Title

Synthetic studies on bioactive natural products: De novo assembly of portimine precursors and custom tailoring of complex catechins

Author

El Khoury, Anton

Publication Date

2022

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Synthetic studies on bioactive natural products: De novo assembly of portimine precursors and custom tailoring of complex catechins.

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Chemistry

by

Anton El Khoury

2022

ABSTRACT OF THE DISSERTATION

Synthetic studies on bioactive natural products: De novo assembly of portimine precursors and custom tailoring of complex catechins.

by

Anton El Khoury

Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2022

Professor Patrick G. Harran, Chair

Nature continues to provide a wide array of structurally novel, biologically active small molecules. This thesis describes synthetic studies on two such compounds. The approach used in each project are different. The first project involves a unique molecule that is produced by Nature in only trace quantities. We attempt to develop the first laboratory synthesis of the compound such that it could become available in sufficient amounts to study its biological properties in detail. In the second project, we work with a compound that is naturally abundant, yet has poor pharmacological properties. In that instance, we use synthesis to selectively modify its complex structure in ways that alter its properties while enabling conjugation to carrier proteins.

Portimine is a marine-derived cyclic imine recently discovered as a selective inducer of apoptosis in cancer cells. Moreover, it showed markedly lower in vivo toxicity relative to other macrocycles in its class. Portimine's biological activities are reminiscent of pro-apoptotic biologics such as TRAIL (TNF-related apoptosis-inducing ligand) and TNFα (tumor necrosis factor alpha). No synthesis of portimine has been published and this work outlines the synthetic studies performed en route to the natural product as well as the exploration and development of novel methodologies along the way.

Another natural product, epigallocatechin-3-gallate (EGCG), is a major catechin found in tea that has been shown to inhibit tau through disaggregation of fibrils. The synthesis of several EGCG analogs as well as the biological assays performed with the ultimate goal of developing an Alzheimer's therapeutic are described.

Chapter one describes the development of a highly diastereo- and enantioselective Mukaiyama-Michael reaction for the synthesis of a key chiral intermediate utilized in the subsequent synthetic studies towards portimine. A stereochemical reassignment of the reported isomers of the desired structure is discussed aimed at the elimination of clear inconsistencies in the published reports. Both the racemic, as well as stereoselective synthesis, of both diastereomers are shown that once and for all establish the spectroscopic assignment of the products. Model studies of portimine including both the synthesis of thiophene-based as well as the more elaborate deoxygenated Diels-Alder precursor synthesized in just 3 steps from the published intermediate are reported as well. Optimization of the homoenolate cross-coupling as well as the development of the highly convergent route allowed for the rapid assembly of the chain containing all of the carbons present in portimine. Subsequent Diels-Alder studies as well as the challenges associated

with utilizing an acyclic precursor provided useful information for the asymmetric synthesis of portimine.

Chapter two describes the synthetic studies toward the natural product. Highly enantio- and diastereoselective aldol reaction as well as the alcohol-directed Narasaka-Prasad reaction allowed for the installation of the key sequence of stereocenters. Both halogenated as well as highly reactive dendralene Diels-Alder precursors have been synthesized which allowed for the in-depth studies of the cycloaddition conditions. The synthesis of a novel heterocycle provided access to the previously unknown motif that will be beneficial for the future syntheses of cyclic imine natural products.

Chapter three discusses the synthesis of the EGCG analogs, and the biological studies associated with their potential as tau disaggregants. The development of the efficient click reaction assisted by copper-stabilizing Sharpless polytriazole ligand allowed for the synthesis of the conjugates of varied lengths. Subsequent nanoparticle conjugation showed the conservation of the biological activity as well as confirmed a previously hypothesized EGCG's mode of action. Diastereoselective B-ring derivatization not only allowed for the installation of the PEGylated linkers at the new position but also for structure-activity relationship studies on EGCG's D-ring shedding light on the importance of gallate phenols as well as the possibility for the installation of fluorine without sacrificing activity. Improved disaggregating activity of synthesized analogs showcased their promise as potential Alzheimer's therapeutics.

The dissertation of Anton El Khoury is approved.

Craig A. Merlic

Hosea M. Nelson

Ellen M. Sletten

Patrick G. Harran, Committee Chair

University of California, Los Angeles

2022

Dedicated to my family for their ever-lasting faith in me:

without you none of this would be possible

TABLE OF CONTENTS

List of Figures, Schemes, Tables and Spectra

Figures

Schemes

Tables

Spectra

List of Abbreviations

Ac	acetyl
Acac	acetylacetonate
AD	Alzheimer's disease
Bn	benzyl
CI	cyclic imine
cryoEM	cryogenic electron microscopy
CSA	camphorsulfonic acid
DA	Diels-Alder
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMA	dimethyl acetamide
DME	1,2-dimethoxyethane
DMF	dimethyl formamide

DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dppbz	1,2-Bis(diphenylphosphino)benzene
ECG	epicatechin gallate
EDC·HCl	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
EGCG	epigallocatechin gallate
ent	reversed stereochemistry
et al.	and others
HWE	Horner–Wadsworth–Emmons
HRMS	High-resolution mass spectrometry
IC_{50}	half maximal inhibitory concentration
KHMDS	potassium bis(trimethylsilyl)amide
LAH	Lithium Aluminum Hydride
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
MTBE	methyl *tert*-butyl ether
ORTEP	Oak Ridge thermal-ellipsoid plot
OTf	triflate

OTs	tosylate
PEG	polyethylene glycol
Pic	picolinyl
PCC	pyridinium chlorochromate
Ph	phenyl
PPTS	pyridinium p-toluenesulfonate
PTSA	p-toluenesulfonic acid
Py	pyridine
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
RT or rt	room temperature
SAR	structure-activity relationship
sp.	species
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBTA	tris((1-benzyl-4-triazolyl)methyl)amine
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran

TMS	trimethylsilyl
TNF	tumor necrosis factor
TLC	thin layer chromatography
TRAIL	TNF-related apoptosis-inducing ligand

ACKNOWLEDGEMENTS

First and foremost, I would like to thank Professor Harran for his endless support and mentorship throughout my Ph.D. career. It is not easy to agree to take in a student with zero experience in organic chemistry and I am grateful to Professor Harran for taking the risk, spending time teaching me from the ground up and providing the environment, where I could have all the help I needed. His continuous faith in me even when I had none helped me get back on my feet every time and try better. Moreover, Professor Harran's continuous search for more opportunities helped me broaden my horizons, learn new techniques, and make new connections through collaborative projects. Thank you, Professor Harran, for converting an insecure, inexperienced first-year graduate student into the confident scientist I am today.

I would also like to thank my thesis committee: Professor Ellen Sletten, Professor Craig Merlic, and Professor Hosea Nelson for all their help and advice. Professor Sletten's chemical biology class, Professor Merlic's safety course as well as Professor Nelson's synthesis lectures all prepared me for graduate-level research.

Both Eisenberg as well as Seidler labs were instrumental in pushing the biology of the EGCG project forward. I am especially grateful to Hope Pan and Paul Seidler for teaching me new techniques and for having a patience to answer all the basic biology questions I had.

I would never be able to survive on a day-to-day basis without my amazing coworkers and friends. Liubo (Rupert) Li, who was my mentor and best friend in graduate school, not only taught me all the techniques I needed to succeed in the lab but also provided an ear when I needed to complain and a helping hand when I was struggling. I will never forget the laughs we

shared and the challenges we overcame together. Alek Lotuzas and Carlos Cruz were amazing friends during my last year at UCLA. The lunches we had together provided a great distraction from work and helped relieve stress during the particularly hard times. Of course, no progress in lab would be made without the hard work of the rest of the team. Francesco Manoni, who helped me settle down during the first days of graduate school as well as the rest of the portimine (Brennan Clement, Emma Greene, and Ashley Michel) and EGCG (Zoe Gleason) teams pushed the boundaries of organic chemistry making amazing discoveries and synthesizing novel compounds.

I will forever cherish the friendships I made in the Harran lab. Hui Ding, Tyler Allred, Luke Sisto, Emily Murzinski, Salvador Bernardino, Ishika Saha, Evan Hurlow, Morris Dweck, Angel Mendoza, Gilbert Walker, and many other rotation and undergraduate students made each workday enjoyable and fun.

I would also like to thank my undergraduate advisor, Igor Kaltashov, for not only mentoring me but also providing me with a piece of my own culture in a new country.

Finally, I will forever be indebted to my amazing family for their eternal love and support. My parents, Yulia and Antoine El Khoury as well as my grandparents, Vladimir and Natalia Kazachenko were my pillars, celebrating all my successes and providing support through all the challenges. None of this would be possible without you, thank you and I love you.

CURRICULUM VITAE

EDUCATION

Ph.D. in Organic Chemistry, University of California – Los Angeles Expected: Summer 2022

M.S. in Organic Chemistry, University of California, Los Angeles, CA 2019

B.S. in Chemistry, University of Massachusetts, Amherst, MA 2017

Bard College at Simon's Rock, Great Barrington, MA 2013-2014

TEACHING EXPERIENCE

Graduate Teaching Assistant, University of California
Organic Structural Methods (Spring 2021, Spring 2019)
General Chemistry for Life Scientists II – Enhanced (Winter 2021)
General and Organic Chemistry Laboratory II (Summer 2018)
Organic Chemistry Laboratory I (Spring 2020, Winter 2019)
Organic Chemistry Laboratory II (Fall 2019)
General Chemistry for Life Scientists I (Summer 2019, Fall 2018, Fall 2017)
General Chemistry for Life Scientists II (Winter 2018)
Organic Reactions and Pharmaceuticals (Winter 2020)
Structure of Organic Molecules (Spring 2018)

Undergraduate Teaching Assistant, University of Massachusetts
General Chemistry Laboratory (Summer 2015, Fall 2015)

High School Tutor, Amherst
- Tutored senior high school students
- Conducted both individual and group sessions

HONORS AND AWARDS

University of California, Los Angeles, CA
- Hanson-Dow Excellence in Teaching Award (Spring 2019)
- Pfizer-UCLA Dissertation Award for Outstanding Contributions to Organic Synthesis (Spring 2022)

University of Massachusetts, Amherst, MA
- Dean's List (Fall 2014, Spring 2015, Fall 2015, Spring 2016)
- Edward Shapiro Scholarship (April 2016, April 2017)
- Oliver Zajicek Memorial Scholarship (April 2017)
- Honors Thesis (defended May 2017)

RESEARCH EXPERIENCE

Graduate Student Researcher, University of California, Los Angeles, CA
Advisor: Dr. Patrick G. Harran July 2017 – present

- Worked on the total synthesis of portimine
- Developed a highly enantio- and diastereoselective variant of a Mukaiyama-Michael reaction
- Designed and synthesized a set of novel EGCG-based tau desaggregants

Undergraduate Student Researcher, University of Massachusetts, Amherst, MA 2016-2017
Advisor: Dr. Igor Kaltashov

- Discovered a novel ruthenium-histidine binding mode for protein labeling

PUBLICATIONS

1. Li, L., **El Khoury, A**., Clement, B. O., Wu, C., Harran, P. G. Asymmetric Organocatalysis Enables Rapid Assembly of Portimine Precursor Chains. *Org. Lett.* 2022*,* 24*,* 14*,* 2607–2612
2. **El Khoury, A**; Seidler, P. M., Eisenberg, D. S., Harran, P.G. Catalytic synthesis of PEGylated EGCG conjugates that disaggregate Alzheimer's tau. *Synthesis*, 2021, 53, A-I
3. Li, L., **El Khoury, A**., Clement, B. O., Harran, P. G. Re-visiting the diastereoselectivity of organocatalytic conjugate addition of 2-trimethylsiloxyfuran to trans-crotonaldehyde. *Tetrahedron Letters*, 2021, 72, 153056
4. Kaltashov, I. A.; **El Khoury, A**; Ren, C; Savinov, S. N. Ruthenium coordination preferences in imidazole-containing systems revealed by electrospray ionization mass spectrometry and molecular modeling: possible cues for the surprising stability of the Ru(III)/tris(hydroxymethyl)-aminomethane/imidazole complexes. *Journal of Mass Spectrometry*, 2019, 55, 2, 1

Chapter One: Model studies directed towards the total synthesis of Portimine

1.1 Introduction

1.1.1 Spiroimine natural products

Dinoflagellates are a family of single-cell eukaryotes that can be found in both seas/oceans as well as occasionally in freshwater reservoirs. Hundreds of their species have been described with more being discovered each year. The continued interest in these small organisms in both chemistry and biology circles stems from two reasons. First, their toxicity and potential danger to humans. In small amounts, they are harmless, however, occasionally they can bloom in large concentrations producing toxins that not only harm aquatic life but can also accumulate in shellfish passing the poison to the consumers[1]. While little information is known so far about the cause of these phenomena, thousands of people each year die from the associated poisoning, causing worldwide health concerns. The second reason is the plethora of bioactive natural products that have been isolated from various dinoflagellate species and shown to exhibit a range of unique biological activities. One of the species that stands out among them is *Vulcanodinium rugosum*, a source of most of the known spiroimine natural products[2]. Since the discovery of the first two members of the family (Pinnatoxin A[3] and Gymnodimine[4]), dozens of related structures have been isolated, which all share a unique cyclic imine framework, some type of a spirocycle system with a cyclohexene ring as well as a macrocyclic ether (**Figure 1)**. While many members of the family have shown a potential to become lead compounds for the development of drugs for a variety of illnesses their high toxicity impeded any ensuing biological studies. This is why portimine[5], one of the most recently isolated cyclic imines attracted a lot of interest from the biochemical as well as the synthetic community.

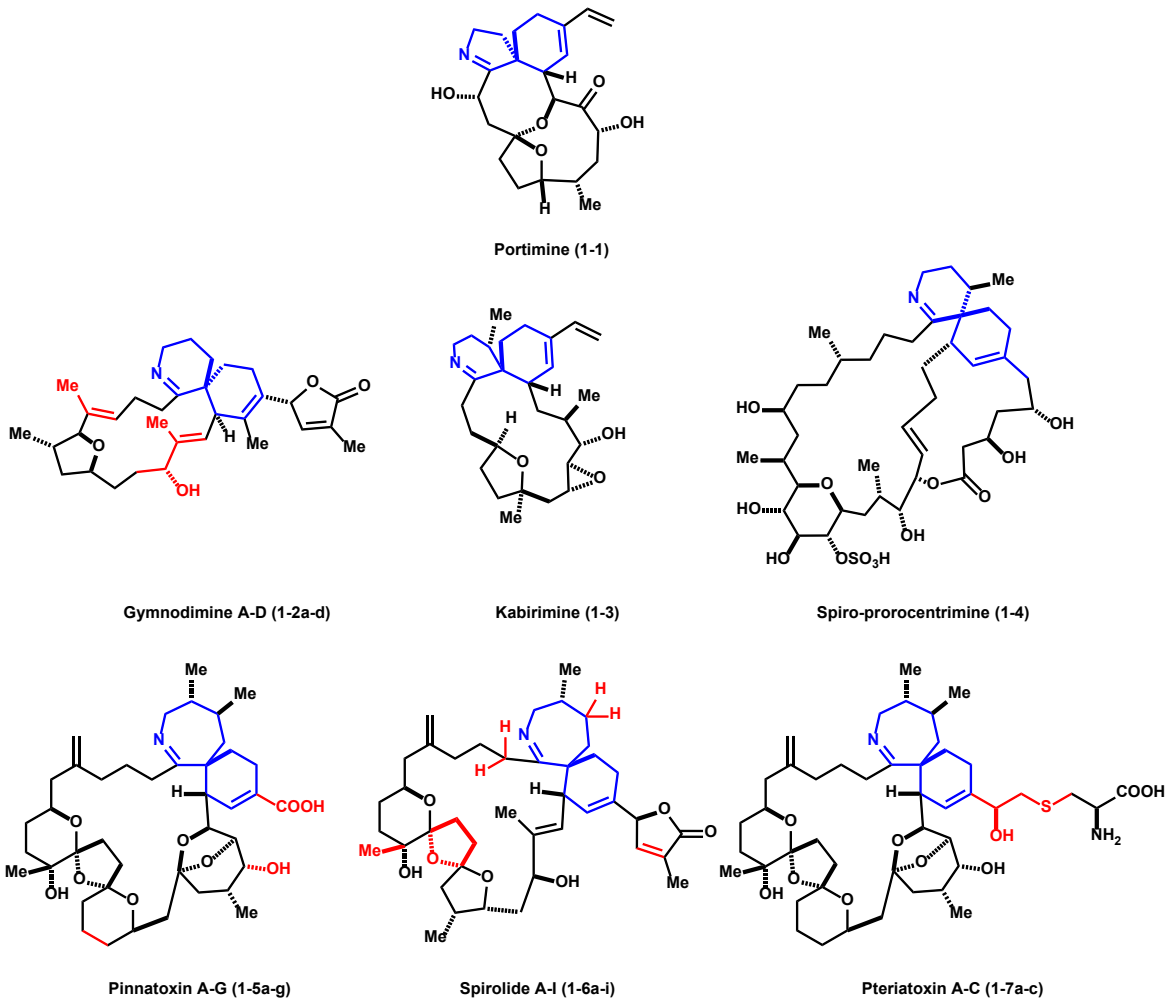


Figure 1. Chemical structures of representative members of spiroimine family of natural products. Blue highlights the key spirocycle while red color displays the positions that vary within the corresponding subcategory.

1.1.2 Proposed biosynthesis of related natural products

Despite the challenges associated with the isolation of a sufficient amount of material as well as the high diversity amongst the members of dinoflagellate-derived natural products, biosyntheses of several cyclic imines have been proposed in the literature. One of the more detailed reports has been published by Walter group,[6] in which the researchers look at 13-desmethyl spirolide C, a

member of the family that contains a commonly encountered 7-membered cyclic imine. The overall labeling pattern is shown in **Figure 2**.

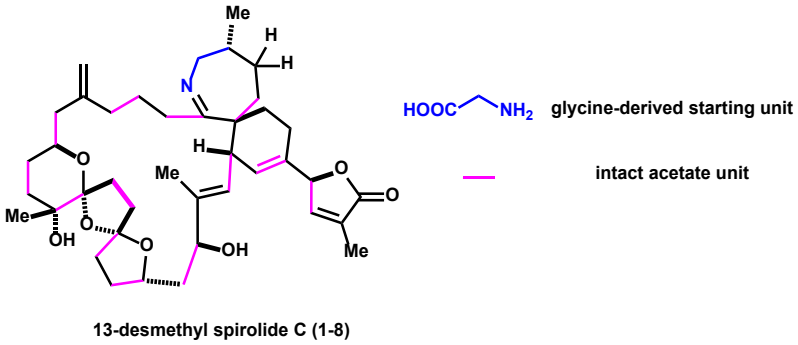
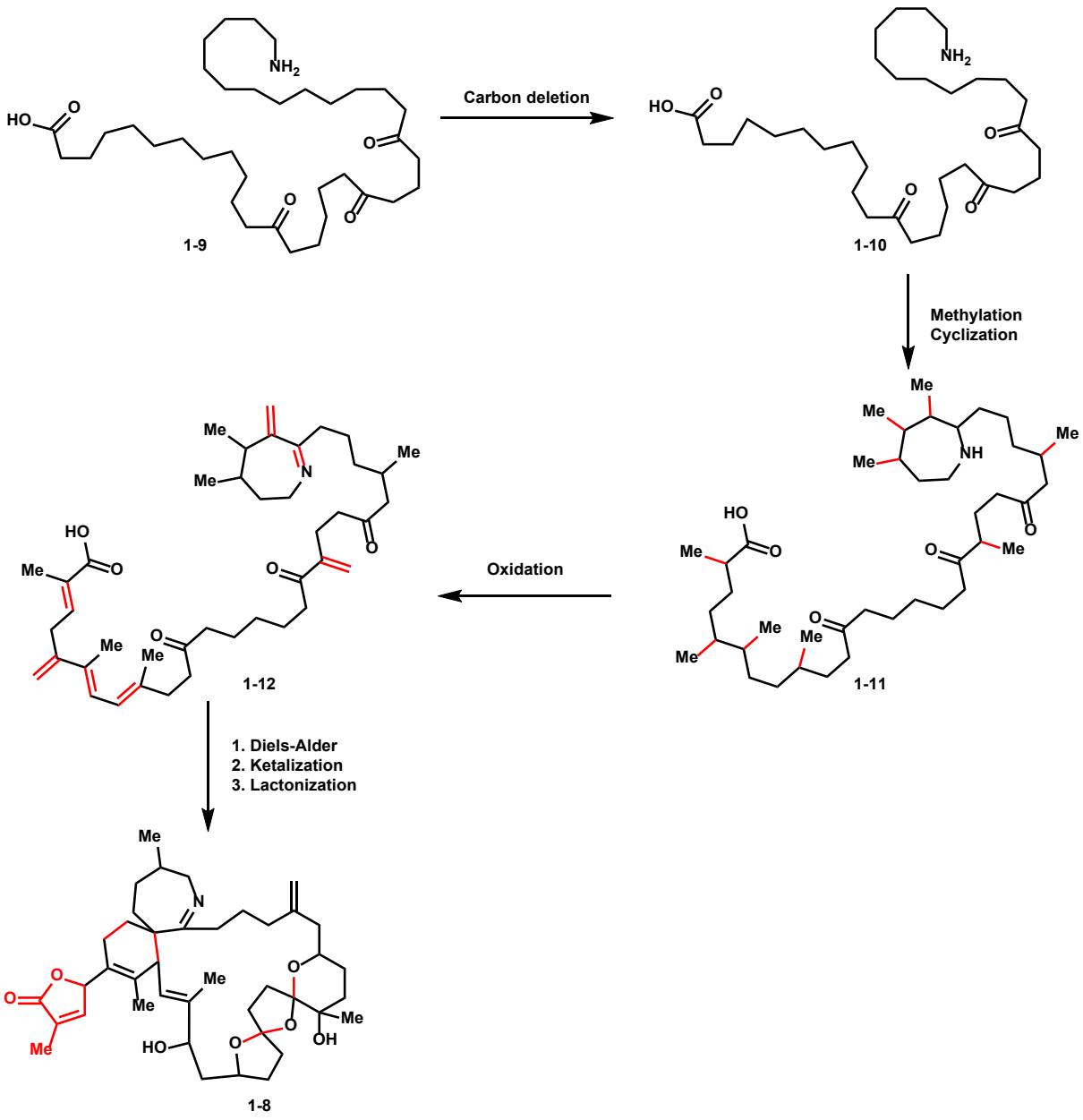


Figure 2. Labeling pattern for 13-desmethyl spirolide C based on the biosynthesis proposed by Walter *et al.*

As can be seen, most of the carbons are polyketide-derived with the glycine considered to be a starter motif for the synthesis of the rest of the chain. A proposed detailed biosynthesis based on the thorough isotope labeling studies and NMR characterizations is shown in **Figure 3**. While the studies have focused on a specific member of the family, the clear structural similarities suggest a common origin and thus the biosynthesis of the related natural products should follow the same general sequence. According to the Walter report, the starting chain is synthesized through a consecutive condensation of acetate units onto a starting glycine followed by the elimination of some of the carbonyls.



Scheme 1. Proposed biosynthesis of 13-desmethyl spirolide C.

This is followed by the Favorski-type carbon deletion. Subsequent aldol condensation onto a backbone followed by the intramolecular cyclization affords a 7-membered cyclic imine. Oxidation of the system results in the unsaturation at multiple sites including a formation of the key imine moiety. Finally, Diels-Alder [4+2] cycloaddition affords a spirocycle that then

undergoes a series of intramolecular cyclizations to afford the sequence of ketals present in the natural product. While several steps in the proposed biosynthesis are still unclear, including, but not limited to the origins of some of the methyl as well as hydroxyl groups, the article provides an important reference point for the subsequent biomimetic total syntheses. Specifically, it highlights the importance of the Diels-Alder reaction for the construction of the key spirocyclic cyclohexene motif, which was later employed in the majority of the synthetic studies towards dinoflagellate derived natural products and will be discussed in the next section.

1.1.3 Previous syntheses of cyclic imine marine toxins

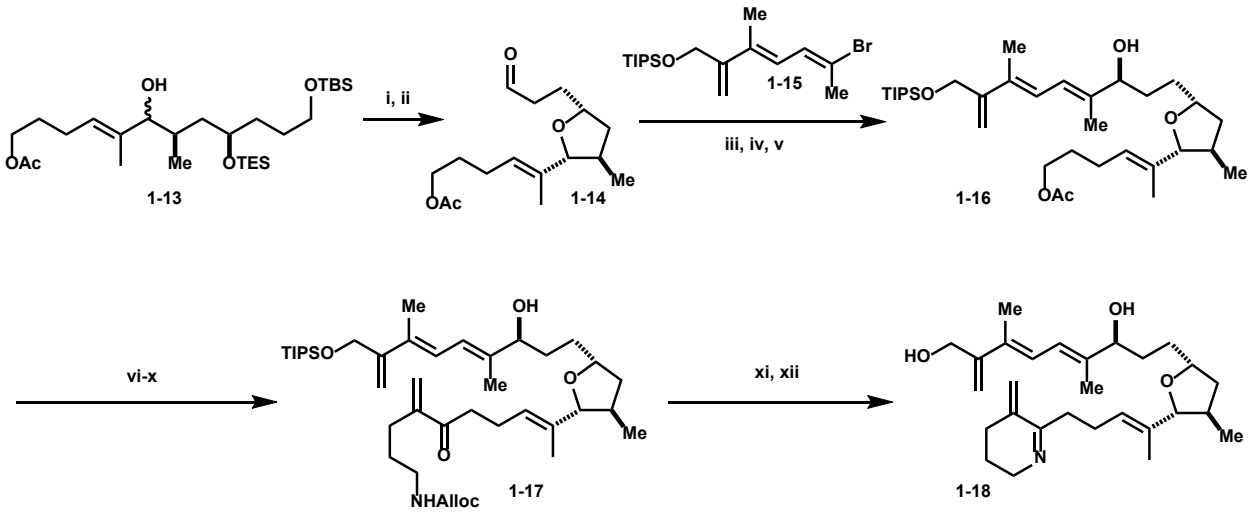
While no total synthesis of portimine has been reported, several other related cyclic imines have been synthesized. While most of them utilized similar biomimetic approaches that include a modular extension of the carbon chain, sequential ketalizations, and a Diels-Alder-based construction of the spirocycle, each synthesis is unique by itself and provides many interesting strategic level reactions that present a good reference point for the development of a novel total synthesis. This section will discuss and compare two approaches toward Gymnodimine A as well as two approaches toward Pinnatoxin A.

1.1.3.1 Synthetic studies towards Gymnodimine A (Kishi 2005)

Gymnodimine A (**Figure 1, 1-2a**) is one of the first members of cyclic imines isolated. It was first discovered in 1995 by the Yasumoto group in New Zealand.[4] While the Yasumoto group established a general structure after isolation, it was only 2 years later that the Munro group assigned a relative and absolute stereochemistry of Gymnodimine based on X-ray analysis of the derivative.[7] Since then two additional analogs were discovered that had a slight variation in the

carbon framework of the parent compound. All of the discovered compounds exhibited high toxicity which is reminiscent of other members of the cyclic imine family. Despite the lack of a beneficial biological activity, gymnodimines attracted interest from the medicinal chemists as detailed studies would allow not only for the identification of the key motifs responsible for its toxicity but also development of the assay that could help determine the presence of the toxin in food or water. Thus, two research groups set on developing a synthetic route aimed at the efficient and scalable production of Gymnodimine A.

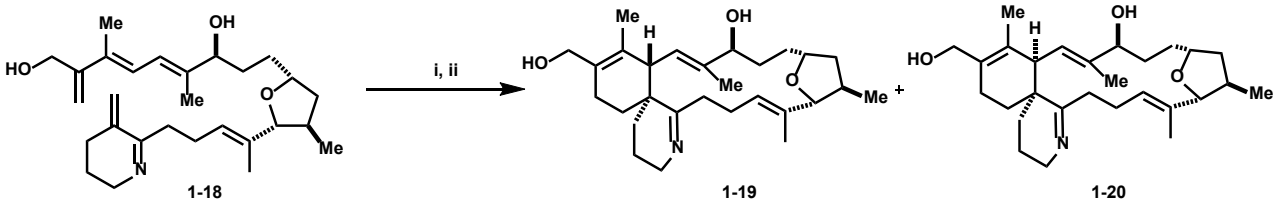
The first study was published by the Kishi group in 2005.[8] While not arriving at the natural product itself, the group developed a biomimetic Diels-Alder cycloaddition that was an important addition to the field as it served as a template for the subsequent synthetic studies. The sequence of steps is outlined in **Scheme 2**.



Conditions: (i) p-TsOH, DCM, 86%, 9:1; (ii) $(COCl)_2$, DMSO, TEA, DCM, 80%; (iii) **1-15**, $NiCl_2$, $CrCl_2$, $Ni(COD)_2$, THF, DMF, t-BuPy, 50 °C, 70%, 1:1; (iv) MnO_2, DCM, 50%; (v) (R)- 2-methyl-CBS-oxazaborolidine, BH_3,DMS, tol, -10 °C, 80%, 6:1; (vi) TESCl, $AgNO_3$, py, DMF, 99%; (vii) DIBAL, DCM, -78 °C, 83%; (viii) PCC, 4 Å MS, DCM, NaOAc, 71%; (ix) 0.5% $NiCl_2$/ $CrCl_2$, DMF, 56%; (x) MnO_2, DCM reflux, 83%; (xi) TBAF, AcOH, THF, 78%; (xii) $(PPh_3)_4Pd$, tol (0.1% AcOH).

Scheme 2. Synthesis of the Diels-Alder precursor.

The synthesis of the Diels-Alder precursor **1-18** was accomplished in 19 steps in the longest linear sequence. Two major disconnections were identified to be the formation of the sterically congested tetrahydrofuran ring as well as the installation of both the diene and dienophile (cyclic imine) for the subsequent cyclization. The group has discovered that acid-catalyzed cyclization of the allylic alcohol **1-13** affords the desired product in a 9:1 diastereomeric ratio. The stereochemistry of the starting alcohol was found to be of no importance as the reaction goes through the formation of the carbocation (S_N1 mechanism). Subsequent multiple oxidation/reduction cycles as well as protecting group manipulations afforded **1-18** in additional 11 steps from the ketalization. At this point, both Diels-Alder partners were installed and studies into the cycloaddition took place.



Conditions: (i) pH 6.5 sodium citrate/HCl buffer, H_2O, 36 °C, 48 h, (ii) benzene, TEA, PivOH, 4 Å MS, 16 h, **1-19:1-20** = 1:1

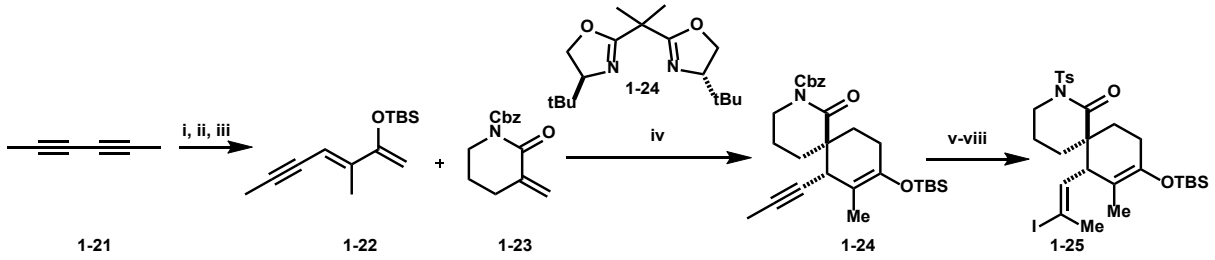
Scheme 3. Diels-Alder studies.

The group discovered that upon stirring **1-18** in the pH 6.5 citric buffer, reaction was completed in 30 h at 36 ºC. Two major products have been identified that came from the endo and exo approach in a 1:1 ration. Interestingly, in the case of the enone substrate, the formation of exclusively endo products was observed suggesting the need for the early imine formation for the desired cycloaddition outcome. Overall, the group demonstrated that the formation of the core of Gymnodimine can occur under aqueous conditions at slightly acidic pH without a need for an

external catalyst or Lewis acid suggesting that the reaction doesn't require an enzyme to proceed in biological systems.

1.1.3.2 Total synthesis of Gymnodimine A (Romo 2011)

Unlike the Kishi group that focused on the Diels-Alder studies and hasn't reached the natural product, the Romo group published a full synthetic route towards Gymnodimine A.[9] Interestingly, while still relying on [4+2] cycloaddition for the formation of the spirocycle, the group took a fundamentally different approach switching the order of steps and performing Diels-Alder early in the sequence.

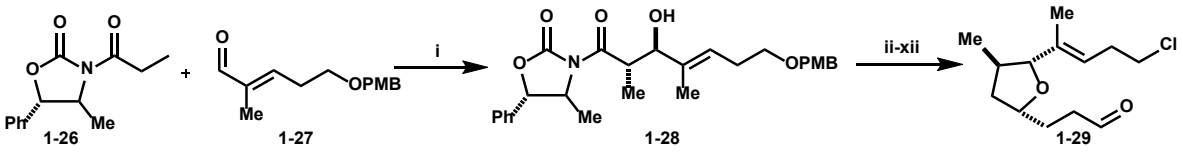


Conditions: (i) $(n\text{-}Bu_3Sn)_2CuCNLi_2$, THF, 78 °C, 67%; (ii) n-BuLi, N-methyl-N-methoxyacetamide, THF, 78 °C, 77%; (iii) Et_3N, TBSOTf, DCM, 78 °C, 90%; (iv) **1-24** (11 mol %), $AgSbF_6$ (20 mol %), $CuCl_2$ (10 mol %), **1-23**, DCM, 85%, exo/endo > 95:5, 95% ee (major diast); (v) n-BuLi, THF, 78 °C, 82%; (vi) KHMDS, TsCl, THF, 80%, (vii) $PdCl_2(PPh_3)_2$, n-BuSnH, THF/hexanes (1:6), 85%; (viii) I_2, DCM, 78 °C, then cyclohexene, 76%.

Scheme 4. Synthesis of fragment **1-25**.

Romo's route is highly convergent and involves the coupling of two fragments synthesized separately through NHK coupling. The first fragment was synthesized from the diyne **1-21** in 8 steps and the route is outlined in **Scheme 4**. The transformation of interest in this sequence is the intermolecular Diels-Alder cycloaddition between exo-methylene lactam **1-23** and dienyne **1-22**. In the presence of Cu-BOX catalyst as well as silver salts, the reaction produced the desired stereoisomer with high dr and ee. This was the first time in the syntheses of cyclic imines that

Diels-Alder was performed intermolecularly and thus it set the standard for the subsequent syntheses that might wish to utilize similar strategy.

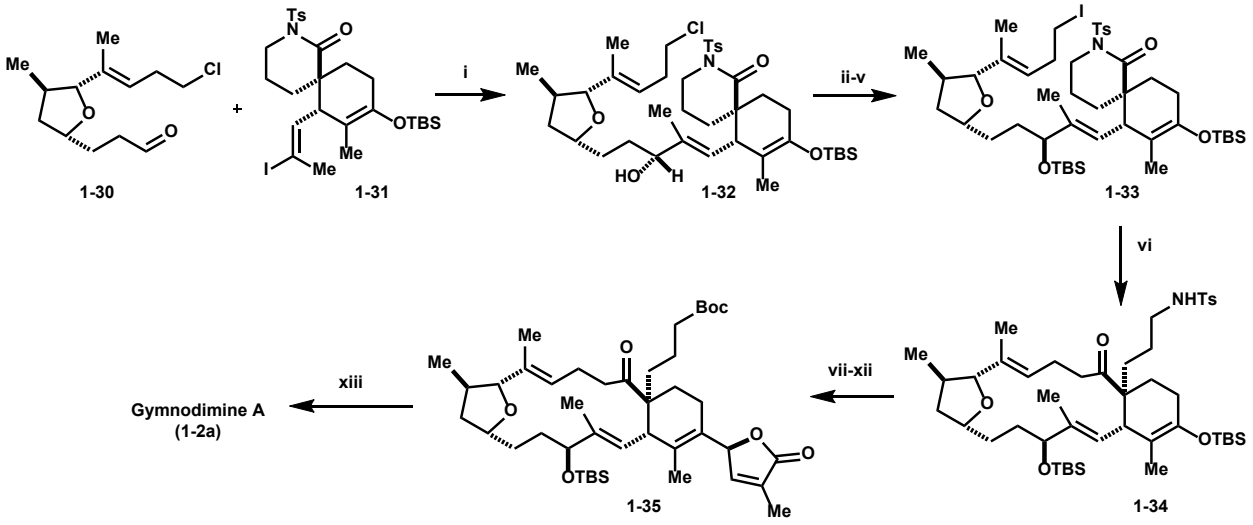


Conditions: (i) n-Bu_2BOTf (2.0 equiv), i-Pr_2NEt, Et_2O, 78 °C, 68%; (ii) NaOMe, MeOH, 80%; (iii) TESOTf, 2,6- lutidine, DCM, 78 °C, 90%; (iv) DIBAL, DCM, 78 °C, 93%; (v) $(COCl)_2$, DMSO, Et_3N, DCM, 99%; (vi) $Ph_3PCH_2(OMe)Cl$, KOtBu, THF, 97%; (vii) p-TSA, MeOH, 86%; (viii) allyl trimethylsilane, BF_3OEt_2, PhMe/DCM (1:1), 78 °C, 71%, α/ β = 4:1; (ix) Na, NH_3(l), THF, 78 °C, 92%; (x) PPh_3, CCl_4, DMF, 65 °C, 85%; (xi) 9-BBN, THF, then NaOH, H_2O_2, 98%; (xii) Dess-Martin periodinane, DCM, $NaHCO_3$, 71%

Scheme 5. Synthesis of fragment **1-29**.

The second fragment was synthesized in 12 steps from the oxazolidinone **1-26** (**Scheme 5**)**.** A prototypical Evans aldol took place directed by the substituents on the chiral auxiliary. This was followed by a series of functional group manipulations with the p-TSA-mediated ketalization to install the key tetrahydrofuran ring. With two fragments now prepared, NHK-coupling was attempted next (**Scheme 6**). Standard Cr/Ni co-catalytic system allowed for the joining of two fragments and the production of the spirocyclic lactam **1-32**. Subsequent oxidation/reduction sequence followed by the Finkelstein displacement of the homoallylic chloride afforded **1-33**. Subsequent macrocyclization required careful optimization. Authors turned to Barbier reaction as the strategy of choice. Interestingly, unlike literature reports published in this area, the reaction didn't require subzero temperatures and instead proceeded smoothly and in satisfactory yield at ambient temperatures. Now, with the macrocycle in hand, a couple of manipulations were required before arriving at the natural product in 7 additional steps. The convergence of the route as well a

series of novel reactivities discovered along the way allowed for the production of both the natural product as well as its analogs.



Conditions: (i) $CrCl_2/NiCl_2$, DMF/THF (1:1), 97% (β-OH/α-OH, 1.3:1); (ii) Dess-Martin periodinane, $NaHCO_3$, DCM, 88%; (iii) (R)-Me-CBS, catecholborane, DCM, 0 °C, 81% (dr, 6:1); (iv) TBSOTf, Et_3N, DCM, 78 °C, 86%; (v) NaI, acetone, 65 °C, 99%.; (vi) t-Buli, Et_2O, 65%; (vii) $(CF_3CO)_2O$, Et_3N, CH2Cl2, SmI_2, 73%; (viii) p-TsOH, THF/DCM/MeOH, 84%; (ix) 71, $TiCl_4$, DCM, 23 °C, 1 min, dr = 1.1:1, 61%; (x) TESCl, imidazole, DMAP, DCM, 76%; (xi) DBU, DCM, 83; (xii) Et_3N, $SOCl_2$, CH2Cl2, 78 °C, 82%,; (xiii) Et_3N, $(Boc)_2O$, DMAP, DCM, then hydrazine, 99%; (xiv) TFA, DCM, high vacuum overnight, 68%.

Scheme 6. Completion of the synthesis.

1.1.3.3 Total synthesis of Pinnatoxin A (Kishi 1998)

The same year as Gymnodimine A, another member of the cyclic imine family was isolated: Pinnatoxin A (**Figure 3**).[3] Even though its absolute stereochemistry was initially misassigned, the isolation group was able to deduce the key structural motifs of the natural product as well as to conduct a series of biological experiments to test whether the compound could be the reason behind the ongoing, at the time, shellfish poisoning outbreak in East Asia.

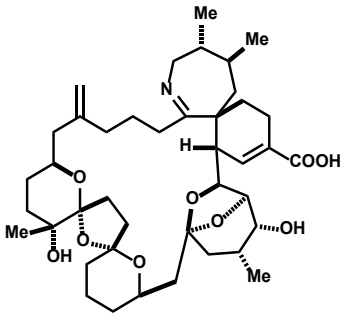
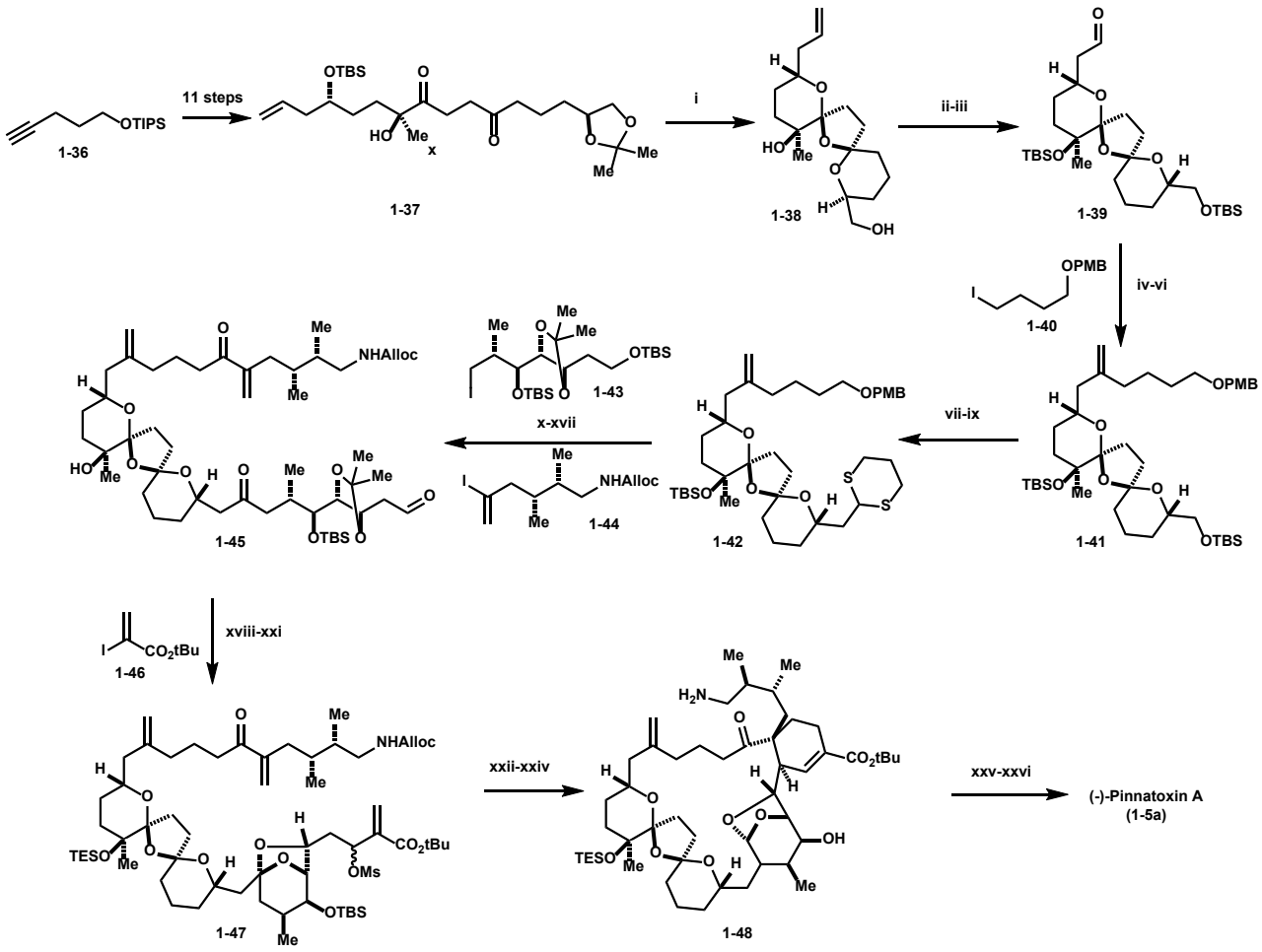


Figure 3. Structure of Pinnatoxin A.

It was found that its, indeed, high toxicity is associated with its role as a calcium channel activator which prompted several research groups to look into trying to synthesize it in order to produce more material for in-depth biological studies. Up to this day, three major total syntheses have been published with the first one being the Kishi's formal synthesis of 1998.[10] Due to the rather long longest linear sequence (37 steps), this section will focus only on the key aspects of each synthesis and the main differences between them.

Kishi's synthesis began with the protected pentynol **1-36** that was elaborated in 11 steps to an intermediate **1-37**. Subsequent ketalization and dihydroxylation/glycol cleavage afforded an aldehyde ready for the first organometallic addition in the route. Lithiation of the iodide **1-40** and its subsequent addition to the chiral aldehyde afforded a mixture of alcohols that were subjected to Swern oxidation and Wittig olefination sequence to install the ketone. On the other side of the molecule, dithiane was installed in three steps following the desilylation, iodination of the resulting alcohol, and S_N2 displacement with 1,3-dithiane. Subsequent lithiation and treatment with the alkyl iodide **1-43** afforded the desired product. PMB ether was then deprotected and oxidized to an aldehyde ready to undergo NHK coupling.



Conditions: (i) CSA, MeOH, 51%; (ii) TBSOTf, 2,6-lutidine, 95%; (iii) OsO_4, NMO; $NaIO_4$, 85%; (iv) 4-iodobutyl-p-methoxybenzyl ether, t-BuLi, Et_2O, -78 °C, 88%; (v) Swern oxidation, 92%; (vi) PPh_3CH_3Br, n-BuLi, 0 °C, 89%; (vii) TBAF, rt, quantitative; (viii) I_2, PPh_3, imidazole, 92%; (ix) 1,3-dithiane, t-BuLi, 10% HMPA/THF, 92%; (x) TBAF, 70 °C, 95% (xi) **1-43**, t-BuLi, 10% HMPA/THF, then addition of **1-42**, 71%; (xii) $(CF_3CO_2)_2IPh$, $CaCO_3$, 82%; (xiii) DDQ, 85%; (xiv) Dess-Martin oxidation, 90%; (xv) **1-44**, 1% $NiCl_2/CrCl_2$, DMSO, 55%; (xvi) HF,pyridine, pyridine, THF, 91%; (xvii) Dess-Martin oxidation, 91%; (xviii) **1-46**, 33% $NiCl_2/CrCl_2$, bispyridinyl ligand, THF, 88%. (xix) TFA, DCM, H_2O, 71%; (xx) MsCl, TEA, -78 °C, 85%; (xxi) TESOTf, 2,6-lutidine, 79%; (xxii) DABCO, TEA, benzene; 70 °C, 0.2 mM diene in dodecane, 78%; (xxiii) HF,pyridine, pyridine, THF, 94%; (xxiv) $Pd(PPh_3)_4$, AcOH, toluene, 82%; (xxv) 200 °C, 1-2 Torr, 70%; (xxvi) 1:1 TFA/DCM, 95%.

Scheme 7. Kishi's total synthesis of (-)-Pinnatoxin A

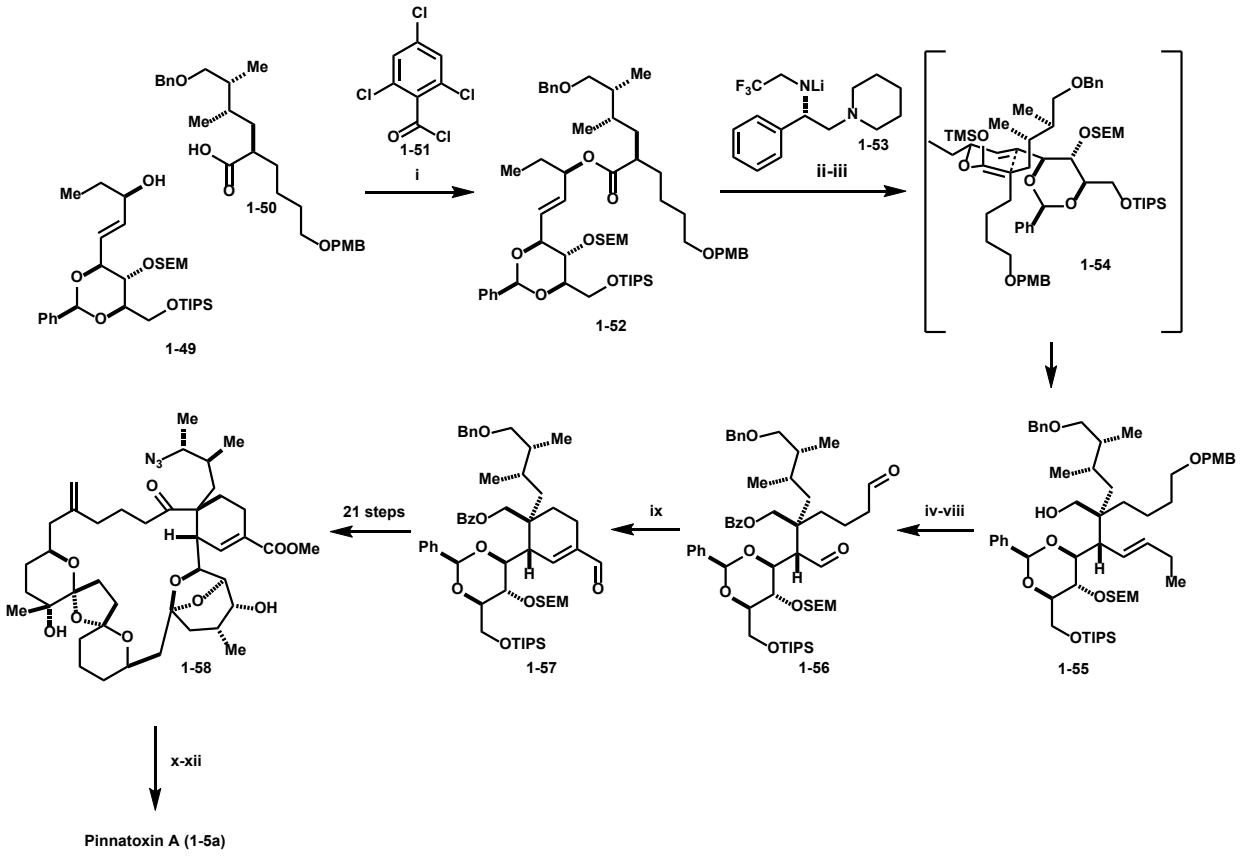
Under the standard Cr^{II}/Ni^{II} catalytic cycle, vinyl iodide **1-44** was added to an aldehyde affording the alcohol that was re-oxidized for the second consecutive NHK coupling. While the rest of the conditions remained the same, the presence of bispyridinyl ligand was found to be necessary to achieve a satisfactory yield. Subsequent acetonide removal resulted in the desired transketalization to form the key bicyclic motif. Finally, masked diene was liberated by the in-situ elimination of the mesylate followed by the Diels-Alder cycloaddition under dilute conditions in dodecane that remarkably afforded 78% combined yield of just three out of eight possible isomers. The desired stereoisomer was then converted into the natural product in four steps: deprotection of both TES and Alloc group, imine formation under vacuum, and final cleavage of the t-butyl group.

Kishi's total synthesis of Pinnatoxin A laid a foundation for the work done in this area in the following years. An in-depth study of the [4+2] cycloaddition performed by the group shed light on the challenges associated with the late-stage formation of the cyclohexene motif and showed the importance of the backbone stereochemistry on the stereochemical outcome. Moreover, an imine formation provided unexpected challenges that showed the difficulties in the construction of 7-membered cyclic imines, something that was not a problem in the previously described syntheses of 6-membered cycle containing natural products.

1.1.3.4 Total synthesis of Pinnatoxin A (Zakarian 2011)

13 years later Zakarian group published their total synthesis of Pinnatoxin A.[11] Contrary to the work done by Kishi and others, the cyclohexene motif was not installed through a Diels-Alder reaction but rather through an aldol condensation. Interestingly, this was the revised version of the

group's original 2008 route. Most of the steps and as well as general disconnection strategies remained the same and are outlined in Scheme **8**.



Conditions: (i) **1-51**, DMAP, Et_3N, benzene, 78%; (ii) **1-53**, THF, -78 °C, then TMSCl; (iii) LAH, Et_2O, 85% over 2 steps; (iv) BzCl, pyridine; (v) DDQ, DCM/H_2O, (vi) O_3, N-methylmorpholine N-oxide, DCM; (vii) $NaBH_4$, EtOH, 77% over 4 steps; (viii) $(COCl)_2$, DMSO, Et_3N, DCM; (ix) $Bn_2NH_2^+CF_3CO_2^-$, toluene, 50 °C, 89%; (x) H_2, Pd/$CaCO_3$, pyridine, EtOH, (xi) triethylammonium mesitoate, toluene, 85 °C, 60 h; (xii) LiOH, THF/H_2O, 43%

Scheme 8. Zakarian's total synthesis of Pinnatoxin A.

The first key step in Zakarian's route was Yamaguchi esterification between carboxylic acid **1-50** (can be prepared in 9 steps from (S-citronellic acid)) and alcohol **1-49** (can be prepared in 10 steps from D-ribose). Subsequently, a highlight of the route, a remarkable Ireland-Claisen rearrangement took place with the assistance of a Koga-type chiral lithiated amide **1-53** delivering

the desired product with exceptional stereoselectivity. **1-55** was then converted into the corresponding aldehyde in 5 steps: protection of the primary alcohol, PMB deprotection, ozonolysis of the alkene with its subsequent reduction, and final oxidation of both alcohols to the corresponding dialdehyde **1-56**. At this point the substrate was set for the aldol condensation to install the key cyclohexene motif present in the natural product. As discussed before this was a rather interesting way of forming this part of the molecule since up to that point Diels-Alder was considered to be the reaction of choice for cyclohexene synthesis. Gratifyingly, the aldol condensation went smoothly, delivering **1-57** in 89% yield. After that, it took 21 steps for the group to reach the intermediate **1-58** that was ready for the installation of the final cyclic imine motif. Herein, the hydrogenation of the azide produced the imine that was directly subjected to the Kishi's conditions (see above) to deliver the natural product following the hydrolysis of the methyl ester.

Zakarian's total synthesis contains multiple unique and elegant strategies for the construction of various motifs common to cyclic imine natural products. The main highlight of the synthesis, however, is the group's rejection of the traditional approach (4+2 cycloaddition) for the sake of forging their own path.

The four total syntheses described here show the plethora of different strategies and approaches available for the construction of the same type of functionality. Besides the discussed work, several other members of cyclic imine natural products have been synthesized with multiple reviews written about them.[12] Each of the published reports further expanded the field by bringing new ways of thinking to the table. The approach discussed in the next sections for the synthesis of portimine continues the trend of exploring new type of reactivities and developing novel methods for total synthesis.

1.1.4 Portimine

Portimine has been isolated in 2013 from the same *V. Rugosum* microalgae as its numerous relatives[13]. 12.5 mg of portimine isolated from 60 L of the corresponding cell culture has been analyzed by 1D and 2D NMR as well as X-ray crystallography followed by extensive biological studies in both human and mouse cell lines. Interestingly, unlike many other members of the cyclic imine family, its structure and biological activity were unique. From a structural standpoint, Portimine was shown to contain an unprecedented 5-membered cyclic imine (vs. 6 and 7-membered in other natural products) as well as a rather interesting, bridged ketal moiety.

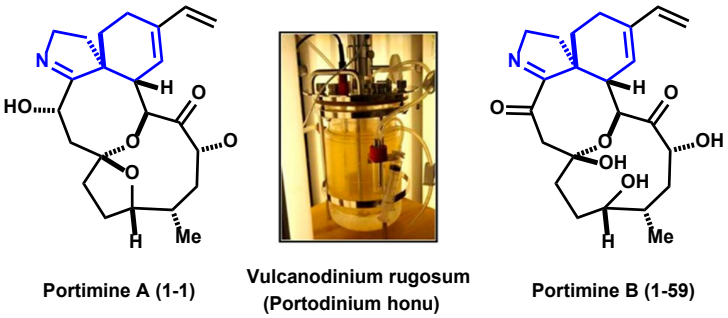


Figure 4. Structures of Portimine A and B and the reactor containing the dinoflagellate source.

What is more important, however, is that it was discovered that portimine has outstanding biological activities.[14] It exhibited lower acute toxicity when administered in mice compared to other members of the cyclic imine family but maintained high potency against a range of cancer cell lines (LC_{50} = 6 nM in Jurkat cells). All the more impressive, portimine showed to be completely dependent on apoptotic signaling for this activity. Unlike many other inducers of apoptosis, no necrosis has been observed in the presence of anti-apoptotic protein Bcl-2, and only after the addition of Bcl-2 inhibitor ABT-737, portimine was awakened. It was suggested that portimine acts through caspase-3 activation, which, while being a known cause of programmed

cell death, has never previously been observed in the cyclic imine family. An interesting additional observation has been made in the original report. Authors stated that portimine's activity resembles that of TRAIL, a known and well-studied pro-apoptotic protein. TRAIL and particularly a development of TRAIL mimetics has been a hot topic for decades yet despite some progress, no viable candidate has been identified thus far. Portimine has the potential to reinvigorate studies in this area. This makes it an extremely attractive target for synthetic studies. In addition, in the subsequent years, portimine has been also identified as a potential anti-HIV-1 as well as antifouling agent[14] further highlighting the need for the expeditious and efficient synthesis as well as subsequent SAR studies.

1.2 Retrosynthetic analysis of portimine

Despite significant advances in the synthesis of cyclic imine natural products, no total synthesis of portimine has yet been published. Due to its low natural abundance, portimine's mode of action was not studied in much detail showcasing a strong need for the development of an efficient synthetic route towards the natural product, which is the main goal of this project. Despite the significant modifications the synthetic plan undergone over the course of the project, the key disconnections remain the same (**Figure 5**). The last step in the synthesis is thought to be the installation of α-OH groups that will allow for the subsequent detailed studies into their importance for portimine's biological activity. The corresponding spirocyclic precursor will be installed through an intramolecular Diels-Alder cycloaddition. Similar type cyclizations have been shown to succeed in the total syntheses of other spirocyclic imines as discussed above.

The DA precursor **1-59** will be derived from the corresponding 1,4-diketone **1-60** through a regioselective ketal formation, oxidation of the alcohol, and aza-Wittig reaction. The plan for the

synthesis of **1-60**, however, has undergone significant changes that will be discussed in the later sections.

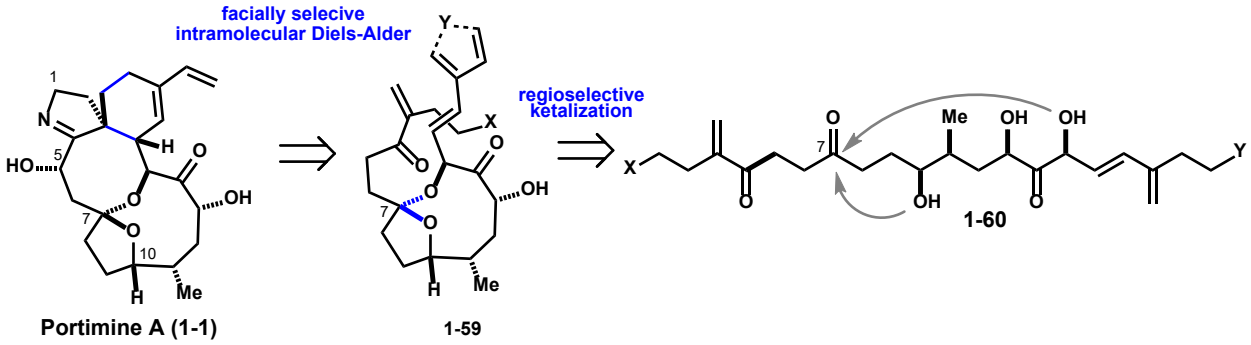


Figure 5. General retrosynthetic analysis of Portimine.

1.3 Model studies towards portimine

1.4.1 1st generation model (thiophene-based)

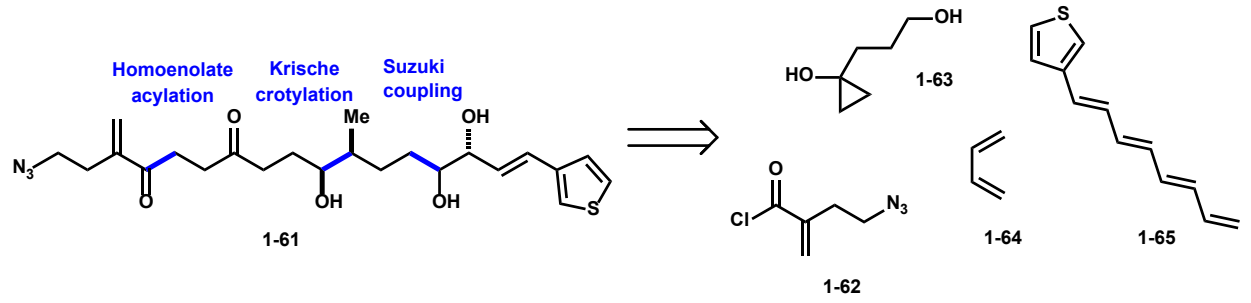
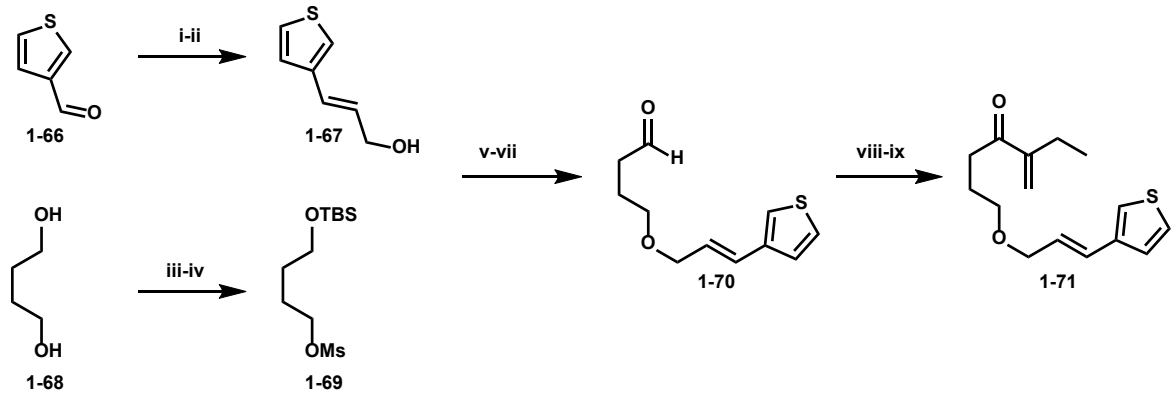


Figure 6. Initial retrosynthesis of a variant of **1-60**.

In the initial retrosynthetic pathway, the diketone **1-61** was thought to be obtained from four different fragments: azido acyl chloride **1-62**, butyrolactone-derived cyclopropanol **1-63**, butadiene, and vinyl iodide **1-65**. It was envisioned that **1-63** could react with either **1-64** or **1-65** as Krische diene partners.[15]

The final target would be then synthesized utilizing the modified Cha procedure[16] for the Pd-catalyzed homoenolate acylation and the stereoselective dihydroxylation. The resulting diketone would be then subjected to the intramolecular DA cycloaddition followed by *in situ* desulfurization.

Both **1-63** and **1-65** have been synthesized and subjected to Krische conditions.[15] It was discovered, however, that **1-65** is unstable to Krische conditions and rapidly decomposes at required temperatures and in the presence of TADDOL acid. This initial observation caused us to reconsider the retrosynthetic plan. However, first, the viability of the thiophene-mediated intramolecular cyclization had to be assessed and thus the model has been constructed containing the key carbon framework of the natural product (**Scheme 9**).

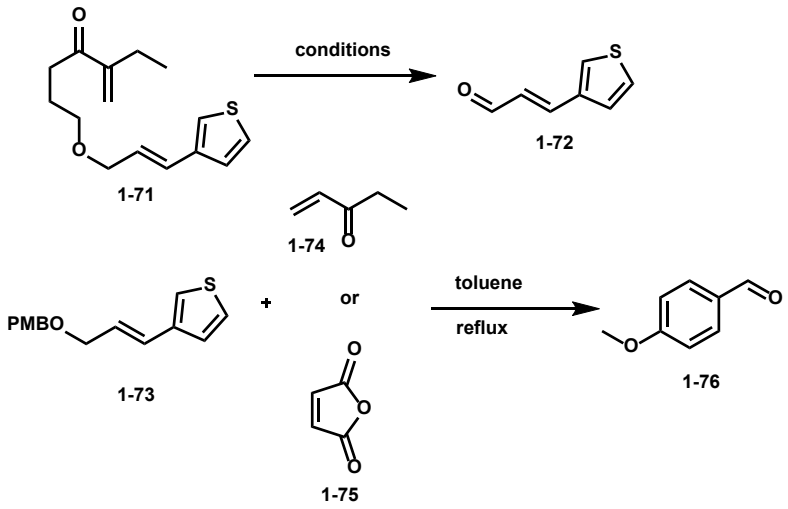


Conditions: (i) $(OEt)_2P(O)CH_2C(O)OEt$, NaH, THF; (ii) DIBAL-H, toluene, -78 ºC, 85% over three steps; (iii) TBSCl, imidazole, DCM; (iv) MsCl, Et_3N, DCM, 90%; (v) NaH, 70 ºC, 57%; (vi) HF·pyr, THF; (vii) DMP, $NaHCO_3$, DCM, 90% over two steps; (viii) 2-bromobutene, nBuLi, iPrMgBr, THF; (ix) DMP, $NaHCO_3$, DCM, 40% over two steps.

Scheme 9. Synthesis of the thiophene-based Diels-Alder model.

Two separate fragments were synthesized independently for the subsequent Williamson ether synthesis. Allylic alcohol **1-67** was produced from commercially available thiophene-3-carboxaldehyde through HWE olefination followed by the DIBAL-H reduction of the resulting ester. On the other side mesylate **1-69** was synthesized through consecutive protection of 1,4-

butanediol with, first, a TBS group and then a mesylate. Two fragments were combined under Williamson conditions to afford an ether that was desilylated and oxidized to produce aldehyde **x**. Transmetalation of 2-bromobutene with nBuLi and its addition to **1-70** afforded alcohol that was then re-oxidized with DMP producing Diels-Alder substrate **1-71**. Unfortunately, when the model system was subjected to the range of common Diels-Alder conditions (Lewis acid or heat), no product was obtained, but the cleavage of the ether ring and generation of **1-72** was observed instead. This result was confirmed by the reaction of the simpler PMB-protected thiophene alcohol **1-73** with known Diels-Alder substrates. Cleavage of the ether was observed again now with the generation of p-methoxybenzaldehyde (**1-76**).



Conditions: reflux: $CHCl_3$, DCM, toluene, DCB, CH_3CN, Lewis Acids: $InCl_3$, $Sc(OTf)_2$, $BF_3{\cdot}Et_2O$

Scheme 10. Diels-Alder initial results.

After such an unexpected outcome, the synthetic plan towards **1-60** was modified to avoid the use of thiophene in the cyclization.

1.4.2 2nd generation model (TBS-variant)

1.4.2.1 Original plan

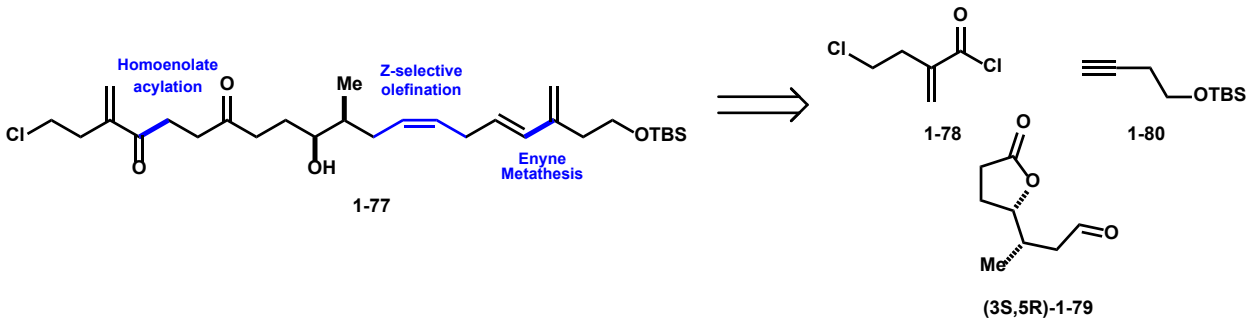


Figure 7. Modified deoxygenated model.

The modified model relied on the late-stage oxygenations of portimine's carbon skeleton. Now, a new variant of **1-60** was expected to be synthesized from 3 building blocks: acid chloride **1-78** for homoenolate acylation, aldehyde **(3S,5R)-1-79** for the installation of the two key stereocenters, and alkyne **1-80** for the synthesis of the diene and subsequent olefination. While known in the literature, no method has been published that allows for the highly diastereo- and enantioselective synthesis of **(3S,5R)-1-79**. The development of a scalable and highly selective organocatalytic method of generating **(3S,5R)-1-79** is discussed in the next section.

1.4.2.2 Re-visiting the Diastereoselectivity of Organocatalytic Conjugate Addition of 2-Trimethylsiloxyfuran to trans-Crotonaldehyde

Nature is a chiral environment and thus recognizes two enantiomers as different substances which can have different and in some cases opposite physical and biological properties evoking different responses in living organisms. Therefore, many guidelines have been developed over time that aimed to reduce the risk associated with using racemic natural products as well as to set standards for the approval of the synthesized drugs. This caused the synthetic community to shift

its attention towards the development of highly stereoselective, scalable, and efficient reactions that allow for the production of optically pure compounds. Multiple different methodologies have been developed including both transition metal-based and organocatalysis. The latter strategy, attractive from both safety and economical perspective has been pioneered by MacMillan's research group in 2000 when they put forth the first asymmetric organocatalytic Diels-Alder reaction[17]. Over the last 20+ years, MacMillan's research group along with other researchers around the world applied this methodology to a range of different chemical transformations which in 2021 led to both David MacMillan himself and Benjamin List being awarded a Nobel Prize in Chemistry. Among the most important application of this method is the organocatalytic Mukaiyama-Michael reaction [18] which allows for the preparation of a wide range of γ-substituted butenolides, which are commonly present in natural products. This method alongside several similar ones reported later has attracted our attention as they could be potentially utilized for the synthesis of two key stereocenters in portimine, the target of our synthetic studies. A desired (3*S*, 5*R*) enantiomer of butenolide **1-81**, a '*syn*' diastereomer resulting from adding 2(5*H*)-furanone (or 2-trimethylsiloxyfuran) to *trans*-crotonaldehyde was established as our synthetic goal (**Figure 8)**.

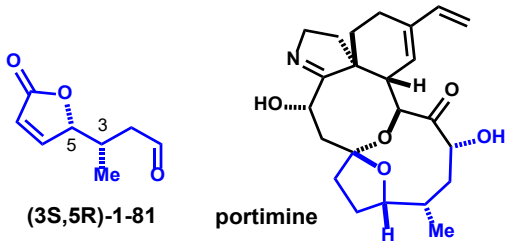
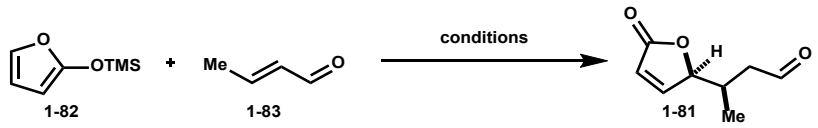


Figure 8. Butenolide 1 maps cleanly onto a segment of portimine A

While present in the original paper[18], the supporting information lacked both the experimental procedure and data for the desired stereoisomer. Moreover, other published reports contained

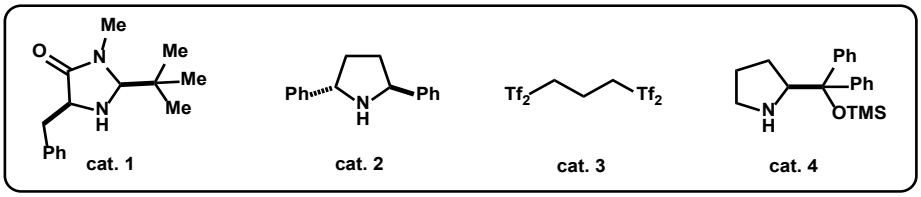
contradicting information[19] and resulted in the formation of either the opposite *anti* diastereomer or had virtually no selectivity (**Table 1**).

Table 1. Previous reports on the synthesis of **1-81**.

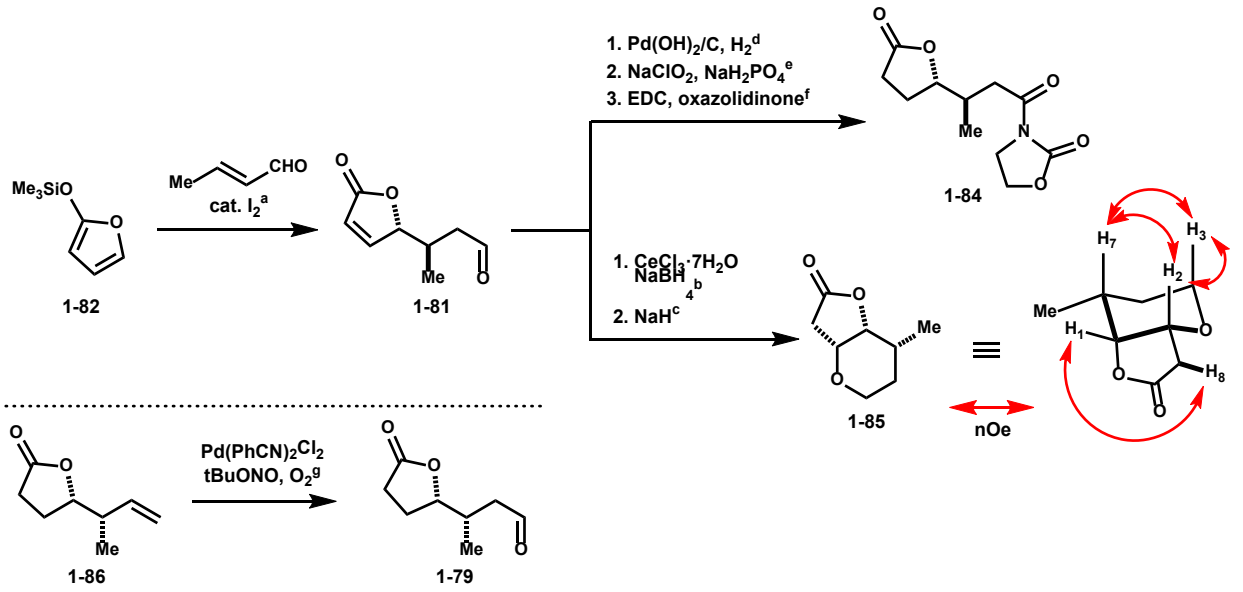


Author	Conditions	Result
MacMillan	Catalyst 1•DNBA (20 mol%), DCM/H_2O	87%, 8:1 *dr*[a]
Pihko	Catalyst 2•4-NBA, $KHSO_4$, DCM, 0 °C	57%, 42:58 *dr*
Taguchi	Catalyst 3, DCM, -78 °C	99%, 1:5.5 *dr*
Ye	Catalyst 4, MeOH, LiOAc, rt	77%, 1:2 *dr*[b]

[a]No data for the product has been provided in the SI
[b]2-furanone was used as a starting material



Our initial goal was to obtain the required spectroscopic data for both diastereomers that could once and for all resolve the contradictions surrounding this area. To achieve that, racemic *anti* diastereomer was synthesized using the procedure developed by Yadav and coworkers.[21] Remarkably, in the presence of just 7 mol% of iodine, **1-82** underwent a Mukaiyama-Michael addition to crotonaldehyde to produce **1-81** as a single diastereomer (**Scheme 11**). Reduction with $NaBH_4$ in the presence of $CeCl_3$ afforded the alcohol that was then conjugately added to the butenolide ring producing bicyclic structure **1-85**. Both *J*-couplings as well as nOe data confirmed the relative stereochemistry that was initially predicted.



Reagents and conditions: (a) *trans*-crotonaldehyde (0.7 eq.), I_2 (7 mol%), Et_2O (0.07 M), -78 °C, 76%, *dr* > 20:1; (b) $CeCl_3 \cdot 7H_2O$ (2.0 eq.), $NaBH_4$ (2.0 eq.), MeOH (0.05 M), 0 °C, 60%; (c) NaH (2.0 eq.), THF (0.05 M), rt, 25%; (d) $Pd(OH)_2/C$ (3 mol%), H_2 (balloon), MeOH (0.3 M), rt; (e) $NaClO_2$ (5.0 eq.), NaH_2PO_4 (6.0 eq.), *t*BuOH: amylene:H_2O (1.5:1:1, 0.05 M), rt; (f) EDCI·HCl (1.4 eq.), oxazolidinone (1.3 eq.), DMAP (1.15 eq.), DCM (0.1 M), rt; 20% from (±)-*anti*-3-1; (g) $Pd(PhCN)_2Cl_2$ (7.5 mol%), *t*BuONO (20 mol%), O_2 (balloon), *t*BuOH (0.05 M), rt, 51% brsm.

Scheme 11. Independent synthesis of both diastereomers of **1-79**.

This assignment was further confirmed through a synthesis of **1-84** (hydrogenation, Pinnick oxidation, and coupling) which structure was confirmed by X-ray crystallography by Katsuki and coworkers.[22] With spectroscopic data for *anti* stereoisomer in hand, we turned our attention to the synthesis of the desired *syn* variant. **1-86** could be easily synthesized under Leighton allylation conditions[23] in which the intermediate alcohol underwent *in situ* lactonization producing the desired product as a single diastereomer. Subsequent aldehyde-selective Wacker oxidation developed by Kang lab afforded **1-79** albeit contaminated with the corresponding ketone.[24]

Nevertheless, this allowed for the characterization of the *anti*-diastereomer of the desired aldehyde. Interestingly, when the same aldehyde was synthesized using the MacMillan's catalytic system, it was produced as a minor stereoisomer further contradicting the originally reported claim. Our assignment, however, was in agreement with that reported by Ye and coworkers[19b] who mistakenly assigned it as *anti* following MacMillan's report.

Following the unambiguous assignment of both diastereomers, we turned our attention towards developing and optimizing an effective and highly-stereoselective way of producing **(3S,5R)-1-81**. After discovering the inability of imidazolidinone catalysts to affect high stereocontrol, we screened several other organocatalysts as well as different acidic additives and solvent (**Table 2**). To our pleasant surprise a much simpler **1-89b**, that can be synthesized in just five steps from commercially available D-proline afforded the desired product in a 5:1 ratio in the presence of TFA in THF. Further increase in selectivity to 8.5:1 was affected through a slow addition of **1-82** (over 7 hours using syringe pump) to the reaction mixture at -20 °C.

This observation could be explained based on the previously performed DFT calculation studies by the Houk group.[25] It was reported that the reaction goes through a closed transition structure.

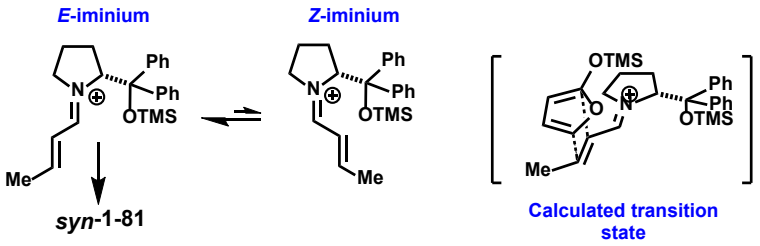
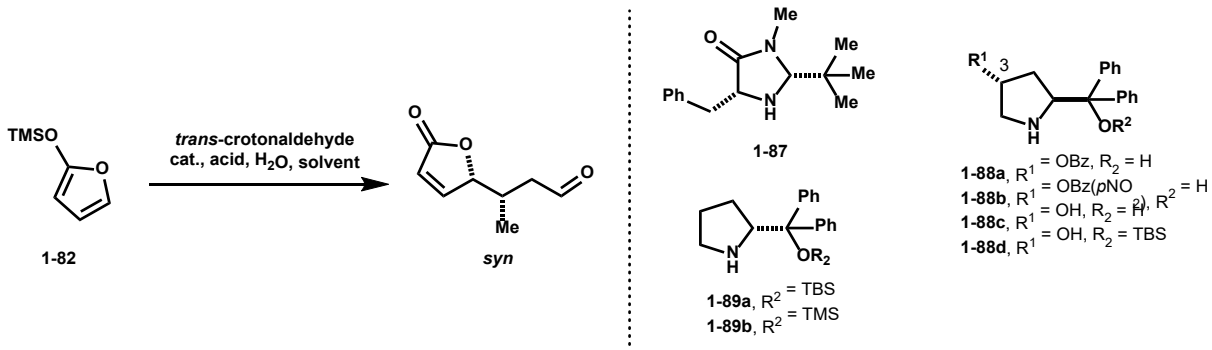


Figure 9. An equilibrium between *E* and *Z*-iminium dictates the outcome of the addition.

Table 2. Optimization studies.[a]



Entry	Catalyst	Acid	Solvent	*dr*[b] (*syn*:*anti*)
1[c]	**1-87**	DCA	$CHCl_3$	1.0:2.1
2[d]	**1-87**	DNBA	$CHCl_3$	1.0:3.3
3	**1-87**	TfOH	$CHCl_3$	1.0:5.2
4[e]	**1-87**	TFA	THF	2.5:1.0
5[f]	**1-88a**	DNBA	DCM	2.5:1.0
6[f]	**1-88a**	DNBA	THF	3.0:1.0
7[f, g]	**1-88a**	TFA	THF	4.0:1.0
8[f]	**1-88b**	TFA	THF	4.0:1.0
9[f]	**1-88c**	TFA	THF	4.0:1.0
10[f]	**1-88d**	TFA	THF	4.3:1.0
11[g]	**1-89a**	TFA	THF	5.3:1.0
12[g, h]	**1-89b**	TFA	THF	5.0:1.0
13[g, i]	**1-89b**	TFA	THF	5.5:1.0
14[g, j]	**1-89b**	**TFA**	**THF**	**8.5:1.0**

[a] Reagents and conditions: **1-82** (1.0 eq.), crotonaldehyde (3.0 eq.), cat. (20 mol%), acid (20 mol%), H_2O (2.0 eq.), solvent (0.1 M), -10 °C.

[b] *dr* measured by ^{1}H NMR.

[c] DCA: dichloroacetic acid, reaction was performed with 5.0 eq. of H_2O in 0.5 M of $CHCl_3$ at -78 °C.

[d] DNBA: 2,4-dinitrobenzoic acid.

[e] Parallel reactions were carried out at -10 °C and 50 °C. Both resulted in similar selectivity.

[f] (3*R*, 5*S*)-**1-81** was the major product.

[g] crotonaldehyde (5.0 eq.), H_2O (3.0 eq.).

[h] The reaction was left at -20 °C overnight after 1 h at -10 °C.

[i] 10 mol% of **1-89** and 13 mol% of TFA was used.

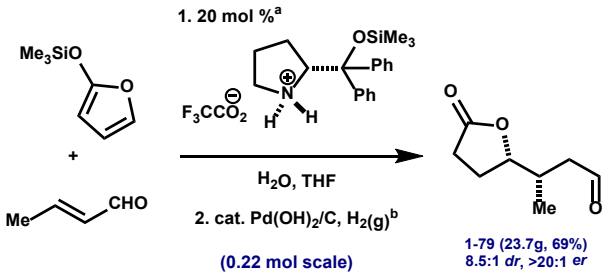
[j] TFA (26 mol%), **1-82** was added over 7 h at -15 °C, *er* > 20:1, measured on a chiral amine derivative by ^{1}H NMR.

Initially, an iminium is formed upon the condensation of the catalyst onto crotonaldehyde. At this point, both *E* and *Z* regioisomers are present in dynamic equilibrium with each other (**Figure 9**). While *E* isomer is expected to be more thermodynamically stable due to steric factors, the rate of the interconversion between isomers might be low. Therefore, slow addition of the nucleophile might allow for the isomerization to take place delivering the desired *syn* product in a higher ratio.

Using the optimized procedure in **Table 2, entry 14**, we have synthesized an isopropyl variant of our aldehyde. The NMR spectrum of the minor diastereomer matched the data reported in MacMillan's publication for the *syn* product further confirming the flaw in the original report. We hypothesize that this being the only substrate lacking the substitute in the C-5 position of the siloxy furan resulted in the unexpected reverse of the selectivity that went unnoticed by the authors. This hypothesis can be supported by the later studies that, indeed, underlined the importance of C-5 substituent for the reaction selectivity.[26]

The newly developed Mukaiyama-Michael variant was successfully applied for the installation of two key stereocenters of portimine that will be discussed in the subsequent chapters. It was scaled up using 35 grams of the 2-trimethylsiloxyfuran that was subsequently hydrogenated with the Pearlman's catalyst (Pd/C caused the simultaneous reduction of the aldehyde). Interestingly, when the reaction was performed in MeOH, various amounts of the corresponding methyl acetal were observed. This issue was easily circumvented using EtOAc instead. The large scale had no effect on either selectivity (8.5:1) or the efficiency (69% over two steps) of the reaction further validating the robustness of the method. The relative stereochemistry of the product was deduced through both the comparison with the material obtained using the aforementioned Leighton's methodology (α_D^{24} = +30.8 and +26.7 respectively) as well as the

synthesis of the corresponding chiral amine through a reductive amination with (*S*)-α-methylbenzylamine.

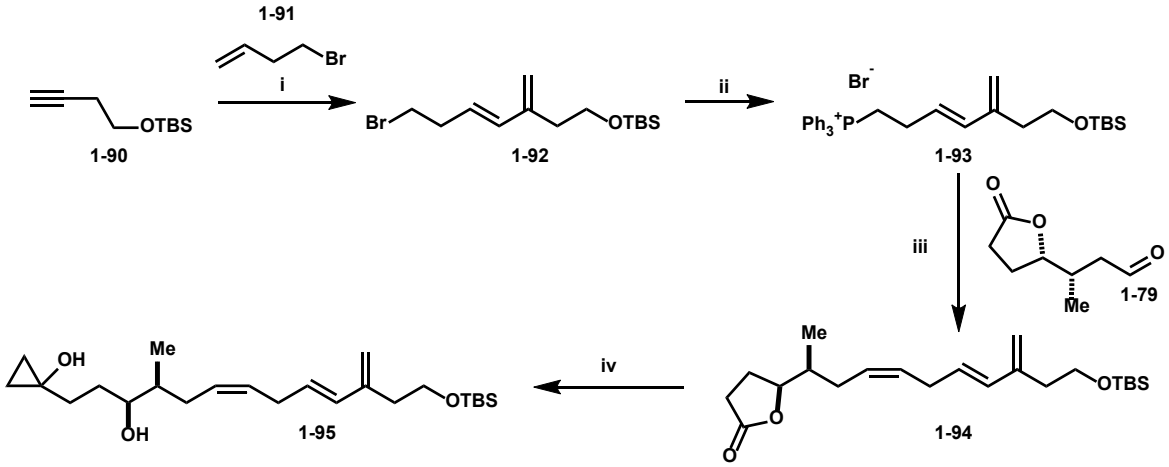


Scheme 12. Optimized Mukaiyama-Michael reaction retains the stereoselectivity and the efficiency on scale.

Now, with **(3S,5R)-1-79** in hand, the developed methodology could be applied to the model studies towards portimine that will be discussed in the next section.

1.4.2.3 Synthesis of the model system

The synthesis of **1-95** is outlined in **Scheme 13**.

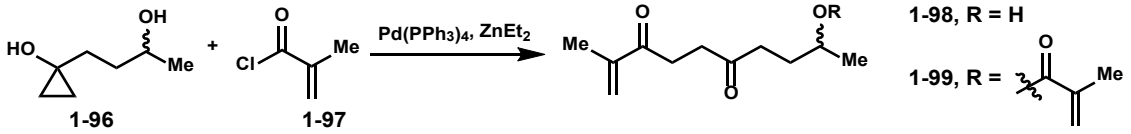


Conditions: (i) Grubbs II (6 mol%), 4-bromobutene (7 eq.), ethylene (balloon), DCM (0.4 M), 70%; (ii) PPh_3 (1.6 eq.), CH_3CN (0.5 M), 80 °C, 80%; (iii) LiHMDS (1.4 eq.), THF (0.1 M), -78 °C to rt, 79%; (iv) Ti(*i*PrO)$_4$ (1 eq.), EtMgBr (2 eq.), THF (0.3 M), 50%.

Scheme 13. Synthesis of the homoenolate precursor **1-95**.

It started with the enyne metathesis of alkyne **1-90** (synthesized from 4-butynol) and 4-bromobutene.[27] It was found that 6 mol% of the catalyst is required to produce the product as a pure (E)-isomer. Lowering of the catalyst loading results in the formation of (Z)-alkene. No equilibration to the desired isomer was observed even after prolonged reaction time (up to 3 days). **1-92** was then converted into the corresponding phosphonium salt. The reaction went only to 70% conversion, however, upon the re-subjection of the recovered starting material to the same reaction conditions, all of it has been converted into the desired salt. With the phosphonium salt **1-93** and lactone **1-79** in hand, Wittig olefination was performed that relied on the unstabilized ylide to produce the desired product as (Z)-isomer. Triene **1-94** was then converted into the corresponding cyclopropanol **1-95** by employing conditions published by Esposito et al.[28] The next step was envisioned to be the homoenolate coupling inspired by the work done by Cha and co-workers.[26]

Table 3. Model studies on homoenolate coupling.



Entry	$ZnEt_2$ (eq.)	**1-97** (eq.)	Solvent	Temp. (°C)	Result
1	1.0	1.5	THF	rt	No reaction
2	-[b]	1.5	THF	rt	No *C*-acylation
3	2.0	2.5	THF	rt	55% **1-98** + 13% **1-99**[c]
4	2.0	2.5	DME	rt	**1-98:1-99** = 80:20[d]
5	2.0	2.5	DMF	0	**1-98:1-99** = 80:20, S.M. left[d]
6	2.0	2.5	THF	0	**1-98:1-99** = 85:15, S.M. left[d]

[a] Reagents and conditions: **1-96**, $ZnEt_2$, $Pd(PPh_3)_4$ (5 mol%), then **1-97** over 1 h, THF (0.1 M), 1 h.
[b] *n*BuLi (2.0 eq.) was used

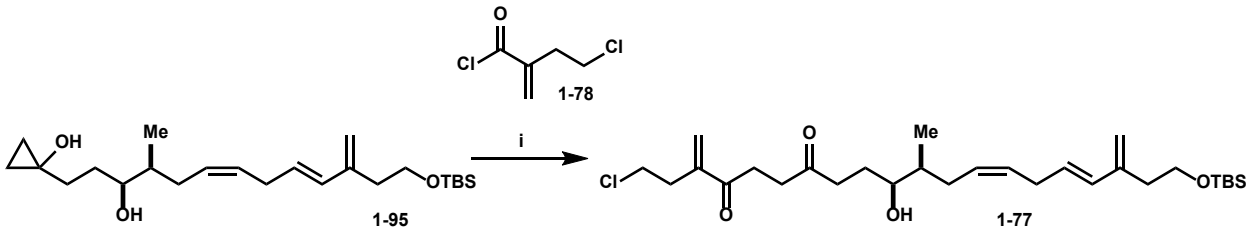
[c] isolated yields
[d] determined by ^{1}H NMR

However, the secondary alcohol was found to interfere with the reaction and thus the model studies were conducted first to try to find conditions that could circumvent this issue. Homoenolates have been used in organic synthesis for decades and thus can be prepared in a variety of ways. Classic methods involve treating 1-siloxycyclopropanes with Lewis acids[29] or cyclopropanols with organozinc bases.[30] The product was then shown to be capable of participating in a variety of transformations including transition-metal catalyzed cross-couplings[31] or standard nucleophilic additions.[32] The former method was of particular interest since it allowed for the formation of 1,4-dicarbonyl compounds that were reminiscent of the motif present in portimine. Therefore, the attention was turned towards the method published by Cha and coworkers who in 2013, reported a Pd-catalyzed cross-coupling with acid chlorides, where homoenolates were generated by treating cyclopropanols with $ZnEt_2$.[26] It was envisioned that the same method could be applied for the synthesis of the Diels-Alder precursor **1-74**.

Firstly, Cha's procedure was attempted between the model methacryloyl chloride **1-97** and cyclopropanol **1-96** derived from γ-valerolactone (**Table 3**). Cha's exact procedure didn't provide any product due to the potential interference of the secondary alcohol in the formation of a homoenolate. Therefore, several other conditions were tested in order to bypass this competitive pathway.

The increase in the amount of Et_2Zn from 1 to 2 equiv. resulted in the formation of the desired product **1-98** along with 13% of the doubly acylated compound **1-99** (entry 3), which can potentially be converted back to **1-98** through a simple ester hydrolysis. The changes in reaction

solvent and reaction temperature have not resulted in either the improved yields or selectivity (entries 4-6).

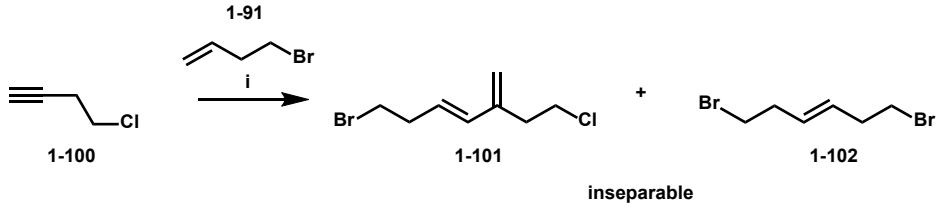


Conditions: (i) Et_2Zn (2 eq.), $Pd(PPh_3)_4$ (5 mol%), **1-75** (2 eq.), THF (0.1 M), 30%.

Scheme 14. Synthesis of the Diels-Alder substrate **1-74**.

After the successful modeling studies, the focus was shifted towards applying optimized homoenolate acylation conditions to the more complex systems. As was expected, cyclopropanol **1-95** underwent homoenolate acylation to produce the desired diketone **1-77**. The lowering of the yield was attributed to the instability of the tetraene. Unfortunately, under thermal conditions, **1-77** didn't react, while in the presence of Lewis acids, decomposition was observed. The latter was attributed to the presence of the silyl protecting group which is known to be unstable to a variety of Lewis acids. Therefore, the focus has been shifted towards the installation of the leaving group (chloride was chosen for stability reasons) that can be eliminated later to produce an alkene present in the natural product.

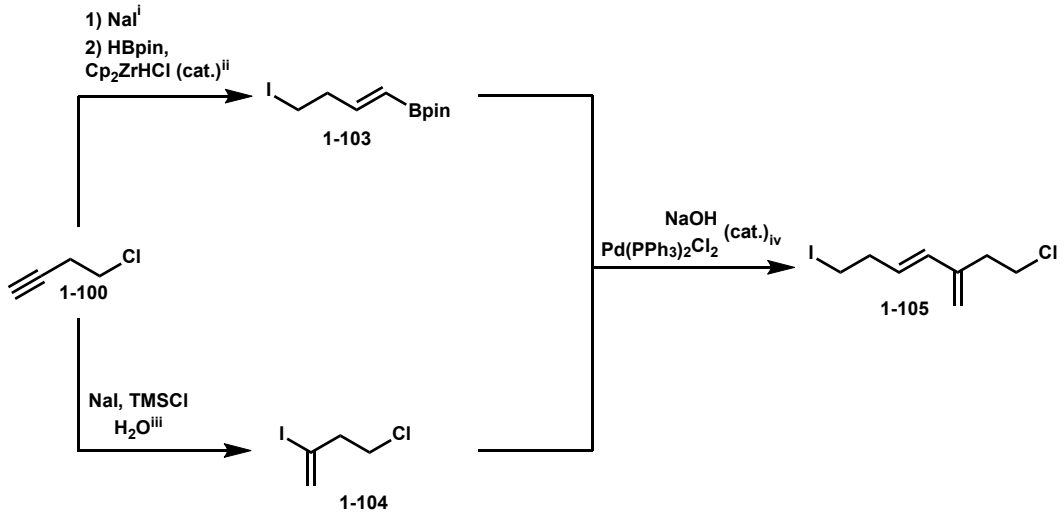
1.4.3 2nd generation model (Cl-variant)



Conditions: (i) Grubbs II (6 mol%), 4-bromobutene (7 eq.), ethylene (balloon), DCM (0.4 M)

Scheme 15. Initial attempts at synthesizing diene **1-101**.

Initial plan was to synthesize **1-101** using the same strategy as was chosen for the silylated version. However, due to the large excess of the alkene partner required for the enyne metathesis, the reaction produced large amounts of the inseparable dimer that had the same polarity as well as similar boiling point as that of the desired product (**Scheme 15**). Moreover, the reaction could not be telescoped since subsequent phosphonium salt formation would potentially produce up to 3 different products. Therefore, the attention was switched to the cross-coupling methods as the strategy for the formation of the diene (**Scheme 16**). Suzuki coupling was chosen as both vinyl iodide and vinyl boronate partners can be easily prepared from the same 4-chlorobutyne starting material, that was in turn prepared from commercially available 4-butynol following literature procedure.[33]

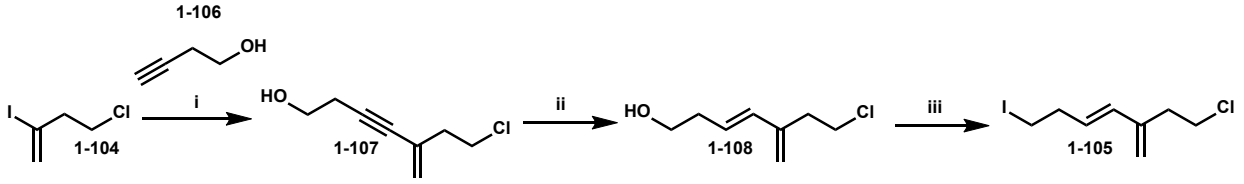


Conditions: (i) NaI (4.0 eq.), acetone (0.25 M), reflux, 3 days, 72%; (ii) Cp_2ZrHCl (5 mol%), HBpin (1.0 eq.), neat, 60 °C, 22 h, 80%; (iii) NaI (2.0 eq.), TMSCl (2.0 eq.), H_2O (1.0 eq.), MeCN (1.2 M), 0 °C to rt, 1 h, 78%; (iv) **1-103** (1.0 eq.), **1-104** (1.0 eq.), $Pd(PPh_3)_2Cl_2$ (5 mol%), THF (0.1 M), 2 M NaOH (0.1 M), rt, 1.5 h, 57%

Scheme 16. First route towards **105**.

Then, hydroiodination with *in situ* generated HI[34] afforded vinyl iodide **1-104**, while Finkelstein reaction followed by the Swartz hydrozirconation/hydroboration reaction afforded vinyl boronate **1-103**.[35] With both coupling partners in hand, Suzuki reaction was attempted next. Interestingly, the coupling turned out to be much more sensitive than expected. Both temperature, as well as a choice of base, played a key role in increasing the yield of the reaction. Increasing the temperature allowed for the minimization of the byproduct (from the E-2 elimination of the iodide), while using NaOH gave better results than $NaHCO_3$ and Na_2CO_3. However, even with the optimized conditions in hand, this sequence required expensive materials (Schwarz's reagent, $Pd(PPh_3)_2Cl_2$) and thus could not be sufficiently scaled up.

To circumvent the aforementioned issues an alternative route towards diene **1-105** was designed next.



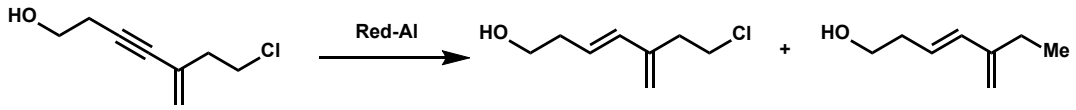
Conditions: (i) 4-butynol (1.05 eq.), $BuNH_2$ (2.0 eq.), $Pd(PPh_3)_4$ (5 mol%), CuI (20 mol%), DMF (0.5 M), rt, overnight, 82%; (ii) Red-Al (1.1 eq.), Et_2O (0.1 M), reflux, 23 h, then Red-Al (0.15 eq.), reflux, 6 h, 54%; (iii) PPh_3 (1.05 eq.), imidazole (1.05 eq.), I_2 (1.05 eq.), DCM (0.4 M), 0 °C to rt, 3.5 h, 87%;

Scheme 17. Modified synthesis of **1-105**.

In the modified route (**Scheme 17**), Sonogashira coupling was used instead of Suzuki as it resulted in both higher yield and lower cost. However, this meant that the alkyne had to be selectively reduced to the *E*-alkene in the subsequent step. Fortunately, it was found that Red-Al[36]

can produce the desired isomer with perfect geometric selectivity. The only issue was the presence of the dechlorinated byproduct which has been reported previously as one of the drawbacks of this reaction.[37] After extensive screening (**Table 4**), the conditions outlined in entry 8 were found to be the most optimal for the desired outcome. It is important to note that even though the ratio of the desired product to the dechlorinated variant is lower than in entry 7, the conversion of the reaction was more important. This was due to the similar polarity of the starting material and the product and thus extreme difficulty in their separation. This could lead to the cross-contamination in the subsequent steps and thus the yield was sacrificed for the conversion. Finally, the Appel reaction cleanly converted homoallylic alcohol into the corresponding iodide.

Table 4. Optimization of Red-Al reduction.[a]

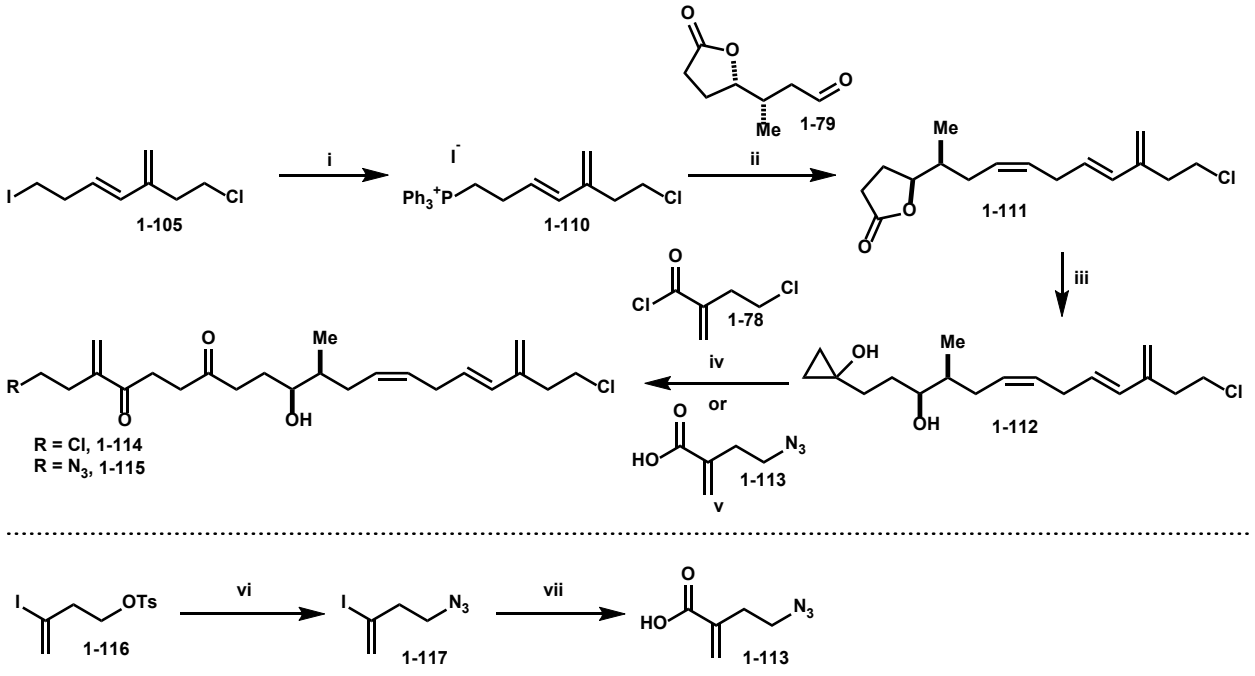


1-107 **1-108** **1-109**

Entry	Red-Al (eq.)	Solvent	Temp. (°C)	Time	**1-107**:**1-108**:**1-109**
1	1.0	THF	Reflux	1 h	2:4:1[a]
2	1.0	THF	-78 to rt (slow)	4 h	18:8:1[a]
3	2.3	THF	rt	overnight	0:0:1
4	2.3	Et_2O	rt	3 h	6:1:0
5	2.3	Et_2O	rt	24 h	0:1:3
6	1.2	Et_2O	rt	overnight	6:14:1
7	1.1	Et_2O	Reflux	32 h	1:10:1
8	1.25[b]	Et_2O	Reflux	29 h	0:6:1

[a] Other side products were observed.
[b] 1.1 eq., reflux for 23 h, then another 0.15 eq., reflux for 6 h.

The rest of the synthesis of the Diels-Alder model was similar to the one outlined for the chloride variant and is shown in **Scheme 18**. Conversion of **1-105** into the corresponding phosphonium salt required moderate heating (30 °C) of the iodide precursor for 3 days. The reaction could not be accelerated as the increase in temperature resulted in the displacement of the homoallylic chloride as well. Subsequent Wittig olefination followed by the Kulinkovich cyclopropanation afforded **1-112** ready for the homoenolate acylation. Unlike the previous model, however, this time azido acryloyl acid was used for the preparation of the corresponding acid chloride. This was done to minimize subsequent functional group manipulations as the azide can be readily reduced and condensed onto the ketone to deliver the imine present in the natural product.



Conditions: (i) PPh_3 (0.95 eq.), MeCN (0.5 M), 30 °C, 3 days, 83%. (ii) **1-110** (1.2 eq.), KHMDS (1.1 eq.), THF (0.1 M), -78 to 0 °C, 20 min., then **1-79** (1.0 eq.), -78 °C, 1 h and rt, 4 h, 71%, Z/E 4:1; (iii) $Ti(OiPr)_4$ (1.2 eq.), EtMgBr (2.2 eq.), THF (0.33 M), 15 °C, 4 h, 90%; (iv) $ZnEt_2$ (2.0 eq.), $Pd(PPh_3)_4$ (5 mol%), **1-78** (1.5 eq.) over 1 h, THF (0.1 M), -78 °C to rt, 32%; (v) **1-113** (3.0 eq.), Ghosez reagent (3.0 eq.), $ZnEt_2$ (2.0 eq.), $Pd(PPh_3)_2Cl_2$ (5 mol%), Bu_4NBr (10 mol%), THF (0.1 M), -78 °C to rt, 30%. (vi)

NaN_3 (3.0 eq.), DMF (0.4 M), 50 °C, 3 h; (vii) $HCOOLi \cdot H_2O$ (3.0 eq.), DIPEA (2.0 eq.), Ac_2O (2.0 eq.), LiCl (3.0 eq.), $Pd_2(dba)_3$ (1 mol%), DMF (0.22 M), 80 °C, 90 min., 76%

Scheme 18. Completion of the synthesis of diketones **1-114** and **1-115**.

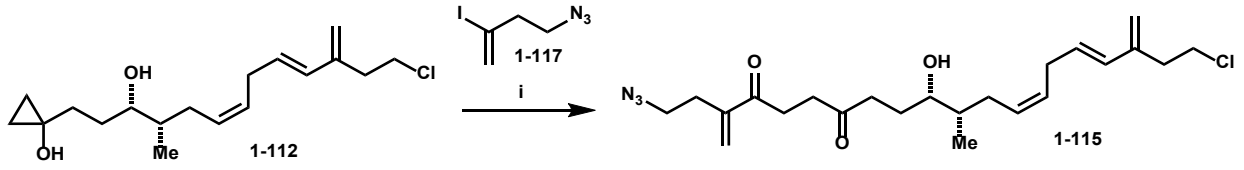
The acid was synthesized in two steps from the reported vinyl iodide **1-116** through the S_N2 displacement with sodium azide followed by the Pd-catalyzed carboxylation.[38] As expected, the acid was found to be unstable in neat form and thus was stored as the DCM solution and used as soon as possible in the homoenolate coupling. To avoid isolating acid chloride and to minimize interference from acidic byproducts, Ghosez's reagent[39] was used instead of the more typical oxalyl or thionyl chloride. This allowed for the mild and rapid conversion with the only byproduct being an inert amide.

Initially, homoenolate acylation was carried out using the optimized conditions outlined in the previous section. However, two issues had to be addressed in this case. First, the ethyl ketone that came from the quenching of the open form of **1-112** was always isolated in amounts comparable to or exceeding that of the desired product. Moreover, the reaction could not be scaled up as with the increase in the amount of starting material used, the yield dropped exponentially with the amount of quenched byproduct simultaneously increasing. For example, trying the reaction on a 1 mmol scale produced no desired product. It was reported that various additives could potentially circumvent that problem by forming higher-order zincates that would increase the rate and conversion of the reaction.[40] However, none of the salts attempted (LiBr, LiCl, and $ZnBr_2$) resulted in any improvement in the reaction. On the contrary, the reaction produced almost exclusively *O*-acylated product previously not observed for this substrate.

The fact that all cyclopropanol was consumed in the reaction suggested a strong preference for the open form, which was different from the observations made for the model system. Thus it was possible that the slow addition of acid chloride was not necessary as *O*-acylation was clearly not an issue in this case. Amazingly, fast addition also resulted in the reaction now being scalable solving two issues at the same time.

With the optimized conditions in hand, cyclopropanol **1-112** was converted into the azido ketone **1-114** in 30% yield. This allowed for the installation of all carbons present in portimine in just 3 steps from the aldehyde **1-79**.

It is important to note that the same compound can be synthesized in one step directly from vinyl iodide **1-117** under carbonylative conditions (**Scheme 19**). However, the reaction proved to be inferior to homoenolate acylation producing the desired product in 21% yield. Both increase in CO pressure as well as variation in the catalyst ($Pd(PPh_3)_2Cl_2$, $Ni(dppp)Cl_2$, $NiCl_2$·diglyme, and $NiCl_2$·diglyme/bpy) produced no observable improvement. However, despite limited success, the reaction is much more atom-efficient and avoids the synthesis of unstable carboxylic acid. Therefore, it is believed that with additional optimization, carbonylative coupling could prove to be superior to the current method.



Conditions: (i) **1-117** (3.0 eq.), $ZnEt_2$ (2.0 eq.), CO (1 atm, balloon), $Pd(PPh_3)_4$ (5 mol%), THF (0.1 M), rt, overnight; 21% yield

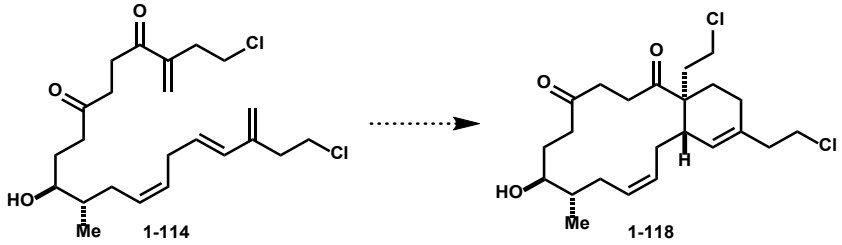
Scheme 19. Alternative synthesis of **1-115**.

1.4.4 Diels-Alder model studies

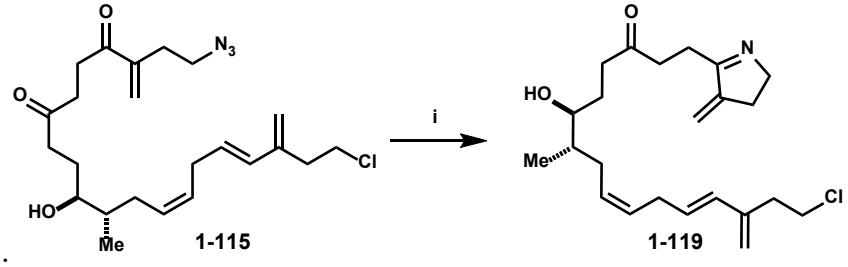
With **1-115** in hand, Diels-Alder studies were conducted to test the reactivity of the deoxygenated portimine analog in order to assess whether the absence of the rigidity of the macrocyclic ether still allows for the successful cycloaddition to take place. Based on the previously published reports on Pinnatoxin syntheses, thermal conditions were thought to be the most promising for the desired transformation. Therefore, both Kishi's dodecane-based conditions as well as other commonly employed solvents at varying temperatures were tested. Interestingly, it was found that the synthesized molecule is unusually resistant and remains intact even at 150 °C. However, upon increasing temperature to 170 °C the compound seemed to start decomposing suggesting the rate of decomposition to be higher than that of the desired reaction. Using other solvents, such as toluene, chlorobenzene, and acetonitrile as well as introducing Lewis acids produced the same outcome with the only difference being the temperature of the decomposition onset. The presence of the secondary alcohol was initially thought to be the reason behind substrate decomposition, however, its protection as a pivalate didn't produce any noticeable differences in substrate's reactivity.

At this point, it was hypothesized that the early installation of the cyclic imine motif might prove beneficial due to markedly different properties of α,β-Unsaturated iminiums, and ketones. Therefore, **1-115** was subjected to standard Aza-Wittig conditions to afford an exo-methylene pyrroline present in the natural product. Unfortunately, the modified substrate didn't display any superior reactivity to its acyclic variant. The same conditions resulted in either decomposition or the absence of reactivity.

Table 5. Condition screening for Diels-Alder cycloaddition.



Entry	Condition	Results
1	Dodecane, 150 °C	No reaction
2	Dodecane, 170 °C	Complex mixture
3	Toluene, 140 °C	No reaction
4	Toluene, 180 °C	Slow decomposition
5	Chlorobenzene, 140 °C	Decomposition
6	MeCN, 100 °C	Decomposition
7	5 M $LiClO_4$ in Et_2O[41], rt	No reaction
8	$AlMe_2NTf_2$, 0 °C	Complex mixture



Conditions: (i) PPh_3 (polymer-bound, 4.1 eq.), toluene (0.01 M), rt, overnight.

Scheme 20. Aza-Wittig cyclization for the synthesis of **1-119**.

All of the aforementioned cycloaddition studies showed that the simplification of portimine's core significantly affects its reactivity in the Diels-Alder reaction. High rotational degrees of freedom present in the model system seemed to limit the number of conformers able to react even at higher temperatures. Therefore, it was hypothesized that the higher oxygenation pattern, as well as early installation of the ketal, might be pivotal for the construction of the cyclohexene motif and so the focus was switched towards the construction of the unaltered portimine's framework.

1.4 Conclusion

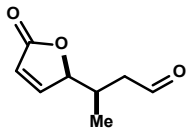
In summary, we have constructed a simplified linear carbon Diels-Alder precursor of portimine. This model served as a testing ground for several key disconnections envisioned for the total synthesis of the natural product. Development of the modified homoenolate acylation as well as comprehensive Diels-Alder studies shed light on the challenges associated with portimine's functional groups and framework and proved valuable in the subsequent synthetic studies towards the real system, that will be discussed in the next chapter. Lastly, this was the first time an exo-methylene pyrroline that contained no substitutions at the C-4 and C-5 positions has been isolated and characterized. This discovery is expected to be important not only for the present project but for the synthesis of other 5-membered imines of this type.

1.5 Experimental Section

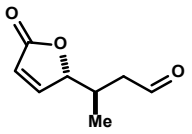
1.5.1 Material and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under positive pressure of argon atmosphere. The dry solvents were dried using activated alumina solvent drying system. Dry methanol used in this manuscript was dried over activated 3Å molecular sieves. (*S*)-(−)-α-methylbenzylamine was purchased from Sigma Aldrich and used without purification. Thin layer chromatography (TLC) was performed on pre-coated plates Sorbent Technologies, silica gel 60 PF_{254} (0.25 mm). TLC were visualized with UV light (254 nm) or stained using $KMnO_4$ or cerium ammonium molybdate (CAM). Flash chromatography was performed on silica gel 60 (240-400 mesh). NMR spectra were recorded on a Bruker Avance (500 MHz) spectrometer using $CDCl_3$ as solvent and referenced relative to residual $CHCl_3$ (δ = 7.26 ppm). Chemical shifts are reported in ppm and coupling constants (*J*) in Hertz. ^{13}C NMR and APT spectra were recorded on the same instruments (125 MHz) with total proton decoupling referenced relative to residual $CHCl_3$ (δ = 77.16 ppm). HSQC, COSY and NOESY NMR experiments were used to aid assignment of NMR peaks when required. Infrared spectra were obtained on Perkin Elmer Spectrum 100 FT-IR or Jasco FT/IR-4100, both are equipped with a universal ATR sampling accessory. High-resolution mass spectra were recorded on Thermo Scientific Exactive® Mass Spectrometer with DART IDCUBE Waters GST Premier, and Waters LCT Premier. Optical rotations were measured on a Rudolph Autopol III Automatic Polarimeter and are quoted in units of 10^{-1} deg cm^2 g^{-1}

1.5.2 Originally Reported ^{1}H NMR of Two Diastereomers of Butenolide 1.



syn-1-79



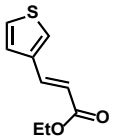
anti-1-79

	Syn-diastereomer	*Anti*-diastereomer
Taguchi[1]	9.80 (1H), 7.41 (1H), 6.18 (1H), 5.14-5.08 (1H), 2.74 (1H), 2.70-2.58 (1H), 2.46 (1H), 0.90 (3H)	9.71 (1H), 7.44 (1H), 6.12 (1H), 4.93 (1H), 2.58 (1H), 2.53-2.40 (1H), 2.38 (2H), 1.09 (3H)
Ye[2]	Not reported	9.79 (1H), 7.43 (1H), 6.18 (1H), 5.12 (1H), 2.73 (1H), 2.67-2.63 (1H), 2.49-2.43 (1H), 0.90 (3H)
Pihko[3]	9.72 (1H), 7.45 (1H), 6.13 (1H), 4.89-4.95 (1H), 2.76-2.33 (3H), 1.11 (3H)	9.77 (1H), 7.41 (1H), 6.15 (1H), 5.08-5.11 (1H), 2.76-2.33 (3H), 0.87 (3H)

1. Yanai, H.; Takahashi, A.; Taguchi, T. *Chem. Commun.* **2010**, *46*, 87282.
2. Luo, X.; Zhou, Z.; Yu, F.; Li, X.; Liang, X.; Ye, J. *Chem. Lett.* **2011**, *40*, 518.
3. Kemppainen, E. K.; Sahoo, G.; Piisola, A.; Hamza, A.; Kotai, B.; Papai, I.; Pihko, P. M. *Chem. Eur. J.* **2014**, *20*, 5983.

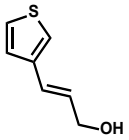
1.5.3 Experimental Procedures

ethyl (E)-3-(thiophen-3-yl)acrylate (1-120)



Triethyl phosphonoacetate (9.5 g, 42.5 mmol, 1.5 eq.) was added dropwise to a solution of NaH (60% dispersion in oil, 1.7 g, 42.5 mmol, 1.5 eq.) in THF (212.5 ml) at 0 °C under the atmosphere of argon. A solution of 3-thiophenecarboxaldehyde (3.18 g, 28.34 mmol, 1 eq.) in THF (53.5 ml) was then added. After stirring at room temperature for 6 h, the mixture was quenched with NH_4Cl, extracted with EtOAc (3x), dried over $MgSO_4$ and concentrated under the reduced pressure. The crude **1-120** was used without purification.

(E)-3-(thiophen-3-yl)prop-2-en-1-ol (1-67)



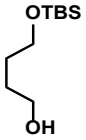
The crude ester **1-120** (28.34 mmol, 1 eq.) was dissolved in toluene (142 ml) at -78 °C under argon. DIBAL-H (1 M in hexanes, 59.5 ml, 59.5 mmol, 2.1 eq.) was added dropwise at -78 °C. After 30 min, the reaction was quenched with Rochelle's salt and the solution was allowed to warm to room temperature. Then water was added, and the stirring was continued overnight at rt. The water layer was separated and extracted with EtOAc (3x), dried over $MgSO_4$ and concentrated at the reduced pressure. The crude mixture was purified by column chromatography on silica gel (hexanes/EtOAc 80:20) to furnish **1-67** (3.37 g) in 85 % yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28-7.26 (m, 1 H), 7.21 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.16 (d, *J* = 2.9 Hz, 1 H,), 6.62 (d, *J* = 15.9 Hz, 1 H), 6.22 (dt, *J* = 15.8, 5.8 Hz, 1H), 4.29 (dd, *J* = 5.8, 1.5 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.3, 128.3, 126.1, 125.5, 125.0, 122.3, 63.7.

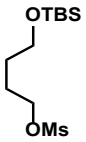
Spectral data for this compound were consistent with those in the literature.[42]

4-((tert-butyldimethylsilyl)oxy)butan-1-ol (1-121)



Imidazole (5.1 g, 75 mmol, 1.3 eq.) was added to the solution of 1,4-butanediol (22.0 g, 244 mmol, 4.25 eq.) in THF (100 ml) at 0 °C under the atmosphere of argon. A solution of TBSCl (8.65 g, 57.4 mmol, 1 eq.) in THF was then added over 20 min *via* syringe pump. After 1 h, the reaction diluted with ether, washed with NH_4Cl and brine. The combined organic layers were dried over $MgSO_4$, filtered and concentrated at the reduced pressure. The crude **1-121** was used without purification.

4-((tert-butyldimethylsilyl)oxy)butyl methanesulfonate (1-69)



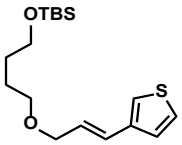
To the solution of monoprotected alcohol **1-121** (57.4 mmol) in DCM (96 ml) was added Et_3N (8.13 g, 80.36 mmol, 1.4 eq.) and MsCl (7.23 g, 63.14 mmol, 1.1 eq.) under the atmosphere of argon. The solution was then stirred at room temperature overnight. The reaction was then quenched with water and extracted with Et_2O (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated at the reduced pressure. The crude product was purified by the column chromatography on silica gel (hexanes/EtOAc 90:10) to furnish **1-69** in 85 % yield over 2 steps.

^{1}H NMR (500 MHz, CDCl3): δ = 4.26 (t, J = 6.6, 2 H), 3.65 (t, J = 6.1 Hz, 2 H), 3.01 (s, 3 H), 1.87-1.80 (m, 2 H), 1.65-1.59 (m, 2 H), 089 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (125 MHz, CDCl3): δ = 70.1, 62.2, 37.4, 28.6, 25.97, 25.92, 18.3, -5.4.

Spectral data for this compound were consistent with those in the literature.[43]

(E)-tert-butyldimethyl(4-((3-(thiophen-3-yl)allyl)oxy)butoxy)silane (1-122)



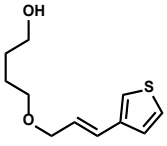
To the solution of **1-67** (348 mg, 2.48 mmol, 1 eq.) in THF (5 ml) was added NaH (60 % dispersion in oil) under the atmosphere of argon. The reaction was then stirred for 30 min. **1-69** (700 mg, 2.48 mmol, 1 eq.) was then added and the mixture was refluxed for 1 day. The water was added and the reaction was extracted with Et_2O (3x), dried over $MgSO_4$ and concentrated under the reduced pressure. The crude product was purified by the column chromatography on silica gel (hexanes/EtOAc 90:10) to furnish **1-122** (461 mg) in 57% yield as a yellow oil.

^{1}H NMR (500 MHz, CDCl3): δ = 7.27-7.25 (m, 1 H), 7.22 (dd, J = 5.0, 1.1 Hz, 1 H), 7.14 (dd, J = 2.8, 1.1 Hz, 1 H), 6.60 (d, J = 16.3 Hz, 1 H), 6.14 (dt, J = 15.9, 6.1 Hz, 1 H), 4.09 (dd, J = 6.1, 1.4 Hz, 2 H), 3.63 (t, J = 6.2 Hz, 2 H), 3.48 (t, J = 6.5 Hz, 2 H), 1.68-1.57 (m, 4 H), 0.88 (s, 9 H), 0.04 (s, 6 H).

^{13}C NMR (125 MHz, CDCl3): δ = 139.5, 126.4, 126.2, 126.0, 125.1, 122.2, 71.3, 70.3, 63.0, 29.5, 26.3, 26.0, 18.3, -5.3.

HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_{17}H_{32}O_2SSi$ 327.1814; found 327.1812.

(E)-4-((3-(thiophen-3-yl)allyl)oxy)butan-1-ol (1-123)



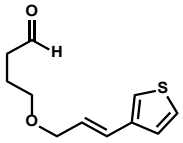
The solution of **1-122** (300 mg, 0.92 mmol, 1 eq.) in THF (9.2 ml) was cooled to 0 °C under the atmosphere of argon. HF·pyr (0.6 ml, 4.6 mmol, 5 eq.) was then added and the solution was warmed to room temperature. After stirring for 3 h, the mixture was quenched with $NaHCO_3$,

extracted with EtOAc, dried over $MgSO_4$ and concentrated under the reduced pressure. The crude alcohol **1-123** was used in the next step without purification.

^{1}H NMR (500 MHz, CDCl3): δ = 7.25 (t, *J* = 3.9 Hz, 1H), 7.20 (d, *J* = 5.0 Hz, 1H), 7.15 (d, *J* = 2.5 Hz, 1H), 6.60 (d, *J* = 15.9 Hz, 1H), 6.12 (dt, *J* = 15.8, 6.2 Hz, 1H), 4.11 (d, *J* = 6.2 Hz, 2H), 3.65 (t, *J* = 5.7 Hz, 2H), 3.51 (t, *J* = 5.7 Hz, 2H), 1.72-1.66 (m, 4H).

^{13}C NMR (125 MHz, CDCl3): δ = 139.5, 126.9, 126.0, 125.7, 125.1, 122.4, 71.5, 70.3, 62.8, 30.2, 26.8.

(E)-4-((3-(thiophen-3-yl)allyl)oxy)butanal (1-70)



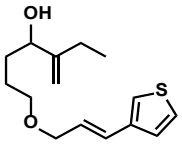
To the solution of the crude alcohol **1-123** (0.92 mmol) in DCM (9.2 ml) at 0 °C under argon was added $NaHCO_3$ (386 mg, 4.6 mmol, 5 eq.) and DMP (780 mg, 1.84 mmol, 2 eq.). The mixture was warmed to room temperature and stirred for 2 h. The 1:1 solution of $NaHCO_3$ and $Na_2S_2O_3$ was then added, and the mixture was stirred until the organic layer turned clear. The reaction was then extracted with EtOAc (3x), dried over $MgSO_4$ and concentrated under the reduced pressure. The crude product was then purified by the column chromatography on silica gel (hexanes/EtOAc 80:20) to furnish **1-70** (174 mg) in 90% yield.

^{1}H NMR (500 MHz, CDCl3): δ = 9.80 (t, *J* = 1.58 Hz, 1H), 7.27-7.25 (m, 1 H), 7.21 (dd, *J* = 5.0, 1.0 Hz, 1 H), 7.15 (dd, *J* = 2.9, 1.2 Hz, 1 H), 6.59 (dd, *J* = 15.9, 0.5 Hz, 1 H), 6.11 (dt, *J* = 15.9, 6.1 Hz, 1 H), 4.08 (dd, *J* = 6.1, 1.5 Hz, 2 H), 3.50 (t, *J* = 6.1 Hz, 2 H), 2.55 (td, *J* = 7.1, 1.6 Hz, 2 H), 1.98-1.91 (m, 2 H).

^{13}C NMR (125 MHz, CDCl3): δ = 202.3, 139.3, 126.7, 126.1, 125.8, 125.0, 122.4, 71.4, 69.1, 40.9, 22.3.

HRMS-ESI (m/z): $[M-H]^-$ calcd. for $C_{11}H_{13}O_2S$ 209.0636; found 209.0648.

(E)-5-methylene-1-((3-(thiophen-3-yl)allyl)oxy)heptan-4-ol (1-124)



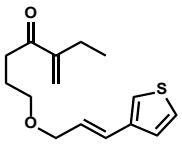
To the solution of I_2 (1 bead) and Mg (109 mg, 4.5 mmol, 1.32 eq.) in THF (4.1 ml, 0.83 M), was added 2-bromo-1-butene (551 mg, 0.41 ml, 4.1 mmol, 1.2 eq.) dropwise. The reaction was refluxed for 30 min and then cooled to room temperature. The resulting mixture was added to **1-70** (714 mg, 3.4 mmol, 1 eq.) in THF (17 ml, 0.2 M) dropwise at 0˚C. The reaction was then stirred for hours. NH_4Cl was then added and the reaction was extracted with EtOAc (3x), dried over $MgSO_4$, filtered and concentrated under the reduced pressure. The crude mixture was purified by the column chromatography (hexanes/EtOAc 80:20) on a silica gel to afford **1-124**.

^{1}H NMR (500 MHz, CDCl3): δ = 7.32-7.25 (m, 1 H), 7.21 (dd, *J* = 5.1, 1.3 Hz, 1 H), 7.15 (d, *J* = 2.7 Hz, 1 H), 6.60 (d, *J* = 16.0 Hz, 1 H), 6.13 (dt, *J* = 15.8, 6.1 Hz, 1 H), 5.04 (s, 1H), 4.85 (s, 1H), 4.11 (dd, *J* = 6.1, 1.3 Hz, 2 H), 4.12-4.05 (m, 1 H), 3.53-3.49 (m, 2 H), 2.19-1.94 (m, 2 H), 1.73-1.57 (m, 4 H), 1.07 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (125 MHz, CDCl3): δ = 153.4, 139.3, 126.7, 126.0, 125.8, 125.1, 122.3, 108.3, 75.1, 71.4, 70.3, 32.8, 26.1, 24.2, 12.2.

HRMS-ESI (m/z): $[M-H]^-$ calcd. for $C_{15}H_{21}O_2S$ 265.1262; found 265.1292.

(E)-5-methylene-1-((3-(thiophen-3-yl)allyl)oxy)heptan-4-one (1-71)

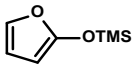


DMP (2 eq.) and $NaHCO_3$ (5 eq.) was added to the solution of alcohol **1-124** (1 eq.) in DCM (0.1 M) at 0 °C under the atmosphere of argon. The solution was stirred for 2 h at room temperature. The reaction was then quenched with $NaHCO_3$:$Na_2S_2O_3$ (1:1) mixture and stirred until no solid

remained in the organic phase. The layers were then separated, and the aqueous layer was extracted with EtOAc (3x), dried over $MgSO_4$ and concentrated under the reduced pressure.

^{1}H NMR (500 MHz, CDCl3): δ = 7.27-7.25 (m, 1 H), 7.20 (dd, *J* = 4.9, 1.3 Hz, 1 H), 7.15 (d, *J* = 3.1 Hz, 1 H), 6.60 (d, *J* = 16.3 Hz, 1 H), 6.13 (dt, *J* = 15.8, 6.1 Hz, 1 H), 6.01 (s, 1H), 5.71 (s, 1H), 4.08 (dd, *J* = 6.2, 1.4 Hz, 2 H), 3.50 (t, *J* = 6.2 Hz, 2 H), 2.81 (t. *J* = 7.2 Hz, 2 H), 2.32-2.26 (m, 2 H), 1.96-1.89 (m, 2 H), 1.02 (t, *J* = 7.4 Hz, 3 H).

(furan-2-yloxy)trimethylsilane (1-82)



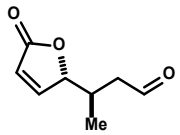
To a solution of 2(5*H*)-furanone (16.9 mL, 238 mmol, 1.0 eq.) in DCM (170 mL, 1.4 M) at 0 °C was added triethylamine (33.7 mL, 285 mmol, 1.2 eq.). Then chlorotrimethylsilane (37.4 mL, 250 mmol, 1.05 eq.) was added dropwise to the resulting red brown solution at the same temperature. The suspension was stirred overnight at room temperature. The reaction was diluted with 100 mL pentane and filtered through a frit funnel into a second flask containing 100 mL pentane. The solution was filtered again then concentrated under reduced pressure to give a red brown oil. (If precipitation formed during concentration, immediately dilute it with pentane and filter the solution again.) The crude product was distilled under vacuum (ca. 100 mbar, 105 °C oil bath) to furnish **1-82** (32.6 g) as a colorless oil in 88% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.82 ((dd, 1 H, *J* = 2.2, 1.1 Hz), 6.21 (dd, 1 H, *J* = 3.2, 2.2 Hz), 5.10 (dd, *J* = 3.2, 1.1 Hz), 0.30 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.8, 132.5, 111.1, 83.4, -0.1.

Spectral data for this compound were consistent with those in the literature.[44]

(*R)-3-((*R**)-5-oxo-2,5-dihydrofuran-2-yl)butanal ((±)-*anti*-1-81)**



To a solution of **1-82** (130.0 mg, 0.842 mmol, 1.5 eq.) and crotonaldehyde (46 µl, 0.555 mmol, 1.0 eq.) in Et_2O (5.6 mL, 0.1 M) at -78 °C was added I_2 (14.1 mg, 0.056 mmol, 10 mol%) under the atmosphere of argon. The mixture was stirred at the same temperature for 2.5 hours. The solution was then quenched with water, washed with $Na_2S_2O_3$ and extracted with Et_2O (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product (*dr* > 20:1) was purified by column chromatography on silica gel (hexanes/EtOAc, 100/0→60:40) to furnish (±)-*anti*-**1-81** (63.2 mg, *dr* > 20:1) as a colorless oil in 74% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.75 (s, 1 H), 7.45 (dd, 1 H, *J* = 5.8, 1.5 Hz), 6.16 (dd, 1 H,), 4.96 (app. dt, 1 H), 2.61 (dd, 1 H, *J* = 17.7, 4.9 Hz), 2.53-2.45 (m, 1 H), 2.40 (ddd, 1 H, *J* = 17.7, 7.4, 1.7 Hz), 1.13, (d, 3 H, *J* = 6.8 Hz)/.

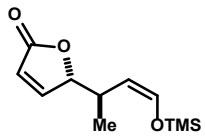
^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.3, 172.6, 154.9, 122.5, 86.2, 45.6, 31.2, 16.7.

Literature spectra reported by Taguchi:[19a]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.71 (1 H, s), 7.44 (1 H, dd, *J* = 5.8, 1.4 Hz), 6.12 (1 H, dd, *J* = 5.8, 2.0 Hz), 4.93 (1 H, dt, *J* = 5.8, 2.0 Hz), 2.58 (1 H, dd, *J* = 17.3, 4.7 Hz), 2.53-2.40 (1 H, m), 2.38 (2 H, ddd, *J* = 17.3, 7.3, 1.4 Hz), 1.09 (3 H, d, *J* = 6.7 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.2, 172.4, 154.7, 122.3, 86.1, 45.5, 31.1, 16.5.

(*S)-5-((*R**,*Z*)-4-((trimethylsilyl)oxy)but-3-en-2-yl)furan-2(5H)-one ((±)-*anti*-1-125)**

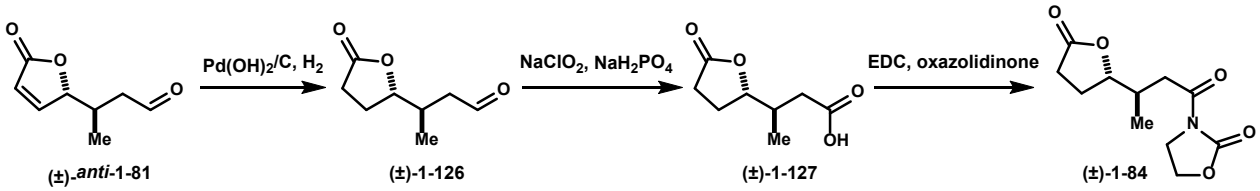


The title compound was obtained after work-up from one of the iodine-catalyzed conjugate addition reactions.

NMR data was collected on crude material.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (dd, *J* = 5.7, 1.5 Hz, 1H), 6.19 (dd, *J* = 5.9, 1.2 Hz, 1H), 6.08 (dd, *J* = 5.7, 2.0 Hz, 1H), 5.04 (dt, *J* = 4.1, 1.8 Hz, 1H), 4.23 (dd, *J* = 8.9, 5.9 Hz, 1H), 3.24 (dddd, *J* = 8.7, 7.1, 4.1, 1.2 Hz, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.18 (s, 9H).

Synthesis of (±)-1-79 from (±)-*anti*-1-81



To the solution of (±)-*anti*-**1-81** (773 mg, 5.01 mmol, 1.0 eq.) in MeOH (17 mL, 0.3 M) was added $Pd(OH)_2/C$ (20 wt %, 50% H_2O, 106 mg, 0.150 mmol, 3 mol%). Then hydrogen gas was bubbled through the solution for 15 minutes and the reaction was stirred for 6 hours under 1 atm of hydrogen. The mixture was filtered through celite and concentrated under reduced pressure to afford crude (±)-**1-126** (709 mg) as a colorless oil. The crude material was used for the next step without further purification.

31.0 mg of the above crude (±)-**1-126** (0.20 mmol) was taken and dissolved in *t*BuOH (1.6 mL) and amylene (2 M in THF, 5.1 mL) was added. In a separate flask $NaClO_2$ (90 mg, 1.0 mmol, 5.0 eq.) and NaH_2PO_4 (144 mg, 1.2 mmol, 6.0 eq.) was dissolved in H_2O (1.1 ml). The resulting solution was added dropwise to the aldehyde solution at 0 °C. The reaction was then stirred at room temperature for 4 hours and poured into water. The mixture was acidified with 1 M HCl to pH 2 and extracted with DCM (3x). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure to provide crude acid (±)-**1-127** that was used in the next step without further purification.

To the solution of crude (±)-**1-127** (0.20 mmol) in DCM (2.3 ml) was added EDCI•HCl (53.7 mg, 0.28 mmol) and DMAP (28.1 mg, 0.23 mmol) at room temperature. The reaction was then stirred for 15 minutes, and oxazolidin-2-one (22.6 mg, 0.26 mmol) was added in one portion. The

resulting solution was stirred at room temperature overnight. The reaction was quenched with 1 M HCl and extracted with DCM (3x). The organic layers were combined and washed with 1 M HCl, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc, 100/0→70:30) to furnish (±)-**1-84** (10 mg, *dr* > 20:1) as a colorless oil in 20% yield over 3 steps.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.47-4.37 (m, 2 H), 4.37-4.28 (m, 1 H), 4.09-3.96 (m, 2 H), 3.27 (dd, 1 H, *J* = 16.9, 6.0 Hz), 2.84 (dd, 1 H, *J* = 16.9, 7.1 Hz), 2.58-2.48 (m, 2 H), 2.45-2.23 (m, 2 H), 1.99-1.86 (m, 1 H), 1.01 (d, 3 H, *J* = 6.8 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.8, 172.3, 153.9, 84.0, 62.3, 42.8, 38.7, 35.3, 29.0, 26.3, 15.6.

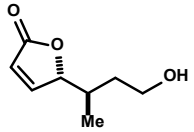
FT-IR (neat): 2970, 2923, 1771, 1697, 1390, 1368, 1224, 1187, 1039, 1024, 916, 762 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_{11}H_{16}NO_5$ 242.10230; found 242.10139.

Literature spectrum reported by Katsuki:[22]

^{1}H NMR (270 MHz, $CDCl_3$): δ = 4.46-4.30 (m, 3 H), 4.09-3.99 (m, 2 H), 3.33 (d, *J* = 5.9 and 16.8 Hz, 1 H), 2.85 (d, *J* =7.3 and 16.8 Hz, 1 H), 2.57-2.51 (m, 2 H), 2.44-2.26 (m, 2 H), 2.02-1.87 (m, 1 H), 1.02 (d, *J* = 6.9 Hz, 3 H).

(*S)-5-((*S**)-4-hydroxybutan-2-yl)furan-2(5*H*)-one ((±)-1-128)**



To a solution of (±)-*anti*-**1-81** (498 mg, 3.23 mmol, 1.0 eq.) and $CeCl_3 \cdot 7H_2O$ (2.41 g, 6.46 mmol, 2.0 eq.) in MeOH (65 mL, 0.05 M) at 0 °C was added $NaBH_4$ (245 mg, 6.46 mmol, 2.0 eq.) under the atmosphere of argon. The reaction was stirred at 0 °C for 30 min, and then quenched with sat. aqueous solution of NH_4Cl and extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4, filtered through silica with EtOAc, and concentrated under reduced pressure. The

crude product was purified by column chromatography on silica gel (hexanes/EtOAc, 100/0→40/60) to furnish (±)-**1-128** (300 mg, *dr* > 20:1) as a light-yellow oil in 60% yield.

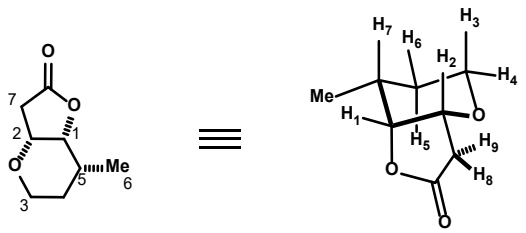
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48 (dd, 1 H, *J* = 5.8, 1.5 Hz), 6.16 (dd, 1 H, *J* = 5.7, 2.0 Hz), 4.99 (app. dt, 1 H), 3.84-3.76 (m, 1 H), 3.76-3.68 (m, 1 H), 2.17-2.07 (m, 1 H), 1.81-1.72 (m, 1 H), 1.52-1.45 (m, 1 H), 1.39 (br. s, 1 H), 1.00 (d, 3 H, *J* = 6.9 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.1, 154.9, 122.6, 87.4, 60.5, 35.0, 33.6, 15.3.

FT-IR (neat): 3439, 3078, 2966, 2931, 1744, 1168, 1094, 1057, 822, 735 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_8H_{13}O_3$ 157.08592; found. 157.08441.

(3a*R,7*R**,7a*R**)-7-methylhexahydro-2*H*-furo[3,2-*b*]pyran-2-one ((±)-1-85)**



To a solution of alcohol **1-128** (100.0 mg, 0.640 mmol, 1.0 eq.) in THF (12.8 mL, 0.05 M) was added NaH (60% in mineral oil, 51.2 mg, 1.28 mmol, 2.0 eq.) at room temperature. The mixture was stirred at room temperature for 40 min. The reaction was then quenched with quick addition of 1 M HCl and extracted with Et_2O (4x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc, 100/0→70/30) to furnish (±)-**1-85** (24.6 mg, *dr* > 20:1) as a colorless oil in 25% yield.

nOe was observed between H_1-H_7, H_2-H_3, H_3-H_7, H_2-H_7 and H_1-H_8.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.21 (app. t, 1 H, **H_1**), 4.16 (dd, 1 H, *J* = 4.1, 2.2 Hz, **H_2**), 3.91 (ddd, 1 H, *J* = 11.5, 4.0, 1.8 Hz, **H_4**), 3.41 (ddd, 1 H, *J* = 12.3, 11.5, 1.8 Hz, **H_3**), 2.66 (dd, 1 H, *J*

= 17.1, 4.1 Hz, **H8**), 2.52 (app. d, 1 H, **H9**), 1.95-1.84 (m, 1 H, **H7**), 1.62 (app. dq, 1 H, **H5**), 1.43 (m, 1 H, **H6**), 1.17 (d, 1 H, *J* = 6.9 Hz, **Me**).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.2 (**C8**), 81.1 (**C1**), 73.4 (**C2**), 66.3 (**C3**), 39.0 (**C7**), 31.7 (**C5**), 27.5 (**C4**), 18.0 (**C6**).

FT-IR (neat): 2963, 2934, 2880, 1776, 1249, 1178, 1150, 1100, 1047, 985, 969, 895 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_8H_{13}O_3$ 157.08592; found 157.08434.

Analysis of relative stereochemistry of **1-85**.

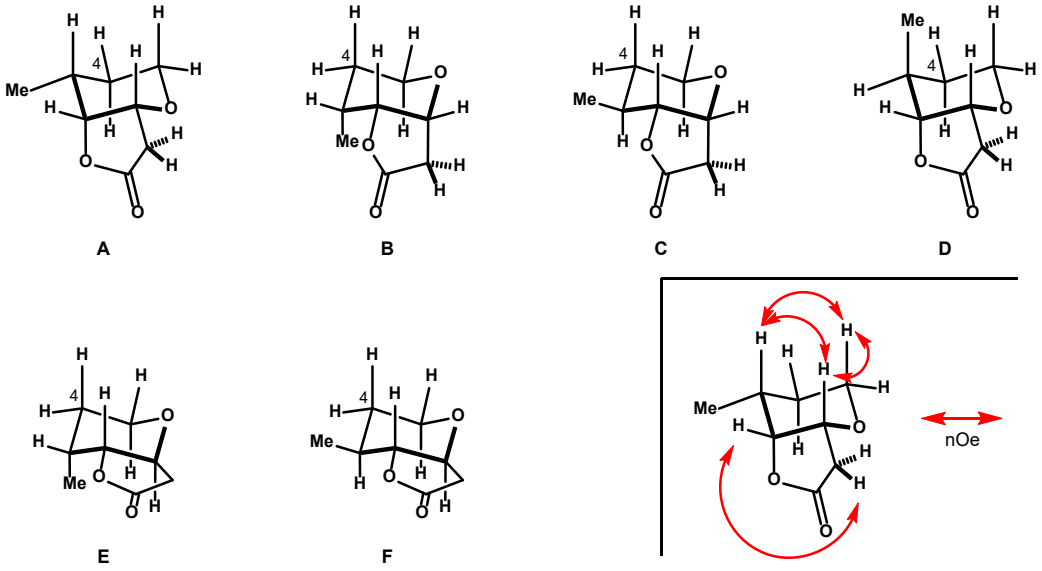
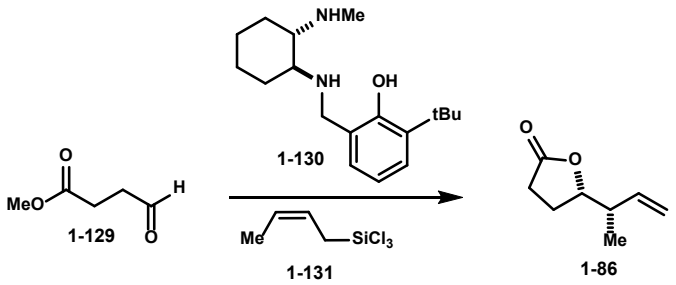


Figure 1. Possible products from the 3-step sequence. A and B are conformers of each other, as are C and D. A and E are derived from *anti*-butenolide. C and F are derived from *syn*-butenolide. The conformers of E and F are not provided because these are unstable *trans*-fused bicycles.

The axial hydrogen atom on C4 showed up as app. dq in ^{1}H NMR, indicating 3 large coupling constants: 1 ^2J and 2 ^3J couplings. Therefore, the neighboring carbons each has one axial hydrogen atom. Structures B, D and E are eliminated. The hydrogen atom on C1 does not have strong coupling, so structures C and F are eliminated, which leaving A as the only structure that can account for the observations. The conclusion is supported by NOESY spectrum.

(*S*)-5-((*S*)-but-3-en-2-yl)dihydrofuran-2(3*H*)-one (1-86)



To the solution of **1-130**[45] (828 mg, 2.84 mmol 1.1 eq.) in DCM (7.5 ml) was added DBU (1.27 ml, 8.51 mmol, 3.3 eq.). The resulting solution was cooled to 0 ºC and silane **1-131**[46] (0.49 ml, 3.10 mmol, 1.2 eq.) was added dropwise. The mixture was warmed to room temperature, stirred for 1 h and then cooled to 0 ºC. Aldehyde **1-129** (300 mg, 2.58 mmol, 1.0 eq.) in DCM (1.9 ml) was added and the solution was stirred at the same temperature for 2 hours. The reaction was concentrated under reduced pressure, and the residue was suspended in Et_2O (15 ml), stirred for 20 min and filtered. The filtrate was treated with TBAF (1 M in THF, 2.84 ml, 2.84 mmol, 1.1 eq.). After 30 min 1 M HCl (30 ml) was added, and the reaction was extracted with Et_2O (3x). The combined organic layers were washed with $NaHCO_3$, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product (*dr* > 20:1) was then purified by column chromatography on silica gel (hexanes/EtOAc, 100/0→70:30) to furnish **1-86** (140 mg) as a colorless oil in 55% yield.

$[\alpha]_D^{23}$ = -4.0 (*c* = 0.1, $CHCl_3$)

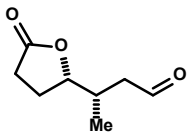
^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.73-5.65 (m, 1 H), 5.18-5.10 (m, 2 H), 4.31 (app. q, 1 H), 2.54-2.48 (m, 2 H), 2.48-2.40 (m, 1 H), 2.25-2.16 (m, 1 H), 1.99-1.89 (m, 1 H), 1.13 (d, 3 H, *J* = 6.8 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.3, 137.7, 117.1, 83.8, 42.8, 29.0, 25.5, 16.0.

FT-IR (neat): 3081, 2978, 2935, 2891, 1771, 1645, 1459, 1420, 1347, 1177, 1019, 1002, 912 cm^{-1}

HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_8H_{13}O_2$ 141.09101; found 141.08955.

Synthesis of 1-79 from 1-86.



$Pd(PhCN)_2Cl_2$ (8.2 mg, 0.021 mmol, 7.5 mol%) was weighed into a vial. The atmosphere was evacuated and refilled with oxygen. Under the atmosphere of oxygen (balloon), *t*BuOH (3.6 mL) and tBuONO (6.8 μL, 0.057 mmol, 20 mol%) were added at room temperature, followed by the addition of **1-86** (40.0 mg, 0.285 mmol, 1.0 eq.) in *t*BuOH (1 mL). The mixture was sparged with oxygen for 1 hour and stirred at room temperature. The reaction reached 66% conversion (by NMR) and stopped progressing after 24 hours. The reaction was quenched by addition of water and extracted with DCM (3x). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was then purified by silica gel chromatography (hexanes/EtOAc, 100/0→60:40) to furnish **1-79** (140 mg) as a colorless oil in 51% (brsm) yield and as a single diastereomer.

$[\alpha]_D^{24}$ = +26.7 (*c* = 0.1, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.78 (t, 1 H, *J* = 1.3 Hz), 4.49-4.44 (m, 1 H), 2.67-2.59 (m, 1 H), 2.58-2.52 (m, 2 H), 2.45-2.37 (m, 2 H), 2.30-2.22 (m, 1 H), 1.99-1.90 (m, 1 H), 1.03 (d, 3 H, *J* = 6.6 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.8, 176.9, 83.1, 46.8, 31.9, 29.0, 25.1, 14.6.

Note: A side product was formed in the reaction, which presumably was methyl ketone. The ratio was 1:1 side product: **1-79**.

General procedure for Table 1 Entries 1-12

To a solution of catalyst in corresponding solvent at designated temperature was added acid and H_2O. The mixture was stirred at the same temperature for 15 minutes. Then *trans*-crotonaldehyde was added and the mixture was stirred for another 15 minutes at the same temperature. Then 2-

trimethylsiloxyfuran (0.32 mmol) was added dropwise to the stirring mixture. The mixture was stirred at the same temperature for 8 hours before it was filtered through a short plug of silica with EtOAc. The filtrate was concentrated under reduced pressure. Diastereomeric ratio was obtained by ^{1}H NMR analysis of the resulting crude material.

Procedure for Table 1 Entry 13

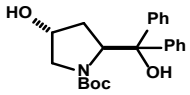
To a solution of (*R*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (72.5 mg, 0.22 mmol, 7.4 mol%) in THF (20 mL) at -20 °C was added TFA (23 μL, 0.29 mmol, 9.9 mol%) and water (0.12 mL, 6.67 mmol, 2.22 eq.). After 15 minutes while maintaining the temperature below -15 °C, crotonaldehyde (4.1 mL, 50 mmol, 5.0 eq.) was added to the solution. The mixture was stirred at -15 °C for 15 minutes. Then 2-(trimethylsiloxy)furan (1.7 mL, 10 mmol, 1.0 eq.) was added dropwise and the solution was stirred at the same temperature for 4 hours. Then (*R*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (25.2 mg, 0.077 mmol, 2.6 mol%), TFA (8 μL, 0.105 mmol, 3.5 mol%) and water (42 μL, 2.34 mmol, 0.78 eq.) in THF (10 mL) was added. The solution was stirred for 4 hours and filtered through a short plug of silica with EtOAc immediately after being removed from the -15 °C bath. The filtrate was concentrated under reduced pressure. Diastereomeric ratio was obtained by ^{1}H NMR analysis of the resulting crude material.

Procedure for Table 1 Entries 14

To a solution of (*R*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (0.65 g, 2.0 mmol, 20 mol%) in THF (100 mL, 0.1 M) at -20 °C was added TFA (0.21 mL, 2.7 mmol, 27 mol%) and water (1.1 mL, 30 mmol, 3.0 eq.). After 15 minutes while maintaining the temperature below -15 °C, crotonaldehyde (4.1 mL, 50 mmol, 5.0 eq.) was added to the solution. The mixture was stirred at -15 °C for 15 minutes. Then 2-(trimethylsiloxy)furan (1.7 mL, 10 mmol, 1.0 eq.) was added over 7 hours using a syringe pump, while keeping the temperature of the reaction at -15 °C. The solution was stirred for another hour at the same temperature after the addition was complete. The reaction mixture was then filtered through a short plug of silica with EtOAc immediately after

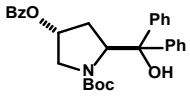
being removed from the -15 °C bath. The filtrate was concentrated under reduced pressure. Diastereomeric ratio was obtained by ^{1}H NMR analysis of the resulting crude material.

tert-butyl (2*S*,4*R*)-4-hydroxy-2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate (1-132)



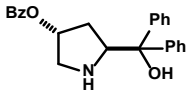
To a solution of *N*-Boc-*trans*-4-hydroxy-L-proline methyl ester (17.0 g, 69.5 mmol, 1.0 eq.) in THF (348 mL, 0.2 M) was added PhMgBr (3 M in Et_2O, 102 mL, 305.8 mmol, 4.4 eq.) dropwise at 0 °C. The resulting mixture was warmed to room temperature and stirred for 3 h. The reaction was quenched by slow addition of sat. aqueous solution of NH_4Cl at 0 °C and extracted with EtOAc (4x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude material that was used for next step without purification.

tert-butyl (2*S*,4*R*)-4-(benzoyloxy)-2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate (1-133)



To a solution of crude **1-132** (69.5 mmol) in DCM (348 mL) at 0 °C was added pyridine (8.4 mL, 104.3 mmol), DMAP (0.85 g, 6.95 mmol) and BzCl (8.1 mL, 69.5 mmol). The mixture was then allowed to stir overnight at room temperature. The reaction was quenched with 1 M HCl (60 mL) and water (300 mL). The DCM layer was collected, and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with 1 M HCl and sat. aqueous solution of $NaHCO_3$, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude material that was used for next step without purification.

(3*R*,5*S*)-5-(hydroxydiphenylmethyl)pyrrolidin-3-yl benzoate (1-88a)



To a suspension of crude **1-133** obtained from the above reaction in dry *i*PrOH (138 mL) was added HCl (5.5 M in *i*PrOH, 126 mL, 695 mmol) at room temperature. The mixture was stirred for 4 hours at the same temperature to afford a viscous suspension. Solvent was then removed from the mixture under reduced pressure. The residue was suspended in water, cooled to 0 °C and the pH was adjusted to 10 with NaOH (2 M). The crude product was extracted with EtOAc (4x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by recrystallization with EtOAc and Hexane to furnish **1-88a** (11.5 g) as an off-white powder in 45% yield over 3 steps.

$[\alpha]_D^{21}$ = -18.0 (*c* = 0.1, MeOH)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.07-8.02 (m, 2 H), 7.64-7.55 (m, 3 H), 7.51-7.43 (m, 4 H), 7.36-7.26 (m, 4 H), 7.25-7.15 (m, 2 H), 5.44-5.39 (m, 1 H), 4.63 (dd, 1 H, *J* = 10.0, 6.4 Hz), 3.43 (dd, 1 H, *J* = 12.1, 4.9 Hz), 3.26-3.21 (m, 1 H), 2.13-2.04 (m, 1 H), 1.80-1.72 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.2, 147.6, 144.7, 133.2, 130.4, 129.7, 128.5, 128.5, 128.2, 126.9, 126.7, 126.1, 125.6, 76.3, 63.8, 52.9, 33.5.

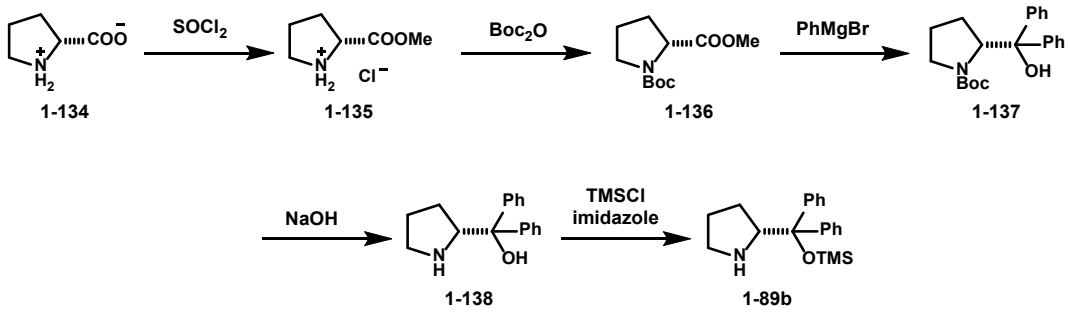
One peak was covered by the signal of $CHCl_3$.

FT-IR (neat): 3413, 3373, 3059, 1714, 1493, 1448, 1417, 1365, 1314, 1277, 1174, 1110, 989, 955, 751, 698, 637 cm^{-1}

Melting point: The compound started to decompose at 140 °C before it melted.

HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_{24}H_{24}NO_3$ 374.17507; found 374.17200.

(*R*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (1-89b)



To a suspension of D-proline (13.8 g, 120 mmol) in dry MeOH (120 mL, 1 M) was added thionyl chloride (8.8 mL, 120 mmol, 1.0 eq.) dropwise at 0 °C. The resulting clear solution was then stirred at room temperature overnight. The solvent was then removed under reduced pressure to give proline methyl ester **1-135** as a yellow foam. The crude material was used for the next step without further purification.

To a suspension of crude **1-135** (120 mmol) in DCM (240 mL, 0.5 M) was added NEt_3 (50.2 mL, 360 mmol, 3.0 eq.) and Boc_2O (28.8 g, 132 mmol, 1.1 eq.) at 0 °C. The reaction mixture was stirred at room temperature overnight. It was then diluted with Et_2O and filtered. The solid cake was washed with Et_2O (3x). The filtrate was washed with sat. aqueous solution of $KHSO_4$. The aqueous layer was extracted with Et_2O (4x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give **1-136** as a yellow oil. The crude material was used for the next step without further purification.

To magnesium (9.04 g, 372 mmol, 3.1 eq.) in Et_2O (150 mL) was added a small bead of iodine. The mixture was heated with a heat gun until the color disappeared. Then bromobenzene (37.8 mL, 360 mmol, 3.0 eq.) was added dropwise at a rate where the reaction maintains gentle reflux. The mixture was ready to use after stirring at room temperature for an hour after the addition was finished. Then crude **1-136** (120 mmol) in THF (120 mL) was added dropwise to the stirring mixture. The addition resulted in gentle reflux. The reaction was stirred for another 90 min after the addition of **1-136** was finished. The mixture was then cooled to 0 °C and quenched carefully with sat. aqueous solution of NH_4Cl. The crude product was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under

reduced pressure. The crude product was recrystallized from boiling EtOAc to give **1-137** (34.9 g) as white crystals in 82% yield over 3 steps.

To **1-137** (42.4 g, 120 mmol) in 200 proof EtOH (600 mL, 0.2 M) was added NaOH (48.0 g, 1.20 mol, 10 eq.). The mixture was refluxed at 90 °C for 70 min. The mixture was then cooled room temperature and the solvent was removed under vacuum. The resulting yellow solid was taken up with water and Et_2O. The aqueous layer was extracted with Et_2O (4x). The combined organic layers were washed with water and brine, then dried with Na_2SO_4. Solvent was removed under reduced pressure to give **1-138** as a white solid. The crude material was used for the next step without further purification.

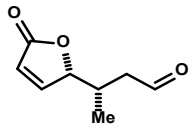
To crude **1-138** (120 mmol) and imidazole (13.9 g, 204 mmol, 1.7 eq.) in THF (316 mL, 0.38 M) was added TMSCl (19.8 mL, 156 mmol, 1.3 eq.) dropwise while maintaining the temperature of the mixture below 30 °C. The reaction mixture was stirred at 50 °C for 5 h. After cooling to room temperature, the reaction was quenched with 15% NaCl aqueous solution. The crude product was extracted with MTBE (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by filtering through a silica gel plug (Et_2O/Hex, 0% to 100%) to afford **1-89b** (34.7 g) as a light-yellow oil in 89% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55 – 7.40 (m, 2H), 7.40 – 7.32 (m, 2H), 7.31 – 7.15 (m, 6H), 4.03 (t, J = 7.2 Hz, 1H), 2.96 – 2.69 (m, 2H), 1.80 – 1.48 (m, 4H), 1.48 – 1.32 (m, 1H), -0.10 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.9, 145.9, 128.6, 127.75, 127.71, 127.67, 127.0, 126.9, 83.3, 65.5, 47.3, 27.6, 25.2, 2.3.

Spectral data for this compound were consistent with those in the literature.[47]

(*S*)-3-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)butanal ((3*S*, 5*R*)-1-81) (large scale synthesis)



x

To a solution of (*R*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (14.4 g, 44.2 mmol, 20 mol%) in THF (2.2 L, 0.1 M) at -20 °C was added TFA (4.42 mL, 57.4 mmol, 26 mol%) and water (11.9 mL, 662 mmol, 3.0 eq.). After 15 minutes while maintaining the temperature below -15 °C, crotonaldehyde (91.5 mL, 1100 mmol, 5.0 eq.) was added to the solution. The mixture was stirred at -15 °C for 15 minutes. Then 2-(trimethylsiloxy)furan (37.8 mL, 221 mmol, 1.0 eq.) was added over 7 hours using a syringe pump, while keeping the temperature of the reaction at -15 °C. The solution was stirred for another hour at the same temperature after the addition was complete. The reaction mixture was then filtered through a short plug of silica with EtOAc immediately after being removed from the -15 °C bath. The filtrate was concentrated under reduced pressure to give crude (3*S*, 5*R*)-**1-81** (*dr* = 8.5:1), which was used to prepare **1-79** without further purification.

The characterization of (3*S*, 5*R*)-**1-81** was conducted on crude material.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.79 (t, 1 H, *J* = 1.1 Hz), 7.42 (dd, 1 H, *J* = 5.8, 1.5 Hz), 6.17 (dd, 1 H, *J* = 5.8, 2.1 Hz), 5.13-5.10 (m, 1 H), 2.73 (ddd, 1 H, *J* = 18.1, 6.4, 0.7 Hz), 2.67-2.61 (m, 1 H), 2.46 (ddd, 1 H, *J* = 18.1, 6.7, 1.2 Hz), 0.90, (d, 3 H, *J* = 7.1 Hz)

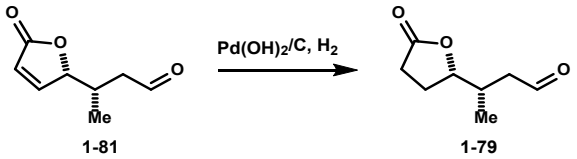
^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.5, 172.9, 154.7, 122.8, 85.3, 47.0, 30.1, 13.8.

Literature spectra reported by Taguchi:[17a]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.80 (1 H, s), 7.41 (1 H, dd, *J* = 5.8, 1.5 Hz), 6.18 (1 H, dd, *J* = 5.8, 2.1 Hz), 5.14-5.08 (1 H, m), 2.74 (1 H, dd, *J* = 17.6, 6.4 Hz), 2.70-2.58 (1 H, m), 2.46 (1 H, dd, *J* = 17.6, 6.6 Hz), 0.90 (3 H, d, *J* = 6.9 Hz),

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.3, 172.7, 154.5, 122.7, 85.2, 46.8, 30.0, 13.7.

Synthesis of 1-79 from (3*S*, 5*R*)-1-81



1-81 1-79

To the solution of crude (3*S*, 5*R*)-**1-81** (221 mmol, 1.0 eq.) in EtOAc (730 mL, 0.3 M) was added $Pd(OH)_2/C$ (20 wt %, 50% H_2O, 3.08 g, 4.38 mmol, 2 mol%). Then hydrogen gas was bubbled through the solution for 30 minutes and the reaction was stirred for 6 hours under 1 atm of hydrogen. The mixture was filtered through celite and concentrated under reduced pressure. The crude product was then purified by silica gel chromatography (hexanes/EtOAc, 100/0→60:40) to furnish **1-79** (23.7 g, *dr* = 9:1) as a light-yellow oil in 69% yield over 2 steps.

$[\alpha]_D^{23}$ = +30.8 (*c* = 0.1, $CHCl_3$)

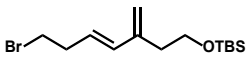
^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.77 (s, 1 H), 4.49-4.41 (m, 1 H), 2.67-2.58 (m, 1 H), 2.58-2.50 (m, 2 H), 2.45-2.35 (m, 2 H), 2.30-2.21 (m, 1 H), 1.99-1.88 (m, 1 H), 1.02 (d, 3 H, *J* = 6.4 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.8, 176.9, 83.1, 46.8, 31.9, 29.0, 25.1, 14.6.

FT-IR (neat): 2970, 2934, 1773, 1724, 1468, 1422, 1390, 1192, 1023, 633 cm^{-1}

HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_8H_{13}O_3$ 157.08592; found 157.08676.

(E)-((7-bromo-3-methylenehept-4-en-1-yl)oxy)(tert-butyl)dimethylsilane (1-92)



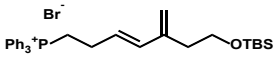
4-bromobutene (0.55 ml, 5.43 mmol, 10 eq.) was added to the solution of **1-90** (100 mg, 0.54 mmol, 1.0 eq.) in DCM (2.1 ml, 0.26 M) under the atmosphere of argon. The solution was then sparged with ethylene gas for 30 min. Grubbs 2nd gen (28 mg, 0.032 mmol, 6 mol%) was added in one portion and the reaction was stirred under the atmosphere of ethylene for 24 hours. The solution was then concentrated, diluted with hexanes, stirred for 3 min and filtered through Celite. After concentrating under reduced vacuum, the crude mixture was purified by the column

chromatography (hexanes/EtOAc 100% to 8:2) on a silica gel to afford **1-92** (120 mg) as a yellow oil in 70% yield.

^{1}H NMR (500 MHz, CDCl3): δ = 6.13 (d, J = 8.1 Hz, 1H), 5.67 (dt, J = 15.8, 7.0 Hz, 1H), 4.99 (d, J = 14.6 Hz, 2H), 3.7 (t, J = 7.2 Hz, 2H), 3.4 (t, J = 7.1 Hz, 2H), 2.66 (qd, J = 7.0, 1.2 Hz, 2H), 2.4 (td, J = 7.2, 1.0 Hz, 2H), 0.89 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (125 MHz, CDCl3): δ = 142.5, 134.9, 126.1, 116.5, 62.4, 36.1, 35.7, 32.4, 25.9, 18.4, -5.2.

(E)-(7-((tert-butyldimethylsilyl)oxy)-5-methylenehept-3-en-1-yl)triphenylphosphonium bromide (1-93)

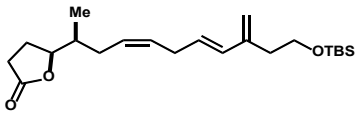


PPh_3 (8.12 g, 31 mmol, 1.6 eq.) was added to the solution of **1-92** (6.15 g, 19.3 mmol, 1.0 eq.) in CH_3CN (39 ml, 0.5 M). The solution was then refluxed at 85 °C overnight and concentrated under the reduced vacuum. Crude residue was diluted with pentane and DCM until full dissolution. Pentane was then added to crush the product. Mother liquor was decanted, and the procedure was repeated 3 times to ensure complete removal of unreacted PPh_3. Solids were combined to furnish **1-93** (11.2 g) as a white foamy solid in 80% yield.

^{1}H NMR (500 MHz, CDCl3): δ = 7.92-7.86 (m, 6H), 7.81-7.76 (m, 3H), 7.72-7.67 (m, 6H), 5.96 (d, J = 15.7 Hz, 1H), 5.70 (dt, J = 15.7, 6.8 Hz, 1H), 4.90 (d, J = 5.3 Hz, 2H), 4.00-3.91 (m, 2H), 3.62 (td, J = 6.8, 1.6 Hz, 2H), 2.59-2.53 (m, 2H), 2.24 (t, J = 6.8 Hz, 2H), 0.84 (s, 9H), 0.00 (s, 6H).

^{13}C NMR (125 MHz, CDCl3): δ = 142.1, 135.1(d), 133.8(d), 130.6(d), 125.5 (d), 118.6, 117.9, 116.9, 61.8, 35.2, 26.0, 23.1, 22.7, 18.3, -5.2.

(S)-5-((S,4Z,7E)-11-((tert-butyldimethylsilyl)oxy)-9-methyleneundeca-4,7-dien-2-yl)dihydrofuran-2(3H)-one (1-94)

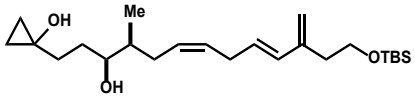


The solution of **1-93** (7.84 g, 13.5 mmol, 1.4 eq.) in THF (33 ml) was cooled to -78 °C. LiHMDS (13 ml, 13 mmol, 1 M in THF, 1.35 eq.) was added dropwise and the solution was warmed to 0 °C. After 20 minutes, the reaction was cooled to -78 °C and **1-79** (1.5 g, 9.65 mmol, 1.0 eq.) in THF (15 ml) was added dropwise. The solution was stirred for 10 min at -78 °C, warmed to room temperature and stirred overnight. The mixture was then quenched with NH_4Cl, extracted with Et_2O (3x), dried over $MgSO_4$ and concentrated under the reduced pressure. The crude product was then purified by the column chromatography on silica gel (hexanes/EtOAc 100% to 7:3) to furnish **1-94** (2.9 g) as a yellow oil in 79% yield.

^{1}H NMR (500 MHz, CDCl3): δ = 6.05 (d, J = 15.8 Hz, 1H), 5.67 (dt, J = 15.8, 6.5 Hz, 1H), 5.55-5.40 (m, 2H), 4.92 (d, J = 21.6 Hz, 2H), 4.39-4.34 (m, 1H), 3.72 (t, J = 7.3 Hz, 2H), 2.85 (t, J = 6.8 Hz, 2H), 2.53 (dd, J = 10.1, 7.0 Hz, 2H), 2.43 (td, J = 7.3, 0.8 Hz, 2H), 2.29-2.16 (m, 2H), 2.03-1.72 (m, 3H), 1.00 (d, J = 6.7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (125 MHz, CDCl3): δ = 177.2, 142.8, 132.5, 129.1, 127.8, 127.7, 115.3, 84.0, 62.5, 38.2, 35.8, 30.6, 30.0, 29.1, 26.0, 25.7, 18.4, 14.6, -5.2.

