **100** was realized by anionic polycyclization of freshly prepared **99** with substituted Nazarov reagent **98** promoted by cesium carbonate. From **100**, the total synthesis of ouabain (**17**) was accomplished in 18 steps (Scheme 15).[43]

[40] P. Srinivas, D. S. Reddy, K. S. Kumar, P. K. Dubey, J. Iqbal, P. Das, *Tetrahedron Lett.* **2008**, *49*, 6084–6086.
[41] a) L. F. Fieser, M. Fieser, Steroids, Reinhold, New York, **1959**, chap. 20. b) A. Arnaud, C. R. *Hebd. Seances Acad. Sci.* **1888**, *106*, 1011. c) A. Arnaud, C. R. *Hebd. Seances Acad. Sci.* **1888**, *107*, 1162.
[42] a) R. Ruel, P. Deslongchamps, *Tetrahedron Lett.* **1990**, *31*, 3961–3964. b) R. Ruel, P. Deslongchamps, *Can. J. Chem.* **1992**, *70*, 1939–1949.
[43] H. Zhang, M. S. Reddy, S. Phoenix, P. Deslongchamps, *Angew. Chem. Int. Ed.* **2008**, *47*, 1272–1275.



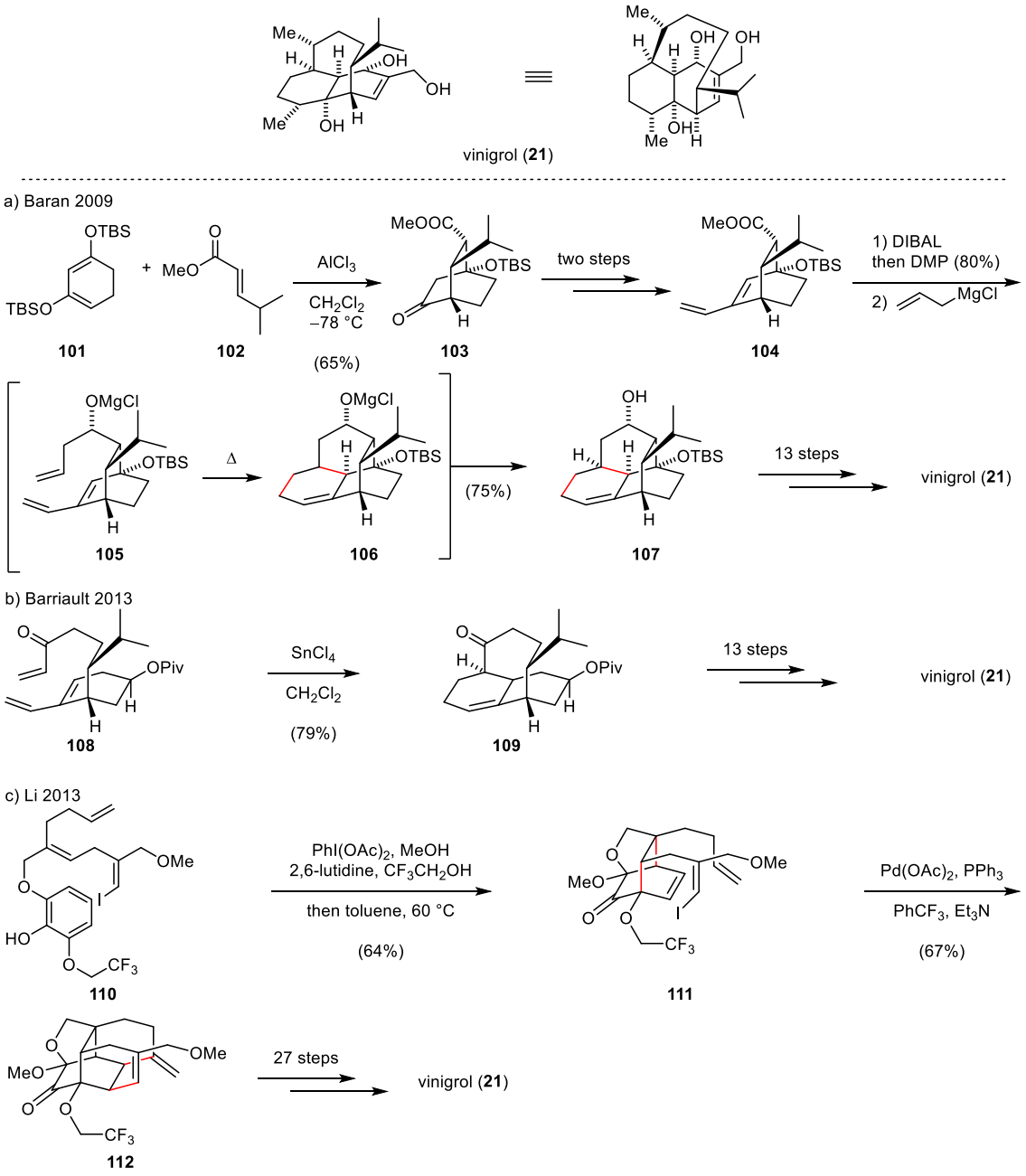
Scheme 15 | Total synthesis of ouabain (**17**).

The diterpene vinigrol (**21**) was isolated 1987 by Hashimoto and co-workers from the fungal strain Virgaria nigra F-5408.[44] The interesting biological activities combined with a highly complex carbon skeleton has attracted numerous synthetic chemists in the last decade.[45] Based on previous results from the Paquette group that showed the difficulties in the formation of the eight membered ring from an pre-existing *cis*-decalin system, Baran and coworkers reported the first total synthesis of vinigrol (**21**) in 2009 (Scheme 16a).[46] The synthesis started with an *endo*-selective Diels–Alder reaction between diene **101** and dienophile **102** affording bicyclic ketone **103**. In the following two steps the vinyl group was introduced by triflation and Stille cross-coupling. After formal reduction of the ester to the aldehyde, allyl magnesium bromide was added forming intermediary alkoxide **105**. Direct heating of **105** to 105 °C initiated an intramolecular Diels–Alder reaction to provide **106**. With this key intermediate in hand, vinigrol (**21**) was finished in 13 steps (Scheme 16a).

A similar strategy for the construction of the decalin core was utilized by Barriault in his formal synthesis of vinigrol (**21**).[47] Instead of forming the Diels–Alder cyclization precursor in situ, **108** was synthesized and treated with thin(IV) chloride at –78 °C to provide the desired vinigrol-core **109** via an intramolecular Diels–Alder reaction.

In the same year, Li published an unprecedented approach to vinigrol (**21**).[48] The first part of the vinigrol scaffold **111** was synthesized via an one-pot oxidative dearomatization/Diels–Alder reaction of cyclization precursor **110**. After the second step, a tandem 6-*exo*-trig Heck cyclization, the complete carbon skeleton **112** was formed and the synthesis of vinigrol (**21**) was completed in 27 linear steps.

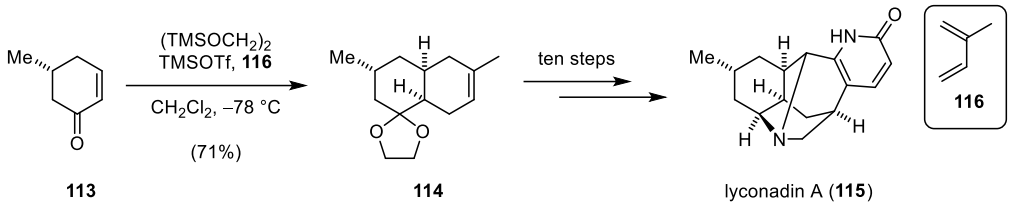
[44] I. Uchida, T. Ando, N. Fukami, K. Yoshida, M. Hashimoto, T. Tada, S. Koda, Y. Morimoto, *J. Org. Chem.* **1987**, *52*, 5292–5293.
[45] For a review see: C. Draghici, J. T. Njardarson, *Tetrahedron* **2015**, *71*, 3775–3793.
[46] a) T. J. Maimone, A. Voica, P. S. Baran, *Angew. Chem. Int. Ed.* **2008**, *47*, 3054–3056. b) T. J. Maimone, J. Shi, S. Ashida, P. S. Baran, *J. Am. Chem. Soc.* **2009**, *131*, 17066–17067.
[47] a) L. Morency, L. Barriault, *Tetrahedron Lett.* **2004**, *45*, 6105–6107. b) J. Poulin, C. M. Grisé-Bard, L. Barriault, *Angew. Chem. Int. Ed.* **2012**, *51*, 2111–2114.
[48] Q. Yang, J. T. Njardarson, C. Draghici, F. Li, *Angew. Chem. Int. Ed.* **2013**, *52*, 8648–8651.



Scheme 16 | Total syntheses of the *cis*-decalin core of vinigrol (**21**).

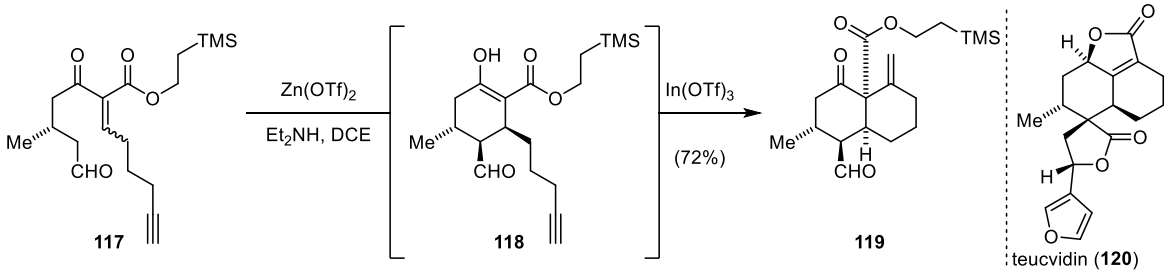
In their retrosynthetic analysis of lyconadin A (**115**), the group of Fukuyama proposed the synthesis of the *cis*-six-seven system via a ring expansion of *cis*-decalin system **114**.[49] The first task in their synthetic route was the construction the *cis*-decalin system **114** via a Diels–Alder cycloaddition between **113** and isoprene (**116**) applying Overman's conditions.[50] From this building block, lyconadin A (**115**) was successfully synthesized in ten further steps (Scheme 17).

[49] T. Nishimura, A. K. Unni, S. Yokoshima, T. Fukuyama, *J. Am. Chem. Soc.* **2011**, *133*, 418–419.
[50] a) B. L. Nilsson, L. E. Overman, J. Read de Alaniz, J. M. Rohde, *J. Am. Chem. Soc.* **2008**, *130*, 11297–11299. b) R. A. Altman, B. L. Nilsson, L. E. Overman, J. Read de Alaniz, J. M. Rohde, V. Taupin, *J. Org. Chem.* **2010**, *75*, 7519–7534.



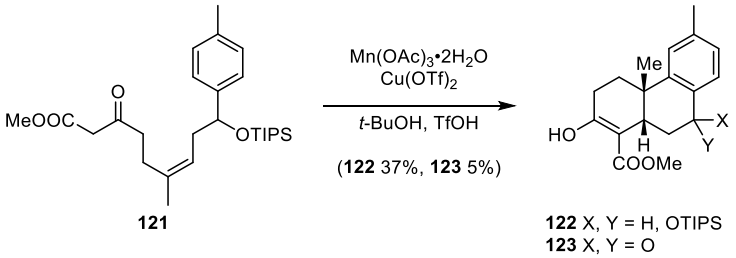
Scheme 17 | Total synthesis of lyconadin A (**115**).

In 2012, the Lee group reported a concise, enantioselective total synthesis of teucvidin (**120**).[51] In this synthesis their recently reported methodology to construct *cis*-fused decalin systems via an amine-induced Michael/Conia-ene cascade cyclization was implemented.[52] Starting from enantiomerically enriched **117**, (*E*:*Z* 1:1) extensive screening revealed the optimal combination of transition metal salts, amine base and solvent. Treatment of **117** with zinc(II) triflate and diethylamine in 1,2-dichloroethane initiated the formation of kinetic Michael adduct **118**. Then, indium(III) triflate and molecular sieves were added and the second part of the cascade reaction, the Conia-ene reaction occurred to afford *cis*-decalin **119** which could be transformed into teucvidin (**120**) in a 12 step sequence.



Scheme 18 | Total synthesis of teucvidin (**120**).

In 2013, the Shoji laboratory reported an efficient methodology to access *cis*-decalin systems via a stereoselective domino cyclization cascade enabling the synthesis of polycyclic steroids with a wide variety of functional groups.[53]

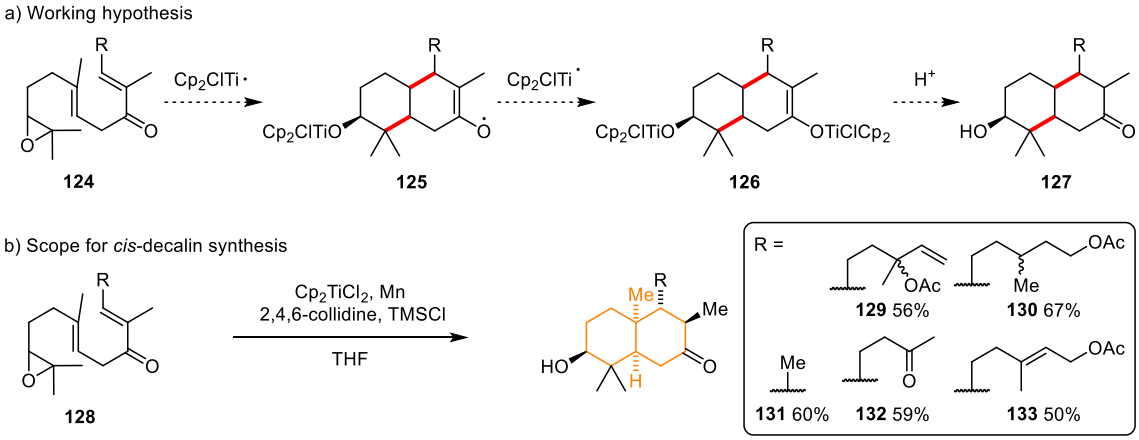


Scheme 19 | Stereoselective construction of *cis*-decalin framework **122** and **123** via radical domino cyclization.

[51] X. Liu, C. Lee, *Org. Lett.* **2012**, *14*, 2886–2889.
[52] W. Li, X. Liu, X. Zhou, C. Lee, *Org. Lett.* **2010**, *12*, 548–551.
[53] E. Suzuki, M. Ueda, S. Ohba, T. Sugai, M. Shoji, *Tetrahedron Lett.* **2013**, *54*, 1589–1592.

Initial exposure of cyclization precursor **121** to manganese(III) acetate and copper(II) acetate in acetic acid at 50 °C gave a mixture of *cis*-and *trans*-fused decalin systems. After intensive optimizations, the combination of manganese(III) acetate and copper(II) triflate in the presence of triflic acid afforded predominately (*cis*:*trans* 4.7:1) the desired *cis*-decalin **122** (and **123**) (Scheme 19).

For the synthesis of various terpenic structures, bioinspired radical cyclizations have proved to be a powerful methodology.[54] In this context, the Cuerva group developed a titanium(III)-catalyzed radical cyclization of epoxypolyprenes (such as **124**) with an internal keto functionality.[55] The enol radical **125** should be trapped by a highly oxophilic titanium radical ($Cp_2ClTi•$) terminating the cyclization cascade. After acidic workup, the cyclization product, ketone **127** can be isolated (Scheme 20a). With this methodology, the final number of rings formed in this cascade reaction depends on the position of the keto group in the cyclization precursor and is not determined by the number of prenyl subunits. To investigate the scope of their methodology, numerous ketoepoxypolyprenes (**128**) were treated with substoichiometric amounts of Cp_2TiCl_2 in combination with Me_3SiCl, 2,4,6-collidine and manganese. Interestingly, all conditions tested lead to the formation of **129**–**133** with a *cis*-fused decalin system (Scheme 20b). This unexpected chemo- and stereoselectivity was elucidated by DFT calculations. Those calculations revealed that the carbonyl group in the cyclization precursor plays an important role in two processes: (1) Stabilization of the formed radical and reaction with oxophilic titanium species and (2) the corresponding side chain is forced by either template or conformational effects to follow a pathway that forms the *cis*-decalin system.

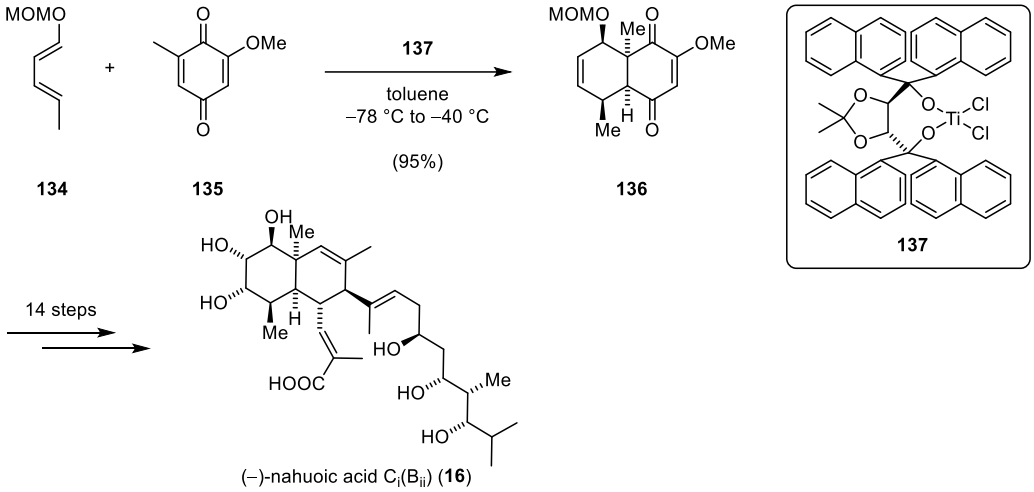


Scheme 20 | Ti(III)-Catalyzed cyclizations of ketoepoxypolyprenes.

In 2017, Smith reported a convergent total synthesis of the recently isolated natural product nahuoic acid $C_i(B_{ii})$ (**16**).[56] All members of the nahuoic acid family feature a highly substituted *cis*-declain core. From a synthetic point of view, the first task was the formation of the decalin core **136** followed by the

[54] For a review see: J. Justicia, L. Álvarez de Cienfuegos, A. G. Campana, D. Miguel, V. Jakoby, A. Gansaüer, J. M. Cuerva, *Chem. Soc. Rev.* **2011**, *40*, 3525−3537.
[55] S. P. Morcillo, D. Miguel, S. Resa, A. Martín-Lasanta, A. Millán, D. Choquesillo-Lazarte, J. M. García-Ruiz, A. J. Mota, J. Justicia, J. M. Cuerva, *J. Am. Chem. Soc.* **2014**, *136*, 6943−6951.
[56] Q. Liu, Y. Deng, A. B. Smith, *J. Am. Chem. Soc.* **2017**, *139*, 13668−13671.

final decoration. For the synthesis of the requisite *cis*-decalin **136**, Smith explored a Lewis acid mediated, asymmetric Diels–Alder reaction (Scheme 21). Probing the chemo- and regioselectivity of this reaction, cycloaddition between **134** and **135** was carried out under thermal conditions giving the desired isomer (±)-**136**.

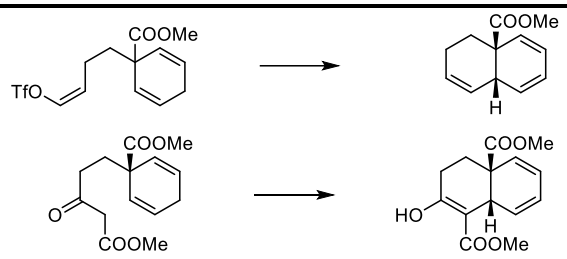
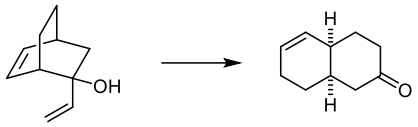
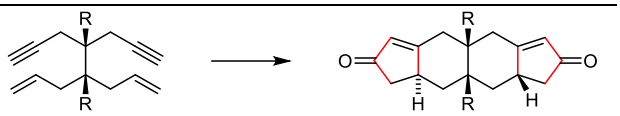
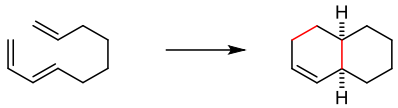
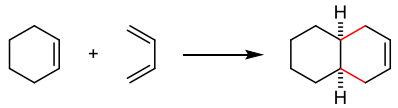
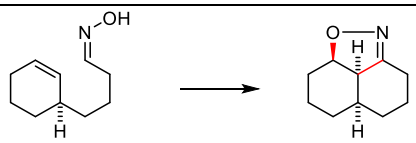
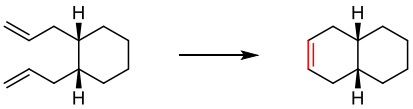
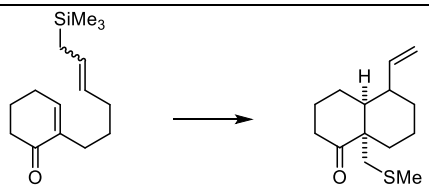
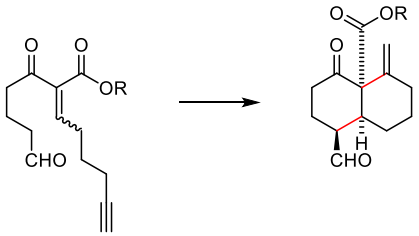
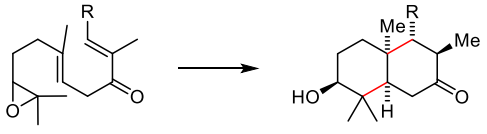


Scheme 21 | Total synthesis of nahuoic acid $C_i(B_{ii})$ (**137**).

Encouraged by this results, the reaction was optimized in terms of Lewis acid, ligand, solvent and temperature. In the end, the cycloaddition catalyzed by chiral titanium complex **137** gave *cis*-decalin **136** in 95% yield with 86% ee. With **136** in hand, Smith and coworker were able to synthesize nahuoic acid $C_i(B_{ii})$ (**16**) after 14 steps.

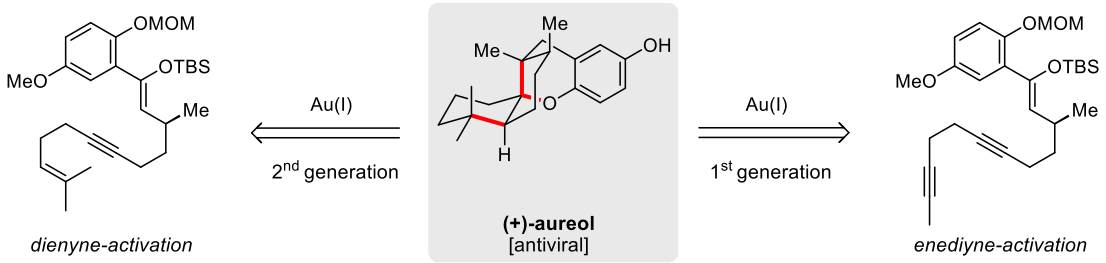
1.1.3 Methods overview

Table 1 | Overview of methods for the synthesis of *cis*-fused decalins.

Palladium catalyzed cross coupling	
Oxy-Cope rearrangement	
Pauon–Khand reaction	
Intramolecular Diels–Alder	
Intermolecular Diels–Alder	
Intramolecular nitrile oxide olefin (INOC)	
Ring-closing metathesis	
Hosomi–Sakurai reaction	
Michael/Conia-ene cascade cyclization	
Radical domino cyclization	

1.2 Results and Discussion

1.2.1 Gold(I)-Catalyzed Enyne Cyclizations: Studies Towards the Total Synthesis of (+)-Aureol



1814

Synthesis R. Wildermuth et al. Special Topic

Gold(I)-Catalyzed Enyne Cyclizations: Studies Toward the Total Synthesis of (+)-Aureol

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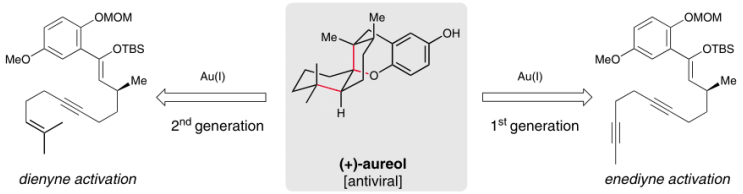


Received: 20.01.2016
Accepted after revision: 01.03.2016
Published online: 12.04.2016
DOI: 10.1055/s-0035-1561589; Art ID: ss-2016-c0046-st

Abstract We report a modular synthetic approach toward the total synthesis of (+)-aureol based on a bioinspired gold(I)-catalyzed enyne cascade cyclization reaction. First, we investigated an array of catalysts to promote a 6-*endo*-dig cyclization of a highly advanced enediyne precursor. Since these studies result exclusively in the formation of the 5-*exo*-dig product, we synthesized and investigated a dienyne cyclization precursor in order to form the benzo[*d*]xanthene skeleton in a stepwise fashion.

Key words meroterpenoids, gold(I) catalysis, natural product synthesis, enynes, cyclization

During the last 30 years, a number of structurally and closely related tetracyclic meroterpenoids such as (+)-aureol (**1**),[1] (+)-strongylin A (**2**),[2] (+)-stachyflin (**3**),[3] and (+)-podosporin A (**4**)[4] have been isolated (Figure 1). All of them, in particular (+)-stachyflin (**3**) as the most potent member of the family, exhibit biological activity against the influenza A (H1N1 strain) virus.[5] The common structural feature of these natural products is the tetracyclic benzo[*d*]xanthene scaffold (ABCD, **5**) that is embedded in a *cis*-fused decalin system (Figure 1).

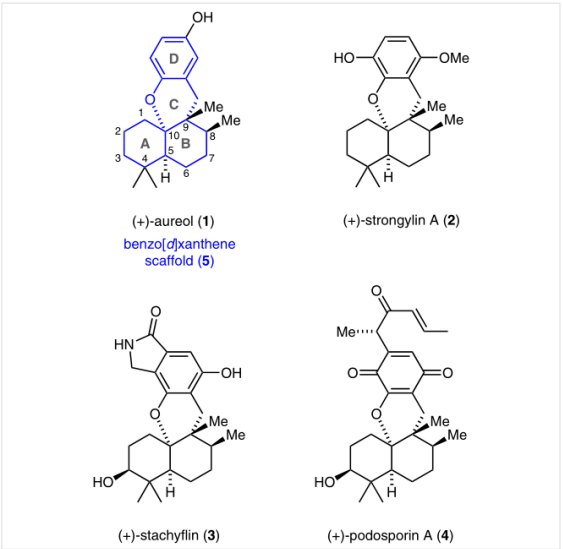
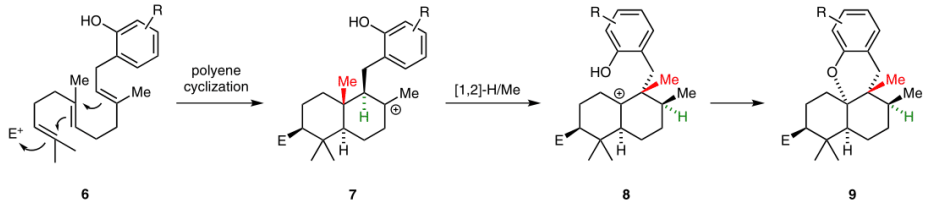


Figure 1 Representative members of structurally related tetracyclic meroterpenoids

The molecular framework of (+)-aureol (**1**) contains four consecutive stereocenters, two of which are quaternary, with the absolute configuration: 1*R*, 2*S*, 3*S* and 6*S*. The *cis*-fused decalin system (AB) is linked to the hydroquinone unit (D) via an ether bond and a methylene bridge forming pyran unit C. Compared to **1**, stachyflin (**3**) and podosporin A (**4**) possess a neopentylic alcohol (8*S*) at C8.

The proposed biosynthetic pathway for compounds **1**–**4** includes a stereospecific polyene cyclization of **6** to form the cationic drimane intermediate **7** (Scheme 1). A sequence of two stereospecific [1,2]-hydride and [1,2]-methyl shifts leads to the formation of the cationic intermediate **8**, which is then trapped by the phenol to give the tetracyclic skeleton **9**.[6] Efforts to mimic this highly orchestrated sequence in the chemical laboratory were previously unsuccessful. With respect to intermediate **7**, attack of the phenol at the tertiary carbon cation occurs faster than the required 1,2-shifts.[7]

Asymmetric syntheses of aureol (**1**) were previously published by George,[6] Marcos,[8] Katoh[9,10] and Schmitz.[11] Common to these syntheses is the use of an already preformed decalin system which is selectively functionalized to form the pyran unit (C) (Scheme 2a).



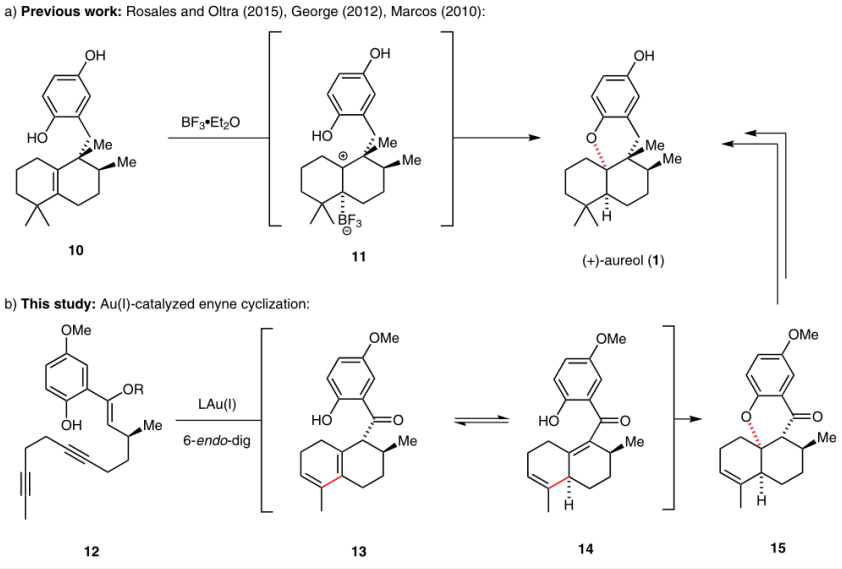
Scheme 1 Generalized biosynthesis of the family of meroterpenoid natural products [E^+= H^+ for aureol (**1**) and strongylin A (**2**); E^+ = 'OH' for stachyflin (**3**) and podosporin A (**4**)]

In 2015, the group of Rosales and Oltra reported a bioinspired racemic synthesis of aureol (**1**) that featured a titanocene(III)-catalyzed radical cyclization cascade for the *de novo* synthesis of the decalin system.[12] In this context, and as part of our recent efforts to develop novel gold(I)-catalyzed cyclization reactions,[13] we designed a bioinspired cascade reaction according to Scheme 2b. Our initial retrosynthetic approach toward **1** was inspired by recent work reported by Toste,[14] Barriault,[15–17] Gagné,[18] Hashmi[19,20] and Corey[21,22] for the cyclization of enynes and relied on a 6-*endo*-dig cascade cyclization of **12**.

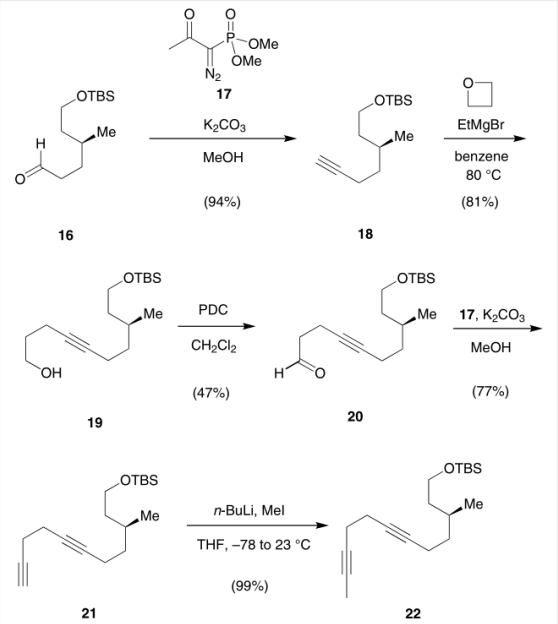
The cyclization precursor **12** contains an enediyne unit which should undergo two consecutive 6-*endo*-dig cyclizations to furnish the decalin framework **13**.[23–26] In the presence of acid,[13] the diene motif of **13** will be protonated to give an allylic tertiary carbocation (compare **11**, Scheme 2a), which either first isomerizes into **14** or is directly trapped by the phenol to furnish **15**. The so-obtained intermediate could be further functionalized via standard transformations to give (+)-aureol (**1**). The developed synthesis of (+)-aureol (**1**) should be flexible enough to incorporate selective modifications in order to access a library of natural and non-natural analogues by simple variations of the arene moiety, e.g., strongylin A (**2**), stachyflin (**3**) and podosporin A (**4**).

We began our synthetic route with the homologation of aldehyde **16**,[27] itself prepared in two steps from (*S*)-(−)-β-citronellol,[28] using Ohira–Bestmann conditions[29] to give **18** in excellent yield (Scheme 3).

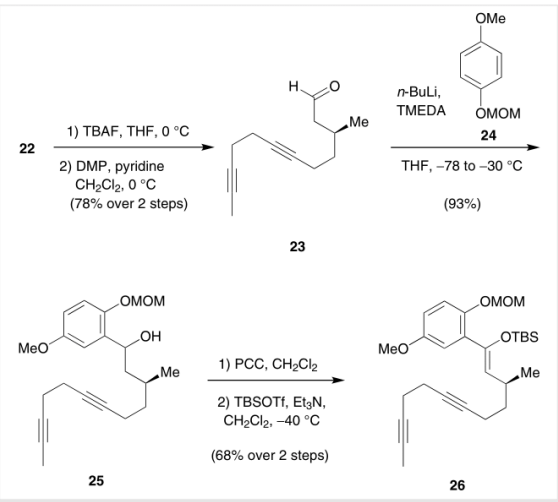
All attempts to access aldehyde **20** directly from alkyne **18** via Ru(II)-[30] or Pd(0)-catalyzed[31] sp–sp^2 coupling resulted in low yields. Therefore, we developed a stepwise sequence that was based on the metalation of **18** with ethylmagnesium bromide followed by nucleophilic ring opening of oxetane at elevated temperature (80 °C). Oxidation of the resulting primary alcohol **19** with pyridinium dichromate (PDC) then gave the corresponding aldehyde **20**. Homologa-



Scheme 2 Strategies for the construction of the tetracyclic carbon skeleton of (+)-aureol (**1**)



Scheme 3 Preparation of enediyne **22**



Scheme 4 Synthesis of the cyclization precursor **26**

tion as above and subsequent methylation of **21** provided diyne **22** in excellent yield.

After cleavage of the silyl ether and oxidation with Dess–Martin periodinane (DMP) to give aldehyde **23**, introduction of the arene unit **24** was accomplished by directed *ortho*-lithiation of **24** and nucleophilic addition to aldehyde **23** (Scheme 4). After oxidation of the benzylic alcohol **25** and silyl enol ether formation, the stage was set to investigate an array of catalysts to promote the cyclization reaction of **26** (Table 1).

Based on Barriault's observation that bulky ligands on the cationic gold center should favor the formation of the 6-*endo*-dig product, we first investigated ligands L1 and L2.[15] Unfortunately, application of [L1AuNCMe]SbF_6 resulted exclusively in the formation of **27** (Table 1, entry 1). Consumption of **26** in the presence of [L1AuNCMe]SbF_6 or [L2AuNCMe]SbF_6 in acetone led to the formation of a novel polycyclic product, the NMR data of which was inconsistent with **27** (Table 1, entries 2 and 5). A detailed analysis of the 2D NMR spectra revealed that the enediyne unit was fully consumed during the course of the reaction, but underwent an undesired 5-*endo*-dig cyclization to give **28**. A plausible mechanism for the formation of **28** is illustrated in Scheme 5.

After activation of the internal alkyne as shown for **30**, nucleophilic attack of the enol ether leads to the formation of intermediate **31**. Protodeauration gives **32**, which undergoes a 5-*endo*-dig cyclization via **33** to form **34**.[32] After protonation of the LAu–C bond to form **35**, desilylation to give **27**, cleavage of the phenolic ether and isomerization of the double bond affords **37**. The latter intermediate undergoes an intramolecular oxa-Michael addition to provide **28**.

While the use of [L3Au]SbF_6[19] in acetone resulted in decomposition, the formation of **27** (21%) was observed in dichloromethane. [Ph_3PAu]SbF_6[15] gave no reaction and **26** was isolated unchanged from the reaction mixture (Table 1, entry 8). Treatment of **26** with indium triiodide[21] (Table 1, entry 9) or the more reactive diiodoindium(III)[22] cationic species (InI_2^+) (Table 1, entry 10) did not result in the formation of a cyclization product, but instead led to cleavage of the MOM group and the TBS enol ether to give ketone **29**. Attempts to activate the alkyne by platinum(II)[18] or mercury(II)[33] resulted in either no conversion or in the formation of a complex mixture (Table 1, entries 11 and 12).

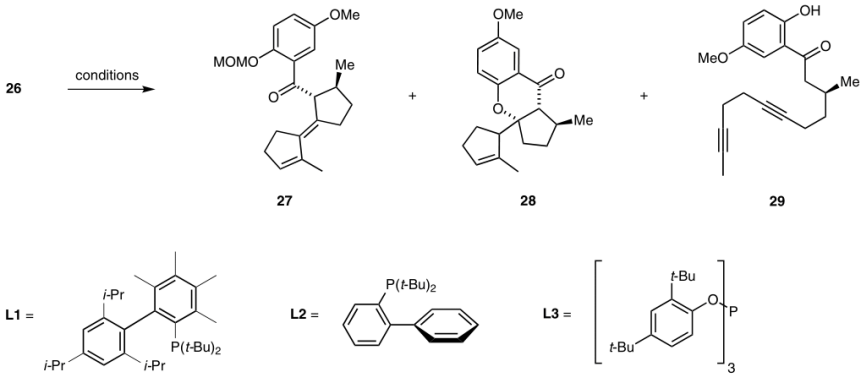
Based on these results, we decided to replace the enediyne, the ability of which to form a gold(I) bis(alkyne) complex[23–25,34] might negatively influence the selectivity, with a dienyne. This substrate class was successfully used previously in a series of 6-*endo*-dig cyclizations.[15]

In our second generation retrosynthesis (Scheme 6), aureol (**1**) was traced back to the known alkene **38** (compare Scheme 2a), which should be accessible from **39** via an acid-catalyzed cationic cyclization. For the formation of **39** from **40** via the envisioned 6-*endo*-dig cyclization, we planned to extend our initial catalyst screening and investigate additional solvents.

The synthesis of the cyclization precursor **40** from aldehyde **20** is shown in Scheme 7.

After Wittig olefination of **20** to give enyne **41**, desilylation with tetra-*n*-butylammonium fluoride followed by oxidation using Dess–Martin periodinane gave aldehyde **42**.

Table 1 Studies on the Cyclization of Enediyne **26**



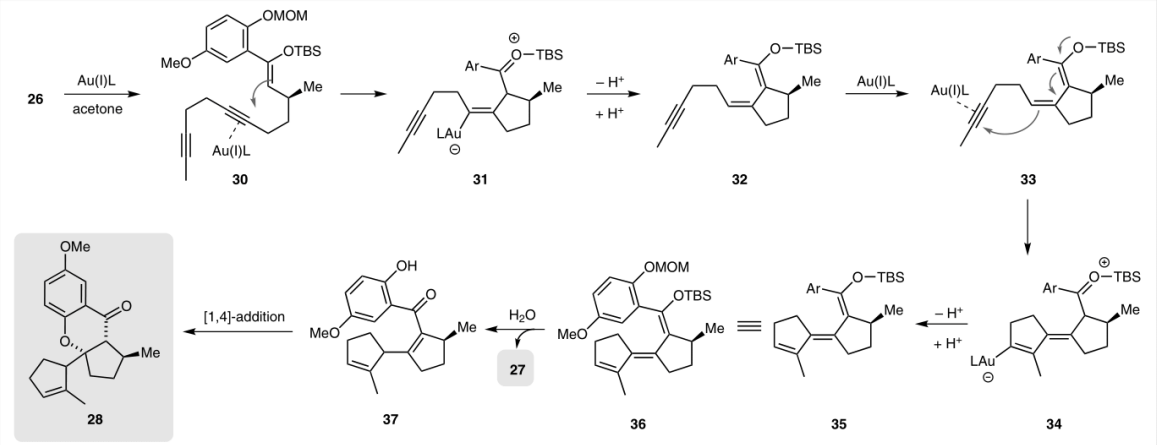
Entry	Catalyst	Solvent	Yield
1	[L1AuNCMe]SbF_6[a]	CH_2Cl_2	**27** (33%)
2	[L1AuNCMe]SbF_6[a]	acetone	**28** (23%)
3	[L1Au]Cl[a]	acetone	no reaction
4	[L1AuNCMe]SbF_6[a]	PhMe	no reaction
5	[L2AuNCMe]SbF_6[a]	acetone	**28** (64%)
6	[L3Au]SbF_6[a]	acetone	decomposition
7	[L3Au]SbF_6[a]	CH_2Cl_2	**27** (21%)
8[b]	[Ph_3PAu]Cl/$AgSbF_6$[b]	CH_2Cl_2	no reaction
9[c]	InI_3[d]	CH_2Cl_2	**29** (89%)
10[c]	InI_3/$AgSbF_6$[d,e]	CH_2Cl_2	**29** (96%)
11	$PtCl_2$[f]	PhMe	complex mixture
12	$Hg(OAc)_2$[g]	CH_2Cl_2	no reaction

[a] 5 mol%.
[b] [PPh_3Au]Cl and $AgSbF_6$ were combined in CH_2Cl_2 (3 mM). After 10 min, the turbid solution was added via a syringe, equipped with a syringe filter (pore size 0.45 μm), to a solution of **26** in CH_2Cl_2 (0.06 M) containing 9% MeOH.
[c] –78 to –20 °C.
[d] 10 mol%.
[e] InI_3 and $AgSbF_6$ were combined in CH_2Cl_2 (5 mM) at 0 °C. After 15 min, a solution of **26** in CH_2Cl_2 (0.1 M) was added at –78 °C.
[f] 20 mol%.
[g] 1.2 equiv.

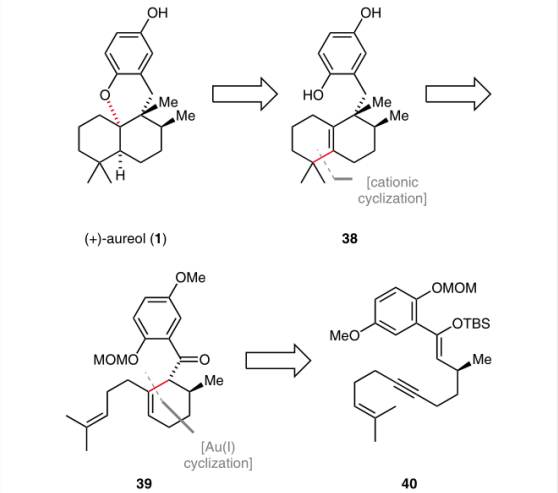
Introduction of the arene unit **24** proceeded in an analogous manner as before and afforded, after generation of the TBS enol ether, the cyclization precursor **40** in good overall yield. With **40** in hand, we were able to investigate an array of catalysts to promote the cyclization reaction (Table 2).

Exposure of **40** to Barriault's gold(I)-catalyst [L1AuNCMe]SbF_6 in either acetone (Table 2, entry 1), methanol (Table 2, entry 2), or dichloromethane (Table 2, entry 3),[15–17] exclusively led to the formation of the five-membered ring products **44** and **45**, whereas the use of toluene only afforded unreacted starting material **40** (Table 2, entries 4 and 8). It was interesting to note that the use of the bulkier ligands L1 (Table 2, entries 1–3) and L4 (Table 2, entry 9) extended the reaction time from 10 minutes (Table 2, entry 5) up to 36 hours (Table 2, entry 9), after which significant amounts of the deprotected cyclization product **45** were isolated. Treatment of **40** with either [Ph_3PAu]Cl/SbF_6 (Table 2, entry 10), indium triiodide (Table 2, entry 11) or InI_2^+ (Table 2, entry 12) only led to cleavage of the TBS enol ether to give **46**. In contrast to the previous cyclization experiments with indium (Table 1), cleavage of the MOM group was not observed at –78 °C.

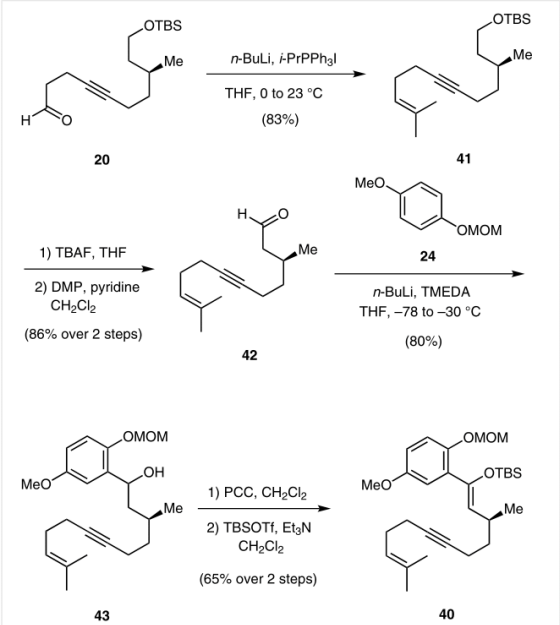
In summary, we have investigated the gold(I)-catalyzed cascade cyclization of two advanced enyne substrates for the synthesis of (+)-aureol (**1**). For the reaction of **26**, we were able to promote a cascade reaction, however, only the 5-*exo*-dig pathway was operative. Exchange of the enediyne **26** for a dienyne precursor **40** had no effect on the selectivity and the 6-*endo*-dig cyclization product was never observed. Despite these initial drawbacks, we are confident



Scheme 5 Proposed mechanism for the formation of **28**



Scheme 6 Second generation retrosynthetic analysis of (+)-aureol (**1**)

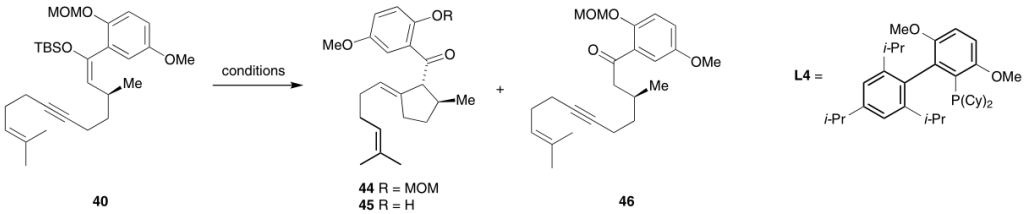


Scheme 7 Preparation of the cyclization precursor **40**

that a precursor can be developed for the successful generation of the decalin framework. Further efforts toward this goal will be reported in due course.

All reactions were performed in dried glassware which had been evacuated while heating with a heat gun (2000 W, 650 °C) and backfilled with N_2 gas three times prior to use. All reaction flasks were fitted with rubber septa under a positive pressure of nitrogen, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula through rubber septa. Solids were added under inert gas atmosphere or were dissolved in appropriate solvents and then transferred via syringe or stainless steel cannula. THF and Et_2O were distilled under N_2 atmosphere from Na/benzophenone prior to use. CH_2Cl_2, Et_3N, diisopropylamine (DIPA), Hünig's base (DIPEA), TMEDA and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) were distilled under N_2 atmosphere from CaH_2 prior to use. DMSO, MeCN, toluene and 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, ABCR) and were used as received. 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 room tempera-

Table 2 Studies on the Cyclization of Dienyne **40**



40

44 R = MOM
45 R = H

46

Entry	Catalyst	Solvent	Yield
1	[L1AuNCMe]SbF_6[a]	acetone	**44** (10%), **45** (58%)
2	[L1AuNCMe]SbF_6[a]	MeOH	**44** (24%), **45** (43%)
3	[L1AuNCMe]SbF_6[a]	CH_2Cl_2	no reaction
4[b]	[L1AuNCMe]SbF_6[a]	PhMe	no reaction
5	[L2AuNCMe]SbF_6[a]	acetone	**45** (73%)
6	[L2AuNCMe]SbF_6[a]	MeOH	**44** (85%)
7[c]	[L2AuNCMe]SbF_6[a]	CH_2Cl_2	**44** (52%)
8[b]	[L2AuNCMe]SbF_6[a]	PhMe	no reaction
9	[L4AuNCMe]SbF_6[a]	MeOH	**45** (69%)
10[d]	[Ph_3PAu]Cl/$AgSbF_6$[e]	CH_2Cl_2	**46** (41%)
11[f]	InI_3[g]	CH_2Cl_2	**46** (92%)
12	InI_3/$AgSbF_6$[g,h]	CH_2Cl_2	**46** (79%)

[a] 5 mol%.
[b] 23 to 50 °C.
[c] –10 to 23 °C.
[d] [Ph_3PAu]Cl and $AgSbF_6$ were combined in CH_2Cl_2 (3 mM). After 10 min, the turbid solution was added via a syringe, equipped with a syringe filter (pore size 0.45 µm), to a solution of **40** in CH_2Cl_2 (0.06 M) containing 9% MeOH.
[e] 5 to 10 mol%.
[f] –78 °C.
[g] 10 mol%.
[h] InI_3 and $AgSbF_6$ were combined in CH_2Cl_2 (5 mM) at 0 °C. After 15 min, a solution of the cyclization precursor in CH_2Cl_2 (0.1 M) was added at –78 °C.

ture (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 aluminum plates precoated with silica gel (0.25 mm, 60 Å pore size, Merck) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to UV light, I_2 dispersed in sand or were stained by submersion in aq $KMnO_4$, cerium ammonium molybdate (CAM) or anisaldehyde (ANIS) solution and were developed by heating with a heat gun. Flash column chromatography was performed as described by Still et al.,[35] employing silica gel (60 Å, 40–63 µm, Merck KGaA). The yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) pure material. Optical rotations were measured using an Anton Paar MCP 200 polarimeter. IR spectra were recorded on a PerkinElmer Spectrum BX II FT-IR system. If required, substances were dissolved in CH_2Cl_2 prior to direct application on the ATR unit. NMR spectra were measured on Bruker Avance III HD 400 MHz and 800 MHz spectrometers equipped with a CryoProbe™, and Bruker AXR300, Varian VXR400 S and Bruker AMX600 spectrometers operating at 400 MHz, 800 MHz, 300 MHz, 400 MHz and 600 MHz for proton nuclei (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). 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). ^1H NMR spectroscopic data are reported as follows: chemical shift [multiplicity, coupling constant(s) (*J*) (Hz), integration intensity). 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. 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 (ionization mode in brackets): MAT 95 (EI) and MAT 90 (ESI) from Thermo Finnigan GmbH. Mass spectra were recorded in high-resolution.

(4*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-4-methylhexanal (16)

To a solution of (–)-(*S*)-citronellol (5.00 g, 32.0 mmol, 1 equiv) and imidazole (4.35 g, 64.0 mmol, 2.00 equiv) in CH_2Cl_2 (200 mL) was added *tert*-butyldimethylsilyl chloride (6.00 g, 40.0 mmol, 1.25 equiv) portionwise at 0 °C. The mixture was allowed to warm to 23 °C. After 3 h, sat. aq NH_4Cl solution (100 mL) was added, the layers were sepa-

rated and the aq layer was extracted with EtOAc (3 × 75 mL). The combined organic layers were washed with sat. aq NaCl solution (100 mL), dried over Na_2SO_4, filtered and the filtrate concentrated to yield the corresponding silyl ether (**47**) as a colorless solid in quantitative yield. Characterization data obtained for **47** were in full agreement with those reported in the literature.[28]

Ozone was bubbled through a solution of **47** (9.60 g, 36.0 mmol, 1 equiv) in CH_2Cl_2 (25 mL), MeOH (25 mL) and pyridine (0.5 mL) at –78 °C. After 30 min, excess ozone was replaced with N_2 before dimethyl sulfide (2.60 g, 41.0 mmol, 1.15 equiv) was added dropwise at –78 °C. The reaction mixture was slowly warmed to 23 °C over 3 h. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (5% EtOAc in hexanes) to yield aldehyde **16** (6.81 g, 77%) as a colorless oil. The obtained characterization data were in full agreement with values reported in the literature.[28]

(3*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-methylhept-6-yne (18)

To a stirred solution of **16** (6.50 g, 26.5 mmol, 1 equiv) and K_2CO_3 (5.51 g, 39.9 mmol, 1.50 equiv) in MeOH (20 mL) was added Bestmann–Ohira reagent (**17**) (5.87 g, 30.6 mmol, 1.15 equiv) dropwise, and the resulting yellow solution was stirred at 23 °C. After 14 h, aq $NaHCO_3$ solution (0.6 M, 20 mL) was added and the aq layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. aq NaCl solution (20 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% EtOAc in hexanes) to yield alkyne **18** (6.01 g, 94%) as a colorless oil. Characterization data obtained for **18** were in full agreement with those reported in the literature.[27]

(8*S*)-10-[(*tert*-Butyldimethylsilyl)oxy]-8-methyldec-4-yn-1-ol (19)

A solution of EtMgBr (17.5 mL, 0.9 M in toluene, 1.20 equiv) was added to a solution of **18** (3.16 g, 13.1 mmol, 1 equiv) in benzene (10 mL) at 0 °C. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 1 h, oxetane (1.53 g, 26.3 mmol, 2.00 equiv) was added and the mixture was heated to 80 °C in a sealed tube. After 3 h, the reaction mixture was diluted with Et_2O (10 mL) and sat. aq NH_4Cl solution (20 mL) was added. The layers were separated and the aq layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (15% EtOAc in hexanes) to yield primary alcohol **19** (3.15 g, 81%) as a colorless oil.

$[\alpha]_D^{22}$ –1.48 (*c* 0.68, CH_2Cl_2); R_f = 0.29 (10% EtOAc in hexanes, CAM, ANIS).

IR (Diamond-ATR, neat): 3343, 2928, 2857, 1471, 1254, 1101, 1058, 1006, 834, 774 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.75 (t, *J* = 6.1 Hz, 2 H), 3.69–3.59 (m, 2 H), 2.33–2.23 (m, 2 H), 2.22–2.07 (m, 2 H), 1.77–1.64 (m, 3 H), 1.57–1.50 (m, 2 H), 1.34–1.29 (m, 2 H), 0.90–0.87 (m, 12 H), 0.05 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 81.0, 79.3, 62.0, 61.4, 39.6, 36.4, 31.7, 28.9, 26.1, 19.3, 18.4, 16.5, 15.5, –5.2, –5.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{35}O_2Si$: 299.2401; found: 299.2403.

(8*S*)-10-[(*tert*-Butyldimethylsilyl)oxy]-8-methyldec-4-ynal (20)

PDC (1.34 g, 3.58 mmol, 2.00 equiv) was added to a stirred solution of **19** (530 mg, 1.79 mmol, 1 equiv) in CH_2Cl_2 (40 mL) containing silica gel (1.9 g) at 23 °C. After 20 h, the solvent was removed and the brown residue was purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to yield aldehyde **20** (251 mg, 47%) as a colorless oil.

$[\alpha]_D^{22}$ –7.05 (*c* 0.23, CH_2Cl_2); R_f = 0.39 (10% EtOAc in hexanes, CAM, ANIS).

IR (Diamond-ATR, neat): 2955, 2360, 1730, 1653, 1559, 1472, 1255, 1092, 896, 836 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.79 (s, 1 H), 3.69–3.56 (m, 2 H), 2.66–2.57 (m, 2 H), 2.53–2.40 (m, 2 H), 2.21–2.06 (m, 2 H), 1.68–1.46 (m, 3 H), 1.37–1.23 (m, 2 H), 0.91–0.84 (m, 12 H), 0.05 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.3, 81.7, 77.8, 61.4, 43.2, 39.7, 36.3, 28.9, 26.1, 19.3, 18.5, 16.5, 12.3, –5.11, –5.14.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{32}O_2{}^{28}Si$: 296.2172; found 296.2168.

(3*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-methylundeca-6,10-diyne (21)

To a solution of **20** (1.56 g, 5.26 mmol, 1 equiv) and K_2CO_3 (1.60 g, 11.6 mmol, 2.20 equiv) in MeOH (20 mL) was added Bestmann–Ohira reagent (**17**) (1.11 g, 5.79 mmol, 1.10 equiv) dropwise, and the resulting yellow solution was stirred at 23 °C. After 14 h, aq $NaHCO_3$ solution (0.6 M, 20 mL) was added and the aq layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. aq NaCl solution (20 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% EtOAc in hexanes) to yield diyne **21** (1.19 g, 77%) as a colorless oil.

$[\alpha]_D^{22}$ –1.44 (*c* 0.835, CH_2Cl_2); R_f = 0.23 (20% EtOAc in hexanes, ANIS).

IR (Diamond-ATR, neat): 3314, 2955, 1472, 1463, 1387, 1255, 1005, 939, 810, 775 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.73–3.51 (m, 2 H), 2.42–2.31 (m, 4 H), 2.24–2.10 (m, 2 H), 2.04–1.95 (m, 1 H), 1.76–1.62 (m, 1 H), 1.60–1.48 (m, 2 H), 1.38–1.23 (m, 2 H), 0.88 (d, *J* = 2.2 Hz, 12 H), 0.04 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 83.2, 81.6, 78.2, 69.1, 61.4, 39.7, 36.4, 28.9, 26.1, 19.3, 19.1, 18.5, 16.5, –5.11, –5.14.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{33}O^{28}Si$: 293.2295; found: 293.2299.

(3*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-methyldodeca-6,10-diyne (22)

A solution of *n*-BuLi (2.08 mL, 2.4 M in hexanes, 5.00 mmol, 1.10 equiv) was added to a solution of **21** in THF (10 mL) at –78 °C. After 20 min, the reaction mixture was allowed to warm to 0 °C. After 30 min, the reaction mixture was cooled to –78 °C, MeI (0.56 mL, 9.09 mmol, 2.00 equiv) was added dropwise and the reaction mixture was allowed to warm to 23 °C. After 3 h, Et_2O (20 mL) and sat. aq NH_4Cl solution (50 mL) were added. The layers were separated and the aq layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with sat. aq NaCl solution (50 mL), dried over Na_2SO_4 filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (1% EtOAc in hexanes) to yield diyne **22** (1.39 g, 99%) as a colorless oil.

$[\alpha]_D^{22}$ –1.60 (*c* 0.75, CH_2Cl_2); R_f = 0.58 (10% EtOAc in hexanes, ANIS).

IR (Diamond-ATR, neat): 2983, 1489, 1328, 1286, 1109, 1013, 910, 876, 603 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.72–3.57 (m, 2 H), 2.31 (s, 3 H), 2.24–2.09 (m, 2 H), 1.78 (s, 3 H), 1.72–1.63 (m, 1 H), 1.60–1.47 (m, 2 H), 1.42–1.17 (m, 3 H), 0.94–0.81 (m, 12 H), 0.05 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 81.3, 78.8, 78.1, 76.5, 61.4, 39.7, 36.4, 28.9, 26.1, 19.6, 19.5, 19.4, 18.5, 16.6, 3.7, –5.11, –5.14.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{19}H_{34}O^{28}Si$: 306.2379; found: 306.2382.

(3*S*)-3-Methyldodeca-6,10-diyn-1-ol (48)

To a solution of **22** (1.39 g, 4.53 mmol, 1 equiv) in THF (24 mL) was added TBAF (5.89 mL, 1 M in THF, 5.89 mmol, 1.30 equiv) at 0 °C. After 2 h, the reaction mixture was diluted with Et_2O (30 mL) and sat. $NaHCO_3$ solution (40 mL). The layers were separated and the aq layer was extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with sat. aq NaCl solution (60 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated. The crude residue was purified by flash column chromatography on silica gel (30% EtOAc in hexanes) to afford alcohol **48** (750 mg, 86%) as a colorless oil. See the supporting information for details.

$[\alpha]_D^{22}$ –3.13 (*c* 5.56, CH_2Cl_2); R_f = 0.38 (30% EtOAc in hexanes, CAM).

IR (Diamond-ATR, neat): 3336, 2920, 2873, 1434, 1340, 1260, 1057, 1011, 962, 845 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.76–3.60 (m, 2 H), 2.35–2.25 (m, 4 H), 2.24–2.10 (m, 2 H), 1.81–1.75 (m, 3 H), 1.74–1.66 (m, 1 H), 1.64–1.48 (m, 2 H), 1.42–1.29 (m, 2 H), 0.90 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 81.1, 79.0, 78.0, 76.5, 61.1, 39.6, 36.2, 28.8, 19.6, 19.5, 19.4, 16.6, 3.6.

HRMS (ESI): *m*/*z* $[M + NH_4]^+$ calcd for $C_{13}H_{24}NO$: 210.1852; found: 210.1854.

(3*S*)-3-Methyldodeca-6,10-diynal (23)

Dess–Martin periodinane (2.48 g, 5.85 mmol, 1.50 equiv) was added to a solution of alcohol **48** (750 mg, 3.90 mmol, 1 equiv) and pyridine (1.58 mL, 19.5 mmol, 5.00 equiv) in CH_2Cl_2 (20 mL) at 0 °C. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 6 h, hexanes (80 mL) was added and the resulting suspension was filtered through a plug of silica (20% EtOAc in hexanes, 200 L). The solvent was removed to yield aldehyde **23** (672 mg, 91%) as a yellow oil.

$[\alpha]_D^{22}$ –11.56 (*c* 3.98, CH_2Cl_2); R_f = 0.50 (20% EtOAc in hexanes, ANIS, CAM).

IR (Diamond-ATR, neat): 2956, 2720, 1723, 1434, 1380, 1179, 1024, 902, 867, 737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (s, 1 H), 2.47–2.40 (m, 1 H), 2.34–2.27 (m, 4 H), 2.27–2.16 (m, 4 H), 1.80–1.76 (m, 3 H), 1.58–1.50 (m, 1 H), 1.48–1.38 (m, 1 H), 0.97 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.8, 80.4, 79.5, 78.0, 76.6, 50.7, 35.9, 27.4, 19.7, 19.6, 19.5, 16.6, 3.6.

HRMS (GC/EI): *m*/*z* $[M – H]^+$ calcd for $C_{13}H_{17}O$: 189.1285; found: 189.1302.

(3*S*)-1-[5-Methoxy-2-(methoxymethoxy)phenyl]-3-methyldodeca-6,10-diyn-1-ol (25)

To a solution of **24** (1.01 g, 5.99 mmol, 1.70 equiv) in THF (15 mL) and *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (1.81 mL, 12.0 mmol, 3.40 equiv) was added a solution of *n*-BuLi (2.49 mL, 2.44 M in hexanes, 5.99 mmol, 1.70 equiv) at –78 °C and the reaction mixture was allowed to warm to –30 °C. After 1.5 h, the reaction mixture was cooled to –78 °C and a solution of aldehyde **23** (670 mg, 3.52 mmol, 1 equiv) in THF (6 mL) was added. The reaction mixture was warmed to –30 °C over 2 h, diluted with Et_2O (30 mL) and sat. aq NH_4Cl solution (30 mL) was added. The layers were separated and the aq layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with sat. aq NaCl solution (50 ml), dried over Na_2SO_4 and filtered. The filtrate was concentrated and the crude residue was filtered through a pad of silica (20% EtOAc in hexanes) to yield benzylic alcohol **25** (1.17 g, 93%) as a yellow oil. The obtained mixture of diastereoisomers was characterized by HRMS and IR and used without further purification.

R_f = 0.13 (20% EtOAc in hexanes, ANIS, CAM).

IR (Diamond-ATR, neat): 3443, 2919, 1608, 1494, 1216, 1150, 1076, 1039, 809, 710 cm^{-1}.

HRMS (ESI): *m*/*z* $[M + NH_4]^+$ calcd for $C_{22}H_{34}O_4N$: 376.2482; found: 376.2487.

(3*S*)-1-[5-Methoxy-2-(methoxymethoxy)phenyl]-3-methyldodeca-6,10-diyn-1-one (49)

PCC (1.21 g, 5.62 mmol, 1.80 equiv) was added to a solution of **25** (1.12 g, 3.12 mmol, 1 equiv) in CH_2Cl_2 (30 mL) containing ground 4 Å MS (1.00 g). After 14 h, the dark brown suspension was filtered through a pad of Celite® and the filtrate was concentrated. The crude residue was purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to yield ketone **49** (901 mg, 81%) as a colorless oil. See the supporting information for details.

$[\alpha]_D^{22}$ +6.23 (*c* 3.02, CH_2Cl_2); R_f = 0.33 (20% EtOAc in hexanes, CAM, UV).

IR (Diamond-ATR, neat): 2919, 1675, 1492, 1417, 1277, 1219, 1193, 1153, 1042, 990 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18–7.09 (m, 2 H), 6.98 (dd, *J* = 9.0, 3.2 Hz, 1 H), 5.24–5.16 (m, 2 H), 3.81 (s, 3 H), 3.52 (s, 3 H), 3.06–2.78 (m, 2 H), 2.34–2.27 (m, 4 H), 2.27–2.15 (m, 3 H), 1.79 (s, 3 H), 1.61–1.55 (m, 1 H), 1.47–1.41 (m, 1 H), 0.96 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.6, 154.5, 150.1, 130.6, 119.3, 116.9, 113.8, 95.5, 80.9, 79.1, 78.0, 76.5, 56.4, 55.9, 50.9, 36.3, 29.2, 19.7, 19.6, 19.5, 16.7, 3.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{29}O_4$: 357.2060; found: 357.2063.

(3*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-[5-methoxy-2-(methoxymethoxy)phenyl]-3-methyldodeca-1-en-6,10-diyne (26)

To a solution of **49** (831 mg, 2.33 mmol, 1 equiv) and Et_3N (649 mL, 4.67 mmol, 2.00 equiv) in CH_2Cl_2 (12 mL) was added TBSOTf (590 mL, 2.57 mmol, 1.1 equiv) at –78 °C. After 45 min, the reaction mixture was allowed to warm to –40 °C. After 2 h, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and aq phosphate buffer solution (pH 7, 30 mL) was added. The layers were separated and the aq layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. aq NaCl solution (40 mL), dried over Na_2SO_4, filtered and the filtrate concentrated. The crude residue was purified by flash column chromatography on silica gel (7% EtOAc in hexanes) to yield enol ether **26** (925 mg, 84%) as a colorless oil.

$[\alpha]_D^{22}$ +22.03 (*c* 2.66, CH_2Cl_2); R_f = 0.64 (20% EtOAc in hexanes, CAM, UV).

IR (Diamond-ATR, neat): 2929, 2856, 1493, 1216, 1194, 1154, 1044, 1006, 836, 779 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07 (d, *J* = 8.9 Hz, 1 H), 6.93 (d, *J* = 3.2 Hz, 1 H), 6.83 (dd, *J* = 8.9, 3.2 Hz, 1 H), 5.21–5.12 (m, 2 H), 4.78 (d, *J* = 9.5 Hz, 1 H), 3.86 (s, 3 H), 3.59 (s, 3 H), 2.93–2.81 (m, 1 H), 2.41 (hept, *J* = 2.5 Hz, 4 H), 2.38–2.21 (m, 2 H), 1.89 (s, 3 H), 1.71–1.51 (m, 2 H), 1.11 (d, *J* = 6.7 Hz, 3 H), 1.02 (s, 9 H), 0.00 (s, 3 H), –0.03 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.3, 148.6, 145.7, 131.4, 119.6, 117.8, 115.6, 113.8, 95.8, 81.8, 78.5, 78.1, 76.5, 56.3, 55.8, 37.3, 29.9, 25.9, 25.8, 20.8, 19.6, 18.4, 17.1, 3.7, –4.2, –4.3.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{28}H_{42}O_4{}^{28}Si$: 470.2852; found:470.2839.

Gold(I)-Catalyzed Cyclization; Typical Procedure (Table 1)

To a solution of **26** (123 mg, 0.261 mmol, 1 equiv) in CH_2Cl_2 (13 mL, 0.02 M) was added the gold(I) complex [L1AuNCMe]SbF_6 (12.5 mg, 13.1 µmol, 5.00 mol%) at 23 °C. After 23 h, the reaction mixture was filtered through a plug of silica, the solvent was removed and the residue was purified by flash column chromatography on silica gel (8% EtOAc in hexanes) to yield **27** (31 mg, 33%) as a yellow oil.

{(2*R*,3*S*)-2′,3-Dimethyl-[1,1′-bi(cyclopentylidene)]-2′-enylidene-2-yl}[5-methoxy-2-(methoxymethoxy)phenyl]methanone (27)

$[\alpha]_D{}^{22}$ +47.8 (*c* 0.48, CH_2Cl_2); R_f = 0.23 (10% EtOAc in hexanes, ANIS, UV).

IR (Diamond-ATR, neat): 2953, 1677, 1493, 1417, 1278, 1221, 1153, 991, 660 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 9.0 Hz, 1 H), 7.21 (d, *J* = 3.2 Hz, 1 H), 7.06 (dd, *J* = 9.0, 3.3 Hz, 1 H), 5.84–5.75 (m, 1 H), 5.31 (s, 2 H), 4.18–4.11 (m, 1 H), 3.88 (s, 3 H), 3.60 (s, 3 H), 2.98–2.74 (m, 2 H), 2.57–2.26 (m, 5 H), 2.21–2.01 (m, 4 H), 1.56–1.43 (m, 1 H), 1.13 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.7, 154.3, 149.8, 141.3, 140.8, 135.0, 131.1, 130.8, 118.7, 116.7, 114.1, 95.2, 65.3, 56.3, 55.8, 38.8, 33.5, 31.6, 29.8, 29.5, 20.7, 17.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{29}O_4$: 357.2060; found: 357.2063.

(1*S*,3a*R*,9a*R*)-7-Methoxy-1-methyl-3a-(2-methylcyclopent-2-en-1-yl)-2,3,3a,9a-tetrahydrocyclopenta[*b*]chromen-9(1*H*)-one (28)

$[\alpha]_D{}^{22}$ +104.0 (*c* 1.40, CH_2Cl_2); R_f = 0.51 (20% EtOAc in hexanes, CAM, UV).

IR (Diamond-ATR, neat): 2926, 2854, 1678, 1485, 1430, 1285, 1215, 1036 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 3.2 Hz, 1 H), 7.09 (dd, *J* = 9.0, 3.2 Hz, 1 H), 6.83 (d, *J* = 9.0 Hz, 1 H), 5.45–5.37 (m, 1 H), 3.80 (s, 3 H), 3.06 (s, 1 H), 2.44–2.33 (m, 1 H), 2.29–2.11 (m, 4 H), 2.03–1.89 (m, 3 H), 1.87–1.80 (m, 3 H), 1.47–1.31 (m, 2 H), 1.11 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 194.6, 153.8, 153.7, 141.0, 128.1, 125.7, 119.9, 119.0, 107.2, 97.5, 60.7, 55.9, 49.7, 38.0, 32.2, 31.9, 30.8, 27.0, 18.8, 17.6.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{20}H_{24}O_3$: 312.1725; found: 312.1724.

(3*S*)-1-(2-Hydroxy-5-methoxyphenyl)-3-methyldodeca-6,10-diyn-1-one (29)

InI_3 (1.2 mg, 2.3 µmol, 10 mol%) and silver hexafluoroantimonate ($AgSbF_6$) (0.8 mg, 2.3 µmol, 10 mol%) were combined in CH_2Cl_2 (0.5 mL) at 0 °C. After 15 min, a solution of the cyclization precursor **26** (11 mg, 23 µmol, 1 equiv) in CH_2Cl_2 (0.25 mL) was added at –78 °C. The reaction mixture was allowed to warm to –20 °C over a period of 30 min, and then diluted with CH_2Cl_2 (4 mL) and sat. aq $NaHCO_3$ solution (6 mL). The layers were separated and the aq layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with sat. aq NaCl solution (12 mL), dried over Na_2SO_4, filtered and the filtrate concentrated. The crude residue was purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to yield phenol **29** (7 mg, 96%) as a yellow oil.

$[\alpha]_D{}^{22}$ +13.44 (*c* 0.83, CH_2Cl_2); R_f = 0.56 (20% EtOAc in hexanes, CAM, UV).

IR (Diamond-ATR, neat): 2920 (br), 1643, 1486, 1338, 1288, 1199, 1042, 907, 839, 772 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 12.01 (s, 1 H), 7.21 (d, *J* = 3.1 Hz, 1 H), 7.11 (dd, *J* = 9.1, 3.1 Hz, 1 H), 6.93 (d, *J* = 9.1 Hz, 1 H), 3.81 (s, 3 H), 3.03 (dd, *J* = 15.5, 5.5 Hz, 1 H), 2.71 (dd, *J* = 15.5, 8.3 Hz, 1 H), 2.36–2.18 (m, 7 H), 1.76 (s, 3 H), 1.65–1.57 (m, 1 H), 1.53–1.45 (m, 1 H), 0.99 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 206.0, 157.1, 151.8, 123.9, 119.5, 119.3, 113.4, 80.6, 79.5, 78.0, 76.5, 56.2, 45.4, 36.2, 29.5, 19.8, 19.5, 16.7, 3.6.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{20}H_{24}O_3$: 312.1725; found: 312.1714.

(3*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3,11-dimethyldodec-10-en-6-yne (41)

To a suspension of isopropyltriphenylphosphonium iodide (*i*-$PrPPh_3I$) (623 mg, 1.44 mmol, 1.70 equiv) in THF (10 mL) was added a solution of *n*-BuLi (0.480 mL, 2.36 M in hexanes, 1.14 mmol, 1.35 equiv) at 0 °C. After 45 min, a solution of **20** (251 mg, 0.846 mmol, 1 equiv) in THF (3 mL) was added at the same temperature and the reaction mixture was allowed to warm to 23 °C. After 30 min, the mixture was diluted with H_2O (30 mL) and the layers were separated. The aq phase was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel (5% EtOAc with hexanes) to yield olefin **41** (228 mg, 83%) as a colorless oil.

$[\alpha]_D{}^{22}$ –0.25 (*c* 0.79, CH_2Cl_2); R_f = 0.39 (10% EtOAc in hexanes, ANIS).

IR (Diamond-ATR, neat): 2955, 1471, 1434, 1377, 1360, 1254, 1093, 896, 835, 774 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.20–5.11 (m, 1 H), 3.70–3.58 (m, 2 H), 2.20–2.10 (m, 6 H), 1.73–1.64 (m, 4 H), 1.62 (s, 3 H), 1.58–1.47 (m, 2 H), 1.38–1.27 (m, 2 H), 0.90–0.86 (m, 12 H), 0.05 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 132.8, 123.3, 123.3, 80.3, 80.1, 61.5, 39.7, 36.5, 28.9, 28.1, 26.1, 25.9, 19.43, 19.35, 18.5, 17.9, 16.6, –5.11, –5.14.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{20}H_{38}O^{28}Si$: 322.2692; found 322.2686.

(3*S*)-3,11-Dimethyldodec-10-en-6-yn-1-ol (50)

To a mixture of **41** (4.32 g, 13.4 mmol, 1 equiv) in THF (10 mL) was added a solution of TBAF (8.30 mL, 1 M in THF, 27.8 mmol, 3.00 equiv) at 0 °C. After 2 h, the reaction mixture was diluted with CH_2Cl_2 (40 mL) and sat. aq NH_4Cl solution (30 mL). The layers were separated and the aq layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. NaCl solution (90 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated. The crude residue was purified by flash column chromatography on silica gel (25% EtOAc in hexanes) to afford alcohol **50** (2.74 g, 98%) as a colorless oil. See the supporting information for details.

$[\alpha]_D{}^{22}$ –1.45 (*c* 0.275, CH_2Cl_2); R_f = 0.59 (40% EtOAc in hexanes, ANIS, CAM).

IR (Diamond-ATR, neat): 3335, 2927, 2358, 2340, 1456, 1435, 1057, 667 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.14 (m, 1 H), 3.80–3.57 (m, 2 H), 2.27–2.05 (m, 6 H), 1.71–1.28 (m, 11 H), 0.91 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.8, 123.3, 80.3, 80.2, 61.2, 39.7, 36.4, 28.9, 28.1, 25.8, 19.40, 19.39, 17.9, 16.6.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{24}O$: 208.1827; found: 208.1807.

(3*S*)-3,11-Dimethyldodec-10-en-6-ynal (42)

To a stirred solution of Dess–Martin periodinane (1.60 g, 3.76 mmol, 2.00 equiv) and pyridine (0.61 mL, 7.53 mmol, 4.00 equiv) in CH_2Cl_2 (10 mL) was added **50** (392 mg, 1.88 mmol, 1 equiv) at 0 °C. After 3 h, the clear yellow solution was diluted with Et_2O (20 mL) and was filtered through a thin pad of Celite®. The residual white solid was washed with Et_2O (30 mL) and the filtrate was concentrated. The crude residue was purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford aldehyde **42** (341 mg, 88%) as a colorless oil.

$[\alpha]_D^{22}$ –2.13 (*c* 0.38, CH_2Cl_2); R_f = 0.86 (43% EtOAc in hexanes, CAM).

IR (Diamond-ATR, neat): 2960, 2919, 2857, 2717, 1725, 1453, 1378, 1107, 1008, 889 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (s, 1 H), 5.16 (s, 1 H), 2.42 (t, *J* = 10.0 Hz, 1 H), 2.34–2.11 (m, 8 H), 1.71 (s, 3 H), 1.62 (s, 3 H), 1.59–1.49 (m, 1 H), 1.47–1.38 (m, 1 H), 0.98 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.9, 132.9, 123.2, 80.8, 79.5, 50.8, 36.1, 28.1, 27.5, 25.9, 19.8, 19.5, 18.0, 16.7.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{22}O$: 206.1671; found: 206.1661.

(3*S*)-1-[5-Methoxy-2-(methoxymethoxy)phenyl]-3,11-dimethyldodec-10-en-6-yn-1-ol (43)

To a solution of **24** (65.0 mg, 0.386 mmol, 1.50 equiv) in THF (1 mL) and *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (0.117 mL, 0.773 mmol, 3.00 equiv) was added a solution of *n*-BuLi (0.173 mL, 2.48 M in hexanes, 0.386 mmol, 1.50 equiv) at –78 °C and the reaction mixture was allowed to warm to –30 °C. After 1.5 h, the reaction mixture was cooled to –78 °C and aldehyde **42** (53.2 mg, 0.258 mmol, 1 equiv) in THF (0.5 mL) was added. The reaction mixture was warmed to –30 °C over 2 h, and then diluted with Et_2O (10 mL) and sat. aq NH_4Cl solution (15 mL). The layers were separated and the aq layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with sat. aq NaCl solution (20 ml), dried over Na_2SO_4 and filtered. The filtrate was concentrated and the crude residue was purified by flash column chromatography on silica gel (20% EtOAc in hexanes) to yield benzylic alcohol **43** (78.1 mg, 80%) as a yellow oil. The obtained mixture of diastereoisomers was characterized by HRMS and IR spectroscopy.

R_f = 0.32 (20% EtOAc in hexanes, CAM).

IR (Diamond-ATR, neat): 3443, 2927, 1737, 1595, 1493, 1463, 1215, 1191, 1076, 998 cm^{-1}.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{23}H_{34}O_4$: 374.2457; found: 374.2458.

(3*S*)-1-[5-Methoxy-2-(methoxymethoxy)phenyl]-3,11-dimethyldodec-10-en-6-yn-1-one (46)

PCC (94.1 mg, 0.437 mmol, 1.50 equiv) was added to a solution of **43** (109 mg, 0.291 mmol, 1 equiv) in CH_2Cl_2 (0.5 mL) containing ground 4 Å MS (80 mg). After 14 h, the dark brown suspension was filtered through a pad of Celite® and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to yield ketone **46** (85 mg, 78%) as a colorless oil.

$[\alpha]_D^{22}$ +8.52 (*c* 3.43, CH_2Cl_2); R_f = 0.72 (30% EtOAc in hexanes, UV, CAM).

IR (Diamond-ATR, neat): 2956, 2915, 1675, 1582, 1492, 1464, 1276, 1219, 1042, 989 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15–7.08 (m, 2 H), 6.96 (dd, *J* = 9.0, 3.2 Hz, 1 H), 5.18 (s, 2 H), 5.16–5.10 (m, 1 H), 3.79 (s, 3 H), 3.49 (s, 3 H), 3.01 (dd, *J* = 16.0, 5.5 Hz, 1 H), 2.78 (dd, *J* = 16.0, 8.1 Hz, 1 H), 2.29–2.07 (m, 7 H), 1.69 (s, 3 H), 1.59 (d, *J* = 7.8 Hz, 4 H), 1.49–1.34 (m, 1 H), 0.94 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.6, 154.5, 150.1, 132.8, 130.6, 123.3, 119.3, 116.9, 113.8, 95.5, 80.4, 80.0, 56.4, 55.9, 50.9, 36.5, 29.2, 28.1, 25.8, 19.7, 19.4, 17.9, 16.7.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{23}H_{32}O_4$: 372.2301; found: 372.2302.

(3*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-[5-methoxy-2-(methoxymethoxy)phenyl]-3,11-dimethyldodeca-1,10-dien-6-yne (40)

To a solution of **46** (169 mg, 0.454 mmol, 1 equiv) and Et_3N (126 µL, 0.907 µmol, 2.00 equiv) in CH_2Cl_2 (5 mL) was added TBSOTf (116 µL, 0.500 mmol, 1.10 equiv) dropwise at –78 °C. After 45 min, the reaction mixture was allowed to warm to –40 °C. After 2 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and aq phosphate buffer solution (pH = 7, 30 mL) was added. The layers were separated and the aq layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with sat. aq NaCl solution (20 mL), dried over Na_2SO_4, filtered and the filtrate concentrated. The crude residue was purified by flash column chromatography on silica gel (7% EtOAc in hexanes) to yield enol ether **40** (192 mg, 87%) as a colorless oil.

$[\alpha]_D^{22}$ +8.73 (*c* 0.97, CH_2Cl_2); R_f = 0.58 (14% EtOAc in hexanes, UV, CAM).

IR (Diamond-ATR, neat): 2954, 2928, 1659, 1494, 1471, 1216, 1154, 1079, 1006, 937 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (d, *J* = 9.0 Hz, 1 H), 6.83 (d, *J* = 3.2 Hz, 1 H), 6.74 (dd, *J* = 9.0, 3.2 Hz, 1 H), 5.21–5.13 (m, 1 H), 5.08 (s, 2 H), 4.69 (d, *J* = 9.5 Hz, 1 H), 3.76 (s, 3 H), 3.49 (s, 3 H), 2.85–2.69 (m, 1 H), 2.35–2.02 (m, 6 H), 1.70 (s, 3 H), 1.62 (s, 3 H), 1.58–1.41 (m, 2 H), 1.05–0.99 (m, 3 H), 0.93–0.91 (m, 9 H), –0.10 (s, 3 H), –0.13 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.3, 148.6, 145.7, 132.8, 131.5, 123.3, 119.7, 117.8, 115.6, 113.8, 95.8, 80.8, 79.8, 56.3, 55.8, 37.4, 29.9, 28.2, 26.3, 25.9, 20.8, 19.5, 18.4, 17.9, 17.1, –4.2, –4.3.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{46}O_4{}^{28}Si$: 487.3238; found: 487.3235.

Gold(I)-Catalyzed Cyclization; Typical Procedure (Table 2)

To a solution of **40** (192 mg, 0.394 mmol, 1 equiv) in MeOH (0.5 mL, 0.8 M) was added the gold(I) complex [L2AuNCMe]SbF_6 (15.2 mg, 19.7 µmol, 5 mol%). After 20 min, the reaction mixture was filtered through a plug of silica, the solvent was removed and the residue was purified by flash column chromatography on silica gel (5% EtOAc in hexanes) to yield **44** (124 mg, 85%) as a yellow oil.

(1*R*,2*S*)-5-Methoxy-2-(methoxymethoxy)phenyl-1-[2-methyl-5-(5-methylhex-4-en-1-ylidene)cyclopentyl]methanone (44)

$[\alpha]_D^{22}$ +25.74 (*c* 0.29, CH_2Cl_2); R_f = 0.47 (10% EtOAc in hexanes, UV, CAM).

IR (Diamond-ATR, neat): 2953, 1683, 1607, 1492, 1220, 1152, 1080, 1042, 1220, 992 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 9.0 Hz, 1 H), 7.02 (d, *J* = 3.2 Hz, 1 H), 6.94 (dd, *J* = 9.0, 3.3 Hz, 1 H), 5.46–5.36 (m, 1 H), 5.18 (s, 2 H), 5.05–4.93 (m, 1 H), 4.10–4.02 (m, 1 H), 3.77 (s, 3 H), 3.48 (s, 3 H), 2.52–2.30 (m, 3 H), 1.98–1.80 (m, 5 H), 1.63 (s, 3 H), 1.53 (s, 3 H), 1.30–1.22 (m, 1 H), 1.01 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.8, 154.4, 149.5, 142.2, 131.7, 131.2, 124.3, 124.0, 118.5, 116.6, 114.1, 95.2, 60.9, 56.3, 55.9, 39.9, 33.5, 33.3, 30.4, 28.0, 25.8, 20.8, 17.8.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{23}H_{32}O_4$: 372.2301; found: 372.2298.

(1*R*,2*S*)-2-Hydroxy-5-methoxyphenyl-1-[2-methyl-5-(5-methylhex-4-en-1-ylidene)cyclopentyl]methanone (45)

$[\alpha]_D^{22}$ +34.45 (*c* 0.14, CH_2Cl_2); R_f = 0.43 (10% EtOAc in hexanes, UV, CAM).

IR (Diamond-ATR, neat): 2954 (br), 1637, 1484, 1355, 1265, 1170, 1042, 999, 828 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 12.19 (s, 1 H), 7.31 (d, *J* = 3.1 Hz, 1 H), 7.13 (dd, *J* = 9.0, 3.1 Hz, 1 H), 6.95 (d, *J* = 9.0 Hz, 1 H), 5.47–5.41 (m, 1 H), 4.99–4.93 (m, 1 H), 3.91 (d, *J* = 6.8 Hz, 1 H), 3.81 (s, 3 H), 2.63–2.55 (m, 1 H), 2.51–2.44 (m, 1 H), 2.38–2.29 (m, 1 H), 2.02–1.95 (m, 1 H), 1.94–1.88 (m, 2 H), 1.81–1.73 (m, 2 H), 1.62 (s, 3 H), 1.49 (s, 3 H), 1.42–1.33 (m, 1 H), 1.15 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 208.9, 157.7, 151.7, 142.5, 132.1, 124.2, 124.0, 123.9, 119.7, 118.8, 113.3, 57.0, 56.1, 42.6, 34.1, 34.0, 30.6, 27.8, 25.8, 20.1, 17.7.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{21}H_{28}O_3$: 328.2038; found: 328.2031.

Acknowledgment

We gratefully acknowledge financial support from the FCI (Sachkostenzuschuss to T.M. and Doktorandenstipendium to K.S.) and the DFG (Emmy Noether Fellowship to T.M.). We thank Dr. Oliver Thorn-Seshold for helpful discussions during the preparation of the manuscript.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561589.

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1.2.2 A Modular Synthesis of Tetracyclic Meroterpenoid Antibiotics

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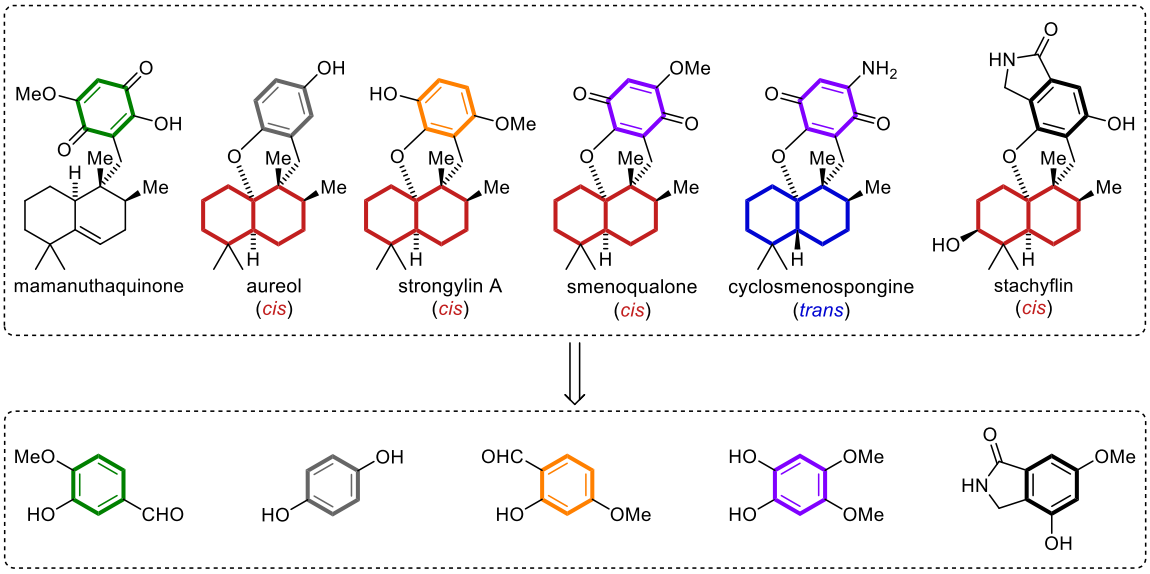

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DOI: 10.1038/s41467-017-02061-7 OPEN

A modular synthesis of tetracyclic meroterpenoid antibiotics

Raphael Wildermuth[1], Klaus Speck[1], Franz-Lucas Haut[1], Peter Mayer[1], Bianka Karge[2], Mark Brönstrup[2] & Thomas Magauer[1,3]

Stachyflin, aureol, smenoqualone, strongylin A, and cyclosmenospongine belong to a family of tetracyclic meroterpenoids, which, by nature of their unique molecular structures and various biological properties, have attracted synthetic and medicinal chemists alike. Despite their obvious biosynthetic relationship, only scattered reports on the synthesis and biological investigation of individual meroterpenoids have appeared so far. Herein, we report a highly modular synthetic strategy that enabled the synthesis of each of these natural products and 15 non-natural derivatives. The route employs an auxiliary-controlled Diels–Alder reaction to enable the enantioselective construction of the decalin subunit, which is connected to variously substituted arenes by either carbonyl addition chemistry or sterically demanding sp^2–sp^3 cross-coupling reactions. The selective installation of either the *cis*- or *trans*-decalin stereochemistry is accomplished by an acid-mediated cyclization/isomerization reaction. Biological profiling reveals that strongylin A and a simplified derivative thereof have potent antibiotic activity against methicillin-resistant *Staphylococcus aureus*.

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Meroterpenoids, which are derived from a mixed biosynthetic terpenoid pathway, display a broad spectrum of biological activities and are equipped with a wealth of structural complexity that originates from highly sophisticated biosynthetic pathways[1–9]. The structurally-related natural products stachyflin (**1**)[10], aureol (**2**)[8,11], smenoqualone (**3**)[12], strongylin A (**4**)[13], cyclosmenospongine (**5**)[14], and mamanuthaquinone (**6**)[15] constitute a unique subclass of polycyclic meroterpenoids that was previously harvested from marine and fungal sources. Since the first isolation of aureol in 1980, considerable interest has arisen to prepare these complex natural products by chemical synthesis and explore their biological activities. Despite the successful synthesis of individual members in a reasonable number of synthetic operations (10–27 linear steps), none of the reported routes[16–24] has enabled a practical access to the whole family of these fascinating natural products (Fig. 1).

Although scattered reports have revealed the antiviral (**1**, **2**, and **4**)[10,13,25], anticancer (**2**, **4**, **5**, and **6**)[13–15,26], and antibiotic (**2**)[27] activities of several members of these natural products, an exhaustive biological screen of **1–6** and fully synthetic derivatives is still unavailable. So far, only a preliminary structure–activity relationship (SAR) study of semi-synthetic analogs of stachyflin (**1**) has been reported, revealing that subtle modifications of the aromatic isoindolinone component have a drastic effect on the observed H1N1 activity[28–32]. Here, we address these limitations and describe a highly modular synthetic platform for the construction of six natural products and 15 fully synthetic molecules that were previously inaccessible using semi-synthesis. Biological profiling reveals that this class of meroterpenoids has potent antibiotic activity against methicillin-resistant *Staphylococcus aureus*.

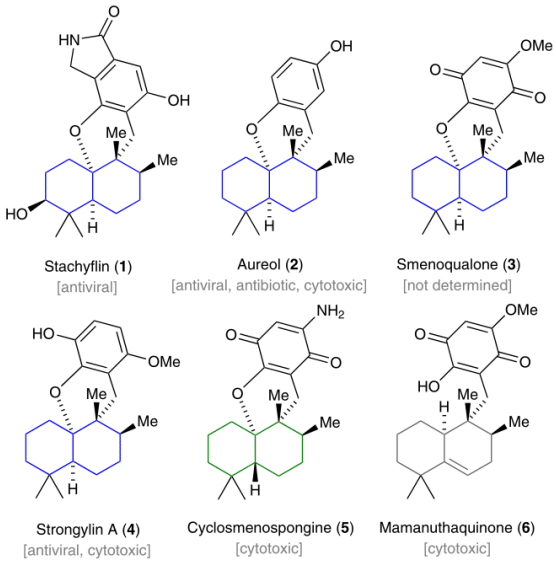

Fig. 1 Selected members of polycyclic meroterpenoids and their reported biological activity. Within this subclass of natural products, two distinct stereochemistries with respect to the decalin subunit have been noted. While compounds **1–4** possess a *cis*-decalin, cyclosmenospongine (**5**) features a unique *trans*-decalin scaffold. Both stereochemistries might biosynthetically originate from a 5,6-dehydrodecalin framework as present in mamanuthaquione (**6**). Color coding: blue, *cis*-decalin; green, *trans*-decalin

Results

Total synthesis of (+)-stachyflin (**1**). As illustrated in Fig. 2a, recent efforts by our group enabled a highly convergent and scalable route to the *trans*-decalin-containing natural product cyclosmenospongine (**5**). The developed synthesis proceeds via the intermediacy of 5-*epi*-aureol (**9**) and enabled production of 420 mg of **5** in a single batch[33]. However, all efforts to adapt this strategy for the construction of the *cis*-decalin subunit of **1–4** were unsuccessful.

We envisioned the synthesis of **1–6** by employing the highly convergent strategy depicted in Fig. 2b. For the retrosynthetic analysis, **1–6** were first traced back to their protected forms **I** and **II**. The carbon–oxygen bond disconnection at C10 leads to the 5,6-dehydrodecalin precursor **III**, which would enable the crucial late-stage assembly of either the *cis*- (kinetic product) or *trans*-decalin (thermodynamic product) by an acid-promoted isomerization/cyclization sequence. This event sets the remaining two of four consecutive stereocenters. To account for maximum modularity and convergence, we opted to break down **III** further into the simple building blocks phenol **IV**, diene **V**, and tiglic acid-derived dienophile **VI** using a sp^2–sp^3 cross-coupling (or nucleophilic addition) and an *exo*-selective, auxiliary-controlled Diels–Alder reaction that was described in seminal work by Danishefsky[34] and Minnaard[35].

We began our investigations with the synthesis of stachyflin (**1**) which contains a rare isoindolinone subunit (Fig. 3a)[36]. As initial efforts to construct intermediate **15** according to a previously reported protocol[37] were low yielding and not reproducible on a large scale, we set out to develop a more robust route. Our synthesis begins with a solvent-free Alder–Rickert reaction between the dimedone-derived *bis*-trimethylsilyl enol ether **10** and dimethyl 2-butynedioate (DMAD)[38] to afford resorcinol **11** (86%). Careful monitoring of the reaction progress enables mono-methylation (Me_2SO_4, K_2CO_3, acetone) of **11** to furnish phenol **12** as a white crystalline solid in 73% yield. Exposure of **12** to a solution of 3,4-dimethoxybenzylamine ($DMBNH_2$) and trimethylaluminum (Me_3Al) effected clean conversion to the corresponding *N*,*N*-3,4-dimethoxydibenzyl phthalamide. The subsequent formation of imide **13** was induced by heating the neat phthalamide at 210 °C under reduced pressure (1 mbar) with simultaneous removal of the liberated *N*,*N*-3,4-dimethoxydibenzyl amine. While bromination (Br_2, CH_2Cl_2 or Br_2, AcOH) of **13** gave predominately the *para*-substituted phenol, exclusive formation of **14** occurred upon treatment with substoichiometric amounts of both iodine (0.6 equiv.) and periodic acid (0.2 equiv.)[39]. Treating a solution of **14** in tetrahydrofuran (1.0 M) in a sealed tube with borane tetrahydrofuran complex (3.0 equiv.) and substoichiometric quantities of sodium borohydride (0.05 equiv.) at elevated temperature (70 °C) effected regioselective reduction of the imide[40]. This protocol was crucial to obtain the product as a single regioisomer in high yield. Protection of the free phenol as its methoxymethyl ether completed the synthesis of isoindolinone **15** (435 mg). The overall sequence to **15** proceeds in six steps and involves only crystalline intermediates, thus making it practical on a large scale.

We then focused on the construction of the 5,6-dehydrodecalin component **25** by employing Fan auxilliary-controlled *exo*-selective Diels–Alder cycloadditon between diene **20** and tiglic acid-derived dienophile **21** (Fig. 3b).

Although the utility of **21** was previously demonstrated by Minnaard for the synthesis of 1-tuberculosinyl adenosine[35], we were uncertain about the capability of **21** to override the inherent substrate selectivity of **20** and the extent of steric hindrance resulting from the benzyl ether at C3. Diene **20** was prepared from a known β-hydroxyketone **17**[41] via a three-step sequence involving

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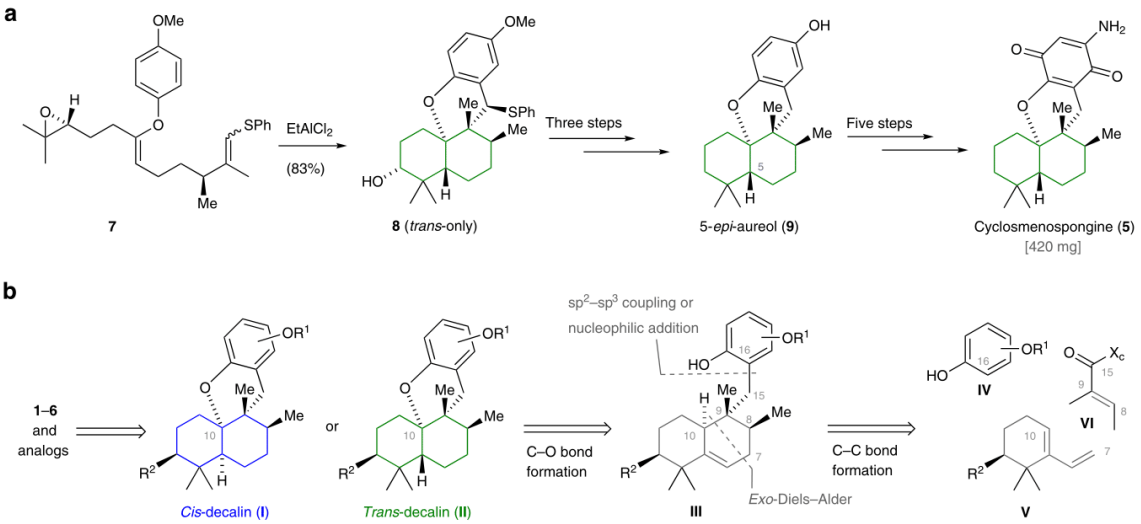

Fig. 2 Strategies for the construction of tetracyclic meroterpenoids. **a** The polyene cyclization reaction of aryl enol ether **7** enabled rapid assembly of the *trans*-decalin substructure of 5-*epi*-aureol (**9**) and cyclosmensopongine (**5**). However, this strategy could not be adapted for the preparation of meroterpenoids containing a *cis*-decalin subunit. **b** Synthesis of the 5,6-dehydrodecalin intermediate **III** should be accomplished by a highly modular, three-component coupling strategy of phenol **IV**, diene **V**, and dienophile **VI**. The ability to construct both *cis*- and *trans*-decalins from a common precursor would allow for the synthesis of **1**–**6** and a variety of non-natural derivatives for biological screening. Color coding: blue, *cis*-decalin, green, *trans*-decalin. R^1 = alkyl, R^2 = H or OBn, X_c = chiral auxiliary

the formation of the benzyl-protected ketone **18**, conversion to the vinyltriflate **19**, and Stille coupling (vinylSn(*n*-Bu_3), $Pd(PPh_3)_4$, LiCl, THF, 75 °C) to install the diene motif. Initial attempts to promote the reaction between **20** and **21** confirmed our concerns that **21** is reluctant to undergo cycloaddition under standard conditions (Me_2AlCl, $(CH_2Cl)_2$, –40 °C to 23 °C). In order to overcome the low reactivity of **20**, we first subjected the reactants solution to high pressure (14 kbar, 23 °C, Me_2AlCl, CH_2Cl_2)[42]. Although the formation of the desired Diels–Alder product **22** was observed under these forcing conditions, the product yield was low due to competing decomposition to an intractable mixture of products. However, the relative stereochemistry of **22** could be validated by single-crystal structure analysis. After further optimization, we found that **22** could be reproducibly obtained in a good yield and excellent diastereoselectivity (dr = 13:1) by conducting the cycloaddition in 1,2-dichloroethane in a sealed tube and slowly warming the reaction mixture from –40 °C to 23 °C. In this context, it is important to note that the chiral auxiliary fully overrides the substrate selectivity and the observed diastereoselectivity corresponds to the optical purity of **20** (83% ee). Further conversion of **22** to iodide **25** via the intermediacy of thioester **23** and alcohol **24** proceeded smoothly to provide 2.3 g of **25** in a single batch.

With both components in hand, we turned our attention to the critical linkage of **15** to **25** (Fig. 4). This process was expected to be exceptionally challenging as it requires carbon–carbon bond formation between C15, which resides at a sterically hindered neopentylic position and C16, itself flanked by two alkyl ether substituents of the arene. From an evaluation of different coupling strategies and based on our recent success to realize challenging carbon–carbon bond formations[43], a sp^2–sp^3 Negishi cross-coupling reaction[44] emerged as the method of choice. To this end, we subjected both coupling partners to an exhaustive screen of reactions conditions (see Supplementary Table 1). We found that the coupling could be efficiently mediated by treating a solution of **25**, Pd-SPhos G2 (20 mol%), and SPhos (20 mol%)[44] in tetrahydrofuran and *N*,*N*-dimethylacetamide (2:1) with the organozinc species derived from **15**. The use of *N*,*N*-dimethylacetamide as a co-solvent and slightly elevated temperature (40 °C) were crucial to reproducibly observe full conversion, short reaction times, and acceptable yields (56%).

Having prepared the 5,6-dehydrodecalin intermediate **26** (330 mg), the stage was set to investigate the key-transformation for the installation of the *cis*-decalin framework. This step was inspired by a previous work on effect-related cascade cyclizations[45] and was realized by first cleaving the methoxymethyl ether in **26**. The so-formed phenol was unstable upon standing and therefore was directly exposed to boron trifluoride etherate at –40 °C. Slowly raising the temperature to –15 °C over a period of 1 h led to full consumption of the phenol. Although the mechanism of this cyclization reaction is still unclear, it may be that protonation of the alkene first affords the C5 carbocation **27**. Whether this directly undergoes stereospecific 1,2-hydride shift to give the C10 carbocation **29** or involves the intermediacy of the C5–C10 alkene **28** is uncertain at this point. At temperatures below –15 °C, trapping of the cation by the phenol is kinetically controlled to exclusively provide the *cis*-decalin. The use of the secondary benzyl-protecting group and maintaining temperatures below –15 °C proved to be essential to minimize ionization of the C3 position and undesirable ring contraction (see Supplementary Methods and Supplementary Fig. 61). Hydrogenolysis of the cyclization product facilitated purification and afforded **30** in 62% yield. For the completion of the synthesis of **1**, the DMB group was removed oxidatively using previously reported conditions (PIFA, benzene)[46]. Finally, cleavage of the methyl ether with potassium *n*-dodecanethiolate (*n*-$C_{12}H_{24}SK$) in *N*,*N*-dimethylformamide (DMF) at 140 °C proceeded smoothly to afford (+)-stachyflin (**1**). Spectroscopic data (^{1}H NMR[13],C NMR, optical rotation) were found to be identical with those reported for natural **1**[10].

Total synthesis of natural products 2–6. Having established a convergent and scalable synthesis of tetracyclic meroterpenoids bearing a *cis*-fused decalin system, we set out to modify the route

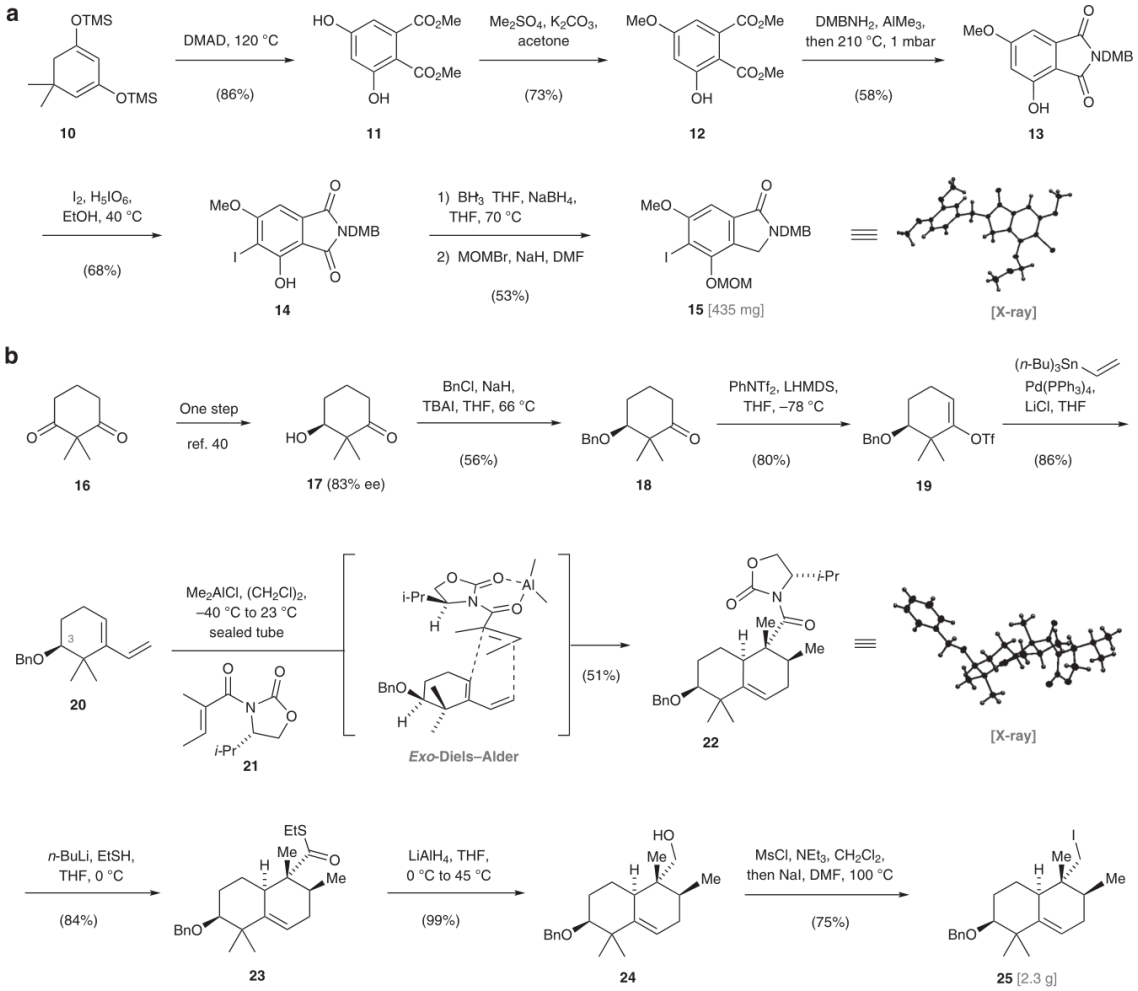

Fig. 3 Synthesis of the isoindolinone component **15** and the dehydrodecalin **25**. **a** The developed de novo synthesis of isoindolinone **15** proceeds in six linear steps and only involves crystalline intermediates. **b** For the construction of the 5,6-dehydrodecalin **25**, an auxiliary-controlled *exo*-selective Diels–Alder cycloaddition was employed. This allowed the production of **25** in eight steps in gram quantities in a single batch. DMAD dimethyl acetylenedicarboxylate, *n*-Bu *n*-butyl, Bn benzyl, DMB 3,4-dimethoxybenzyl, DMF *N*,*N*-dimethylformamide, LHMDS lithium hexadimethylsilazide, MOM methoxymethyl, Ms methanesulfonyl, TBAI tetrabutylammonium iodide, Tf trifluoromethanesulfonyl, THF tetrahydrofuran

in order to incorporate selective modifications and expand our library of natural and non-natural analogs. For the asymmetric synthesis of **2**–**6**, which are derived from the common 3-deoxy-5,6-dehydrodecalin subunit **33**, we utilized the previously reported two-step sequence by Minnaard (Fig. 5)[35]. Thioester **32** underwent smooth Fukuyama reduction[47] to give aldehyde **33**, whose relative stereochemistry was validated by single-crystal structure analysis (see Supplementary Fig. 62). Pleasingly, the use of the less sterically demanding arene component **34**[48] enabled replacement of the previously required sp^2–sp^3 cross-coupling reaction and thus simplified the installation of the crucial C15–C16 carbon–carbon bond. The *ortho*-directed lithiation of **34** followed by 1,2-addition to **33** gave a mixture of diastereoisomeric benzyl alcohols. Application of the two-step Barton–McCombie deoxygenation protocol (CS_2, MeI, NaHMDS, then AIBN, *n*-Bu_3SnH, 90 °C)[49] reproducibly provided **35** in good yield (72%). For the completion of the synthesis of aureol (**2**), both methoxymethyl ethers of **35** were first cleaved upon exposure to hydrochloric acid in methanol. The resulting hydroquinone was prone to oxidation and therefore was not purified but directly subjected to the optimized cyclization conditions ($BF_3{\cdot}OEt_2$, CH_2Cl_2, –40 °C to –10 °C) to afford 193 mg of (+)-aureol (**2**) in a single batch. From there, the non-natural 5-*epi*-derivative **9** was prepared by thermal isomerization of the *cis*-decalin using hydroiodic acid in benzene at 90 °C (87%)[50].

In addition, cyclosmenospongine (**5**) was accessible by subjecting **9** to our previously developed functionalization sequence[33]. In a similar vein, mamanuthaquinone (**6**) was synthesized by the coupling between **33** and arene **36** to give **37**. Compound **37** was deprotected and then oxidized (salcomine, O_2) to give **6**, which slowly decomposed upon storage at –20 °C. Having demonstrated the generality and versatility of the developed modular synthetic platform, further structural modifications could be efficiently made by simple variation of the arene and decalin component, and adjustment of the cyclization conditions. While kinetic conditions ($BF_3{\cdot}OEt_2$,

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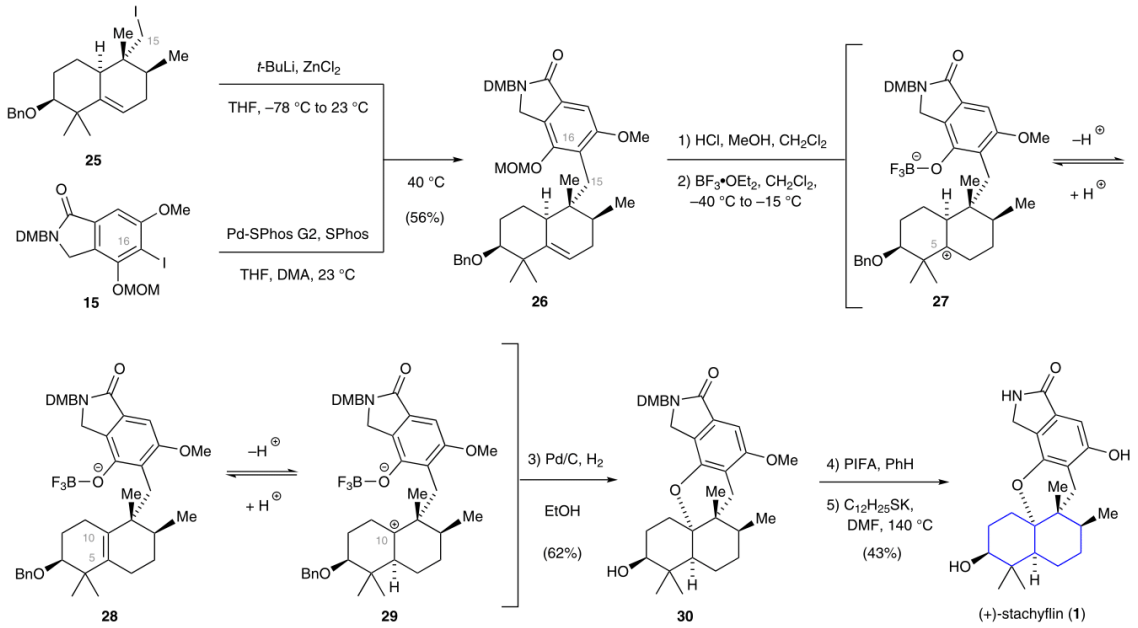

Fig. 4 Component coupling and total synthesis of (+)-stachyflin (1). The sp^2–sp^3 Negishi cross-coupling reaction between arene **15** and iodide **25** provided the precursor for the intended cyclization reaction. Promotion of this step was accomplished by the addition of excess boron trifluoride etherate (10 equiv.) at low temperature (-40 °C) to exclusively produce the *cis*-decalin **30**. At temperatures exceeding -15 °C, competing ionization of the C3 position and ring-contraction prevailed (byproduct not shown, see Supplementary Methods). *t*-BuLi *tert*-butyllithium, DMA *N*,*N*-dimethylacetamide, PIFA phenyliodine bis (trifluoroacetate), SPhos 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, SPhos-Pd G2 chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl) [2-(2′-amino-1,1′-biphenyl)]palladium(II)

CH_2Cl_2, −40 °C to −10 °C) gave the *cis*-decalin framework exclusively, equilibration under thermodynamic conditions (HI, benzene, 90 °C) afforded the *trans*-decalin as the only stereoisomer.

In this manner, (+)-smenoqualone (**3**) and (+)-strongylin A (**4**), and 15 fully synthetic tetracyclic analogs that were previously inaccessible via semi-synthesis could be prepared (Fig. 6 and Supplementary Methods). With the synthetic natural products **1**–**5** as well as the analogs **9** and **38**–**51** at hand, a basic phenotypic bioprofile of meroterpenoids was recorded in antibacterial and antiproliferative assays. Antimicrobial activities were tested against members of the ESKAPE panel[51], consisting of the gram-positive bacteria methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterococcus faecium*, the gram-negative bacteria *Escherichia coli, Pseudomonas aeruginosa, Acinetobacter baumannii*, and *Klebsiella pneumonia*, and the yeast fungus *Candida albicans*. All compounds proved to be inactive against gram-negative pathogens and *C. albicans*. However, several analogs inhibited the growth of the MRSA-type strain DSM 11822 and the MRSA clinical isolate RKI 11-02670 with the following SARs (Fig. 6 and Supplementary Table 21): the highest activities were observed for **40**, with EC_{50} values of 0.2 and 0.6 µM against DSM 11822 and RKI 11-02670, respectively, and for strongylin A (**4**), which was active with EC_{50} values of 1 and 1 µM. Surprisingly, the combination of the heteroatom functionalities of **4** and **40** led to a pronounced drop of activity, as demonstrated by 3-hydroxy-strongylin (**48**) (83/49 µM). Related compounds with 3-hydroxy function and a *para*-quinone unit like **49** or a heterocycle as found in stachyflin (**1**), **43** and **44** had also had little or no activity. In line with this, a non-hydroxylated, contracted cyclopentene ring, as present in the stachyflin analog **39**, led to re-gained activity (6/8 µM). On the other hand, a lack of functionalities at the decalin and aromatic subunit also led to inactive compounds, as demonstrated by **41** and **42**. While the mono-hydroxylated aureol **2** exhibited a potency (5/5 µM) comparable to **4**, the oxidation of the methylated hydroquinone to a *para*-quinone as present in **46** was associated with a pronounced drop of anti-MRSA activity to 33/20 µM. A clear activity ranking for a *cis*- vs. *trans*-configuration of the decalin ring was not evident: the *trans* isomer was more potent in the **46** vs. **47**, **3** vs. **51**, and **5** vs. **50** pairs, while the opposite was true for the **4** vs. **45** and the **43** vs. **44** pairs. The antiproliferative activities of the compounds in the four mammalian cell lines L929, KB-3-1, MCF-7, and FS4-LTM were tested using a WST-1 assay that quantifies the metabolic activity of the cell population (Supplementary Table 22). The highest activities were observed for **40** (EC_{50} values of 7–14 µM) and **49** (EC_{50} values of 8–21 µM), both hydroxylated at the C3 position. The observation that the SAR did not parallel the antimicrobial activity suggests that a separation of antibiotic and cytotoxic activities is possible, and an even larger split may be obtained by further structural optimization.

Discussion

In summary, we established a highly modular and robust synthetic platform for the construction of variously substituted meroterpenoid scaffolds. Our efforts culminated in the enantioselective total syntheses of (+)-stachflin (**1**), (+)-aureol (**2**), (+)-smenoqualone (**3**), (+)-stronglin A (**4**), (−)-cyclosmenospongine (**5**), and (−)-mamanuthaquinone (**6**). Key steps include an asymmetric Diels–Alder reaction to install the 4,5-dehydrodecalin framework, either a highly efficient sp^2–sp^3-Negishi cross-coupling reaction or a nucleophilic addition reaction to

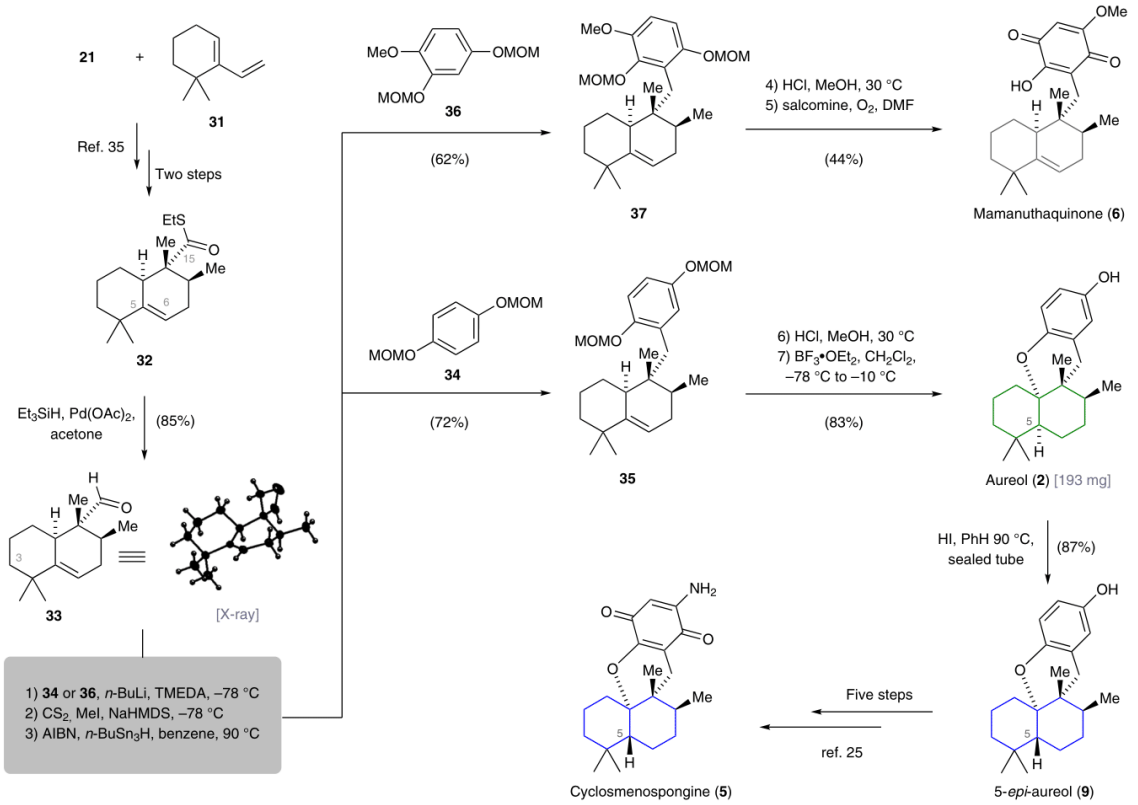

Fig. 5 Chemical synthesis of (+)-aureol (**2**), (-)-cyclosmenospongine (**5**), (-)-mamanuthaquinone (**6**), and (+)-5-*epi*-aureol (**9**). The 3-deoxy-5,6-dehydrodecalin unit **33** was accessed in three steps from the known coupling of **21** and **31**. Installation of the C15–C16 carbon–carbon bond was accomplished by *ortho*-directed lithiation of **34** or **36** and nucleophilic addition to **33**. AIBN azobisisobutyronitrile, NaHMDS sodium hexadimethylsilazide, TMEDA *N,N,N,N′*-tetramethylethylenediamine

forge the crucial C15–C16 carbon–carbon bond, and an acid-mediated cyclization to selectively generate either stereoisomers of the decalin subunit. Simultaneous structural variation of more than one coupling component leads to rapid expansion of the compound library. The library of natural and fully synthetic molecules obtained so far was screened against a panel of bacterial pathogens and mammalian cell lines. Notably, the pronounced antibiotic activity of **40**, (+)-strongylin A (**4**), and (+)-aureol (**2**) against MRSA in the low-μM range appears promising. The reported SAR suggests that a further enhancement of activity is possible, e.g., through modifications at the aromatic ring, and such modifications enabled by the described synthetic platform.

Methods

NMR spectroscopy. NMR spectra were measured on a Bruker Avance III HD (400 MHz for proton nuclei, 100 MHz for carbon nuclei) spectrometer equipped with a CryoProbe^{TM}, Bruker AXR300 (300 MHz for proton nuclei, 75 MHz for carbon nuclei), Varian VXR400 S (400 MHz for proton nuclei, 100 MHz for carbon nuclei), Bruker AMX600 (600 MHz for proton nuclei, 150 MHz for carbon nuclei), or Bruker Avance HD 800 (800 MHz for proton nuclei, 200 MHz for carbon nuclei). Proton chemical shifts are expressed in parts per million (ppm, δ scale) and the residual protons in the NMR solvent ($CHCl_3$, $\delta = 7.26$ ppm; C_6D_5H, $\delta = 7.16$ ppm; DMSO-*d*6, $\delta = 2.50$ ppm) were used as internal reference. Carbon chemical shifts are expressed in parts per million (δ scale, assigned carbon atom) and the residual solvent peaks ($CDCl_3$, $\delta = 77.16$ ppm; C_6D_6, $\delta = 128.06$ ppm; DMSO-*d*6, $\delta = 39.52$ ppm) were used as internal reference. The NMR spectroscopic data are reported as follows: chemical shift in ppm (multiplicity, coupling constants *J* (Hz), integration intensity) for ^{1}H NMR spectra and chemical shift in ppm for ^{13}C NMR spectra. Multiplicities are abbreviated as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Signals in the NMR spectra were assigned by the information obtained from 2D NMR experiments: homonuclear correlation spectroscopy (COSY), total correlation spectroscopy (TOCSY), heteronuclear single quantum coherence (HSQC), and heteronuclear multiple bond coherence (HMBC). The software MestReNOVA 11.0 from Mestrelab Research S. L was used to analyze and process all raw fid files.

Mass spectrometry. High resolution mass spectra (HRMS) were measured at the Department of Chemistry, Ludwig-Maximilians-University Munich, on the following instruments by electron impact (EI) or electron spray (ESI) techniques: MAT 95 (EI) and MAT 90 (ESI) from Thermo Finnigan GmbH.

IR spectroscopy. Infrared spectra (IR) were recorded on a PerkinElmer Spectrum BX II FT-IR system from 4000 to 600 cm^{-1}. Substances were directly applied on the ATR unit as a thin film or a thin powder layer. The data are represented as 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: $[\alpha]_\lambda^\varphi = [\alpha] \cdot 100 \cdot c^{-1} \cdot d^{-1}$. The wave length λ is reported in nm (sodium D line, $\lambda = 589$ nm), the measuring temperature ϕ in °C; α represents the recorded optical rotation, *c* the concentration of the analyte in g mL^{-1}, and *d* the length of the cuvette in dm. Thus, the specific rotation is given in 10^{-1} deg cm^2 g^{-1}. The values for the specific rotation are reported as follows: specific rotation (concentration g 100 mL^{-1}; solvent).

Melting points. Melting points were determined on a B-450 melting point apparatus from BÜCHI Labortechnik AG.

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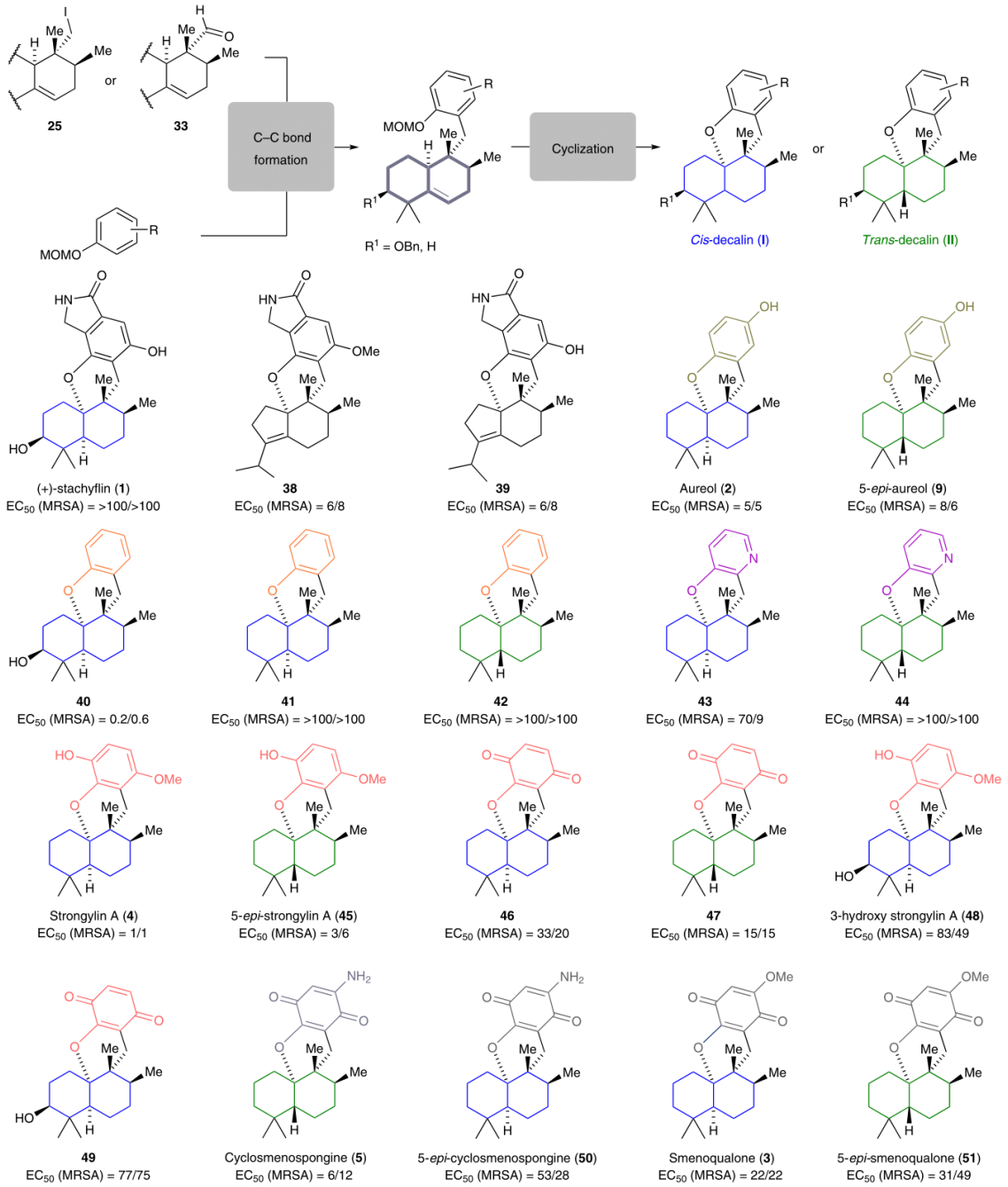

Fig. 6 Extension of the modular synthetic platform. Structural variation of the arene and decalin component enabled rapid extension of the natural products library and provided access to several non-natural analogs that were previously inaccessible via semi-synthesis. Each of the shown molecules depicted was prepared in seven or fewer steps starting from iodide **25** or aldehyde **33**. Color coding was used to indicate the decalin stereochemistry (coding: blue, *cis*-decalin; green, *trans*-decalin) and to highlight the modified arene component. The effective concentrations (EC_{50} values) that inhibited the growth of two MRSA strains (DSM 11822/RKI 11-02670) are given in μM

Data availability. CCDC 1534418 (**15**), 1534416 (**22**), and 1534618 (**33**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre. The authors declare that all the data supporting the findings of this study are available within the article (and its supplementary information files).

Received: 1 August 2017 Accepted: 2 November 2017
Published online: 12 December 2017

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Acknowledgements

T.M. acknowledges the German Research Foundation (Emmy Noether Project MA5999/2-1), the European Research Council under the European Union's Horizon 2020 research and innovation program (grant agreement No 714049) and the Funds of the Chemical Industry (Sachkostenzuschuss and Dozentenpreis). We thank Dr. Kevin Mellem (Revolution Medicines) and Dr. Bryan Matsuura (LMU Munich) for helpful discussions.

Author contributions

R.W., K.S., F.-L.H., and T.M. conceived the synthetic route. R.W., K.S., F.-L.H., and B.K. conducted all experimental work and analyzed the results. R.W., M.B., and T.M. analyzed the data and wrote the manuscript.

Additional information

Supplementary Information accompanies this paper at https://doi.org/10.1038/s41467-017-02061-7.

Competing interests: The authors declare no competing financial interests.

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1.3 Conclusion and Outlook

In Part I of this thesis, a general entry to the aureol family of meroterpenoid natural products was developed, which cumulated in the total synthesis of stachyflin, aureol, smenoqualone, strongylin A, cyclosmenospongine and mamanuthaquinone. The route employs an auxiliary-controlled Diels–Alder reaction to enable the enantioselective construction of the decalin subunit, which is connected to variously substituted arenes by either carbonyl addition chemistry or sterically demanding sp^2–sp^3 cross-coupling reactions and an acid mediated cyclization to selectively generate either stereoisomer of the decalin subunit. Simultaneous structural variation of more than one coupling component leads to rapid expansion of the compound library and 15 non-natural derivatives were obtained.

The library of natural and fully synthetic molecules obtained so far was screened against a panel of bacterial pathogens and mammalian cell lines in collaboration with the group of Prof. Dr. Mark Brönstrup (Helmholtz Centre for Infection, Braunschweig). Notably, the pronounced antibiotic activity of a non-natural derivative**,** (+)-strongylin A and (+)-aureol against methicillin-resistant *Staphylococcus aureus* in the low μM range appears promising. The reported SAR suggests that a further enhancement to activity is possible, e.g. through modifications at the aromatic ring, and such modifications enabled by the described synthetic platform.

PART II

TOWARDS THE TOTAL SYNTHESIS OF CORNEXISTIN

2.1 Introduction

2.1.1 The nonadride family

2.1.1.1 Isolation and biological activity

The natural products glauconic acid (**138**), glaucanic acid (**139**), byssochlamic acid (**140**),[57] rubratoxin A (**141**), B (**142**) and C (**143**),[58] scytalidin (**144**),[59] desoxyscytalidin (**145**),[60] heveadride (**146**),[61] homoheveadride (**147**),[62] cornexistin (**148**),[63] hydroxycornexistin (**149**)[64] and phomoidrides A (**150**), B (**151**),[65] C (**152**) and D (**153**)[66] isolated and characterized over the last century from various fungal sources (Figure 3) belong to the nonadride family. Homoheveadride (**147**) is the only nonadride isolated from lichen (*cladonia polycarpoides*). The terminus "nonadride" was introduced in 1962 and first described a family of natural products that was biosynthetically derived from dimerization of two C9-building blocks.[67] Later, the term evolved and now includes compounds that possess the core structure of nonandrides (highlighted in blue), a nine-membered carbocycle fused to one or two maleic anhydride units whereas cornexistin (**148**) and hydroxycornexistin (**149**) are the only congeners that feature just one maleic anhydride moiety. To date, the fungal metabolites phomoidrides A (**150**), B (**151**), C (**152**) and D (**153**) are the most complex members of the nonadride family and feature a bicyclo[4.3.1]deca-1,6-diene framework, sharing the same biosynthetical pathway as the other congeners.[68] From a structural point, one major difference from other members of the nonadride family is the geometry of the double bond embedded in the nine-membered carbocycle highly increasing the structural complexity of those natural products.

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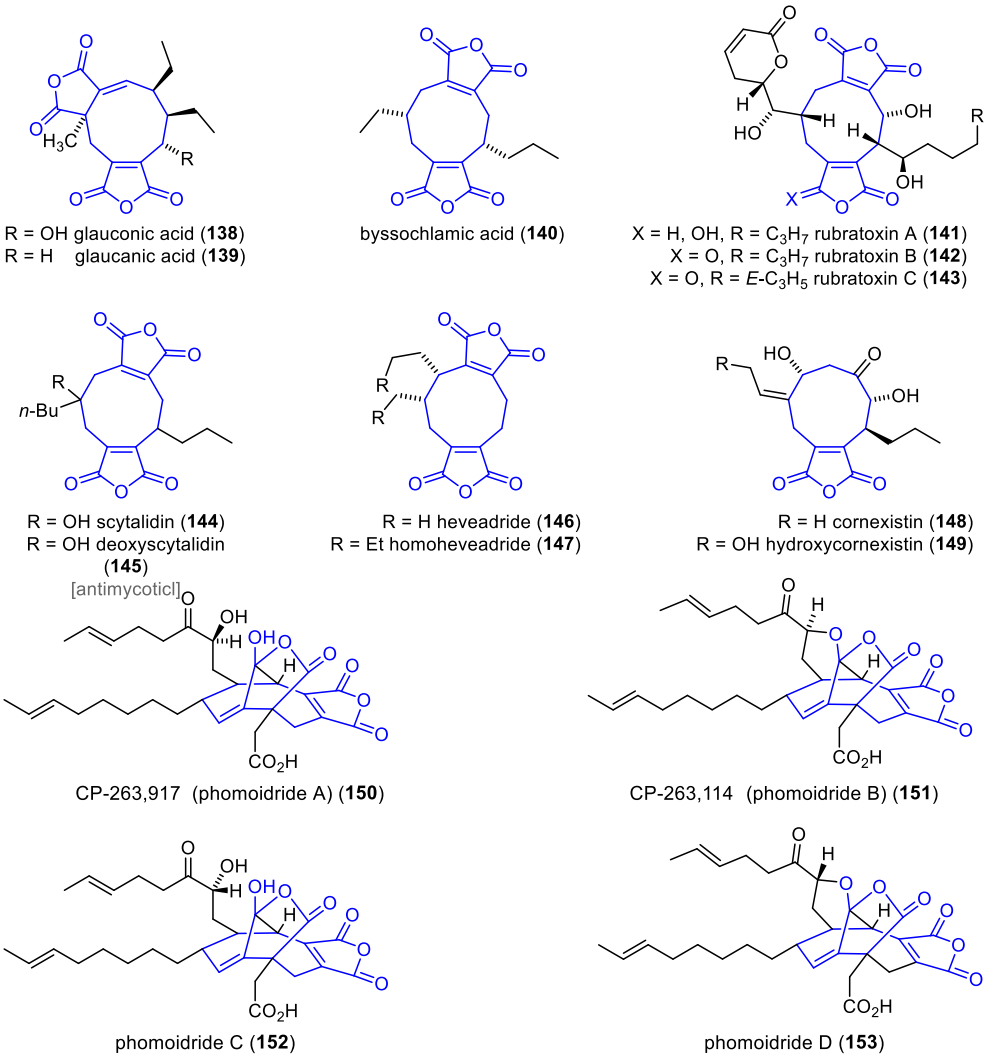

Figure 3 | Members of the nonadride family of natural products.

All members of this family show various biological activities whereas cornexistin (**148**) and hydrocornexistin (**149**) show outstanding post-emergence herbicidal activity against *monocotyledonous* plants that grow in association with corn.[63,64] Compared to commercially available herbicides like glyphosate or bialaphos, **148** shows the same or greater herbicidal activity. Additionally, cornexistin (**148**) shows herbicidal effects against *dicotyledonous* plants but with non-selective killing effects. Corn seeds were able to tolerate cornexistin making it a non-selective, broad spectrum herbicide with selectivity to corn (Figure 4). This effect was experimentally visualized by treatment of a sample containing corn and nine different weeds was treated with cornexistin (0.5 kg/ha). After 25 weeks, the control sample shows corn growing in association with weeds. The sample on the right was sprayed with cornexistin on day nine and shows excellent growth inhibition of annual weeds. Additionally, cornexistin showed no activity against gram-positive and negative bacteria and fungi (1 mg/mL) and low toxicity in mice (LD_{50} > 1 g/kg (o.p.); 100 mg/kg (i.p.)).

Figure 4 | Selective herbicidal activity of cornexistin (**148**): a) control; b) treated with cornexistin.

2.1.1.2 Biosynthesis

In 1965, a biosynthesis for byssochlamic acid (**140**), heveadride (**146**) and glaucanic acid (**139**) was postulated by Barton and Sutherland.[57c] This hypothesis was verified in 2016 for the biosynthetic pathway to byssochlamic acid (**140**) through genome and transcriptome sequencing, gene disruption, and heterologous expression by R. J. Cox.[69] Based on these results, a general biosynthetic pathway to nonadrides was postulated (Scheme 22). Catalyzed by the citrate-synthase-like enzyme oxaloacetate (**155**) is reacted with a polyketide building block **154** (chain length and pattern of reduction can vary for different natural products) which is either released as the free acid (X = OH) or the CoA-thioester (X = SCoA) from the PKS by the BfL1 hydrolase. In the following step, dehydration by the methylcitrate dehydratase homologue gives **156** and its decarboxylated homologs **157** and **158**. KI-like enzymes can now dimerize **156** with either **157** or **158** in a head-to-tail or a head-to-head fashion to form byssochlamic acid type, glauconic acid type and heveadride type nonadrides.

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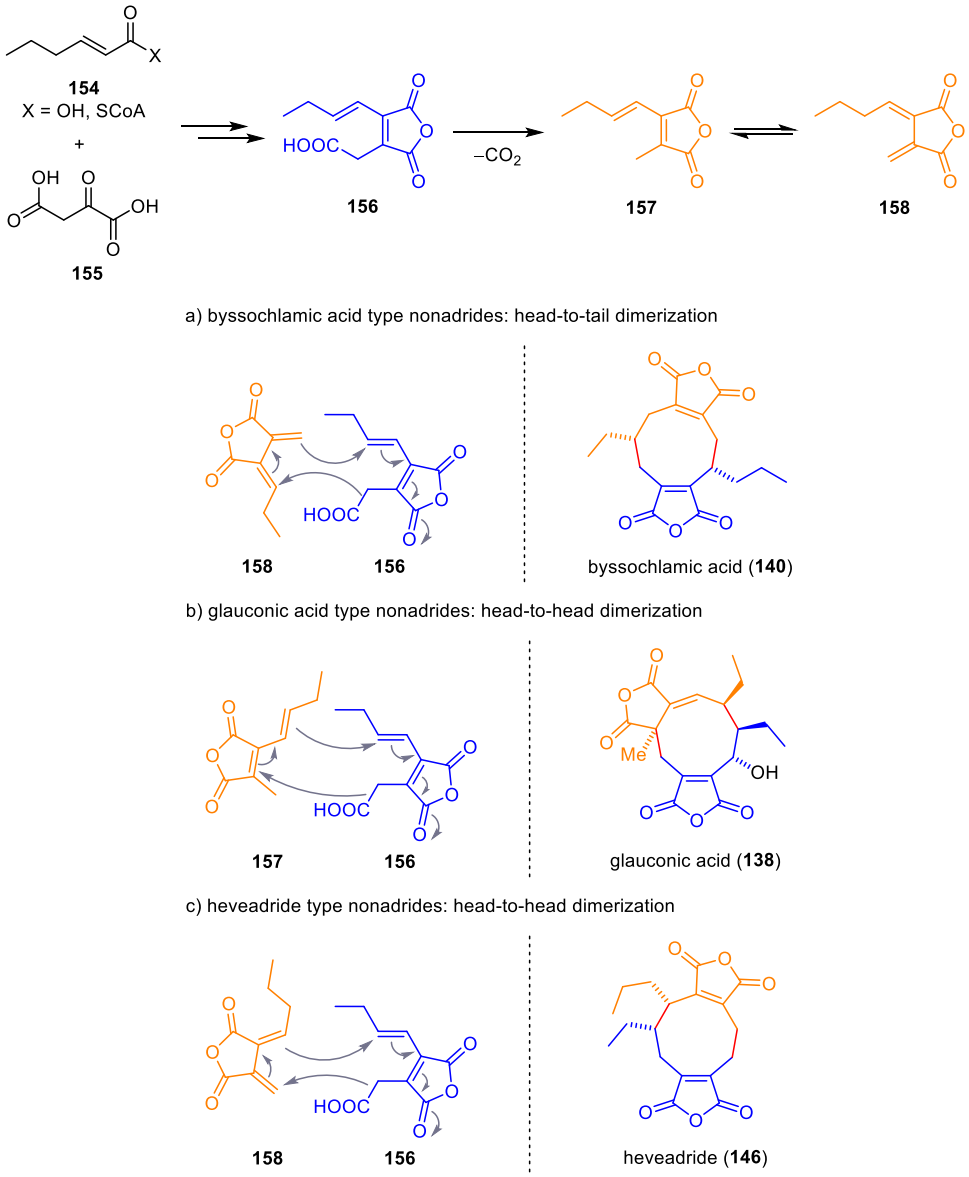
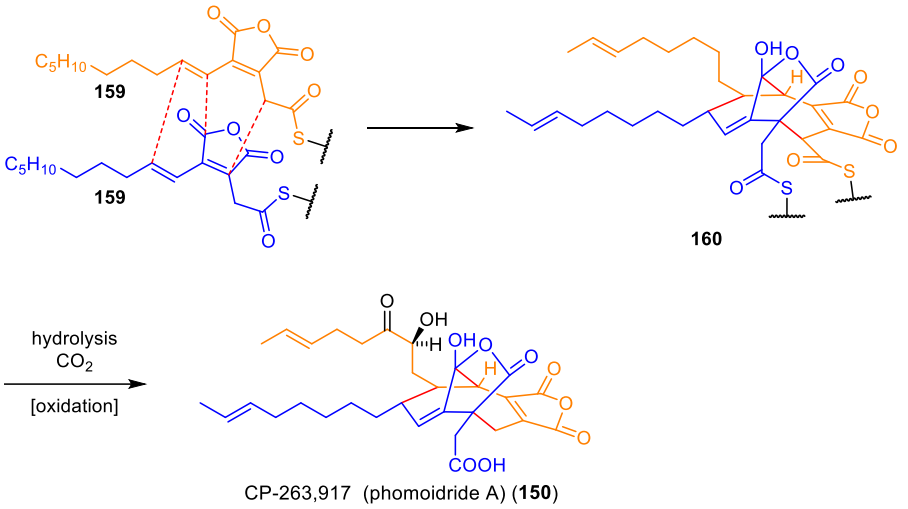


Scheme 22 | Proposed biosynthetic pathway to nonandrides **140**, **138** and **146** adopted by R. J. Cox.[69]

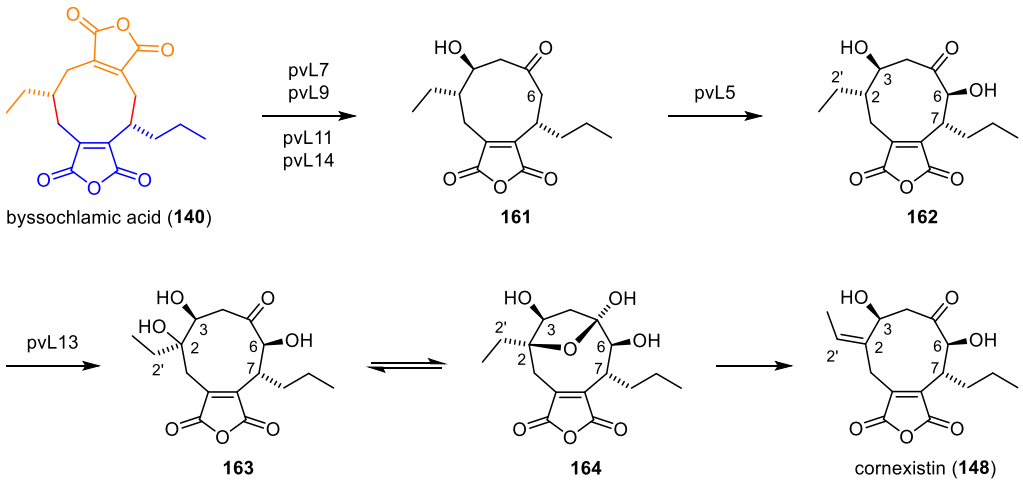
In 2000, the group of Sulikowski outlined a biosynthesis for the highly complex nonadrides phomoidrides A (**150**), B (**151**).[68,70] For the dimerization of **159** it is believed that both reaction partners have to be covalently attached (analog to polyketide and fatty acid biosynthesis via thioester bonds) to an enzyme active site. It is hypothesized that the dimerization proceeds in a stepwise fashion as a series of two Michael additions followed by an transannular Dieckmann condensation resulting in the carbon skeleton **160**. After the final steps featuring hydrolysis, decarboxylation, and oxidation **150** is obtained.

[70] T. T. Dabrah, T. Kaneko, W. Massefski, E. B. Whipple, *J. Am. Chem. Soc.* **1997**, *119*, 1594–1598.



Scheme 23 | Proposed biosyntheses of **150**.

In 2017, the group of R. J. Cox elucidated the biosynthetic pathway of cornexistin (**148**) in *in vitro* experiments with fungus *P. variotii* (Scheme 24). Since a very low titre of byssochlamic acid (**140**) was observed in this fungal system, **140** was expected to be an intermediate of the biosynthetic pathway of cornexistin (**148**). However, this hypothesis could not be verified by feeding experiments. If **140** was fed to the maleidride PKS KO strain of *P. variotii*, no synthesis of cornexistin (**148**) was observed. This shows, that **140** is not able to penetrate the cell membrane or is unable to access the compartment where biosynthesis occurs. A biosynthetic key step includes the oxidative removal of one of the maleic anhydride unit in **140** to give **161**. The group of R. J. Cox was able to show that proteins encoded by *pvL7*, *pvL9*, *pvL11* and *pvL14* are involved in this step.



Scheme 24 | Proposed biosynthesis of cornexistin (**148**) adopted from R. J. Cox.

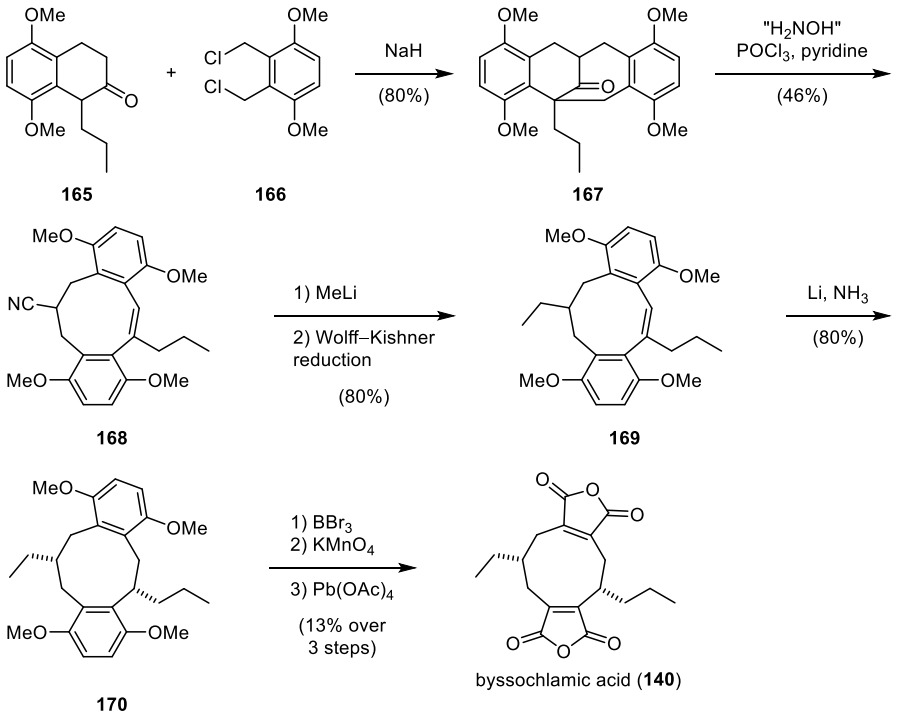
The nine-membered carbocycle is now decorated by oxygenases encoded by *pvL5* and *pvL13*. Selective hydroxylation at C-6 position followed by hydroxylation at C-2 should lead to intermediate **163**. However, only the respective hemiacetal **164** could be isolated and characterized. To date, the exact

mechanism of the last step from **164** to **148** is not fully elucidated. It is assumed, that the elimination can be catalyzed by *pvL13* encoded multifunctional cytochrome P450 oxidases.

2.1.2 Literature Syntheses

2.1.2.1 Byssochlamic acid

In 1972, the group of Stork accomplished the total synthesis of byssochlamic acid (**140**) being the first total synthesis of a nonadride natural product.[71] Ketone **165** and 2,3-dichloromethyl- 1,4-dimethoxybenzene (**166**) were coupled in a double alkylation sequence under basic conditions in excellent yield. Formation of the nine-membered carbocycle **168** was achieved by transforming **167** into the oxime (no conditions are reported) followed by fragmentation with phosphorus oxychloride in pyridine. 1,2-addition of methyllithium and subsequent Wolff–Kishner reduction of the resulting imine gave access to **169**.



165 **166** **167** **168** **169** **170**

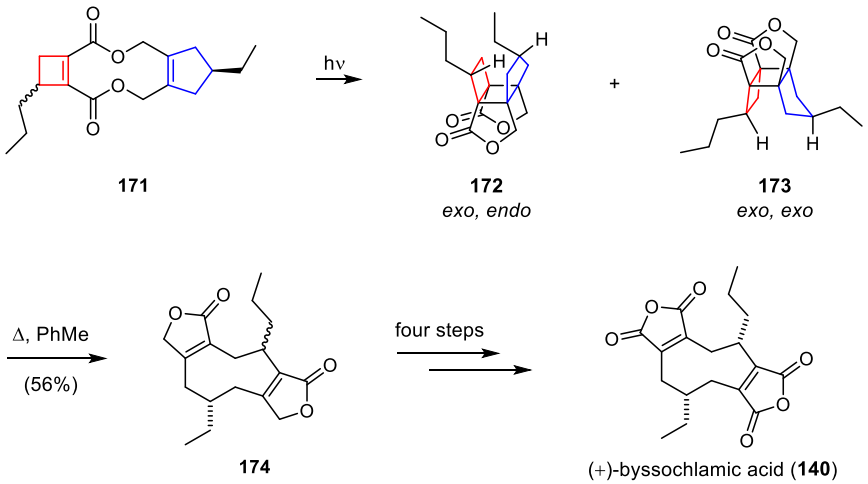
Scheme 25 | First racemic total synthesis of byssochlamic acid (**140**) by Stork.

Due to sterical hindrance, catalytic hydrogenation of the double bond was unsuccessful to access **170**. However, Birch reduction lead to the formation of a single product which was later characterized as the desired isomer **170** by single crystal X-ray structure analysis. Next, the substituted benzene rings had to be converted into maleic anhydride moieties. This was accomplished by initial cleavage of the methyl

[71] G. Stork, J. M. Tabak, J. F. Blount, *J. Am. Chem. Soc.* **1972**, *94*, 4735–4737.

ether with boron tribromide. The resulting unstable hydroquinone was directly oxidized with potassium permanganate followed by treatment with lead tetraacetate in acetic acid to give byssochlamic acid (**140**).

The White group demonstrated the applicability of a [2+2]-photoaddition/cycloreversion strategy for the synthesis of nine-membered carbocycles in their asymmetric total synthesis of (+)-byssochlamic acid (**140**).[72] Irradiation of a 1:1 mixture of diastereomers of dilactone **171** resulted in a [2+2]-cycloaddition and formation of the two stereoisomeric photoadducts **172** and **173** (1:1 mixture) (Scheme 26). Thermally induced cycloreversion led to cleavage of the four-membered rings and gave the nine-membered carbocycle **174** in good yield over two steps.



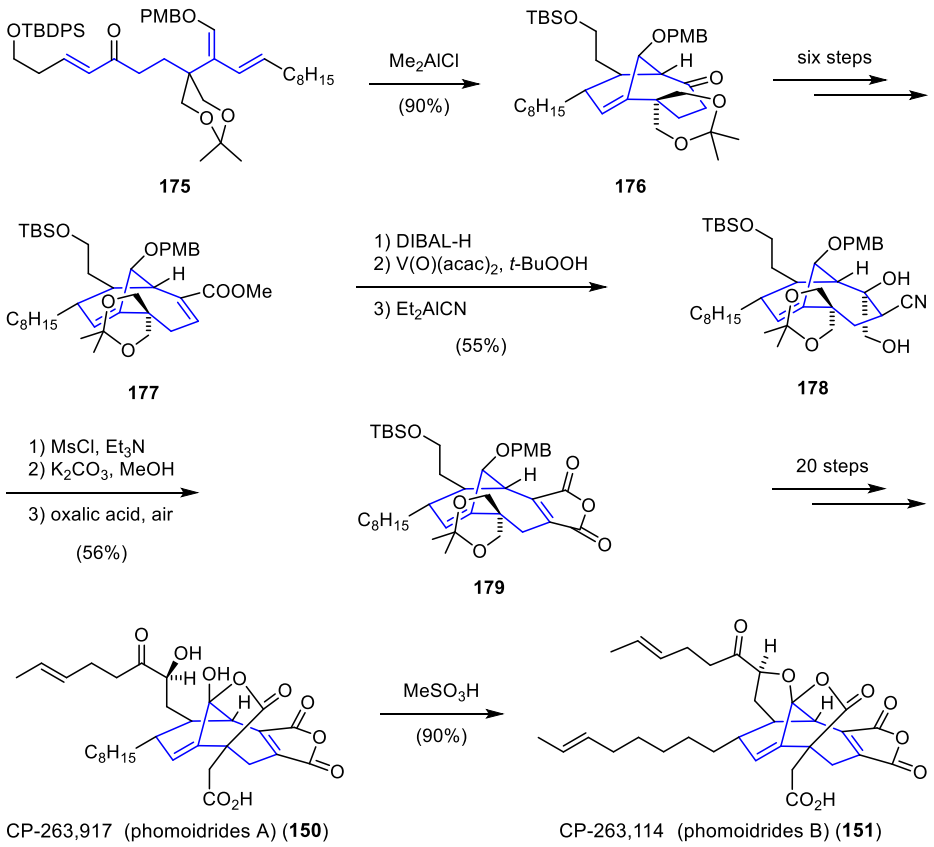
Scheme 26 | [2+2]-Photoaddition/cycloreversion strategy for the asymmetric total synthesis of **140**.

2.1.2.2 Phomoidrides A and B

In the last decades, several groups have targeted phomoidrides A (**150**) and B (**151**) due to their strong biological activities and structural complexity.[73] In 1999, Nicolaou published the first racemic total synthesis of phomoidrides A (**150**) and B (**151**) (Scheme 27).[74] The formation of the bicyclo[4.3.1]decene core **176** was accomplished by a type II intramolecular Diels–Alder reaction of cyclization precursor **175**. For the introduction of the maleic anhydride moiety, carboxylic ester **177** was converted into nitrile **178** followed by a one-pot tandem sequence including mesylation of the primary

[72] a) J. D. White, M. P. Dillon, R. J. Butlin, *J. Am. Chem. Soc.* **1992**, *114*, 9673–9674; b) J. D. White, J. Kim, N. E. Drapela, *J. Am. Chem. Soc.* **2000**, *122*, 8665–8671.
[73] For a review see: D. A. Spiegel, J. T. Njardarson,I. M. McDonald, J. L. Wood *Chem. Rev.* **2003**, *103*, 2691–2727.
[74] a) K. C. Nicolaou, J. Jung,W. H. Yoon, K. C. Fong,H. S. Choi, Y. He, Y. L. Zhong, P. S. Baran, *J. Am. Chem. Soc.* **2002**, *124*, 2183–2189. b) K. C. Nicolaou, P. S. Baran, Y. L. Zhong, K. C. Fong, H. S. Choi, *J. Am. Chem. Soc.* **2002**, *124*, 2190–2201. c) K. C. Nicolaou, J. Jung, W. H. Yoon, K. C. Fong, H. S. Choi, Y. He, Y. L. Zhong, P. S. Baran, *J. Am. Chem. Soc.* **2002**, *124*, 2183–2189. d) K. C. Nicolaou, P. S. Baran, Y. L. Zhong, K. C. Fong, Y. He, W. H. Yoon, H. S. Choi, *Angew. Chem. Int. Ed.* **1999**, *38*, 1676–1678. e) K. C. Nicolaou, P. S. Baran, Y. L. Zhong, H. S. Choi, W. Yoon, Y. He, K. C. Fong, *Angew. Chem. Int. Ed.* **1999**, *38*, 1669–1675. f) K. C. Nicolaou, Y. He, K. C. Fong, W. H. Yoon, H. S. Choi, Y. L. Zhong, P. S. Baran, *Org. Lett.* **1999**, *1*, 63–66. g) K. C. Nicolaou, P. S. Baran, *Angew. Chem. Int. Ed.* **2002**, *41*, 2678–2720. h) K. C. Nicolaou.M. W. Harter, L. Boulton, B. Jandeleit, *Angew. Chem. Int. Ed.* **1997**, *36*, 1194–1196.

alcohol, epoxide formation, β-elimination, cyclization, autoxidation and ammonia release. Maleic anhydride **179** was then converted into **150** in 20 steps. The last cyclization from phomoidrides A (**150**) to phomoidrides B (**151**) was accomplished by treatment of **150** with methanesulfonic acid in chloroform. Interconversion studies showed that by treatment of **151** with lithium hydroxide in a tetrahydrofuran, water mixture can be converted back into **150**. Later, Nicolaou developed an enantioselective synthesis of phomoidrides A (**150**) and B (**151**).[75]



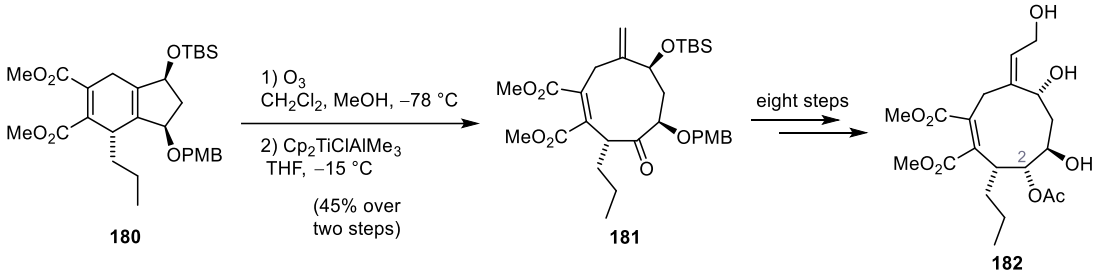
Scheme 27 | First racemic total synthesis of phomoidrides A (**150**) and B (**151**) by Nicolaou. The type II IMDA reaction and formation of the anhydride are highlighted.

To date, additional three total syntheses of phomoidrides A (**150**) and B (**151**) have been reported by Fukuyama,[76] Shair[77] and Danishefsky.[78]

[75] a) K. C. Nicolaou, J. Jung, W. H. Yoon, Y. He, Y. L. Zhong, P. S. Baran, *Angew. Chem. Int. Ed.* **2000**, *39*, 1829–1832. b) K. C. Nicolaou, Y. L. Zhong, P. S. Baran, J. Jung, H. S. Choi, W. H. Yoon, *J. Am. Chem. Soc.* **2002**, *124*, 2202–2211.
[76] a) N. Waizumi, T. Itoh, T. Fukuyama, *Tetrahedron Lett.* **1998**, *39*, 6015–6018. b) N. Waizumi, T. Itoh, T. Fukuyama, *J. Am. Chem. Soc.* **2000**, *122*, 7825–7826.
[77] a) C. Chen, M. E. Layton, M. D. Shair, *J. Am. Chem. Soc.* **1998**, *120*, 10784–10785. b) C. Chen, M. E. Layton, S. M. Sheehan, M. D. Shair, *J. Am. Chem. Soc.* **2000**, *122*, 7424–7425.
[78] a) D. F. Meng, Q. Tan, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **1999**, *38*, 3197–3201. b) O. Y. Kwon, D. S. Su, D. F. Meng, W. Deng, D. C. D'Amico, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **1998**, *37*, 1877–1880. c) O. Y. Kwon, D. S. Su, D. F. Meng, W. Deng, D. C. D'Amico, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **1998**, *37*, 1880–1882. d) D. F. Meng, S. J. Danishefsky. *Angew. Chem. Int. Ed.* **1999**, *38*, 1485–1488. e) Q. Tan, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2000**, **39**, 4509–4511.

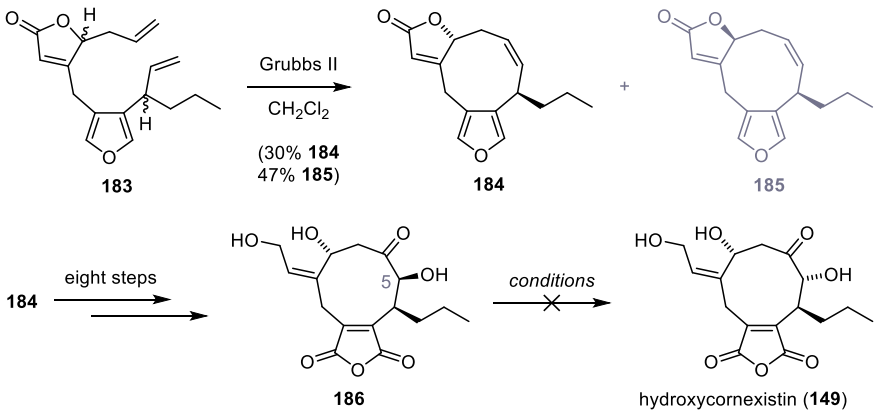
2.1.2.3 Cornexistin and hydroxycornexistin

Cornexistin (**148**) and hydroxycornexistin (**149**) show both significant herbicidal activity against certain young annual and perennial *monocotyledonous* and *dicotyledonous* plants with weak phytotoxicity to corn. Due to their potent herbicidal bioactivity and the synthetically unexplored nonadrine skeleton, **148** and **149** have been targeted in several synthetic studies. The first attempt to access the nine-membered ring of **148** and **149** by the Taylor group in 2007 features a ring expansion of **180** to **181** via an ozonolysis-olefination sequence. However, the Taylor group was never able to invert the stereochemistry of the C-2 hydroxyl group of **181** (Scheme 1).[79]



Scheme 28 | Synthetic route to the nine-membered carbocycle of **148** and **149** by the Taylor group.

The Clark group was confronted with a similar problem in their synthesis of the carbocyclic core structure of the cornexistins by ring-closing metathesis.



Scheme 29 | Synthesis of (±)-5-*epi*-hydroxycornexistin (**186**).

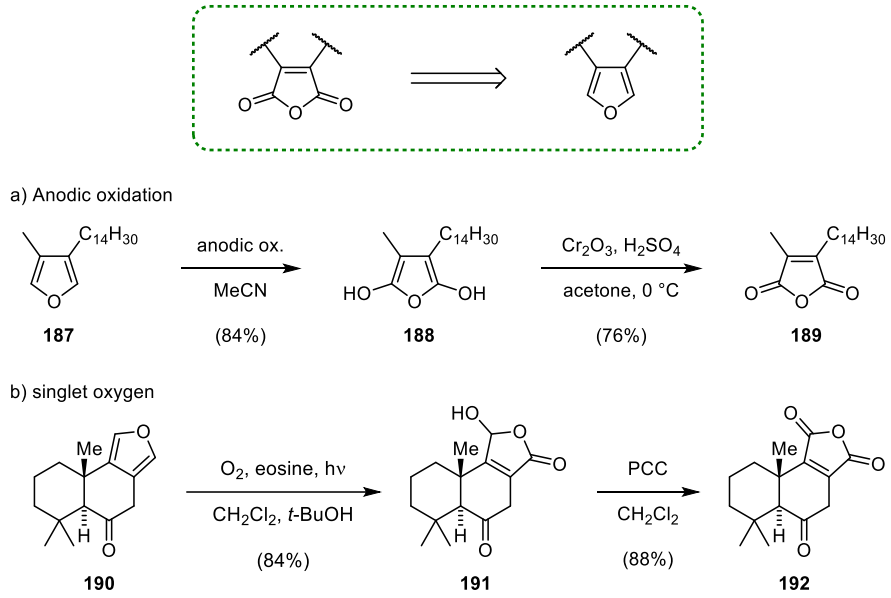
Treatment of a diastereomeric mixture of **183** with Grubbs' second generation catalyst (20 mol%) gave the desired nine-membered ring as a mixture of diastereomers **184** and **185**. The desired, minor isomer **184** was further transformed into 5-*epi*-hydroxycornexistin (**186**) in eight steps. Despite numerous

[79] J. C. Tung, W. Chen, B. C. Noll, S. C. Fields, W. H. Dent, F. R. Green, R. E. Taylor, *Synthesis* **2007**, *15*, 2388–2396.

effords to invert the stereochemistry of the hydroxy function at C-2 position, **149** could never be prepared.[80]

2.1.3 Maleic Anhydride

One of the key moieties that feature all members of the nonadride family is the maleic anhydride. Since an anhydride is a highly reactive species by default, it should be installed late stage in a synthetic route. Therefore, synthetically useful retrons for a maleic anhydride unit are needed. In the following selection the most common retrons and conversion thereof into maleic anhydrides are shown.

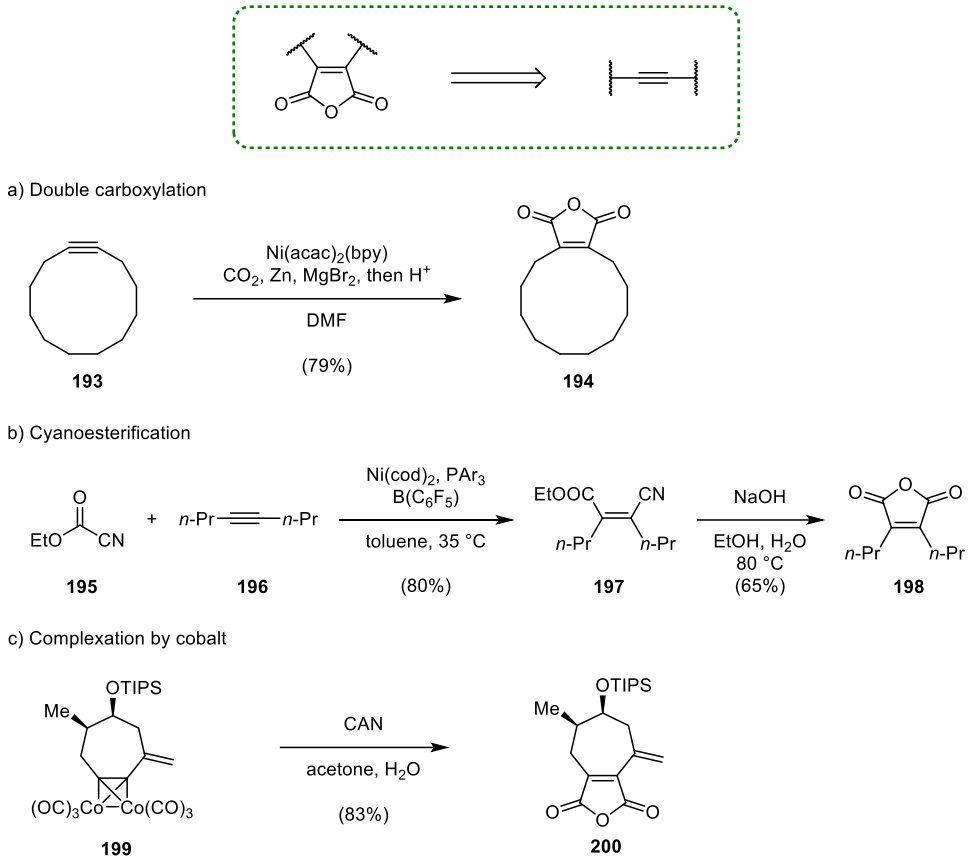


Scheme 30 | Furan as a retron for maleic anhydride by either a) anodic oxidation or b) photooxidation.

The furan, already containing the carbon/oxygen core, is one of the most common retrons for a maleic anhydride motive. In 1975, the group of Magnusson reported a stepwise procedure by initial anodic oxidation of furan **187** to **188**. The electrolysis product **188** was then oxidized under Jones conditions to the desired anhydride **189** (Scheme 30a).[81] Similar to the anodic oxidation procedure, exposure of **190** to singlet oxygen generated a mixture of diastereo-and regioisomers of lactol **191**. Further oxidation with pyridiniuim chlorochromate gave then the maleic anhydride **192**. Especially the photochemical protocol has been applied in several total syntheses.[82]

[80] a) F. Marlin, B. Nay, C. Wilson, J. S. Clark, *Org. Lett.* **2003**, *5*, 89–89. b) J. M. Northall, F. Marlin, B. Nay, C. Wilson, A. J. Blake, M. J. Waring, J. S. Clark, *Org. Biomol. Chem.* **2008**, *6*, 4012–4025.
[81] J. Froborg, G. Magnusson, S. Thóren, *J. Org. Chem.* **1975**, *40*, 122–123.
[82] For selected examples see: a) P.F. Vlad et al., *Tetrahedron* **2013**, *69*, 918–926. b) T. Nakano, J. Villamizar, M. A. Maillo, *J. Chem. Res.* **1998**, 560–561. c) C. L. Hugelshofer, T. Magauer, *J. Am. Chem. Soc.* **2015**, *137*, 3807−3810.

In 2014, the group of Tsuji reported a nicker-catalyzed double carboxylation of internal alkynes with carbon dioxide (1 atm). The reaction proceeds under carbon dioxide atmosphere at ambient temperature in the presence of a nickel catalyst, zinc as a reducing agent and magnesium bromide. With this methodology, various internal alkynes such as **193** could be transformed into the corresponding maleic anhydride **194** (Scheme 31a).[83]



Scheme 31 | Alkynes as a retron for maleic anhydrides.

Similar to this methodology, the group of Ogoshi demonstrated that cyanoformates (**195**) add across alkynes (**196**) to give β-cyano acrylates (**197**). Those highly functionalized adducts could be hydrolyzed to give disubstituted maleic anhydride **198** (Scheme 31b).[84]

The hexacarbonyldicobalt acetylene complex (**199**) was found to be a viable precursor for a maleic anhydride unit (**200**) first reported by P. Chen (Scheme 31c).[85] This transformation was found by attempted oxidative decomplexation of **199** with ceric ammonium nitrate (CAN) forming the maleic anhydride **200** in excellent yield. Although the mechanism for this transformation is still under investigation, this methodology has been applied in numerous synthetic sequences.[86]

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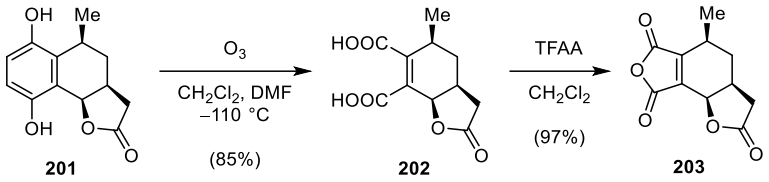
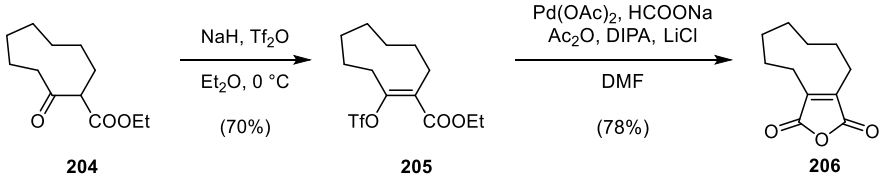
[83] T. Fujihara, Y. Horimoto, T. Mizoe, F. B. Sayyed, Y Tani, J. Terao, S Sakaki, Y Tsuji, *Org. Lett.* **2014**, *16*, 4960−4963.
[84] Y. Hirata, A. Yada, E. Morita, Y. Nakao, T. Hiyama, M. Ohashi, S. Ogoshi, *J. Am. Chem. Soc.* **2010**, *132*, 10070–10077.
[85] M. J. Schottelius, P. Chen, *Helv. Chim. Acta* **1998**, *81*, 2341–2347.
[86] For selected examples see: K. Tanino, T. Shimizu, M. Miyama, I. Kuwajima, *J. Am. Chem. Soc.* **2000**, *122*, 6116–6117. b) K. Mitachi, T. Yamamoto, F Kondo, T. Shimizu, M. Miyashita, K. Tanino, *Chem. Lett.* **2010**, *39*, 630–632. c) M. Kinebuchia, R. Uematsua, K. Tanino, *Tetrahedron Lett.* **2017** *58*, 1382–1386.



Scheme 32 | Ozonolytic conversion of hydroquinone **201** into maleic anhydride **203**.

Inspired by Stork's synthesis of byssochlamic acid (**140**), the group of U. Koert reported the first literature precedence of a selective ozonolytic conversion of hydroquinone **201** into maleic anhydride **203**. Although, ozonolysis of the corresponding benzoquinone of **201** also led to the formation of the dicarboxylic acid, a significant amount of side products was isolated. It is hypothesized that the phenolic hydroxyl groups led to a precoordination of ozone which then leads to the observed high selectivity of the oxidative cleavage (Scheme 32).



Scheme 33 | Synthesis of a maleic anhydride fused to a nine-membered carbocycle.

As demonstrated by K. I. Booker-Milburn, β-ketoesters such as **204** could be easily transformed into enol triflate **205**. In a subsequent palladium-mediated carbonylation, the maleic anhydride **206** could be installed (Scheme 33).[87] In 2018, this sequence was also applied for the installation of the maleic anhydride moiety in Wood's total synthesis of phomoidride D.[88]

[87] M. J. Ralph, D. C. Harrowven, S. Gaulier, S. Ng, K. I. Booker-Milburn, *Angew. Chem. Int. Ed.* **2015**, *54*, 1527–1531.
[88] J. C. Leung, A. A. Bedermann, J. T. Njardarson, D. A. Spiegel, G. K. Murphy, N. Hama, B. M. Twenter, P. Dong, T. Shirahata, I. M. McDonald, M. Inoue, N. Taniguchi, T. C. McMahon, C. M. Schneider, N. Tao, B. M. Stoltz, J. L. Wood, *Angew. Chem. Int. Ed.* **2018**, *57*, 1991–1994.

