Progress Towards the Biomimetic Total Synthesis of Meroterpenoid Natural Products

Thesis submitted for the degree of Doctor of Philosophy

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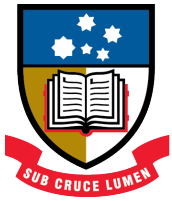

THE UNIVERSITY of ADELAIDE

To my family

Table of Contents

Declaration

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I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

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Stefania Alessandra Sassnink

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List of Abbreviations

Ac	acetyl
aq.	aqueous
ATP	adenosine triphosphate
Bn	benzyl
BPAP	bicyclic polyprenylated acylphloroglucinol
br	broad
Bu	butyl
BuLi	butyl lithium
calc.	calculated
CAM	ceric ammonium molybdate
CAN	ceric ammonium nitrate
CoA	coenzyme A
COSY	correlated spectroscopy
d	doublet (NMR)
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisopropylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMA	*N*,*N*-dimethylaniline
DMAPP	dimethylallyl pyrophosphate, prenyl pyrophosphate
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
eq.	equivalents

epi	epimer
ESI	electron spray ionisation
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
$Eu(fod)_3$	tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium
FT	Fourier transformation
g	gram
h	hour(s)
HFIP	hexafluoro-2-propanol
HMBC	heteronuclear multiple bond connectivity
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation spectroscopy
Hz	Hertz
IPP	isopentenyl pyrophosphate
IR	infrared spectroscopy
J	coupling constant (NMR)
LDA	lithium diisopropylamine
m	multiplet (NMR)
m-CPBA	*meta*-chloroperoxybenzoic acid
m.p.	melting point
m/z	mass units
Me	methyl
MeCN	acetonitrile

MeOH	methanol
MPAP	monocyclic polyprenylated acylphloroglucinol
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
o.n.	overnight
P13K	phosphatidylinositol 3-kinase
PE	petroleum ether
PIDA	phenyliodine(III) diacetate
PIFA	phenyliodine(III) bis(trifluoroacetate)
PPAP	polycyclic polyprenylated acylphloroglucinol
PP	pyrophosphate
ppm	parts per million
q	quartet
rt	room temperature
r.s.m.	recovered starting material
R_f	retention factor
s	singlet (NMR)
t	triplet (NMR)
TBAF	tetra-*n*-butylammonium flouride
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
THF	tetrahydrofuran
THN	1,3,6,8-tetrahydroxynaphthalene
TLC	thin layer chromatography
TMS	trimethylsilyl

UV	ultraviolet light
δ	chemical shift (NMR)

Abstract

This thesis outlines synthetic efforts towards three different natural product families.

Norascyronones A, B and C are complex polycyclic polyprenylated acylphloroglucinols (PPAPs) isolated from *Hypericum ascyron* in 2019. A total synthesis of norascyronone C was achieved in 8 steps from commercially available 3-ethoxy-2-cyclohexanone. With norascyronone C in hand, the biosynthetically-inspired radical cascade reaction to norascyronone A was explored. We discovered intriguing reactivity under radical oxidation conditions. A similar synthetic approach was taken in the efforts of synthesising a structurally related (not yet published) natural product. These synthetic efforts led to the synthesis of a precursor which we propose to be an "undiscovered natural product". Investigation of the key radical cyclisation gave access to several structurally unique side products.

The furaquinocin and neomarinone natural product family is a class of meroterpenoid natural products isolated from marine *actinomycete* bacteria. We proposed that the dihydrobenzofuran motif could be installed by aromatic Claisen rearrangement followed by intramolecular cyclisation of a geranyl or farnesyl side chain. A synthetic model system was developed to investigate this biomimetic theory. Several rearranged intermediates with fascinating structures have been made through three different synthetic routes.

Furobinordentatin, furobiclausarin and claudimerines-A and -B are dimeric pyranocoumarin natural products isolated from *Citrus* plants. We proposed and investigated two possible pathways to access these dimeric natural products from simpler precursor molecules, nordentatin and clausarin. Nordentatin was successfully synthesised in 5 steps from

commercially available phloroglucinol. With the synthetic precursor in hand, the oxidative dimerisation was attempted. However, even after an extensive screening of reaction conditions we were unable to access the dimeric natural products.

Chapter One

Thesis Introduction

1.1 Natural Products as Drug Leads

Since ancient times, traditional medicine has taken advantage of leaves and roots of certain plants to cure diseases and alleviate pain.[1–3] Other plants were used to make stimulants or poisons and, in many cases, both beneficial and malign effects were observed for the same plant. Prior to the development of modern analytical chemistry techniques, physicians did not have the tools to connect these observed effects to specific substances in the plant. Today, we know that these remedial effects originate from natural products and their interactions with biological targets.[1–3]

Natural products are a loosely defined class of compounds, which occur in living organisms. They are secondary metabolites, which originate from simpler precursor molecules, such as amino acids, isoprenoid units, fatty acids and other small molecules. In contrast to primary metabolites, they are usually not essential for the growth, development or reproduction of the harbouring organism. Although many of their functions remain still unknown, many are thought to result from the adaptation to new environments or as defence mechanisms against predators.[4]

Historically, one of the most well-known examples of natural product-derived drugs is acetylsalicylic acid (**1.01**, aspirin), an analgesic and anti-inflammatory agent discovered in 1899 (Figure 1.1).[5] Aspirin (**1.01**) is derived from the natural product salicin (**1.02**), which was first isolated from the bark of the willow tree *Salix alba* L.[5] The observed curative effects of aspirin originate from the main metabolite formed from salicin, salicylic acid (**1.03**). However, **1.03** had an unpleasant taste and induced vomiting. Simple acetylation of the

hydroxyl group gave aspirin (**1.01**), which displayed the same beneficial properties as the natural product but was also more palatable.[6]

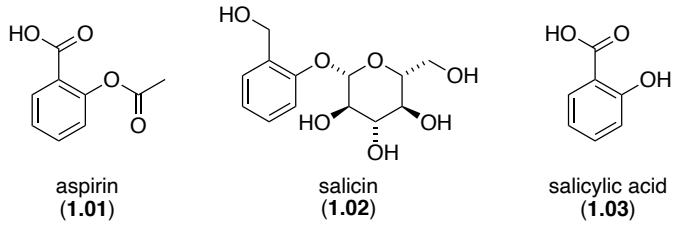


Figure 1.1: Structures of the synthetic derivative aspirin (1.01) and the natural products salicin (1.02) and salicylic acid (1.03).

Two more notorious natural products are the alkaloids morphine (**1.04**), codeine (**1.05**) and their synthetic derivative, heroin (**1.06**) (Figure 1.2). Morphine (**1.04**) and codeine (**1.05**) were first isolated from the opium poppy plant, *Papaver somniferum* L. in 1803.[7] To date, morphine (**1.04**) and codeine (**1.05**) have several medicinal uses, including mitigating pain and suppressing cough. Acetylation of morphine (**1.04**) in refluxing acetic anhydride affords diacetylmorphine (**1.06**, heroin), which is an even more potent analgesic but is also more addictive than both morphine (**1.04**) and codeine (**1.05**).[8,9] The highly addictive effects of all three drugs resulted in their restricted use in modern medicine.[7]

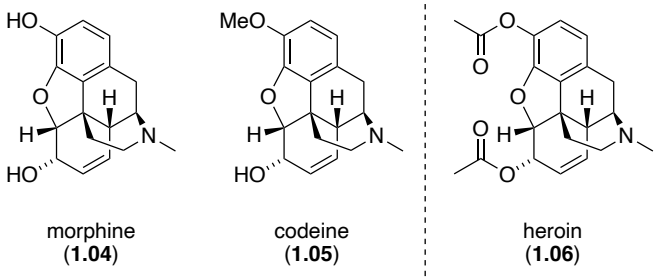


Figure 1.2: Structures of morphine (1.04), codeine (1.05) and their synthetic derivative heroin (1.06).

Another milestone in drug discovery was the isolation of quinine (**1.07**) from the bark of the Cinchona tree (*Cinchona officialis*) (Figure 1.3).[10,11] The indigenous Quechua people of Peru used the powder obtained from grounding the bark of this tree to treat fevers, in particular those resulting from malaria. The Jesuits imported this bark to Europe, which enabled scientists to isolate the active compound. Since the elucidation of its structure by Rabe in 1908 and its first formal total synthesis by Woodward in 1945, quinine (**1.07**) has served as an inspiration for the design of several related malaria drugs, such as chloroquine (**1.08**) and mefloquine (**1.09**) (Figure 1.3).[12–14]

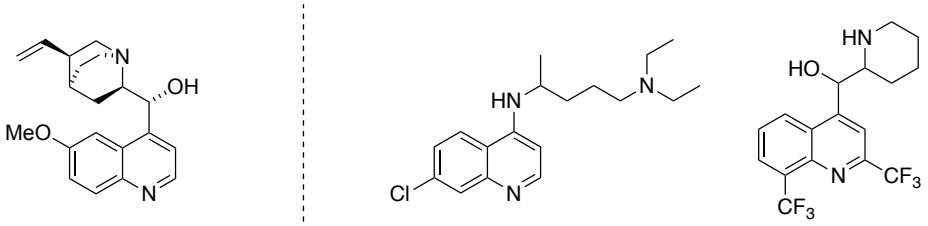
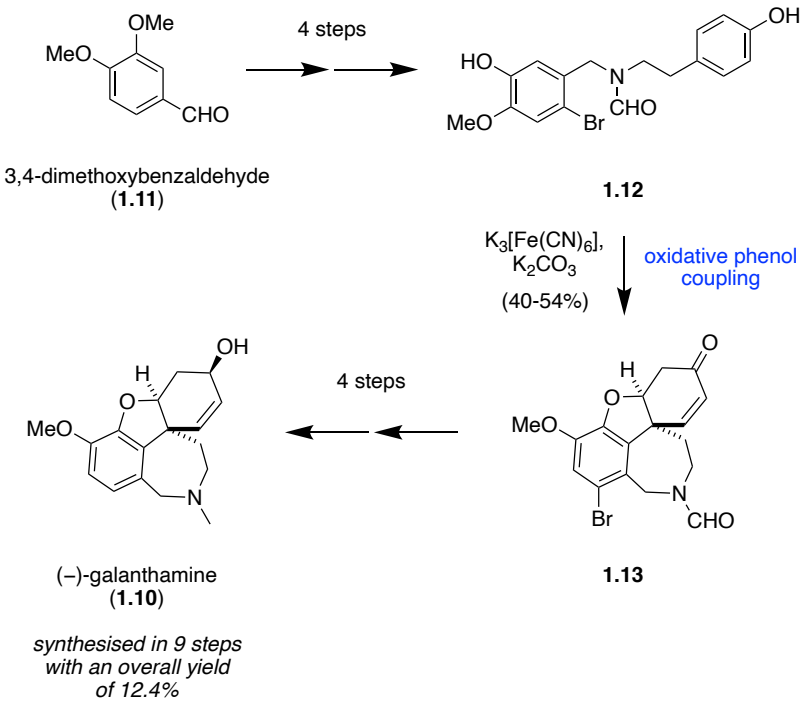


Figure 1.3: Structure of quinine (1.07) and its synthetic analogues chloroquine (1.08) and mefloquine (1.09).

The diverse bioactivity of these compounds makes them a versatile and unique source of novel drug leads. According to a study from 2011, 47% of new drugs in the past 30 years are either natural products or derived from natural products.[15–17] However, extraction of active compounds from their natural sources can be difficult and sometimes afford only small quantities due to their limited availability in organisms.[18] Therefore, the total synthesis of natural products is an important application of organic chemistry for accessing not only the desired compounds in increased quantities but also for identifying synthetic routes to various analogues of the natural products, which might have better pharmacological properties.[18]

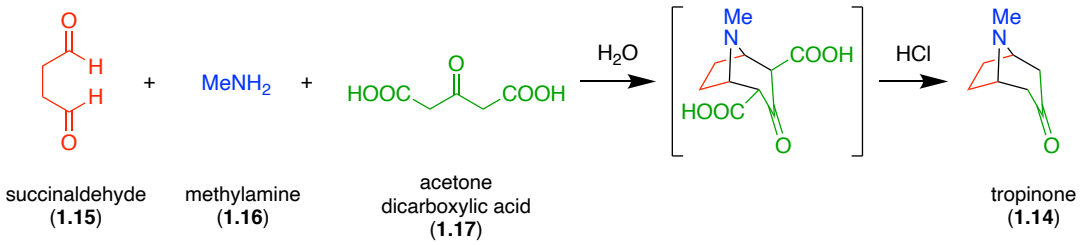
An impressive example of an industrial total synthesis of a natural product is that of the alkaloid (–)-galanthamine (**1.10**), which is used to treat mild to moderate Alzheimer's disease symptoms (Scheme 1.1).[19] The natural product was first isolated in the 1950s from the bulbs and flowers of the Caucasian snowdrop (*Galanthus woronowii*). However, its difficult and expensive isolation procedure created the need for an efficient and high-yielding total synthesis of the compound.[20] In 1999, the Jordis group, in cooperation with Sanochemia AG, reported the total synthesis of (–)-galanthamine (**1.10**) in 9 steps from commercially available 3,4-dimethoxybenzaldehyde (**1.11**) with an overall yield of 12.4%.[19] The key step of the synthesis was a biomimetic oxidative phenol coupling of biaryl **1.12** leading to tetracyclic intermediate **1.13**. This key transformation can be performed on a 12 kg scale, which allows easy access to large quantities of the desired natural product target.



Scheme 1.1: Total synthesis of (–)-galanthamine (1.10).[19]

1.2 Biomimetic Total Synthesis of Natural Products

An important subdiscipline of organic synthetic chemistry is biomimetic total synthesis. Breslow introduced the term 'biomimetic chemistry' in 1972 as "the branch of organic chemistry which attempts to imitate natural reactions and enzymatic processes as a way to improve the power of organic chemistry."[21–23] Although coined in 1972, the first total synthesis considered biomimetic was actually Robinson's one-pot synthesis of the alkaloid tropinone (**1.14**) in 1917 (Scheme 1.2).[24] This remarkable synthesis achieved high molecular complexity through two consecutive Mannich reactions (the first intermolecular and the second intramolecular) from three simple precursor molecules: succinaldehyde (**1.15**), methylamine (**1.16**) and acetone dicarboxylic acid (**1.17**). This reaction is considered biomimetic because all three precursor molecules are also used in the biosynthesis of tropinone (**1.14**).

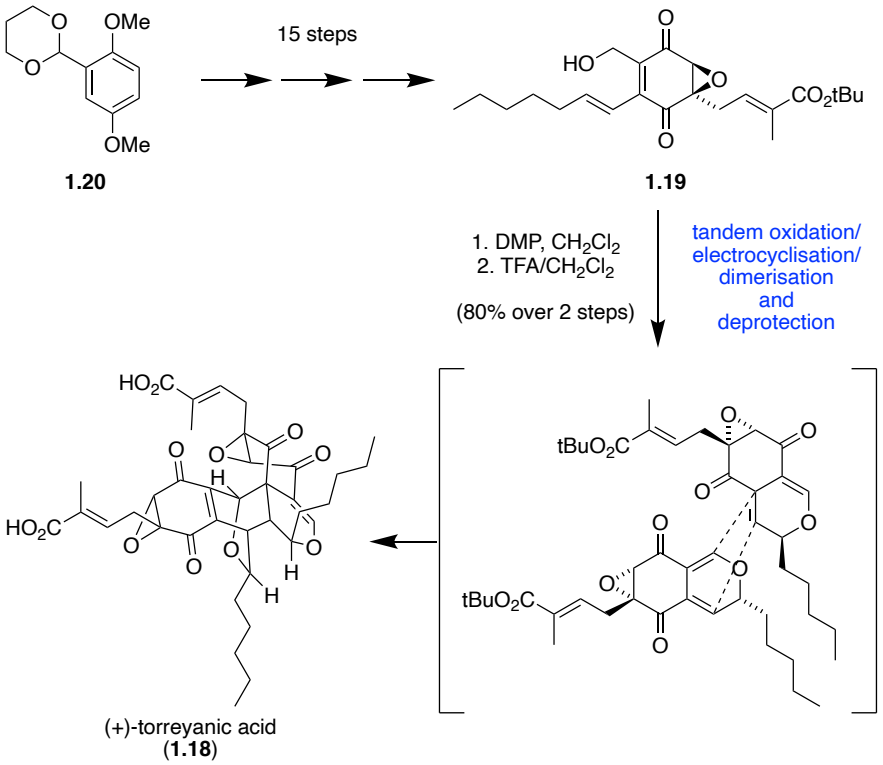


Scheme 1.2: Biomimetic total synthesis of tropinone (1.14) by Robinson in 1917.[24]

Commonly, nature takes the most efficient and elegant path to reach a product target. Biomimetic synthesis tries to mimic natural processes, which often results in good atom and redox economy and can minimise the need for protecting groups.[25] Another advantage of biomimetic synthesis is that it can shed some light on the biosynthesis and the biosynthetic pathways of nature and, therefore, support previously stated biosynthetic hypotheses.

Additionally, utilising biosynthetic intermediates often gives access to the whole natural product family instead of just one particular target.

An impressive example of an elegant biomimetic total synthesis is Porco's total synthesis of (+)-torreyanic acid (**1.18**) (Scheme 1.3).[26,27] Porco's group utilised an oxidation/electrocyclisation/Diels-Alder dimerisation cascade to build high complexity in the final step of their synthesis, which commenced with preparing the quinone epoxide **1.19** in 15 linear steps from **1.20**. The key step of the biomimetic synthesis was the following Dess-Martin oxidation which initiated a tandem oxidation/electrocyclisation/dimerisation cascade to afford (+)-torreyanic acid (**1.18**) as a single enantiomer in 80% yield.



Scheme 1.3: Biomimetic total synthesis of (+)-torreyanic acid (1.18) by Porco *via* a biomimetic tandem oxidation/elctrocyclisation/Diels-Alder dimerisation cascade.[26]

1.3 Meroterpenoid Natural Products

Meroterpenoids are natural products of mixed biosynthetic origins, which are partially derived from terpenoids.[28] The highest abundance of meroterpenoid natural products is found in fungi and marine organisms, however, they are also present in various plants and animal species. Commonly connected to polyketides, alkaloids, phenols, and amino acids, these hybrid molecules display a vast chemical diversity (a few examples are shown in Figure 1.4). Furaquinocin A (**1.21**), a potent antibiotic, and liphagal (**1.22**), a PI3K-inhibitor, were both isolated from marine organisms.[29,30] Another notable example is the natural product hyperforin (**1.23**), which is the active compound in St. John's wort and is used as treatment for mild to moderate depression.[31,32] The recently isolated meroterpenoid guajadial (**1.24**) is the active ingredient in a plant used to treat diabetes in indigenous African and Asian folk medicine.[33] The last example is the cannabinoid tetrahydrocannabinol (THC, **1.25**), which is the main psychoactive compound in cannabis.[34]

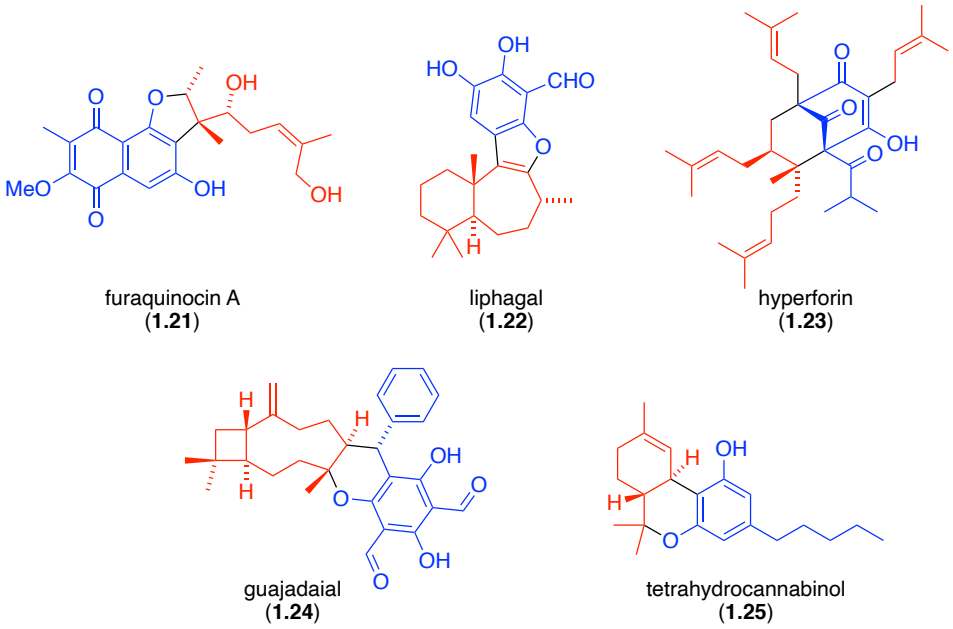
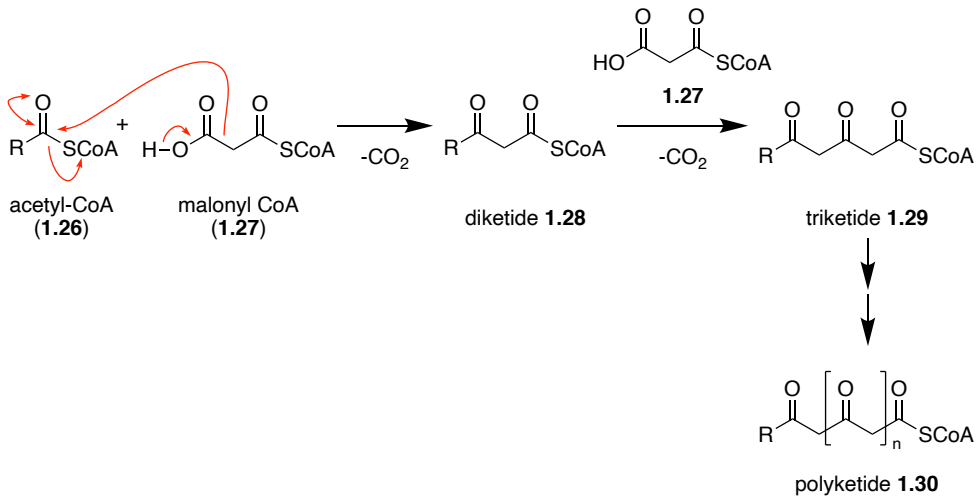


Figure 1.4: Examples of meroterpenoid natural products (the terpene derived fragment is shown in red and the polyketide fragment is shown in blue).

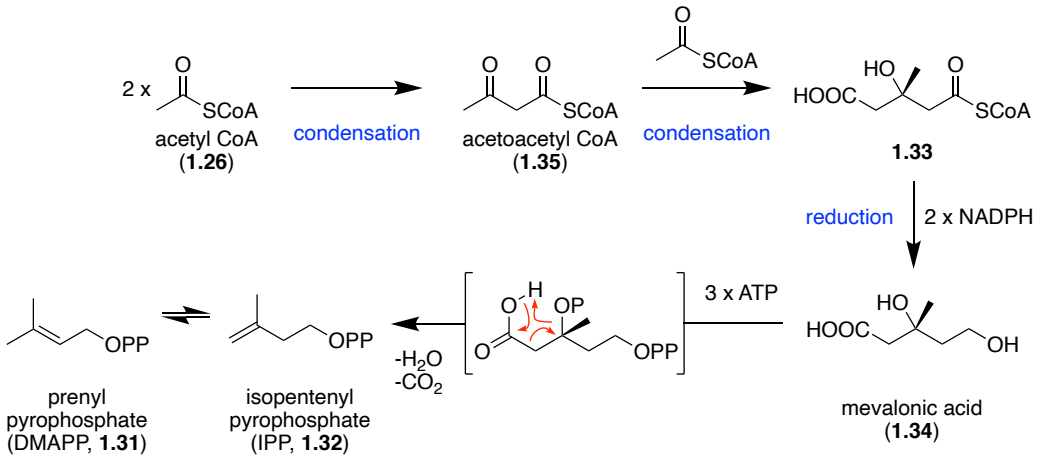
Most of these examples have a highly oxidised aromatic core, which is derived from a polyketide building block. This polyketide unit originates from stepwise condensation of acetyl CoA (**1.26**) or propionyl CoA (not shown), with malonyl CoA (**1.27**) or methylmalonyl CoA (not shown), followed by decarboxylation (Scheme 1.4). The first condensation forms a diketide (**1.28**), subsequent condensation reactions give rise to triketides (**1.29**), tetraketides and longer linear polyketide carbon chains (**1.30**).



Scheme 1.4: Biosynthesis of linear polyketides.

Additional modifications, such as reductions, dehydrations and cyclisations give access to a plethora of structurally diverse natural products.

The polyketide moiety is then alkylated with terpenoid fragments to form meroterpenoid natural products.[35] The terpene building blocks originate from C5 isoprene units, such as prenyl pyrophosphate (dimethylallyl pyrophosphate, DMAPP, **1.31**) and isopentenyl pyrophosphate (IPP, **1.32**) (Scheme 1.5).[36] Both of these C5 units are derived from acetyl CoA (**1.26**). Three units of acetyl CoA (**1.26**) undergo condensation to **1.33**, which is subsequently reduced with NADPH to mevalonic acid (**1.34**). Mevalonic acid (**1.34**) is phosphorylated with ATP and undergoes rearrangement under elimination of CO_2 and H_2O to form IPP (**1.32**) which can then isomerise to DMAPP (**1.31**). Condensation of IPP (**1.32**) and DMAPP (**1.31**) forms geranyl pyrophosphate, a C10 monoterpene. Addition of more IPP units give access to C15 sesquiterpenes, C20 diterpenes and higher-molecular-weight terpenes.



Scheme 1.5: Biosynthesis of the terpene units, dimethylallyl pyrophosphate (DMAPP, 1.31) and isopentenyl pyrophosphate (IPP, 1.32) *via* the mevalonate pathway.

Most terpenoid natural products are biosynthetically assembled through the shown mevalonate pathway, however, an alternative non-mevalonate or methyl D-erythritol-4-phosphate pathway also exists in nature.[36]

1.4 References

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Chapter Two

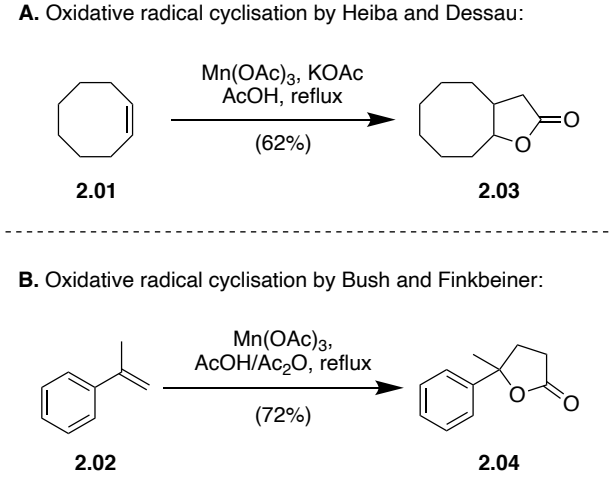
Progress Towards the Biomimetic Synthesis of Norascyronone A, B and C and Related Natural Products

Parts of the synthesis of the norascyronone natural product family were conducted in collaboration with Quang Dung Phan.

2.1 Introduction

2.1.1 Oxidative Radical Cyclisation Reactions in Organic Synthesis

In the past forty years, extensive research has been carried out on exploring oxidative radical cyclisations as means to build highly complex structures from simple precursor molecules.[1,2] In 1968, the first examples of an oxidative radical cyclisation with $Mn(OAc)_3$ as the oxidant were independently reported by Heiba and Dessau and Bush and Finkbeiner.[3,4] Both groups independently discovered that refluxing the oxidant in acetic acid would generate a radical which can then add to an alkene (**2.01** and **2.02**) and after a second single-electron oxidation give a γ-lactone (**2.03** and **2.04**) (Scheme 2.1).

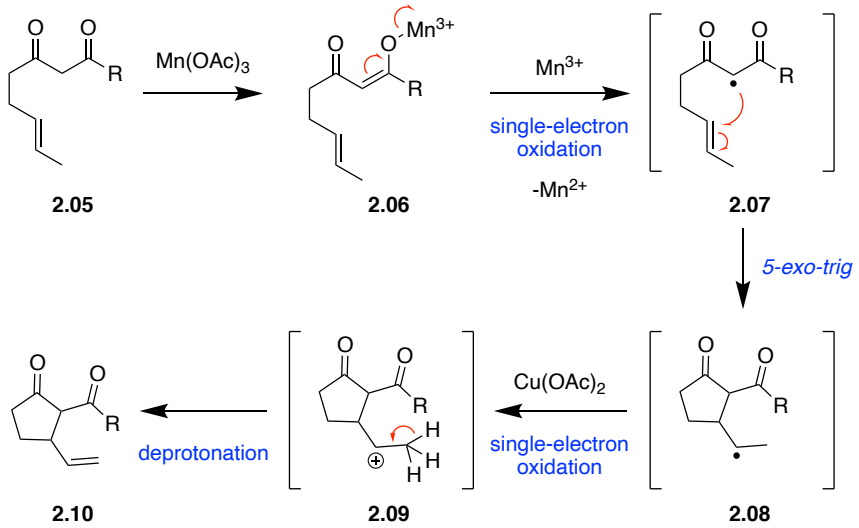


Scheme 2.1: a) Oxidative radical cyclisation of 2.01 with $Mn(OAc)_3$ to give γ-lactone 2.03 by Heiba and Dessau in 1968.[3] b) Oxidative radical cyclisation of 2.02 with $Mn(OAc)_3$ to give γ-lactone 2.04 by Bush and Finkbeiner in 1968.[4]

In 1971, Heiba and Dessau discovered that the addition of a Cu(II)-salt, such as $Cu(OAc)_2$, as a co-oxidant can accelerate the oxidation of the secondary radical up to 350 times.[5,6] Shortly after, they described that β-keto esters and similar dicarbonyl compounds could be oxidised to

radicals at room temperature in acetic acids.[7] Since then, manganese-based oxidative radical cyclisations have been of interest to many synthetic groups.[8–10]

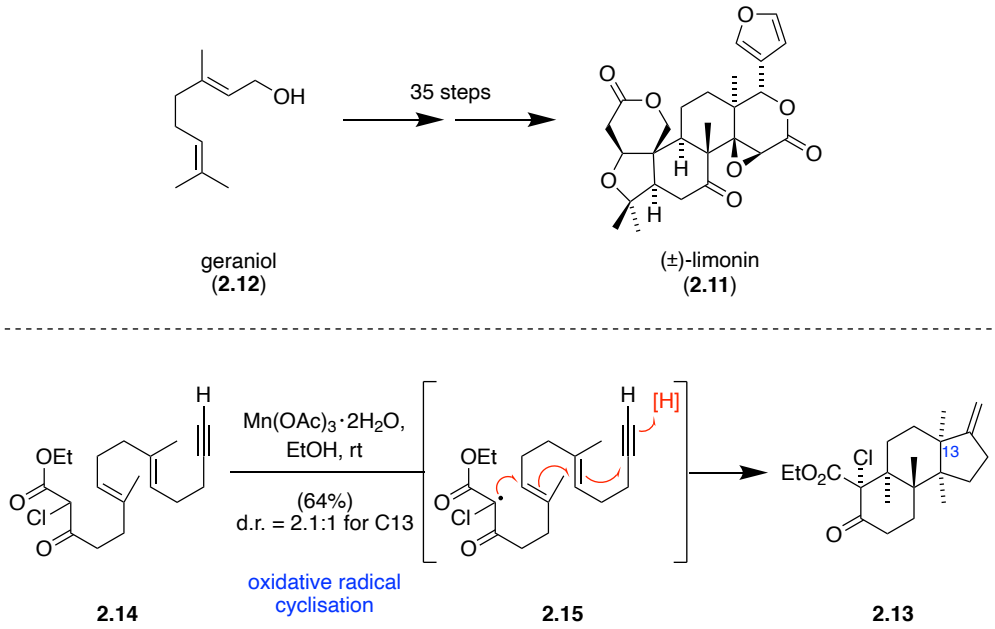
Mechanistically speaking, the formal loss of a hydrogen atom is often achieved by the loss of a proton and subsequent oxidation of the resulting anion to form the desired radical species. As shown in Scheme 2.2, the proposed mechanism by Snider commences with the manganese ion binding to the dicarbonyl compound **2.05**. This facilitates the formation of enolate intermediate **2.06**, which subsequently can be oxidised to a radical species **2.07**. The radical is stabilised by delocalisation between the carbonyl groups. Then, the radical can undergo a *5-exo-trig* cyclisation to pentacycle **2.08** which is further oxidised in a single-electron oxidation to form carbocation **2.09**.[11] Deprotonation terminates the oxidative radical cyclisation giving the final product **2.10**.[8]



Scheme 2.2: Proposed mechanism of oxidative radical cyclisation with $Mn(OAc)_3$ and $Cu(OAc)_2$ by Snider.[8]

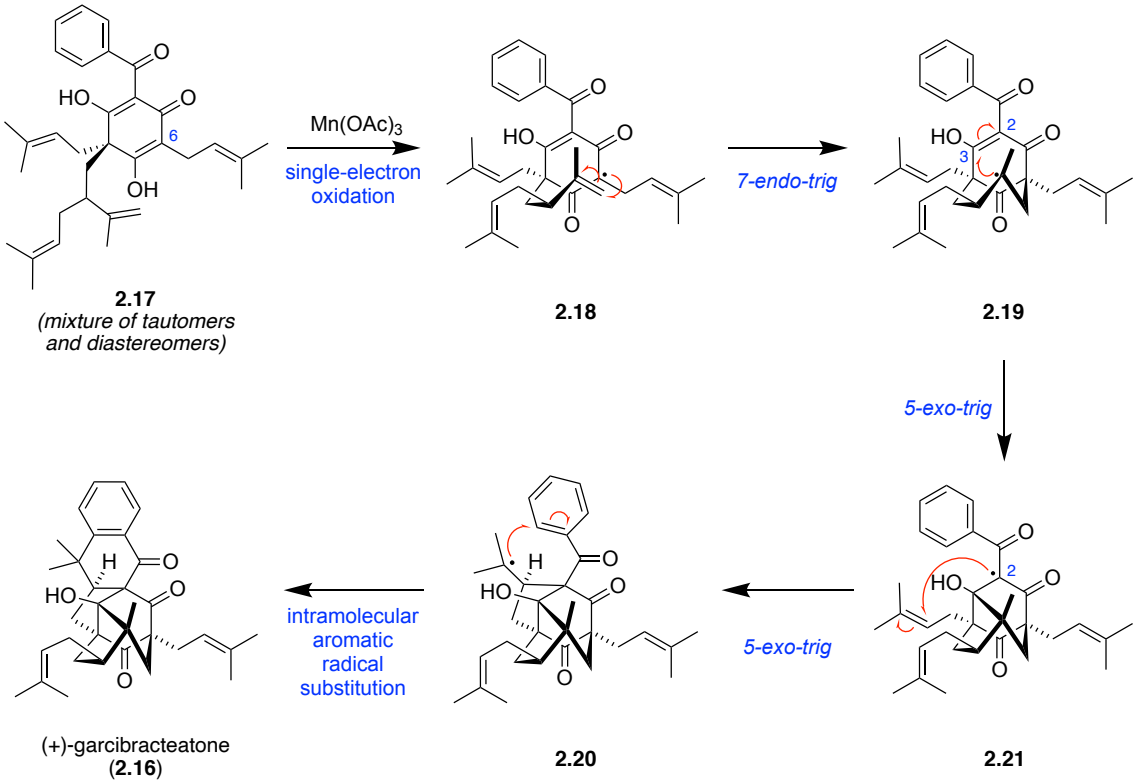
There are many recent examples where oxidative radical cyclisations were utilised to form complex natural products.[10,12–17] A very impressive example is the total synthesis of (±)-

limonin (**2.11**) from geraniol (**2.12**) in 2015 by Yamashita and co-workers (Scheme 2.3).[17] One of their key steps was an oxidative radical cascade promoted by $Mn(OAc)_3$ in ethanol at room temperature giving tricyclic intermediate **2.13** in 64% yield.



Scheme 2.3: Total synthesis of (±)-limonin (2.11) by Yamashita and co-workers in 2015 and oxidative radical cyclisation key step of intermediate 2.14 to tricycle 2.13.[17]

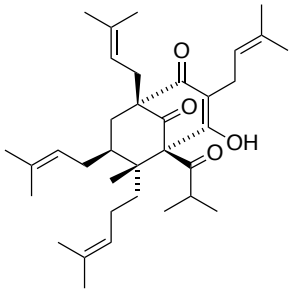
Another impressive example is the biomimetic total synthesis of (+)-garcibracteatone (**2.16**) in 2014 by the George group (Scheme 2.4).[18,19] Their key step was a Mn(III)-mediated oxidative cyclisation cascade from **2.17** to (+)-garcibracteatone (**2.16**). First, single-electron oxidation at C-6 position formed radical intermediate **2.18** which underwent *7-endo-trig* cyclisation to **2.19**. The tertiary radical **2.19** then underwent two successive *5-exo-trig* cyclisations to intermediate **2.20**. Termination of the radical cascade by intramolecular aromatic radical substitution gave (±)-garcibracteatone (**2.16**) in 14% yield. In this cascade of radical cyclisations, 4 rings, 4 C-C bonds and 4 stereocentres were formed in one step.



Scheme 2.4: Biomimetic total synthesis of garcibracteatone (2.16) by the George group.[18,19]

2.1.2 Polycyclic Polyprenylated Acylphloroglucinol Natural Products

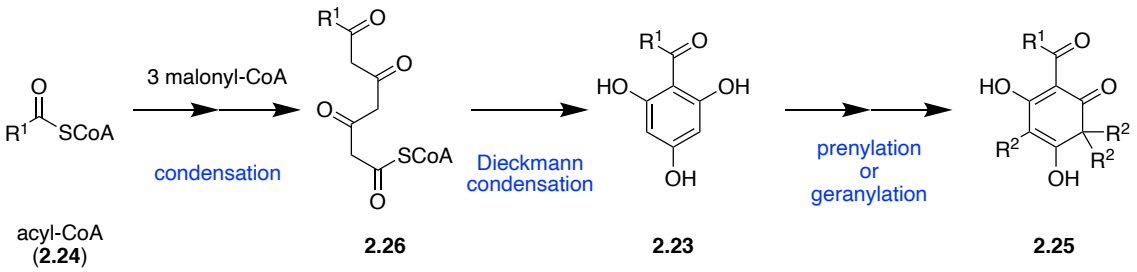
Polycyclic polyprenylated acylphloroglucinols (PPAPs) are a large class of natural products isolated from plants of the *Clusiacea* and *Hypericaceae* families. To date, more than 700 PPAP compounds have been isolated.[20] Their structural key feature is a highly oxidised phloroglucinol core which is commonly substituted by isoprenyl or geranyl side chains.[21,22] Many PPAPs have been shown to display a large range of biological properties; this in combination with their challenging structures made them an attractive synthetic target for synthetic chemists in the last two decades.[23,24] The first identified PPAP, hyperforin (**2.22**) (Figure 2.1), was isolated in 1971 from *H. perforatum* (St. John's wort) and is known for its use as a potent antidepressant.[25]



hyperforin
(**2.22**)

Figure 2.1: Structure of hyperforin (2.22).

PPAPs originate biosynthetically from simpler monocyclic polyprenylated acylphloroglucinols (MPAPs), which are derived from acylphloroglucinols (Scheme 2.5).[26–29] Acylphloroglucinols **2.23** are biogenetically synthesised through the polyketide biosynthetic pathway. One acyl-CoA (**2.24**) unit and three malonyl-CoA units undergo Claisen condensation followed by Dieckmann condensation to give acylphloroglucinols **2.23**. Enzymatic alkylation with prenyl or geranyl pyrophosphate would form the MPAPs **2.25** which could then undergo cyclisation events to form a wide range of PPAP natural products.



acyl-CoA
(**2.24**)

2.26

2.23

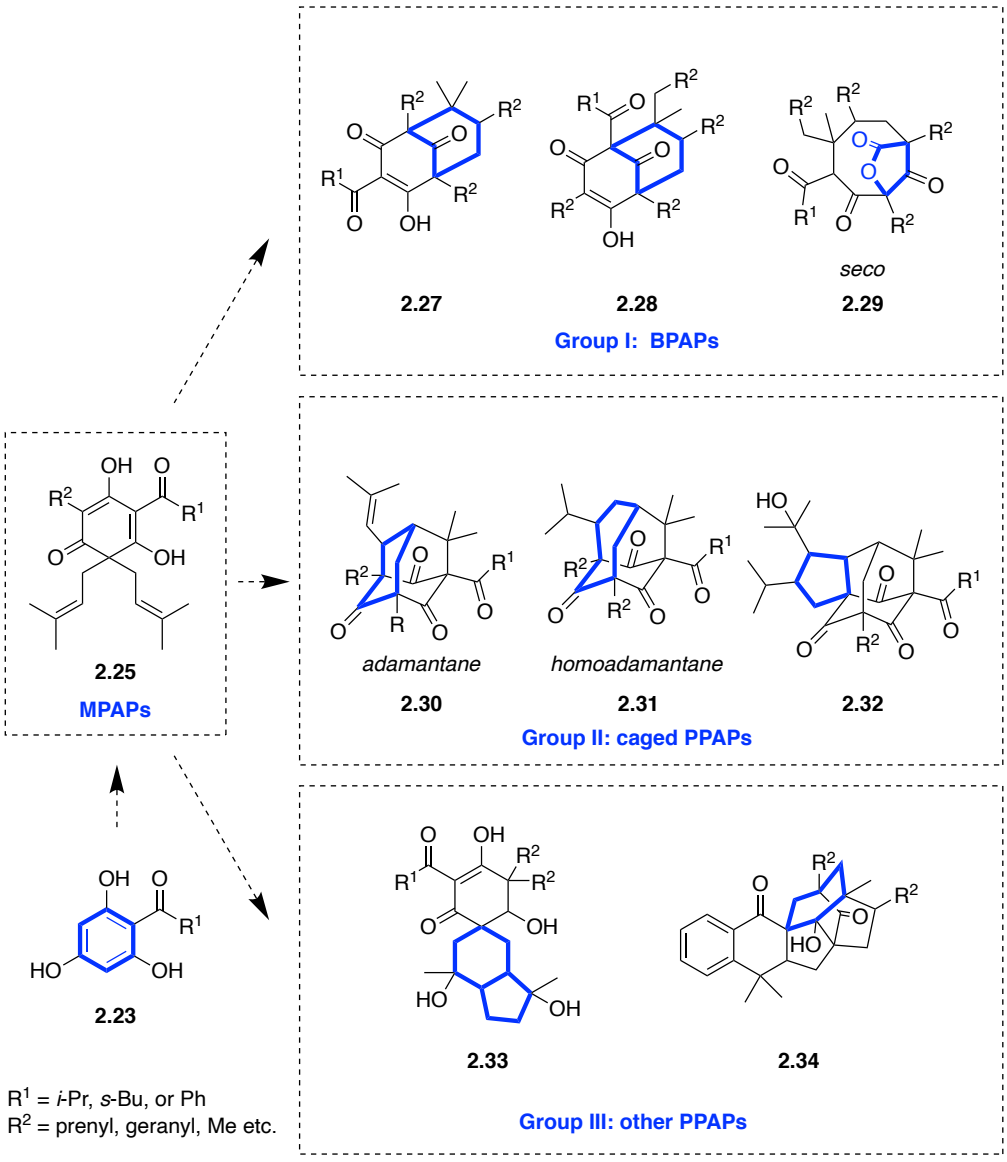
2.25

R^1 = Ph, *i*-Pr, etc.
R^2 = prenyl or geranyl

Scheme 2.5: Biosynthesis of MPAPs 2.25 from acyl-CoA (2.24) and malonyl-CoA.[26–29]

Formerly, PPAPs have been classified into three groups (type A, B and C) depending on the relative position of the acyl group on the phloroglucinol core.[21] However, in 2018, Yang,

Grossman and Xu proposed a new classification based on their different scaffolds.[22] All PPAPs are now divided into three main groups (I – III) (Scheme 2.6). Bicyclic polyprenylated acylphloroglucinols (BPAPs) and the related *seco*-BPAPs are categorised as group I. This is the largest group with approximately 60% of known PPAPs. All caged PPAPs with adamantane and homoadamantane skeletons are classified as group II PPAPs. All other biosynthetically related compounds fall into group III.



Scheme 2.6: Examples of the new classification of PPAPs by Yang, Grossman and Xu in 2018.[22]

2.1.3 Isolation, Biosynthesis and Previous Work on Yezo'otogirins A to C

Yezo'otogirins A to C (**2.35** to **2.37**) are tricyclic meroterpenoids which were first isolated in 2009 from the plant *Hypericum yezoense*.[30] Pre-yezo'otogirin A (**2.38**) was co-isolated and proposed to be the biosynthetic precursor of yezo'otogirin A (**2.35**) (Figure 2.2).

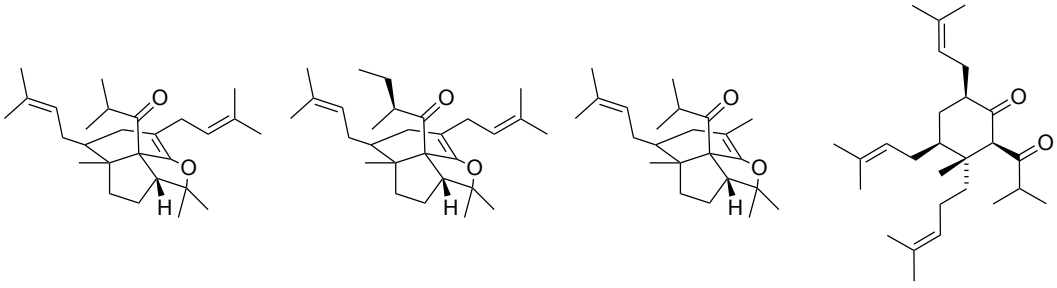
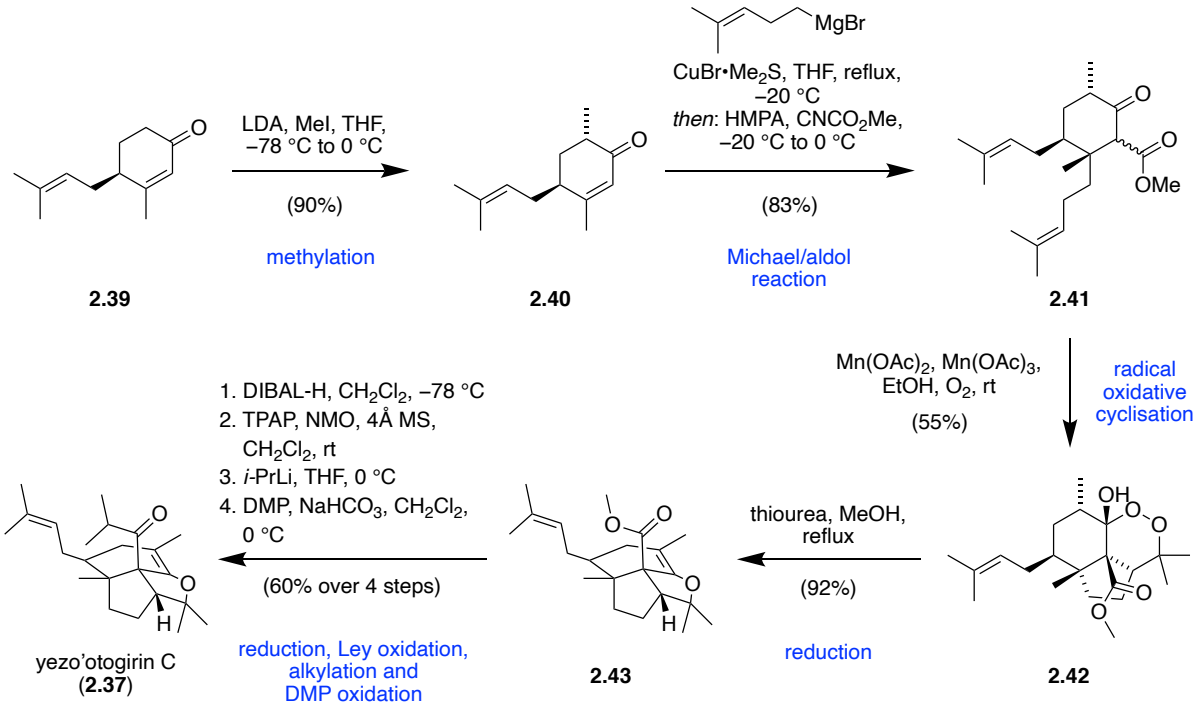


Figure 2.2: Yezo'otogirins A (2.35), B (2.36) and C (2.37) and pre-yezo'otogirin A (2.38).

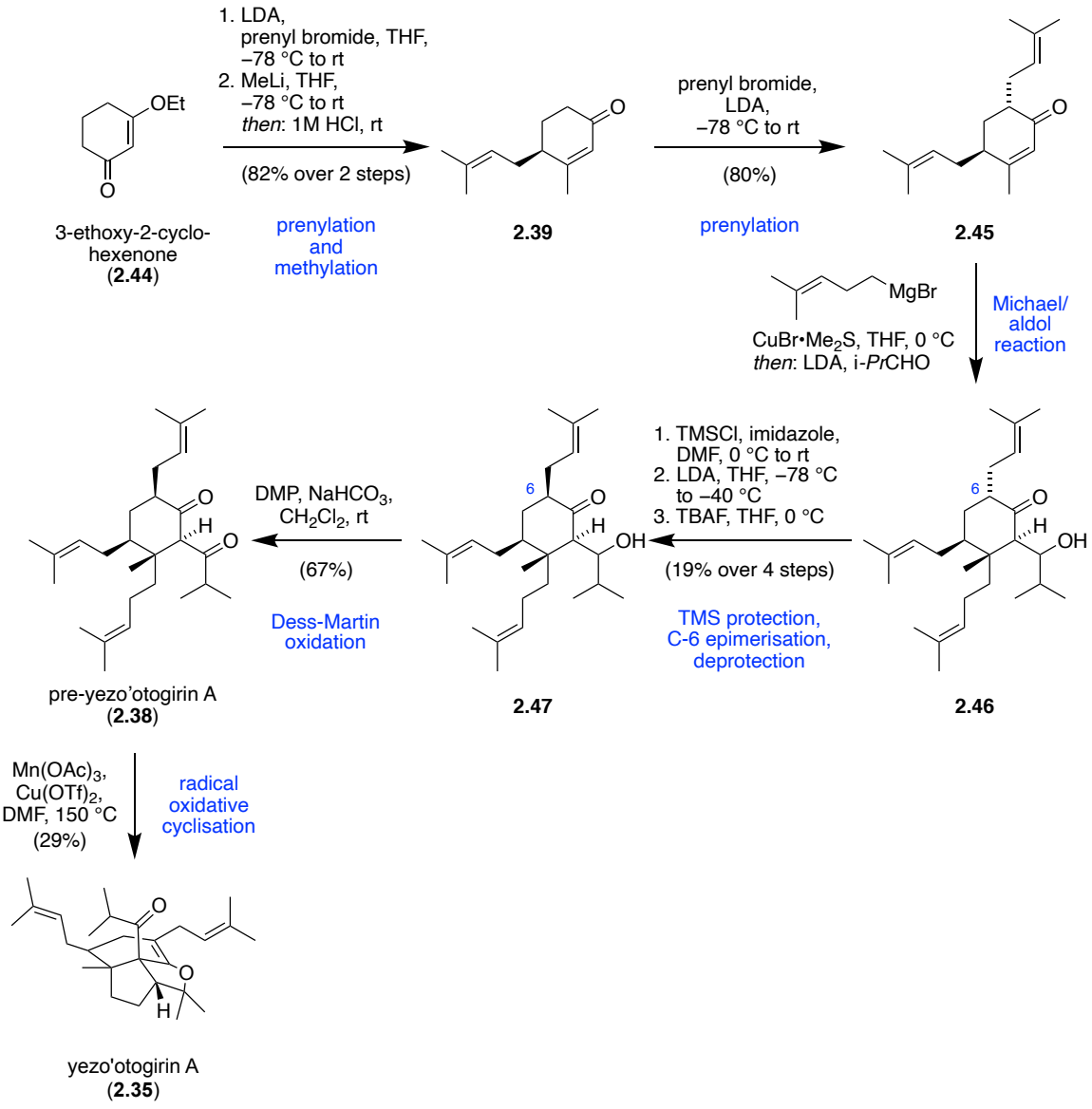
The first total synthesis of (±)-yezo'otogirin C (**2.37**) was achieved by Lee in eight steps in 2014 (Scheme 2.7).[31] In the first step, α,β-unsaturated ketone **2.39** was methylated with iodomethane in 90% yield. Then, intermediate **2.40** underwent conjugate addition of homoprenyl magnesium bromide followed by subsequent reaction with methyl cyanoformate to afford diketone **2.41** in 83% yield. The key step of this synthetic route was oxidation of diketone **2.41** with $Mn(OAc)_3$ in the presence of air to give endoperoxide **2.42** in 55% yield. Endoperoxide **2.42** was reduced with thiourea followed by ring closure to intermediate **2.43**. Reduction of the methyl ester and subsequent Ley oxidation of the obtained hydroxyl group to the corresponding aldehyde gave the precursor for the nucleophilic propylation. Alkylation with propyl lithium and Dess-Martin oxidation of the alcohol moiety afforded yezo'otogirin C (**2.37**) in 60% yield over 4 steps.



Scheme 2.7: Bioinspired total synthesis of yezo'otogirin C (2.37) by Lee.[31]

At the same time, our group worked on the biomimetic total synthesis of yezo'otogirin A (**2.35**), also published in 2014 (Scheme 2.8).[32] Our synthesis commenced with prenylation and subsequent methylation of 3-ethoxy-2-cyclohexenone (**2.44**) to afford unsaturated ketone **2.39** in 82% over two steps. A second prenylation of ketone **2.39** afforded diprenylated compound **2.45** in 80% yield. The following step was a 1,4-addition of the *in situ* formed cuprate of homoprenyl magnesium bromide to Michael acceptor **2.45** and subsequent aldol reaction with isopropyl aldehyde to give β-hydroxyketone **2.46**. The following three steps were necessary to epimerise the C-6 group as the diastereomer with the opposite configuration showed no reactivity in forming the natural product **2.35**. Hence, the hydroxyl group was TMS-protected, then the C-6 group was epimerised with LDA and afterwards, the TMS group was removed with TBAF. Hydroxyketone **2.47** was then oxidised with Dess-Martin periodinane to

pre-yezo'otogirin A (**2.38**) in 67% yield. Oxidative radical cyclisation with $Mn(OAc)_3$ and $Cu(OTf)_2$ in DMF at reflux temperature gave yezo'otogirin A (**2.35**) in 29% yield.



Scheme 2.8: Biomimetic total synthesis of yezo'otogirin A (2.35) by our group in 2014.[32]

2.1.4 Isolation and Proposed Biosynthesis of Norascyronones A to C

In 2019, three new *nor*-BPAP derivatives, norascyronones A (**2.48**), B (**2.49**) and C (**2.50**) were isolated from the plant *Hypericum ascyron* (Figure 2.3).[33] The chemical structures of all three norascyronones were elucidated by extensive 2D NMR spectroscopy experiments. The structure of norascyronone A (**2.48**) could be further confirmed by single-crystal X-ray analysis.

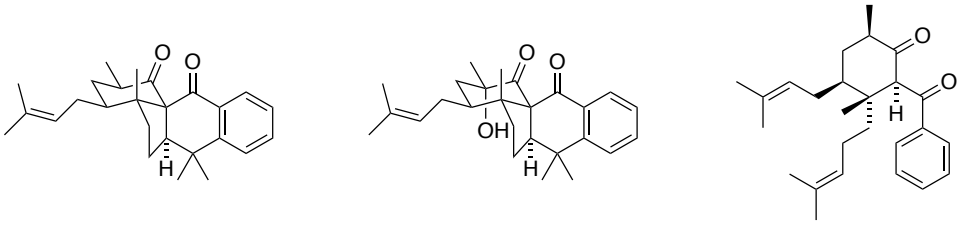
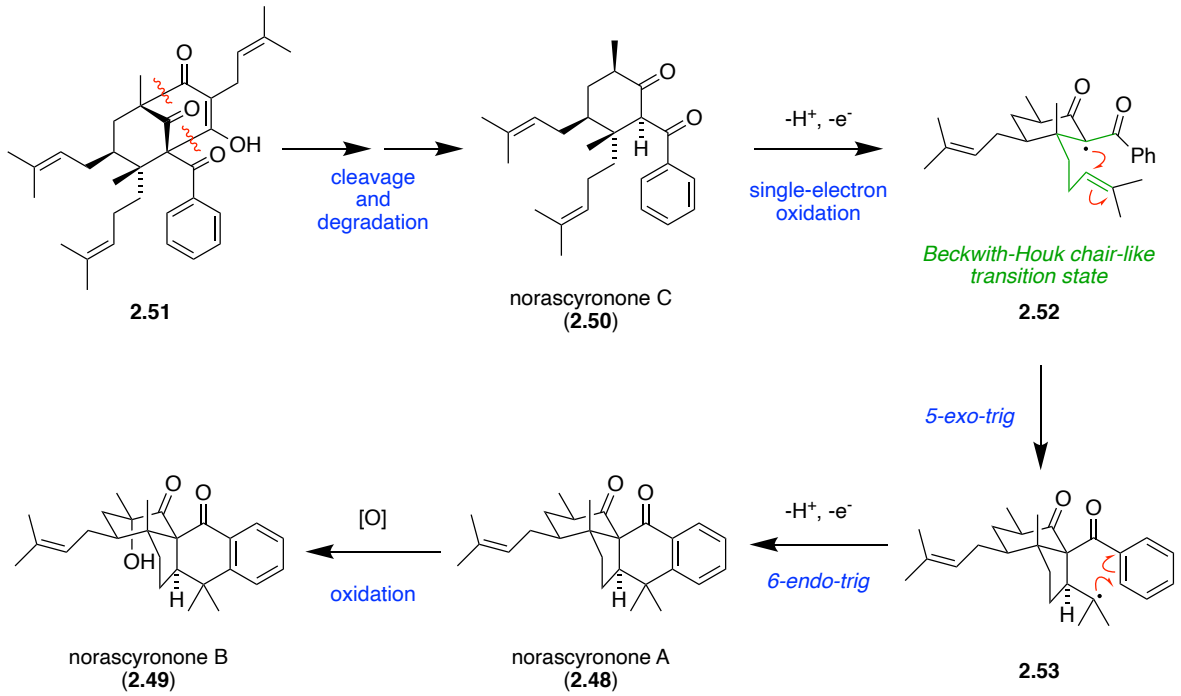


Figure 2.3: Structures of norascyronones A (2.48), B (2.49) and C (2.50).

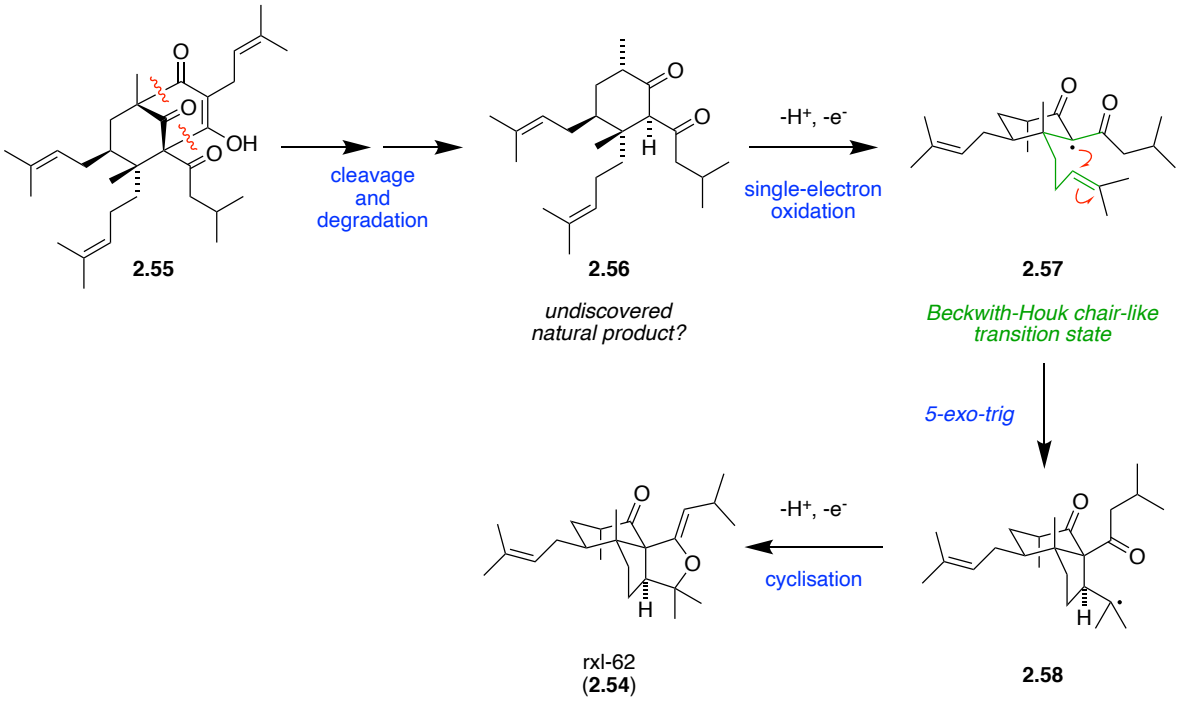
Norascyronone A (**2.48**) and B (**2.49**) share a 6/6/5/6 ring system and are presumably biosynthetically derived from norascyronone C (**2.50**) *via* an oxidative radical cyclisation. In their isolation paper, Yang and Xu also proposed a plausible biosynthesis of norascyronones A (**2.48**) and B (**2.49**) from their biogenetic precursor norascyronone C (**2.50**) (Scheme 2.9). Norascyronone C (**2.50**) is presumably formed by degradation of **2.51**. Single-electron oxidation of the β-carbonyl group of norascyronone C (**2.50**) could give stabilised radical **2.52** which forms a Beckwith-Houk chair-like transition state.[34–37] Radical intermediate **2.52** could then undergo a *5-exo-trig* cyclisation to **2.53** followed by a *6-endo-trig* cyclisation to give norascyronone A (**2.48**). Oxidation of the C-6 position would form norascyronone B (**2.49**).



Scheme 2.9: Proposed biosynthesis of norascyronones A (2.48) and B (2.49) from norascyronone C (2.50).

2.1.5 Isolation and Proposed Biosynthesis of Related Natural Product Rxl-62

In the same year, our collaborator Gang Xu at Kunming Institute of Botany isolated a new natural product, provisionally named rxl-62 (**2.54**) (unpublished). Based on the structural similarity of rxl-62 (**2.54**), we proposed that the biosynthesis follows an analogous pathway to the biosynthesis of norascyronones A (**2.48**) and B (**2.49**) from norascyronone C (**2.50**) (Scheme 2.10). Degradation of **2.55** would form diketone **2.56** which we propose to be an undiscovered natural product. Single-electron oxidation of the β-carbonyl group of **2.56** could give stabilised radical **2.57** which forms a Beckwith-Houk chair-like transition state. **2.57** would then undergo a *5-exo-trig* cyclisation to form tertiary racial species **2.58** which could cyclise to give natural product **2.54**.