1-((3S,4S,6Z,9E)-13-((tert-butyldimethylsilyl)oxy)-3-hydroxy-4-methyl-11-methylenetrideca-6,9-dien-1-yl)cyclopropan-1-ol (1-95)



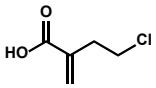
To the solution of **1-94** (2.25 g, 6.1 mmol, 1 eq.) in THF (18 ml, 0.33 M) was added Ti(O*i*Pr)$_4$ (1.8 ml, 6.1 mmol, 1 eq.) and the reaction was cooled to 15 °C. EtMgBr (4.3 ml, 12.8 mmol, 3 M in Et_2O, 2.1 eq.) was the added over 2 hours (syringe pump). The mixture was stirred for additional 2 hours, quenched with NH_4Cl, H_2O, extracted with EtOAc (3x), dried with $MgSO_4$

and concentrated under the reduced vacuum. Crude product was used directly in the next step without further purification.

^{1}H NMR (500 MHz, CDCl3): δ = 6.06 (d, J = 15.8 Hz, 1H), 5.69 (dt, J = 15.8, 6.5 Hz, 1H), 5.47 (t, J = 9.9 Hz, 2H), 4.94 (s, 1H), 4.89 (s, 1H), 3.71 (t, J = 7.3 Hz, 2H), 3.64-3.63 (m, 1H), 2.87-2.85 (m, 2H), 2.43 (t, J = 7.3 Hz, 2H), 2.25-2.17 (m, 1H), 2.02-1.96 (m, 1H), 1.83-1.75 (m, 1H), 1.70-1.66 (m, 2H), 1.63-1.54 (m, 2H), 0.92 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.78-0.72 (m, 2H), 0.47-0.42 (m, 2H), 0.04 (s, 6H).

^{13}C NMR (125 MHz, CDCl3): δ = 142.9, 132.3, 129.2, 128.3, 128.2, 115.2, 75.2, 62.6, 55.7, 39.4, 35.9, 35.8, 31.4, 31.0, 30.6, 26.0, 18.4, 14.1, 13.8, 13.5, -5.2.

4-chloro-2-methylenebutanoic acid (1-139)



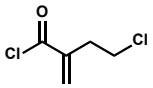
The acid was synthesized following a literature procedure.[48] To a solution of dppbz (313 mg, 0.700 mmol, 7 mol%) and Ni(acac)$_2$ (129 mg, 0.500 mmol, 5 mol%) in toluene (20 mL, 0.5 M) was added chlorobutyne (**1-100**, 904 µL, 10.0 mmol), formic acid (566 µL, 15.0 mmol, 1.5 eq.) and Piv$_2$O (407 µL, 2.00 mmol, 20 mol%) at room temperature. The reaction was then stirred at 100 °C for 24 h. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane 0/100 to 4/6) to furnish **1-139** (740 mg) as a yellow oil in 55% yield.

Note: Pivalic acid coeluted with the desired product. This issue can is not consequential in the long term as pivaloyl chloride can be easily removed in the next step.

^{1}H NMR (500 MHz, CDCl3): δ = 6.47 (s, 1H), 5.84 (s, 1H), 3.68 (t, J = 6.7 Hz, 2H), 2.77 (t, J = 6.7 Hz, 2H).

^{13}C NMR (125 MHz, CDCl3): δ =171.6, 135.6, 130.8, 42.6, 35.0.

4-chloro-2-methylenebutanoyl chloride (1-78)

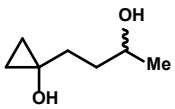


To a solution of acid **1-139** (4.14 g, 30.8 mmol) in DCM (31 mL, 1 M) was added oxalyl chloride (2.73 mL, 32.3 mmol, 1.05 eq.) dropwise and 5 small drops of DMF at 0 °C. The reaction was stirred overnight at room temperature. Solvent was then removed under reduced pressure. The crude product was distilled under vacuum to give **1-78** (2.24 g) as a colorless oil in 48% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.73 (s, 1H), 6.20 (t, J = 1.1 Hz, 1H), 3.66 (t, J = 6.5 Hz, 2H), 2.82 (td, J = 6.6, 1.1 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.6, 140.9, 136.6, 42.1, 35.4.

1-(3-hydroxybutyl)cyclopropan-1-ol (1-96)



To a solution of γ-Valerolactone (8.85 mL, 92.8 mmol) in THF (281 mL, 0.33 M) at 10-15 °C was added Ti(O*i*Pr)$_4$ (34.4 mL, 116 mmol, 1.25 eq.). Then EtMgBr (3 M in Et_2O, 81.3 mL, 244 mmol, 2.62 eq.) was added over 2 h at the same temperature. The reaction mixture was stirred at below 20 °C for another 2 h after the addition was finished. The reaction was quenched with sat. aqueous solution of NH_4Cl and the mixture was stirred vigorously until it turned white. The crude product was extracted with EtOAc (6x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane 0/100 to 4/6) to furnish **1-96** (11.2 g) as a light-yellow sticky oil in 93% yield.

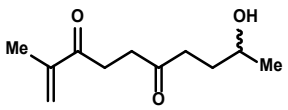
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.00 – 3.87 (m, 1H), 1.80 – 1.55 (m, 4H), 1.25 (d, J = 6.2 Hz, 3H), 0.76 (qd, J = 3.3, 2.0 Hz, 2H), 0.54 – 0.37 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 68.5, 55.8, 36.0, 35.3, 24.1, 14.1, 13.7.

Representative procedure for Table 1

To a solution of **1-96** (39.1 mg, 0.300 mmol) in THF (2.2 mL) was added $ZnEt_2$ (1 M in hexane, 0.6 mL, 0.600 mmol, 2.0 eq.) at room temperature. The reaction was stirred for 15 min and $Pd(PPh_4)_3$ (17.2 mg, 0.0150 mmol, 5 mol%) was added to the reaction. Then acryloyl chloride (73.3 μL, 0.750 mmol, 2.5 eq.) in THF (0.8 mL) was added to the reaction over 1 h at room temperature. The reaction mixture was stirred for another 20 min and quenched with sat. aqueous solution of NH_4Cl. The crude product was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane 0/100 to 4/6) to furnish **1-98** (32 mg) as a yellow oil in 55% yield.

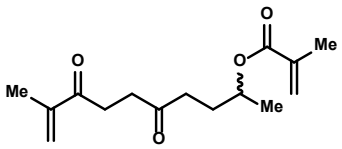
9-hydroxy-2-methyldec-1-ene-3,6-dione (1-98)



^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.03 (s, 1H), 5.79 (d, J = 1.6 Hz, 1H), 3.81 (ddd, J = 8.2, 6.2, 4.0 Hz, 1H), 3.05 – 2.99 (m, 2H), 2.77 – 2.71 (m, 2H), 2.67 (d, J = 4.3 Hz, 2H), 1.90 – 1.85 (m, 4H), 1.80 (dtd, J = 14.3, 7.2, 4.0 Hz, 1H), 1.70 (ddd, J = 14.3, 8.2, 7.0 Hz, 1H), 1.20 (d, J = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.5, 200.4, 144.2, 125.1, 67.6, 39.4, 36.5, 32.8, 31.6, 23.8, 17.7.

9-methyl-5,8-dioxodec-9-en-2-yl methacrylate (1-99)

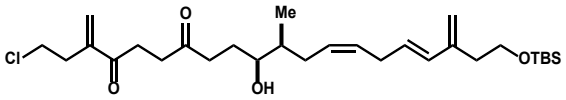


The title compound was isolated alongside with **1-98** in 13% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.09 – 6.06 (m, 1H), 6.05 – 6.01 (m, 1H), 5.82 – 5.76 (m, 1H), 5.54 (t, *J* = 1.6 Hz, 1H), 5.02 – 4.92 (m, 1H), 3.06 – 2.94 (m, 2H), 2.77 – 2.64 (m, 2H), 2.56 (ddd, *J* = 8.1, 6.5, 4.9 Hz, 2H), 1.96 – 1.92 (m, 3H), 1.92 – 1.87 (m, 1H), 1.87 – 1.85 (m, 3H), 1.35 – 1.18 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 208.8, 200.3, 167.2, 144.2, 136.8, 125.4, 125.1, 70.7, 38.9, 36.4, 31.5, 29.9, 20.2, 18.5, 17.7.

(10S,11S,13Z,16E)-20-((tert-butyldimethylsilyl)oxy)-1-chloro-10-hydroxy-11-methyl-3,18-dimethyleneicosa-13,16-diene-4,7-dione (1-77)

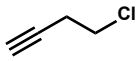


To a solution of **1-95** (86.0 mg, 0.21 mmol) in THF (1.1 mL) was added $ZnEt_2$ (1.0 M in hexane, 0.42 mL, 0.42 mmol, 2.0 eq.) dropwise at -78 °C. The mixture was stirred for 10 min at -78 °C, warmed to room temperature and stirred for additional 15 min. Then $Pd(PPh_3)_4$ (12.1 mg, 0.010 mmol, 5 mol%) was added. After another 15 min at room temperature, a solution of **1-78** (0.53 M in THF, 1.0 ml, 0.53 mmol, 2.5 eq.) in THF (1.0 mL) was added over 1 h using a syringe pump. The reaction was stirred for additional 1 h after the addition was finished. It was then quenched with sat. aqueous solution of NH_4Cl and extracted with EtOAc (4x). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc/hexane 0/100 to 3/7) to furnish **1-77** (33.0 mg) as a yellow oil in 30% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.20 (s, 1H), 6.05 (d, *J* = 15.8 Hz, 1H), 5.93 (s, 1H), 5.69 (dt, *J* = 15.6, 6.3 Hz, 1H), 5.47-5.66 (m, 1H), 4.94 (s, 1H), 4.88 (s, 1H), 3.71 (t, *J* = 7.3 Hz, 2H), 3.59 (t, *J* = 6.7 Hz, 2H), 3.61-3.48 (m, 1H), 3.02-2.66 (m, 10H), 2.43 (t, *J* = 7.2 Hz, 2H), 2.28-1.68 (m, 4H), 1.27-1.24 (m, 1H), 0.89 (m, 12H), 0.04 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.2, 199.6, 144.1, 142.9, 132.3, 129.2, 128.22, 128.19, 127.5, 115.2, 74.4, 62.6, 53.4, 43.0, 40.0, 39.3, 36.3, 35.8, 34.6, 31.5, 30.9, 30.6, 28.2, 26.0, 18.4, -5.2.

4-chlorobut-1-yne (1-100)



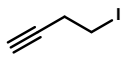
1-100 was synthesized following a literature procedure.[49] A mixture of 3-butyn-1-ol (21.1 mL, 279 mmol) and pyridine (1.79 mL, 22.2 mmol, 8 mol%) in a round-bottomed flask was cooled to 0 °C. Thionyl chloride (20.3 mL, 279 mmol, 1.0 eq.) was added dropwise to control the generation of the corrosive gas. After the addition was complete, the reaction was stirred at 65 °C (reflux) for additional 30 minutes. Short path distillation from the mixture at 110-130 °C afforded **1-100** (23.4 g) as a colorless liquid in 94% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.61 (t, J = 7.1 Hz, 2H), 2.67 (td, J = 7.1, 2.6 Hz, 2H), 2.08 (t, J = 2.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 80.4, 70.6, 42.1, 23.0.

Spectral data for this compound were consistent with those in the literature.[49]

4-iodobut-1-yne (1-140)



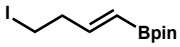
To a solution of 4-chlorobut-1-yne (**1-100**, 7.5 g, 85 mmol) in acetone (340 mL, 0.25 M) was added NaI (50 g, 334 mmol, 4.0 eq.) and the reaction mixture was refluxed for 3 days. The suspension was then cooled to room temperature and filtered. The filtrate was then concentrated under reduced pressure at room temperature (Volatile!). The residue was diluted with water and sat. aqueous solution of $Na_2S_2O_3$. The crude product was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give **1-140** (11 g) as a yellow oil in 72% yield. The material was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.24 (t, J = 7.2 Hz, 2H), 2.79 (td, J = 7.3, 2.6 Hz, 2H), 2.23 – 2.16 (t, J = 2.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 82.9, 70.4, 23.8, 0.96.

Spectral data for this compound were consistent with those in the literature.[50]

(*E*)-2-(4-iodobut-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1-103)



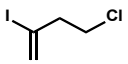
1-103 was synthesized following a literature procedure.[39] To a mixture of Cp_2ZrHCl (430 mg, 1.67 mmol, 5 mol%) and HBpin (4.84 mL, 33.34 mmol, 1.0 eq.) was added 4-iodobut-1-yne (**1-140**, 6.00 g, 33.34 mmol) dropwise at room temperature. The reaction mixture was stirred at 60 °C for 22 h. The reaction was then cooled to room temperature and directly loaded to a short silica gel plug. Firstly, unreacted 4-iodobut-1-yne was flushed out with 5% EtOAc/hexane. The product was then eluted with 50% EtOAc/hexane. Solvent was removed under reduced pressure to give **1-103** (8.2 g) as a yellow solid in 80% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.49 (dt, J = 18.0, 6.3 Hz, 1H), 5.51 (d, J = 18.0 Hz, 1H), 3.18 (t, J = 7.4 Hz, 2H), 2.77 – 2.70 (m, 2H), 1.27 (s, 12H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.3, 116.1, 83.4, 39.8, 24.9, 2.84.

HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_{10}H_{19}BIO_2$ 309.05173; found 309.05151.

4-chloro-2-iodobut-1-ene (1-104)



1-104 was synthesized following a literature procedure.[38] To a solution of NaI (33.9 g, 226 mmol, 2.0 eq.) in acetonitrile (97 mL, 1.2 M) was added TMSCl (28.7 mL, 226 mmol, 2.0 eq.) at room temperature, resulting in a pale yellow suspension. After 5 min, water (2.03 mL, 113 mmol, 1.0 eq.) was added, and the reaction was stirred at room temperature for additional 10 min. Then 4-chlorobut-1-yne (**1-100**, 9.82 mL, 113 mmol) was added dropwise to the mixture. The reaction was stirred for 1 h at room temperature and quenched with water. The crude product was extracted with Et_2O (3x). The combined organic layers were washed with sat. aqueous solution of $Na_2S_2O_3$

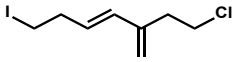
and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 100% hexanes) to furnish **1-104** (19.0 g) as a yellow oil in 78% yield.

Note: The color of the compound darkens over time, therefore it is recommended that it is used shortly after the preparation.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.18 (d, *J* = 1.5 Hz, 1H), 5.86 (d, *J* = 1.7 Hz, 1H), 3.64 (t, J = 6.6 Hz, 2H), 2.81 (tdd, J = 6.6, 1.3, 0.6 Hz, 2H).

Spectral data for this compound were consistent with those in the literature.[38]

(E)-7-chloro-1-iodo-5-methylenehept-3-ene (1-105)



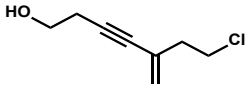
Route I: Suzuki coupling: 2 M NaOH solution was preparing by dissolving NaOH (27 g, 675 mmol) in water (337 mL) and sparged with argon for 20 min. 2 M NaOH was then added to a solution of **1-103** (10.4 g, 33.7 mmol), **1-104** (7.30 g, 33.7 mmol, 1.0 eq.) and $Pd(PPh_3)_2Cl_2$ (1.18 g, 1.69 mmol, 5 mol%) in THF (337 mL, 0.1 M). The reaction was stirred at room temperature for 1.5 h and quenched with 1 M HCl. The crude product was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 100% hexane) to furnish **1-105** (5.18 g) as a yellow oil in 57% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.13 (d, *J* = 16.0 Hz, 1H), 5.62 (d, *J* = 15.8 Hz, 1H), 5.10 (d, *J* = 1.4 Hz, 1H), 5.05 (d, *J* = 1.4 Hz, 1H), 3.64 (t, *J* = 7.5 Hz, 2H), 3.19 (t, *J* = 7.1 Hz, 2H), 2.73 – 2.65 m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.9, 133.7, 128.6, 117.3, 43.1, 36.7, 35.7, 5.3.

HRMS-ESI (m/z): $[M]^{\cdot+}$ calcd. for $C_8H_{12}ClI$ 269.9672; found 269.9670.

7-chloro-5-methylenehept-3-yn-1-ol (1-107)

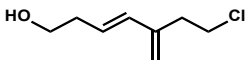


To a solution of **1-104** (29.5 g, 136 mmol) in DMF (273 mL, 0.5 M) was added $Pd(PPh_3)_4$ (3.94 g, 3.41 mmol, 5 mol%) and CuI (5.19 g, 27.3 mmol, 20 mol%) at room temperature. The reaction was sparged with Ar for 10 min (to degass the solution), after which $BuNH_2$ (27 mL, 273 mmol, 2.0 eq.) and 3-butyn-1-ol (10.8 mL, 143 mmol, 1.05 eq.) were added. The reaction was then stirred at room temperature overnight, after which it was diluted with Et_2O and filtered through celite. The filtrate was washed with 1 M HCl and sat. aqueous solution of $NaHCO_3$. Both aqueous layers were then extracted with Et_2O (2x each). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 100% hexane) to furnish **1-107** (17.8 g) as a brown oil in 82% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.41 (s, 1H), 5.30 (s, 1H), 3.74 (t, J = 6.3 Hz, 2H), 3.68 (t, J = 6.9 Hz, 2H), 2.58 (td, J = 6.6, 3.6 Hz, 4H), 1.84 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 127.6, 123.5, 87.5, 81.5, 61.2, 42.7, 40.4, 23.8.

(E)-7-chloro-5-methylenehept-3-en-1-ol (1-108)



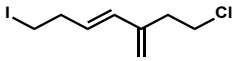
To **1-107** (624 mg, 4.00 mmol) in Et_2O (40 mL, 0.1 M) was added Red-Al (60% in toluene, 1.4 mL, 4.40 mmol, 1.1 eq.) dropwise at -20 °C. The reaction mixture was then refluxed for 23 h. It was then cooled to room temperature and another portion of Red-Al (0.19 mL, 0.60 mmol, 0.15 eq.) was added. The reaction was refluxed for additional 6 h, cooled to 0 °C and quenched with 1 M HCl (Careful!). The mixture was extracted with EtOAc (3x), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc/hexane 0/100 to 2/8) to furnish **1-108** (347 mg) as a pink oil in 54% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.17 (ddd, J = 16.2, 2.2, 1.3 Hz, 1H), 5.70 (dt, J = 15.9, 7.1 Hz, 1H), 5.07 (d, J = 1.4 Hz, 1H), 4.99 (d, J = 1.6 Hz, 1H), 3.70 (t, J = 6.3 Hz, 2H), 3.63 (t, J = 7.5 Hz, 2H), 2.69 (td, J = 7.5, 1.2 Hz, 2H), 2.39 (qd, J = 6.3, 1.4 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.0, 134.2, 126.3, 116.7, 62.1, 43.1, 36.3, 35.6.

HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_8H_{14}ClO$ 159.05712; found 159.05714.

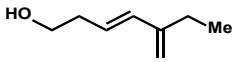
(E)-7-chloro-1-iodo-5-methylenehept-3-ene (1-105)



Route II: Appel reaction: To a solution of triphenylphosphine (13.5 g, 51.4 mmol, 1.05 eq.) and imidazole (3.50 g, 51.4 mmol, 1.05 eq.) in DCM (100 mL) was added I_2 (13.0 g, 51.4 mmol, 1.05 eq.) portionwise at 0 °C. Then **1-108** (7.86 g, 48.9 mmol) in DCM (22 mL) was added. The reaction was warmed to room temperature and stirred for 3.5 h. The mixture was then filtered through a silica gel plug and flushed with 10% Et_2O in hexane. The filtrate was concentrated under reduced pressure to give **1-105** (11.5 g) as a yellow oil in 87% yield.

Spectral data for this compound were consistent with those reported for **Route I**.

(E)-5-methylenehept-3-en-1-ol (1-109)

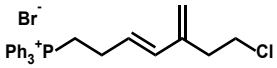


The title compound was obtained by stirring **1-107** with 2.3 eq. of Red-Al in THF overnight at room temperature.

NMR spectrum was taken using crude material.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.20 (dd, J = 15.8, 1.9 Hz, 1H), 5.69 (dt, J = 15.8, 7.2 Hz, 1H), 4.96 – 4.89 (m, 2H), 3.69 (t, J = 6.3 Hz, 2H), 2.38 (td, J = 6.9, 5.6 Hz, 2H), 2.22 (qt, J = 7.4, 1.1 Hz, 2H), 1.10 (t, J = 7.4 Hz, 3H).

(E)-(7-chloro-5-methylenehept-3-en-1-yl)triphenylphosphonium bromide (1-110)

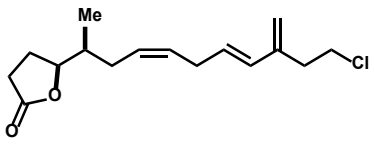


To a solution of iodide **1-105** (4.33 g, 16.1 mmol) in MeCN (32 mL, 0.5 M) was added PPh_3 (3.99 g, 15.2 mmol, 0.95 eq.). The reaction was then stirred at 30 °C for 3 days after which it was concentrated under reduced pressure. The residue was dissolved in minimum volume of DCM and pentane was added to precipitate out the product. Solvent was then decanted and the process was repeated twice. Resulting solid was dried under high vacuum to afford **1-110** (8.53 g) as a white foam in 83% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 – 7.76 (m, 9H), 7.75 – 7.66 (m, 6H), 6.04 (d, J = 15.9 Hz, 1H), 5.99 – 5.88 (m, 1H), 5.02 (s, 1H), 4.97 (s, 1H), 3.97 – 3.83 (m, 2H), 3.60 (t, J = 6.9 Hz, 2H), 2.64 – 2.48 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.4, 135.3 (d, J = 3.1 Hz), 134.0, 133.9 (d, J = 10.3 Hz), 130.7 (d, J = 12.5 Hz), 126.2 (d, J = 14.2 Hz), 118.1 (d, J = 85.8 Hz), 117.9, 43.2, 35.3, 26.0 ((d, J = 3.4 Hz), 23.2 (d, J = 48.5 Hz).

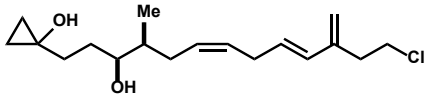
(S)-5-((S,4Z,7E)-11-chloro-9-methyleneundeca-4,7-dien-2-yl)dihydrofuran-2(3H)-one (1-111)



To a solution of **1-110** (970 mg, 1.82 mmol, 1.2 eq.) in THF (10.2 mL) at -78 °C was added LiHMDS (1 M in THF, 1.67 mL, 1.67 mmol, 1.1 eq.) dropwise. The resulting mixture was warmed to 0 °C and stirred for 20 min. After cooling the reaction back to -78 °C, **1-79** (237 mg, 1.52 mmol) in THF (5 mL) was added dropwise. The reaction was then stirred for 1 h at -78 °C, warmed to room temperature and stirred for additional 4 h. The mixture was then quenched with sat. aqueous solution of NH_4Cl and extracted with EtOAc (4x). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc/hexane 0/100 to 1/4) to furnish **1-111** (304 mg) as a yellow oil in 71% yield and 4:1 *Z*/*E* selectivity.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.13 – 5.98 (m, 1H), 5.66 (dt, *J* = 15.7, 6.5 Hz, 1H), 5.59 – 5.37 (m, 2H), 5.03 (s, 1H), 4.96 (s, 1H), 4.42 – 4.32 (m, 1H), 3.66 – 3.56 (m, 2H), 2.86 (t, *J* = 6.8 Hz, 2H), 2.72 – 2.62 (m, 2H), 2.57 – 2.47 (m, 2H), 2.32 – 2.13 (m, 2H), 2.06 – 1.87 (m, 2H), 1.75 (tt, *J* = 8.2, 5.9 Hz, 1H), 0.99 (d, *J* = 6.7 Hz, 3H).

1-((3S,4S,6Z,9E)-13-chloro-3-hydroxy-4-methyl-11-methylenetrideca-6,9-dien-1-yl)cyclopropan -1-ol (1-112)



To a solution of **1-111** (400 mg, 1.41 mmol) in THF (4.3 mL, 0.33 M) at 10-15 °C was added Ti(O*i*Pr)$_4$ (0.5 mL, 1.69 mmol, 1.2 eq.). Then EtMgBr (3 M in Et_2O, 1.03 mL, 3.1 mmol, 2.2 eq.) was added over 2 h at the same temperature. The reaction mixture was stirred for another 2 h after the addition was finished (the temperature has to be kept below 20 °C). The reaction was quenched with sat. aqueous solution of NH_4Cl and stirred vigorously until it turned white. The crude product was extracted with EtOAc (6x). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc/hexane 0/100 to 4/6) to furnish **1-112** (396 mg) as a yellow sticky oil in 90% yield.

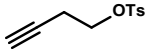
Note: The crude material could also be used directly for the next step.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.07 (dd, J = 15.9, 1.7 Hz, 1H), 5.73 – 5.63 (m, 1H), 5.56 – 5.42 (m, 2H), 5.03 (s, 1H), 4.95 (s, 1H), 3.65 – 3.59 (m, 3H), 2.90 – 2.85 (m, 2H), 2.72 – 2.63 (m, 2H), 2.28 – 2.13 (m, 1H), 2.06 – 1.89 (m, 1H), 1.85 – 1.74 (m, 1H), 1.73 – 1.53 (m, 4H), 0.91 (dd, J = 6.9, 5.4 Hz, 3H), 0.79 – 0.69 (m, 2H), 0.50 – 0.40 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.1, 131.4, 129.5, 128.6, 127.9, 116.0, 75.2, 55.7, 43.1, 39.3, 35.9, 35.7, 31.4, 31.0, 30.6, 14.0, 13.8, 13.4.

HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_{18}H_{30}ClO_2$ 313.1929; found 313.1909.

but-3-yn-1-yl 4-methylbenzenesulfonate (1-141)



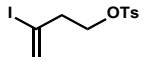
The title compound was synthesized following a literature procedure.[50] To a solution of 3-butyn-1-ol (15.0 g, 214 mmol) in DCM (268 mL, 0.8 M) were added TsCl (53.0 g, 278 mmol, 1.3 eq.), NEt_3 (59.7 mL, 428 mmol, 2.0 eq.) and $NMe_3 \cdot HCl$ (2.05 g, 21.4 mmol, 10 mol%). The mixture was then stirred at 0 °C for 1 h. The reaction was quenched with H_2O and stirred for another 2 h (to quench unreacted TsCl). The crude product was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was filtered through short silica plug (EtOAc/hexane 6/4). The solvent was removed under reduced pressure to give **1-141** (48.0 g) as a yellow oil. The crude material was used for the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.80 (d, J = 8.4 Hz, 2H), 7.35 (dd, J = 8.6, 0.8 Hz, 2H), 4.10 (t, J = 7.1 Hz, 2H), 2.55 (td, J = 7.1, 2.7 Hz, 2H), 1.97 (t, J = 2.7 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.1, 132.9, 130.0, 128.1, 78.5, 70.9, 67.6, 21.8, 19.6.

Spectral data for this compound were consistent with those in the literature.[50]

3-iodobut-3-en-1-yl 4-methylbenzenesulfonate (1-116)

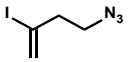


To a solution of NaI (64.2 g, 428 mmol, 2.0 eq.) in MeCN (186 mL, 1.15 M) was added TMSCl (54.3 mL, 428 mmol, 2.0 eq.) dropwise at room temperature. After 5 min, H_2O (6.44 mL, 357 mmol, 1.67 eq.) was added dropwise and the mixture was stirred for 20 min. Crude **1-141** (214 mmol) was then added as a MeCN solution. The mixture was stirred for 1 h at room temperature, quenched with H_2O and extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc/hexane 0/100 to 2/8) to furnish **1-116** (19.3 g, 26% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, J = 8.4 Hz, 2H), 7.36 (dd, J = 8.7, 0.7 Hz, 2H), 6.11 (d, J = 1.6 Hz, 1H), 5.79 (d, J = 1.6 Hz, 1H), 4.13 (t, J = 6.2 Hz, 2H), 2.72 (tdd, J = 6.2, 1.3, 0.6 Hz, 2H), 2.46 (s, 3H).

Spectral data for this compound were consistent with those in the literature.[51]

4-azido-2-iodobut-1-ene (1-117)

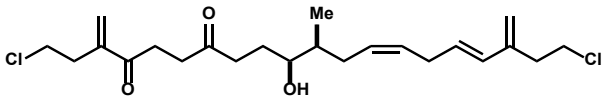


To a solution of **1-116** (8.85 g, 25.1 mmol) in DMF (63 mL, 0.4 M) was added NaN_3 (4.9 g, 75.4 mmol, 3.0 eq.). The mixture was stirred for 3 h at 50 °C. The reaction was cooled to room temperature and diluted with Et_2O. The organic layer was washed with water (3x). The combined aqueous layers were extracted with Et_2O once. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was passed through short silica plug (Et_2O/hexane 1/9). The filtrate was concentrated under reduced pressure to afford **1-117** (4.97 g) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.20 (d, J = 1.5 Hz, 1H), 5.85 (d, J = 1.7 Hz, 1H), 3.45 (t, J = 6.6 Hz, 2H), 2.64 (t, J = 6.6 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 128.7, 106.3, 50.2, 44.7.

(10S,11S,13Z,16E)-1,20-dichloro-10-hydroxy-11-methyl-3,18-dimethyleneicosa-13,16-diene-4,7-dione (1-114)



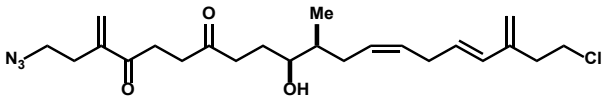
To a solution of **1-102** (62.0 mg, 0.20 mmol) in THF (1.4 mL) was added $ZnEt_2$ (0.86 M in hexane, 0.47 mL, 0.40 mmol, 2.0 eq.) dropwise at -78 °C. The mixture was stirred for 10 min at -78 °C, warmed to room temperature and stirred for additional 15 min. Then $Pd(PPh_3)_4$ (11.7 mg, 0.010 mmol, 5 mol%) was added. After another 15 min at room temperature, a solution of **1-78** (37.0 mg, 0.30 mmol, 1.5 eq.) in THF (0.6 mL) was added over 1 h using a syringe pump. The reaction was stirred for additional 1 h after the addition was finished. It was then quenched with sat. aqueous solution of NH_4Cl and extracted with EtOAc (4x). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc/hexane 0/100 to 3/7) to furnish **1-114** (27.9 mg) as a colorless oil in 32% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.22 (s, 1H), 6.07 (d, J = 15.8 Hz, 1H), 5.94 (s, 1H), 5.74 – 5.62 (m, 1H), 5.55 – 5.38 (m, 2H), 5.03 (s, 1H), 4.95 (s, 1H), 3.65 – 3.56 (m, 4H), 3.52 – 3.36 (m, 1H), 3.08 – 2.90 (m, 2H), 2.89 – 2.79 (m, 2H), 2.78 – 2.62 (m, 7H), 2.24 – 2.13 (m, 1H), 2.08 – 2.03 (m, 1H), 2.01 – 1.89 (m, 1H), 1.76 – 1.67 (m, 1H), 0.90 (d, J = 6.9 Hz, 3H).

The material contains *Z*/*E* isomers at a ratio of 4:1. 2H overlapped with water on the ^{1}H spectrum.

HRMS-ESI (m/z): $[M\text{-}OH]^+$ calcd. for $C_{23}H_{33}Cl_2O_2$ 411.18521; found 411.18430.

(10*S*,11*S*,13*Z*,16*E*)-1-azido-20-chloro-10-hydroxy-11-methyl-3,18-dimethyleneicosa-13,16-diene-4,7-dione (1-115)



Cross coupling with acyl chloride: To azido acid **1-113** (270 mg, 1.91 mmol, 3.0 eq.) in DCM (1.9 mL) was added Ghosez's reagent (0.25 mL, 1.91 mmol, 3.0 eq.) at 0 °C. The mixture was stirred for 15 min at 0 °C and 15 min at room temperature. Then it was diluted with THF (3.0 mL) and was ready to use. The acyl chloride is not very stable, so it may be better to use it immediately.

In another flask, to a solution of cyclopropanol **1-112** (200 mg, 0.638 mmol) in THF (9.8 mL) was added $ZnEt_2$ (0.88 M in hexane, 1.45 mL, 1.28 mmol, 2.0 eq.) dropwise at -78 °C. The mixture was stirred for 10 min at -78 °C and 15 min at room temperature. Then $Pd(PPh_3)_2Cl_2$ (22.4 mg, 0.0319 mmol, 5 mol%) and Bu_4NBr (20.6 mg, 0.064 mmol, 10 mol%) was added at the same time. After another 15 min at room temperature, the solution of acyl chloride was added to the reaction mixture as fast as possible. The reaction was stirred for 45 min and quenched with sat. aqueous solution of NH_4Cl. The crude product was extracted with EtOAc (4x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane 0/100 to 3/7) to furnish **1-115** (83.7 mg) as a colorless oil in 30% yield, together with an amide generated from Ghosez reagent. The amide can be removed by a second purification by column chromatography. The material could also be used without further purification.

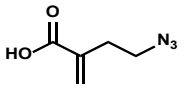
Carbonylative cross coupling: To a solution of cyclopropanol **1-112** (31.3 mg, 0.100 mmol) in THF (1.0 mL, 0.1 M) was added $ZnEt_2$ (1.0 M in hexane, 0.20 mL, 0.200 mmol, 2.0 eq.) at -78 °C. The reaction was left at the same temperature for 10 min and then warmed to room temperature. After 15 min at room temperature, $Pd(PPh_3)_4$ (5.8 mg, 0.0050 mmol, 5 mol%) was added to the reaction and the mixture was sparged with CO for 5 min. Then vinyl iodide **1-117** (66.9 mg, 0.300 mmol, 3.0 eq.) was added, and the reaction was stirred overnight at room temperature. The reaction was quenched with sat. aqueous solution of NH_4Cl. The crude product was extracted with EtOAc (4x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated

under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane 0/100 to 3/7) to furnish **1-115** (9.1 mg) as a colorless oil in 21% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.21 (s, 1H), 6.07 (d, J = 16.0 Hz, 1H), 5.94 (s, 1H), 5.74 – 5.62 (m, 1H), 5.52 – 5.40 (m, 2H), 5.03 (s, 1H), 4.95 (s, 1H), 3.62 (t, J = 7.5 Hz, 2H), 3.56 – 3.46 (m, 1H), 3.42 – 3.32 (m, 2H), 3.08 – 2.98 (m, 2H), 2.90 – 2.73 (m, 3H), 2.73 – 2.63 (m, 3H), 2.62 – 2.52 (m, 2H), 2.25 – 2.11 (m, 1H), 2.08 – 2.03 (m, 1H), 2.03 – 1.91 (m, 1H), 1.79 – 1.69 (m, 1H), 0.90 (d, J = 6.8 Hz, 3H).

The material contains *Z*/*E* isomers at a ratio of 4:1. 3H overlapped with water on the ^{1}H spectrum.

4-azido-2-methylenebutanoic acid (1-113)



The title compound was synthesized using a literature procedure.[42] $HCOOLi \cdot H_2O$ (941 mg, 13.5 mmol, 3.0 eq.), DIPEA (1.56 mL, 8.97 mmol, 2.0 eq.) and Ac_2O (0.85 mL, 8.97 mmol, 2.0 eq.) were dissolved in DMF (7 mL). The mixture was stirred for 1 h at room temperature. In a separate flask were mixed dry LiCl (570 mg, 13.5 mmol, 3.0 eq.), DMF (13 mL), **1-117** (1.00 g, 4.48 mmol), BHT (one bead) and $Pd_2(dba)_3$ (41.1 mg, 0.448 mmol, 1 mol%) and the mixture was stirred until full dissolution. The resulting solution was then transferred to the first flask. The reaction was stirred for 90 min at 80 °C. The mixture was then cooled to room temperature, diluted with EtOAc and washed with 2 M HCl and water (2x). The combined aqueous layers were extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc/hexane 0/100 to 4/6) to furnish **1-113** (481 mg) as a red oil in 76% yield.

Note: The product slowly turned from light-yellow to red when it was left under high vacuum to remove acetic acid that coeluted with the compound. The product was stored at -20 °C as a DCM

solution (80 mg/mL, with one small bead of BHT). Due to its high instability, it should be used as soon as possible.

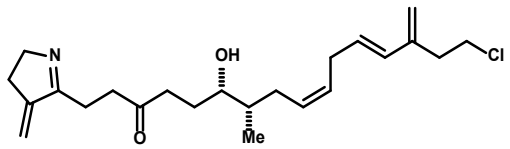
^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.44 (d, J = 1.0 Hz, 1H), 5.83 (app. q, 1H), 3.46 (t, J = 6.9 Hz, 2H), 2.61 (td, J = 6.9, 1.2 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.5, 136.1, 130.4, 50.0, 31.5.

FT-IR (neat): 3184 (broad), 2940, 2099, 1698, 1630, 1441, 1297, 1216, 1162, 963, 912, 833, 779, 601

HRMS-ESI (m/z): [M+H]+ calcd. for $C_5H_7N_3O_2Na$ 164.0436; found 164.0448.

(6*S*,7*S*,9*Z*,12*E*)-16-chloro-6-hydroxy-7-methyl-14-methylene-1-(4-methylene-3,4-dihydro-2*H*-pyrrol-5-yl)hexadeca-9,12-dien-3-one (1-119)



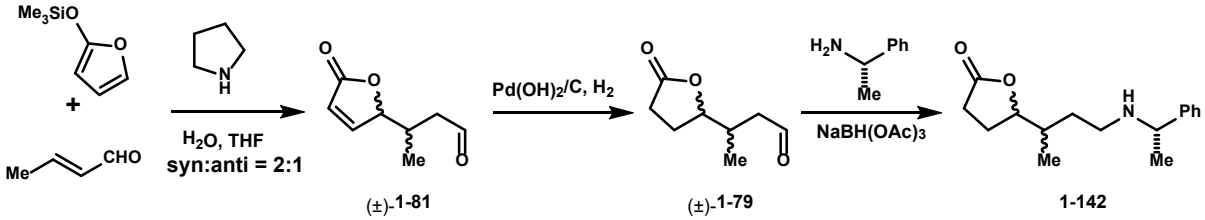
To a solution of **1-115** (114 mg, 0.261 mmol) in toluene (26 mL, 0.01 M) was added polymer-bound PPh_3 (100-200 mesh, ~3 mmol/g, 357 mg, 1.07 mmol, 4.1 eq.). The reaction was stirred overnight at room temperature. The mixture was then filtered through cotton and the filtrate was concentrated under reduced pressure. The crude material was used without further purification.

An analytical sample was purified (column chromatography, MeOH/EtOAc) for ^{1}H NMR.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.11 – 5.98 (m, 1H), 5.77 – 5.61 (m, 1H), 5.53 – 5.38 (m, 2H), 5.38 – 5.31 (m, 1H), 5.31 – 5.24 (m, 1H), 5.02 (s, 1H), 4.94 (s, 1H), 3.92 – 3.76 (m, 2H), 3.66 – 3.57 (m, 2H), 3.49 – 3.41 (m, 1H), 2.98 – 2.52 (m, 10H), 2.23 – 1.93 (m, 3H), 1.96 – 1.48 (m, 4H), 0.90 (d, J = 6.8 Hz, 3H).

1.5.4 Determination of Enantiomeric Ratio of x

Preparation and reductive amination of a racemic mixture

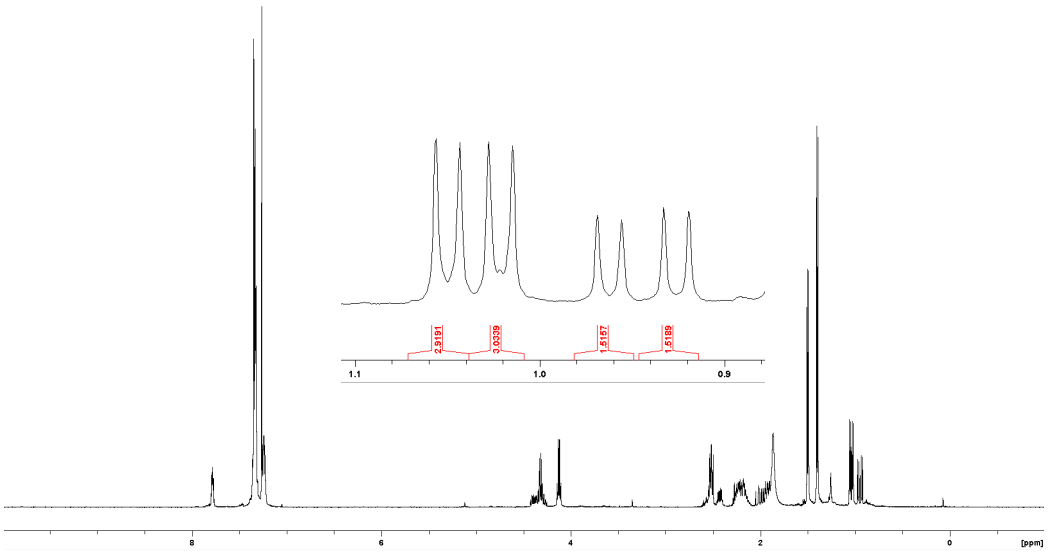


To a solution of pyrrolidine (9.1 mg, 0.128 mmol, 10 mol%) in THF (13 mL, 0.1 M) at -10 °C was added TFA (9.8 μL, 0.128 mmol, 10 mol%) and water (69.1 μL, 3.84 mmol, 3.0 eq.). After 15 minutes at -10 °C, crotonaldehyde (0.53 mL, 6.40 mmol, 5.0 eq.) was added to the solution. The mixture was stirred at -15 °C for 15 minutes. Then 2-(trimethylsiloxy)furan (200 mg, 1.28 mmol, 1.0 eq.) was added dropwise. The solution was stirred overnight at room temperature. The reaction mixture was then filtered through a short plug of silica with EtOAc immediately after being removed from the -15 °C bath. The filtrate was concentrated under reduced pressure to afford a racemic mixture of **1-81** (*syn:anti* = 2:1).

The crude material was dissolved in MeOH (4.3 mL, 0.3 M) and $Pd(OH)_2/C$ (20 wt%, 50% H_2O, 27.0 mg, 0.038 mmol, 3 mol%) was added. Then hydrogen gas was bubbled through the solution for 15 minutes and the reaction was stirred for 6 hours under 1 atm of hydrogen. The mixture was filtered through celite and concentrated under reduced pressure.

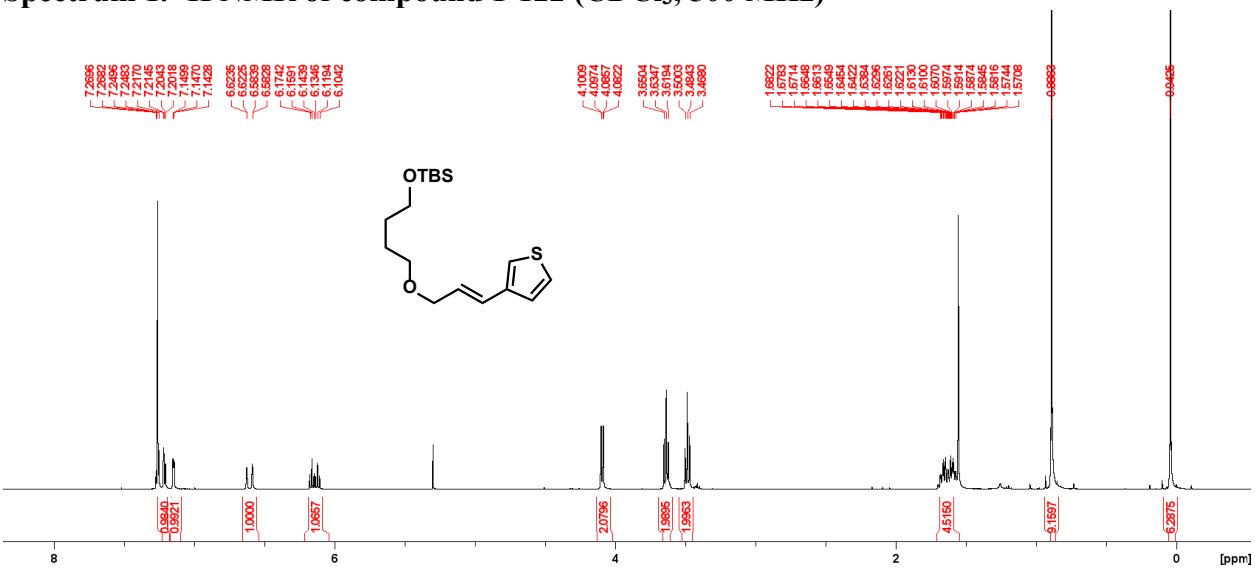
25 mg of the crude mixture was taken and dissolved in THF (0.64 mL, 0.25 M). Then (*S*)-phenylethanamine (41 μL, 0.32 mmol, 2.0 equiv) and sodium triacetoxyborohydride (51 mg, 0.24 mmol, 1.5 equiv) were added at room temperature. The mixture was stirred for 15 min then quenched with sat. aqueous solution of $NaHCO_3$ and stirred for 1 hour. The reaction was extracted with EtOAc (3x), dried over Na_2SO_4 and concentrated under reduced pressure.

^1H NMR of racemic crude material ($CDCl_3$, 500 MHz)

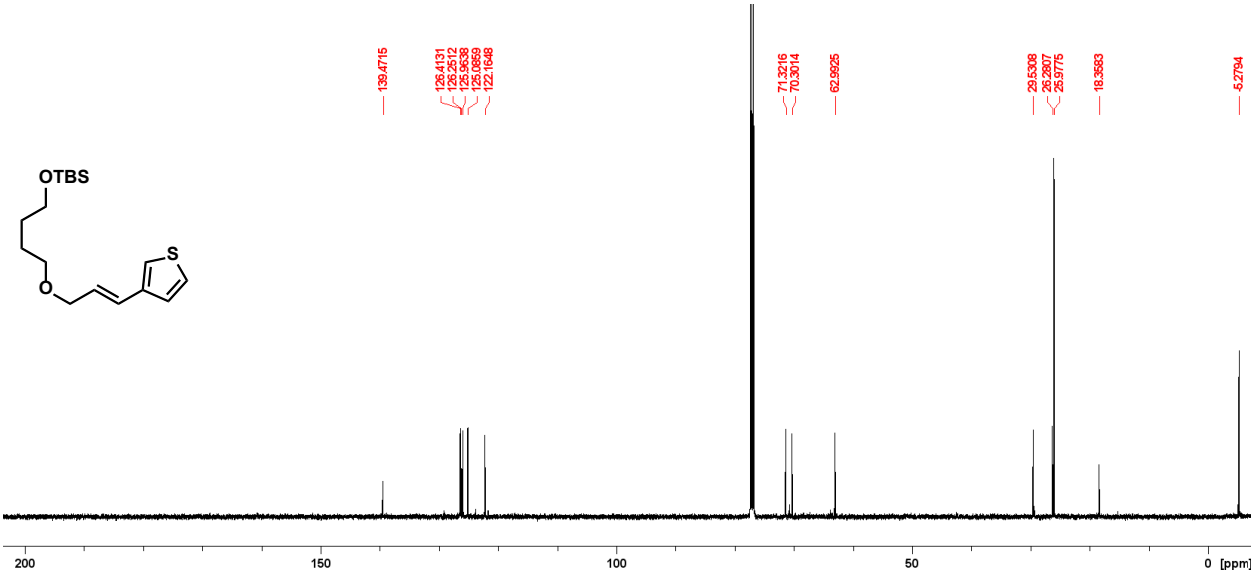


1.5.5 NMR Spectra

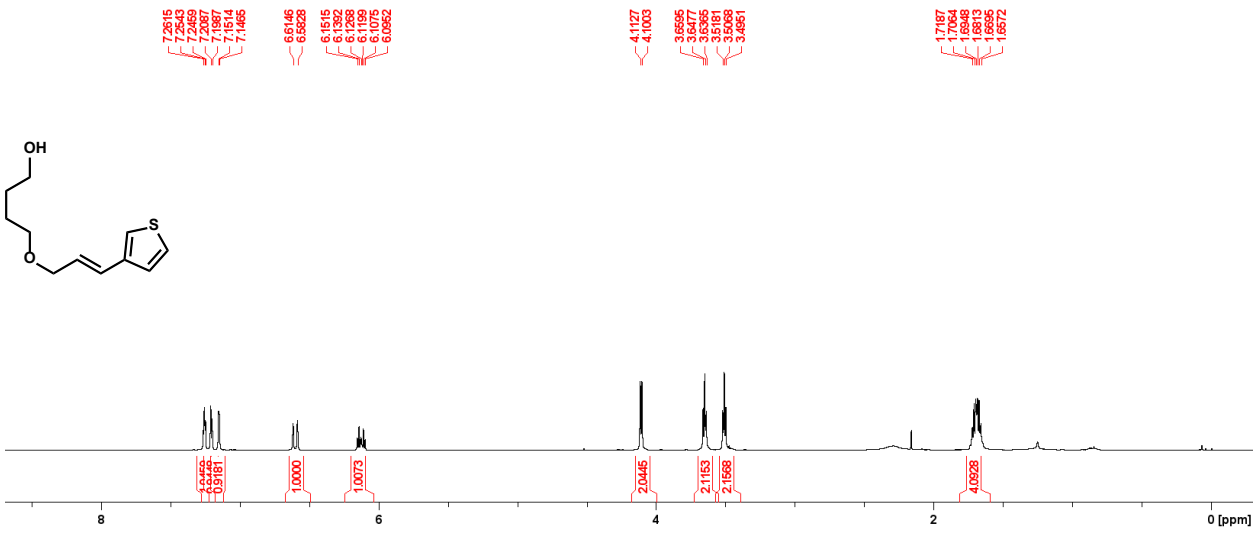
Spectrum 1. ^{1}H NMR of compound 1-122 ($CDCl_3$, 500 MHz)



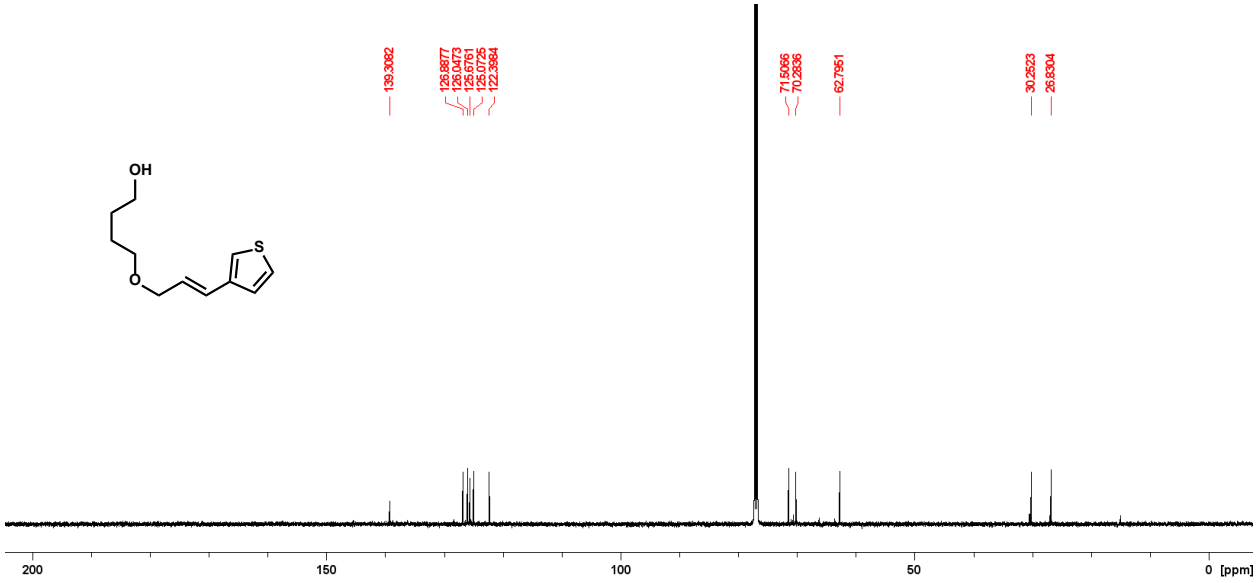
Spectrum 2. ^{13}C NMR of compound 1-122 ($CDCl_3$, 125 MHz)



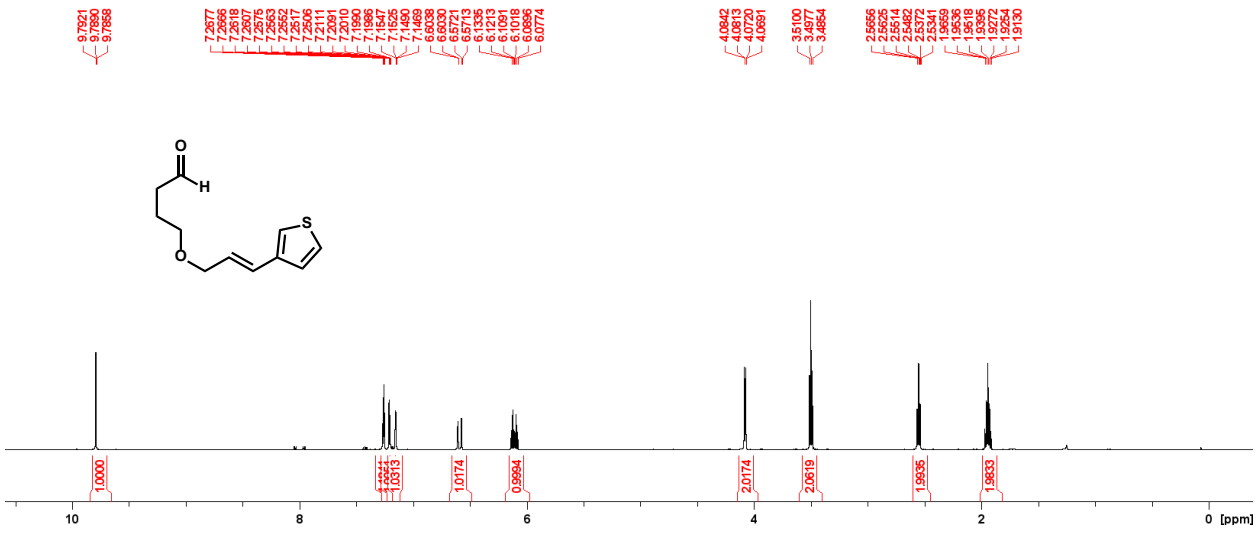
Spectrum 3. ^{1}H NMR of compound 1-123 ($CDCl_3$, 500 MHz)



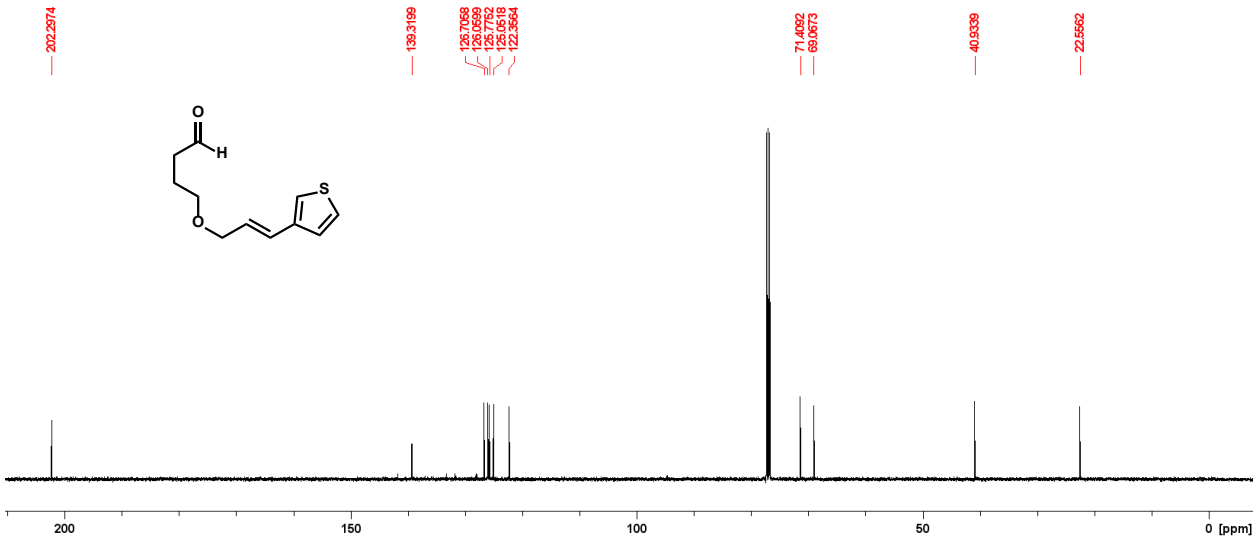
Spectrum 4. ^{13}C NMR of compound 1-123 ($CDCl_3$, 125 MHz)



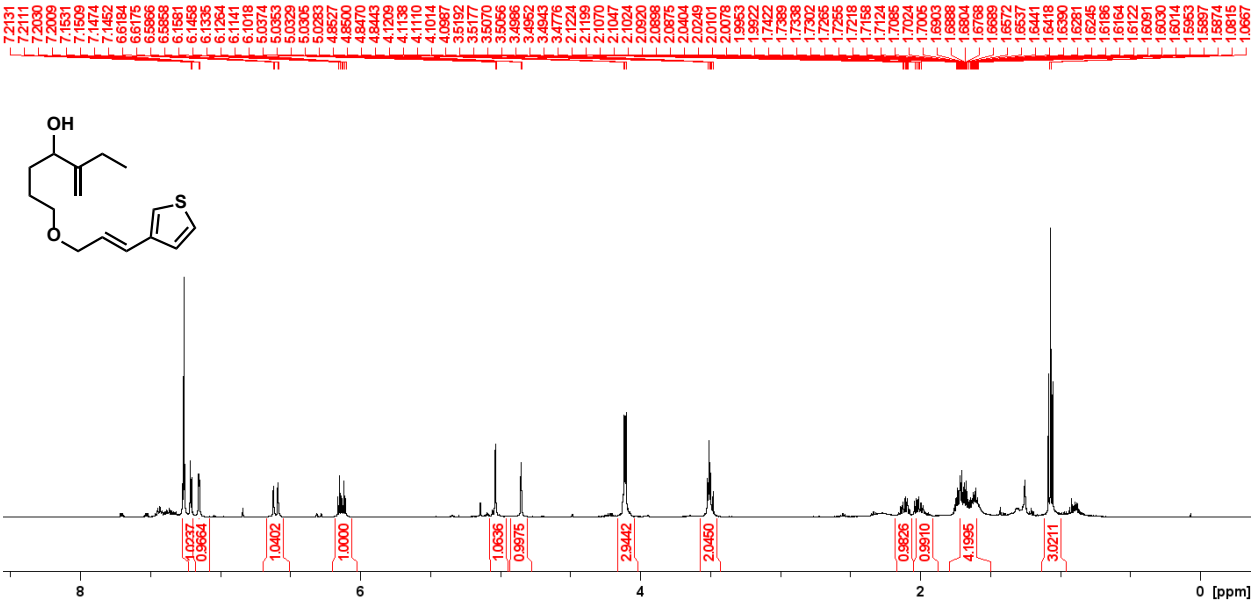
Spectrum 5. ^{1}H NMR of compound 1-70 ($CDCl_3$, 500 MHz)



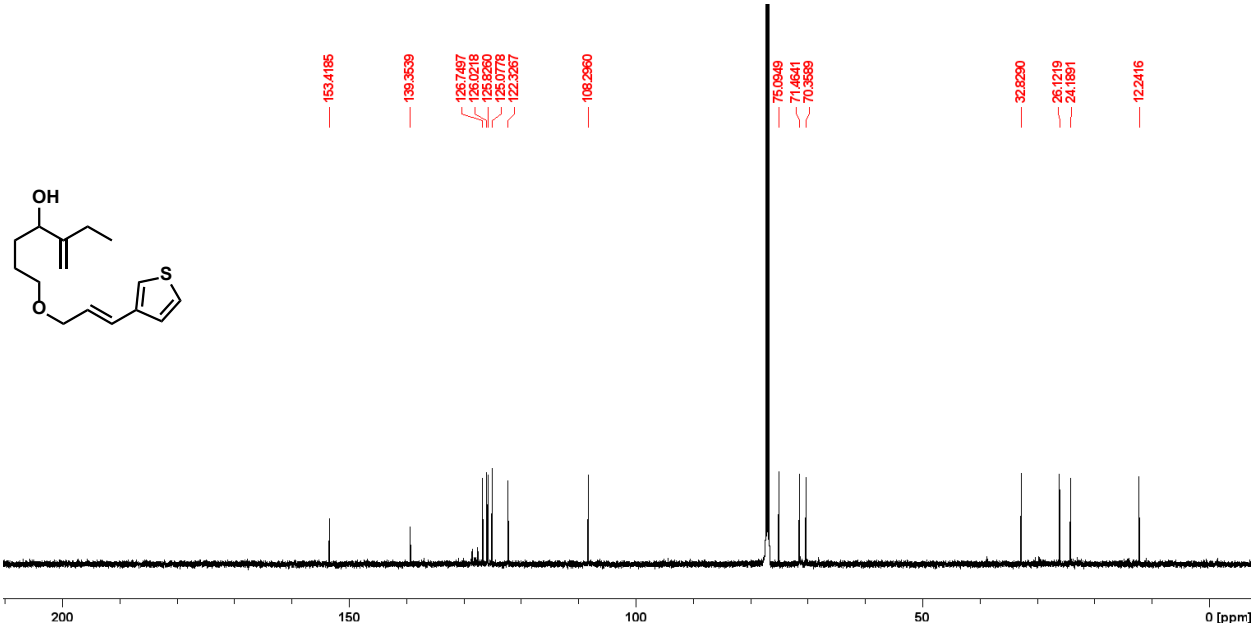
Spectrum 6. ^{13}C NMR of compound 1-70 ($CDCl_3$, 125 MHz)



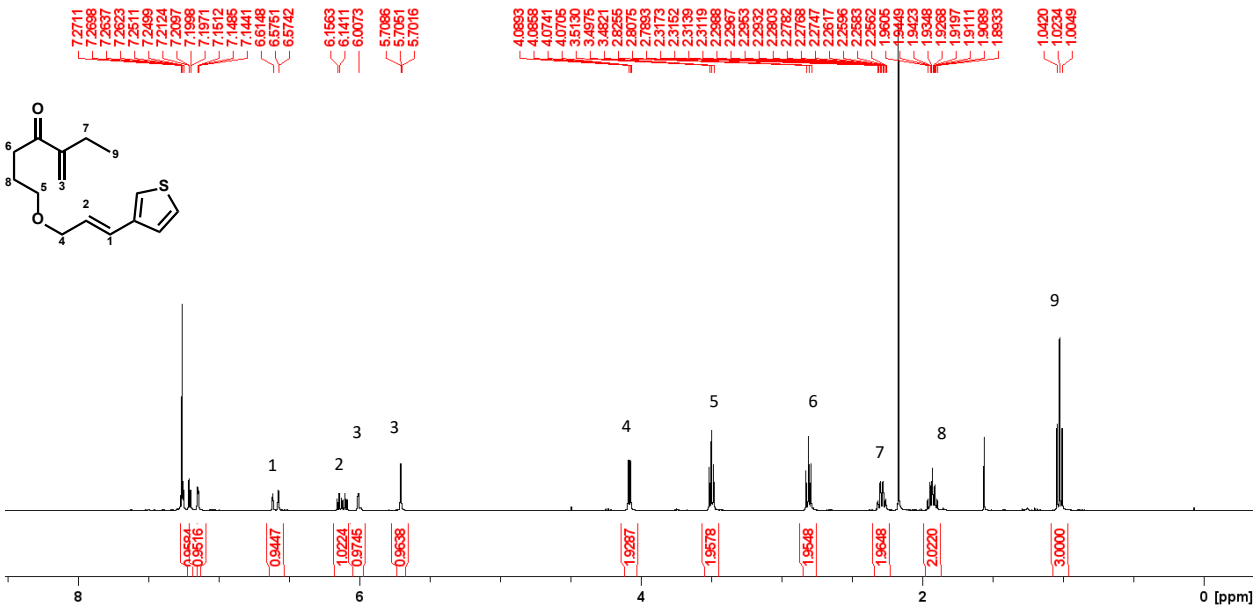
Spectrum 7. ^{1}H NMR of compound 1-124 ($CDCl_3$, 500 MHz)



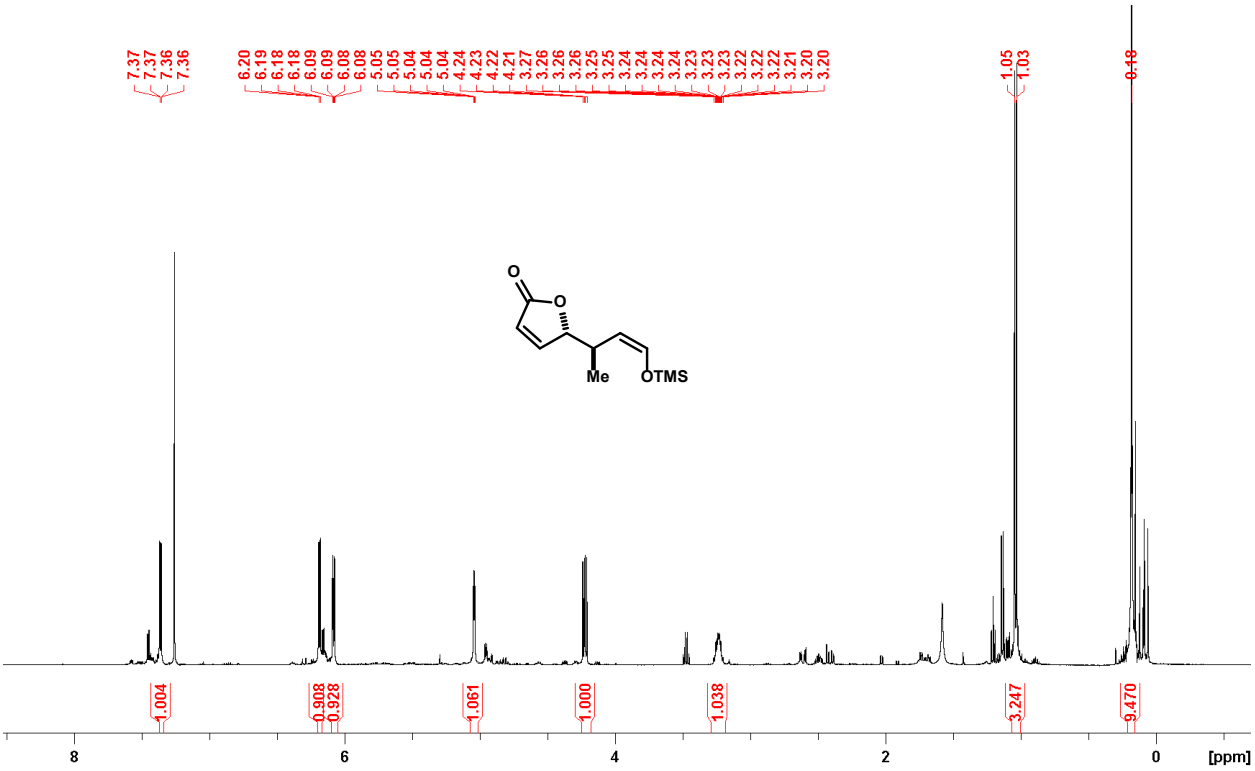
Spectrum 8. ^{13}C NMR of compound 1-124 ($CDCl_3$, 125 MHz)



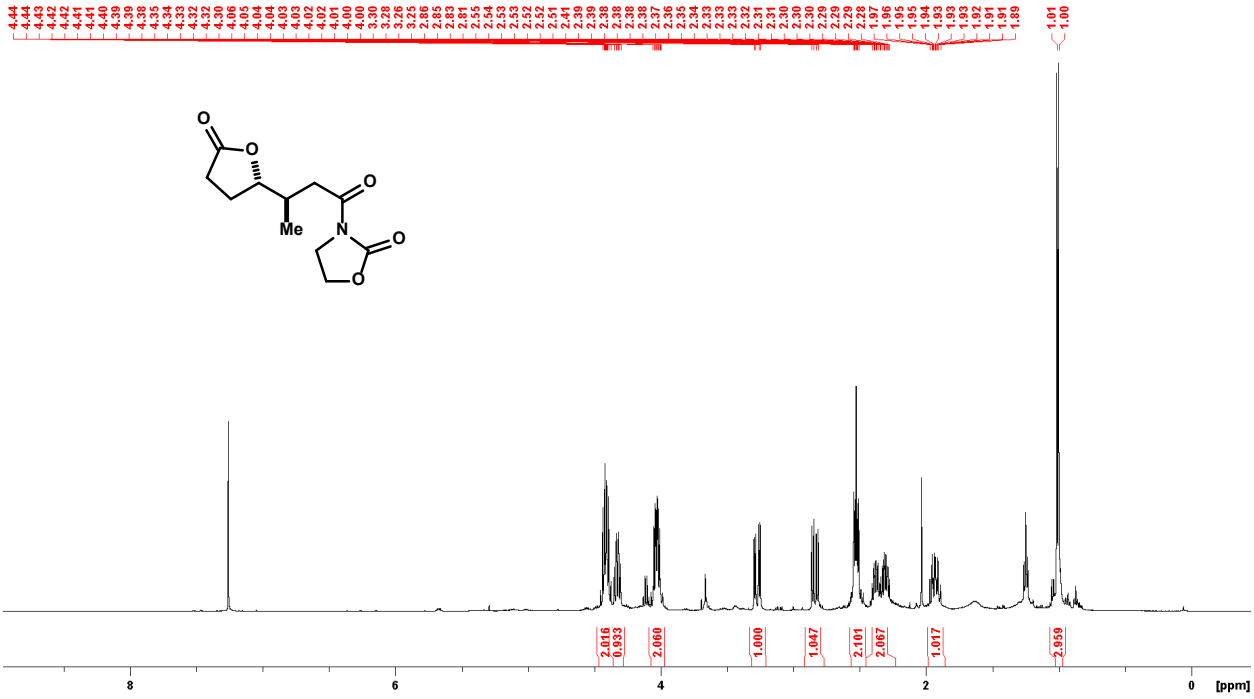
Spectrum 9. ^{1}H NMR of compound 1-71 ($CDCl_3$, 500 MHz)



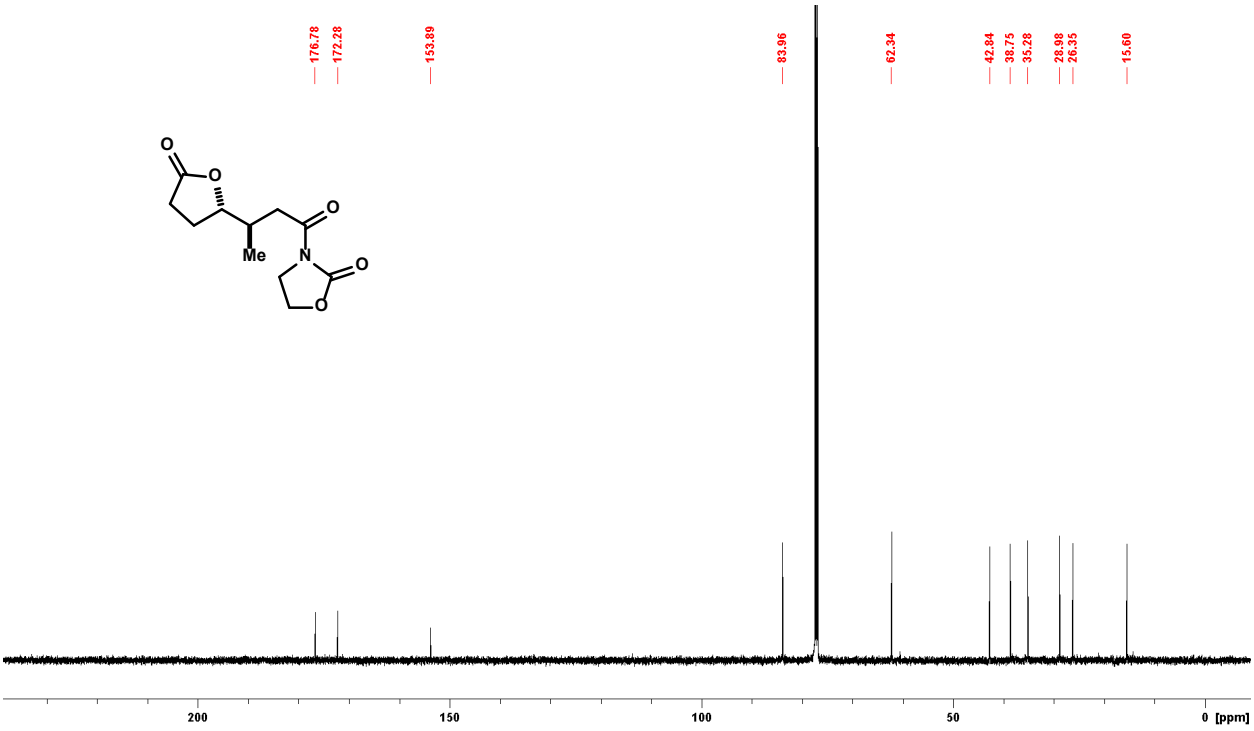
Spectrum 10.^{1}H NMR of compound 1-125 ($CDCl_3$, 500 MHz) – crude material



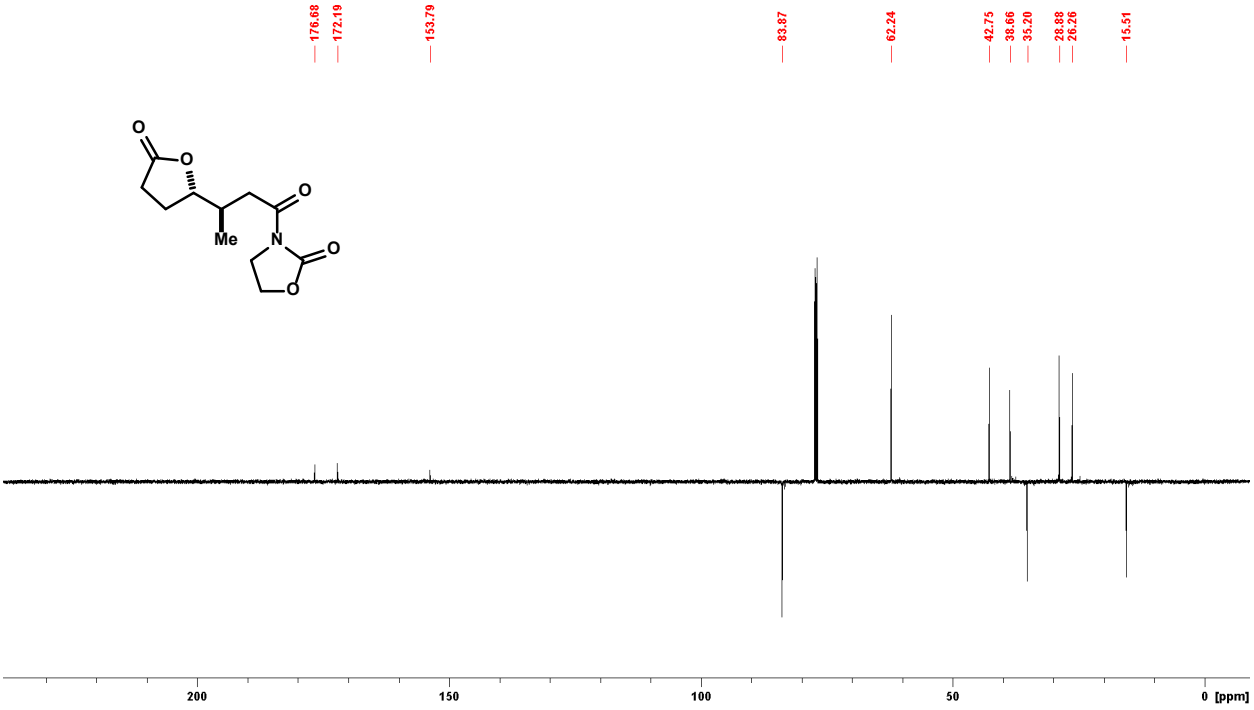
Spectrum 11. ^{1}H NMR of compound (±)-1-84 ($CDCl_3$, 500 MHz)



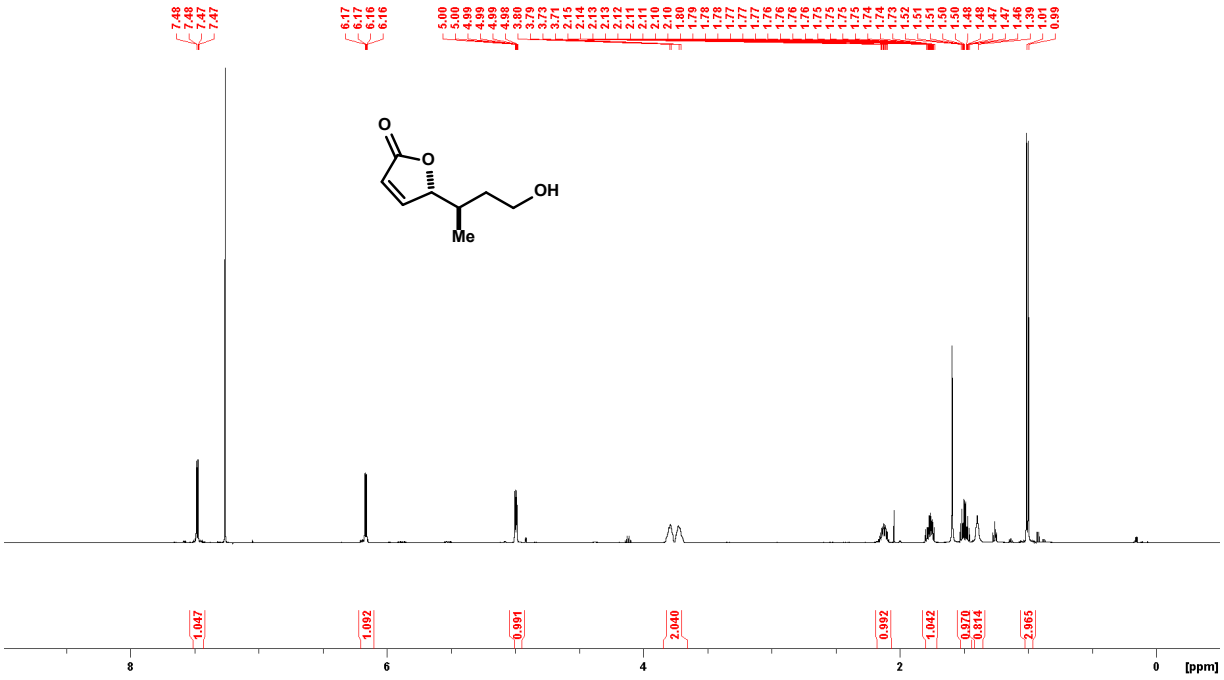
Spectrum 12. ^{13}C NMR of compound (±)-1-84 ($CDCl_3$, 125 MHz)



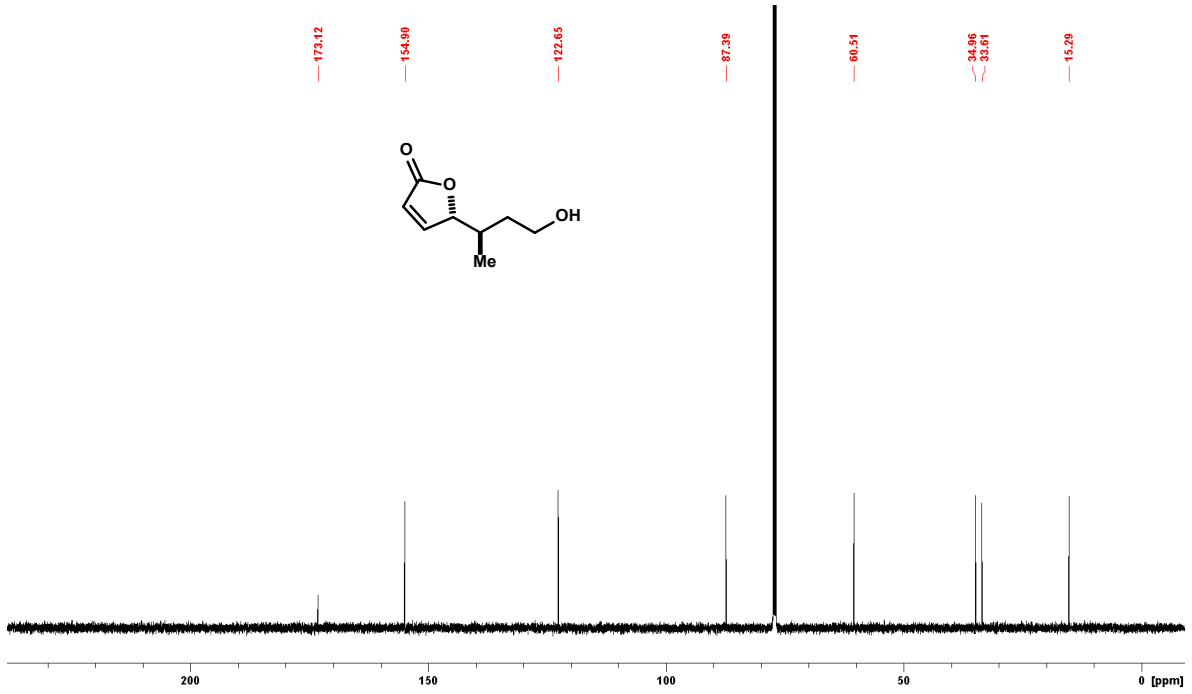
Spectrum 13. APT NMR of compound (±)-1-84 ($CDCl_3$, 125 MHz)



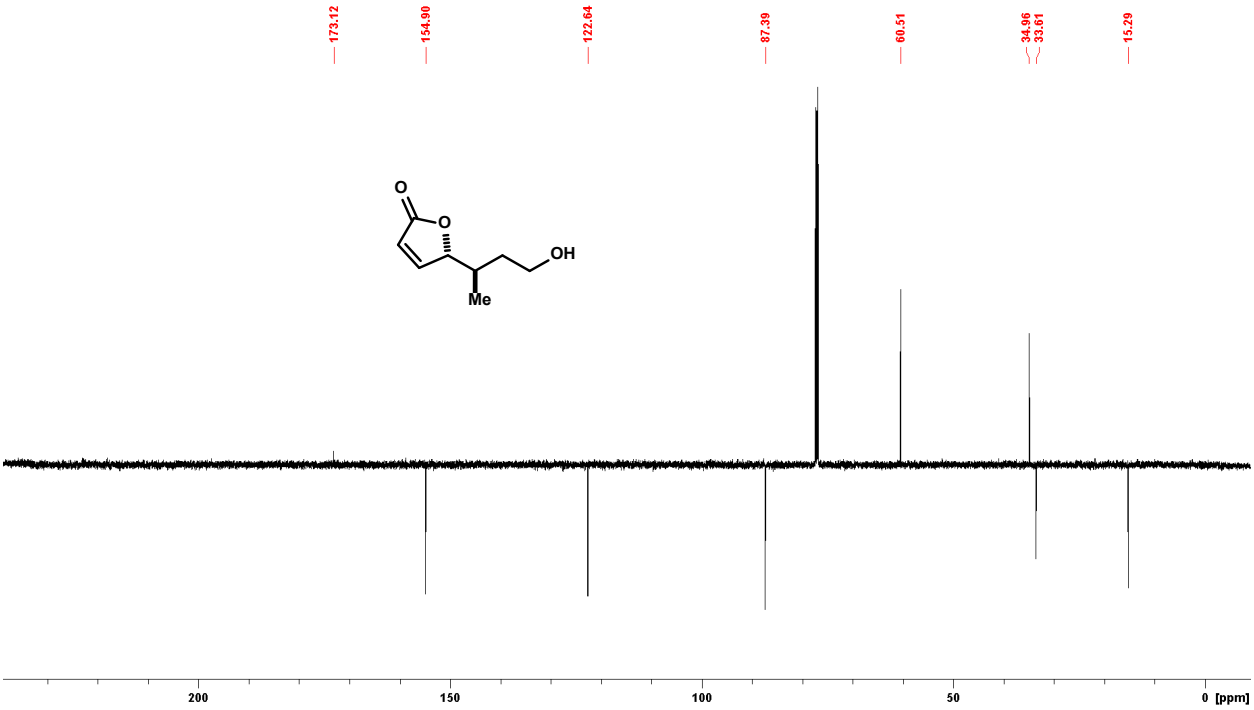
Spectrum 14. ^{1}H NMR of compound (±)-1-128 ($CDCl_3$, 500 MHz)



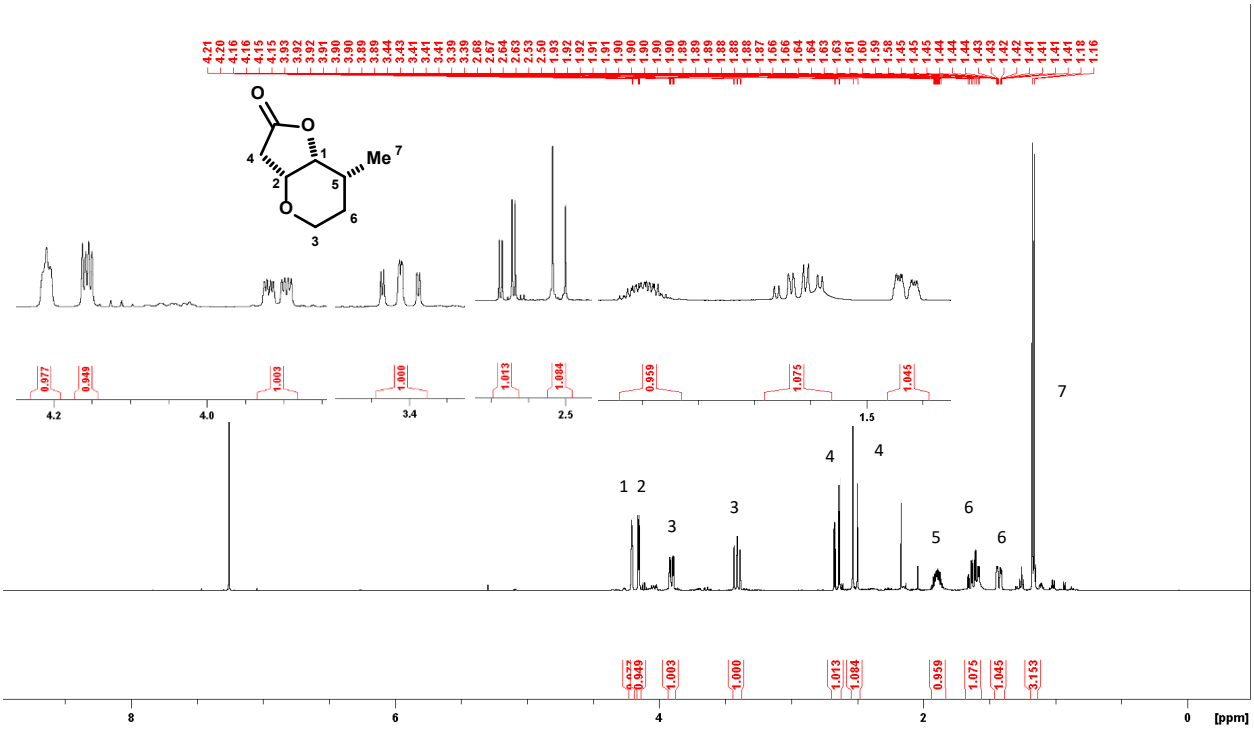
Spectrum 15. ^{13}C NMR of compound (±)-1-128 ($CDCl_3$, 125 MHz)



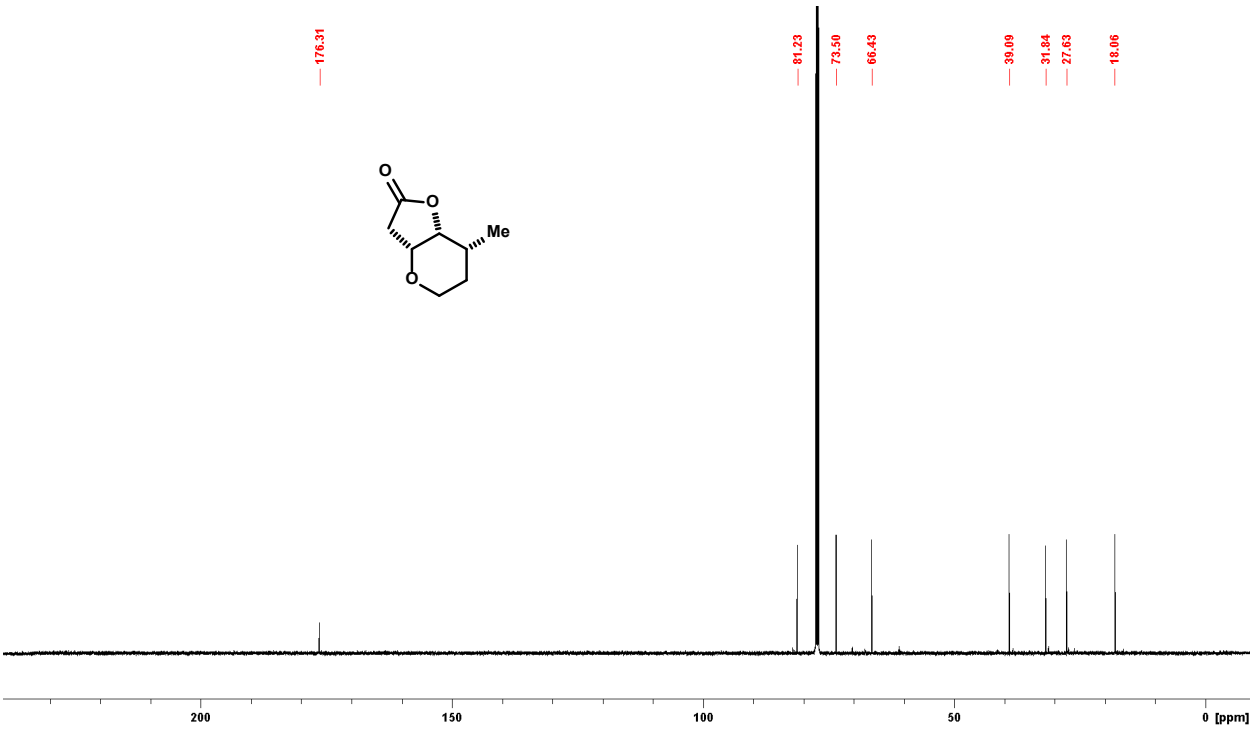
Spectrum 16. APT NMR of compound (±)-1-128 ($CDCl_3$, 125 MHz)



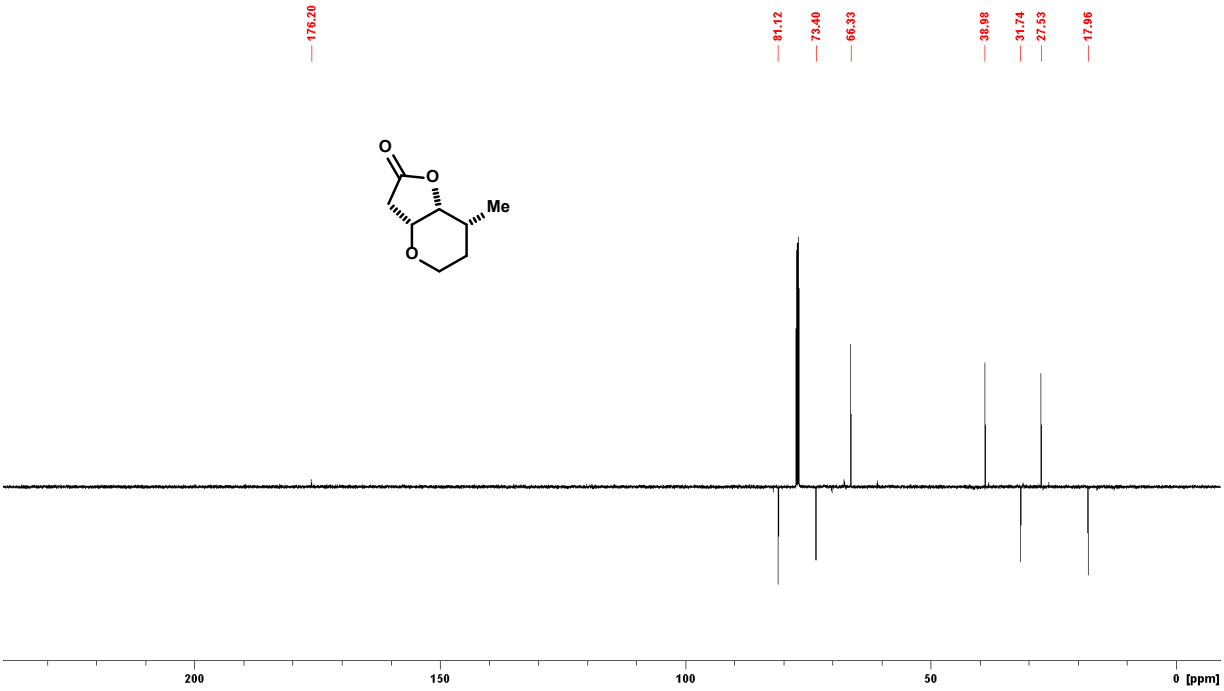
Spectrum 17. ^{1}H NMR of compound (±)-1-85 ($CDCl_3$, 500 MHz)



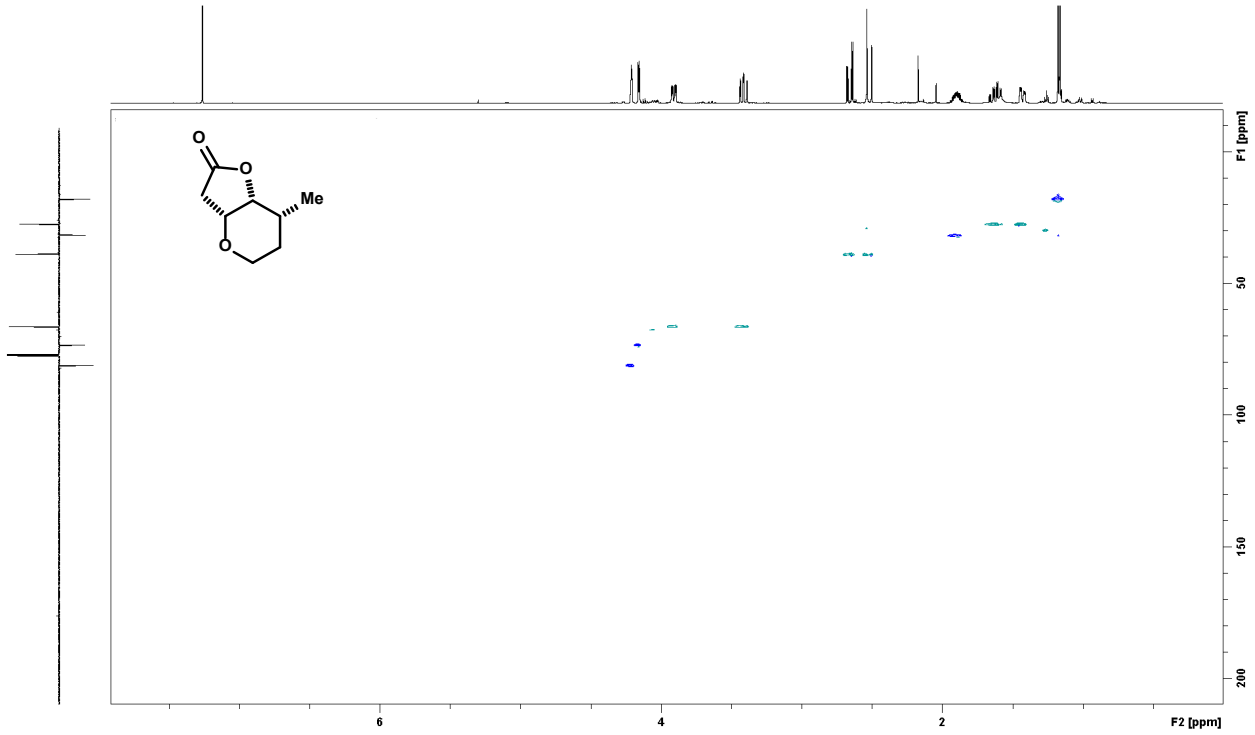
Spectrum 18. ^{13}C NMR of compound (±)-1-85 ($CDCl_3$, 125 MHz)



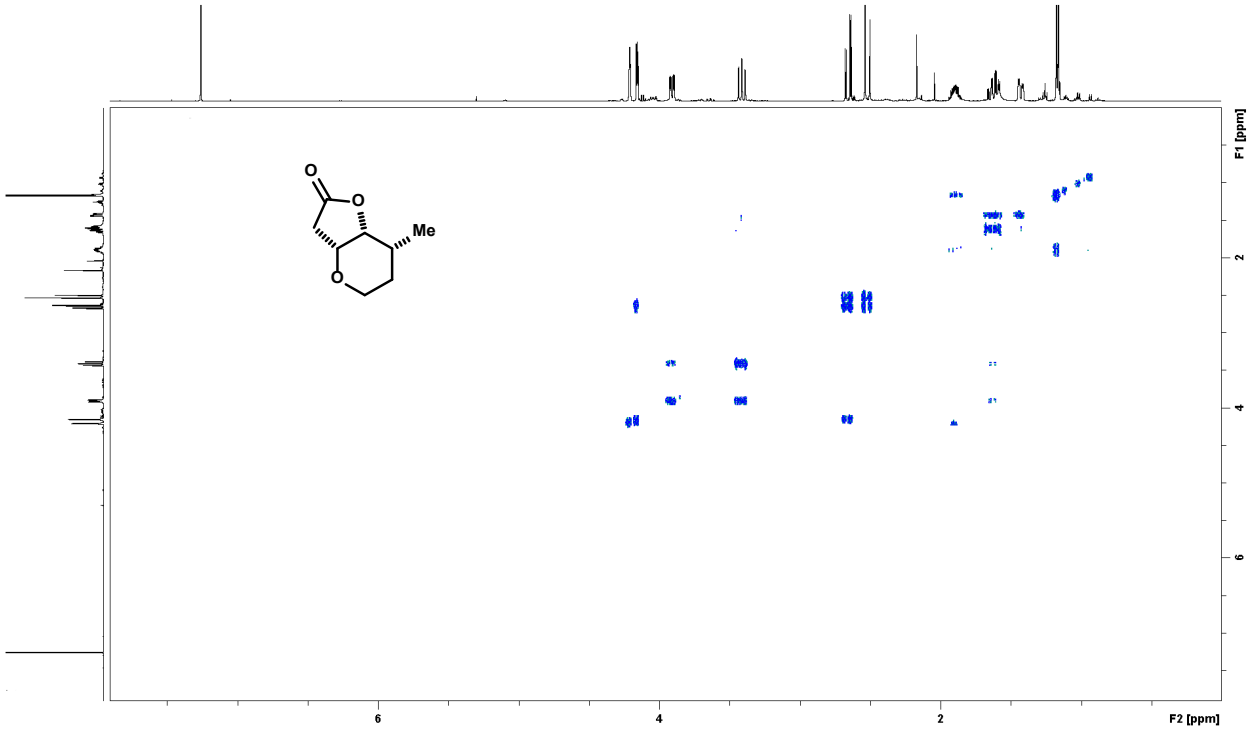
Spectrum 19. APT NMR of compound (±)-1-85 ($CDCl_3$, 125 MHz)



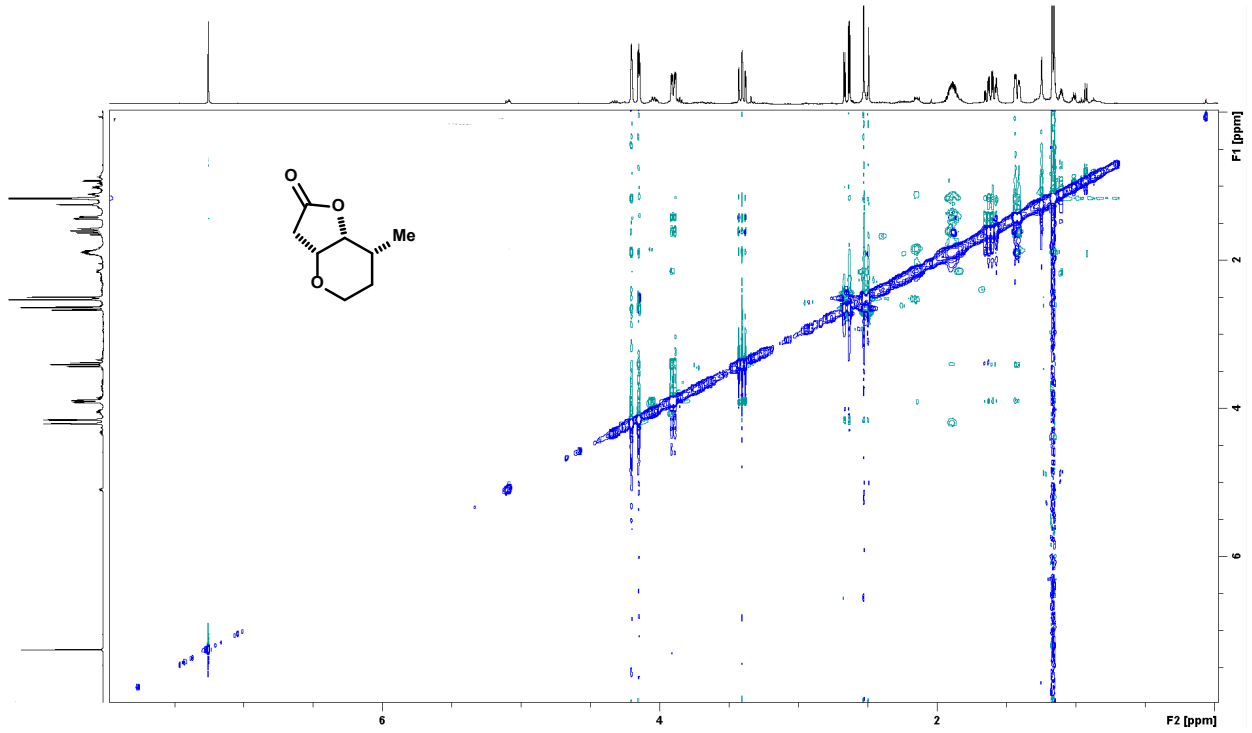
Spectrum 20. HSQC spectrum of compound (±)-1-85 ($CDCl_3$, 400 MHz)



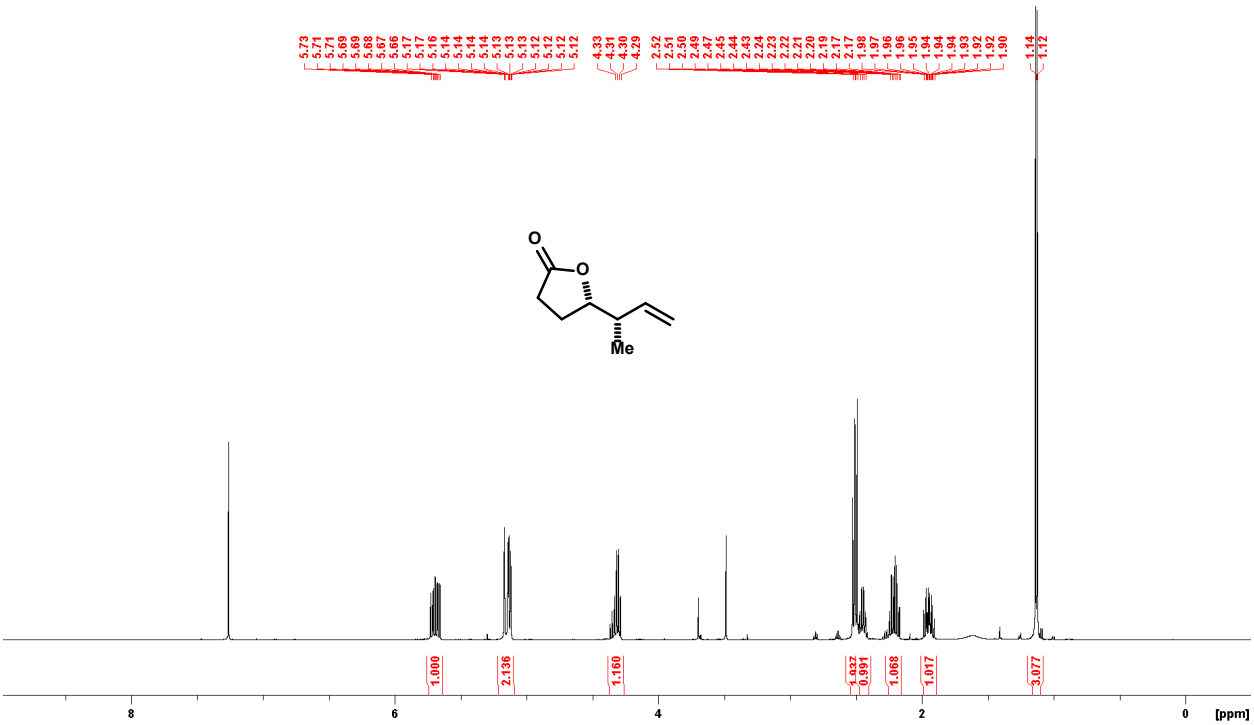
Spectrum 21. COSY spectrum of compound (±)-1-85 ($CDCl_3$, 400 MHz)



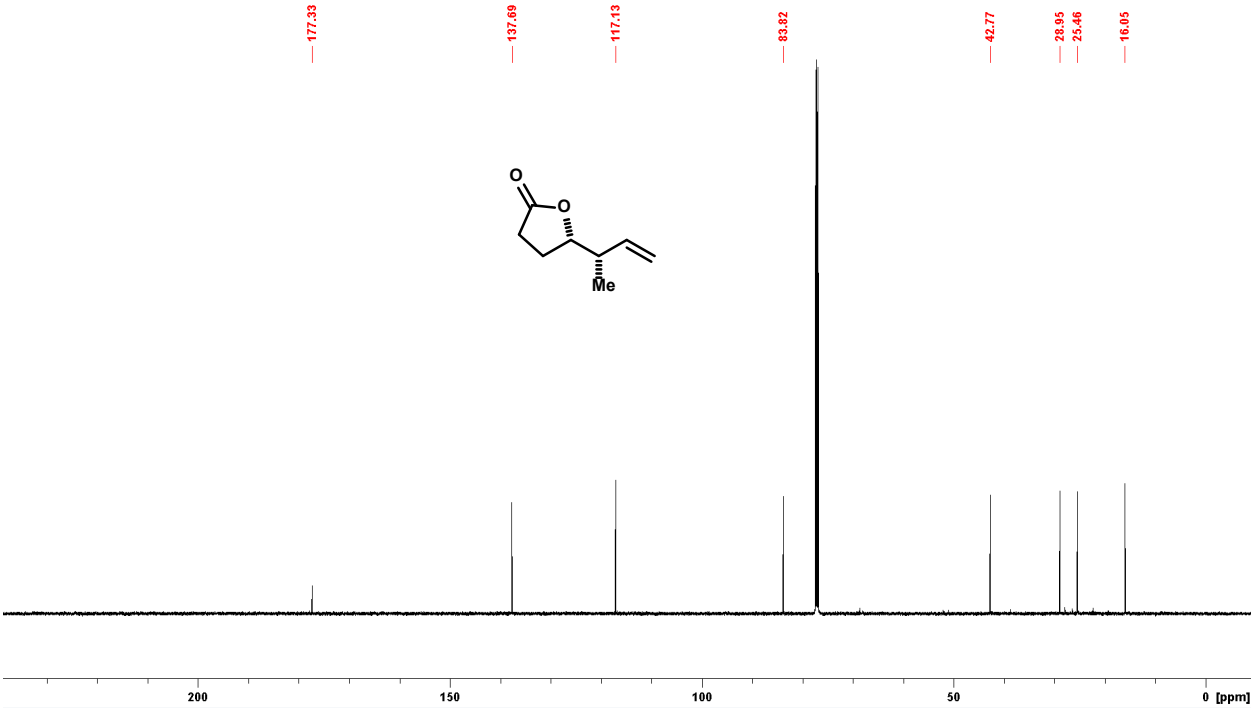
Spectrum 22. NOESY spectrum of compound (±)-1-85 ($CDCl_3$, 500 MHz)



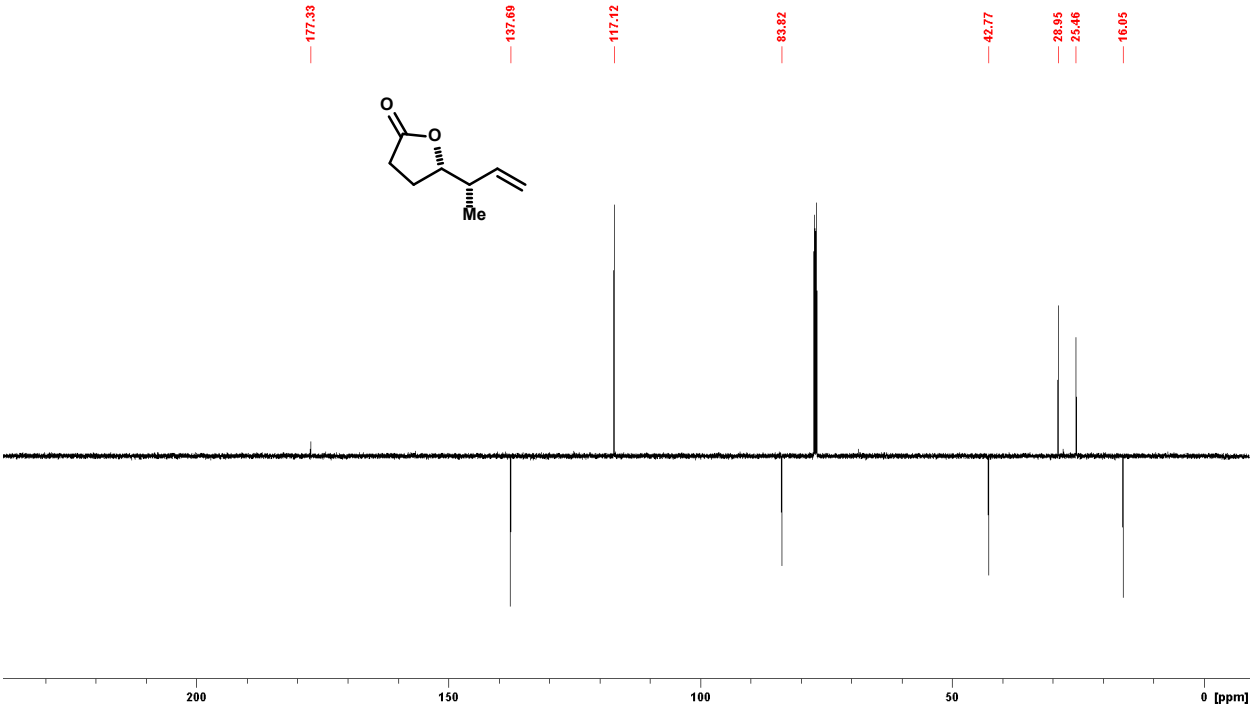
Spectrum 23. ^{1}H NMR of compound 1-86 ($CDCl_3$, 500 MHz)



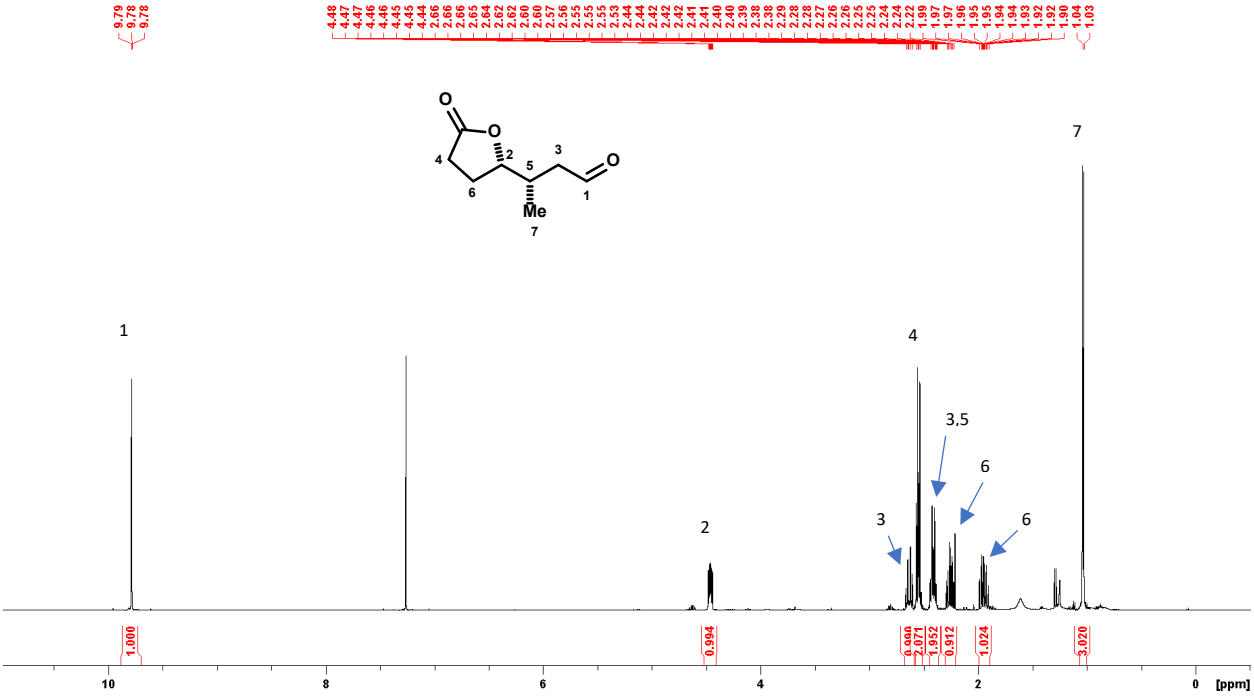
Spectrum 24. ^{13}C NMR of compound 1-86 ($CDCl_3$, 125 MHz)



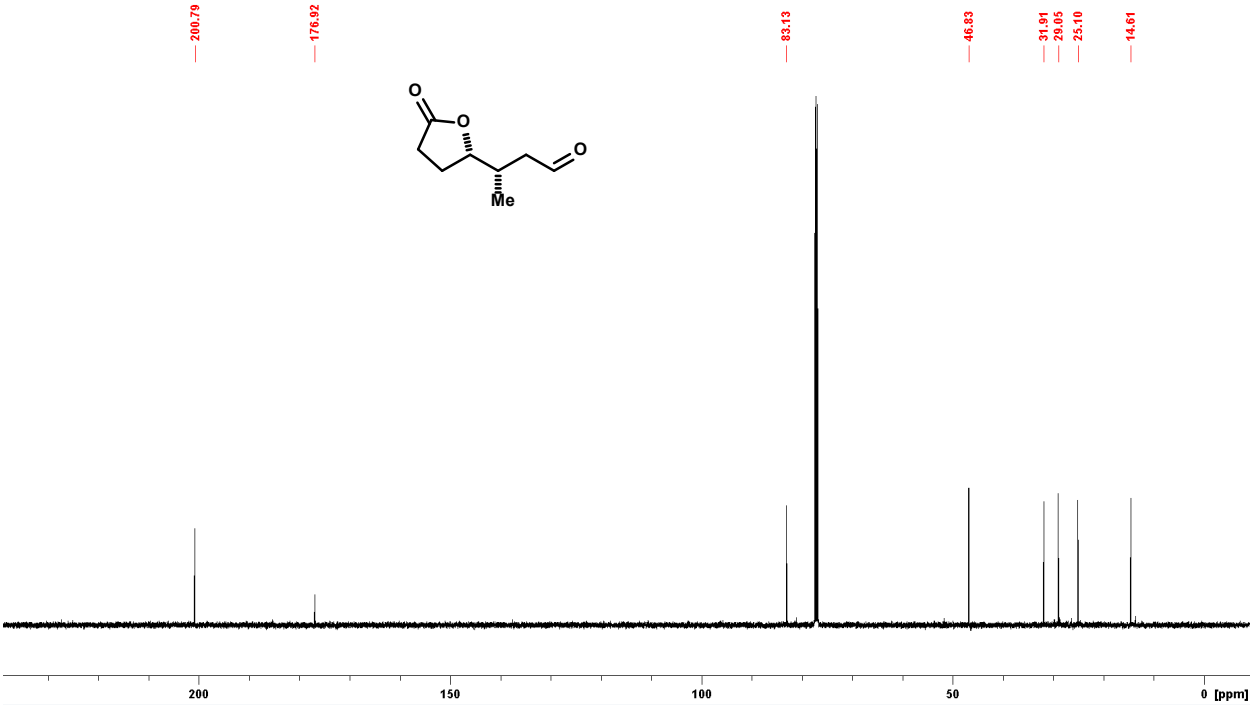
Spectrum 25. APT NMR of compound 1-86 ($CDCl_3$, 125 MHz)



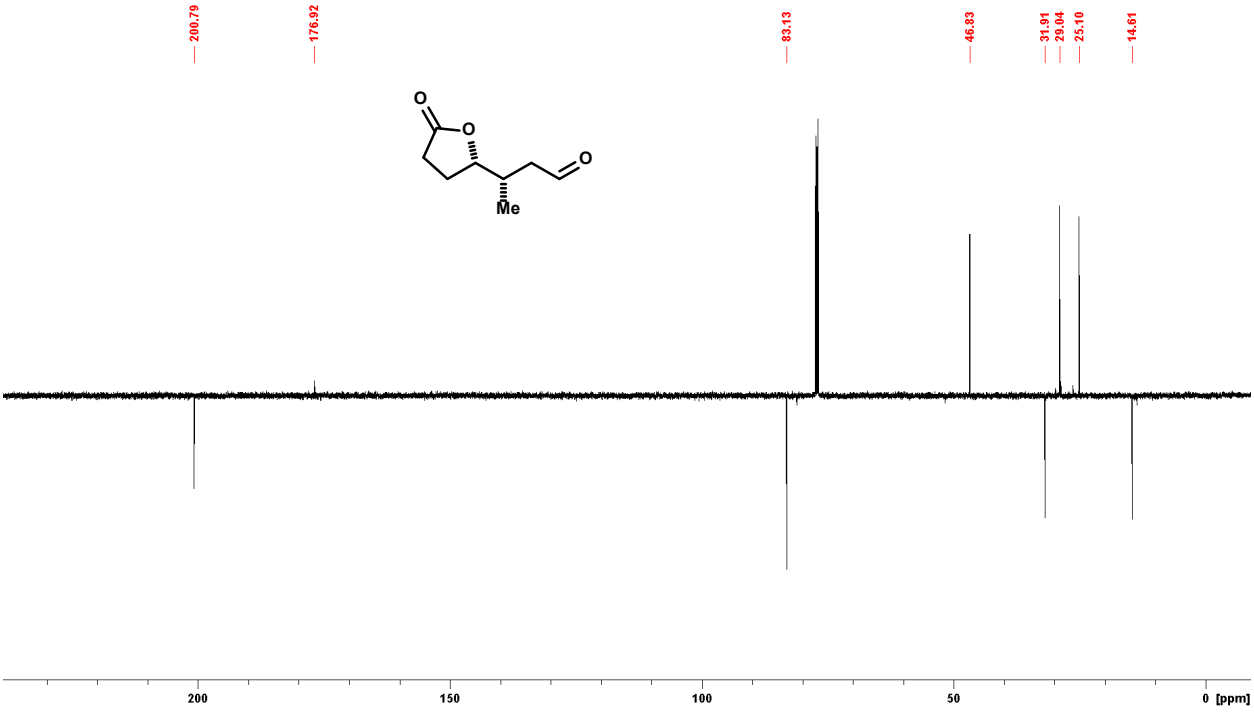
Spectrum 26. ^{1}H NMR of compound 1-79 (synthesized from 1-82) ($CDCl_3$, 500 MHz)



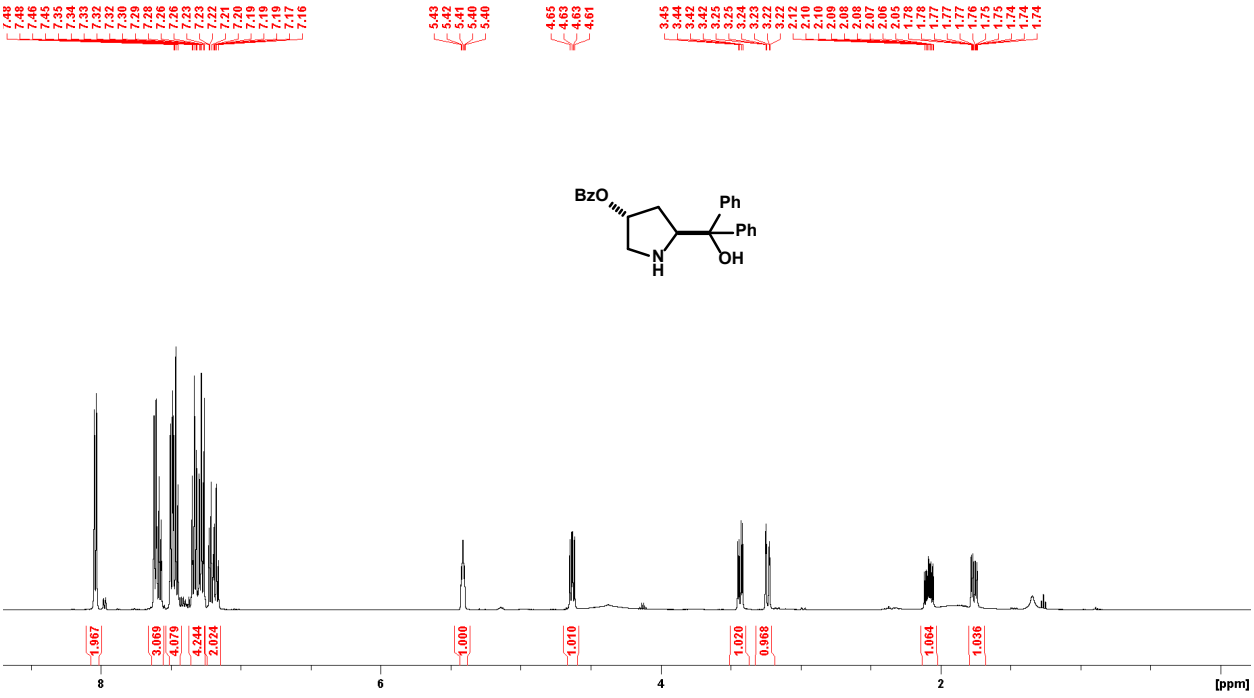
Spectrum 27. ^{13}C NMR of compound 1-79 (synthesized from 1-82) ($CDCl_3$, 125 MHz)



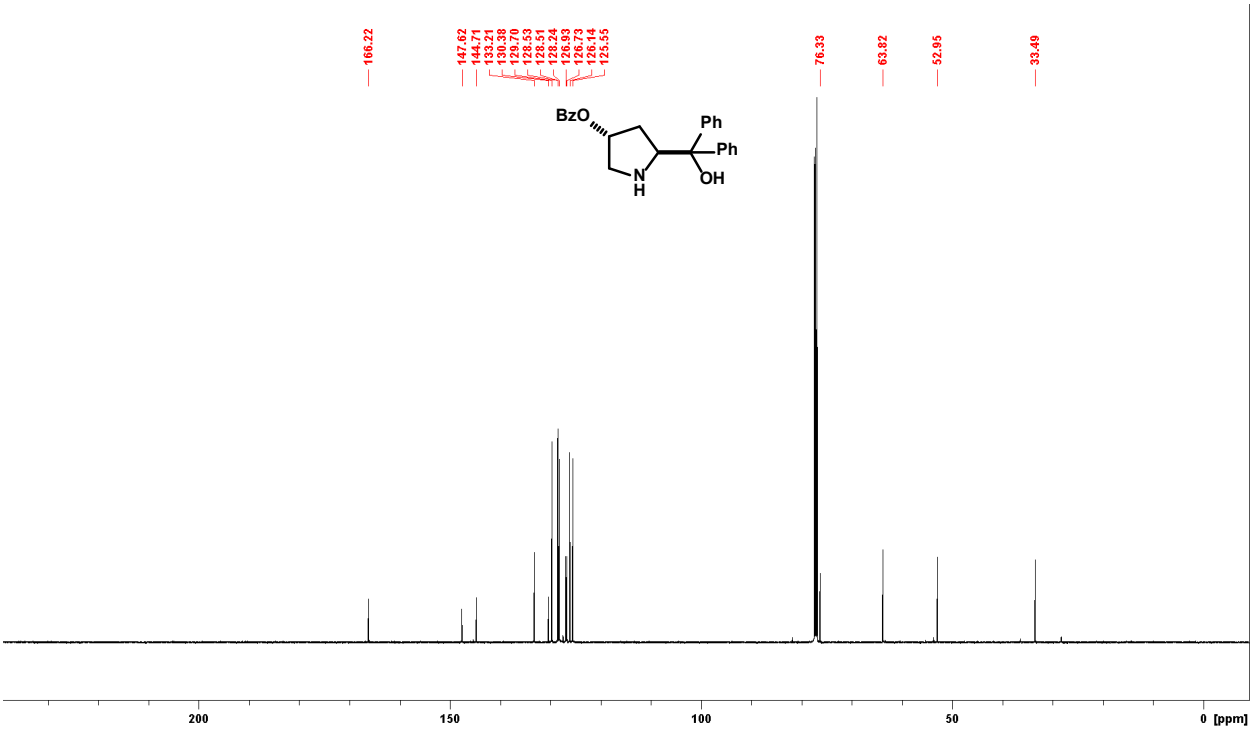
Spectrum 28. APT NMR of compound 1-79 (synthesized from 1-82) ($CDCl_3$, 125 MHz)



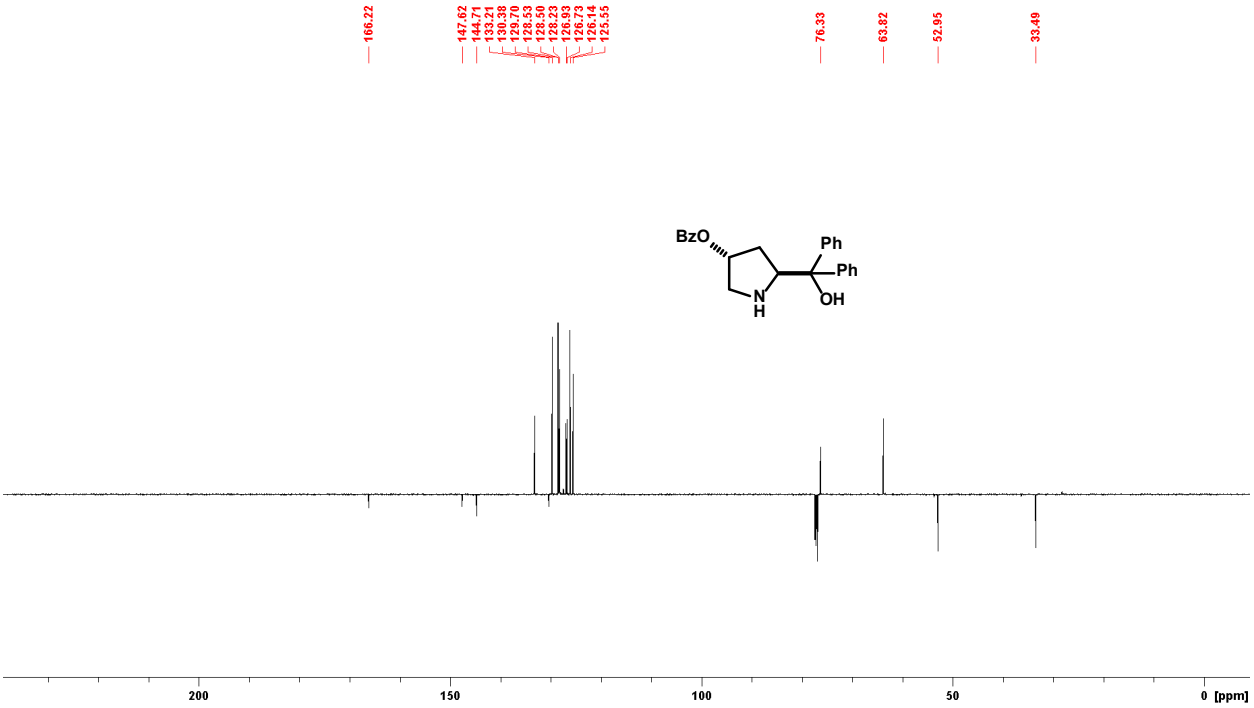
Spectrum 29. ^{1}H NMR of compound 1-88a ($CDCl_3$, 500 MHz)



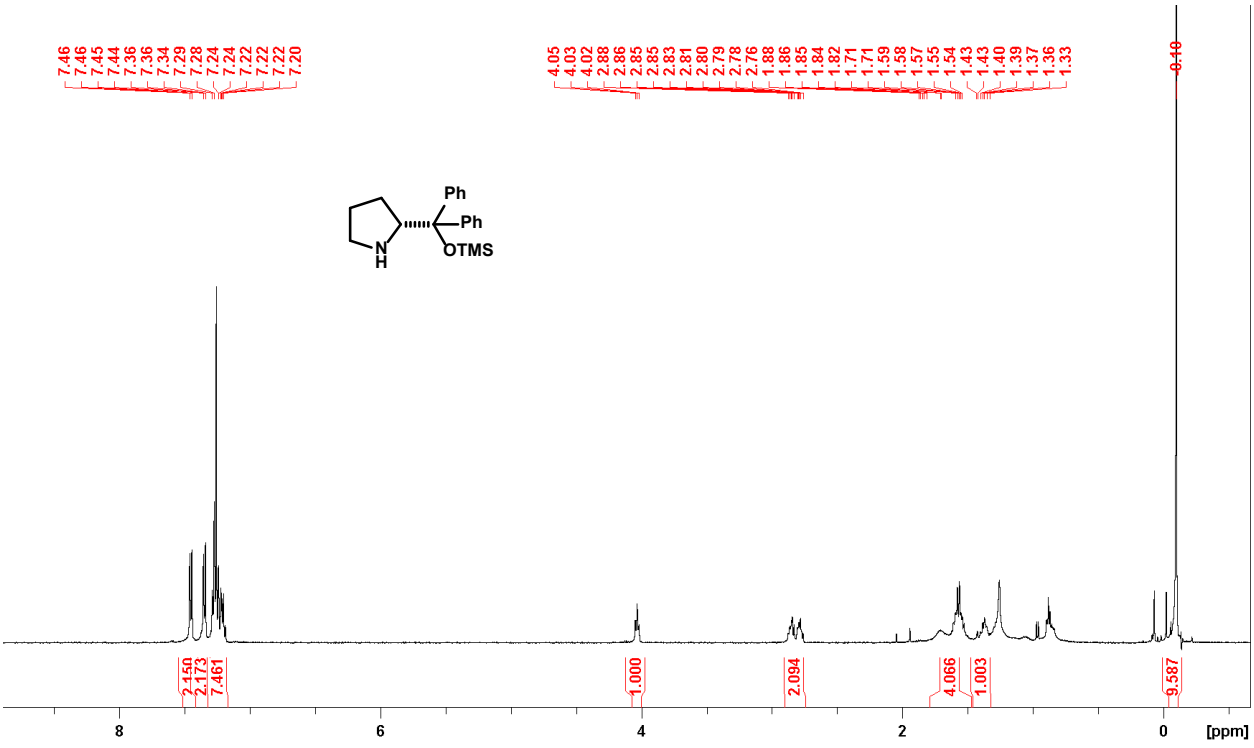
Spectrum 30. ^{13}C NMR of compound 1-88a ($CDCl_3$, 125 MHz)



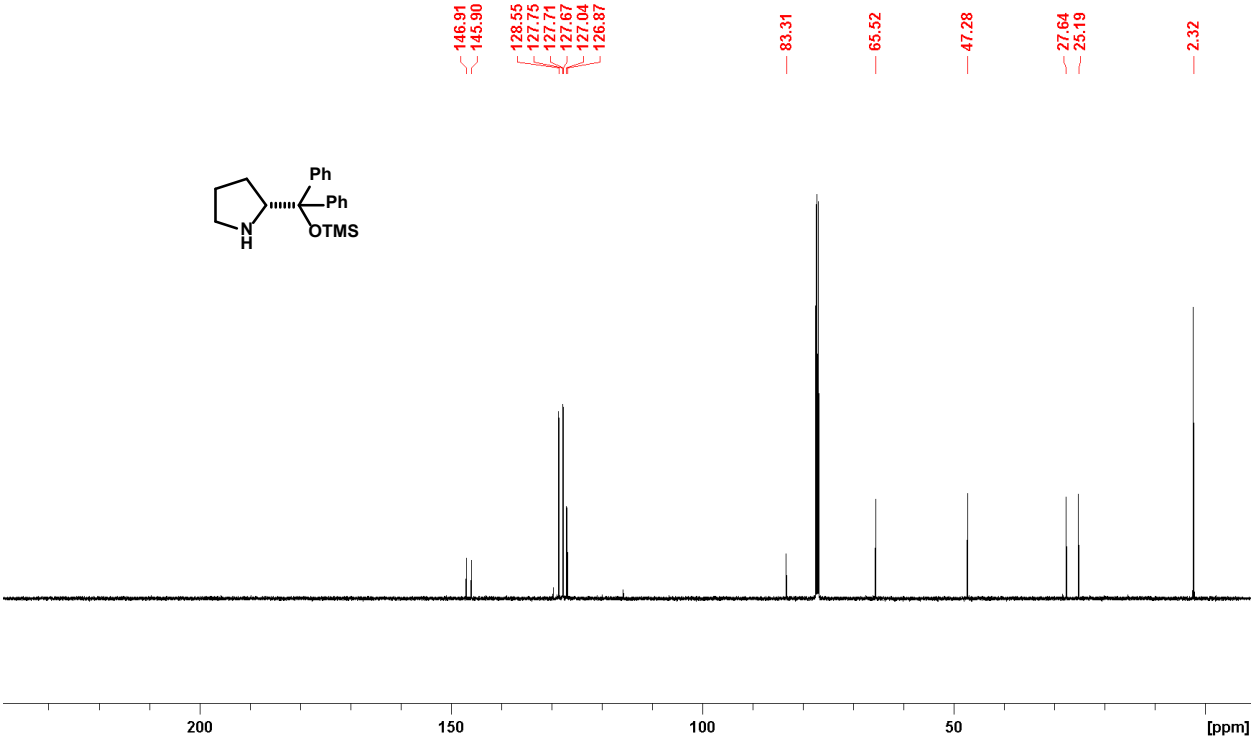
Spectrum 31. APT NMR of compound 1-88a ($CDCl_3$, 125 MHz)



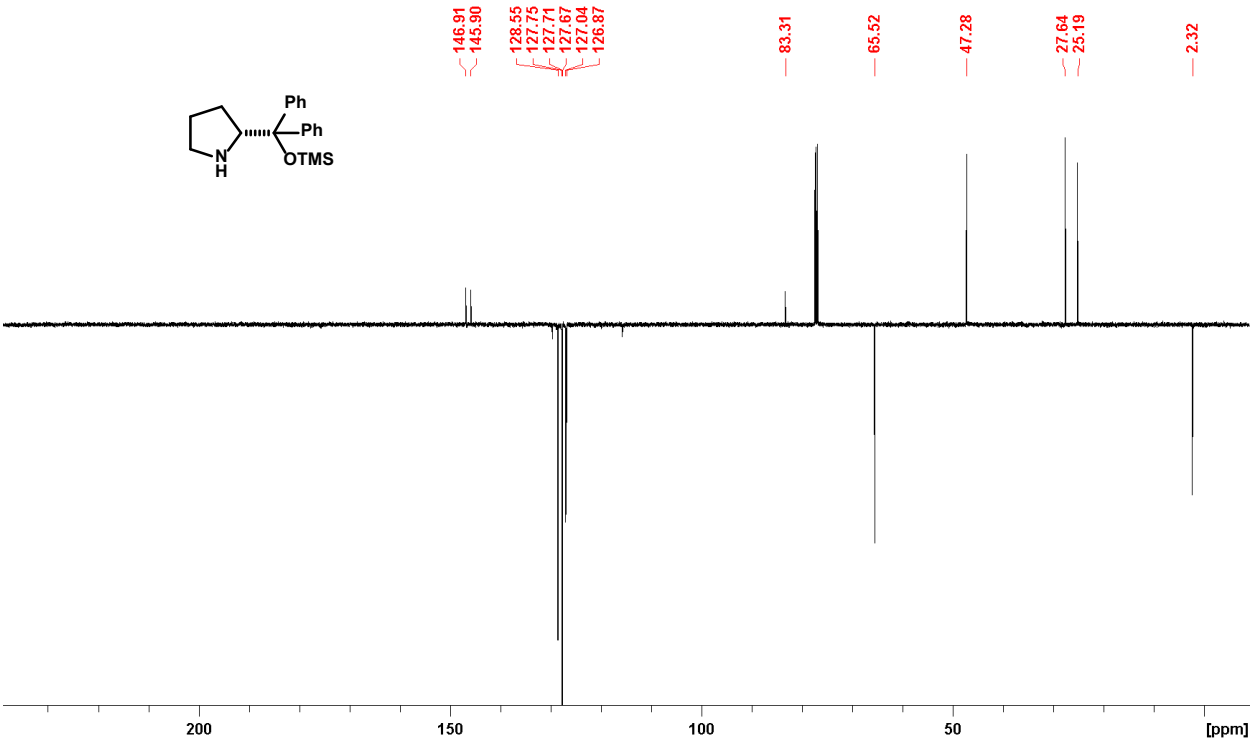
Spectrum 32. ^{1}H NMR of compound 1-89b ($CDCl_3$, 500 MHz)



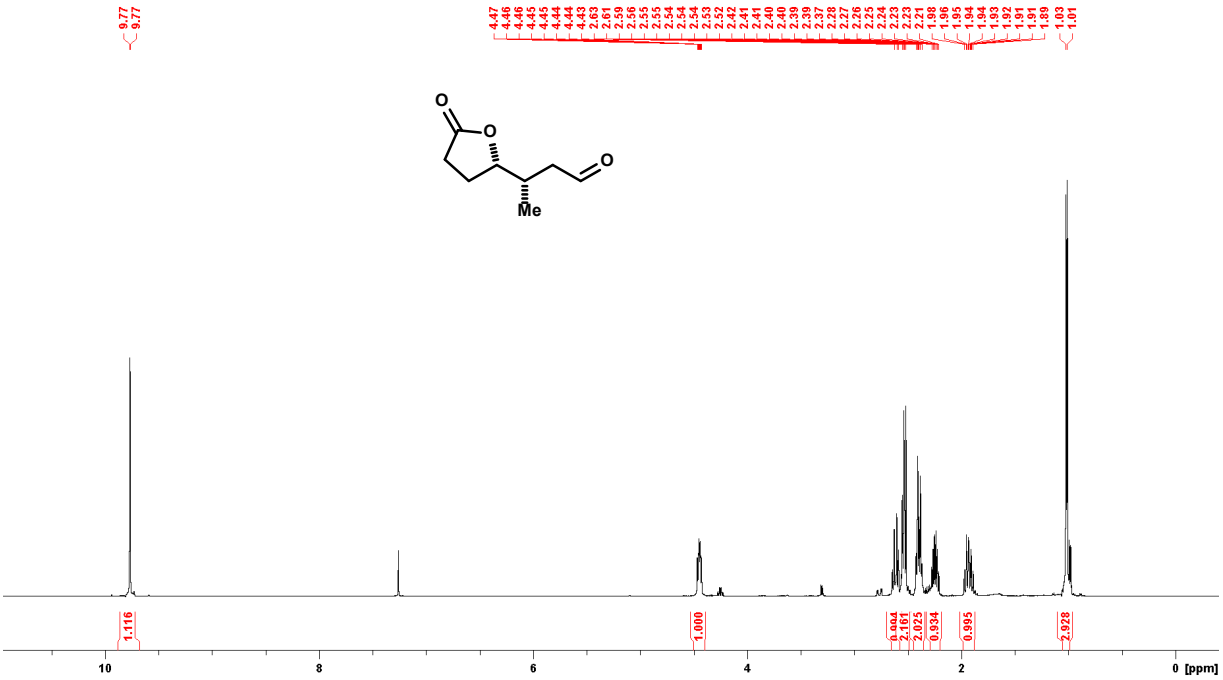
Spectrum 33. ^{13}C NMR of compound 1-89b ($CDCl_3$, 125 MHz)



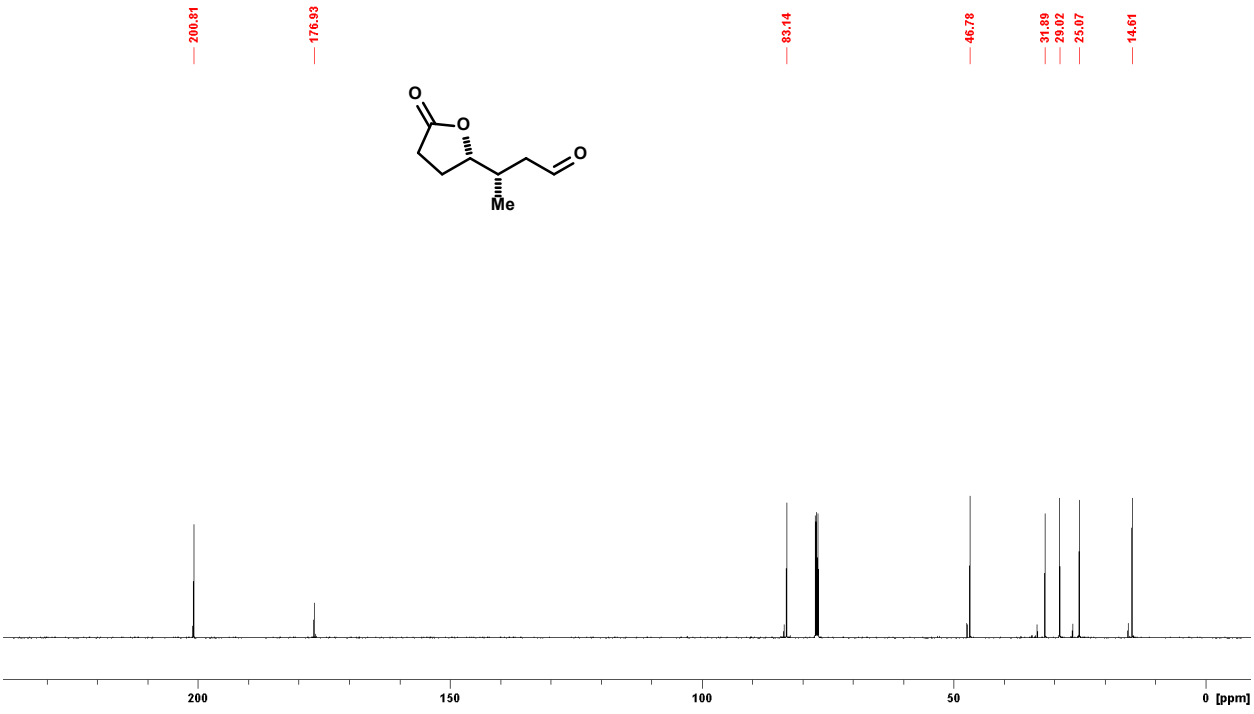
Spectrum 34. APT NMR of compound 1-89b ($CDCl_3$, 125 MHz)



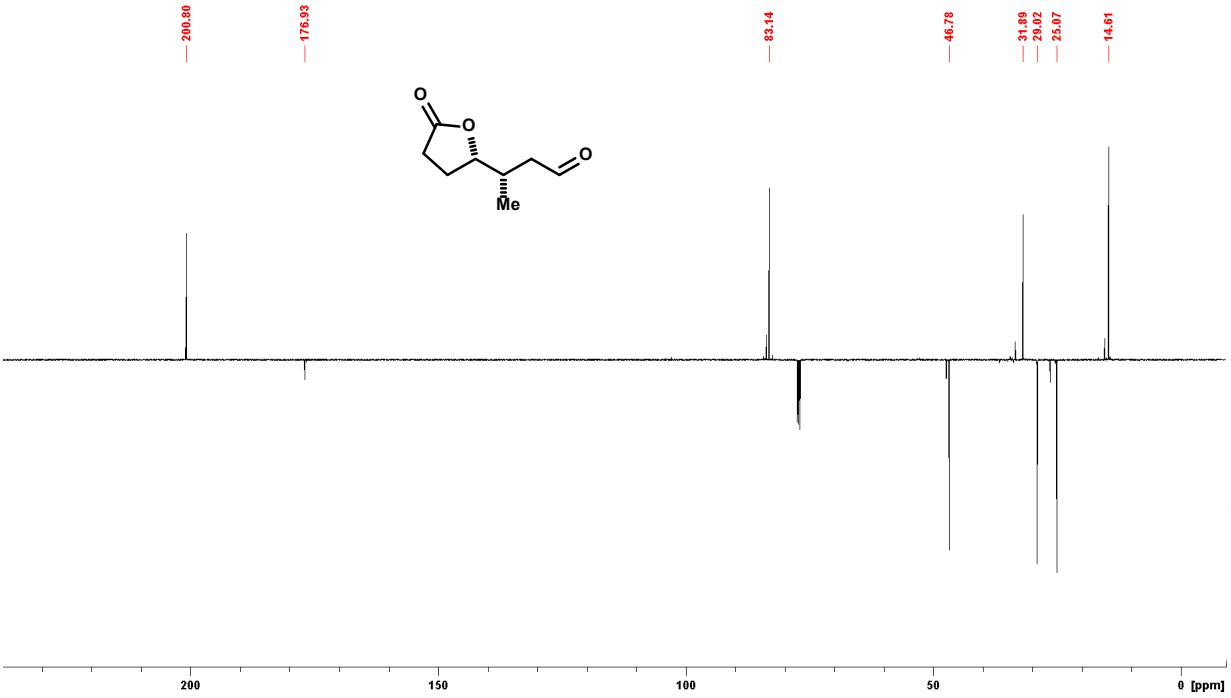
Spectrum 35. ^{1}H NMR of compound 1-79 (synthesized from (3*S*, 5*R*)-1-81) ($CDCl_3$, 500 MHz)



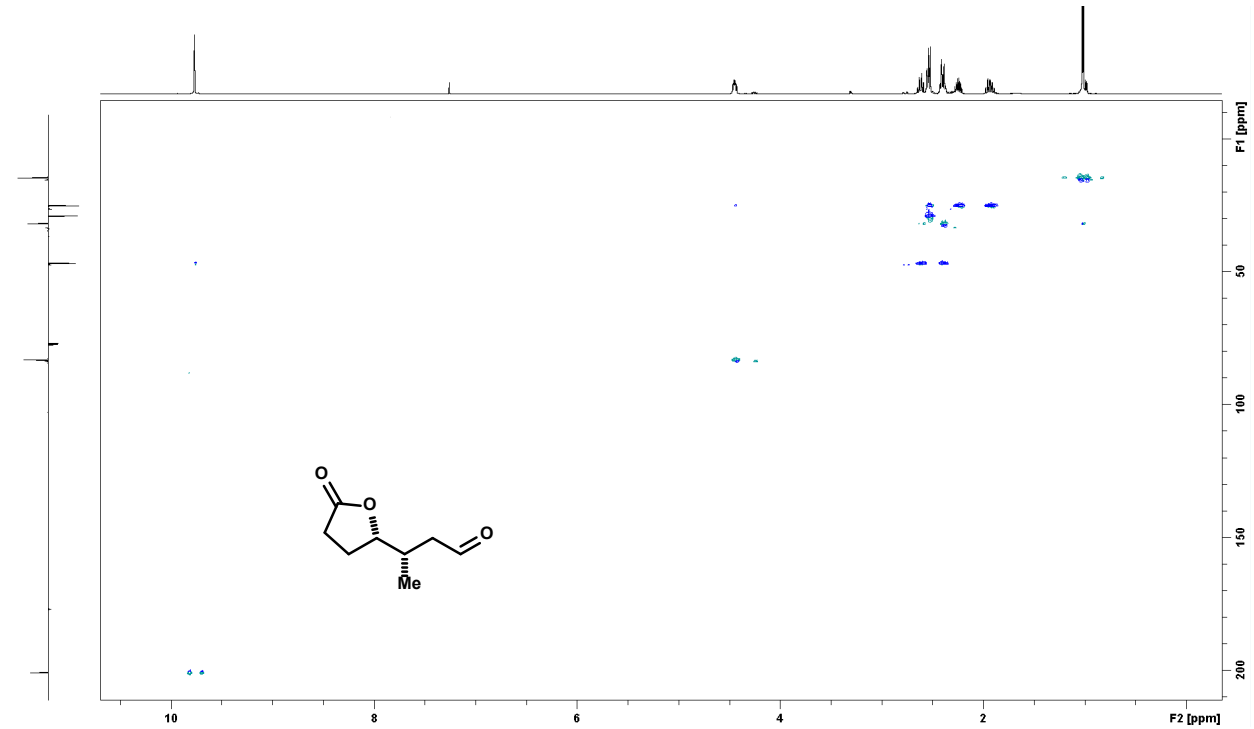
Spectrum 36. ^{13}C NMR of compound 1-79 (synthesized from (3*S*, 5*R*)-1-81) ($CDCl_3$, 125 MHz)



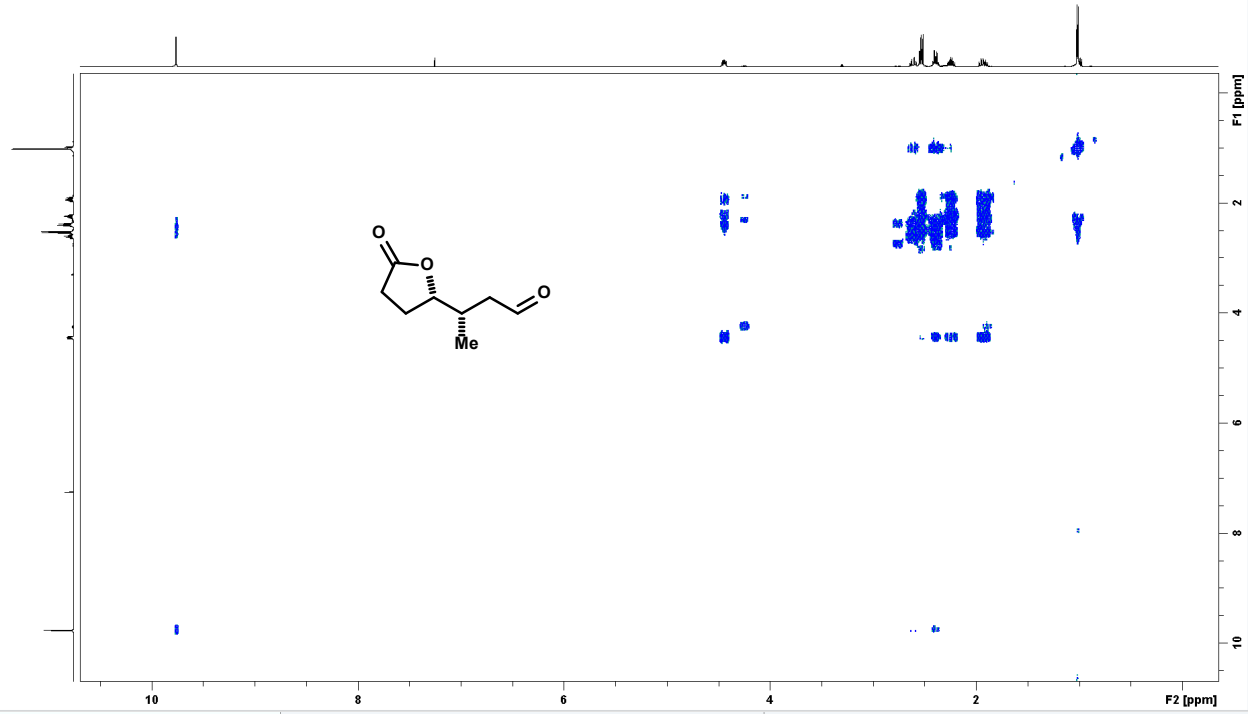
Spectrum 37. APT NMR of compound 1-79 (synthesized from (3*S*, 5*R*)-1-81) ($CDCl_3$, 125 MHz)



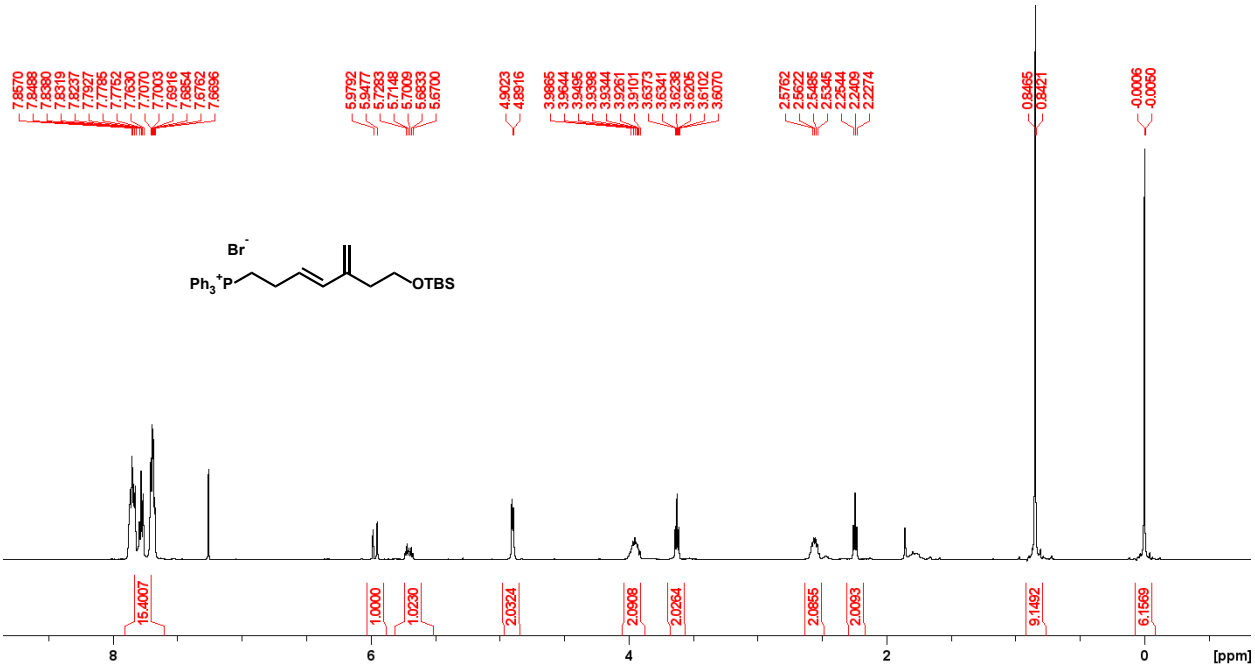
Spectrum 38. HSQC spectrum of compound 1-79 (synthesized from (3*S*, 5*R*)-1-81) ($CDCl_3$, 400 MHz)



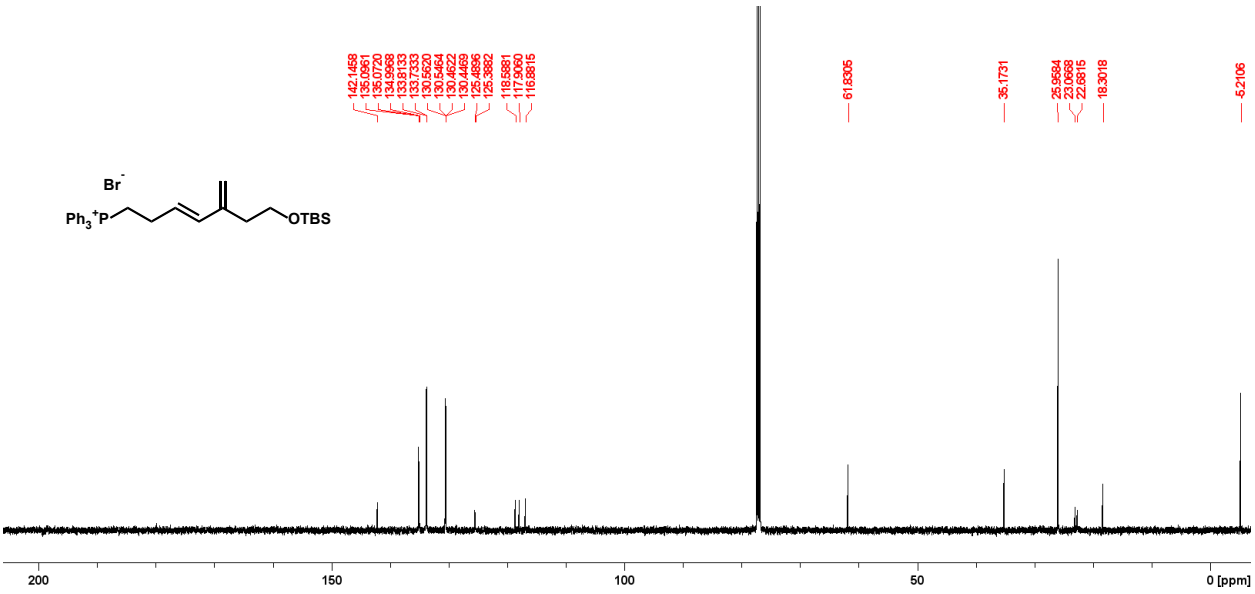
Spectrum 39. COSY spectrum of compound 1-79 (synthesized from (3*S*, 5*R*)-1-81) ($CDCl_3$, 400 MHz)



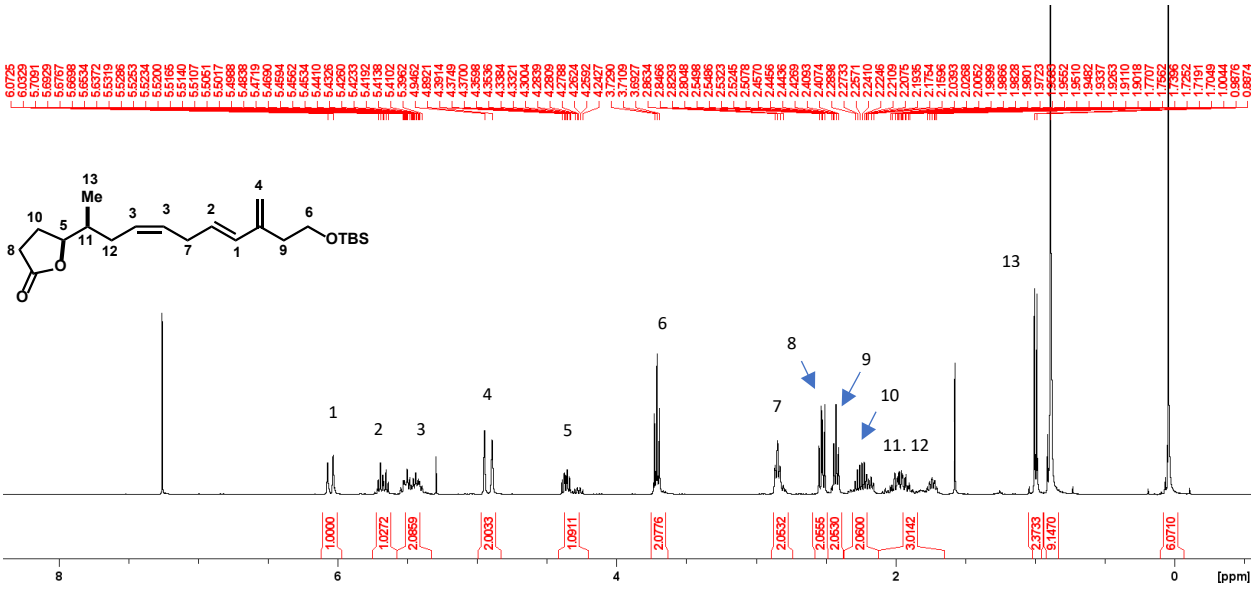
Spectrum 40. ^{1}H NMR of compound 1-93 ($CDCl_3$, 500 MHz)



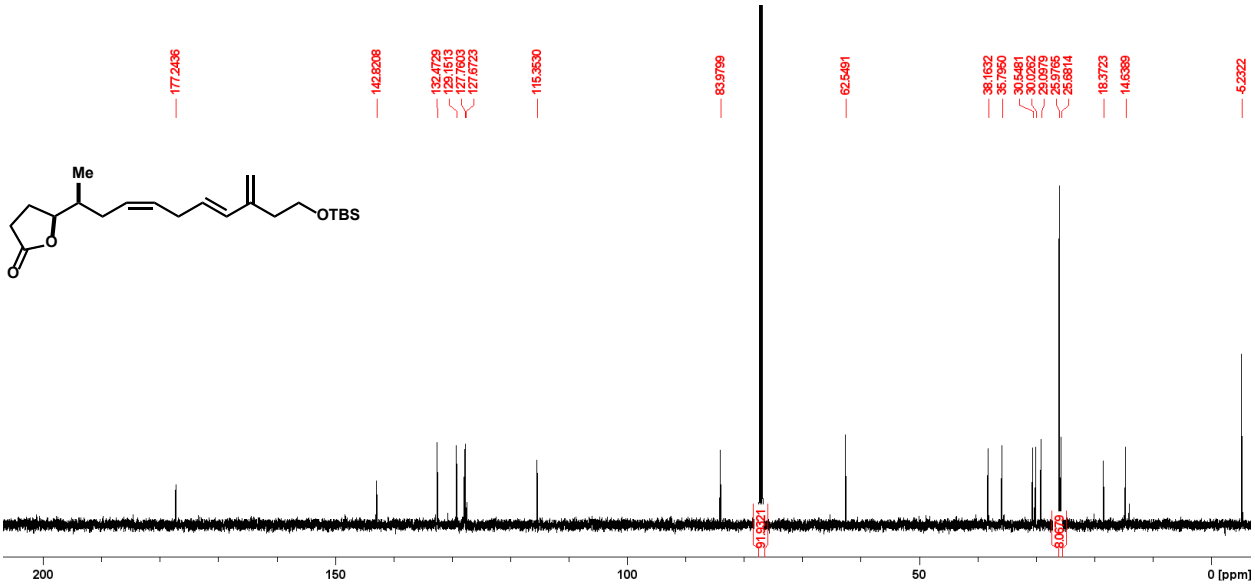
Spectrum 41. ^{13}C NMR of compound 1-93 ($CDCl_3$, 125 MHz)



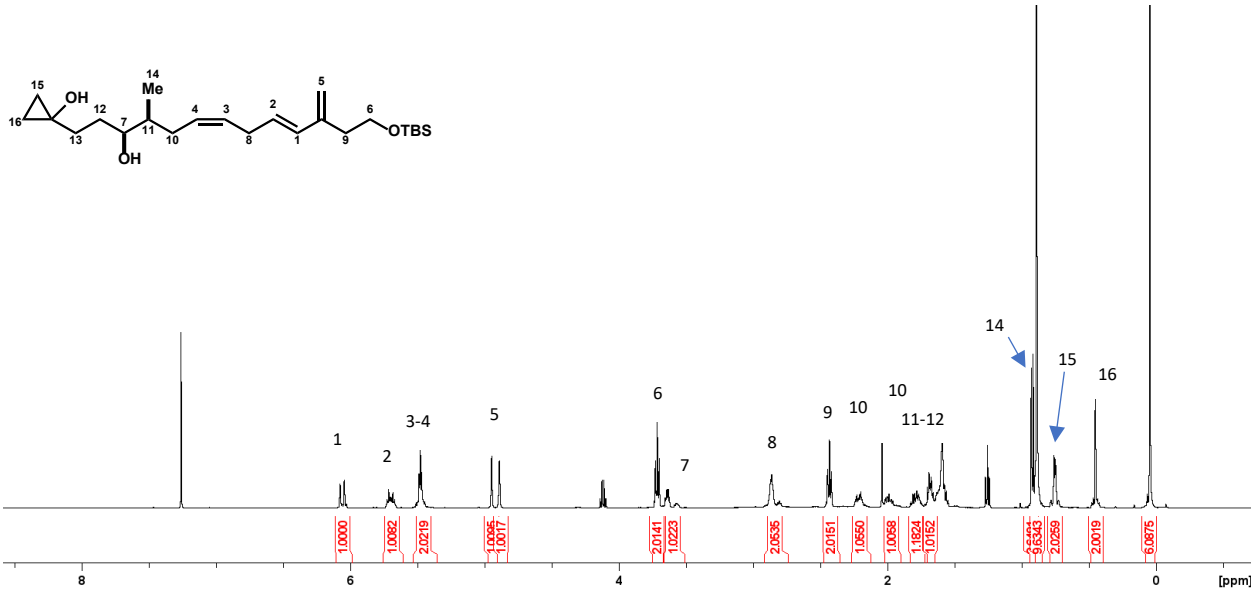
Spectrum 42. ^{1}H NMR of compound 1-94 ($CDCl_3$, 500 MHz)



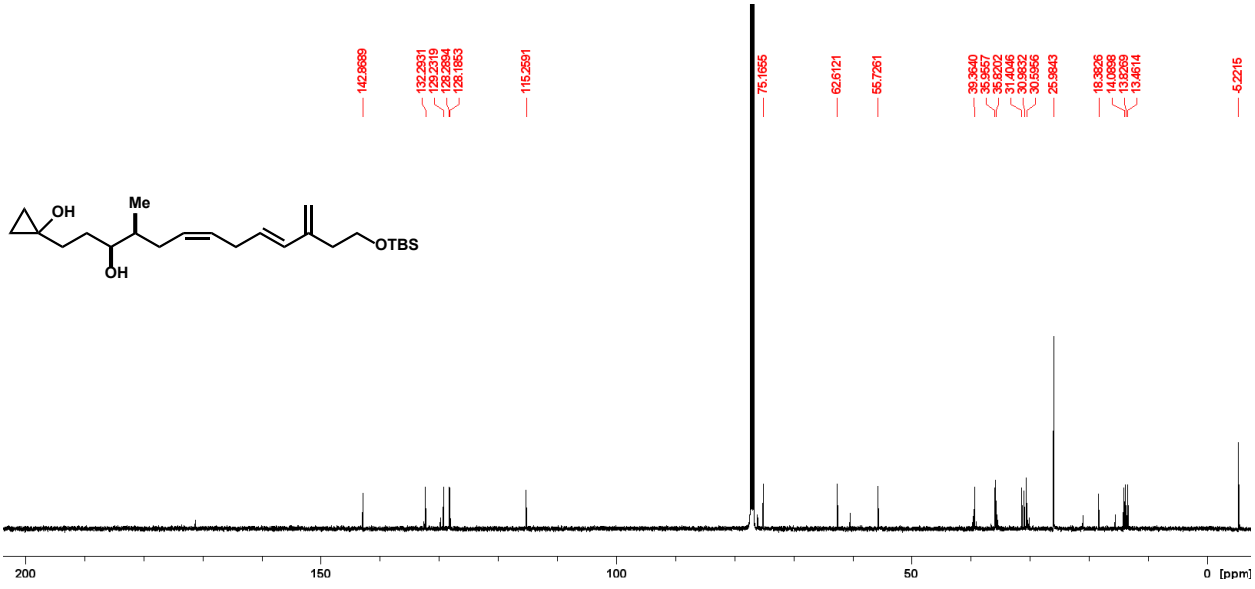
Spectrum 43. ^{13}C NMR of compound 1-94 ($CDCl_3$, 125 MHz)



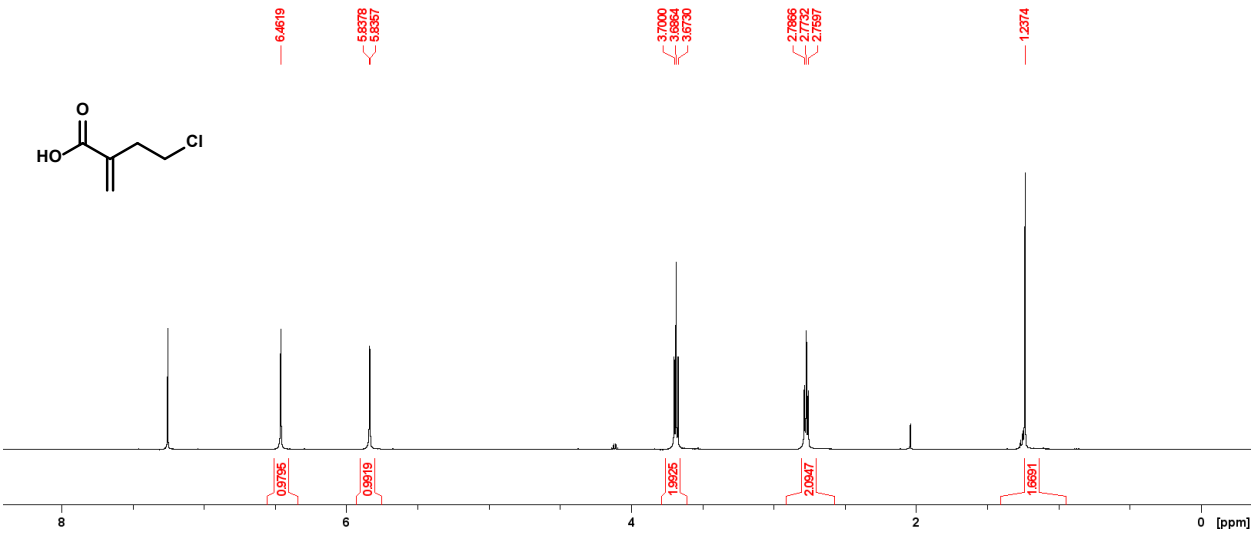
Spectrum 44. ^{1}H NMR of compound 1-95 ($CDCl_3$, 500 MHz)