2.1.4 9-Membered Carbocycles: Strategies and Tactics for their Synthesis

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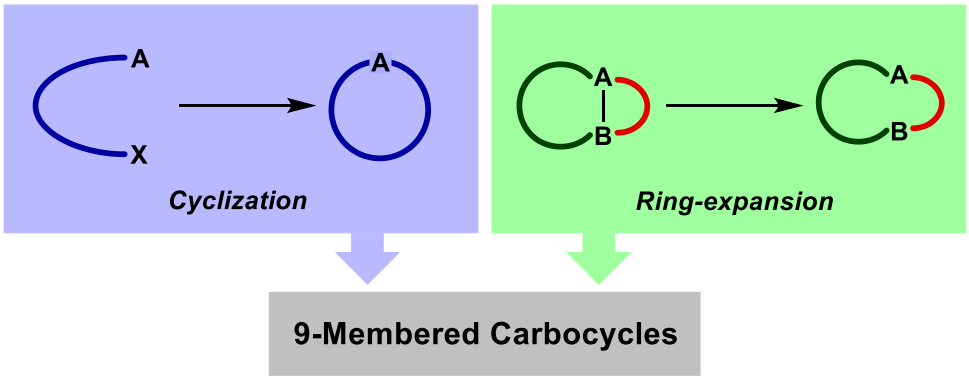
T. Huber[†], R. E. Wildermuth[†], T. Magauer, *Chem. Eur. J.* **2018**, *24*, 12107–12120.

[†] These authors contributed equally to this work.



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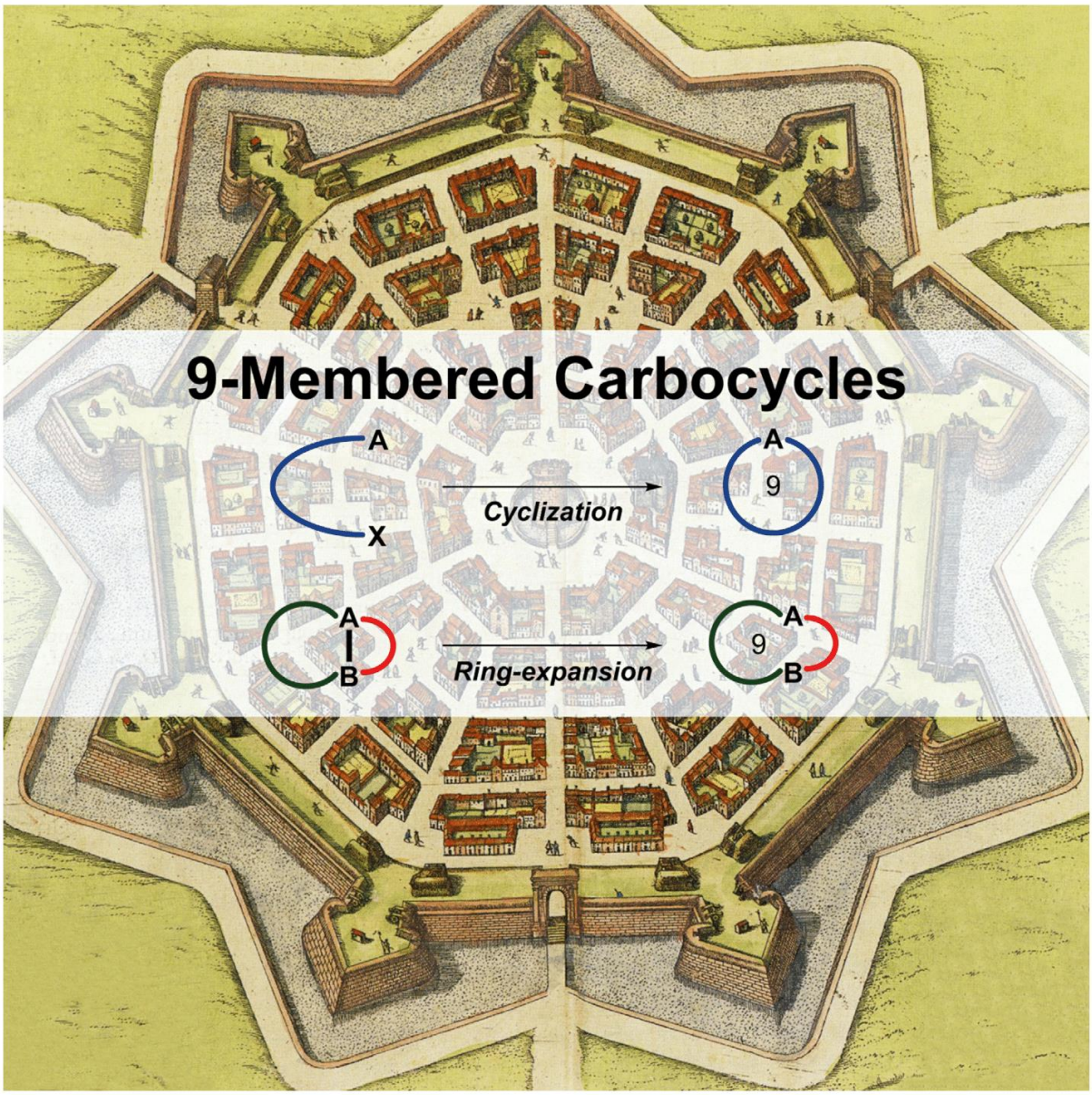
Cyclic Compounds

9-Membered Carbocycles: Strategies and Tactics for their Synthesis

Tatjana Huber[+],[b] Raphael E. Wildermuth[+],[a] and Thomas Magauer*[a]



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Abstract: Many natural products comprising a nine-membered carbocyclic core structure exhibit interesting biological effects. However, only a minority have succumbed to their synthesis in the past. The synthesis of functionalized nine-membered carbocycles still remains a challenging goal for synthetic chemists, mainly due to their high ring strain. Different strategies to overcome the unfavorable enthalpic and entropic factors associated with their formation are highlighted in this Concept article. The presented methods are classified into two different categories: (1) the ring-expansion of smaller rings or the ring-contraction of larger rings and (2) the direct cyclization of acyclic precursors.

1. Introduction

Functionalized nine-membered carbocyclic rings are incorporated in a variety of natural products with diverse biological activities. To date, their use in drug discovery is limited to enediyne anticancer antibiotics, such as neocarzinostatin, consisting of the labile chromophore **1**, which is non-covalently bound to an apoprotein (Figure 1).[1] Other natural products with remarkable biological activities, such as rubratoxin A (**2**),[2] α-viniferin (**3**)[3] and protoxenicin A (**4**),[4] exemplify the potential of nine-membered carbocyclic ring-containing natural products as lead compounds. The underrepresentation of these natural products can be mainly attributed to the difficulties associated with the synthesis of such ring systems. Besides their preparation by total synthesis, the modification of easily isolable nine-membered carbocyclic ring-containing natural products, such as caryophyllene, is another strategy for drug discovery and will not be covered in this article.

In general, carbocyclic rings are classified according to the number of atoms in their ring and their distinct properties. The group of medium-sized carbocycles, consisting of eight to eleven carbon atoms, is characterized by its relatively high ring strain compared to the most prevalent five-, six- and seven-membered rings and large rings (≥ twelve carbon atoms). The observed conformations of carbocyclic rings are a result of the system to minimize the angle and torsional strain. In medium-sized rings, additional transannular interactions of ring substituents on non-adjacent carbon atoms contribute significantly to the ring strain energy (Table 1).[5] Nine-membered carbocycles do not adopt a single low-energy conformation to relieve its ring strain. Instead, they have several conformations of similar energies, separated by low energy barriers, which can be interconverted by pseudorotation.[6]

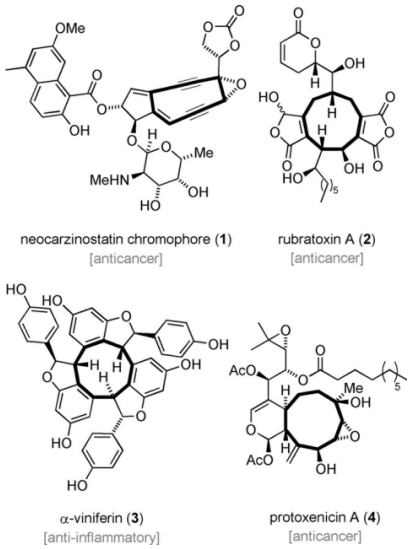

Figure 1. Selected nine-membered carbocyclic ring-containing bioactive natural products. The nine-membered rings are highlighted with bold bonds.

Table 1. Strain energy of cycloalkanes.

Ring size	6	7	8	9	10	11	12
Strain energy [kcal mol^{-1}]	1.4	7.6	11.9	15.5	16.4	15.3	11.8

It is noteworthy that planar chirality is commonly observed in constrained nine-membered carbocycles incorporating an *E*-configured olefin. In these molecules, the energy barrier of rotation about one or more C–C single bonds is high enough for the isolation of the conformers. The enantiomerically pure and optically active carbocycles can be either obtained by resolution of the racemic mixture or by synthesis from centrochiral precursors. For example, the two enantiomers of *trans*-cyclononene, **5** and *ent*-**5**, can be separated by coordination to a chiral platinum complex, followed by isolation of the two resulting diastereomeric complexes.[7] While enantiomerically pure *trans*-cyclononene (**5**) has a racemization half-life of about 4 min at 0 °C, more constrained *E*-cyclononenes, such as enone **6**,[8] maintain their planar chiral information at room temperature for longer periods and can be used as chiral precursors for further stereo- and regioselective transformations (Scheme 1).

The synthesis of medium-sized rings is a long-standing challenge for synthetic chemists, mainly due to unfavorable enthalpic and entropic factors. About 100 years ago, it was com-

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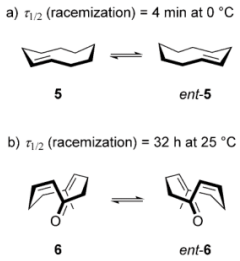
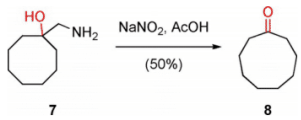


Scheme 1. Rate of racemization for two different *E*-cyclononenes.

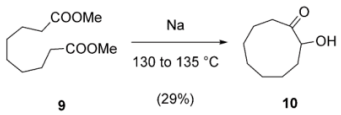
monly believed that carbocyclic rings containing more than eight carbon atoms were impossible to synthesize. In 1926, Ruzicka was the first to disregard this theory by elucidating the structures of the first macrocyclic natural products civetone, that exhibits a 17-membered ring,[9] and muscone, bearing a 15-membered ring.[10]

He also developed a method for the preparation of larger carbocycles containing between ten and 18 carbon atoms by vacuum pyrolysis of the thorium salts of acyclic dicarboxylic acids at 300–500 °C using a copper flask.[11] Based on this method, the synthesis of nine-membered rings could only be achieved in very low yields. Ruzicka's effort in exploring the synthesis and properties of larger rings was rewarded with the Nobel prize in chemistry in 1939, together with Butenandt, for his work on "polymethylenes and higher terpenes".[12] In 1943, he reported the first efficient three-step synthesis of cyclononanone (**8**) via a Tiffenau–Demjanow rearrangement[13] of 1-(aminomethyl)cyclooctan-1-ol (**7**), itself prepared from cyclooctanone in two steps, upon treatment with sodium nitrite and acetic acid (Scheme 2).[14]



Scheme 2. Synthesis of cyclononanone (**8**) by Ruzicka.

In 1947, Prelog and Stoll finally succeeded in developing the first reliable one-step procedure for the synthesis of medium-sized carbocycles, including nine-membered rings, from dicarboxylic acid esters by acyloin condensation (Scheme 3).[15] Despite its harsh reaction conditions, this method has become a widely used transformation for the synthesis of medium-sized rings.[16]



Scheme 3. Synthesis of 2-hydroxycyclononan-1-one (**10**) by acyloin condensation.

Today, medium-sized rings are still the most difficult ones to access. Although several methods for the preparation of substituted nine-membered carbocycles have been reported in the past decades, no generally applicable method has been described. In this Concept article, strategies for accessing nine-membered carbocycles are classified into two categories: (1) ring-expansion/-contraction reactions and (2) cyclization reactions of acyclic precursors.

2. Ring-Expansion Reactions

Many published methods for the preparation of nine-membered carbocycles rely on ring-expansion strategies and the reactions associated with them are (1) fragmentation reactions, (2) radical ring-expansion/-contraction reactions and (3) pericyclic reactions.

2.1. Fragmentation reactions

Most ring-expansion reactions are fragmentation reactions of fused bicyclic compounds. Whereas classical head-to-tail cyclizations of acyclic precursors are often not predictable and suffer from low scalability, the synthesis of fused bicyclic substrates as precursors for ring-expansion reactions only requires the preparation of five- to seven-membered rings by cyclization reactions. A great variety of reliable methods for their formation exists, which facilitates synthetic planning.

The most famous fragmentation reaction for the synthesis of nine-membered carbocycles is the Grob fragmentation reaction,[17] which is still widely used today.[18] In this reaction, a molecule of the form **11** is heterolytically cleaved into three fragments (Scheme 4). The choice of the leaving group Y thereby determines the thermodynamic driving force of this irreversible reaction.

This strong thermodynamic driving force makes the Grob fragmentation a powerful synthetic tool in compensating the high ring strains associated with the formation of nine-membered carbocyclic rings. In the last 50 years, mainly 1,3-diols in-

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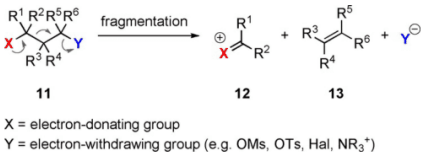
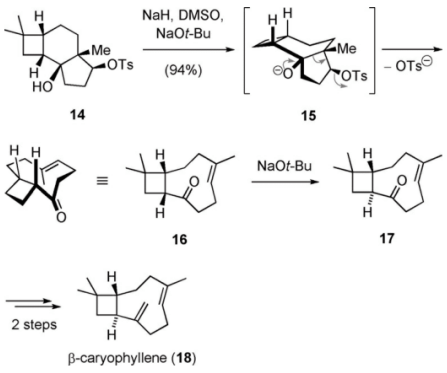


Scheme 4. General Grob fragmentation of 1,3-diheterosubstituted compounds.

corporated in fused 5,6-bicyclic ring systems were employed for Grob fragmentation approaches of complex natural products containing a nine-membered carbocycle. In these rigid bicyclic systems, the bond that is broken and the leaving group are fixed in an *anti*-periplanar alignment.[19] Thus, the fragmentation proceeds in a concerted and highly stereospecific fashion, allowing the prediction of the configuration of the product.

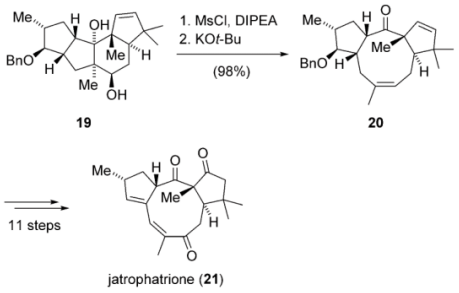
The total synthesis of the first nine-membered carbocyclic ring-containing natural product reported in 1964, was a significant milestone in the field. The Corey group reported the successful total synthesis of the sesquiterpene β-caryophyllene (**18**), where the *E*-configured cyclononene ring was installed by sodium hydride mediated ring-expansion of bicyclic monotosylated 1,3-diol **14** (Scheme 5).[20]



Scheme 5. Grob fragmentation approach to β-caryophyllene (**18**).

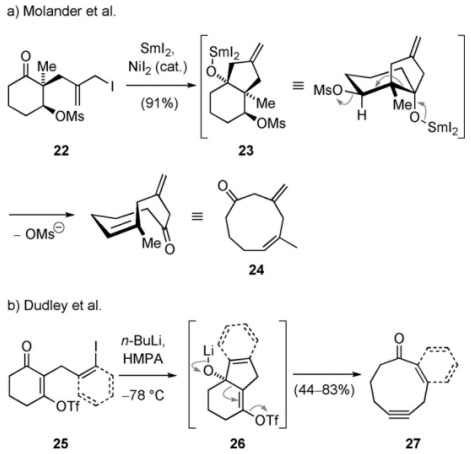
Another compelling example that demonstrates the applicability of Grob fragmentations for the total synthesis of complex natural products, is the total synthesis of the tricyclic diterpenoid jatrophatrione (**21**) by Paquette (Scheme 6). First, mesylation of the sterically less congested secondary alcohol in tetracycle **19** resulted in the formation of a monomesylated 1,3-diol, which was readily fragmented upon treatment with potassium *tert*-butoxide (KO*t*Bu) to construct the *Z*-configured cyclononene fragment **20** of jatrophatrione (**21**).[21]

In recent years, the Grob fragmentation was applied to cascade reactions, thus allowing formation of the fragmentation precursor and fragmentation in one-pot. For example, Molander and co-workers accessed eight-, nine- and ten-membered rings by a samarium diiodide-mediated cyclization/frag-



Scheme 6. Paquette's jatrophatrione (**21**) synthesis.

mentation cascade of simple iodocycloalkanones.[22] In this domino reaction, samarium(III) alkoxide **23** was formed by a samarium diioide-mediated intramolecular cyclization of δ-iodoketone **22**, which then fragmented to afford cyclononene **24** (Scheme 7 a). In a conceptually related approach, the Dudley group accessed highly strained cycloalkynes of medium ring size.[23] The first step was an iodine-lithium exchange of a vinyl or phenyl iodide **25** with *n*-butyllithium, followed by an intramolecular 1,2-addition of the generated organolithium species to the ketone (Scheme 7 b). An ensuing alkynogenic fragmentation of the resultant lithium alkoxide **26** afforded the cycloalkynes **27**. The formation of these strained products was likely driven by the release of a triflate anion.



Scheme 7. Molander's and Dudley's cyclization/fragmentation cascades.

While the rearrangement of oximes to their corresponding amides, known as the Beckmann rearrangement, is a widely used transformation, the Beckmann fragmentation is less commonly used in total synthesis.[24] It is a variant of the Beckmann rearrangement for substrates that have a quaternary carbon atom in the *anti*-position to the hydroxyl group of an oxime. In this reaction, oximes are converted to nitriles instead of amides. The reaction was the key step in the total synthesis of (±)-byssochlamic acid (**30**) by Stork.[25] Treatment of tetracyclic

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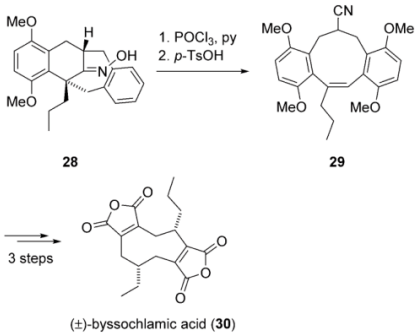
oxime **28** with phosphoryl trichloride ($POCl_3$) and pyridine resulted in the isolation of a mixture of *Z*-cyclononene **29** and its propylidene double bond isomer, which was isomerized with *para*-toluene sulfonic acid (*p*-TsOH) to give **29** in good yield (Scheme 8).



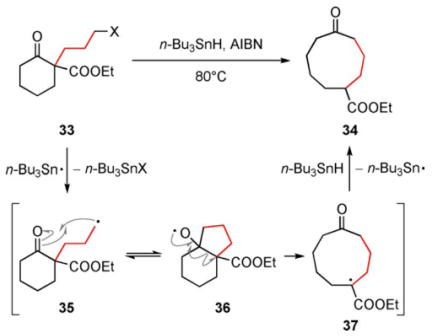
Scheme 8. Beckmann rearrangement approach to (±)-byssochlamic acid (**30**).

2.2. Radical ring-expansion reactions

Free radical-mediated ring-expansion reactions have been frequently utilized in the synthesis of medium-sized rings in the past.[26] Radical fragmentations can usually be conducted under mild reaction conditions and are operationally simple. Furthermore, a variety of functional groups are tolerated. The drawbacks of radical reactions are the formation of side products. Besides quenching of the generated radical, competing intramolecular 1,5-hydrogen atom abstraction followed by radical quenching is the main undesired reaction pathway.[27] In order to circumvent these unwanted pathways, the reactions are often carried out in highly diluted solutions along with slow addition of the reagents.

Dowd and Beckwith were the pioneers of radical ring-expansion reactions and their synthetic strategy, known as the Dowd–Beckwith reaction, and variants thereof are the most widely used radical fragmentation strategies. Their method was described as a one-, three-, or four-carbon ring-expansion and is shown in Scheme 9.[28] These early examples allowed the efficient preparation of rings containing up to eleven carbon atoms. As starting materials, they used β-keto esters, which were readily accessible by Dieckmann condensation of linear diesters.[29] These β-keto esters could be easily alkylated with a variety of electrophiles to introduce the radical precursors.

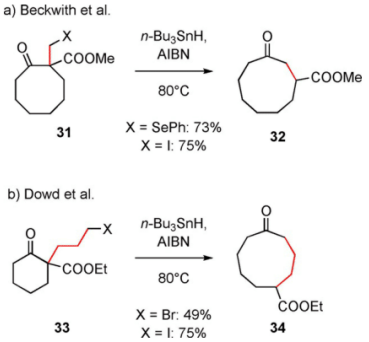
Mechanistically, the reaction commences with the generation of the primary alkyl radical **35** from the halide or selenide substituent (Scheme 10). Subsequent intramolecular cyclization



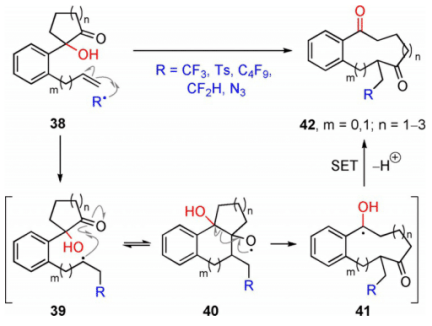
Scheme 10. Mechanism for the Dowd–Beckwith reaction.

results in the formation of the high-energy oxygen-centered radical **36**. Radical ring-opening of bicycle **36** leads to **37** with the tertiary radical stabilized by the ester group,[30] providing the driving force for the fragmentation. Hydrogen abstraction from tributyltin hydride finally gives the nine-membered cyclic ketone **34** and generates a tributylstannyl radical, which propagates the radical chain reaction. The use of β-keto esters as substrates thereby not only facilitated the preparation of the radical precursors by alkylation, but also rendered the cyclic ketone more electron-deficient and thus activated it for the radical cyclization.

In a modern variant of the Dowd–Beckwith reaction, Liu reported the synthesis of benzannulated medium-sized ketones by radical fragmentation.[31] Addition of azide, difluoromethyl, trifluoromethyl, tosyl or perfluoroalkyl radicals to the terminal alkene functionality of a cyclic α-hydroxy ketone **38** results in the formation of secondary radical **39** (Scheme 11). The gener-



Scheme 9. Radical ring-expansion by Beckwith and Dowd.



Scheme 11. Liu's method for the synthesis of medium-ring sized benzannulated ketones.

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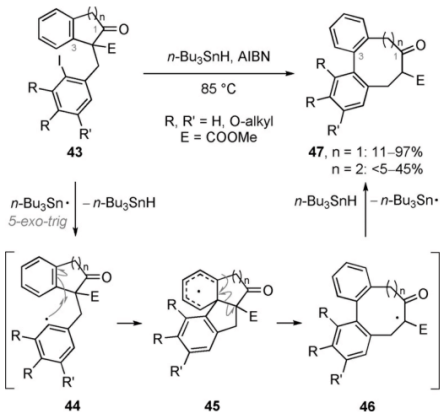
ation of the respective radicals was realized using either hypervalent iodine(III) reagents and catalytic amounts of copper(I) iodide (R = CF_3, N_3) or single-electron reduction under photoredox catalysis (R = Ts, C_4F_9, CF_2H). The following reversible intramolecular attack of the ketone affords the 6,6,5-tricyclic system **40**, which is fragmented to medium-sized carbocycle **41**. The radical fragmentation is thermodynamically driven by the formation of a stabilized α-hydroxy benzylic radical **41**. A final single-electron transfer (SET) to the photoredox or copper(I) catalyst and the loss of a proton affords the cyclic diketone **42**.

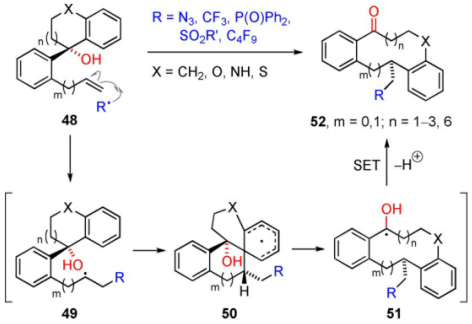
The presented examples for radical ring-expansion reactions were so far based on alkyl radical cyclizations onto ketones to form highly reactive oxygen-centered radicals, followed by fragmentation reactions. The next two examples describe high-energy carbon-centered radicals as intermediates in radical fragmentation reactions. The Harrowven group reported a procedure for the synthesis of eight- and nine-membered β-keto esters by radical *ipso*-substitution (Scheme 12).[32] First, genera-



Scheme 12. Synthesis of eight- and nine-membered β-keto esters by radical *ipso*-substitution at C3 position.

tion of an aryl radical **44** and subsequent *5-exo-trig* cyclization via radical *ipso*-substitution at C3 position gives the delocalized radical **45**. Rearomatization of the acceptor ring by radical fragmentation affords tertiary radical **46**, which is stabilized by the ester functionality. The eight- and nine-membered β-keto esters **47** are then obtained by hydrogen abstraction from tributyltin hydride. The yields for the nine-membered carbocycles were only moderate, which the authors attributed to the formation of significant amounts of the corresponding *ortho*-cyclization products, formed via a *6-endo-trig* cyclization of the aryl radical **44** to the tetralone ring.

Building upon their previous work on the construction of benzannulated medium-sized rings via ring-expansion, the Liu group reported on the synthesis of carbocycles of medium and large ring size by using a radical *ipso*-substitution strategy in 2016.[33] Generation of the radicals was realized by using hypervalent iodine(III) reagents and copper(I) cyanide (R = N_3, CF_3), alkyl or aryl sulfonyl chlorides (R = SO_2R', C_4F_9) and copper(I) iodide, or diphenylphosphine oxide and silver(I) nitrate (R = $P(O)Ph_2$). The first step of their procedure is the addition of the generated radicals to the terminal alkene of substrate **48** (Scheme 13). The secondary radical **49** undergoes a 1,4- or 1,5-aryl migration/ring-expansion sequence to afford neutral ketyl radical **51**. The migration presumably proceeds through spiro radical intermediate **50**.[34] Oxidation of the tertiary radical **51** to the ketone by the copper or silver catalyst and loss of a proton gives the ring-expanded medium-sized cyclic or macrocyclic ketones **52**. Furthermore, the authors demonstrated that the use of enantiomerically pure alcohols enabled isolation of enantioenriched medium-sized rings through radical chirality transfer during the ring-expansion.



Scheme 13. Radical aryl migration/ring-expansion sequence for the synthesis of medium-sized cyclic or macrocyclic ketones.

2.3. Pericyclic ring-expansion reactions

2.3.1. Sigmatropic reactions

Sigmatropic rearrangements were well explored for the synthesis of medium-sized rings in past decades.[35] Previously employed [1,2]-sigmatropic rearrangements for the synthesis of nine-membered carbocycles are the pinacol rearrangement,[36] the semi-pinacol rearrangement,[37] the Tiffenau–Demjanow rearrangement[13] and related homologation reactions of cyclic ketones involving diazo compounds.[38] The Tiffenau–Demjanow rearrangement has not found further application in the synthesis of nine-membered carbocycles in recent years, which can be mainly attributed to its harsh reaction conditions. The semi-pinacol rearrangement is a synthetically useful reaction and can be realized by using a variety of Lewis acids at low temperatures.[39] The reaction therefore tolerates a variety of functional groups. A recent example for the utilization of the semi-pinacol rearrangement for the synthesis of medium-sized rings was reported by Liu and Yeung. They treated a variety of 1-vinylcycloalkan-1-ols **53** with 1,3-dibromo-5,5-dimethylhydantoin (DBH, **54**) to activate the olefin by bromonium ion formation and isolated the corresponding one-carbon homologated β-bromo ketones **56** (Scheme 14).[37b] These substrates allowed further ring-expansion by the Dowd–Beckwith reaction to afford ketones **57**.

Pertaining the use of [3,3]-sigmatropic rearrangements for the synthesis of nine-membered carbocycles, in particular, the oxy-Cope and the Claisen rearrangements are used. This can

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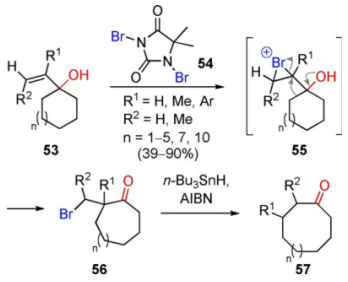
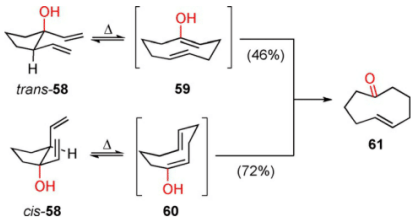


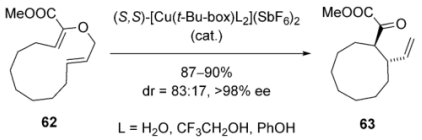
Scheme 14. Semi-pinacol rearrangement and subsequent Dowd–Beckwith reaction for the synthesis of medium-sized carbocycles.

be mainly attributed to the broad applicability and irreversibility of these processes, which can be credited to the formation of a thermodynamically more stable C=O double bond.[40] The oxy-Cope rearrangement can either be carried out thermally or by treatment with base to induce an anionic rearrangement. The latter has the advantages of an exceptional rate acceleration and of greater functional group tolerance due to decreased reaction temperatures. The utilization of the oxy-Cope rearrangement for the synthesis of nine-membered carbocycles was first described by Kato in 1980.[41] The thermal activation (220 °C) of an 81:19 mixture of the isomers *trans*-**58** and *cis*-**58** led to the isolation of (*E*)-5-cyclononen-1-one (**61**) as a single isomer in good yield (Scheme 15). The stereochemical outcome of this reaction can be explained by the chair-like transition-state geometries as depicted in Scheme 15.



Scheme 15. Thermal oxy-Cope rearrangement.

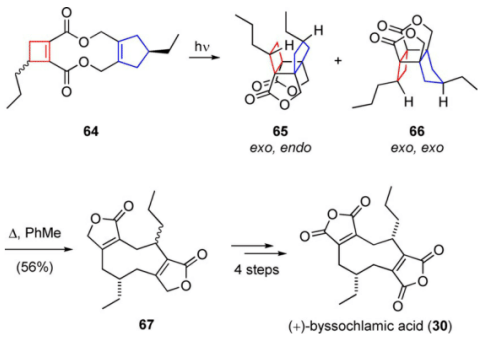
The reaction was later performed as an anionic oxy-Cope rearrangement by treatment of *trans*-**58** with potassium hydride at 0 °C and afforded the ring expanded product **61** in 86% yield.[42] In 2012, the Hiersemann group utilized a catalytic asymmetric Gosteli–Claisen rearrangement for the synthesis of nine-membered carbocycles.[43] In their work, 13-membered cyclic 2-alkoxycarbonyl-substituted allyl vinyl ethers, such as **62**, were transformed to nine-membered carbocycles in the presence of different chiral bis(oxazoline) copper(II) catalysts. The good diastereoselectivity of this reaction results from the preference of the substrate to adopt a chair-like transition state. The reaction could also be performed in an uncatalyzed fashion by heating **62** to 140 °C, resulting in the formation of racemic **63** in 92% yield (d.r. = 94:6) (Scheme 16).



Scheme 16. Synthesis of nine-membered carbocycles by asymmetric Gosteli–Claisen rearrangement.

2.3.2. Cycloaddition and -reversion

The White group demonstrated the applicability of a [2+2]-photoaddition/cycloreversion strategy[44] for the synthesis of nine-membered carbocycles in their asymmetric total synthesis of (+)-byssochlamic acid (**30**).[45] Irradiation of a 1:1 mixture of diastereomers of dilactone **64** resulted in a [2+2]-cycloaddition and formation of the two stereoisomeric photoadducts **65** and **66** (1:1 mixture) (Scheme 17). Thermally induced cycloreversion led to cleavage of the four-membered rings and gave the nine-membered carbocycle **67** in good yield over two steps.



Scheme 17. [2+2]-Photoaddition/cycloreversion strategy for the asymmetric total synthesis of byssochlamic acid (**30**).

2.4. Miscellaneous

Recently, the synthesis of nine- and ten-membered carbocycles from phthalates via a dearomatization/cyclization/ring-opening cascade has been described.[46] First, the phthalates were converted to fused 5,6-bicyclic systems **69** by reduction of **68** with sodium metal and alkylation with 1,3-dibromopropane (Scheme 18). A stereoselective ring-opening was then induced by treatment of the fused bicyclic system with lithium/naphthalene to give bis-enolate **71**, presumably formed by bond cleavage of intermediate dianion diradical **70**. Stereoselective protonation with acetic acid afforded the nine-membered carbocyclic dienes **72**.

3. Transannular Ring-Contraction Reactions

Besides using ring-expansion reactions of fused bicyclic systems for the preparation of medium-sized rings, trans-annular ring contraction reactions can also be employed for the production of smaller, more strained rings. The applicability of this

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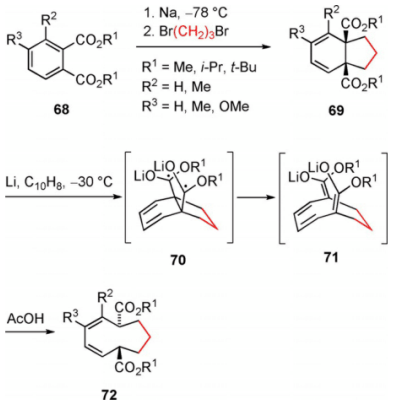
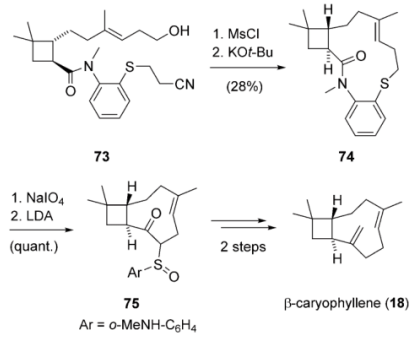


Scheme 18. Synthesis of nine-membered carbocycles **72** via stereoselective reductive ring-opening.

strategy for the synthesis of cyclononenes was demonstrated by the Oishi group in 1984, who developed a ring contraction strategy for the total synthesis of β-caryophyllene (**18**).[47] First, the 13-membered ring was prepared by conversion of alcohol **73** to the corresponding mesylate, followed by potassium *tert*-butoxide-mediated generation of a thiolate anion and subsequent cyclization to afford the 13-membered lactam **74** (Scheme 19). An intramolecular acyl transfer reaction was then employed to form the cyclononene ring. Sodium periodate oxidation of sulfide **74** to the corresponding sulfoxide and subsequent deprotonation with lithium diisopropylamide (LDA) led to the formation of cyclononene **75** in quantitative yield.



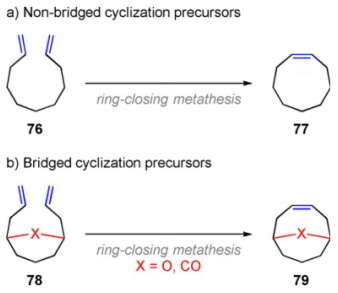
Scheme 19. Ring-contraction strategy by Oishi for the total synthesis of β-caryophyllene (**18**).

4. Cyclization Reactions of Acyclic Precursors

The construction of nine-membered carbocycles by ring-expansion reactions is a good strategy to compensate the high ring strain. However, it often requires the formation of complex, fused polycyclic substrates, themselves already challenging synthetic targets. In contrast, the formation of nine-membered carbocyclic rings from acyclic precursors enables a more conservative retrosynthetic C–C bond disconnection. In the following chapters, the strategies and reactions for the synthesis of nine-membered carbocycles from acyclic precursors by (1) ring-closing olefin metathesis, (2) cycloaddition, (3) intramolecular cross-coupling, (4) Conia-ene cyclization, (5) Friedel–Crafts cyclization, (6) Nozaki–Hiyama–Kishi reaction and (7) samarium(II)-promoted cyclizations will be discussed.

4.1. Ring-closing metathesis

Recently, the ring-closing metathesis (RCM) reaction has become one of the most powerful methods to construct medium-sized carbocycles from acyclic precursors.[48] To date, no example for the formation of *E*-or *Z*-cyclononene (**77**) from diene **76** by RCM has been reported (Scheme 20a). Functionalized nine-membered carbocycles could be successfully obtained from linear precursors containing some sort of conformational constraint. Substrates that are not conformationally predisposed for such cyclization reactions can be tuned by attaching an intramolecular tether (**78**). These substrates can then undergo low energy cyclization pathways via six- or seven-membered transition state structures (Scheme 20b). After cyclization, the temporary tether is degraded to provide the nine-membered carbocycle. In the following section, two examples for the formation of nine-membered carbocycles from non-bridged cyclization precursors and one example for bridged cyclization precursors are shown.



Scheme 20. Ring-closing metathesis as a powerful method to form nine-membered carbocycles.

In 2008, the Altmann group described the total synthesis of the *Xenia* diterpenoid blumiolide C (**83**).[49] The, *Z*-configured double bond of the nine-membered ring was formed by ring-closing metathesis of diene **80** (Scheme 21). Preliminary experiments showed that protection of the allylic alcohol as *p*-methoxy benzyl (PMB) ether was crucial for the success of this transformation. After final optimizations, the best result was obtained by treatment of **80** with Hoveyda–Grubbs II catalyst (**81**) (50 mol%) in toluene at elevated temperature (90 °C) to give **82** in 66% yield. This unprecedented construction of the [7.4.0]oxabicyclic ring system via RCM showed that the use of sterically congested alkenes required unusually high catalyst loadings to obtain *Z*-cyclononene **82** in sufficient yields.

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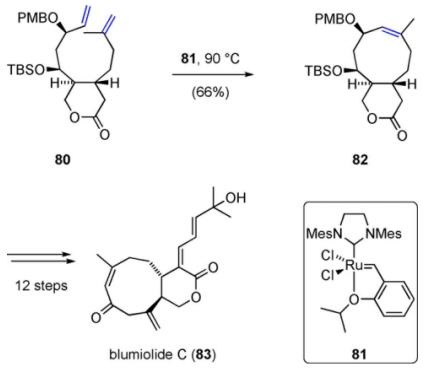
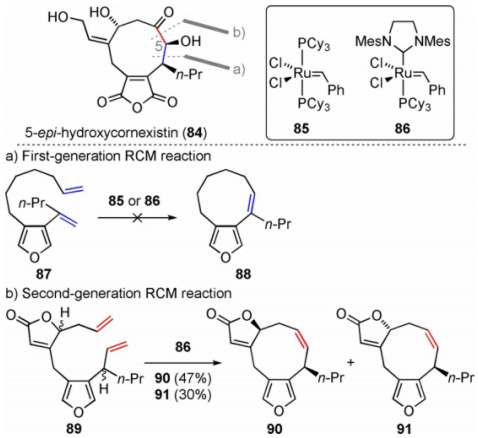


Scheme 21. Application of the RCM reaction in Altmann's total synthesis of blumiolide C (**83**).

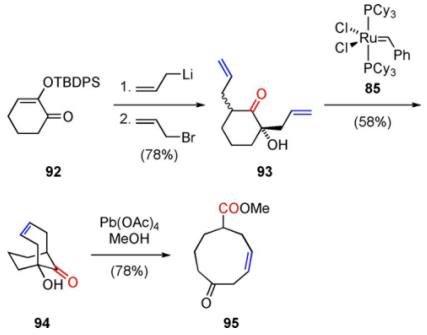
The Clark group was confronted with a similar problem in their synthesis of the carbocyclic core structure of the cornexistins by ring-closing metathesis.[50] Initial attempts to form nine-membered carbocycle **88** by treatment of diene **87** with either Grubbs' first (**85**) or Grubbs' second generation catalyst (**86**) failed to give the desired product (Scheme 22 a). To avoid the



Scheme 22. Synthesis of an intermediate in route to 5-*epi*-hydroxycornexistin (**84**).

use of a trisubstituted, conjugated double bond in the RCM reaction, such as in **87**, another C–C bond in the nine-membered ring was retrosynthetically disconnected which led to the revised cyclization precursor **89** (Scheme 22 b). Treatment of a diastereomeric mixture of **89** with Grubbs' second generation catalyst (**86**) (20 mol%) gave the desired nine-membered ring as a mixture of diastereomers **90** and **91**. The desired, minor isomer **91** was further transformed into 5-*epi*-hydroxycornexistin (**84**) in eight steps.

The last two examples described the formation of nine-membered carbocycles by RCM of acyclic precursors bearing sufficient conformational constraint. The group of Mascareñas reported the synthesis of tethered eight- and nine-membered carbocycles through a ring-closing metathesis/ring-fragmentation reaction sequence.[51] For the synthesis of nine-membered carbocycles, cyclization precursor **93** was readily prepared from ketone **92** in two steps and could be further transformed to alkene **94** upon treatment with Grubbs' first generation catalyst (**85**) (5 mol%) (Scheme 23). The introduction of the keto-bridging tether was found to be crucial for the formation of the nine-membered ring under these relatively mild conditions. In the final step, oxidative cleavage of the carbonyl bridge with lead(IV) acetate afforded *Z*-configured cyclononenone **95**.



Scheme 23. Formation of the nine-membered carbocycle via RCM reaction facilitated by a carbonyl tether.

In summary, the ring-closing metathesis reaction displays a powerful method for the construction of nine-membered carbocycles. Dienes containing some sort of conformational constraint, introduced by either substituents on the linear cyclization precursor or by intramolecular tethering, undergo smooth nine-membered ring formation. However, substrates without conformational preorder or with sterically hindered double bonds (tri- or tetra substituted) exhibit low reactivity in RCM reactions and show either no reaction or require high catalyst loadings.

4.2. Cycloaddition

Transition-metal-catalyzed cycloaddition reactions are also powerful tools for the preparation of nine-membered carbocycles. For example, the Ito group described an interesting one-step procedure for the synthesis of C_{2v}-symmetric nine-membered carbocycles via a [4+4+1]-cycloaddition by the palladium-catalyzed carbonylation of vinylallenes.[52] Mechanistically, the authors proposed that the sequence commences with the formation of five-membered palladacycle **97**, bound to another molecule of vinylallene **96** (Scheme 24). Subsequent C–C bond formation gives bis(π-allyl)-palladium intermediate **98**, whose resonance structure, σ-di(alkenyl)palladium intermediate **99**, is more stable. Migratory insertion of carbon monoxide into the Pd–C bond to give **100**, followed by reductive elimination affords the corresponding nine-membered cyclic ketones **101**.

The synthesis of medium-sized carbocycles via a tandem isomerization/intramolecular [3+2]-cross-cycloaddition (IMCC) was reported by the Wang group.[53] The *E*-configured enone

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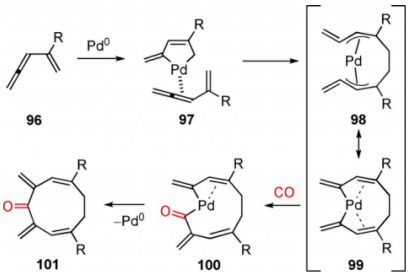
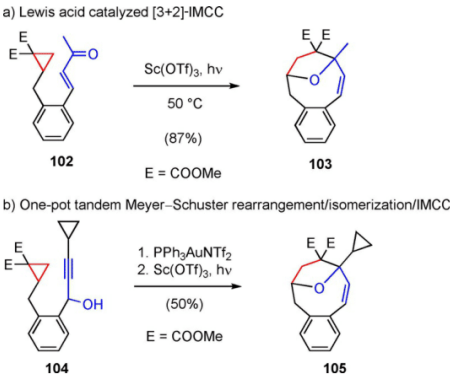


Scheme 24. Proposed mechanism for the [4+4+1]-cycloaddition to form cyclic ketones.

moiety in substrate **102** was either installed by Horner–Wadsworth–Emmons olefination or by an aldol condensation. For the desired cycloaddition, the double bond had to be isomerized to the corresponding *Z*-enone. The carbonyl oxygen should thereby get closer to the reactive site of the cyclopropane to initiate the cycloaddition. This was realized by irradiation of enone **102** with ultraviolet (UV) light, giving a mixture of the *E*- and *Z*-isomer. The latter was directly consumed in the subsequent Lewis acid-catalyzed [3+2]-cycloaddition to afford oxygen bridged cyclononene **103** (Scheme 25 a). Under constant irradiation, this process continues until **102** is fully consumed. In further studies, the scope was extended to propargylic alcohols (e.g. **104**) that could be easily prepared by nucleophilic 1,2-addition of terminal alkynes to benzaldehydes.

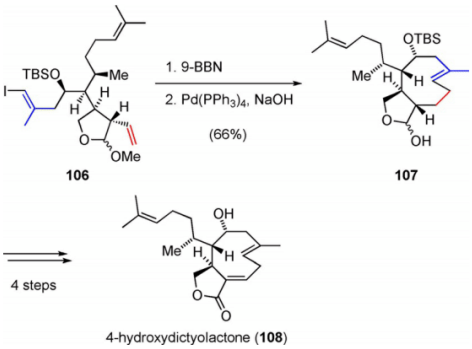


Scheme 25. Formation of nine-membered carbocycles via a) Lewis acid catalyzed isomerization/intramolecular [3+2]-cross-cycloaddition (IMCC) or b) one-pot tandem Meyer–Schuster rearrangement/isomerization/IMCC.

As part of their studies, Wang also developed a one-pot protocol featuring a Meyer–Schuster rearrangement[54] and the previously developed isomerization/intramolecular [3+2]-cross-cycloaddition (Scheme 25 b). In summary, these strategies constitute an efficient method for the construction of nine-membered rings and for the construction of carbocycle-based oxabicyclo[4.2.1] skeletons.

4.3. Intramolecular cross-coupling

Although no general procedure for the direct closure of nine-membered rings by cyclization of acyclic precursors via palladium-catalyzed cross coupling reactions has been described to date, scattered applications of this strategy have been demonstrated in natural product synthesis. In 2009, the Williams group reported the stereocontrolled total synthesis of 4-hydroxydictyolactone (**108**), a member of the xenicane diterpenoid family, featuring a rare nonconjugated *E,Z*-cyclononadiene motif (Scheme 26).[55] The formation of the *E*-cyclononene ring was accomplished by employing an intramolecular *B*-alkyl Suzuki cross coupling reaction of **106**. First, the hydroboration step was optimized to regioselectively target the monosubstituted double bond. Initial cyclization studies employing $PdCl_2$(dppf) as catalyst and thallium carbonate as base under optimized dilution conditions only afforded the desired product **107** in low yields. Eventually, the use of $Pd(PPh_3)_4$ as catalyst proved to be the key for achieving a high yielding cyclization and 4-hydroxydictyolactone (**108**) could be synthesized in four additional steps.



Scheme 26. Formation of the *E,Z*-cyclononadiene motif **107** by a *B*-alkyl Suzuki macrocyclization.

Another palladium-catalyzed method for the construction of nine-membered rings was reported by the group of Corey in the synthesis of antheliolide A (**111**) (Scheme 27).[56] This marine natural product features a unique 6,5,6,4,9-pentacyclic framework and due to the embedded functionalities, the range of methods for the formation of the *E*-cyclononene was limited. The construction of the challenging 5,4,9-tricycle **110** from allylic methoxy carbonyl derivative **109** was finally realized by intramolecular Tsuji–Trost reaction of **109** by treatment with catalytic amounts of $Pd_2(dba)_3$·$CHCl_3$. For the conversion of **110** to antheliolide A (**111**) eight additional steps were required.

4.4. Conia-ene cyclization

The Conia-ene reaction is a useful reaction for the formation of five- to seven-membered rings.[57] In 2007, the group of Nakamura reported the first example of an indium(III)-catalyzed

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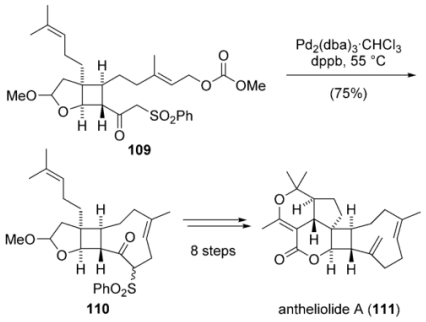
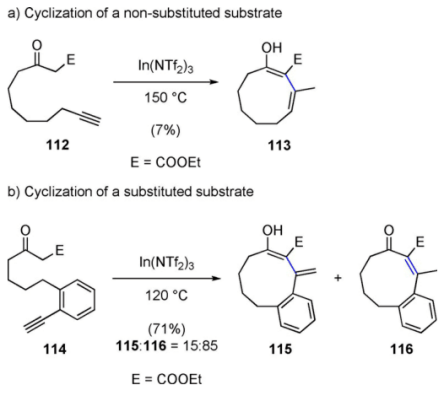


Scheme 27. Palladium-catalyzed formation of *E*-cyclononene **110** applied in the total synthesis of antheliolide A (**111**).

cycloisomerization of ω-alkynyl-β-keto esters to access five- to fifteen-membered carbocycles.[58] Mechanistically, the indium catalyst activates the β-keto ester by formation of an indium(III) enolate that then activates the terminal alkyne unit by coordination. Due to this double activation by the catalyst, entropic and enthalpic factors normally restraining the formation of medium-sized rings could be circumvented. Nevertheless, the transannular steric repulsion from generic cyclononane **113** impeded the cyclization of **112** and gave the nine-membered ring product in only 7% yield (Scheme 28a). However, substrates containing sp^2 carbon atoms led to efficient nine-membered ring formation. Consequently, β-keto ester **114**, featuring a phenylene motif, smoothly afforded the isomeric nine-membered carbocycles **115** and **116** (Scheme 28b).

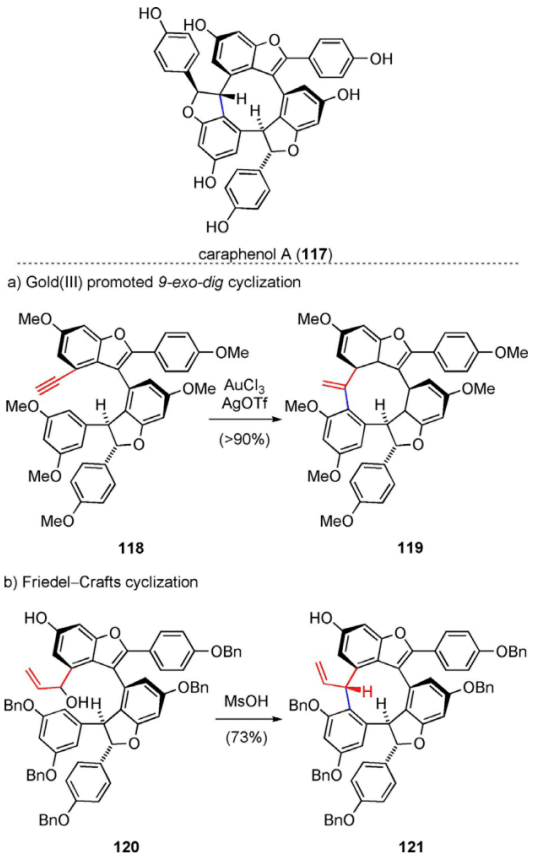
With this methodology, a broad range of nine-membered carbocycles could be synthesized in good yields. To date, no example of nine-membered ring formation with a non-terminal alkyne has been reported.



Scheme 28. In^{III}-mediated Conia-ene cyclization of a) the non-substituted precursor **112** and b) the substituted substrate **114**.

4.5. Friedel–Crafts cyclization

For the total synthesis of caraphenol A (**117**), the Snyder group investigated different approaches for the formation of the nine-membered carbocycle.[59] The envisioned late-stage formation of the nine-membered ring depends on a method compatible with highly functionalized substrates. In this context, the first reported gold(III) promoted *9-exo-dig* ring closure of **118** to **119** has been reported (Scheme 29a). The success and the efficiency (yield >90%) of this cyclization reaction originates from the high conformational control of substrate **118**. Since **119** proved to be a dead end for the total synthesis of caraphenol A (**117**), a second-generation approach based on a Brønsted acid-mediated Friedel–Crafts cyclization of **120** was pursued (Scheme 29b). Exposure of **120** to an excess of methanesulfonic acid resulted in clean formation of nine-membered ring **121** in excellent yields (73%). Eventually, the Snyder group was able to synthesize more than 600 mg of the final product caraphenol A (**117**).



Scheme 29. Nine-membered carbocycle formation via a) gold(III) promoted *9-exo-dig* ring closure and b) Friedel–Crafts cyclization applied in the total synthesis of caraphenol A (**117**).

4.6. Nozaki–Hiyama–Kishi reaction

Recently, the Nozaki–Hiyama–Kishi (NHK) reaction has become a viable method for the formation of nine-membered rings and has been applied in studies towards the total synthesis of pestalotiopsin A (**122**) and in the total synthesis of cristaxenicin

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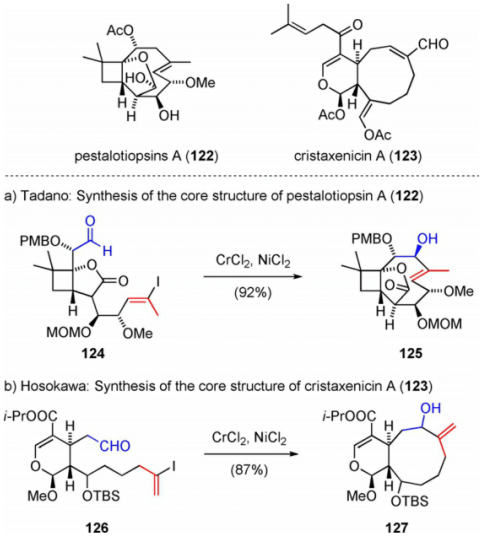
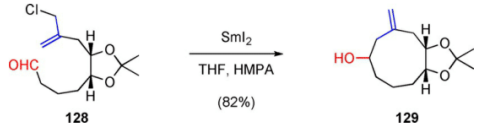
A (**123**).[60] In 2008, the group of Tadano published the first total synthesis of the sesquiterpenoid pestalotiopsin A (**122**) bearing an unprecedented oxatricyclic structure with a cyclobutane ring fused to a γ-lactol and an *E*-cyclononene ring. The latter was constructed by a highly efficient (92%), intramolecular NHK reaction giving **125** as a single diastereomer (Scheme 30a). In 2016, the intramolecular NHK reaction was applied in Hosokawa's synthesis of the core structure of cristaxenicin A (**123**) (Scheme 30b). Treatment of vinyl iodide (**126**) with $CrCl_2$ in the presence of $NiCl_2$ gave nine-membered carbocycle **127** in high yield (87%), but as an inconsequential mixture of diastereomers.



Scheme 30. The Nozaki–Hiyama–Kishi reaction applied in a) the total synthesis of pestalotiopsin A (**122**) and b) the formation of the core structure of cristaxenicin A (**123**).

4.7. Samarium(II)-promoted cyclizations

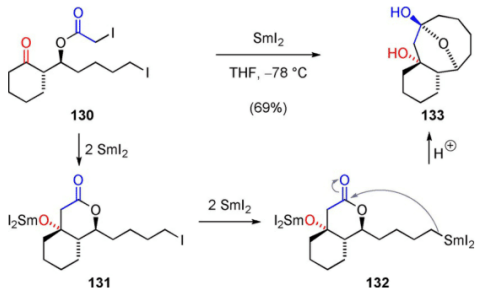
Samarium(II) iodide, first introduced and utilized as a reducing agent in 1980, has recently become a popular reagent for the formation of medium-sized carbocycles.[61] In the following examples, both radical and anionic formations of bridged and non-bridged nine-membered carbocycles are discussed. The group of Miyashita demonstrated that treatment of aldehyde **128** with samarium(II) iodide in the presence of hexamethylphosphoramide (HMPA) led to the formation of cyclononanol **129** in excellent yields (82%) (Scheme 31).[62] It is noteworthy that the reductive cyclization was completed within seconds



Scheme 31. Reductive cyclization promoted by samarium(II) iodide.

after addition of the SmI_2/HMPA mixture to the substrate and did not require high dilution conditions.

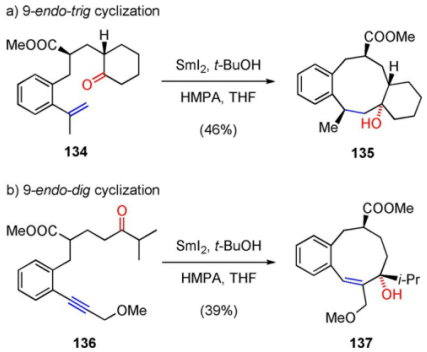
In the last decades, the group of Molander has published several samarium(II) iodide-based annulative routes for the construction of oxygen bridged cyclononenes.[63] In their recent report, nine-membered carbocycles were accessed via a one-pot Reformatsky reaction followed by a nucleophilic acyl substitution (Scheme 32). Treatment of **130** with samarium(II)



Scheme 32. Proposed mechanism of the samarium(II) iodide promoted sequential Reformatsky/nucleophilic acyl substitution for the formation of oxygen bridged nine-membered carbocycles.

iodide gives β-hydroxy lactone **131** in a Reformatsky reaction.[64] Alkoxide **132** undergoes a nucleophilic acyl substitution reaction to form stereodefined nine-membered carbocycle **133**. This method facilitates an efficient access to a variety of nine-membered carbocyclic derivatives under mild conditions.

The Reissig group demonstrated the use of a samarium(II) iodide-induced radical cyclization as a powerful tool for the formation of medium-sized benzannulated carbocycles.[65] Exposure of **134** to the developed cyclization conditions, promoted a *9-endo-trig* cyclization to give tricyclic compound **135** in only moderate yields but with excellent stereoselectivity (Scheme 33a). If alkynyl-substituted substrate **136** was subjected to these conditions, the nine-membered ring **137** was formed via a *9-endo-dig* cyclization mode in moderate yield (Scheme 33b). Although it exhibits moderate efficiency, this



Scheme 33. Samarium(II) promoted intramolecular a) carbonyl-alkene or b) carbonyl-alkyne coupling to construct nine-membered carbocycles.

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methodology rapidly provides access to highly substituted nine-membered carbocycle derivatives.

5. Conclusion

In the last century, the increasing interest in medium-sized carbocycles has led to the development of several powerful and practical protocols. Despite the advancement in recent years, the synthesis of highly-substituted nine-membered rings remains a great challenge. Several natural products have eluded their synthesis in recent years and in many cases, the available methods were not compatible with their delicate molecular framework. In this Concept article, we have shown strategies and tactics for accessing nine-membered carbocycles classified into two main categories: ring-expansion/-contraction reactions and cyclization reactions of acyclic precursors. In summary, no general procedure for the synthesis of nine-membered rings has been reported to date, but the ongoing effort of synthetic chemists has created a variety of methods to form highly complex nine-membered carbocycles.

Acknowledgements

We gratefully acknowledge financial support from the Funds of the European Research Council under the European Union's Horizon 2020 research and innovation program (grant agreement No 714049), the Chemical Industry (Sachkostenzuschuss and Dozentenpreis to T.M.), the German Research Foundation (Emmy Noether Fellowship, SFB 749 and SFB TRR 152 to T.M.) and the German National Academic Foundation (Fellowship to T.H.). We thank Dr. David Barber (Bayer AG) for helpful discussions during the preparation of this manuscript.

Conflict of interest

The authors declare no conflict of interest.

Keywords: carbocycles · cyclization · fragmentation · nine-membered ring · ring-expansion

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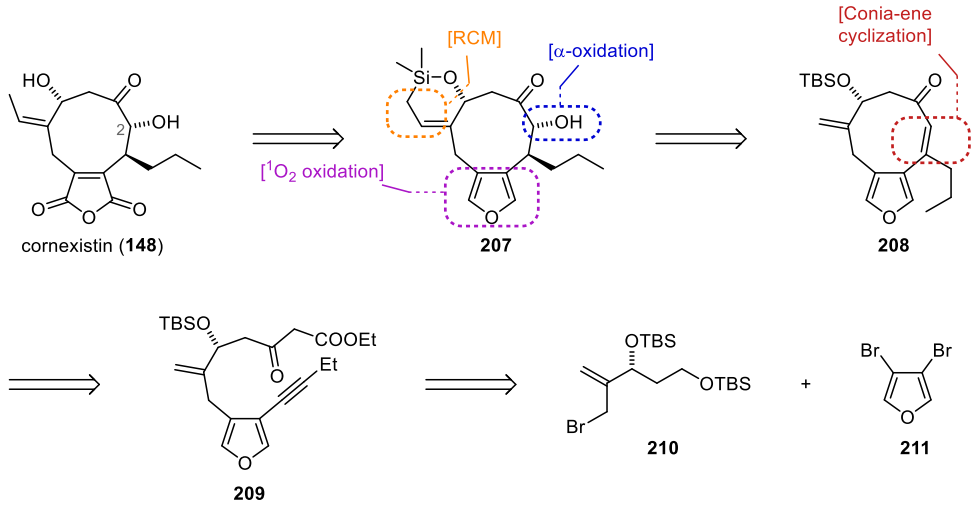
Manuscript received: December 13, 2017
Accepted manuscript online: January 22, 2018
Version of record online: March 13, 2018

2.2 Results and Discussion

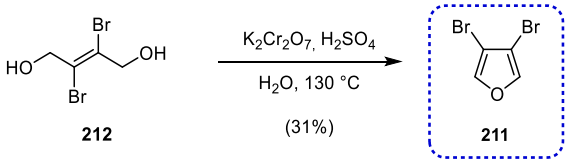
2.2.1 First Generation: Conia-ene cyclization

For the synthesis of cornexistin (**148**) we envisioned to synthesize the carbon skeleton **208** via a Conia-ene cyclization of β-keto ester **209**. The hydroxyl moiety at C-2 should be introduced by alpha hydroxylation, the exocyclic *Z*-configured double bond by intramolecular ring-closing metathesis with an allyl silyl ether and the anhydride moiety by oxidation of the furan with singlet oxygen. The cyclization precursor **209** can be dissected into two readily building blocks, allyl bromide **210** and 3,4-dibromofuran **211**.



Scheme 34 | Retrosynthetic analysis of **148**.

The synthesis of 3,4-dibromofuran (**211**) has been reported by several groups with yields in the range of 40–83%.[89] However, we were never able to reproduce those results and **211** was only isolated in traces.

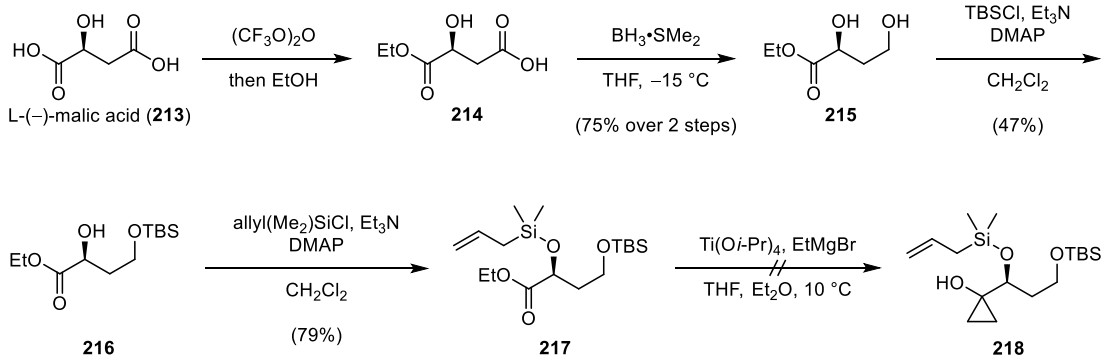


Scheme 35 | Synthesis of 3,4-dibromofuran (**211**)

[89] a) G. A. Kraus, X. Wang, Synth. Commun. **1998**, *28*, 1093–1096. b) S. P. H. Mee, V. Lee, J. E. Baldwin, A. Cowley, *Tetrahedron* **2004**, *60*, 3695–3712. c) D. Rennison, S. Bova, M. Cavalli, F. Ricchelli, A. Zulian, B. Hopkins, M. A. Brimble, *Bioorg. Med. Chem.* **2007**, *15*, 2963–2974. d) J. Min, P. Wang, S. Srinivasan, J. C. Nwachukwu, P. Guo, M. Huang, K. E. Carlson, J. A. Katzenellenbogen, K. W. Nettles, H. Zhou, *J. Med. Chem.* **2013**, *56*, 3346–3366.

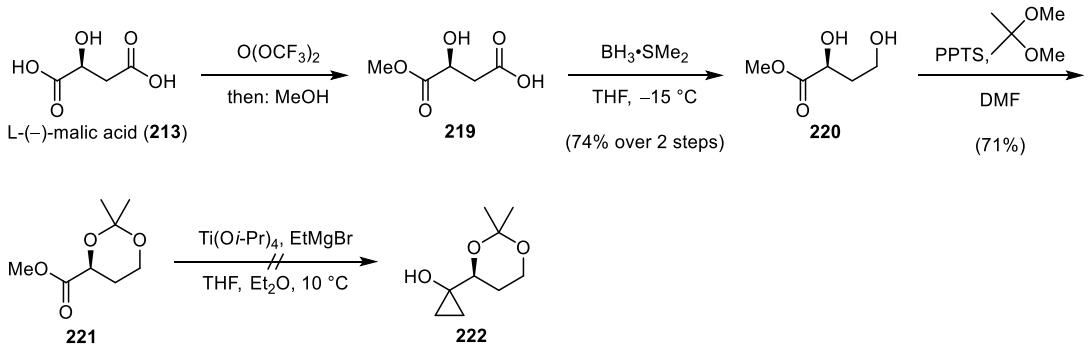
Constant removal of the product from the reaction mixture by water steam distillation was the key to success to isolate five grams of **211** in a single batch with reproducible yield of around 30% (Scheme 35).[90]

With **211** in hand we now investigated the synthesis of allyl bromide **210**. Starting from L-(–)-malic acid (**213**), one carboxylic acid group was selectively esterified by first formation of the mixed anhydride with trifluoroacetic anhydride followed by reaction with ethanol. Reduction of the free carboxylic acid functionality with borane dimethylsulfide complex afforded diol **215** in good overall yield. After silyl protection of the primary alcohol, the secondary alcohol **216** was protected with allyl(chloro)dimethylsilane The disilyl ether **217** turned out to be instable and thus the envisioned Kulinkovich reaction failed (Scheme 36).[91]



Scheme 36 | Envisioned formation of **218** via Kulinkovich reaction.

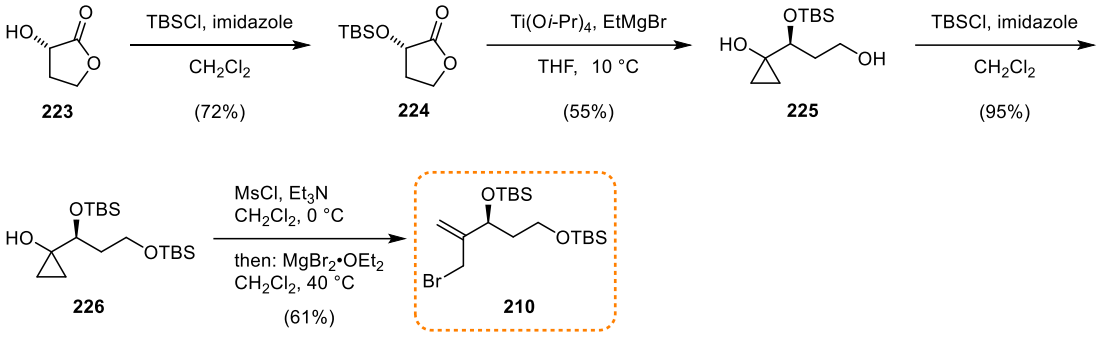
Then, we focused on the synthesis of another precursor for the Kulinkovich reaction without the labile silyl protection group. Starting from L-(–)-malic acid (**213**), **221** was synthesized accordingly to the foregoing protocol and was subjected to Kulinkovich conditions. Unfortunately, no conversion to **222** was observed (Scheme 37).[92]



Scheme 37 | Envisioned formation of **222** via Kulinkovich reaction.

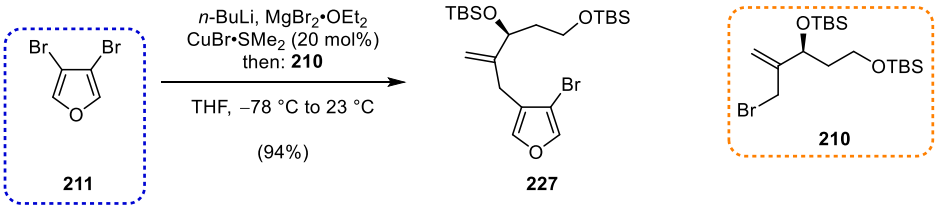
[90] See supporting information for reaction setup.
[91] For the synthesis of **216** see: A. T. Radosevich, C. Musich, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 1090–1091.
[92] A. Mames, S. Stecko, P. Mikołajczyk, M. Soluch, B. Furman, M. Chmielewski, *J. Org. Chem.* **2010**, *75*, 7580–7587.

Giving the fact, that the Kulinkovich reaction is more favored if ring strain is released during the reaction, malic acid derivative **223**[93] was TBS protected and then successfully converted into cyclopropanol **225** under Kulikovich conditions. It was crucial for a successful reaction to add the ethyl Grignard over a period of four hours keeping the temperature at 10 °C, as well as the use of freshly distilled titanium *iso*-propoxide. The primary alcohol of **225** was then protected by silyl ether formation to give **226**. The tertiary alcohol was mesylated, followed by magnesium bromide etherate promoted fragmentation to give allylbromide **210** (Scheme 36).



Scheme 38 | Synthesis of allyl bromide **210**.

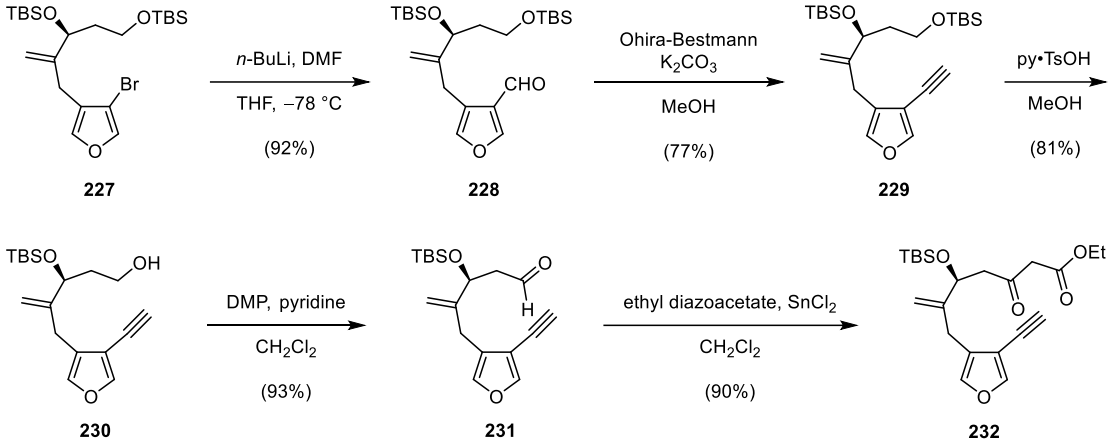
With allylbromide **210** in hands, we now investigated the coupling of **210** and **211**. The monometalation of **211** was already investigated in earlier studies working in excellent yields.[94] Dibromide **211** was first treated with *n*-butyl lithium followed by addition of magnesium bromide etherate to form the corresponding Grignard compound. Allyl bromide **210** was then coupled in presence of catalytic amounts of copper(I)-bromide to afford **227** in very good yield (Scheme 39).



Scheme 39 | Fragment coupling yielding of **210** and **211**.

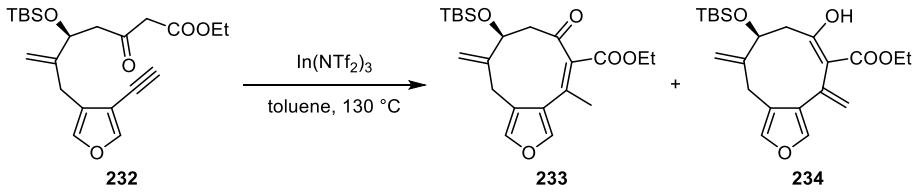
Formylation of **227**, by bromine/lithium exchange followed by addition of *N*,*N*-dimethylformamide, gave aldehyde **228** that was treated with the Ohira–Bestmann reagent to give alkyne **229**. Subsequent selective cleavage of the primary TBS-ether with pyridinium *p*-toluenesulfonate provided alcohol **230** in good overall yields. After oxidation with Dess–Martin periodinane, **231** was transformed into cyclization precursor **232** by Buechner–Curtius–Schlotterbeck reaction (Scheme 40).

[93] S. Yang, S. E. Denmark, *J. Am. Chem. Soc.* **2004**, *126*, 12432–12440.
[94] T. Huber (2017) Studies Toward the Total Syntheses of Waixenicin A and Jerantinine E. PhD Thesis. LMU Munich.



Scheme 40 | Synthesis of cyclization precursor **232**.

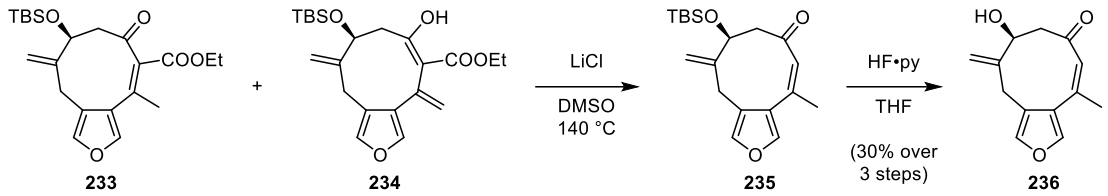
In 2007, the group of E. Nakamura published an indium catalyzed Conia-ene cyclization of ω-alkynyl-β-ketoesters into six to fifteen-membered rings.[95] For nine-membered rings, the cyclization proceeds smoothly if the cyclization precursor contains two or more sp^2-centers due to reduced ring strain. Based on this methodology we started to investigate the cyclization of our substrate **232** (Scheme 41).



Scheme 41 | Indium(III) promoted 9-*exo*-dig cyclization of **232**.

After treatment of **232** with indium(III) tris(trifluoromethanesulfonimide) in toluene at 100 °C, traces of an inseparable mixture, composed of two compounds was isolated. Based on 2D-NMR spectroscopic data, one showed a new *exo*-methylene group (**234**) the other a new methyl group (**233**). The reaction conditions were further optimized ($In(NTf_2)_3$ 1 mol%, toluene, 120 °C) to give a mixture of **233** and **234** (yield 35–45%). It was crucial for the reaction mixture to keep the catalyst loading below 3%, otherwise full decomposition was observed.

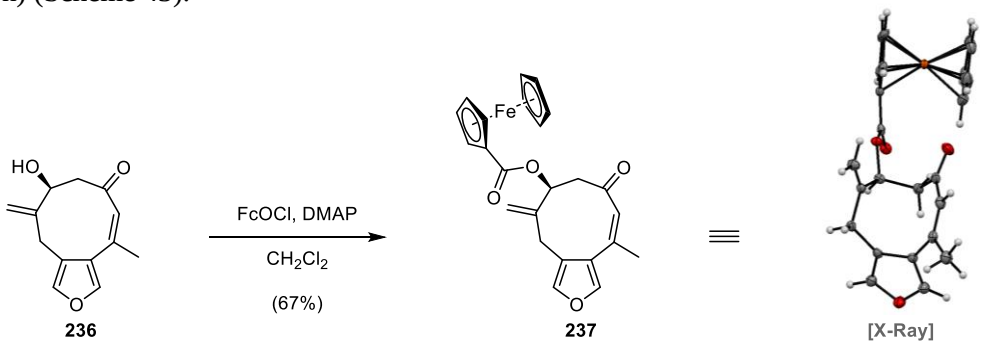
[95] a) H.Tsuji, K. Yamagata, Y. Itoh, K. Endo, M. Nakamura, E. Nakamura, *Angew. Chem. Int. Ed.* **2007**, *46*, 8060–8062. b) Y. Itoh, H. Tsuji, K.Yamagata, K. Endo, I. Tanaka, M. Nakamura, E. Nakamura, *J. Am. Chem. Soc.* **2008**, *130*, 17161–17167.



Scheme 42 | Synthesis of nine-membered carbocycle **236**.

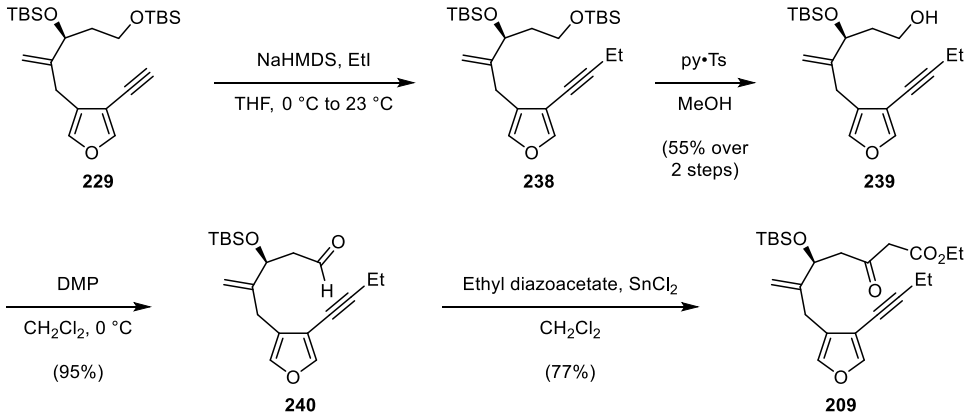
Decarboxylation of the isomeric mixture of β-keto esters **233** and **234** following the Krapcho protocol gave a mixture of **235** and **236** with the silyl ether partially cleaved. The crude mixture was directly treated with pyridinium hydrofluoride to yield the free alcohol **236** in 30% yield over three steps.

At this point we were interested in the nine-membered ring's conformation as well as in an unambiguous structural confirmation of **236**. Unfortunately, owing to the oily texture of **236**, crystals for X-Ray diffraction analysis could not be collected. Therefore, the secondary alcohol was transformed into the ferrocene carboxylic ester **237** and crystals suitable for single-crystal X-ray diffraction were obtained by recrystallization from ethyl acetate. The crystal structure reveals a boat-like conformation of the nine-membered ring blocking the β-side of the enone and exposing its α-side (e.g. for Weitz–Scheffer epoxidation) (Scheme 43).



Scheme 43 | Formation of the ferrocene carboxylic ester **237**.

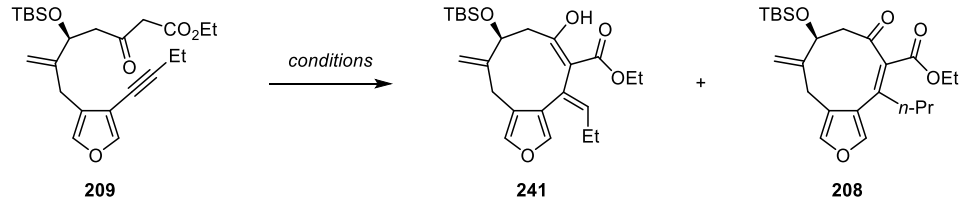
Encouraged by this results we then investigated extension of the scope to non-terminal alkynes. Synthesis of the desired cyclization precursor commenced with alkyne **229** which was deprotonated with sodium bis(trimethylsilyl)amide and then alkylated with ethyl iodide to give **238**. Selective deprotection of the primary silyl ether provided the free primary alcohol **239** that was subjected to the already established oxidation (DMP). The subsequent Roskamp reaction sequence yielding decent quantities of cyclization precursor **209** (Scheme 44).



Scheme 44 | Synthesis of the non-terminal alkyne **209**.

After extensive screening, no condition was found to selectively form the nine-membered ring (Table 2). This result correlates with the reported cyclization strategies[95] in which non-terminal alkynes were never used as cyclization precursors. For the proposed double activation of the 1,3-diketone and the alkyne, a non-terminal alkyne differs electronically as well as sterically from a terminal alkyne preventing the desired cyclization. Due to this drawback, we decided to abandon this route, and focus on an approach that was investigated in parallel and already gave some promising results.

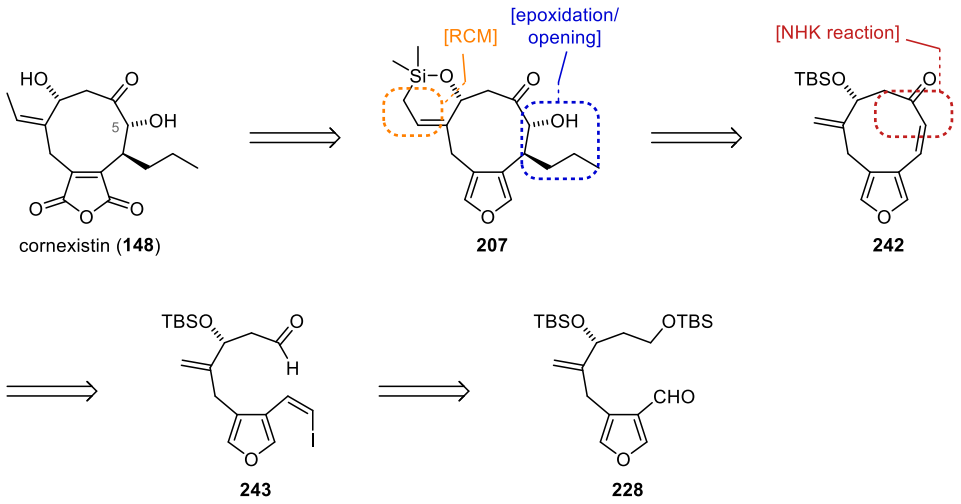
Table 2 | Selected screening conditions for the 9-*exo*-dig cyclization of the non-terminal alkyne **209**.



Entry	Catalyst	Solvent	Temperature	Time	Result
1	$In(NTf_2)_3$	Toluene	140 °C	8 h	no reaction
2	$In(NTf_2)_3$	Toluene	180 °C	24 h	no reaction
3	$In(OTf)_3$, DBU	Toluene	120 °C	12 h	decomposition

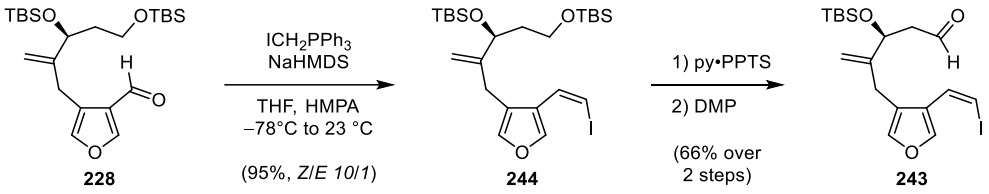
2.2.2 Second Generation: NHK reaction at the eastern half

In parallel, the formation of the nine-membered ring via an intramolecular Nozaki–Hiyama–Kishi (NHK) reaction was investigated. We envision a modular synthetic route that introduces the C-2-hydroxy group via enantioselective epoxidation of enone **242**, followed by epoxide opening using a metalated propyl species. This would lead to **243** as cyclization precursor for an intramolecular Barbier-type reaction. The *Z*-iodide moiety should be available by Stork–Wittig olefination of aldehyde **228**, a substrate already used in the forgoing approach and available in large quantities (Scheme 45).



Scheme 45 | 2nd Generation retrosynthetic analysis of **148**.

Following a modified Stork–Wittig protocol, aldehyde **228** was transformed into vinyl iodide **244** in excellent yields and high *Z*-selectivity (*Z*/*E* 10/1).[96] It is noteworthy, if potassium bis(trimethylsilyl)amide was used as base, a 1:1 mixture of (*E*)-**244** and (*Z*)-**244** was obtained. After selective cleavage of the primary silyl ether, **244** was oxidized with Dess–Martin periodinane to give the desired cyclization precursor **243** in very good yields (Scheme 46).

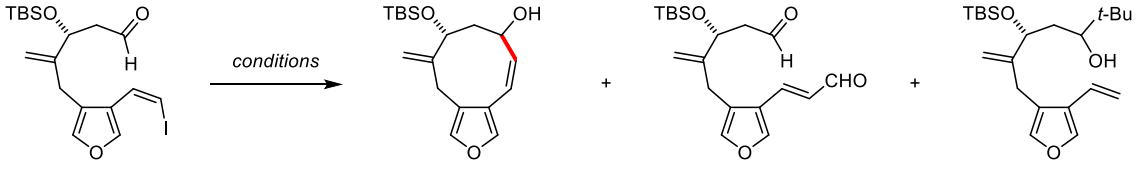


Scheme 46 | Synthesis of the cyclization precursor **243**.

In literature, three examples for the formation of a nine-membered carbocycle via an intramolecular NHK reaction haven been reported.[97] Inspired by these conditions, we began to investigate the formation of the nine-membered carbocycle **244**. Following the NHK protocol ($CrCl_2$, $NiCl_2$, DMF), the nine-membered carbocycle **244** was obtained as a single diastereomer.

[96] J. J. Mousseau, J. A. Bull, C. L. Ladd, A. Fortier, D. S. Roman, A. B. Charette, *J. Org. Chem.* **2011**, *76*, 8243–8261.
[97] For a review see: T. Huber, R. Wildermuth, T. Magauer, *Chem. Eur. J.* **2018**, *24*, 12107–12120.

Table 3 | Screening of the nine-membered ring formation.

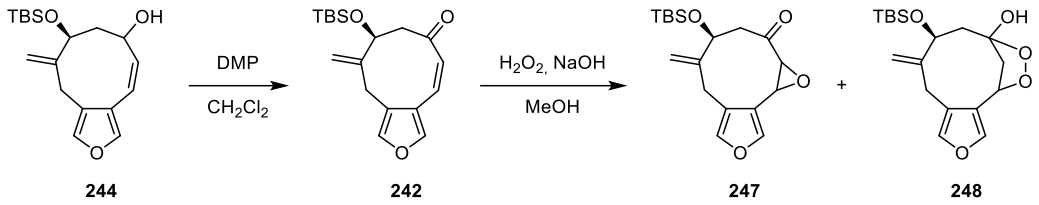


243 **244** *single diastereomer* **245** **246**

Entry	Catalyst	Solvent	Conc.	Yield
1	$CrCl_2$ (7.5equiv), $NiCl_2$ (0.07 equiv)	DMSO/Me_2S	0.005 M	**244** (23%)
2	$CrCl_2$ (7.5equiv), $NiCl_2$ (0.07 equiv)	DMF	0.005 M	**244** (28%) **245** (traces)
3	$CrCl_2$ (7.5equiv), $Ni(acac)_2$ (0.07 equiv)	DMF	0.005 M	**244** (26%) **245** (traces)
4	$CrCl_2$ (7.5equiv), $NiCl_2$ (0.07 equiv)	DMF	0.05 M	**244** (17%)
5	$CrCl_2$ (7.5equiv), $NiCl_2$ (1 equiv)	DMF	0.005 M	**244** (23%) **245** (17%)
6	$CrCl_2$ (7.5equiv), $NiCl_2$ (0.07 equiv)	DMF	0.005 M	**244** (17%)[a]
7	*t*-BuLi (2.6 equiv)	THF	0.005 M	**244**:**246** (1:3)[b]
8	*t*-BuLi (2.6 equiv)	THF	0.005 M	**244**:**246** (1:2)[c]
9	In	DMA	0.005 M	n.r.[d]
10	In, LiCl	THF	0.01 M	n.r.[e]
11	In, LiCl	THF, H_2O	0.01 M	n.r.[e]
12	Mg	THF	0.005 M	n.r.
13	Zn, TMSCl, $(BrCH_2)_2$	THF	0.005 M	n.r.

[a] 100 mg scale; [b] –78 °C; [c] –100 °C; [d] 23 °C to 100 °C; [e] 0 °C to 55 °C, n.r. no reaction.

Encouraged by this initial result, different solvents, nickel(II) sources and concentrations were investigated (Table 3). DMSO, Me_2S and DMF as solvent gave the desired product **244** in similar yields (Entry 1 and 2). Since DMF showed slightly better yields and significant shorter reaction times (DMF 16 h, DMSO/Me_2S 40 h), DMF was used as solvent of choice for further screening reactions. Applying $Ni(acac)_2$ as the nickel(II) source gave **244** in 26% yield (Entry 3). It is noteworthy, that $Ni(acac)_2$ decreased the reaction time to 6 hours. Increasing the concentration by a factor of ten, led to a drastic decrease of the yield and and a significant number of byproducts was formed (Entry 4). If nickel(II) chloride was applied in stoichiometric amounts, significant amounts of side product **245** were formed (Entry 5). Although, all Nozaki–Hiyama–Kishi reaction conditions provided the nine-membered carbocycle **244**, we were not able to improve the yield of this transformation. With *tert*-butyllithium, we were able to perform an iodine/lithium exchange followed by subsequent intramolecular Barbier reaction to yield an inseparable mixture of the desired product **244** and **246** (Entry 7). In order to suppress the 1,2-addition of *tert*-butyllithium, we decreased to temperature to –100 °C and to our delight, the amount of side product **246** decreased as well (Entry 8). Unfortunately, we were not able to tune this reaction to a viable transformation on preparative scale. Metalation with indium, zinc or magnesium were also not successful and starting material was recovered (Entry 9–13).



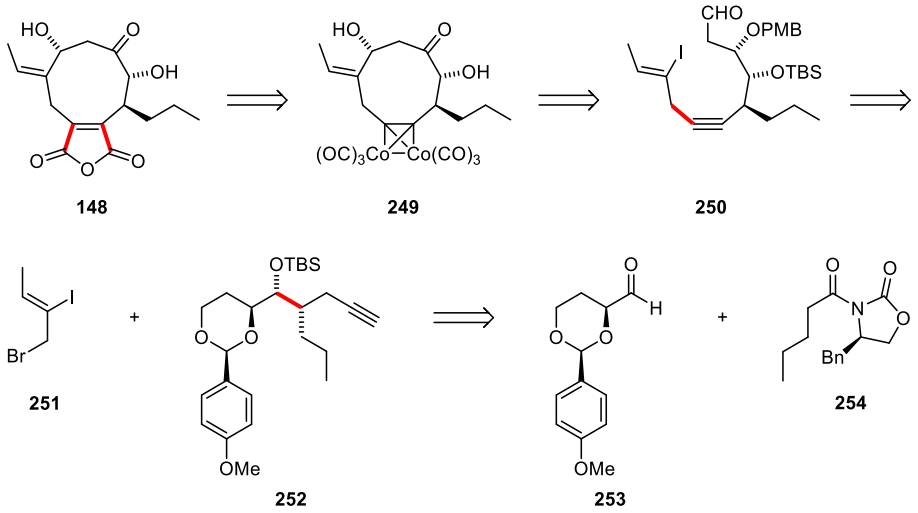
Scheme 47 | Oxidation of **244** to enone **242** and Scheffer–Weitz epoxidation to **247**.

With hands on small quantities of the cyclization product, **244** was oxidized to enone **242** with Dess–Martin periodinane. Enone **242** was then subjected to the Scheffer–Weitz epoxidation protocol giving an inseparable mixture of two compounds. Based on 2D-NMR spectroscopic data, one was assigned to the desired epoxide **247** as a single diastereoisomer. This synthetic studies have shown that the NHK-reaction possess a viable method for the formation of nine-membered carbocycle. Unfortunately, the product was only obtained in low yield which further decreased upon scale-up and also the following steps were low yielding with just traces of the desired products (<1 mg). Thus, a new route, employing a precursor that already contains the complete decoration of cornexistin (**148**) was devolved.

2.2.3 Third Generation: NHK reaction at the western half

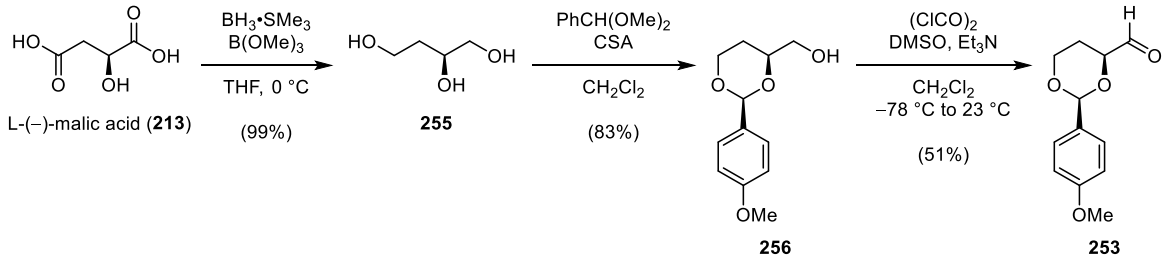
In our new strategy, the nine-membered carbocycle should be formed via a late-stage NHK reaction. The anhydride moiety should be derived from an alkyne complexed by dicobalt octacarbonyl (*cf.* Chapter 2.1.3). Contrary to our initial approach, the challenging stereocenters on the eastern part of cornexistin (**148**) should already be set in the beginning of our route. The *Z*-configured exocyclic double bond should be introduced by alkylation of alkyne **252** with **251**. The *anti*-geometry of the hydroxyl- and the *n*-propyl group in the eastern part of the molecule could be accessed by a *syn*-Evans-aldol reaction of aldehyde **253** and valeroyl derivative **254**[98].

[98] F. Soucy, L. Grenier, M. L. Behnke, A. T. Destree, T. A. McCormack, J. Adams, L. Plamondon, *J. Am. Chem. Soc.* **1999**, *121*, 9967–9976.



Scheme 48 | 3rd generation retrosynthetic analysis of cornexistin (**148**).

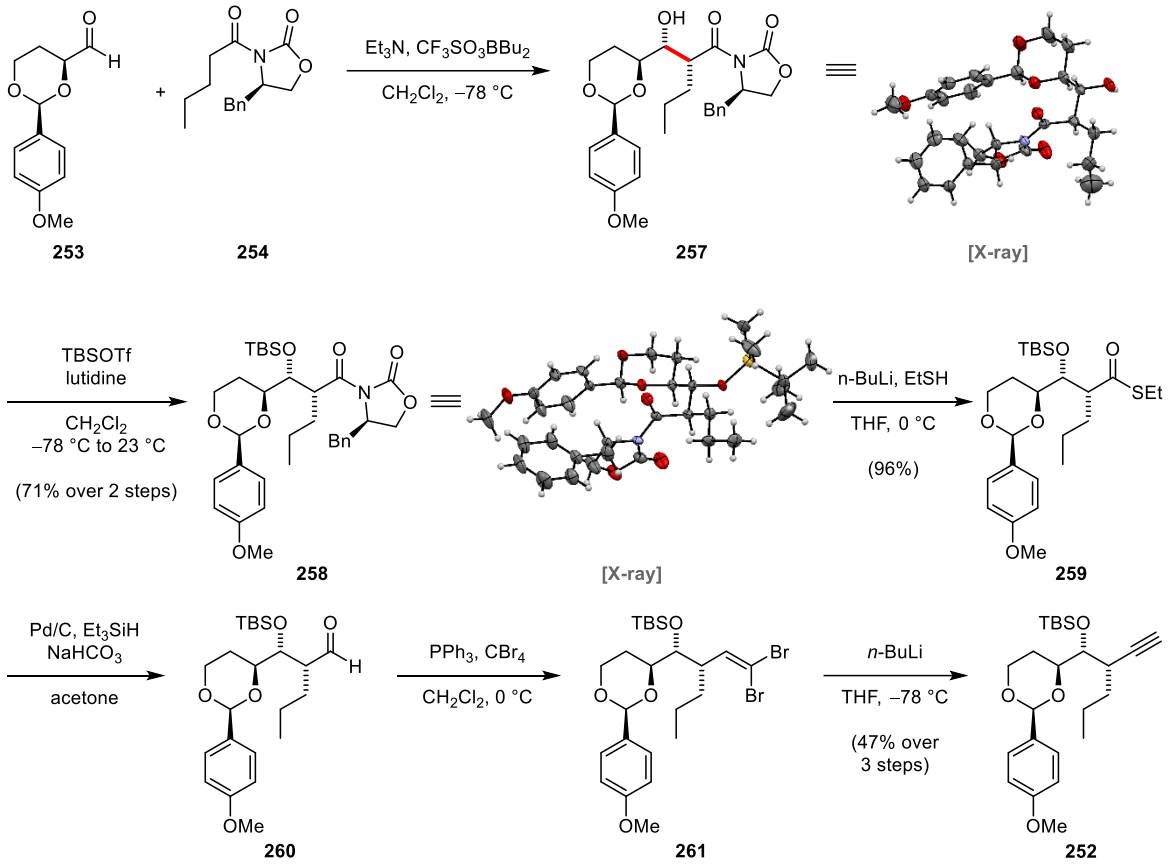
After borane reduction of L-(–)-malic acid (**213**) to triol **255**, benzylidene acetal **256** was formed in excellent yield. Swern oxidation of the primary alcohol provided the desired aldehyde **253**, that proved to be prone to polymerization and was therefore directly used in the following step.[99]



Scheme 49 | Synthesis of aldehyde 253.

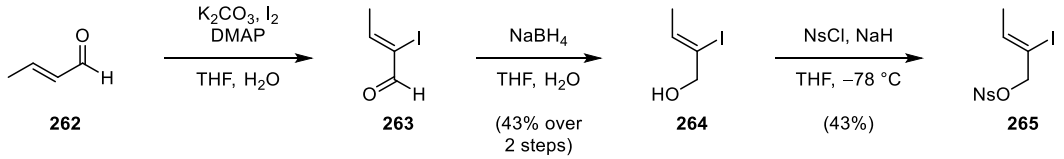
With aldehyde **253** and **254** in hand, we investigated the *syn*-Evans-aldol reaction. With dibutylboryl trifluoromethanesulfonate as Lewis acid, **257** was obtained as a single diastereoisomer. It is noteworthy, that the quality of the dibutylboryl trifluoromethanesulfonate (1 M in CH_2Cl_2) determines the success of the aldol reaction in terms of diastereoselectivity and yield. The stereochemistry was unambiguously assigned by X-ray single crystal diffraction. After silyl protection of the secondary alcohol, **258** was obtained in good yields and large quantities over two steps. Slow recrystallization from a mixture of hexanes and ethyl acetate yielded crystals suitable for X-ray single crystal diffraction (Scheme 50).

[99] a) L. W. Erickson, E. L. Lucas, E. J. Tollefson, E. R. Jarvo, *J. Am. Chem. Soc.* **2016**, *138*, 14006–14011. b) W. R. Judd, S. Ban, J. Aubé, *J. Am. Chem. Soc.* **2006**, *128*, 13736–13741. c) R. W. Hoffmann, G. Mas, T. Brandl, *Eur. J. Org. Chem.* **2002**, 3455–3464.



Scheme 50 | Synthesis of alkyne **252** and X-ray structures of **257** and **258**.

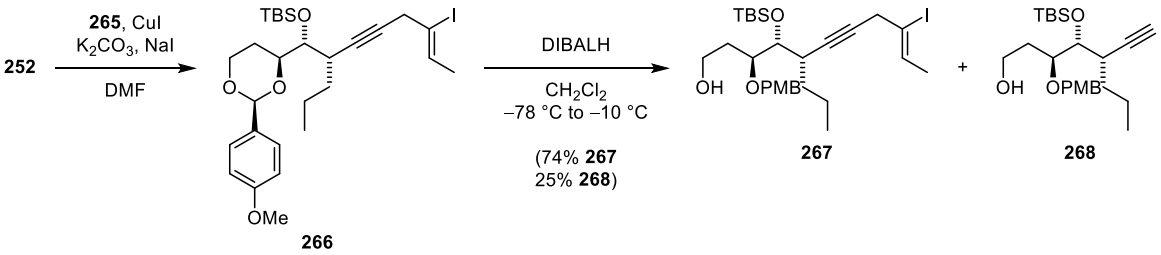
Since the benzylidene acetal might be cleaved under reductive conditions, we decided to remove the Evans-auxiliary by first formation of the thioester **259** which can then be further reduced under mild conditions. The odorless alternative with dodecanethiol also provided the respective thioester but in lower yield (46%). Thioester **259** was then reduced to aldehyde **260** applying the Fukuyama protocol.[100] Due to the acidic nature of Pd/C,[101] it was crucial to buffer the reaction mixture with sodium bicarbonate, otherwise cleavage of the benzylidene acetal was observed. Homologation with Ohira–Bestmann reagent led to the formation of a complex mixture and only traces of alkyne **252** were isolated. Fortunately, following the Corey–Fuchs homologation[102] protocol provided **252** in good overall yield (Scheme 50).



Scheme 51 | Synthesis of *Z*-iodide **265**.

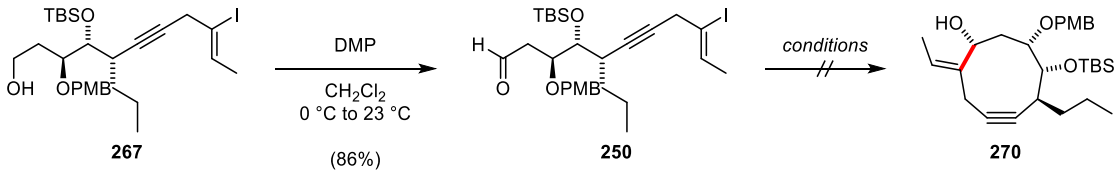
[100] For a review see: T. Fukuyma, H. Tokuyama, *Aldrichimica Acta* **2004**, *37*, 87–96.
[101] For the preparation of Pd/C see: *Org. Synth.* **1946**, *26*, 77.
[102] E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, 13, 3769–3772.

The synthesis of the *Z*-iodide **265** commenced with a reported sequence for allylic alcohol by the Cook group, starting from crotonaldehyde (**262**).[103] The allylic alcohol **264** was then converted into a good leaving. Although, nosylate **265** proved to be unstable on silica, sufficient quantities (500 mg) of **265** were obtained as a solid that was substantially more stable than the respective allyl bromide **251** (Scheme 51).



Scheme 52 | Fragment coupling of **252** and **265** followed by reductive opening of the PMB-acetal.

With both fragments **252** and **265** in hands, we turned our attention to the S_N2 displacement with alkyne **252**.[104] To our delight, the S_N2 pathway was predominately operative and only traces of the S_N2' product were observed. The coupling product **266** was obtained as an inseparable mixture with unreacted alkyne **252**. After reductive opening of the benzylidene acetal of **266** and **252**, we were able to separate the desired product **267** from **268** (Scheme 50).



Scheme 53 | Synthesis of cyclization precursor **250** and attempted cyclization.

After oxidation with Dess–Martin periodinane, the stage was set to investigate the cyclization of **250**. Unfortunately, various conditions to form **270** ($CrCl_2$, $NiCl_2$, $Ni(acac)_2$, *t*-BuLi) only resulted in the isolation of a dehalogenated species. This indicates, metalation at the vinylic position occurred but the cyclization is geometrically disfavored. Further investigating this hypothesis, the system was geometrically optimized by formally exchanging the sp hybridized carbons of the alkyne by sp^2 hybridized carbons (Figure 5).

[103] W. Yin, M. S. Kabir, Z. Wang, S. K. Rallapalli, J. Ma, J. M. Cook, *J. Org. Chem.* **2010**, *75*, 3339–3349.
[104] a) D. F. Taber, P. Gu, R. Li, *J. Org. Chem.* **2009**, *74*, 5516–5522. b) Brandon R. Smith, J. T. Njardarson, *Org. Lett.*, **2017**, *19*, 5316–5319.

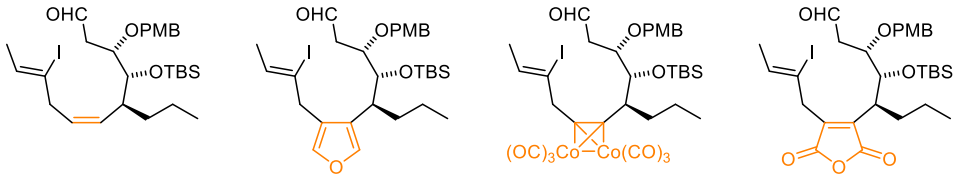


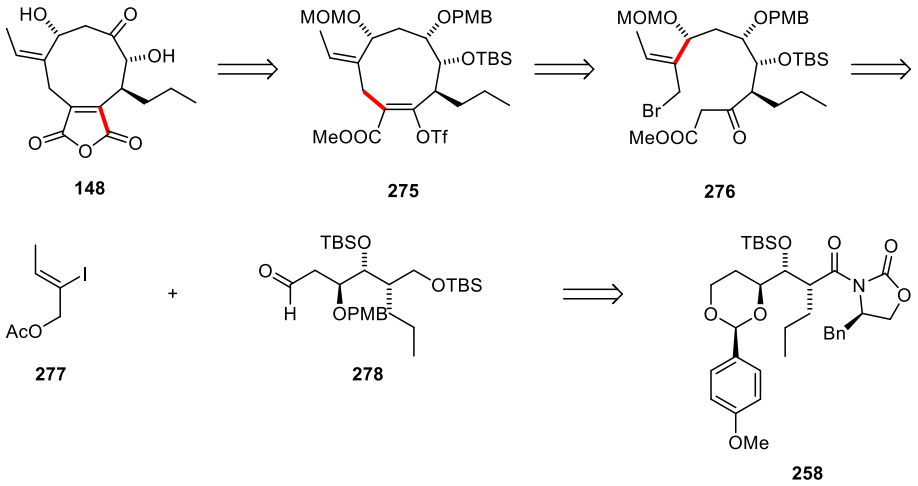
Figure 5 | Geometrical optimizations.

Alkene **271** should serve as a proof of concept showing that a *Z*-configured double bond facilitates the cyclization. But selective reduction of **269** with diimide only resulted in a complex mixture.[105] Alkynes can undergo a [3+2] cycloaddition with 4-phenyl-oxazole[106] forming 3,4-substituted furans.[107] However, this reaction requires relatively harsh conditions (200 °C, neat) and lead in our case just to decomposition of the starting material. We successfully synthesized cyclization precursor **273** by complexation of alkyne **269** with dicobalt octacarbonyl followed by oxidation of the alcohol. But this complex was highly instable and decomposed under NHK conditions. Also the oxidation of **273** directly to the anhydride resulted in a complex mixture.[85,86] At this stage, we decided to abandon this route, due to more promising developments in our group.

2.2.4 Fourth Generation: Intermolecular alkylation

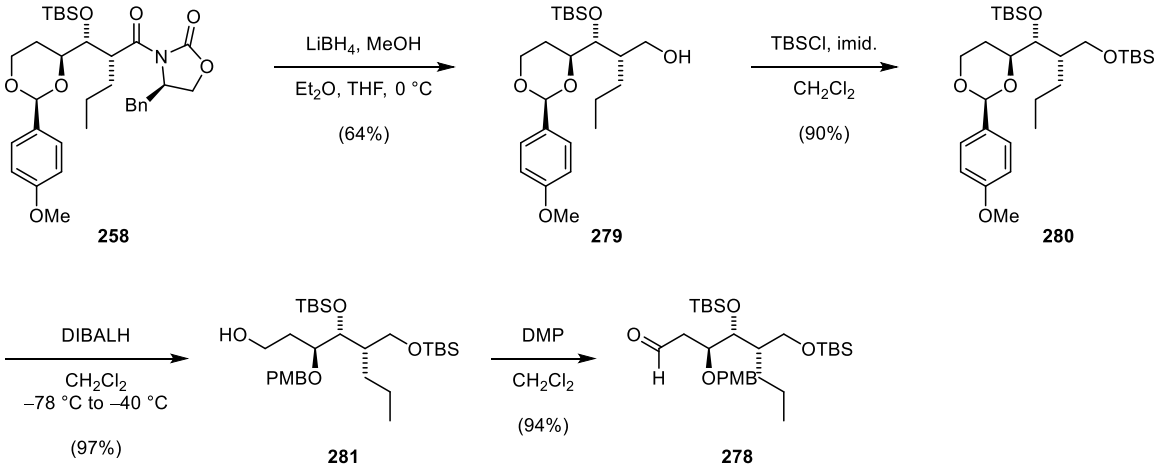
Based on this results, we developed a new route to cornexistin, still employing *syn*-Evans-aldol building block **258** from the previous route. The anhydride moiety should be formed by palladium catalyzed carbonylation of enol triflate **275**. The key step, the formation of the nine-membered ring should be realized by an intramolecular allylation of β–keto ester **276**. The cyclization precursor can be dissected into the building blocks **277** and **278** which is readily available from **258** (Scheme 54).

[105] D. J. Pasto, R. T. Taylor, *Org. React.* **1991**, *40*, 91–155.
[106] For the synthesis of this reagent see: S. E. Whitney, M. Winters, B. Rickborn, *J. Org. Chem.* **1990**, *55*, 929–935.
[107] J. Boukouvalas, C. Thibault, R. P. Loach, *Synlett* **2014**, *25*, 2139–2142.



Scheme 54 | 4th Generation retrosynthetic analysis of cornexistin (**148**).

Our synthesis commenced with aldol product **258** and reduction of the Evans-auxiliary to the primary alcohol **279**. Although literature reports excellent yields (up to 96%) for this step,[108] we were never able to obtain **279** in more than 64% yield. The primary alcohol was then silyl protected and after reductive opening of the benzylidene acetal and oxidation of the primary alcohol, we were able to obtain 1.3 g of aldehyde **278** (Scheme 55).

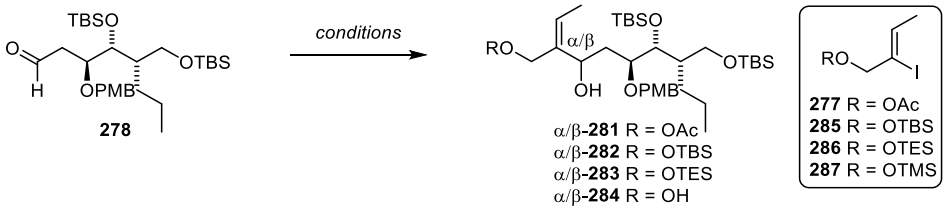


Scheme 55 | Synthesis of aldehyde **278**.

Next, the addition of *Z*-viny-iodide **277** into aldehyde **278** via an intramolecular Nozaki–Hiyama–Kishi reaction was investigated (Table 4). Unfortunately, treatment of a mixture of iodide **277** and aldehyde **278** in DMF with chromium(II) chloride and catalytic amount of nickel(II) chloride did not show any formation of the desired product (Entry 1).[109] Also all halogen/metal exchange attempts of **285** just resulted in the isolation of the starting material (Entry 2–4).

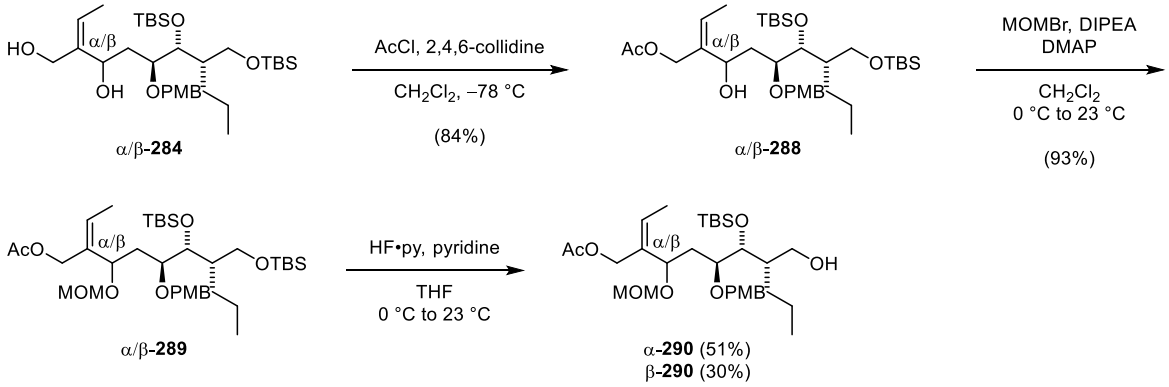
[108] E. M. Stang, M. C. White, *Nat. Chem* **2009**, *1*, 547–551.
[109] R. E. Taylor, J. P. Ciavarri, *Org. Lett.* **1999**, *1*, 467–470.

Table 4 | Conditions for the introduction of the *Z*-methyl building block.



Entry	R	Conditions	Solvent	Yield
1	OAc	$CrCl_2$, $NiCl_2$	DMF	n.r.
2	OTBS	Mg	Et_2O	n.r.
3	OTBS	*t*-BuLi	Et_2O	n.r.
4	OTBS	*n*-BuLi	THF	n.r.
5	OTES	$CrCl_2$, $NiCl_2$	DMF	α/β-**283** (64%)
6	OTMS	$CrCl_2$, $NiCl_2$ then HCl	DMF	α/β-**284** (41%)

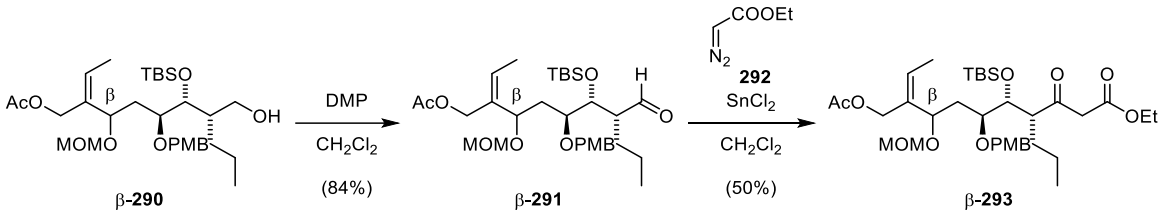
To our surprise, TES-protected iodide **286** reacted under NHK conditions forming allylic alcohol as a mixture of α-**283** and β-**283** isomers (d.r. 2.1). Since the TES-ether had to be cleaved in the next step (60% HF•py in THF, 0 °C) and therefore increasing the overall step count of our route, TMS-protected iodide **287** was coupled with aldehyde **278**. Upon acidic workup, the TMS-ether was cleaved giving an inseparable mixture of α-**284** and β-**284**.



Scheme 56 | Synthesis and separation of the diastereomers α-**290** and β-**290** by column chromatography.

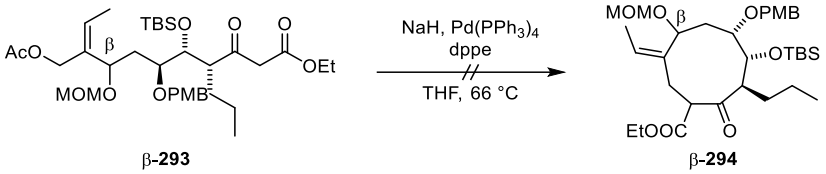
Diol **284** was acetylated at the primary alcohol followed by formation of the MOM-ether of the secondary alcohol giving an inseparable mixture of the α/β-**289** isomers. The primary TBS-ether was then selectively cleaved by treatment with hydrogen fluoride in pyridine. At this step, we were able to separate α-**290** from β-**290** by flash column chromatography on silica gel. With the separated isomers in hand, we continued to investigate two different cyclization approaches. With the minor β-**290** isomer, we proceeded to investigate a palladium-catalyzed cyclization.[110] The synthesis of cyclization precursor β-**293** for this strategy proceeded uneventfully in two steps (Scheme 57).

[110] a) P. A. Clarke, R. J. G. Black, A. J. Blake, *Tetrahedron Lett.* **2006**, *47* 1453–1455. b) P. A. Clarke, R. J. G. Black, M. Iqbal, *Synlett* **2010**, 543–546.



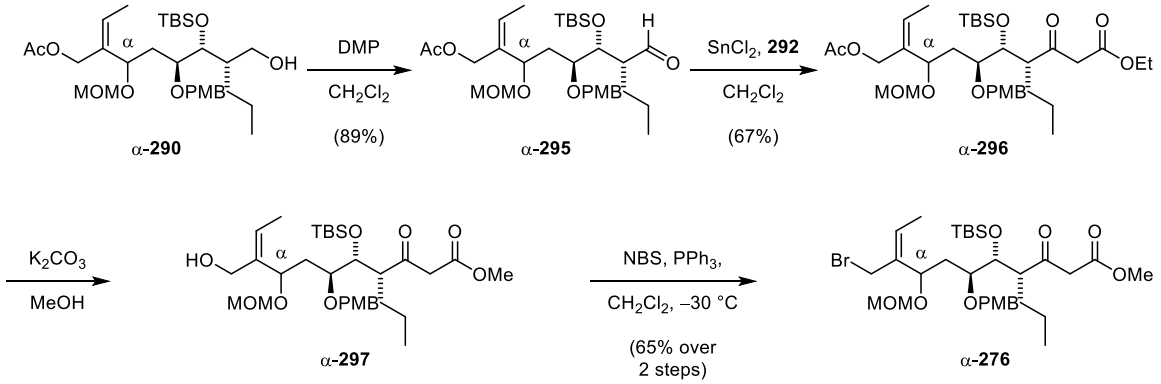
Scheme 57 | Synthesis of cyclization precursor β-**293**.

Unfortunately, treatment of β-**293** with the reported conditions only resulted in a complex mixture with no evidence of the desired product β-**294** (Scheme 58).



Scheme 58 | Attempted palladium catalyzed cyclization of **293**.

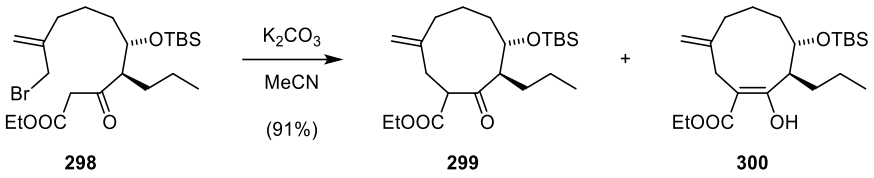
In parallel, major isomer α-**290** was converted into cyclization precursor α-**276** by oxidation of the primary alcohol with Dess–Martin periodinane, Roskamp reaction, saponification of the acetyl protecting group and Appel reaction. It is noteworthy, that cleavage of the acetyl protecting group in methanol with potassium carbonate lead to transesterification of the ethyl ester to the methyl ester. With allybromide α-**276** in hand, the base promoted cyclization was investigated.



Scheme 59 | Synthesis of the cyclization precursor α-**276**.

The envisioned key-step, the formation of the nine-membered ring via intramolecular alkylation, was investigated by C. Steinborn.[111] In this preliminary studies, we were able to shows that isomeric nine-membered carbocycles **299** and **300** can be formed in excellent yield by treatment of **298** with potassium carbonate in acetonitrile (Scheme 60).

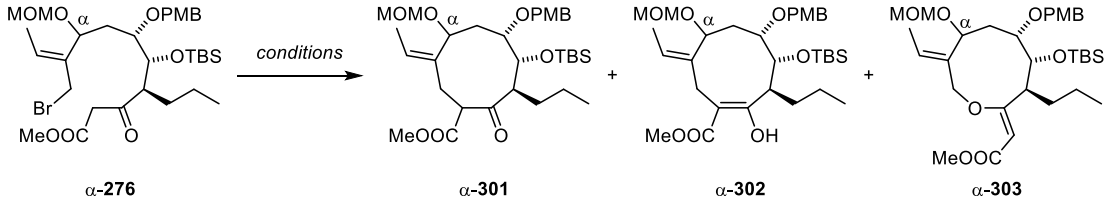
[111] C. Steinborn (2018) Synthetic studies towards herbicidal natural products. Master Thesis. LMU Munich.



Scheme 60 | Formation of the nine-membered carbocycle of model substrate α-**298**.

Based on this result, we adopted those conditions for the cyclization of α-**276**, giving a mixture of α-**301** (single isomer), enol α-**302** and *O*-alkkylation product α-**303** (Table 5, Entry 3). Encouraged by this result, various bases were tested of which lithium and sodium carbonate did not show any reaction (Entry 1, 2). Cesium and silver carbonate showed increased formation of the undesired *O*-alkylation product α-**303** (Entry 4, 5) accompanied by a significant amount of side products. Changing the solvent from acetonitrile to DMF, did not improve the product distribution in favor of α-**301** or α-**302** (Entry 7, 8). The best result was obtained with DBU in acetonitrile giving a 2:1 mixture of the desired product and *O*-alkylation product α-**303**. On preparative scale, these conditions provided a mixture of α-**301** or α-**302** in 56% yield.

Table 5 | Screening of cyclization conditions.



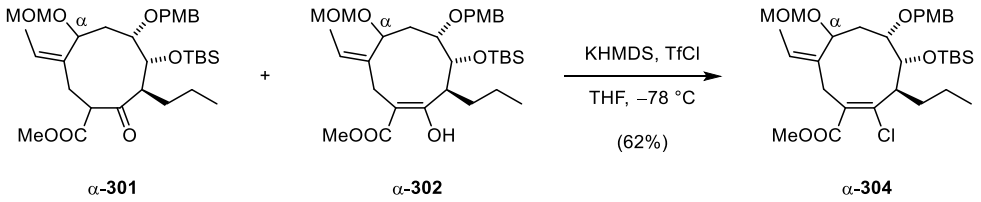
Entry	Base	Solvent	Yield 301:302:303
1[a]	Li_2CO_3	MeCN	n.r.
2[a]	Na_2CO_3	MeCN	n.r.
3[a]	K_2CO_3	MeCN	1.7:0.1:1
4[a]	Cs_2CO_3	MeCN	1.5:0.2:1
5[a]	Ag_2CO_3	MeCN	1.3:0.0:1
6[a]	DBU	MeCN	2.0:0.3:1
7[a]	NaH	DMF	0.4:0.4:1
8[a]	Cs_2CO_3	DMF	1.0:0.7:1
9[b]	DBU	MeCN	56% (mixture of **301** and **302**)

n.r. no reaction; [a] reactions were performed on 10 mg scale of **276** in 0.5 mL of solvent. [b] isolated yield; reaction was performed on 45 mg scale of α-**276** in 3.5 mL of solvent.

With cyclized products α-**301** and α-**302** in hand, we turned our attention to the formation of the enoltriflate. Treatment of a mixture of α-**301** and α-**302** with common triflation agents (Tf_2O, Comins and McMurry reagent)[112] did not show any formation of the desired product. In this context, we tried to form the enol-mesylate with methanesulfonyl chloride in the presence of base. To our surprise, when α-**301** and α-**302** were reacted with triflic chloride in the presence of KHMDS, a new compound was

[112] a) N. Su, J.A. Theorell, D. J. Wink, T. G. Driver, *Angew. Chem. Int. Ed.* **2015**, *54*, 12942–12946. b) V. Saini, M. O'Dair, M. S. Sigman, *J. Am. Chem. Soc.* **2015**, *137*, 608–611.

formed within 10 minutes. After careful analysis of the obtained spectroscopic data (NMR, HRMS), the formed compound was assigned to chloride α-**304**.

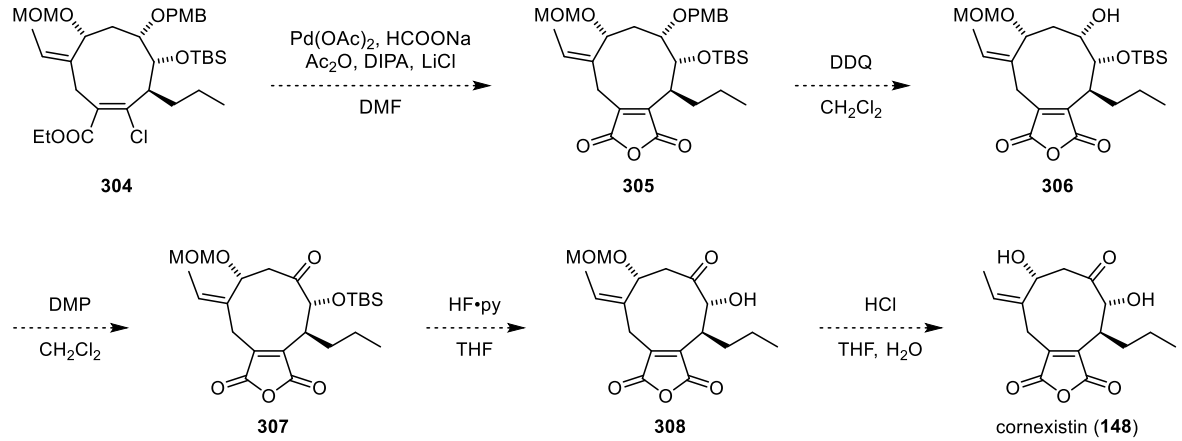


α-**301** α-**302** α-**304**

Scheme 61 | Formation of vinyl chloride α-**304**.

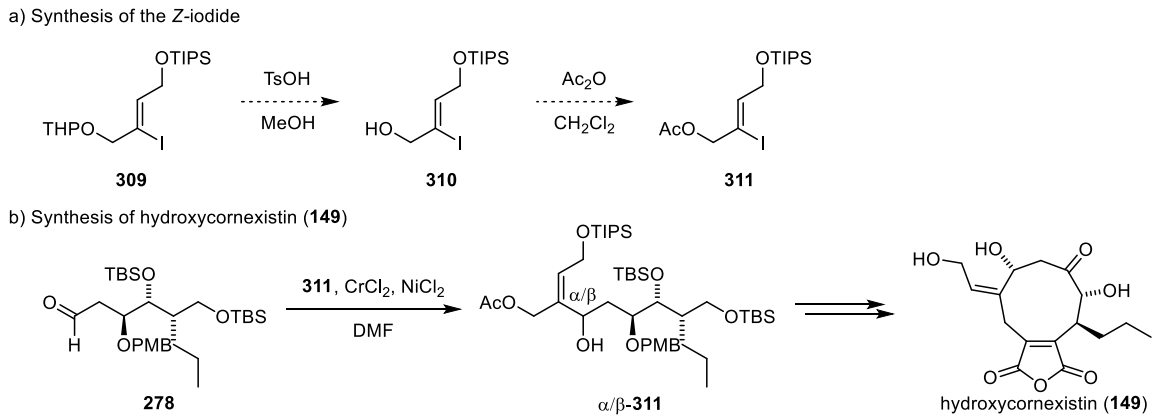
2.3 Conclusion and Outlook

In summary, we have established a synthetic route towards cornexistin that addresses all the shortcoming of earlier synthesis. The challenging *anti*-relationship of the C-3 *n*-propyl side chain and the C-2 hydroxy group was set by an auxiliary controlled *syn*-Evans-aldol reaction. The *Z*-configured double bound was introduced via an intermolecular NHK reaction forming the third stereocenter as a diastereomeric mixture (d.r. 2:1). Nine-membered ring-formation was realized via an intramolecular alkylation of a β-keto-ester and subsequent treatment of the cyclization product with triflic chloride provided chloride **304**.



Scheme 62 | Remaining steps towards cornexistin (**148**)

In the last steps, the anhydride moiety should be formed from **304** by palladium catalyzed carbonylation (*cf.* Chapter 2.1.3). After oxidative cleavage of the PMB-ether and subsequent oxidation of the secondary alcohol, global deprotection of the silyl ether and the MOM-ether would then provide cornexistin (**148**) (Scheme 62).



Scheme 63 | a) Synthesis of the *Z*-iodide **308** and b) fragment coupling of **278** and **308** for the synthesis of hydroxycornexistin (**149**).

The structurally related natural product hydroxycornexistin (**149**) could then be synthesized accordingly. Intermolecular NHK reaction of iodide **311** (Scheme 63a) and aldehyde **278** would provide allylic alcohol **311** which could be transformed into hydroxycornexistin (**149**) according to the synthesis of cornexistin (**148**) (Scheme 63b).

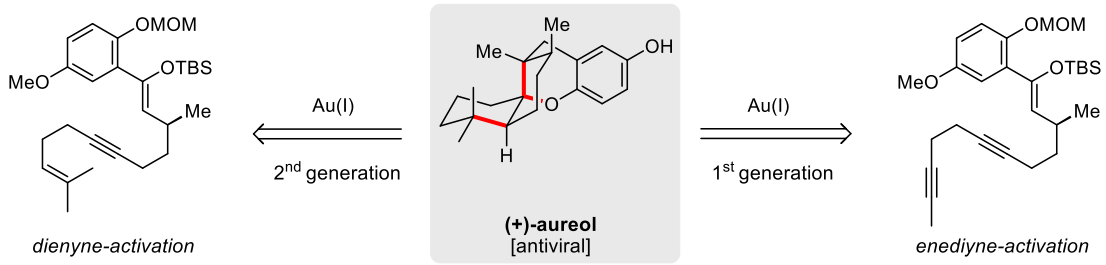
In future work, biological studies of cornexistin and hydroxycornexistin and derivatization thereof to further increase their herbicidal activity will be pursued in cooperation with Bayer Crop Science in Frankfurt, Germany.

EXPERIMENTAL SECTION

3.1 Supporting Information for Chapter 1.2.1

Gold(I)-Catalyzed Enyne Cyclizations: Studies Towards the Total Synthesis of (+)-Aureol

R. Wildermuth, K. Speck, T. Magauer, *Synthesis*, **2016**, 48, 1814–1824.



Synthesis

Reviews and Full Papers in Chemical Synthesis

Supporting Information
for DOI: 10.1055/s-0035-1561589

Thieme

Supporting Information for

Gold(I)-Catalyzed Enyne Cyclizations: Studies Towards the Total Synthesis of (+)-Aureol

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1. General Experimental Details

All reactions were performed in flame-dried glassware fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula through rubber septa. Solids were added under inert gas counter flow or were dissolved in appropriate solvents. Low temperature-reactions were carried out in a Dewar vessel filled with a cooling agent: acetone/dry ice (−78 °C), H_2O/ice (0 °C). Reaction temperatures above room temperature were conducted in a heated oil bath. The reactions were magnetically stirred and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC), using aluminium plates precoated with silica gel (0.25 mm, 60 Å pore size, *Merck*) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), were stained by submersion in aqueous potassium permanganate solution ($KMnO_4$), anisaldehyde (ANIS), or ceric ammonium molybdate solution (CAM), and were developed by heating with a heat gun. Flash column chromatography was performed as described by Still et al.,[1] employing silica gel (60 Å, 40–63 µm, *Merck KGaA*). The yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) pure material.

1.1 Materials

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled under N_2 atmosphere from Na/benzophenone prior to use. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), diisopropylamine (DIPA), Hünig's base (DIPEA), *N*,*N*,*N*',*N*'-tetramethylethane-1,2-diamine (TMEDA) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) were distilled under nitrogen atmosphere from CaH_2 prior to use. Dimethyl sulfoxide (DMSO), acetonitrile (MeCN), benzene, toluene 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, ABCR*) and were used as received. Solvents for extraction, crystallization and flash column chromatography were purchased in technical grade and distilled under reduced pressure prior to use. The molarity of *n*-butyllithium solutions was determined by titration against diphenylacetic acid as an indicator (average of three determinations).[2]

[1] W.C. Still, M.Kahn, A. J. Mitra, *Org. Chem*. **1978**, *43*, 2923.
[2] W. G. Kofron, L. M. Baclawski, *J. Org. Chem.* **1976**, *41*, 1879.

1.2 NMR spectroscopy

NMR spectra were measured on a *Bruker* Avance III HD 400 MHz and 800 MHz spectrometer equipped with a CryoProbe™, *Bruker* AXR300, *Varian* VXR400 S and *Bruker* AMX600 spectrometers operating at 400 MHz, 800 MHz, 300 MHz, 400 MHz and 600 MHz for proton nuclei (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, methanol-d_3: δ 4.78, acetone-d_5: δ 2.05, $CDHCl_2$: δ 5.32). 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_3OD: δ 49.00, acetone-d_6: δ 29.84, CD_2Cl_2: δ 54.00). ^1H NMR spectroscopic data are reported as follows: Chemical shift in ppm (multiplicity, coupling constants *J* (Hz), integration intensity, assigned proton). The multiplicities are abbreviated with s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). In case of combined multiplicities, the multiplicity with the larger coupling constant is stated first. Except for multiplets, the chemical shift of all signals, as well for centrosymmetric multiplets, is reported as the center of the resonance range. Additionally to ^1H and ^{13}C NMR measurements, 2D NMR techniques such as homonuclear correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond coherence (HMBC) were used to assist signal assignment. Coupling constants *J* are reported in Hz. All raw fid files were processed and the spectra analyzed using the program *MestReNOVA 9.0* from *Mestrelab Research S. L.*

1.3 Mass spectrometry

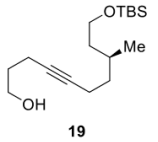
All mass spectra were measured by the analytic section of the Department of Chemistry, *Ludwig-Maximilians-Universität München*. Mass spectra were recorded on the following spectrometers (ionisation mode in brackets): MAT 95 (EI) and MAT 90 (ESI) from *Thermo Finnigan GmbH*. Mass spectra were recorded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

1.4 IR spectroscopy

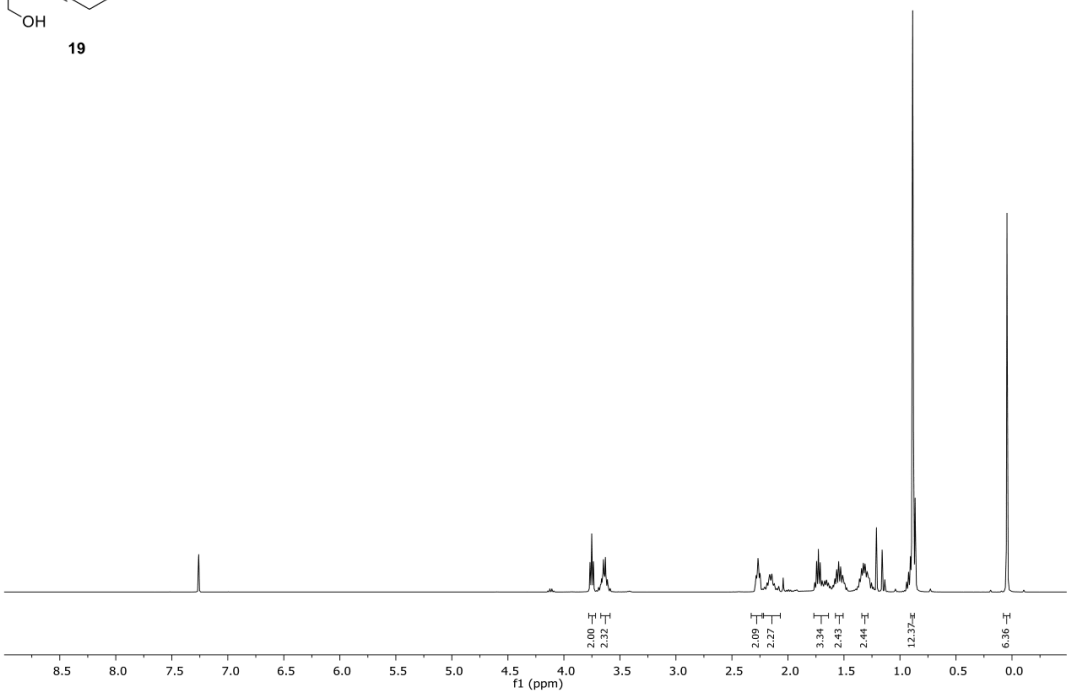
IR spectra were recorded on a *PerkinElmer* Spectrum BX II FT-IR system. If required, substances were dissolved in CH_2Cl_2 prior to direct application on the ATR unit. Data are represented as follows:

frequency of absorption (cm^{-1}), and intensity of absorption (*vs* = very stong, *s* = strong, *m* = medium, *w* = weak, *br* = broad).

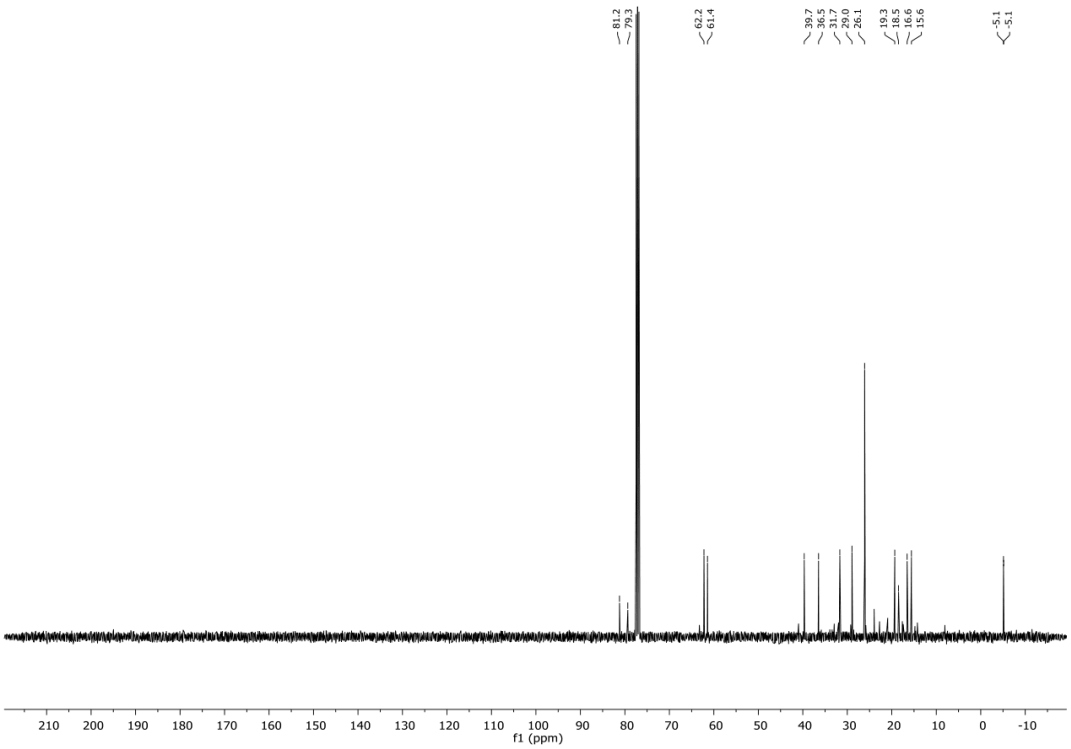
^{1}H NMR (400 MHz, $CDCl_3$)



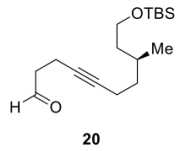
19



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

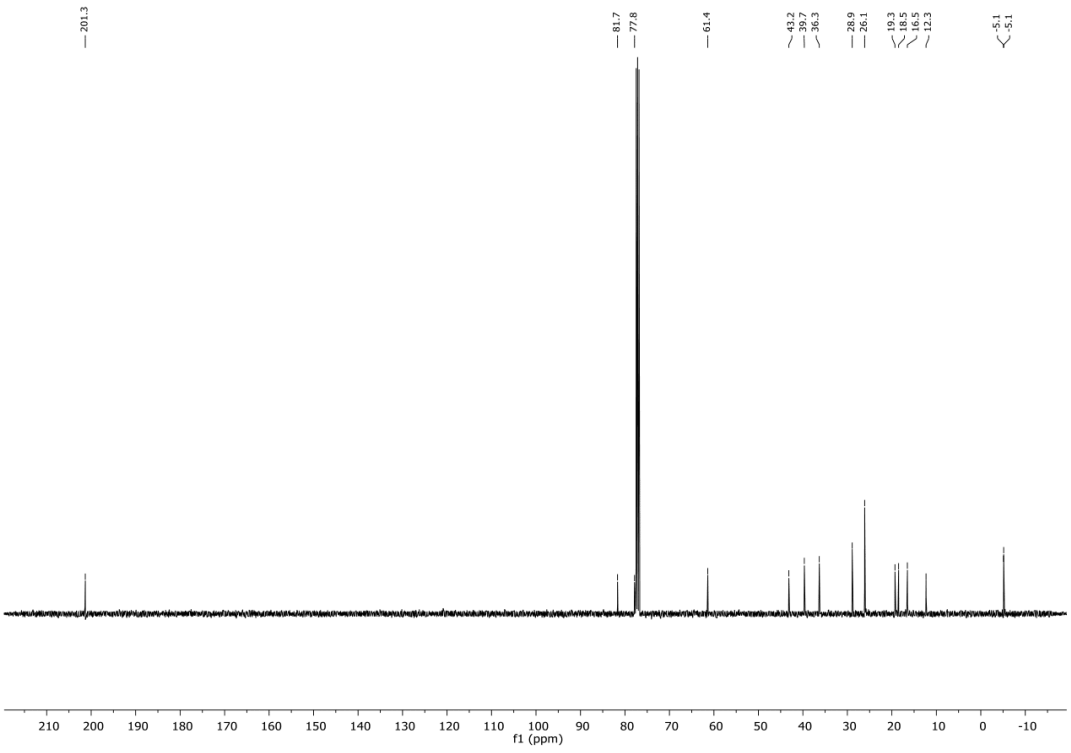


^{1}H NMR (400 MHz, $CDCl_3$)

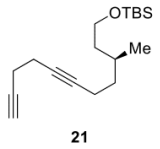


20

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

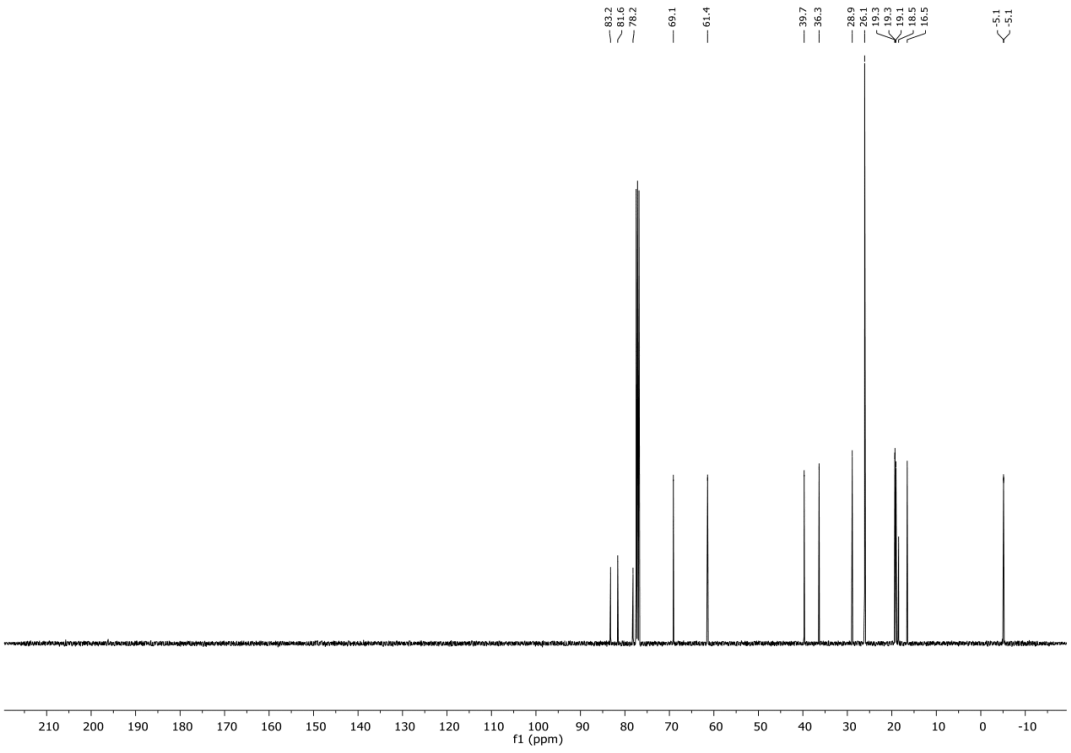


^{1}H NMR (400 MHz, $CDCl_3$)

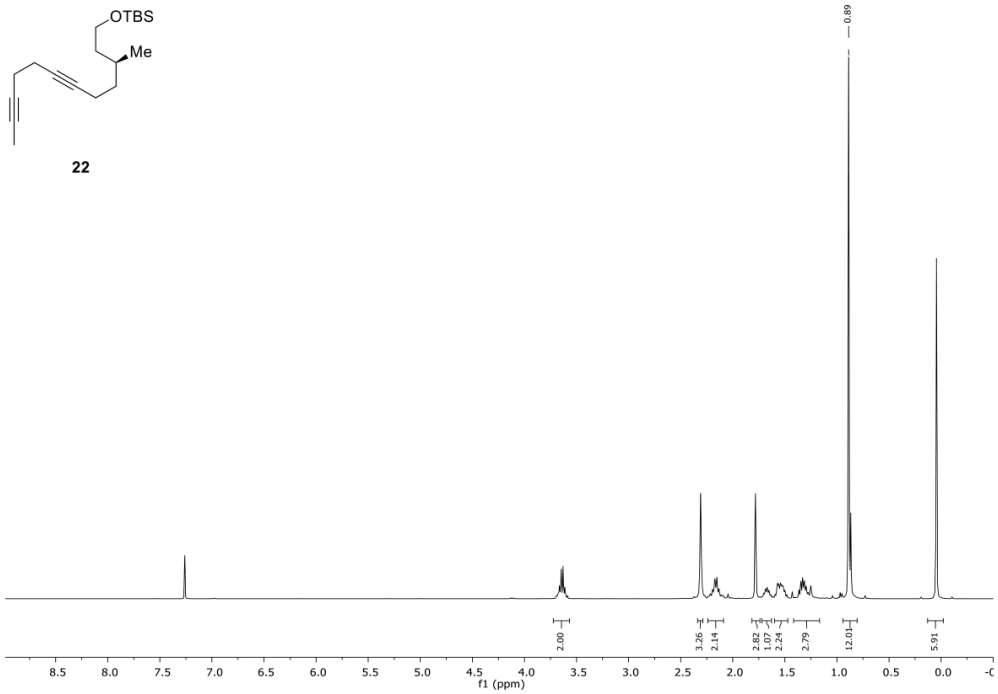


21

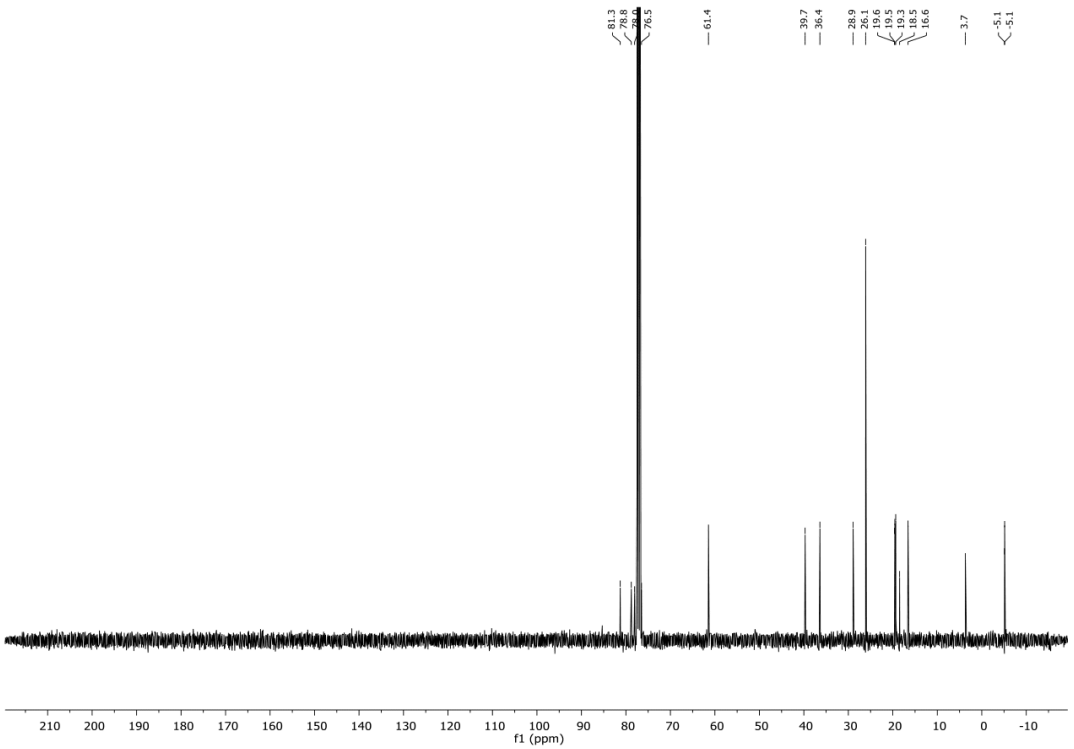
^{13}C NMR (101 MHz, $CDCl_3$)



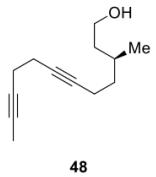
^{1}H NMR (400 MHz, $CDCl_3$)



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

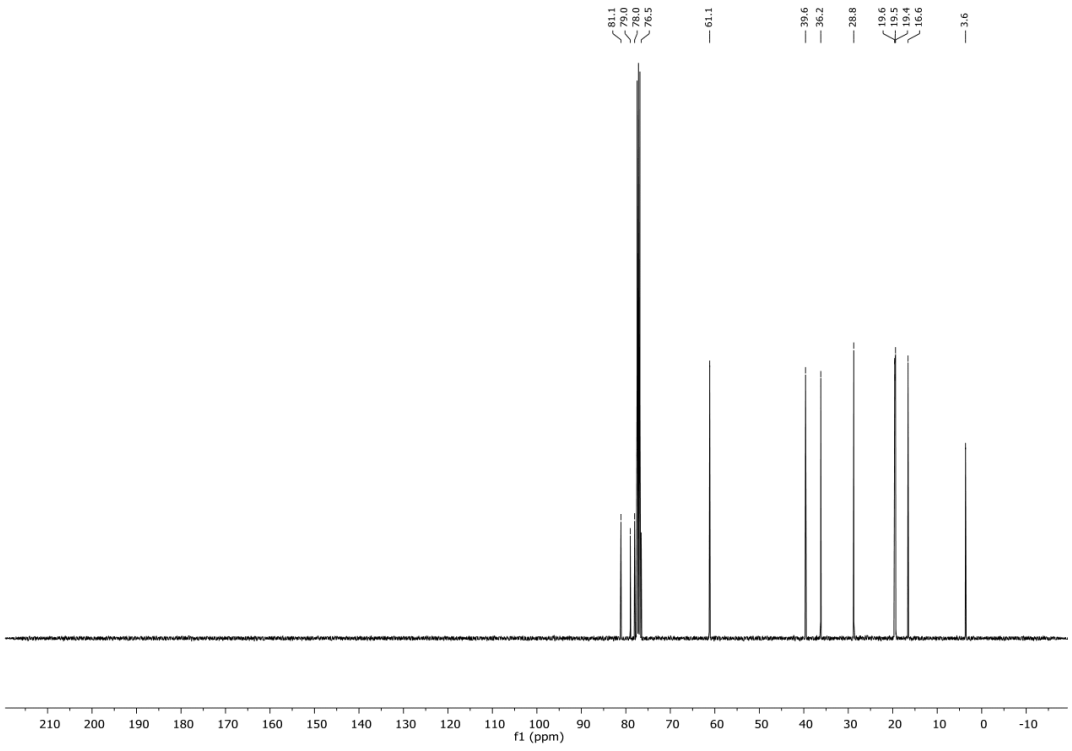


^{1}H NMR (400 MHz, $CDCl_3$)

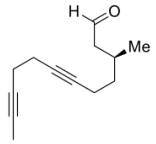


48

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

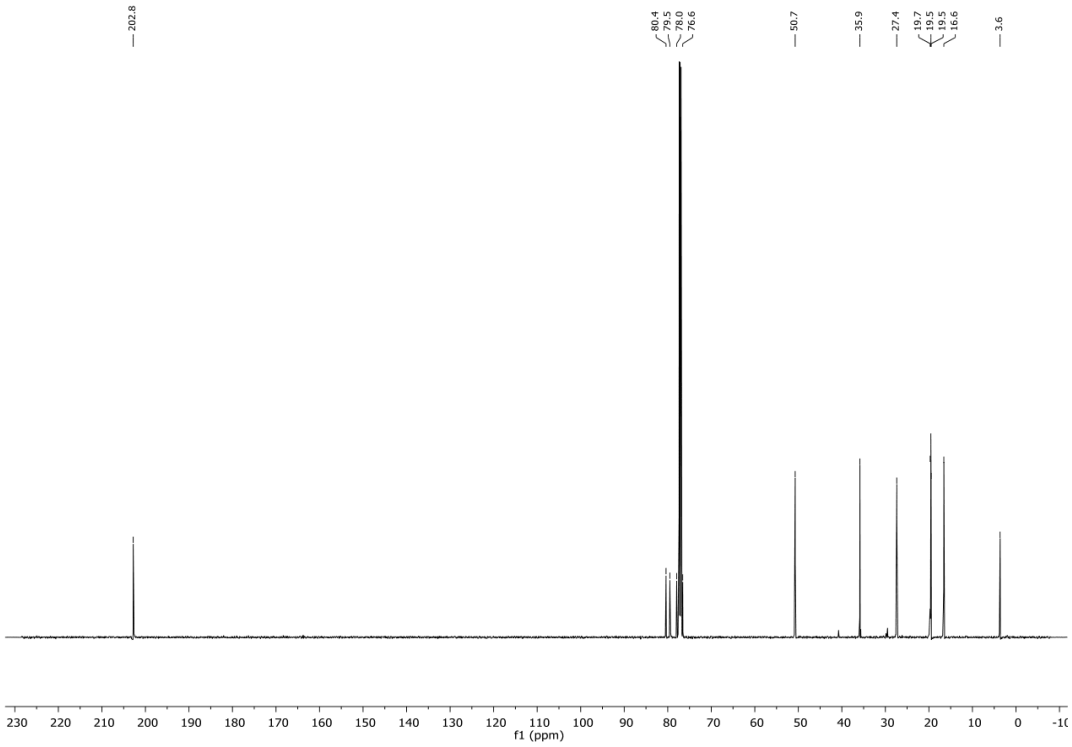


^{1}H NMR (600 MHz, $CDCl_3$)

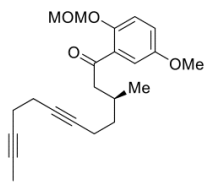


23

^{13}C NMR (151 MHz, $CDCl_3$)

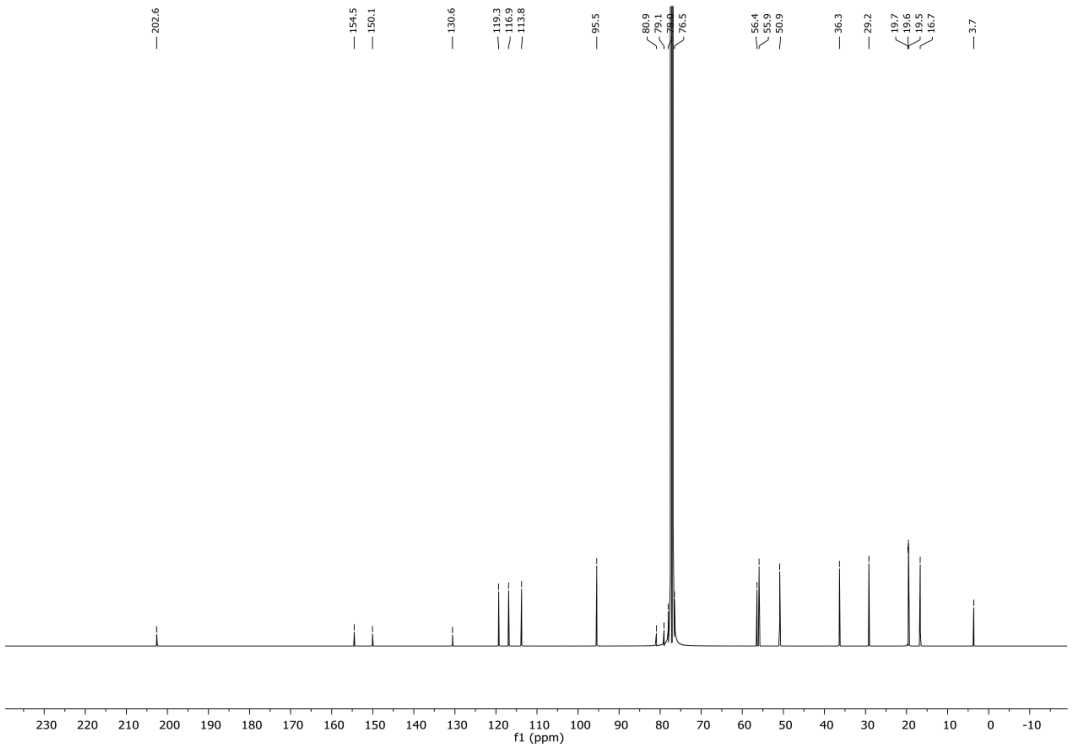


^{1}H NMR (800 MHz, $CDCl_3$)

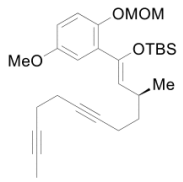


49

^{13}C NMR (201 MHz, $CDCl_3$)

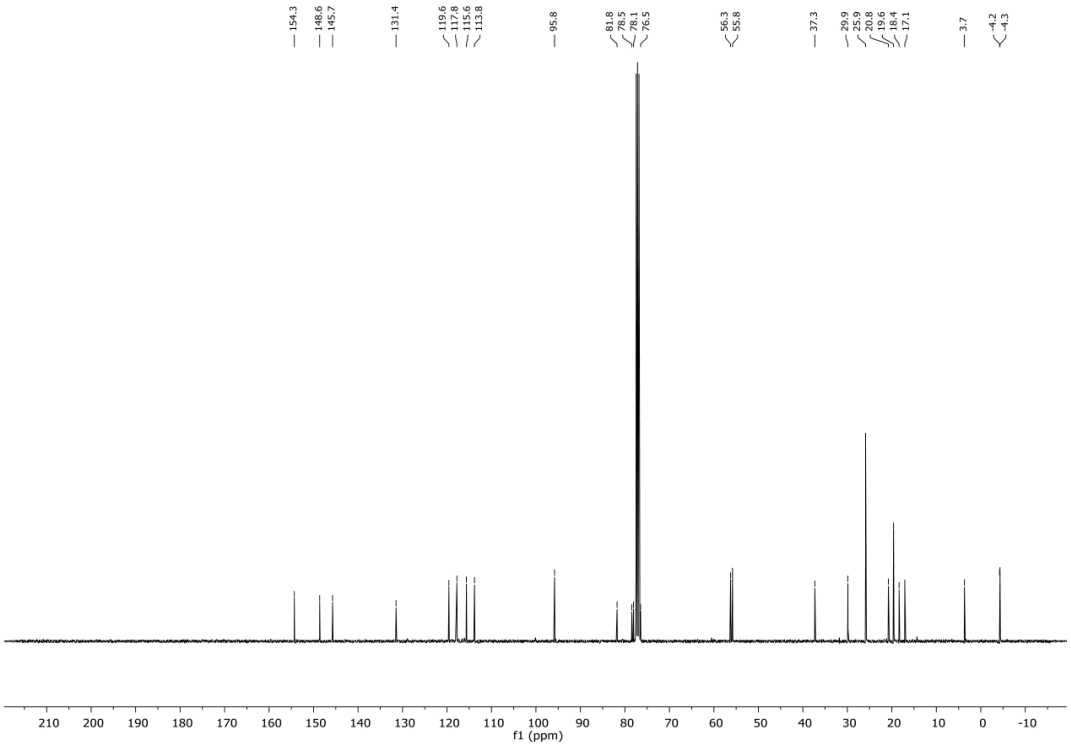


^{1}H NMR (400 MHz, $CDCl_3$)

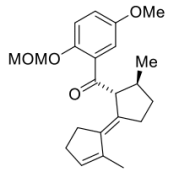


26

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

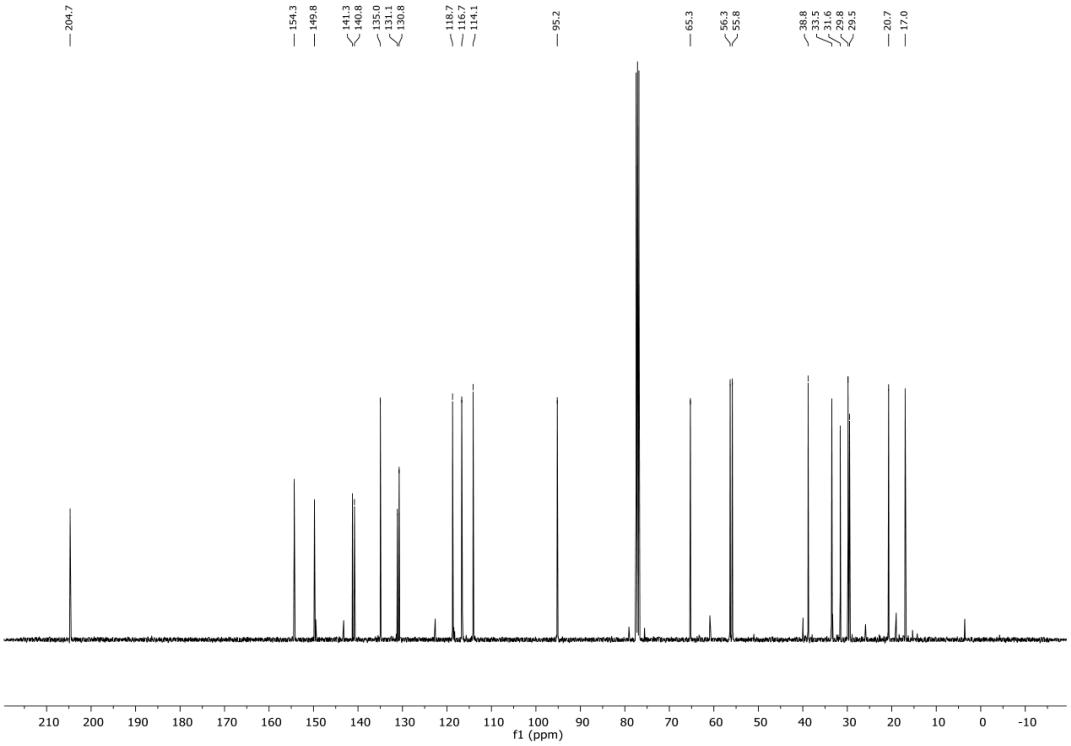


^{1}H NMR (400 MHz, $CDCl_3$)

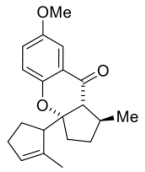


27

^{13}C NMR (151 MHz, $CDCl_3$)

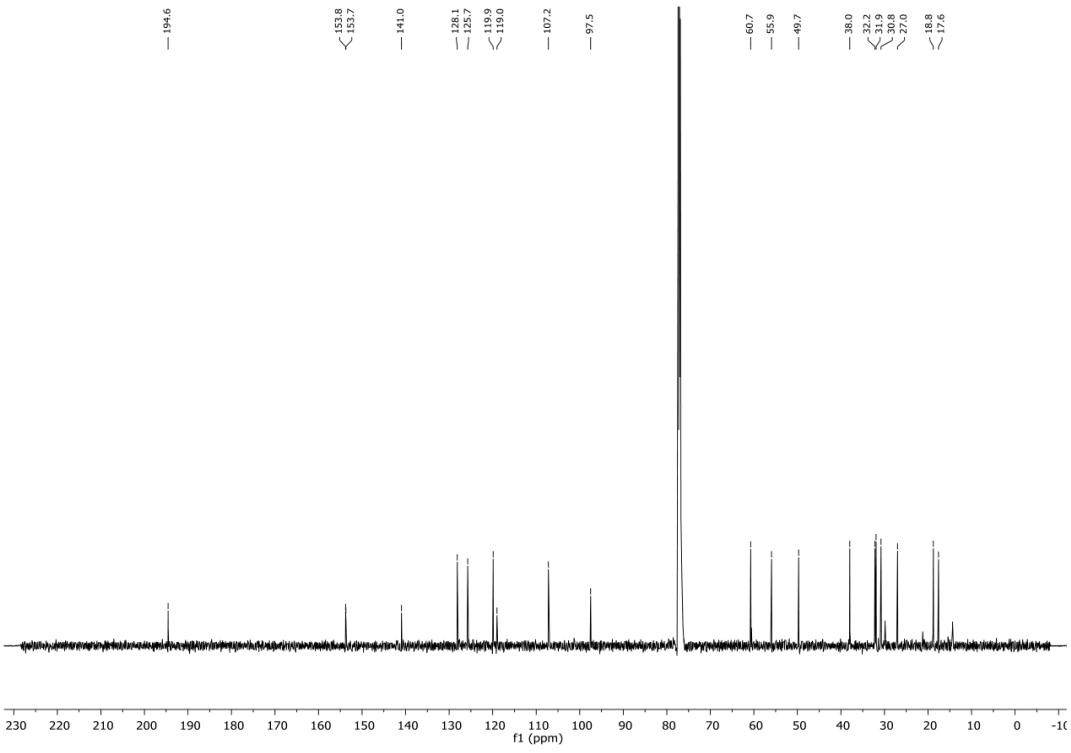


^{1}H NMR (600 MHz, $CDCl_3$)

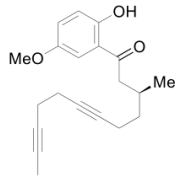


28

^{13}C NMR (151 MHz, $CDCl_3$)



^{1}H NMR (600 MHz, $CDCl_3$)



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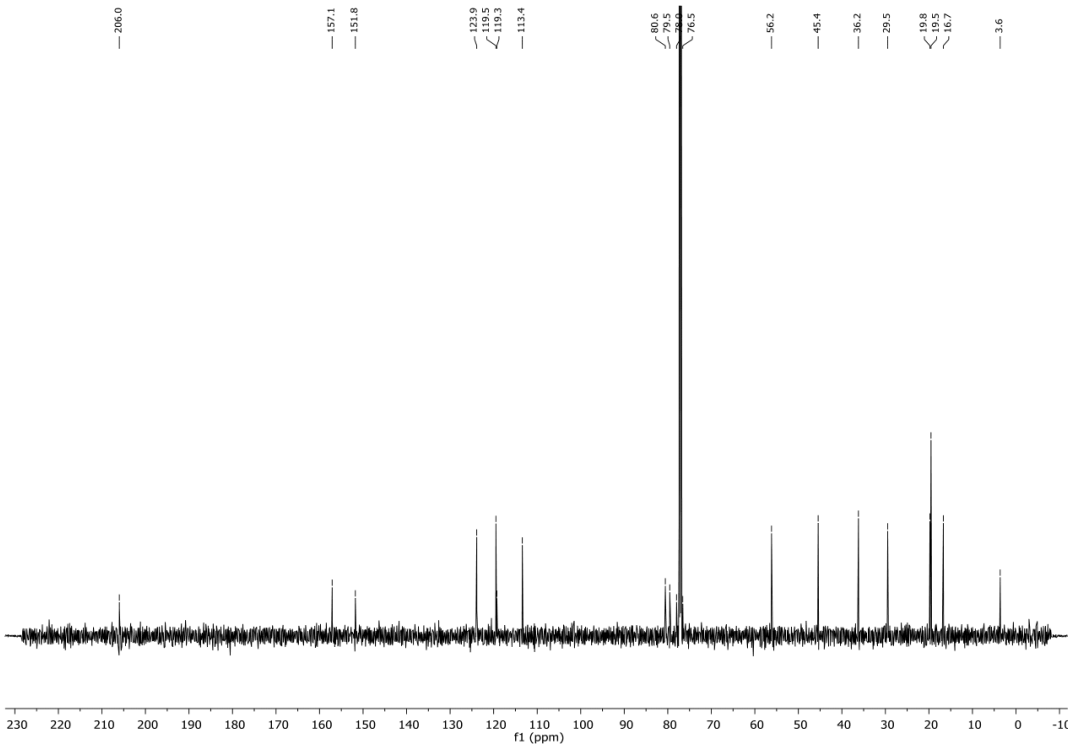
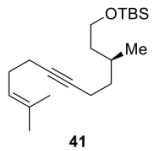
^{13}C NMR (151 MHz, $CDCl_3$)

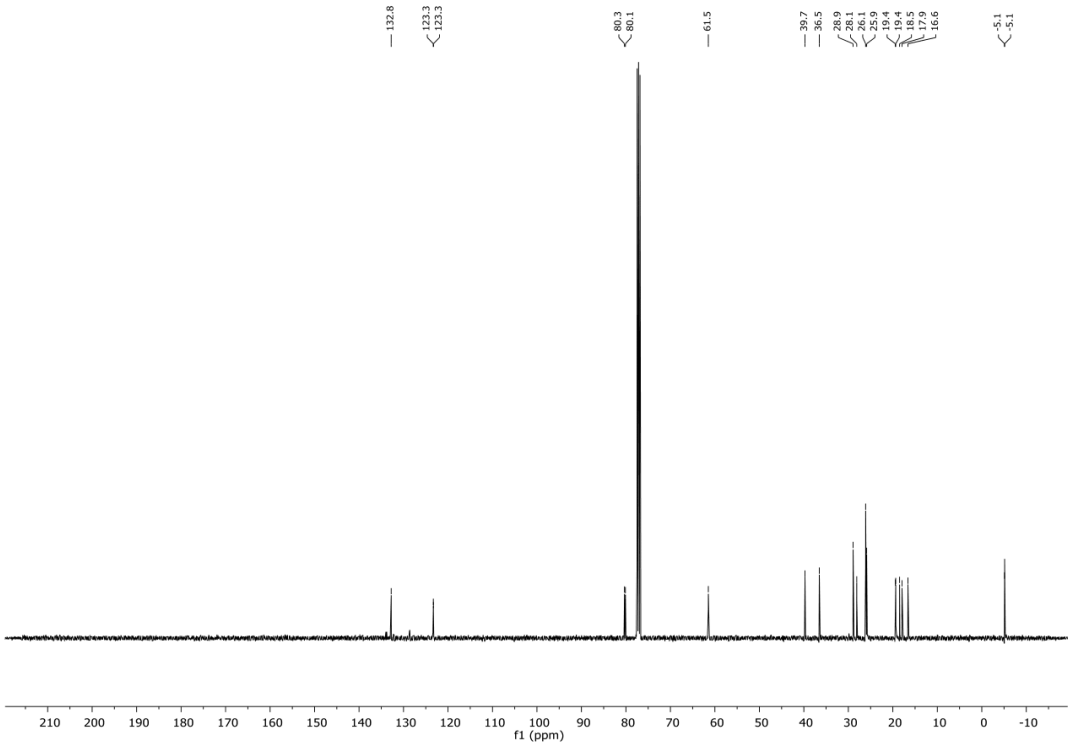


^{1}H NMR (400 MHz, $CDCl_3$)

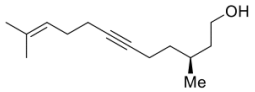


41

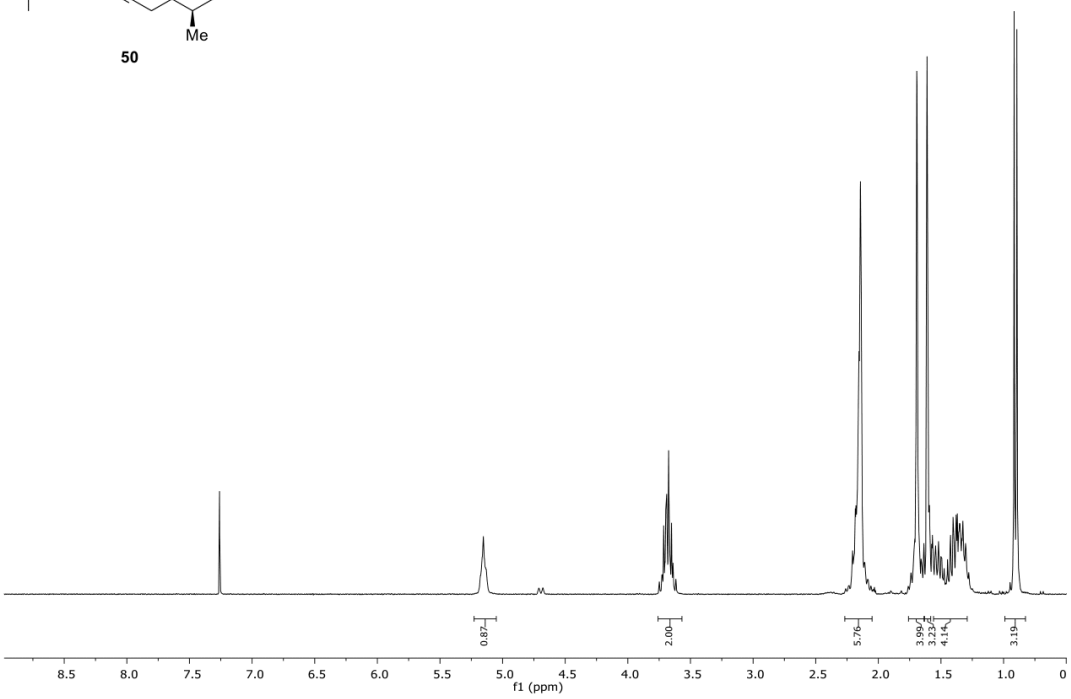
^{13}C NMR (101 MHz, $CDCl_3$)



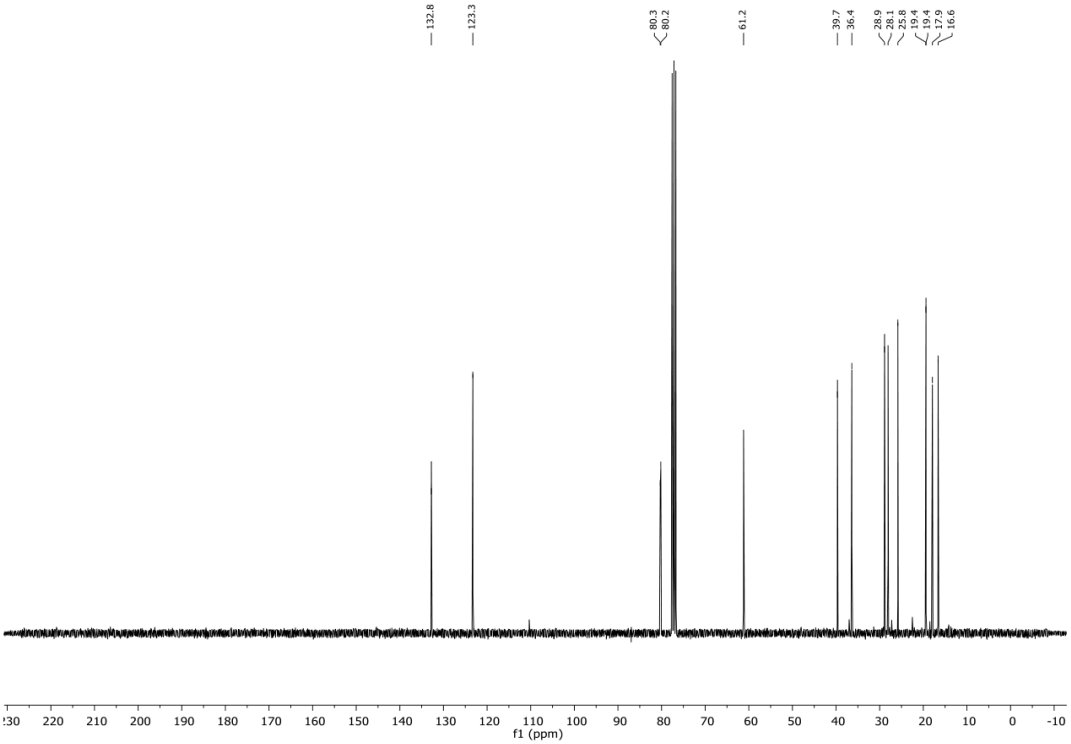
^{1}H NMR (300 MHz, $CDCl_3$)



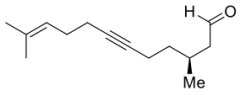
50



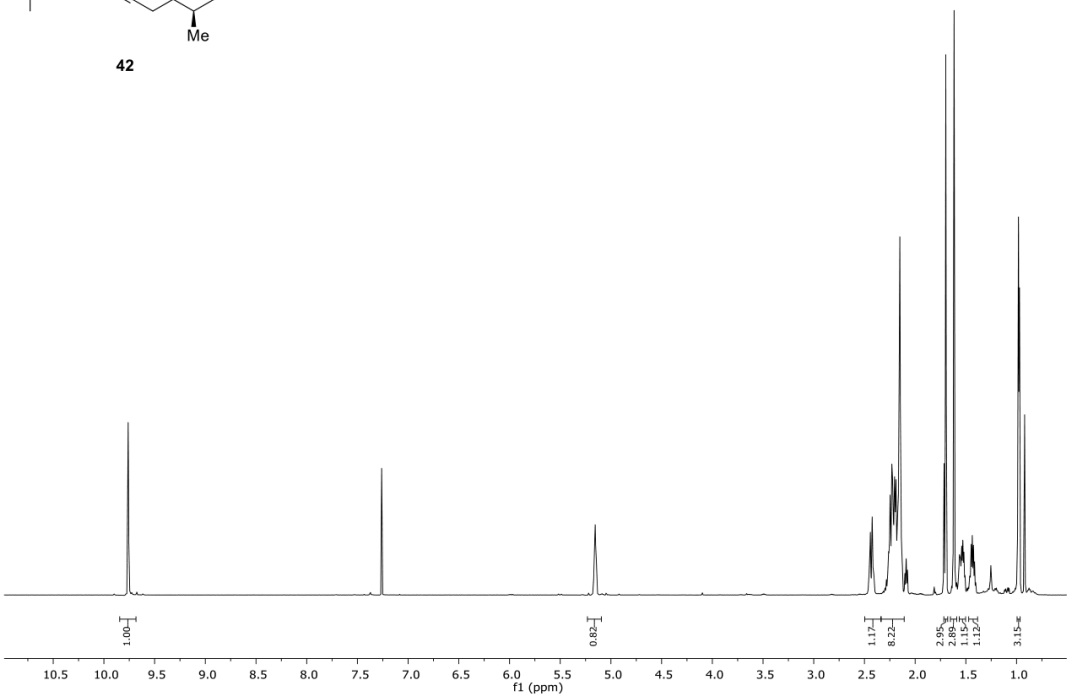
^{13}C NMR (75 MHz, $CDCl_3$)



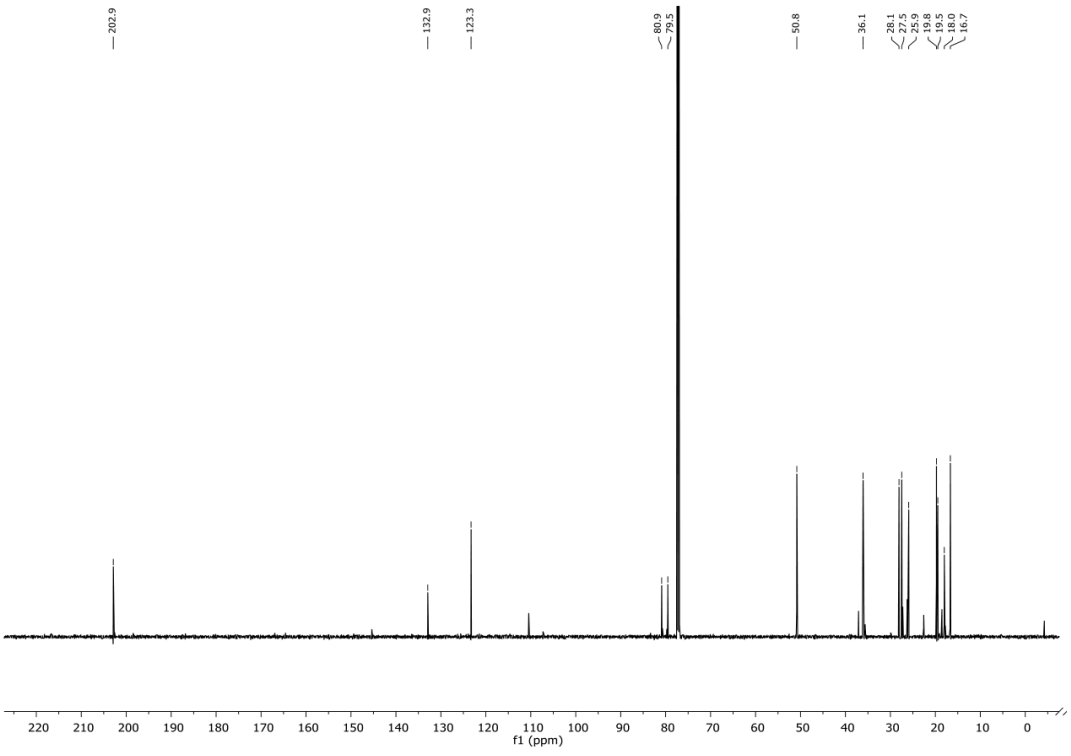
^{1}H NMR (400 MHz, $CDCl_3$)



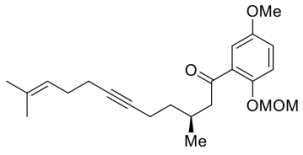
42



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

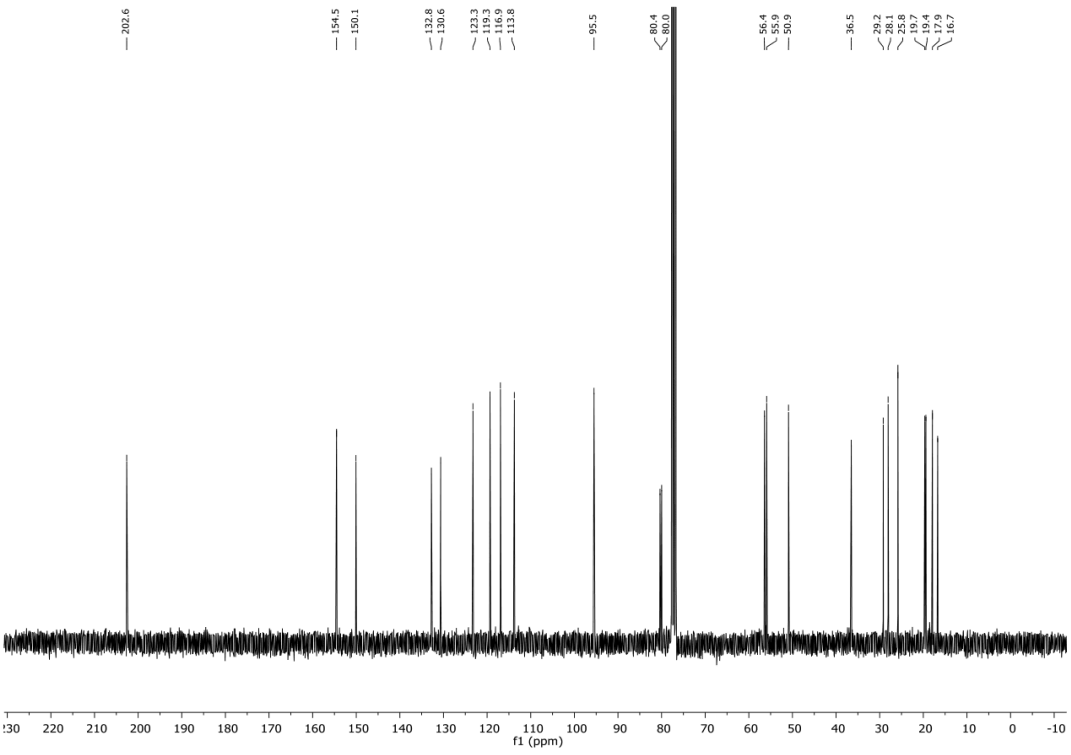


^{1}H NMR (300 MHz, $CDCl_3$)

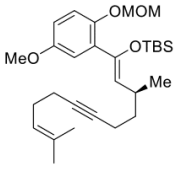


46

^{13}C NMR (75 MHz, $CDCl_3$)

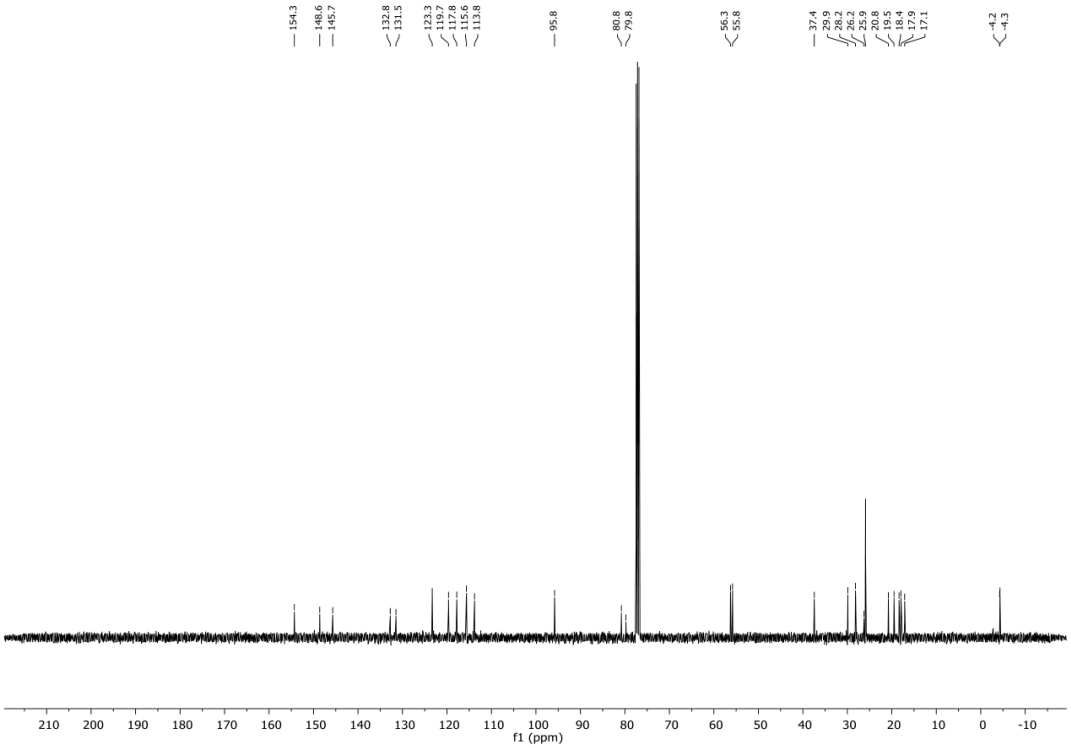


^{1}H NMR (400 MHz, $CDCl_3$)

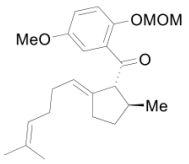


40

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

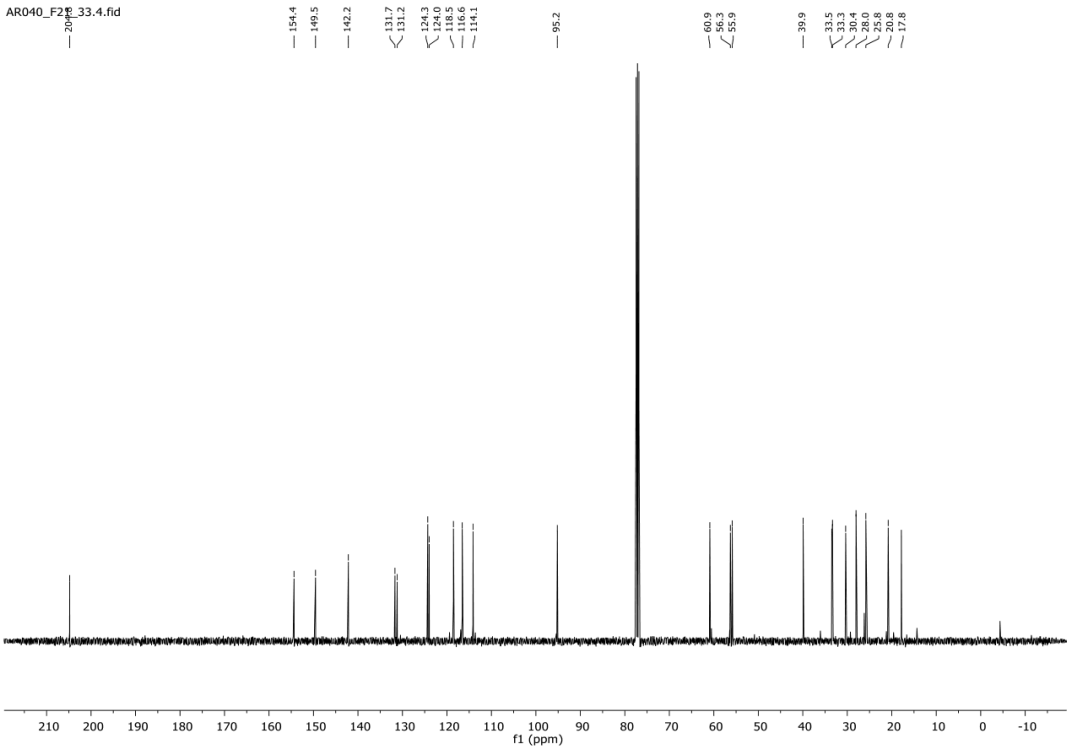


^{1}H NMR (400 MHz, $CDCl_3$)

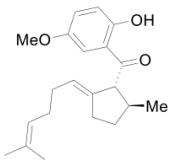


44

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

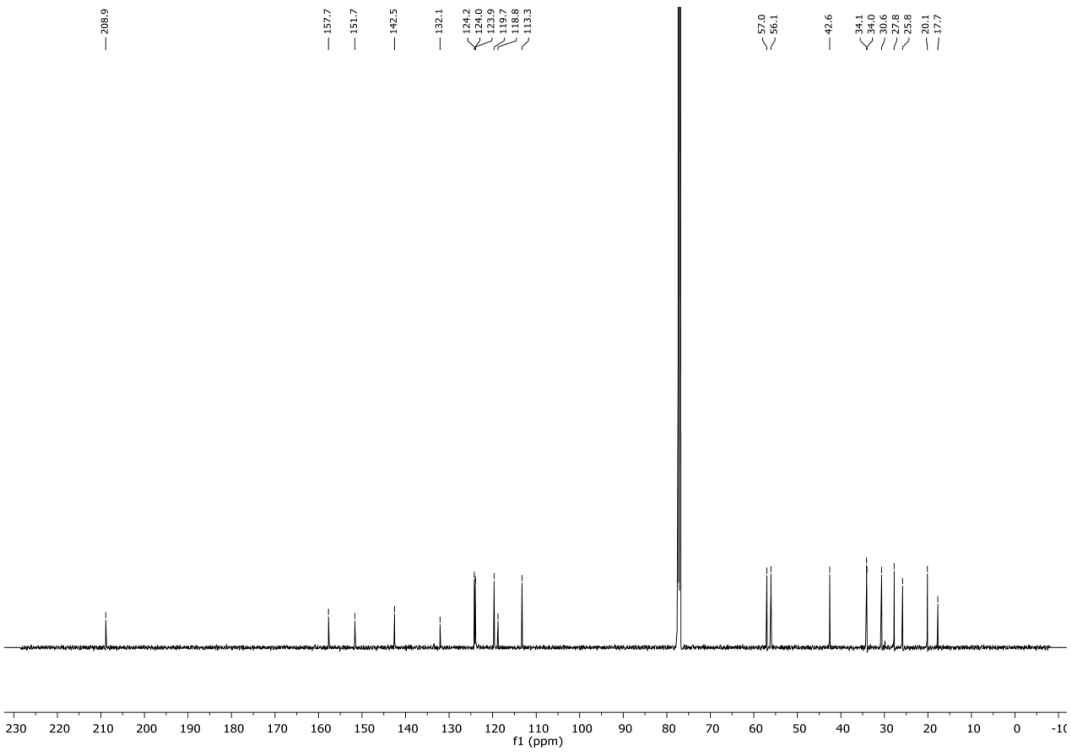


^{1}H NMR (600 MHz, $CDCl_3$)



45

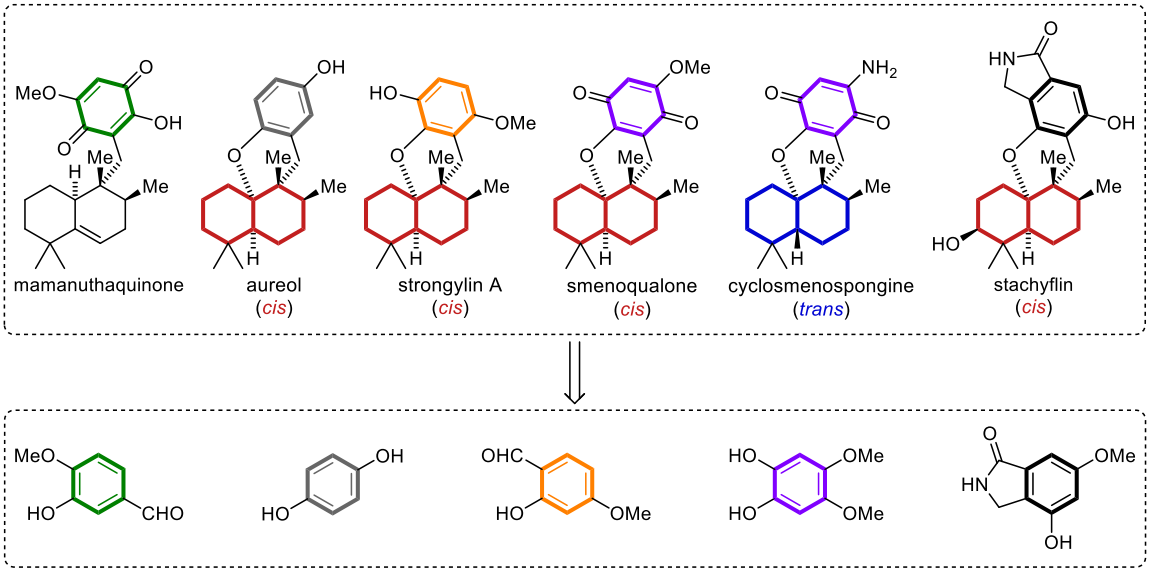
^{13}C NMR (151 MHz, $CDCl_3$)



3.2 Supporting Information for Chapter 1.2.2

A Modular Synthesis of Tetracyclic Meroterpenoid Antibiotics

R. Wildermuth, K. Speck, F.-L. Haut, P. Mayer, B. Karge, M. Brönstrup, T. Magauer, *Nat. Commun.* **2017**, *8*, 2083.



Supplementary Methods

General Experimental Details

All reactions were carried out in dried glassware that was evacuated while heating (heat gun, 2000 W, 650 °C) and backfilled with inert gas (nitrogen) three times, unless otherwise noted. All reaction flasks were sealed with a rubber septum and were kept under a constant positive pressure of nitrogen. Solids were added to the reaction mixture under inert gas counter flow. Liquids were added through rubber septa via stainless steel cannula or via syringe equipped with a stainless steel cannula. Low temperature experiments were carried out in a Dewar vessel filled with acetone/dry ice (–78 °C) or water/ice (0 °C). Temperatures above 23 °C were carried out in a heated silicon oil (CAS Number 63148-62-9) bath. All reaction vessels were equipped with a magnetic stir bar and reactions were monitored by analytical thin-layer chromatography (TLC) on precoated, fluorescent indicator (254 nm) impregnated aluminum plates (0.25 mm, 60 Å pore size, Merck). The TLC plates were visualized by exposure to ultraviolet light (UV, 254 nm, 366 nm), stained with either aqueous potassium permanganate solution ($KMnO_4$), ceric ammonium molybdate solution (CAM) or p-anisaldehyde solution (Anis) and were developed by heating with a heatgun. Purifications by flash-column chromatography on silica gel (60 Å, 40–63 µm, Merck KGaA) was performed according the procedure described by Still et al..[1] All yields refer to isolated, chromatographically and spectroscopically (^1H and ^{13}C NMR) pure material.