Scheme 2.10: Proposed biosynthetic pathway of rxl-62 (2.54) from 2.55.

2.1.6 Project Aims

The main objective of this project was to gain insight into the biosynthesis of norascyronones A (**2.48**), B (**2.49**) and C (**2.50**) and the recently discovered natural product rxl-62 (**2.54**) by developing a biosynthetically-inspired total synthesis (Figure 2.4).

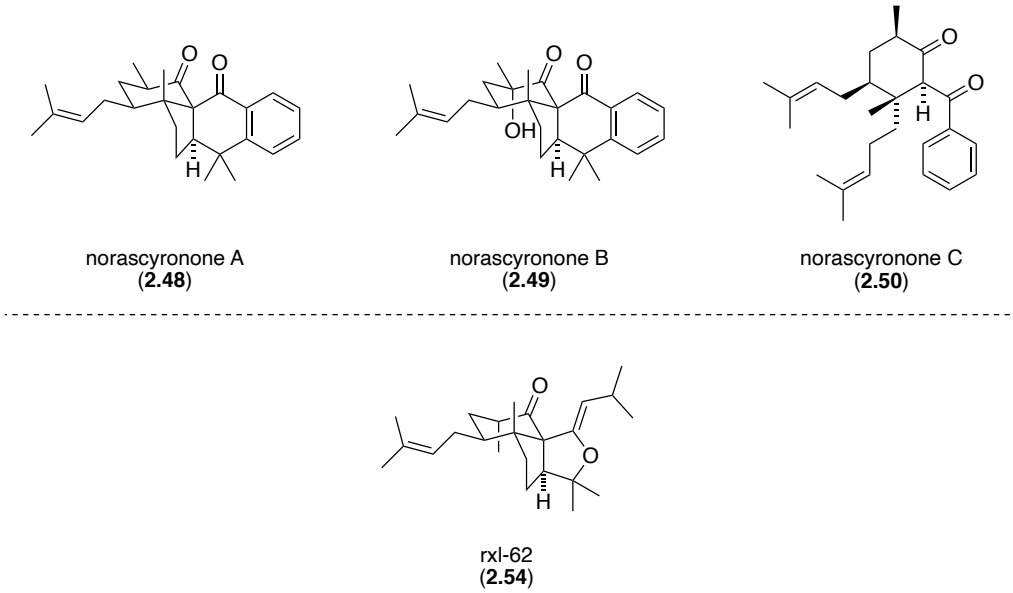
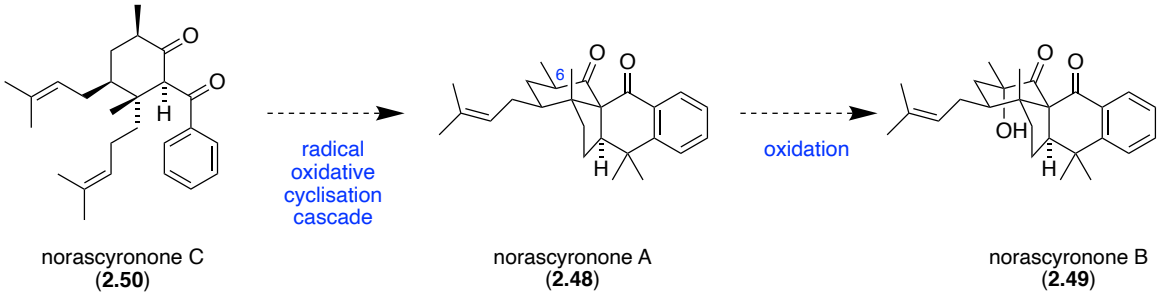


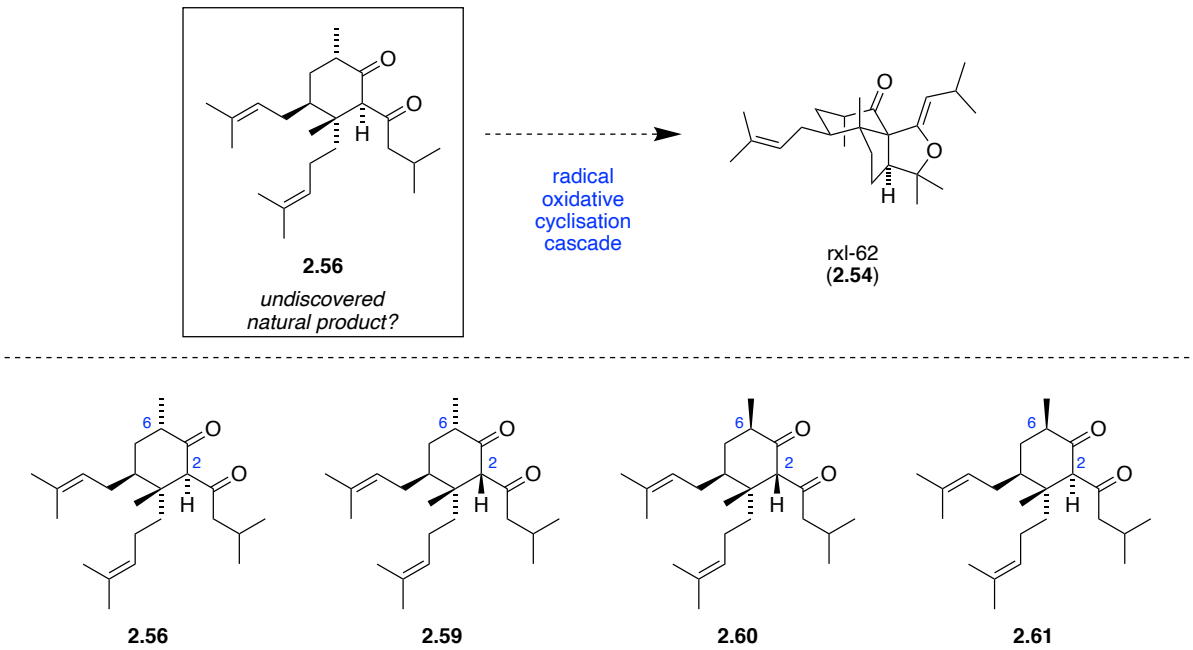
Figure 2.4: Structures of natural product target molecules: norascyronones A (2.48), B (2.49) and C (2.50) and rxl-62 (2.54).

In particular, we were interested to investigate whether norascyronone C (**2.50**) was the biosynthetic precursor to norascyronones A (**2.48**) and B (**2.49**) (Scheme 2.11). First, we planned to synthesise norascyronone C (**2.50**) following a modified protocol from our group. Ideally, norascyronone C (**2.50**) would undergo oxidative radical cyclisation to norascyronone A (**2.48**). Hydroxylation of the C-6 position could potentially give norascyronone B (**2.49**).



Scheme 2.11: Proposed biomimetic pathway from norascyronone C (2.50) to norascyronone A (2.48) and B (2.49).

Furthermore, we desired to synthesise recently discovered natural product rxl-62 (**2.54**) which we proposed to follow a similar biosynthetic pathway (Scheme 2.12). We also proposed that **2.56** is an undiscovered natural product and the biogenetic precursor to **2.54**. To investigate this proposal, we planned to synthesise all four possible diastereomeric diketones (**2.56**, **2.59**, **2.60** and **2.61**) and attempt the oxidative radical cyclisation.

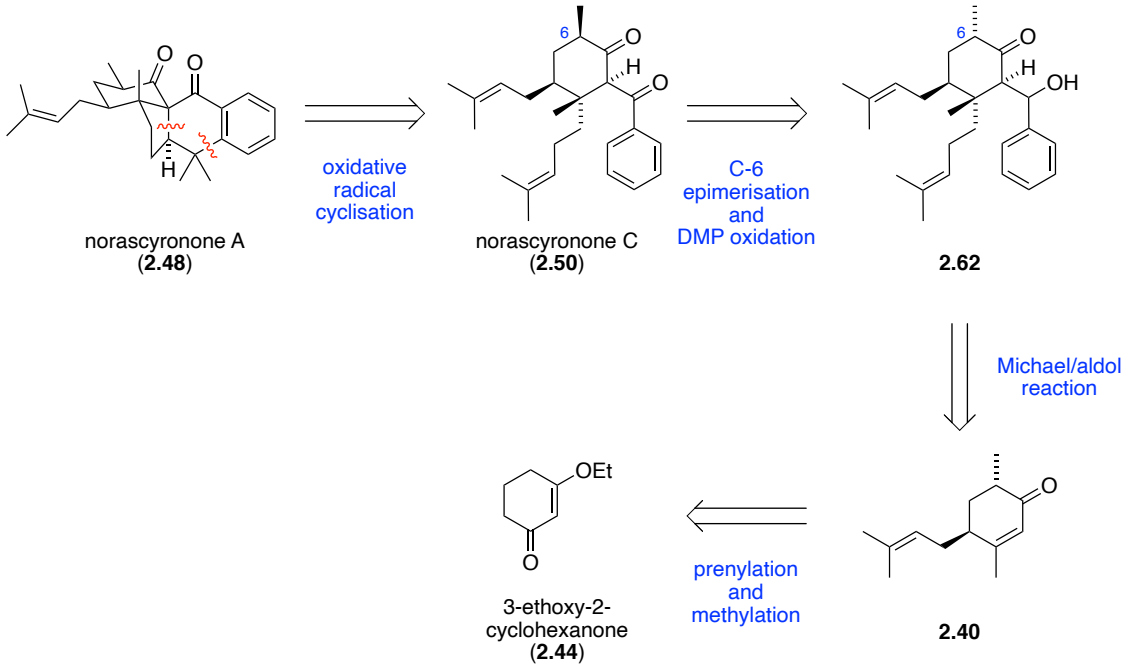


Scheme 2.12: Proposed biomimetic pathway to new natural product rxl-62 (2.54) and structures of all four possible C-2/C-6 diastereomers (2.56 and 2.59 to 2.61).

2.2 Results and Discussion

2.2.1 Retrosynthetic Analysis of Norascyronones A and C

The proposed retrosynthetic analysis of the natural products norascyronone A (**2.48**) and C (**2.50**) is based on the successful synthesis of yezo'otogirins A (**2.35**) and C (**2.37**) within the George group (Scheme 2.13).[32]



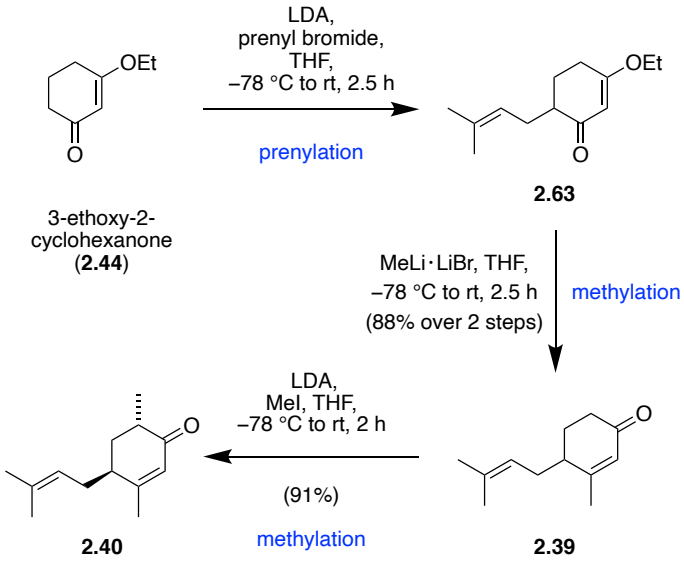
Scheme 2.13: Retrosynthetic analysis of the natural products norascyronones A (2.48) and C (2.50) starting from commercially available 3-ethoxy-2-cyclohexanone (2.44).

It was envisioned that norascyronone A (**2.48**) could be obtained through an oxidative radical cascade reaction from norascyronone C (**2.50**). There is promising literature precedence for similar Mn(III)/Cu(II)-mediated oxidative radical cyclisation reactions by our group.[18,32] Norascyronone C (**2.50**) should be accessible from hydroxyketone **2.62** by epimerisation of the C-6 methyl group and Dess-Martin oxidation of the alcohol moiety. Hydroxyketone **2.62** could

be synthesised by Michael addition of known unsaturated ketone **2.40** with homoprenyl bromide and subsequent aldol reaction with benzaldehyde. Ketone **2.40** could easily be prepared in three steps from 3-ethoxy-2-cyclohexanone (**2.44**) in good yields.

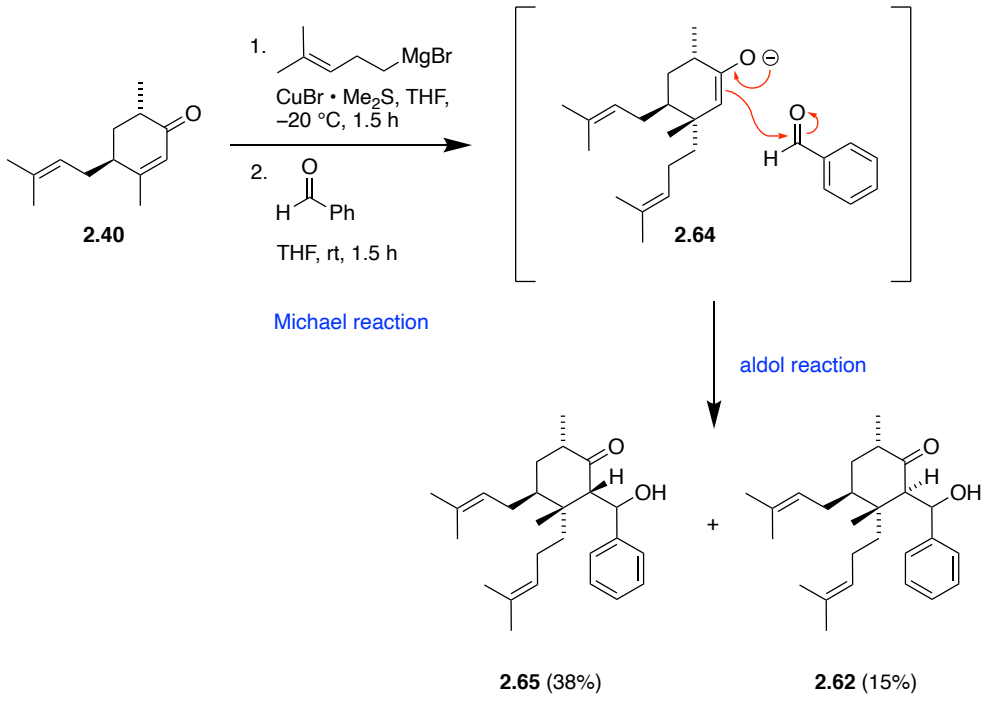
2.2.2 Total Synthesis of 2-epi-norascyronone C and Norascyronone C

Our forward synthesis commenced with the preparation of Michael/aldol precursor **2.40** in three steps (Scheme 2.14). Prenylation of 3-ethoxy-2-cyclohexanone (**2.44**) gave ketone **2.63**, which was used in the next step without the need for purification. Alkylation with methyl lithium yielded unsaturated ketone **2.39** in 88% yield over two steps. A second methylation with iodomethane afforded desired precursor **2.40** in 91% yield. We presume that the diastereoselectivity of the latter methylation is due to the steric hindrance of the prenyl group. The analytical data matched those reported in literature confirming the success of the synthesis.[31,32,38]



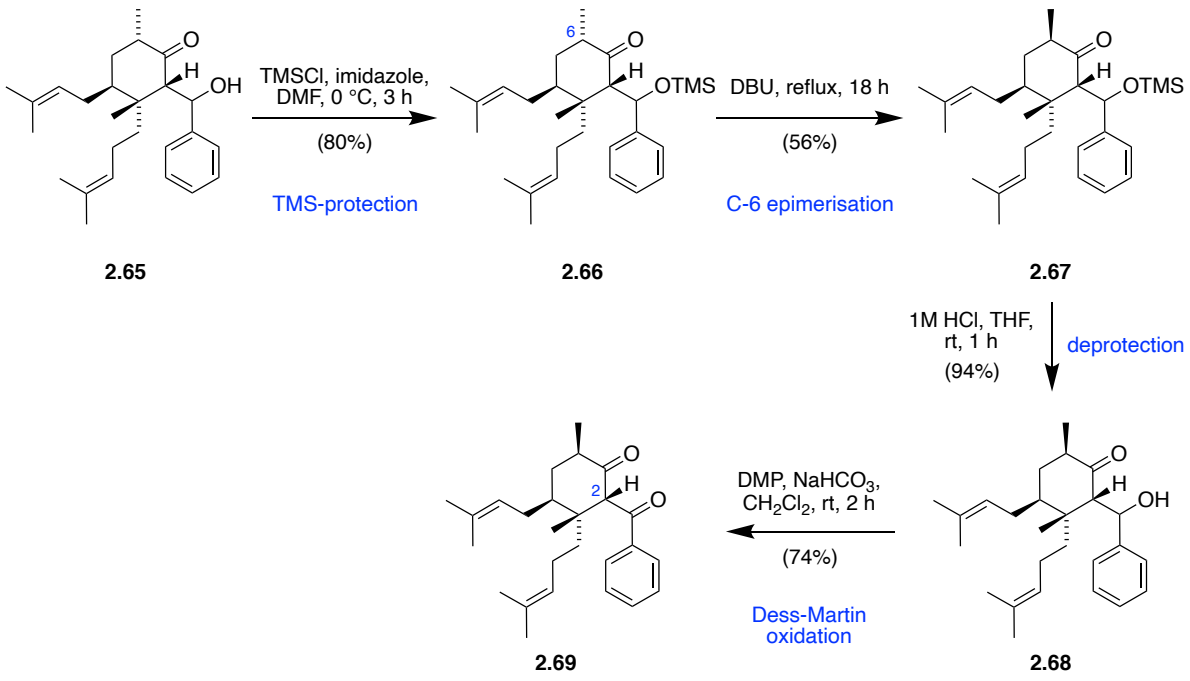
Scheme 2.14: Synthesis of Michael/aldol precursor 2.40 from 3-ethoxy-2-cyclohexanone (2.44) in three steps.

The first key step of the synthesis was the following Michael/aldol reaction of intermediate **2.40**. Conjugate addition of an organocuprate species, made *in situ* from homoprenyl magnesium bromide and copper(I) bromide, to unsaturated ketone **2.40** gave the corresponding enolate **2.64** which was immediately trapped with benzaldehyde to afford hydroxyketones **2.65** and **2.62** as a pair of diastereomers in 53% yield (Scheme 2.15). We believe that the high diastereoselectivity of the conjugated addition results from the steric hindrance of the bulky prenyl group of **2.40**. Presumably, the aldol reaction would give the anti-aldol product, however, the relative stereochemistry was never assigned as the stereocentre was lost during the synthesis.



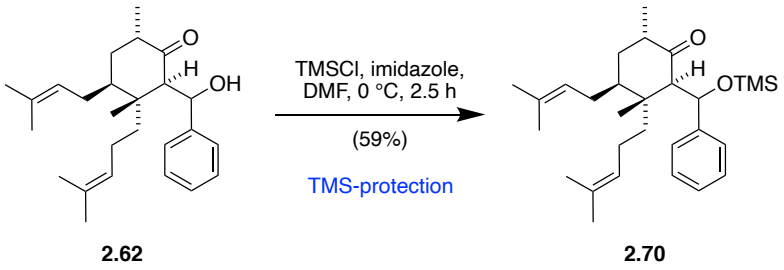
Scheme 2.15: Michael/aldol reaction of precursor 2.40 to afford the diastereomeric hydroxyketones 2.65 and 2.62 in 38% and 15% yield, respectively.

Our prior research on the synthesis of yezo'otogirins A (**2.35**) and C (**2.37**) revealed that the required epimerisation of the C-6 methyl group had to be performed on the hydroxyketone rather than on the diketone. Hence, we decided to attempt this known sequence on the norascyronone system (Scheme 2.16). We chose to perform the epimerisation sequence on the major diastereomer **2.65** first. Protection of the alcohol moiety with TMS chloride yielded TMS-protected intermediate **2.66** in 80% yield. Base-induced epimerisation with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave desired intermediate **2.67** in 56% yield. Deprotection of the TMS-group using 1M HCl in THF afforded desired hydroxyketone **2.68** in excellent yields and Dess-Martin oxidation of **2.68** yielded diketone **2.69** which is the C-2 epimer of natural product norascyronone C (**2.50**).



Scheme 2.16: Diastereoselective synthesis of 2-epi-norascyronone C (2.69) from hydroxyketone 2.65.

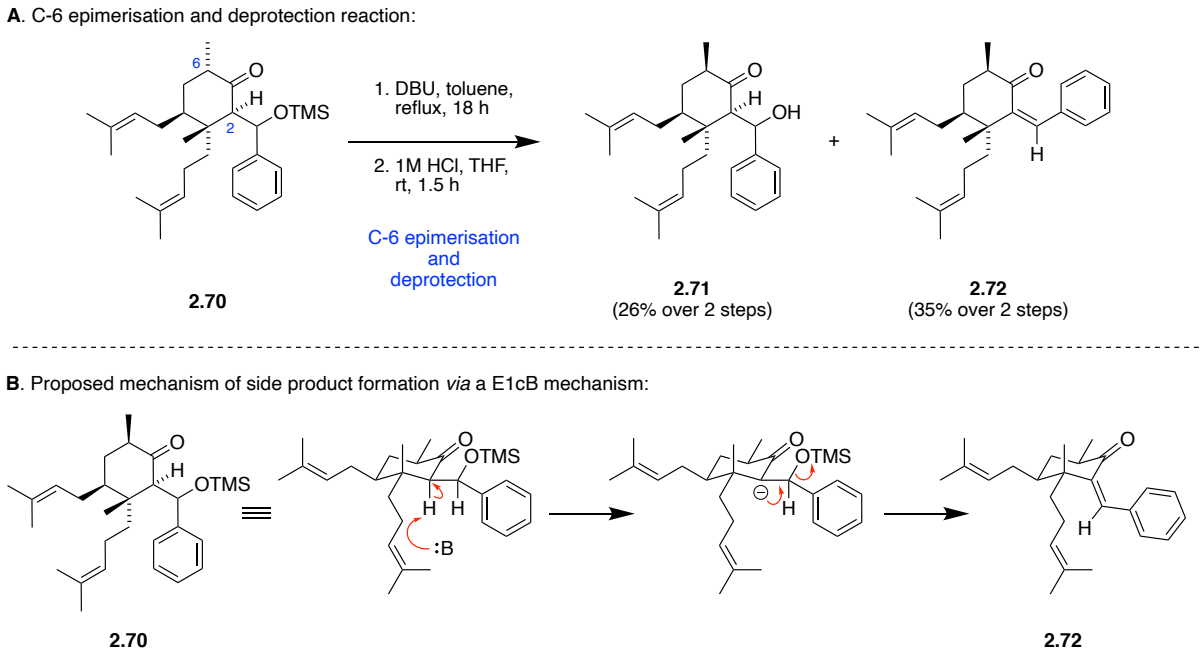
We then attempted the same epimerisation sequence on the minor diastereomer **2.62**. The hydroxyl group of **2.62** was protected with TMSCl affording silyl ether **2.70** in modest yields of 59% (Scheme 2.17).



2.62 **2.70**

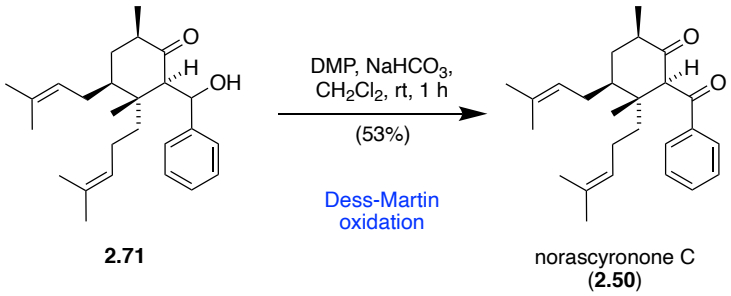
Scheme 2.17: TMS-protection of minor diastereomer 2.62 in 59% yield.

The protected intermediate **2.70** was then subjected to the same epimerisation conditions with DBU (Scheme 2.18, **A.**). However, TLC analysis indicated that two compounds had formed during the reaction with almost identical R_f values. As it was impossible to isolate the desired epimerised compound, we decided to perform the deprotection step on the crude reaction mixture. Luckily, the R_f values of the products were different enough to allow simple purification by flash column chromatography on silica gel. The desired hydroxyketone **2.71** was afforded in 26% over 2 steps (Scheme 2.18, **A.**). Thorough analysis of the spectroscopic data led us to the structural assignment of **2.72**. We propose that only diastereomer **2.70** with the C-2 proton in axial position can form the required antiperiplanar transition state that allows deprotonation and desilylation, giving **2.72** as elimination product in 35% over 2 steps *via* a E1cB mechanism (Scheme 2.18, **B.**). The E/Z geometry of side product **2.72** has not been determined.



Scheme 2.18: A. DBU epimerisation of C-6 methyl group, TMS deprotection and identification of undesired side product 2.72. B. Proposed side product formation *via* a E1cB mechanism.

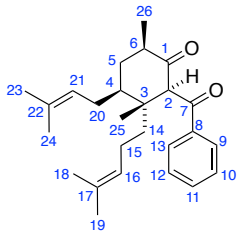
Norascyronone C (**2.50**) was successfully synthesised from hydroxyketone **2.71** *via* Dess-Martin oxidation in 53% yield (Scheme 2.19).



Scheme 2.19: Synthesis of natural product norascyronone C (2.50) from hydroxyketone 2.71 in 53% yield.

A comparison of the NMR data for both natural and synthetic norascyronone C (**2.50**) was found to match (Table 2.1), confirming the successful synthesis.

Table 2.1: Comparison of ^{13}C and ^{1}H NMR data of natural and synthetic 2.50 in $CDCl_3$.



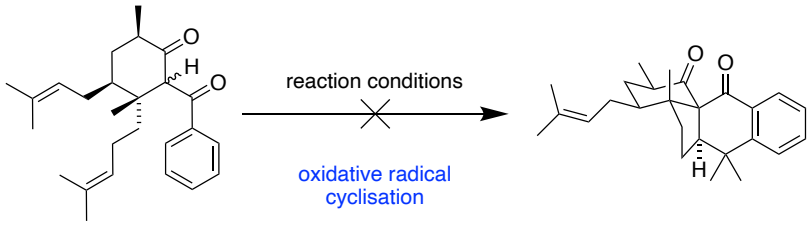
Position	^{13}C NMR data of natural 2.50 150 MHz	^{13}C NMR data of synthetic 2.50 125 MHz	^{1}H NMR data of natural 2.50 600 MHz	^{1}H NMR data of synthetic 2.50 500 MHz
1	209.6	209.6	-	-
2	63.7	63.6	4.55 (s)	4.60 (s, 1H)
3	46.3	46.5	-	-
4	42.8	43.1	1.94 (m)	2.03 – 1.95 (m, overlap, 1H)
5	37.1	37.4	2.13, m 1.25 (q, 12.3 Hz)	2.23 – 2.19 (m, 1H), 1.33 – 1.28 (m, 1H)
6	45.4	45.6	2.55 (m)	2.60 (dp, 12.8, 6.6 Hz, 1H)
7	196.8	197.0	-	-
8	138.5	138.8	-	-
9	127.5	127.7	7.71 (d, 7.8 Hz)	7.77 (d, 7.3 Hz, 1H)
10	128.6	128.8	7.35 (t, 7.8 Hz)	7.41 (t, 7.7 Hz, 1H)
11	132.7	132.8	7.44 (t, 7.8 Hz)	7.50 (t, 7.4 Hz, 1H)
12	128.6	128.8	7.35 (t, 7.8 Hz)	7.41 (t, 7.7 Hz, 1H)
13	127.5	127.7	7.71 (d, 7.8 Hz)	7.77 (d, 7.3 Hz, 1H)
14	36.4	36.7	1.50 (m)	1.60 – 1.54 (m, 1H)
15	22.0	22.3	1.91 (overlap) 1.65 (m)	2.03 – 1.95 (m, overlap, 1H), 1.74 – 1.69 (m, 1H)
16	123.6	123.8	4.80 (t, 7.0 Hz)	4.87 (t, 7.1 Hz, 1H)
17	131.7	131.9	-	-
18	25.5	25.7	1.44 (s)	1.50 (s, 3H)
19	17.3	17.5	1.27 (s)	1.34 (s, 3H)
20	26.9	27.2	2.11 (m) 1.70 (overlap)	2.19 – 2.15 (m, 1H) 1.78 – 1.75 (m, 1H)
21	123.0	123.2	5.09 (t, 7.2 Hz)	5.16 (t, 7.2 Hz, 1H)
22	132.9	133.1	-	-
23	17.9	18.1	1.56 (s)	1.63 (s, 3H)
24	25.9	26.1	1.68 (s)	1.75 (s, 3H)
25	17.6	17.8	1.07 (s)	1.14 (s, 3H)
26	14.4	14.6	0.98 (d, 6.6 Hz)	1.04 (d, 6.4 Hz, 3H)

*Signals are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constants, integration).

2.2.3 Attempted Radical Cyclisation Reaction to Norascyronone A and Synthesis of 6-epi-Norascyronone A

With norascyronone C (**2.50**) and 2-epi-norascyronone C (**2.69**) in hand, we turned our focus towards the oxidative radical cyclisation reaction. All attempted reaction conditions are summarised in Table 2.2.

Table 2.2: Attempted oxidative radical cyclisation of diastereomeric diketones 2.50 and 2.69 to norascyronone A (2.48).



2.50/2.69 norascyronone A (**2.48**)

Entry	Diasteromer	Conditions	Yield[#]
1	**2.69**	$Mn(OAc)_3$, $Cu(OAc)_2$, AcOH, rt, 18 h	n.r.
2	**2.69**	$Mn(OAc)_3$, AcOH, rt to 120 °C, 18 h	mostly residual s.m., some isomerisation to norascyronone C (**2.50**)
3	**2.69**	$Mn(OAc)_3$, DMF, reflux, 3 h	mostly residual s.m., some isomerisation to norascyronone C (**2.50**)
4	**2.69**	$Mn(OAc)_3$, EtOH, DIPEA, reflux, 4 h	mostly residual s.m., some isomerisation to norascyronone C (**2.50**)
5	**2.69**	$Mn(OAc)_3$, $Cu(OTf)_2$, DMF, 150 °C, 3 h	mostly residual s.m., some isomerisation to norascyronone C (**2.50**)
6	**2.50**	$Mn(OAc)_3$, $Cu(OTf)_2$, DMF, 150 °C, 3 h	slow decomposition

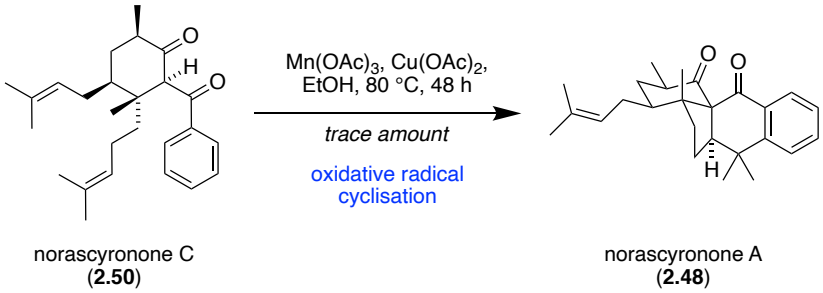
[#]All results are indicated by TLC analysis, standard aqueous work up and crude ^{1}H NMR analysis.

First, the oxidative radical cyclisation was attempted with $Mn(OAc)_3$ and $Cu(OAc)_2$ in acetic acid at room temperature following a literature procedure by our group but no reaction occurred even after prolonged reaction times (entry 1).[18] Next, we attempted the cyclisation under the same reaction conditions, but omitting the Cu-salt. No reaction occurred after stirring the mixture at room temperature, but, after heating the reaction to 120 °C for 18 h, the starting material started to epimerise slowly to norascyronone C (**2.50**) (entry 2). In entry 3, we decided to change solvents to DMF and after heating the starting material at reflux for 3 h, TLC analysis indicated some epimerisation to norascyronone C (**2.50**) as well as mostly residual starting material. Next, the reaction was performed in ethanol with the addition of diisopropylethylamine (DIPEA). After 4 h at reflux, residual starting material was observed, along with some epimerisation to **2.50**. When heating **2.69** at 150 °C for 3 h the same outcome was observed, and performing the same reaction conditions on the other diastereomer **2.50** led to decomposition of the starting material (entries 5 and 6).

Unfortunately, none of the attempted oxidative radical cyclisation reactions of the epimers **2.69** and **2.50** led to the formation of the natural product norascyronone A (**2.48**). However, we observed epimerisation to norascyronone C (**2.50**) under most of the reaction conditions with **2.69**.

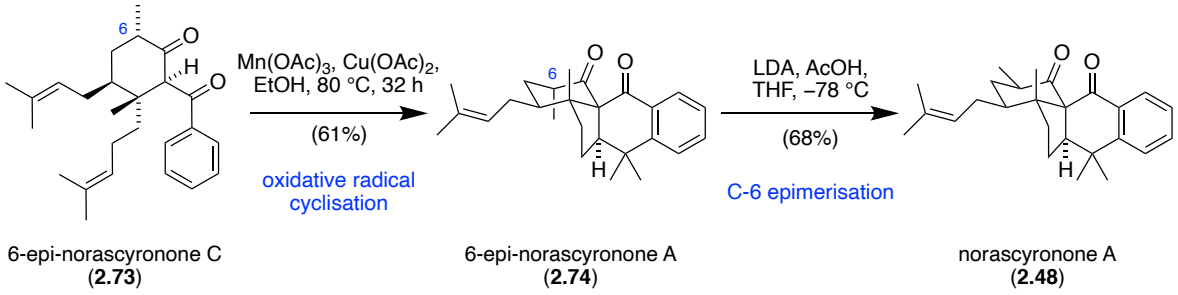
While we were still working on the radical cyclisation key step in the synthesis of norascyronone A (**2.48**) and B (**2.49**), an alternative route for the total synthesis of all three norascyronones (A, B and C) was reported by Lan, Huang, Yang and co-workers.[39] Most interestingly, the authors were unable to synthesise norascyronone A (**2.48**) and B (**2.49**) from the presumed biosynthetic precursor norascyronone C (**2.50**) which was consistent with our findings (see above). Only a trace amount of the natural product norascyronone A (**2.48**) was

afforded from norascyronone C (**2.50**) on heating with $Mn(OAc)_3$ and $Cu(OAc)_2$ in ethanol at 80 °C for 48 h (Scheme 2.20). They reported that the majority of the starting material decomposed under these conditions.



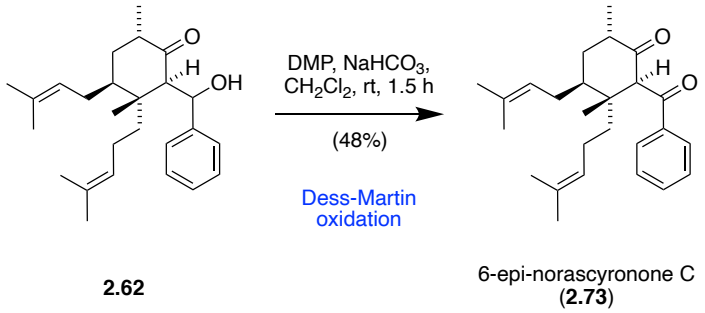
Scheme 2.20: Synthesis of norascyronone A (2.48) from norascyronone C (2.50) in trace amounts by Lan, Huang and Yang.[39]

The group reported that they had to circumvent this problem by performing the radical cascade key step on the unnatural C-6 epimer of norascyronone C (**2.50**) (Scheme 2.21). When treating **2.73** with $Mn(OAc)_3$ and $Cu(OAc)_2$ in ethanol at 80 °C for 32 h, they obtained 6-epi-norascyronone A (**2.74**) in 61% yield. Simple C-6 epimerisation with LDA in acetic acid and THF gave norascyronone A (**2.48**) in 68% yield.



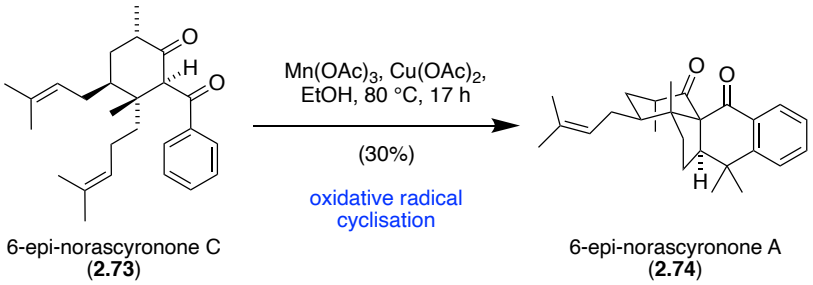
Scheme 2.21: Synthesis of 6-epi-norascyronone A (2.48) by Lan, Huang, Yang and co-workers in 61% yield and final conversion to norascyronone A (2.48) in 68% yield.[39]

We were curious if we could reproduce these results. Hence, we performed Dess-Martin oxidation on hydroxyketone **2.62** to obtain 6-epi-norascyronone C (**2.73**) (Scheme 2.22).



Scheme 2.22: DMP oxidation of hydroxyketone 2.62 to 6-epi-norascyronone C (2.73).

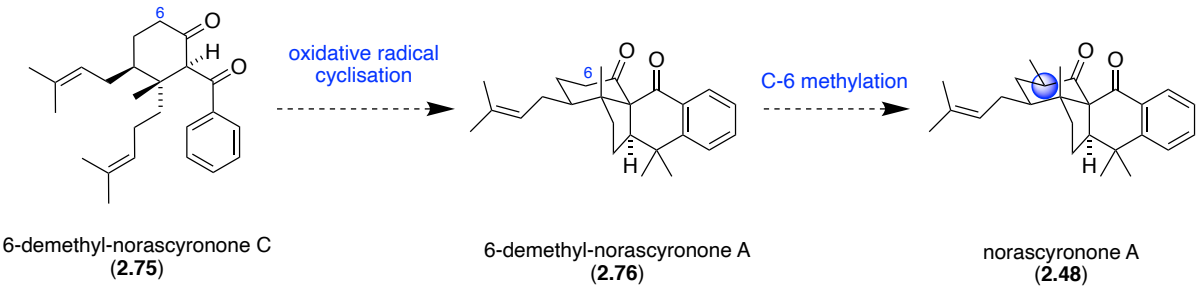
Diketone **2.73** was then subjected to the same oxidative cyclisation conditions as reported by Lan, Huang, Yang and co-workers. 6-epi-norascyronone A (**2.74**) was afforded in 30% yield after 17 h at 80 °C (Scheme 2.23).



Scheme 2.23: Radical oxidative cyclisation of 6-epi-norascyronone C (2.73) to 6-epi-norascryronone A (2.74).

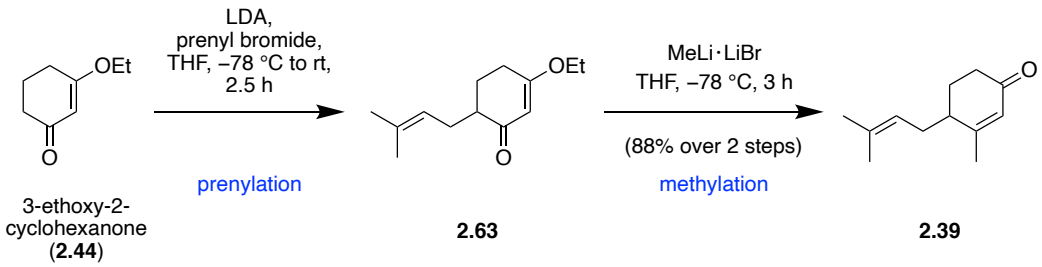
2.2.4 Attempted Radical Cyclisation Reaction of 6-Demethyl-Norascyronone C

This contradiction to the proposed biosynthesis of norascyronones A (**2.48**) and C (**2.50**) sparked our interest. We were curious whether it was possible to successfully achieve the radical cyclisation from 6-demethyl-norascyronone C (**2.75**) to 6-demethyl-norascyronone A (**2.76**) and perform the necessary methylation at the C-6 position as the final step (Scheme 2.24).



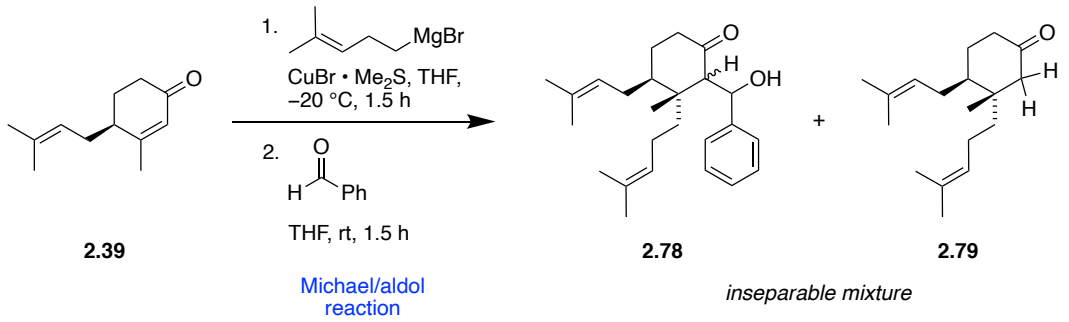
Scheme 2.24: Proposed synthesis of norascyronone A (2.48) from 6-demethyl-norascyronone C (2.75).

To investigate this pathway, unsaturated ketone **2.39** was prepared through the same synthetic route as described above (see Scheme 2.14) within 2 steps from 3-ethoxy-2-cyclohexanone (**2.44**) in 88% overall yield (Scheme 2.25).



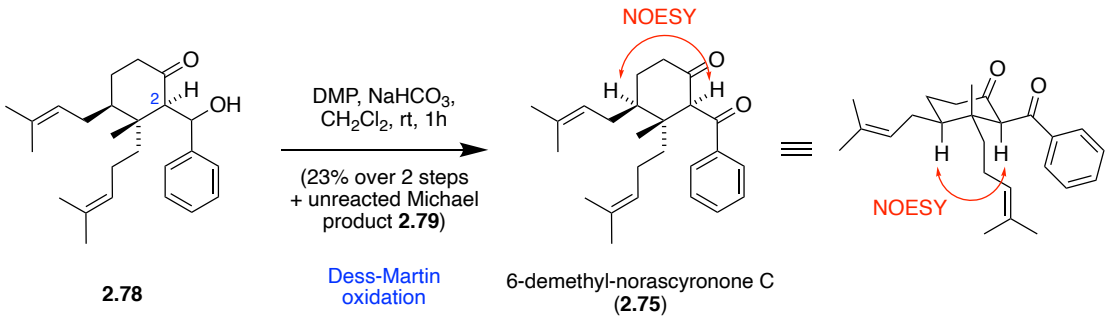
Scheme 2.25: Synthesis of Michael/aldol precursor 2.39 from 3-ethoxy-2-cyclohexanone (2.44) within 2 steps.

Unsaturated ketone **2.39** was subsequently subjected to our established Michael/aldol conditions affording hydroxyketone **2.78** and Michael product **2.79** in an inseparable mixture (Scheme 2.26). In contrast to the synthesis of **2.62** and **2.65**, only one of the possible diastereomers was observed. However, due to the impurity the relative stereochemistry of the hydroxyketone could not be determined in this step.



Scheme 2.26:Michael/aldol reaction of precursor 2.39 to yield an inseparable mixture of hydroxyketone 2.78 and Michael product 2.79.

We decided to perform the following Dess-Martin oxidation on the mixture of compounds which yielded the desired diketone **2.75** in 23% yield over 2 steps (Scheme 2.27). Extensive analysis by spectroscopic methods, in particular NOESY experiments, allowed us to assign the relative stereochemistry of the diketone. A strong NOESY correlation (shown in red) between the α-hydrogen at 4.60 ppm and the C-H multiplet at 1.91 ppm suggests the correct assignment of 6-demethyl-norascyronone C (**2.75**).

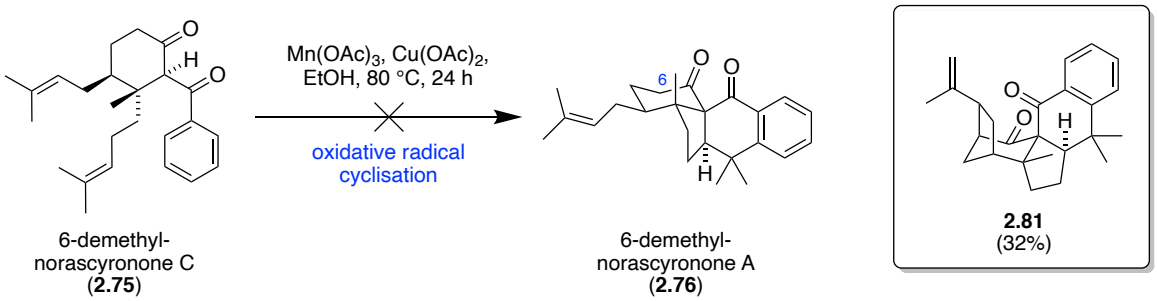


2.78

6-demethyl-norascyronone C
(**2.75**)

Scheme 2.27: Dess-Martin oxidation of hydroxyketone 2.78 to 6-demethyl-norascyronone C (2.75) in 23% yield (important NOESY correlation shown in red).

We then turned our focus toward the desired oxidative radical cyclisation of 6-demethyl-norascryronone C (**2.75**) (Scheme 2.28). When we subjected the diketone to our previously established conditions, we observed the formation of a new compound. Analysis of the spectroscopic data, however, indicated that the reaction did not lead to the formation of the desired natural product analogue, 6-demethyl-norascryonone A (**2.76**).



6-demethyl-
norascyronone C
(**2.75**)

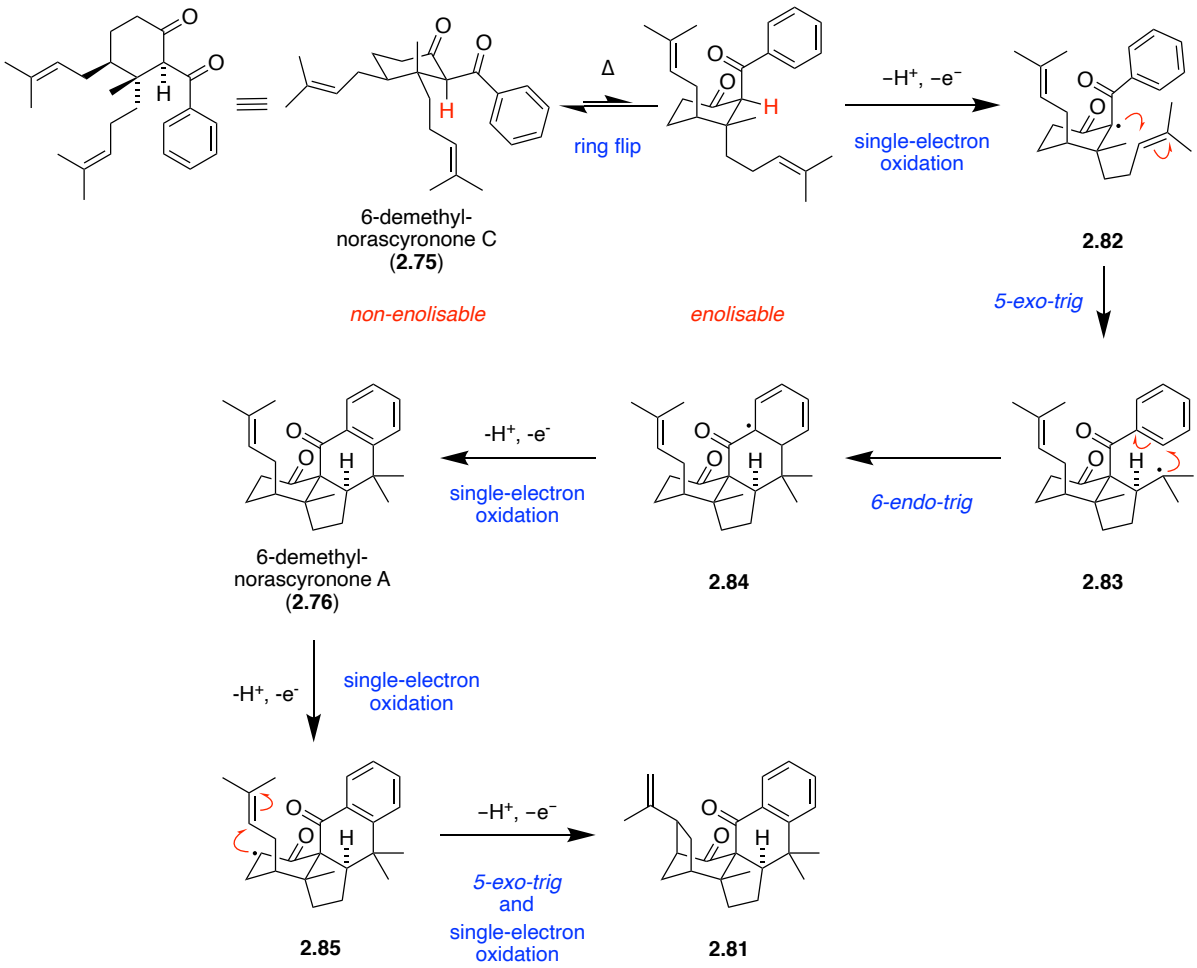
6-demethyl-
norascyronone A
(**2.76**)

2.81
(32%)

Scheme 2.28: Attempted oxidative radical cyclisation of 6-demethyl-norascyronone C (2.75).

The ^{1}H NMR spectra of the right-hand side of the molecule showed significant similarities to the published spectra of norascyronone A (**2.48**) indicating that the cyclisations were successful. However, a sharp singlet at 4.77 ppm with an integration of two that corresponded to a terminal alkene led us to the conclusion that a third cyclisation occurred on the prenyl side

chain to form the structure of **2.81** in 32% yield. We proposed the following mechanism for the formation of side product **2.81** (Scheme 2.29).

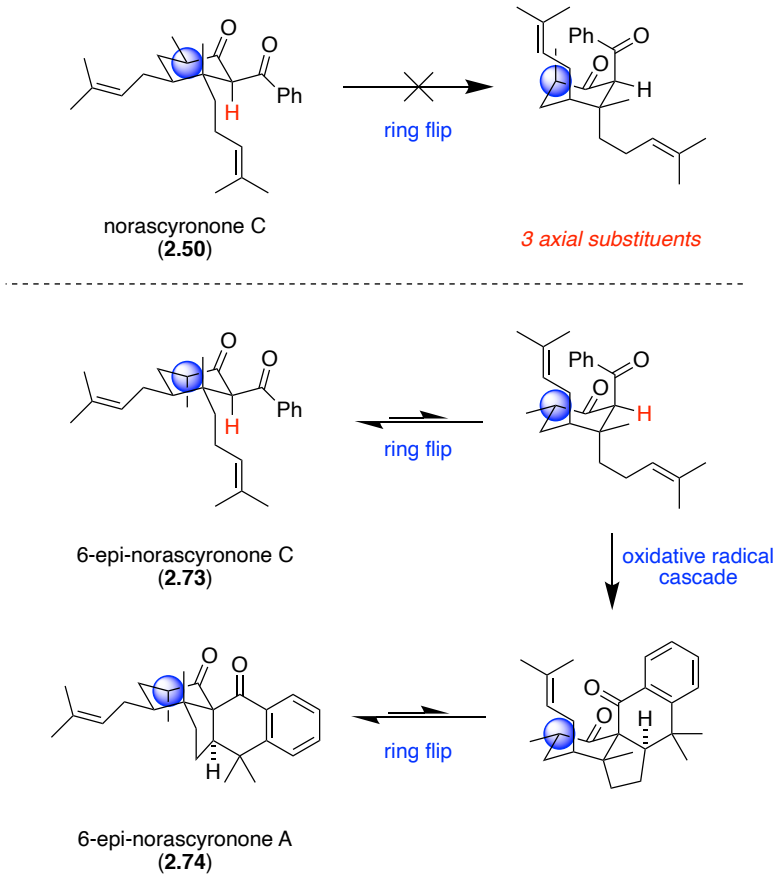


Scheme 2.29: Proposed mechanism of side product formation *via* a thermic ring flip.

Under application of heat, the non-enolisable ring conformer of 6-demethyl-norascyronone C (**2.75**) performs a ring flip to its energetically higher isomer (all large substituents are now in axial position). This conformer undergoes single-electron oxidation of the β-carbonyl group to form stabilised radical **2.82**. The radical intermediate then undergoes a *5-exo-trig* cyclisation to **2.83** followed by *6-endo-trig* cyclisation to **2.84** and another single-electron oxidation to give 6-demethyl-norascyronone A (**2.76**). Surprisingly, the reaction does not stop here but

another single-electron oxidation of **2.76** gives secondary radical species **2.85** which then forms a tertiary radical *via 5-exo-trig* cyclisation with the prenyl side chain. A final single-electron oxidation terminates the radical cascade giving the isolated side product **2.81**. In this radical cascade reaction, 3 new C-C bonds and 3 rings are formed.

In conclusion, the stereochemistry of the C-6 methyl group (shown in blue) plays a vital role in the reactivity of the norascyronone systems (Scheme 2.30). We propose that a ring flip is required for the formation of the tetracyclic ring system of the natural product norascyronone A (**2.48**).



Scheme 2.30: Reactivity in regard to the required ring flip of norascyronone C (2.50) and 6-epi-norascyronone C (2.74).

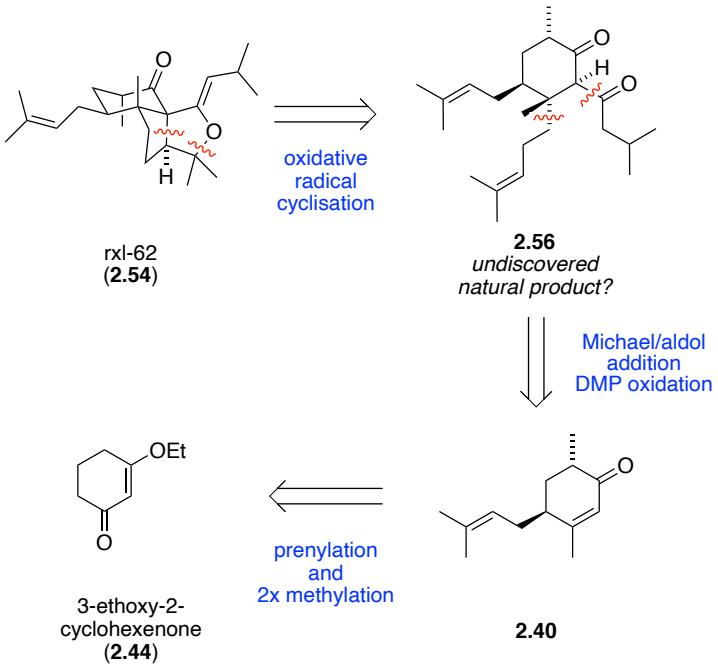
This ring flip is unfavoured for norascyronone C (**2.50**) as it forces three large substituents on the top face in axial position creating unfavoured 1,3-diaxial interactions. In contrast to that, the ring flip of 6-epi-norascyronone C (**2.73**) is possible as it only forces two large substituents on the top face in axial position, which allows the system to undergo the oxidative radical cascade forming the natural product analogue 6-epi-norascyronone A (**2.74**).

As we were unable to establish an alternative synthetic route for norascyronone A (**2.48**) from 6-demethyl-norascyronone C (**2.75**), we instead decided to adapt this synthetic sequence to the synthesis of a related natural product, rxl-62 (**2.54**).

2.2.5 Retrosynthetic Analysis of Related Natural Product Rxl-62

The closely related natural product rxl-62 (**2.54**) was isolated early in 2020. Our proposed retrosynthetic analysis of this natural product is based on the successful synthesis of yezo'otogirins A (**2.35**) and C (**2.37**) within the George group and our previous synthetic efforts towards the total synthesis of norascyronones A (**2.48**) and C (**2.50**) (Scheme 2.31).

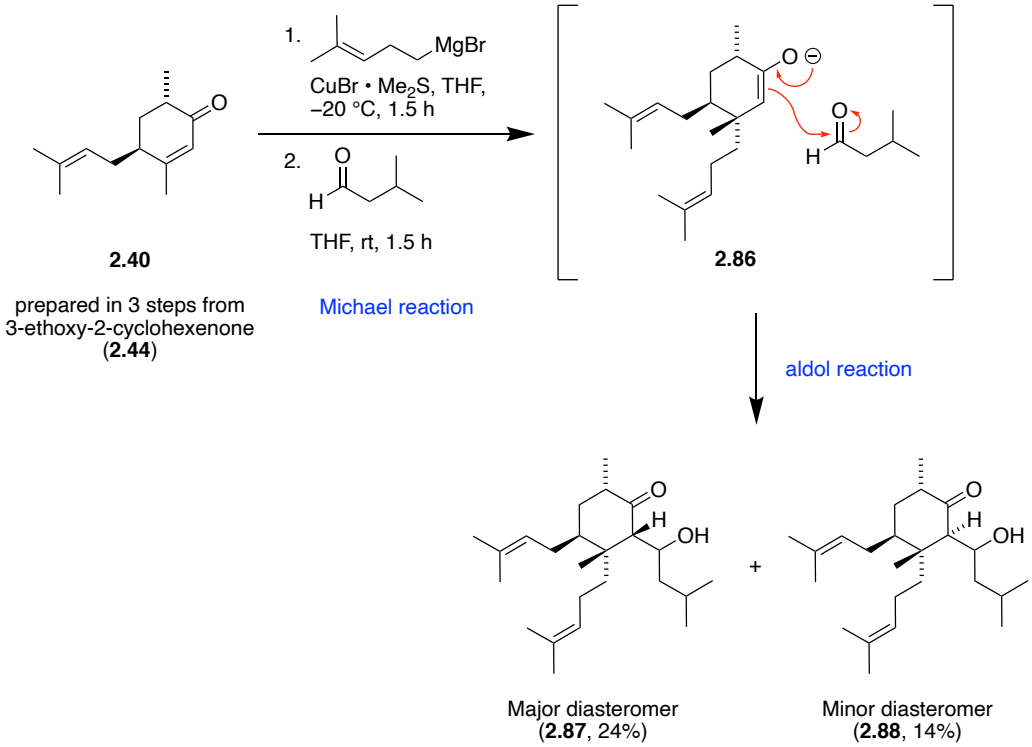
It was envisioned that the 6/5/5 ring system of natural product rxl-62 (**2.54**) could be accessed from diketone **2.56** by an oxidative radical cyclisation using $Mn(OAc)_3$ as oxidant and $Cu(OTf)_2$ as co-oxidant. Diketone **2.56** could be obtained *via* Dess-Martin oxidation and Michael/aldol addition from unsaturated ketone **2.40**, which can be easily prepared from 3-ethoxy-2-cyclohexenone (**2.44**) in 3 steps following our optimised procedure as discussed in more detail in section 2.2.2.[31,32,38]



Scheme 2.31: Proposed retrosynthetic route to access natural product rxl-62 (2.54).

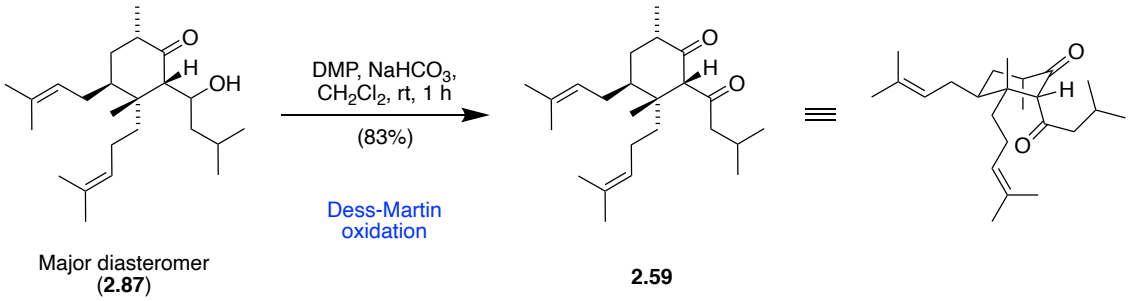
2.2.6 Synthesis of Diastereomeric Diketones 2.56 and 2.59

Our forward synthesis commenced with 1,4-addition of an organocuprate species made from homoprenyl magnesium bromide and copper(I) bromide to unsaturated ketone **2.40**. The resulting enolate **2.86** was subsequently trapped with isovaleraldehyde giving the two diastereomeric hydroxyketones **2.87** and **2.88** in a 1.7 to 1 ratio in 38% overall yield (Scheme 2.32).



Scheme 2.32: Synthesis of hydroxyketones 2.87 and 2.88 *via* Michael/aldol reaction.

The following step was the Dess-Martin oxidation of the major diastereomer **2.87**, which gave diketone **2.59** in good yields of 83% (Scheme 2.33).



Scheme 2.33: Dess-Martin oxidation of hydroxyketone 2.87 to diketone 2.59.

The relative stereochemistry of the substituents was assigned by spectroscopic methods. A visible NOESY correlation between the methyl singlet at 1.04 ppm and the α-hydrogen at 3.62 ppm (Figure 2.5) confirms the proposed stereochemistry of diketone **2.59**. Furthermore, the absence of a correlation between the methyl doublet at 1.00 ppm and the α-hydrogen at 3.62 ppm suggests correct assignment of this structure.