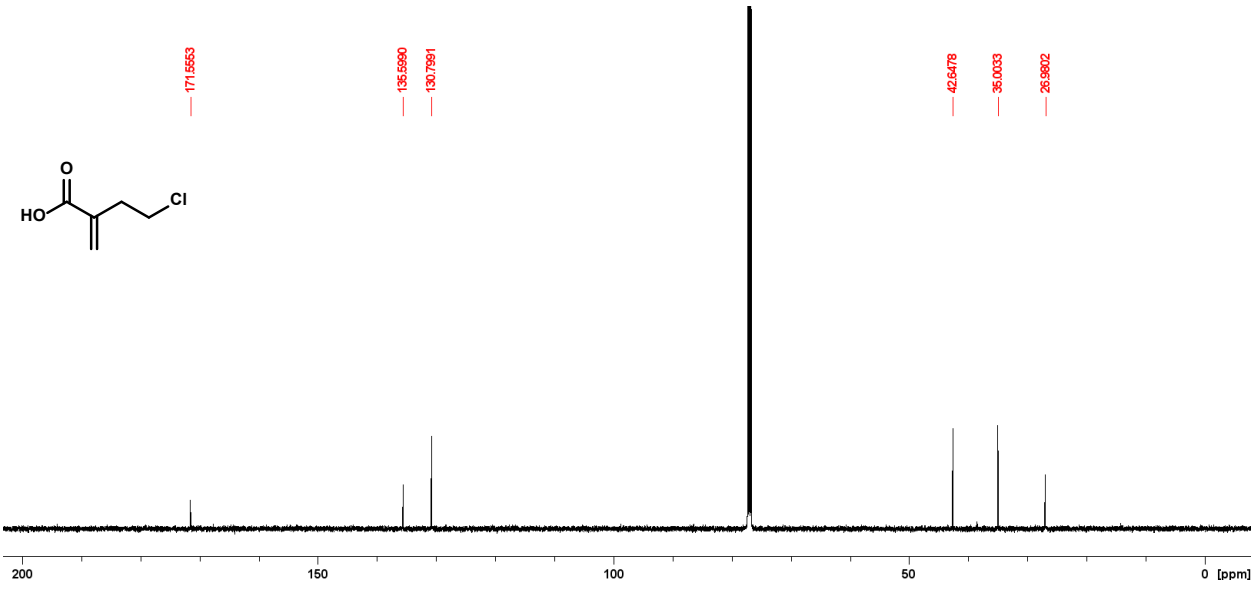
Spectrum 45. ^{13}C NMR of compound 1-95 ($CDCl_3$, 125 MHz)



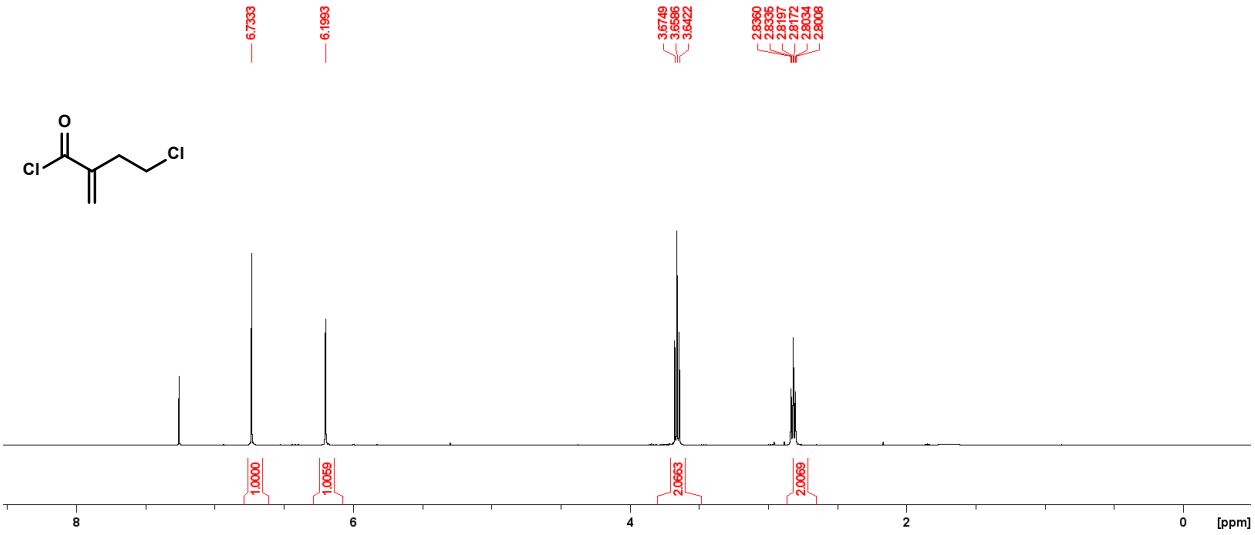
Spectrum 46. ^{1}H NMR of compound 1-139 ($CDCl_3$, 500 MHz)



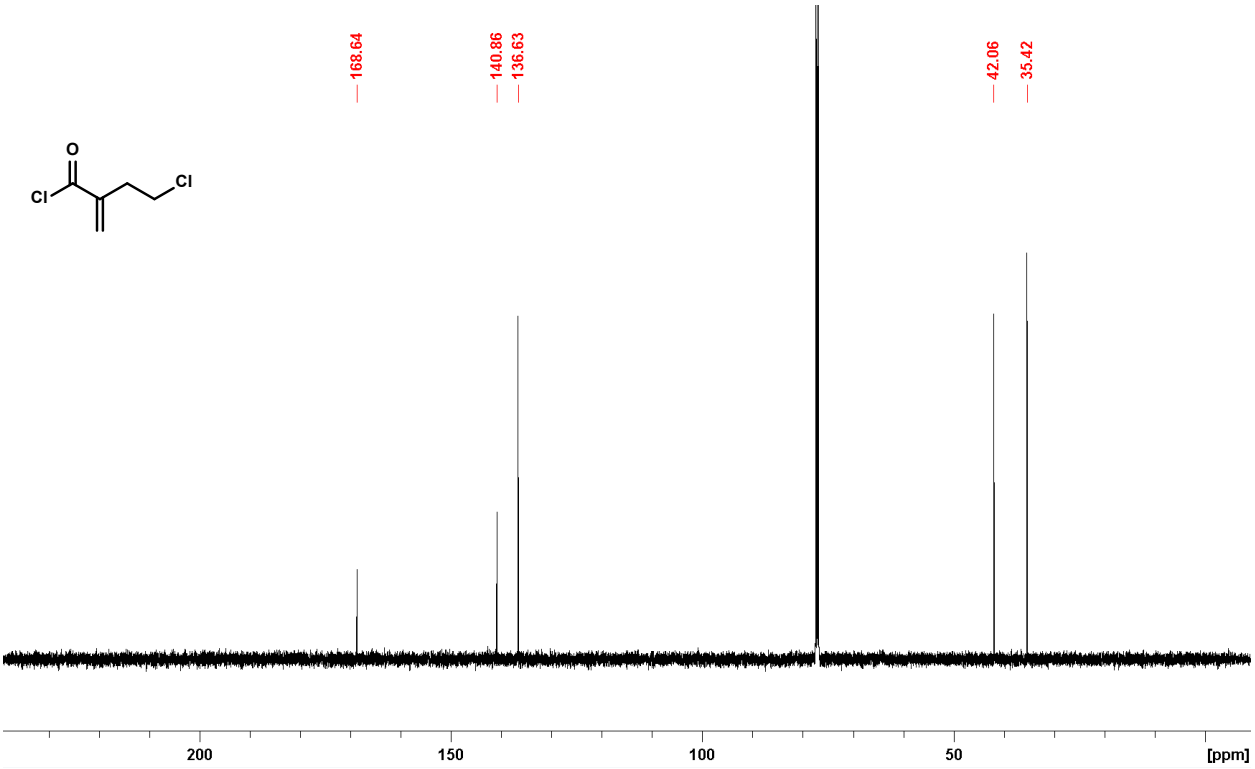
Spectrum 47. ^{13}C NMR of compound 1-139 ($CDCl_3$, 125 MHz)



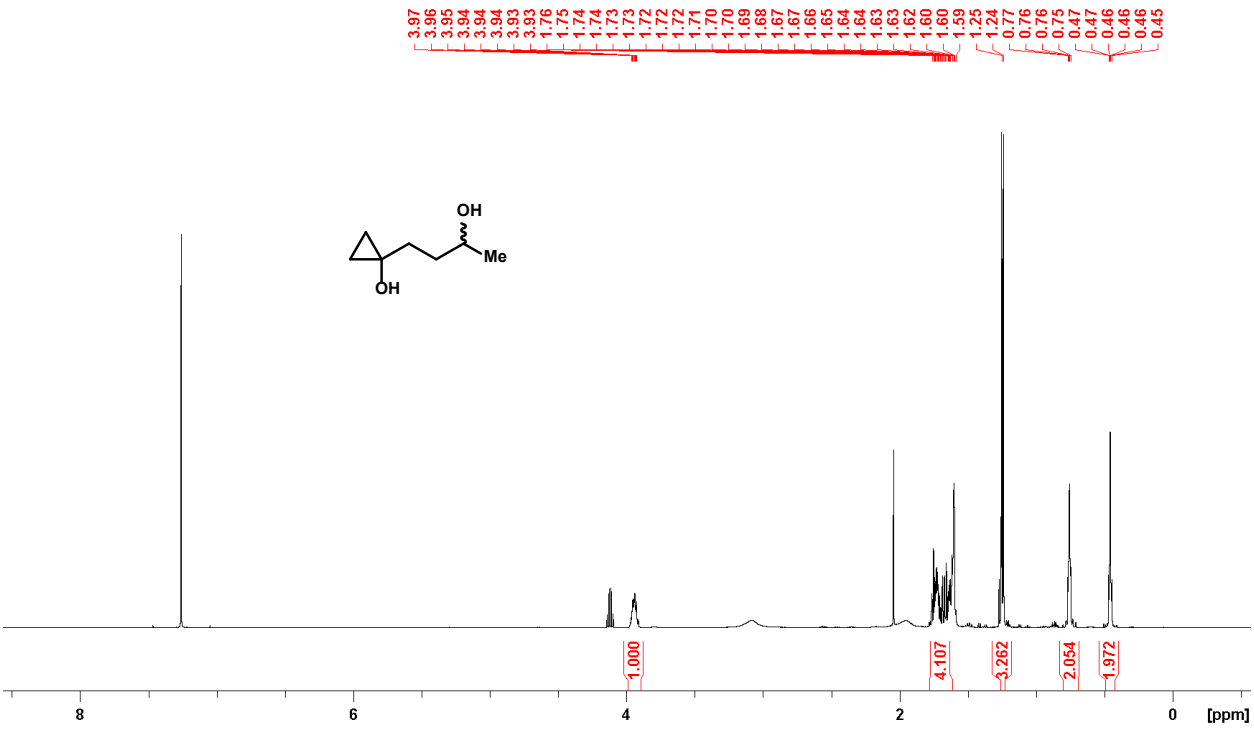
Spectrum 48. ^{1}H NMR of compound 1-78 ($CDCl_3$, 500 MHz)



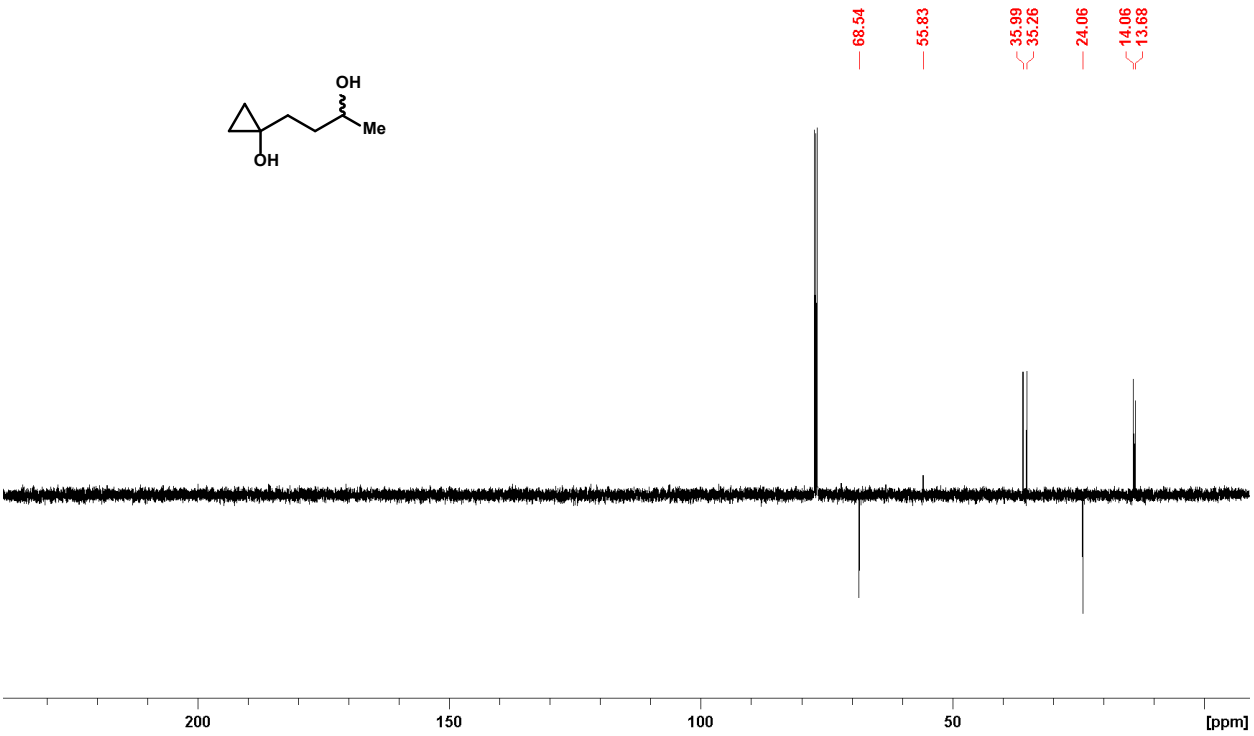
Spectrum 49. ^{13}C NMR of compound 1-78 ($CDCl_3$, 125 MHz)



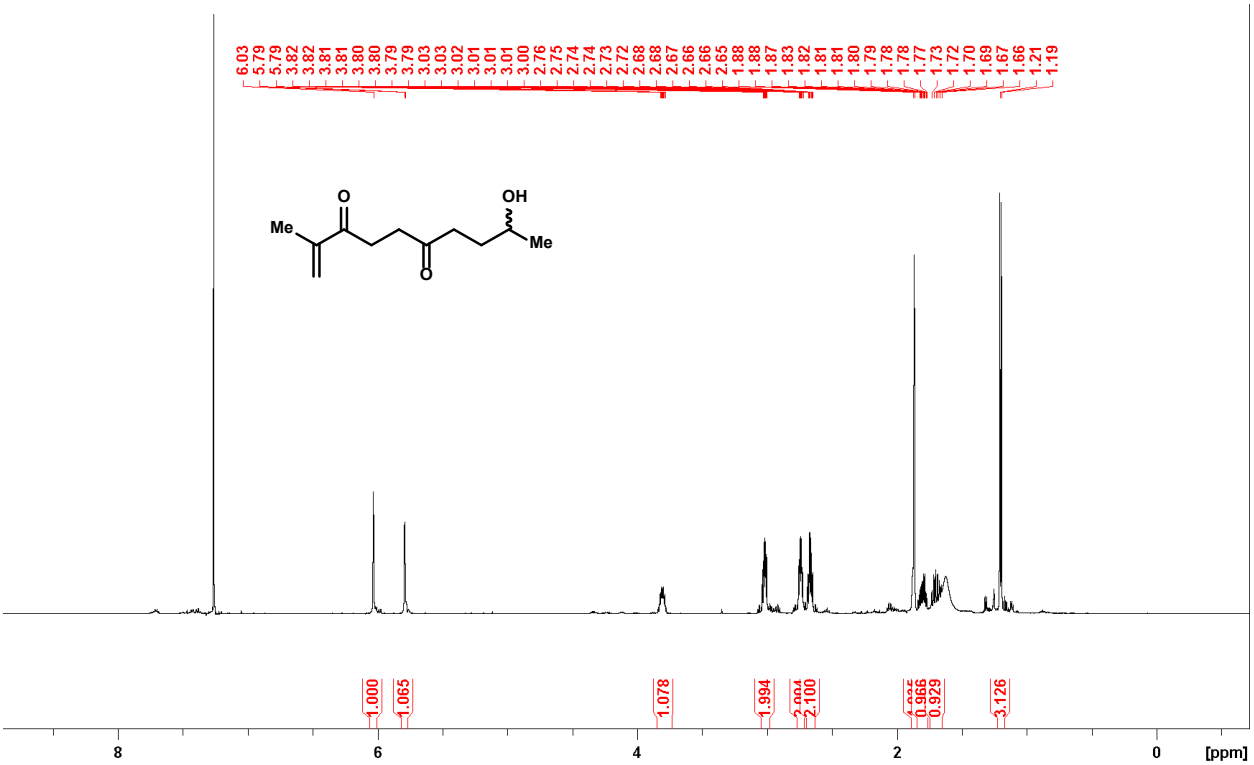
Spectrum 50. ^{1}H NMR of compound 1-96 ($CDCl_3$, 500 MHz)



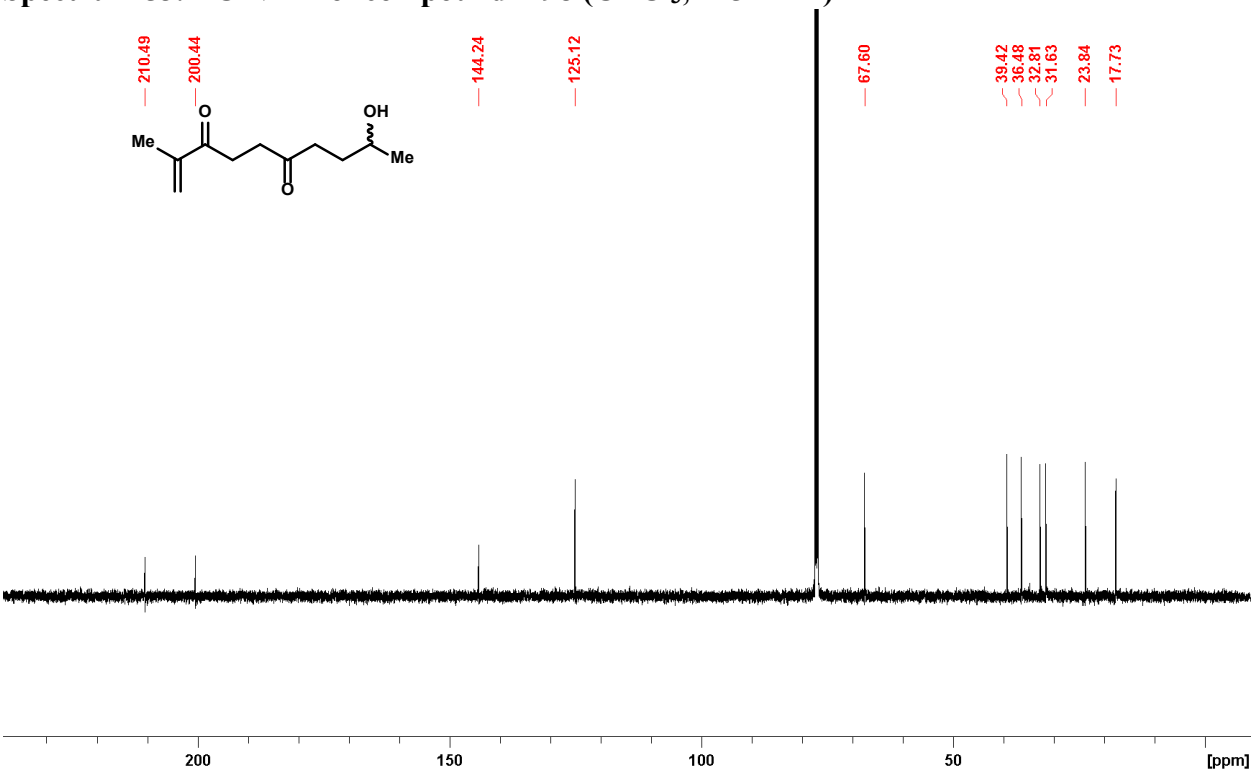
Spectrum 51. APT NMR of compound 1-96 ($CDCl_3$, 500 MHz)



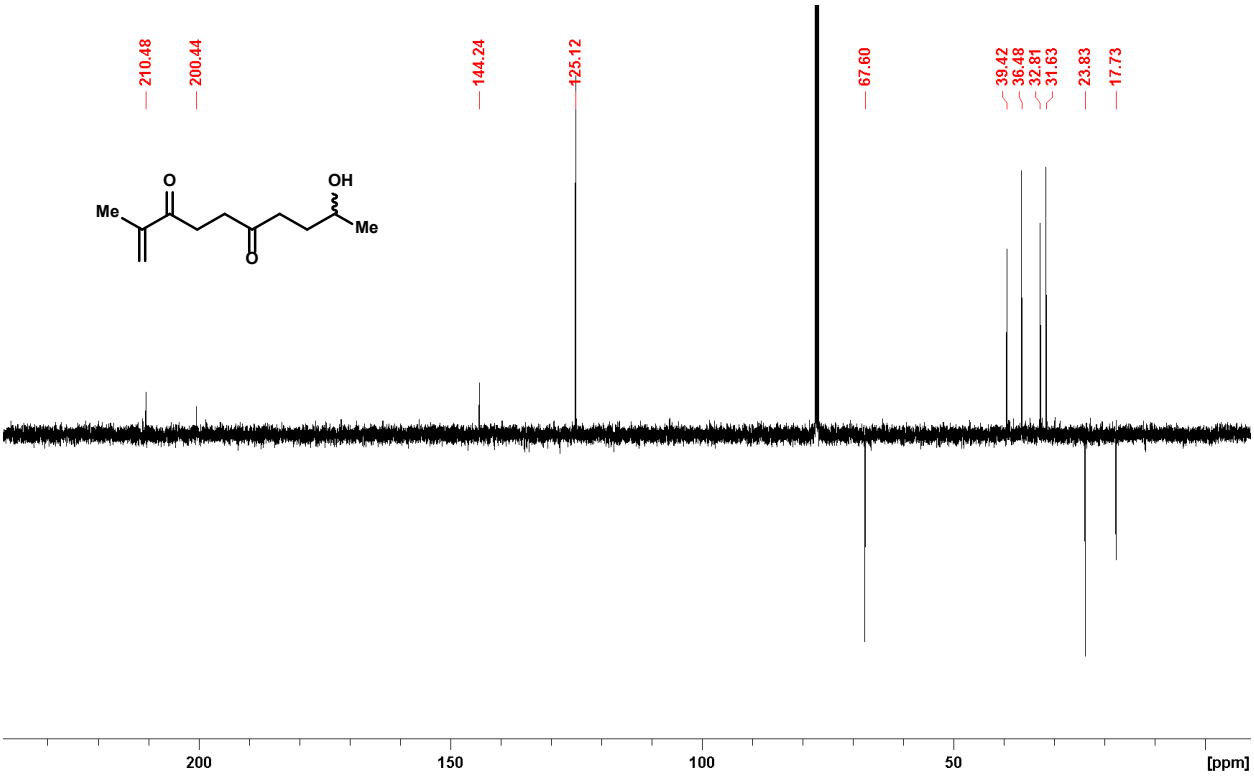
Spectrum 52. ^{1}H NMR of compound 1-98 ($CDCl_3$, 500 MHz)



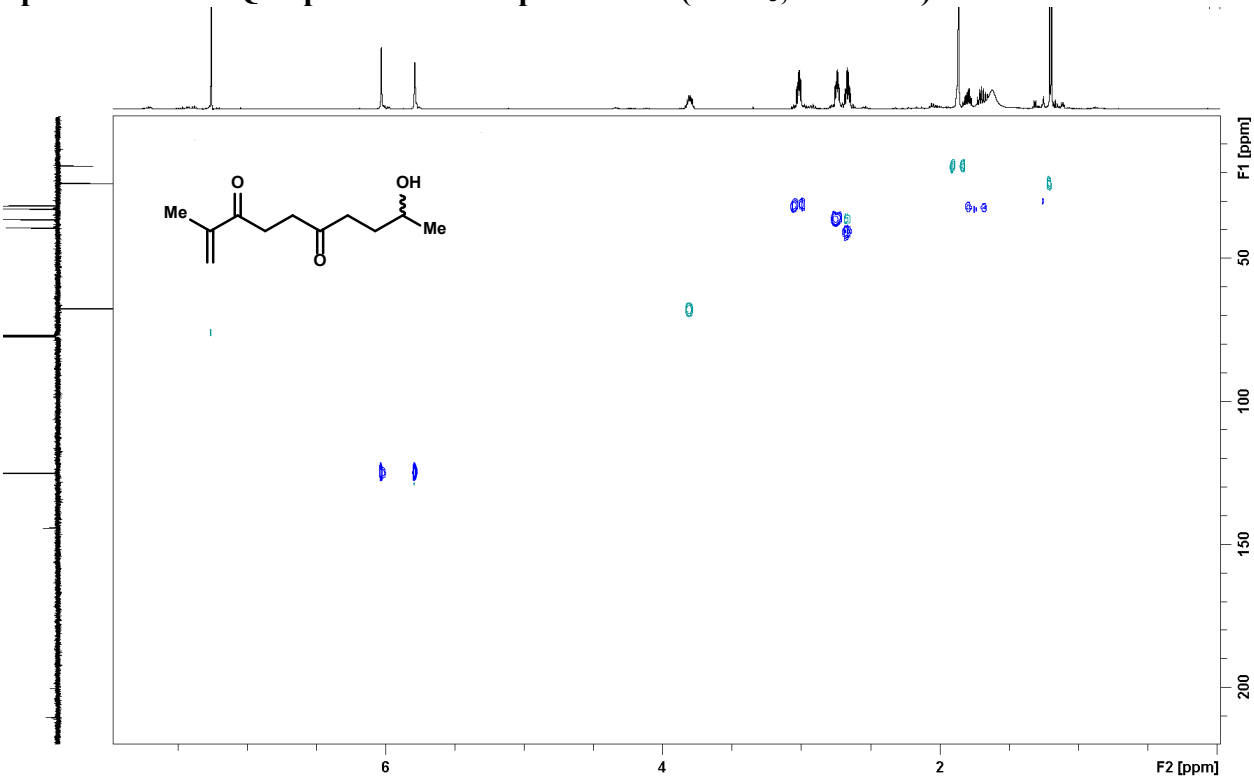
Spectrum 53. ^{13}C NMR of compound 1-98 ($CDCl_3$, 125 MHz)



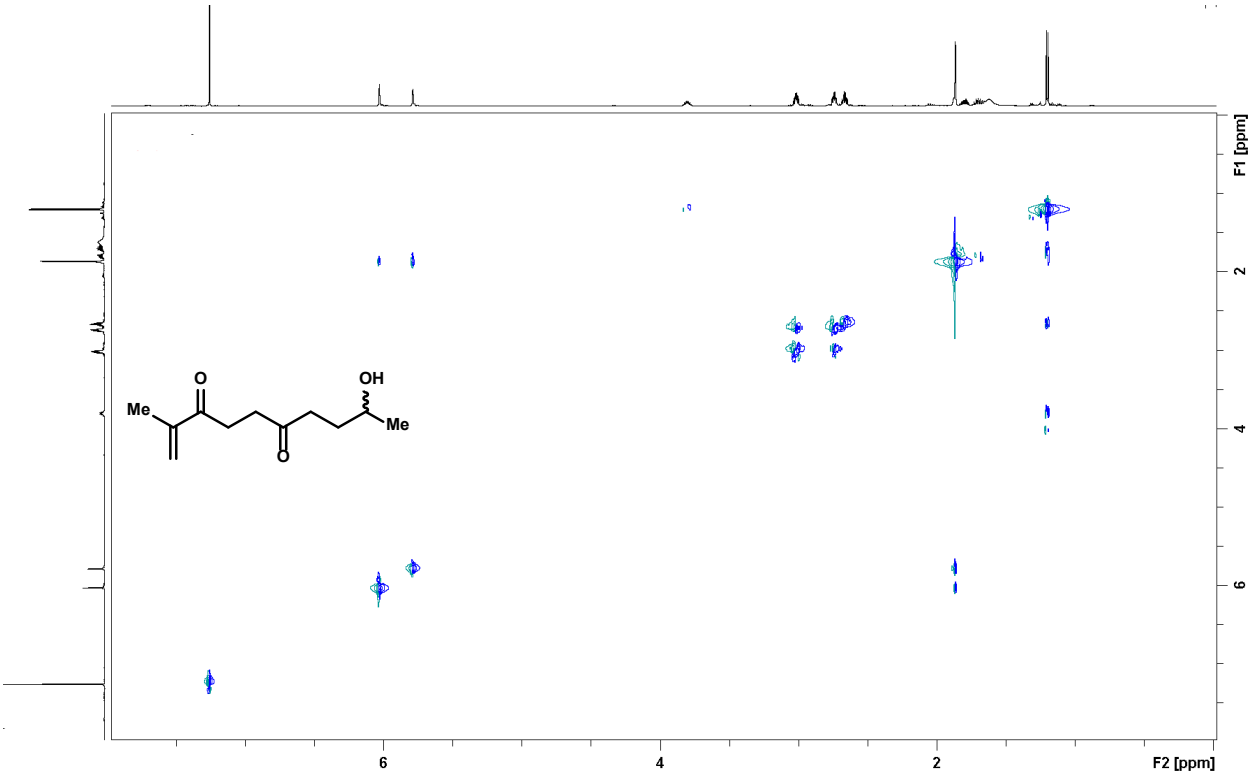
Spectrum 54. APT NMR of compound 1-98 ($CDCl_3$, 125 MHz)



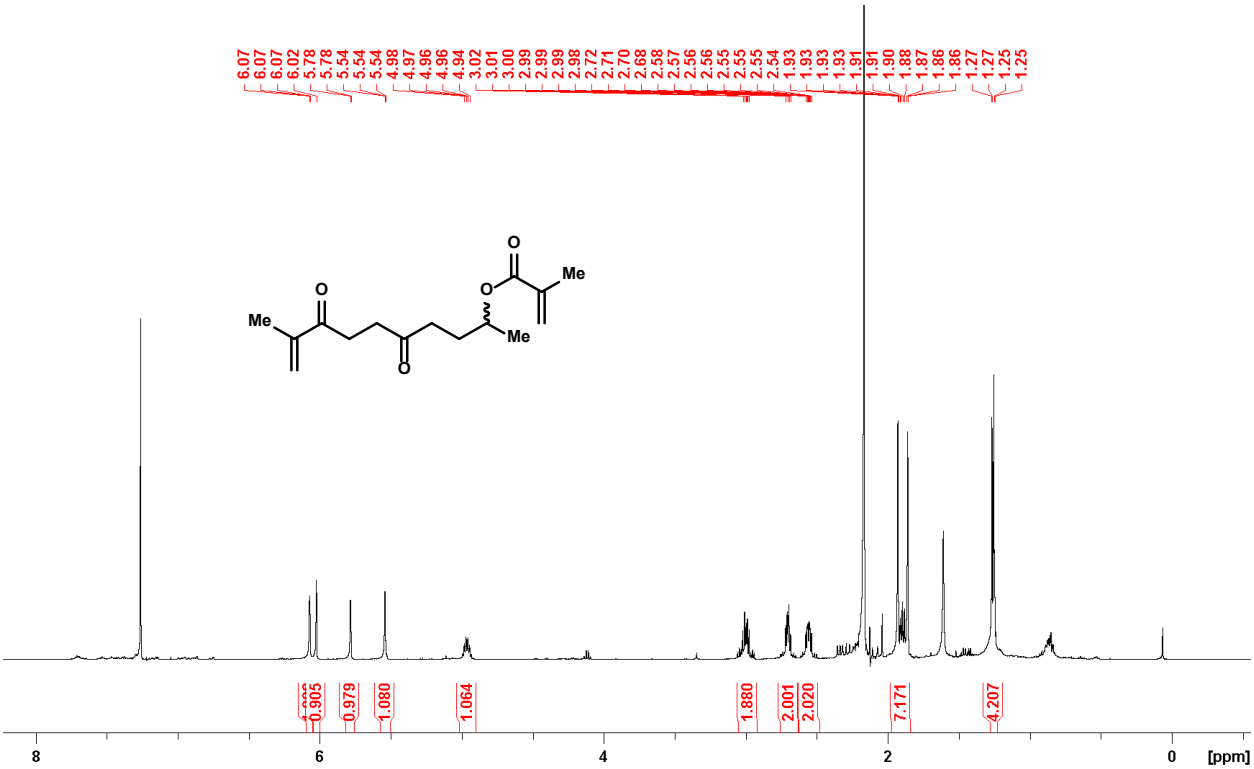
Spectrum 55. HSQC spectrum of compound 1-98 ($CDCl_3$, 500 MHz)



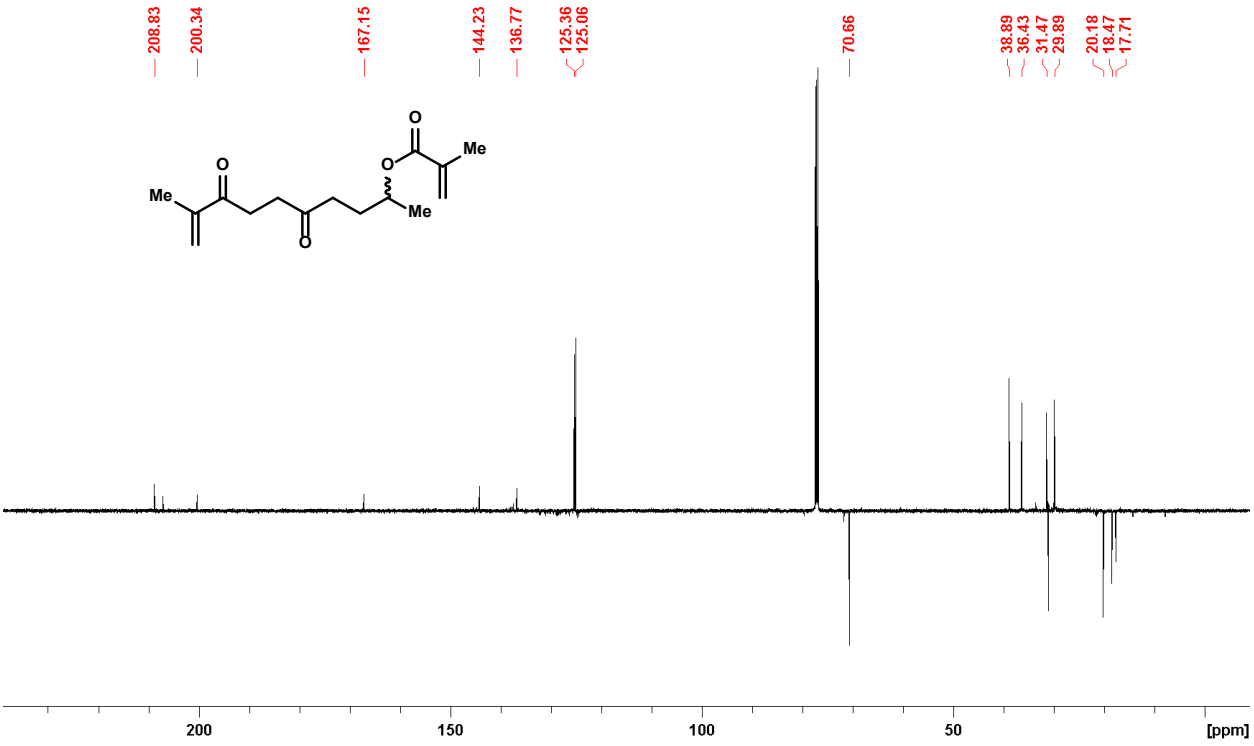
Spectrum 56. TOCSY of compound 1-98 ($CDCl_3$, 500 MHz)



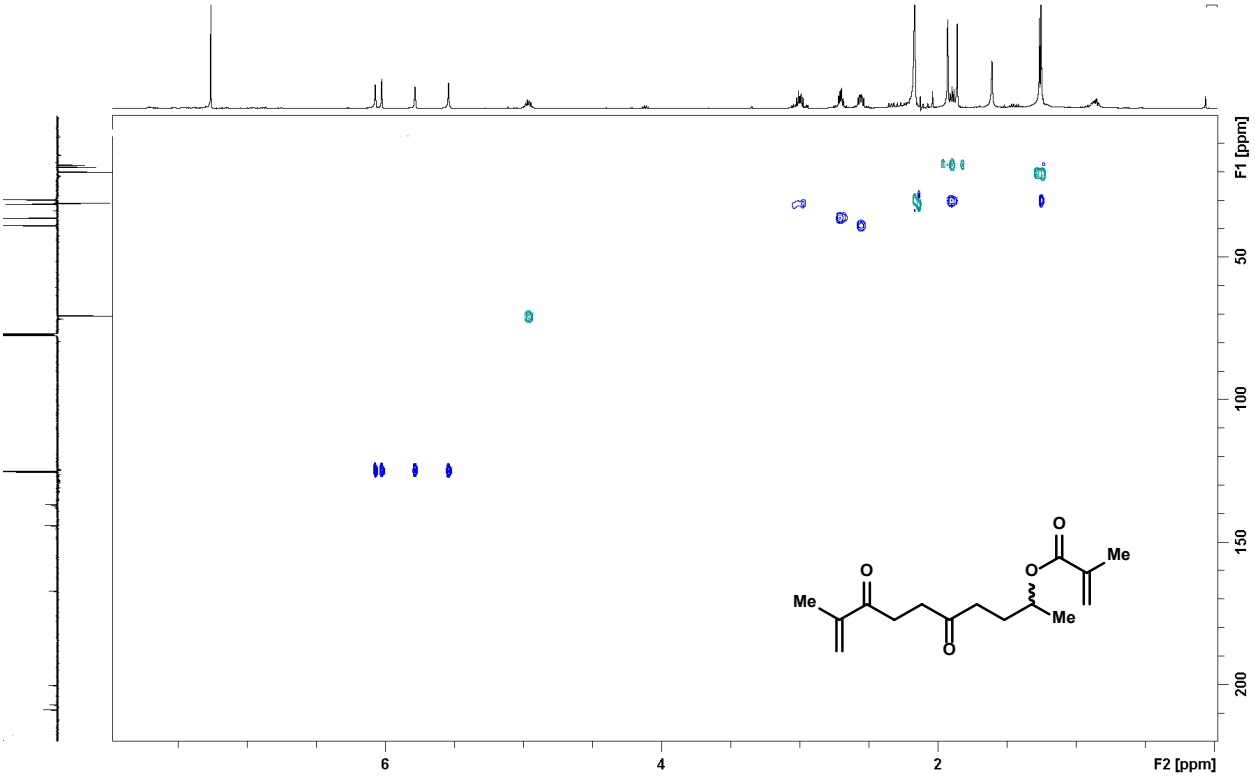
Spectrum 57. ^{1}H NMR of compound 1-99 ($CDCl_3$, 500 MHz)



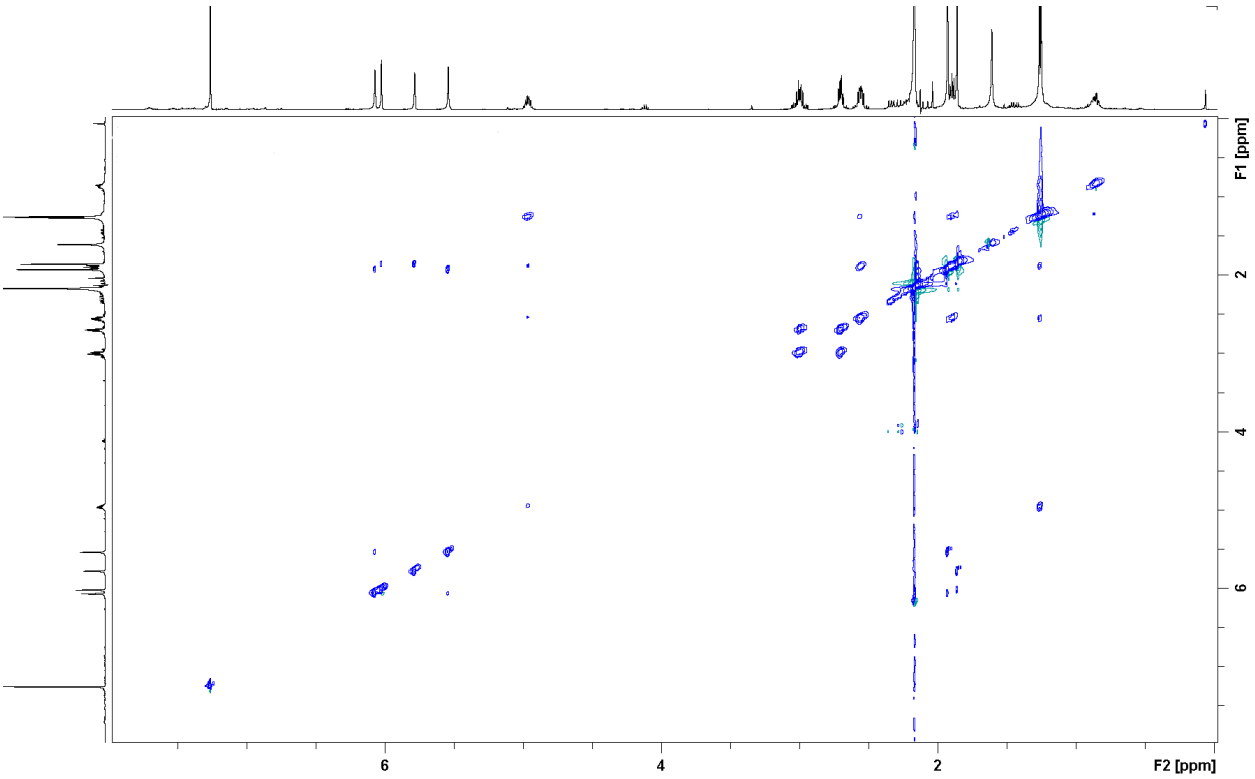
Spectrum 58. APT NMR of compound 1-99 ($CDCl_3$, 125 MHz)



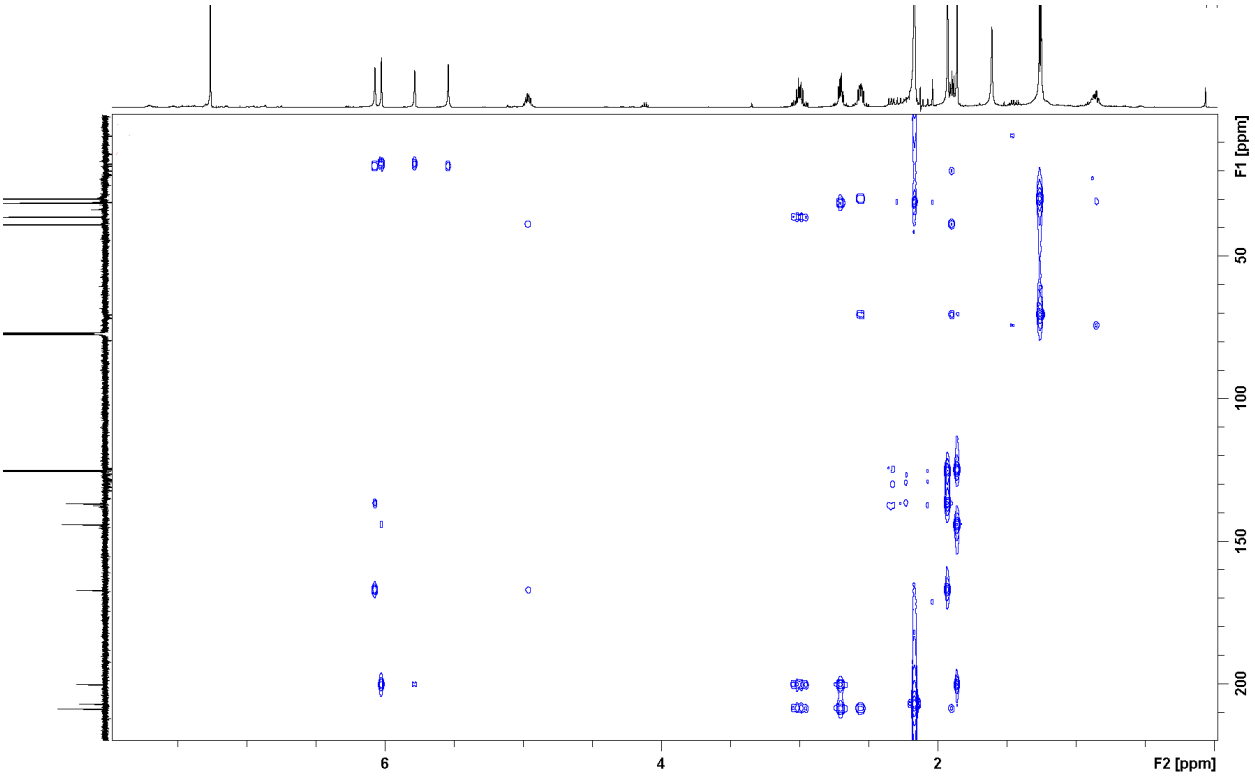
Spectrum 59. HSQC spectrum of compound 1-99 ($CDCl_3$, 500 MHz)



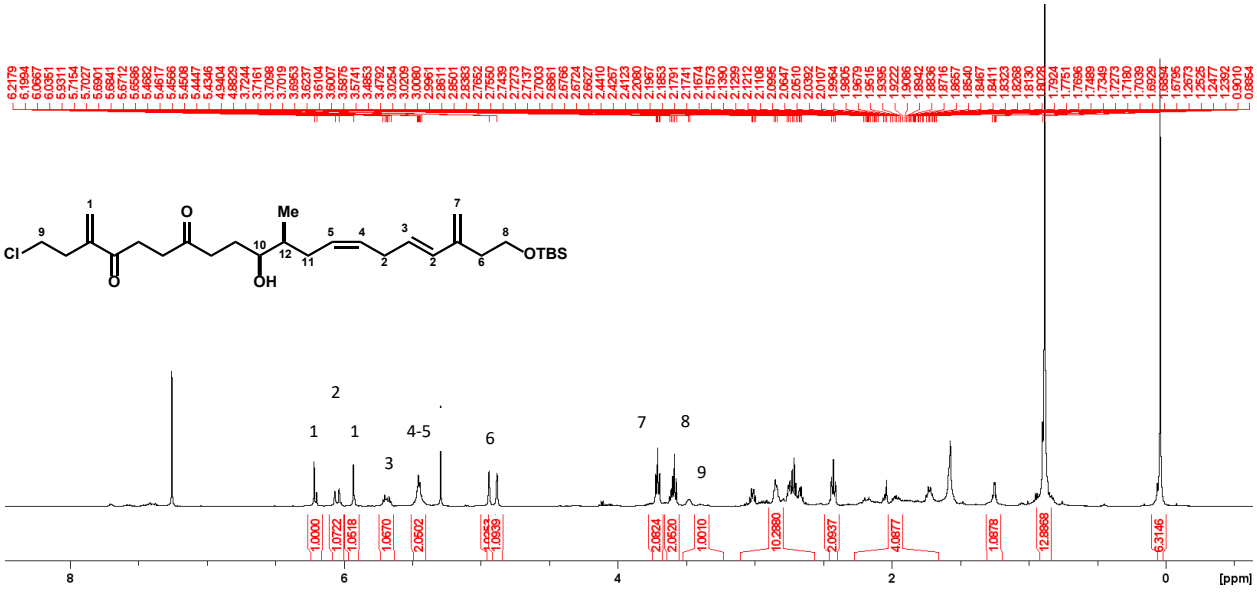
Spectrum 60. TOCSY of compound 1-99 ($CDCl_3$, 500 MHz)



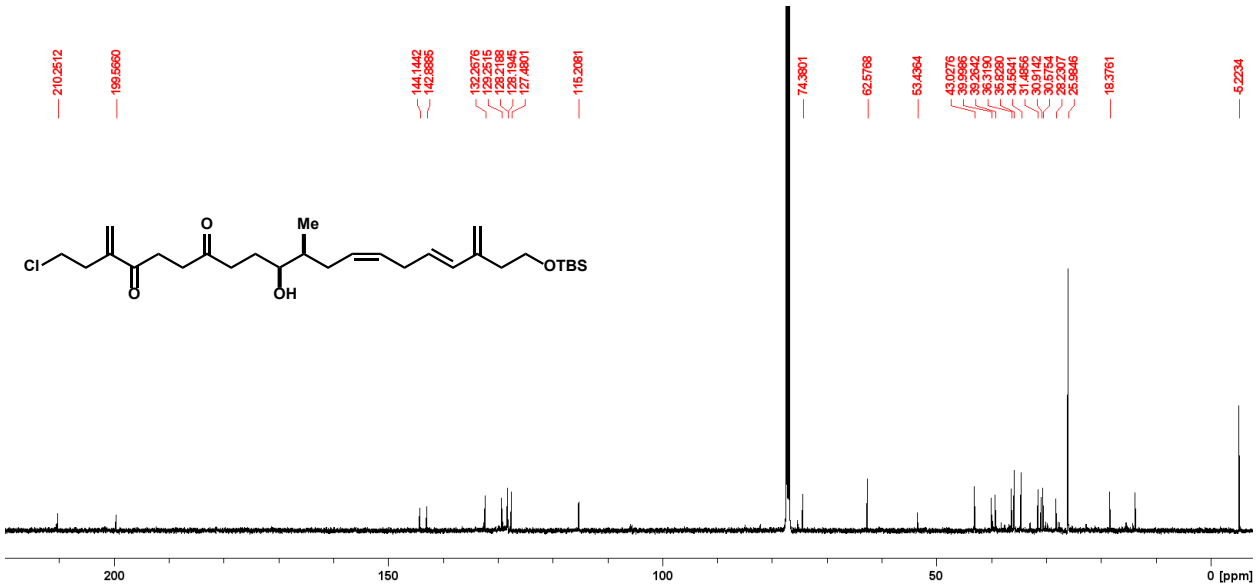
Spectrum 61. HMBC spectrum of compound 1-99 ($CDCl_3$, 500 MHz)



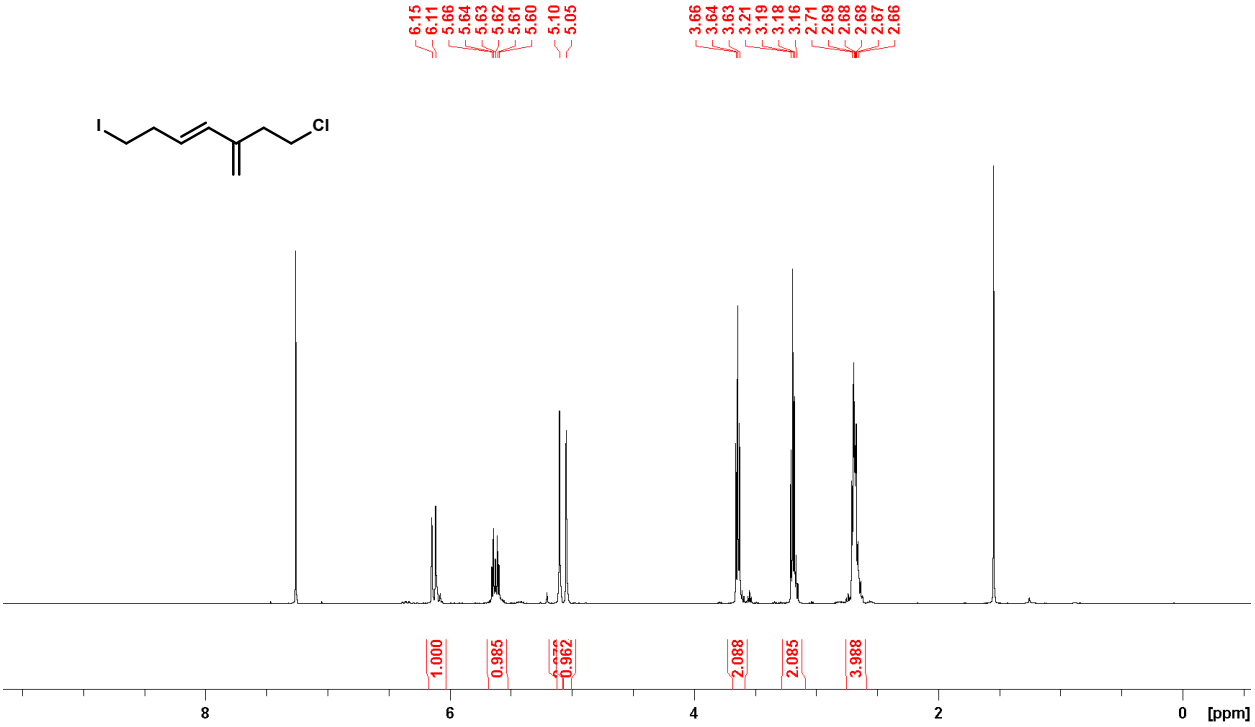
Spectrum 62. ^{1}H NMR of compound 1-77 ($CDCl_3$, 500 MHz)



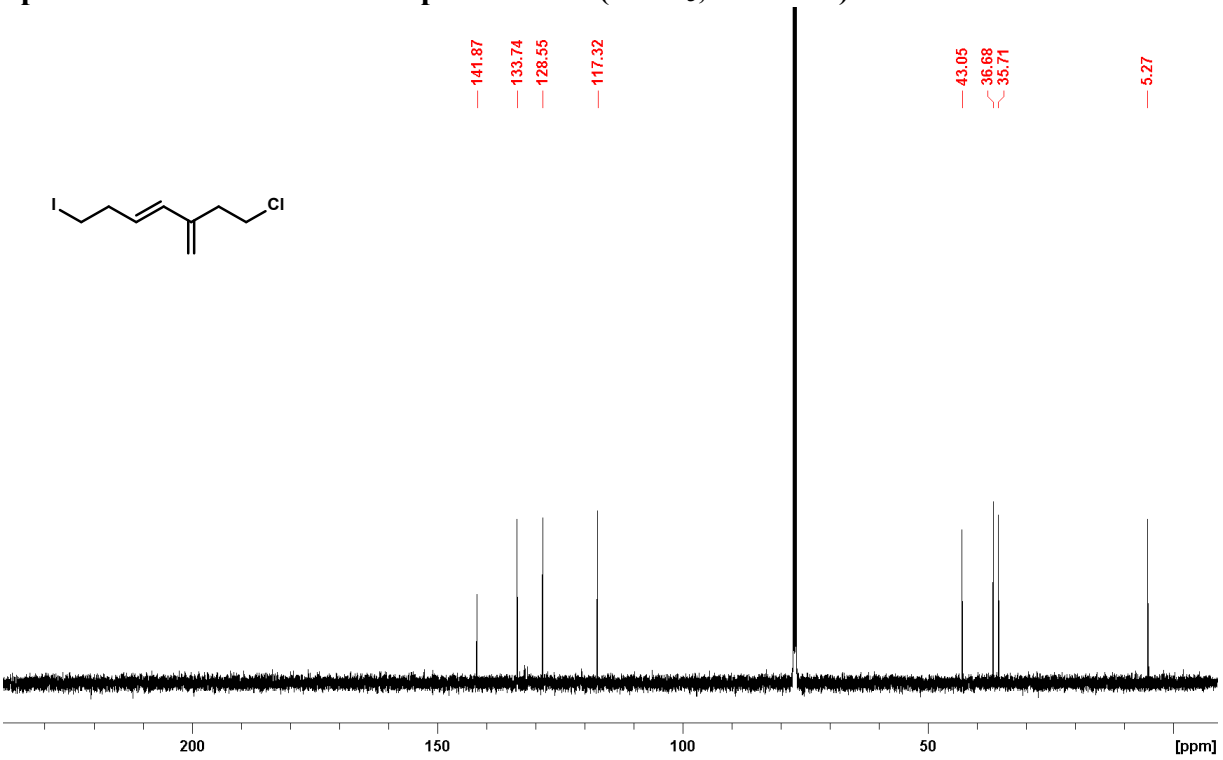
Spectrum 63. ^{13}C NMR of compound 1-77 ($CDCl_3$, 125 MHz)



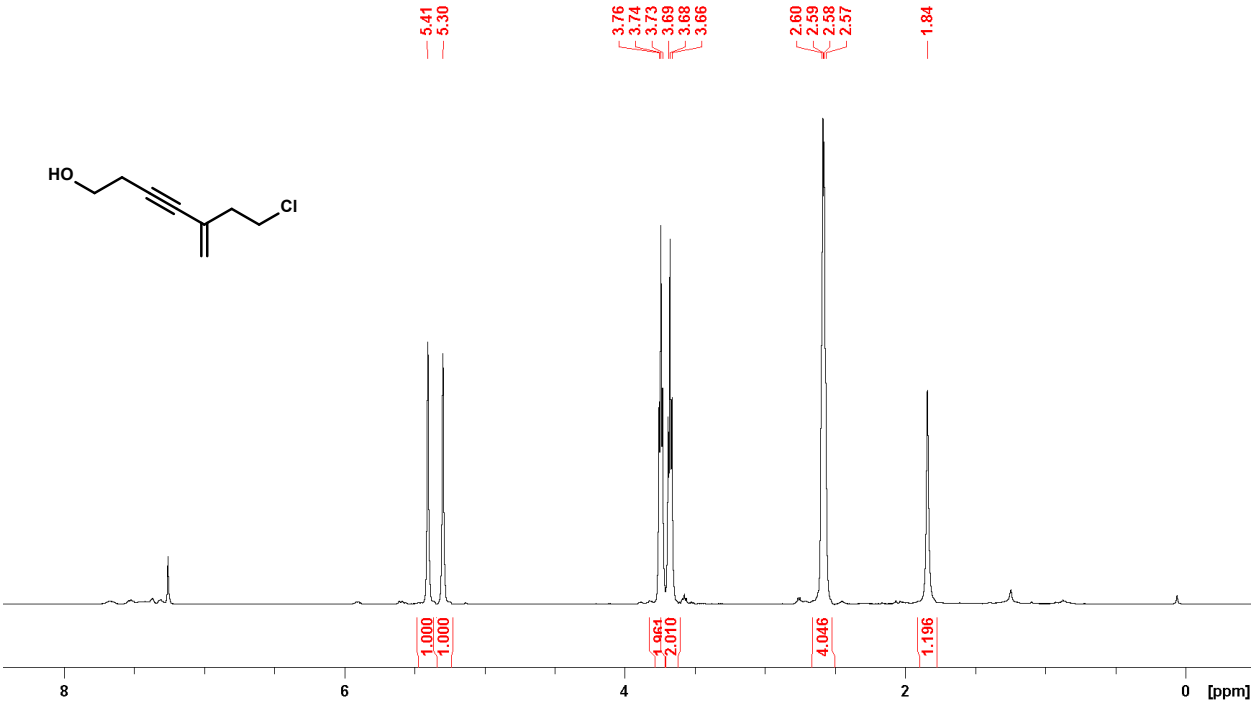
Spectrum 64. ^{1}H NMR of compound 1-105 ($CDCl_3$, 500 MHz)



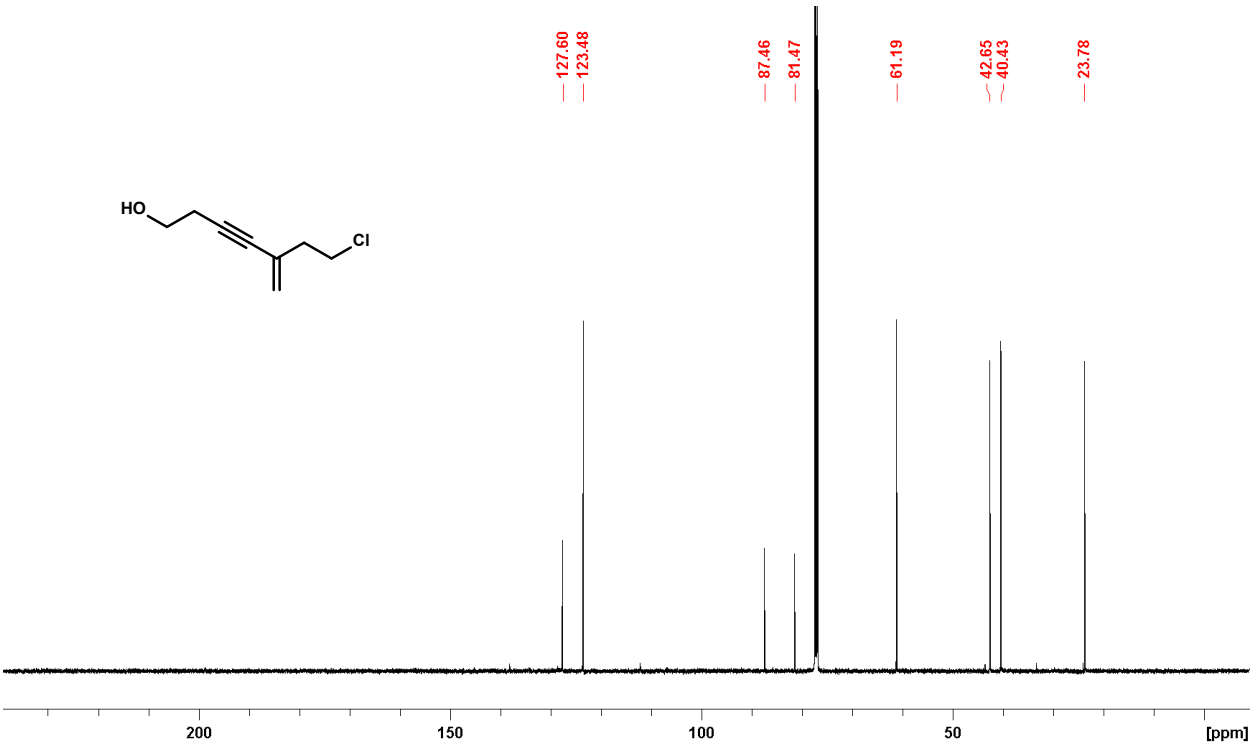
Spectrum 65. ^{13}C NMR of compound 1-105 ($CDCl_3$, 125 MHz)



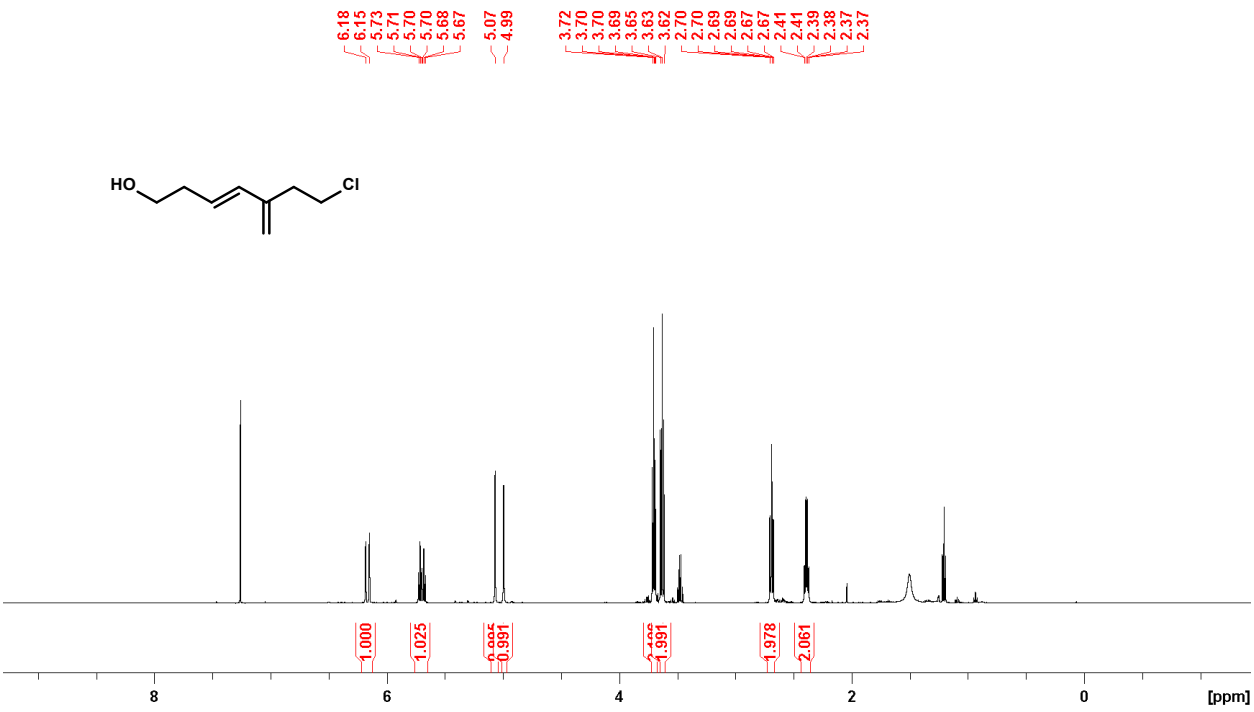
Spectrum 66. ^{1}H NMR of compound 1-107 ($CDCl_3$, 500 MHz)



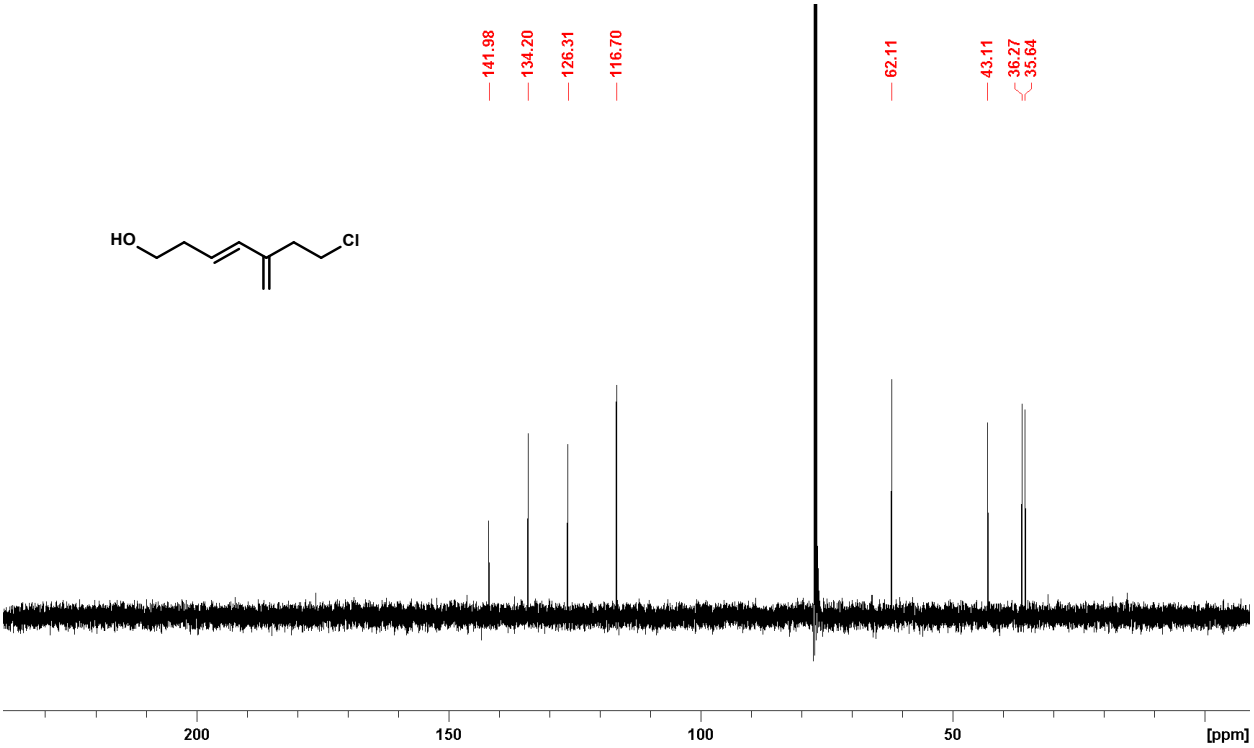
Spectrum 67. ^{13}C NMR of compound 1-107 ($CDCl_3$, 125 MHz)



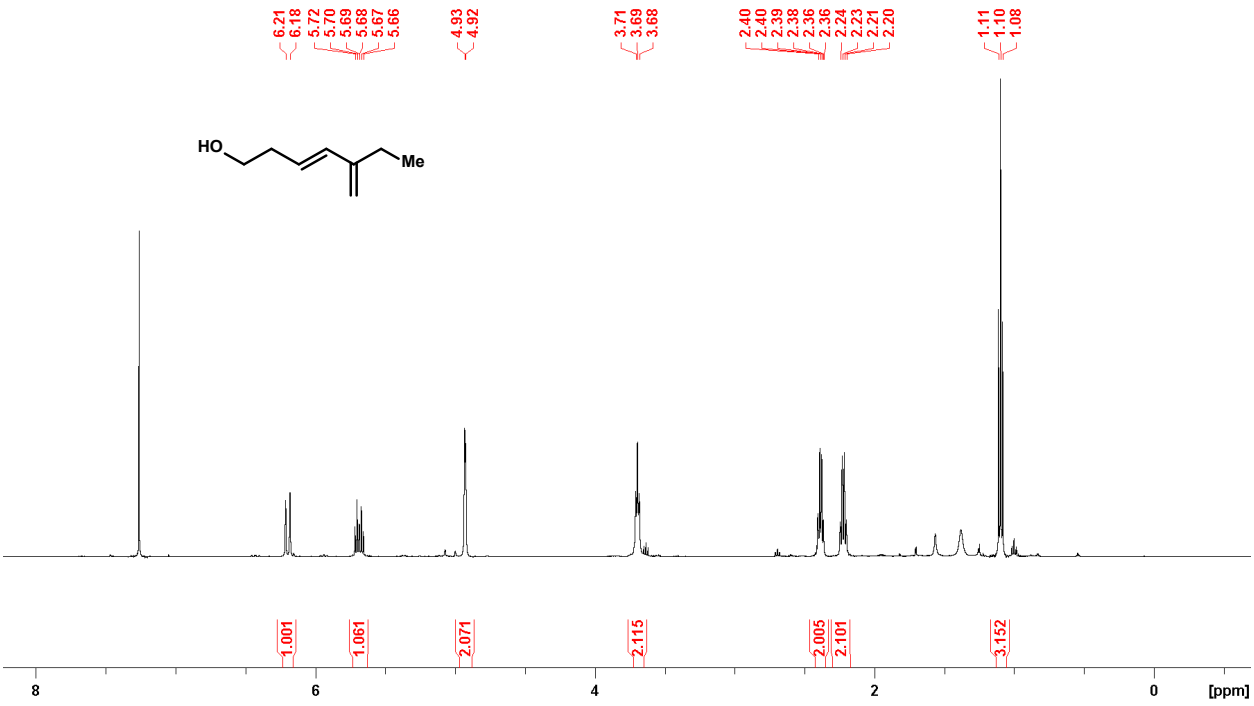
Spectrum 68. ^{1}H NMR of compound 1-108 ($CDCl_3$, 500 MHz)



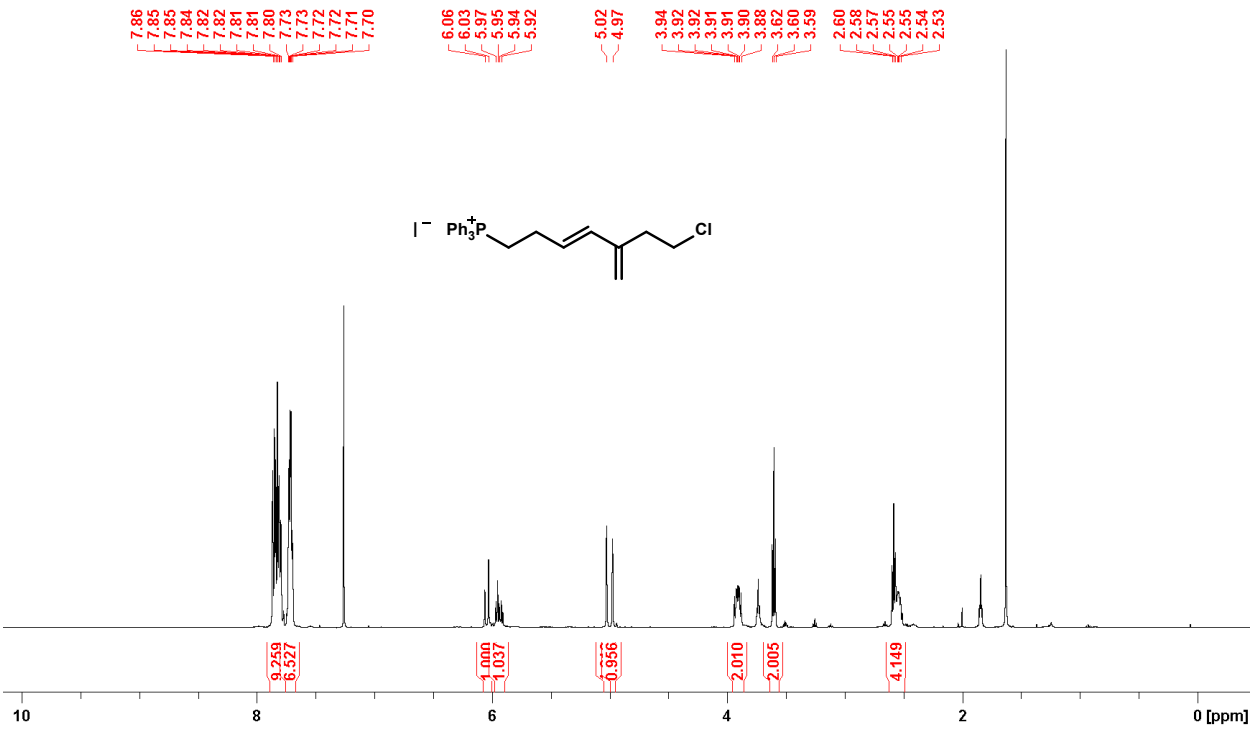
Spectrum 69. ^{13}C NMR of compound 1-108 ($CDCl_3$, 125 MHz)



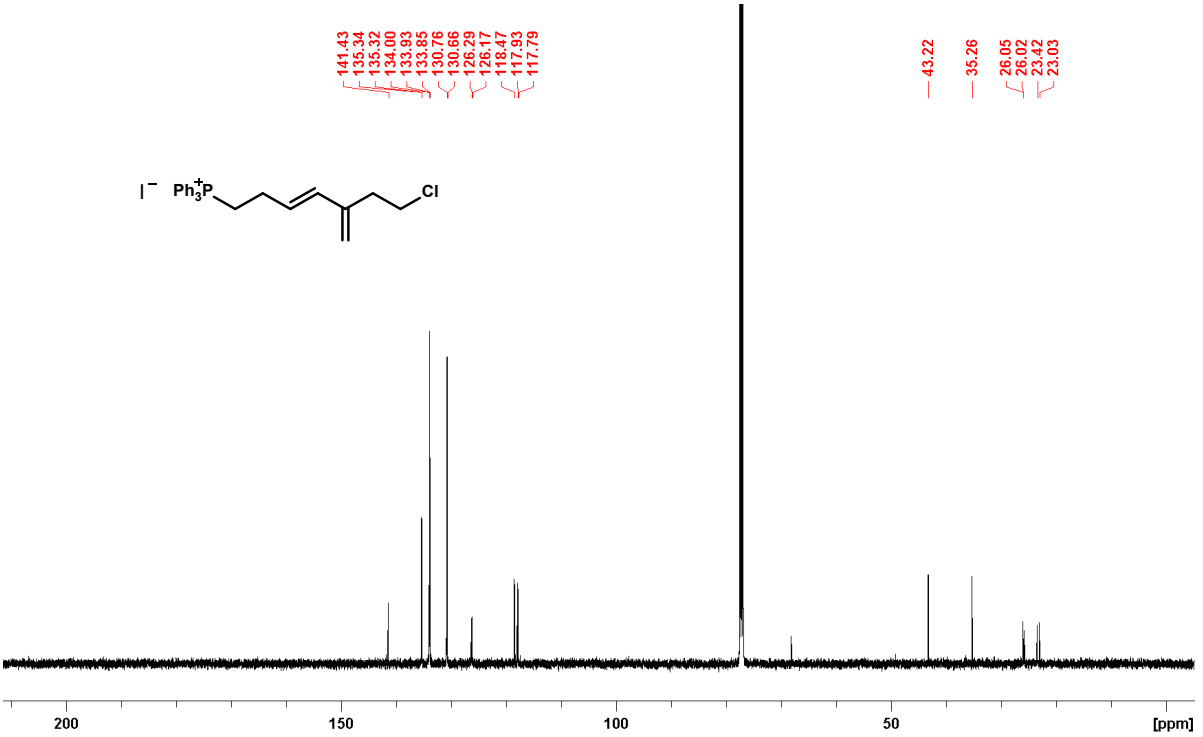
Spectrum 70. ^{1}H NMR of compound 1-109 ($CDCl_3$, 500 MHz) – Crude material



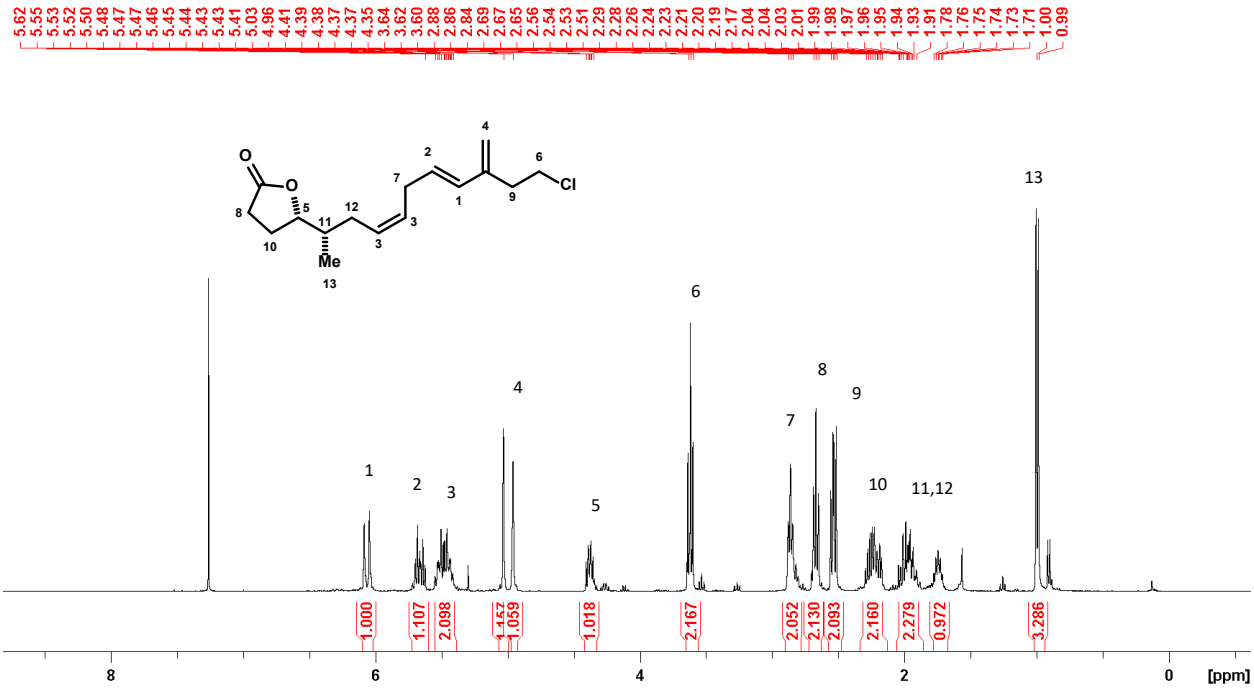
Spectrum 71. ^{1}H NMR of compound 1-110 ($CDCl_3$, 500 MHz)



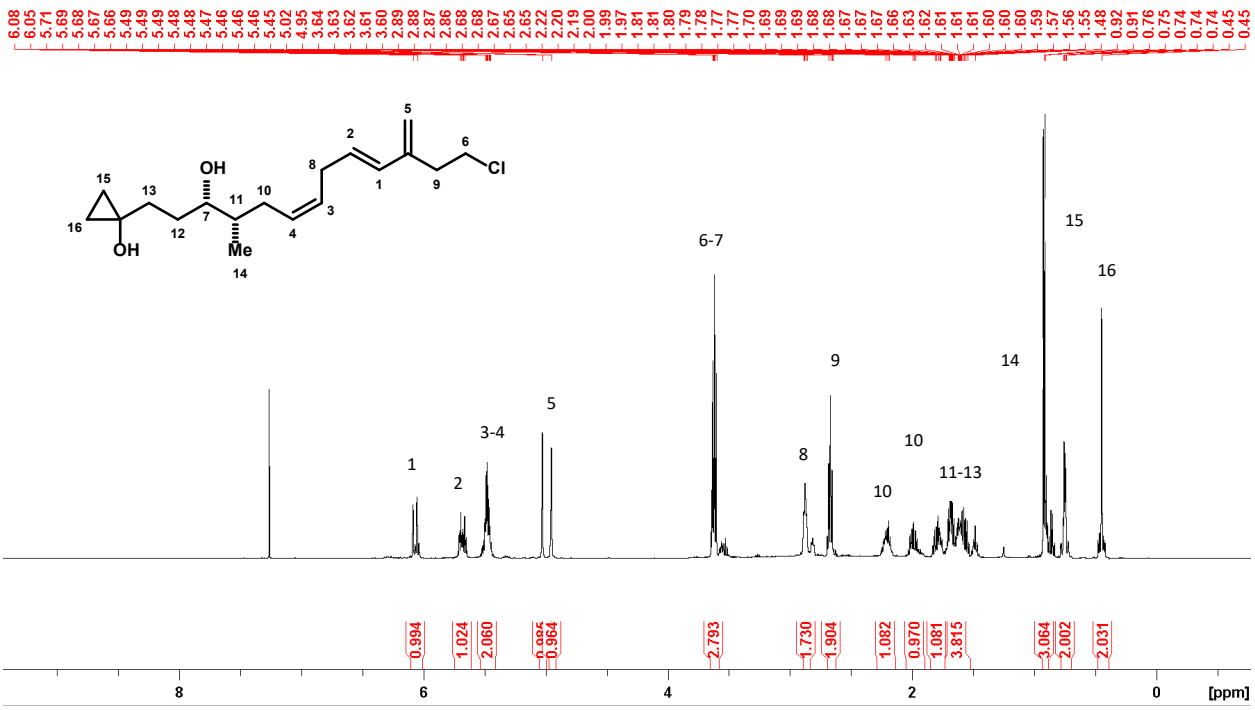
Spectrum 72. ^{13}C NMR of compound 1-110 ($CDCl_3$, 125 MHz)



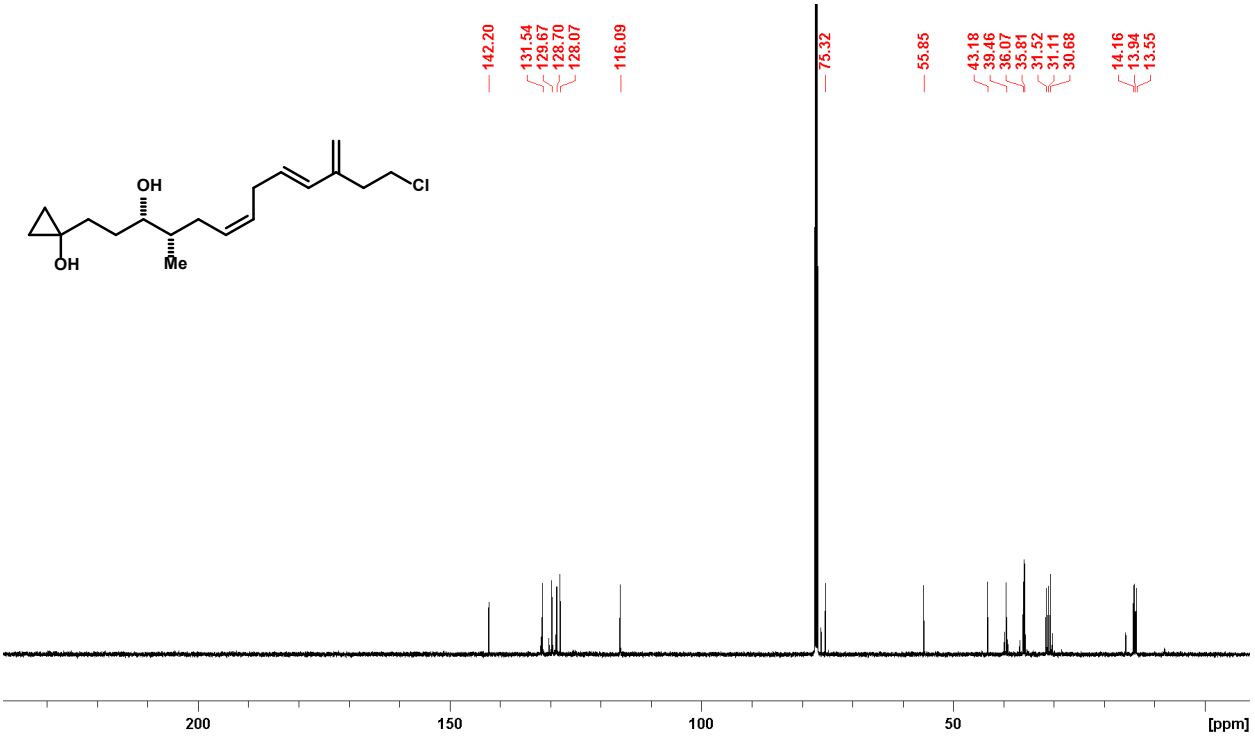
Spectrum 73. ^{1}H NMR of compound 1-111 ($CDCl_3$, 400 MHz)



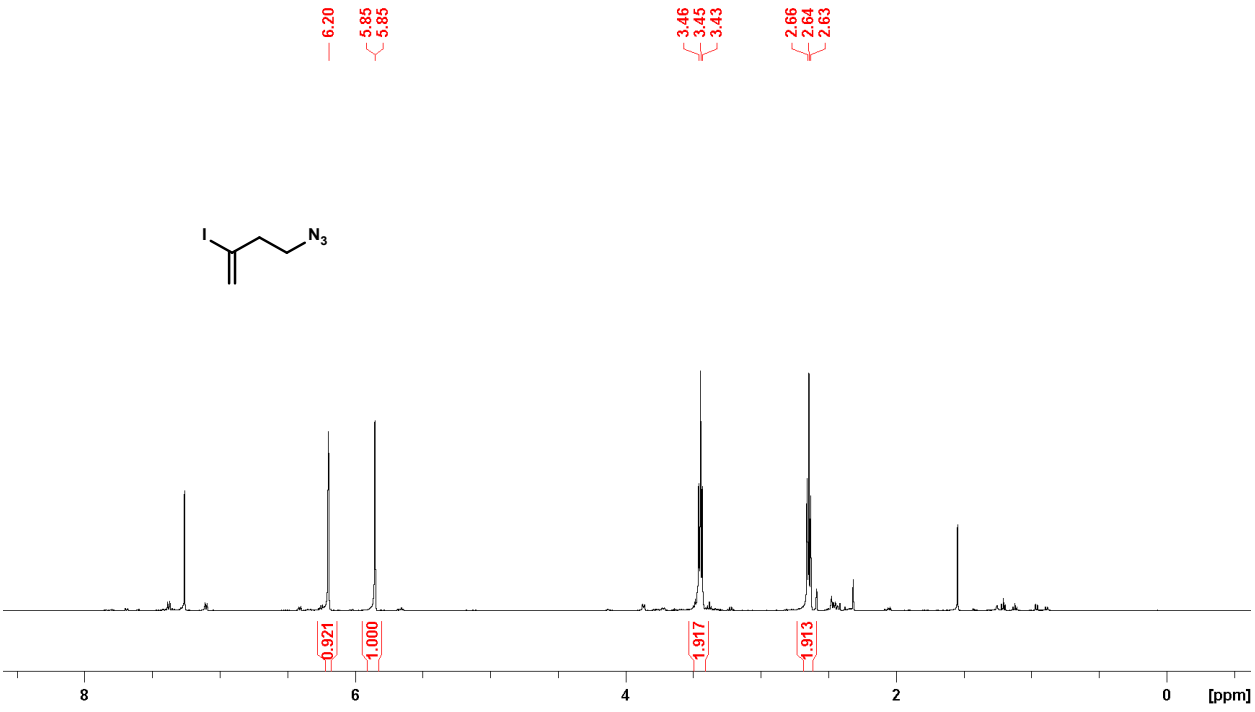
Spectrum 74. ^{1}H NMR of compound 1-112 ($CDCl_3$, 500 MHz)



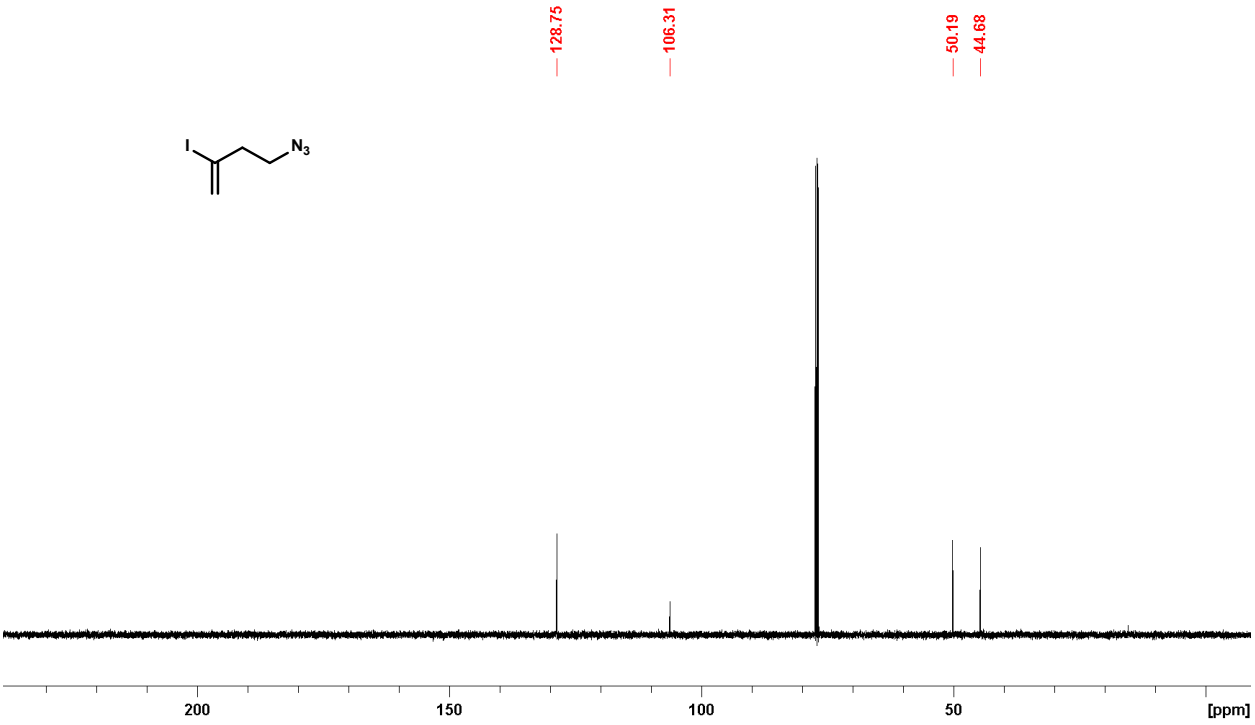
Spectrum 75. ^{13}C NMR of compound 1-112 ($CDCl_3$, 125 MHz)



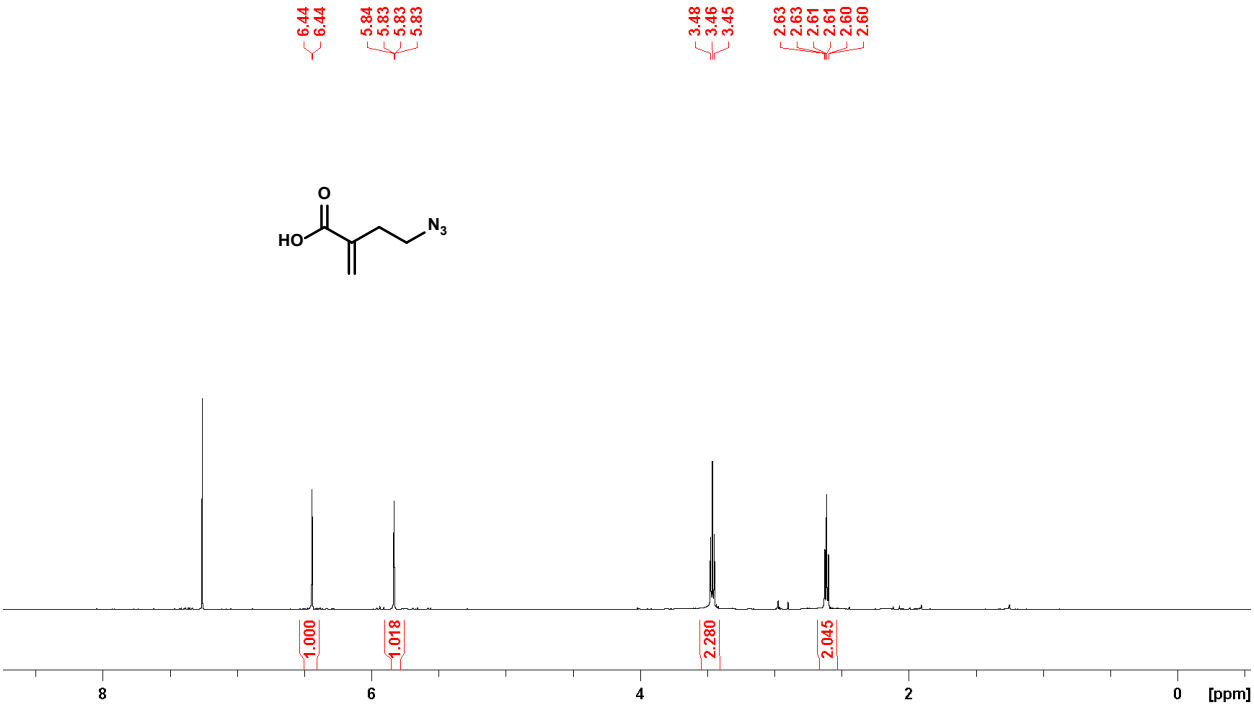
Spectrum 76. ^{1}H NMR of compound 1-117 ($CDCl_3$, 500 MHz)



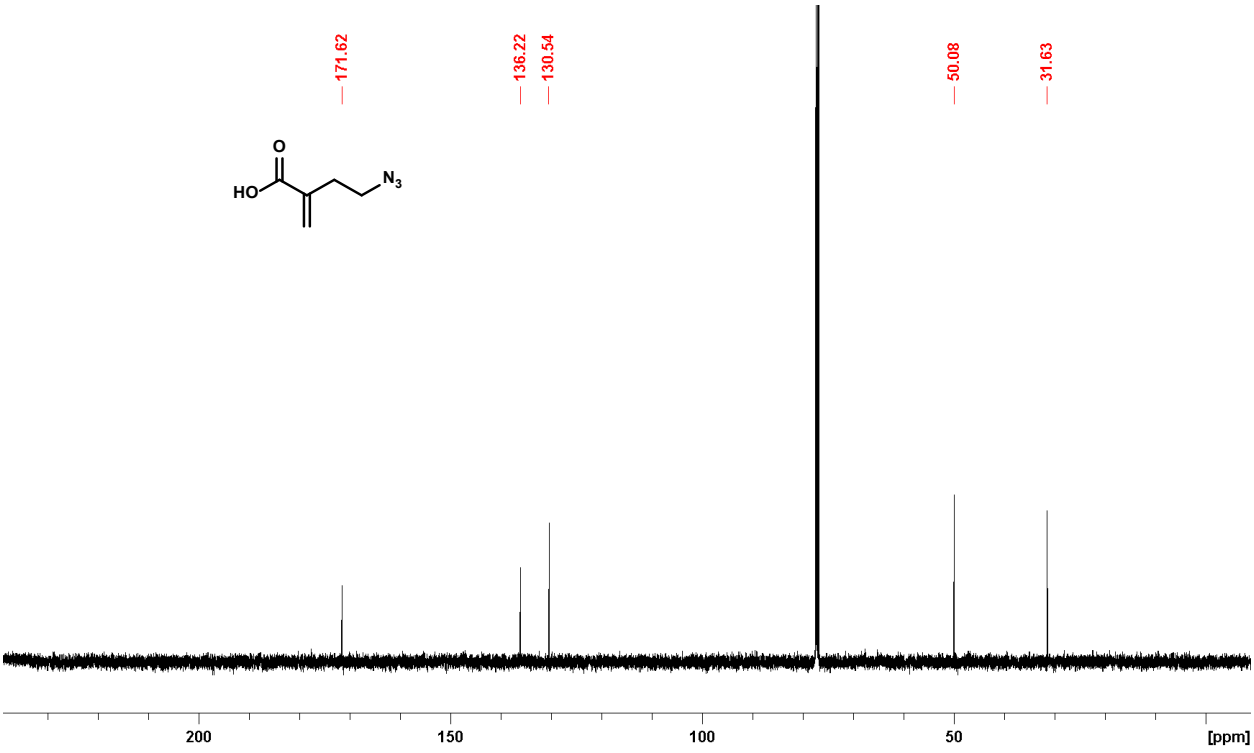
Spectrum 77. ^{13}C NMR of compound 1-117 ($CDCl_3$, 125 MHz)



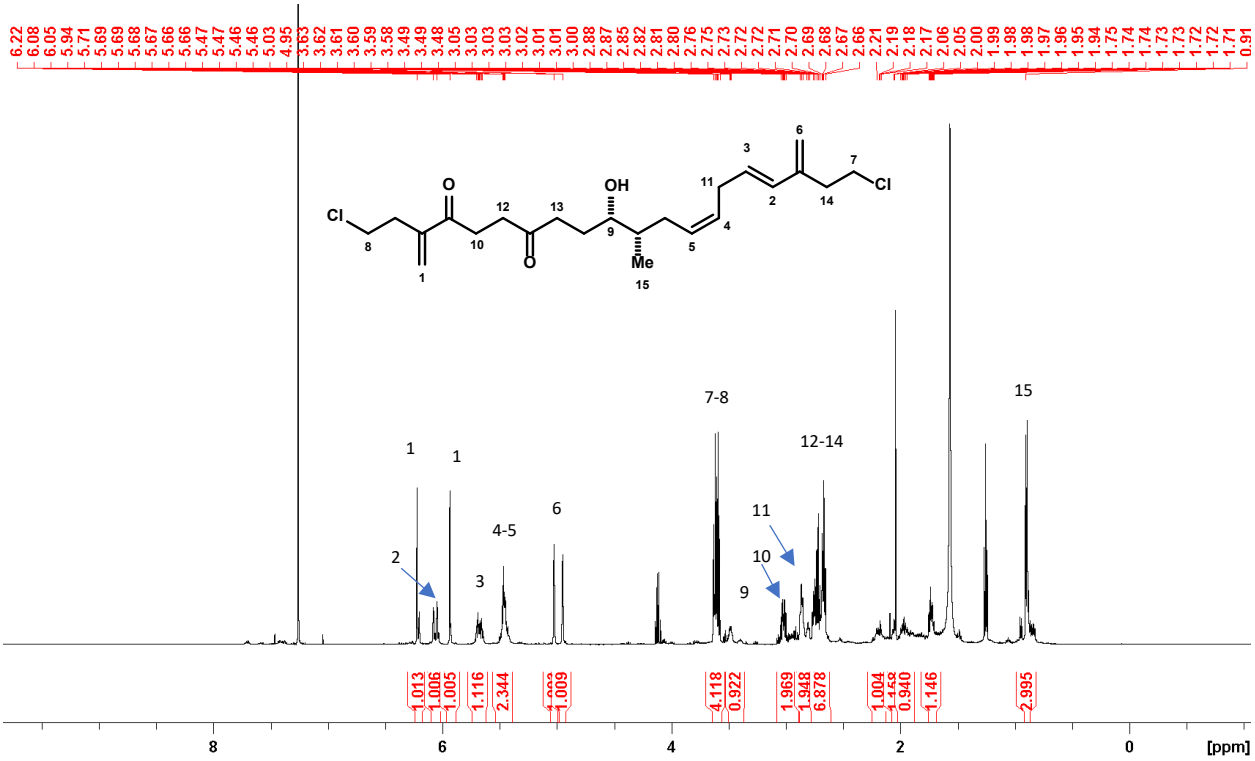
Spectrum 78. ^{1}H NMR of compound 1-113 ($CDCl_3$, 500 MHz)



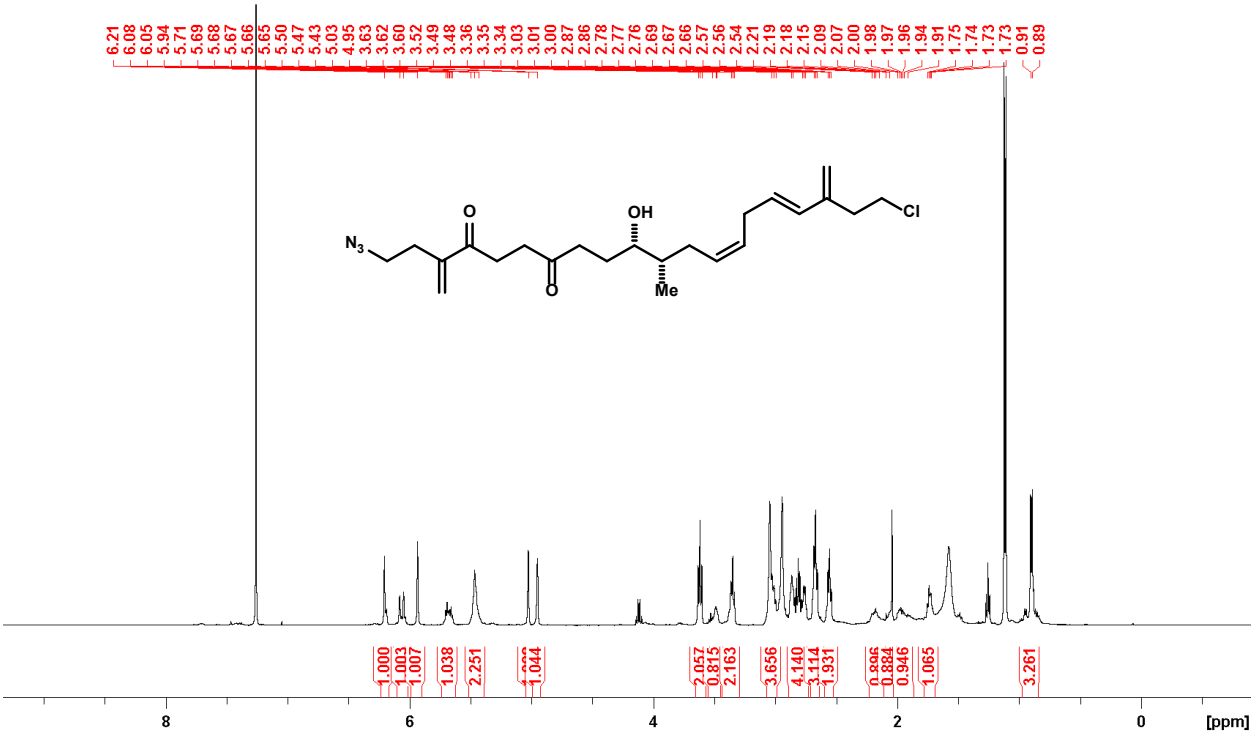
Spectrum 79. ^{13}C NMR of compound 1-113 ($CDCl_3$, 125 MHz)



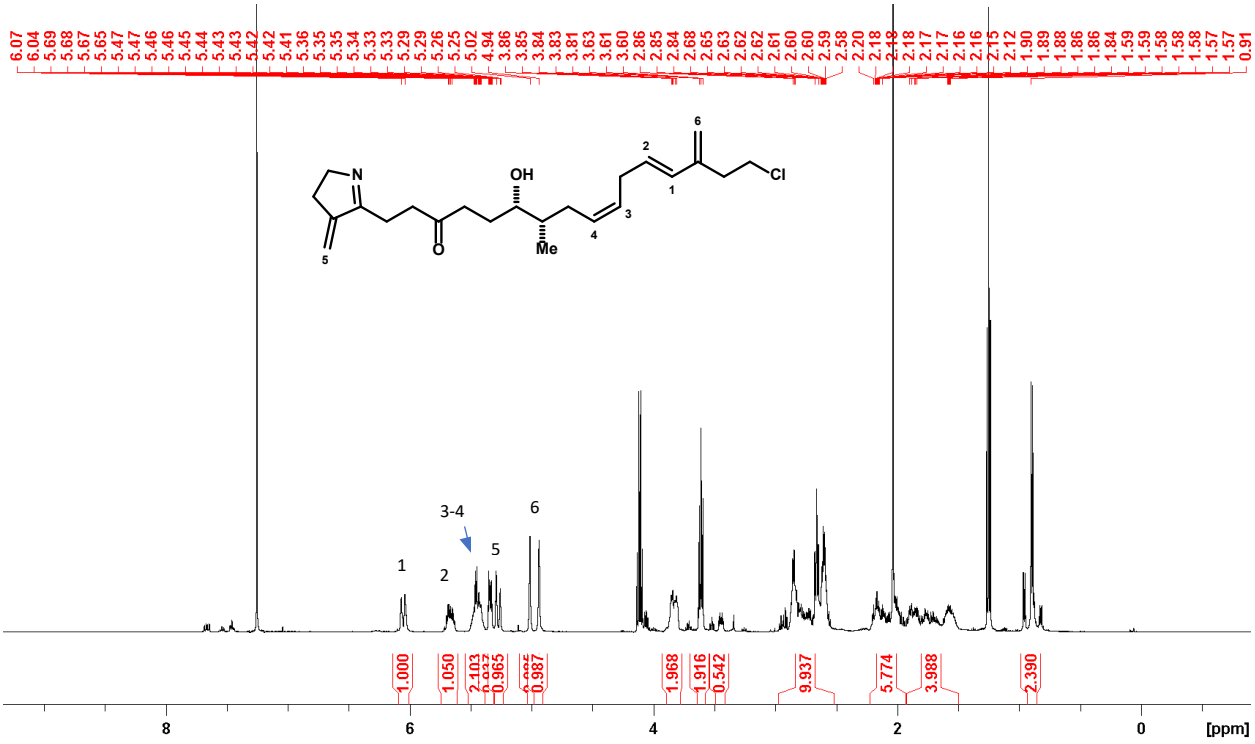
Spectrum 80. ^{1}H NMR of compound 1-114 ($CDCl_3$, 500 MHz)



Spectrum 81. ^{1}H NMR of compound 1-114 ($CDCl_3$, 500 MHz)



Spectrum 82. ^{1}H NMR of compound 1-119 ($CDCl_3$, 500 MHz)



Chapter Two: Asymmetric Organocatalysis Enables Rapid Assembly of Portimine Precursor Chains.

2.1 Synthesis of the Diels-Alder precursor for the intramolecular cycloaddition

Based on the preliminary results obtained from the model studies, it was suggested that oxygenation might play an essential role in the construction of the portimine macrocyclic core. Therefore, the focus was shifted towards the early installation of the key oxygenated stereocenters as shown in the revised retrosynthesis of portimine (**Figure 10**).

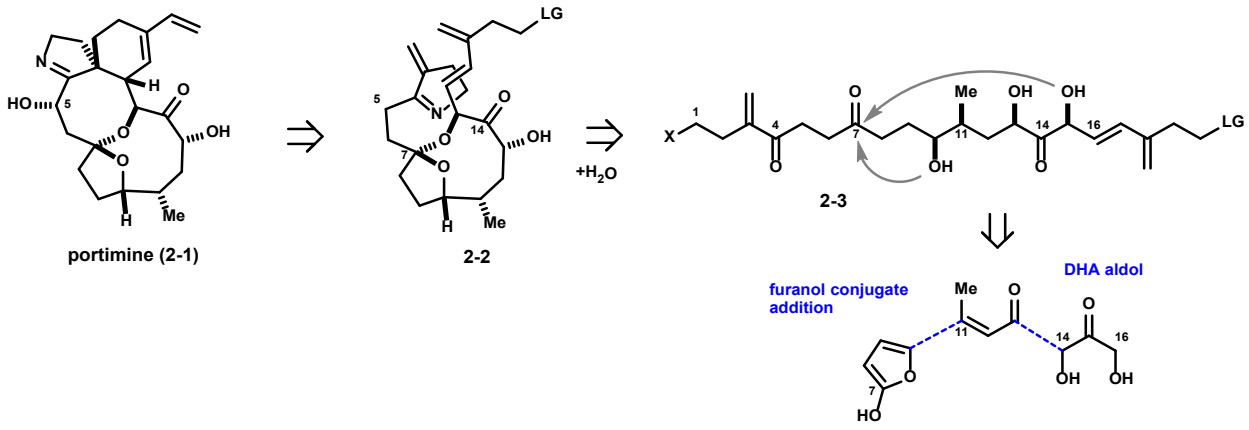
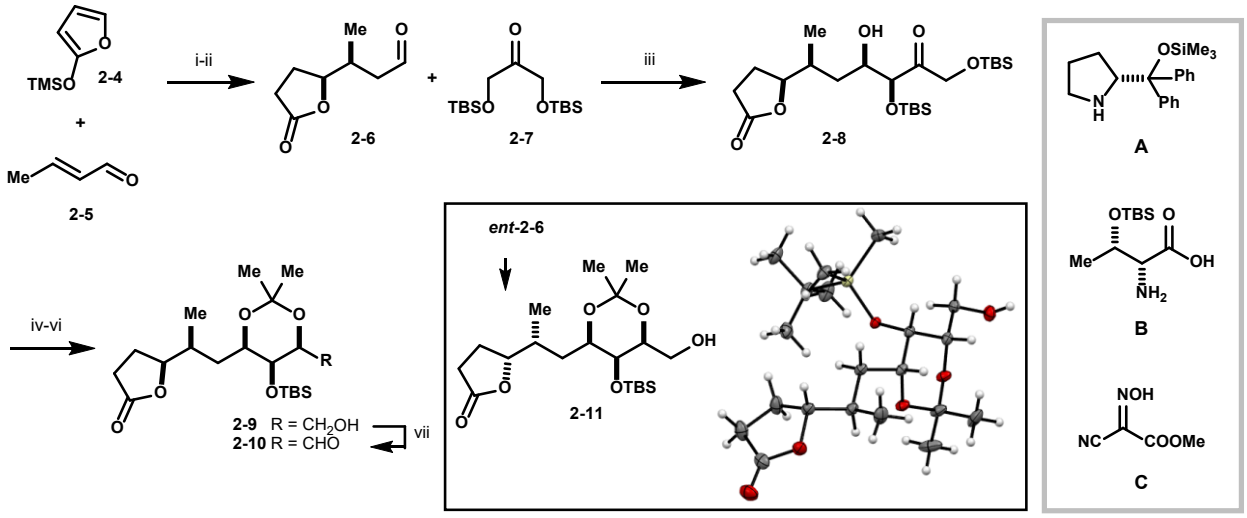


Figure 10. Revised retrosynthetic analysis of portimine.

Here, we have pursued a cycloaddition substrate (i.e. **2-2**) that lacks the C5 hydroxyl group, such that its hydrated chain precursor, namely **2-3**, could be built by appending a dienophile to the main chain late in the sequence via 1,4-diketone synthesis. We further mapped carbons 14-16 onto dihydroxyacetone and carbons 7-10 onto dihydrofuranone, such that the stereo tetrad in 3 could derive from sequential organocatalytic additions to a crotonaldehyde lynchpin. The forward synthesis is outlined below (**Scheme 21**).

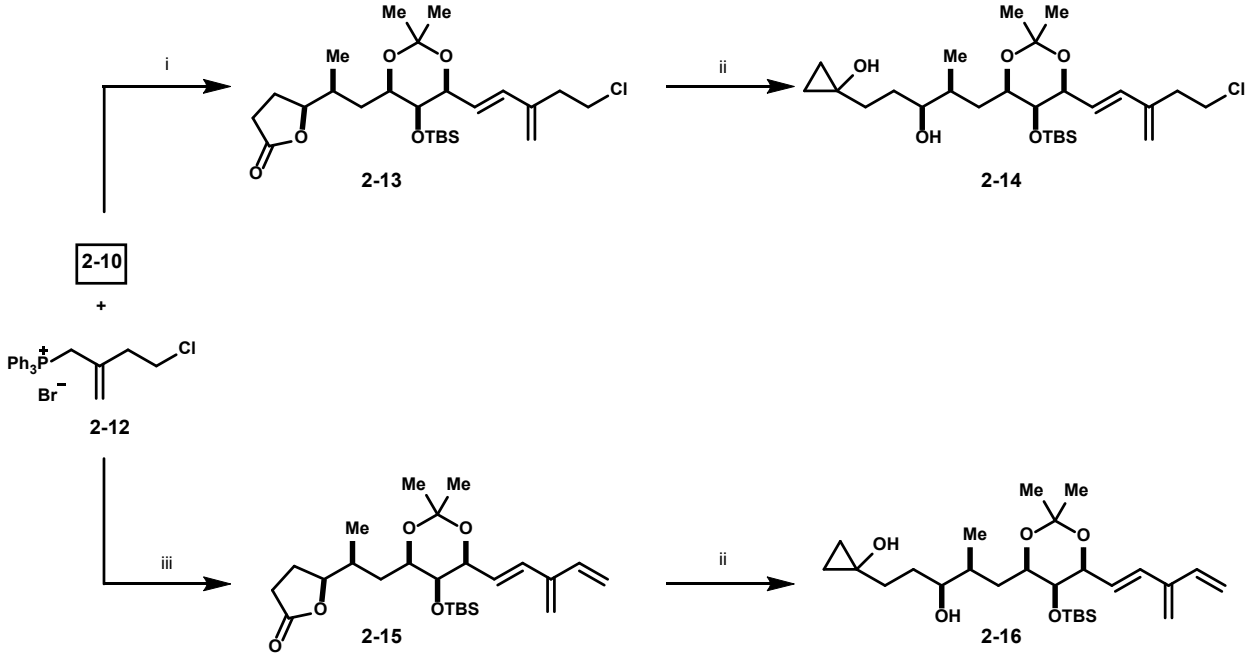


Conditions: (i) 2-(trimethylsiloxy)furan (1.0 eq.), crotonaldehyde (5.0 eq.), **A** (20 mol%), TFA (26 mol%), H_2O (3.0 eq.), THF (0.1 M), -15 °C; (ii) $Pd(OH)_2/C$ (2 mol%), H_2 (balloon), EtOAc (0.3 M), rt, 69% over 2 steps, 8.5:1 d.r., e.r. >20:1; iii) **2-7** (3.0 eq.), **B** (20 mol%), **C** (20 mol%), water (1 M), rt, 2 days, 75%, 13:1 d.r.; iv) Et_2BOMe (1.1 eq.), THF (0.13 M), MeOH (0.5 M), 1 h, then $NaBH_4$ (1.1 eq.), -78 °C, 5 h, 10:1 d.r.; (v) dimethoxypropane (20 eq.), PTSA (10 mol%), THF (0.1 M), rt, overnight; (vi) HF·py (34 eq.), py (50 v% of HF·py), THF (0.1 M), 0 °C, 30 min., rt, 1 h; (vii) $(COCl)_2$ (1.2 eq.), DMSO (1.3 eq.), DCM (0.05 M), -78 °C, 50 min., then DIPEA (2.4 eq.), -78 °C to rt, 10 min. Inset: The enantiomer of **2-6** was elaborated to a diastereomer of **2-9**. The structure of that molecule (**2-11**) was confirmed by *X-ray* crystallography (ORTEP drawn with 50% probability ellipsoids, CCDC #2123677).

Scheme 21. Sequential asymmetric organocatalytic addition reactions followed by directed reduction establish five stereocenters on a ten-carbon fragment.

Stirring a mixture of 2-trimethylsiloxyfuran with commercial crotonaldehyde in the presence of 20 mol% of *D*-proline derived catalyst **A**[52] gave, after hydrogenation of the crude mixture over $Pd(OH)_2/C$, butyrolactone **2-6** (**Scheme 21**). Under optimized conditions,[4] '*syn*' diastereomer (+)-**2-6** was isolated in good yield and selectivity in 20-gram batches. Compound **2-6** was then engaged in a selective cross aldol reaction with dihydroxy acetone derivative **2-7** using a silylated *D*-threonine organocatalyst acting in concert with co-catalytic methyl cyanoglyoxalate oxime.[53] The

resultant *syn* aldol product **2-8** formed efficiently at room temperature in a water solvent. Small amounts of an isomeric substance, most likely an *anti*-aldol adduct, were detected by ^{1}H NMR and mass spectrometry but not isolated in this experiment. Instead, crude **2-8** was treated with diethylmethoxyborane and $NaBH_4$ to reduce the ketone selectively to a *syn* 1,3-diol product.[54] The crude diol was then ketalized with dimethoxy propane, treated with HF/pyridine to cleave the primary silyl ether, and the incipient alcohol was oxidized under Swern conditions to afford a single isomer of aldehyde **2-10**. Stereochemistry assigned to **2-8**/**2-9** was consistent with spectroscopic data and corroborated by the X-ray structure of diastereomer **2-11** (Scheme 1, inset). The latter was synthesized from the enantiomer of **2-6** (made using catalyst *ent*-**A**) employing the same sequence of reactions used to generate **2-10**.



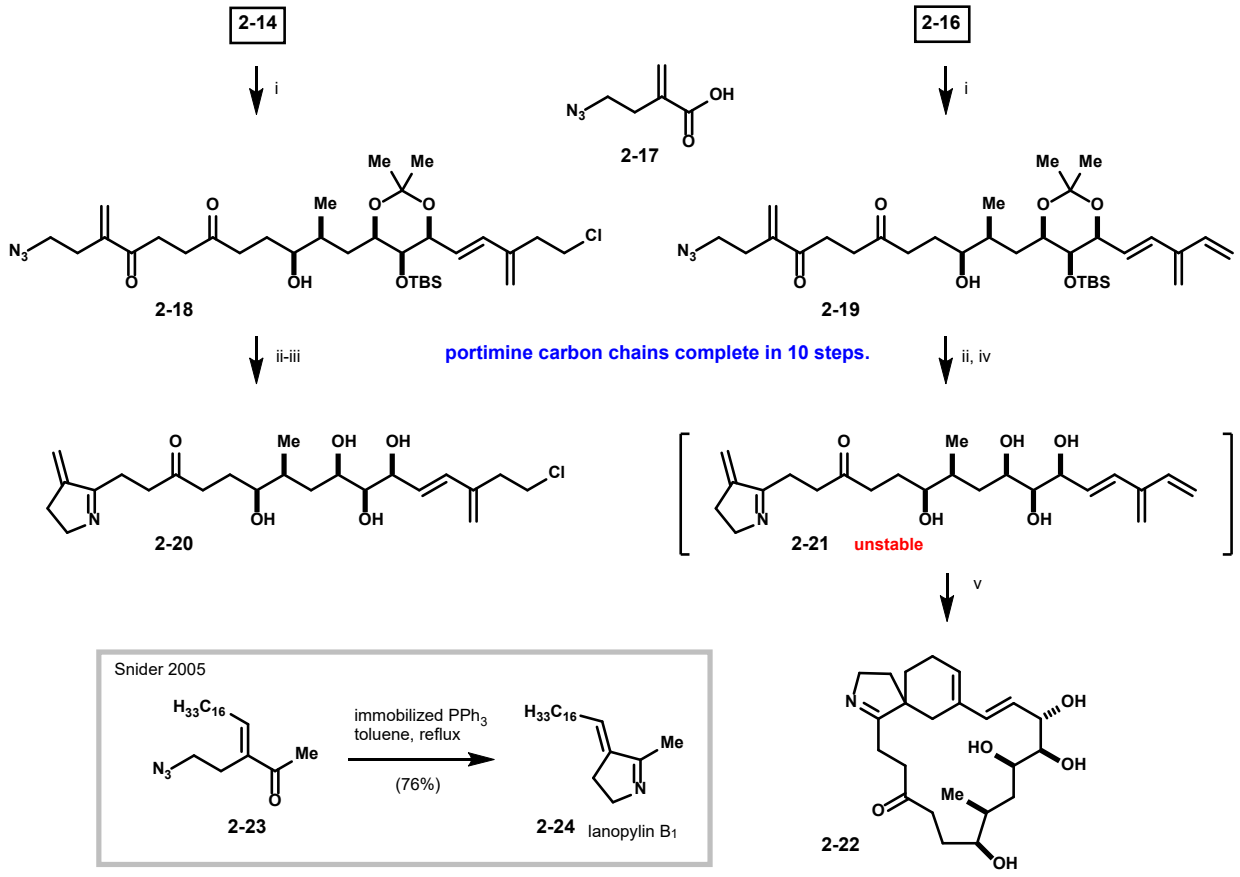
Conditions: (i) **2-12** (1.5 eq.), KHMDS (1.4 eq.), THF (0.02 M), -78 °C to rt, overnight, 21% over 5 steps); ii) $Ti(OiPr)_4$ (2.4 eq.), EtMgBr (4.4 eq.), THF (0.2 M), 15 °C, 4 h; iii) KHMDS (1.35 eq.), THF (0.02 M), -78 °C to rt, overnight, then KHMDS (1.35 eq.), 8 h, 28% over 5 steps.

Scheme 22. Synthesis of cyclopropanols **2-14** and **2-16**.

Having established the target oxygenation pattern stereoselectively and in differentiated form, the remaining segments of the portimine chain were appended to this core. Reaction of aldehyde **2-10** with the ylide derived from treating allylic phosphonium salt **2-12** with KHMDS afforded E-disubstituted diene **2-13** (**Scheme 22**). Compound **2-13** was only the second purified intermediate in the sequence. Chromatography provided pure **2-13** in 21% overall yield (74% per step average over 5 steps) from **2-8**. Notably, if the olefination of **2-10** was not quenched, but instead treated with a second equivalent of KHMDS, [3]dendralene **2-15** was formed in situ via dehydrochlorination. In that case, workup and chromatography provided pure **2-15** in 25% yield (over 5 steps) from **2-8**.

The butyrolactone in both **2-13** and **2-15** reacted efficiently with the Kulinkovich reagent derived from treating $Ti(OiPr)_4$ with EtMgBr to afford cyclopropanols **2-14** and **2-16**, respectively.[32] Previously optimized conditions (2 equiv. of Et_2Zn at -78˚C, followed by 5 mol% $PdCl_2(PPh_3)_2$, 10 mol% Bu_4NBr[44], followed by the rapid addition of a freshly prepared THF solution of acid chloride) allowed for azido diketone **2-18** to be isolated in 25% overall yield from **2-14 (Scheme 23)**. The same protocol was effective on **2-16**, wherein homologation product **2-19** was isolated in 27% overall yield from **2-16**.

Structures **2-18** and **2-19** harbor all of the carbon present in portimine. They were synthesized in only eight steps from known butyrolactone **2-4** Notably, ^{13}C NMR indicated **2-18** existed predominately in keto form. There was no indication of equilibria being established with hemiketal tautomers, even after prolonged storage. Moreover, the hydroxyl protecting groups in **2-18** could be removed hydrolytically under mild conditions. ^{13}C spectra of the resultant polyol again showed two carbonyl resonances.



Conditions: (i) **2-17** (3.0 eq.), Ghosez's reagent (3.0 eq.), $ZnEt_2$ (2.0 eq.), $Pd(PPh_3)_2Cl_2$ (5 mol%), Bu_4NBr (10 mol%), THF (0.1 M), -78 °C to rt, 25% from **2-14** and 27% from **2-16**; ii) HF (48% aq. solution, 10 v% of MeCN), MeCN (0.005 M), 0 °C to rt, 45 min., 43%; iii) PPh_3 (polymer-bound, 4.1 eq.), toluene (0.01 M), rt, overnight; iv) PPh_3 (polymer-bound, 7.0 eq.), toluene (0.002 M), rt, overnight; v) pH 6.5 citric acid buffer (prepared as reported by Kishi[24]), EtOH, 37 °C, 2 days, 10% from **2-19**.

Scheme 23. Synthesis of the spirocycle **2-22**.

Using Staudinger chemistry developed by Snider for the synthesis of lanopylin B1,[55] treatment of the crude deprotection product with polymer-bound phosphine resulted in Wittig imination of the enone carbonyl to afford methylidene pyrroline **2-21**. Iminyl keto tetraol **2-21** was unstable and degraded on standing. Nonetheless, it allowed for the preliminary Diels-Alder studies to be

conducted looking into the potential of both azido ketone and imine as a dienophile partner. The results are shown below (**Table 6**).

Table 6. Diels-Alder studies.

Entry	Substrate	Condition	Outcome
1	**2-18**	Toluene, 140 °C	Complex mixture
2	**2-18**	Toluene, 105 °C	Slow decomposition
3	**2-25**[a]	$BF_3 \cdot Et_2O$ (3 eq.), rt	No reaction
4	**2-25**	Toluene, 4Å MS, 120 °C	No reaction
5	**2-25**	Toluene, 4Å MS, 140 °C	Decomposition
6	**2-25**	ATPH[147], rt	No reaction
7	**2-25**	5 M $LiClO_4$ in Et_2O, rt	No reaction
8	**2-20**	pH 6.5 citric acid buffer, 37 °C	Complex mixture
9	**2-20**	$Yb(OTf)_3$, rt	Formation of an unidentified isomer
10	**2-20**	$HSbF_6$, 0 °C	Michael addition[c]
11	**2-20**	5 M $LiClO_4$ in Et_2O, rt	Michael addition[c]
12	**2-21**	**pH 6.5 citric acid buffer, 37 °C**	**2-22 (10%)[b]**

[a]**2-25** is a fully deprotected azido ketone
[b]Isolated yield
[c]Proposed based on the disappearance of terminal alkene protons

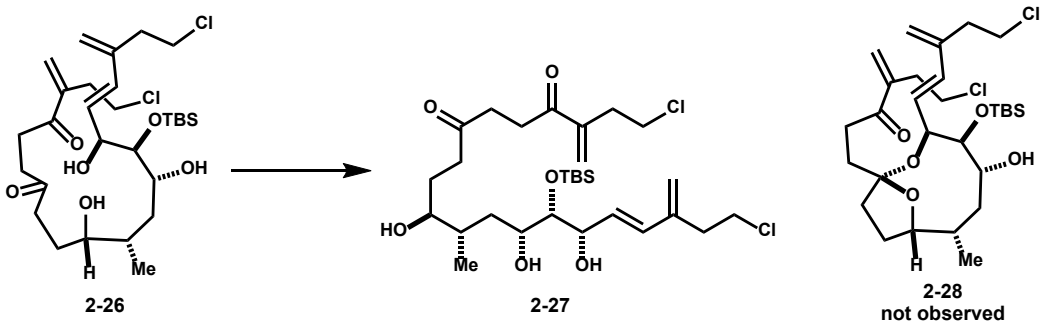
Unfortunately, none of the initial attempts yielded any of the desired product. Most of the conditions resulted either in the complete decomposition of the starting material or its complete recovery. In some cases, the disappearance of the exocyclic methylene protons on the crude ^1H NMR suggested an expected Michael-type reactivity, however, none of the Michael adducts have been isolated. However, when [3]dendralene congener **2-19** was elaborated in an identical manner to **2-21** and subjected to Kishi's citric buffer conditions,[24] a new product has been observed and isolated in 10% yield over two steps. Not surprisingly, without geometric constraints provided by internal ketalization (e.g. see **2-2 Figure 10**), cycloaddition occurred at the less hindered diene component of the dendralene motif. That said, the reaction generated largely one diastereomer (unassigned stereochemistry at the spiro carbon) and confirmed that the methylidene pyrroline was

a competent dienophile. This prompted us into looking more into the reactivity of this previously overlooked 5-membered pyrroline, which will be discussed in the later section.

2.2 Transketalization attempts

One of the core motifs of portimine and related natural products is the macrocyclic ether. It was hypothesized that the steric constraints associated with the formation of the ether bridge could promote cycloaddition by forcing two branches of the otherwise linear precursor together. Therefore, several transketalization attempts have been conducted with the results shown below (**Table 7**).

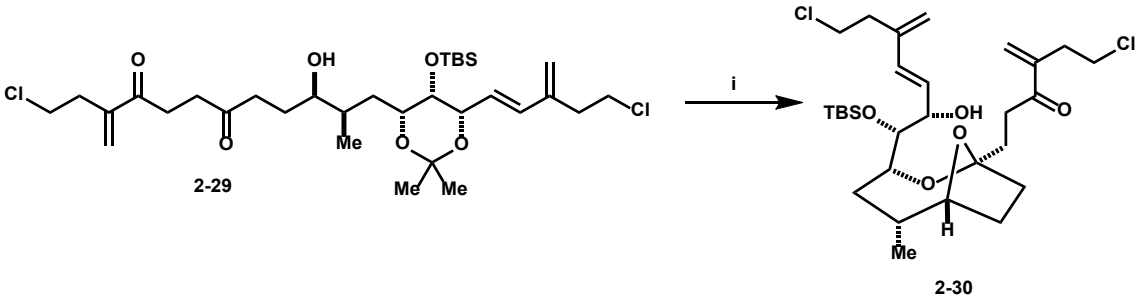
Table 7. Transketalization studies**.**



Entry	Condition	Result
1	TFA, wet DCM	**2-27** (38% yield)
2	PTSA·H_2O, DCM	**2-27**
3	4 Å MS, Amberlyst-15, DCM	No reaction
4	PPTS, DCM	No reaction
5	CSA, DCM	No reaction
6	2 M HCl in THF	Decomposition
7	Tropylium·BF_4	Decomposition

Unexpectedly, **2-26** turned out to be resistant to standard ketalization conditions and none of the desired product was observed. Acidic conditions mostly led to either acetonide removal with

no subsequent ketalization or recovery of the starting material. Interestingly, in the presence of Tropylium·BF_4 complex complete decomposition was observed with no formation of the ketal. It is important to note that this situation drastically changed for the diastereomeric analog of **2-26** that we prepared in the early studies has been exposed to the acidic medium. In this case, in the presence of TFA, **2-29** underwent a clean conversion to the corresponding ketal **2-30**.



Conditions: (i) wet TFA in DCM, rt, 1 h, 61%.

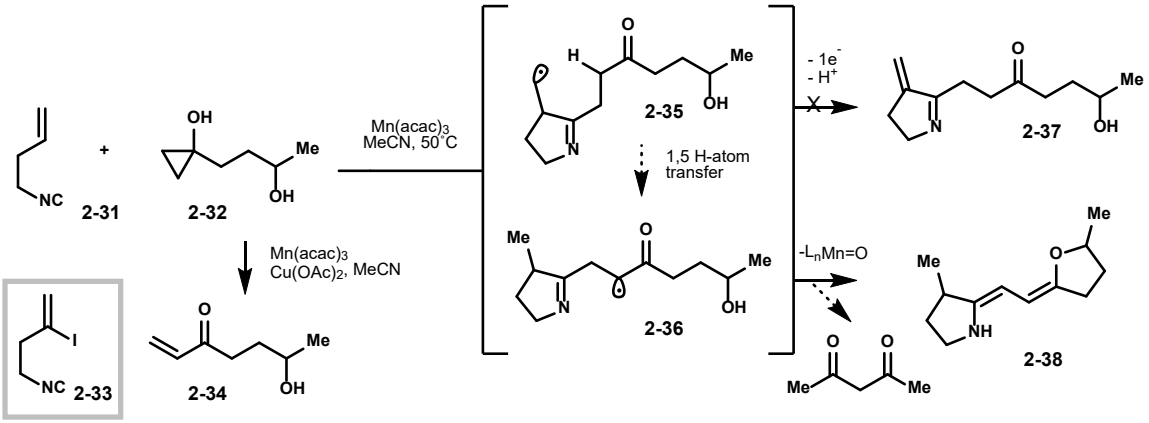
Scheme 24. Transketalization of **2-29**.

Interestingly, this process underwent with the undesired regiochemistry suggesting the substrate's preference for an 8-membered cycle over a 10-membered one. We hypothesized that initial Diels-Alder cycloaddition could be essential for the preferential formation of the larger ring and thus focused our attention on the Diels-Alder studies. Previously unsuccessful intramolecular cycloaddition attempts prompted us into looking into intermolecular alternatives.

2.3 Development of a novel heterocycle and studies into its reactivity

In 2017 Dai group reported manganese-mediated cyclopropanol opening with its subsequent coupling to various aromatic isocyanides to form phenanthridines.[56] Inspired by this approach, we decided to try to adapt it to the formation of the desired methylidene pyrroline through homolytic cleavage of the cyclopropanol followed by the capture of the incipient β-keto alkyl radical with butenyl isonitrile (**Scheme 25**). We modeled this process using cyclopropanol **2-32**. Diol **2-32** was

derived from the Kulinkovich ring opening of γ-valerolactone. Mixing **2-32** with 2 equiv. of freshly prepared 3-butenyl isonitrile in the presence of $Mn(acac)_3$ and $Cu(OAc)_2$ gave predominately enone **2-34**. It appeared Cu^{II} was intercepting the organomanganese species derived from **2-32** faster than it reacted with **2-31**. We repeated the reaction in the absence of $Cu(OAc)_2$.

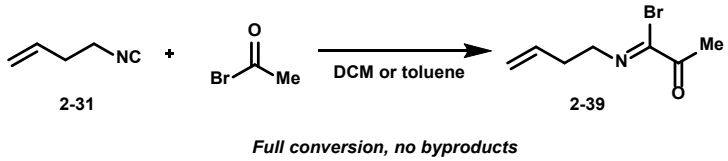


Scheme 25. Model system attempts to form the methylidene pyrroline motif.

In that case, we isolated a previously unknown type of amino oxy 1,3-diene (**2-38**) as a mixture of diastereomers. This result was interpreted in terms of an alkyl radical derived from **2-32** capturing **2-31**[57] to afford an iminyl radical that cyclizes (5-exo trig) onto the pendant alkene to afford primary radical **2-35**. The goal was for this radical to be oxidized in situ to form methylidene **2-37**. However, in the absence of Cu^{II}, we speculated that 1,5 H-atom transfer in this system was facile, and that conversion of the resultant stabilized radical **2-36** to **2-38** could be driven by the loss of a manganese-oxo complex. We attempted to prevent the formation of **2-38** using co-oxidants other than $Cu(OAc)_2$. Unfortunately, none of those tested proved effective. Likewise, replacing **2-31** with vinyl iodide **2-33** in the $Mn(acac)_3$ reaction also failed to generate **2-37**. Despite unsuccessful attempts at direct coupling, we were still interested in ways of converting isocyanide **2-31** into the corresponding pyrroline. To our knowledge, there have been

no reports on the structure containing no substituents at 4 and 5 positions of the ring. Development of its efficient synthesis would thus be of great benefit to studies of portimine and related natural products.

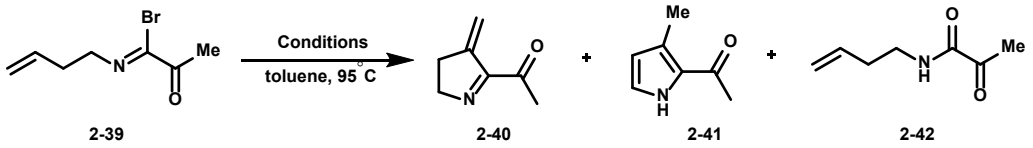
Our initial attempts have been inspired by work done by Zhu group[58] that used Heck chemistry to generate 5-, 6- and 7-membered heterocycles. However, their substrates required substitution at the α-position of the isocyanide as well as worked only with aryl halides as coupling partners. Neither of these requirements worked for the desired system. Therefore, we decided to switch from intermolecular Heck to its intramolecular alternative. To do that we reacted 3-butenyl isocyanide with acetyl bromide following traditional Nef chemistry[59] to afford the corresponding imidoyl bromide **2-39** in high purity.



Scheme 26. Formation of the imidoyl bromide **2-39**.

With **2-39** in hand, the next step was to screen conditions for the intramolecular Heck coupling. Standard conditions employing $Pd(OAc)_2$ and PPh_3 as a pre-catalyst system and cesium pivalate as a base afforded some of the desired product **2-40** along with pyrrole **2-41** and unexpected amide **2-42**. It is hypothesized that the latter is produced through an *in-situ* formation of the nitrilium ion by bromide elimination that later gets captured by water upon work-up. Therefore, conditions had to be screened to improve initial results (**Table 8**).

Table 8. Optimization of Heck cross-coupling reaction.

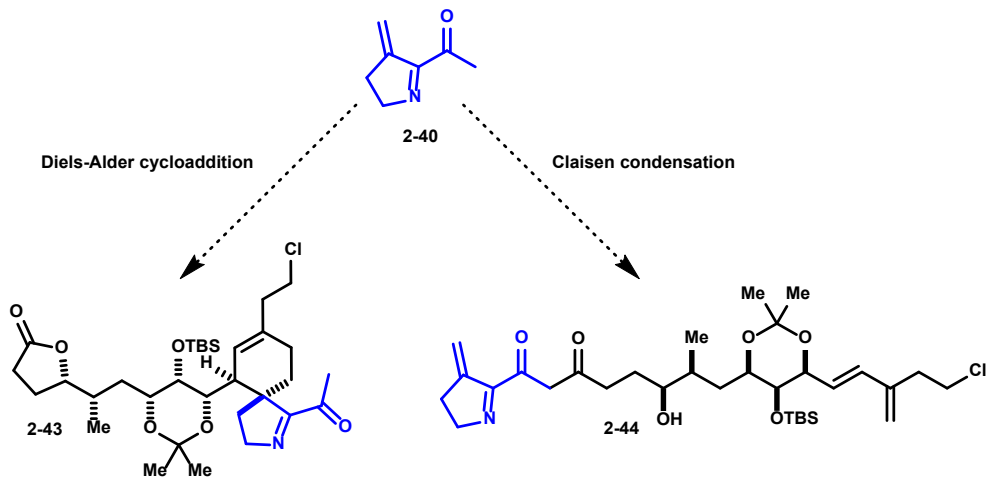


2-39 2-40 2-41 2-42

Entry	Base	Catalyst	Result
1	CsOPiv	$Pd(OAc)_2/PPh_3$	3.5:1:2.5
2	$NaHCO_3$	$Pd(OAc)_2/PPh_3$	No product
3	Et_3N	$Pd(OAc)_2/PPh_3$	Complex mixture[a]
4	Pyridine	$Pd(OAc)_2/PPh_3$	No product
5	NaOAc	$Pd(OAc)_2/PPh_3$	No product
6	2,6-lutidine	$Pd(OAc)_2/PPh_3$	No product
7	$AgCO_3$	$Pd(OAc)_2/PPh_3$	1:0:1.4
8	$AgCO_3$	$Pd(PPh_3)_4$	1.5:0:1 (20%)[b]
9[c]	$AgCO_3$	$Pd(PPh_3)_4$	12:0:1 (50%)[b]

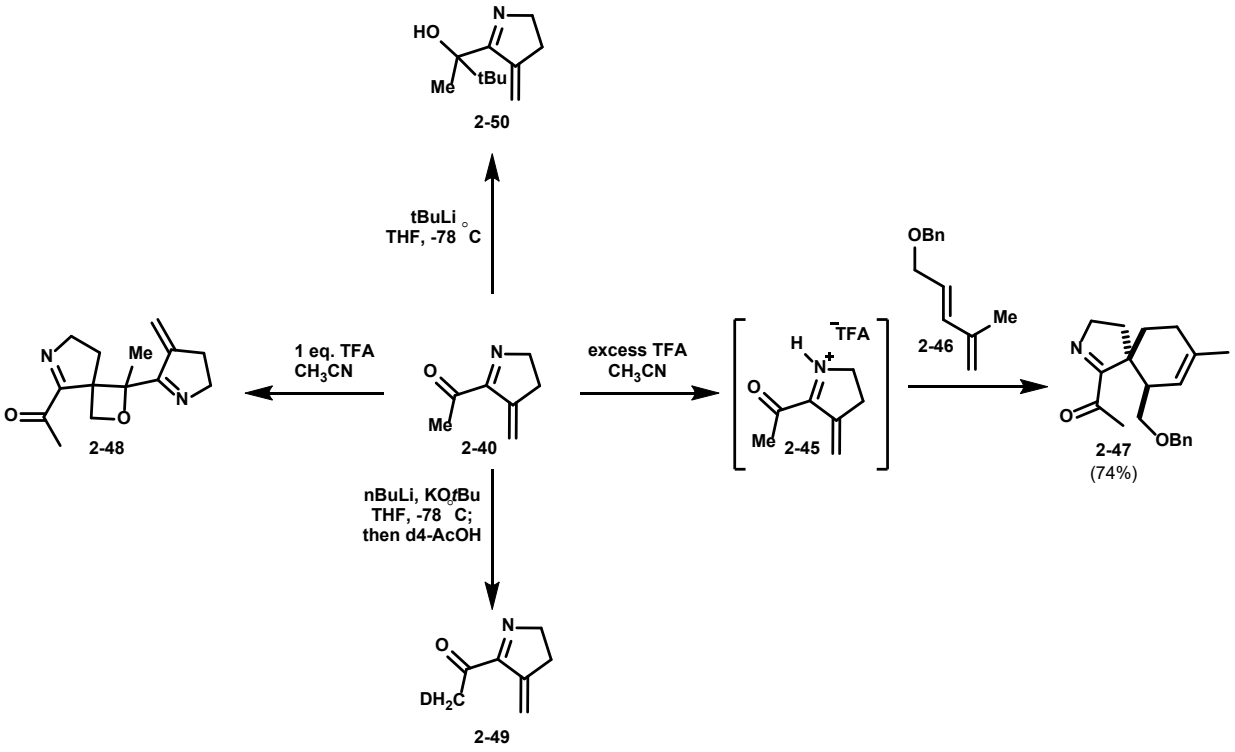
[a]Complex mixture contained all of 3 shown compounds as well as multiple byproducts
[b]Isolated yield after chromatography
[c]The solution of **2-39** in toluene was added to the preheated (90 °C) suspension of the catalytic mixture over 15 minutes

Out of all the bases screened, $AgCO_3$ showed the best result, with no pyrrole formation. $Pd(PPh_3)_4$ showed to be a superior catalyst to $Pd(OAc)_2/PPh_3$ system. Lastly, the slow addition of imidoyl bromide to the preheated catalyst mixture allowed for the minimal production of **2-42**. This went in accordance with the hypothesized mechanism of amide formation as slow addition allowed for the coupling to occur at a fast enough rate to prevent the elimination of bromide. With pyrroline **2-40** in hand, the next steps were to probe its reactivity. Two routes were envisioned that could alleviate previous challenges.



Scheme 27. Two possible pathways could simplify the construction of the portimine chain.

On one hand, pyrroline was expected to be a much more activated dienophile. Although no reports have been published on 5-membered imines, Evans described a method for the formation of salts from related 6- and 7-membered ring systems.[60] These substrates showed a high propensity towards [4+2] reaction. Utilizing this method would allow us for the early installation of the spirocycle with the subsequent intramolecular condensation/lactone opening that would position us right on the verge of completion of the total synthesis (**Scheme 27**). On the other hand, the sequence of events could be reversed with the Claisen condensation occurring first followed by the intramolecular cycloaddition that now would be governed by the sterics and stereochemistry of the substrate. Our preliminary studies on both approaches are summarized in **Scheme 28**. While **2-40** showed to be either unreactive or unstable in the presence of various Lewis acids ($Cu(OTf)_2$, $SnCl_4$, $TiCl_4$, BF_3Et_2O, $MgBr_2{\bullet}Et_2O$) and upon heating, it was readily able to form a salt in the presence of an excess amount of TFA (~100 eq.). Interestingly, however, while a stoichiometric amount of acid should be enough to protonate the only basic site on the molecule, in the presence of 1 eq. of TFA, **2-40** underwent dimerization to cleanly afford **2-48**.

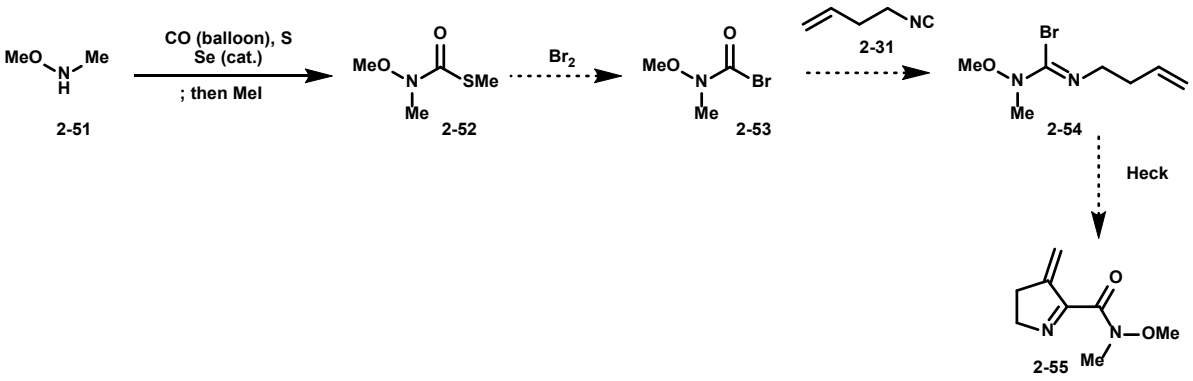


Scheme 28. Studies on the reactivity of **2-40**.

It is hypothesized that the reaction goes through a stepwise mechanism in which the initial protonation of pyrroline increases the electrophilicity of the exo-methylene motif. The ketone on another molecule on **2-40** attacks the terminal side of the double bond followed by the intramolecular closure of the 4-membered oxetane ring. While the exact stereochemistry is currently unknown, the reaction generates only one diastereomer. Despite this initial discovery, it was later found that the slow addition of pyrroline to the solution of acid is capable of promoting Diels-Alder in the stoichiometric quantities showcasing promise for the application of this methodology to the real system, which is currently being studied.

On the Claisen route, it was discovered that even though **2-40** can successfully form an enolate in the presence of either KHMDS or Schlosser's base (confirmed by the *in situ* deuteration with d4-AcOH), the enolate is unreactive towards any attempted electrophiles (BnBr, valerolactone,

benzaldehyde, methyl benzoate). Interestingly, during the base screen, tBuLi, famous for being a strong, non-nucleophilic base, actually added to the ketone affording the corresponding tertiary alcohol **2-50**. This showcased an extreme electrophilicity of the methyl ketone and inspired us to consider an analog of **2-40** that could take advantage of this reactivity.



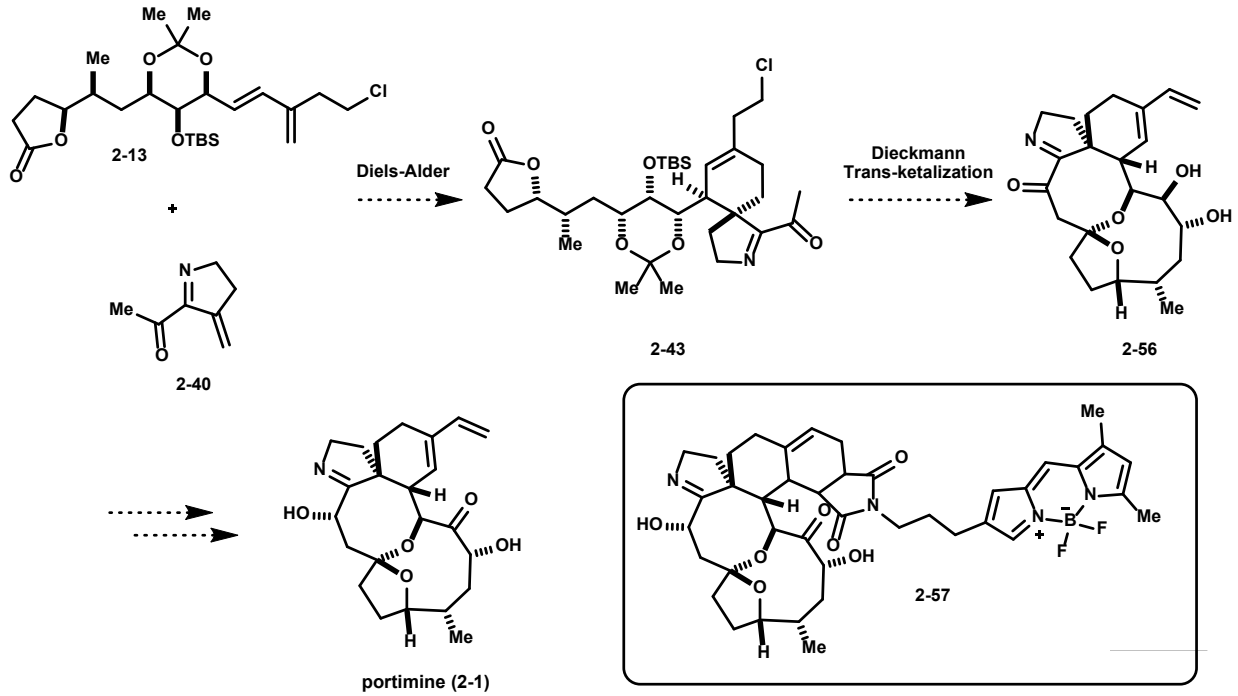
Scheme 29. Proposed synthesis of Weinreb amide **2-55**.

Weinreb amides are known to be extremely potent electrophiles capable of a selective mono-addition of nucleophiles due to the chelating effect of the methoxy substituent on the nitrogen. It was hypothesized that corresponding pyrroline **2-55** could take advantage of this reactivity by utilizing the umpolung strategy in which **2-55** will act as an electrophile instead of a nucleophile as planned before. It was discovered that compounds like **2-52** are known and can be easily synthesized in one step from the corresponding amine.[61] It is envisioned that **2-52** can in turn be converted into the corresponding acid bromide **2-53** which will then be subjected to the same sequence of events as for **2-39**. These studies are currently ongoing.

2.4 Future Directions

Overall, despite unusual reactivity, pyrroline **2-40** was found to be a competent dienophile capable of producing a desired cycloadduct in a high yield with the correct regiochemistry.

Successful implementation of the aforementioned methodology will place us right on the verge of completion of the first total synthesis of portimine, which will not only provide access to the numerous analogs of portimine but also allow for the in-depth studies of its mechanism of action through construction of various fluorescent probes, an example of which is shown in **Scheme 30**.



Scheme 30. Proposed completion of the synthesis and development of the fluorescent probe.

2.5 Conclusion

Two different approaches were pursued for the construction of the key spirocyclic motif of portimine. Linear substrates containing all carbon atoms of portimine, ready for the intramolecular Diels-Alder addition were synthesized in a highly efficient manner from the commercially available TMS-furanone taking advantage of the power of organocatalysis. While initial cycloaddition studies didn't yield the desired outcome, numerous alternative conditions are possible and are currently being pursued.

The intermolecular approach allowed for the synthesis of the novel heterocycle and the studies of its reactivity. Unprecedented dimerization has been reported and preliminary Diels-Alder studies have been successful. Implementation of the developed methodology to the real system would allow for the completion of the first total synthesis of portimine.

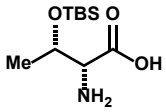
2.6 Experimental Section

2.6.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under positive pressure of argon at room temperature. The dry solvents were dried using activated alumina solvent drying system. Methanol (MeOH) was dried over activated 3Å molecular sieves. Thin layer chromatography (TLC) was performed on pre-coated plates Sorbent Technologies, silica gel 60 PF_{254} (0.25 mm). TLC were visualized with UV light (254 nm) or stained using $KMnO_4$ or cerium ammonium molybdate (CAM). Flash chromatography was performed on silica gel 60 (240-400 mesh). The photochemistry experiments were conducted in an RPR-100 Photochemical Reactor (Rayonet©) using 300 nm fluorescent tubes. NMR spectra were recorded on a Bruker Avance (500 MHz) spectrometer using $CDCl_3$ or DMSO-d_6 as solvent and referenced relative to residual $CHCl_3$ (δ = 7.26 ppm), CD_3OD (δ = 3.31 ppm) or DMSO (δ = 2.50 ppm). Chemical shifts are reported in ppm and coupling constants (J) in Hertz. ^{13}C NMR and APT spectra were recorded on the same instruments (125 MHz) with total proton decoupling referenced relative to residual $CHCl_3$ (δ = 77.16 ppm), CD_3OD (δ = 49.0 ppm) or DMSO (δ = 39.52 ppm). HSQC, HMBC, COSY and NOESY NMR experiments were used to aid assignment of NMR peaks when required. All melting points are uncorrected. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. High-resolution mass spectra were recorded on Thermo Scientific Exactive® Mass Spectrometer with DART ID-CUBE Waters GST Premier, and Waters LCT Premier. Optical rotations were measured on a Rudolph Autopol III Automatic Polarimeter and are quoted in units of 10^{-1} deg cm^2 g^{-1}.

2.6.2 Experimental Procedures

(2*R*,3*S*)-2-amino-3-((*tert*-butyldimethylsilyl)oxy)-*N*-((*R*)-2-hydroxy-1,2,2-triphenylethyl)butanamide (B)



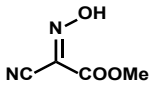
The title compound was synthesized following a literature procedure.[62] To a suspension of *D*-threonine (2.38 g, 20.0 mmol) in pyridine (200 mL, 0.1 M) was added imidazole (2.72 g, 40.0 mmol, 2.0 eq.) and TBSCl (3.32 g, 22.0 mmol, 1.1 eq.) at room temperature. The reaction was stirred for 2 days at room temperature. Pyridine was then removed under reduced vacuum. The residue was stirred with H_2O/hexane (total 200 mL, 1:1) for 4 h. The solid was filtered, washed with hexane and dried under high vacuum to give **B** (1.1 g) as a white solid in 23% yield.

^{1}H NMR (500 MHz, DMSO): δ = 4.36 (dt, J = 8.1, 4.1 Hz, 1H), 3.07 (s, 1H), 1.18 (d, J = 6.3 Hz, 2H), 0.83 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (125 MHz, DMSO): δ = 168.5, 67.4, 59.5, 25.8, 21.6, 17.8, -4.8, -4.9.

The spectra matched those reported in the literature.[62]

methyl (*Z*)-2-cyano-2-(hydroxyimino)acetate (C)



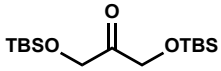
The title compound was synthesized following a literature procedure.[63] To cyanomethyl acetate (1.76 mL, 20.0 mmol) and $NaNO_2$ (1.66 g, 24.0 mmol, 1.2 eq.) in water (8.0 mL, 2.5 M) was added AcOH (1.51 mL, 26.4 mmol, 1.32 eq.) dropwise at 0 °C. The reaction was stirred for 4 h at room temperature. It was then cooled to 0 °C and acidified with conc. HCl to pH 1. The crude product was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting solid was triturated with hexane

to remove residue AcOH. It was then dried under high vacuum to give **C** (2.45 g) as an off-white solid in 95% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.17 (s, 1H), 3.99 (s, 3H).

The spectra matched those reported in the literature.[63]

2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-one (2-7)

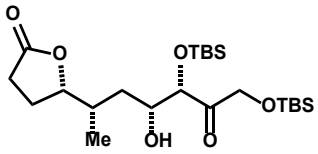


To a suspension of dihydroxyacetone (2.7 g 30 mmol) in DCM (100 mL, 0.3 M) was added imidazole (4.3 g, 63 mmol, 2.1 eq.) and TBSCl (9.5 g, 63 mmol, 2.1 eq.) portionwise at 0 °C. The reaction was stirred was then refluxed overnight. The mixture was then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure. The residue was passed through a short silica plug (EtOAc/hexane 1/9) and concentrated under reduced pressure to give **2-7** (9.5 g) as a colorless oil in >95% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.41 (s, 4H), 0.92 (s, 18H), 0.09 (s, 12H).\

The spectra matched those reported in the literature.[64]

(*S*)-5-((1*R*,3*S*)-1-hydroxy-3-((*S*)-5-oxotetrahydrofuran-2-yl)butyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-one (2-8)



A flask containing aldehyde **2-6** (9.74 g, 62.3 mmol) and disiloxyacetone **2-7** (59.6 g, 187 mmol, 3.0 eq.) was evacuated under high vacuum and refilled with argon. Then *O*-TBS-threonine (2.91 g, 12.5 mmol, 20 mol%), oxime **C** (1.60 g, 12.5 mmol, 20 mol%) and water (62 mL, 1 M) were added to the mixture. The flask was purged with argon and the reaction was stirred vigorously (but not splashing) for 48 h at room temperature to give a thick light-yellow suspension. Then Et_2O and

sat. aqueous solution of $NaHCO_3$ was added. The two layers were separated, and the aqueous layer was extracted with Et_2O (4x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product (13:1 *dr*) was purified by column chromatography on silica gel (EtOAc/hexane 0/100 to 3/7) to furnish alcohol **2-8** (22.1 g) as a light-yellow oil in 75% yield and 13:1 *dr*. The reaction was repeated several times at deca-gram scale and yields were 69%-75%.

Note: $NaHCO_3$ solution was used to remove the oxime. If it was not removed during the workup, it would co-elute with the aldol product during column chromatography. The reaction can also be performed with 1.3 eq. of disiloxyacetone, giving the product in 47% yield and same *dr*.

$[\alpha]_D^{25}$ = +15.3 (*c* = 0.1, $CHCl_3$)

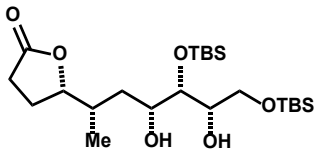
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.55 – 4.48 (m, 1H), 4.47 (d, *J* = 3.2 Hz, 2H), 4.30 (d, *J* = 3.0 Hz, 1H), 3.95 (d, *J* = 9.8 Hz, 1H), 2.57 – 2.48 (m, 2H), 2.38 (br. s, 1H), 2.25 (dddd, *J* = 12.6, 8.1, 6.8, 5.5 Hz, 1H), 2.00 – 1.89 (m, 2H), 1.66 (ddd, *J* = 14.2, 7.1, 3.5 Hz, 1H), 1.44 (ddd, *J* = 14.1, 9.9, 6.0 Hz, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.94 (s, 9H), 0.92 (s, 9H), 0.14 – 0.04 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.5, 177.2, 83.0, 79.0, 70.9, 68.7, 36.5, 34.7, 29.2, 25.93, 25.86, 25.5, 18.6, 18.3, 15.2, -4.7, -4.8, -5.28, -5.34.

FT-IR (neat): 3472, 2953, 2929, 2886, 2857, 1773, 1735, 1472, 1255, 1187, 1107, 1006, 837, 778, cm^{-1}

HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_{23}H_{47}O_6Si_2$ 475.29057; found 475.29099.

(*S*)-5-((2*S*,4*R*,5*S*,6*S*)-5,7-bis((*tert*-butyldimethylsilyl)oxy)-4,6-dihydroxyheptan-2-yl)dihydrofuran-2(3*H*)-one (2-58)



To a solution of ketone **2-8** (1.44 g, 3.04 mmol) in THF (24 mL) and MeOH (6.1 mL) was added Et_2BOMe (0.44 mL, 3.35 mmol, 1.1 eq.) dropwise at -78 °C. the mixture was stirred at the same

temperature for 1 h. Then $NaBH_4$ (127 mg, 3.35 mmol, 1.1 eq.) was added and the mixture was stirred for 5 h at -78 °C. The reaction was quenched by slow addition of sat. aqueous solution of NH_4Cl at -78 °C. The mixture was warmed to room temperature and the crude product was extracted with EtOAc (4x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was azeotroped with MeOH (6x) to give crude **2-58** (10:1 *dr* for the newly formed stereocenters) as a yellow oil. This material was used for the next step without further purification.

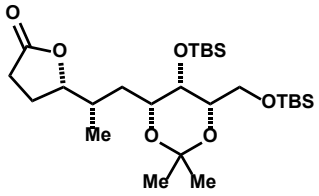
An analytical sample was purified for characterization.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.54 (ddd, J = 8.4, 6.8, 5.1 Hz, 1H), 3.85 – 3.80 (m, 1H), 3.72 – 3.55 (m, 4H), 2.59 – 2.42 (m, 4H), 2.32 – 2.20 (m, 1H), 2.01 – 1.89 (m, 2H), 1.61 (ddd, J = 14.1, 7.1, 3.8 Hz, 1H), 1.45 (ddd, J = 14.0, 9.4, 6.1 Hz, 1H), 1.04 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 14.3 Hz, 18H), 0.13 (d, J = 6.0 Hz, 6H), 0.08 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.4, 83.3, 74.8, 72.9, 68.8, 63.6, 37.1, 34.8, 29.3, 26.1, 26.0, 25.6, 18.4, 18.4, 15.3, -4.1, -4.2, -5.2, -5.2.

HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_{23}H_{49}O_6Si_2$ 477.30622; found 477.30655.

(*S*)-5-((*S*)-1-((4*R*,5*S*,6*S*)-5-((*tert*-butyldimethylsilyl)oxy)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)propan-2-yl)dihydrofuran-2(3*H*)-one (2-59)



To a solution of crude diol **2-58** (3.04 mmol) and dimethoxypropane (7.48 mL, 60.8 mmol, 20 eq.) in THF (20 mL) was added PTSA (57.8 mg, 0.304 mmol, 10 mol%) in THF (10 mL) at room temperature. The reaction mixture was stirred overnight at room temperature. It was then quenched with sat. aqueous solution of $NaHCO_3$ until the solution turned basic. The crude product was extracted with EtOAc (4x). The combined organic layers were washed with brine, dried over

Na_2SO_4 and concentrated under reduced pressure to give crude **2-59** as a yellow oil. This material was used for the next step without further purification.

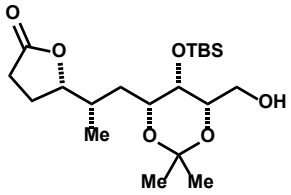
An analytical sample was purified for characterization.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.48 (ddd, *J* = 8.5, 6.7, 5.7 Hz, 1H), 3.91 – 3.78 (m, 1H), 3.76 – 3.66 (m, 1H), 3.63 (dd, *J* = 9.9, 7.0 Hz, 1H), 3.53 (dd, *J* = 9.9, 5.8 Hz, 1H), 3.36 (t, *J* = 1.2 Hz, 1H), 2.58 – 2.46 (m, 2H), 2.37 – 2.19 (m, 1H), 2.03 – 1.85 (m, 2H), 1.86 – 1.70 (m, 1H), 1.41 – 1.32 (m, 1H), 1.39 (s, 3H), 1.35 (s, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.05 (d, *J* = 13.9 Hz, 6H), 0.05 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.6, 98.3, 83.6, 74.4, 70.4, 66.3, 62.6, 34.8, 34.7, 29.8, 29.3, 26.3, 26.0, 25.7, 19.3, 18.7, 18.4, 15.3, -3.6, -3.9, -5.0, -5.1.

HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_{26}H_{53}O_6Si_2$ 517.33752; found 517.33771.

(*S*)-5-((*S*)-1-((4*R*,5*S*,6*S*)-5-((*tert*-butyldimethylsilyl)oxy)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl)propan-2-yl)dihydrofuran-2(3*H*)-one (2-9)



To a solution of crude **2-59** (3.04 mmol) in THF (24 mL) at 0 °C was added a THF solution of HF·py and pyridine, which was prepared by adding pyridine (1.4 mL) dropwise to HF·py (70%, 2.7 mL) in THF (6.5 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C and 1 h at room temperature. The reaction was then carefully quenched by addition of sat. aqueous solution and solid of $NaHCO_3$. The crude product was extracted with EtOAc (4x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give crude **2-9** as a yellow oil. This material was used for the next step without further purification.

Note: It is important to basify the solution until pH >7. Otherwise, the ketal will be removed upon concentration. Pyridine can be washed off with $CuSO_4$ when necessary.

An analytical sample was purified for characterization.

$[\alpha]_D^{25}$ = +23.0 (*c* = 0.1, $CHCl_3$)

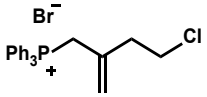
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.49 (ddd, *J* = 8.5, 6.8, 5.7 Hz, 1H), 3.92 – 3.86 (m, 2H), 3.79 – 3.71 (m, 1H), 3.57 – 3.49 (m, 1H), 3.31 (t, *J* = 1.4 Hz, 1H), 2.57 – 2.48 (m, 2H), 2.34 – 2.20 (m, 1H), 2.01 – 1.87 (m, 2H), 1.81 – 1.70 (m, 2H), 1.43 (s, 3H), 1.39 (s, 3H), 1.33 (ddd, *J* = 14.2, 7.3, 2.5 Hz, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.93 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.6, 98.7, 83.5, 74.3, 70.2, 67.0, 63.8, 34.7, 34.5, 29.9, 29.3, 26.2, 25.7, 19.4, 18.5, 15.3, -3.4, -3.8.

FT-IR (neat): 3460, 2929, 2885, 2856, 1771, 1473, 1463, 1379, 1253, 1192, 1168, 1095, 973, 836, 775 cm^{-1}

HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_{20}H_{39}O_6Si$ 403.25104; found 403.25140.

(4-chloro-2-methylenebutyl)triphenylphosphonium bromide (2-12)



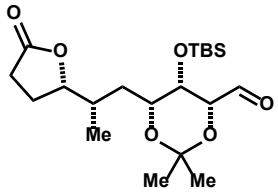
A mixture of 2-(bromomethyl)-4-chlorobut-1-ene[65] (2.97 g, 16.2 mmol) and PPh_3 (4.25 g, 16.2 mmol, 1.0 eq.) in toluene (33 mL, 0.5 M) was refluxed for 4.5 h. The mixture was then filtered. The solid was washed with anhydrous toluene and Et_2O (3x). It was then collected and dried under vacuum to give phosphonium bromide **2-12** (6.6 g) as white solid in 91% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85 – 7.77 (m, 6H), 7.77 – 7.70 (m, 3H), 7.70 – 7.59 (m, 6H), 5.12 (d, *J* = 5.0 Hz, 1H), 4.93 (d, *J* = 4.9 Hz, 1H), 4.68 (d, *J* = 15.2 Hz, 2H), 3.59 (t, *J* = 6.4 Hz, 2H), 2.29 (t, *J* = 6.4 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.13 (d, *J* = 3.0 Hz), 134.05 (d, *J* = 9.9 Hz), 133.11 (d, *J* = 9.6 Hz), 130.32 (d, *J* = 12.8 Hz), 121.83 (d, *J* = 10.0 Hz), 117.87 (d, *J* = 85.8 Hz), 42.04, 39.74 (d, *J* = 3.5 Hz), 30.47 (d, *J* = 48.7 Hz).

Note: 1H NMR may vary if the sample is at different concentration.

(4*R*,5*S*,6*R*)-5-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethyl-6-((*S*)-2-((*S*)-5-oxotetrahydrofuran-2-yl)propyl)-1,3-dioxane-4-carbaldehyde (2-10)



To $(COCl)_2$ (0.31 mL, 3.65 mmol, 1.2 eq.) in DCM (51 mL) was added DMSO (0.28 mL, 3.95 mmol, 1.3 eq.) dropwise at -78 °C. The reaction was stirred for 15 min at -78 °C and crude alcohol **2-9** (3.04 mmol) in DCM (10 mL) was added dropwise. After 50 min at -78 °C, DIPEA (1.27 mL, 7.30 mmol, 2.4 eq.) was added dropwise. The mixture was stirred for 10 min at -78 °C and another 10 min at room temperature. The reaction was then quenched by addition of sat. aqueous solution of NH_4Cl. The crude product was extracted with EtOAc (4x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give crude aldehyde **2-10**. The crude material was used for the next step without further purification.

$[\alpha]_D^{25}$ = +39.0 (*c* = 0.1, $CHCl_3$)

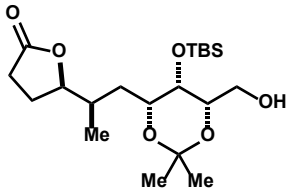
^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.52 (s, 1H), 4.48-4.42 (m, 1H), 4.13 (s, 1H), 3.89 (dd, J = 10.3, 1.4 Hz, 1H), 3.73 (t, J = 1.4 Hz, 1H), 2.53-2.50 (m, 2H), 2.29-2.22 (m, 1H), 1.97-1.87 (m, 2H), 1.76-1.70 (m, 1H), 1.47 (s, 3H), 1.41 (s, 3H), 1.37-1.28 (m, 1H), 1.00 (d, J = 6.9 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 3H), -0.06 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = = 202.4, 177.3, 98.9, 83.3, 78.8, 70.0, 67.4, 34.4, 34.2, 29.5, 29.1, 26.0, 25.9, 25.4, 19.0, 18.4, 15.1, -3.6, -4.2.

FT-IR (neat): 2987, 2939, 1772, 1748, 1383, 1193, 1089 cm^{-1}

HRMS-ESI (m/z): $[M+Na]^+$ Calcd. For $C_{20}H_{36}O_6SiNa$ 423.2179; Found 423.2199**.**.

(*R*)-5-((*R)*-1-((4*R*,5*S*,6*S*)-5-((*tert*-butyldimethylsilyl)oxy)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl)propan-2-yl)dihydrofuran-2(3*H*)-one (2-11)



The compound was prepared following the procedure for the synthesis of **2-9**. The crude product was purified by column chromatography on silica gel (EtOAc/hexane 0/100 to 3/7) to furnish alcohol **2-11** as a white solid. The solid was dissolved in minimum volume of EtOAc and hexane was added slowly until the white precipitate persisted. Then 2 drops of EtOAc were added and the solution became clear. A single crystal of the product was obtained after 2-days' slow evaporation. The structure was confirmed by X-ray diffraction.

R_f = 0.2 (hexanes/EtOAc 7:3)

Melting point: 122-126 °C.

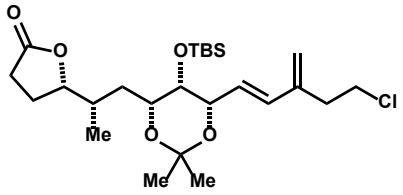
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.27 (dt, *J* = 8.5, 6.6 Hz, 1H), 3.90 (ddd, *J* = 8.0, 4.0, 1.4 Hz, 1H), 3.82 (dt, *J* = 10.9, 1.8 Hz, 1H), 3.74 (dd, *J* = 10.9, 8.0 Hz, 1H), 3.58 – 3.49 (m, 1H), 3.30 (s, 1H), 2.54 (dd, *J* = 10.0, 6.9 Hz, 2H), 2.29 – 2.20 (m, 1H), 2.03 – 1.74 (m, 4H), 1.42 (s, 3H), 1.40 (s, 3H), 1.01 – 0.91 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.93 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.4, 98.9, 85.7, 74.2, 69.3, 67.2, 63.8, 35.3, 33.6, 29.9, 29.2, 26.2, 26.0, 19.3, 18.5, 14.1, -3.4, -3.9.

FT-IR (neat): 3461, 2929, 1772, 1379, 1253, 1192, 1168, 1095 cm^{-1}

HRMS (ESI) m/z: [M-H]- Calcd. for $C_{20}H_{37}O_6Si$ 401.2365; Found 401.2360.

(*S*)-5-((*S*)-1-((4*R*,5*S*,6*S*)-5-((*tert*-butyldimethylsilyl)oxy)-6-((E)-5-chloro-3-methylenepent-1-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propan-2-yl)dihydrofuran-2(3*H*)-one (2-13)



To phosphonium **2-12** (1.95 g, 4.47 mmol, 1.5 eq.) in THF (130 mL) was added KHMDS (0.5 M in toluene, 8.36 mL, 4.18 mmol, 1.4 eq.) dropwise at -78 °C. The mixture was stirred for 1 h at -78 °C and crude aldehyde **2-10** (2.98 mmol) in THF (20 mL) was added dropwise. The reaction was stirred at -78 °C for 3 h. It was then allowed to slowly warm up to room temperature inside the dry ice-acetone bath and stirred overnight. The reaction was quenched by addition of sat. aqueous solution of NH_4Cl. The crude product was extracted with EtOAc (4x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane 0/100 to 2/8) to furnish diene **2-13** (310 mg) as a viscous light-yellow oil in 21% yield over 5 steps.