Materials

Diethyl ether (Et_2O) tetrahydrofuran (THF) were distilled under nitrogen atmosphere from sodium/benzophenone prior to use. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), diisopropylamine (DIPA), Hünig's base (DIPEA), N,N,N′,N′-tetramethylethan-1,2-diamin (TMEDA), N,N-dimethylacetamide (DMAA) were distilled under nitrogen atmosphere from calcium hydride (CaH_2) prior to use. Chlororform ($CHCl_3$), N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile (MeCN), acetone, toluene (PhMe), and methanol (MeOH) were purchased from Acros Organics as 'extra dry' reagents and used as received. Other reagents and solvents were purchased from chemical suppliers (Sigma-Aldrich, Acros Organics, Alfa Aesar, Strem Chemicals, ABCR) and were used as received unless otherwise noted. Hexanes, ethyl acetate, dichloromethane and diethyl ether for flash-column chromatography on silica gel, extraction and crystallization were purchased in technical grade and distilled prior to use. Zinc chloride ($ZnCl_2$) solution (1 M) was prepared by dissolving anhydrous zinc chloride (140 °C, <0.1 mbar, 24 h) (100 mmol, 136 g) in tetrahydrofuran (100 mL). The concentration of n-butyllithium (n-BuLi) and t-butyllithium (t-BuLi) solutions was determined by titration against diphenylacetic acid (average of three determinations).[2]

NMR spectroscopy

NMR spectra were measured on a Bruker Avance III HD (400 MHz for proton nuclei, 100 MHz for carbon nuclei) spectrometer equipped with a CryoProbe™, Bruker AXR300 (300 MHz for proton nuclei, 75 MHz for carbon nuclei), Varian VXR400 S (400 MHz for proton nuclei, 100 MHz for carbon nuclei), Bruker AMX600 (600 MHz for proton nuclei, 150 MHz for carbon nuclei) or Bruker Avance HD 800 (800 MHz for proton nuclei, 200 MHz for carbon nuclei). Proton chemical shifts are expressed in parts per million (ppm, δ scale) and residual proton in the NMR solvent ($CHCl_3$, δ = 7.26 ppm; C_6D_5H, δ = 7.16 ppm; DMSO-d6 δ = 2.50 ppm) were used as internal reference. Carbon chemical shifts are expressed in parts per million (δ scale, assigned carbon atom) and are residual solvent peaks ($CDCl_3$, δ = 77.16 ppm; C_6D_6, δ = 128.06 ppm, DMSO-d6, δ = 39.52 ppm) were used as internal reference. The NMR spectroscopic data are reported as follows: Chemical shift in ppm (multiplicity, coupling constants J (Hz), integration intensity) for ^1H NMR spectra and chemical shift in ppm for ^{13}C NMR spectra. Multiplicities are abbreviated as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Signals in the NMR spectra were assigned by information obtained from 2D NMR experiments: Homonuclear correlation spectroscopy (COSY), total correlation spectroscopy (TOCSY), heteronuclear single

quantum coherence (HSQC) and heteronuclear multiple bond coherence (HMBC). The software MestReNOVA 11.0 from Mestrelab Research S. L was used to analyze and process all raw fid files.

Mass spectrometry

High resolution mass spectra (HRMS) were measured at the Department of Chemistry, Ludwig-Maximilians-University Munich on the following instruments by electron impact (EI) or electron spray (ESI) techniques: MAT 95 (EI) and MAT 90 (ESI) from Thermo Finnigan GmbH.

IR spectroscopy

Infrared spectra (IR) were recorded on a PerkinElmer Spectrum BX II FT-IR system from 4000 cm^{-1} to 600 cm^{-1}. Substances were directly applied on the ATR unit as a thin film or a thin powder layer. Data are represented as 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 according to Supplementary Equation 1.

$$[\alpha]_{\lambda}^{\varphi} = \frac{[\alpha] \cdot 100}{c \cdot d} \quad (1)$$

The wave length λ is reported in nm (sodium D line, λ = 589 nm), the measuring temperature ϕ in °C. α represents the recorded optical rotation, c the concentration of the analyte in g/mL and d the length of the cuvette in dm. Thus, the specific rotation is given in 10^{-1}·deg·cm^2·g^{-1}. The values for the specific rotation are reported as follows: specific rotation (concentration g/100 mL; solvent).

Melting Points

Melting points were determined on a B-450 melting point apparatus from BÜCHI Labortechnik AG.

X-Ray Crystallographic Data

The data collections were performed by Dr. Peter Mayer (Ludwig-Maximilians-Universität Munich) on one of the following instruments: Oxford Diffraction Xcalibur diffractometer, Bruker D8Quest diffractometer or Bruker D8Venture at 100 K or at 173 K using MoKα-radiation (λ = 0.71073 Å, graphite monochromator). The CrysAlisPro software (version 1.171.33.41) was used for the integration, scaling and multi-scan absorption correction of the data. The structures were solved by direct methods with SIR97[3] and refined by least-squares methods against F2 with SHELXL-97.[4] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. Further details are summarized in the tables at the different sections.

Antibacterial assays

Overnight cultures of the bacteria were grown aerobically at 37 °C in Müller Hinton broth with added 1% glucose and pH 7.2 for Gram-negative strains, or with Trypticase soy yeast extract medium (TSY–30 g/l trypticase soy broth, 3 g/L yeast extract, pH 7.2) for Gram-positive strains. The cultures were adjusted to an OD600nm of 0.001, which resulted in a final start OD600nm of 0.0005 in the test. 25 µL of test culture was added to 25 µL of a serial dilution of the test compounds in the appropriate medium for the different strains in accordance with standardized procedures in 384 well plates (DIN 58940-7: Medical microbiology – susceptibility testing of

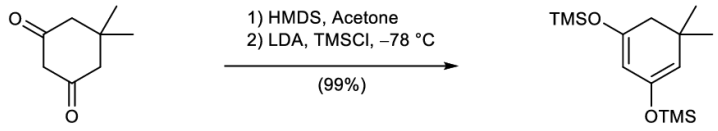
microbial pathogens to antimicrobial agents – determination of the minimum bactericidal concentration (MBC) with the method of micro boullion dilution; text in German and English). Test compounds from stock solutions in DMSO were used at final concentrations of 100, 50, 25, 12.5, 6,25, 3.125, 1.56, 0.78, 0.39, 0.2 µM. As positive control compounds, Linezolid (both MRSA strains), Ciprofloxacin (E. faecium, E. coli, A. baumannii, K. pneumonia), Amikacin (P. aeruginosa) and Amphotericin (C. albicans) were applied. The highest DMSO concentration in the assay was 1%, which had no apparent effect on the growth of the bacteria. After an incubation time of 18 h at 37 °C under moist conditions, the optical density at 600 nm was measured with a Fusion Universal Microplate Analyser (Perkin–Elmer, Waltham, USA). The lowest concentration that completely suppressed growth defined the MIC values. The following bacterial strains were used. Gram-negative: Acinetobacter baumannii (DSM 30007), Escherichia coli (DSM 1116), Klebsiella pneumoniae (DSM 11678) and Pseudomonas aeruginosa PA7 (DSM 24068). Gram-positive: Enterococcus faecium (DSM 20477), Staphylococcus aureus MRSA (clinical isolate, RKI 11-02670) and Staphylococcus aureaus MRSA (DSM 11822). The EC_{50} and MIC values were determined by curve fitting with Sigma Plot.

Antiproliferative assays

The effect of compounds on cell viability was probed with a WST-1 test using the procedure of Ishiyama et al.[5] as modified by Sasse et al.[6] The following cell lines were used: mouse fibroblast cell line L929 (DSM ACC 2), human cervix carcinoma cell line KB-3-1 (DSM ACC 158) and human breast cancer cell line MCF-7 (DSM ACC 115). In addition, the conditional immortalized human fibroblast cell line FS4-LTM (InScreenex, Braunschweig, Germany) was used without doxycyclin to induce primary cell-like behavior (Pub. No.: US2011/0189142 A2). The subconfluent cells were briefly washed with Earle's Balanced Salt Solution (Gibco) without Ca and Mg, trypsinized and re-suspended in Dulbecco's modified eagle's medium that contained 5% fetal bovine serum (FBS; L929, KB-31, FS4-LTM) or Roswell Park Memorial Institute medium that contained 5% FBS, 0.5% Minimum Essential Medium Non-Essential Amino Acids, Gibco (MEM NEAA), 0.5% GlutaMAX (Gibco) and insulin at 5 µg/mL (MCF-7). 25 µL of serial dilutions of the test compounds (100–0.2 µM), that were made with a pipetting robot (epMotion, Eppendorf, Hamburg, Germany), were added to 25 µL aliquots of a cell suspension (1500 cells for KB3-1 and L929, 3000 cells for MCF-7 and 7500 cells for FS4-LTM) in 384 well microtiter plates. Blank and solvent controls were incubated under identical conditions. After an incubation period of 5 days (for L929, KB-3-1, and MCF-7) or 24h (for FS4-LTM), 3 µL WST-1 (ready to use solution by Roche) was added. The incubation time of the plates at 37 °C varied between the cell lines from 20 min for KB-3-1, L929 for 30 min, FS4-LTM for 1 h and 2 h for MCF-7 before measuring absorbance at 450 nm (reference 600 nm) with an Infinite 200 PRO plate reader (Tecan, Männedorf, Switzerland). As positive control compounds, Auranofin and Staurosporin were applied. The absorbance of the solvent control was set to 100%. The EC_{50} values were determined with Sigma Plot.

Synthesis of (+)-Stachyflin (1), 38 and 39

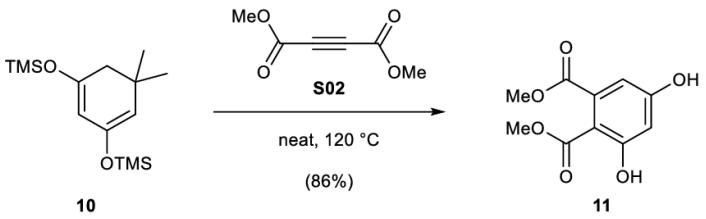
Diene 10



S01 **10**

To a suspension of dimedone (**S01**) (24.8 g, 177 mmol, 1 equiv) in dichloromethane (450 mL) was added hexamethyldisilazane (HMDS) (51.8 mL, 244 mmol, 1.38 equiv) and the resulting solution was stirred at 23 °C. After 23 h, the solution was concentrated and the residue was added dropwise to a solution of lithium diisopropylamine (195 mmol, 1.10 equiv), itself freshly prepared by the addition of n-butyllithium (2.4 M in hexanes, 81.1 mL, 195 mmol, 1.10 equiv) to a solution of diisopropylamine (27.5 mL, 195 mmol, 1.10 equiv) in tetrahydrofuran (350 mL) at –78 °C, over a period of 30 min. After 60 min, chlorotrimethylsilane (21.1 g, 195 mmol, 1.10 equiv) was added and the reaction mixture was allowed to warm to 23 °C. After 90 min, the reaction mixture was filtered and the filtrate was concentrated. The residue was dissolved in pentane, the so-obtained mixture was filtered through a plug of Celite® and the solvent was removed under reduced pressure. This process was repeated twice, yielding **10** (50.3 g, 99%) as a pale yellow oil. The obtained characterization data were in full agreement with the values previously reported.[7]

Dimethyl-3,5-dihydroxyphthalate 11



A mixture of dimethyl acetylenedicarboxylate (**S02**) (12.6 g, 88.4 mmol, 1 equiv) and diene **10** (50.3 g, 177 mmol, 2.00 equiv) was heated to 120 °C. After 17 h, the reaction mixture was diluted with a mixture of ethyl acetate-hexanes (2:3, 400 mL) and the resulting suspension was filtered through a plug of Celite®. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (30% ethyl acetate in hexanes initially, grading to 50% ethyl acetate in hexanes). The obtained yellowish solid was dissolved in a minimum amount of hot dichloromethane and precipitated by the addition of hexanes to give **11** (17.2 g, 86%) as a white powder.

TLC (40% ethyl acetate in hexanes): R_f = 0.32 ($KMnO_4$, UV).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 10.96 (s, 1H), 6.45 (d, J = 2.5 Hz, 1H), 6.40 (d, J = 2.5 Hz, 1H), 5.73 (s, 1H), 3.87 (s, 6H).

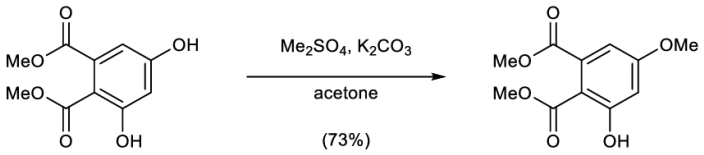
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 169.9, 169.5, 164.1, 161.3, 137.9, 108.4, 105.2, 103.5, 53.2, 53.1.

IR (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$ = 3343, 3202, 2952, 1671, 1615, 1588, 1437, 1238, 1194, 1154, 1024, 849, 729.

HRMS (ESI) calc. for $C_{10}H_9O_6^-$ $[M–H]^-$: 225.0405; found: 225.0406.

Melting point: 125–126 °C.

Dimethyl 3-hydroxy-5-methoxyphthalate 12



11 **12**

To a solution of phenol **11** (10.0 g, 44.2 mmol, 1 equiv) in acetone (200 mL) were added potassium carbonate (9.17 g, 66.3 mmol, 1.50 equiv) and dimethyl sulfate (5.58 g, 44.2 mmol, 1.00 equiv). After 3.5 h, the reaction mixture was filtered through a plug of Celite® and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to yield phthalate **12** (7.79 g, 73%) as a colorless solid

TLC (30% ethyl acetate in hexanes): R_f = 0.44 ($KMnO_4$, UV).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.00 (s, 1H), 6.48 (d, J = 2.5 Hz, 1H), 6.45 (d, J = 2.5 Hz, 1H), 3.85 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H).

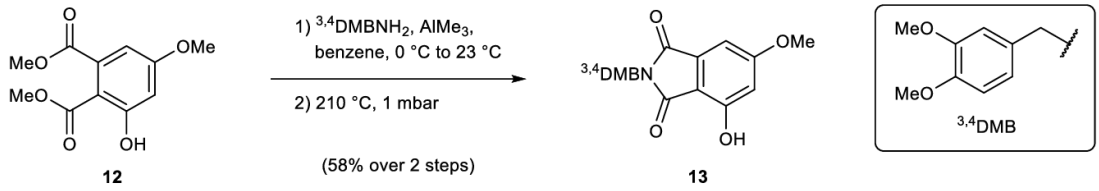
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 169.7, 169.6, 164.8, 164.2, 137.5, 108.1, 103.0, 102.6, 56.1, 53.0, 52.9.

IR (Diamond-ATR, neat): $\tilde{\upsilon}_{max}$ = 2954, 1733, 1615, 1501, 1433, 1264, 1197, 1149, 1022, 759.

HRMS (ESI) calc. for $C_{11}H_{11}O_6^-$ [M–H]$^-$: 239.0561; found: 239.0563.

Melting point: 68–69 °C.

Imide 13



To a solution of 3,4-dimethoxybenzylamine (^{3,4}DMBNH$_2$) (15.8 mL, 104 mmol, 5.00 equiv) in benzene (13 mL) was added trimethylaluminium (2.0 M in toluene, 51.0 mL, 102 mmol, 4.90 equiv) at 0 °C and the solution was allowed to warm to 23 °C. After 40 min, a solution of diester **12** (5.00 g, 20.8 mmol, 1 equiv) in benzene (24 mL) was added to the yellow suspension. The transfer was quantified with benzene (2 × 3 mL). The reaction mixture was heated to 70 °C. After 3 h, the mixture was allowed to cool to 23 °C and ethyl acetate (400 mL) was added. The organic layer was washed with aqueous hydrochloric acid solution (2 M, 2 × 200 mL) and saturated aqueous sodium chloride solution (200 mL). The washed organic extract was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give the phthalamide (10.6 g) as a yellow solid.

The crude phthalamide (10.6 g) was placed in a bulb-to-bulb distillation apparatus. (Set up: flask **1** was filled with starting material, flask **2** was in heating device, flask **3** as trap at 23 °C, flask **4** was cooled to –78 °C, Supplementary Figure 1). The oven was carefully heated to 210 °C under high vacuum (1 mbar) for 60 min. The dark orange residue remaining in flask **1** was recrystallized from ethanol (40 mL) to yield **13** (5.05 g, 58% over 2 steps) as pale yellow crystalline solid.

TLC (dichloromethane): R_f = 0.25 (UV, $KMnO_4$).

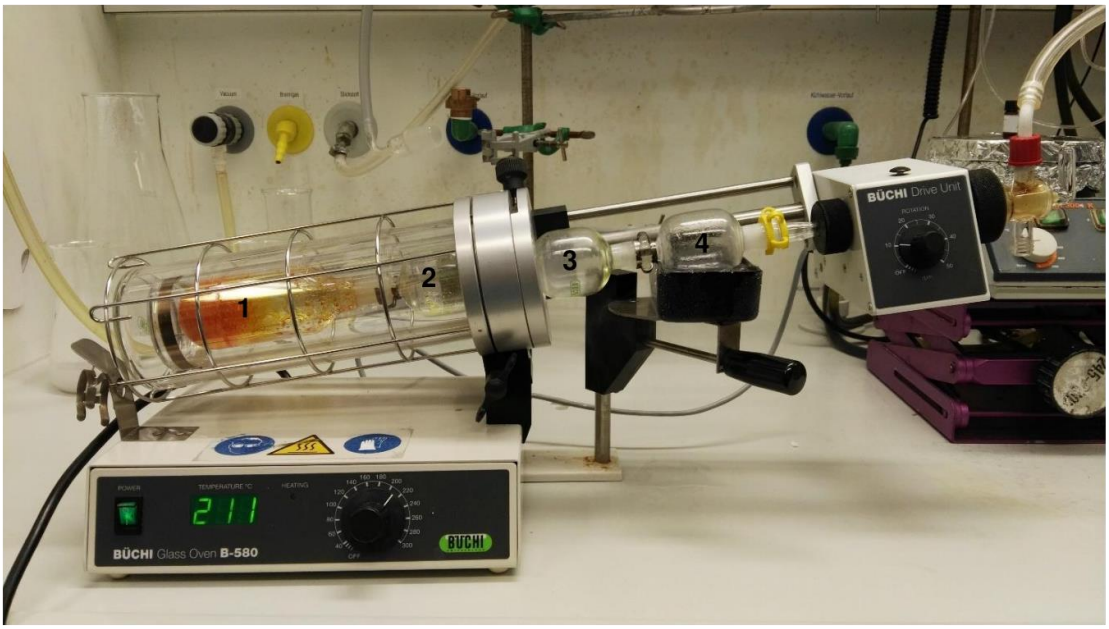
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.51 (br s, 1H), 7.00–6.96 (m, 2H), 6.93 (d, J = 2.0 Hz, 1H), 6.80 (m, 1H), 6.56 (d, J = 2.0 Hz, 1H), 4.70 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 169.8, 167.7, 167.0, 156.3, 149.1, 148.8, 134.0, 129.0, 121.3, 112.0, 111.1, 107.7, 105.9, 104.2, 56.4, 56.0, 56.0, 41.4.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3440, 2939, 1693, 1624, 1516, 1400, 1260, 1156, 1026, 758.

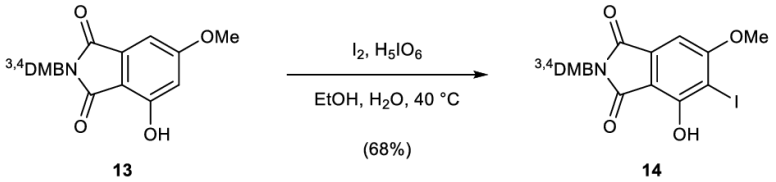
HRMS (EI) calc. for $C_{18}H_{17}NO_6$ 343.1050 $[M]^+$; found: 343.1046.

Melting point: 155–157 °C.



Supplementary Figure 1 Bulb-to-bulb setup: flask **1** was filled with starting material, flask **2** was in heating device, flask **3** as trap at 23 °C, flask **4** was cooled to –78 °C.

Iodide 14



13 **14**

To a suspension of phenol **13** (5.05 g, 14.7 mmol, 1 equiv) and iodine (2.24 g, 8.83 mmol, 0.60 equiv) in ethanol (60 mL) was added a solution of periodic acid (671 mg, 2.94 mmol, 0.20 equiv) in water (3.5 mL) and the reaction mixture was heated to 40 °C. After 30 h, dichloromethane (200 mL) was added, the organic layer was washed with saturated aqueous sodium thiosulfate solution (2 × 150 mL) and saturated sodium chloride solution (150 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (3% methanol in dichloromethane) to yield **14** (4.70 g, 68%) as an off-white solid.

TLC (4% methanol in dichloromethane): R_f = 0.70 (UV, $KMnO_4$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.11 (br s, 1H), 7.00–6.94 (m, 2H), 6.89 (s, 1H), 6.80 (d, J = 8.0 Hz, 1H), 4.72 (s, 2H), 4.01 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H),

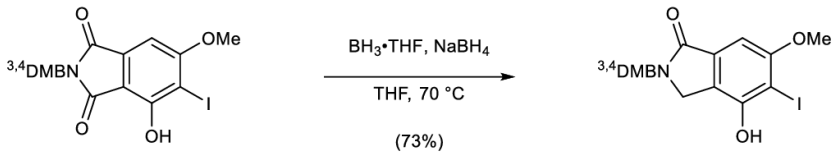
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 169.5, 167.5, 165.3, 155.5, 149.2, 149.0, 133.9, 128.8, 121.4, 112.1, 111.3, 108.1, 99.3, 82.0, 57.6, 56.1, 56.1, 41.7.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3413, 2940, 1693, 1620, 1393, 1259, 1158, 1061, 1025, 729.

HRMS (EI) calc. for $C_{18}H_{16}{}^{127}INO_4$ $[M]^+$: 469.0017; found: 469.0009.

Melting point: 214–216 °C.

Isoindolinone S03



14 **S03**

To a solution of iodide **14** (810 mg, 1.73 mmol, 1 equiv) in tetrahydrofuran (9 mL) was added a solution of borane tetrahydrofuran complex (1.00 M in tetrahydrofuran, 2.16 mL, 2.16 mmol, 3.00 equiv) at 23 °C. After the gas evolution ceased, sodium borohydride (3.27 mg, 0.09 mmol, 0.05 equiv) was added at 23 °C and the mixture was heated to 70 °C in a pressure flask. After 17 h, the reaction mixture was cooled to 23 °C, diluted with aqueous hydrochloric acid solution (1 M, 75 mL) and extracted with ethyl acetate (4 × 75 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (1% methanol in dichloromethane) to give **S03** (573 mg, 73%) as an off-white powder.

TLC (2% methanol in dichloromethane): R_f = 0.23 (UV, $KMnO_4$).

^{1}H NMR ($CDCl_3$, 599 MHz): δ = 6.92 (s, 1H), 6.85–6.77 (m, 3H), 6.22 (s, 1H), 4.69 (s, 2H), 4.21 (s, 2H), 3.94 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H).

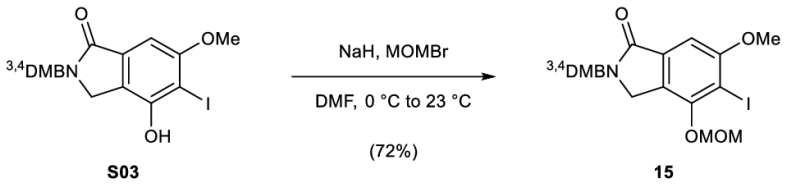
^{13}C NMR ($CDCl_3$, 151 MHz): δ = 168.0, 159.4, 151.0, 149.5, 148.8, 135.3, 129.5, 120.7, 119.7, 111.5, 111.2, 97.9, 82.6, 57.2, 56.1, 56.1, 47.4, 46.6.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2937, 1649, 1514, 1466, 1350, 1259, 1138, 1082, 1026, 729.

HRMS (EI) calc. for $C_{18}H_{18}{}^{127}INO_5$ $[M]^+$: 455.0224; found: 455.0222.

Melting point: 198–200 °C.

Methoxymethyl ether 15



S03 **15**

To a solution of amide **S03** (550 mg, 1.21 mmol, 1 equiv) in N,N-dimethylformamide (24 mL) was added sodium hydride (60% dispersion in mineral oil, 72.5 mg, 1.81 mmol, 1.50 equiv) at 0 °C. After 1 h, bromomethyl methyl ether (130 µL, 1.57 mmol, 1.30 equiv) was added and the reaction mixture was allowed to warm to 23 °C. After 2.5 h, the reaction mixture was diluted with saturated aqueous ammonium chloride solution (40 mL) and ethyl acetate (40 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (4 × 30 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (50% ethyl acetate in hexanes) to give **15** (435 mg, 72%) as a white crystalline solid.

TLC (2% methanol in dichloromethane): R_f = 0.31 (UV, $KMnO_4$).

^{1}H NMR ($CDCl_3$, 599 MHz): δ = 7.11 (s, 1H), 6.86–6.79 (m, 3H), 5.12 (s, 2H), 4.71 (s, 2H), 4.32 (s, 2H), 3.96 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.52 (s, 3H).

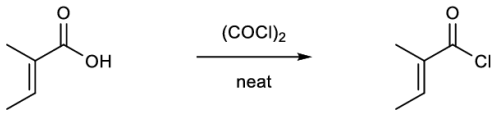
^{13}C NMR ($CDCl_3$, 151 MHz): δ = 167.6, 160.2, 153.1, 149.5, 148.8, 135.8, 129.4, 124.5, 120.6, 111.4, 111.3, 101.2, 98.1, 88.4, 57.5, 57.2, 56.1, 56.1, 48.0, 46.5.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2933, 1678, 1609, 1512, 1461, 1257, 1132, 1045, 1023, 762.

HRMS (EI) calc. for $C_{20}H_{22}{}^{127}INO_4$ $[M]^+$: 499.0486; found: 499.0483.

Melting point: 106–108 °C.

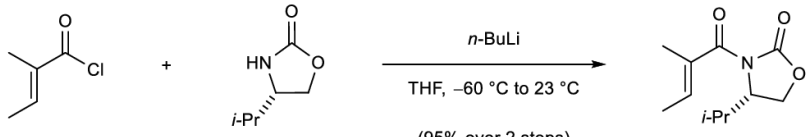
(E)-2-Methylbut-2-enoyl chloride (S05)



S04 **S05**

(E)-2,3-Dimethylacrylic acid (**S04**) (29.3 g, 293 mmol, 1 equiv) was added portionwise to oxalyl chloride (29.5 mL, 304 mmol, 1.30 equiv) followed by one drop of N,N-dimethylformamide. After 2.5 h, excess oxalyl chloride was removed under reduced pressure to give **S05** (34.7 g, 99%) as a colorless liquid. Acid chloride **S05** was used directly used in the next step without further purification.

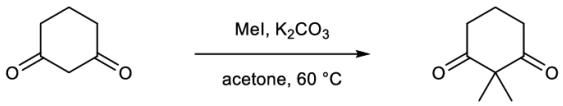
Oxazolidinone 21



S05 **S06** **21**

A solution of n-butyllithium (2.5 M in hexanes, 99.0 mL, 248 mmol, 1.10 equiv) was added dropwise to a solution of **S06** (29.1 g, 225 mmol, 1 equiv) in tetrahydrofuran (600 mL) at −78 °C. After 15 min, **S05** (34.7 g, 293 mmol, 1.30 equiv) was slowly added to the reaction mixture via cannula at −78 °C. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 14 h, aqueous hydrochloric acid (2 M, 1 L) was added to the reaction mixture, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 300 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to yield **21** (45.1 g, 95%) as a yellow solid. The obtained analytical data were in full agreement with those previously reported.[8]

2,2-Dimethyl-1,3-cyclohexadione (16)

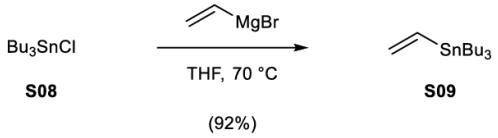


S07 (39%) **16**

A suspension of 1,3-cyclohexadione (**S07**) (38.0 g, 340 mmol, 1 equiv), potassium carbonate (93.7 g, 680 mmol, 2.00 equiv) and iodomethane (61.0 mL, 980 mmol, 2.90 equiv) in acetone (300 mL) was heated to 60 °C. After 3 h, excess iodomethane was removed by distillation into a cooling finger (cooled to –78 °C). The residue was diluted with chloroform (300 mL) and water (150 mL). The layers were separated, the aqueous layer was extracted with chloroform (2 × 150 mL) and the combined organic extracts were dried over sodium

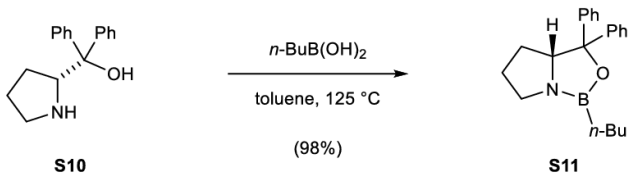
sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (30% ethyl acetate in hexanes) to yield **16** (18.5 g, 39%) as a yellow oil. The obtained analytical data were in full agreement with those values reported in literature.[9]

Tributyl(vinyl)tin (S09)



A solution of tributyltin chloride (**S08**) (42.0 mL, 155 mmol, 1 equiv) in tetrahydrofuran (50 mL) was slowly added to a solution of vinylmagnesium bromide (1.0 M in tetrahydrofuran, 310 mL, 310 mmol, 2.00 equiv) via a dropping funnel over a period of 2 h. Upon complete addition, the reaction mixture was heated to 70 °C. After 18 h, the reaction mixture was cooled to 23 °C and saturated aqueous ammonium chloride solution (100 mL) was carefully added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 100 mL). The combined organic extracts were concentrated and the residue was purified by vacuum distillation (10 mbar, 128 °C) to yield **S09** (45.1 g, 92%) as a colorless oil. The obtained analytical data were in full agreement with those values reported in literature.[10]

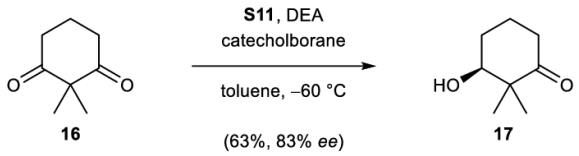
(R)-(+)-2-Methyl-CBS-oxazaborilidine (S11)



(R)-(+)-2-Methyl-CBS-oxazaborilidine (**S11**) was prepared according to the procedure described by E. J. Grabowski.[11]

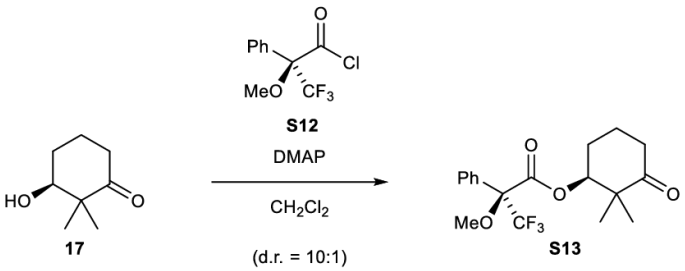
A solution of (R)-(+)-diphenyl-2-pyrrolidinemethanol (**S10**) (5.25 g, 20.7 mmol, 1 equiv) and butylboronic acid (2.10 g, 20.7 mmol, 1 equiv) in toluene (250 mL) in a two-necked, round-bottomed flask equipped with an additional funnel (containing a cotton plug and 100 g of 4 Å molecular sieves) was heated to 125 °C. After 16 h, the reaction mixture was allowed to cool to 23 °C and the solvent was removed to give **S11** (6.80 g, 98%) as a colorless oil. The obtained analytical data were in full agreement with those values reported in literature.[11]

Alcohol 17



To a solution of (R)-(+)-2-methyl-CBS-oxazaborilidine (**S11**) (6.80 g, 22.3 mmol, 0.10 equiv), N,N-diethylaniline (DEA) (14.8 mL, 92.7 mmol, 0.500 equiv) and 2,2-dimethyl-1,3-cyclohexadione (**16**) (26.0 g, 185 mmol, 1 equiv) in toluene (200 mL) was added a solution of catecholborane (19.8 mL, 185 mmol, 1.00 equiv) in toluene (200 mL) via a dropping funnel over a period of 2.5 h at –60 °C. Upon complete addition, methanol (50 mL) was added and the mixture was diluted with diethyl ether (100 mL). The organic layer was washed with a 1:1 mixture of saturated sodium bicarbonate solution (50 mL) and aqueous sodium hydroxide solution (1 M, 50 mL). The aqueous layer was extracted with ethyl acetate (3 × 100 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (300 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to yield **17** (16.7 g, 63%, 83% ee) as a yellow oil. The obtained analytical data were in full agreement with those values reported in literature.[12]

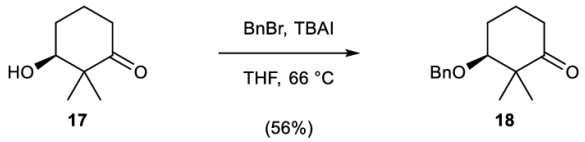
Mosher ester S13



The enantiomeric excess of alcohol **17** was determined as 83% by ^{1}H-NMR analysis of its corresponding-MTPA ester **S13** according to the procedure described by E. J. Corey.[12]

To a solution of alcohol **17** (10.0 mg, 70.0 µmol, 1 equiv) in dichloromethane (1 mL) were added 4-dimethylaminopyridine (34.4 mg, 28.0 µmol, 4.00 equiv) and (R)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (**S12**) (20.0 µL, 110 µmol, 1.50 equiv) at 23 °C. After 1 h, water (2 mL) and dichloromethane (3 mL) were added and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 3 mL) and the combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated to give **S13** as a yellow oil. The obtained analytical data were in full agreement with those values reported in literature.

Benzyl ether 18



To a solution of alcohol **17** (14.0 g, 98.5 mmol, 1 equiv) in tetrahydrofuran (360 mL) was added sodium hydride (60% mineral oil dispersion, 4.33 g, 108 mmol, 1.10 equiv) at 0 °C. After 30 min, tetrabutylammonium iodide (TBAI) (72.7 g, 197 mmol, 2.00 equiv) and benzyl bromide (29.4 mL, 246 mmol, 2.5 equiv) were added subsequently and the resulting suspension was heated to 66 °C. After 14 h, the reaction mixture was allowed to cool to 23 °C, saturated aqueous ammonium chloride solution (300 mL) and diethyl ether (100 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 200 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (200 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (hexanes initially, grading to 5% ethyl acetate in hexanes) to yield **18** (12.7 g, 56%) as a colorless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.18 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.25 (m, 4H), 7.23–7.18 (m, 1H), 4.56 (d, J = 11.8 Hz, 1H), 4.34 (d, J = 11.8 Hz, 1H), 3.37–3.31 (m, 1H), 2.33 (td, J = 6.4, 1.9 Hz, 2H), 2.01–1.90 (m, 2H), 1.88–1.78 (m, 1H), 1.61–1.51 (m, 1H), 1.13–1.11 (m, 6H).

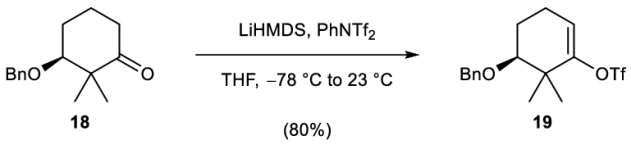
^{13}C NMR (101 MHz, $CDCl_3$): δ = 213.9, 138.4, 128.1, 127.3, 127.3, 84.4, 71.1, 50.8, 37.1, 24.3, 23.2, 20.3, 20.3.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2943, 2870, 1706, 1453, 1118, 1090, 1074, 1066, 1028, 737.

HRMS (EI) calc. for $C_{15}H_{20}O_2$ $[M]^+$: 232.1458; found: 232.1463.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +9.1 ° (c = 6.80, CH_2Cl_2).

Triflate 19



To a solution of benzyl ether **18** (12.0 g, 51.7 mmol, 1 equiv) in tetrahydrofuran (200 mL) was added lithium bis(trimethylsilyl)amide solution (1.00 M in tetrahydrofuran, 67.1 mL, 67.1 mmol, 1.30 equiv) at –78 °C. After 1 h, N-phenylbis(trifluoromethanesulfonimide) (24.0 g, 67.1 mmol, 1.30 equiv) was added portionwise. Upon complete addition, the reaction mixture was allowed to warm to 23 °C. After 2.5 h, saturated aqueous ammonium chloride solution (200 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 50 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (2% ethyl acetate in hexanes) to yield **19** (15.1 g, 80%) as a colorless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.50 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.37 (m, 4H), 7.35–7.30 (m, 1H), 5.69 (t, J = 4.1 Hz, 1H), 4.71 (d, J = 11.8 Hz, 1H), 4.50 (d, J = 11.8 Hz, 1H), 3.40 (dd, J = 9.0, 2.7 Hz, 1H), 2.38–2.25 (m, 1H), 2.24–2.11 (m, 1H), 2.00–1.89 (m, 1H), 1.84–1.73 (m, 1H), 1.28–1.16 (m, 6H).

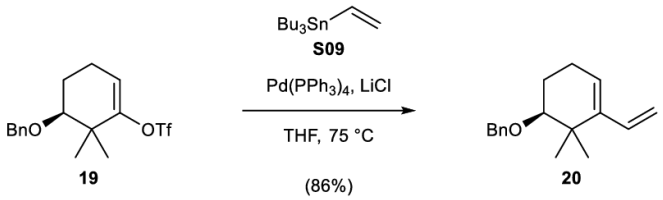
^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.9, 138.6, 128.5, 127.7, 127.6, 118.5 (q, J = 319.3 Hz), 115.5, 82.0, 71.7, 40.6, 24.7, 21.8, 21.1, 20.7.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2978, 2945, 2874, 1411, 1208, 1143, 1025, 983, 874, 698.

HRMS (EI) calc. for $C_{16}H_{19}F_3O_4{}^{32}S$ $[M]^+$: 364.0951; found: 364.0947.

$[\alpha]_D^{20}$ = +22.1° (c = 1.07, CH_2Cl_2).

Diene 20



Note: benzene was degassed via freeze-pump-thaw (three cycles) prior to use.

To a mixture of lithium chloride (6.98 g, 165 mmol, 5.00 equiv) and tetrakis(triphenylphosphine)palladium(0) (1.90 g, 1.65 mmol, 5.00 mol%) in degassed tetrahydrofuran (235 mL) was added triflate **19** (13.6 g, 35.0 mmol, 1 equiv) and tributyl(vinyl)tin (**S09**) (20.5 mL, 70.0 mmol, 2.00 equiv) at 23 °C in an Ace® pressure tube. After complete addition, the tube was sealed and the mixture was heated to 75 °C. After 18 h, aqueous ammonia solution (10%, 100 mL) was added to the dark brown reaction mixture and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 50 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (hexanes initially, grading to 2% ethyl acetate in hexanes) to yield diene **20** (6.83 g, 86%) as a colorless oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.69 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 5H), 6.38–6.20 (m, 1H), 5.81–5.68 (m, 1H), 5.36–5.27 (m, 1H), 5.01–4.91 (m, 1H), 4.71 (d, J = 11.7 Hz, 1H), 4.47 (d, J = 11.7 Hz, 1H), 3.32–3.23 (m, 1H), 2.29–2.19 (m, 1H), 2.13–2.02 (m, 1H), 1.94–1.84 (m, 1H), 1.77–1.66 (m, 1H), 1.14–1.08 (m, 6H).

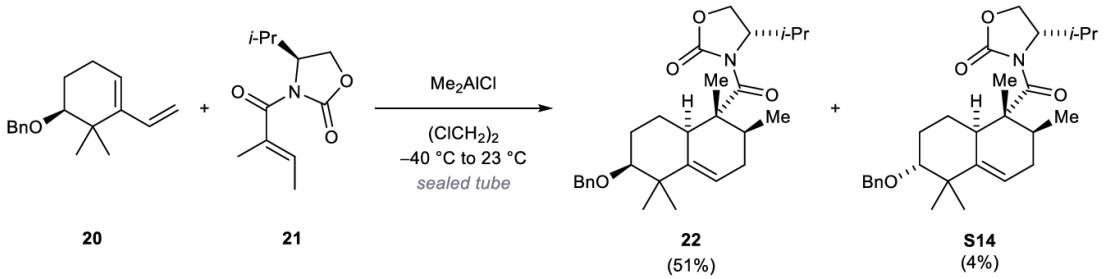
^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.9, 139.2, 136.4, 128.2, 127.5, 127.3, 121.6, 113.6, 83.0, 71.3, 38.6, 26.2, 23.8, 22.3, 22.1.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3028, 2965, 2940, 2869, 1454, 1359, 1096, 907, 735, 697.

HRMS (EI) calc. for $C_{17}H_{22}O$ $[M]^+$: 242,1665; found: 242.1677.

$[\alpha]_D^{20}$ = +29.0° (c = 1.45, CH_2Cl_2).

Diels-Alder product 22 and S14



20 **21** **22** (51%) **S14** (4%)

A solution of dimethylaluminium chloride (1.00 M in hexanes, 82.9 mL, 82.9 mmol, 3.00 equiv) was added dropwise to a solution of dienophile **21** (7.59 g, 35.9 mmol, 1.30 equiv) in 1,2-dichloroethane (100 mL) at –40 °C in an oven dried Ace® round-bottom pressure flask (Sigma Aldrich, product number: Z567205) under nitrogen over a period of 30 min. After 30 min, a solution of diene **20** (6.70 g, 27.6 mmol, 1 equiv) in 1,2-dichlorethane (65 mL) was added dropwise over a period of 20 min to the reaction mixture. The transfer was quantitated with 1,2-dichloroethane (2 × 5 mL). After complete addition, the pressure tube was sealed and the reaction mixture was allowed to warm to 23 °C. After 40 h, the reaction mixture was cooled to 0 °C and aqueous hydrochloric acid (2 M, 200 mL) was carefully added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (4% ethyl acetate in hexanes initially, grading to 10% ethyl acetate in hexanes) to yield the **22** (6.43 g, 51%) as colorless solid and **S14** (483 mg, 4%) as colorless solid. Recrystallization from ethyl acetate gave crystals of both epimers **22** and **S14** suitable for single-crystal X-ray diffraction.

Major diastereomer 22:

TLC (20% ethyl acetate in hexanes): R_f = 0.69 (UV, CAM).

^{1}H NMR (599 MHz, $CDCl_3$): δ = 7.32 (dd, J = 3.9, 1.4 Hz, 4H), 7.26–7.23 (m, 1H), 5.56–5.48 (m, 1H), 4.61–4.53 (m, 2H), 4.35 (d, J = 12.3 Hz, 1H), 4.29 (t, J = 8.7 Hz, 1H), 4.26–4.18 (m, 1H), 3.45 (d, J = 12.7 Hz, 1H), 3.22–3.11 (m, 2H), 2.41–2.31 (m, 1H), 2.02–1.93 (m, 1H), 1.91–1.83 (m, 1H), 1.83–1.74 (m, 2H), 1.73–1.65 (m, 1H), 1.15 (s, 3H), 1.08 (s, 3H), 1.07–1.03 (m, 4H), 0.94–0.90 (m, 6H), 0.80 (d, J = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 178.0, 153.1, 142.4, 139.5, 128.3, 127.6, 127.3, 118.2, 83.1, 70.4, 62.9, 61.2, 53.6, 41.2, 36.8, 31.4, 29.8, 29.0, 28.3, 25.8, 23.7, 22.4, 18.6, 16.5, 14.6, 12.4.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2963, 2874, 1777, 1682, 1454, 1383, 1240, 1196, 1117, 747.

HRMS (ESI) calc. for: $C_{28}H_{43}N_2O_4$ 471.3217 $[M+NH_4]^+$; found: 471.3225.

$[\alpha]_D^{20}$ = +46.6° (c = 0.56, CH_2Cl_2).

Melting point: 133–141 °C

Minor diastereomer S14:

TLC (20% ethyl acetate in hexanes): R_f = 0.69 (UV, CAM).

^{1}H NMR (800 MHz, $CDCl_3$): δ = 7.36–7.31 (m, 4H), 7.27–7.25 (m, 1H), 5.59 (d, J = 6.0 Hz, 1H), 4.63 (d, J = 12.1 Hz, 1H), 4.56 (d, J = 8.2 Hz, 1H), 4.43 (d, J = 12.1 Hz, 1H), 4.32–4.27 (m, 1H), 4.21 (dd, J = 9.2, 2.3 Hz, 1H), 3.38–3.32 (m, 1H), 3.21–3.14 (m, 1H), 2.93 (dd, J = 11.5, 4.2 Hz, 1H), 2.38–2.31 (m, 1H), 2.02–1.97 (m, 1H), 1.97–1.92 (m, 1H), 1.76–1.70 (m, 1H), 1.54–1.47 (m, 1H), 1.40–1.35 (m, 1H), 1.24–1.20 (m, 1H), 1.18 (s, 3H), 1.06 (s, 3H), 1.01 (s, 3H), 0.93–0.90 (m, 6H), 0.80 (d, J = 6.8 Hz, 3H).

^{13}C NMR (201 MHz, $CDCl_3$): δ = 177.8, 153.0, 144.3, 139.5, 128.3, 127.5, 127.4, 117.9, 84.4, 71.6, 62.9, 61.1, 53.3, 42.5, 36.9, 31.2, 29.6, 28.3, 26.3, 26.2, 24.6, 22.5, 18.6, 16.4, 14.6, 12.6.

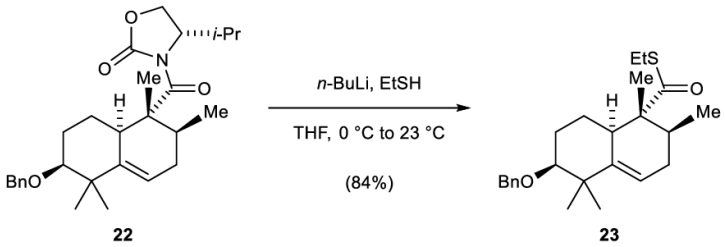
IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2963, 2873, 1772, 1679, 1381, 1358, 1192, 1090, 1062, 914, 732.

HRMS (ESI) calc. for: $C_{28}H_{43}N_2O_4$ 471.3217 $[M+NH_4]^+$; found: 471.3226.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +18.7° (c = 1.19, CH_2Cl_2).

Melting point: 126–132 °C

Thioester 23



A solution of n-butyllithium (2.22 M in hexanes, 27.5 mL, 61.1 mmol, 4.70 equiv) was added dropwise to a solution of ethanethiol (4.82 mL, 65.0 mmol, 5.00 equiv) in tetrahydrofuran (200 mL) at 0 °C. After complete addition, the reaction mixture was allowed to warm to 23 °C. After 30 min, a solution of oxazolidinone **22** (5.90 g, 13.0 mmol, 1 equiv) in tetrahydrofuran (60 mL) was slowly added. The transfer was quantitated with tetrahdydrofuran (2 × 5 mL). After 21 h, saturated aqueous ammonium chloride solution (200 mL) was added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes initially, grading to 10% ethyl acetate in hexanes) to yield **23** (4.20 g, 84%) as a colorless oil.

TLC (9% ethyl acetate in hexanes): R_f = 0.32 (UV, CAM).

^{1}H NMR (599 MHz, $CDCl_3$): δ = 7.34–7.30 (m, 4H), 7.28–7.24 (m, 1H), 5.51–5.45 (m, 1H), 4.57 (d, J = 12.1 Hz, 1H), 4.34 (d, J = 12.1 Hz, 1H), 3.17–3.13 (m, 1H), 2.92–2.82 (m, 3H), 2.05–1.91 (m, 2H), 1.89–1.76 (m, 2H), 1.74–1.63 (m, 2H), 1.29–1.22 (m, 4H), 1.16 (s, 3H), 1.08–1.02 (m, 6H), 0.81 (d, J = 6.7 Hz, 3H).

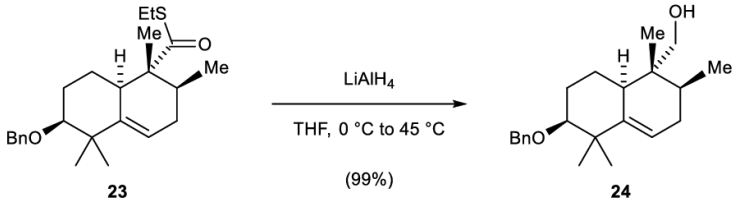
^{13}C NMR (151 MHz, $CDCl_3$): δ = 208.2, 142.7, 139.4, 128.3, 127.6, 127.3, 117.9, 82.8, 70.3, 56.8, 42.9, 40.9, 36.9, 31.6, 29.4, 25.9, 23.2, 23.2, 21.0, 15.9, 14.9, 9.6.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2963, 2929, 2872, 1669, 1453, 1383, 1113, 950, 909, 731.

HRMS (ESI) calc. for $C_{24}H_{38}NO_2S^+$ $[M+NH_4^+]^+$: 404.2618; found: 404.2607.

$[\alpha]_D^{20}$ = +3.22° (c = 3.29, CH_2Cl_2).

Alcohol 24



23 **24**

Lithium aluminium hydride (1.96 g, 51.7 mmol, 5.00 equiv) was added portionwise to a solution of thioester **23** (4.00 g, 10.3 mmol, 1 equiv) at 0 °C. After complete addition, the reaction mixture was heated to 45 °C. After 3 h, the reaction mixture was cooled to 0 °C, diluted with diethyl ether (100 mL) and saturated aqueous potassium sodium tartrate solution (400 mL) was carefully added. After stirring vigorously for 1 h, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 150 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to yield **24** (3.40 g, 99%) as a colorless oil.

TLC (15% ethyl acetate in hexanes): R_f = 0.15 (CAM).

^{1}H NMR (599 MHz, $CDCl_3$): δ = 7.34–7.30 (m, 4H), 7.26–7.23 (m, 1H), 5.52–5.49 (m, 1H), 4.59 (d, J = 12.5 Hz, 1H), 4.36 (d, J = 12.4 Hz, 1H), 3.55–3.50 (m, 1H), 3.49–3.41 (m, 1H), 3.18–3.13 (m, 1H), 2.51–2.42 (m, 1H), 1.93–1.81 (m, 3H), 1.76–1.67 (m, 2H), 1.56–1.49 (m, 2H), 1.23 (s, 1H), 1.15 (s, 3H), 1.03 (s, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.57 (s, 3H).

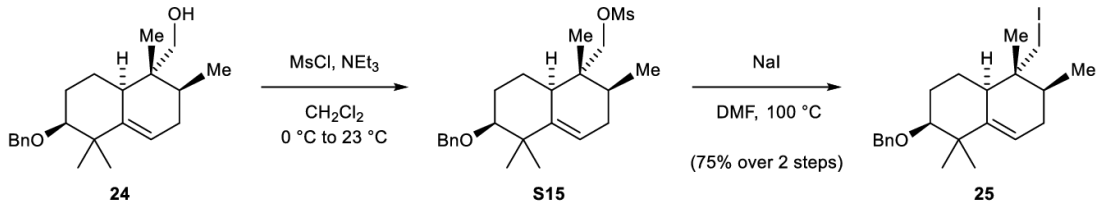
^{13}C NMR (151 MHz, $CDCl_3$): δ = 143.6, 139.6, 128.3, 127.7, 127.3, 118.3, 83.0, 70.3, 65.8, 41.1, 39.5, 37.4, 32.0, 31.6, 29.1, 26.0, 23.7, 20.5, 15.1, 11.5.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3359, 2952, 2873, 1453, 1380, 1102, 1061, 1039, 733, 696.

HRMS (EI) calc. for $C_{22}H_{32}O_2$ $[M]^+$: 328.2397; found: 328.2403.

$[\alpha]_D^{20}$ = +50.9° (c = 0.89, CH_2Cl_2).

Iodide 25



24 **S15** **25**

Methanesulfonyl chloride (1.63 mL, 21.0 mmol, 3.00 equiv) was added to a solution of alcohol **24** (2.30 g, 7.00 mmol, 1 equiv) and triethylamine (5.84 mL, 42.0 mmol, 6.00 equiv) in dichloromethane (45 mL) at 0 °C. After 30 min, the orange, turbid reaction mixture was allowed to warm to 23 °C. After 3 h, dichloromethane (50 mL) and pH 7 phosphate buffer (100 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 60 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to give mesylate **S15** as an orange oil. The so-obtained mesylate was directly used in the following reaction without further purification.

To a solution of crude mesylate **S15** (2.85 g, 7.00 mmol, 1 equiv) in N,N-dimethylformamide (60 mL) was added sodium iodide (8.39 g, 56.0 mmol, 8.00 equiv) and the resulting orange suspension was heated to 100 °C. After 39 h, the reaction mixture was cooled to 23 °C and saturated, aqueous sodium thiosulfate solution (200 mL) and diethyl ether (200 mL) were added. The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 100 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (pentane initially, grading to 40% diethyl ether in pentane) to yield iodide **25** (2.30 g, 75% over 2 steps) as a brown oil and unreacted starting alcohol **24** (379 mg, 17%) as a colorless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.33 (CAM).

^{1}H NMR (800 MHz, $CDCl_3$): δ = 7.36–7.32 (m, 4H), 7.28–7.25 (m, 1H), 5.52–5.47 (m, 1H), 4.61 (d, J = 12.3 Hz, 1H), 4.38 (d, J = 12.3 Hz, 1H), 3.45 (d, J = 10.3 Hz, 1H), 3.23 (d, J = 10.3 Hz, 1H), 3.19–3.17 (m, 1H), 2.46–2.39 (m, 1H), 1.95–1.88 (m, 2H), 1.79–1.72 (m, 2H), 1.63–1.57 (m, 1H), 1.55–1.50 (m, 1H), 1.40–1.36 (m, 1H), 1.17 (s, 3H), 1.06 (s, 3H), 0.87 (s, 3H), 0.83 (d, J = 6.7 Hz, 3H).

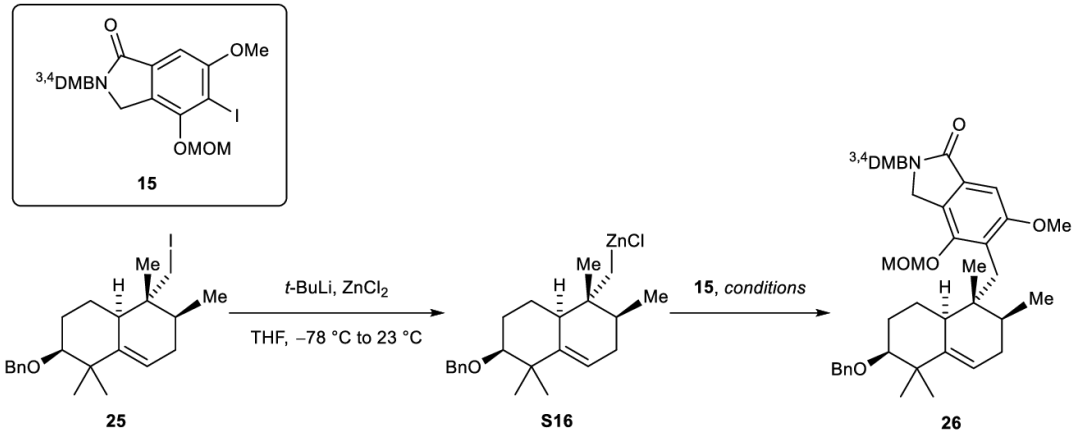
^{13}C NMR (201 MHz, $CDCl_3$): δ = 143.2, 139.5, 128.3, 127.6, 127.3, 118.1, 82.9, 70.3, 41.1, 41.0, 37.4, 35.2, 31.6, 29.3, 25.9, 23.4, 22.2, 19.9, 14.6, 12.4.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2960, 2871, 1453, 1380, 1231, 1182, 1110, 907, 732.

HRMS (EI) calc. for $C_{22}H_{31}{}^{127}IO$ $[M]^+$: 438.1414; found: 438.1419.

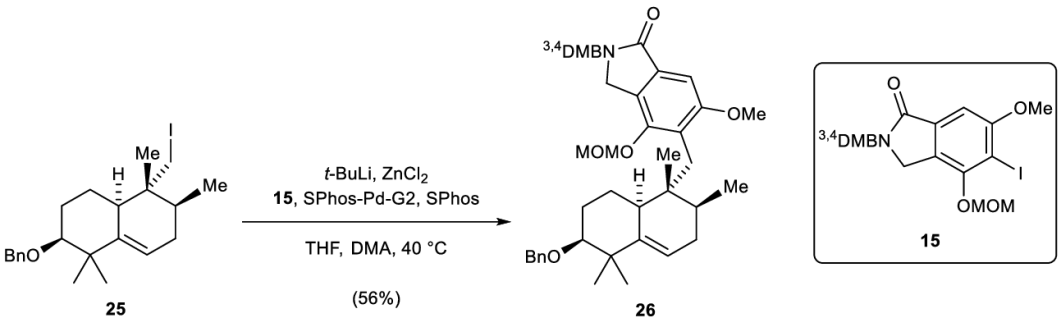
$[\alpha]_D^{20}$ = +6.25° (c = 0.80, CH_2Cl_2).

Cyclization precursor 26



Supplementary Table 1 Conditions investigated for the sp^2–sp^3 Negishi cross coupling. n.r.: no reaction; [1] isolated yield of analytically pure product, [2] 60 µmol (**15**) scale, [3] 870 µmol (**15**) scale

Entry	Catalyst (20 mol%)	Additive	Solvent	Temperature	Yield
1	$Pd(dba)_2$, SPhos	-	THF	23 °C to 60 °C	n.r.
2	$Pd(dba)_2$, SPhos	DMA (25vol%)	THF	23 °C to 60 °C	n.r.
3	$Pd(PPh_3)_4$	-	THF	23 °C to 60 °C	n.r.
4	$Pd(PPh_3)_4$	DMA (25vol%)	THF	23 °C to 60 °C	n.r.
5	Pd-SPhos-G2, SPhos	-	THF	60 °C	n.r.
6	Pd-SPhos-G2, SPhos	DMA (25vol%)	THF	60 °C	37%[1]
7	Pd-SPhos-G2, SPhos	-	THF	23 °C	n.r.
8	Pd-SPhos-G2, SPhos	DMA (25vol%)	THF	40 °C	61%[1,2]
9	Pd-SPhos-G2, SPhos	DMA (25vol%)	THF	40 °C	56%[1,3]



Note: Tetrahydrofuran was dried according to the procedure described by B. Williams prior to use.[13]

To a mixture of alkyl iodide **25** (554 mg, 1.26 mmol, 1.45 equiv) and a solution of zinc chloride (1.00 M in tetrahydrofuran, 1.39 mL, 1.39 mmol, 1.60 equiv) in tetrahydrofuran (1.2 mL) was added dropwise a solution of tert-butyllithium (1.50 M in pentane, 1.80 mL, 2.70 mmol, 3.10 equiv) at –78 °C. After 50 min, the mixture was allowed to warm to 23 °C. After 20 min, the mixture was added to a mixture of aryl iodide **15** (435 mg, 870 µmol, 1 equiv), SPhos (71.3 mg, 174 µmol, 0.20 equiv) and SPhos-Pd-G2 (125 mg, 174 µmol, 0.20 equiv) in tetrahydrofuran (2.2 mL) and freshly distilled (over CaH_2) N,N-dimethylacetamide (2.2 mL) and the reaction mixture was directly placed in a preheated oil bath at 40 °C. After 7 h, the reaction mixture was allowed to cool to 23 °C, and ethyl acetate (50 mL) and saturated aqueous ammonium chloride solution (60 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (2 × 60 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (70 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in benzene) to yield **26** (332 mg, 56%) as a yellow foam.

TLC (50% ethyl acetate in hexanes): R_f = 0.14 (UV, CAM).

^{1}H NMR (599 MHz, $CDCl_3$): δ = 7.30–7.26 (m, 4H), 7.24–7.21 (m, 1H), 7.15 (s, 1H), 6.88–6.86 (m, 2H), 6.84–6.82 (m, 1H), 5.46–5.41 (m, 1H), 4.99 (s, 2H), 4.76–4.69 (m, 2H), 4.48 (d, J = 12.5 Hz, 1H), 4.36–4.27 (m, 2H), 4.25 (d, J = 12.5 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.49 (s, 3H), 3.03–3.01 (m, 1H), 2.92 (d, J = 12.9 Hz, 1H), 2.66 (d, J = 12.9 Hz, 1H), 2.59–2.55 (m 1H), 1.91–1.85 (m, 2H), 1.61–1.56 (m, 1H), 1.55–1.51 (m, 1H), 1.44–1.35 (m, 1H), 1.22–1.14 (m, 1H), 1.07 (s, 3H), 1.01 (d, J = 6.7 Hz, 3H), 0.96 (s, 3H), 0.85–0.78 (m, 1H), 0.76 (s, 3H).

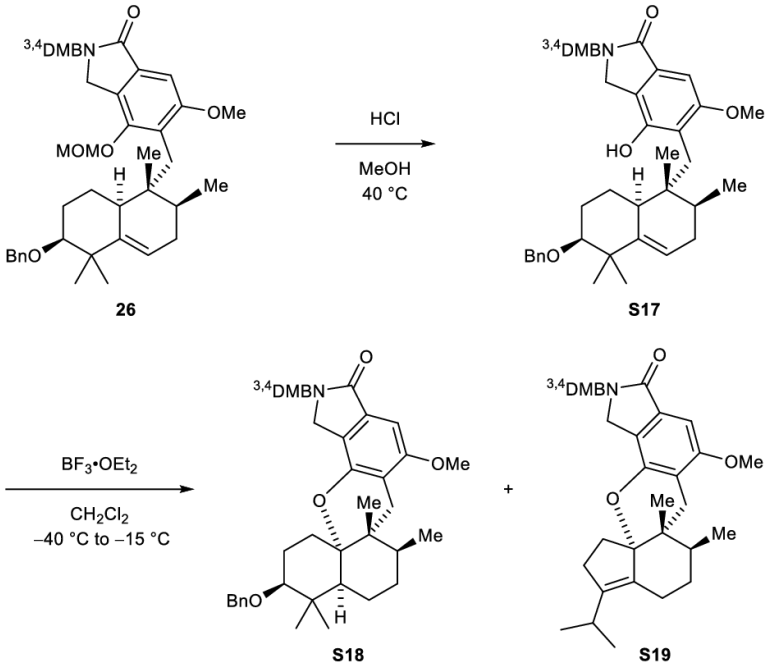
^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.4, 160.1, 152.4, 149.4, 148.7, 144.5, 139.4, 132.6, 129.9, 128.2, 127.8, 127.3, 126.6, 123.8, 120.7, 117.5, 111.6, 111.3, 100.5, 97.6, 82.7, 70.2, 57.1, 56.1, 56.1, 55.9, 48.6, 46.5, 42.0, 41.4, 41.3, 38.9, 35.4, 32.0, 28.5, 25.8, 24.5, 23.8, 16.5, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2933, 1686, 1514, 1464, 1259, 1259, 1237, 1152, 1055, 735.

HRMS (EI) calc. for $C_{42}H_{53}NO_7$ $[M]^+$: 683.3817; found: 683.3800.

$[\alpha]_D^{20}$ = +22.4° (c = 0.19, CH_2Cl_2).

Pentacycle S17 and S18



A solution of hydrochloric acid (~1.25 M in methanol, 10 mL) was added to a solution of **26** (290 mg, 424 µmol, 1 equiv) in dichloromethane (5 mL) and the reaction mixture was heated to 40 °C. After 1 h, the reaction mixture was diluted with dichloromethane (30 mL) and saturated aqueous sodium bicarbonate solution (70 mL) was added. The layers were separated, the aqueous layer was extracted with dichloromethane (3 × 60 mL) and the combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated to yield **S17** as a yellow foam that was directly used in the following step without further purification.

A solution of boron trifluoride diethyl etherate (48% in diethyl ether, 1.11 mL, 4.24 mmol, 10.0 equiv) was added dropwise to a solution of the crude phenol **S17** (271 mg, 424 µmol, 1 equiv) in dichloromethane (40 mL) at –40 °C and the reaction mixture was allowed to slowly warm to –15 °C over a period of 1 h. After 5 h, saturated aqueous sodium bicarbonate solution (50 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered through a short plug of silica to yield a mixture of **S18** (83%) and rearranged **S19** (17%) as a colorless foam that was used in the following step without further purification.

Analytically pure samples of **S18** and **S19** were obtained by normal-phase semi-preparative HPLC purification using 5% i-propanol in n-heptane as eluent (flow rate: 15 mL/min; column: Microsorb 60-8 Si Dynamax 250 × 21.4mm (R00083121C); detection: 254 nm; retention times: 21.9 min for **S18** and 23.3 min for **S19**) to give **S18** as colorless foam and **S19** as colorless solid. Recrystallization of **S19** from diethyl ether gave crystals suitable for single-crystal X-ray diffraction.

For S18:

TLC (50% ethyl acetate in benzene): R_f = 0.30 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.32 (m, 4H), 7.30–7.26 (m, 1H), 6.91 (s, 1H), 6.86–6.79 (m, 3H), 4.95 (d, J = 14.8 Hz, 1H), 4.62 (d, J = 12.1 Hz, 1H), 4.46 (d, J = 14.8 Hz, 1H), 4.36 (d, J = 12.1 Hz, 1H), 4.21–4.08 (m, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.23–3.07 (m, 2H), 2.27–2.10 (m, 4H), 2.06–1.99 (m, 1H), 1.85–1.69 (m, 3H), 1.66–1.58 (m, 1H), 1.56–1.50 (m, 1H), 1.32 (d, J = 13.5 Hz, 1H), 1.10 (d, J = 7.4 Hz, 3H), 1.00–0.94 (m, 6H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.2, 158.6, 149.4, 148.6, 147.3, 139.7, 131.7, 130.2, 128.3, 127.2, 127.2, 121.0, 120.4, 114.0, 111.3, 111.1, 95.9, 84.1, 82.4, 71.7, 56.1, 56.1, 55.9, 47.6, 46.4, 45.0, 39.8, 38.6, 37.7, 32.3, 30.7, 28.0, 27.1, 24.4, 23.8, 21.0, 20.4, 17.3.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2958, 1688, 1606, 1515, 1464, 1368, 1263, 1121, 1084, 737.

HRMS (EI) calc. for $C_{40}H_{49}NO_6$ $[M]^+$: 639.3554; found: 639.3557.

$[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ = +90.1° (c = 0.69, CH_2Cl_2).

For S19:

TLC (50% ethyl acetate in benzene): R_f = 0.30 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (s, 1H), 6.87–6.84 (m, 2H), 6.81 (d, J = 8.4 Hz, 1H), 4.69 (s, 2H), 4.10 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 2.96 (d, J = 18.1 Hz, 1H), 2.83–2.72 (m, 1H), 2.46–2.38 (m, 1H), 2.37–2.31 (m, 1H), 2.28 (d, J = 18.1 Hz, 1H), 2.23–2.09 (m, 2H), 2.08–2.00 (m, 1H), 1.79–1.69 (m, 1H), 1.66–1.61 (m, 1H), 1.47 (d, J = 12.6 Hz, 1H), 1.30–1.25 (m, 1H), 1.03 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 6.8 Hz, 3H), 0.78 (s, 3H), 0.75 (d, J = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.2, 158.6, 149.3, 148.9, 148.6, 143.4, 131.9, 131.6, 130.3, 121.8, 120.8, 113.6, 111.6, 111.0, 96.1, 95.2, 56.1, 56.0, 56.0, 47.4, 46.5, 37.7, 32.0, 31.6, 30.5, 29.3, 28.0, 27.1, 22.4, 22.2, 20.7, 16.0, 15.8.

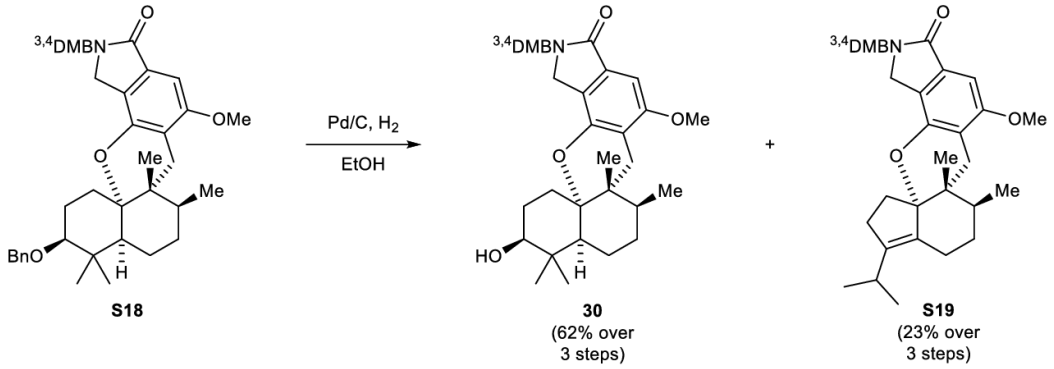
IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2930, 1680, 1602, 1466, 1365, 1258, 1144, 1106, 1024, 764.

HRMS (EI) calc. for $C_{33}H_{41}NO_5$ $[M]^+$: 531.2979; found: 531.2976.

$[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ = –54.3° (c = 0.47, CH_2Cl_2).

Melting point: 175 °C

Neopentylic alcohol 30



S18 **30** (62% over 3 steps) **S19** (23% over 3 steps)

A crude mixture of **S18** and **S19** (424 µmol, 1 equiv) in ethanol (20 mL) was treated with palladium on carbon (10 wt.%, 451 mg, 424 µmol, 1.00 equiv) at 23 °C. An atmosphere of hydrogen was maintained by sparging with a stream of pure hydrogen gas through a stainless steel needle for 2 min and vigorous stirring of the suspension was then continued under hydrogen atmosphere at 23 °C. After 14 h, the reaction mixture was filtered through a pad of Celite® and the filter cake was thoroughly rinsed with dichloromethane (70 mL). The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in benzene initially, grading to 50% ethyl acetate in benzene) to give alcohol **30** (145 mg, 62% over 3 steps) as a colorless foam and **S19** (59 mg, 26% over 2 steps) as a colorless foam. The obtained analytical data for **30** were in full agreement with those values previously reported.[14]

TLC (benzene with 50% EtOAc): R_f = 0.32 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (s, 1H), 6.87–6.79 (m, 3H), 4.94 (d, J = 14.8 Hz, 1H), 4.47 (d, J = 14.8 Hz, 1H), 4.21–4.07 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.52 (s, 1H), 3.14 (d, J = 18.2 Hz, 1H), 2.48–2.35 (m, 1H), 2.30–2.21 (m, 1H), 2.22–2.16 (m, 1H), 2.12–1.97 (m, 2H), 1.81–1.71 (m, 2H), 1.69–1.59 (m, 2H), 1.59–1.57 (m, 1H), 1.57–1.52 (m, 1H), 1.33 (d, J = 12.2 Hz, 1H), 1.12 (d, J = 7.5 Hz, 3H), 0.96 (s, 3H), 0.95 (s, 3H), 0.90–0.85 (m, 3H).

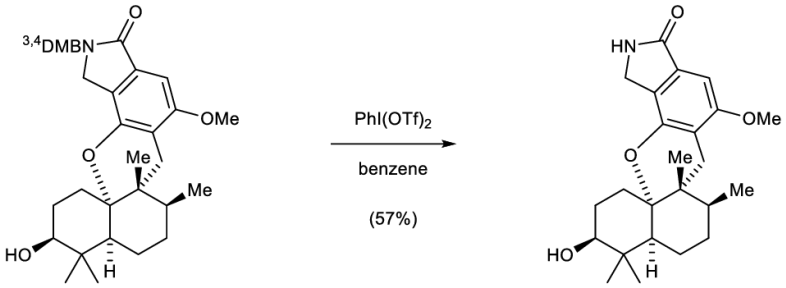
^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.1, 158.4, 149.3, 148.5, 147.1, 131.7, 130.0, 120.8, 120.3, 113.8, 111.2, 111.1, 95.9, 83.8, 74.6, 56.0, 55.9, 55.8, 47.5, 46.3, 44.7, 39.5, 37.9, 37.6, 32.2, 30.3, 28.1, 26.3, 25.9, 24.1, 23.7, 20.2, 17.1.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3447, 2935, 2871, 1673, 1606, 1515, 1463, 1260, 1120, 974.

HRMS (EI) calc. for $C_{33}H_{43}NO_6$ $[M]^+$: 549,3085; found: 549.3093.

$[\alpha]_D^{20}$ = +106.0 ° (c = 0.20, $CHCl_3$); lit. $[\alpha]_D^{28}$ = +71.7 ° (c = 2.82, $CHCl_3$)[14]

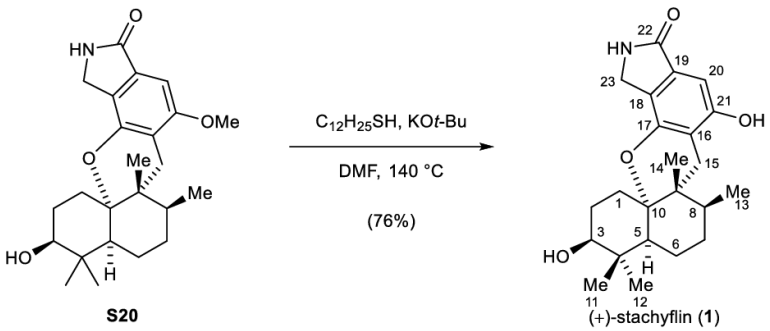
O-Methyl-stachyflin (S20)



30 **S20**

Phenyliodine(III) bis(trifluoroacetate) (PIFA) (1.19 g, 2.77 mmol. 16.0 equiv) was added in small portions (1 equiv every 30 min) to a solution of **30** (95.0 mg, 173 µmol, 1 equiv) in benzene (24 mL). After 10 h, saturated aqueous sodium thiosulfate solution was added (60 mL) and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution. The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (1% methanol in dichloromethane initially, grading to 5% methanol in dichloromethane) to give **S20** (39.0 mg, 57%) as a colorless solid. The obtained analytical data for **30** were in full agreement with those previously reported.[14]

(+)-Stachyflin (1)



Potassium tert-butoxide (25.3 mg, 225 µmol, 3.00 equiv) was added to a solution of O-methyl-stachyflin (**S20**) (30.0 mg, 75.1 µmol, 1 equiv) and 1-dodecanethiol (71.9 µL, 30.0 µmol, 4.00 equiv) in N,N-dimethylformamide (3 mL) at 23 °C. After 5 min, the bright yellow solution was heated to 140 °C. After 75 min, the dark orange reaction mixture was allowed to cool to 23 °C and saturated aqueous ammonium chloride solution (50 mL) was added. The mixture was extracted with ethyl acetate (4 × 40 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (2 × 40 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (1% methanol in dichloromethane initially, grading to 5% methanol in dichloromethane) to yield (+)-stachyflin (**1**) (22.1 mg, 76%) as a colorless solid.

TLC (5% methanol in dichloromethane): R_f = 0.19 (UV, CAM).

^{1}H NMR (599 MHz,DMSO-d6): δ = 9.65 (s, 1H, Ar-OH), 8.26 (s, 1H, N-H), 6.60 (s, 1H, H-20), 4.43 (s, 1H), 4.16 (dd, $^2J_{23A/23B}$ = 17.0 Hz, $^3J_{23A/NH}$ = 1.1 Hz, 1H, H-23$_A$), 4.05 (dd, $^2J_{23B/23A}$ = 17.0 Hz, $^3J_{23B/NH}$ = 1.1 Hz, 1H, H-23$_B$), 3.07 (d, $^2J_{15A/15B}$ = 17.8 Hz, 1H, H-15$_A$), 3.33 (m, 1H, H-3; re-assigned based on HSQC correlations), 2.37–2.30 (m, 1H, H-2$_A$), 2.25–2.18 (m, 1H, H-1$_A$), 2.18–2.11 (m, 1H, H-6$_A$), 2.09 (d, $^2J_{15B/15A}$ = 17.8 Hz, 1H, H-15$_B$), 2.01–1.93 (m, 1H, H-7$_A$), 1.75–1.71 (m, 1H, H-8), 1.67–1.61 (m, 1H, H-6$_B$), 1.59–1.51 (m, 2H, H-1$_B$, H-2$_B$), 1.46 (dd, $^3J_{5/6A/6B}$ = 13.0 Hz, $^3J_{5/6A/6B}$ = 3.9 Hz, 1H, H-5), 1.27 –1.24 (m, 1H, H-7$_B$), 1.09 (d, $^3J_{13/8}$ = 7.5 Hz, 3H, H-13), 0.92 (s, 3H, H-14), 0.88 (s, 3H, H-12), 0.83 (s, 3H, H-11).

^{13}C NMR (101 MHz,DMSO-d6): δ = 170.4 (C-22), 155.9 (C-21), 147.2 (C-17), 131.6 (C-19), 120.8 (C-18), 112.1 (C-16), 99.1 (C-20), 83.3 (C-10), 72.2 (C-3), 44.4 (C-5), 42.6 (C-23), 39.1 (C-8; re-assigned based on HSQC correlations), 37.5 (C-4), 37.1 (C-9), 32.0 (C-15), 30.1 (C-11), 27.6 (C-7), 27.1 (C-12), 25.8 (C-2), 23.5 (C-1), 23.5 (C-6), 20.0 (C-14), 17.0 (C-13).

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3350, 2927, 2356, 2334, 1693, 1600, 1478, 1358, 1066, 974.

HRMS (EI) calc. for $C_{23}H_{31}NO_4$ $[M]^+$: 385.2248; found: 385.2250.

$[\alpha]_D^{20}$ = +129.3 ° (c = 0.53, MeOH); lit. $[\alpha]_D^{24.5}$ = +138.7 ° (c = 1.0, MeOH) (+)-stachyflin.[15]

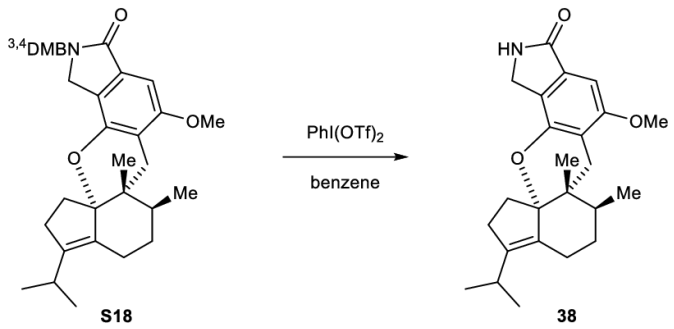
Supplementary Table 2 Comparison of ^{1}H NMR data for synthetic and natural (+)-stachyflin (**1**).

Proton	Synthetic (599 MHz, DMSO-d6)	Natural (600 MHz, DMSO-d6)[15]	Δ: δ (ppm)
1A	2.25–2.18 (m, 1H)	2.21 (m, 1H)	+ 0.01
1B	1.59–1.51 (m, 2H)	1.57 (m, 1H)	– 0.01
2A	2.37–2.30 (m, 1H)	2.34 (m, 1H)	– 0.01
2B	1.59–1.51 (m, 2H)	1.54 (m, 1H)	± 0.00
3	3.33 (m, 1H)	3.34 (m, 1H)	– 0.01
5	1.46 (dd, J = 13.0, 3.9 Hz, 1H)	1.46 (dd, J = 13.0, 3.0 Hz, 1H)	± 0.00
6A	2.18–2.11 (m, 1H)	2.12 (m, 1H)	+ 0.03
6B	1.67–1.61 (m, 1H)	1.64 (m, 1H)	± 0.00
7A	2.01–1.93 (m, 1H)	1.97 (m, 1H)	± 0.00
7B	1.27–1.24 (m, 1H)	1.25 (m, 1H)	± 0.01
8	1.75–1.71 (m, 1H)	1.73 (m, 1H)	± 0.00
11	0.83 (s, 3H)	0.83 (s, 3H)	± 0.00
12	0.88 (s, 3H)	0.89 (s, 3H)	– 0.01
13	1.09 (d, J = 7.5 Hz, 3H)	1.09 (d, J = 7.5 Hz, 3H)	± 0.00
14	0.92 (s, 3H)	0.92 (s, 3H)	± 0.00
15A	3.07 (d, J = 17.8 Hz, 1H)	3.07 (d, J = 17.9 Hz, 1H)	± 0.00
15B	2.09 (d, J = 17.8 Hz, 1H)	2.09 (d, J = 17.9 Hz, 1H)	± 0.00
20	6.60 (s, 1H)	6.61 (s)	– 0.01
23A	4.16 (dd, J = 17.0, 1.1 Hz, 1H)	4.16 (d, J = 16.8 Hz, 1H)	± 0.00
23B	4.05 (dd, J = 17.0, 1.1 Hz, 1H)	4.06 (d, J = 16.8 Hz, 1H)	– 0.01
Alk-OH	4.43 (s, 1H)	4.46 (d, J = 3.0 Hz, 1H)	– 0.03
Ar-OH	9.65 (s, 1H)	9.70 (s)	– 0.05
NH	8.26 (s, 1H)	8.29 (s)	– 0.03

Supplementary Table 3 Comparison of ^{13}C NMR data for synthetic and natural (+)-stachyflin (**1**).

Carbon	Synthetic (101 MHz, DMSO-d6)	Natural (150 MHz, DMSO-d6)[15]	Δ: δ (ppm)
1	23.5	23.4	+ 0.1
2	25.8	25.6	+ 0.1
3	72.2	72.1	+ 0.1
4	37.5	37.3	+ 0.2
5	44.4	44.2	+ 0.2
6	23.5	23.3	+ 0.2
7	27.6	27.5	+ 0.1
8	39.1	39.0	+ 0.1
9	37.1	37.0	+ 0.1
10	83.3	83.2	+ 0.1
11	30.1	30.0	+ 0.1
12	27.1	26.9	+ 0.2
13	17.0	16.9	+ 0.1
14	20.0	19.8	+ 0.2
15	32.0	31.8	+ 0.2
16	112.1	111.9	+ 0.2
17	147.2	147.1	+ 0.1
18	120.8	120.7	+ 0.1
19	131.6	131.5	+ 0.1
20	99.1	99.0	+ 0.1
21	155.9	155.8	+ 0.1
22	170.4	170.4	± 0.0
23	42.6	42.4	+ 0.2

Isoindole-3-one 38



S18 **38**

Phenyliodine(III) bis(trifluoroacetate) (228 mg, 530 µmol, 10.0 equiv) was added to a solution of **S18** (28.2 mg, 53.0 µmol, 1 equiv) in benzene (5 mL). After 18 h, additional phenyliodine(III) bis(trifluoroacetate) (PIFA) (182 mg, 424 µmol. 8.00 equiv) was added in small portions over a period of 4 h (2 equiv/h). After 1 h, saturated aqueous sodium thiosulfate solution (50 mL) was added and the biphasic mixture was extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (2× 80 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentered. The residue was filtered through a plug of silica, the filtercake was rinsed with a mixture of 5% methanol in dichloromethane and used without further purification. An analytically pure sample of **38** was obtained by normal-phase semi-preparative HPLC purification using 10% iso-propanol in n-heptane as eluent (flow rate: 15 mL/min; column: Microsorb 60-8 Si Dynamax 250 × 21.4mm (R00083121C); detection: 254 nm; retention time: 13.7 min).

TLC (5% methanol in dichloromethane): R_f = 0.31 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (s, 1H), 6.23 (s, 1H), 4.29 (s, 2H), 3.87 (s, 3H), 2.99 (d, J = 18.1 Hz, 1H), 2.86–2.75 (m, 1H), 2.51–2.42 (m, 1H), 2.42–2.34 (m, 1H), 2.31 (d, J = 18.1 Hz, 1H), 2.27–2.13 (m, 2H), 2.12–2.03 (m, 1H), 1.82–1.75 (m, 1H), 1.72–1.64 (m, 1H), 1.56–1.46 (m, 1H), 1.36–1.24 (m, 1H), 1.06 (d, J = 6.9 Hz, 3H), 1.02 (d, J = 6.9 Hz, 3H), 0.81 (s, 3H), 0.77 (d, J = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.2, 158.7, 149.2, 143.4, 132.0, 130.7, 124.3, 114.1, 95.8, 95.2, 56.0, 43.4, 37.7, 32.1, 31.6, 30.5, 29.3, 28.0, 27.1, 22.5, 22.2, 20.8, 16.1, 15.8.

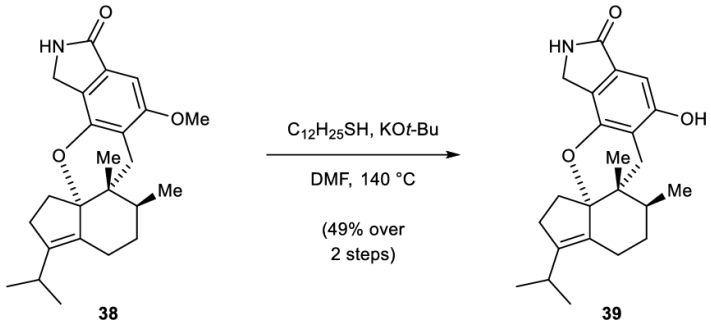
IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2926, 2971, 1697, 1583, 1573, 1427, 1378, 1174, 1001, 934.

HRMS (EI) calc. for $C_{24}H_{31}NO_3$ $[M]^+$: 381.2298; found: 381.2296.

$[\boldsymbol{\alpha}]_D^{20}$ = –14.6° (c = 0.27, CH_2Cl_2).

Melting point: 143–150 °C

Phenol 39



Potassium tert-butoxide (29.7 mg, 265 µmol, 5.00 equiv) was added to a solution of crude **38** (20.2 mg, 53.0 µmol, 1 equiv) and 1-dodecanethiol (76.2 µL, 318 µmol, 6.00 equiv) in N,N-dimethylformamide (0.9 mL) at 23 °C. After 5 min, the bright yellow suspension was heated to 140 °C. After 45 min, the dark orange reaction mixture was allowed to cool to 23 °C and saturated aqueous ammonium chloride solution (30 mL) was added and the aqueous layer was extracted with ethyl acetate (4 × 30 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (2 × 40 mL), the washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered through a short plug of silica, the filtercake was rinsed with a mixture of 5% methanol in dichloromethane and was purified by normal-phase semi-preparative HPLC purification using 5% iso-propanol in n-heptane grading to 15% iso-propanol in n-heptane over 30 min as eluent (flow rate: 15 mL/min; column: Microsorb 60-8 Si Dynamax 250 × 21.4mm (R00083121C); detection: 254 nm; retention times: 14.3 min) to give **39** (9.0 mg, 49% over 2 steps) as a colorless solid

TLC (5% methanol in dichloromethane): R_f = 0.28 (UV, CAM).

^{1}H NMR (599 MHz, $CDCl_3$): δ = 7.07 (s, 1H), 6.41 (s, 1H), 4.28 (s, 2H), 3.01 (d, J = 17.8 Hz, 1H), 2.85–2.76 (m, 1H), 2.52–2.42 (m, 1H), 2.42–2.34 (m, 2H), 2.26–2.15 (m, 2H), 2.11–2.05 (m, 1H), 1.86–1.76 (m, 1H), 1.73–1.67 (m, 1H), 1.56–1.46 (m, 1H), 1.35–1.24 (m, 1H), 1.06 (d, J = 6.9 Hz, 3H), 1.02 (d, J = 6.9 Hz, 3H), 0.81 (s, 3H), 0.77 (d, J = 6.9 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 172.5, 155.4, 149.5, 143.5, 132.0, 130.5, 123.4, 113.3, 100.9, 95.4, 43.6, 37.8, 32.1, 31.6, 30.5, 29.3, 27.9, 27.1, 22.5, 22.2, 20.8, 16.1, 15.8.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3234, 2935, 2959, 1683, 1609, 1465, 1360, 1240, 1076, 934.

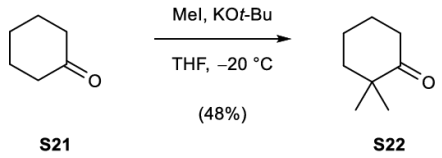
HRMS (EI) calc. for $C_{23}H_{28}NO_3$ $[M]^+$: 367.2142; found: 367.246.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –85.3° (c = 0.15, CH_2Cl_2).

Melting point: 156–161 °C

Synthesis of Aldehyde 33

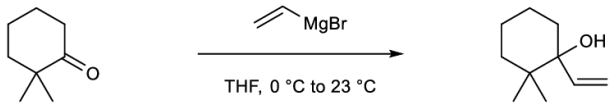
2,2-Dimethylcyclohexan-1-one (S22)



S21 **S22**

Note: The alkylation was carried out in three parallel 12.3 g batches.
Potassium tert-butoxide (29.6 g, 263 mmol, 2.10 equiv) was added to a solution of cyclohexanone (**S21**) (12.3 g, 125 mmol, 1 equiv) and methyl iodide (37.3 g, 263 mmol, 2.10 equiv) in tetrahydrofuran (600 mL) at −20 °C. After 15 h, saturated aqueous ammonium chloride solution (200 mL) was added to the reaction mixture. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 150 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% diethyl ether in pentane) to yield **S22** (7.67 g, 48%) as a colorless oil. The obtained analytical data were in full agreement with those previously reported.[16]

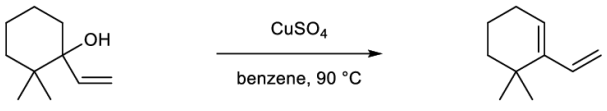
2,2-Dimethyl-1-vinylcyclohexan-1-ol (S23)



S22 **S23**

A solution of **S22** (23.0 g, 182 mmol, 1 equiv) in tetrahydrofuran (90 mL) was added dropwise to a solution of vinylmagnesium bromide (1 M in tetrahydroduran, 219 mL, 219 mmol, 1.20 equiv) over a period of 45 min at 0 °C. After 1.5 h, saturated aqueous ammonium chloride solution (500 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (2 × 300 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to yield crude **S23** as a yellow oil. The residue was used without further purification in the next step.

Diene 31

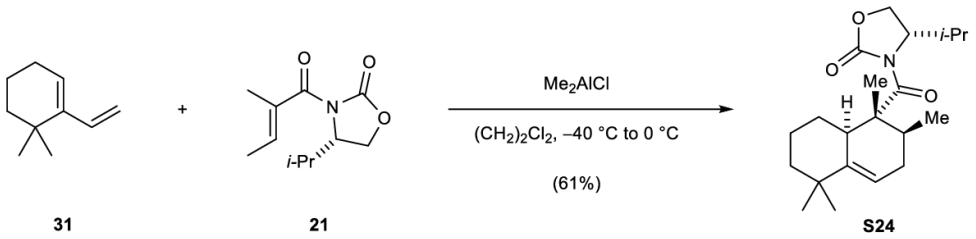


S23 (71% over 2 steps) **31**

Note: $CuSO_4 \cdot 5H_2O$ was dried over night in a 140 °C oven.

To a solution of crude **S23** (28.1 g, 182 mmol, 1 equiv) in benzene (400 mL) was added anhydrous copper(II) sulfate (63.9 g, 400 mmol, 2.20 equiv) and the reaction mixture was heated to 90 °C under Dean-Stark conditions. After 16 h, the reaction mixture was allowed to cool to 23 °C, filtered through a pad of Celite® and was washed thoroughly with n-pentane. The filtrate was carefully concentrated (>220 mbar, 30 °C) and the residue was purified by flash-column chromatography on silica gel (n-pentane) to yield **31** as a yellow oil (17.7 g, 71% over 2 steps). The obtained analytical data were in full agreement with those previously reported.[17]

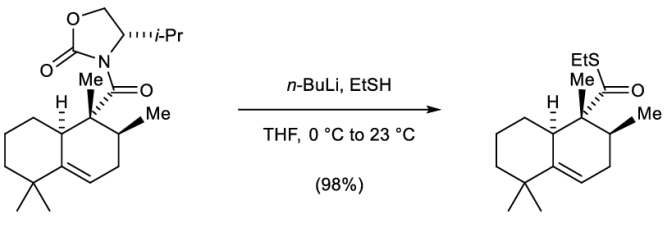
5,6-Dehydrodecalin S24



31 **21** **S24**

5,6-Dehydrogecalin **S24** was prepared according to the procedure described by A. J. Minnaard[18]:
A solution of dimethylaluminium chloride (1 M in hexanes, 93.0 mL, 93.0 mmol, 2.20 equiv) was added dropwise to a solution of **21** (9.83 g, 46.5 mmol, 1.10 equiv) in 1,2-dichloroethane (250 mL) over a period of 15 min at −40 °C. After 20 min, a solution of **30** (8.00 g, 42.3 mmol, 1 equiv) in 1,2-dichloroethane (100 mL) was added over a period of 15 min to the reaction mixture. After complete addition, the reaction mixture was allowed to warm to 23 °C. After 36 h, aqueous hydrogen chloride solution (1 M, 100 mL) was carefully added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (14% diethyl ether in n-pentane) to yield **S24** as a yellow highly viscous oil (9.02 g, 61%). The obtained analytical data were in full agreement with those previously reported.

Thioester 32

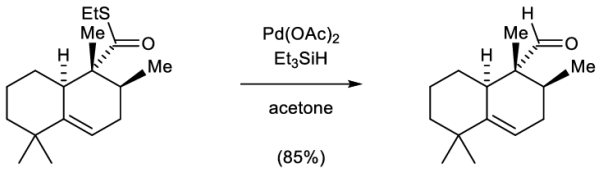


S24 **32**

A solution of n-butyllithium (2.40 M in hexanes 50.8 mL, 122 mmol, 4.70 equiv) was added dropwise to a solution of ethanethiol (11.3 mL, 153 mmol, 5.90 equiv) in tetrahydrofuran (250 mL) at 0 °C. After complete addition, the reaction mixture was slowly allowed to warm to 23 °C. After 30 min, a solution of **S24** (9.02 g,

26.0 mmol, 1 equiv) in tetrahydrofuran (70 mL) was added. After 7 h, diethyl ether (100 mL) and saturated aqueous ammonium chloride solution (100 mL) were added. The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 100 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (2% diethyl ether in n-pentane) to yield **32** as a yellow oil (7.10 g, 98%). The obtained analytical data were in full agreement with those previously reported.[18]

Aldehyde 33

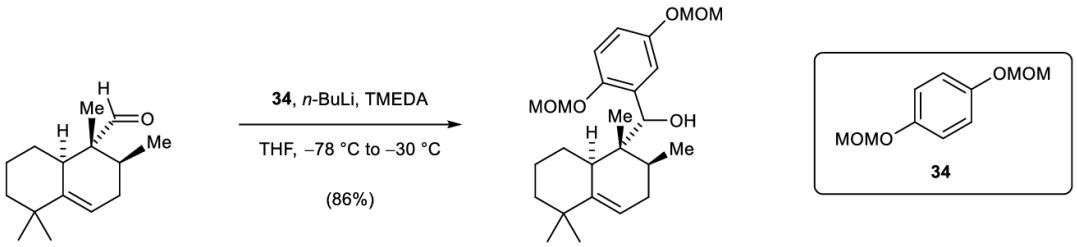


32 **33**

Triethylsilane (1.07 g, 9.20 mmol, 1.20 equiv) was added to a solution of thioester **32** (2.15 g, 7.67 mmol, 1 equiv) and palladium(II) acetate (103 mg, 460 µmol, 0.060 equiv) in acetone (60 mL). After 2.5 h, the dark brown solution was filtered through a plug of silica, the filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (2% ethyl acetate in hexanes) to provide **33** (1.43 g, 85%) as a colorless solid. The obtained analytical data were in full agreement with those previously reported.[18] Recrystallization from diethyl ether gave crystals suitable for single-crystal X-ray diffraction.

Synthesis of (+)-Aureol (2) and 5-epi-Aureol (9)

Benzylic alcohol (S25)



33 **S25**

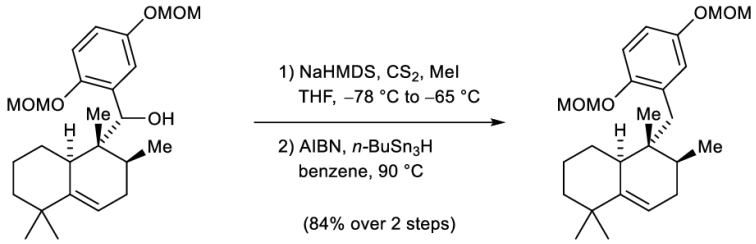
To a solution of **34**[19] (1.16 g, 5.85 mmol, 1.60 equiv) in tetrahydrofuran (8.5 mL) and freshly distilled N,N,N′,N′-tetramethylethane-1,2-diamine (TMEDA) (over CaH_2, 1.65 mL, 11.0 mmol, 3.00 equiv) was added a solution of n-butyllithium (2.40 M in hexanes, 2.28 mL, 5.48 mmol, 1.50 equiv) at –78 °C. After complete addition, the solution was allowed to warm to –30 °C. After 1.5 h, the reaction mixture was cooled to –78 °C and a solution of aldehyde **33** (805 mg, 3.65 mmol, 1 equiv) in tetrahydrofuran (3.5 mL) was added. The reaction mixture was allowed to warm to –30 °C over a period of 2 h, then diethyl ether (40 mL) and saturated aqueous ammonium chloride solution (40 mL) was added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 40 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to yield **S25** (1.32 g, 86%) as a colorless oil. The inconsequential mixture of diastereoisomers was partially characterized by HRMS and IR spectroscopy.

TLC (10% ethyl acetate in hexanes): $R_f = 0.29$ (CAM).

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3496, 2952, 1492, 1381, 1218, 1188, 1150, 1078, 1004, 922.

HRMS (EI) calcd for $C_{25}H_{38}O_5$ $[M]^+$: 418.2714; found: 418.2708.

Methoxymethyl-ether 35



S25 **35**

A solution of sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 15.4 mL, 15.4 mmol, 5.00 equiv) was added dropwise to a solution of **S25** (1.29 g, 3.08 mmol, 1 equiv) in tetrahydrofuran (24 mL) at −78 °C. After 30 min, carbon disulfide (3.72 mL, 61.6 mmol, 20.0 equiv) was added dropwise to the orange solution and the resulting red solution was allowed to warm to −65 °C. After 1 h, methyl iodide (3.84 mL, 61.6 mmol, 20.0 equiv) was slowly added to the reaction mixture. After 1 h, saturated aqueous ammonium chloride solution (20 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered through a plug of silica and the obtained residue was used without further purification.

Note: benzene was degassed via freeze-pump-thaw (three cycles) prior to use.
A solution of the xanthogenate (1.57 g, 3.08 mmol, 1 equiv), 2,2'-azobis(2-methylpropionitrile) (AIBN) (253 mg, 1.54 mmol, 0.500 equiv) and tributyltin hydride (6.72 g, 23.1 mmol, 7.50 equiv) in benzene (50 mL) was heated to 90 °C. After 1.5 h, the reaction mixture was cooled to 23 °C and directly purified by flash-column chromatography on silica gel (hexanes initially, grading to 3% ethyl acetate in hexanes) to yield **35** as a colorless oil (1.05 g, 84% over 2 steps).

TLC (10% ethyl acetate in hexanes): R_f = 0.53 (CAM).

^{1}H NMR (599 MHz, $CDCl_3$): δ = 7.04 (d, J = 8.9 Hz, 1H), 6.91 (d, J = 3.0 Hz, 1H), 6.83 (d, J = 8.9 Hz, 1H), 5.39–5.36 (m, 1H), 5.15 (d, J = 6.6 Hz, 1H), 5.10 (s, 2H), 5.09 (d, J = 6.6 Hz, 1H), 3.49 (s, 3H), 3.47 (s, 3H), 2.82 (d, J = 13.6 Hz, 1H), 2.55 (d, J = 13.6 Hz, 1H), 2.13 (m, 1H), 1.96 (m, 1H), 1.80 (m, 2H), 1.55–1.47 (m, 2H), 1.47–1.42 (m, 1H), 1.39–1.34 (m, 1H), 1.17 m, 1H), 1.04 (d, J = 6.7 Hz, 3H), 1.02 (s, 3H), 0.95 (m, 1H), 0.90 (s, 3H), 0.78 (s, 3H).

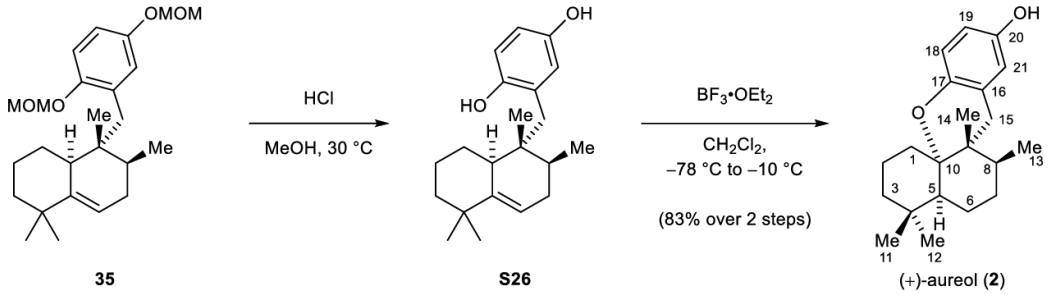
^{13}C NMR (151 MHz, $CDCl_3$): δ = 152.0, 151.6, 146.8, 130.5, 120.5, 115.4, 115.0, 114.8, 95.7, 95.4, 56.1, 56.0, 41.5, 40.3, 39.9, 37.5, 36.5, 34.7, 31.8, 29.9, 29.9, 28.3, 22.7, 16.8, 16.4.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2926, 1495, 1455, 1219, 1189, 1149, 1075, 1010, 922, 81.

HRMS (EI) calcd for $C_{25}H_{38}O_4$ $[M]^+$: 402.2765; found: 402.2757.

$[\alpha]_D^{22}$ = + 28.68° (c = 0.96, CH_2Cl_2).

(+)-Aureol (2)



A solution of hydrochloric acid (~1.25 M in methanol, 9 mL) was added to a solution of **35** (300 mg, 744 µmol, 1 equiv) in dichloromethane (3 mL) and the resulting solution was heated to 30 °C. After 5 h, the reaction mixture was diluted with dichloromethane (25 mL) and saturated aqueous sodium bicarbonate solution (25 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to yield **S26** as a colorless foam that was directly used in the following step.

A solution of boron trifluoride diethyl etherate (48% in diethyl ether, 1.95 mL, 7.44 mmol, 10.0 equiv) was added dropwise to a solution of the crude para-hydroquinone **S26** (234 mg, 744 µmol, 1 equiv) in dichloromethane (30 mL) at –78 °C. After complete addition, the reaction mixture was allowed to warm to –10 °C over a period of 1.5 h. After 2 h at –10 °C, saturated aqueous ammonium chloride solution (20 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to yield (+)-aureol (**2**) (193 mg, 83% over two steps) as a colorless foam.

TLC (20% ethyl acetate in hexanes): R_f = 0.43 (CAM).

^{1}H NMR (800 MHz, $CDCl_3$): δ = 6.61 (d, $^3J_{18/19}$ = 8.6 Hz, 1H, H-18), 6.56 (dd, $^3J_{18/19}$ = 8.6 Hz, $^4J_{18/21}$ = 3.0 Hz, 1H, H-19), 6.49 (d, $^4J_{21/19}$ = 3.0 Hz, 1H), 4.32 (s, 1H, O-H), 3.38 (d, $^2J_{15A/15B}$ = 17 Hz, 1H, H-15$_A$), 2.10–1.99 (m, 2H, 1$_A$, 2$_A$), 1.97 (d, $^2J_{15B/15A}$ = 17 Hz, 1H, H-15$_B$), 1.84–1.75 (m, 2H, H-7), 1.71–1.64 (m, 2H, H-6$_A$, H-8), 1.60–1.53 (m, 1H, H-6$_B$), 1.50–1.45 (m, 1H, H-2$_B$), 1.45–1.40 (m, 2H, H-3$_A$, H-5), 1.37–1.33 (m, 1H, H-1$_B$), 1.20–1.17 (m, 1H, H-3$_B$), 1.11 (d, $^3J_{13/8}$ = 7.5 Hz, 3H, H-13), 1.06 (s, 3H, H-11), 0.92 (s, 3H, H-14), 0.78 (s, 3H, H-14).

^{13}C NMR (201 MHz, $CDCl_3$): δ = 148.3 (C-20), 145.8 (C-17), 122.2 (C-16), 117.2 (C-18), 115.0 (C-19), 114.0 (C-21), 82.3 (C-10), 44.0 (C-5), 39.3 (C-8), 38.1 (C-9), 37.3 (C-15), 33.9 (C-4), 33.8 (C-3), 31.9 (C-12), 29.8 (C-11), 29.3 (C-7), 27.9 (C-1), 22.2 (C-6), 20.2 (C-14), 18.3 (C-2), 17.3 (C-13).

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3344, 2933, 1494, 1450, 1231, 1185, 1171, 1158, 952, 907, 733.

HRMS (EI) calcd for $C_{21}H_{30}O_2$ $[M]^+$: 314.2240; found: 314.2234.

$[\alpha]_D^{20}$ = +73.5 ° (c = 1.19, CCl_4); lit. $[\alpha]_D^{25}$ = +65.0 ° (c = 2.00, CCl_4) (+)-aureol.[20]

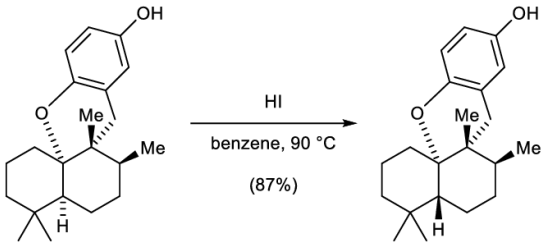
Supplementary Table 4 Comparison of ^{1}H NMR data for natural and synthetic (+)-aureol (**2**).

Proton	Synthetic (800 MHz, $CDCl_3$)	Natural (n.a., $CDCl_3$)[20]	Δ: δ (ppm)
1A	2.10–1.99 (m, 2H)	Not reported	
1B	1.37–1.33 (m, 1H)		
2A	2.10–1.99 (m, 2H)		
2B	1.50–1.45 (m, 1H)		
3A	1.45–1.40 (m, 2H)		
3B	1.20–1.17 (m, 1H)		
5	1.45–1.40 (m, 2H)		
6A	1.71–1.64 (m, 2H)		
6B	1.60–1.53 (m, 1H)		
7	1.84–1.75 (m, 2H)		
8	1.71–1.64 (m, 2H)		
11	1.06 (s, 3H)	1.06 (s, 3H)	± 0.00
12	0.78 (s, 3H)	0.78 (s, 3H)	± 0.00
13	1.11 (d, J = 7.5 Hz, 3H)	1.11 (d, J = 7 Hz, 3H)	± 0.00
14	0.92 (s, 3H)	0.92 (s, 3H)	± 0.00
15A	3.38 (d, 1H)	3.38 (d, J = 16 Hz, 1H)	+ 0.00
15B	1.97 (d, J = 17.0 Hz, 1H),	1.96 (d, J = 16 Hz, 1H)	+ 0.01
18	6.61 (d, J = 8.6 Hz, 1H),	6.62 (m, 2H)	
19	6.56 (dd, J = 8.6, 3.0 Hz, 1H),		
21	6.49 (d, J = 3.0 Hz, 1H),	6.50 (br s, 1H)	– 0.01
OH	4.32 (s, 1H)	Not reported	

Supplementary Table 5 Comparison of ^{13}C NMR data for natural and synthetic (+)-aureol (**2**).

Carbon	Synthetic (201 MHz, $CDCl_3$)	Natural (n.a., $CDCl_3$)[20]	Δ: δ (ppm)
1	27.9	27.9	± 0.0
2	18.3	18.4	– 0.1
3	33.8	33.9	– 0.1
4	33.9	33.9	± 0.0
5	44.0	44.0	± 0.0
6	22.2	22.2	± 0.0
7	29.3	29.3	± 0.0
8	39.3	39.3	± 0.0
9	38.1	38.1	± 0.0
10	82.3	82.4	– 0.1
11	29.8	29.8	± 0.0
12	31.9	31.9	± 0.0
13	17.3	17.3	± 0.0
14	20.2	20.2	± 0.0
15	37.3	37.4	– 0.1
16	122.2	122.2	± 0.0
17	145.8	145.8	± 0.0
18	117.2	117.2	– 0.1
19	115.0	115.2	– 0.2
20	148.3	148.2	+ 0.1
21	114.0	114.2	– 0.2

Epi-aureol (9)

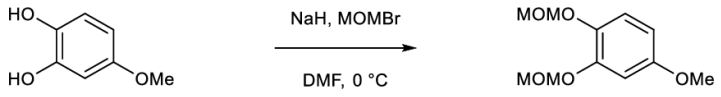


(+)-aureol (**2**) 5-*epi*-aureol (**9**)

A solution of hydroiodic acid (57 wt.% in H_2O, 63.0 µL, 477 µmmol, 10.0 equiv) was added to a solution of (+)-aureol (**2**) (15.0 mg, 47.7 µmol, 1 equiv) in benzene (4 mL) in a pressure tube. The tube was sealed and the reaction mixture was heated to 90 °C. After 24 h, the reaction mixture was cooled to 23 °C and saturated aqueous sodium bicarbonate solution (15 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to yield 5-epi-aureol (**9**) (13.0 mg, 87% over two steps) as a colorless foam. The obtained analytical data were in in full agreement with those values reported in literature.[21]

Synthesis of (+)-Strongylin A (4), 5-epi-Strongylin A (45), 46, 47, 3-Hydroxy-strongylin A (48) and 49

Arene Unit S28



S27 (80%) **S28**

To a solution of **S27**[22] (675 mg, 4.28 mmol, 1 equiv) in N,N-dimethylformamide (25 mL) was added in small portions sodium hydride (60% mineral oil dispersion, 482 mg, 12.0 mmol, 2.50 equiv) at 0 °C. After 30 min, bromomethyl methylether (1.51 g, 12.0 mmol, 2.50 equiv) was added dropwise to the dark green suspension and the resulting mixture was allowed to warm to 23 °C. After 13 h, saturated aqueous ammonium chloride solution (60 mL) and diethyl ether (80 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 60 mL). The combined organic extracts were washed with aqueous saturated sodium chloride solution (50 mL), the washed solution was dried over sodium sulfate, the dried solution was filtered and filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to provide **S28** (879 mg, 80%) as a colorless oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.23 (UV, CAM).

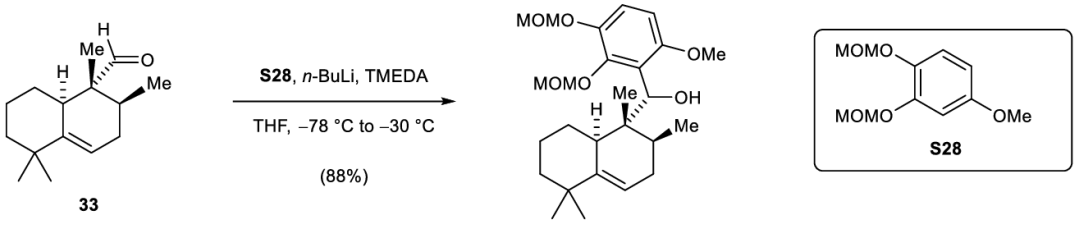
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06 (d, J = 8.8 Hz, 1H), 6.78 (d, J = 2.9 Hz, 1H), 6.47 (dd, J = 8.8, 2.9 Hz, 1H), 5.21 (s, 2H), 5.14 (s, 2H), 3.76 (s, 3H), 3.52 (s, 3H), 3.51 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.5, 148.5, 141.3, 118.4, 106.2, 104.2, 96.5, 95.5, 56.3, 56.2, 55.8.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2902, 2829, 1609, 1506, 1259, 1219, 1150, 1072, 1039, 984, 921.

HRMS (EI) calcd for: $C_{11}H_{16}O_5$ $[M]^+$: 228.0992; found: 228.0989.

Benzylic alcohol S29



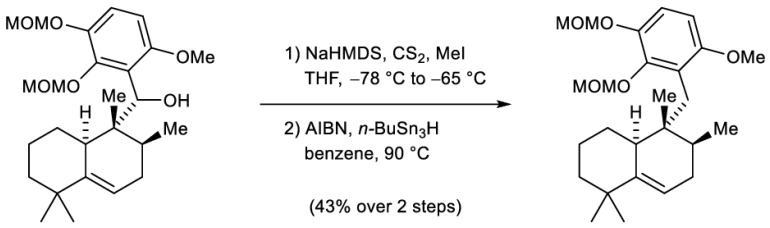
To a solution of **S28** (109 mg, 478 µmol, 1.40 equiv) in tetrahydrofuran (2 mL) and freshly distilled N,N,N′,N′-tetramethylethane-1,2-diamine (over CaH_2, 150 µL, 1.02 mmol, 3.00 equiv) was added a solution of n-butyllithium (2.44 M in hexanes, 128 µL, 443 µmol, 1.30 equiv) at –78 °C. After 10 min, the reaction mixture was allowed to warm to –30 °C. After 1.5 h, the reaction mixture was cooled to –78 °C and a solution of aldehyde **33** (75.2 mg, 341 µmol, 1 equiv) in tetrahydrofuran (1 mL) was added. The reaction mixture was allowed to warm to –30 °C over a period of 2 h. Diethyl ether (15 mL) and saturated aqueous ammonium chloride solution (15 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (20 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to yield **S29** (153 mg, 88%) as a colorless oil. The inconsequential mixture of diastereoisomers was partially characterized by HRMS and IR spectroscopy.

TLC (10% ethyl acetate in hexanes): $R_f = 0.23$ (CAM).

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3552, 2925, 1591, 1483, 1357, 1251, 1152, 1069, 977, 924, 805.

HRMS (EI) calcd for $C_{26}H_{40}O_6$ $[M]^+$: 448.2819; found: 448.2816.

Olefin S30



S29 **S30**

A solution of sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 1.53 mL, 1.53 mmol, 5.00 equiv) was added dropwise to a solution of **S29** (137 mg, 305 µmol, 1 equiv) in tetrahydrofuran (2 mL) at −78 °C. After 30 min, carbon disulfide (370 µL, 610 µmol, 20.0 equiv) was slowly added and the reaction mixture was allowed to warm to −65 °C. After 1 h, methyl iodide (380 µL, 6.10 mmol, 20.0 equiv) was slowly added to the reaction mixture. After 1 h, saturated aqueous ammonium chloride solution (10 mL) and ethyl acetate (10 mL) were added to the reaction mixture, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered through a short plug of silica and the obtained residue was used without further purification.

Note: benzene was degassed via freeze-pump-thaw (three cycles) prior to use.
A degassed solution of the xanthogenate (164 mg, 305 µmol, 1 equiv), 2,2'-azobis(2-methylpropionitrile) (AIBN) (25.0 mg, 152 µmol, 0.500 equiv) and tributyltin hydride (666 mg, 2.29 mmol, 7.50 equiv) in benzene (6 mL) was heated to 90 °C. After 4 h, the reaction mixture was cooled to 23 °C and directly purified by flash-column chromatography on silica gel (hexanes initially, grading to 3% ethyl acetate in hexanes) to yield **S30** as a colorless oil (57.0 mg, 43% over 2 steps).

TLC (20% ethyl acetate in hexanes): R_f = 0.35 (CAM).

^{1}H NMR (800 MHz, C_6D_6): δ = 6.99 (d, J = 8.9 Hz, 1H), 6.28 (d, J = 8.9 Hz, 1H), 5.61–5.54 (m, 1H), 5.15–5.09 (m, 2H), 4.92–4.88 (m, 2H), 3.41 (s, 3H), 3.35 (s, 3H), 3.24 (d, J = 12.9 Hz, 1H), 3.22 (s, 3H), 2.97 (d, J = 12.9 Hz, 1H), 2.90–2.86 (m, 1H), 2.01–1.97 (m, 2H), 1.79–1.74 (m, 1H), 1.61–1.54 (m, 1H), 1.51–1.47 (m, 1H), 1.46–1.40 (m, 2H), 1.27–1.22 (m, 1H), 1.21 (s, 3H), 1.17 (d, J = 6.7 Hz, 3H), 1.16 (s, 3H), 1.06 (s, 3H), 0.94–0.88 (m, 1H).

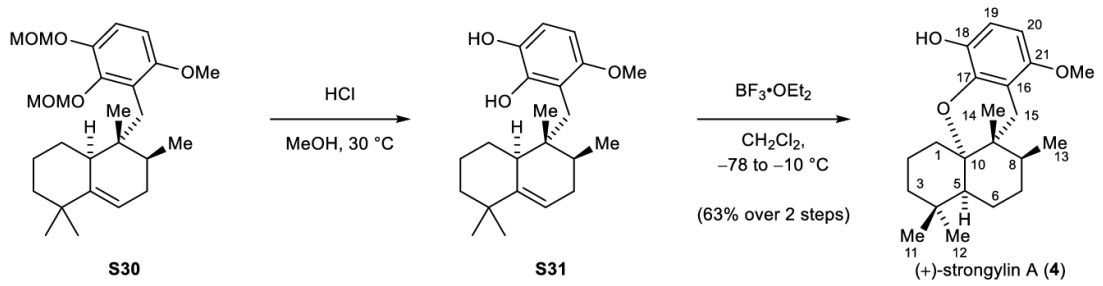
^{13}C NMR (201 MHz, C_6D_6): δ = 154.7, 148.6, 147.7, 144.5, 125.0, 115.8, 115.6, 105.5, 99.6, 96.4, 57.5, 55.8, 55.1, 42.6, 41.9, 41.2, 39.4, 36.9, 35.9, 32.3, 31.5, 30.2, 28.4, 23.4, 16.8, 14.8.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2928, 2837, 1483, 1464, 1250, 1154, 1069, 1038, 983, 951, 801.

HRMS (EI) calcd for $C_{26}H_{40}O_5$ $[M]^+$: 432.2870; found: 432.2865.

$[\alpha]_D^{20}$ = +13.1 ° (c = 5.38, CH_2Cl_2).

(+)-Strongylin A (4)



A solution of hydrochloric acid (~1.25 M in methanol, 4 mL) was added to a solution of **S30** (33.0 mg, 76.0 µmol, 1 equiv) in dichloromethane (2 mL) and the resulting solution was heated to 30 °C. After 6.5 h, the reaction mixture was diluted with dichloromethane (5 mL) and saturated aqueous sodium bicarbonate solution (10 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to yield **S31** as a colorless solid that was directly used in the following step.

A solution of boron trifluoride diethyl etherate (48% in diethyl ether, 140 µL, 534 µmol, 7.00 equiv) was added dropwise to a solution of crude hydroquinone **S31** (26.0 mg, 76.0 µmol, 1 equiv) in dichloromethane (3 mL) at –78 °C and the reaction mixture was allowed to warm to –30 °C over a period of 30 min. After 1.5 h, saturated aqueous ammonium chloride solution (10 mL) and dichloromethane (5 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to yield (+)-strongylin A (**4**) (16.6 mg, 63% over two steps) as a colorless foam.

TLC (20% ethyl acetate in hexanes): R_f = 0.50 (CAM).

^{1}H NMR (400 MHz, C_6D_6): δ = 6.96 (d, $^3J_{19/20}$ = 8.6 Hz, 1H, H-19), 6.13 d, $^3J_{20/19}$ = 8.6 Hz, 1H, H-20), 5.12 (s, 1H, O-H), 3.42 (s, 3H. H-22), 3.23 (d, $^2J_{15A/15B}$ = 17.7 Hz, 1H, H-15$_A$), 2.33 (d, $^2J_{15B/15A}$ = 17.7 Hz, 1H, H-15$_B$), 1.93–1.78 (m, 2H, H-2$_A$, H7$_A$), 1.69–1.51 (m, 3H, H-1$_A$, H-1$_B$, H-8), 1.45–1.36 (m, 2H, H-5, H-6$_A$), 1.33–1.18 (m, 3H, H-2$_B$, H-3$_A$, H-6$_B$), 1.12–1.04 (m, 5H, H-3$_B$, H-7$_B$, H-12), 0.88 (d, $^3J_{13/8}$ = 7.6 Hz, 3H, H-13), 0.82 (s, 3H, H-14), 0.64 (s, 3H, H-11).

^{13}C NMR (101 MHz, C_6D_6): δ = 151.4 (C-21), 139.8 (C-17), 139.6 (C-18), 111.5 (C-19), 110.7 (C-16), 100.9 (C-20), 83.9 (C-10), 55.0 (C-22), 44.0 (C-5), 39.8 (C-8), 38.3 (C-9), 34.0 (C-3), 33.5 (C-4), 32.9 (C-15), 32.2 (C-11), 29.5 (C-1), 29.3 (C-12), 28.0 (C-7), 22.7 (C-6), 20.3 (C-14), 18.9 (C-2), 17.4 (C-13).

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3567, 2953, 1490, 1384, 1264, 1182, 1107, 1089, 946.

HRMS (EI) calcd for $C_{22}H_{32}O_3$ $[M]^+$: 344.2346; found: 344.2346.

$[\alpha]_D^{20}$ = +66.3° (c = 1.46, CH_2Cl_2); lit. $[\alpha]_D^{20}$ = +72.0° (c = 0.012, CH_2Cl_2) (+)-strongylin A.[23]

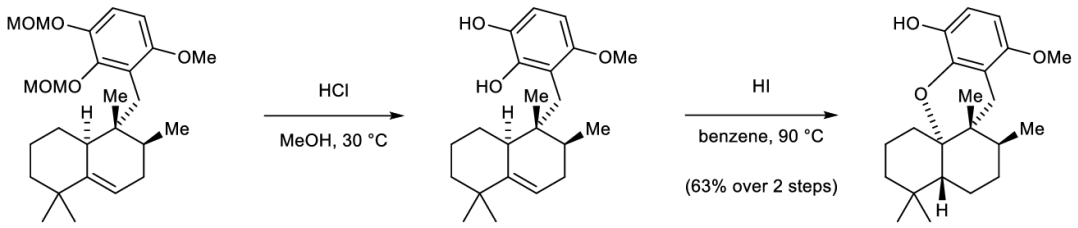
Supplementary Table 6 Comparison of ^{1}H NMR data for natural and synthetic (+)-strongylin A (**4**).

Proton	Synthetic (400 MHz, C_6D_6)	Natural (360 MHz, C_6D_6)[23]	Δ: δ (ppm)
1	1.69–1.51 (m, 3H)	1.66 (2H, m, 2H)	
2A	1.93–1.78 (m, 2H)	1.86 (m, 2H)	± 0.00
2B	1.33–1.18 (m, 3H)	1.32 (m, 1H)	
3A	1.33–1.18 (m, 3H)	1.25 (m, 2H)	
3B	1.12–1.04 (m, 5H)	1.12 (m, 2H)	
5	1.45–1.36 (m, 2H)	1.43 (m, 1H)	
6A	1.45–1.36 (m, 2H)	1.41 (m, 1)H	
6B	1.33–1.18 (m, 3H)	1.25 (m, 2H)	± 0.00
7A	1.93–1.78 (m, 2H)	1.86 (m, 2H)	± 0.00
7B	1.12–1.04 (m, 5H)	1.12 (m ,2H)	
8	1.69–1.51 (m, 3H)	1.60 (m, 1H)	
11	0.64 (s, 3H)	0.65 (s, 3H)	– 0.01
12	1.12–1.04 (m, 5H)	1.09 (s, 3H)	
13	0.88 (d, J = 7.6 Hz, 3H)	0.90 (d, J = 7.6 Hz, 3H)	– 0.02
14	0.82 (s, 3H)	0.82(s, 3H)	± 0.00
15A	3.23 (d, J = 17.7 Hz, 1H)	3.20 (d, J = 7.7 Hz, 1H)	+ 0.03
15B	2.33 (d, J = 17.7 Hz, 1H)c	2.30 (d, J= 7.7 Hz, 1H)	+ 0.03
19	6.96 (d, J = 8.6 Hz, 1H)	6.91 (d, J = 8.6 Hz, 1H)	+ 0.05
20	6.13 (d, J = 8.6 Hz, 1H)	6.13 (d, J = 8.6, 1H)	± 0.00
22	3.42 (s, 3H)	3.44 (s, 3H)	– 0.02
OH	5.12 (s, 1H)	5.12 (s, 1H)	± 0.00

Supplementary Table 7 Comparison of ^{13}C NMR data for natural and synthetic (+)-strongylin A (**4**).

Carbon	Synthetic (101 MHz, C_6D_6)	Natural (90 MHz, C_6D_6)[23]	Δ: δ (ppm)
1	29.5	29.5	± 0.0
2	18.9	18.9	± 0.0
3	34.0	34.0	± 0.0
4	33.5	33.5	± 0.0
5	44.0	44.0	± 0.0
6	22.7	22.7	± 0.0
7	28.0	27.9	+ 0.1
8	39.8	39.8	± 0.0
9	38.3	38.3	± 0.0
10	83.9	83.8	+ 0.1
11	32.2	32.1	+ 0.1
12	29.3	29.2	+ 0.1
13	17.4	17.4	± 0.0
14	20.3	20.5	– 0.2
15	32.9	32.8	+ 0.1
16	110.7	110.7	± 0.0
17	139.8	139.7	+ 0.1
18	139.6	139.4	+ 0.2
19	111.5	111.5	± 0.0
20	100.9	100.8	+ 0.1
21	151.4	151.3	+ 0.1
22	55.0	55.0	± 0.0

5-epi-strongylin A (45)



S30 **S31** 5-*epi*-strongylin A (**45**)

A solution of hydrochloric acid (~1.25 M in methanol, 9 mL) was added to a solution of **S30** (117 mg, 270 µmol, 1 equiv) in dichloromethane (7 mL) at 23 °C and the mixture was heated to 30 °C. After 6 h, the reaction mixture was diluted with dichloromethane (30 mL) and saturated aqueous sodium bicarbonate solution (20 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to yield **S31** as a colorless solid that was directly used in the following reaction.

A solution of hydroiodic acid (57 wt.% in water, 357 µL, 2.70 mmol, 10.0 equiv) was added to a solution of the crude hydroquinone **S31** (93.2 mg, 270 µmol, 1 equiv) in benzene (10 mL) in an Ace® pressure tube. The tube was sealed and the reaction mixture was heated to 90 °C. After 16 h, the reaction mixture was cooled to 23 °C and saturated aqueous sodium bicarbonate solution (15 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to yield epi-strongylin A (**45**) (59.0 mg, 63% over two steps) as a colorless foam.

TLC (20% ethyl acetate in hexanes): $R_f = 0.47$ (CAM).

^{1}H NMR (800 MHz, C_6D_6): δ = 6.99 (d, J = 8.6 Hz, 1H), 6.13 (d, J = 8.6 Hz, 1H), 5.38 (s, 1H), 3.40 (s, 3H), 2.98 (d, J = 17.8 Hz, 1H), 2.30 (dd, J = 17.8, 1.0 Hz, 1H), 1.69–1.61 (m, 2H), 1.60–1.51 (m, 2H), 1.40–1.35 (m, 1H), 1.32–1.25 (m, 3H), 1.14–1.06 (m, 2H), 1.04 (s, 3H), 1.03–0.96 (m, 2H), 0.81 (s, 3H), 0.74 (s, 3H), 0.68 (d, J = 6.8 Hz, 3H).

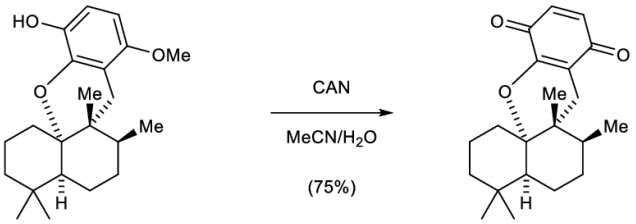
^{13}C NMR (201 MHz, C_6D_6): δ = 149.8, 138.88, 138.86, 109.9, 109.2, 100.0, 81.5, 53.7, 44.5, 40.1, 35.9, 31.8, 31.1, 30.6, 29.1, 27.0, 27.0, 21.3, 20.6, 16.7, 15.7, 15.0.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3557, 2938, 1618, 1489, 1390, 1264, 1170, 1083, 918, 788.

HRMS (EI) calcd for $C_{22}H_{32}O_3$ $[M]^+$: 344.2346; found: 344.2336.

$[\alpha]_D^{20}$ = –8.7° (c = 0.21, CH_2Cl_2).

Quinone 46



(+)-strongylin A (**4**) **46**

A solution of diammonium cerium(IV) nitrate (28.2 mg, 51.5 µmol, 2.50 equiv) in water (2.5 mL) was added dropwise to a solution of strongylin A (**4**) (7.10 mg, 21.0 µmol, 1 equiv) in acetonitrile (2.5 mL) over a period of 40 min at 0 °C. After 2 h, the bright yellow solution was diluted with water (10 mL) and the mixture was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (7% diethyl ether in pentane) to yield **46** (5.10 mg, 75%) as a yellow oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.25 (UV, CAM).

^{1}H NMR (599 MHz, $CDCl_3$): δ = 6.64 (d, J = 10.2, 1H), 6.57 (d, J = 10.2 Hz, 1H), 2.86 (d, J = 18.7 Hz, 1H), 2.17–2.06 (m, 1H), 2.05–1.97 (m, 1H), 1.94 (d, J = 18.7 Hz, 1H), 1.89–1.80 (m, 2H), 1.80–1.72 (m, 2H), 1.60–1.51 (m, 2H), 1.44–1.35 (m, 3H), 1.25–1.21 (m, 1H), 1.09 (d, J = 7.5, 1.2 Hz, 3H), 0.99 (s, 3H), 0.87 (s, 3H), 0.83 (s, 3H).

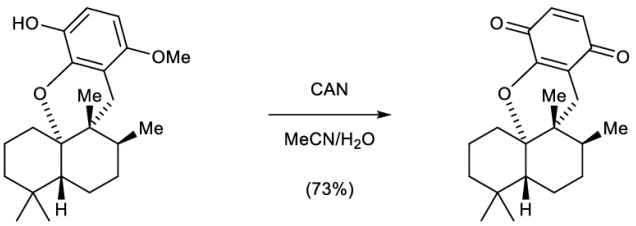
^{13}C NMR (151 MHz, $CDCl_3$): δ = 187.4, 181.6, 150.6, 137.0, 134.0, 117.9, 87.5, 45.1, 39.2, 38.1, 33.9, 33.6, 32.1, 30.9, 29.8, 29.1, 27.9, 22.6, 20.3, 18.4, 17.3.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2931, 2360, 1675, 1646, 1598, 1393, 1220, 1048, 839, 733.

HRMS (EI) calcd for $C_{21}H_{28}O_3$ $[M]^+$: 328.2033; found: 328.2043.

$[\alpha]_D^{20}$ = +22.3 ° (c = 1.20, CH_2Cl_2).

Quinone 47



5-*epi*-strongylin A (**45**) **47**

A solution of diammonium cerium(IV) nitrate (35.8 mg, 65.3 µmol, 2.50 equiv) in water (3 mL) was added dropwise to a solution of epi-strongylin A (**45**) (9.00 mg, 26.0 µmol, 1 equiv) in acetonitrile (3 mL) over a period of 30 min at 0 °C. After 2 h, the bright yellow solution was diluted with water (10 mL) and the mixture was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried over 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 hexanes) to yield **47** (6.30 mg, 73%) as a yellow solid.

TLC (20% ethyl acetate in hexanes): R_f = 0.50 (UV, CAM).

^{1}H NMR (599 MHz, $CDCl_3$): δ = 6.63 (d, J = 10.1 Hz, 1H), 6.58 (d, J = 10.1 Hz, 1H), 2.55 (d, J = 19.2 Hz, 1H), 1.99 (d, J = 19.2 Hz, 1H), 1.70–1.64 (m, 1H), 1.64–1.58 (m, 3H), 1.53–1.41 (m, 4H), 1.39–1.33 (m, 2H), 1.31–1.27 (m, 1H), 1.23–1.18 (m, 1H), 1.16 (s, 3H), 0.96 (s, 3H), 0.93 (s, 3H), 0.78 (d, J = 6.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 187.2, 181.6, 152.1, 137.0, 134.2, 117.8, 86.2, 45.8, 41.8, 37.3, 33.6, 32.61, 32.60, 30.4, 29.4, 26.9, 22.3, 22.0, 18.0, 17.0, 16.5.

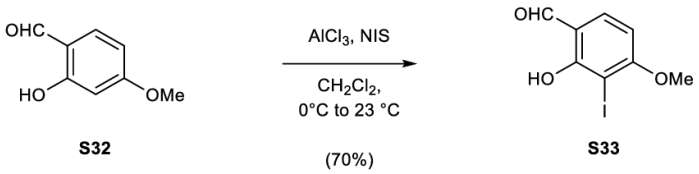
IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2942, 1677, 1645, 1595, 1387, 1344, 1202, 1162, 1041, 898, 839, 731.

HRMS (EI) calcd for $C_{21}H_{28}O_3$: 328.2033 $[M]^+$; found: 328.2035.

$[\alpha]_D^{20}$ = –1.9 ° (c = 0.17, CH_2Cl_2).

Melting point: 138–143 °C

2-Hydroxy-3-iodo-4-methoxybenzaldehyde (S33)

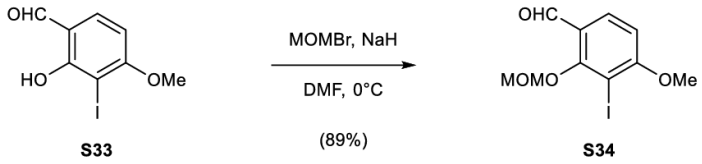


S32 (70%) **S33**

2-Hydroxy-3-iodo-4-methoxybenzaldehyde (**S33**) was synthesized according to a procedure described by U. Schilde:[24]

Aluminum trichloride (1.17 g, 8.81 mmol, 1 equiv) was added to a solution of aldehyde **S32** (1.34 g, 8.81 mmol, 1 equiv) in dichloromethane (40 mL) at –20 °C. After 15 min, N-iodosuccinimide (NIS) (2.18 g, 9.96 mmol, 1.10 equiv) was added to the bright orange solution and the reaction mixture was allowed to warm to 23 °C. After 13 h, aqueous hydrochloric acid solution (2 M, 100 mL) and dichloromethane (60 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 100 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to yield aldehyde **S33** (1.72 g, 70%) as a colorless solid. The obtained analytical data were in full agreement with those previously reported.

3-Iodo-4-methoxy-2-(methoxymethoxy)benzaldehyde (S34)



S33 **S34**

To a solution of **S33** (1.05 g, 3.78 mmol, 1 equiv) in N,N-dimethylformamide (40 mL) was added sodium hydride (60% mineral oil dispersion, 196 mg, 4.91 mmol, 1.30 equiv) at 0 °C. After 60 min, bromomethyl methylether (339 µL, 4.15 mmol, 1.10 equiv) was added dropwise to the dark brown suspension that became clear upon addition. After 1 h, saturated aqueous ammonium chloride solution (60 mL) was added and the mixture was extracted with diethyl ether (3 × 60 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (25% ethyl acetate in hexanes) to provide **S34** (1.08 g, 89%) as a colorless solid.

TLC (30% ethyl acetate in hexanes): R_f = 0.38 (UV, $KMnO_4$).

^{1}H NMR (599 MHz, $CDCl_3$): δ = 10.18 (d, J = 0.8 Hz, 1H), 7.88 (d, J = 8.7 Hz, 1H), 6.76 (dd, J = 8.7, 0.8 Hz, 1H), 5.18 (s, 2H), 3.98 (s, 3H), 3.63 (s, 3H).

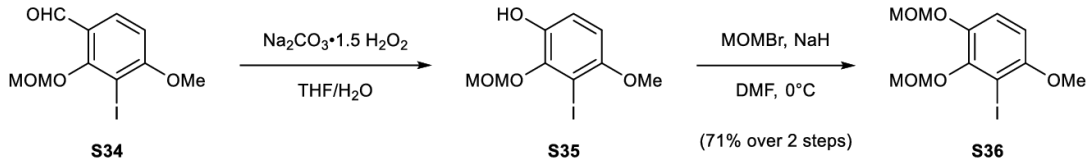
^{13}C NMR (151 MHz, $CDCl_3$): δ = 189.1, 164.5, 162.2, 130.6, 125.1, 107.6, 101.7, 85.2, 58.6, 57.1.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2940,1683, 1583, 1376, 1283, 1248, 1120, 1059, 962, 900.

HRMS (EI) calc. for $C_{10}H_{11}O_4{}^{127}I$ $[M]^+$: 321.9697; found: 321.9695.

Melting point: 67 °C.

2-Iodo-1-methoxy-3,4-bis(methoxymethoxy)benzene (S36)



Sodium percarbonate (143mg, 914 µmol, 1 equiv) was added to a solution of **S34** (254 mg, 914 µmol, 1 equiv) in tetrahydrofuran (20 mL) and water (8 mL). After 1.5 h, saturated aqueous sodium thiosulfate solution (20 mL) and diethyl ether (20 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was directly used in the following reaction without further purification.

Sodium hydride (60% mineral oil dispersion, 84.0 mg, 2.10 mmol, 2.30 equiv) was added to a solution of crude **S35** (283 mg, 914 µmol, 1 equiv) in N,N-dimethyl formamide (5 mL) at 0 °C. After 1 h, bromomethyl methylether (153 µL, 1.87 µmol, 2.05 equiv) was added and the reaction mixture was allowed to warm to 23 °C. After 1 h, water (40 mL) and diethyl ether (40 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 30 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (70 mL) and the washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (25% ethyl acetate in hexanes) to provide **S36** (147 mg, 71% over 2 steps) as a colorless oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.23 (UV, CAM).

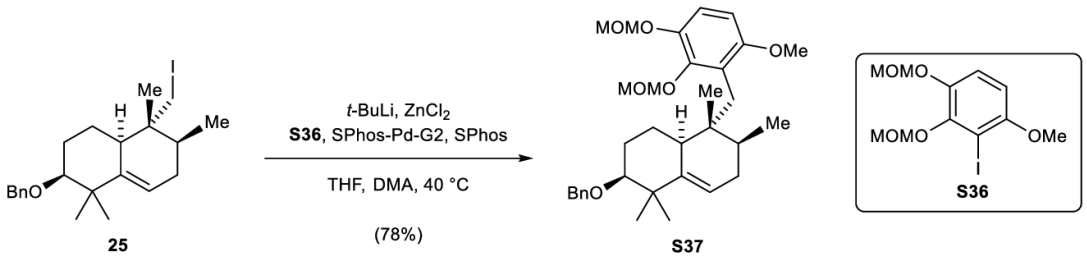
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (d, J = 9.0 Hz, 1H), 6.55 (d, J = 9.0 Hz, 1H), 5.21 (s, 2H), 5.11 (s, 2H), 3.84 (s, 3H), 3.68 (s, 3H), 3.50 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.8, 148.4, 144.3, 118.2, 106.4, 99.2, 96.4, 85.7, 58.6, 57.0, 56.4.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2954, 2900, 2833, 1477, 1436, 1251, 1154, 1069, 971, 923.

HRMS (EI) calc. for $C_{11}H_{15}{}^{127}IO_5$ $[M]^+$: 353.9959; found: 353.9960.

Olefin S37



Note: Tetrahydrofuran was dried according to the procedure described by B. Williams prior to use.[13]
To a solution of alkyl iodide **25** (278 mg, 634 µmol, 1.50 equiv) and a solution of zinc chloride (1.00 M in tetrahydrofuran, 676 µL, 676 µmol, 1.6 equiv) in tetrahydrofuran (6 mL) was added dropwise a solution of tert-butyllithium (1.50 M in pentane, 902 µL, 1.35 mmol, 3.2 equiv) at –78 °C. After 50 min, the mixture was allowed to warm to 23 °C. After 20 min, the mixture was transferred into a mixture of aryl iodide **S36** (150 mg, 423 µmol, 1 equiv), SPhos (17.4 mg, 42.3 µmol, 0.100 equiv) and SPhos-Pd-G2 (30.5 mg, 42.3 µmol, 0.100 equiv) in tetrahydrofuran (3 mL) and N,N-dimethylacetamide (3 mL) and the reaction mixture was directly placed in a preheated oil bath (35 °C). diethyl ether (50 mL) and saturated aqueous ammonium chloride solution (50 mL) were added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (80 mL), the washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (9% ethyl acetate in hexanes) to yield **S37** (178 mg, 78%) as a yellow oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.60 (UV, CAM).

^{1}H NMR (599 MHz, $CDCl_3$): δ = 7.31–7.26 (m, 4H), 7.24–7.21 (m, 1H), 6.95 (d, J = 8.9 Hz, 1H), 6.53 (d, J = 8.9 Hz, 1H), 5.48–5.39 (m, 1H), 5.13–5.09 (m, 2H), 5.07 (s, 2H), 4.50 (d, J = 12.4 Hz, 1H), 4.26 (d, J = 12.4 Hz, 1H), 3.76 (s, 3H), 3.59 (s, 3H), 3.51 (s, 3H), 3.03 (d, J = 2.7 Hz, 1H), 2.94 (d, J = 12.9 Hz, 1H), 2.68–2.62 (m, 2H), 1.94–1.82 (m, 2H), 1.65–1.59 (m, 1H), 1.56–1.51 (m, 1H), 1.50–1.44 (m, 1H), 1.23–1.14 (m, 1H), 1.08 (s, 3H), 1.03 (d, J = 6.8 Hz, 3H), 0.99 (s, 3H), 0.91–0.87 (m, 1H), 0.79 (s, 3H).

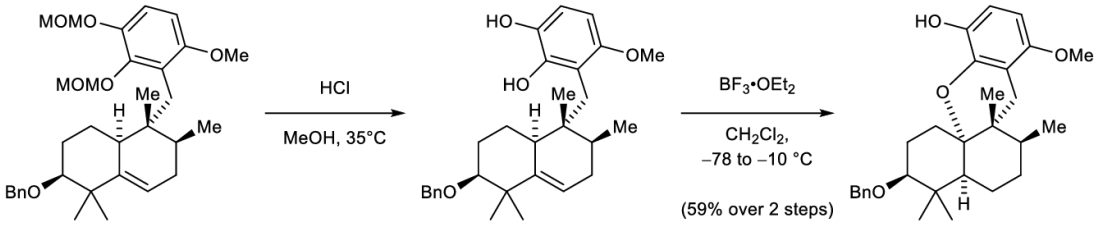
^{13}C NMR (151 MHz, $CDCl_3$): δ = 154.5, 148.0, 144.8, 143.8, 139.6, 128.2, 127.9, 127.2, 124.9, 117.5, 115.5, 105.4, 99.3, 96.4, 82.9, 70.2, 57.9, 56.4, 55.5, 41.7, 41.3, 40.9, 39.1, 35.4, 32.1, 28.6, 25.8, 24.5, 23.8, 16.4, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2950, 1483, 1252, 1154, 1068, 1038, 984, 951, 736, 698.

HRMS (EI) calc. for $C_{33}H_{46}O_{cc}$ $[M]^+$: 538.3289; found: 538.3303.

$[\alpha]_D^{20}$ = +18.1° (c = 0.85, CH_2Cl_2).

Phenol S39



S37 **S38** **S39**

A solution of hydrochloric acid (~1.25 M in methanol, 12 mL) was added to a solution of **S37** (145 mg, 269 µmol, 1 equiv) in dichloromethane (6 mL) and the resulting solution was heated to 35 °C. After 1 h, the reaction mixture was diluted with dichloromethane (25 mL) and saturated aqueous sodium bicarbonate solution (25 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated to yield **S38** as a yellow oil that was directly used in the following reaction without further purification.

A solution of boron trifluoride diethyl etherate (48% in diethyl ether, 707 µL, 2.69 mmol, 10.0 equiv) was added dropwise to a solution of the crude **S38** (83.4 mg, 269 µmol, 1 equiv) in dichloromethane (35 mL) at –50 °C. After 15 min, the reaction mixture was allowed to warm to –15 °C. After 30 min, saturated aqueous sodium bicarbonate solution (50 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (hexanes with 5% ethyl acetate) to yield **S39** (71.4 mg, 59% over 2 steps) as a colorless, highly viscous oil.

TLC (20% ethyl acetate): R_f = 0.61 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.33 (m, 4H), 7.32–7.26 (m, 1H), 6.69 (d, J = 8.6 Hz, 1H), 6.27 (d, J = 8.6 Hz, 1H), 4.94 (s, 1H), 4.66 (d, J = 12.0 Hz, 1H), 4.40 (d, J = 12.0 Hz, 1H), 3.78 (s, 3H), 3.23–3.11 (m, 2H), 2.34–2.21 (m, 2H), 2.20–2.10 (m, 2H), 2.09–1.99 (m, 1H), 1.96–1.88 (m, 1H), 1.82–1.71 (m, 3H), 1.63–1.56 (m, 1H), 1.35–1.29 (m, 1H), 1.13 (d, J = 7.5 Hz, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 0.92 (s, 3H).

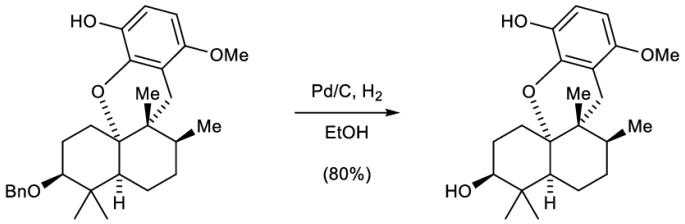
^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.0, 139.8, 139.2, 138.6, 128.3, 127.2, 127.1, 110.7, 110.7, 100.3, 84.4, 82.4, 71.8, 55.5, 44.4, 39.7, 38.4, 38.1, 32.0, 30.2, 28.0, 27.2, 24.4, 23.8, 21.4, 20.3, 17.3.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3564, 2938, 2874, 1490, 1384, 1264, 1185, 1085, 908, 732.

HRMS (EI) calc. for $C_{29}H_{38}O_4$ $[M]^+$: 4 50.2765; found: 450.2762.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +73.6° (c = 1.48, CH_2Cl_2).

3-Hydroxy-strongylin A (48)



S39 **48**

A solution of **S39** (62.0 mg, 138 µmol, 1 equiv) in ethanol (5 mL) was treated with palladium on carbon (10 wt.%, 146 mg, 138 µmol, 1 equiv) at 23 °C. An atmosphere of hydrogen was maintained by sparging with a stream of pure hydrogen gas through a stainless steel needle for 2 min and vigorous stirring of the suspension was then continued under hydrogen atmosphere at 23 °C. After 14 h, the reaction mixture was filtered through a pad of Celite®. The filtercake was thoroughly rinsed with dichloromethane (40 mL). The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to give 3-hydroxy-strongylin A (**47**) (40.0 mg, 80%) as a colorless solid. Recrystallization from ethyl acetate gave crystals suitable for single-crystal X-ray diffraction.

TLC (30% ethyl acetate in hexanes): R_f = 0.27 (UV, CAM).

^{1}H NMR (400 MHz, C_6D_6): δ = 6.95 (d, J = 8.6 Hz, 1H), 6.12 (d, J = 8.6 Hz, 1H), 4.99 (s, 1H), 3.41 (s, 3H), 3.28 (d, J = 17.5 Hz, 1H), 3.18–3.12 (m, 1H), 2.35 (d, J = 17.5 Hz, 1H), 2.24–2.04 (m, 3H), 1.90–1.78 (m, 1H), 1.62–1.50 (m, 3H), 1.50–1.42 (m, 1H), 1.37–1.27 (m, 1H), 1.19–1.10 (m, 1H), 1.00–0.95 (m, 6H), 0.87 (s, 3H), 0.76 (s, 1H), 0.74 (s, 3H).

^{13}C NMR (101 MHz, C_6D_6): δ = 151.4, 139.6, 139.5, 111.5, 110.9, 100.8, 84.2, 74.3, 55.0, 44.2, 40.0, 38.2, 37.8, 32.7, 30.0, 28.3, 26.7, 26.5, 24.3, 24.1, 20.4, 17.2.

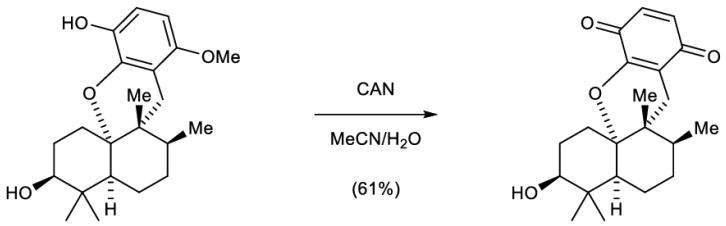
IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3472, 3157, 2986, 2963, 2874, 1605, 1464, 1265, 1096, 979.

HRMS (EI) calc. for $C_{22}H_{32}O_4$ $[M]^+$: 360.2295; found: 360.2302.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +66.8° (c = 0.79, CH_2Cl_2).

Melting point: 187 °C.

Quinone 49



47 **49**

A solution of diammonium cerium(IV) nitrate (35.7 mg, 65.2 µmol, 2.50 equiv) in water (2.5 mL) was added dropwise to a solution of 3-hydroxy-strongylin A (**47**) (9.40 mg, 26.1 µmol, 1 equiv) in acetonitrile (2.5 mL) over a period of 1 h at 0 °C. After 2 h, the bright yellow solution was diluted with water (10 mL) and the mixture was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to yield **48** (5.50 mg, 61%) as a yellow oil.

TLC (30% ethyl acetate in hexanes): R_f = 0.37 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.65 (d, J = 10.1 Hz, 1H), 6.57 (d, J = 10.1 Hz, 1H), 3.56 (s, 1H), 2.87 (d, J = 19.0 Hz, 1H), 2.62–2.50 (m, 1H), 2.25 (td, J = 13.6, 3.9 Hz, 1H), 2.08 (td, J = 13.6, 4.9 Hz, 1H), 2.01–1.86 (m, 2H), 1.82–1.72 (m, 3H), 1.71–1.63 (m, 1H), 1.61–1.50 (m, 1H), 1.49–1.42 (m, 1H), 1.37–1.30 (m, 1H), 1.11 (d, J = 7.4 Hz, 3H), 0.99 (s, 3H), 0.96 (s, 3H), 0.90 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 187.3, 181.6, 150.3, 137.1, 133.9, 118.1, 87.6, 74.3, 45.3, 39.3, 38.1, 38.1, 30.7, 30.4, 28.2, 26.6, 26.0, 24.3, 23.6, 20.4, 17.1.

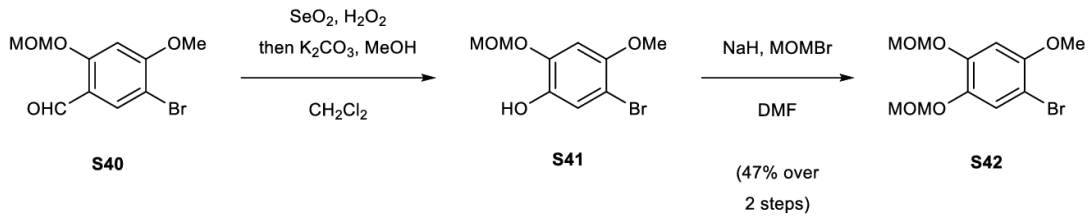
IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3540, 2928, 2876, 1675, 1645, 1596, 1394, 1193, 1050, 970.

HRMS (EI) calcd for $C_{21}H_{28}O_4$ $[M]^+$: 344.1982; found: 344.1981.

$[\alpha]_D^{20}$ = +112.0° (c = 0.10, $CHCl_3$).

Synthesis of 5-epi-Cyclosmenospongine (49), (+)-Smenoqualone (3) & 5-epi-Smenoqualone (50)

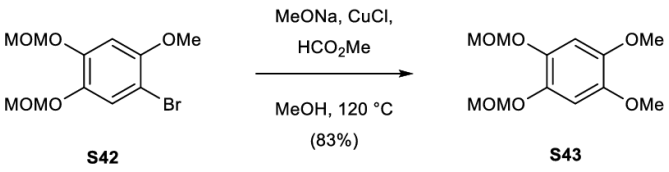
Bromide S42



Benzaldehyde **S40**[24,25] (1.48 g, 5.38 mmol, 1 equiv) was added to a solution of selenium dioxide (47.8 mg, 430 µmol, 8.0 mol%) and hydrogen peroxide (30% in water, 1.21 mL, 11.8 mmol, 2.20 equiv) in dichloromethane (30 mL). After 14 h, saturated aqueous ammonium chloride solution (40 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was dissolved in methanol (40 mL) and an aqueous solution of potassium carbonate (14%, 10 mL) was added. After 1 h, the reaction mixture was extracted with dichloromethane (3 × 30 mL), the combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated to give crude **S41** (924 mg) as a yellow oil that was used without further purification.

To a solution of crude **S41** (924 mg, 3.51 mmol, 1 equiv) in N,N-dimethylformamide (12 mL) was added sodium hydride (60% mineral oil dispersion, 211 g, 5.27 mmol, 1.50 equiv) at 0 °C. After 1 h, bromomethyl methyl ether (344 µL, 4.21 mmol, 1.20 equiv) was added and the reaction mixture was allowed to warm to 23 °C. After 1.5 h, water (20 mL) was added and the mixture was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (40 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20 ethyl acetate in hexanes) to provide **S42** (510 mg, 48% over 2 steps) as a yellow oil. The obtained analytical data were in full agreement with those previously reported.[26]

Arene S43



S42 **S43**

A mixture of aryl bromide **S42** (503 mg, 1.64 mmol, 1 equiv), sodium methoxide (177 mg, 3.28 mmol, 2.00 equiv), copper(I) chloride (6.49 mg, 65.5 µmol, 0.04 equiv) and formic acid methyl ester (40.6 µL, 65.5 µmol, 0.40 equiv) in methanol (1 mL) was heated to 120 °C in a pressure tube. After 13 h, the reaction mixture was cooled to 23 °C, dichloromethane (10 mL) and saturated aqueous ammonium chloride solution (10 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes initially, grading to 50% ethyl acetate in hexanes) to provide **S43** (350 mg, 83%) as a colorless oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.22 (UV, CAM).

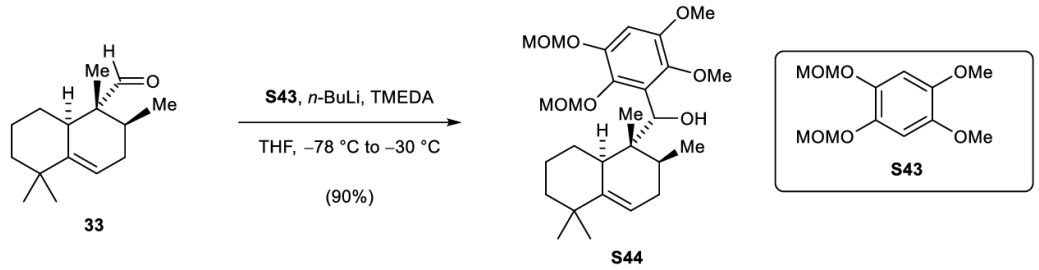
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.79 (s, 2H), 5.14 (s, 4H), 3.83 (s, 6H), 3.53 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.6, 141.2, 104.2, 96.9, 56.7, 56.4.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2937, 2830, 1512, 1465, 1384, 1214, 1191, 1151, 1009, 908, 729.

HRMS (EI) calcd for $C_{12}H_{18}O_6$ $[M]^+$: 258.1098; found: 258.1098.

Benzylic alcohol (S44)



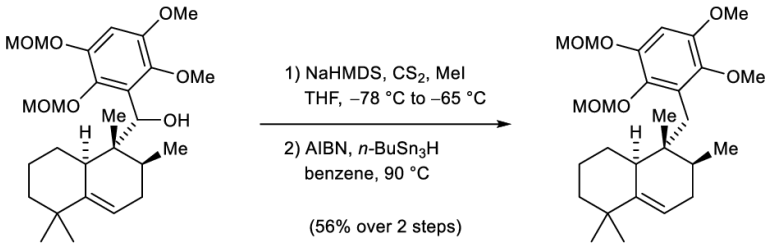
To a solution of **S43** (327 mg, 1.27 mmol, 1.40 equiv) in tetrahydrofuran (6 mL) and freshly distilled N,N,N′,N′-tetramethylethane-1,2-diamine (over CaH_2, 409 µL, 2.71 mmol, 3.00 equiv) was added a solution of n-butyllithium (2.44 M in hexanes 0.45 mL, 1.13 mmol, 1.25 equiv) at –78 °C. The reaction mixture was allowed to warm to –60 °C. After 1.5 h, the yellow suspension was cooled to –78 °C and a solution of aldehyde **33** (199 mg, 904 µmol, 1 equiv) in tetrahydrofuran (4 mL) was added to give a clear yellow solution. The reaction mixture was warmed to –30 °C over a period of 2 h. Diethyl ether (30 mL) and saturated aqueous ammonium chloride solution (40 mL) were added. The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 30 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (50 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to yield **S44** (391 mg, 90%) as a colorless oil. The mixture of inseparable diastereoisomers was partially characterized by HRMS and IR spectroscopy.

TLC (30% ethyl acetate in hexanes): $R_f = 0.35$ (CAM).

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3559, 2928, 1592, 1482, 1435, 1227, 1153, 1035, 948.

HRMS (EI) calcd for $C_{27}H_{42}O_7$ $[M]^+$: 478.2925; found: 478.2925.

Olefin S45



S44 **S45**

A solution of sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 3.90 mL, 3.90 mmol, 5.00 equiv) was added dropwise to a solution of **S44** (373 mg, 779 µmol, 1 equiv) in tetrahydrofuran (10 mL) at −78 °C. After 30 min, carbon disulfide (940 µL, 15.6 mmol, 20.0 equiv) was slowly added and the reaction mixture was allowed to warm to −65 °C. After 1 h, methyl iodide (970 µL, 15.6 mmol, 20.0 equiv) was slowly added to the reaction mixture. After 1 h, saturated aqueous ammonium chloride solution (25 mL) and ethyl acetate (30 mL) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered through a short plug of silica and the obtained crude xanthogenate was used without further purification.