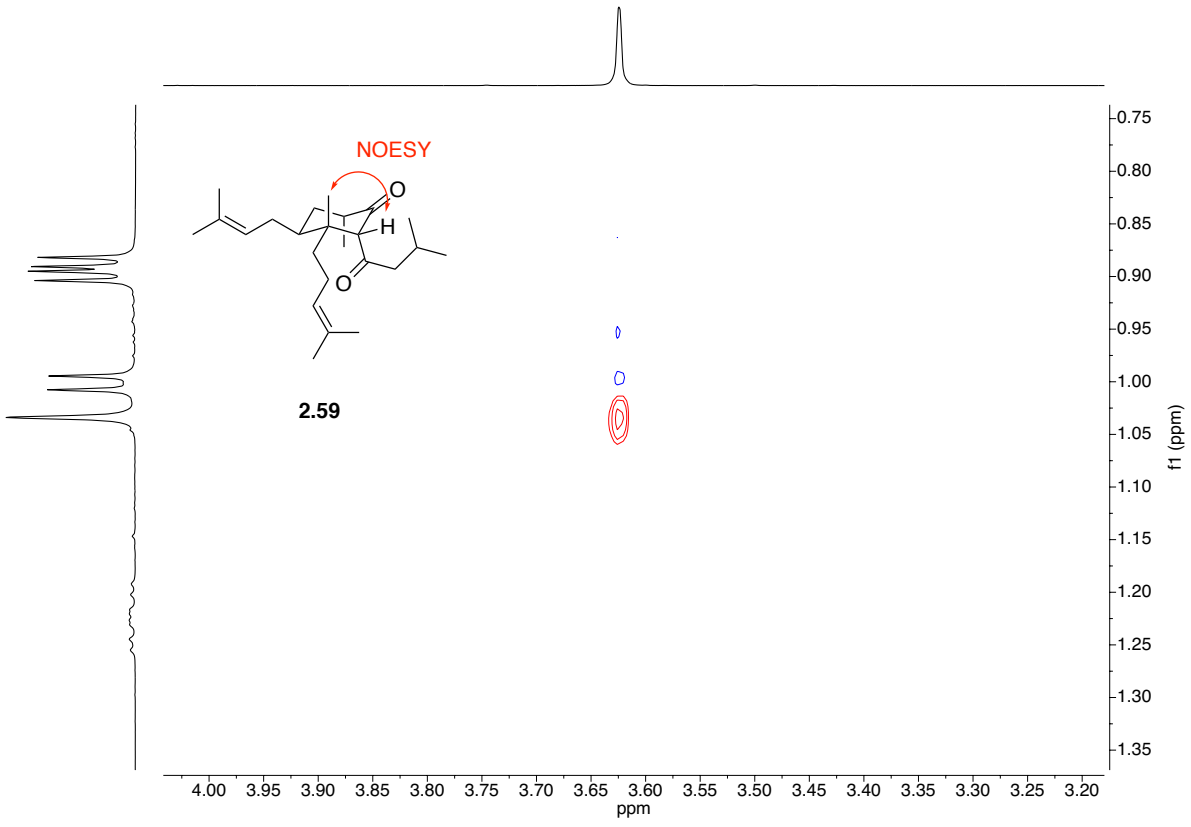
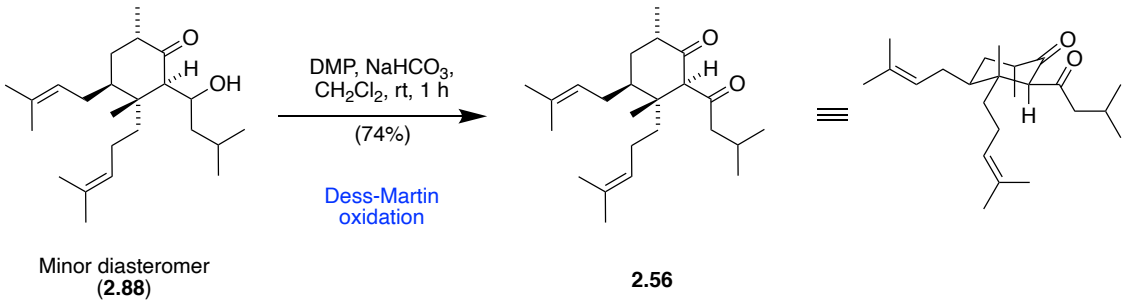


Figure 2.5: NOESY spectra for diastereomer 2.59.

The same oxidation conditions were used for the minor diastereomer, oxidising **2.88** with Dess-Martin periodinane and $NaHCO_3$ to the corresponding ketone **2.56** in 74% yield (Scheme 2.34).



Scheme 2.34: Dess-Martin oxidation of hydroxyketone 2.88 to diketone 2.56.

As shown in Figure 2.6, there is an obvious NOESY correlation between the methyl doublet at 1.21 ppm and the α-hydrogen at 3.79 ppm, which confirms our proposed relative stereochemistry of diketone **2.56**.

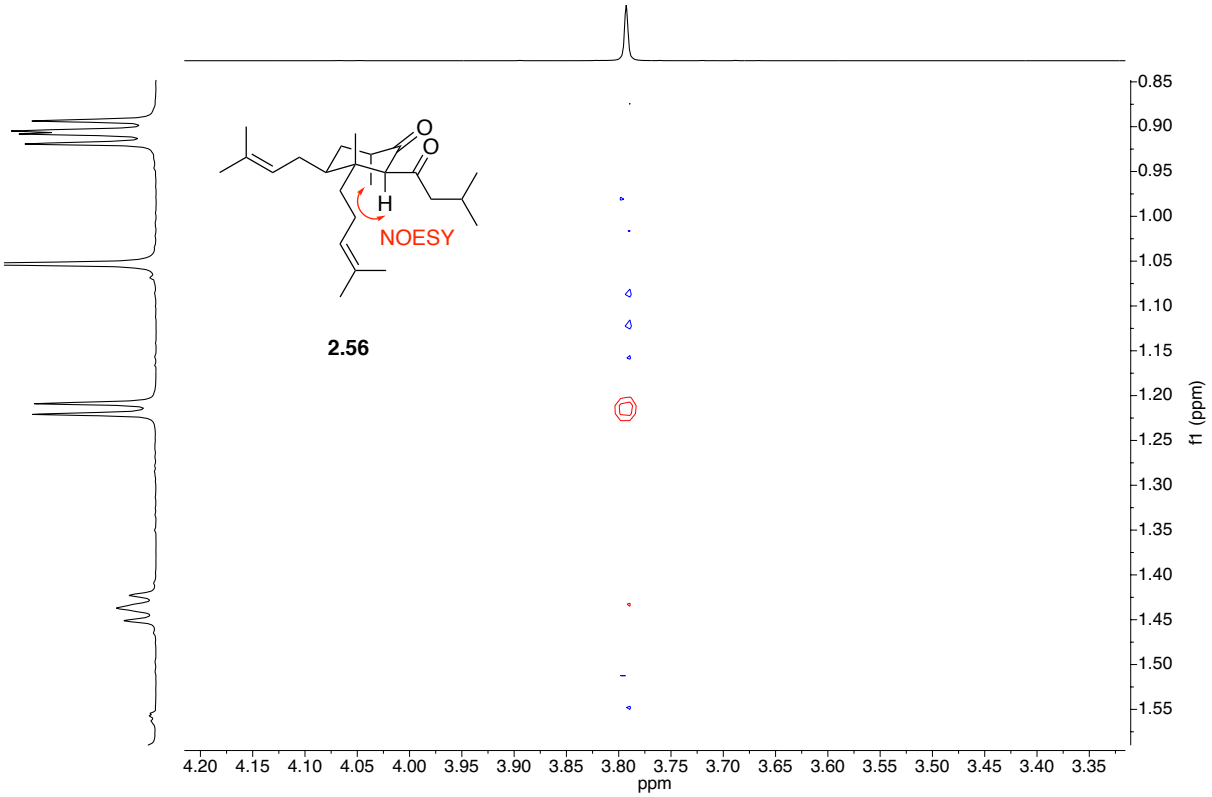
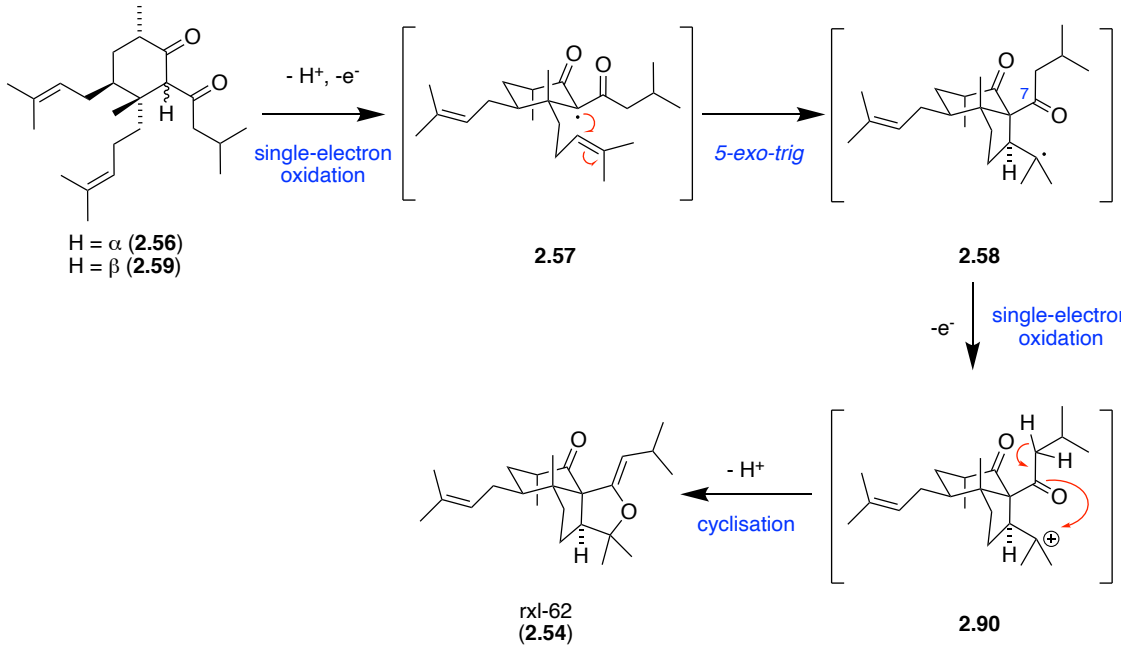


Figure 2.6: NOESY spectra of diketone 2.56.

2.2.7 Attempted Radical Cyclisation Reaction and Isolation of Side Product 2.89

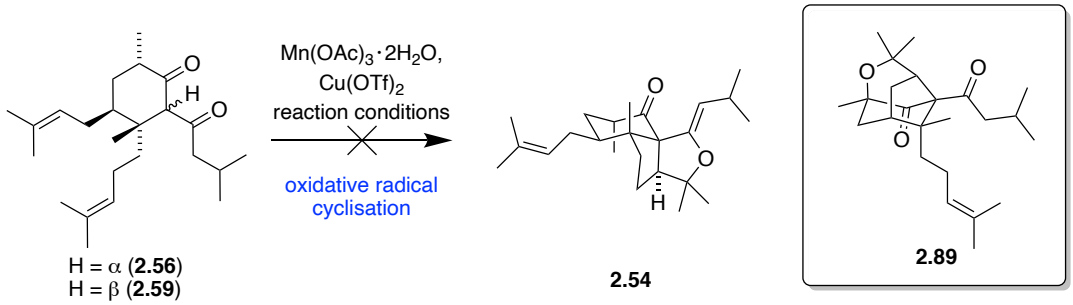
With diketones **2.56** and **2.59** in hand, the oxidative radical cyclisation key step was investigated. It was envisioned that single electron oxidation of the β-dicarbonyl group of **2.56**/**2.59** would give stabilised radical **2.57**, which then could undergo a *5-exo-trig* cyclisation with the homoprenyl side chain to form tertiary radical **2.58**. Another one-electron oxidation would transform the tertiary radical into cationic intermediate **2.90** which then could be attacked by the C-7 carbonyl oxygen to form the 6/5/5 ring system of natural product rxl-62 (**2.54**) (Scheme 2.35).



Scheme 2.35: Proposed reaction mechanism for formation of natural product 2.54 in oxidative radical cyclisation cascade.

The reaction conditions listed in Table 2.3 were chosen according to similar transformations that have been previously utilised by our group and our synthetic efforts towards the total synthesis of norascyronone A (**2.48**) from norascyronone C (**2.50**).[18,19,32]

Table 2.3: Screened reaction conditions for oxidative radical cyclisation of diketones 2.56 and 2.59 using $Mn(OAc)_3$ and $Cu(OTf)_2$ as oxidants.



Entry	Diasteromer	Conditions[#]	Yield
1	**2.59**	reflux, 3 h	decomposition[†]
2	**2.59**	rt, 3 days	no reaction[†]
3	**2.59**	60 °C, 1.5 h	no reaction[†]
4	**2.59**	100 °C, 4.5 h	**2.89** (14%)[*]
5	**2.59**	no $Cu(OTf)_2$ added, 100 °C, o.n.	r.s.m. (14%)[*], **2.89** (7%)[*]
6	**2.56**	60 °C, o.n.	r.s.m. (50%)[*], **2.89** (10%)[*]
7	**2.56**	100 °C, 3 h	**2.89** (34%)[*]

[#]All reactions were performed in DMF with 4 eq. of $Mn(OAc)_3$ and 2 eq. of $Cu(OTf)_2$ except for entry 5 which was carried out without $Cu(OTf)_2$. The reaction flasks were left open to air. [†] Indicated by TLC analysis. [*]All yields are isolated yields after purification by flash column chromatography on silica gel.

Treatment of **2.59** with $Mn(OAc)_3$ and $Cu(OTf)_2$ in refluxing DMF led to decomposition of the starting material (entry 1). Stirring starting material **2.59** in DMF at room temperature for 3 days (entry 2) or heating it to 60 °C for 1.5 hours (entry 3) did not lead to any reaction at all. When heated to 100 °C for 4.5 hours, TLC analysis showed the formation of a new compound along with residual starting material and some decomposition. The new compound was isolated, purified by flash column chromatography and identified as cyclised diketone **2.89**.

We were interested if the side product formation would still occur without addition of $Cu(OTf)_2$ as co-oxidant. Hence, we treated diketone **2.59** with $Mn(OAc)_3$ in absence of $Cu(OTf)_2$ which also led to the formation of side product **2.89** (entry 5). Interestingly, the reaction was much slower. A few reaction conditions were repeated on the other diastereomer **2.56**. We heated

2.56 to 60 °C overnight which afforded 10% of the same side product **2.89** along with 50% recovered starting material (entry 6). The best conditions for producing side product **2.89** (see entry 4) were tested on diketone **2.56** affording 34% of cyclised side product **2.89** (entry 7).

The structure of side product **2.89** was mainly assigned by spectroscopic methods, such as ^{1}H, ^{13}C and 2D NMR and IR spectroscopy, as well as mass spectrometry. We were also able to grow a single crystal of side product **2.89** which confirmed our structural assignment by X-ray crystallography (Figure 2.7).

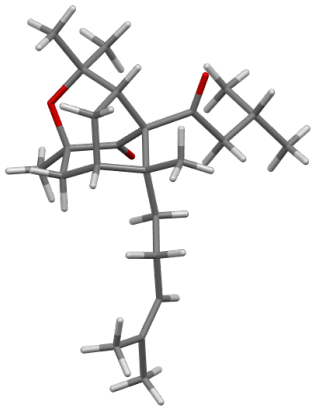
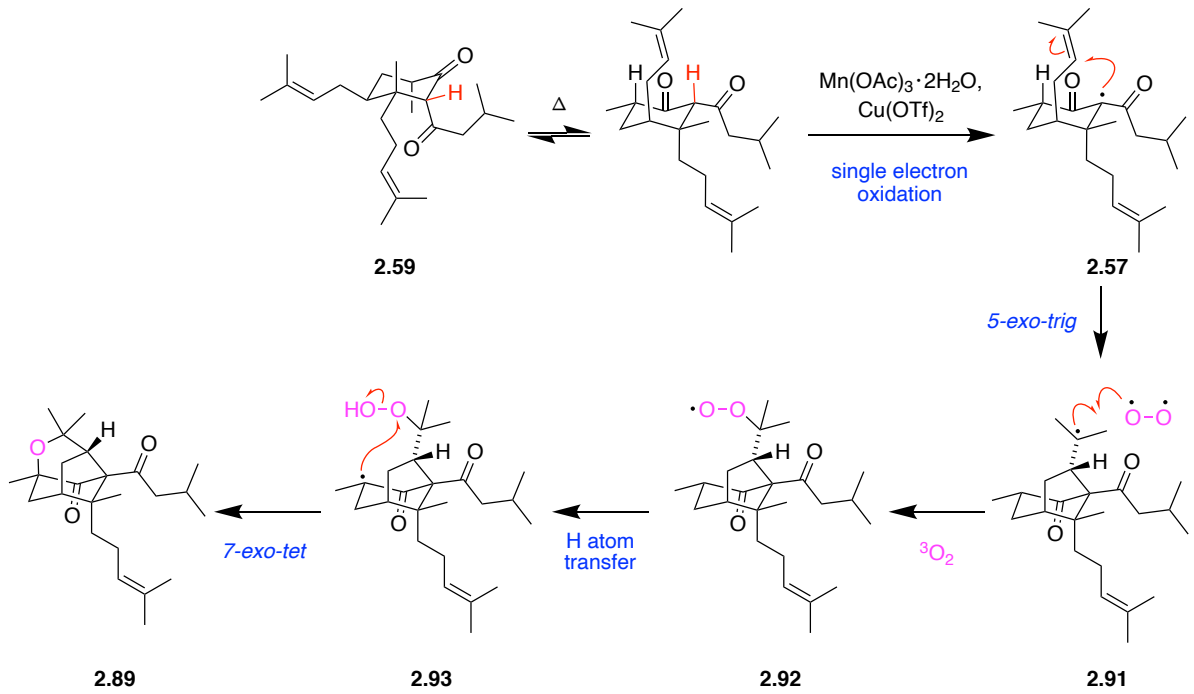


Figure 2.7: X-ray structure of isolated side product 2.89.

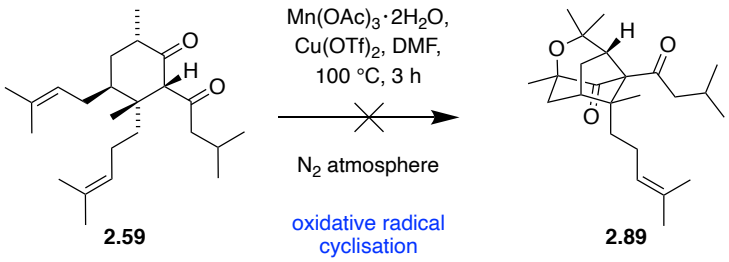
We believe that the first step in the formation of side product **2.89** is a thermal ring flip of **2.59** to its energetically unfavoured ring conformer (Scheme 2.36). In this conformation, the prenyl side chain is in close proximity to the α-position of the diketone unit. One-electron oxidation with $Mn(OAc)_3$ forms stabilised radical species **2.57** which undergoes *5-exo-trig* cyclisation with the prenyl side chain to give tertiary radical intermediate **2.91**. Radical **2.91** subsequently

attacks oxygen from the air to give peroxy radical **2.92**. H-atom transfer and *7-exo-tet* cyclisation of the intermediate **2.93** forms the observed side product **2.89**.



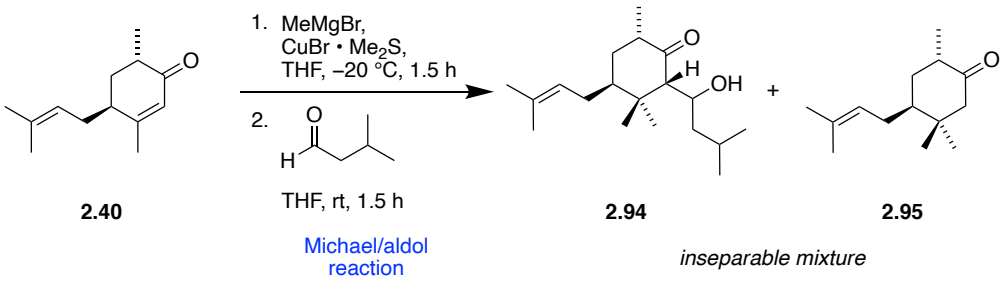
Scheme 2.36: Proposed reaction mechanism of side product formation.

To support our proposed mechanism, this reaction was carried out under the same reaction conditions but under a strict nitrogen atmosphere to ensure the complete absence of oxygen. As expected, after 3 hours at 100 °C, no side product **2.89** was formed (Scheme 2.37).



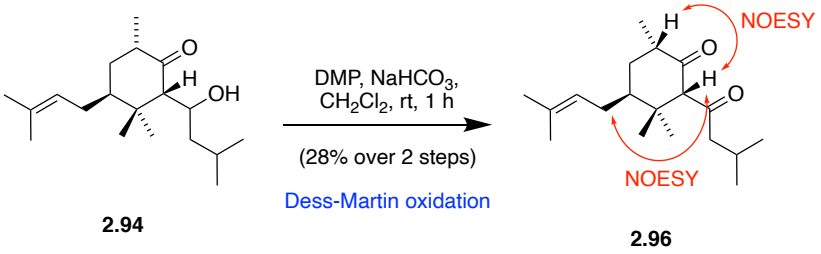
Scheme 2.37: No side product formation when performing the radical oxidative cyclisation in a N_2 atmosphere.

To further support our mechanistic proposal, we designed a model study exchanging the homoprenyl group for a second methyl group. Our proposal was that it would be energetically more favoured for the system to perform the required ring flip with a methyl group in axial position than the homoprenyl group. The Michael addition was performed with methyl magnesium bromide followed by aldol reaction with isovaleraldehyde to give hydroxyketone **2.94** and Michael adduct **2.95** in an inseparable mixture of compounds (Scheme 2.38). We decided to take the mixture through to the next step without trying to purify the hydroxyketone any further.



Scheme 2.38: Michael/aldol reaction of intermediate 2.40.

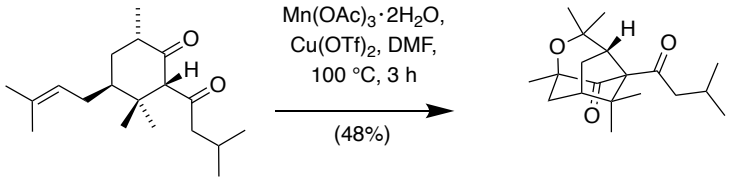
Next, the mixture was oxidised with Dess-Martin periodinane yielding diketone **2.96** in 28% yield over 2 steps (the Michael adduct was not isolated) (Scheme 2.39). NOESY experiments confirmed the relative stereochemistry of the compound to be as assigned.



2.94 **2.96**

Scheme 2.39: Dess-Martin oxidation of hydroxyketone 2.94 to diketone 2.96 (important NOESY correlations shown in red).

With diketone **2.96** in hand, we then attempted the key radical cyclisation using the same reaction conditions as developed on the previous system. **2.96** was heated at 100 °C for 3 h with $Mn(OAc)_3$ and $Cu(OTf)_2$ in DMF affording the desired cyclised product **2.97** in 48% yield (Scheme 2.40). The relative stereochemistry was confirmed by thorough analysis of the acquired spectroscopic data. Unfortunately, all attempts to increase the relatively modest yields around 50% by variation of equivalents, concentration, reaction time and temperature remained unsuccessful.



2.96 oxidative radical cyclisation **2.97**

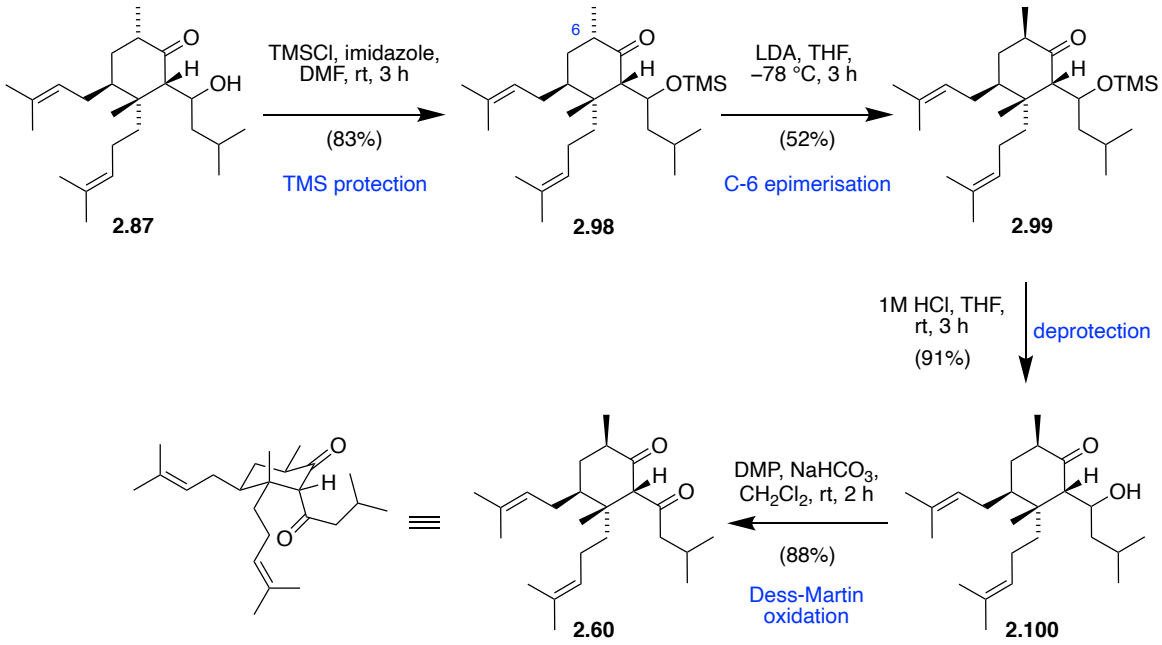
Scheme 2.40: Radical oxidative cyclisation of diketone to side product 2.97.

Although we initially expected a more significant increase in yield for the oxidative radical cyclisation reaction of **2.96** to **2.97** (in comparison to the radical cyclisation of **2.56**/**2.59** to **2.89**), we still believe that the observed improvement supports our mechanistic proposal.

2.2.8 Synthesis of Epimers and Attempted Radical Cyclisation Reaction

During the attempted synthesis of norascyronone A (**2.48**), we realised the importance of the stereochemistry of the C-6 methyl group for the outcome of the oxidative radical cyclisation reaction. Lan, Huang, Yang and co-workers reported that only the unnatural configuration of the C-6 methyl group afforded the desired radical cyclisation product, which could then epimerise into the natural product.[39] Therefore, we were curious if changing the stereochemistry of the C-6 methyl group would provide a different outcome for our oxidative radical cyclisation step.

Hence, the alcohol moiety of **2.87** was converted into its TMS-protected derivative **2.98** with TMS chloride and imidazole in 83% yield (Scheme 2.41). Upon treatment with freshly prepared LDA in dry THF, protected alcohol **2.98** underwent epimerisation of the C-6 methyl group. The epimerised intermediate **2.99** was obtained in a moderate yield of 52%. In the following step, the TMS protecting group was removed with 1M HCl in THF to give epimerised hydroxy ketone **2.100** in 91% yield. Dess-Martin oxidation of hydroxyketone **2.100** to diketone **2.60** yielded the desired C-6 epimer in 88% yield.



Scheme 2.41: Synthetic route from hydroxy ketone 2.87 to epimerised diketone 2.60.

The relative stereochemistry of **2.60** was confirmed by spectroscopic methods. As shown in Figure 2.8, there is a strong NOESY correlation between the singlet of the methyl group at 0.76 ppm and the singlet of the α-proton at 3.57 ppm. Surprisingly, we did not observe a correlation between the α-proton and the doublet of the epimerised C-6 methyl group at 0.96 ppm. However, the additional IR and HRMS data support the assignment of this product as a stereoisomer of **2.59**.

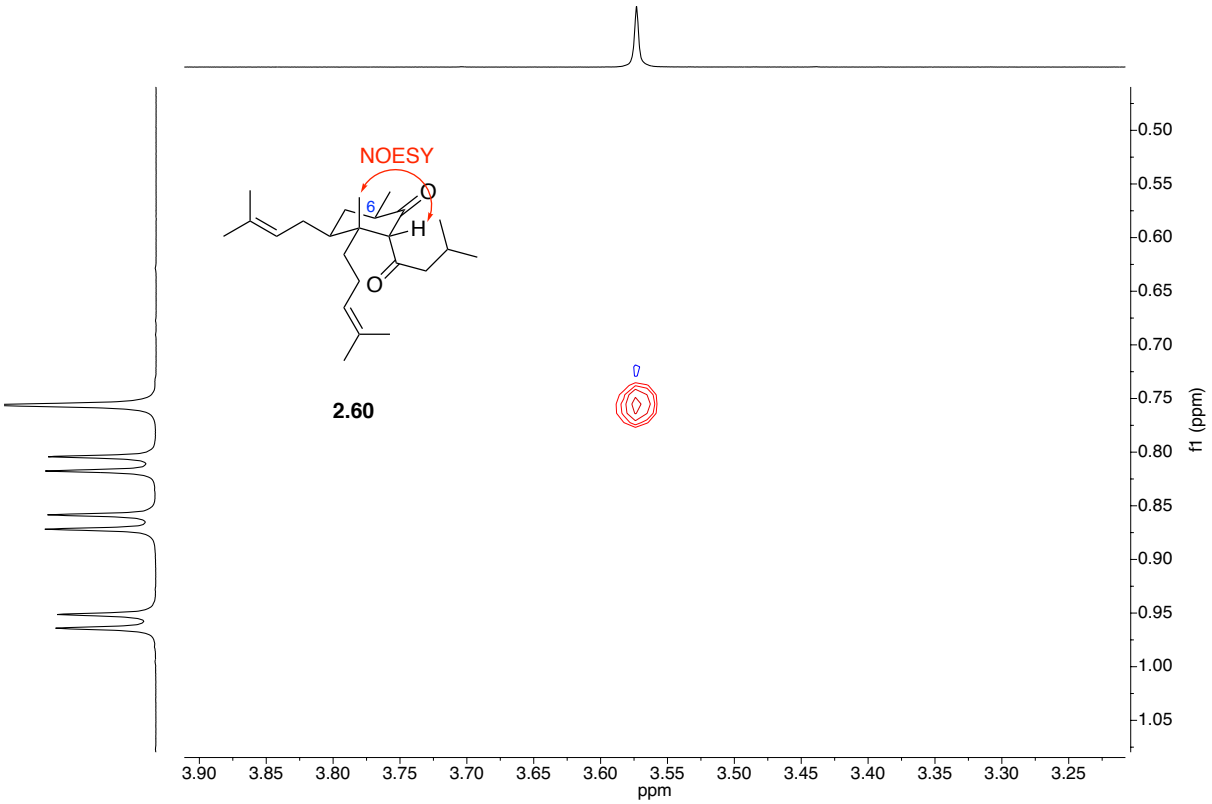
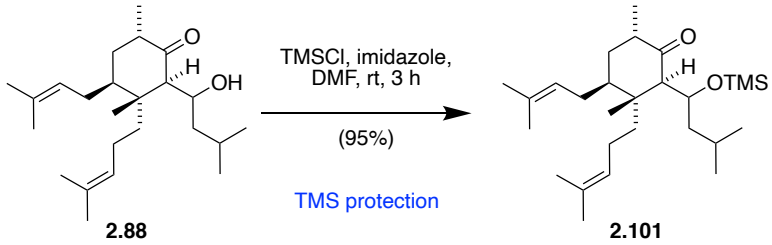


Figure 2.8: NOESY spectra of diastereomer 2.60.

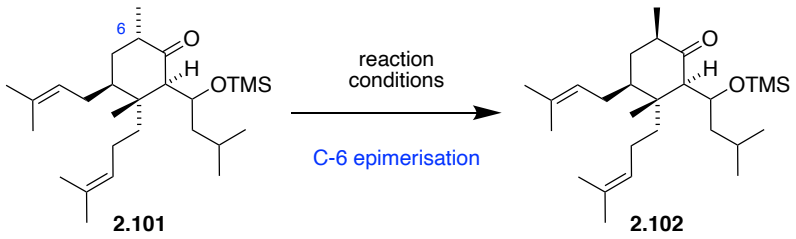
Analogously, the minor diastereomer **2.88** was TMS-protected with TMS chloride and imidazole to give protected hydroxyketone **2.101** in 95% yield (Scheme 2.42).



Scheme 2.42: TMS protection of hydroxyketone 2.88 in 95% yield.

The TMS-protected intermediate **2.101** was then subjected to the same epimerisation conditions as shown in Scheme 2.41 (Table 2.4, entry 1).

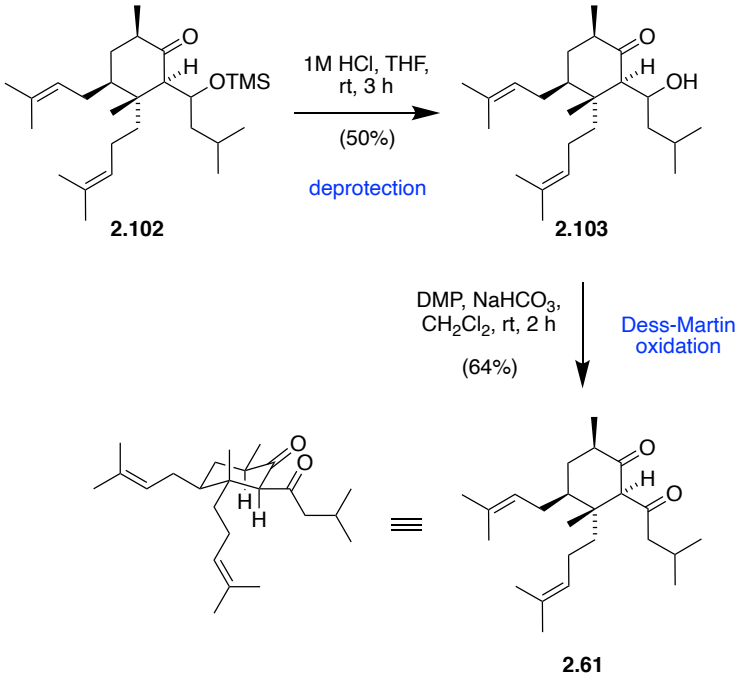
Table 2.4: Screening of reaction conditions for epimerisation of 2.101.



2.101 2.102

Entry	Reagent	Conditions	Yield
1	LDA	dry THF, –78 °C, 3 h *then* rt, 45 min	2:1 ratio of product to s.m.
2	DBU	toluene, reflux, o.n.	5:1 ratio of product to s.m. (62% yield)

Upon work-up and purification by flash column chromatography, the ^{1}H NMR showed an inseparable 2:1 mixture of product **2.102** and starting material **2.101**, with identical R_f values (Table 2.4, entry 1). When heating protected alcohol **2.101** at reflux in toluene with DBU as a base we were able to improve this ratio to a 5:1 mixture of **2.102** to **2.101** in 62% yield. Further attempted purification resulted in no improvement in product purity; therefore, we decided to move forward with the synthesis with the starting material present as a minor impurity. TMS-protected alcohol **2.102** was deprotected using 1M HCl in THF to give epimerised hydroxyketone **2.103** in 50% yield (Scheme 2.43). Hydroxyketone **2.103** was then oxidised with Dess-Martin periodinane to desired diketone **2.61** in 64% yield.



Scheme 2.43: TMS deprotection and Dess-Martin oxidation of intermediate 2.102 to desired diketone 2.61.

Thorough analysis of the acquired spectroscopic data confirmed the relative stereochemistry of **2.61**. There is a strong NOESY correlation between the α-proton at 3.67 ppm and the epimerised C-6 proton at 2.41 ppm which supports our assignment (Figure 2.9).

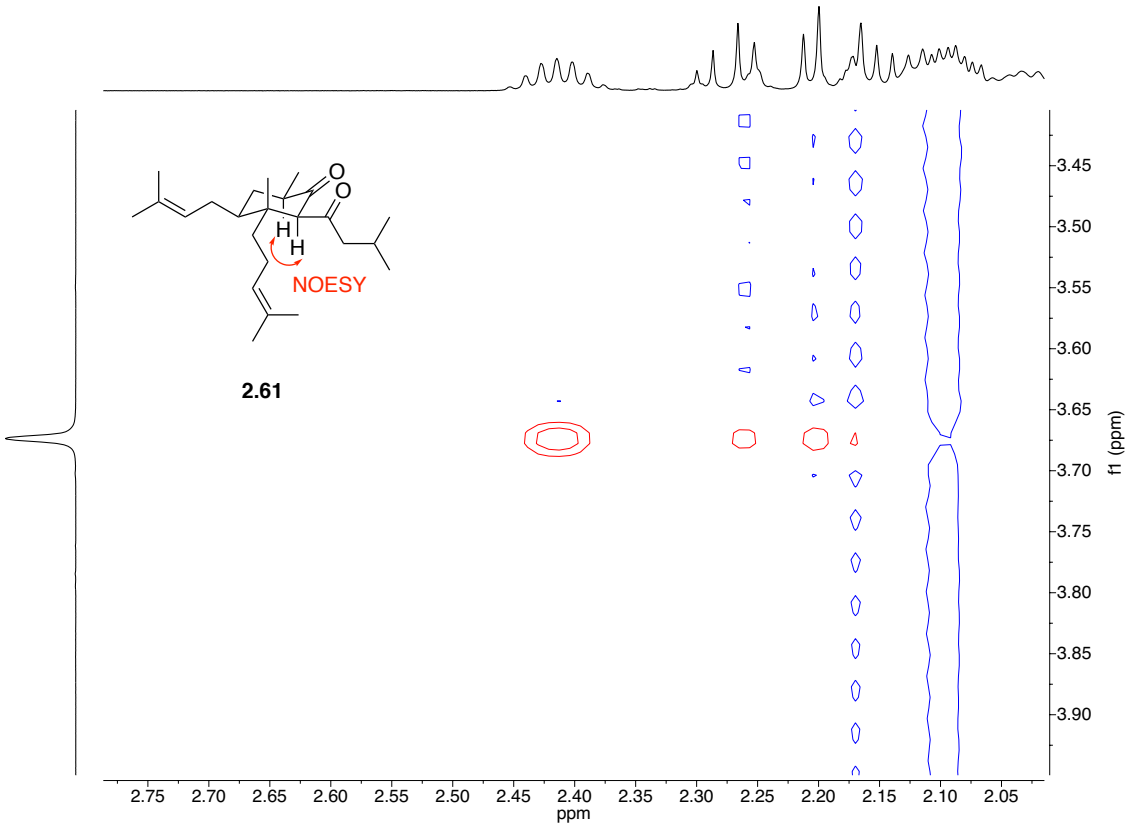
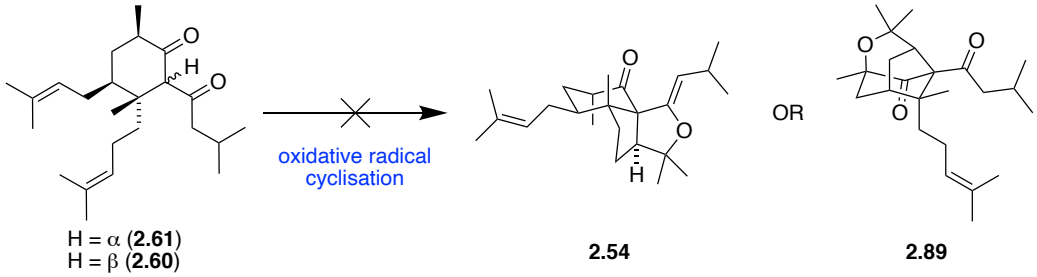


Figure 2.9: NOESY spectra of diketone 2.61.

Having isolated the two diketones **2.60** and **2.61**, we focussed our attention on the oxidative radical cyclisation reaction using $Mn(OAc)_3$ and $Cu(OTf)_2$ (Table 2.5). We were curious to see if any of the two epimerised diketones **2.60** and **2.61** would form either the natural product rxl-62 (**2.54**) or the previously isolated side product **2.89**.

Table 2.5: Screening of reaction conditions for oxidative radical cyclisation of diastereomers 2.60 and 2.61 to form either natural product 2.54 or previously isolated side product 2.89.



H = α (**2.61**)
H = β (**2.60**)

2.54 **2.89**

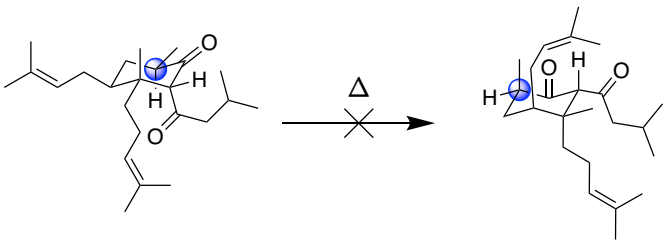
Entry	Isomer	Oxidant/co-oxidant	Conditions	Yield*
1	**2.61**	$Mn(OAc)_3$, $Cu(OTf)_2$	DMF, 100 °C, 4 h	r.s.m. (32%)
2	**2.60**	$Mn(OAc)_3$, $Cu(OTf)_2$	DMF, 100 °C, 5 h	no reaction#
3	**2.60**	$Mn(OAc)_3$, $Cu(OTf)_2$	DMF, 100 °C, o.n.	decomposition#
4	**2.60**	$Mn(OAc)_3$, $Cu(OAc)_2$	AcOH, 60 °C, 3 days	r.s.m. (13%)

*All percentage yields are isolated yields after purification by flash column chromatography on silica gel. #Indicated by TLC analysis.

Hence, we subjected isomer **2.61** to the best conditions identified for the diastereomers **2.56** and **2.59** (entry 1). Heating the starting material to 100 °C in DMF for 4 h did not lead to any product formation. After purification, we were able to recover 32% starting material. The same conditions were performed on the other diastereomer **2.60** (entry 2), which again resulted in no reaction after heating for 5 h. Continued heating at 100 °C overnight led to full decomposition of the starting material (entry 3). In entry 4, compound **2.60** was heated with $Mn(OAc)_3$ and $Cu(OAc)_2$ in acetic acid at 60 °C for 3 days, which resulted in 13% recovered starting material but no formation of any other identifiable compound.

We concluded that the stereochemistry of the C-6 methyl group has an important role in the formation of side product **2.89** as both diastereomers with the methyl group in equatorial position do not show any reactivity under the attempted oxidation conditions. This observation

might be due to this chair conformation being less prone to performing a thermal ring flip, compared to the alternative axial conformation, necessary for formation of side product **2.89** (Scheme 2.44).



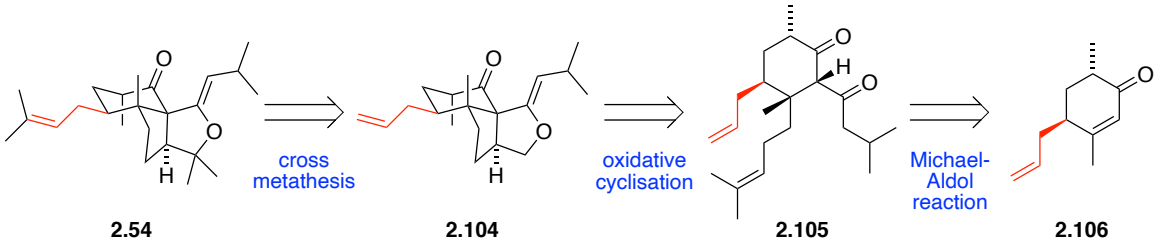
Scheme 2.44: Ring flip seems to be unfavoured for diastereomers with C-6 methyl group in equatorial position.

2.2.9 Model System Studies: Allyl System

As the precursors **2.56** and **2.59** showed an undesired reactivity for the first cyclisation step by reacting with the prenyl side chain instead of the homoprenyl group, we decided to investigate an alternative synthetic route. By exchanging the prenyl group for an allyl group we hoped to bypass this reactivity problem as the formation of a primary radical would be less favoured than a tertiary radical.

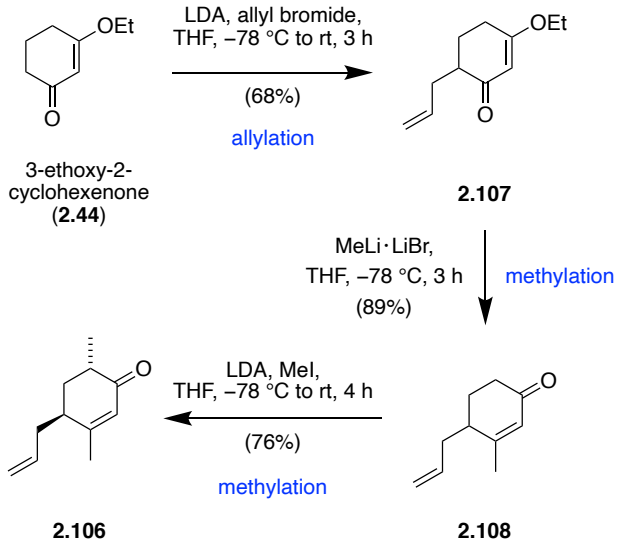
As shown in Scheme 2.45, the final step of this synthesis would require cross metathesis to install the prenyl side chain of natural product rxl-62 (**2.54**). Oxidative radical cyclisation with manganese acetate and copper triflate is predicted to form the desired 6/5/5 ring system of natural product analogue **2.104** from **2.105**. Diketone **2.105** could be synthesised by Dess-Martin oxidation and Michael/aldol reaction of unsaturated ketone **2.106** following our

established synthetic route. Precursor **2.106** can be easily prepared on a multigram scale from 3-ethoxy-2-cyclohexenone (**2.44**).



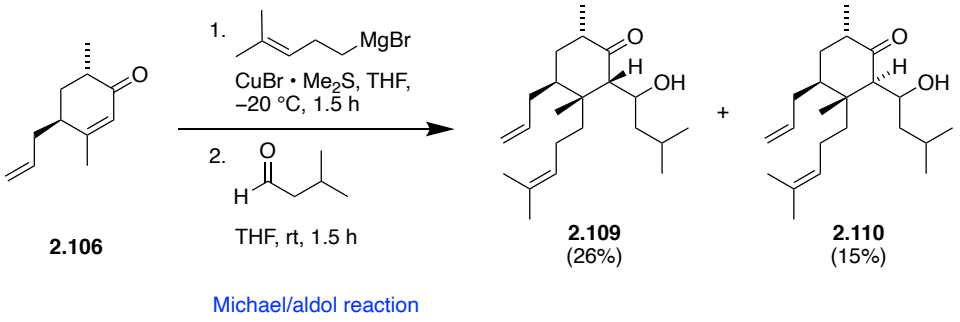
Scheme 2.45: Retrosynthetic analysis of allyl model system.

Our forward synthesis started with allylation of 3-ethoxy-2-cyclohexenone (**2.44**) which gave **2.107** in 68% yield, followed by nucleophilic addition of methyl lithium under elimination of water to afford unsaturated ketone **2.108** in 89% yield. Ketone **2.108** was then methylated with iodomethane to afford Michael/aldol precursor **2.106** in 76% yield (Scheme 2.46).



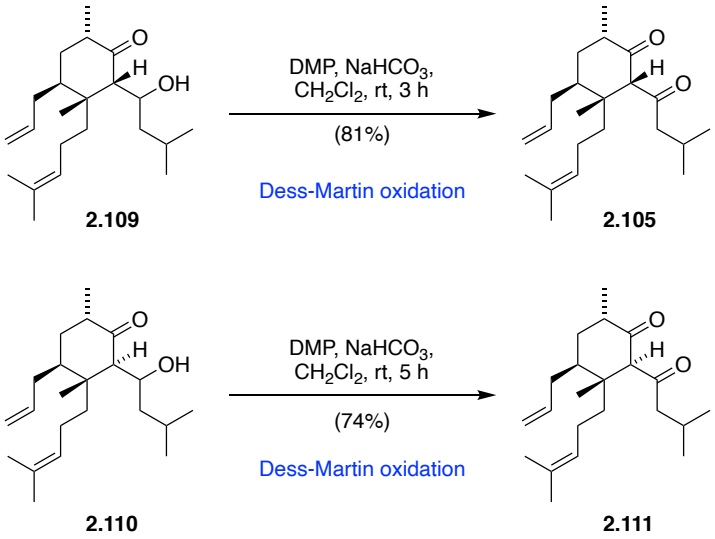
Scheme 2.46: Synthesis of Michael/aldol precursor 2.106.

Precursor **2.106** was then subjected to our previously optimised conditions for the Michael/aldol reaction. Conjugate addition of a cuprate species made from homoprenyl magnesium bromide and copper(I) bromide to unsaturated ketone **2.106** followed by aldol reaction of enolate intermediate with isovaleraldehyde afforded diastereomeric hydroxyketones **2.109** and **2.110** in a 1.7 to 1 ratio and 41% overall yield (Scheme 2.47).



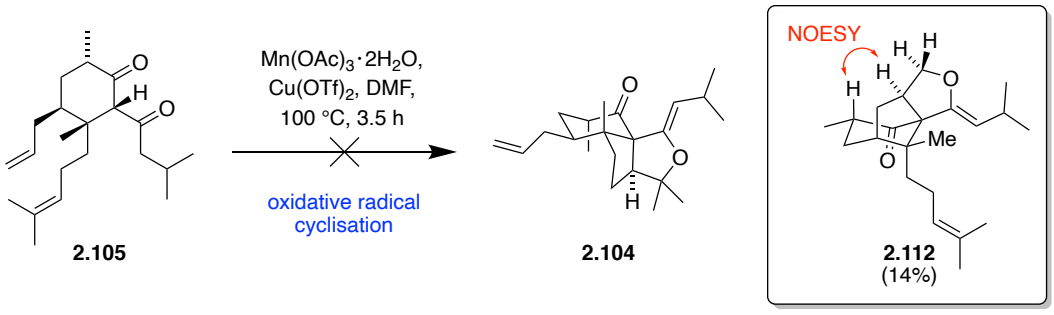
Scheme 2.47: Michael addition and subsequent aldol reaction of model system precursor 2.106 to give hydroxyketones 2.109 and 2.110.

Oxidation of hydroxyketone **2.109** and **2.110** with Dess-Martin periodinane gave the corresponding diketones **2.105** and **2.111** in 81% and 74% yield, respectively (Scheme 2.48).



Scheme 2.48: Oxidation of hydroxyketones 2.109 and 2.110 to the corresponding diketones 2.105 and 2.111.

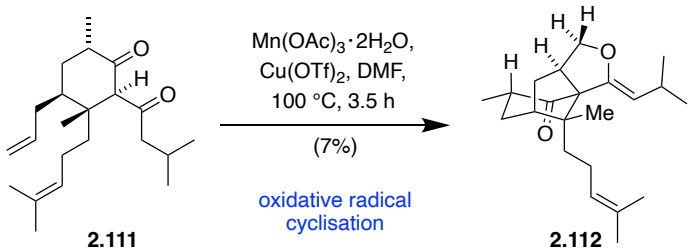
Oxidative radical cyclisation of both diketones was then investigated, for which we were optimistic that cyclisation would occur on the homoprenyl side chain instead of the allyl group. This would then form a tertiary radical intermediate that could cyclise again with the ketone moiety of the isovaleraldehyde side group to afford natural product analogue **2.104**. Upon heating substrate **2.105** with $Mn(OAc)_3$ and $Cu(OTf)_2$ in DMF at 100 °C for 3.5 h, we observed formation of a new compound (Scheme 2.49).



Scheme 2.49:Radical oxidative cyclisation on 2.105 afforded cyclised side product 2.112 in 14% yield (significant NOESY correlations shown in red).

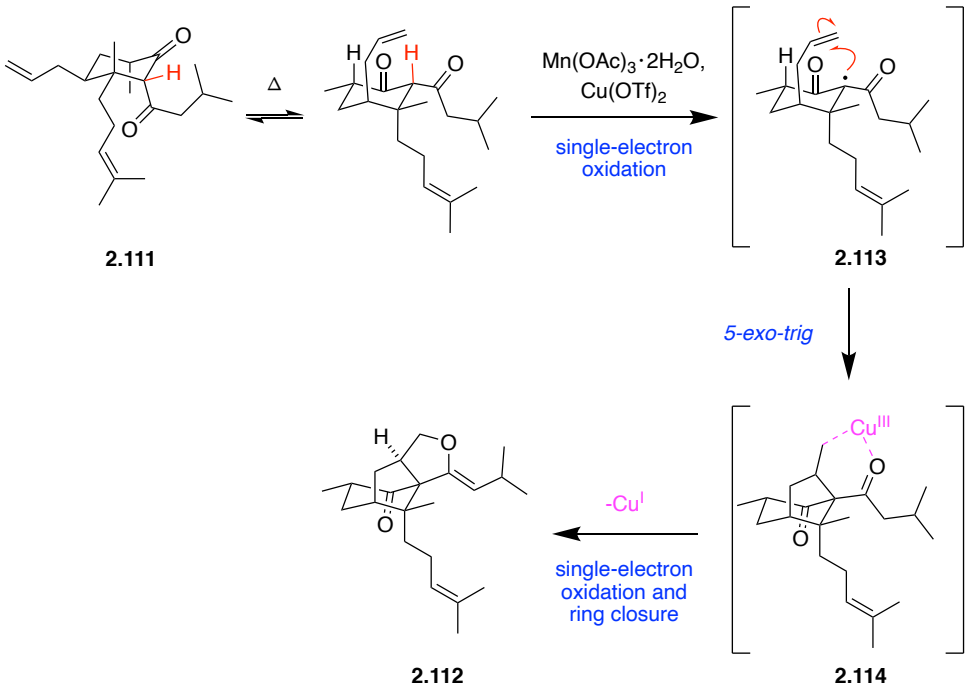
Unfortunately, analysis of the acquired spectroscopic data suggested that the desired natural product analogue **2.104** was not formed under the chosen reaction conditions. It was immediately obvious that the signals of the homoprenyl group were still present while the signals of the allyl group had disappeared. Excitingly, the experimental data also indicated that the desired dihydrofuran moiety of natural product **2.54** was formed. Thorough analysis of the data led us to the structural assignment of **2.112**.

When we repeated the same reaction conditions on the other diastereomer **2.111**, we isolated the same side product **2.112** in 7% yield (Scheme 2.50).



Scheme 2.50: Formation of the same side product 2.112 with diastereomer 2.111 in 7% yield.

As shown in Scheme 2.51, the proposed mechanism of the formation of side product **2.112** starts with a thermal ring flip of **2.111** to its more energetic ring conformer. Intermediate **2.111** is then oxidised with $Mn(OAc)_3$ to radical species **2.113** which undergoes *5-exo-trig* cyclisation with the allyl sidechain forming primary radical **2.114**. We believe that the primary radical is stabilised by copper in the 6-membered transition state shown for intermediate **2.114**.[40] Another single-electron oxidation gives a primary carbocation, which can then be attacked by oxygen to give the 5-membered ring moiety of **2.112**.

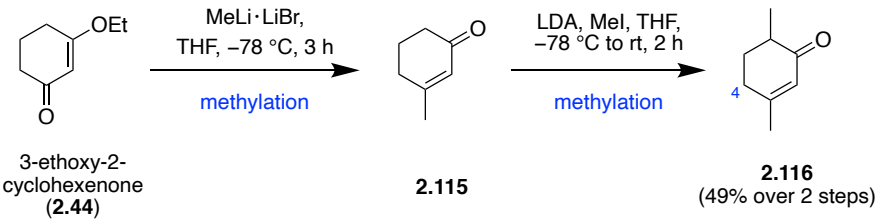


Scheme 2.51: Our proposed mechanism for formation of side product 2.112.

In conclusion, this model system has shown an unexpected reactivity under oxidative radical cyclisation conditions. The first radical species **2.113** preferentially attacks the allyl side group, creating a primary radical species **2.114** instead of cyclising with the homoprenyl side chain. Hence, we aimed to investigate the reactivity of this system when no side chain was present.

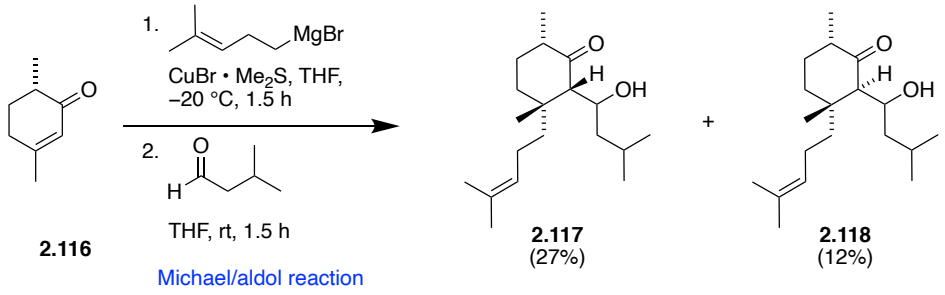
2.2.10 Model System Studies: No side chain

As a final model study, we investigated the reactivity of the system without any side chain attached to the C-4 position. For that, 3-ethoxy-2-cyclohexenone (**2.44**) was methylated with methyl lithium to give ketone **2.115**. Ketone **2.115** was taken on to the next step without the need for purification. Methylation with iodomethane afforded desired unsaturated ketone **2.116** in 49% yield over two steps (Scheme 2.52).



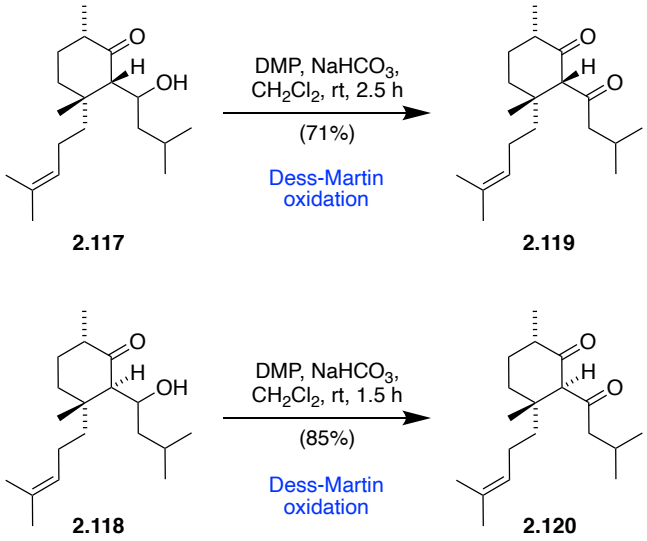
Scheme 2.52: Synthesis of Michael/aldol precursor 2.116 starting from 3-ethoxy-2-cyclohexenone (2.44) in 49% yield over 2 steps.

Unsaturated ketone **2.116** was then subjected to the same Michael/aldol conditions previously optimised to afford hydroxyketones **2.117** and **2.118** in a 2:1 ratio in 39% yield (Scheme 2.53).



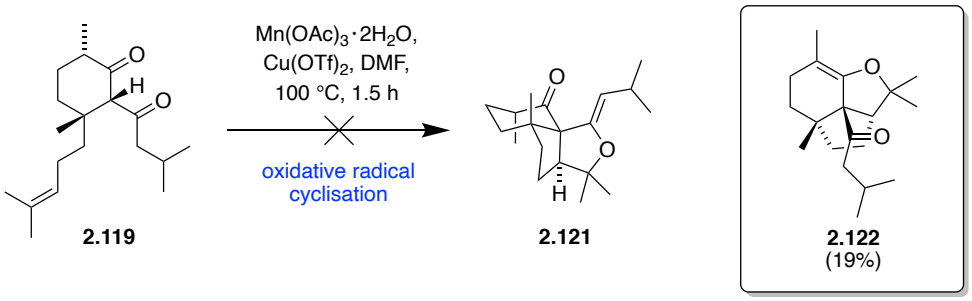
Scheme 2.53: 1,4-addition and subsequent aldol reaction of precursor 2.116 to give two diastereomers 2.117 and 2.118 in 27% and 12% yield, respectively.

Both diastereomers **2.117** and **2.118** were then oxidised with Dess-Martin periodinane to the corresponding diketones **2.119** and **2.120** in 71% and 85% yield, respectively (Scheme 2.54).



Scheme 2.54: Dess-Martin oxidation of diastereomers 2.117 and 2.118 to diketones 2.119 and 2.120 in 71% and 85% yield, respectively.

Next, **2.119** was subjected to the radical oxidative cyclisation reaction conditions with $Mn(OAc)_3$ and $Cu(OTf)_2$ in DMF at 100 °C (Scheme 2.55). After 1.5 hours, TLC analysis showed the formation of a new compound which was isolated and purified by flash column chromatography.

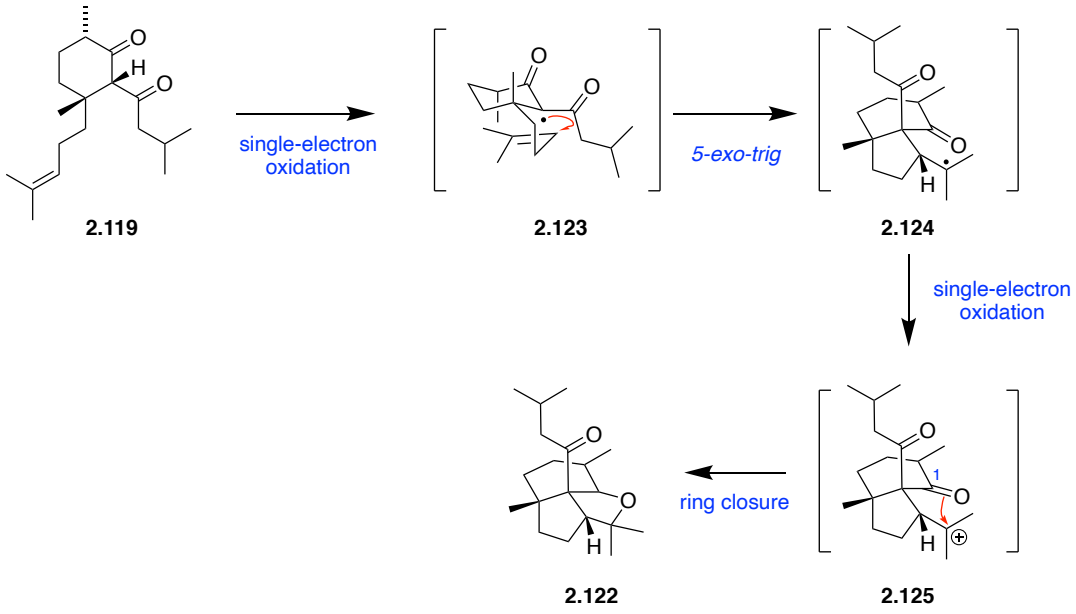


Scheme 2.55: Oxidative radical cyclisation of diketone 2.119 with $Mn(OAc)_3$ and $Cu(OTf)_2$ to form side product 2.122 instead of desired natural product analogue 2.121.

Unfortunately, analysis of obtained spectroscopic data for this product indicated that instead of the formation of desired cyclised compound **2.121** another cyclised side product **2.122** was

obtained. The 6/5/5 ring system structure of cyclised product **2.122** is closely related to the yezo'otogirins. Our group has previously utilised a similar model system while working on the total synthesis of yezo'otogirin A. Comparison of the ^{1}H NMR spectra of the model system to our new synthesised compound **2.122** showed significant similarities which confirmed our structural assignment.

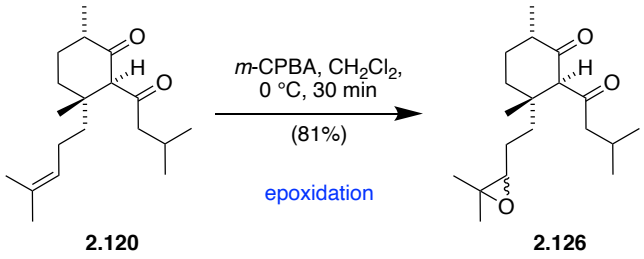
As shown in Scheme 2.56, we believe that, after single electron oxidation, the radical species **2.123** reacts with the homoprenyl group in a *5-exo-trig* cyclisation. This first cyclisation step is the desired formation of natural product analogue **2.121**. However, the tertiary radical species **2.124** undergoes a second single electron oxidation to the tertiary carbocation species **2.125,** which is then attacked by the C-1 carbonyl group instead of the isovaleraldehyde carbonyl.



Scheme 2.56: Proposed mechanism for side product formation.

As a last attempt, we were curious whether it was possible to use the designed model system to perform the desired cyclisations stepwise rather than in one cyclisation cascade. For that, we

decided to epoxidise the homoprenyl side chain (Scheme 2.57). Diketone **2.120** was treated with *m*-CPBA in CH_2Cl_2 which gave epoxide **2.126** after 30 min in 81% yield.