$[\alpha]_D^{25}$ = +57.0 (*c* = 0.1, $CHCl_3$)

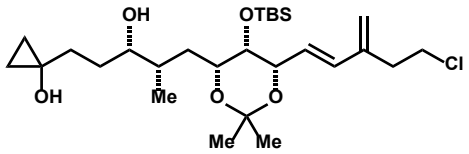
^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.96 (dd, *J* = 11.6, 1.2 Hz, 1H), 5.75 (dd, *J* = 11.7, 8.8 Hz, 1H), 5.12 (d, *J* = 1.7 Hz, 1H), 4.95 (t, *J* = 1.7 Hz, 1H), 4.72 (dt, *J* = 8.9, 1.2 Hz, 1H), 4.50 (ddd, *J* = 8.4, 6.7, 5.5 Hz, 1H), 3.92 (dd, *J* = 10.7, 1.2 Hz, 1H), 3.56 (td, *J* = 6.8, 1.3 Hz, 2H), 3.21 (t, *J* = 1.4 Hz, 1H), 2.59 – 2.49 (m, 4H), 2.28 (dtd, *J* = 12.9, 7.2, 6.1 Hz, 1H), 1.99 – 1.88 (m, 2H), 1.78 (ddd, *J* = 14.1, 10.6, 5.3 Hz, 1H), 1.42 (s, 3H), 1.40 (s, 3H), 1.36 – 1.29 (m, 1H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.96 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.6, 141.5, 131.9, 131.5, 117.3, 98.6, 83.4, 70.5, 70.1, 69.9, 42.9, 39.8, 34.7, 34.6, 30.1, 29.3, 26.2, 25.6, 19.6, 18.6, 15.2, -3.3, -3.4.

FT-IR (neat): 2955, 2928, 2856, 1774, 1462, 1379, 1254, 1189, 1162, 1034, 958, 910, 866 cm^{-1}

HRMS-ESI (m/z): $[M+NH_4]^+$ calcd. for $C_{25}H_{47}ClNO_5Si$ 504.29065; found 504.29175.

1-((3*S*,4*S*)-5-((4*R*,5*S*,6*S*)-5-((*tert*-butyldimethylsilyl)oxy)-6-((*E*)-5-chloro-3-methylenepent-1-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)-3-hydroxy-4-methylpentyl)cyclopropan-1-ol (2-14)



To lactone **2-13** (327 mg, 0.671 mmol) in THF (3.4 mL, 0.2 M) was added $Ti(OiPr)_4$ (0.48 mL, 1.61 mmol, 2.4 eq.) at 10. Then EtMgBr (3.0 M in Et_2O, 0.98 mL, 2.95 mmol, 4.4 eq.) was added over 2 h, while keeping the water bath at about 15 °C. The reaction was then stirred at the same temperature until all starting material was consumed based on TLC (about 2 h). It was then carefully quenched by dropwise addition of sat. aqueous solution of NH_4Cl. The bilayer mixture was stirred until the dark-blue color disappeared and the mixture became totally white. The crude product was extracted with EtOAc (4x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give crude cyclopropanol **2-14**. The crude product was used for the next step without further purification.

The characterization data were collected on crude material.

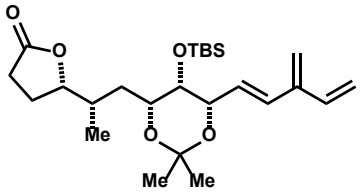
^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.97 (d, J = 11.7 Hz, 1H), 5.76 (dd, J = 11.7, 8.9 Hz, 1H), 5.12 (s, 1H), 4.96 (s, 1H), 4.75 (d, J = 8.9 Hz, 1H), 3.97 – 3.90 (m, 1H), 3.71 – 3.66 (m, 1H), 3.56 (t, J = 6.7 Hz, 2H), 3.23 (s, 1H), 2.56 (t, J = 6.8 Hz, 2H), 1.95 – 1.83 (m, 3H), 1.81 – 1.71 (m, 1H), 1.65 – 1.57 (m, 1H), 1.53 – 1.38 (m, 8H), 1.00 – 0.89 (m, 12H), 0.80 – 0.67 (m, 2H), 0.49 – 0.39 (m, 2H), 0.05 (s, 3 H), 0.04 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.5, 132.0, 131.4, 117.2, 99.1, 75.5, 70.6, 70.4, 69.3, 55.8, 42.9, 39.7, 38.1, 36.8, 36.3, 32.7, 29.8, 26.3, 19.6, 18.6, 14.1, 13.4, 11.6, -3.3, -3.3.

FT-IR (neat): 3371, 2957, 2938, 2886, 2857, 1463, 1379, 1255, 1200, 1164, 1085, 1037, 955, 866, 733 cm^{-1}

HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_{27}H_{50}ClO_5Si$ 517.31106; found 517.31274.

(*S*)-5-((*S*)-1-((4*R*,5*S*,6*S*)-5-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethyl-6-((*E*)-3-methylenepenta-1,4-dien-1-yl)-1,3-dioxan-4-yl)propan-2-yl)dihydrofuran-2(3*H*)-one (2-15)



To phosphonium **2-12** (30 mg, 0.068 mmol, 1.35 eq.) in THF (0.2 mL) was added KHMDS (0.5 M in toluene, 0.14 mL, 0.068 mmol, 1.35 eq.) dropwise at -78 °C. The mixture was stirred for 1 h at -78 °C and aldehyde **2-10** (20 mg, 0.050 mmol) in THF (0.18 mL) was added dropwise. The reaction was stirred at -78 °C for 3 h. It was then allowed to slowly warm up to room temperature inside the dry ice-acetone bath and stirred overnight. Then KHMDS (0.5 M in toluene, 0.14 mL, 0.068 mmol, 1.35 eq.) was added and the reaction was stirred at room temperature for 8 h. The reaction was quenched by addition of sat. aqueous solution of NH_4Cl. The crude product was extracted with EtOAc (4x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane 0/100 to 2/8) to furnish dendralene **2-15** as a viscous light-yellow oil.

$[\alpha]_D^{25}$ = +65.0 (*c* = 0.1, $CHCl_3$)

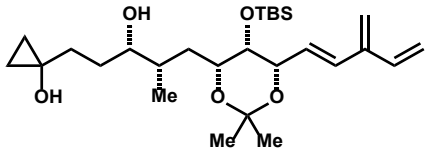
^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.41 (dd, *J* = 17.5, 10.6 Hz, 1H), 6.20 (d, *J* = 11.5 Hz, 1H), 5.83 (dd, *J* = 11.6, 8.9 Hz, 1H), 5.25 – 5.17 (m, 2H), 5.13 (d, *J* = 10.3 Hz, 1H), 5.03 (d, *J* = 1.6 Hz, 1H), 4.56 (d, *J* = 8.9 Hz, 1H), 4.49 (ddd, *J* = 8.5, 6.8, 5.5 Hz, 1H), 3.90 – 3.87 (m, 1H), 3.17 (t, *J* = 1.4 Hz, 1H), 2.57 – 2.47 (m, 2H), 2.34 – 2.22 (m, 1H), 1.99 – 1.89 (m, 2H), 1.77 (ddd, *J* = 14.1, 10.6, 5.2 Hz, 1H), 1.40 (s, 3H), 1.38 (s, 3H), 1.35 – 1.26 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.96 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.6, 143.0, 138.1, 131.6, 129.6, 118.2, 116.4, 98.5, 83.4, 70.7, 69.9, 34.63, 34.58, 30.1, 29.3, 26.3, 25.8, 25.6, 19.6, 18.6, 15.2, -3.2, -3.4.

FT-IR (neat): 2990, 1777, 1473, 1464, 1380, 1257, 1198, 1163, 1085 cm^{-1}

HRMS-ESI (m/z): $[M+NH_4]^+$ calcd. for $C_{25}H_{46}NO_5Si$ 468.31398; found 468.31305.

1-((3*S*,4*S*)-5-((4*R*,5*S*,6*S*)-5-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethyl-6-((*E*)-3-methylenepenta-1,4-dien-1-yl)-1,3-dioxan-4-yl)-3-hydroxy-4-methylpentyl)cyclopropan-1-ol (2-16)



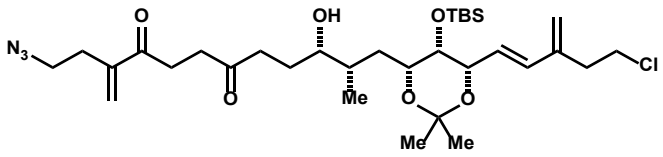
To lactone **2-15** (1.86 g, 4.13 mmol) in THF (205 mL, 0.02 M) was added Ti(O*i*Pr)$_4$ (2.9 mL, 9.90 mmol, 2.4 eq.) at 10 °C. Then EtMgBr (3.0 M in Et$_2$O, 6.1 mL, 18.2 mmol, 4.4 eq.) was added over 2 h, while keeping the water bath at about 15 °C. The reaction was then stirred at the same temperature until all starting material was consumed based on TLC (about 2 h). It was then carefully quenched by dropwise addition of sat. aqueous solution of NH$_4$Cl. The bilayer mixture was stirred until the dark-blue color disappeared and the mixture became totally white. The crude product was extracted with EtOAc (4x). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure to afford crude cyclopropanol **2-16**. The crude product was used for the next step without further purification.

An analytical sample was purified for NMR:

^{1}H NMR (500 MHz, CDCl$_3$): δ = 6.42 (dd, *J* = 17.5, 10.6 Hz, 1H), 6.22 (d, *J* = 11.6, 1H), 5.84 (dd, *J* = 11.6, 8.9 Hz, 1H), 5.26 – 5.18 (m, 2H), 5.14 (d, *J* = 11.6 1H), 5.04 (d, *J* = 1.7 Hz, 1H), 4.58 (d, *J* = 8.8 Hz, 1H), 4.01 – 3.76 (m, 2H), 3.68 (dt, *J* = 9.4, 2.3 Hz, 1H), 3.19 (t, *J* = 1.4 Hz, 1H), 1.95 – 1.81 (m, 3H), 1.81 – 1.70 (m, 1H), 1.64 – 1.58 (m, 1H), 1.53 – 1.48 (m, 1H), 1.48 – 1.39 (m, 7H), 0.97 (s, 9H), 0.93 (d, *J* = 7.1 Hz, 3H), 0.80 – 0.67 (m, 2H), 0.49 – 0.38 (m, 2H), 0.08 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 143.0, 138.1, 131.4, 129.8, 118.2, 116.4, 99.0, 75.5, 70.9, 70.2, 69.3, 55.8, 38.1, 36.8, 36.3, 32.7, 29.8, 26.3, 19.5, 18.6, 14.1, 13.4, 11.6, -3.2, -3.3.

(10*S*,11*S*)-1-azido-12-((4*R*,5*S*,6*S*)-5-((*tert*-butyldimethylsilyl)oxy)-6-((*E*)-5-chloro-3-methylenepent-1-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)-10-hydroxy-11-methyl-3-methylenedodecane-4,7-dione (2-18)



To azido acid **2-17** (42.3 mg, 0.300 mmol, 3.0 eq.) in DCM (0.3 mL) was added Ghosez's reagent (39.7 μL, 0.300 mmol, 3.0 eq.) at 0 °C. The mixture was stirred for 15 min at 0 °C and 15 min at room temperature. Then it was diluted with THF (1.0 mL) and was ready to use. The acyl chloride is not very stable, so it may be better to use it immediately.

In another vial, to a solution of cyclopropanol **2-14** (51.7 mg, 0.100 mmol) in THF (1.0 mL) was added $ZnEt_2$ (1 M in hexane, 0.20 mL, 0.200 mmol, 2.0 eq.) dropwise at -78 °C. The mixture was stirred for 10 min at -78 °C and 15 min at room temperature. Then $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.0050 mmol, 5 mol%) and Bu_4NBr (3.2 mg, 0.010 mmol, 10 mol%) was added at the same time. After another 15 min at room temperature, the solution of acyl chloride was added to the reaction mixture as fast as possible. The reaction was stirred for 45 min and quenched with sat. aqueous solution of NH_4Cl. The crude product was extracted with EtOAc (4x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane 0/100 to 3/7) to furnish **2-18** (16 mg) as a colorless oil in 25% yield, together with an amide generated from Ghosez reagent. The amide can be removed by a second purification by column chromatography. The material could also be used without further purification.

$[\alpha]_D^{25}$ = +27.0˚ (*c* = 0.1, $CHCl_3$)

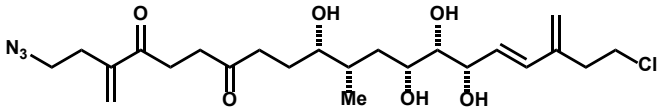
^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.20 (s, 1H), 5.96 (d, J = 11.7 Hz, 1H), 5.93 (s, 1H), 5.76 (dd, J = 11.7, 8.9 Hz, 1H), 5.11 (s, 1H), 4.95 (s, 1H), 4.73 (dt, J = 8.9, 1.2 Hz, 1H), 3.92 (d, J = 10.7 Hz, 1H), 3.56 (t, J = 6.8 Hz, 2H), 3.55 – 3.50 (m, 1 H), 3.35 (t, J = 6.9 Hz, 2H), 3.22 (t, J = 1.4 Hz, 1H), 3.03 – 2.98 (m, 2H), 2.78 – 2.73 (m, 2H), 2.74-2.67 (m, 1H), 2.67 – 2.58 (m, 1H), 2.58 – 2.52 (m, 4H), 1.87 – 1.73 (m, 2H), 1.73 – 1.63 (m, 1H), 1.46 – 1.37 (m, 8H), 0.96 (s, 9H), 0.91 (d, J = 7.0 Hz, 3H), 0.04 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.2, 199.7, 144.7, 141.5, 131.9, 131.5, 127.2, 117.2, 98.9, 74.0, 70.6, 70.3, 69.5, 50.1, 42.9, 40.4, 39.8, 37.4, 36.5, 35.4, 31.6, 31.1, 29.9, 28.9, 26.3, 19.6, 18.6, 12.2, -3.3, -3.3.

FT-IR (neat): 3440, 2957, 2931, 2887, 2857, 2098, 1715, 1678, 1630, 1462, 1378, 1254, 1198, 1163, 1085, 1037, 936, 659.

HRMS-ESI (m/z): $[M+H]^+$ calcd. for $C_{32}H_{54}ClN_3O_6SiNa$ 662.3363; found 662.3380.

(10*S*,11*S*,13*R*,14*S*,15*S*,*E*)-1-azido-20-chloro-10,13,14,15-tetrahydroxy-11-methyl-3,18-dimethyleneicos-16-ene-4,7-dione (2-25)



To a solution of **2-18** (77 mg, 0.12 mmol) in MeCN (9 mL) was added HF (48% aq. solution, 1.0 mL) in MeCN (1.0 mL) at 0 °C. The reaction was then stirred for 3 h at room temperature. The mixture was diluted water and extracted with EtOAc (3x). The combined organic layers were washed with sat. aqueous solution of $NaHCO_3$. The aqueous layer was back extracted with EtOAc (2x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane 0/100 to 4/6) to furnish **2-25** (25 mg) as a colorless oil in 43% yield,

Note: the reaction could also be done in 0.05 M of aq. HF/MeCN (1/10) and finished within 30 min.

$[\alpha]_D^{25}$ = +10.0˚ (*c* = 0.1, $CHCl_3$)

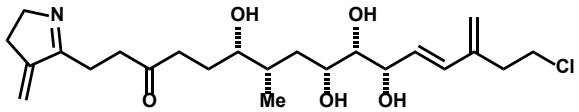
^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.21 (s, 1H), 5.98 (d, *J* = 11.7 Hz, 1H), 5.93 (t, *J* = 1.1 Hz, 1H), 5.69 (dd, *J* = 11.6, 9.4 Hz, 1H), 5.14 (s, 1H), 5.11 (s, 1H), 4.52 (dd, *J* = 9.5, 4.3 Hz, 1H), 4.03 (ddd, *J* = 8.1, 6.0, 3.3 Hz, 1H), 3.62 – 3.52 (m, 2H), 3.40 – 3.32 (m, 3H), 3.30 (s, 1H), 3.11 – 3.01 (m, 1H), 3.01 – 2.91 (m, 2H), 2.83 – 2.71 (m, 2H), 2.71 – 2.63 (m, 1H), 2.62 – 2.52 (m, 5H), 2.15 – 2.07 (m, 1H), 1.97 – 1.83 (m, 2H), 1.73 (ddt, *J* = 14.1, 9.1, 7.0 Hz, 1H), 1.59 (dt, *J* = 12.4, 7.8 Hz, 1H), 1.00 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.7, 199.8, 144.6, 141.1, 132.6, 131.7, 127.3, 117.6, 86.4, 78.7, 75.8, 69.4, 50.1, 43.0, 39.9, 39.8, 38.7, 36.7, 36.5, 31.5, 31.1, 27.9, 17.3.

FT-IR (neat): 3425, 2955, 2928, 2872, 2097, 1713, 1676, 1529, 1400, 1369, 1261, 1067, 926, 792, 659 cm^{-1}.

HRMS-ESI (m/z): $[M-H_2O+Na]^+$ calcd. for $C_{23}H_{34}ClN_3NaO_5$ 490.2079; found. 490.2110

(6*S*,7*S*,9*R*,10*S*,11*S*,*E*)-16-chloro-6,9,10,11-tetrahydroxy-7-methyl-14-methylene-1-(4-methylene-3,4-dihydro-2*H*-pyrrol-5-yl)hexadec-12-en-3-one (2-20)



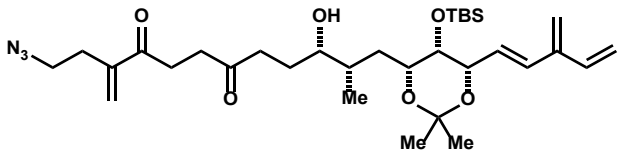
To a solution of **2-25** (20 mg, 0.041 mmol) in toluene (10 mL, 4.1 mM) was added polymer-bound PPh_3 (100-200 mesh, ~3 mmol/g, 55 mg, 0.16 mmol, 4.0 eq.). The reaction was stirred overnight at room temperature. The mixture was then filtered through cotton and the filtrate was concentrated under reduced pressure. The crude material was used without further purification.

The NMR data were collected on crude material.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.02 – 5.94 (m, 1H), 5.73 – 5.64 (m, 1H), 5.34 (t, J = 2.9 Hz, 1H), 5.26 (t, J = 2.5 Hz, 1H), 5.14 (s, 1H), 5.11 (dd, J = 3.6, 2.2 Hz, 1H), 4.51 (ddd, J = 9.4, 4.5, 1.0 Hz, 1H), 4.06 – 3.96 (m, 1H), 3.87 – 3.80 (m, 2H), 3.63 – 3.50 (m, 2H), 3.40 – 3.32 (m, 1H), 3.29 (dd, J = 4.5, 3.4 Hz, 1H), 2.96 – 2.84 (m, 2H), 2.71 – 2.46 (m, 8H), 2.14 – 2.05 (m, 1H), 1.98 – 1.81 (m, 2H), 1.79 – 1.64 (m, 1H), 1.64 – 1.52 (m, 1H), 0.99 (d, J = 6.7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.4, 173.5, 150.0, 141.0, 132.5, 131.8, 117.6, 108.4, 86.4, 78.6, 75.9, 69.1, 57.7, 43.0, 39.9, 39.7, 38.9, 38.6, 36.7, 29.8, 28.0, 22.8, 17.3.

(10*S*,11*S*)-1-azido-12-((4*R*,5*S*,6*S*)-5-((tert-butyldimethylsilyl)oxy)-2,2-dimethyl-6-((*E*)-3-methylenepenta-1,4-dien-1-yl)-1,3-dioxan-4-yl)-10-hydroxy-11-methyl-3-methylenedodecane-4,7-dione (2-19)



To azido acid **2-17** (194 mg, 1.37 mmol, 3.0 eq.) in DCM (0.5 mL) was added Ghosez's reagent (182 µL, 1.37 mmol, 3.0 eq.) at 0 °C. The mixture was stirred for 15 min at 0 °C and 15 min at room temperature. Then it was diluted with THF (1.5 mL) and was ready to use. The acyl chloride is not very stable, so it may be better to use it immediately.

In another vial, to a solution of cyclopropanol **2-16** (220 mg, 0.458 mmol) in THF (1.0 mL) was added $ZnEt_2$ (1 M in hexane, 0.92 mL, 0.916 mmol, 2.0 eq.) dropwise at -78 °C. The mixture was stirred for 10 min at -78 °C and 15 min at room temperature. Then $Pd(PPh_3)_2Cl_2$ (16.1 mg, 0.023 mmol, 5 mol%) and Bu_4NBr (14.8 mg, 0.046 mmol, 10 mol%) was added at the same time. After another 15 min at room temperature, the solution of acyl chloride was added to the reaction mixture as fast as possible. The reaction was stirred for 45 min and quenched with sat. aqueous solution of NH_4Cl. The crude product was extracted with EtOAc (4x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane 0/100 to 3/7) to furnish **2-19** (75 mg) as a light-yellow oil in 27% yield, together with an amide generated from Ghosez reagent. The amide can be removed by a second purification by column chromatography. The material could also be used without further purification.

$[\alpha]_D^{25}$ = +35.0˚ (*c* = 0.1, $CHCl_3$)

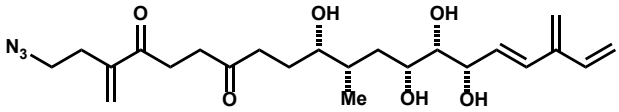
^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.41 (dd, *J* = 17.5, 10.6 Hz, 1H), 6.23 – 6.16 (m, 2H), 5.92 (s, 1H), 5.83 (dd, *J* = 11.6, 9.0 Hz, 1H), 5.27 – 5.17 (m, 2H), 5.13 (d, *J* = 10.7 Hz, 1H), 5.03 (s, 1H), 4.57 (d, *J* = 8.8, 1H), 3.87 (d, *J* = 10.3, Hz, 1H), 3.58 – 3.49 (m, 1H), 3.34 (t, *J* = 6.9 Hz, 2H), 3.19 – 3.15 (m, 1H), 3.03 – 2.96 (m, 2H), 2.79 – 2.72 (m, 2H), 2.73 – 2.66 (m, 1H), 2.66 – 2.58 (m, 1H), 2.55 (t, *J* = 6.9 Hz, 2H), 1.93 – 1.72 (m, 3H), 1.52 – 1.37 (m, 8H), 0.96 (s, 9H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.06 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.2, 199.7, 144.7, 143.0, 138.1, 131.5, 129.7, 127.2, 118.2, 116.4, 98.9, 74.0, 70.9, 70.2, 69.5, 50.1, 40.4, 37.5, 36.5, 35.4, 31.5, 31.1, 29.9, 28.9, 26.3, 19.5, 18.6, 12.1, -3.2, -3.3.

FT-IR (neat): 3350, 2988, 2099, 1714, 1681, 1379, 1256, 1200, 1164, 1084, 1041, 1023 cm^{-1}.

HRMS-ESI (m/z): $[M+Na]^+$ calcd. for $C_{32}H_{53}N_3NaO_6Si$ 626.3596; found 626.3605.

(10*S*,11*S*,13*R*,14*S*,15*S*,*E*)-1-azido-10,13,14,15-tetrahydroxy-11-methyl-3,18-dimethyleneicosa-16,19-diene-4,7-dione (2-60)



To a solution of **2-19** (75.1 mg, 0.124 mmol) in MeCN (2.0 mL) was added HF (48% aq. solution, 0.25 mL) in MeCN (0.5 mL) at 0 °C. The reaction was then stirred for 45 min at room temperature. The reaction was quenched by careful addition of sat. aqueous solution of $NaHCO_3$. The crude product was extracted with EtOAc (4x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane 0/100 to 4/6) to furnish **2-60**(24 mg) as a colorless oil in 43% yield.

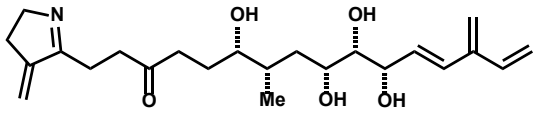
^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.41 (dd, J = 17.5, 10.5 Hz, 1H), 6.26 – 6.18 (m, 2H), 5.93 (s, 1H), 5.80 (dd, J = 11.6, 9.3 Hz, 1H), 5.27 – 5.07 (m, 4H), 4.41 (dd, J = 9.3, 3.9 Hz, 1H), 4.07 – 3.97 (m, 1H), 3.39 – 3.22 (m, 4H), 3.11 – 2.86 (m, 3H), 2.83 – 2.62 (m, 4H), 2.61 – 2.51 (m, 3H), 2.15 – 2.03 (m, 1H), 1.97 – 1.80 (m, 2H), 1.77 – 1.67 (m, 1H), 0.99 (d, J = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.7, 199.8, 144.6, 142.6, 138.3, 132.3, 130.0, 127.3, 118.6, 116.1, 86.4, 78.9, 75.7, 69.8, 50.1, 39.8, 38.7, 36.7, 36.5, 31.5, 31.1, 27.9, 17.3.

FT-IR (neat): 3357, 2954, 2101, 1714, 1674, 1540, 1457, 1415, 1388, 1269, 1066 cm^{-1}.

HRMS-ESI (m/z): $[M-2H_2O+Na]^+$ Calcd. for $C_{23}H_{32}N_3NaO_4$ 437.2291; Found. 437.2287.

(6*S*,7*S*,9*R*,10*S*,11*S*,*E*)-6,9,10,11-tetrahydroxy-7-methyl-14-methylene-1-(4-methylene-3,4-dihydro-2*H*-pyrrol-5-yl)hexadeca-12,15-dien-3-one (2-21)

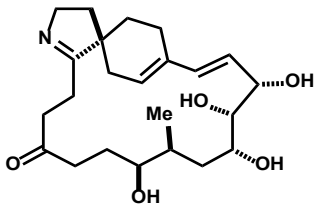


To a solution of **2-60** (25 mg, 0.055 mmol) in toluene (21 mL) was added polymer-bound PPh_3 (100-200 mesh, ~3 mmol/g, 128 mg, 0.16 mmol, 7.0 eq.). The reaction was stirred overnight at room temperature. The mixture was then filtered through cotton and the filtrate was concentrated under reduced pressure. The crude material was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.40 (dd, J = 17.4 Hz, 10.6 Hz, 1H), 6.25-6.16 (d, J = 10.7 Hz, 1H), 5.80-5.76 (m, 1H), 5.33 (t, J = 2.94 Hz, 1H), 5.25 (s, 1H), 5.21-5.08 (m, 4H), 4.40 (dd, J = 9.66 Hz, 3.22 Hz, 1H), 4.02-3.96 (m, 1H), 3.84-3.81 (t, J =6.20 Hz, 2H), 3.35-3.26 (m, 2H), 2.91-2.87 (m, 1H), 2.66-2.63 (m, 2H), 2.50-2.53 (m, 5H), 2.11-2.00 (m, 1H), 1.96-1.80 (m, 2H), 1.75-1.66 (m, 1H), 1.62-1.51 (m, 1H), 0.99-0.97 (m, 3H).

HRMS-ESI (m/z): $[M\text{-}H_2O+Na]^+$ Calcd. for $C_{23}H_{33}NNaO_4$ 410.2307; Found. 410.2309.

(3a*R*,9*S*,10*S*,11*R*,13*S*,14*S*,*E*)-9,10,11,14-tetrahydroxy-13-methyl-2,3,9,10,11,12,13,14,15,16,18,19-dodecahydro-3a,6-ethanocyclooctadeca[b]pyrrol-17(4*H*)-one (2-22)



To citric acid (33 g) in water (865 mL) was added NaOH (21 g) at 0 °C. The solution was warmed to room temperature after NaOH fully dissolved. Then conc. HCl (ca. 1.6 mL) was added to adjust the pH to 6.3-6.5. Then to the buffer solution at 37 °C was added crude **2-21** (0.055 mmol) in EtOH. The solution was stirred at 37 °C for 2 days and the pH was adjusted to 11 with solid K_2CO_3. The crude product was extracted with chloroform (4x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was

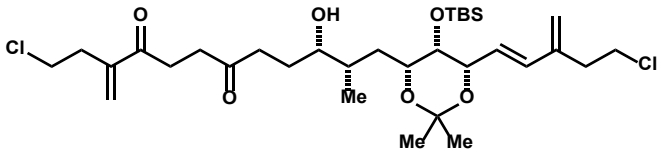
purified by column chromatography on silica gel (MeOH/DCM 0/100 to 1/10) then PTLC (MeOH/EtOAc/DCM 5/30/70) to furnish **2-22** (2 mg) as a colorless oil in 10% yield over 2 steps. The stereochemistry of the quaternary carbon was assigned based on *exo*/*α*-approach of the dienophile.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.06 (d, *J* = 10.7 Hz, 1H), 5.93 (app. s, 1H), 5.35 – 5.27 (m, 1H), 4.06 (t, *J* = 9.6 Hz, 1H), 3.92 (dd, *J* = 8.8, 5.3 Hz, 1H), 3.79 – 3.70 (m, 1H), 3.69 – 3.57 (m, 1H), 3.35 (ddd, *J* = 8.7, 6.7, 4.1 Hz,1H), 3.17 (d, *J* = 9.5 Hz, 1H), 3.09 – 2.99 (m, 1H), 2.85 – 2.71 (m, 1H), 2.64 – 2.53 (m, 1H), 2.49 – 2.38 (m, 3H), 2.38 – 2.28 (m, 1H), 2.25 – 2.03 (m, 3H), 2.02 – 1.88 (m, 4H), 1.88 – 1.68 (m, 3H), 1.68 – 1.51 (m, 2H), 0.95 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 215.1, 183.1, 138.0, 134.4, 128.0, 125.2, 86.8, 77.9, 76.7, 70.3, 55.8, 50.4, 41.4, 40.2, 39.1, 37.7, 37.4, 33.9, 30.6, 28.3, 27.2, 27.1, 17.1.

HRMS-ESI (m/z): $[M\text{-}H_2O+Na]^+$ calcd. for $C_{23}H_{33}NNaO_4$ 410.2302; found 410.2333.

(10*S*,11*S*)-12-((4*R*,5*S*,6*S*)-5-((*tert*-butyldimethylsilyl)oxy)-6-((*E*)-5-chloro-3-methylenepent-1-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)-1-chloro-10-hydroxy-11-methyl-3-methylenedodecane-4,7-dione (2-26)



To a solution of the corresponding cyclopropanol (51.7 mg, 0.100 mmol) in THF (0.5 mL) was added $ZnEt_2$ (1 M in hexane, 0.20 mL, 0.200 mmol, 2.0 eq.) dropwise at -78 °C. The mixture was stirred for 10 min at -78 °C and 15 min at room temperature. Then $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.0050 mmol, 5 mol%) and Bu_4NBr (3.2 mg, 0.010 mmol, 10 mol%) was added at the same time. After another 15 min at room temperature, acyl chloride (30.6 mg, 0.200 mmol, 2.0 eq.) in THF (0.5 mL) was added dropwise to the reaction. The reaction was stirred for 90 min and quenched with sat. aqueous solution of NH_4Cl. The crude product was extracted with EtOAc (4x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane

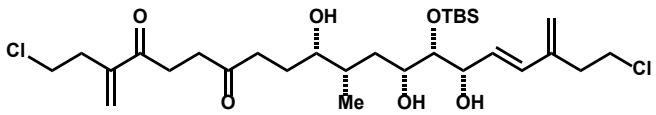
0/100 to 3/7) to furnish **2-26** (25.3 mg) as a light-yellow oil in 40% yield, together with 40 mol% of the product resulting from the quench of the homoenolate. The material was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.22 (s, 1H), 5.97 (s, 1H), 5.93 (t, J = 1.1 Hz, 1H), 5.76 (dd, J = 11.7, 8.9 Hz, 1H), 5.11 (d, J = 1.7 Hz, 1H), 4.95 (s, 1H), 4.76 – 4.71 (m, 1H), 3.92 (d, J = 10.9 Hz, 2H), 3.63 – 3.51(m, 5H), 3.22 (t, J = 1.4 Hz, 1H), 3.05 – 2.98 (m, 2H), 2.79 – 2.67 (m, 4H), 2.56 (t, J = 6.8 Hz, 2H), 1.88 – 1.54 (m, 5H), 1.51 – 1.46 (m, 1H), 1.44 (s, 3H), 1.44 (s, 3H), 0.96 (s, 9H), 0.91 (d, J = 7.1 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.2, 199.7, 144.3, 141.5, 131.9, 131.5, 127.5, 117.2, 98.9, 74.0, 70.6, 70.3, 69.5, 43.2, 42.9, 40.4, 39.8, 37.5, 36.5, 35.4, 34.7, 31.6, 29.9, 28.9, 26.3, 19.6, 18.6, 12.2, -3.3, -3.3.

HRMS-ESI (m/z): $[M\text{-}OH]^+$ calcd. for $C_{32}H_{53}Cl_2O_5Si$ 615.30338; found 615.30341.

(10*S*,11*S*,13*R*,14*S*,15*S*,*E*)-14-((*tert*-butyldimethylsilyl)oxy)-1,20-dichloro-10,13,15-trihydroxy-11-methyl-3,18-dimethyleneicos-16-ene-4,7-dione (2-27)



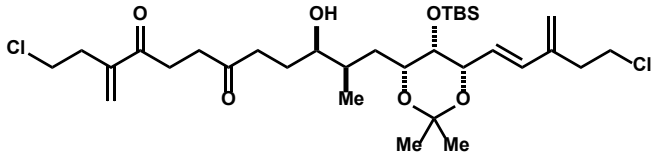
A mixture of TFA (0.6 mL), DCM (2.4 mL) and water (1.2 mL) was separated using a separation funnel. The organic layer was collected and added into a flask containing **2-26** (22.5 mg, 0.0355 mmol) at room temperature. The mixture was stirred for 1 h at the same temperature. The reaction was quenched with solid $NaHCO_3$ and filtered through a short silica plug (EtOAc). The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane 0/100 to 3/7) to furnish **2-27** (8.1 mg) as a colorless oil in 38% yield

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.22 (s, 1H), 5.93 (s, 1H), 5.88 (d, J = 11.7 Hz, 1H), 5.68 (ddd, J = 11.2, 9.2, 1.4 Hz, 1H), 5.13 (s, 1H), 5.10 (s, 1H), 4.52 (t, J = 8.3 Hz, 1H), 3.96 (q, J = 7.1 Hz, 1H), 3.66 – 3.50 (m, 5H), 3.30 – 3.22 (m, 1H), 3.01 (t, J = 6.7 Hz, 2H), 2.79 – 2.65 (m, 6H), 2.64

– 2.51 (m, 3H), 2.04 – 1.89 (m, 2H), 1.86 – 1.75 (m, 1H), 1.71 – 1.58 (m, 1H), 1.55 – 1.48 (m, 1H), 0.98 (d, J = 6.7 Hz, 3H), 0.93 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.3, 199.6, 144.3, 141.1, 134.0, 130.4, 127.5, 117.6, 85.7, 79.5, 78.1, 67.8, 43.2, 43.0, 40.0, 40.0, 38.5, 36.4, 36.1, 34.7, 31.5, 28.1, 26.2, 18.5, 17.6, -3.7, -4.5.

(10*R*,11*R*)-12-((4*R*,5*S*,6*S*)-5-((*tert*-butyldimethylsilyl)oxy)-6-((*E*)-5-chloro-3-methylenepent-1-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)-1-chloro-10-hydroxy-11-methyl-3-methylenedodecane-4,7-dione (2-29)



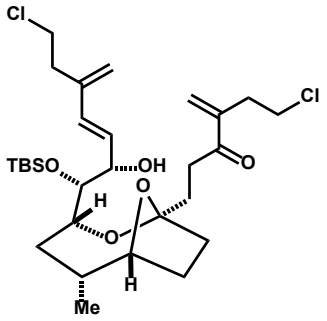
The compound was prepared following the procedure for the synthesis of **2-18**. The crude product was purified by column chromatography on silica gel (EtOAc/hexane 0/100 to 3/7) to furnish **2-29** as a light-yellow oil in 46% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.21 (s, 1H), 6.00 – 5.90 (m, 2H), 5.76 (dd, J = 11.6, 8.9 Hz, 1H), 5.10 (d, J = 1.7 Hz, 1H), 4.95 (d, J = 1.9 Hz, 1H), 4.72 (d, J = 8.8 Hz, 1H), 3.88 – 3.79 (m, 1H), 3.63 – 3.51 (m, 4H), 3.51 – 3.44 (m, 1H), 3.23 (s, 1H), 3.04 – 2.95 (m, 2H), 2.81 – 2.59 (m, 5H), 2.55 (t, J = 6.7 Hz, 2H), 1.90 – 1.64 (m, 4H), 1.53 – 1.36 (m, 8H), 0.95 (s, 9H), 0.88 (d, J = 6.8 Hz, 3H), 0.05 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.2, 199.7, 144.3, 141.5, 131.9, 131.5, 127.5, 117.2, 98.9, 73.7, 71.6, 70.5, 70.5, 43.2, 42.9, 40.1, 39.7, 36.4, 36.4, 34.7, 31.6, 30.0, 27.5, 26.3, 19.6, 18.6, 15.0, -3.3, -3.4.

HRMS-ESI (m/z): $[M\text{-}OH]^+$ calcd. for $C_{32}H_{53}Cl_2O_5Si$ 615.30338; found 615.30157.

1-((1*S*,3*R*,5*R*,6*R*)-3-((1*R*,2*S*,*E*)-1-((*tert*-butyldimethylsilyl)oxy)-7-chloro-2-hydroxy-5-methylenehept-3-en-1-yl)-5-methyl-2,9-dioxabicyclo[4.2.1]nonan-1-yl)-6-chloro-4-methylenehexan-3-one (2-30)



A mixture of TFA (0.6 mL), DCM (2.1 mL) and water (1.1 mL) was separated using a separation funnel. The organic layer was collected and added into a flask containing **2-29** (20 mg, 0.032 mmol) at room temperature. The mixture was stirred for 1 h at the same temperature. The reaction was quenched with solid $NaHCO_3$ and filtered through a short silica plug (EtOAc). The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane 0/100 to 1/10) to furnish **2-30** (11 mg) as a colorless oil in 61% yield

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.14 (s, 1H), 5.89 (s, 1H), 5.83 (d, J = 12.0 Hz, 1H), 5.59 (dd, J = 11.8, 9.5 Hz, 1H), 5.14 (s, 1H), 5.10 (d, J = 1.5 Hz, 1H), 4.70 (t, J = 9.1 Hz, 1H), 4.36 – 4.29 (m, 1H), 3.85 (dd, J = 10.4, 4.7 Hz, 1H), 3.65 – 3.53 (m, 5H), 2.89 (ddd, J = 16.9, 10.3, 5.6 Hz, 1H), 2.82 – 2.69 (m, 4H), 2.64 – 2.53 (m, 2H), 2.04 – 1.88 (m, 4H), 1.86 – 1.72 (m, 4H), 1.44 – 1.32 (m, 1H), 0.92 (s, 9H), 0.83 (d, J = 6.9 Hz, 3H), 0.11 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.8, 144.5, 140.8, 134.6, 129.5, 127.1, 118.0, 108.0, 84.9, 76.4, 73.4, 66.2, 43.3, 43.0, 40.1, 38.5, 36.6, 34.8, 33.7, 32.9, 32.7, 26.0, 21.8, 18.3, 16.5, -4.0, -4.5.

FT-IR (neat): 2956, 2931, 2857, 1680, 1470, 1380, 1326, 1255, 1197,1174, 1103, 1037 cm^{-1}

HRMS-ESI (m/z): $[M-H]^-$ calcd. for $C_{29}H_{49}Cl_2O_5Si$ 575.27208; found 575.27057.

N-(but-3-en-1-yl)formamide (2-61)

A solution of 4-Bromo-1-butene (11.2 g, 83.3 mmol), sodium diformylamide (9.5 g, 100 mmol, 1.2 eq.), 15-crown-5 (1.84 g, 8.3 mmol, 10 mol%) and anhydrous NaI (375 mg, 2.5 mmol, 3 mol%) in acetonitrile (208 mL, 0.4 M) was refluxed overnight. The reaction mixture was then filtered, and the filtrate was concentrated under reduce pressure. The residue was dissolved in MeOH (104 mL, 0.8 M) and KOH (234 mg, 4.2 mmol, 5 mol%) was added. The mixture was stirred for 20 min and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane 0/100 to 2/1) to furnish formamide **2-61** (7.0 g) in 85% yield.

Note: The product was isolated as a mixture of rotamers (5:1).

Spectral data for this compound were consistent with those in the literature.[66]

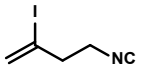
4-isocyanobut-1-ene (2-31)

To a solution of **2-61** (2.77 g, 28.3 mmol) and NEt_3 (16.7 mL, 113.1 mmol, 4.0 eq.) in DCM (56 mL, 0.5 M) was added $POCl_3$ (2.90 mL, 31.1 mmol, 1.1 eq.) dropwise at 0 °C. The reaction was stirred for 4 h at room temperature and then carefully quenched with sat. aqueous solution of $NaHCO_3$. The crude product was extracted with Et_2O (3x). The combined organic layers were diluted with pentane and filtered through a short silica plug (Et_2O/pentane 1/1). The filtrate was concentrated at 0 °C under reduced pressure to give **2-31** (1.1 g) in 48% yield as a light brown oil. Residue solvent could be removed by blowing argon over the oil.

Note: The title compound has a strong unpleasant smell.

Spectral data for this compound were consistent with those in the literature.[57]

2-iodo-4-isocyanobut-1-ene (2-33)

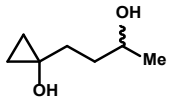


The title compound was synthesized following the same procedure used for **2-31**. The corresponding formamide were synthesized from 3-iodo-3-butenyl toluenesulfonate.[67]

Note: The title compound has a strong unpleasant smell.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.28 – 6.21 (m, 1H), 5.92 – 5.87 (m, 1H), 3.62 – 3.54 (m, 2H), 2.76 – 2.68 (m, 2H).

1-(3-hydroxybutyl)cyclopropan-1-ol (2-32)

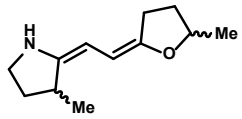


To a solution of γ-Valerolactone (8.85 mL, 92.8 mmol) in THF (281 mL, 0.33 M) at 10-15 °C was added Ti(O*i*Pr)$_4$ (34.4 mL, 116 mmol, 1.25 eq.). Then EtMgBr (3 M in Et_2O, 81.3 mL, 244 mmol, 2.62 eq.) was added over 2 h at the same temperature. The reaction mixture was stirred at below 20 °C for another 2 h after the addition was finished. The reaction was quenched with sat. aqueous solution of NH_4Cl and the mixture was stirred vigorously until it turned white. The crude product was extracted with EtOAc (6x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane 0/100 to 4/6) to furnish **2-32** (11.2 g) as a light-yellow sticky oil in 93% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.00 – 3.87 (m, 1H), 1.80 – 1.55 (m, 4H), 1.25 (d, J = 6.2 Hz, 3H), 0.76 (qd, J = 3.3, 2.0 Hz, 2H), 0.54 – 0.37 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 68.5, 55.8, 36.0, 35.3, 24.1, 14.1, 13.7.

(*E*)-3-methyl-2-((*E*)-2-(5-methyldihydrofuran-2(3H)-ylidene)ethylidene)pyrrolidine (2-38)



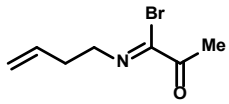
To a mixture of isocyanide **2-33** (52.5 µL, 0.602 mmol, 2.0 eq.), $Mn(acac)_3$ (233 mg, 0.662 mmol, 2.2 eq.) in MeCN (2.5 mL) 50 °C was added cyclopropanol **2-32** (39.2 mg, 0.300 mmol) in MeCN (0.5 mL) over 2 h. The mixture was stirred for another hour at the same temperature after the addition was finished. The reaction mixture was then filtered through silica gel plug (EtOAc/hexane 1/1). The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane 1:1 to 100% EtOAc) to furnish **2-38** (23 mg) in 20% yield as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.89 (d, J = 2.8 Hz, 1H), 5.69 (d, J = 2.6 Hz, 1H), 3.94 – 3.83 (m, 2H), 3.75 (dq, J = 10.2, 7.7 Hz, 1H), 3.19 (h, J = 7.1 Hz, 1H), 2.74 – 2.51 (m, 4H), 2.09 – 1.97 (m, 1H), 1.81 – 1.70 (m, 2H), 1.27 (d, J = 6.8 Hz, 3H), 1.23 (d, J = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.2, 126.9, 108.2, 97.3, 68.0, 44.0, 38.4, 37.1, 32.3, 23.8, 23.3, 20.0.

HRMS (ESI) m/z: [M+H]+ Calcd. for $C_{12}H_{20}NO$ 194.1539; Found 194.1535.

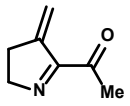
(Z)-N-(but-3-en-1-yl)-2-oxopropanimidoyl bromide (2-39)



To a solution of isocyanide **2-31** (337 mg, 3.69 mmol, 1.0 eq in DCM (3.7 mL, 1.0 M) was added acetyl bromide (287 µL, 3.88 mmol, 1.05 eq.) dropwise. The mixture was stirred for 1 hour and the concentrated under reduced pressure. Imidoyl bromide was used directly for the coupling without purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.93-5.84 (m, 1H), 5.16 (dq, J = 17.2, 1.5 Hz, 1H), 5.11 (d, J = 10.4 Hz, 1H), 3.76 (t, J = 7.0 Hz, 2H), 2.52 (q, J = 7.1 Hz, 2H), 2.52 (s, 3H).

1-(4-methylene-3,4-dihydro-2H-pyrrol-5-yl)ethan-1-one (2-40) (Table 8, entry 9)



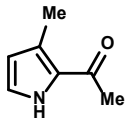
$Pd(PPh_3)_4$ (427 mg, 0.369 mmol, 10 mol%) and $AgCO_3$ (1.53 g, 5.54 mmol, 1.5 eq.) were mixed in toluene (28 ml) and heated to 95 °C. In a separate vial crude imidoyl bromide **2-39** was dissolved in toluene (9 ml) and added to the preheated catalyst mixture over 10 minutes using the syringe pump. The reaction was stirred for additional 2 minutes, cooled to room temperature, diluted with pentane and immediately purified by column chromatography on silica gel (pentane/Et_2O 100% to 8:2) to furnish **2-40** (230 mg) in 50% yield as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.07 (td, J = 2.9, 0.5 Hz, 1H), 5.45 (td, J = 2.7, 0.7 Hz, 1H), 4.08 (m, 2H), 2.71-2.67 (m, 2H), 2.52 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.1, 168.2, 145.3, 114.1, 58.3, 30.6, 27.8.

HRMS (ESI) m/z: $[M+H]^+$ Calcd. for $C_7H_{10}NO$ 124.0762; Found 124.0766.

1-(3-methyl-1H-pyrrol-2-yl)ethan-1-one (2-41)

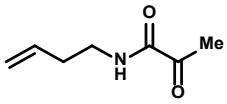


If CsOPiv is used instead of $AgCO_3$, pyrrole **2-41** can be isolated alongside the desired product.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.88 (t, J = 2.6 Hz, 1H), 6.08 (t, J = 2.4, Hz, 1H), 2.44 (s, 3H), 2.39 (s, 3H).

Spectral data for this compound were consistent with those in the literature.[68]

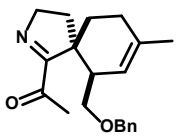
N-(but-3-en-1-yl)-2-oxopropanamide (2-42)



^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.79-5.71 (m, 1H), 5.13-5.09 (m, 1H), 3.37 (q, J = 6.2 Hz, 2H), 2.47 (s, 3H), 2.30 (qt, J = 6.8, 2.6 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.1, 160.1, 134.5, 117.7, 38.3, 33.4, 24.4.

(±)-1-((5R,6R)-6-((benzyloxy)methyl)-8-methyl-2-azaspiro[4.5]deca-1,7-dien-1-yl)ethan-1-one (2-47)



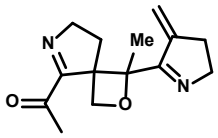
To the solution of TfOH (40 µL, 0.447 mmol, 1.1 eq.) in MeCN (2 ml) was added the solution of **2-40** (50.0 mg, 0.406 mmol, 1.0 eq.) in MeCN (1.5 ml) dropwise. The formation of the salt can be confirmed by ^{1}H NMR and occurs within 20 minutes. Then, the solution of **2-46** (99.4 mg, 0.528 mmol, 1.3 eq.) in MeCN (0.5 ml) was added dropwise. The reaction was stirred for an additional hour and then concentrated under the reduced vacuum. The residue was purified by column chromatography on silica gel (pentane:Et_2O 100% to 8:2) to furnish **2-47** (92 mg) in 73% yield as a colorless oil (dr = 7:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32-7.22 (m, 5H), 5.14 (d, J = 3.5 Hz, 1H), 4.31 (d, J = 12.2 Hz, 1H), 4.16 (d, J = 12.2 Hz, 1H), 4.0 (dd, J = 16.7 Hz, 8.9 Hz, 1H), 3.91-3.83 (m, 1H), 3.40 (t, J = 9.8 Hz, 1H), 3.25 (dd, J = 9.8, 2.7 Hz, 1H), 2.81-2.74 (m, 1H), 2.32-2.31 (m, 1H), 2.24 (s, 3H), 2.00-1.92 (m, 3H), 1.83-1.79 (m, 1H), 1.65 (s, 3H), 1.43-1.40 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.1, 177.0, 138.0, 136.5, 128.3, 127.5, 127.4, 119.9, 71.9, 70.4, 56.9, 53.6, 42.4, 37.7, 27.9, 27.5, 27.2, 23.6.

HRMS (ESI) m/z: $[M+H]^+$ Calcd. for $C_{20}H_{26}NO_2$ 312.1964; Found 312.1986.

1-(2-methyl-2-(4-methylene-3,4-dihydro-2H-pyrrol-5-yl)-1-oxa-6-azaspiro[3.4]oct-5-en-5-yl)ethan-1-one (2-48)



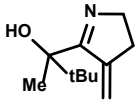
To the solution of **2-40** (15.0 mg, 0.122 mmol, 1 eq.) in MeCN (1.22 ml, 0.1 M) was added TFA (9.85 μL, 0.128 mmol, 1.05 eq.) dropwise. The reaction was stirred for 30 minutes and then concentrated under the reduced pressure to deliver **2-48** as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.40 (s, 1H), 6.07 (s, 1H), 4.43 (d, J = 15.4 Hz, 1H), 4.31-4.26 (m, 1H), 4.20-4.14 (ddd, J = 19.1, 8.8, 4.1 Hz, 1H), 4.05 (t, J = 7.6 Hz, 1H), 4.03-3.96 (m, 1H), 3.86 (d, J = 15.4 Hz, 1H), 3.43-3.36 (m, 2H), 3.00-2.95 (ddd, J = 14.7, 8.2, 4.1 Hz, 1H), 2.51 (s, 3H), 2.11-2.03 (m, 1H), 1.34 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.5, 184.2, 171.7, 136.8, 127.2, 78.2, 68.8, 59.8, 59.4, 51.5, 31.3, 30.4, 27.1, 20.5.

HRMS (ESI) m/z: $[M+H]^+$ Calcd. for $C_{14}H_{19}N_2O_2$ 247.1447; Found 247.1484.

3,3-dimethyl-2-(4-methylene-3,4-dihydro-2H-pyrrol-5-yl)butan-2-ol (2-50)



The solution of **2-40** (11.0 mg, 0.089 mmol, 1 eq.) in THF (0.89 ml, 0.1 M) cooled to -78 °C. tBuLi (60 μL, 1.65 M in pentane, 0.098 mmol, 1.1 eq.) was added dropwise and the reaction was stirred for 30 minutes. The mixture was then quenched with H_2O, extracted with EtOAc (3x), dried with

$MgSO_4$, filtered and concentrated under the reduced pressure. The residue was purified by column chromatography on silica gel (pentane:Et_2O 100% pentane to 8:2) to furnish **2-50.**

Note: due to high volatility of the compound, the NMR and mass were taken on the solution of **2-50** in pentane/Et_2O.

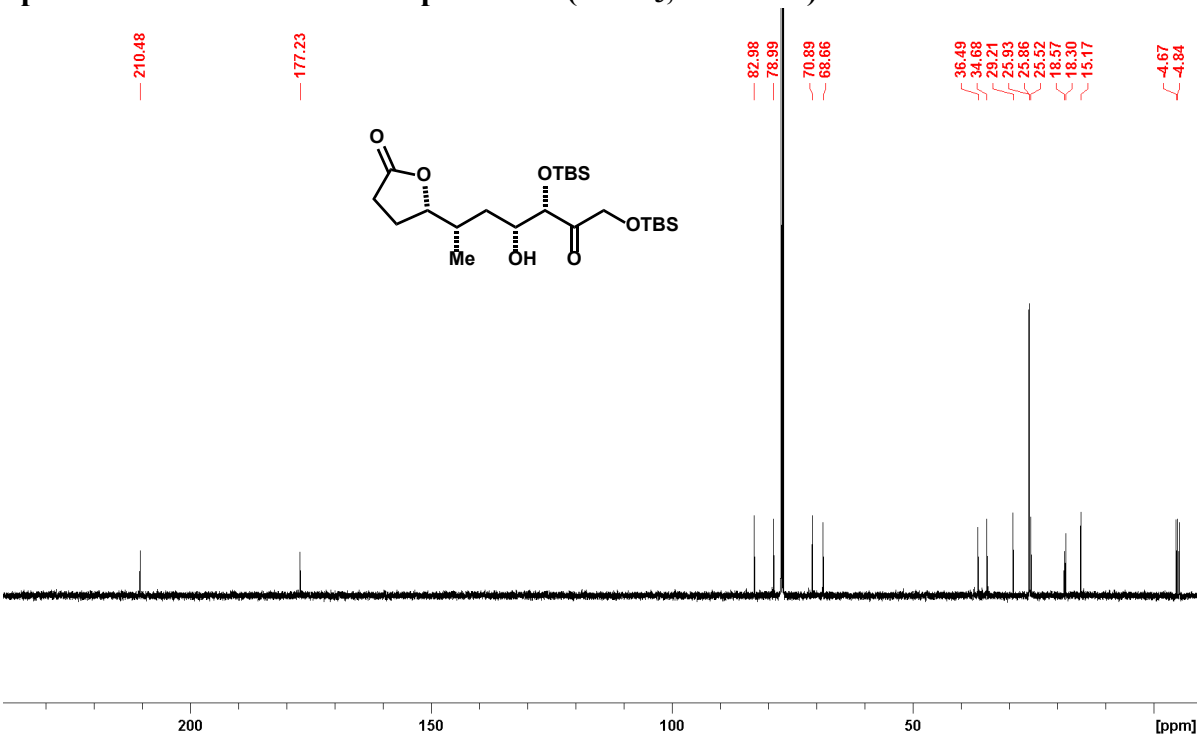
^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.50 (t, J = 2.67 Hz, 1H), 5.43 (t, J = 2.40 Hz, 1H), 4.63 (br s, 1H, OH), 3.94-3.87 (m, 2H), 2.82-2.76 (m, 2H), 1.53 (s, 3H), 1.01 (s, 9H).

HRMS (ESI) m/z: $[M+H]^+$ Calcd. for $C_{11}H_{20}NO$ 182.1545; Found 182.1132.

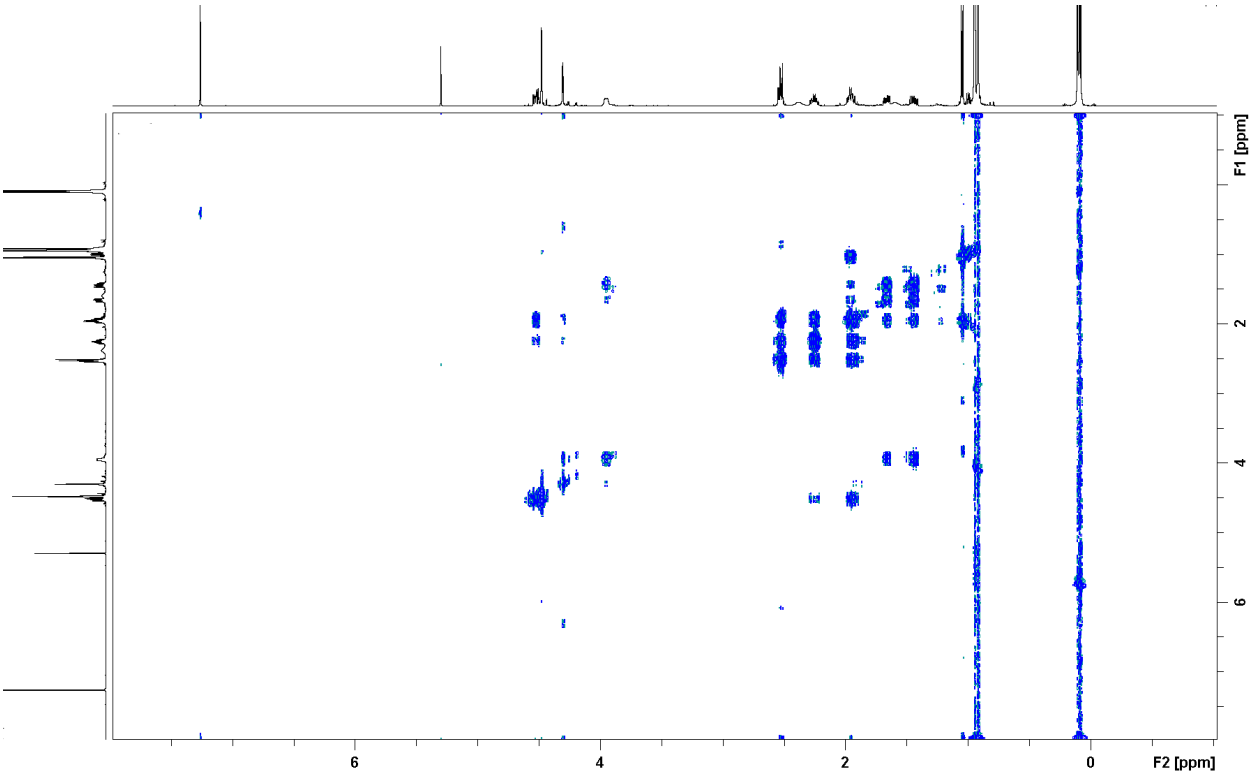
2.6.3 NMR Spectra

Spectrum 83. ^{1}H NMR of compound 2-8 ($CDCl_3$, 500 MHz)

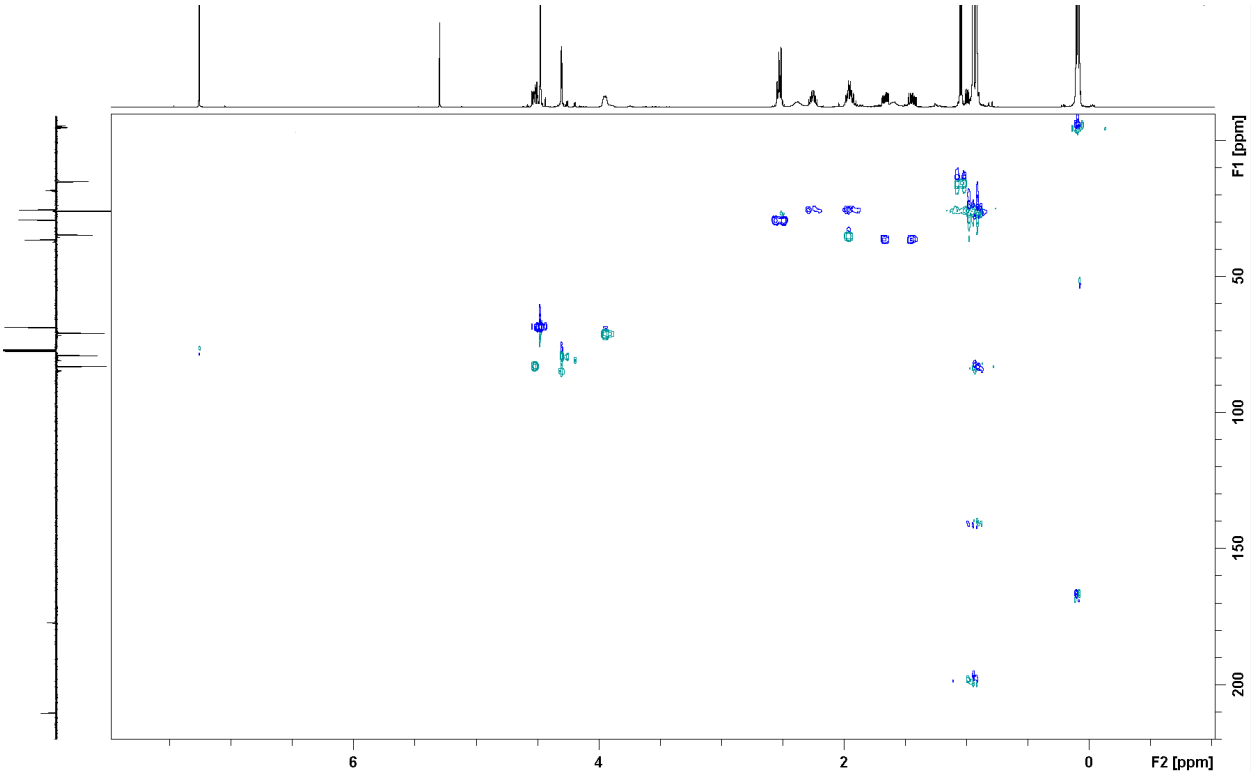
Spectrum 84. ^{13}C NMR of compound 2-8 ($CDCl_3$, 125 MHz)

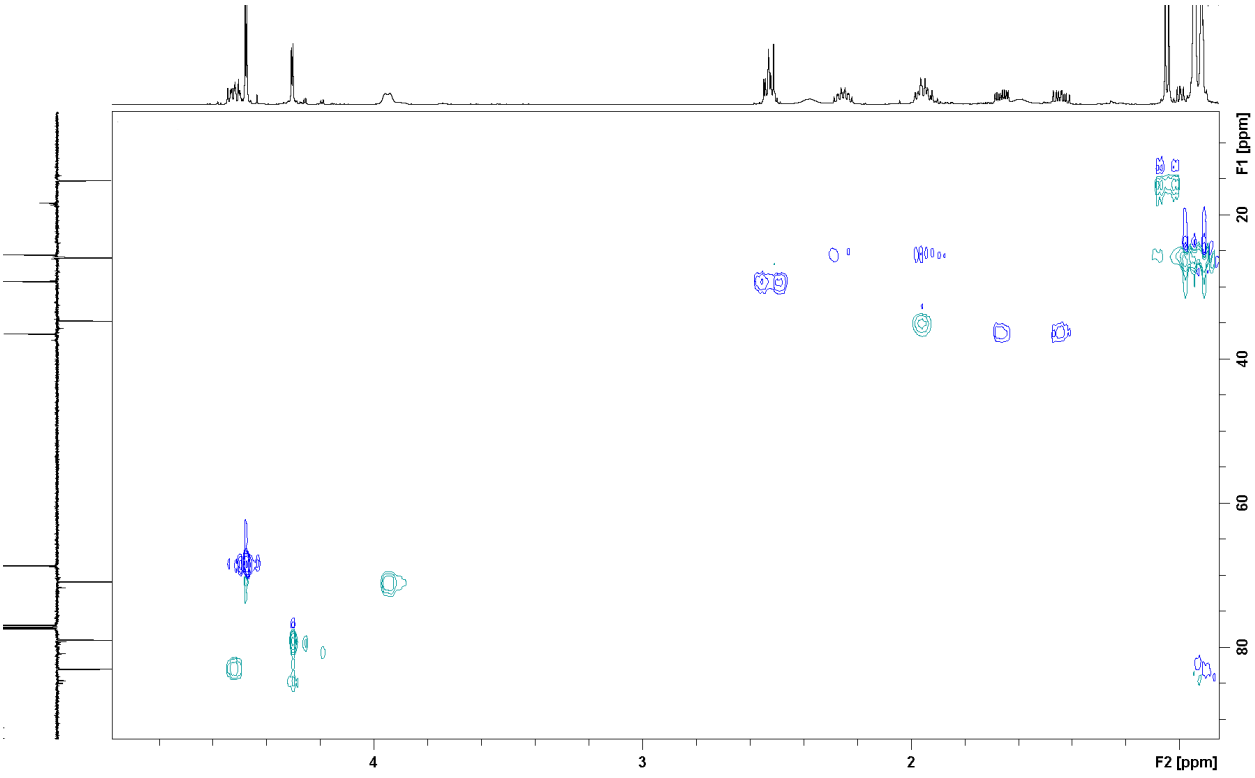


Spectrum 85. COSY spectrum of compound 2-8 ($CDCl_3$, 500 MHz)

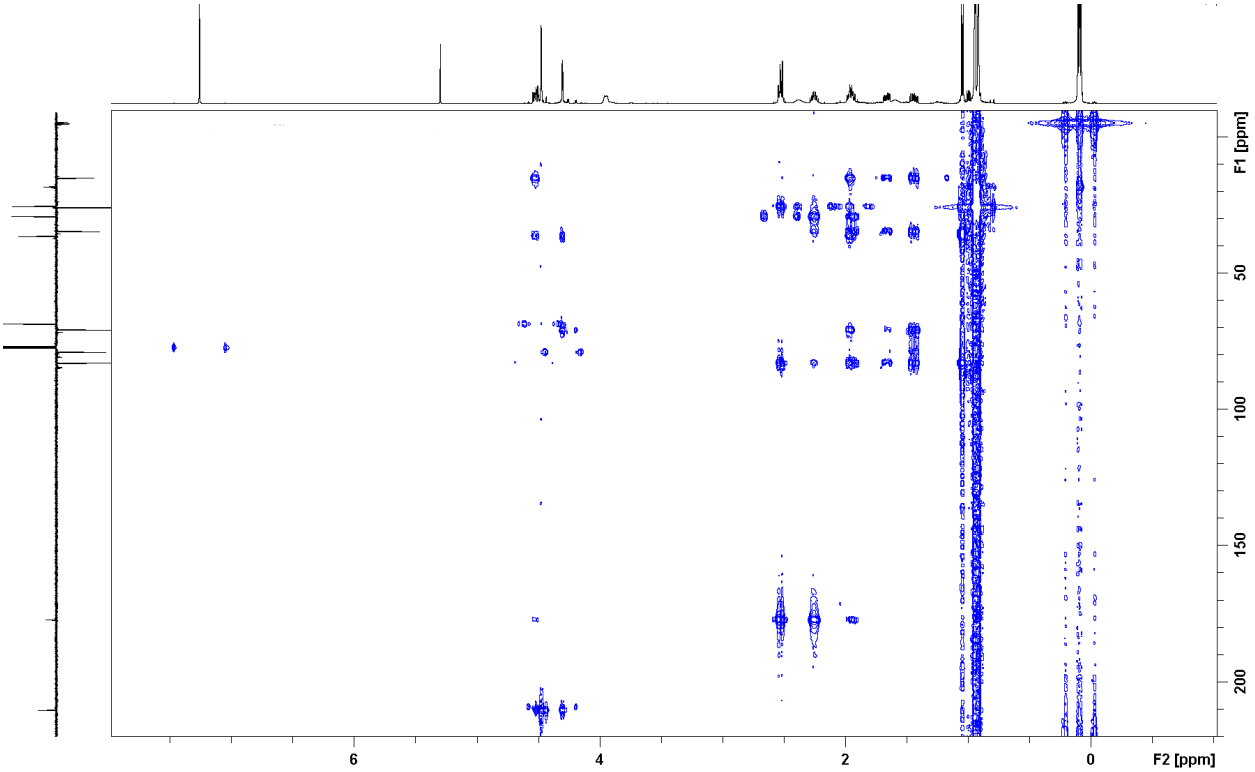


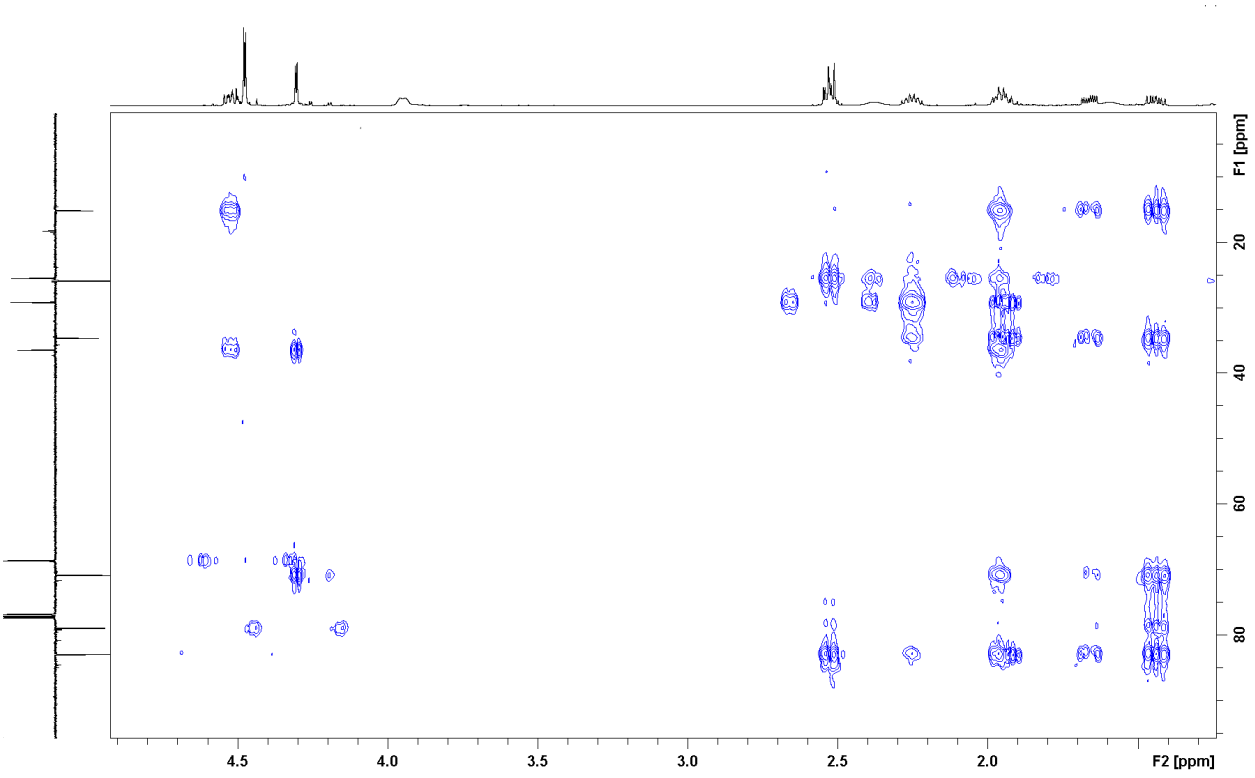
Spectrum 86. HSQC spectrum of compound 2-8 ($CDCl_3$, 500 MHz)



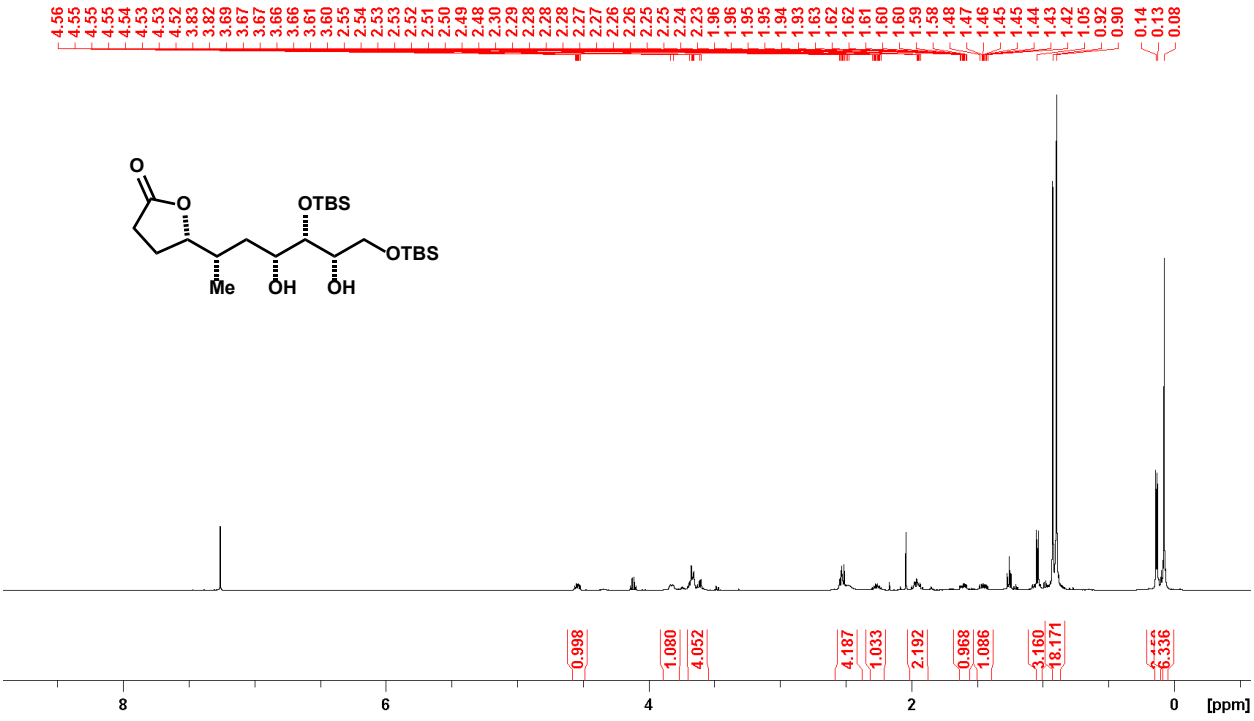


Spectrum 87. HMBC spectrum of compound 2-8 ($CDCl_3$, 500 MHz)

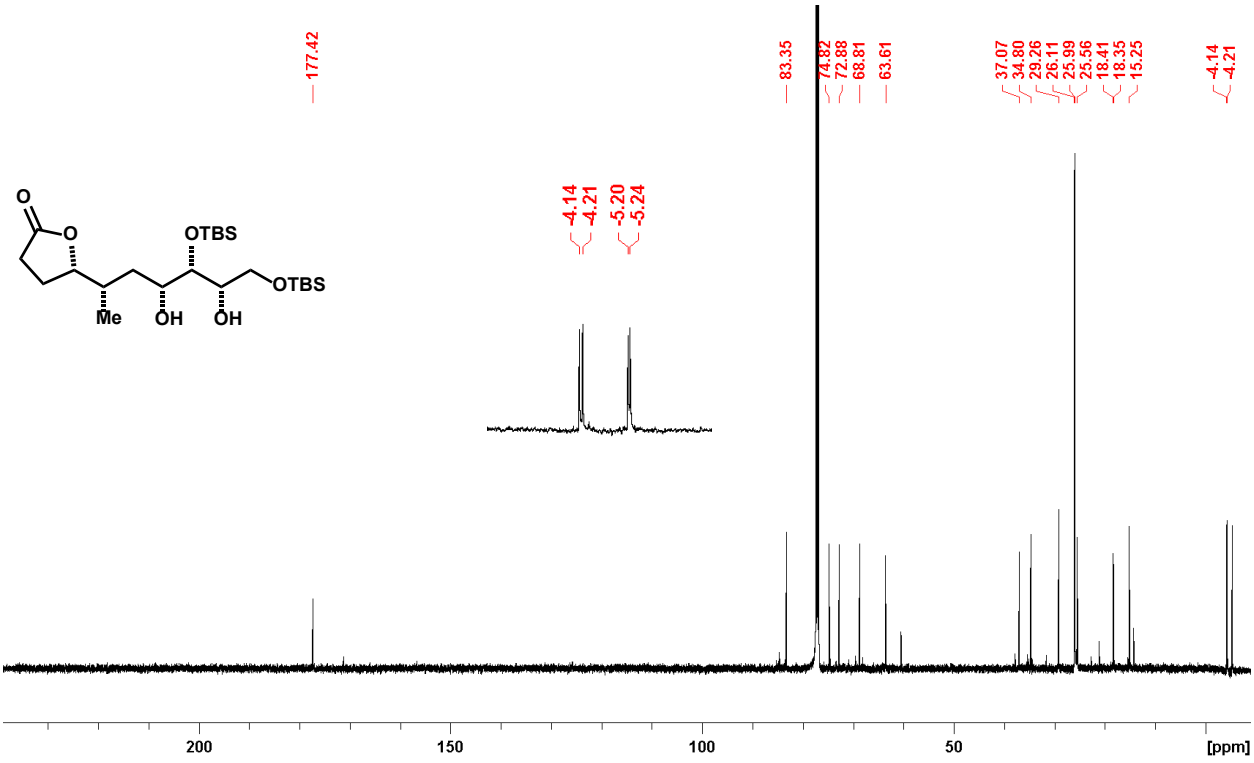



F1 [ppm]
20
40
60
80
4.5
4.0
3.5
3.0
2.5
2.0
F2 [ppm]

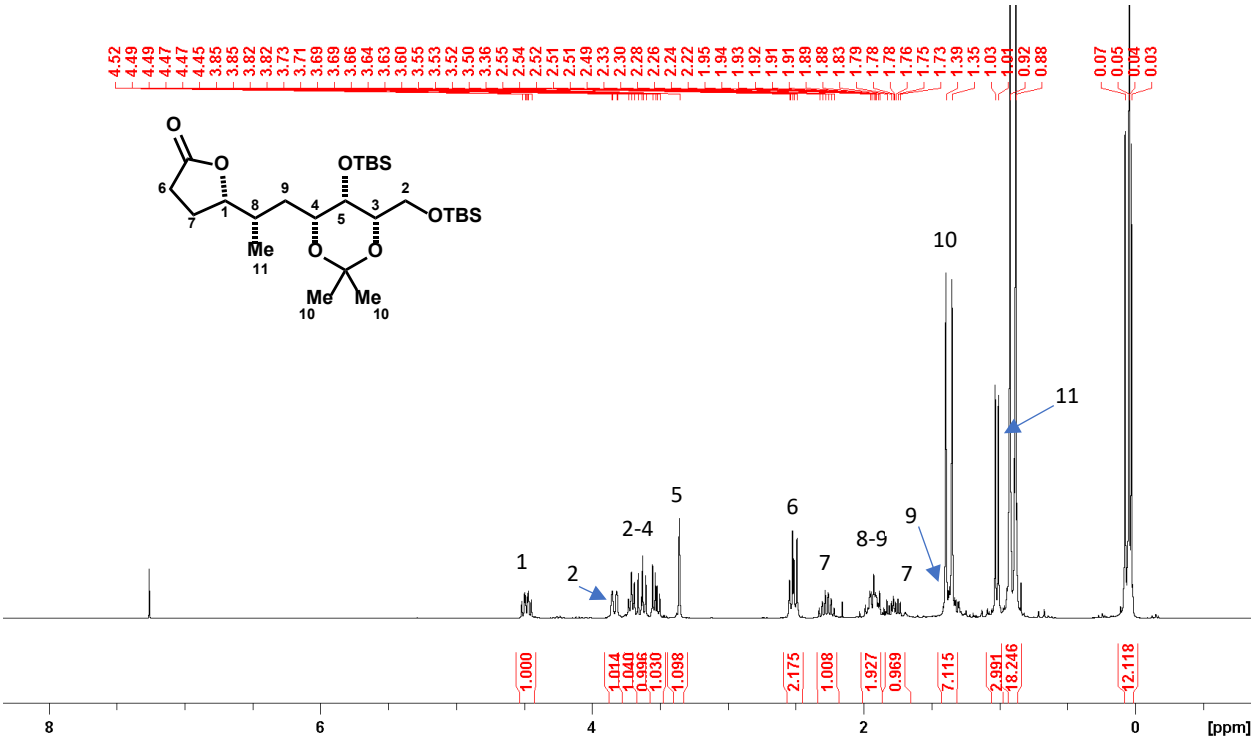
Spectrum 88. ^{1}H NMR of compound 2-58 ($CDCl_3$, 500 MHz)



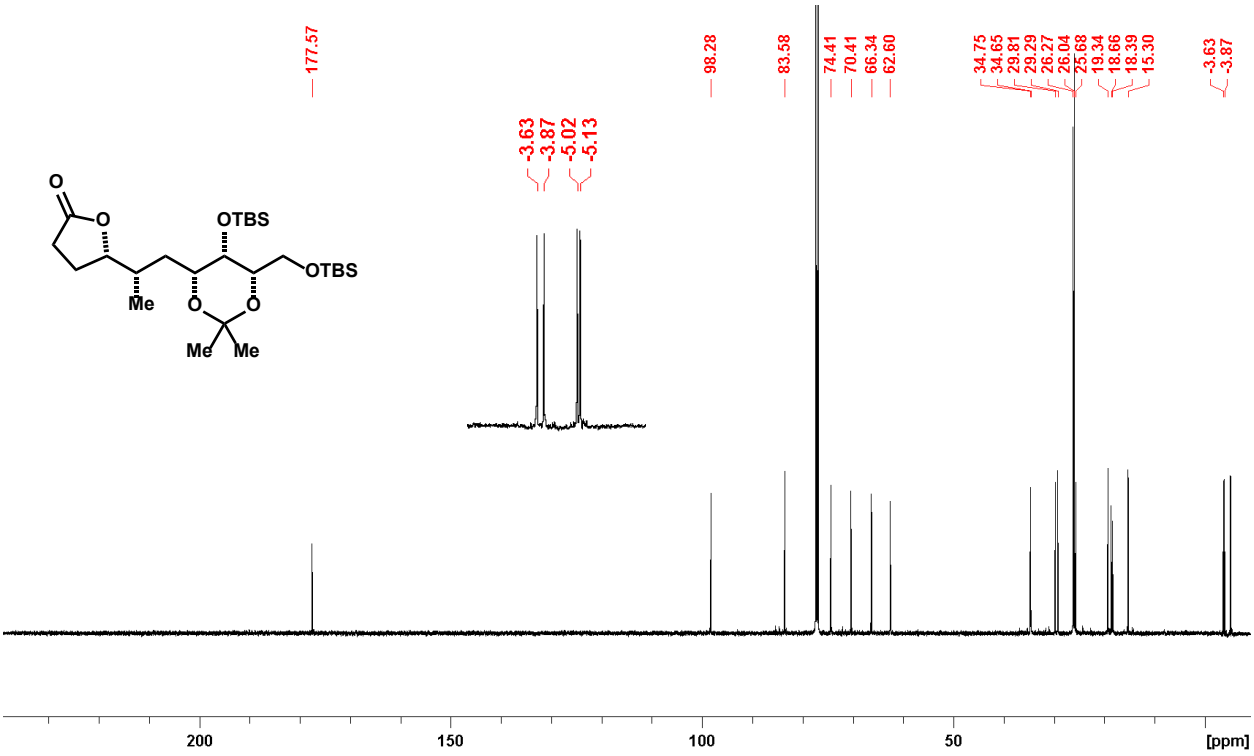
Spectrum 89. ^{13}C NMR of compound 2-58 ($CDCl_3$, 125 MHz)



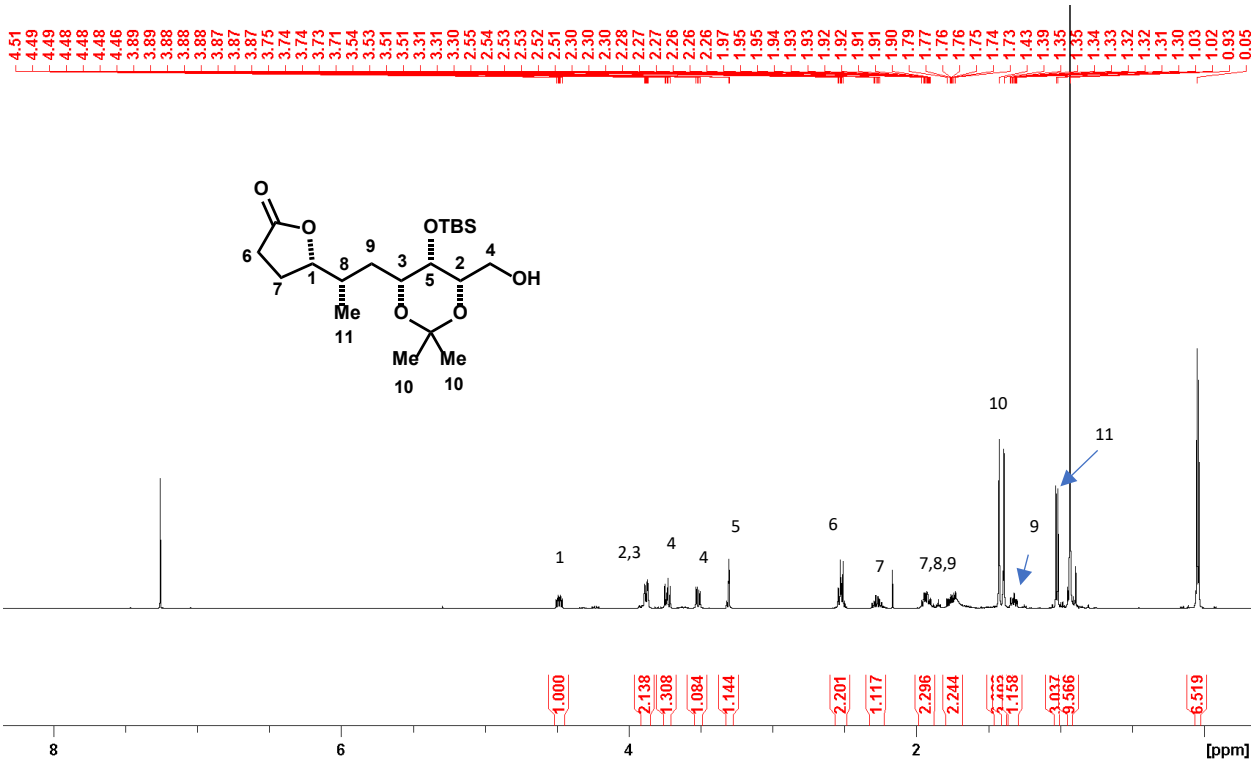
Spectrum 90. ^{1}H NMR of compound 2-59 ($CDCl_3$, 400 MHz)



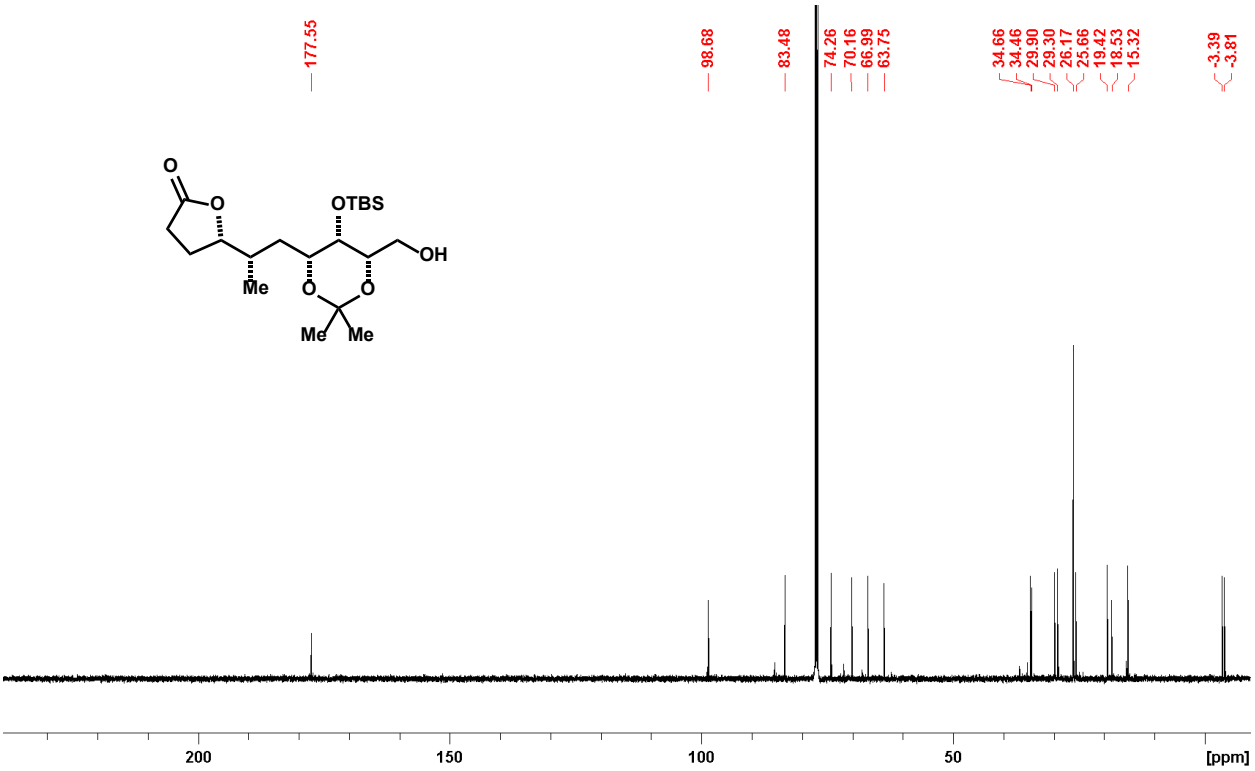
Spectrum 91. ^{13}C NMR of compound 2-59 ($CDCl_3$, 125 MHz)



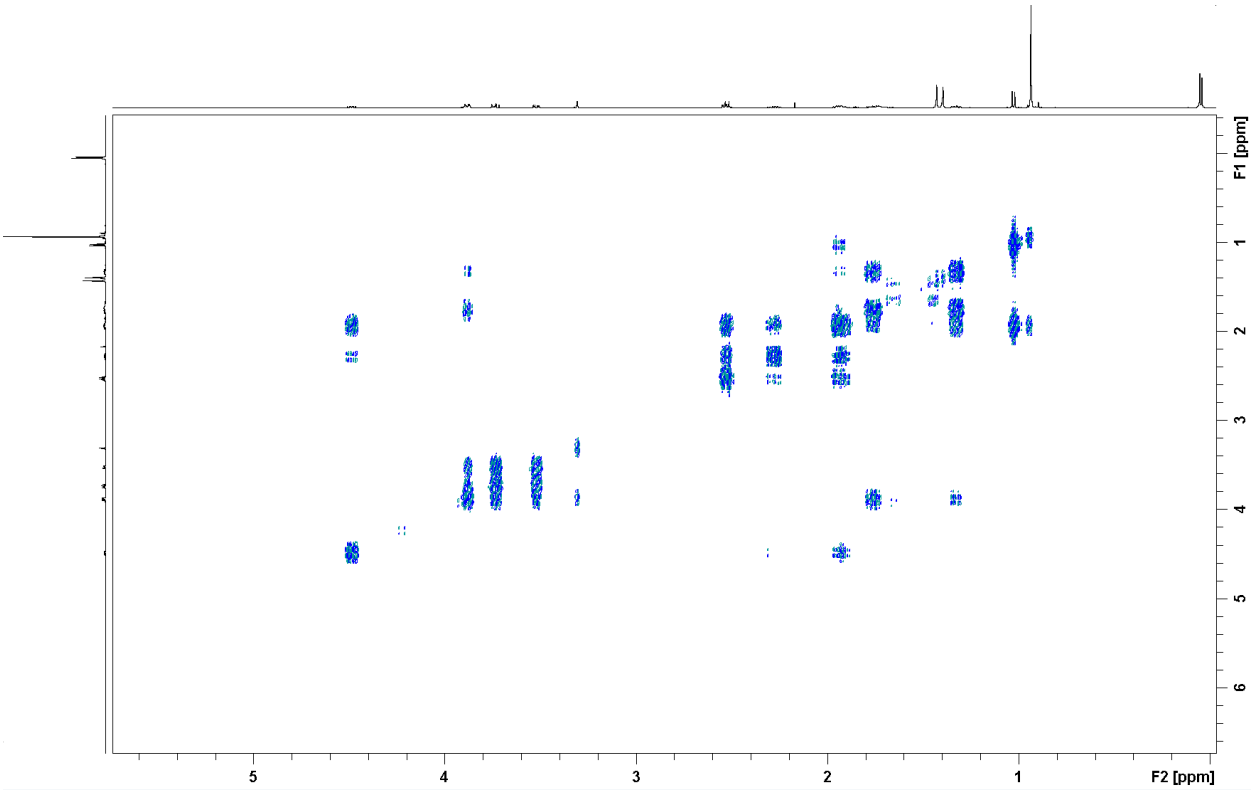
Spectrum 92. ^{1}H NMR of compound 2-9 ($CDCl_3$, 500 MHz)



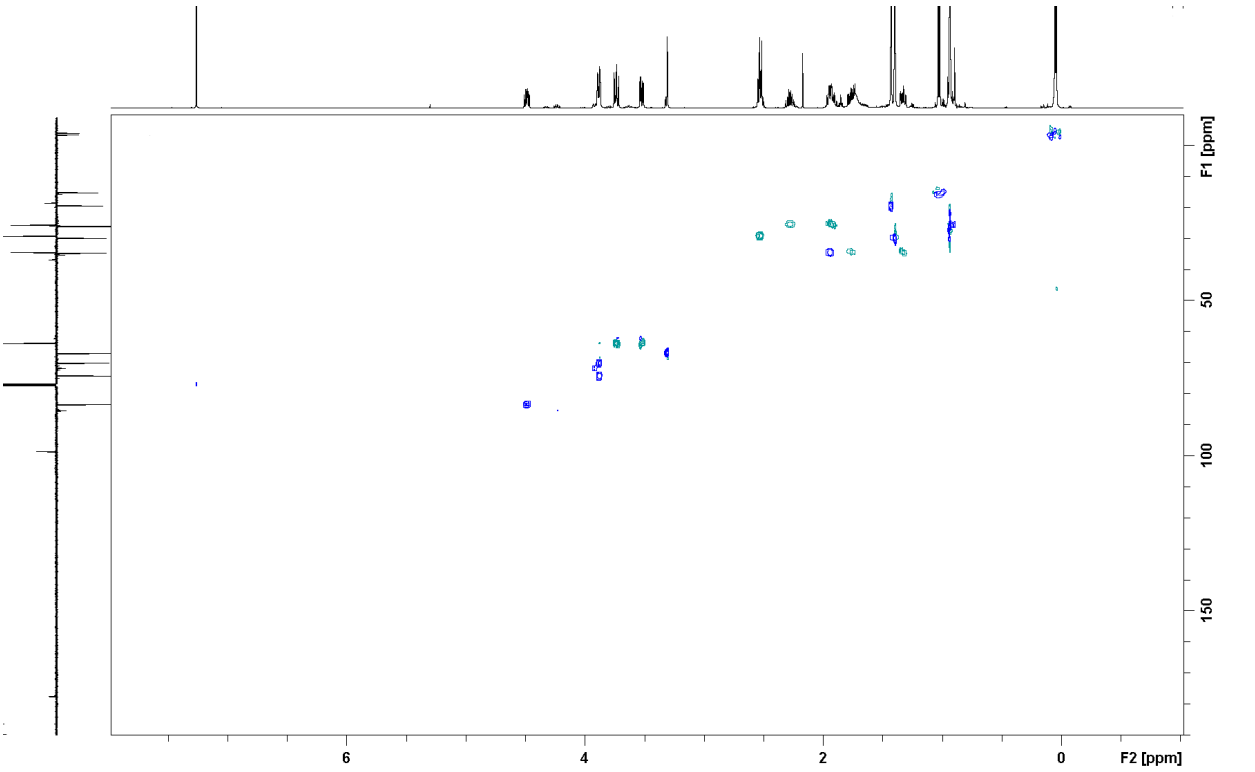
Spectrum 93. ^{13}C NMR of compound 2-9 ($CDCl_3$, 125 MHz)

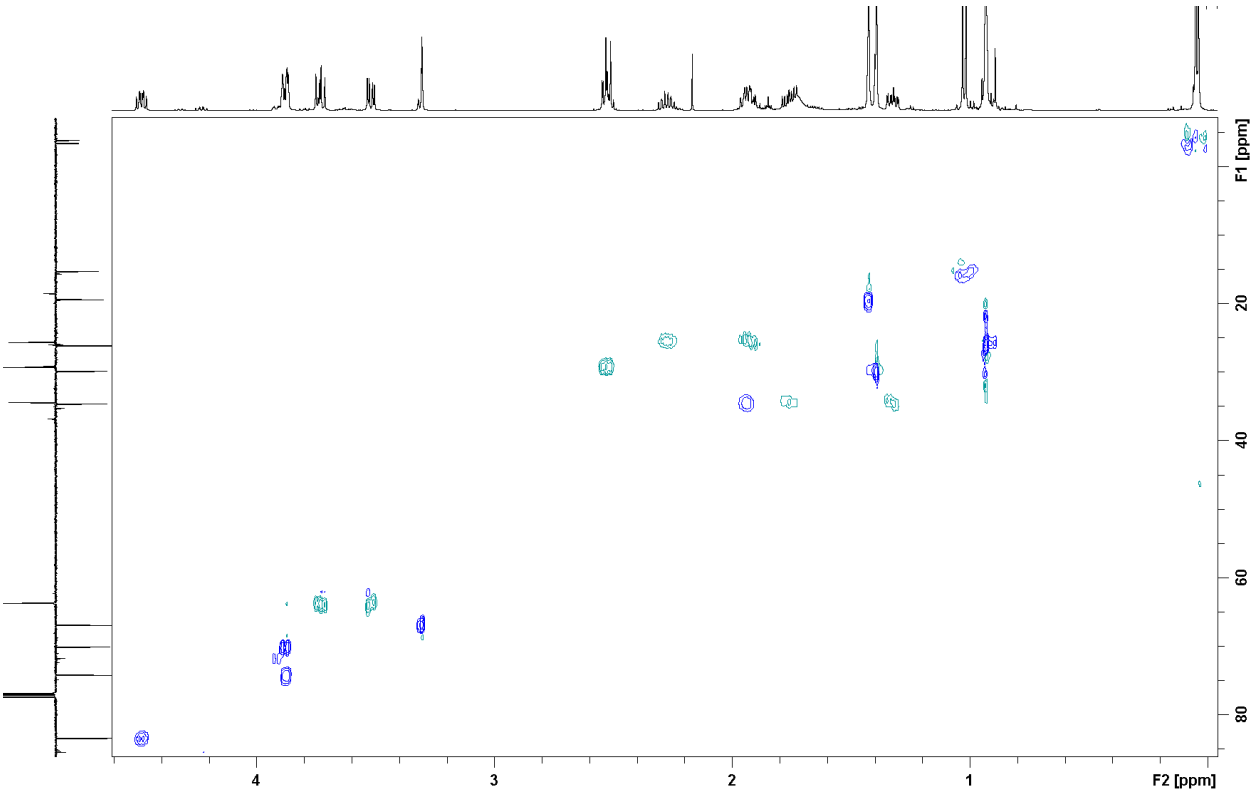


Spectrum 94. COSY spectrum of compound 2-9 ($CDCl_3$, 500 MHz)

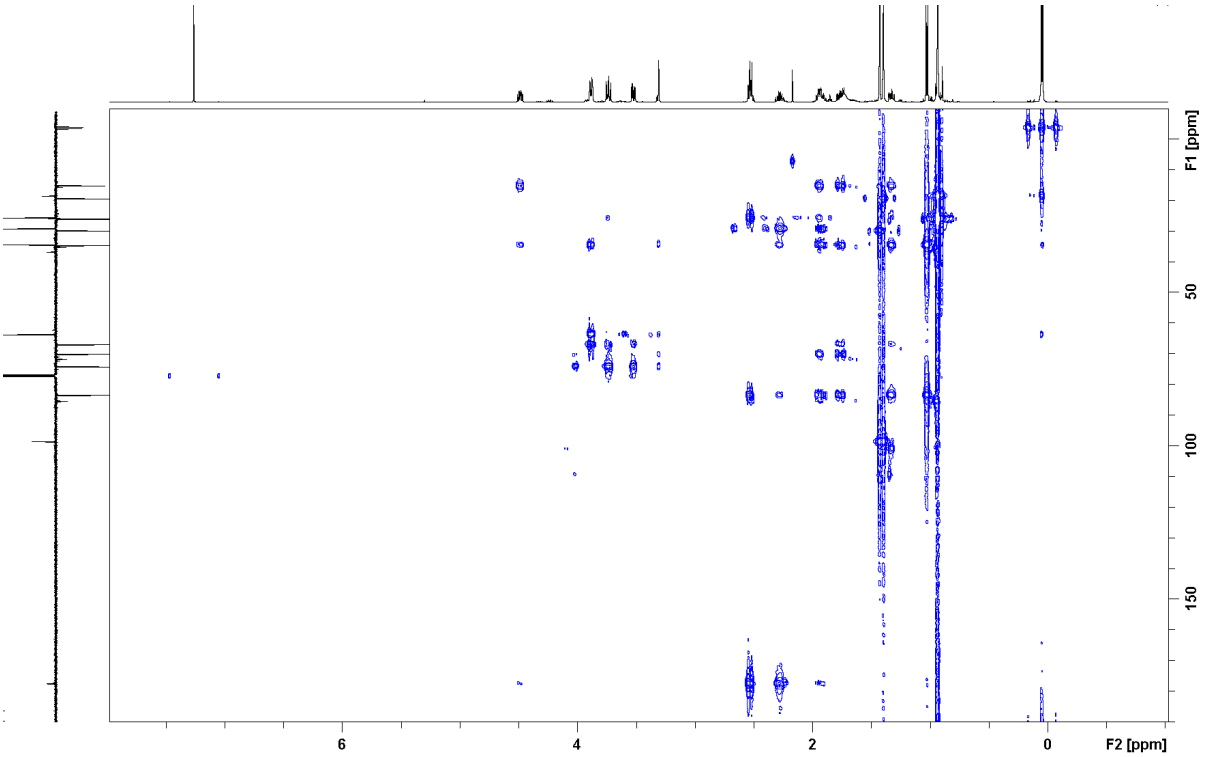


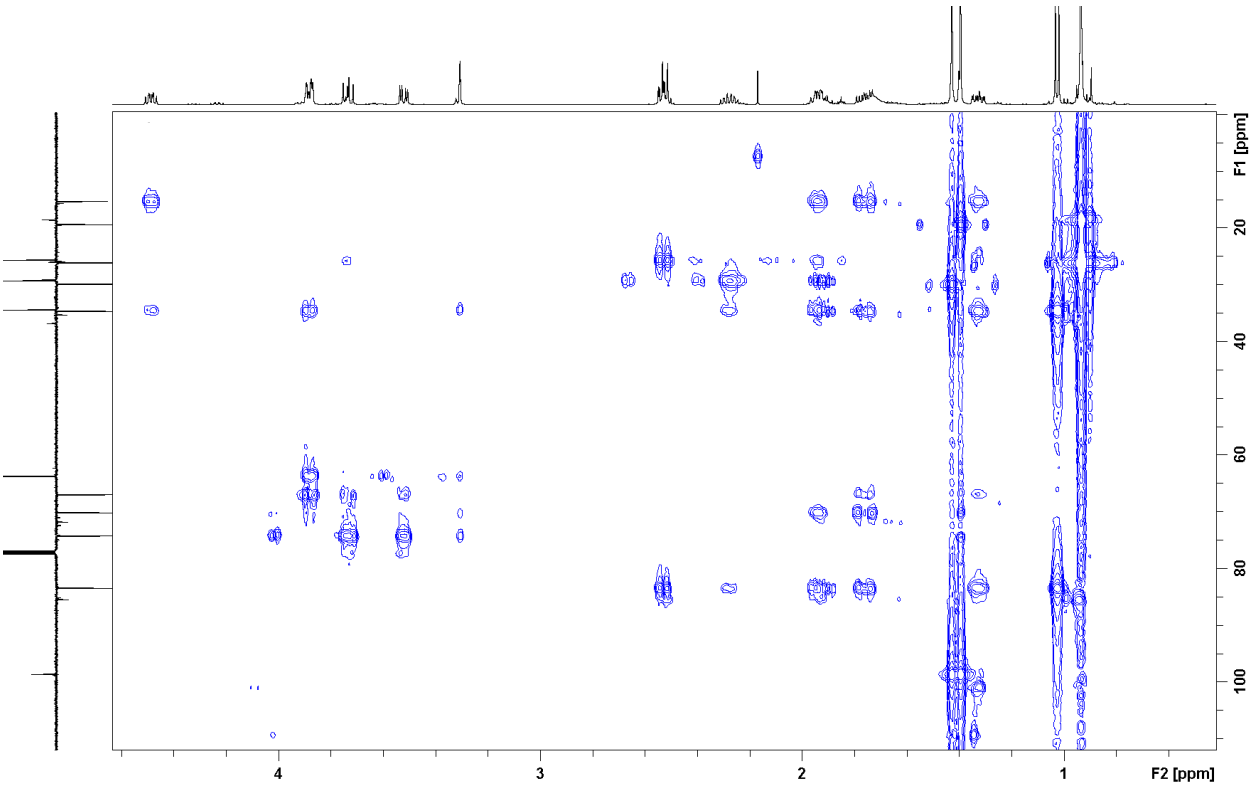
Spectrum 95. HSQC NMR of compound 2-9 ($CDCl_3$, 500 MHz)



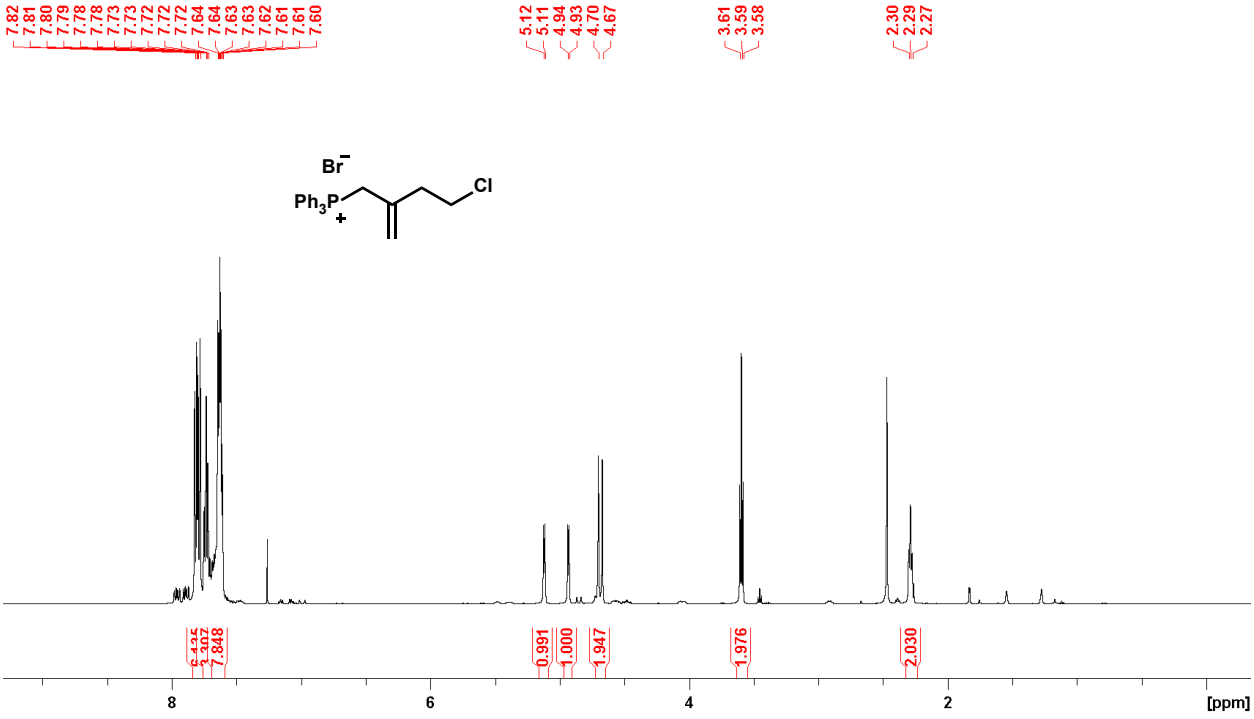


Spectrum 96. HMBC NMR of compound 2-9 ($CDCl_3$, 500 MHz)

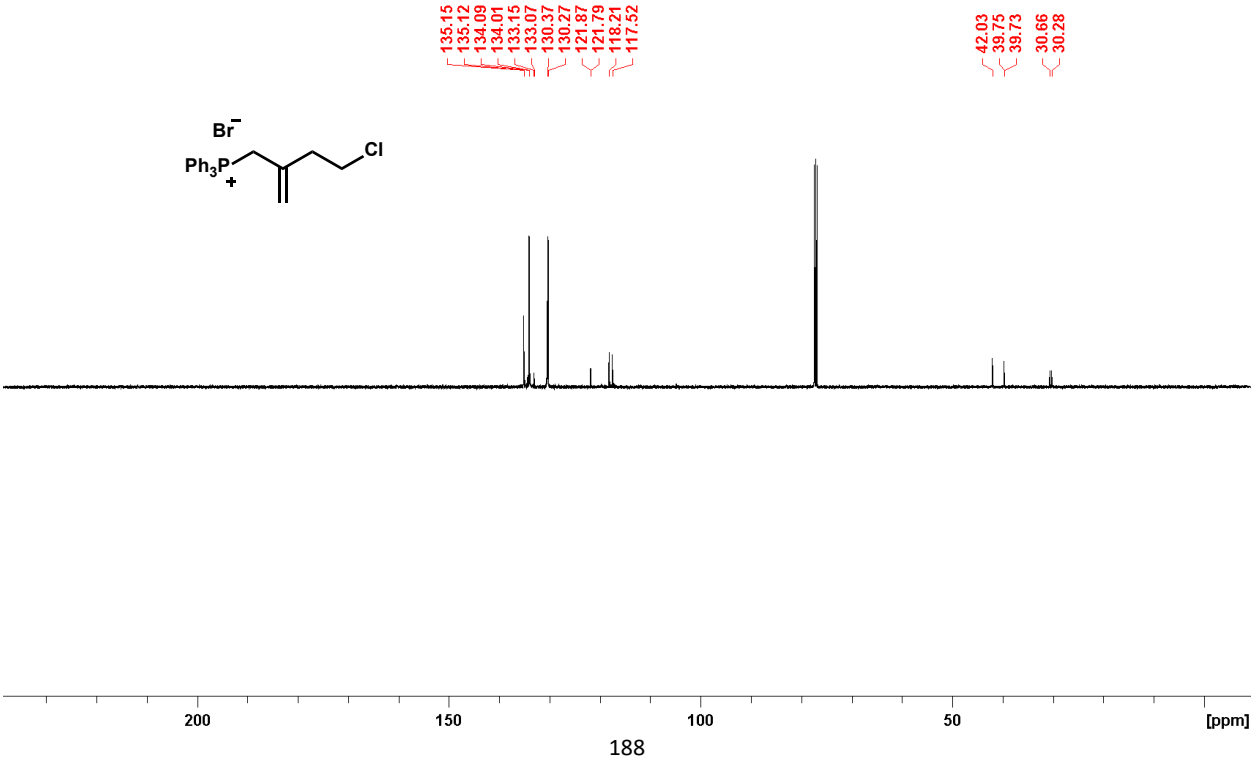



F1 [ppm]
20
40
60
80
100
4
3
2
1
F2 [ppm]

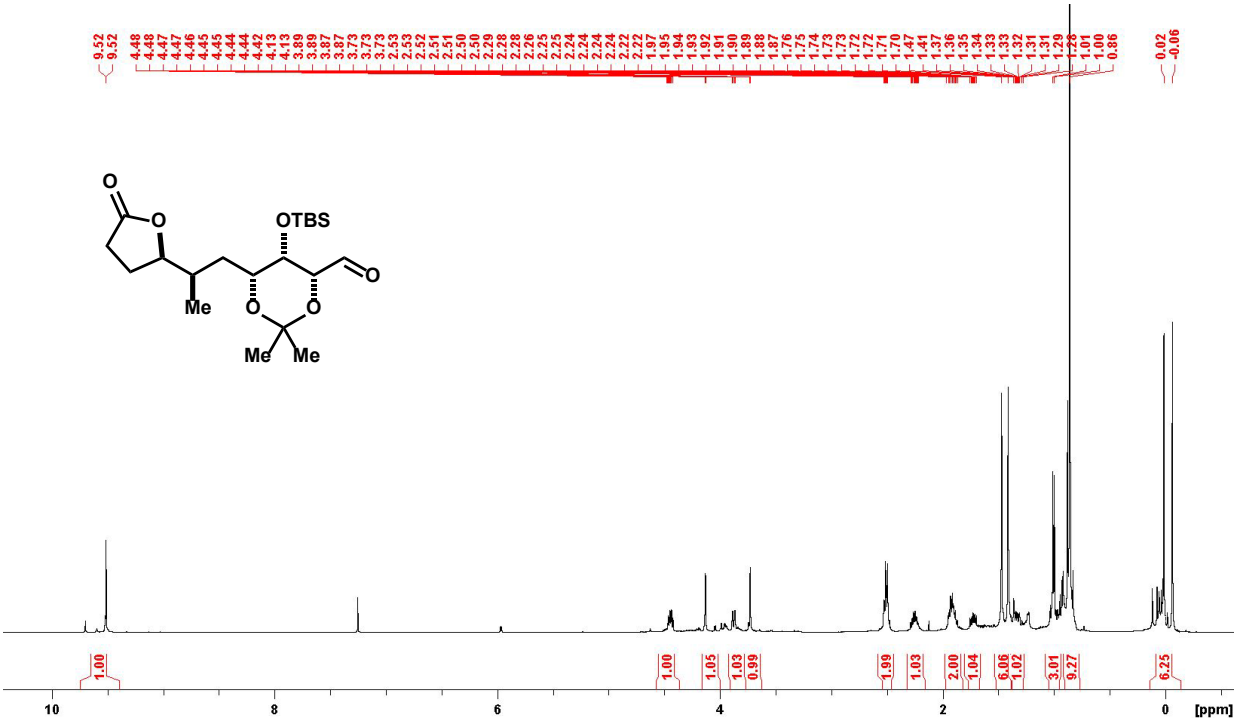
Spectrum 97. ^{1}H NMR of compound 2-12 ($CDCl_3$, 500 MHz)



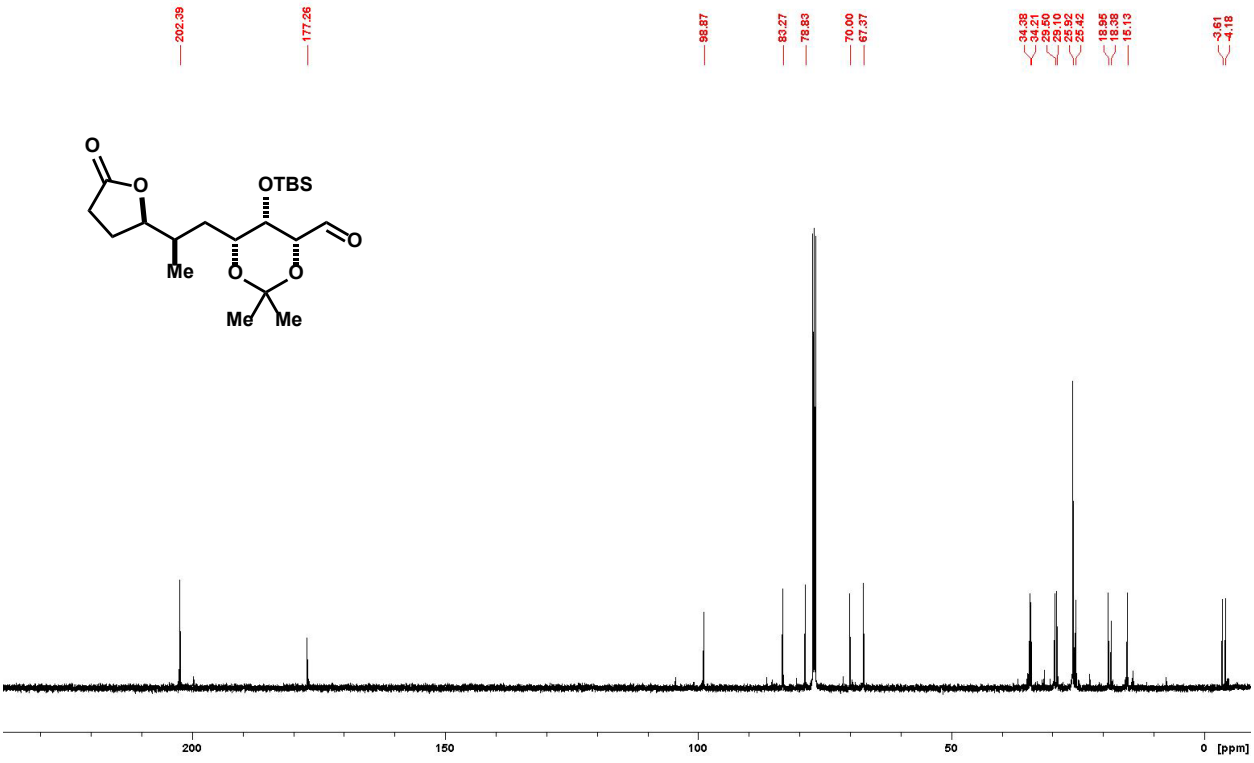
Spectrum 98. ^{13}C NMR of compound 2-12 ($CDCl_3$, 125 MHz)



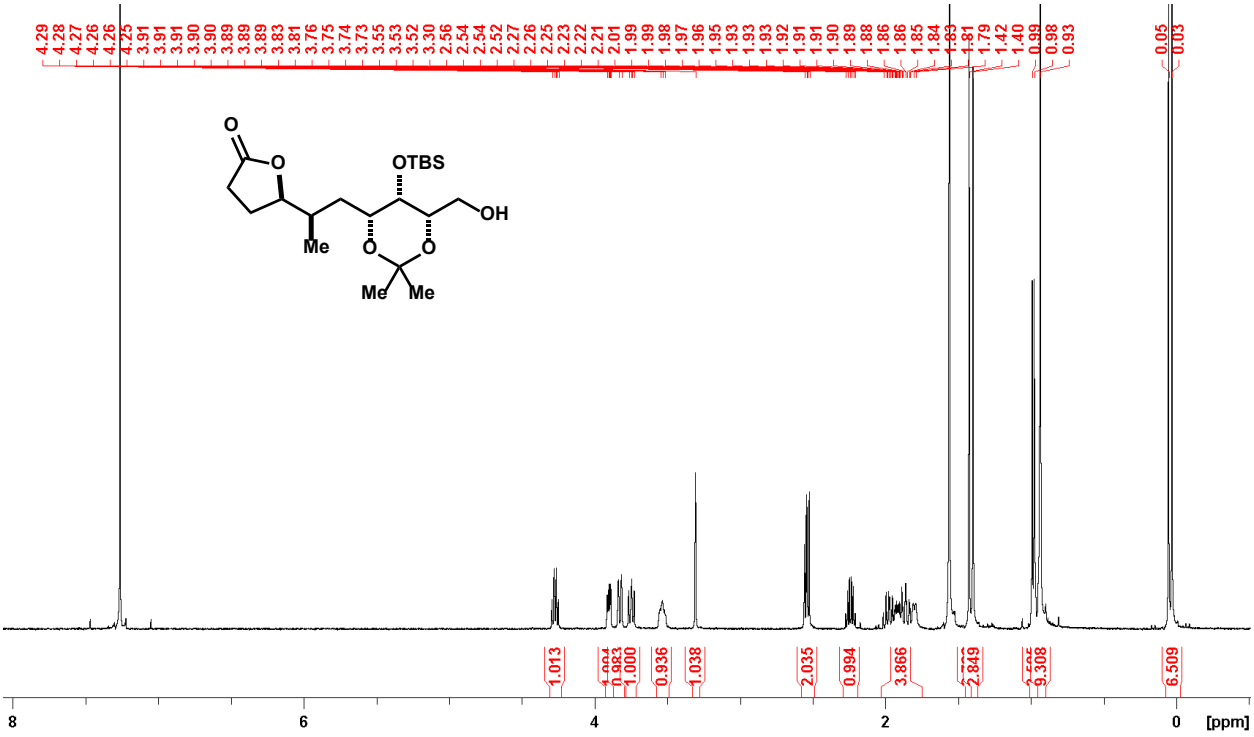
Spectrum 99. ^{1}H NMR of compound 2-10 ($CDCl_3$, 500 MHz)



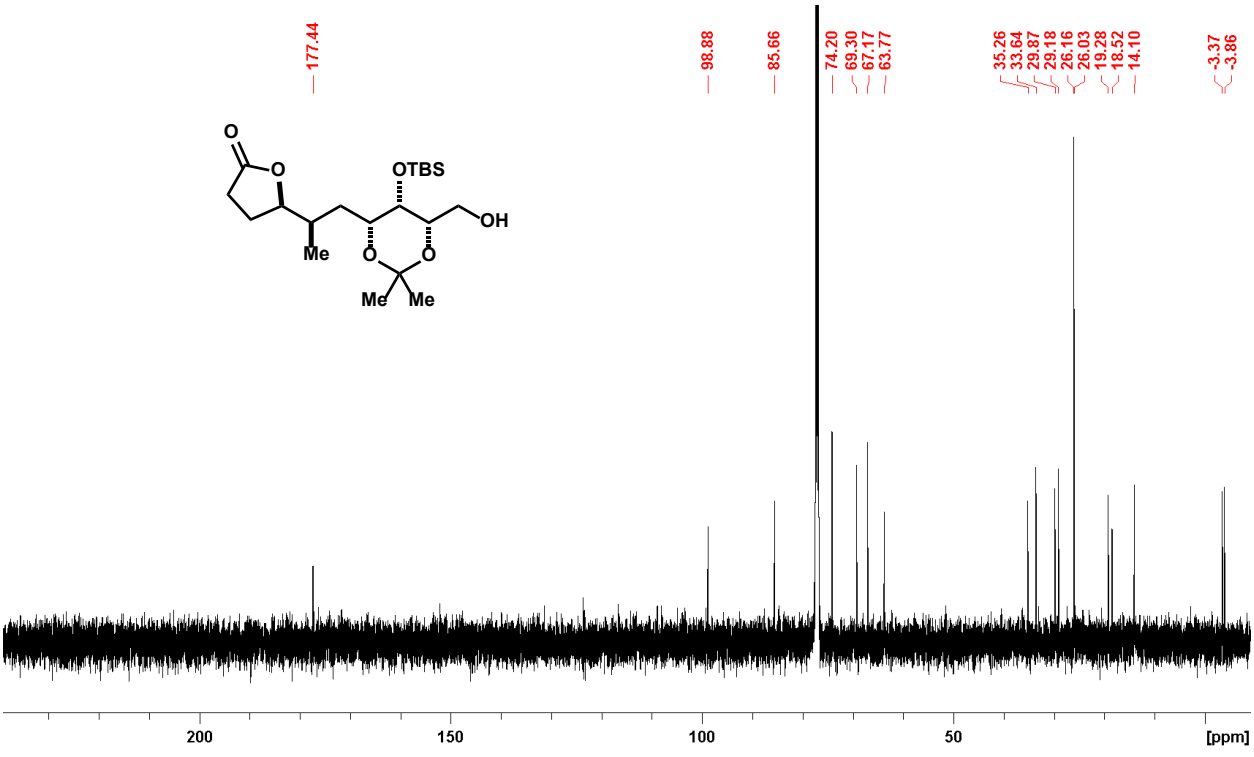
Spectrum 100. ^{13}C NMR of compound 2-10 ($CDCl_3$, 125 MHz)



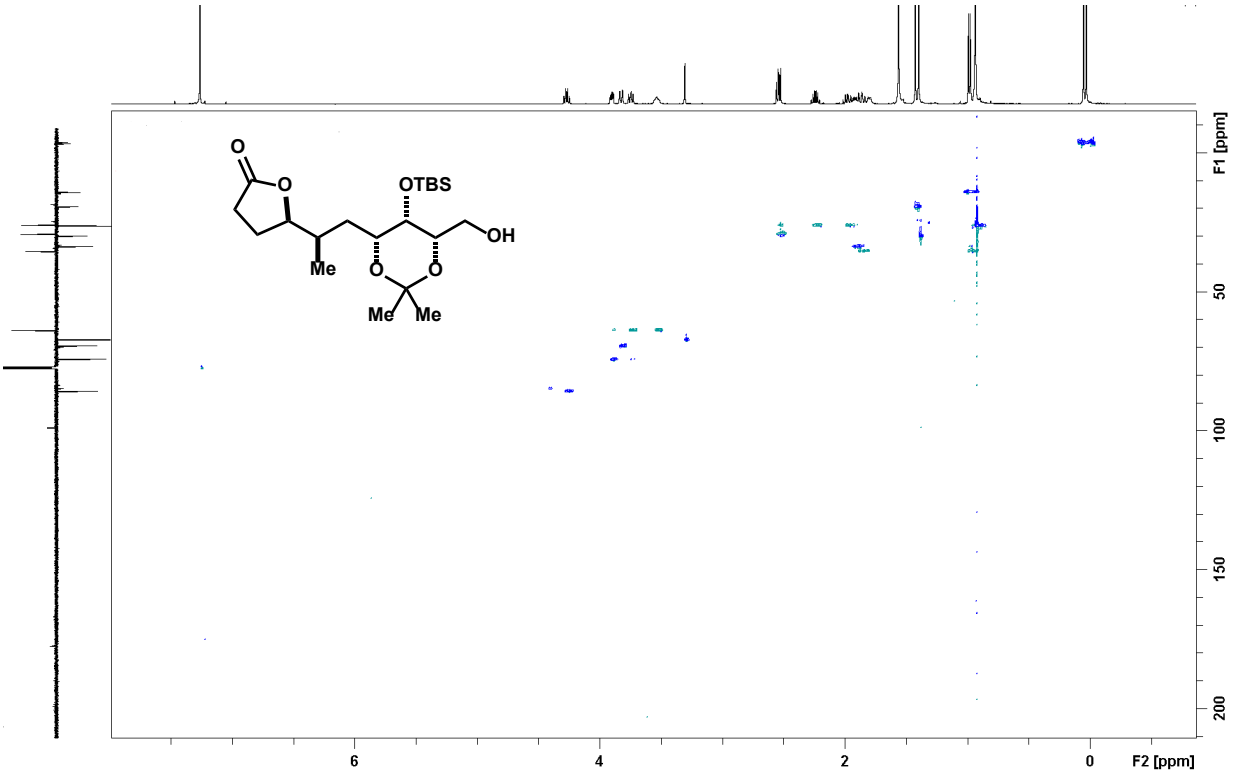
Spectrum 101. ^{1}H NMR of compound 2-11 ($CDCl_3$, 500 MHz)



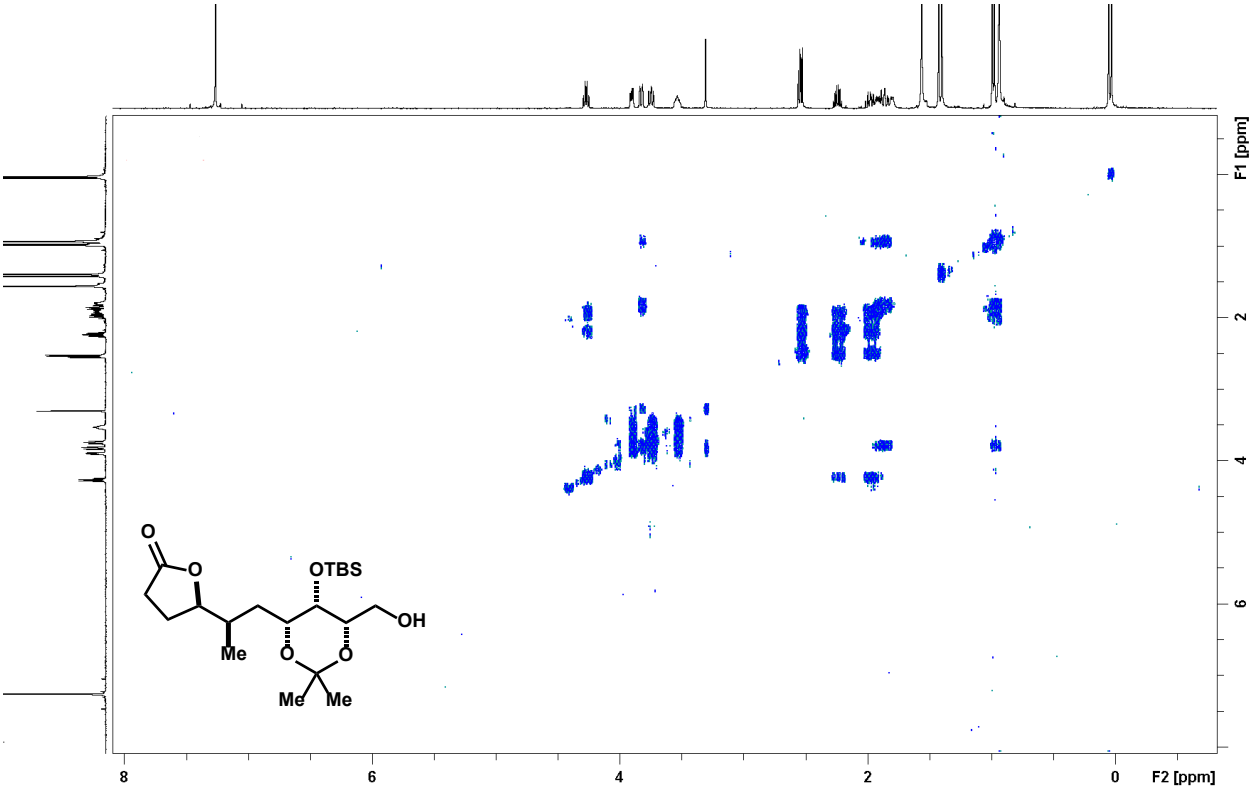
Spectrum 102. ^{13}C NMR of compound 2-11 ($CDCl_3$, 125 MHz)



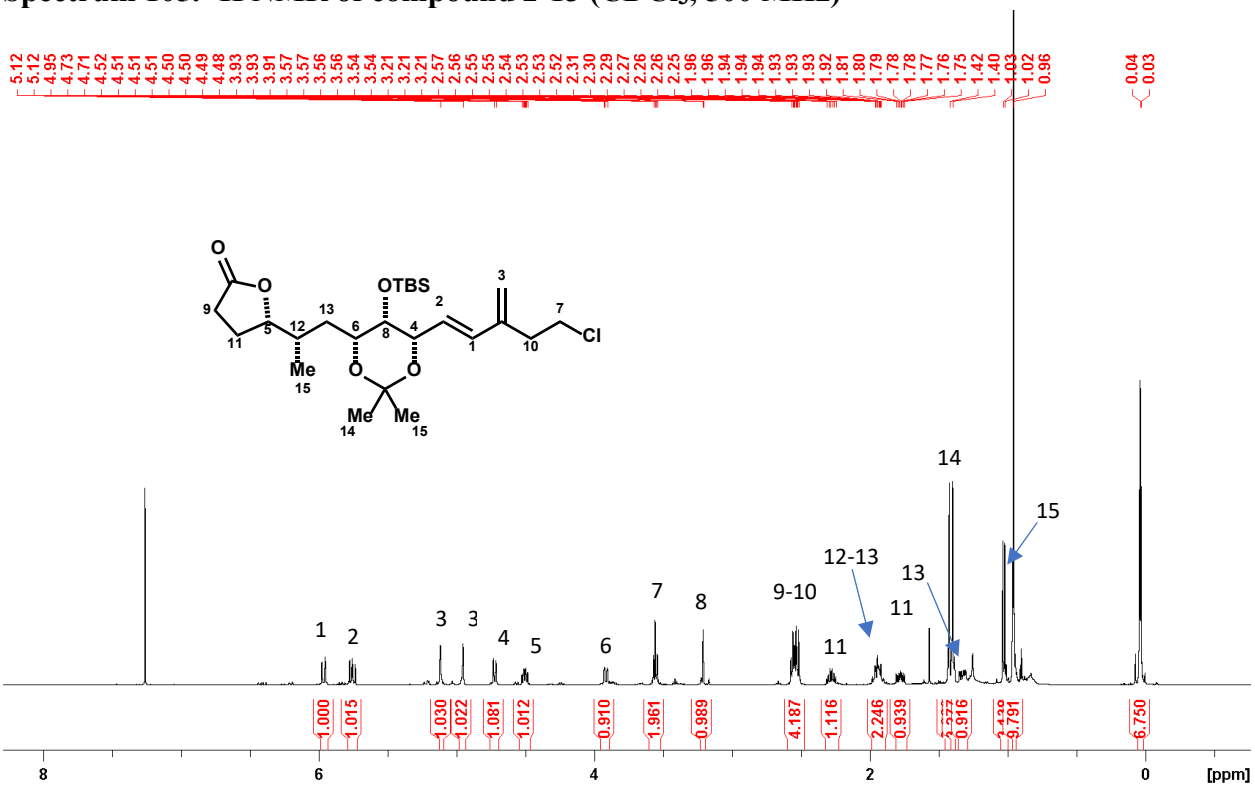
Spectrum 103. HSQC spectrum of compound 2-11 ($CDCl_3$, 400 MHz)



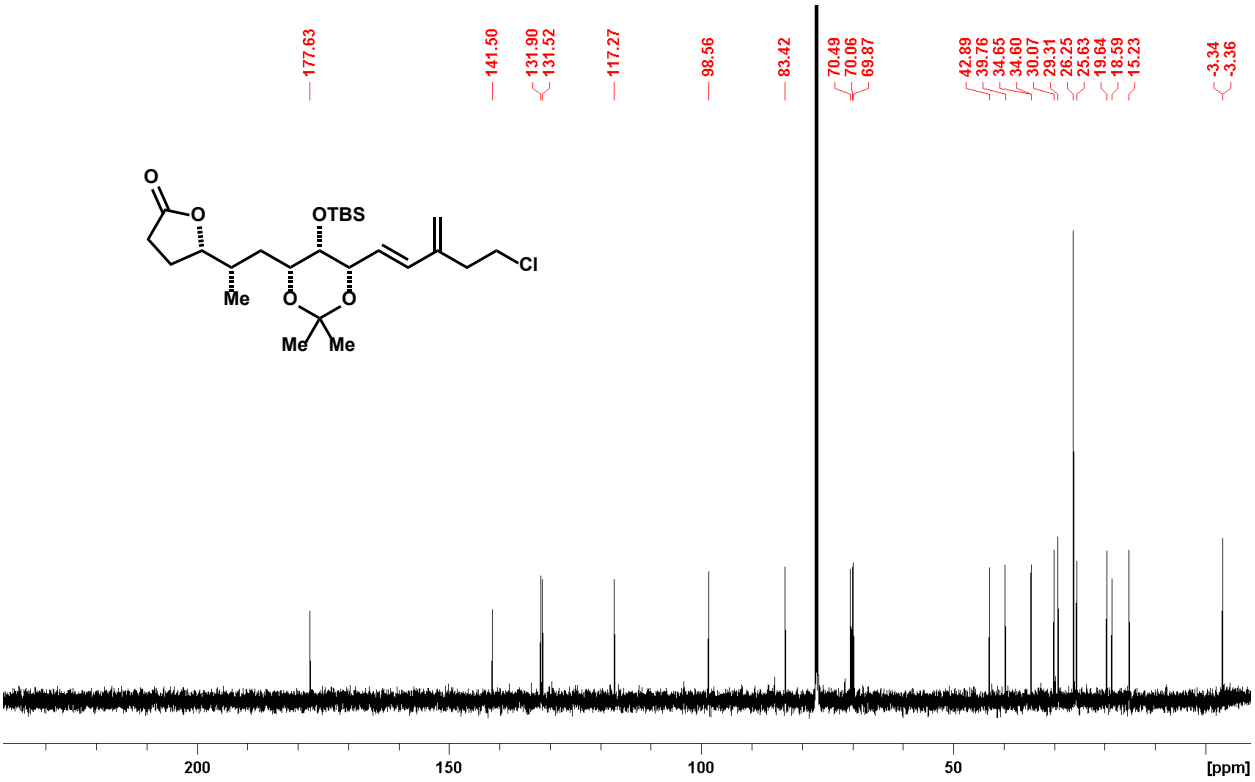
Spectrum 104. COSY spectrum of compound 2-11 ($CDCl_3$, 400 MHz)



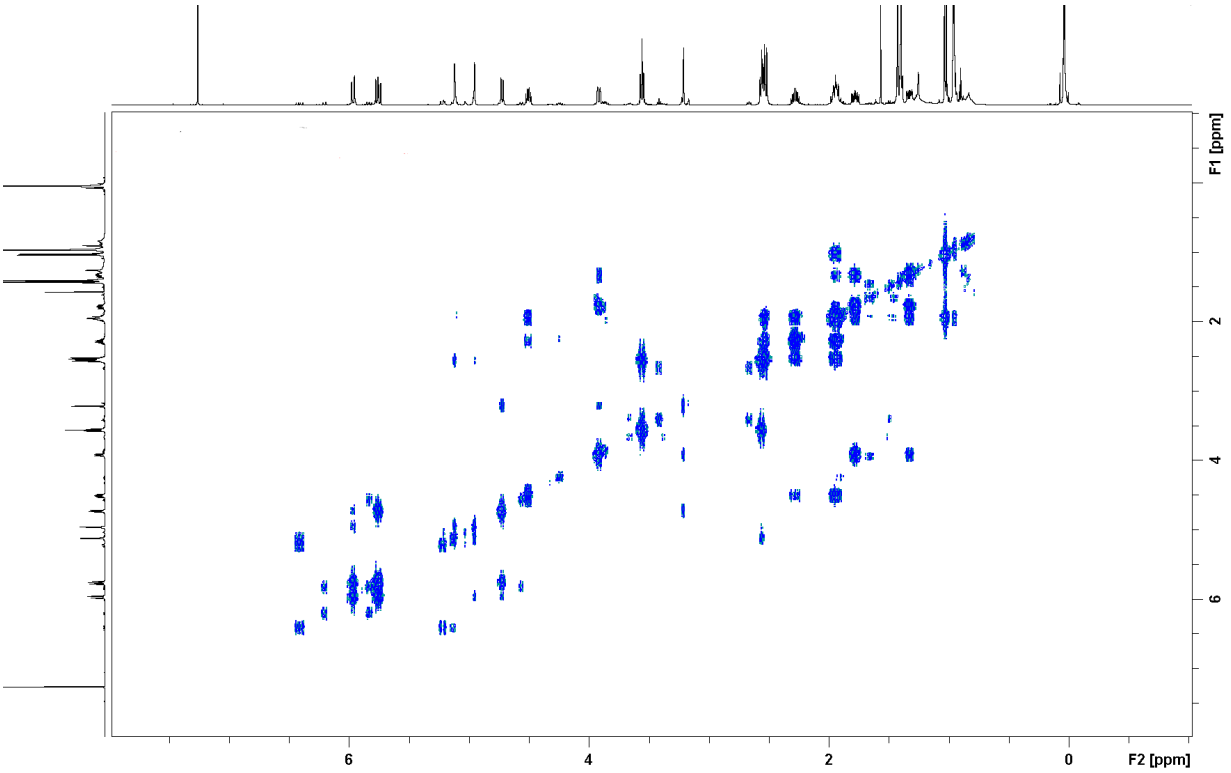
Spectrum 105. ^{1}H NMR of compound 2-13 ($CDCl_3$, 500 MHz)



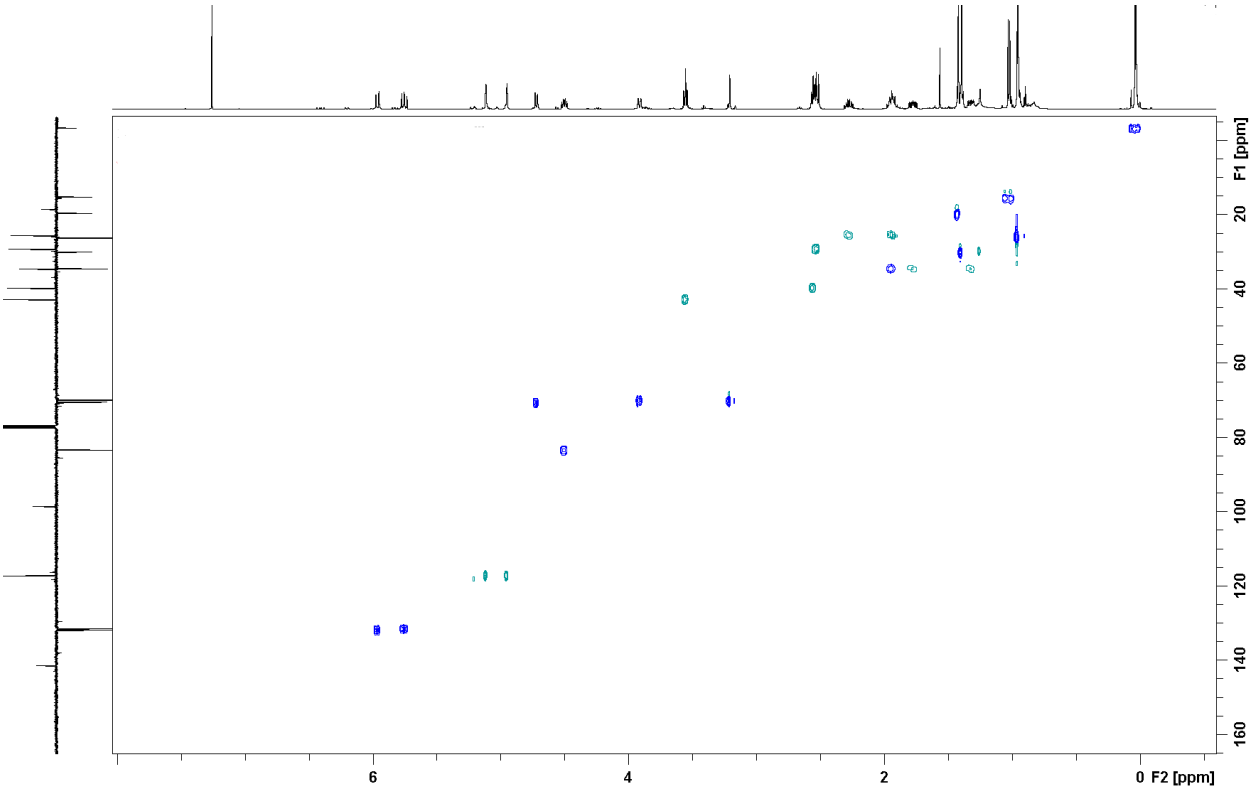
Spectrum 106. ^{13}C NMR of compound 2-13 ($CDCl_3$, 125 MHz)

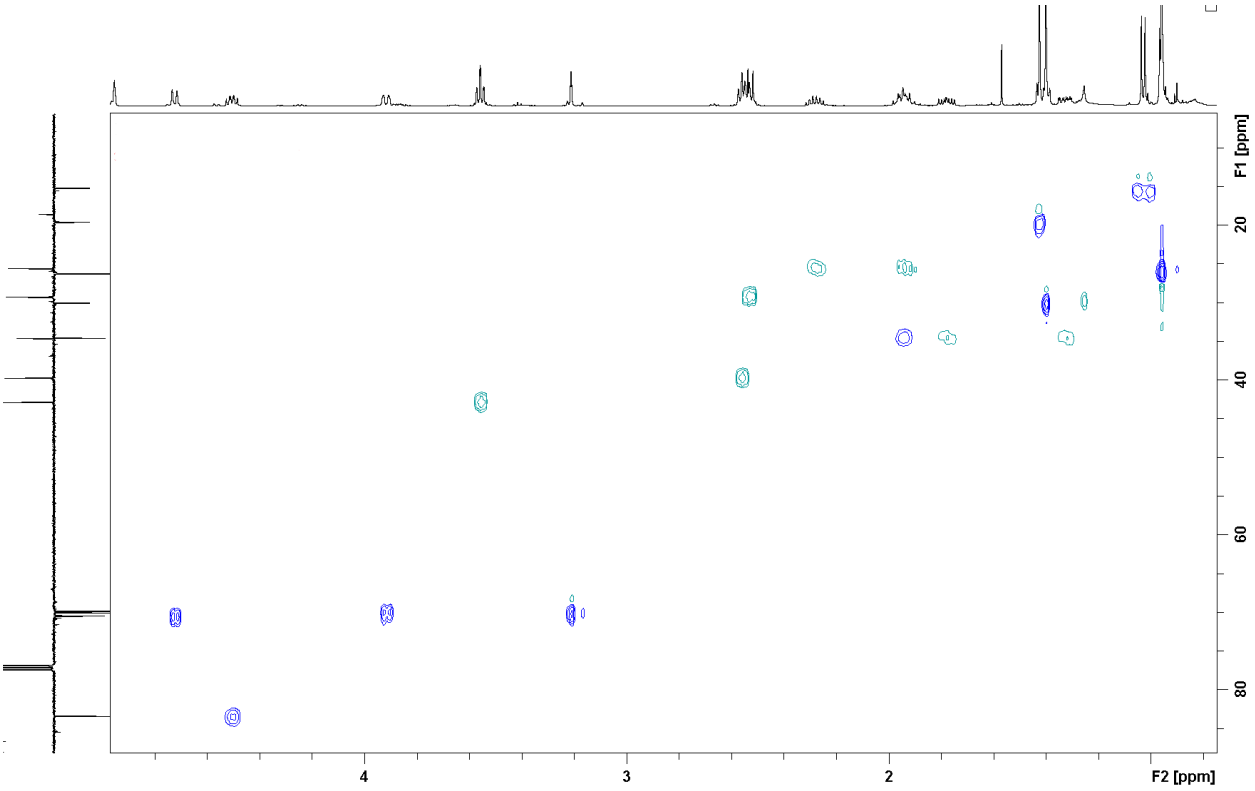


Spectrum 107. COSY spectrum of compound 2-13 ($CDCl_3$, 500 MHz)

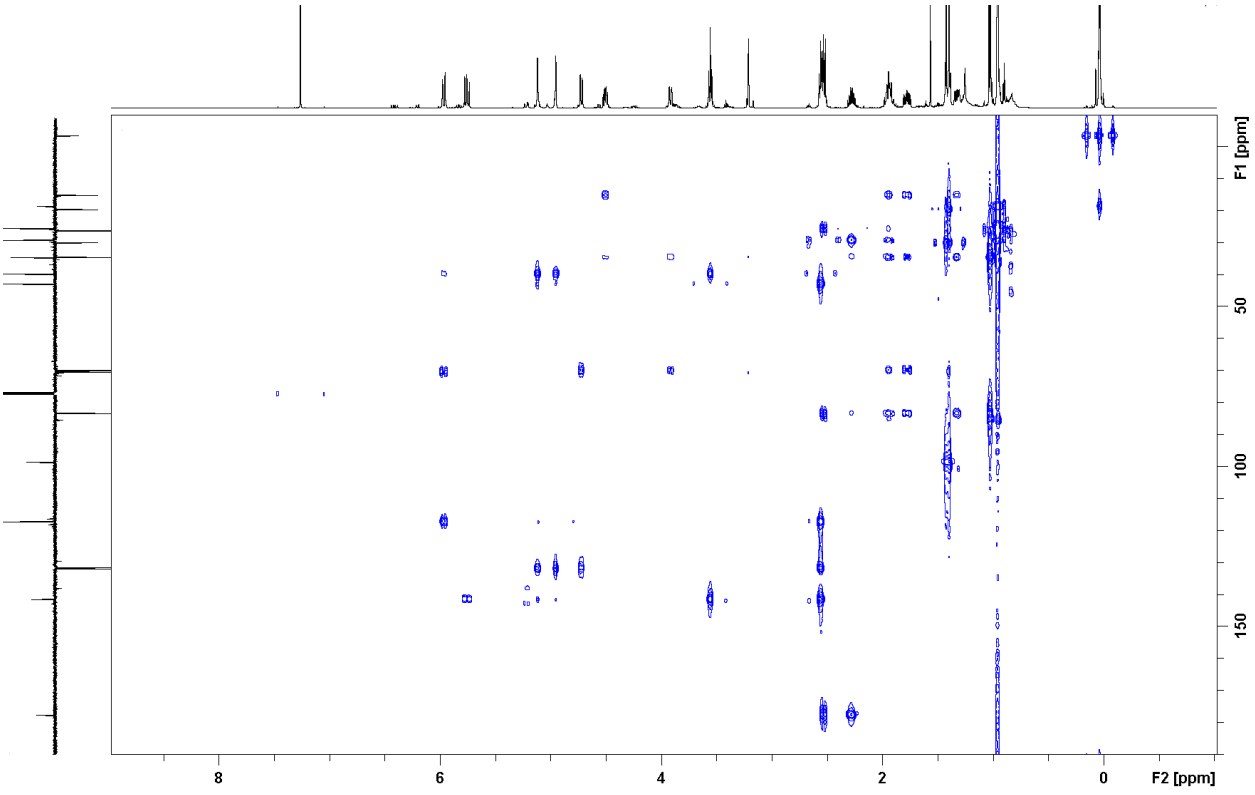


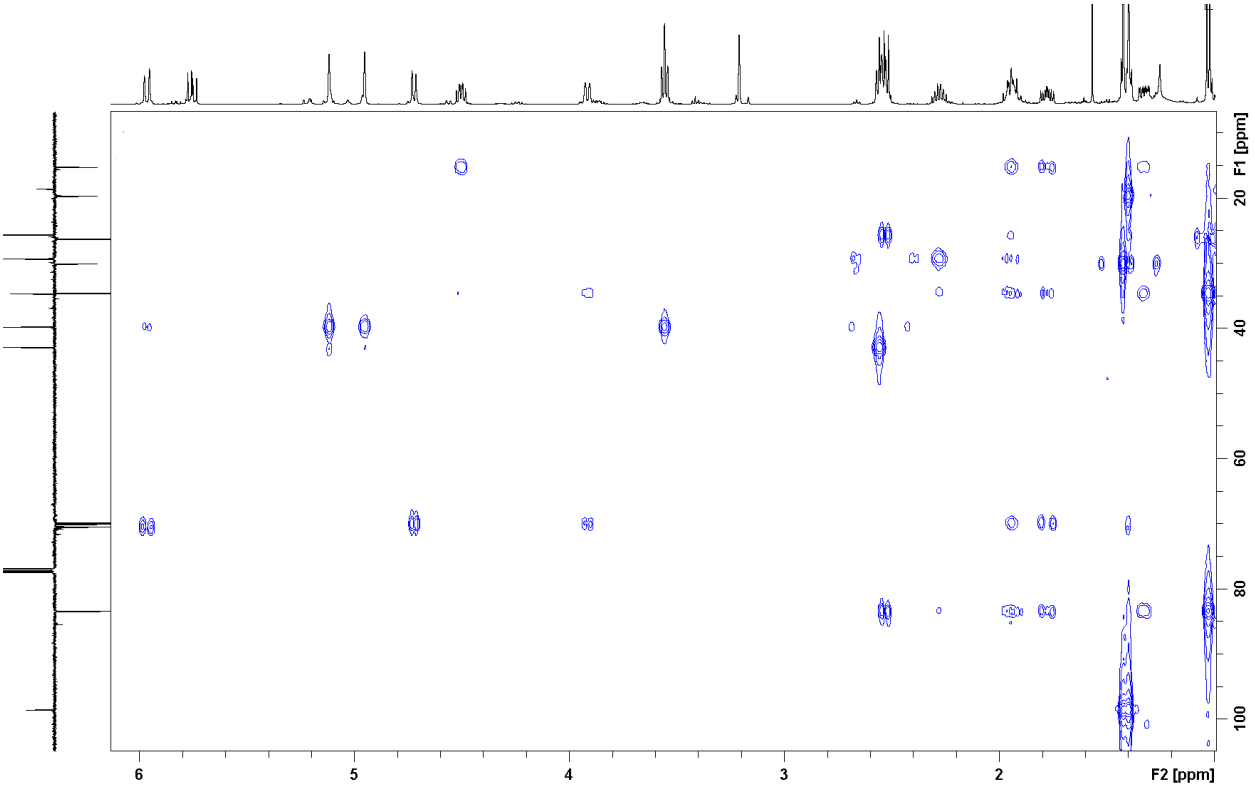
Spectrum 108. HSQC spectrum of compound 2-13 ($CDCl_3$, 500 MHz)



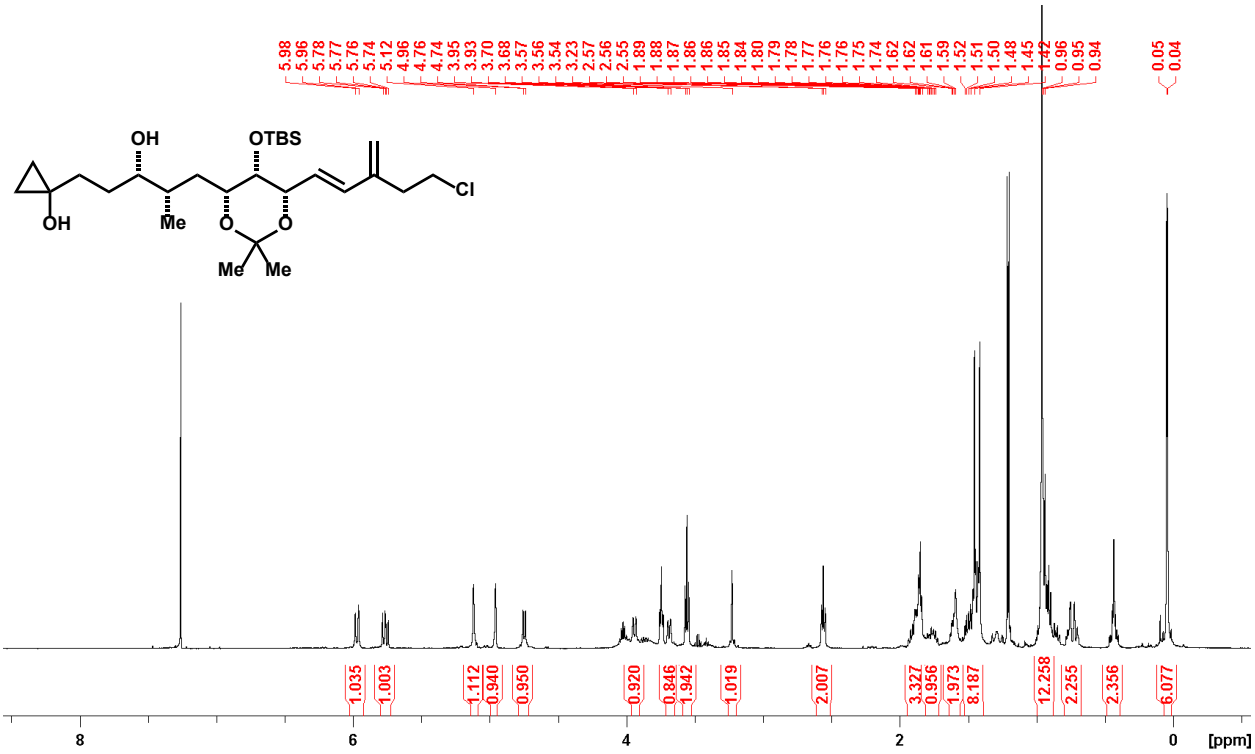


Spectrum 109. HMBC spectrum of compound 2-13 ($CDCl_3$, 500 MHz)

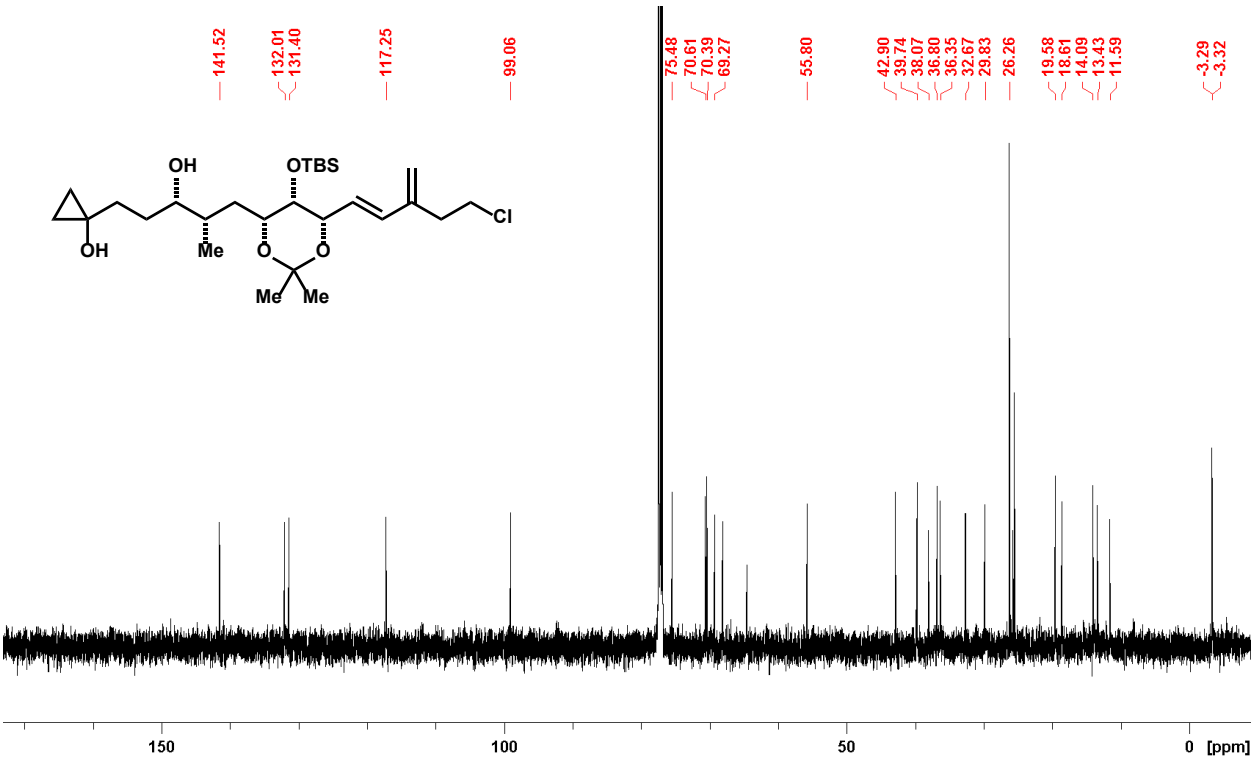



F1 [ppm]
20
40
60
80
100
6
5
4
3
2
F2 [ppm]

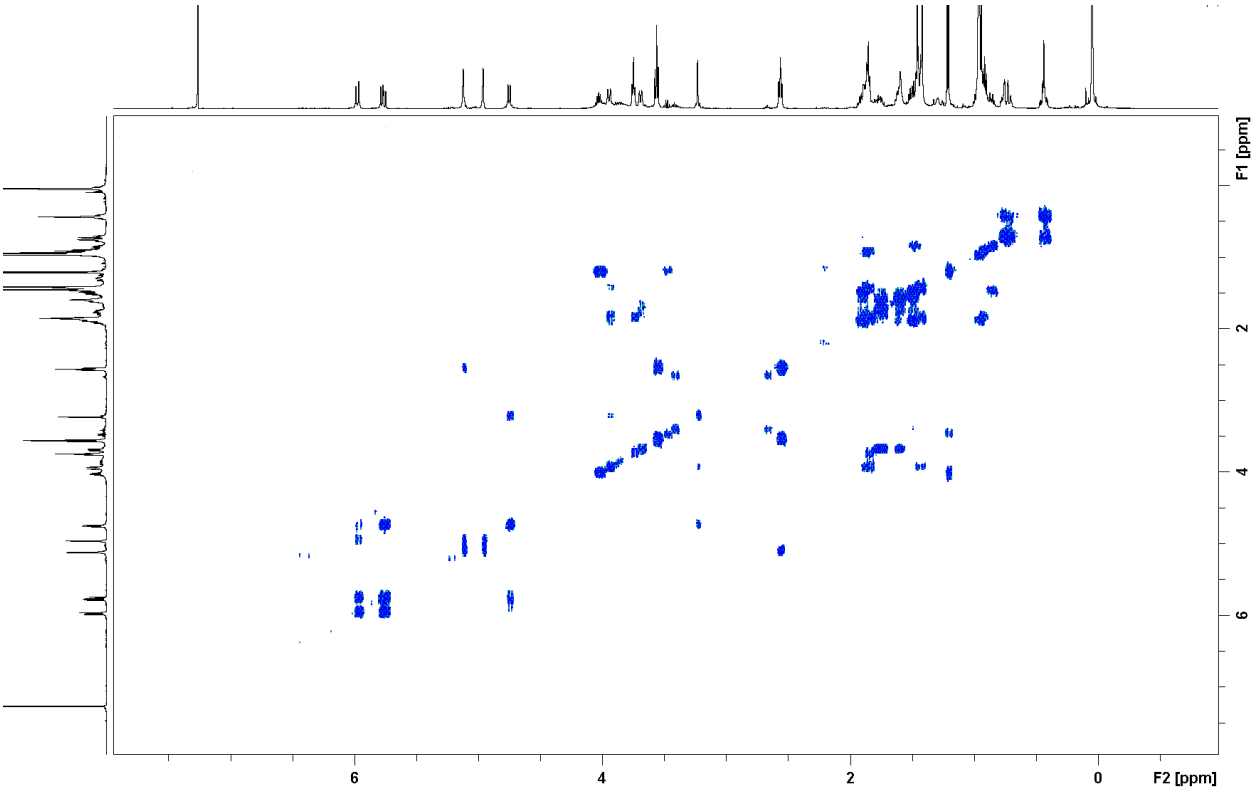
Spectrum 110. ^{1}H NMR of compound 2-14 ($CDCl_3$, 500 MHz)



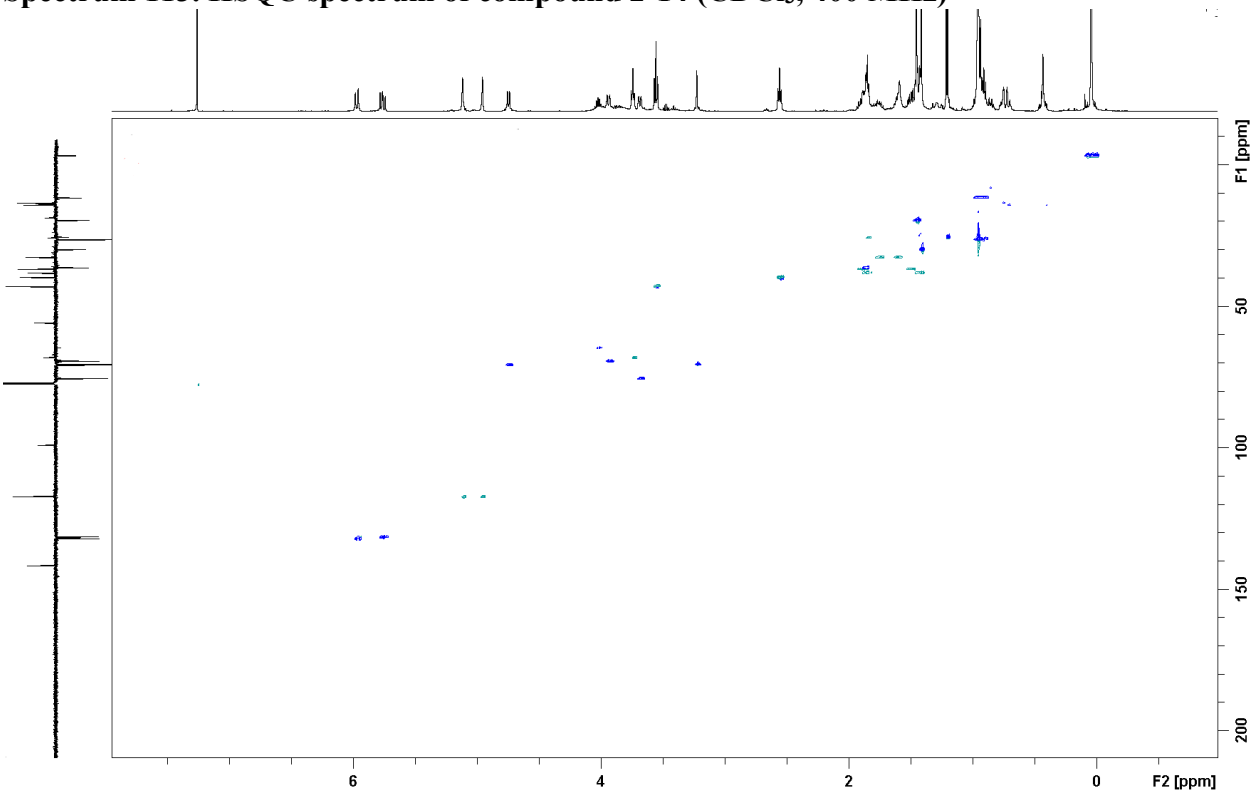
Spectrum 111. ^{13}C NMR of compound 2-14 ($CDCl_3$, 125 MHz)

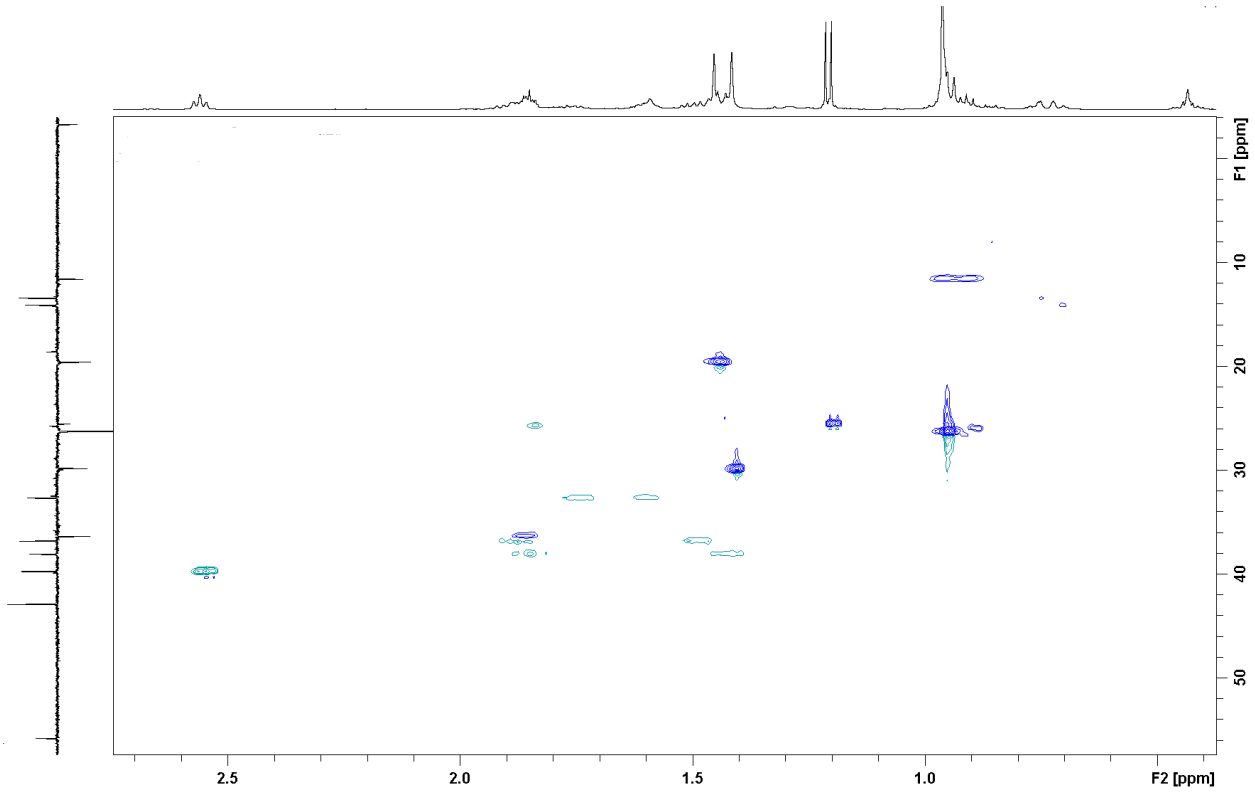


Spectrum 112. COSY spectrum of compound 2-14 ($CDCl_3$, 400 MHz)