Note: benzene was degassed via freeze-pump-thaw (three cycles) prior to use.
A degassed solution of the xanthogenate (420 mg, 779 µmol, 1 equiv), 2,2'-azobis(2-methylpropionitrile) (AIBN) (64.0 mg, 390 µmol, 0.50 equiv) and tributyltin hydride (1.04 mL, 3.90 mmol, 5.00 equiv) in benzene (25 mL) was heated to 90 °C. After 7.5 h, the reaction mixture was cooled to 23 °C and directly purified by flash-column chromatography on silica gel (3% ethyl acetate in hexanes) to yield **S45** as a colorless oil (202 mg, 56% over 2 steps).

TLC (20% ethyl acetate in hexanes): R_f = 0.34 (CAM).

^{1}H NMR (800 MHz, $CDCl_3$): δ = 6.66 (s, 1H), 5.41–5.36 (m, 1H), 5.17–5.12 (m, 2H), 5.02–4.98 (m, 2H), 3.83 (s, 3H), 3.72 (s, 3H), 3.59 (s, 3H), 3.52 (s, 3H), 2.85 (d, J = 12.8 Hz, 1H), 2.60 (d, J = 12.8 Hz, 1H), 2.59–2.55 (m, 1H), 1.97–1.90 (m, 1H), 1.84–1.78 (m, 1H), 1.56–1.52 (m, 1H), 1.44–1.37 (m, 1H), 1.34–1.28 (m, 2H), 1.19–1.14 (m, 1H), 1.11–1.06 (m, 1H), 1.03–0.99 (m, 9H), 0.75 (s, 3H), 0.72–0.66 (m, 1H).

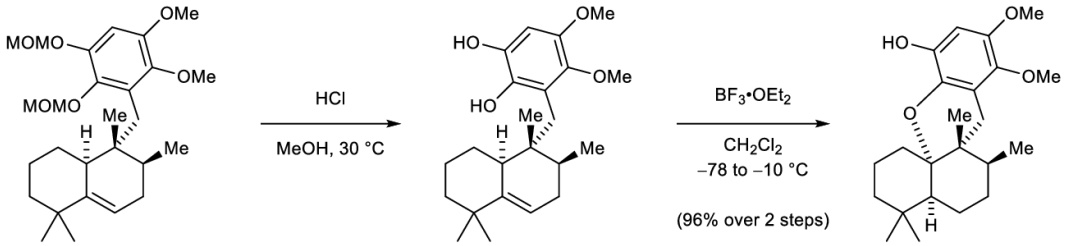
^{13}C NMR (201 MHz, $CDCl_3$): δ = 149.2, 147.7, 145.8, 143.8, 140.9, 129.8, 114.7, 101.6, 99.5, 96.5, 60.4, 57.8, 56.5, 56.3, 42.1, 41.7, 40.9, 38.9, 36.7, 36.2, 31.8, 31.1, 30.0, 28.1, 23.0, 16.6, 14.8.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2973, 2840, 1593, 1483, 1338, 1239, 1154, 1049, 956, 731.

HRMS (EI) calcd for $C_{27}H_{42}O_6$ $[M]^+$: 462.2976; found: 462.2972.

$[\alpha]_D^{20}$ = +24.3° (c = 0.41, CH_2Cl_2).

Phenol S47



S45 **S46** **S47**

A solution of hydrochloric acid (~1.25 M in methanol, 3 mL) was added to a solution of **S45** (24.4 mg, 52.7 µmol, 1 equiv) in dichloromethane (1 mL) and the resulting solution was heated to 30 °C. After 4 h, the reaction mixture was diluted with dichloromethane (5 mL) and saturated aqueous sodium bicarbonate solution (3 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to yield **S46** as a yellow foam that was directly used in the following step.

A solution of boron trifluoride diethyl etherate (48% in diethyl ether, 138 µL, 527 µmol, 10.0 equiv) was added dropwise to a solution of the crude hydroquinone **S46** (19.7 mg, 52.7 µmol, 1 equiv) in dichloromethane (3 mL) at –78 °C. After complete addition, the reaction mixture was allowed to warm to –10 °C over a period of 30 min. After 1.5 h, saturated aqueous ammonium chloride solution (5 mL) and dichloromethane (5 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to yield **S47** (19.0 mg, 96% over two steps) as an amorphous solid.

TLC (20% ethyl acetate in hexanes): R_f = 0.58 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, C_6D_6): δ = 6.64 (s, 1H), 5.26 (s, 1H), 3.78 (s, 3H), 3.37 (s, 3H), 3.28 (d, J = 17.6 Hz, 1H), 2.26 (d, J = 17.6 Hz, 1H), 1.91–1.75 (m, 2H), 1.67–1.58 (m, 2H), 1.54–1.48 (m, 1H), 1.46–1.39 (m, 2H), 1.31–1.21 (m, 3H), 1.12 (s, 4H), 1.09–1.05 (m, 1H), 0.89 (d, J = 7.5 Hz, 3H), 0.82 (s, 3H), 0.67 (s, 3H).

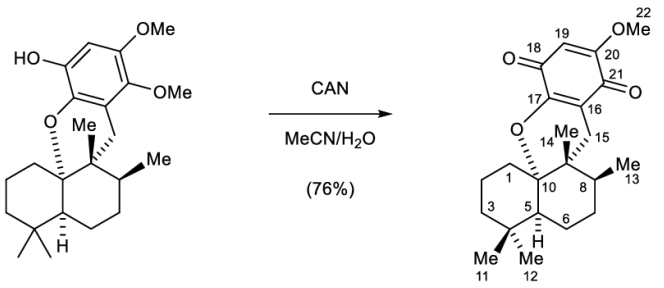
^{13}C NMR (101 MHz, C_6D_6): δ = 146.3, 140.9, 140.5, 132.8, 116.1, 99.9, 83.4, 60.1, 56.2, 44.1, 39.7, 38.4, 34.1, 33.6, 33.1, 32.2, 29.5, 29.3, 27.9, 22.7, 20.2, 18.9, 17.4.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2934, 2279, 1618, 1492, 1329, 1259, 1188, 1049, 811.

HRMS (EI) calcd for $C_{23}H_{34}O_4$ $[M]^+$: 374.2452; found: 374.2449.

$[\alpha]_D^{20}$ = +45.8° (c = 1.46, CH_2Cl_2).

(+)-Smenoqualone (3)



S47 (+)-smenoqualone (**3**)

A solution of ammonium cerium(IV) nitrate (55.1 mg, 100 µmol, 2.20 equiv) in water (3 mL) was added dropwise over a period of 40 min to a solution of phenol **S47** (17.1 mg, 45.7 µmol, 1 equiv) in acetonitrile (3 mL) at 0 °C. After 3 h, the bright yellow solution was diluted with water (5 mL) and diethyl ether (5 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% diethyl ether in pentane initially, grading to 30% diethyl ether in pentane) to provide (+)-smenoqualone (**3**) (12.4 mg, 76%) as a bright yellow foam.

TLC (30% ethyl acetate in hexanes): R_f = 0.35 (UV, CAM).

^{1}H NMR (800 MHz, $CDCl_3$): δ = 5.73 (s, 1H, H-19), 3.81 (s, 3H, H-3), 2.85 (d, $^2J_{15A/15B}$ = 18.3 Hz, 1H, H-15$_A$), 2.15–2.07 (m, 1H, H-2$_A$), 2.04–1.98 (m, 1H, H-7$_A$), 1.95 (d, $^2J_{15B/15A}$ = 18.3 Hz, 1H, H-15$_B$), 1.89–1.85 (m, 1H, H-1$_A$), 1.84–1.79 (m, 1H, H-1$_B$), 1.79–1.76 (m, 1H, H-8), 1.76–1.72 (m, 1H, H-6$_A$), 1.59–1.55 (m, 1H, H-6$_B$), 1.54–1.50 (m, 1H, H-2$_B$), 1.42–1.35 (m, 3H, H-3$_A$), 1.25–1.22 (m, 1H, H-3$_B$), 1.09 (d, $^3J_{13/8}$ = 7.6 Hz, 3H, H-13), 1.00 (s, 3H, H-12), 0.85 (s, 3H, H-14), 0.82 (s, 3H, H-11).

^{13}C NMR (201 MHz, $CDCl_3$): δ = 181.53 (C-21), 181.47 (C-18), 159.5 (C-20), 151.1 (C-17), 115.2 (C-16), 104.6 (C-19), 87.8 (C-10), 56.3 (C-22), 45.1 (C-5), 39.0 (C-8), 38.0 (C-9), 33.7 (C-4), 33.4 (C-3), 31.9 (C-11), 30.7 (C-15), 29.7 (C-12), 28.9 (C-1), 27.7 (C-7), 22.4 (C-6), 20.1 (C-14), 18.3 (C-2), 17.1 (C-13).

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2938, 1665, 1646, 1602, 1457, 1342, 1276, 1220, 1037, 842.

HRMS (EI) calcd for $C_{22}H_{30}O_4$ $[M]^+$: 358.2139; found: 358.2139.

$[\alpha]_D^{20}$ = +84.3° (c 0.37, $CHCl_3$); $[\alpha]_D^{n.a.}$ = +70° (c = 0.001, $CHCl_3$) for (+)-smenoqualone.[27] n.a.: Temperature not available

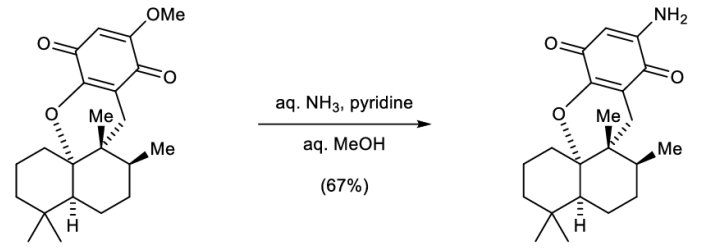
Supplementary Table 8 Comparison of ^{1}H NMR data for natural and synthetic (+)-smenoqualone (**3**).

Proton	Synthetic (800 MHz, $CDCl_3$)	Natural	Δ: δ (ppm)
1A	1.89–1.85 (m, 1H)	Not reported	
1B	1.84–1.79 (m, 1H)		
2A	2.15–2.07 (m, 1H)		
2B	1.54–1.50 (m, 1H)		
3A	1.42–1.35 (m, 3H)		
3B	1.25–1.22 (m, 1H)		
5	1.42–1.35 (m, 3H)		
6A	1.76–1.72 (m, 1H)		
6B	1.59–1.55 (m, 1H)		
7A	2.04–1.98 (m, 1H)		
7B	1.42–1.35 (m, 3H)		
8	1.79–1.76 (m, 1H)		
11	0.82 (s, 3H).		
12	1.00 (s, 3H)		
13	1.09 (d, J = 7.6 Hz, 3H)		
14	0.85 (s, 3H)		
15A	2.85 (d, J = 18.3 Hz, 1H)		
15B	1.95 (d, J = 18.3 Hz, 1H)		
19	5.73 (s, 1H)		
22	3.81 (s, 3H)		

Supplementary Table 9 Comparison of ^{13}C NMR data for natural and synthetic (+)-smenoqualone (**3**).

Carbon	Synthetic (201 MHz, $CDCl_3$)	Natural (75 MHz, $CDCl_3$)[27]	Δ: δ (ppm)
1	28.9	28.9	± 0.0
2	18.3	18.3	± 0.0
3	33.4	33.4	± 0.0
4	33.7	33.7	± 0.0
5	45.1	45.1	± 0.0
6	22.4	22.5	– 0.1
7	27.7	27.7	± 0.0
8	39.0	39.0	± 0.0
9	38.0	37.9	+ 0.1
10	87.8	87.8	± 0.0
11	31.9	31.9	± 0.0
12	29.7	29.7	± 0.0
13	17.1	17.1	± 0.0
14	20.1	20.1	± 0.0
15	30.7	30.7	± 0.0
16	115.2	115.3	– 0.1
17	151.1	151.1	± 0.0
18	181.5	181.5	± 0.0
19	104.6	104.7	– 0.1
20	159.5	159.5	± 0.0
21	181.5	181.5	+0.0
22	56.3	56.3	± 0.0

5-Epi-cyclosmenospongine (49)



(+)-smenoqualone (**3**) 5-*epi*-cyclosmenospongine (**50**)

To a solution of (+)-smenoqualone (**3**) (6.70 mg, 18.7 µmol, 1 equiv) and pyridine (600 µL) in aqueous methanol (50%, 6 mL) was added aqueous ammonia (25%, 600 µL) at 23 °C. After 14 h, the reaction mixture was concentrated, water (5 mL) was added and the aqueous layer was extracted with diethyl ether (4 × 10 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Sephadex® LH-20 (9% ethanol in chloroform) to yield 5-epi-cyclosmenospongine (**50**) (4.30 mg, 67%) as a dark red oil.

TLC (30% ethyl acetate in hexanes): R_f = 0.19 (UV, $KMnO_4$).

^{1}H NMR (800 MHz, $CDCl_3$): δ = 5.53 (s, 1H), 5.10 (s, 2H), 2.83 (d, J = 18.1 Hz, 1H), 2.18–2.09 (m, 1H), 2.05–1.98 (m, 1H), 1.92–1.86 (m, 2H), 1.85–1.79 (m, 1H), 1.78–1.71 (m, 2H), 1.57–1.55 (m, 1H), 1.53–1.49 (m, 1H), 1.44–1.39 (m, 2H), 1.39–1.35 (m, 1H), 1.26–1.22 (m, 1H), 1.09 (d, J = 7.6 Hz, 3H), 1.03 (s, 3H), 0.87 (s, 3H), 0.82 (s, 3H).

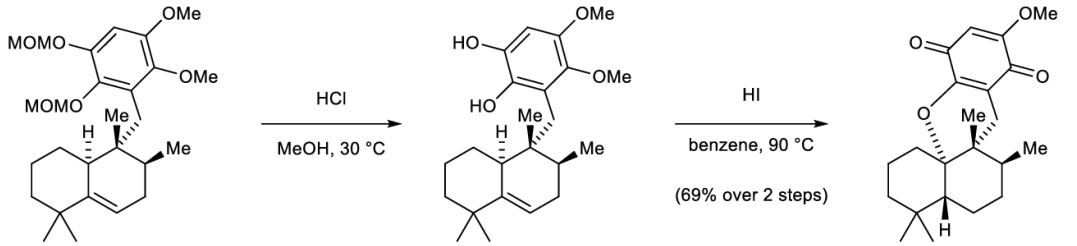
^{13}C NMR (201 MHz, $CDCl_3$): δ = 182.8, 180.3, 153.2, 147.7, 113.0, 99.2, 88.0, 45.3, 39.2, 38.1, 33.9, 33.6, 32.1, 30.7, 29.9, 29.1, 27.9, 22.6, 20.2, 18.5, 17.3.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3448, 3338, 1936, 2873, 2360, 2340, 1593, 1373, 1226, 943.

HRMS (EI) calcd for $C_{21}H_{29}NO_3$ $[M]^+$: 343.2142; found: 343.2135.

$[\alpha]_D^{20}$ = +492.3° (c = 0.16, CH_2Cl_2).

5-Epi-smenoqualone (50)



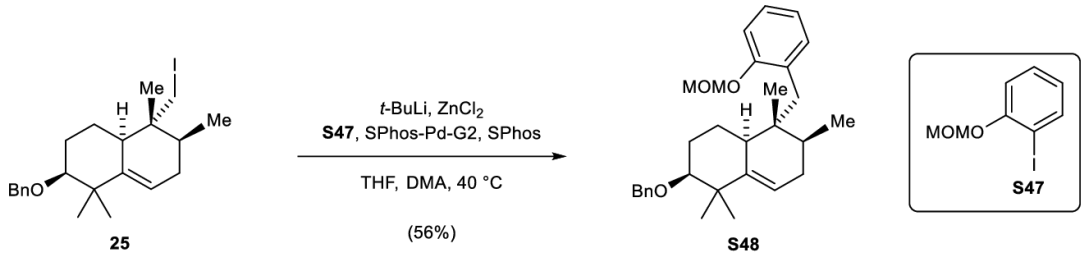
S45 **S46** 5-*epi*-smenoqualone (**51**)

A solution of hydrochloric acid (~1.25 M in methanol, 4 mL) was added to a solution of **S45** (64.0 mg, 138 µmol, 1 equiv) in dichloromethane (2 mL) and the mixture was heated to 40 °C. After 2 h, the reaction mixture was diluted with dichloromethane (20 mL) and saturated aqueous sodium bicarbonate solution (30 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to yield **S46** as a yellow oil that was directly used in the following reaction.

A solution of hydroiodic acid (57 wt.% in H_2O, 183 µL, 1.38 mmol, 10.0 equiv) was added to a solution of crude **S46** (51.7 mg, 138 µmol, 1 equiv) in benzene (5 mL) in an Ace® pressure tube. The tube was sealed and the reaction mixture was heated to 90 °C. After 20 h, the reaction mixture was cooled to 23 °C, saturated aqueous sodium bicarbonate chloride solution (15 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to yield 5-epi-smenoqualone (**51**) (34.2 mg, 69% over two steps) as a bright yellow solid. The obtained analytical data were in full agreement with those values previously reported by our group.[21]

Synthetic Analogues 40, 41, 42, 43 and 44

Olefin S48



Note: Tetrahydrofuran was dried according to the procedure described by B. Williams prior to use.[13]
To a mixture of alkyl iodide **25** (120 mg, 274 µmol, 1.50 equiv) and a solution of zinc chloride (1.00 M in tetrahydrofuran, 292 µL, 292 µmol, 1.6 equiv) in tetrahydrofuran (3 mL) was added dropwise a solution of tert-butyllithium (1.50 M in pentane, 389 µL, 584 µmol, 3.20 equiv) at –78 °C. After 50 min, the mixture was allowed to warm to 23 °C. After 20 min, the mixture was added to a mixture of aryl iodide **S47**[28] (435 mg, 870 µmol, 1 equiv), SPhos (71.3 mg, 174 µmol, 0.200 equiv) and SPhos-Pd-G2 (125 mg, 174 µmol, 0.20 equiv) in tetrahydrofuran (2.2 mL) and freshly distilled (over CaH_2) N,N-dimethylacetamide (2.2 mL) and the reaction mixture was directly placed in a preheated oil bath at 40 °C. After 15 min, the reaction mixture was allowed to cool to 23 °C and ethyl acetate (20 mL) and saturated aqueous ammonium chloride solution (20 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (2 × 20 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (40 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (1% ethyl acetate in hexanes) to yield methoxymethyl-ether **S48** (46.1 mg, 56%) as a colorless oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.47 (UV, CAM).

^{1}H NMR (800 MHz, $CDCl_3$): δ = 7.34–7.29 (m, 4H), 7.26–7.23 (m, 1H), 7.20 (dd, J = 7.6, 1.7 Hz, 1H), 7.16–7.13 (m, 1H), 7.10 (dd, J = 8.2, 1.3 Hz, 1H), 6.92 (td, J = 7.6, 1.3 Hz, 1H), 5.42 (d, J = 5.7 Hz, 1H), 5.21 (d, J = 6.6 Hz, 1H), 5.15 (d, J = 6.6 Hz, 1H), 4.57 (d, J = 12.4 Hz, 1H), 4.33 (d, J = 12.4 Hz, 1H), 3.50 (s, 3H), 3.08 (s, 1H), 2.87 (d, J = 13.7 Hz, 1H), 2.61 (d, J = 13.7 Hz, 1H), 2.22–2.17 (m, 1H), 1.98–1.92 (m, 1H), 1.90–1.84 (m, 1H), 1.84–1.78 (m, 1H), 1.58–1.51 (m, 3H), 1.49–1.44 (m, 1H), 1.09 (s, 3H), 1.07 (d, J = 6.7 Hz, 3H), 0.88 (s, 3H), 0.83 (s, 3H).

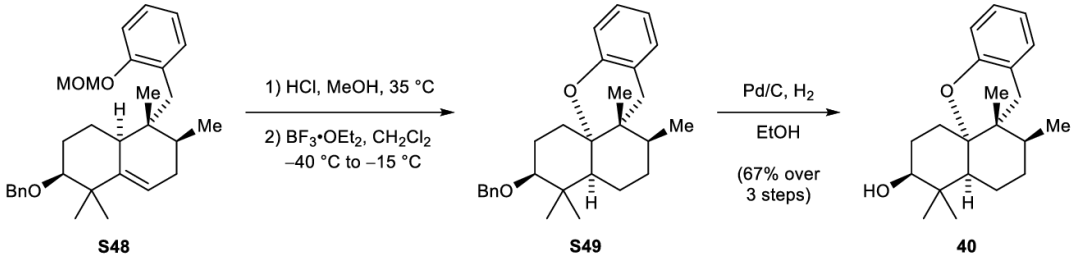
^{13}C NMR (201 MHz, $CDCl_3$): δ = 156.7, 139.6, 132.1, 129.2, 128.2, 128.2, 127.8, 127.8, 127.3, 127.2, 121.3, 117.5, 114.3, 95.1, 83.0, 70.3, 70.3, 56.2, 56.2, 41.2, 39.9, 39.7, 37.2, 34.8, 32.0, 28.6, 25.8, 24.4, 22.7, 16.7.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2952, 1493, 1453, 1232, 1154, 1077, 1051, 1004, 754, 697.

HRMS (EI) calc. for $C_{30}H_{40}O_3$ $[M]^+$: 448.2972; found: 448.2933.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +55.2° (c = 0.91, $CHCl_3$).

Alcohol 40



S48 **S49** **40**

A solution of hydrochloric acid (~1.25 M in methanol, 1.5 mL) was added to a solution of **S48** (36.0 mg, 80.2 µmol, 1 equiv) in dichloromethane (1 mL) and the resulting solution was heated to 35 °C. After 1 h, the reaction mixture was diluted with dichloromethane (8 mL) and saturated aqueous sodium bicarbonate solution (10 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated yielding a yellow foam that was directly used in the following reaction.

A solution of boron trifluoride diethyl etherate (48% in diethyl ether, 211 µL, 802 µmol, 10.0 equiv) was added dropwise to a solution of the crude phenol (32.2 mg, 80.2 µmol, 1 equiv) in dichloromethane (5 mL) at –40 °C and the reaction mixture was allowed to warm to –10 °C. After 0.5 h, saturated aqueous sodium bicarbonate solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was directly used in the following step.

A solution of crude **S49** (32.2 mg, 80.2 µmol, 1 equiv) in ethanol (3 mL) was treated with oalladium on carbon (10 wt.%, 85.4 mg, 80.2 µmol, 1 equiv) at 23 °C. An atmosphere of hydrogen was maintained by sparging with a stream of pure hydrogen gas through a stainless steel needle for 2 min and vigorous stirring of the suspension was then continued under hydrogen atmosphere at 23 °C. After 14 h, the reaction mixture was filtered through a pad of Celite®. The filtercake was thoroughly rinsed with dichloromethane (50 mL). The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (6% ethyl acetate in hexanes) to give **40** (17.0 mg, 67% over 3 steps) as a colorless oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.28 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10–7.03 (m, 1H), 7.00 (d, J = 7.3 Hz, 1H), 6.81 (t, J = 7.3 Hz, 1H), 6.69 (d, J = 8.1 Hz, 1H), 3.60–3.53 (m, 1H), 3.44 (d, J = 17.0 Hz, 1H), 2.62–2.50 (m, 1H), 2.30–2.19 (m, 1H), 2.16–2.01 (m, 2H), 2.00–1.90 (m, 1H), 1.79–1.61 (m, 4H), 1.58–1.45 (m, 2H), 1.39–1.29 (m, 1H), 1.14 (d, J = 7.5 Hz, 3H), 1.05 (s, 3H), 0.99–0.93 (m, 6H).

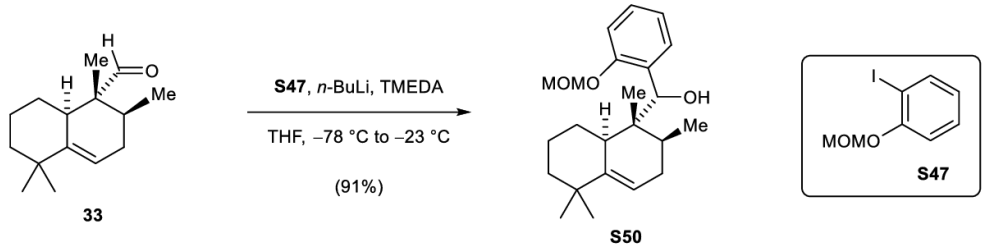
^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.6, 129.2, 126.8, 121.6, 119.5, 116.6, 82.9, 75.0, 44.7, 39.6, 38.3, 38.2, 37.1, 30.8, 28.3, 26.5, 26.0, 24.1, 23.9, 20.3, 17.3.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3434, 2960, 2872, 1589, 1490, 1455, 1257, 974, 908, 732.

HRMS (EI) calc. for $C_{21}H_{30}O_2$ $[M]^+$: 314.2240; found: 314.2245.

$[\boldsymbol{a}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +18.9° (c = 0.55, $CHCl_3$).

Benzylic alcohol S50



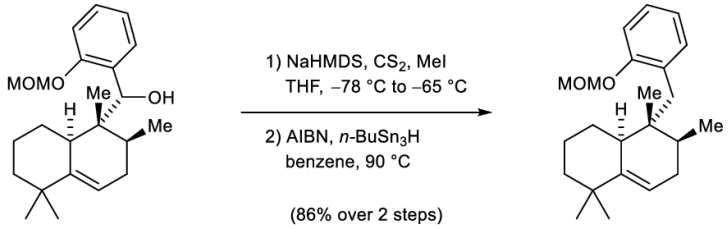
To a solution of iodide **S47** (168 mg, 635 µmol, 1.40 equiv) in tetrahydrofuran (1.5 mL) and freshly distilled N,N,N′,N′-tetramethylethane-1,2-diamine (over CaH_2, 192 µL, 1.27 mmol, 2.80 equiv) was added a solution of n-butyllithium (2.22 M in hexanes, 266 µL, 590 µmol, 1.30 equiv) at –78 °C and the reaction mixture was allowed to warm to –30 °C. After 45 min, the reaction mixture was cooled to –78 °C and a solution of aldehyde **33** (100 mg, 454 µmol, 1 equiv) in tetrahydrofuran (0.5 mL) was added. The reaction mixture was allowed to warm to 23 °C over a period of 30 min. Diethyl ether (10 mL) and saturated aqueous ammonium chloride solution (10 mL) was added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 10 mL).The combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the crude product was purified by flash-column chromatography on silica gel (9% ethyl acetate in hexanes) to yield **S50** (148 mg, 91%) as a colorless oil. The inconsequential mixture of diastereoisomers was partially characterized by HRMS and IR spectroscopy.

TLC (10% ethyl acetate in hexanes): $R_f = 0.44$ (CAM).

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3480, 2954, 2924, 1488, 1452, 1229, 1153, 997, 923, 755.

HRMS (ESI) calcd for $C_{23}H_{35}O_3^+$ $[M+H]^+$: 359.2581; found: 359.2586.

Methoxymethyl-Ether S51



S50 **S51**

A solution of sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 2.02 mL, 2.02 mmol, 5.00 equiv) was added dropwise to a solution of **S50** (145 mg, 404 µmol, 1 equiv) in tetrahydrofuran (5 mL) at −78 °C. After 30 min, carbon disulfide (488 µL, 8.09 mmol, 20.0 equiv) was added dropwise to the orange solution and the resulting red solution was allowed to warm to −65 °C. After 1 h, methyl iodide (504 µL, 8.09 mmol, 20.0 equiv) was added to the reaction mixture. After 1 h, saturated aqueous ammonium chloride solution (20 mL) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered through a plug of silica and the obtained crude product was used without further purification.

Note: benzene was degassed via freeze-pump-thaw (three cycles) prior to use.
A degassed solution of the xanthogenate (145 mg, 404 µmol, 1 equiv), 2,2'-azobis(2-methylpropionitrile) (AIBN) (33.2 mg, 202 µmol, 0.500 equiv) and tributyltin hydride (817 µL, 3.03 mmol, 7.50 equiv) in benzene (6.5 mL) was heated to 90 °C. After 1.5 h, the reaction mixture was cooled to 23 °C and directly purified by flash-column chromatography on silica gel (hexanes initially, grading to 2% ethyl acetate in hexanes) to yield **S51** as a colorless oil (119 mg, 86% over 2 steps).

TLC (5% ethyl acetate in hexanes): R_f = 0.37 (CAM).

^{1}H NMR (599 MHz, $CDCl_3$): δ = 7.19 (dd, J = 7.6, 1.7 Hz, 1H), 7.16–7.10 (m, 2H), 6.94–6.90 (m, 1H), 5.39–5.36 (m, 1H), 5.22 (d, J = 6.7 Hz, 1H), 5.16 (d, J = 6.7 Hz, 1H), 3.51 (s, 3H), 2.85 (d, J = 13.7 Hz, 1H), 2.60 (d, J = 13.7 Hz, 1H), 2.14 –2.10 (m, 1H), 2.01–1.95 (m, 1H), 1.85–1.77 (m, 2H), 1.56–1.52 (m, 1H), 1.52–1.48 (m, 1H), 1.46–1.41 (m, 1H), 1.39–1.35 (m, 1H), 1.17 (td, J = 13.2, 4.5 Hz, 1H), 1.05 (d, J = 6.7 Hz, 3H), 1.02 (s, 3H), 0.97–0.93 (m, 1H), 0.89 (s, 3H), 0.79 (s, 3H).

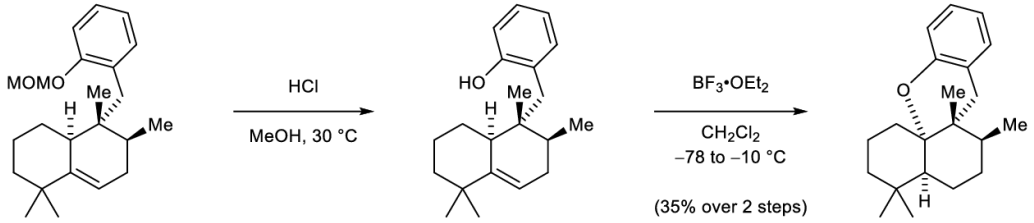
^{13}C NMR (151 MHz, $CDCl_3$): δ = 156.7, 146.8, 132.1, 129.1, 127.2, 121.2, 115.0, 114.2, 95.1, 56.2, 41.6, 40.3, 39.8, 37.3, 36.6, 34.8, 31.8, 30.0, 29.9, 28.3, 22.8, 16.8, 16.5.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2956, 2928, 1493, 1453, 1232, 1155, 1078, 1008, 923, 754.

HRMS (EI) calcd for $C_{23}H_{34}O_2$ $[M]^+$: 342.2553; found: 342.2553.

$[\alpha]_D^{20}$ = +35.6° (c = 1.53, CH_2Cl_2).

Tetracycle 41



S51 **S52** **41**

A solution of hydrochloric acid (~1.25 M in methanol, 1.5 mL) was added to a solution of **S51** (27.0 mg, 78.8 µmol, 1 equiv) in dichloromethane (0.5 mL) and the resulting solution was heated to 35 °C. After 1 h, the reaction mixture was diluted with dichloromethane (8 mL) and saturated aqueous sodium bicarbonate solution (10 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated to provide **S52** as a colorless foam that was used in the following reaction without further purification.

A solution of boron trifluoride diethyl etherate (48% in diethyl ether, 207 µL, 788 µmol, 10.0 equiv) was added dropwise to a solution of crude phenol **S52** (23.5 mg, 78.8 µmol, 1 equiv) in dichloromethane (2 mL) at –40 °C and the reaction mixture was allowed to warm to –10 °C over a period of 2.5 h. After 0.5 h, saturated aqueous sodium bicarbonate solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (hexanes initially, grading to 2% ethyl acetate in hexanes) to yield **41** (8.3 mg, 35% over two steps) as a colorless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.68 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06 (t, J = 7.4 Hz, 1H), 6.99 (d, J = 7.4 Hz, 1H), 6.80 (t, J = 7.4 Hz, 1H), 6.73 (d, J = 8.1 Hz, 1H), 3.43 (d, J = 16.9 Hz, 1H), 2.19–1.99 (m, 3H), 1.88–1.76 (m, 2H), 1.75–1.65 (m, 2H), 1.64–1.55 (m, 1H), 1.54–1.42 (m, 3H), 1.40–1.33 (m, 1H), 1.25–1.17 (m, 1H), 1.12 (d, J = 7.5 Hz, 3H), 1.08 (s, 3H), 0.92 (s, 3H), 0.79 (s, 3H).

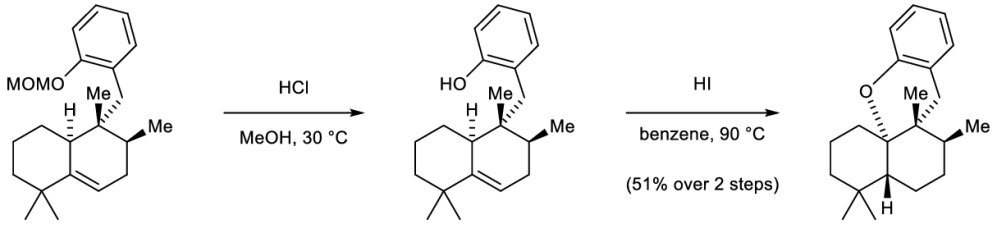
^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.9, 129.2, 126.8, 121.5, 119.4, 116.7, 82.8, 44.5, 39.5, 38.2, 37.2, 34.1, 33.9, 32.1, 30.0, 29.4, 28.0, 22.4, 20.3, 18.5, 17.5.

IR (Diamond-ATR,neat): $\tilde{\nu}_{max}$ = 2932, 2872, 2362, 2335, 1590, 1492, 1456, 1260, 960, 750.

HRMS (EI) calcd for $C_{21}H_{30}O$ $[M]^+$: 298.2291; found: 298.2299.

$[\alpha]_D^{20}$ = +101.1° (c = 0.12, CH_2Cl_2)

Tetracycle 42



S51 **S52** **42**

A solution of hydrochloric acid (~1.25 M in methanol, 1.5 mL mmol, equiv) was added to a solution of **S51** (26.5 mg, 77.4 µmol, 1 equiv) in dichloromethane (0.5 mL) and the resulting solution was heated to 35 °C. After 1 h, the reaction mixture was diluted with dichloromethane (8 mL) and saturated aqueous sodium bicarbonate solution (10 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated to yield **S52** as a colorless foam that was directly used in the following reaction without further purification.

A solution of hydroiodic acid (57 wt.% in water 102 µL, 774 µmol, 10.0 equiv) was added to a solution of the crude phenol **S52** (23.1 mg, 77.4 µmol, 1 equiv) in benzene (2 mL) in an Ace® pressure tube. The tube was sealed and the reaction mixture was heated to 90 °C. After 16 h, the reaction mixture was cooled to 23 °C and saturated aqueous sodium bicarbonate solution (10 mL) was added. The mixture was extracted with dichloromethane (3 × 10 mL), the combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (n-heptane) to yield **42** (11.8 mg, 51% over two steps) as a colorless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.76 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12–7.07 (m, 1H), 7.00–6.96 (m, 1H), 6.84–6.78 (m, 2H), 2.59 (d, J = 4.0 Hz, 2H), 1.79–1.63 (m, 4H), 1.61–1.54 (m, 1H), 1.52–1.26 (m, 6H), 1.25–1.16 (m, 1H), 1.14 (s, 3H), 0.93 (s, 3H), 0.93 (s, 3H), 0.76 (d, J = 6.8 Hz, 3H).

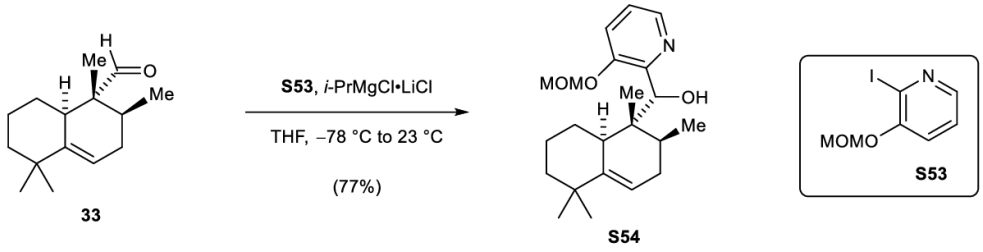
^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.9, 129.5, 127.2, 121.3, 119.6, 117.0, 81.6, 45.8, 42.1, 37.4, 33.6, 33.6, 32.8, 31.9, 30.7, 29.0, 22.6, 22.0, 18.0, 17.1, 16.4.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2949, 1586, 1488, 1456, 1387, 1254, 1171, 1036, 935, 750.

HRMS (EI) calcd for $C_{21}H_{30}O$ $[M]^+$: 298.2291; found: 298.2291.

$[\alpha]_D^{20}$ = +25.5° (c = 0.13, CH_2Cl_2).

Benzylic alcohol S54



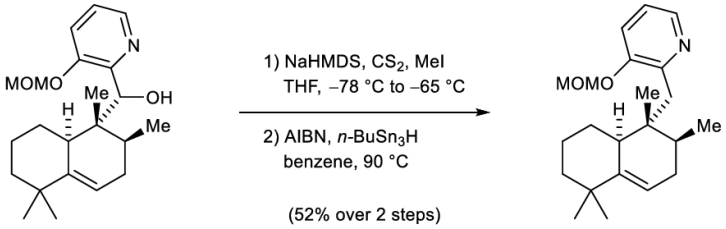
To a solution of **S53**[29] (178 mg, 672 µmol, 1.40 equiv) in tetrahydrofuran (1.5 mL) was added a solution of isopropylmagnesium chloride lithium chloride complex (1.30 M in tetrahydrofuran, 517 µL, 672 µmol, 1.40 equiv) at –40 °C. After 15 min, a solution of aldehyde **33** (106 mg, 480 µmol, 1 equiv) in tetrahydrofuran (0.5 mL) was added and the reaction mixture was allowed to warm to 23 °C. After 24 h, diethyl ether (10 mL) and saturated aqueous ammonium chloride solution (10 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 10 mL).The combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over magnesium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to yield **S54** (133 mg, 91%) as a colorless oil. The inconsequential mixture of diastereoisomers was partially characterized by HRMS and IR spectroscopy.

TLC (10% ethyl acetate in hexanes): $R_f = 0.11$ (CAM).

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3468, 2955, 2925, 1448, 1408, 1265, 1154, 1082, 1040, 986.

HRMS (ESI) calcd for $C_{22}H_{34}NO_3^+$ $[M+H]^+$: 360.2533; found: 360.2533.

Methoxymethyl-ether S55



S54 **S55**

A solution of sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 1.78 mL, 1.78 mmol, 5.00 equiv) was added dropwise to a solution of **54** (128 mg, 356 µmol, 1 equiv) in tetrahydrofuran (5 mL) at −78 °C. After 35 min, carbon disulfide (430 µL, 7.12 mmol, 20.0 equiv) was added dropwise to the orange solution and the resulting red solution was allowed to warm to −65 °C. After 1 h, methyl iodide (443 µL, 7.12 mmol, 20.0 equiv) was added to the reaction mixture. After 1 h, saturated aqueous ammonium chloride solution (20 mL) was added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered through a plug of silica and the obtained residue was used without further purification.

Note: benzene was degassed via freeze-pump-thaw (three cycles) prior to use.
A degassed solution of the xanthogenate (160 mg, 356 µmol, 1 equiv), 2,2'-azobis(2-methylpropionitrile) (AIBN) (29.2 mg, 178 µmol, 0.500 equiv) and tributyltin hydride (720 µL, 2.67 mmol, 7.50 equiv) in benzene (6.5 mL) was heated to 90 °C. After 2 h, the reaction mixture was cooled to 23 °C and directly purified by flash-column chromatography on silica gel (hexanes initially, grading to 5% ethyl acetate in hexanes) to yield **S55** as a colorless oil (64.0 mg, 52% over 2 steps).

TLC (10% ethyl acetate in hexanes): R_f = 0.38 (UV, $KMnO_4$).

^{1}H NMR (599 MHz, $CDCl_3$): δ = 8.19 (dd, J = 4.7, 1.5 Hz, 1H), 7.38 (dd, J = 8.2, 1.5 Hz, 1H), 7.04 (dd, J = 8.2, 4.7 Hz, 1H), 5.40 (dt, J = 5.7, 2.1 Hz, 1H), 5.21 (d, J = 6.9 Hz, 1H), 5.17 (d, J = 6.9 Hz, 1H), 3.50 (s, 3H), 3.00 (d, J = 13.4 Hz, 1H), 2.79 (d, J = 13.4 Hz, 1H), 2.38 (d, J = 12.6 Hz, 1H), 1.95–1.87 (m, 1H), 1.82–1.76 (m, 1H), 1.66 (d, J = 12.2 Hz, 1H), 1.62–1.56 (m, 1H), 1.51–1.46 (m, 1H), 1.46–1.40 (m, 1H), 1.38–1.34 (m, 1H), 1.20–1.14 (m, 1H), 1.06 (d, J = 6.7 Hz, 3H), 1.02 (s, 3H), 0.98–0.92 (m, 1H), 0.91 (s, 3H), 0.81 (s, 3H).

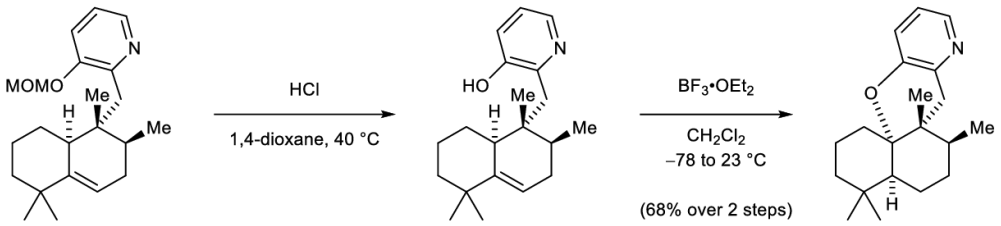
^{13}C NMR (151 MHz, $CDCl_3$): δ = 152.7, 151.4, 146.7, 141.8, 121.7, 120.7, 115.5, 95.0, 56.4, 41.5, 41.0, 40.6, 39.6, 36.4, 35.4, 31.9, 29.9, 29.6, 28.5, 22.8, 16.4, 16.0.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2929, 1584, 1446, 1380, 1260, 1156, 1081, 1065, 995, 799.

HRMS (ESI) calcd for $C_{22}H_{34}NO_2^+$ $[M+H^+]^+$: 344.2584; found: 344.2584.

$[\alpha]_D^{22}$ = +45.4° (c = 0.55, CH_2Cl_2).

Pyrindine 43



S55 **S56** **43**

A solution of hydrochloric acid (4 M in 1,4-dioxane, 0.5 mL, 2.00 mmol, 43.0 equiv) was added to a solution of **S55** (16.0 mg, 46.6 µmol, 1 equiv) in dichloromethane (1 mL) and the resulting solution was heated to 40 °C. After 6 h, the reaction mixture was diluted with dichloromethane (8 mL) and saturated aqueous sodium bicarbonate solution (10 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated to yield **S56** as a colorless foam that was directly used in the following reaction without further purification.

A solution of boron trifluoride diethyl etherate (48% in diethyl ether, 122 µL, 466 µmol, 10.0 equiv) was added dropwise to a solution of the crude phenol **S56** (14.0 mg, 46.6 µmol, 1 equiv) in dichloromethane (2.5 mL) at –40 °C and the reaction mixture was allowed to warm to 23 °C over a period of 2.5 h. After 7 h, saturated aqueous sodium bicarbonate solution (10 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (15% ethyl acetate in n-heptane) to yield **43** (9.5 mg, 68% over two steps) as an amorphous solid.

TLC (20% ethyl acetate in hexanes): R_f = 0.21 (UV, CAM).

^{1}H NMR (800 MHz, DMSO-d6): δ = 9.56 (s, 1H), 7.92 (dd, J = 4.5, 1.5 Hz, 1H), 7.06 (dd, J = 8.1, 1.6 Hz, 1H), 6.97 (dd, J = 8.1, 4.6 Hz, 1H), 2.96 (d, J = 13.3 Hz, 1H), 2.68 (d, J = 13.2 Hz, 1H), 2.27–2.20 (m, 1H), 1.98–1.90 (m, 1H), 1.92–1.82 (m, 3H), 1.82–1.76 (m, 1H), 1.56–1.49 (m, 2H), 1.43–1.37 (m, 1H), 1.37–1.32 (m, 1H), 1.29–1.25 (m, 1H), 0.93 (s, 3H), 0.92 (s, 3H), 0.84 (s, 3H), 0.76 (d, J = 6.8 Hz, 3H).

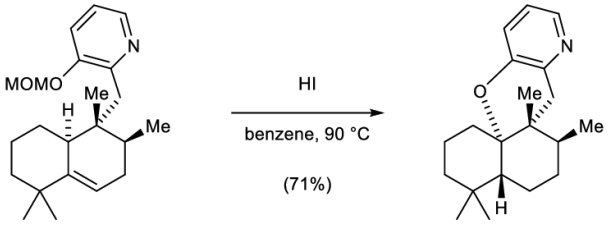
^{13}C NMR (201 MHz, DMSO-d6): δ = 151.9, 148.0, 138.9, 133.8, 132.4, 121.6, 120.9, 41.9, 39.2, 38.5, 33.9, 33.2, 28.4, 28.1, 26.1, 25.9, 21.8, 21.2, 19.6, 15.8.

IR (Diamond-ATR,neat): $\tilde{\nu}_{max}$ = 2926, 2612, 1576, 1456, 1378, 1359, 1287, 1173, 1115, 798.

HRMS (EI) calcd for $C_{20}H_{29}NO$ $[M]^+$: 299.2244; found: 299.2243.

$[\alpha]_D^{20}$ =+51.6° (c = 0.17, CH_2Cl_2)

Pyridine 44



S55 **44**

A solution of hydroiodic acid (57 wt.% in water, 154 µL, 1.16 mmol, 40.0 equiv) was added to a solution of **S55** (10.0 mg, 29.1 µmol, 1 equiv) in benzene (1.5 mL) in an Ace® pressure tube. The tube was sealed and heated to 90 °C. After 17 h, the reaction mixture was cooled to 23 °C and saturated aqueous sodium bicarbonate solution (8 mL) and saturated aqueous sodium thiosulfate (2 mL) were added. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in n-heptane) to yield **44** (6.20 mg, 71%) as colorless amorphous solid. Recrystallization from ethyl acetate gave crystals suitable for single-crystal X-ray diffraction.

TLC (20% ethyl acetate in hexanes): R_f = 0.27 (UV, CAM).

^{1}H NMR (599 MHz, $CDCl_3$)): δ = 8.09 (dd, J = 4.6, 1.5 Hz, 1H), 7.09 (dd, J = 8.2, 1.5 Hz, 1H), 7.04 (dd, J = 8.2, 4.6 Hz, 1H), 2.86 (d, J = 18.0 Hz, 1H), 2.70 (d, J = 18.0 Hz, 1H), 1.74–1.57 (m, 5H), 1.53–1.48 (m, 1H), 1.47–1.38 (m, 3H), 1.34–1.28 (m, 2H), 1.21 (td, J = 13.5, 3.5 Hz, 1H), 1.10 (s, 3H), 0.97 (s, 3H), 0.93 (s, 3H), 0.80 (d, J = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 149.2, 143.5, 141.2, 124.0, 122.5, 82.6, 45.7, 41.9, 38.3, 36.7, 33.6, 32.7, 32.4, 30.6, 29.0, 22.5, 21.9, 17.9, 17.1, 16.4.

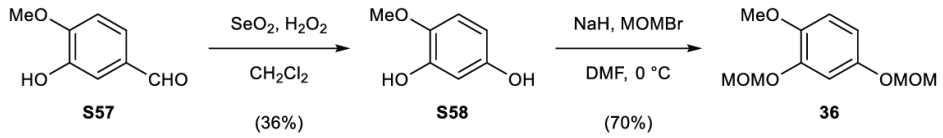
IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2948, 1438, 1258, 1170, 1107, 1016, 931, 908, 805, 720.

HRMS (ESI) calcd for $C_{20}H_{30}NO^+$ $[M+H]^+$: 300.2322; found: 300.2321.

$[\alpha]_D^{20}$ = +54.9° (c = 0.12, CH_2Cl_2).

Synthesis of (–)-Mamanuthaquinone (6)

Arene 36



Selenium dioxide (233 mg, 2.10 mmol, 0.0800 equiv) was added to a solution of iso-vanillin (**S57**) (4.00 g, 26.3 mmol, 1 equiv) and hydrogenperoxide (30% in water, 5.91 mL, 57.8 mmol, 2.20 equiv) in dichloromethane (70 mL). After 16 h, water (30 mL) was added. The layers were separated and the organic layer was washed with saturated aqueous sodium bicarbonate solution (30 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to yield **S58** (1.32 g, 36%) as a clear, colorless solid. The obtained analytical data were in full agreement with those values reported in the literature.[30]

Sodium hydride (60% mineral oil dispersion, 771 mg, 19.3 mmol, 2.50 equiv) was slowly added to a solution of bisphenol **S58** (1.08 g, 7.71 mmol, 1 equiv) in N,N-dimethylformamide (30 mL) at 0 °C. After 1 h, bromomethyl methyl ether (1.29 mL, 15.8 mmol, 2.05 equiv) was added to the dark brown suspension and the reaction mixture was allowed to warm to 23 °C. After 5 h, water (40 mL) was carefully added and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic extracts 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. The residue was purified by flash-column chromatography on silica gel (30% ethyl acetate in hexanes) to yield **36** (1.23 g, 70%) as a colorless oil.

TLC (20% ethyl acetate in hexanes): $R_f = 0.20$ (CAM).

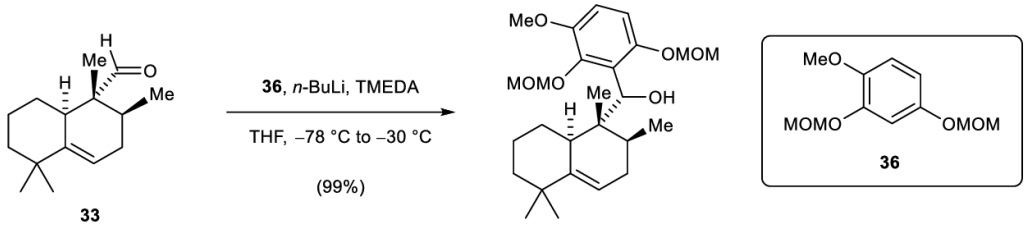
^{1}H NMR (599 MHz, $CDCl_3$): δ = 6.90 (d, J = 2.8 Hz, 1H), 6.80 (d, J = 8.9 Hz, 1H), 6.67 (dd, 8.9, 2.8 Hz, 1H), 5.21 (s, 2H), 5.10 (s, 2H), 3.83 (s, 3H), 3.51 (s, 3H), 3.48 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 151.5, 147.1, 145.1, 112.4, 109.0, 106.8, 95.5, 95.2, 56.4, 56.2, 55.9.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2902, 2363, 1596, 1505, 1226, 1150, 1130, 1074, 998, 922.

HRMS (EI) calcd for $C_{11}H_{16}O_5$ $[M]^+$: 228.0992; found: 228.0984.

Benzylic alcohol S59



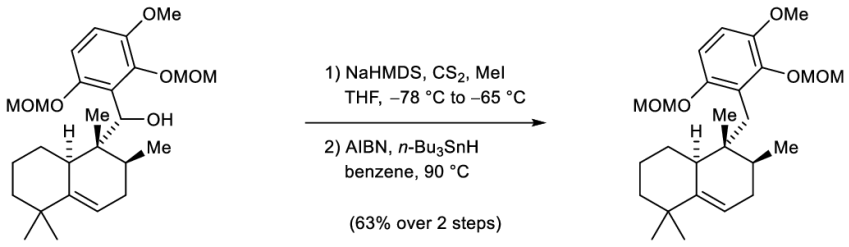
To a solution of **36** (224 mg, 981 µmol, 1.40 equiv) in tetrahydrofuran (4 mL) and freshly distilled (over CaH_2) N,N,N′,N′-tetramethylethane-1,2-diamine (317 µL, 2.10 mmol, 3.00 equiv) was added a solution of n-butyllithium (2.44 M in hexanes 362 µL, 911 µmol, 1.30 equiv) at –78 °C. The reaction mixture was allowed to warm to –30 °C. After 1.5 h, the reaction mixture was cooled to –78 °C and aldehyde **33** (154 mg, 700 µmol, 1 equiv) in tetrahydrofuran (2 mL) was added. The reaction mixture was warmed to –30 °C over a period of 2 h, then diethyl ether (30 mL) and saturated aqueous ammonium chloride solution (30 mL) were added. The layers were separated, the aqueous layer was extracted with diethyl ether (3 × 20 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (40 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to yield **S59** (313 mg, 99%) as a colorless oil. The mixture of inseparable diastereoisomers was characterized by HRMS and IR spectroscopy.

TLC (20% ethyl acetate in hexanes): $R_f = 0.18$ (CAM).

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3565, 2953, 1508, 1484, 1256, 1229, 1154, 1077, 1027, 924.

HRMS (EI) calcd for $C_{26}H_{40}O_6$ $[M]^+$: 448.2819; found: 448.2841.

Olefin 37



S59 **37**

A solution of sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 3.49 mL, 3.49 mmol, 5.00 equiv) was added dropwise to a solution of **S59** (313 mg, 698 µmol, 1 equiv) in tetrahydrofuran (7 mL) at −78 °C. After 30 min, carbon disulfide (842 µL, 14.0 mmol, 20.0 equiv) was slowly added and the reaction mixture was allowed to warm to −65 °C. After 1 h, methyl iodide (869 µL, 14.0 mmol, 20.0 equiv) was slowly added to the reaction mixture. After 1 h, saturated aqueous ammonium chloride solution (25 mL) and ethyl acetate (30 mL) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered through a short plug of silica and the obtained residue was used without further purification.

Note: benzene was degassed via freeze-pump-thaw (three cycles) prior to use.
A degassed solution of the xanthogenate (376 mg, 698 µmol, 1 equiv), 2,2'-azobis(2-methylpropionitrile) (AIBN) (56.6 mg, 344 µmol, 0.500 equiv) and tributyltin hydride (1.50 g, 5.17 mmol, 7.50 equiv) in benzene (25 mL) was heated to 90 °C. After 6 h, the reaction mixture was directly purified by flash-column chromatography on silica gel (3% ethyl acetate in hexanes) to yield **37** as a colorless oil (190 mg, 63% over 2 steps).

TLC (20% ethyl acetate in hexanes): R_f = 0.34 (CAM).

^{1}H NMR (800 MHz, , C_6D_6): δ = 6.94 (d, J = 8.9 Hz, 1H), 6.48 (d, J = 8.9 Hz, 1H), 5.62–5.56 (m, 1H), 5.13 (q, J = 5.8 Hz, 2H), 4.98–4.88 (m, 2H), 3.42 (s, 3H), 3.30 (s, 3H), 3.26 (d, J = 12.9 Hz, 1H), 3.23 (s, 3H), 3.00 (d, J = 12.9 Hz, 1H), 2.96–2.91 (m, 1H), 2.04–1.99 (m, 2H), 1.84–1.77 (m, 1H), 1.67–1.58 (m, 1H), 1.53–1.48 (m, 1H), 1.46–1.40 (m, 2H), 1.28–1.23 (m, 1H), 1.22 (s, 3H), 1.18 (d, J = 6.8 Hz, 3H), 1.16 (s, 3H), 1.09 (s, 3H), 0.97–0.89 (m, 1H).

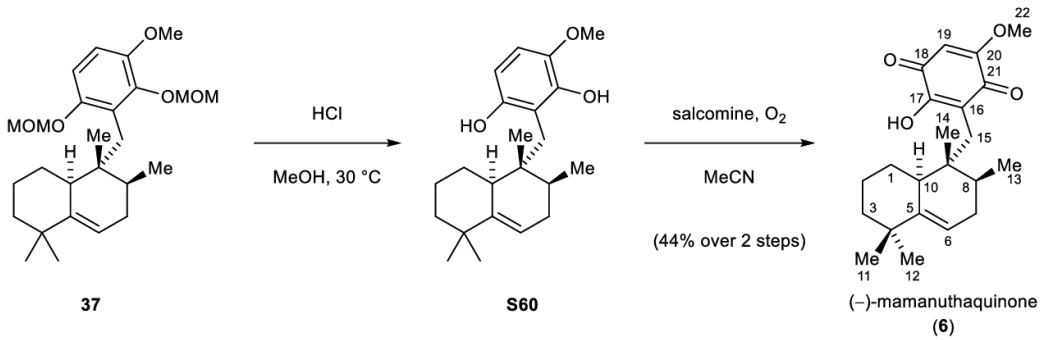
^{13}C NMR (201 MHz, C_6D_6): δ = 151.9, 147.8, 147.7, 147.5, 126.0, 115.5, 111.3, 109.7, 99.5, 95.8, 57.4, 56.0, 55.8, 42.6, 41.9, 41.2, 39.6, 36.9, 36.3, 32.3, 31.5, 30.3, 28.4, 23.4, 16.8, 15.0.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2930, 1484, 1251, 1152, 1075, 1038, 982, 925, 801, 720.

HRMS (EI) calcd for $C_{26}H_{40}O_5$ $[M]^+$: 432.2870; found: 432.2868.

$[\alpha]_D^{20}$ = +1.61 ° (c = 0.66, CH_2Cl_2)

(–)-Mamanuthaquinone (6)



37 **S60** (–)-mamanuthaquinone (**6**)

A solution of hydrochloric acid (~1.25 M in methanol, 3 mL) was added to a solution of **37** (33.0 mg, 76.3 µmol, 1 equiv) in dichloromethane (1 mL) and the resulting solution was heated to 30 °C. After 5 h, the reaction mixture was diluted with dichloromethane (5 mL) and saturated aqueous sodium bicarbonate solution (5 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to yield **S60** as a brown foam that was directly used in the following reaction.

N,N′-Bis(salicylidene)ethylenediaminocobalt(II) (19.8 mg, 61.0 mmol, 0.800 equiv) was added to a solution of crude phenol **S60** (26.3 mg, 76.3 µmol, 1 equiv) in N,N-dimethylformamide (6 mL) at 23 °C and oxygen was passed through the reaction mixture for 20 min. After 60 min, water (20 mL) was added and the mixture was extracted with diethyl ether (4 × 20 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (40% ethyl acetate in hexanes with 0.5% acetic acid) to give (–)-mamanuthaquinone (**6**) (12.0 mg, 44% over 2 steps) as a bright yellow oil.

TLC (40% ethyl acetate in hexanes with 0.5% acetic acid), R_f = 0.21 (UV, CAM).

^{1}H NMR (599 MHz, $CDCl_3$): δ = 7.43 (s, 1H, O-H), 5.87 (s, 1H, H-19), 5.44–5.34 (m, 1H, H-6), 3.87 (s, 3H, H-22), 2.61 (d, $^2J_{15A/15B}$ = 13.2 Hz, 1H, H-15$_A$), 2.48 (d, $^2J_{15B/15A}$ = 13.2 Hz, 1H, H-15$_B$), 2.11 (br d, $^3J_{10/1A}$ = 12.4 Hz, 1H, H-10), 2.02–1.96 (m, 1H, H-7$_A$), 1.83 (d, $^3J_{1A/10}$ = 12.4 Hz, 1H, H-1$_A$), 1.80–1.74 (m, 1H, H-7$_B$), 1.51–1.48 (m, 1H, H-2$_A$), 1.46–1.35 (m, 3H, H-2$_B$, H-3$_A$, H-8), 1.17–1.13 (m, 1H, H-3$_B$), 1.03 (s, 3H, H-11), 1.00 (d, $^3J_{13/8}$ = 7.0 Hz, 3H, H-13), 0.97–0.94 (m, 4H, H-1$_B$, H-12), 0.75 (s, 3H, H-14).

^{13}C NMR (201 MHz, $CDCl_3$): δ = 182.6 (C-18), 182.4 (C-21), 161.8 (C-20), 153.0 (C-17), 146.5 (C-5), 118.5 (C-16), 115.1 (C-6), 102.2 (C-19), 57.0 (C-22), 41.9 (C-10), 41.5 (C-3), 41.1 (C-9), 36.7 (C-8), 36.6 (C-4), 32.9 (C-15), 31.7 (C-7), 30.8 (C-1), 29.9 (C-11), 28.2 (C-12), 22.9 (C-2), 16.8 (C-13), 16.2 (C-14).

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3344, 2924, 2891, 2363, 1645, 1608, 1446, 1350, 1234, 1035.

HRMS (EI) calcd for $C_{22}H_{30}O_4$ [M]$^+$: 358.2139; found: 358.2145.

$[\alpha]_D^{20}$ = –258.4° (c = 0.16, CH_2Cl_2); lit. $[\alpha]_{546}^{n.a.}$ = –31° (c = 0.058, $CHCl_3$). n.a. not available[31]*

* This lamp (λ = 546 nm) was not accessible in our laboratory.

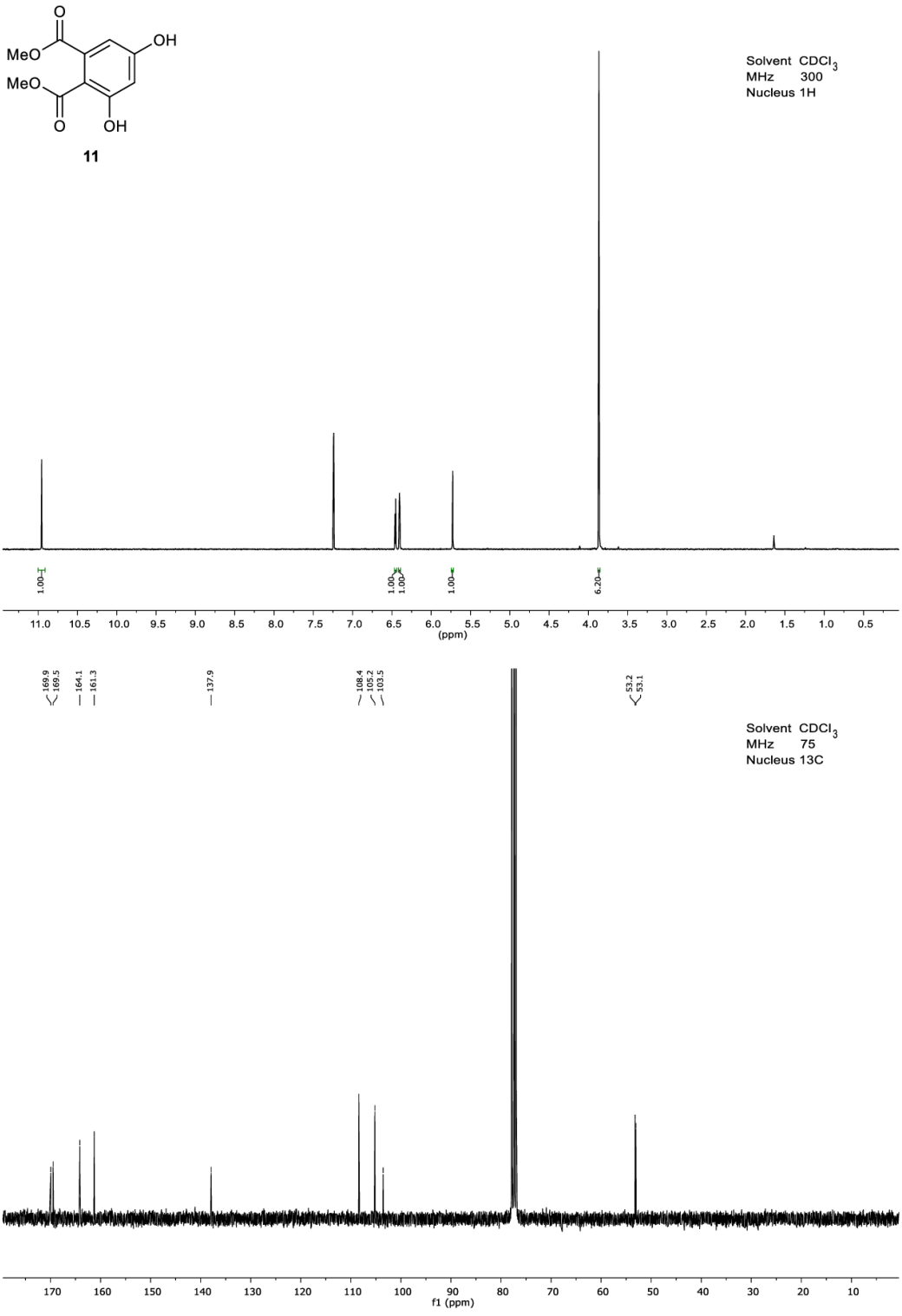
Supplementary Table 10 Comparison of ^{1}H NMR data for natural and synthetic (–)-mamanuthaquinone (**6**).

Proton	Synthetic (599 MHz, $CDCl_3$)	Natural (500 MHz, $CDCl_3$)[31]	Δ: δ (ppm)
1A	1.83 (d, J = 12.4 Hz, 1H)	1.79 (br d, 1H)	+0.04
1B	0.97–0.94 (m, 4H)	0.90 (s, 1H)	
2A	1.51–1.48 (m, 1H)	1.33–1.45 (m, 4H)	
2B	1.46–1.35 (m, 3H)		
3A	1.46–1.35 (m, 3H)		
3B	1.17–1.13 (m, 1H)	1.12 (ddd, J = 13.5, 13.5, 4.3 Hz, 1H)	+ 0.03
6	5.44–5.34 (m, 1H)	5.35 (br s, 1H)	+ 0.04
7A	1.99 (d, J = 17.8 Hz, 1H)	1.95 (ddd, J = 18, 17.5, 4.5 Hz, 1H)	+0.04
7B	1.80–1.74 (m, 1H)	1.73 (m, 1H)	+ 0.04
8	1.46–1.35 (m, 3H)	1.33–1.45 (m, 4H)	
10	2.11 (d, J = 12.4 Hz, 1H)	2.08 (br d, J = 13 Hz, 1H)	+0.03
11	1.03 (s, 3H),	0.99 (s, 3H)	+0.04
12	0.97–0.94 (m, 4H)	0.92 (s, 3H)	
13	1.00 (d, J = 7.0 Hz, 3H)	0.96 (d, J = 7 Hz, 3H)	+0.04
14	0.75 (s, 3H).	0.73 (s, 3H)	+0.02
15A	2.61 (d, J = 13.2 Hz, 1H)	2.58 (d = 13.0 Hz, 1H)	+0.03
15B	2.48 (d, J = 13.1 Hz, 1H)	2.45 (d, J = 13.0 Hz, 1H)	+0.03
19	5.87 (s, 1H)	5.84 (s, 1H)	+0.03
22	3.87 (s, 3H)	3.84 (s, 3H)	+0.03
OH	7.43 (s, 1H)	7.45 (s, 1H)	–0.02

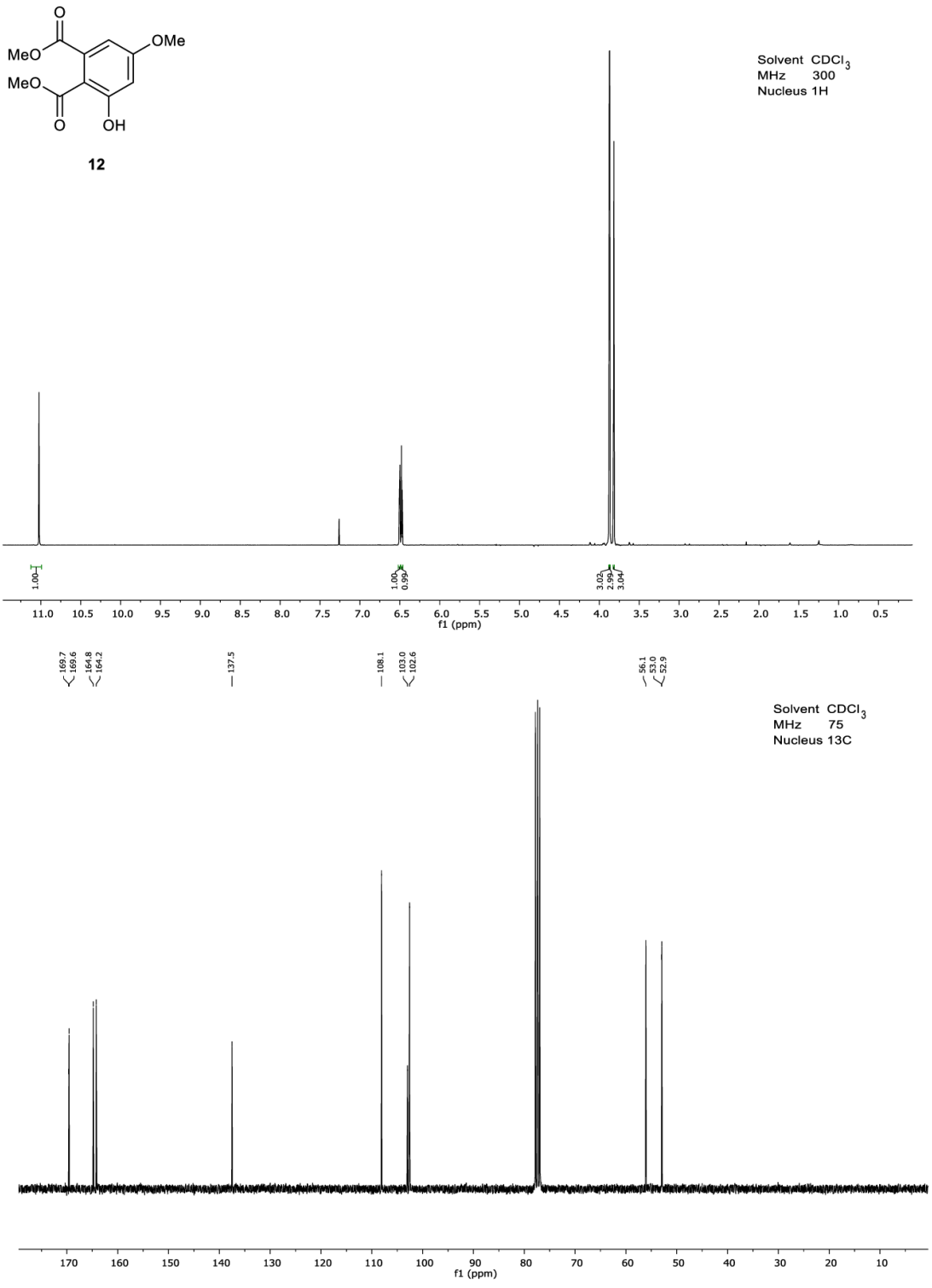
Supplementary Table 11 Comparison of ^{13}C NMR data for natural and synthetic (–)-mamanuthaquinone (**6**). n.a. not available

Carbon	Synthetic (201 MHz, $CDCl_3$)	Natural (n.a., $CDCl_3$)[31]	Δ: δ (ppm)
1	30.8	30.6	+ 0.2
2	22.9	22.7	+ 0.2
3	41.5	41.2	+ 0.3
4	36.6	36.3	+ 0.3
5	146.5	146.3	+ 0.2
6	115.1	114.8	+ 0.3
7	31.7	31.5	+ 0.2
8	36.7	36.4	+ 0.3
9	41.1	40.9	+ 0.2
10	41.9	41.7	+ 0.2
11	29.9	29.7	+ 0.2
12[#]	28.2	27.9	+ 0.3
13[#]	16.8	16.5	+ 0.3
14	16.2	16.0	+ 0.2
15	32.9	32.7	+ 0.2
16	118.5	118.3	+ 0.2
17	153.0	152.8	+ 0.2
18	182.6	182.4	+ 0.2
19	102.2	102.0	+ 0.2
20	161.8	161.5	+ 0.3
21	182.4	182.0	+ 0.4
22	57.0	56.8	+ 0.2

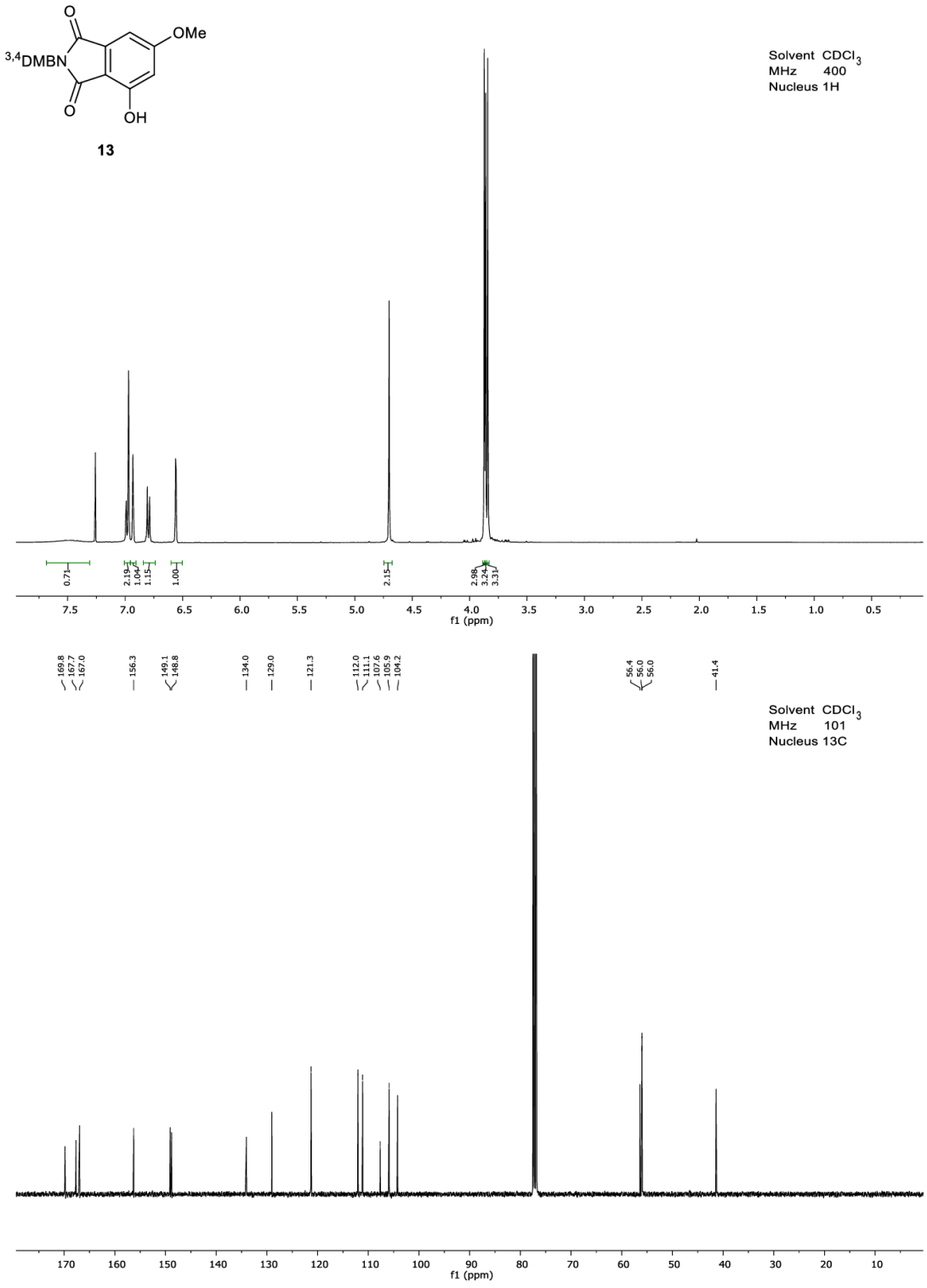
[#] Carbon was reassigned by us on the basis of 2D-NMR studies



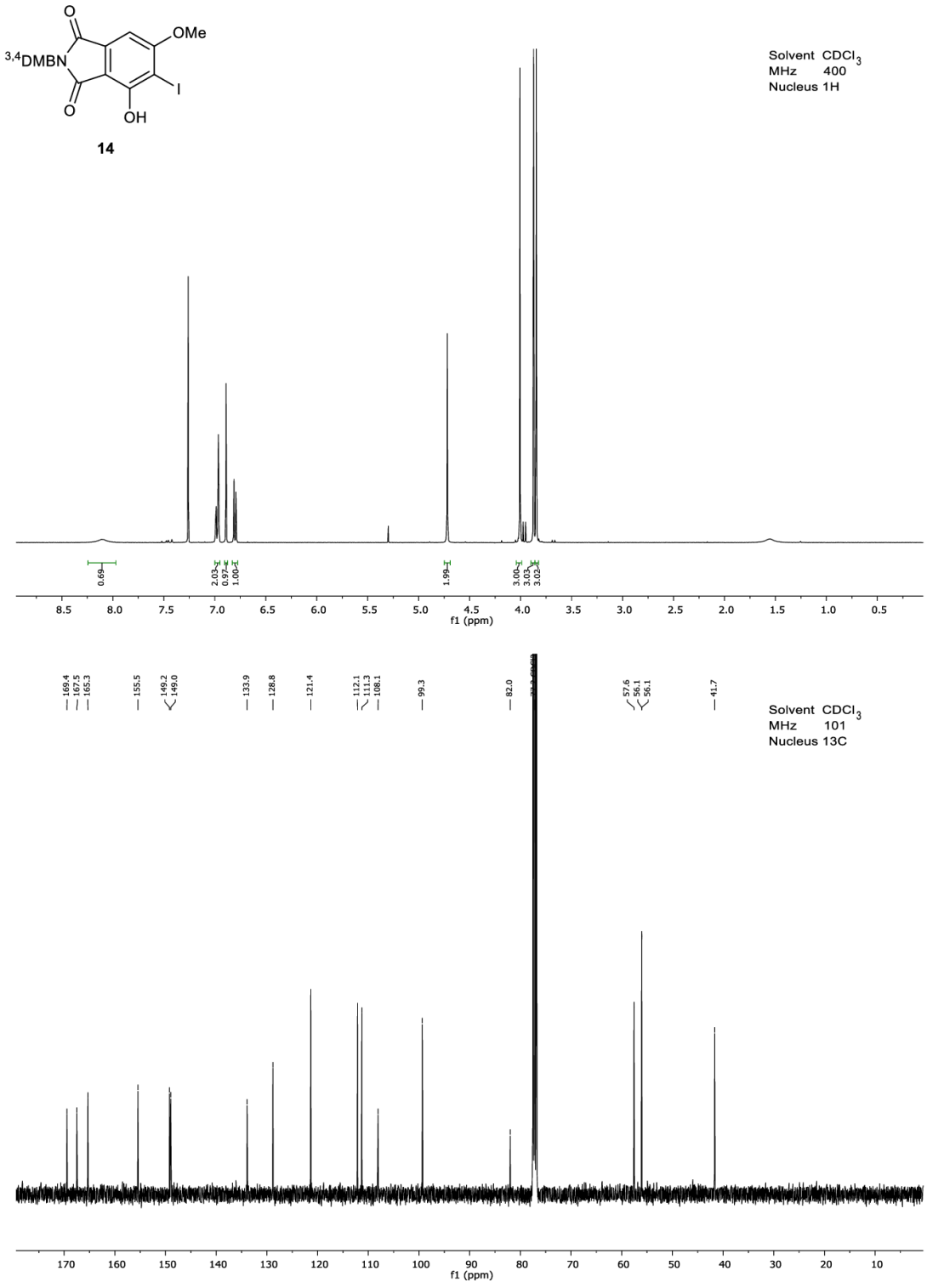
Supplementary Figure 2 ^{1}H and ^{13}C NMR Spectra for **11** in $CDCl_3$.



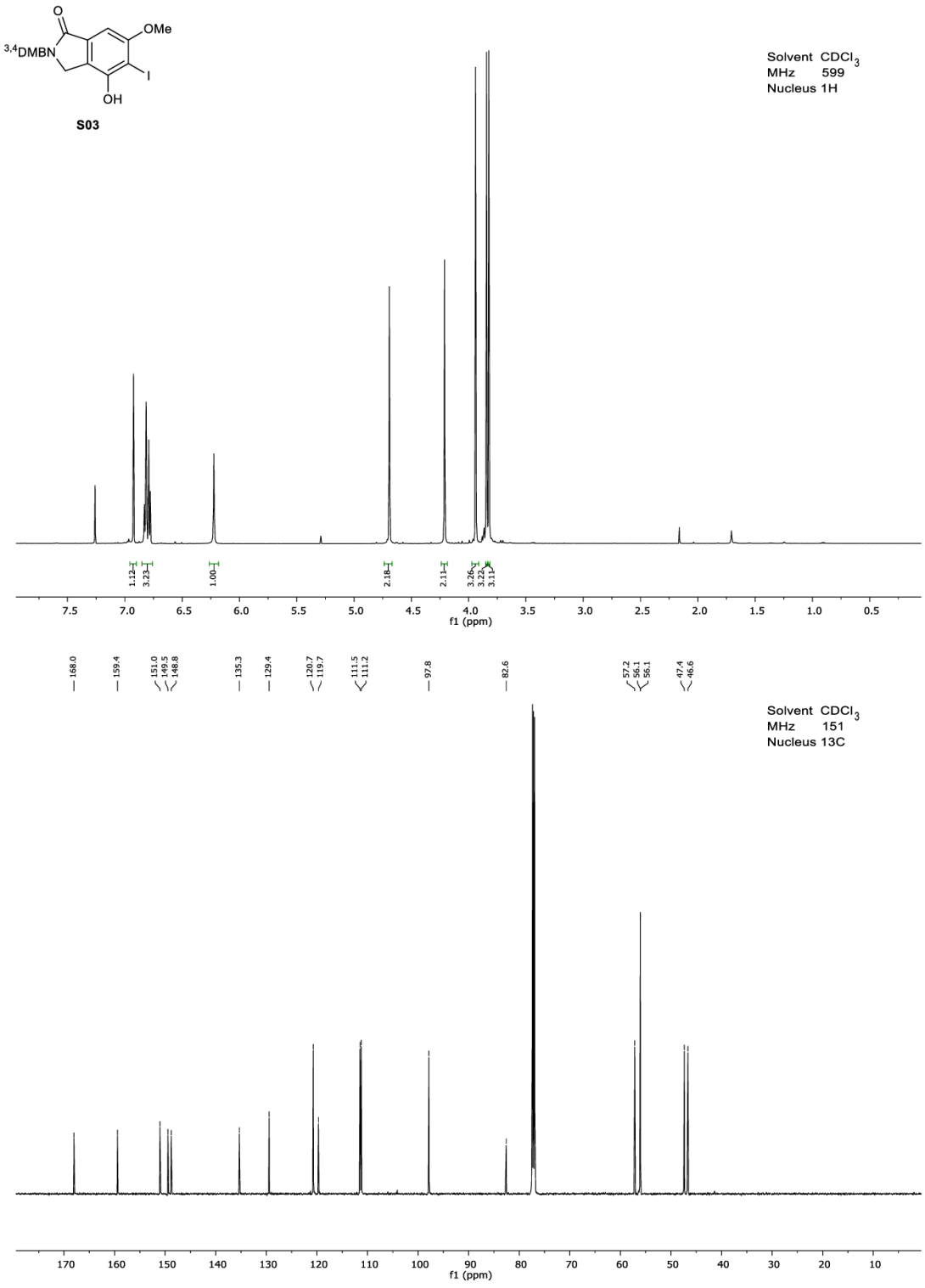
Supplementary Figure 3 ^{1}H and ^{13}C NMR Spectra for **12** in $CDCl_3$.



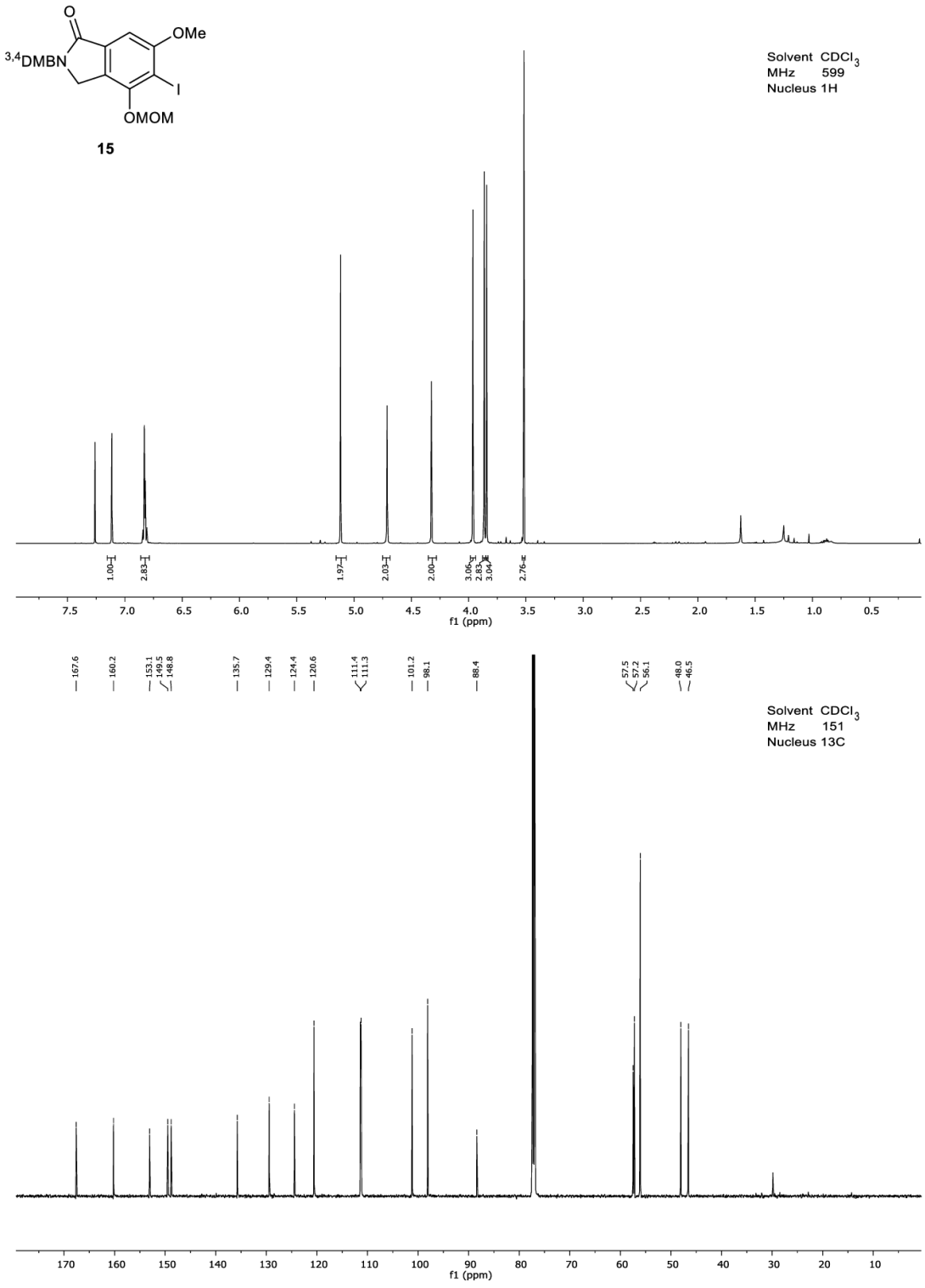
Supplementary Figure 4 ^{1}H and ^{13}C NMR Spectra for **13** in $CDCl_3$.



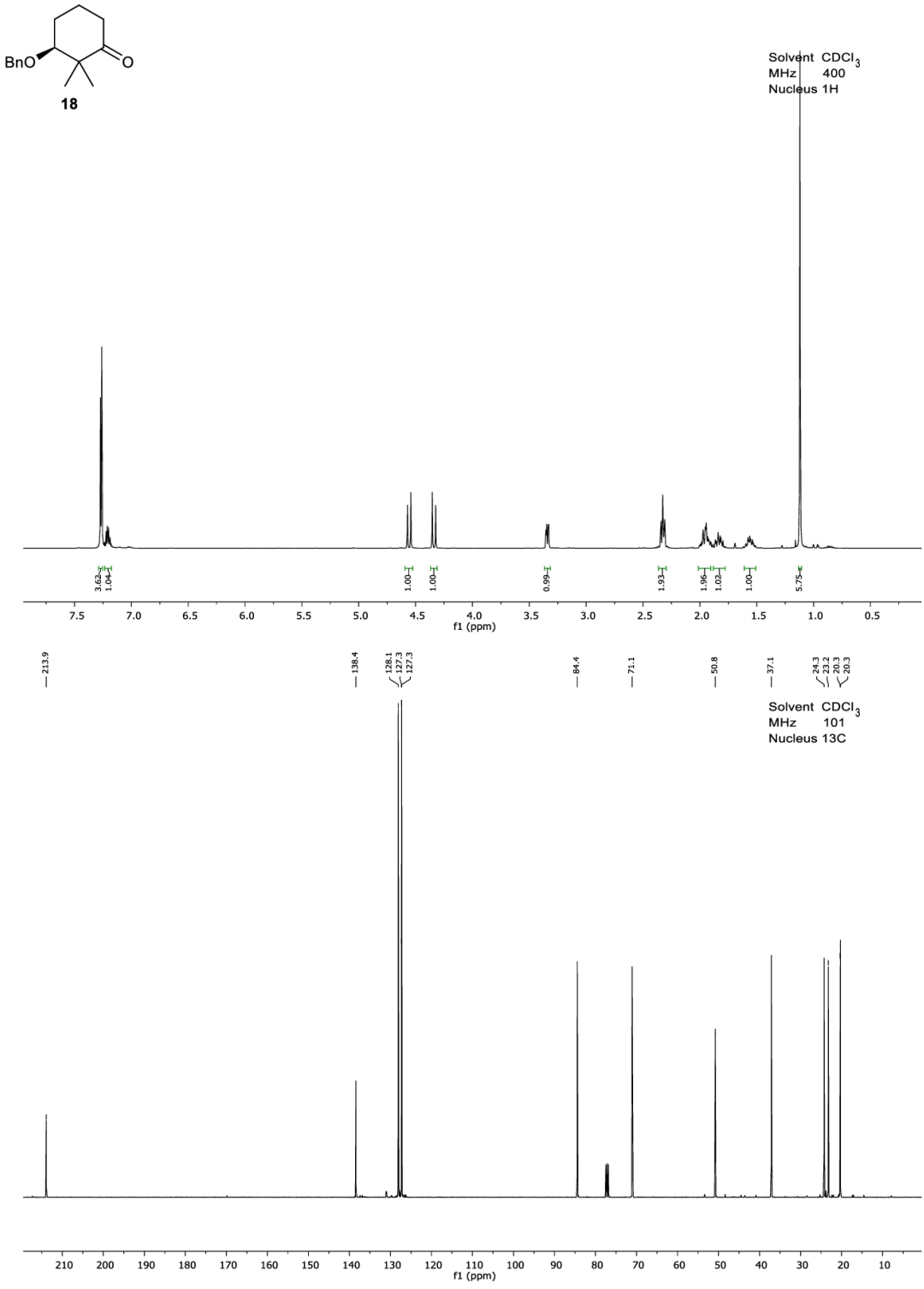
Supplementary Figure 5 ^{1}H and ^{13}C NMR Spectra for **14** in $CDCl_3$.



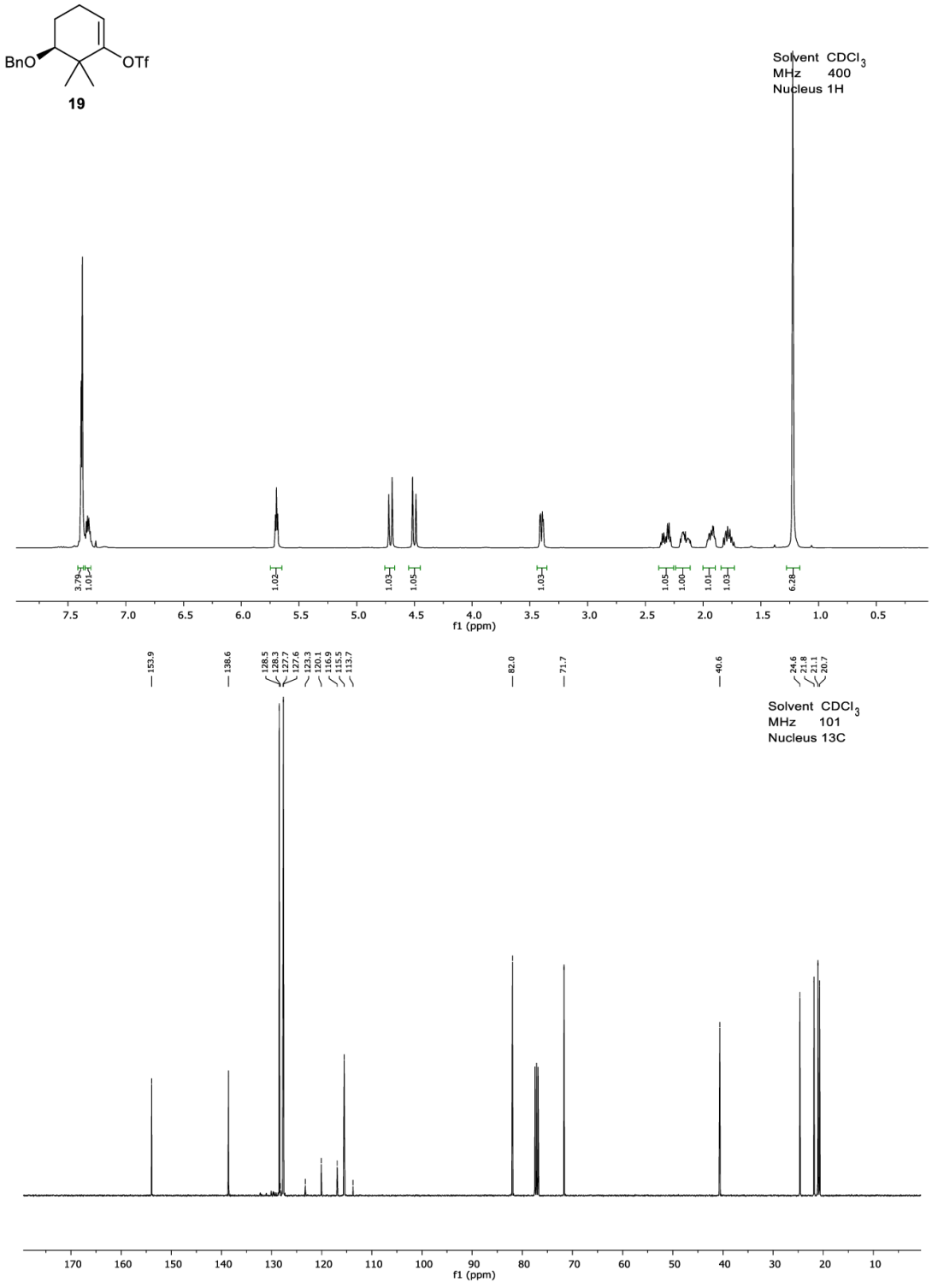
Supplementary Figure 6 ^{1}H and ^{13}C NMR Spectra for **S03** in $CDCl_3$.



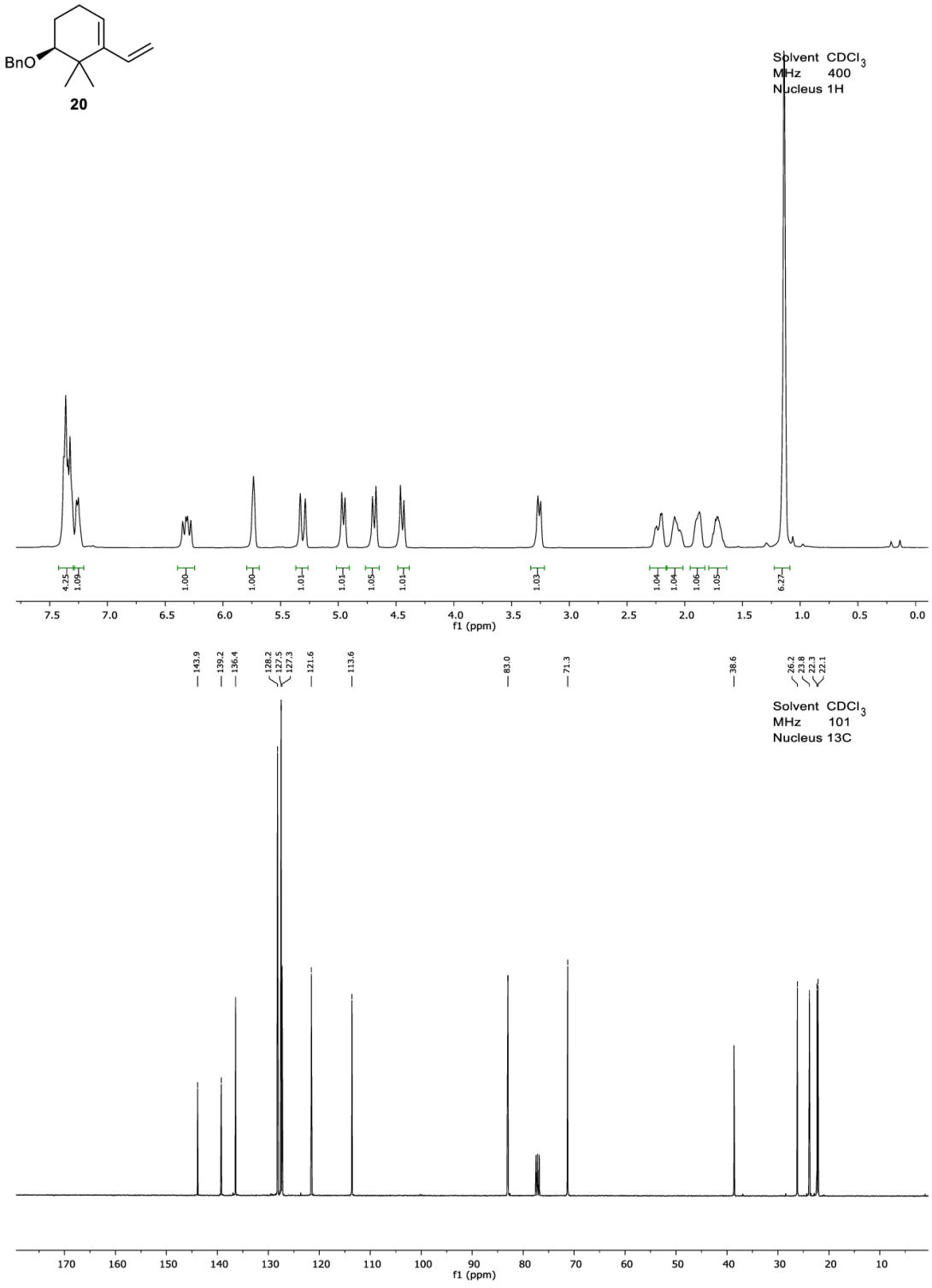
Supplementary Figure 7 ^{1}H and ^{13}C NMR Spectra for **15** in $CDCl_3$.



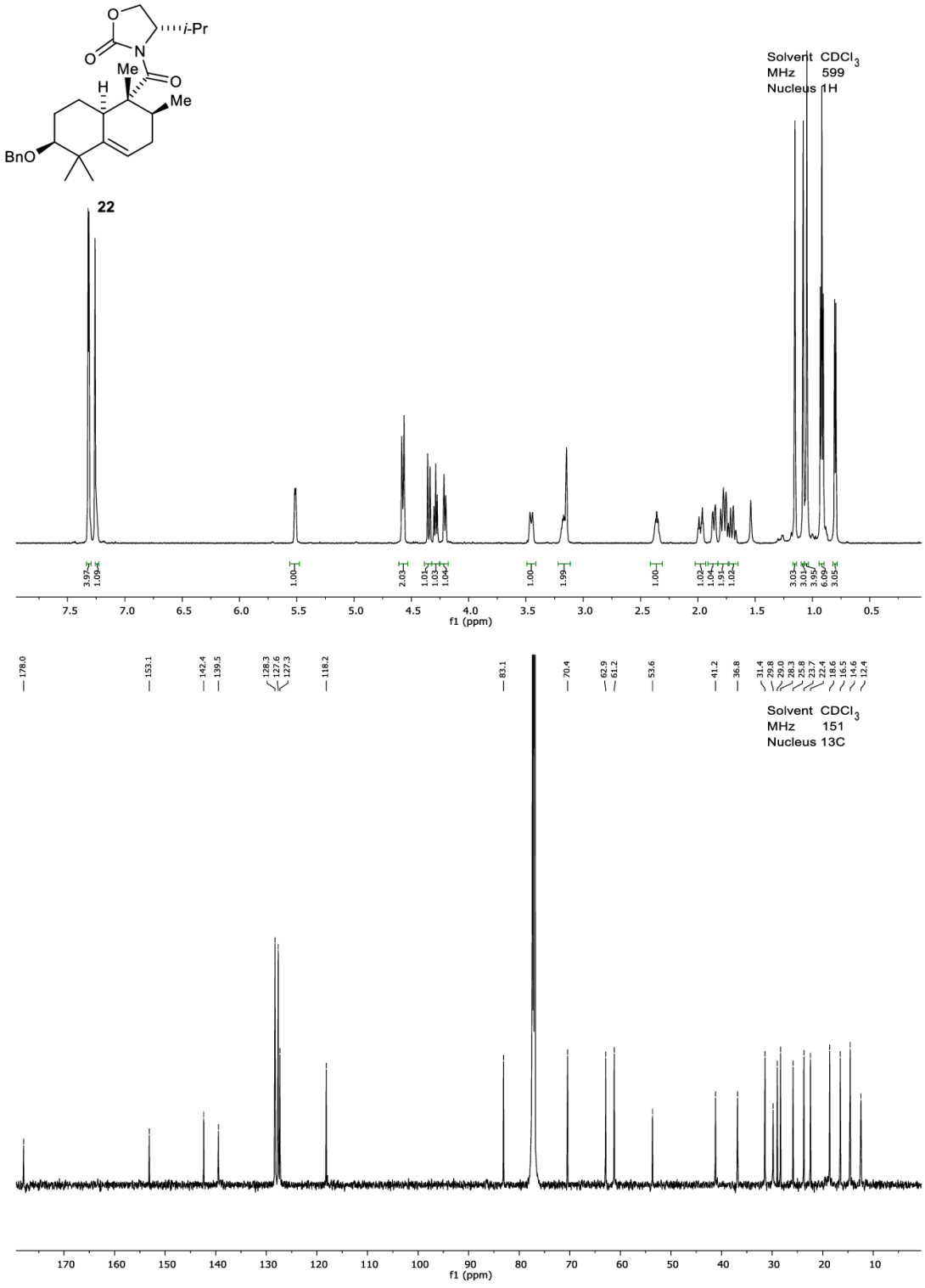
Supplementary Figure 8 ^{1}H and ^{13}C NMR Spectra for **18** in $CDCl_3$.



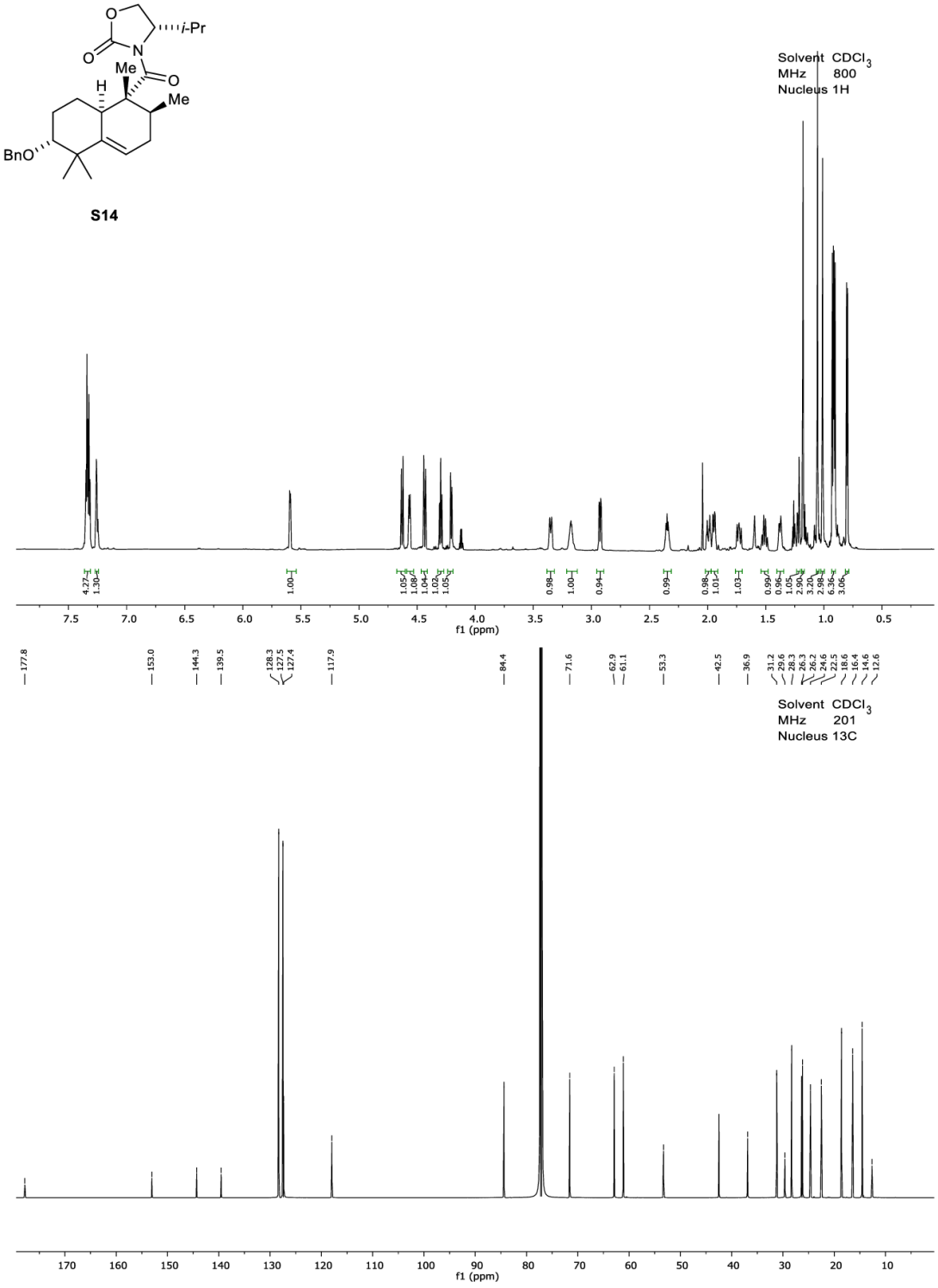
Supplementary Figure 9 ^{1}H and ^{13}C NMR Spectra for **19** in $CDCl_3$.



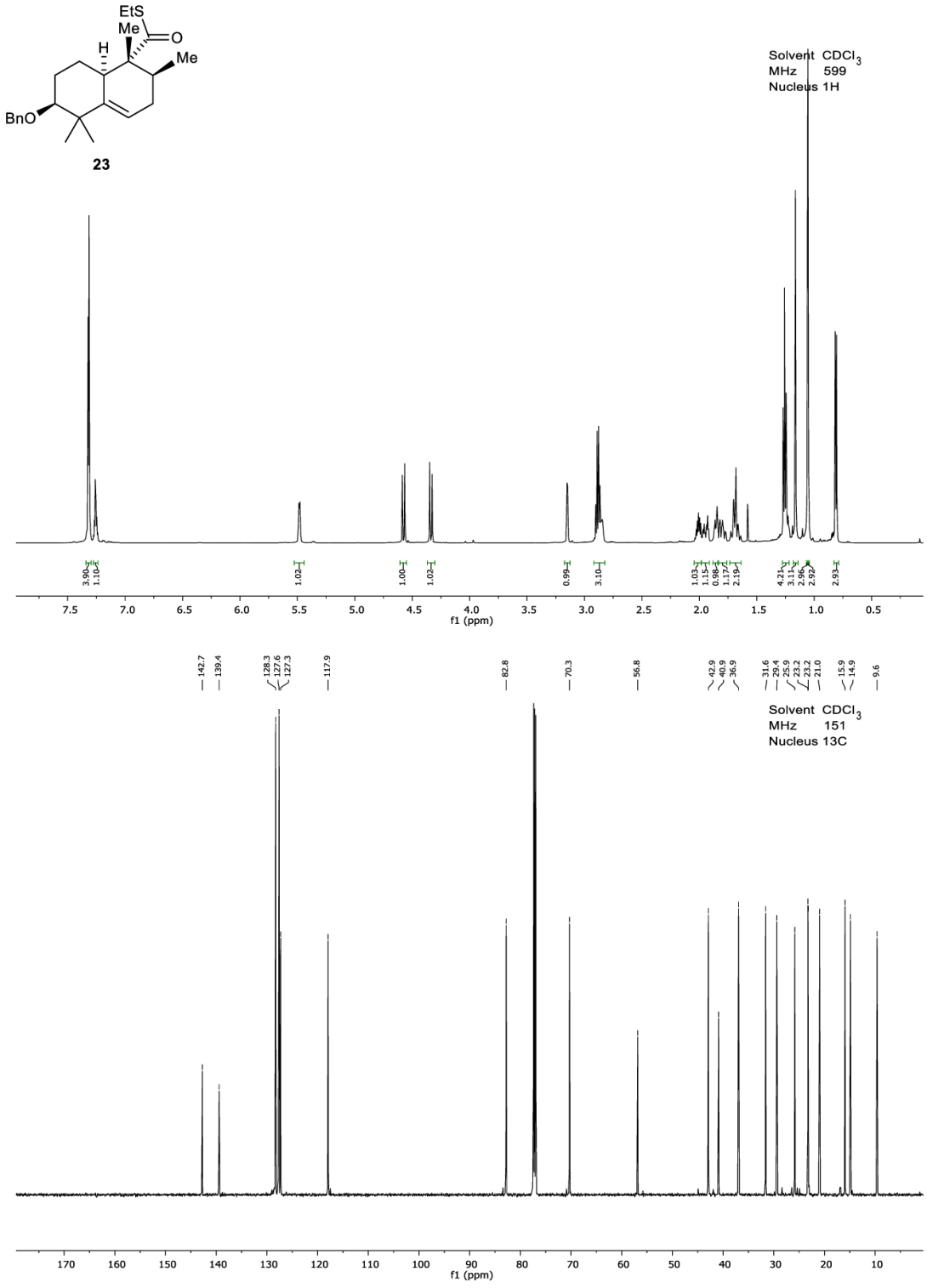
Supplementary Figure 10 ^{1}H and ^{13}C NMR Spectra for **20** in $CDCl_3$.



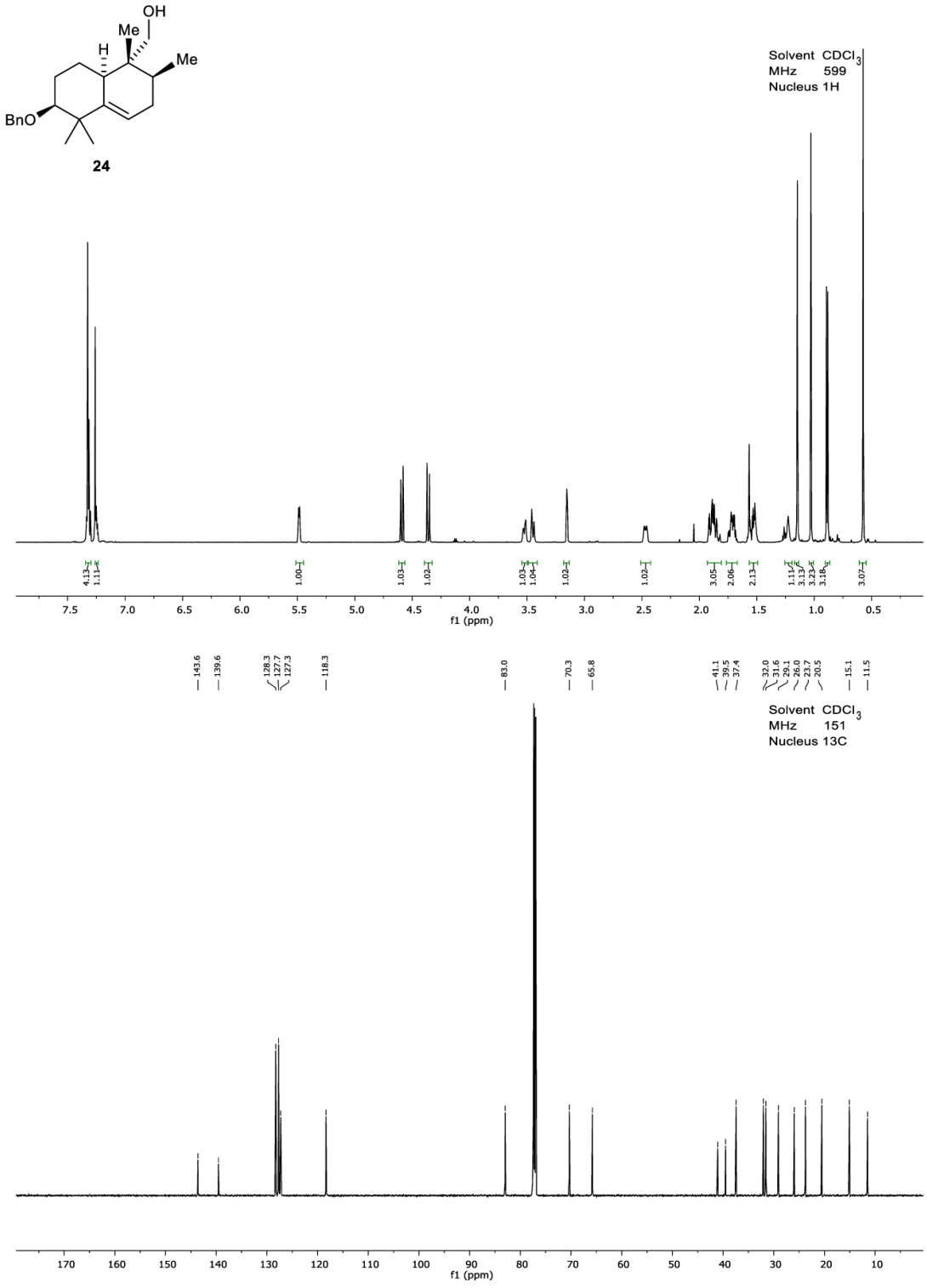
Supplementary Figure 11 ^{1}H and ^{13}C NMR Spectra for **22** in $CDCl_3$.



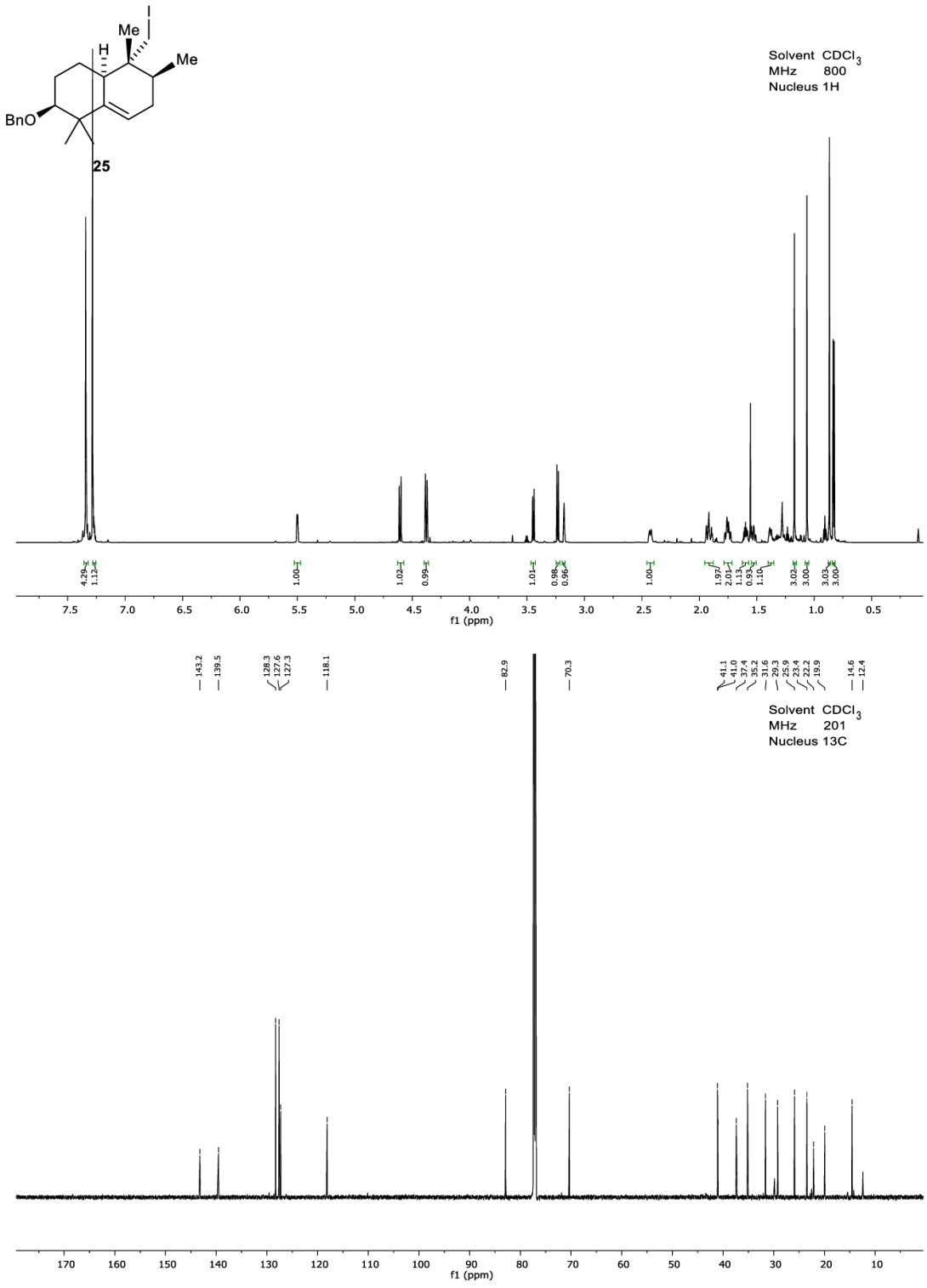
Supplementary Figure 12 ^{1}H and ^{13}C NMR Spectra for **S14** in $CDCl_3$.



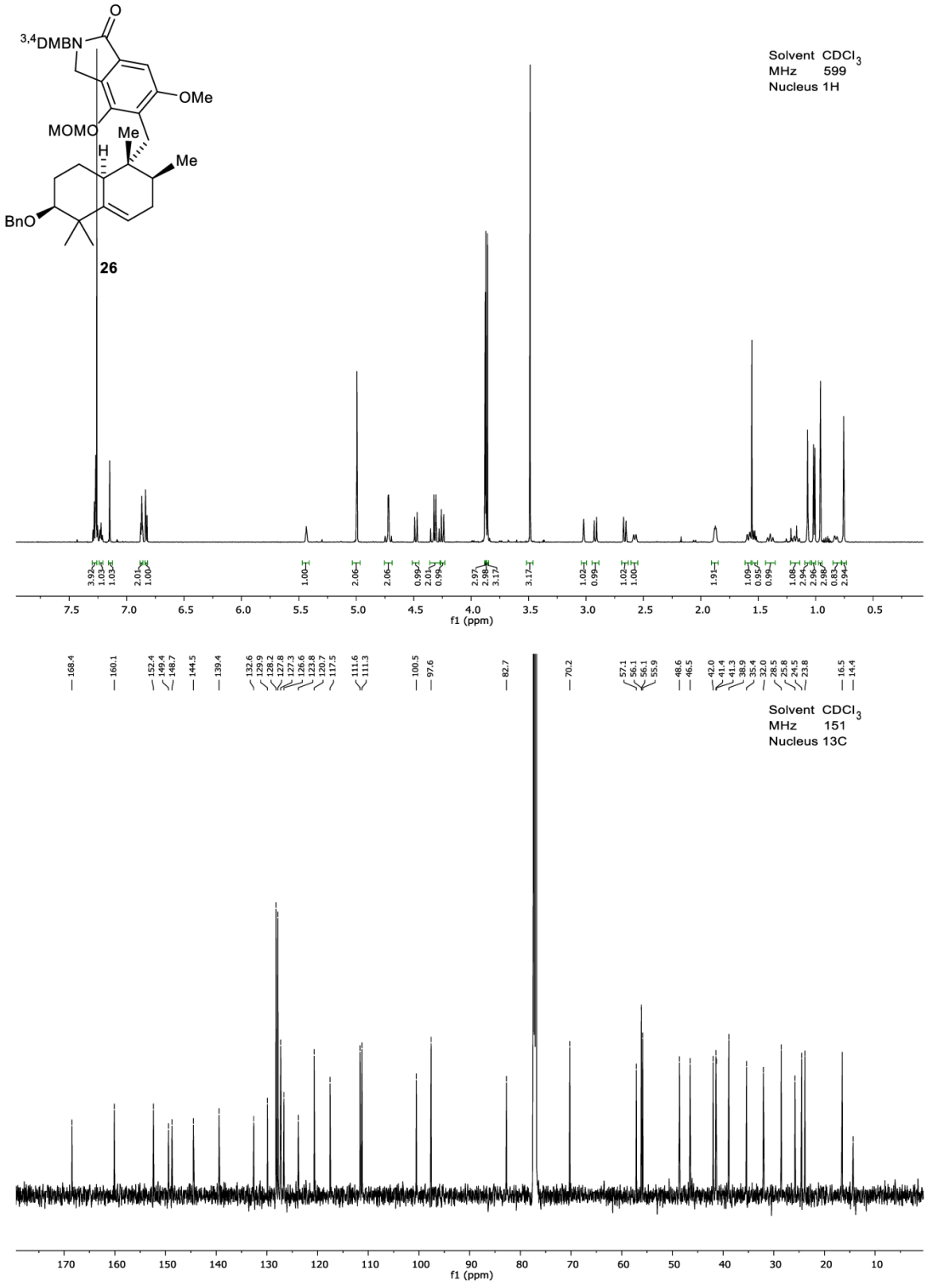
Supplementary Figure 13 ^{1}H and ^{13}C NMR Spectra for **23** in $CDCl_3$.



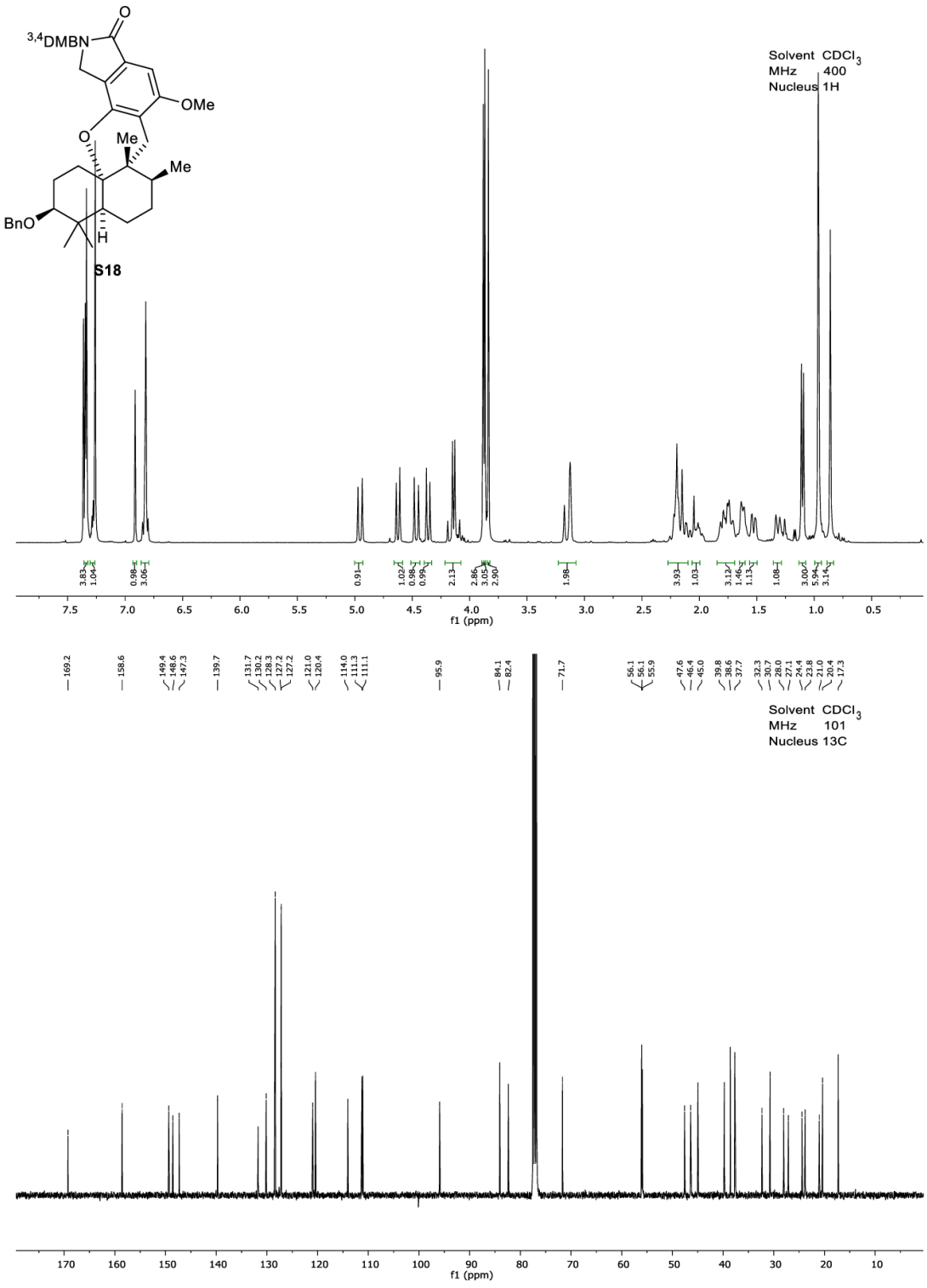
Supplementary Figure 14 ^{1}H and ^{13}C NMR Spectra for **24** in $CDCl_3$.



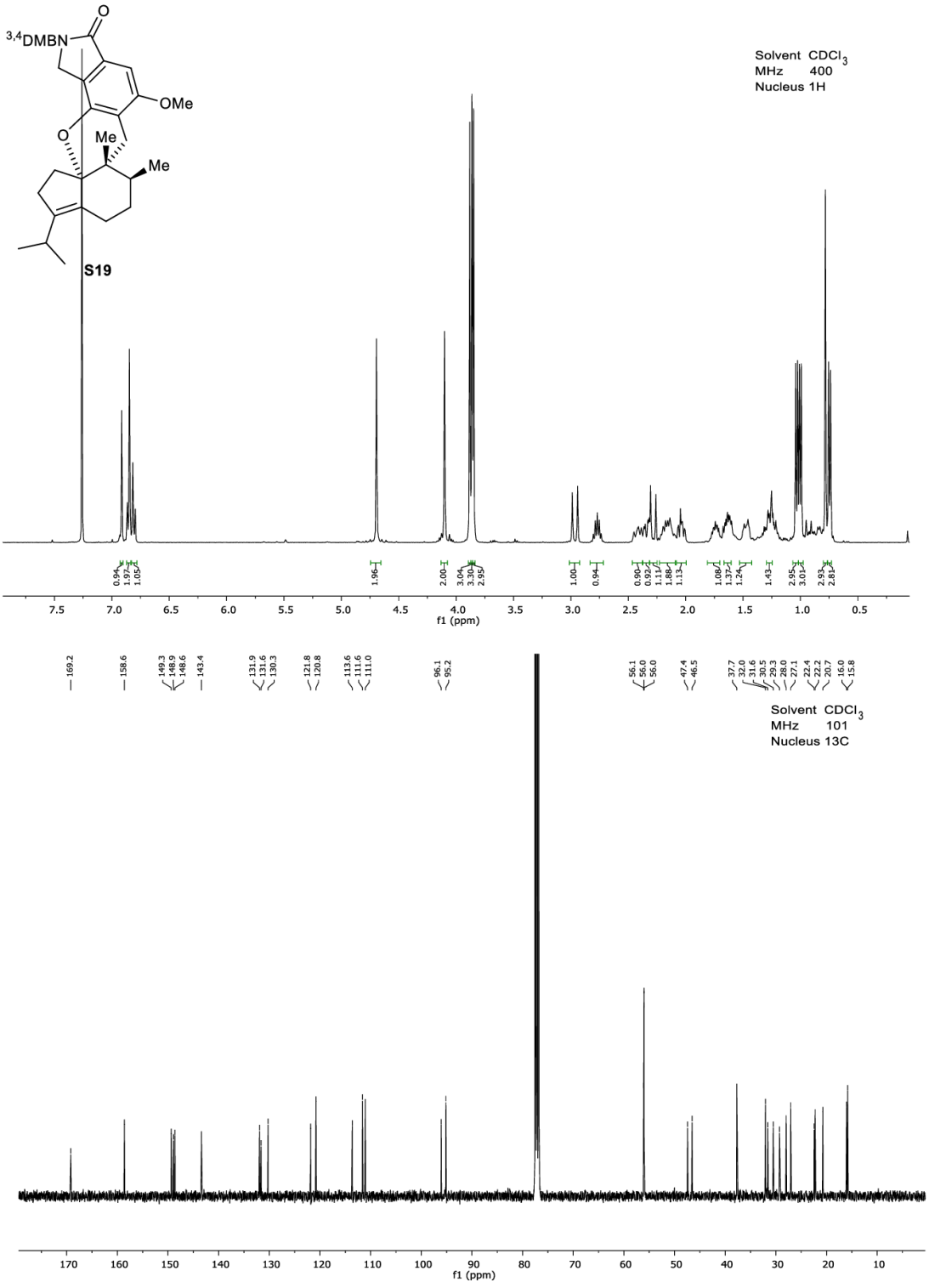
Supplementary Figure 15 ^{1}H and ^{13}C NMR Spectra for **25** in $CDCl_3$.



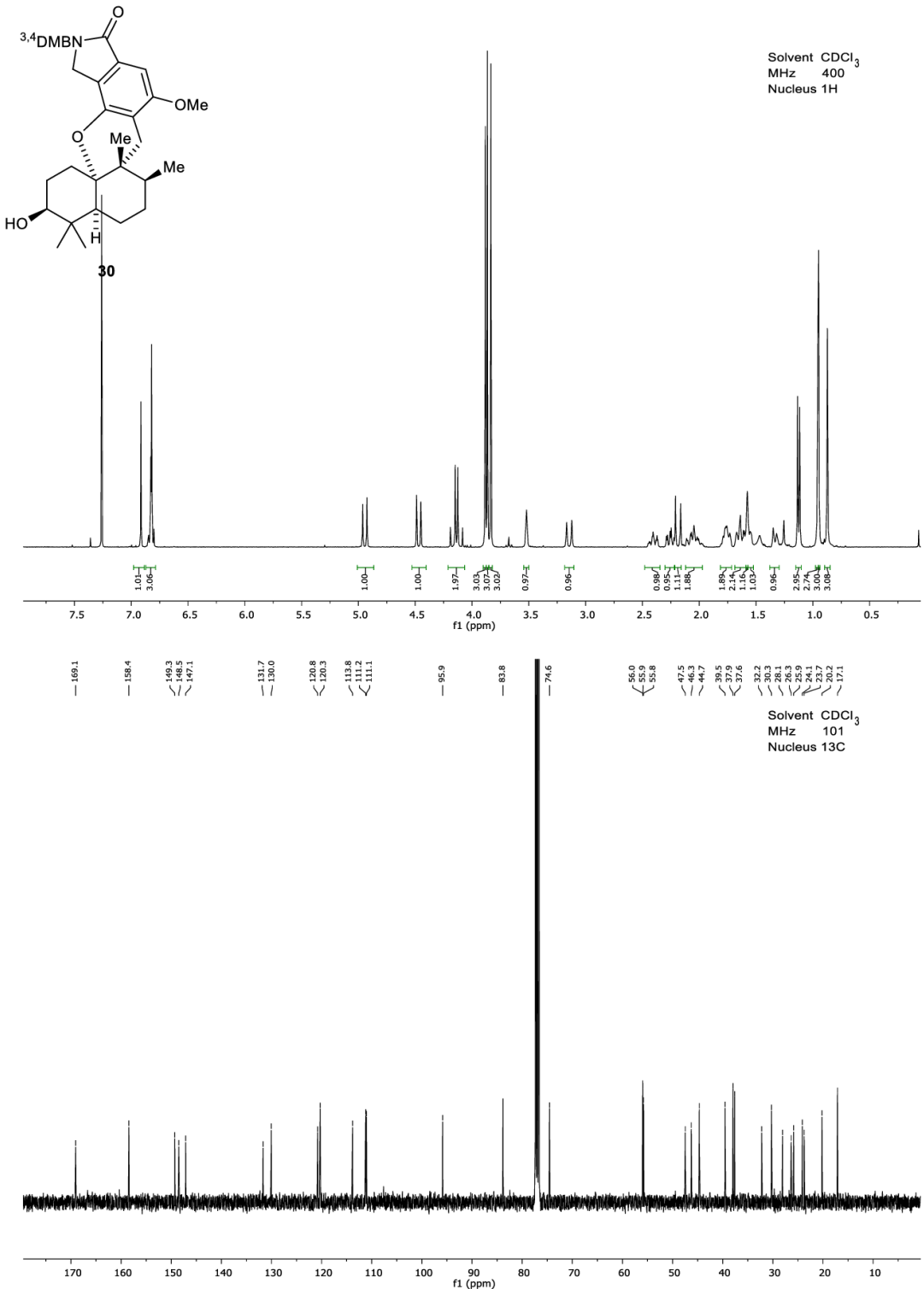
Supplementary Figure 16 ^{1}H and ^{13}C NMR Spectra for **26** in $CDCl_3$.



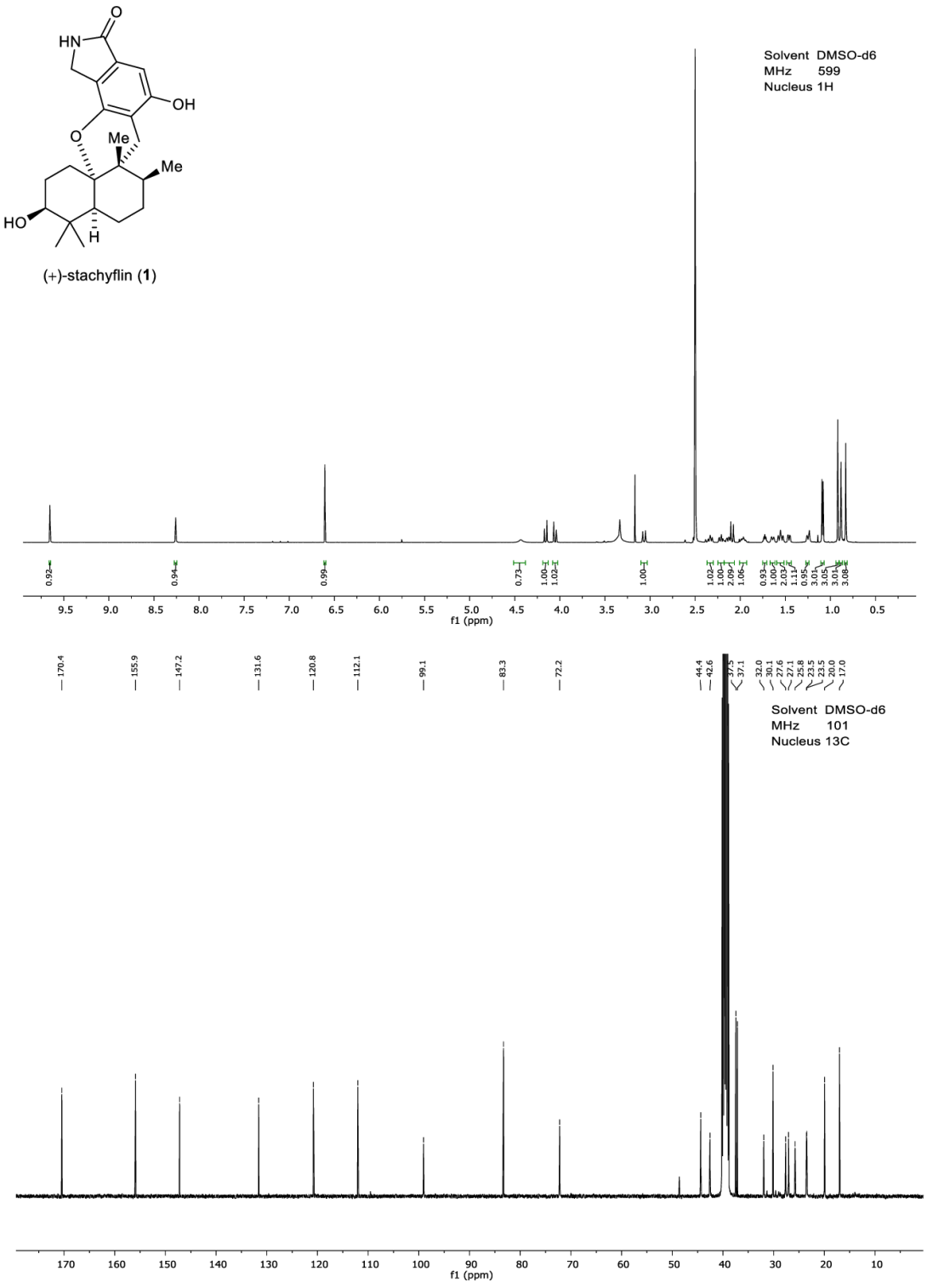
Supplementary Figure 17 ^{1}H and ^{13}C NMR Spectra for **S18** in $CDCl_3$.



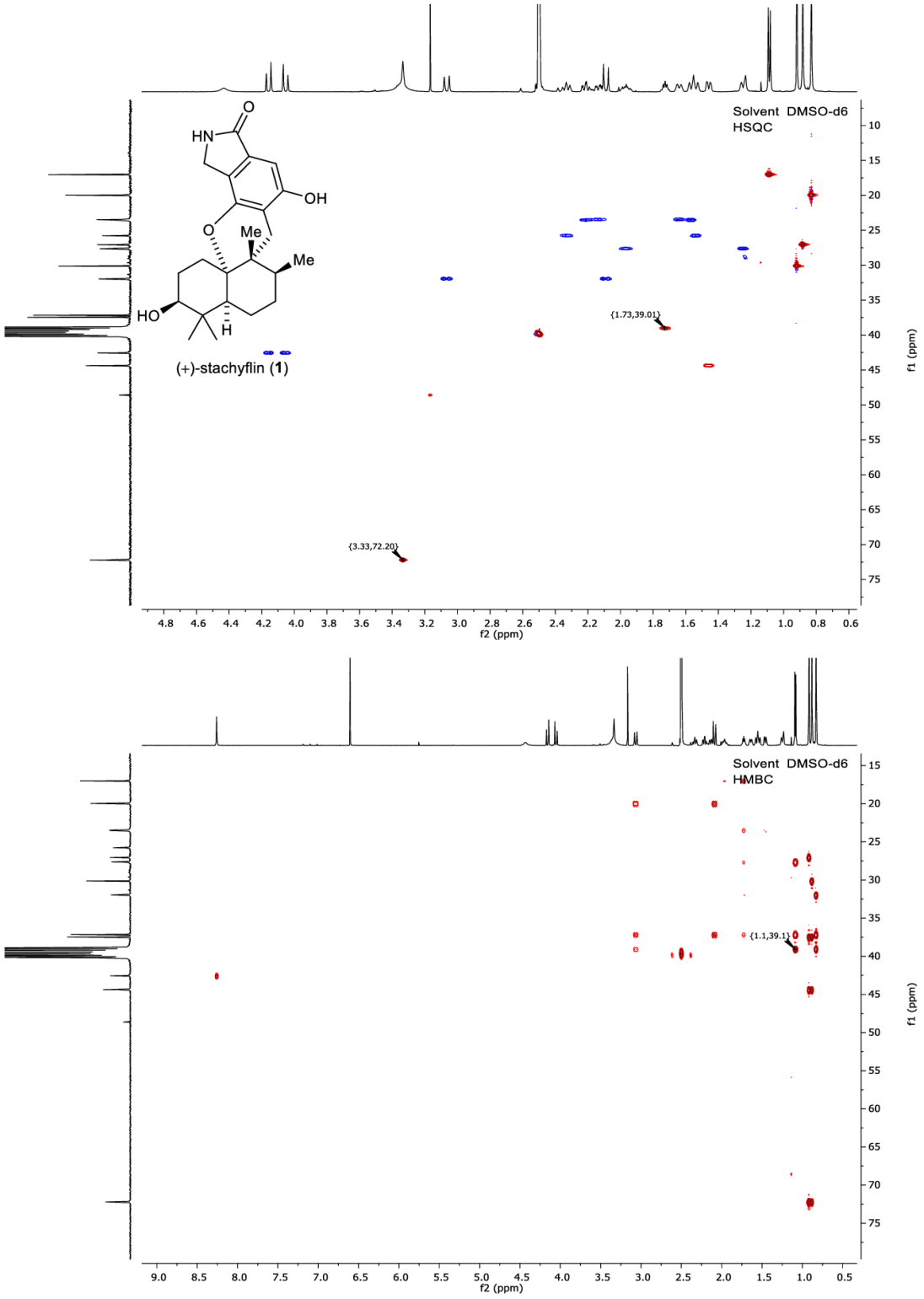
Supplementary Figure 18 ^{1}H and ^{13}C NMR Spectra for **S19** in $CDCl_3$.



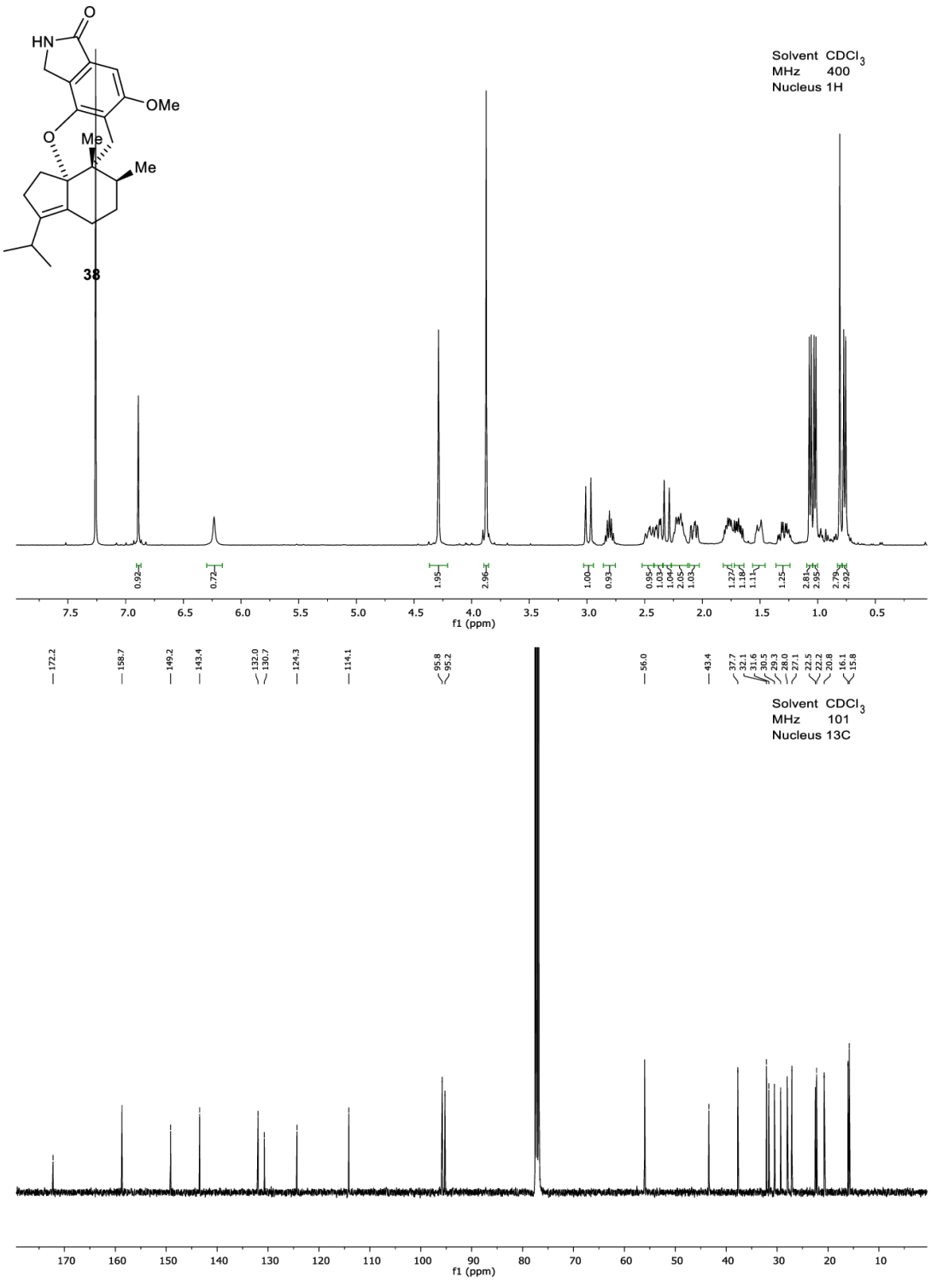
Supplementary Figure 19 ^{1}H and ^{13}C NMR Spectra for **30** in $CDCl_3$.



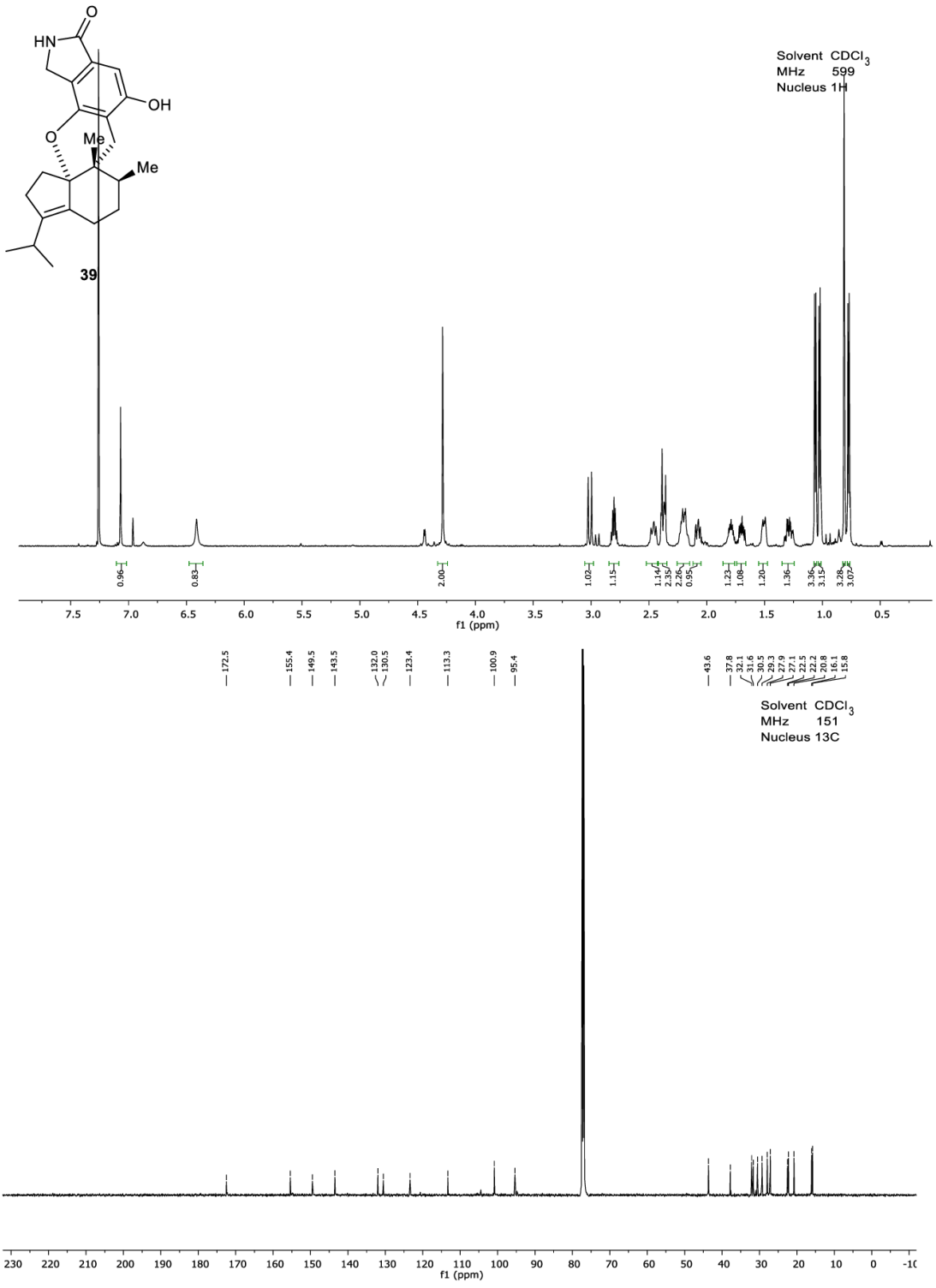
Supplementary Figure 20 ^{1}H and ^{13}C NMR Spectra for **1** in DMSO-d6.



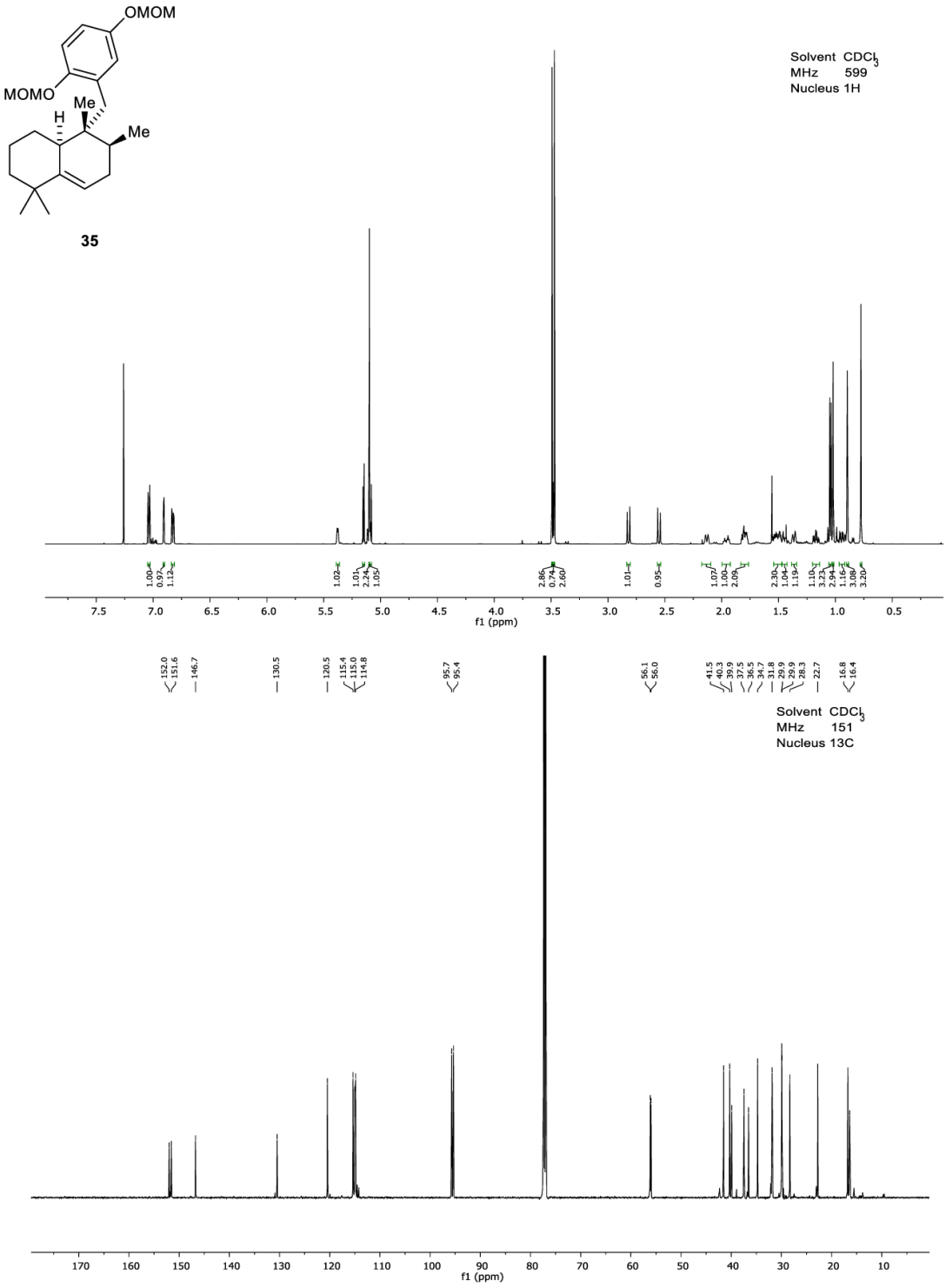
Supplementary Figure 21 HSQC and HMBC NMR Spectra for **1** in DMSO-d6.



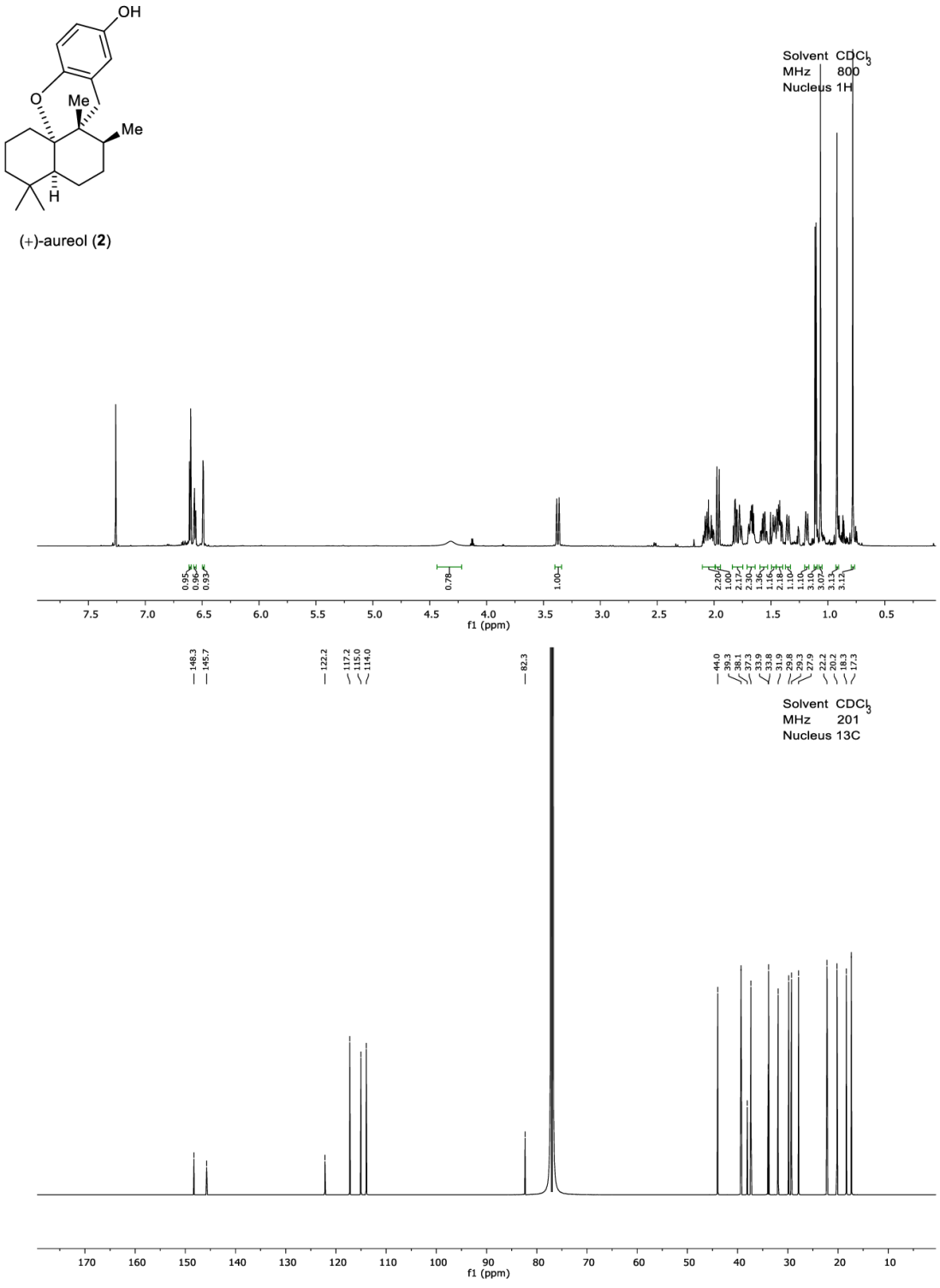
Supplementary Figure 22 ^{1}H and ^{13}C NMR Spectra for **38** in $CDCl_3$.



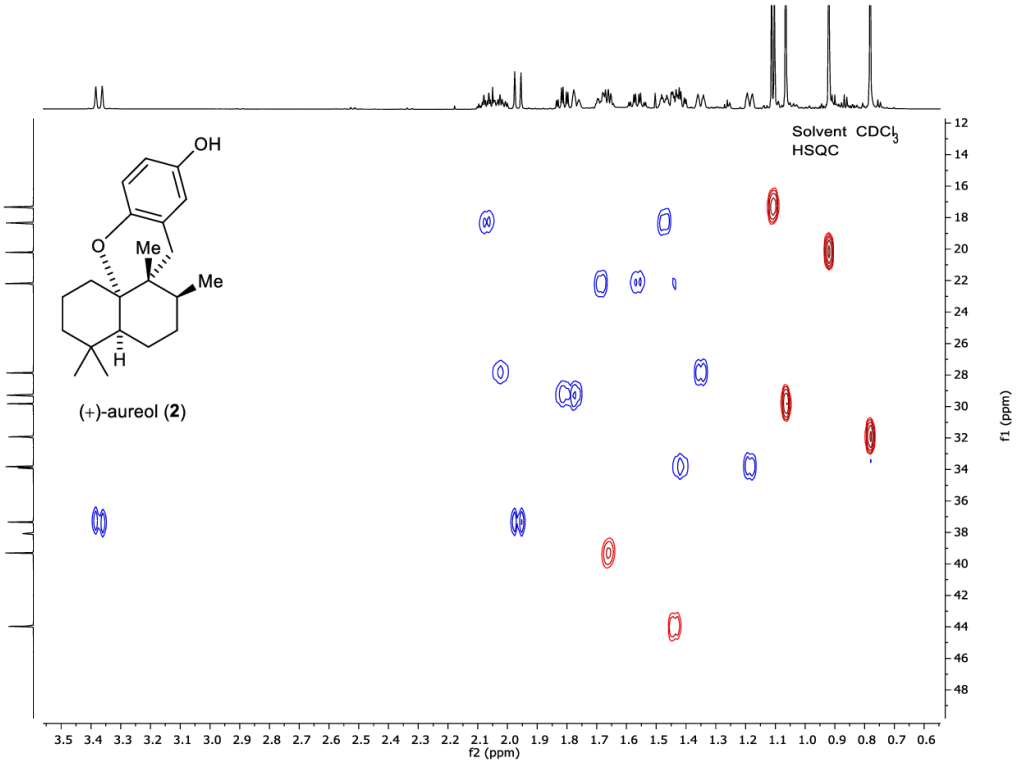
Supplementary Figure 23 ^{1}H and ^{13}C NMR Spectra for **39** in $CDCl_3$.



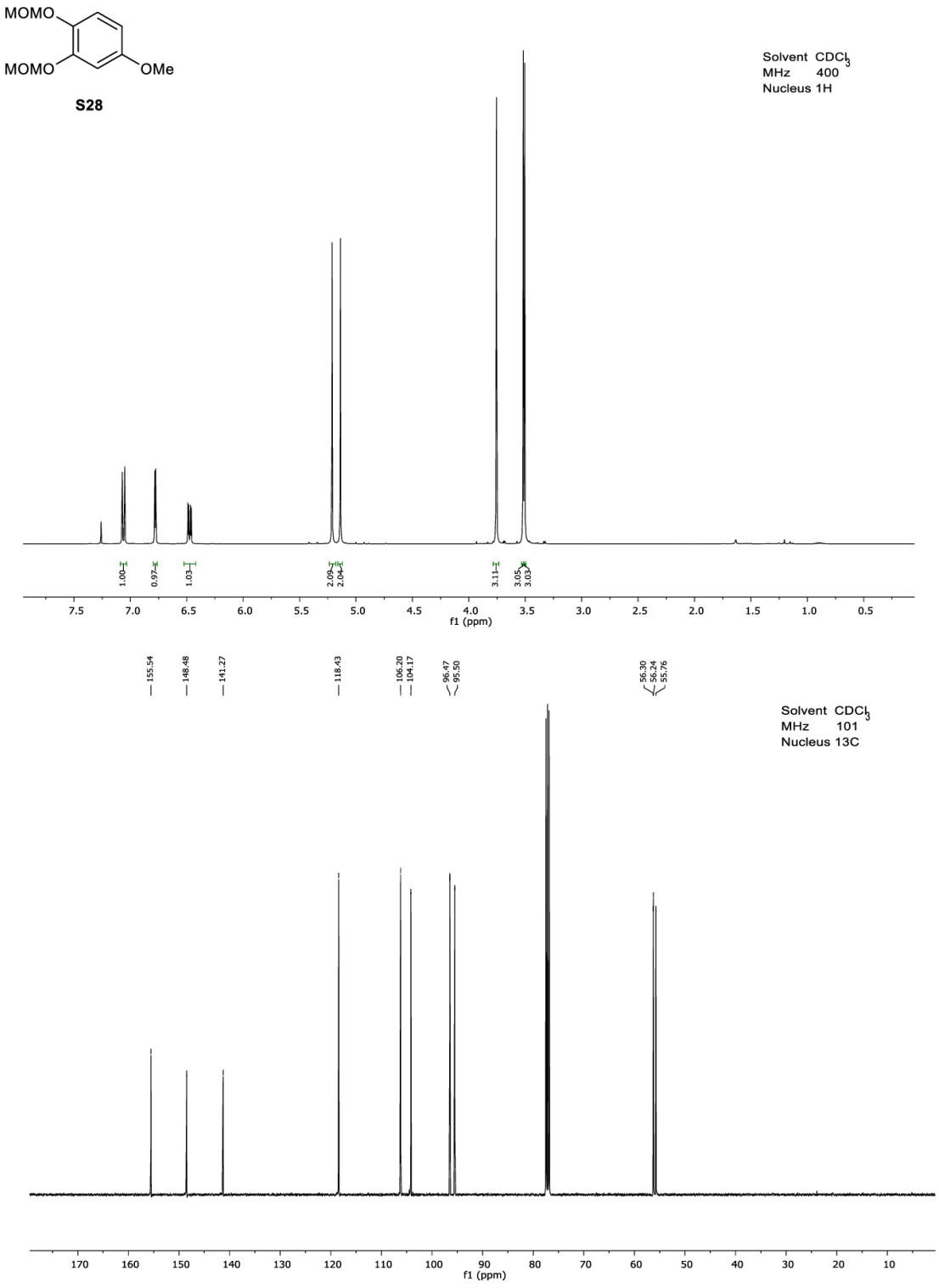
Supplementary Figure 24 ^{1}H and ^{13}C NMR Spectra for **35** in $CDCl_3$.



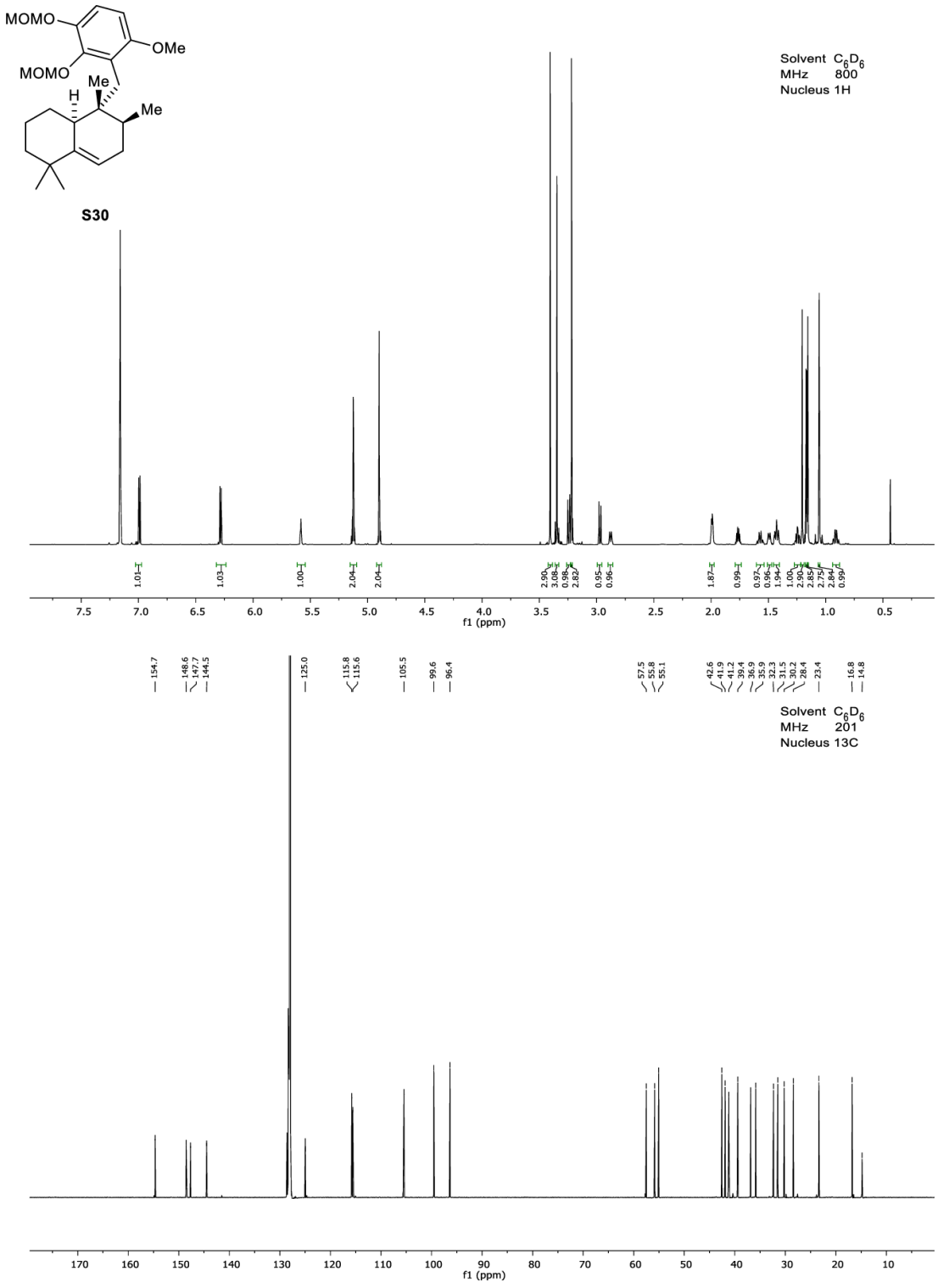
Supplementary Figure 25 ^{1}H and ^{13}C NMR Spectra for **2** in $CDCl_3$.



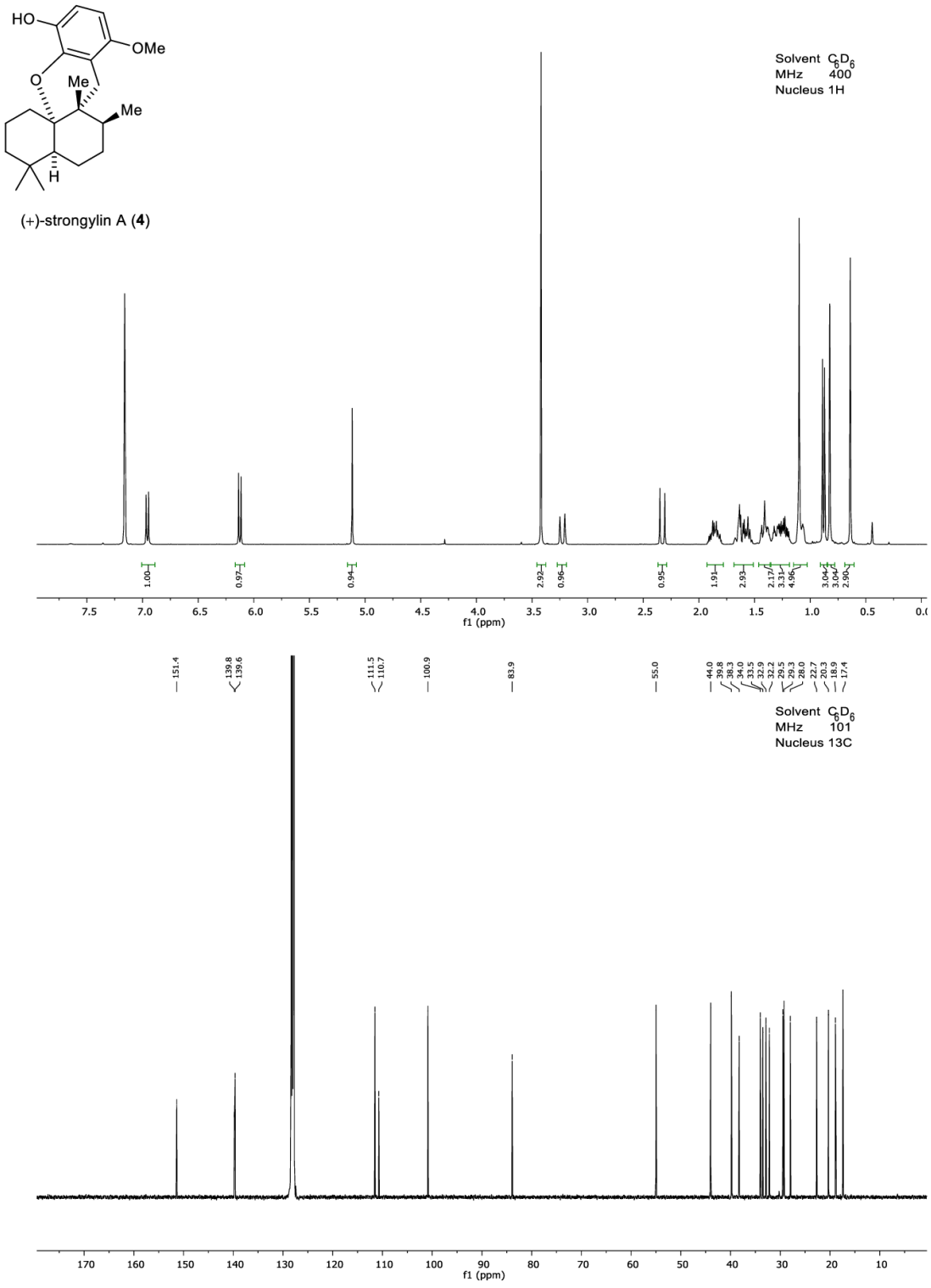
Supplementary Figure 26 HSQC NMR Spectra for **2** in $CDCl_3$.



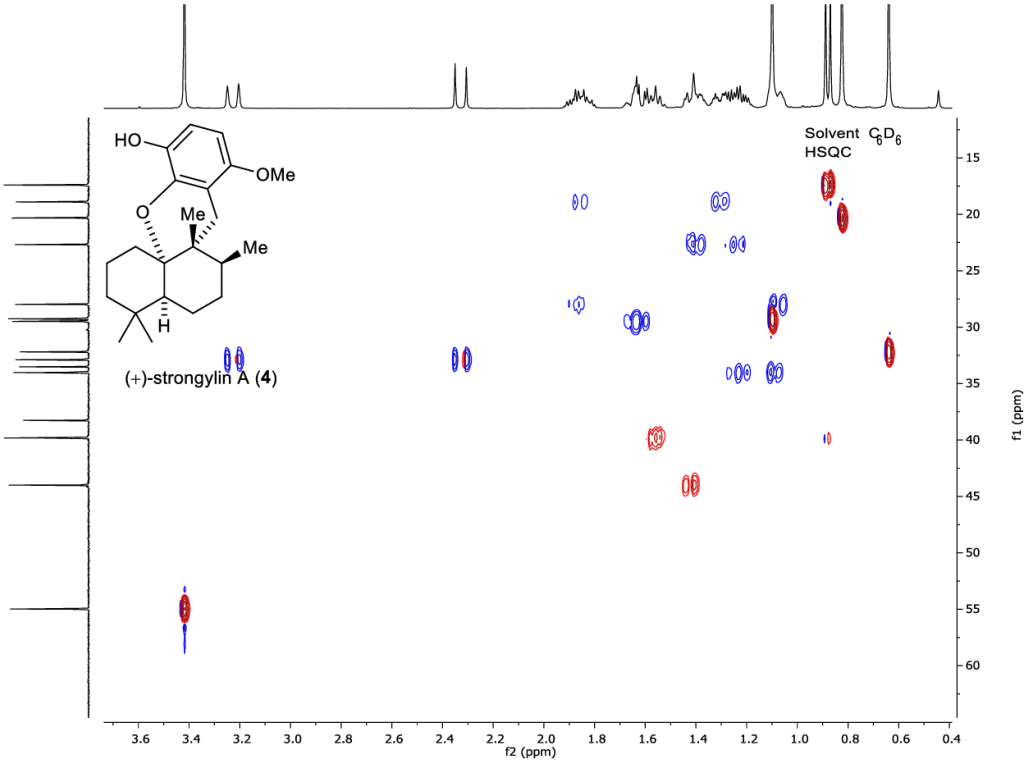
Supplementary Figure 27 ^{1}H and ^{13}C NMR Spectra for **S28** in $CDCl_3$.



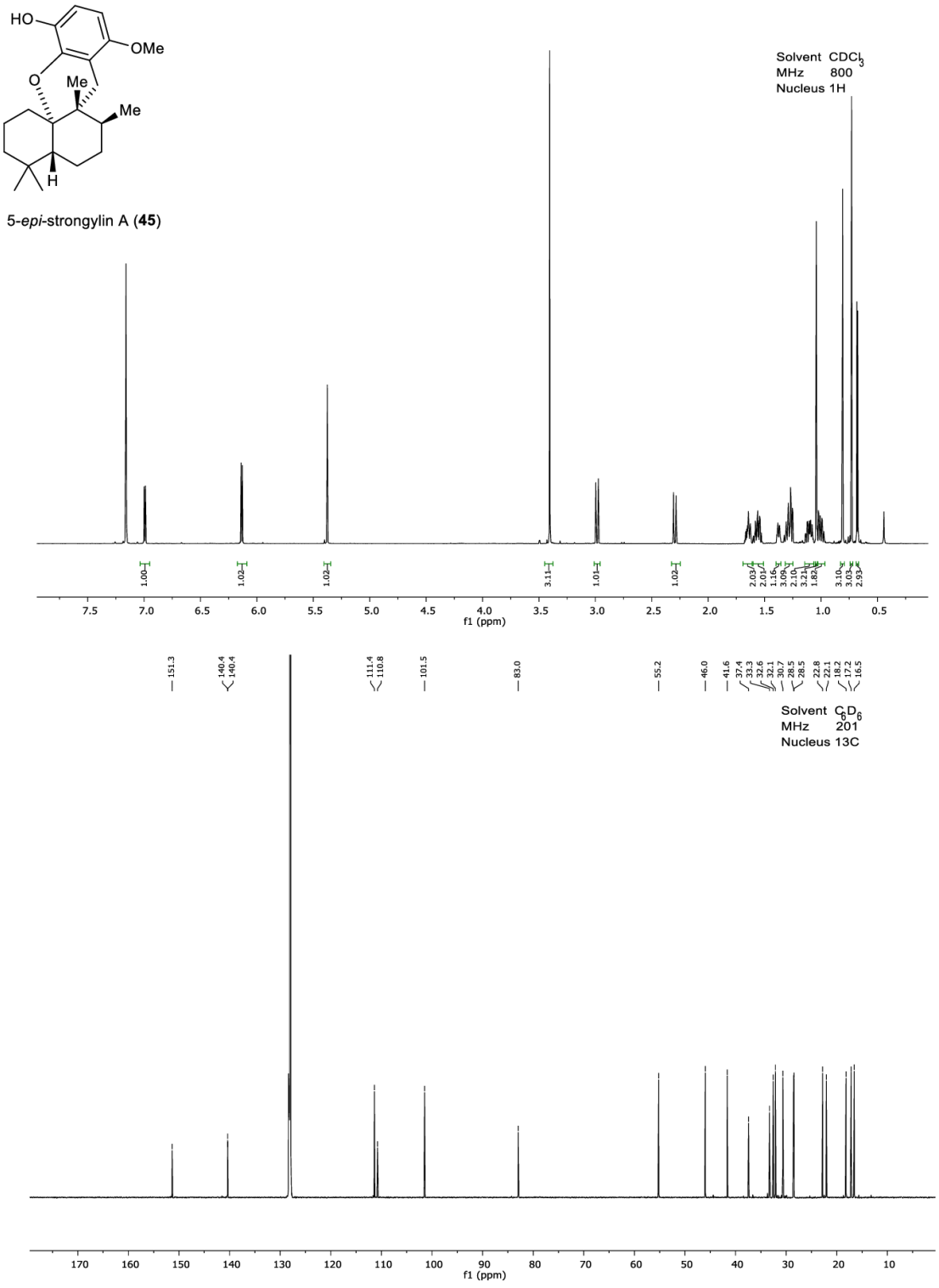
Supplementary Figure 28 ^{1}H and ^{13}C NMR Spectra for **S30** in C_6D_6.