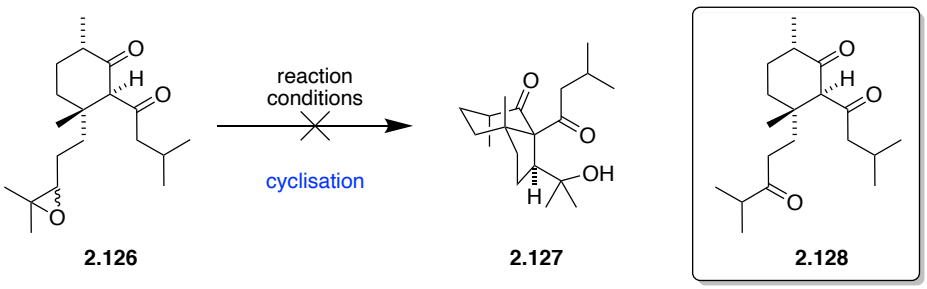


2.120 **2.126**

Scheme 2.57: *m*-CPBA epoxidation of alkene to 2.126.

Epoxide **2.126** was then subjected to cyclisation conditions as outlined in Table 2.6.

Table 2.6: Attempted cyclisation of 2.126 to 2.127.



2.126 **2.127** **2.128**

Entry	Base	Conditions	Yield*
1	K_2CO_3	acetone, rt, 5 h	no reaction
2	Cs_2CO_3	THF, rt, 2 h	slow decomposition
3	KOH	MeOH, rt, 2 h	decomposition
4	LDA (2 M)	THF, –78 °C, 2 h	decomposition
5	$BF_3 \cdot OEt_2$	CH_2Cl_2, 0 °C, 35 min	**2.128** (65%)
6	$TiCl_4$	THF, 0 °C, 1 h	decomposition

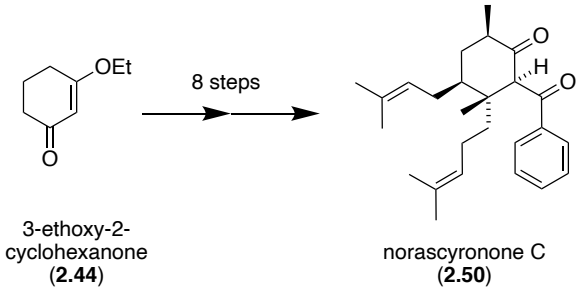
*All percentage yields are isolated yields after purification by flash column chromatography on silica gel. All other outcomes were indicated by TLC analysis.

In entry 1 to 4, we attempted the desired cyclisation under basic conditions. Epoxide **2.126** was treated with potassium carbonate in acetone which did not lead to any reaction after 5 h at room temperature (entry 1). Treatment with caesium carbonate in THF led to slow decomposition of the starting material (entry 2). Subjecting the epoxide **2.126** to stronger bases such as potassium hydroxide (entry 3) or LDA (entry 4) led to quick degradation of the starting material. When we treated epoxide **2.126** with boron trifluoride diethyl etherate, we isolated triketone **2.128** in 65% yield instead of the desired cyclised product **2.127** (entry 5). Analysis of the obtained spectroscopic data showed a new carbonyl signal at 214.3 ppm. Lastly, we attempted the cyclisation with $TiCl_4$ which led to decomposition of epoxide **2.126** (entry 6).

2.3 Conclusion and Future Directions

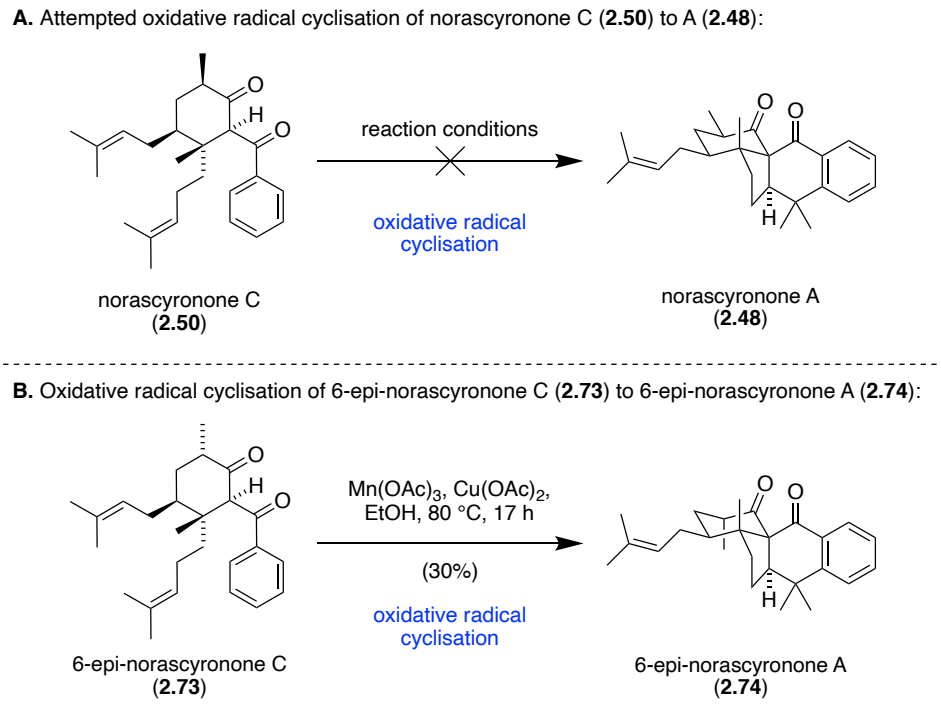
In summary, we have been able to gain significant insight into the reactivity of various PPAP diketones in regard to oxidative radical cyclisation cascades. Several radical oxidation conditions led to new and previously unreported compounds.

We successfully synthesised the natural product norascyronone C (**2.50**) in 8 steps from 3-ethoxy-2-cyclohexanone (**2.44**) (Scheme 2.58).



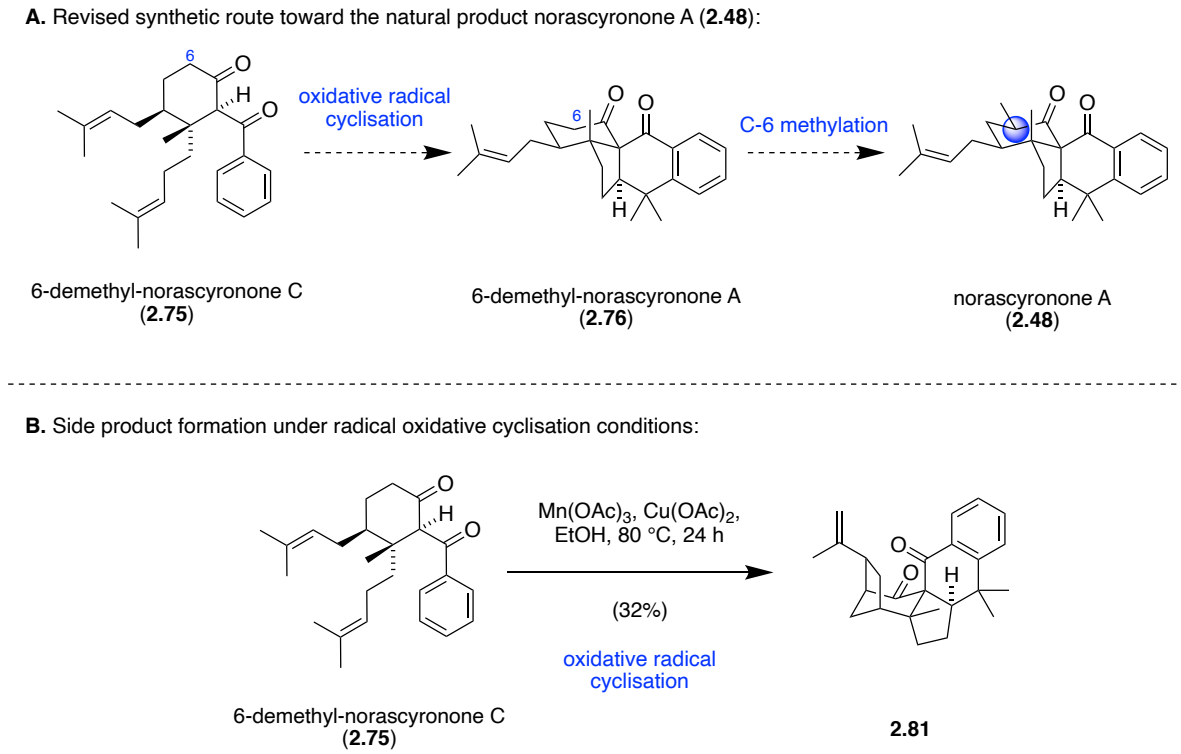
Scheme 2.58: 8-step synthesis of natural product norascyronone C (2.50) from 3-ethoxy-2-cyclohexenone (2.44).

We then went on to investigate the radical cyclisation of norascyronone C (**2.50**) to norascyronone A (**2.48**) (Scheme 2.59, **A**); however, we discovered that the desired natural product was not formed under any of the attempted reaction conditions. When performing the cascade with the C-6 epimer **2.73**, we successfully synthesised 6-epi-norascyronone A (**2.74**) in 30% yield (Scheme 2.59, **B**). We concluded that the position of the methyl group at the C-6 position must have a fundamental effect on the formation of the tetracyclic core structure.



Scheme 2.59: A. Attempted oxidative radical cyclisation of norascyronone C (2.50) to A (2.48); B. Oxidative radical cyclisation of 6-epi-norascryonone C (2.73) to 6-epi-norascyronone A (2.74) in 30% yield.

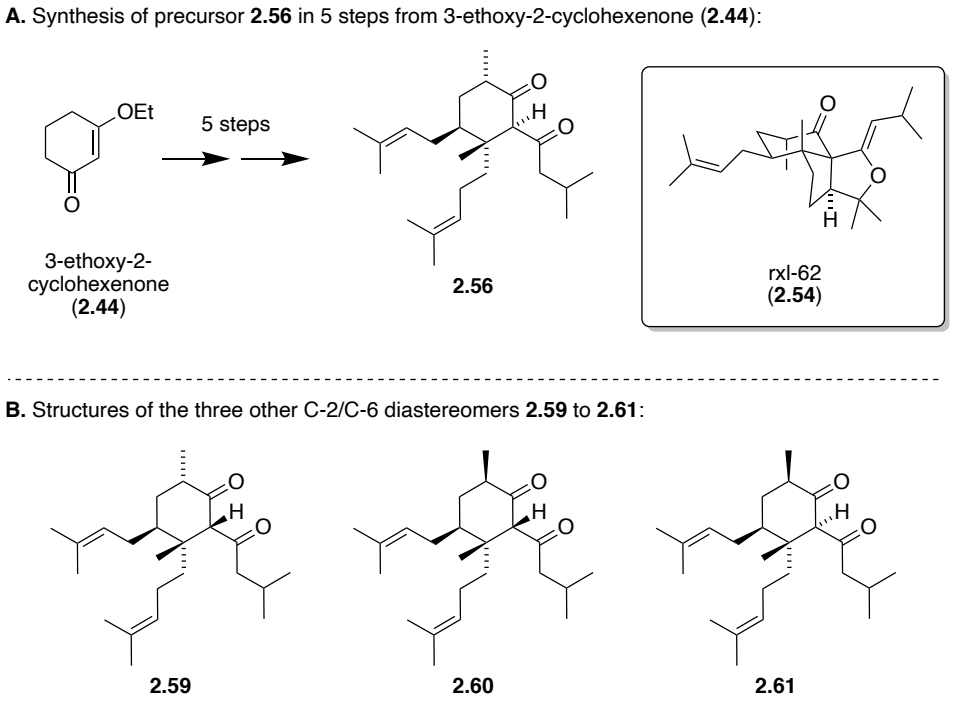
We decided to change the order of steps in the sequence (Scheme 2.60, **A**). We proposed that we could perform the oxidative radical cyclisation on 6-demethyl-norascyronone C (**2.75**) and introduce the methyl group in the very last step of the synthesis. However, the key radical cascade led to the isolation of a novel side product **2.81** with a unique scaffold (Scheme 2.60, **B**).



Scheme 2.60: A. Revised synthetic route toward natural product norascyronone A (2.48); B. Formation of side product 2.81 through radical oxidative cyclisation.

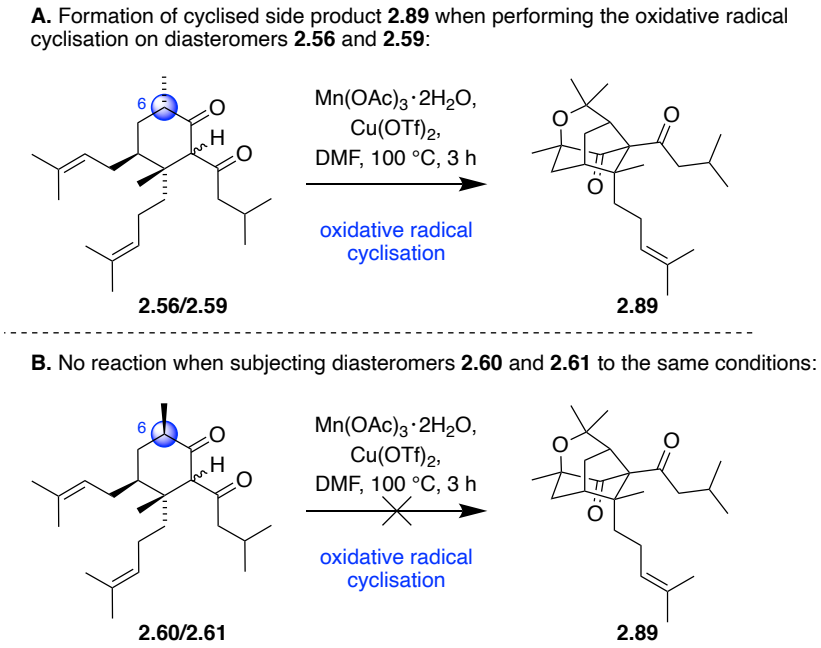
As future directions, it would be interesting to investigate how the discovered reactivity of norascyronone C (**2.50**) and 6-epi-norascyronone C (**2.73**) may lead to a revision of the proposed biosynthesis of norascyronone A (**2.48**) and B (**2.49**). It would be desirable to address the question if norascyronone C (**2.50**) is a direct precursor to norascyronone A (**2.48**) and B (**2.49**) and if so, how Nature circumvents the observed reactivity problem.

From the norascyronone project, we moved on to a new unpublished natural product rxl-62 (**2.54**) which is structurally closely related to the norascyronone family. We synthesised an essential precursor **2.56**, which we propose to be an undiscovered natural product, in 5 steps from 3-ethoxy-2-cyclohexanone (**2.44**) (Scheme 2.61, **A**). Additionally, we synthesised the other three possible C-2/C-6 diastereomers **2.59** to **2.61** (Scheme 2.61, **B**).



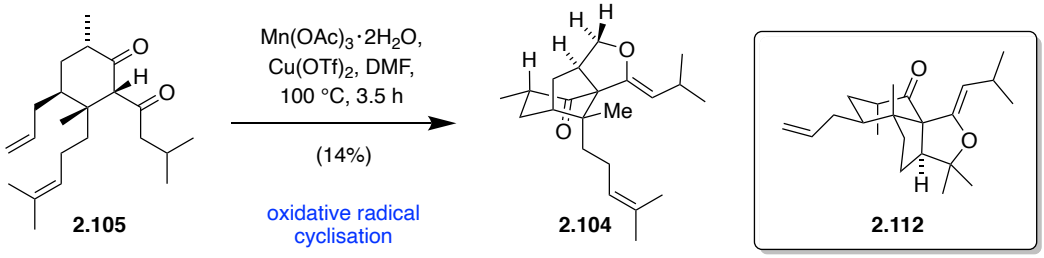
Scheme 2.61: A. Synthesis of diketone 2.56 in 5 steps from 3-ethoxy-2-cyclohexenone (2.44); B. Structures of remaining diastereomers 2.59 to 2.61.

With all four diastereomers in hand, we attempted the oxidative radical cyclisation hoping it would form the natural product rxl-62 (**2.54**) (Scheme 2.62). Surprisingly, subjecting diastereomers **2.56** and **2.59** to our established $Mn(OAc)_3/Cu(OTf)_2$ conditions formed a unknown side product **2.89** with an interesting scaffold (Scheme 2.62, **A.**). When using the same conditions on the diastereomers **2.60** and **2.61**, no reaction occurred which again showed us how important the orientation of the C-6 methyl group is for the outcome of the experiment (Scheme 2.62, **B.**).



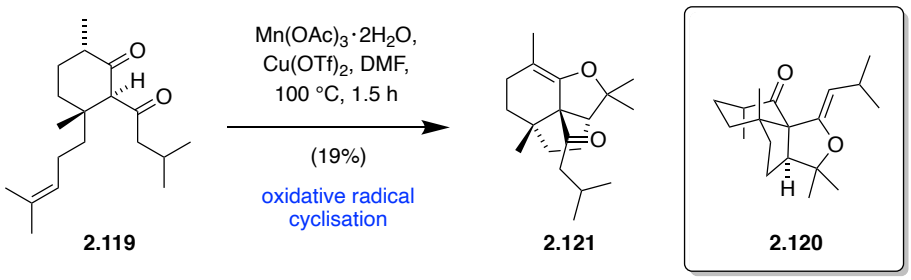
Scheme 2.62: A. Formation of side product 2.89 when subjecting diastereomers 2.56 and 2.59 to oxidative radical cyclisation conditions. B. No reaction when performing the same conditions on diastereomers 2.60 and 2.61.

When we exchanged the prenyl side chain for an allyl group, another side product **2.112** was formed under oxidative radical cyclisation conditions (Scheme 2.63). Surprisingly, the side product **2.112** exhibits the same dihydrofuran moiety as the natural product analogue **2.104**. The same side product was formed with the C-2 epimer of **2.105** in 7% yield (not shown).



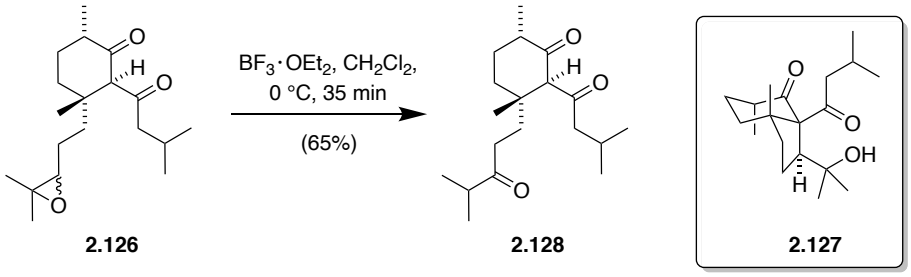
Scheme 2.63: Formation of side product 2.112 under oxidative radical cyclisation conditions.

Lastly, we decided to omit the side chain and perform the cyclisation on this model system (Scheme 2.64). When we performed the key cascade on diketone 2.119, cyclised side product **2.121** was isolated in 19% yield. The scaffold of **2.121** shows striking similarity to the yezo'otogirin natural product family.



Scheme 2.64: Formation of side product 2.121 when subjecting diketone 2.119 to oxidative radical cyclisation conditions.

As a final attempt, we tried to perform a stepwise cyclisation of epoxide **2.126** with Brønsted bases and Lewis acids. Unfortunately, we were not able to form the desired cyclised compound **2.127**. However, we isolated triketone **2.128** in 65% yield when using Lewis acid $BF_3 \cdot OEt_2$ (Scheme 2.65).



Scheme 2.65: Treatment of epoxide 2.126 with Lewis acid $BF_3 \cdot OEt_2$ formed triketone 2.128 in 65% yield.

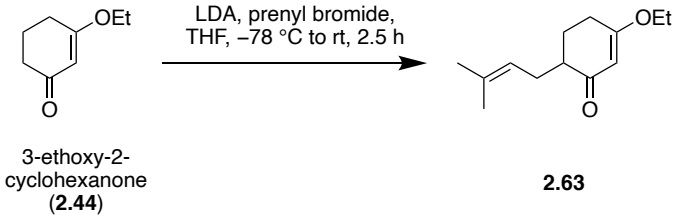
Further investigations into the oxidative cyclisation are currently underway. As all side product formations commenced with a thermal ring flip to an energetically higher conformation, it might be worthwhile to investigate more radical cyclisation conditions at lower temperatures.

2.4 Supporting Information

2.4.1 General Methods

All chemicals used were purchased from commercial suppliers and used as received. Unless otherwise stated, all reactions were performed under an inert atmosphere of N_2. All organic extracts were dried over anhydrous magnesium sulfate. Thin layer chromatography was performed using aluminium sheets coated with silica gel F_{254}. Visualisation was aided by viewing under a UV lamp and staining with ceric ammonium molybdate followed by heating. All R_f values were measured to the nearest 0.05. Flash column chromatography was performed using 40-63 micron grade silica gel. Melting points were recorded on a Reichart Thermovar Kofler microscope apparatus and are uncorrected. Infrared spectra were recorded using an FT-IR spectrometer as the neat compounds. High field NMR spectra were recorded using both a 500 MHz spectrometer (^{1}H at 500 MHz, ^{13}C at 125 MHz) and 600 MHz spectrometer (^{1}H at 600 MHz, ^{13}C at 150 MHz) as indicated. The solvent used for spectra was $CDCl_3$ unless otherwise specified. ^{1}H chemical shifts are reported in ppm on the δ-scale relative to TMS (δ 0.0) and ^{13}C NMR are reported in ppm relative to $CDCl_3$ (δ 77.16). Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (quin) quintet, (sext) sextet, (hept) heptet and (m) multiplet. All *J*-values were rounded to the nearest 0.1 Hz. ESI high resolution mass spectra were recorded on an ESI-TOF mass spectrometer.

2.4.2 Experimental Procedures



3-ethoxy-2-cyclohexanone (**2.44**)

2.63

To a solution of diisopropylamine (12.0 mL, 85.6 mmol, 1.2 eq.) in dry THF (50 mL) at 0 °C was added *n*-BuLi (2.5 M in hexanes, 34.2 mL, 85.6 mmol, 1.2 eq.). The solution was stirred at 0 °C for 30 min before being cooled to −78 °C. 3-Ethoxy-2-cyclohexanone (**2.44**, 10.0 g, 71.3 mmol, 1 eq.) dissolved in dry THF (20 mL) was added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 50 min. Prenyl bromide (9.0 mL, 79.9 mmol, 1.12 eq.) was added dropwise to the solution. The reaction mixture was stirred at −78 °C for one hour, then at 0 °C for 30 min. The reaction mixture was carefully quenched with saturated aqueous NH_4Cl solution (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 80 mL). The combined organic layers were washed with H_2O (100 mL) and saturated aqueous NaCl solution (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Crude **2.63** was used in the next step without the need for further purification.

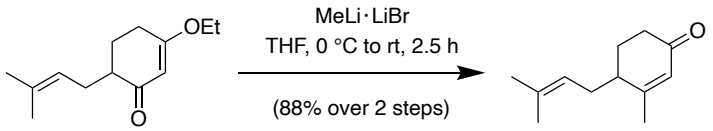
Partial Data for **2.63**:

R_f: 0.20 [PE:Et_2O 2:1]

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.33 (s, 1H), 5.12 (ddt, J = 9.4, 6.6, 1.3 Hz, 1H), 3.89 (qd, J = 7.1, 3.0 Hz, 2H), 2.59 – 2.49 (m, 1H), 2.44 – 2.38 (m, 2H), 2.25 – 2.17 (m, 1H), 2.16 – 2.00 (m, 2H), 1.71 (s, 3H), 1.69 – 1.65 (m, 1H), 1.62 (s, 3H), 1.36 (t, J = 7.0 Hz, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 201.3, 176.9, 133.3, 122.0, 102.4, 64.2, 45.6, 28.2, 28.1, 25.9, 25.8, 17.8, 14.2 ppm.

The analytical data match those previously described in the literature.[31]



2.63 **2.39**

To a solution of crude ketone **2.63** (71.3 mmol, 1 eq.) in dry THF (50 mL) at 0 °C was slowly added MeLi·LiBr solution (1.5 M in Et_2O, 107 mmol, 1.5 eq.). The reaction mixture was stirred at 0 °C for 1 h. Then, the solution was allowed to warm to room temperature and stirred for 1.5 h. 1 M HCl solution (50 mL) was slowly added and the reaction mixture was stirred at room temperature for another 30 min. The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (80 mL) and with saturated aqueous NaCl solution (80 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 20:1 → 5:1] to yield **2.39** (11.1 g, 62.3 mmol, 88% over 2 steps) as a yellow oil.

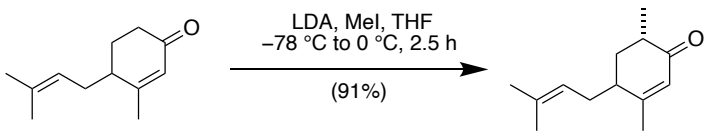
Partial Data for **2.39**:

R_f: 0.20 [PE:Et_2O 3:1]

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.85 (s, 1H), 5.23 – 5.04 (m, 1H), 2.43 (ddd, J = 17.1, 10.7, 5.0 Hz, 1H), 2.35 – 2.25 (m, 3H), 2.24 – 2.13 (m, 1H), 2.06 – 1.99 (m, 1H), 1.98 (s, 3H), 1.93 – 1.83 (m, 1H), 1.73 (s, 3H), 1.63 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 199.6, 165.6, 133.9, 126.9, 121.8, 40.0, 34.0, 29.8, 26.5, 25.8, 23.0, 17.9 ppm.

The analytical data match those previously described in the literature.[31]



2.39 **2.40** d.r. 9:1

To a solution of diisopropylamine (4.90 mL, 35.1 mmol, 1.2 eq.) in dry THF (100 mL) at 0 °C was added *n*-BuLi (2.5 M in hexanes, 21.0 mL, 33.6 mmol, 1.2 eq.). The solution was stirred at 0 °C for 30 min before being cooled to −78 °C. Unsaturated ketone **2.39** (5.00 g, 28.1 mmol, 1 eq.) dissolved in dry THF (10 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 30 min before iodomethane (2.62 mL, 42.1 mmol, 1.5 eq.) was slowly added. The reaction mixture was stirred for 30 min at −78 °C, then the reaction mixture was allowed to warm to 0 °C and stirred for 1.5 h. The reaction mixture was carefully quenched with aqueous NH_4Cl solution (100 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 80 mL). The combined organic layers were washed with saturated aqueous NaCl solution (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 10:1 → 8:1] to yield a 9:1 mixture of **2.40** (4.91 g, 25.5 mmol, 91%) as a yellow oil.

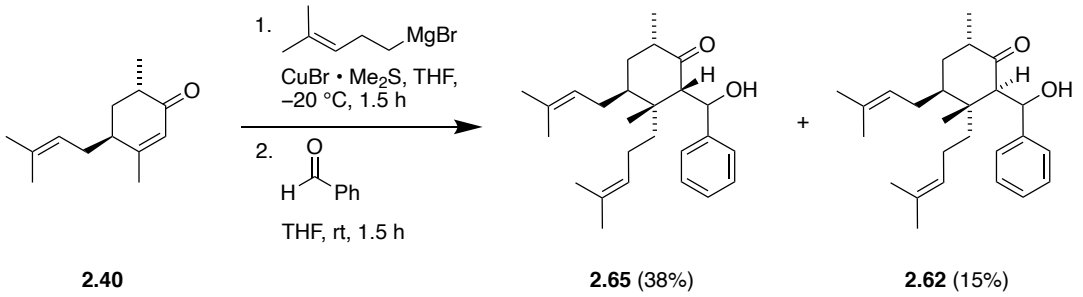
Partial Data for **2.40**:

R_f: 0.25 [PE:Et_2O 3:1]

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.80 (s, 1H), 5.16 (ddt, J = 8.1, 5.1, 1.5 Hz, 1H), 2.46 (tt, J = 12.0, 6.8 Hz, 1H), 2.38 – 2.15 (m, 3H), 1.96 (s, 3H), 1.95 – 1.91 (m, 1H), 1.79 – 1.75 (m, 1H), 1.74 (s, 3H), 1.63 (s, 3H), 1.11 (d, J = 6.8 Hz, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 201.9, 164.6, 133.8, 126.2, 122.6, 40.1, 36.1, 34.8, 29.7, 25.8, 22.9, 17.8, 15.4 ppm.

The analytical data match those previously described in the literature.[28]



2.40 **2.65** (38%) **2.62** (15%)

A suspension of Mg granules (500 mg, 20.6 mmol, 2 eq.) in dry THF (20 mL) and dibromoethane (0.2 mL) was carefully heated to 40 °C for 10 min. To the suspension, a solution of homoprenyl bromide (2.24 mL, 16.7 mmol, 1.6 eq.) in dry THF (2 mL) was added dropwise. The reaction mixture was stirred at 40 °C for 45 min. Then, the reaction mixture was slowly added to a suspension of CuBr·Me_2S (216 mg, 1.04 mmol, 0.1 eq.) in dry THF (16 mL) at –20 °C. The reaction mixture was stirred at –20 °C for 15 min before a solution of ketone **2.40** (2.00 g, 10.4 mmol, 1 eq.) in dry THF (2 mL) was added dropwise. The reaction mixture was stirred for 1 h at –20 °C. Then, a solution of benzaldehyde (1.40 mL, 13.5 mmol, 1.3 eq.) in dry THF (2 mL) was added and the reaction mixture was allowed to warm to room temperature. The mixture was stirred at room temperature for 1.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (70 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 70 mL). The combined organic layers were washed with saturated aqueous NaCl solution (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 40:1 → 30:1] to yield **2.65** (1.50 g, 3.93 mmol, 38%) as a yellow oil. Further elution yielded **2.62** (605 mg, 1.58 mmol, 15%) as a yellow oil.

Data for **2.65**:

$\mathbf{R_f}$ = 0.40 [PE:Et_2O 5:1]

IR (neat): 3489, 2967, 2928, 1691, 1450, 1378, 1115, 732, 698 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32 (d, *J* = 4.3 Hz, 4H), 7.22 (p, *J* = 4.3 Hz, 1H), 5.16 – 5.12 (m, 1H), 5.10 (tt, *J* = 7.0, 1.5 Hz, 1H), 5.01 (d, *J* = 10.0 Hz, 1H), 4.95 (dd, *J* = 10.0, 2.3 Hz, 1H), 2.85 (s, 1H), 2.47 – 2.37 (m, 1H), 2.29 – 2.19 (m, 2H), 2.01 (ddd, *J* = 14.1, 11.8, 4.9 Hz, 1H), 1.95 – 1.83 (m, 4H), 1.78 – 1.75 (m, 1H), 1.74 (s, 3H), 1.68 (s, 3H), 1.63 (s, 3H), 1.59 (s, 3H), 1.56 – 1.53 (m, 1H), 1.34 (ddd, *J* = 13.9, 11.7, 5.3 Hz, 1H), 1.19 (s, 3H), 0.92 (d, *J* = 6.3 Hz, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 217.9, 145.6, 133.1, 131.6, 128.4, 126.9, 126.1, 124.6, 123.7, 71.9, 61.4, 46.6, 41.6, 40.8, 36.7, 34.2, 26.2, 26.0, 25.8, 24.9, 21.7, 18.1, 17.8, 14.2 ppm.

HRMS (ESI): calculated for $C_{26}H_{38}NaO_2$ 405.2764 $[M+Na]^+$, found 405.2773.

Data for **2.62**:

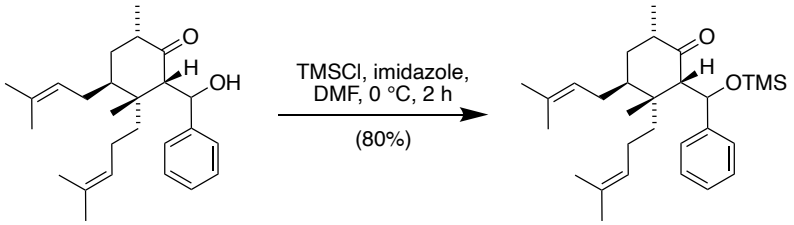
R_f = 0.35 [PE:Et_2O 5:1]

IR (neat): 3495, 2967, 2925, 1693, 1449, 1376, 1101, 753, 698 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 – 7.32 (m, 2H), 7.30 (dd, *J* = 8.5, 6.8 Hz, 2H), 7.21 – 7.18 (m, 1H), 5.09 (dddt, *J* = 9.0, 7.6, 6.2, 1.4 Hz, 2H), 5.01 – 4.97 (m, 1H), 4.69 (d, *J* = 11.1 Hz, 1H), 3.16 (d, *J* = 1.7 Hz, 1H), 2.40 (tt, *J* = 7.2, 5.0 Hz, 1H), 2.21 – 2.13 (m, 2H), 2.04 – 1.95 (m, 2H), 1.77 – 1.73 (m, 3H), 1.72 (s, 3H), 1.69 (s, 3H), 1.68 – 1.67 (m, 1H), 1.64 (s, 3H), 1.61 (s, 3H), 1.07 (s, 3H), 1.02 (d, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 221.2, 145.3, 132.9, 132.1, 128.3, 126.7, 125.4, 123.7, 123.21, 71.6, 56.0, 46.9, 45.4, 37.8, 37.0, 35.0, 27.6, 26.1, 25.9, 21.6, 18.5, 18.1, 17.9, 17.4 ppm.

HRMS (ESI): calculated for $C_{26}H_{38}NaO_2$ 405.2764 $[M+Na]^+$, found 405.2779.



2.65 **2.66**

To a solution of **2.65** (726 mg, 1.90 mmol, 1 eq.) in DMF (30 mL) at 0 °C was added imidazole (646 mg, 9.49 mmol, 6 eq.) and TMSCl (720 μL, 5.69 mmol, 4 eq.). The reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and diluted with H_2O (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with saturated aqueous NaCl solution (3 x 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 80:1] to yield **2.66** (689 mg, 1.51 mmol, 80%) as a colourless oil.

Data for **2.66**:

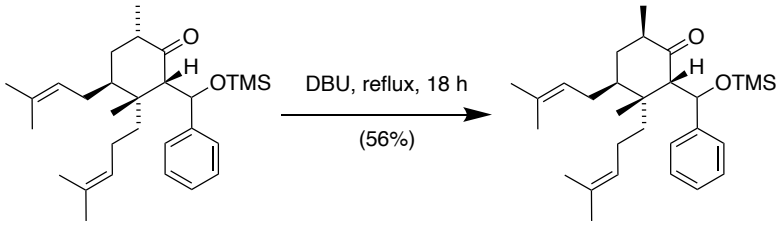
R_f = 0.70 [8:1 PE:Et_2O]

IR (neat): 2967, 2930, 1709, 1455, 1377, 1247, 1048, 872, 839, 703 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.32 (m, 2H), 7.30 – 7.25 (m, 2H), 7.25 – 7.20 (m, 1H), 5.18 (d, J = 8.0 Hz, 1H), 5.11 – 5.05 (m, 1H), 5.04 – 4.98 (m, 1H), 3.02 (d, J = 8.1 Hz, 1H), 2.57 (dt, J = 12.3, 6.3 Hz, 1H), 2.32 (ddd, J = 14.2, 10.5, 8.4 Hz, 1H), 2.17 – 2.12 (m, 1H), 1.85 (ddd, J = 13.6, 5.9, 2.1 Hz, 1H), 1.80 – 1.74 (m, 1H), 1.72 (s, 3H), 1.66 (s, 3H), 1.64 (s, 3H), 1.63 – 1.59 (m, 1H), 1.53 (s, 3H), 1.50 – 1.46 (m, 1H), 1.46 – 1.41 (m, 1H), 1.35 – 1.28 (m, 2H), 0.98 (d, J = 6.4 Hz, 3H), 0.42 (s, 3H), -0.07 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 212.2, 144.5, 132.7, 131.5, 128.3, 128.1, 127.6, 124.6, 124.3, 72.7, 64.4, 45.2, 41.9, 41.2, 35.8, 34.6, 26.5, 26.0, 25.8, 25.0, 21.5, 18.1, 17.7, 14.7, 0.4 ppm.

HRMS (ESI): calculated for $C_{29}H_{46}NaO_2Si$ 477.3159 $[M+Na]^+$, found 477.3159.



2.66 **2.67**

To a solution of **2.66** (233 mg, 0.512 mmol, 1 eq.) in toluene (4 mL) was added DBU (780 µL, 5.12 mmol, 10 eq.). The reaction mixture was stirred at reflux for 18 h. The mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 80:1 $\rightarrow$ 60:1] to give **2.67** (130 mg, 0.286 mmol, 56%) as a colourless oil.

Data for **2.67**:

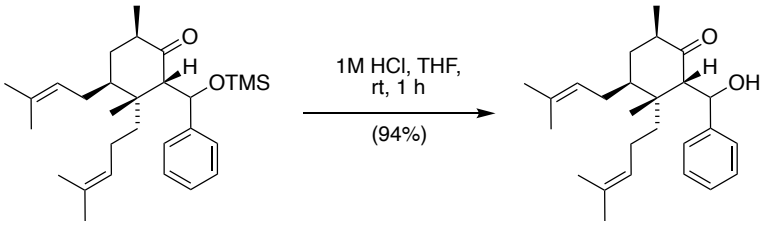
R_f = 0.50 [8:1 PE:Et_2O]

IR (neat): 2965, 2927, 1708, 1457, 1368, 1247, 1051, 868, 835, 705 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.26 (m, 2H), 7.24 – 7.19 (m, 1H), 7.19 – 7.14 (m, 2H), 5.18 – 5.15 (m, 1H), 5.14 (d, *J* = 4.4 Hz, 1H), 4.92 (tt, *J* = 6.9, 1.5 Hz, 1H), 3.08 (dt, *J* = 12.8, 6.5 Hz, 1H), 2.44 (d, *J* = 4.3 Hz, 1H), 2.38 (dddt, *J* = 12.5, 10.7, 4.3, 2.8 Hz, 1H), 2.26 – 2.19 (m, 1H), 2.10 (ddd, *J* = 13.5, 6.8, 4.3 Hz, 1H), 1.95 (tt, *J* = 12.7, 6.2 Hz, 1H), 1.83 – 1.77 (m, 1H), 1.76 (s, 3H), 1.69 (s, 3H), 1.68 – 1.65 (m, 1H), 1.63 (s, 3H), 1.62 (s, 3H), 1.61 – 1.53 (m, 2H), 1.15 (q, *J* = 12.8 Hz, 1H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.75 (s, 3H), 0.00 (s, 9H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 213.6, 143.5, 132.2, 131.5, 128.3, 127.7, 126.5, 124.5, 124.2, 74.0, 66.6, 44.6, 43.5, 41.7, 38.0, 36.6, 28.5, 26.0, 25.8, 22.1, 18.9, 18.1, 17.9, 14.7, 0.4 ppm.

HRMS (ESI): calculated for $C_{29}H_{46}NaO_2Si$ 477.3159 $[M+Na]^+$, found 477.3161.



2.67 **2.68**

To a solution of **2.67** (90.0 mg, 0.198 mmol, 1 eq.) in THF (10 mL) at room temperature was added 1M aqueous HCl solution (400 µL, 0.396 mmol, 2 eq.). The mixture was stirred at room temperature for 1 h. The mixture was quenched with saturated aqueous NaCl solution (15 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with saturated aqueous NaCl solution (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 20:1 → 10:1] to yield **2.68** (71.3 mg, 0.186 mmol, 94%) as a colourless oil.

Data for **2.68**:

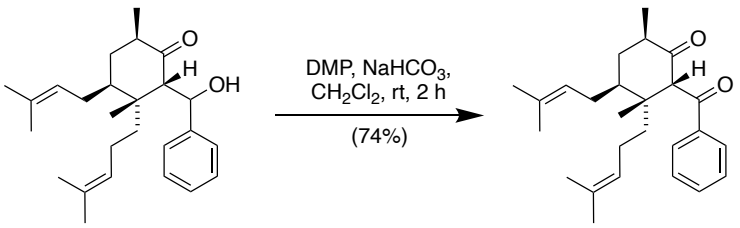
R_f = 0.35 [3:1 PE:Et_2O]

IR (neat): 355, 2967, 2932, 1685, 1446, 1379, 1060, 741, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.32 (m, 2H), 7.32 – 7.29 (m, 2H), 7.29 – 7.25 (m, 1H), 5.20 – 5.14 (m, 2H), 4.75 (dddd, *J* = 7.4, 5.9, 2.8, 1.5 Hz, 1H), 2.99 (dp, *J* = 13.1, 6.5 Hz, 1H), 2.61 (d, *J* = 5.4 Hz, 1H), 2.32 – 2.24 (m, 1H), 2.24 – 2.19 (m, 1H), 2.11 (ddd, *J* = 13.6, 6.8, 4.1 Hz, 2H), 1.90 (ddt, *J* = 12.6, 10.0, 4.7 Hz, 1H), 1.75 (s, 3H), 1.69 – 1.65 (m, 1H), 1.64 (s, 3H), 1.63 (s, 3H), 1.61 – 1.57 (m, 1H), 1.54 (s, 3H), 1.19 (q, *J* = 12.4 Hz, 1H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.79 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 214.6, 144.0, 132.5, 131.4, 128.8, 128.1, 126.3, 124.6, 124.0, 72.8, 65.1, 44.4, 43.5, 41.6, 37.3, 36.8, 28.6, 26.0, 25.8, 22.2, 19.5, 18.1, 17.9, 15.0 ppm.

HRMS (ESI): calculated for $C_{26}H_{38}NaO_2$ 405.2764 $[M+Na]^+$, found 405.2764.



2.68 **2.69**

To a solution of **2.68** (78.0 mg, 0.204 mmol, 1 eq.) in CH_2Cl_2 (10 mL) at room temperature was added $NaHCO_3$ (34.0 mg, 0.408 mmol, 2 eq.) and Dess-Martin periodinane (173 mg, 0.408 mmol, 2 eq.). The reaction mixture was stirred at room temperature for 2 h. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and diluted with H_2O (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (2 x 20 mL) and saturated aqueous NaCl solution (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 40:1] to yield **2.69** (57.6 mg, 0.151 mmol, 74%) as a colourless oil.

Data for **2.69**:

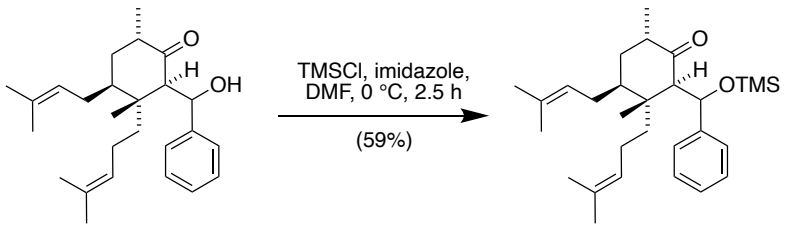
R_f = 0.65 [3:1 PE:Et_2O]

IR (neat): 2966, 2927, 2857, 1701, 1662, 1448, 1379, 1356, 1214, 1001, 818, 685 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.09 – 8.02 (m, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 5.21 (t, *J* = 7.2 Hz, 1H), 4.86 (t, *J* = 6.7 Hz, 1H), 4.49 (s, 1H), 2.93 – 2.85 (m, 1H), 2.80 (dp, *J* = 12.7, 6.4 Hz, 1H), 2.25 – 2.19 (m, 1H), 2.14 (ddd, *J* = 13.6, 6.3, 4.2 Hz, 1H), 1.81 – 1.75 (m, 1H), 1.74 (s, 3H), 1.70 – 1.63 (m, 2H), 1.62 (s, 3H), 1.53 (s, 3H), 1.51 – 1.43 (m, 2H), 1.28 – 1.24 (m, 1H), 1.22 (s, 3H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 209.2, 196.0, 138.0, 133.5, 132.6, 131.8, 128.9, 128.9, 124.0, 123.9, 69.7, 46.4, 41.8, 41.4, 38.0, 37.9, 28.2, 26.0, 25.7, 22.7, 19.0, 18.1, 17.3, 14.4 ppm.

HRMS (ESI): calculated for $C_{26}H_{36}NaO_2$ 403.2608 $[M+Na]^+$, found 403.2609.



2.62 **2.70**

To a solution of **2.62** (404 mg, 1.06 mmol, 1 eq.) in DMF (15 mL) at 0 °C was added imidazole (359 mg, 5.28 mmol, 6 eq.) and TMSCl (400 µL, 3.18 mmol, 4 eq.). The reaction mixture was stirred at 0 °C for 2.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and diluted with H_2O (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with saturated aqueous NaCl solution (3 x 40 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 80:1 → 70:1] to yield **2.70** (283 mg, 0.622 mmol, 59%) as a light yellow oil.

Data for **2.70**:

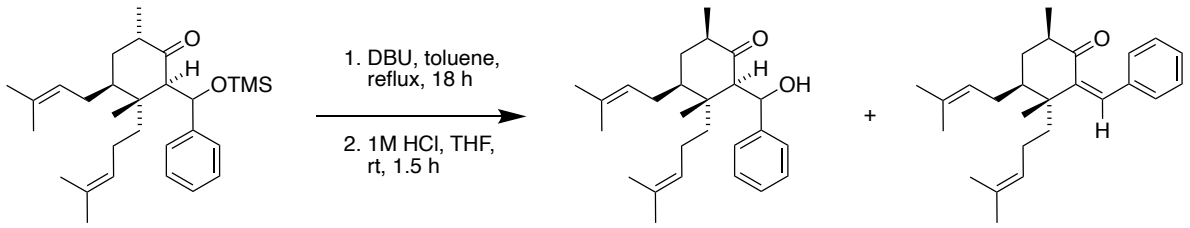
R_f = 0.60 [8:1 PE:Et_2O]

IR (neat): 2966, 2927, 1713, 1454, 1376, 1250, 1055, 872, 839, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.33 (m, 2H), 7.31 – 7.25 (m, 2H), 7.25 – 7.20 (m, 1H), 5.16 (d, *J* = 6.4 Hz, 1H), 5.11 – 5.05 (m, 1H), 4.94 (tt, *J* = 7.1, 1.3 Hz, 1H), 2.85 – 2.76 (m, 2H), 2.33 – 2.25 (m, 1H), 2.20 (ddd, *J* = 13.9, 10.9, 8.4 Hz, 1H), 1.90 – 1.76 (m, 3H), 1.73 (s, 3H), 1.66 (s, 3H), 1.64 (s, 3H), 1.61 – 1.56 (m, 1H), 1.55 (s, 3H), 1.49 (dtd, *J* = 11.4, 5.8, 2.7 Hz, 1H), 1.22 (ddd, *J* = 10.5, 6.0, 3.9 Hz, 2H), 1.04 (d, *J* = 6.6 Hz, 3H), 0.80 (s, 3H), -0.11 (s, 9H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 213.6, 144.8, 132.7, 131.5, 128.3, 127.6, 127.6, 124.3, 124.3, 73.9, 65.1, 43.1, 40.9, 40.9, 40.0, 34.4, 28.4, 26.0, 25.8, 22.0, 20.5, 18.1, 17.8, 15.2, 0.24 ppm.

HRMS (ESI): calculated for $C_{29}H_{46}NaO_2Si$ 477.3159 $[M+Na]^+$, found 477.3159.



2.70

2.71
(26% over 2 steps)

2.72
(35% over 2 steps)

To a solution of **2.70** (118 mg, 0.259 mmol, 1 eq.) in toluene (4 mL) was added DBU (390 µL, 2.59 mmol, 10 eq.). The reaction mixture was stirred at reflux for 18 h. The mixture was cooled to room temperature and concentrated *in vacuo*. The residue was immediately re-dissolved in THF (8 mL) at room temperature and 1M aqueous HCl solution (350 µL, 0.347 mmol, 1.3 eq.) was added to the solution. The mixture was stirred at room temperature for 1.5 h. Then, the solution was quenched with saturated aqueous NaCl solution (15 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl solution (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 70:1] to yield dehydrated side product **2.72** (32.8 mg, 0.090 mmol, 35%) as a light yellow oil. Further elution afforded pure **2.71** (25.4 mg, 0.066 mmol, 26% over 2 steps) as a colourless oil.

Data for **2.71**:

R_f = 0.45 [6:1 PE:Et_2O]

IR (neat): 3490, 2968, 2926, 2875, 1694, 1449, 1376, 1121, 954, 749, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.28 (m, 4H), 7.23 – 7.17 (m, 1H), 5.16 – 5.06 (m, 2H), 4.98 (s, 2H), 2.89 (s, 1H), 2.29 (dt, *J* = 12.6, 6.3 Hz, 1H), 2.17 (dt, *J* = 12.9, 6.3 Hz, 2H), 2.13 – 2.05 (m, 1H), 1.99 (dq, *J* = 13.7, 7.2, 6.3 Hz, 1H), 1.95 – 1.87 (m, 1H), 1.82 – 1.74 (m, 2H), 1.73 (s, 3H), 1.70 (s, 3H), 1.70 – 1.66 (m, 1H), 1.65 (s, 3H), 1.62 (s, 3H), 1.22 (q, *J* = 12.6 Hz, 1H), 1.04 (s, 3H), 0.88 (d, *J* = 6.0 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 218.7, 145.5, 133.0, 132.1, 128.3, 126.7, 125.7, 123.8, 123.3, 71.81, 60.7, 47.0, 46.4, 42.9, 38.1, 36.8, 27.6, 26.0, 25.9, 21.5, 18.7, 18.1, 17.9, 14.0 ppm.

HRMS (ESI): calculated for $C_{26}H_{38}NaO_2$ 405.2764 $[M+Na]^+$, found 405.2759.

Data for dehydrated side product **2.72**:

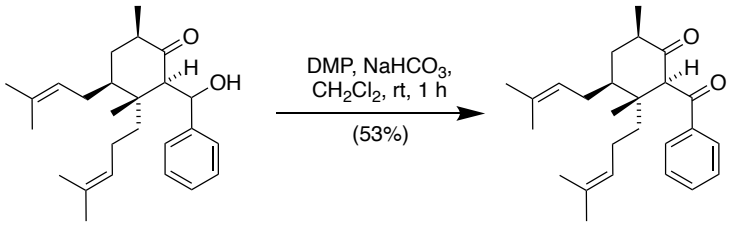
R_f = 0.60 [6:1 PE:Et_2O]

IR (neat): 2967, 2927, 2878, 1698, 1448, 1377, 1150, 985, 747, 694 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 – 7.24 (m, 2H), 7.23 – 7.17 (m, 3H), 6.22 (s, 1H), 5.18 – 5.14 (m, 1H), 5.07 – 5.03 (m, 1H), 2.67 (dp, *J* = 13.0, 6.4 Hz, 1H), 2.37 – 2.26 (m, 1H), 2.20 – 2.11 (m, 1H), 1.98 (ddd, *J* = 13.6, 6.8, 2.4 Hz, 1H), 1.95 – 1.89 (m, 2H), 1.79 – 1.74 (m, 1H), 1.73 (s, 3H), 1.71 (ddd, *J* = 10.7, 4.6, 2.4 Hz, 1H), 1.65 (s, 3H), 1.63 (s, 3H), 1.58 (s, 3H), 1.43 (ddd, *J* = 13.7, 10.4, 6.3 Hz, 1H), 1.31 (ddd, *J* = 13.9, 10.4, 6.8 Hz, 1H), 1.22 (s, 3H), 1.06 (d, *J* = 6.4 Hz, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 209.6, 148.2, 136.4, 132.8, 131.8, 128.7, 128.3, 127.4, 127.1, 124.3, 123.7, 48.4, 43.8, 42.8, 39.5, 33.6, 27.0, 26.0, 25.8, 22.4, 21.1, 18.1, 17.7, 14.5 ppm.

HRMS (ESI): calculated for $C_{26}H_{37}O$ 365.2839 $[M+H]^+$, found 365.2839.



2.71 norascyronone C (**2.50**)

To a solution of **2.71** (42.1 mg, 0.110 mmol, 1 eq.) in CH_2Cl_2 (2 mL) at room temperature was added $NaHCO_3$ (18.5 mg, 0.220 mmol, 2 eq.) and Dess-Martin periodinane (93.3 mg, 0.220 mmol, 2 eq.). The reaction mixture was stirred at room temperature for 1 h. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were consecutively washed with saturated aqueous $NaHCO_3$ solution (10 mL) and saturated aqueous NaCl solution (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 10:1] to yield norascyronone C (**2.50**, 22.0 mg, 0.058 mmol, 53%) as a colourless oil.

Data for norascyronone C (**2.50**):

R_f = 0.45 [3:1 PE:Et_2O]

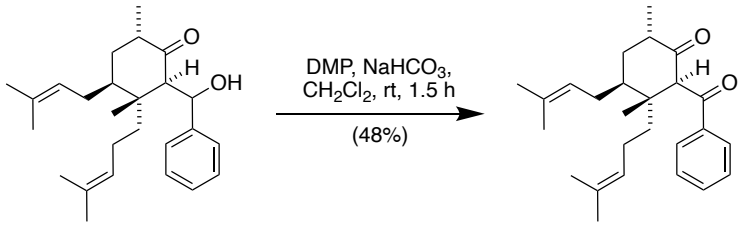
IR (neat): 2967, 2928, 1710, 1686, 1448, 1376, 1337, 1219, 1064, 736, 688 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.3 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 2H), 5.16 (t, *J* = 7.2 Hz, 1H), 4.87 (t, *J* = 7.1 Hz, 1H), 4.60 (s, 1H), 2.60 (dp, *J* = 12.8, 6.6 Hz, 1H), 2.23 – 2.19 (m, 1H), 2.19 – 2.15 (m, 1H), 2.03 – 1.95 (m, 2H), 1.78 – 1.75 (m, 1H), 1.75 (s, 3H), 1.74 – 1.69 (m, 1H), 1.63 (s, 3H), 1.60 – 1.54 (m, 2H), 1.50 (s, 3H), 1.34 (s, 3H), 1.33 – 1.28 (m, 1H), 1.14 (s, 3H), 1.04 (d, *J* = 6.4 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 209.6, 197.0, 138.8, 133.1, 132.8, 131.9, 128.8, 127.7, 123.8, 123.2, 63.6, 46.5, 45.6, 43.1, 37.4, 36.7, 27.2, 26.1, 25.7, 22.3, 18.1, 17.8, 17.5, 14.6 ppm.

HRMS (ESI): calculated for $C_{26}H_{37}O_2$ 381.2788 $[M+H]^+$, found 381.2789.

The analytical data match those previously described in the literature.[30,32]



2.62

6-epi-norascyronone C
(**2.73**)

To a solution of **2.62** (107 mg, 0.280 mmol, 1 eq.) in CH_2Cl_2 (10 mL) at room temperature was added $NaHCO_3$ (24.0 mg, 0.280 mmol, 1 eq.) and Dess-Martin periodinane (237 mg, 0.559 mmol, 2 eq.). The reaction mixture was stirred at room temperature for 1.5 h. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (10 mL) and diluted with H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with saturated aqueous NaCl solution (40 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 50:1] to yield 6-epi-norascyronone C (**2.73**,51.3 mg, 0.135 mmol, 48%) as a yellow oil.

Data for 6-epi-norascyronone C (**2.73**):

R_f = 0.40 [3:1 PE:Et_2O]

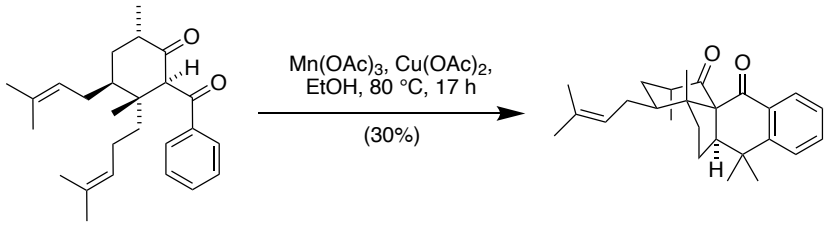
IR (neat): 2971, 2930, 1710, 1687, 1447, 1381, 1219, 1113, 912, 732, 689 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 – 7.77 (m, 2H), 7.54 – 7.50 (m, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 5.15 – 5.05 (m, 1H), 4.89 (tt, *J* = 6.8, 1.5 Hz, 1H), 4.78 (s, 1H), 2.73 (td, *J* = 6.8, 3.3 Hz, 1H), 2.22 – 2.14 (m, 1H), 2.04 – 1.93 (m, 2H), 1.92 – 1.86 (m, 1H), 1.86 – 1.80 (m, 2H), 1.79 – 1.75 (m, 1H), 1.74 (s, 3H), 1.64 (s, 3H), 1.55 – 1.53 (m, 2H), 1.52 (s, 3H), 1.39 (s, 3H), 1.38 (d, *J* = 7.4 Hz, 3H), 1.15 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 212.6, 197.6, 138.9, 133.1, 132.9, 131.9, 128.8, 127.9, 123.8, 123.3, 60.6, 46.2, 43.8, 38.4, 37.6, 34.3, 27.2, 26.1, 25.7, 22.4, 18.4, 18.2, 18.2, 17.5 ppm.

HRMS (ESI): calculated for $C_{26}H_{36}NaO_2$ 403.2608 $[M+Na]^+$, found 403.2615.

The analytical data match those previously described in the literature.[32]



6-epi-norascyronone C (**2.73**)

6-epi-norascyronone A (**2.74**)

To a solution of 6-epi-norascyronone C (**2.73**, 68.0 mg, 0.179 mmol, 1 eq.) in EtOH (2 mL) at room temperature was added $Mn(OAc)_3 \cdot 2\ H_2O$ (96.0 mg, 0.357 mmol, 2 eq.) and $Cu(OAc)_2 \cdot H_2O$ (36.0 mg, 0.179 mmol, 1 eq.). The reaction mixture was heated at 80 °C for 17 h. The mixture was allowed to cool to room temperature, quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and diluted with H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl solution (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 40:1] to yield 6-epi-norascyronone A (**2.74**, 20.2 mg, 0.053 mmol, 30%) as a colourless oil.

Data for 6-epi-norascyronone A (**2.74**):

R_f = 0.15 [3:1 PE:Et_2O]

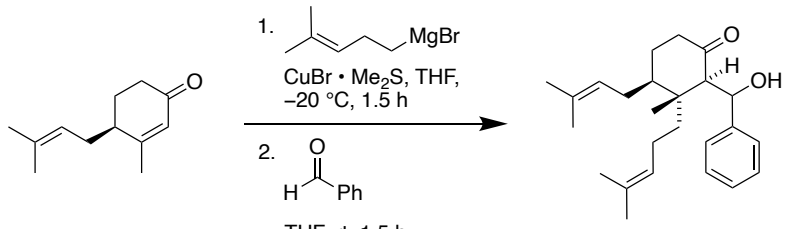
IR (neat): 2965, 2930, 1701, 1665, 1461, 1448, 1381, 1231, 1065, 839, 766 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 – 7.67 (m, 1H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.33 – 7.25 (m, 2H), 5.02 (t, *J* = 7.0 Hz, 1H), 3.33 (p, *J* = 7.2 Hz, 1H), 3.18 (dd, *J* = 12.0, 7.1 Hz, 1H), 2.43 (td, *J* = 13.1, 9.1 Hz, 1H), 1.97 – 1.89 (m, 1H), 1.87 – 1.80 (m, 1H), 1.80 – 1.73 (m, 1H), 1.69 (s, 3H), 1.61 – 1.58 (m, 1H), 1.57 (s, 3H), 1.47 (s, 3H), 1.40 – 1.29 (m, 3H), 1.18 (td, *J* = 12.3, 6.0 Hz, 1H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.06 (s, 3H), 0.79 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 214.1, 197.9, 150.2, 135.2, 133.1, 133.0, 127.5, 126.8, 124.5, 123.0, 72.7, 57.3, 51.9, 47.4, 42.3, 41.6, 36.2, 35.8, 32.4, 29.3, 28.5, 26.2, 25.9, 18.5, 18.0, 16.9 ppm.

HRMS (ESI): calculated for $C_{26}H_{34}NaO_2$ 401.2451 $[M+Na]^+$, found 401.2457.

The analytical data match those previously described in the literature.[32]



2.39 **2.78**

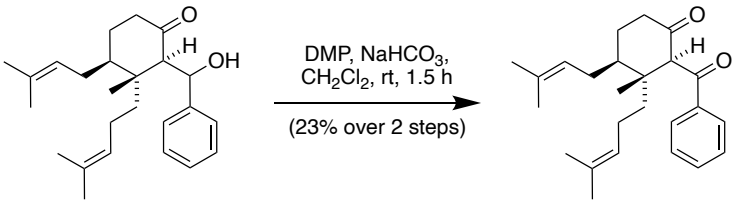
A suspension of Mg granules (539 mg, 22.4 mmol, 2 eq.) in dry THF (20 mL) and dibromoethane (0.2 mL) was carefully heated to 40 °C for 10 min. To the suspension, a solution of homoprenyl bromide (2.40 mL, 18.0 mmol, 1.6 eq.) in dry THF (2 mL) was added dropwise. The reaction mixture was stirred at 40 °C for 50 min. Then, the reaction mixture was slowly added to a suspension of CuBr·Me_2S (231 mg, 1.12 mmol, 0.1 eq.) in dry THF (16 mL) at –20 °C. The reaction mixture was stirred at –20 °C for 10 min before a solution of ketone **2.39** (2.00 g, 11.2 mmol, 1 eq.) in dry THF (2 mL) was added dropwise. The reaction mixture was stirred for 1 h at –20 °C. Then, a solution of benzaldehyde (1.49 mL, 14.6 mmol, 1.3 eq.) in dry THF (2 mL) was added and the reaction mixture was allowed to warm to room temperature. The mixture was stirred at room temperature for 1.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (70 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 70 mL). The combined organic layers were consecutively washed with saturated aqueous NH_4Cl solution (100 mL) and saturated aqueous NaCl solution (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 40:1 → 30:1] to yield an inseparable mixture of Michael product and **2.78** as a yellow oil. The mixture was used in the next step without any further purification.

Partial data for **2.78**:

R_f = 0.35 [3:1 PE:Et_2O]

IR (neat): 3487, 2965, 2914, 1709, 1445, 1376, 1228, 1116, 979, 851, 695 cm^{-1}.

HRMS (ESI): calculated for $C_{25}H_{36}NaO_2$ 391.2608 $[M+Na]^+$, found 391.2624.



2.78 **2.75**

To a solution of **2.78** (2.10 mmol, 1 eq.) in CH_2Cl_2 (20 mL) at room temperature was added $NaHCO_3$ (169 mg, 2.03 mmol, 2 eq.) and Dess-Martin periodinane (861 mg, 2.03 mmol, 2 eq.). The reaction mixture was stirred at room temperature for 1.5 h. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and diluted with H_2O (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with saturated aqueous NaCl solution (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 30:1 → 15:1] to yield **2.75** (175 mg, 0.476 mmol, 23% over 2 steps) as a light yellow oil.

Data for **2.75**:

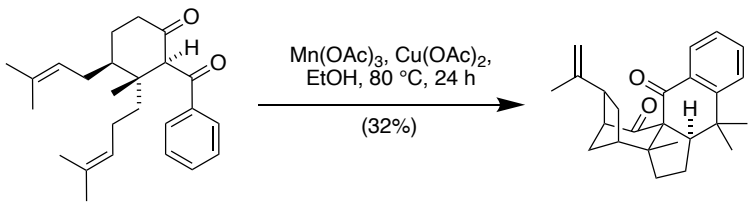
R_f = 0.35 [3:1 PE:Et_2O]

IR (neat): 2967, 2928, 1712, 1678, 1447, 1334, 1219, 1191, 852, 768, 689 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.2 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 5.17 – 5.12 (m, 1H), 4.85 (ddt, *J* = 8.5, 7.1, 1.5 Hz, 1H), 4.60 (s, 1H), 2.58 – 2.44 (m, 2H), 2.24 – 2.17 (m, 1H), 2.18 – 2.12 (m, 1H), 2.00 (dt, *J* = 14.6, 7.9 Hz, 1H), 1.92 (ddt, *J* = 12.2, 10.3, 3.7 Hz, 1H), 1.84 – 1.76 (m, 1H), 1.74 (s, 3H), 1.72 – 1.67 (m, 1H), 1.63 (s, 3H), 1.62 – 1.59 (m, 1H), 1.58 – 1.52 (m, 2H), 1.50 (s, 3H), 1.33 (s, 3H), 1.18 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 208.9, 197.1, 138.8, 133.2, 132.9, 131.9, 128.8, 127.8, 123.7, 123.1, 63.8, 46.0, 43.0, 41.8, 36.9, 27.7, 27.2, 26.0, 25.7, 22.2, 18.1, 17.9, 17.4 ppm.