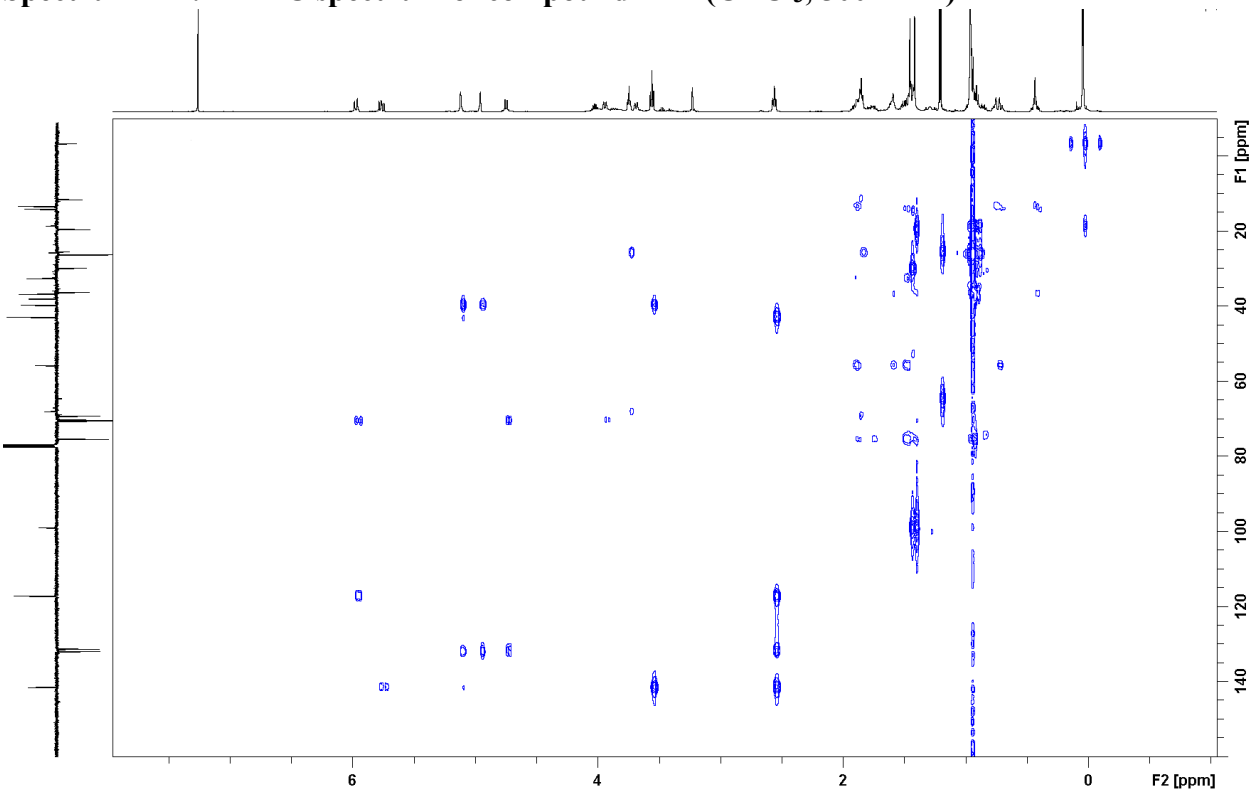


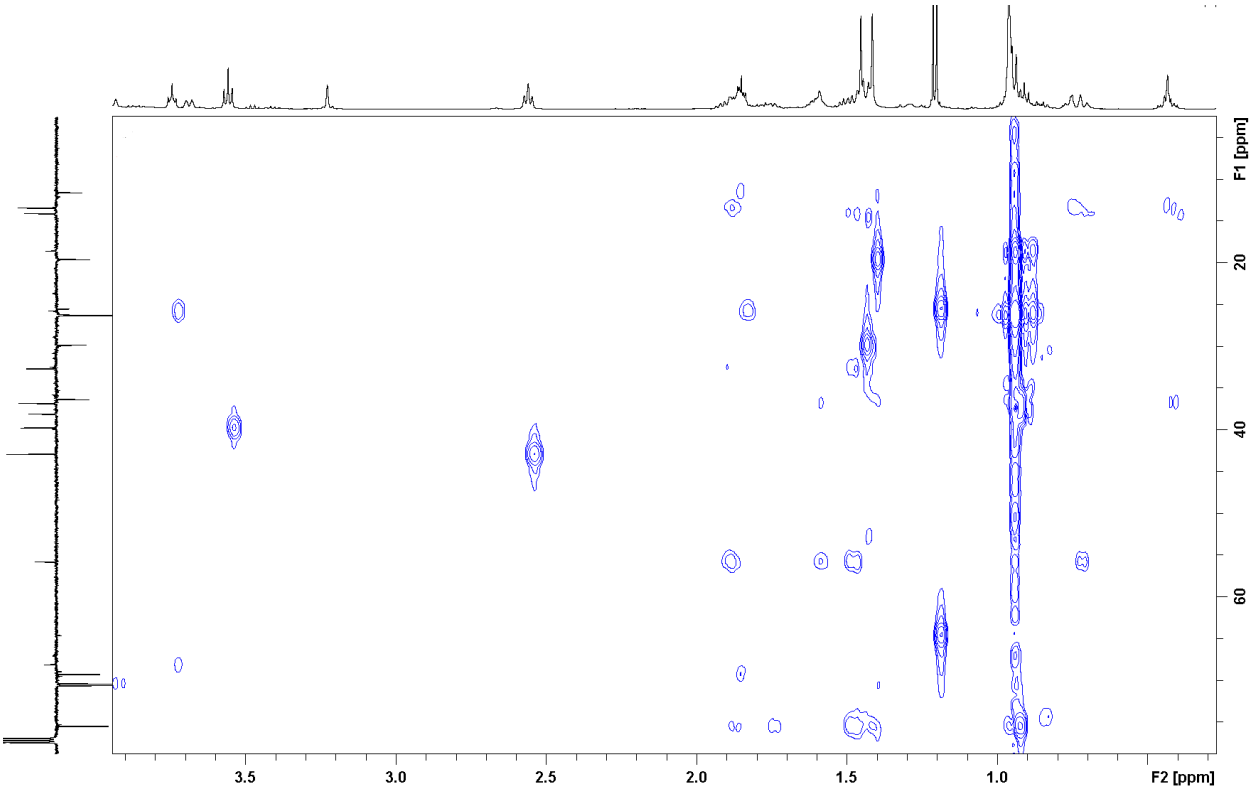
Spectrum 113. HSQC spectrum of compound 2-14 ($CDCl_3$, 400 MHz)



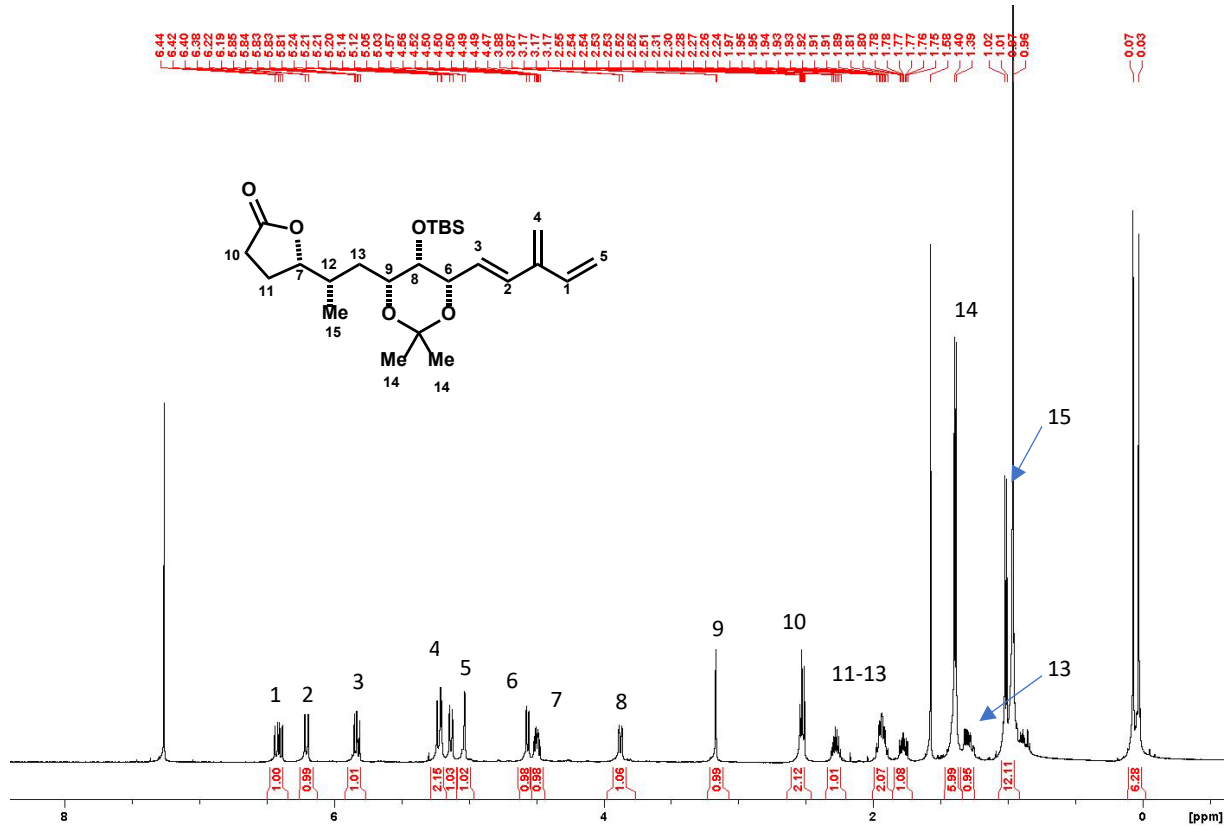


Spectrum 114. HMBC spectrum of compound 2-14 ($CDCl_3$, 500 MHz)

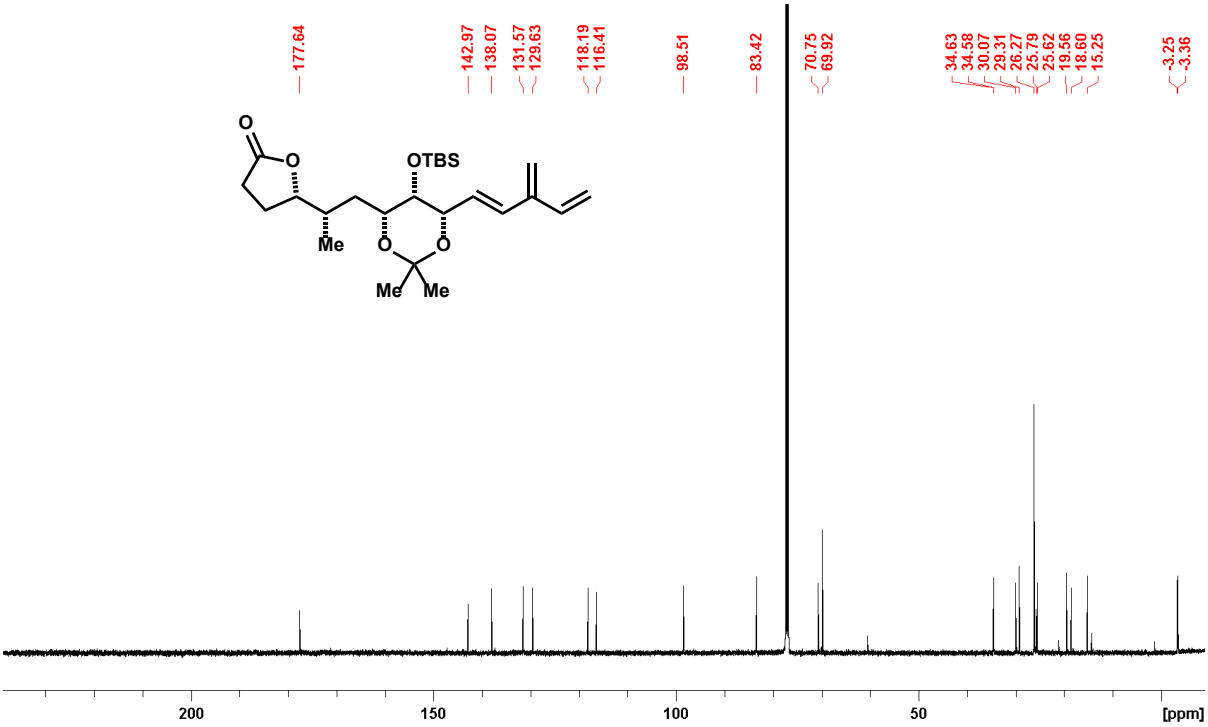



F1 [ppm]
20
40
60
3.5
3.0
2.5
2.0
1.5
1.0
F2 [ppm]

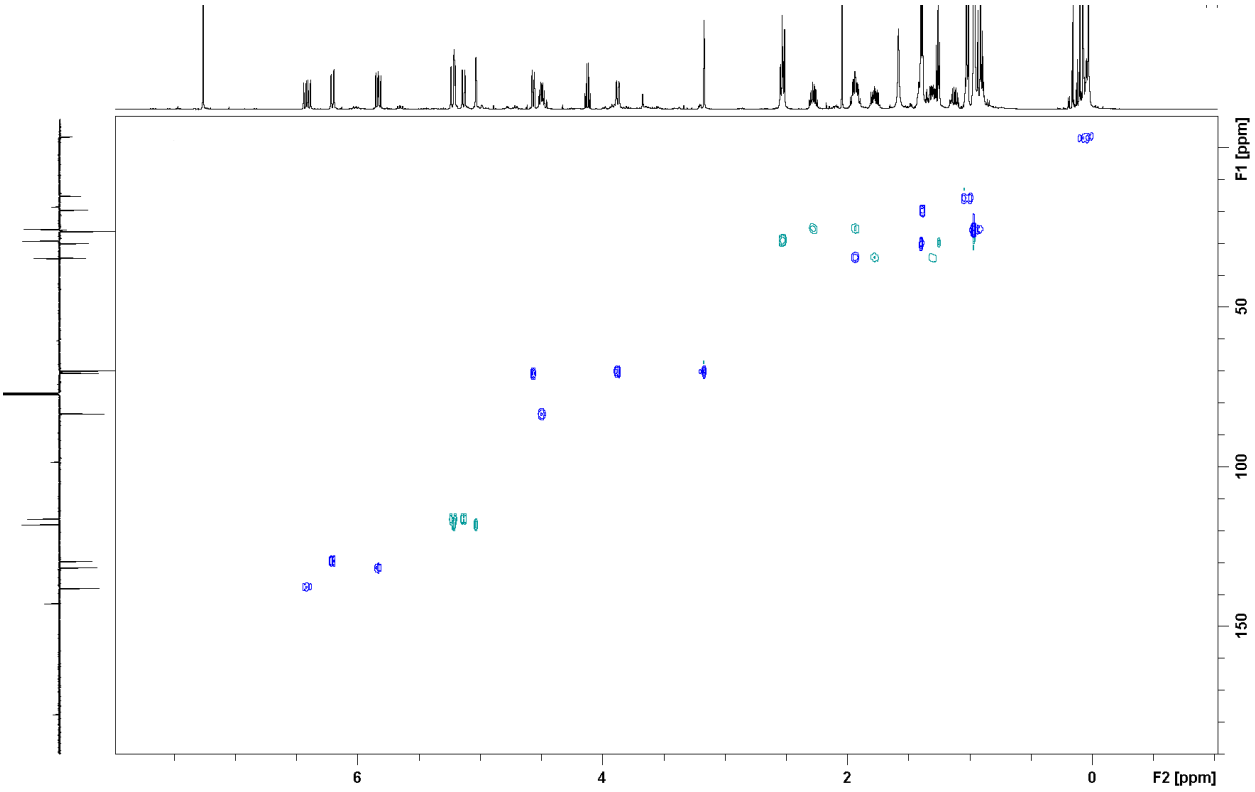
Spectrum 115. ^{1}H NMR of compound 2-15 ($CDCl_3$, 500 MHz)



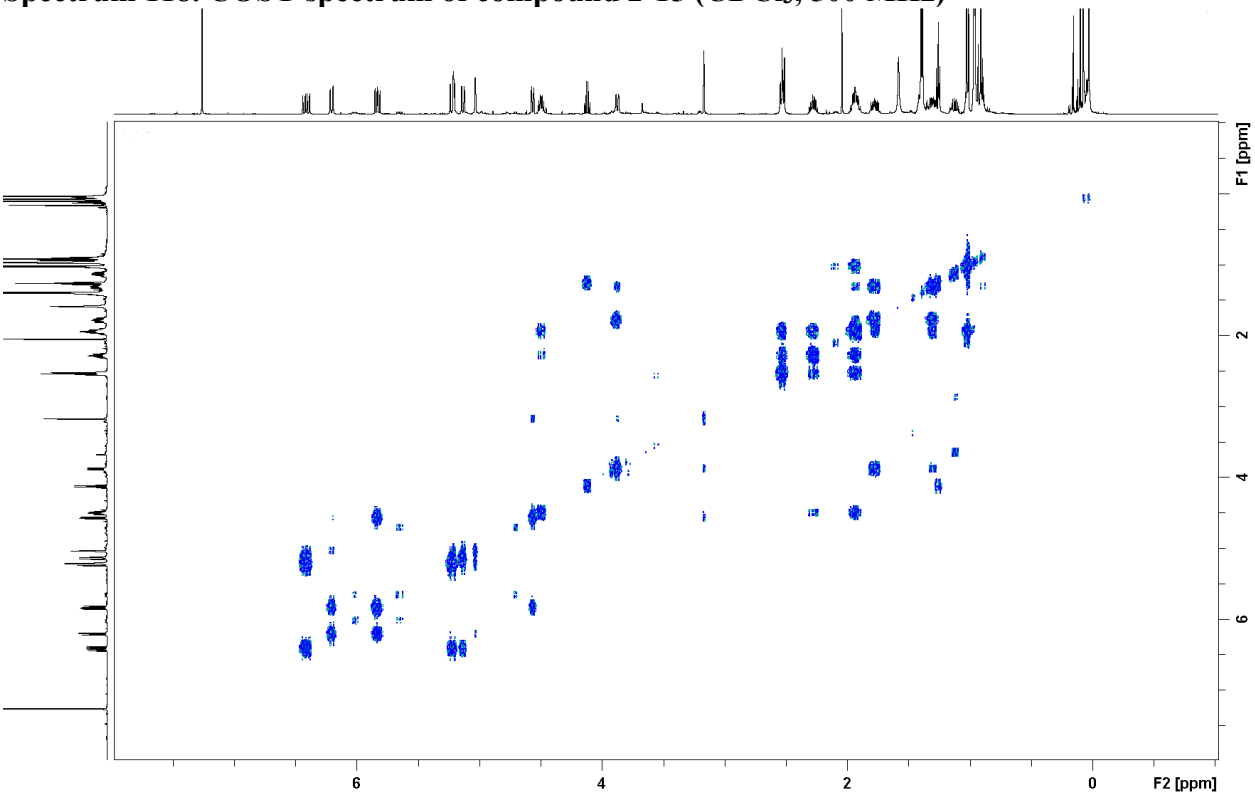
Spectrum 116. ^{13}C NMR of compound 2-15 ($CDCl_3$, 125 MHz)



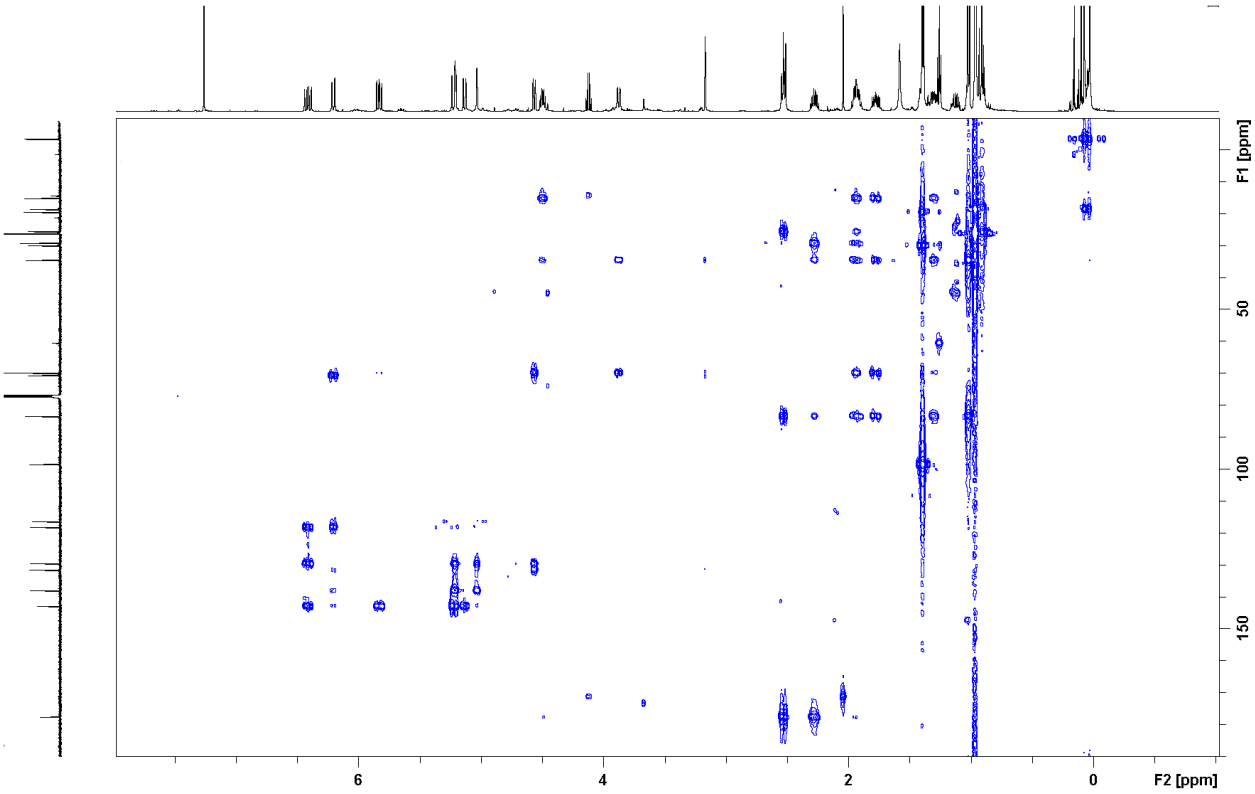
Spectrum 117. HSQC spectrum of compound 2-15 ($CDCl_3$, 500 MHz)



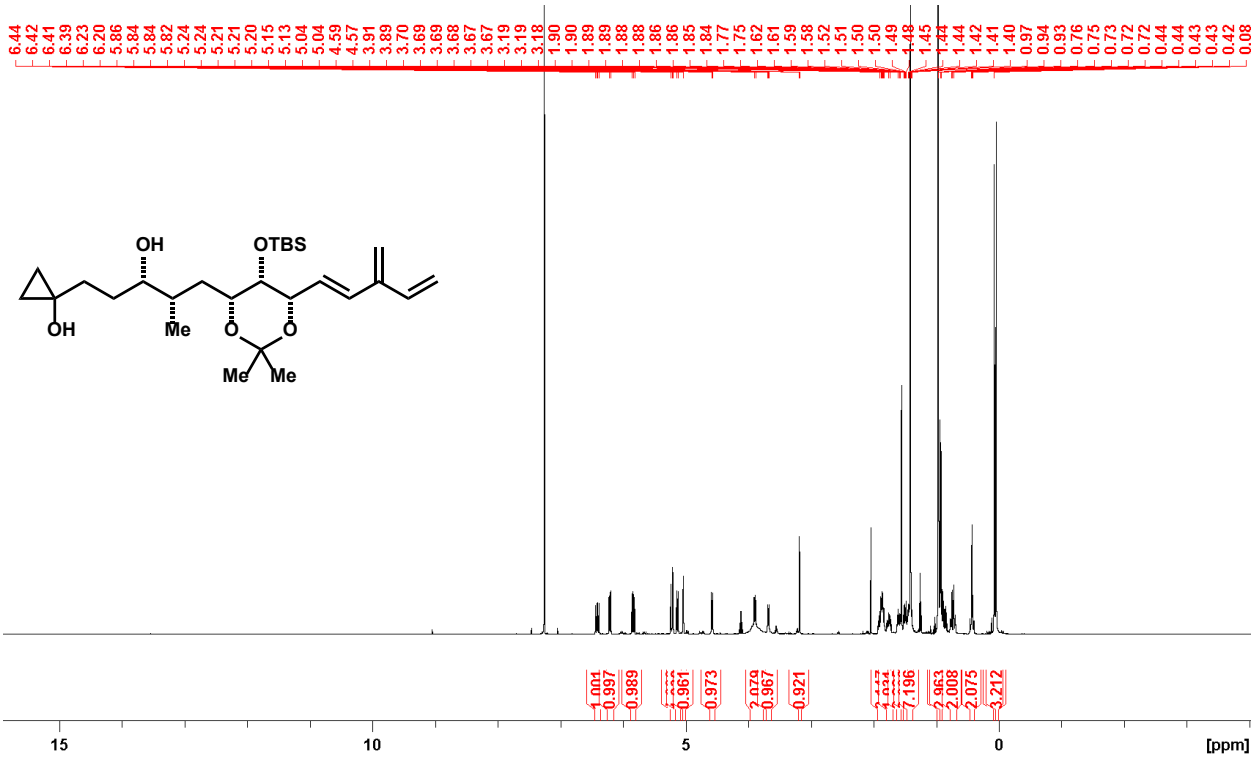
Spectrum 118. COSY spectrum of compound 2-15 ($CDCl_3$, 500 MHz)



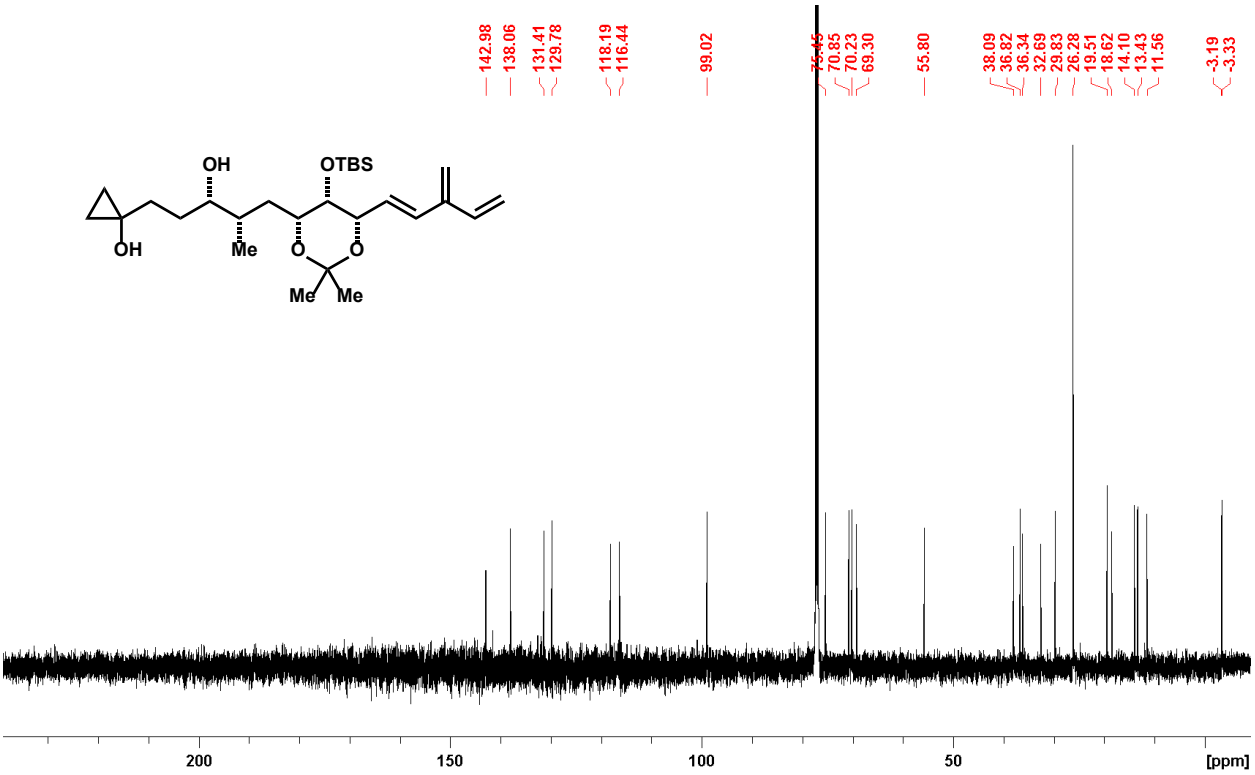
Spectrum 119. HMBC spectrum of compound 2-15 ($CDCl_3$, 500 MHz)



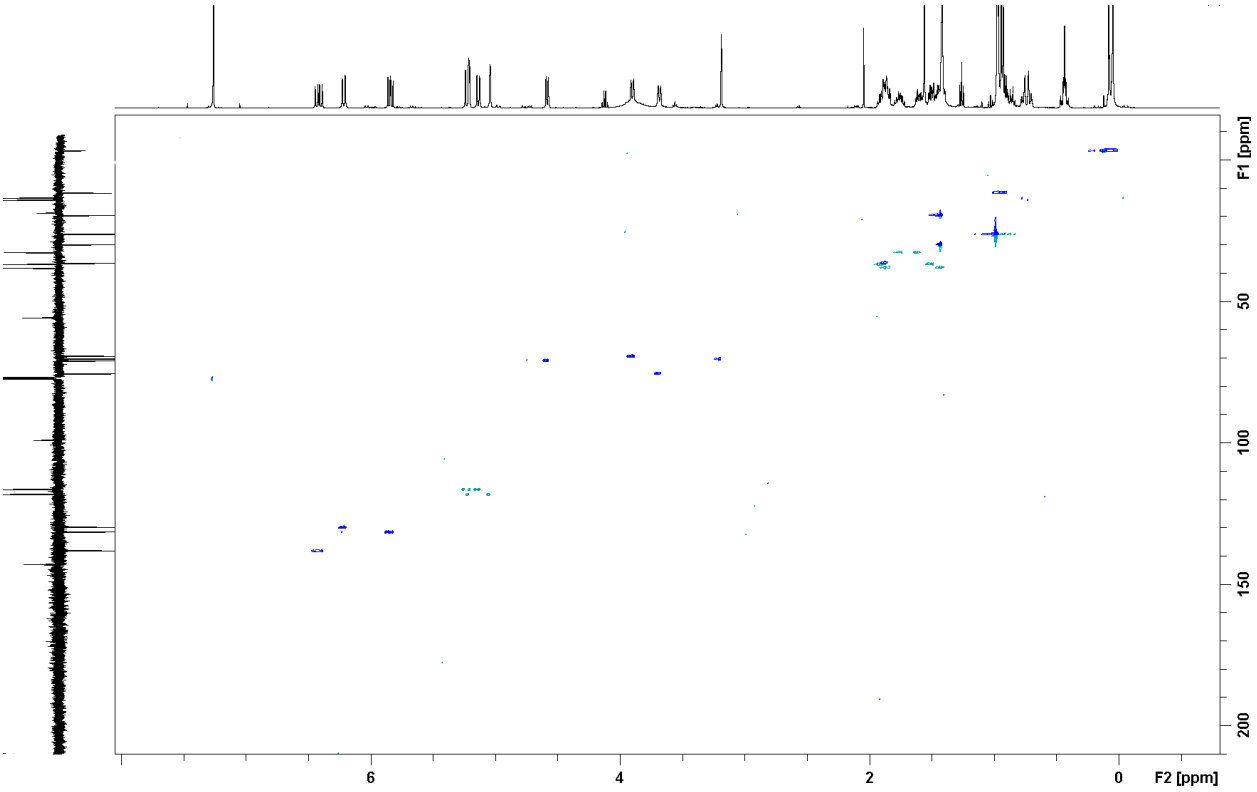
Spectrum 120. ^{1}H NMR of compound 2-16 ($CDCl_3$, 500 MHz)



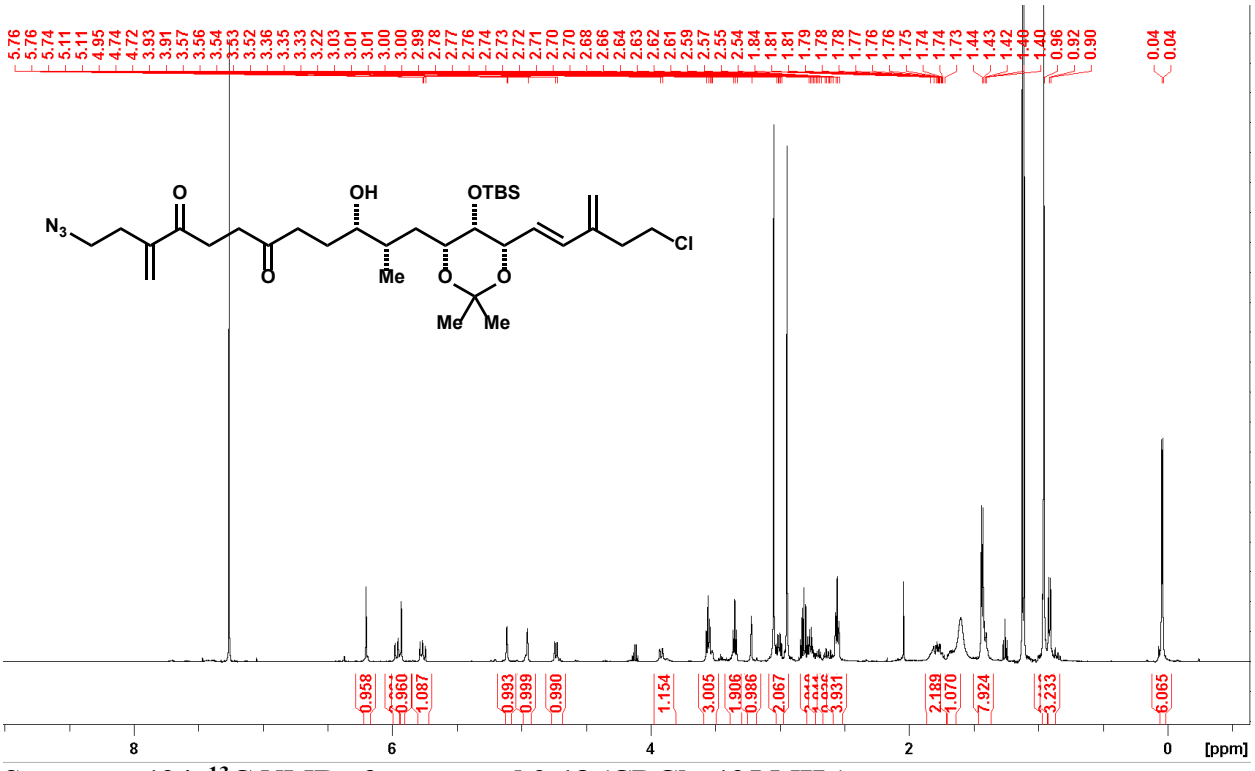
Spectrum 121. ^{13}C NMR of compound 2-16 ($CDCl_3$, 125 MHz)



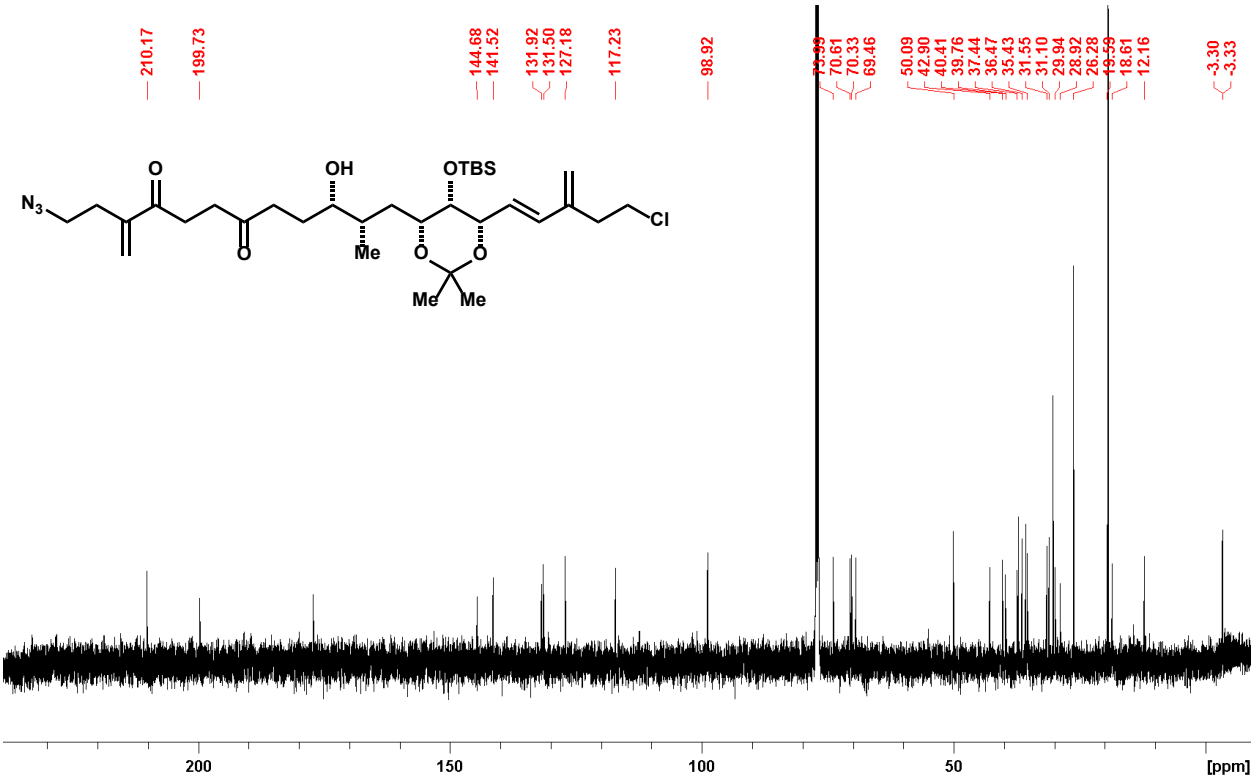
Spectrum 122. HSQC spectrum of compound 2-16 ($CDCl_3$, 400 MHz)



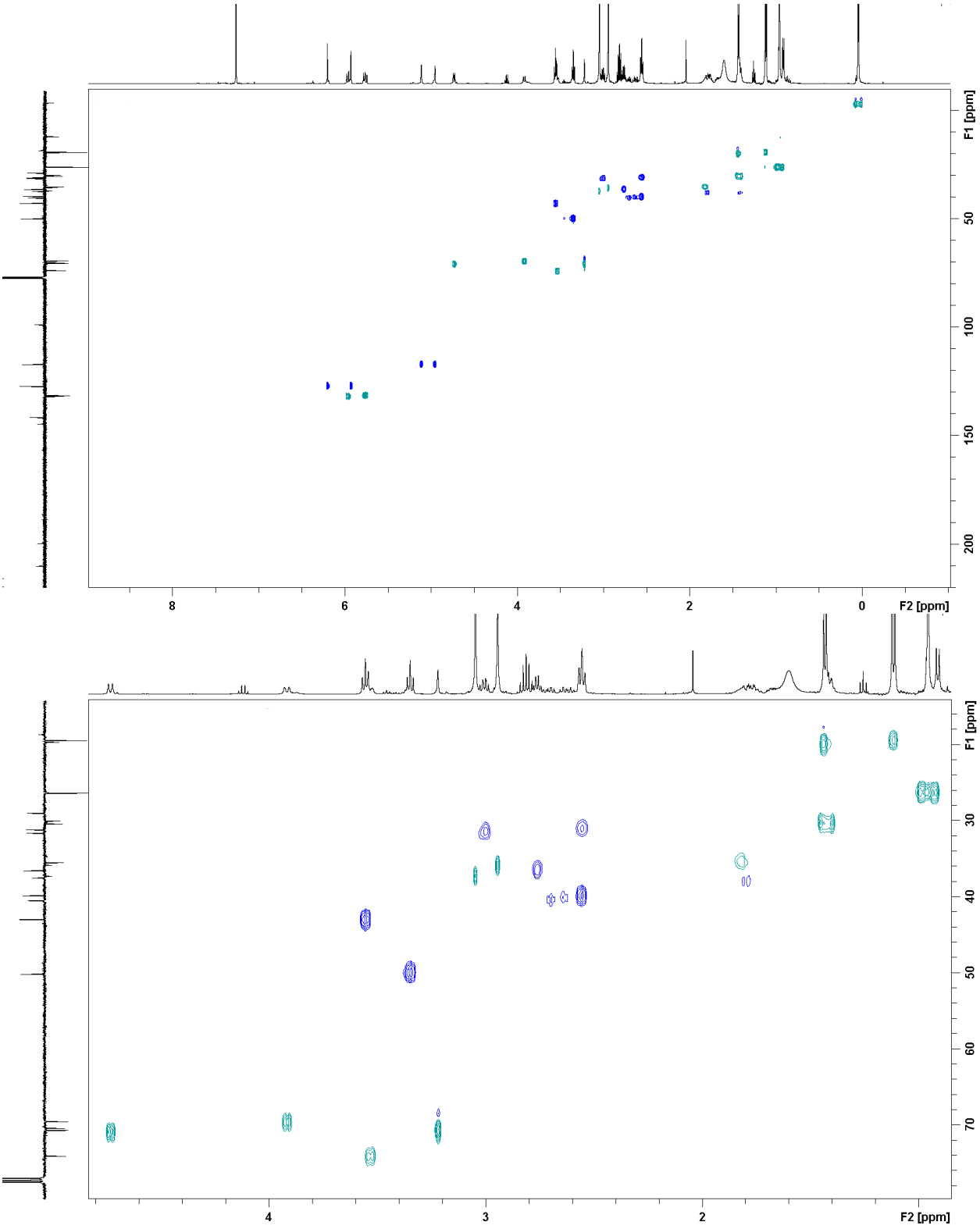
Spectrum 123. ^{1}H NMR of compound 2-18 ($CDCl_3$, 500 MHz)



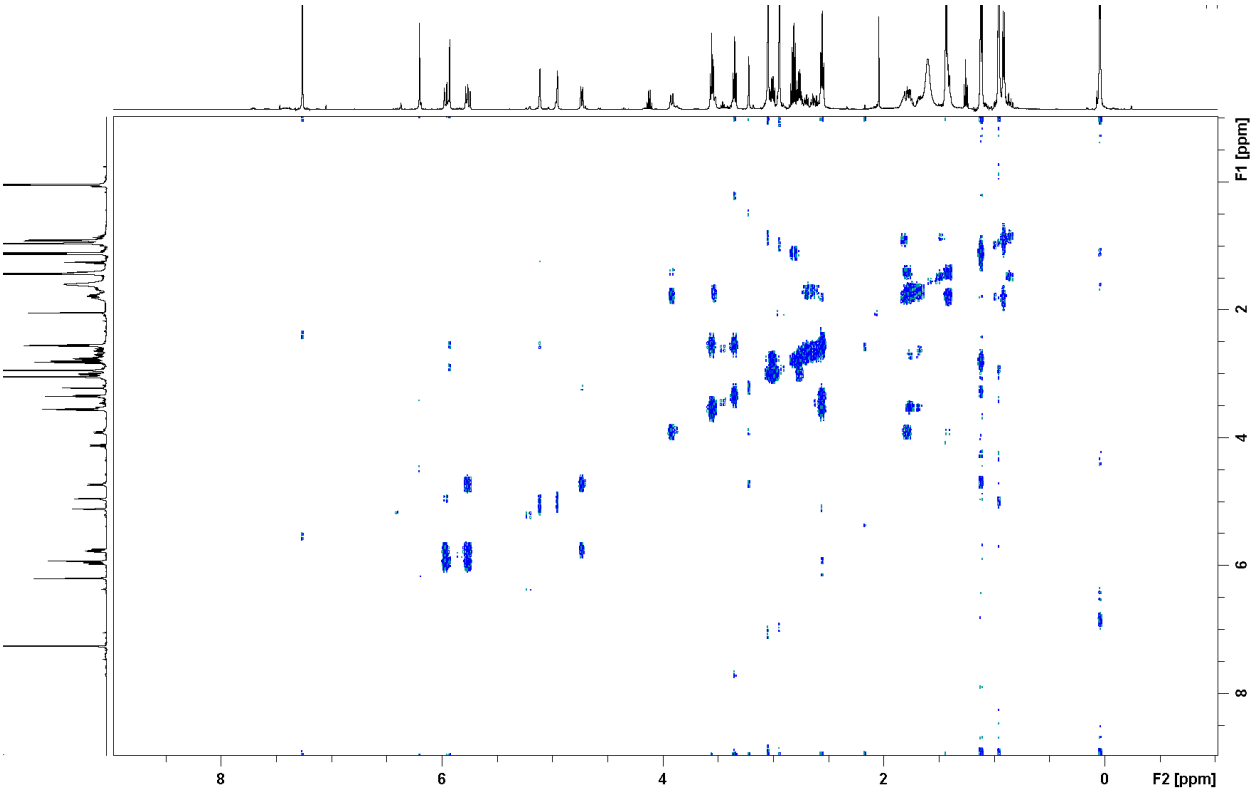
Spectrum 124. ^{13}C NMR of compound 2-18 ($CDCl_3$, 125 MHz)



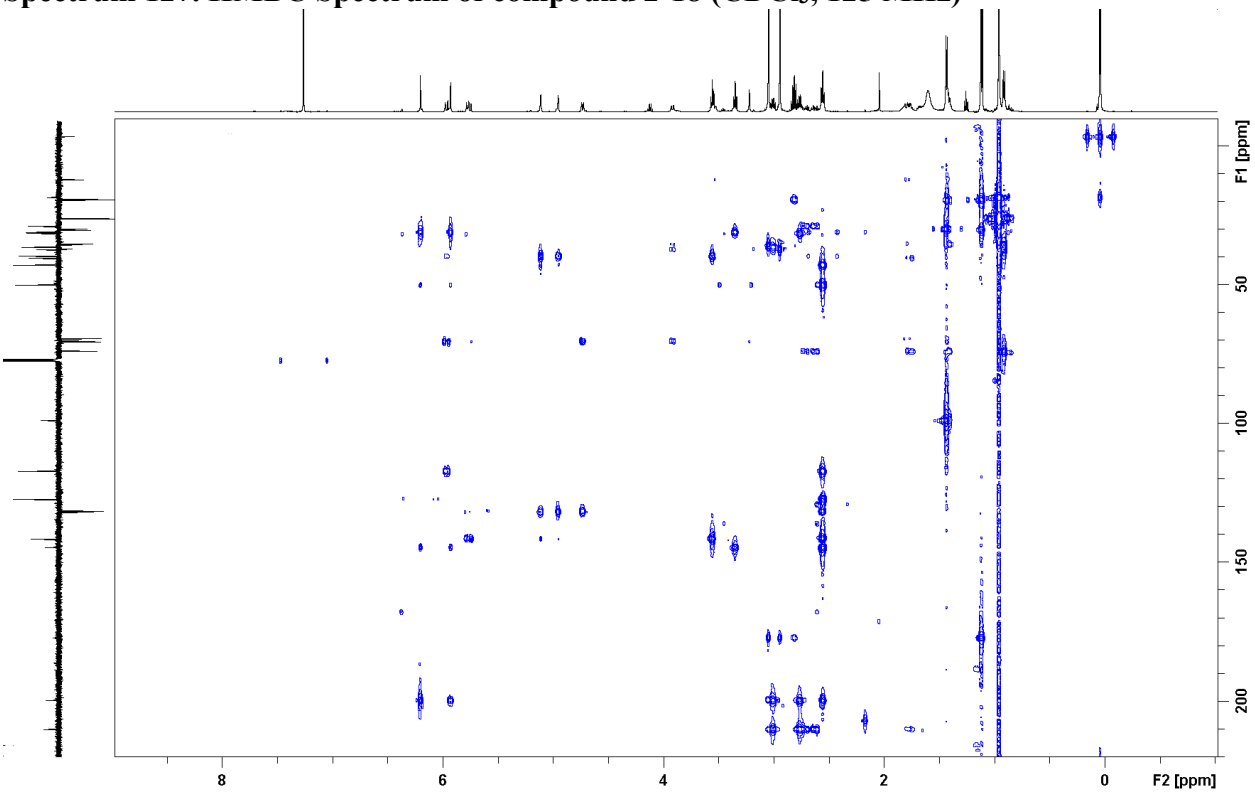
Spectrum 125. HSQC Spectrum of compound 2-18 ($CDCl_3$, 500 MHz)



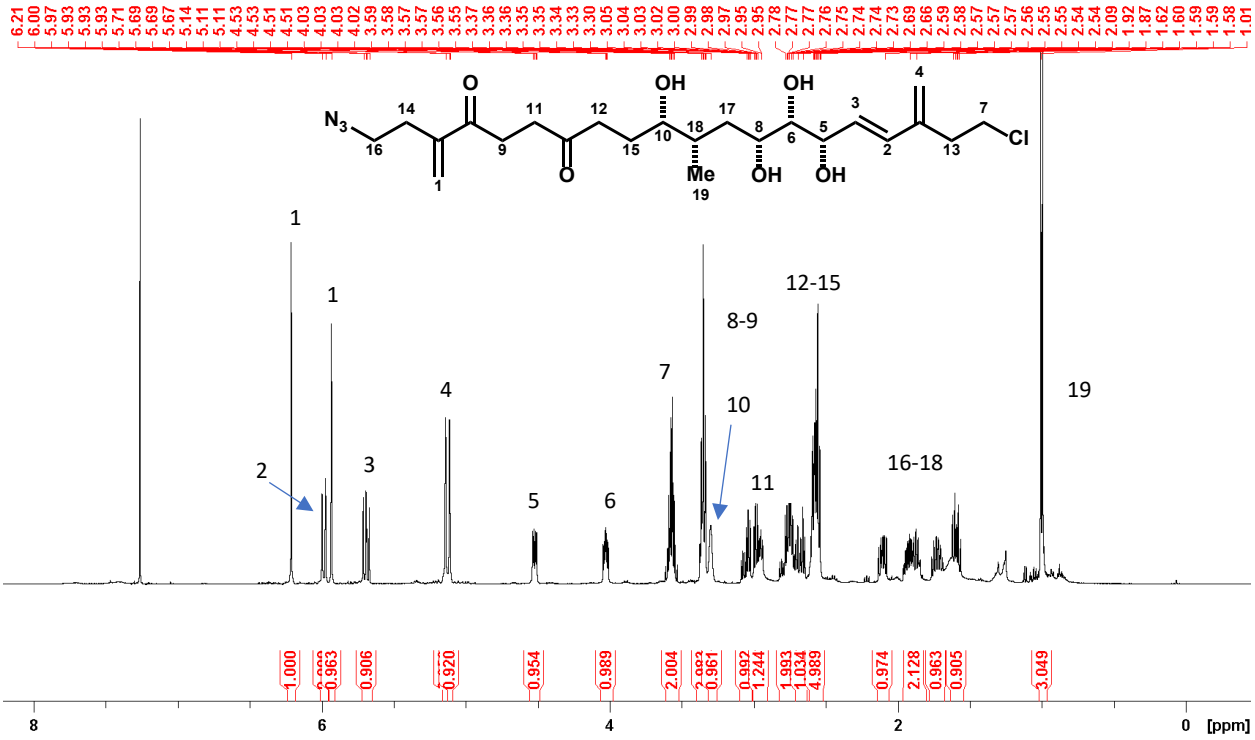
Spectrum 126. COSY Spectrum of compound 2-18 ($CDCl_3$, 500 MHz)



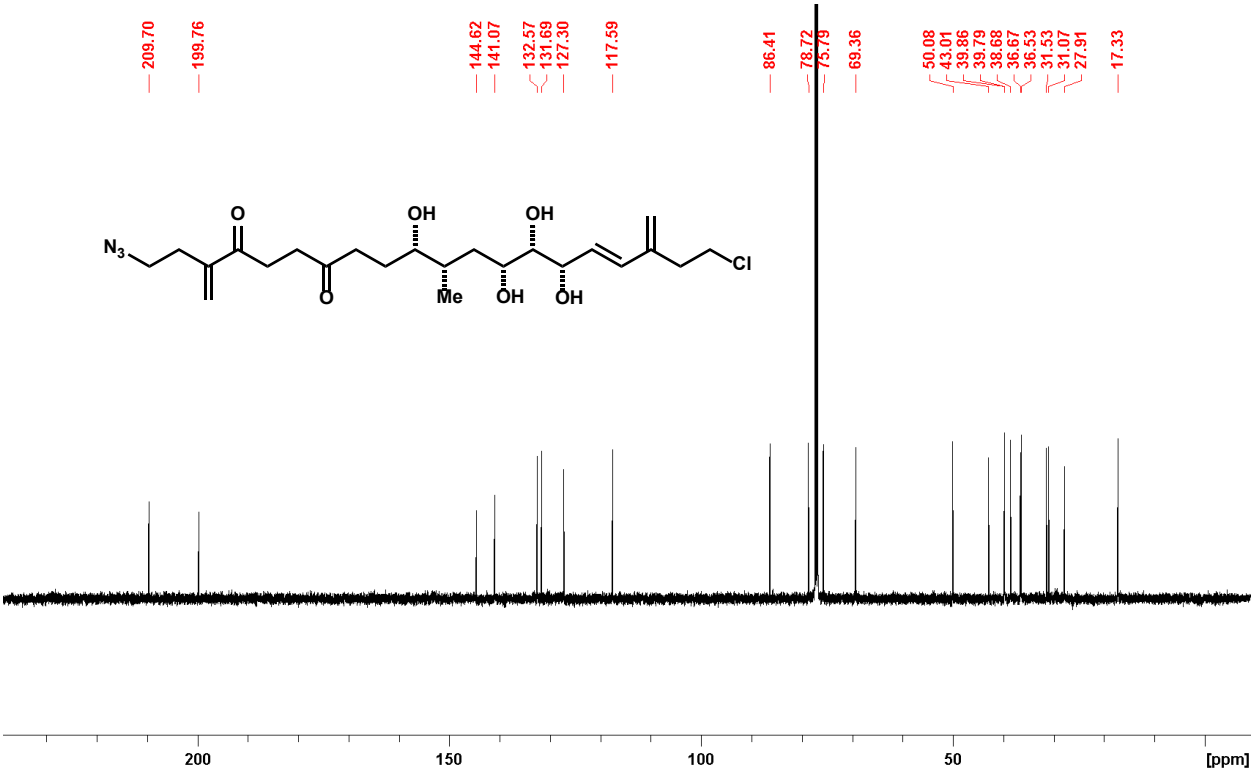
Spectrum 127. HMBC Spectrum of compound 2-18 ($CDCl_3$, 125 MHz)



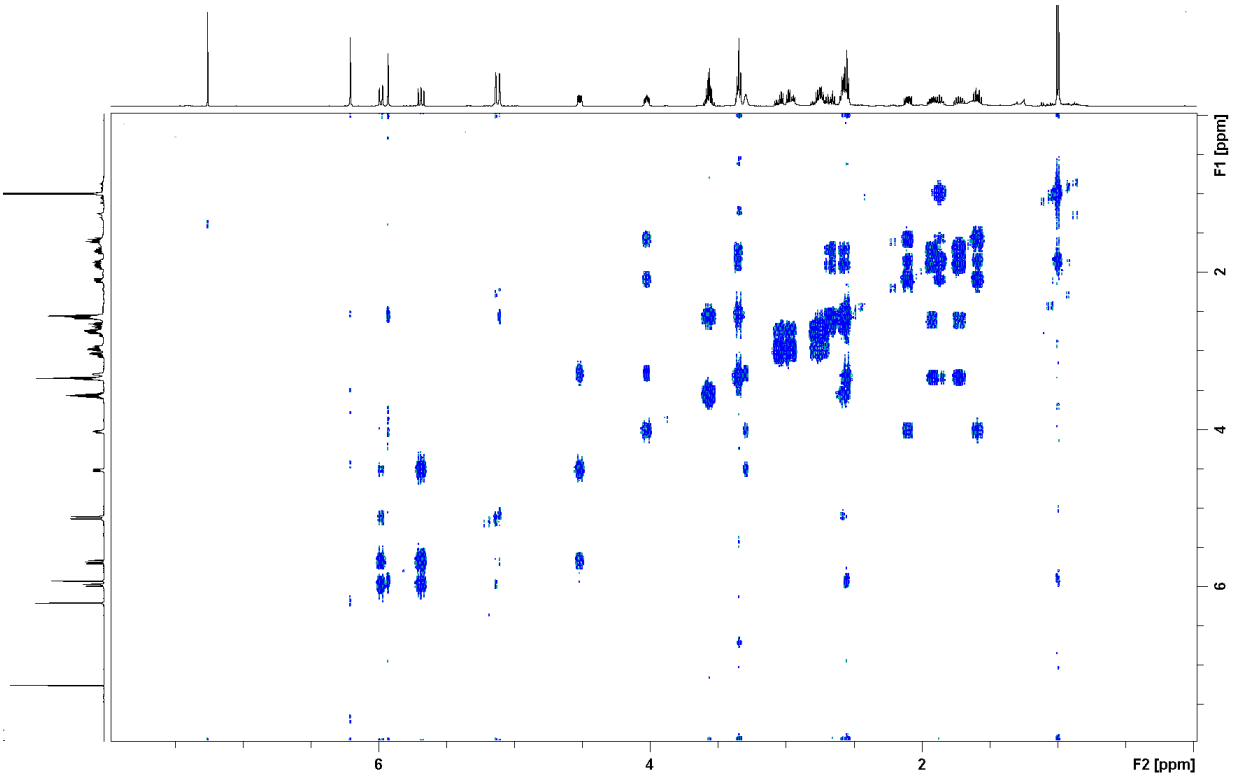
Spectrum 128. ^{1}H NMR of compound 2-25 ($CDCl_3$, 500 MHz)



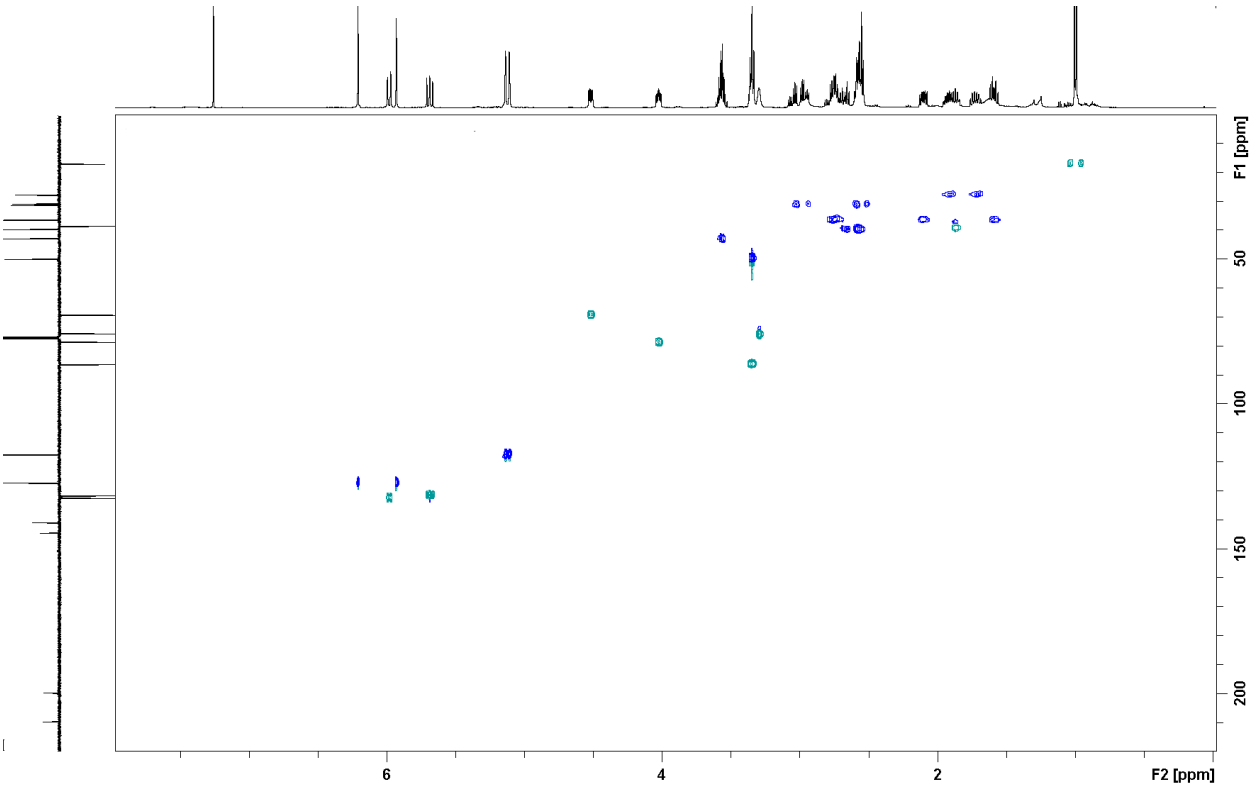
Spectrum 129. ^{13}C NMR of compound 2-25 ($CDCl_3$, 125 MHz)

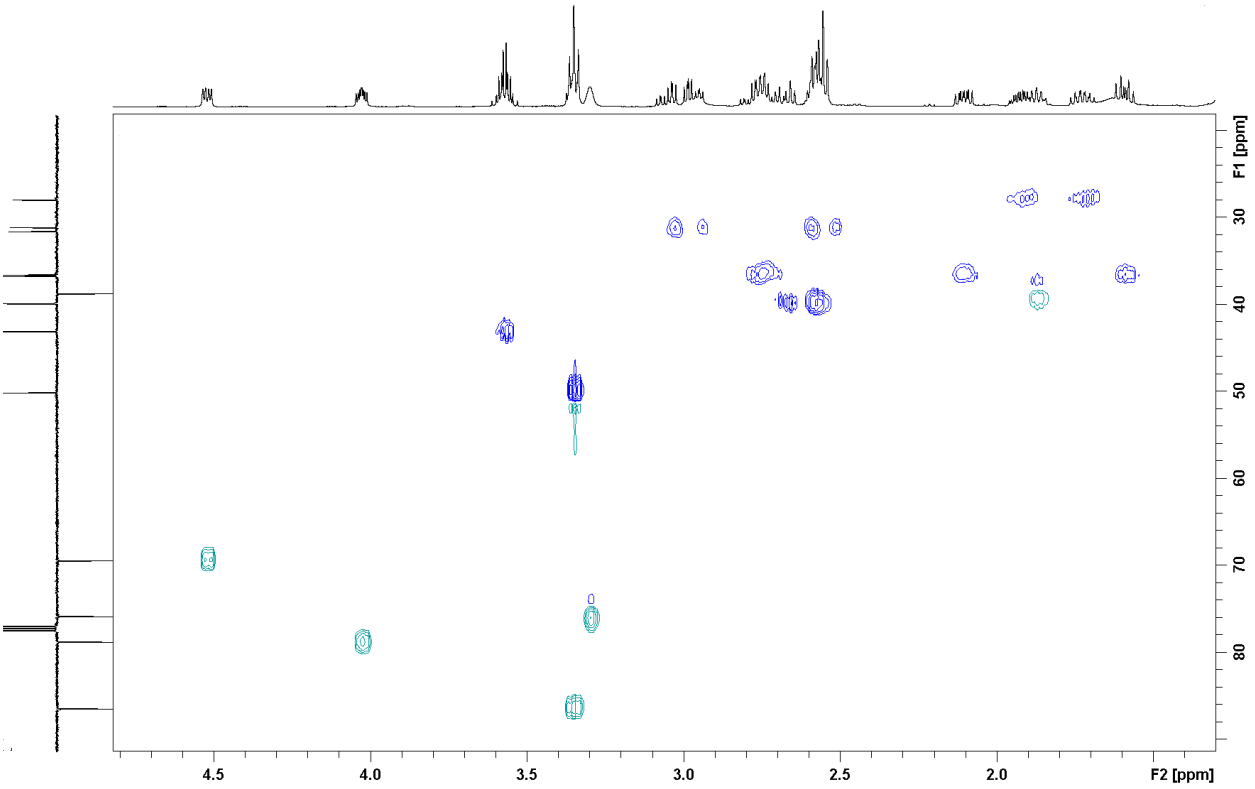


Spectrum 130. COSY spectrum of compound 2-25 ($CDCl_3$, 500 MHz)

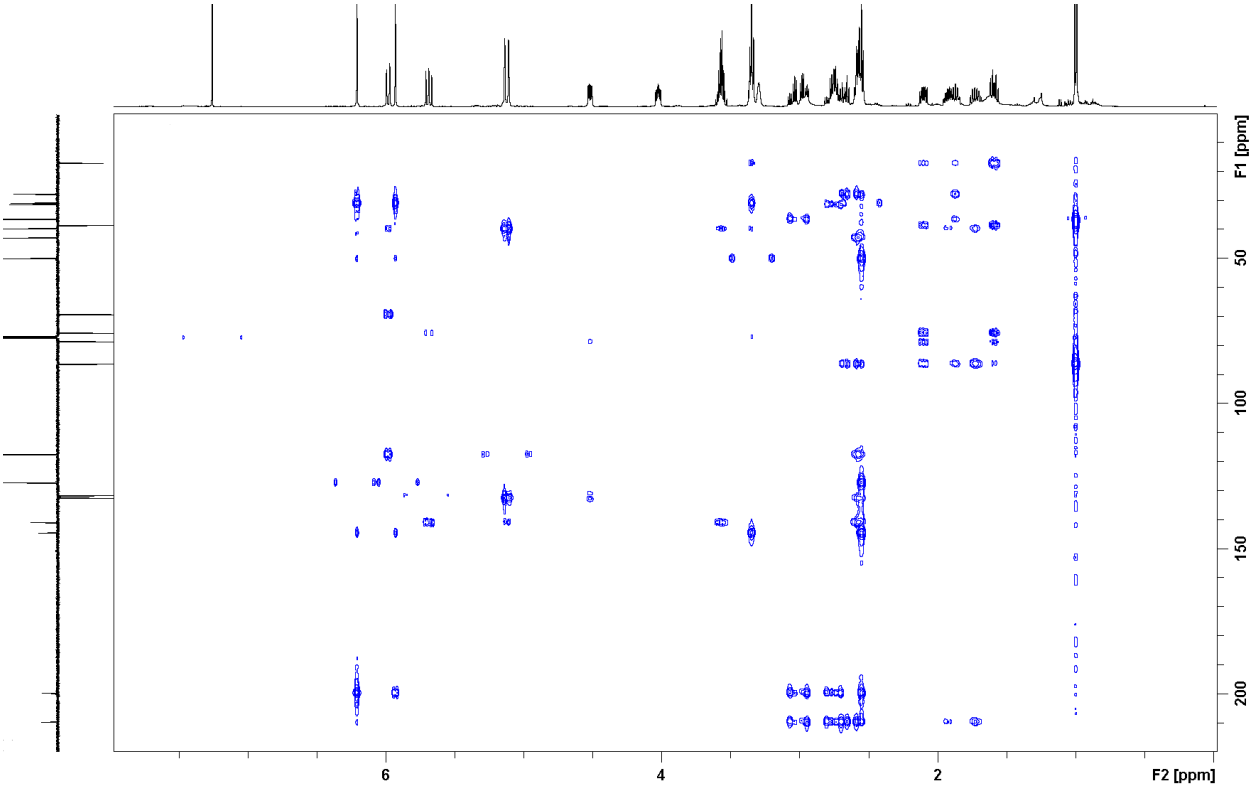


Spectrum 131. HSQC spectrum of compound 2-25 ($CDCl_3$, 500 MHz)



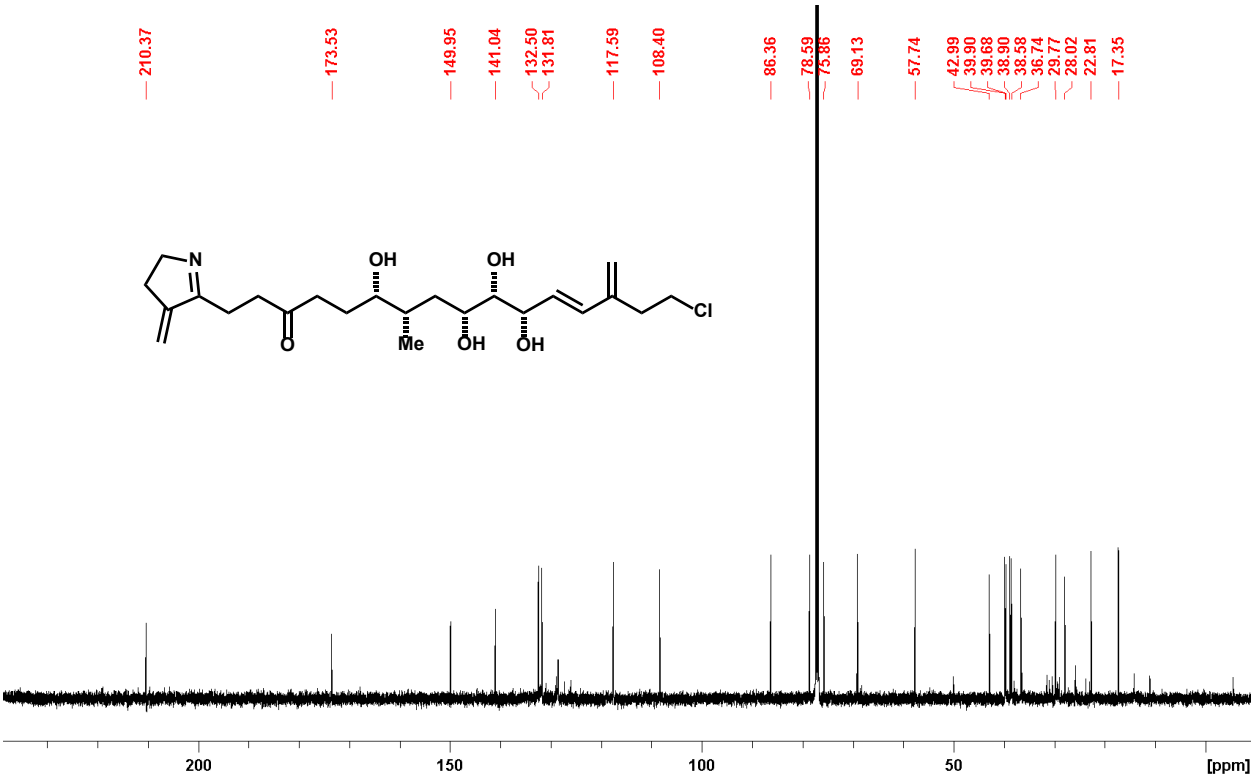


Spectrum 132. HMBC spectrum of compound 2-25 ($CDCl_3$, 500 MHz)

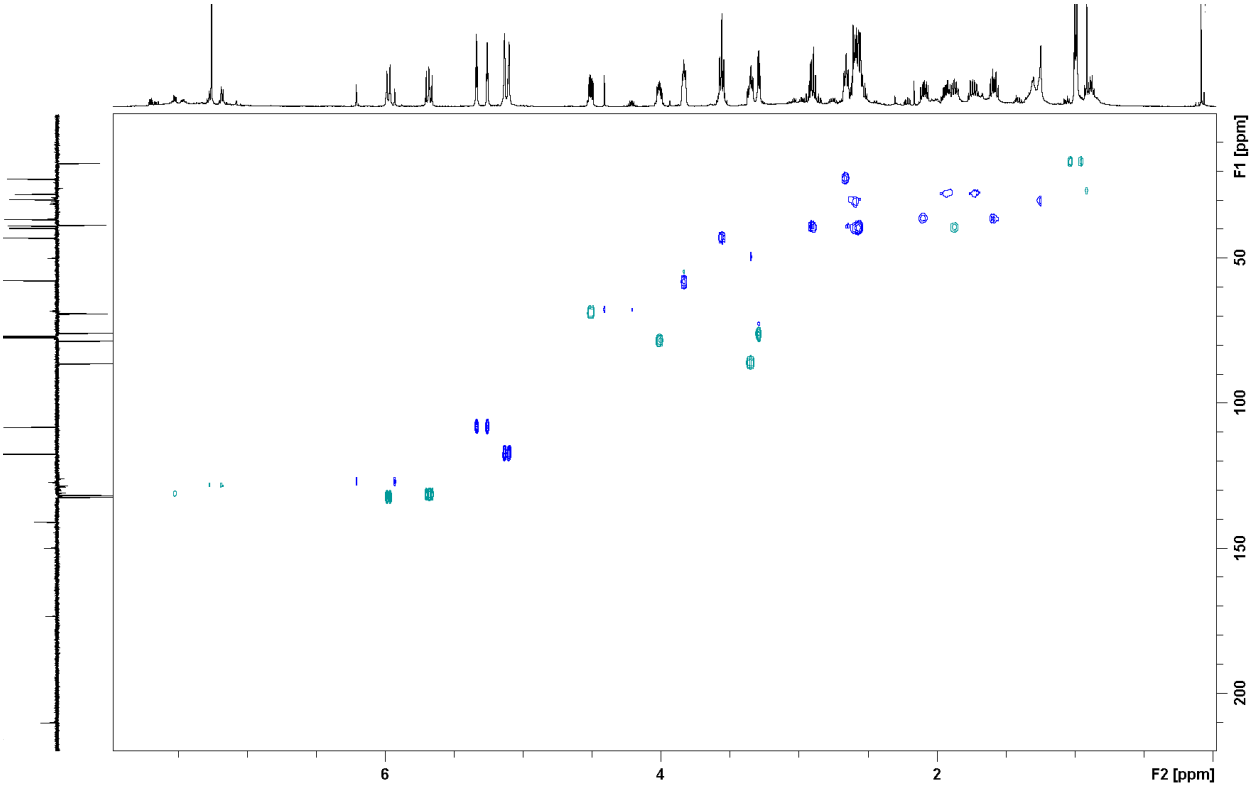


Spectrum 133. ^{1}H NMR of compound 2-20 ($CDCl_3$, 500 MHz)

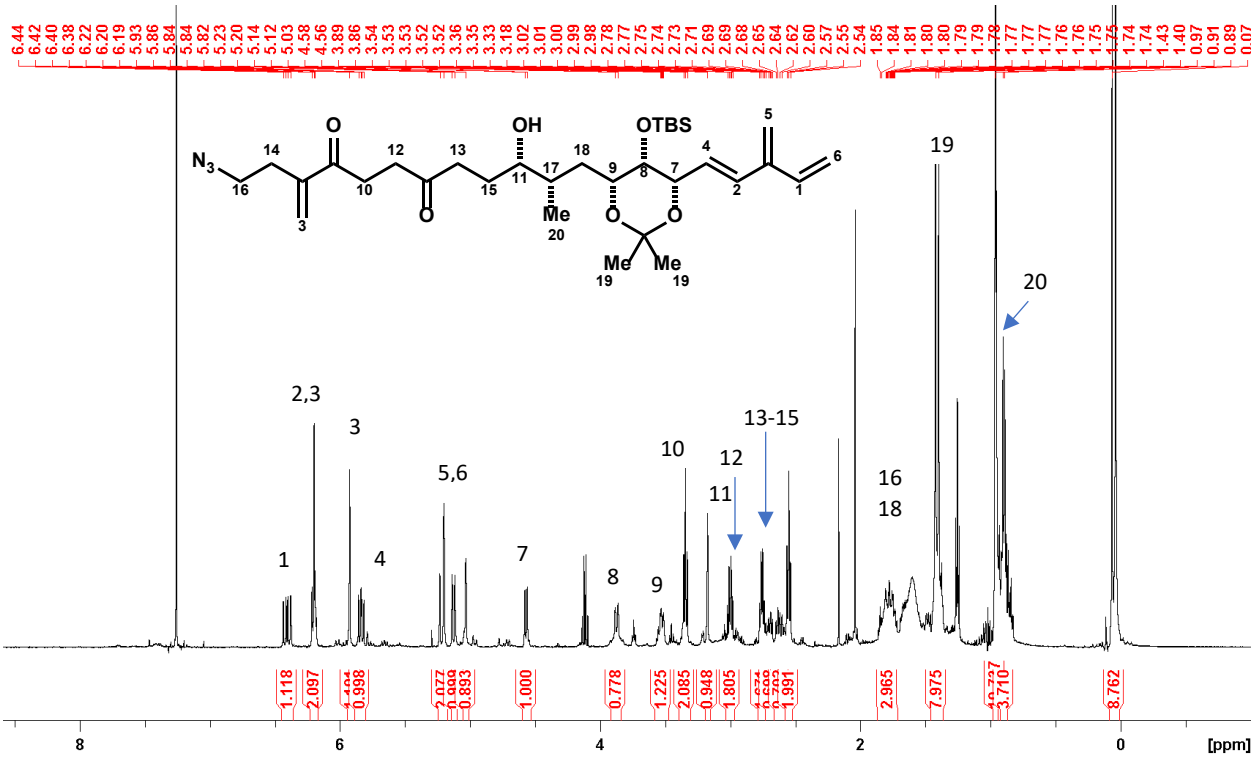
Spectrum 134. ^{13}C NMR of compound 2-20 ($CDCl_3$, 125 MHz)



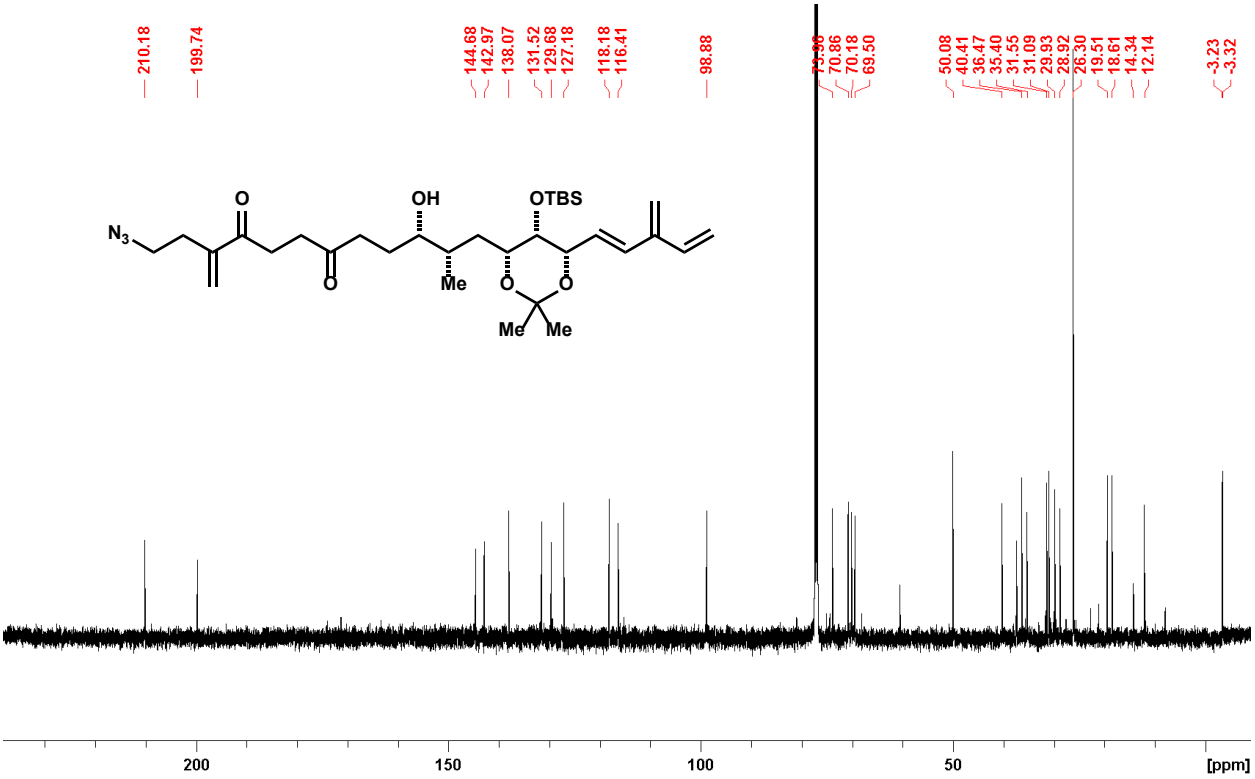
Spectrum 135. HSQC spectrum of compound 2-20 ($CDCl_3$, 500 MHz)



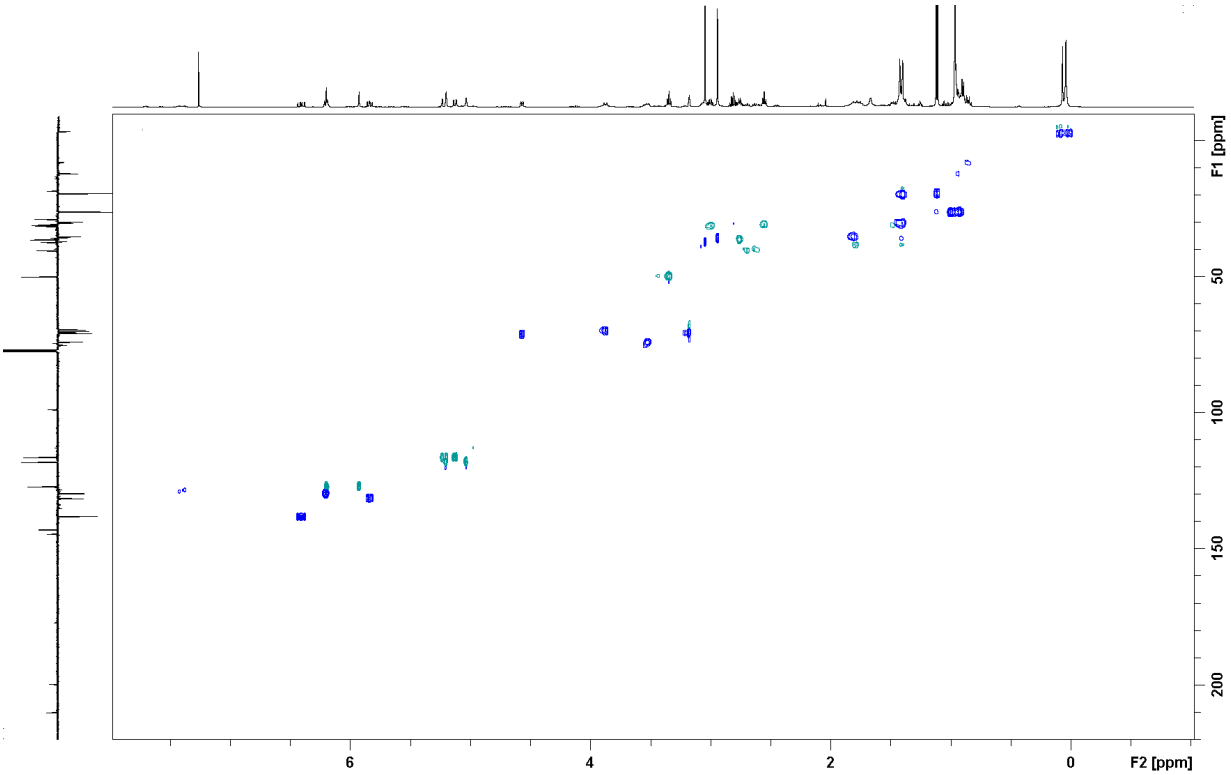
Spectrum 136. ^{1}H NMR of compound 2-19 ($CDCl_3$, 500 MHz)



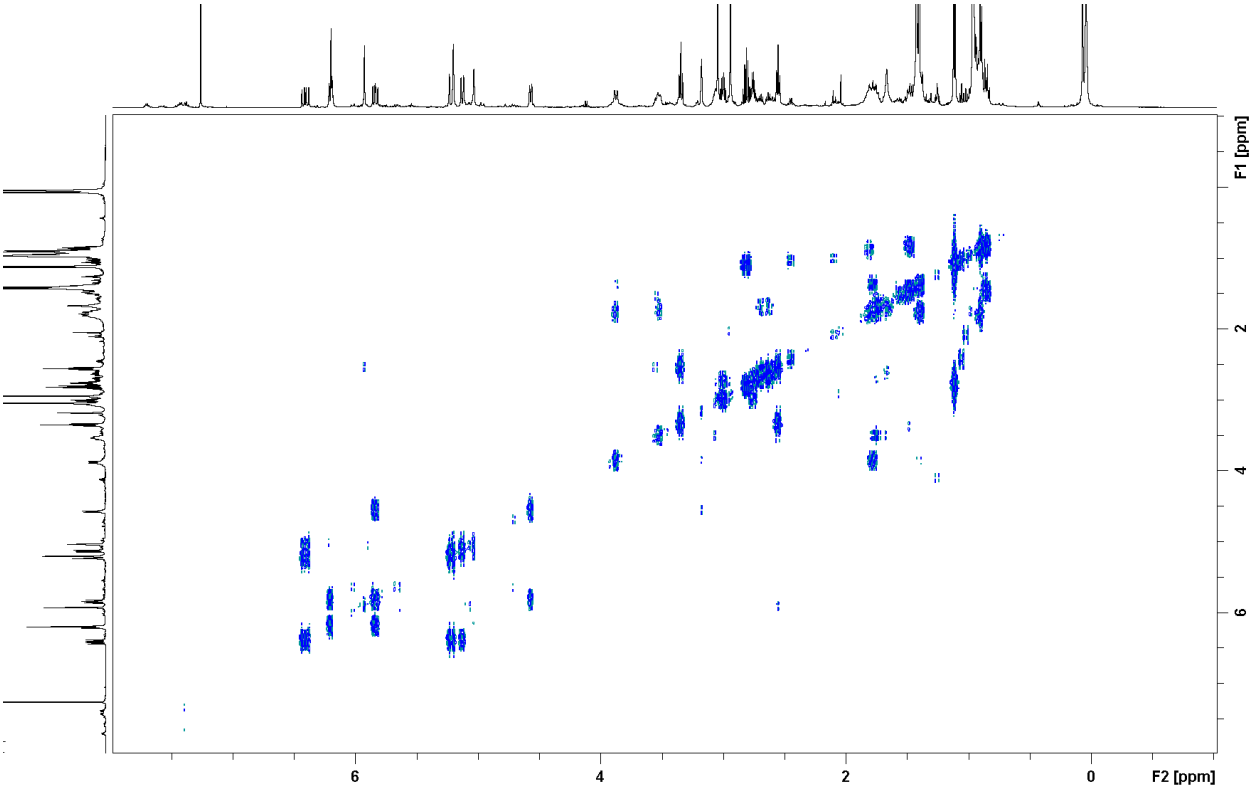
Spectrum 137. ^{13}C NMR of compound 2-19 ($CDCl_3$, 125 MHz)



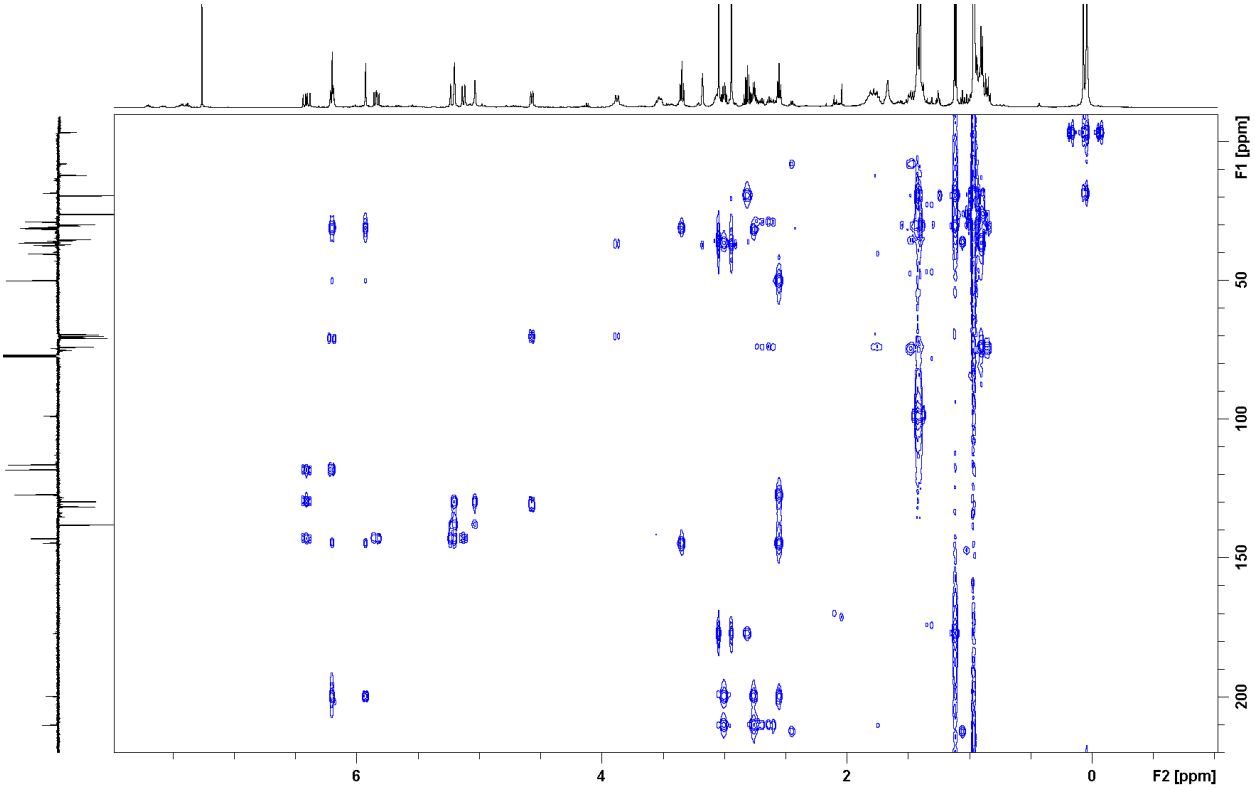
Spectrum 138. HSQC spectrum of compound 2-19 ($CDCl_3$, 500 MHz)



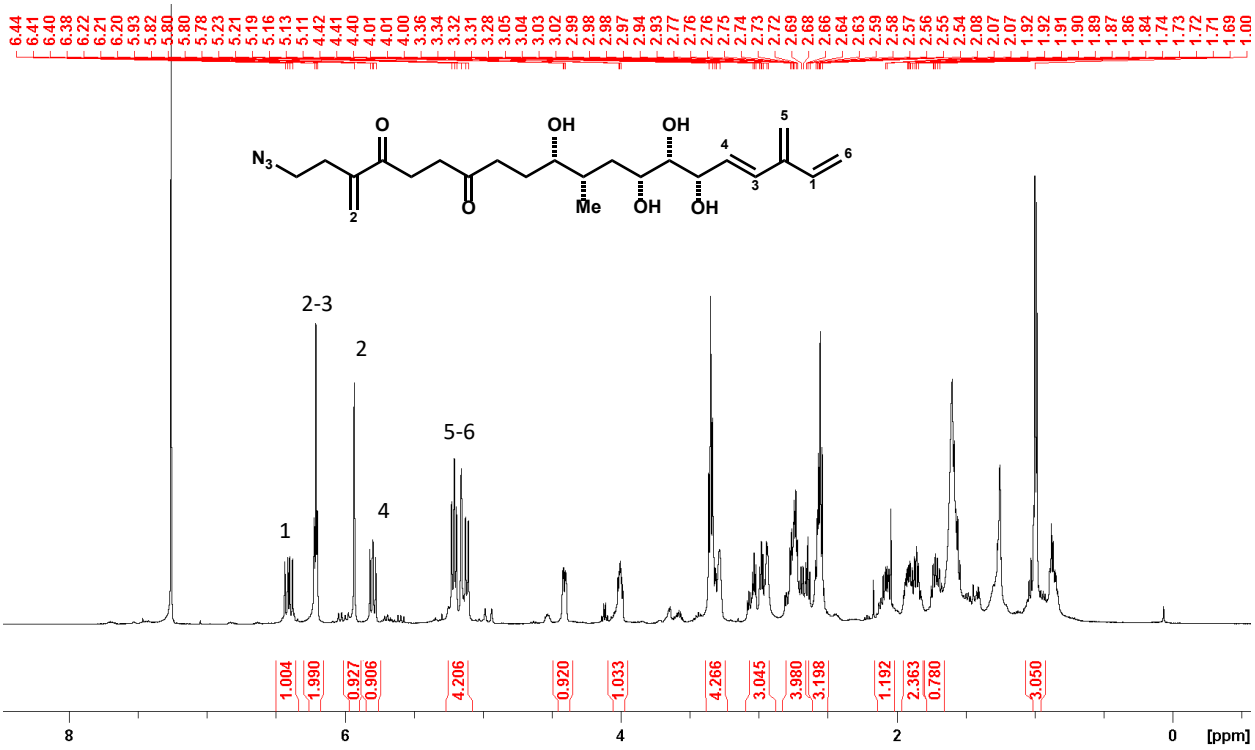
Spectrum 139. COSY spectrum of compound 2-19 ($CDCl_3$, 500 MHz)



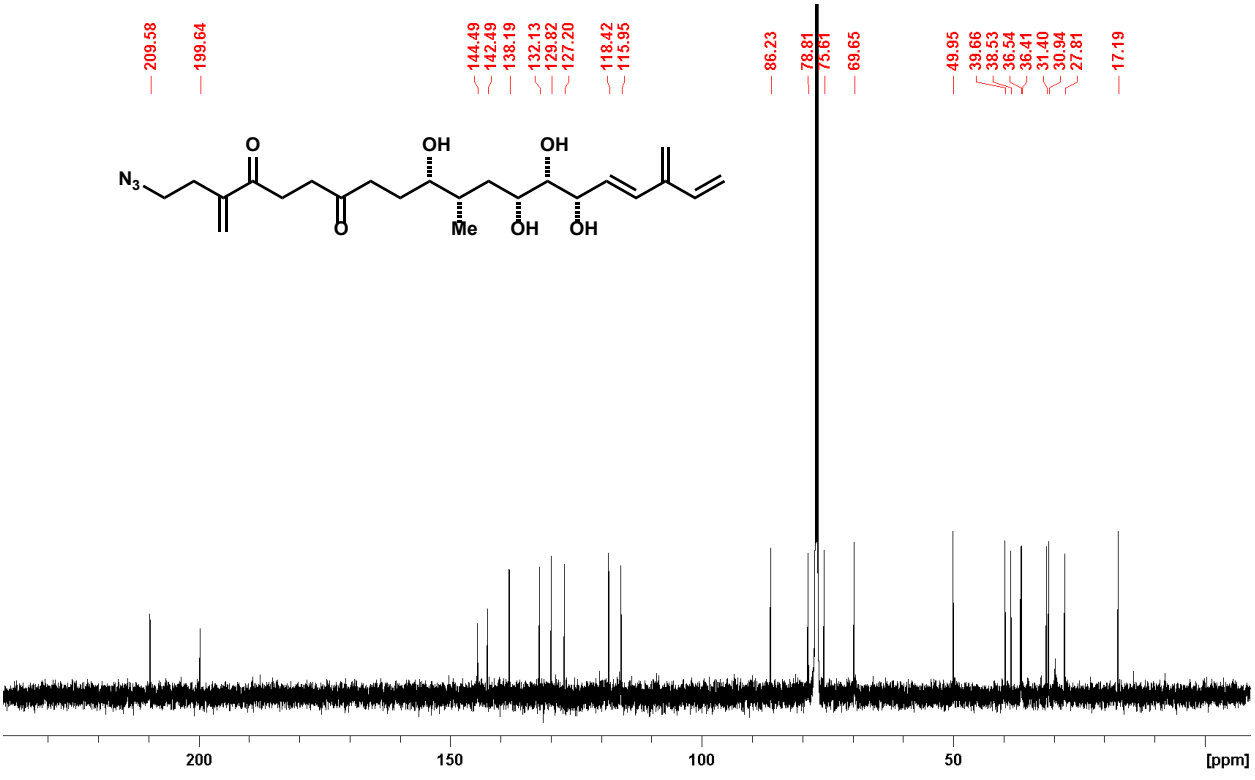
Spectrum 140. HMBC spectrum of compound 2-19 ($CDCl_3$, 500 MHz)



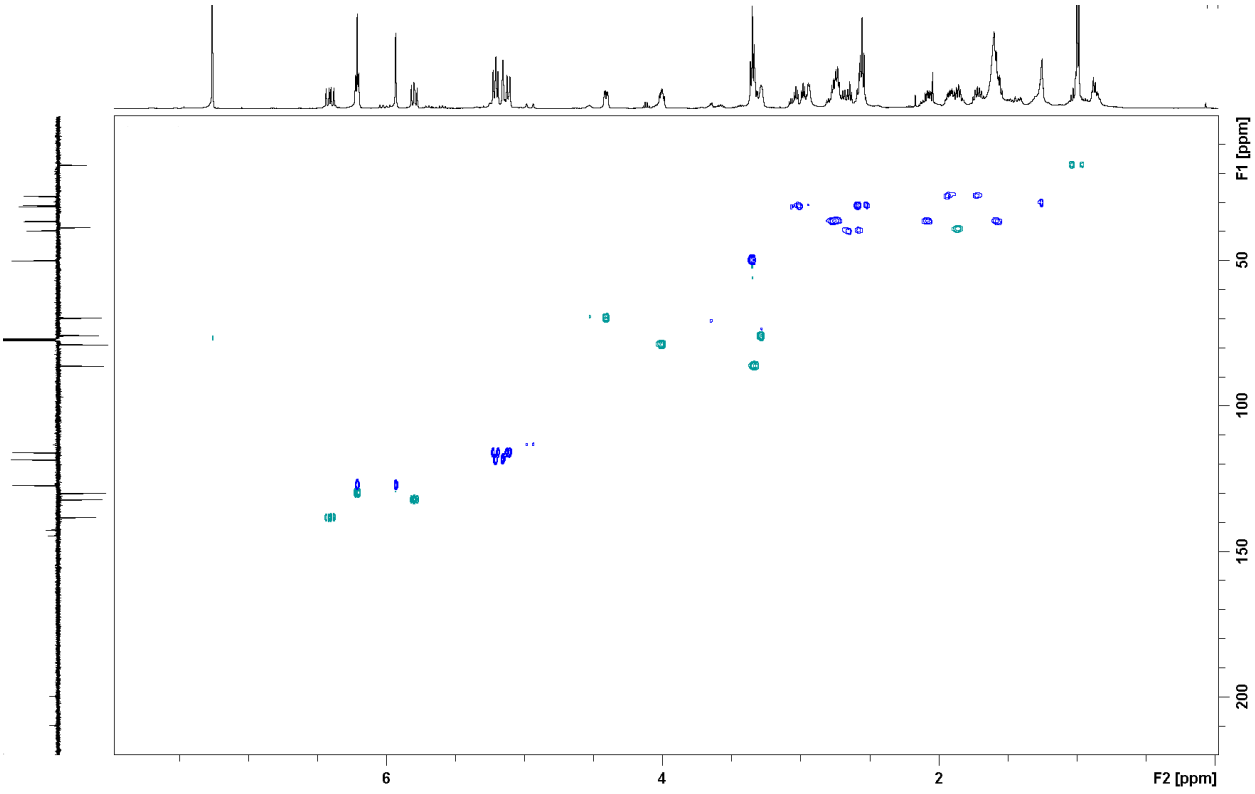
Spectrum 141. ^{1}H NMR of compound 2-60 ($CDCl_3$, 500 MHz)



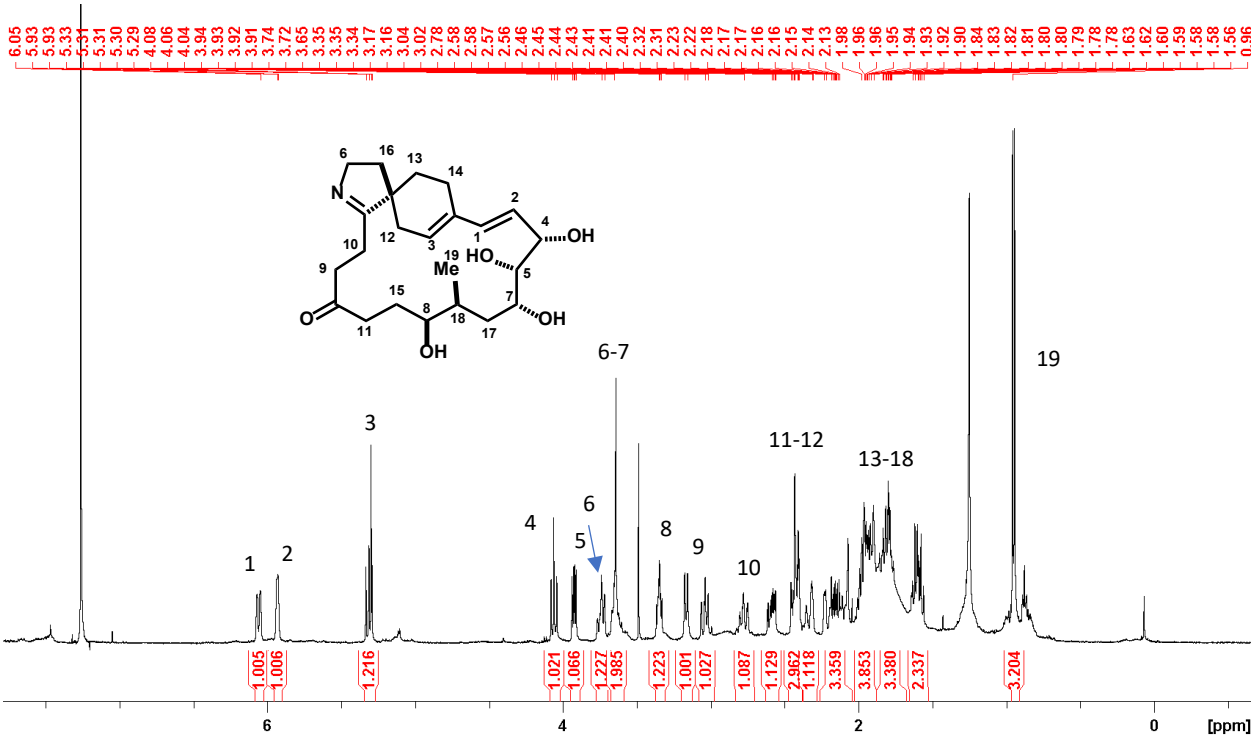
Spectrum 142. ^{13}C NMR of compound 2-60 ($CDCl_3$, 125 MHz)



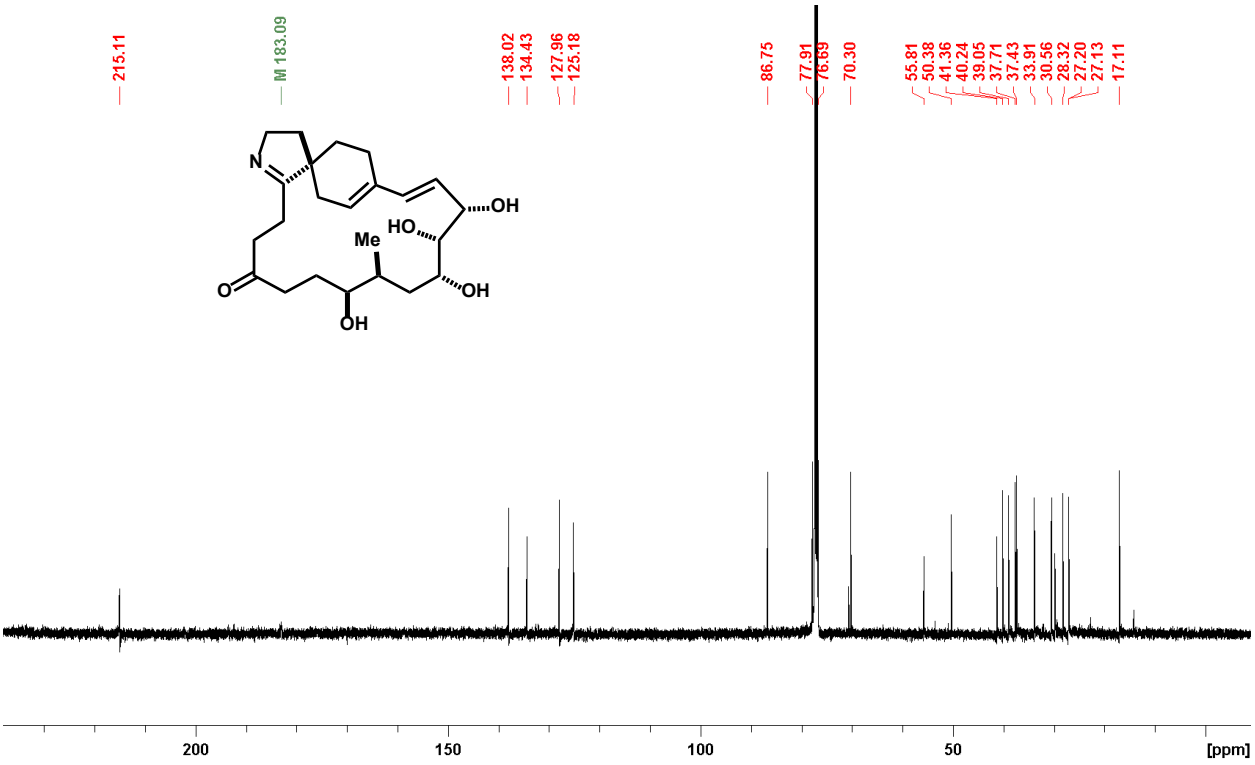
Spectrum 143. HSQC spectrum of compound 2-60 ($CDCl_3$, 500 MHz)



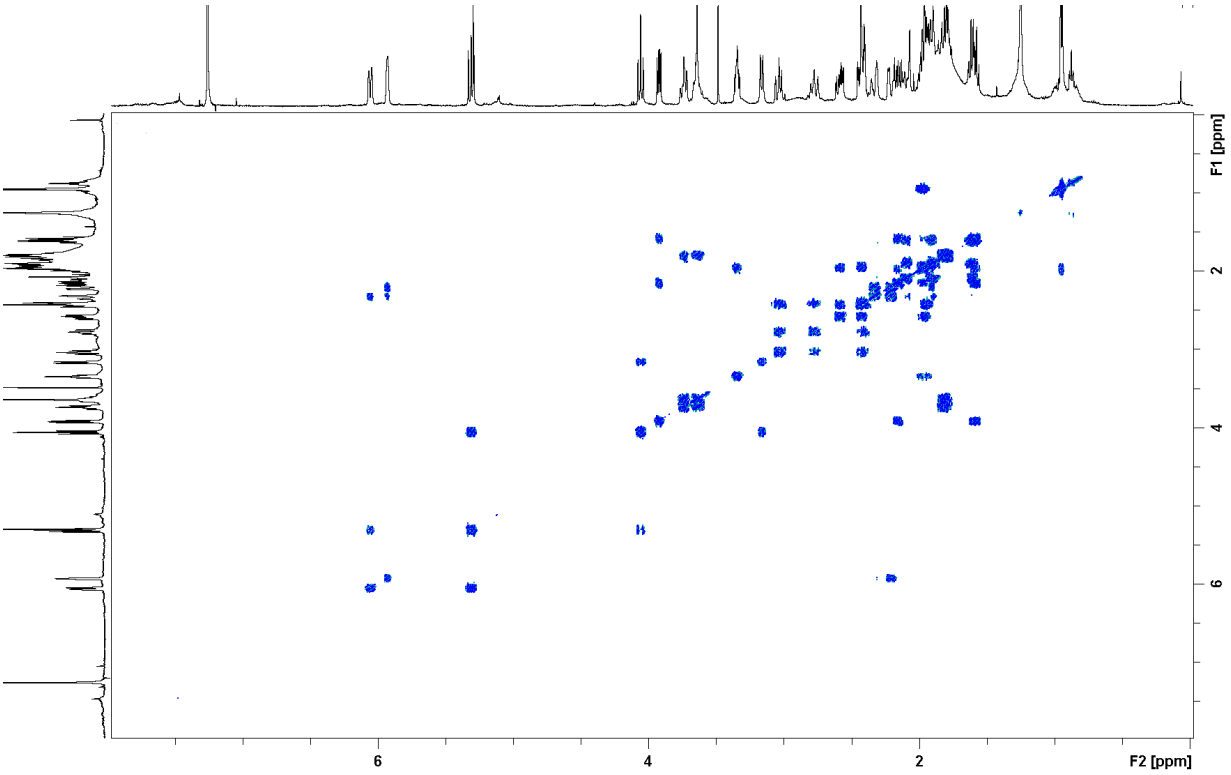
Spectrum 144. ^{1}H NMR of compound 2-22 ($CDCl_3$, 500 MHz)



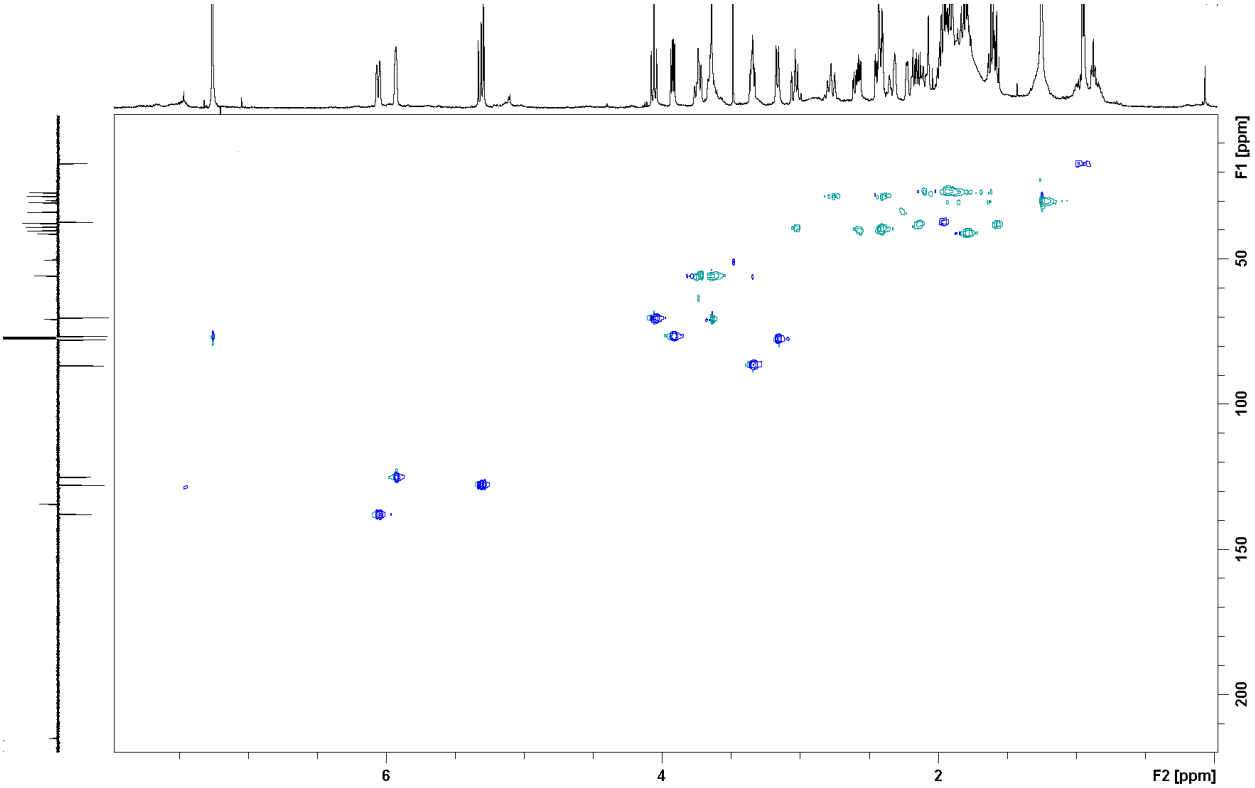
Spectrum 145. ^{13}C NMR of compound 2-22 ($CDCl_3$, 125 MHz)

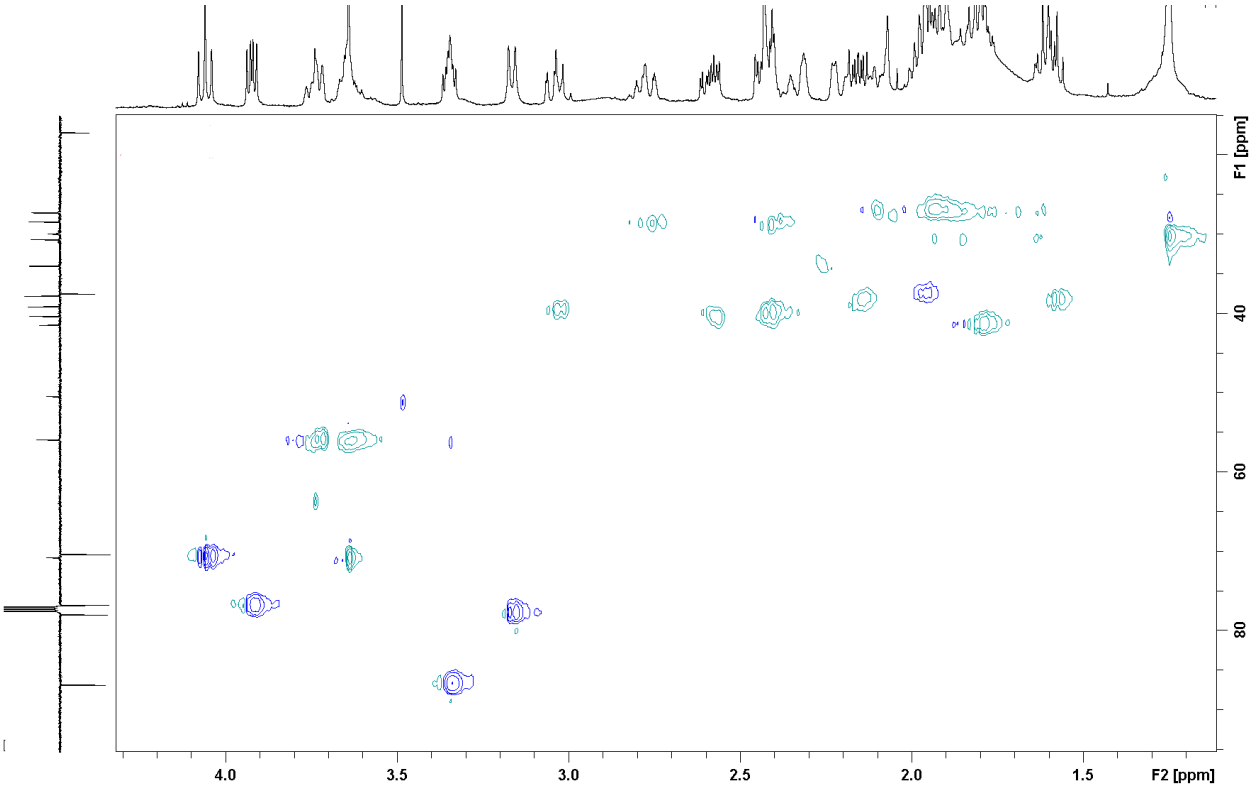


Spectrum 146. COSY spectrum of compound 2-22 ($CDCl_3$, 500 MHz)

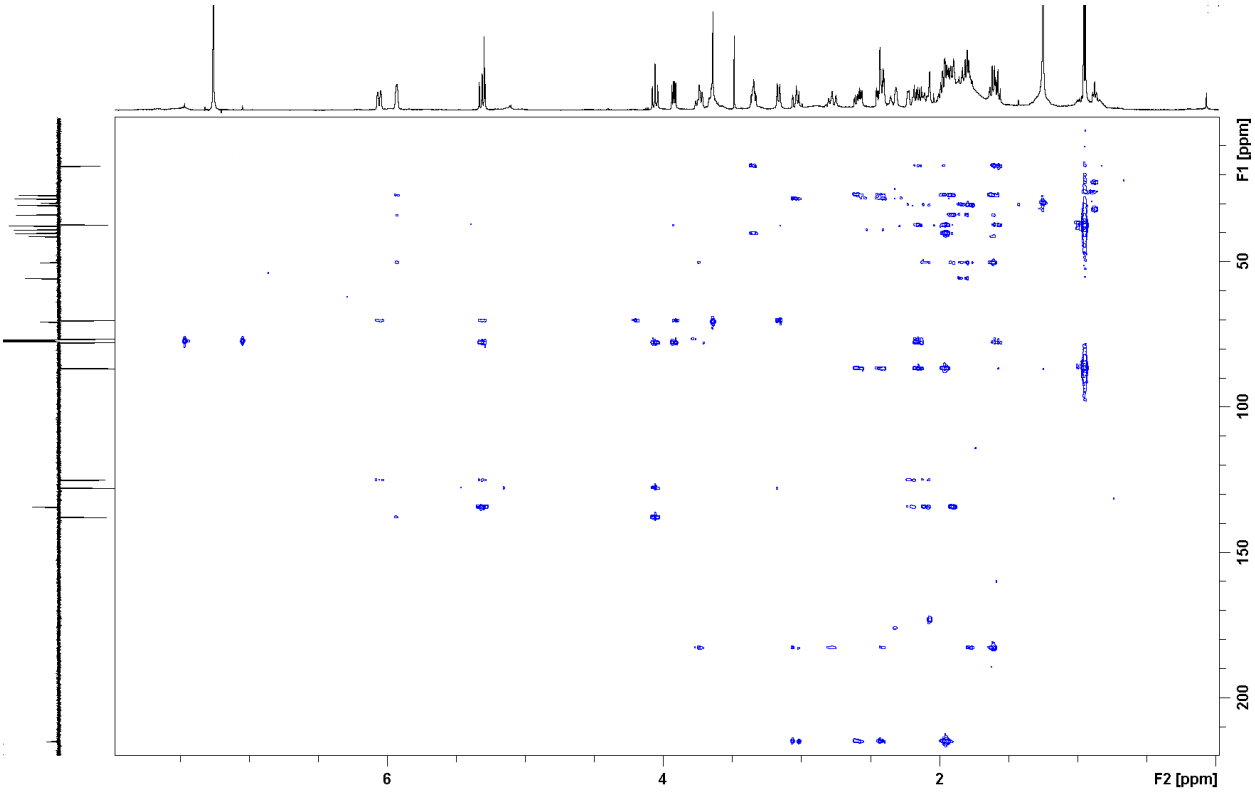


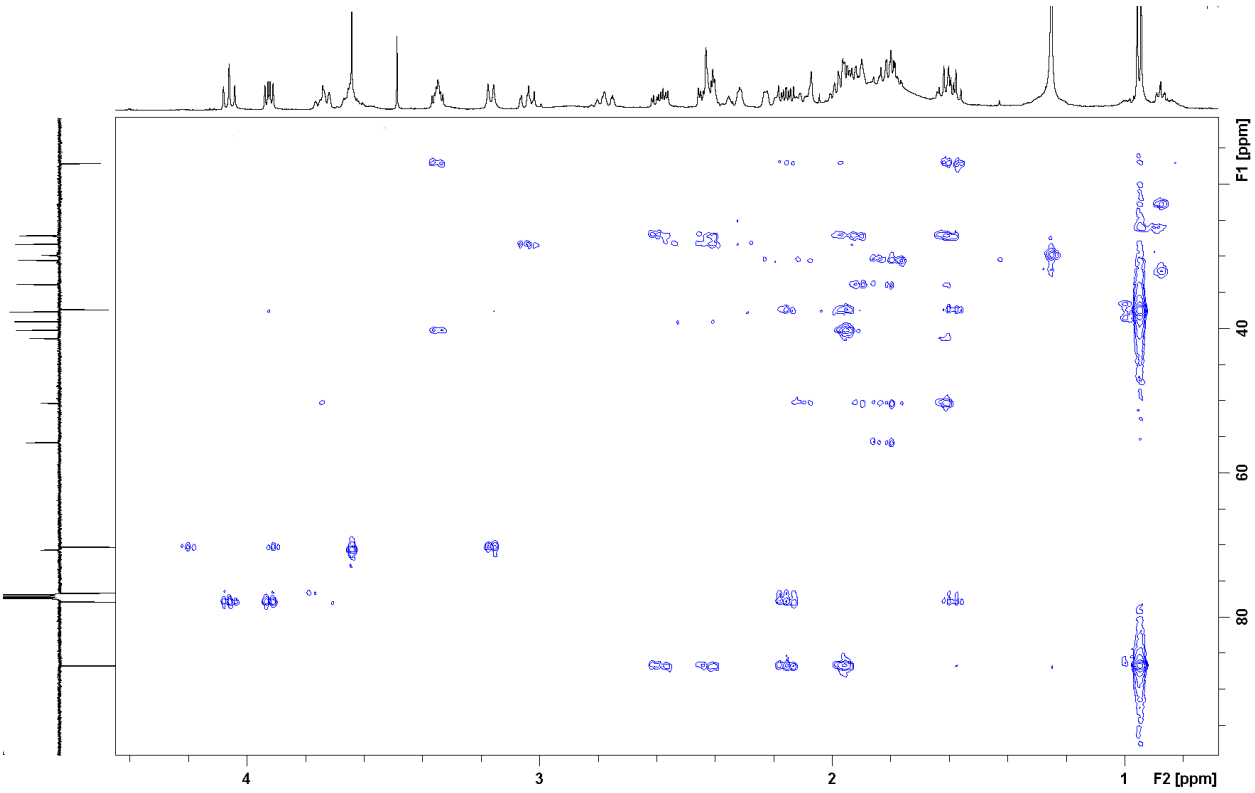
Spectrum 147. HSQC spectrum of compound 2-22 ($CDCl_3$, 500 MHz)





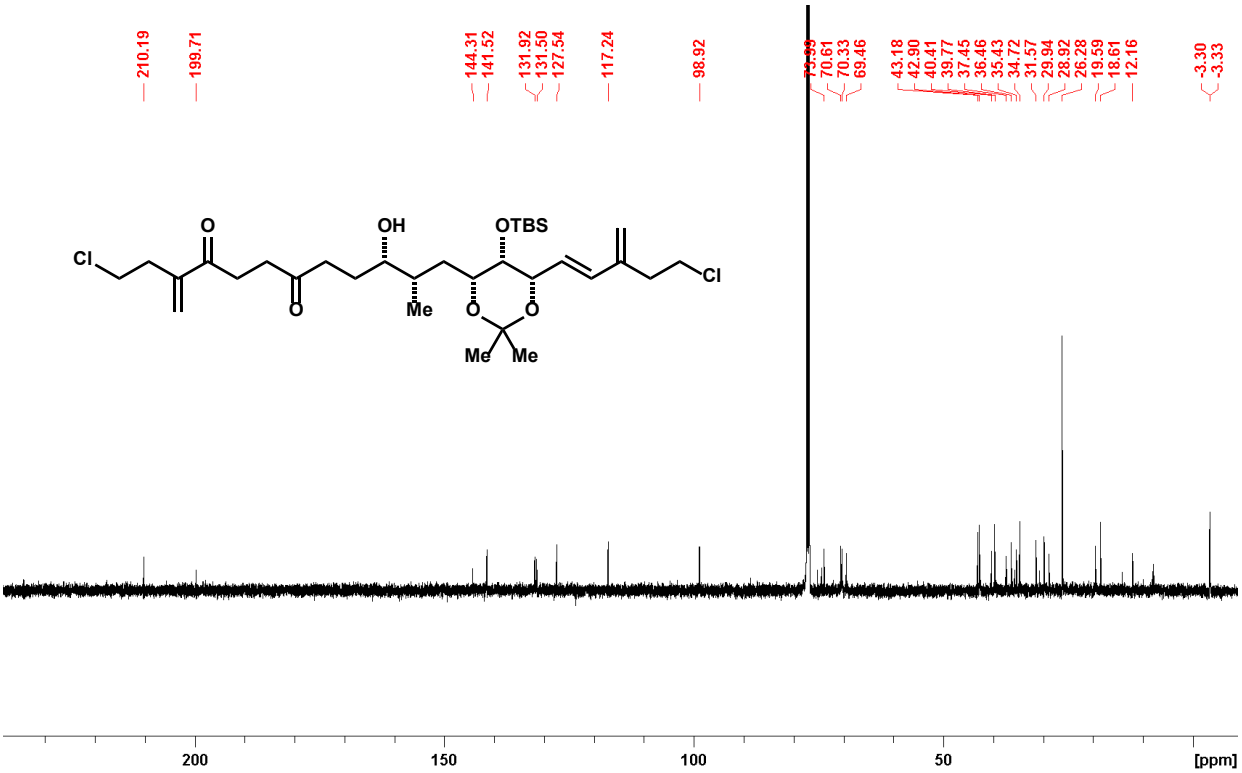
Spectrum 148. HMBC spectrum of compound 2-22 ($CDCl_3$, 500 MHz)



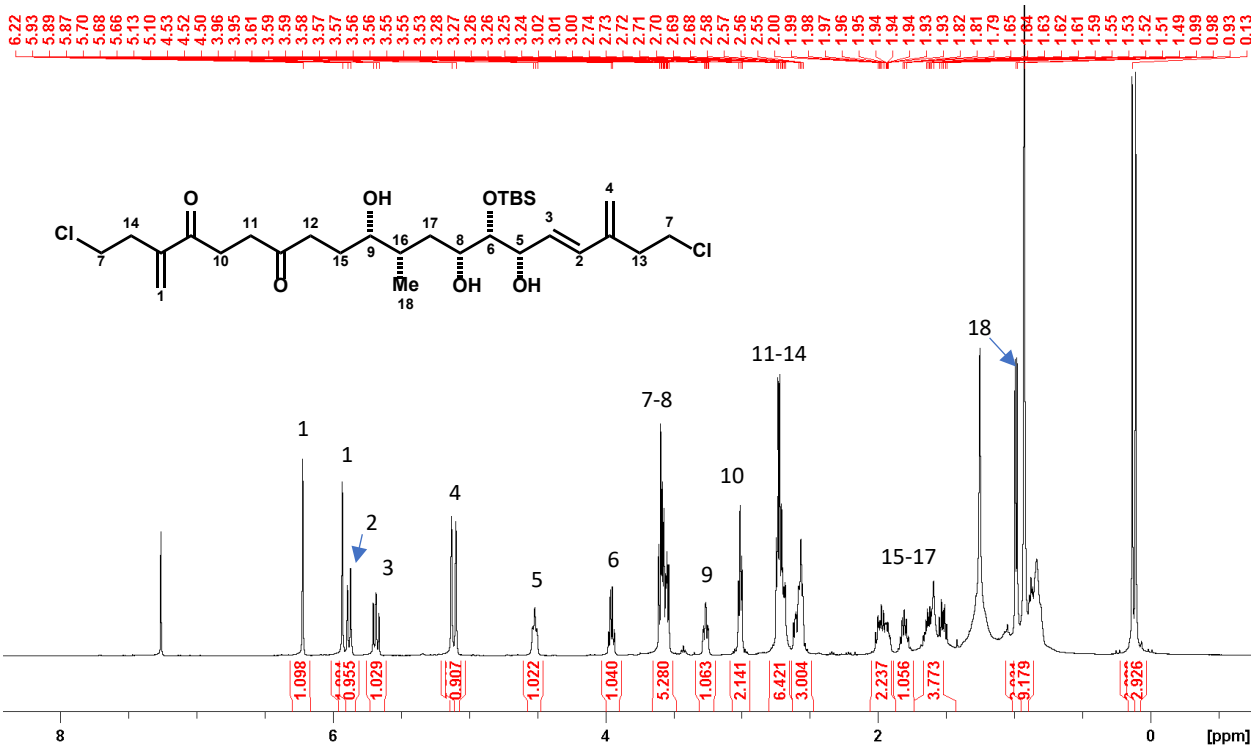

F1 [ppm]
40
60
80
4
3
2
1
F2 [ppm]

Spectrum 149. ^{1}H NMR of compound 2-26 ($CDCl_3$, 500 MHz)

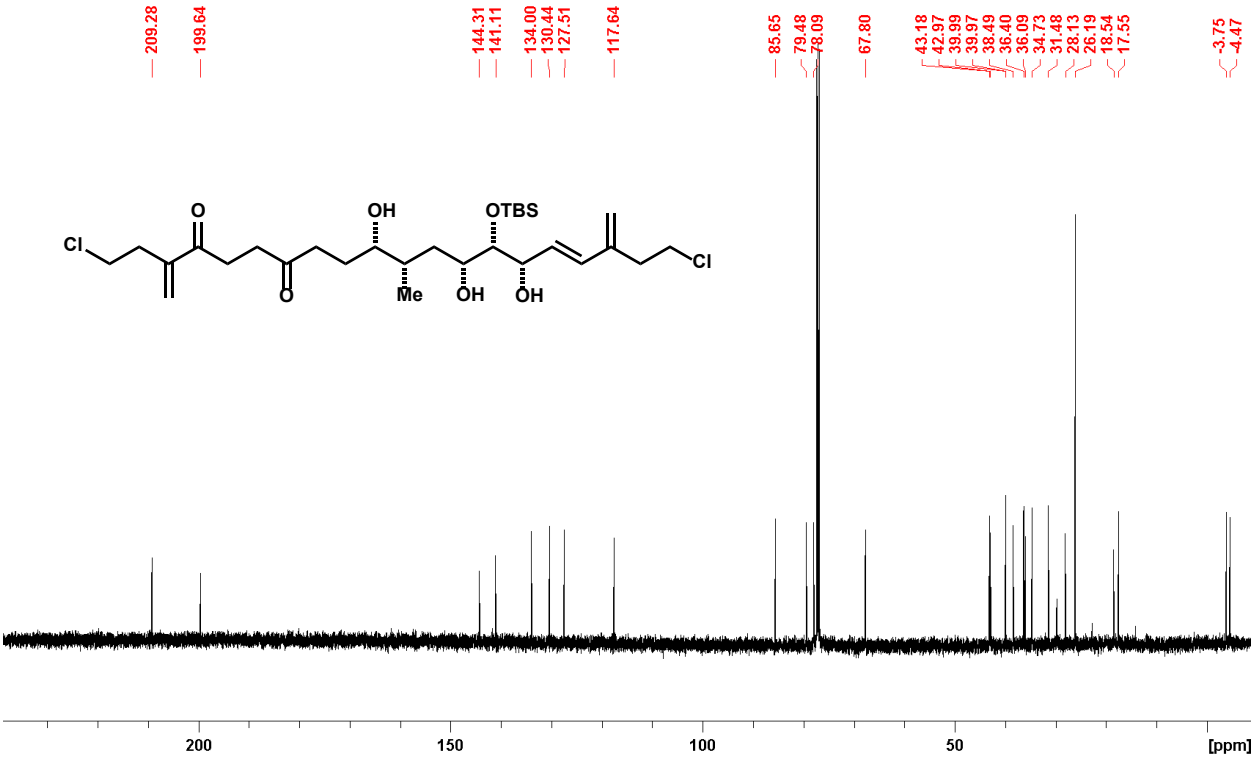
Spectrum 150. ^{13}C NMR of compound 2-26 ($CDCl_3$, 125 MHz)



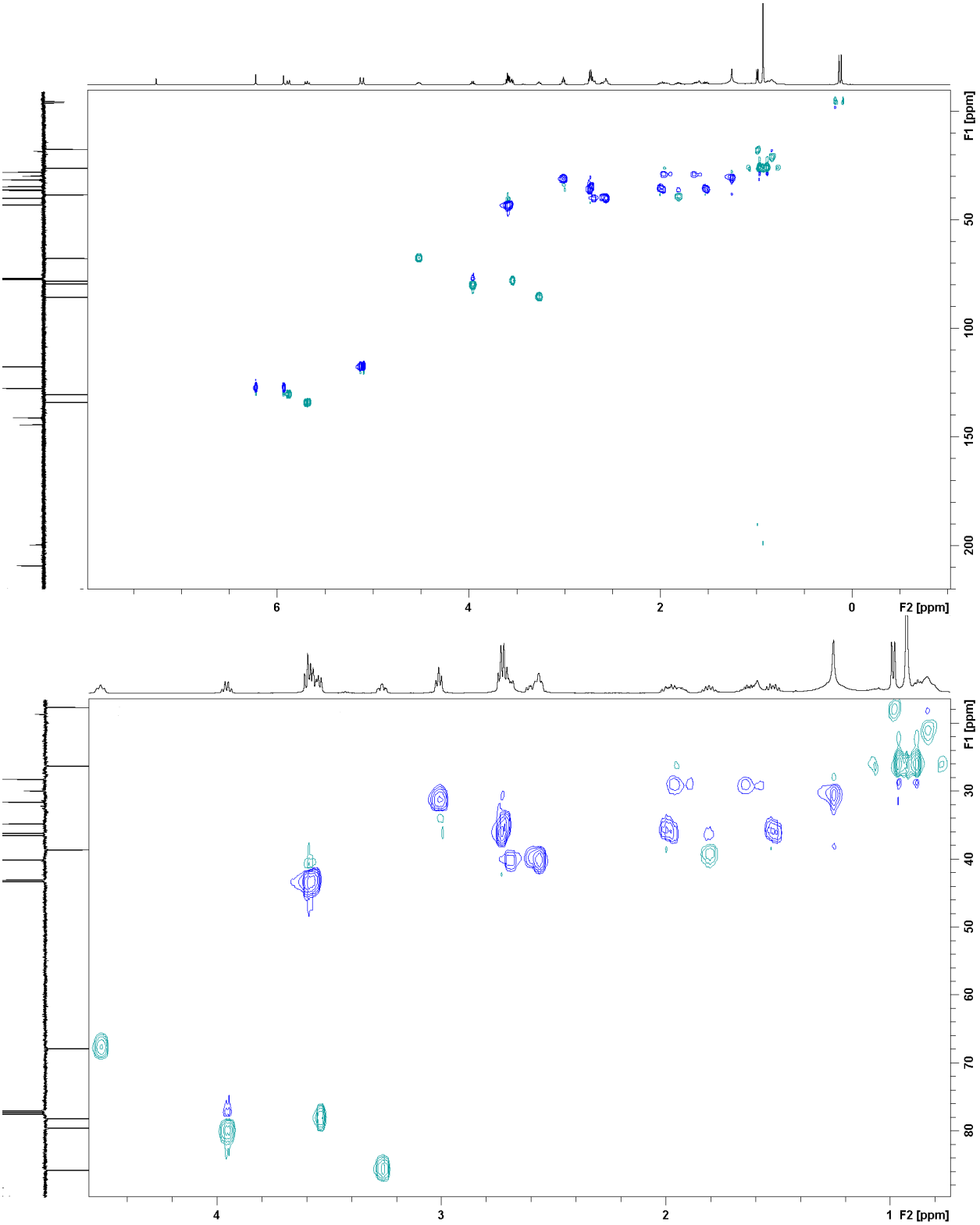
Spectrum 151. ^{1}H NMR of compound 2-27 ($CDCl_3$, 500 MHz)



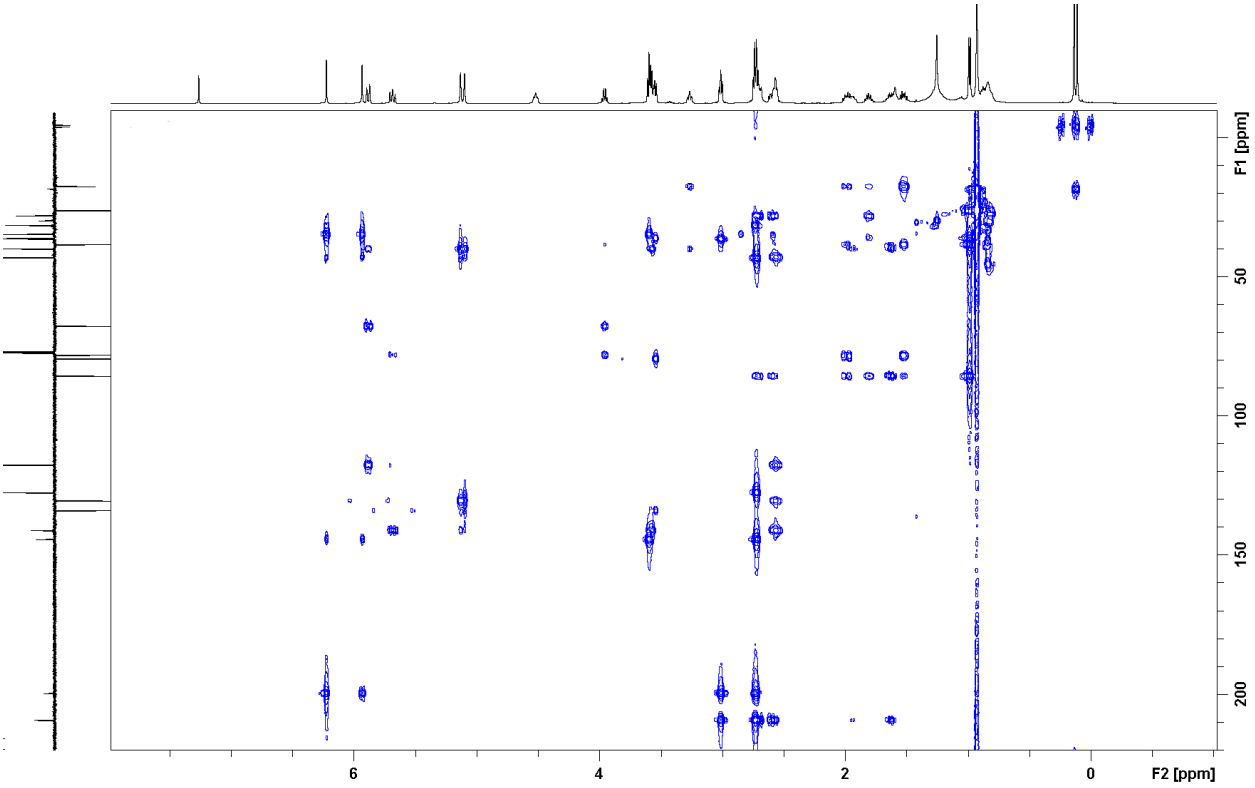
Spectrum 152. ^{13}C NMR of compound 2-27 ($CDCl_3$, 125 MHz)



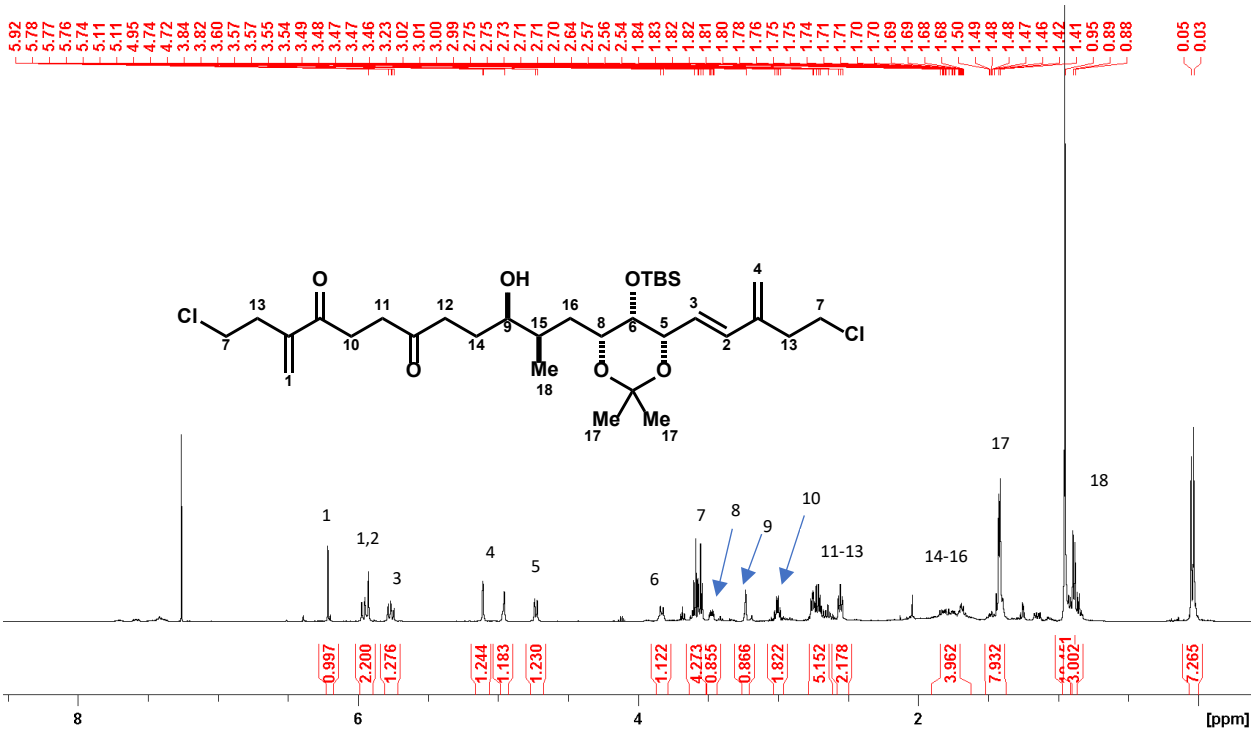
Spectrum 153. HSQC Spectrum of compound 2-27 ($CDCl_3$, 500 MHz)



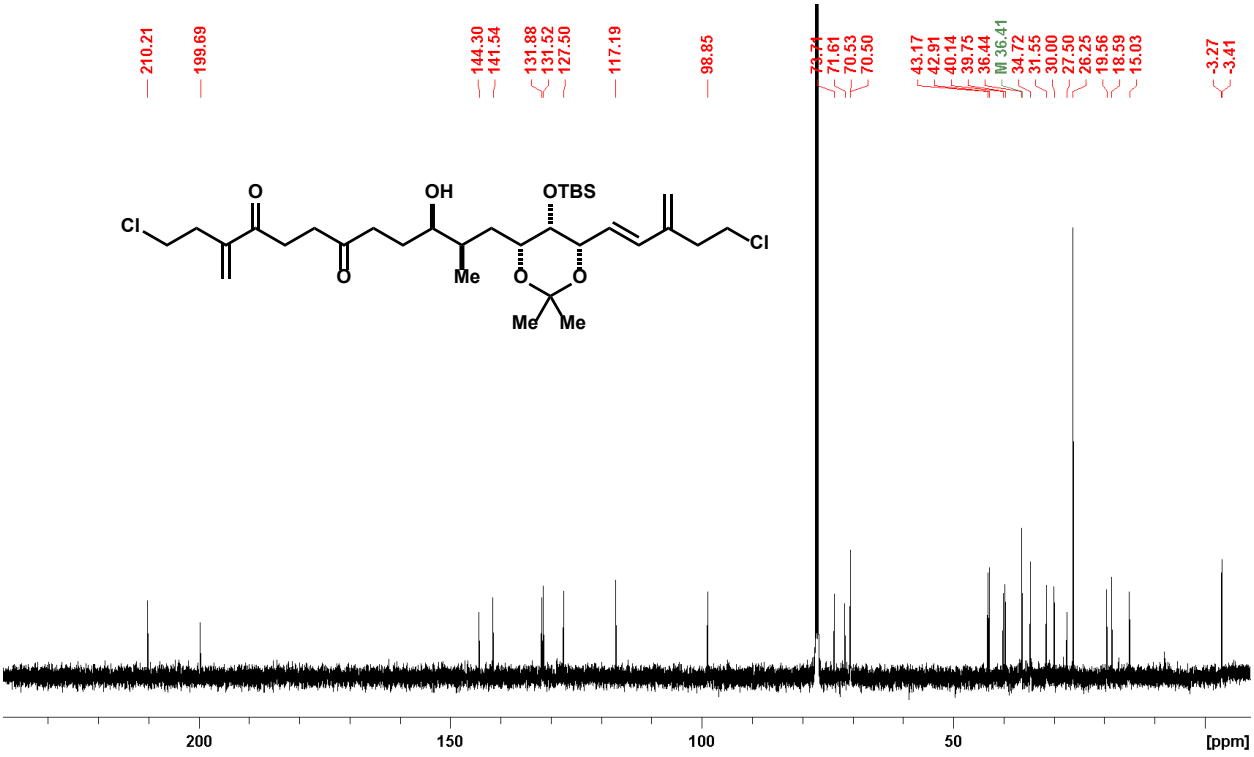
Spectrum 154. HMBC Spectrum of compound 2-27 ($CDCl_3$, 500 MHz)



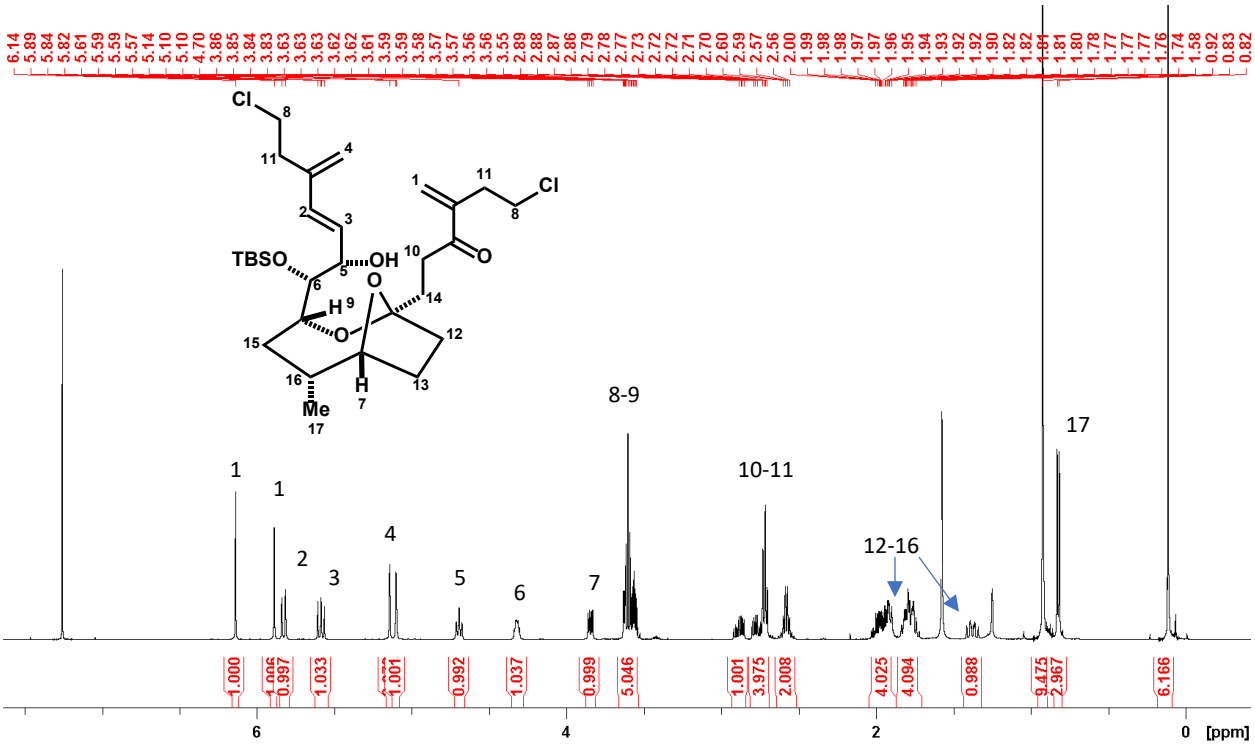
Spectrum 155. ^{1}H NMR of compound 2-29 ($CDCl_3$, 500 MHz)



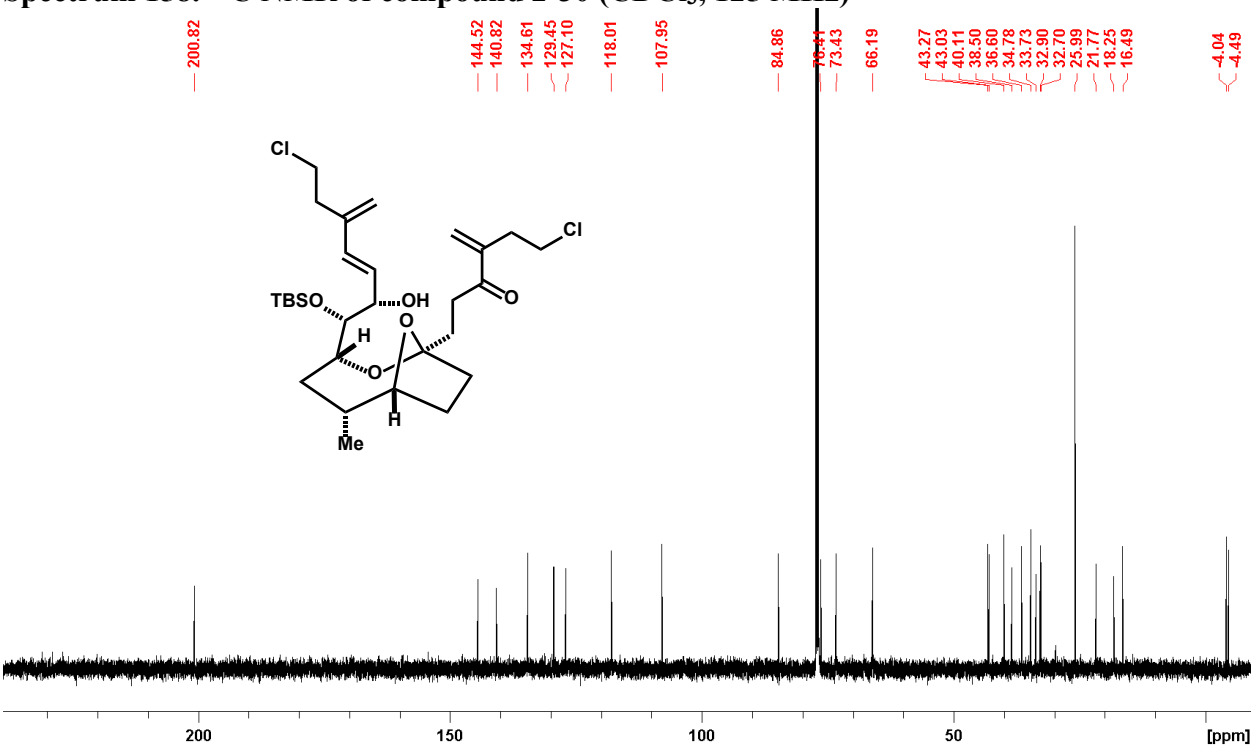
Spectrum 156. ^{13}C NMR of compound 2-29 ($CDCl_3$, 125 MHz)



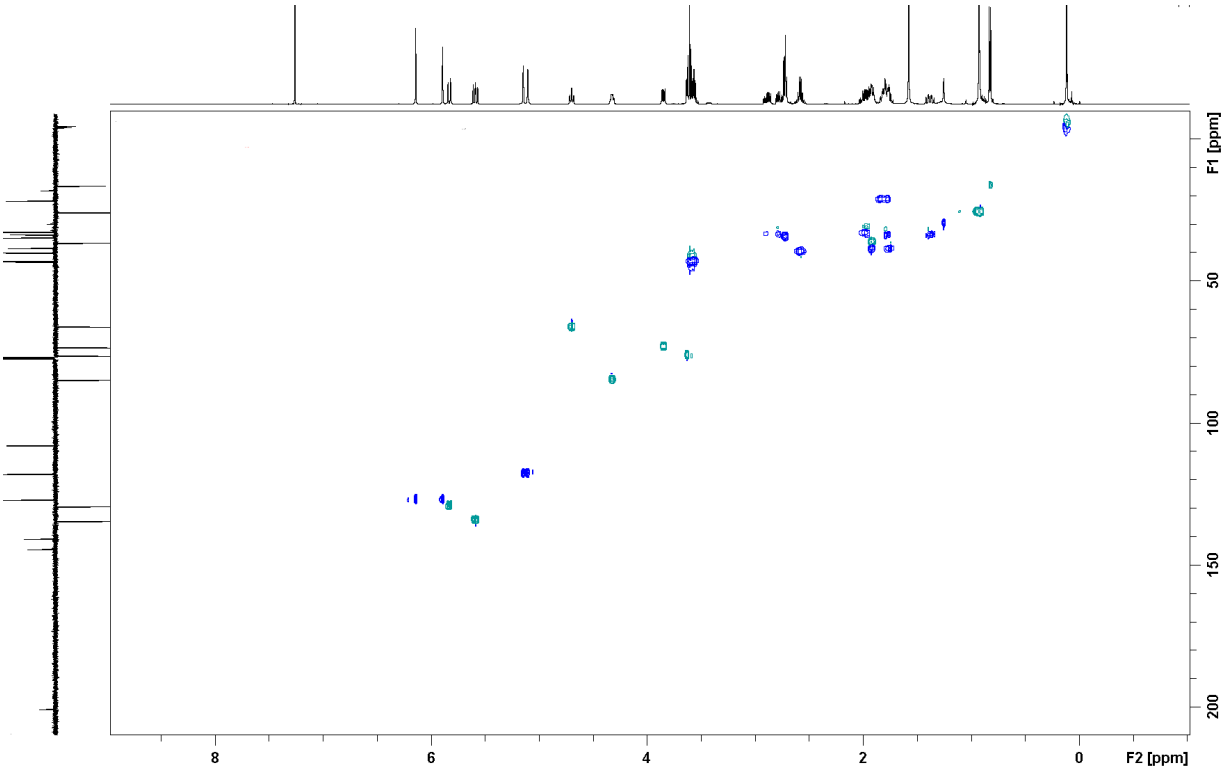
Spectrum 157. ^{1}H NMR of compound 2-30 ($CDCl_3$, 500 MHz)



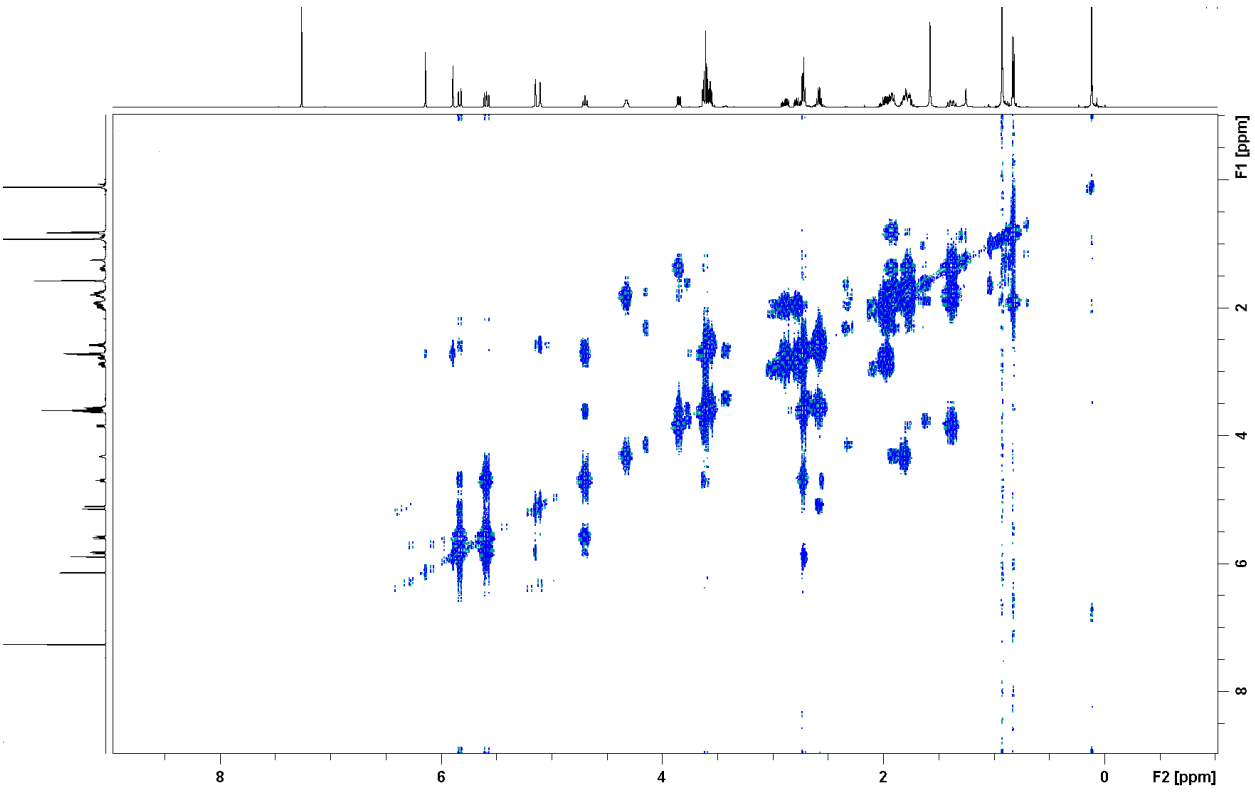
Spectrum 158. ^{13}C NMR of compound 2-30 ($CDCl_3$, 125 MHz)



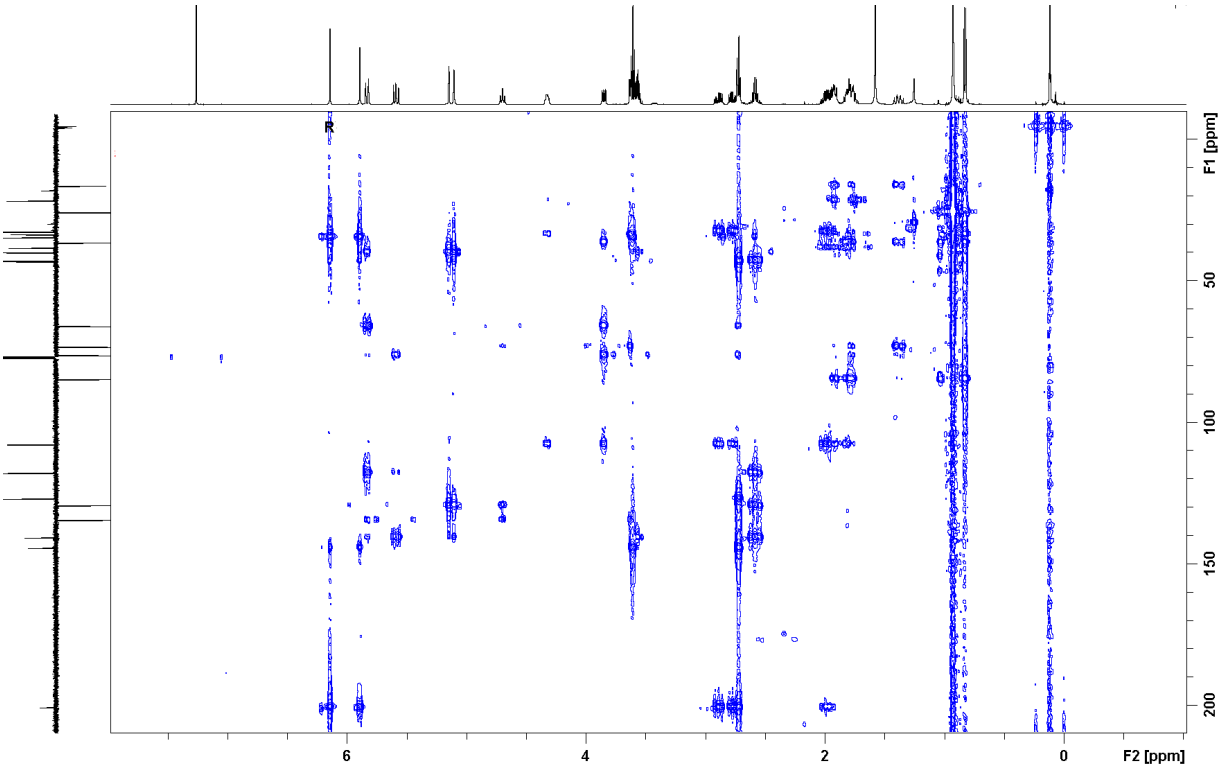
Spectrum 159. HSQC spectrum of compound 2-30 ($CDCl_3$, 500 MHz)



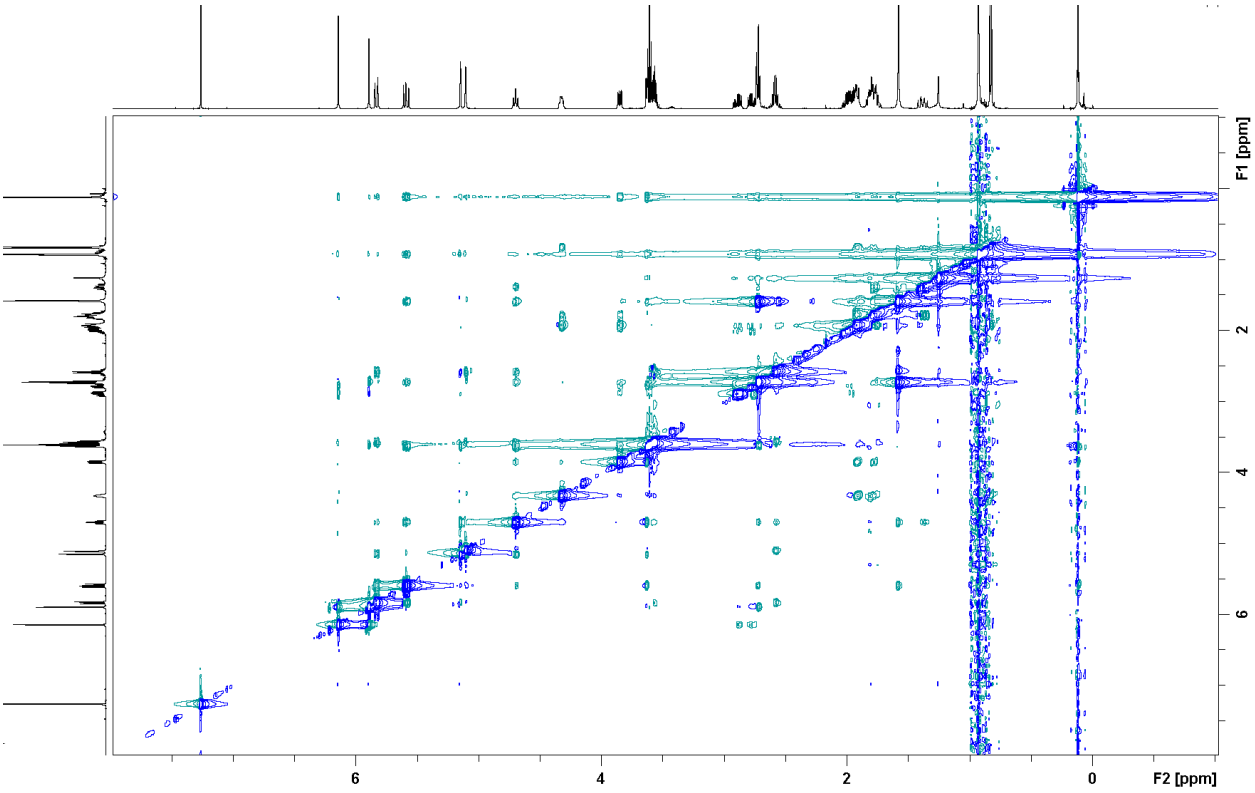
Spectrum 160. COSY spectrum of compound 2-30 ($CDCl_3$, 500 MHz)



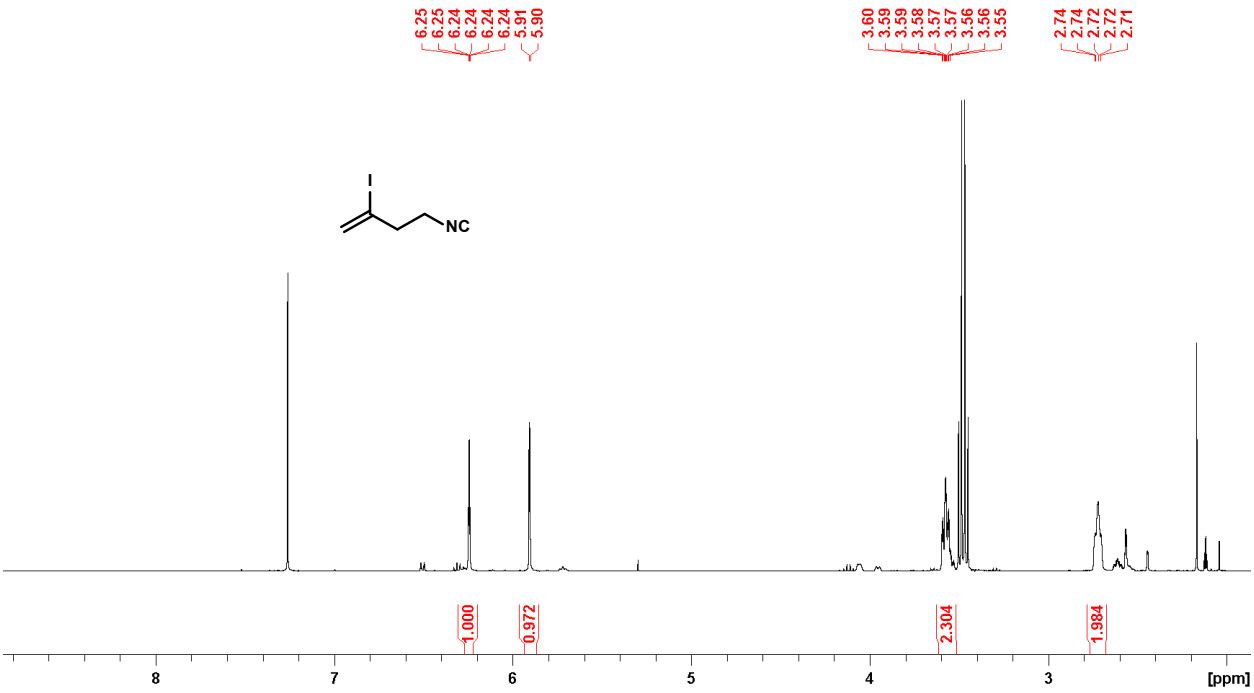
Spectrum 161. HMBC spectrum of compound 2-30 ($CDCl_3$, 500 MHz)



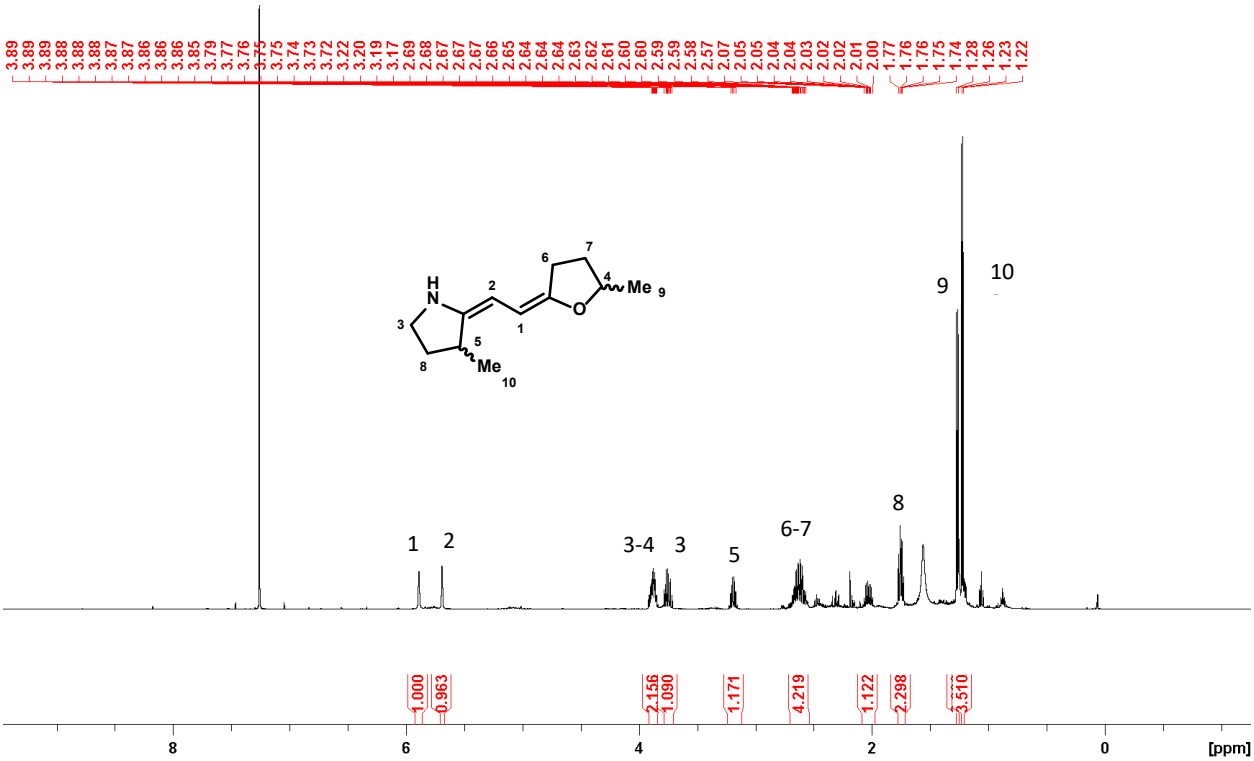
Spectrum 162. NOESY spectrum of compound 2-30 ($CDCl_3$, 500 MHz)



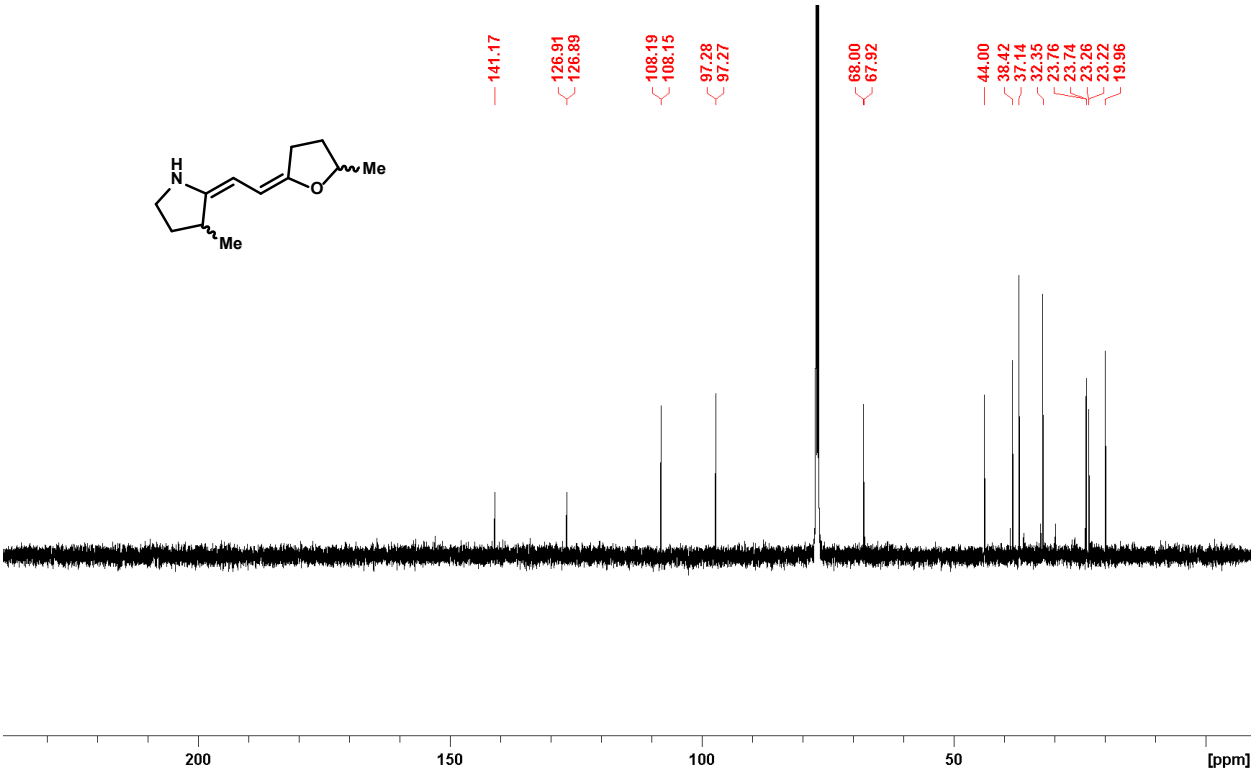
Spectrum 163. ^{1}H NMR of compound 2-33 ($CDCl_3$, 400 MHz)



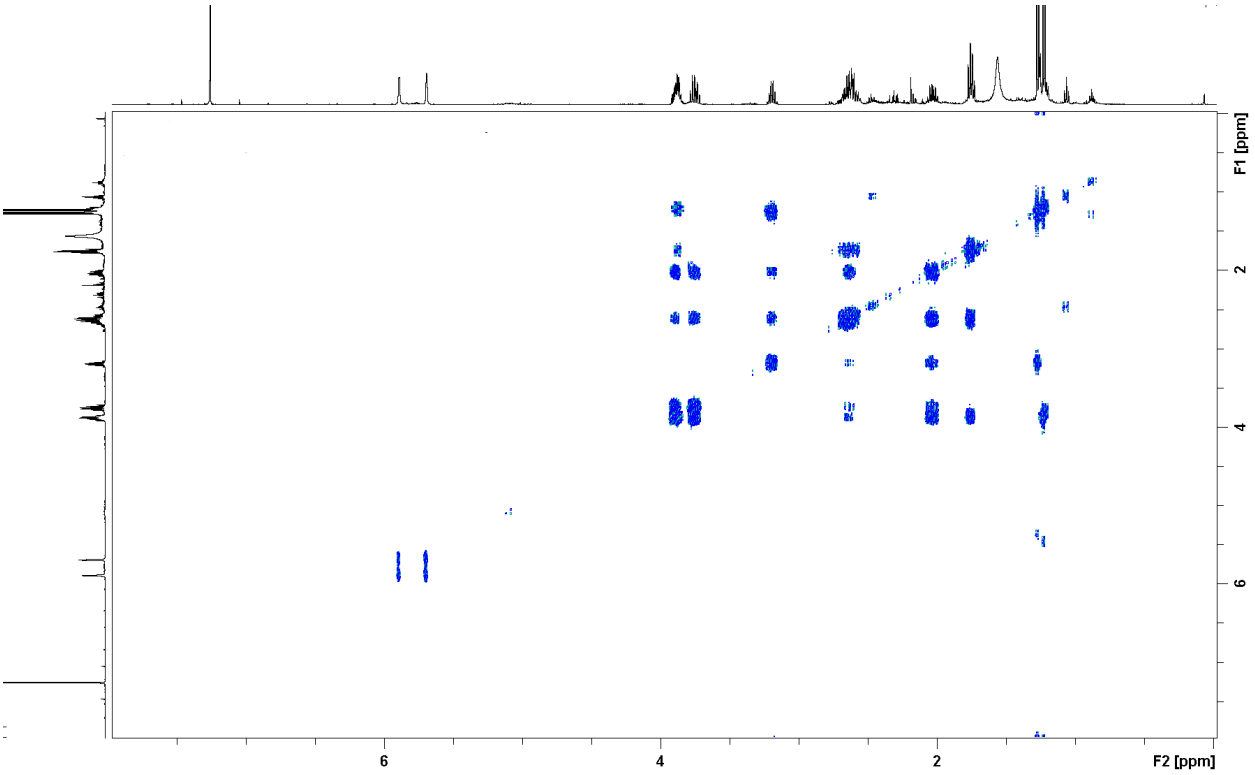
Spectrum 164. ^{1}H NMR of compound 2-38 ($CDCl_3$, 500 MHz)