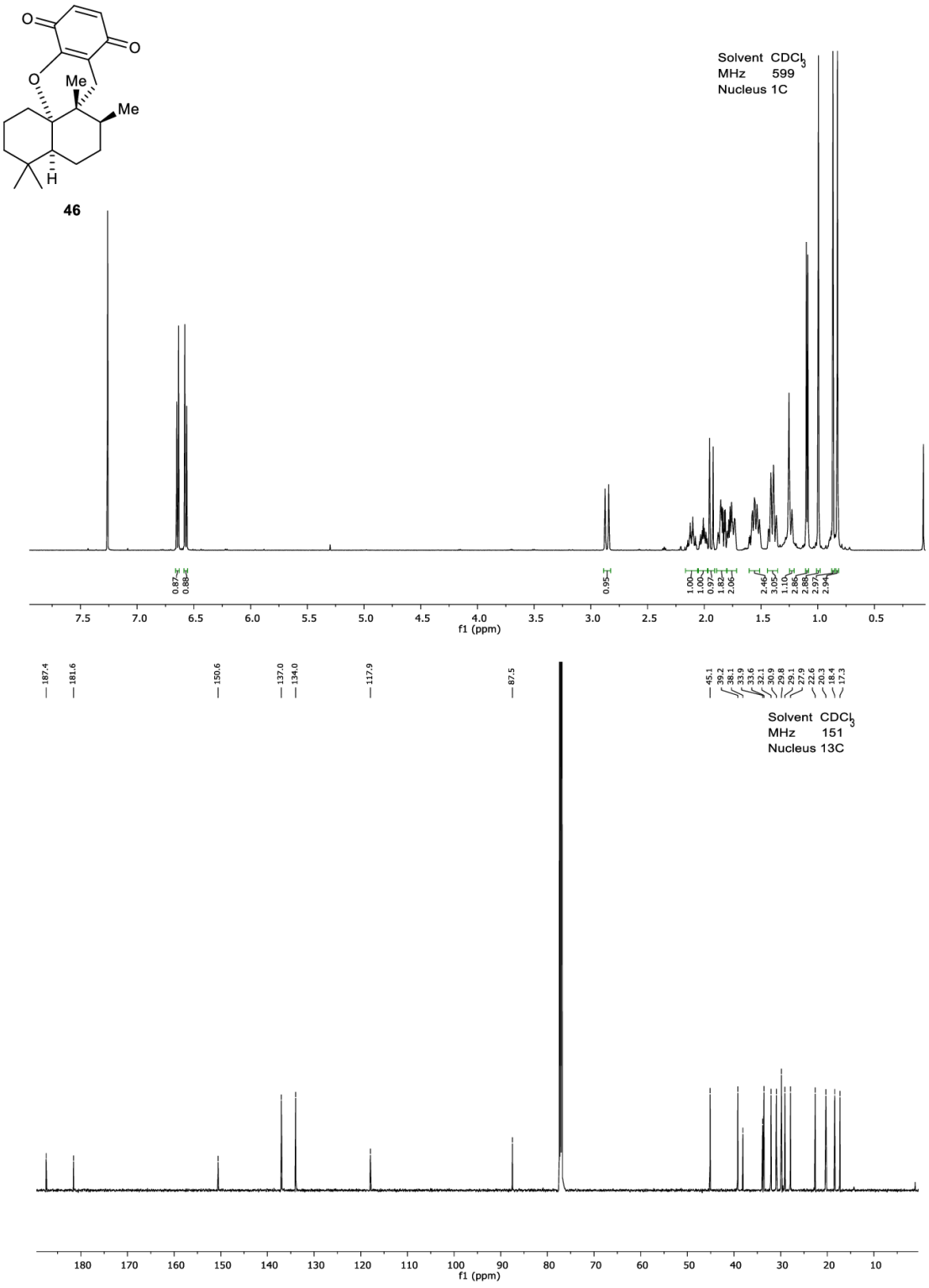
Supplementary Figure 29 ^{1}H and ^{13}C NMR Spectra for **4** in C_6D_6.



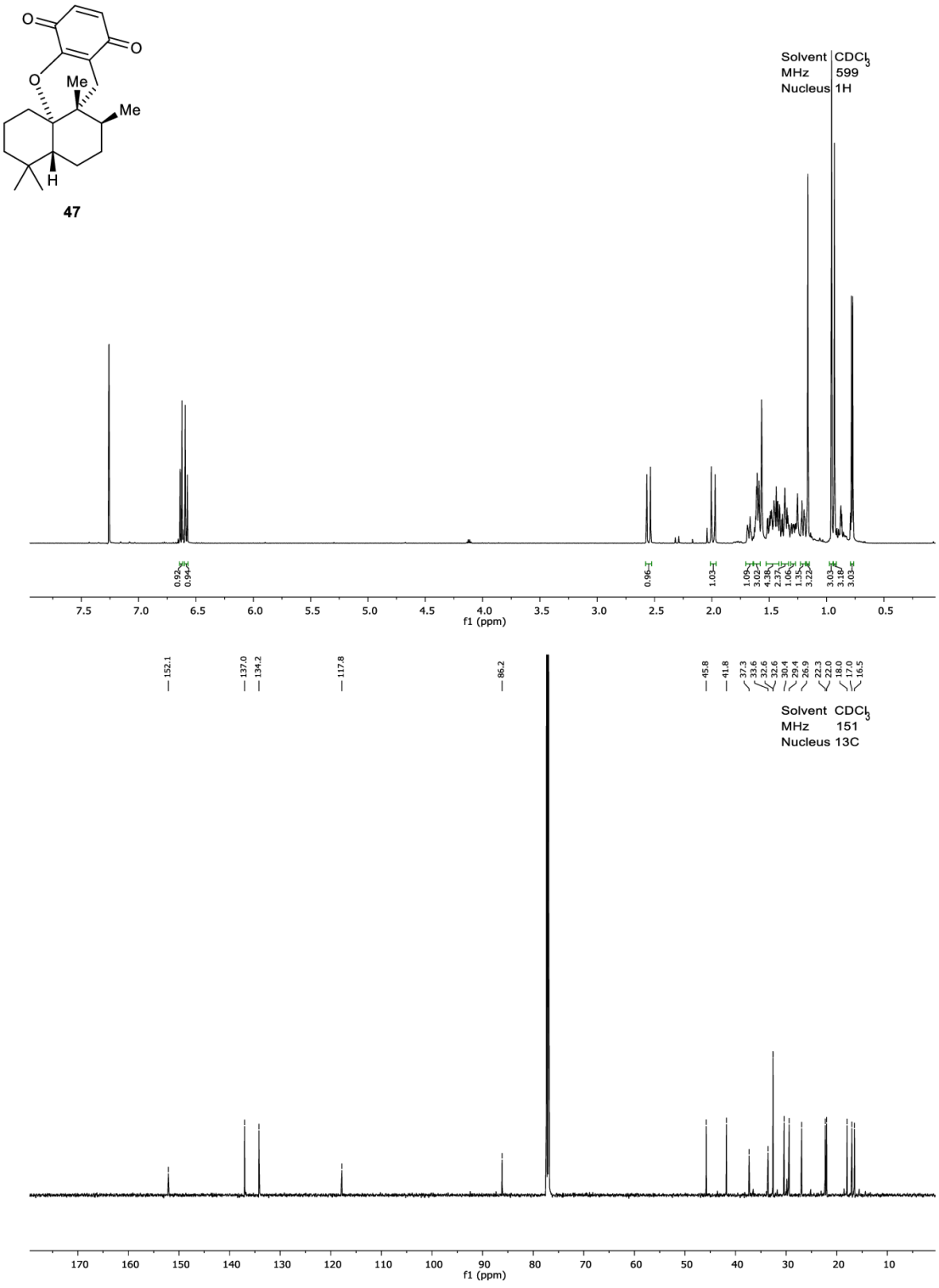
Supplementary Figure 30 HSQC NMR Spectra for **4** in C_6D_6.



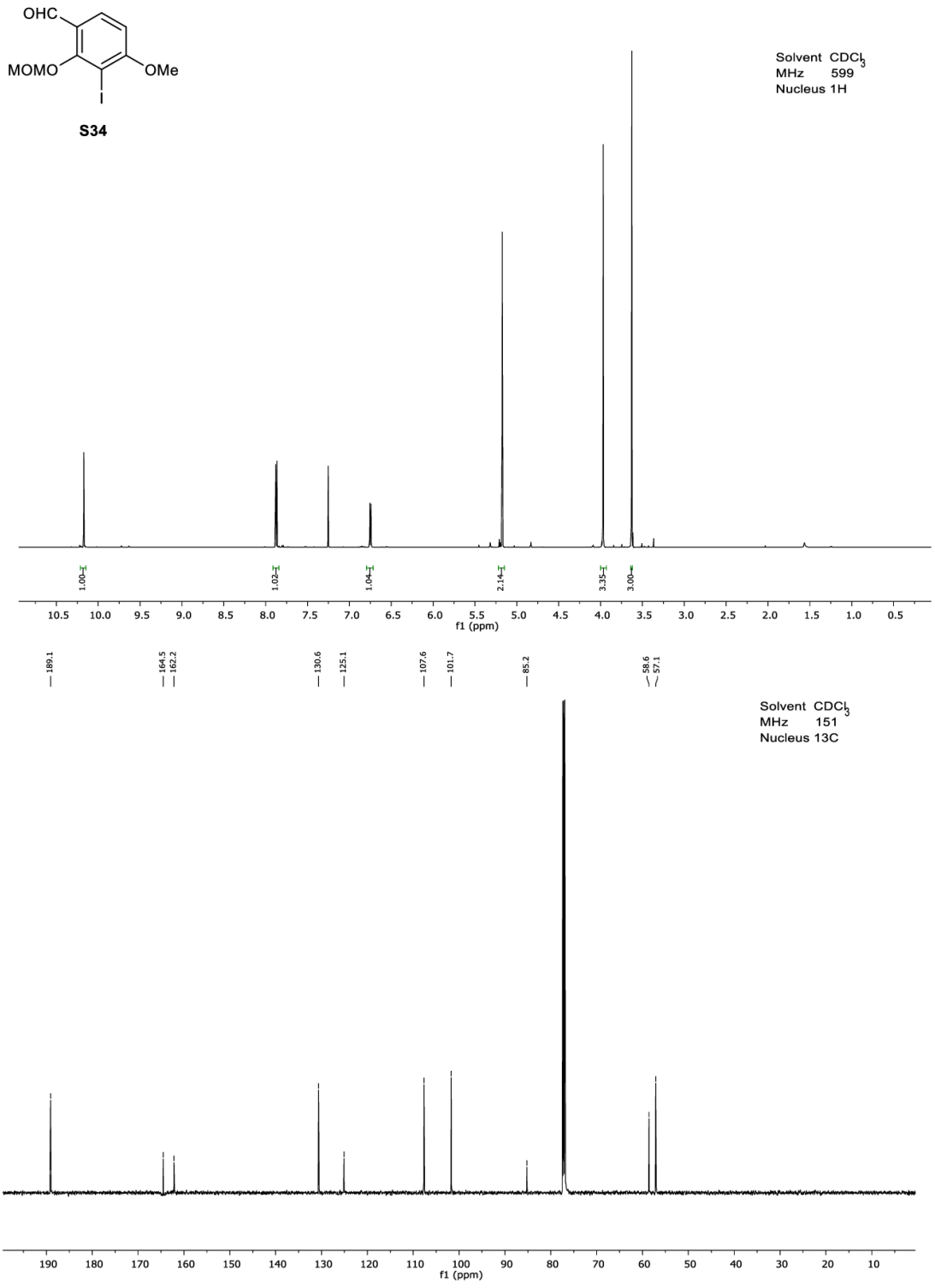
Supplementary Figure 31 ^{1}H and ^{13}C NMR Spectra for **45** in $CDCl_3$.



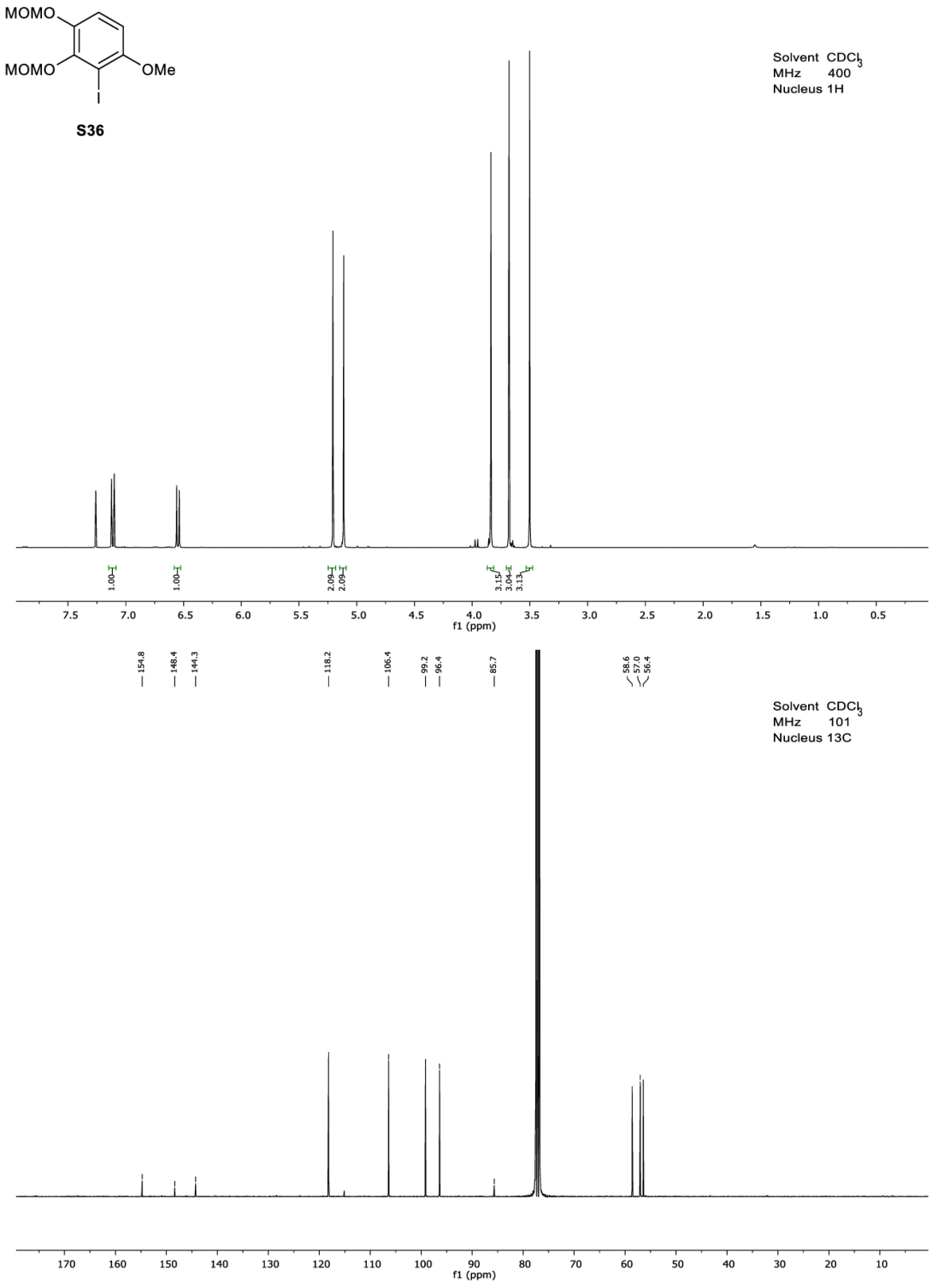
Supplementary Figure 32 ^{1}H and ^{13}C NMR Spectra for **46** in $CDCl_3$.



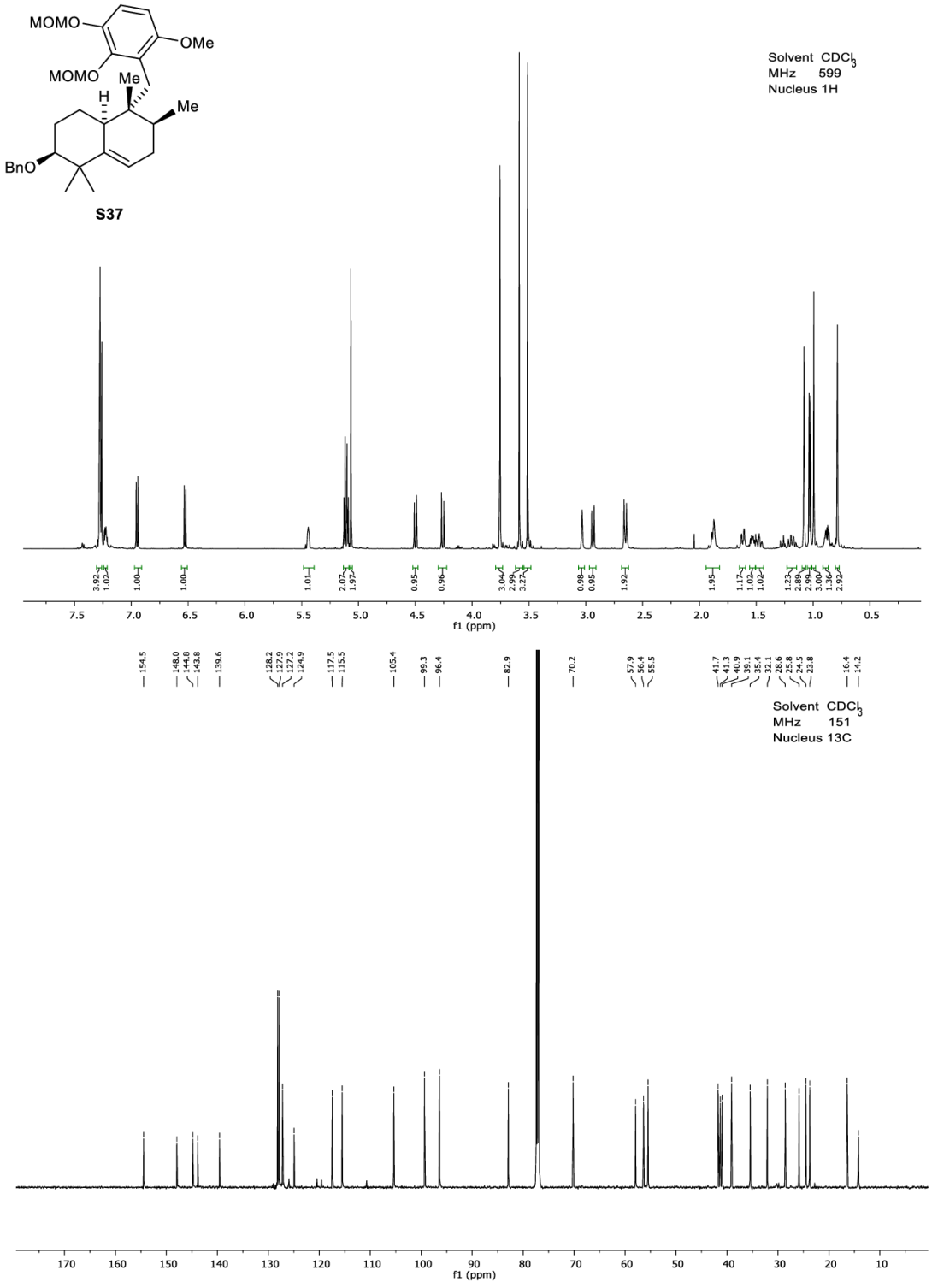
Supplementary Figure 33 ^{1}H and ^{13}C NMR Spectra for **47** in $CDCl_3$.



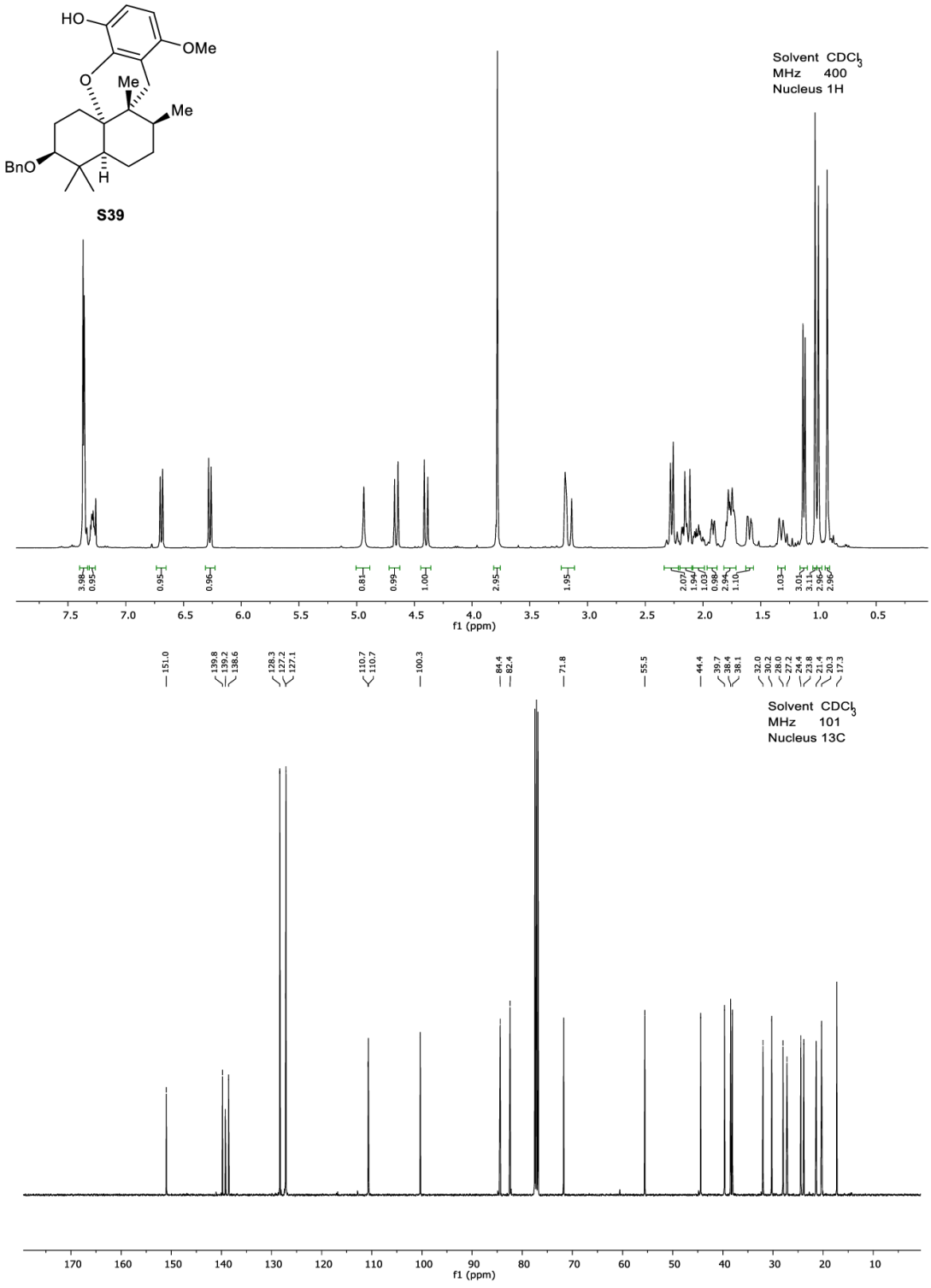
Supplementary Figure 34 ^{1}H and ^{13}C NMR Spectra for **S34** in $CDCl_3$.



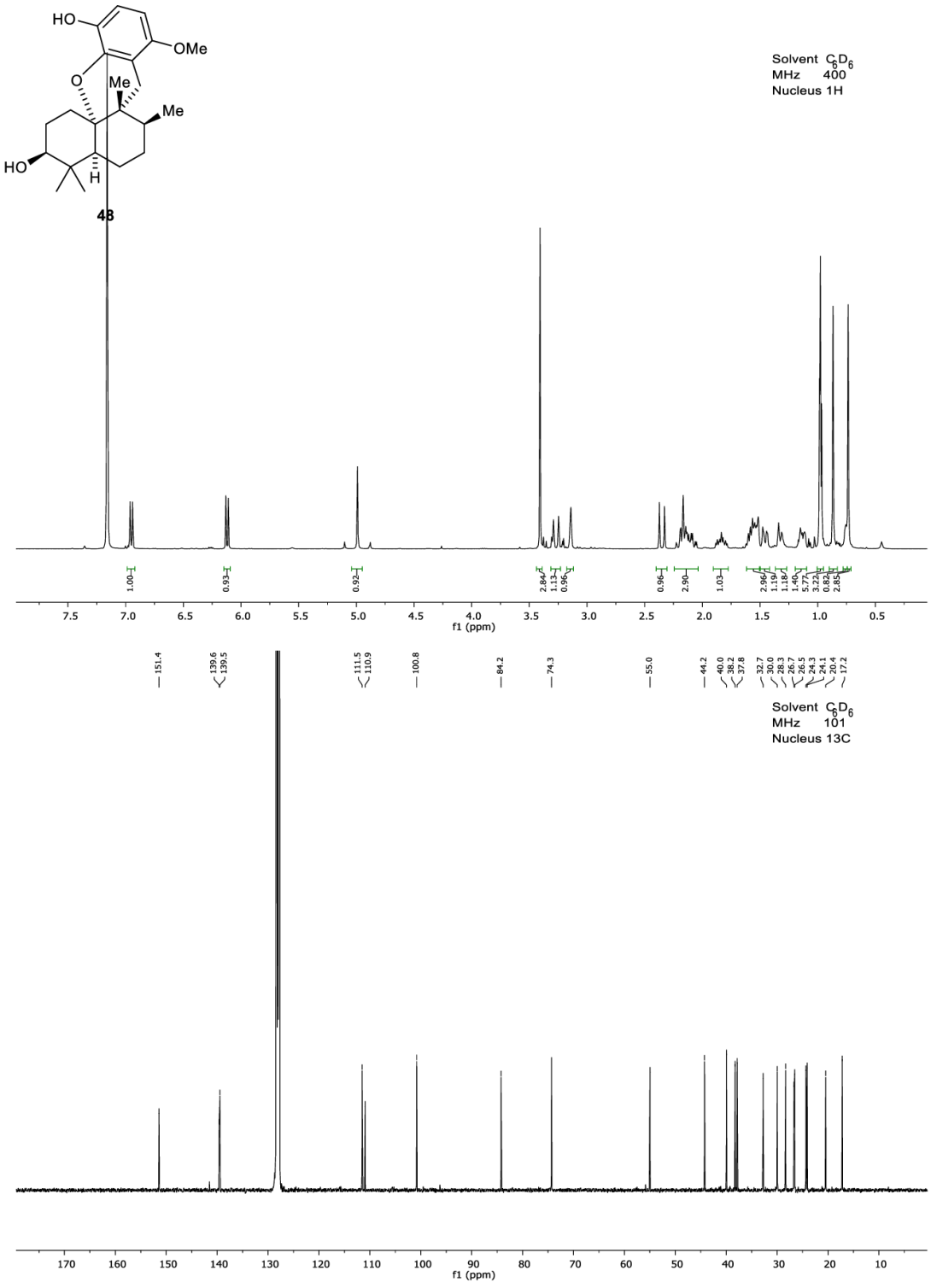
Supplementary Figure 35 ^{1}H and ^{13}C NMR Spectra for **S36** in $CDCl_3$.



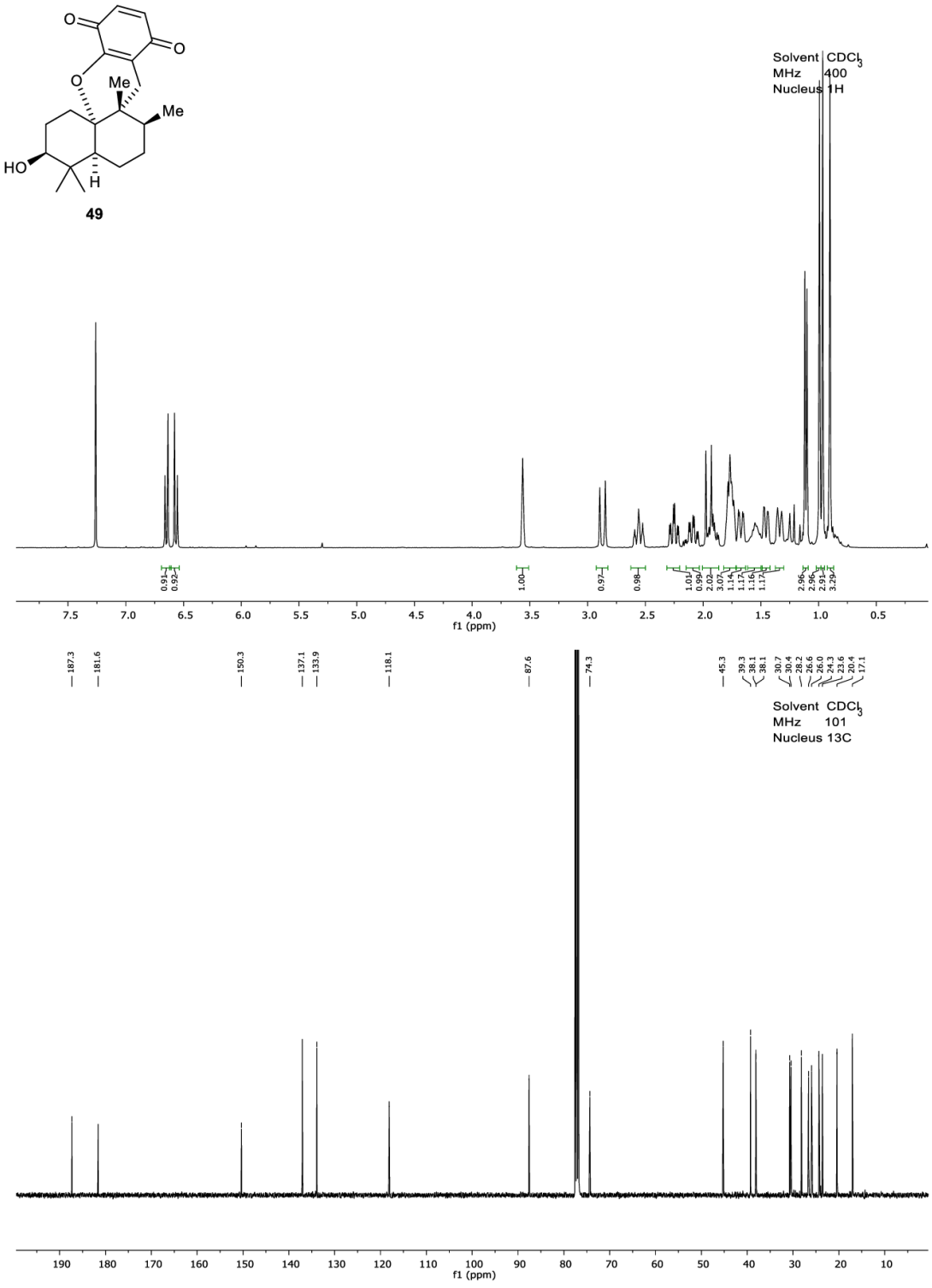
Supplementary Figure 36 ^{1}H and ^{13}C NMR Spectra for **S37** in $CDCl_3$.



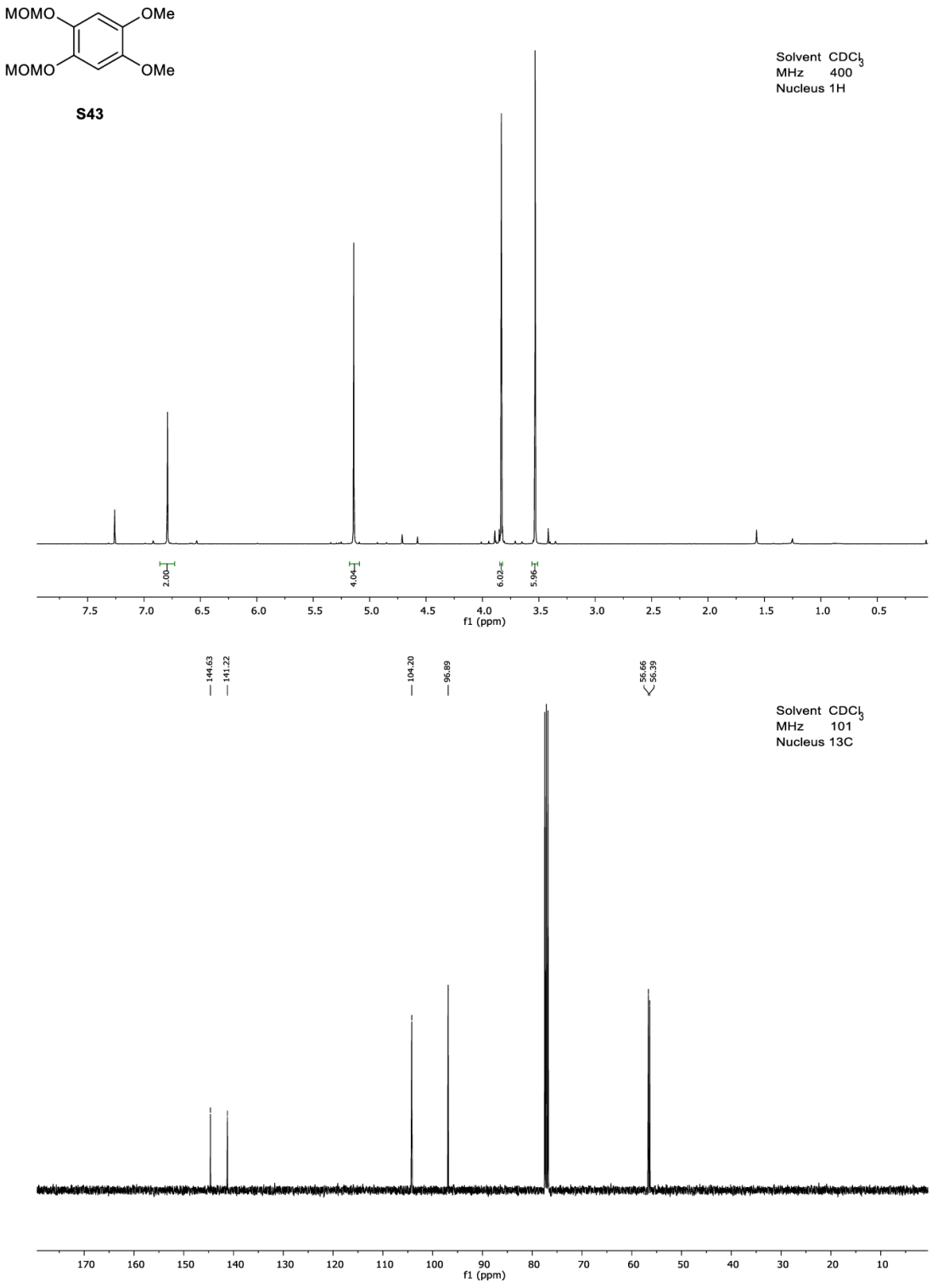
Supplementary Figure 37 ^{1}H and ^{13}C NMR Spectra for **S39** in $CDCl_3$.



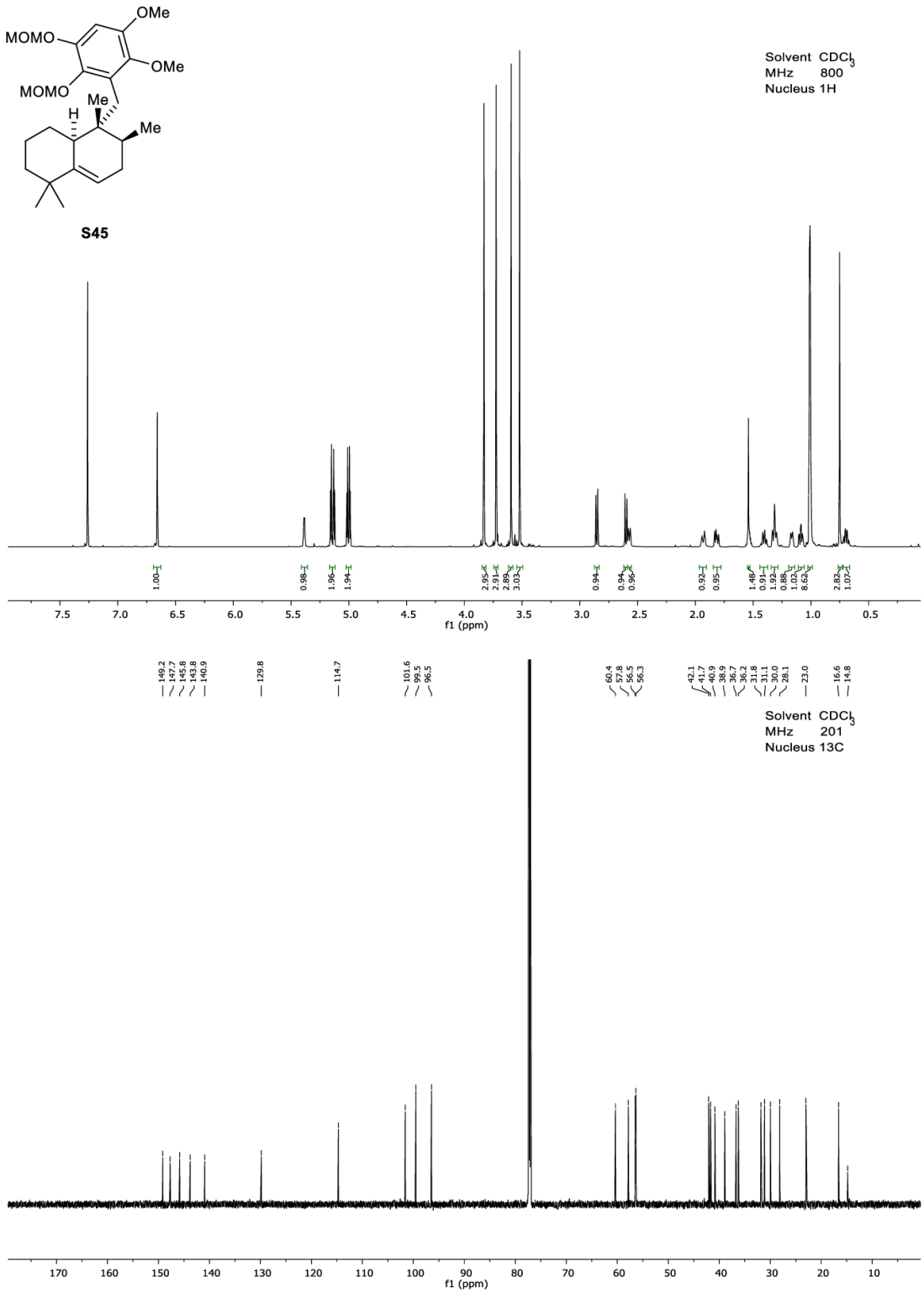
Supplementary Figure 38 ^{1}H and ^{13}C NMR Spectra for **48** in C_6D_6.



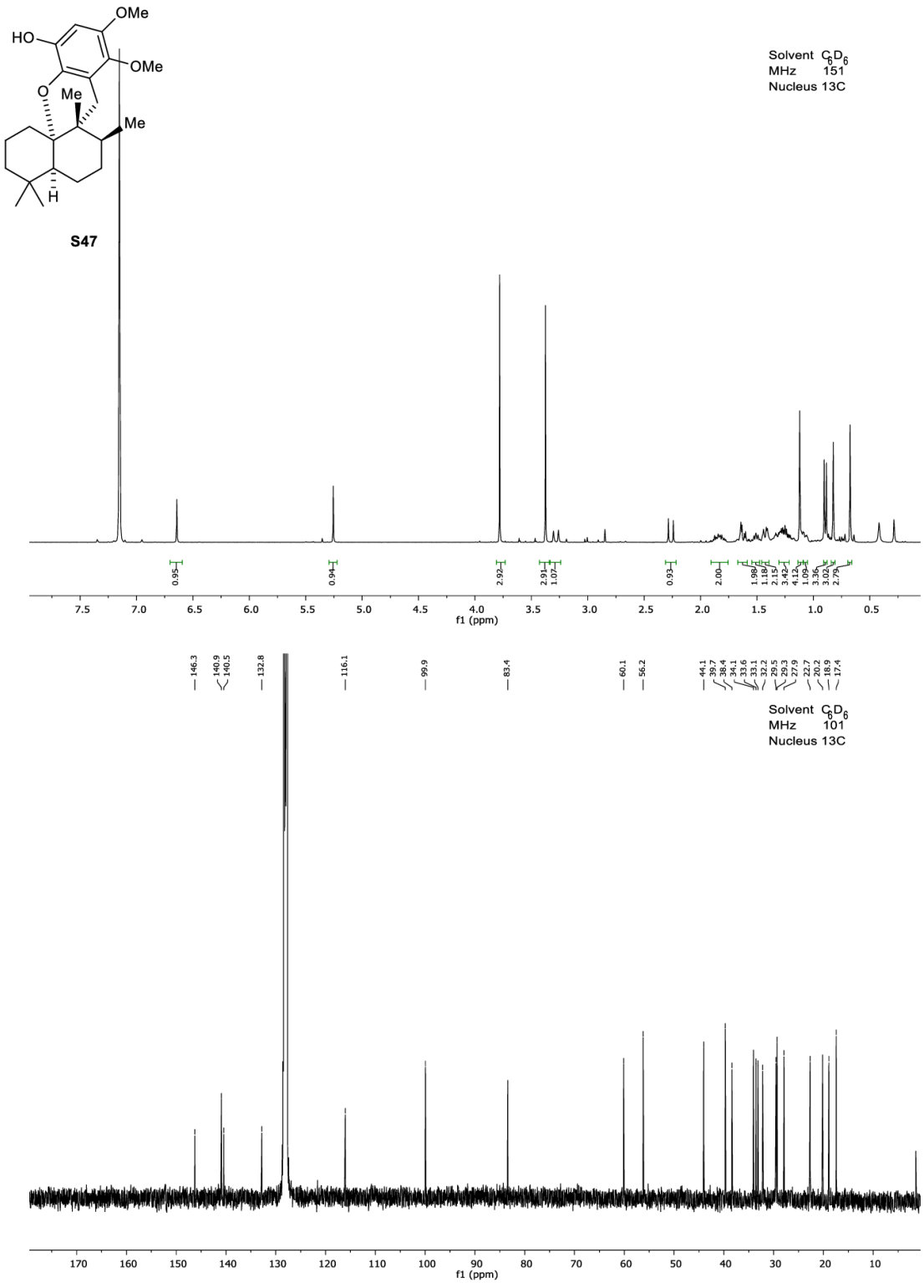
Supplementary Figure 39 ^{1}H and ^{13}C NMR Spectra for **49** in $CDCl_3$.



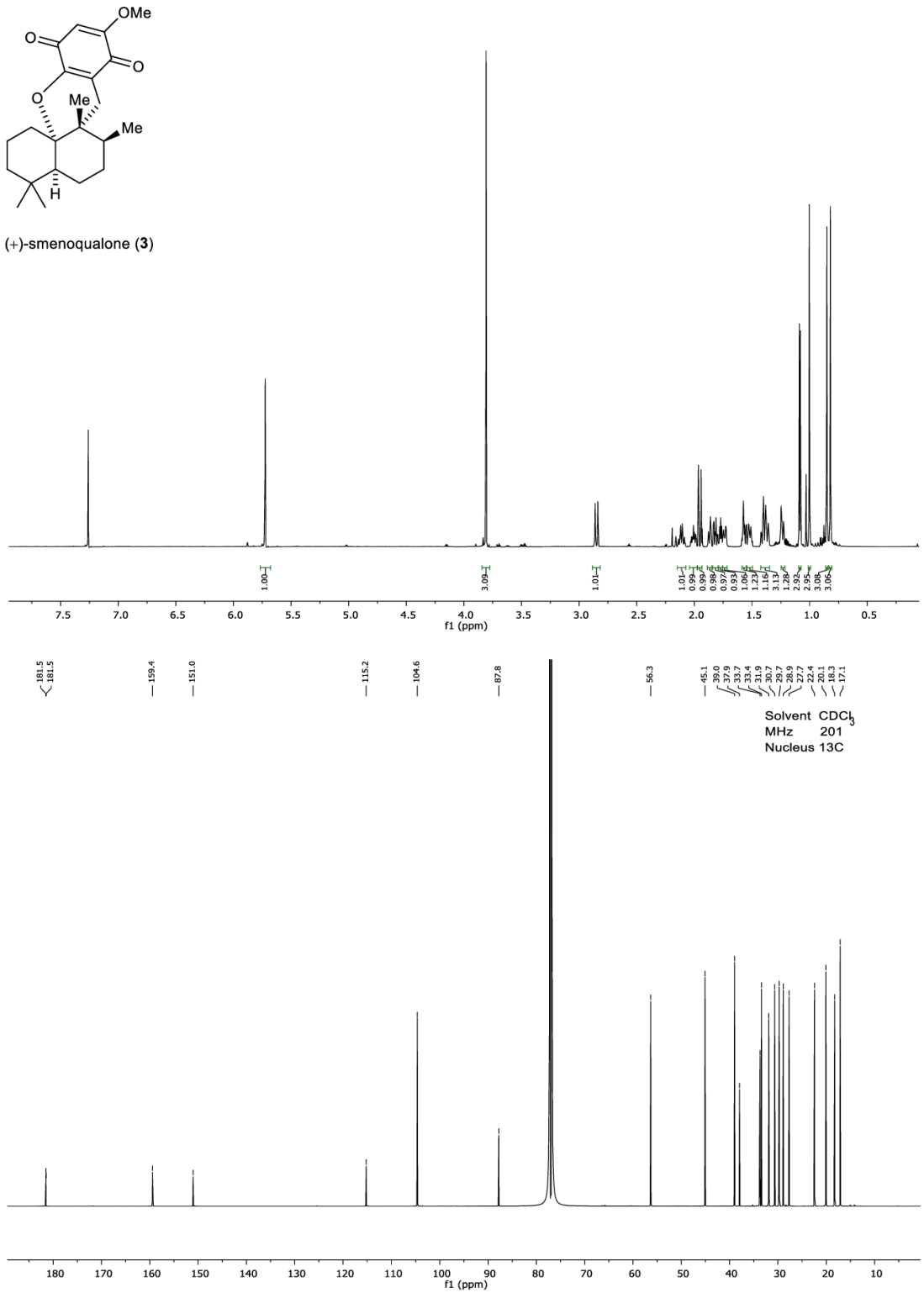
Supplementary Figure 40 ^{1}H and ^{13}C NMR Spectra for **S43** in $CDCl_3$.



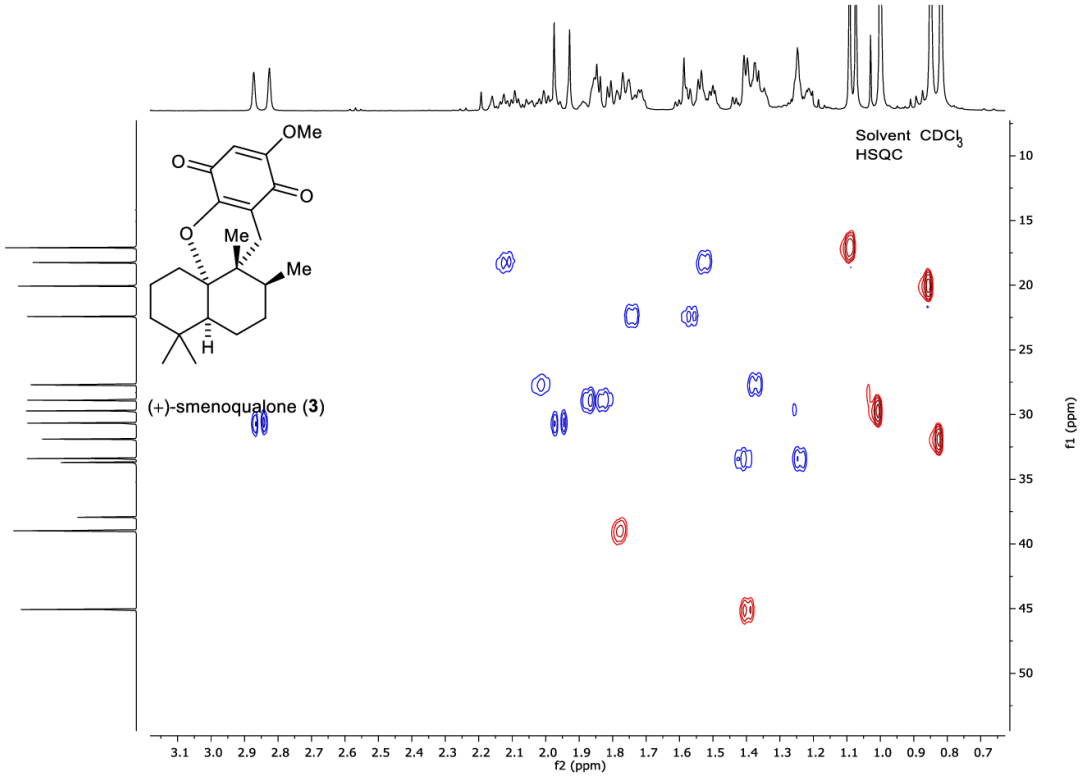
Supplementary Figure 41 ^{1}H and ^{13}C NMR Spectra for **S45** in $CDCl_3$.



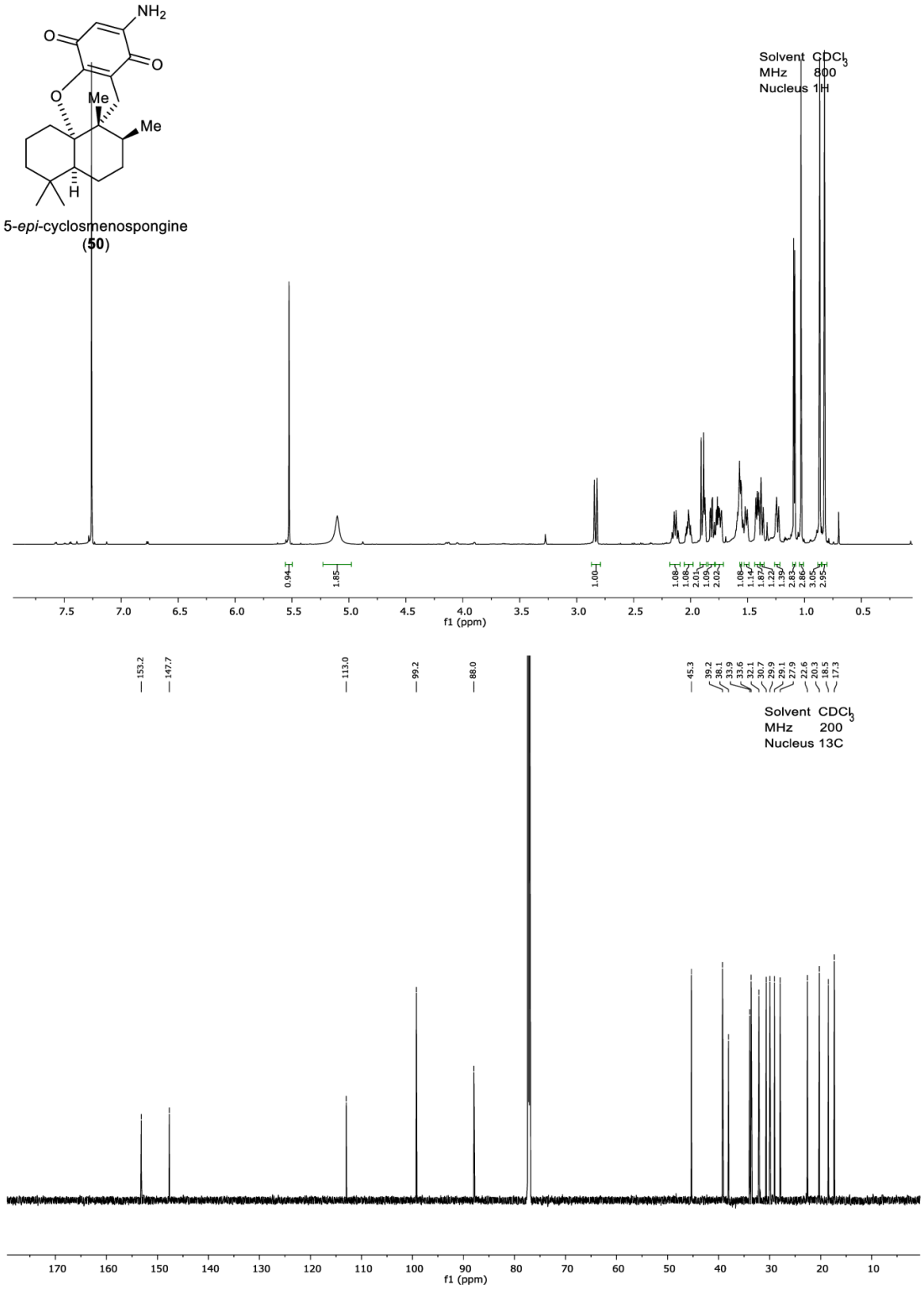
Supplementary Figure 42 ^{1}H and ^{13}C NMR Spectra for **S47** in C_6D_6.



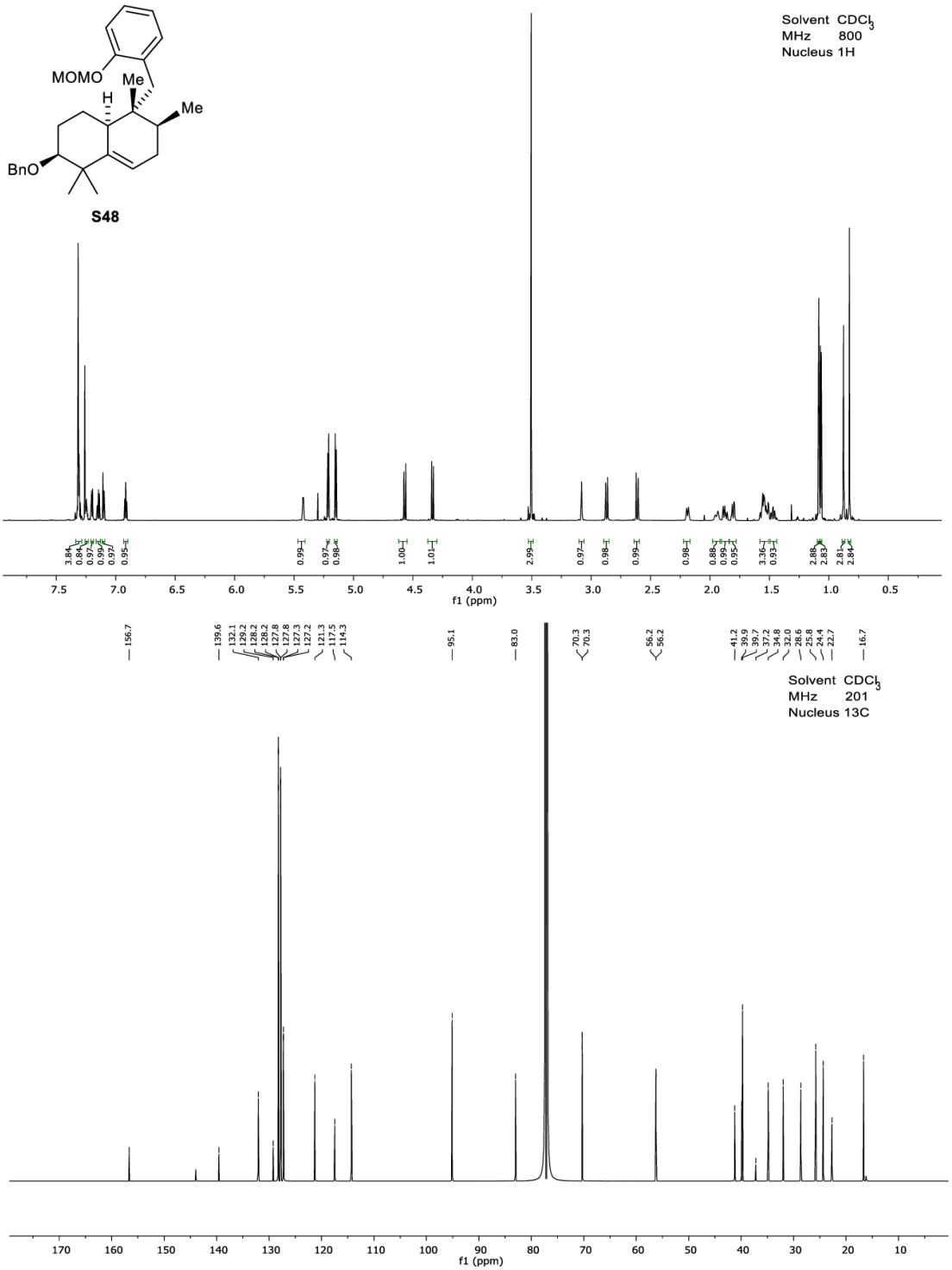
Supplementary Figure 43 ^{1}H and ^{13}C NMR Spectra for **3** in $CDCl_3$.



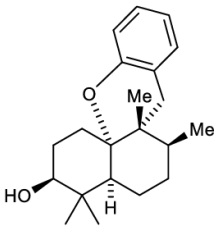
Supplementary Figure 44 HSQC C NMR Spectra for **3** in $CDCl_3$.



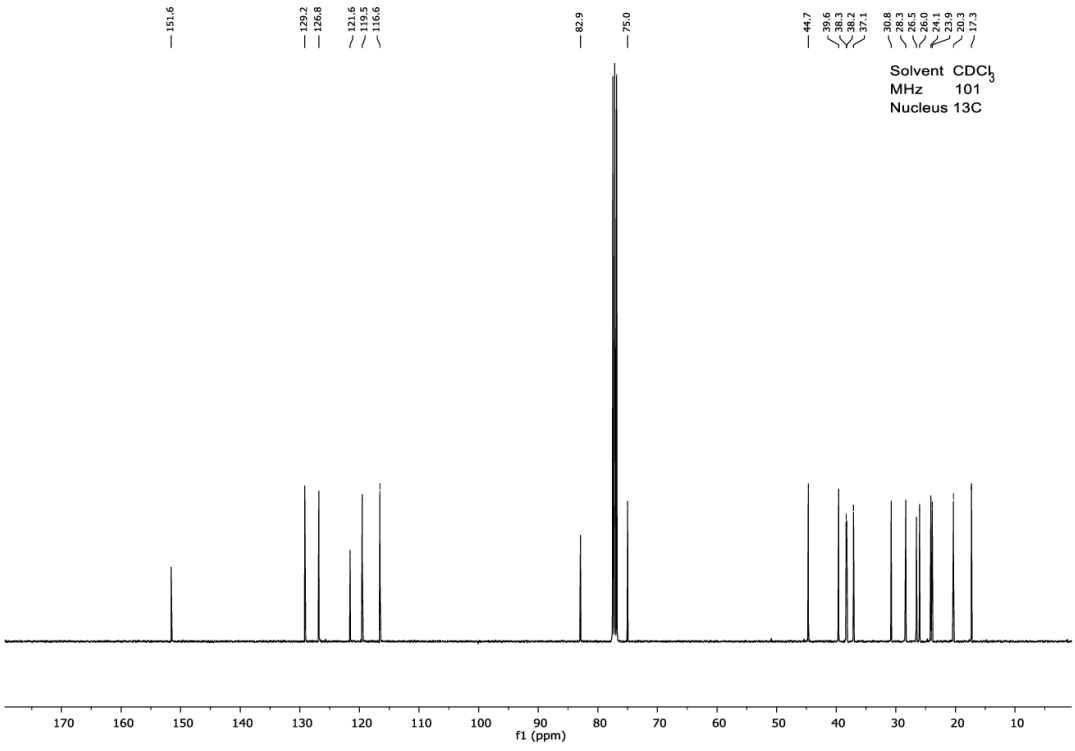
Supplementary Figure 45 ^{1}H and ^{13}C NMR Spectra for **50** in $CDCl_3$.



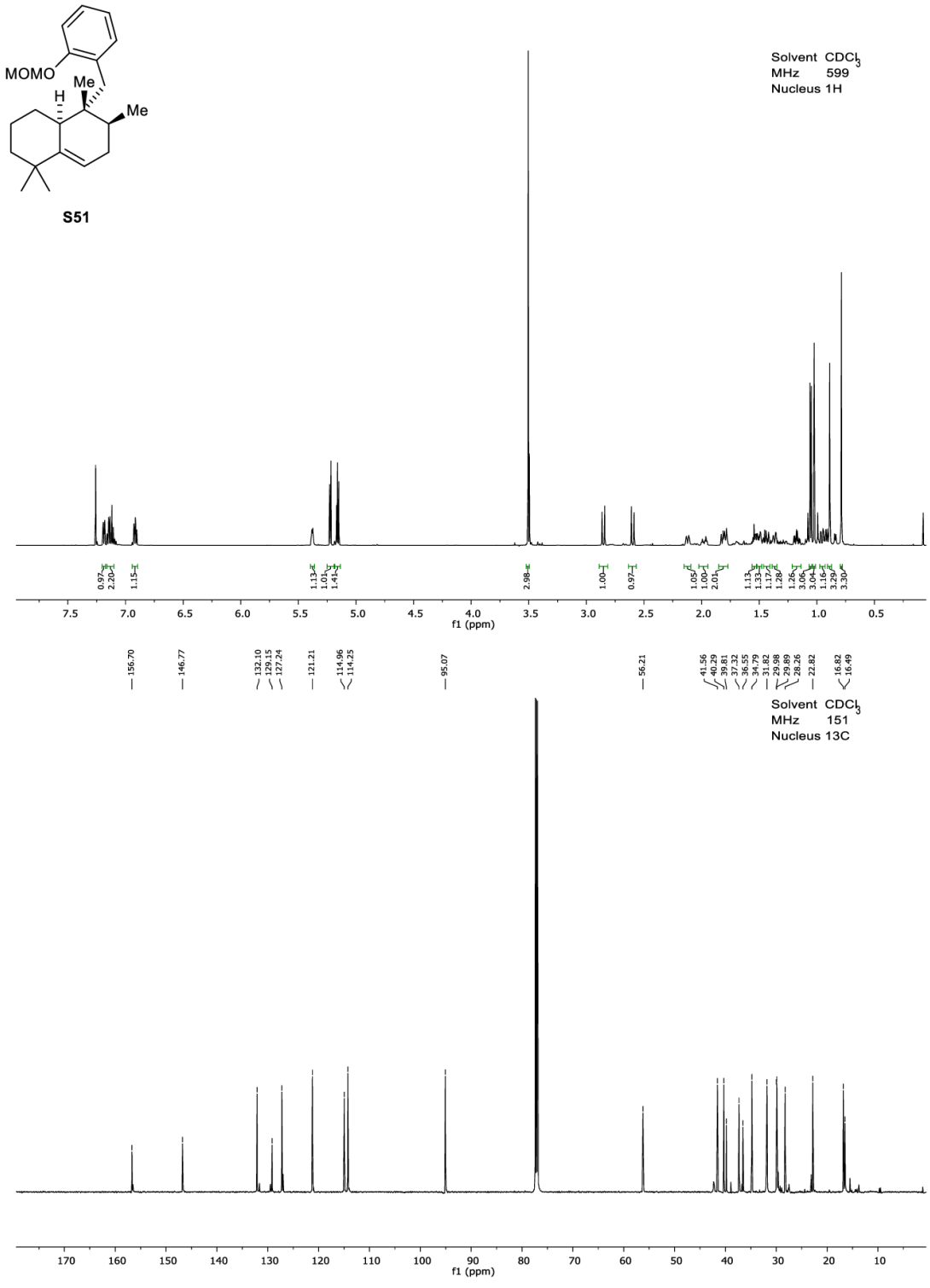
Supplementary Figure 46 ^{1}H and ^{13}C NMR Spectra for **S48** in $CDCl_3$.



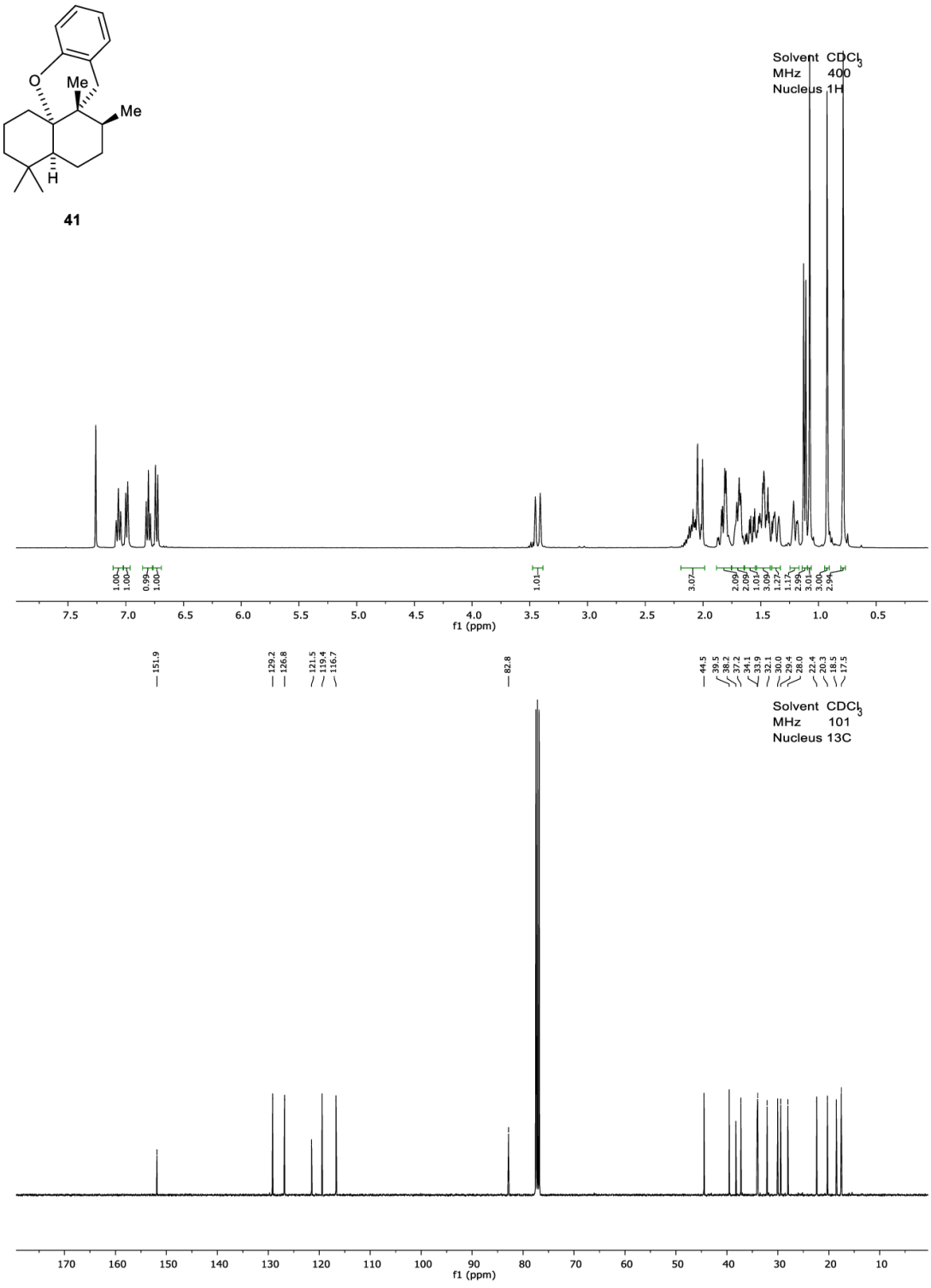
40



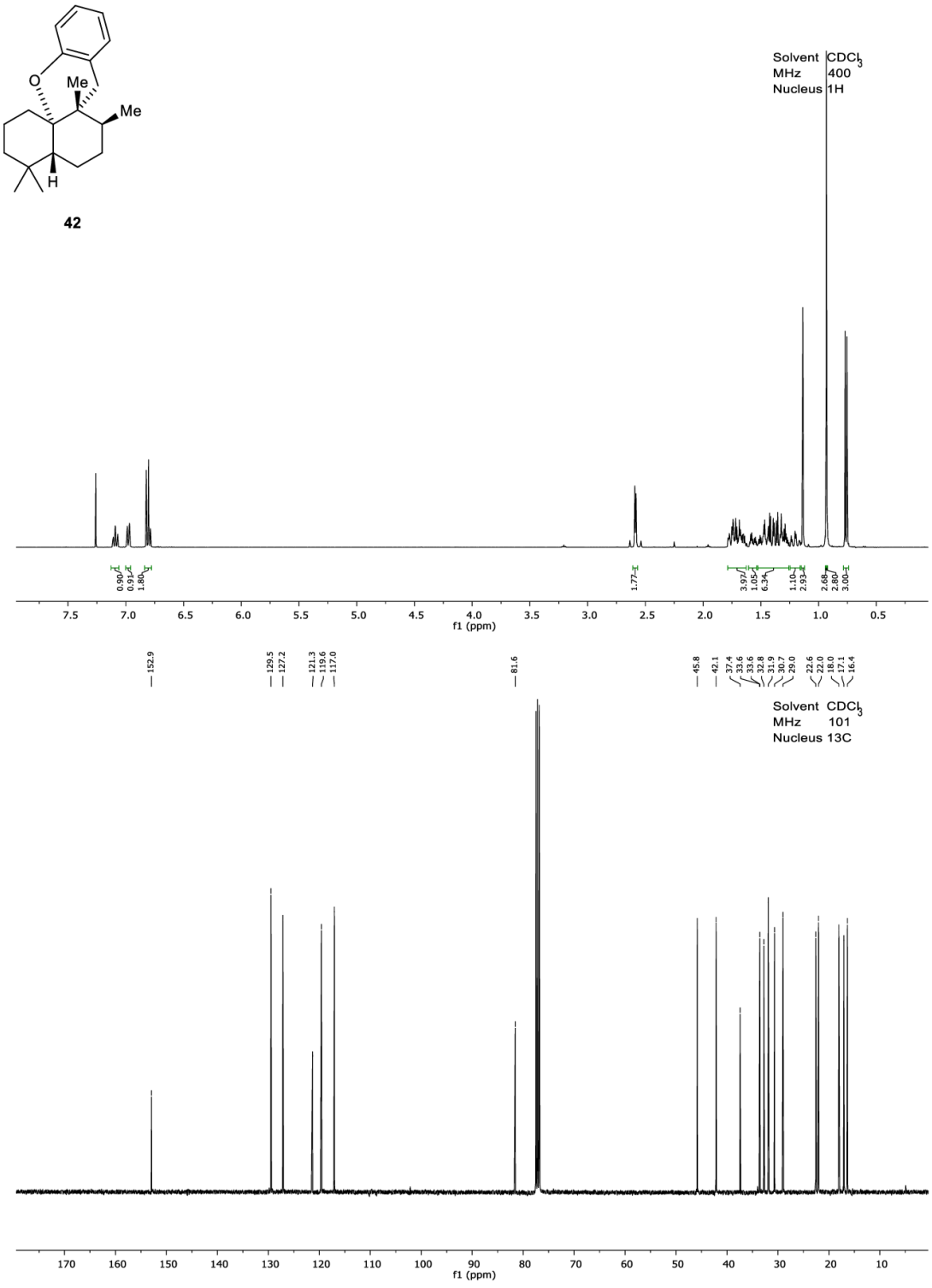
Supplementary Figure 47 ^{1}H and ^{13}C NMR Spectra for **40** in $CDCl_3$.



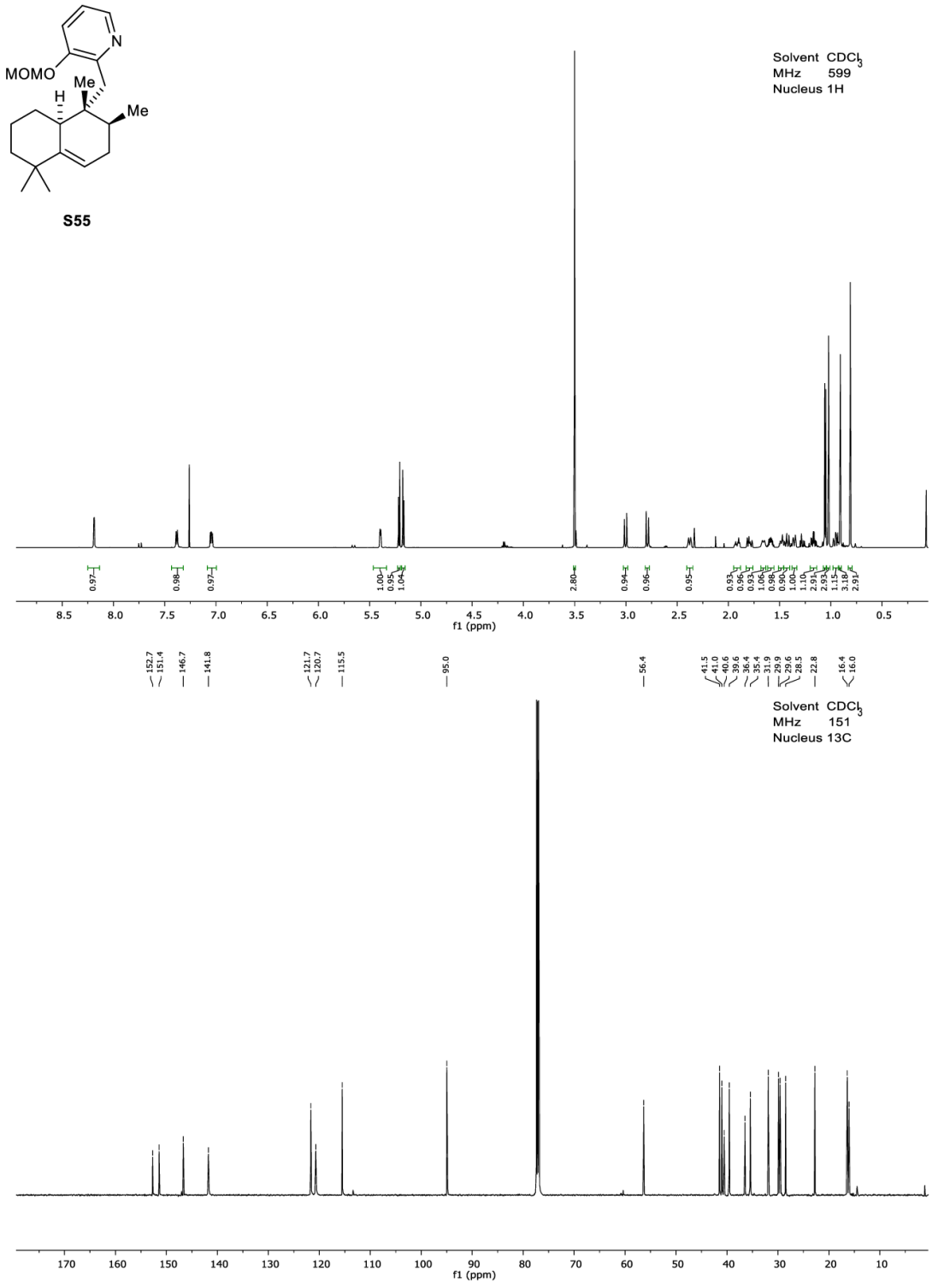
Supplementary Figure 48 ^{1}H and ^{13}C NMR Spectra for **S51** in $CDCl_3$.



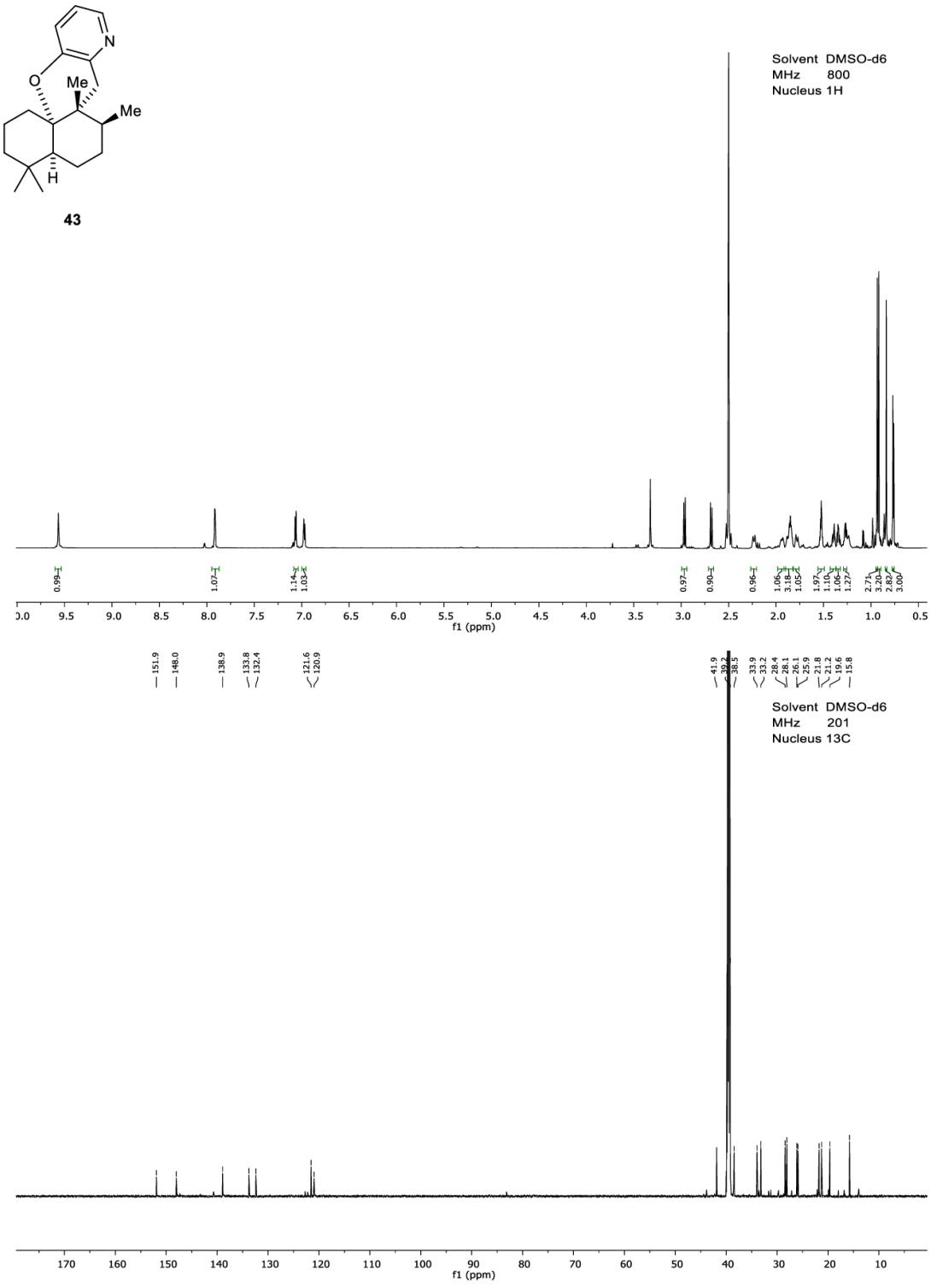
Supplementary Figure 49 ^{1}H and ^{13}C NMR Spectra for **41** in $CDCl_3$.



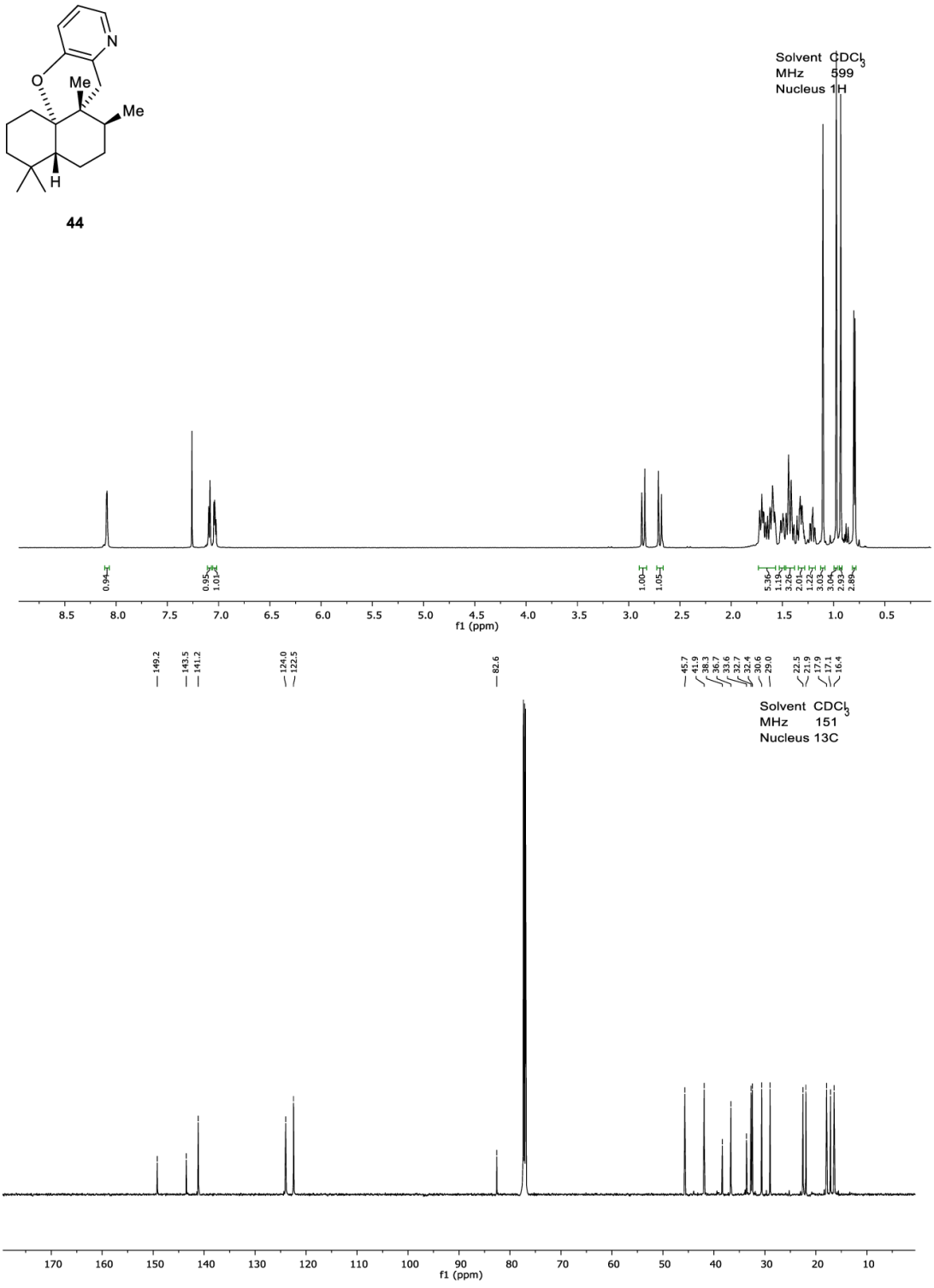
Supplementary Figure 50 ^{1}H and ^{13}C NMR Spectra for **42** in $CDCl_3$.



Supplementary Figure 51 ^{1}H and ^{13}C NMR Spectra for **S55** in $CDCl_3$.

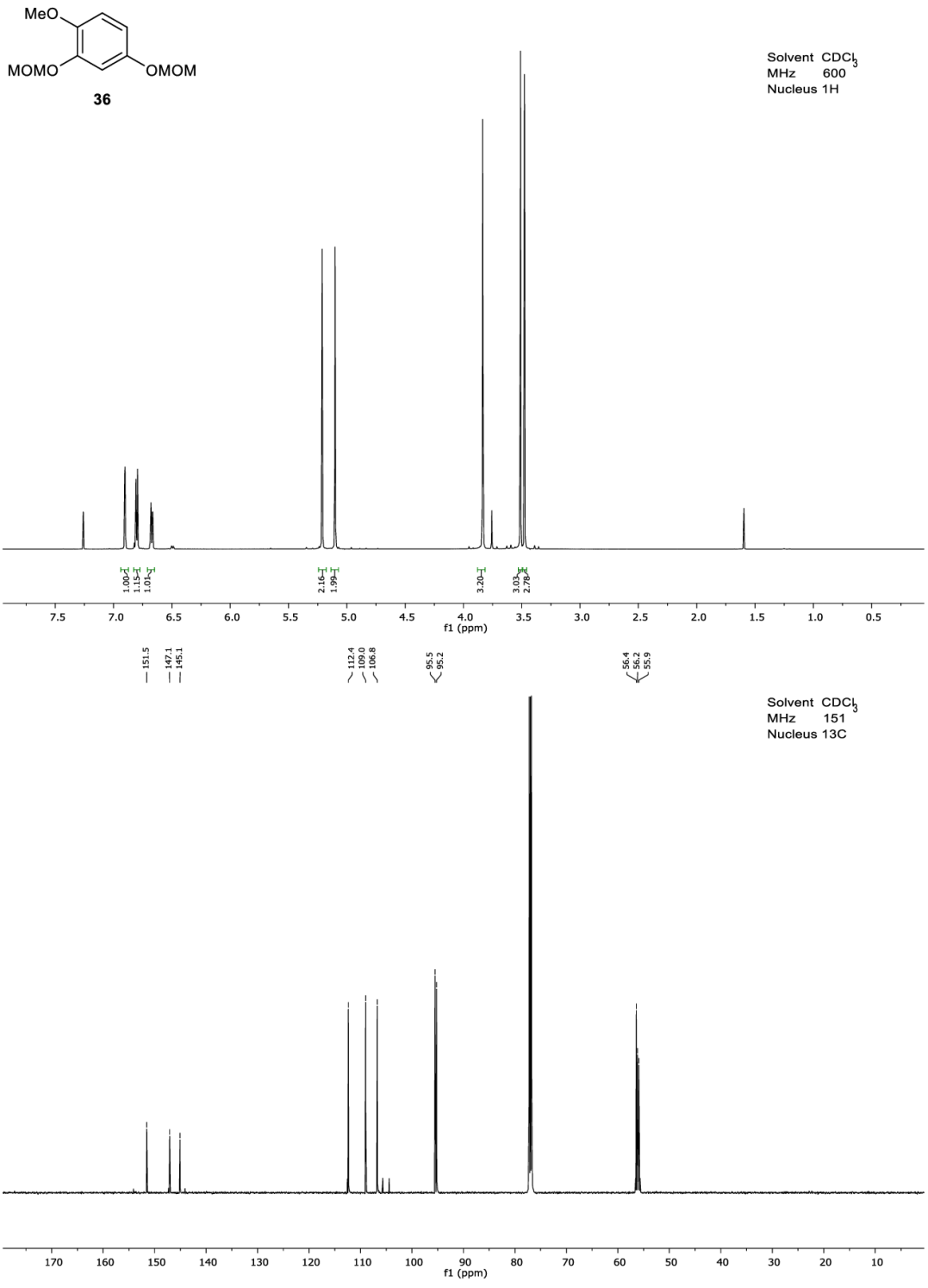


Supplementary Figure 52 ^{1}H and ^{13}C NMR Spectra for **43** in DMSO-d6.

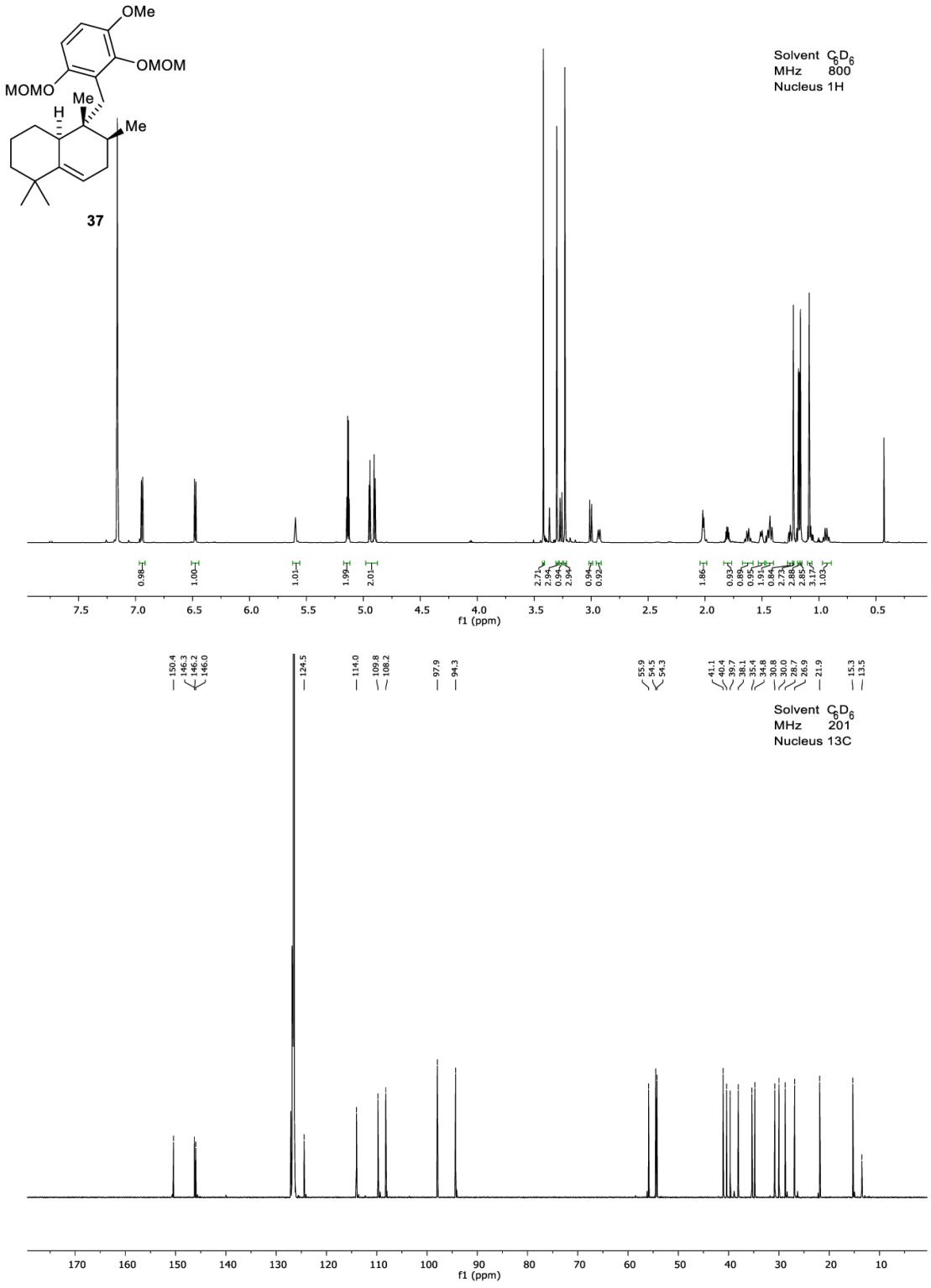


44

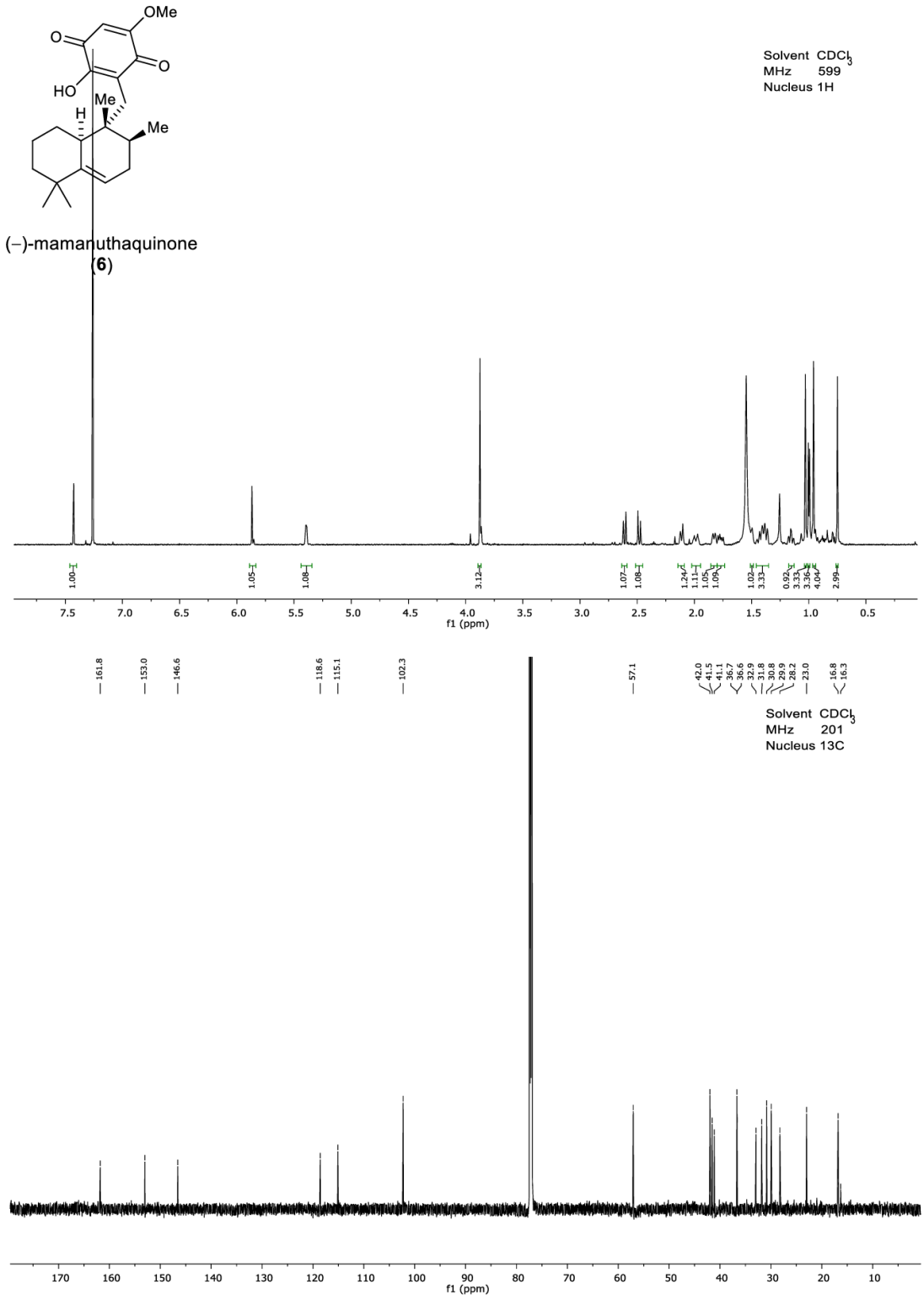
Supplementary Figure 53 ^{1}H and ^{13}C NMR Spectra for **44** in $CDCl_3$.



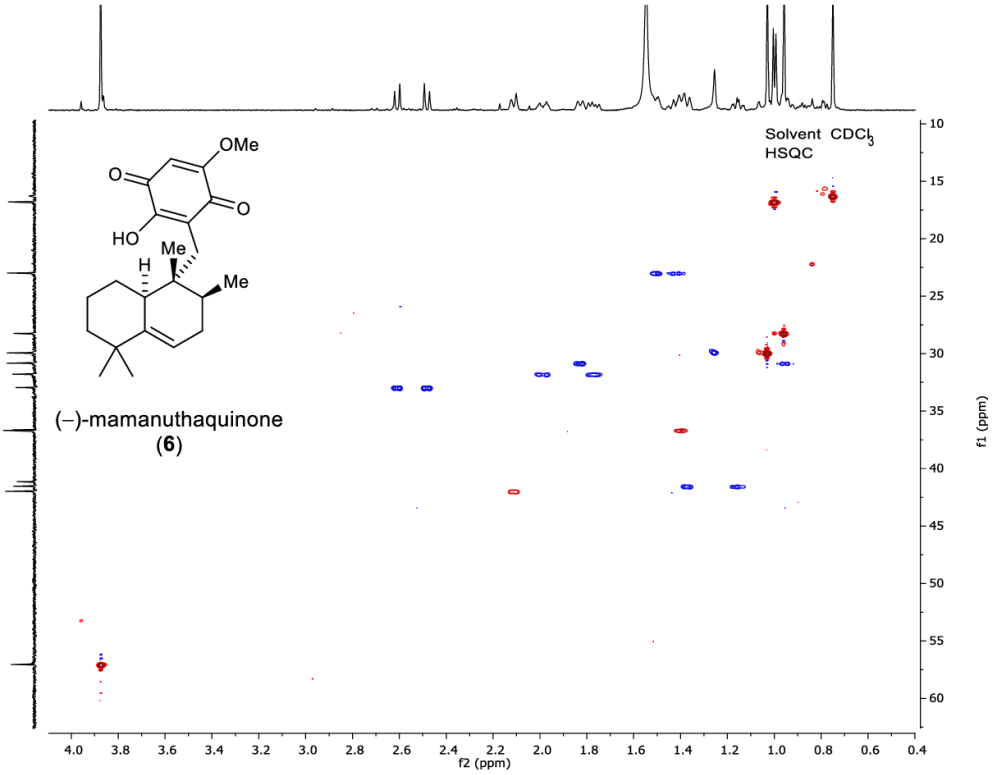
Supplementary Figure 54 ^{1}H and ^{13}C NMR Spectra for **36** in $CDCl_3$.



Supplementary Figure 55 ^{1}H and ^{13}C NMR Spectra for **37** in C_6DC_6.

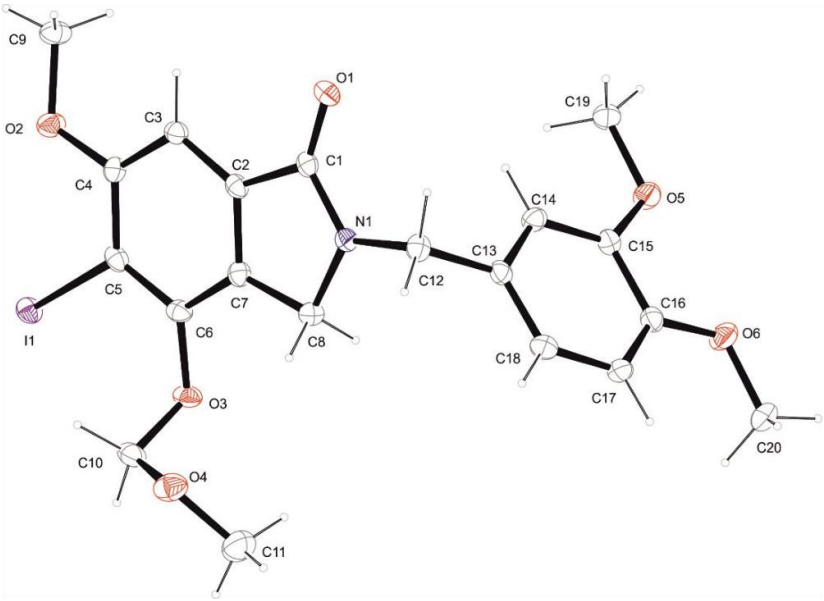


Supplementary Figure 56 ^{1}H and ^{13}C NMR Spectra for **6** in $CDCl_3$.

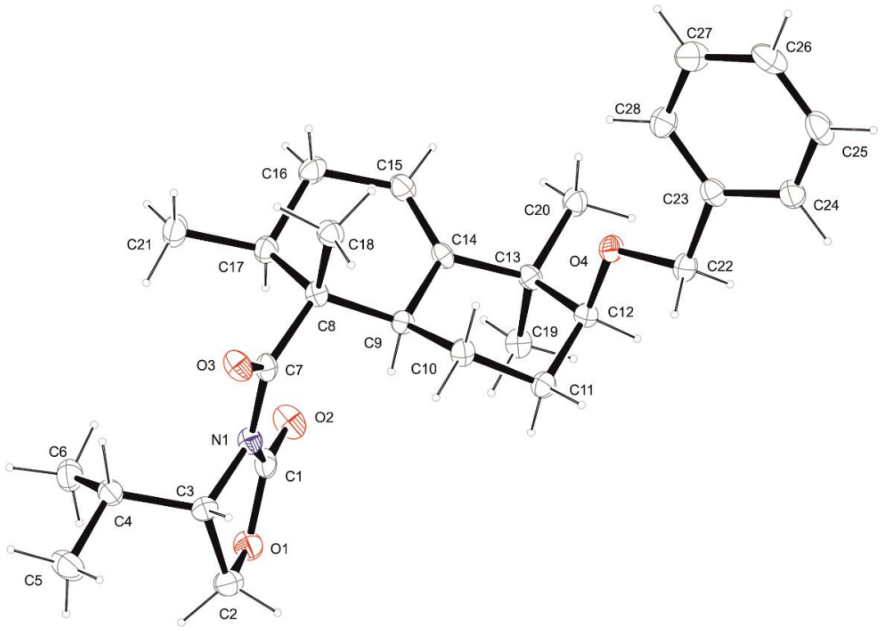


Supplementary Figure 57 HSQC NMR Spectra for **2** in $CDCl_3$.

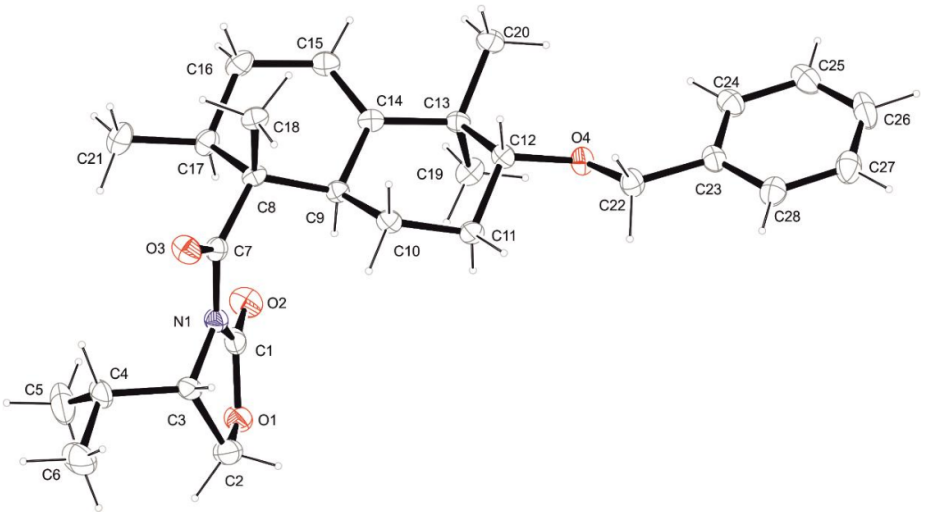
X-Ray Crystallographic Data



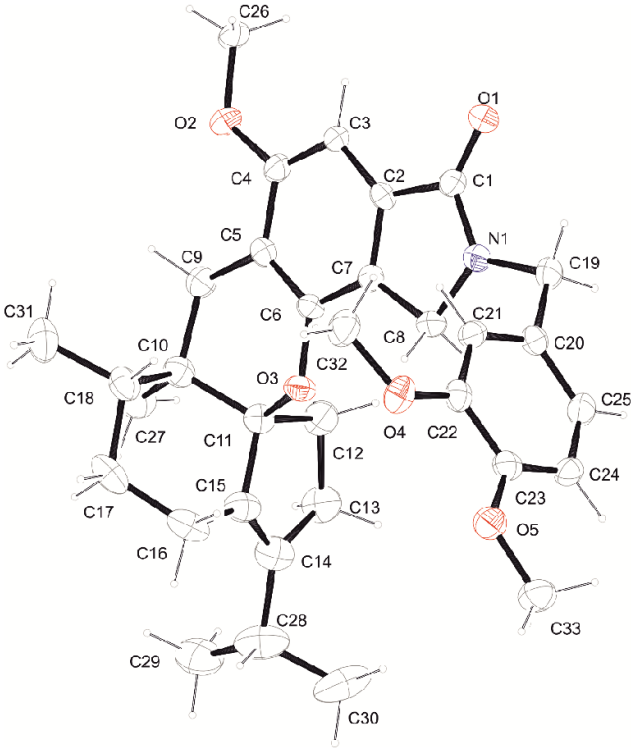
Supplementary Figure 58 CCDC 1534418 contains the supplementary crystallographic data for isoindole **15**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



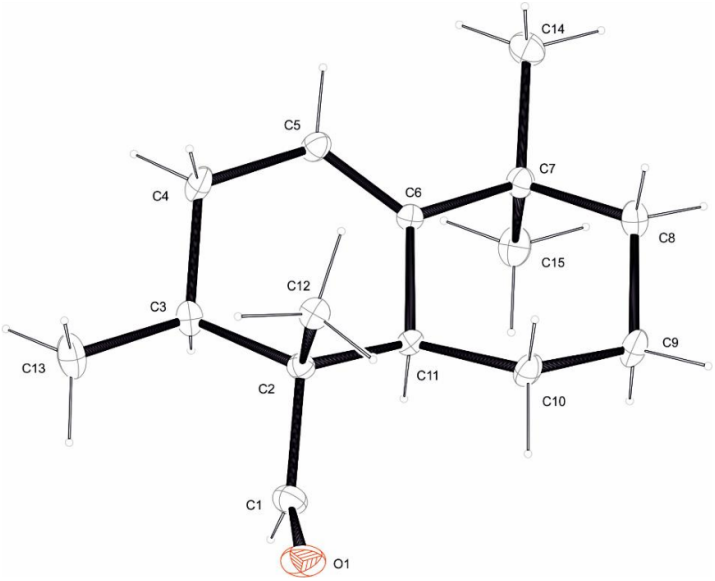
Supplementary Figure 59 CCDC 1534416 contains the supplementary crystallographic data for oxazolidone **22**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



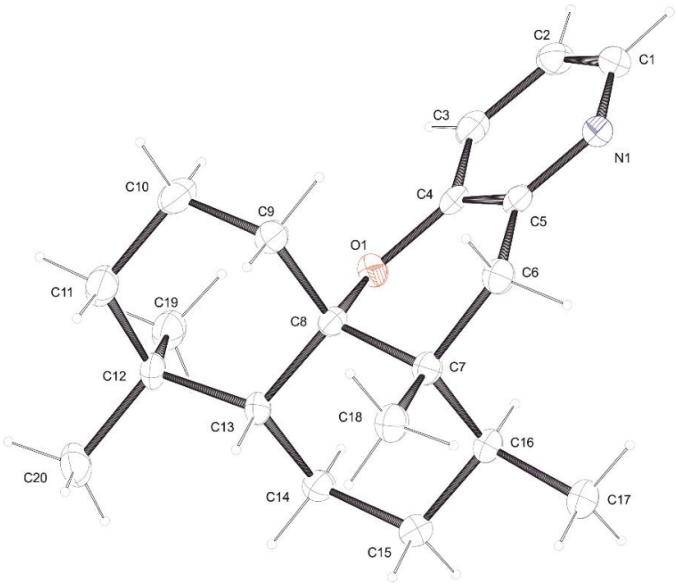
Supplementary Figure 60 CCDC 1534417 contains the supplementary crystallographic data for oxazolidone **S14**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



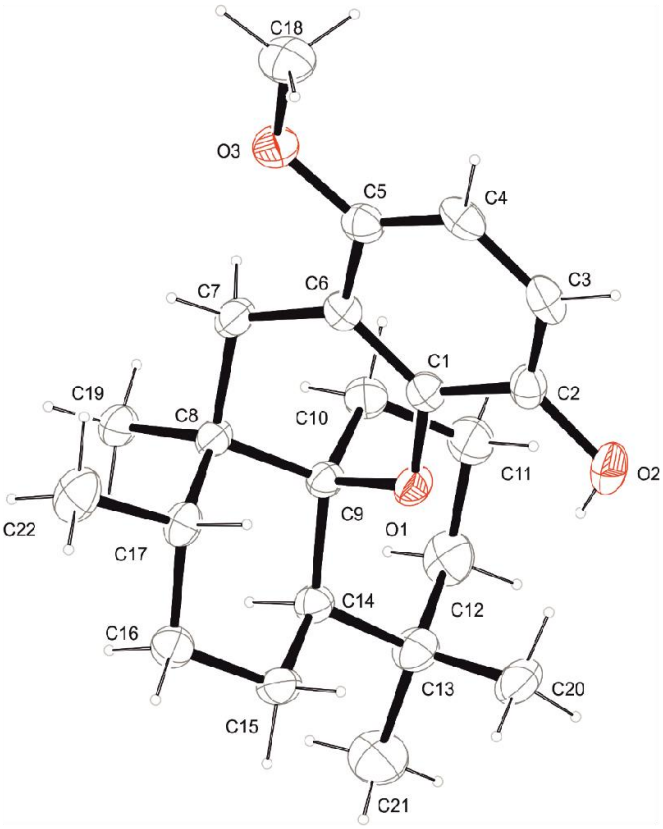
Supplementary Figure 61 CCDC 1534419 contains the supplementary crystallographic data for pentacycle **S19**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



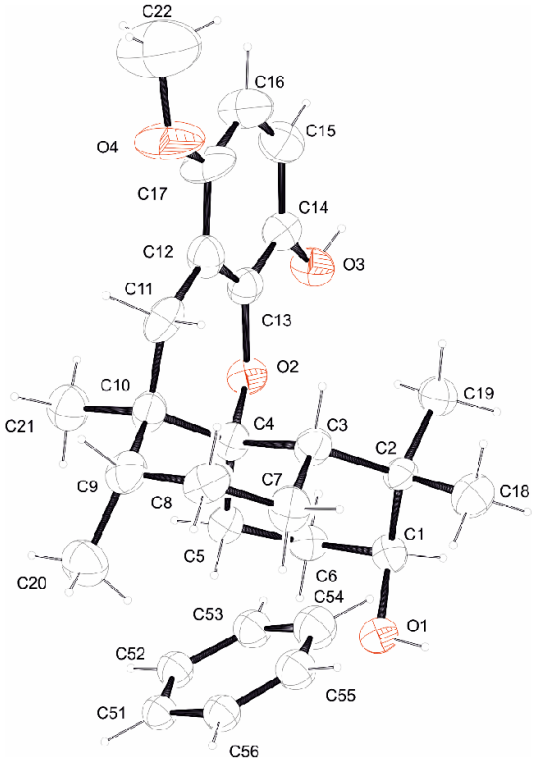
Supplementary Figure 62 CCDC 1534618 contains the supplementary crystallographic data for aldehyde **33**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



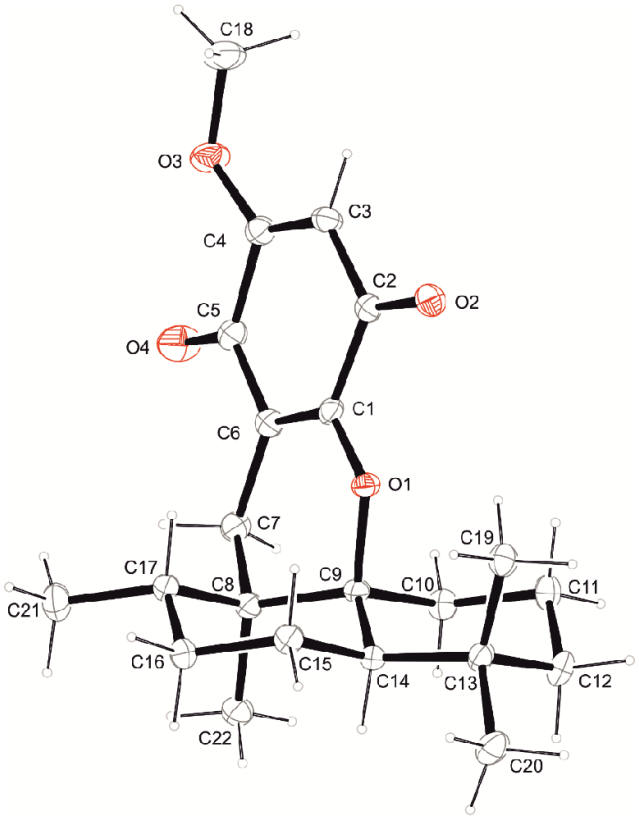
Supplementary Figure 63 CCDC 1534421 contains the supplementary crystallographic data for pyridine **44**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



Supplementary Figure 64 CCDC 1509377 contains the supplementary crystallographic data for 5-epi-strongylin A (**45**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



Supplementary Figure 65 CCDC 1534420 contains the supplementary crystallographic data for 3-hydroxy-strongylin A (**48**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



Supplementary Figure 66 CCDC 1534580 contains the supplementary crystallographic data for 5-epi-smenoqualone (**51**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supplementary Table 12 Crystallographic data for isoindole 15.

net formula	$C_{20}H_{22}INO_6$
M_r/g mol^{-1}	499.28
crystal size/mm	0.100 × 0.070 × 0.050
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21/c 1'
a/Å	11.5389(3)
b/Å	10.9523(3)
c/Å	15.9781(4)
α/°	90
β/°	100.7260(10)
γ/°	90
V/Å^3	1983.99(9)
Z	4
calc. density/g cm^{-3}	1.672
μ/mm^{-1}	1.651
absorption correction	Multi-Scan
transmission factor range	0.6975–0.7461
refls. measured	25091
R_{int}	0.0469
mean σ(I)/I	0.0427
θ range	3.193–30.504
observed refls.	4958
x, y (weighting scheme)	0.0187, 1.1451
hydrogen refinement	constr
refls in refinement	6066
parameters	257
restraints	0
R(F_{obs})	0.0284
$R_w(F^2)$	0.0624
S	1.046
shift/error$_{max}$	0.002
max electron density/e Å^{-3}	0.642
min electron density/e Å^{-3}	−0.549

Supplementary Table 13 Crystallographic data for oxazolidone 22.

net formula	$C_{28}H_{39}NO_4$
M_r/g mol^{-1}	453.60
crystal size/mm	0.100 × 0.030 × 0.020
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P 21 21 21'
a/Å	10.5044(2)
b/Å	13.8351(3)
c/Å	34.2367(8)
α/°	90
β/°	90
γ/°	90
V/Å^3	4975.60(18)
Z	8
calc. density/g cm^{-3}	1.211
μ/mm^{-1}	0.080
absorption correction	Multi-Scan
transmission factor range	0.8985–0.9705
refls. measured	21786
R_{int}	0.0375
mean σ(I)/I	0.0688
θ range	3.176–28.282
observed refls.	9666
x, y (weighting scheme)	0.0342, 1.3785
hydrogen refinement	constr
Flack parameter	0.5(5)
refls in refinement	11844
parameters	607
restraints	0
$R(F_{obs})$	0.0494
$R_w(F^2)$	0.1085
S	1.025
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.288
min electron density/e Å^{-3}	−0.246

Supplementary Table 14 Crystallographic data for oxazolidone S13.

net formula	$C_{28}H_{39}NO_4$
M_r/g mol^{-1}	453.60
crystal size/mm	0.100 × 0.060 × 0.020
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'C 1 2 1'
a/Å	21.1557(11)
b/Å	6.9835(3)
c/Å	18.5788(10)
α/°	90
β/°	113.077(2)
γ/°	90
V/Å^3	2525.2(2)
Z	4
calc. density/g cm^{-3}	1.193
μ/mm^{-1}	0.079
absorption correction	Multi-Scan
transmission factor range	0.8764–0.9705
refls. measured	11053
R_{int}	0.0308
mean σ(I)/I	0.0629
θ range	3.362–28.280
observed refls.	5097
x, y (weighting scheme)	0.0364, 0.7835
hydrogen refinement	constr
Flack parameter	−0.8(6)
refls in refinement	6217
parameters	304
restraints	1
$R(F_{obs})$	0.0475
$R_w(F^2)$	0.0986
S	1.022
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.247
min electron density/e Å^{-3}	−0.184

Supplementary Table 15 Crystallographic data for pentacycle S18.

net formula	$C_{33}H_{41}NO_5$
M_r/g mol^{-1}	531.67
crystal size/mm	0.080 × 0.070 × 0.030
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P 21 21 21'
a/Å	9.2680(3)
b/Å	13.5377(6)
c/Å	22.8966(10)
α/°	90
β/°	90
γ/°	90
V/Å^3	2872.8(2)
Z	4
calc. density/g cm^{-3}	1.229
μ/mm^{-1}	0.082
absorption correction	Multi-Scan
transmission factor range	0.9145–0.9705
refls. measured	22538
R_{int}	0.0659
mean σ(I)/I	0.0688
θ range	3.138–26.360
observed refls.	4535
x, y (weighting scheme)	0.0462, 0.6830
hydrogen refinement	constr
Flack parameter	0.6(8)
refls in refinement	5852
parameters	359
restraints	0
R(F_{obs})	0.0516
$R_w(F^2)$	0.1189
S	1.042
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.231
min electron density/e Å^{-3}	−0.239

Supplementary Table 16 Crystallographic data for aldehyde 33.

net formula	$C_{15}H_{24}O$
M_r/g mol^{-1}	220.34
crystal size/mm	0.100 × 0.070 × 0.050
T/K	153.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21 1'
a/Å	7.1180(3)
b/Å	8.2644(3)
c/Å	11.4134(5)
α/°	90
β/°	94.5133(16)
γ/°	90
V/Å^3	669.32(5)
Z	2
calc. density/g cm^{-3}	1.093
μ/mm^{-1}	0.066
absorption correction	Multi-Scan
transmission factor range	0.9195–0.9593
refls. measured	7512
R_{int}	0.0204
mean σ(I)/I	0.0292
θ range	3.262–28.255
observed refls.	2940
x, y (weighting scheme)	0.0457, 0.1045
hydrogen refinement	constr
Flack parameter	−0.2(4)
refls in refinement	3068
parameters	149
restraints	1
$R(F_{obs})$	0.0328
$R_w(F^2)$	0.0910
S	1.068
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.223
min electron density/e Å^{-3}	−0.160

Supplementary Table 17 Crystallographic data for pyridine 43.

net formula	$C_{20}H_{29}NO$
M_r/g mol^{-1}	299.44
crystal size/mm	0.100 × 0.030 × 0.020
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P 21 21 21'
a/Å	6.5144(10)
b/Å	15.165(2)
c/Å	16.776(2)
α/°	90
β/°	90
γ/°	90
V/Å^3	1657.3(4)
Z	4
calc. density/g cm^{-3}	1.200
μ/mm^{-1}	0.072
absorption correction	Multi-Scan
transmission factor range	0.7177–0.9705
refls. measured	13220
R_{int}	0.0975
mean σ(I)/I	0.0852
θ range	3.355–25.328
observed refls.	2336
x, y (weighting scheme)	0.0453, 0.7034
hydrogen refinement	constr
Flack parameter	0.3(10)
refls in refinement	3019
parameters	203
restraints	0
R(F_{obs})	0.0576
$R_w(F^2)$	0.1354
S	1.062
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.182
min electron density/e Å^{-3}	−0.274

Supplementary Table 18 Crystallographic data for 5-epi-strongylin A (44).

net formula	$C_{22}H_{32}O_3$
M_r/g mol^{-1}	344.47
crystal size/mm	0.100 × 0.040 × 0.030
T/K	153.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P 21 21 21'
a/Å	9.7896(4)
b/Å	10.6910(5)
c/Å	18.2352(10)
α/°	90
β/°	90
γ/°	90
V/Å^3	1908.51(16)
Z	4
calc. density/g cm^{-3}	1.199
μ/mm^{-1}	0.078
absorption correction	Multi-Scan
transmission factor range	0.9329–0.9705
refls. measured	22500
R_{int}	0.0375
mean σ(I)/I	0.0317
θ range	3.600–28.276
observed refls.	4252
x, y (weighting scheme)	0.0464, 0.3655
hydrogen refinement	C-H constr, O-H refall
Flack parameter	0.3(4)
refls in refinement	4731
parameters	235
restraints	0
R(F_{obs})	0.0395
$R_w(F^2)$	0.0985
S	1.042
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.249
min electron density/e Å^{-3}	−0.216

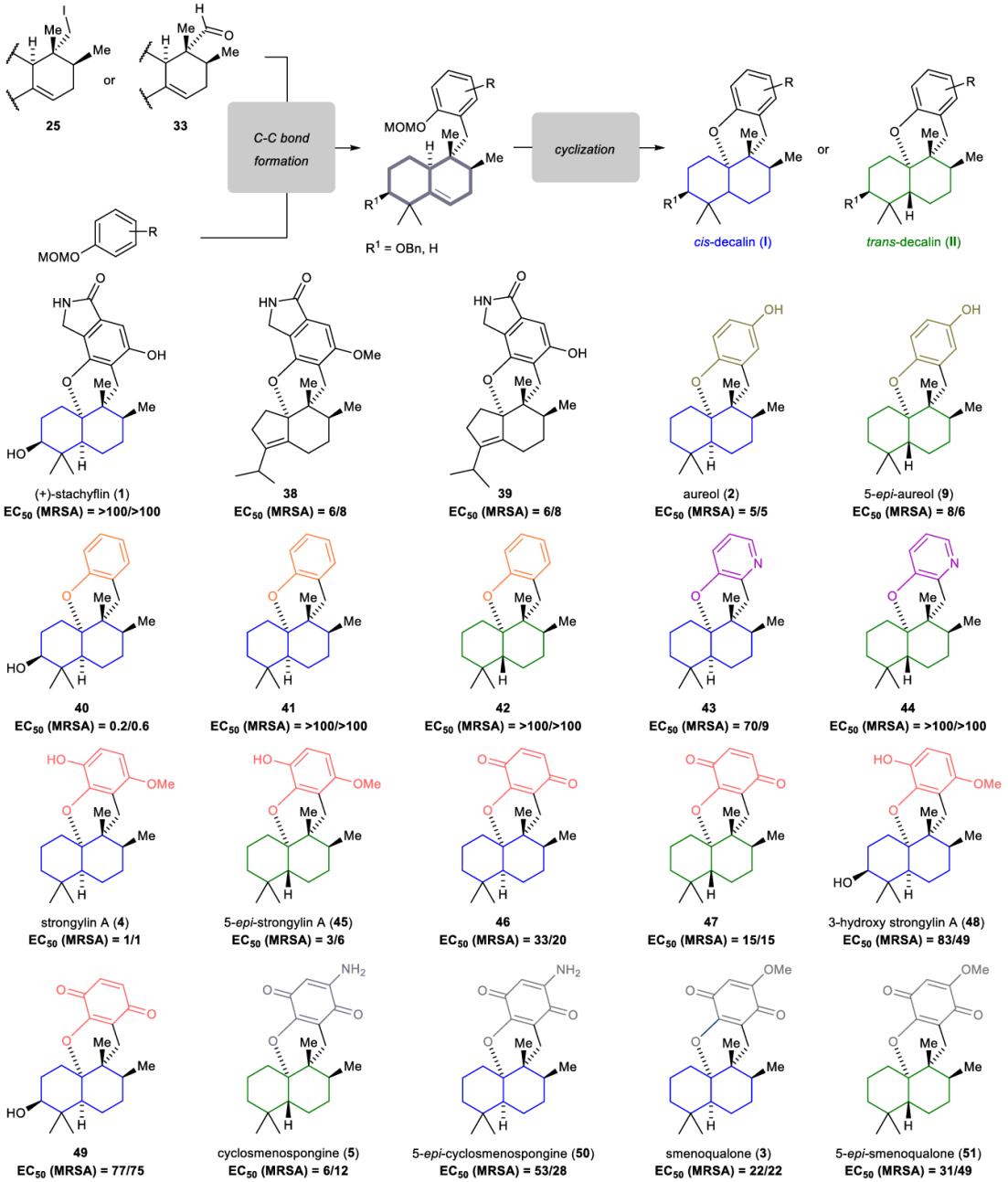
Supplementary Table 19 Crystallographic data for 3-hydroxy-strongylin A (47).

net formula	$C_{25}H_{35}O_4$
M_r/g mol^{-1}	399.53
crystal size/mm	0.080 × 0.060 × 0.020
T/K	173.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21 1'
a/Å	13.5556(9)
b/Å	13.8798(11)
c/Å	15.6721(14)
α/°	90
β/°	103.108(4)
γ/°	90
V/Å^3	2871.9(4)
Z	4
calc. density/g cm^{-3}	0.924
μ/mm^{-1}	0.061
absorption correction	Multi-Scan
transmission factor range	0.7873–0.9705
refls. measured	8128
R_{int}	0.1132
mean σ(I)/I	0.1198
θ range	3.225–23.256
observed refls.	5284
x, y (weighting scheme)	0.1620, 0.0
hydrogen refinement	constr
Flack parameter	0.0(10)
refls in refinement	8128
parameters	532
restraints	7
R(F_{obs})	0.0931
$R_w(F^2)$	0.2635
S	1.035
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.568
min electron density/e Å^{-3}	−0.305

Supplementary Table 20 Crystallographic data for 5-epi-smenoqualone (50).

net formula	$C_{22}H_{30}O_4$
M_r/g mol^{-1}	358.46
crystal size/mm	0.080 × 0.050 × 0.030
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P 21 21 21'
a/Å	6.77460(10)
b/Å	11.7096(3)
c/Å	23.4581(6)
α/°	90
β/°	90
γ/°	90
V/Å^3	1860.88(7)
Z	4
calc. density/g cm^{-3}	1.279
μ/mm^{-1}	0.086
absorption correction	Multi-Scan
transmission factor range	0.8996–0.9705
refls. measured	11364
R_{int}	0.0360
mean σ(I)/I	0.0502
θ range	3.473–28.278
observed refls.	3970
x, y (weighting scheme)	0.0409, 0.3301
hydrogen refinement	constr
Flack parameter	−0.1(6)
refls in refinement	4554
parameters	240
restraints	0
$R(F_{obs})$	0.0424
$R_w(F^2)$	0.0956
S	1.038
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.269
min electron density/e Å^{-3}	−0.245

Antibacterial assays



Supplementary Figure 67 Color-coding was used to indicate the decalin stereochemistry (blue = cis-decalin, green = trans-decalin) and to highlight the modified arene component. The effective concentrations (EC_{50} values) that inhibited the growth of two MRSA strains (DSM 11822/RKI 11-02670) are given in μM.

Supplementary Table 21 Antibacterial activities of meroterpenoids against Gram-positive pathogens[1)]. EC_{50} and MIC values are given in µM.

	MRSA DSM		MRSA RKI		E. faecium	
Cmpd no	**MIC**	**EC_{50}**	**MIC**	**EC_{50}**	**MIC**	**EC_{50}**
1	>100	>100	>100	>100	>100	>100
2	10	5	5	5	12	8
3	76	22	56	22	>100	14
4	1.4	1	2	1	>100	>100
5	13	6	15	12	>100	20
9	11	8	10	6	10	8
38	13	6	11	8	100	15
39	15	6	12	8	100	15
40	0.8	0.2	4	0.6	>100	>100
41	>100	>100	>100	>100	>100	>100
42	>100	>100	>100	>100	>100	>100
43	100	70	12	9	>100	>100
44	>100	>100	>100	>100	>100	>100
45	6	3	6	6	35	13
46	47	33	22	20	>100	80
47	29	15	22	15	52	32
48	>100	83	94	49	>100	>100
49	>100	77	>100	75	>100	100
50	77	53	37	28	>100	>100
51	46	31	68	49	>100	13
Linezolid	1.3	0.6	0.6	0.2		
Ciprofloxacin					20	7

1) All compounds were inactive (>100 µM) against Acinetobacter baumannii (DSM 30007), Escherichia coli (DSM 1116), Klebsiella pneumoniae (DSM 11678) and Pseudomonas aeruginosa PA7 (DSM 24068).

Antiproliferative assays

Supplementary Table 22 Antiproliferative activities of meroterpenoids against four mammalian cell lines. EC_{50} values are given in μM.

Cmpd no	L929	KB-3-1	MCF-4	FS4-LTM
1	51	51	32	>100
2	>100	16	14	25
3	30	25	15	61
4	49	12	12	25
5	14	12	27	26
9	14	11	23	33
38	19	25	15	25
39	34	29	23	26
40	7	7	9	14
41	>100	>100	>100	>100
42	>100	>100	>100	>100
43	40	20	13	21
44	>100	75	>100	>100
45	>100	40	27	>100
46	9	24	13	32
47	3	13	13	>100
48	45	87	43	69
49	10	21	8	16
50	54	24	28	46
51	27	56	25	45
Auranofin	1.2	1.2	1.1	1.7
Staurosporine	0.5	2.2	1.8	2.0

2

Supplementary References

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3.3 Supporting Information for Chapter 2.2

3.3.1 General Experimental Details

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

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

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

High resolution mass spectra (HRMS) were recorded on a Varian MAT CH7A or a Varian MAT 711 MS instrument by electron impact (EI) or electrospray ionization (ESI) techniques at the Department of Chemistry, Ludwig-Maximilians-University Munich or a Thermo Scientific™ LTQ Orbitrap XL™ Hybrid Ion Trap-Orbitrap Mass Spectrometer at the Institute of Organic Chemistry and Center for Molecular Biosciences, University of Innsbruck.

Infrared spectra (IR) were recorded from 4000 cm^{-1} to 450 cm^{-1} on a Bruker™ ALPHA FT-IR Spectrometer from Bruker. Samples were prepared as a neat film or a film by evaporation of a solution

in $CDCl_3$. IR data in frequency of absorption (cm^{-1}) is reported as follows: *w* = weak, *m* = medium, *s* = strong, *br* = broad or combinations thereof.

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

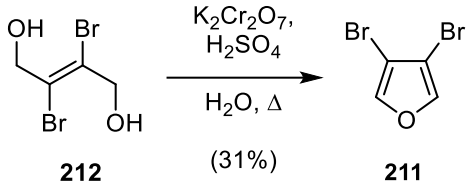
Optical rotation values were recorded on a Schmidt+Haensch UniPol L1000 Peltier polarimeter. The specific rotation is calculated as follows: $[\alpha]_{\lambda}^{T} = \frac{\propto \times 100}{c \times d}$. Thereby, the wavelength λ is reported in nm and the measuring temperature in °C. α represents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

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

All yields are isolated, unless otherwise specified.

3.3.2 First Generation: Conia-ene cyclization

3,4-Dibromofuran (211)



212 **211**

To a solution of *trans*-2,3-dibromo-2-butene-1,4-diol (**212**) (20.0 g, 81.3 mmol, 1 equiv) in aqueous sulfuric acid (7.5%, 50 mL), which was heated to 130 °C, was added dropwise a solution of potassium dichromate (24.7 g, 84.0 mmol, 1.05 equiv) in concentrated sulfuric acid (21 mL) and water (95 mL) over a period of 90 min. Bromide **211** was constantly distilled from the reaction mixture by water steam distillation (Figure 6). After 2 h, the distillate was extracted with *n*-pentane (3 × 250 mL) and the combined organic extracts were washed with aqueous saturated sodium bicarbonate (100 mL) and aqueous saturated sodium chloride solution (100 mL). The washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated (>200 mbar, 20 °C) to yield **211** (98% in *n*-pentane, 5.77 g, 31%) as a yellow oil. The obtained analytical data for **211** were in full agreement with those reported in the literature.[113] The crude product was used without further purification.

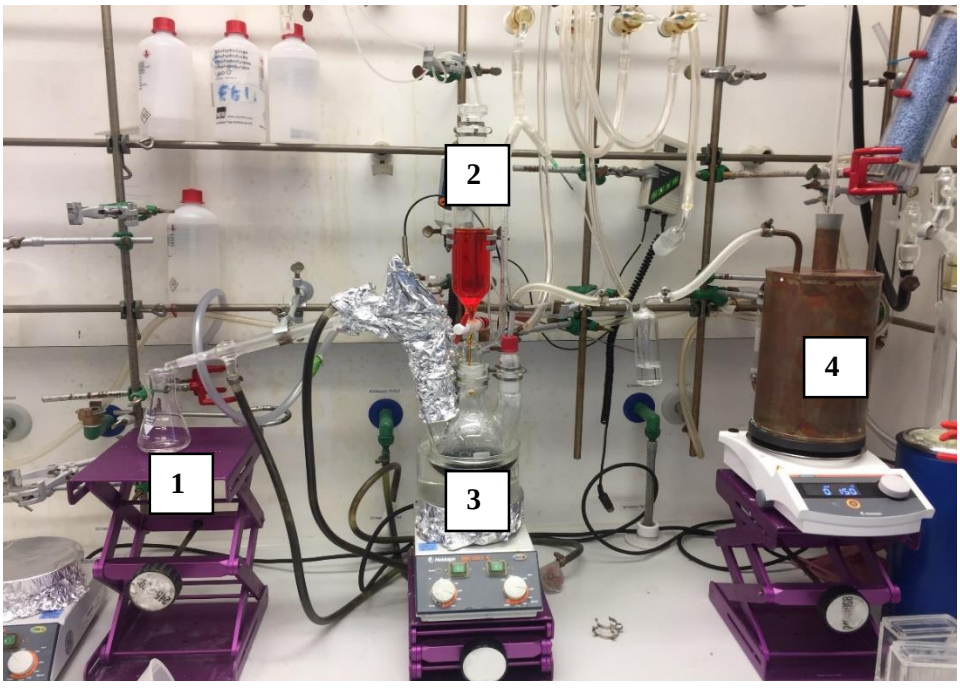
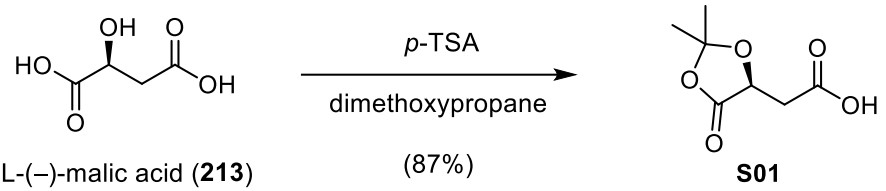


Figure 6 | Experimental set-up for the synthesis of 3,4-dibromofuran (**211**): **1** distillate; **2** potassium dichromate in aqueous sulfuric acid; **3** reaction mixture (130 °C); **4** water steam generator (150 °C).

[113] J. Min, P. Wang, S. Srinivasan, J. C. Nwachukwu, P. Guo, M. Huang, K. E. Carlson, J. A. Katzenellenbogen, K. W. Nettles, H. Zhou, *J. Med. Chem.* **2013**, *56*, 3346–3366.

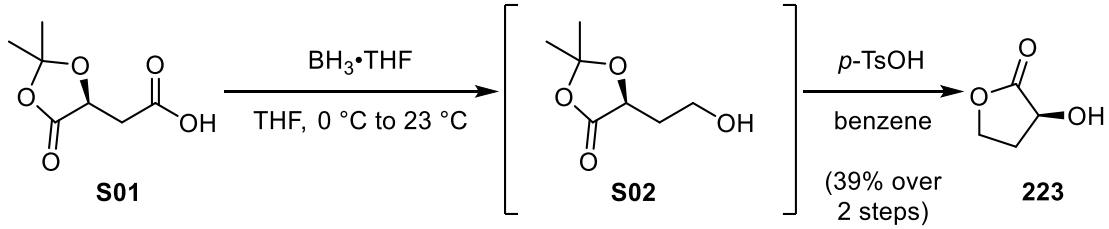
Ketal S01



*Ketal **S01** was prepared according to the procedure described by S. E. Denmark.*[114]

To a suspension of L-(–)-malic acid (**213**) (50.0 g, 373 mmol, 1 equiv) in 2,2-dimethoxypropane (185 mL, 1.49 mol, 4.00 equiv) was added *p*-toluenesulfonic acid monohydrate (709 mg, 3.73 mmol, 0.0100 equiv) at 23 °C. After 3 h, a solution of sodium bicarbonate (313 mg, 3.73 mmol, 0.0100 equiv) in water (200 mL) and dichloromethane (150 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 150 mL). The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated to give **S01** (56.4 g, 87%) as a colorless solid. The obtained characterization data were in full agreement with the values previously reported.

(*R*)-3-hydroxydihydrofuran-2(3H)-one (223)



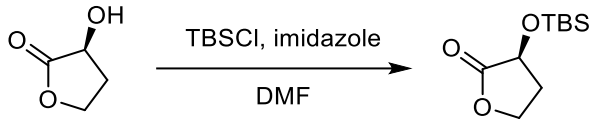
*(R)-3-hydroxydihydrofuran-2(3H)-one (**223**) was prepared according to the procedure described by S. E. Denmark.*[114]

A solution of borane tetrahydrofuran complex (1 M in tetrahydrofuran, 335 mL, 335 mmol, 1.10 equiv) was added to a solution of **S01** (53.1 g, 305 mmol, 1 equiv) in tetrahydrofuran (300 mL) over a period of 1 h at 0 °C. After 1 h at 0 °C, the clear yellow reaction mixture was allowed to warm to 23 °C. After 19 h, methanol (150 mL) was added over a period of 1 h. The reaction mixture was concentrated to give **S02** as a colorless oil that was used without further purification.

p-Toluenesulfonic acid monohydrate (612 mg, 3.22 mmol, 0.0100 equiv) was added to a solution of crude **S02** in benzene (500 mL). After 24 h, the reaction mixture was concentrated and the residue was purified by flash column chromatography on silica gel (70% ethyl acetate in hexanes) to give **223** (12.9 g, 39% over 2 steps) as a colorless oil. The obtained characterization data were in full agreement with the values previously reported.

[114] S. Yang, S. E. Denmark, *J. Am. Chem. Soc.* **2004**, *126*, 12432–12440.

Silyl ether 224



223 (63%) **224**

tert-Butyldimethylchlorosilane (20.9 g, 139 mmol, 1.10 equiv) was added to a solution of **223** (12.9 g, 126 mmol, 1 equiv) and imidazole (18.9 g, 278 mmol, 2.20 equiv) in *N*,*N*-dimethylformamide (500 mL). After 12 h, water (1 L) and diethyl ether (500 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 500 mL). The combined organic extracts were sequentially washed with aqueous lithium chloride solution (10wt%, 1 L) and saturated aqueous sodium chloride (1 L) solution. The washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to give **224** (17.2 g, 63%) as a yellow oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.47 ($KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.43–4.33 (m, 2H), 4.22–4.15 (m, 1H), 2.50–2.41 (m, 1H), 2.27–2.16 (m, 1H), 0.91 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H).

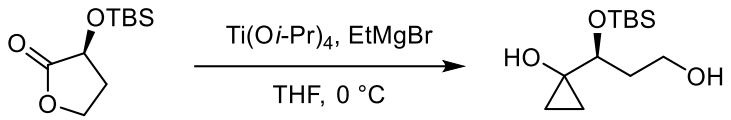
^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.1, 68.3, 64.9, 32.4, 25.8, 18.3, –4.6, –5.1.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2954, 2858, 1783, 1472, 1361, 1252, 1148, 1020, 836, 778.

HRMS (EI) calc. for $C_9H_{17}O_3Si$ $[M–CH_3]^+$: 201.0941; found: 201.0935.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +33.4° (*c* = 13.1, CH_2Cl_2).

Cyclopropanol 225



224 (90%) **225**

A solution of ethylmagnesium bromide (3 M in diethyl ether, 39.4 mL, 118 mmol, 3.00 equiv) was added to a solution of **224** (8.53 g, 39.4 mmol, 1 equiv) and freshly distilled titanium(IV) *iso*-propoxide (13.0 mL, 43.4 mmol, 1.10 equiv) in tetrahydrofuran (150 mL) over a period of 4 h at 0 °C. After complete addition, saturated aqueous ammonium chloride solution (30 mL) was added to the black solution. The resulting grey suspension was filtered through a plug of Celite®. The filtrate was concentrated and the residue was purified by flash column chromatography on silica gel (40% ethyl acetate in hexanes) to give **225** (8.70 g, 90%) as a colorless oil.

TLC (40% ethyl acetate in hexanes): R_f = 0.15 ($KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88–3.80 (m, 1H), 3.71–3.64 (m, 1H), 3.39 (t, *J* = 5.4 Hz, 1H), 3.08–3.01 (m, 2H), 2.01–1.91 (m, 1H), 1.89–1.80 (m, 1H), 0.89 (s, 9H), 0.86–0.81 (m, 1H), 0.77–0.71 (m, 1H), 0.56–0.48 (m, 2H), 0.07 (s, 3H), 0.06 (s, 3H).

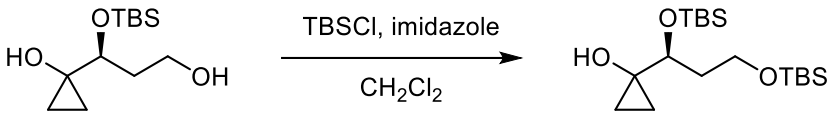
^{13}C NMR (101 MHz, $CDCl_3$): δ = 74.6, 58.6, 58.3, 37.4, 26.0, 18.2, 14.1, 10.4, –4.1, –4.7.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3348, 2955, 2930, 2858, 1472, 1253, 1097, 1013, 836, 775.

HRMS (ESI) calc. for $C_{12}H_{30}O_3NSi^+$ $[M+NH_4]^+$: 264.1989; found: 264.1990.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –4.96° (*c* = 1.61, CH_2Cl_2).

Silyl ether 226



225 **226**

tert-Butyldimethylchlorosilane (7.04 g, 46.7 mmol, 1.30 equiv) was added to a solution of **225** (8.86 g, 36.0 mmol, 1 equiv) and imidazole (6.36 g, 93.5 mmol, 2.6 equiv) in dichloromethane (300 mL). After 3 h, saturated aqueous sodium bicarbonate solution (300 mL) was added to the white suspension. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 150 mL). The combined organic extracts were dried over 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 hexanes) to give **226** (11.6 g, 89%) as a colorless oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.55 ($KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.84–3.77 (m, 1H), 3.72–3.64 (m, 1H), 3.44 (t, *J* = 6.0 Hz, 1H), 3.25 (s, 1H), 1.95–1.80 (m, 2H), 0.89 (s, 9H), 0.88 (s, 9H), 0.81–0.76 (m, 1H), 0.73–0.67 (m, 1H), 0.56–0.47 (m, 2H), 0.07 (s, 3H), 0.07–0.02 (m, 9H).

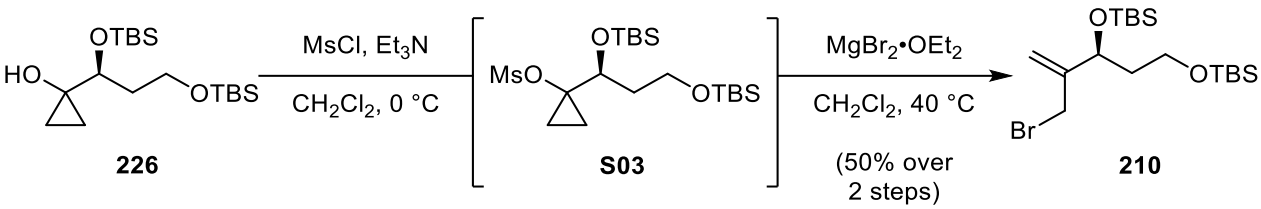
^{13}C NMR (101 MHz, $CDCl_3$): δ = 74.0, 59.5, 58.3, 38.0, 26.0, 26.0, 18.3, 18.3, 13.4, 10.4, –4.1, –4.6, –5.2, –5.2.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3424, 2955, 2930, 2858, 1472, 1464, 1255, 1095, 835, 775.

HRMS (ESI) calc. for $C_{18}H_{41}O_3Si_2^+$ $[M+H]^+$: 361,2589; found: 361.2589.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +2.52° (*c* = 1.58, CH_2Cl_2).

Allyl bromide 210



Methanesulfonyl chloride (3.42 mL, 43.3 mmol, 2.00 equiv) was added to a solution of **226** (7.80 g, 21.6 mmol, 1 equiv) and triethylamine (12.0 mL, 86.5 mmol, 4.00 equiv) in diethyl ether (120 mL) at 0 °C. After 1 h, aqueous phosphate buffer solution (pH = 7) (120 mL) was added to the white suspension. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 100 mL). The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated.

The residue was dissolved in dichloromethane (130 mL). Magnesium bromide ethyl etherate (15.6 g, 60.6 mmol, 2.80 equiv) was added and the suspension was heated to 40 °C. After 2 h, the reaction mixture was cooled to 23 °C, water (150 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (2 × 100 mL). The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (1% ethyl acetate in hexanes) to give **210** (4.53 g, 50% over 2 steps) as a colorless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.68 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.30–5.25 (m, 2H), 4.51 (dd, *J* = 7.3, 4.9 Hz, 1H), 4.05–3.96 (m, 2H), 3.73–3.60 (m, 2H), 1.83–1.70 (m, 2H), 0.90 (s, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05–0.03 (m, 6H), 0.02 (s, 3H).

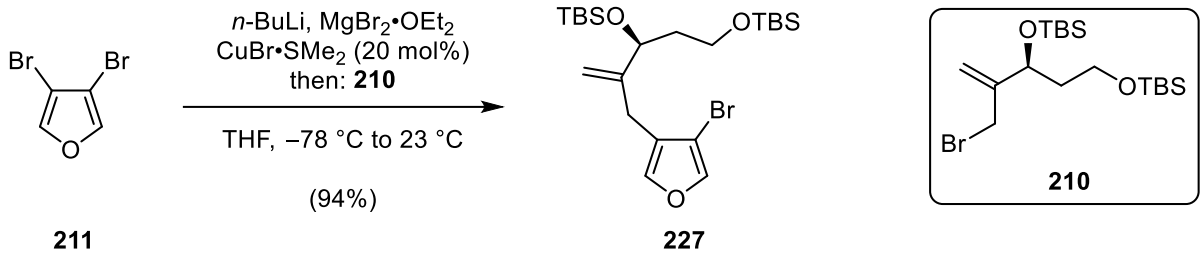
^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.0, 116.0, 70.5, 59.4, 40.3, 32.2, 26.1, 26.0, 18.4, 18.3, –4.6, –5.0, –5.1, –5.2.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2955, 2930, 2886, 2858, 1472, 1255, 1098, 920, 835, 776.

HRMS (EI) calc. for $C_{18}H_{39}{}^{81}BrO_2Si_2$ $[M]^+$: 424.1651; found: 424.1607.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +2.94° (*c* = 1.63, CH_2Cl_2).

Bromofuran 227



211 **227**

A solution of *n*-butyllithium (2.2 M in hexanes, 9.77 mL, 21.7 mmol, 3.90 equiv) was added to a solution of **211** (6.28 g, 25.0 mmol, 4.50 equiv) in tetrahydrofuran (63 mL) at –78 °C. After 30 min, the reaction mixture was allowed to warm to 0 °C and magnesium bromide ethyl etherate (6.03 g, 23.4 mmol, 4.20 equiv) and copper(I) bromide dimethyl sulfide complex (229 mg, 1.11 mmol, 0.200 equiv) were added. After 30 min, a solution of **210** (2.36 g, 5.56 mmol, 1 equiv) in tetrahydrofuran (30 mL) was added at 0 °C. After complete addition, the red solution was allowed to warm to 23 °C. After 2 h, water (150 mL) and diethyl ether (100 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 100 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution. The washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (1% diethyl ether in *n*-pentane) to give **227** (2.57 g, 94%) as a yellow oil.

TLC (2% diethyl ether in *n*-pentane): R_f = 0.30 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (s, 1H), 7.22 (s, 1H), 5.05 (s, 1H), 4.65 (s, 1H), 4.34 (t, *J* = 6.2 Hz, 1H), 3.73–3.60 (m, 2H), 3.20 (d, *J* = 17.5 Hz, 1H), 3.06 (d, *J* = 7.5 Hz, 1H), 1.80–1.72 (m, 2H), 0.90 (s, 9H), 0.90 (s, 9H), 0.05 (d, *J* = 1.8 Hz, 9H), 0.02 (s, 3H).

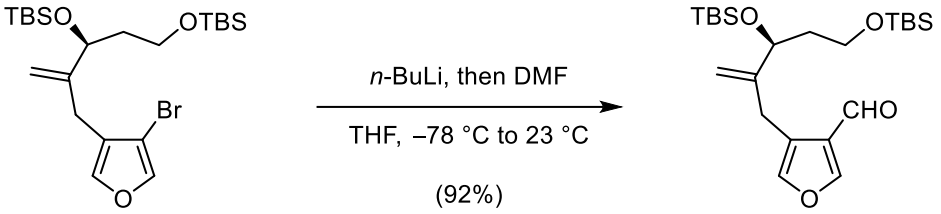
^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.9, 141.0, 140.9, 122.8, 111.3, 103.3, 72.6, 59.6, 39.9, 25.9, 25.9, 25.0, 18.3, 18.2, –4.7, –5.1, –5.3.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ =2955, 2929, 2857, 1472, 1361, 1256, 1088, 908, 835, 776.

HRMS (EI) calc. for $C_{22}H_{40}BrO_3Si_2$ $[M–H]^-$: 487.1694; found: 487.1683.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –1.8° (*c* = 0.46, CH_2Cl_2).

Aldehyde 228



227 **228**

A solution of *n*-butyllithium (2.4 M in hexanes, 1.57 mL, 3.82 mmol, 2.00 equiv) was added to a solution of **227** (936 mg, 1.91 mmol, 1 equiv) in tetrahydrofuran (12 mL) at –78 °C. After 2 h, *N*,*N*-dimethylformamide (1.48 mL, 19.1 mmol, 10.0 equiv) was added to the orange solution at –78 °C and the reaction mixture was allowed to warm to 23 °C. After 1 h, saturated aqueous ammonium chloride solution (100 mL) and diethyl ether (70 mL) was added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 70 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (200 mL). The washed solution was dried over 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 hexanes) to give **228** (770 mg, 92%) as a colorless oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.37 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.92 (d, *J* = 0.7 Hz, 1H), 8.00 (d, *J* = 1.6 Hz, 1H), 7.27 (s, 1H), 5.03 (s, 1H), 4.62 (s, 1H), 4.35 (dd, *J* = 7.3, 5.1 Hz, 1H), 3.73–3.59 (m, 2H), 3.46–3.33 (m, 2H), 1.83–1.69 (m, 2H), 0.89 (s, 9H), 0.89 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H).

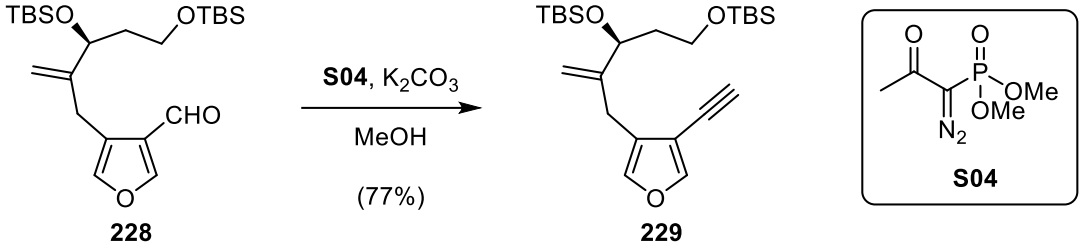
^{13}C NMR (101 MHz, $CDCl_3$): δ = 185.1, 152.5, 150.0, 143.1, 127.5, 121.7, 111.0, 72.8, 59.7, 40.0, 26.1, 26.0, 25.0, 18.4, 18.3, –4.6, –5.0, –5.2.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2954, 2929, 2885, 2857, 1694, 1255, 1089, 1048, 835, 775.

HRMS (ESI) calc. for $C_{23}H_{42}NaO_4Si_2^+$ $[M+Na]^+$: 461.2514; found: 461.2489.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –23.7° (*c* = 0.21, CH_2Cl_2).

Alkyne 229



Potassium carbonate (2.43 g, 17.5 mmol, 10.0 equiv) was added to a solution of **228** (770 mg, 1.75 mmol, 1 equiv) and **S04** (674 mg, 3.51 mmol, 2.00 equiv) in methanol (12 mL). After 6 h, water (60 mL) and diethyl ether (60 mL) were added to the bright yellow suspension. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (150 mL). The washed solution was dried over 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 hexanes) to give **229** (586 mg, 77%) as a colorless oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.64 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 1.6 Hz, 1H), 7.18 (dq, *J* = 2.5, 1.6 Hz, 1H), 5.05 (s, 1H), 4.70 (s, 1H), 4.33 (t, *J* = 6.2 Hz, 1H), 3.70–3.62 (m, 2H), 3.25 (d, *J* = 16.6 Hz, 1H), 3.13 (d, *J* = 16.6 Hz, 1H), 3.06 (s, 1H), 1.75 (q, *J* = 6.4 Hz, 2H), 0.90 (s, 9H), 0.90 (s, 9H), 0.05–0.03 (m, 9H), 0.01 (s, 3H).

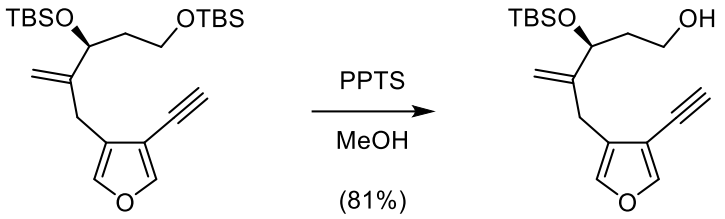
^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.5, 146.8, 140.6, 124.3, 111.3, 108.7, 81.3, 74.4, 72.8, 59.8, 40.1, 26.1, 26.0, 25.1, 18.4, 18.4, –4.5, –5.0, –5.1, –5.1.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3315, 2955, 2929, 2857, 1472, 1256, 1256, 1089, 1051, 835, 776.

HRMS (ESI) calc. for $C_{24}H_{42}NaO_3Si_2^+$ $[M+Na]^+$: 457.2565; found: 457.2541.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –42.6° (*c* = 0.25, CH_2Cl_2).

Alcohol 230



229 **230**

Pyridine *p*-toluenesulfonate (353 mg, 1.41 mmol, 1 equiv) was added to a solution of **229** (611 mg, 1.41 mmol, 1 equiv) in methanol (16 mL). After 3.5 h, saturated aqueous sodium bicarbonate solution (50 mL) and ethyl acetate (50 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (150 mL). The washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes initially, grading to 20% ethyl acetate in hexanes) to give **230** (363 mg, 81%) as a colorless oil.

TLC (30% ethyl acetate in hexanes): R_f = 0.32 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (s, 1H), 7.20 (s, 1H), 5.17 (s, 1H), 4.83 (s, 1H), 4.40 (t, *J* = 5.5 Hz, 1H), 3.84–3.75 (m, 1H), 3.74–3.66 (m, 1H), 3.22 (d, *J* = 16.8 Hz, 1H), 3.11 (d, *J* = 16.8 Hz, 1H), 3.08 (s, 1H), 2.32 (s, 1H), 1.93–1.78 (m, 2H), 0.90 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H).

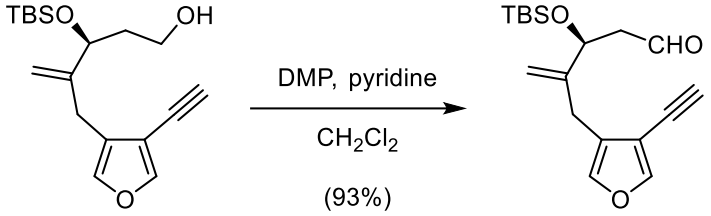
^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.6, 146.9, 140.6, 124.0, 111.9, 108.6, 81.4, 74.6, 74.3, 60.2, 37.9, 26.0, 26.0, 18.3, –4.6, –5.2.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3400, 3305, 2954, 2929, 2887, 2857, 1256, 1083, 1051, 837.

HRMS (ESI) calc. for $C_{18}H_{28}NaO_3Si^+$ $[M+Na]^+$: 343.1700; found: 343.1682.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –13.9° (*c* = 0.14, CH_2Cl_2).

Aldehyde 231



230 **231**

Dess–Martin periodinane (624 mg, 1.47 mmol, 1.30 equiv) was added to a solution of **230** (363 mg, 1.13 mmol, 1 equiv) and pyridine (357 µL, 4.42 mmol, 3.90 equiv) in dichloromethane (10 mL) at 0 °C. After 15 min, the white suspension was allowed to warm to 23°C. After 9 h, the reaction mixture was directly purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to give **231** (337 mg, 93%) as a colorless oil.

TLC (30% ethyl acetate in hexanes): R_f = 0.54 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (dd, *J* = 2.9, 2.1 Hz, 1H), 7.62 (d, *J* = 1.6 Hz, 1H), 7.21 (dt, *J* = 1.6, 0.9 Hz, 1H), 5.19 (s, 1H), 4.84 (s, 1H), 4.67 (dd, *J* = 7.4, 4.4 Hz, 1H), 3.24 (d, *J* = 16.7 Hz, 1H), 3.15 (d, *J* = 16.7 Hz, 1H), 3.08 (s, 1H), 2.67 (ddd, *J* = 15.7, 7.4, 2.9 Hz, 1H), 2.55 (ddd, *J* = 15.7, 4.4, 2.1 Hz, 1H), 0.88 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H).

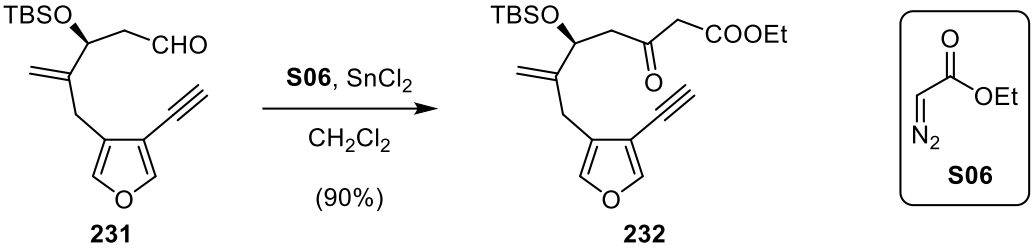
^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.9, 148.1, 147.0, 140.7, 123.8, 112.6, 108.5, 81.6, 74.3, 71.2, 50.2, 25.9, 25.8, 18.2, –4.5, –5.1.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3311, 2954, 2927, 2856, 1726, 1257, 1098,1050, 837, 778.

HRMS (ESI) calc. for $C_{18}H_{26}NaO_3Si^+$ $[M+Na]^+$: 341.1543; found: 341.1541.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –177.8° (*c* = 0.03, CH_2Cl_2).

β-Ketoester 232



231 **232**

Tin(II) chloride (100 mg, 529 µmol, 0.500 equiv) was added to a solution of **231** (337 mg, 1.06 mmol, 1 equiv) and **S06** (223 µL, 2.12 mmol, 2.00 equiv) in dichloromethane (8 mL). After 24 h, saturated aqueous ammonium chloride solution (50 mL) and dichloromethane (50 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to give **232** (387 mg, 90%) as a colorless oil.

*Note: **232** was isolated as a mixture of keto-enol tautomers. Only the signals for the keto-tautomer are reported (assigned by 2D NMR analysis).*

TLC (30% ethyl acetate in hexanes): R_f = 0.54 (UV, CAM).

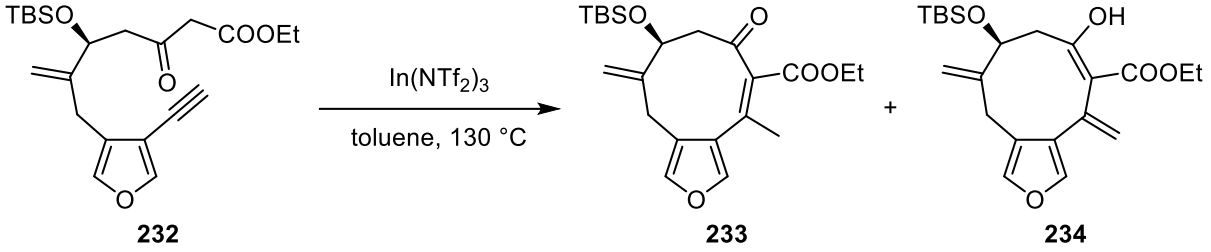
^{1}H NMR (400 MHz, $CDCl_3$): 7.61 (s, 1H), 7.20 (s, 1H), 5.15 (s, 1H), 4.78 (s, 1H), 4.66 (dd, *J* = 8.4, 3.7 Hz, 1H), 4.21–4.15 (m, 2H), 3.47 (s, 2H), 3.24–3.11 (m, 2H), 3.09 (s, 1H), 2.85 (dd, *J* = 15.1, 8.3 Hz, 1H), 2.64 (dd, *J* = 15.2, 3.7 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.4, 167.2, 148.3, 146.9, 140.7, 123.8, 112.5, 108.5, 81.6, 74.3, 72.3, 61.4, 51.1, 50.2, 25.9, 25.5, 18.2, 14.2, –4.6, –5.2.

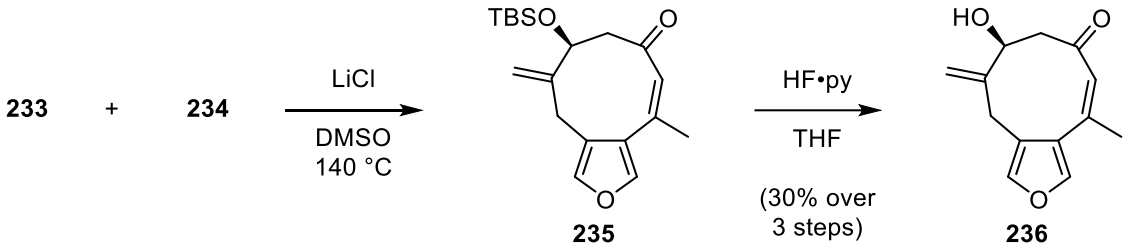
IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3293, 2929, 2857, 1745, 1718, 1251, 1078, 1049, 835, 778.

HRMS (ESI) calc. for $C_{22}H_{32}NaO_5Si^+$ $[M+Na]^+$: 427.1911; found: 427.1896.

Nine-membered carbocycle 233 and 234



A Schlenk flask was charged with a solution of indium(III) tris(trifluoromethanesulfonimide) (0.0140 M in acetonitrile, 97.1 µL, 1.36 µmol, 0.0100 equiv). The solvent was removed under vacuum (0.1 mbar) at 60 °C. After 1 h, a solution of **232** (55.0 mg, 136 µmol, 1 equiv) in toluene (5 mL) was added at 23 °C and the reaction mixture was heated to 130 °C. After 3 h, the reaction mixture was allowed to cool to 23 °C, diethyl ether (20 mL) was added and the yellow solution was filtered through a plug of silica. The filtrate was concentrated to yield a mixture of **233** and **234** that was directly used in the following step without further purification.



Lithium chloride (28.8 mg, 680 µmol, 5.00 equiv) was added to a solution of the crude mixture of **233** and **234** in dimethyl sulfoxide (1 mL) and the suspension was heated to 145 °C. After 2.5 h, the reaction mixture was allowed to cool to 23 °C, aqueous lithium chloride (10wt%, 50 mL) and diethyl ether (50 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution. The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was dissolved in tetrahydrofuran (0.8 mL) and pyridine hydrofluoride (pyridine ~30%, hydrogen fluoride ~70%; 0.2 mL) was added at 0 °C. After 1 h the reaction mixture was allowed to warm to 23 °C. After 2 h, saturated aqueous sodium bicarbonate solution (20 mL) was added followed by the addition of solid sodium bicarbonate until the gas evolution deceased. The biphasic mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with saturated sodium chloride solution. The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to give **236** (9 mg, 30% over 3 steps) as a colorless oil.

TLC (30% ethyl acetate in hexanes): R_f = 0.09 (UV, $KMnO_4$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.45 (s, 1H), 7.34 (s, 1H), 6.04 (d, *J* = 1.4 Hz, 1H), 5.09–5.05 (m, 1H), 5.05–5.02 (m, 1H), 4.52–4.46 (m, 1H), 3.44 (d, *J* = 16.0 Hz, 1H), 3.29 (d, *J* = 16.0 Hz, 1H), 2.92–2.88 (m, 1H), 2.71 (dd, *J* = 12.6, 7.1 Hz, 1H), 2.57 (d, *J* = 7.1 Hz, 1H), 2.20 (d, *J* = 1.4 Hz, 3H).

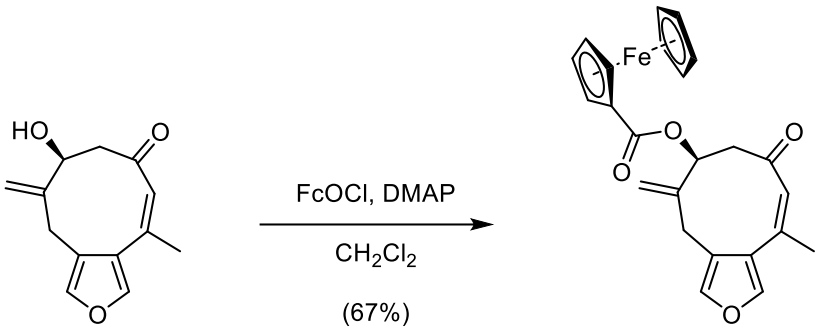
^{13}C NMR (151 MHz, $CDCl_3$): δ = 200.8, 147.1, 144.7, 141.7, 141.4, 131.2, 125.9, 122.4, 114.1, 72.5, 45.6, 29.3, 28.9.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3406, 2927, 1635, 1527, 1438, 1377, 1143, 1056, 1021, 876.

HRMS (ESI) calc. for $C_{13}H_{14}NaO_3^+$ $[M+Na]^+$: 241.0835; found: 241.0828.

$[\boldsymbol{a}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –40.4° (*c* = 0.17, CH_2Cl_2).

Ferrocene carboxylic ester 237

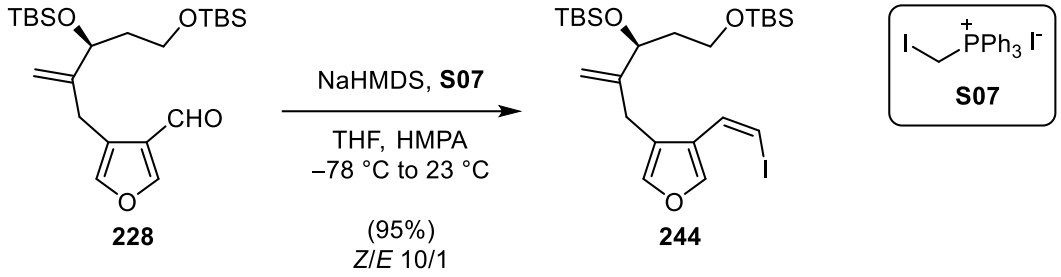


236 **237**

To a suspension of ferrocene carboxylic acid (15.6 mg, 67.8 µmol, 2.00 equiv) in dichloromethane (1.0 mL) was added oxalyl chloride solution (2 M in dichloromethane, 37.3 µL, 74.6 µmol, 2.20 equiv), followed by 1 drop of *N*,*N*-dimethylformamide at 23 °C. After 45 min, toluene (1 mL) was added and the mixture was concentrated. To a solution of **236** (7.40 mg, 33.9 µmol, 1 equiv) and 4-dimethylaminopyridine (41.4 mg, 339 µmol, 10.0 equiv) in dichloromethane (0.5 mL) was added a solution of the freshly prepared ferrocenecarboxylic acid chloride in dichloromethane (0.5 mL) at 23 °C. After 2 h, the reaction mixture was directly purified by flash-column chromatography on silica gel (dichloromethane) to yield **237** (9.70 mg, 67%) as an orange foam. Crystallization from ethyl acetate gave crystals suitable for X-ray diffraction.

3.3.3 Second Generation: NHK reaction at the eastern half

Vinyl iodide 244



A solution of sodium hexamethyldisilazide (1 M in tetrahydrofuran, 1.51 mL, 1.51 mmol, 1.30 equiv) was added to a suspension of **S07** (810 mg, 1.51 mmol, 1.30 equiv) in tetrahydrofuran (4 mL) at 0 °C. After 30 min, the yellow suspension was cooled to –78 °C and hexamethylphosphoric triamide (310 µL, 1.75 mmol, 1.50 equiv) was added. After 5 min, a solution of **228** (516 mg, 1.16 mmol, 1 equiv) in tetrahydrofuran (1 mL) was added. After 10 min, the reaction mixture was allowed to warm to 23 °C. After 1.5 h, water (20 mL) and diethyl ether (20 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (60 mL). The washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (1% ethyl acetate in cyclohexane) to give **244** (625 mg, 95%, *Z*/*E* 10/1) as a colorless oil.

TLC (10% ethyl acetate in cyclohexane): R_f = 0.64 (UV, CAM).

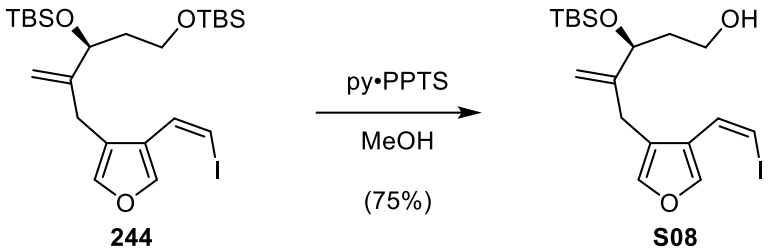
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (s, 1H), 7.24 (s, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 8.4 Hz, 1H), 5.03 (s, 1H), 4.62 (s, 1H), 4.35–4.30 (m, 1H), 3.71–3.58 (m, 2H), 3.24 (d, *J* = 17.1 Hz, 1H), 3.07 (d, *J* = 17.1 Hz, 1H), 1.78–1.70 (m, 2H), 0.91 (s, 9H), 0.90 (s, 9H), 0.06–0.05 (m, 6H), 0.05 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.6, 141.1, 140.6, 129.7, 122.5, 121.8, 111.7, 79.4, 72.8, 59.7, 40.0, 26.1, 26.0, 24.7, 18.4, 18.3, –4.5, –4.9, –5.1.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2953, 2928, 2886, 2856, 1471, 1314, 1143, 1090, 835, 775.

HRMS (ESI) mass not found

Alcohol S08



244 **S08**

Pyridine p-toluenesulfonate (28.2 mg, 111 µmol, 0.100 equiv) was added to a solution of **244** (625 mg, 1.11 mmol, 1 equiv) in methanol (12 mL). After 24 h, pyridine p-toluenesulfonate (28.2 mg, 111 µmol, 0.100 equiv) was added. After 3 h, saturated aqueous sodium bicarbonate solution (50 mL) and ethyl acetate (50 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (150 mL). The washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) to give **S08** (373 mg, 75%) as a colorless oil.

TLC (20% ethyl acetate in cyclohexane): R_f = 0.23 (UV, CAM).

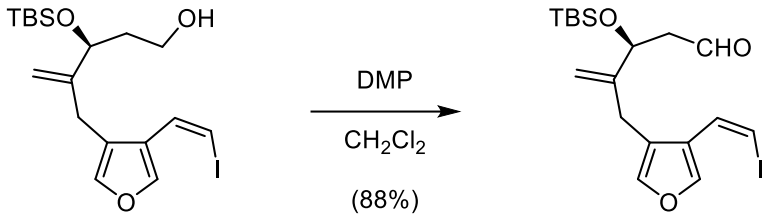
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (s, 1H), 7.24 (s, 1H), 7.03 (dd, *J* = 8.6, 0.8 Hz, 1H), 6.48 (d, *J* = 8.6 Hz, 1H), 5.14 (s, 1H), 4.73 (s, 1H), 4.39–4.33 (m, 1H), 3.78–3.68 (m, 2H), 3.19 (d, *J* = 17.1 Hz, 1H), 3.06 (d, *J* = 17.1 Hz, 1H), 2.22 (s, 1H), 1.85–1.79 (m, 2H), 0.90 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.9, 141.2, 140.5, 129.5, 122.4, 121.4, 112.3, 79.8, 74.4, 60.1, 38.1, 25.9, 25.7, 18.2, –4.6, –5.1.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3371, 2953, 2928, 2856, 1432, 1252, 1055, 836, 796, 776.

HRMS (ESI) calc. for $C_{18}H_{29}NaO_3Si^+$ $[M+Na]^+$: 471.0823; found: 471.0800.

Aldehyde 243



S08 **243**

Dess–Martin periodinane (388 mg, 915 µmol, 1.10 equiv) was added to a solution of **S08** (373 mg, 832 µmol, 1 equiv) in dichloromethane (12 mL). After 1 h, cyclohexane (5 mL) was added and the mixture was directly purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane) to give **243** (326 mg, 88%) as a colorless oil.

TLC (20% ethyl acetate in cyclohexane): R_f = 0.49 (UV, CAM).

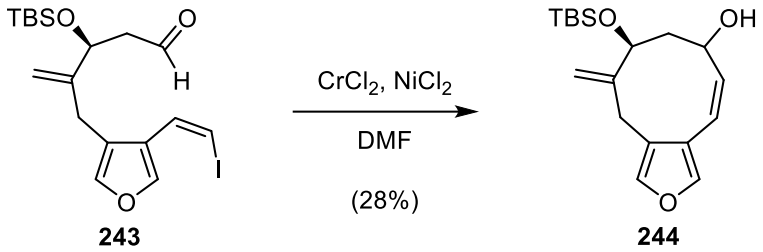
^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.76–9.73 (m, 1H), 8.40 (s, 1H), 7.25 (s, 1H), 7.01 (d, *J* = 8.6 Hz, 1H), 6.49 (d, *J* = 8.6 Hz, 1H), 5.17 (s, 1H), 4.75 (s, 1H), 4.66–4.63 (m, 1H), 3.21 (d, *J* = 17.3 Hz, 1H), 3.08 (d, *J* = 17.3 Hz, 1H), 2.69–2.64 (m, 1H), 2.55–2.51 (m, 1H), 0.88 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 201.6, 148.1, 141.3, 140.6, 129.3, 122.3, 121.1, 113.0, 80.1, 71.2, 50.2, 25.8, 25.4, 18.2, –4.5, –5.0.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2954, 2929, 2887, 2857, 1726, 1255, 1096, 1056, 837, 777.

HRMS (ESI) calc. for $C_{18}H_{27}INaO_3Si^+$ $[M+Na]^+$: 469.0666; found: 469.0643.

Nine-membered carbocycle 244



243 **244**

Note: N,N-Dimethylformamide was degassed via freeze-pump-thaw (three cycles) prior to use.

Chromium(II) chloride (51.6 mg, 420 µmol, 7.50 equiv) and nickel(II) chloride (444 µg, 3.36 µmol, 0.0600 equiv) were placed in a flamedried 50 mL Schlenk flask. The flask was evacuated and backfilled with nitrogen three times. The solids were suspended in *N*,*N*-dimethylformamide (11 mL) followed by the addition of a solution of **243** (25.0 mg, 56.0 µmol, 1 equiv) in *N*,*N*-dimethylformamide (0.5 mL). After 24 h, water (100 mL) and diethyl ether (100 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 80 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (150 mL). The washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane) to give **244** (5.10 mg, 28%) as a yellow oil.

TLC (30% ethyl acetate in cyclohexane): R_f = 0.41 (UV, $KMnO_4$).

^{1}H NMR (600 MHz, $CDCl_3$): 7.29 (s, 1H), 7.17 (s, 1H), 6.16 (d, *J* = 11.0 Hz, 1H), 5.75 (dd, *J* = 11.0, 8.5 Hz, 1H), 5.09 (s, 1H), 5.04 (s, 1H), 4.46 (t, *J* = 5.6 Hz, 1H), 4.33–4.27 (m, 1H), 3.33 (d, *J* = 14.9 Hz, 1H), 3.06 (d, *J* = 14.9 Hz, 1H), 2.11 (ddd, *J* = 13.6, 5.6, 3.7 Hz, 1H), 2.01 (ddd, *J* = 13.6, 9.5, 5.6 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H).