HRMS (ESI): calculated for $C_{25}H_{35}O_2$ 367.2632 $[M+H]^+$, found 367.2634.



2.75 **2.81**

To a solution of **2.75** (85.0 mg, 0.232 mmol, 1 eq.) in EtOH (4 mL) at room temperature was added $Mn(OAc)_3 \cdot 2\ H_2O$ (249 mg, 0.928 mmol, 4 eq.) and $Cu(OAc)_2 \cdot H_2O$ (92.6 mg, 0.464 mmol, 2 eq.). The reaction mixture was heated at reflux for 24 h. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (30 mL) and saturated aqueous NaCl solution (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 40:1] to yield **2.81** (26.6 mg, 0.0733 mmol, 32%) as a light yellow oil.

Data for **2.81**:

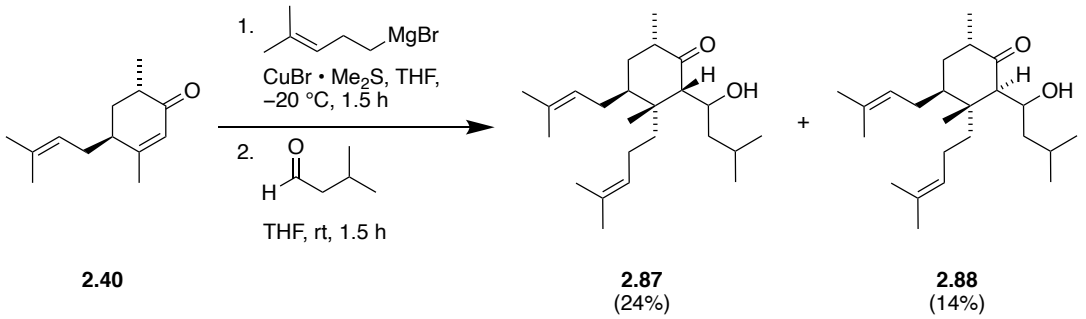
R_f = 0.55 [3:1 PE:Et_2O]

IR (neat): 2963, 2873, 1704, 1665, 1599, 1451, 1337, 1234, 1022, 884, 762 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.49 (td, *J* = 7.6, 1.5 Hz, 1H), 7.35 – 7.28 (m, 2H), 4.77 (s, 2H), 3.58 (dd, *J* = 9.1, 5.8 Hz, 1H), 2.81 (d, *J* = 4.3 Hz, 1H), 2.54 (dd, *J* = 11.6, 6.6 Hz, 1H), 2.22 (ddd, *J* = 13.9, 9.0, 2.1 Hz, 1H), 2.15 – 2.07 (m, 1H), 2.07 – 1.99 (m, 1H), 1.97 – 1.89 (m, 2H), 1.83 (s, 3H), 1.83 – 1.78 (m, 1H), 1.65 (ddd, *J* = 14.0, 7.1, 5.7 Hz, 1H), 1.43 (s, 3H), 1.33 (s, 3H), 1.27 – 1.24 (m, 2H), 0.76 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 213.2, 201.1, 150.5, 148.5, 136.0, 133.0, 127.5, 126.7, 124.7, 108.4, 71.6, 58.9, 56.9, 51.8, 47.4, 43.3, 40.1, 37.2, 37.2, 29.9, 29.8, 29.1, 26.7, 25.0, 22.9 ppm.

HRMS (ESI): calculated for $C_{25}H_{31}O_2$ 363.2319 $[M+H]^+$, found 363.2325.



2.40 **2.87** (24%) **2.88** (14%)

A suspension of Mg granules (250 mg, 10.3 mmol, 2 eq.) in dry THF (10 mL) and dibromoethane (0.2 mL) was carefully heated to 40 °C for 10 min. To the suspension, a solution of homoprenyl bromide (1.12 mL, 8.36 mmol, 1.6 eq.) in dry THF (2 mL) was added dropwise. The reaction mixture was stirred at 40 °C for 45 min. Then, the reaction mixture was slowly added to a suspension of CuBr·Me_2S (108 mg, 0.519 mmol, 0.1 eq.) in dry THF (8 mL) at –20 °C. The reaction mixture was stirred at –20 °C for 30 min before a solution of ketone **2.40** (1.00 g, 5.19 mmol, 1 eq.) in dry THF (2 mL) was added dropwise. The reaction mixture was stirred for 1 h at –20 °C. Then, a solution of isovaleraldehyde (0.73 mL, 6.65 mmol, 1.3 eq.) in dry THF (2 mL) was added and the reaction mixture was allowed to warm to room temperature. The mixture was stirred at room temperature for 1.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with saturated aqueous NaCl solution (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 50:1] to yield **2.87** (449 mg, 1.24 mmol, 24%) as a yellow oil. Further elution yielded **2.88** (265 mg, 0.731mmol, 14%) as a yellow oil.

Data for **2.87**:

R_f = 0.55 [PE:Et_2O 6:1]

IR (neat): 3516, 2963, 2929, 1692, 1454, 1378, 1135, 1102, 948, 842 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.16 (ddt, *J* = 7.2, 5.4, 1.4 Hz, 1H), 5.06 (dddd, *J* = 7.1, 5.7, 2.9, 1.5 Hz, 1H), 3.82 (tt, *J* = 2.8, 1.1 Hz, 2H), 2.47 (dp, *J* = 12.5, 5.8 Hz, 1H), 2.35 (s, 1H), 2.23 (t, *J* = 7.3 Hz, 2H), 2.02 (ddd, *J* = 14.4, 11.8, 5.1 Hz, 1H), 1.94 – 1.87 (m, 1H), 1.86 – 1.77 (m, 2H), 1.75 (s, 3H), 1.74 – 1.71 (m, 1H), 1.69 (dd, *J* = 5.7, 3.5 Hz, 1H), 1.66 (s, 3H), 1.64 (s, 3H), 1.61 – 1.53 (m, 1H, overlap), 1.57 (s, 3H), 1.24 (ddd, *J* = 14.3, 11.7, 5.5 Hz, 1H), 1.16 (s, 3H), 1.14 – 1.07 (m, 1H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 6.6, 3H, overlap), 0.90 (d, *J* = 6.6, 3H, overlap) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 218.2, 133.0, 131.3, 124.8, 123.9, 68.1, 58.9, 48.0, 46.4, 41.7, 40.6, 36.7, 34.3, 26.2, 26.0, 25.8, 25.1, 24.2, 23.5, 22.1, 21.7, 18.1, 17.7, 14.3 ppm.

HRMS (ESI): calculated for $C_{24}H_{43}O_2$ 363.3258 $[M+H]^+$, found 363.3257.

Data for **2.88**:

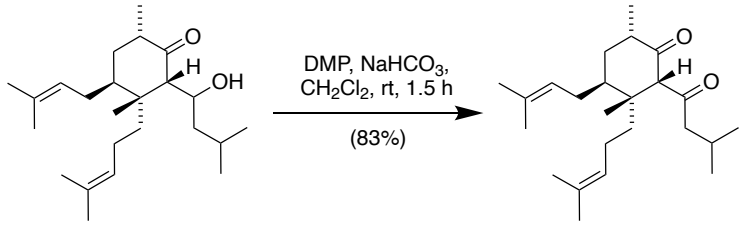
R_f = 0.25 [PE:Et_2O 6:1]

IR (neat): 3517, 2958, 2926, 1693, 1453, 1385, 1202, 1139, 1102, 949, 842 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.07 (tdd, *J* = 7.0, 3.3, 1.9 Hz, 2H), 3.88 (td, *J* = 10.7, 3.7 Hz, 1H), 3.61 (d, *J* = 11.5 Hz, 1H), 2.56 (s, 1H), 2.47 (ddd, *J* = 7.5, 5.6, 2.0 Hz, 1H), 2.19 – 2.11 (m, 1H), 2.03 (dt, *J* = 12.3, 6.3 Hz, 1H), 1.95 (dddd, *J* = 12.8, 10.6, 4.7, 3.0 Hz, 1H), 1.84 (ddt, *J* = 8.9, 6.7, 3.3 Hz, 1H), 1.78 – 1.73 (m, 3H), 1.72 – 1.63 (m, 2H, overlap), 1.72 (s, 3H), 1.69 (s, 3H), 1.63 – 1.59 (m, 2H, overlap), 1.61 (s, 3H), 1.60 (s, 3H), 1.20 (d, *J* = 7.3 Hz, 3H), 1.03 – 0.98 (m, 1H), 0.97 (s, 3H), 0.92 (d, *J* = 6.7 Hz, 3H, overlap), 0.90 (d, *J* = 6.6 Hz, 3H, overlap) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 222.0, 132.8, 131.8, 123.9, 123.4, 67.9, 54.7, 47.6, 46.5, 45.5, 37.5, 36.9, 34.8, 27.7, 26.0, 25.9, 24.9, 23.8, 22.0, 21.6, 18.3, 18.1, 18.1, 17.9 ppm.

HRMS (ESI): calculated for $C_{24}H_{43}O_2$ 363.3258 $[M+H]^+$, found 363.3256.



2.87 **2.59**

To a solution of **2.87** (434 mg, 1.20 mmol, 1 eq.) in CH_2Cl_2 (20 mL) at room temperature was added $NaHCO_3$ (201 mg, 2.39 mmol, 2 eq.) and Dess-Martin periodinane (1.02 g, 2.39 mmol, 2 eq.). The reaction mixture was stirred at room temperature for 1.5 h. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with saturated aqueous NaCl solution (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 40:1] to yield **2.59** (356 mg, 0.987 mmol, 83%) as a yellow oil.

Data for **2.59**:

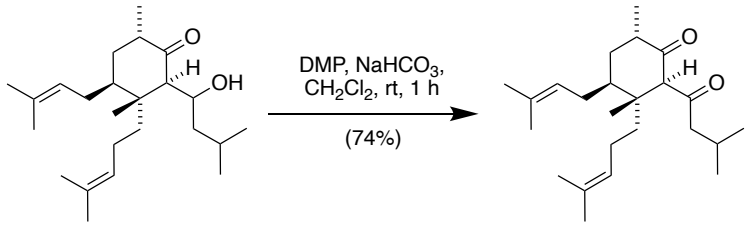
R_f = 0.50 [PE:Et_2O 6:1]

IR (neat): 3411, 2962, 2930, 1722, 1703, 1454, 1377, 1366, 1138, 1067, 722 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.16 (ddp, *J* = 8.8, 5.8, 1.4 Hz, 1H), 5.09 – 5.03 (m, 1H), 3.63 (s, 1H), 2.55 – 2.46 (m, 1H), 2.33 (dd, *J* = 16.9, 7.2 Hz, 1H), 2.29 – 2.20 (m, 2H), 2.20 – 2.07 (m, 3H), 1.86 (dddt, *J* = 23.1, 10.7, 7.8, 3.6 Hz, 3H), 1.81 – 1.77 (m, 1H), 1.75 (s, 3H), 1.67 (s, 3H), 1.65 (s, 3H), 1.61 – 1.57 (m, 1H), 1.56 (s, 3H), 1.23 (ddd, *J* = 14.3, 12.0, 5.2 Hz, 1H), 1.04 (s, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H, overlap), 0.89 (d, *J* = 6.6 Hz, 3H, overlap) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 209.9, 206.6, 133.1, 131.5, 124.5, 123.7, 68.5, 54.6, 45.1, 41.2, 39.8, 35.1, 33.5, 26.2, 26.0, 25.8, 24.2, 22.8, 22.5, 22.4, 21.6, 18.1, 17.7, 15.1 ppm.

HRMS (ESI): calculated for $C_{24}H_{41}O_2$ 361.3101 $[M+H]^+$, found 361.3099.



2.88 **2.56**

To a solution of **2.88** (265 mg, 0.73 mmol, 1 eq.) in CH_2Cl_2 (10 mL) at room temperature was added $NaHCO_3$ (123 mg, 1.46 mmol, 2 eq.) and Dess-Martin periodinane (620 mg, 1.46 mmol, 2 eq.). The reaction mixture was stirred at room temperature for 1 h. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl solution (25 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 40:1] to yield **2.56** (194 mg, 0.539 mmol, 74%) as a yellow oil.

Data for **2.56**:

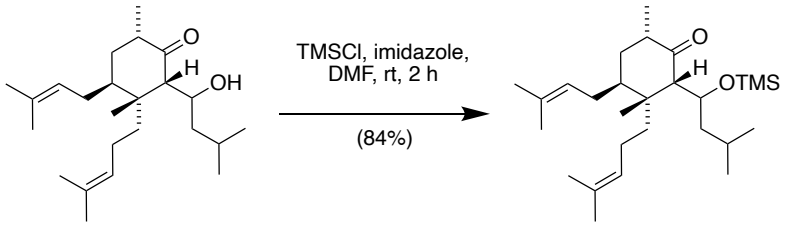
R_f = 0.45 [6:1 PE:Et_2O]

IR (neat): 3406, 2963, 2929, 1724, 1700, 1455, 1382, 1365, 1145, 1053, 843 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.09 – 5.04 (m, 1H), 5.03 – 4.99 (m, 1H), 3.79 (s, 1H), 2.63 (pd, *J* = 7.0, 3.6 Hz, 1H), 2.31 (dd, *J* = 17.0, 6.4 Hz, 1H), 2.21 (dd, *J* = 17.1, 6.8 Hz, 1H), 2.18 – 2.09 (m, 2H), 2.02 (dt, *J* = 17.1, 7.3 Hz, 1H), 1.89 – 1.80 (m, 3H), 1.78 – 1.73 (m, 1H), 1.72 (s, 3H), 1.69 (t, *J* = 3.9 Hz, 1H), 1.67 (s, 3H), 1.61 (s, 3H), 1.60 (s, 3H), 1.44 (dd, *J* = 9.6, 7.3 Hz, 2H), 1.21 (d, *J* = 7.1 Hz, 3H), 1.05 (s, 3H), 0.91 (d, *J* = 6.3 Hz, 3H, overlap), 0.90 (d, *J* = 6.7 Hz, 3H, overlap) ppm.

^{13}C NMR (150 MHz, CDCl3): δ 212.9, 207.2, 133.0, 131.9, 123.8, 123.3, 66.1, 54.7, 45.3, 43.3, 38.1, 38.0, 33.9, 27.0, 26.0, 25.9, 23.9, 22.8, 22.6, 22.2, 18.3, 18.1, 17.9, 17.8 ppm.

HRMS (ESI): calculated for $C_{24}H_{41}O_2$ 361.3101 $[M+H]^+$, found 361.3106.



2.87 **2.98**

To a solution of **2.87** (700 mg, 1.93 mmol, 1 eq.) in DMF (25 mL) at room temperature was added imidazole (788 mg, 11.6 mmol, 6 eq.) and TMSCl (980 µL, 7.72 mmol, 4 eq.). The reaction mixture was stirred at room temperature for 2 h. The reaction was diluted with saturated aqueous NH_4Cl solution (30 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with saturated aqueous NaCl solution (3 x 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 60:1] to yield **2.98** (705 mg, 1.62 mmol, 84%) as a yellow oil.

Data for **2.98**:

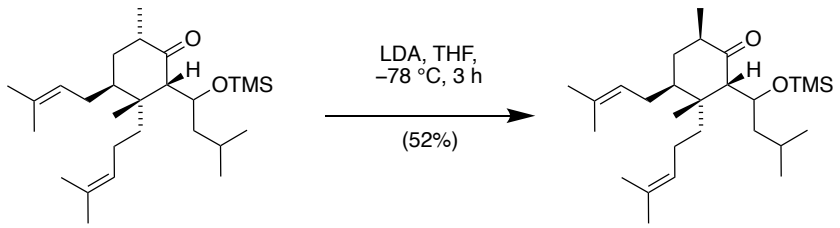
R_f = 0.65 [6:1 PE:Et_2O]

IR (neat): 2958, 2928, 1710, 1454, 1377, 1249, 1066, 837, 749 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.15 (ddt, *J* = 7.6, 4.5, 1.5 Hz, 1H), 5.02 (ddq, *J* = 7.2, 5.7, 1.4 Hz, 1H), 4.17 (ddd, *J* = 8.1, 4.9, 3.2 Hz, 1H), 2.60 (dd, *J* = 3.3, 1.1 Hz, 1H), 2.37 (dp, *J* = 13.0, 6.6 Hz, 1H), 2.28 – 2.13 (m, 2H), 1.84 (tdd, *J* = 13.7, 6.6, 3.9 Hz, 3H), 1.74 (s, 3H), 1.73 – 1.66 (m, 2H), 1.65 (s, 6H), 1.64 – 1.59 (m, 1H), 1.57 (s, 3H), 1.55 – 1.48 (m, 2H), 1.43 (ddd, *J* = 12.9, 8.0, 5.2 Hz, 1H), 1.21 (ddd, *J* = 14.2, 11.8, 5.5 Hz, 1H), 1.15 (s, 3H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.4 Hz, 3H, overlap), 0.90 (d, *J* = 6.4 Hz, 3H, overlap), 0.10 (s, 9H) ppm

^{13}C NMR (150 MHz, $CDCl_3$): δ 216.0, 135.2, 133.8, 127.3, 126.7, 72.4, 62.0, 48.3, 47.7, 43.8, 43.8, 39.5, 36.2, 29.0, 28.5, 28.3, 28.0, 26.0, 26.0, 24.8, 24.1, 20.5, 20.2, 17.5, 3.4 ppm.

HRMS (ESI): calculated for $C_{27}H_{51}O_2Si$ 435.3653 $[M+H]^+$, found 435.3655.



2.98 **2.99**

To a solution of diisopropylamine (413 µL, 2.94 mmol, 3.2 eq.) in dry THF (5 mL) at 0 °C was added *n*-BuLi (2.5 M in hexane, 1.18 mL, 2.94 mmol, 3.2 eq.). The reaction was stirred at 0 °C for 30 min before being cooled to –78 °C. A solution of **2.98** (400 mg, 0.92 mmol, 1 eq.) in dry THF (5 mL) was added to the reaction mixture. The reaction was stirred at –78 °C for 3 h. The mixture was quenched with saturated aqueous NH_4Cl solution (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl solution (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 60:1] to yield **2.99** (207 mg, 0.48 mmol, 52%) as a yellow oil.

Data for **2.99**:

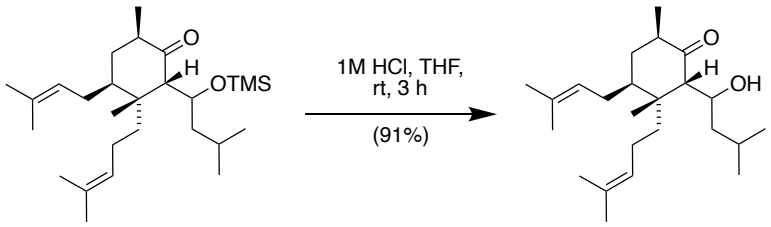
R_f = 0.60 [6:1 PE:Et_2O]

IR (neat): 2961, 2929, 1702, 1453, 1384, 1252, 1070, 887, 840 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.13 – 5.04 (m, 2H), 4.12 (ddd, *J* = 9.1, 4.8, 2.8 Hz, 1H), 2.88 (dp, *J* = 13.1, 6.5 Hz, 1H), 2.35 (dddd, *J* = 12.5, 10.7, 4.4, 2.7 Hz, 1H), 2.19 – 2.15 (m, 1H), 2.14 (d, *J* = 2.8 Hz, 1H), 2.00 (ddd, *J* = 13.6, 6.9, 4.4 Hz, 1H), 1.96 (dd, *J* = 13.0, 6.3 Hz, 1H), 1.81 (tq, *J* = 11.9, 5.4 Hz, 1H), 1.70 (s, 6H), 1.68 – 1.61 (m, 1H), 1.60 (s, 3H), 1.59 (s, 3H, overlap), 1.61 – 1.58 (m, 1H, overlap), 1.55 – 1.50 (m, 2H), 1.24 (ddd, *J* = 13.8, 9.1, 4.8 Hz, 1H), 1.16 – 1.06 (m, 2H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H, overlap), 0.85 (d, *J* = 6.6 Hz, 3H, overlap), 0.74 (s, 3H), 0.16 (s, 9H) ppm.

^{13}C NMR (150 MHz, CDCl3): δ 218.6, 134.5, 134.2, 127.1, 126.9, 71.8, 64.6, 49.5, 47.2, 45.6, 43.7, 40.4, 39.1, 31.1, 28.5, 28.4, 27.1, 26.3, 24.7, 24.7, 21.7, 20.6, 20.4, 17.3, 3.6 ppm.

HRMS (ESI): calculated for $C_{27}H_{50}NaO_2Si$ 457.3472 $[M+Na]^+$, found 457.3481.



2.99 **2.100**

To a solution of **2.99** (126 mg, 0.29 mmol, 1 eq.) in THF (8 mL) at 0 °C was added 1M aqueous HCl solution (0.6 mL, 0.58 mmol, 2 eq.). The mixture was stirred at 0 °C for 4 h. Then, the reaction mixture was allowed to warm to room temperature and stirred for another 3 h. The mixture was diluted with saturated aqueous NaCl solution (15 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl solution (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 30:1 → 10:1] to yield **2.100** (95.3 mg, 0.26 mmol, 91%) as a white solid.

Data for **2.100**:

R_f = 0.25 [6:1 PE:Et_2O]

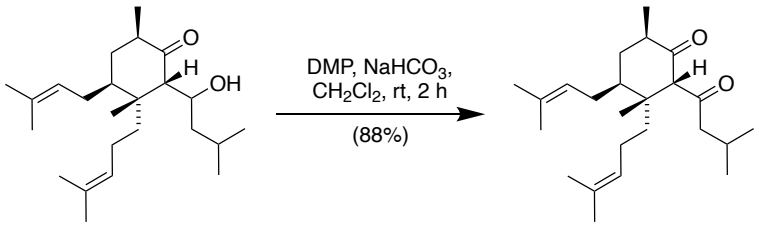
Mp = 112 – 113 °C

IR (neat): 3446, 2937, 2869, 1682, 1456, 1377, 1091, 1056, 849 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.15 – 5.05 (m, 2H), 4.08 (ddd, *J* = 8.9, 7.3, 3.8 Hz, 1H), 2.78 (dt, *J* = 13.1, 6.5 Hz, 1H), 2.28 – 2.14 (m, 2H), 2.08 (d, *J* = 2.9 Hz, 1H), 2.03 (ddd, *J* = 13.6, 6.8, 4.0 Hz, 1H), 1.97 (dt, *J* = 13.1, 6.5 Hz, 1H), 1.82 (dt, *J* = 12.9, 6.8 Hz, 1H), 1.71 (s, 3H), 1.69 (s, 3H), 1.67 – 1.61 (m, 2H), 1.54 (dd, *J* = 4.6, 1.6 Hz, 1H), 1.28 (ddd, *J* = 14.3, 9.5, 5.0 Hz, 1H), 1.23 – 1.18 (m, 1H), 1.18 – 1.11 (m, 1H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.78 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 216.2, 132.3, 131.6, 124.6, 124.2, 67.7, 63.7, 46.6, 45.0, 43.2, 41.7, 37.3, 37.1, 28.7, 26.0, 25.9, 24.7, 23.6, 22.4, 21.8, 19.8, 18.1, 17.9, 15.0 ppm.

HRMS (ESI): calculated for $C_{24}H_{43}O_2$ 363.3258 $[M+H]^+$, found 363.3258.



2.100 **2.60**

To a solution of **2.100** (131 mg, 0.36 mmol, 1 eq.) in CH_2Cl_2 (10 mL) at room temperature was added $NaHCO_3$ (60 mg, 0.72 mmol, 2 eq.) and Dess-Martin periodinane (306 mg, 0.72 mmol, 2 eq.). The reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with saturated aqueous $NaHCO_3$ solution (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with saturated aqueous NaCl solution (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 20:1] to yield **2.60** (114 mg, 0.317 mmol, 88%) as a white solid.

Data for **2.60**:

R_f = 0.55 [6:1 PE:Et_2O]

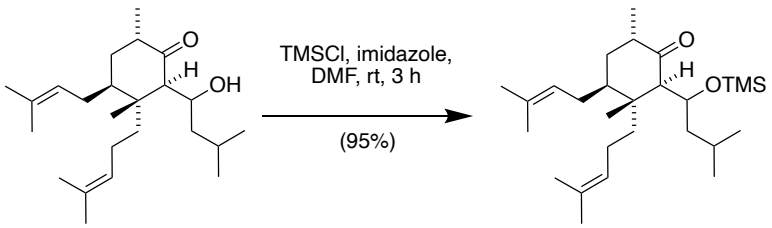
Mp = 65 – 68 °C

IR (neat): 2964, 2930, 2871, 1695, 1452, 1377, 1366, 1163, 1047, 833 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.14 (ddt, *J* = 8.9, 5.4, 1.6 Hz, 1H), 5.02 – 4.96 (m, 1H), 3.56 (s, 1H), 2.60 (dq, *J* = 12.6, 6.2 Hz, 2H), 2.39 (dd, *J* = 17.7, 6.9 Hz, 1H), 2.31 (dd, *J* = 17.7, 6.5 Hz, 1H), 2.19 – 2.12 (m, 1H), 2.09 – 2.03 (m, 2H), 1.88 (ddt, *J* = 13.0, 8.7, 3.8 Hz, 1H), 1.70 (s, 3H), 1.65 (s, 3H), 1.64 – 1.60 (m, 2H), 1.58 (s, 3H, overlap), 1.59 – 1.54 (m, 1H, overlap), 1.55 (s, 3H), 1.46 (dp, *J* = 14.9, 6.9, 5.5 Hz, 1H), 1.14 (q, *J* = 12.8 Hz, 1H), 0.95 (d, *J* = 6.4 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H), 0.75 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 208.8, 206.1, 132.5, 131.9, 124.1, 123.8, 75.4, 53.5, 45.2, 42.1, 40.9, 37.6, 37.3, 28.0, 26.0, 25.8, 23.7, 22.7, 22.5, 22.3, 18.8, 18.0, 17.8, 14.4 ppm.

HRMS (ESI): calculated for $C_{24}H_{41}O_2$ 361.3101 $[M+H]^+$, found 361.3085.



2.88 **2.101**

To a solution of **2.88** (496 mg, 1.34 mmol, 1 eq.) in DMF (20 mL) at room temperature was added imidazole (558 mg, 8.20 mmol, 6 eq.) and TMSCl (680 µL, 5.36 mmol, 4 eq.). The reaction mixture was stirred at room temperature for 3 h. The reaction was diluted with saturated aqueous NH_4Cl solution (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with saturated aqueous NaCl solution (3 x 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 60:1] to yield **2.101** (553 mg, 1.27 mmol, 95%) as a yellow oil.

Data for **2.101**:

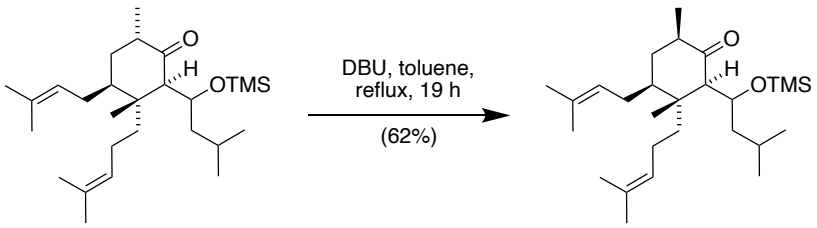
R_f = 0.60 [6:1 PE:Et_2O]

IR (neat): 2959, 2928, 1707, 1450, 1376, 1250, 1059, 837, 751 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.07 – 5.00 (m, 2H), 4.06 (ddd, *J* = 8.5, 5.1, 1.6 Hz, 1H), 2.72 (dp, *J* = 9.7, 6.7 Hz, 1H), 2.34 (s, 1H), 2.14 (dd, *J* = 13.9, 5.7 Hz, 1H), 1.93 – 1.85 (m, 2H), 1.85 – 1.81 (m, 1H), 1.81 – 1.74 (m, 2H), 1.70 (s, 3H), 1.67 (s, 3H), 1.61 (s, 3H), 1.60 – 1.58 (m, 1H), 1.58 (s, 3H), 1.54 – 1.48 (m, 1H), 1.48 – 1.41 (m, 1H), 1.37 – 1.31 (m, 2H), 1.31 – 1.25 (m, 1H), 1.05 (s, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.09 (s, 9H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 216.2, 132.4, 131.6, 124.3, 123.4, 70.1, 57.7, 46.1, 41.9, 41.8, 39.9, 39.7, 34.6, 28.2, 26.0, 25.9, 25.1, 23.7, 22.5, 21.8, 19.5, 18.1, 17.8, 15.8, 1.0 ppm.

HRMS (ESI): calculated for $C_{27}H_{51}O_2Si$ 435.3653 $[M+H]^+$, found 435.3667.



2.101 **2.102**

5:1 mixture of product to s.m.

To a solution of **2.101** (550 mg, 1.27 mmol, 1 eq.) in toluene (15 mL) was added DBU (1.9 mL, 12.7 mmol, 10 eq.). The reaction mixture was stirred at reflux for 19 h. The mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 80:1] to give an inseparable 5:1 mixture of **2.102** to s.m. (322 mg, 0.741 mmol, 62%) as a light yellow oil.

Data for **2.102**:

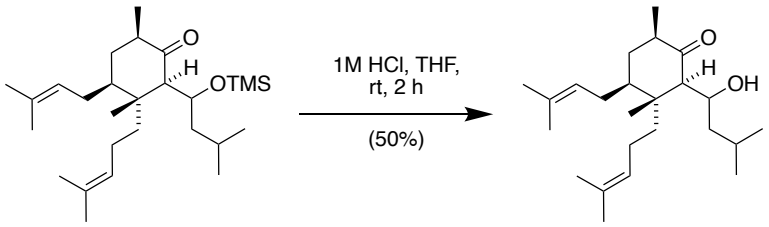
R_f = 0.60 [6:1 PE:Et_2O]

IR (neat): 2958, 2927, 1709, 1451, 1377, 1250, 1151, 1046, 837 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.16 – 5.11 (m, 1H), 5.09 (ddt, *J* = 7.8, 6.3, 1.5 Hz, 1H), 4.12 (ddd, *J* = 7.5, 5.2, 2.3 Hz, 1H), 2.59 (s, 1H), 2.31 – 2.23 (m, 1H), 2.16 – 2.01 (m, 3H), 1.96 – 1.86 (m, 1H), 1.86 – 1.76 (m, 2H), 1.73 (s, 3H), 1.70 (s, 3H), 1.68 – 1.63 (m, 2H), 1.61 (d, *J* = 3.8 Hz, 6H), 1.54 – 1.47 (m, 2H), 1.43 (ddd, *J* = 14.6, 12.8, 5.4 Hz, 1H), 1.15 (q, *J* = 12.7 Hz, 1H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 6.3 Hz, 3H, overlap), 0.90 (d, *J* = 6.3 Hz, 3H, overlap), 0.81 (s, 3H), 0.10 (s, 9H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 213.6, 132.6, 131.4, 124.7, 123.7, 69.9, 59.8, 45.8, 45.6, 45.5, 44.0, 37.4, 36.9, 27.2, 26.1, 25.9, 25.5, 23.6, 22.6, 21.9, 19.4, 18.1, 18.0, 14.6, 0.9 ppm.

HRMS (ESI): calculated for $C_{27}H_{51}O_2Si$ 435.3653 $[M+H]^+$, found 435.3659.



2.102 **2.103**

To a solution of **2.102** (136 mg, 0.313 mmol, 1 eq.) in THF (8 mL) at room temperature was added 1M aqueous HCl solution (0.6 mL, 0.627 mmol, 2 eq.). The reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with saturated aqueous NH_4Cl solution (15 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with saturated aqueous NaCl solution (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 60:1] to yield **2.103** (57.1 mg, 0.157 mmol, 50%) as a light yellow oil.

Data for **2.102**:

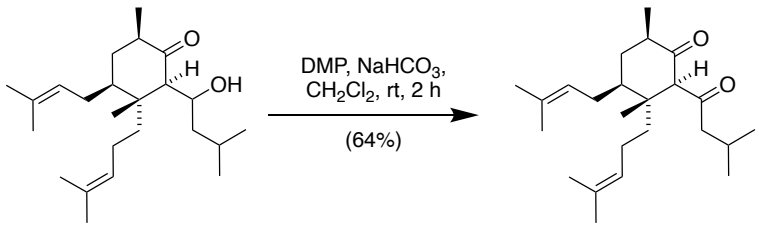
R_f = 0.25 [6:1 PE:Et_2O]

IR (neat): 3514, 2956, 2929, 2870, 1695, 1451, 1377, 1139, 1127, 841 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.12 (tdd, *J* = 6.1, 3.1, 1.4 Hz, 1H), 5.07 (ddd, *J* = 8.5, 5.5, 1.4 Hz, 1H), 3.86 (td, *J* = 10.8, 3.7 Hz, 1H), 3.77 (d, *J* = 11.5 Hz, 1H), 2.42 – 2.36 (m, 1H), 2.35 (s, 1H), 2.18 – 2.11 (m, 1H), 2.09 (td, *J* = 6.7, 3.8 Hz, 1H), 2.02 (dt, *J* = 12.4, 6.4 Hz, 1H), 1.85 (dddd, *J* = 13.8, 11.7, 4.5, 2.3 Hz, 2H), 1.77 – 1.70 (m, 2H, overlap), 1.73 (s, 3H), 1.69 (s, 3H), 1.68 – 1.57 (m, 2H, overlap) 1.61 (s, 6H, overlap), 1.22 (q, *J* = 12.7 Hz, 1H), 1.04 – 0.99 (m, 1H), 0.97 (d, *J* = 6.3 Hz, 3H), 0.93 (s, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 219.3, 132.8, 131.8, 123.9, 123.5, 68.1, 59.3, 47.7, 46.7, 46.5, 42.8, 38.1, 36.7, 27.6, 26.0, 25.9, 24.9, 23.8, 21.9, 21.5, 18.5, 18.0, 17.8, 14.1 ppm.

HRMS (ESI): calculated for $C_{24}H_{43}O_2$ 363.3258 $[M+H]^+$, found 363.3256.



2.103 **2.61**

To a solution of **2.103** (57.0 mg, 0.157 mmol, 1 eq.) in CH_2Cl_2 (10 mL) at room temperature was added $NaHCO_3$ (26.0 mg, 0.314 mmol, 2 eq.) and Dess-Martin periodinane (133 mg, 0.314 mmol, 2 eq.). The reaction mixture was stirred at room temperature for 2 h. The mixture was quenched with 1M aqueous HCl solution (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with saturated aqueous NH_4Cl solution (30 mL) and saturated aqueous NaCl solution (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 60:1] to yield **2.61** (36.2 mg, 0.100 mmol, 64%) as a white solid.

Data for **2.61**:

R_f = 0.45 [6:1 PE:Et_2O]

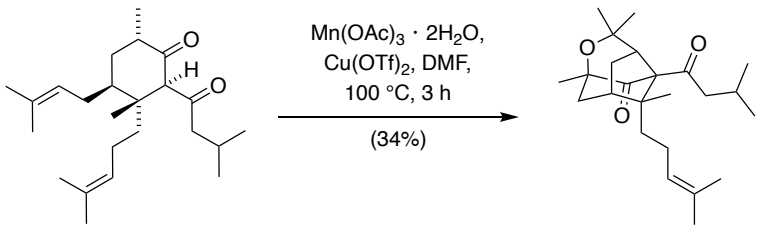
Mp = 52 – 55 °C

IR (neat): 2966, 2928, 2869, 1715, 1702, 1453, 1379, 1366, 1128, 1060, 843 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.11 (ddp, *J* = 8.8, 5.9, 1.4 Hz, 1H), 5.00 (ddt, *J* = 7.1, 5.6, 1.5 Hz, 1H), 3.68 (s, 1H), 2.49 – 2.36 (m, 1H), 2.32 – 2.24 (m, 1H), 2.23 – 2.16 (m, 2H), 2.10 (ddt, *J* = 11.5, 8.3, 5.3 Hz, 2H), 2.02 (dt, *J* = 12.7, 5.8 Hz, 1H), 1.88 – 1.76 (m, 2H), 1.73 (s, 3H), 1.72 – 1.69 (m, 1H), 1.67 (s, 3H), 1.61 (s, 3H), 1.59 (s, 3H), 1.52 – 1.44 (m, 2H), 1.21 (dt, *J* = 13.6, 12.4 Hz, 1H), 1.01 (d, *J* = 6.6 Hz, 3H, overlap), 1.00 (s, 3H, overlap), 0.92 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.4 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 210.5, 206.7, 133.1, 131.9, 123.8, 123.1, 68.5, 54.6, 45.8, 45.6, 42.5, 37.0, 36.8, 26.9, 26.0, 25.9, 23.8, 22.9, 22.6, 22.1, 18.1, 17.8, 17.7, 14.5 ppm.

HRMS (ESI): calculated for $C_{24}H_{41}O_2$ 361.3101 $[M+H]^+$, found 361.3115.



2.56 **2.89**

To a solution of **2.56** (47.9 mg, 0.133 mmol, 1 eq.) in DMF at room temperature was added $Mn(OAc)_3 \cdot 2\ H_2O$ (142 mg, 0.531 mmol, 4 eq.) and $Cu(OTf)_2$ (96.0 mg, 0.266 mmol, 2 eq.). The reaction mixture was heated at 100 °C for 3 h. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl solution (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 40:1 → 30:1] to yield **2.89** (16.3 mg, 0.0435 mmol, 34%) as a white crystalline solid.

Data for **2.89**:

R_f = 0.45 [5:1 PE:Et_2O]

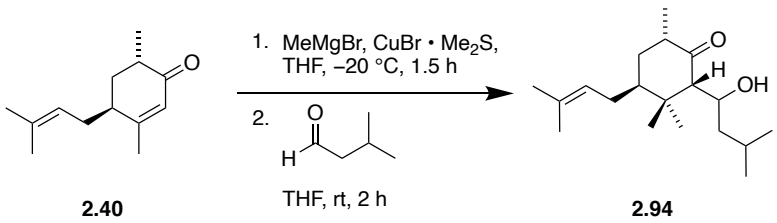
Mp = 56 – 59 °C

IR (neat): 2967, 2935, 1718, 1690, 1464, 1370, 1237, 1154, 1134, 1107, 976, 724 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.07 (ddt, *J* = 8.5, 7.0, 1.4 Hz, 1H), 3.53 (d, *J* = 10.3 Hz, 1H), 3.23 – 3.15 (m, 1H), 2.28 (t, *J* = 6.7 Hz, 1H), 2.26 – 2.24 (m, 1H), 2.24 – 2.16 (m, 1H), 2.04 – 1.97 (m, 3H), 1.87 – 1.78 (m, 3H), 1.69 (s, 3H), 1.58 (s, 3H), 1.51 (td, *J* = 13.1, 4.7 Hz, 1H), 1.35 (td, *J* = 13.2, 4.9 Hz, 1H), 1.27 (s, 3H), 1.19 (s, 3H), 0.97 – 0.92 (m, 12H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 211.4, 206.3, 132.3, 123.9, 77.2, 76.7, 74.5, 57.9, 52.9, 49.8, 43.0, 42.3, 35.4, 30.1, 29.0, 27.5, 25.8, 24.5, 23.7, 23.6, 23.0, 22.7, 22.6, 17.8 ppm.

HRMS (ESI): calculated for $C_{24}H_{39}O_3$ 375.2894 $[M+H]^+$, found 375.2895.



2.40 **2.94**

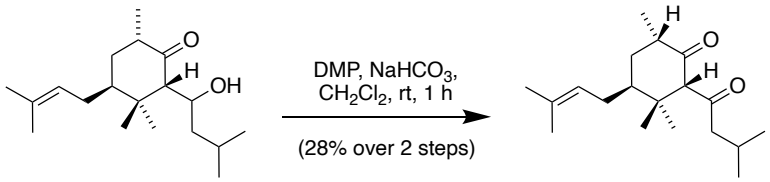
To a suspension of CuBr·Me_2S (214 mg, 1.04 mmol, 0.1 eq.) in dry THF (20 mL) at –20 °C was slowly added MeMgBr (3 M in Et_2O, 5.5 mL, 16.6 mmol, 1.6 eq.). The reaction mixture was stirred at –20 °C for 30 min before a solution of ketone **2.40** (2.00 g, 10.4 mmol, 1 eq.) in dry THF (5 mL) was added dropwise. The reaction mixture was stirred for 1 h at –20 °C. Then, a solution of isovaleraldehyde (1.45 mL, 13.5 mmol, 1.3 eq.) in dry THF (4 mL) was added and the reaction mixture was allowed to warm to room temperature. The mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (80 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 80 mL). The combined organic layers were washed with saturated aqueous NaCl solution (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 50:1] to yield an inseparable mixture of the Michael adduct and **2.94** as a yellow oil. The mixture was used in the next step without any further purification.

Partial data for **2.94**:

R_f = 0.50 [3:1 PE:Et_2O]

IR (neat): 3659, 3519, 2971, 1931, 1693, 1458, 1391, 1252, 1157, 957, 842 cm^{-1}.

HRMS (ESI): calculated for $C_{19}H_{35}O_2$ 295.2632 $[M+H]^+$, found 295.2631.



2.94 **2.96**

To a solution of **2.94** (0.832 mmol, 1 eq.) in CH_2Cl_2 (10 mL) at room temperature was added $NaHCO_3$ (91.0 mg, 1.09 mmol, 2 eq.) and Dess-Martin periodinane (461 mg, 1.09 mmol, 2 eq.). The reaction mixture was stirred at room temperature for 1 h. The mixture was quenched with saturated aqueous NaCl solution (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O solution (30 mL) and saturated aqueous NaCl solution (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 60:1] to yield **2.96** (67.5 mg, 0.231 mmol, 28% over 2 steps) as a colourless oil.

Data for **2.96**:

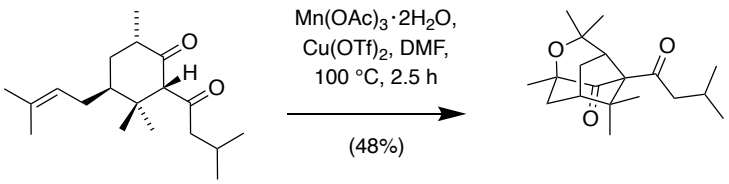
R_f = 0.55 [3:1 PE:Et_2O]

IR (neat): 2963, 2927, 2871, 1720, 1702, 1452, 1367, 1260, 1102. 1068, 726 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.14 (ddt, *J* = 8.6, 5.9, 1.4 Hz, 1H), 3.58 (s, 1H), 2.50 (dp, *J* = 13.0, 6.5 Hz, 1H), 2.39 – 2.29 (m, 2H), 2.27 – 2.21 (m, 1H), 2.21 – 2.12 (m, 2H), 1.89 (ddd, *J* = 13.9, 6.6, 3.4 Hz, 1H), 1.74 (s, 3H), 1.71 – 1.67 (m, 1H), 1.66 (s, 3H), 1.49 (dq, *J* = 11.4, 3.6 Hz, 1H), 1.17 (s, 3H), 1.04 (s, 3H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H, overlap), 0.91 (d, *J* = 6.6 Hz, 3H, overlap) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 210.1, 206.8, 133.0, 123.6, 68.3, 54.7, 45.8, 42.5, 41.0, 34.0, 26.5, 26.0, 25.8, 25.5, 24.2, 22.8, 22.5, 18.0, 15.0 ppm.

HRMS (ESI): calculated for $C_{19}H_{33}O_2$ 293.2475 $[M+H]^+$, found 293.2475.



2.96 **2.97**

To a solution of **2.96** (55.0 mg, 0.188 mmol, 1 eq.) in DMF (5 mL) at room temperature was added $Mn(OAc)_3 \cdot 2\ H_2O$ (202 mg, 0.752 mmol, 4 eq.) and $Cu(OTf)_2$ (136 mg, 0.376 mmol, 2 eq.). The reaction mixture was heated at 100 °C for 2.5 h. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (15 mL) and diluted with H_2O (15 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with saturated aqueous NaCl solution (3 x 40 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 40:1 → 20:1] to yield **2.97** (27.8 mg, 0.091 mmol, 48%) as a colourless oil.

Data for **2.97**:

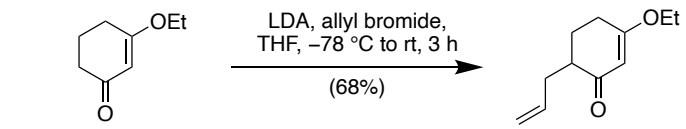
R_f = 0.40 [3:1 PE:Et_2O]

IR (neat): 2956, 2933,1721, 1695, 1466, 1373, 1291, 1138, 1074, 983 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.52 (d, *J* = 10.4 Hz, 1H), 3.20 (q, *J* = 8.9 Hz, 1H), 2.32 – 2.22 (m, 3H), 2.00 (d, *J* = 12.8 Hz, 1H), 1.94 (dt, *J* = 14.5, 2.8 Hz, 1H), 1.81 (dd, *J* = 14.4, 2.6 Hz, 1H), 1.79 – 1.74 (m, 1H), 1.26 (s, 3H), 1.19 (s, 3H), 1.13 (s, 3H), 0.98 – 0.93 (m, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 211.4, 206.2, 74.4, 54.9, 52.3, 49.6, 46.8, 43.5, 30.2, 29.9, 28.9, 27.4, 25.8, 24.3, 23.6, 23.0, 22.7, 22.4 ppm.

HRMS (ESI): calculated for $C_{19}H_{31}O_3$ 307.2268 $[M+H]^+$, found 307.2273.



3-ethoxy-2-cyclohexenone (**2.44**)

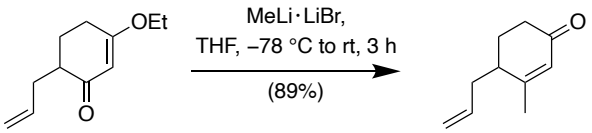
2.107

To a solution of diisopropylamine (6.00 mL, 42.8 mmol, 1.2 eq.) in dry THF (25 mL) at 0 °C was added *n*-Buli (2.5 M in hexane, 17.1 mL, 42.8 mmol, 1.2 eq.). The reaction mixture was stirred at 0 °C for 30 min before being cooled to –78 °C. To the solution was added 3-ethoxy-2-cyclohexenone (**2.44**, 5.0 g, 35.7 mmol, 1 eq.) and the mixture was stirred for another 30 min at –78 °C. Then, allyl bromide (3.40 mL, 39.3 mmol, 1.1 eq.) was added and the reaction mixture was stirred at –78 °C for 1 h. The reaction was allowed to warm to room temperature and stirred for another 2 h. The mixture was quenched with saturated aqueous NH_4Cl solution (25 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with saturated aqueous NH_4Cl solution (30 mL) and saturated aqueous NaCl solution (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 5:1] to yield **2.107** (4.38 g, 24.3 mmol, 68%) as a yellow oil.

Partial data for **2.107**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.89 – 5.72 (m, 1H), 5.33 (s, 1H), 5.15 – 5.06 (m, 1H), 5.06 – 5.00 (m, 1H), 3.89 (ddd, J = 7.3, 5.5, 2.2 Hz, 2H), 2.70 – 2.59 (m, 1H), 2.42 (qd, J = 5.2, 2.6 Hz, 2H), 2.25 (dddd, J = 10.3, 8.9, 5.0, 1.2 Hz, 1H), 2.19 – 2.02 (m, 2H), 1.77 – 1.66 (m, 1H), 1.36 (t, J = 7.0 Hz, 3H) ppm.

The analytical data match those reported in literature.[34]



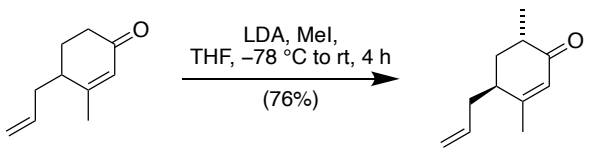
2.107 **2.108**

To a solution of ketone **2.107** (4.38 g, 24.3 mmol, 1 eq.) in dry THF (25 mL) at –78 °C was slowly added MeLi·LiBr (1.5 M in diethyl ether, 24.0 mL, 36.5 mmol, 1.5 eq.). The reaction mixture was stirred for 3 h at –78 °C before being warmed to room temperature and stirred for another 30 min. The reaction was carefully quenched with 1M aqueous HCl solution (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (50 mL) and saturated aqueous NaCl solution (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 5:1 → 4:1] to yield **2.108** (3.23 g, 21.5 mmol, 89%) as a yellow oil.

Partial data for **2.108**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.85 (s, 1H), 5.78 (dddd, *J* = 16.6, 10.1, 7.8, 6.3 Hz, 1H), 5.16 – 5.05 (m, 2H), 2.49 – 2.37 (m, 2H), 2.37 – 2.15 (m, 3H), 2.04 (dddd, *J* = 15.7, 10.2, 5.7, 4.2 Hz, 1H), 1.98 (s, 3H), 1.91 (dddd, *J* = 13.4, 6.5, 4.0, 1.5 Hz, 1H) ppm.

The analytical data match those reported in literature.[35]



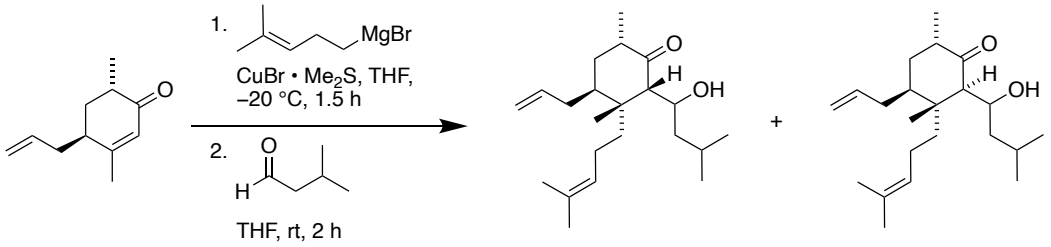
2.108 **2.106**

To a solution of diisopropylamine (3.64 mL, 25.8 mmol, 1.2 eq.) in dry THF (30 mL) at 0 °C was added *n*-Buli (2.5 M in hexane, 10.4 mL, 25.8 mmol, 1.2 eq.). The reaction mixture was stirred at 0 °C for 30 min before being cooled to –78 °C. Ketone **2.108** (3.23 g, 21.5 mmol, 1 eq.) dissolved in dry THF (7.5 mL) was added slowly and the mixture was stirred for another 30 min at –78 °C. Then, iodomethane (1.50 mL, 23.7 mmol, 1.1 eq.) was added and the reaction mixture was stirred at –78 °C for 30 min. The reaction was allowed to warm to room temperature and stirred for 3 h. The mixture was quenched with saturated aqueous NH_4Cl solution (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with saturated aqueous NaCl solution (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 10:1 → 5:1] to yield **2.106** (2.76 g, 16.8 mmol, 76%) as a yellow oil.

Partial data for **2.106**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.92 – 5.62 (m, 2H), 5.19 – 5.04 (m, 2H), 2.58 – 2.37 (m, 2H), 2.35 – 2.14 (m, 2H), 2.01 (dddd, *J* = 13.5, 4.9, 2.9, 0.8 Hz, 1H), 1.96 (s, 3H), 1.78 (td, *J* = 12.9, 5.0 Hz, 1H), 1.11 (d, *J* = 6.8 Hz, 3H) ppm.

The analytical data match those reported in literature.[34]



2.106 **2.109** (26%) **2.110** (15%)

A suspension of Mg granules (586 mg, 24.4 mmol, 2 eq.) in dry THF (20 mL) and dibromoethane (0.2 mL) was carefully heated to 40 °C for 10 min. To the suspension, a solution of homoprenyl bromide (2.60 mL, 19.5 mmol, 1.6 eq.) in dry THF (3 mL) was added dropwise. The reaction mixture was stirred at 40 °C for 45 min. Then, the reaction mixture was slowly added to a suspension of CuBr·Me_2S (250 mg, 1.22 mmol, 0.1 eq.) in dry THF (16 mL) at –20 °C. The reaction mixture was stirred at –20 °C for 30 min before a solution of ketone **2.106** (2.00 g, 12.2 mmol, 1 eq.) in dry THF (3 mL) was added dropwise. The reaction mixture was stirred for 1 h at –20 °C. Then, a solution of isovaleraldehyde (1.70 mL, 15.9 mmol, 1.3 eq.) in dry THF (3 mL) was added and the reaction mixture was allowed to warm to room temperature. The mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (100 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 70 mL). The combined organic layers were washed with saturated aqueous NaCl solution (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 50:1 → 20:1] to yield **2.109** (1.07 mg, 3.20 mmol, 26%) as a yellow oil. Further elution yielded **2.110** (604 mg, 1.81 mmol, 15%) as a yellow oil.

Data for **2.109**:

R_f = 0.55 [PE:Et_2O 6:1]

IR (neat): 3514, 2958, 2929, 2870, 1691, 1457, 1379, 1139, 997, 912 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.85 – 5.77 (m, 1H), 5.13 – 5.00 (m, 3H), 3.82 – 3.81 (m, 1H), 2.48 – 2.44 (m, 1H), 2.44 – 2.39 (m, 1H), 2.32 (s, 1H), 2.26 – 2.18 (m, 1H), 2.03 (ddd, *J* = 14.5, 11.9, 5.0 Hz, 1H), 1.94 (ddd, *J* = 13.9, 6.5, 2.2 Hz, 1H), 1.89 – 1.83 (m, 2H), 1.82 – 1.75 (m, 2H), 1.72 – 1.66 (m, 1H), 1.65 (s, 3H), 1.61 – 1.58 (m, 1H), 1.57 (s, 3H), 1.26 (ddd, *J* = 14.4, 11.7, 5.5 Hz, 1H), 1.15 (s, 3H), 1.13 – 1.07 (m, 1H), 0.97 (d, *J* = 6.3 Hz, 3H), 0.92 – 0.89 (m, 6H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 218.0, 138.1, 131.4, 124.7, 116.4, 68.0, 58.8, 48.0, 46.3, 41.2, 39.4, 36.6, 33.8, 32.4, 25.8, 25.1, 24.2, 23.4, 22.1, 21.7, 17.7, 14.2 ppm.

HRMS (ESI): calculated for $C_{22}H_{39}O_2$ 335.2945 $[M+H]^+$, found 335.2945.

Data for **2.110**:

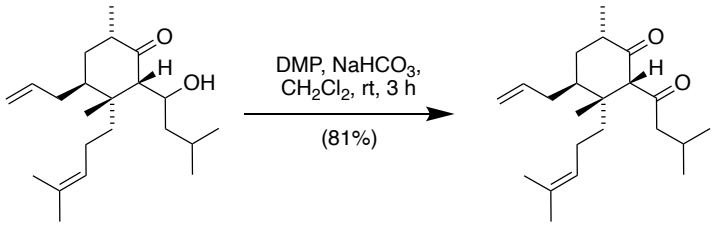
R_f = 0.40 [PE:Et_2O 6:1]

IR (neat): 3517, 2956, 2929, 2870, 1693, 1457, 1386, 1138, 991, 911 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.84 – 5.70 (m, 1H), 5.08 (ddt, *J* = 7.1, 4.3, 1.5 Hz, 1H), 5.05 (dq, *J* = 6.4, 1.8 Hz, 1H), 5.02 (dd, *J* = 1.6, 0.9 Hz, 1H), 3.89 (tdd, *J* = 11.3, 4.0, 1.1 Hz, 1H), 3.58 (d, *J* = 11.5 Hz, 1H), 2.57 (s, 1H), 2.49 (tt, *J* = 7.3, 5.4 Hz, 1H), 2.33 (dddd, *J* = 15.5, 6.0, 3.0, 1.6 Hz, 1H), 2.11 – 1.97 (m, 2H), 1.88 – 1.80 (m, 2H), 1.79 – 1.76 (m, 1H), 1.76 – 1.73 (m, 1H), 1.73 – 1.71 (m, 1H), 1.70 (s, 3H), 1.69 – 1.64 (m, 2H), 1.62 (s, 3H), 1.55 (ddd, *J* = 15.2, 11.8, 5.2 Hz, 1H), 1.20 (d, *J* = 7.3 Hz, 3H), 1.00 (ddd, *J* = 13.3, 8.9, 4.0 Hz, 1H), 0.95 (s, 3H), 0.93 – 0.89 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 221.7, 137.6, 131.9, 123.8, 116.4, 67.9, 54.7, 47.6, 46.4, 45.4, 36.8, 36.7, 34.6, 33.7, 25.9, 24.9, 23.7, 22.0, 21.5, 18.3, 18.1, 17.8 ppm.

HRMS (ESI): calculated for $C_{22}H_{39}O_2$ 335.2945 $[M+H]^+$, found 335.2945.



2.109 **2.105**

To a solution of **2.109** (148 mg, 0.442 mmol, 1 eq.) in CH_2Cl_2 (40 mL) at room temperature was added $NaHCO_3$ (74 mg, 0.885 mmol, 2 eq.) and Dess-Martin periodinane (375 mg, 0.885 mmol, 2 eq.). The reaction mixture was stirred at room temperature for 3 h. The mixture was diluted with saturated aqueous $NaHCO_3$ solution (40 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with saturated aqueous NaCl solution (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 40:1] to yield **2.105** (130 mg, 0.392 mmol, 81%) as a colourless oil.

Data for **2.105**:

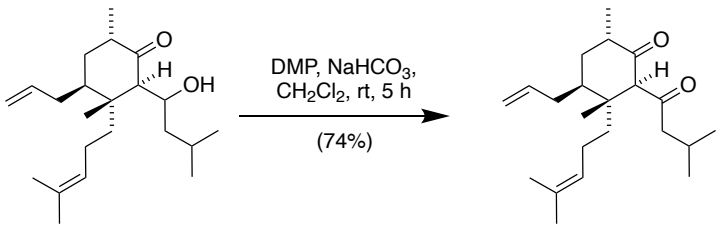
R_f = 0.55 [6:1 PE:Et_2O]

IR (neat): 2961, 2929, 2872, 1722, 1703, 1457, 1377, 1366, 912 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.82 (dddd, *J* = 17.0, 10.0, 8.7, 5.2 Hz, 1H), 5.16 – 5.01 (m, 3H), 3.60 (s, 1H), 2.54 – 2.48 (m, 1H), 2.48 – 2.43 (m, 1H), 2.33 (dd, *J* = 16.9, 7.2 Hz, 1H), 2.22 (dd, *J* = 17.0, 6.3 Hz, 1H), 2.19 – 2.13 (m, 2H), 2.13 – 2.09 (m, 1H), 1.96 – 1.92 (m, 1H), 1.90 (dt, *J* = 6.5, 3.6 Hz, 1H), 1.85 (dt, *J* = 12.8, 6.4 Hz, 1H), 1.77 (tt, *J* = 13.1, 6.2 Hz, 1H), 1.65 (s, 3H), 1.63 – 1.58 (m, 1H), 1.57 (s, 3H), 1.25 (ddd, *J* = 14.3, 12.1, 5.2 Hz, 1H), 1.03 (s, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H, overlap), 0.90 (d, *J* = 6.5 Hz, 3H, overlap) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 209.8, 206.5, 137.9, 131.6, 124.4, 116.6, 68.5, 54.5, 44.9, 40.9, 38.6, 35.2, 33.1, 32.5, 25.8, 24.2, 22.8, 22.5, 22.2, 21.6, 17.7, 15.2 ppm.

HRMS (ESI): calculated for $C_{22}H_{37}O_2$ 332.2788 $[M+H]^+$, found 333.2790.



2.110 **2.111**

To a solution of **2.110** (65 mg, 0.194 mmol, 1 eq.) in CH_2Cl_2 (20 mL) at room temperature was added $NaHCO_3$ (33 mg, 0.389 mmol, 2 eq.) and Dess-Martin periodinane (165 mg, 0.389 mmol, 2 eq.). The reaction mixture was stirred at room temperature for 3 h. Then, another portion of Dess-Martin periodinane (165 mg, 0.389 mmol, 2 eq.) were added and the reaction was stirred at room temperature for 2 h. The mixture was diluted with saturated aqueous NH_4Cl solution (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with saturated aqueous NaCl solution (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 40:1] to yield **2.111** (48 mg, 0.144 mmol, 74%) as a colourless oil.

Data for **2.111**:

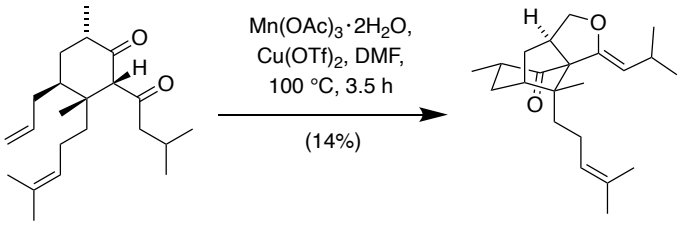
R_f = 0.40 [6:1 PE:Et_2O]

IR (neat): 2960, 2929, 2872, 1725, 1702, 1458, 1383, 1366, 911 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.76 (dddd, *J* = 16.9, 10.2, 8.0, 5.8 Hz, 1H), 5.10 – 4.98 (m, 3H), 3.81 (s, 1H), 2.67 – 2.58 (m, 1H), 2.31 (dd, *J* = 16.9, 6.4 Hz, 2H), 2.24 – 2.17 (m, 1H), 2.17 – 2.11 (m, 1H), 2.03 (dq, *J* = 16.5, 7.0 Hz, 1H), 1.93 – 1.79 (m, 3H), 1.79 – 1.70 (m, 2H), 1.68 (s, 3H), 1.61 (s, 3H), 1.44 (ddd, *J* = 10.2, 7.1, 5.2 Hz, 2H), 1.22 (d, *J* = 7.2 Hz, 3H), 1.04 (s, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 212.6, 207.0, 137.6, 132.0, 123.7, 116.6, 66.0, 54.8, 45.2, 43.1, 38.0, 37.1, 33.7, 33.1, 25.9, 23.9, 22.8, 22.6, 22.2, 18.3, 17.8, 17.8 ppm.

HRMS (ESI): calculated for $C_{22}H_{37}O_2$ 333.2788 $[M+H]^+$, found 333.2791.



2.105 **2.112**

To a solution of **2.105** (43.0 mg, 0.129 mmol, 1 eq.) in DMF (4 mL) at room temperature was added $Mn(OAc)_3 \cdot 2\ H_2O$ (139 mg, 0.517 mmol, 4 eq.) and $Cu(OTf)_2$ (93.0 mg, 0.258 mmol, 2 eq.). The reaction mixture was heated at 100 °C for 3.5 h. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (30 mL) and saturated aqueous NaCl solution (3 x 30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 40:1 → 20:1] to yield **2.112** (5.9 mg, 0.0186 mmol, 14%) as a pale yellow oil.