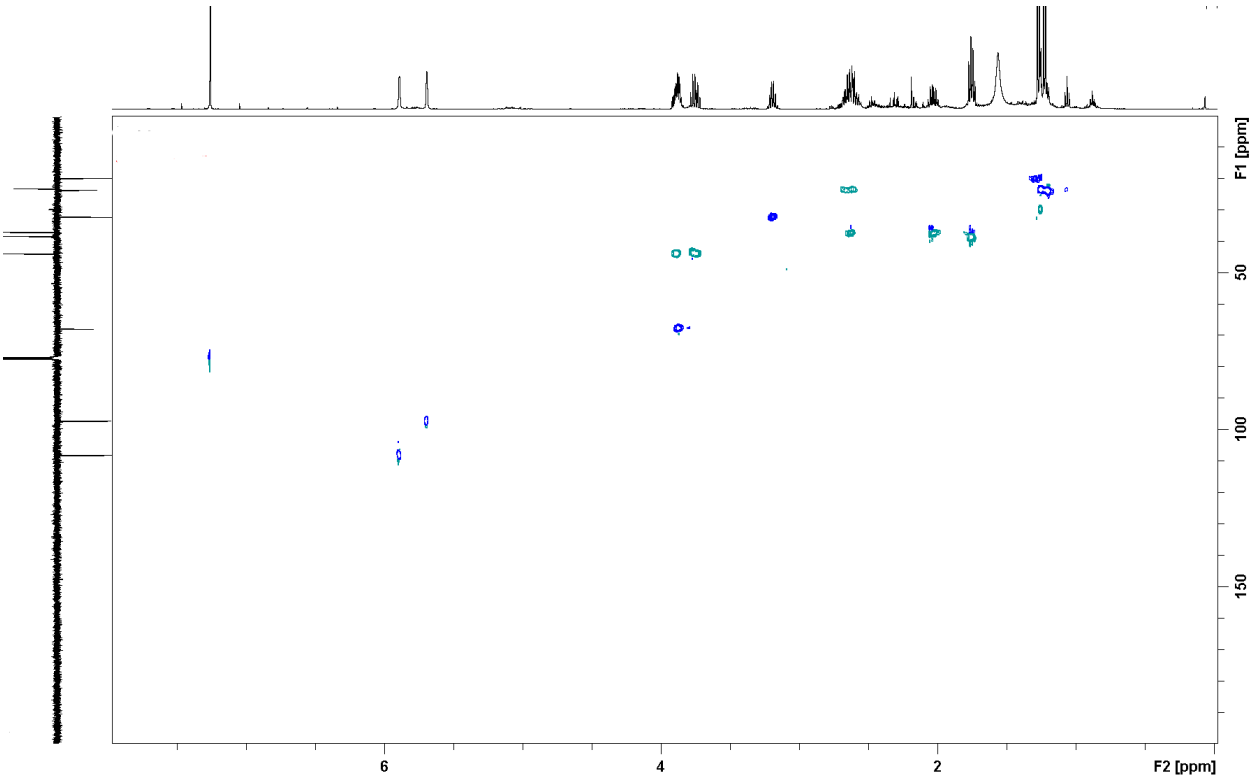
Spectrum 165. ^{13}C NMR of compound 2-38 ($CDCl_3$, 125 MHz)



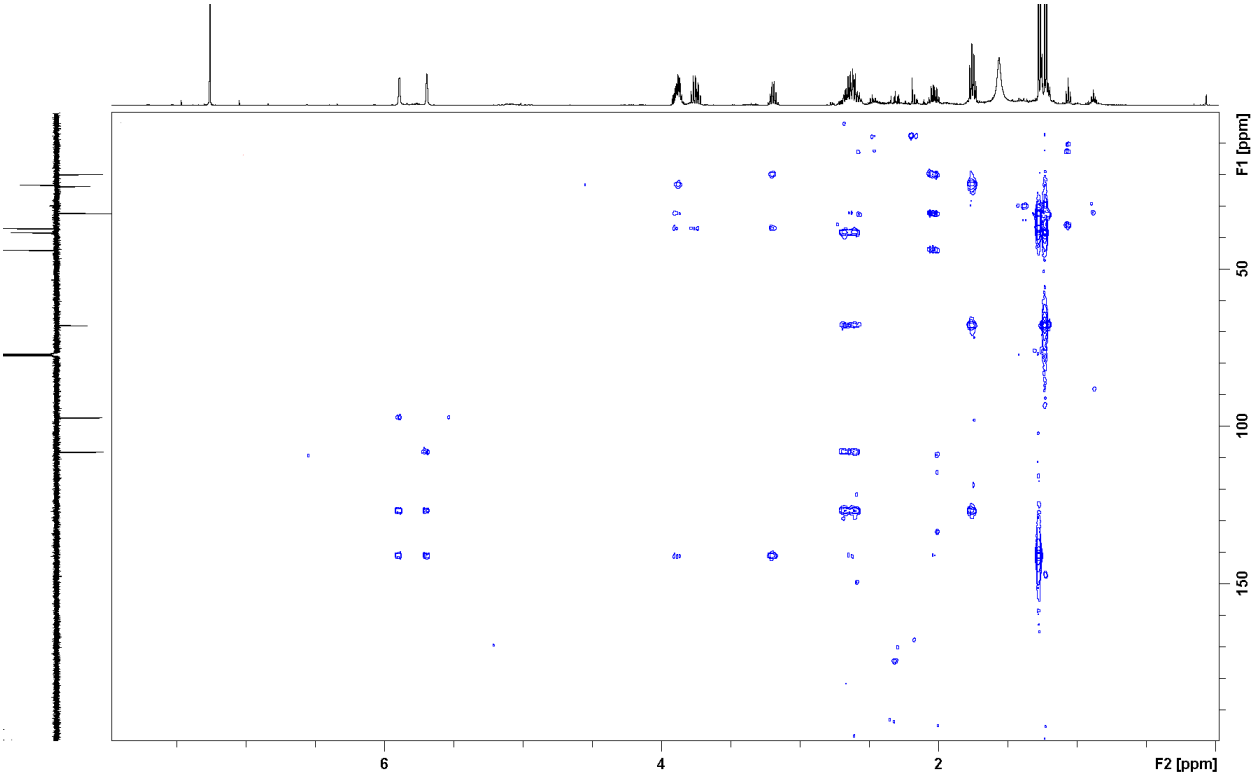
Spectrum 166. COSY spectrum of compound 2-38 ($CDCl_3$, 500 MHz)



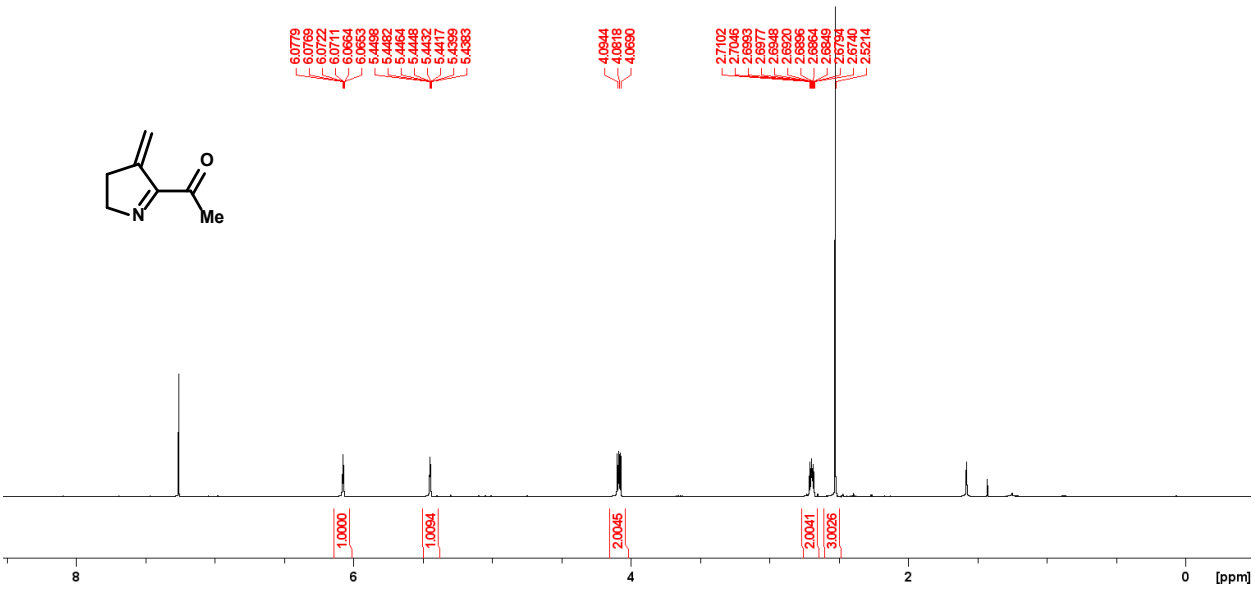
Spectrum 167. HSQC spectrum of compound 2-38 ($CDCl_3$, 500 MHz)



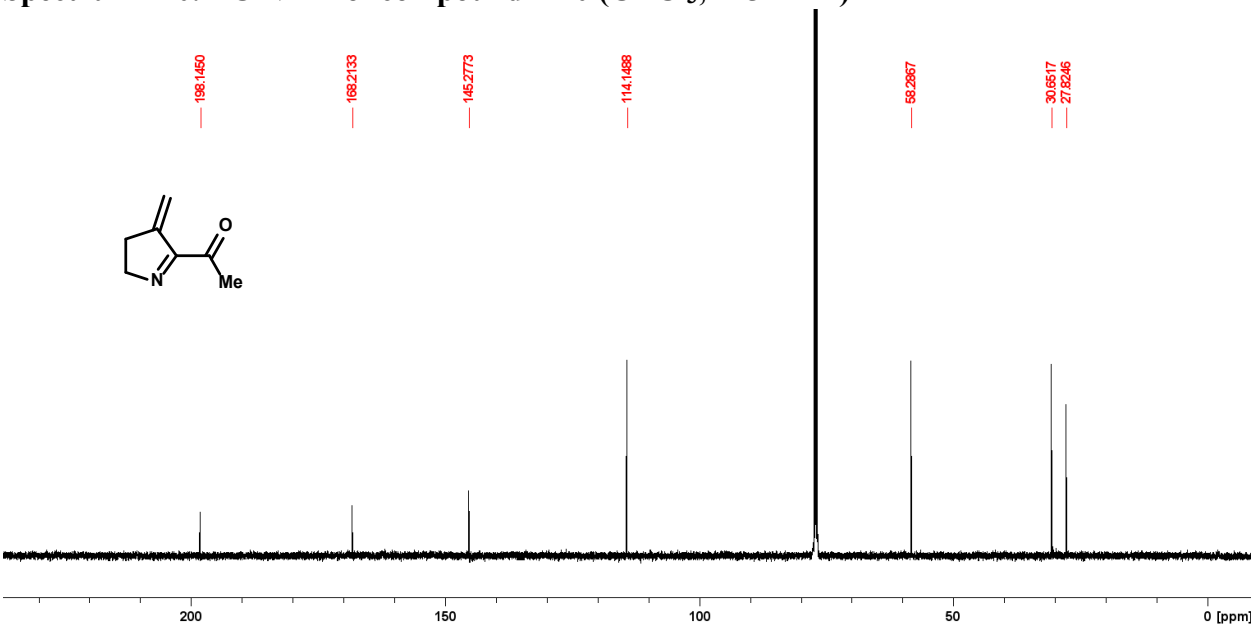
Spectrum 168. HMBC spectrum of compound 2-38 ($CDCl_3$, 500 MHz)



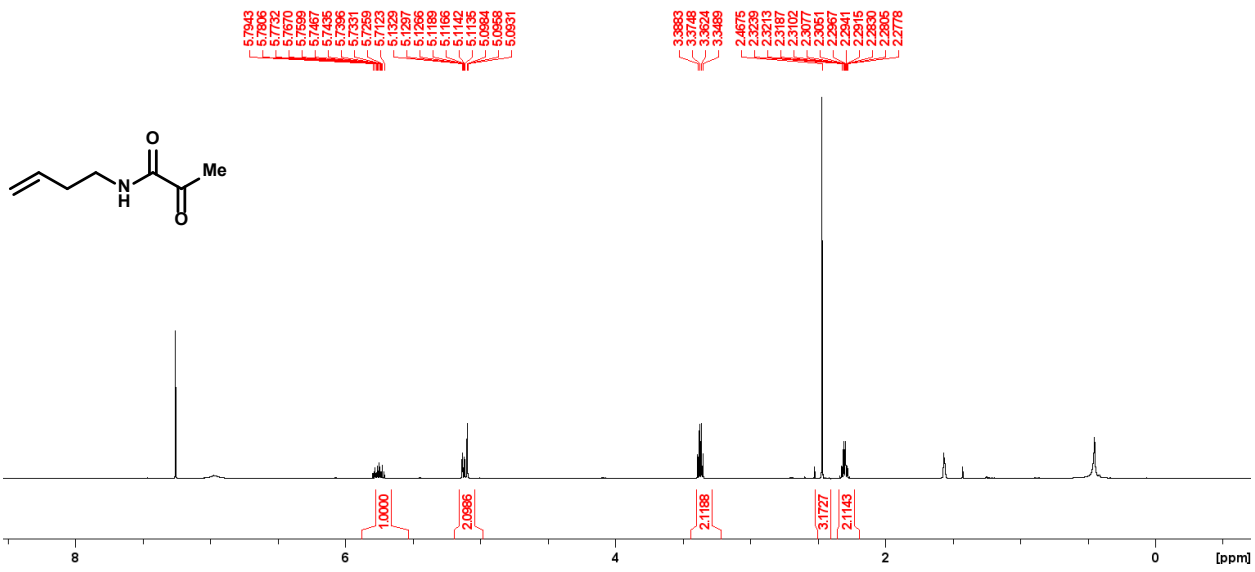
Spectrum 169. ^{1}H NMR of compound 2-40 ($CDCl_3$, 500 MHz)



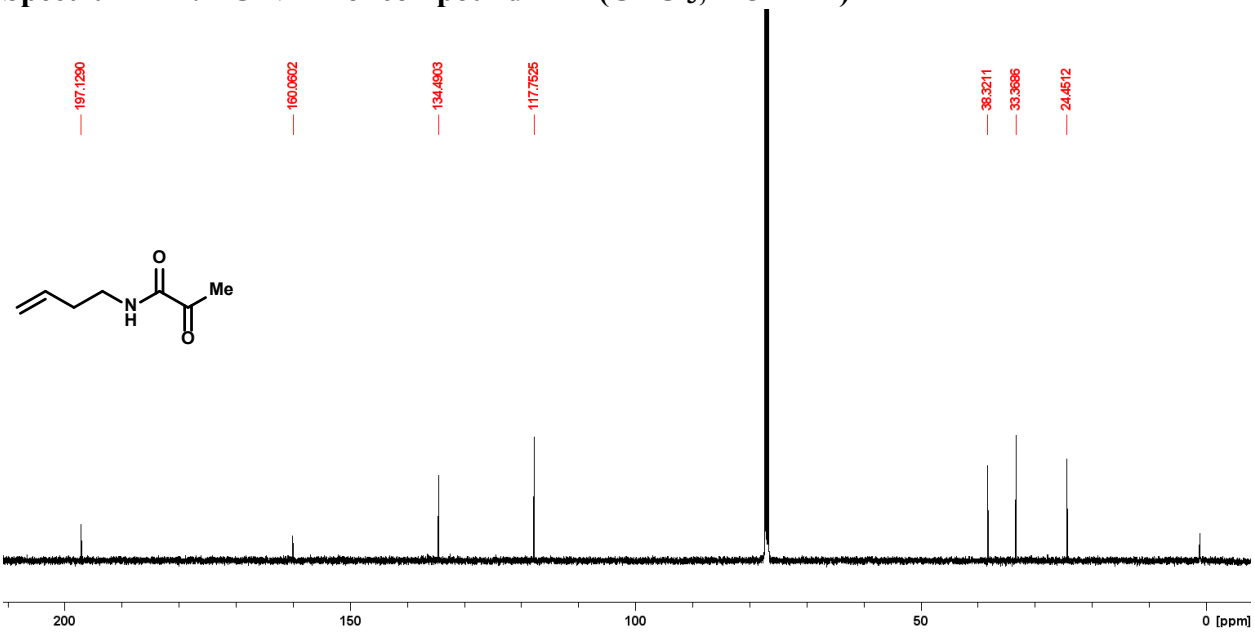
Spectrum 170. ^{13}C NMR of compound 2-40 ($CDCl_3$, 125 MHz)



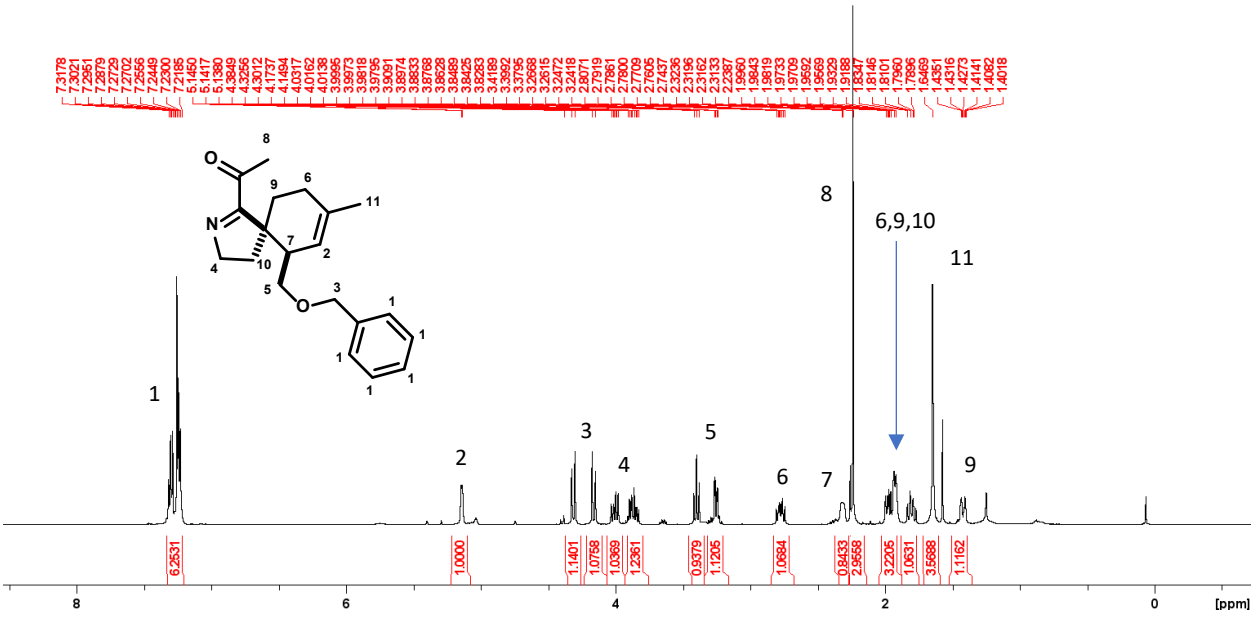
Spectrum 171. ^{1}H NMR of compound 2-42 ($CDCl_3$, 500 MHz)



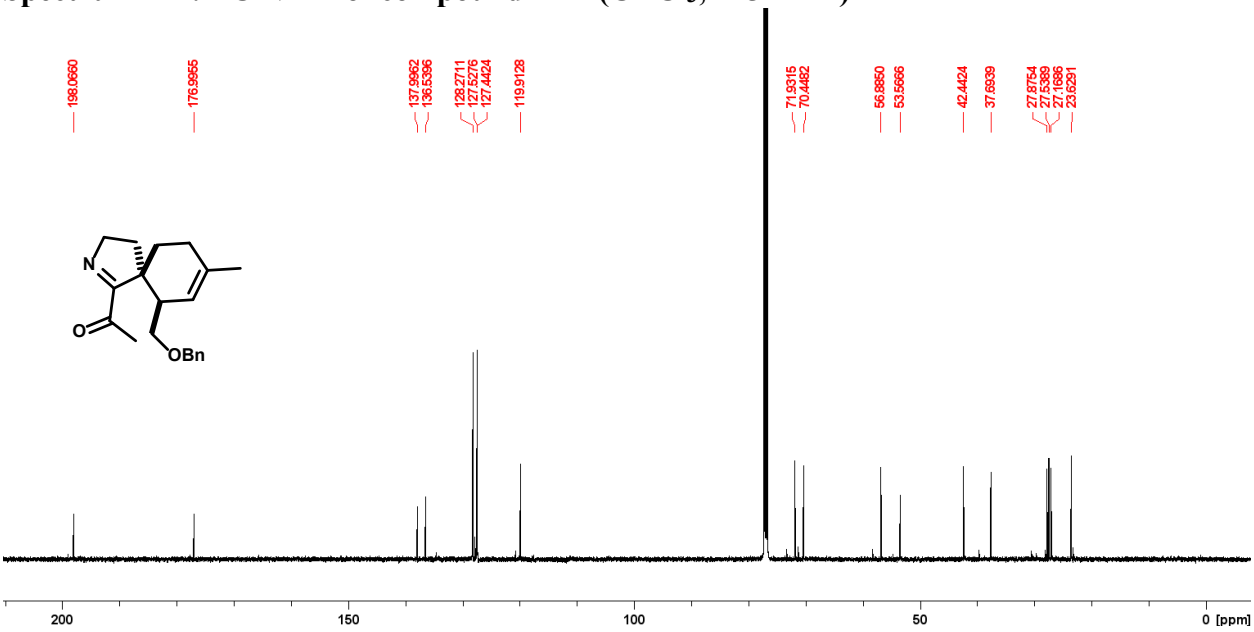
Spectrum 172. ^{13}C NMR of compound 2-42 ($CDCl_3$, 125 MHz)



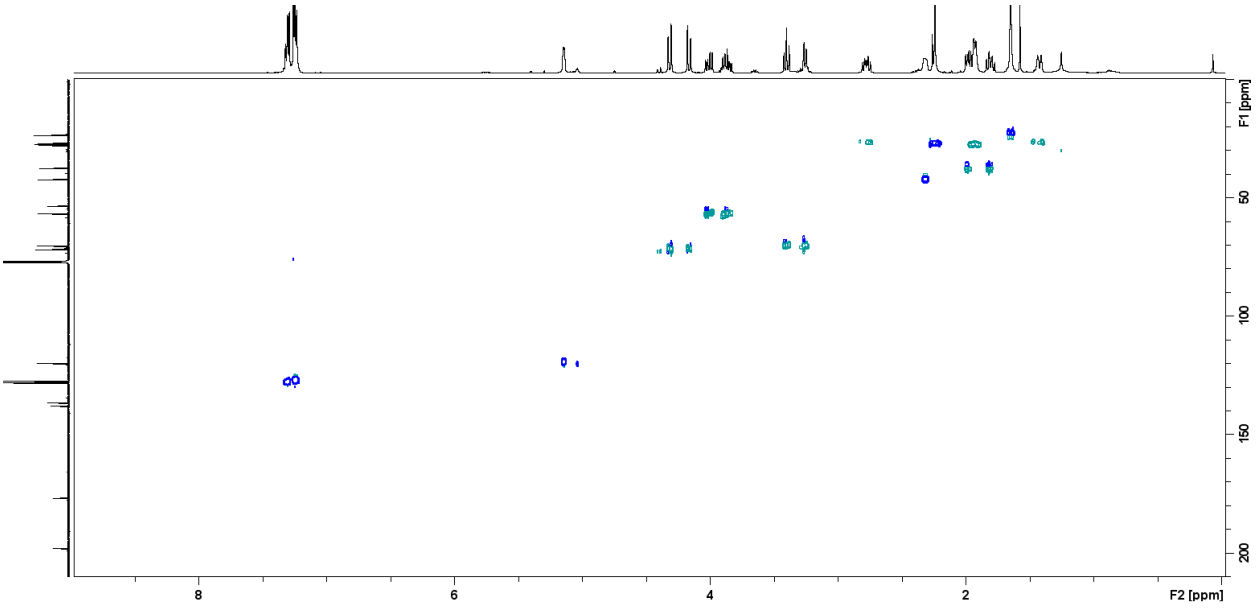
Spectrum 173. ^{1}H NMR of compound (±)-2-47 ($CDCl_3$, 500 MHz)



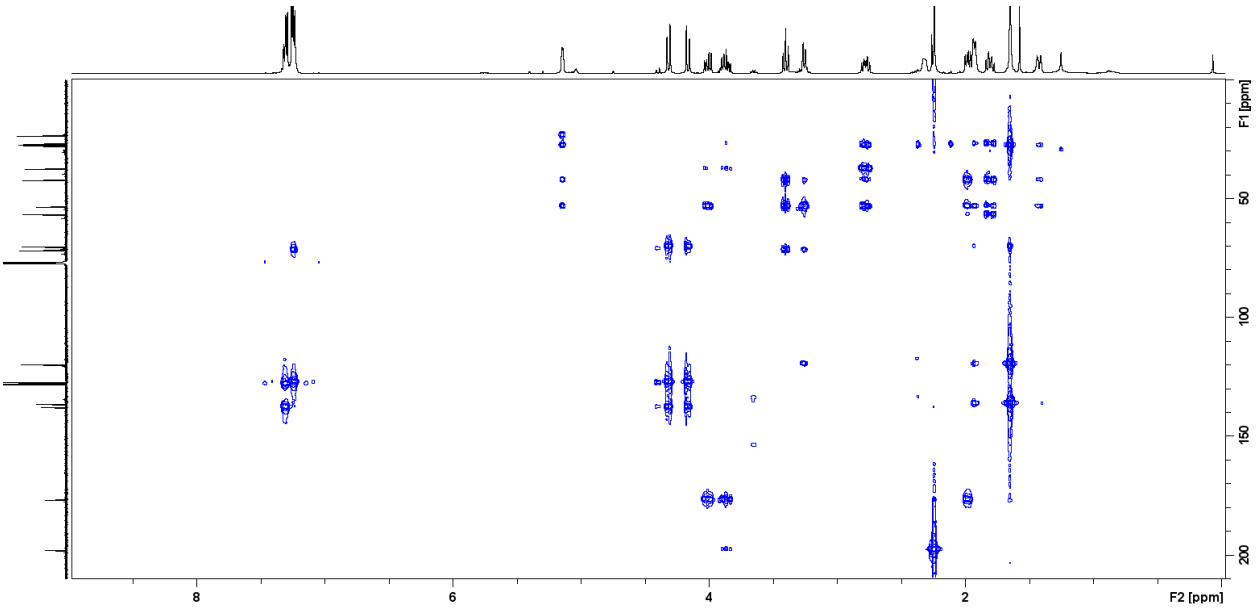
Spectrum 174. ^{13}C NMR of compound 2-47 ($CDCl_3$, 125 MHz)



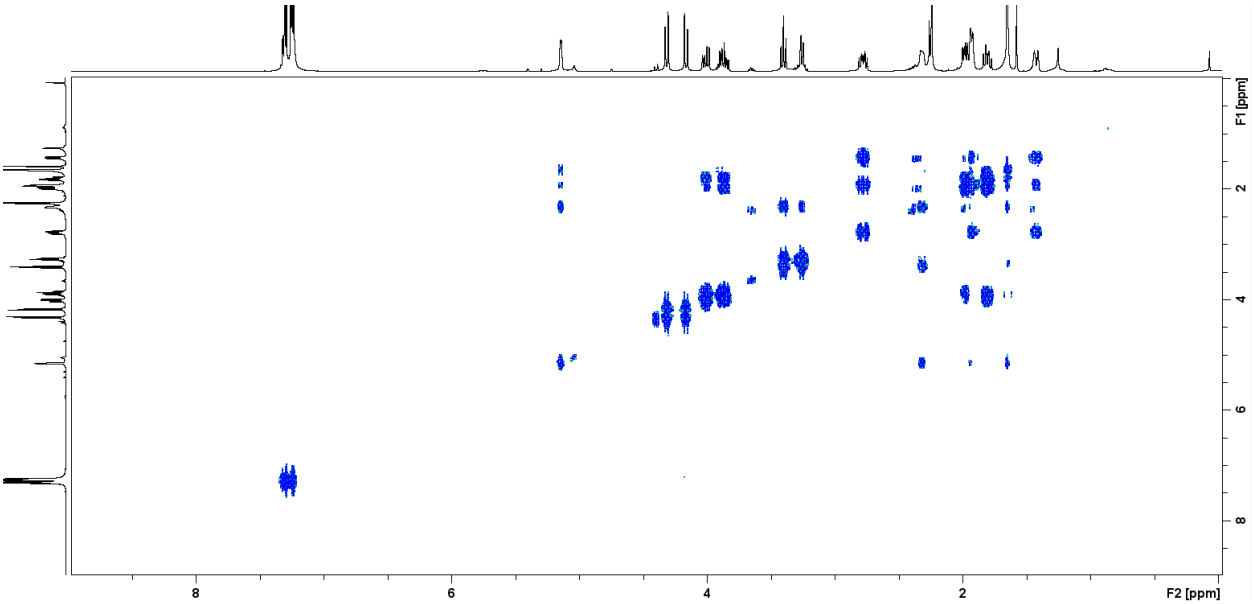
Spectrum 175. HSQC spectrum of compound 2-47 ($CDCl_3$, 500 MHz)



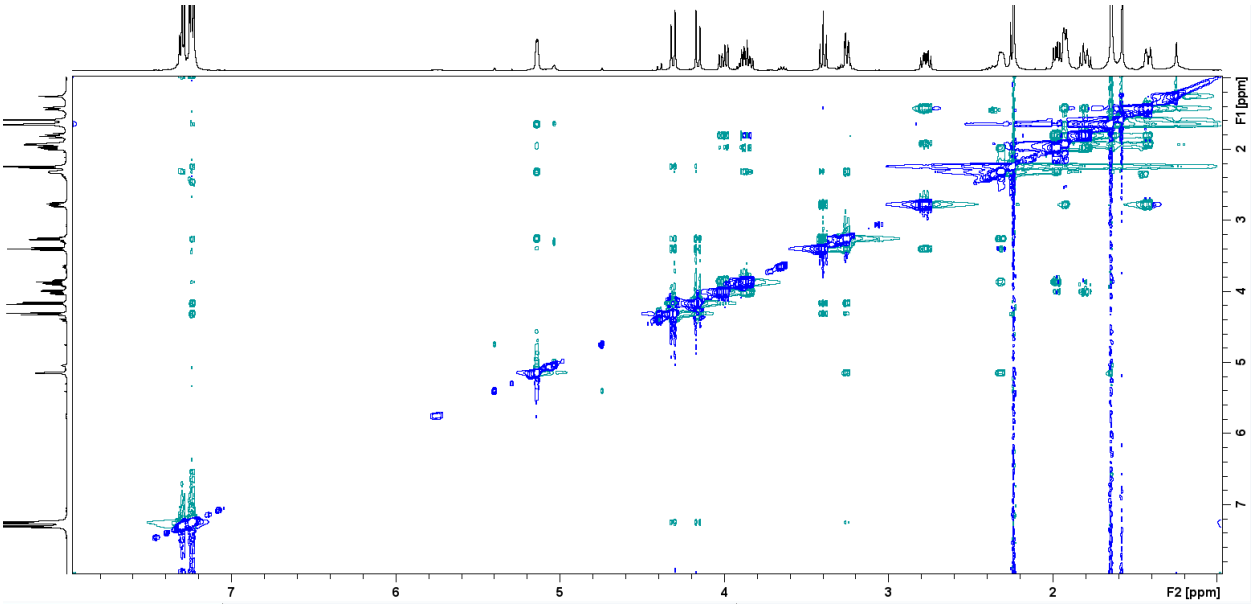
Spectrum 176. HMBC spectrum of compound 2-47 ($CDCl_3$, 500 MHz)



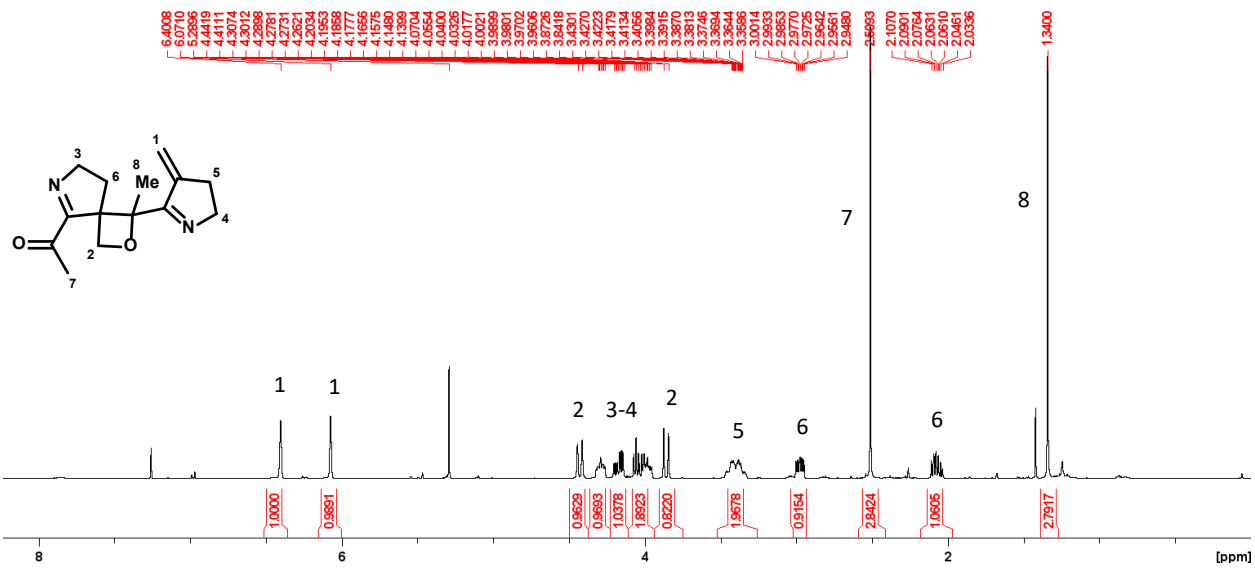
Spectrum 177. COSY spectrum of compound 2-47 ($CDCl_3$, 500 MHz)



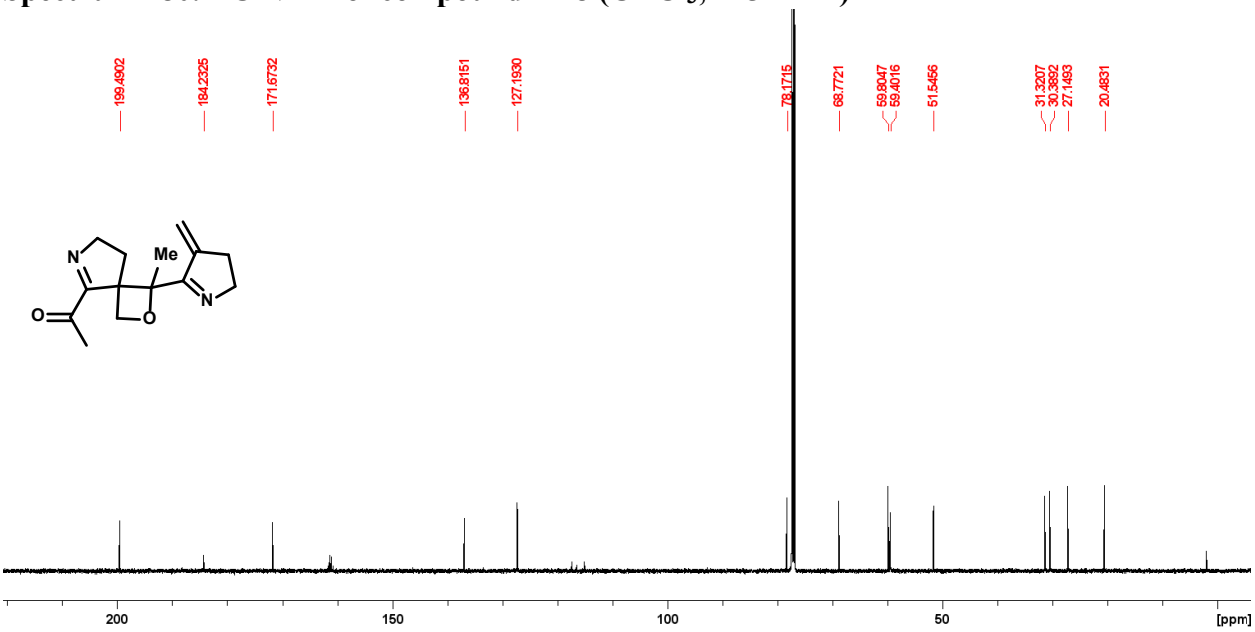
Spectrum 178. NOESY spectrum of compound 2-47 ($CDCl_3$, 500 MHz)



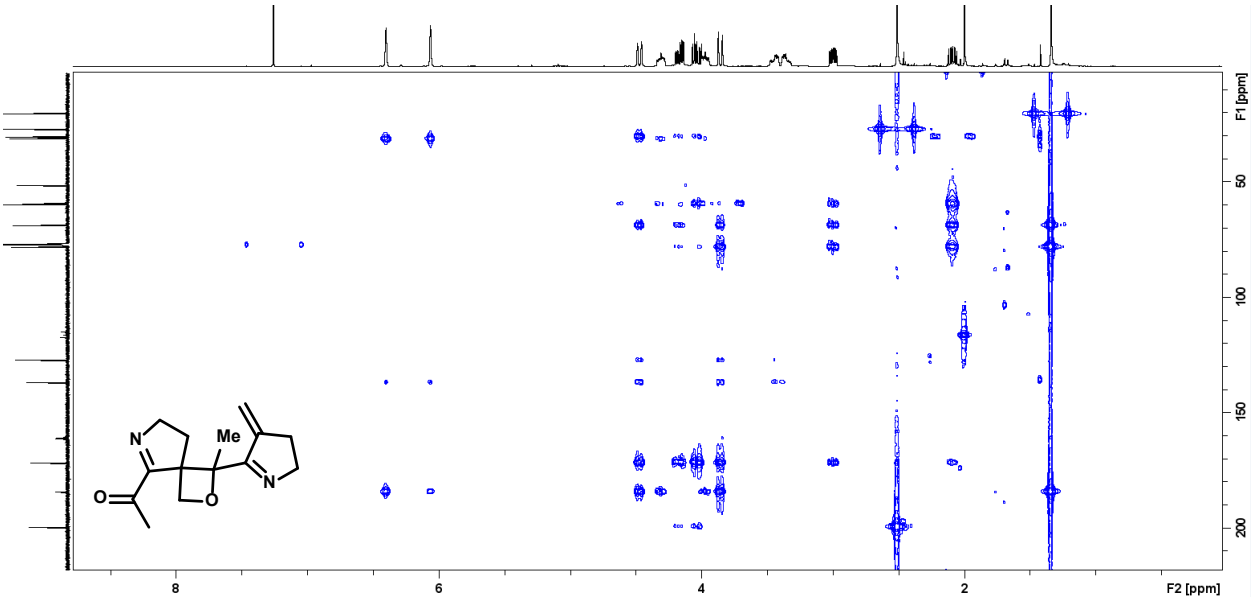
Spectrum 179. ^{1}H NMR of compound 2-48 ($CDCl_3$, 500 MHz)



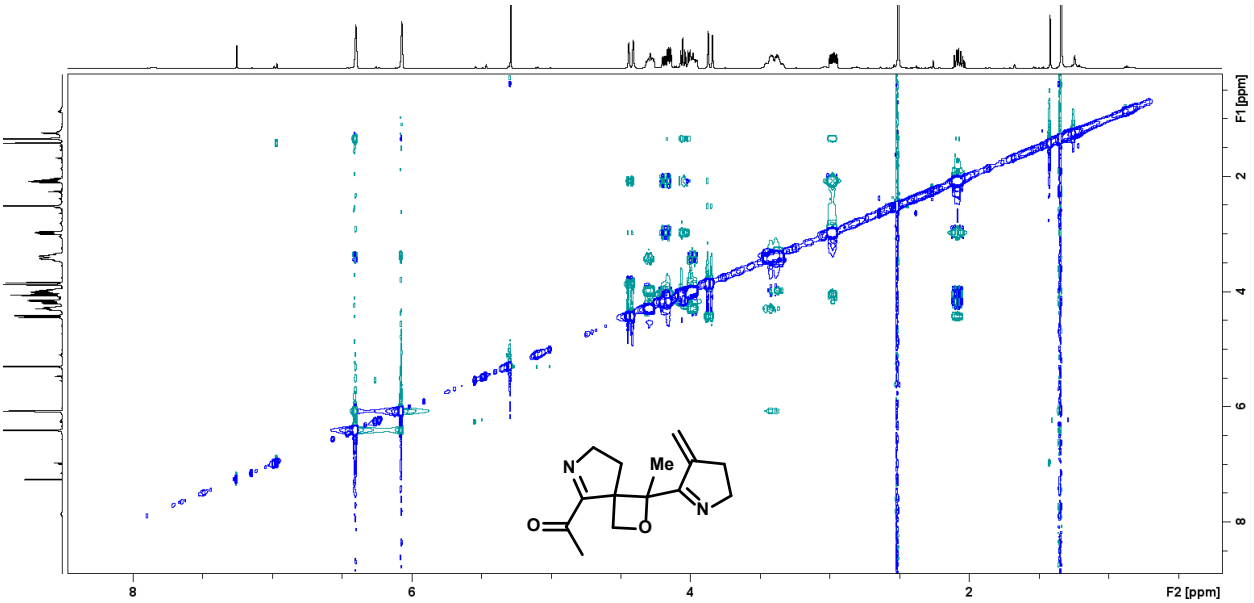
Spectrum 180. ^{13}C NMR of compound 2-48 ($CDCl_3$, 125 MHz)



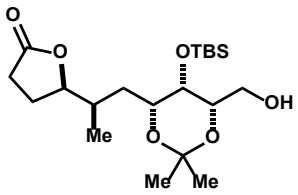
Spectrum 181. HMBC spectrum of compound 2-48 ($CDCl_3$, 500 MHz)



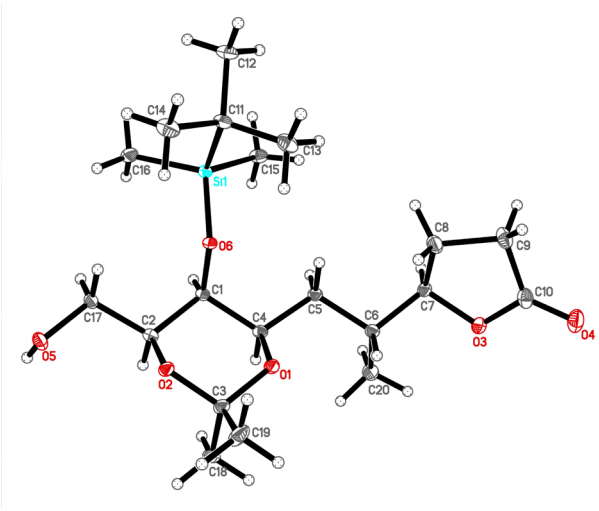
Spectrum 182. NOESY spectrum of compound 2-48 ($CDCl_3$, 500 MHz)



2.6.4 Crystallographic data



2-11




```
_audit_creation_method      SHELXL-2014/6
_chemical_name_systematic     ?
_chemical_name_common       ?
_chemical_melting_point      ?
_chemical_formula_moiety     'C20 H38 O6 Si, 0.082(O)'
_chemical_formula_sum
 'C20 H38 O6.08 Si'
_chemical_formula_weight     403.87

loop_
 _atom_type_symbol
 _atom_type_description
 _atom_type_scat_dispersion_real
 _atom_type_scat_dispersion_imag
 _atom_type_scat_source
'C' 'C'  0.0181  0.0091
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'H' 'H'  0.0000  0.0000
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'O' 'O'  0.0492  0.0322
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'Si' 'Si'  0.2541  0.3302
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

_space_group_crystal_system    orthorhombic
_space_group_IT_number      19
_space_group_name_H-M_alt     'P 21 21 21'
_space_group_name_Hall      'P 2ac 2ab'

_shelx_space_group_comment
;
The symmetry employed for this shelxl refinement is uniquely defined
by the following loop, which should always be used as a source of
```

symmetry information in preference to the above space-group names.
They are only intended as comments.
;

loop_
 _space_group_symop_operation_xyz
 'x, y, z'
 '-x+1/2, -y, z+1/2'
 '-x, y+1/2, -z+1/2'
 'x+1/2, -y+1/2, -z'

_cell_length_a 7.28230(10)
_cell_length_b 9.6453(2)
_cell_length_c 32.8173(6)
_cell_angle_alpha 90
_cell_angle_beta 90
_cell_angle_gamma 90
_cell_volume 2305.09(7)
_cell_formula_units_Z 4
_cell_measurement_temperature 100(2)
_cell_measurement_reflns_used 9771
_cell_measurement_theta_min 2.69
_cell_measurement_theta_max 71.81

_exptl_crystal_description platelet
_exptl_crystal_colour colourless
_exptl_crystal_density_meas ?
_exptl_crystal_density_method ?
_exptl_crystal_density_diffrn 1.164
_exptl_crystal_F_000 883
_exptl_transmission_factor_min ?
_exptl_transmission_factor_max ?
_exptl_crystal_size_max .25
_exptl_crystal_size_mid .2
_exptl_crystal_size_min .1
_exptl_absorpt_coefficient_mu 1.152
_shelx_estimated_absorpt_T_min ?
_shelx_estimated_absorpt_T_max ?
_exptl_absorpt_correction_type multi-scan
_exptl_absorpt_correction_T_min 0.64
_exptl_absorpt_correction_T_max 0.75
_exptl_absorpt_process_details 'SADABS V2014/2 (Bruker AXS Inc.)'
_exptl_absorpt_special_details ?
_diffrn_ambient_temperature 100(2)
_diffrn_radiation_wavelength 1.54178

```
_diffrn_radiation_type      CuK\a
_diffrn_source          'I\mS micro--focus source'
_diffrn_measurement_device_type  'Bruker APEX-II CCD'
_diffrn_measurement_method    '\f and \w scans'
_diffrn_detector_area_resol_mean 8.3333
_diffrn_reflns_number       13499
_diffrn_reflns_av_unetI/netI   0.0316
_diffrn_reflns_av_R_equivalents  0.0263
_diffrn_reflns_limit_h_min    -8
_diffrn_reflns_limit_h_max    8
_diffrn_reflns_limit_k_min    -11
_diffrn_reflns_limit_k_max    11
_diffrn_reflns_limit_l_min    -40
_diffrn_reflns_limit_l_max    37
_diffrn_reflns_theta_min     2.693
_diffrn_reflns_theta_max     71.799
_diffrn_reflns_theta_full     67.679
_diffrn_measured_fraction_theta_max  0.972
_diffrn_measured_fraction_theta_full 0.996
_diffrn_reflns_Laue_measured_fraction_max  0.972
_diffrn_reflns_Laue_measured_fraction_full  0.996
_diffrn_reflns_point_group_measured_fraction_max  0.959
_diffrn_reflns_point_group_measured_fraction_full 0.994
_reflns_number_total       4315
_reflns_number_gt         4120
_reflns_threshold_expression   'I > 2\s(I)'
_reflns_Friedel_coverage     0.706
_reflns_Friedel_fraction_max   0.942
_reflns_Friedel_fraction_full   0.990
```

Chapter Three: Synthesis and Biological Studies of EGCG Conjugates as Potent Disaggregants of Alzheimer's tau

3.1 Introduction

Alzheimer's disease (AD) is the 6th leading cause of death in the United States and 7th in the world. Personal and economic burdens associated with this most common type of dementia are enormous. Approximately 6.8 million Americans currently suffer from the disease. By 2050, its annual costs to the healthcare system are anticipated to reach $1.1 trillion.[69] Despite decades of research and numerous attempts at treatment, much is still unknown about the etiology of Alzheimer's. Two main markers have been identified: plaques of aggregated β-amyloid and neurofibrillary tangles of tau. However, the precise cause of the cognitive decline and effective drug targets have been elusive. Early focus on β-amyloid led to clinical trials of multiple therapeutic candidates with limited success.[70] Those failed trials called into question the hypothesis that amyloid plaques play a decisive role in cognitive decline. Recent advances in imaging[71] showed tau tangles to be the best predictors of Alzheimer's progression as well as the species responsible for driving brain atrophy. Oligomeric and fibrillar tau appear to be promising targets for therapeutics. The polyphenolic flavonoid (–)-epigallocatechin gallate (EGCG) inhibits thee aggregation of proteins involved in neurogenerative amyloidoses including huntingtin, amyloid-β, and α-synuclein.[72] Wobst et al.[73] reported that EGCG blocks the fibrillization of tau by sequestering unfolded protein monomers. Recently, cryoEM was used to determine the binding site for EGCG on fibrils of tau deriving from the brain tissue of a donor with AD.[74] Relative to the apo AD-tau fibril, the bound form contains EGCG wedged into an interfacial cleft (Figure 1).

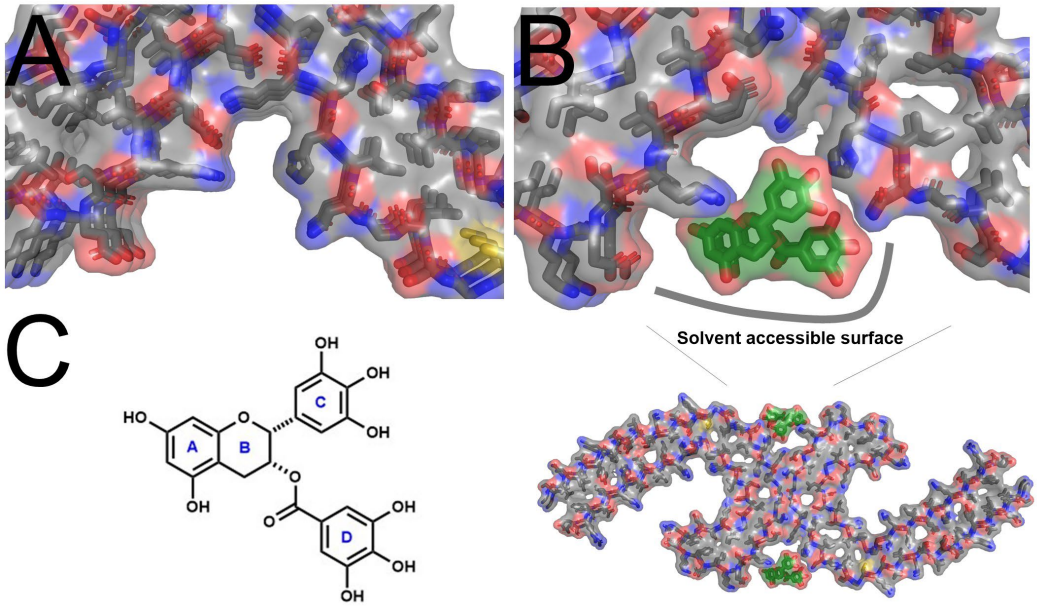


Figure 11. CryoEM structure of non-liganded AD-tau fibrils (A, PDB 6HRE) and fibrils bound to disaggregant EGCG (B). EGCG is rendered green with oxygens shown in red. Residues from the Tau protein are rendered grey with oxygens red, nitrogens blue, and sulfur gold. The surface on EGCG that remains solvent accessible in the fibril-bound pose is labeled. C: Chemical structure of EGCG showing the nomenclature of ring systems. Density map of EGCG-tau binding cleft (green: EGCG, blue/grey: tau fibril).

The structure of EGCG bound to AD tau indicated positions on the small molecule that might serve as anchor points for nanoparticle conjugation, wherein the ability to bind tau fibrils would be retained. Despite numerous reports of therapeutic potential for EGCG, the compound is prone to auto-oxidation, has poor pharmacokinetics, and is largely excluded from the brain when administered systemically. Stable conjugation to brain penetrant nanoparticles was seen as potential means to offset those limitations.[75] We selected Ferumoxytol as a nanoparticle carrier. Ferumoxytol exhibits moderate brain penetration, with penetration increasing coincident with pathologies that alter the neurovascular unit. As best modeled (Figure **11B**), the tau bound form of EGCG oriented its A-ring C5 phenol and a major portion of the gallate D-ring towards solvent. We sought to selectively derivatize the natural product at two positions along this periphery with

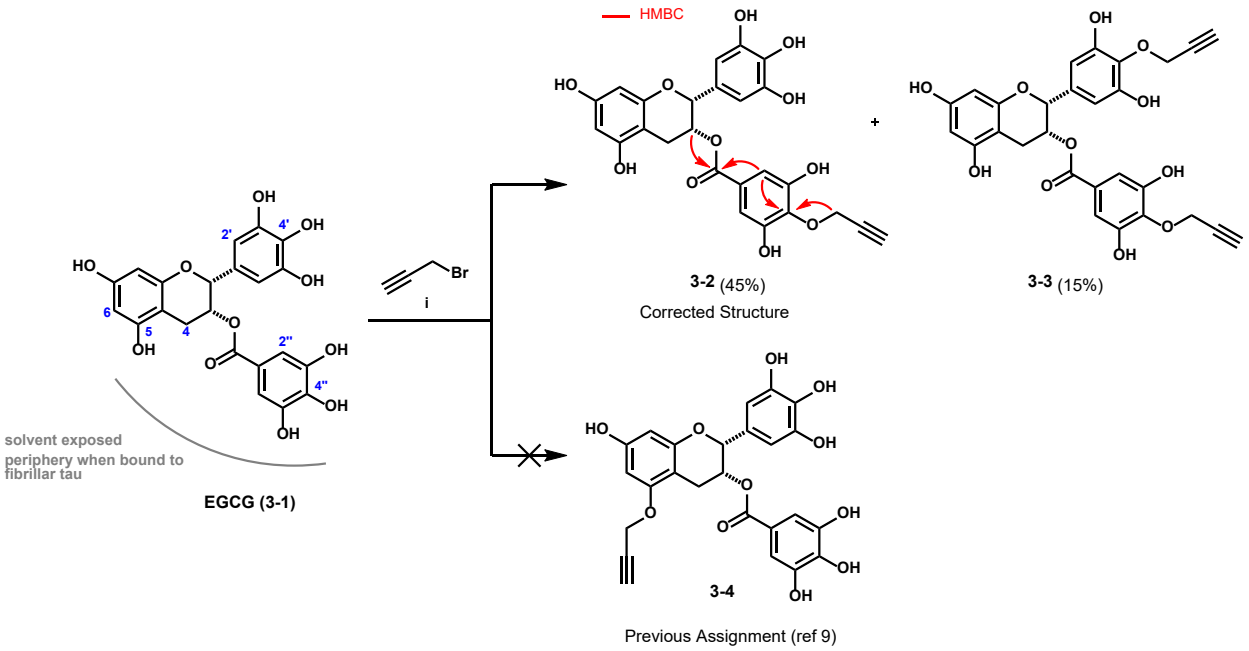
end-functionalized ethylene glycol chains of varying lengths: para-phenol on the D ring, and methylene carbon at the B ring. The following sections especially the one concerning D ring derivatization are partially adapted from our publication in April 2021.[76] Imaging and biological studies have been done in collaboration with the Eisenberg lab (Hope Pan and Ke Hou) at UCLA as well as Seidler lab at USC.

3.2 D-ring derivatization and nanoparticle conjugation

Our initial studies aimed at selectively derivatizing A-ring due to its seeming insignificance to the EGCG-tau binding. Remarkably, Wang and co-workers had reported that a sodium salt of EGCG reacted with propargyl bromide in DMF at 80 ˚C to afford predominately A-ring mono-ether, along with lesser amounts of further propargylated compounds.[77] Inspired by this publication, we repeated this reaction and found spectroscopic data for the major etherification product was inconsistent with structure **3-4** (**Scheme 31**). HMBC spectra showed a correlation between the propargylic methylene protons (OCH_2, 4.76 ppm) and C-4'' (137.0 ppm). C4'' exhibited coupling with C2''-H (6.89 ppm), and C2''-H also correlated to the carbonyl carbon (165.7 ppm). C5 (95.2 ppm), the linkage site assigned in **3-4**, exhibited correlations to C6-H and the C4 methylene protons, but not to the propargyl group or D ring aryl protons. These data indicated the proper structure assignment should be ether **3-2**, wherein alkylation had occurred at the para phenol of the gallate ester. This phenol is presumably the most acidic in EGCG.

A second product isolated from the reaction was doubly etherified and showed HMBC correlations between a second propargylic methylene (OCH_2, 4.67 ppm) and C4'(137.0 ppm), and between C4' and C2'-H (6.53 ppm). Data indicated the second propargyl ether formed on Ring C. A third minor isomer has been observed by NMR and mass spectrum which was hypothesized to

be a triply propargylated compound finally suggesting the involvement of the A ring in the reaction. However, its minuscule amounts as well as coelution with other byproducts rendered the unambiguous structure assignment challenging. These observations confirmed that the phenols on Ring A are the least susceptible to alkylation under basic conditions and thus cannot be easily derivatized from the commercially available starting material. However, based on the current CryoEM structure, para phenol on the D ring points outside the binding cleft and thus might not be involved in the key binding interactions. With this in mind, D ring derivatizations were carried out further.



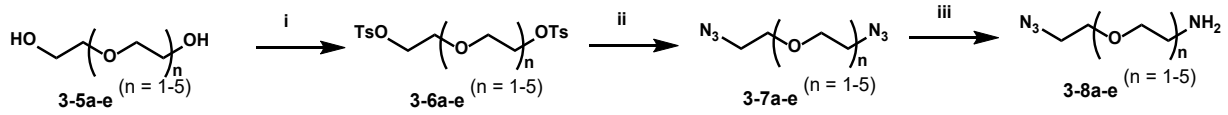
Conditions: (i) NaH (1.5 eq.), propargyl bromide (1.1 eq.), DMF (0.3 M), 80 °C, overnight, 33% or K_2CO_3 (0.5 eq.), propargyl bromide (1.1 eq.), DMF (0.2 M), rt, 45%

Scheme 31. Reassignment of the monopropargylated product **3-2**.

Firstly, however, conditions were screened to optimize the formation of **3-2** while avoiding the use of NaH in DMF - a potentially explosive combination, particularly when heated.[78] It was

eventually found that treating EGCG with 1 eq. propargyl bromide and 0.5 eq. powdered K_2CO_3 in DMF at room temperature afforded **3-2** in 45% isolated yield – versus the 33% yield obtained using the NaH/DMF procedure.

We next synthesized a set of glycol-based amino azides with chain lengths varying from 5 to 17 atoms (**Scheme 32**).



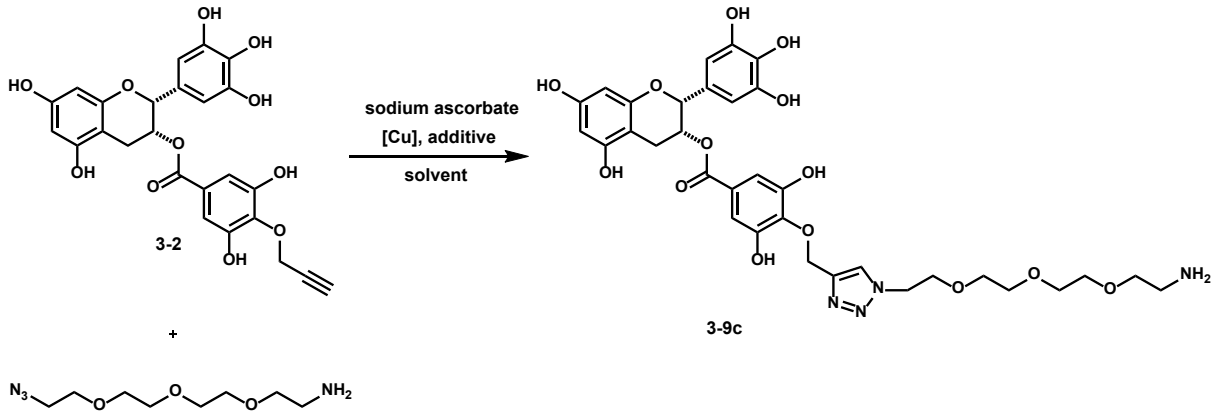
Conditions: (i) TsCl (2.1 eq.), KOH (8.0 eq.), DCM (0.6 M), rt, 4 h; (ii) NaN_3 (4.0 eq.), DMF (0.6 M), 80 °C, overnight; (iii) PPh_3 (1.0 eq.), THF/Et_2O/H_2O (5/1/5, 0.6 M), rt, overnight, 70-90%

Scheme 32. Synthesis of the amino azides.

The subsequent goal was to produce EGCG conjugates with incrementally increasing chain lengths. Cycloaddition reaction conditions were first optimized with **3-2** using copper catalysis (**Table 9**). Standard conditions[79] using catalytic Cu(II) and sodium ascorbate in aqueous THF (**Table 9**, entries 1 & 2), failed to cycloadd **3-2** to **3-8c** due to substrate insolubility. When THF was replaced with tBuOH, desired triazole **3-9** was detected, but only in trace quantities (entry 3). An attempt to replace sodium ascorbate with Cu^{o} [80] was unsuccessful (entry 4), as was the use of stoichiometric Cu(I) (entry 6). Notably, when stoichiometric amounts of $CuSO_4$ were employed (entry 5), starting materials were consumed and a highly insoluble precipitate formed. The use of the H_2O/DMSO cosolvent mixture resulted in the formation of the product in a 12% yield (entry 7), which remained unchanged even in the presence of an excess of aminoazide partner (entry 8). We suspected this material was a copper/product complex and hypothesized that earlier attempts

at catalysis may have been poisoned by amino polyphenol **3-8c**. To fortify the copper catalyst against possible product sequestration, we turned to polydentate ligands reported by Sharpless.[81] Gratifyingly, in the presence of tris((1-benzyl-4-triazolyl)methyl)amine (TBTA), 20 mol% of $CuSO_4$ rapidly catalyzed the cycloaddition of **3-8c** to **3-2** in H_2O/DMSO at room temperature to afford triazole adduct **3-9c** in 52% isolated yield (entry 9). When the catalyst load was decreased from 20 to 5 mol%, isolated yield decreased, and conversion plateaued at roughly 80%.

Table 9. Click optimization studies.



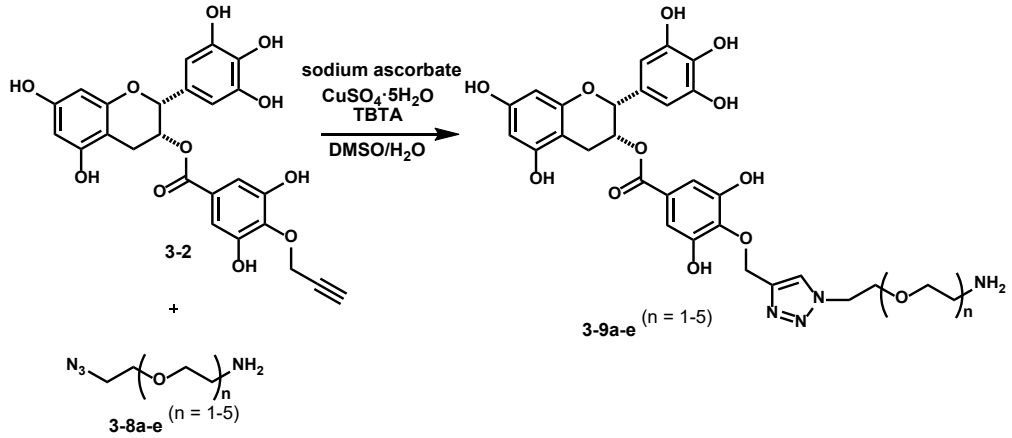
Entry	[Cu]	Additive	Solvent (4:1)	Yield[b]
1	$Cu(OAc)_2$ (0.2 eq.)	-	H_2O/THF	0%
2	$CuSO_4•5H_2O$ (0.2 eq.)	-	H_2O/THF	0%
3	$CuSO_4•5H_2O$ (0.2 eq.)	-	H_2O/^{t}BuOH	trace
4[c]	$CuSO_4•5H_2O$ (0.2 eq.)	-	H_2O/^{t}BuOH	0%
5	$CuSO_4•5H_2O$ (1 eq.)	-	H_2O/^{t}BuOH	-[d]
6[e]	CuBr (1 eq.)	-	H_2O/DMSO	-[f]
7	$CuSO_4•5H_2O$ (0.5 eq.)	-	H_2O/DMSO	12%
8[g]	$CuSO_4•5H_2O$ (0.5 eq.)	-	H_2O/DMSO	12%
9	**$CuSO_4•5H_2O$ (0.2 eq.)**	**TBTA[h]**	**H_2O/DMSO**	**52%**

[a]Reaction conditions: **3-2** (1 mmol), **3-8c** (1 mmol), [Cu], additive (50 mol%), sodium ascorbate (2.0 eq.), solvent (0.1 M), 1 h.
[b]Isolated yield
[c]Cu (powder) was used as a reductant instead of sodium ascorbate
[d]Reaction resulted in the formation of insoluble precipitate
[e]No sodium ascorbate
[f]Complex mixture
[g] 2 mmol of **3-8c** was used
[h]TBTA = tris((1-benzyl-4-triazolyl)methyl)amine

The reactions required no workup, and the product was easily purified as its TFA salt via preparative reversed-phase HPLC (see the experimental section for details).

Using the conditions shown in **Table 9**, entry 9, a set of EGCG conjugates having increasing chain lengths were synthesized (**Table 10**). As the number of glycol units increased, the yield of triazole products **3-9a-e** decreased slightly. But in all cases, analytically pure product was isolated readily using preparative reversed phase HPLC.

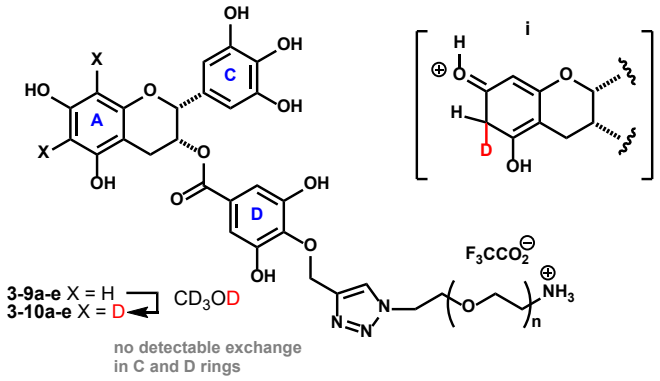
Table 10. Synthesis of PEGylated EGCG derivatives of variable length



Compound	n	Yield(%)[b]
3-9a	1	68
3-9b	2	58
3-9c	3	52
3-9d	4	46
3-9e	5	45

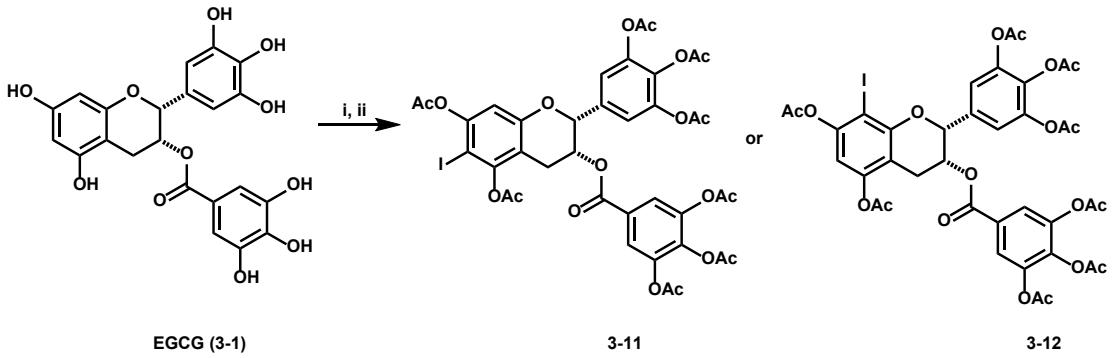
Interestingly, when analyzing amine salts **3-9a-e** by ^{1}H NMR in protic solvents (i.e. CD_3OD or D_2O), the aryl protons in the A-ring (5.93 ppm) quickly disappeared. Their integration (relative to stable resonances) decreased ~75% in 3 hours. Overnight storage of the NMR samples saw the complete disappearance of both signals. HRMS identified the products as [M+1]+2 ions, indicating C-H bonds in the A ring had been replaced by C-D bonds. Notably, C-H bonds in the C and D

rings showed no exchange, even after prolonged storage. Deuteration of flavonoids has been observed in the gas phase by mass spectrometry.[82] Jordheim and coworkers reported anthocyanidin natural products are deuterated in 15 vol % TFA in CD_3OD over a period of days.[83] Rapid deuteration of compounds **3-9a-e** at room temperature may derive from the acidity of their amine salt appendages, wherein deuteration of the A-ring was presumably occurring via a dearomatized species of type i (**Scheme 33**). The A-ring appeared to be considerably more reactive than the C and D rings.



Scheme 33. Rapid and selective A-ring deuteration of EGCG conjugates.

Along those lines, we observed that EGCG itself would react with N-iodo succinimide to rapidly and selectively iodinate the A-ring, although the regiochemistry of the reaction could not be unambiguously assigned (**Scheme 34**). Interestingly, the selectivity of the reaction was heavily dependent on the solvent, as when conducted in acetonitrile or dichloromethane, the selectivity was significantly diminished, in some cases, even completely inverting.



Conditions: (i) NIS (1 eq.), acetone (0.06 M), 1 h; (ii) Ac_2O (0.2 M), pyridine (0.4 M), overnight, 60% over 2 steps

Scheme 34. Selective iodination of EGCG.

This unique reactivity of the A-ring was, while intriguing, also problematic for the characterization of newly synthesized compounds. Even though the compounds are soluble in both d-DMSO and d-Acetone, only d-MeOH provided a clean and easily assignable spectrum. Therefore, rapid NMR analysis was necessary to prevent untimely deuteration and the samples could not be recycled as even after a short storage period (the time it takes to run NMR), the mixture of non- and deuterated substrates was already present. Nevertheless, all of the linker conjugates have been fully characterized and carried forward into biological studies.

We next tested if the D-ring site of triazole-linked amino PEGylation would interfere with tau fibril disaggregation observed for EGCG. AD crude brain extracts have been shown to seed aggregation of fluorescently labeled tau in HEK293 recipient biosensor cells expressing an aggregation-prone fragment of tau called K18[84], and seeding is inhibited by EGCG.[74a]

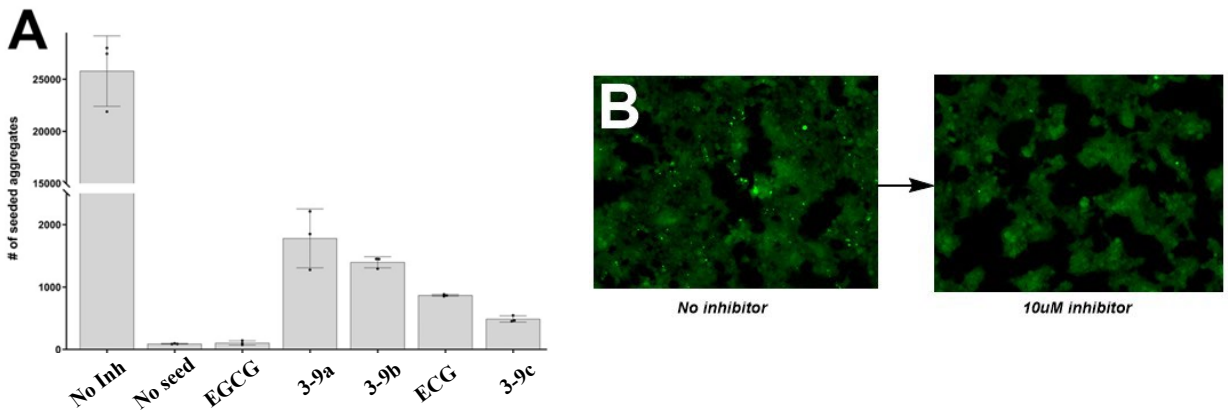


Figure 12. Linker conjugated EGCG analogs retain inhibitory activity towards AD crude brain extracts. (A) Seeding by crude AD brain extract pre-treated with EGCG or experimental linker-conjugated analogs, as indicated. Inhibitor activity is read-out by measuring seeding in tau biosensor cells. Seeding is taken as a proxy for the fibril load that is contained within the AD crude brain extracts. Reduction in fibril load following treatment with experimental linker-conjugated analogs of EGCG reduces prion-like seeding by AD-tau nearly as effectively as EGCG itself. (B) Representative fluorescence images of tau biosensor cells experiments from A. Intracellular aggregates seeded by crude AD brain extracts are identified as puncta (green dots in the "No inhibitor" treated sample, left fluorescence micrograph). Inhibitor treatment reduces the number of puncta (right fluorescence micrograph). The number of puncta as a function of inhibitor pre-treatment is plotted in A.

We compared inhibition of seeding by EGCG and D-ring analogs (**3-9a-c**) as a preliminary proof-of-concept. Crude extract of autopsied brain tissue of a donor with AD was pre-incubated with inhibitors (10 μM final concentration on cells) for 16-18 hours and resulting homogenates were added to the cells for imaging 3 days later. The data obtained is shown in **Figure 12**.

Intracellular tau aggregates are seen as bright green puncta in cells that were seeded with crude AD brain extract in the absence of inhibitor. The number of puncta in inhibitor-treated cells are a proxy used to assess the disaggregating activity of EGCG-linked nanoparticles. To our delight, all of the EGCG-linker conjugates inhibited seeding by AD brain extracts by at least 90% with **3-9c** displaying potency nearly on par with EGCG itself. As a comparison with other analogs of EGCG, we tested ECG, which lacks the *meta*-OH group of the C ring. Consistent with the structure

of EGCG bound to tau, which shows no contact with the *meta*-OH, ECG was seen to inhibit seeding as well as the linker-conjugated analogs and nearly as well as the parent natural product, EGCG. These data demonstrate that D ring derivatizations are well tolerated, consistent with our observation that the D ring remains largely solvent-exposed in the binding cleft of tangled tau filaments from AD brain.

EGCG is subject to off-target binding and rapid metabolism, which restricts its therapeutic potential. We reason that covalent conjugation of EGCG to nanoparticles may reduce binding to metabolic and off-target proteins, which accommodate EGCG inside of buried active sites of globular proteins that are sterically inaccessible to nanoparticle-bound molecules of EGCG. Thus, we sought to synthesize a series of EGCG-nanoparticle conjugates that varied by linker length to identify a minimal linker that retains interaction of EGCG with the solvent exposed binding cleft of fibrillar tau.

Ferumoxytol is an FDA approved carbohydrate-coated iron nanoparticle with widespread use in the clinic with applications ranging from anemia treatment to off-label MR imaging of neurovasculature.[85] We conjugated an expanded series of EGCG bearing linkers of incrementally increasing length, **3-9a-e**, to Ferumoxytol nanoparticles using standard amidation conditions (sulfo-NHS, EDC, 2 h, rt). Unlike previous inclusion-based, labile EGCG nanoparticle formulations that release EGCG at sites of action,[86] we loaded the small molecule via covalent attachment. Covalent conjugation is likely to reduce off-target binding and has added potential to improve potency by exploiting the multivalency of the nanoparticle (each nanoparticle displays ~50 potential linking sites).

We tested the activity of Ferumoxytol conjugated EGCG analogs using the biosensor cell assay described above, except we omitted the pre-incubation step such that our assay more closely resembled the scenario of therapeutic intervention, for which there is no pre-incubation period. Nanoparticle conjugated EGCG derivative was mixed with crude AD brain extract and immediately transfected into tau biosensor cells (**Figure 13**).

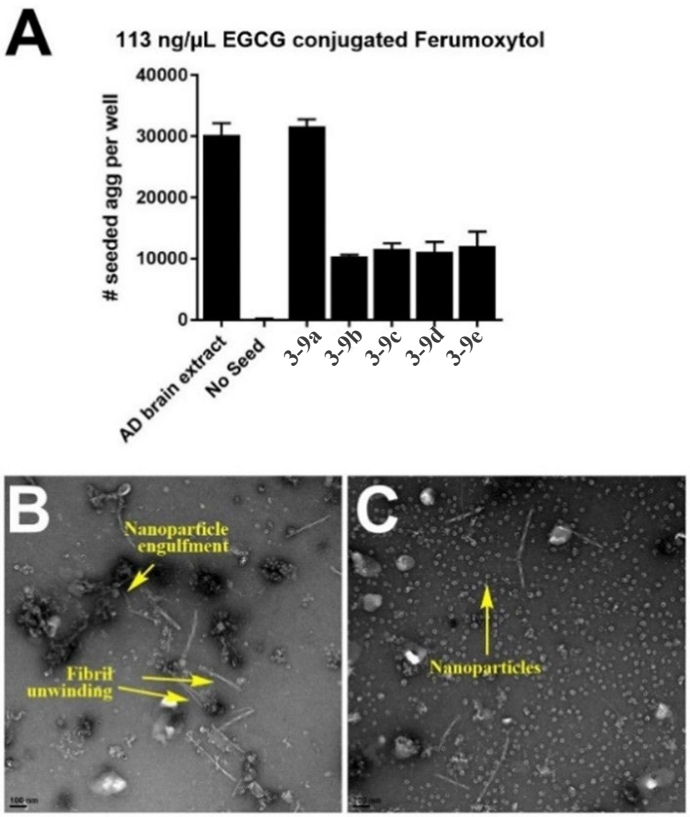
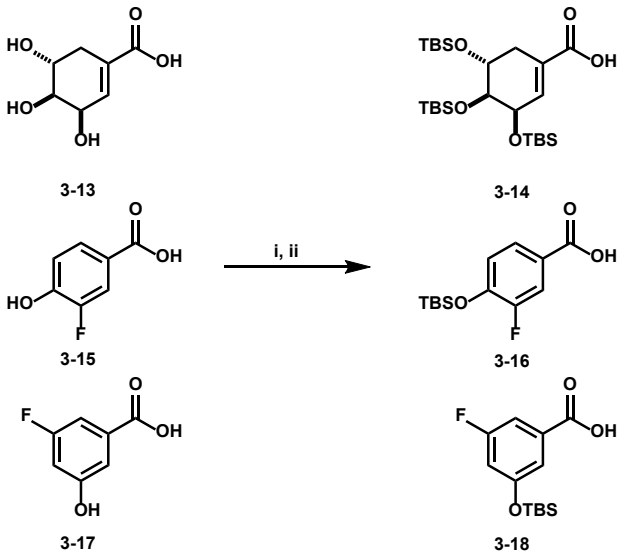


Figure 13. Nanoparticle-conjugated EGCG retains inhibitor activity and clusters with fibrils of AD-tau. (A) Seeding by crude AD brain extract measured in tau biosensor cells that were co-transfected with nanoparticles coupled to EGCG by linkers of varying length. (B-C) Negative-stain electron micrographs of EGCG-conjugated and non-conjugated nanoparticles. Nanoparticle coupled with EGCG analog 5c (B) cluster with fibrils of AD-tau. No clustering is seen between non-conjugated nanoparticles and AD-tau fibrils (C).

We find that all the analogs except for the compound with the shortest linker (**3-9a**) exhibited desired activity inhibiting seeding by at least 50%. Overall, our data demonstrates that nanoparticle conjugates retain the inhibitory properties of the parent compound, and underscores that functional EGCG nanoparticles can be successfully designed based on information that is gleaned from the cryoEM structure. As added evidence of its inhibitory action, we also observed an interesting effect of EGCG nanoparticle incubation with tau paired helical filaments purified from AD brain by negative-stain electron microscopy. Nanoparticles loaded with **3-9c** form dense clouds that engulf AD-tau fibrils, in some cases apparently unwinding the paired helical filament (**Figure 13B**). Non-conjugated control nanoparticles exhibited no apparent interaction with AD-tau fibrils (**Figure 13C**). This confirmed that synthesized amino polyphenolic conjugates retain the ability to disaggregate AD brain-derived tau–both as isolated species and when loaded onto Ferumoxytol nanoparticles. These promising results provide a blueprint for future work wherein further refinements to the EGCG molecule and optimized nanoparticulate formulations could provide means to deliver a potent tau fibril disaggregant to the brains of Alzheimer's patients.

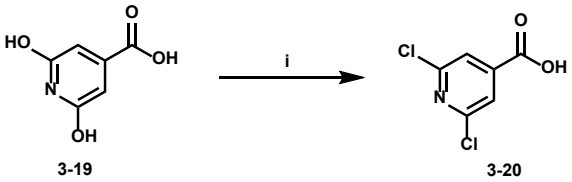
3.3 Synthesis and biological studies of D-ring ester variants of EGCG

The synthesis and conjugation of EGCG derivatives that contained PEGylated linkers at the para-position of the gallate motif indicated that this position was not crucial for the binding interaction between the natural product and tau. However, the observed diminishing activity to that of the parent natural product suggested that the D ring participates in the binding to some extent. This prompted us into studying the importance of the phenols as well as the conformation of the ester. Four alternatives to gallic acids have been synthesized as shown in **Schemes 35 and 36.**



Conditions: (i) TBSCl (5.6 eq.), imidazole (10 eq.), DMF (0.4 M), overnight; (ii) THF (0.065 M), H_2O (0.2 M), CH_3COOH (0.065 M), overnight, 70% over two steps[87].

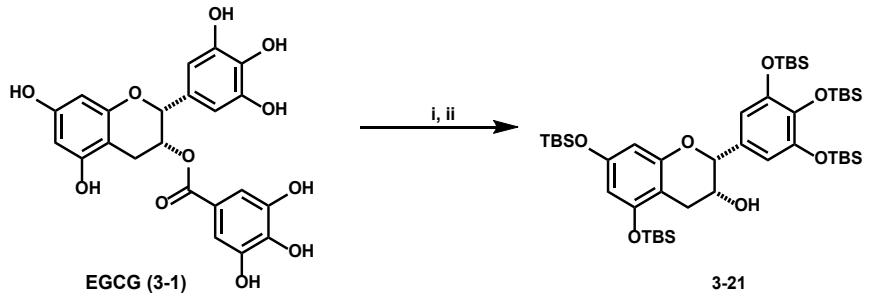
Scheme 35. Synthesis of TBS-protected acids.



Conditions: (i) $POCl_3$, Bu_4NCl, 140 °C, 24 h, 70%[88].

Scheme 36. Synthesis of the 2,6-dichloroisonicotinic acid.

For the alcohol partner, EGCG was converted into TBS-protected EGC in two steps: full protection followed by the LAH reduction[89] (**Scheme 37**).



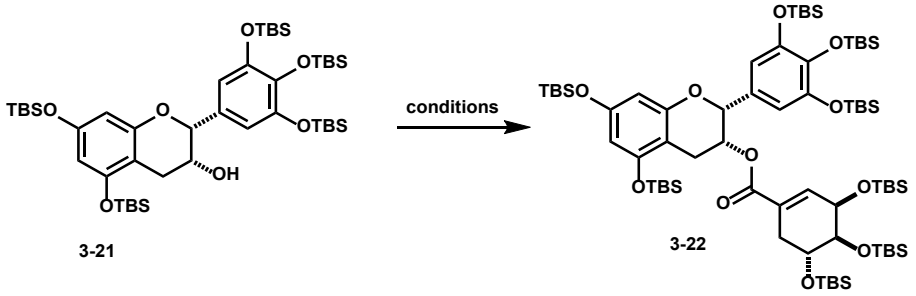
Conditions: (i) TBSCl (20 eq.), imidazole (20 eq.), DMF (0.4 M), overnight; (ii) LAH (2.0 eq.), THF (0.1 M), 3 h, 34% over 2 steps.

Scheme 37. Synthesis of the alcohol for the subsequent esterification.

With both alcohol and acid in hand, esterification was attempted next. However, initial attempts following the literature reports for similar systems[89] afforded no detectable amount of product. It was hypothesized that the steric hindrance of TBS groups impeded the reaction progress. Therefore, optimization studies were conducted on the shikimic variant as it was expected to be the least reactive in the series.

Firstly, conditions were screened to directly couple **3-21** and **3-14** with standard Steglich esterification reagents. However, in the presence of catalytic DMAP and DCC, the reaction gave no product even at elevated temperatures. Only upon addition of 5 eq. of the acid and DCC, and 6 eq. of DMAP the reaction produced the desired product with the full conversion of the starting material. However, an enormous amount of starting acid required as well as the dicyclohexyl urea formed as a byproduct deemed the method impractical.

Table 11. Esterification optimization studies.



Entry	Conditions	Temperature	Solvent	Yield
1	DCC (2 eq.), DMAP (cat.), acid (2 eq.)	rt	DCM	0%
2	DCC (2 eq.), DMAP (cat.), acid (2 eq.)	40 °C	DCM	0%
3	DCC (2 eq.), DMAP (2.0 eq.), acid (2 eq.)	rt	DCM	0%
4	**DCC (5 eq.), DMAP (6.0 eq.), acid (5 eq.)**	**40 °C**	**DCM**	**70%**
5	Yamaguchi reagent (3 eq.), acid (1.5 eq.), DMAP (2.0 eq.), Et_3N (2.4 eq.)	60 °C	Toluene	50%[a]
6[b]	$(COCl)_2$ (1.7 eq.), acid (1.7 eq.), DMAP (2.5 eq.)	40 °C	DCM	0%
7[b]	Ghosez's reagent (1.87 eq.), acid (1.7 eq.), DMAP (2.5 eq.)	40 °C	DCM	%[c]
8[b]	Ghosez's reagent (1.87 eq.), acid (1.7 eq.), DMAP (2.5 eq.)	80 °C	DCE	%[c]
9[b]	Ghosez's reagent (1.87 eq.), acid (1.7 eq.), pyridine (2.5 eq.)	40 °C	DCM	0%
10[b,d]	Ghosez's reagent (1.87 eq.), acid (1.7 eq.), triethylamine (2.5 eq.)	40 °C	DCM	0%
11[b,e]	Ghosez's reagent (1.87 eq.), acid (1.7 eq.), triethylamine (3.0 eq.), DMAP (0.3 eq.)	40 °C	DCM	50%[c]

[a]Based on ^{1}H NMR integration (impurity coelutes with the product).
[b]Acid chloride was pre-formed in the separate flask and then added to the alcohol
[c]Based on ^{1}H NMR conversion of starting material to product
[d]Triethylamine was used as a DMAP substitute
[e]Triethylamine was stirred with alcohol for 30 min before the addition of acid chloride

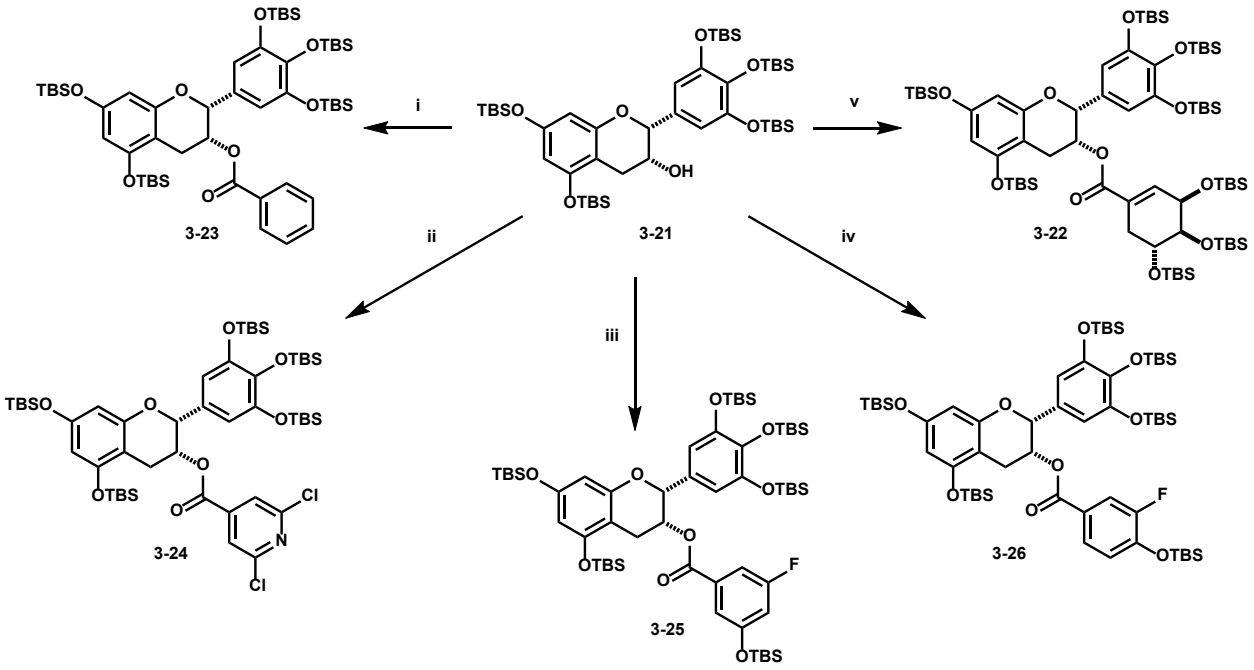
Therefore, alternative conditions were tested. First, Yamaguchi esterification[90] was tried as this reaction proved its utility in a plethora of total syntheses. To our delight, the reaction gave the desired product with just 1.5 eq. of the acid. However, upon purification, an impurity coeluted with the desired product that is hypothesized to come from the Yamaguchi reagent. While, theoretically, this issue could prove to be inconsequential in the long term since final products would be purified by HPLC, we didn't want to carry impure material through the sequence and thus turned our attention to other methods of acid derivatization. Formation of acid chlorides and their subsequent coupling to alcohol in the presence of catalytic DMAP has been a method of choice for decades for the formation of a variety of esters. Dozens of different reagents exist that can cleanly and efficiently convert a carboxylic acid into a corresponding acid chloride with oxalyl chloride being the most common. While oxalyl chloride did indeed convert **3-14** into its acid chloride, the reaction produced HCl in the process and thus had to be concentrated before its addition to the alcohol, increasing the number of manipulations required for this simple reaction. At this point, the successful utilization of Ghosez's reagent[91] for a portimine project pushed us to consider it as an alternative to oxalyl chloride. Gratifyingly, the formation of the acid chloride was clean, and esterification did provide the desired product, albeit with only 50% conversion. None of the attempts to improve the initial result (increase in the amount of reagent, temperature, time) were successful. While there are other methods that could further improve the reaction, for the sake of time, initial modified Steglich conditions were used to produce enough of **3-22** for subsequent studies.

Unexpectedly, when the same conditions were applied to fluorinated hydroxybenzoic acid **3-15** an inseparable impurity was observed in a significant amount with its identity currently

unknown. Fortunately, when Ghosez's method was applied instead, the reaction went cleanly to full completion.

Lastly, in the case of citrazinate and benzoate variants, reported conditions worked well on the first try, delivering the desired product in 80% yield.

Combined conditions for each of the analogs are shown on **Scheme 38**.

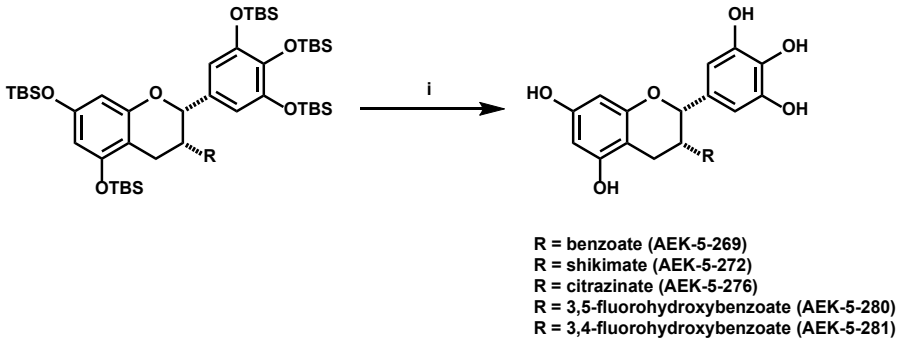


Conditions: (i) benzoic acid (3.0 eq.), DMAP (2.5 eq.), DCC (2.5 eq.), DCM (0.05 M), 2 days, 88%; (ii) **3-20** (2.5 eq.), DMAP (2.2 eq.), DCC (2.2 eq.), DCM (0.05 M), 2 days, 80%; (iii) **3-18** (2.0 eq.), Ghosez's reagent (2.5 eq.), DMAP (2.2 eq.), rt, DCM (0.1 M), overnight, 82%; (iv) **3-16** (1.7 eq.), Ghosez's reagent (1.87 eq.), DMAP (2.5 eq.), DCM (0.1 M), 35 °C, overnight, 75%; (v) **3-14** (5.0 eq.), DCC (5.0 eq.), DMAP (6.0 eq.), DCM (0.1 M), 40 °C, overnight, 80%.

Scheme 38. Synthesis of the TBS-protected D-ring analogs.

With five protected D-ring analogs in hand, the next step was a global deprotection. Several conditions were tested, including TBAF, KHF_2, TFA, HCl, HF•Et_3N, and HF•pyridine. Only the latter two gave the desired product in all five cases. TBAF cleanly deprotected **3-24**, however no

reaction was observed for other variants. Other reagents provided no product even at elevated temperatures (up to 70 °C). The main issue at this step in the sequence was purification due to the extremely high polarity of all five esters especially the ones containing additional phenols in the D-ring. Therefore, HPLC was chosen once again as the best purification method. In the traditional water/acetonitrile solvent system, all five reactions were successfully purified to deliver desired EGCG analogs in a 40-60% yield.



Conditions: (i) HF•pyridine (40 eq.), pyridine (40 eq.), THF (0.04 M), overnight, 40-60%

Scheme 39. Completion of the D-ring series.

Upon completion of the D-ring series, each of the analogs have been subjected to the same biosensor assay as described above. The results are displayed on **Figure 14**. As expected, complete elimination of the ester motif (EGC) or change in the electronics and nature of the ring (citrazinate) essentially kills the activity. Interestingly, however, the trend clearly shows that while important, D-ring phenols are not essential for the compound's disaggregation function as both benzoate and shikimate analogs inhibit seeding by at least 60%.

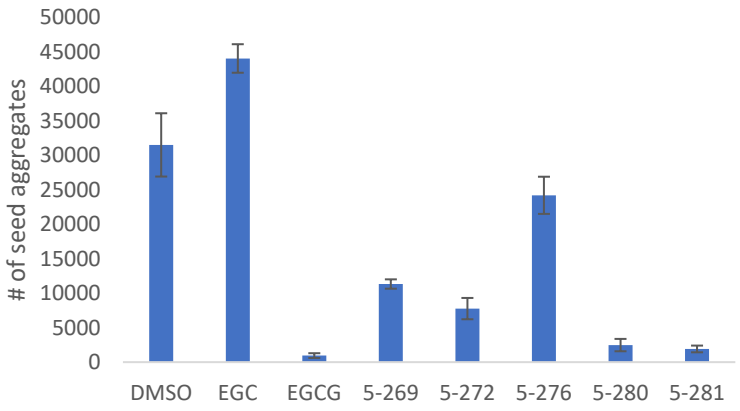


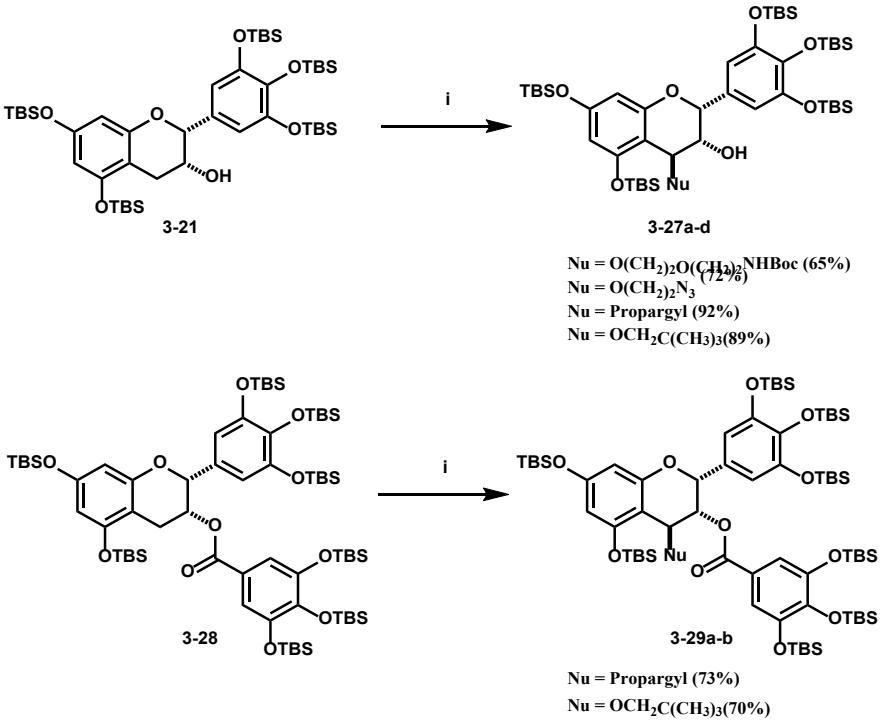
Figure 14. Seeding by crude AD brain extract pre-treated with EGCG or D-ring variants, as indicated. Inhibitor activity is read-out by measuring seeding in tau biosensor cells. Seeding is taken as a proxy for the fibril load that is contained within the AD crude brain extracts.

Nevertheless, the introduction of one phenol at para or meta position improved activity significantly putting both **AEK-5-280** and **AEK-5-281** in the same range of efficacy as EGCG itself. While it is not clear whether fluorination had any positive effect on tau disaggregation, it is expected to improve the analogs' metabolic stability and thus the last two analogs were chosen as the best candidates for the subsequent studies. Additionally, cellular toxicity studies further confirmed that chosen analogs have no detrimental effect on the cells themselves, as even at concentrations up to 5μM, the cell viability remains close to 100%.

3.4 Investigation into B-ring derivatization

All the studies performed up to this moment called for the same conclusion: D ring plays a role in the EGCG-tau binding and thus, while resistant to minor changes (removal of some of the phenols) needs to stay intact to retain the compounds' desired activity. Therefore, another site had to be chosen for linker conjugation that, according to the cryoEM structure would have the minimal effect on the structure and conformation of EGCG. As discussed before, A-ring initially seemed

like the most viable option, however none of the conditions attempted were selective for that specific position. At this time, we have come across a published method for the stereoselective derivatization of the B-ring with a variety of heteroatom-based nucleophiles.[92] We have decided to try to adapt the published methodology to our substrates. To our delight, both TBS-EGC and TBS-EGCG performed well in the reaction involving a range of nucleophiles (**Scheme 40**). The reaction is thought to produce through the formation of the methide quinone that then gets trapped by a nucleophile. The reaction generates a single diastereomer which can be explained by the sterics effect of both hydroxyl (or gallate for EGCG) and C-ring.

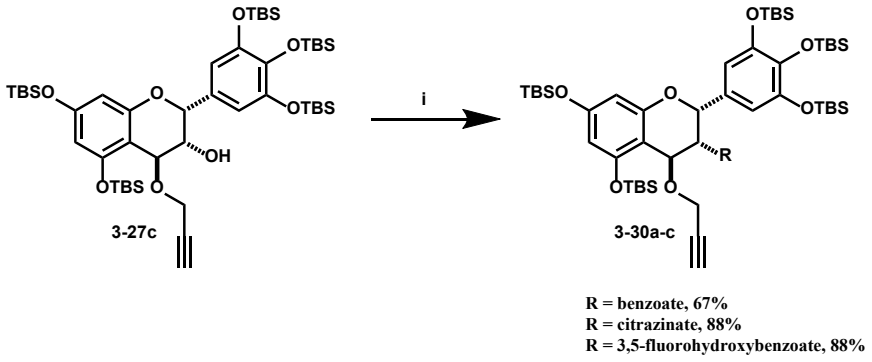


Conditions: (i) Nucleophile (9.0 eq.), DDQ (2.2 eq.), DMAP (2.2 eq.), DCM (0.08 M.), 3 h, 65-92%

Scheme 40. DDQ-mediated B-ring derivatization

Tert-butyl alcohol was the only nucleophile that delivered no product, which was attributed to a well-known sluggishness of tert-butyl alcohol in radical reactions. This is attributed to the low

reactivity of the formed radical due to both high steric hindrance and stability. Besides that, the reaction tolerated Boc-protected amines, azides, and several alcohols (propargyl, neopentyl among others). Both propargyl and azide-based nucleophiles were of particular interest to us due to their potential for the subsequent click reaction with the PEGylated linkers. Therefore, a set of esters were installed onto the alcohol following the same conditions as described above to deliver a set of analogs containing a handle at the B-ring.



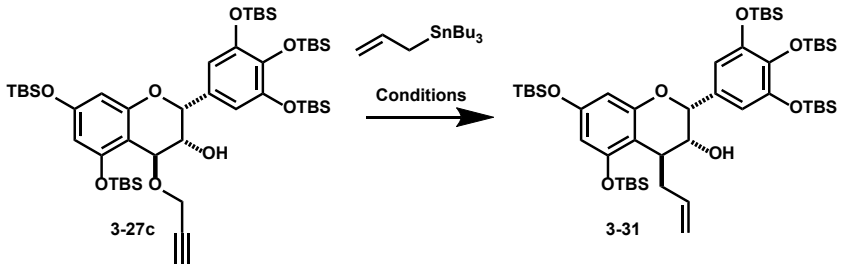
Conditions: (i) For benzoate: benzoic acid (3.0 eq.), DMAP (2.5 eq.), DCC (2.5 eq.), DCM (0.05 M), 2 days, 67%; for citrazinate: **3-20** (2.5 eq.), DMAP (2.2 eq.), DCC (2.2 eq.), DCM (0.05 M), 2 days, 88%; for 3,5-fluorohydroxybenzoate: **3-25** (1.7 eq.), Ghosez's reagent (1.87 eq.), DMAP (2.5 eq.), DCM (0.1 M), 35°C, overnight, 88%

Scheme 41. Esterification of B-ring analogs

With the set of propargylated esters in hand, TBS-deprotection was attempted next. However, under the same conditions as discussed above, the compounds decomposed producing no observable product. Rapid change of color upon the addition of Olah's reagent suggested the formation of the methide quinone which can be explained by the weak C-O bond at the newly created stereocenter. The only solution to this problem was envisioned to be the conversion to the stable C-C bond at the same position. Alharthy *et al.* reported that the propargyl group can be easily substituted by several different carbon-based nucleophiles, including an allyl group which

was of most interest to us.[93] However, all of the reported examples were performed on either Bn or OMe-protected catechins. Nevertheless, we have first attempted to perform the reaction on TBS-variants due to the high efficiency and ease of their synthesis. Unfortunately, none of the Lewis acids (BF_3•Et_2O, $SnCl_2$, $TiCl_4$, TMSOTf) produced any product and resulted in either complete recovery of the starting material or its decomposition (**Table 12**). Therefore, the attention was switched towards the synthesis of the benzylated analogs instead.

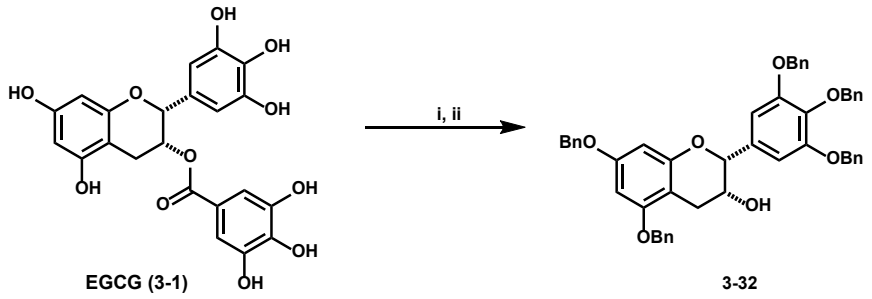
Table 12. Attempted allylation of **3-27c**



Entry	Conditions	Temperature	Observation
1	BF_3•Et_2O	-78 °C	Recovered s.m.
2	BF_3•Et_2O	rt	Recovered s.m.
3	$SnCl_4$	-78 °C	Recovered s.m.
4	$TiCl_4$	-78 °C	Decomposition
5	TMSOTf	-78 °C	Decomposition
6	$FeCl_3$	rt	Decomposition
7[a]	BF_3•Et_2O	-78 °C	Decomposition

[a]allyltrimethylsilane was used instead of allyltributyltin

Benzylated EGC was synthesized according to the published procedure[94] (**Scheme 42**) Benzylation produced a large number of byproducts inseparable by a traditional silica gel chromatography. Only further recrystallization of combined fractions afforded clean material.

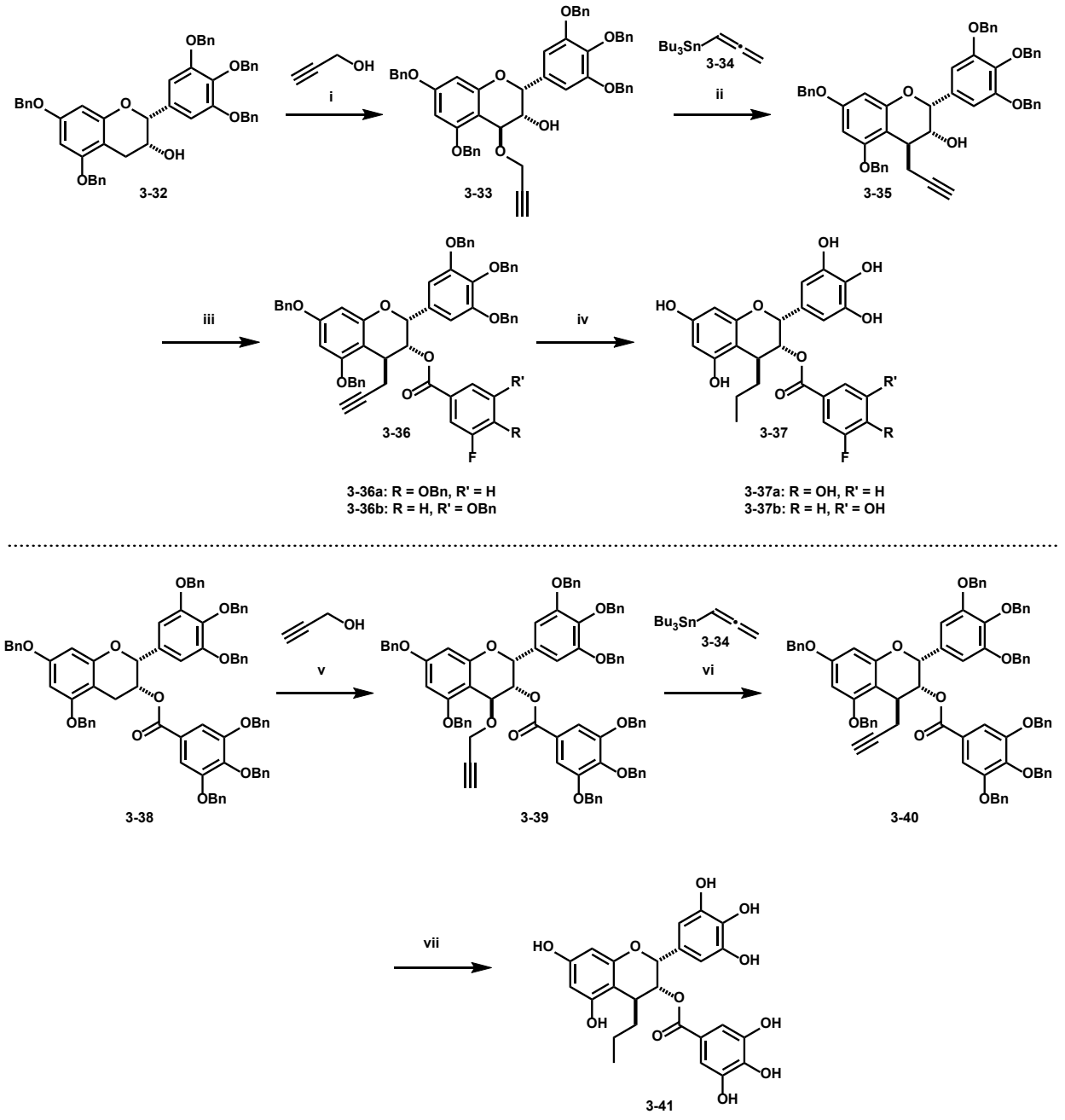


Conditions: (i) BnBr (12 eq.), K_2CO_3 (10 eq.), DMF (0.2 M), overnight, 45%; (ii) K_2CO_3 (8 eq.), DCM/MeOH (1:1. 0.04 M), overnight, 87%

Scheme 42. Synthesis of benzylated EGC**.**

This prompted us to investigate other conditions for the reaction, including different bases (NaH, KO*t*Bu), solvents (CH_3CN, acetone, DMSO), and reagents (BnCl and BnOTs). Unfortunately, all of the attempted conditions produced either no product or resulted in no visible improvement.

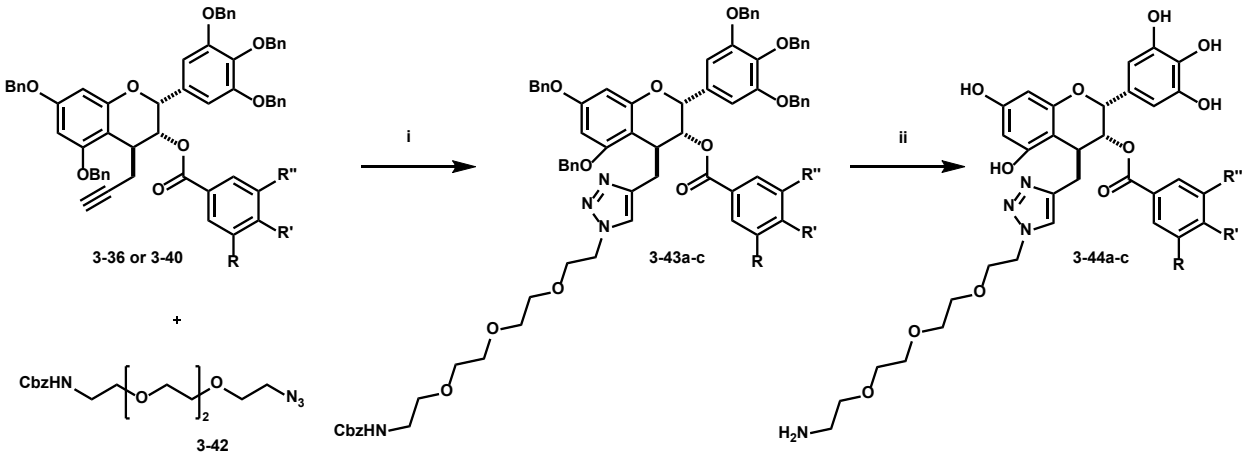
Nevertheless, enough of **3-32** could be synthesized to drive further studies. Subsequent DDQ propargylated performed as discussed above produced **3-33** in 80% yield. Gratifyingly, in the case of the benzylated analog, allylation afforded the desired product in 76% yield. In line with our previous A-ring derivatizations, we wished to install a propargyl unit at the B ring to be utilized in the click cycloaddition. To achieve that, we have synthesized the allene variant of the tin reagent[95] and subjected it to the same BF_3•Et_2O mediated conditions. The reaction worked albeit with slightly lower efficiency producing the product in 51%. The rest of the mass was attributed to the competing dimerization in which the propargyl unit is displaced by another molecule of **3-32**. The side reaction is thought to be temperature-dependent and thus additional optimization studies can alleviate the problem and further improve the reaction. Subsequent esterification was performed following the optimized conditions as discussed in **Section 3.3**.



Conditions: (i) propargyl alcohol (9.0 eq.), DDQ (2.1 eq.), DMAP (2.1 eq.), DCM (0.08 M), 3 h, 74%; (ii) **3-34** (2.4 eq.), BF_3•Et_2O (2.1 eq.), DCM (0.07 M), -78 °C to rt, 1 h, 53%; (iii) acid (1.7 eq.), Ghosez reagent (1.87 eq.), DMAP (2.5 eq.), DCM (0.1 M), 35 °C, overnight, 88%; (iv) $Pd(OH)_2$/C (1.4 eq.), EtOAc (0.01 M), H_2 (balloon), 3 h, 70%; (v) propargyl alcohol (9.0 eq.), DDQ (2.1 eq.), DMAP (2.1 eq.), DCM (0.08 M), 3 h, 86%; (vi) **3-34** (2.4 eq.), BF_3•Et_2O (2.1 eq.), DCM (0.07 M), -78 °C to rt, 1 h, 76%; (vii) $Pd(OH)_2$/C (1.4 eq.), EtOAc (0.01 M), H_2 (balloon), 3 h, 70%

Scheme 43. Synthesis of B-ring alkylated derivatives.

Finally, hydrogenation using Pearlman's catalyst caused global benzyl deprotection as well as alkyne reduction to the corresponding propyl group. The same sequence of reactions was performed on the benzylated EGCG. This sequence demonstrated the feasibility of the B-ring derivatization and thus prompted us to shift the attention towards an installation of the linker at this position.



	R	R'	R"
3-36a	F	OBn	H
3-36b	F	H	OBn
3-40	OBn	OBn	OBn

	R	R'	R"
3-43a	F	OBn	H
3-43b	F	H	OBn
3-43c	OBn	OBn	OBn

	R	R'	R"
3-44a	F	OH	H
3-44b	F	H	OH
3-44c	OH	OH	OH

Conditions: (i) **3-36** or **3-40** (1.0 eq.), $CuSO_4 \bullet 5H_2O$ (0.2 eq.), sodium ascorbate (2.1 eq.), TBTA (0.5 eq.), H_2O/DMSO/THF (1:1:1 0.05 M), overnight, 60-70%%; (ii) Pd/C (1.0 eq.), HCl (60 eq.), H_2 (balloon), MeOH/EtOAc (1:1, 0.01 M), 3 h, 40-50%

Scheme 44. Synthesis of B-ring triazoles.

Our previously published conditions for the click reaction afforded all three analogs in good yield. Interestingly, however, the hydrogenation conditions that worked well for the analogs lacking the linker afforded no product in this case. After minor modifications, we found that switching to Pd/C as well as adding HCl to form the corresponding ammonium salt *in situ* solved the problem and allowed us to produce fully deprotected B-ring conjugates. All of the compounds

exhibited lower toxicity (measured as % cell viability at 50uM of the inhibitor) than that of EGCG showcasing great promise as potential drug candidates (**Figure 15**).

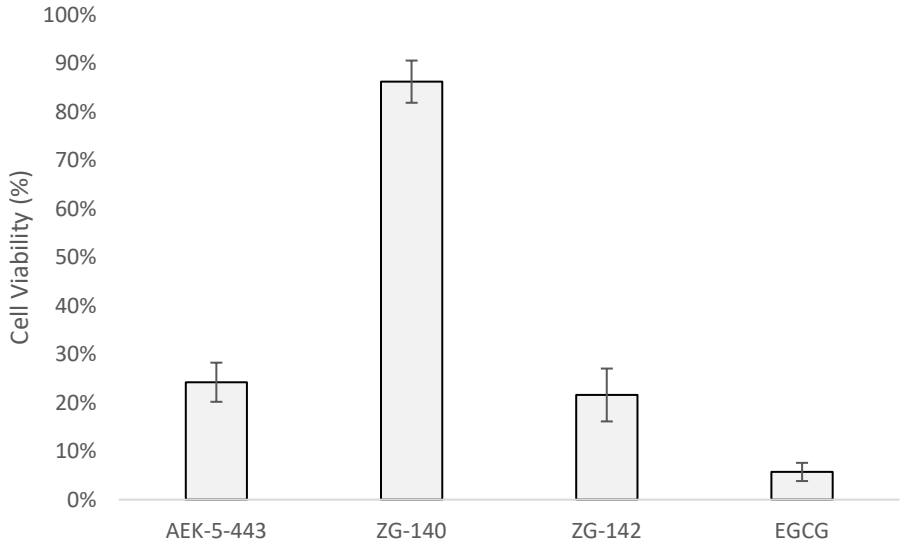


Figure 15. N2A viability at 50 uM of the analog.

Both PEGylated and propylated analogs have been subjected to the same assay as described above. IC50 values were calculated based on the dose-response data with datapoints taken at 0, 0.2, 0.5, 1, 2, 5 and 10 uM analog concentration. Interestingly, all of the propylated analogs exhibited lower IC50 values than that of EGCG itself (4.47 uM), suggesting that the absence of the bulky triazole heterocycle can have a beneficial effect on the aggregation power of the compounds (**Figure 16)**. This prompted us to move our attention towards the synthesis of linear diyne linking systems.

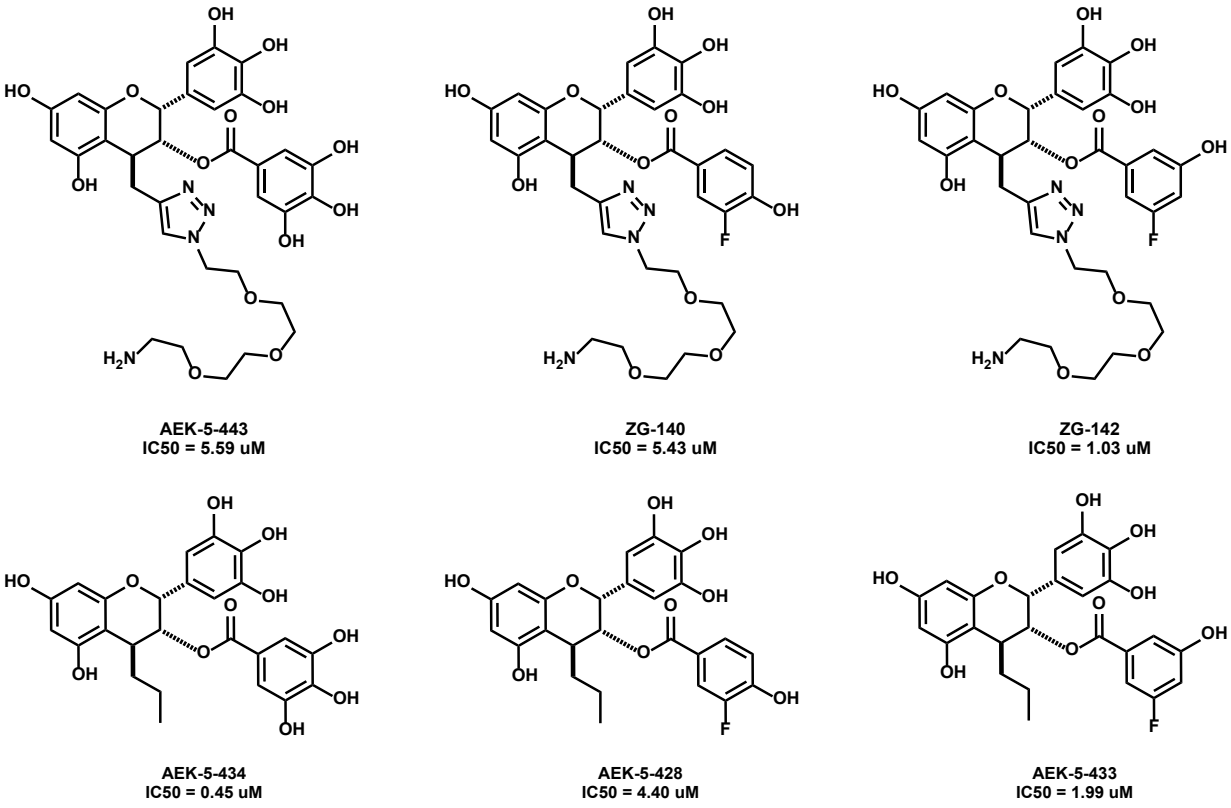
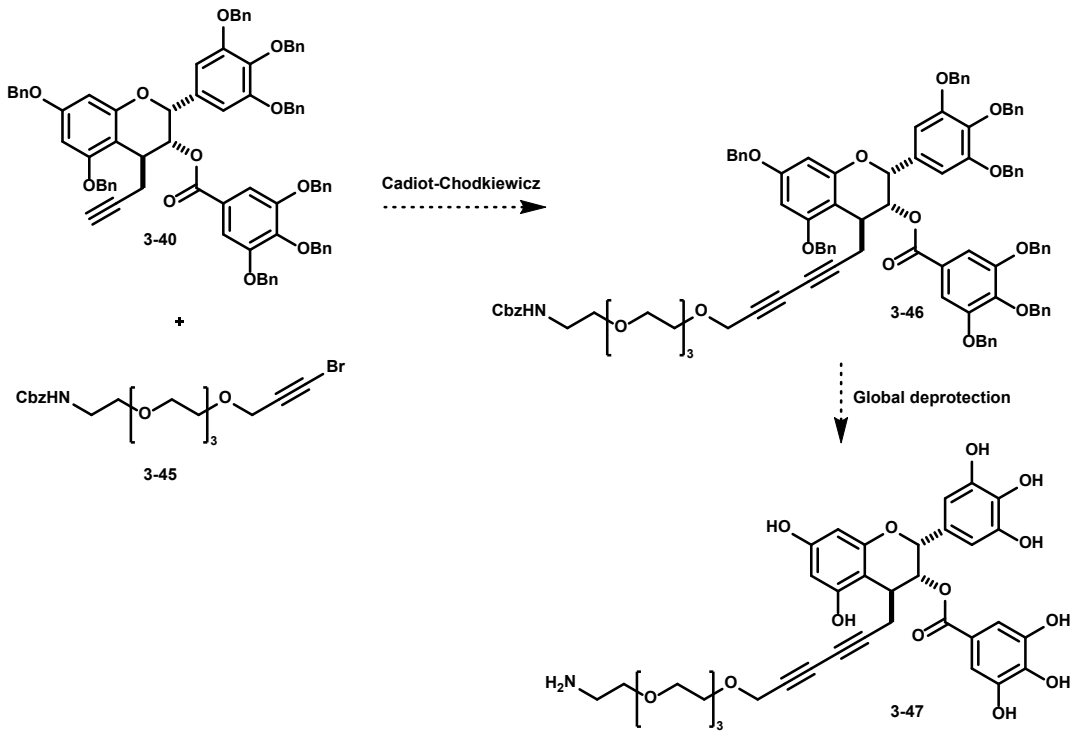
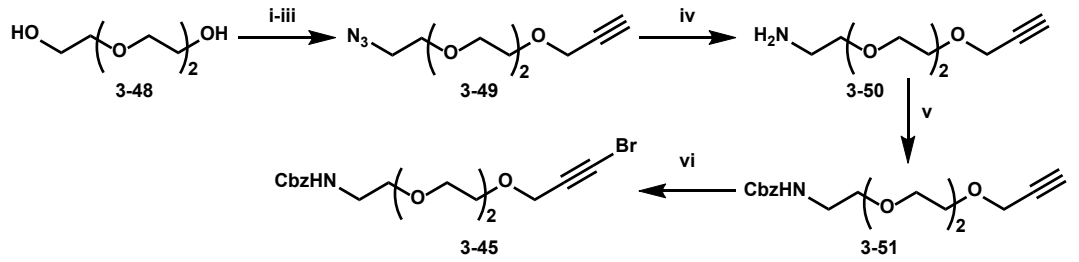


Figure 16. Biological data on B-ring analogs.

Initial biological data suggested that the presence of the triazole has a negative impact on the disaggregation activity of the analogs. This can be confirmed by comparing corresponding propylated derivatives that exhibited lower IC50 than both their triazole analogs as well as EGCG itself. This suggested that the bulky heterocycle is potentially interfering with the EGCG-tau binding and thus its elimination can result in further increase in activity. Therefore, our attention was turned towards the synthesis of linear conjugates. It was envisioned that Cadiot-Chodkiewicz coupling between **3-40** and modified linker **3-45** followed by the global deprotection would be the best method for the installation of the linear diyne system (**Scheme 45**). **3-45** was synthesized according as shown in **Scheme 46**.



Scheme 45. Plan for the synthesis of linear analogs.

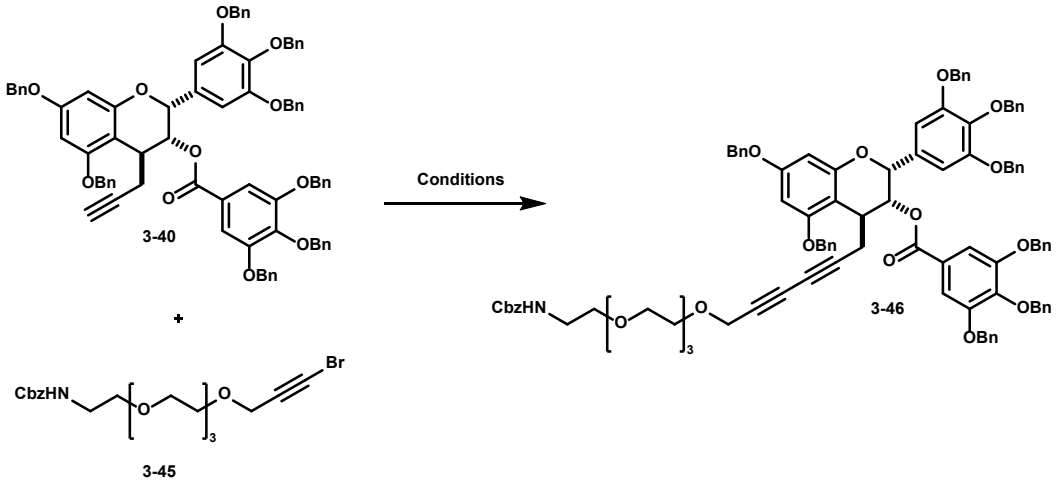


Conditions: (i) **3-48** (2.0 eq.), propargyl bromide (1.0 eq.), NaH (1.3 eq.), THF (2.0 M), overnight 30%; (ii) MsCl (1.2 eq.), Et_3N (1.22 eq.), THF (0.1 M). 45 min; (iii) NaN_3 (1.22 eq.), DMF (0.27 M), 60 °C, overnight, 60% over 2 steps; (iv) 1,3-propanedithiol (7.0 eq.), Et_3N (8 eq.), MeOH (0.1 M), overnight; (v) Cbz-Cl (3.5 eq.), Na_2CO_3 (5.0 eq.), H_2O (0.1 M), 0 °C, 45 min, 90% over 2 steps; (vi) NBS (1.2 eq.), $AgNO_3$ (0.2 eq.), acetone (0.1 M), 4 h.

Scheme 46. Synthesis of **3-45**.

With **3-45** in hand, coupling was attempted next. Optimization studies are shown below in **Table 13**.

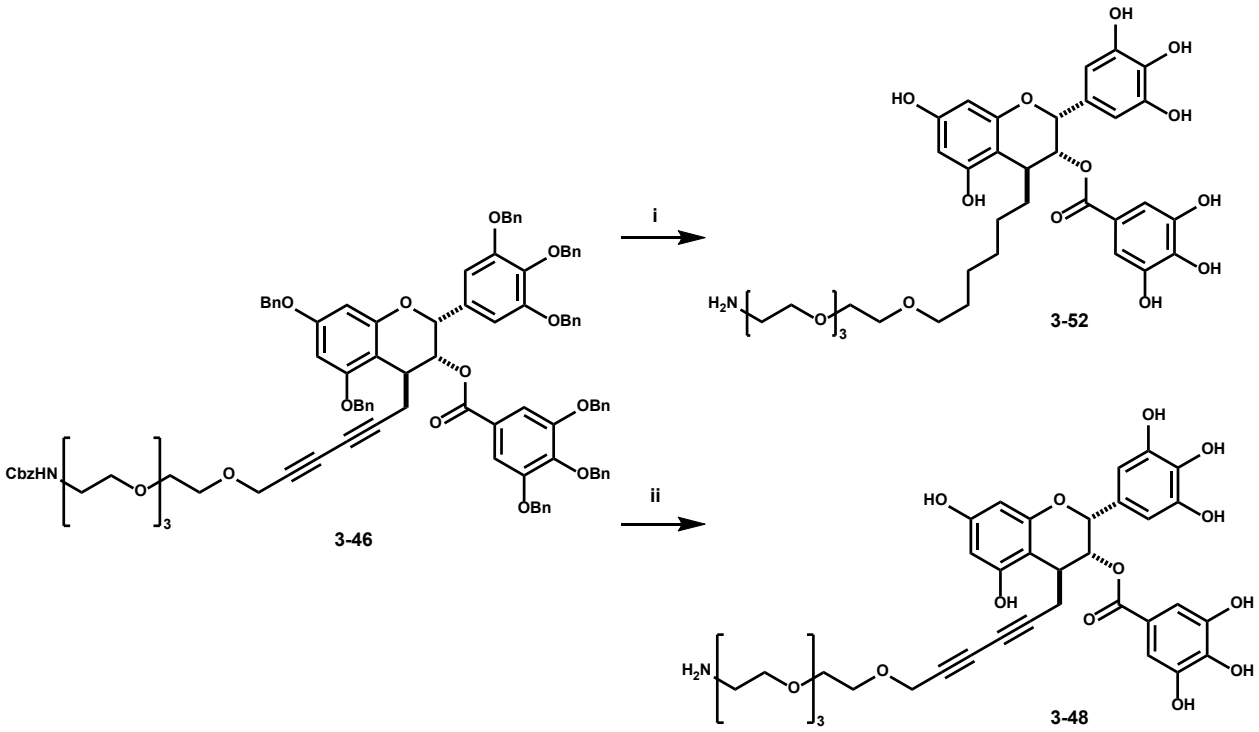
Table 13. Cadiot-Chodkiewicz optimization studies.



Entry	Conditions	Yield
1	$Pd(PPh)_2Cl_2$ (15 mol%), CuI (10 mol%), DIPA	30%[a]
2	$Pd(PPh)_2Cl_2$ (15 mol%), CuI (10 mol%), DIPA, -78 °C to rt	30%[a]
3	CuI (10 mol%), pyrrolidine	No reaction
4	$Pd(PPh)_2Cl_2$ (10 mol%), TBAF (6.0 eq.)	No reaction
5	$(allylPdCl)_2$ (10 mol%), P*t*Bu_3 (40 mol%), DIPA	30%[b]
6	$(allylPdCl)_2$ (10 mol%), P*t*Bu_3 (40 mol%), DIPA, 60 °C	Decomposition
7	$(allylPdCl)_2$ (10 mol%), P*t*Bu_3 (40 mol%), DABCO	Decomposition

[a]~30% of the corresponding homocoupling product was isolated alongside the desired product
[b]no homocoupling product was observed

With **3-46** in hand, deprotection was attempted next. Both hydrogenation to deliver fully saturated linking system as well as a selective BCl_3 promoted de-benzylation developed by Okano *et al.*[96] to maintain the di-yne system were performed and shown in **Scheme 47**. Interestingly, BCl_3 was found to be selective for Bn groups leaving Cbz intact. However, upon the addition of excess TFA, complete deprotection was observed on HPLC-MS (Note: minor amounts of mono- and bis-N-methylated products were detected as well). Currently, the search for the best method for purification and isolation of **3-47** and **3-52** is ongoing.



Conditions: (i) Pd/C (1.0 eq.), HCl (64 eq.), EtOAc/MeOH (1:1, 0.01 M), overnight; (ii) BCl_3 (1.0 M in DCM, 15 eq.), pentamethyl benzene (30 eq.), DCM (0.02 M), -78 °C; then TFA.

Scheme 47. Synthesis of **3-47** and **3-52**.

3.5 Future Directions

Two directions are currently being pursued: one based on the analog conjugation to nanoparticles, and another based on nanobody conjugation. Nanobodies have recently emerged as a superior way of targeted drug delivery compared to the traditional methods.[97] Their low toxicity, small size, and high specificity make them invaluable for the development of cancer therapeutics. Moreover, Eisenberg's lab engineered a nanobody that has been shown to be brain penetrant. A general representation of the current plan is shown in **Figure 17**. Amide coupling of a linker with glutaric anhydride would allow for the installation of the carboxylate as the linker terminus. This would allow for the conjugation with the lysine residues on the nanobody of which there are

multiple. In addition, the installation of the cleavable linker such as the one present in Enhertu® would allow for the protease cleavage of the conjugates after being delivered to the brain.

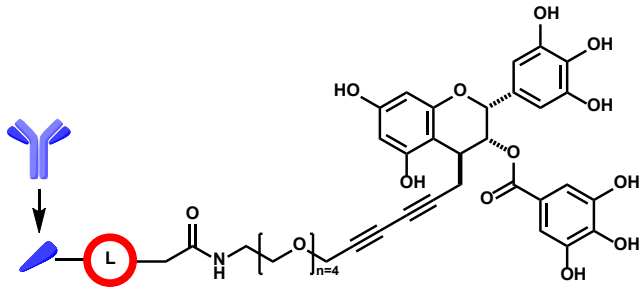


Figure 17. General representation of an EGCG analog conjugated to a nanobody.

3.6 Conclusion

In summary, both B- and D-ring derivatization of EGCG have been reported. Initial nanoparticle conjugation studies of D-ring linkers were successful showcasing its potential and further confirming our initial hypothesis on EGCG's mode of action. Modifications to the D-ring shed light on the importance of the aromaticity and gallate phenols as well as allowed for the installation of fluorine which is expected to have a beneficial effect on the metabolic stability of the analogs. B-ring derivatization allowed for the simultaneous installation of the linker and replacement of the gallate without sacrificing the activity of the parent natural product. Developed methodology will allow for the exploration of multiple proposed directions towards a more stable and more active analog that will drive further studies into the development of Alzheimer's therapeutics.

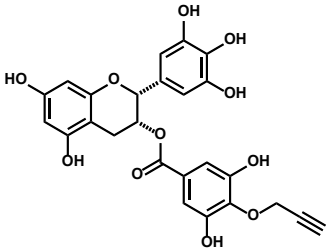
3.7 Experimental Section

3.7.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under positive pressure of argon at room temperature. The dry solvents were dried using activated alumina solvent drying system. Methanol (MeOH) was dried over activated 3Å molecular sieves. Thin layer chromatography (TLC) was performed on pre-coated plates Sorbent Technologies, silica gel 60 PF_{254} (0.25 mm). TLC were visualized with UV light (254 nm) or stained using $KMnO_4$ or cerium ammonium molybdate (CAM). Flash chromatography was performed on silica gel 60 (240-400 mesh). The photochemistry experiments were conducted in an RPR-100 Photochemical Reactor (Rayonet©) using 300 nm fluorescent tubes. NMR spectra were recorded on a Bruker Avance (500 MHz) spectrometer using $CDCl_3$, CD_3OD or Acetone-d6 as solvent and referenced relative to residual $CHCl_3$ (δ = 7.26 ppm), CD_3OD (δ = 3.31 ppm) or Acetone-d6 (δ = 2.05 ppm). Chemical shifts are reported in ppm and coupling constants (*J*) in Hertz. ^{13}C NMR and APT spectra were recorded on the same instruments (125 MHz) with total proton decoupling referenced relative to residual $CHCl_3$ (δ = 77.16 ppm), CD_3OD (δ = 49.0 ppm) or Acetone-d6 (δ = 29.84 and 206.26 ppm). HSQC, HMBC, COSY and NOESY NMR experiments were used to aid assignment of NMR peaks when required. All melting points are uncorrected. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. High-resolution mass spectra were recorded on Thermo Scientific Exactive® Mass Spectrometer with DART ID-CUBE Waters GST Premier, and Waters LCT Premier. Optical rotations were measured on a Rudolph Autopol III Automatic Polarimeter and are quoted in units of 10^{-1} deg cm^2 g^{-1}.

3.7.2 Experimental Procedures

(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 3,5-dihydroxy-4-(prop-2-yn-1-yloxy)benzoate and (2R,3R)-2-(3,5-dihydroxy-4-(prop-2-yn-1-yloxy)phenyl)-5,7-dihydroxychroman-3-yl 3,5-dihydroxy-4-(prop-2-yn-1-yloxy)benzoate (3-2)



To NaH (15.7 mg, 0.65 mmol, 1.5 eq.) at 0 °C was added a solution of EGCG (200 mg, 0.44 mmol, 1.0 eq.) in dry DMF (1.45 mL, 0.3 M). The resulting mixture was stirred at room temperature for 30 minutes. Propargyl bromide (53 μL, 0.48 mmol, 1.1 eq., 80% w/w) was then added and the reaction was heated to 80 °C and stirred overnight. Upon cooling to room temperature, the reaction was concentrated in vacuo and subjected to flash column chromatography (silica gel, $CHCl_3$/MeOH 100:0 to 15:1 to 13:1 to 11:1). Desired mono-propargylated product (TLC: $CHCl_3$/MeOH 8:2, R_f = 0.3) was obtained in 33% yield (72 mg) (decomposes at >120 °C), $[\alpha]_D^{21}$= -162.0˚ (*c* = 0.1, MeOH) along with 15% of bispropargylated product (R_f = 0.6), $[\alpha]_D^{21}$= -133.0˚ (*c* = 0.1, MeOH) as white solids.

Monopropargylated product (**3-2**):

FT-IR (neat): 3358, 3290, 2124, 1697, 1606, 1522, 1454, 1371, 1347, 1242, 1196, 1147, 1056, 1039, 1017, 826, 769, 640 cm–1.

^{1}H NMR (500 MHz, CD_3OD): δ = 6.89 (s, 2 H, Gal H-2, H-6), 6.47 (s, 2 H, H-2', H-6'), 5.93 (s, 2 H, H-6, H-8), 5.52 (m, 1 H, H-3), 4.95 (s, 1 H, H-2), 4.76 (d, J = 2.4 Hz, 2 H, OCH2R), 2.99-2.94 (dd, J = 17.3, 4.5 Hz, 1 H, H-4α), 2.85-2.80 (dd, J = 17.3, 2.3 Hz, 1 H, H-4β), 2.77 (t, J = 2.4 Hz, 1 H, ≡CH).

^{13}C NMR (125 MHz, CD_3OD): δ = 165.7, 156.5, 156.4, 155.8, 150.5, 145.3, 137.0, 132.4, 129.3, 125.7, 108.7, 105.4, 97.9, 95.2, 94.5, 78.6, 77.1, 75.3, 68.9, 58.6, 25.4.

HRMS (ESI): m/z calcd for $C_{25}H_{20}O_{11}$ $[M+H]^+$: 497.1039; found: 497.1102.

Bispropargylated product (**3-3**):

FT-IR (neat): 3359, 3282, 2926, 2858, 2362, 2124, 1695, 1601, 1519, 1451, 1363, 1235, 1174, 1142, 1049, 1014, 982, 754, 736, 711,632 cm–1.

^{1}H NMR (500 MHz, CD_3OD): δ = 6.88 (s, 2 H, Gal H-2, H-6), 6.50 (s, 2 H, H-2', H-6'), 5.94 (s, 2 H, H-6. H-8), 5.55 (m, 1 H, H-3), 4.99 (s, 1 H, H-2), 4.76 (d, J = 2.4 Hz, 2 H, OCH2R), 4.66 (d, J = 2.4 Hz, 2 H, OCH2R'), 3.01-2.95 (dd, J = 17.4, 4.6 Hz, 1 H, H-4α), 2.86-2.81 (dd, J = 17.3, 2.2 Hz, 1 H, H-4β), 2.77 (t, J = 2.4 Hz, 1 H, ≡CH), 2.71 (t, J = 2.4 Hz, 1 H, ≡CH').

^{13}C NMR (125 MHz, CD_3OD): δ = 165.6, 156.6, 156.5, 155.6, 150.5, 150.4, 137.0, 134.8, 132.3, 125.6, 108.7, 105.5, 97.9, 95.2, 94.5, 79.0, 78.6, 78.1, 75.3, 75.0, 68.8, 58.8, 58.6, 26.4.

HRMS (ESI): m/z calcd for $C_{28}H_{23}O_{11}$ $[M+H]^+$: 535.1240 ; found: 535.1252.

Alternative procedure (using K_2CO_3/DMF)

To EGCG (1 g, 2.18 mmol, 1.0 eq.) in DMF (11 mL, 0.2 M) at 0 °C was added K_2CO_3 (166 mg, 1.2 mmol, 0.5 eq.) in one portion. The reaction was stirred at room temperature for 1 hour. Propargyl bromide (0.24 mL, 2.18 mmol, 1.1 eq., 80% w/w) was then added and the reaction was stirred at the same temperature overnight. The mixture was then concentrated in vacuo and purified as above furnishing the product in 45% yield (491 mg) along with 10 % of bispropargylated side product. All the analytical data matched the one obtained using an original procedure.

Preparation of amino azides x; General Procedure 1.

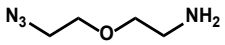
The corresponding diol (1.0 eq.) was dissolved in DCM (0.6 M), followed by the addition of TsCl (2.1 eq.). The reaction was cooled to 0 °C. KOH (8.0 eq.) was then added in one portion, the reaction was warmed to room temperature and stirred for 4 hours. The mixture was then diluted with H_2O (100 mL) and extracted with DCM (3x100 mL). The combined organic layers were dried

($MgSO_4$), filtered and concentrated in vacuo. The crude white solid was used directly in the next step.

To the crude bis-tosylate (1.0 eq.) in DMF (0.6 M) under Ar was added NaN_3 (4.0 eq.). The reaction was stirred overnight at 80 °C. The mixture was then cooled to room temperature, diluted with H_2O (100 mL) and extracted with EtOAc (3x100 mL). Combined organic layers were washed with H_2O (2x50 mL), brine (2x50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting bis-azide was used directly in the next step without purification.

Crude bis-azide from the previous step (1.0 eq.) was dissolved in THF/Et_2O/H_2O (5/1/5, 0.6 M). PPh_3 (1.0 eq.) in Et_2O (0.7 M) was then added over 1 hour using a syringe pump. The resulting solution was stirred at room temperature overnight at which time precipitate formation was observed. The reaction was diluted with H_2O (100 mL) and washed with Et_2O (3x100 mL). The aqueous layer was then basified via the addition of solid NaOH to pH=11 and extracted with DCM (3x100 mL). Combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product (TLC: DCM/MeOH 8:2 R_f = 0.2) was purified via flash column chromatography (silica gel, DCM/MeOH/Et_3N 100:0:0 to 90:10:0 to 80:10:10) to give the desired amino azide.

2-(2-azidoethoxy)ethan-1-amine (3-8a)[98]



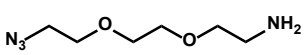
Compound was prepared according to **General Procedure 1**.

Yield: 90%, yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.65 (t, J = 5.0 Hz, 2 H, 4-H), 3.54 (t, J = 5.1 Hz, 2 H, 2-H), 3.38 (t, J = 5.0 Hz, 2 H, 5-H), 2.90 (t, J = 5.1 Hz, 2 H, 1-H), 2.40 (s, 2 H, NH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 72.7, 70.0, 50.7, 41.6.

2-(2-(2-azidoethoxy)ethoxy)ethan-1-amine (3-8b)[99]



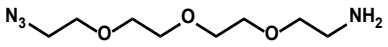
Compound was prepared according to **General Procedure 1**.

Yield: 90%, yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.68-3.63 (m, 6 H, 4-H, 5-H, 8-H), 3.53 (t, *J* = 5.0 Hz, 2 H, 2-H), 3.39 (t, *J* = 5.2 Hz, 2 H, 6-H), 2.88 (t, 5.0 Hz, 2 H, 1-H), 2.17 (s, 2 H, NH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 73.0, 70.7, 70.3, 70.1, 50.7, 41.6.

2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethan-1-amine (3-c)[100]



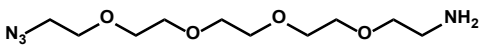
Compound was prepared according to **General Procedure 1**.

Yield: 85%, yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.68-3.60 (m, 10 H, 3-H, 4-H, 5-H, 6-H, 7-H), 3.50 (t, *J* = 5.1 Hz, 2 H, 2-H), 3.39 (t, *J* = 5.1 Hz, 2 H, 8-H), 2.86 (t, *J* = 5.1 Hz, 2 H, 1-H), 1.89 (s, 2 H, NH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 73.1, 70.71, 70.66, 70.6, 70.3, 70.1, 50.7, 41.7.

14-azido-3,6,9,12-tetraoxatetradecan-1-amine (3-8d)[101]



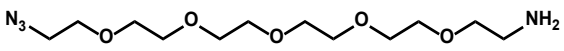
Compound was prepared according to **General Procedure 1**.

Yield: 73%, yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.72-3.60 (m, 14 H, 3-H, 4-H, 5-H, 6-H, 7-H, 8-H, 9-H), 3.55 (t, *J* = 3.0 Hz, 2 H, 2-H), 3.38 (t, *J* = 4.7 Hz, 2 H, 10-H), 2.90 (t, *J* = 4.7 Hz, 2 H, 1-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 71.9, 70.7-70.0 (wide peak), 50.7, 41.4.

17-azido-3,6,9,12,15-pentaoxaheptadecan-1-amine (3-8e)[102]



Compound was prepared according to **General Procedure 1**.

Yield: 70%, yellow oil.

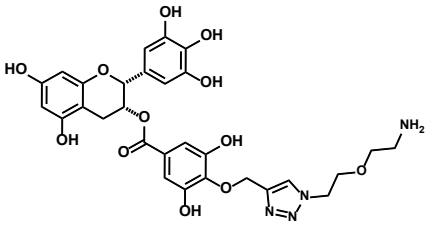
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.96 (t, *J* = 3.2 Hz, 2 H, 11-H), 3.62-3.80 (m, 18 H, 2-H, 3-H, 4-H, 5-H, 6-H, 7-H, 8-H, 9-H, 10-H), 3.50 (t, *J* = 4.90 Hz, 2 H, 12-H), 3.15 (t, *J* = 4.90 Hz, 2 H, 1-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 70.6-69.8 (wide peak), 66.9, 50.7, 40.6.

Click reaction with PEGylated linkers; General Procedure 2.

To a flame-dried microwave vial was added **3-2** (40 mg, 0.081 mmol, 1.0 eq) and the corresponding azide (0.081 mmol, 1.0 eq.). In a separate vial, a solution of $CuSO_4$•$5H_2O$ (4 mg, 0.016 mmol, 0.2 eq.), sodium ascorbate (34 mg, 0.17 mmol, 2.0 eq.), TBTA (21 mg, 0.04 mmol, 0.5 eq.) in DMSO/H_2O (4:1, 0.81 mL, 0.1 M) was prepared and added to the first flask. The reaction was stirred at room temperature for 1 h. The crude mixture was purified by preparative reverse-phase HPLC (33-60% MeCN/H_2O + 0.1% (v/v) TFA in 8.5 min) to give the title compounds (t_R = 5.2 min).

(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 4-((1-(2-(2-aminoethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dihydroxybenzoate (3-9a)



Compound was prepared according to **General Procedure 2**.

Yield: 35 mg, 68%, white solid. $[\alpha]_D^{21}$ = -81˚ (*c* = 0.1, MeOH).

FT-IR (neat): 3374, 2951, 2934, 1676, 1626, 1523, 1448, 1370, 1196, 1146, 1061, 1015, 770, 724, 650, 612 cm^{-1}

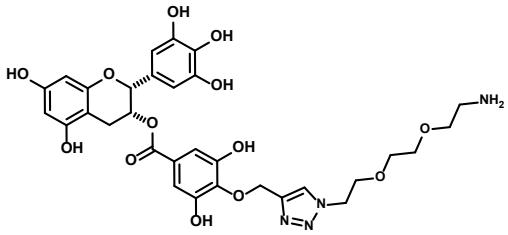
^{1}H NMR (500 MHz, CD_3OD): δ = 7.88 (s, 1 H, triazole-H), 6.87 (s, 2 H, Gal H-2, H-6), 6.50 (s, 2 H, H-2', H-6'), 5.95 (s, 2 H, H-6, H-8), 5.54 (m, 1 H, H-3), 5.25 (s, 2 H, O**CH_2**R), 4.97 (s, 1 H, H-2), 4.56 (t, *J* = 4.8 Hz, 2 H, N-**CH_2**$CH_2OCH_2CH_2NH_2$), 3.83-3.75 (m, 2 H, N-

CH_2**CH_2**$OCH_2CH_2NH_2$), 3.50-3.48 (m, 2 H, N-CH_2CH_2O**CH_2**CH_2NH_2), 3.01-2.97 (m, 3 H, N-$CH_2CH_2OCH_2$**CH_2**NH_2, and H-4α), 2.86-2.82 (dd, *J* = 17.3, 2.2 Hz, 1 H, H-4β).

^{13}C NMR (125 MHz, CD_3OD): δ = 165.6, 156.5, 156.5, 155.8, 150.4, 145.3, 137.1, 132.3, 129.4, 125.7, 124.9, 108.8, 105.4, 97.8, 95.1, 94.5, 77.0, 69.1, 69.0, 66.3, 63.9, 49.9, 39.0, 25.4.

HRMS (ESI): m/z calcd for $C_{29}H_{32}N_4O_{12}$ $[M+H]^+$: 627.1938; found: 627.1954.

(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 4-((1-(2-(2-(2-aminoethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dihydroxybenzoate (3-9b)



Compound was prepared according to **General Procedure 2**.

Yield: 32 mg, 58%, white solid. $[\alpha]_D^{21}$ = -73˚ (*c* = 0.1, MeOH).

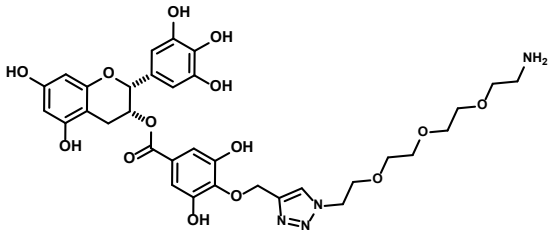
FT-IR (neat): 3170, 2964, 2952, 1678, 1627, 1609, 1523, 1450, 1376, 1347, 1201, 1146, 1058, 1039, 969, 836, 720, 677, 602 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.90 (s, 1 H, triazole-H), 6.88 (s, 2 H, Gal H-2, H-6), 6.50 (s, 2 H, H-2', H-6'), 5.95 (s, 2 H, H-6. H-8), 5.53-5.52 (m, 1 H, H-3), 5.26 (s, 2 H, O**CH_2**R), 4.97 (s, 1 H, H-2), 4.52-4.50 (t, *J* = 4.6 Hz, 2 H, N-**CH_2**$CH_2OCH_2CH_2OCH_2CH_2NH_2$), 3.82-3.73 (m, 2 H, N-$CH_2$**$CH_2$**$OCH_2CH_2OCH_2CH_2NH_2$), 3.50-3.48 (m, 2 H, N-$CH_2CH_2OCH_2CH_2O$**$CH_2$**$CH_2$ NH_2), 3.41 (m, 4 H, N-CH_2CH_2O**CH_2CH_2**$OCH_2CH_2NH_2$), 3.02-2.96 (m, 3 H, N-$CH_2CH_2OCH_2$ CH_2OCH_2**CH_2**NH_2, and H-4α), 2.86-2.82 (dd, *J* = 18.1, 1.9 Hz, 1 H, H-4β).

^{13}C NMR (125 MHz, CD_3OD): δ = 165.6, 156.54, 156.46, 155.8, 150.4, 145.3, 137.1, 132.3, 129.4, 125.6, 108.9, 105.3, 97.8, 95.1, 94.5, 77.0, 70.1, 69.8, 68.98, 68.95, 66.3, 63.8, 53.7, 50.1, 39.3, 25.5.

HRMS (ESI): m/z calcd for $C_{31}H_{35}N_4O_{13}$ $[M+H]^+$: 671.2201; found: 671.2170

(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 4-((1-(2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dihydroxybenzoate (3-9c)



Compound was prepared according to **General Procedure 2**.

Yield: 30 mg, 52%, white solid. $[\alpha]_D^{21}$ = -62˚ (*c* = 0.1, MeOH).

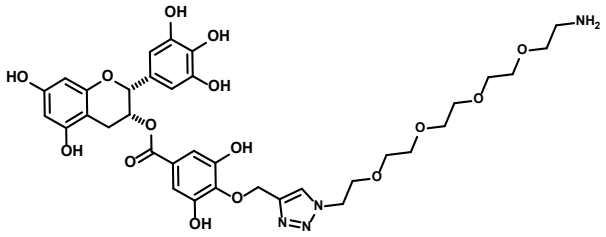
FT-IR (neat): 3203, 2970, 1674, 1602, 1523, 1437, 1368, 1200, 1143, 1060, 981, 831, 718, 647, 622, 610 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.87 (s, 1 H, triazole-H), 6.89 (s, 2 H, Gal H-2, H-6), 6.50 (s, 2 H, H-2', H-6'), 5.94 (s, 2 H, H-6. H-8), 5.54-5.53 (m, 1 H, H-3), 5.25 (s, 2 H, O**CH_2**R), 4.97 (s, 1 H, H-2), 4.52 (t, *J* = 4.9 Hz, 2 H, N-**CH_2**$CH_2(OCH_2CH_2)_2OCH_2CH_2NH_2$),), 3.81-3.73 (m, 2 H, N-CH_2**CH_2**$(OCH_2CH_2)_2OCH_2CH_2NH_2$), 3.59-3.57 (m, 2 H, N-$CH_2CH_2(OCH_2CH_2)_2OCH_2$**$CH_2$** NH_2), 3.54-3.47 (m, 4 H, N-$CH_2CH_2(O$**CH_2**$CH_2)_2OCH_2CH_2NH_2$, 3.45-3.42 (m, 4 H, N-CH_2CH_2 $(OCH_2$**CH_2**$)_2OCH_2CH_2NH_2$), 3.07-3.05 (t, *J* = 5.5 Hz, 2 H, N-$CH_2CH_2(OCH_2CH_2)_2OCH_2$**$CH_2$** NH_2), 3.01-2.96 (dd, *J* = 17.3, 4.5 Hz, 1 H, H-4α), 2.86-2.82 (dd, *J* = 17.3, 2.3 Hz, 1 H, H-4β).

^{13}C NMR (125 MHz, CD_3OD): δ = 165.6, 156.54, 156.48, 155.8, 150.4, 145.3, 137.0, 132.3, 129.4, 125.6, 124.9, 108.9, 105.3, 97.8, 95.1, 94.5, 77.0, 70.0, 69.9, 69.6, 69.0, 66.3, 63.9, 50.1, 39.3, 25.5.

HRMS (ESI): m/z calcd for $C_{33}H_{38}N_4O_{14}Na$ $[M+Na]^+$: 737.2282; found: 737.2308

(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 4-((1-(14-amino-3,6,9,12-tetraoxatetradecyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dihydroxybenzoate (3-9d)



Compound was prepared according to **General Procedure 2**.

Yield: 28 mg, 46%, white solid. $[\alpha]_D^{21}$ = -69˚ (c = 0.1, MeOH).

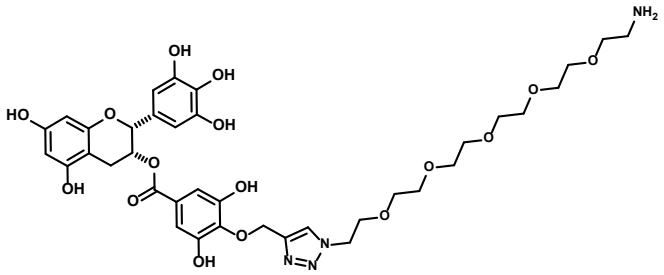
FT-IR (neat): 3179, 2926, 1681, 1627, 1523, 1451, 1372, 1349, 1203, 1146, 1061, 1038, 831, 726, 641, 618 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.90 (s, 1 H, triazole-H), 6.87 (s, 2 H, Gal H-2, H-6), 6.48 (s, 2 H, H-2', H-6'), 5.93 (s, 2 H, H-6. H-8), 5.52-5.53 (m, 1 H, H-3), 5.23 (s, 2 H, O**CH_2**R), 4.95 (s, 1 H, H-2), 4.51-4.48 (t, J = 4.7 Hz, 2 H, N-**CH_2**$CH_2(OCH_2CH_2)_3OCH_2CH_2NH_2$),), 3.78-3.70 (m, 2 H, N-CH_2**CH_2**$(OCH_2CH_2)_3OCH_2CH_2NH_2$), 3.61-3.58 (m, 2 H, N-$CH_2CH_2(OCH_2CH_2)_3OCH_2$ **CH_2**NH_2), 3.55-3.50 (m, 6 H, N-$CH_2CH_2(O$**CH_2**$CH_2)_3OCH_2CH_2NH_2$), 3.46-3.40 (m, 6 H, N-$CH_2CH_2(OCH_2$**CH_2**$)_3OCH_2CH_2NH_2$), 3.05-3.03 (t, J = 5.0 Hz, 2 H, N-$CH_2CH_2(OCH_2CH_2)_3$ OCH_2**CH_2**NH_2, 3.00-2.94 (dd, J = 17.5, 4.6 Hz, 1 H, H-4α), 2.85-2.80 (dd, J = 17.5, 1.8 Hz, 1 H, H-4β).

^{13}C NMR (125 MHz, CD_3OD): δ = 165.6, 156.50, 156.45, 155.8, 150.4, 145.3, 137.2, 132.3, 129.4, 125.6, 125.0, 108.9, 105.3, 97.8, 95.1, 94.5, 77.0, 70.05, 69.94, 69.88, 69.82, 69.78, 69.5, 69.0, 68.9, 66.3, 64.0, 50.1, 39.2, 25.5.

HRMS (ESI): m/z calcd for $C_{35}H_{42}N_4O_{15}Na$ $[M+Na]^+$: 781.2544; found: 781.2525

(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 4-((1-(17-amino-3,6,9,12,15-pentaoxaheptadecyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-dihydroxybenzoate (3-9e)



Compound was prepared according to **General Procedure 2**.

Yield: 29 mg, 45%, white solid. $[\alpha]_D^{21}$ = -79˚ (c = 0.1, MeOH).

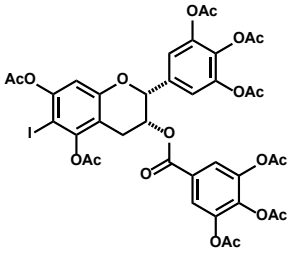
FT-IR (neat): 3307, 2908, 1678, 1625, 1521, 1449, 1374, 1349, 1238, 1201, 1147, 1096, 845, 772, 722, 652, 633 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.90 (s, 1 H, triazole-H), 6.87 (s, 2 H, Gal H-2, H-6), 6.49 (s, 2 H, H-2', H-6'), 5.93 (s, 2 H, H-6. H-8), 5.52-5.53 (m, 1 H, H-3), 5.24 (s, 2 H, O**CH_2**R), 4.95 (s, 1 H, H-2), 4.52-4.50 (t, J = 4.7 Hz, 2 H, N-**CH_2**$CH_2(OCH_2CH_2)_4OCH_2CH_2NH_2$),), 3.82-3.71 (m, 2 H, N-CH_2**CH_2**$(OCH_2CH_2)_4OCH_2CH_2NH_2$), 3. 63-3.60 (m, 2 H, N-$CH_2CH_2(OCH_2CH_2)_4OCH_2$ **CH_2**NH_2), 3.57-3.38 (m, 16 H, N-CH_2CH_2(O**CH_2CH_2**$)_4OCH_2CH_2NH_2$, 3.01-2.94 (m, 3 H, N-$CH_2CH_2(OCH_2CH_2)_4OCH_2$**$CH_2$**$NH_2$, H-4α), 2.85-2.80 (dd, J = 17.5, 1.8 Hz, 1 H, H-4β).

^{13}C NMR (125 MHz, CD_3OD): δ = 165.6, 156.56, 156.49, 155.8, 150.4, 145.3, 143.6, 137.2, 132.3, 129.4, 125.6, 124.9, 108.9, 105.3, 97.8, 95.1, 94.5, 77.0, 69.94, 69.87, 69.84, 69.80, 69.76, 69.70, 69.68, 69.43, 69.0, 68.9, 66.3, 63.9, 50.0, 39.2, 25.5.

HRMS (ESI): m/z calcd for $C_{37}H_{47}N_4O_{16}$ $[M+H]^+$: 803.2987; found: 803.2997

5-((((2R,3R)-5,7-diacetoxy-6-iodo-2-(3,4,5-triacetoxyphenyl)chroman-3-yl)oxy)carbonyl) benzene-1,2,3-triyl triacetate (3-11)



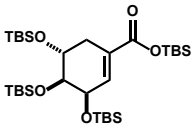
To a solution of EGCG (100 mg, 0.22 mmol) in acetone (2.0 mL, 0.1 M) was rapidly added NIS (58 mg, 0.26 mmol, 1.2 eq.), and the mixture was stirred for 1 h. Then a reaction was concentrated and immediately redissolved in Ac_2O (1.0 ml. 0.2 M). Pyridine (0.6 ml, 0.37 M) was then added and the reaction was stirred for 24 h. The mixture was then poured into ice water and filtered. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc 1:3) to furnish **3-11** (91.0 mg) as a yellow solid in 45% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61 (s, 2H), 7.22 (s, 2H), 6.81 (s, 1H), 5.61 (t, *J* = 3.4 Hz, 1H), 5.18 (s, 1H), 3.12-2.97 (m, 2H), 2.36-2.22 (m, 24H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.2, 167.6, 167.5, 167.4, 166.7, 166.2, 163.5, 155.2, 151.1, 150.8, 143.5, 143.5, 143.4, 139.0, 134.7, 134.5, 127.3, 122.4, 118.8, 118.6, 111.6, 109.8, 67.8, 26.8, 21.2, 21.0, 20.61, 20.59, 20.18, 20.16, 14.2.

HRMS (ESI): m/z calcd for $C_{38}H_{33}INaO_{19}$ $[M+H]^+$: 943.0558; found: 943.0577

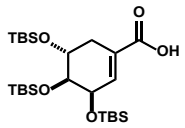
tert-butyldimethylsilyl (3R,4S,5R)-3,4,5-tris((tert-butyldimethylsilyl)oxy)cyclohex-1-ene-1-carboxylate (3-53)



To a solution of shikimic acid (5.00 g, 28.7 mmol) in DMF (57.4 mL, 0.5 M) was added TBSCl (43.3 g, 287 mmol, 10 eq.) and imidazole (21.5 g, 316 mmol, 11 eq.), and the mixture was stirred at 70 °C overnight. Then the reaction was cooled to room temperature, diluted with water and

extracted with DCM (3x). Combined organic layers were washed with brine (2x), dried with $MgSO_4$, filtered, and concentrated under the reduced pressure to afford crude **3-53** that was used in the next step without further purification.

(3R,4S,5R)-3,4,5-tris((tert-butyldimethylsilyl)oxy)cyclohex-1-ene-1-carboxylic acid (3-14).

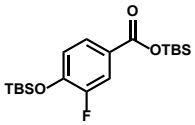


Crude **3-53** (9.3 g, 15 mmol) was dissolved in THF (74 ml, 0.2 M) followed by the addition of CH_3COOH (74 ml, 0.2 M) and H_2O (49 ml, 0.3 M). The reaction was stirred overnight and then poured into ice water. The organic layer was extracted with EtOAc (3x), dried with $MgSO_4$, filtered and concentrated under reduced pressure. Crude acid was dried (1 mbar, 60 °C) for 6 hours to remove silicon byproducts and afford **3-14** (4.0 g) in 53% as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): 6.81 (s, 1H), 4.63 (t, *J* = 1.5 Hz), 4.00 (t, *J* = 2.1 Hz, 1H), 3.75 (t, *J* = 1.6 Hz, 1H), 2.58 (dq, *J* = 17.9, 3.1 Hz, 1H), 2.15 (dd, *J* = 18.2, 3.1 Hz, 1H), 0.93 (s, 9H), 0.86 (s, 9H), 0.83 (s, 9H), 0.11-0.05 (m, 18H).

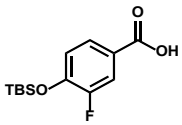
Spectral data for this compound were consistent with those in the literature.[103]

tert-butyldimethylsilyl 4-((tert-butyldimethylsilyl)oxy)-3-fluorobenzoate (3-54)



To a solution of 3,4-fluorohydroxybenzoic acid (5.00 g, 32 mmol) in DMF (80 mL, 0.4 M) was added TBSCl (27 g, 180 mmol, 5.6 eq.) and imidazole (22 g, 320 mmol, 10 eq.), and the mixture was stirred at room temperature overnight. Then the reaction was diluted with Et_2O and washed with water. Organic layer was dried with $MgSO_4$, filtered, and concentrated under the reduced pressure to afford crude **3-54** that was used in the next step without further purification.

4-((tert-butyldimethylsilyl)oxy)-3-fluorobenzoic acid (3-16)



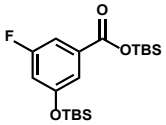
Crude **3-54** (12 g, 32 mmol) was dissolved in THF (160 ml, 0.2 M) followed by the addition of CH_3COOH (160 ml, 0.2 M) and H_2O (110 ml, 0.3 M). The reaction was stirred overnight and then poured into ice water. The organic layer was extracted with EtOAc (3x), dried with $MgSO_4$, filtered and concentrated under reduced pressure. Crude acid was dried (1 mbar, 60 °C) for 6 hours to remove silicon byproducts and afford **3-16** (4.9 g) in 56% as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.80-7.77 (m, 2H), 6.96 (t, *J* = 8.4 Hz), 1.00 (s, 9H), 0.2305 (s, 3H), 0.2285 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6, 154.6, 152.7, 148.8, 121.2 (d), 122.8 (d), 121.9 (d), 118.5 (d), 25.5, 18.4, -4.7.

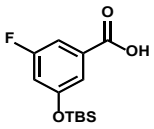
HRMS (ESI): m/z calcd for $C_{13}H_{18}FO_3Si$ $[M-H]^-$: 269.1009; found: 269.1197.

tert-butyldimethylsilyl 3-((tert-butyldimethylsilyl)oxy)-5-fluorobenzoate (3-55)



To a solution of 3,5-fluorohydroxybenzoic acid (5.00 g, 32 mmol) in DMF (80 mL, 0.4 M) was added TBSCl (27 g, 180 mmol, 5.6 eq.) and imidazole (22 g, 320 mmol, 10 eq.), and the mixture was stirred at room temperature overnight. Then the reaction was diluted with Et_2O and washed with water. Organic layer was dried with $MgSO_4$, filtered, and concentrated under the reduced pressure to afford crude **3-55** that was used in the next step without further purification.

3-((tert-butyldimethylsilyl)oxy)-5-fluorobenzoic acid (3-18)



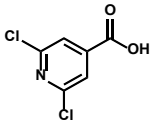
Crude **3-55** (12 g, 32 mmol) was dissolved in THF (160 ml, 0.2 M) followed by the addition of CH_3COOH (160 ml, 0.2 M) and H_2O (110 ml, 0.3 M). The reaction was stirred overnight and then poured into ice water. The organic layer was extracted with EtOAc (3x), dried with $MgSO_4$, filtered and concentrated under reduced pressure. Crude acid was dried (1 mbar, 60 °C) for 6 hours to remove silicon byproducts and afford **3-18** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42-7.36 (m, 2H), 6.80 (dt, *J* = 9.8, 2.3 Hz), 0.99 (s, 9H), 0.24 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8 (d), 164.0, 162.1, 157.2 (d), 131.5 (d), 177.7 (d), 133.1 (d), 110.1 (d), 25.6, 18.2, -4.5.

HRMS (ESI): m/z calcd for $C_{13}H_{18}FO_3Si$ $[M-H]^-$: 269.1009; found: 269.1184.

2,6-dichloroisonicotinic acid (3-20)



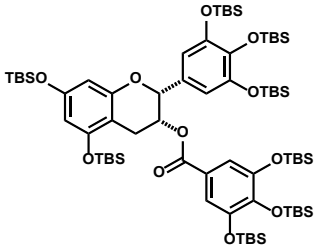
To a solution of citrazinic acid (3.00 g, 19.3 mmol) in $POCl_3$ (6.0 mL, 3.33 eq.) was added Bu_4NCl (5.38 g, 19.3 mmol, 1.0 eq.) and the mixture was stirred at 140 °C overnight. Then the reaction was cooled to room temperature and poured into ice water. The mixture was then stirred for 2 hours and filtered. The filtrate was washed with water and dissolved in EtOAc. The organic solution was washed with NH_4Cl, dried with $MgSO_4$ and concentrated under the reduced pressure to afford **3-20** (2.6 g) as a red solid in 70% yield.

^{1}H NMR (500 MHz, DMSO-d6): δ = 7.82 (s, 2H).

^{13}C NMR (125 MHz, DMSO-d6): δ = 164.2, 150.6, 145.2, 123.4.

Spectral data for this compound were consistent with those in the literature.[88]

(2R,3R)-5,7-bis((tert-butyldimethylsilyl)oxy)-2-(3,4,5-tris((tert-butyldimethylsilyl)oxy) phenyl)chroman-3-yl 3,4,5-tris((tert-butyldimethylsilyl)oxy)benzoate (3-56)



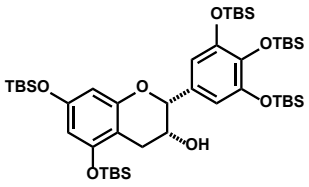
To a solution of EGCG (5.00 g, 15.3 mmol) in DMF (27 mL, 0.4 M) was added imidazole (11.1 g, 164 mmol, 15 eq.). The reaction was cooled to 0 °C and TBSCl (24.7 g, 164 mmol, 15 eq.) was added in one portion. The mixture was stirred overnight at room temperature, quenched with water, extracted with hexane (3x). Combined organic layers were washed with water (3x) and brine (3x), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc 95:5) to furnish a mixture of products (partially protected EGCG derivatives) that was directly subjected to the next step.

Note: Separation of the mixture is not necessary since the impurities can be easily removed in the subsequent step. If desired, pure TBS-EGCG can be obtained by performing careful column chromatography (100% hexane to 95:5 hexane/EtOAc in 1% increments).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.04 (s, 2H), 6.58 (s, 2H), 6.15 (d, *J* = 2.2 Hz, 1H), 5.93 (d, *J* = 2.2 Hz, 1H), 5.57 (t, *J* = 3.0 Hz, 1H), 5.29 (s, 1H), 5.00 (s, 1H), 2.93 (s, 2H), 0.97-0.85 (m, 72H), 0.19-0.06 (m, 48H).

Spectral data for this compound were consistent with those in the literature.[89]

(2R,3R)-5,7-bis((tert-butyldimethylsilyl)oxy)-2-(3,4,5-tris((tert-butyldimethylsilyl)oxy) phenyl)chroman-3-ol (3-21)



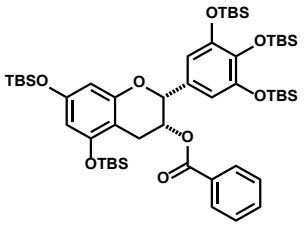
Solution of crude **3-56** (13.6 g, 9.9 mmol) in THF (99 mL, 0.1 M) was cooled to 0 °C. LAH (752 mg, 19.8 mmol, 2 eq.) was added in multiple portions. The mixture was then stirred at room temperature 3 hours and then diluted with Et_2O. Reaction was carefully quenched with saturated Na_2SO_4 (Caution: quench has to be added slowly as the reaction rapidly generates hydrogen gas). The mixture was filtered, and the solid was additionally washed with Et_2O. The filtered liquid was concentrated under the reduced pressure.