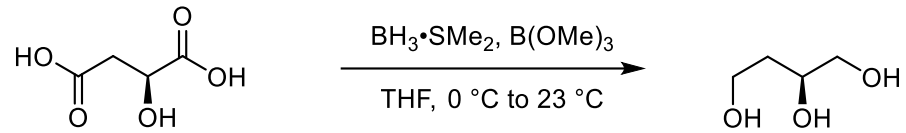
^{13}C NMR (151MHz, $CDCl_3$): 150.0, 140.1, 140.0, 139.6, 124.6, 121.9, 118.2, 114.2, 72.9, 67.3, 46.1, 25.9, 25.8, 18.3, –4.8, –4.9.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 33763, 2943, 2921, 2874, 1403, 1289, 1100, 821, 799, 741.

HRMS (EI) calc. for $C_{18}H_{28}NaO_3Si$ $[M+Na]^+$: 343.1700; found: 343.1717.

3.3.4 Third Generation: NHK reaction at the western half

Triol 255

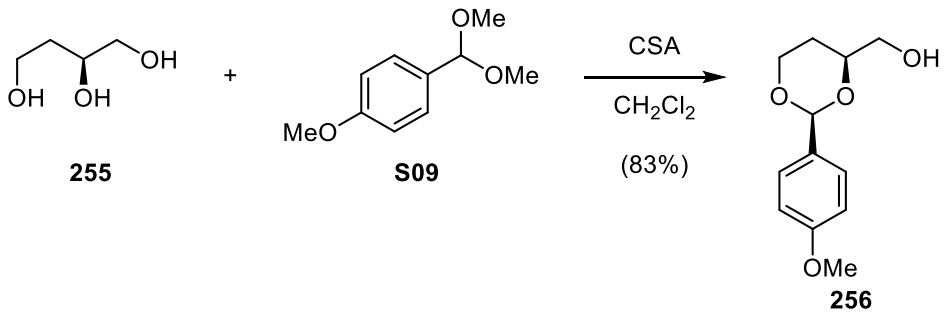


L-(–)-malic acid (**213**) (99%) **255**

*Triol **255** was prepared according to the procedure described by E. R. Jarvo.*[115]

L-(–)-malic acid (**213**) (4.32 g, 31.3 mmol, 1 equiv) was added to a solution of borane dimethyl sulfide (8.89 mL, 100 mmol, 3.20 equiv) and boric acid trimethyl ester (10.8 mL, 93.8 mmol, 3.00 equiv) in tetrahydrofuran (100 mL) at 0 °C. After complete addition, the reaction mixture was allowed to warm to 23°C. After 24 h, methanol (30 mL) was added dropwise over a period of 1 h. The reaction mixture was concentrated to provide **255** (3.32 g, 99%) as a colorless oil. The obtained analytical data for **255** were in full agreement with those values previously reported.

Acetal 256

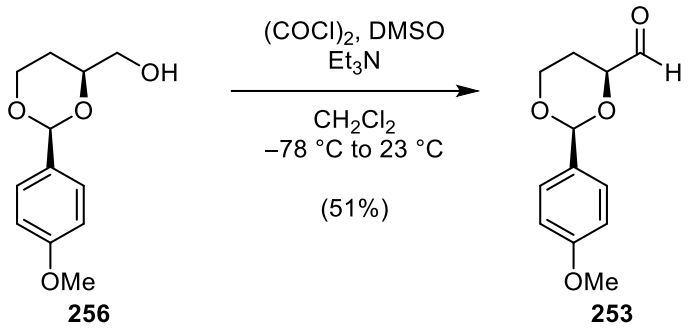


255 **S09** **256**

Camphor sulfonic acid (377 mg, 1.59 mmol, 0.0500 equiv) and *p*-anisaldehyde dimethyl acetal (**S09**) (7.21 mL, 41.4 mmol, 1.30 equiv) were added to a solution of **255** (3.38 g, 31.9 mmol) in dichloromethane (160 mL). After 12 h, imidazole (219 mg, 3.19 mmol, 0.100 equiv) was added and the reaction mixture was concentrated. The residue was purified by flash column chromatography on silica gel (35% ethyl acetate in cyclohexane) to give **256** (5.15 g, 83%) as a colorless oil. The obtained analytical data for **256** were in full agreement with those values previously reported.[116]

[115] L. W. Erickson, E. L. Lucas, E. J. Tollefson, E. R. Jarvo, *J. Am. Chem. Soc.* **2016**, *138*, 14006–14011.
[116] W. R. Judd, S. Ban, J. Aubé, *J. Am. Chem. Soc.* **2006**, *128*, 13736–13741.

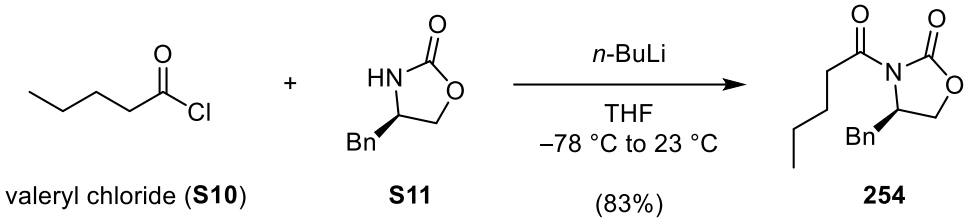
Aldehyde 253



Dimethyl sulfoxide (7.28 mL, 103 mmol, 2.30 equiv) was added to a solution of oxalyl chloride (4.76 mL, 49.1 mmol, 1.10 equiv) in dichloromethane (160 mL) at –78 °C over a period of 5 min. After 15 min, a solution of **256** (10.0 g, 44.6 mmol, 1 equiv) in dichloromethane (60 mL) was added over a period of 10 min. After 1 h, trimethylamine (24.8 mL, 178 mmol, 4.00 equiv) was added to the turbid solution and the mixture was allowed to warm to 23 °C. After 30 min, water (200 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (2 × 100 mL). The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane initially, grading to 50% ethyl acetate in cyclohexane) to give **253** (5.00 g, 51%) as a colorless oil. The obtained analytical data for **253** were in full agreement with those values previously reported.[117]

*Note: **253** was used immediately in the following reaction, due to its tendency to polymerize.*

Oxazolidinone 254



valeryl chloride (**S10**) **S11** **254**

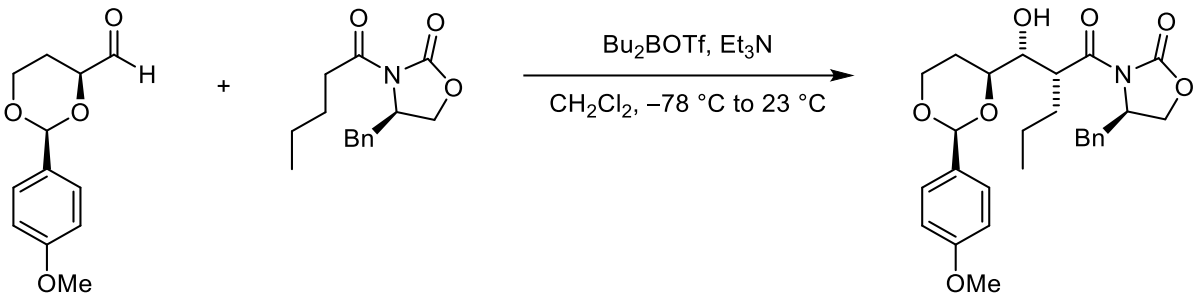
A solution of *n*-butyllithium (2.4 M in hexanes, 16.6 mL, 39.9 mmol, 1.10 equiv) was added to a solution of **S11** (6.42 g, 36.2 mmol, 1 equiv) in tetrahydrofuran (100 mL) at –78 °C. After 1 h, valeryl chloride (**S10**) (4.95 mL, 39.9 mmol, 1.10 equiv) was added to the orange reaction mixture. After 30 min, the reaction mixture was allowed to warm to warm to 23 °C. After 2 h, water (300 mL) and ethyl acetate (100 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 150 mL). The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane initially, grading to 50% ethyl acetate in cyclohexane)

[117] R. W. Hoffmann, G. Mas, T. Brandl, *Eur. J. Org. Chem.* **2002**, 3455–3464.

to give **254** (7.84 g, 83%) as a colorless solid. The obtained analytical data for **254** were in full agreement with those values previously reported.[118]

[118] G. B Gennäs, V. Talman, O. Aitio, E. Ekokoski, M. Finel, R. K. Tuominen, J. Yli-Kauhaluoma, *J. Med. Chem.* **2009**, *52*, 3969–3981.

Alcohol 257



253 **254** **257**

A solution of bibutylboron triflate (1 M in dichloromethane, 19.2 mL, 19.2 mmol, 1.10 equiv) was added via syringe pump over a period of 10 min to a solution of **254** (4.56 g, 17.5 mmol, 1 equiv) in dichloromethane (60 mL) at –78 °C. After 10 min, triethylamine (3.27 mL, 23.6 mmol, 1.35 equiv) was added via syringe pump over a period of 10 min. After 15 min, the yellow solution was allowed to warm to 0 °C. After 1 h, the reaction mixture was cooled to –78 °C and a solution of **253** (5.04 g, 22.7 mmol, 1.30 equiv) in dichloromethane (15 mL) was added via syringe pump over a period of 10 min. After addition, the reaction mixture was allowed to gradually warm to 23 °C. After 12 h, the reaction mixture was cooled to 0 °C and a mixture of methanol (10 mL) and aqueous phosphate buffer solution (pH = 7) (20 mL) followed by a mixture of methanol (10 mL) and hydrogen peroxide solution (30wt% in water) were added sequentially. After 1 h, water (200 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (2 × 200 mL). The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was filtered through a plug of silica and the obtained residue was used without further purification. An analytically pure sample of **257** was obtained by normal-phase semi-preparative HPLC purification using 10% *iso*-propanol in *n*-heptane initially, grading to 20% *iso*-propanol over in *n*-heptane over 30 min as eluent (flow rate: 15 mL/min; column: Microsorb 60-8 Si Dynamax 250 × 21.4mm (R00083121C); detection: 254 nm; retention time: 10.7 min). Recrystallization from ethyl acetate gave crystals suitable for single-crystal X-ray diffraction.

TLC (30% ethyl acetate in cyclohexane): R_f = 0.14 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.36 (m, 2H), 7.33–7.25 (m, 3H), 7.15–7.11 (m, 2H), 6.86–6.81 (m, 2H), 5.38 (s, 1H), 4.29–4.22 (m, 2H), 4.22–4.16 (m, 1H), 3.96–3.89 (m, 2H), 3.86–3.80 (m, 1H), 3.76 (dd, *J* = 8.9, 3.8 Hz, 1H), 3.70 (s, 3H), 3.34 (dd, *J* = 13.3, 3.5 Hz, 1H), 3.17 (t, *J* = 8.6 Hz, 1H), 2.48 (dd, *J* = 13.3, 10.4 Hz, 1H), 2.24 (d, *J* = 5.1 Hz, 1H), 1.93–1.82 (m, 3H), 1.82–1.71 (m, 1H), 1.41–1.33 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.8, 160.3, 153.7, 135.7, 131.2, 129.3, 129.0, 127.9, 127.3, 113.7, 101.5, 79.4, 75.2, 67.1, 65.7, 55.4, 55.3, 45.3, 38.4, 31.8, 28.8, 20.1, 14.5.

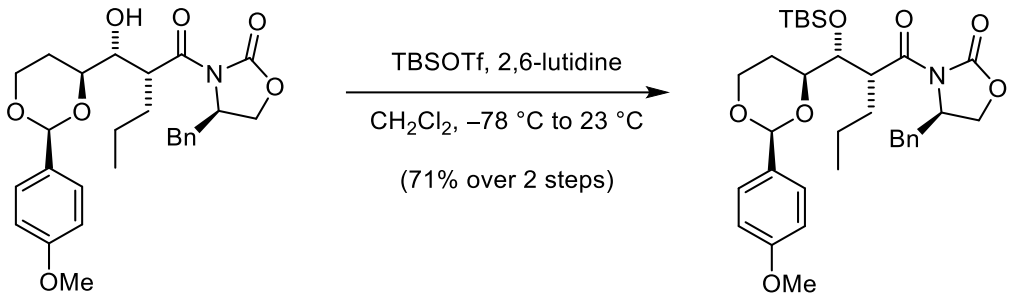
IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3469, 2960, 2929, 2870, 1775, 1696, 1385, 1250, 1211, 1101.

HRMS (ESI) calc. for $C_{27}H_{33}NNaO_7^+$ $[M+Na]^+$: 506.2149; found: 506.2108.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –15.3° (*c* = 0.67, CH_2Cl_2).

Melting point: 123 °C.

Silyl ether 258



257 **258**

Tert-butyldimethylsilyl trifluoromethanesulfonate (5.33 mL, 22.8 mmol, 1.30 equiv) was added to a solution of **257** (8.46 g, 17.5 mmol, 1 equiv) and 2,6-lutidine (10.4 mL, 87.5 mmol, 5.00 equiv) in dichloromethane (250 mL) at –78 °C. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 2.5 h, water (250 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (2 × 200 mL). The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) to give **258** (7.40 g, 71% over two steps) as a colorless solid. Recrystallization from ethyl acetate gave crystals suitable for single-crystal X-ray diffraction.

TLC (10% ethyl acetate in cyclohexane): R_f = 0.31 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.18 (m, 2H), 7.16–7.10 (m, 2H), 7.10–7.04 (m, 1H), 6.97–6.92 (m, 2H), 6.67–6.62 (m, 2H), 5.16 (s, 1H), 4.09–4.01 (m, 2H), 3.95–3.87 (m, 1H), 3.83 (dd, *J* = 8.9, 7.4 Hz, 1H), 3.75–3.61 (m, 2H), 3.50 (s, 3H), 3.48 (dd, *J* = 8.9, 4.0 Hz, 1H), 3.19 (dd, *J* = 13.2, 3.4 Hz, 1H), 2.71 (t, *J* = 8.5 Hz, 1H), 2.22 (dd, *J* = 13.2, 10.7 Hz, 1H), 1.73–1.58 (m, 2H), 1.57–1.51 (m, 1H), 1.51–1.41 (m, 1H), 1.20–1.08 (m, 2H), 0.79–0.72 (m, 12H), 0.00 (s, 3H), -0.03 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.8, 160.3, 153.6, 135.8, 131.3, 129.2, 128.9, 128.1, 127.2, 113.5, 101.8, 81.5, 76.1, 67.2, 65.4, 55.3, 55.3, 47.2, 38.4, 33.7, 29.0, 26.2, 20.1, 18.4, 14.4, –3.2, –3.4.

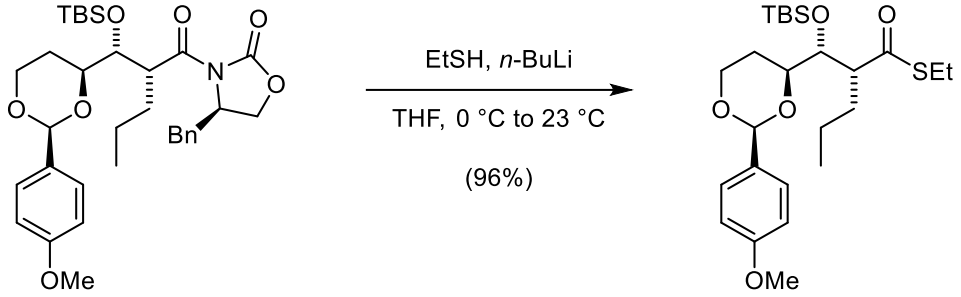
IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2957, 2928, 2853, 1777, 1695, 1431, 1384, 1250, 1104, 861.

HRMS (ESI) calc. for $C_{33}H_{47}NNaO_7Si^+$ $[M+Na]^+$: 620.3014; found: 620.2965.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –34.4° (*c* = 0.16, CH_2Cl_2).

Melting point: 141 °C.

Thioester 259



258 **259**

A solution of *n*-butyllithium (2.4 M, in hexanes, 2.20 mL, 5.29 mmol, 2.00 equiv) was added to a solution of ethanethiol (593 µL, 7.93 mmol, 3.00 equiv) in tetrahydrofuran (15 mL) at 0 °C. After 30 min, the white suspension was cooled to –78 °C and a solution of **258** (1.58 g, 2.64 mmol, 1 equiv) in tetrahydrofuran (15 mL) was added. After addition, the reaction mixture was allowed to gradually warm to 23 °C. After 1 h, saturated aqueous ammonium chloride solution (100 mL) and diethyl ether (80 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 80 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (200 mL). The washed solution was dried over 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 cyclohexane) to give **259** (1.23 g, 96%) as a colorless oil.

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

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.37 (m, 2H), 6.89–6.84 (m, 2H), 5.42 (s, 1H), 4.29 (ddd, *J* = 11.4, 5.1, 1.4 Hz, 1H), 4.01 (dd, *J* = 7.0, 3.8 Hz, 1H), 3.95–3.87 (m, 1H), 3.85–3.80 (m, 1H), 3.79 (s, 3H), 2.94–2.83 (m, 2H), 2.82–2.74 (m, 1H), 2.08–1.96 (m, 1H), 1.76–1.68 (m, 2H), 1.59–1.53 (m, 1H), 1.45–1.35 (m, 1H), 1.26 (t, *J* = 7.4 Hz, 4H), 0.94–0.88 (m, 12H), 0.08 (s, 3H), 0.06 (s, 3H).

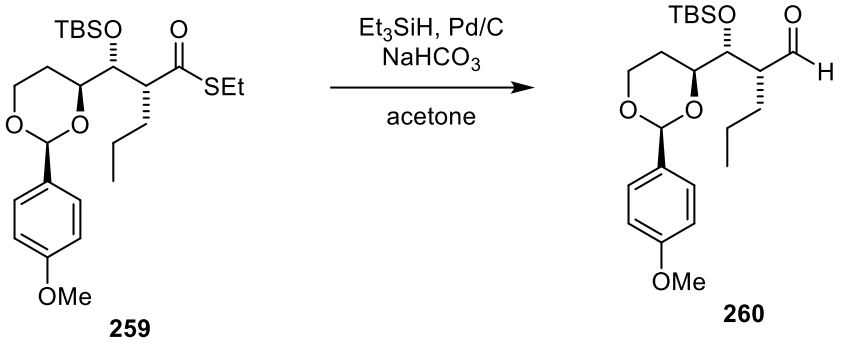
^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.6, 159.8, 131.2, 127.5, 113.4, 101.4, 78.7, 75.8, 67.0, 57.5, 55.3, 31.4, 26.2, 25.6, 23.4, 20.7, 18.5, 14.8, 14.2, –3.6, –4.5.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2953, 2930, 2858, 1775, 1600, 1510, 1253, 1160, 1053, 836.

HRMS (ESI) *mass not found*.

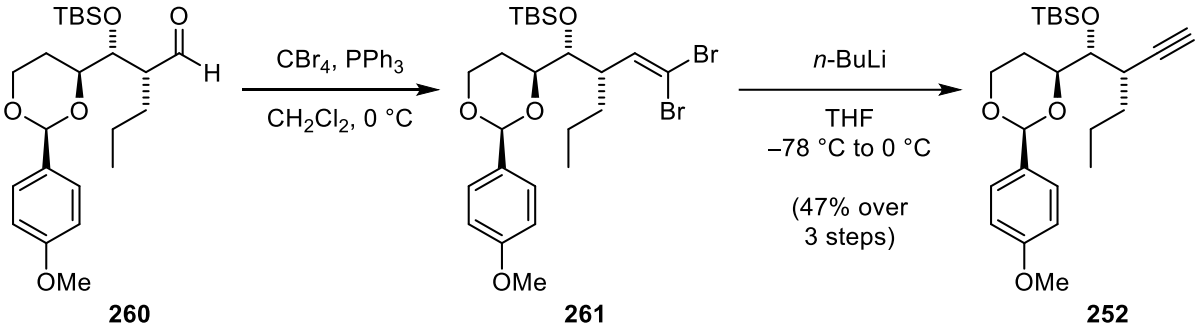
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +16.7° (*c* = 1.03, CH_2Cl_2).

Alkyne 252



259 **260**

Sodium hydrogen carbonate (2.14 g, 25.5 mmol, 10.0 equiv) was added to a suspension of palladium on carbon (10 wt.%, 271 mg, 255 µmol, 0.100 equiv). After 1 h, a solution of **259** (1.23 g, 2.55 mmol, 1 equiv) was added followed by the addition of triethylsilane (831 µL, 5.10 mmol, 2.00 equiv). After 2 h, the reaction mixture was filtered through a plug of silica and the obtained residue was used without further purification.



260 **261** **252**

Triphenylphosphine (2.03 g, 7.65 mmol, 3.00 equiv) was added to a solution of carbon tetrabromide (1.28 g, 3.82 mmol, 1.50 equiv) in dichloromethane (20 mL) at 0°C. After 30 min the dark orange solution was cooled to –78 °C and a solution of crude **260** (1.08 g, 2.55 mmol, 1 equiv) in dichloromethane (20 mL) was added. After 15 min, the reaction mixture was allowed to warm to 0 °C. After 3 h, saturated, aqueous sodium chloride solution (100 mL) and diethyl ether (100 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 90 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (200 mL). The washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was filtered through a plug of silica and the obtained residue was used without further purification.

A solution of *n*-butyllithium (2.4 M, in hexanes, 2.13 mL, 5.10 mmol, 2.00 equiv) was added to a solution of crude **261** (1.47 g, 2.55 mmol, 1 equiv) in tetrahydrofuran (14 mL) at –78 °C. After 3 h, the yellow solution was allowed to warm to 0 °C. After 1 h, water (90 mL) diethyl ether (100 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 100 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (200 mL). The washed solution was dried over 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 cyclohexane) to give **252** (497 mg, 47% over 3 steps) as a colorless oil.

TLC (20% ethyl acetate in cyclohexane): R_f = 0.50 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.39 (m, 2H), 6.91–6.84 (m, 2H), 5.49 (s, 1H), 4.35–4.27 (m, 1H), 4.23–4.16 (m, 1H), 4.02–3.94 (m, 1H), 3.82–3.79 (m, 4H), 2.58–2.51 (m, 1H), 2.12 (d, *J* = 2.5 Hz, 1H), 2.08–1.97 (m, 1H), 1.71–1.36 (m, 5H), 0.96–0.90 (m, 12H), 0.11 (s, 3H), 0.09 (s, 3H).

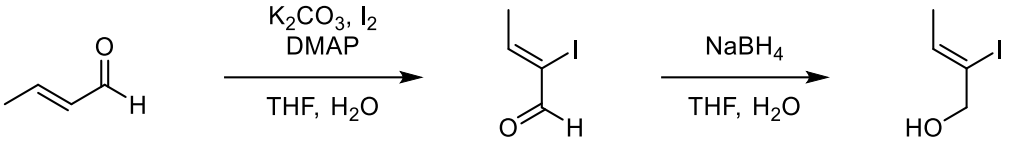
^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.9, 131.4, 127.5, 113.5, 101.4, 85.5, 78.7, 76.4, 71.4, 67.1, 55.4, 35.4, 32.8, 26.2, 25.6, 20.4, 18.5, 14.0, –3.5, –4.4.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3308, 2957, 2929, 2856, 1518, 1248, 1129, 1107, 831, 779.

HRMS (ESI) calc. for $C_{24}H_{38}NaO_4Si^+$ $[M+Na]^+$: 441.2432; found: 441.2417.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +13.6° (*c* = 1.11, CH_2Cl_2).

Allylic alcohol 264



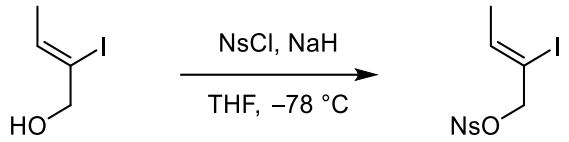
262 **263** (43% over 2 steps) **264**

264 was prepared according to a procedure described by J. M. Cook[119]:

Potassium carbonate (11.8 g, 85.6 mmol, 1.20 equiv), iodine (36.6 g, 143 mmol, 2.00 equiv) and *N*,*N*-dimethylpyridin-4-amine (1.76 g, 14.3 mmol, 0.200 equiv) were added to a solution of crotonaldehyde (**262**) (5.91 mL, 71.3 mmol, 1 equiv) in a mixture of tetrahydrofuran (175 mL) and water (175 mL). After 5 h, ethyl acetate (200 mL) and saturated aqueous sodium thiosulfate solution were added. The layers were separated and the organic phase was washed with saturated aqueous sodium thiosulfate solution (2 × 100 mL). The washed solution was concentrated, the residue was dissolved in a mixture of tetrahydrofuran (150 mL) and water (15 mL) followed by the slow addition of sodium borohydride (1.38 g, 35.7 mmol, 0.500 equiv). After 1 h, water (200 mL) and ethyl acetate (100 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (300 mL). The washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) to give **264** (6.07 mg, 43% over 2 steps) as a colorless oil. The obtained analytical data for **264** was in full agreement with those values previously reported.

[119] W. Yin, M. S. Kabir, Z. Wang, S. K. Rallapalli, J. Ma, J. M. Cook, *J. Org. Chem.* **2010**, *75*, 3339–3349.

Nosylate 265



264 (43%) **265**

Sodium hydride (60% mineral oil dispersion, 302 mg, 7.55 mmol, 2.50 equiv) was added to a solution of **264** in tetrahydrofuran (24 mL) at –78 °C. After 1 h, 4-nitrobenzenesulfonyl chloride (837 mg, 3.78 mmol, 1.25 equiv) was added. After 1 h, water (100 mL) and diethyl ether (80 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 70 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane) to give **265** (500 mg, 43%) as an off-white solid.

TLC (30% ethyl acetate in cyclohexane): R_f = 0.46 (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44–8.36 (m, 2H), 8.15–8.08 (m, 2H), 6.12 (qt, *J* = 6.4, 1.0 Hz, 1H), 4.87 (p, *J* = 1.0 Hz, 2H), 1.74 (dt, *J* = 6.5, 1.0 Hz, 3H).

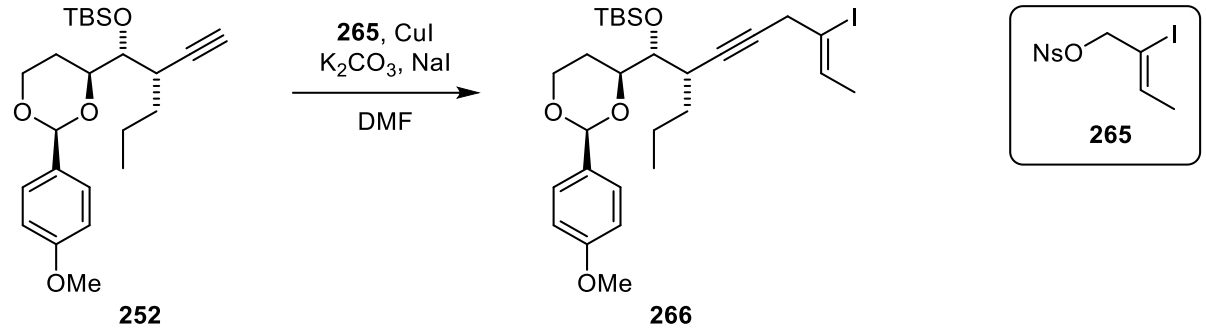
^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.8, 142.3, 139.2, 129.5, 124.4, 97.2, 78.8, 21.7.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3106, 2956, 1531, 1404, 1371, 1350, 1185, 1094, 924, 836.

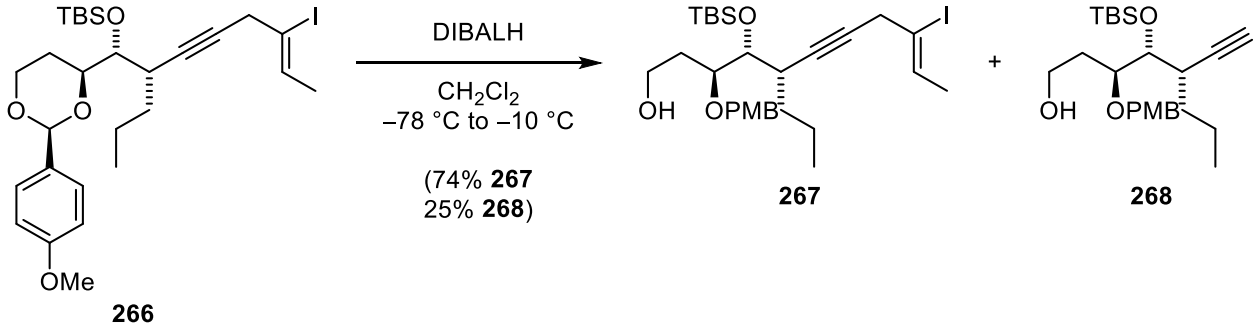
HRMS (ESI) *mass not found*.

Melting point: 75 °C decomposition.

Alcohol 267



Copper(I) iodide (150 mg, 786 µmol, 1 equiv), potassium carbonate (304 mg, 2.20 mmol, 2.80 equiv) and sodium iodide (131 mg, 865 µmol, 1.10 equiv) were added to a solution of **252** (395 mg, 944 µmol, 1.20 equiv) in *N*,*N*-dimethylformamide (5 mL). After 20 min, **265** (301 mg, 786 µmol, 1 equiv) was added. After 12 h, saturated ammonium chloride solution (50 mL) and diethyl ether (50 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) to give an inseparable mixture of **266** and unreacted **252**. The mixture was used in the following reaction without further purification.



A solution of diisobutylaluminum hydride (1 M in toluene, 5.90 mL, 5.90 mmol, 7.50 equiv) was added to the foregoing mixture of **266** and **252** in dichloromethane (8 mL) at –78 °C. The reaction mixture was allowed to warm to –10 °C over a period of 5 h. The reaction mixture was diluted with diethyl ether (100 mL) and water (240 µL), aqueous sodium hydroxide solution (15 wt.%, 240 µL) and water (590 µL) were added sequentially at 0 °C. After 15 min, magnesium sulfate was added. After 15 min, the suspension was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) to give **267** (347 mg, 74% over 2 steps) and **268** (82.0 mg, 25% over 2 steps) as colorless oils.

For 267:

TLC (20% ethyl acetate in cyclohexane): R_f = 0.33 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.23 (m, 2H), 6.87–6.84 (m, 2H), 5.85 (qt, *J* = 6.4, 1.6 Hz, 1H), 4.58 (d, *J* = 11.3 Hz, 1H), 4.39 (d, *J* = 11.3 Hz, 1H), 4.05 (ddt, *J* = 9.1, 3.9, 2.0 Hz, 1H), 3.83 (dt, *J* = 9.1, 2.5 Hz, 1H), 3.79 (s, 3H), 3.70–3.64 (m, 2H), 3.43–3.39 (m, 2H), 2.52 (s, 1H), 2.38–2.31 (m, 1H),

1.95–1.85 (m, 1H), 1.76–1.64 (m, 5H), 1.63–1.52 (m, 1H), 1.41–1.29 (m, 2H), 1.27 (dd, *J* = 6.4, 5.5 Hz, 1H), 0.94–0.88 (m, 12H), 0.09 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.4, 131.1, 130.2, 129.9, 113.9, 102.6, 84.3, 80.6, 80.1, 74.8, 71.0, 60.8, 55.3, 36.2, 36.1, 33.9, 30.7, 26.2, 22.0, 20.4, 18.6, 14.0, –3.5, –4.8.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3436, 2956, 2929, 2857, 1612, 1513, 1248, 1062, 1038, 834.

HRMS (ESI) calc. for $C_{28}H_{46}IO_4Si^+$ $[M+H]^+$: 601.2205; found: 601.2186.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –9.0° (*c* = 0.27, CH_2Cl_2).

For 268:

TLC (20% ethyl acetate in cyclohexane): R_f = 0.25 (UV, CAM).

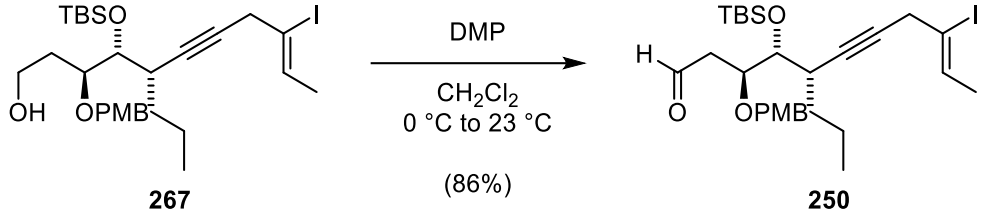
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.27–7.24 (m, 2H), 6.87–6.84 (m, 2H), 4.57 (d, *J* = 11.3 Hz, 1H), 4.37 (d, *J* = 11.2 Hz, 1H), 4.01–3.97 (m, 1H), 3.84 (dt, *J* = 9.0, 1.7 Hz, 1H), 3.78 (s, 3H), 3.71–3.61 (m, 2H), 2.37–2.31 (m, 1H), 2.10 (dd, *J* = 2.5, 1.3 Hz, 1H), 1.94–1.86 (m, 1H), 1.71–1.66 (m, 2H), 1.61–1.54 (m, 1H), 1.39–1.30 (m, 2H), 0.90 (t, *J* = 7.2, 1.3 Hz, 3H), 0.87 (s, 9H), 0.07 (d, *J* = 1.3 Hz, 3H), 0.06 (d, *J* = 1.3 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 159.4, 130.2, 130.0, 114.0, 85.1, 80.1, 74.7, 72.0, 71.1, 60.8, 55.4, 35.8, 33.6, 30.8, 26.2, 20.3, 18.6, 14.0, –3.5, –4.7.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3439, 3308, 2956, 2929, 2857, 1613, 1587, 1247, 1036, 833.

HRMS (ESI) calc. for $C_{24}H_{40}NaO_4Si^+$ $[M+Na]^+$: 443,2588; found: 443.2574.

Aldehyde 250



267 **250**

Dess–Martin periodinane (49.6 mg, 117 µmol, 1.30 equiv) was added to a solution of **267** (54.0 mg, 242 µmol, 1 equiv) dichloromethane (2 mL) at 0 °C. After 15 min, the white suspension was allowed to warm to 23°C. After 2 h, the reaction mixture was directly purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane) to give **250** (46 mg, 86%) as a colorless oil.

TLC (20% ethyl acetate in cyclohexane): R_f = 0.33 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.73 (dd, *J* = 3.0, 1.7 Hz, 1H), 7.25–7.22 (m, 2H), 6.87–6.84 (m, 2H), 5.90–5.83 (m, 1H), 4.57 (d, *J* = 11.3 Hz, 1H), 4.48–4.43 (m, 1H), 4.40–4.37 (m, 1H), 3.85 (dd, *J* = 8.5, 1.9 Hz, 1H), 3.80 (s, 3H), 3.44–3.40 (m, 2H), 2.73–2.65 (m, 1H), 2.58–2.53 (m, 1H), 2.33–2.26 (m, 1H), 1.76 (dt, *J* = 6.4, 1.5 Hz, 3H), 1.67–1.57 (m, 1H), 1.40–1.33 (m, 1H), 1.31–1.26 (m, 1H), 0.94–0.90 (m, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (assigned by HSQC correlations): δ = 202.5, 131.2, 129.6, 112.9, 76.4, 75.0, 71.0, 55.0, 43.8, 43.7, 36.7, 36.0, 33.6, 26.1, 21.9, 13.9.

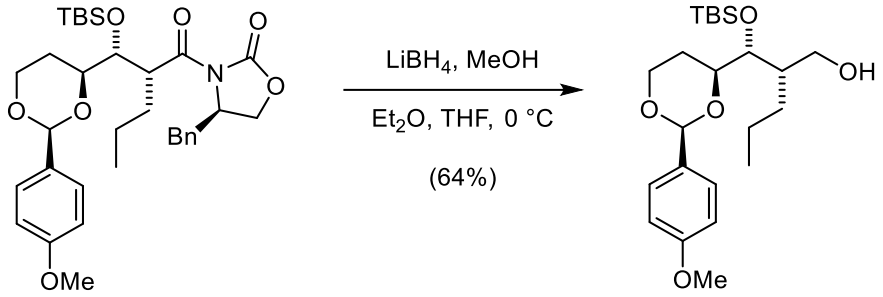
IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2956, 2928, 2856, 1727, 1613, 1514, 1249, 1135, 1037, 835.

HRMS (ESI) calc. for $C_{28}H_{43}O_4ISi^+$ $[M+Na]^+$: 621.1868; found: 621.1849.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +7.4° (*c* = 0.32, CH_2Cl_2).

3.3.5 Fourth Generation: Intermolecular alkylation

Alcohol 279



258 **279**

A solution of lithium borohydride (2 M in tetrahydrofuran, 7.80 mL, 15.6 mmol, 2.00 equiv) was added to a solution of **258** (4.66 g, 7.79 mmol, 1 equiv) and methanol (632 µL, 15.6 mmol, 2.00 equiv) in a mixture of diethyl ether (100 mL) and tetrahydrofuran (5 mL) at 0 °C. After 3 h, water (150 mL) and ethyl acetate (50 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (300 mL). The washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane initially, grading to 20% ethyl acetate in cyclohexane) to give **279** (2.12 g, 64%) as a colorless oil.

TLC (20% ethyl acetate in cyclohexane): R_f = 0.28 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.36 (m, 2H), 6.89–6.86 (m, 2H), 5.46 (s, 1H), 4.29 (ddd, *J* = 11.4, 5.0, 1.5 Hz, 1H), 4.01–3.94 (m, 2H), 3.91 (dd, *J* = 6.1, 3.0 Hz, 1H), 3.80 (s, 3H), 3.70 (d, *J* = 8.4 Hz, 2H), 2.52 (s, 1H), 1.97–1.90 (m, 2H), 1.69–1.65 (m, 1H), 1.47–1.40 (m, 1H), 1.40–1.33 (m, 2H), 1.23–1.16 (m, 1H), 0.92–0.88 (m, 12H), 0.13 (s, 3H), 0.12 (s, 3H).

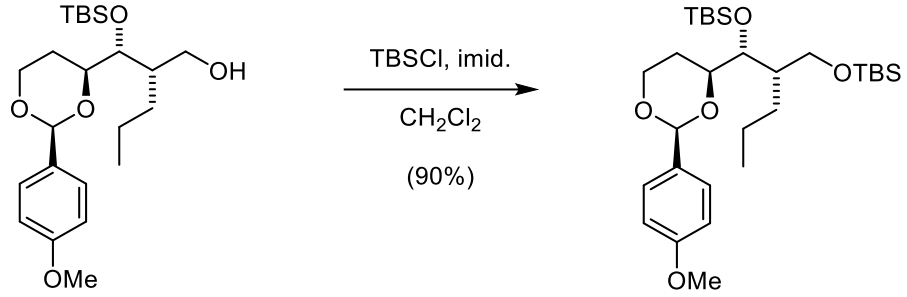
^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.0, 131.3, 127.4, 113.7, 101.3, 78.2, 76.7, 67.2, 64.2, 55.4, 44.9, 30.3, 28.7, 26.1, 21.5, 18.3, 14.5, –4.0, –4.3.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3457, 2956, 2928, 2856, 1518, 1248, 1103, 1035, 830, 777.

HRMS (ESI) calc. for $C_{23}H_{41}O_5Si^+$ $[M+H]^+$: 425.2718; found: 425.2708.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +1.2° (*c* = 0.65, CH_2Cl_2).

Silyl ether 280



279 **280**

Tert-butyldimethylsilyl chloride (841 mg, 5.47 mmol, 1.10 equiv) was added to a solution of **279** (2.11 g, 4.97 mmol, 1 equiv) and imidazole (983 mg, 9.94 mmol, 2.00 equiv) in dichloromethane (50 mL). After 3 h, water (100 mL) and dichloromethane (50 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 100 mL). The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane) to give **280** (2.42 g, 90%) as a colorless oil.

TLC (30% ethyl acetate in cyclohexane): R_f = 0.64 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (dd, *J* = 8.3, 1.6 Hz, 2H), 6.88 (dd, *J* = 8.3, 1.6 Hz, 2H), 5.45 (s, 1H), 4.33–4.26 (m, 1H), 3.99–3.88 (m, 3H), 3.80 (s, 3H), 3.65–3.60 (m, 1H), 3.59–3.53 (m, 1H), 2.01–1.89 (m, 1H), 1.82–1.74 (m, 1H), 1.64–1.58 (m, 1H), 1.57–1.51 (m, 1H), 1.44–1.31 (m, 2H), 1.25–1.19 (m, 1H), 0.94–0.90 (m, 21H), 0.11 (s, 3H), 0.09 (s, 3H), 0.06 (s, 6H).

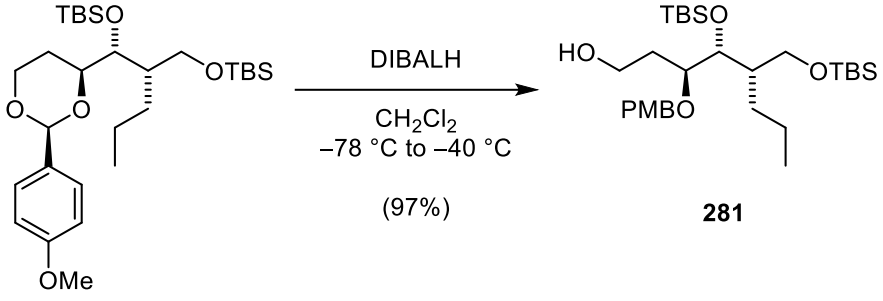
^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.8, 131.7, 127.4, 113.5, 101.2, 78.9, 74.6, 67.2, 63.0, 55.3, 43.7, 29.1, 27.6, 26.2, 26.0, 21.4, 18.5, 18.3, 14.6, –3.6, –4.4, –5.2, –5.3.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ =2955, 2929, 2856, 1518, 1463, 1249, 1104, 1039, 833, 775.

HRMS (ESI) calc. for $C_{29}H_{54}NaO_5Si_2^+$ $[M+Na]^+$: 561.3402; found: 561.3393.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –7.9° (*c* = 0.54, CH_2Cl_2).

Alcohol 281



280 **281**

A solution of diisobutylaluminum hydride (1 M in toluene, 25.2 mL, 25.2 mmol, 6.00 equiv) was added to a solution of **280** (2.26 g, 4.19 mmol, 1 equiv) in dichloromethane (35 mL) at –78 °C. The reaction mixture was allowed to warm to –40 °C over a period of 3 h. The reaction mixture was diluted with diethyl ether (200 mL) and saturated aqueous sodium potassium tartrate solution (200 mL) were added. The biphasic mixture was stirred vigorously for 2 h. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 150 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (300 mL). The washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) to give **281** (2.19 g, 97%) as a colorless oil.

TLC (30% ethyl acetate in cyclohexane): R_f = 0.41 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.22 (m, 2H), 6.91–6.84 (m, 2H), 4.65 (d, *J* = 11.1 Hz, 1H), 4.38 (d, *J* = 11.1 Hz, 1H), 4.03 (dd, *J* = 5.7, 2.1 Hz, 1H), 3.80 (s, 3H), 3.75–3.67 (m, 3H), 3.57 (dd, *J* = 10.3, 3.9 Hz, 1H), 3.49 (dd, *J* = 10.3, 6.2 Hz, 1H), 2.54 (s, 1H), 1.95–1.86 (m, 1H), 1.72–1.64 (m, 1H), 1.64–1.49 (m, 2H), 1.46–1.33 (m, 1H), 1.30–1.15 (m, 2H), 0.93–0.87 (m, 21H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 6H).

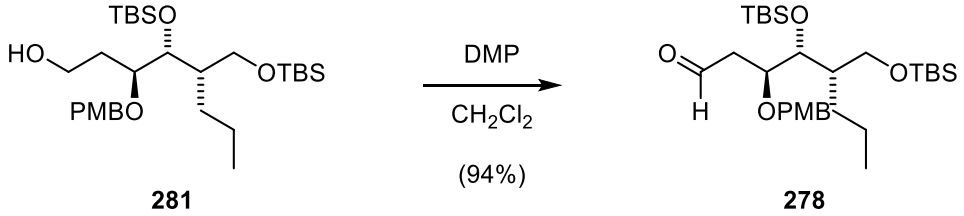
^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.3, 130.6, 129.6, 114.0, 81.4, 73.2, 71.6, 62.6, 61.1, 55.4, 44.2, 32.0, 29.4, 26.3, 26.0, 21.2, 18.6, 18.3, 14.6, –3.5, –4.8, –5.2, –5.4.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ =3440, 2954, 2929, 2856, 1514, 1248, 1050, 830, 773, 678.

HRMS (ESI) calc. for $C_{29}H_{57}O_5Si_2^+$ $[M+H]^+$: 541.3739; found: 541.3729.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –9.8° (*c* = 0.32, CH_2Cl_2).

Aldehyde 278



281 **278**

Dess–Martin periodinane (1.36 g, 2.57 mol, 1.30 equiv) was added to a solution of **281** (1.39 g, 2.57 mmol, 1 equiv) in dichloromethane (30 mL) at 0 °C. After 15 min, the white suspension was allowed to warm to 23°C. After 2 h, the reaction mixture was directly purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) to give **278** (1.30 g, 94%) as a colorless oil.

TLC (30% ethyl acetate in cyclohexane): R_f = 0.60 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (dd, *J* = 2.8, 1.5 Hz, 1H), 7.25–7.20 (m, 2H), 6.88–6.82 (m, 2H), 4.58 (d, *J* = 11.1 Hz, 1H), 4.41 (d, *J* = 11.1 Hz, 1H), 4.07 (ddd, *J* = 8.3, 3.4, 2.3 Hz, 1H), 4.02 (dd, *J* = 5.6, 2.3 Hz, 1H), 3.79 (s, 3H), 3.59 (dd, *J* = 10.4, 3.7 Hz, 1H), 3.49 (dd, *J* = 10.4, 6.2 Hz, 1H), 2.71 (ddd, *J* = 17.0, 8.3, 2.8 Hz, 1H), 2.53 (ddd, *J* = 17.0, 3.4, 1.5 Hz, 1H), 1.57–1.43 (m, 2H), 1.42–1.33 (m, 1H), 1.30–1.16 (m, 2H), 0.92–0.89 (m, 12H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 6H).

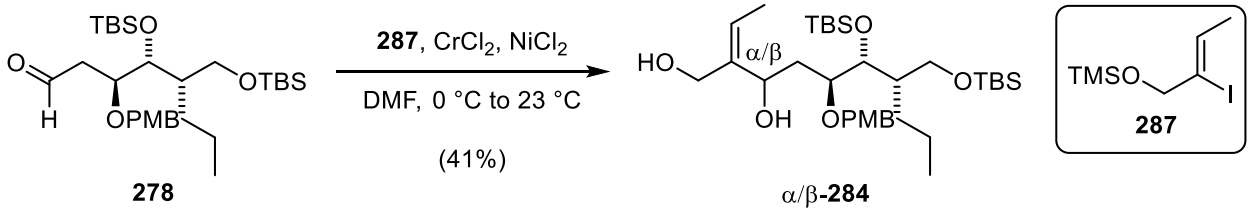
^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.5, 159.3, 130.5, 129.5, 113.8, 76.8, 73.7, 71.5, 62.3, 55.3, 44.7, 44.6, 29.5, 26.2, 26.0, 21.1, 18.5, 18.3, 14.5, –3.6, –4.7, –5.3, –5.4.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2954, 2929, 2857, 1727, 1613, 1514, 1249, 1075, 832, 775.

HRMS (ESI) calc. for $C_{29}H_{54}NaO_5Si_2^+$ $[M+Na]^+$: 561.3402; found: 561.3391.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –8.0° (*c* = 0.21, CH_2Cl_2).

Diol α-284 and β-284



Note: N,N-Dimethylformamide was degassed via freeze-pump-thaw (three cycles) prior to use.

A mixture of chromium(II) chloride (2.08 g, 16.9 mmol, 7.00 equiv) and nickel(II) chloride (31.9 mg, 241 µmol, 0.100 equiv) was added in one portion to a solution of **278** (1.30 g, 2.41 mmol, 1 equiv) and **287** (4.56 g, 16.9 mmol, 7.00 equiv) in *N*,*N*-dimethylformamide (60 mL) at 0 °C. After addition, the dark green reaction mixture was allowed to warm to 23 °C. After 48 h, aqueous hydrochloric acid (1 M, 200 mL) and ethyl acetate (200 mL) were added sequentially. The biphasic mixture was stirred vigorously for 15 min. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 150 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (400 mL). The washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (15% ethyl acetate in cyclohexane initially, grading to 30% ethyl acetate in cyclohexane) to give an inseparable mixture of α-**284** and β-**284** (609 mg, 41%) as a yellow oil. An analytically pure sample of α-**284** and β-**284** were obtained by normal-phase semi-preparative HPLC purification using 5% *iso*-propanol in *n*-heptane as eluent (flow rate: 15 mL/min; column: Microsorb 60-8 Si Dynamax 250 × 21.4mm (R00083121C); detection: 254 nm; retention time: α-**284** 10.5 min; β-**284** 9.32 min).

For α-284

TLC (30% ethyl acetate in cyclohexane): R_f = 0.26 (UV, CAM).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.26–7.24 (m, 2H), 6.90–6.87 (m, 2H), 5.52 (q, *J* = 6.9 Hz, 1H), 4.89 (d, *J* = 10.7 Hz, 1H), 4.70 (d, *J* = 10.7 Hz, 1H), 4.46 (s, 1H), 4.39 (d, *J* = 10.9 Hz, 1H), 4.34 (d, *J* = 11.9 Hz, 1H), 4.07 (dd, *J* = 6.2, 1.6 Hz, 1H), 3.90 (d, *J* = 11.8 Hz, 1H), 3.83 (ddd, *J* = 9.4, 3.1, 1.6 Hz, 1H), 3.81 (s, 3H), 3.54 (dd, *J* = 10.3, 4.0 Hz, 1H), 3.50 (dd, *J* = 10.3, 6.0 Hz, 1H), 3.10 (s, 1H), 2.18–2.09 (m, 1H), 1.61 (d, *J* = 6.9 Hz, 3H), 1.61–1.56 (m, 1H), 1.54–1.50 (m, 1H), 1.47 (q, *J* = 6.5, 4.8 Hz, 1H), 1.43–1.36 (m, 1H), 1.27–1.17 (m, 2H), 0.92–0.88 (m, 21H), 0.10 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 159.5, 141.2, 129.8, 129.8, 123.6, 114.1, 83.3, 73.1, 71.9, 70.2, 66.2, 62.6, 55.4, 44.2, 35.5, 29.3, 26.3, 26.0, 21.1, 18.6, 18.4, 14.6, 13.2, –3.5, –4.8, –5.2, –5.3.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3406, 2955, 2929, 2857, 1514, 1250, 1077, 1038, 834, 775.

HRMS (ESI) calc. for $C_{33}H_{62}NaO_6Si_2^+$ $[M+Na]^+$: 633.3977; found: 633.3950.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –8.5° (*c* = 0.26, CH_2Cl_2).

For β-284

TLC (30% ethyl acetate in cyclohexane): R_f = 0.26 (UV, CAM).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.29–7.26 (m, 2H), 6.89–6.86 (m, 2H), 5.50 (q, *J* = 6.9 Hz, 1H), 4.89 (dd, *J* = 9.6, 3.2 Hz, 1H), 4.66 (d, *J* = 11.3 Hz, 1H), 4.35 (d, *J* = 11.3 Hz, 1H), 4.30 (d, *J* = 11.9 Hz, 1H), 4.07 (dd, *J* = 6.2, 1.9 Hz, 1H), 3.98 (d, *J* = 11.9 Hz, 1H), 3.81 (s, 3H), 3.72 (dt, *J* = 9.3, 2.6 Hz, 1H), 3.57 (dd, *J* = 10.3, 4.0 Hz, 1H), 3.52 (dd, *J* = 10.3, 5.7 Hz, 1H), 2.46 (s, 2H), 1.73 (qdd, *J* = 14.7, 9.3, 3.0 Hz, 2H), 1.62 (d, *J* = 6.9 Hz, 3H), 1.60 (dd, *J* = 7.4, 2.9 Hz, 1H), 1.49–1.44 (m, 1H), 1.39 (dp, *J* = 10.4, 7.4, 5.8 Hz, 1H), 1.27–1.18 (m, 2H), 0.91 (s, 9H), 0.89 (s, 12H), 0.07 (s, 3H), 0.06 (s, 3H), 0.06–0.04 (m, 6H).

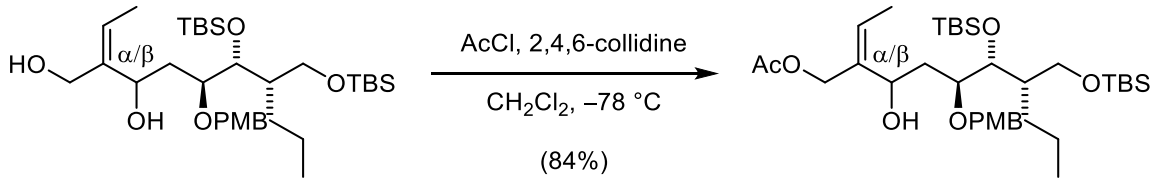
^{13}C NMR (151 MHz, $CDCl_3$): δ = 159.3, 141.2, 130.8, 129.6, 123.8, 114.0, 78.4, 73.3, 71.4, 68.0, 66.3, 62.6, 55.4, 44.1, 36.4, 29.4, 26.3, 26.1, 21.1, 18.6, 18.4, 14.6, 13.2, –3.5, –4.8, –5.2, –5.3.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ =3365, 2955, 2929, 2857, 1514, 1249, 1040, 1005, 834, 775.

HRMS (ESI) calc. for $C_{33}H_{62}NaO_6Si_2^+$ $[M+Na]^+$: 633.3977; found: 633.3919.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –32.3° (*c* = 0.17, CH_2Cl_2).

Allylic alcohol α-288 and β-288



α/β-**284** α/β-**288**

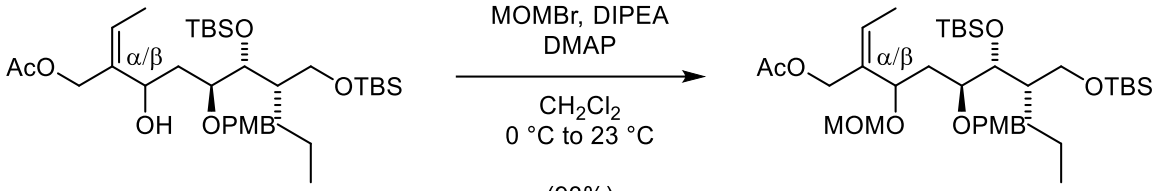
Acetyl chloride (70.1 µL, 973 µmol, 1.05 equiv) was added to a solution of α-**284** and β-**284** (566 mg, 926 µmol, 1 equiv) and 2,4,6-collidine (249 µL, 1.85 mmol, 2.00 equiv) in dichloromethane (9 mL) at –78 °C. After, 2.5 h, aqueous hydrochloric acid (1 M, 100 mL) and dichloromethane (80 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 80 mL). The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) to give an inseparable mixture of α-**288** and β-**288** (508 mg, 84%) as a colorless oil. The mixture of diastereoisomers was partially characterized by HRMS and IR spectroscopy.

TLC (30% ethyl acetate in cyclohexane): Rf = 0.47 (UV, CAM).

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ =3495, 2955, 2929, 2857, 1741, 1514, 1250, 1079, 835, 775.

HRMS (ESI) calc. for $C_{35}H_{64}NaO_7Si_2^+$ $[M+Na]^+$: 675.4083; found: 675.4041.

MOM-ether α-289 and β-289



α/β-**288** α/β-**289**

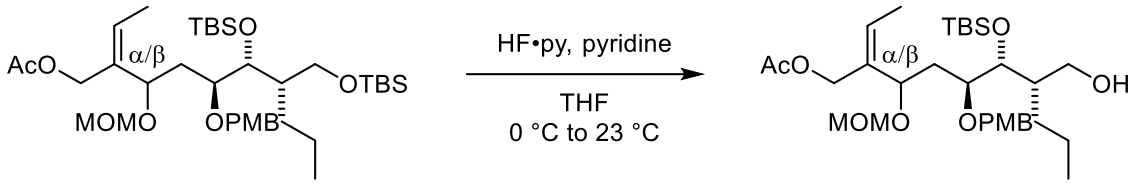
Bromomethyl methyl ether (705 µL, 7.78 mmol, 10.0 equiv) was added to a solution of **288** (508 mg, 778 µmol, 1 equiv) and *N*-ethyl-*N*-isopropylpropan-2-amine (2.72 mL, 15.6 mmol, 20.0 equiv) in dichloromethane (10 mL) at 0 °C. after addition, the reaction mixture was allowed to warm to 23 °C. After 24 h, the reaction mixture was cooled to 0 °C and bromomethyl methyl ether (353 µL, 3.89 mmol, 5.00 equiv) and *N*-ethyl-*N*-isopropylpropan-2-amine (1.36 mL, 7.78 mmol, 10.0 equiv) were added. After addition the reaction mixture was allowed to warm to 23 °C. After 24 h, the reaction mixture was cooled to 0 °C and bromomethyl methyl ether (353 µL, 3.89 mmol, 5.00 equiv) and *N*-ethyl-*N*-isopropylpropan-2-amine (1.36 mL, 7.78 mmol, 10.0 equiv) were added. After addition the reaction mixture was allowed to warm to 23 °C. After 12 h, water (100 mL) and dichloromethane (80 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 90 mL). The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) to give an inseparable mixture of α-**289** and β-**289** (503 mg, 93%) as a colorless oil. The mixture of diastereoisomers was partially characterized by HRMS and IR spectroscopy.

TLC (30% ethyl acetate in cyclohexane): R_f = 0.57(UV, CAM).

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2954, 2929, 2857, 1743, 1514, 1248, 1091, 1034, 833, 775.

HRMS (ESI) calc. for $C_{37}H_{68}NaO_8Si_2^+$ $[M+Na]^+$: 719.4345; found: 719.4335.

Primary alcohol α-290 and β-290



α/β-**289**

α-**290** (51%)
β-**290** (30%)

Pyridine hydrofluoride (~70% hydrogen fluoride, ~30% pyridine, 1.50 mL, 57.7 mmol, 80.0 equiv) was added to a solution of **289** (503 mg, 722 µmol, 1 equiv) and pyridine (10.5 mL, 130 mmol, 180 equiv) in tetrahydrofuran in a 50 mL Falcon® tube at 0 °C. After 1 h, the reaction mixture was allowed to warm to 23 °C. After 24 h, the reaction mixture was poured on a solution of saturated aqueous sodium bicarbonate solution (200 mL). Ethyl acetate (150 ml) was added and the biphasic mixture was stirred vigorously for 15 min. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 150 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (400 mL). The washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (15% ethyl acetate in cyclohexane initially, grading to 25% ethyl acetate in cyclohexane) to give α-**290** (215 mg, 51%) as a colorless oil and β-**290** (126 mg, 30%) as a colorless oil.

For α-290

TLC (40% ethyl acetate in cyclohexane): R_f = 0.43 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.24 (m, 2H), 6.88–6.84 (m, 2H), 5.85 (q, *J* = 7.2, 6.6 Hz, 1H), 4.82 (dd, *J* = 9.3, 5.3 Hz, 1H), 4.70 (d, *J* = 11.1 Hz, 1H), 4.62 (dt, *J* = 12.9, 1.2 Hz, 1H), 4.57–4.50 (m, 2H), 4.47 (d, *J* = 6.5 Hz, 1H), 4.31 (d, *J* = 11.1 Hz, 1H), 3.98 (dd, *J* = 4.9, 2.2 Hz, 1H), 3.79 (s, 3H), 3.68 (dd, *J* = 11.1, 3.8 Hz, 1H), 3.54 (dd, *J* = 11.1, 7.4 Hz, 1H), 3.51–3.47 (m, 1H), 3.34 (s, 3H), 2.22 (s, 1H), 2.13–2.04 (m, 4H), 1.91 (ddd, *J* = 14.5, 9.3, 2.8 Hz, 1H), 1.76–1.69 (m, 1H), 1.67 (d, *J* = 7.2 Hz, 3H), 1.50–1.38 (m, 2H), 1.32–1.23 (m, 2H), 0.93–0.85 (m, 12H), 0.08 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.0, 159.1, 132.9, 130.9, 129.7, 128.8, 113.8, 93.6, 79.5, 75.6, 71.9, 69.5, 64.4, 62.7, 55.5, 55.4, 45.0, 35.2, 30.1, 26.1, 21.3, 21.2, 18.4, 14.5, 13.5, –3.9, –4.9.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3509, 2955, 2927, 2856, 1740, 1514, 1248, 1093, 1035, 835.

HRMS (ESI) calc. for $C_{31}H_{54}NaO_8Si^+$ $[M+Na]^+$: 605.3480; found: 605.3464.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –20.3° (*c* = 0.16, CH_2Cl_2).

For β-290

TLC (40% ethyl acetate in cyclohexane): R_f = 0.37 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.27 (m, 2H), 6.89–6.84 (m, 2H), 5.79–5.73 (m, 1H), 4.74 (dd, *J* = 10.6, 1.6 Hz, 2H), 4.54–4.48 (m, 3H), 4.43–4.35 (m, 2H), 3.99 (dd, *J* = 4.9, 1.6 Hz, 1H), 3.82–3.78 (m, 4H), 3.75 (dd, *J* = 11.4, 3.3 Hz, 1H), 3.60 (dd, *J* = 11.4, 7.1 Hz, 1H), 3.35 (s, 3H), 2.81 (s, 1H), 2.03 (s, 3H), 1.98–1.89 (m, 1H), 1.74–1.68 (m, 1H), 1.68–1.60 (m, 4H), 1.50–1.38 (m, 2H), 1.37–1.29 (m, 2H), 0.94–0.89 (m, 12H), 0.08 (s, 3H), 0.07 (s, 3H).

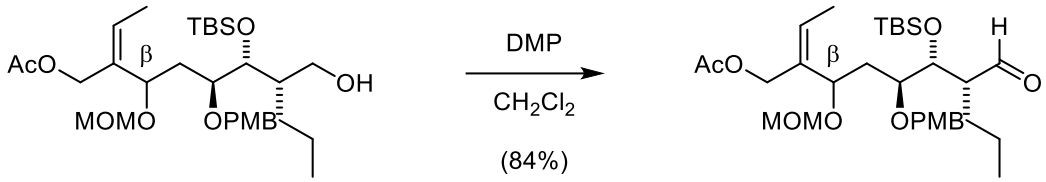
^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.0, 159.3, 134.6, 131.0, 129.4, 129.2, 113.9, 94.7, 78.9, 76.4, 72.7, 70.5, 65.3, 62.1, 56.2, 55.4, 45.5, 37.3, 30.4, 26.1, 21.2, 21.2, 18.3, 14.5, 13.1, –4.0, –4.9.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3499, 2954, 2626, 2855, 1740, 1514, 1248, 1034, 1248, 1034, 834, 775.

HRMS (ESI) calc. for $C_{31}H_{54}NaO_8Si^+$ $[M+Na]^+$: 605.3480; found: 605.3466.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –42.0° (*c* = 0.20, CH_2Cl_2)

Aldehyde β-291



β-**290** β-**291**

Dess–Martin periodinane (118 mg, 279 µmol, 1.30 equiv) was added to a solution of β-**290** (125 mg, 214 µmol, 1 equiv) dichloromethane (1 mL) at 0 °C. After 30 min, the reaction mixture was directly purified by flash column chromatography on silica gel (20% ethyl acetate in cyclohexane) to give β-**291** (105 mg, 84%) as a colorless oil.

TLC (30% ethyl acetate in cyclohexane): R_f = 0.43 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (d, *J* = 2.1 Hz, 1H), 7.30–7.27 (m, 2H), 6.88–6.85 (m, 2H), 5.80–5.70 (m, 1H), 4.73–4.67 (m, 2H), 4.53–4.50 (m, 2H), 4.48 (d, *J* = 6.7 Hz, 1H), 4.44 (d, *J* = 10.9 Hz, 1H), 4.35 (d, *J* = 6.7 Hz, 1H), 4.19 (dd, *J* = 6.7, 2.1 Hz, 1H), 3.80 (s, 3H), 3.63 (dt, *J* = 10.1, 1.8 Hz, 1H), 3.31 (s, 3H), 2.55–2.47 (m, 1H), 2.03 (s, 3H), 1.88–1.78 (m, 1H), 1.73–1.64 (m, 5H), 1.57–1.48 (m, 1H), 1.46–1.36 (m, 1H), 1.35–1.23 (m, 1H), 0.94–0.87 (m, 12H), 0.08 (s, 3H), 0.05 (s, 3H).

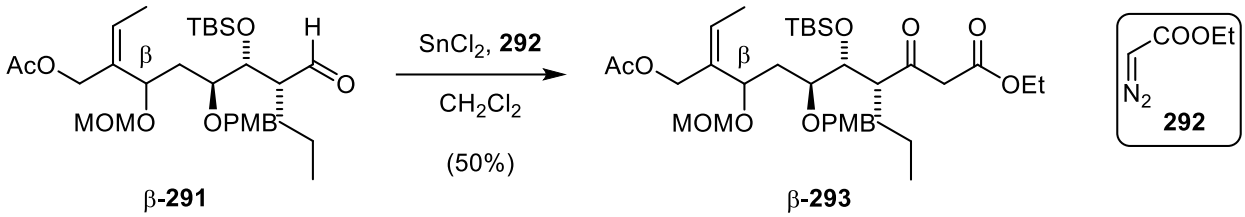
^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.4, 170.9, 159.2, 134.5, 130.9, 129.4, 129.1, 113.8, 94.6, 79.4, 73.4, 72.5, 70.1, 65.1, 56.1, 55.4, 55.4, 36.6, 28.1, 26.1, 21.2, 21.0, 18.4, 14.4, 13.1, –3.8, –4.9.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2955, 2930, 2856, 1737, 1463, 1247, 1089, 1026, 834, 776.

HRMS (ESI) calc. for $C_{31}H_{52}NaO_8Si^+$ $[M+Na]^+$: 603.3324; found: 603.3303.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –46.9° (*c* = 0.21, CH_2Cl_2)

β-Ketoester β-293



β-**291** β-**293**

Ethyl diazoacetate (**292**) (84.9 µL, 702 µmol, 4.00 equiv) and tin(II) chloride (20.0 mg, 105 µmol, 0.600 equiv) were sequentially added to a solution of β-**291** (102 mg, 176 µmol, 1 equiv) in dichloromethane (0.4 mL). After 12 h, water (20 mL) and dichloromethane (20 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (15% ethyl acetate in cyclohexane) to give β-**293** (58.4 mg, 50%) as a colorless oil.

*Note: β-**293** was isolated as keto/enol-tautomers (2:1). In the 1H NMR spectrum only well separated signals for the keto-tautomer are reported. In the 13C NMR all peaks of both tautomers are reported.*

TLC (30% ethyl acetate in cyclohexane): R_f = 0.34 (UV, CAM).

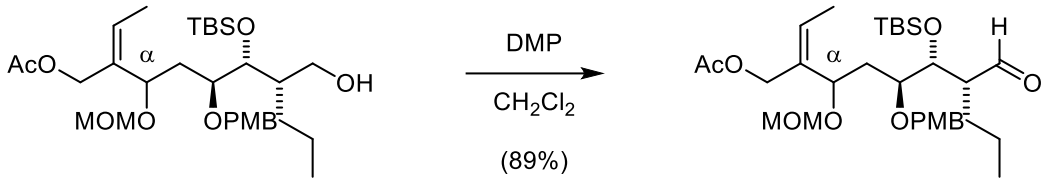
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.45 (d, *J* = 6.7 Hz, 1H), 3.79 (s, 3H), 2.80–2.69 (m, 1H), 2.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 206.59, 178.26, 172.75, 170.97, 166.97, 159.17, 159.12, 134.84, 134.44, 131.01, 130.86, 129.50, 129.43, 129.01, 128.31, 113.79, 113.71, 94.64, 94.54, 92.09, 78.73, 78.42, 74.11, 73.14, 71.60, 71.09, 70.12, 70.00, 65.13, 65.01, 61.61, 61.17, 60.09, 56.15, 55.72, 55.43, 55.36, 55.34, 51.80, 49.80, 35.79, 35.31, 32.22, 31.58, 26.25, 26.19, 21.23, 20.56, 20.48, 18.59, 18.51, 14.42, 14.41, 14.29, 14.22, 14.17, 13.06, 13.03, –3.53, –3.66, –4.81, –4.89.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2957, 2932, 2857, 1741, 1465, 1247, 1230, 1155, 1032, 835.

HRMS (ESI) calc. for $C_{35}H_{58}NaO_{10}Si^+$ $[M+Na]^+$: 689.3691; found: 689.3661.

Aldehyde α-295



α-**290** α-**295**

Dess–Martin periodinane (190 mg, 448 µmol, 1.30 equiv) was added to a solution of α-**290** (201 mg, 214 µmol, 1 equiv) dichloromethane (1 mL) at 0 °C. After 1 h, the reaction mixture was directly purified by flash column chromatography on silica gel (20% diethyl ether in *n*-pentane) to give α-**295** (177 mg, 89%) as a colorless oil.

TLC (30% ethyl acetate in cyclohexane): R_f = 0.47 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.71 (d, *J* = 2.2 Hz, 1H), 7.27–7.23 (m, 2H), 6.88–6.84 (m, 2H), 5.86 (q, *J* = 7.0 Hz, 1H), 4.79 (dd, *J* = 8.5, 6.0 Hz, 1H), 4.61 (d, *J* = 11.2 Hz, 1H), 4.56–4.52 (m, 3H), 4.45 (d, *J* = 6.6 Hz, 1H), 4.33 (d, *J* = 11.2 Hz, 1H), 4.23 (dd, *J* = 6.1, 2.9 Hz, 1H), 3.79 (s, 3H), 3.35–3.29 (m, 4H), 2.53–2.46 (m, 1H), 2.06 (s, 3H), 2.05–1.97 (m, 1H), 1.83 (ddd, *J* = 14.5, 8.5, 3.2 Hz, 1H), 1.74–1.66 (m, 2H), 1.65 (d, *J* = 7.0 Hz, 3H), 1.44–1.34 (m, 1H), 1.30–1.22 (m, 1H), 0.92–0.87 (m, 12H), 0.09 (s, 3H), 0.02 (s, 3H).

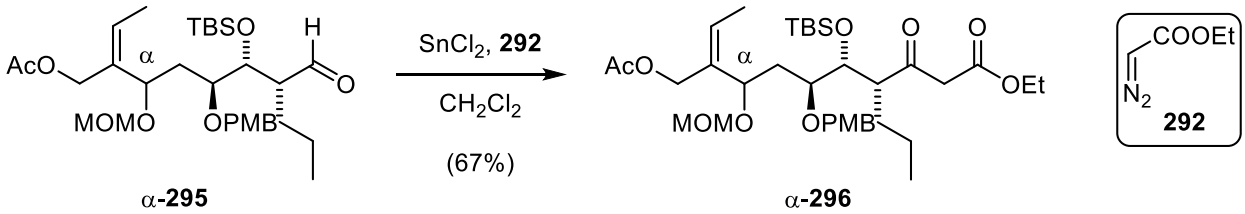
^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.4, 170.8, 159.1, 132.8, 130.7, 130.3, 128.9, 113.8, 93.6, 79.4, 73.0, 71.5, 69.1, 64.3, 55.6, 55.4, 55.3, 34.4, 27.8, 26.1, 21.2, 21.0, 18.4, 14.3, 13.5, –3.8, –4.8.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2955, 2931, 2857, 1741, 1514, 1248, 1094, 1034, 836, 777.

HRMS (ESI) calc. for $C_{31}H_{52}NaO_8Si^+$ $[M+Na]^+$: 603.3324; found: 603.3311.

$[\boldsymbol{a}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +18.0° (*c* = 0.10, CH_2Cl_2)

β-Ketoester α-296



α-**295** α-**296**

Ethyl diazoacetate (**292**) (101 µL, 702 µmol, 3.00 equiv) and tin(II) chloride (26.5 mg, 139 µmol, 0.500 equiv) were sequentially added to a solution of α-**295** (102 mg, 176 µmol, 1 equiv) in dichloromethane (0.5 mL). After 12 h, water (20 mL) and dichloromethane (20 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% diethyl ether in *n*-pentane) to give α-**296** (125 mg, 67%) as a colorless oil.

*Note: α-**296** was isolated as keto/enol-tautomers (2:1). In the 1H NMR spectrum only well separated signals for the keto-tautomer are reported. In the 13C NMR all peaks of both tautomers are reported.*

TLC (30% ethyl acetate in cyclohexane): R_f = 0.43 (UV, CAM).

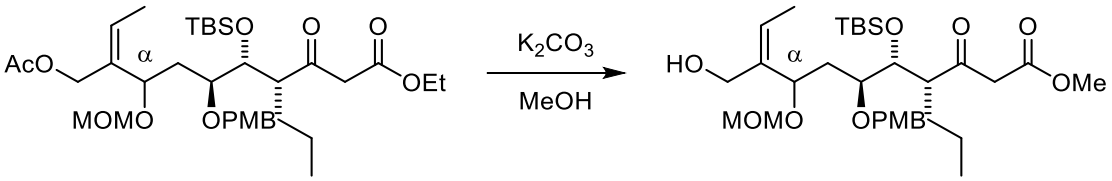
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87–5.81 (m, 1H), 3.80 (s, 3H), 3.50 (d, *J* = 3.9 Hz, 2H), 3.33 (s, 3H), 3.17–3.12 (m, 1H), 2.77 (td, *J* = 8.4, 4.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 205.74, 178.32, 172.61, 170.85, 167.06, 159.06, 159.00, 133.06, 132.84, 130.90, 130.79, 129.88, 129.59, 128.86, 128.81, 113.78, 113.72, 93.61, 93.53, 91.72, 79.39, 78.74, 73.95, 73.20, 71.23, 70.70, 69.40, 69.30, 64.51, 64.41, 61.28, 60.19, 55.56, 55.45, 55.37, 55.37, 55.36, 55.31, 50.66, 49.66, 34.44, 33.99, 31.77, 31.20, 26.27, 26.19, 21.24, 21.20, 20.56, 20.53, 18.61, 18.48, 14.42, 14.36, 14.26, 14.16, 13.46, 13.36, –3.50, –3.74, –4.88, –4.91.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2956, 2932, 2858, 1742, 1711, 1514, 1230, 1033, 835, 777.

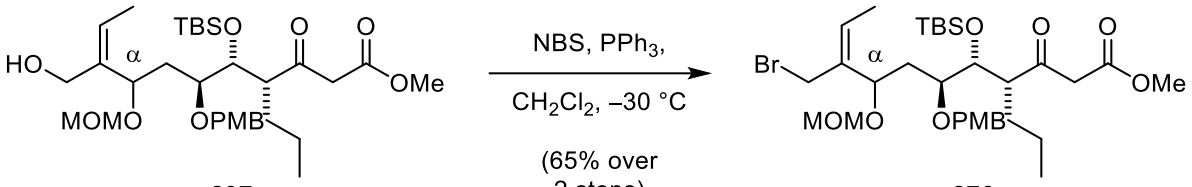
HRMS (ESI) calc. for $C_{35}H_{58}NaO_{10}Si^+$ $[M+Na]^+$: 689.3691; found: 689.3684.

Allyl bromide α-276



α-**296** α-**297**

Potassium carbonate (74.6 mg, 540 µmol, 3.00 equiv) was added to a solution of α-**296** (118 mg, 177 µmol, 1 equiv) in methanol (2 mL). After 24 h, water (50 mL) and diethyl ether (50 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (150 mL). The washed solution was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was filtered through a plug of silica and the obtained crude product (α-**297**) was used without further purification.



α-**297** α-**276**

N-Bromosuccinimide (38.2 mg, 212 µmol, 1.20 equiv) was added to a solution of crude α-**297** (108 mg, 177 µmol, 1 equiv) and triphenylphosphine (56.3 mg, 212 µmol, 1.20 equiv) at –30 °C. After 1 h, *n*-pentane (2 mL) was added and the white suspension was directly purified by flash column chromatography on silica gel (5% diethyl ether in *n*-pentane initially, grading to 30% diethyl ether in *n*-pentane) to give α-**276** (77.3 mg, 65% over 2 steps) as a colorless oil.

*Note: α-**276** was isolated as keto/enol-tautomers (2:1). In the 1H NMR spectrum only well separated signals for the keto-tautomer are reported. In the 13C NMR all peaks of both tautomers are reported.*

TLC (30% ethyl acetate in cyclohexane): R_f = 0.49 (UV, CAM).

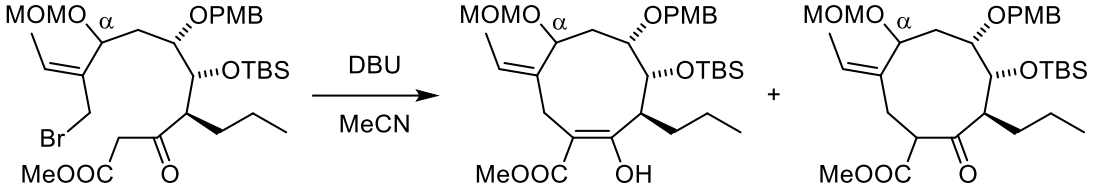
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.09 (q, *J* = 7.1 Hz, 1H), 3.81 (s, 3H), 3.54 (s, 2H), 3.35 (s, 3H), 2.87–2.80 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 205.53, 178.60, 172.91, 167.51, 159.05, 159.03, 134.96, 134.84, 134.04, 133.31, 130.77, 130.77, 128.88, 128.75, 113.80, 113.75, 93.73, 93.71, 91.39, 79.39, 78.61, 73.95, 73.22, 71.34, 70.68, 70.06, 69.94, 55.49, 55.46, 55.39, 55.36, 55.36, 52.28, 51.33, 50.54, 49.45, 34.59, 34.04, 33.00, 32.93, 31.68, 31.05, 26.26, 26.19, 20.57, 20.51, 18.61, 18.47, 14.33, 14.10, 13.87, 13.83, –3.51, –3.69, –4.86, –4.93.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2954, 2931, 2857, 1751, 1712, 1514, 1246, 1028, 834, 776.

HRMS (ESI) calc. for $C_{32}H_{53}BrNaO_8Si$ $[M+Na]^+$: 695.2585; found: 695.2562.

Cyclization products α-301 and α-302



α-**276** α-**301** (25%) α-**302** (32%)

Diazabicycloundecene (20.2 µL, 134 µmol, 2.00 equiv) was added to a solution of α-**276** (45.0 mg, 66.8 µmol, 1 equiv) in acetonitrile (3.5 mL). After 12 h, the yellow solution was diluted with diethyl ether (2 mL) and filtered through a plug of silica. The filtrate was concentrated and the residue was purified normal-phase semi-preparative HPLC purification using 1% *iso*-propanol in *n*-heptane initially, grading to 3% *iso*-propanol over in *n*-heptane over 45 min as eluent (flow rate: 15 mL/min; column: Microsorb 60-8 Si Dynamax 250 × 21.4mm (R00083121C); detection: 254 nm; retention time: α-**301** 6.7 min; α-**302** 8.7 min) to give α-**301** (10.0 mg, 25%) as a colorless oil and α-**302** (12.3 mg, 32%) as a colorless oil.

For α-301

TLC (20% ethyl acetate in cyclohexane): R_f = 0.42 (UV, CAM).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 12.94 (s, 1H), 7.17–7.12 (m, 2H), 6.82–6.78 (m, 2H), 5.67 (q, *J* = 7.3 Hz, 1H), 4.60 (dd, *J* = 8.3, 6.0 Hz, 1H), 4.57–4.51 (m, 2H), 4.35 (d, *J* = 11.4 Hz, 1H), 4.27 (d, *J* = 11.4 Hz, 1H), 3.91 (d, *J* = 9.9 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.35 (s, 3H), 3.18–3.13 (m, 2H), 3.09–3.04 (m, 1H), 2.74 (d, *J* = 15.6 Hz, 1H), 2.40–2.34 (m, 1H), 1.83–1.77 (m, 1H), 1.77–1.71 (m, 1H), 1.70–1.63 (m, 1H), 1.51 (d, *J* = 7.1 Hz, 3H), 1.35–1.25 (m, 1H), 1.13–1.06 (m, 1H), 0.90 (s, 9H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 175.5, 174.0, 159.1, 138.6, 130.5, 129.9, 126.9, 113.7, 102.4, 93.5, 77.8, 74.2, 72.2, 70.4, 55.5, 55.4, 51.7, 45.1, 32.9, 31.0, 26.3, 26.3, 20.6, 18.7, 14.3, 13.6, –3.4, –4.7.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2996, 2897, 2847, 1597, 1635, 1211, 1187, 1048, 866, 774.

HRMS (ESI) calc. for $C_{32}H_{52}NaO_8Si$ $[M+Na]^+$: 615.3324; found: 615.3279.

For α-302

TLC (20% ethyl acetate in cyclohexane): R_f = 0.23 (UV, CAM).

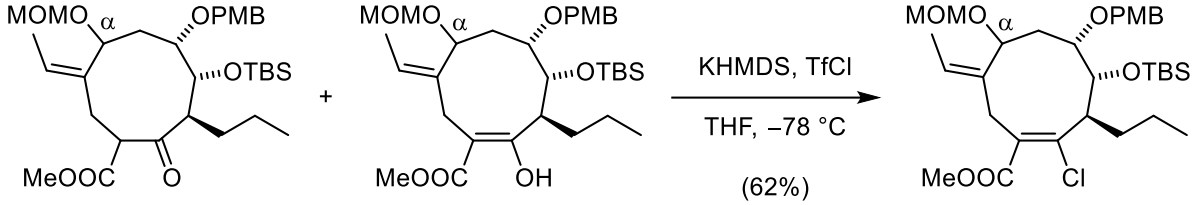
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.3 Hz, 2H), 6.87–6.83 (m, 2H), 5.79–5.69 (m, 1H), 4.74–4.66 (m, 1H), 4.53–4.47 (m, 1H), 4.47–4.41 (m, 1H), 4.40–4.33 (m, 1H), 4.26–4.19 (m, 1H), 4.02 (d, *J* = 9.0 Hz, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.62–3.56 (m, 1H), 3.35 (s, 3H), 3.01–2.94 (m, 1H), 2.87–2.75 (m, 2H), 2.41–2.31 (m, 1H), 2.18–2.10 (m, 1H), 1.90–1.80 (m, 1H), 1.74–1.64 (m, 1H), 1.56–1.50 (m, 1H), 1.48–1.42 (m, 3H), 1.21–1.09 (m, 2H), 0.89–0.82 (m, 12H), 0.04 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 208.7, 168.8, 159.3, 132.1, 131.1, 130.4, 129.6, 113.8, 93.3, 75.4, 71.0, 70.7, 64.5, 55.6, 55.4, 52.4, 51.0, 33.9, 32.1, 26.7, 26.2, 26.0, 19.3, 18.7, 14.4, 13.0, –3.4, –4.9.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2953, 2930, 2856, 1640, 1609, 1245, 1144, 1033, 835, 777.

HRMS (ESI) calc. for $C_{32}H_{52}NaO_8Si$ $[M+Na^+]^+$: 615.3324; found: 615.3291.

Chloride α-304



α-**301** α-**302** α-**304**

A solution of potassium 1,1,1-trimethyl-*N*-(trimethylsilyl)silanaminide (1 M in tetrahydrofuran, 38.1 µL, 38.1 µmol, 2.00 equiv) was added to a solution of α-**301** and α-**302** in tetrahydrofuran (0.5 mL) at –78 °C. After 45 min, frifluoromethanesulfonyl chloride (4.06 µL, 38.1 µmol, 2.00 equiv) was added and the reaction mixture was allowed to warm to 23 °C. After 10 min, two drops of saturated aqueous sodium bicarbonate solution were added and the mixture was filtered through a plug of silica. The filtrate was concentrated and the residue was purified normal-phase semi-preparative HPLC purification using 1% *iso*-propanol in *n*-heptane initially, grading to 3% *iso*-propanol over in *n*-heptane over 45 min as eluent (flow rate: 15 mL/min; column: Microsorb 60-8 Si Dynamax 250 × 21.4mm (R00083121C); detection: 190 nm; retention time: 6.2 min) to give α-**304** (7.2 mg, 62%) as a colorless.

TLC (20% ethyl acetate in cyclohexane): R_f = 0.42 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.21 (m, 2H), 6.88–6.83 (m, 2H), 6.10 (qd, *J* = 7.1, 1.6 Hz, 1H), 4.63 (dd, *J* = 12.1, 5.4 Hz, 1H), 4.49 (d, *J* = 6.5 Hz, 1H), 4.45–4.39 (m, 2H), 4.30 (d, *J* = 11.2 Hz, 1H), 4.09 (dd, *J* = 8.4, 1.9 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.40 (d, *J* = 15.5 Hz, 1H), 3.35 (s, 3H), 3.29 (dt, *J* = 8.8, 5.1 Hz, 1H), 3.04–2.93 (m, 1H), 2.69 (d, *J* = 15.5 Hz, 1H), 2.04–1.94 (m, 1H), 1.93–1.79 (m, 3H), 1.49–1.41 (m, 4H), 1.39–1.28 (m, 1H), 0.91 (t, *J* = 7.3 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 205.2, 169.5, 159.3, 134.9, 130.6, 129.5, 129.5, 113.9, 93.1, 76.3, 74.4, 74.0, 71.5, 71.0, 55.6, 55.4, 53.7, 51.4, 37.0, 34.1, 32.4, 26.3, 19.0, 18.7, 14.5, 13.3, –3.4, –4.9.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2955, 2932, 2856, 1748, 1514, 1248, 1083, 1027, 834, 777.

HRMS (ESI) calc. for $C_{32}H_{51}ClKO_7Si$ $[M+K]^+$: 649.2724; found: 649.2921.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +12.5° (*c* = 0.48, CH_2Cl_2)

3.3.6 X-Ray Crystallographic Data

Ferrocenecarboxylate ester 237

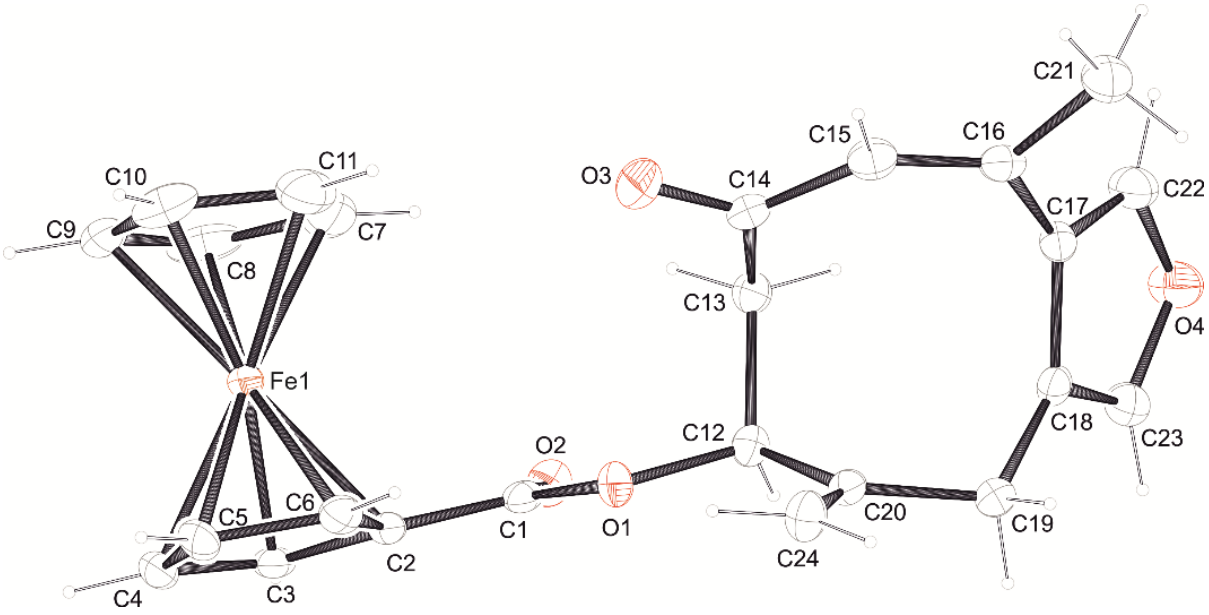


Table 6 | Crystallographic data for **237**.

net formula	$C_{24}H_{22}FeO_4$
M_r/g mol^{-1}	430.26
crystal size/mm	0.080 × 0.070 × 0.020
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P 21 21 21'
a/Å	5.99760(10)
b/Å	12.6528(3)
c/Å	25.3750(7)
α/°	90
β/°	90
γ/°	90
V/Å^3	1925.62(8)
Z	4
calc. density/g cm^{-3}	1.484
μ/mm^{-1}	0.812
absorption correction	Multi-Scan
transmission factor range	0.6846–0.7454
refls. measured	10370
R_{int}	0.0328
mean σ(I)/I	0.0446
θ range	3.211–26.366
observed refls.	3651
x, y (weighting scheme)	0.0248, 0.2800
hydrogen refinement	constr
Flack parameter	0.004(8)
refls in refinement	3927
parameters	263

restraints	12
$R(F_{obs})$	0.0274
$R_w(F^2)$	0.0642
S	1.041
shift/error$_{max}$	0.002
max electron density/e Å^{-3}	0.461
min electron density/e Å^{-3}	−0.221

Secondary alcohol 257

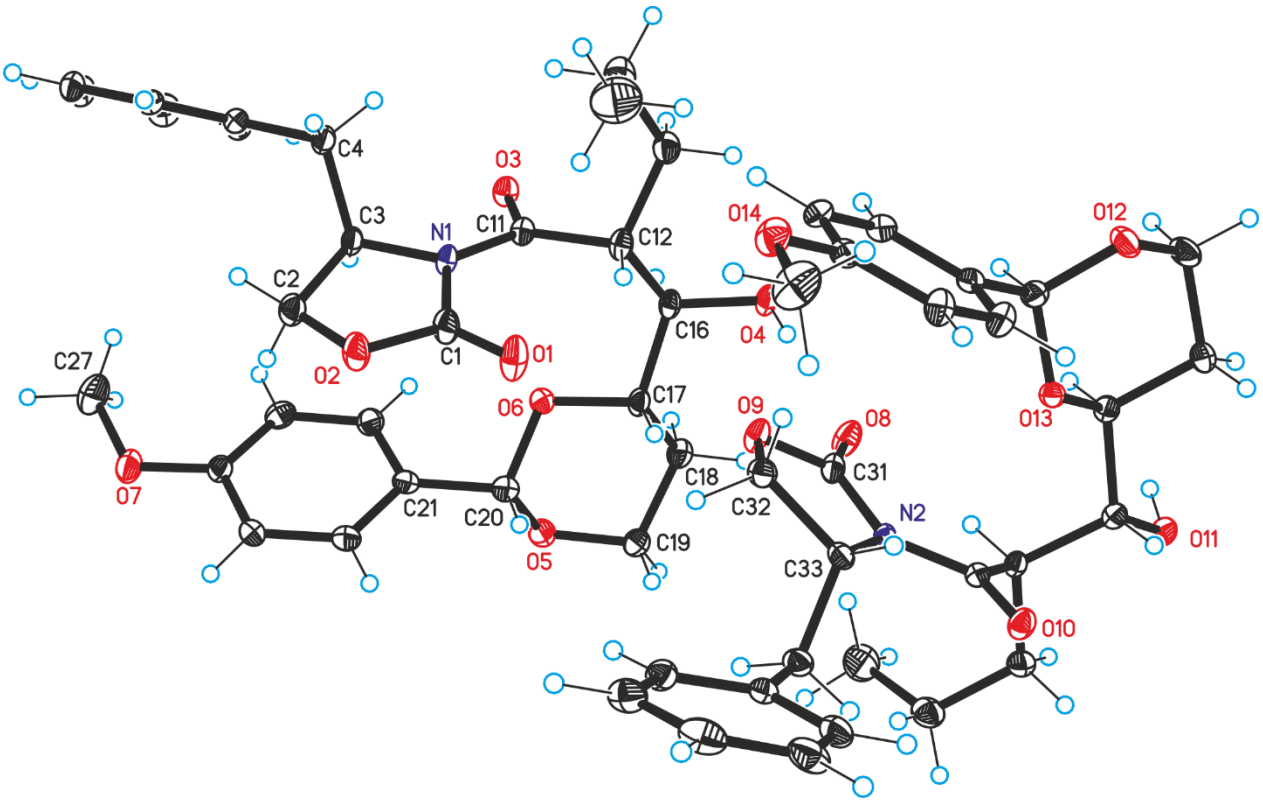


Table 7 | Crystallographic data for **257**.

Empirical formula	C27H33 N O7
Formula weight	483.54
Temperature	183(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$ (no. 4)
Unit cell dimensions	a = 9.4935(6) Å, α= 90°. b = 27.1375(16) Å, β= 90.337(2)°. c = 9.9811(6) Å, γ = 90°.
Volume	2571.4(3) $Å^3$
Z	4
Density (calculated)	1.249 Mg/m^3
Absorption coefficient	0.090 mm^{-1}
F(000)	1032
Crystal size	0.180 x 0.160 x 0.080 mm^3

Theta range for data collection	2.145 to 24.499°.
Index ranges	-11<=h<=11, -30<=k<=31, -11<=l<=11
Reflections collected	37669
Independent reflections	8413 [R(int) = 0.0558]
Completeness to theta = 24.499°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.955 and 0.932
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8413 / 3 / 642
Goodness-of-fit on F^2	1.048
Final R indices [I>2sigma(I)]	R1 = 0.0460, wR2 = 0.0938
R indices (all data)	R1 = 0.0772, wR2 = 0.1029
Absolute structure parameter	0.1(4)
Extinction coefficient	0.0138(13)
Largest diff. peak and hole	0.601 and -0.207 e.$Å^{-3}$

Silyl ether 258

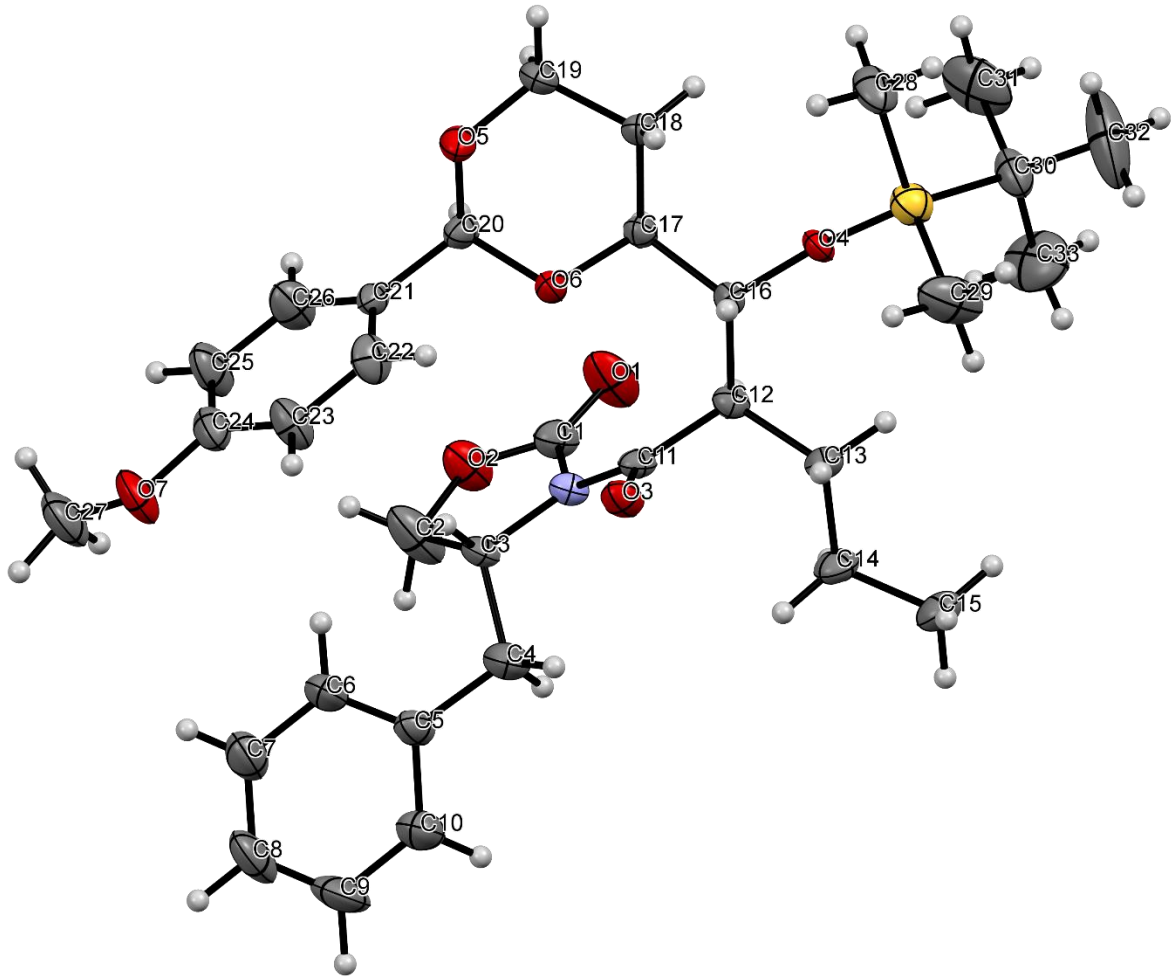
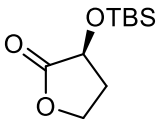


Table 8 | Crystallographic data for **258**.

Empirical formula	C33 H47 N O7 S
Formula weight	601.77
Temperature	183(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$ (no. 4)
Unit cell dimensions	a = 15.6831(13) Å, α= 90°. b = 7.1153(6) Å, β= 116.788(2)°. c = 16.4777(13) Å, γ = 90°.
Volume	1641.4(2) $Å^3$
Z	2
Density (calculated)	1.218 Mg/m^3

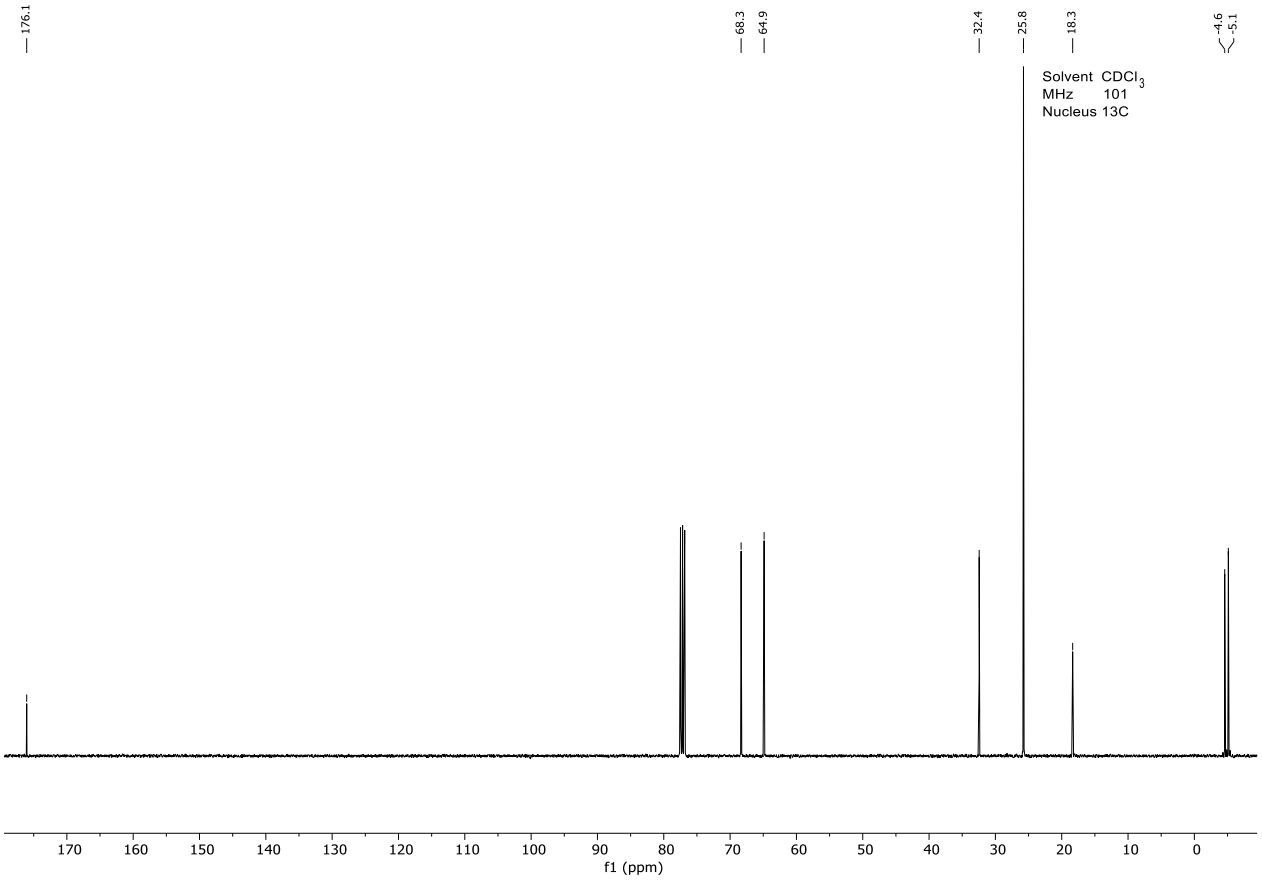
Absorption coefficient	0.145 mm^{-1}
F(000)	648
Crystal size	0.210 x 0.180 x 0.080 mm^3
Theta range for data collection	2.481 to 23.248°.
Index ranges	-17<=h<=17, -7<=k<=7, -17<=l<=18
Reflections collected	14339
Independent reflections	4699 [R(int) = 0.0494]
Completeness to theta = 23.248°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.958 and 0.888
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4699 / 1 / 381
Goodness-of-fit on F^2	1.038
Final R indices [I>2sigma(I)]	R1 = 0.0478, wR2 = 0.1100
R indices (all data)	R1 = 0.0699, wR2 = 0.1184
Absolute structure parameter	0.15(4)
Extinction coefficient	0.013(3)
Largest diff. peak and hole	0.201 and -0.399 $e.Å^{-3}$

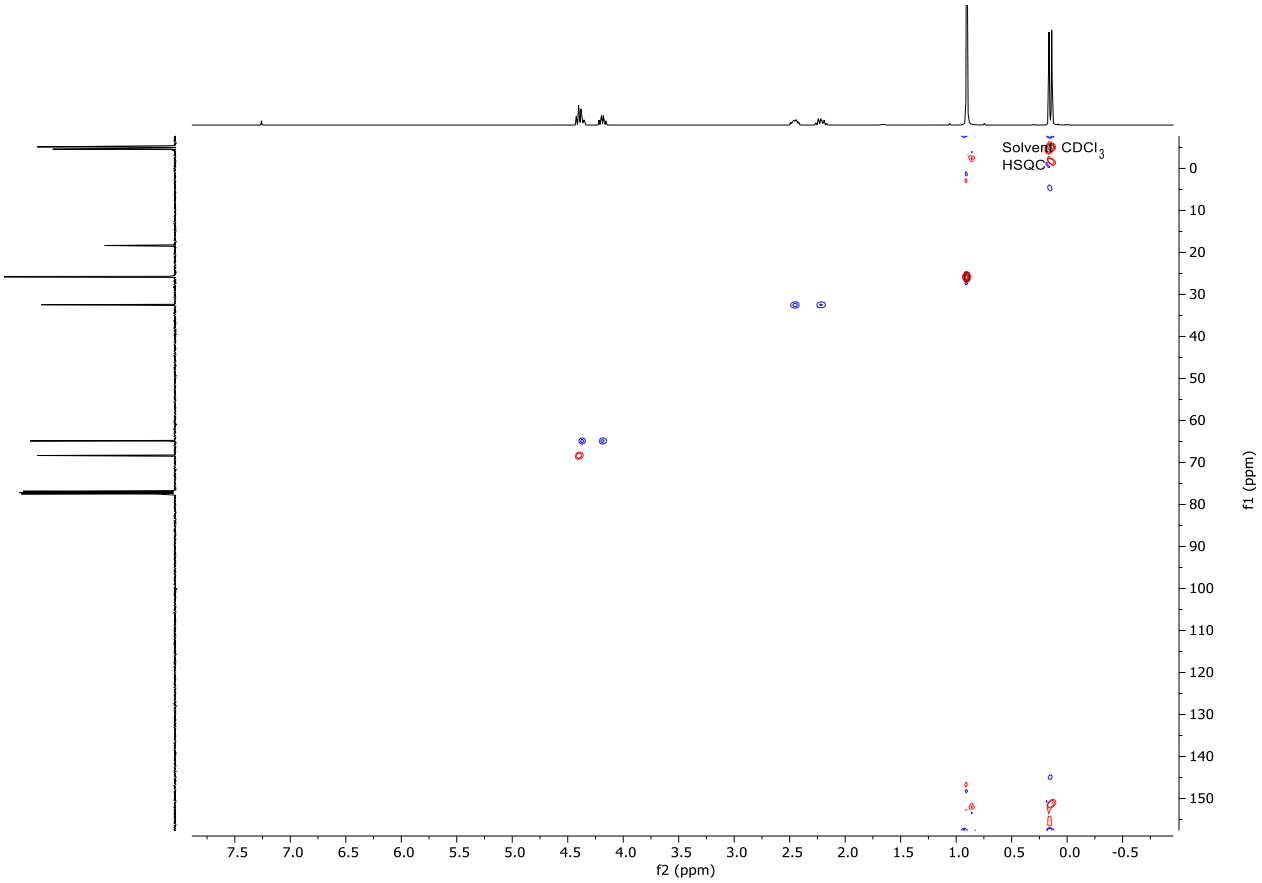
3.3.7 ^{1}H and ^{13}C NMR Spectra

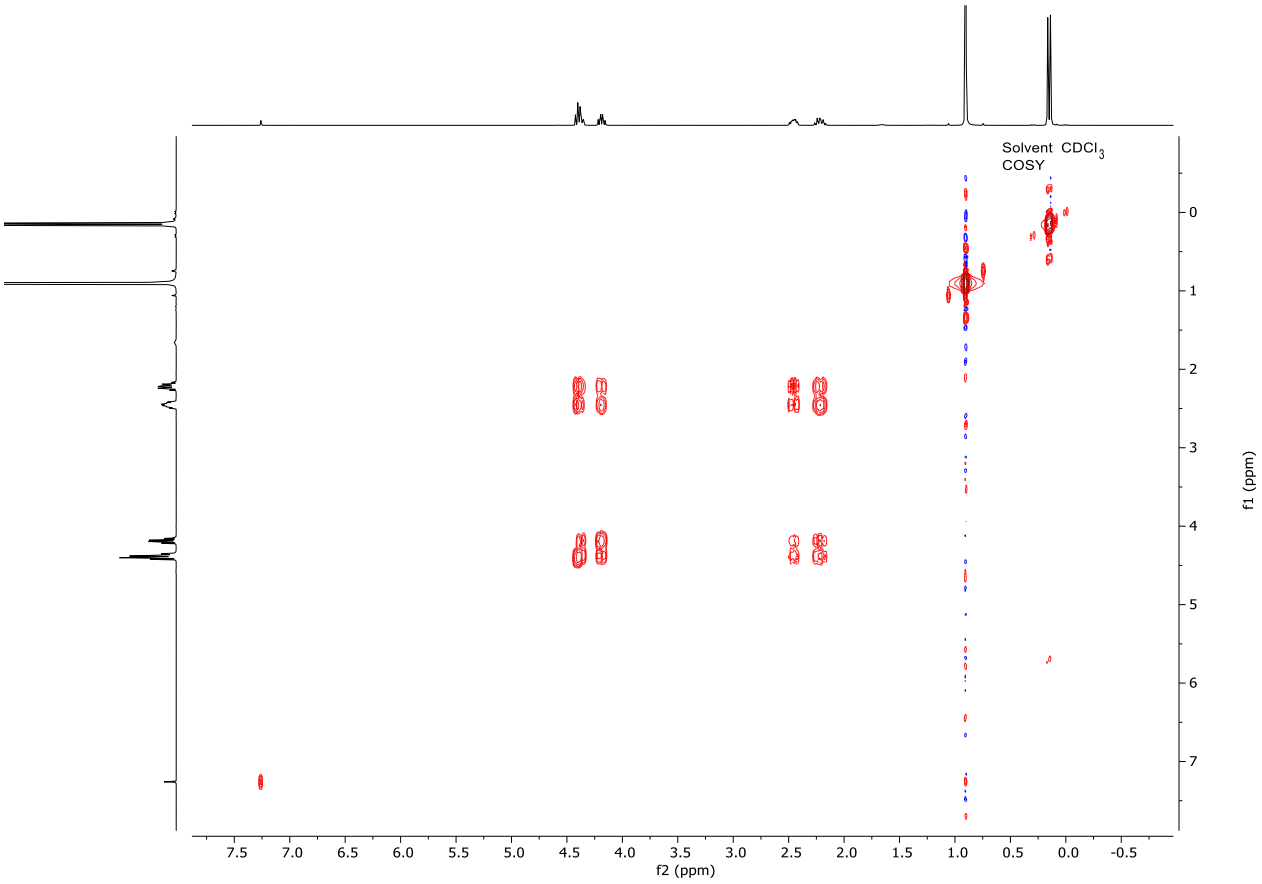

OTBS
O
O

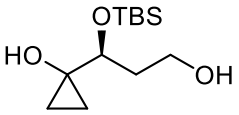
224

Solvent CDCl3
MHz 400
Nucleus 1H
2.00
1.02
1.02
1.01
9.15
2.97
2.95
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)

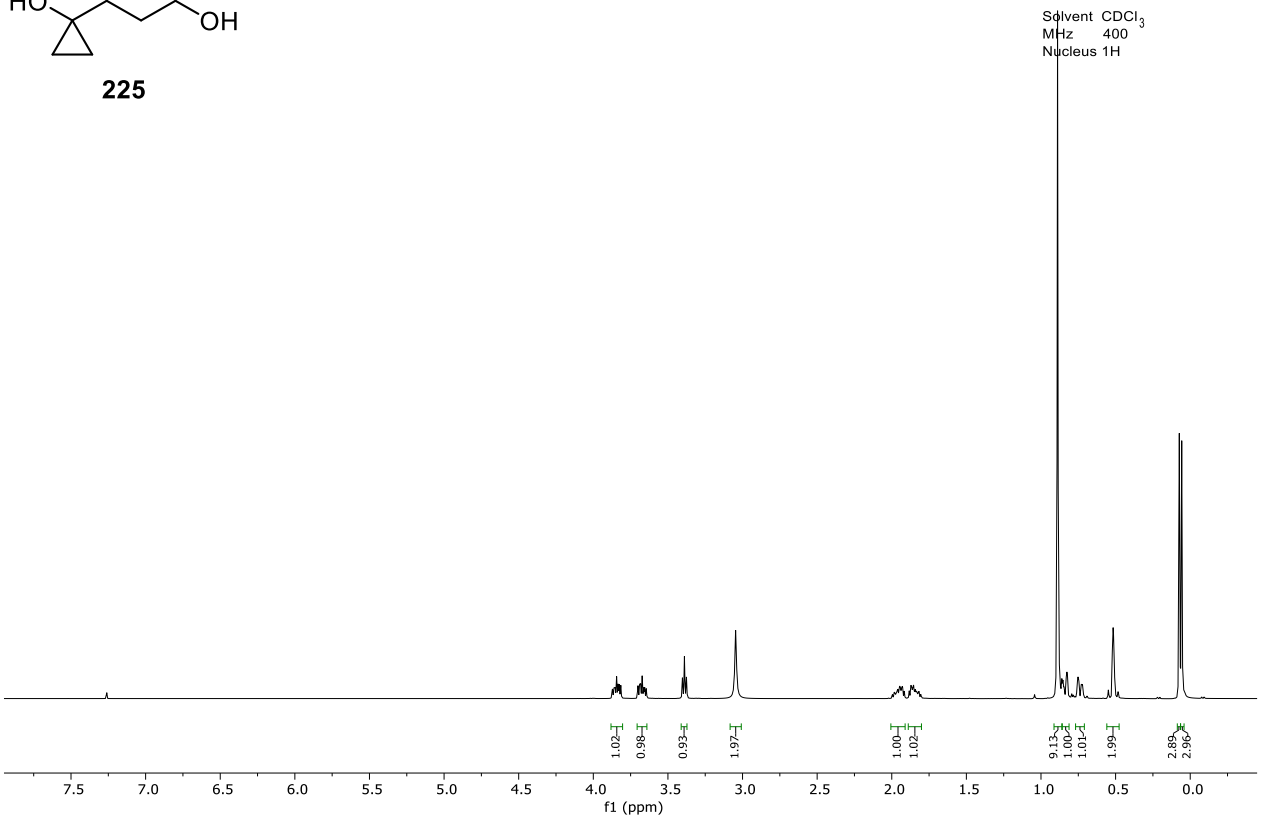

176.1
68.3
64.9
32.4
25.8
18.3
-4.6
-5.1
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

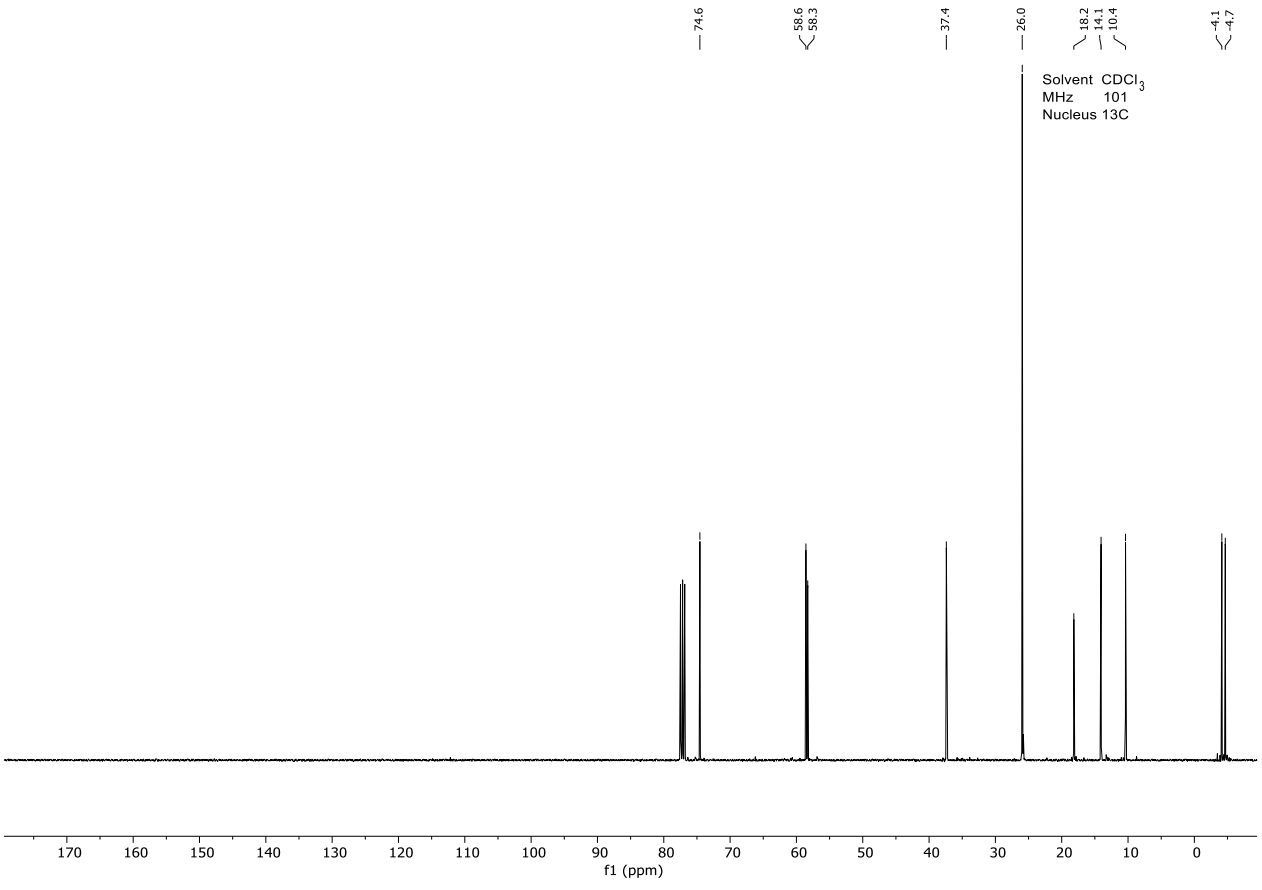

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

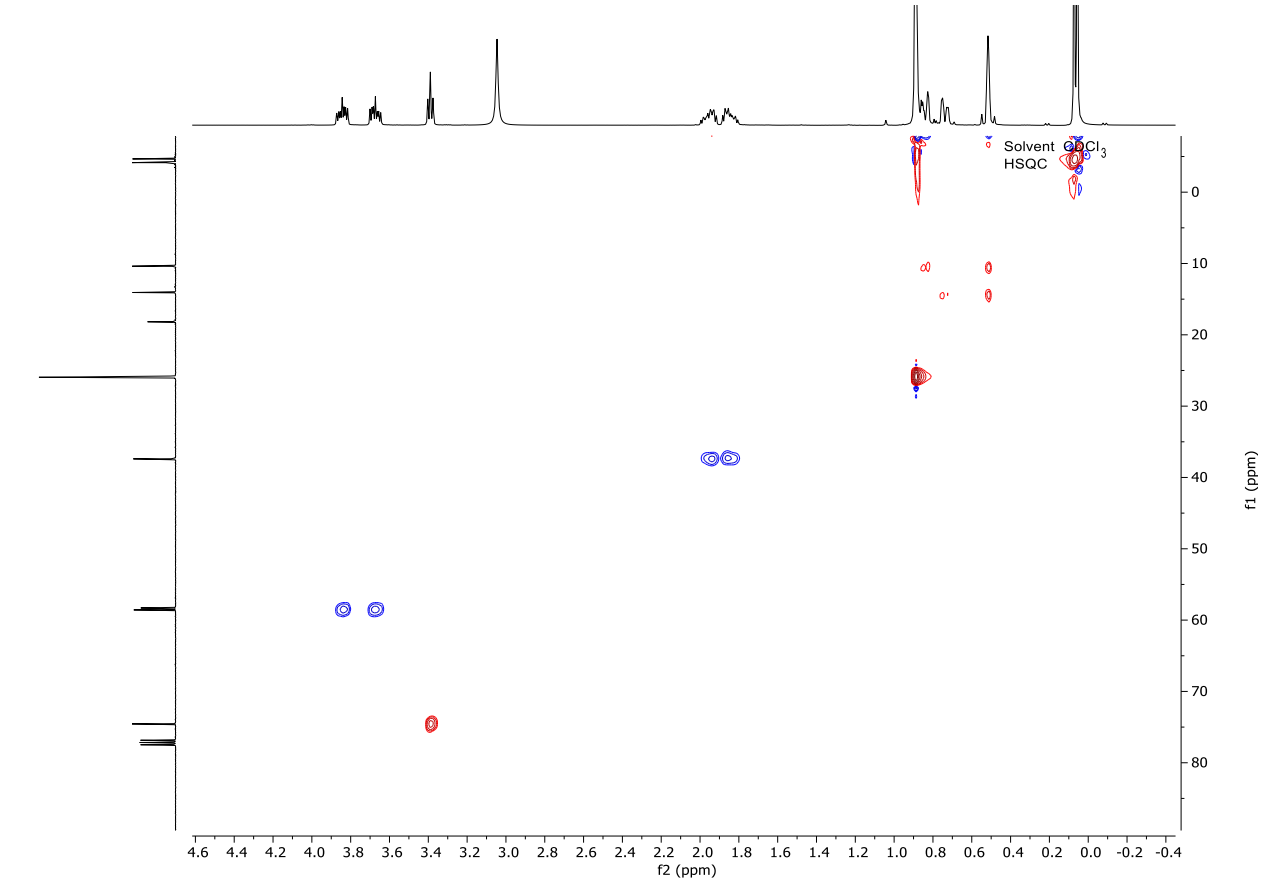

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

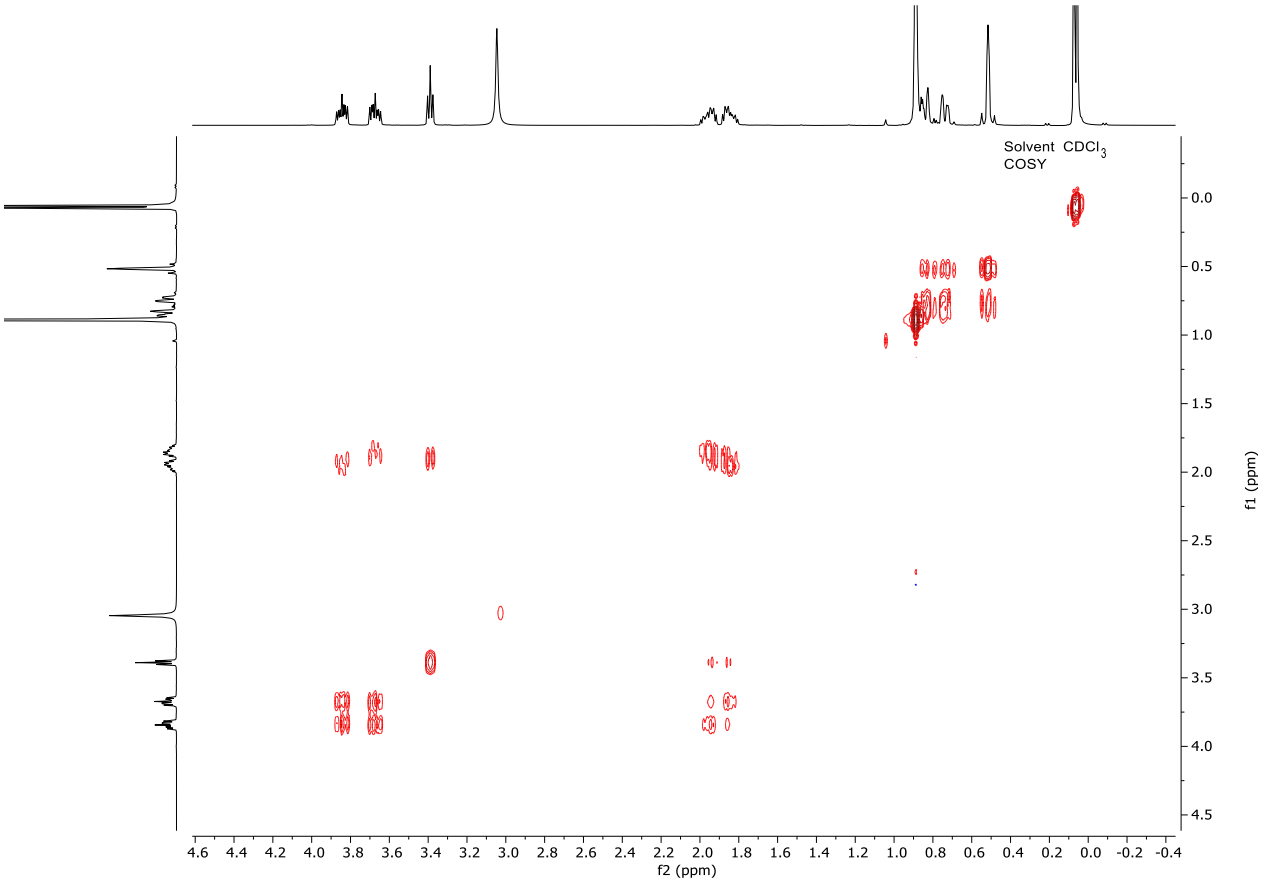

OTBS
HO
OH

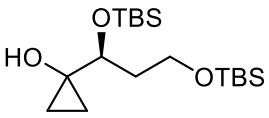
225


Solvent CDCl3
MHz 400
Nucleus 1H
1.02
0.98
0.93
1.97
1.00
1.02
9.13
1.00
1.01
1.99
2.89
2.96
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)

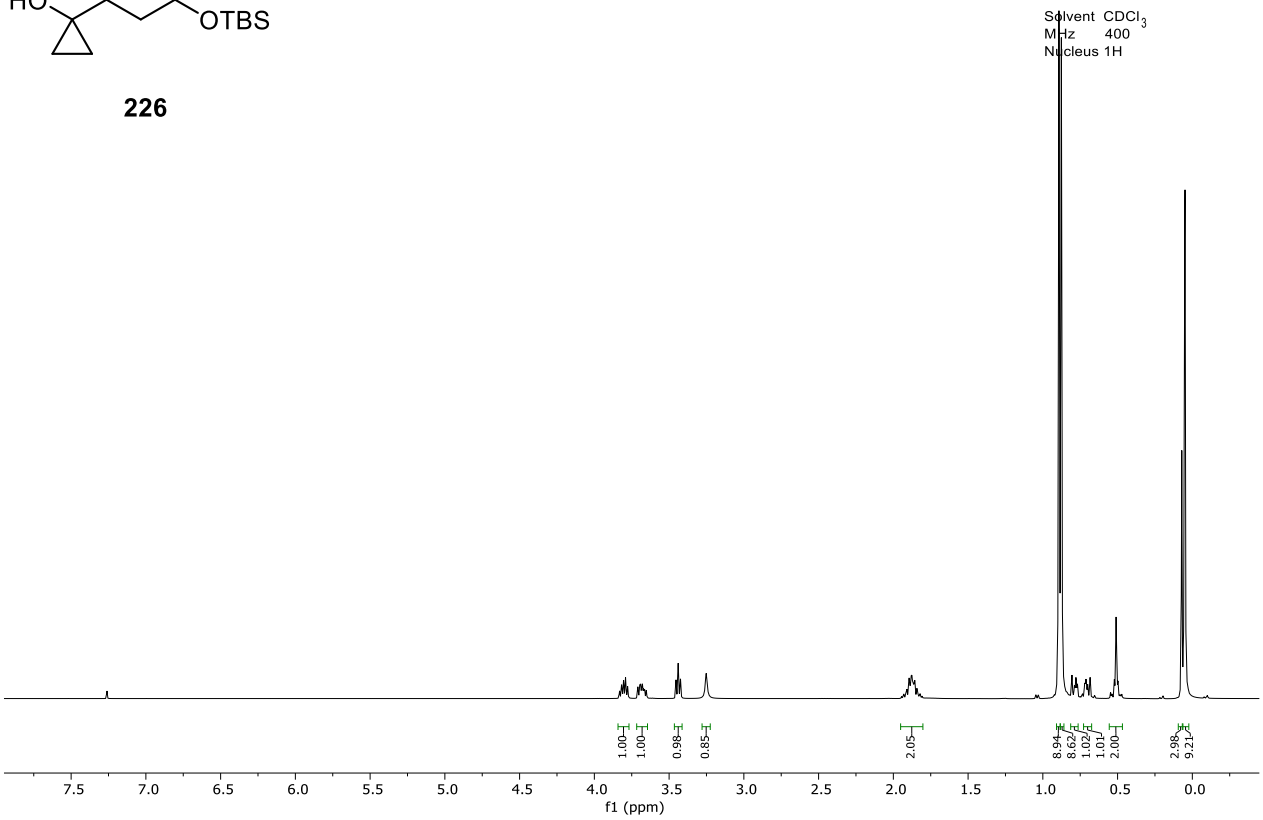

74.6
58.6
58.3
37.4
26.0
18.2
14.1
10.4
-4.1
-4.7
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

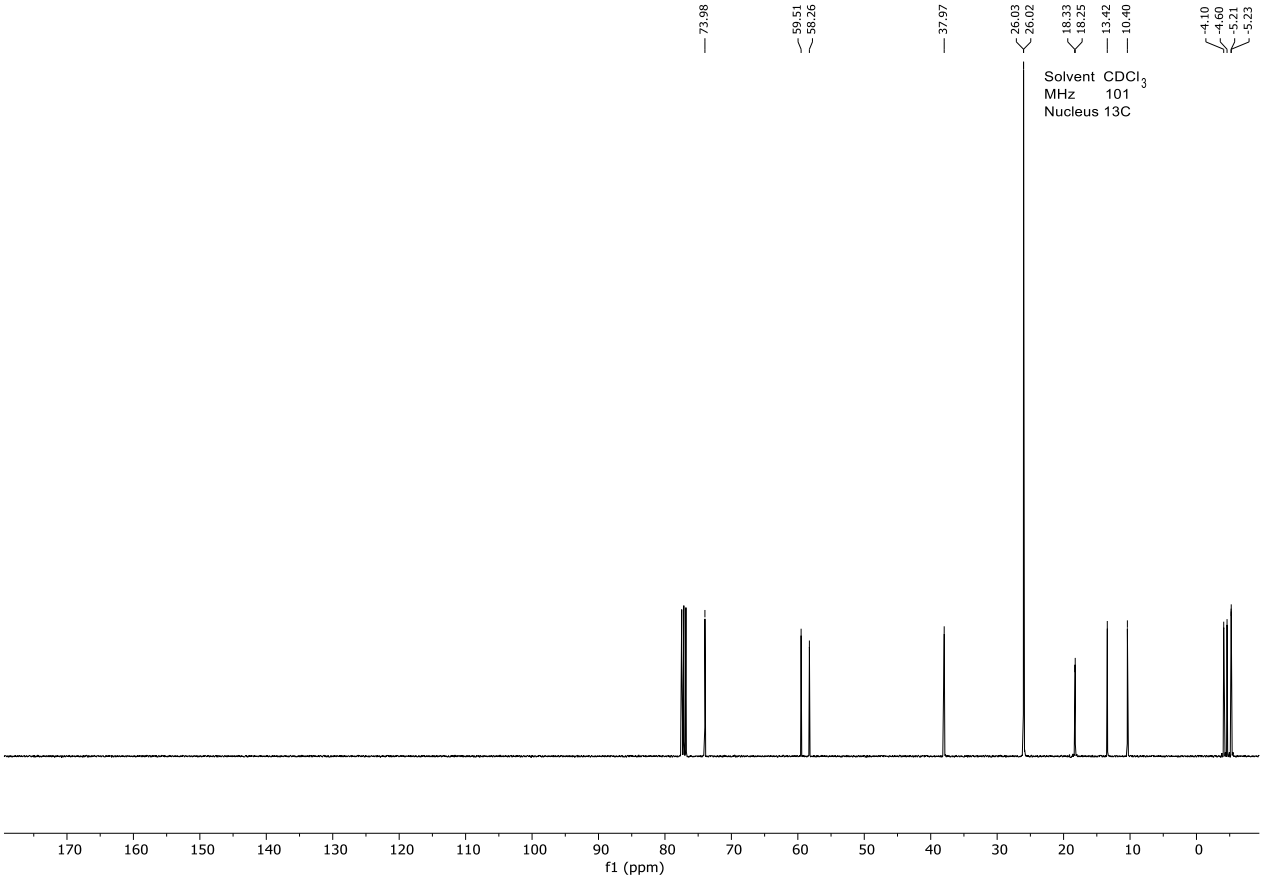

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

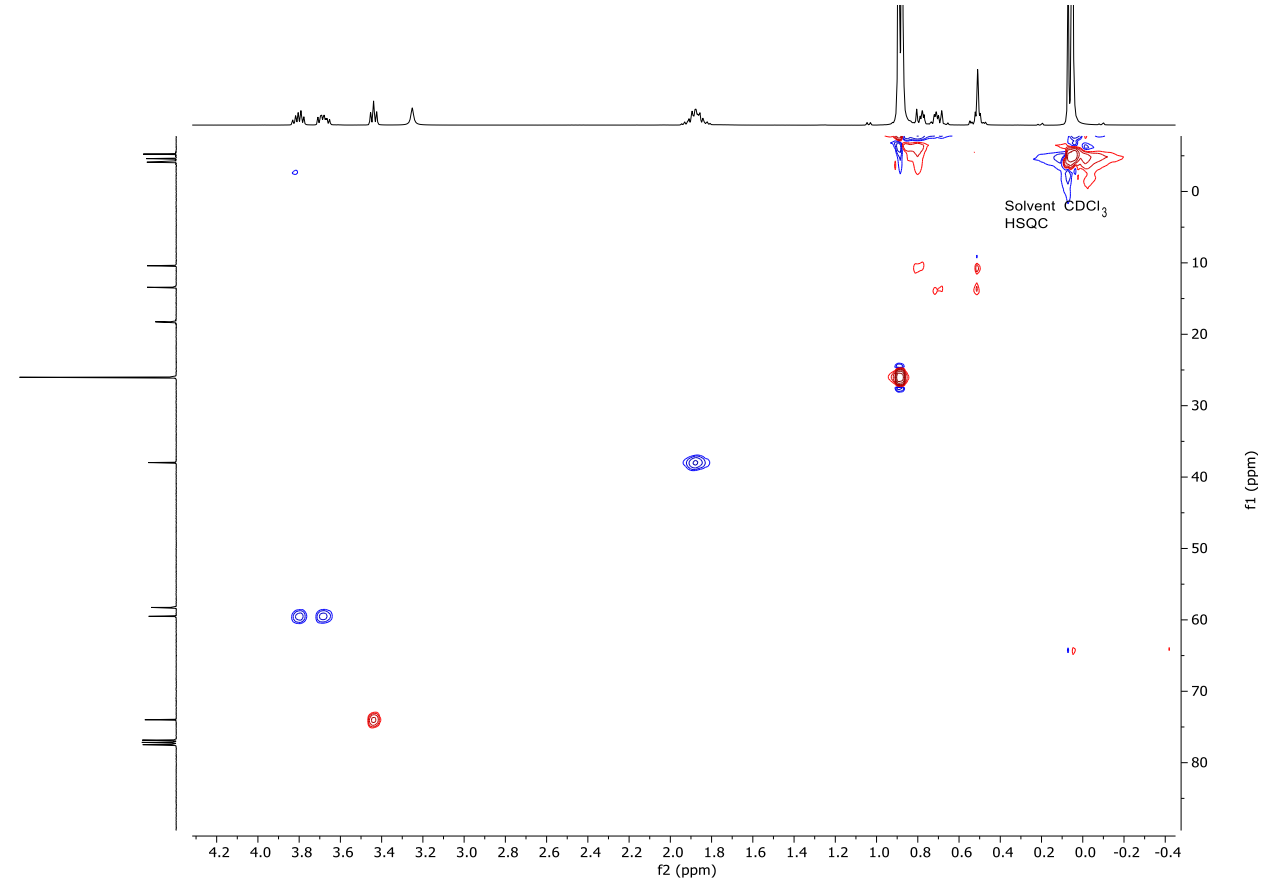

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

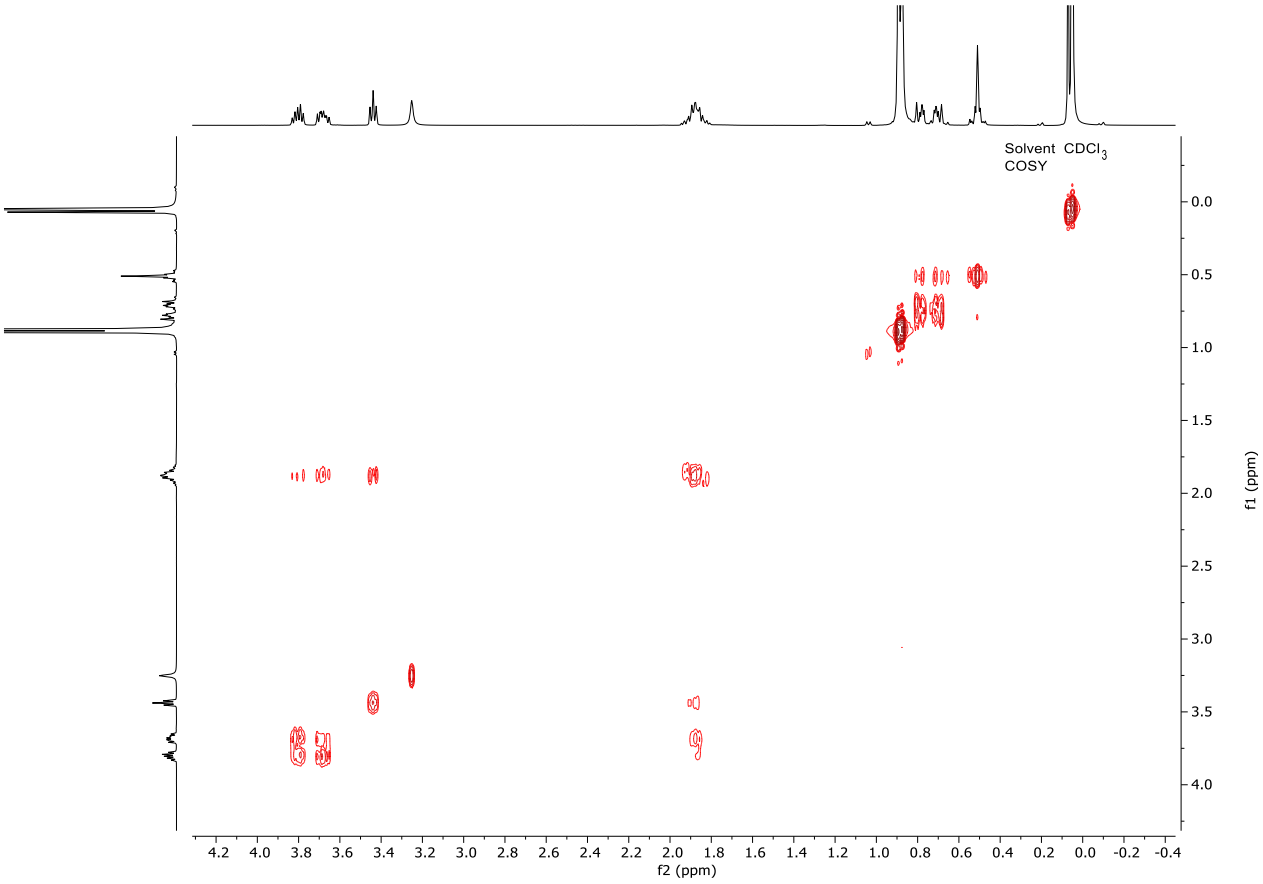

OTBS
HO
OTBS

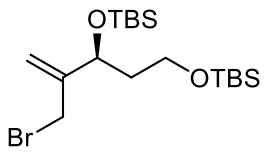
226


Solvent CDCl3
MHz 400
Nucleus 1H
1.00
1.00
0.98
0.85
2.05
8.94
8.62
1.02
1.01
2.00
2.98
9.21
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)


73.98
59.51
58.26
37.97
26.03
26.02
18.33
18.25
13.42
10.40
-4.10
-4.60
-5.21
-5.23
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

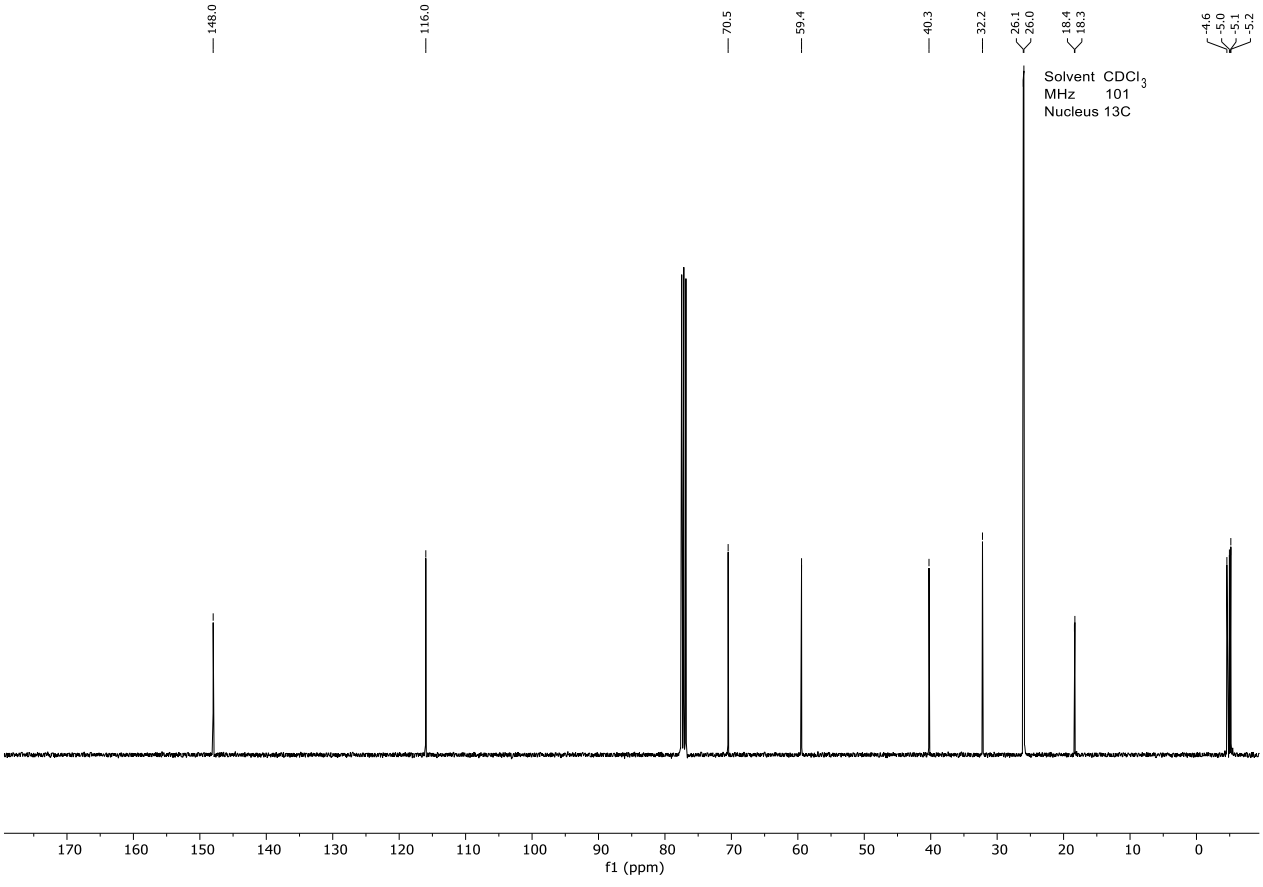

Solvent CDCl3
HSQC
f2 (ppm)
f1 (ppm)

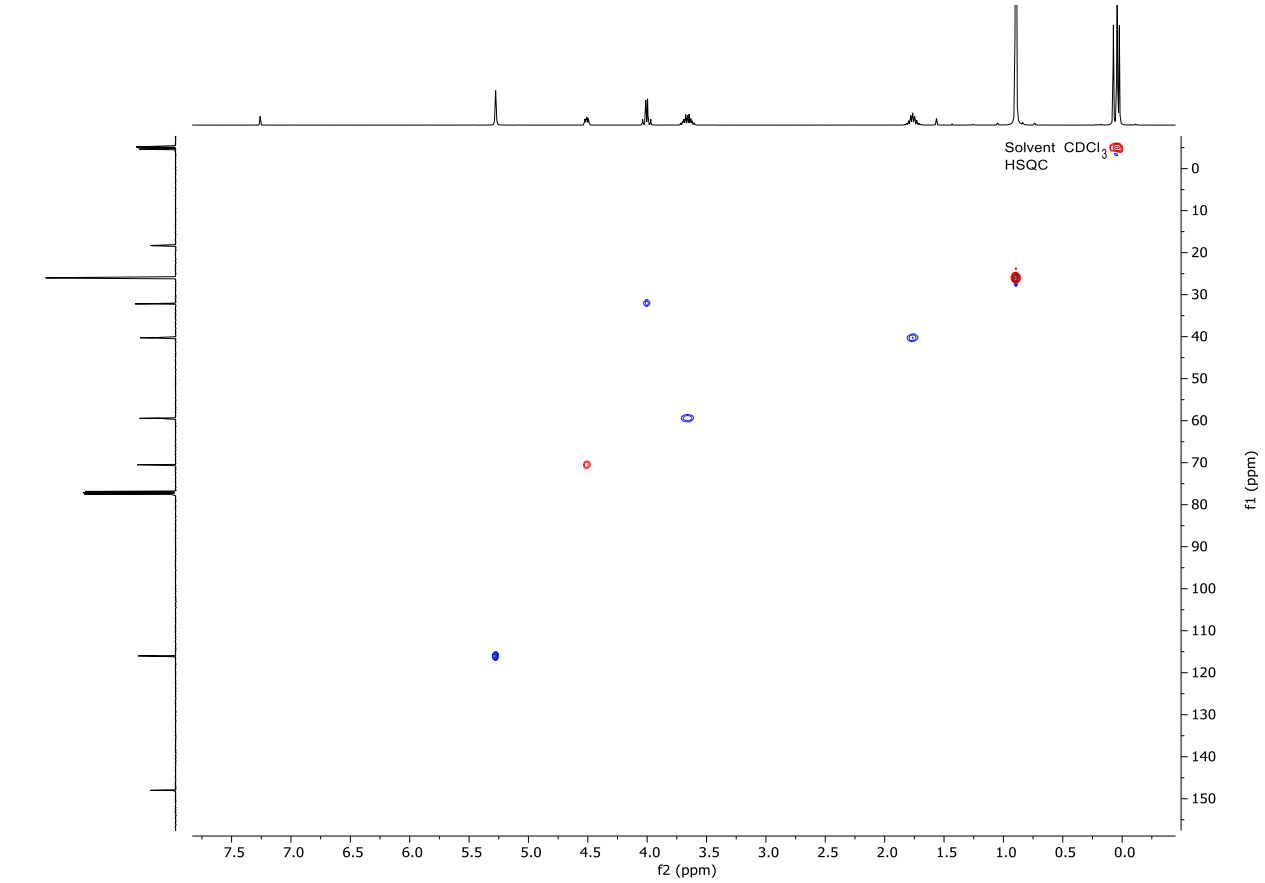

Solvent CDCl3
COSY
f2 (ppm)
f1 (ppm)

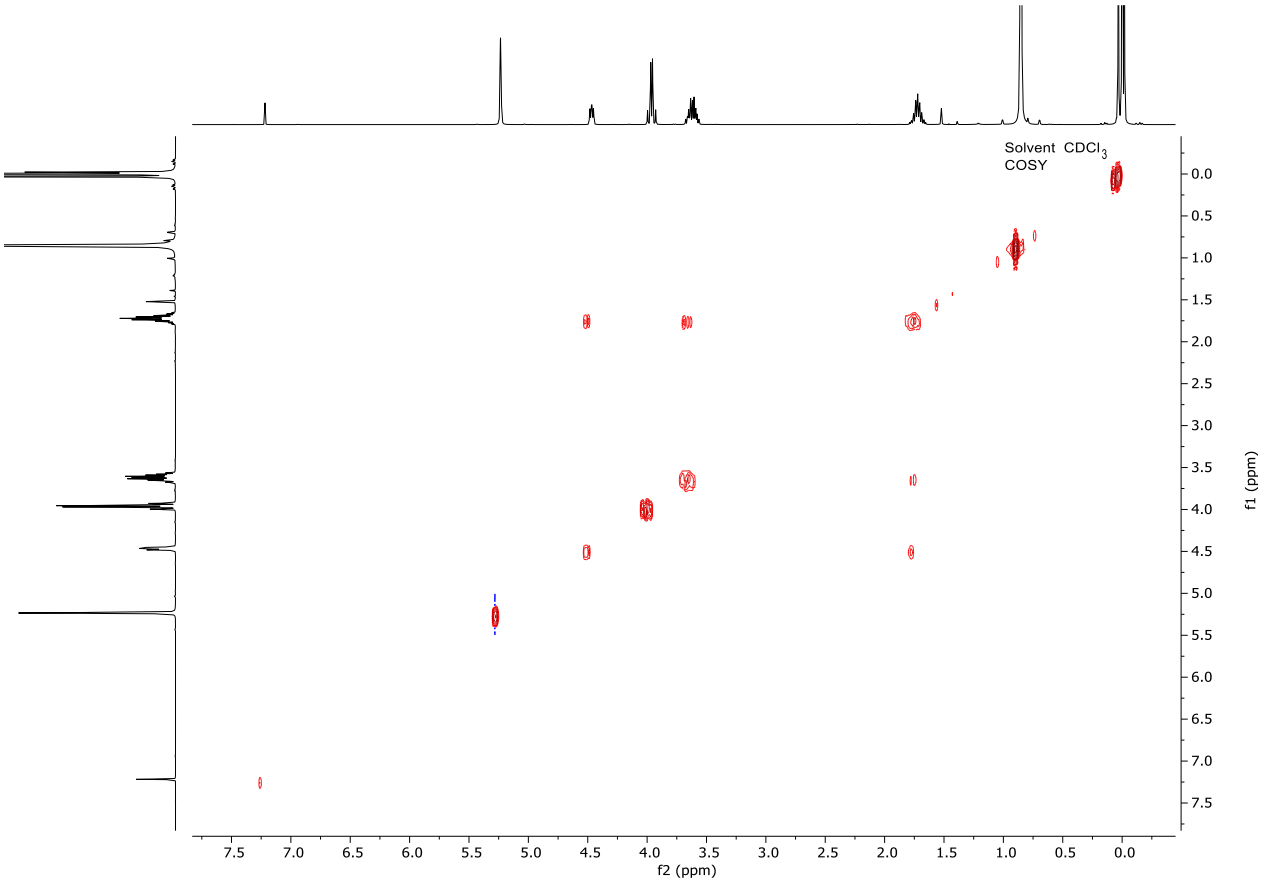

OTBS
OTBS
Br

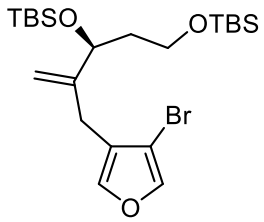
210

Solvent CDCl3
MHz 400
Nucleus 1H
1.99
0.98
2.01
2.05
2.00
8.97
8.81
3.03
5.86
3.10
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)


148.0
116.0
70.5
59.4
40.3
32.2
26.1
26.0
18.4
18.3
-4.6
-5.0
-5.1
-5.2
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

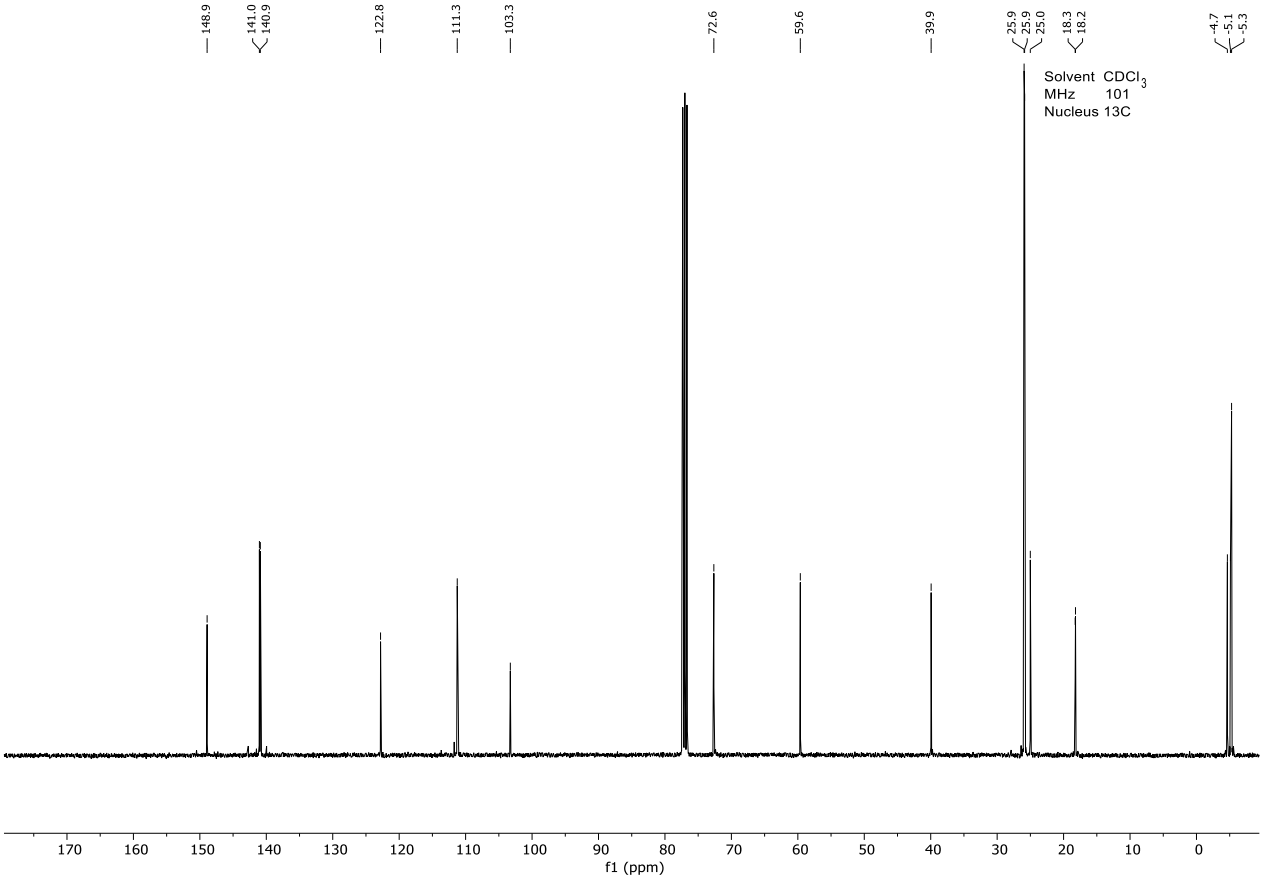

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

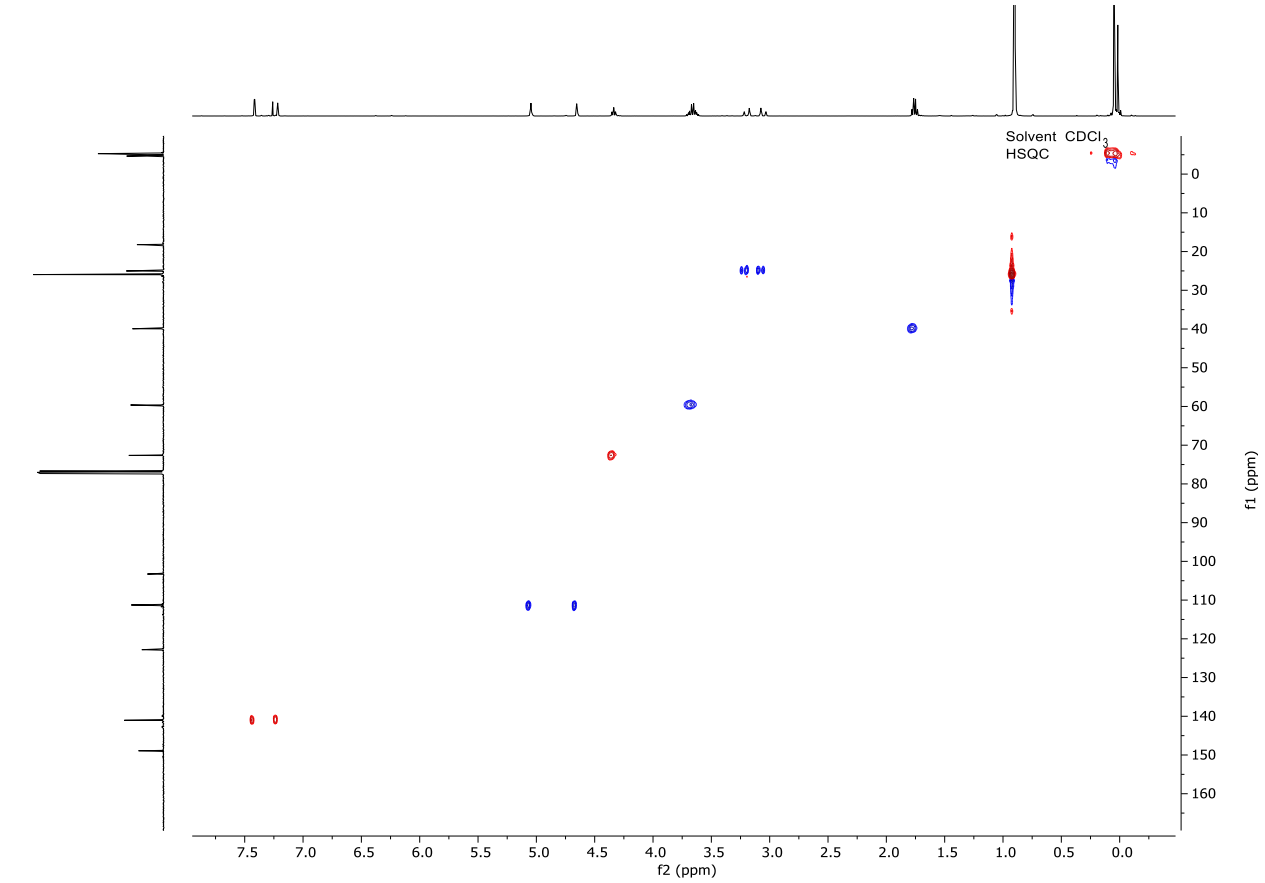

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

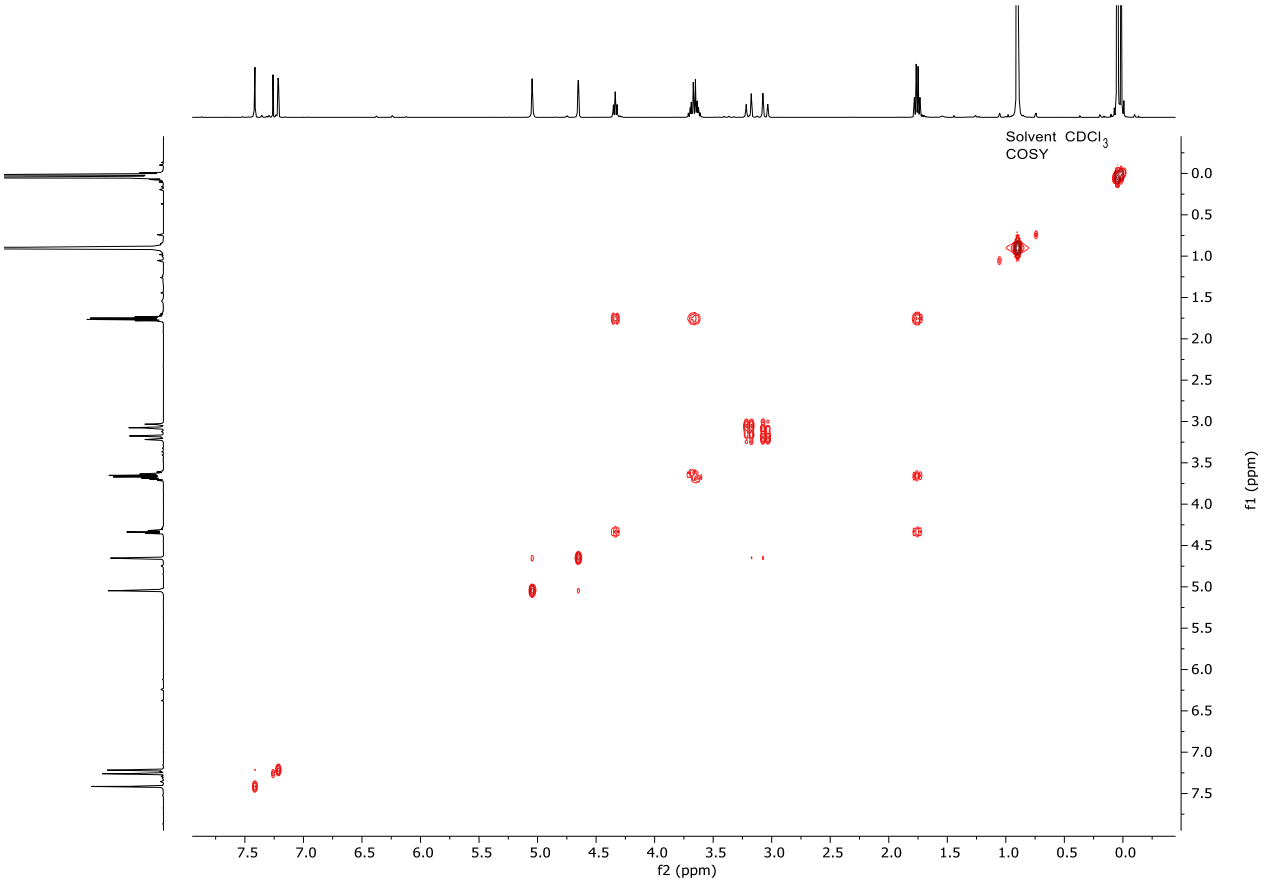

TBSO
OTBS
Br
O

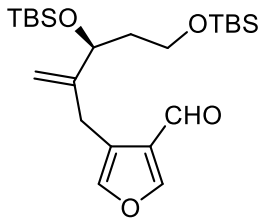
227

Solvent CDCl3
MHz 400
Nucleus 1H
0.90
0.90
1.08
1.02
1.00
2.19
1.03
1.01
2.01
9.07
9.27
9.22
2.71
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)


148.9
141.0
140.9
122.8
111.3
103.3
72.6
59.6
39.9
25.9
25.9
25.0
18.3
18.2
-4.7
-5.1
-5.3
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

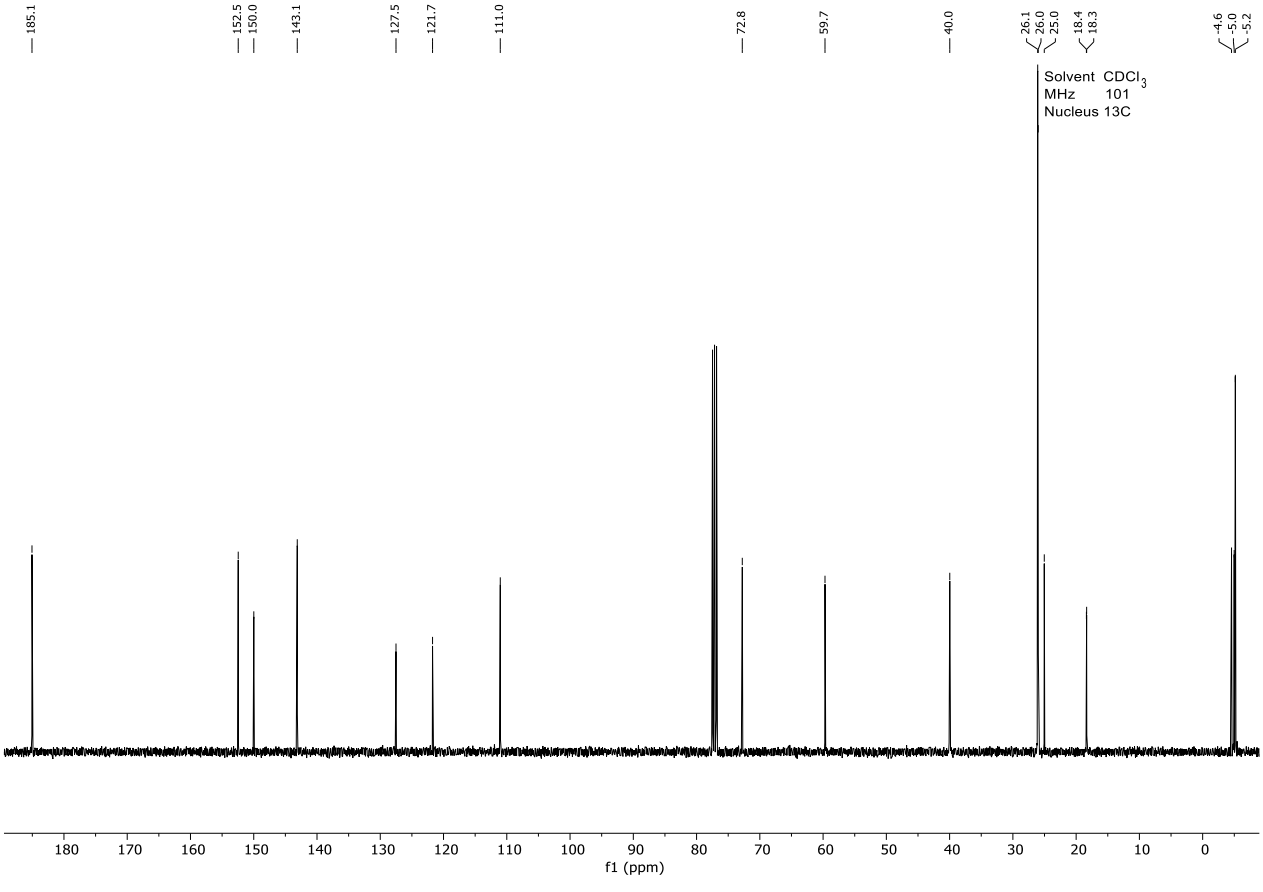

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

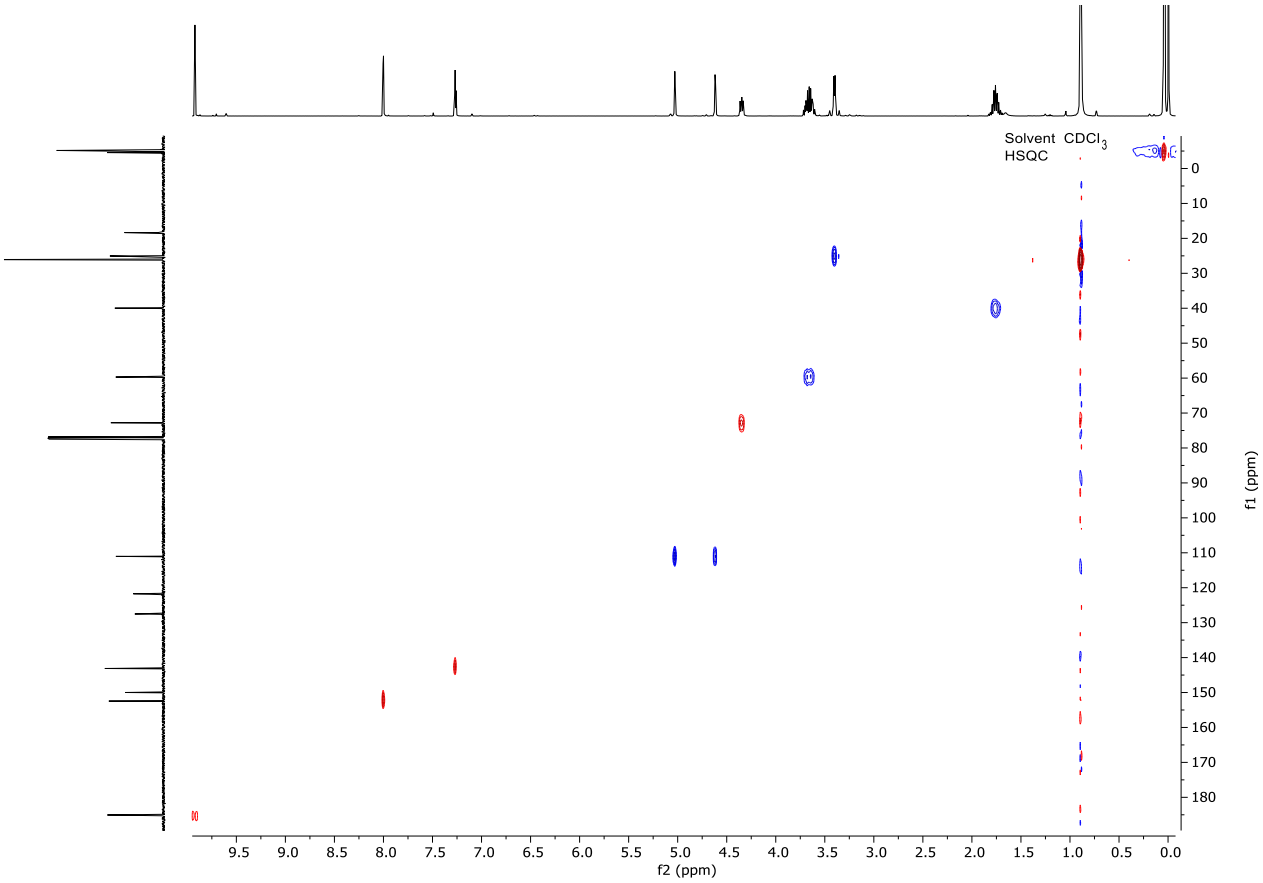

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

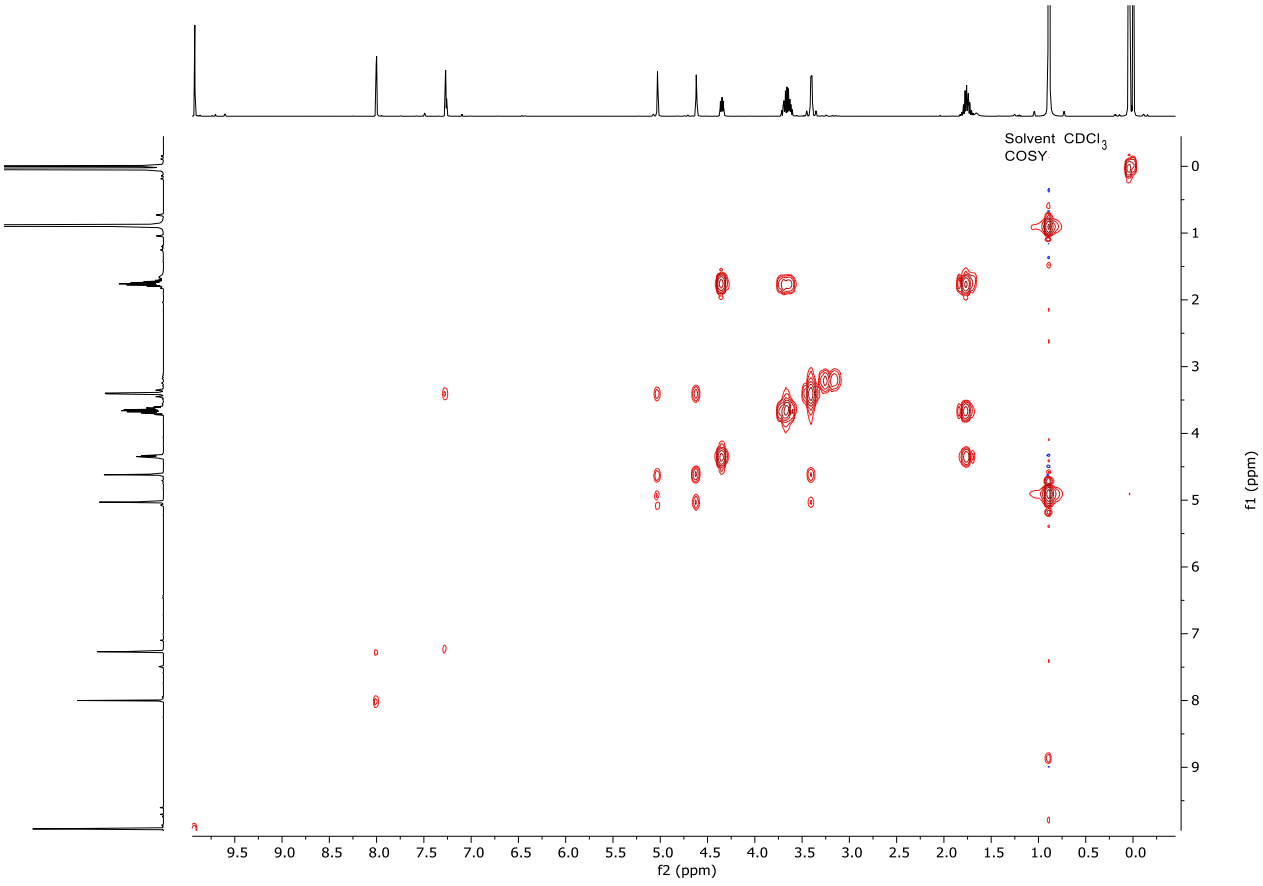

TBSO
OTBS
CHO
O

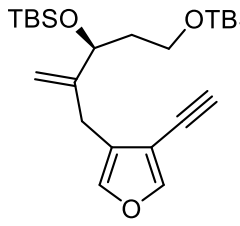
228

Solvent CDCl3
MHz 400
Nucleus 1H
0.94
0.94
0.91
1.00
1.02
1.04
2.19
2.06
2.13
9.34
8.95
2.95
2.94
3.08
2.82
f1 (ppm)


185.1
152.5
150.0
143.1
127.5
121.7
111.0
72.8
59.7
40.0
26.1
26.0
25.0
18.4
18.3
-4.6
-5.0
-5.2
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