Data for **2.112**:

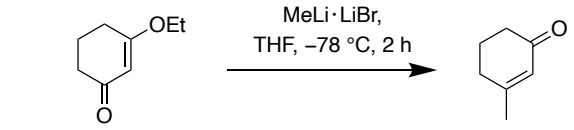
R_f = 0.20 [5:1 PE:Et_2O]

IR (neat): 2953, 2925, 2868, 1714, 1457, 1378, 1070, 1047, 700 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.05 (tt, *J* = 7.1, 1.4 Hz, 1H), 4.36 (d, *J* = 8.8 Hz, 1H), 4.29 (dd, *J* = 10.2, 8.6 Hz, 1H), 3.76 (t, *J* = 8.4 Hz, 1H), 3.00 – 2.92 (m, 1H), 2.74 – 2.66 (m, 1H), 2.56 – 2.50 (m, 1H), 2.34 (dt, *J* = 6.4, 3.2 Hz, 1H), 2.17 – 2.14 (m, 1H), 2.09 – 2.04 (m, 1H), 2.00 (dd, *J* = 13.5, 9.3 Hz, 1H), 1.91 (ddd, *J* = 13.6, 9.0, 2.8 Hz, 1H), 1.84 (ddt, *J* = 12.8, 6.2, 3.2 Hz, 1H), 1.67 (s, 3H), 1.61 – 1.57 (m, 1H, overlap), 1.59 (s, 3H, overlap), 1.32 – 1.28 (m, 1H), 1.07 (d, *J* = 6.5 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.98 (s, 3H), 0.85 – 0.82 (m, 1H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 209.9, 147.7, 131.9, 124.3, 110.2, 75.7, 72.2, 52.4, 47.5, 45.2, 38.7, 36.7, 35.3, 33.9, 25.8, 25.6, 24.0, 23.6, 23.0, 21.3, 17.8, 15.3 ppm.

HRMS (ESI): calculated for $C_{22}H_{35}O_2$ 331.2632 $[M+H]^+$, found 331.2633.



3-ethoxy-2-cyclohexenone (**2.44**)

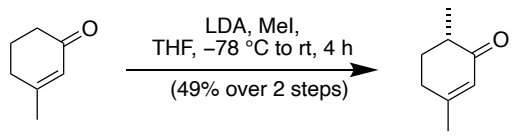
2.115

To a solution of 3-ethoxy-2-cyclohexenone (**2.44**, 5.00 g, 35.7 mmol, 1 eq.) in dry THF (30 mL) at –78 °C was slowly added MeLi·LiBr (1.5 M in diethyl ether, 36.0 mL, 53.5 mmol, 1.5 eq.). The reaction mixture was stirred for 2 h at –78 °. The reaction was allowed to warm to room temperature and carefully quenched with 1M aqueous HCl solution (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (50 mL) and saturated aqueous NaCl solution (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product **2.115** was used without the need for further purification in the next step.

Partial data for **2.115**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.90 – 5.86 (m, 1H), 2.37 – 2.32 (m, 2H), 2.28 (t, *J* = 6.0 Hz, 2H), 2.03 – 1.98 (m, 2H), 1.96 (s, 3H) ppm.

The analytical data match those reported in literature.[36]



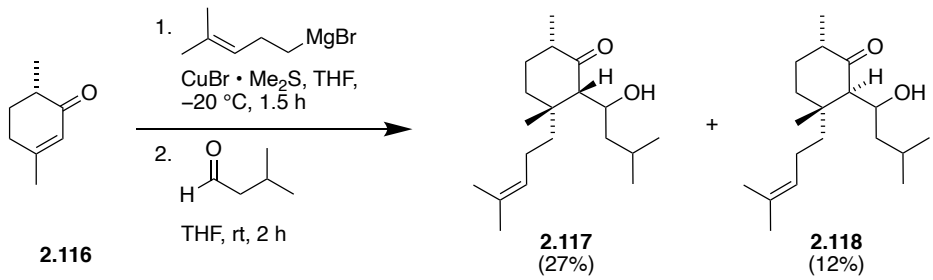
2.115 **2.116**

To a solution of diisopropylamine (6.00 mL, 42.8 mmol, 1.2 eq.) in dry THF (30 mL) at 0 °C was added *n*-Buli (2.5 M in hexane, 17.1 mL, 42.8 mmol, 1.2 eq.). The reaction mixture was stirred at 0 °C for 30 min before being cooled to –78 °C. Ketone **2.115** (35.7 mmol, 1 eq.) dissolved in dry THF (10 mL) was added slowly and the mixture was stirred for another 30 min at –78 °C. Then, iodomethane (2.40 mL, 39.3 mmol, 1.1 eq.) was added and the reaction mixture was stirred at –78 °C for 30 min. The reaction was allowed to warm to room temperature and stirred for 3 h. The mixture was quenched with saturated aqueous NH_4Cl solution (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with saturated aqueous NaCl solution (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 9:1 → 5:1] to yield **2.116** (2.16 g, 17.4 mmol, 49% over 2 steps) as a yellow oil.

Partial data for **2.116**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.85 (s, 1H), 2.46 – 2.18 (m, 3H), 2.11 – 2.00 (m, 1H), 1.94 (s, 3H), 1.77 – 1.59 (m, 2H), 1.13 (d, J = 6.9 Hz, 3H) ppm.

The analytical data match those reported in literature.[37,38]



A suspension of Mg granules (391 mg, 16.1 mmol, 2 eq.) in dry THF (8 mL) and dibromoethane (0.2 mL) was carefully heated to 40 °C for 10 min. To the suspension, a solution of homoprenyl bromide (1.70 mL, 12.8 mmol, 1.6 eq.) in dry THF (2 mL) was added dropwise. The reaction mixture was stirred at 40 °C for 45 min. Then, the reaction mixture was slowly added to a suspension of CuBr·Me_2S (167 mg, 0.805 mmol, 0.1 eq.) in dry THF (2 mL) at –20 °C. The reaction mixture was stirred at –20 °C for 30 min before a solution of ketone **2.116** (1.00 g, 8.05 mmol, 1 eq.) in dry THF (2 mL) was added dropwise. The reaction mixture was stirred for 1 h at –20 °C. Then, a solution of isovaleraldehyde (1.20 mL, 10.5 mmol, 1.3 eq.) in dry THF (2 mL) was added and the reaction mixture was allowed to warm to room temperature. The mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with saturated aqueous NaCl solution (70 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 50:1 → 30:1] to yield **2.117** (1.01 g, 3.44 mmol, 27%) as a yellow oil. Further elution yielded **2.118** (442 mg, 1.50 mmol, 12%) as a yellow oil.

Data for **2.117**:

$\mathbf{R_f}$ = 0.50 [PE:Et_2O 6:1]

IR (neat): 3513, 2956, 2930, 2868, 1691, 1456, 1378, 1138, 1083, 927, 841 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.08 (t, *J* = 6.9 Hz, 1H), 3.95 – 3.85 (m, 2H), 2.45 – 2.34 (m, 1H), 2.14 (s, 1H), 1.97 (ddd, *J* = 13.0, 6.5, 3.5 Hz, 1H), 1.94 – 1.86 (m, 2H), 1.86 – 1.81 (m, 2H), 1.80 – 1.75 (m, 1H), 1.69 – 1.67 (m, 1H), 1.65 (s, 3H), 1.57 (s, 3H), 1.54 – 1.44 (m, 2H), 1.23 – 1.16 (m, 1H), 1.14 (s, 3H), 1.09 (ddd, *J* = 12.9, 8.3, 4.4 Hz, 1H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 218.0, 131.2, 124.8, 68.0, 64.6, 47.9, 46.7, 44.3, 36.3, 33.3, 32.2, 26.6, 25.8, 25.1, 23.4, 22.2, 22.2, 17.7, 14.3 ppm.

HRMS (ESI): calculated for $C_{19}H_{35}O_2$ 295.2632 $[M+H]^+$, found 295.2637.

Data for **2.118**:

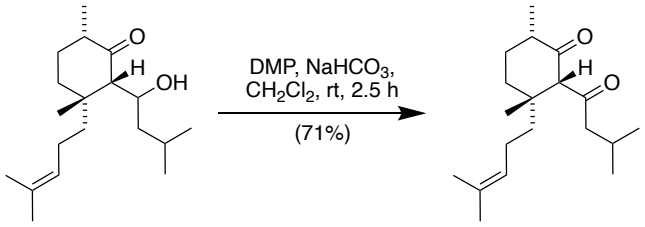
R_f = 0.35 [PE:Et_2O 6:1]

IR (neat): 3516, 2956, 2930, 2868, 1692, 1455, 1377, 1169, 1138, 1078, 934, 840 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.09 (dddd, *J* = 7.1, 5.7, 2.9, 1.5 Hz, 1H), 3.84 (dddd, *J* = 11.2, 9.9, 4.0, 1.1 Hz, 1H), 3.70 (d, *J* = 11.4 Hz, 1H), 2.39 (dtd, *J* = 12.7, 6.3, 1.3 Hz, 1H), 2.25 (s, 1H), 2.01 (dddd, *J* = 13.2, 6.5, 4.0, 2.5 Hz, 2H), 1.91 – 1.87 (m, 1H), 1.87 – 1.84 (m, 1H), 1.84 – 1.80 (m, 1H), 1.74 – 1.70 (m, 1H), 1.69 (s, 3H), 1.61 (s, 3H), 1.59 – 1.42 (m, 4H), 1.04 (s, 3H), 1.03 – 1.01 (m, 1H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 218.9, 131.8, 124.3, 67.7, 60.6, 47.6, 46.7, 44.2, 41.8, 37.4, 32.6, 25.9, 24.9, 23.7, 22.4, 22.2, 22.0, 17.8, 14.2 ppm.

HRMS (ESI): calculated for $C_{19}H_{35}O_2$ 295.2632 $[M+H]^+$, found 295.2635.



2.117 **2.119**

To a solution of **2.117** (770 mg, 2.61 mmol, 1 eq.) in CH_2Cl_2 (50 mL) at room temperature was added $NaHCO_3$ (439 mg, 5.22 mmol, 2 eq.) and Dess-Martin periodinane (4.40 g, 10.4 mmol, 4 eq.). The reaction mixture was stirred at room temperature for 2.5 h before being filtered through a pad of Celite™. The filtrate was diluted with saturated aqueous NH_4Cl solution (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with saturated aqueous NaCl solution (70 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 60:1] to yield **2.119** (540 mg, 1.85 mmol, 71%) as a light yellow oil.

Data for **2.119**:

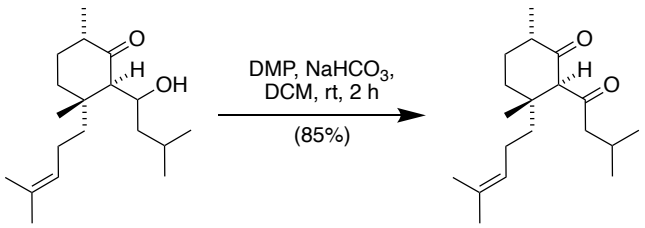
R_f = 0.40 [6:1 PE:Et_2O]

IR (neat): 2960, 2929, 2870, 1706, 1455, 1377, 1366, 1058, 834, 710 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.07 (tp, *J* = 7.0, 1.4 Hz, 1H), 3.45 (s, 1H), 2.51 – 2.38 (m, 1H), 2.28 (dd, *J* = 16.4, 7.0 Hz, 1H), 2.21 – 2.16 (m, 1H), 2.16 – 2.11 (m, 1H), 2.11 – 2.05 (m, 1H), 1.99 (ddd, *J* = 12.8, 6.3, 2.7 Hz, 1H), 1.91 – 1.86 (m, 1H), 1.86 – 1.78 (m, 2H), 1.65 (s, 3H), 1.57 (s, 3H), 1.49 (d, *J* = 9.9 Hz, 2H), 1.16 (ddd, *J* = 14.4, 10.8, 6.4 Hz, 1H), 1.06 (s, 3H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 209.5, 206.8, 131.4, 124.6, 73.4, 54.7, 45.5, 43.2, 35.7, 32.0, 31.2, 25.8, 25.7, 24.3, 22.8, 22.5, 21.9, 17.7, 14.8 ppm.

HRMS (ESI): calculated for $C_{19}H_{33}O_2$ 293.2475 $[M+H]^+$, found 293.2480.



2.118 **2.120**

To a solution of **2.118** (440 mg, 1.49 mmol, 1 eq.) in CH_2Cl_2 (25 mL) at room temperature was added $NaHCO_3$ (250 mg, 2.99 mmol, 2 eq.) and Dess-Martin periodinane (1.25 g, 2.99 mmol, 2 eq.). The reaction mixture was stirred at room temperature for 2 h before being filtered through a pad of SiO_2. The mixture was diluted with saturated aqueous $NaHCO_3$ solution (25 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with saturated aqueous NaCl solution (70 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 60:1] to yield **2.120** (369 mg, 1.26 mmol, 85%) as a light yellow oil.

Data for **2.120**:

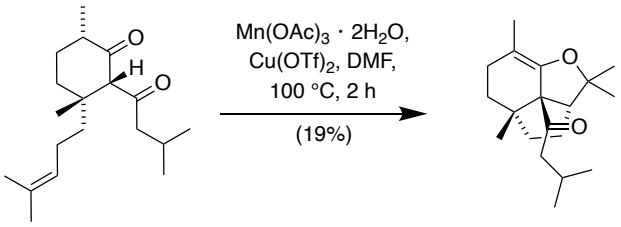
R_f = 0.35 [6:1 PE:Et_2O]

IR (neat): 2961, 2929, 2870, 1706, 1454, 1378, 1366, 1056, 834, 707 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.03 (tt, *J* = 7.1, 1.5 Hz, 1H), 3.51 (s, 1H), 2.46 – 2.39 (m, 1H), 2.28 (ddd, *J* = 16.4, 6.8, 2.8 Hz, 1H), 2.21 – 2.12 (m, 3H), 2.05 – 1.95 (m, 2H), 1.88 (td, *J* = 8.6, 7.4, 5.7 Hz, 1H), 1.76 (td, *J* = 14.0, 4.2 Hz, 1H), 1.67 (s, 3H), 1.59 (s, 3H), 1.56 – 1.52 (m, 1H), 1.43 – 1.37 (m, 2H), 1.10 (s, 3H), 1.03 (d, *J* = 6.4 Hz, 3H), 0.93 – 0.89 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 210.2, 206.9, 131.8, 124.2, 70.4, 54.6, 45.5, 43.5, 41.7, 37.2, 31.5, 25.8, 24.0, 22.9, 22.6, 22.6, 20.5, 17.7, 14.6 ppm.

HRMS (ESI): calculated for $C_{19}H_{33}O_2$ 293.2475 $[M+H]^+$, found 293.2475.



2.119 **2.122**

To a solution of **2.119** (35.0 mg, 0.120 mmol, 1 eq.) in DMF (4 mL) at room temperature was added $Mn(OAc)_3 \cdot 2H_2O$ (129 mg, 0.480 mmol, 4 eq.) and $Cu(OTf)_2$ (87.0 mg, 0.240 mmol, 2 eq.). The reaction mixture was heated at 100 °C for 2 h. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl solution (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 50:1] to yield **2.122** (6.6 mg, 0.023 mmol, 19%) as a yellow oil.

Data for **2.122**:

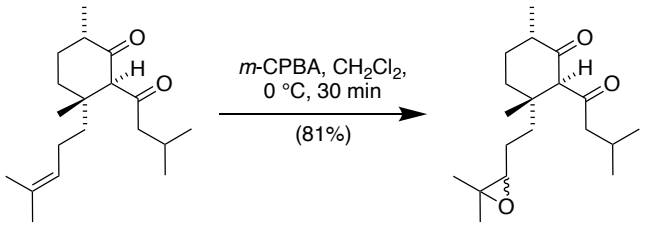
R_f = 0.65 [5:1 PE:Et_2O]

IR (neat): 2957, 2929, 1698, 1461, 1366, 1166, 1149, 1119, 842 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.17 (dd, *J* = 10.7, 3.2 Hz, 1H), 2.53 (dd, *J* = 17.6, 6.2 Hz, 1H), 2.28 – 2.23 (m, 1H), 2.23 – 2.19 (m, 1H), 2.12 (dt, *J* = 13.3, 6.6 Hz, 1H), 2.09 – 2.02 (m, 1H), 1.84 (dtd, *J* = 13.3, 10.9, 7.5 Hz, 1H), 1.72 (dd, *J* = 11.6, 8.0 Hz, 1H), 1.64 (d, *J* = 1.1 Hz, 3H), 1.60 (d, *J* = 4.8 Hz, 1H), 1.57 (d, *J* = 1.8 Hz, 2H), 1.27 – 1.22 (m, 1H), 1.21 (s, 3H), 1.15 (s, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.84 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 212.0, 148.3, 105.6, 85.0, 72.0, 52.4, 50.0, 45.6, 37.8, 30.6, 30.3, 26.8, 25.5, 24.9, 24.2, 24.2, 22.9, 22.8, 15.5 ppm.

HRMS (ESI): calculated for $C_{19}H_{31}O_2$ 291.2319 $[M+H]^+$, found 291.2323.



2.120 **2.126**

To a solution of diketone **2.120** (220 mg, 0.75 mmol, 1 eq.) in CH_2Cl_2 (30 mL) at 0 °C was added *m*-CPBA (77%, 168 mg, 0.75 mmol, 1 eq.). The reaction mixture was stirred at 0 °C for 30 min. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (3 x 50 mL) and with saturated aqueous NaCl solution (50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 3:1] to yield **2.126** (188 mg, 0.609 mmol, 81%) as an inseparable 1:1 mixture of diastereomers.

Partial data for **2.126**:

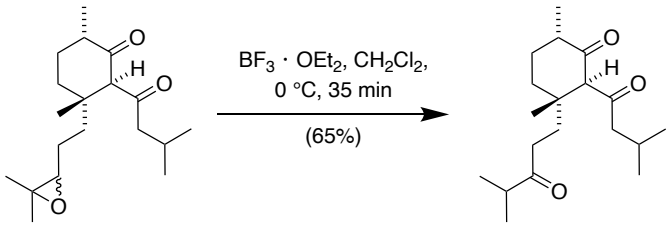
R_f = 0.30 [1:1 PE:Et_2O]

IR (neat): 2958, 2930, 2871, 1720, 1703, 1459, 1378, 1366, 1122, 1059, 870 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.55 – 3.49 (m, 2H), 2.65 (dt, *J* = 8.3, 5.6 Hz, 2H), 2.51 – 2.42 (m, 2H), 2.30 (dt, *J* = 16.5, 6.5 Hz, 2H), 2.23 – 2.18 (m, 2H), 2.18 – 2.12 (m, 2H), 2.06 – 1.98 (m, 2H), 1.82 – 1.67 (m, 2H), 1.61 – 1.47 (m, 8H), 1.30 (s, 6H), 1.26 (s, 6H), 1.11 (s, 6H), 1.04 (dd, *J* = 8.0, 6.3 Hz, 6H), 0.96 – 0.87 (m, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 210.0, 209.8, 206.9, 206.7, 72.9, 72.9, 70.5, 70.1, 64.4, 64.3, 58.6, 58.5, 54.5, 54.3, 45.5, 45.5, 43.1, 42.9, 38.1, 37.1, 35.5, 31.4, 31.4, 31.1, 28.0, 25.5, 24.9, 24.0, 23.7, 23.6, 23.1, 22.8, 22.5, 20.5, 20.0, 18.7, 18.6, 14.5 ppm.

HRMS (ESI): calculated for $C_{19}H_{33}O_3$ 309.2424 $[M+H]^+$, found 309.2427.



2.126 **2.128**

To a solution of epoxide **2.126** (41.4 mg, 0.134 mmol, 1 eq.) in CH_2Cl_2 (10 mL) at 0 °C was added $BF_3.OEt_2$ (17 µL, 0.134 mmol, 1 eq.). The reaction mixture was stirred at 0 °C for 35 min. The mixture was quenched with saturated aqueous NH_4Cl solution (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl solution (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 3:1] to yield **2.128** (27.1 mg, 0.088 mmol, 65%) as a yellow oil.

Data for **2.128**:

R_f = 0.35 [2:1 PE:Et_2O]

IR (neat): 2961, 2931, 2871, 1702, 1456, 1381, 1366, 1057, 708 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.48 (s, 1H), 2.60 (p, *J* = 6.9 Hz, 1H), 2.50 – 2.33 (m, 3H), 2.29 (dd, *J* = 16.8, 7.1 Hz, 1H), 2.23 – 2.18 (m, 1H), 2.18 – 2.11 (m, 1H), 2.06 – 1.98 (m, 1H), 1.74 – 1.64 (m, 2H), 1.62 (dt, *J* = 6.5, 2.0 Hz, 1H), 1.57 – 1.49 (m, 2H), 1.09 (s, 3H, overlap), 1.09 (s, 3H, overlap), 1.08 (d, *J* = 2.0 Hz, 3H), 1.03 (d, *J* = 6.4 Hz, 3H), 0.94 – 0.88 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 214.3, 209.7, 206.9, 70.9, 54.6, 45.5, 42.9, 41.1, 37.4, 35.3, 34.9, 31.4, 24.0, 22.9, 22.5, 19.8, 18.5, 18.4, 14.5 ppm.

HRMS (ESI): calculated for $C_{19}H_{33}O_3$ 309.2424 $[M+H]^+$, found 309.2427.

2.5 References

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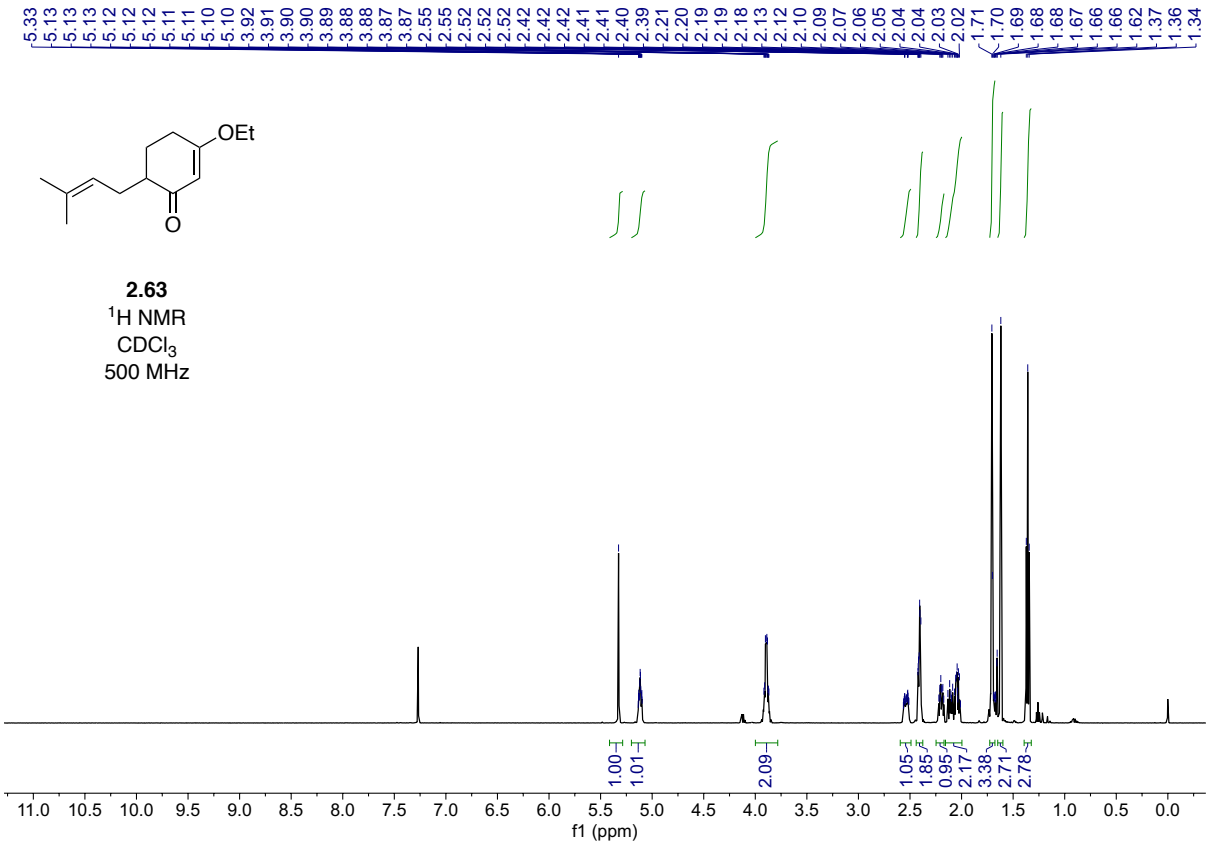
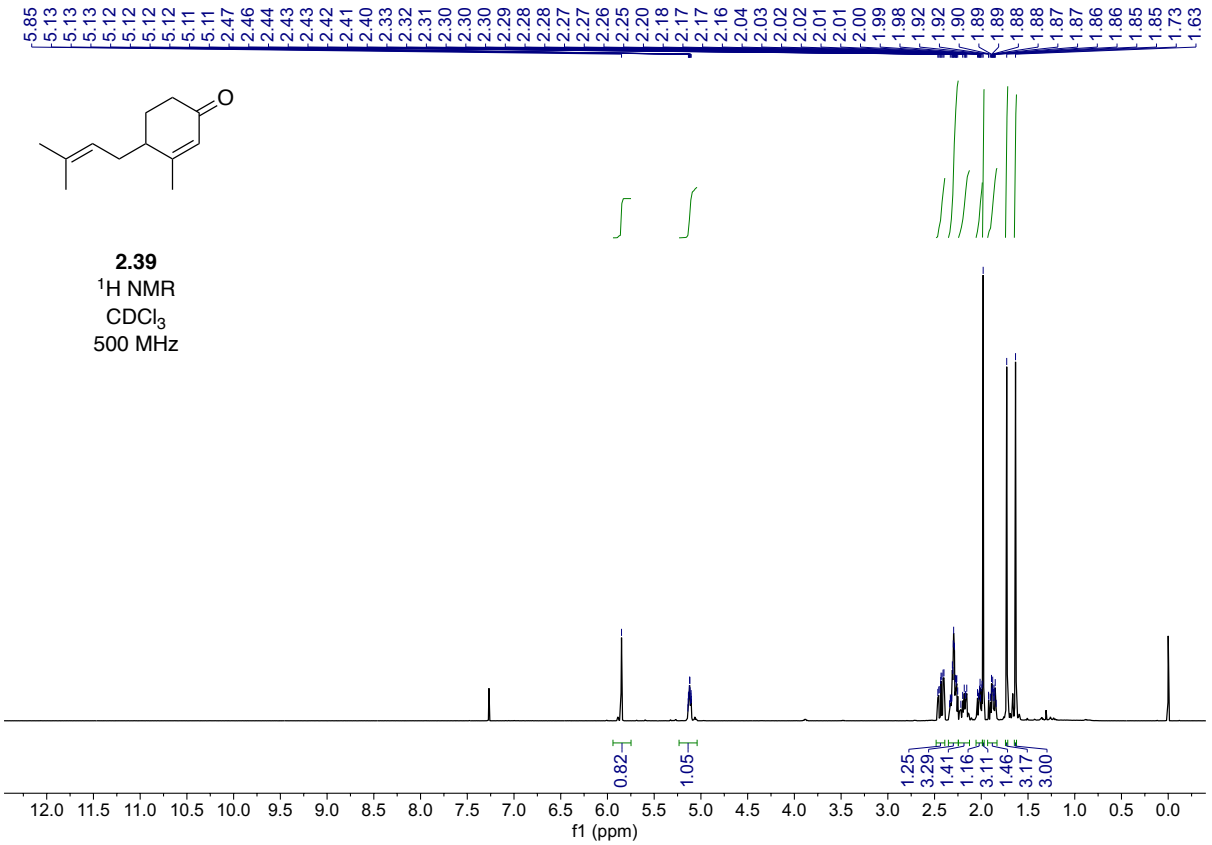
2.6 Appendix

2.6.1 NMR Spectra





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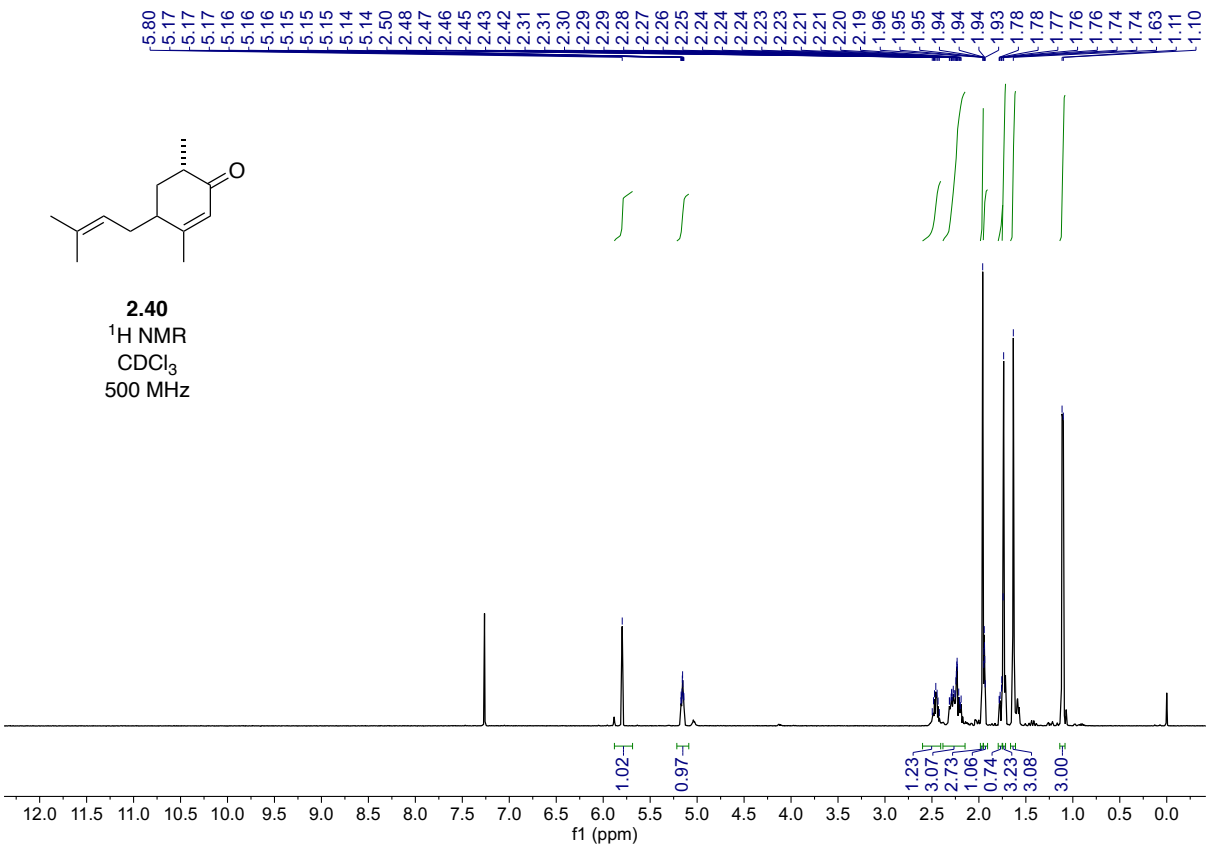