The crude product was purified by column chromatography on silica gel (100% hexanes to hexanes/EtOAc 95:5) to furnish **3-21** (4.56 g) as a white solid in 34% yield over two steps.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.60 (s, 2H), 6.10 (d, *J* = 2.3 Hz, 1H), 5.96 (d, *J* = 2.3 Hz, 1H), 4.84 (s, 1H), 4.18 (m, 1H), 2.85 (qt, *J* = 16.4, 4.3 Hz, 2H), 1.00-0.93 (m, 45), 0.23-0.12 (m, 30).

Spectral data for this compound were consistent with those in the literature.[89]

(2R,3R)-5,7-bis((tert-butyldimethylsilyl)oxy)-2-(3,4,5-tris((tert-butyldimethylsilyl)oxy) phenyl)chroman-3-yl benzoate (3-23)

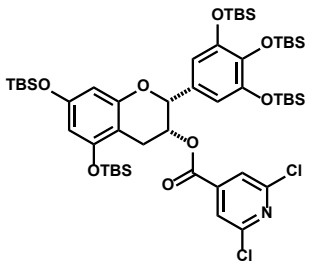


To a solution of **3-21** (200 mg, 0.23 mmol) in DCM (4.6 mL, 0.05 M) were added DMAP (69.6 mg, 0.57 mmol, 2.5 eq.) and DCC (118 mg, 0.57 mmol, 2.5 eq.). The reaction was cooled to 0 °C and benzoic acid (83.5 mg, 0.684 mmol, 3.0 eq.) was added in one portion. The mixture was stirred at room temperature for 2 days, filtered through cotton and concentrated under the reduced

pressure. The crude product was purified by column chromatography on silica gel (100% hexanes to hexanes/EtOAc 95:5) to furnish **3-23** (200 mg) as a white solid in 88% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 7.1 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 2H), 6.60 Hz (s, 2H), 6.20 (d, *J* = 2.3 Hz, 1H), 5.98 (d, *J* = 2.3 Hz, 1H), 5.64 (m, 1H), 5.04 (s, 1H), 3.00 (d, *J* = 3.5 Hz, 2H), 0.99 (s, 9H), 0.96 (s, 9H), 0.94 (s, 9H), 0.85 (s, 18H), 0.22-0.04 (m, 30H).

(2R,3R)-5,7-bis((tert-butyldimethylsilyl)oxy)-2-(3,4,5-tris((tert-butyldimethylsilyl)oxy) phenyl)chroman-3-yl 2,6-dichloroisonicotinate (3-24)



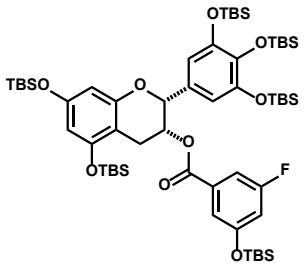
To a solution of **3-21** (200 mg, 0.23 mmol) in DCM (4.6 mL, 0.05 M) were added DMAP (61.3 mg, 0.5 mmol, 2.2 eq.) and DCC (103 mg, 0.5 mmol, 2.2 eq.). The reaction was cooled to 0 °C and **3-20** (109 mg, 0.57 mmol, 2.5 eq.) was added in one portion. The mixture was stirred at room temperature for 2 days, filtered through cotton and concentrated under the reduced pressure. The crude product was purified by column chromatography on silica gel (100% hexanes to hexanes/EtOAc 95:5) to furnish **3-24** (190 mg) as a white solid in 80% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55 (s, 2H), 6.55 (s, 2H), 6.20 (d, *J* = 2.3 Hz, 1H), 6.00 (d, *J* = 2.3 Hz, 1H), 5.67-5.66 (m, 1H), 5.01 (s, 1H), 3.00 (qd, *J* = 17.7, 5.1 Hz, 2H), 0.99-0.87 (m, 45H), 0.22-0.02 (m, 30H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.8, 155.3, 155.3, 154.7, 151.3, 148.6, 142.3, 138.1, 129.1, 122.6, 111.8, 104.2, 102.9, 101.7, 76.2, 10.6, 26.3, 26.2, 26.1, 25.75, 25.72, 18.7, 18.4, 18.3, 18.2, -3.69, -3.72, -3.9, -4.1, -4.2, -4.3.

HRMS (ESI): m/z calcd for $C_{51}H_{86}Cl_2NO_8Si_5$ $[M+H]^+$: 1050.4577; found: 1050.4580.

(2R,3R)-5,7-bis((tert-butyldimethylsilyl)oxy)-2-(3,4,5-tris((tert-butyldimethylsilyl)oxy) phenyl)chroman-3-yl 3-((tert-butyldimethylsilyl)oxy)-5-fluorobenzoate (3-25)



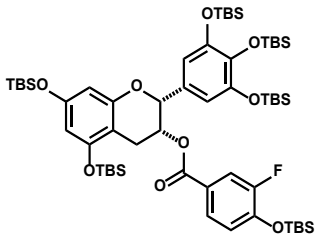
3-21 (52.4 mg, 0.194 mmol, 1.7 eq.) was dissolved in DCM (0.6 ml) and cooled to 0 °C. Ghosez's reagent (37.7 µl, 0.285 mmol, 2.5 eq.) was added dropwise and the reaction was stirred at room temperature for 1 hour. In the separate flask, **3-18** (100 mg, 0.114 mmol) was dissolved in DCM (1 ml). Acid chloride was then added (with the additional DCM rinse to ensure the complete transfer) followed by DMAP (34.8 mg, 0.285 mmol, 2.5 eq.). The reaction was stirred at room temperature overnight and concentrated under the reduced pressure. The crude product was purified by column chromatography on silica gel (100% hexanes to hexanes/EtOAc 95:5) to furnish **3-25** (110 mg) as a white solid in 82% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.12-7.07 (m, 2H), 6.65 (dt, *J* = 9.9, 2.3 Hz, 1H), 6.58 (s, 2H), 6.19 (d, *J* = 2.3 Hz, 1H), 5.97 (d, *J* = 2.3 Hz, 1H), 5.62 (m, 1H), 5.01 (s, 1H), 2.98 (d, *J* = 3.4 Hz, 2H), 0.98-0.85 (m, 54H), 0.21-0.04 (m, 36H).

^{13}C NMR (125 MHz, $CDCl_3$): δ =164.3 (d), 163.8, 161.9, 156.8 (d), 155.5, 155.1, 154.7, 148.5, 137.9, 132.4 (d), 129.6, 117.1 (d), 112.1, 111.9, 109.7(d), 104.0, 103.5, 101.6, 68.9, 26.5, 26.19, 26.11, 25.8, 25.7, 25.60, 25.55, 18.7, 18.4, 18.3, 18.1, -3.72, -3.73, -3.94, -4.1, -4.21, -4.23-4.36, -4.37, -4.5, -4.6.

HRMS (ESI): m/z calcd for $C_{58}H_{102}FO_9Si_6$ $[M+H]^+$: 1129.6123; found: 1129.6140.

(2R,3R)-5,7-bis((tert-butyldimethylsilyl)oxy)-2-(3,4,5-tris((tert-butyldimethylsilyl)oxy) phenyl)chroman-3-yl 4-((tert-butyldimethylsilyl)oxy)-3-fluorobenzoate (3-26)



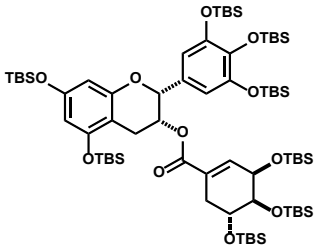
3-21 (52.4 mg, 0.194 mmol, 1.7 eq.) was dissolved in DCM (0.6 ml) and cooled to 0 °C. Ghosez's reagent (28.2 µl, 0.213 mmol, 1.87 eq.) was added dropwise and the reaction was stirred at room temperature for 1 hour. In the separate flask, **3-16** (100 mg, 0.114 mmol) was dissolved in DCM (1 ml). Acid chloride was then added (with the additional DCM rinse to ensure the complete transfer) followed by DMAP (34.8 mg, 0.285 mmol, 2.5 eq.). The reaction was stirred at 35 °C overnight and concentrated under the reduced pressure. The crude product was purified by column chromatography on silica gel (100% hexanes to hexanes/EtOAc 95:5) to furnish **3-26** (87 mg) as a white solid in 75% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51 (m, 2H), 6.80 (t, *J* = 8.4 Hz, 1H), 6.58 (s, 2H), 6.19 (d, *J* = 2.2 Hz, 1H), 5.97 (d, *J* = 2.2 Hz, 1H), 5.59 (m, 1H), 5.01 (s, 1H), 2.97 (s, 2H), 0.98-0.86 (m, 54H), 0.21-0.03 (m, 36H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.5, 155.5, 155.0, 154.7, 154.4, 152.5, 148.4, 147.8 (d), 137.8, 129.7, 126.6, 123.9 (d), 121.6, 118.0 (d), 112.1, 104.0 (d), 101.5, 68.6, 26.2, 26.1, 25.8, 25.7, 25.5, 18.7, 18.4, 18.33, 18.29, 18.26, -3.71, -3.73, -3.9, -4.1, -4.21, -4.23, -4.4, -4.7.

HRMS (ESI): m/z calcd for $C_{58}H_{102}FO_9Si_6$ $[M+H]^+$: 1129.6123; found: 1129.6279.

(2R,3R)-5,7-bis((tert-butyldimethylsilyl)oxy)-2-(3,4,5-tris((tert-butyldimethylsilyl)oxy) phenyl)chroman-3-yl (3R,4S,5R)-3,4,5-tris((tert-butyldimethylsilyl)oxy)cyclohex-1-ene-1-carboxylate (3-22)



To a solution of **3-21** (300 mg, 0.34 mmol) in DCM (3.4 mL, 0.1 M) were added DMAP (251 mg, 2.05 mmol, 6 eq.), **3-14** (884 mg, 1.71 mmol, 5 eq.) and DCC (353 mg, 1.71 mmol, 5 eq.). The reaction was stirred at 40 °C overnight, quenched with water, and extracted with DCM (3x). Combined organic layers were dried with $MgSO_4$, filtered and concentrated under the reduced pressure. The crude product was purified by column chromatography on silica gel (100% hexanes to hexanes/EtOAc 95:5) to furnish **3-22** (377 mg) as a white solid in 80% yield along with an inseparable impurity.

Note: Proton NMR peaks are tabulated for the coeluted mixture that was carried forward.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.81 (s, 1H), 6.60 (s, 2H), 6.10 (s, 1H), 5.92 (s, 1H), 5.51 (s, 1H), 4.98 (s, 1H), 4.44 (s, 1H), 3.89 (s, 1H), 3.63 (s, 1H), 2.87 (s, 2H), 2.36 (d, *J* = 17.3 Hz, 1H), 2.03 (d, *J* = 17.3 Hz, 1H), 0.97-0.77 (m, 72H), 0.19-0.01 (m, 48).

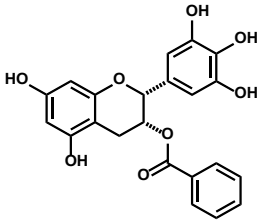
HRMS (ESI): m/z calcd for $C_{70}H_{135}O_{11}Si_8$ $[M+H]^+$: 1375.8159; found: 1375.8849.

TBS-deprotection of D-ring variants: General Procedure 3.

Note: The deprotection reaction has to be run in the plastic vessel as HF will react and etch the glass containers as well as affect the yield and efficiency of the reaction.

To a solution of the corresponding ester (1 eq.) in THF (0.04 M) were added HF•pyridine (40 eq.) and pyridine (40 eq.). The reaction was stirred overnight at room temperature and directly purified by preparative reverse-phase HPLC.

(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl benzoate (AEK-5-269)



Compound was prepared according to **General Procedure 3**.

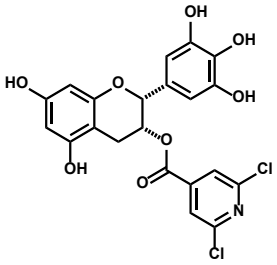
Yield: 25 mg, 40%, white solid.

^{1}H NMR (500 MHz, Acetone-d6): δ = 7.88 (d, *J* = 8.4 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 6.63 (s, 2H), 6.04 (d, *J* = 2.3 Hz, 1H), 6.03 (d, *J* = 2.3 Hz, 1H), 5.60-5.59 (m, 1H), 5.11 (s, 1H), 3.07 (dd, *J* = 17.4, 4.6 Hz, 1H), 2.96 (dd, *J* = 17.4, 2.8 Hz, 1H).

^{13}C NMR (125 MHz, Acetone-d6): δ = 165.2, 157.0, 156.5, 156.1, 145.4, 132.9, 132.2, 130.4, 129.8, 129.3, 128.4, 105.6, 97.9, 95.5, 94.8, 77.0, 69.2, 25.5.

Spectral data for this compound were consistent with those in the literature.[104]

(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 2,6-dichloroisonicotinate (AEK-5-276)



Compound was prepared according to **General Procedure 3**.

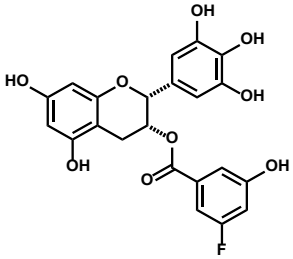
Yield: 55 mg, 60%, red solid. $[\alpha]_D^{21}$ = -108˚ (*c* = 0.1, MeOH).

^{1}H NMR (500 MHz, Acetone-d6): δ = 7.67 (s, 2H), 6.59 (s, 2H), 6.06 (d, *J* = 2.3 Hz, 1H), 6.03 (d, *J* = 2.3 Hz, 1H), 5.68-5.67 (m, 1H), 5.12 (s, 1H), 3.12 (dd, *J* = 17.6, 4.7 Hz, 1H), 2.96 (dd, *J* = 17.3, 2.1 Hz, 1H).

^{13}C NMR (125 MHz, Acetone-d6): δ = 161.7, 157.1, 156.5, 155.9, 150.8, 145.6, 143.4, 132.3, 129.3, 122.6, 105.3, 97.5, 95.7, 94.9, 76.5, 71.3, 25.2.

HRMS (ESI): m/z calcd for $C_{21}H_{16}Cl_2NO_8$ $[M+H]^+$: 480.0253; found: 480.0270.

(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 3-fluoro-5-hydroxy benzoate (AEK-5-280)



Compound was prepared according to **General Procedure 3**.

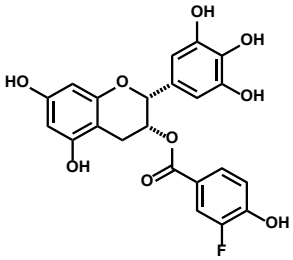
Yield: 20 mg, 52%, white solid.

^{1}H NMR (500 MHz, Acetone-d6): δ = 7.22 (s, 1H), 7.04 (d, *J* = 9.1 Hz, 1H), 6.75 (d, *J* = 10.3 Hz, 1H), 6.05 (d, *J* = 2.2 Hz, 1H), 6.02 (d, *J* = 2.2 Hz, 1H), 5.59 (s, 1H), 5.09 (s, 1H), 3.07 (dd, *J* = 17.4, 5.4 Hz, 1H), 2.94 (d, *J* = 17.5 Hz, 1H).

^{13}C NMR (125 MHz, Acetone-d6): δ = 164.1 (d), 164.07, 162.2, 159.0 (d), 157.0, 156.5, 156.1, 145.4, 133.0 (d), 132.2, 129.6, 112.4, 107.2, 107.0, 106.8, 105.6, 97.8, 95.6, 94.9, 76.9, 69.6, 48.8, 25.5.

HRMS (ESI): m/z calcd for $C_{22}H_{18}FO_9$ $[M+H]^+$: 445.0935; found: 445.0943

(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 3-fluoro-4-hydroxy benzoate (AEK-5-28)



Compound was prepared according to **General Procedure 3**.

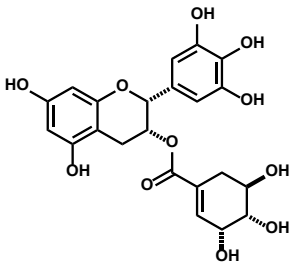
Yield: 18 mg, 51%, white solid.

^{1}H NMR (500 MHz, Acetone-d6): δ = 7.57 (m, 2H), 7.00 (t, *J* = 8.5 Hz, 1H), 6.04 (d, *J* = 2.2 Hz, 1H), 6.02 (d, *J* = 2.2 Hz, 1H), 5.54 (m, 1H), 5.09 (s, 1H), 3.05 (dd, *J* = 17.4, 4.5 Hz, 1H), 2.93 (dd, *J* = 17.4, 2.2 Hz, 1H).

^{13}C NMR (125 MHz, Acetone-d6): δ = 164.1, 157.0, 156.5, 156.1, 151.6, 149.7, 149.5 (d), 145.4, 132.2, 129.8, 126.7 (d), 122.3 (d), 117.4, 117.1, 116.9, 105.6, 97.8, 95.5, 94.8, 77.0, 69.2, 25.5.

HRMS (ESI): m/z calcd for $C_{22}H_{18}FO_9$ $[M+H]^+$: 445.0935; found: 445.0942.

(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl (3R,4S,5R)-3,4,5-tri hydroxycyclohex-1-ene-1-carboxylate (AEK-5-272)



Compound was prepared according to **General Procedure 3**.

Yield: 30 mg, 67%, white solid.

^{1}H NMR (500 MHz, Acetone-d6): δ = 6.66 (m, 1H), 6.57 (s, 1H), 6.04 (d, *J* = 2.3 Hz, 1H), 5.98 (d, *J* = 2.3 Hz, 1H), 5.40 (m, 1H), 5.01 (s, 1H), 4.31 (s, 1H), 3.91 (m, 1H), 3.62 (m, 1H), 2.99 (dd, *J* = 17.2, 5.1 Hz, 1H), 2.84 (dd, *J* = 17.4, 2.1 Hz, 1H), 2.53 (dd, *J* = 18.1, 4.7 Hz, 1H).

Note: Last proton on the shikimate ring is hidden under the acetone peak.

^{13}C NMR (125 MHz, Acetone-d6): δ = 165.5, 156.9, 156.5, 156.1, 145.3, 138.2, 132.3, 129.6, 129.2, 105.8, 97.9, 95.5, 94.9, 77.0, 71.5, 68.8, 67.0, 65.8, 30.5, 25.5.

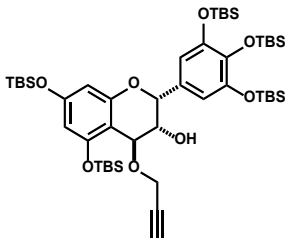
HRMS (ESI): m/z calcd for $C_{22}H_{23}O_{11}Na$ $[M+Na]^+$: 485.1060; found: 485.1068.

DDQ-mediated B-ring oxidation: General Procedure 4.

To a solution of **3-21** in DCM (0.08 M) were added the corresponding nucleophile (9 eq.) and DDQ (2.2 eq.). The reaction was stirred for 4 h at room temperature followed by the addition of DMAP (2.2 eq.). After additional 10 minutes the reaction was concentrated under the reduced pressure. The crude product was purified by column chromatography on silica gel (100% hexanes to hexanes/EtOAc 95:5) to furnish the desired product.

Note: The reaction always produces a single diastereomer regardless of the identity of the nucleophile.

(2R,3R,4S)-5,7-bis((tert-butyldimethylsilyl)oxy)-4-(prop-2-yn-1-yloxy)-2-(3,4,5-tris((tert-butyldimethylsilyl)oxy)phenyl)chroman-3-ol (3-27c)



Compound was prepared according to **General Procedure 4**.

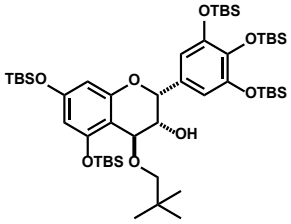
Yield: 92%, white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.67 (s, 2H), 6.11 (d, *J* = 2.2 Hz, 1H), 6.01 (d, *J* = 2.2 Hz, 1H), 5.13 (s, 1H), 4.66 (d, *J* = 3.1 Hz, 1H), 4.40 (d, *J* = 2.4 Hz, 2H), 4.19 (m, 1H), 2.44 (t, *J* = 2.4 Hz, 1H), 1.51 (d, *J* = 5.8 Hz, OH, 1H), 1.03-0.94 (m, 45H), 0.31-0.13 (m, 30H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.2, 156.8, 156.2, 148.8, 138.0, 129.4, 112.3, 104.1, 103.9, 101.3, 80.8, 74.2, 74.0, 70.8, 68.3, 56.9, 26.2, 26.0, 25.7, 18.8, 18.5, 18.4, 18.2, -3.57, -3.59, -3.83, -3.87, -3.89, -3.93, -4.36, -4.38.

HRMS (ESI): m/z calcd for $C_{48}H_{87}O_8Si_5$ $[M+H]^+$: 931.5247; found: 931.5225.

(2R,3R,4S)-5,7-bis((tert-butyldimethylsilyl)oxy)-4-(neopentyloxy)-2-(3,4,5-tris((tert-butyl dimethylsilyl)oxy)phenyl)chroman-3-ol (3-27d)



Compound was prepared according to **General Procedure 4**.

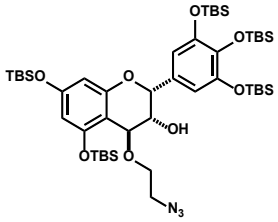
Yield: 89%, white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.63 (s, 2H), 6.10 (d, *J* = 2.2 Hz, 1H), 6.00 (d, *J* = 2.2 Hz, 1H), 5.09 (s, 1H), 4.46 (d, *J* = 3.03 Hz, 1H), 3.93-3.91 (m, 1H), 3.43 (d, *J* = 8.4 Hz, 1H), 3.30 (d, *J* = 8.4 Hz, 1H), 1.46 (d, *J* = 6.2 Hz, OH, 1H), 1.02-0.90 (m, 54H), 0.29-0.13 (m, 30H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.0, 156.7, 156.1, 148.8, 137.8, 129.8, 112.1, 104.9, 103.7, 101.0, 79.1, 74.4, 69.4, 68.3, 32.0, 26.9, 26.23, 26.21, 26.1, 25.7, 18.8, 18.5, 18.4, 18.2, -3.60, -3.61, -3.8, -3.90, -3.94, -4.35, -4.37.

HRMS (ESI): m/z calcd for $C_{50}H_{95}O_8Si_5$ [M]: 963.5873; found: 963.5848.

(2R,3R,4S)-4-(2-azidoethoxy)-5,7-bis((tert-butyldimethylsilyl)oxy)-2-(3,4,5-tris((tert-butyl dimethylsilyl)oxy)phenyl)chroman-3-ol (3-27b)



Compound was prepared according to **General Procedure 4**.

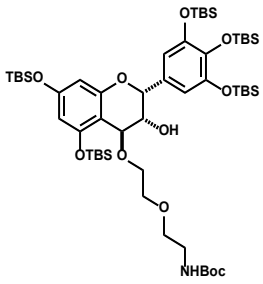
Yield: 60%, white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.66 (s, 2H), 6.12 (s, 1H), 6.01 (s, 1H), 5.15 (s, 1H), 4.60 (d, *J* = 2.7 Hz, 1H), 3.98 (m, 1H), 3.94-3.84 (m, 2H), 3.47-3.41 (m, 1H), 3.26 (dt, *J* = 13.0, 3.6 Hz, 1H), 1.49 (d, *J* = 5.5 Hz, OH, 1H), 1.01-0.94 (m, 45H), 0.30-0.13 (m, 30H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.1, 156.8, 156.3, 148.8, 137.9, 129.3, 112.2, 103.9, 103.8, 101.4, 74.1, 69.9, 68.5, 67.7, 51.1, 26.2, 26.15, 25.98, 25.66, 18.8, 18.48, 18.43. 18.2, -3.61, -3.63, -3.78, -3.88, -3.94, -4.34, -4.37.

HRMS (ESI): m/z calcd for $C_{47}H_{88}N_3O_8Si_5$ $[M+H]^+$: 962.5418; found: 962.5419.

tert-butyl(2-(2-(((2R,3R,4S)-5,7-bis((tert-butyldimethylsilyl)oxy)-3-hydroxy-2-(3,4,5-tris((tert-butyldimethylsilyl)oxy)phenyl)chroman-4-yl)oxy)ethoxy)ethyl)carbamate (3-27a)



Compound was prepared according to **General Procedure 4**.

Yield: 60%, white solid.

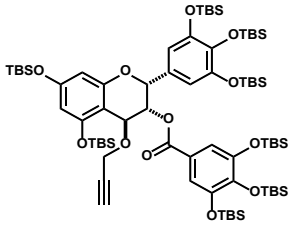
^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.65 (s, 2H), 6.10 (d, *J* = 2.2 Hz, 1H), 6.00 (d, *J* = 2.2 Hz, 1H), 5.08 (s, 1H), 4.94 (broad, NH, 1H), 4.57 (d, *J* = 3.0 Hz, 1H), 4.02-4.00 (m, 1H), 3.90-3.81 (m, 2H),

3.60 (t, *J* = 4.9 Hz, 2H), 3.54-3.47 (m, 2H), 3.28 (m, 2H), 1.40 (s, 9H), 1.02-0.94 (m, 45H), 0.30-0.12 (m, 30H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.99, 156.96, 156.2, 155.9, 148.8, 137.9, 129.5, 112.3, 104.4, 103.9, 101.3, 79.2, 74.2, 70.7, 70.3, 70.2, 68.2, 68.1, 40.3, 28.4, 26.23, 26.21, 26.0, 25.7, 18.8, 18.5, 18.4, 18.2, -3.58, -3.59, -3.8, -3.91, -3.94, -4.36, -4.38.

HRMS (ESI): m/z calcd for $C_{54}H_{101}NO_{11}Si_5Na$ $[M+Na]^+$: 1102.6119; found: 1102.6292.

(2R,3R,4S)-5,7-bis((tert-butyldimethylsilyl)oxy)-4-(prop-2-yn-1-yloxy)-2-(3,4,5-tris((tert-butyldimethylsilyl)oxy)phenyl)chroman-3-yl 3,4,5-tris((tert-butyldimethylsilyl)oxy) benzoate (3-29a)



Compound was prepared according to **General Procedure 4**.

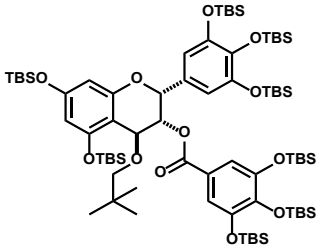
Yield: 150 mg, 73%, white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.97 (s, 2H), 6.65 (s, 2H), 6.15 (d, *J* = 2.2 Hz, 1H), 5.94 (d, *J* = 2.2 Hz, 1H), 5.61-5.60 (m, 1H), 5.35 (s, 1H), 4.62 (d, *J* = 3.2 Hz, 1H), 4.46 (d, *J* = 2.4 Hz, 2H), 2.49 (t, *J* = 2.4 Hz, 1H), 0.97-0.86 (m, 72H), 0.19-0.05 (m, 48H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.6, 157.1, 156.5, 156.4, 148.4, 148.2, 143.2, 137.9, 129.4, 121.2, 115.5, 112.6, 104.3, 103.7, 101.6, 80.6, 74.4, 72.8, 69.0, 68.4, 57.0, 26.22, 26.16, 26.13, 26.07, 25.89, 25.6, 18.73, 18.68, 18.42, 18.41, 18.38, 18.12, -3.64, -3.67, -3.72, -3.80, -3.82, -3.90, -3.97, -4.0, -4.1, -4.3, -4.4.

HRMS (ESI): m/z calcd for $C_{73}H_{132}O_{12}Si_8Na$ $[M+Na]^+$: 1447.7771; found: 1447.8301.

(2R,3R,4S)-5,7-bis((tert-butyldimethylsilyl)oxy)-4-(neopentyloxy)-2-(3,4,5-tris((tert-butyldimethylsilyl)oxy)phenyl)chroman-3-yl 3,4,5-tris((tert-butyldimethylsilyl) oxy)benzoate (3-29b)



Compound was prepared according to **General Procedure 4**.

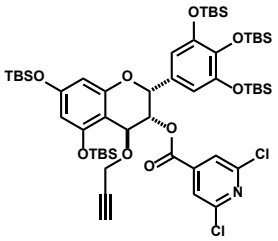
Yield: 74 mg, 70%, white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.00 (s, 2H), 6.63 (s, 2H), 6.16 (d, *J* = 2.3 Hz, 1H), 5.94 (d, *J* = 2.3 Hz, 1H), 5.36 (dd, *J* = 3.1, 0.8 Hz, 1H), 5.29 (s, 1H), 4.46 (d, *J* = 3.1 Hz, 1H), 3.51 (d, *J* = 8.4 Hz, 1H), 3.47 (d, *J* = 8.4 Hz, 1H), 0.97-0.86 (m, 81H), 0.21-0.02 (m, 48H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.8, 156.59, 156.57, 156.4, 148.5, 148.2, 143.1, 137.8, 129.8, 121.3, 115.4, 112.6, 105.3, 103.6, 101.4, 79.4, 73.3, 68.8, 67.5, 32.0, 26.9, 26.22, 26.15, 26.13, 26.08, 25.97, 25.6, 18.74, 18.69, 18.42, 18.40, 18.38, 18.1, -3.64, -3.70, -3.72, -3.80, -3.86, -3.98, -4.04, -4.09, -4.3, -4.4.

HRMS (ESI): m/z calcd for $C_{75}H_{140}O_{12}Si_8Na$ $[M+Na]^+$: 1479.8397; found: 1479.9242.

(2R,3R,4S)-5,7-bis((tert-butyldimethylsilyl)oxy)-4-(prop-2-yn-1-yloxy)-2-(3,4,5-tris((tert-butyldimethylsilyl)oxy)phenyl)chroman-3-yl 2,6-dichloroisonicotinate (3-30b)



To a solution of **3-27b** (100 mg, 0.107 mmol) in DCM (10.7 mL, 0.01 M) were added DMAP (28.8 mg, 0.236 mmol, 2.2 eq.) and DCC (48.7 mg, 0.236 mmol, 2.2 eq.). The reaction was cooled

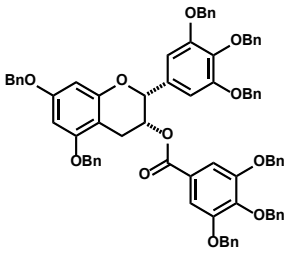
to 0 °C and **3-20** (51.5 mg, 0.268 mmol, 2.5 eq.) was added in one portion. The mixture was stirred at room temperature for 2 days, filtered through cotton and concentrated under the reduced pressure. The crude product was purified by column chromatography on silica gel (100% hexanes to hexanes/EtOAc 95:5) to furnish **3-30b** (100 mg) as a white solid in 88% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 (s, 2H), 6.60 (s, 2H), 6.2 (d, *J* = 2.2 Hz, 1H), 6.04 (d, *J* = 2.2 Hz, 1H), 5.68 (dd, *J* = 3.1, 1.5 Hz, 1H), 5.38 (s, 1H), 4.72 (d, *J* = 3.1 Hz, 1H), 4.45 (d, *J* = 2.4 Hz, 1H), 2.52 (t, *J* = 2.4 Hz, 1H), 0.99 (s, 9H), 0.93 (s, 18H), 0.88 (s, 18H), 0.27-0.02 (m, 30H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.4, 157.6, 156.4, 156.2, 151.4, 148.6, 141.8, 138.1, 128.6, 122.5, 112.2, 112.0, 104.1, 103.5, 101.6, 80.3, 74.8, 72.4, 71.0, 68.1, 57.0, 26.20, 26.16, 26.12, 26.06, 25.95, 25.88, 25.69, 18.7, 18.6, 18.4, 18.3, -3.67, -3.71, -3.79, -3.80, -3.96, -4.1, -4.3.

HRMS (ESI): m/z calcd for $C_{54}H_{88}Cl_2NO_9Si_5$ $[M+H]^+$: 1106.4678; found: 1106.4703.

(2R,3R)-5,7-bis(benzyloxy)-2-(3,4,5-tris(benzyloxy)phenyl)chroman-3-yl 3,4,5-tris(benzyloxy)benzoate (3-38)

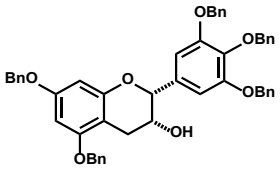


To a solution of EGCG (5.00 g, 10.9 mmol) in DCM (50.0 mL, 0.218 M) were added K_2CO_3 (15.1, 109 mmol, 10 eq.). The reaction was cooled to 0 °C and BnBr (15.6 ml, 131 mmol, 12 eq.) was added in dropwise. The mixture was stirred at room temperature for 24 hours, quenched with water and extracted with EtOAc (3x). Combined organic layers were dried with $MgSO_4$, filtered and concentrated under the reduced pressure The crude product was purified by column chromatography on silica gel (100% hexanes to hexanes/EtOAc 8:2 in 5% gradient) to furnish a mixture of C- and O-alkylated products. The desired product was then recrystallized (hexanes/EtOAc system) to afford **3-38** (5.8 g) as a white solid in 45% yield.

^{1}H NMR (500 MHz, $CDCl_3$): 7.42-7.19 (m, 42H), 6.73 (s, 2H), 6.39 (d, *J* = 2.2 Hz, 1H), 6.34 (d, *J* = 2.2 Hz, 1H), 5.66 (s, 1H), 5.05-4.65 (m, 17H), 3.11-3.08 (m, 2H).

Spectral data for this compound were consistent with those in the literature.[94]

(2R,3R)-5,7-bis(benzyloxy)-2-(3,4,5-tris(benzyloxy)phenyl)chroman-3-ol (3-32)

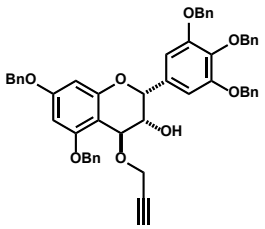


3-38 (3.9 g, 3.3 mmol) was dissolved in DCM/MeOH (83 ml, 0.04 M) and cooled to 0 °C. K_2CO_3 (3.7 g, 26 mmol, 8 eq.) was added in one portion and the reaction was stirred at room temperature overnight. The mixture was then quenched with NH_4Cl and extracted with EtOAc (3x). Combined organic layers were dried with $MgSO_4$, filtered and concentrated under the reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc 100% to 8:2) to furnish **3-32** (2.2 g) as a white solid in 87% yield.

^{1}H NMR (500 MHz, $CDCl_3$): 7.44-7.26 (m, 25H), 6.82 (s, 2H), 6.29 (s, 2H), 5.14-5.03 (m, 10H), 4.90 (s, 1H), 4.21 (s, 1H), 3.02 (d, *J* = 17.1 Hz, 1H), 2.93 (d, *J* = 17.2, 4.2 Hz, 1H), 1.65 (d, *J* = 5.4 Hz, OH, 1H).

Spectral data for this compound were consistent with those in the literature.[94]

(2R,3R,4S)-5,7-bis(benzyloxy)-4-(prop-2-yn-1-yloxy)-2-(3,4,5-tris(benzyloxy)phenyl) chroman-3-ol (3-33)



Compound was prepared according to **General Procedure 4**.

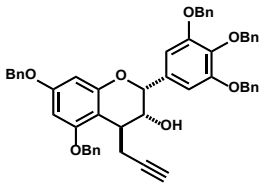
Yield: 2.0 g, 83%, white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44-7.26 (m, 25H), 6.84 (s, 2H), 6.30 (d, *J* = 2.2 Hz, 1H), 6.27 (d, *J* = 2.2 Hz, 1H), 5.16-5.00 (m, 10H), 4.73 (d, *J* = 2.9 Hz, 1H), 4.31 (t, *J* = 2.7 Hz, 2H), 4.13-4.11 (m, 1H), 2.30 (t, *J* = 2.3 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.8, 159.7, 156.0, 153.1, 138.4, 137.8, 137.0, 136.6, 136.5, 133.1, 128.65, 128.61, 128.58, 128.50, 128.19, 128.15, 128.11, 127.9, 127.8, 127.6, 127.56, 106.3, 101.5, 94.5, 94.2, 80.6, 75.2, 74.9, 74.1, 71.3, 70.5, 70.1, 69.9, 68.9, 57.3,

HRMS (ESI): m/z calcd for $C_{53}H_{47}O_8$ $[M+H]^+$: 811.3271; found: 811.3307.

(2R,3R,4S)-5,7-bis(benzyloxy)-4-(prop-2-yn-1-yl)-2-(3,4,5-tris(benzyloxy)phenyl)chroman-3-ol (3-35)



To a solution of **3-33** (2.0 g, 0.107 mmol) in DCM (35.0 mL, 0.07 M) was added **3-34** (1.8 ml, 5.9 mmol, 2.4 eq.). The reaction was cooled to -78 °C and BF_3•Et_2O (0.63 ml, 4.9 mmol, 2.0 eq.) was added dropwise. The mixture was slowly warmed to room temperature (~1 h), quenched with $NaHCO_3$ and extracted with EtOAc (3x). Combined organic layers were dried with $MgSO_4$, filtered and concentrated under the reduced pressure. The crude product was purified by column

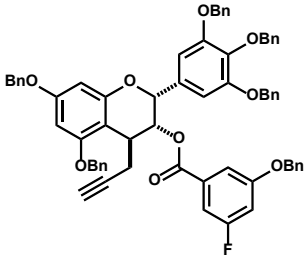
chromatography on silica gel (100% hexanes to hexanes/EtOAc 8:2) to furnish **3-35** (880 mg) as a white solid in 45% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45-7.26 (m, 25H), 6.84 (s, 2H), 6.29 (s, 2H), 5.15-5.01 (m, 11H), 4.28 (d, *J* = 5.0 Hz, 1H), 3.35-3.32 (ddd, *J* = 10.7, 3.7, 1.7 Hz 1H), 3.0 (dt, *J* = 17.2, 3.7 Hz, 1H), 2.35 (ddd, *J* = 17.4, 10.8, 2.6 Hz, 1H), 2.07 (t, *J* = 2.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.4, 158.5, 154.8, 153.1, 138.4, 137.8, 137.0, 136.8, 133.5, 128.64, 128.60, 128.5, 128.4, 128.2, 128.1, 127.94, 127.91, 127.84, 127.81, 127.62, 127.59, 126.9, 106.1, 103.3, 94.6, 94.3, 81.7, 75.2, 74.7, 71.4, 71.0, 70.1, 70.0, 69.0, 36.6, 23.2.

HRMS (ESI): m/z calcd for $C_{53}H_{49}O_7$ $[M+3H]^+$: 797.3478; found: 797.3471.

(2R,3R,4S)-5,7-bis(benzyloxy)-4-(prop-2-yn-1-yl)-2-(3,4,5-tris(benzyloxy)phenyl)chroman-3-yl 3-(benzyloxy)-5-fluorobenzoate (3-36b)



3-35 (80.6 mg, 0.33 mmol, 1.7 eq.) was dissolved in DCM (2.0 ml) and cooled to 0 °C. Ghosez's reagent (47.6 µl, 0.36 mmol, 1.87 eq.) was added dropwise and the reaction was stirred at room temperature for 1 hour. In the separate flask, **3-18** (153 mg, 0.19 mmol) was dissolved in DCM (2 ml). Acid chloride was then added (with the additional DCM rinse to ensure the complete transfer) followed by DMAP (58.8 mg, 0.48 mmol, 2.5 eq.). The reaction was stirred at 35 °C for 4 h and concentrated under the reduced pressure. The crude product was purified by column chromatography on silica gel (100% hexanes to hexanes/EtOAc 8:2) to furnish **3-36b** (140 mg) as a white solid in 70% yield.

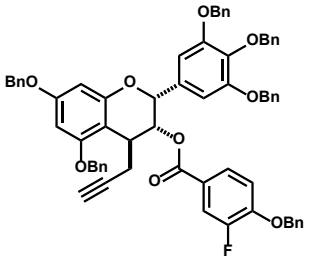
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43-7.29 (m, 28H), 7.22-7.19 (m, 4H), 6.80 (m, 3H), 6.36 (d, *J* = 2.2 Hz, 1H), 6.31 (d, *J* = 2.2 Hz, 1H), 5.74 (s, 1H), 5.31 (s, 1H), 5.07-4.82 (m, 12H), 3.40 (ddd,

J = 10.0, 4.1, 1.7 Hz, 1H), 3.06 (dt, *J* = 17.4, 3.0 Hz, 1H), 2.60 (ddd, *J* = 17.4, 10.0, 2.6 Hz, 1H), 2.17 (t, *J* = 2.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.0 (d), 159.3, 158.1, 155.3, 152.9, 138.2, 137.7, 137.0, 136.7, 136.5, 135.7, 133.0, 128.72, 128.67, 128.64, 128.57, 128.4, 128.36, 128.11, 128.08, 128.01, 127.8, 127.74, 127.70, 127.69, 127.5, 127.1, 111.9, 109.2 (d), 107.4 (d), 106.4, 102.9, 94.7, 94.2, 81.1, 75.1, 74.1, 71.8, 71.7, 71.3, 70.5, 70.2, 70.1, 34.7, 23.3.

HRMS (ESI): m/z calcd for $C_{67}H_{56}FO_9$ $[M+H]^+$: 1023.3908; found: 1023.3896.

(2R,3R,4S)-5,7-bis(benzyloxy)-4-(prop-2-yn-1-yl)-2-(3,4,5-tris(benzyloxy)phenyl)chroman-3-yl 4-(benzyloxy)-3-fluorobenzoate (3-36a)



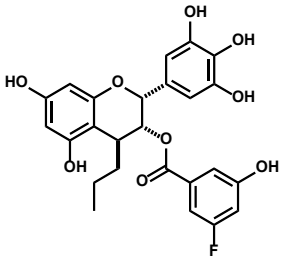
3-35 (73.7 mg, 0.3 mmol, 1.7 eq.) was dissolved in DCM (2.0 ml) and cooled to 0 °C. Ghosez's reagent (43.6 µl, 0.33 mmol, 1.87 eq.) was added dropwise and the reaction was stirred at room temperature for 1 hour. In the separate flask, **3-16** (140 mg, 0.176 mmol) was dissolved in DCM (2 ml). Acid chloride was then added (with the additional DCM rinse to ensure the complete transfer) followed by DMAP (53.8 mg, 0.44 mmol, 2.5 eq.). The reaction was stirred at 35 °C for 4 h and concentrated under the reduced pressure. The crude product was purified by column chromatography on silica gel (100% hexanes to hexanes/EtOAc 8:2) to furnish **3-36a** (140 mg) as a white solid in 75% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64 (m, 2H), 7.47-7.31 (m, 27H), 7.22-7.20 (m, 3H), 6.88 (t, *J* = 8.5 Hz, 1H), 6.81 (s, 2H), 6.35 (d, *J* = 2.2 Hz, 1H), 6.30 (d, *J* = 2.2 Hz, 1H), 5.74 (s, 1H), 5.31 (s, 1H), 5.09-4.82 (m, 12H), 3.38 (ddd, *J* = 10.0, 4.2, 1.6 Hz, 1H), 3.05 (dt, *J* = 17.5, 3.9 Hz, 1H), 2.60 (ddd, *J* = 17.4, 10.0, 2.8 Hz, 1H), 2.17 (t, *J* = 2.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.9, 159.3, 158.1, 155.3, 152.9, 152.8, 150.9 (d), 150.8, 138.2, 137.7, 137.0, 136.7, 136.5, 135.6, 133.1, 128.7, 128.65, 128.57, 128.52, 128.43, 128.37, 128.13, 128.08, 128.0, 127.8, 127.73, 127.70, 127.5, 127.3, 127.1, 126.9, 122.9 (d), 117.6 (d), 114.1, 106.5, 103.0, 94.7, 94.1, 81.2, 75.1, 74.2, 71.8, 71.3, 71.2, 71.0, 70.2, 70.1, 34.7, 23.2.

HRMS (ESI): m/z calcd for $C_{67}H_{56}FO_9$ $[M+H]^+$: 1023.3908; found: 1023.3948.

(2R,3R,4S)-5,7-dihydroxy-4-(prop-2-yn-1-yl)-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 3-fluoro-5-hydroxybenzoate (3-37b)



To a solution of **3-36b** (50.0 mg, 0.049 mmol) in EtOAc (4.9 mL, 0.01 M) was added $Pd(OH)_2/C$ (48.0 mg, 0.0684 mmol, 20 wt%, 1.4 eq.). The reaction was sparged with hydrogen gas (balloon) for 5 minutes and then stirred for 3 hours. The mixture was then filtered through celite and concentrated under the reduced pressure. The obtained product was analytically pure by both HPLC and NMR and thus directly submitted for the biological studies.

$[\alpha]_D^{21}$ = -145.00˚ (c = 0.1, MeOH).

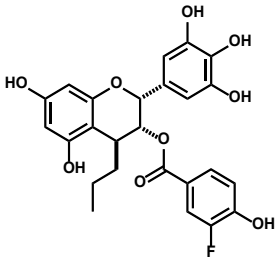
FT-IR (neat): 3455, 3317, 2972, 2932, 1716, 1623, 1607, 1508, 1449, 1372, 1333, 1299, 1146, 1033, 860, 823, 767, 737, 672, 629 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.05 (m, 2H), 6.92 (d, J = 9.4 Hz, 1H), 6.63 (dt, J = 10.5, 2.1 Hz, 1H), 6.48 (s, 2H), 5.96 (d, J = 2.3 Hz, 1H), 5.95 (d, J = 2.3 Hz, 1H), 5.38 (s, 1H), 5.04 (s, 1H), 2.96 (dq, J = 10.2, 1.8 Hz, 1H), 2.04-1.96 (m, 1H), 1.79-1.69 (m, 1H), 1.66-1.56 (m, 1H), 1.51-1.44 (m, 1H), 1.05 (t, J = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, CD_3OD): δ = 164.7 (d), 164.2, 162.3, 159.4 (d), 156.7 (d), 155.1, 145.5, 132.5 (d), 132.3, 129.3, 112.3, 107.0 (d), 106.5 (d), 105.1, 102.9, 95.4, 94.2, 73.1, 72.1, 36.9, 35.5, 19.9, 13.1.

HRMS (ESI): m/z calcd for $C_{25}H_{24}FO_9$ $[M+H]^+$: 487.1404; found: 487.1423.

(2R,3R,4S)-5,7-dihydroxy-4-(prop-2-yn-1-yl)-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 3-fluoro-4-hydroxybenzoate (3-37a)



To a solution of **3-36a** (44.3 mg, 0.0433 mmol) in EtOAc (4.33 mL, 0.01 M) was added $Pd(OH)_2/C$ (42.6 mg, 0.0426 mmol, 20 wt%, 1.4 eq.). The reaction was sparged with hydrogen gas (balloon) for 5 minutes and then stirred for 3 hours. The mixture was then filtered through celite and concentrated under the reduced pressure. The obtained product was analytically pure by both HPLC and NMR and thus directly submitted for the biological studies.

$[\alpha]_D^{21}$ = -113.00˚ (c = 0.1, MeOH).

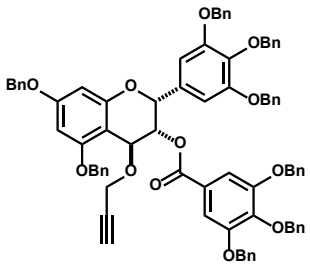
FT-IR (neat): 3458, 3347, 2959, 2923, 1699, 1616, 1519, 1454, 1372, 1279, 1218, 1149, 1027, 826, 733, 679, 636 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.45 (ddd, J = 20.6, 8.2, 2.1 Hz, 2H), 6.83 (t, J = 8.5 Hz, 1H), 6.48 (s, 2H), 5.97 (d, J = 2.3 Hz, 1H), 2.95 (d, J = 2.3 Hz, 1H), 5.34 (s, 1H), 5.04 (s, 1H), 2.96 (d, J = 9.2 Hz, 1H), 2.02-1.95 (m, 1H), 1.77-1.70 (m, 1H), 1.65-1.57 (m, 1H), 1.51-1.43 (m, 1H), 1.05 (t, J = 1.05 Hz, 3H).

^{13}C NMR (125 MHz, CD_3OD): δ = 165.1 (d), 156.7 (d), 155.1, 152.0, 150.8 (d), 150.1, 145.4, 132.2, 129.4, 126.6 (d), 120.8 (d), 117.1 (d), 116.8 (d), 105.1, 103.0, 95.4, 94.1, 73.2, 71.7, 36.9, 35.5, 19.4, 13.1.

HRMS (ESI): m/z calcd for $C_{25}H_{24}FO_9$ $[M+H]^+$: 487.1404; found: 487.1426.

(2R,3R,4S)-5,7-bis(benzyloxy)-4-(prop-2-yn-1-yloxy)-2-(3,4,5-tris(benzyloxy)phenyl) chroman-3-yl 3,4,5-tris(benzyloxy)benzoate (3-39)



Compound was prepared according to **General Procedure 4**.

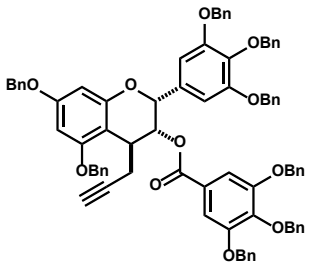
Yield: 930 mg, 79%, white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43-7.19 (m, 40H), 6.77 (s, 2H), 6.38 (d, *J* = 1.9 Hz, 1H), 6.34 (d, *J* = 1.9 Hz, 1H), 5.57 (d, *J* = 2.6 Hz, 1H), 5.32 (s, 1H), 5.12-4.91 (m, 12H), 4.80 (d, *J* = 11.4 Hz, 2H), 4.71 (d, *J* = 2.6 Hz, 1H), 4.68 (d, *J* = 11.4 Hz, 2H), 4.41 (qd, *J* = 31.2, 2.2 Hz, 2H), 2.39 (t, *J* = 2.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.4, 160.8, 159.4, 156.5, 152.9, 152.4, 142.9, 138.5, 137.8, 137.4, 136.9, 136.5, 136.4, 136.3, 132.6, 128.63, 128.61, 128.58, 128.51, 128.4, 128.28, 128.21, 128.19, 128.1, 127.9, 127.81, 127.77, 127.73, 127.51, 127.49, 124.4, 109.1, 106.9, 101.9, 94.3, 94.1, 80.3, 75.13, 75.07, 74.5, 74.3, 71.2, 71.0, 70.4, 70.2, 69.6, 68.5, 57.6.

HRMS (ESI): m/z calcd for $C_{81}H_{68}NaO_{12}$ $[M+Na]^+$: 1255.4608; found: 1255.4861.

(2R,3R,4S)-5,7-bis(benzyloxy)-4-(prop-2-yn-1-yl)-2-(3,4,5-tris(benzyloxy)phenyl)chroman-3-yl 3,4,5-tris(benzyloxy)benzoate (3-40)



To a solution of **3-39** (930 mg, 0.75 mmol) in DCM (10.8 mL, 0.07 M) was added **3-34** (0.5 ml, 1.68 mmol, 2.23 eq.). The reaction was cooled to -78 °C and BF_3•Et_2O (0.19 ml, 1.51 mmol, 2.0

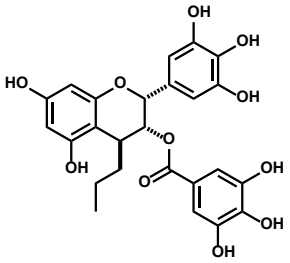
eq.) was added dropwise. The mixture was slowly warmed to room temperature (~1 h), quenched with $NaHCO_3$ and extracted with EtOAc (3x). Combined organic layers were dried with $MgSO_4$, filtered and concentrated under the reduced pressure. The crude product was purified by column chromatography on silica gel (100% hexanes to hexanes/EtOAc 8:2) to furnish **3-40** (790 mg) as a white solid in 86% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45-7.20 (m, 40H), 6.82 (s, 2H), 6.46 (d, *J* = 2.1 Hz, 1H), 6.40 (d, *J* = 2.2 Hz, 1H), 5.82 (s, 1H), 5.36 (s, 1H), 5.13-4.95 (m, 12H), 4.87 (d, *J* = 11.5 Hz, 2H), 4.73 (d, *J* = 11.5 Hz, 2H), 3.44 (d, *J* = 7.6 Hz, 1H), 3.12 (dt, *J* = 17.6 Hz, 3.8 Hz, 1H), 2.65 (ddd, *J* = 17.3, 10.0, 2.4 Hz, 1H), 2.22 (t, *J* = 2.5 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.5, 159.4, 158.2, 155.5, 152.9, 152.3, 142.7, 138.5, 137.8, 137.5, 136.9, 136.6, 136.5, 136.4, 133.1, 128.68, 128.64, 128.57, 128.55, 128.4, 128.2, 128.3, 128.11, 128.08, 128.04, 127.9, 127.83, 127.81, 127.76, 127.72, 127.56, 127.51, 127.1, 124.9, 109.1, 106.8, 103.3, 94.6, 94.2, 81.1, 75.2, 75.1, 74.4, 71.8, 71.3, 71.0, 70.9, 70.2, 70.1, 35.0, 23.2.

HRMS (ESI): m/z calcd for $C_{81}H_{69}O_{11}$ $[M+H]^+$: 1217.4840; found: 1217.4834.

(2R,3R,4S)-5,7-dihydroxy-4-propyl-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 3,4,5-trihydroxybenzoate (3-41)



To a solution of **3-40** (50.0 mg, 0.0411 mmol) in EtOAc (4.11 mL, 0.01 M) was added $Pd(OH)_2/C$ (40.4 mg, 0.058 mmol, 20 wt%, 1.4 eq.). The reaction was sparged with hydrogen gas (balloon) for 5 minutes and then stirred for 3 hours. The mixture was then filtered through celite and concentrated under the reduced pressure. The obtained product was analytically pure by both HPLC and NMR and thus directly submitted for the biological studies.

$[\alpha]_D^{21}$ = -100.00˚ (*c* = 0.1, MeOH).

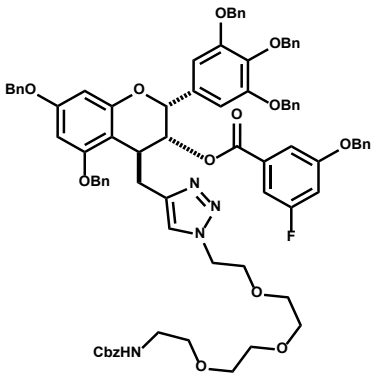
FT-IR (neat): 3372, 2959, 2926, 1691, 1620, 1541, 1516, 1458, 1379, 1343, 1239, 1149, 1085, 1035, 823, 769, 729, 701, 654, 629 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 6.88 (s, 2H), 6.49 (s, 2H), 5.94 (m, 2H), 5.35 (s, 1H), 5.00 (s, 1H), 2.92 (d, *J* = 10.2 Hz, 1H), 2.05-1.95 (m, 1H), 1.82-1.68 (m, 1H), 1.66-1.56 (m, 1H), 1.49-1.39 (m, 1H), 1.04 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, CD_3OD): δ = 166.2 156.7, 156.3, 155.2, 145.4, 144.9, 132.3, 129.5, 119.7, 108.7, 105.4, 103.2, 95.3, 94.2, 73.4, 71.1, 37.0, 35.7, 29.3, 20.0, 13.1.

HRMS (ESI): m/z calcd for $C_{25}H_{25}O_{11}$ $[M+H]^+$: 501.1397; found: 501.1389.

(2R,3R,4S)-5,7-bis(benzyloxy)-4-((1-(3-oxo-1-phenyl-2,7,10,13-tetraoxa-4-azapentadecan-15-yl)-1H-1,2,3-triazol-4-yl)methyl)-2-(3,4,5-tris(benzyloxy)phenyl)chroman-3-yl 3-(benzyloxy)-5-fluorobenzoate (3-43b)



Compound was prepared according to **General Procedure 2**.

Note 1: Cbz-protected linker was used as an azide partner, synthesized according to the published procedure.[105]

Note 2: Small amount of THF had to be added to the reaction to increase the solubility of the starting material.

Note 3: The reaction has been filtered through a silica plug (hexane/EtOAc 100% to EtOAc in 10% increments) to remove TBTA. The resulting crude mixture (product and unreacted linker) has been carried forward in the next step.

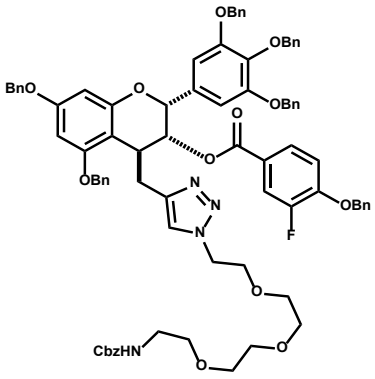
Yield: 63 mg, 55%, white solid (based on relative integration to unreacted linker).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57 (t, *J* = 9.6 Hz, 2H), 7.47-7.16 (m, 36H), 6.85 (m, 3H), 6.35 (d, *J* = 11.6 Hz, 2H), 5.38 (s, 1H), 5.29 (s, 1H), 5.17 (s, 1H), 5.11-4.82 (m, 14H), 4.43 (t, *J* = 5.4 Hz, 2H), 3.8 (t, *J* = 4.7 Hz, 2H), 3.55-3.42 (m, 12H), 3.35-3.33 (m, 3H), 3.1 (dd, *J* = 15.1, 10.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.8, 159.1, 158.1, 156.4, 155.2, 152.8, 150.8 (d), 145.1, 138.1, 137.8, 137.0, 136.7 (d), 136.6, 135.6, 133.2, 128.72, 128.66, 128.62 128.52, 128.51, 128.4, 128.2, 128.1, 128.0, 127.8, 127.70, 127.67, 127.6, 127.36, 127.27, 126.7 (d), 123.0 (d), 122.6, 117.5, 117.3, 114.0, 106.3, 104.1, 94.8, 94.1, 75.1, 73.9, 71.2, 71.0, 70.6, 70.47, 70.43, 70.20, 70.16, 70.12, 70.0, 69.6, 66.8, 50.2, 40.9, 36.4, 30.6.

HRMS (ESI): m/z calcd for $C_{83}H_{80}FN_4O_{14}$ $[M+H]^+$: 1375.5656; found: 1375.5729.

(2R,3R,4S)-5,7-bis(benzyloxy)-4-((1-(3-oxo-1-phenyl-2,7,10,13-tetraoxa-4-azapentadecan-15-yl)-1H-1,2,3-triazol-4-yl)methyl)-2-(3,4,5-tris(benzyloxy)phenyl)chroman-3-yl 4-(benzyloxy)-3-fluorobenzoate (3-43)



Compound was prepared according to **General Procedure 2**.

Note 1: Cbz-protected linker was used as an azide partner, synthesized according to the published procedure.[105]

Note 2: Small amount of THF had to be added to the reaction to increase the solubility of the starting material.

Note 3: The reaction has been filtered through a silica plug (hexane/EtOAc 100% to EtOAc in 10% increments) to remove TBTA. The resulting crude mixture (product and unreacted linker) has been carried forward in the next step.

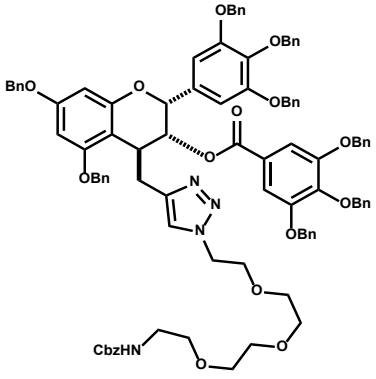
Yield: 98 mg, 60%, white solid (based on relative integration to unreacted linker).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49-7.14 (m, 38H), 6.84 (s, 2H), 6.76 (dt, *J* = 10.3, 2.3 Hz, 1H), 6.37 (d, *J* = 2.2 Hz, 1H), 6.35 (d, *J* = 2.2 Hz, 1H), 5.40 (s, 1H), 5.30 (s, 1H, NH), 5.18 (s, 1H), 5.10-4.83 (m, 14H), 4.44 (t, *J* = 4.8 Hz, 2H), 3.80 (t, *J* = 5.0 Hz, 2H), 3.64-3.32 (m, 14H), 3.08 (dd, *J* = 15.2, 10.4 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.0, 163.8 (d), 162.0, 159.8, 159.8, 159.2, 158.0, 156.4, 155.2, 152.8, 145.1, 138.0, 137.8, 137.0, 136.7 (d), 136.6, 135.7, 133.2, 132.6, 132.5 (d), 128.7, 128.65, 128.63, 128.52, 128.51, 128.4, 128.19, 128.13, 128.0, 127.8, 127.7, 127.6, 127.4, 122.6, 112.0, 109.1 (d), 107.2 (d), 106.3, 103.9, 94.8, 94.2, 75.1, 73.8, 71.7, 71.1, 70.69, 70.65, 70.62, 70.59, 70.52, 70.46, 70.43, 70.2, 70.1, 70.0, 69.9, 69.6, 66.7, 50.2, 40.8, 36.4, 30.5.

HRMS (ESI): m/z calcd for $C_{83}H_{79}FN_4O_{14}Na$ $[M+Na]^+$: 1397.5475; found: 1397.5996.

(2R,3R,4S)-5,7-bis(benzyloxy)-4-((1-(3-oxo-1-phenyl-2,7,10,13-tetraoxa-4-azapentadecan-15-yl)-1H-1,2,3-triazol-4-yl)methyl)-2-(3,4,5-tris(benzyloxy)phenyl)chroman-3-yl 3,4,5-tris(benzyloxy)benzoate (3-43c)



Compound was prepared according to **General Procedure 2**.

Note 1: Cbz-protected linker was used as an azide partner, synthesized according to the published procedure.[105]

Note 2: Small amount of THF had to be added to the reaction to increase the solubility of the starting material.

Note 3: The reaction has been filtered through a silica plug (hexane/EtOAc 100% to EtOAc in 10% increments) to remove TBTA. The resulting crude mixture (product and unreacted linker) has been carried forward in the next step.

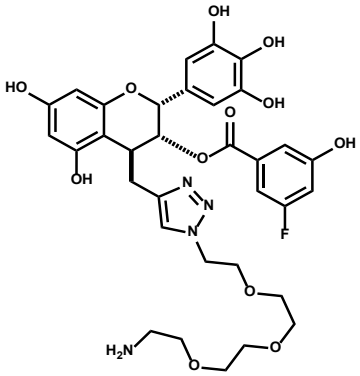
Yield: 180 mg, 70%, white solid (based on relative integration to unreacted linker).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40-7.16 (m, 48H), 6.80 (s, 2H), 6.42 (d, *J* = 2.00 Hz, 1H), 6.38 (d, *J* = 2.05 Hz, 1H), 5.43 (s, 1H), 5.29 (s, 1H, NH), 5.20 (s, 1H), 5.11-4.86 (m, 14H), 4.81 (d, *J* = 11.3 Hz, 2H), 4.68 (d, *J* = 11.3 Hz, 2H), 4.43 (m, 2H), 3.80 (t, *J* = 4.66 Hz, 2H), 3.57-3.42 (m, 12H), 3.33 (m, 2H), 3.10 (dd, *J* = 15.0, 11.0 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.4, 159.2, 158.2, 156.4, 155.4, 152.8, 152.3, 145.1, 142.7, 138.3, 137.8, 137.5, 136.97, 136.74, 136.67, 136.58, 136.39, 133.2, 128.64, 128.56, 128.52, 128.50, 128.40, 128.33, 128.27, 128.19, 128.14, 128.11, 128.08, 127.89, 127.79, 127.76, 127.69, 127.64, 127.57, 127.36, 125.0, 122.5, 109.0, 106.7, 104.3, 94.6, 94.1, 75.1, 75.0, 74.1, 71.2, 71.0, 70.86, 70.58, 70.48, 70.43, 70.21, 70.14, 69.96, 69.61, 66.7, 50.2, 40.8, 36.6, 30.5.

HRMS (ESI): m/z calcd for $C_{97}H_{93}N_4O_{16}$ $[M+H]^+$:1569.6587; found: 1569.6555.

(2R,3R,4S)-4-((1-(2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 3-fluoro-5-hydroxybenzoate (3-44b)



To a solution of **3-43b** (64.0 mg, 0.0465 mmol) in EtOAc/MeOH (4.65 mL, 0.01 M) were added Pd/C (44.6 mg, 0.042 mmol, 10 wt%, 0.9 eq.) and HCl (72.9 µL, 2.98 mmol, 64 eq.). The reaction was sparged with hydrogen gas (balloon) for 5 minutes and then stirred for 3 hours. The mixture was then filtered through celite and concentrated under the reduced pressure. The crude mixture was purified by preparative reverse-phase HPLC (33-60% MeCN/H_2O + 0.1% (v/v) TFA in 8.5 min) to give **3-44b** (20 mg) as an off-white solid in 61% yield.

$[\alpha]_D^{21}$ = -50.00˚ (c = 0.1, MeOH).

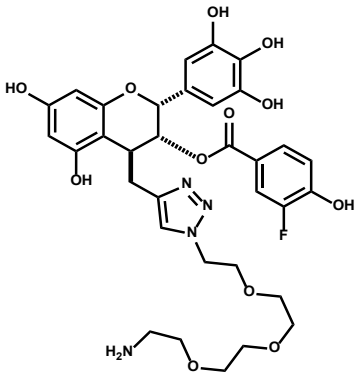
FT-IR (neat): 3235, 2955, 2930, 1685, 1609, 1519, 1458, 1339, 1207, 1146, 1027, 848, 805, 766, 718, 654, 614 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.89 (s, 1H), 7.03 (s, 1H), 6.91 (d, J = 8.2 Hz, 1H), 6.65 (dt, J = 10.3, 2.1 Hz, 1H), 6.46 (s, 2H), 6.02 (d, J = 2.2 Hz, 1H), 5.99 (d, J = 2,2 Hz, 1H), 5.20 (s, 1H), 4.93 (s, 1H), 4.60 (m, 2H), 3.91-3.89 (m, 2H), 3.60-3.45 (m, 12H), 3.07 (t, J = 4.7 Hz, 2H), 3.01 (dd, J = 15.0, 11.0 Hz, 1H).

^{13}C NMR (125 MHz, CD_3OD): δ = 164.4 (d), 162.2, 158.9 (d), 157.2, 156.9, 155.5, 145.4, 132.4 (d), 129.0, 123.2, 112.1, 106.7 (d), 106.5 (d), 105.1, 100.9, 95.5, 94.4, 73.0, 71.8, 70.1, 70.0, 69.8, 69.6, 69.2, 66.3, 50.2, 39.3, 36.2, 29.3.

HRMS (ESI): m/z calcd for $C_{33}H_{37}FN_4O_{12}Na$ $[M+Na]^+$:723.2290; found: 723.2289.

(2R,3R,4S)-4-((1-(2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 3-fluoro-4-hydroxybenzoate (3-44a)



To a solution of **3-43a** (85.0 mg, 0.062 mmol) in EtOAc/MeOH (6.2 mL, 0.01 M) were added Pd/C (59.2 mg, 0.056 mmol, 10 wt%, 0.9 eq.) and HCl (97 µL, 3.96 mmol, 64 eq.). The reaction was sparged with hydrogen gas (balloon) for 5 minutes and then stirred for 3 hours. The mixture was then filtered through celite and concentrated under the reduced pressure. The crude mixture was purified by preparative reverse-phase HPLC (33-60% MeCN/H_2O + 0.1% (v/v) TFA in 8.5 min) to give **3-44a** (23 mg) as an off-white solid in 53% yield.

$[\alpha]_D^{21}$ = -64.00˚ (c = 0.1, MeOH).

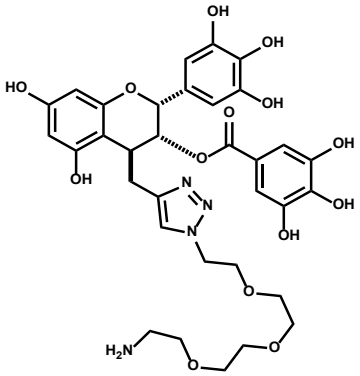
FT-IR (neat): 3289, 2959, 2926, 1681, 1623, 1519, 1462, 1304, 1279, 1200, 1143, 1024, 830, 797, 762, 729, 675, 639 cm^{-1}.

^{1}H NMR (500 MHz, Acetone-d6): δ = 7.96 (s, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.45 (d, J = 11.6 Hz, 1H), 6.98 (t, J = 8.5 Hz, 1H), 6.59 (s, 2H), 6.11 (s, 1H), 6.06 (s, 1H), 5.36 (s, 1H), 5.13 (s, 1H), 4.61 (t, J = 4.8 Hz, 2H), 3.94-3.92 (m, 4H), 3.77 (t, J = 4.7 Hz, 2H), 3.59 (m, 2H), 3.52-3.45 (m, 6H), 3.38 (d, J = 9.4 Hz, 1H), 3.07 (dd, J = 14.9, 10.8 Hz, 1H), 2.57-2.50 (m, 1H).

^{13}C NMR (125 MHz, Acetone-d6): δ = 163.8, 157.4, 157.0, 155.8, 151.6, 149.7 (d), 145.6, 144.8, 132.1, 129.6, 126.7, 122.9, 121.9 (d), 117.5, 117.0 (d), 105.6, 101.5, 96.0, 94.8, 73.1, 71.5, 70.3, 70.2, 70.15, 70.07, 69.4, 67.2, 50.2, 48.8, 47.8, 36.3, 29.8.

HRMS (ESI): m/z calcd for $C_{33}H_{37}FN_4O_{12}Na$ $[M+Na]^+$:723.2290; found: 723.2350.

(2R,3R,4S)-4-((1-(2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 3,4,5-trihydroxybenzoate (3-44c)



To a solution of **3-43c** (100.0 mg, 0.064 mmol) in EtOAc/MeOH (6.4 mL, 0.01 M) were added Pd/C (67.8 mg, 0.064 mmol, 10 wt%, 1.0 eq.) and HCl (100 µL, 4.08 mmol, 64 eq.). The reaction was sparged with hydrogen gas (balloon) for 5 minutes and then stirred for 3 hours. The mixture was then filtered through celite and concentrated under the reduced pressure. The crude mixture was purified by preparative reverse-phase HPLC (33-60% MeCN/H_2O + 0.1% (v/v) TFA in 12.5 min) to give **3-44c** (33 mg) as an off-white solid in 72% yield.

$[\alpha]_D^{21}$ = -74.00˚ (c = 0.1, MeOH).

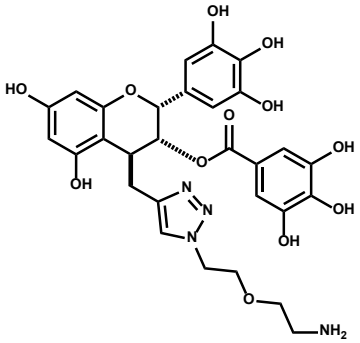
FT-IR (neat): 3347, 2955, 2926, 1674, 1623, 1545, 1451, 1350, 1207, 1149, 1024, 797, 726, 664, 639 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.94 (s, 1H), 6.86 (s, 2H), 6.47 (s, 2H), 6.01 (d, J = 2.0 Hz, 1H), 5.97 (d, J = 2.2 Hz, 1H), 5.15 (s, 1H), 4.93 (s, 1H), 4.59 (t, J = 4.9 Hz, 2H), 3.93-3.85 (m, 2H), 3.56-3.41 (m, 12H), 3.04 (t, J = 4.8 Hz, 2H), 2.98 (dd, J = 15.1, 11.0 Hz, 1H).

^{13}C NMR (125 MHz, CD_3OD): δ = 165.7, 157.08, 157.04, 156.9, 155.5, 145.3, 145.1, 144.9, 138.4, 132.3, 129.2, 123.4, 119.9, 108.8, 105.4, 101.2, 95.4, 94.4, 73.3, 70.7, 70.0, 69.9, 69.8, 69.6, 69.1, 66.2, 50.3, 39.2, 36.3, 29.4.

HRMS (ESI): m/z calcd for $C_{33}H_{39}N_4O_{14}$ $[M+H]^+$:715.2463; found: 715.2479.

(2R,3R,4S)-4-((1-(2-(2-aminoethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 3,4,5-trihydroxybenzoate (3-57)



To a solution of the corresponding ester (124.0 mg, 0.084 mmol) in EtOAc/MeOH (8.4 mL, 0.01 M) were added Pd/C (89.1 mg, 0.084 mmol, 10 wt%, 1.0 eq.) and HCl (131 μL, 5.36 mmol, 64 eq.). The reaction was sparged with hydrogen gas (balloon) for 5 minutes and then stirred for 3 hours. The mixture was then filtered through celite and concentrated under the reduced pressure. The crude mixture was purified by preparative reverse-phase HPLC (33-60% MeCN/H_2O + 0.1% (v/v) TFA in 12.5 min) to give **3-57** (40 mg) as an off-white solid in 65% yield.

$[\alpha]_D^{21}$ = -76.00˚ (c = 0.1, MeOH).

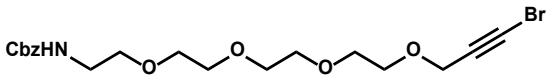
FT-IR (neat): 3255, 2952, 2934, 1695, 1684, 1541, 1458, 1336, 1203, 1149, 1039, 1027, 808, 729, 672, 650, 636 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.96 (s, 1H), 6.82 (s, 2H), 6.45 (s, 2H), 6.01 (d, J = 2.3 Hz, 1H), 5.97 (d, J = 2.3 Hz, 1H), 5.16 (t, J = 1.3 Hz, 1H), 4.99 (s, 1H), 4.64 (dd, J = 6.1, 3.7 Hz, 2H), 3.94 (td, J = 5.1, 0.9 Hz, 2H), 3.62 (t, J = 5.1 Hz, 2H), 3.56 (dd, J = 15.3, 3.7 Hz, 1H), 3.27-3.26 (m, 1H), 3.05-2.99 (m, 2H), 2.93 (dd, J = 15.2, 11.4 Hz, 1H).

^{13}C NMR (125 MHz, CD_3OD): δ = 166.0, 157.1, 156.9, 155.5, 145.4, 145.3, 144.9, 138.5, 132.3, 129.2, 123.2, 119.8, 108.8, 105.3, 101.3, 95.4, 94.4, 73.2, 70.5, 69.3, 66.5, 50.0, 39.2, 36.5, 29.4.

HRMS (ESI): m/z calcd for $C_{29}H_{31}N_4O_{12}$ $[M+H]^+$:627.1938; found: 627.1932.

benzyl (15-bromo-3,6,9,12-tetraoxapentadec-14-yn-1-yl)carbamate (3-48)



A solution of **3-48** (39.2 g, 202 mmol, 2.0 eq.) in THF (9.0 mL, 100 ml, 2.0 M) was cooled to 0°C. NaH (5.2 g, 131 mmol, 1.3 eq.) was added and the solution was stirred for 1h. Propargyl bromide (15.0 g, 101 mmol, 1.0 eq.) was then added and the reaction was warmed up to room temperature and stirred overnight. The mixture was quenched with H_2O, extracted with DCM (3x), dried, filtered and concentrated under the reduced pressure. The crude product was purified by column chromatography on silica gel (100% hexanes to hexanes/EtOAc 8:2) to furnish **3-58** (13.7 g) as a yellow oil in 58% yield.

The spectra matched those reported in the literature.[106]

3-58 (13.67 g, 58.9 mmol, 1.0 eq.) was dissolved in THF (559 ml, 0.1 M) followed by the addition of Et_3N (10.0 ml, 7.26 g, 71.8 mmol, 1.22 eq.) and MsCl (5.5 ml, 8.09 g, 70.6 mmol, 1.2 eq.) dropwise. The solution was stirred for 45 minutes, filtered and concentrated under the reduced pressure. Crude material was then re-dissolved in DCM, washed with 10% citric acid, brine, dried, filtered and concentrated under the reduced pressure. IMPORTANT: NMR analysis should show no presence of DCM as any of amount of it can be hazardous in the next step and potentially explosive.

To the solution of crude **3-59** (58.9 mmol) in DMF (218 ml, 0.27 M) was added NaN_3 (4.67 g, 72.8 mmol, 1.22 eq.). The reaction was stirred at 60 °C overnight, then cooled, diluted with H_2O and extracted with Et_2O (3x). Combined organic layers were washed with H_2O, brine, dried, filtered and concentrated under the reduced pressure to afford azide **3-49** which was used directly in the next step without further purification.

Crude azide **3-49** (2.0 g, 7.77 mmol) was dissolved in MeOH (77 ml, 0.1 M). Et_3N (8.7 ml, 6.3 g, 62.2 mmol, 8 eq.) and 1,3-propanedithiol (5.5 ml, 5.9 g, 54.4 mmol, 7 eq.) were added and the reaction was stirred at room temperature for 2 days and then acidified with HCl. Resulting solution was washed with DCM (3x) and then basified with solid NaOH. Aqueous layer was then extracted

with DCM, dried, filtered and concentrated under the reduced pressure to afford amine **3-50** which was used in the next step without further purification.

Crude amine **3-5** (1.90 g, 8.2 mmol) was dissolved in H_2O (82 ml, 0.1 M). Na_2CO_3 (4.35 g, 41.1 mmol, 5 eq.) was then added and the reaction was cooled to 0 °C. Cbz-Cl (4.1 ml, 4.9 g, 28.8 mmol, 3.5 eq.) was added dropwise and the solution was stirred at the same temperature for 45 minutes, neutralized with 1 M HCl, extracted with DCM (3x), dried, filtered and concentrated under the reduced pressure. The crude product was purified by column chromatography on silica gel (100% hexanes to hexanes/EtOAc 1:1 in 10% increments) to furnish **3-51** (2.10 g) as a colorless oil in 70% yield after two steps.

To the solution of amine **3-51** (2.10 g, 5.75 mmol) in acetone (57.5 ml, 0.1 M) were added NBS (1.23 g, 6.90 mmol, 1.2 eq.) and $AgNO_3$ (195 mg, 1.15 mmol, 0.2 eq.). Reaction was stirred for 4 hours, filtered through Celite and concentrated under the reduced pressure. The crude product was purified by column chromatography on silica gel (100% hexanes to hexanes/EtOAc 1:1 in 10% increments) to furnish **3-45** as a colorless oil.

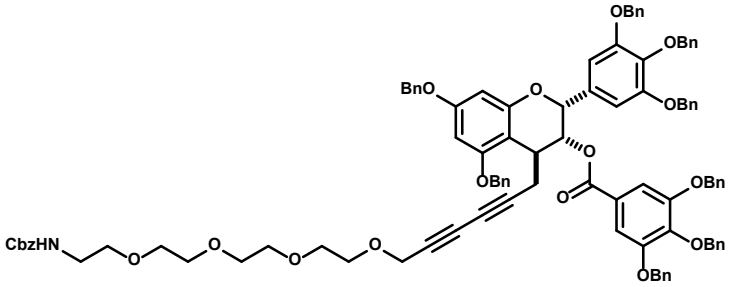
Note: Product always coelutes with some of the succinimide. However, the impurity has not effect on the subsequent coupling.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36-7.29 (m, 5H), 5.41 (br s, 1H, NH), 5.09 (s, 2H), 4.19 (s, 2H), 3.63-3.61 (m, 12 H), 3.56 (t, *J* = 4.99 Hz, 2H), 3.39 (q, *J* = 5.20 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.5, 136.6, 128.5, 128.15, 128.08, 76.2, 70.61, 70.57, 70.53, 70.35, 70.28, 70.1, 69.2, 66.6, 59.4, 46.1, 40.9.

HRMS (ESI): m/z calcd for $[M+H]^+$: $C_{19}H_{27}NO_6Br$ $[M+H]^+$:444.1022; found: 444.1042.

(2R,3R,4S)-5,7-bis(benzyloxy)-4-(3-oxo-1-phenyl-2,7,10,13,16-pentaoxa-4-azadocosa-18,20-diyn-22-yl)-2-(3,4,5-tris(benzyloxy)phenyl)chroman-3-yl 3,4,5-tris(benzyloxy)benzoate (3-46)



3-45 (60.8 mg, 0.137 mmol) and **3-40** (200 mg, 0.164 mmol, 1.2 eq.) were dissolved in THF (1.64 ml, 0.1 M). $Pd(PPh_3)_4$ (14.4 mg, 0.0205 mmol, 15 mol%) and CuI (2.61 mg, 0.0137 mmol, 10 mol%) were added followed by the *i*Pr_2NH (38.6 uL, 0.274 mmol, 2.0 eq.). The reaction was stirred for 3 hours, diluted with hexanes and immediately purified by column chromatography on silica gel (100% hexanes to hexanes/EtOAc 1:1 in 10% increments) to furnish **3-46** as a yellow solid.

Note: Product coelutes with **3-45**.

^{1}H NMR (500 MHz, $CDCl_3$) (desired product): δ = 7.39-7.19 (m, 47H), 6.78 (s, 2H), 6.42 (s, 1H), 6.35 (s, 1H), 5.66 (s, 1H), 5.41 (br s, 1H, NH), 5.29 (s, 1H), 5.11-4.67 (m, 18H), 4.20 (s, 2H), 3.64-3.53 (m, 14H), 3.41-3.37 (m, 3H), 3.14 (dd, *J* = 17.8, 3.0 Hz, 1H), 2.79 (dd, *J* = 17.8, 9.3 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.4, 159.5, 158.2, 156.5, 155.5, 152.9, 152.3, 142.8, 138.5, 137.8, 137.5, 136.9, 136.65, 136.62. 136.5, 136.4, 132.9, 128.7, 128.64, 128.57, 128.52, 128.4, 128.3, 128.2, 128.15, 128.11, 127.90, 127.85, 127.81, 127.7, 127.63, 127.56, 127.2, 124.8, 109.1, 106.8, 102.9, 94.6, 94.2, 75.1, 75.06, 74.5, 73.0, 71.25, 71.18, 71.10, 71.02, 70.62, 70.59, 70.54, 70.51, 70.36, 70.34, 70.26, 70.20, 70.13, 70.08, 70.05, 59.4, 59.0, 40.9, 34.9, 29.7.

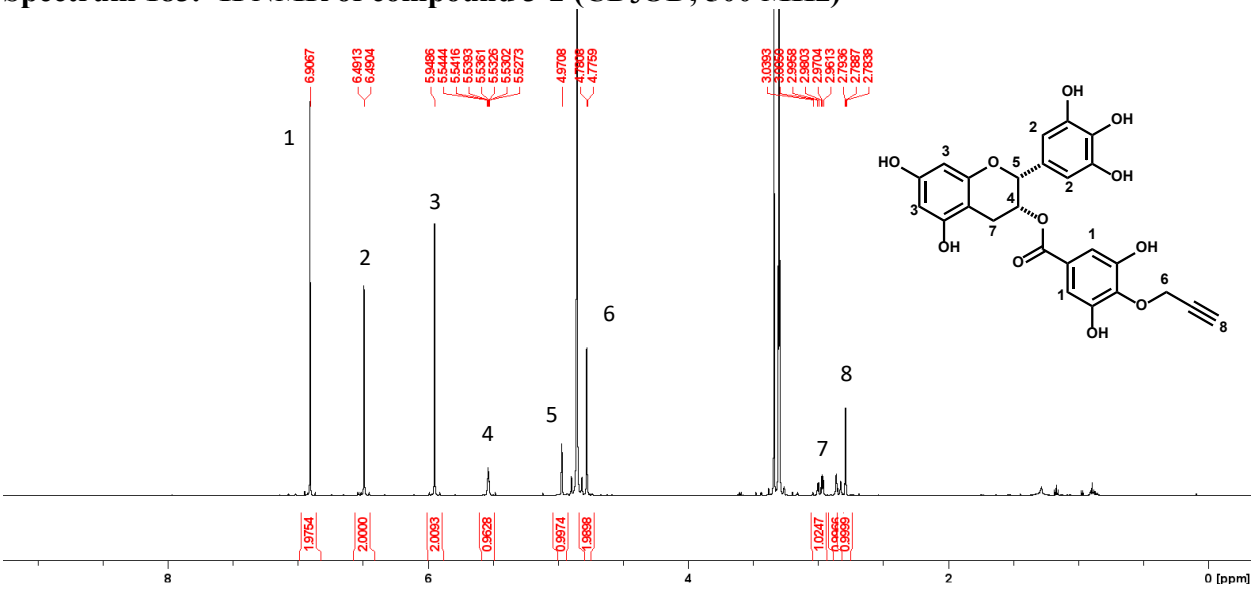
HRMS (ESI): m/z calcd for $[M+H]^+$: $C_{100}H_{93}NO_{17}Na$ $[M+H]^+$:1602.6341; found: 1602.7834.

^{1}H NMR (500 MHz, $CDCl_3$) (homocoupling product): δ = 7.38-7.17 (m, 84H), 6.77 (s, 4H), 6.40 (s, 2H), 6.33 (s, 2H), 5.66 (s, 2H), 5.32 (s, 2H), 5.05-4.64 (m, 32H), 3.41 (d, *J* = 5.9 Hz, 2H), 3.12 (d, *J* = 17.3 Hz, 2H), 2.79 (dd, *J* = 17.8, 9.2 Hz, 2H).

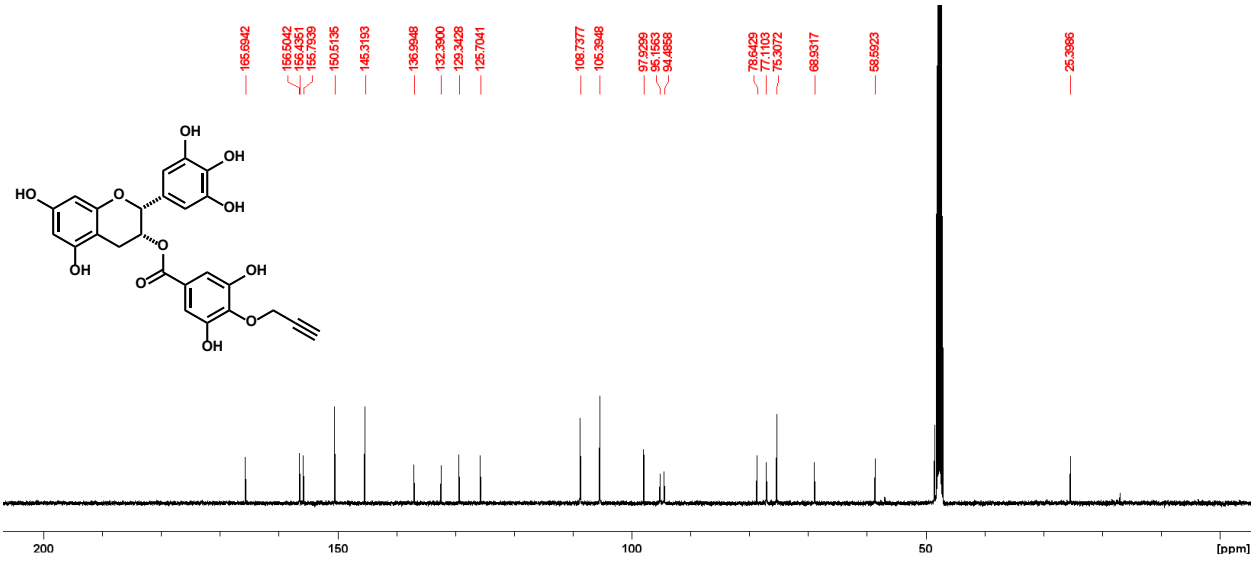
^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.3, 159.4, 158.2, 155.5, 152.9, 152.3, 142.7, 138.5, 137.8, 137.5, 136.9, 136.6, 136.44, 136.41, 132.9, 128.7, 128.6, 128.55, 128.49, 128.36, 128.27, 128.19, 128.08, 128.06, 127.9, 127.82, 127.79, 127.73, 127.69, 127.59, 127.57, 127.1, 124.8, 109.1, 106.8, 102.9, 94.6, 94.2, 75.1, 75.0, 74.6, 71.23, 71.17, 71.0, 70.17, 70.1, 68.5, 35.0, 29.7.

3.7.3 NMR Spectra

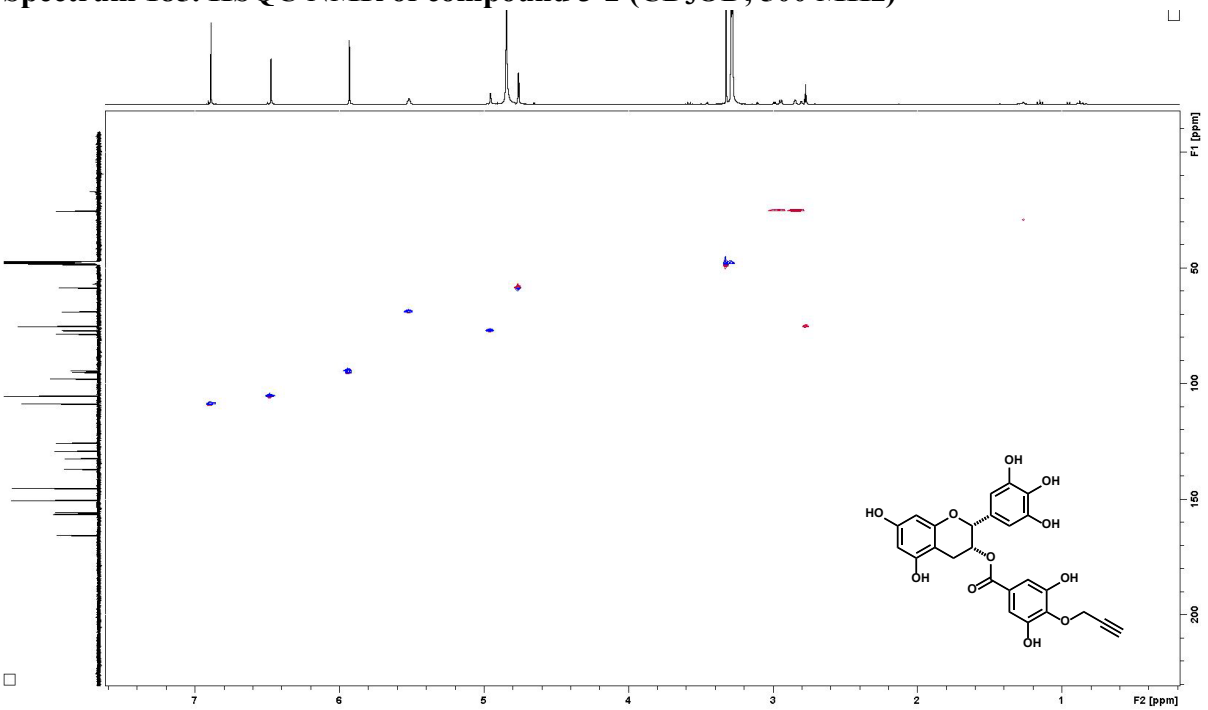
Spectrum 183. ^{1}H NMR of compound 3-2 (CD_3OD, 500 MHz)



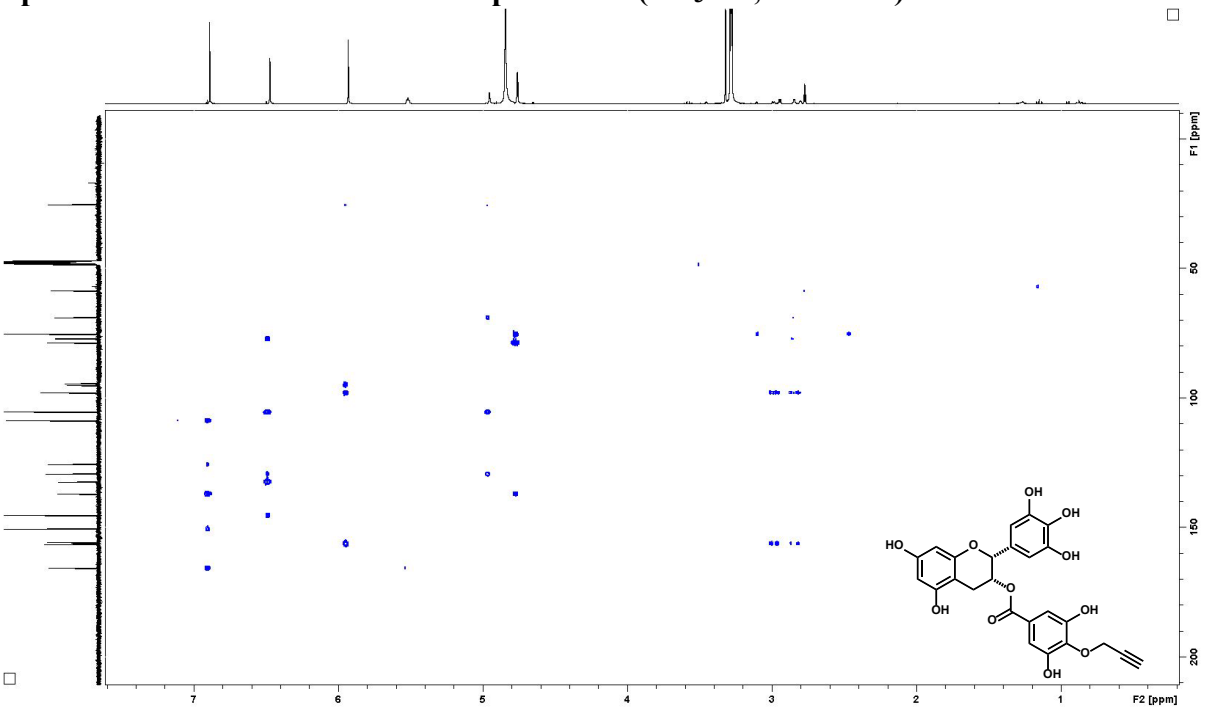
Spectrum 184. ^{13}C NMR of compound 3-2 (CD_3OD, 125 MHz)



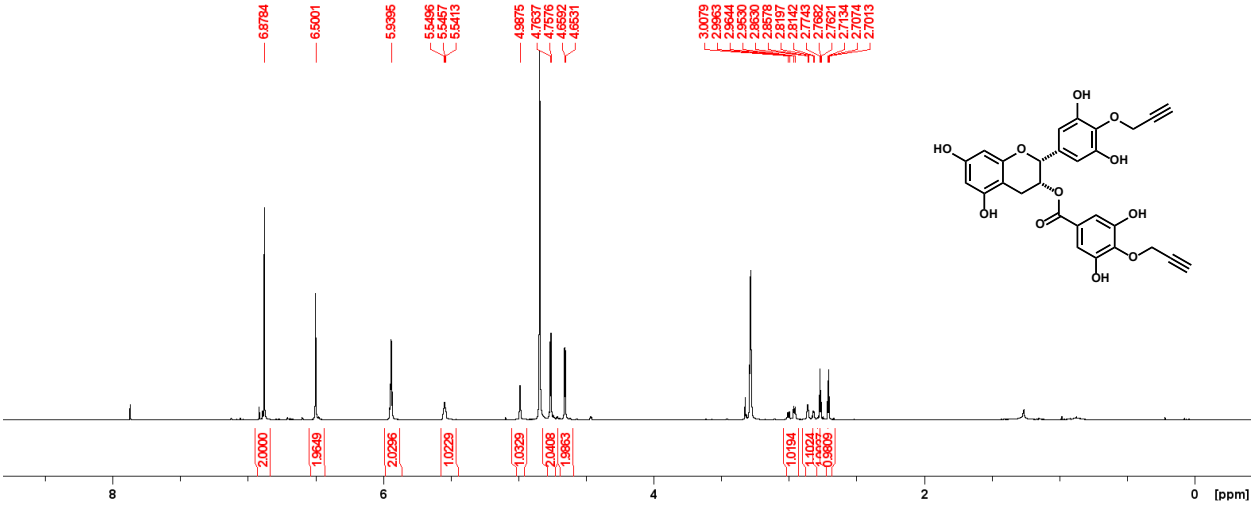
Spectrum 185. HSQC NMR of compound 3-2 (CD_3OD, 500 MHz)



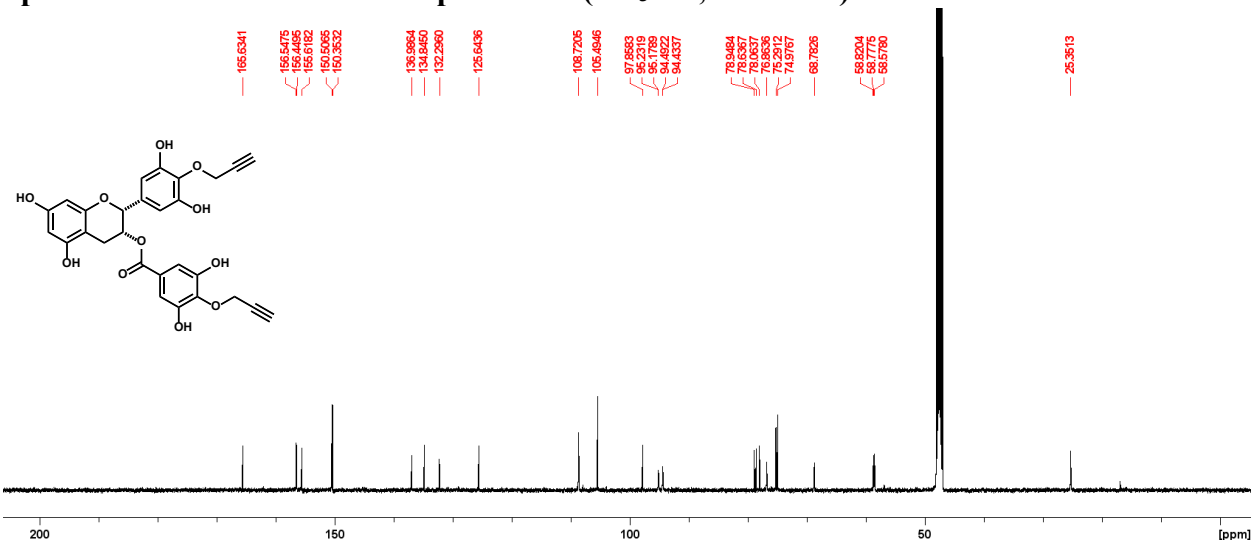
Spectrum 186. HMBC NMR of compound 3-2 (CD_3OD, 500 MHz)



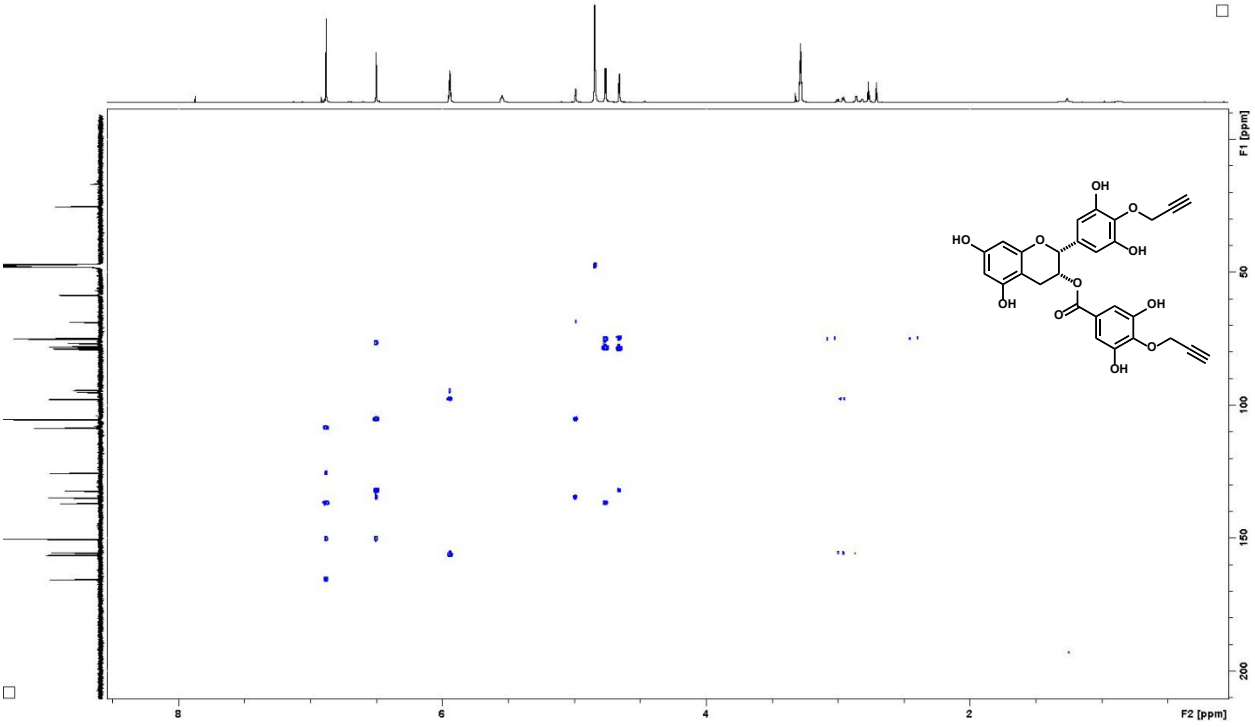
Spectrum 187. ^{1}H NMR of compound 3-3 (CD_3OD, 500 MHz)



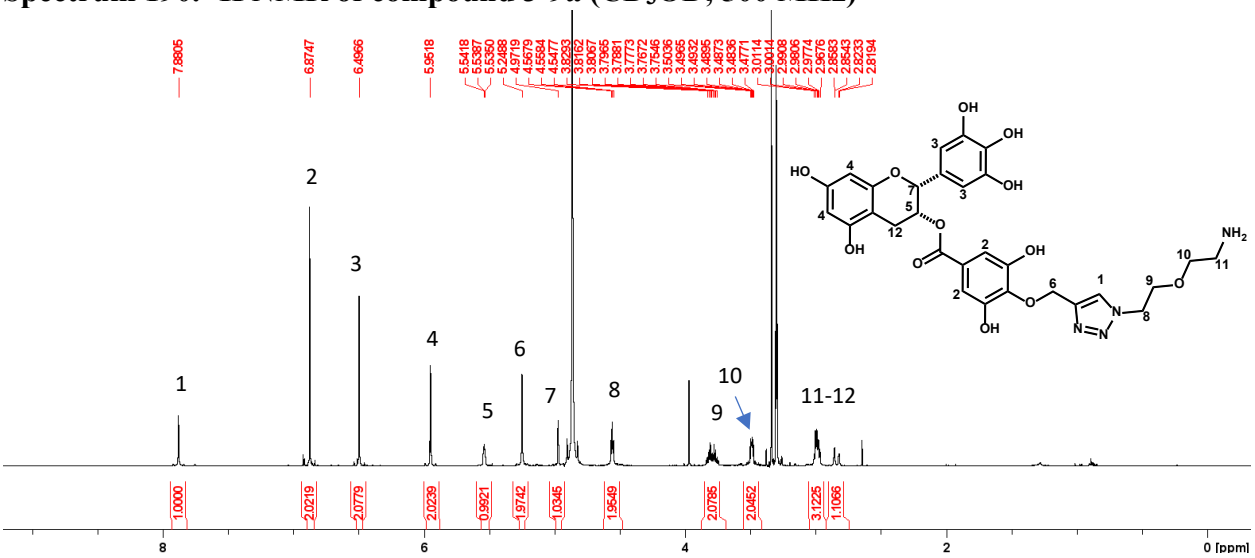
Spectrum 188. ^{13}C NMR of compound 3-3 (CD_3OD, 125 MHz)



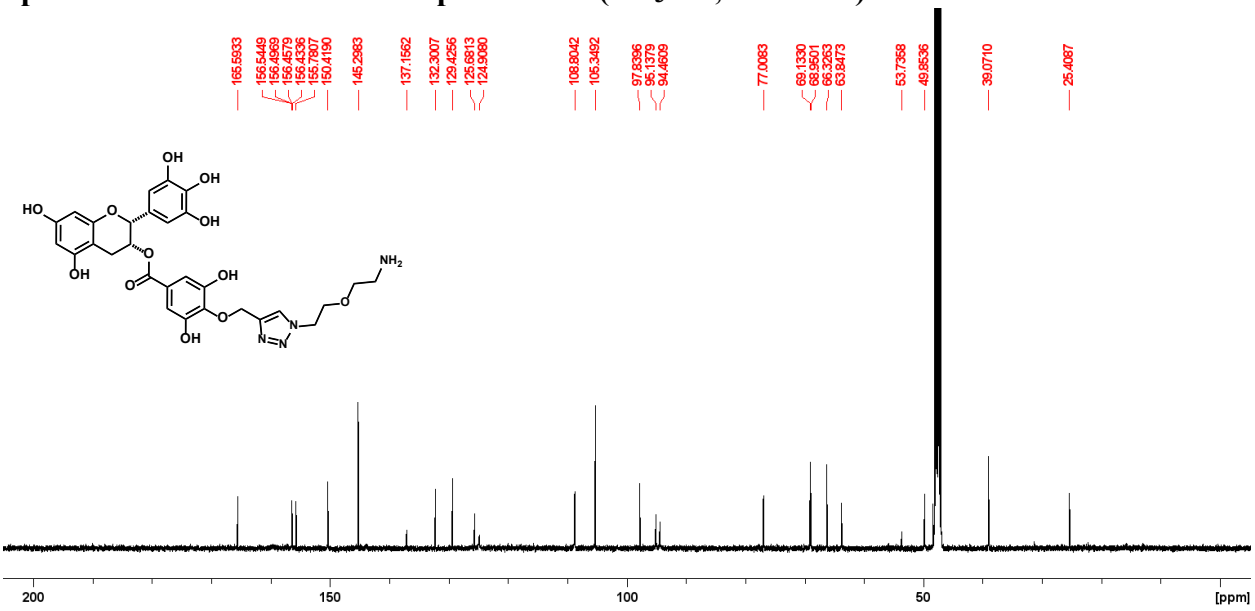
Spectrum 189. HSQC NMR of compound 3-3 (CD_3OD, 125 MHz)



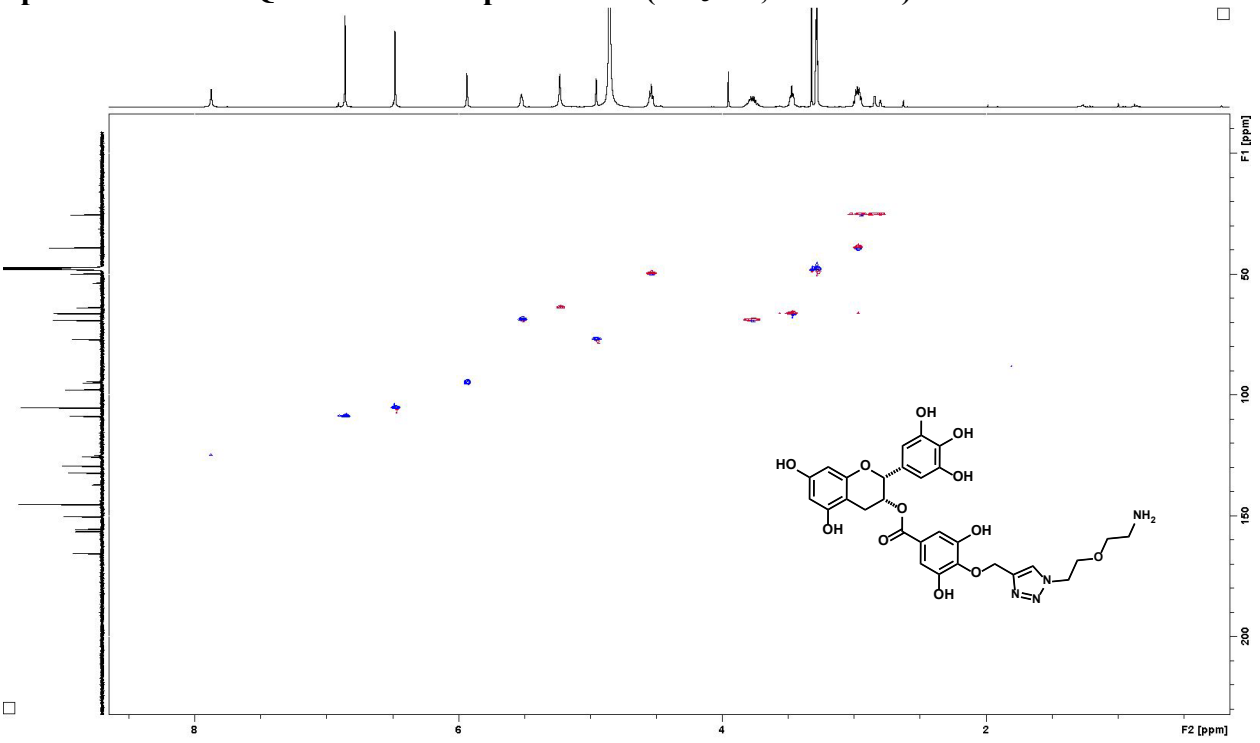
Spectrum 190. ^{1}H NMR of compound 3-9a (CD_3OD, 500 MHz)



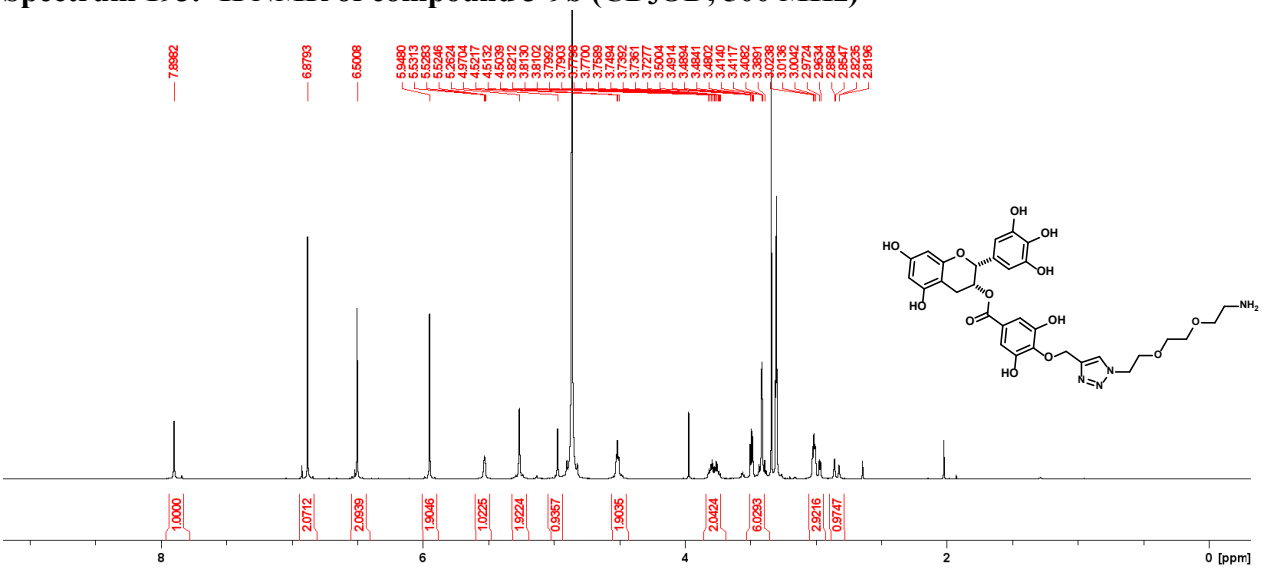
Spectrum 191. ^{13}C NMR of compound 3-9a (CD_3OD, 125 MHz)



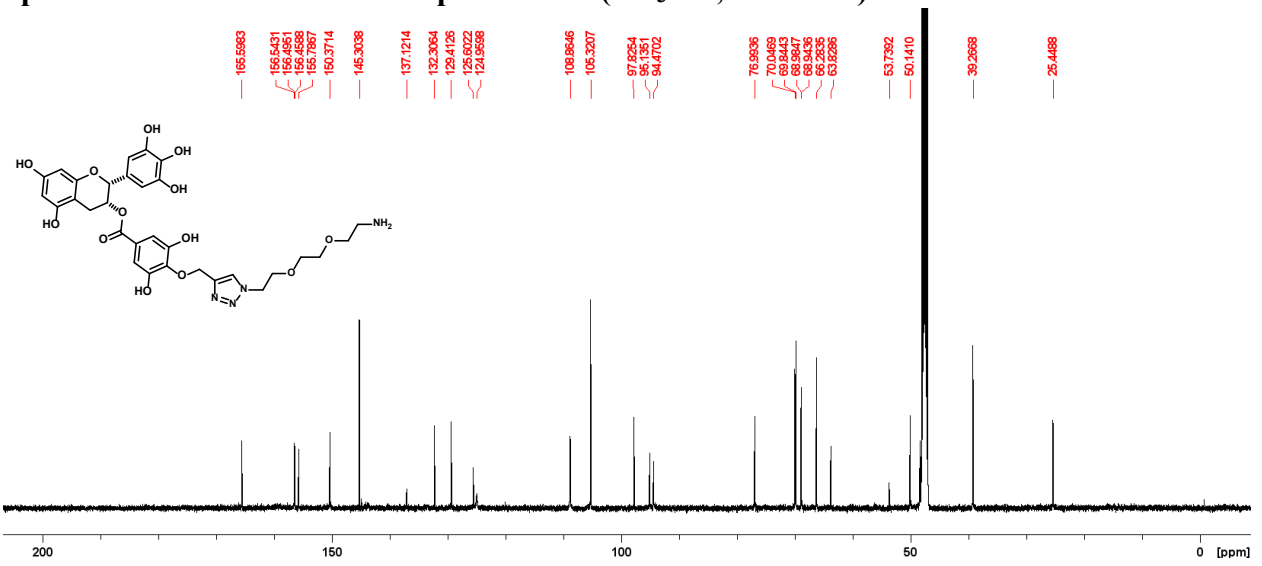
Spectrum 192. HSQC NMR of compound 3-9a (CD_3OD, 500 MHz)



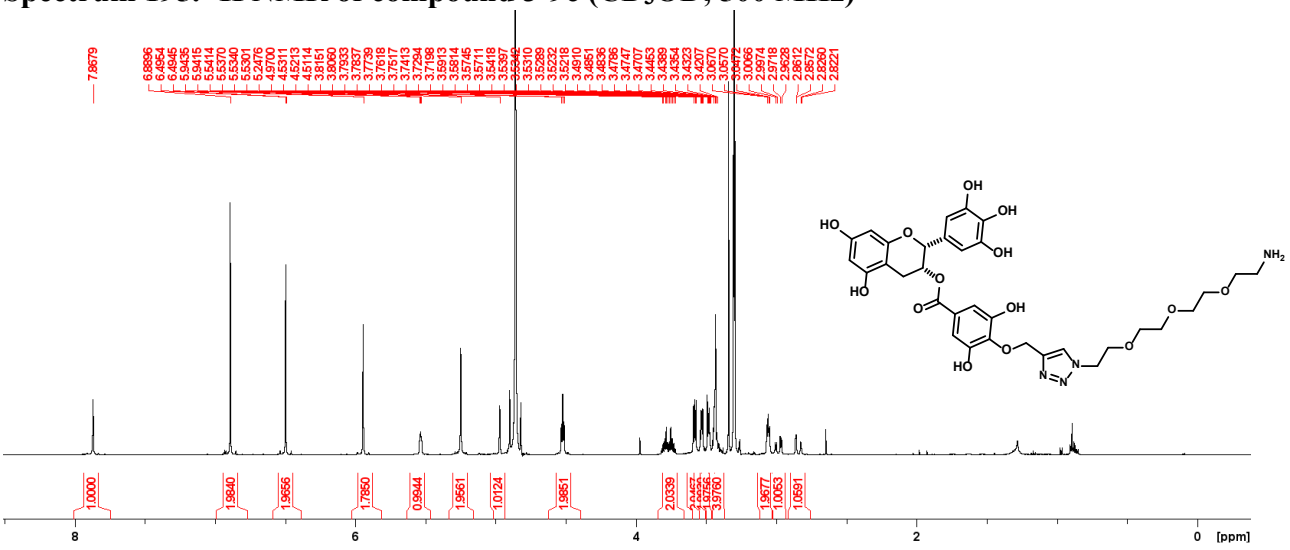
Spectrum 193. ^{1}H NMR of compound 3-9b (CD_3OD, 500 MHz)



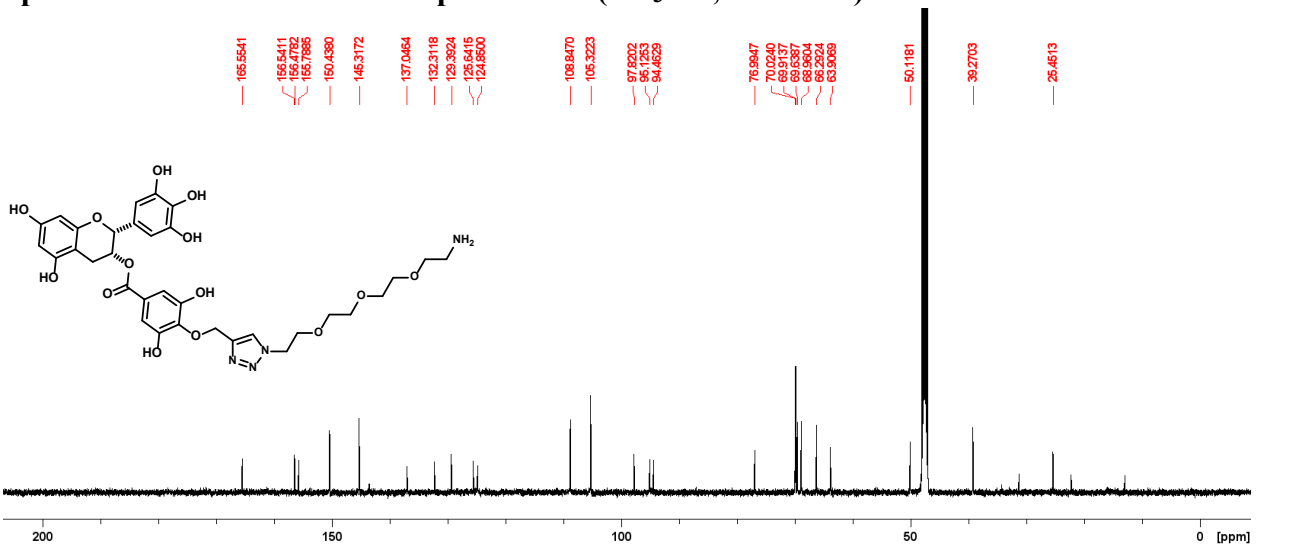
Spectrum 194. ^{13}C NMR of compound 3-9b (CD_3OD, 125 MHz)



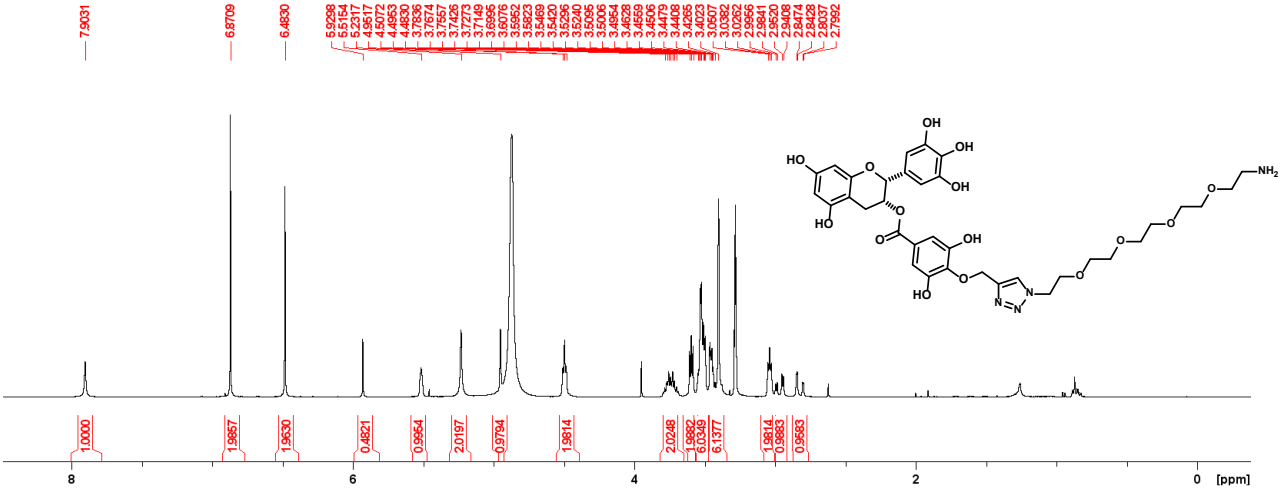
Spectrum 195. ^{1}H NMR of compound 3-9c (CD_3OD, 500 MHz)



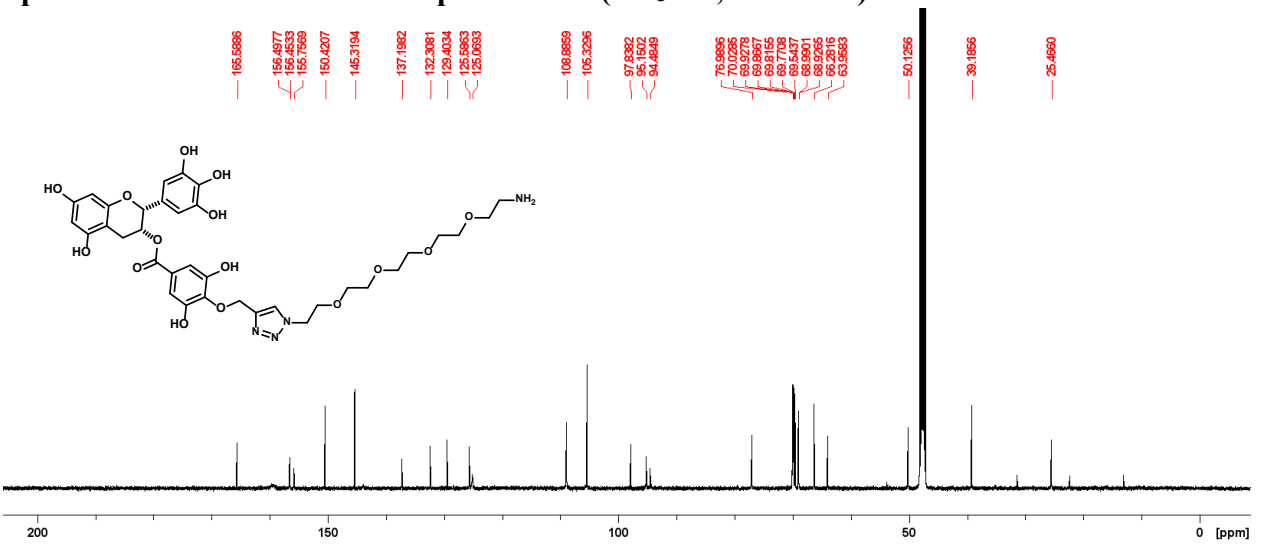
Spectrum 196. ^{13}C NMR of compound 3-9c (CD_3OD, 125 MHz)



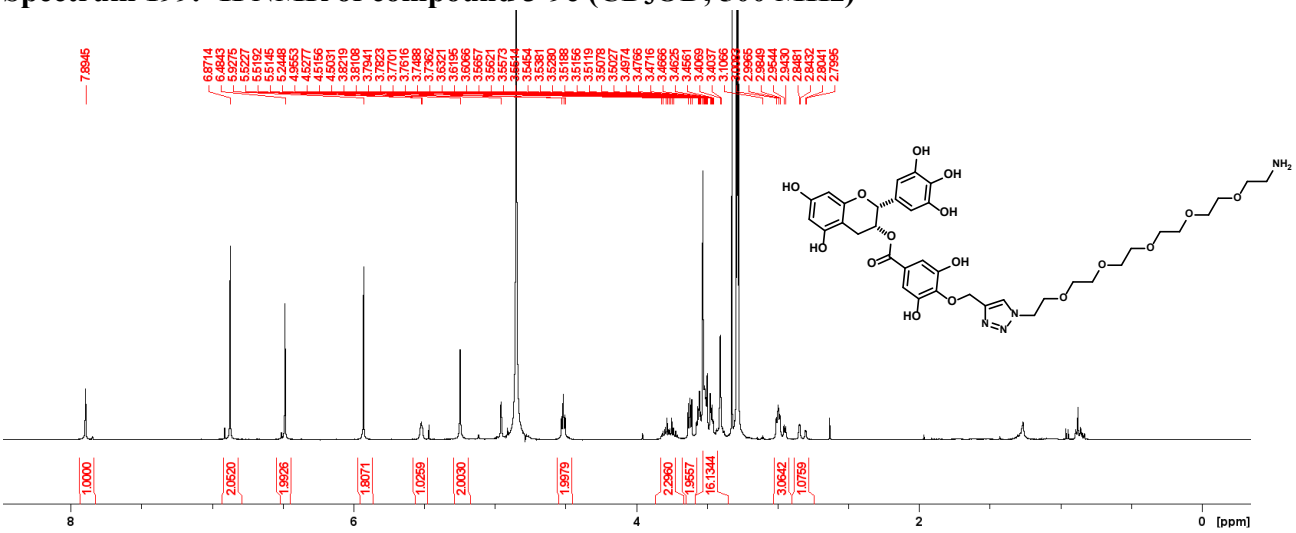
Spectrum 197. ^{1}H NMR of compound 3-9d (CD_3OD, 500 MHz)



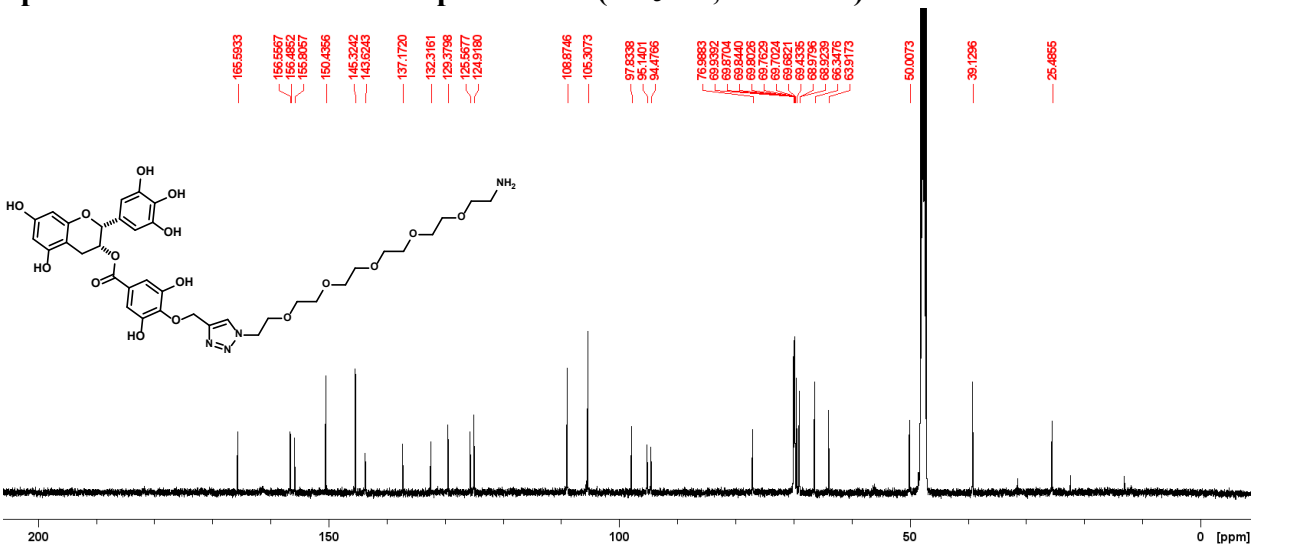
Spectrum 198. ^{13}C NMR of compound 3-9d (CD_3OD, 125 MHz)



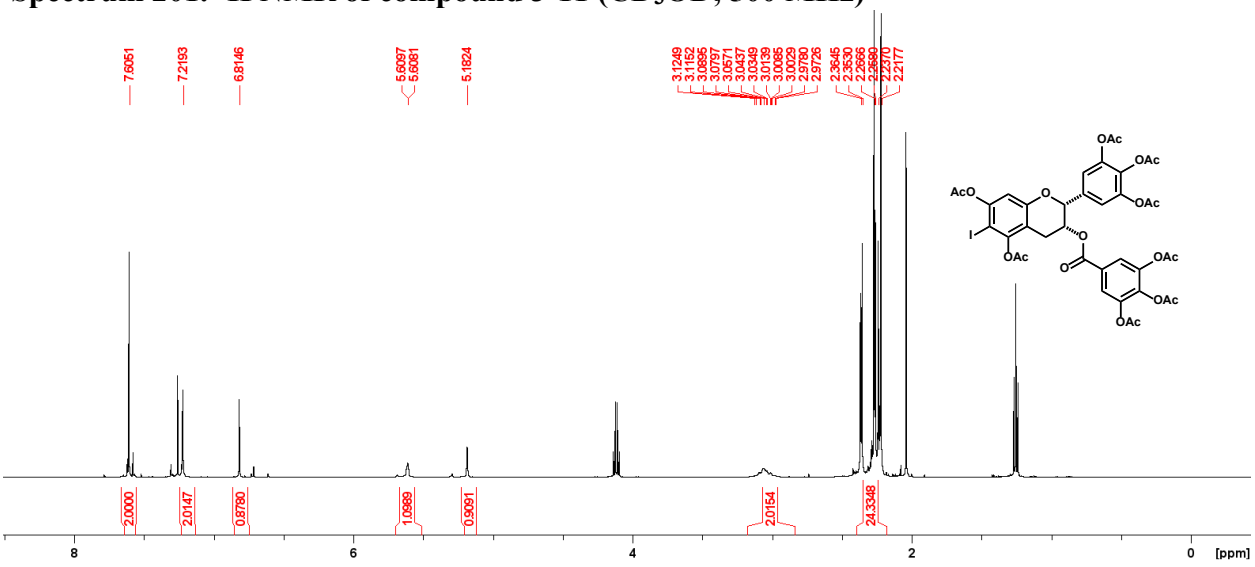
Spectrum 199. ^{1}H NMR of compound 3-9e (CD_3OD, 500 MHz)



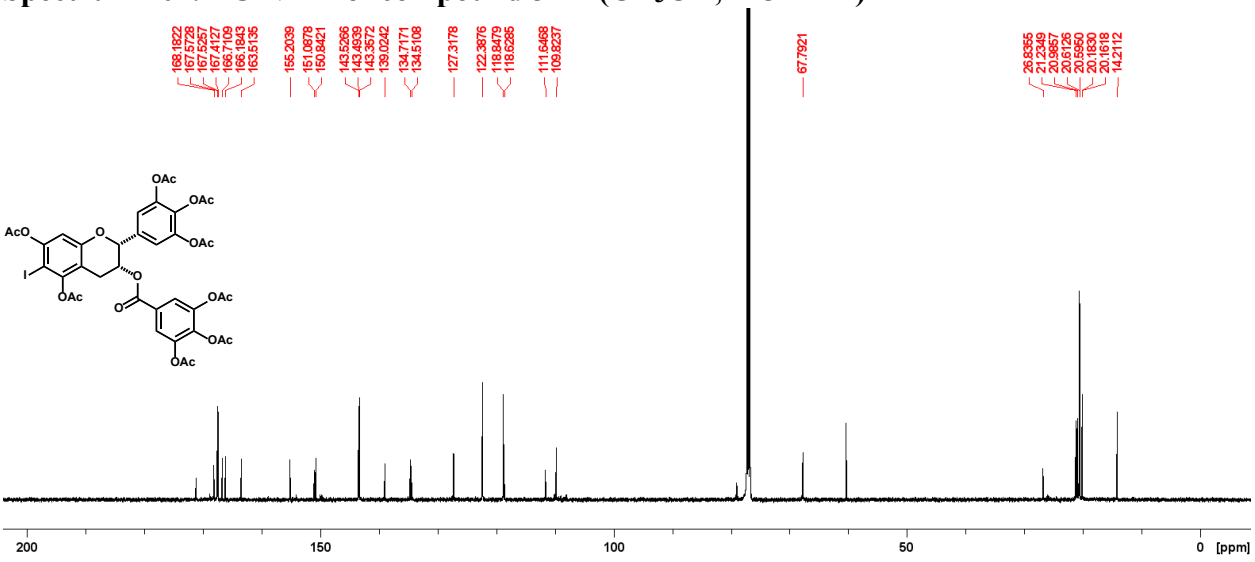
Spectrum 200. ^{13}C NMR of compound 3-9e (CD_3OD, 125 MHz)



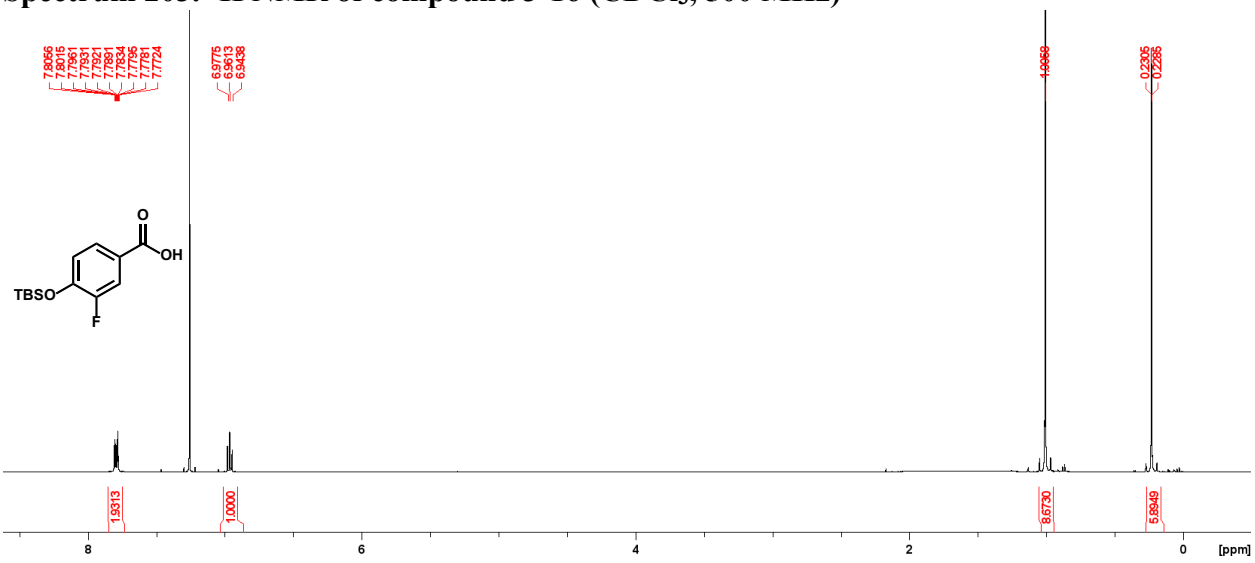
Spectrum 201. ^{1}H NMR of compound 3-11 (CD_3OD, 500 MHz)



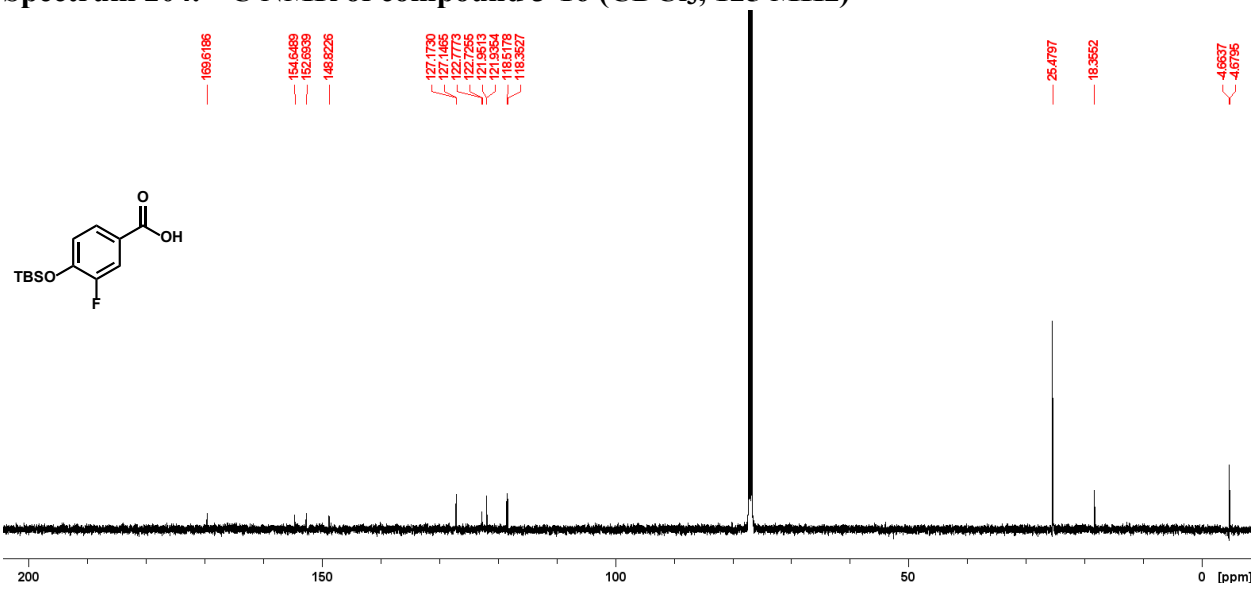
Spectrum 202. ^{13}C NMR of compound 3-11 (CD_3OD, 125 MHz)



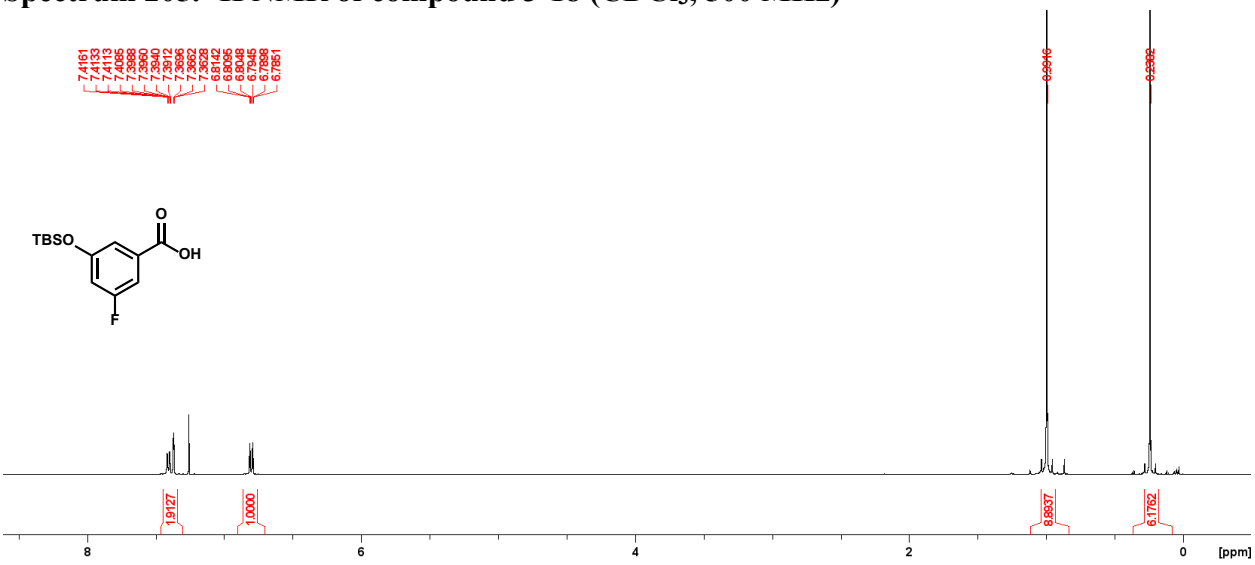
Spectrum 203. ^{1}H NMR of compound 3-16 ($CDCl_3$, 500 MHz)



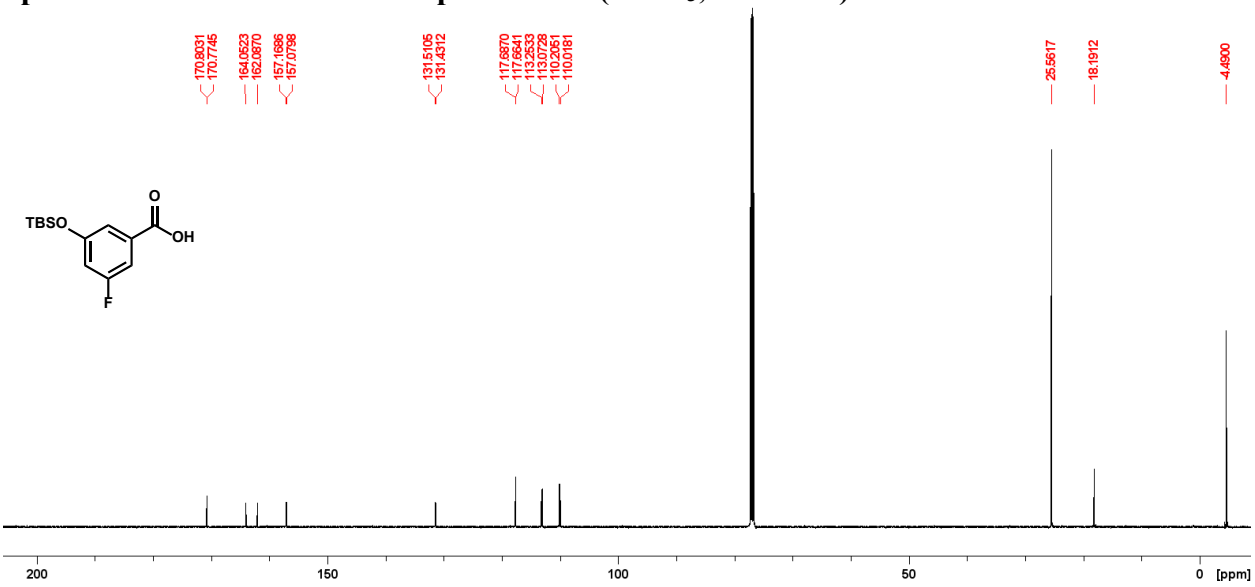
Spectrum 204. ^{13}C NMR of compound 3-16 ($CDCl_3$, 125 MHz)



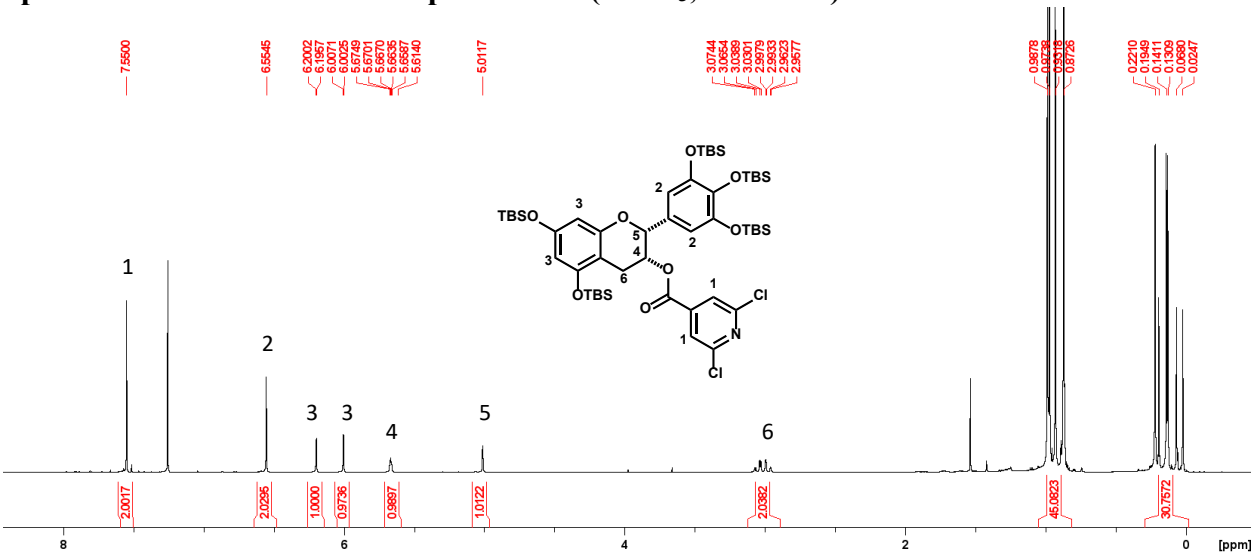
Spectrum 205. ^{1}H NMR of compound 3-18 ($CDCl_3$, 500 MHz)



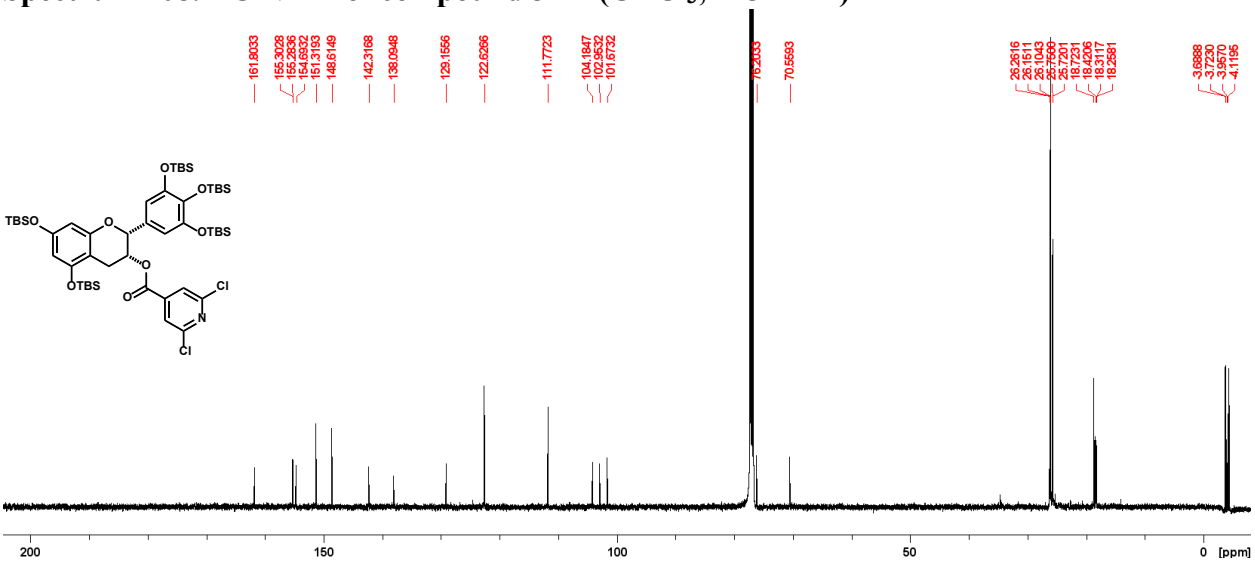
Spectrum 206. ^{13}C NMR of compound 3-18 ($CDCl_3$, 125 MHz)



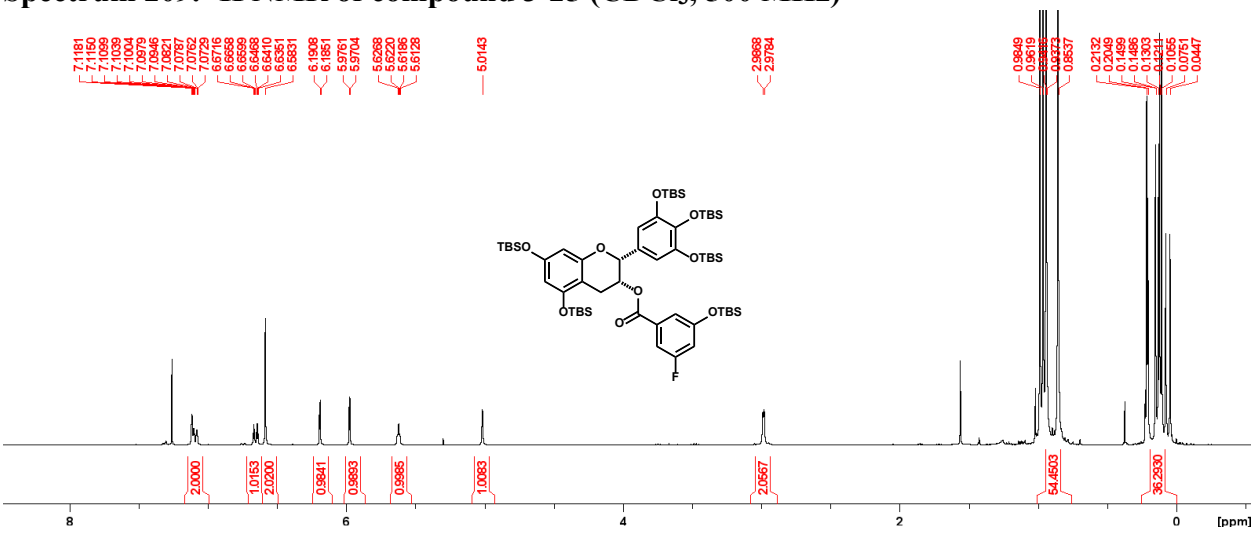
Spectrum 207. ^{1}H NMR of compound 3-24 ($CDCl_3$, 500 MHz)



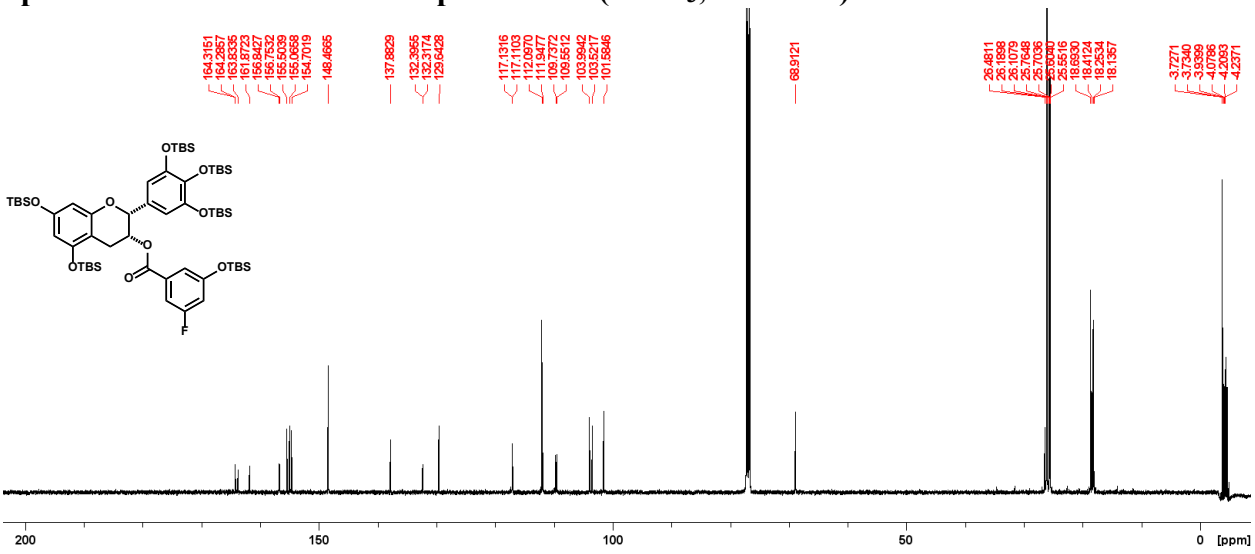
Spectrum 208. ^{13}C NMR of compound 3-24 ($CDCl_3$, 125 MHz)



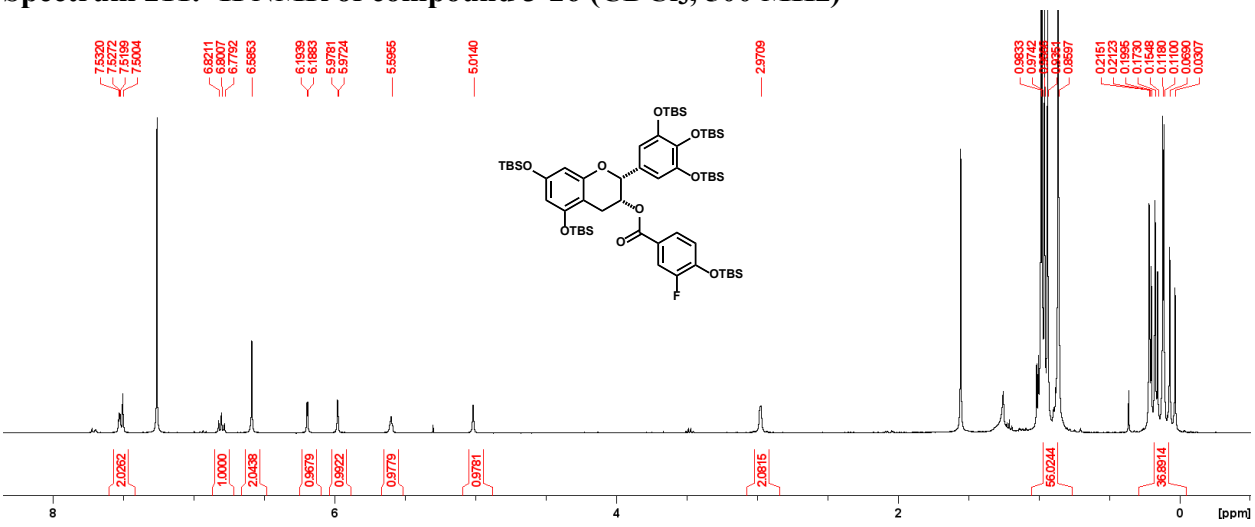
Spectrum 209. ^{1}H NMR of compound 3-25 ($CDCl_3$, 500 MHz)



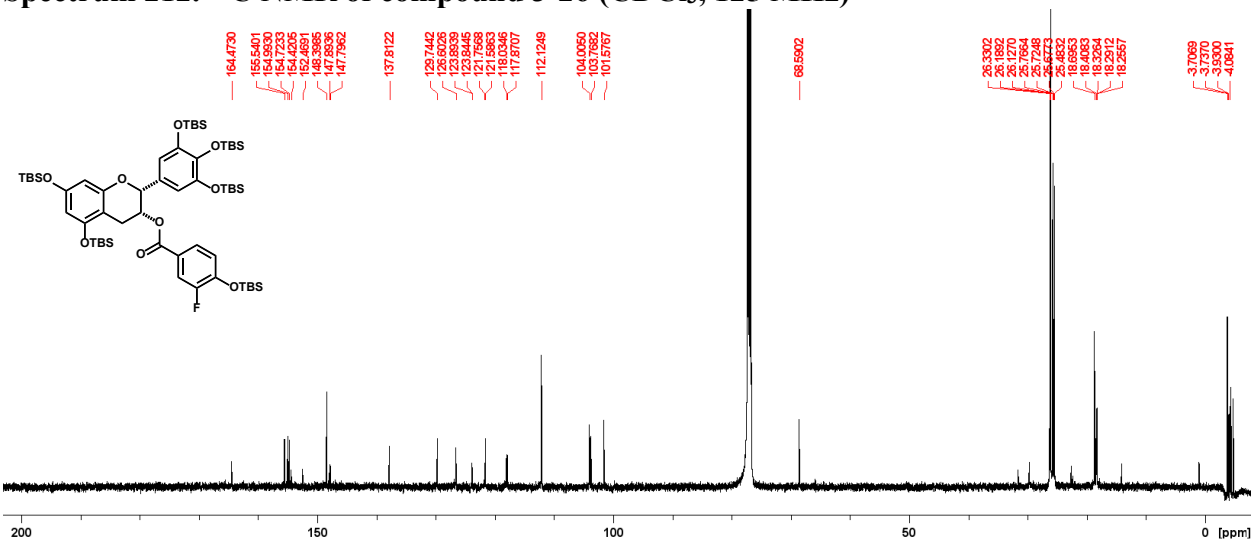
Spectrum 210. ^{13}C NMR of compound 3-25 ($CDCl_3$, 125 MHz)



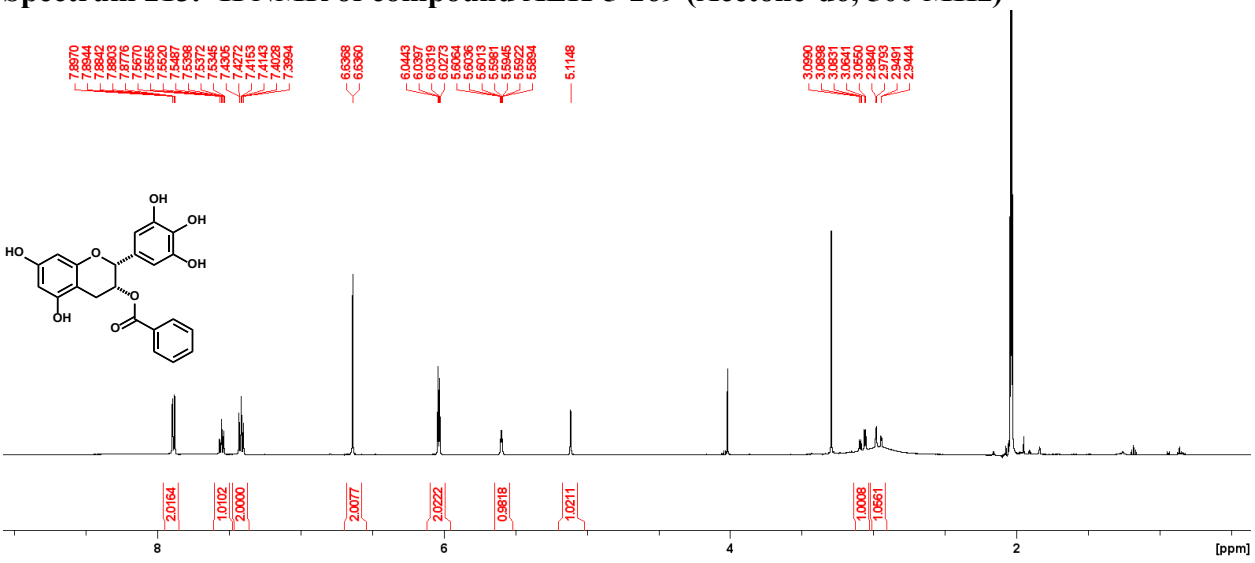
Spectrum 211. ^{1}H NMR of compound 3-26 ($CDCl_3$, 500 MHz)



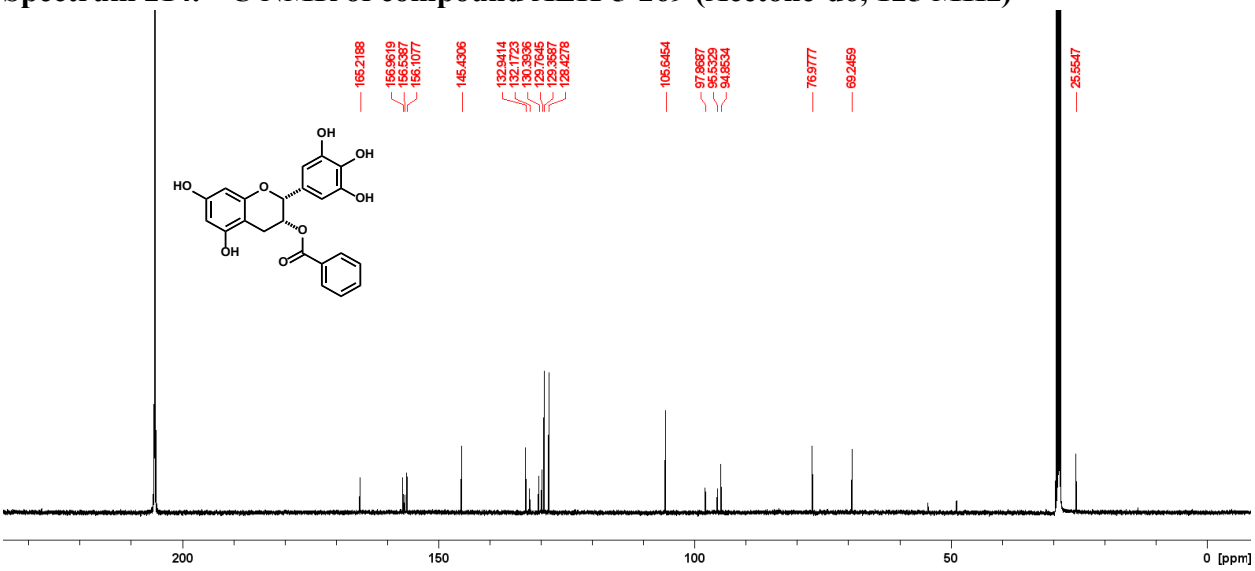
Spectrum 212. ^{13}C NMR of compound 3-26 ($CDCl_3$, 125 MHz)



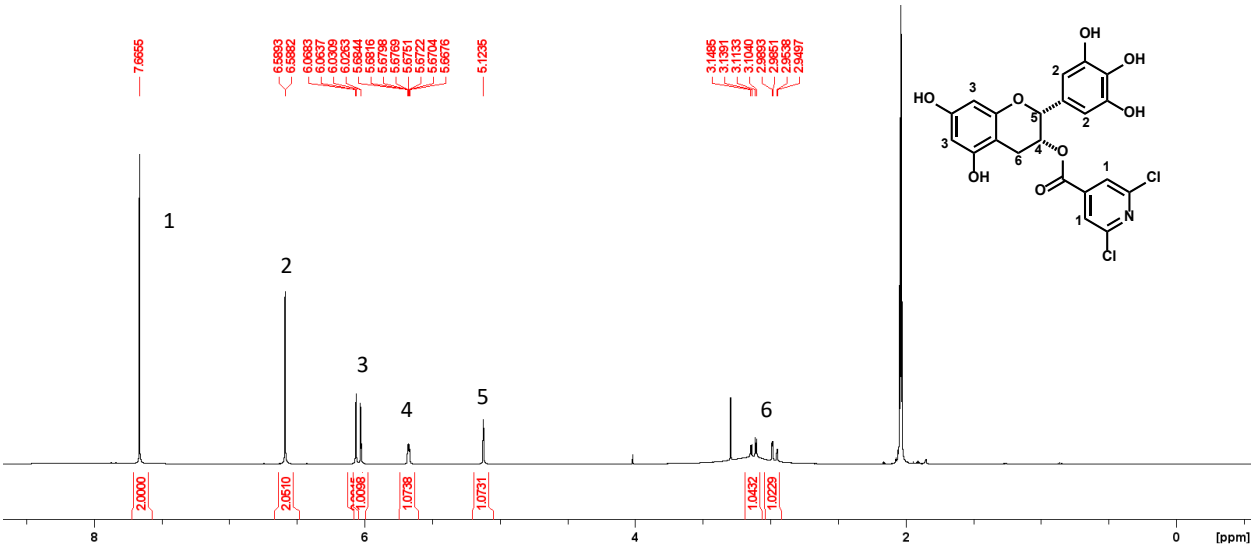
Spectrum 213. ^{1}H NMR of compound AEK-5-269 (Acetone-d6, 500 MHz)



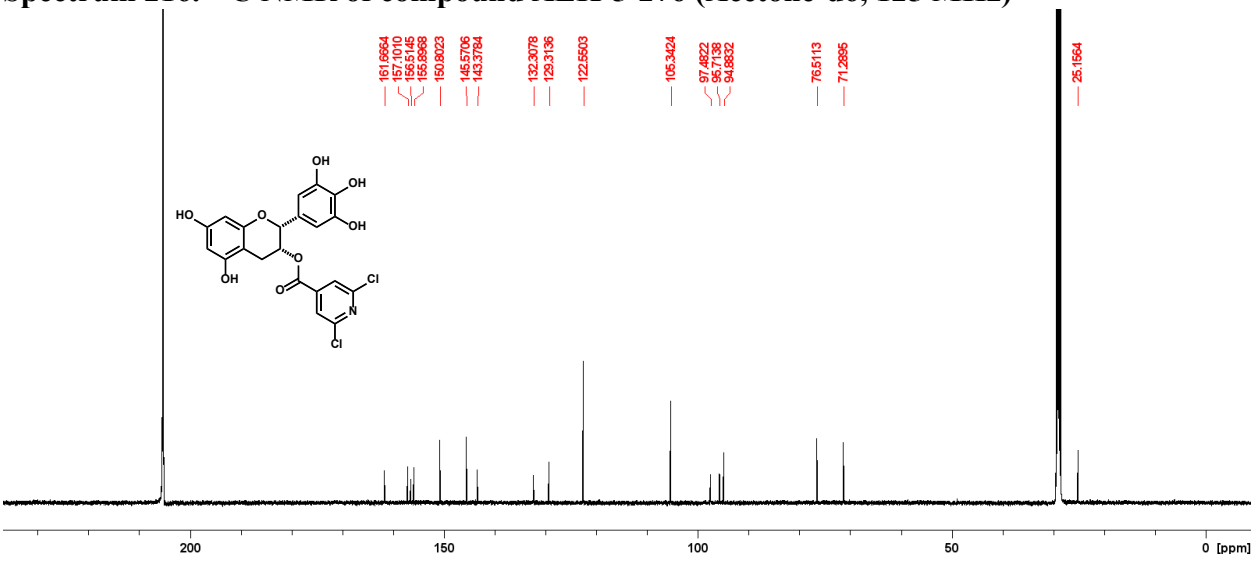
Spectrum 214. ^{13}C NMR of compound AEK-5-269 (Acetone-d6, 125 MHz)



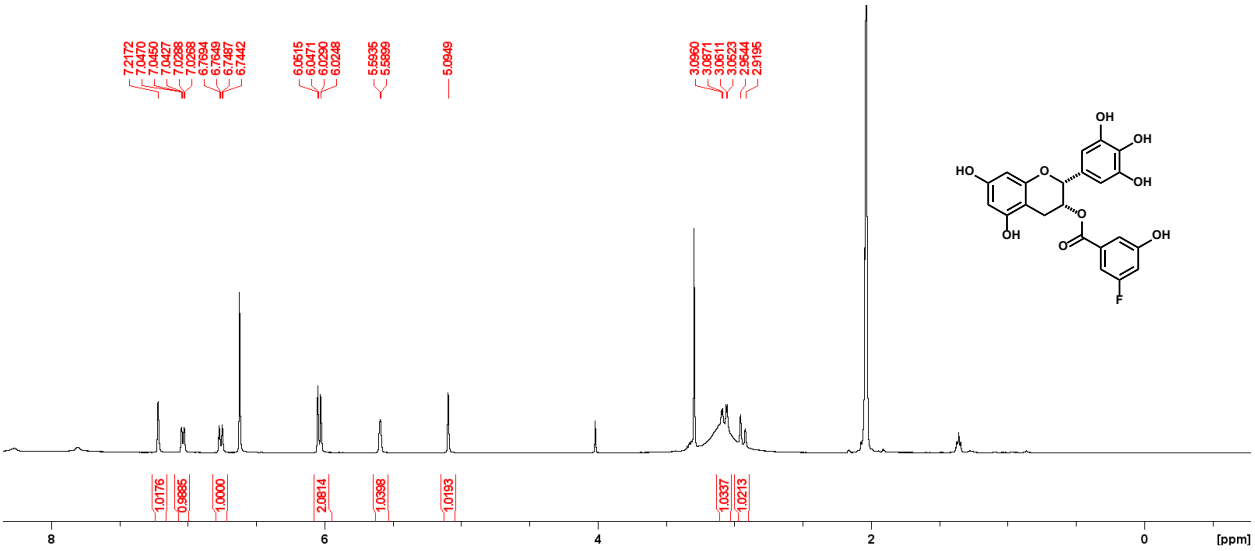
Spectrum 215. ^{1}H NMR of compound AEK-5-276 (Acetone-d6, 500 MHz)



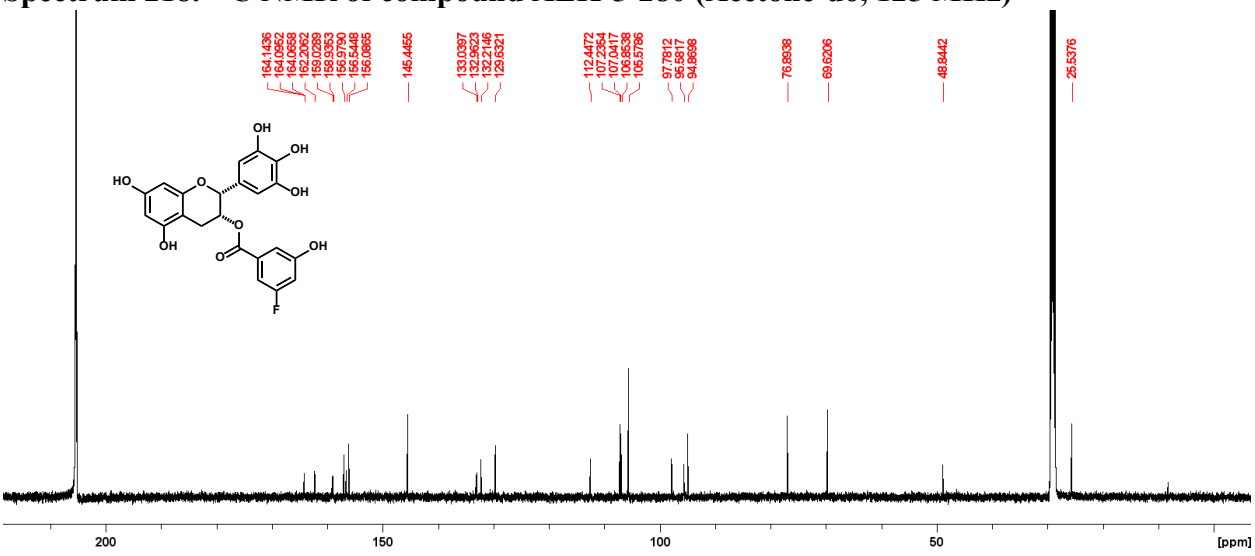
Spectrum 216. ^{13}C NMR of compound AEK-5-276 (Acetone-d6, 125 MHz)



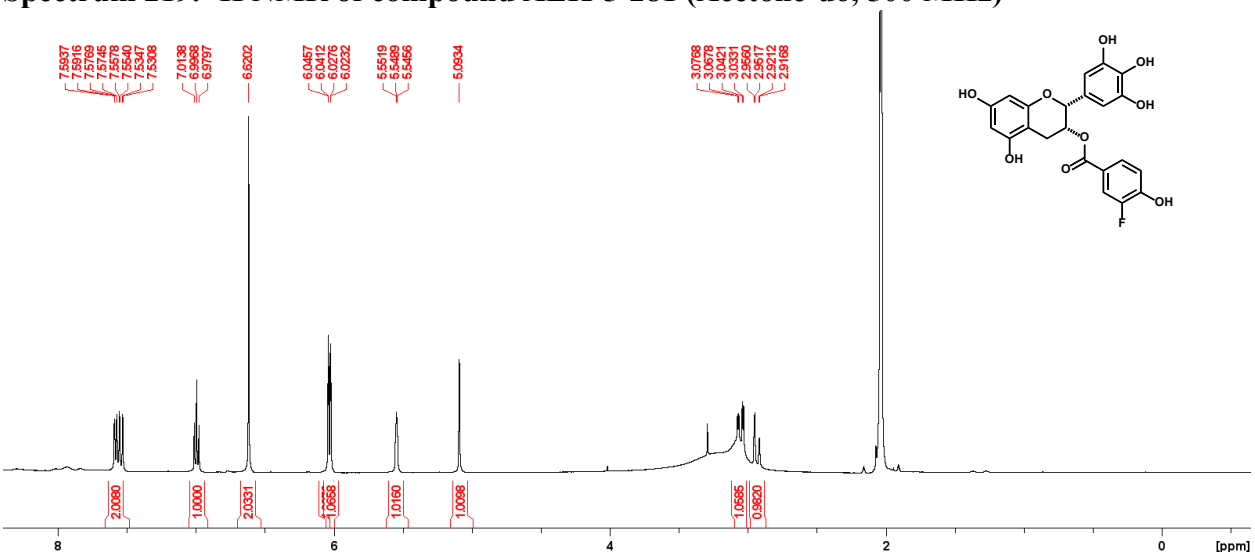
Spectrum 217. ^{1}H NMR of compound AEK-5-280 (Acetone-d6, 500 MHz)