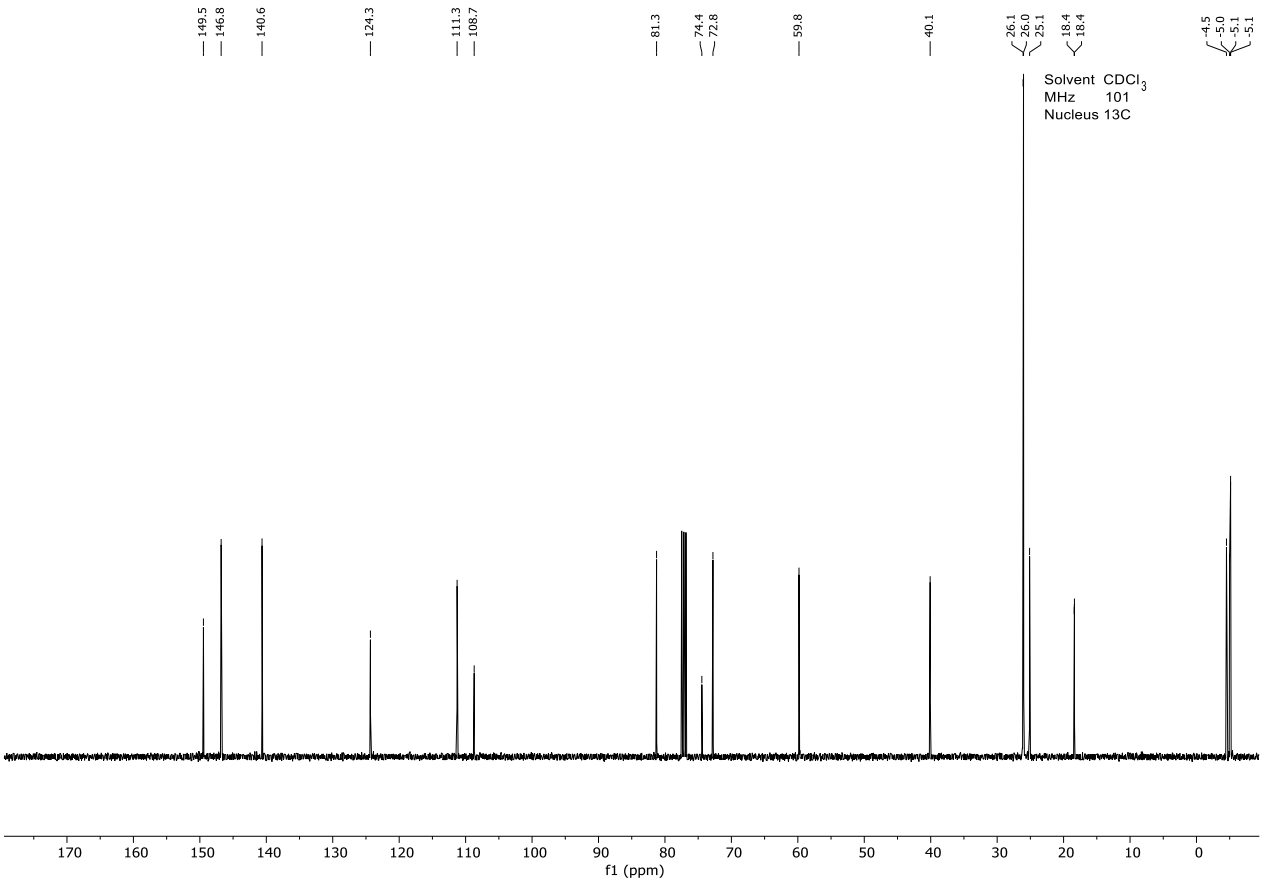

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

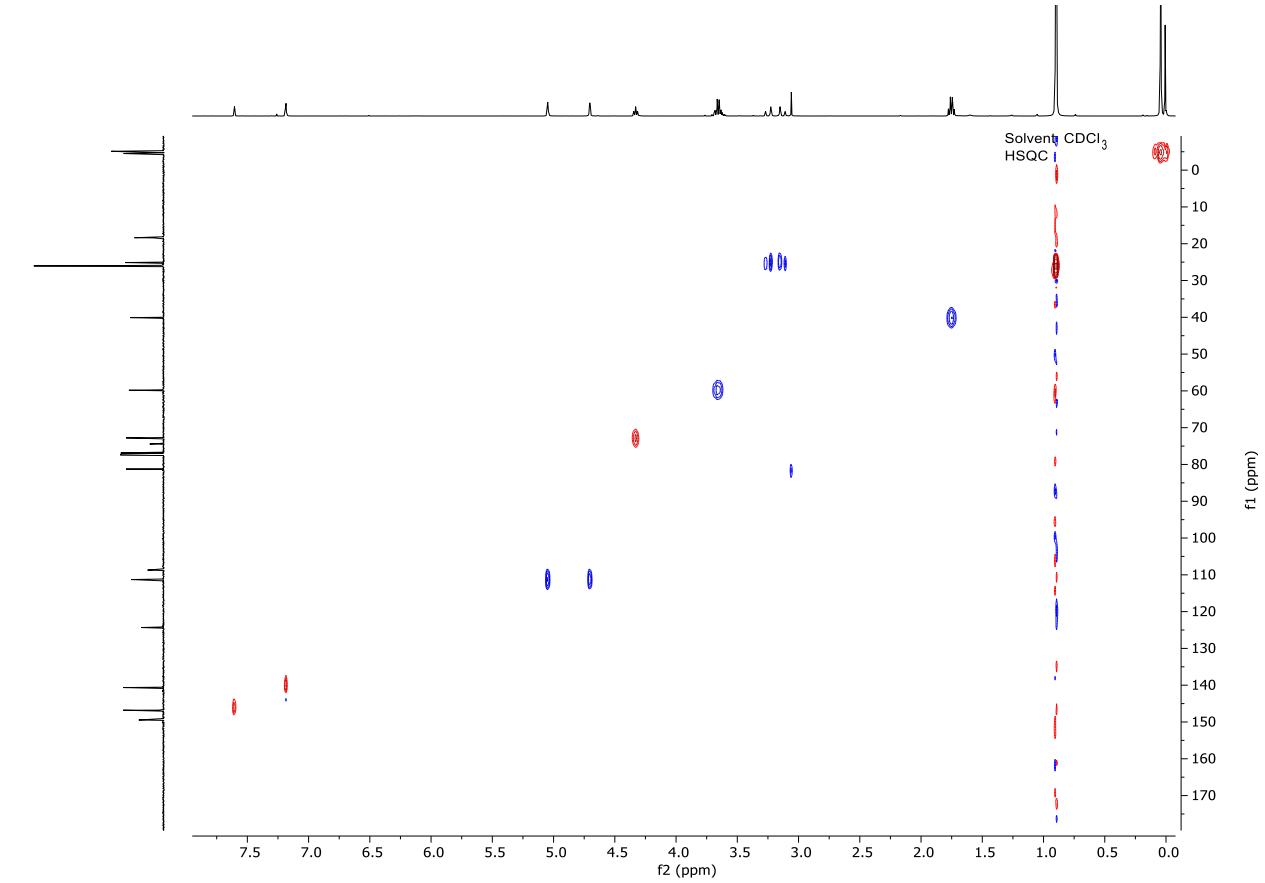

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

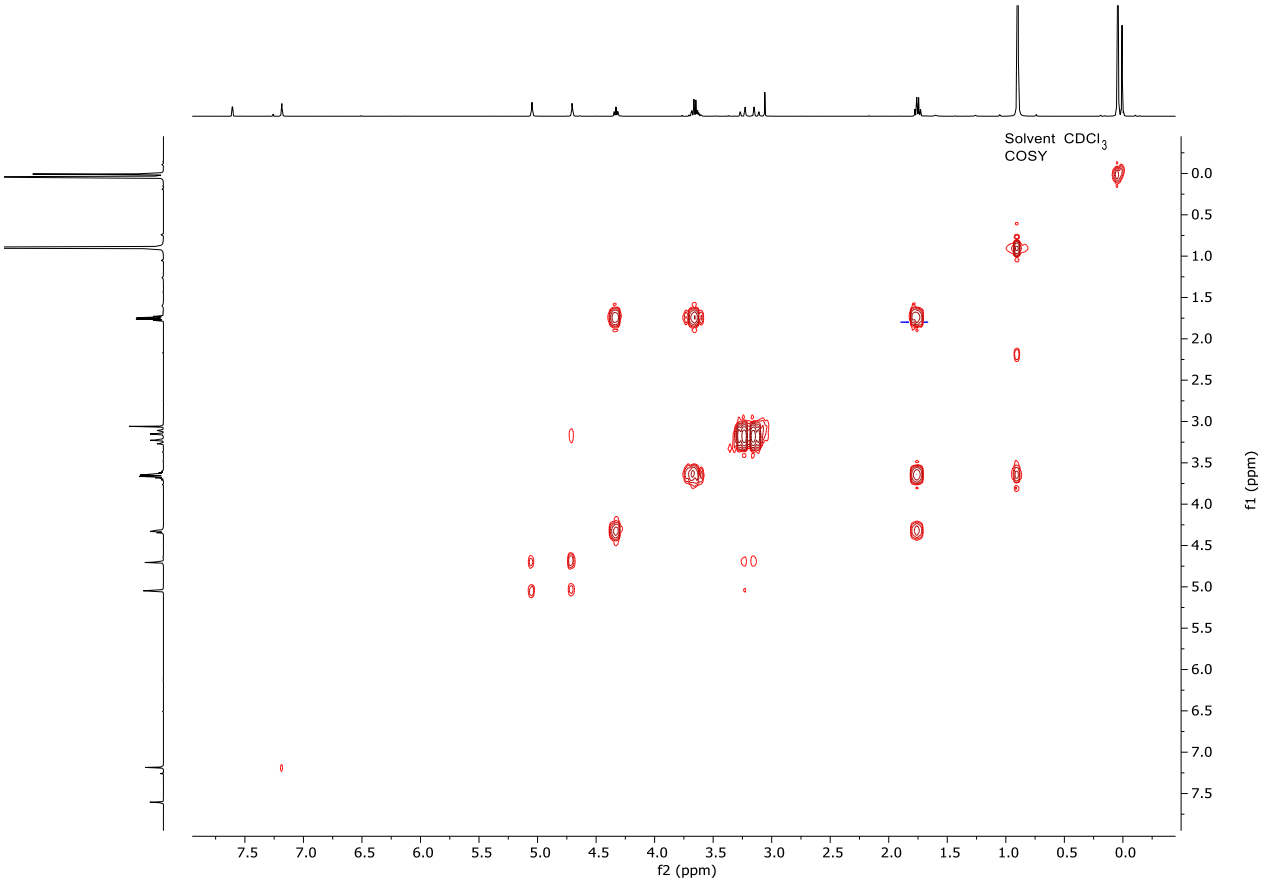

TBSO
OTBS
O

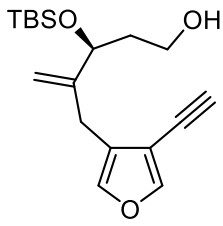
229

Solvent CDCl3
MHz 400
Nucleus 1H
0.61
1.00
1.19
1.08
1.17
2.27
1.13
1.13
0.79
2.32
9.09
9.45
9.38
3.13
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)


149.5
146.8
140.6
124.3
111.3
108.7
81.3
74.4
72.8
59.8
40.1
26.1
26.0
25.1
18.4
18.4
-4.5
-5.0
-5.1
-5.1
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

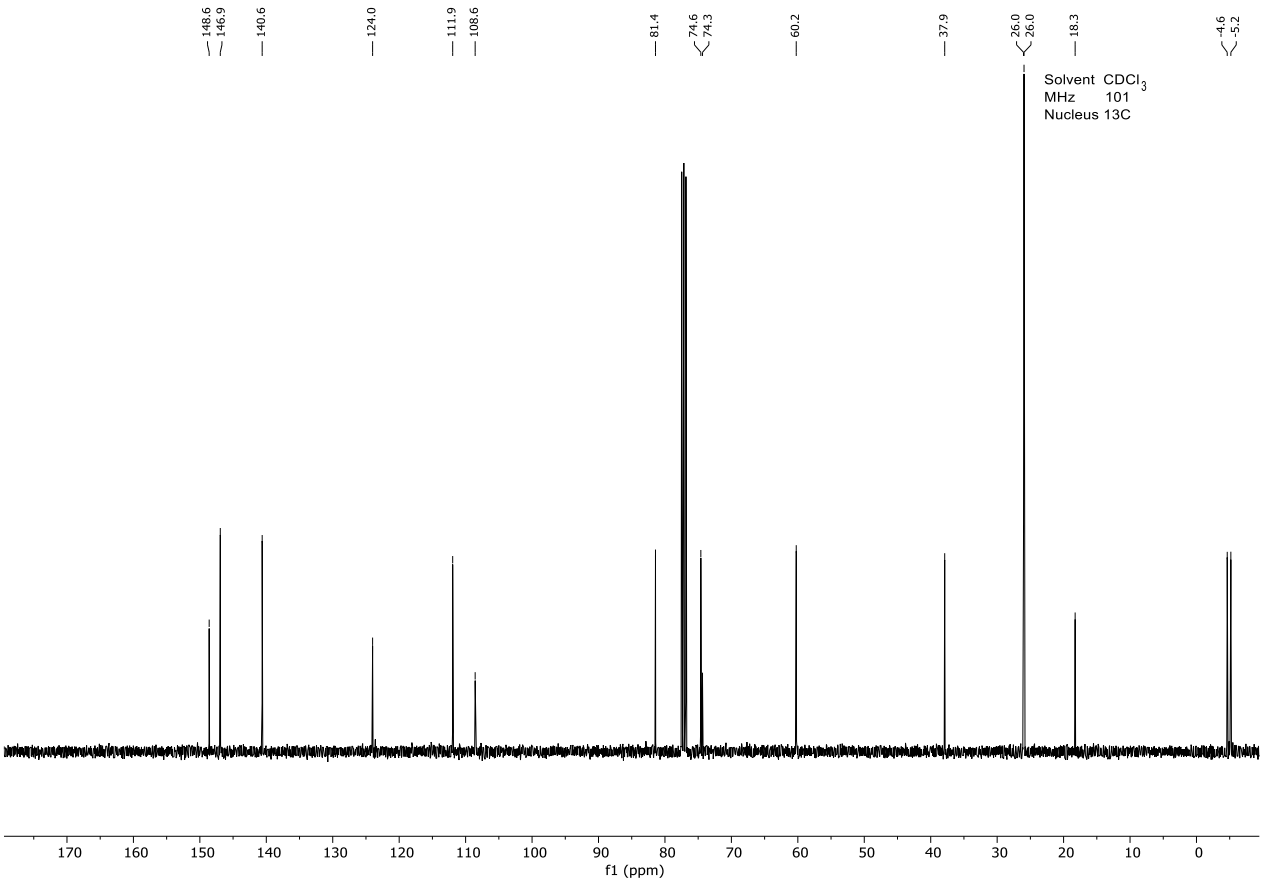

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

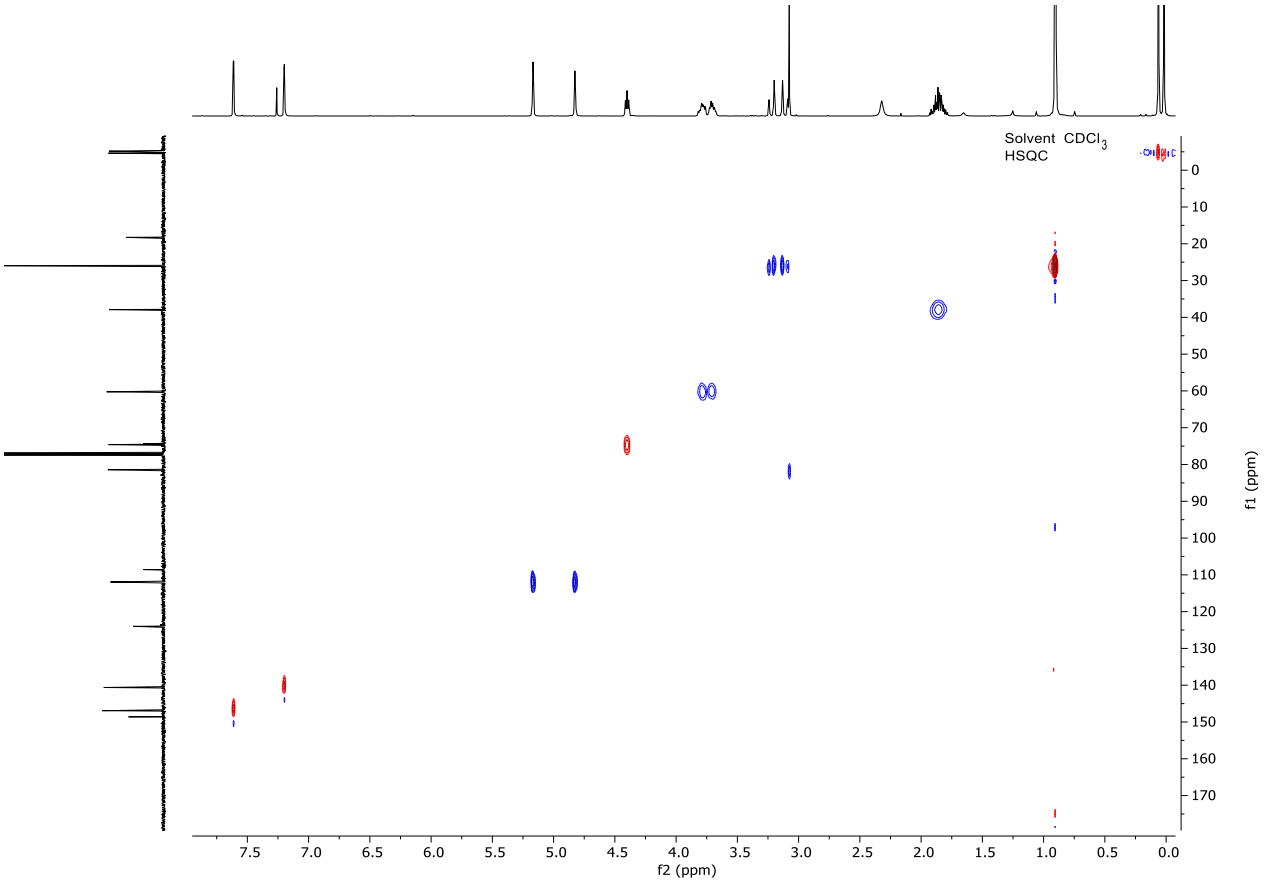

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

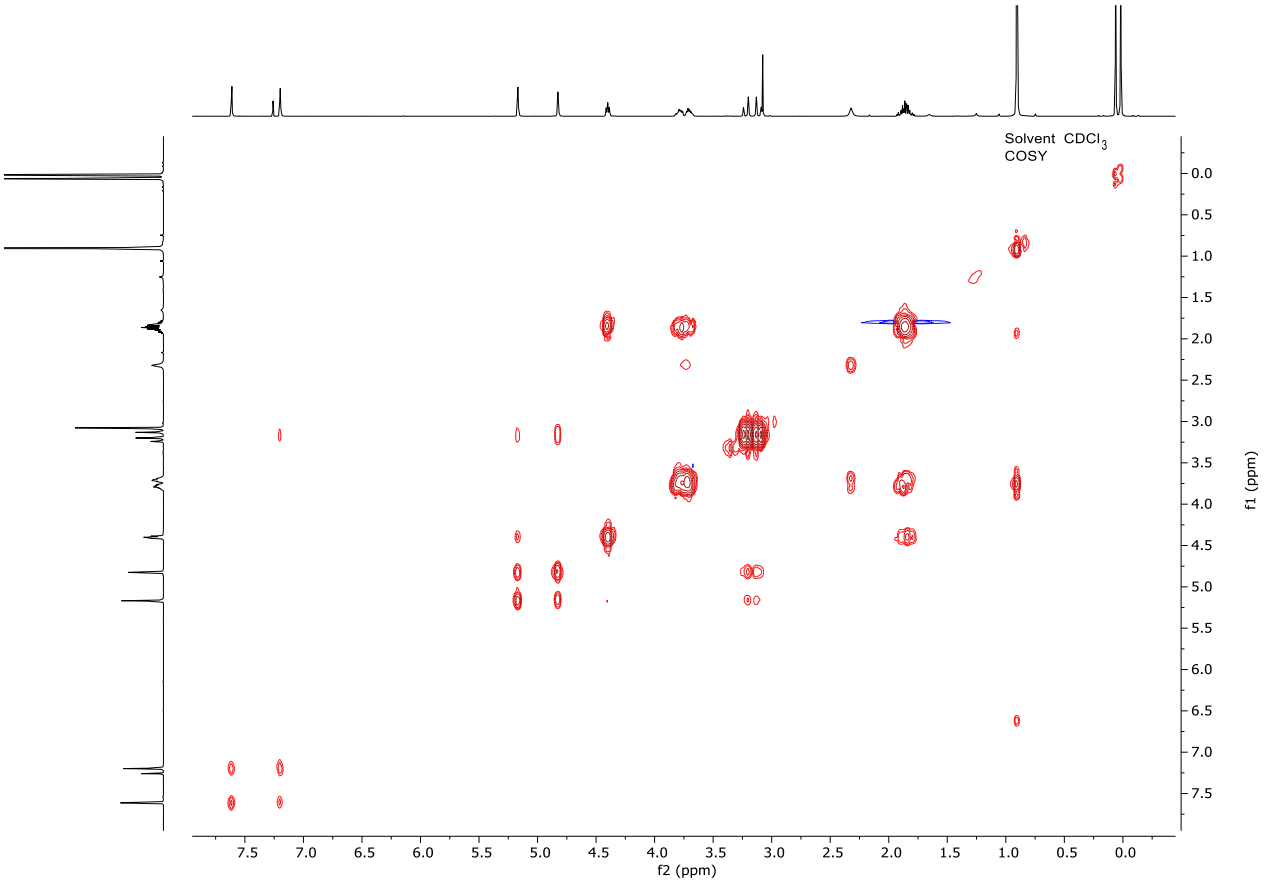

TBSO
OH
O

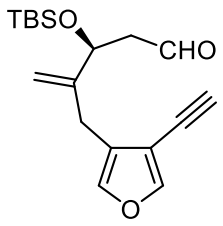
230

Solvent CDCl3
MHz 400
Nucleus 1H
0.88
0.91
1.00
0.98
0.97
0.98
1.01
0.98
1.01
0.83
0.89
1.98
8.87
2.92
2.89
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)


148.6
146.9
140.6
124.0
111.9
108.6
81.4
74.6
74.3
60.2
37.9
26.0
26.0
18.3
-4.6
-5.2
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

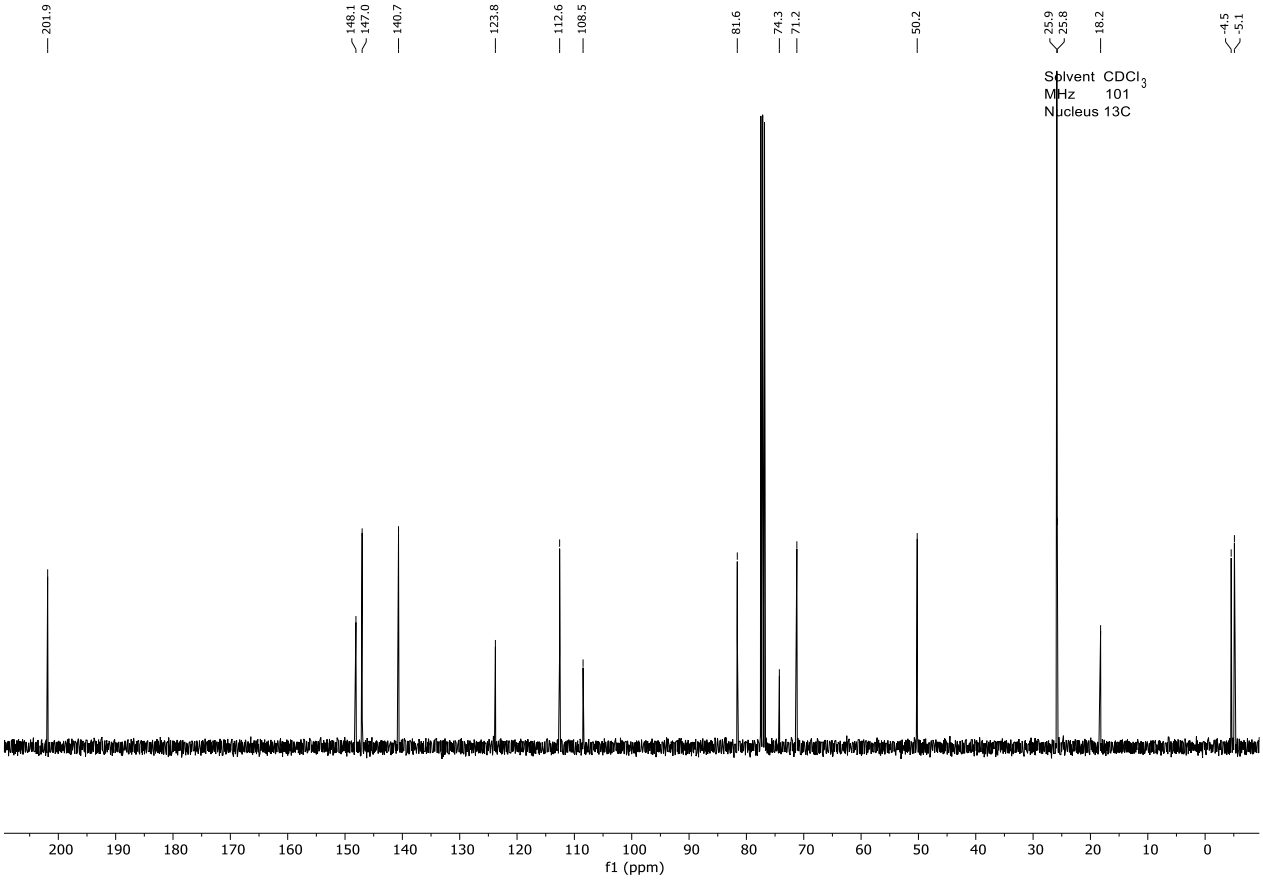

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

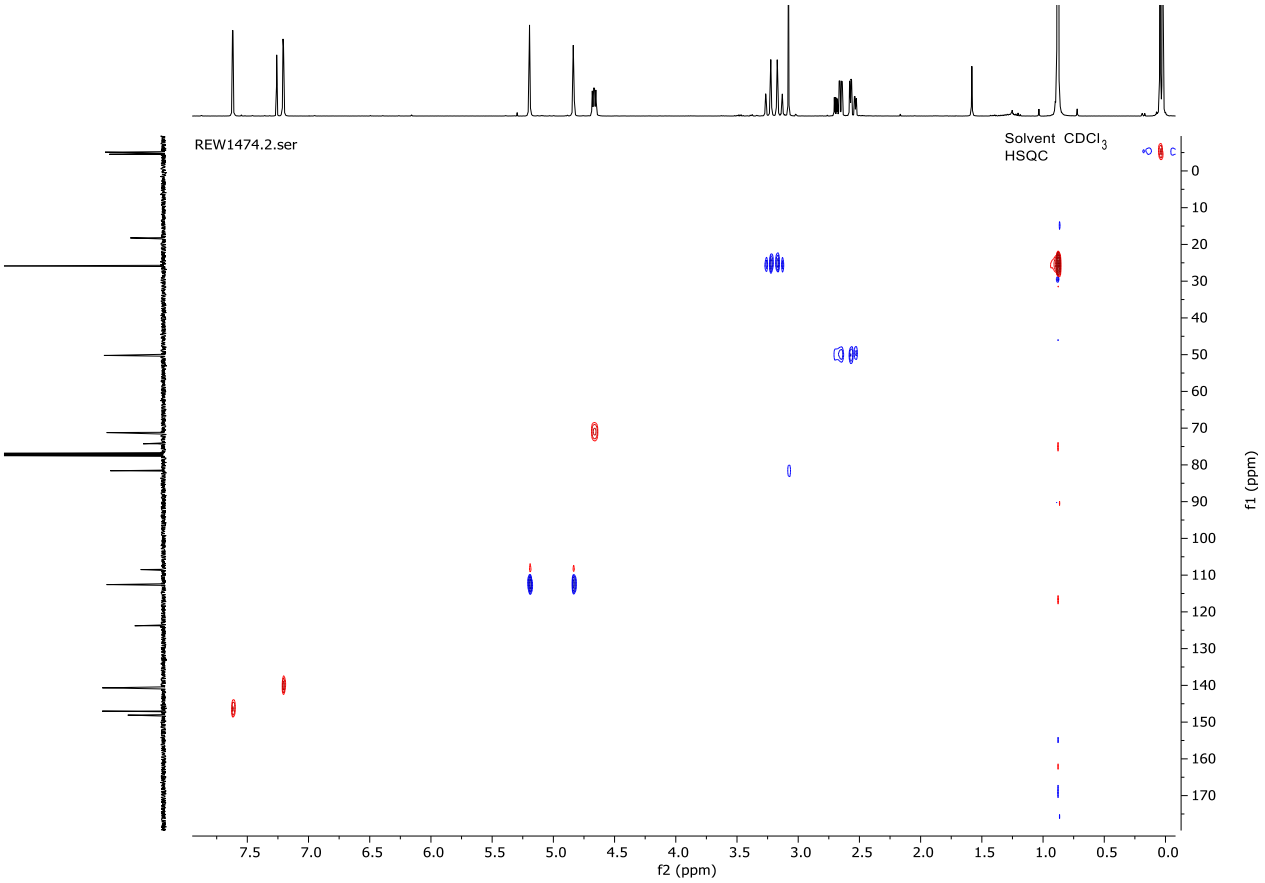

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

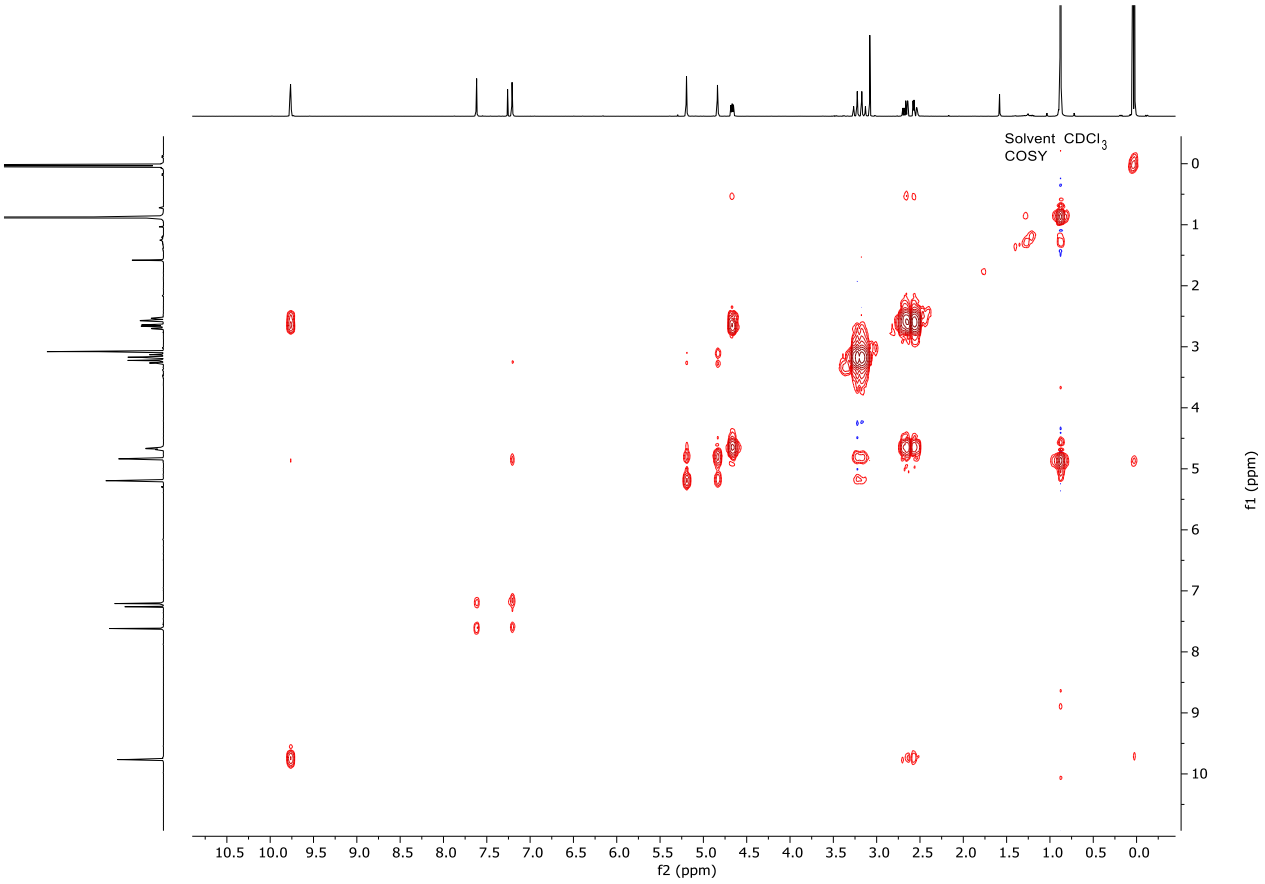

TBSO
CHO
O

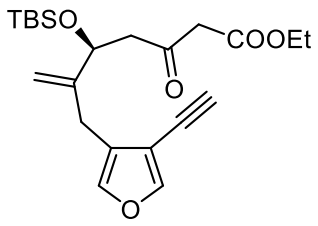
231

Solvent CDCl3
MHz 400
Nucleus 1H
0.92
0.89
0.93
1.00
0.99
0.97
0.99
1.00
0.89
0.98
0.99
8.98
2.93
2.94
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)


201.9
148.1
147.0
140.7
123.8
112.6
108.5
81.6
74.3
71.2
50.2
25.9
25.8
18.2
-4.5
-5.1
Solvent CDCl3
MHz 101
Nucleus 13C
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

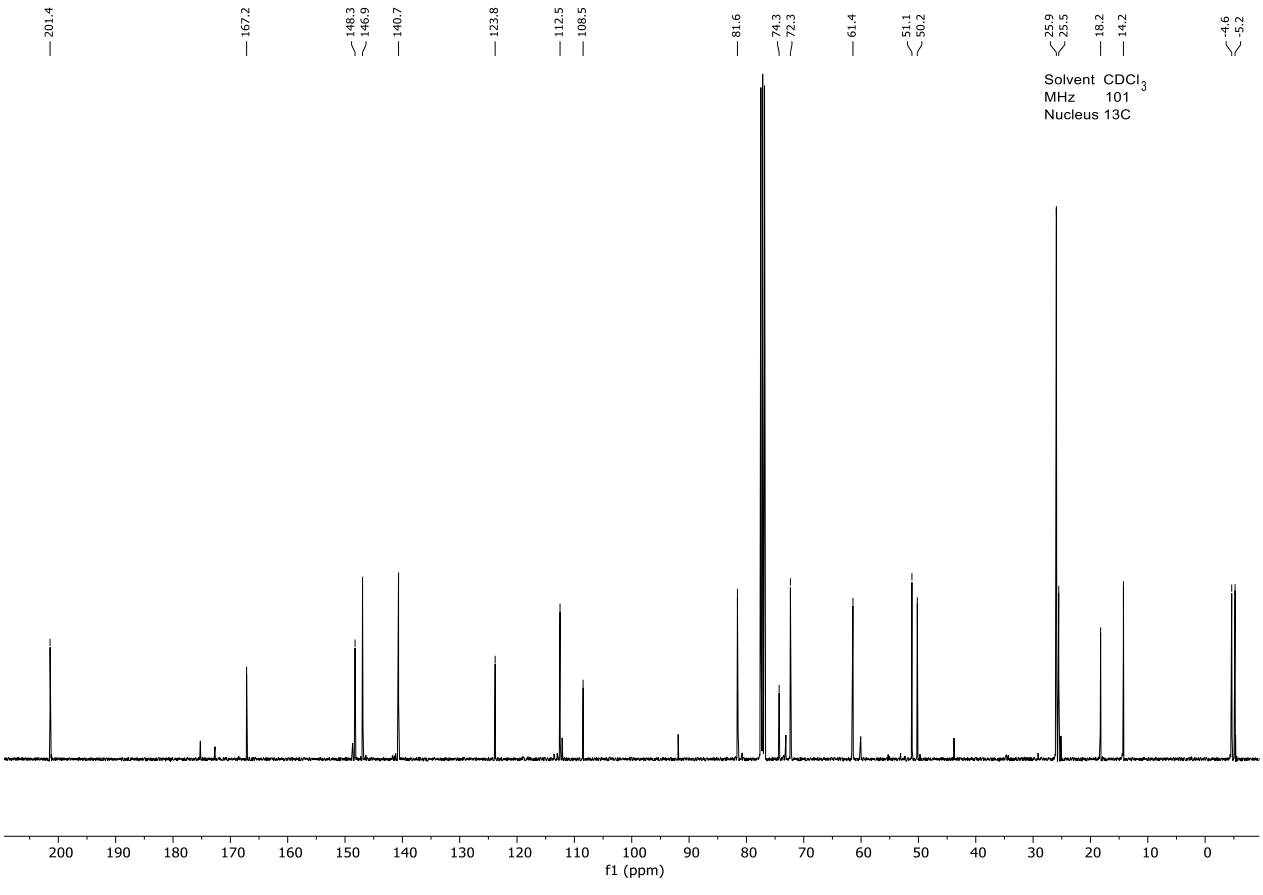

REW1474.2.ser
Solvent CDCl3
HSQC
f2 (ppm)
f1 (ppm)

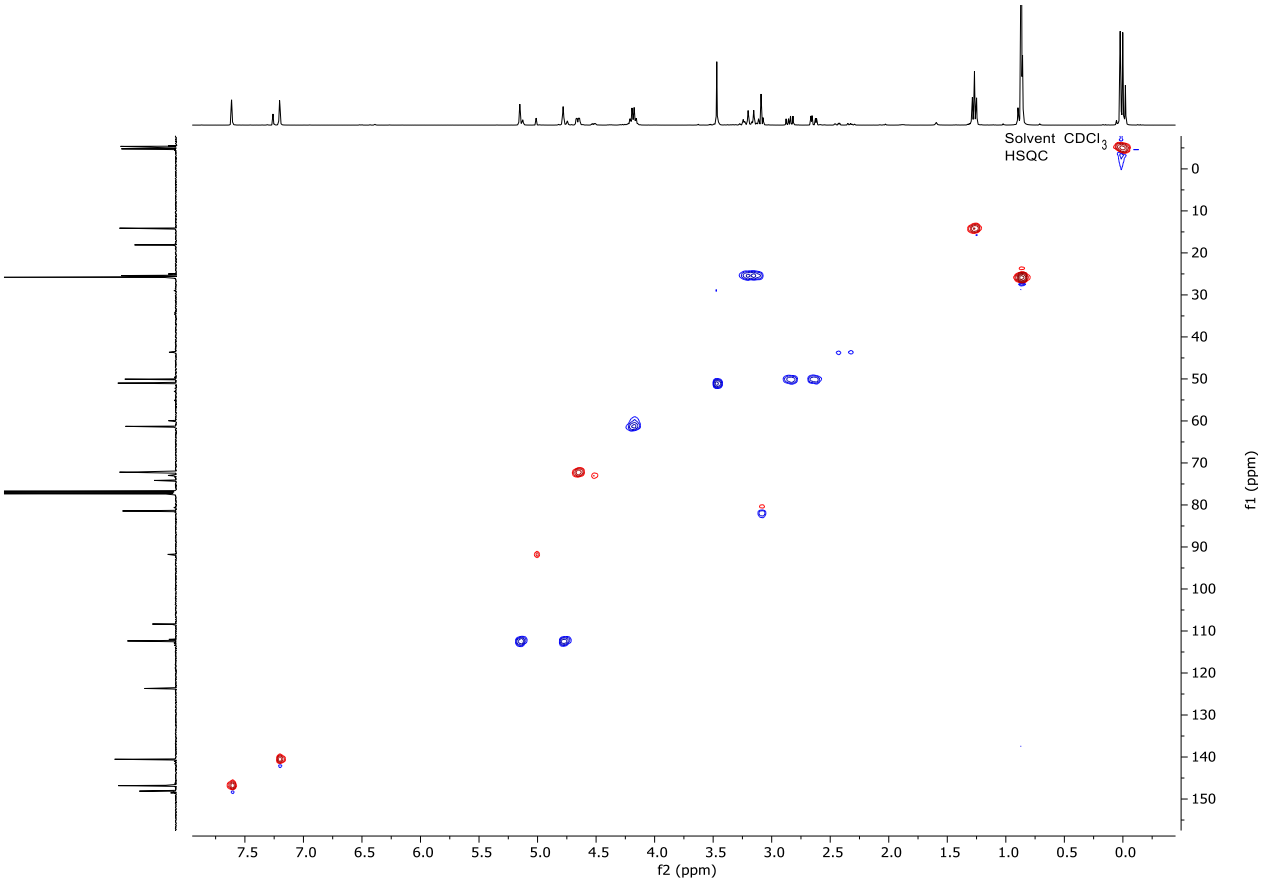

Solvent CDCl3
COSY
f2 (ppm)
f1 (ppm)

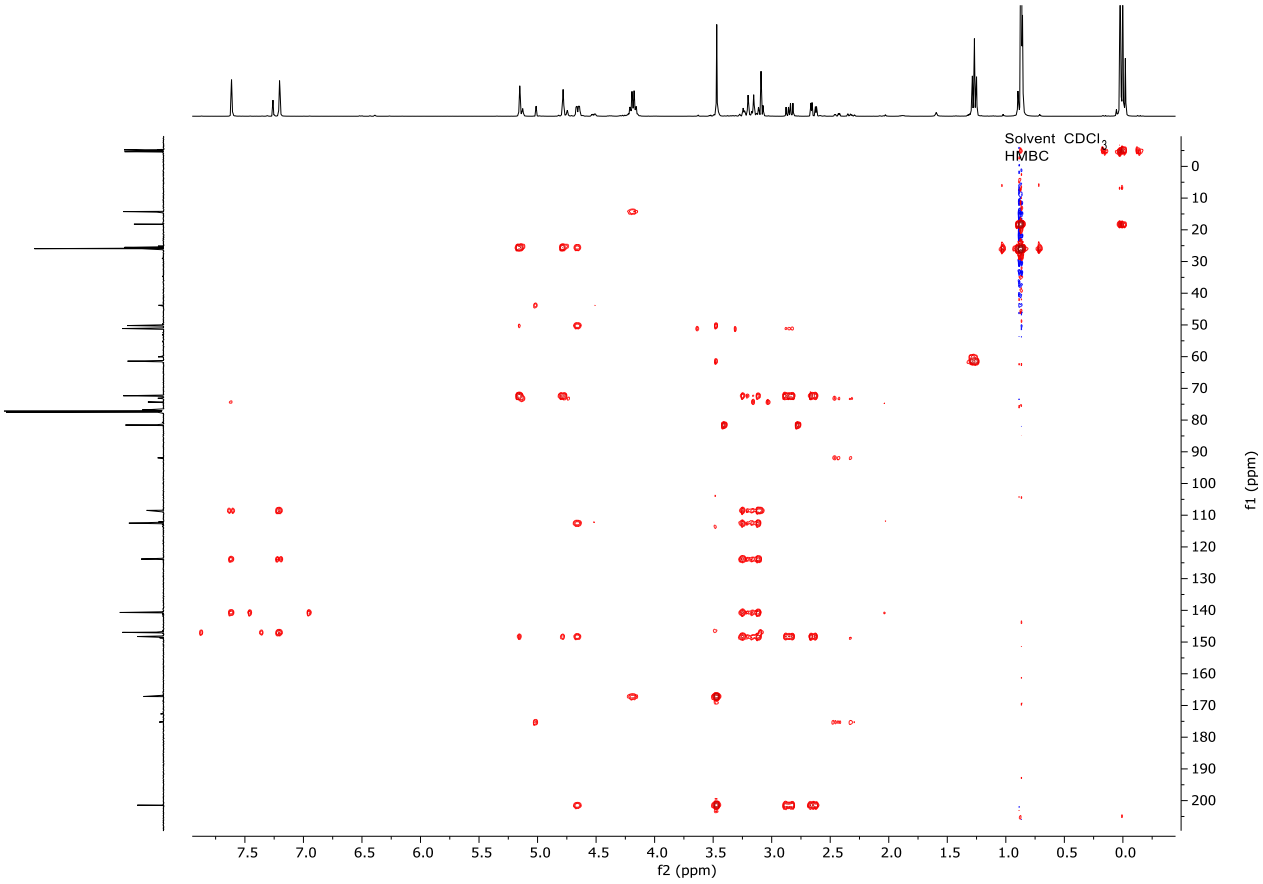

TBSO
COOEt
O
O

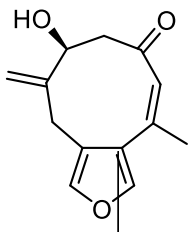
232

Solvent CDCl3
MHz 400
Nucleus 1H
1.11
1.18
1.00
0.97
0.97
2.25
2.01
2.32
0.97
1.00
0.98
3.47
8.98
2.94
3.11
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


201.4
167.2
148.3
146.9
140.7
123.8
112.5
108.5
81.6
74.3
72.3
61.4
51.1
50.2
25.9
25.5
18.2
14.2
-4.6
-5.2
Solvent CDCl3
MHz 101
Nucleus 13C
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

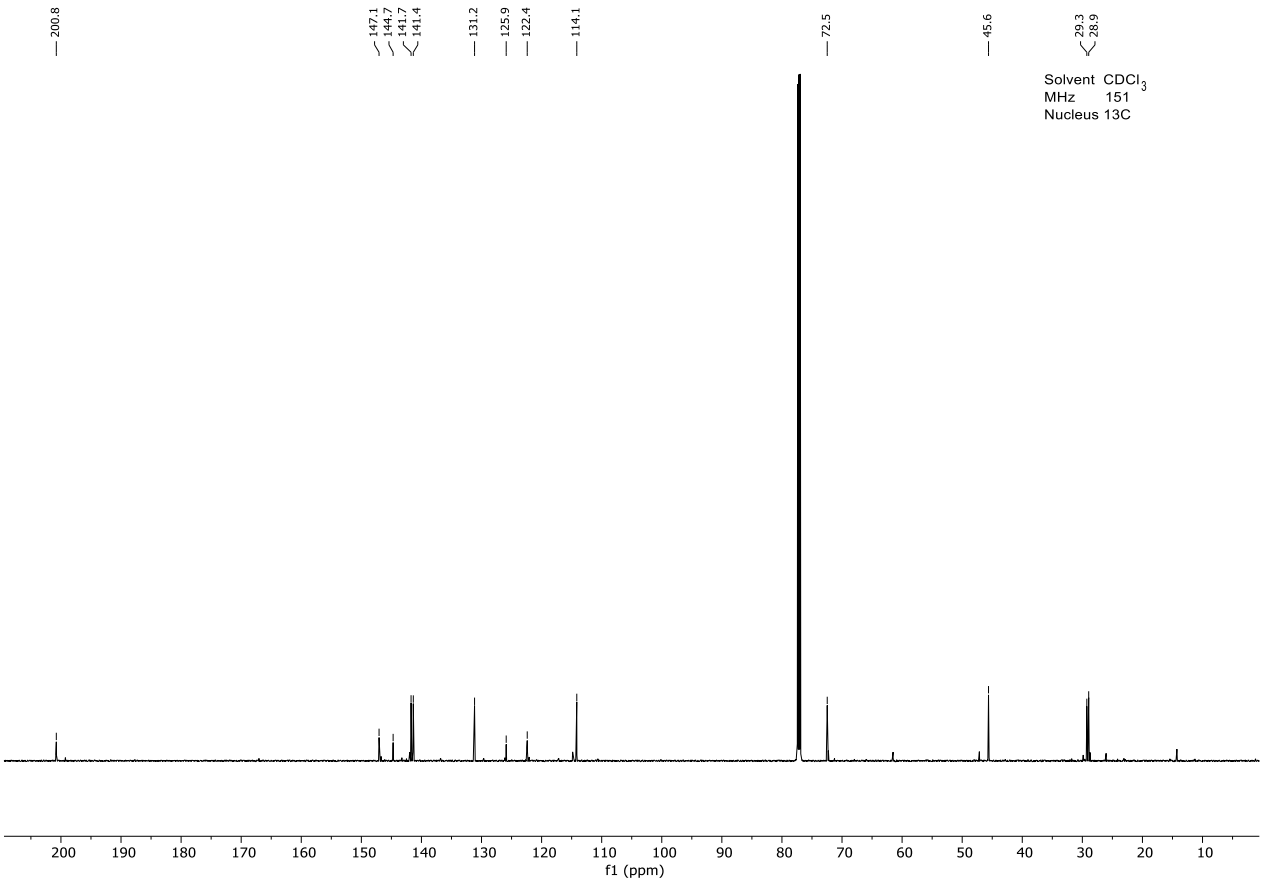

Solvent CDCl3
HSQC
f2 (ppm)
f1 (ppm)

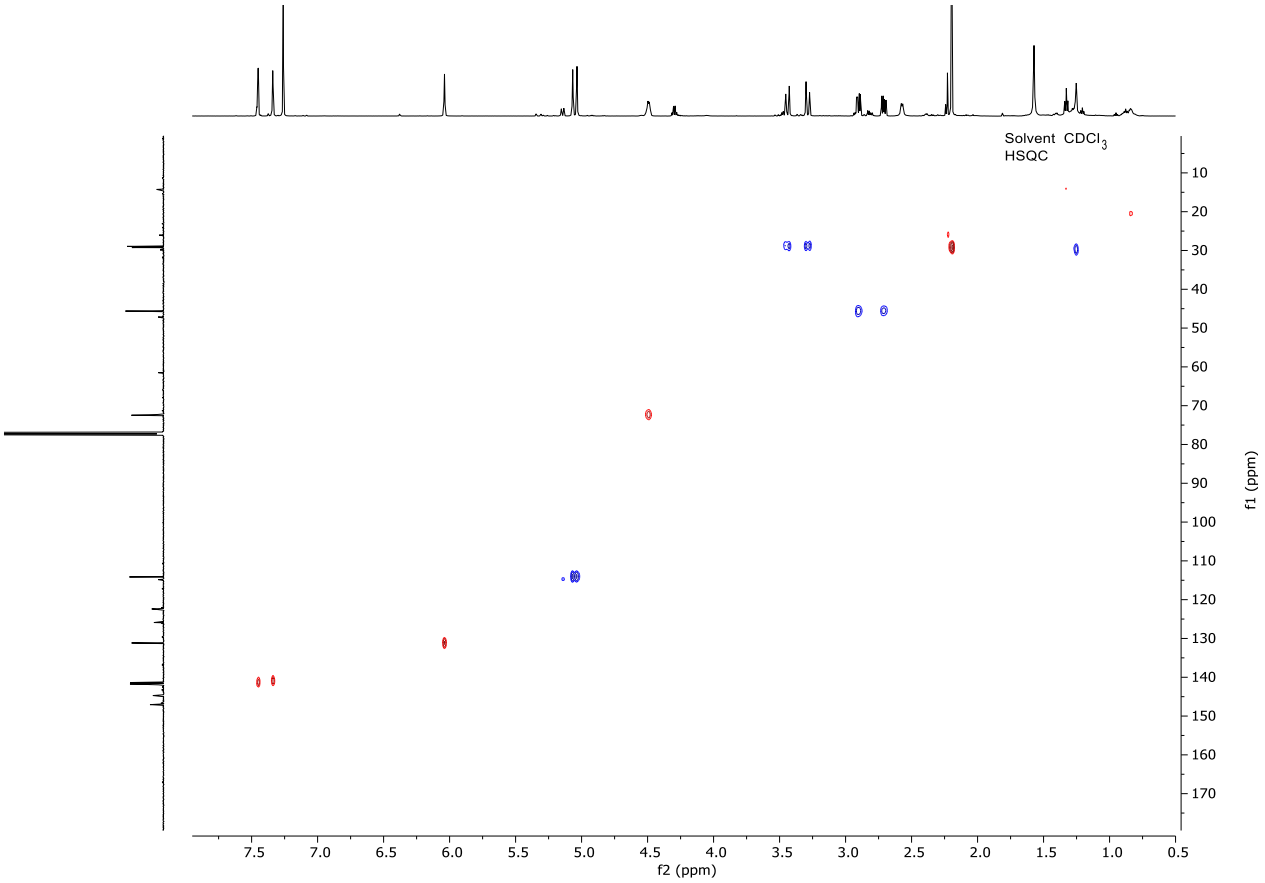

Solvent CDCl3
HMBC
f2 (ppm)
f1 (ppm)

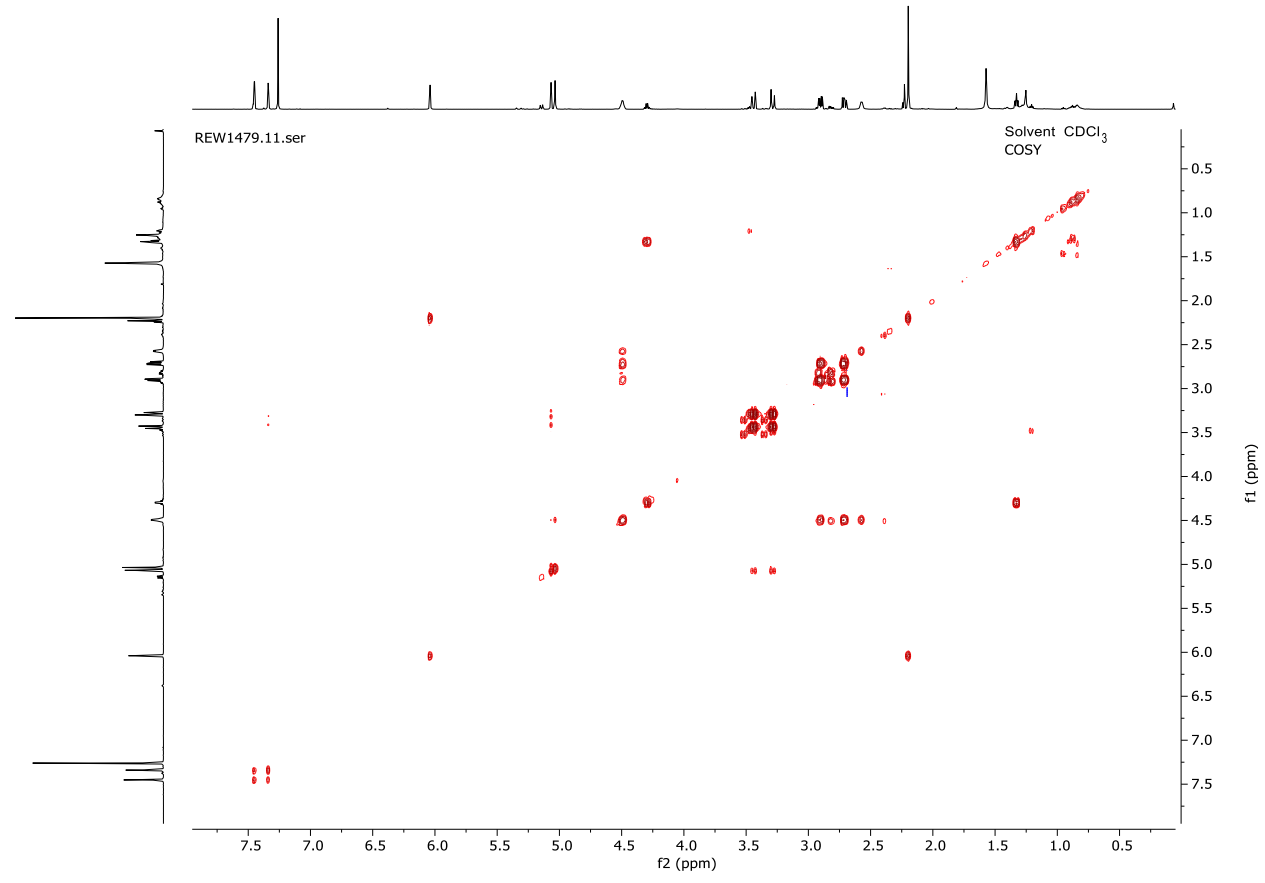

HO
O
O

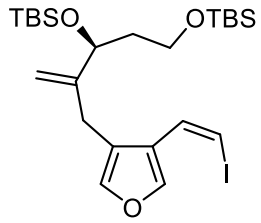
236

Solvent CDCl3
MHz 600
Nucleus 1H
0.90
1.08
1.00
1.06
1.06
1.15
1.17
1.25
1.16
1.05
0.94
3.21
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
f1 (ppm)


200.8
147.1
144.7
141.7
141.4
131.2
125.9
122.4
114.1
72.5
45.6
29.3
28.9
Solvent CDCl3
MHz 151
Nucleus 13C
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

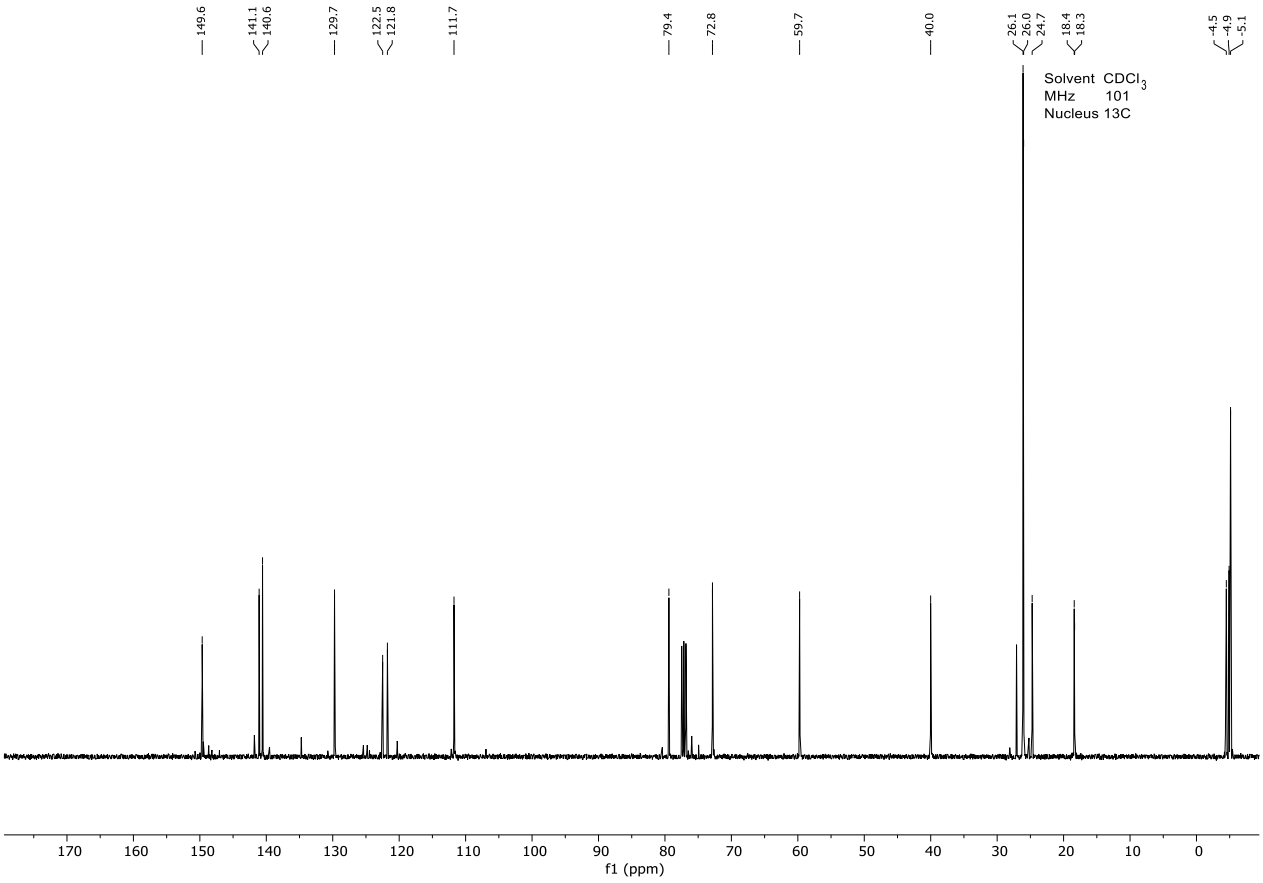

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

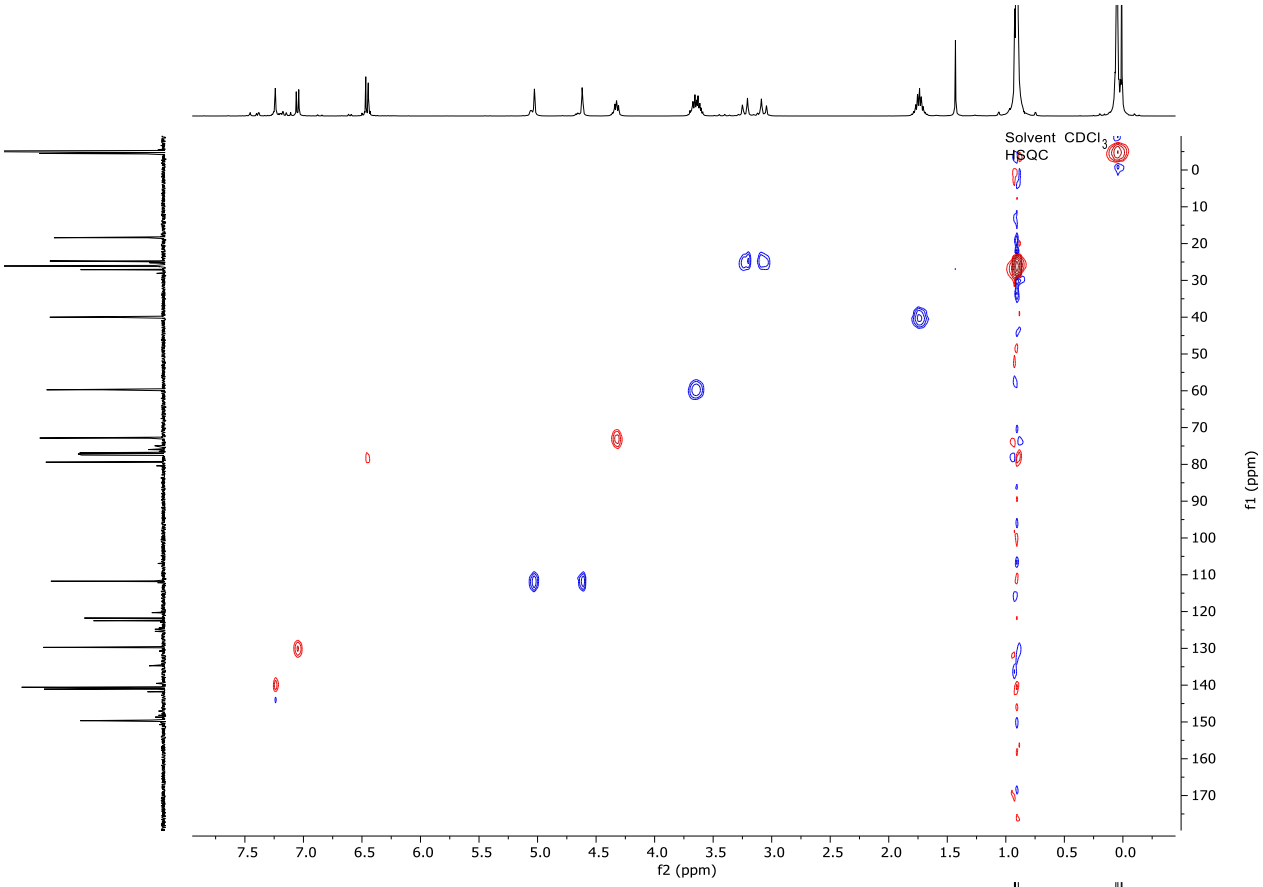

REW1479.11.ser
Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

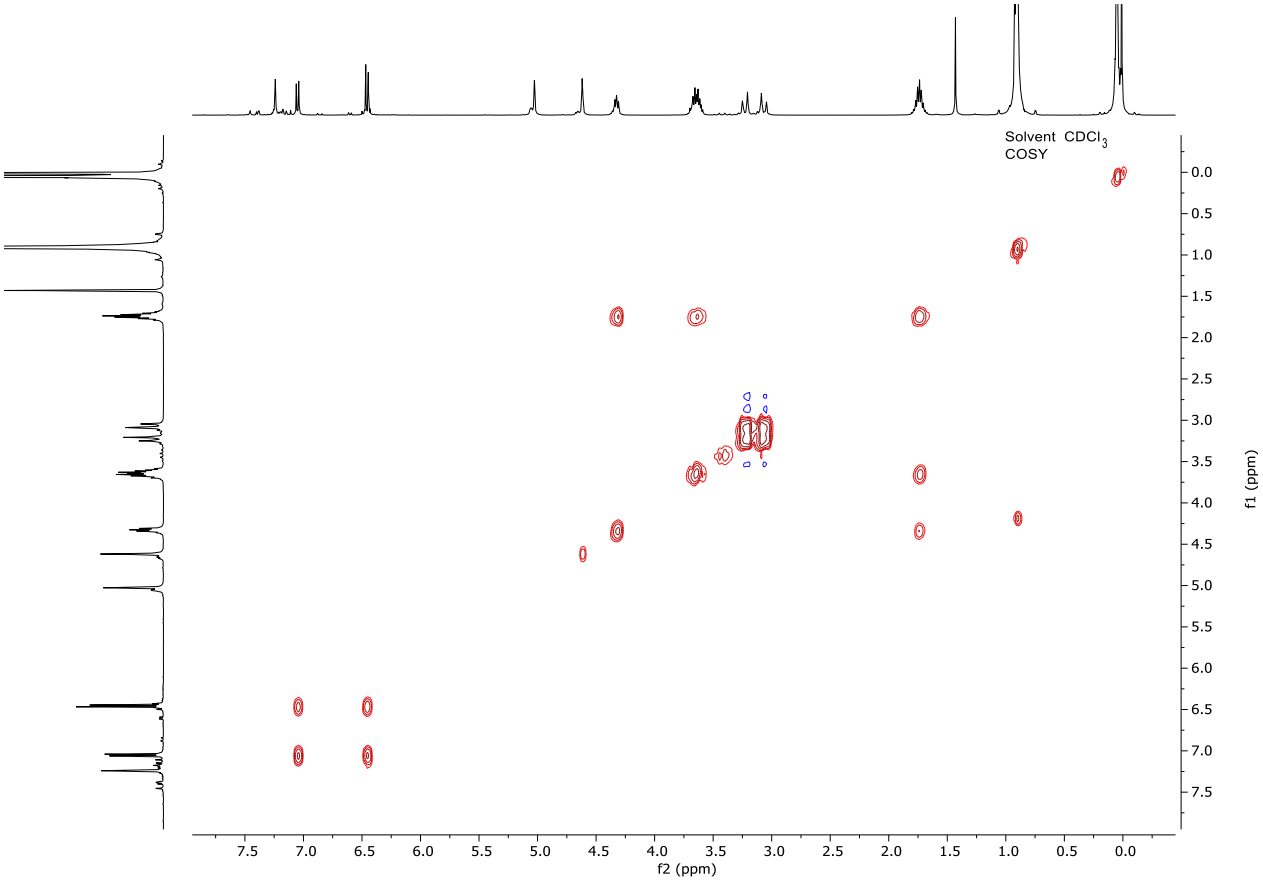

TBSO
OTBS
I
O

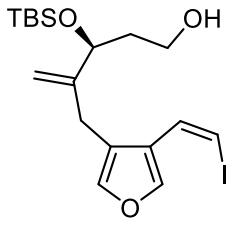
244

Solvent CDCl3
MHz 400
Nucleus 1H
0.93
1.00
1.07
1.06
1.21
1.30
3.20
1.27
1.24
2.71
10.88
9.62
5.88
3.09
2.82
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)


149.6
141.1
140.6
129.7
122.5
121.8
111.7
79.4
72.8
59.7
40.0
26.1
26.0
24.7
18.4
18.3
-4.5
-4.9
-5.1
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

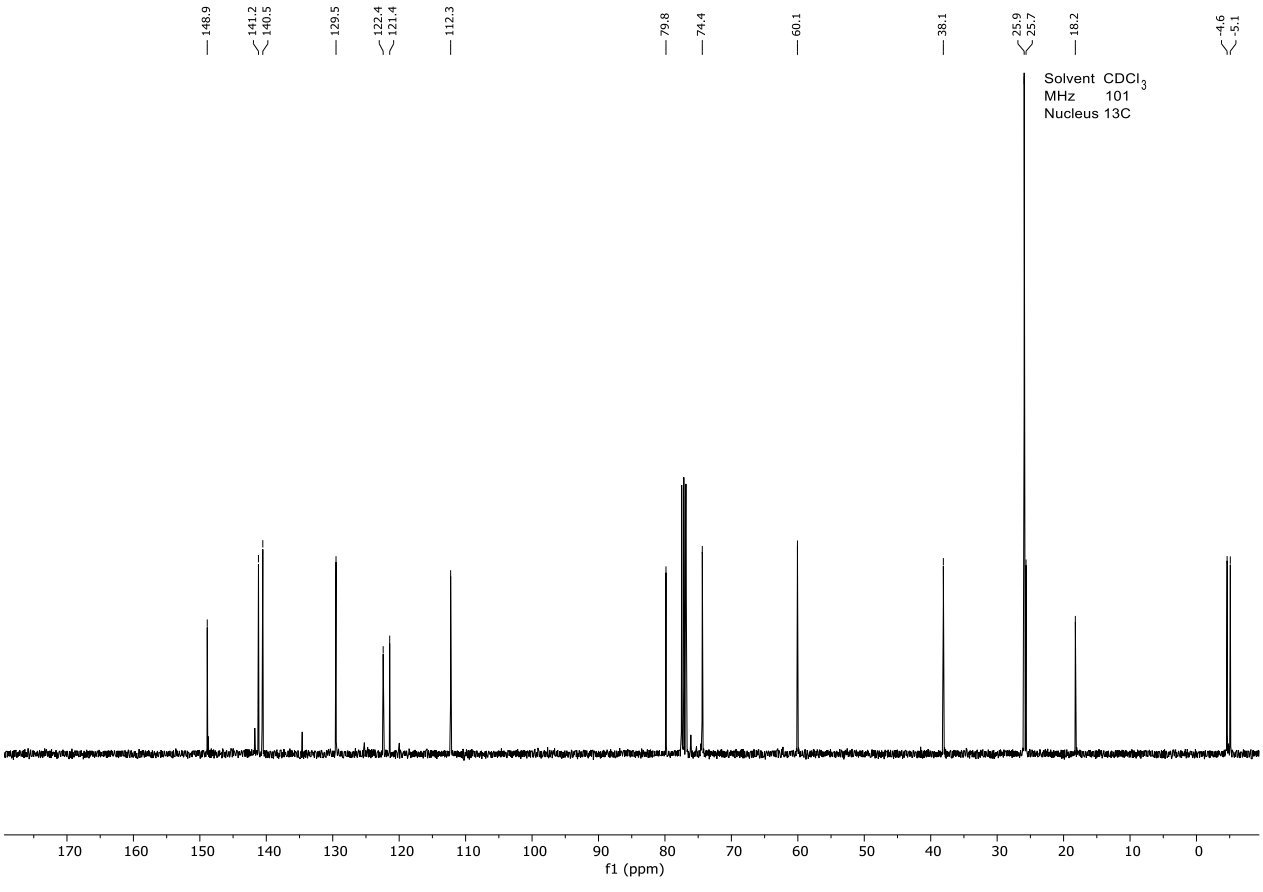

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

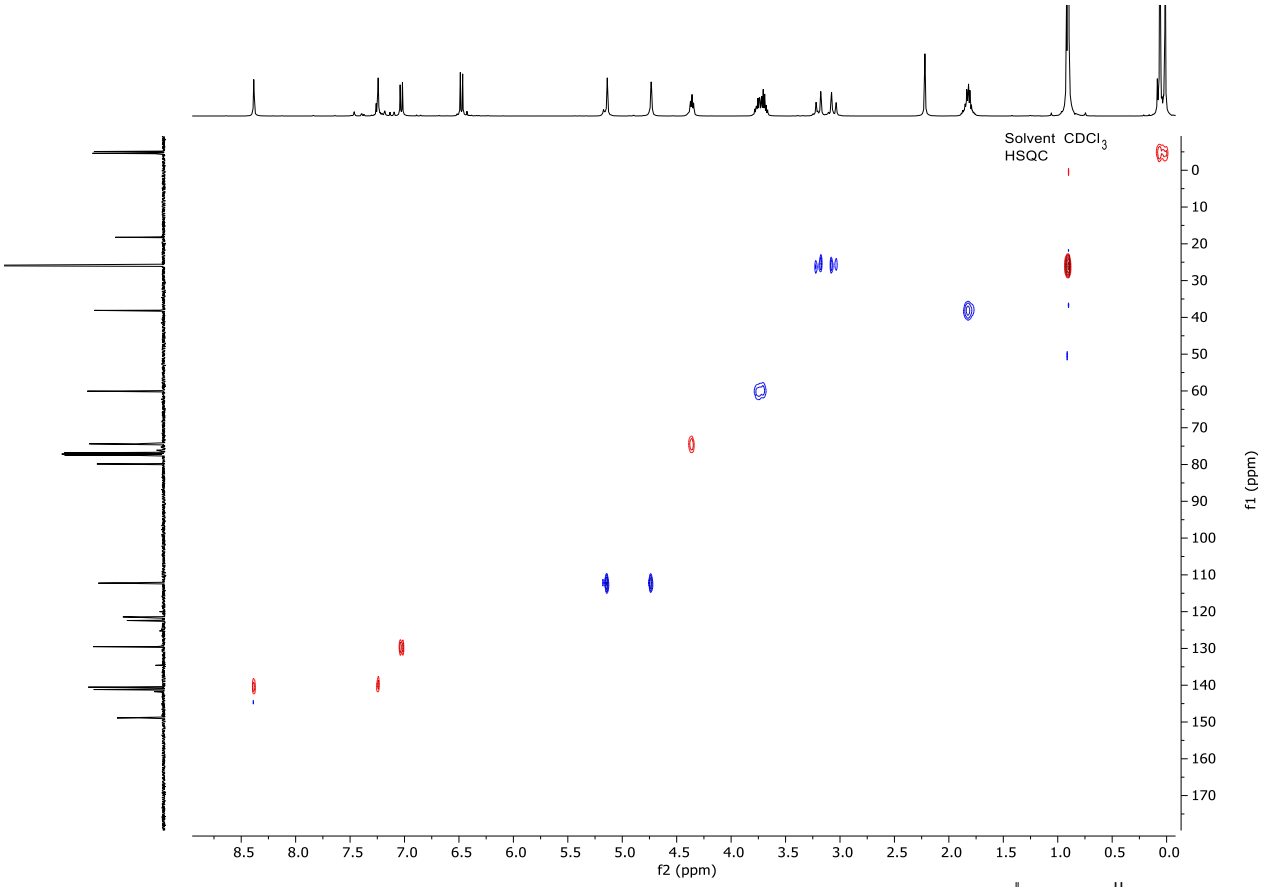

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

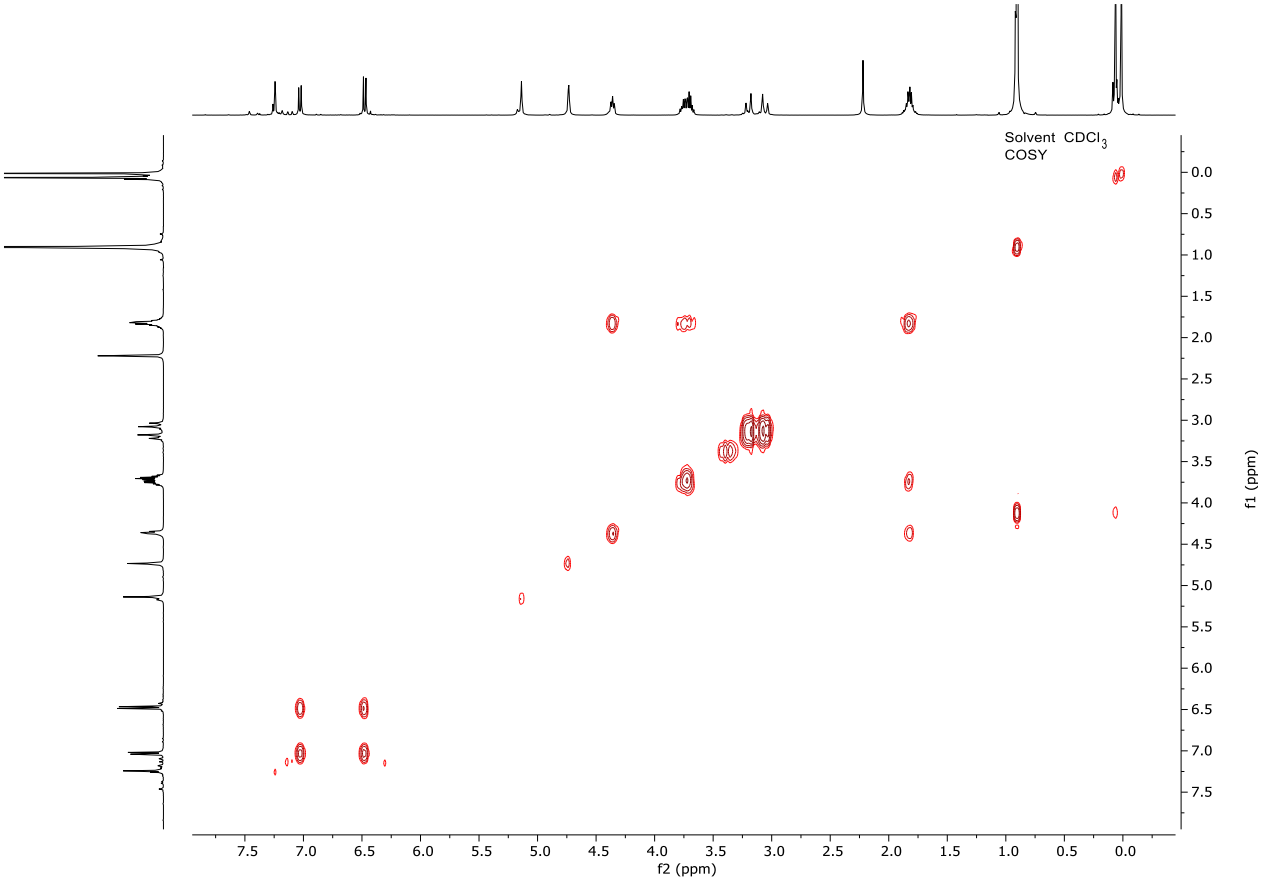

TBSO
OH
I
O

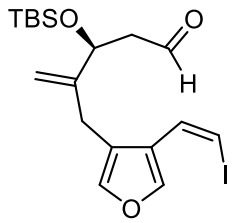
S08

Solvent CDCl3
MHz 400
Nucleus 1H
0.89
0.89
0.98
1.00
1.01
1.19
1.19
2.47
1.20
1.16
1.42
2.20
9.22
2.95
3.03
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)


148.9
141.2
140.5
129.5
122.4
121.4
112.3
79.8
74.4
60.1
38.1
25.9
25.7
18.2
-4.6
-5.1
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

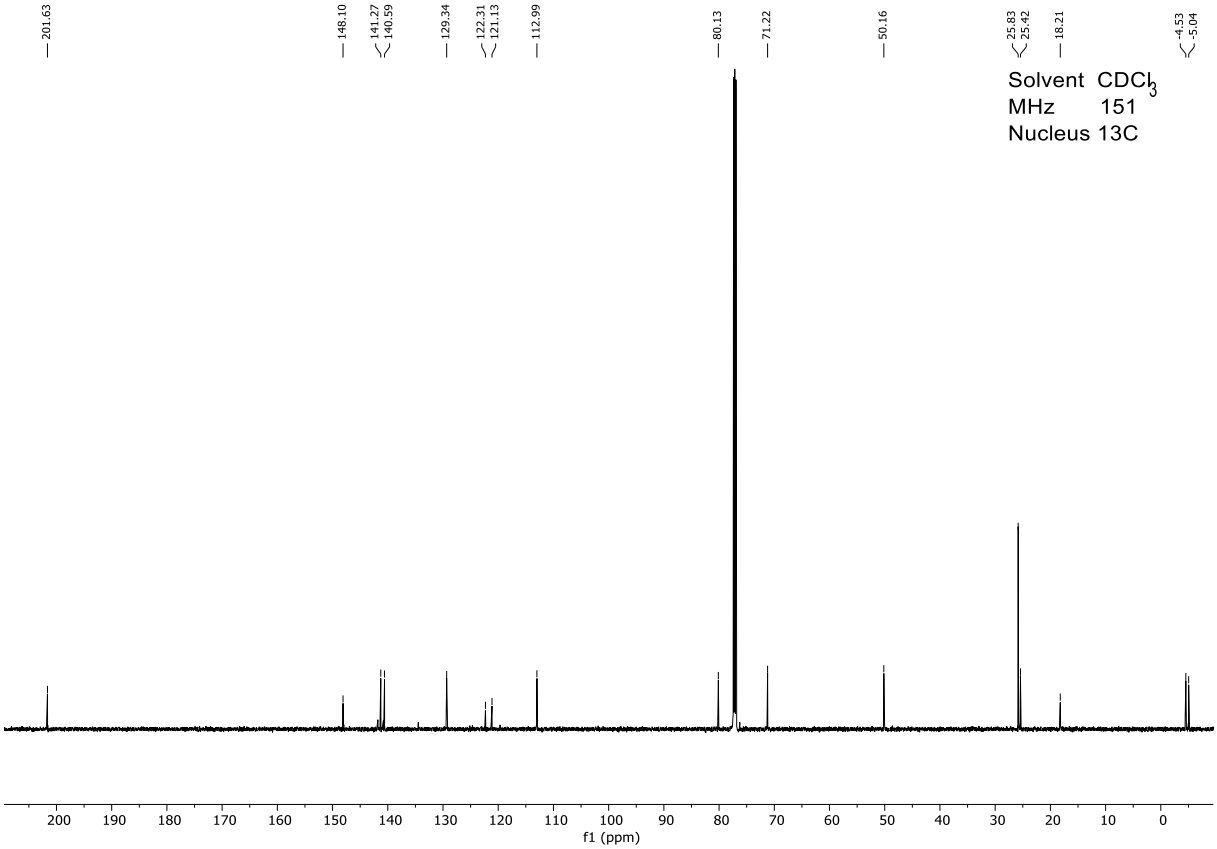

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

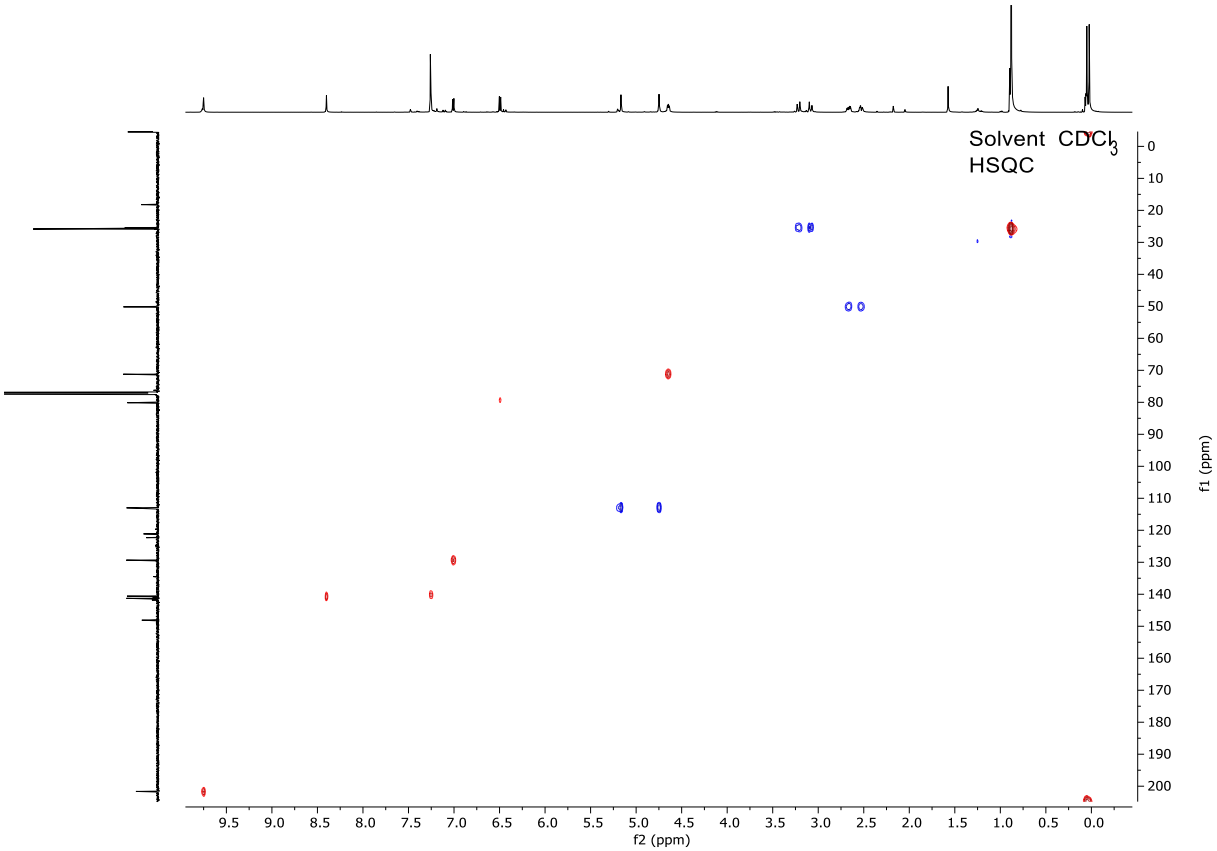

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

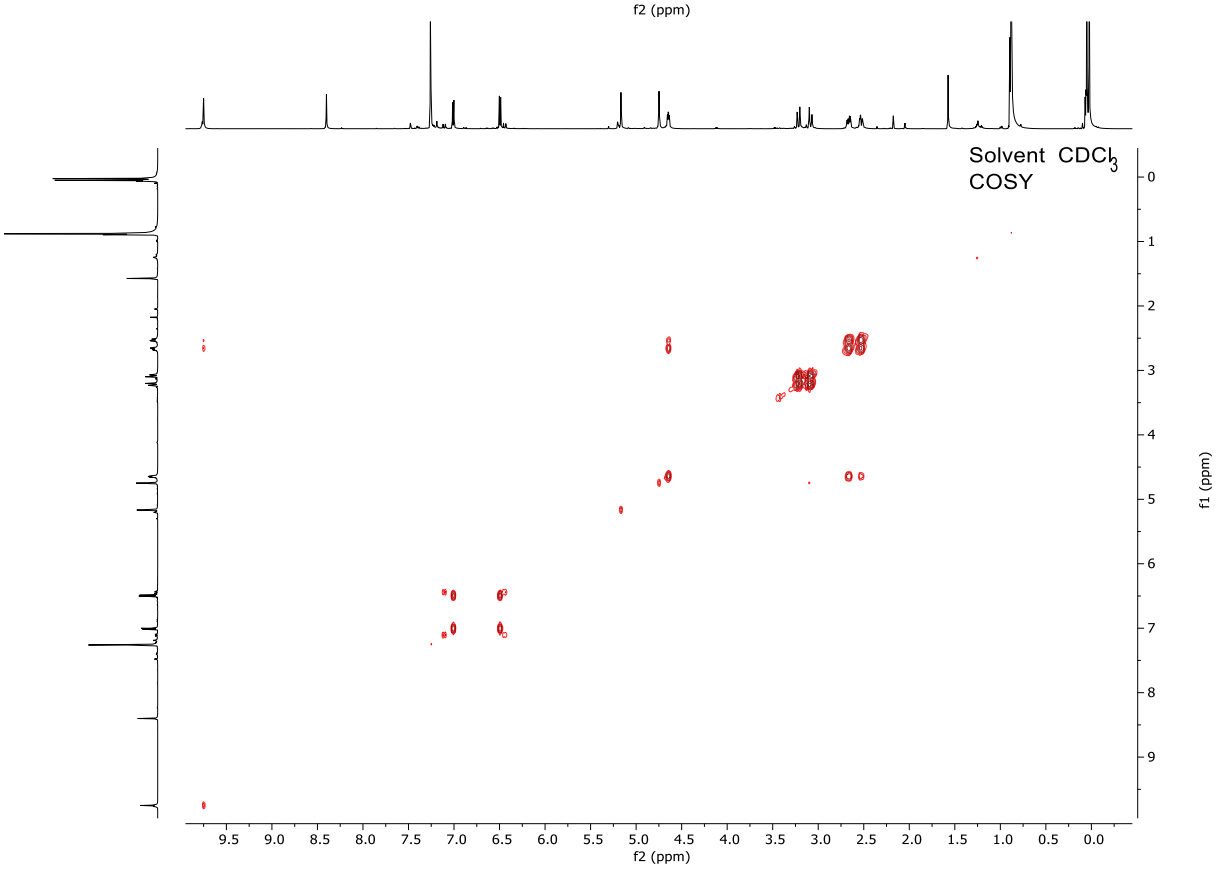

TBSO
O
H
I
O

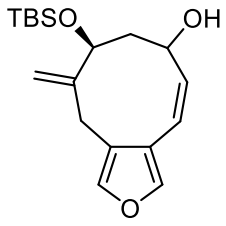
243

Solvent CDCl3
MHz 600
Nucleus 1H
1.00
0.83
1.01
1.00
0.96
1.04
1.12
1.08
1.11
1.22
1.23
1.16
8.97
3.08
2.92
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)


201.63
148.10
141.27
140.59
129.34
122.31
121.13
112.99
80.13
71.22
50.16
25.83
25.42
18.21
-4.53
-5.04
Solvent CDCl3
MHz 151
Nucleus 13C
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

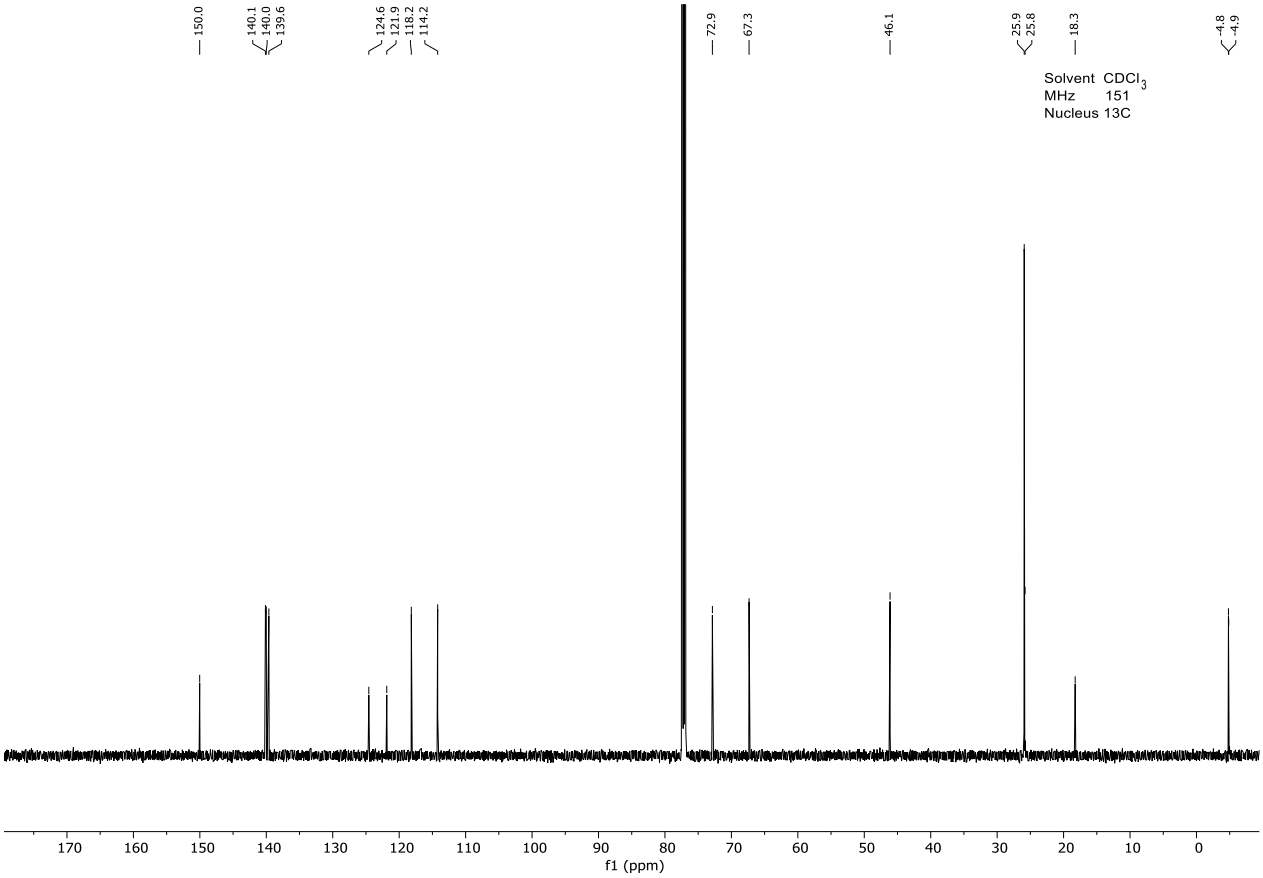

Solvent CDCl3
HSQC
f2 (ppm)
f1 (ppm)

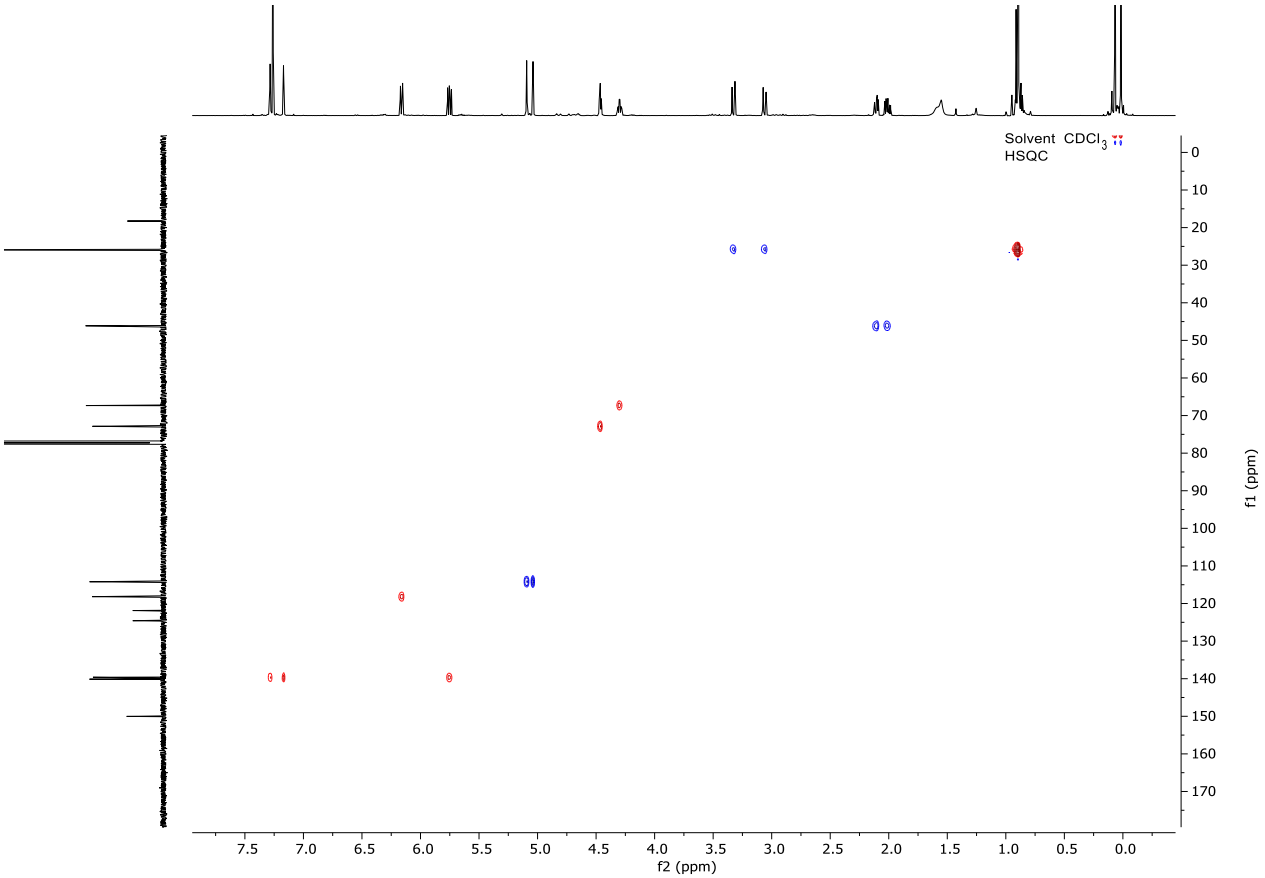

Solvent CDCl3
COSY
f2 (ppm)
f1 (ppm)

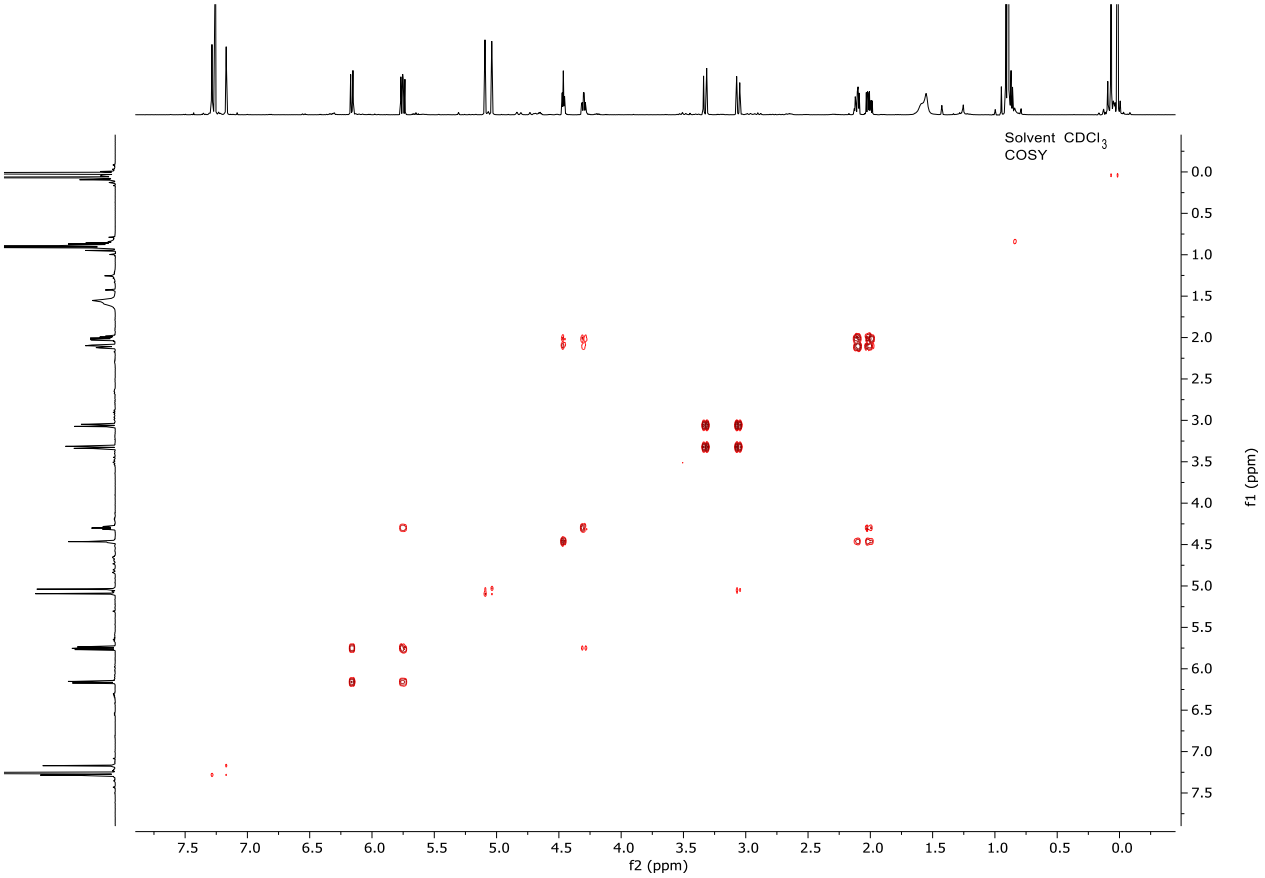

TBSO
OH
O

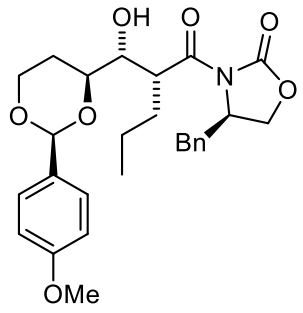
244

Solvent CDCl3
MHz 600
Nucleus 1H
1.02
0.90
1.00
0.97
1.02
1.01
1.01
0.99
1.01
1.02
1.06
1.11
1.02
9.33
3.15
3.22
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)


150.0
140.1
140.0
139.6
124.6
121.9
118.2
114.2
72.9
67.3
46.1
25.9
25.8
18.3
-4.8
-4.9
Solvent CDCl3
MHz 151
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

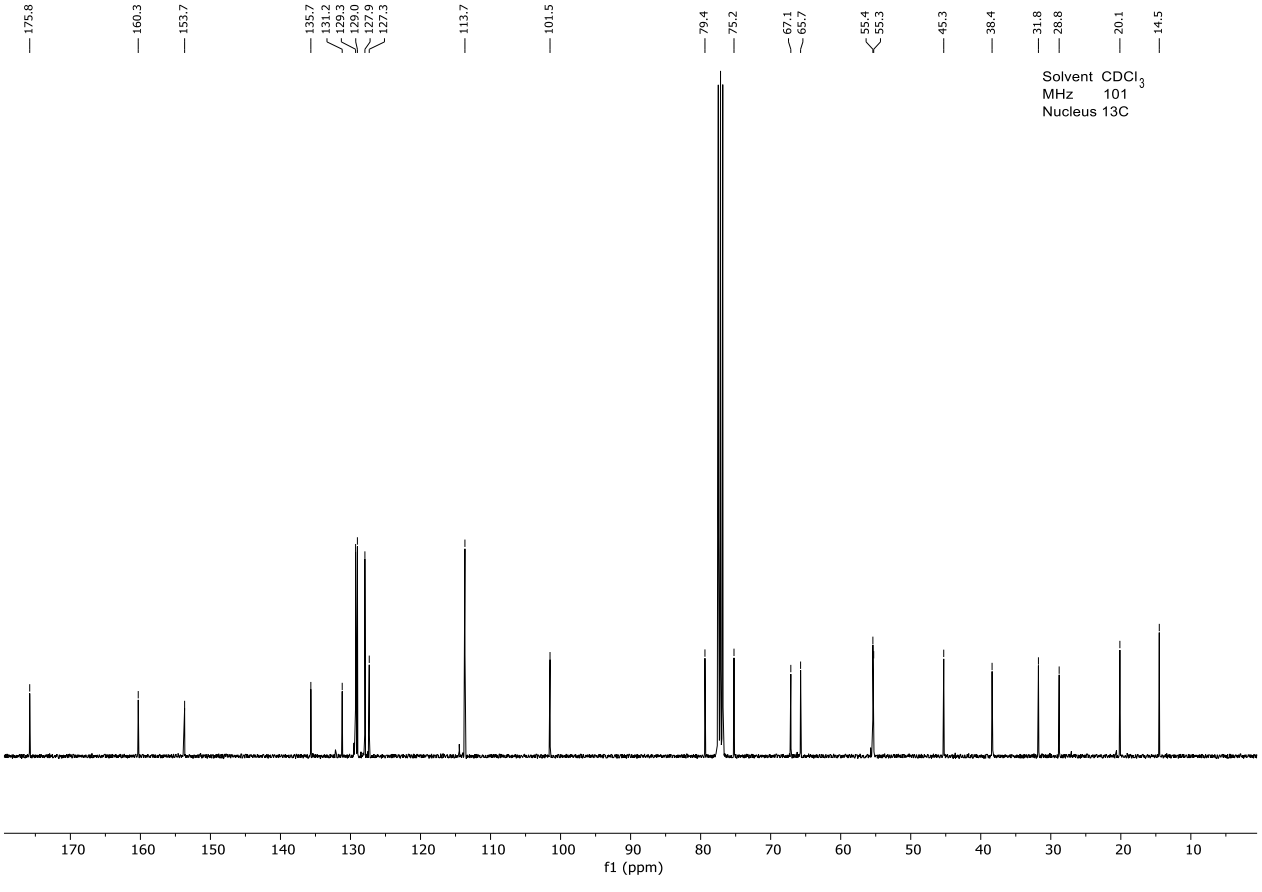

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

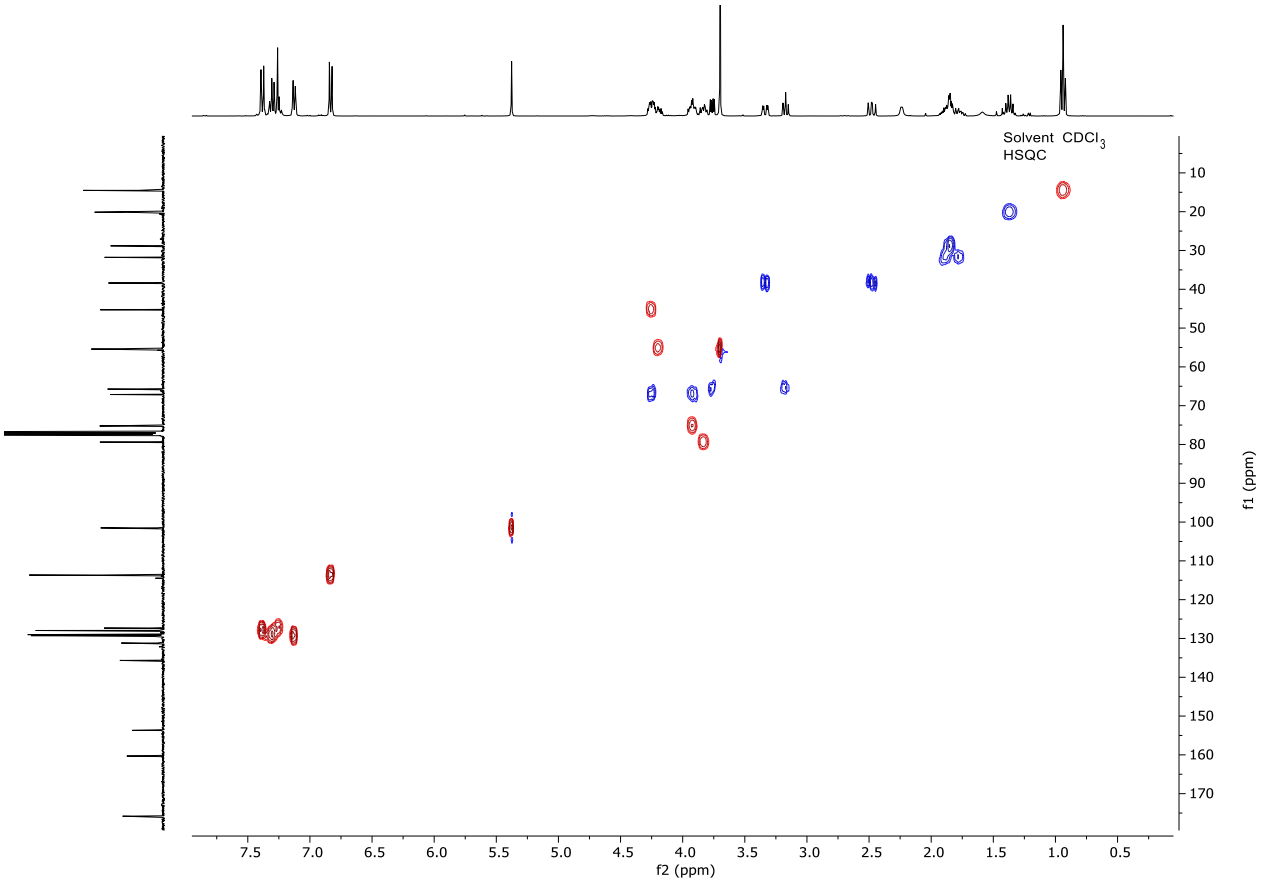

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

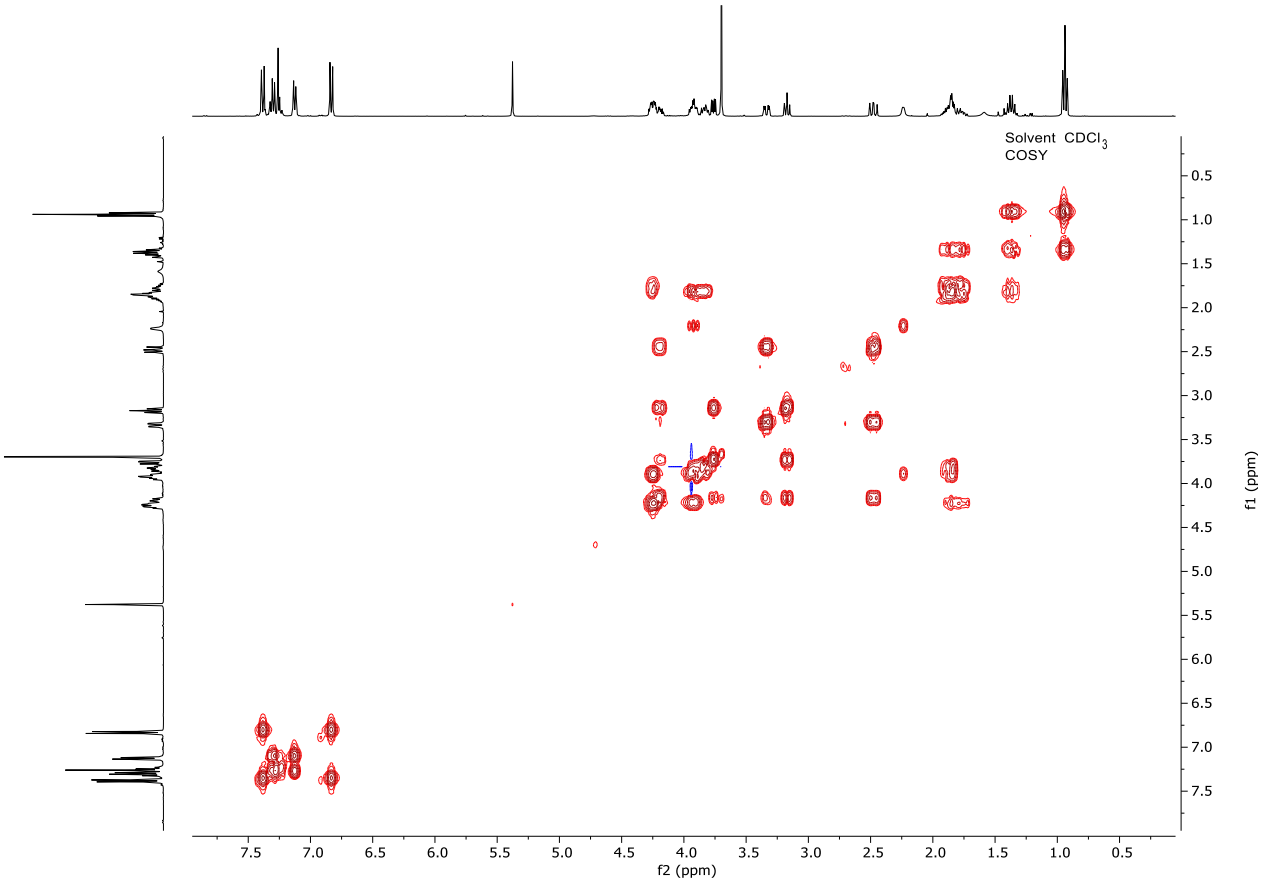

OH
O
O
N
O
O
O
Bn
OMe

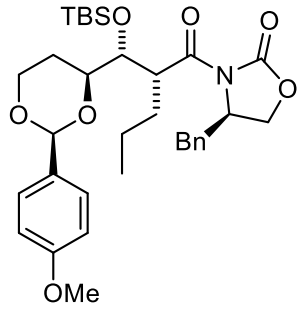
257

Solvent CDCl3
MHz 400
Nucleus 1H
1.95
3.42
2.01
2.03
0.99
2.14
0.96
2.11
1.11
1.03
2.96
1.05
1.00
1.00
0.93
3.24
1.01
1.95
3.26
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)


175.8
160.3
153.7
135.7
131.2
129.3
129.0
127.9
127.3
113.7
101.5
79.4
75.2
67.1
65.7
55.4
55.3
45.3
38.4
31.8
28.8
20.1
14.5
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

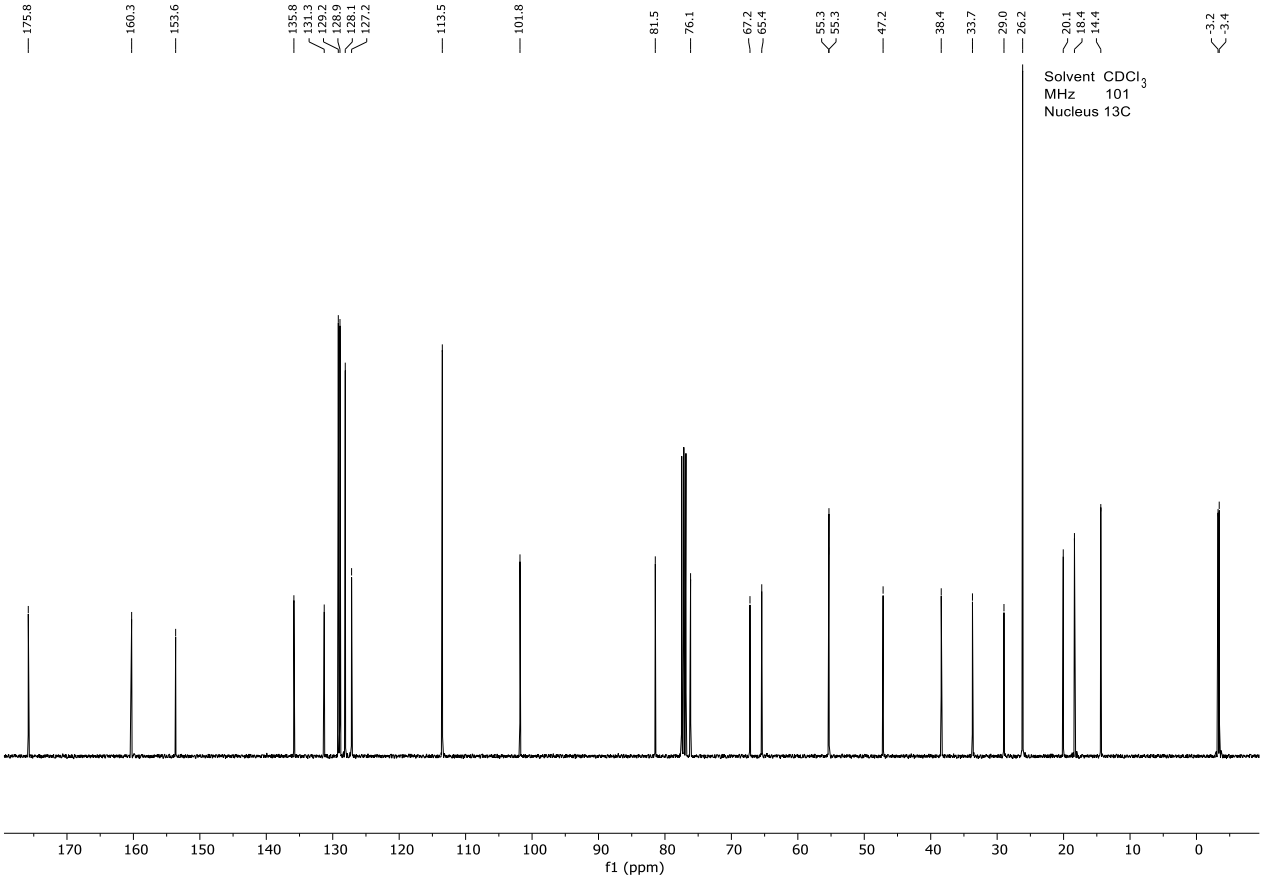

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

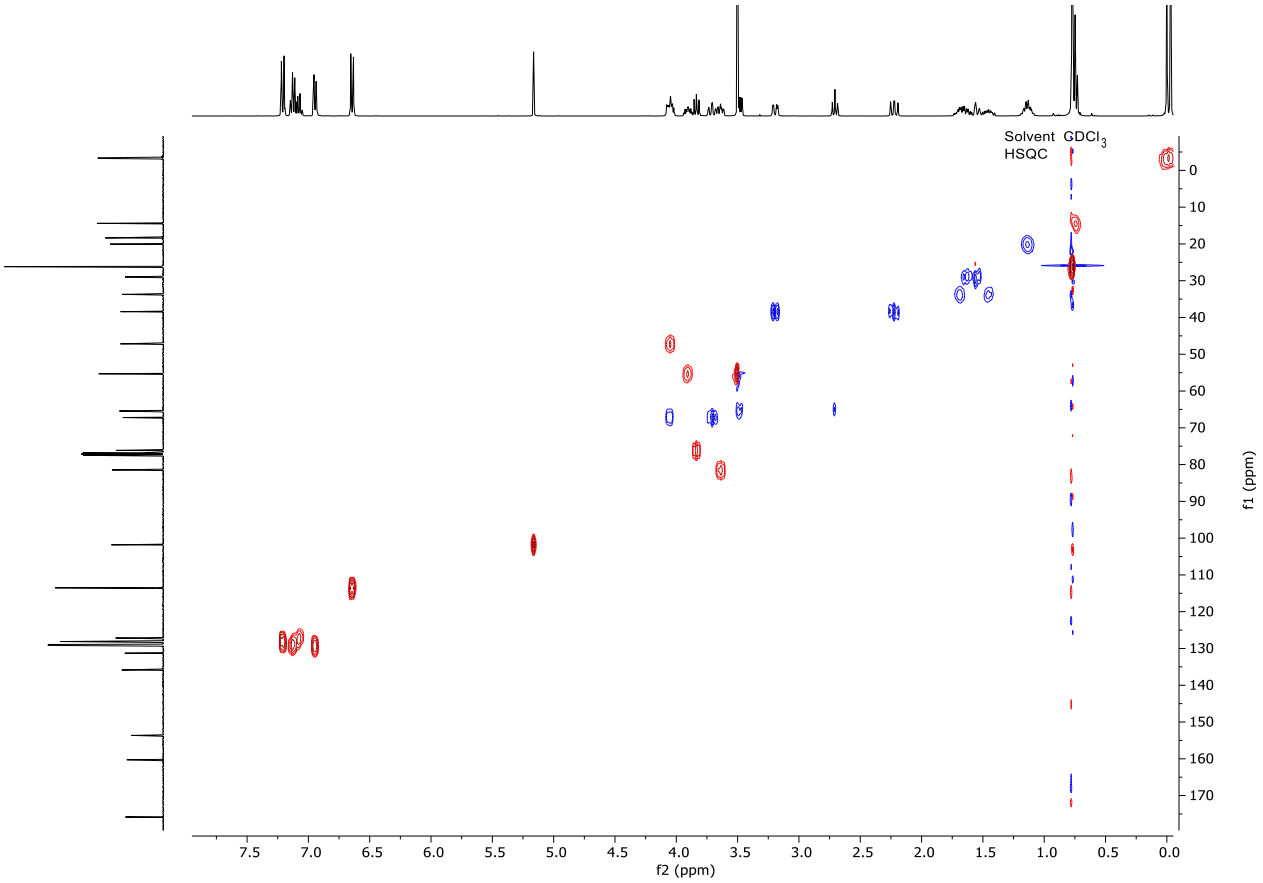

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

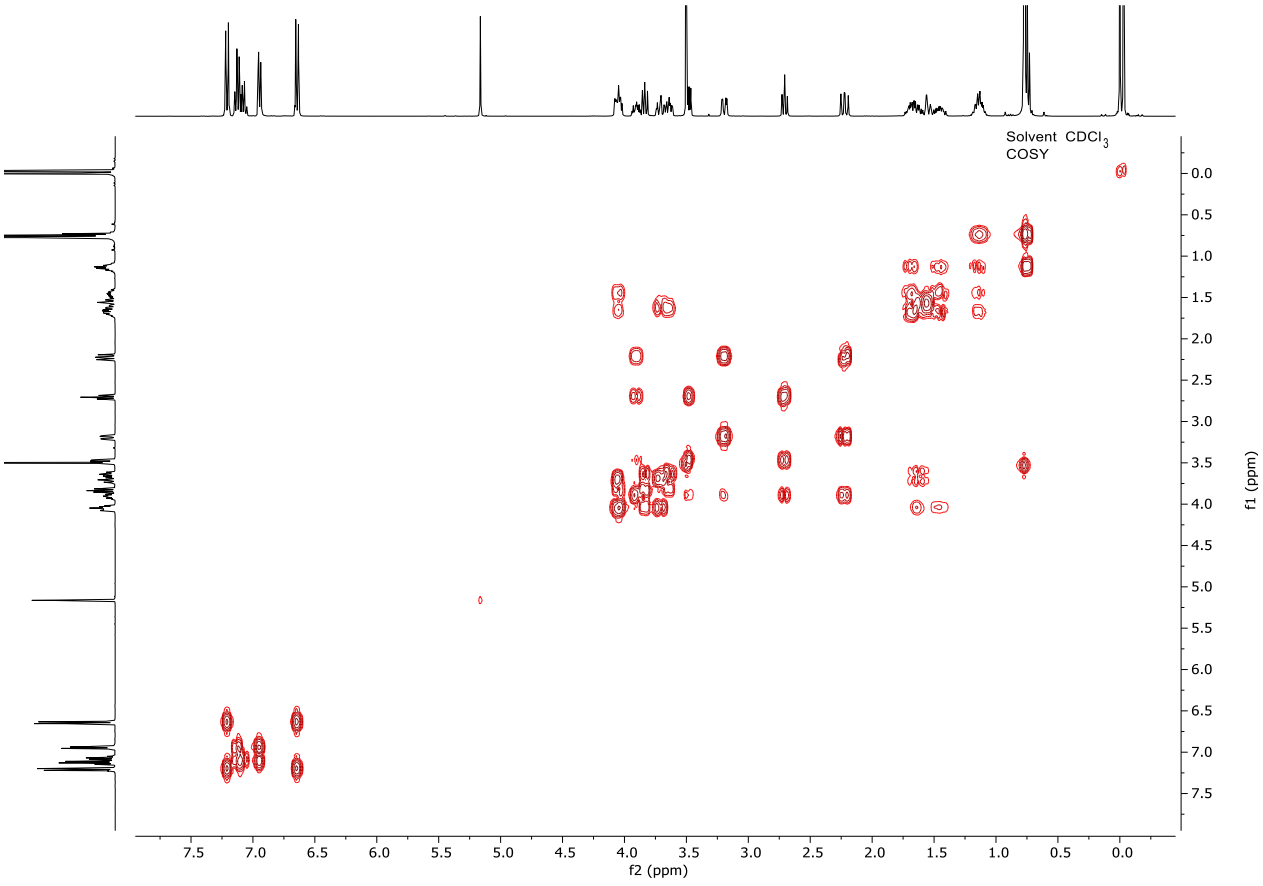

TBSO
O
O
N
O
O
O
Bn
OMe

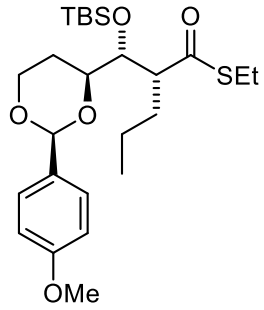
258

Solvent CDCl3
MHz 400
Nucleus 1H
1.97
1.96
1.13
1.96
1.97
0.95
1.96
1.00
0.99
2.05
2.80
1.05
0.97
0.97
0.99
1.98
0.96
0.99
2.04
11.75
2.91
2.91
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)


175.8
160.3
153.6
135.8
131.3
129.2
128.9
128.1
127.2
113.5
101.8
81.5
76.1
67.2
65.4
55.3
55.3
47.2
38.4
33.7
29.0
26.2
20.1
18.4
14.4
-3.2
-3.4
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

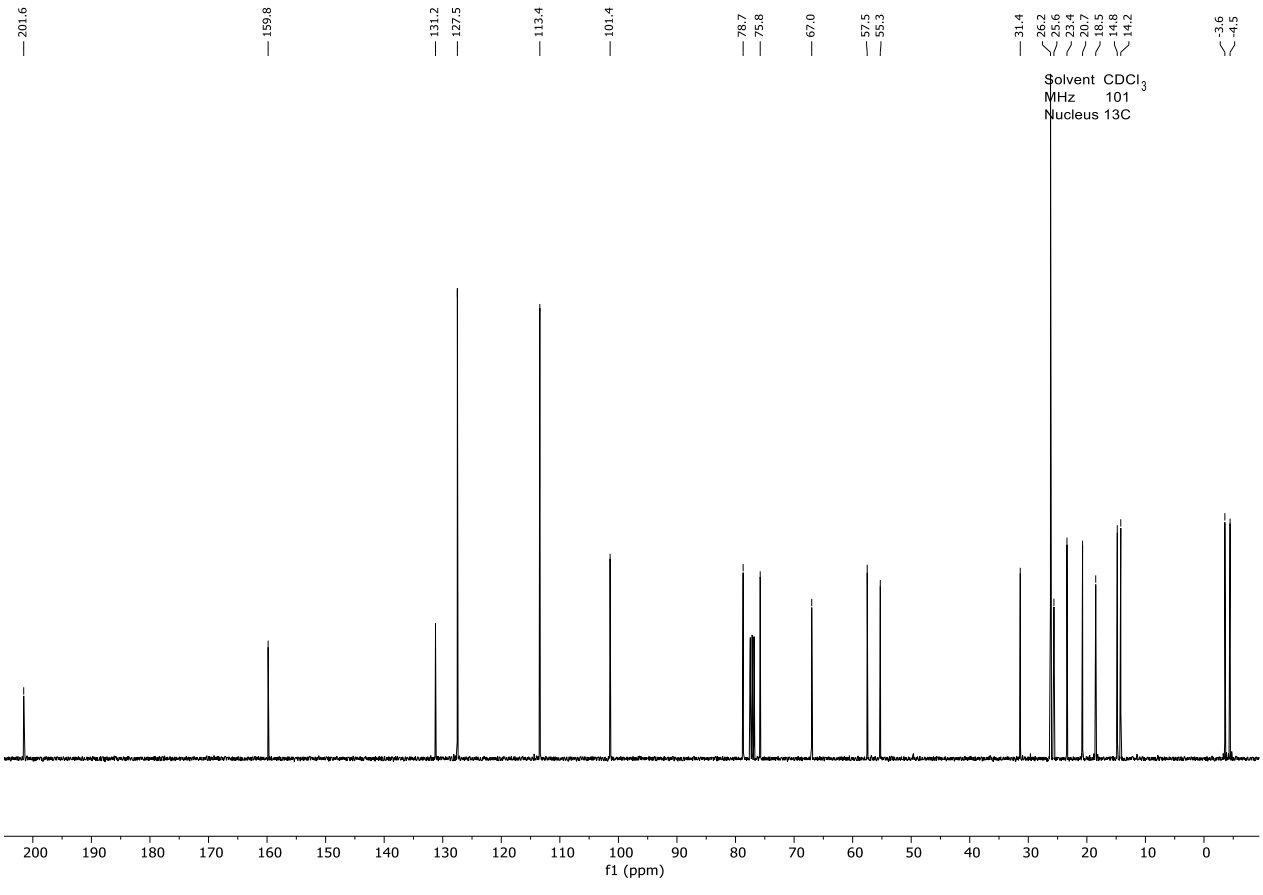

Solvent GDCl3
HSQC
f1 (ppm)
f2 (ppm)

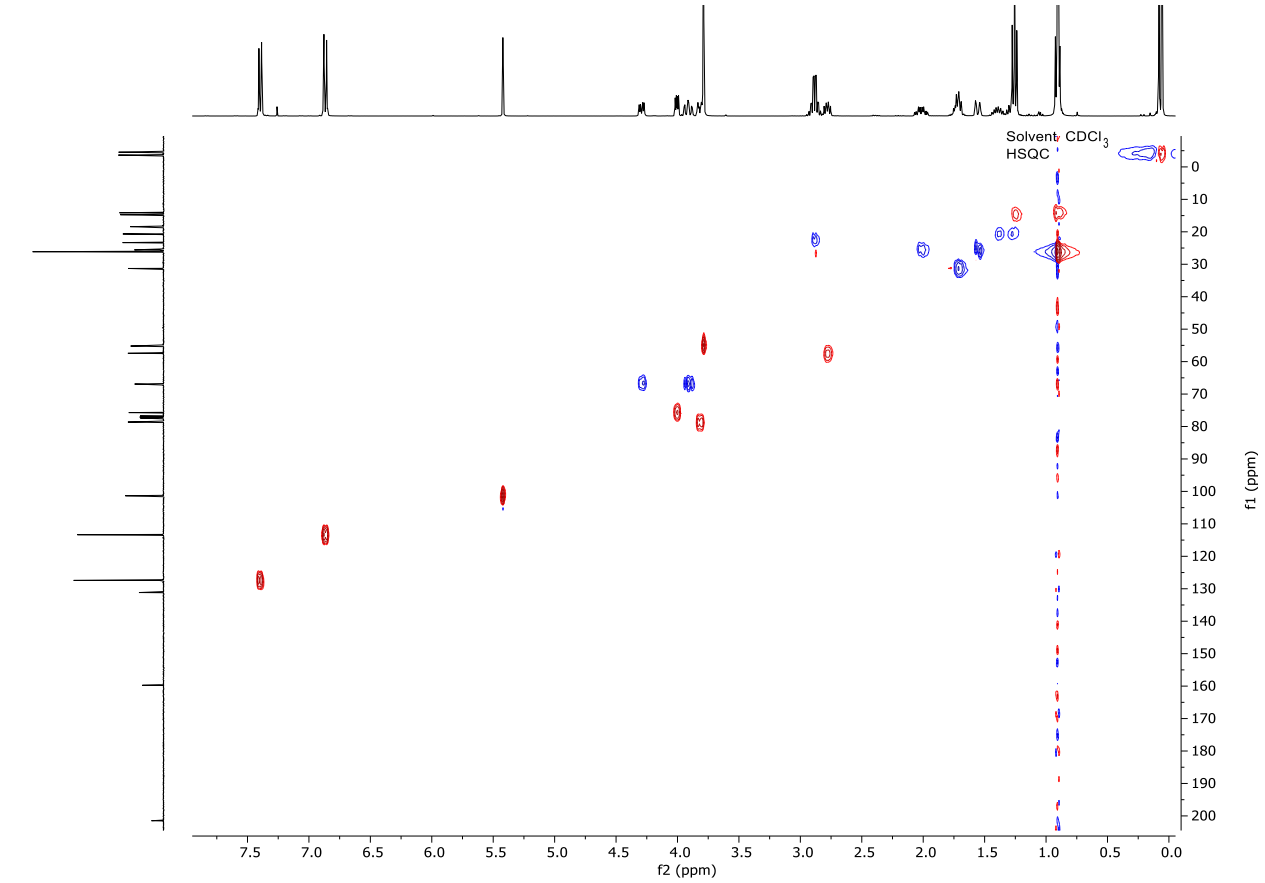

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

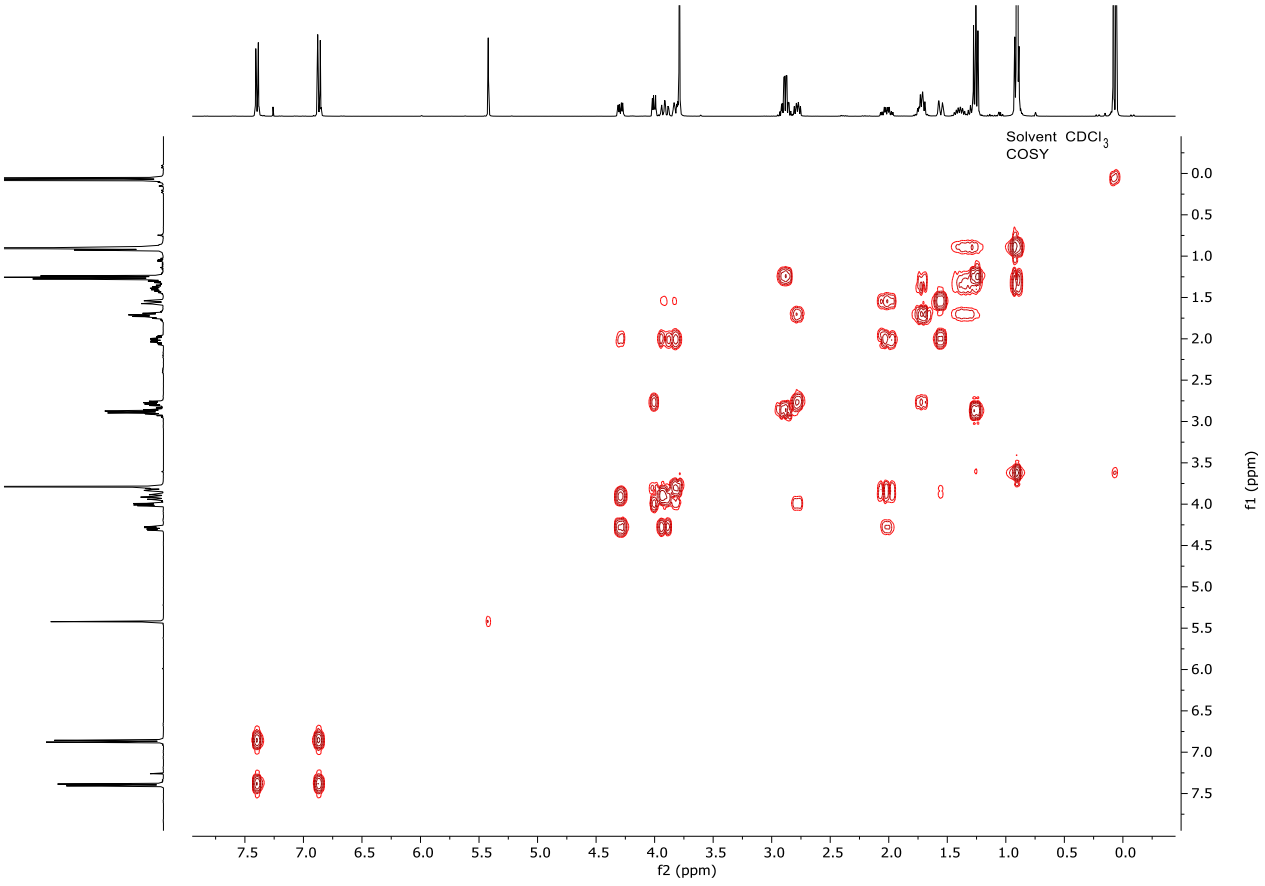

TBSO
O
SEt
O
O
OMe

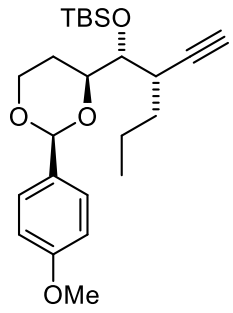
259

Solvent CDCl3
MHz 400
Nucleus 1H
2.02
2.03
1.00
1.01
1.02
1.05
1.04
3.01
2.07
1.06
1.04
1.95
0.99
1.06
4.20
12.28
3.15
3.03
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)


201.6
159.8
131.2
127.5
113.4
101.4
78.7
75.8
67.0
57.5
55.3
31.4
26.2
25.6
23.4
20.7
18.5
14.8
14.2
-3.6
-4.5
Solvent CDCl3
MHz 101
Nucleus 13C
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

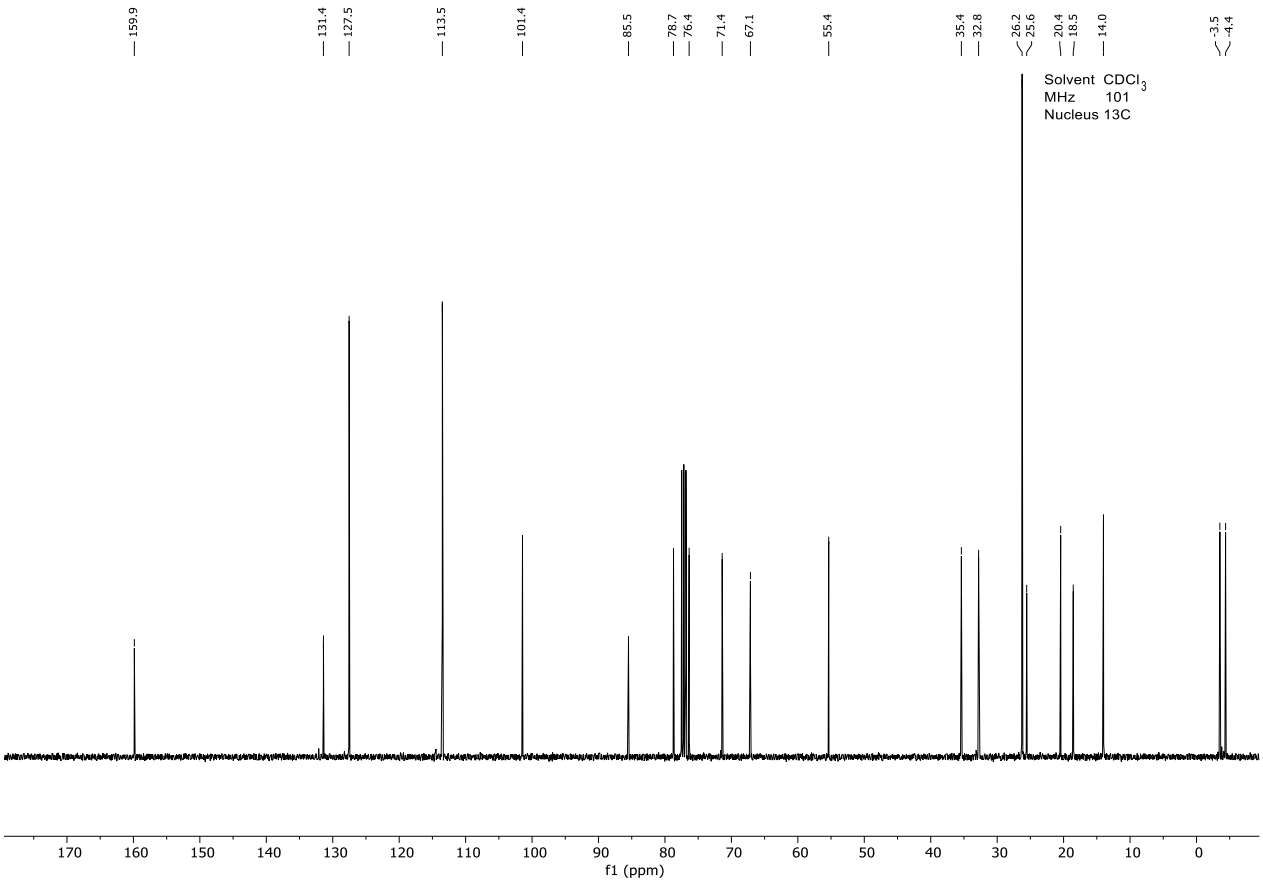

Solvent CDCl3
HSQC
f2 (ppm)
f1 (ppm)

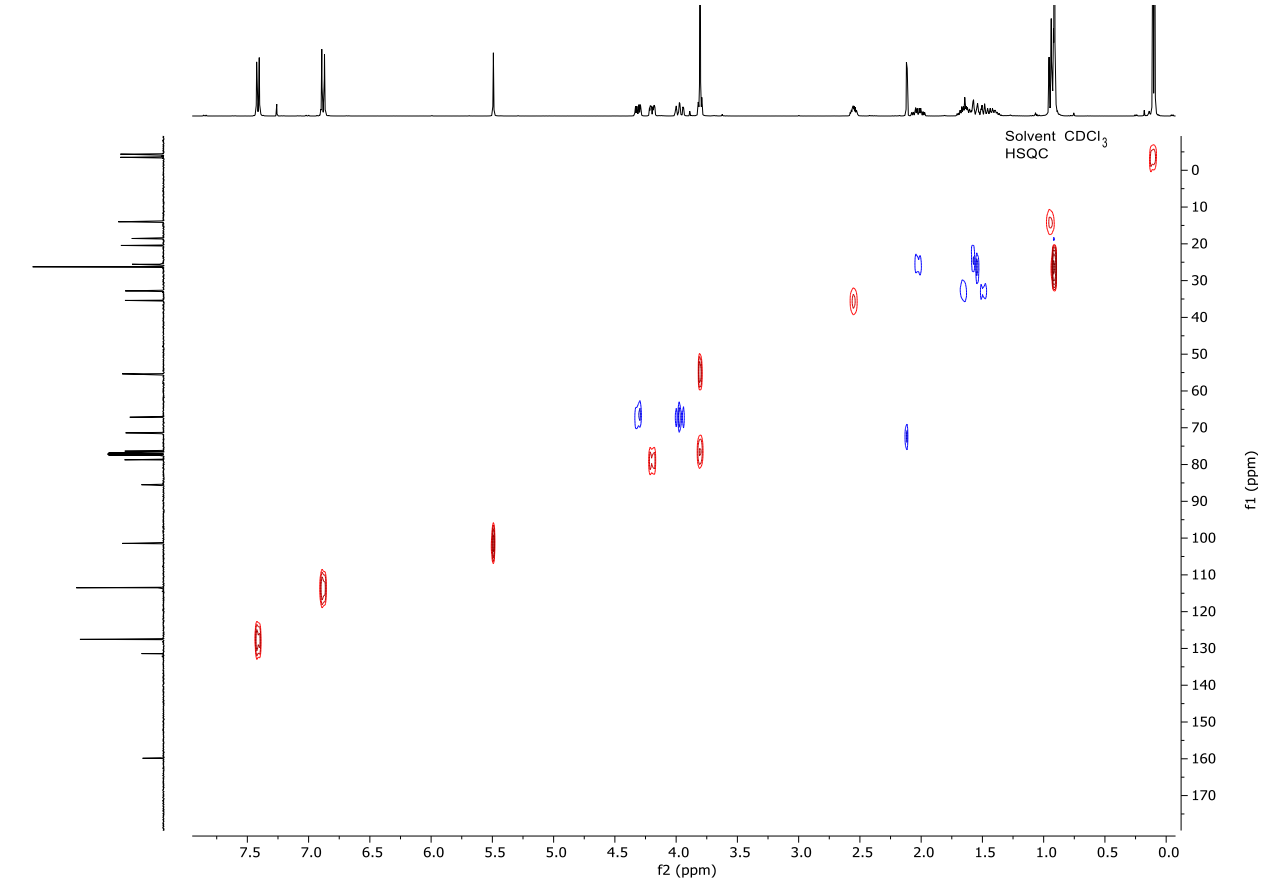

Solvent CDCl3
COSY
f2 (ppm)
f1 (ppm)

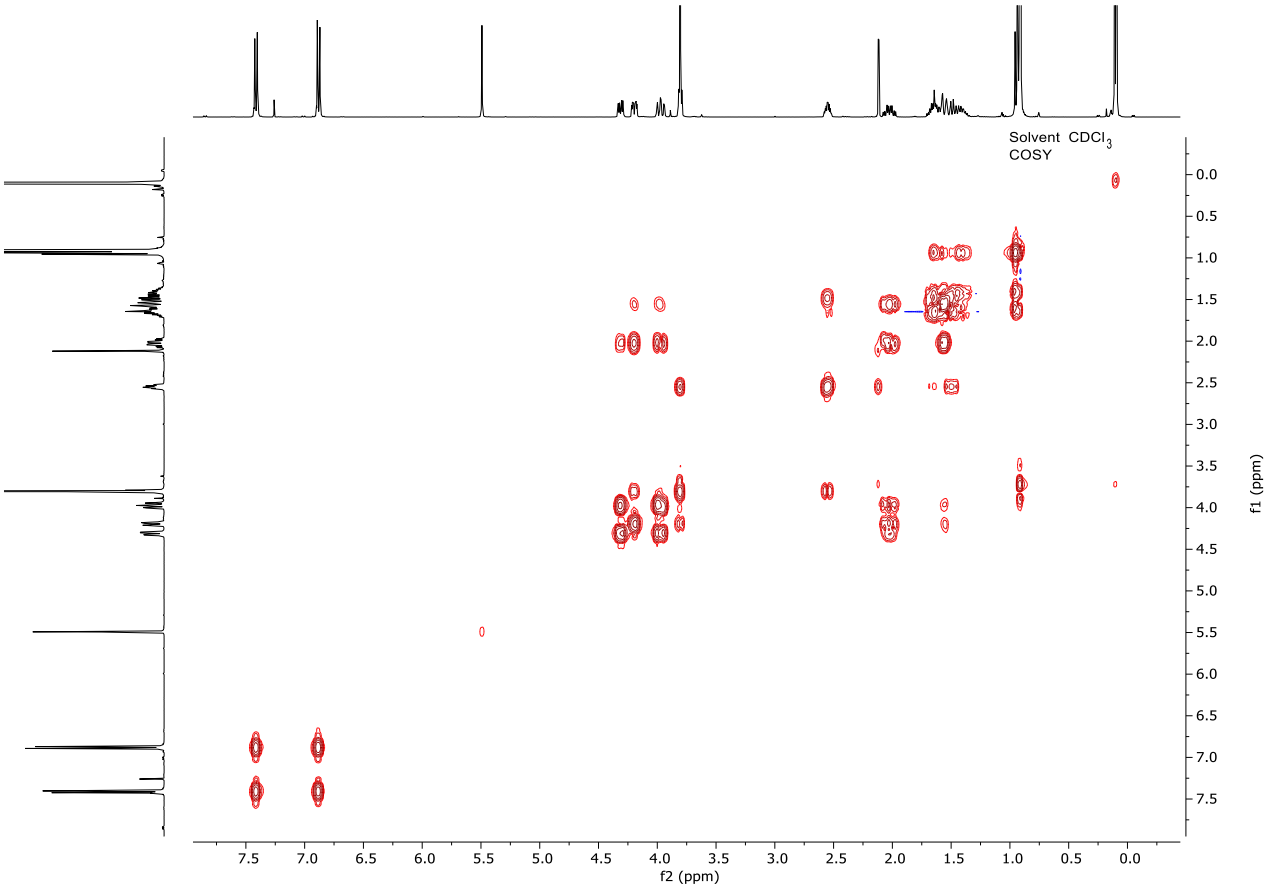

TBSO
O
O
OMe

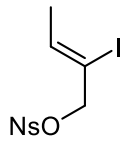
252

Solvent CDCl3
MHz 400
Nucleus 1H
2.00
2.02
1.00
1.00
0.99
1.02
3.95
0.98
0.92
1.02
5.22
12.05
3.01
2.81
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)


159.9
131.4
127.5
113.5
101.4
85.5
78.7
76.4
71.4
67.1
55.4
35.4
32.8
26.2
25.6
20.4
18.5
14.0
-3.5
-4.4
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

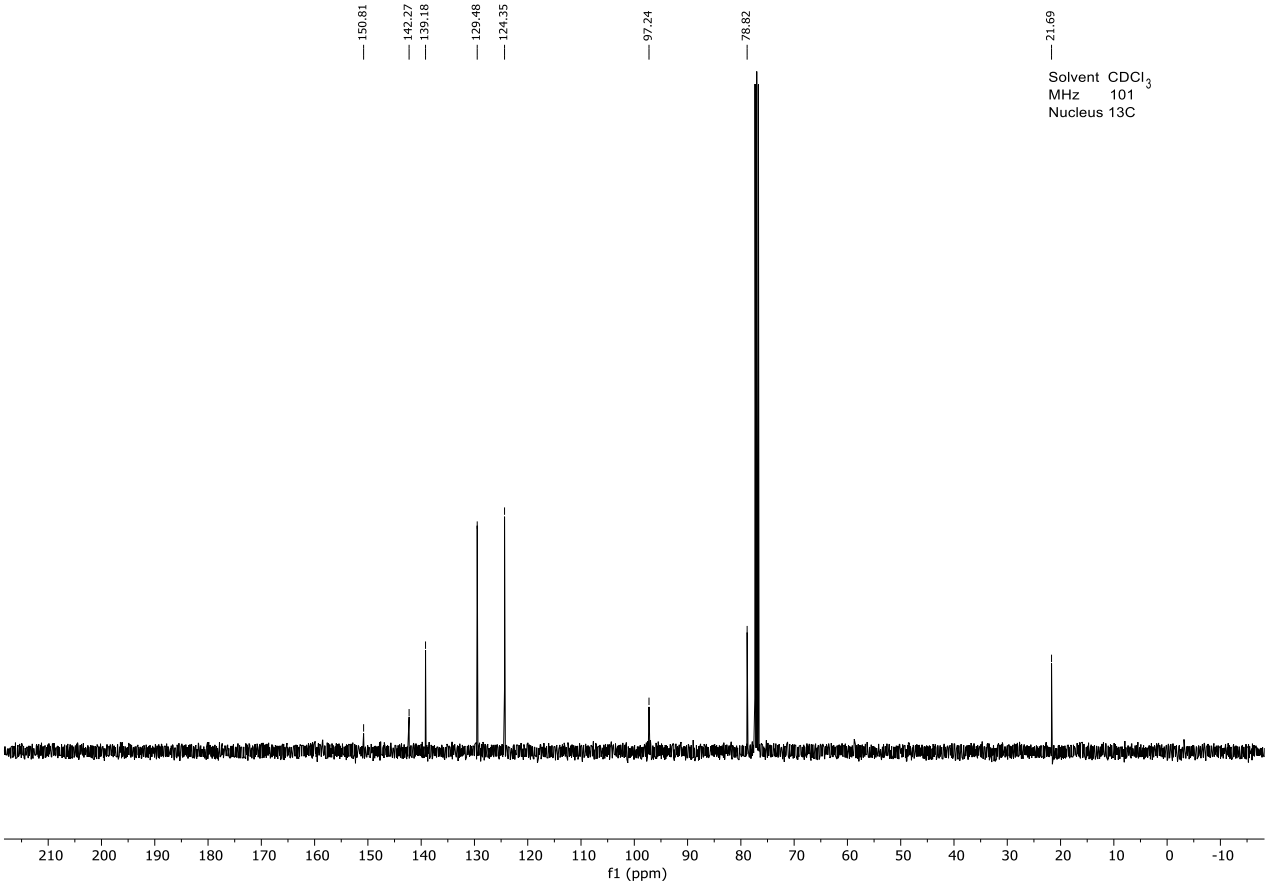

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

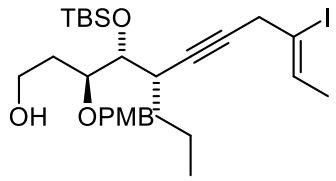

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)


I
NsO

265

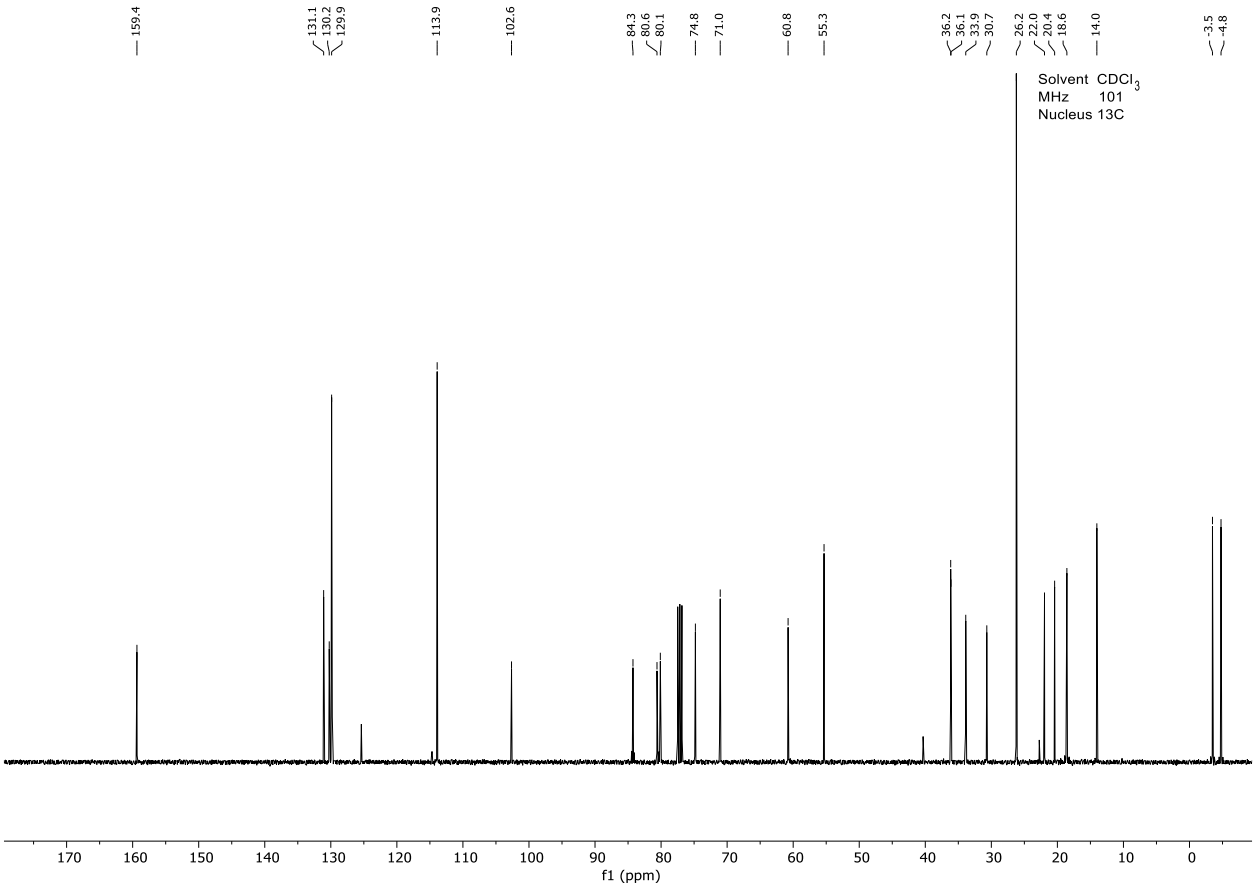
Solvent CDCl3
MHz 400
Nucleus 1H
2.01
2.00
1.00
2.08
3.08
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

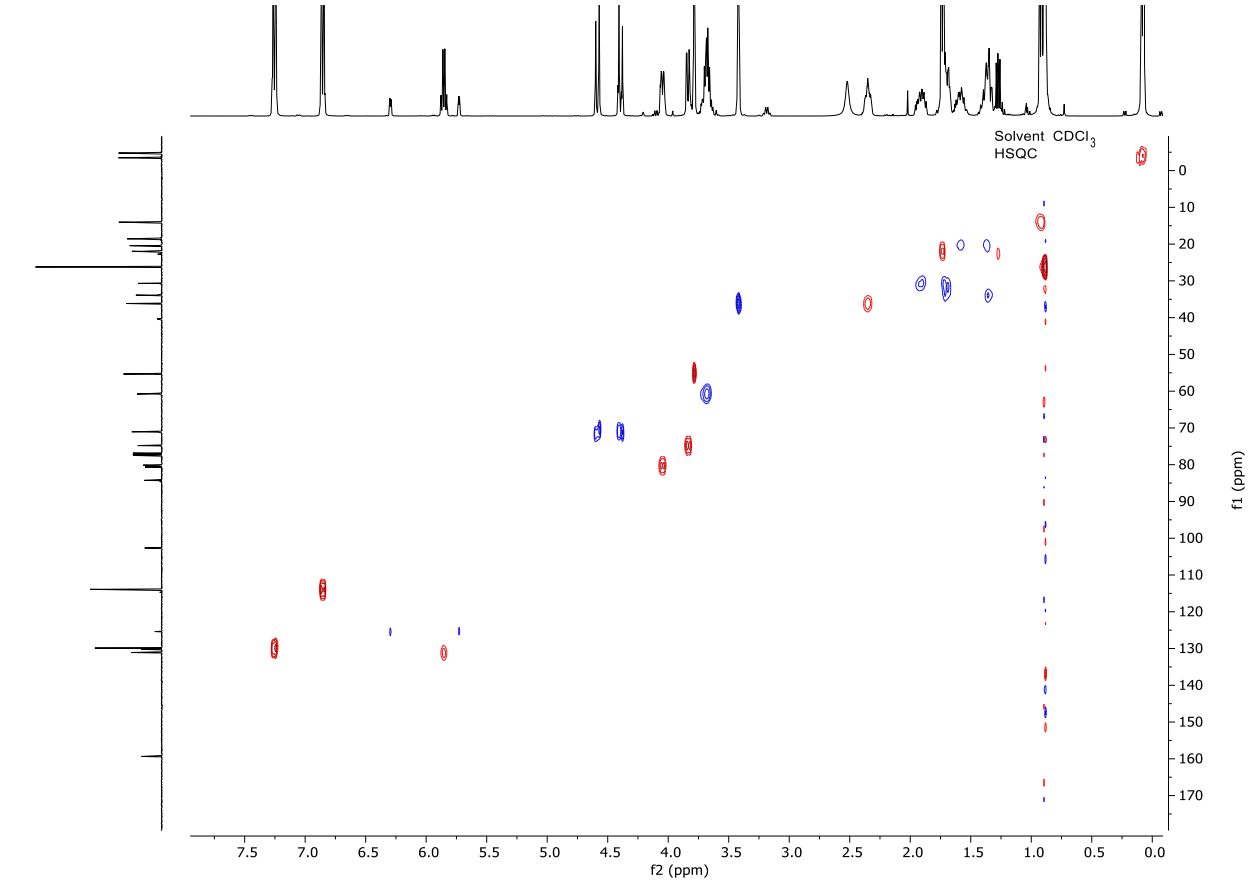

150.81
142.27
139.18
129.48
124.35
97.24
78.82
21.69
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

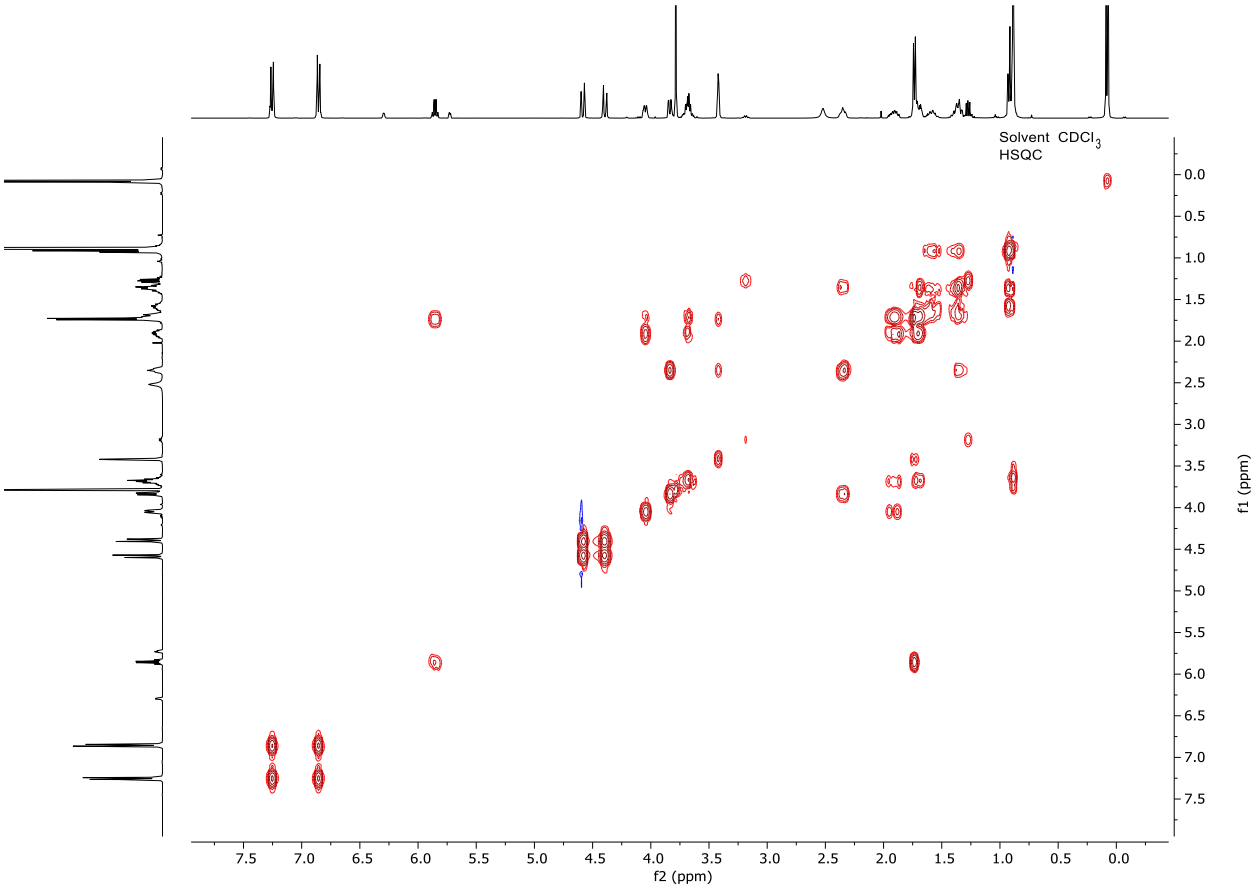

TBSO
I
OH
OPMB

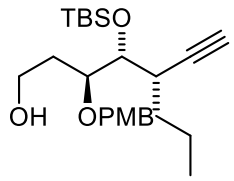
267

Solvent CDCl3
MHz 400
Nucleus 1H
2.08
2.02
0.88
1.09
0.99
1.07
1.13
3.30
1.80
1.72
0.20
0.98
1.08
1.09
4.90
1.11
2.26
0.77
12.06
2.91
2.87
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)


159.4
131.1
130.2
129.9
113.9
102.6
84.3
80.6
80.1
74.8
71.0
60.8
55.3
36.2
36.1
33.9
30.7
26.2
22.0
20.4
18.6
14.0
-3.5
-4.8
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

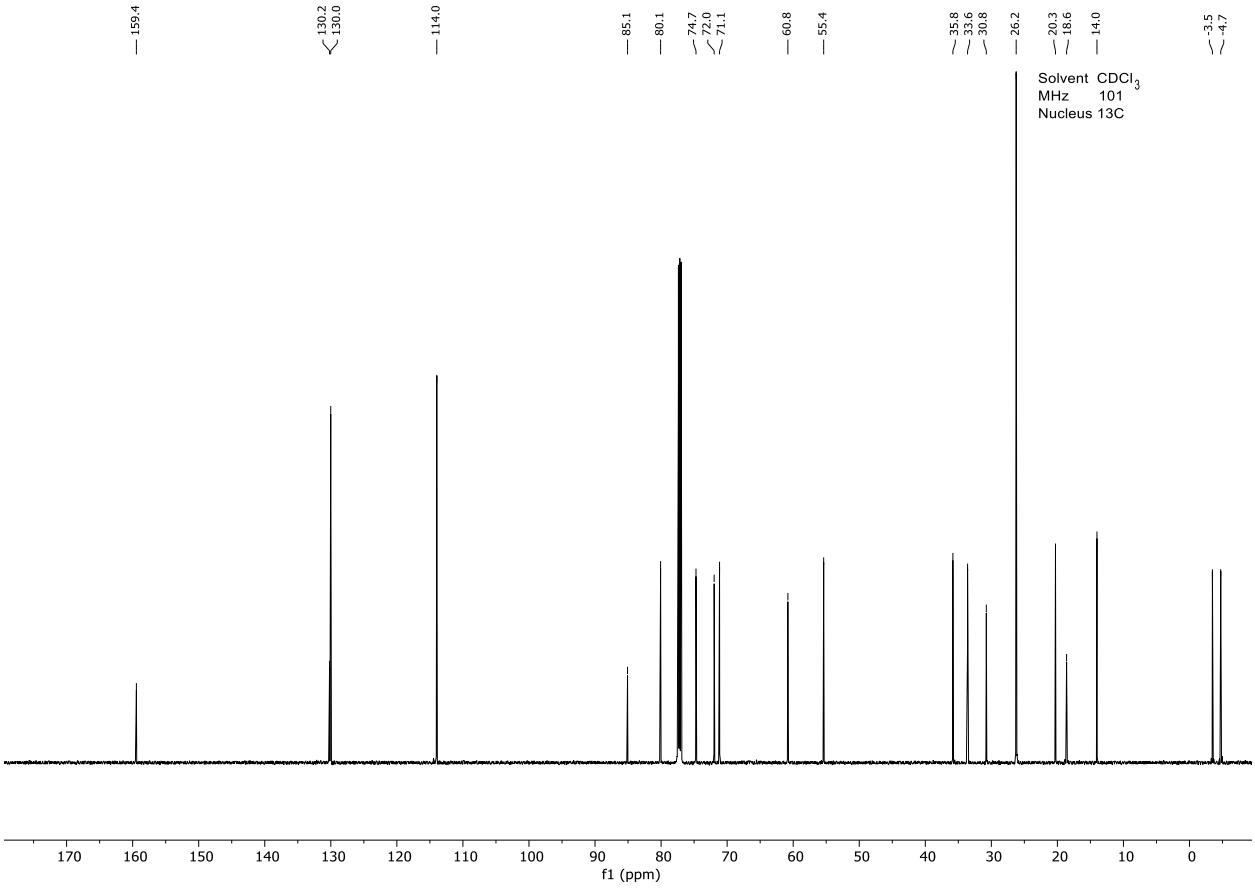

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

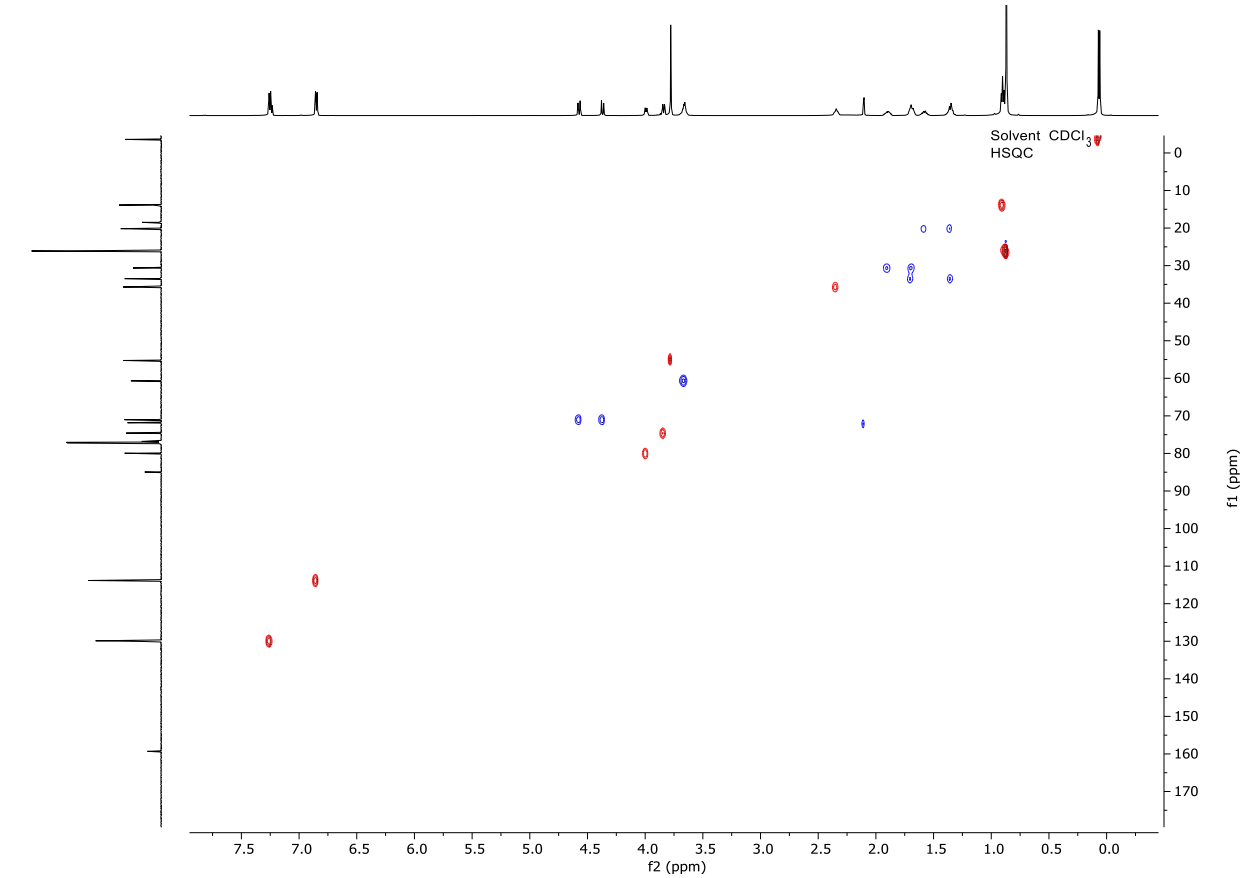

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

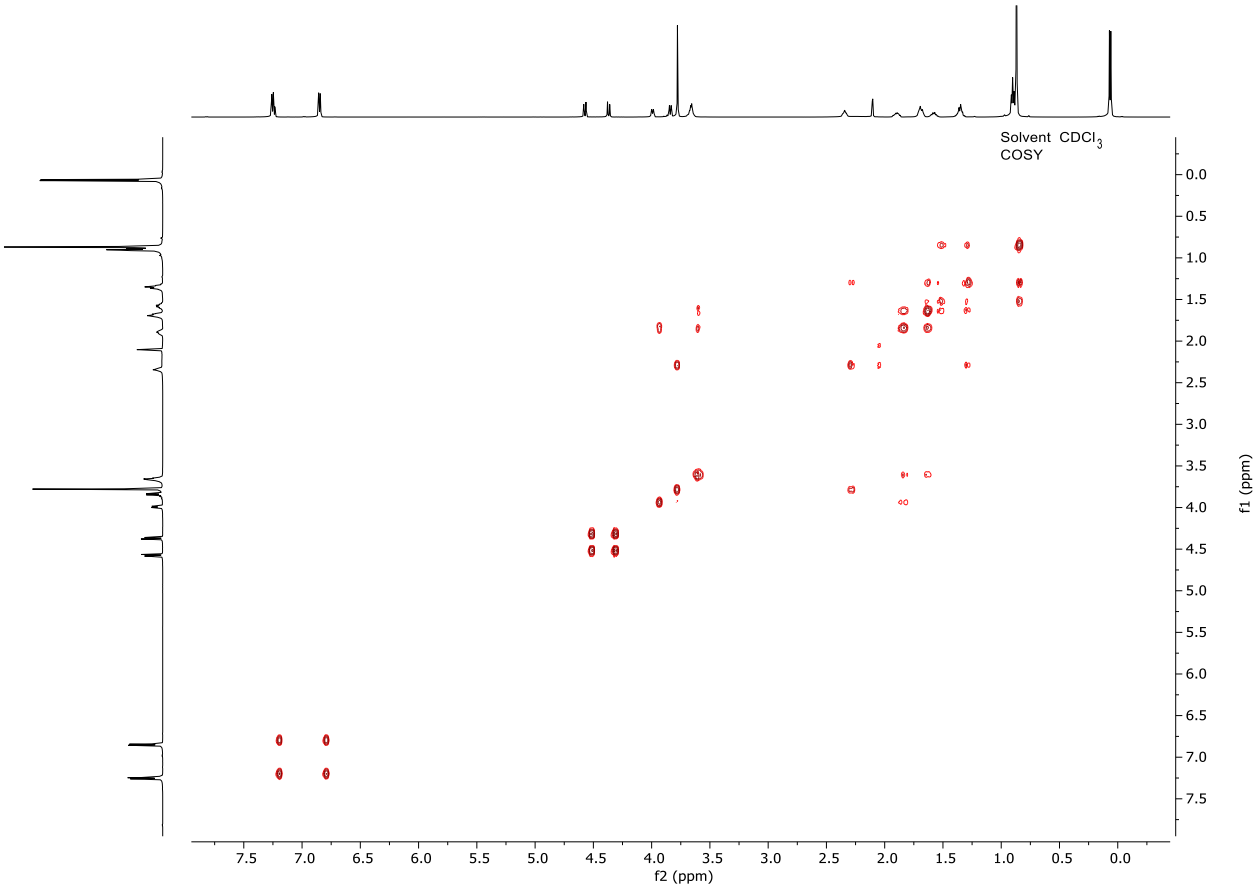

TBSO
OH
OPMB

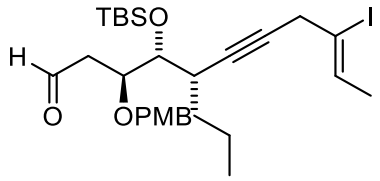
268

Solvent CDCl3
MHz 400
Nucleus 1H
1.93
1.86
0.94
1.00
0.99
1.12
3.02
2.15
1.08
0.91
1.01
1.88
1.00
2.07
3.32
8.79
3.05
2.85
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)


159.4
130.2
130.0
114.0
85.1
80.1
74.7
72.0
71.1
60.8
55.4
35.8
33.6
30.8
26.2
20.3
18.6
14.0
-3.5
-4.7
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

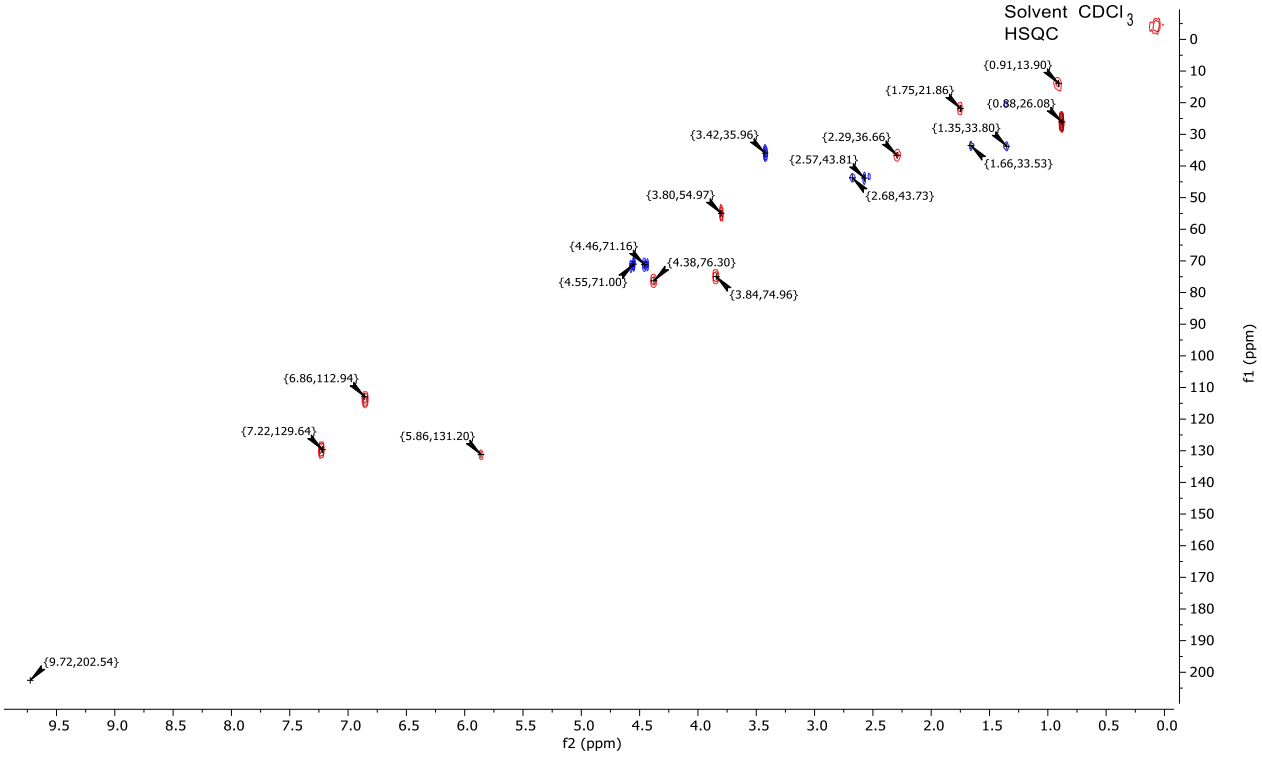

Solvent CDCl3
HSQC
f2 (ppm)
f1 (ppm)

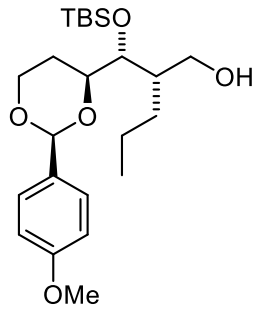

Solvent CDCl3
COSY
f2 (ppm)
f1 (ppm)


TBSO
I
H
O
OPMB

250

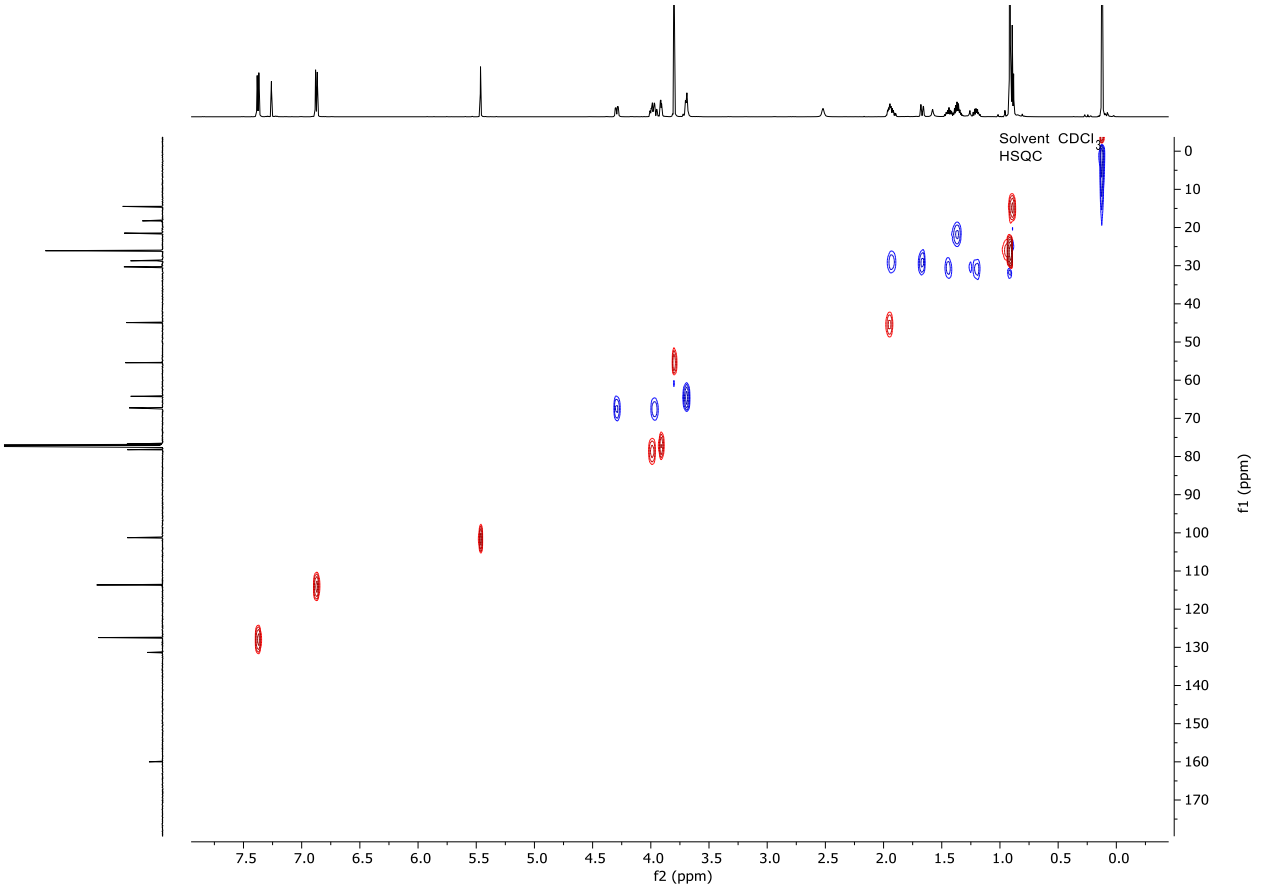
Solvent CDCl3
MHz 400
Nucleus 1H
1.08
2.01
2.31
1.00
1.26
1.23
1.16
1.17
3.25
2.03
1.14
0.98
1.19
3.07
1.47
1.43
0.70
3.23
8.98
3.16
2.79
f1 (ppm)