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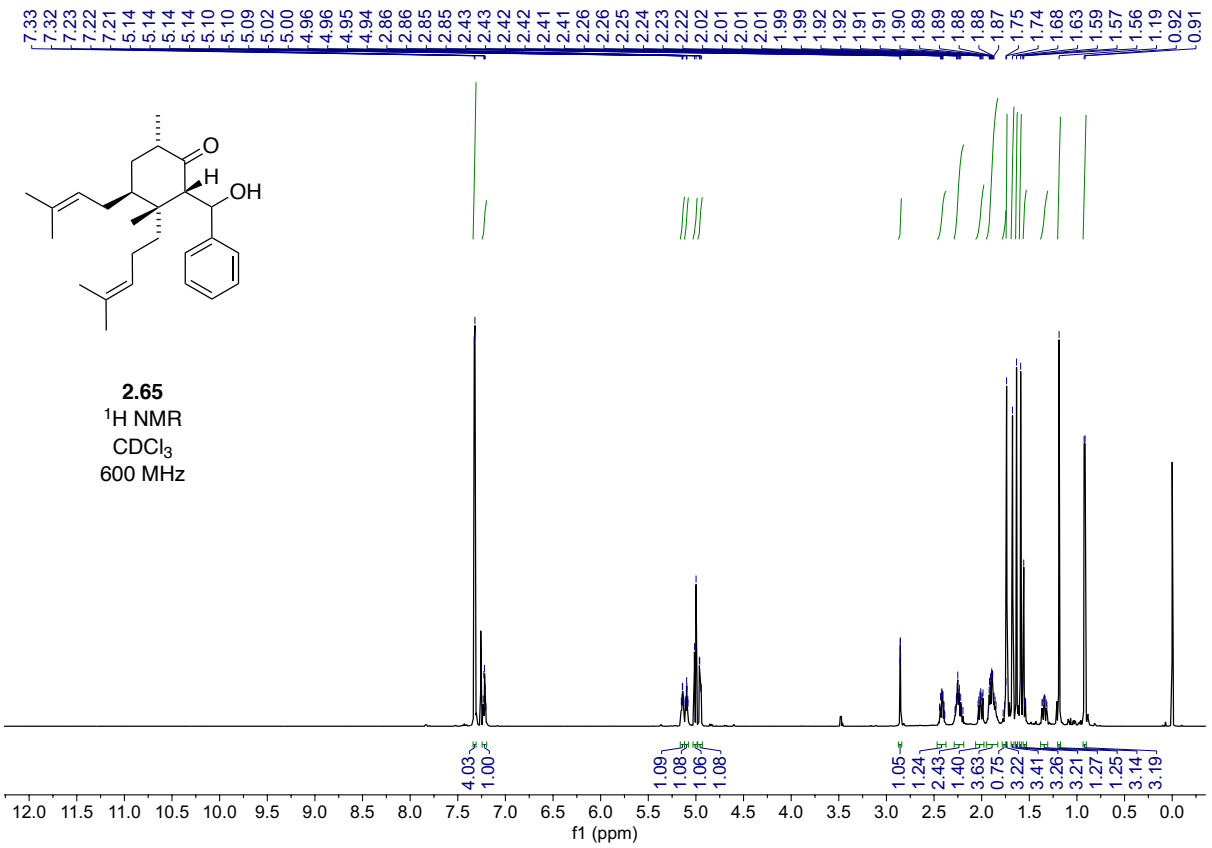
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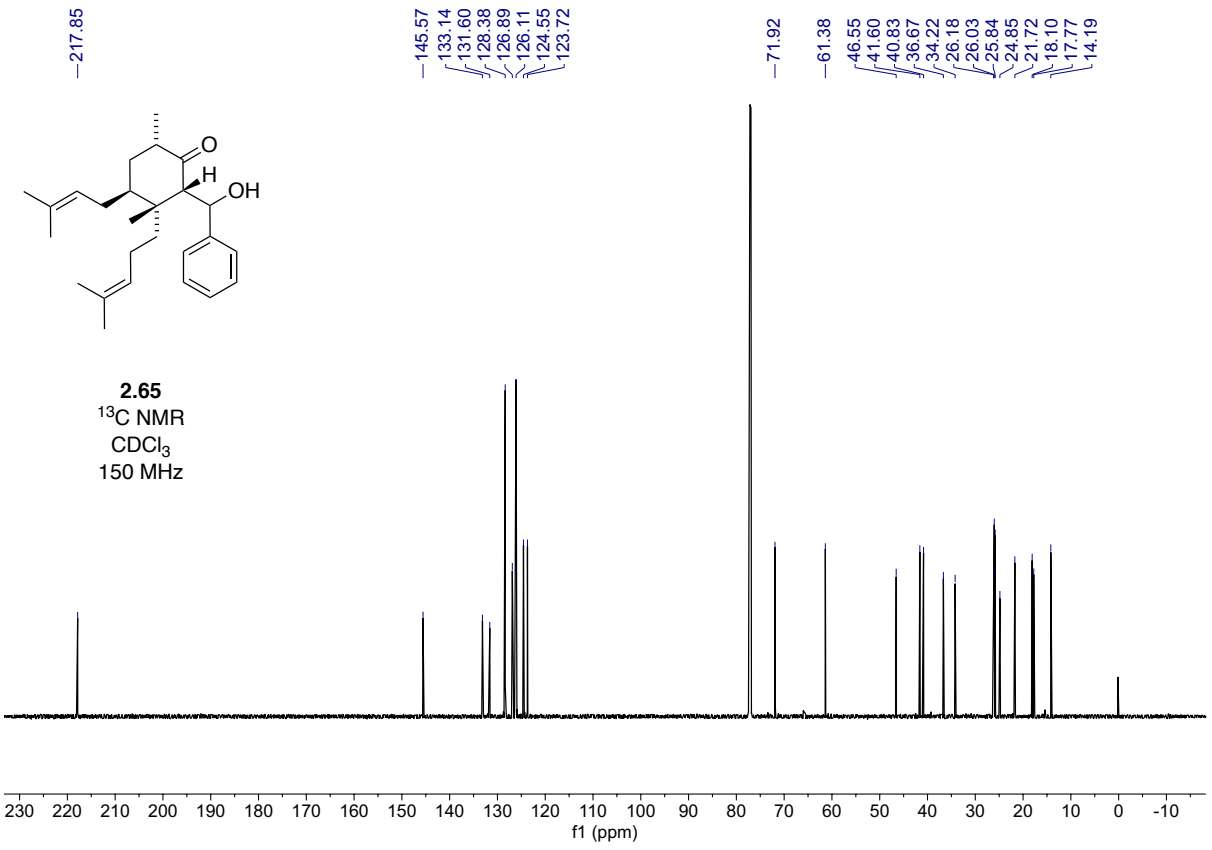
O
H
OH
2.65
1H NMR
CDCl3
600 MHz
4.03 1.00 1.09 1.08 1.06 1.08 1.05 1.24 2.43 1.40 3.63 0.75 3.22 3.41 3.26 3.21 1.27 1.25 3.14 3.19
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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H
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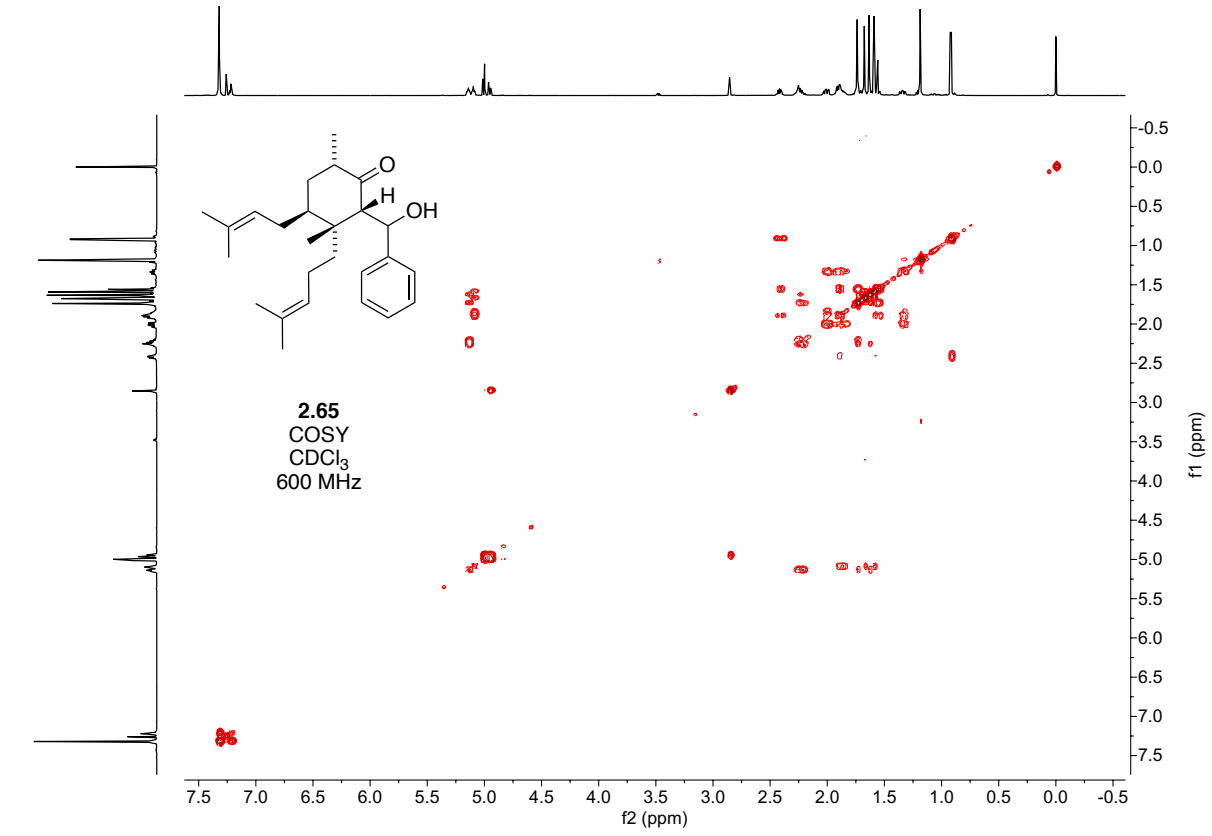
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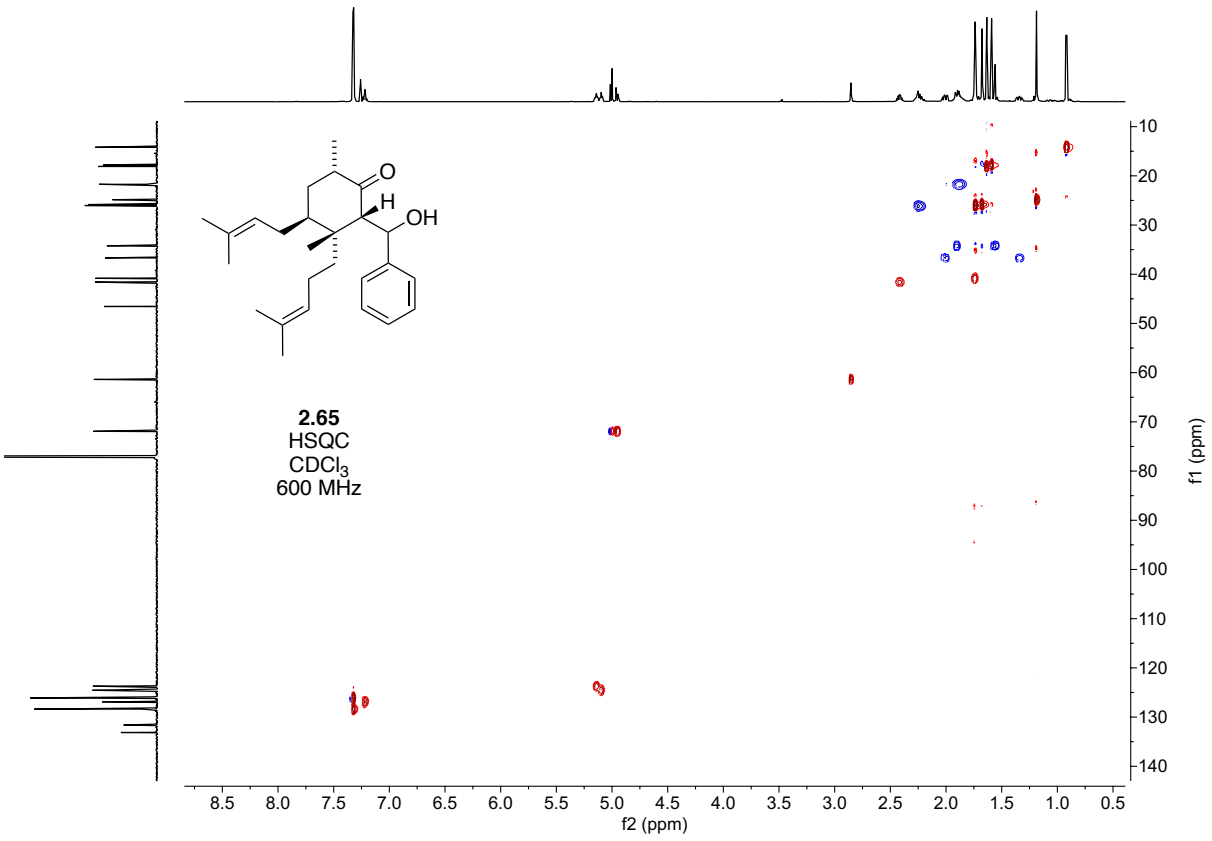
2.65
COSY
CDCl3
600 MHz
f2 (ppm)
f1 (ppm)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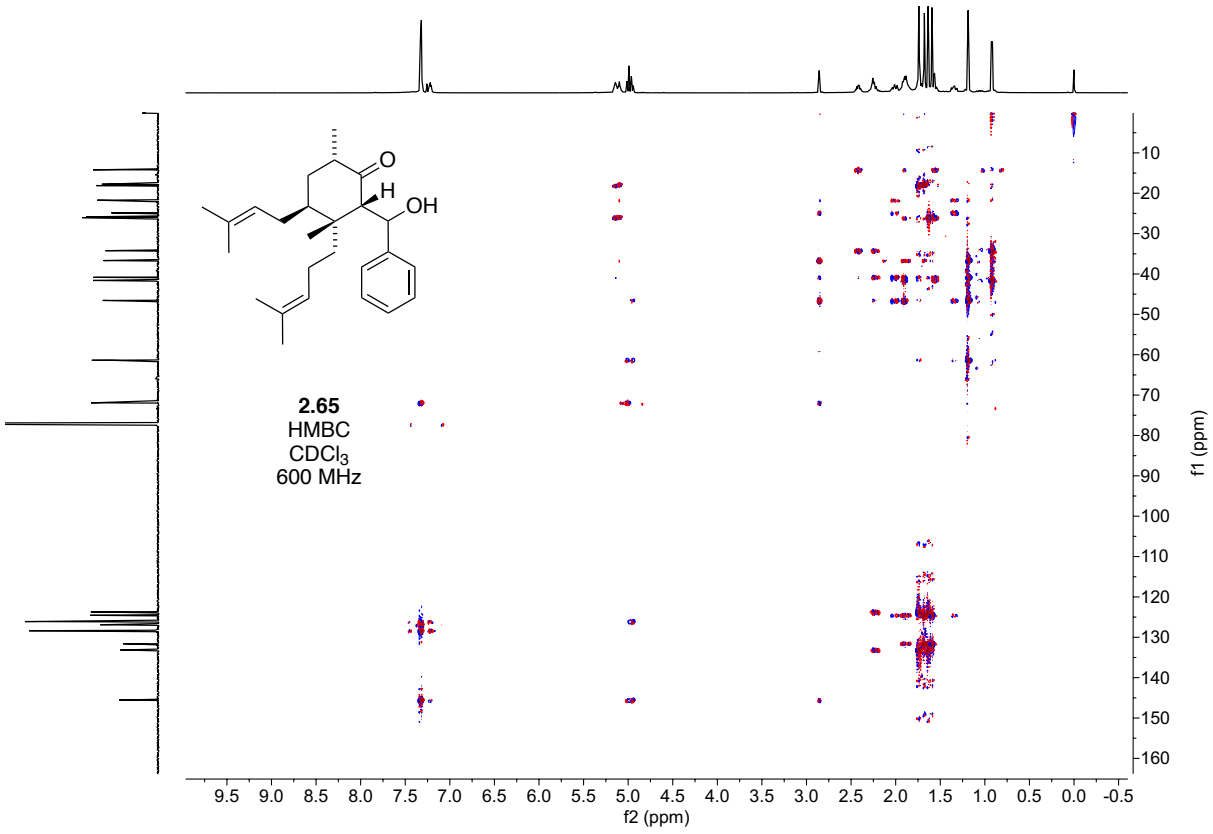
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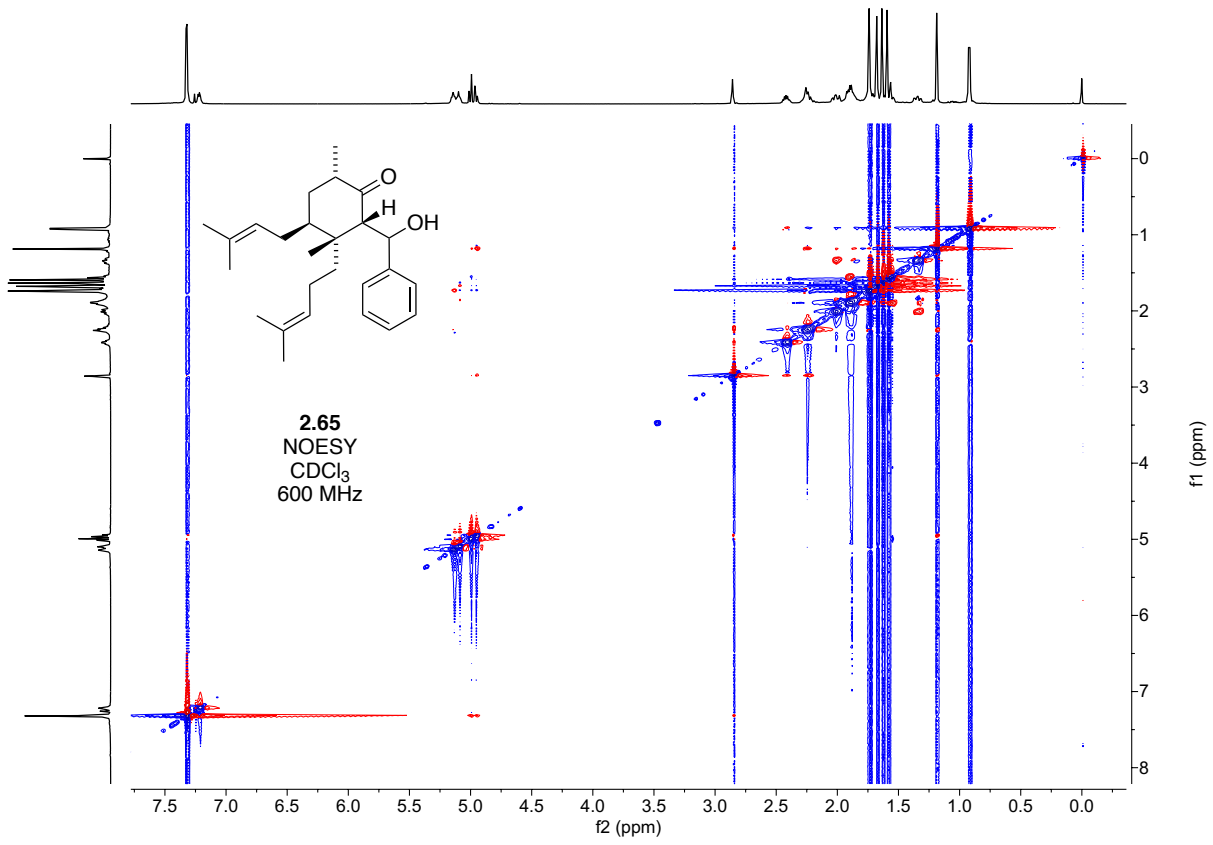
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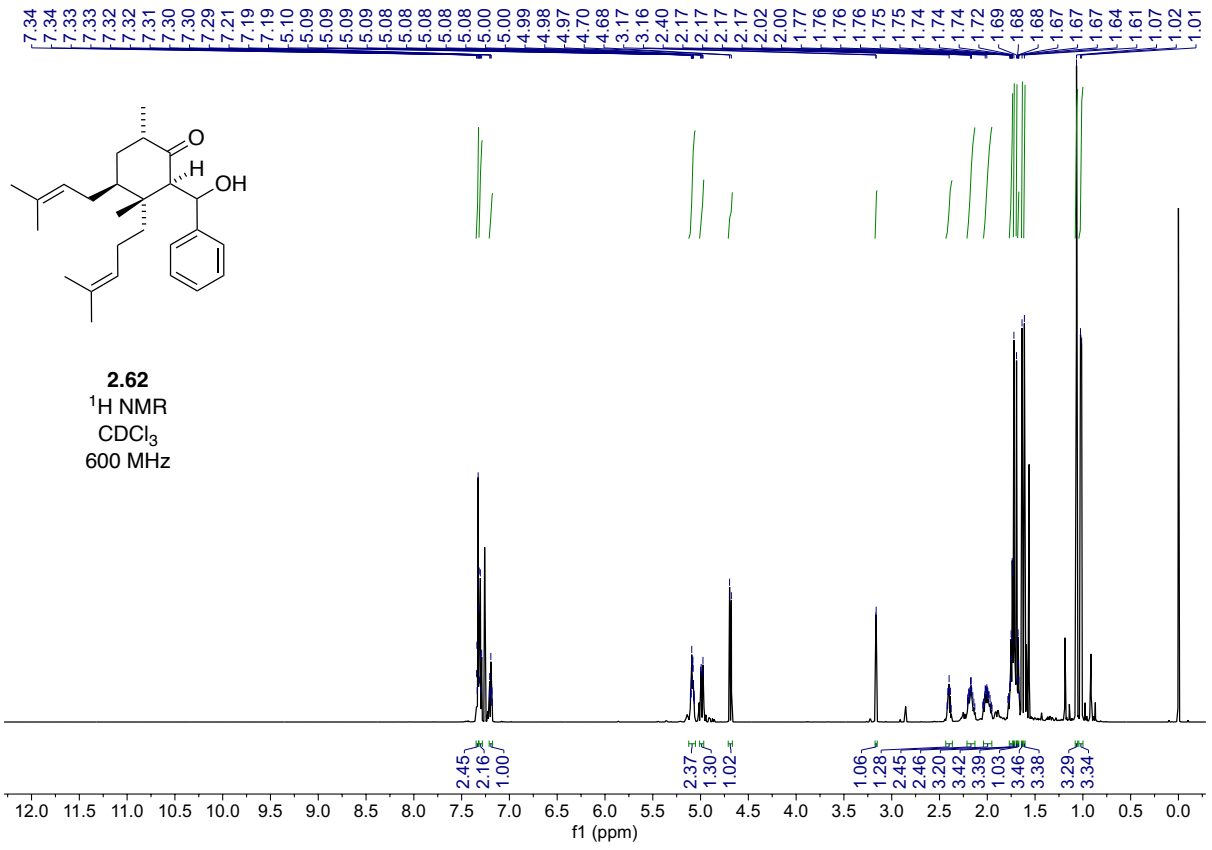
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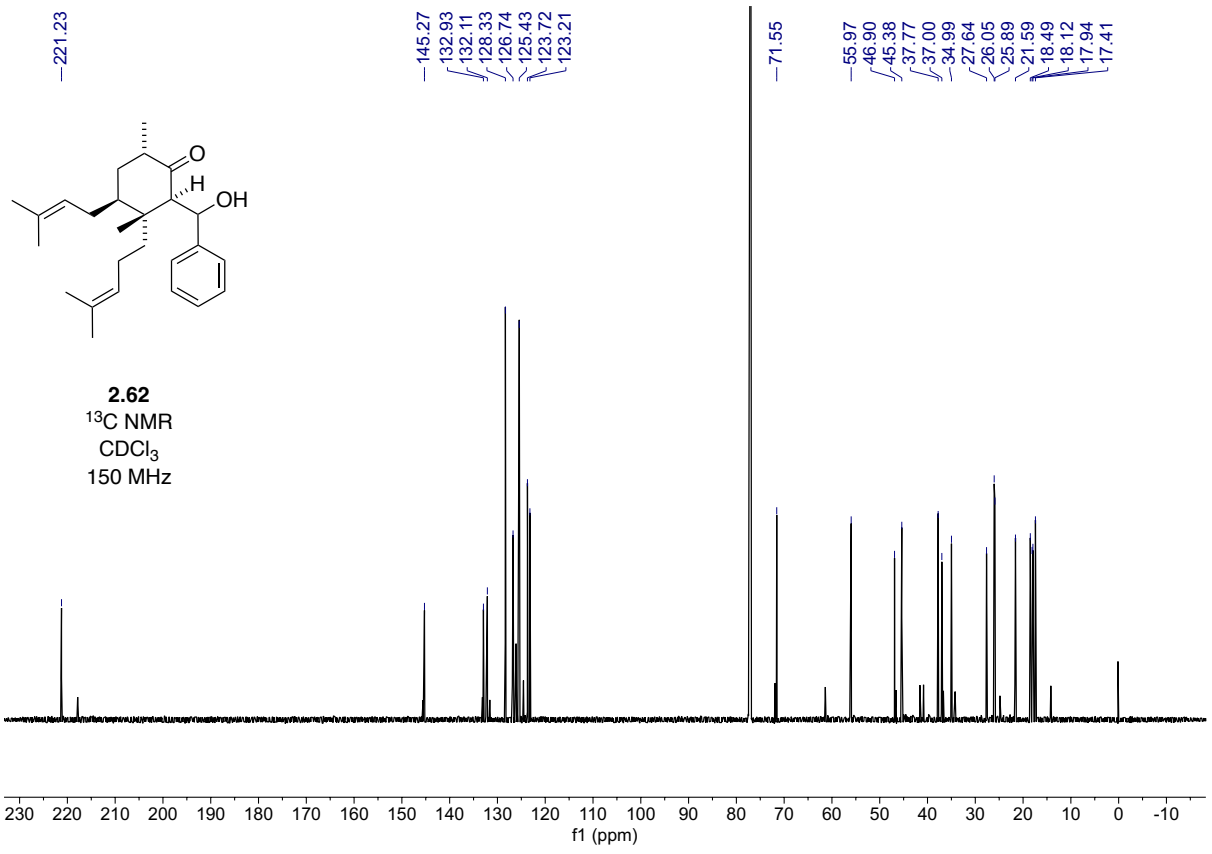
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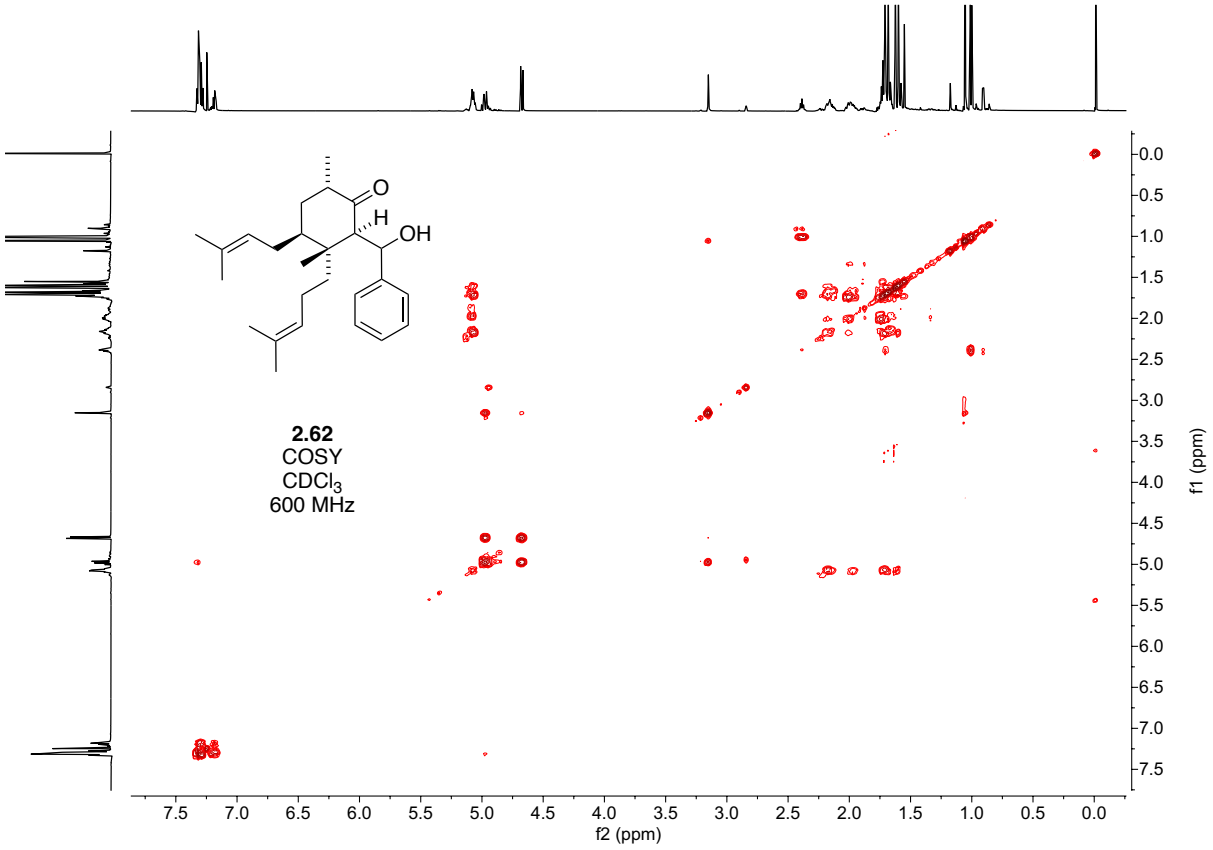
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H
OH
2.62
COSY
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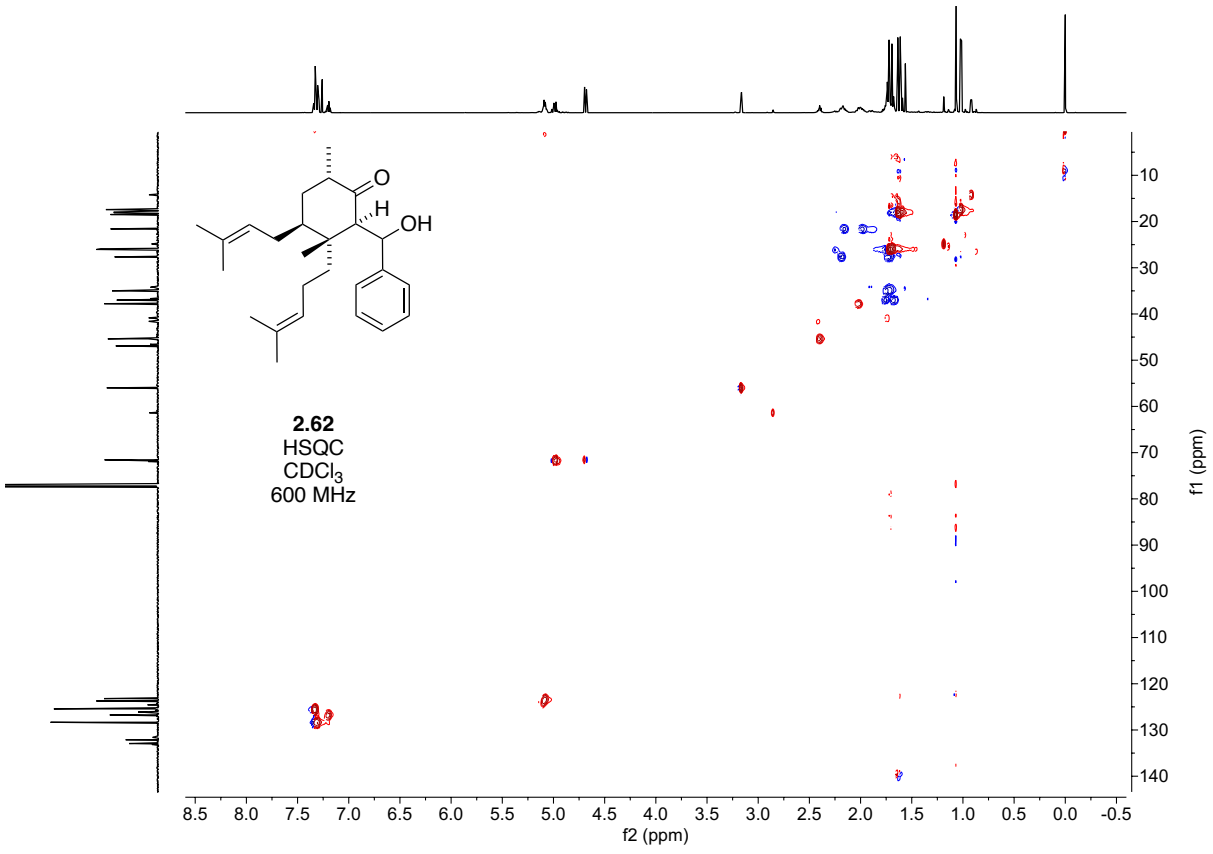
f1 (ppm)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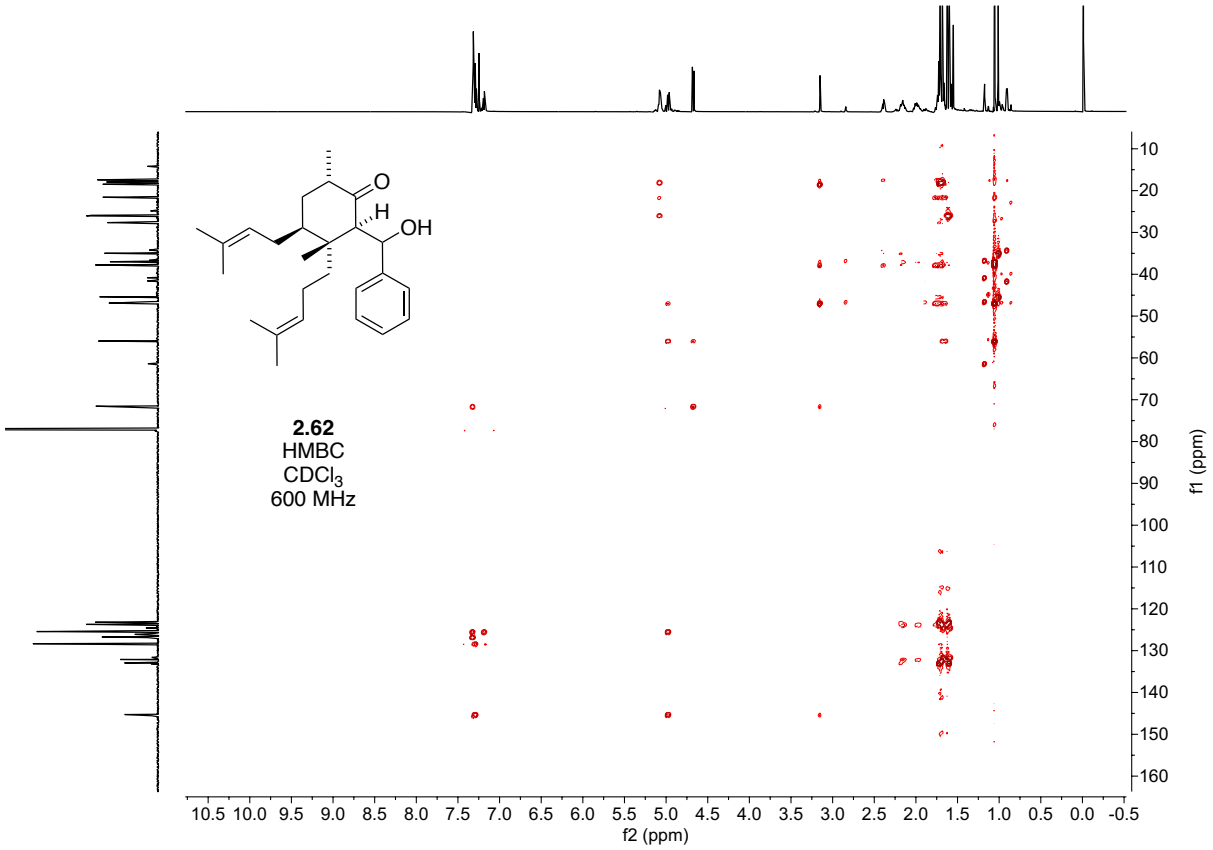
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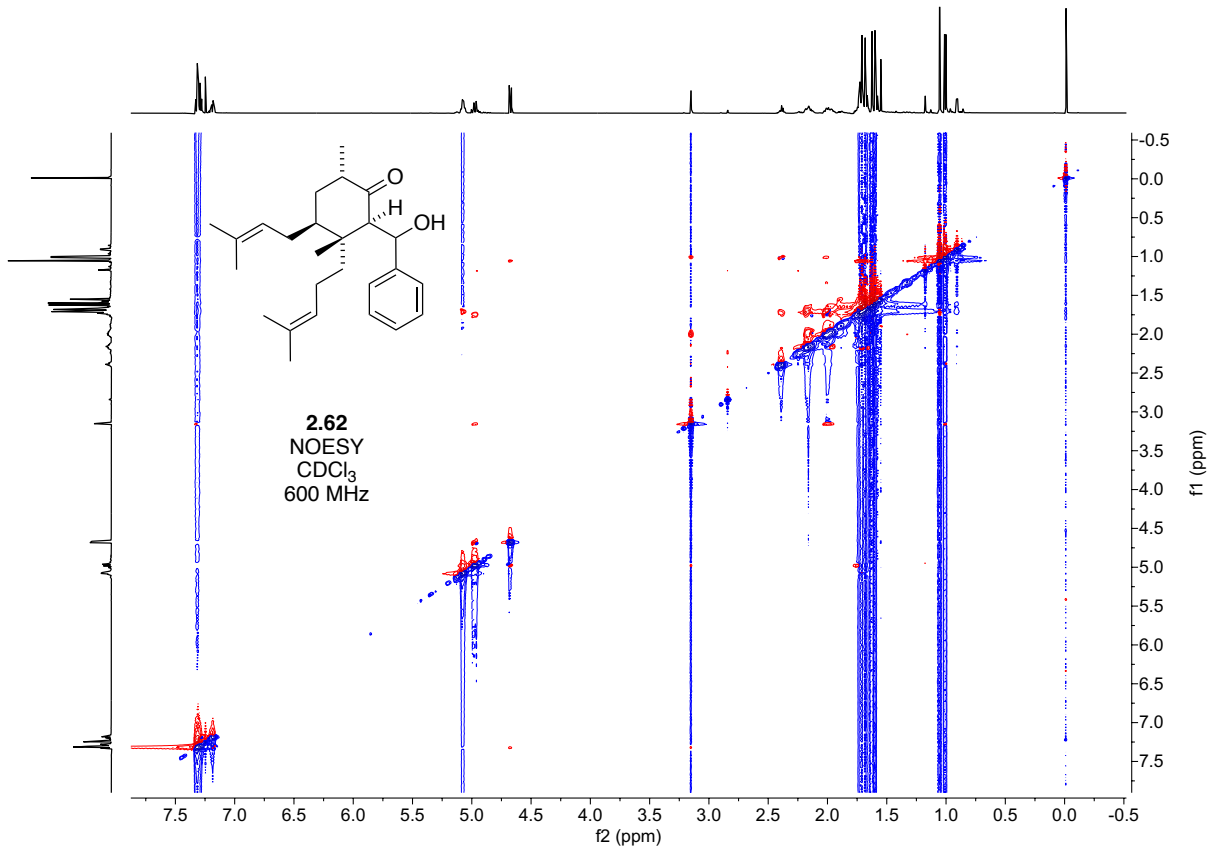
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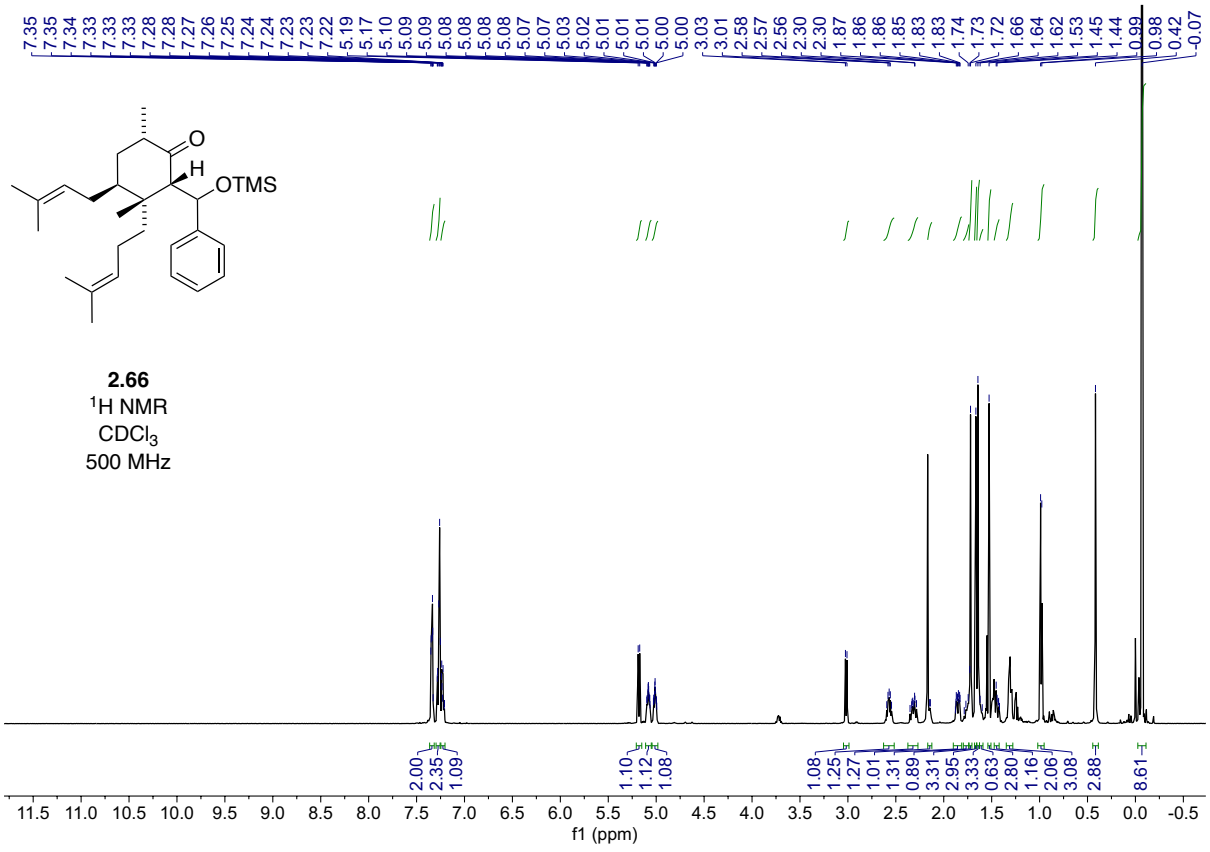
600 MHz
f1 (ppm)
f2 (ppm)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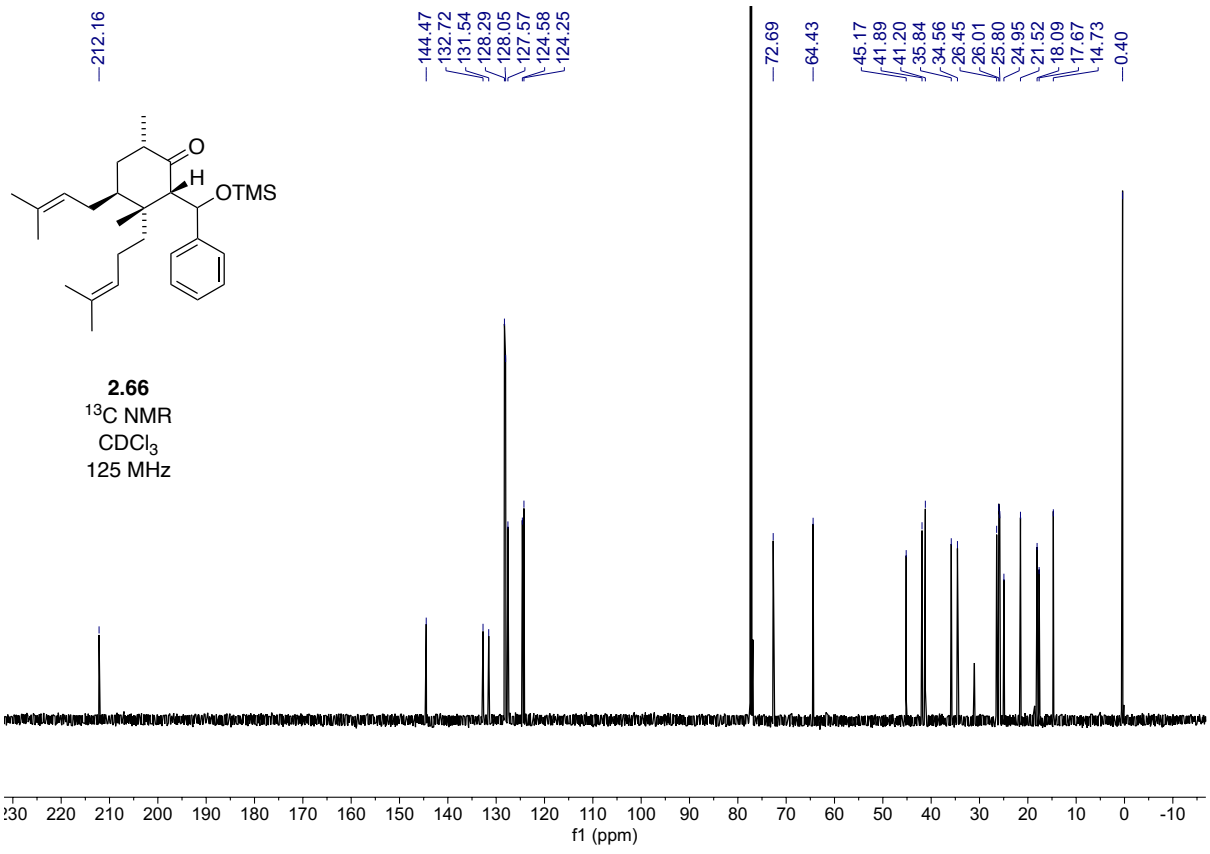
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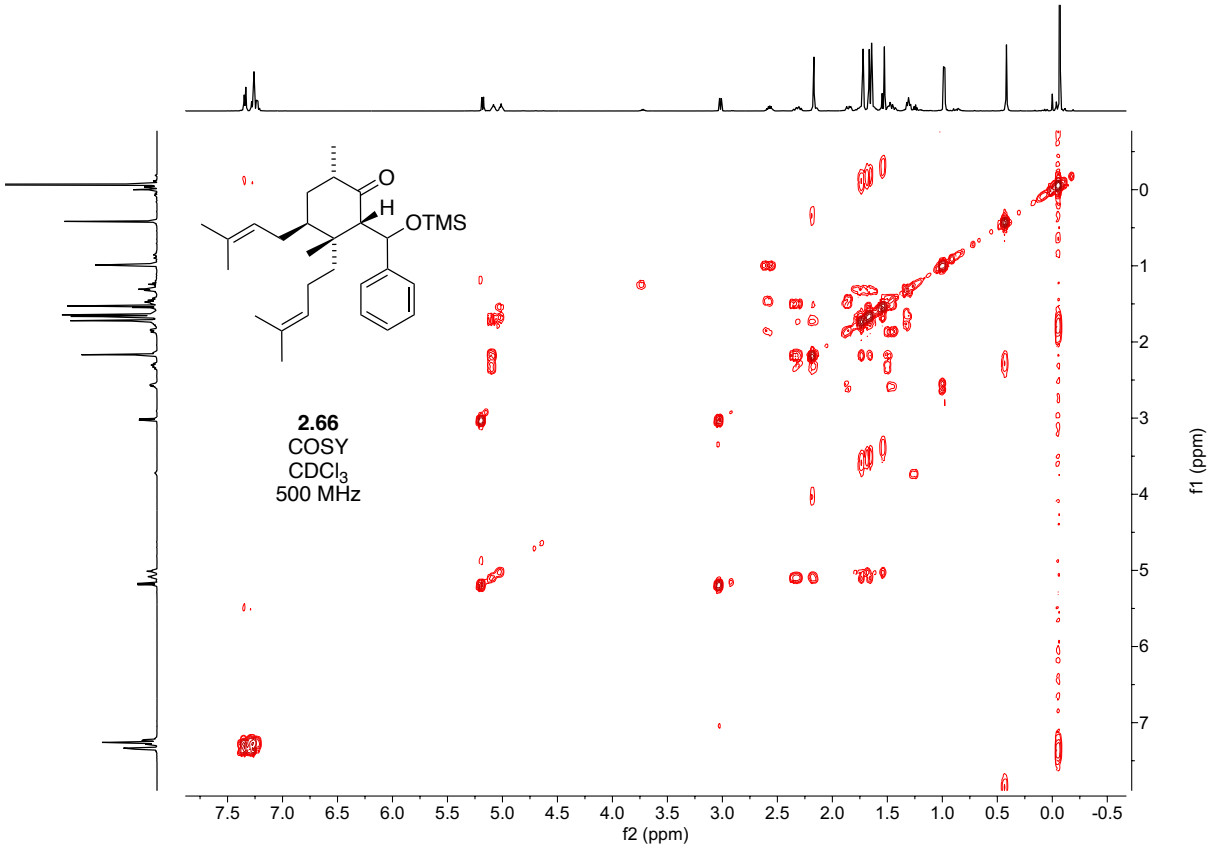
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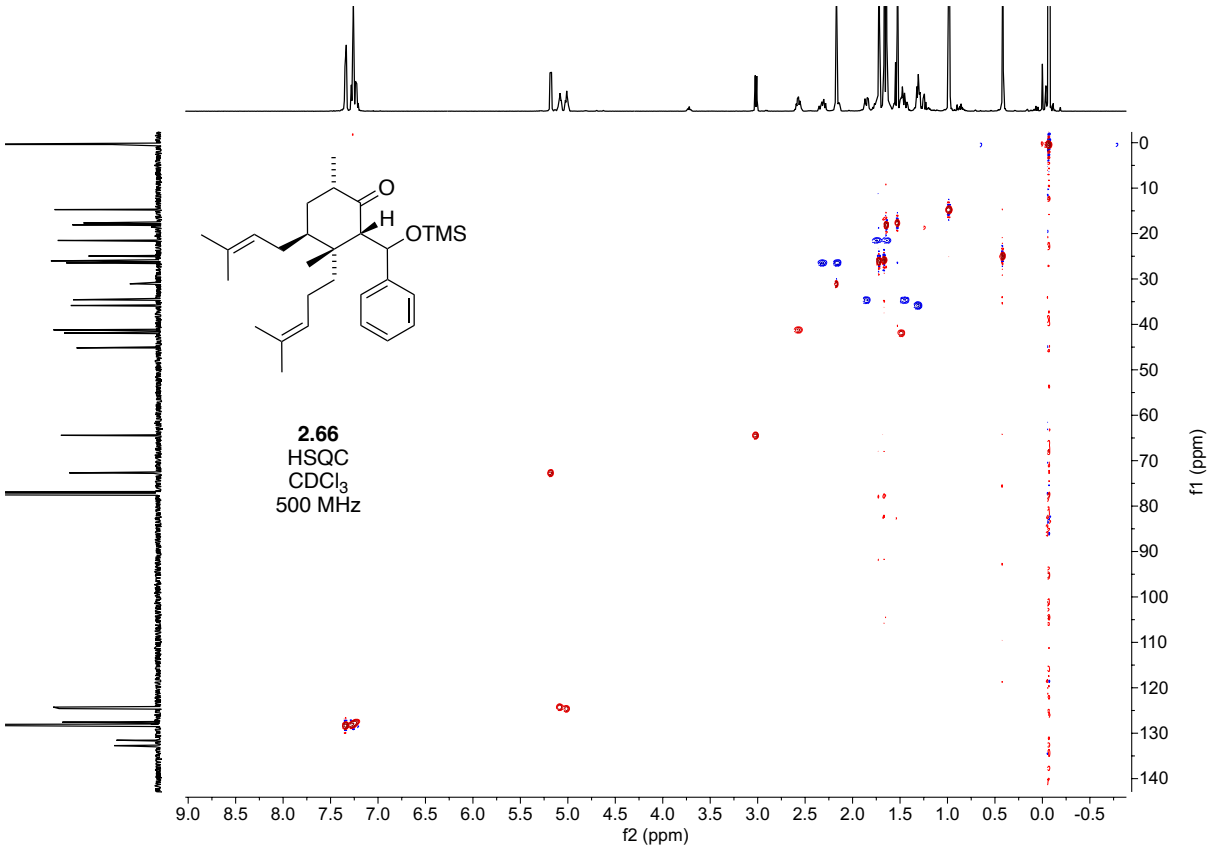
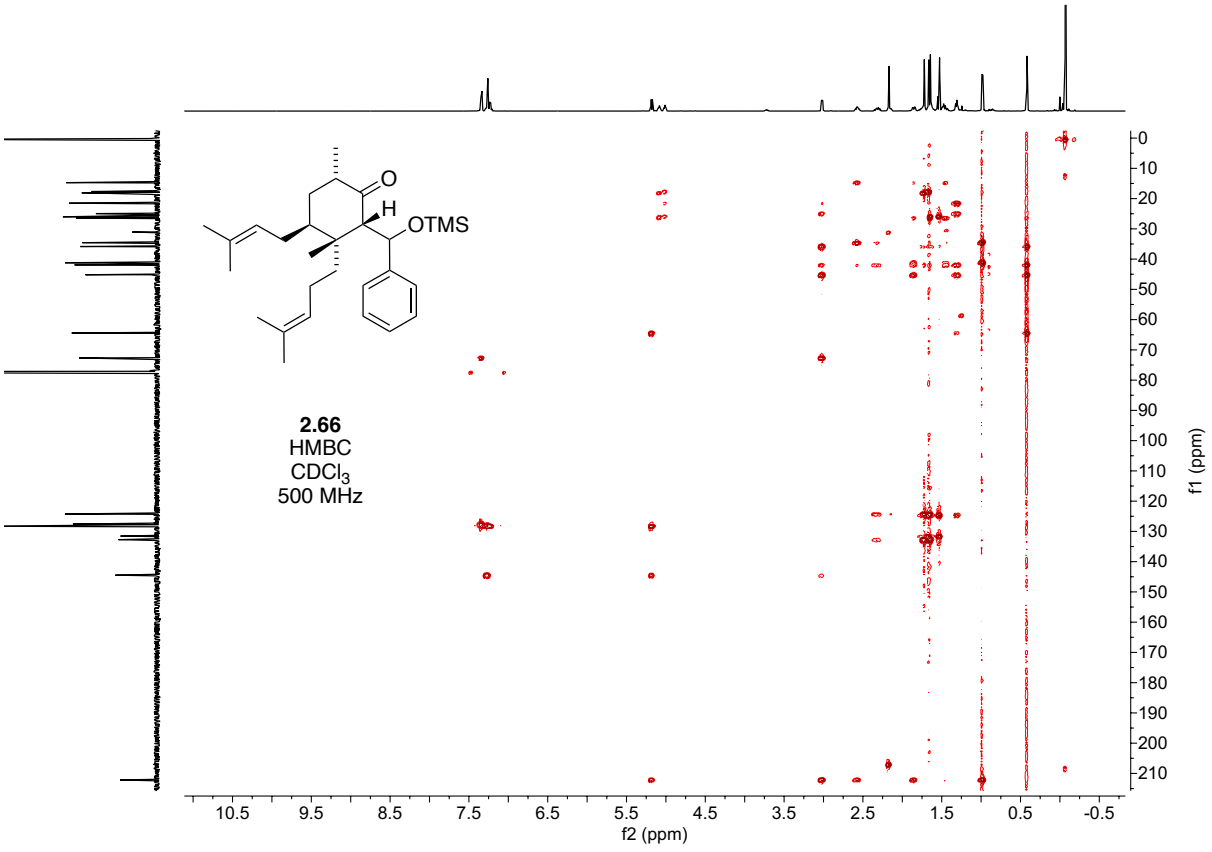
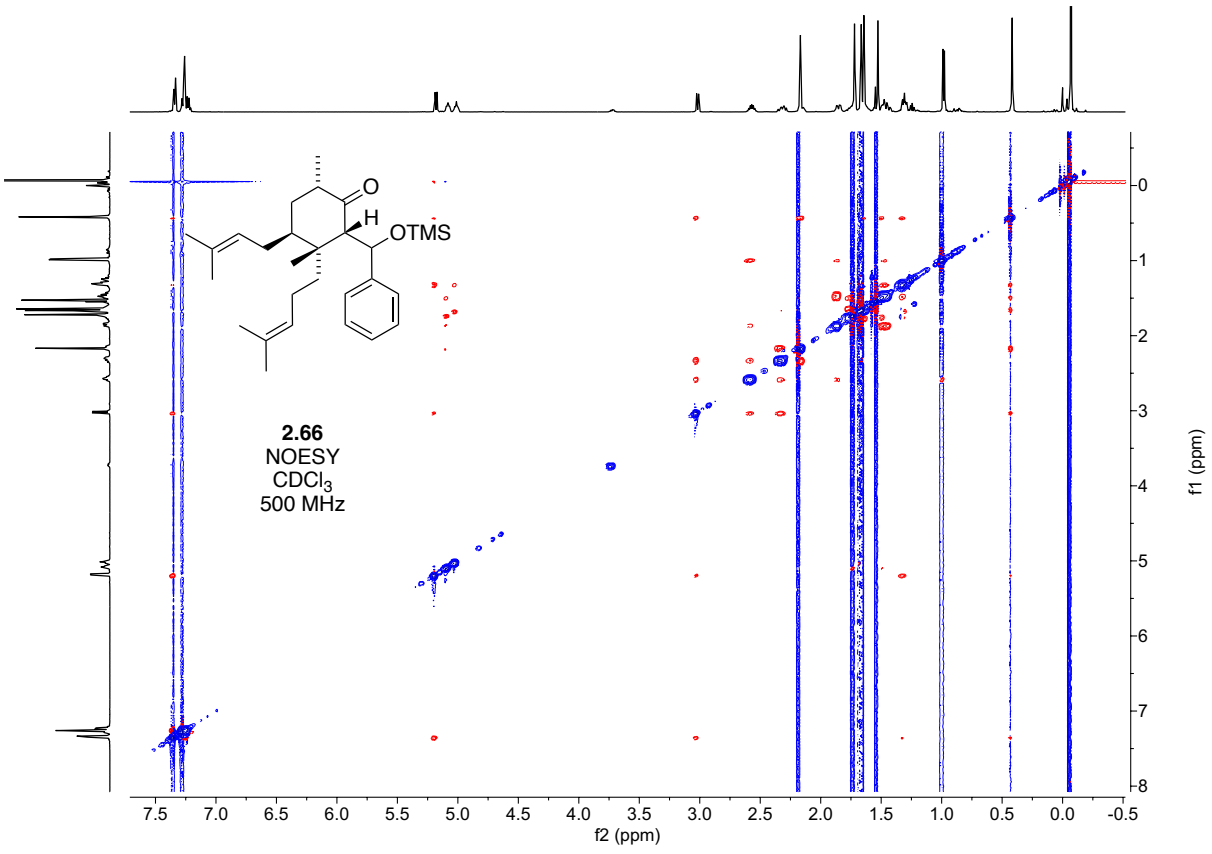
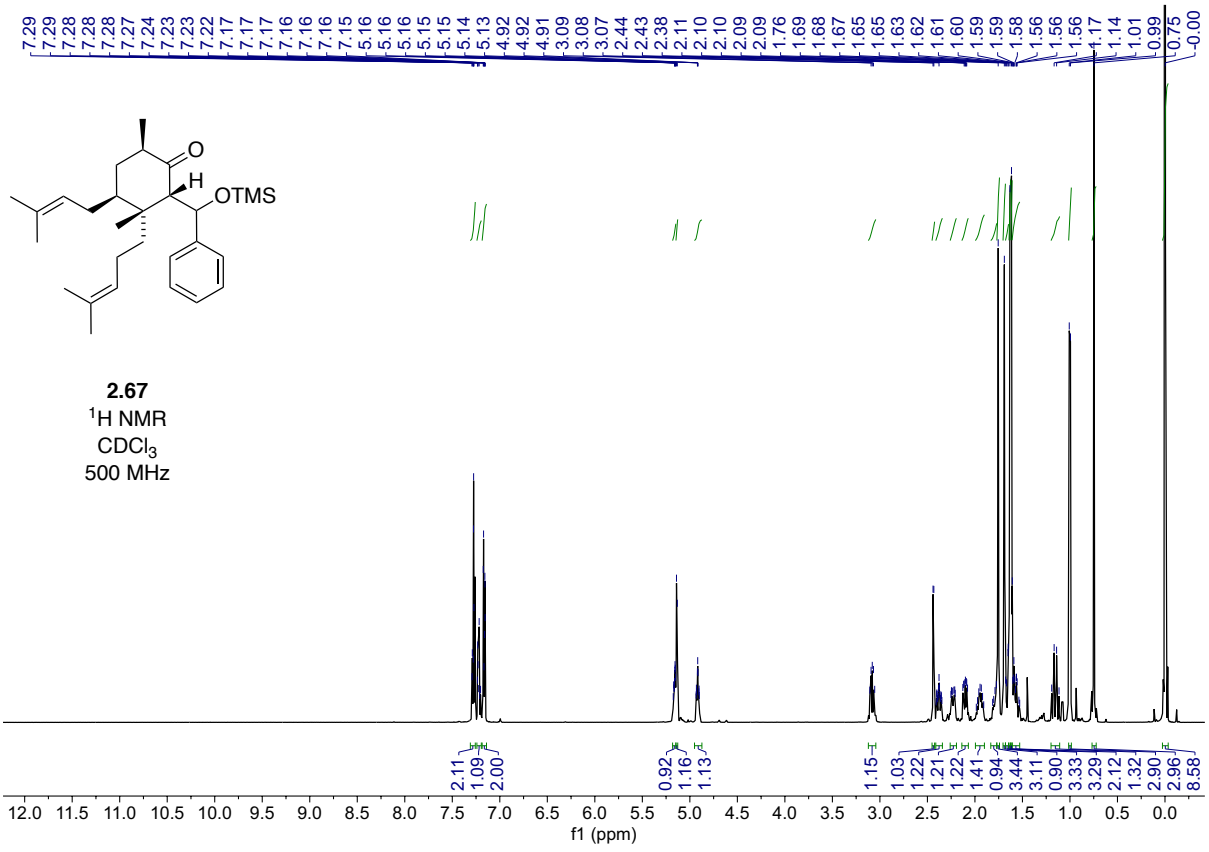
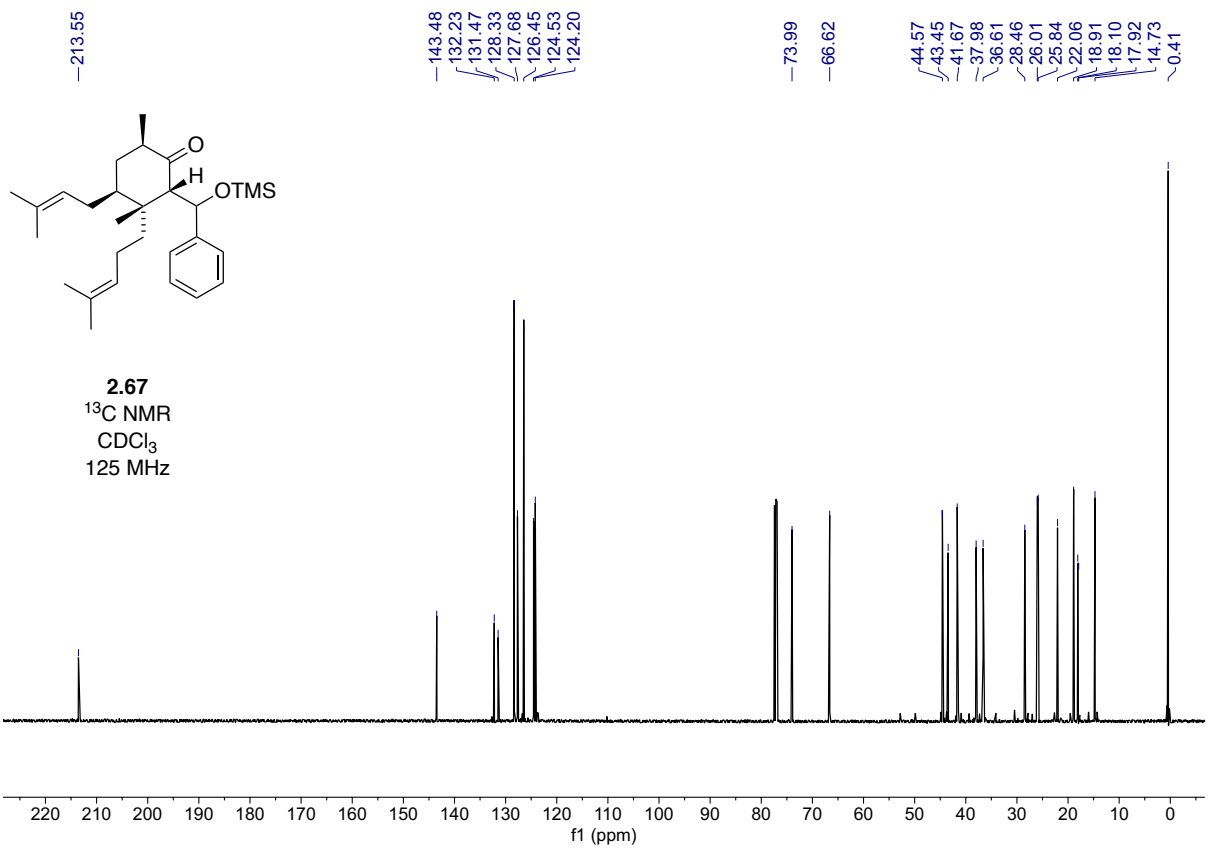
500 MHz
f2 (ppm)
f1 (ppm)

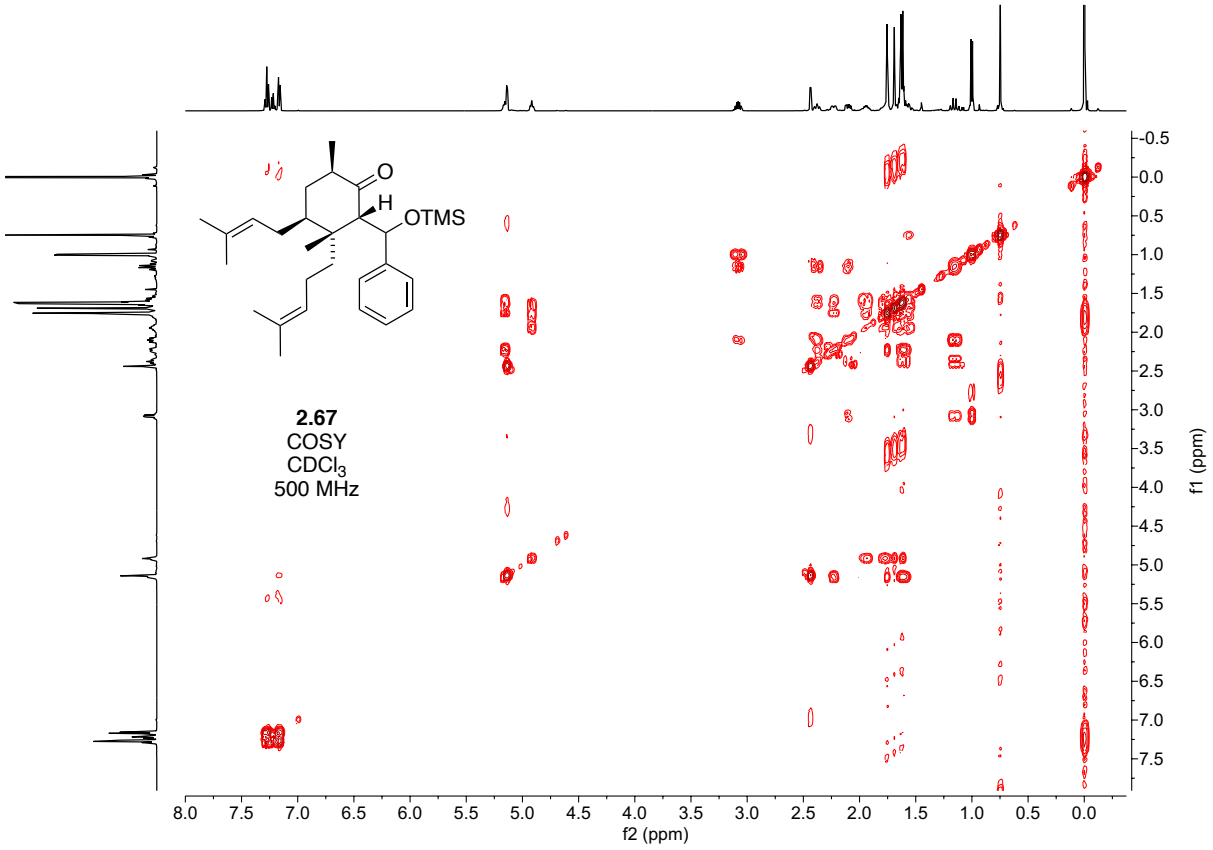

O
H
OTMS
2.66
HSQC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

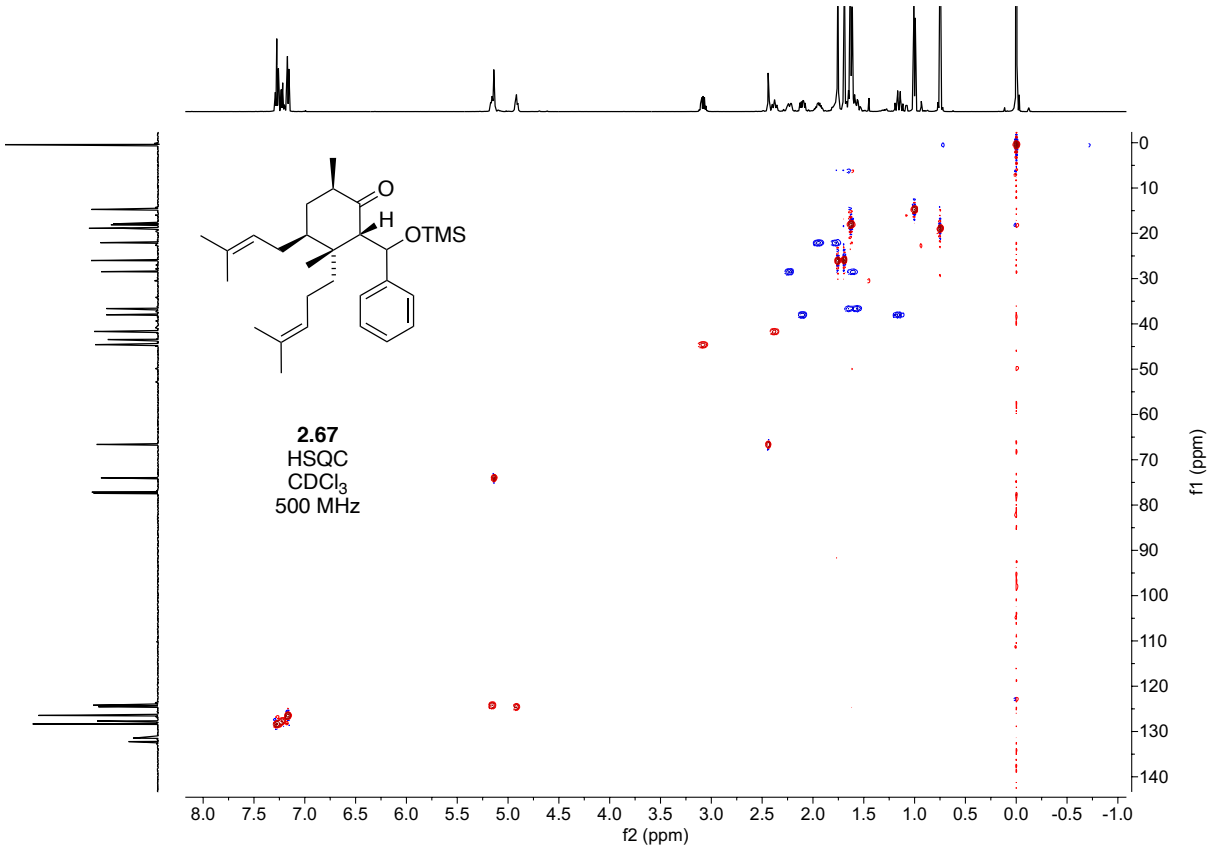

O
H
OTMS
2.66
HMBC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

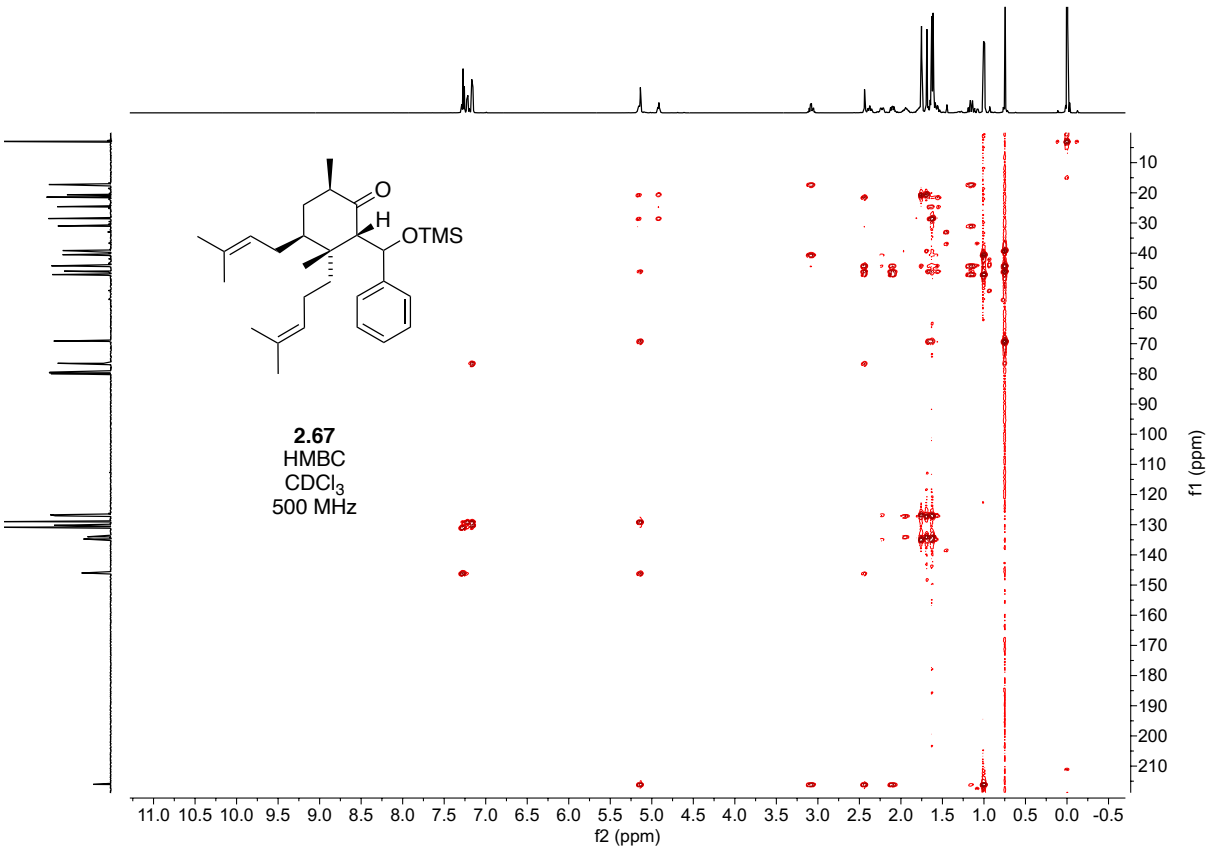

O
H
OTMS
2.66
NOESY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

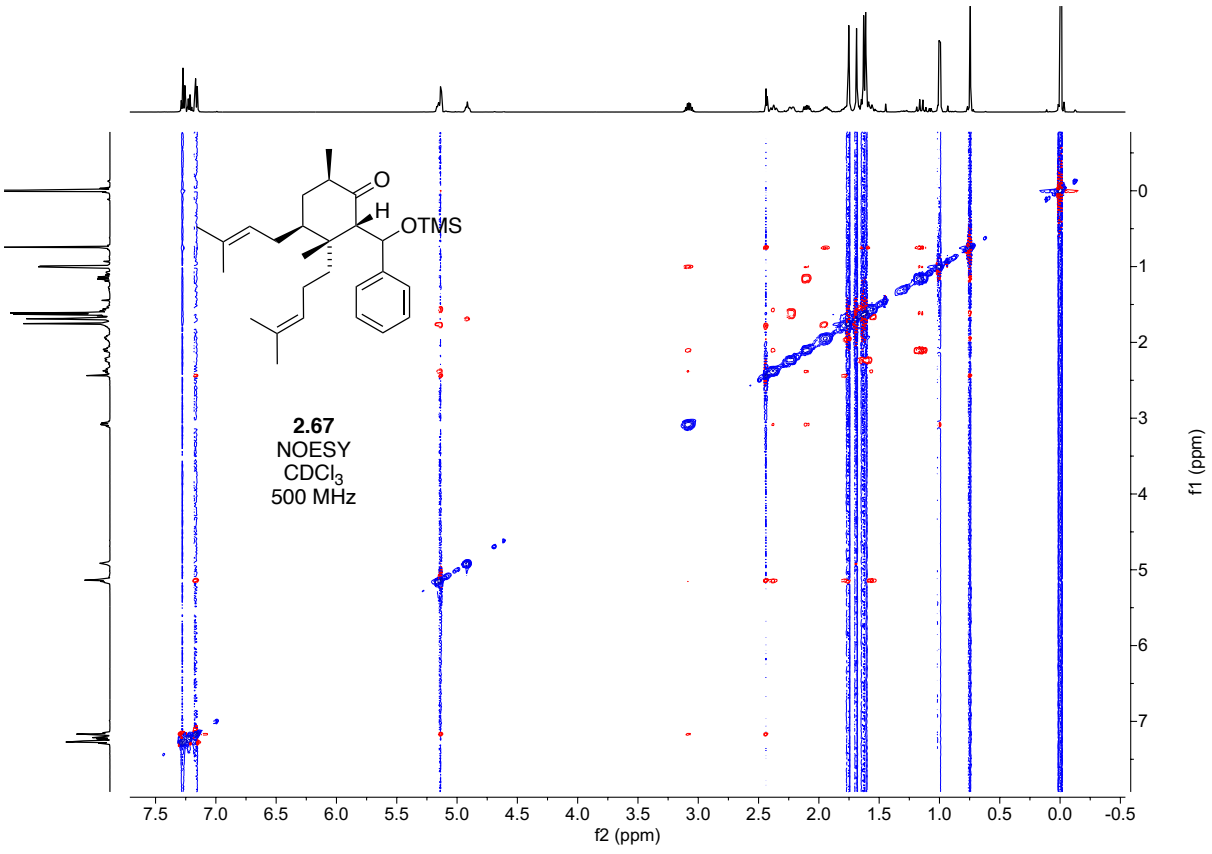

O
H
OTMS
2.67
1H NMR
CDCl3
500 MHz
f1 (ppm)

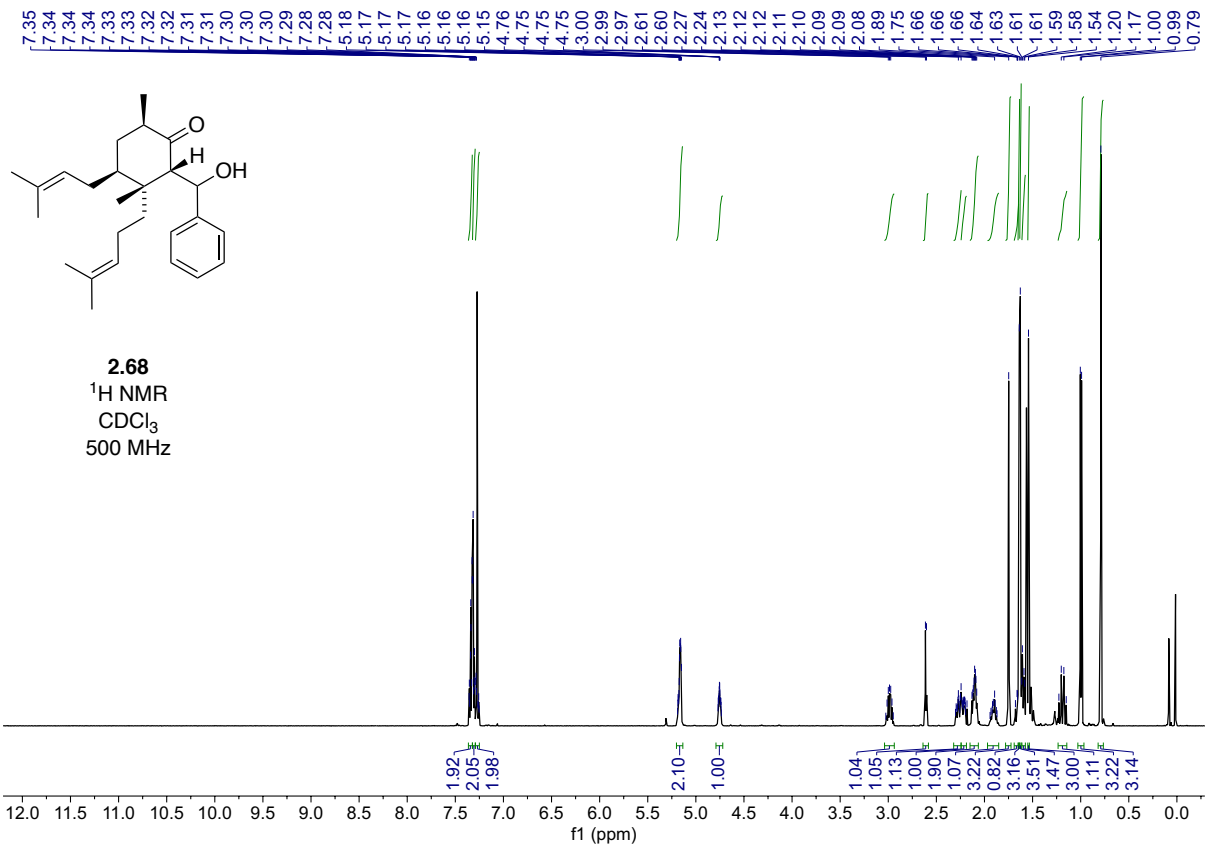

O
H
OTMS
2.67
13C NMR
CDCl3
125 MHz
f1 (ppm)

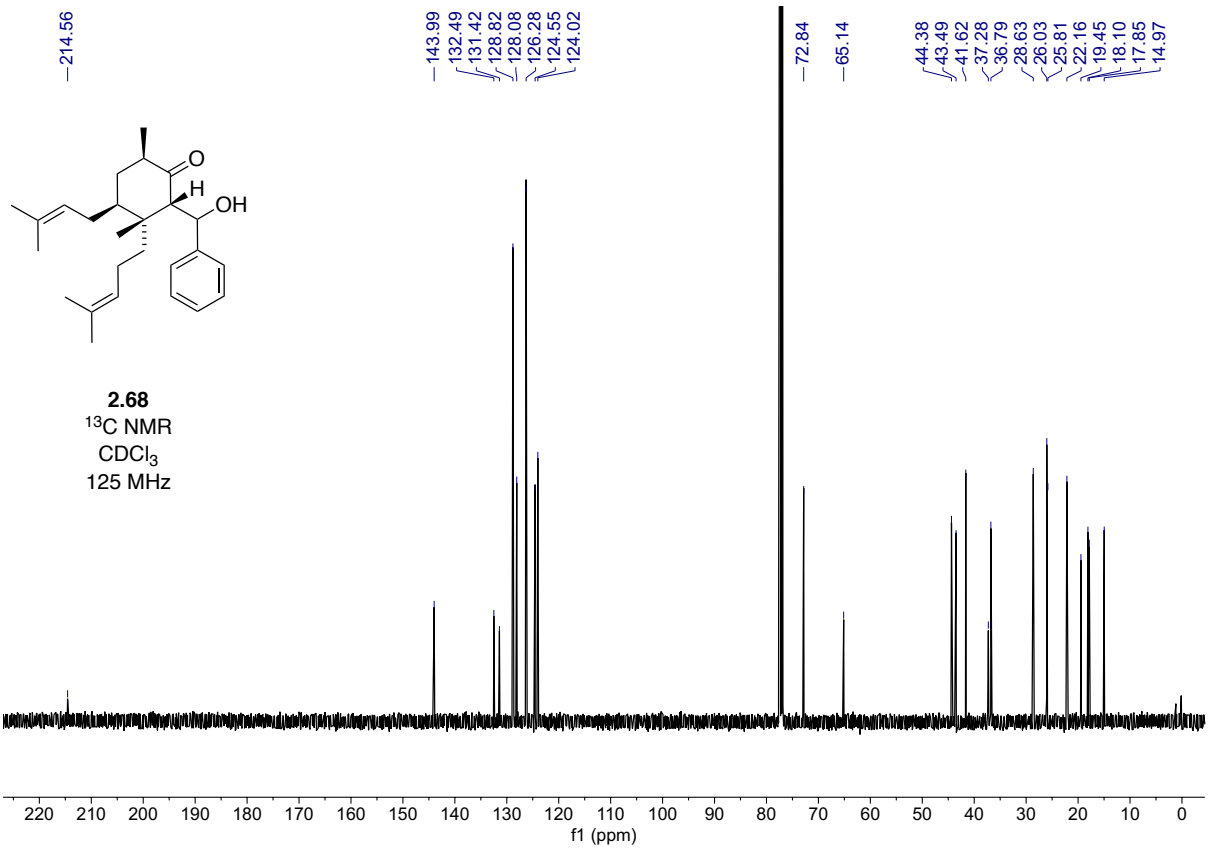

O
H
OTMS
2.67
COSY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

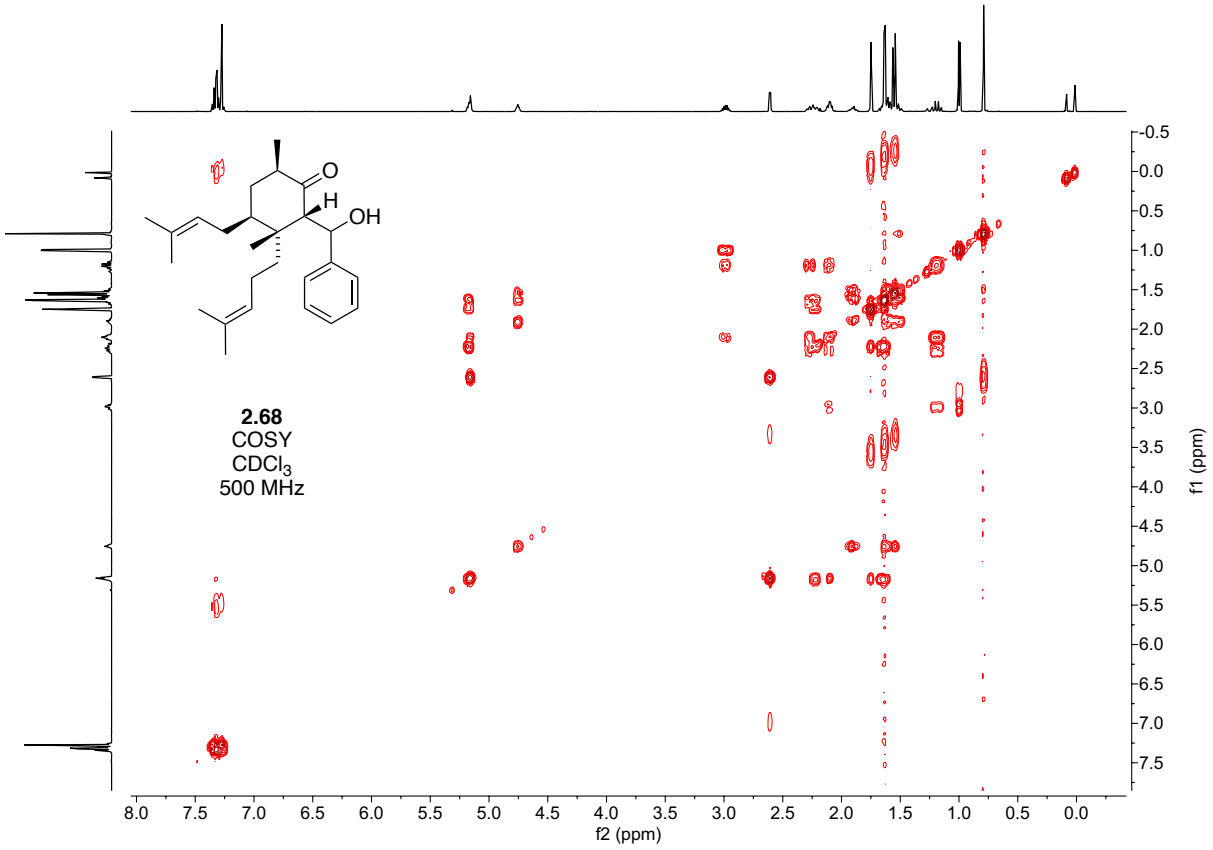

O
H
OTMS
2.67
HSQC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

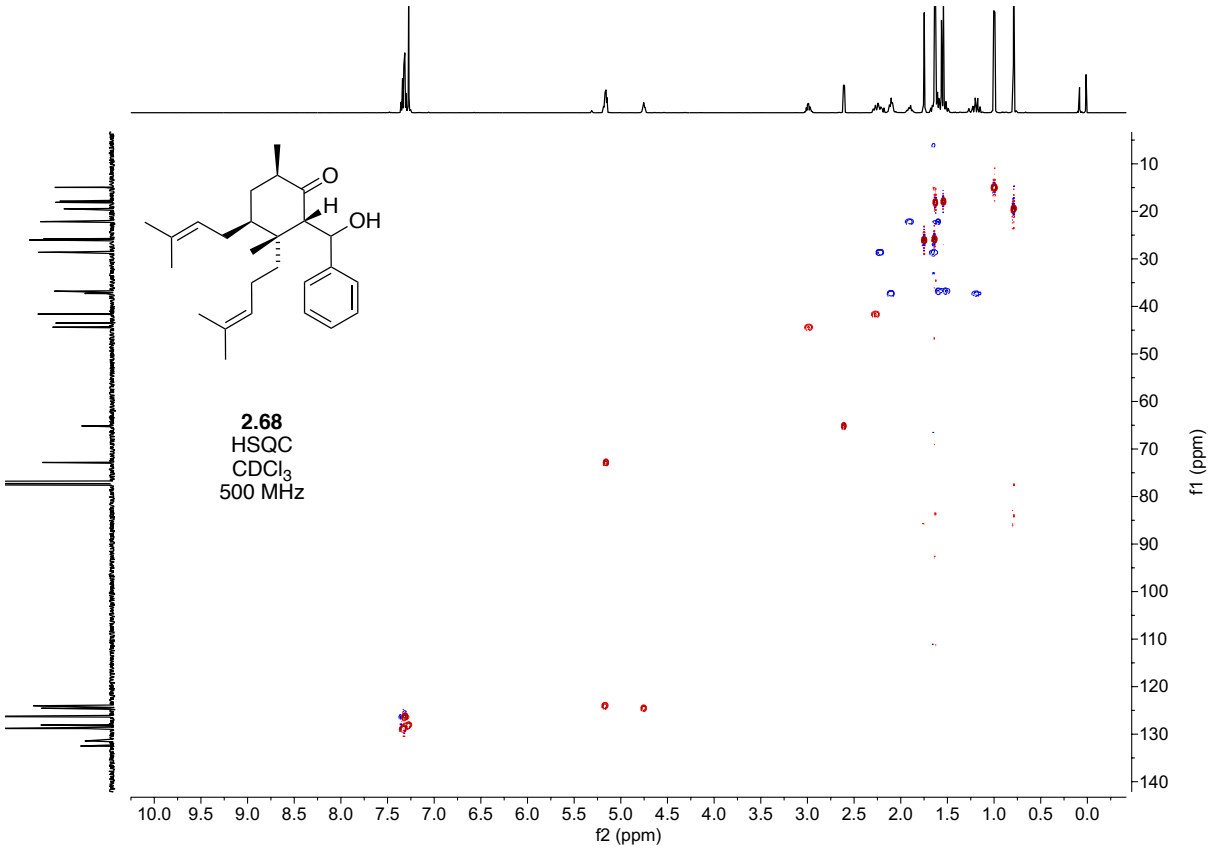

O
H
OTMS
2.67
HMBC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

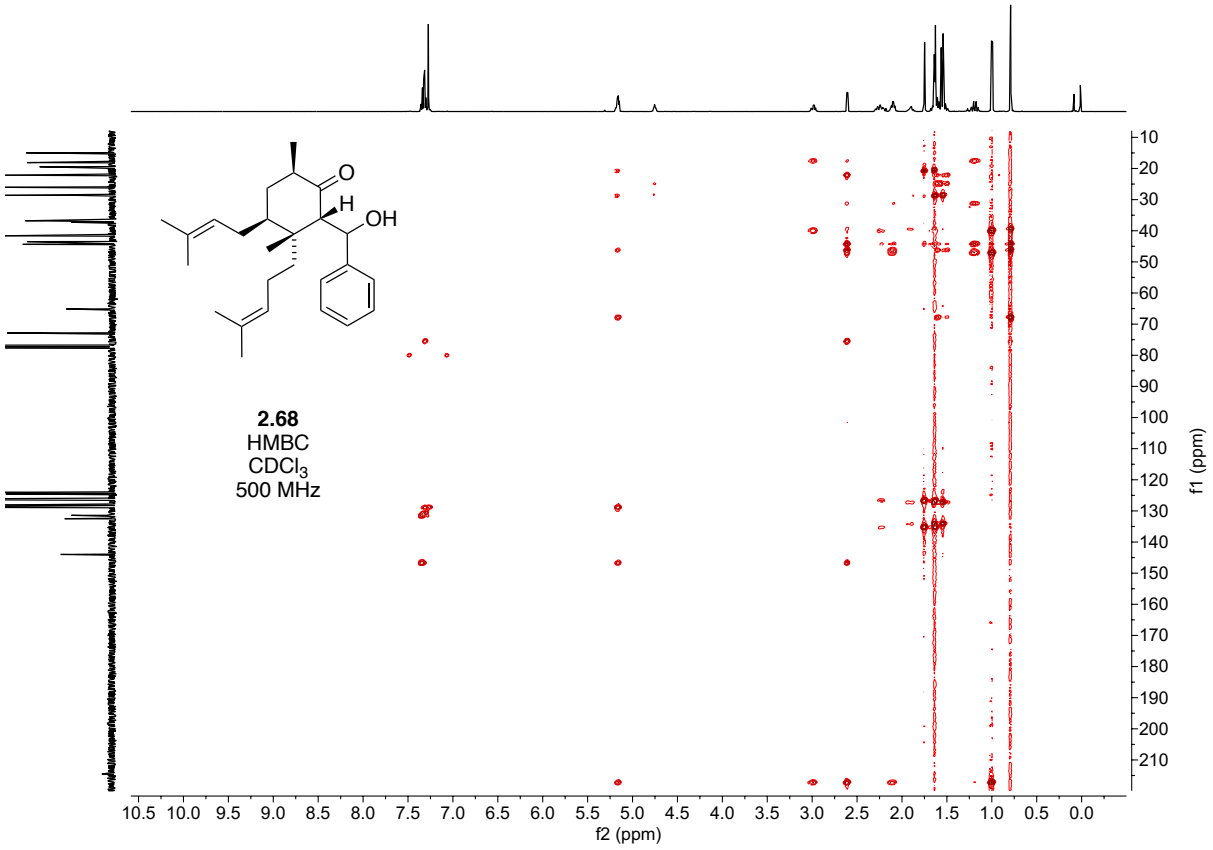

O
H
OTMS
2.67
NOESY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

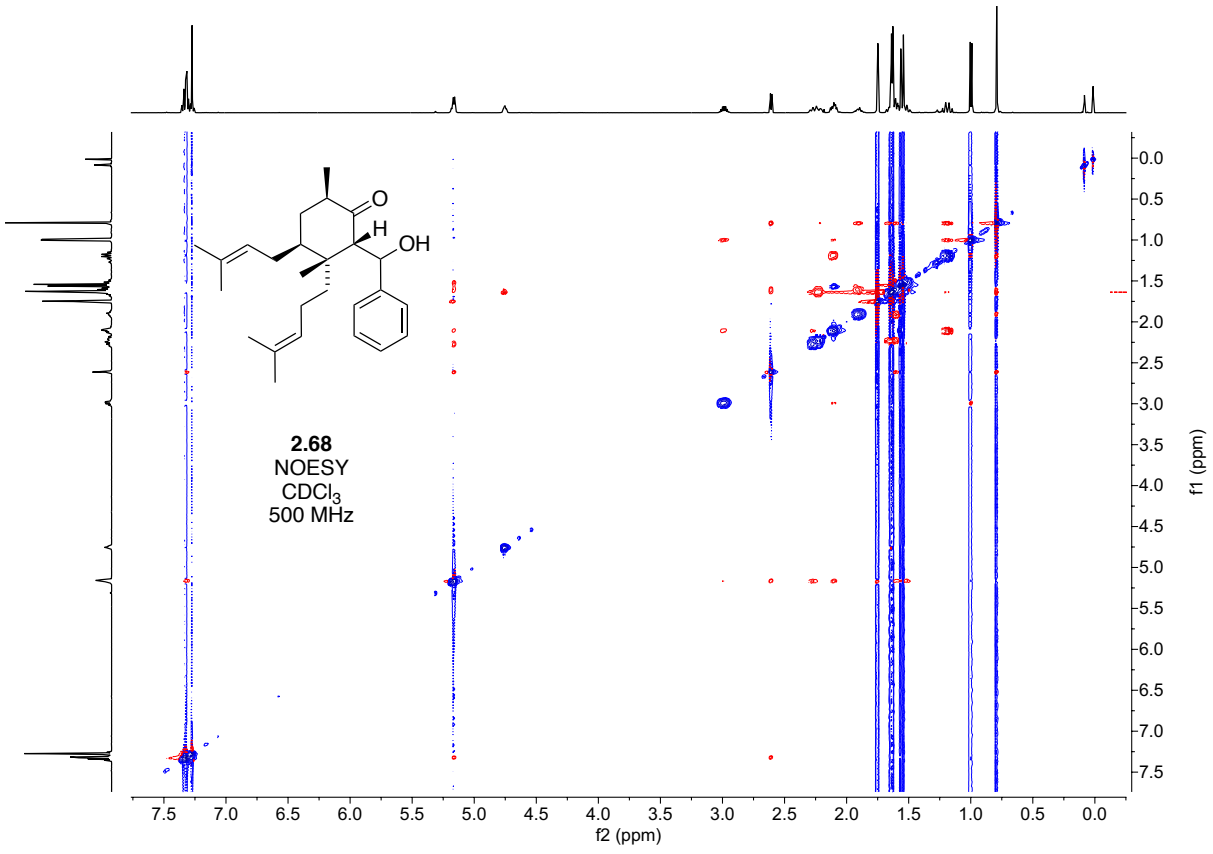

7.35 7.34 7.34 7.34 7.33 7.33 7.32 7.32 7.31 7.31 7.30 7.30 7.30 7.29 7.28 7.28 5.18 5.17 5.17 5.17 5.16 5.16 5.16 5.15 4.76 4.75 4.75 4.75 3.00 2.99 2.97 2.61 2.60 2.27 2.24 2.13 2.12 2.12 2.11 2.10 2.09 2.09 2.08 1.89 1.75 1.66 1.66 1.66 1.64 1.63 1.61 1.61 1.61 1.59 1.58 1.54 1.20 1.17 1.00 0.99 0.79
O
H
OH
2.68
1H NMR
CDCl3
500 MHz
1.92 2.05 1.98 2.10 1.00 1.04 1.05 1.13 1.00 1.90 1.07 3.22 0.82 3.16 3.51 1.47 3.00 1.11 3.22 3.14
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