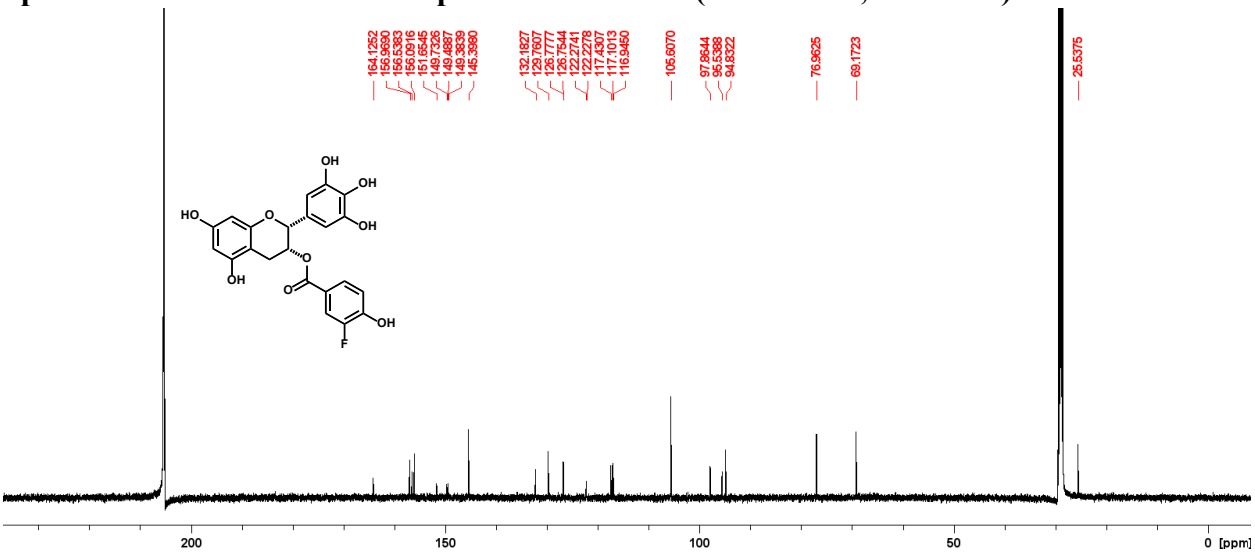
Spectrum 218. ^{13}C NMR of compound AEK-5-280 (Acetone-d6, 125 MHz)



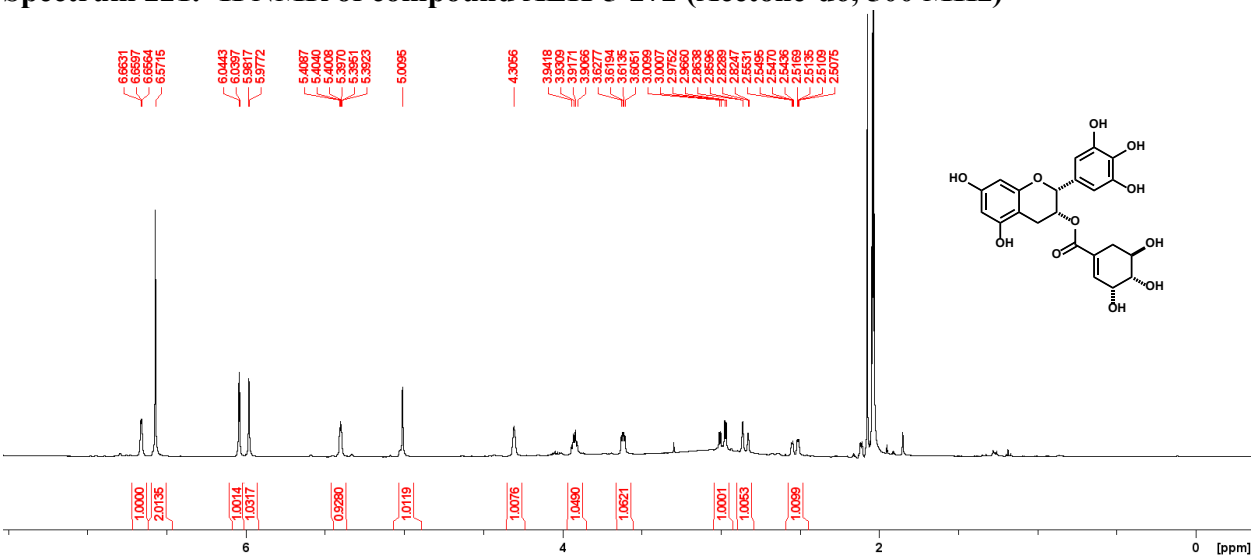
Spectrum 219. ^{1}H NMR of compound AEK-5-281 (Acetone-d6, 500 MHz)



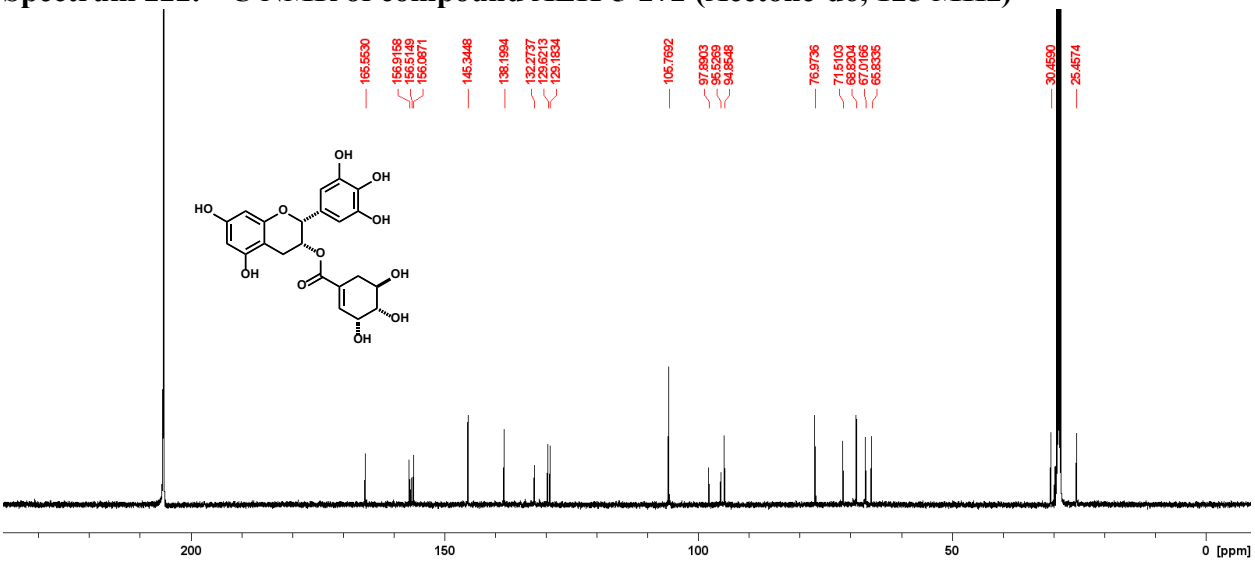
Spectrum 220. ^{13}C NMR of compound AEK-5-281 (Acetone-d6, 125 MHz)



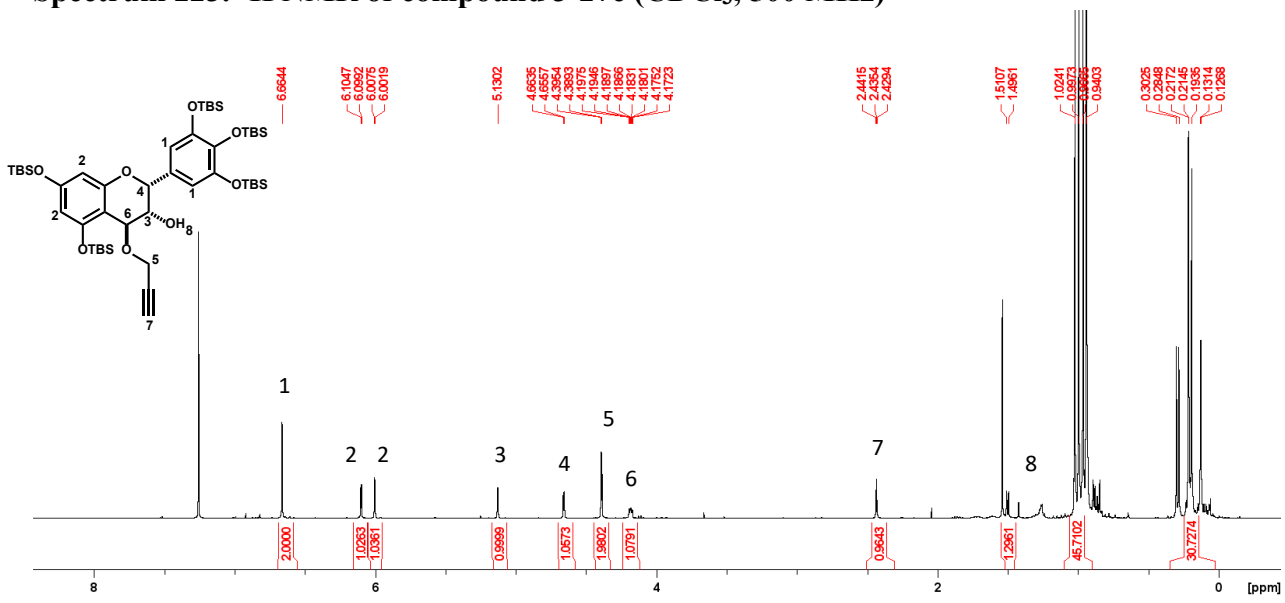
Spectrum 221. ^{1}H NMR of compound AEK-5-272 (Acetone-d6, 500 MHz)



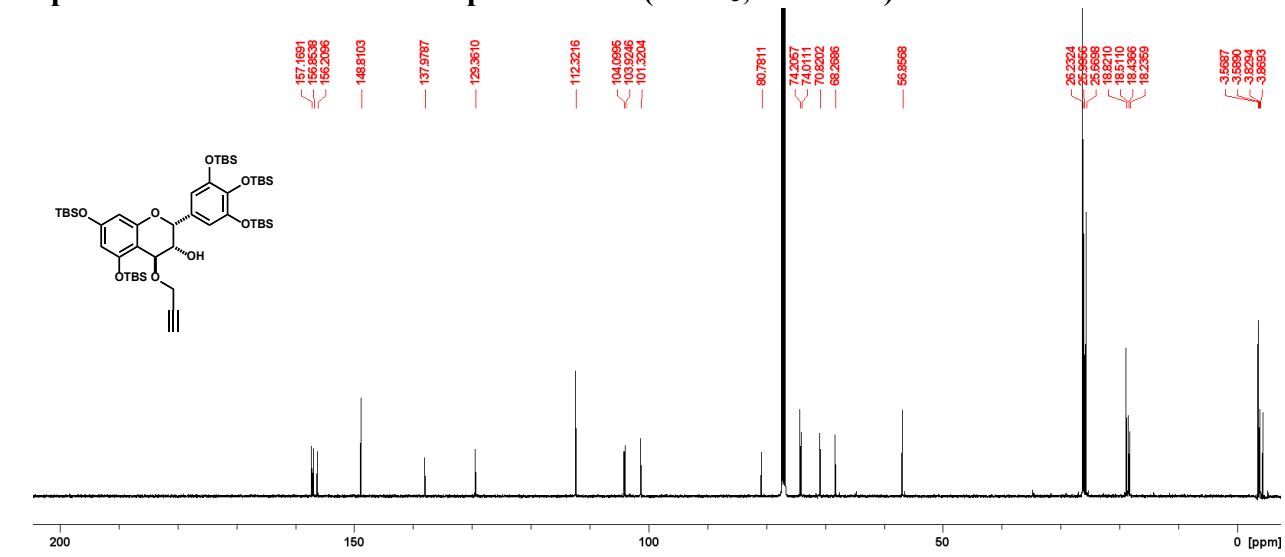
Spectrum 222. ^{13}C NMR of compound AEK-5-272 (Acetone-d6, 125 MHz)



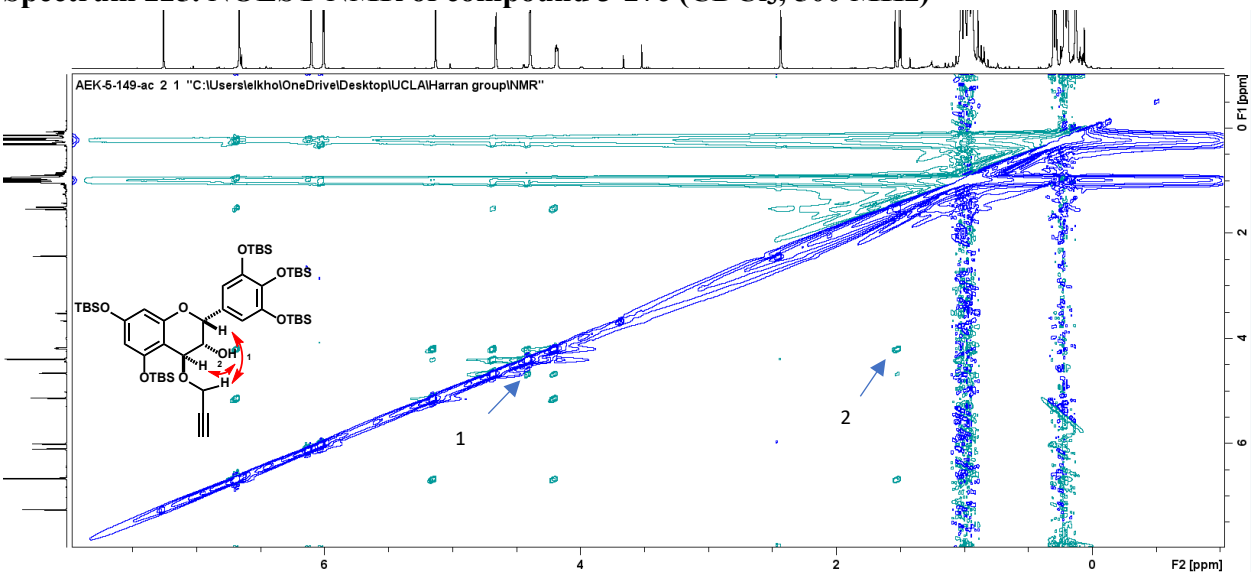
Spectrum 223. ^{1}H NMR of compound 3-27c ($CDCl_3$, 500 MHz)



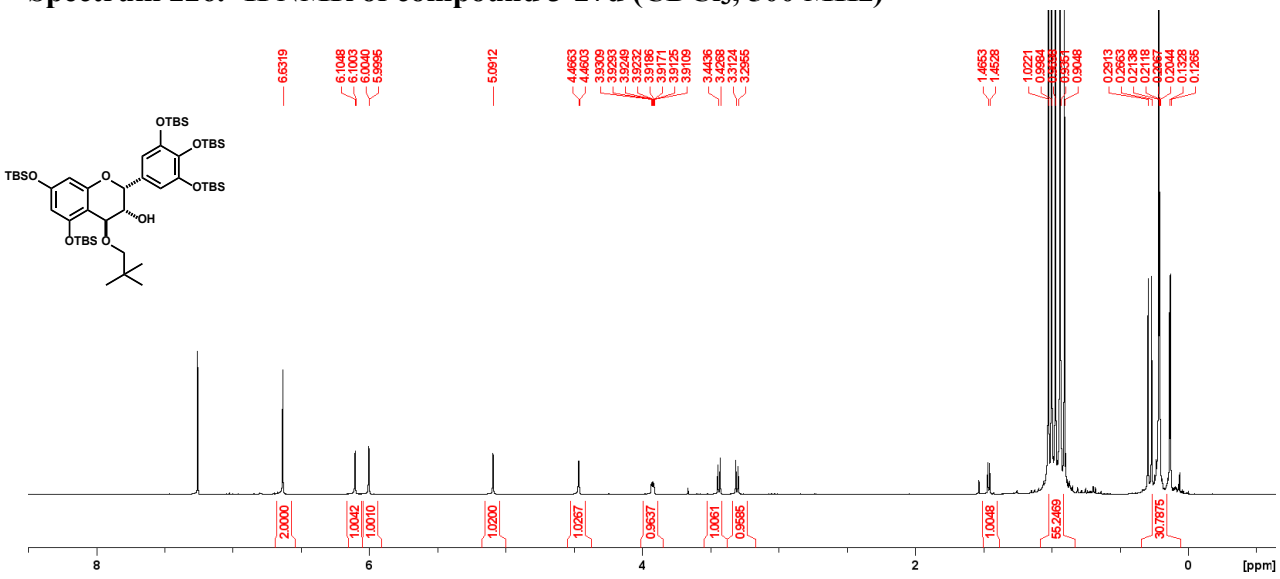
Spectrum 224. ^{13}C NMR of compound 3-27c ($CDCl_3$, 125 MHz)



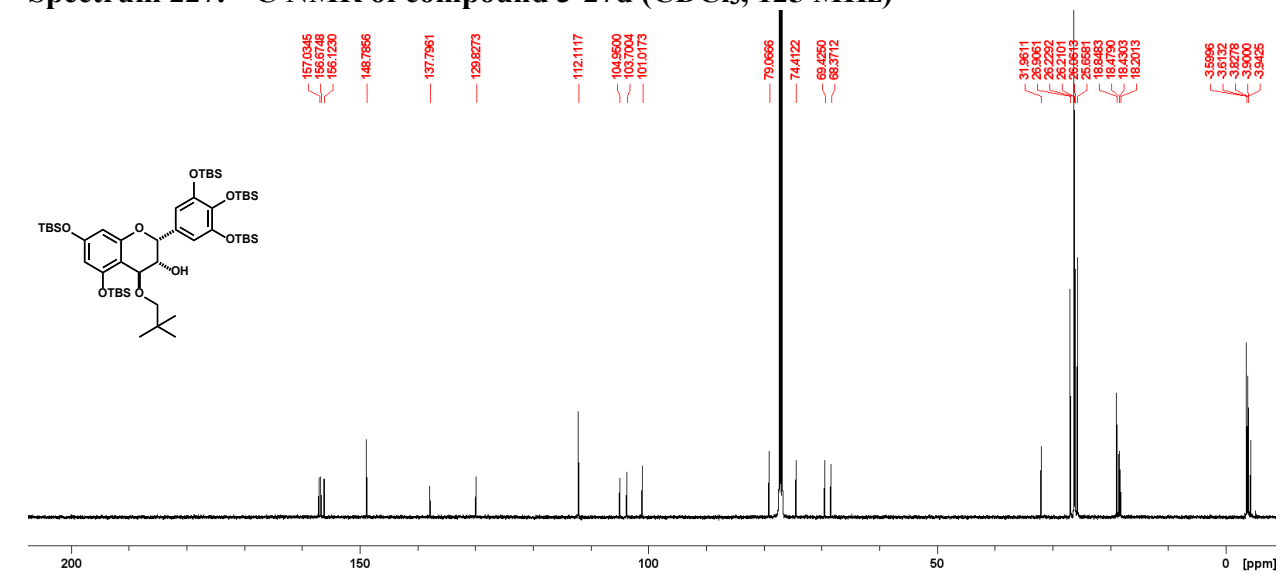
Spectrum 225. NOESY NMR of compound 3-27c ($CDCl_3$, 500 MHz)



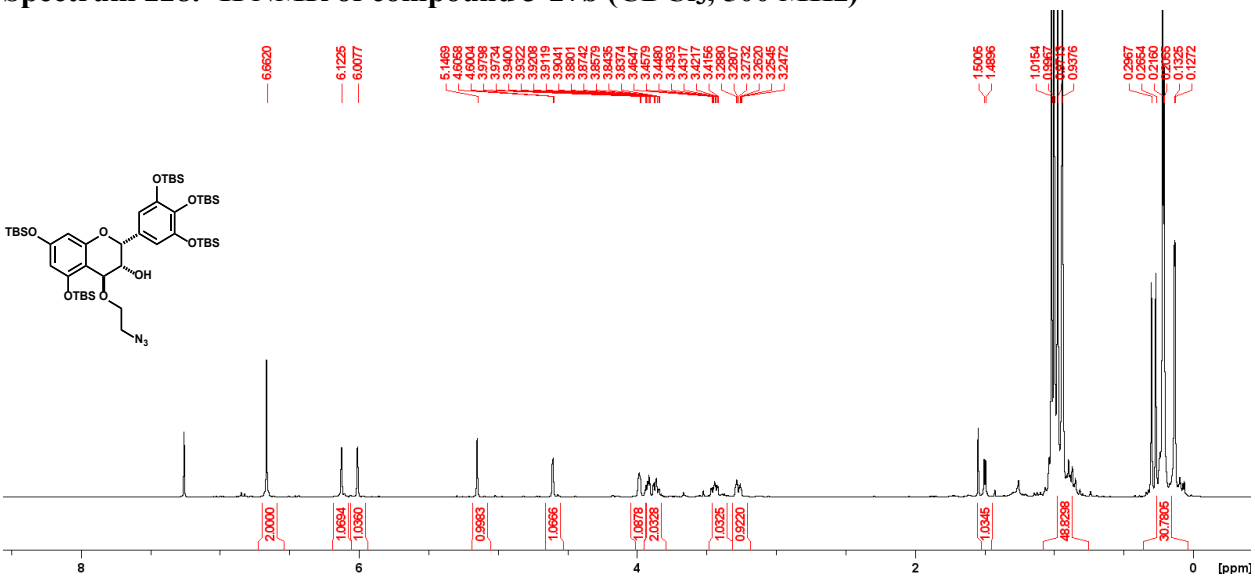
Spectrum 226. ^{1}H NMR of compound 3-27d ($CDCl_3$, 500 MHz)



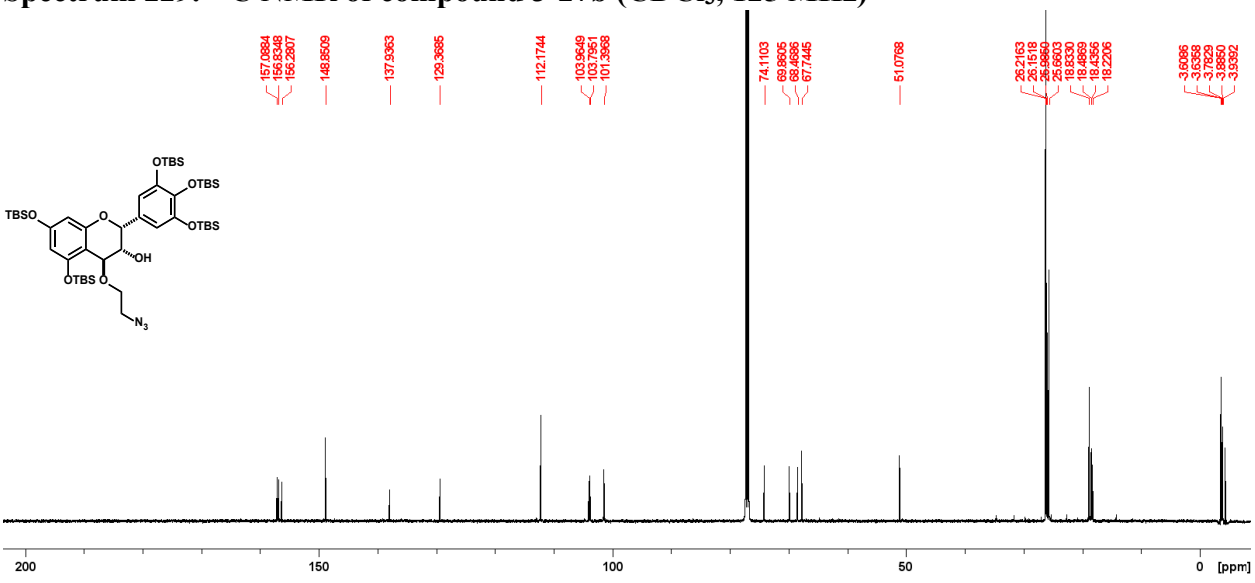
Spectrum 227. ^{13}C NMR of compound 3-27d ($CDCl_3$, 125 MHz)



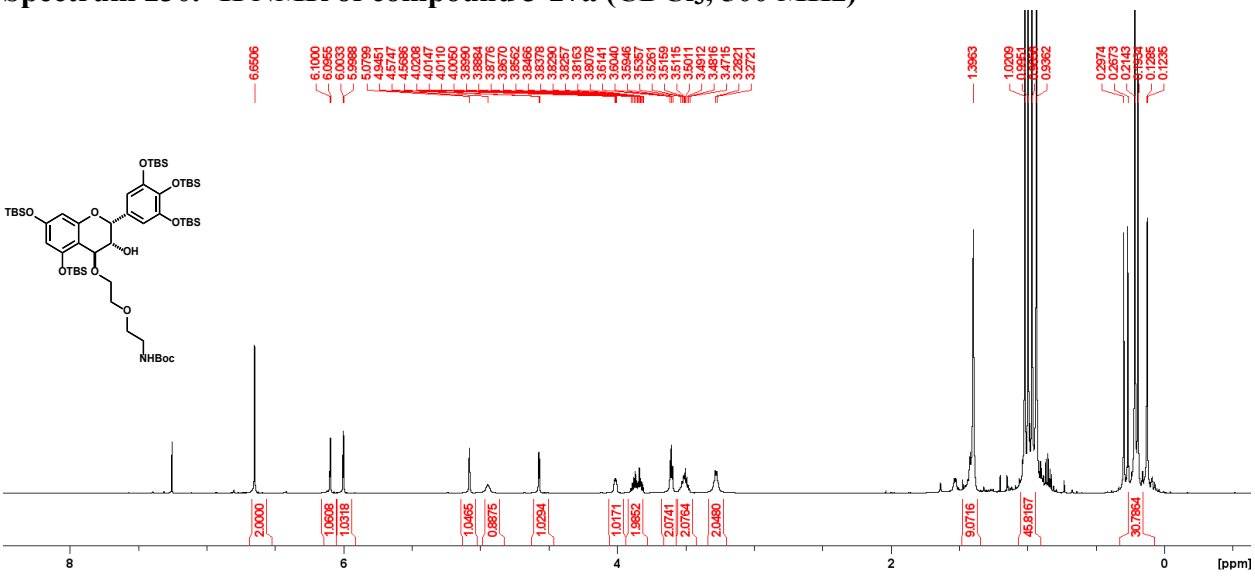
Spectrum 228. ^{1}H NMR of compound 3-27b ($CDCl_3$, 500 MHz)



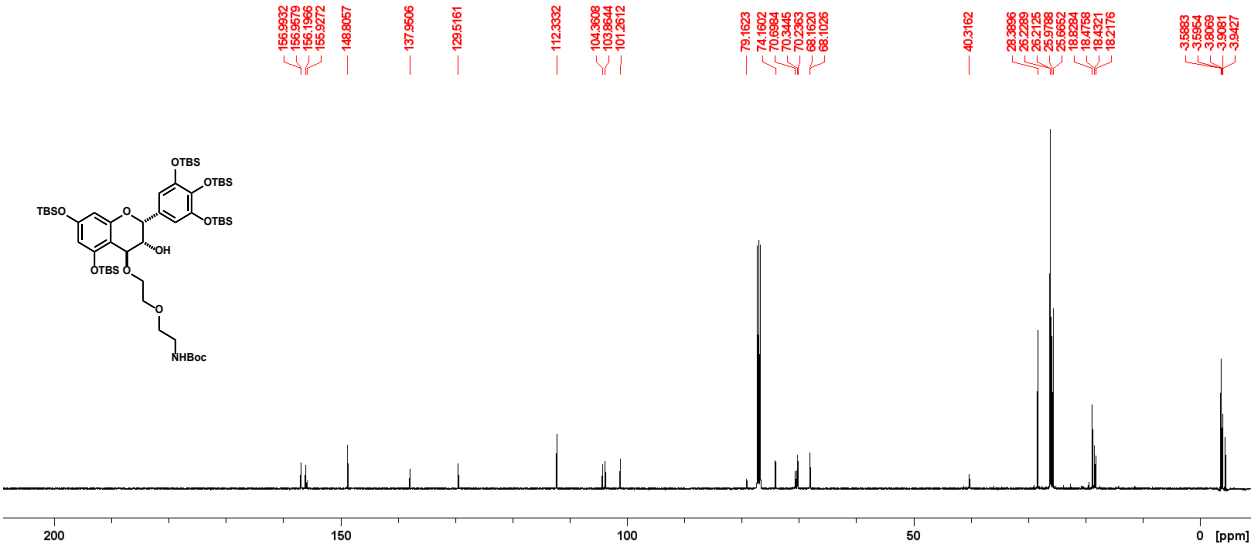
Spectrum 229. ^{13}C NMR of compound 3-27b ($CDCl_3$, 125 MHz)



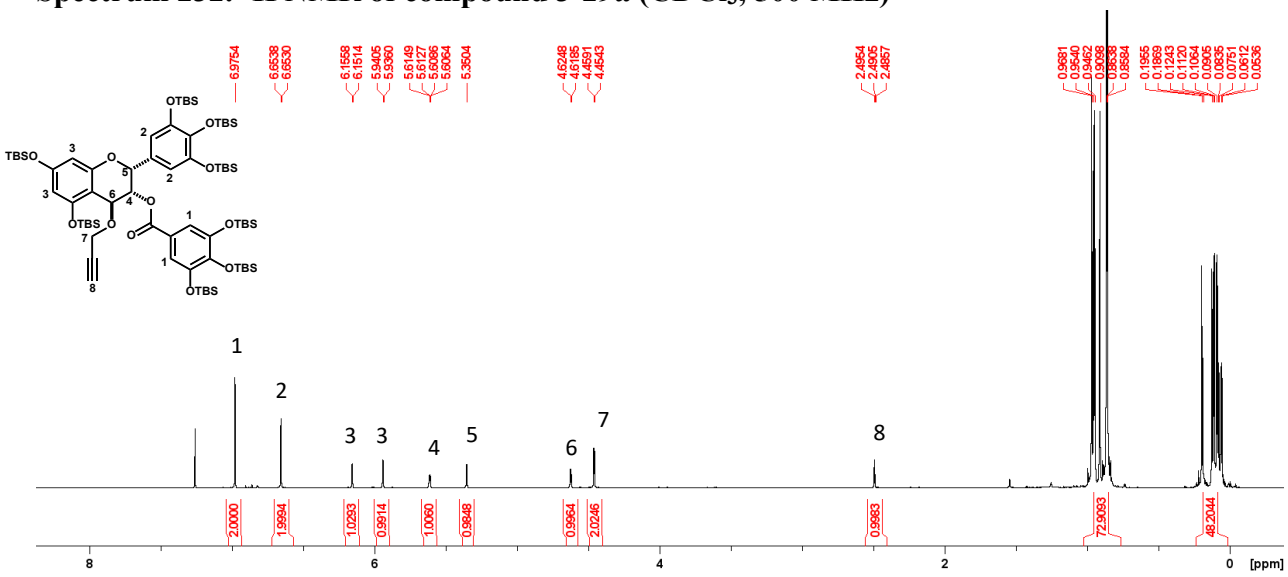
Spectrum 230. ^{1}H NMR of compound 3-27a ($CDCl_3$, 500 MHz)



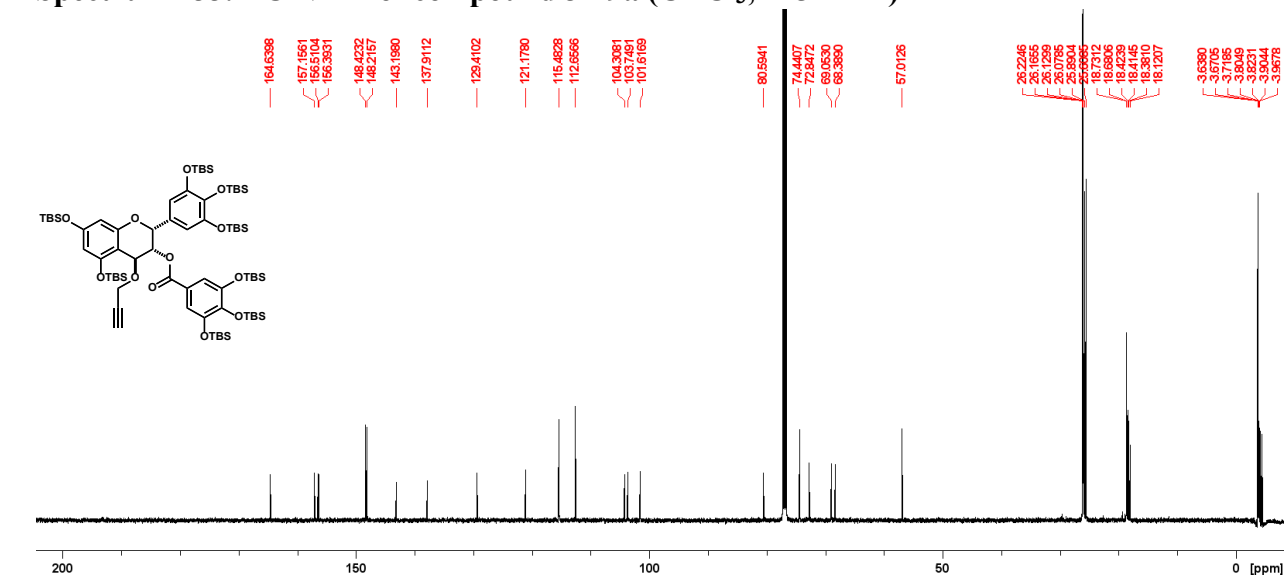
Spectrum 231. ^{13}C NMR of compound 3-27a ($CDCl_3$, 125 MHz)



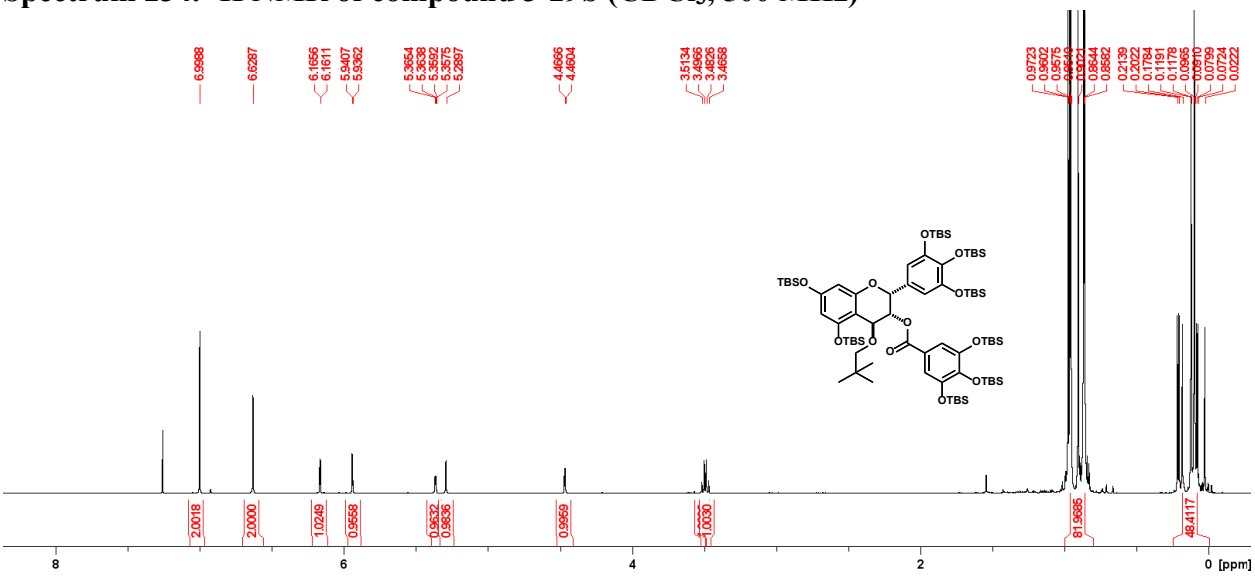
Spectrum 232. ^{1}H NMR of compound 3-29a ($CDCl_3$, 500 MHz)



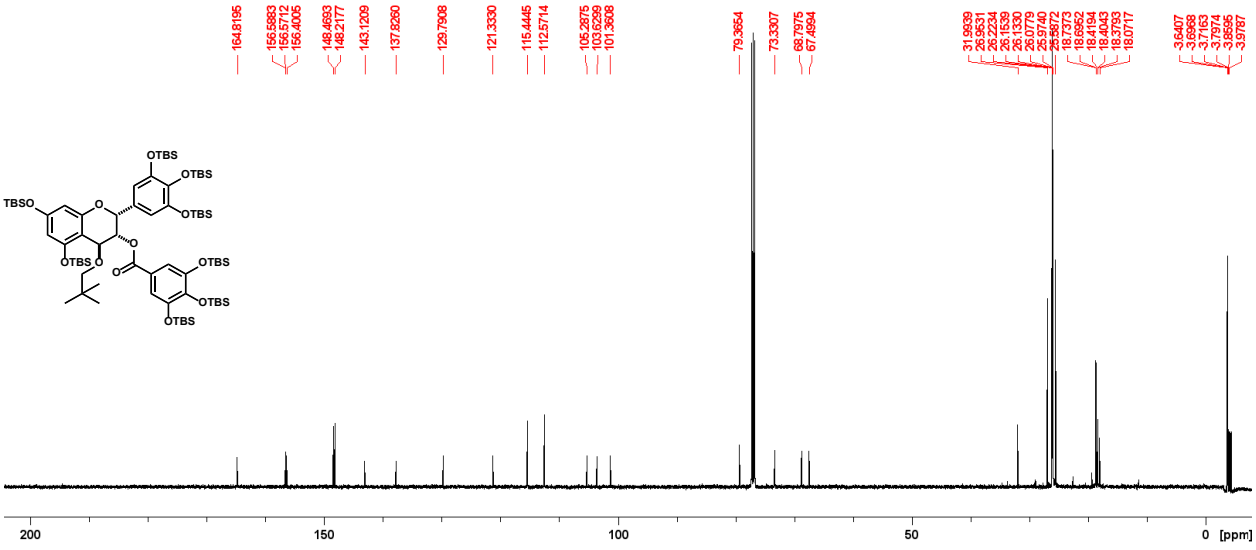
Spectrum 233. ^{13}C NMR of compound 3-29a ($CDCl_3$, 125 MHz)



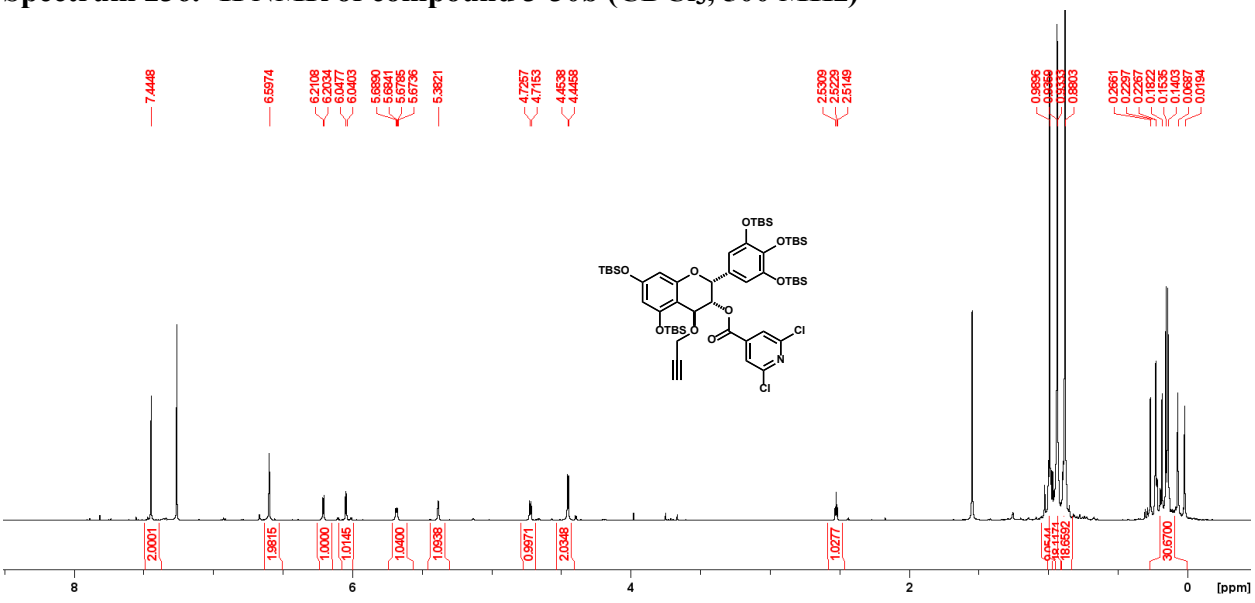
Spectrum 234. ^{1}H NMR of compound 3-29b ($CDCl_3$, 500 MHz)



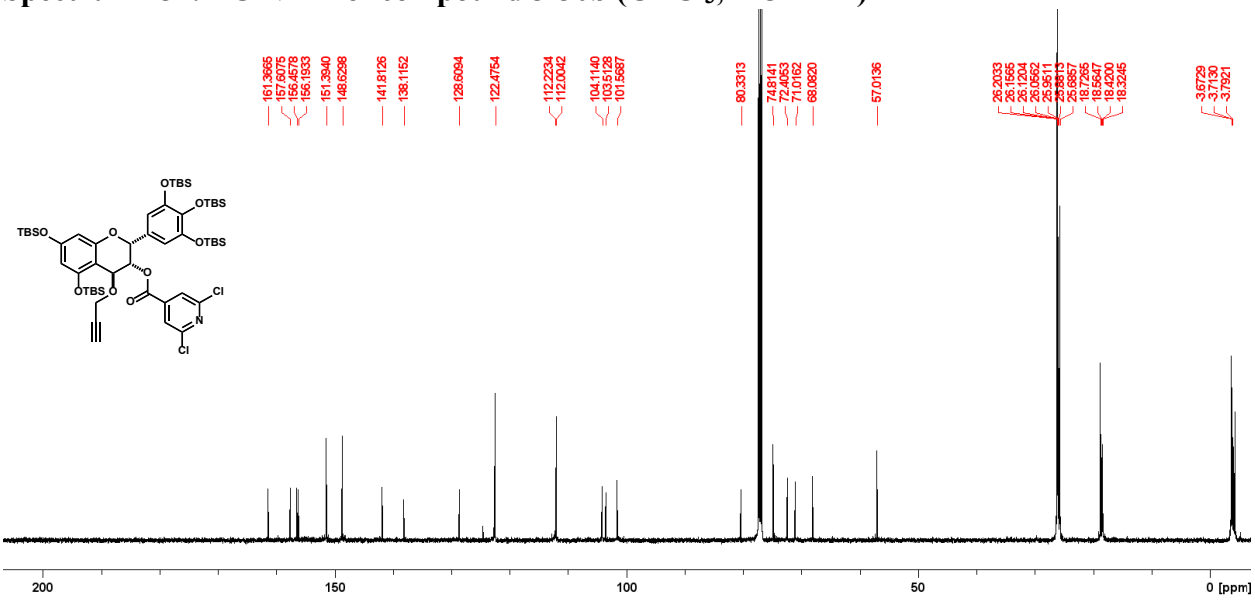
Spectrum 235. ^{13}C NMR of compound 3-29b ($CDCl_3$, 125 MHz)



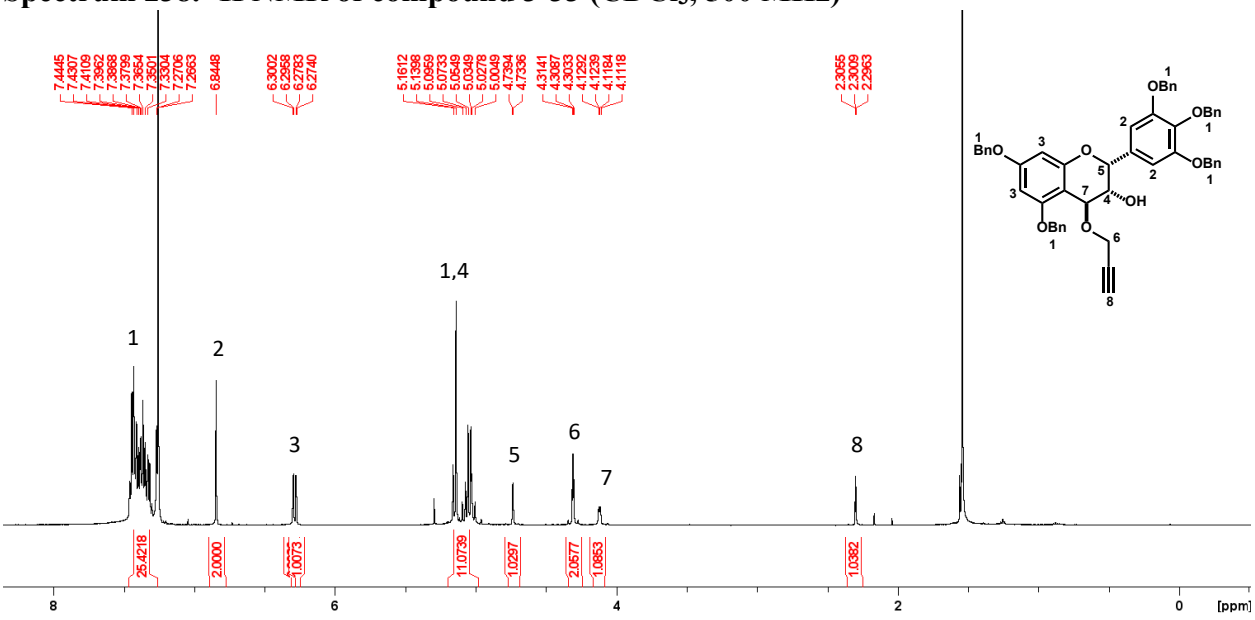
Spectrum 236. ^{1}H NMR of compound 3-30b ($CDCl_3$, 500 MHz)



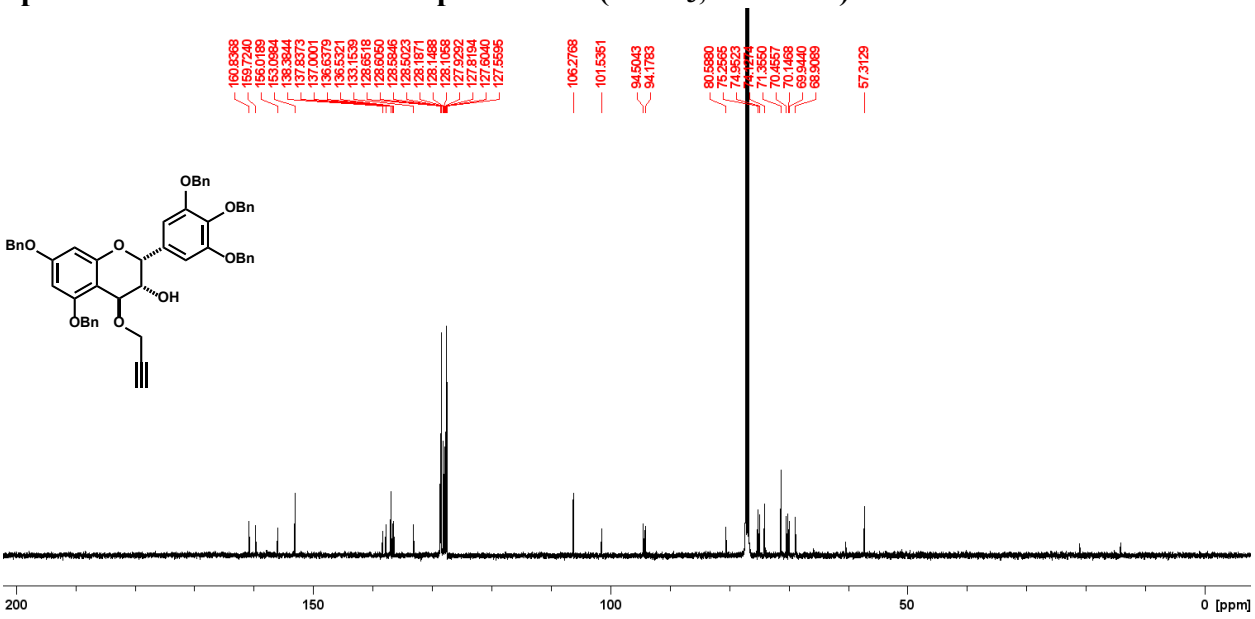
Spectrum 237. ^{13}C NMR of compound 3-30b ($CDCl_3$, 125 MHz)



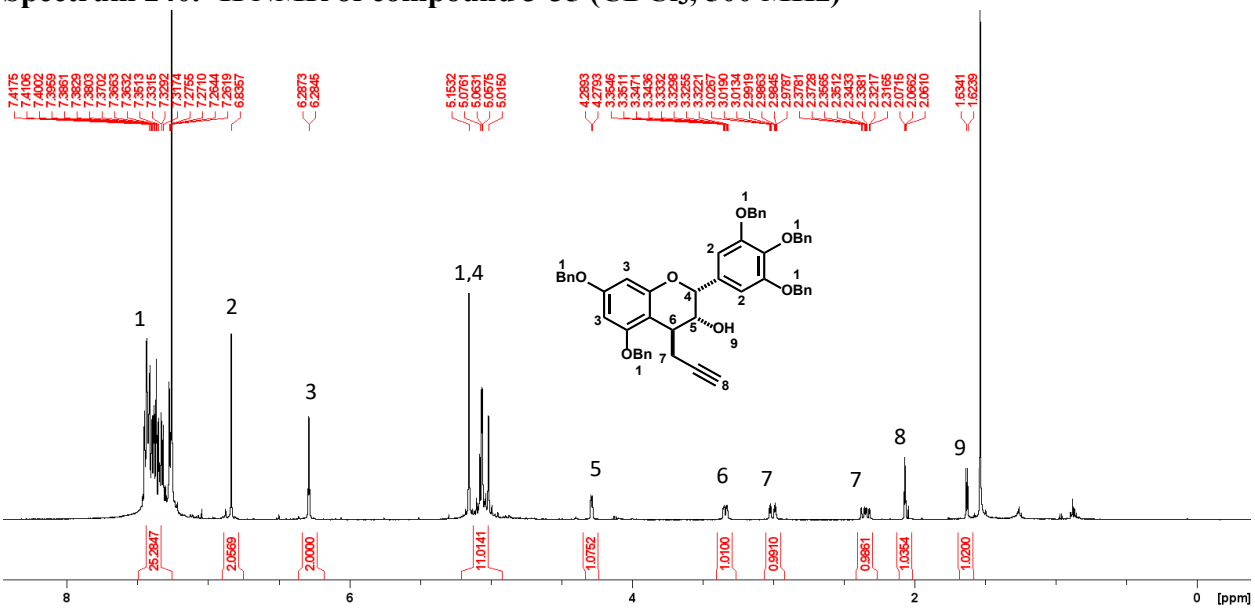
Spectrum 238. ^{1}H NMR of compound 3-33 ($CDCl_3$, 500 MHz)



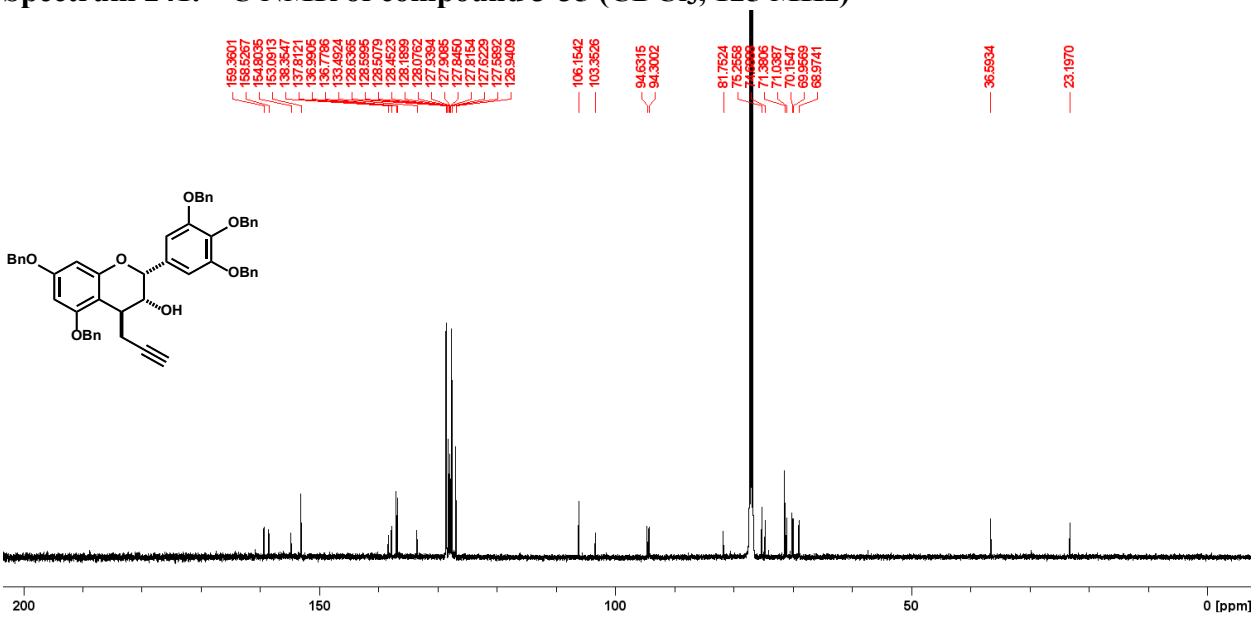
Spectrum 239. ^{13}C NMR of compound 3-33 ($CDCl_3$, 125 MHz)



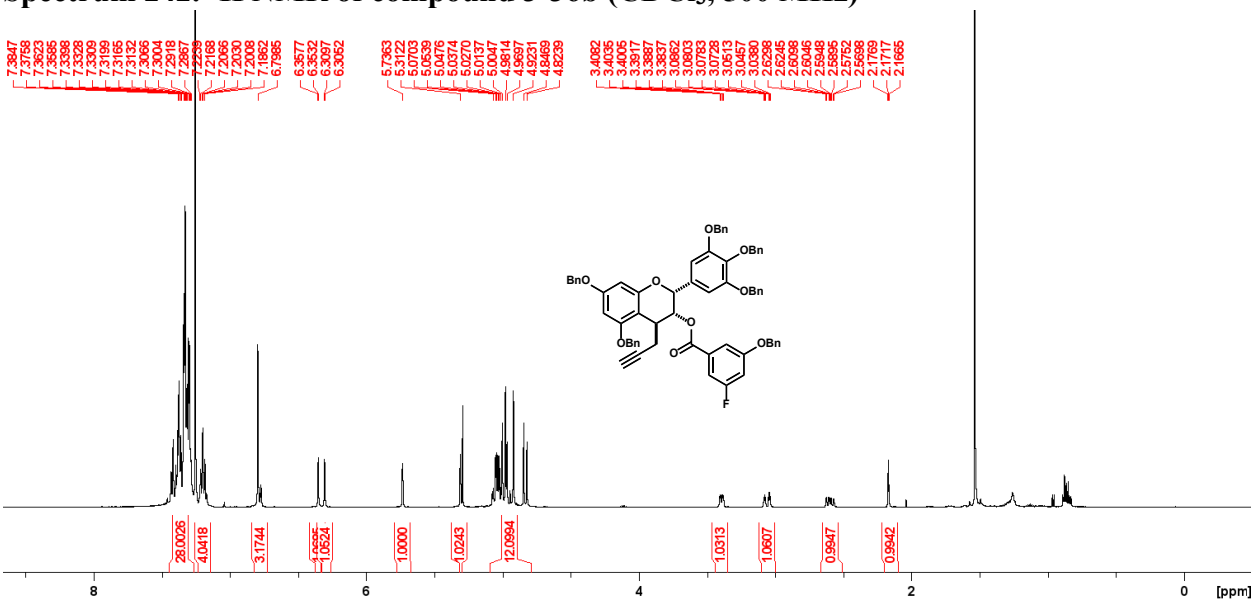
Spectrum 240. ^{1}H NMR of compound 3-35 ($CDCl_3$, 500 MHz)



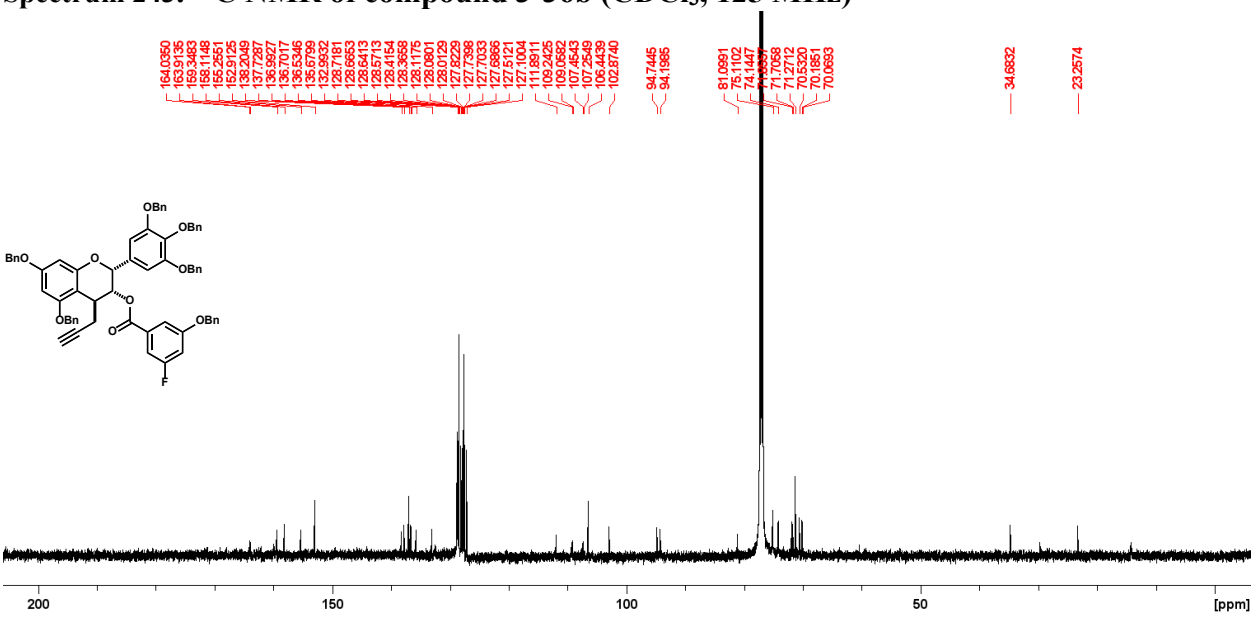
Spectrum 241. ^{13}C NMR of compound 3-35 ($CDCl_3$, 125 MHz)



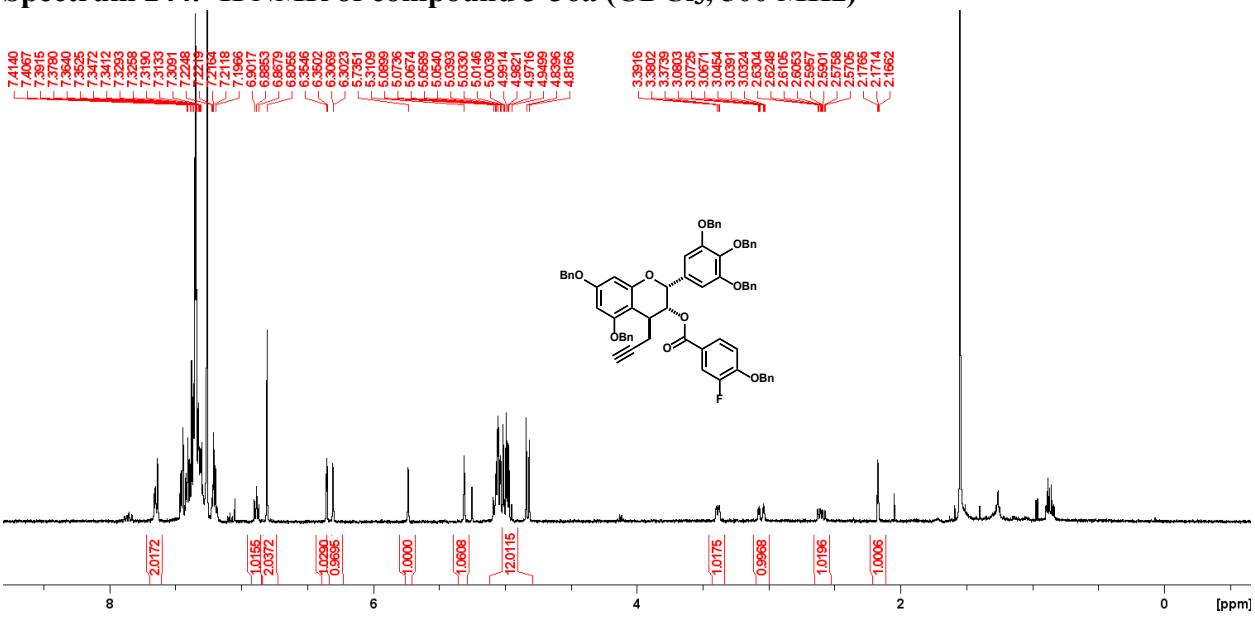
Spectrum 242. ^{1}H NMR of compound 3-36b ($CDCl_3$, 500 MHz)



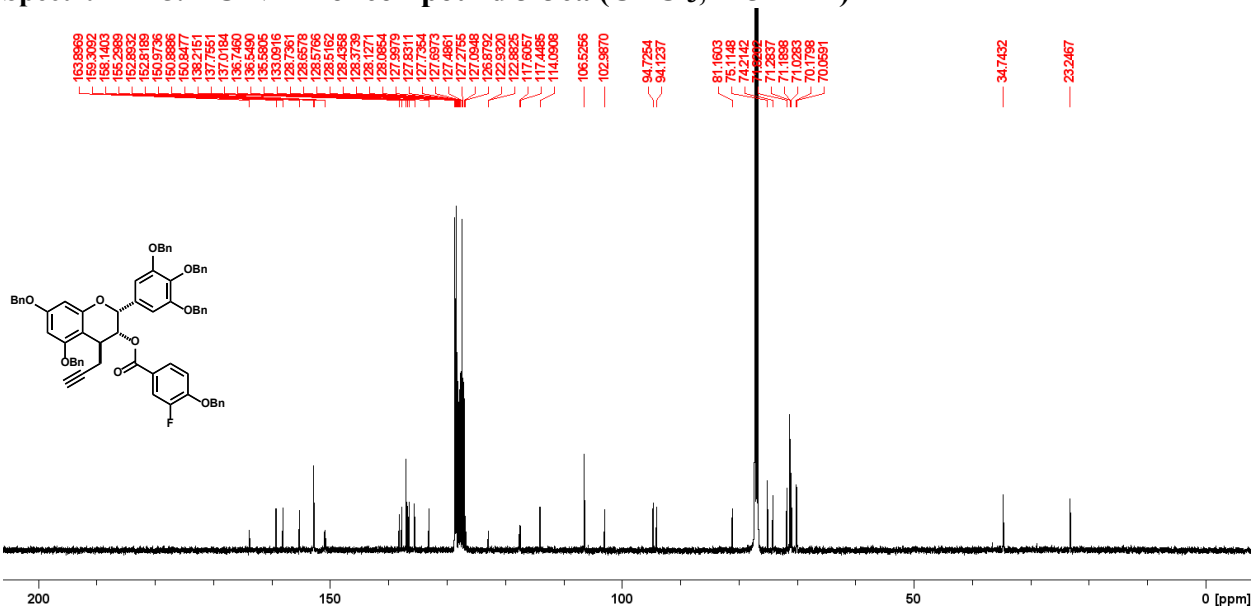
Spectrum 243. ^{13}C NMR of compound 3-36b ($CDCl_3$, 125 MHz)



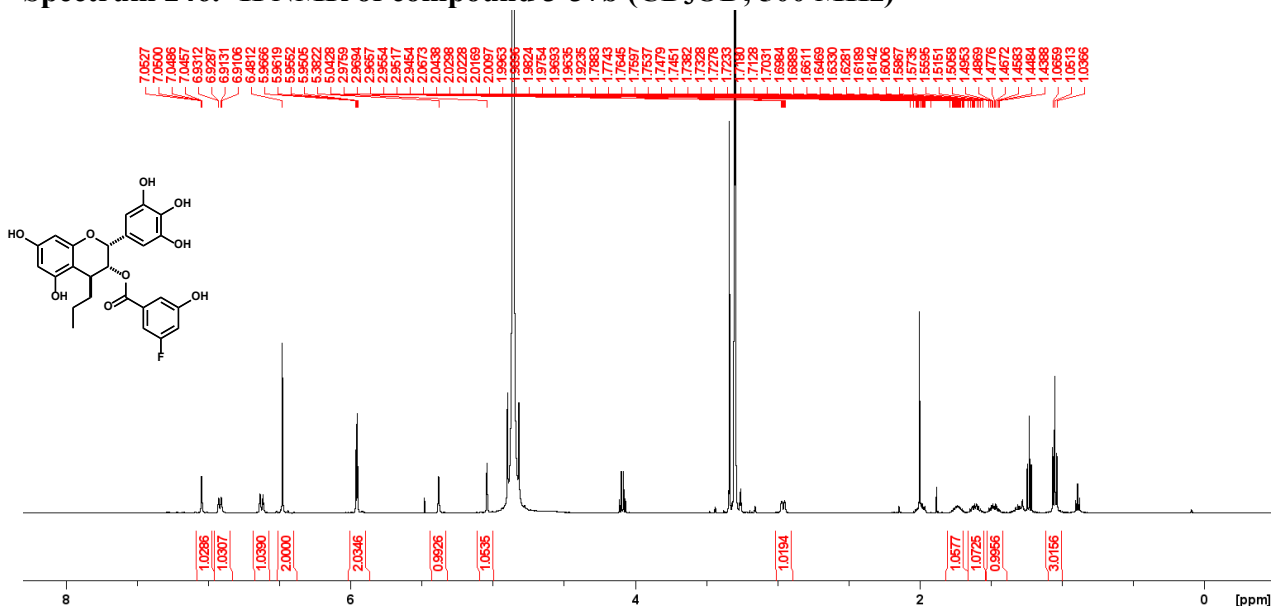
Spectrum 244. ^{1}H NMR of compound 3-36a ($CDCl_3$, 500 MHz)



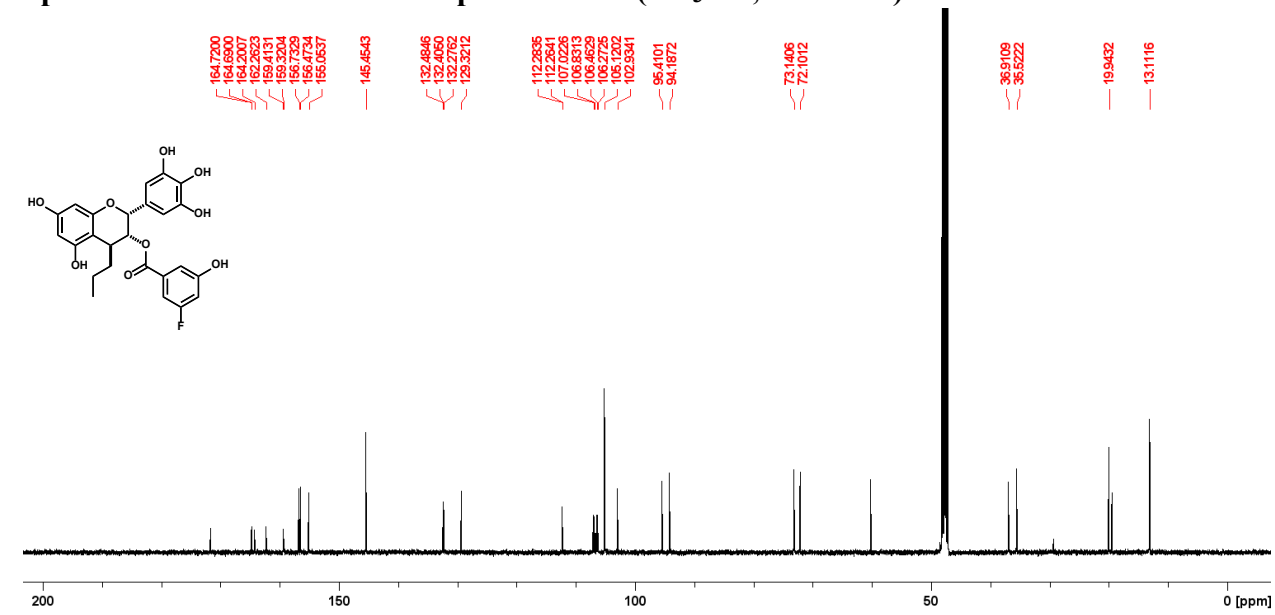
Spectrum 245. ^{13}C NMR of compound 3-36a ($CDCl_3$, 125 MHz)



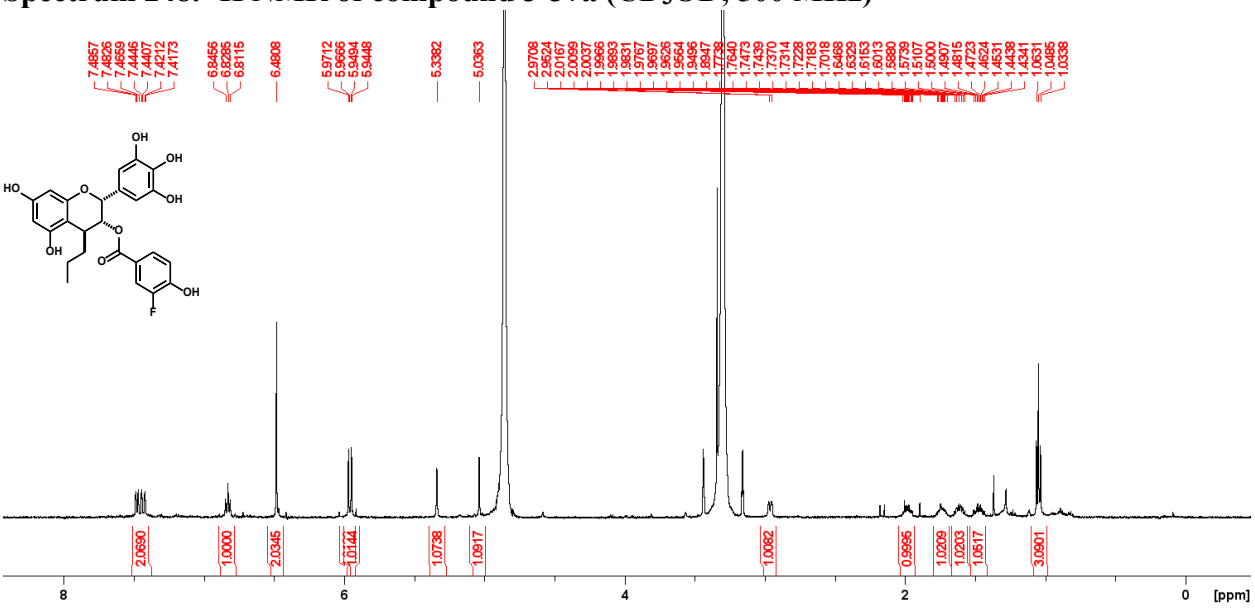
Spectrum 246. ^{1}H NMR of compound 3-37b (CD_3OD, 500 MHz)



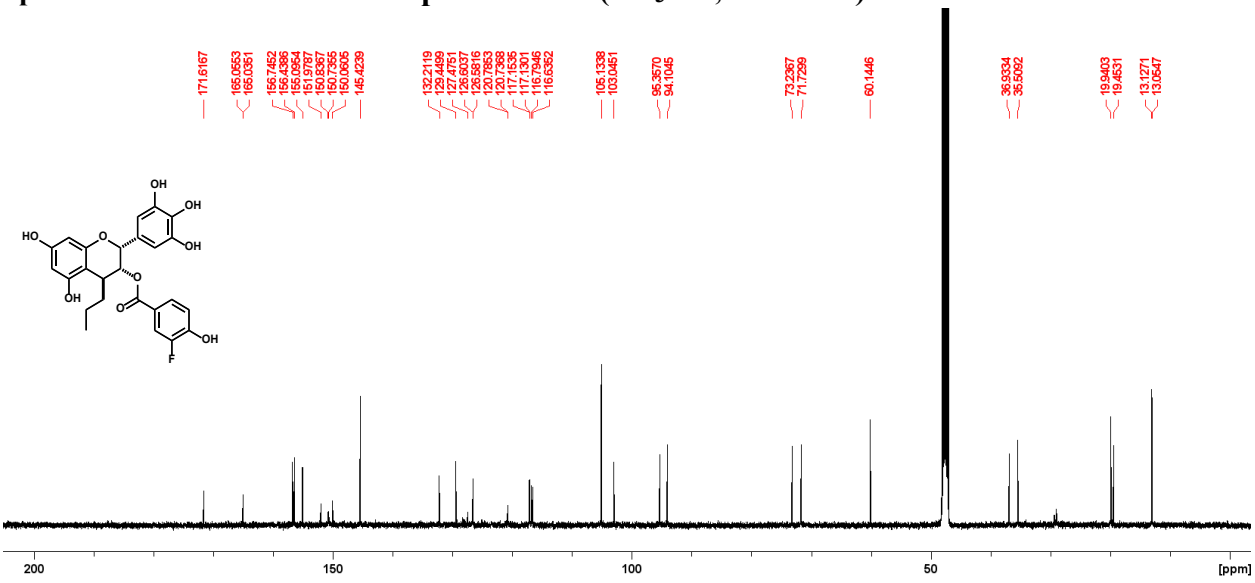
Spectrum 247. ^{13}C NMR of compound 3-37b (CD_3OD, 125 MHz)



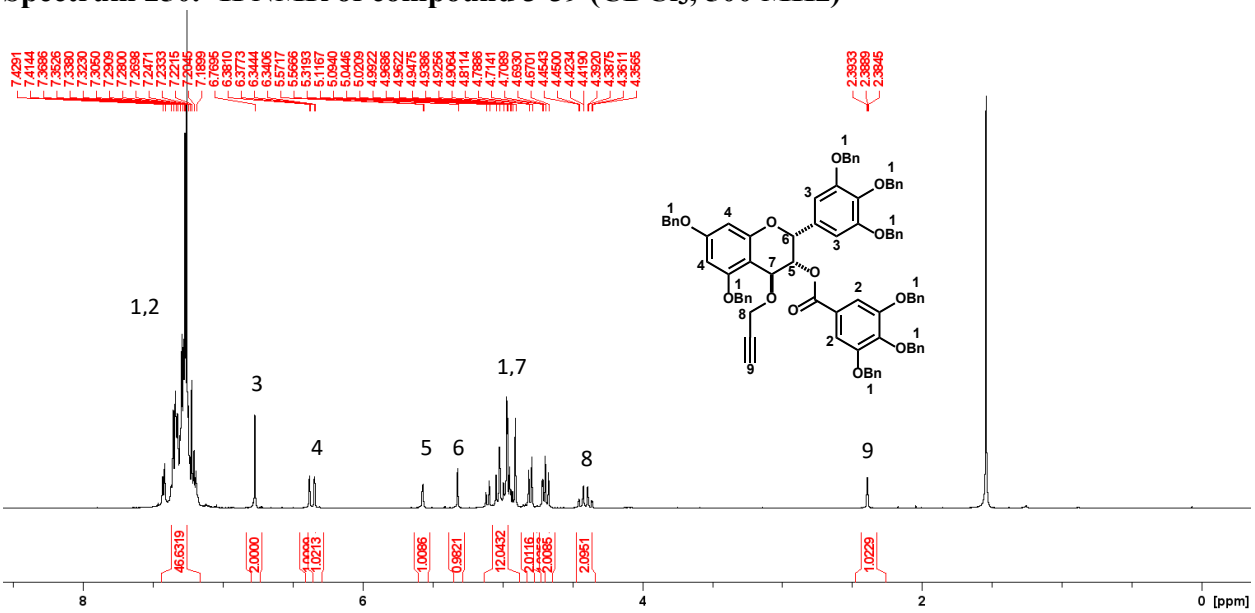
Spectrum 248. ^{1}H NMR of compound 3-37a (CD_3OD, 500 MHz)



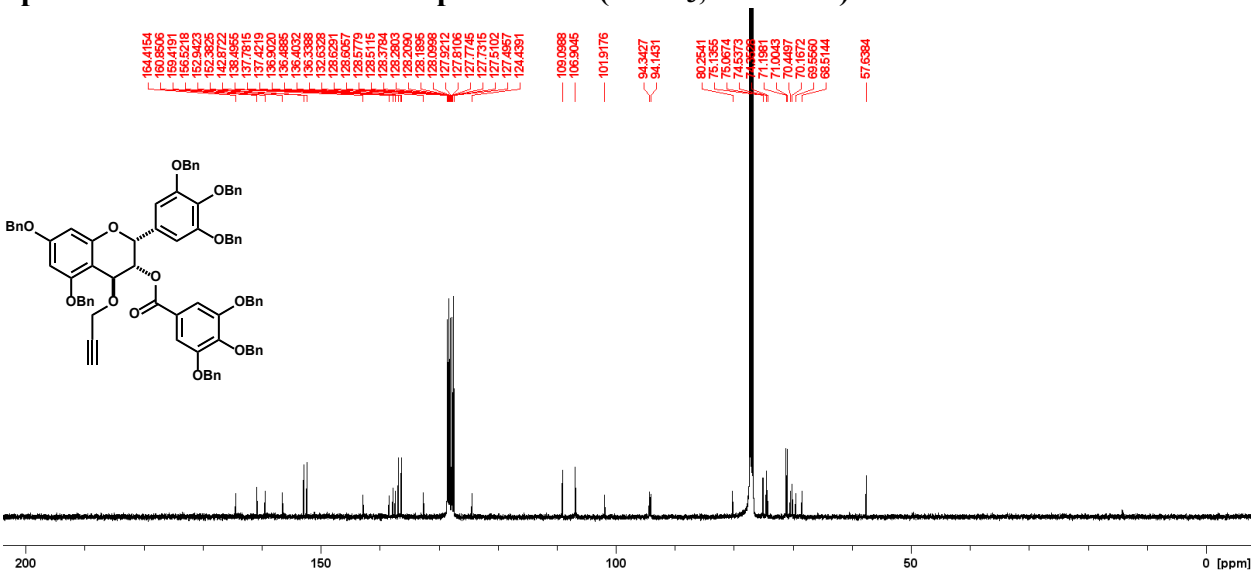
Spectrum 249. ^{13}C NMR of compound 3-37a (CD_3OD, 125 MHz)



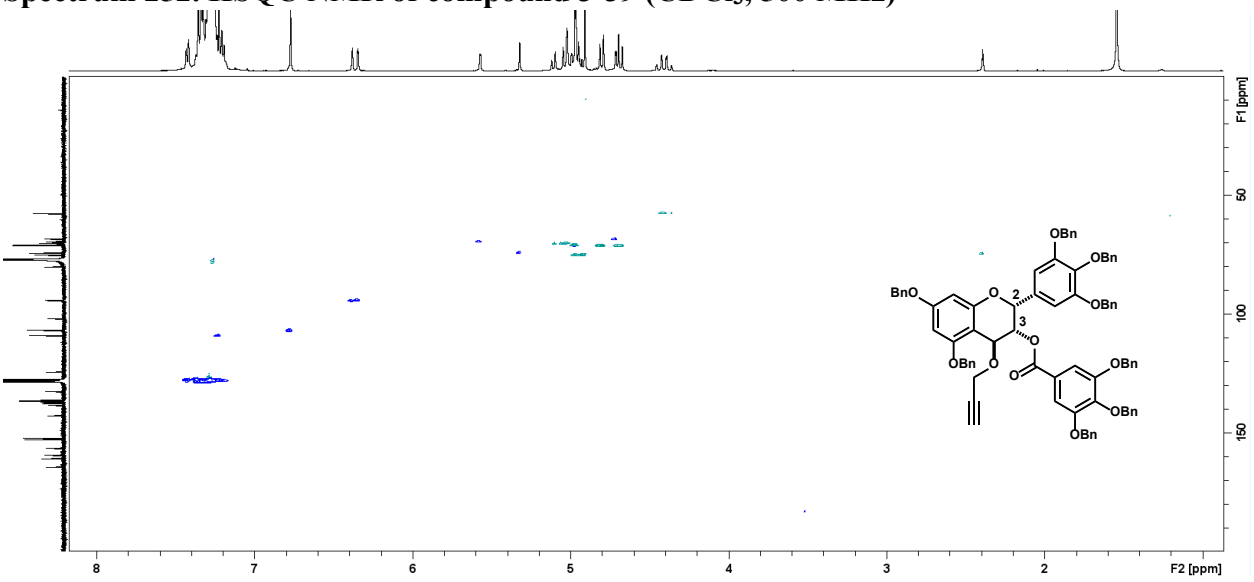
Spectrum 250. ^{1}H NMR of compound 3-39 ($CDCl_3$, 500 MHz)



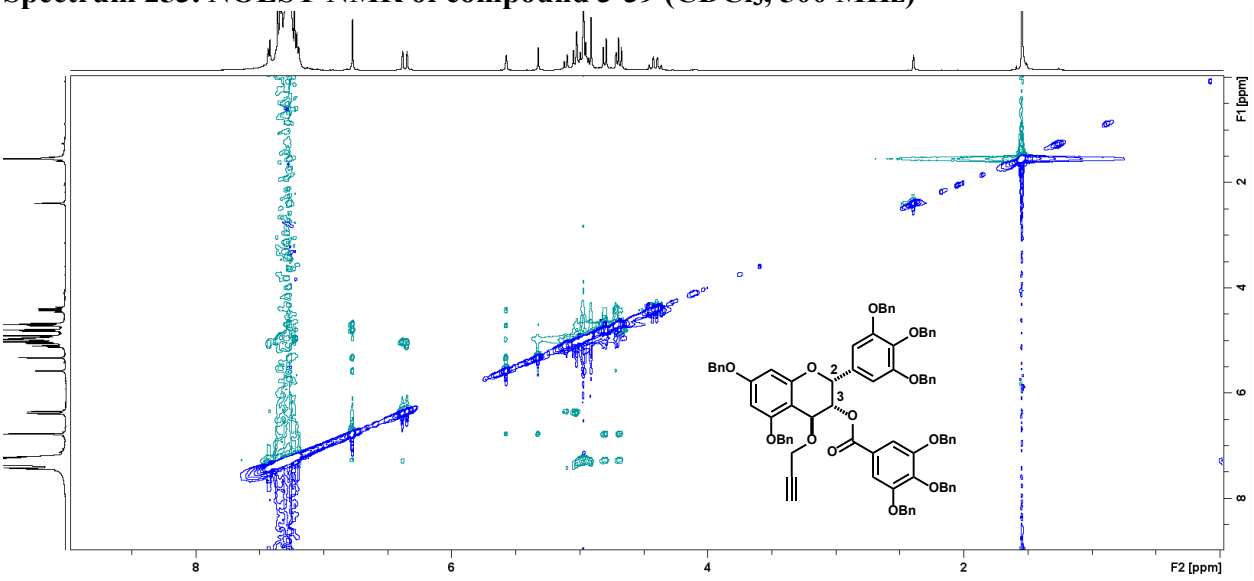
Spectrum 251. ^{13}C NMR of compound 3-39 ($CDCl_3$, 125 MHz)



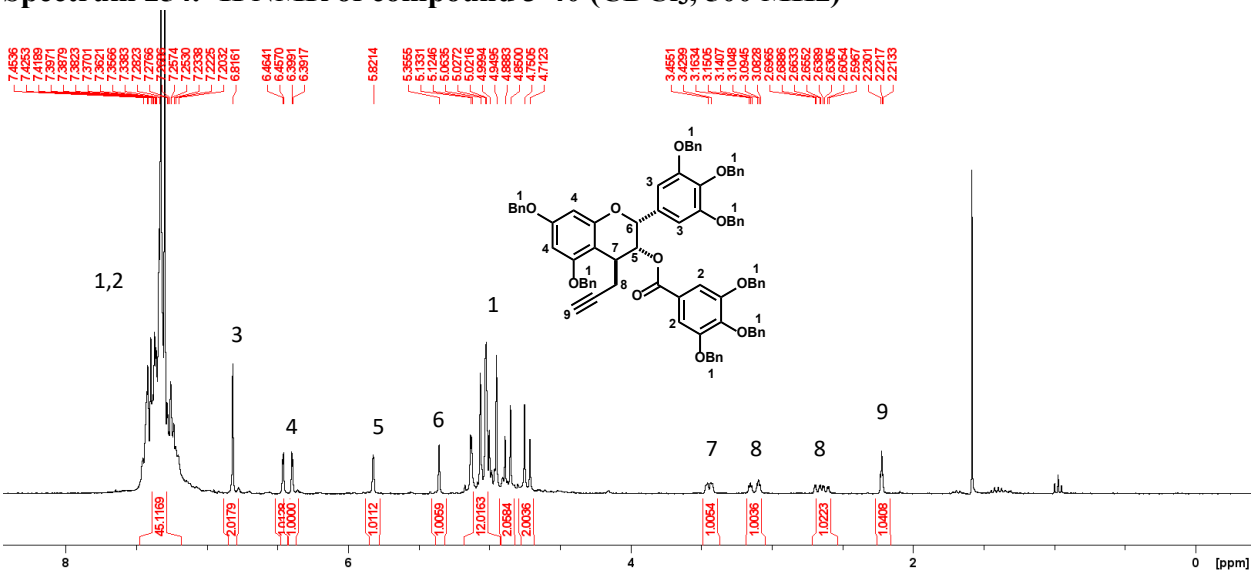
Spectrum 252. HSQC NMR of compound 3-39 ($CDCl_3$, 500 MHz)



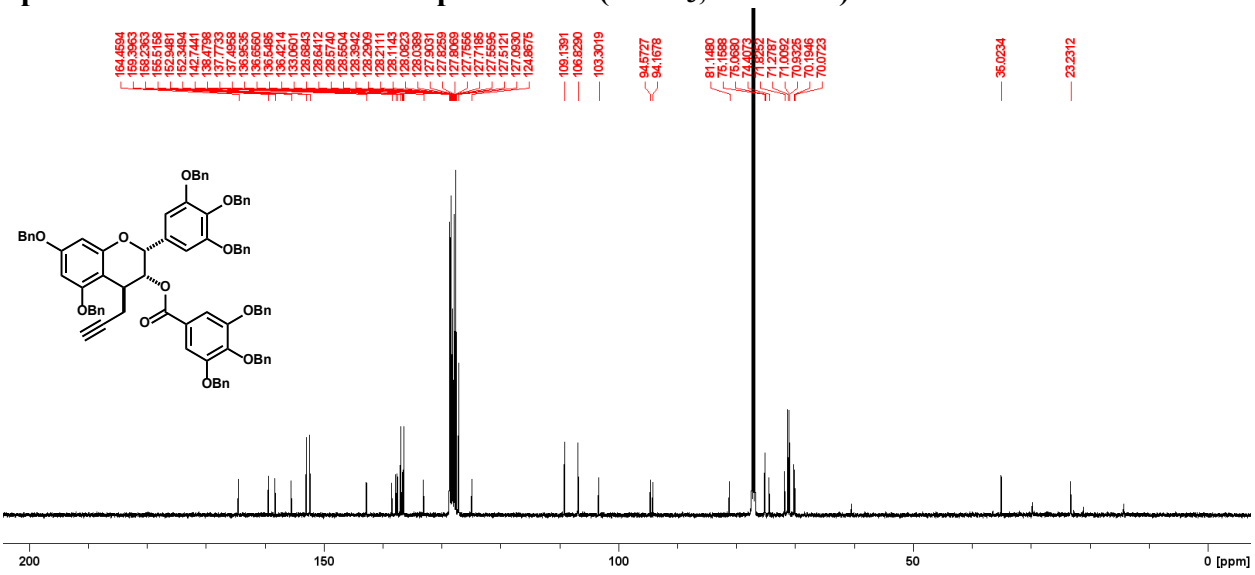
Spectrum 253. NOESY NMR of compound 3-39 ($CDCl_3$, 500 MHz)



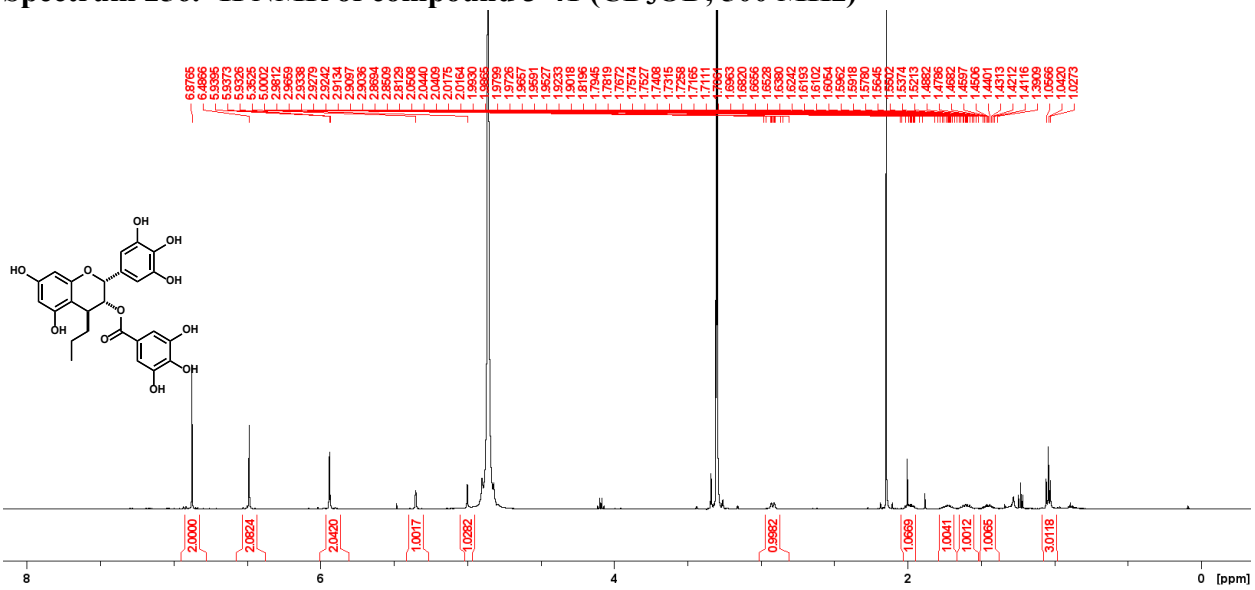
Spectrum 254. ^{1}H NMR of compound 3-40 ($CDCl_3$, 500 MHz)



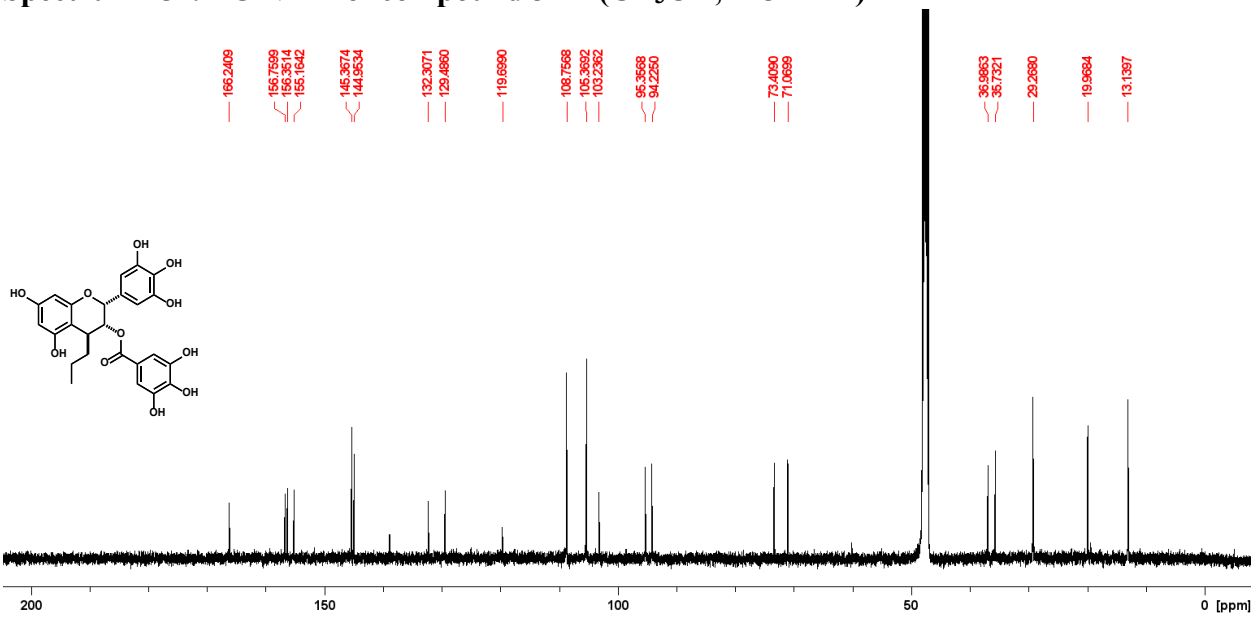
Spectrum 255. ^{13}C NMR of compound 3-40 ($CDCl_3$, 125 MHz)



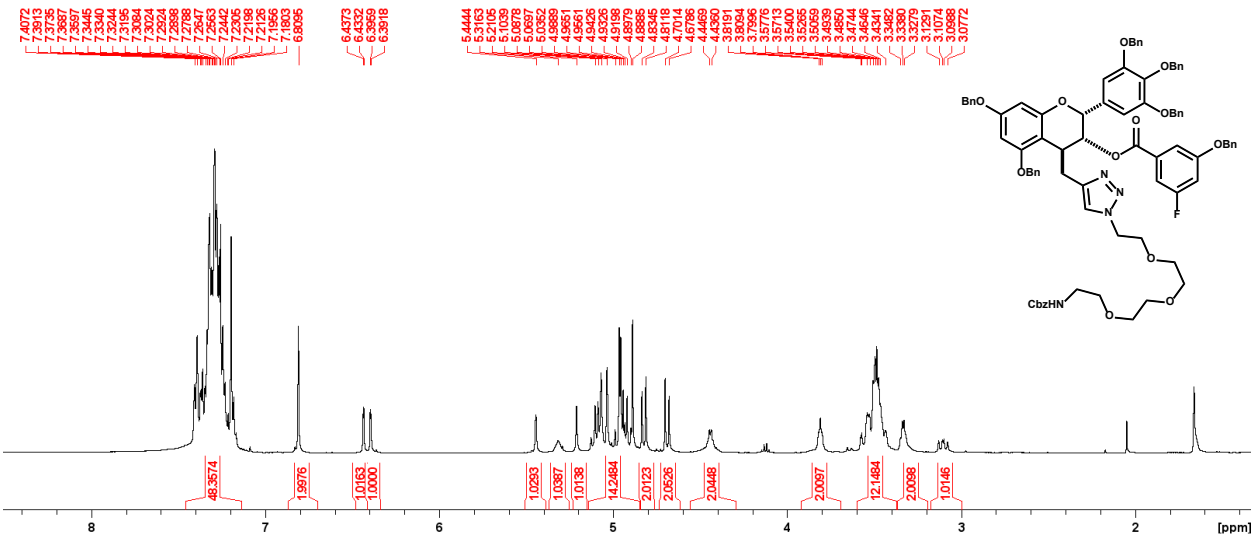
Spectrum 256. ^{1}H NMR of compound 3-41 (CD_3OD, 500 MHz)



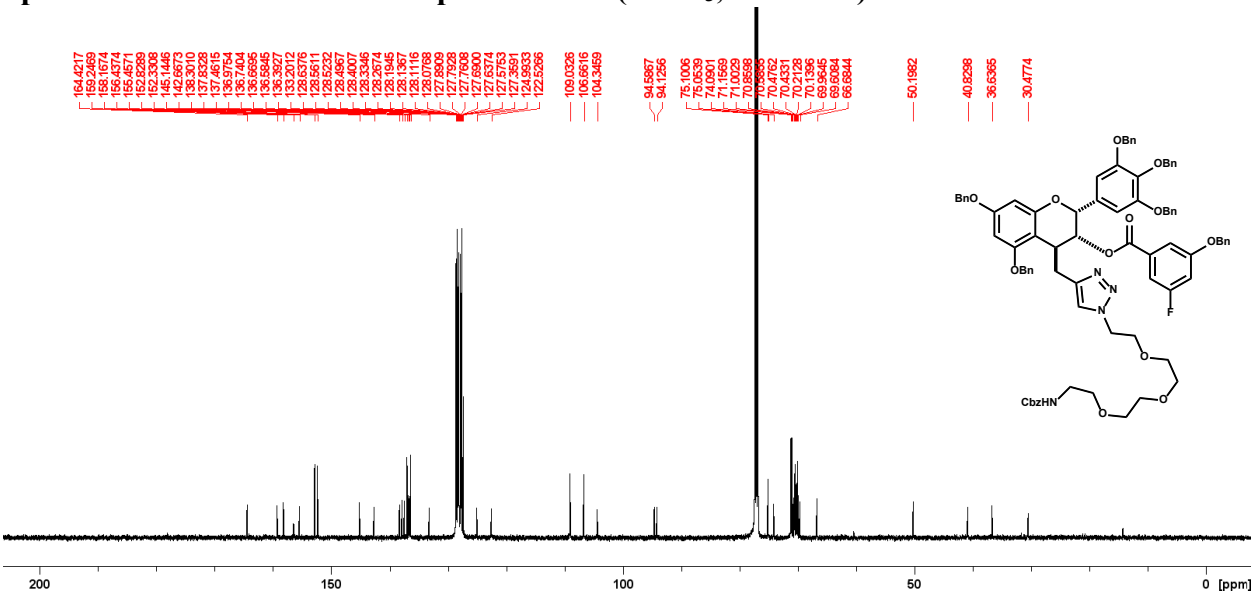
Spectrum 257. ^{13}C NMR of compound 3-41 (CD_3OD, 125 MHz)



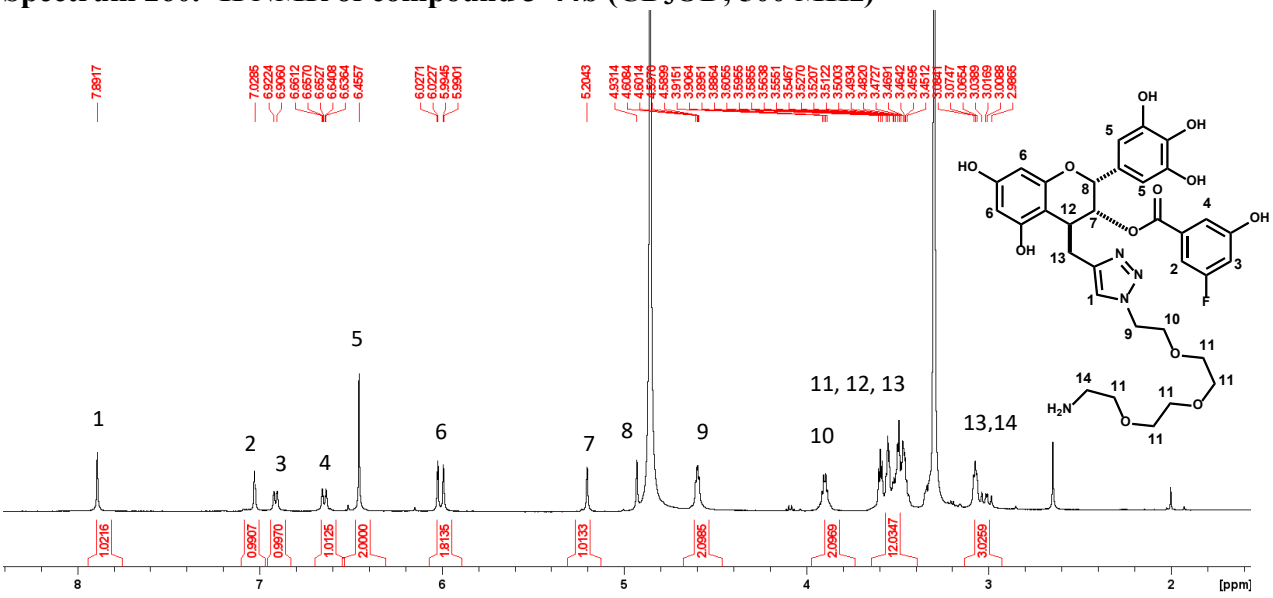
Spectrum 258. ^{1}H NMR of compound 3-43b ($CDCl_3$, 500 MHz)



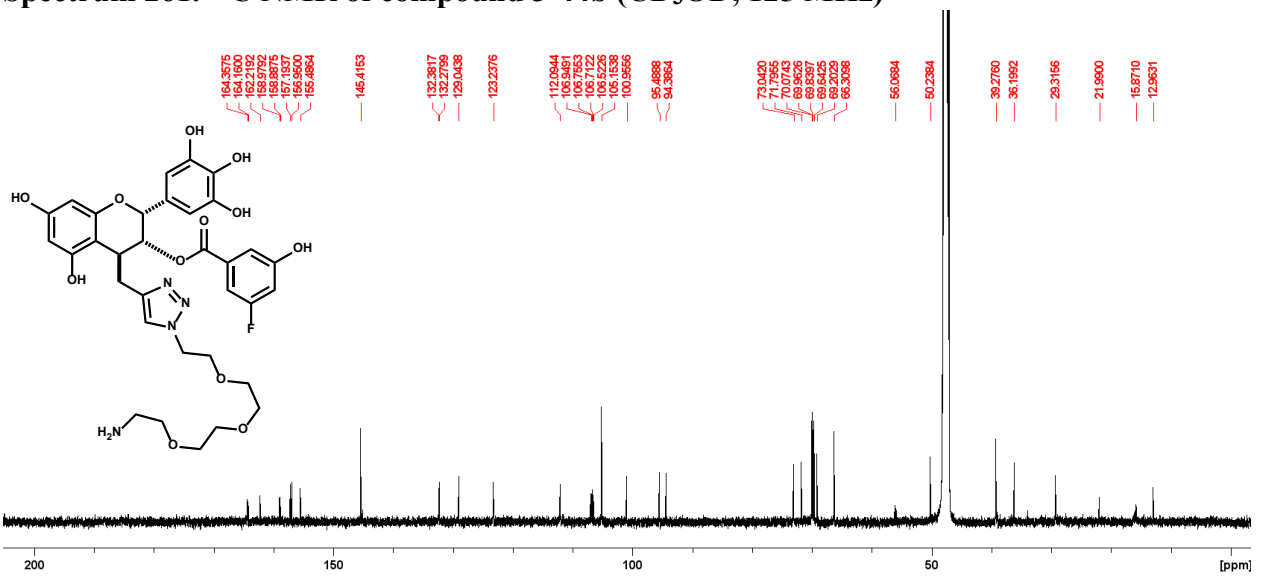
Spectrum 259. ^{13}C NMR of compound 3-43b ($CDCl_3$, 125 MHz)



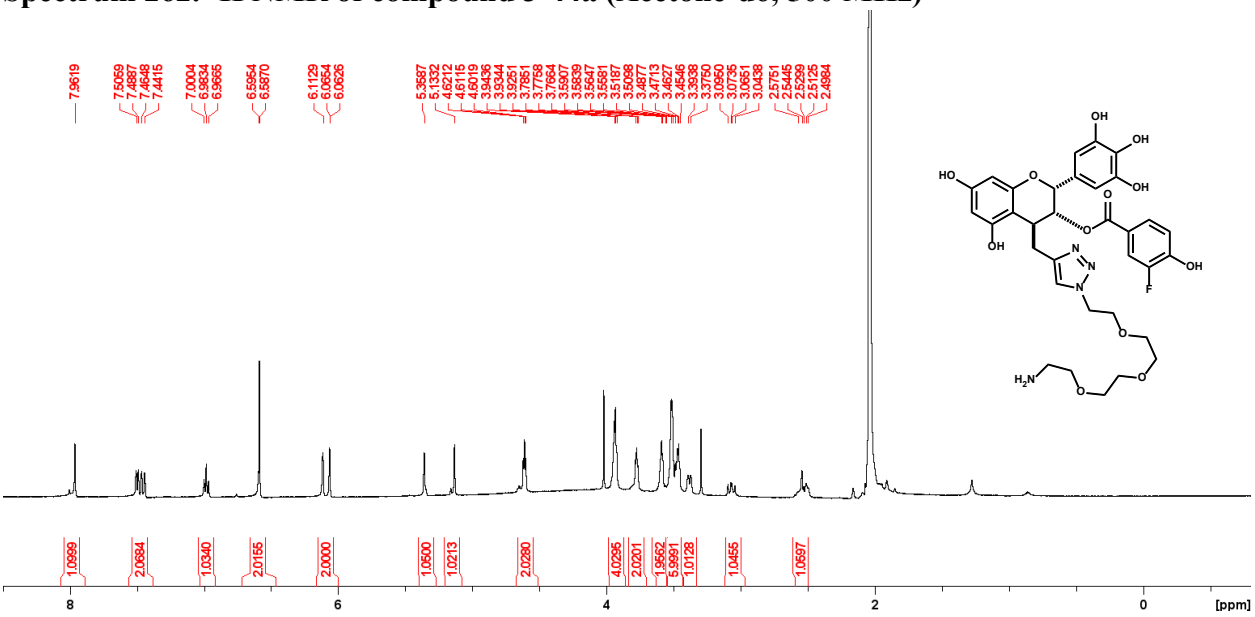
Spectrum 260. ^{1}H NMR of compound 3-44b (CD_3OD, 500 MHz)



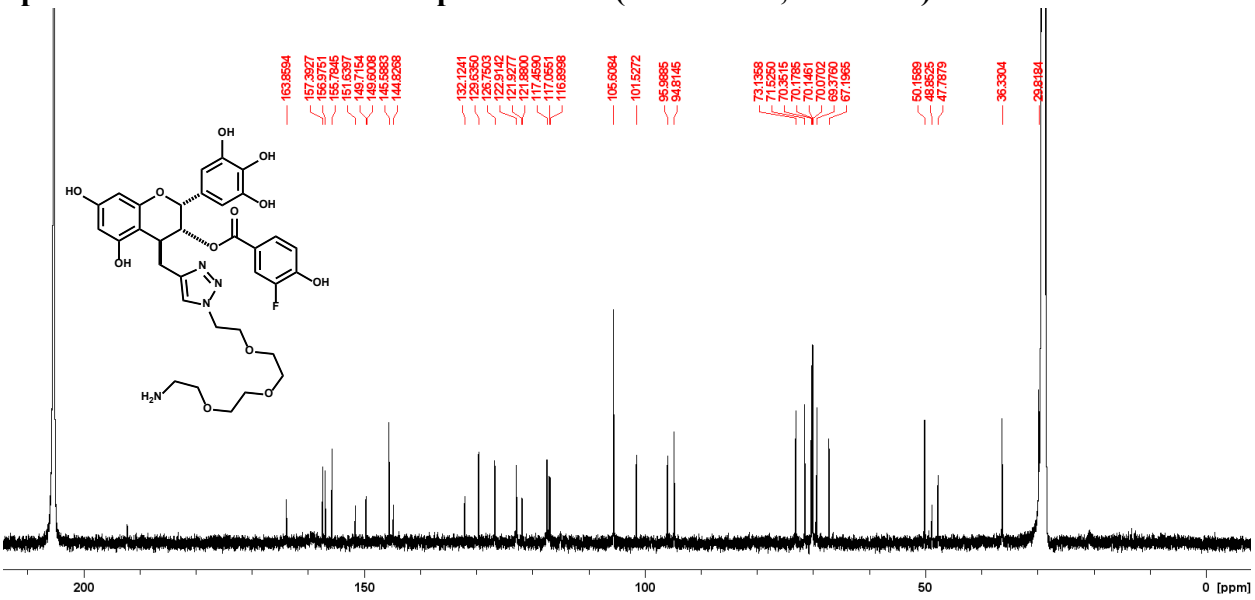
Spectrum 261. ^{13}C NMR of compound 3-44b (CD_3OD, 125 MHz)



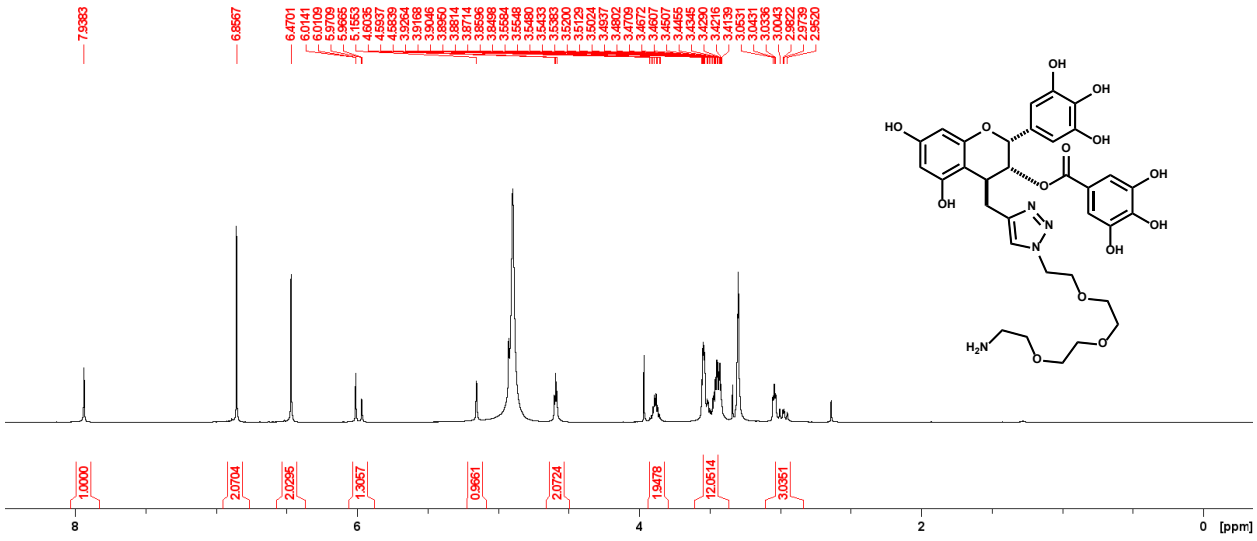
Spectrum 262. ^{1}H NMR of compound 3-44a (Acetone-d6, 500 MHz)



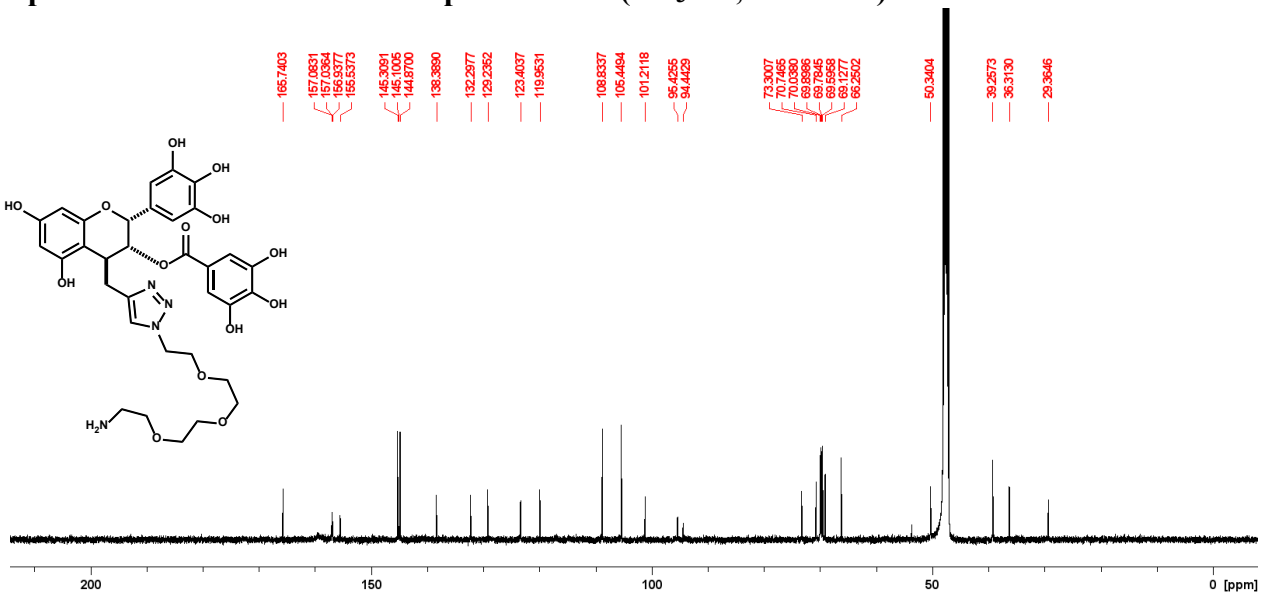
Spectrum 263. ^{13}C NMR of compound 3-44a (Acetone-d6, 125 MHz)



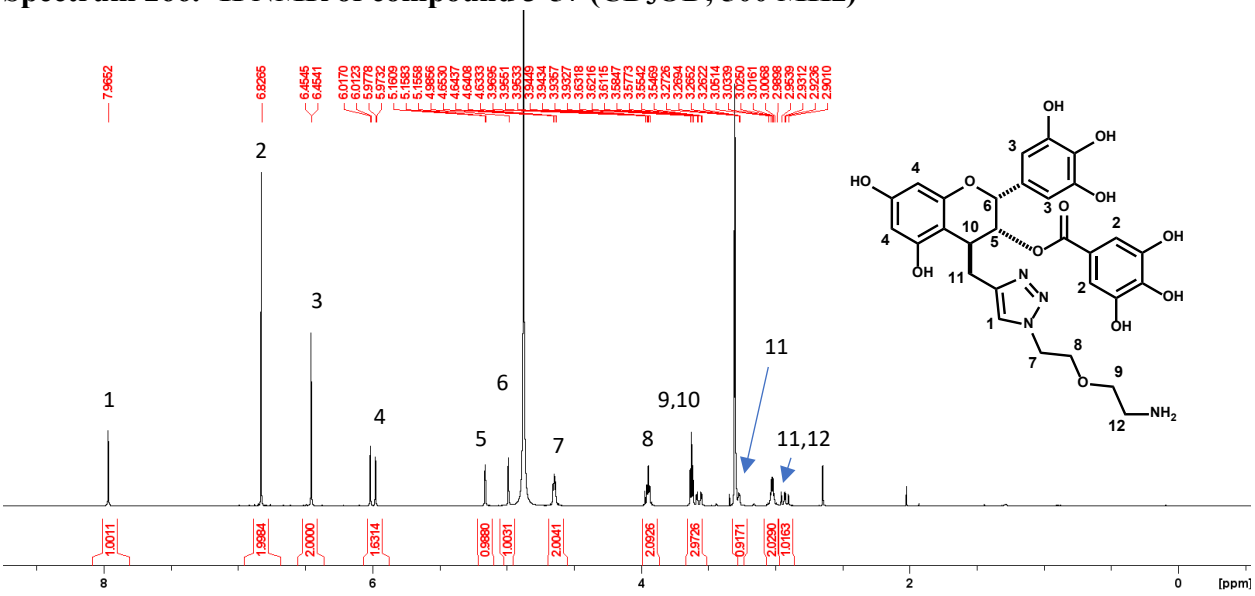
Spectrum 264. ^{1}H NMR of compound 3-44c (CD_3OD, 500 MHz)



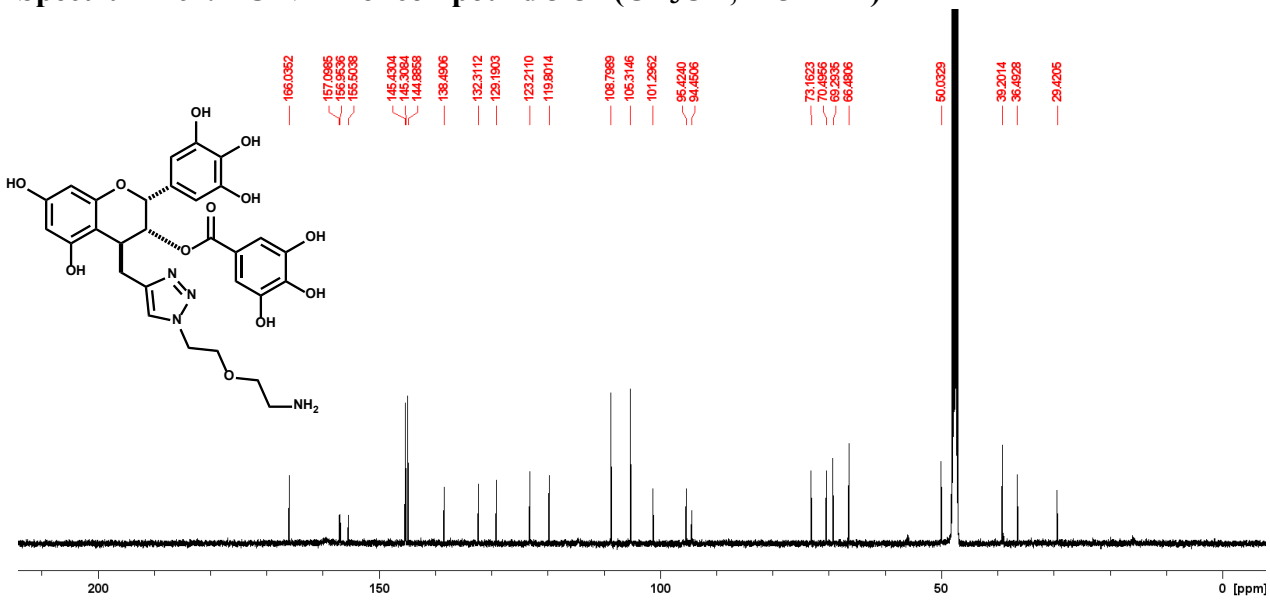
Spectrum 265. ^{13}C NMR of compound 3-44c (CD_3OD, 125 MHz)



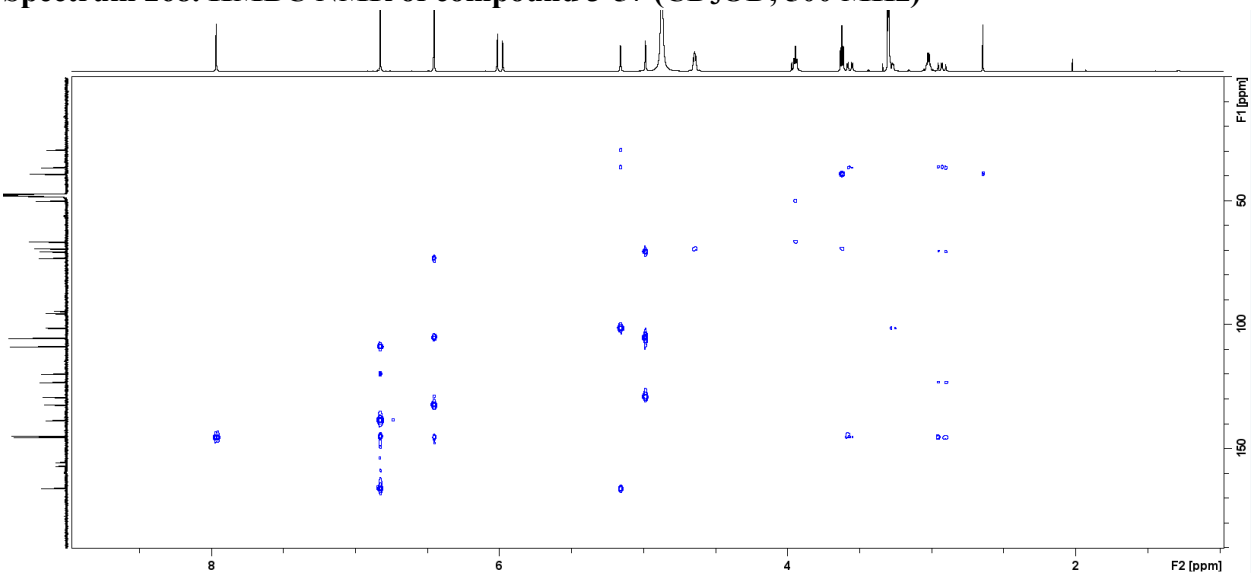
Spectrum 266. ^{1}H NMR of compound 3-57 (CD_3OD, 500 MHz)



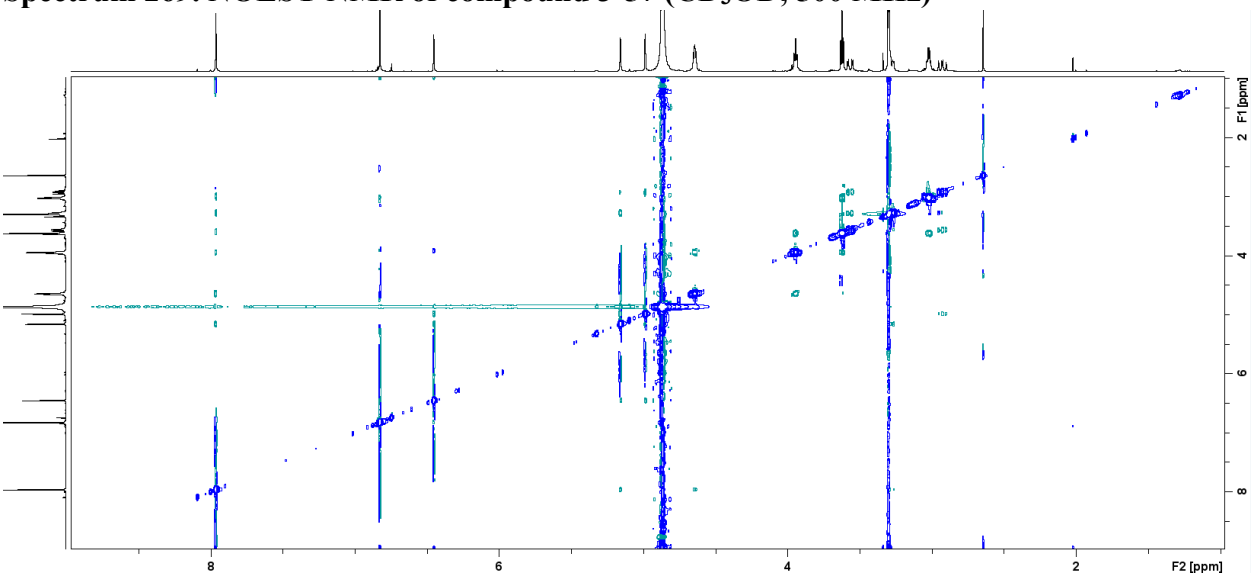
Spectrum 267. ^{13}C NMR of compound 3-57 (CD_3OD, 125 MHz)



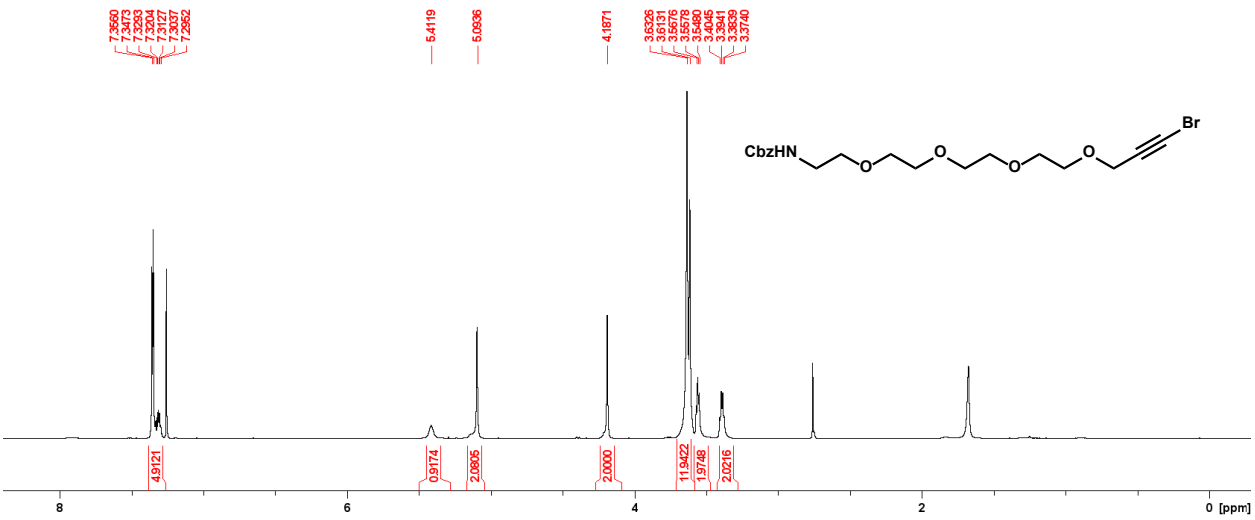
Spectrum 268. HMBC NMR of compound 3-57 (CD_3OD, 500 MHz)



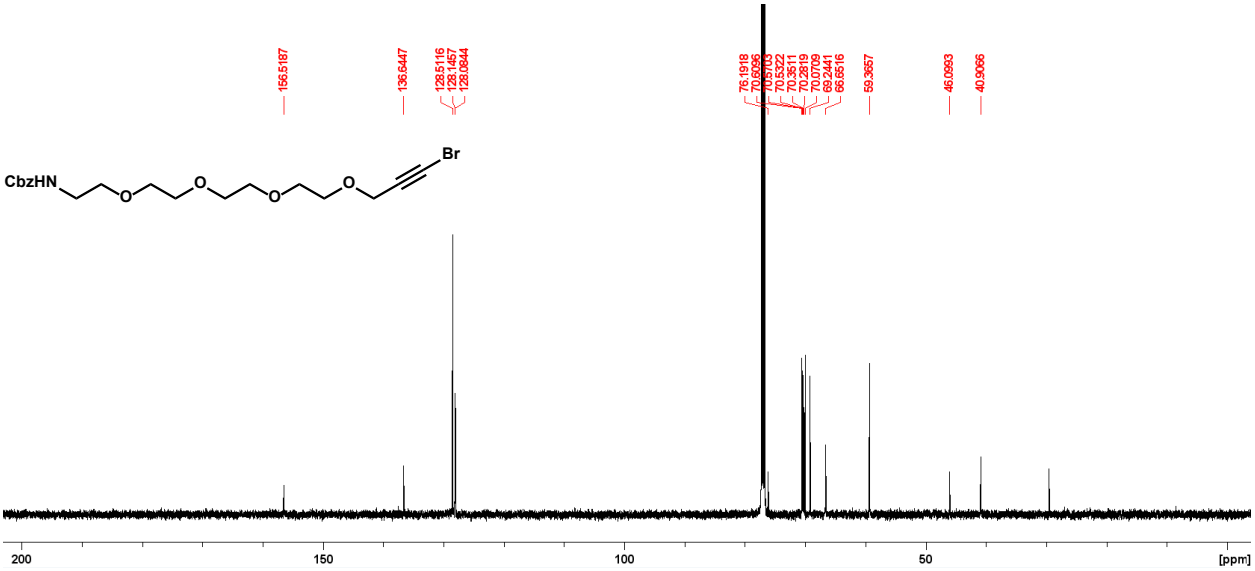
Spectrum 269. NOESY NMR of compound 3-57 (CD_3OD, 500 MHz)



Spectrum 270. ^{1}H NMR of compound 3-48 (CD_3OD, 500 MHz)



Spectrum 271. ^{13}C NMR of compound 3-48 (CD_3OD, 125 MHz)



Reference and Notes

1) Brand, L. E.; Campbell, L.; Bresnan, E. Karenia: The biology and ecology of a toxic genus *Harmful Alga*e **2012**, *14*, 156-178.

2) Molgó, J.; Marchot, P.; Aráoz, R.; Benoit, E.; Iorga, B. I.; Zakarian, A.; Taylor, P.; Bourne, Y.; Servent, D. Cyclic imine toxins from dinoflagellates: a growing family of potent antagonists of the nicotinic acetylcholine receptors *J. Neurochem.* **2017**, *142*, 41–51.

3) D. Uemura, T. Chou, T. Haino, A. Nagatsu, S. Fukuzawa, S. Z., Zheng, H. S. Chen, Pinnatoxin A: a toxic amphoteric macrocycle from the Okinawan bivalve Pinna muricata *J. Am. Chem. Soc.* **1995**, *117*, 1155 – 1156.

4) Seki, T.; Satake, M.; Mackenzie, L.; Kaspar, H. F.; Yasumoto, T. Gymnodimine, a new marine toxin of unprecedented structure isolated from New Zealand oysters and the dinoflagellate, Gymnodinium sp. *Tetrahedron Lett.* **1995**, *36*, 7093-7096.

5) Selwood, A. I.; Wilkins, A. L.; Munday, R.; Shi, F.; Rhodes, L. L.; Holland, P. T. Portimine: A bioactive metabolite from the benthic dinoflagellate Vulcanodinium rugosum *Tetrahedron Lett.* **2013**, *54*, 4705–4707.

6) MacKinnon, S. L.; Cembella, A. D.; Burton, I. W.; Lewis, N.; LeBlanc, P.; Walter, J. A. Biosynthesis of 13-Desmethyl Spirolide C by the Dinoflagellate *Alexandrium o stenfeldii J. Org. Chem.* **2006**, *71*, 8724-8731.

7) Stewart, M.; Blunt, J. W.; Munro, M. H. G.; Robinson, W. T.; Hannah, D. J. The absolute stereochemistry of the New Zealand shellfish toxin gymnodimine *Tetrahedron Lett.* **1997**, *38*, 4889–4890.

8) Johannes, J. W.; Wenglowsky, S.; Kishi, Y. Biomimetic Macrocycle-Forming Diels−Alder Reaction of an Iminium Dienophile: Synthetic Studies Directed Toward Gymnodimine *Org. Lett.* **2005**, *7*, 18, 3997-4000.

9) Kong, K.; Moussa, Z.; Lee, C.; Romo, D. Total synthesis of the spirocyclic imine marine toxin (-)-gymnodimine and an unnatural C4-epimer *J. Am. Chem. Soc.* **2011**, *133*, 19844–19856.

10) McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. Total synthesis of pinnatoxin A *J. Am. Chem. Soc.* **1998**, *120*, 7647–7648.

11) Stivala, C. E.; Zakarian, A. Total synthesis of (+)-pinnatoxin A *J. Am. Chem. Soc.* **2008**, *130*, 3774–3776.

12) Stivala, C. E.; Benoit, E.; Aráoz, R.; Servent, D.; Novikov, A.; Molgó, J.; Zakarian, A. Synthesis and biology of cyclic imine toxins, an emerging class of potent, globally distributed marine toxins *Nat. Prod. Rep.* **2015**, *32*, 411–435.

13) Cuddihy, S. L.; Drake, S.; Harwood, D. T.; Selwood, A. I.; McNabb, P. S.; Hampton, M. B. The marine cytotoxin portimine is a potent and selective inducer of apoptosis *Apoptosis* 2016, *21*, 1447-1452.

14) a) Izumida, M.; Suga, K.; Ishibashi, F.; Kubo, Y. The Spirocyclic Imine from a Marine Benthic Dinoflagellate, Portimine, Is a Potent Anti-Human Immunodeficiency Virus Type 1 Therapeutic Lead Compound *Mar. Drugs* 2019, *17*, 495. b) Brooke, D. G.; Cervin, G.; Champeau, O.; Harwood, D. T.; Pavia, H.; Selwood, A. I.; Svenson, J.; Tremblay, L. A.; Cahill, P. L. Antifouling activity of portimine, select semisynthetic analogues, and other microalga-derived spirocyclic imines *Biofouling* 2018, *34*, 950–961.

15) Kim, I. S.; Ngai, M. Y.; Krische, M. J. Enantioselective iridium-catalyzed carbonyl allylation from the alcohol or aldehyde oxidation level via transfer hydrogenative coupling of allyl acetate: Departure from chirally modified allyl metal reagents in carbonyl addition *J. Am. Chem. Soc.* **2008**, *130*, 14891–14899.

16) Parida, B. B.; Das, P. P.; Niocel, M.; Cha, J. K. C-Acylation of cyclopropanols: Preparation of functionalized 1,4-diketones *Org. Lett.* **2013**, *15*, 1780–1783.

17) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. New strategies for organic catalysis: The first highly enantioselective organocatalytic Diels - Alder reaction *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

18) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. The First Enantioselective Organocatalytic Mukaiyama−Michael Reaction: A Direct Method for the Synthesis of Enantioenriched γ-Butenolide Architecture *J. Am. Chem. Soc.* **2003**, *125*.

19) (a) Yanai, H.; Takahashi, A.; Taguchi, T., 1,4-Addition of silicon dienoates to alpha,beta-unsaturated aldehydes catalyzed by in situ-generated silicon Lewis acid. *Chem Commun (Camb)* **2010,** *46*, 8728-8730; (b) Luo, X.; Zhou, Z.; Yu, F.; Li, X.; Liang, X.; Ye, J., Asymmetric Vinylogous Michael Reaction of α,β-Unsaturated Aldehyde with Buteno-4-lactone. *Chem. Lett.* **2011,** *40*, 518-520; (c) Kemppainen, E. K.; Sahoo, G.; Piisola, A.; Hamza, A.; Kotai, B.; Papai, I.; Pihko, P. M., Mukaiyama-Michael reactions with trans-2,5-diarylpyrrolidine catalysts: enantioselectivity arises from attractive noncovalent interactions, not from steric hindrance. *Chemistry a european journal* **2014,** *20*, 5983-5993; (d) Li, X.; Lu, M.; Dong, Y.; Wu, W.; Qian, Q.; Ye, J.; Dixon, D. J., Diastereodivergent organocatalytic asymmetric vinylogous Michael reactions. *Nat Commun* **2014,** *5*, 4479; (e) Quintard, A.; Lefranc, A.; Alexakis, A., Highly enantioselective direct vinylogous Michael addition of gamma-butenolide to enals. *Org. Lett.* **2011,** *13*, 1540-1543; (f) Wang, J.; Qi, C.; Ge, Z.; Cheng, T.; Li, R., Efficient direct asymmetric vinylogous Michael addition reactions of gamma-butenolides to chalcones catalyzed by vicinal primary-diamine salts. *Chem Commun (Camb)* **2010,** *46*, 2124-2126; (g) Zhang, Y.; Yu, C.; Ji, Y.; Wang, W., Diastereo- and enantioselective organocatalytic direct conjugate addition of gamma-butenolide to chalcones. *Chem Asian J* **2010,** *5*, 1303-1306; (h) Huang, H.; Yu, F.; Jin, Z.; Li, W.; Wu, W.; Liang, X.; Ye, J., Asymmetric vinylogous Michael reaction of alpha,beta-unsaturated ketones with gamma-butenolide under multifunctional catalysis. *Chem Commun (Camb)* **2010,** *46*, 5957-5959; (i) Terada, M.; Ando, K., Enantioselective direct vinylogous Michael addition of functionalized furanones to nitroalkenes catalyzed by an axially chiral guanidine base. *Org. Lett.* **2011,** *13*, 2026-2029; (j) Manna, M. S.; Kumar, V.; Mukherjee, S., Catalytic enantioselective construction of quaternary stereocenters by direct vinylogous Michael addition of deconjugated butenolides to nitroolefins. *Chem Commun (Camb)* **2012,** *48*, 5193-5195; (k) Simlandy, A. K.; Mukherjee, S., Catalytic asymmetric formal gamma-allylation of deconjugated butenolides. *Org. Biomol. Chem.* **2016,** *14*, 5659-5664; (l) Wang, Z. H.; Wu, Z. J.; Huang, X. Q.; Yue, D. F.; You, Y.; Xu, X. Y.; Zhang, X. M.; Yuan, W. C., Diastereo- and enantioselective direct vinylogous Michael addition of gamma-substituted butenolides to 2-enoylpyridines catalyzed by chiral bifunctional amine-squaramides. *Chem Commun (Camb)* **2015,** *51*, 15835-15838; (m) Das, U.; Chen, Y. R.; Tsai, Y. L.; Lin, W., Organocatalytic enantioselective direct vinylogous Michael addition of gamma-substituted butenolides to 3-aroyl acrylates and 1,2-diaroylethylenes. *Chemistry a european journal* **2013,** *19*, 7713-7717; (n) Zhang, W.; Tan, D.; Lee, R.; Tong, G.; Chen, W.; Qi, B.; Huang, K. W.; Tan, C. H.; Jiang, Z., Highly enantio- and diastereoselective reactions of gamma-substituted butenolides through direct vinylogous conjugate additions. *Angew. Chem. Int. Ed.* **2012,** *51*, 10069-10073; (o) Guo, Y.-L.; Jia, L.-N.; Peng, L.; Qi, L.-W.; Zhou, J.; Tian, F.; Xu, X.-Y.; Wang, L.-X., Highly enantioselective direct vinylogous Michael addition of γ-substituted deconjugated butenolides to maleimides catalyzed by chiral squaramides. *RSC Adv.* **2013,** *3*; (p) Kemppainen, E. K.; Sahoo, G.; Valkonen, A.; Pihko, P. M., Mukaiyama-Michael reactions with acrolein and methacrolein: a catalytic enantioselective synthesis of the C17-C28 fragment of pectenotoxins. *Org. Lett.* **2012,** *14*, 1086-1089.

20) Li, L.; El Khoury, A.; Clement, B. O.; Harran, P. G., Re-visiting the diastereoselectivity of organocatalytic conjugate addition of 2-trimethylsiloxyfuran to trans-crotonaldehyde. *Tetrahedron Lett.* **2021,** *72*, 153056.

21) Yadav, J. S.; Reddy, B. V. S.; Narasimhulu, G.; Reddy, N. S.; Reddy, P. J., Iodine-catalyzed 1,4-addition of 2-(trimethylsilyloxy)furan to α,β-unsaturated ketones: a facile synthesis of γ-butenolides. *Tetrahedron Lett.* **2009,** *50*, 3760-3762.

22) Kitajima, H.; Ito, K.; Katsuki, T., A new methodology for the stereoselective synthesis of 4-substituted butenolides: Asymmetric Michael addition reaction of 2-(trimethylsilyloxy)furans to oxazolidinone enoates. *Tetrahedron* **1997,** *53*, 17015-17028

23) Suen, L. M.; Steigerwald, M. L.; Leighton, J. L., A new and more powerfully activating diamine for practical and scalable enantioselective aldehyde crotylsilylation reactions. *Chem Sci* **2013,** *4*, 2413-2417.

24) Ning, X. S.; Wang, M. M.; Yao, C. Z.; Chen, X. M.; Kang, Y. B., tert-Butyl Nitrite: Organic Redox Cocatalyst for Aerobic Aldehyde-Selective Wacker-Tsuji Oxidation. *Org. Lett.* **2016,** *18*, 2700-2703.

25) Gordillo, R.; Carter, J.; Houk, K. N., Theoretical Explorations of Enantioselective Alkylation Reactions of Pyrroles and Indoles Organocatalyzed by Chiral Imidazolidinones. *Adv. Synth. Catal.* **2004,** *346*, 1175-1185.

26) Kemppainen, E. K.; Sahoo, G.; Piisola, A.; Hamza, A.; Kotai, B.; Papai, I.; Pihko, P. M., Mukaiyama-Michael reactions with trans-2,5-diarylpyrrolidine catalysts: enantioselectivity arises from attractive noncovalent interactions, not from steric hindrance. *Chemistry a european journal* **2014,** *20*, 5983-5993

27) Lee, H. Y.; Gyu Kim, B.; Snapper, M. L. A stereoselective enyne cross metathesis *Org. Lett.* **2003**, *5*, 1855–1858.

28) Esposito, A.; Taddei, M. The Kulinkovich reaction on lactones. A convenient approach to functionalized cyclopropanols *J. Org. Chem.* **2000**, *65*, 9245–9248.

29) Nakamura, E.; Shimada, J.; Kuwajima, I., A ring-opening reaction of 1-siloxy-1-alkoxycyclopropanes. Preparation of Main-Group metal homoenolates of alkyl propionate. *Organometallics* **2002,** *4*, 641-646.

30) Cirrincione, G.; Das, P. P.; Parida, B. B.; Cha, J. K., Organozinc-promoted ring opening of cyclopropanols. *Arkivoc* **2012,** *2012*, 74-84.

31) (a) Ryu, I.; Ikebe, M.; Sonoda, N.; Yamato, S.-y.; Yamamura, G.-h.; Komatsu, M., Chemistry of ketone α,β-dianions. Acylation reactions of dianion cuprates by acid chlorides. *Tetrahedron Lett.* **2002,** *43*, 1257-1259; (b) Shen, Z. L.; Goh, K. K.; Cheong, H. L.; Wong, C. H.; Lai, Y. C.; Yang, Y. S.; Loh, T. P., Synthesis of water-tolerant indium homoenolate in aqueous media and its application in the synthesis of 1,4-dicarbonyl compounds via palladium-catalyzed coupling with acid chloride. *J. Am. Chem. Soc.* **2010,** *132*, 15852-15855; (c) Nomura, K.; Matsubara, S., Stereospecific construction of chiral tertiary and quaternary carbon by nucleophilic cyclopropanation with bis(iodozincio)methane. *Chem Asian J* **2010,** *5*, 147-152; (d) Fujimura, T.; Aoki, S.; Nakamura, E., Synthesis of 1,4-keto esters and 1,4-diketones via palladium-catalyzed acylation of siloxycyclopropanes. Synthetic and mechanistic studies. *J. Org. Chem* **2002,** *56*, 2809-2821; (e) Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I., Palladium- and platinum-catalyzed reaction of siloxycyclopropanes with acid chlorides. A homoenolate route to 1,4-dicarbonyl compounds. *Tetrahedron Lett.* **1989,** *30*, 6541-6544; (f) Oshino, H.; Nakamura, E.; Kuwajima, I., Catalytic homo-Reformatskii reaction. Ambident chemical reactivities of the zinc homoenolate of propionate. *J. Org. Chem* **2002,** *50*, 2802-2804; (g) Parida, B. B.; Das, P. P.; Niocel, M.; Cha, J. K., C-acylation of cyclopropanols: preparation of functionalized 1,4-diketones. *Org. Lett.* **2013,** *15*, 1780-1783.

32) (a) Crimmins, M. T.; Nantermet, P. G., Homoenolates and Other Functionalized Organometallics. A Review. *Org. Prep. Proced. Int.* **1993,** *25*, 41-81; (b) Kuwajima, I.; Nakamura, E., Metal homoenolates from siloxycyclopropanes. In *Top. Curr. Chem.*, 1990; Vol. 155, pp 1-39; (c) Mills, L. R.; Rousseaux, S. A. L., Modern Developments in the Chemistry of Homoenolates. *Eur. J. Org. Chem.* **2019,** *2019*, 8-26.

33) Cabrero-Antonino, J. R.; Leyva-Perez, A.; Corma, A., Regioselective hydration of alkynes by iron^{III} Lewis/Bronsted catalysis. *Chemistry - A European Journal* **2012,** *18*, 11107-11114.

34) Dieter, R. K.; Chen, N.; Watson, R. T., Copper mediated scalemic organolithium reagents in alkaloid syntheses. *Tetrahedron* **2005,** *61*, 3221-3230.

35) Szymaniak, A. A.; Zhang, C.; Coombs, J. R.; Morken, J. P., Enantioselective Synthesis of Nonracemic Geminal Silylboronates by Pt-Catalyzed Hydrosilylation. *ACS Catal* **2018,** *8*, 2897-2901.

36) (a) Crousse, B.; Alami, M.; Linstrumelle, G., Stereoselective Reduction of Conjugated Homopropargylic Alcohols to (E)-Homoallylic Alcohols by Sodium Bis(2-methoxyethoxy) Aluminium Hydride. *Synlett* **1997,** *1997*, 992-994; (b) Denmark, S. E.; Jones, T. K., (E)-3-(Trimethylsilyl)-2-propen-1-ol. An improved preparation. *J. Org. Chem* **2002,** *47*, 4595-4597.

37) Ashby, E. C.; Pham, T. N.; Amrollah-Madjdabadi, A., Concerning the mechanism of reaction of lithium aluminum hydride with alkyl halides. *J. Org. Chem* **2002,** *56*, 1596-1603.

38) Cacchi, S.; Fabrizi, G.; Goggiamani, A., Palladium-catalyzed hydroxycarbonylation of aryl and vinyl halides or triflates by acetic anhydride and formate anions. *Org. Lett.* **2003,** *5*, 4269-4272.

39) Devos, A.; Remion, J.; Frisque-Hesbain, A.-M.; Colens, A.; Ghosez, L., Synthesis of acyl halides under very mild conditions. *J. Chem. Soc., Chem. Commun.* **1979**.

40) (a) Achonduh, G. T.; Hadei, N.; Valente, C.; Avola, S.; O'Brien, C. J.; Organ, M. G., On the role of additives in alkyl-alkyl Negishi cross-couplings. *Chem Commun (Camb)* **2010,** *46*, 4109-4111; (b) McCann, L. C.; Organ, M. G., On the remarkably different role of salt in the cross-coupling of arylzincs from that seen with alkylzincs. *Angew. Chem. Int. Ed.* **2014,** *53*, 4386-4389; (c) Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A.; O'Brien, C. J.; Valente, C., A user-friendly, all-purpose Pd-NHC (NHC=N-heterocyclic carbene) precatalyst for the negishi reaction: a step towards a universal cross-coupling catalyst. *Chemistry* **2006,** *12*, 4749-4755; (d) McCann, L. C.; Hunter, H. N.; Clyburne, J. A.; Organ, M. G., Higher-order zincates as transmetalators in alkyl-alkyl negishi cross-coupling. *Angew. Chem. Int. Ed.* **2012,** *51*, 7024-7027.

41) (a) Waldmann, H., LiClO4 in Ether—an Unusual Solvent. *Angew. Chem. Int. Ed.* **1991,** *30*, 1306-1308; (b) Grieco, P. A.; Nunes, J. J.; Gaul, M. D., Dramatic rate accelerations of Diels-Alder reactions in 5 M lithium perchlorate-diethyl ether: the cantharidin problem reexamined. *J. Am. Chem. Soc.* **2002,** *112*, 4595-4596.

42) Kotoku, N.; Fujioka, S.; Nakata, C.; Yamada, M.; Sumii, Y.; Kawachi, T.; Arai, M.; Kobayashi, M. Concise synthesis and structure-activity relationship of furospinosulin-1, a hypoxia-selective growth inhibitor from marine sponge *Tetrahedron* **2011**, *67*, 6673–6678.

43) Duan, J.; Du, Y. F.; Pang, X.; Shu, X. Z. Ni-catalyzed cross-electrophile coupling between vinyl/aryl and alkyl sulfonates: Synthesis of cycloalkenes and modification of peptides *Chem. Sci.* **2019**, *10*, 8706–8712.

44) Boeckman, R. K.; Pero, J. E.; Boehmler, D. J. Toward the Development of a General Chiral Auxiliary. Enantioselective Alkylation and a New Catalytic Asymmetric Addition of Silyloxyfurans: Application to a Total Synthesis of (-)-Rasfonin. *J. Am. Chem. Soc.* **2006**, *128*, 11032-11033

45) Suen, L. M.; Steigerwald, M. L.; Leighton, J. L., A new and more powerfully activating diamine for practical and scalable enantioselective aldehyde crotylsilylation reactions. *Chem Sci* **2013,** *4*, 2413-2417.

46) Cao, W.; Tan, D.; Lee, R.; Tan, C. H., Enantioselective 1,2-Anionotropic Rearrangement of Acylsilane through a Bisguanidinium Silicate Ion Pair. *J. Am. Chem. Soc.* **2018,** *140*, 1952-1955.

47) Robert K. Boeckman, J.; Tusch, D. J.; Biegasiewicz, K. F., (S)-1,1-Diphenylprolinol Trimethylsilyl Ether. *Organic Syntheses* **2015,** *92*, 309-319.

48) Fu, M.-C.; Shang, R.; Cheng, W.-M.; Fu, Y., Nickel-Catalyzed Regio- and Stereoselective Hydrocarboxylation of Alkynes with Formic Acid through Catalytic CO Recycling. *ACS Catalysis* **2016,** *6*, 2501-2505.

49) Cabrero-Antonino, J. R.; Tejeda-Serrano, M.; Quesada, M.; Vidal-Moya, J. A.; Leyva-Perez, A.; Corma, A., Bimetallic nanosized solids with acid and redox properties for catalytic activation of C-C and C-H bonds. *Chem Sci* **2017,** *8*, 689-696.

50) Darses, B.; Michaelides, I. N.; Sladojevich, F.; Ward, J. W.; Rzepa, P. R.; Dixon, D. J., Expedient construction of the [7-5-5] all-carbon tricyclic core of the Daphniphyllum alkaloids daphnilongeranin B and daphniyunnine D. *Org. Lett.* **2012,** *14*, 1684-1687.

51) Sugiyama, H.; Yokokawa, F.; Shioiri, T., Asymmetric total synthesis of (-)-mycothiazole. *Org. Lett.* **2000,** *2*, 2149-2152.

52) Robert K. Boeckman, J.; Tusch, D. J.; Biegasiewicz, K. F., (S)-1,1-Diphenylprolinol Trimethylsilyl Ether. *Organic Syntheses* **2015,** *92*, 309-319.

53) Cordova, A.; Mridha, M.; Ma, G.; Palo-Nieto, C.; Afewerki, S., Development of an Amino Acid/Hydroxy Oxime Dual Catalyst Sys-tem for Highly Stereoselective Direct Asymmetric Aldol Reactions in the Presence of Water. *Synthesis* **2016,** *49*, 383-390.

54) (a) Narasaka, K.; Pai, H. C., Stereoselective Synthesis Of-meso(Orerythro) 1,3-Diols from β-Hydroxyketones. *Chem. Lett.* **1980,** *9*, 1415-1418; (b) Narasaka, K.; Pai, F.-C., Stereoselective reduction of β hydroxyketones to 1,3-diols highly selective 1,3-asymmetric induc-tion via boron chelates. *Tetrahedron* **1984,** *40*, 2233-2238; (c) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repič, O.; Shapiro, M. J., 1,3- diastereoselective reduction of β-hydroxyketones utilizing alkoxydialkylboranes. *Tetrahedron Lett.* **1987,** *28*, 155-158.

55) Snider, B. B.; Zhou, J., Synthesis of lanopylin B1. *J. Org. Chem.* **2005,** *70*, 1087-1088.

56) Dai, M.; Davis, D.; Haskins, C., Radical Cyclopropanol Ring Opening Initiated Tandem Cyclizations for Efficient Synthesis of Phenanthridines and Oxindoles. *Synlett* **2017,** *28*, 913-918.

57) Chrostowska, A.; Matrane, A.; Maki, D.; Khayar, S.; Ushiki, H.; Graciaa, A.; Belachemi, L.; Guillemin, J. C., Are unsaturated iso-cyanides so different from the corresponding nitriles? *Chemphyschem* **2012,** *13*, 226-236.

58) Wang, J.; Tang, S.; Zhu, Q. Intramolecular Imidoylative Heck Reaction: Synthesis of Cyclic Ketoimines from Functionalized Isocyanide *Org. Lett.* **2016**, *18*, 3074–3077.

59) Nef, J. U. Ueber das zweiwerthige Kohlenstoffatom *Justus Liebigs Ann. Chem.* **1892**, *270*, 267–335.

60) Marcoux, D.; Bindschädler, P.; Speed, A. W. H.; Chiu, A.; Pero, J. E.; Borg, G. A.; Evans, D. A. Effect of counterion structure on rates and diastereoselectivities in α,β-unsaturated iminium-ion diels-alder reactions *Org. Lett.* **2011**, *13*, 3758–3761.

61) Mizuno, T.; Kino, T.; Takatoshi, I.; Miyata, T. Synthesis of aromatic urea herbicides by the selenium-assisted carbonylation using carbon monoxide with sulfur *Synth. Commun.* **2000**, *30*, 1675–1688.

62) Ma, G.; Bartoszewicz, A.; Ibrahem, I.; Córdova, A., Highly Enantioselective Co-Catalytic Direct Aldol Reactions by Combination of Hydrogen-Bond Donating and Acyclic Amino Acid Catalysts. *Adv. Synth. Catal.* **2011,** *353*, 3114-3122.

63) Meyer, K. G., Improved Synthesis of 3-Aminofurazan-4-Carboxylic Acid. *Org. Prep. Proced. Int.* **2004,** *36*, 361-362.

64) Ravindar, K.; Sridhar Reddy, M.; Deslongchamps, P. A highly efficient access to spiroketals, mono-unsaturated spiroketals, and furans: Hg(II)-catalyzed cyclization of alkyne diols and triols *Org. Lett.* **2011**, *13*, 3178–3181.

65) (a) Zhu, J.; Chen, G.; Song, G. Method for preparing 3-chloropropionate. Patent CN101333163B, 2011; (b) Kulinkovich, O. G.; Kozyrkov, Y. Y.; Bekish, A. V.; Matiushenkov, E. A.; Lysenko, I. L., A Convenient Way for the Conversion of Carboxylic Esters into 2-Substituted Allyl Halides. *Synthesis* **2005**, 1713-1717; (c) Matyushenkov, E. A.; Kulinkovich, O. G., Transformation of carboxylic acid esters into 2-substituted allyl halides through tertiary

cyclopropyl sulfonates. Application in the synthesis of (±)-ipsenol and (±)-ipsdienol, components of Ips typographus spark beetle pheromone. *Russ. J. Org. Chem.* **2006,** *42*, 491-495.

66) Ricardo, M. G.; Marrrero, J. F.; Valdes, O.; Rivera, D. G.; Wessjohann, L. A., A Peptide Backbone Stapling Strategy Enabled by the Multicomponent Incorporation of Amide N-Substituents. *Chemistry* **2019,** *25*, 769-774.

67) Sugiyama, H.; Yokokawa, F.; Shioiri, T. Total synthesis of mycothiazole, a polyketide heterocycle from marine sponges *Tetrahedron* **2003**, *59*, 6579–6593.

68) Knowles, J. P.; Booker-Milburn, K. I. Unusually Facile Thermal Homodienyl-[1,5]-Hydrogen Shift Reactions in Photochemically Generated Vinyl Aziridines *Chem. - A Eur. J.* **2016**, *22*, 11429–11434.

69) *Alzheimer's & Dementia* **2020**, *16*, 391.

70) Gouras, G. K.; Olsson, T. T.; Hansson, O. β-amyloid Peptides and Amyloid Plaques in Alzheimer's Disease *Neurotherapeutics* **2015**, *12*, 3–11.

71) Murray, M. E.; Lowe, V. J.; Graff-Radford, N. R.; Liesinger, A. M.; Cannon, A.; Przybelski, S. A.; Rawal, B.; Parisi, J. E.; Petersen, R. C.; Kantarci, K.; Ross, O. A.; Duara, R.; Knopman, D. S.; Jack, C. R.; Dickson, D. W. Clinicopathologic and 11C-Pittsburgh compound B implications of Thal amyloid phase across the Alzheimer's disease spectrum *Brain* **2015**, *138*, 1370–1381.

72) (a) Bieschke, J.; Russ, J.; Friedrich, R. P.; Ehrnhoefer, D. E.; Wobst, H.; Neugebauer, K.; Wanker, E. E. EGCG remodels mature α-synuclein and amyloid-β fibrils and reduces cellular toxicity *PNAS* **2010**, *107*, 7710-7715. (b) Debnath, K.; Shekhar, S.; Kumar, V.; Jana, N. R.; Jana, N. R. Efficient Inhibition of Protein Aggregation, Disintegration of Aggregates, and Lowering of Cytotoxicity by Green Tea Polyphenol-Based Self-Assembled Polymer Nanoparticles *ACS Applied Materials and Interfaces* **2016**, *8*, 20309-20318.

73) Wobst, H. J.; Sharma, A.; Diamond, M. I.; Wanker, E. E.; Bieschke, J. The green tea polyphenol (-)-epigallocatechin gallate prevents the aggregation of tau protein into toxic oligomers at substoichiometric ratios *FEBS Lett.* **2015**, *589*, 77–83.

74) (a) Seidler, P. M.; Boyer, D. R.; Sawaya, M. R.; Ge, P.; Shin, W. S.; DeTure, M. A.; Dickson, D. W.; Jiang, L.; Eisenberg, D. S. CryoEM reveals how the small molecule EGCG binds to Alzheimer's brain-derived tau fibrils and initiates fibril disaggregation *bioRxiv* **2020**,

2020.05.29.124537. (b) Sonawane, S. K.; Chidambaram, H.; Boral, D.; Gorantla, N. V.; Balmik, A. A.; Dangi, A.; Ramasamy, S.; Marelli, U. K.; Chinnathambi, S. EGCG impedes human Tau aggregation and interacts with Tau *Sci. Rep.* **2020**, *10*, 12579.

75) (a) Lu, M.; Cohen, M. H.; Rieves, D.; Pazdur, R. FDA report: Ferumoxytol for intravenous iron therapy in adult patients with chronic kidney disease *American Journal of Hematology* **2010**, *85*, 315-319. (b) Muldoon, L. L.; Sandor, M.; Pinkston, K. E.; Neuwelt, E. A. Imaging, distribution, and toxicity of superparamagnetic iron oxide magnetic resonance nanoparticles in the rat brain and intracerebral tumor *Neurosurgery* **2005**, *57*, 785-796. (c) Neubert, J.; Wagner, S.; Kiwit, J.; Bräuer, A. U.; Glumm, J. New findings about iron oxide nanoparticles and their different effects on murine primary brain cells *International Journal of Nanomedicine* **2015**, *10*, 2033-2049. (d) Nguyen, K. L.; Yoshida, T.; Kathuria-Prakash, N.; Zaki, I. H.; Varallyay, C. G.; Semple, S. I.; Saouaf, R.; Rigsby, C. K.; Stoumpos, S.; Whitehead, K. K.; Griffin, L. M.; Saloner, D.; Hope, M. D.; Prince, M. R.; Fogel, M. A.; Schiebler, M. L.; Roditi, G. H.; Radjenovic, A.; Newby, D. E.; Neuwelt, E. A.; Bashir, M. R.; Hu, P.; Paul Finn, J. Multicenter Safety and Practice for Off-Label Diagnostic Use of Ferumoxytol in MRI *Radiology* **2019**, *293*, 554-564.

76) El Khoury, A; Seidler, P. M., Eisenberg, D. S., Harran, P.G. Catalytic synthesis of PEGylated EGCG conjugates that disaggregate Alzheimer's tau. *Synthesis*, **2021**, *53*, A-I

77) Wang, J.; Sun, P.; Wang, Q.; Zhang, P.; Wang, Y.; Zi, C.; Wang, X.; Sheng, J. (-)-Epigallocatechin-3-gallate derivatives combined with cisplatin exhibit synergistic inhibitory effects on non-small-cell lung cancer cells *Cancer Cell Int.* **2019**, *19*, 266.

78) Yang, Q.; Sheng, M.; Henkelis, J. J.; Tu, S.; Wiensch, E.; Zhang, H.; Zhang, Y.; Tucker, C.; Ejeh, D. E. Explosion Hazards of Sodium Hydride in Dimethyl Sulfoxide, N, N-Dimethylformamide, and N, N-Dimethylacetamide *Org. Process Res. Dev.* **2019**, *23*, 2210–2217.

79) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. Copper(I)-catalyzed synthesis of azoles. DFT study predicts unprecedented reactivity and intermediates *J. Am. Chem. Soc.* **2005**, *127*, 210–216.

80) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. A stepwise huisgen cycloaddition process: Copper(I)-catalyzed regioselective "ligation" of azides and terminal alkynes *Angew. Chemie - Int. Ed.* **2002**, *41*, 2596–2599.

81) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. Polytriazoles as copper(I)-stabilizing ligands in catalysis *Org. Lett.* **2004**, *6*, 2853–2855.

82) Madhusudanan, K. P.; Sachdev, K.; Harrison, D. A.; Kulshreshtha, D. K. Gas phase hydrogen/deuterium exchange reactions in chemical ionization mass spectra of flavonoids *Int. J. Mass Spectrom. Ion Process.* **1984**, *62*, 289–295.

83) Jordheim, M.; Fossen, T.; Songstad, J.; Andersen, Ø. M. Reactivity of anthocyanins and pyranoanthocyanins. Studies on aromatic hydrogen-deuterium exchange reactions in methanol *J. Agric. Food Chem.* **2007**, *55*, 8261–8268.

84) (a) Clavaguera, F.; Akatsu, H.; Fraser, G.; Crowther, R. A.; Frank, S.; Hench, J.; Probst, A.; Winkler, D. T.; Reichwald, J.; Staufenbiel, M.; Ghetti, B.; Goedert, M.; Tolnay, M. Brain homogenates from human tauopathies induce tau inclusions in mouse brain *PNAS* **2013**, *110*, 9535-9540. (b) Hyman, B. T. Tau Propagation, Different Tau Phenotypes, and Prion-like Properties of Tau *Neuron* **2014**, *82*, 1189-1190. (c) Seidler, P. M.; Boyer, D. R.; Murray, K. A.; Yang, T. P.; Bentzel, M.; Sawaya, M. R.; Rosenberg, G.; Cascio, D.; Williams, C. K.; Newell, K. L.; Ghetti, B.; DeTure, M. A.; Dickson, D. W.; Vinters, H. V.; Eisenberg, D. S. Structure-based inhibitors halt prion-like seeding by Alzheimer's disease–and tauopathy–derived brain tissue samples *Journal of Biological Chemistry* **2019**, *294*, 16451-16464.

85) (a) Muldoon, L. L.; Sandor, M.; Pinkston, K. E.; Neuwelt, E. A. Imaging, distribution, and toxicity of superparamagnetic iron oxide magnetic resonance nanoparticles in the rat brain and intracerebral tumor *Neurosurgery* **2005**, *57*, 785-796. (b) Toth, G. B.; Varallyay, C. G.; Horvath, A.; Bashir, M. R.; Choyke, P. L.; Daldrup-Link, H. E.; Dosa, E.; Finn, J. P.; Gahramanov, S.; Harisinghani, M.; Macdougall, I.; Neuwelt, A.; Vasanawala, S. S.; Ambady, P.; Barajas, R.; Cetas, J. S.; Ciporen, J.; DeLoughery, T. J.; Doolittle, N. D.; Fu, R.; Grinstead, J.; Guimaraes, A. R.; Hamilton, B. E.; Li, X.; McConnell, H. L.; Muldoon, L. L.; Nesbit, G.; Netto, J. P.; Petterson, D.; Rooney, W. D.; Schwartz, D.; Szidonya, L.; Neuwelt, E. A. Current and potential imaging applications of ferumoxytol for magnetic resonance imaging *Kidney International* **2017**, *92*, 47-66. (c) Nguyen, K.-L.; Yoshida, T.; Kathuria-Prakash, N.; Zaki, I. H.; Varallyay, C. G.; Semple, S. I.; Saouaf, R.; Rigsby, C. K.; Stoumpos, S.; Whitehead, K. K.; Griffin, L. M.; Saloner, D.; Hope, M. D.; Prince, M. R.; Fogel, M. A.; Schiebler, M. L.; Roditi, G. H.; Radjenovic, A.; Newby, D. E.; Neuwelt, E. A.; Bashir, M. R.; Hu, P.; Finn, J. P. Multicenter Safety and Practice for Off-Label Diagnostic Use of Ferumoxytol in MRI *Radiology* **2019**, *293*, 554-564. (d) Lu, M.; Cohen, M. H.; Rieves, D.; Pazdur, R. FDA report: Ferumoxytol for intravenous iron therapy in adult patients with chronic kidney disease *Am. J. Hematol.* **2010**, *85*, 315–319. (e) Enteshari Najafabadi, R.; Kazemipour, N.; Esmaeili, A.; Beheshti, S.; Nazifi, S. Using superparamagnetic iron oxide nanoparticles to enhance bioavailability of quercetin in the intact rat brain *BMC Pharmacol. Toxicol.* **2018**, *19*, 59.

86) (a) He, A.; Guan, X.; Song, H.; Li, S.; Huang, K. Encapsulation of (−)-epigallocatechin-gallate (EGCG) in hordein nanoparticles *Food Biosci.* **2020**, *37*, 100727. (b) Radhakrishnan, R.; Kulhari, H.; Pooja, D.; Gudem, S.; Bhargava, S.; Shukla, R.; Sistla, R. Encapsulation of biophenolic phytochemical EGCG within lipid nanoparticles enhances its stability and cytotoxicity against

cancer *Chem. Phys. Lipids* **2016**, *198*, 51–60. (c) (1) Sanna, V.; Singh, C. K.; Jashari, R.; Adhami, V. M.; Chamcheu, J. C.; Rady, I.; Sechi, M.; Mukhtar, H.; Siddiqui, I. A. Targeted nanoparticles encapsulating (-)-epigallocatechin-3-gallate for prostate cancer prevention and therapy *Sci. Rep.* **2017**, *7*, 41573. (d) Smith, A.; Giunta, B.; Bickford, P. C.; Fountain, M.; Tan, J.; Shytle, R. D. Nanolipidic particles improve the bioavailability and α-secretase inducing ability of epigallocatechin-3-gallate (EGCG) for the treatment of Alzheimer's disease *Int. J. Pharm.* **2010**, *389*, 207–212. (e) Zou, L. qiang; Peng, S. feng; Liu, W.; Gan, L.; Liu, W. lin; Liang, R. hong; Liu, C. mei; Niu, J.; Cao, Y. lin; Liu, Z.; Chen, X. Improved in vitro digestion stability of (-)-epigallocatechin gallate through nanoliposome encapsulation *Food Res. Int.* **2014**, *64*, 492–499.

87) Tan, Y. J.; Ali, A.; Tee, S. Y.; Teo, J. T.; Xi, Y.; Go, M. L.; Lam, Y. Galloyl esters of trans-stilbenes are inhibitors of FASN with anticancer activity on non-small cell lung cancer cells *Eur. J. Med. Chem.* **2019**, *182*, 111597.

88) McCarney, E. P.; Byrne, J. P.; Twamley, B.; Martínez-Calvo, M.; Ryan, G.; Möbius, M. E.; Gunnlaugsson, T. Self-assembly formation of a healable lanthanide luminescent supramolecular metallogel from 2,6-bis(1,2,3-triazol-4-yl)pyridine (btp) ligands *Chem. Commun.* **2015**, *51*, 14123–14126.

89) Lin, S. F.; Lin, Y. H.; Lin, M.; Kao, Y. F.; Wang, R. W.; Teng, L. W.; Chuang, S. H.; Chang, J. M.; Yuan, T. T.; Fu, K. C.; Huang, K. P.; Lee, Y. S.; Chiang, C. C.; Yang, S. C.; Lai, C. L.; Liao, C. Bin; Chen, P.; Lin, Y. S.; Lai, K. T.; Huang, H. J.; Yang, J. Y.; Liu, C. W.; Wei, W. Y.; Chen, C. K.; Hiipakka, R. A.; Liao, S.; Huang, J. J. Synthesis and structure-activity relationship of 3-O-acylated (-)-epigallocatechins as 5α-reductase inhibitors *Eur. J. Med. Chem.* **2010**, *45*, 6068–6076.

90) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. A Rapid Esterification by Means of Mixed Anhydride and Its Application to Large-ring Lactonization *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

91) Devos, A.; Remion, J.; Frisque-Hesbain, A. M.; Colens, A.; Ghosez, L. Synthesis of acyl halides under very mild conditions *J. Chem. Soc. Chem. Commun.* **1979**, 1180–1181.

92) Saito, A.; Nakajima, N.; Tanaka, A.; Ubukata, M. Synthetic studies of proanthocyanidins. Part 2: Stereoselective gram-scale synthesis of procyanidin-B3 *Tetrahedron* **2002**, *58*, 7829–7837.

93) Alharthy, R. D.; Hayes, C. J. Procyanidin B3 synthesis: a study of leaving group and Lewis acid activator effects upon interflavan bond formation *Tetrahedron Lett.* **2010**, *51*, 1193–1195.

94) Hamada, Y.; Takano, S.; Ayano, Y.; Tokunaga, M.; Koashi, T.; Okamoto, S.; Doi, S.; Ishida, M.; Kawasaki, T.; Hamada, M.; Nakajima, N.; Saito, A. Structure-activity relationship of oligomeric flavan-3-ols: Importance of the upper-unit B-ring hydroxyl groups in the dimeric structure for strong activities *Molecules* **2015**, *20*, 18870–18885.

95) Carofiglio, T.; Marton, D.; Tagliavini, G. New Simple Route to Allylstannanes by Zinc-Mediated Coupling of Allyl Bromides with Bu3SnCl or Bu2SnCl2 in an H2O (NH4Cl)/THF Medium *Organometallics* **1992**, *11*, 2961–2963.

96) Okano, K.; Okuyama, K. I.; Fukuyama, T.; Tokuyama, H. Mild debenzylation of aryl benzyl ether with BCl3 in the presence of pentamethylbenzene as a non-lewis-basic cation scavenger *Synlett* **2008**, *2008*, 1977–1980.

97) a) Yang, E. Y.; Shah, K. Nanobodies: Next Generation of Cancer Diagnostics and Therapeutics *Front. Oncol.* **2020**, *10*. b) Joubert, N.; Beck, A.; Dumontet, C.; Denevault-Sabourin, C. Antibody–drug conjugates: The last decade *Pharmaceuticals* **2020**, *13*, 1–30.

98) Tran, F.; Odell, A. V.; Ward, G. E.; Westwood, N. J. A modular approach to triazole-containing chemical inducers of dimerisation for yeast three-hybrid screening *Molecules* **2013**, *18*, 11639–11657.

99) Friscourt, F.; Fahrni, C. J.; Boons, G. J. A fluorogenic probe for the catalyst-free detection of azide-tagged molecules *J. Am. Chem. Soc.* **2012**, *134*, 18809–18815.

100) Bertozzi, C. R.; Bednarski, M. D. The Synthesis of Heterobifunctional Linkers for the Conjugation of Ligands to Molecular Probes *J. Org. Chem.* **1991**, *56*, 4326–4329.

101) Brauch, S.; Henze, M.; Osswald, B.; Naumann, K.; Wessjohann, L. A.; Van Berkel, S. S.; Westermann, B. Fast and efficient MCR-based synthesis of clickable rhodamine tags for protein profiling *Org. Biomol. Chem.* **2012**, *10*, 958–965.

102) Wang, H.; Raghupathi, K. R.; Zhuang, J.; Thayumanavan, S. Activatable dendritic 19F probes for enzyme detection *ACS Macro Lett.* **2015**, *4*, 422–425.

103) Díaz-Quiroz, D. C.; Cardona-Félix, C. S.; Viveros-Ceballos, J. L.; Reyes-González, M. A.; Bolívar, F.; Ordoñez, M.; Escalante, A. Synthesis, biological activity and molecular modelling studies of shikimic acid derivatives as inhibitors of the shikimate dehydrogenase enzyme of Escherichia coli *J. Enzyme Inhib. Med. Chem.* **2018**, *33*, 397–404.

104) Wang, S.; Jin, R.; Wang, R.; Hu, Y.; Dong, X.; Xu, A. e. The design, synthesis and biological evaluation of pro-EGCG derivatives as novel anti-vitiligo agents *RSC Adv.* **2016**, *6*, 106308–106315.

105) Martin, O. M.; Mecozzi, S. Synthesis and self-assembly of amphiphilic semifluorinated calix[4]arenes Supramol. Chem. **2005**, *17*, 9–15.

106) Pal, K.; Sharma, A.; Koner, A. L. Synthesis of Two-Photon Active Tricomponent Fluorescent Probe for Distinguishment of Biotin Receptor Positive and Negative Cells and Imaging 3D-Spheroid *Org. Lett.* **2018**, *20*, 6425–6429.