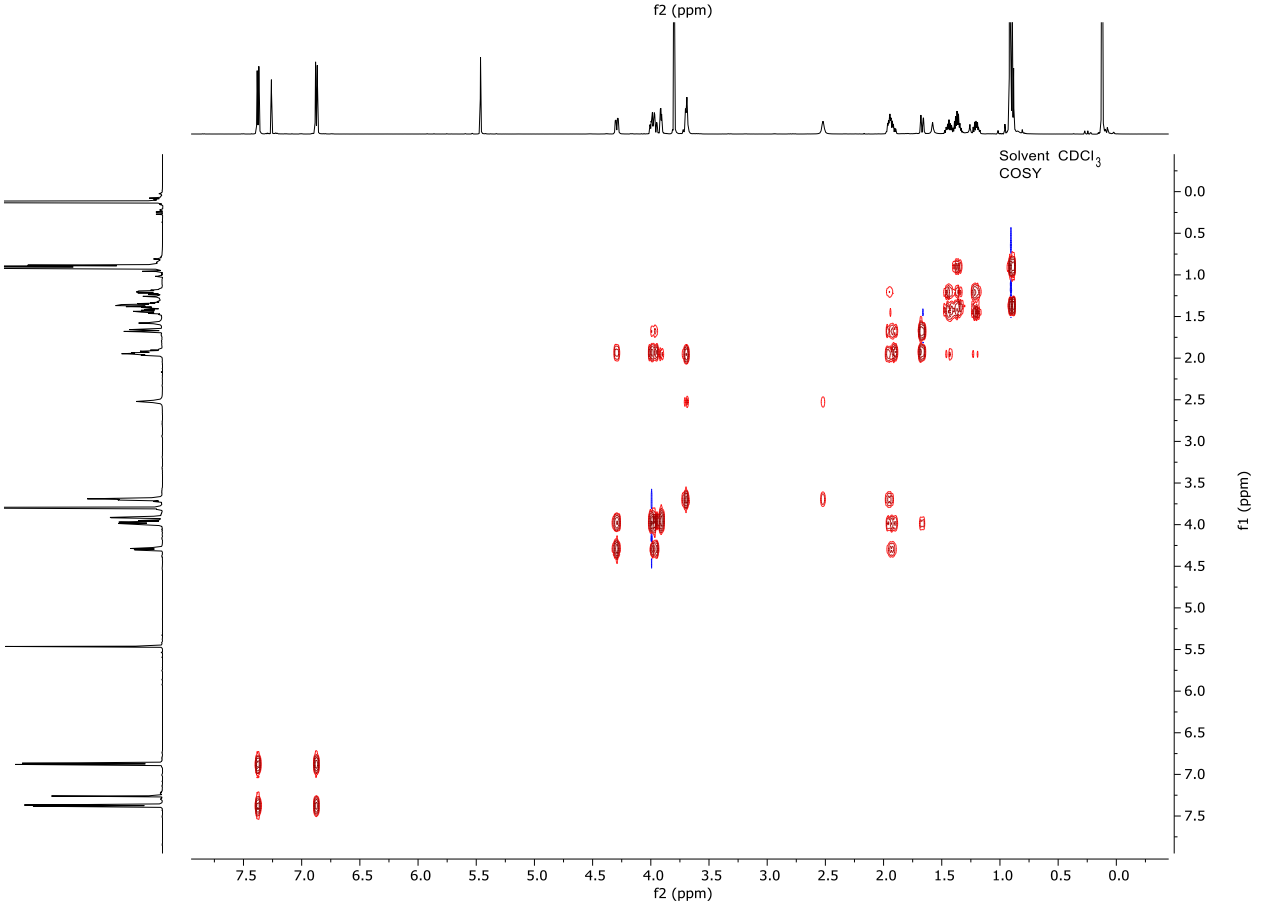

Solvent CDCl3
HSQC
{0.91,13.90}
{1.75,21.86}
{0.88,26.08}
{1.35,33.80}
{3.42,35.96}
{2.29,36.66}
{1.66,33.53}
{2.57,43.81}
{2.68,43.73}
{3.80,54.97}
{4.46,71.16}
{4.38,76.30}
{4.55,71.00}
{3.84,74.96}
{6.86,112.94}
{7.22,129.64}
{5.86,131.20}
{9.72,202.54}
f2 (ppm)
f1 (ppm)

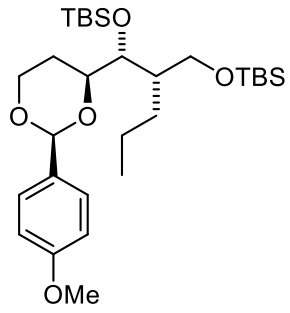

TBSO
OH
O
O
OMe

279

Solvent CDCl3
MHz 400
Nucleus 1H
2.00
2.02
1.00
1.01
2.05
1.01
3.08
1.90
0.87
1.99
1.01
1.15
1.96
1.02
12.09
2.78
2.93
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)
160.0
131.3
127.4
113.7
101.3
78.2
76.7
67.2
64.2
55.4
44.9
30.3
28.7
26.1
21.5
18.3
14.5
-4.0
-4.3
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

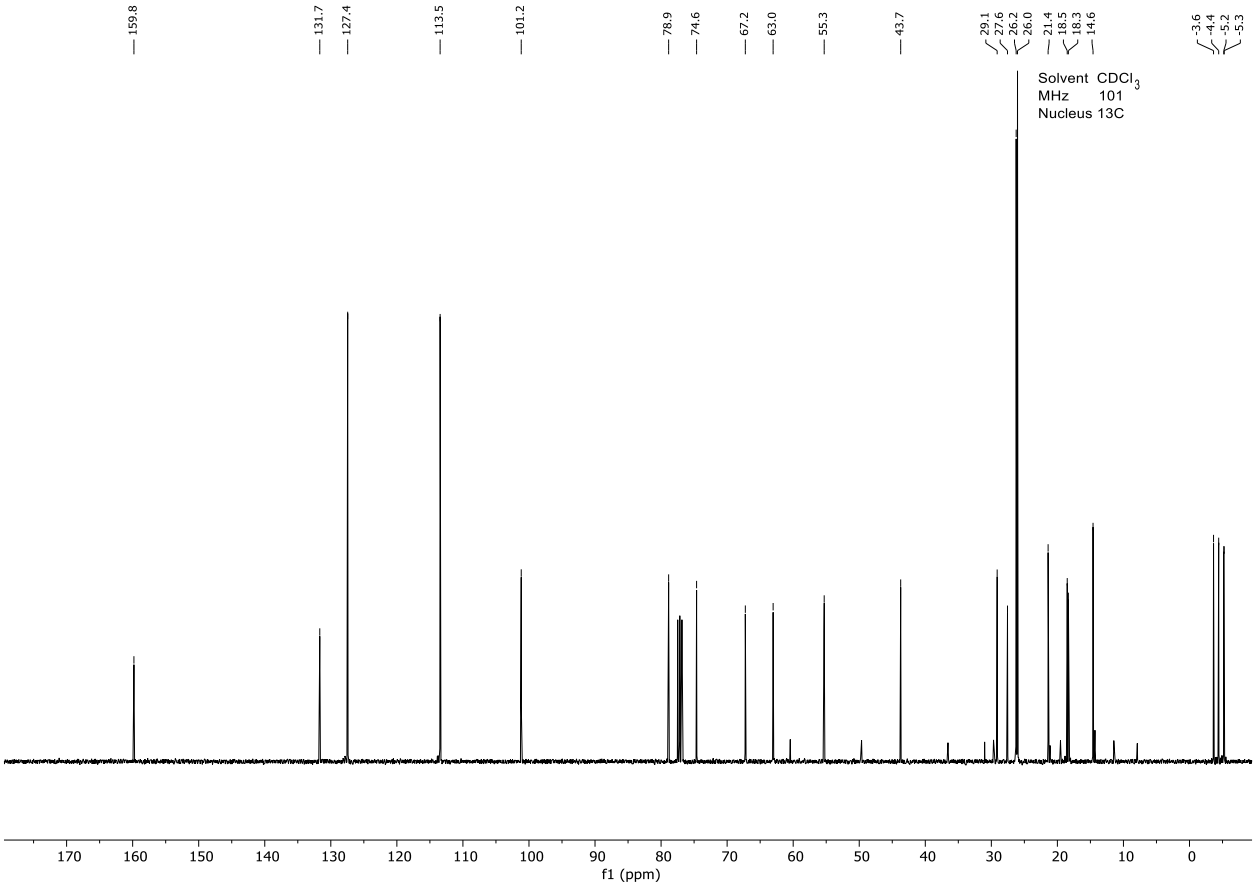

Solvent CDCl3
HSQC
f2 (ppm)
f1 (ppm)

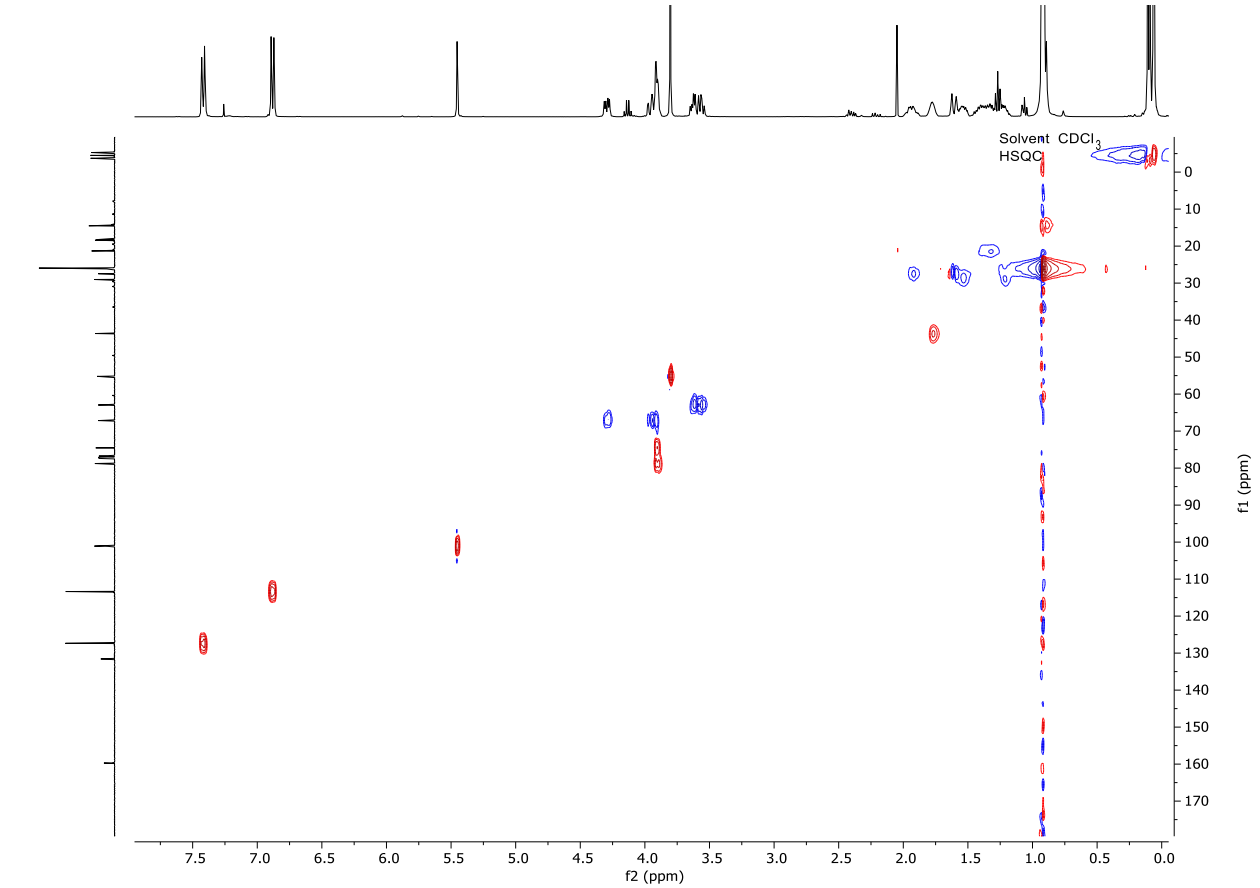

Solvent CDCl3
COSY
f2 (ppm)
f1 (ppm)

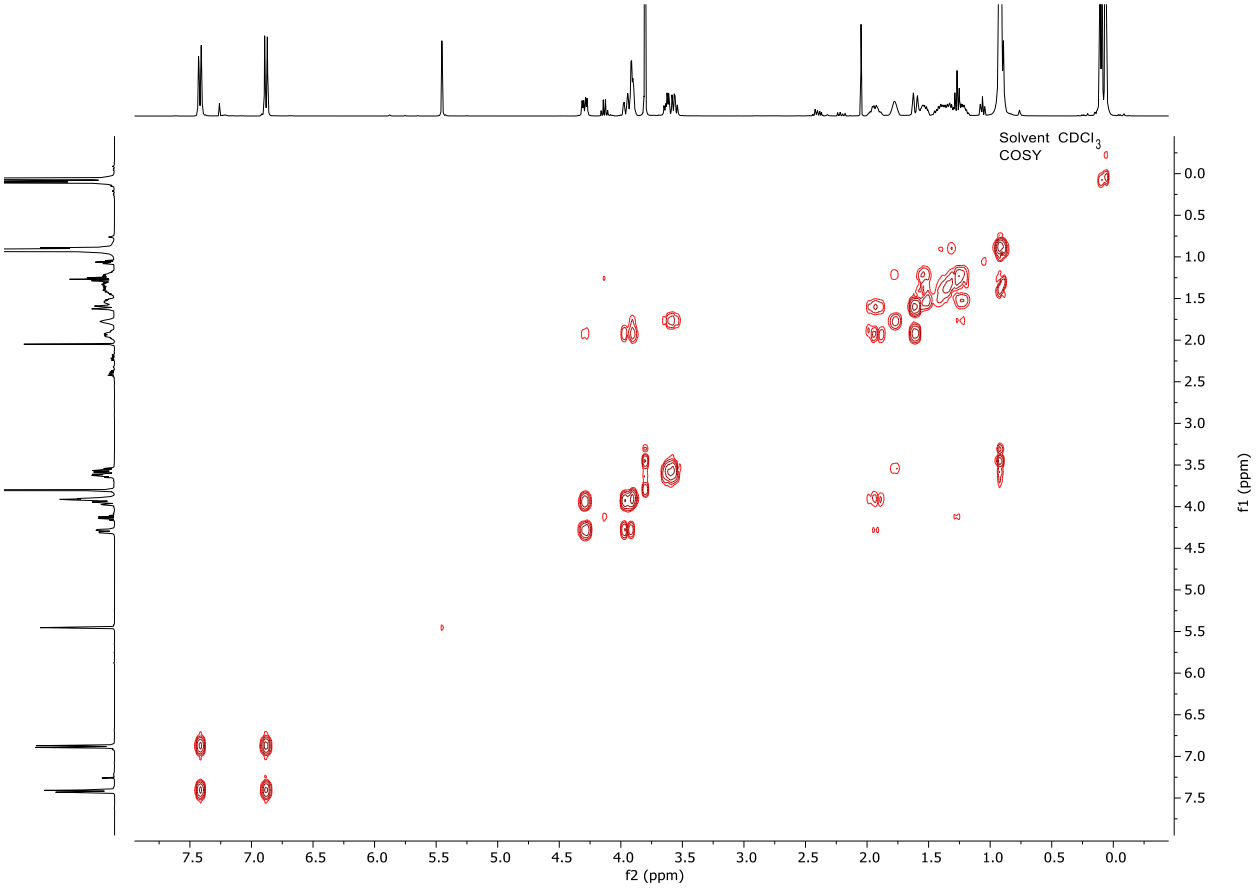

TBSO
OTBS
O
O
OMe

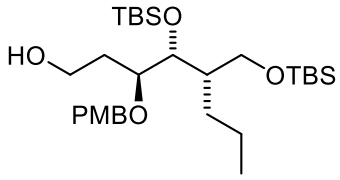
280

Solvent CDCl3
MHz 400
Nucleus 1H
2.04
2.08
1.00
1.05
3.11
3.15
1.06
1.02
1.12
1.06
1.04
0.90
2.02
0.94
21.20
3.02
2.94
6.21
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)


159.8
131.7
127.4
113.5
101.2
78.9
74.6
67.2
63.0
55.3
43.7
29.1
27.6
26.2
26.0
21.4
18.5
18.3
14.6
-3.6
-4.4
-5.2
-5.3
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

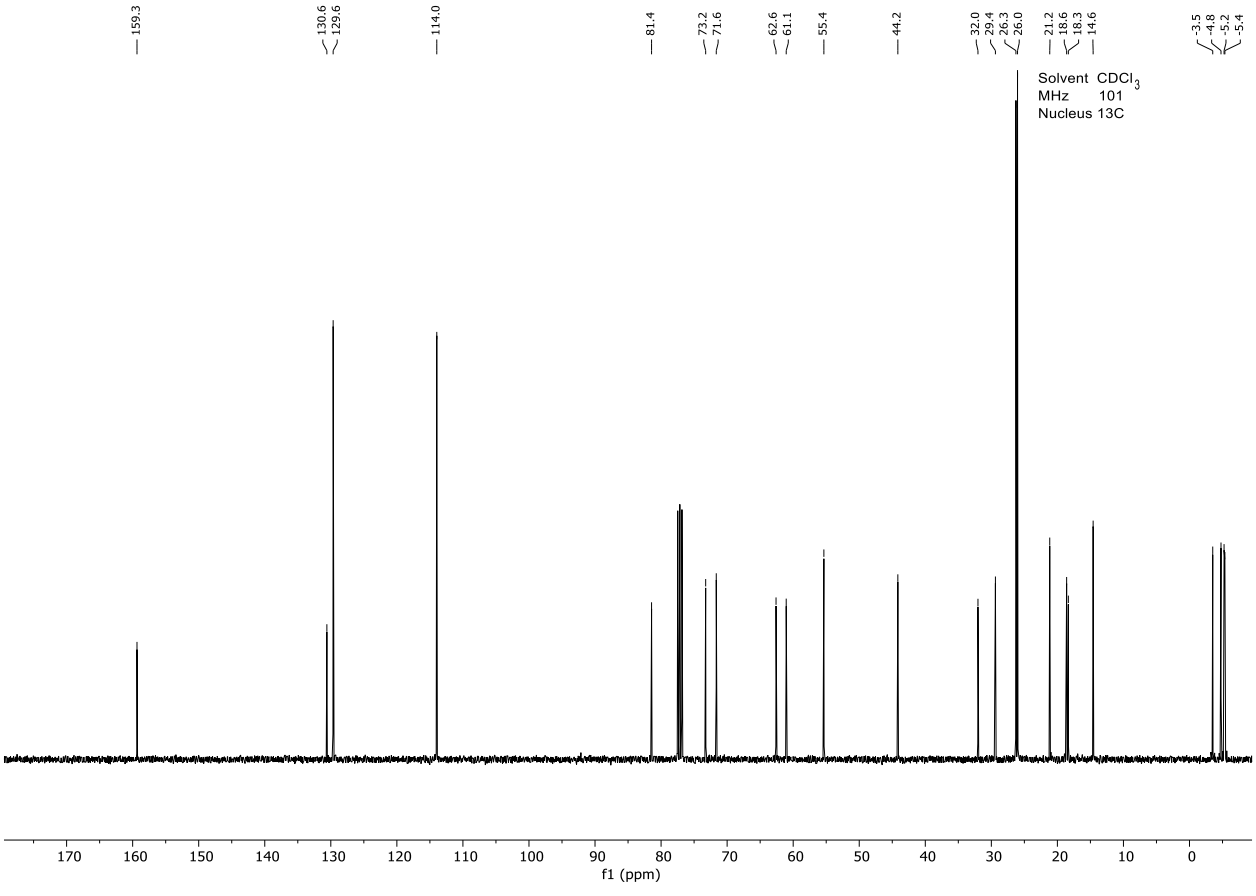

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

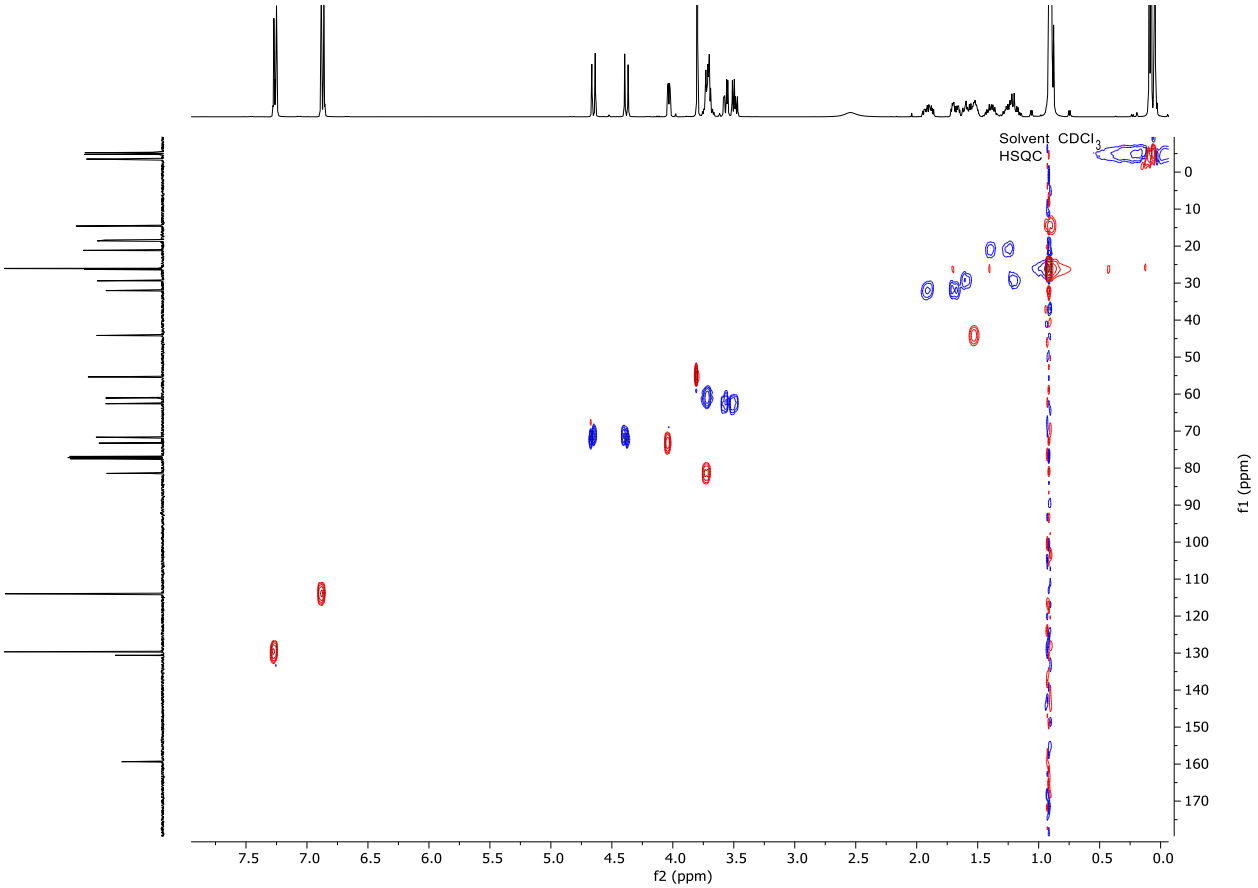

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

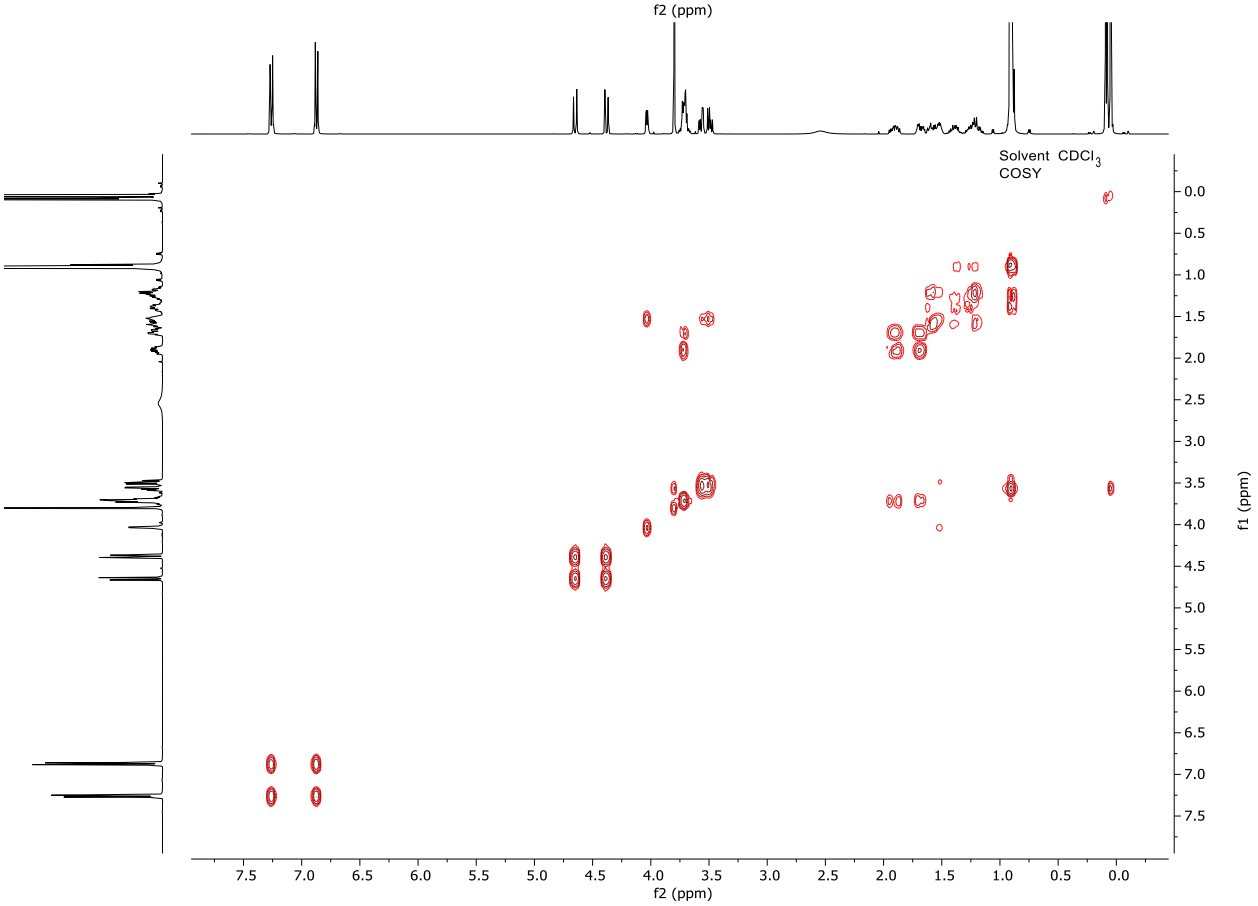

TBSO
HO
OTBS
PMBO

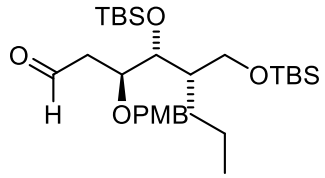
281

Solvent CDCl3
MHz 400
Nucleus 1H
2.15
2.04
1.00
1.00
1.02
3.10
2.97
1.00
1.00
0.86
0.98
1.01
2.00
1.02
2.03
21.08
2.92
2.85
5.90
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)


159.3
130.6
129.6
114.0
81.4
73.2
71.6
62.6
61.1
55.4
44.2
32.0
29.4
26.3
26.0
21.2
18.6
18.3
14.6
-3.5
-4.8
-5.2
-5.4
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

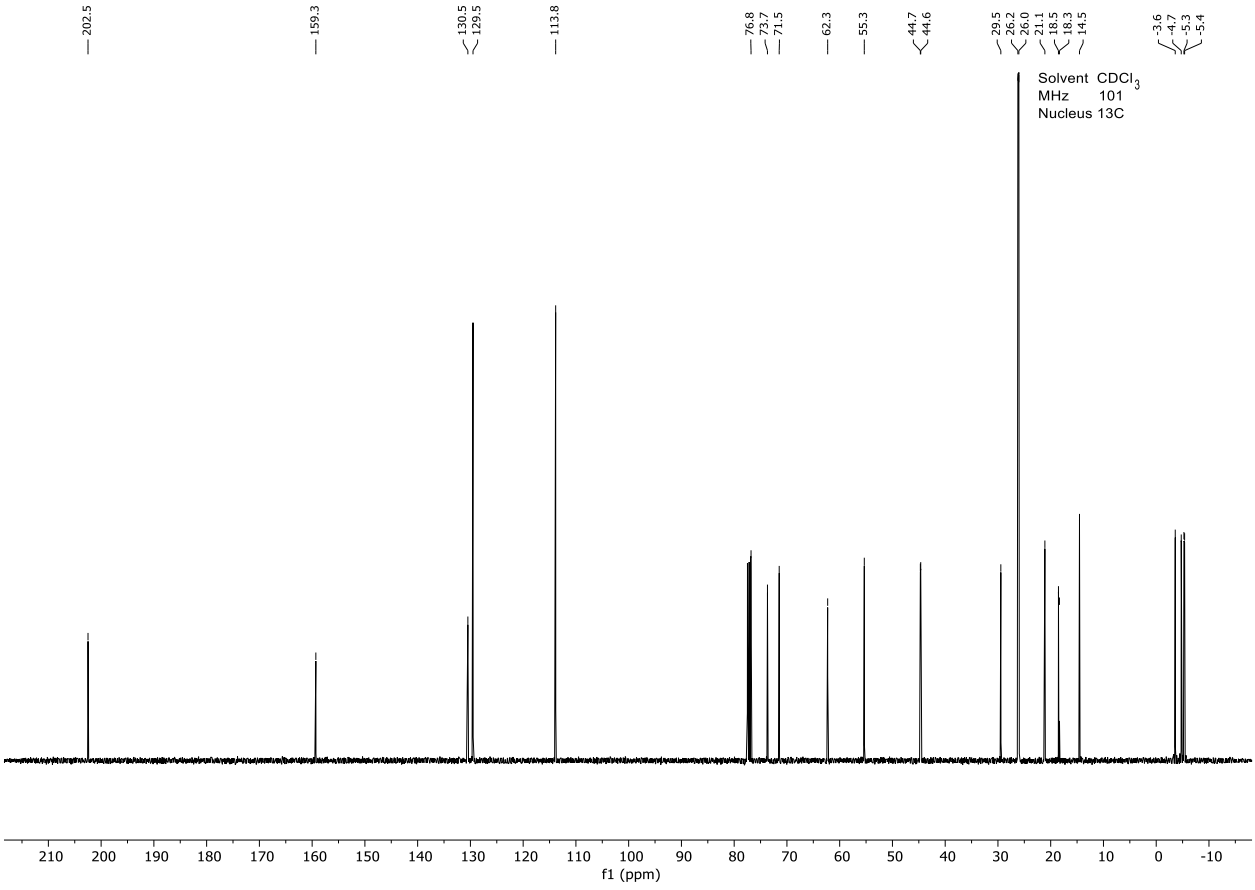

Solvent CDCl3
HSQC
f2 (ppm)
f1 (ppm)

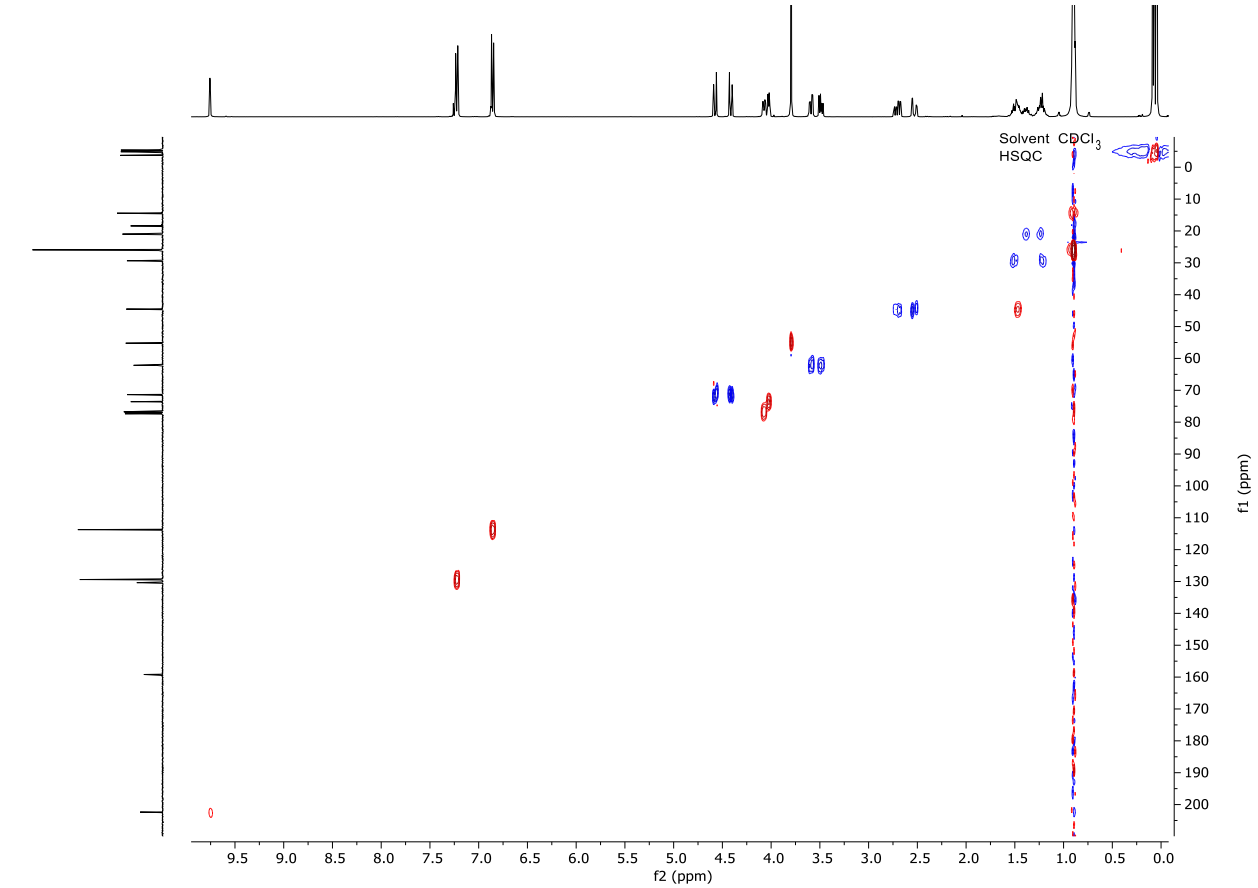

Solvent CDCl3
COSY
f2 (ppm)
f1 (ppm)

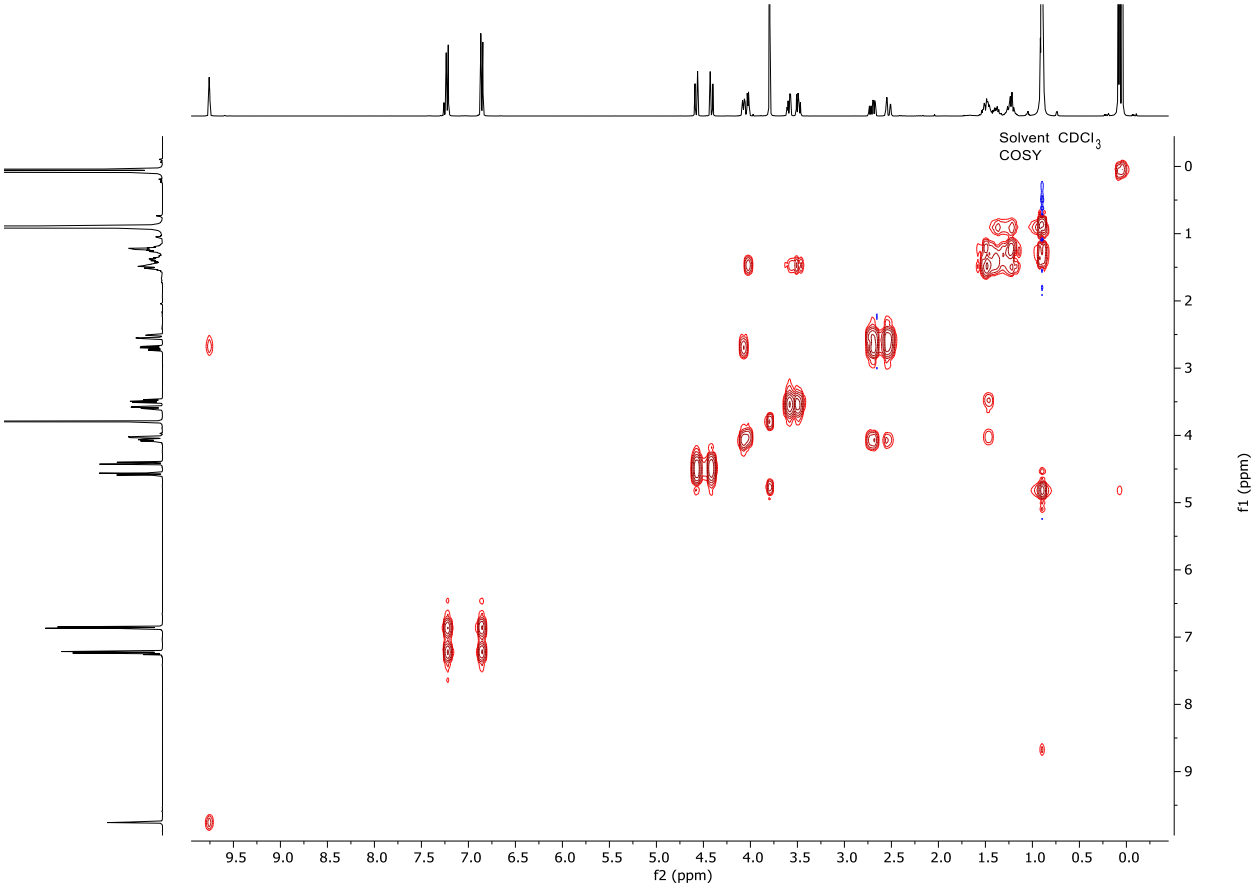

TBSO
O
H
OPMB
OTBS

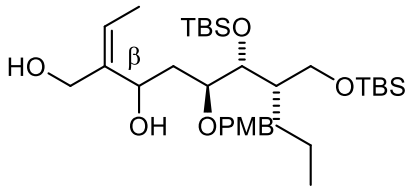
278

Solvent CDCl3
MHz 400
Nucleus 1H
0.97
1.97
2.01
1.00
0.97
1.01
0.98
3.02
1.00
0.98
0.99
1.00
2.16
1.01
2.16
11.94
9.00
3.10
2.96
5.98
f1 (ppm)


202.5
159.3
130.5
129.5
113.8
76.8
73.7
71.5
62.3
55.3
44.7
44.6
29.5
26.2
26.0
21.1
18.5
18.3
14.5
-3.6
-4.7
-5.3
-5.4
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

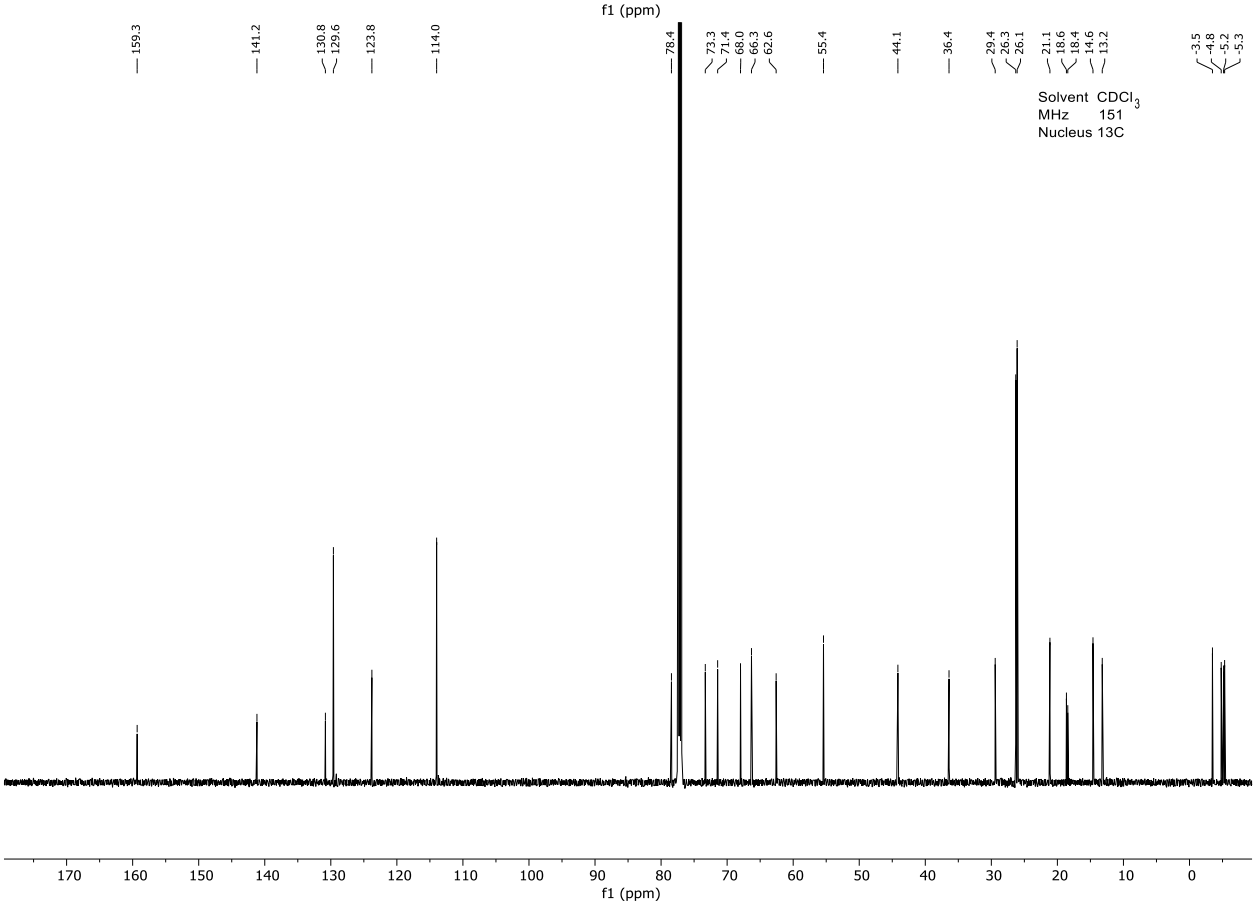

Solvent CDCl3
HSQC
f2 (ppm)
f1 (ppm)

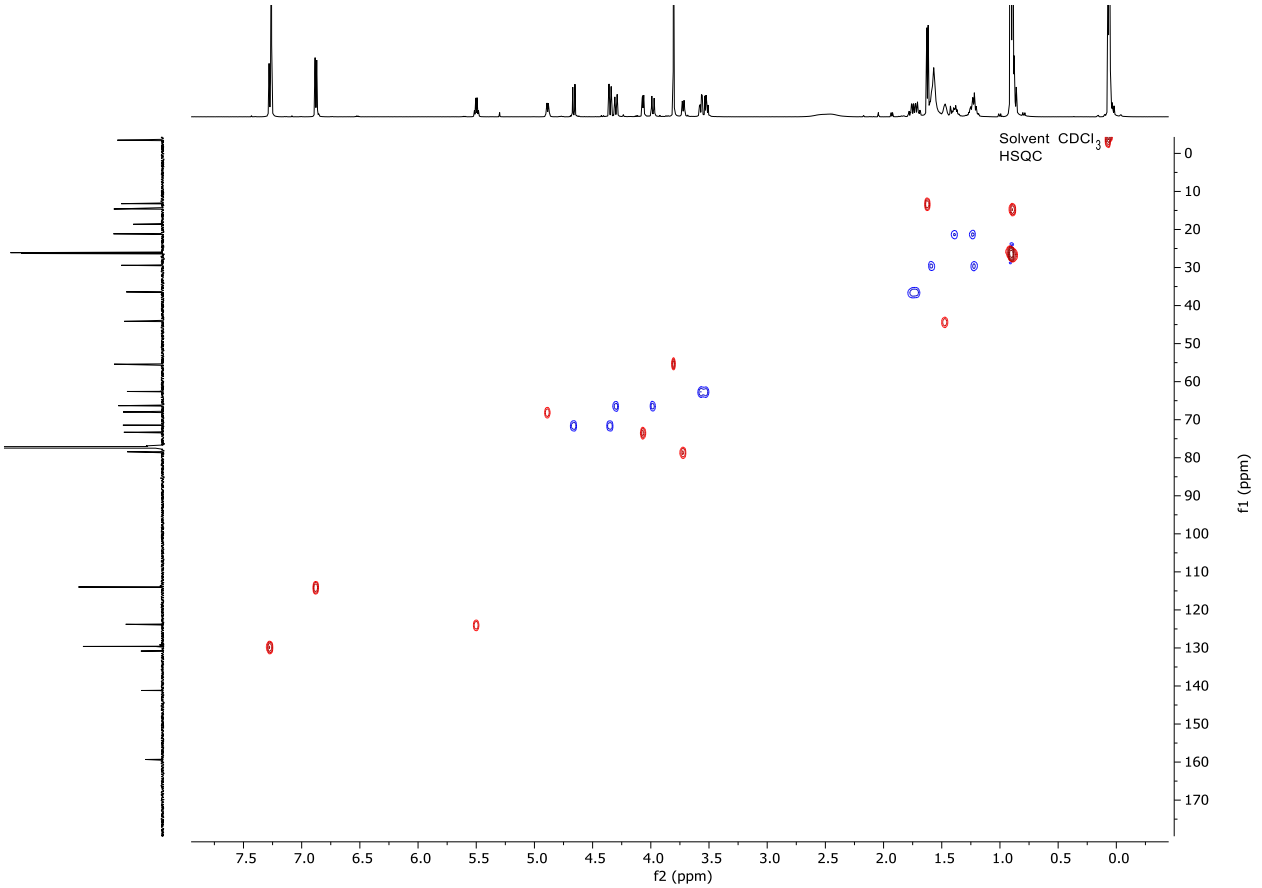

Solvent CDCl3
COSY
f2 (ppm)
f1 (ppm)

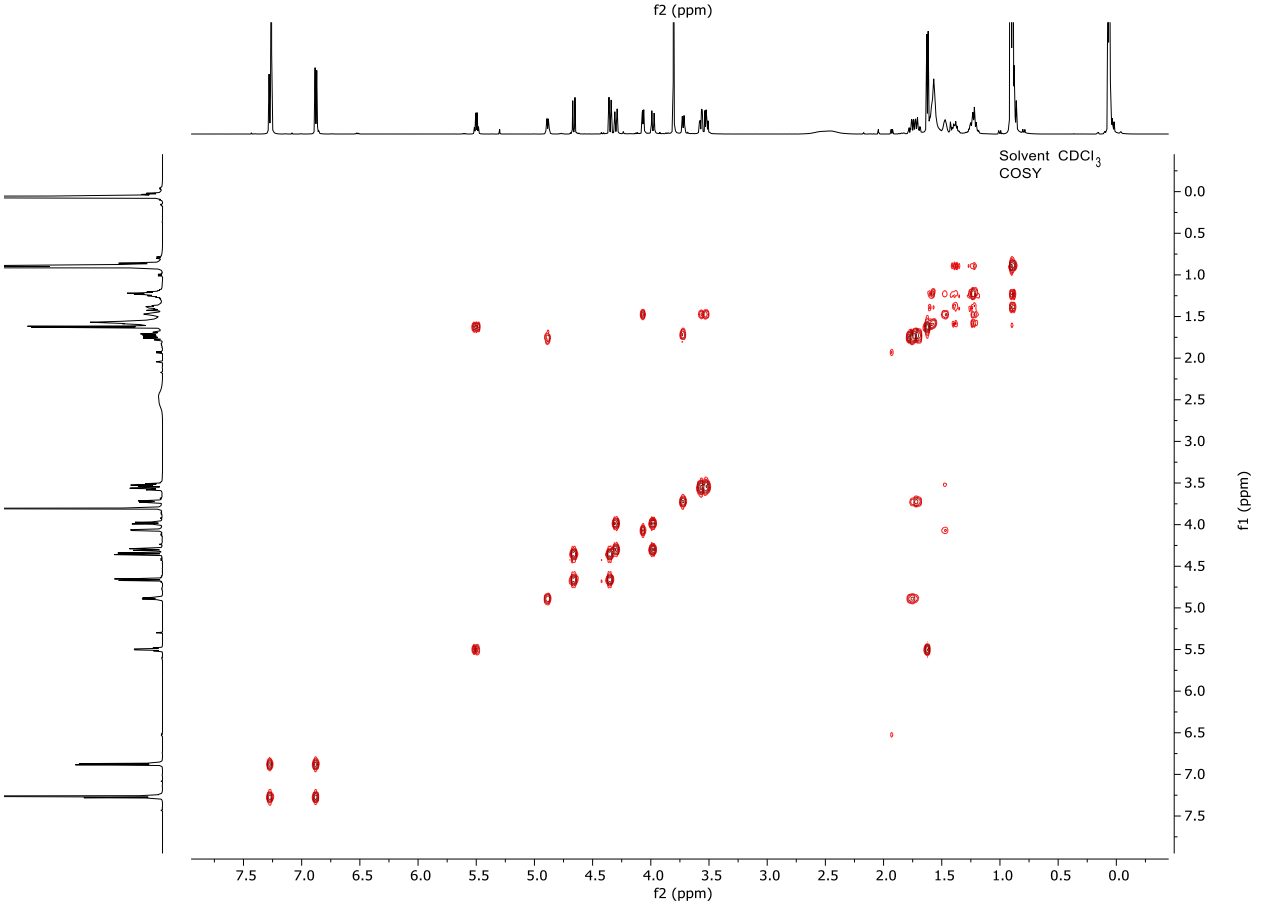

TBSO
β
HO
OTBS
OH
OPMB

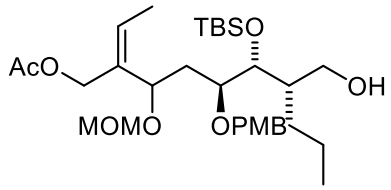
β-**284**

Solvent CDCl3
MHz 600
Nucleus 1H
2.30
2.00
0.97
0.95
0.98
1.00
0.97
1.02
0.98
3.18
1.02
0.98
1.06
1.71
2.20
3.02
1.05
1.18
1.13
2.45
9.12
12.15
2.80
2.70
5.95
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)


159.3
141.2
130.8
129.6
123.8
114.0
78.4
73.3
71.4
68.0
66.3
62.6
55.4
44.1
36.4
29.4
26.3
26.1
21.1
18.6
18.4
14.6
13.2
-3.5
-4.8
-5.2
-5.3
Solvent CDCl3
MHz 151
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

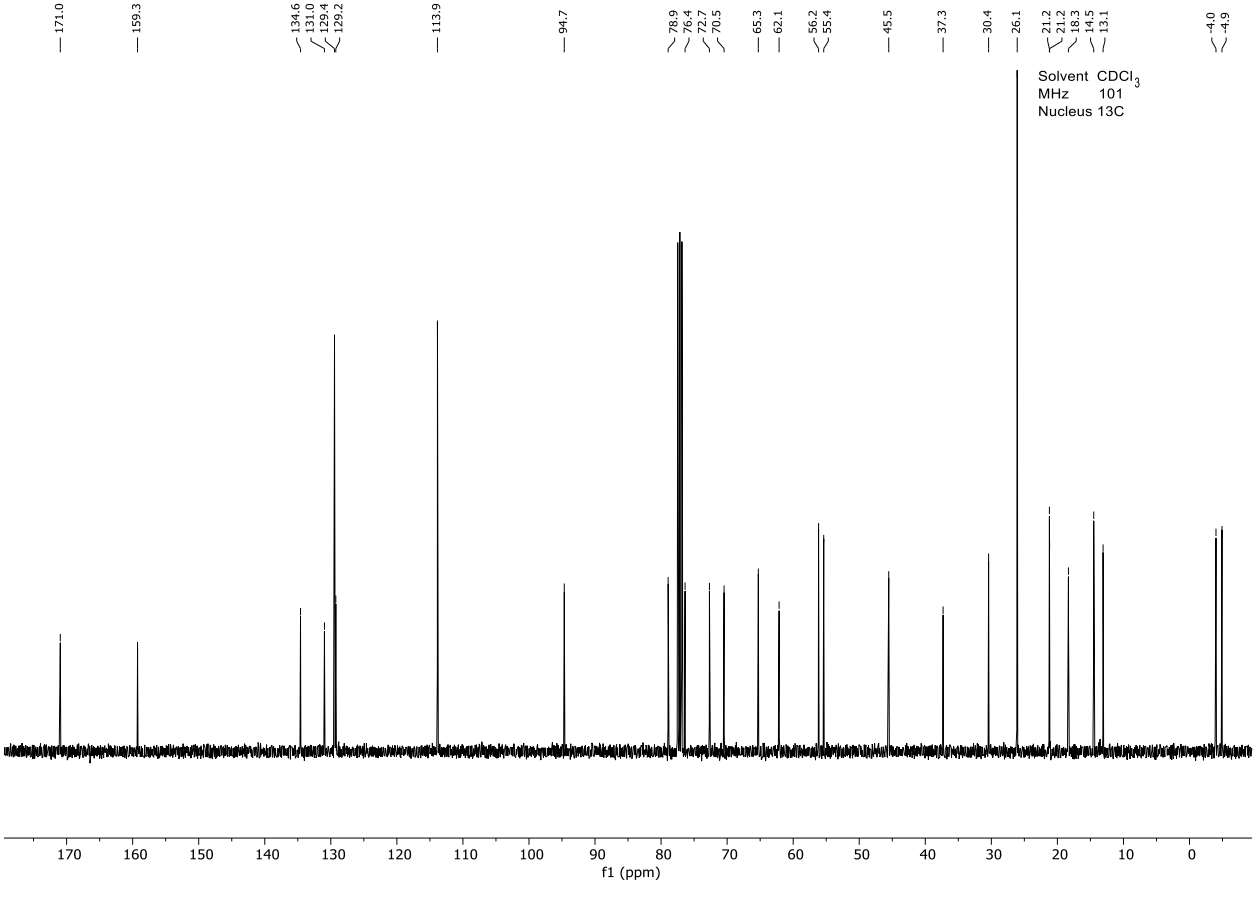

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

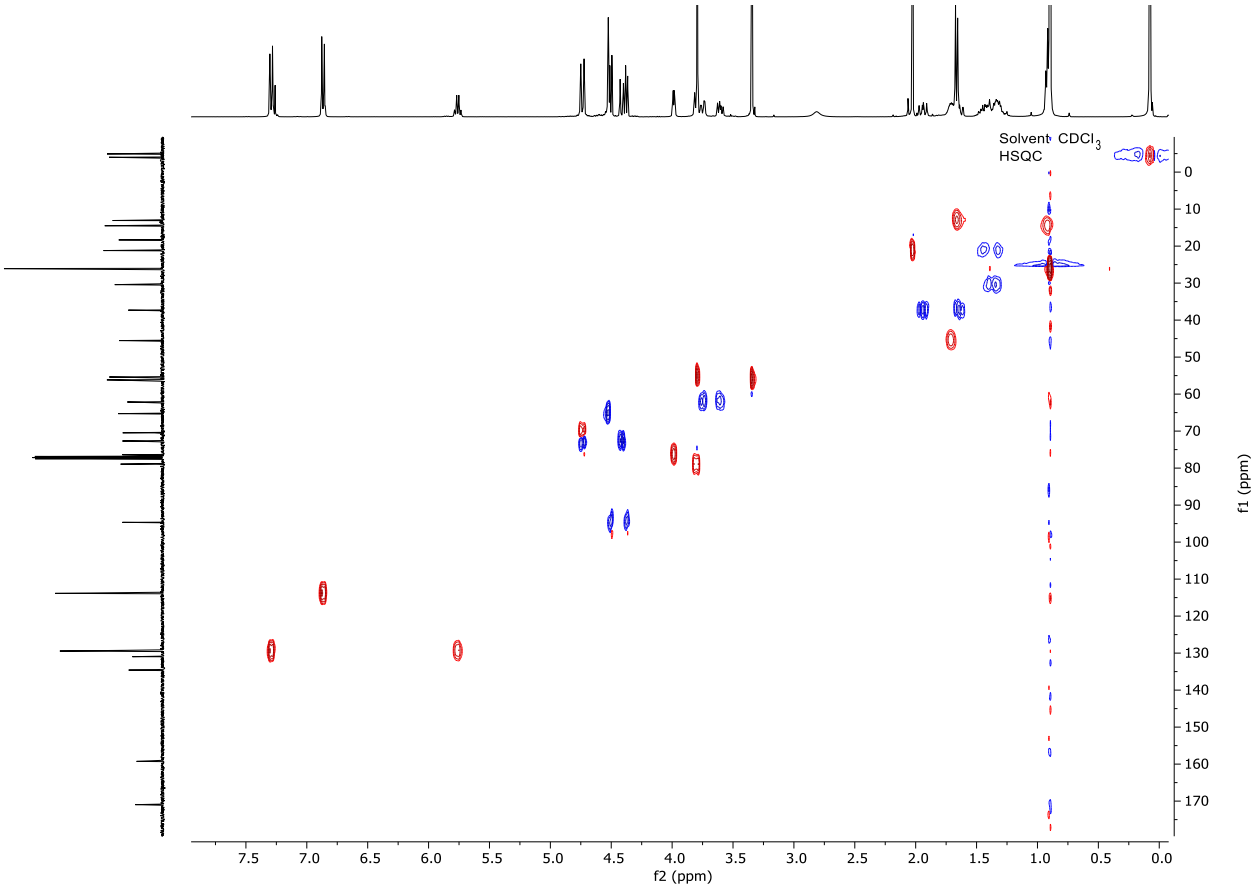

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

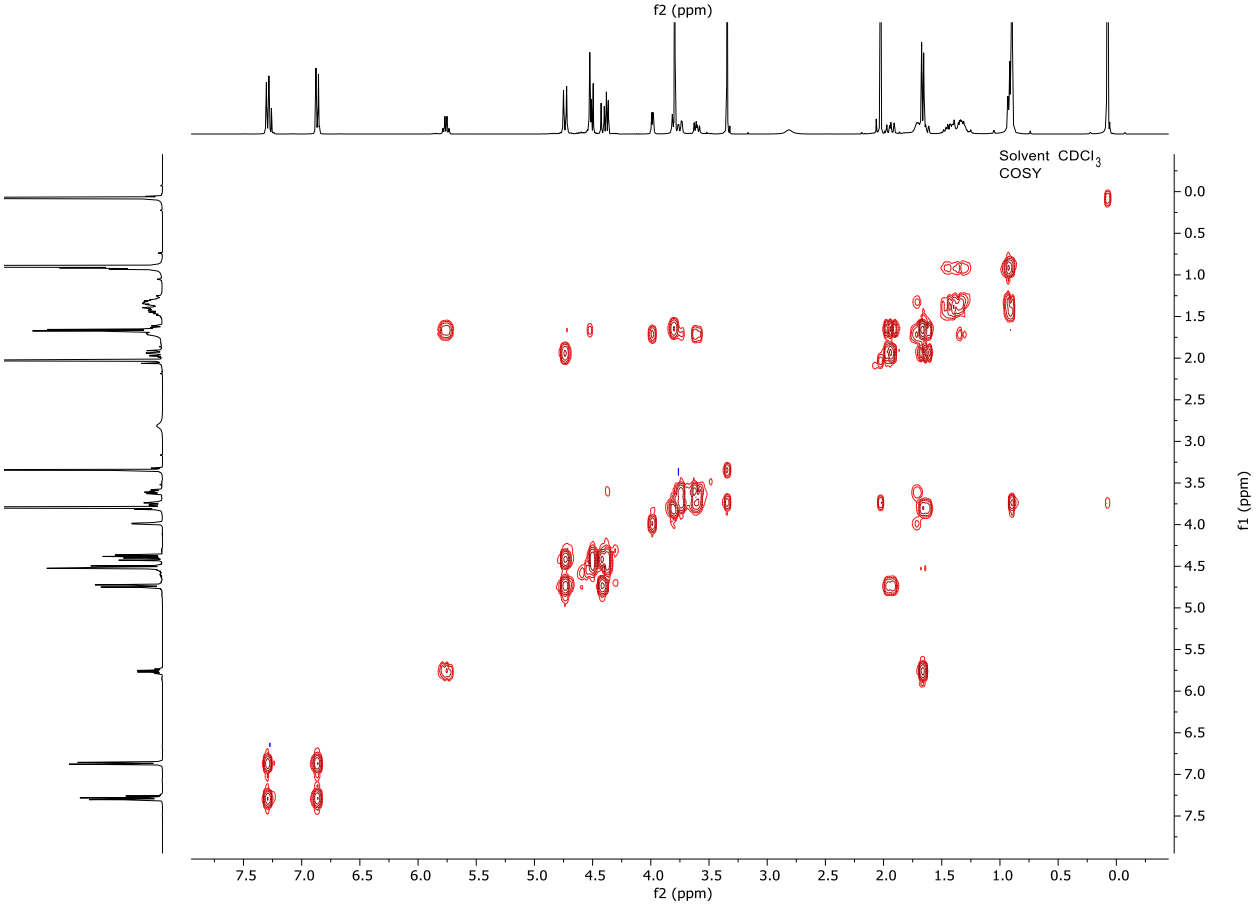

TBSO
AcO
OH
MOMO
OPMB

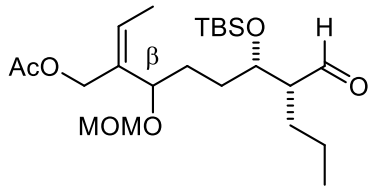
β-**290**

Solvent CDCl3
MHz 400
Nucleus 1H
1.98
2.12
1.00
2.02
3.04
1.97
1.07
4.21
1.04
1.00
3.15
0.85
3.07
1.12
1.40
4.16
2.07
2.15
12.27
2.89
2.87
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


171.0
159.3
134.6
131.0
129.4
129.2
113.9
94.7
78.9
76.4
72.7
70.5
65.3
62.1
56.2
55.4
45.5
37.3
30.4
26.1
21.2
21.2
18.3
14.5
13.1
-4.0
-4.9
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

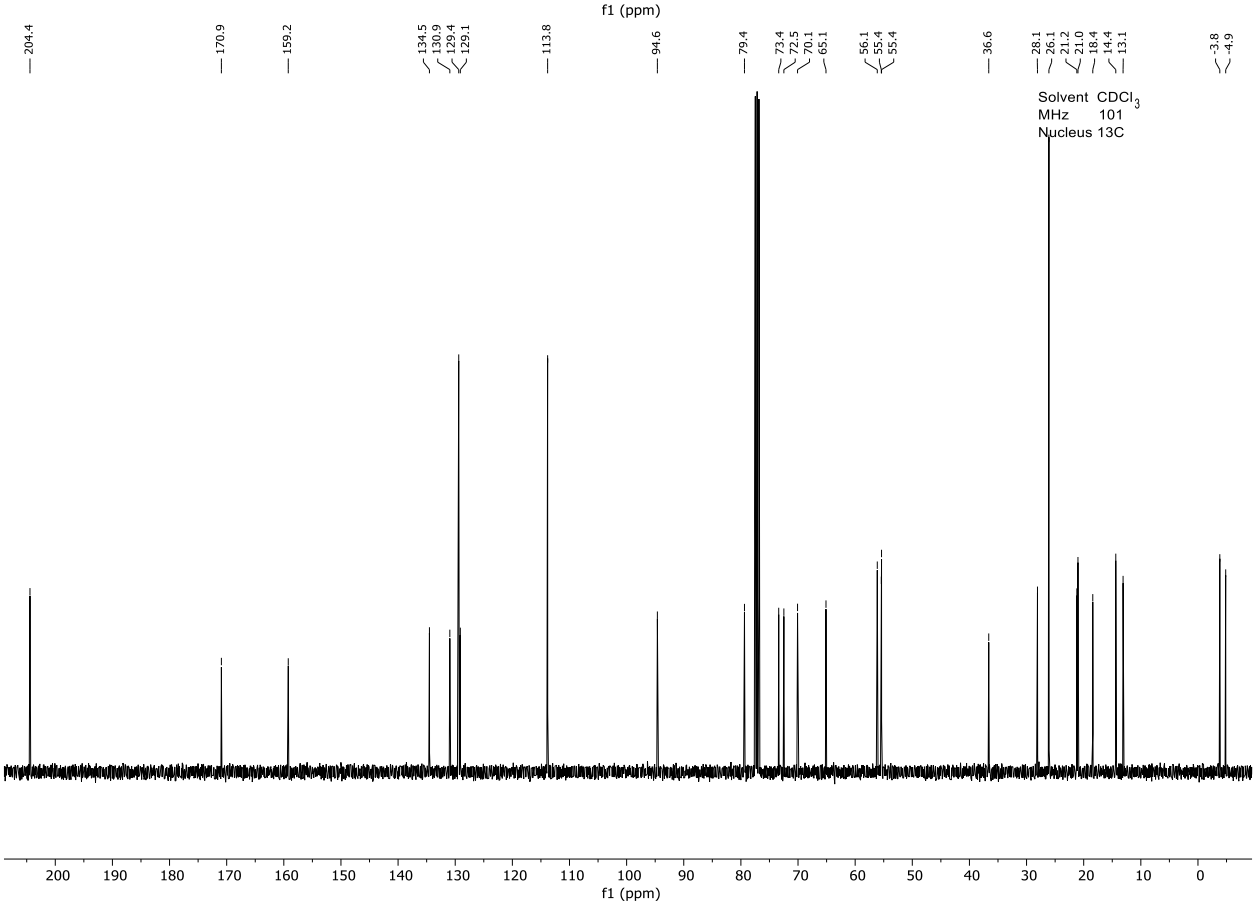

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

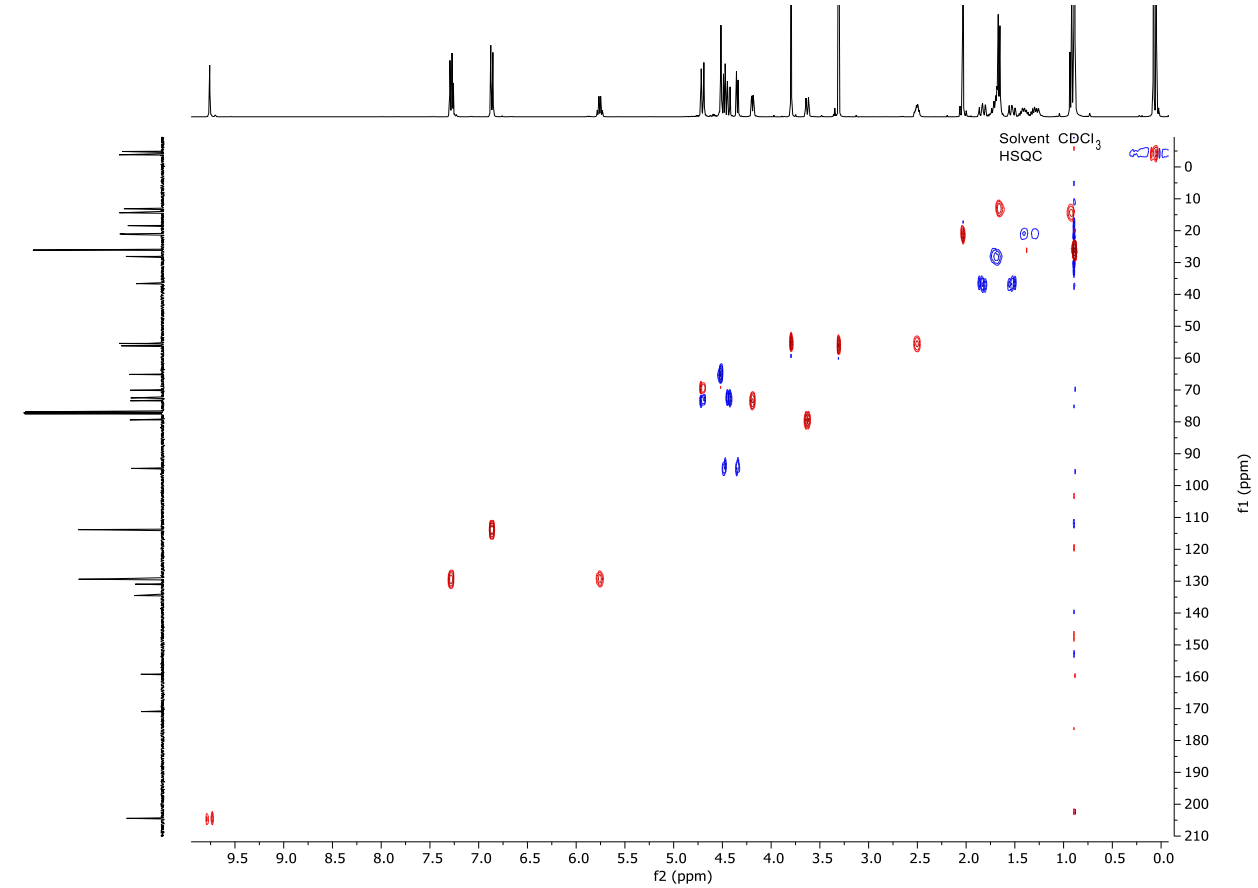

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

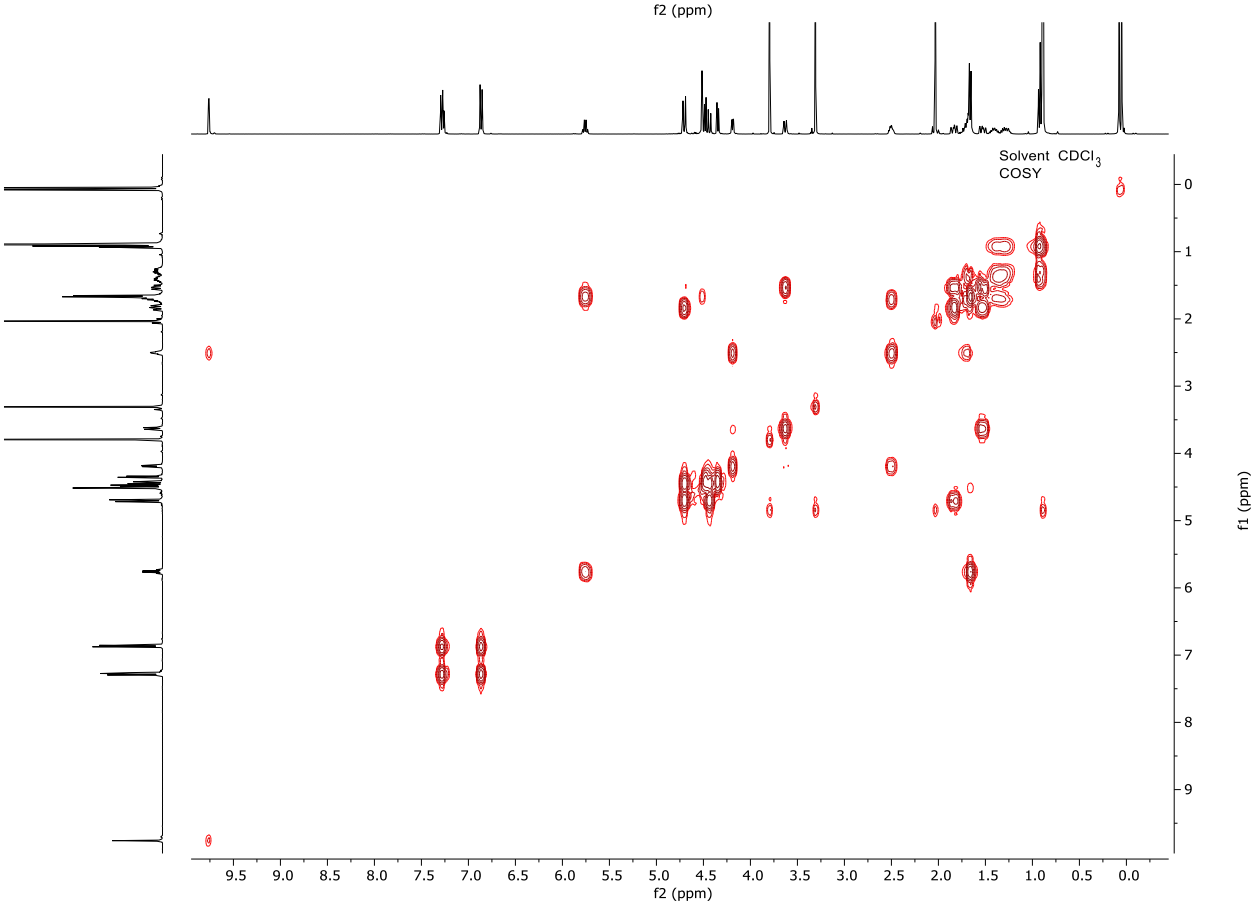

TBSO
H
AcO
β
O
MOMO

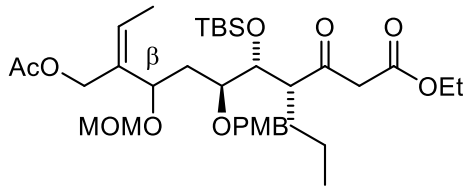
β-**291**

Solvent CDCl3
MHz 400
Nucleus 1H
0.89
1.83
1.96
1.00
2.01
1.91
0.96
0.94
0.97
0.96
3.08
0.95
2.96
1.00
2.92
1.04
5.25
1.00
0.99
1.24
12.39
3.15
2.95
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)


204.4
170.9
159.2
134.5
130.9
129.4
129.1
113.8
94.6
79.4
73.4
72.5
70.1
65.1
56.1
55.4
55.4
36.6
28.1
26.1
21.2
21.0
18.4
14.4
13.1
-3.8
-4.9
Solvent CDCl3
MHz 101
Nucleus 13C
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

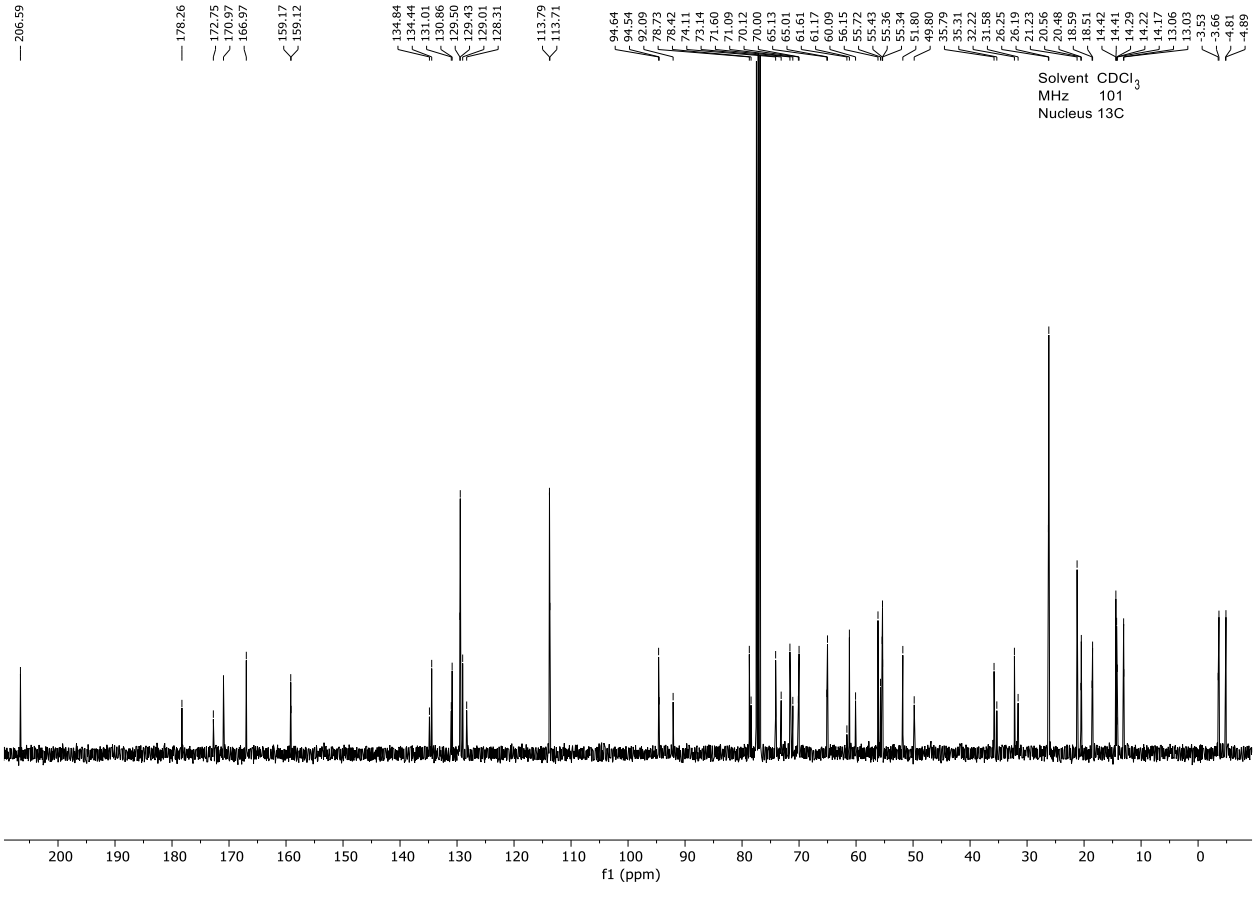

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

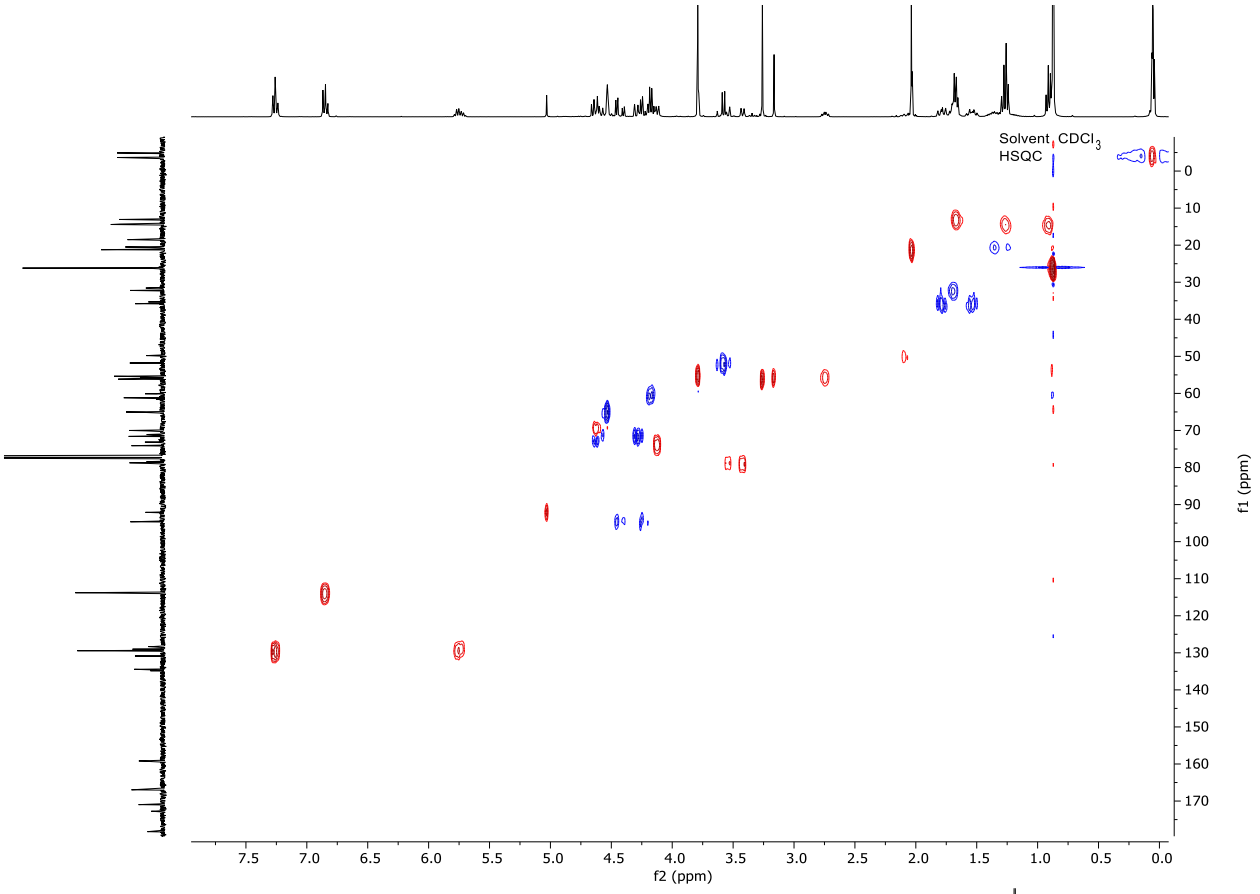

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

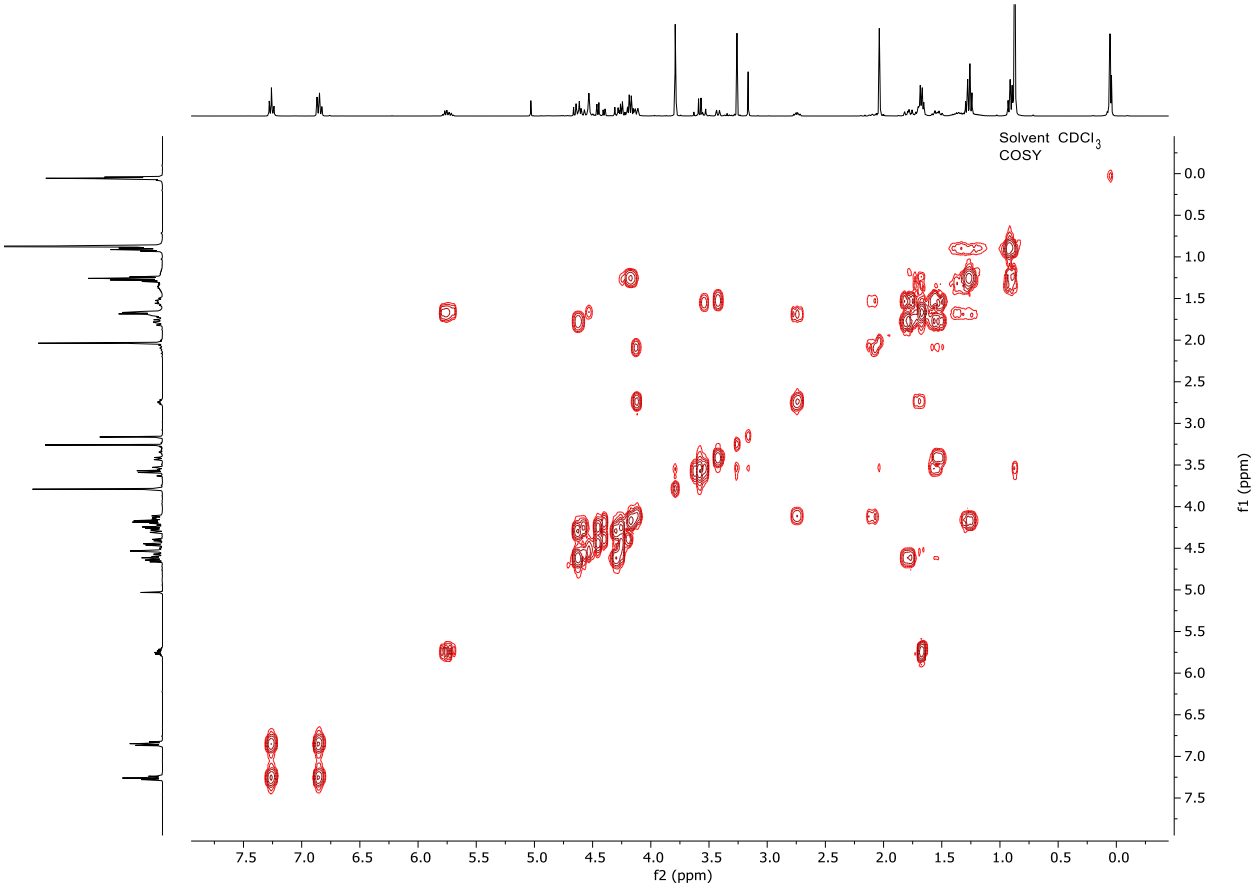

TBSO
O
O
AcO
β
OEt
MOMO
OPMB

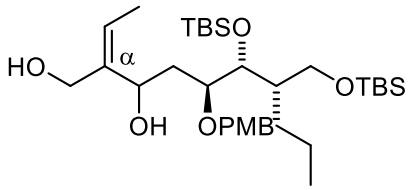
β-**293**

Solvent CDCl3
MHz 400
Nucleus 1H
0.55
0.49
1.02
0.53
3.13
1.50
1.55
1.00
2.89
1.55
f1 (ppm)


206.59
178.26
172.75
170.97
166.97
159.17
159.12
134.84
134.44
131.01
130.86
129.50
129.43
129.01
128.31
113.79
113.71
94.64
94.54
92.09
78.73
78.42
74.11
73.14
71.60
71.09
70.12
70.00
65.13
65.01
61.61
61.17
60.09
56.15
55.72
55.43
55.36
55.34
51.80
49.80
35.79
35.31
32.22
31.58
26.25
26.19
21.23
20.56
20.48
18.59
18.51
14.42
14.41
14.29
14.22
14.17
13.06
13.03
-3.53
-3.66
-4.81
-4.89
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

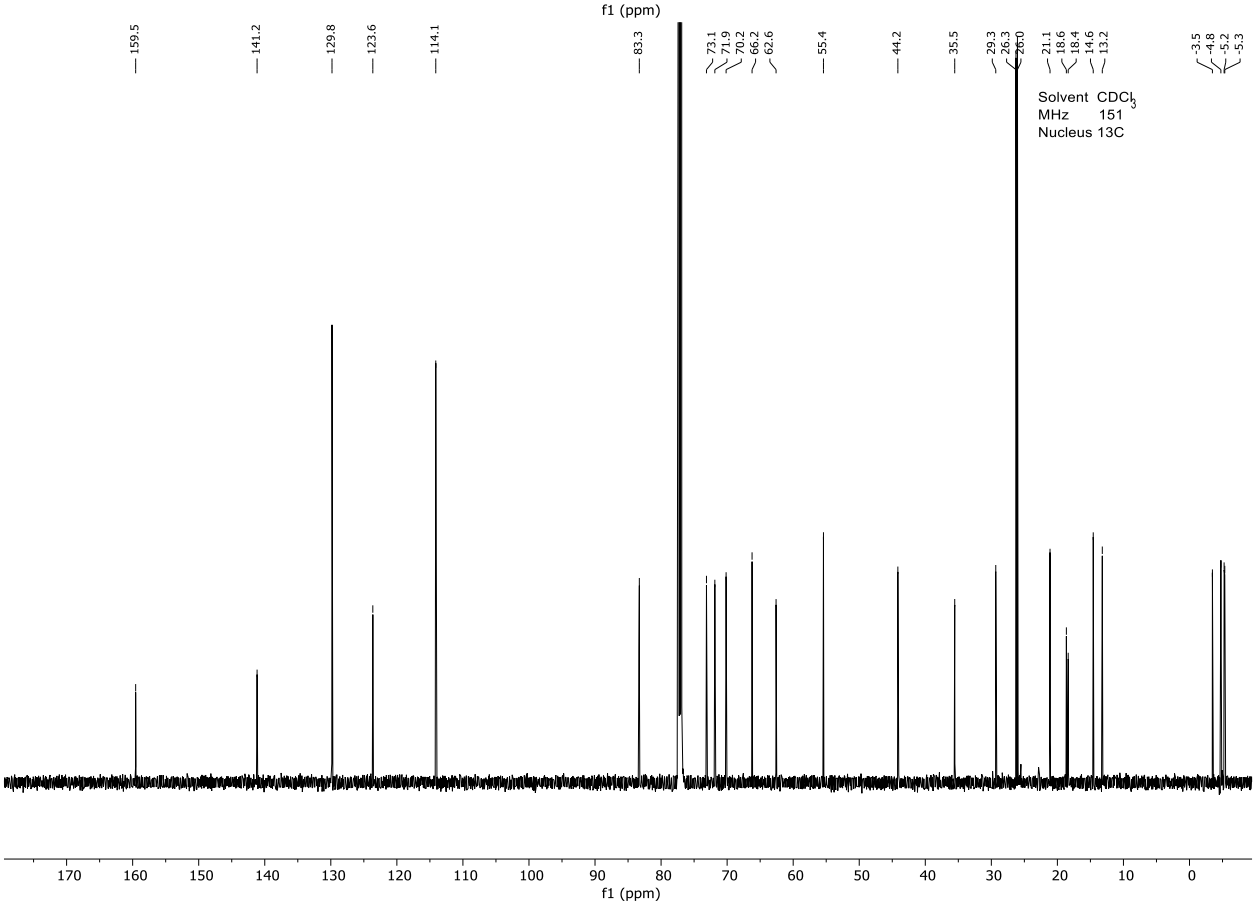

Solvent CDCl3
HSQC
f2 (ppm)
f1 (ppm)

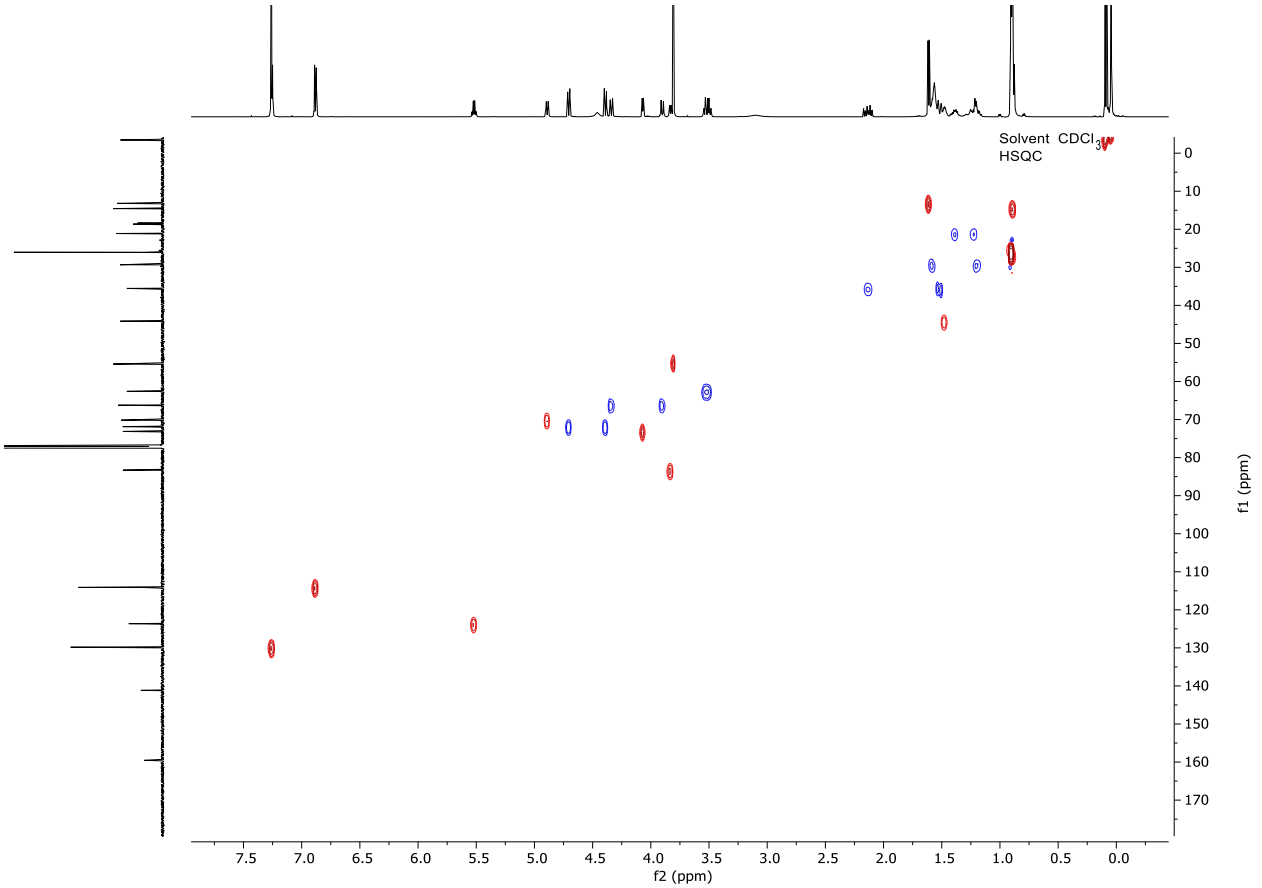

Solvent CDCl3
COSY
f2 (ppm)
f1 (ppm)

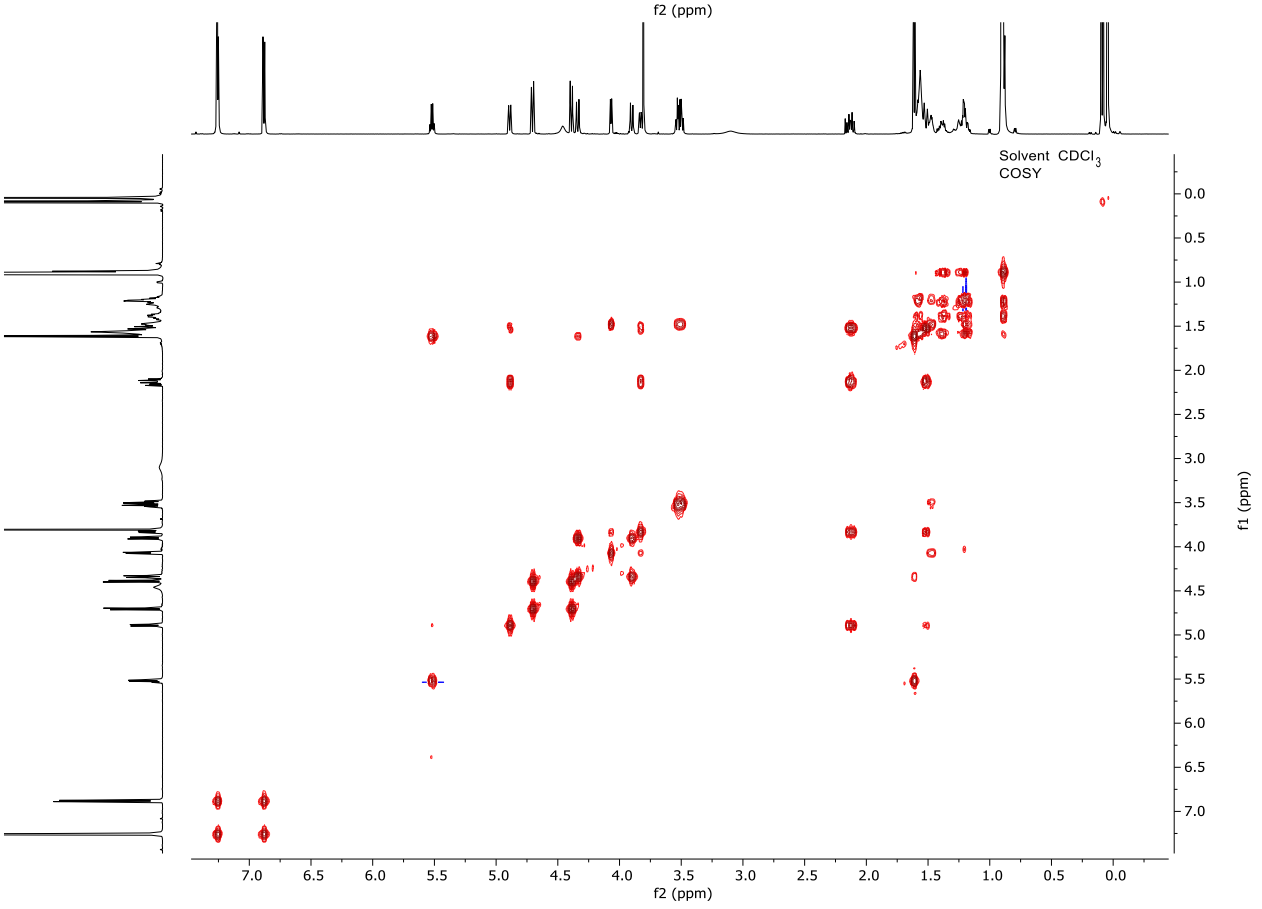

TBSO
α
HO
OTBS
OH
OPMB

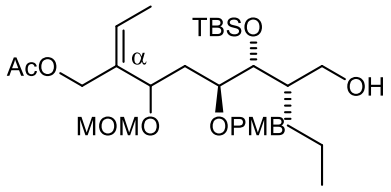
α-**284**

Solvent CDCl3
MHz 600
Nucleus 1H
2.36
2.01
1.00
0.99
0.99
0.72
1.02
1.02
0.97
0.91
0.98
3.12
0.99
1.02
0.67
1.12
3.12
1.29
1.30
1.03
1.15
2.90
21.25
2.86
3.13
2.78
2.96
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)


159.5
141.2
129.8
123.6
114.1
83.3
73.1
71.9
70.2
66.2
62.6
55.4
44.2
35.5
29.3
26.3
26.0
21.1
18.6
18.4
14.6
13.2
-3.5
-4.8
-5.2
-5.3
Solvent CDCl3
MHz 151
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

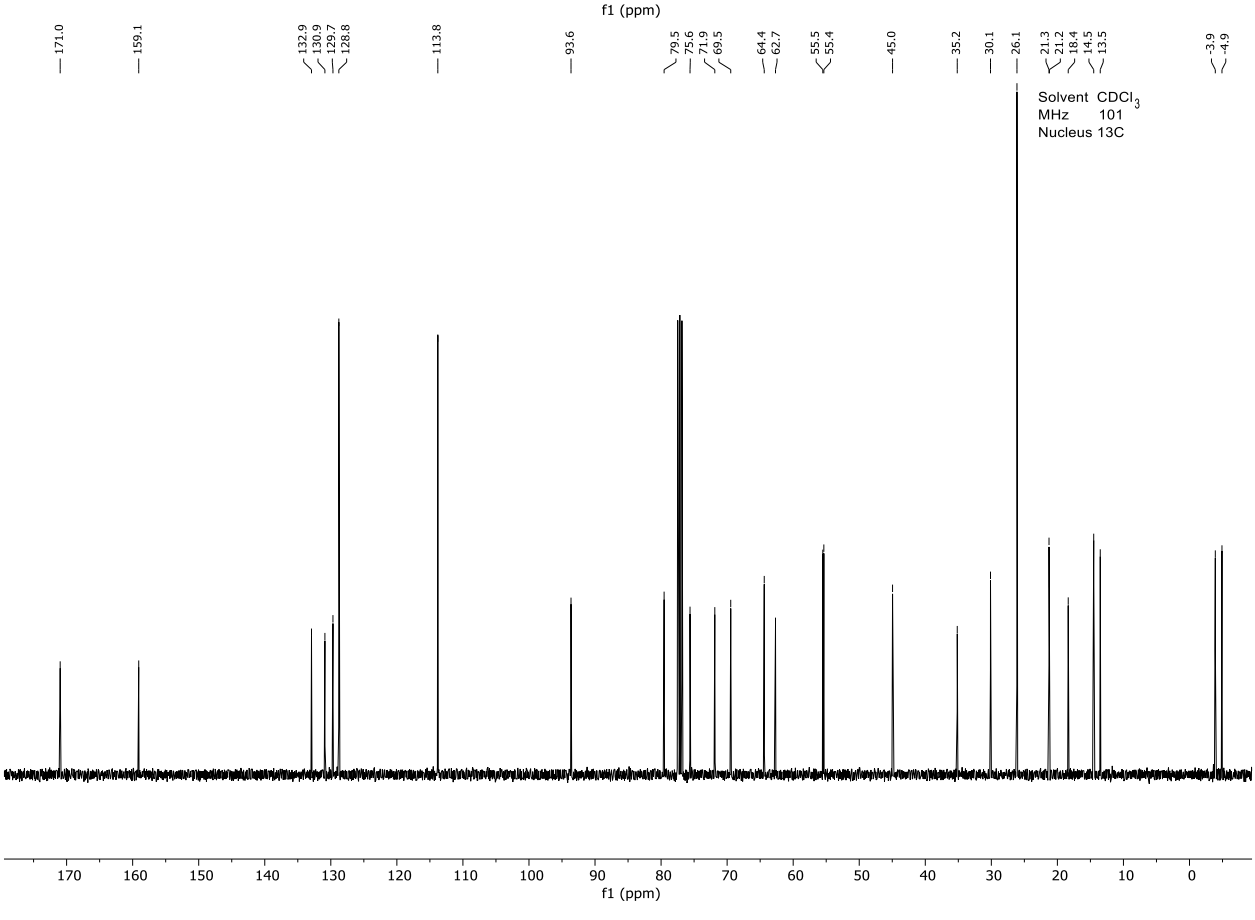

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

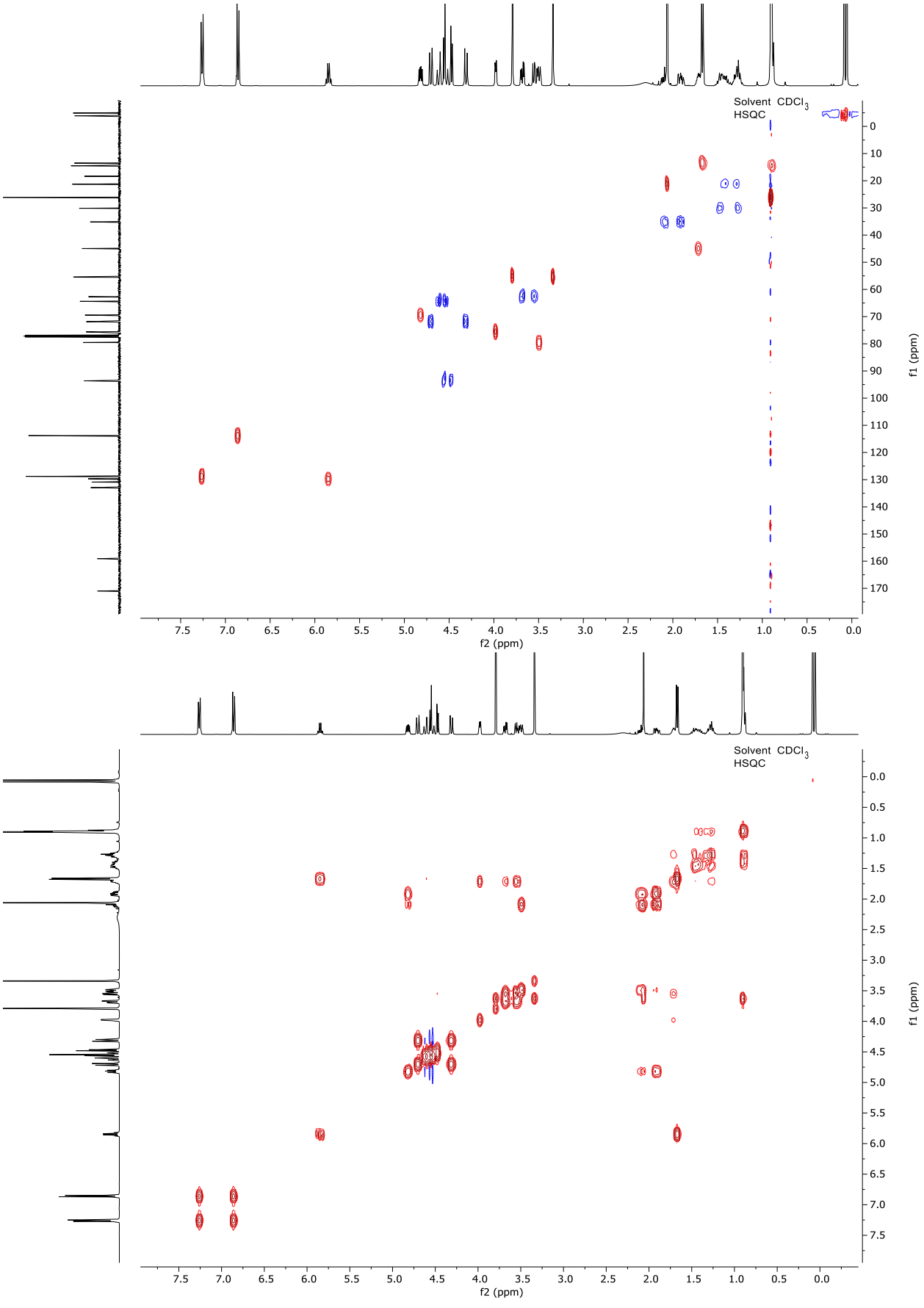

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

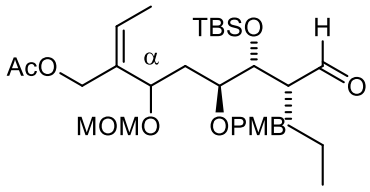

TBSO
α
AcO
OH
MOMO
OPMB

α-**290**

Solvent CDCl3
MHz 400
Nucleus 1H
2.12
1.96
1.00
0.98
0.98
1.01
2.05
0.94
0.98
1.00
3.06
0.98
1.06
0.92
3.02
0.95
4.04
1.00
0.98
3.10
1.88
1.95
12.32
3.08
3.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

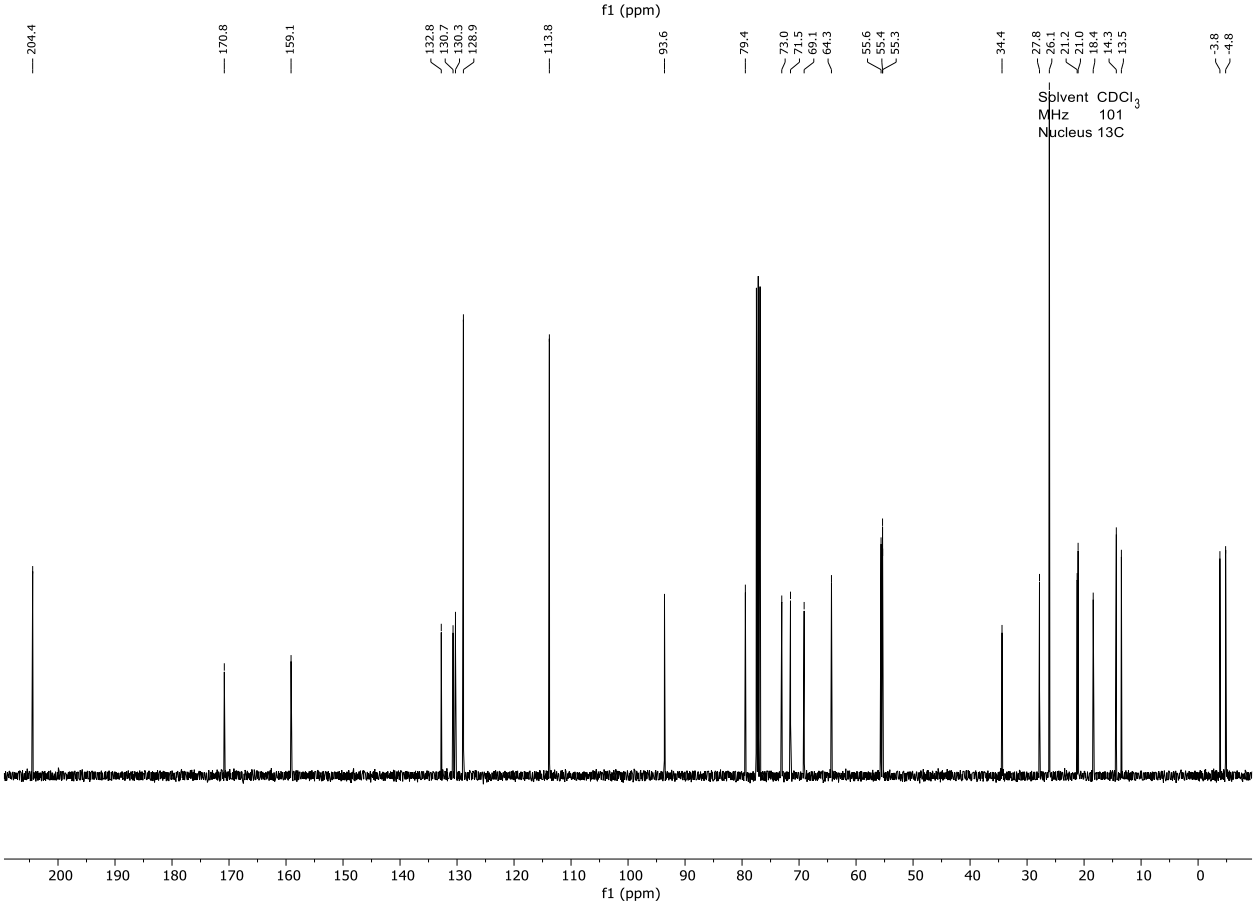

171.0
159.1
132.9
130.9
129.7
128.8
113.8
93.6
79.5
75.6
71.9
69.5
64.4
62.7
55.5
55.4
45.0
35.2
30.1
26.1
21.3
21.2
18.4
14.5
13.5
-3.9
-4.9
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

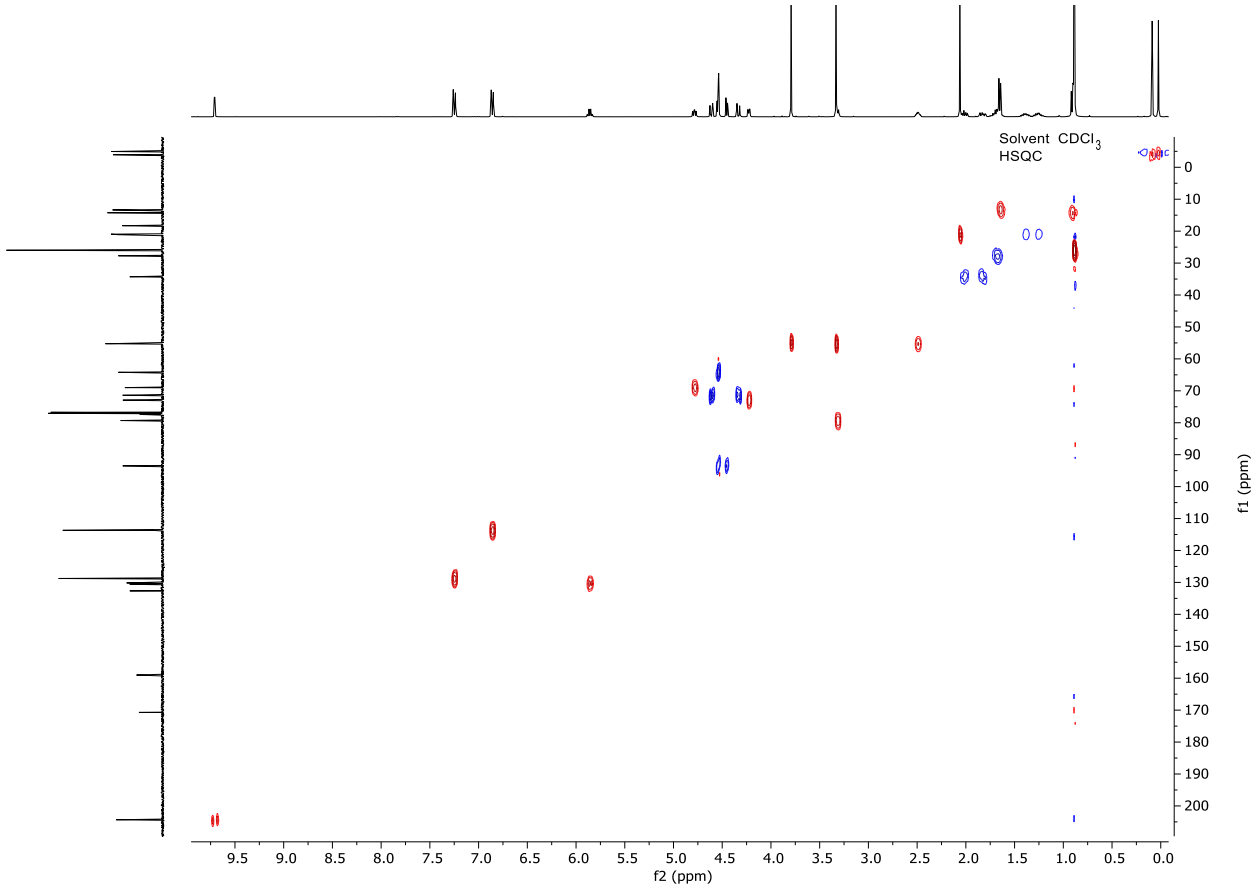

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)
Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

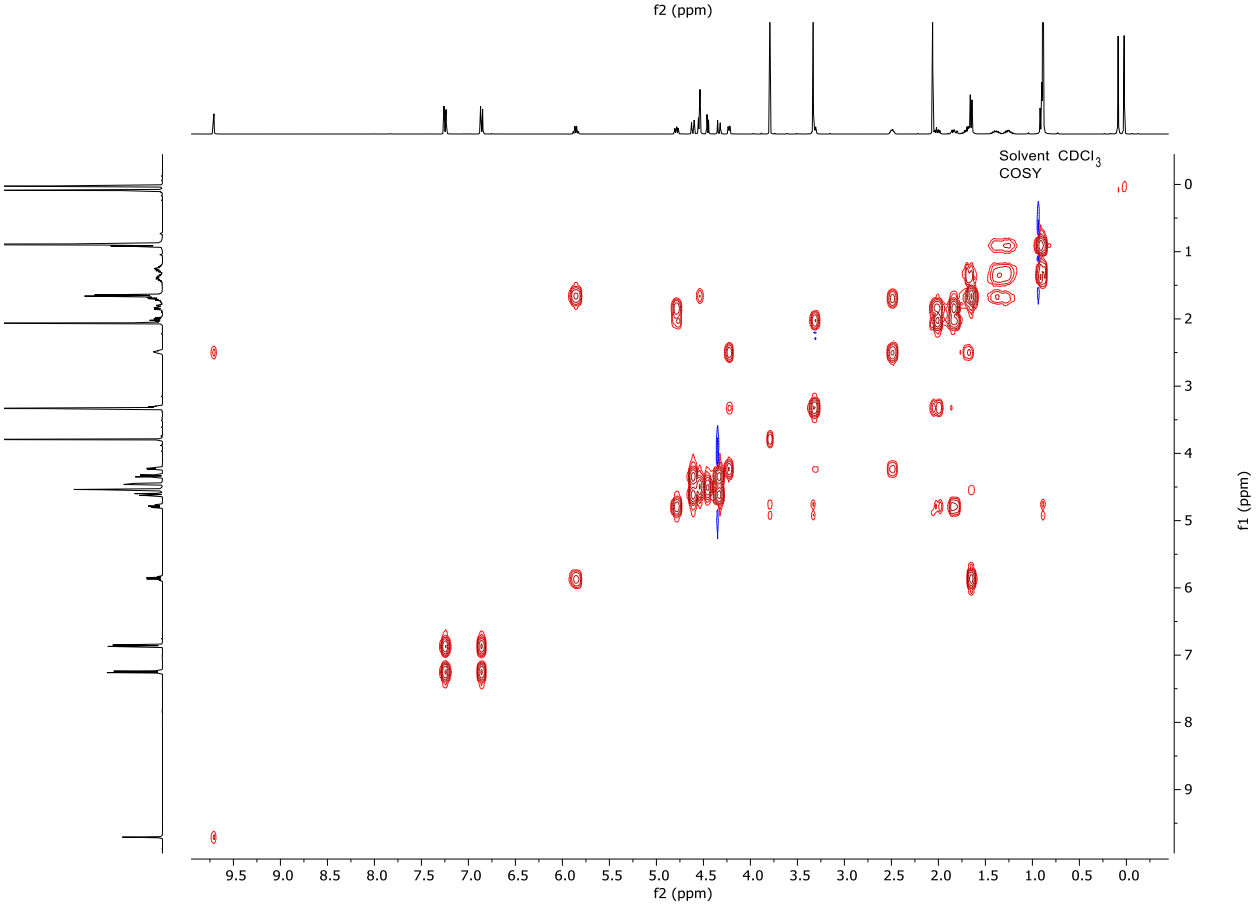

TBSO
H
AcO
α
O
MOMO
OPMB

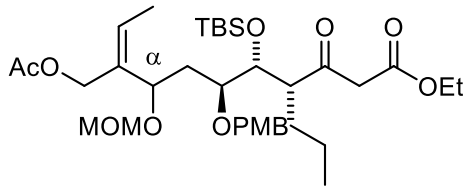
α-**295**

Solvent CDCl3
MHz 400
Nucleus 1H
0.95
2.12
1.97
1.00
1.00
0.99
2.93
0.97
0.96
0.97
3.04
3.99
0.99
3.07
0.97
1.03
1.83
2.97
1.00
1.00
12.00
3.12
2.97
f1 (ppm)


204.4
170.8
159.1
132.8
130.7
130.3
128.9
113.8
93.6
79.4
73.0
71.5
69.1
64.3
55.6
55.4
55.3
34.4
27.8
26.1
21.2
21.0
18.4
14.3
13.5
-3.8
-4.8
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

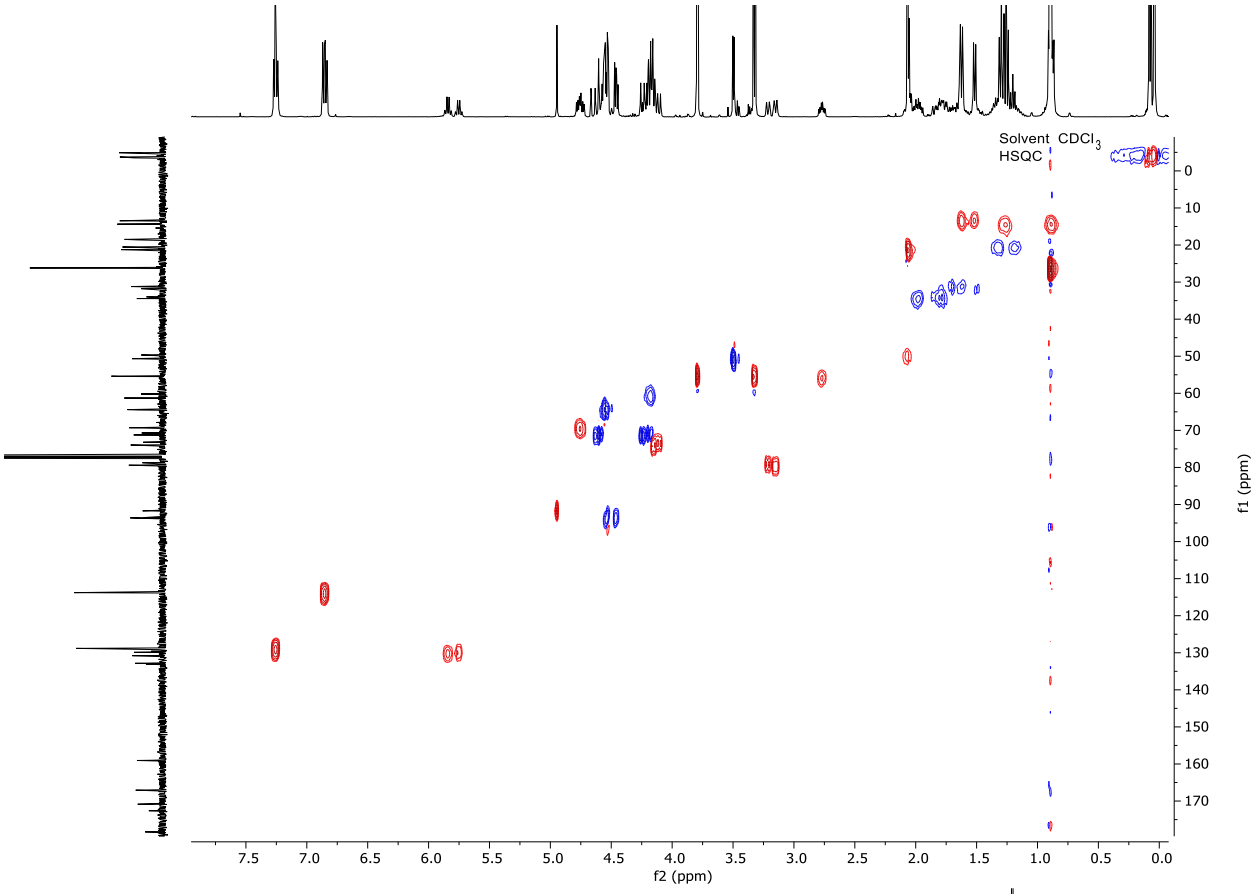

Solvent CDCl3
HSQC
f2 (ppm)
f1 (ppm)

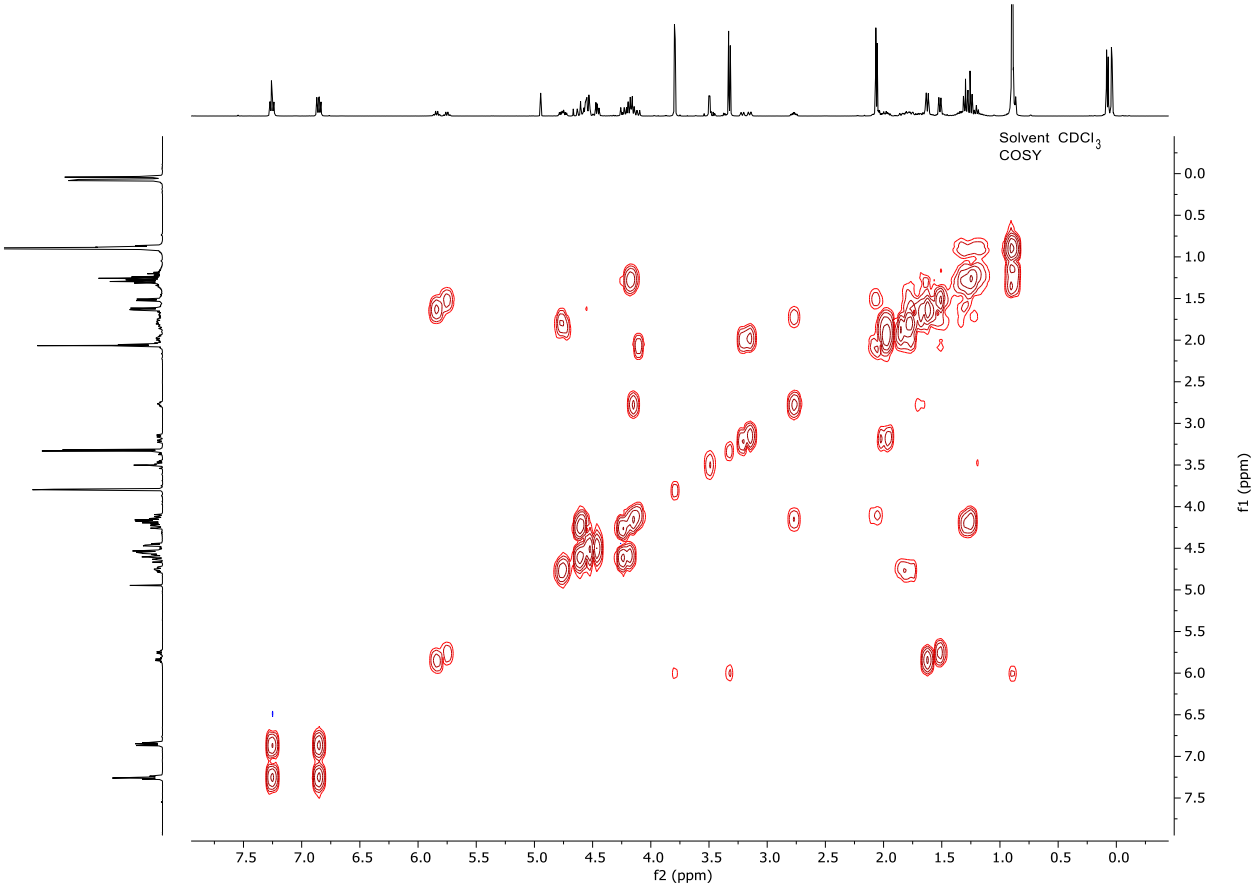

Solvent CDCl3
COSY
f2 (ppm)
f1 (ppm)

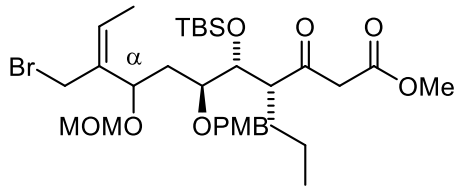

TBSO
O
O
AcO
α
OEt
MOMO
OPMB

α-**296**

Solvent CDCl3
MHz 400
Nucleus 1H
1.00
2.75
1.77
2.92
0.95
0.93
f1 (ppm)
205.74
178.32
172.61
170.85
167.06
159.06
159.00
133.06
132.84
130.90
130.79
129.88
129.59
128.86
128.81
113.78
113.72
93.61
93.53
91.72
79.39
78.74
73.95
73.20
71.23
70.70
69.40
69.30
64.51
64.41
61.28
60.19
55.56
55.45
55.37
55.37
55.36
55.31
50.66
49.66
34.44
33.99
31.77
31.20
26.27
26.19
21.24
21.20
20.56
20.53
18.61
18.48
14.42
14.36
14.26
14.16
13.46
13.36
-3.50
-3.74
-4.88
-4.91
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

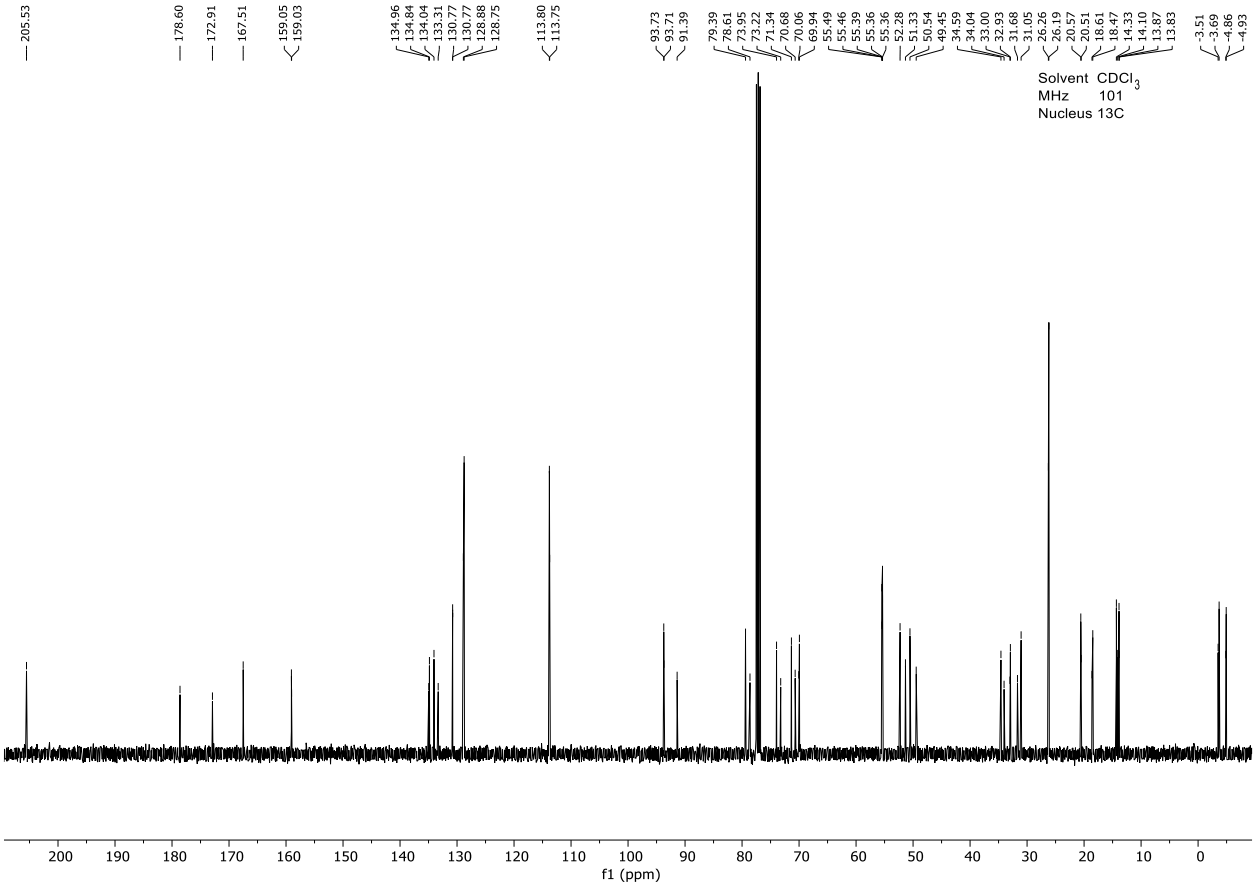

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

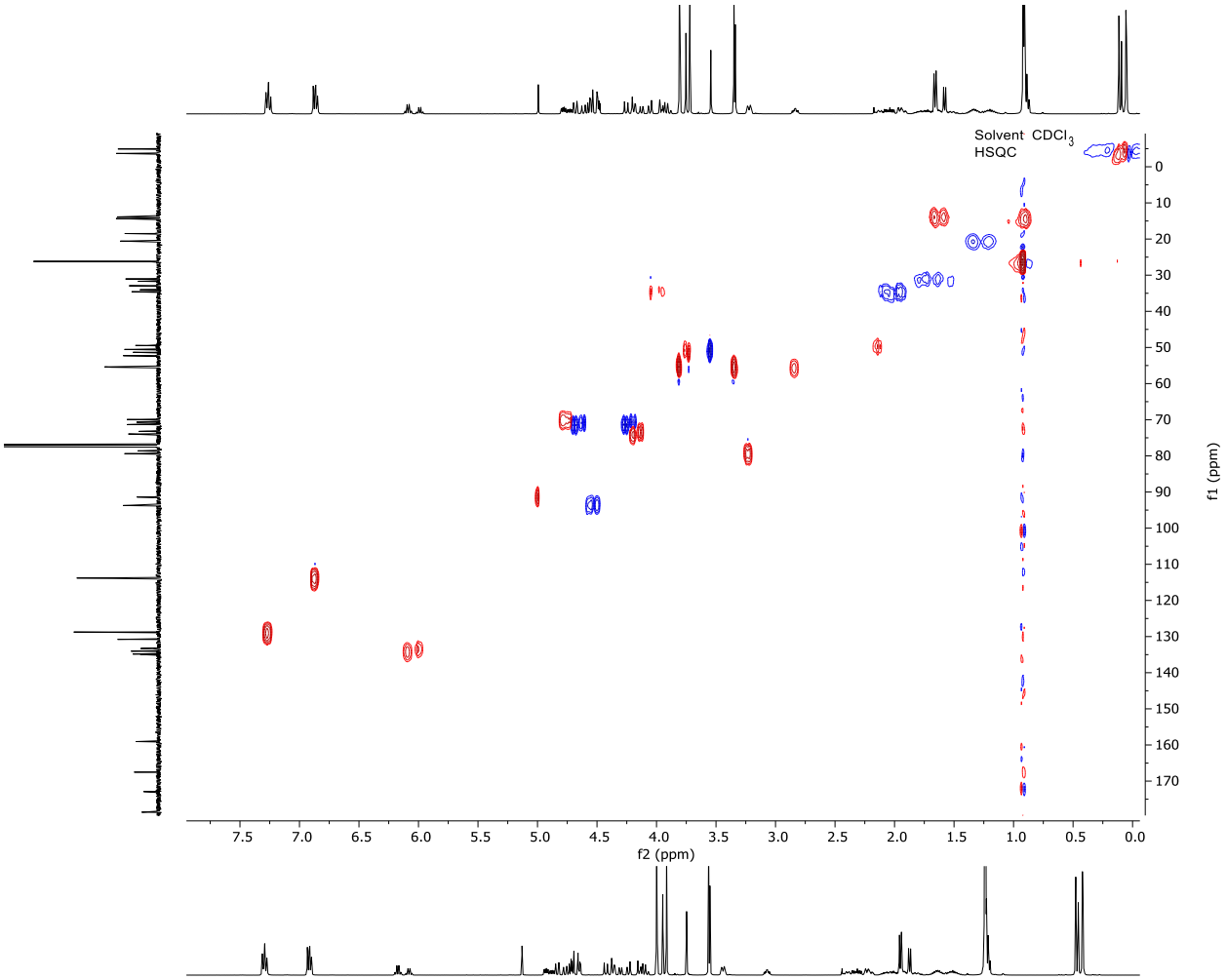

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

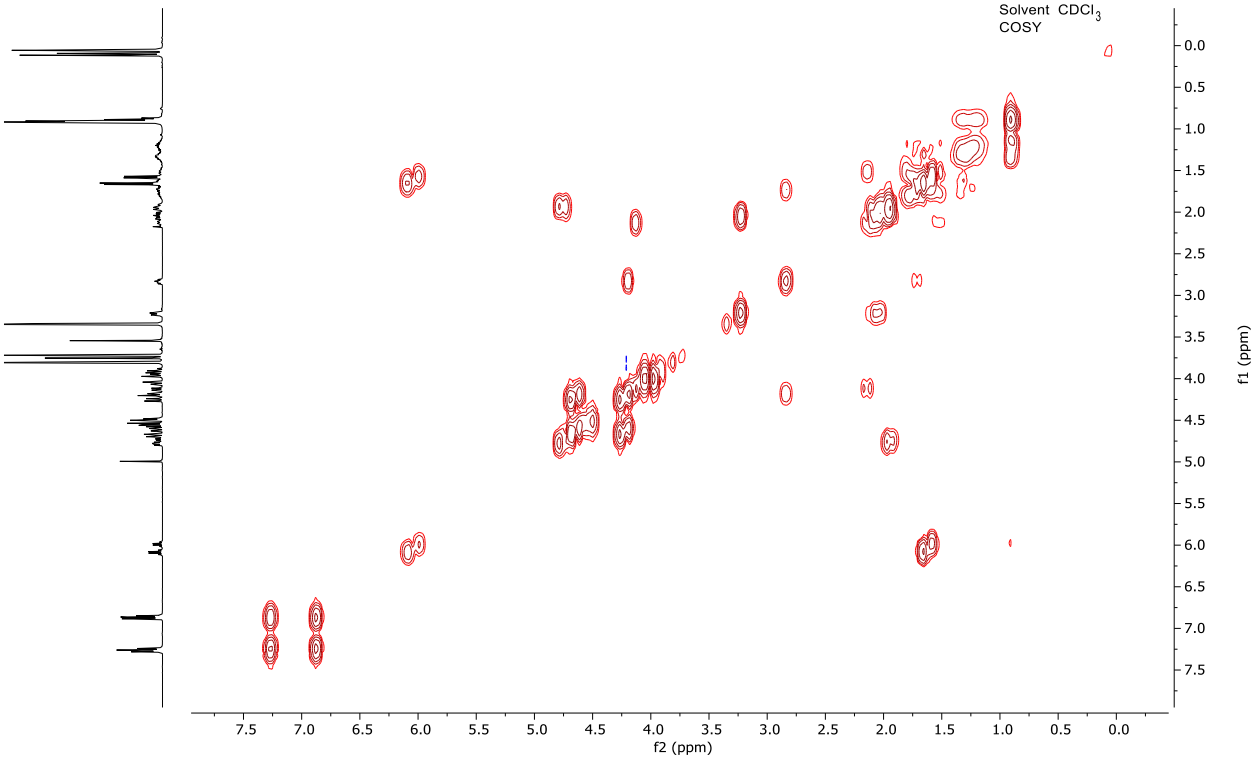

TBSO
O
O
α
Br
OMe
MOMO
OPMB

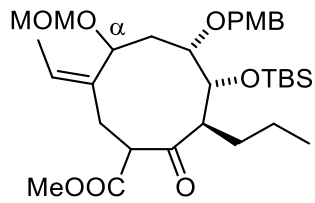
α-**276**

Solvent CDCl3
MHz 400
Nucleus 1H
1.00
3.11
1.91
3.04
1.00
f1 (ppm)


205.53
178.60
172.91
167.51
159.05
159.03
134.96
134.84
134.04
133.31
130.77
130.77
128.88
128.75
113.80
113.75
93.73
93.71
91.39
79.39
78.61
73.95
73.22
71.34
70.68
70.06
69.94
55.49
55.46
55.39
55.36
55.36
52.28
51.33
50.54
49.45
34.59
34.04
33.00
32.93
31.68
31.05
26.26
26.19
20.57
20.51
18.61
18.47
14.33
14.10
13.87
13.83
-3.51
-3.69
-4.86
-4.93
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

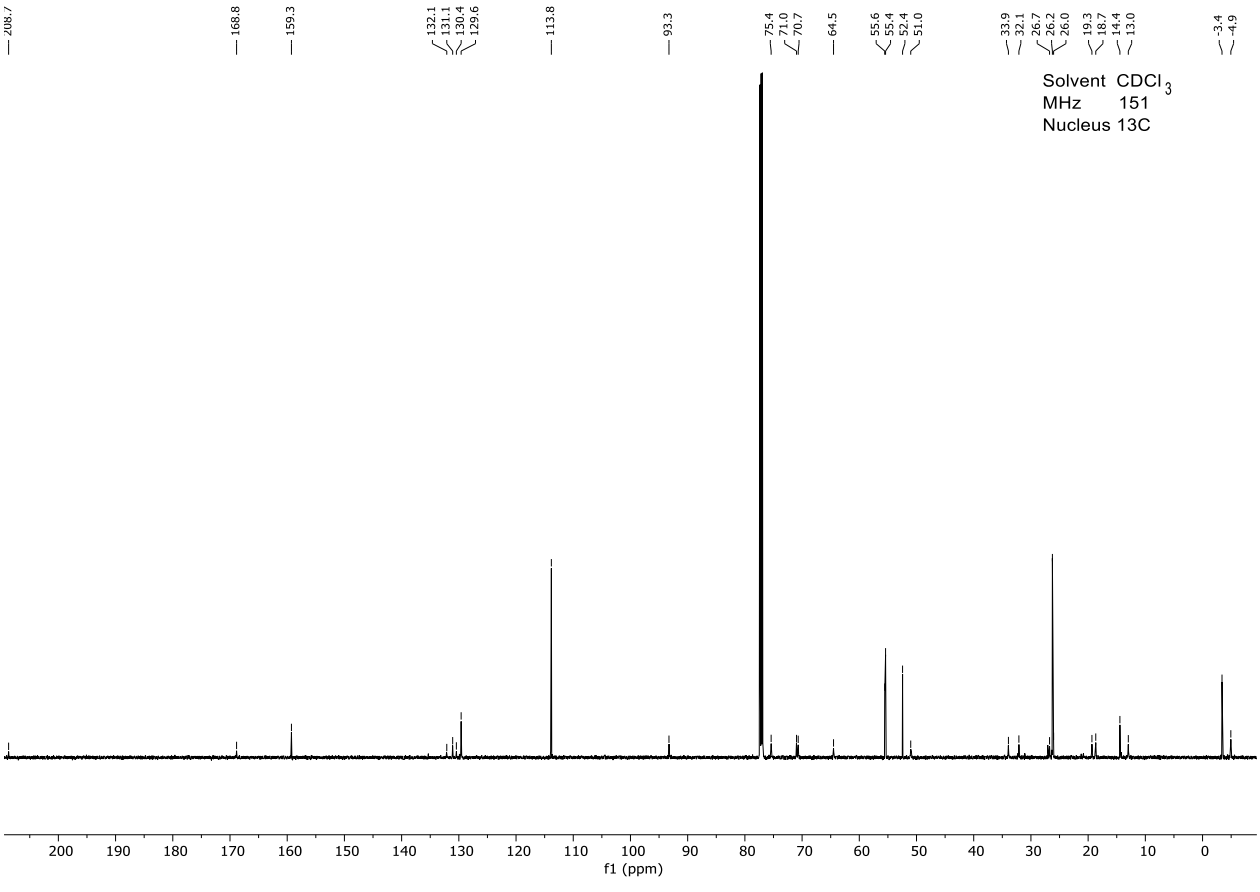

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

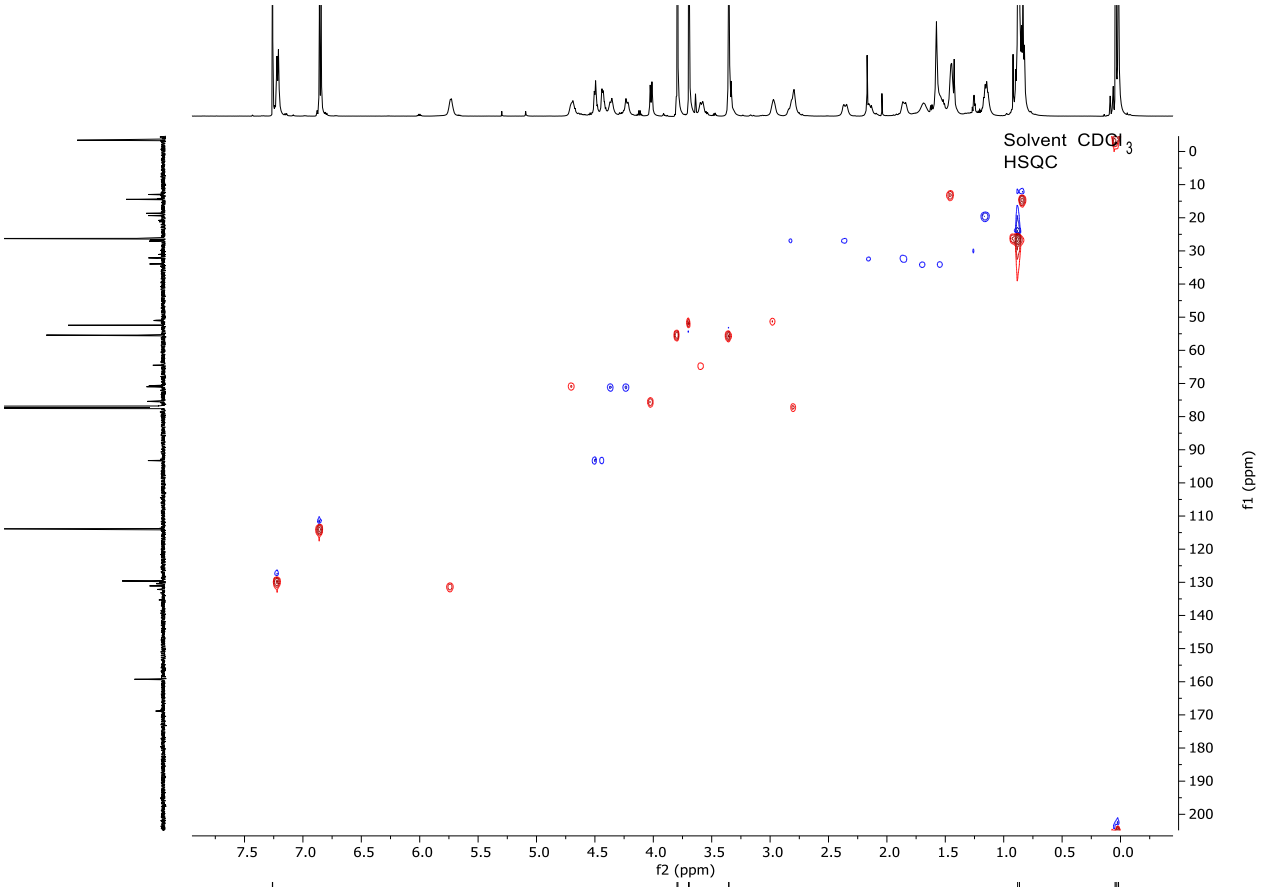

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

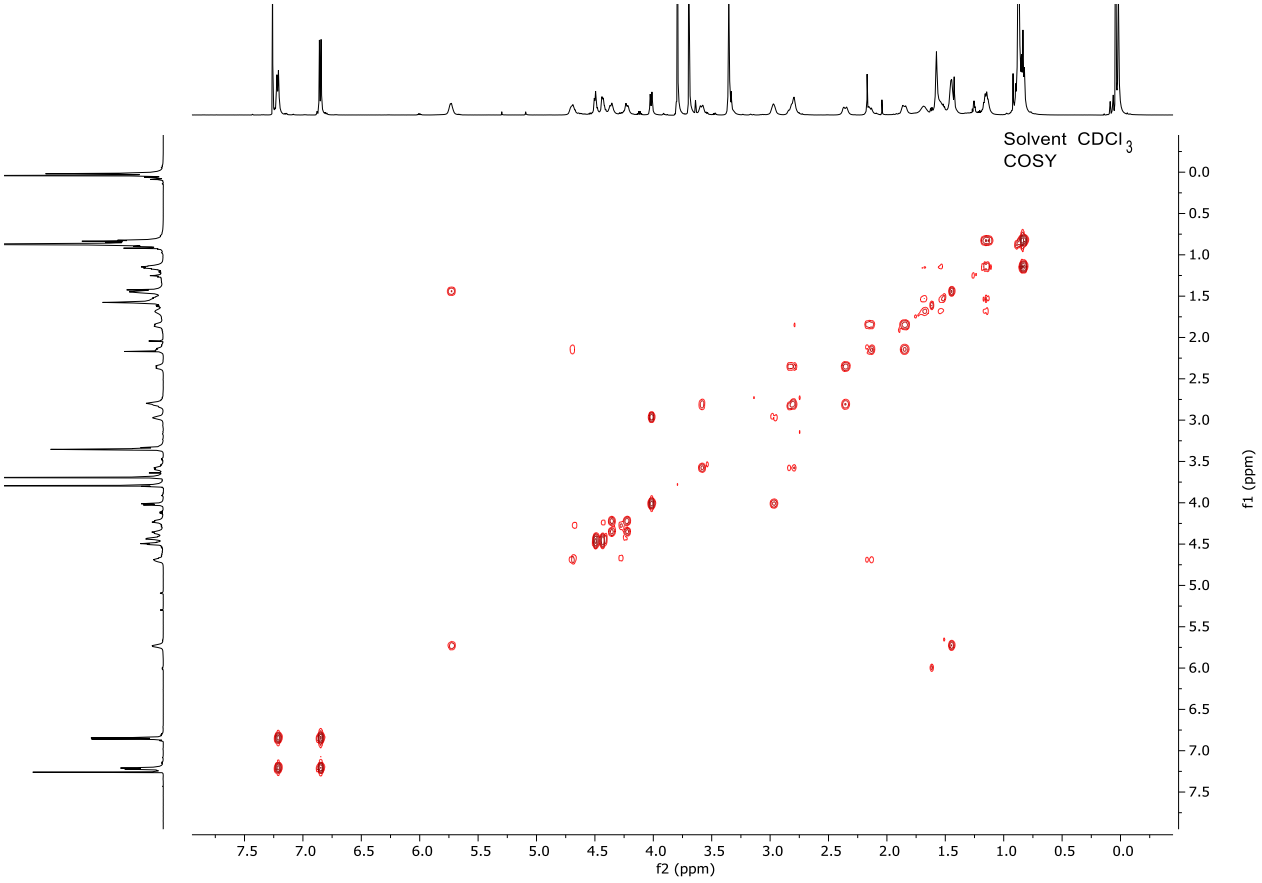

MOMO
α
OPMB
OTBS
MeOOC
O

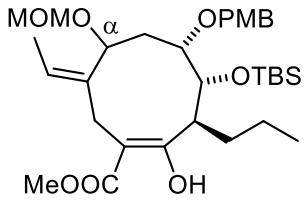
α-**301**

Solvent CDCl3
MHz 600
Nucleus 1H
2.15
2.12
1.00
0.97
1.17
1.23
1.00
0.94
0.99
3.29
3.13
0.90
2.90
0.91
1.81
0.90
1.08
1.17
1.23
1.42
3.04
2.39
12.23
3.05
3.13
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)


208.7
168.8
159.3
132.1
131.1
130.4
129.6
113.8
93.3
75.4
71.0
70.7
64.5
55.6
55.4
52.4
51.0
33.9
32.1
26.7
26.2
26.0
19.3
18.7
14.4
13.0
-3.4
-4.9
Solvent CDCl3
MHz 151
Nucleus 13C
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

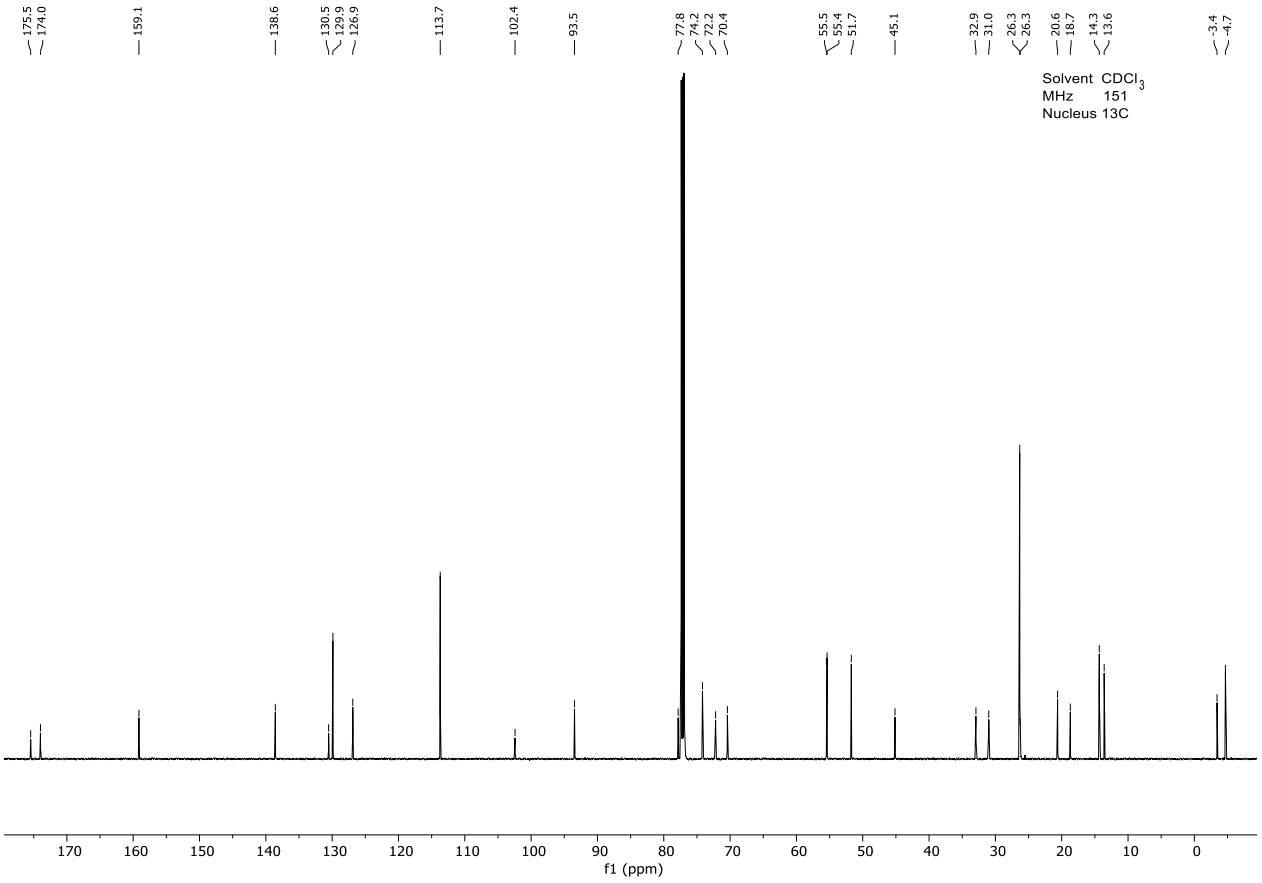

Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

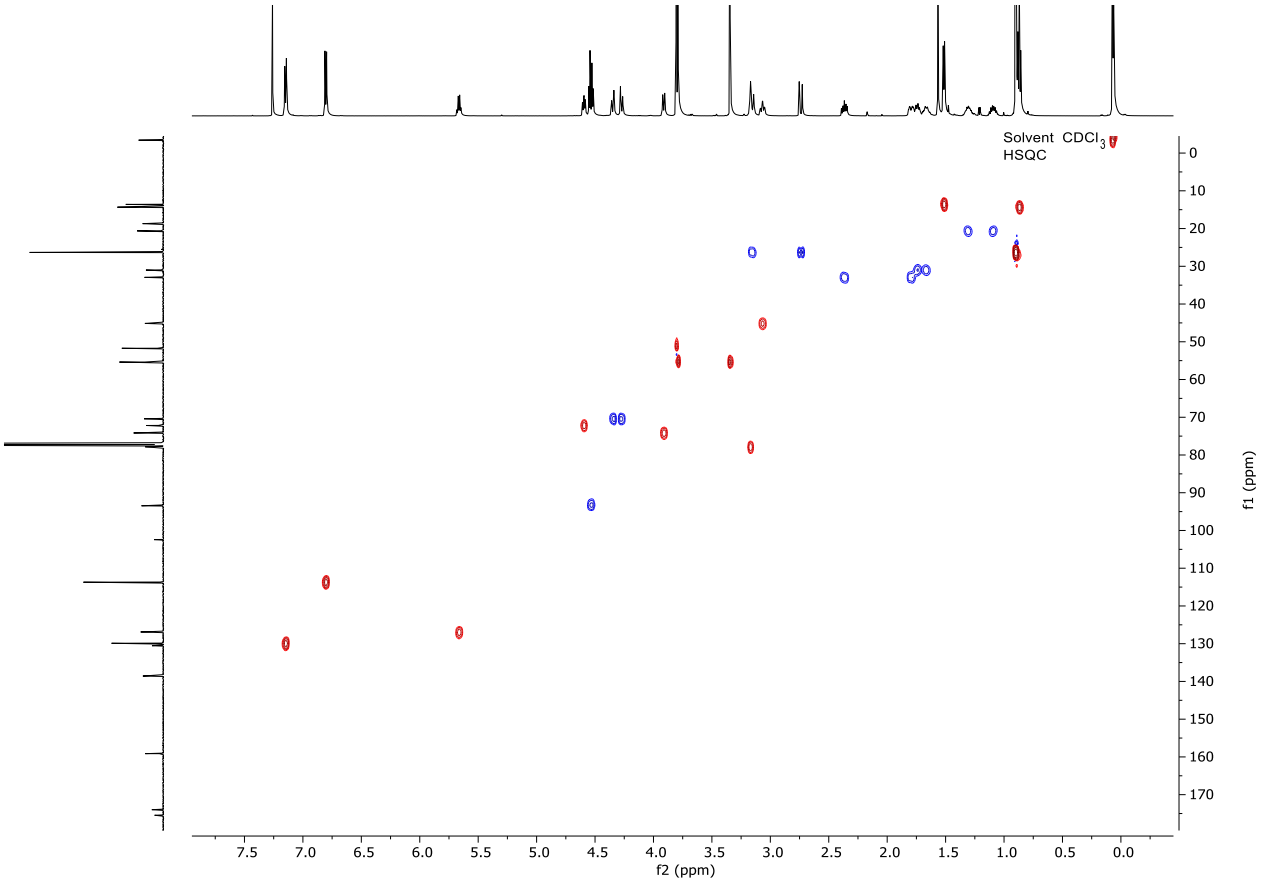

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

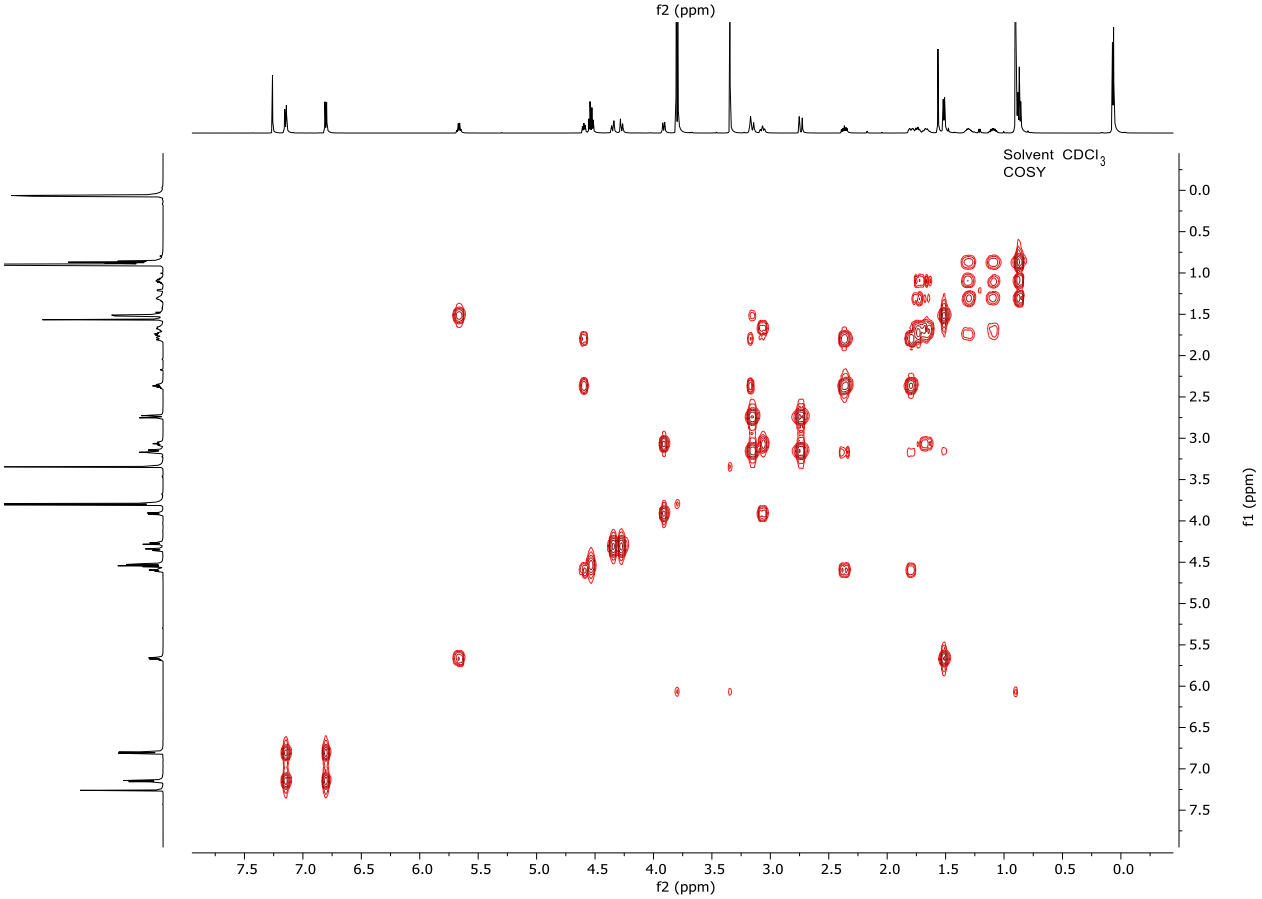

MOMO
α
OPMB
OTBS
MeOOC
OH

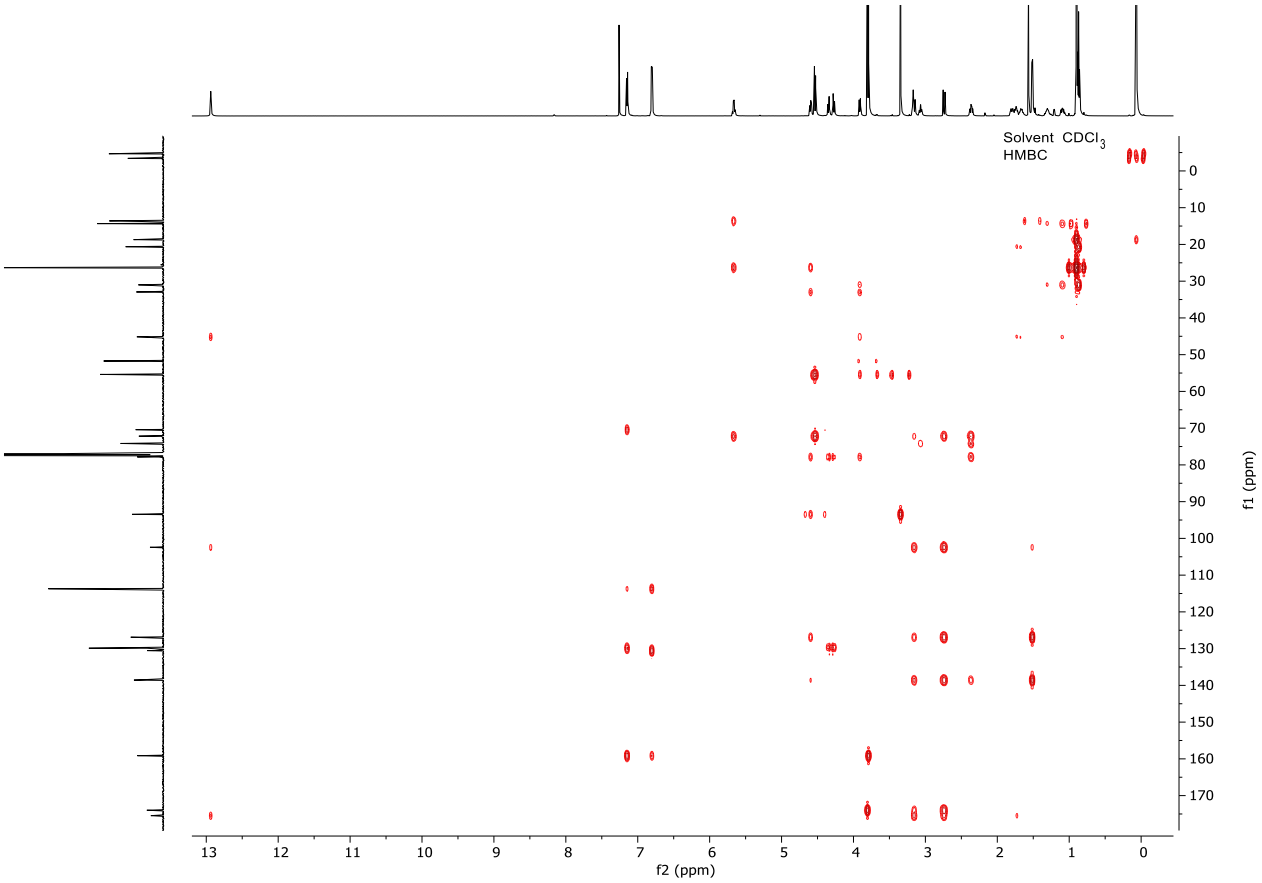
α-**302**

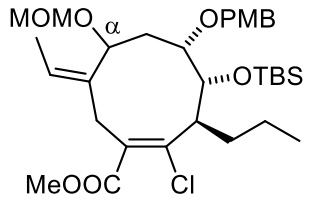
Solvent CDCl3
MHz 600
Nucleus 1H
0.93
1.92
1.93
1.00
0.95
1.97
0.98
1.04
1.02
2.67
3.12
2.76
1.86
1.00
0.97
0.97
1.04
1.00
1.04
2.97
1.15
0.99
8.52
3.26
2.57
2.75
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


175.5
174.0
159.1
138.6
130.5
129.9
126.9
113.7
102.4
93.5
77.8
74.2
72.2
70.4
55.5
55.4
51.7
45.1
32.9
31.0
26.3
26.3
20.6
18.7
14.3
13.6
-3.4
-4.7
Solvent CDCl3
MHz 151
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)

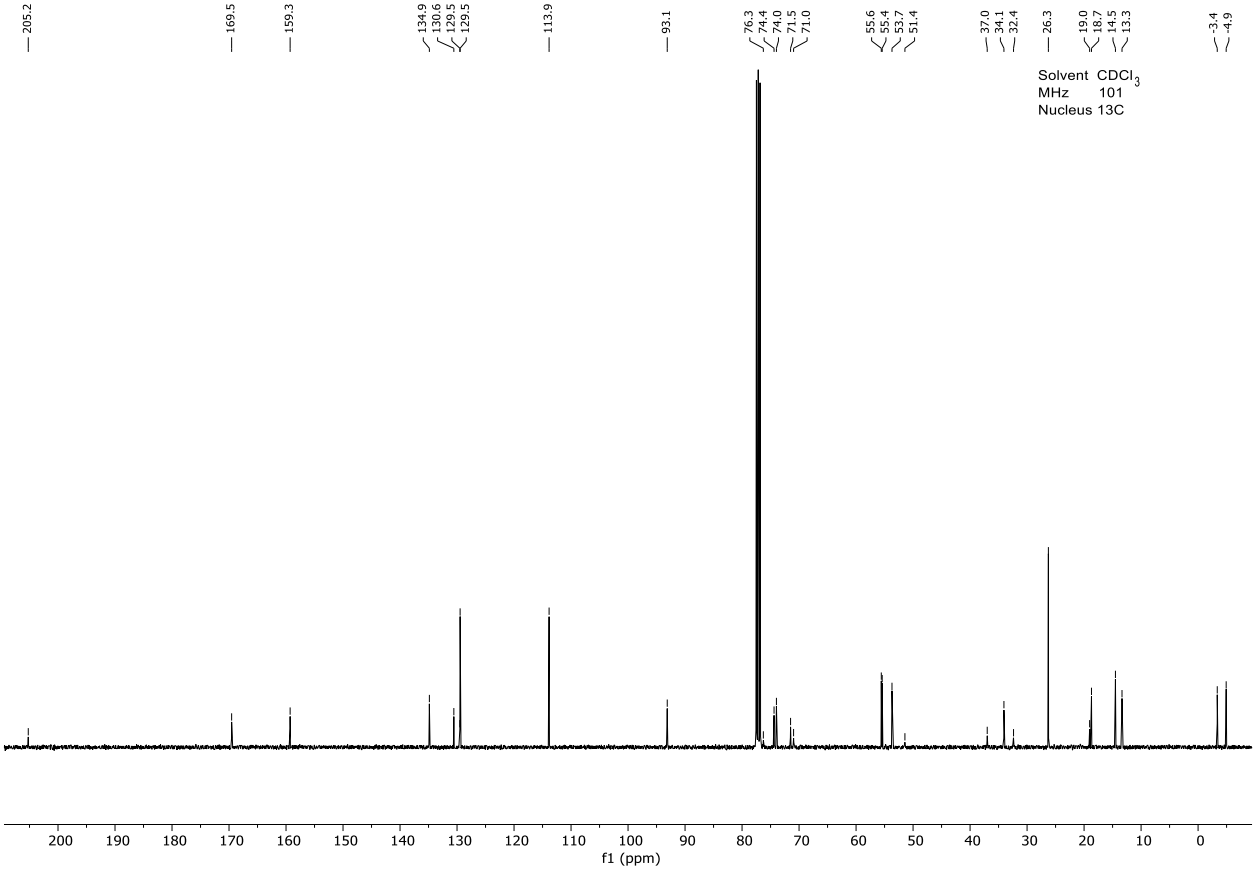

Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)

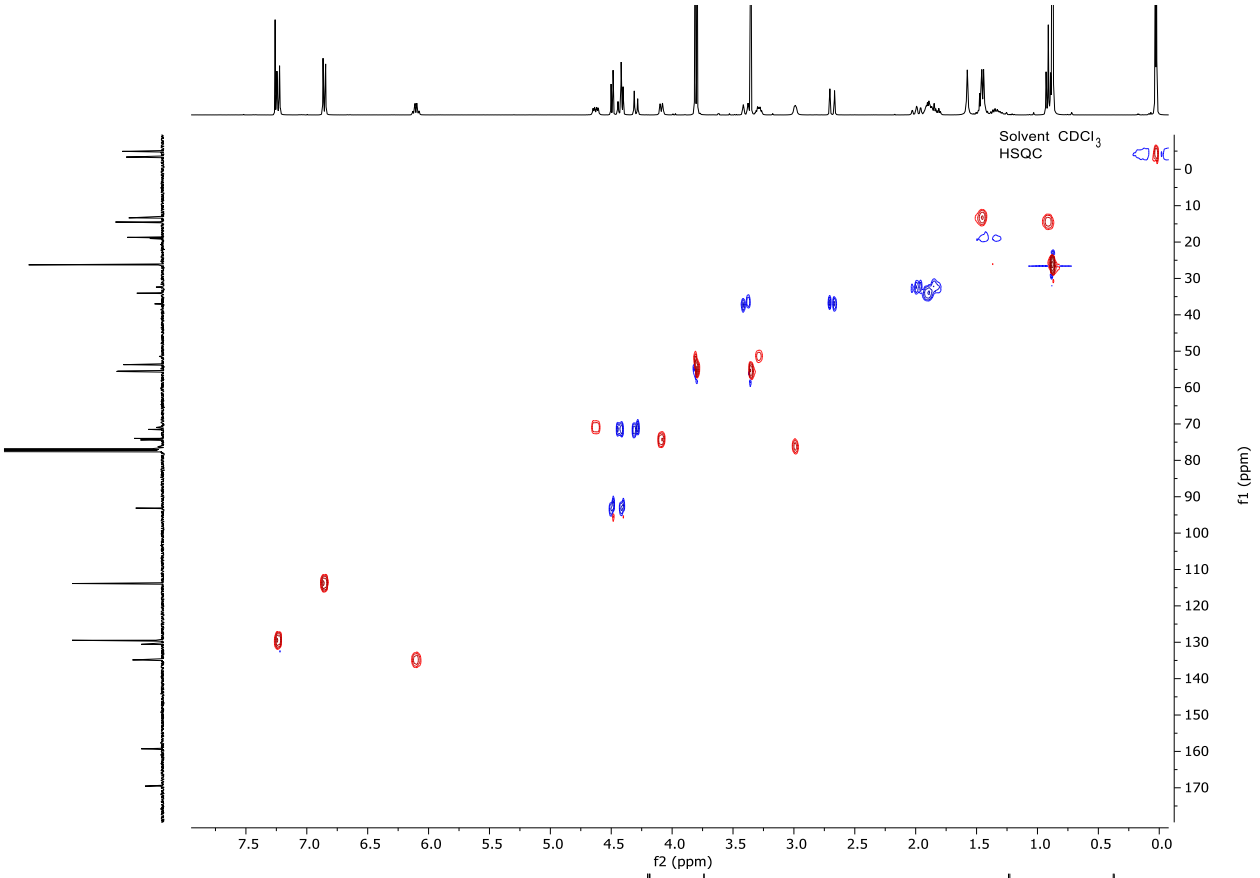

Solvent CDCl3
HMBC
f2 (ppm)
f1 (ppm)

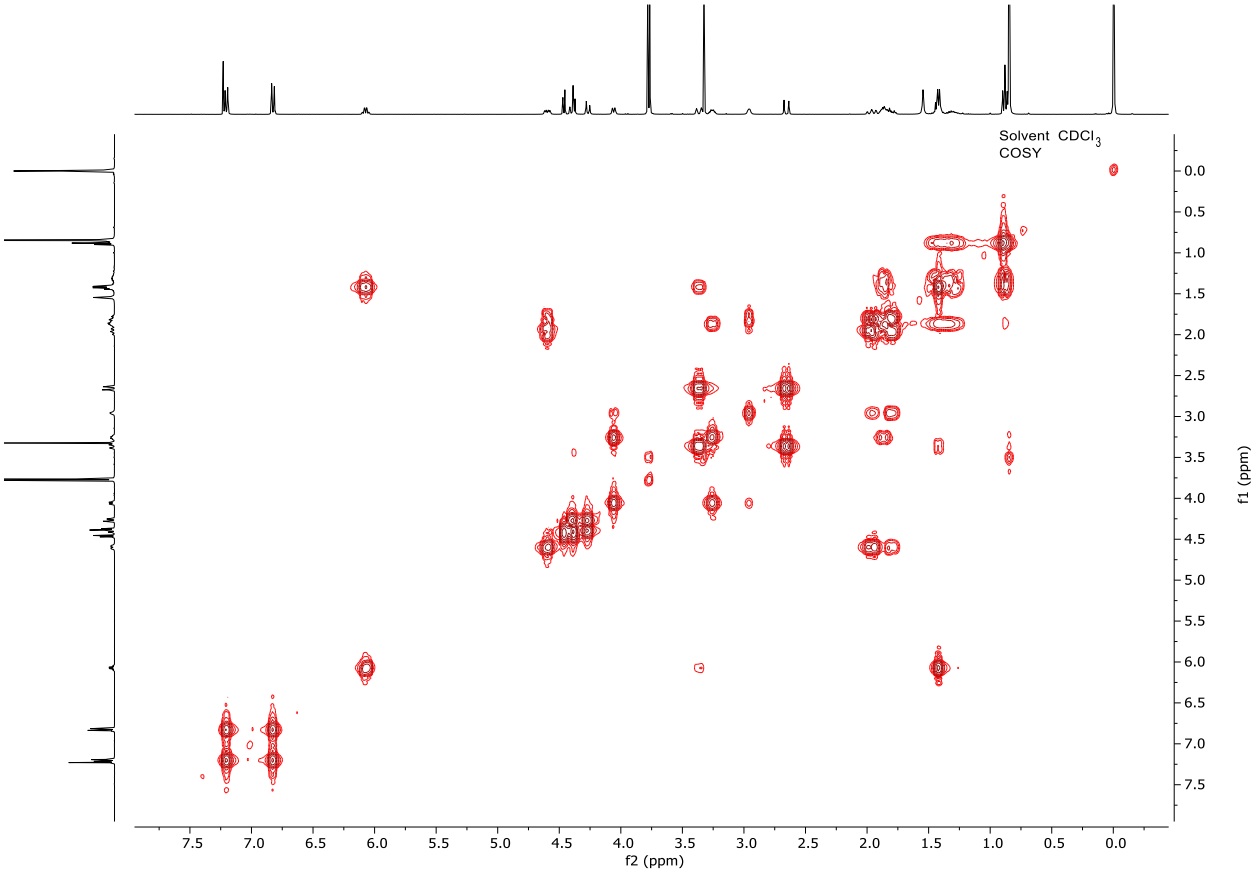

MOMO
α
OPMB
OTBS
MeOOC
Cl

α-**304**

Solvent CDCl3
MHz 400
Nucleus 1H
2.00
2.01
1.00
0.97
1.01
1.97
0.98
0.97
2.99
3.06
1.00
3.01
0.98
0.97
0.98
1.04
2.94
4.15
1.08
3.32
8.88
2.91
2.86
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)


205.2
169.5
159.3
134.9
130.6
129.5
129.5
113.9
93.1
76.3
74.4
74.0
71.5
71.0
55.6
55.4
53.7
51.4
37.0
34.1
32.4
26.3
19.0
18.7
14.5
13.3
-3.4
-4.9
Solvent CDCl3
MHz 101
Nucleus 13C
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Solvent CDCl3
HSQC
f1 (ppm)
f2 (ppm)


Solvent CDCl3
COSY
f1 (ppm)
f2 (ppm)