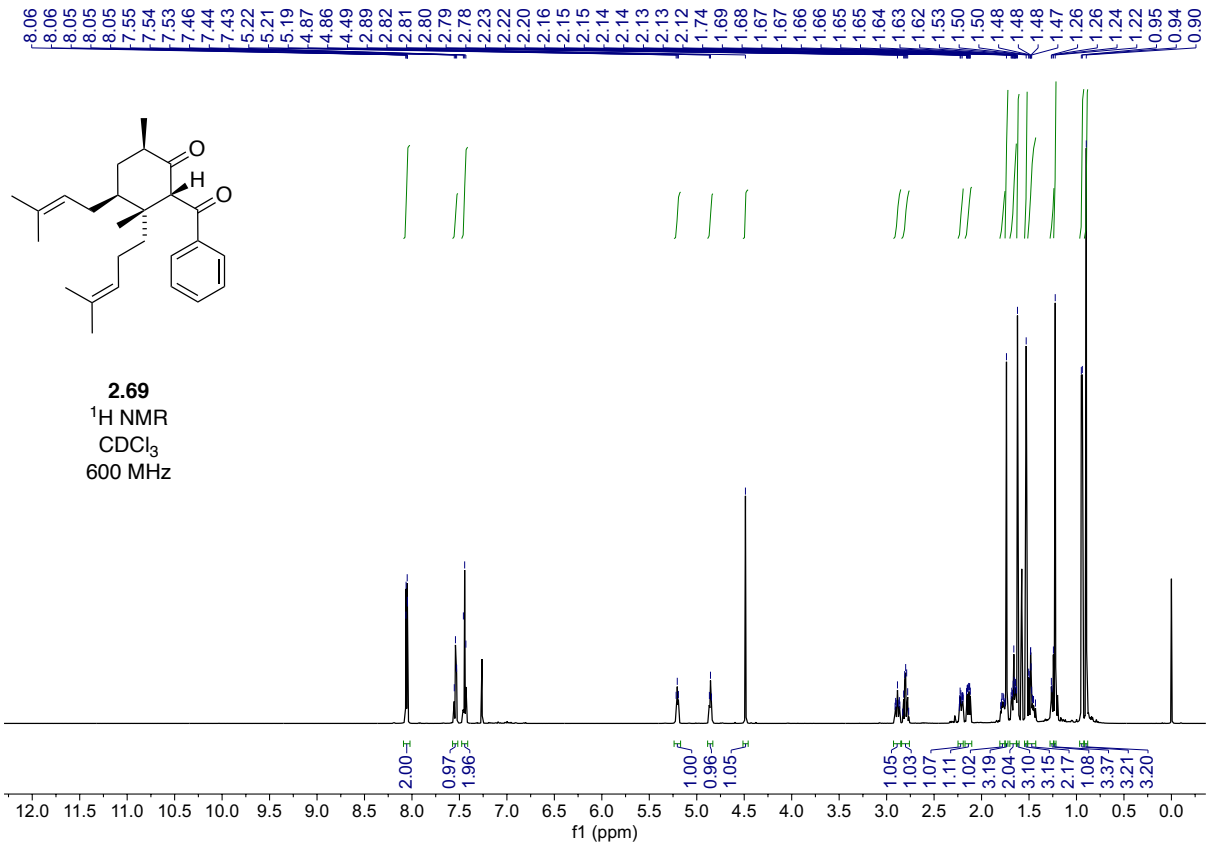

214.56
143.99 132.49 131.42 128.82 128.08 126.28 124.55 124.02
72.84
65.14
44.38 43.49 41.62 37.28 36.79 28.63 26.03 25.81 22.16 19.45 18.10 17.85 14.97
O
H
OH
2.68
13C NMR
CDCl3
125 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
H
OH
2.68
COSY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

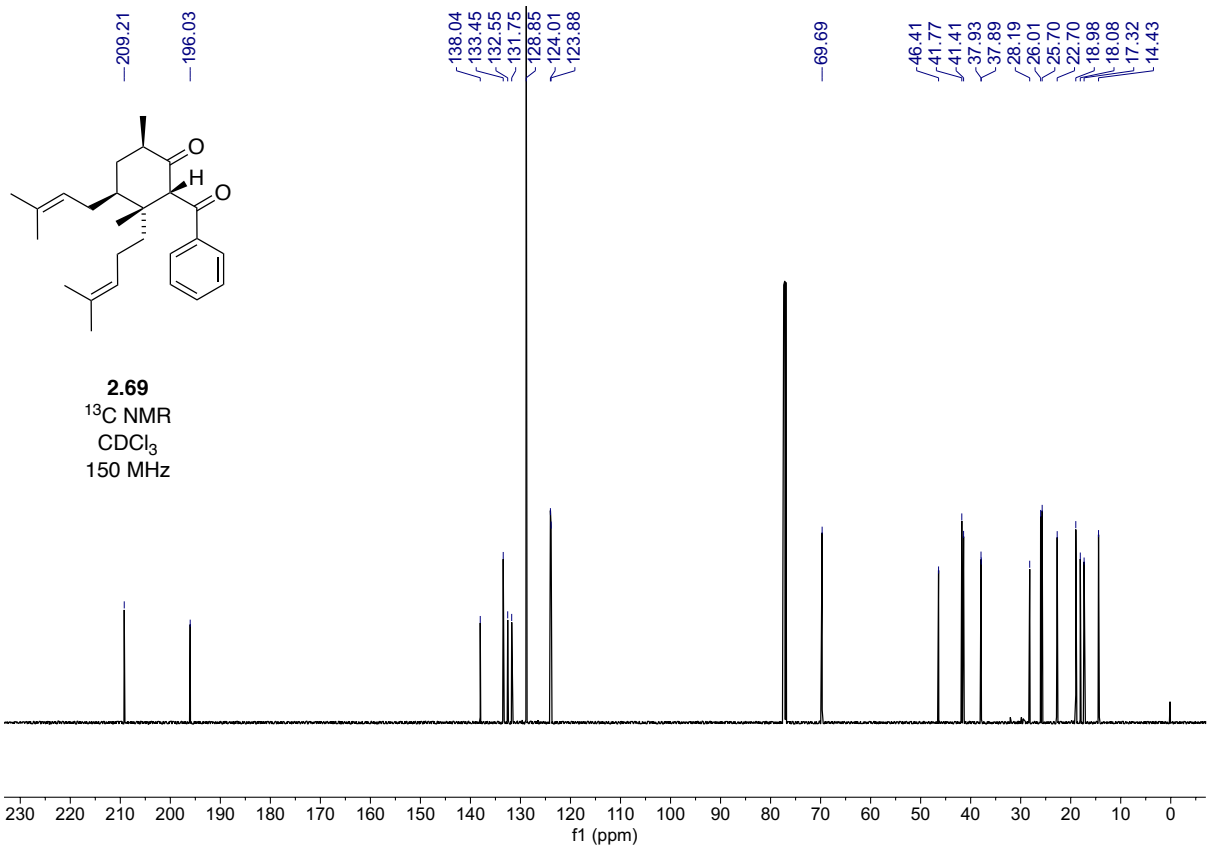

O
H
OH
2.68
HSQC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)


O
H
OH
2.68
HMBC
CDCl3
500 MHz
f1 (ppm)
f2 (ppm)

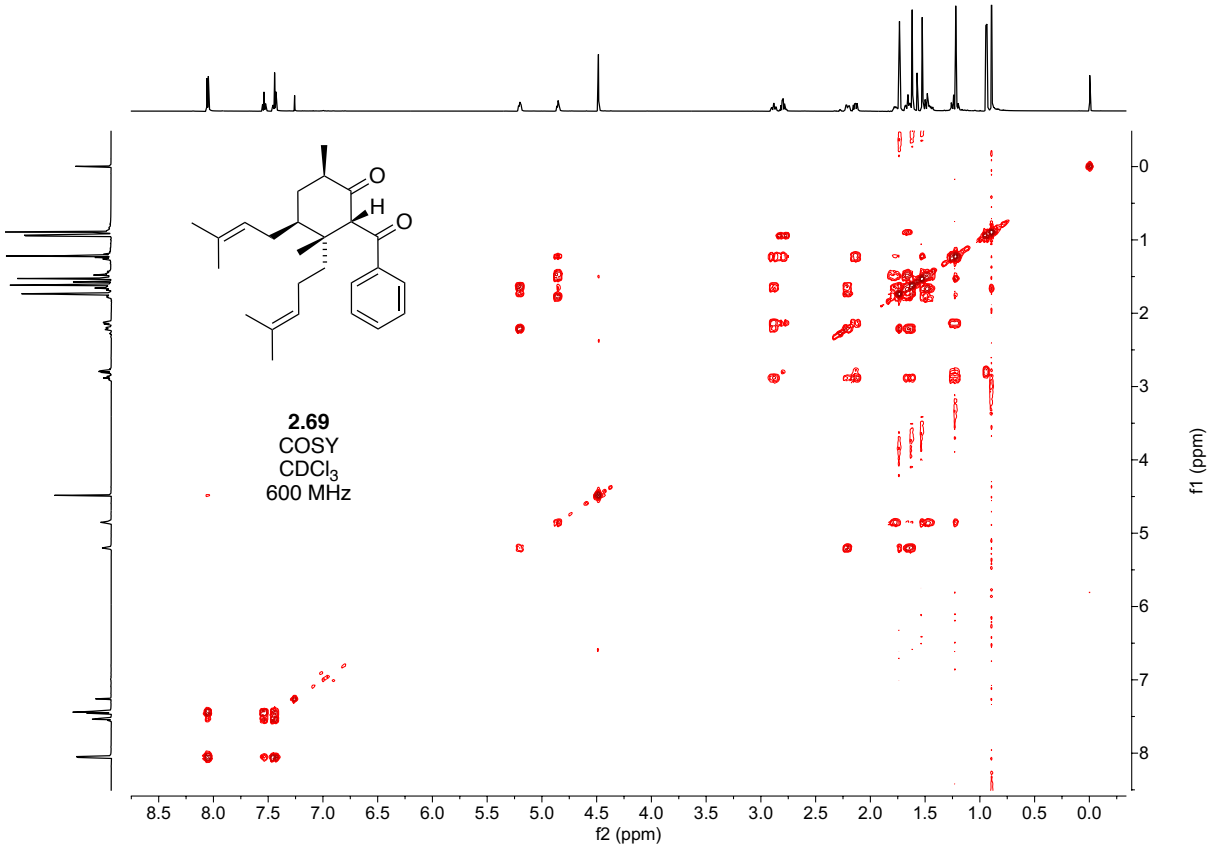

O
H
OH
2.68
NOESY
CDCl3
500 MHz
f1 (ppm)
f2 (ppm)

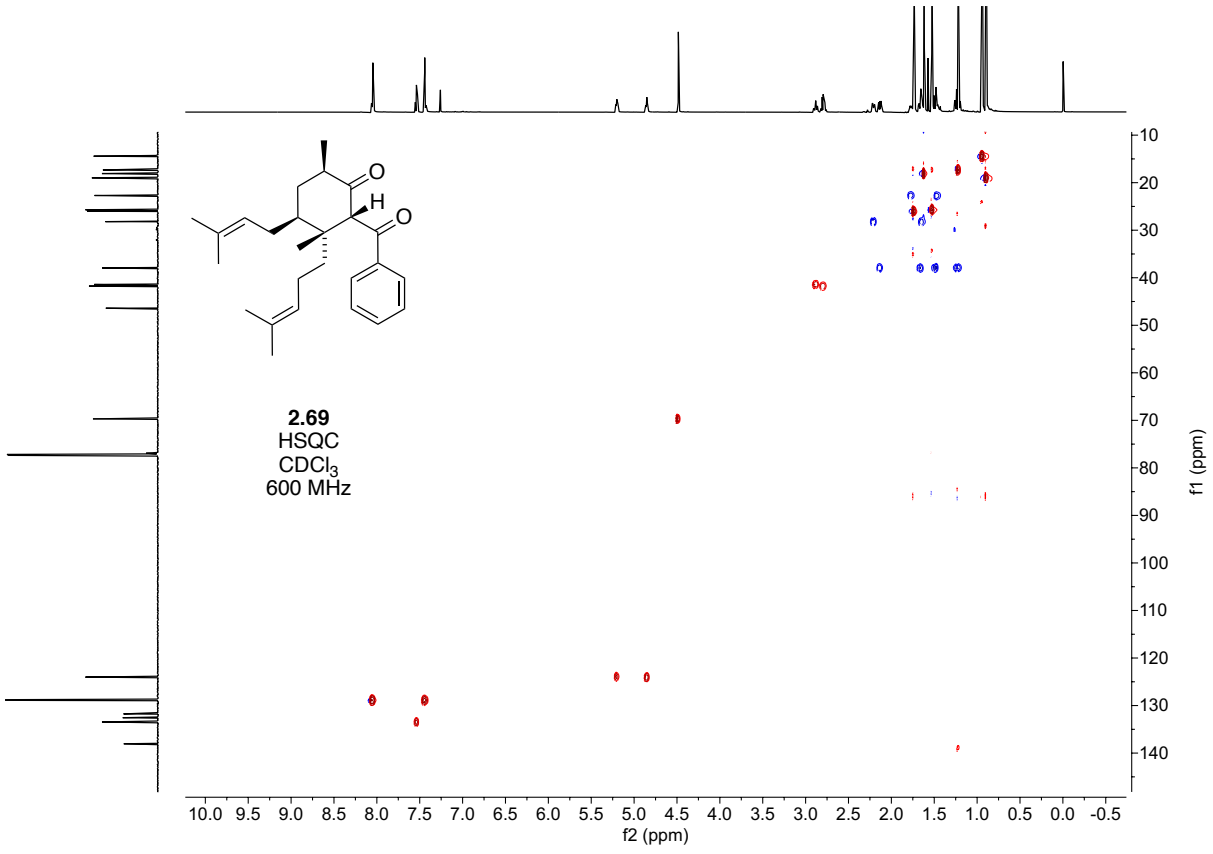


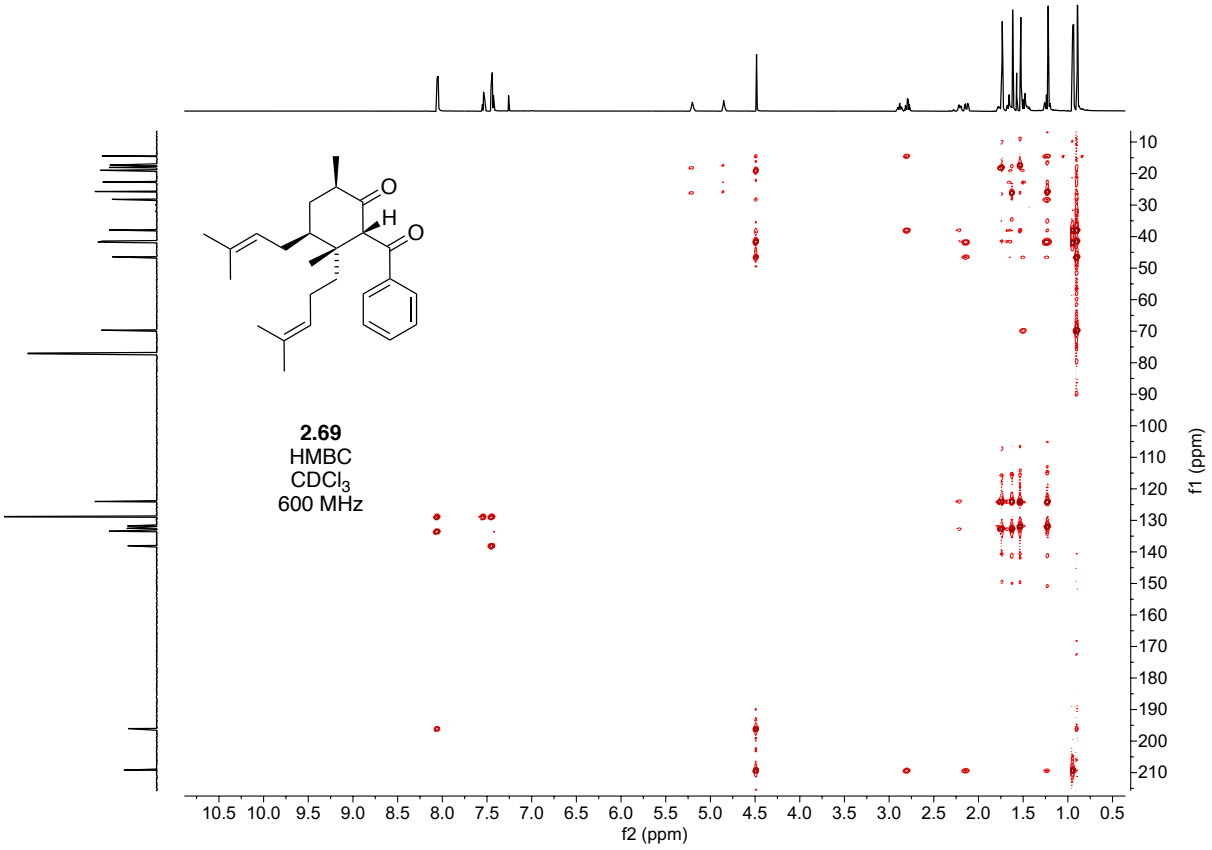
2.69
^{1}H NMR
$CDCl_3$
600 MHz

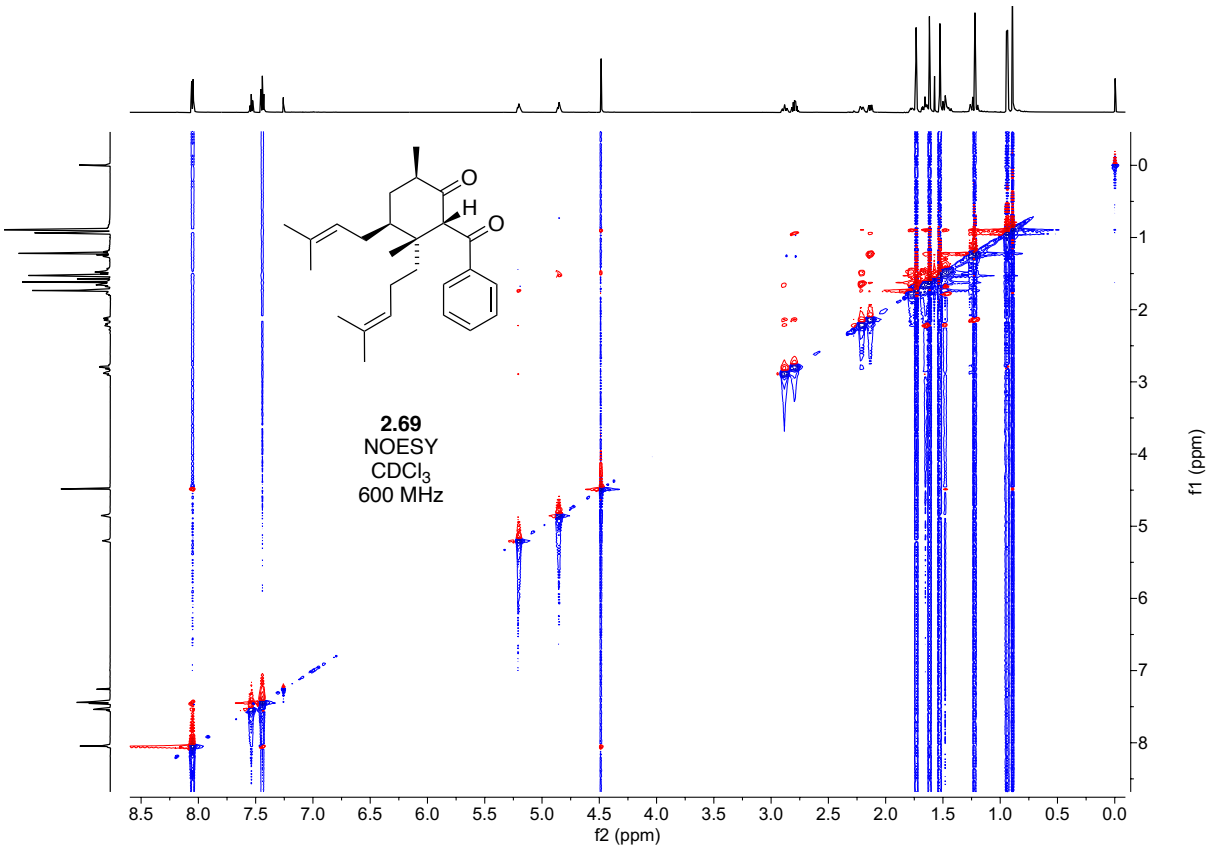


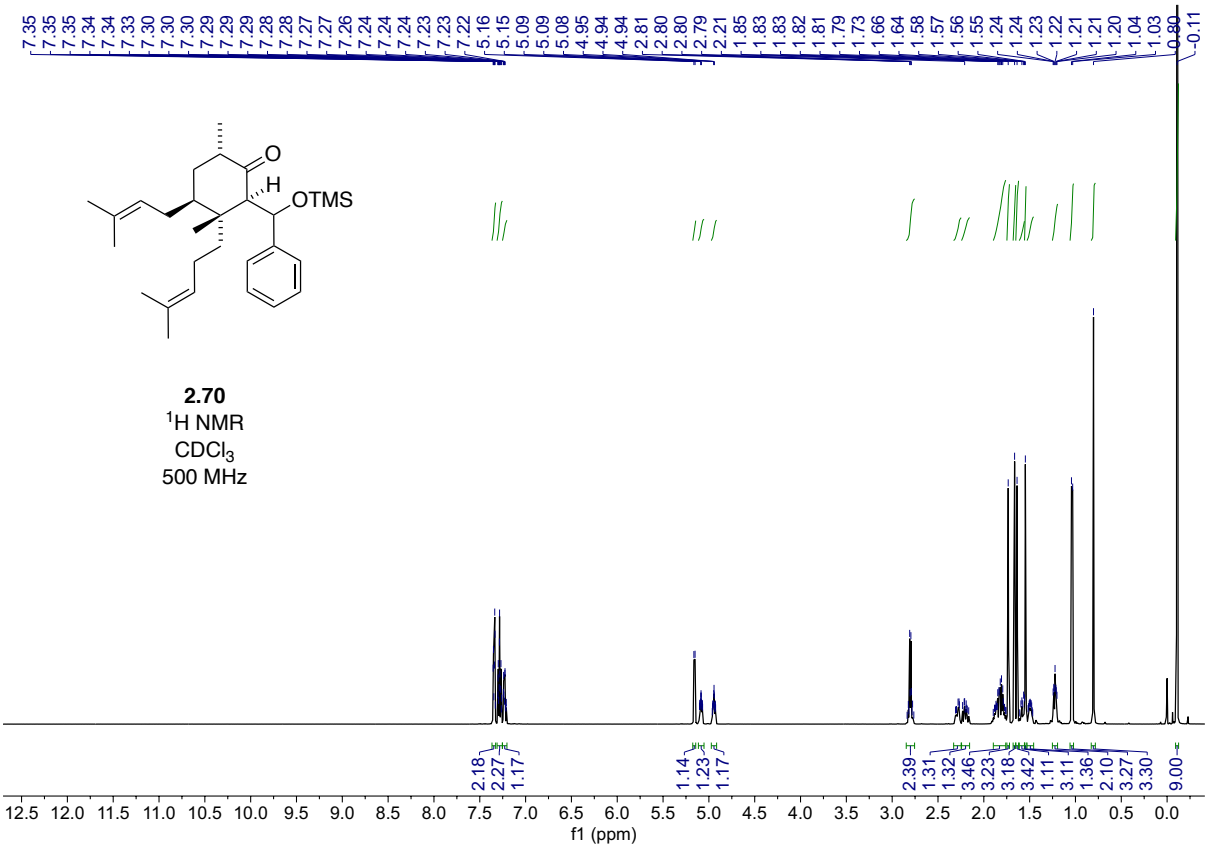
2.69
^{13}C NMR
$CDCl_3$
150 MHz

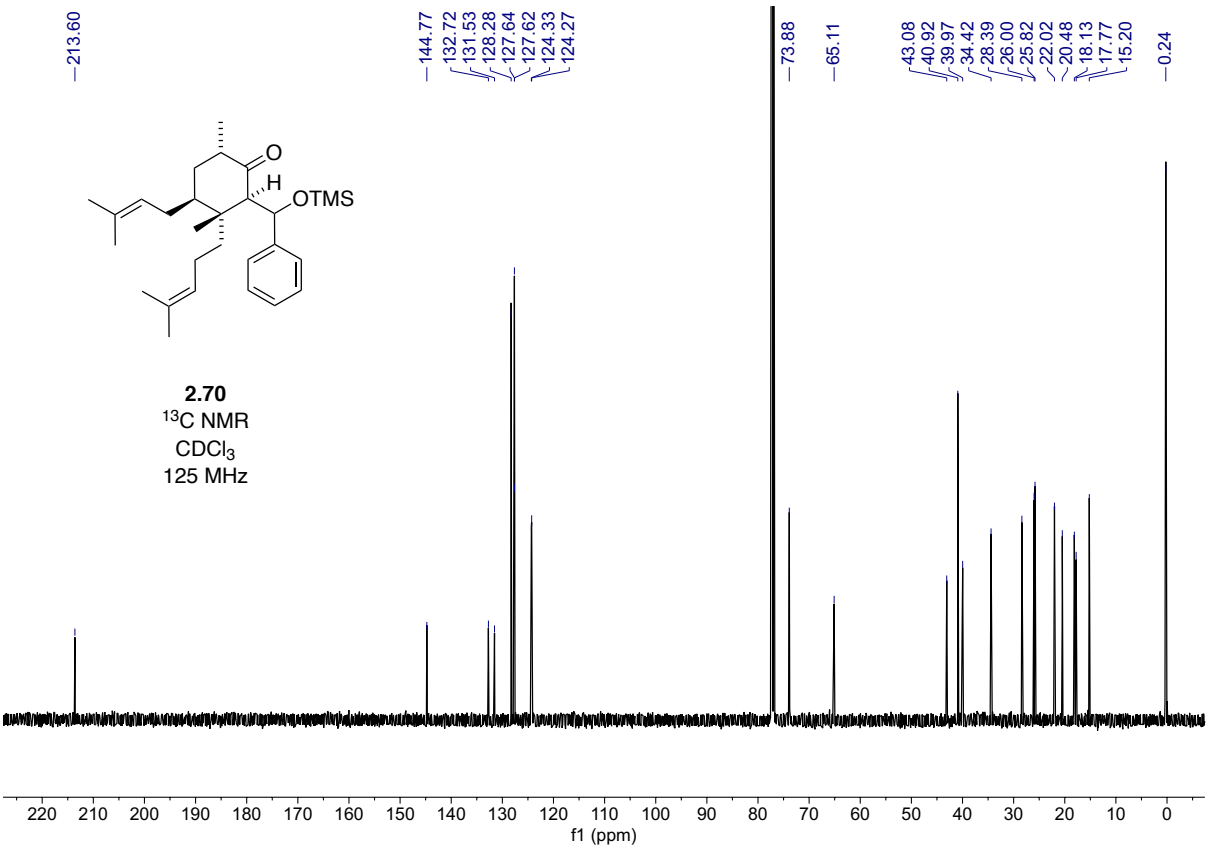

O
H
O
2.69
COSY
CDCl3
600 MHz
f1 (ppm)
f2 (ppm)

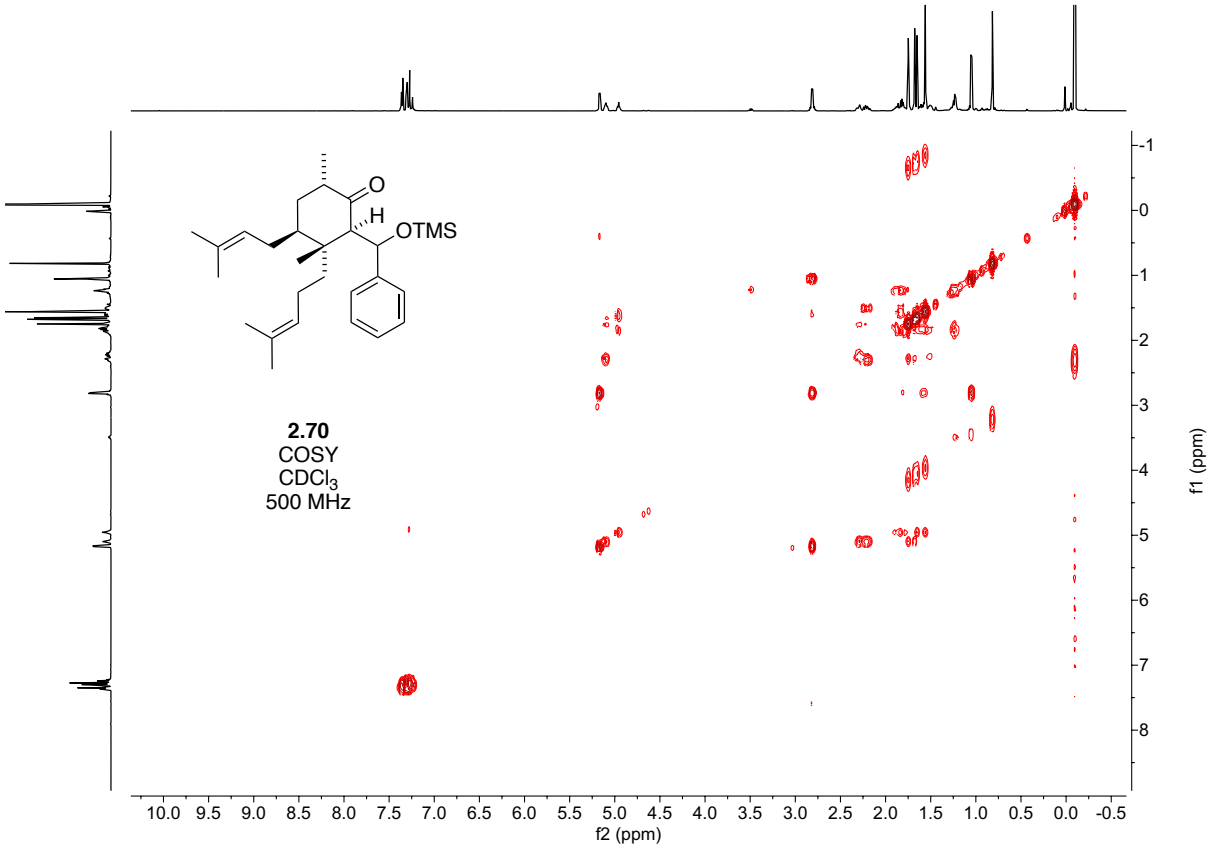

O
H
O
2.69
HSQC
CDCl3
600 MHz
f1 (ppm)
f2 (ppm)

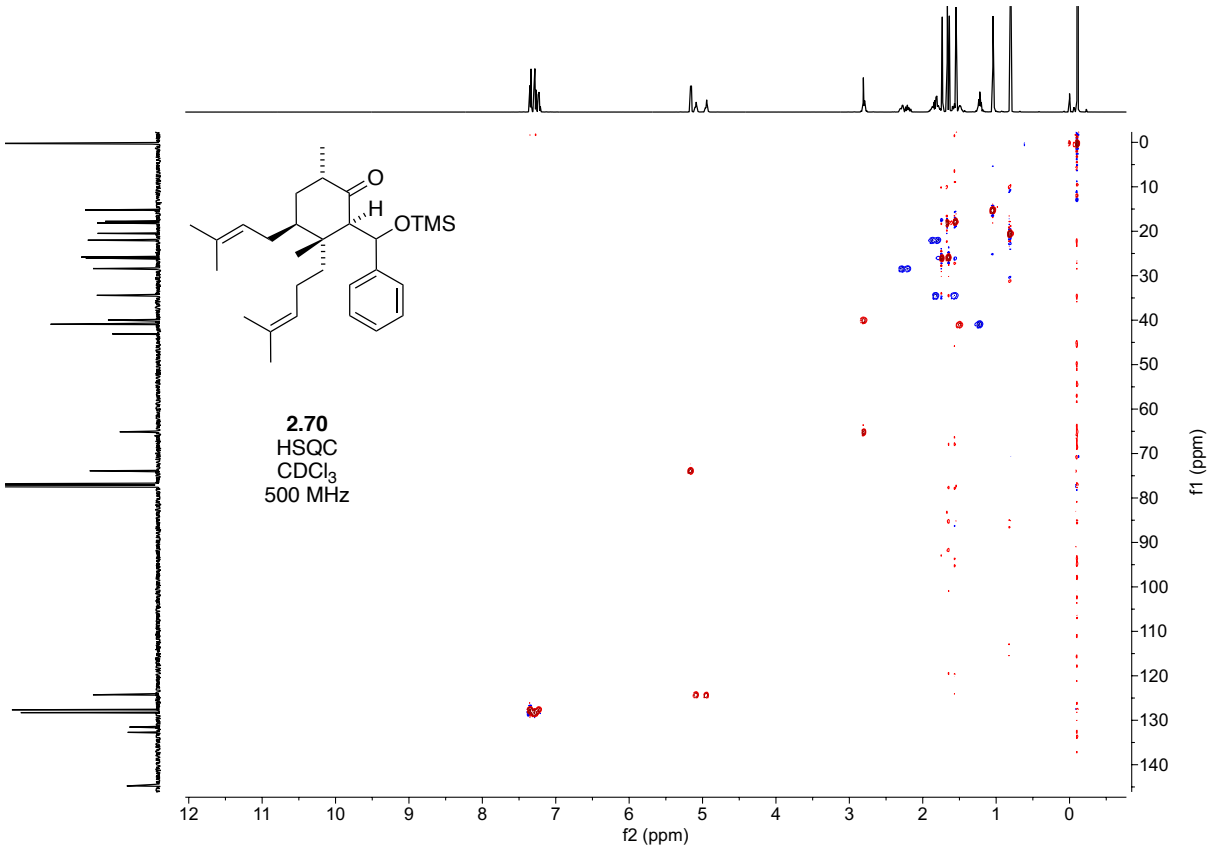

O
H
O
2.69
HMBC
CDCl3
600 MHz
f2 (ppm)
f1 (ppm)

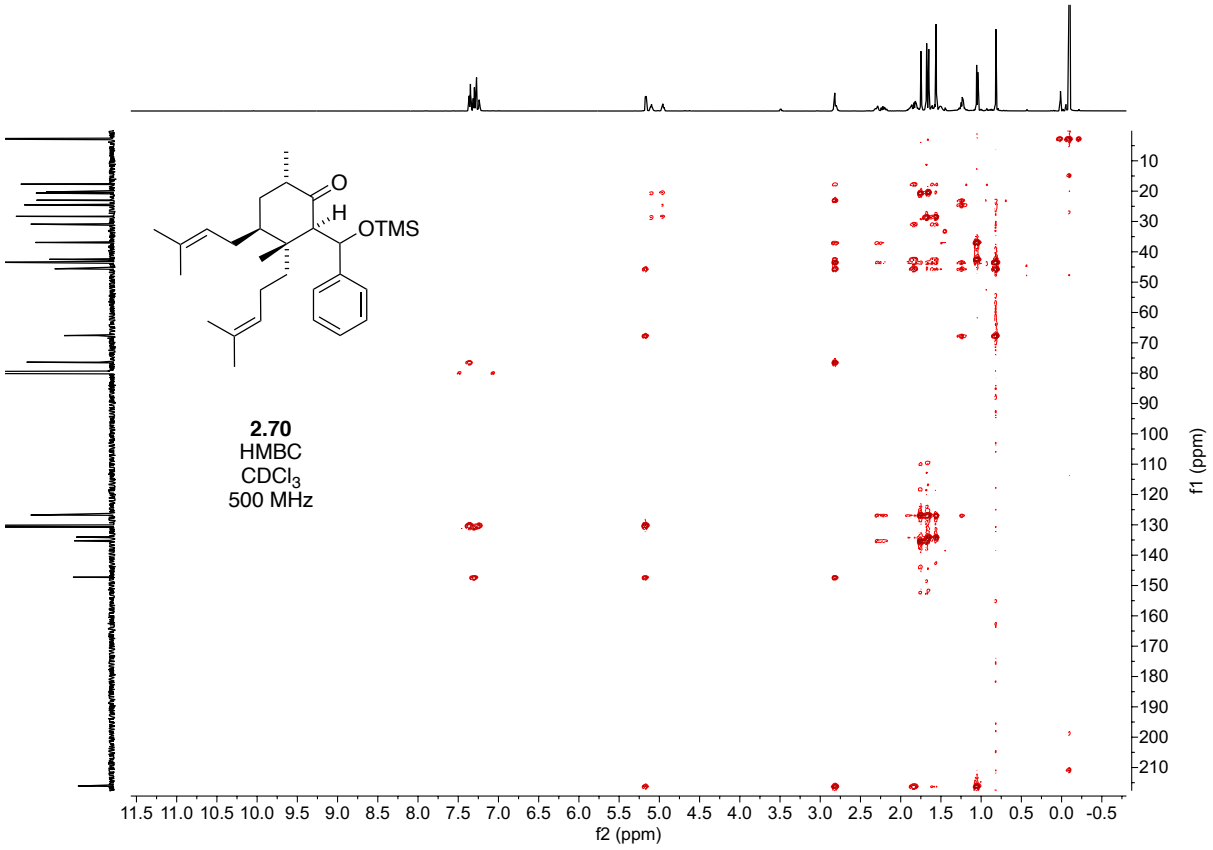

O
H
O
2.69
NOESY
CDCl3
600 MHz
f2 (ppm)
f1 (ppm)

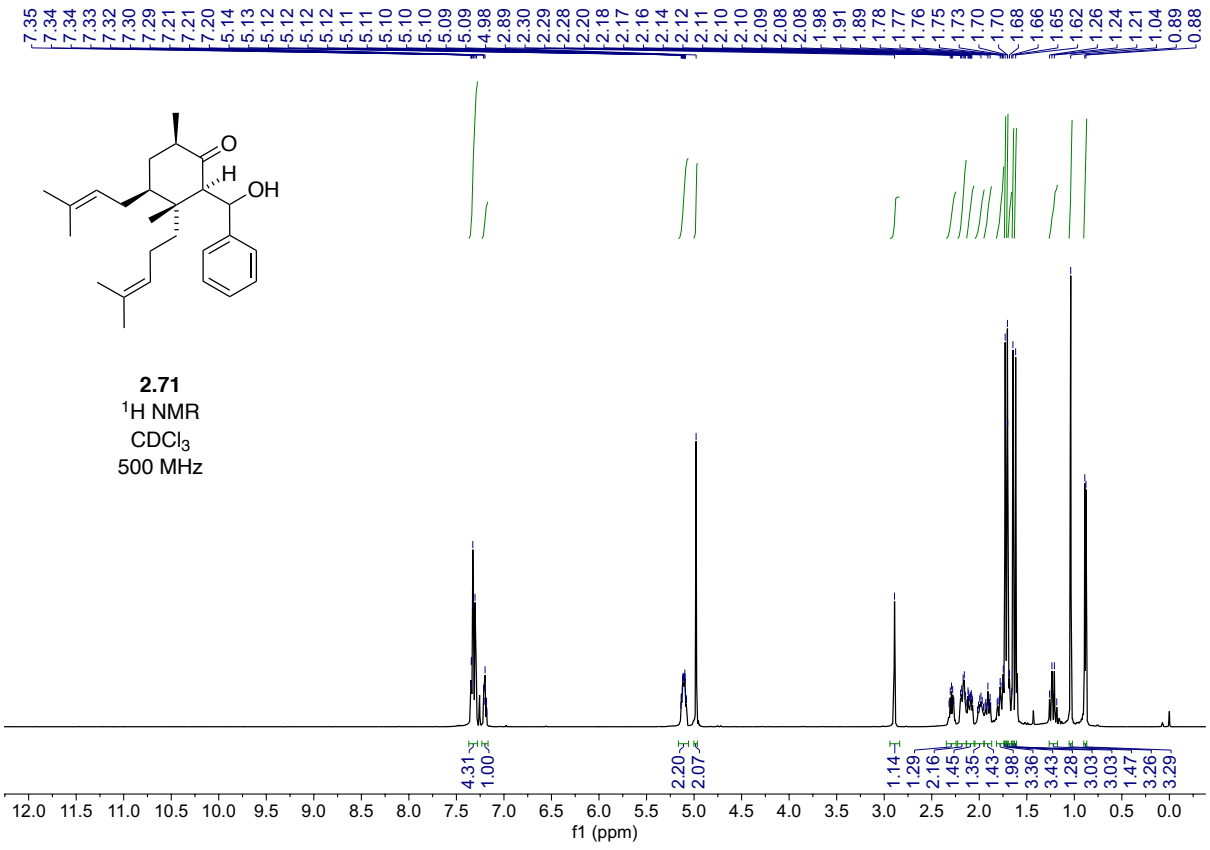

O
H
OTMS
2.70
1H NMR
CDCl3
500 MHz
f1 (ppm)

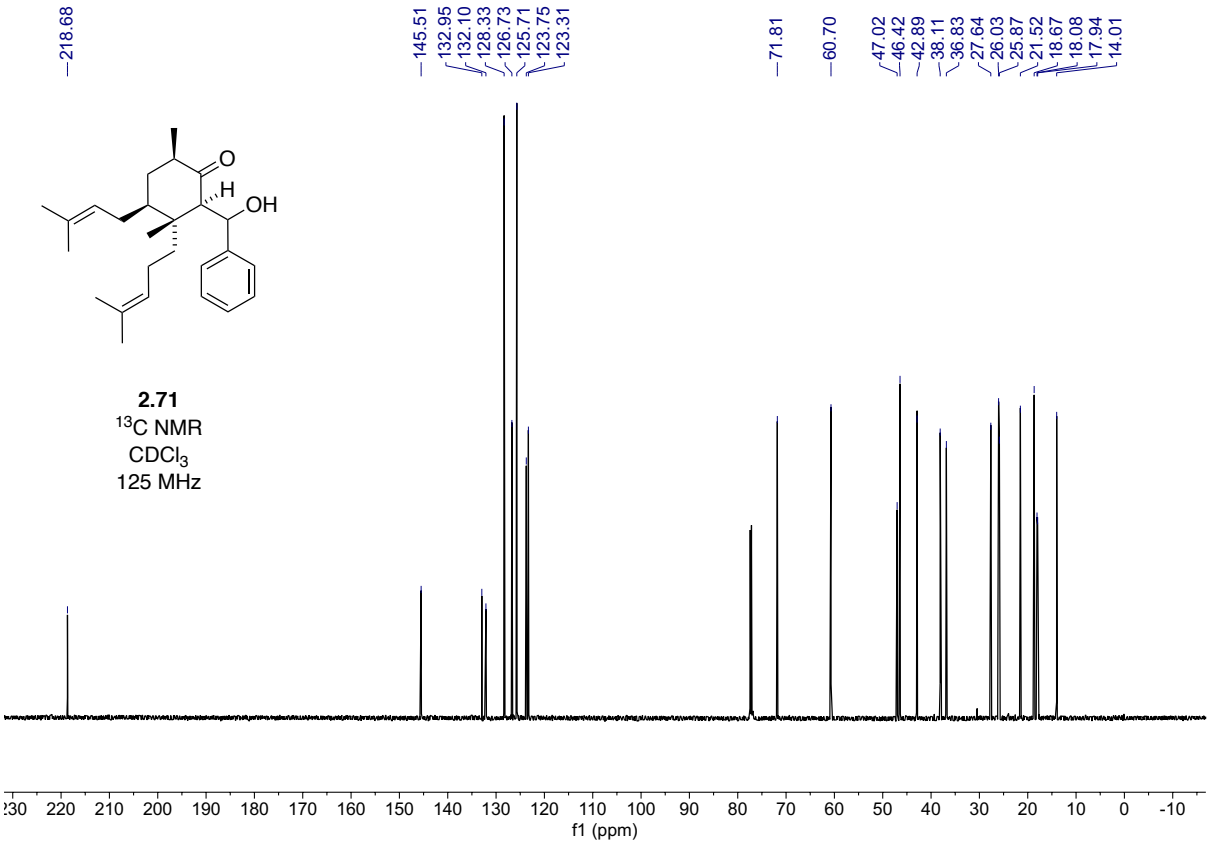

O
H
OTMS
2.70
13C NMR
CDCl3
125 MHz
f1 (ppm)

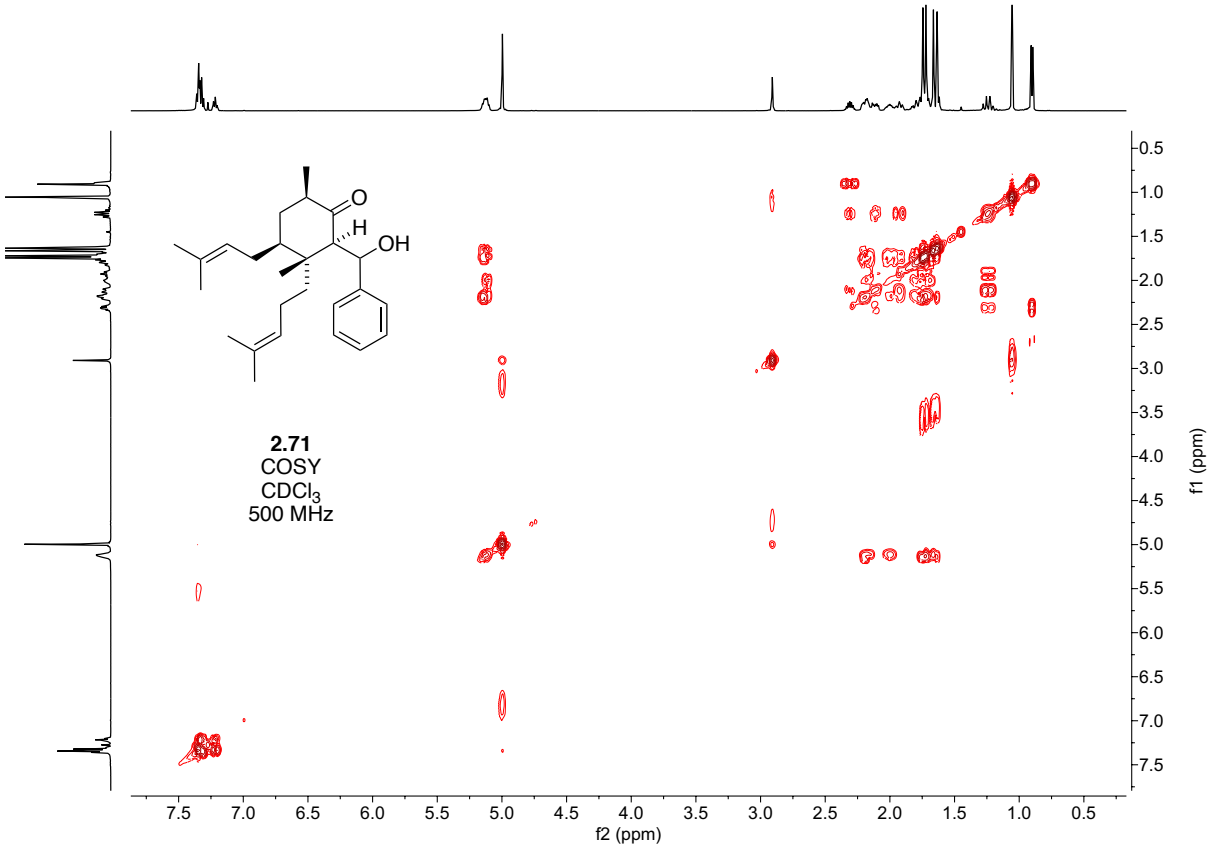

O
H
OTMS
2.70
COSY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

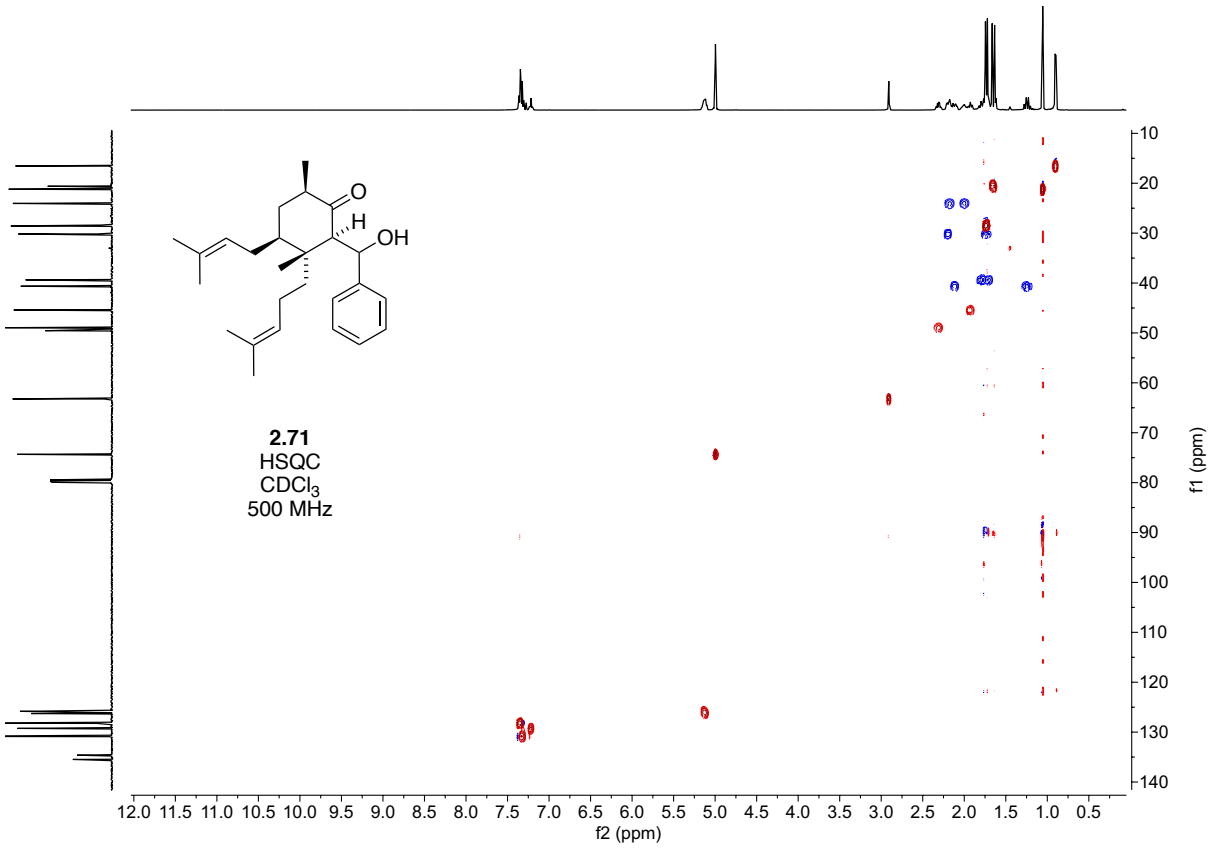

O
H
OTMS
2.70
HSQC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

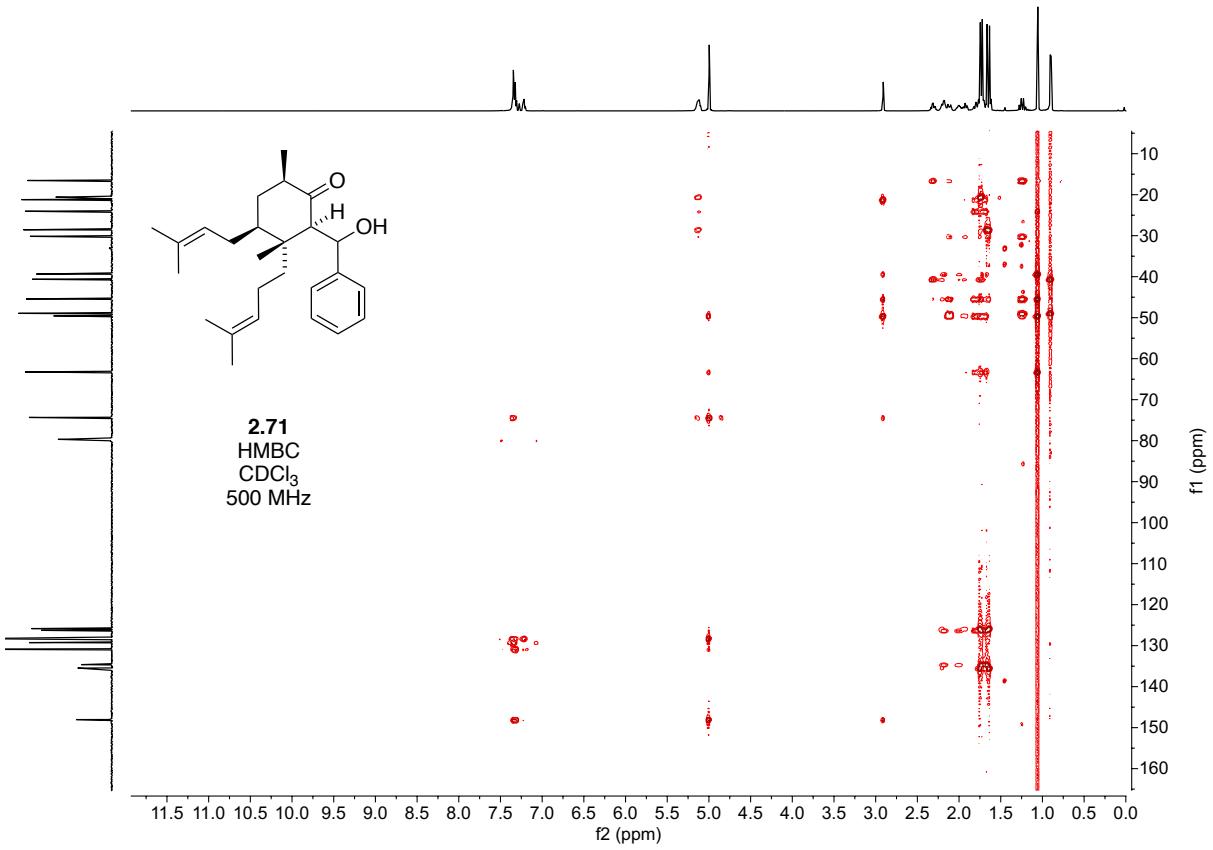

O
H
OTMS
2.70
HMBC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

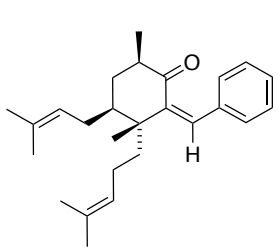

O
H
OH
2.71
1H NMR
CDCl3
500 MHz
f1 (ppm)


O
H
OH
2.71
13C NMR
CDCl3
125 MHz
f1 (ppm)

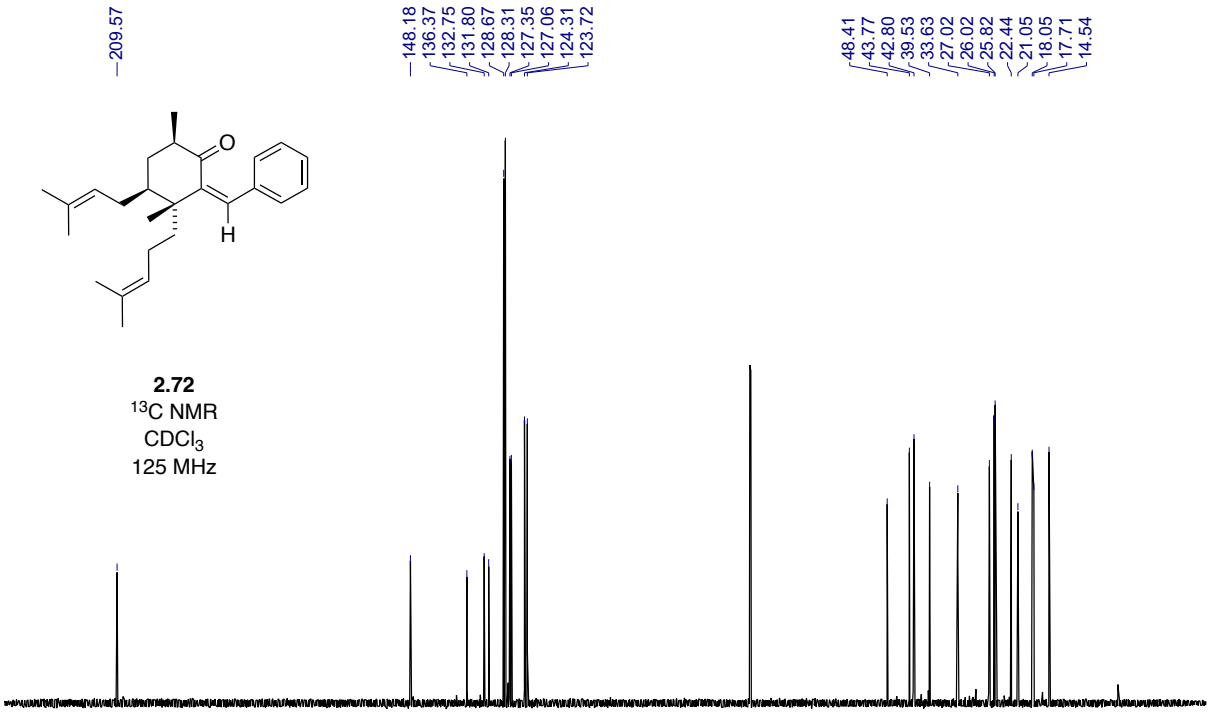

O
H
OH
2.71
COSY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)


O
H
OH
2.71
HSQC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

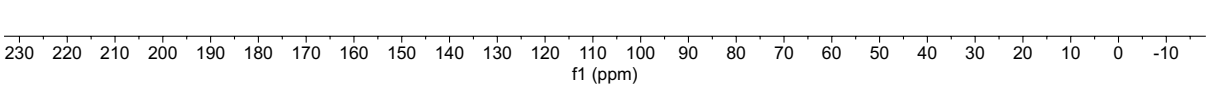

O
H
OH
2.71
HMBC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

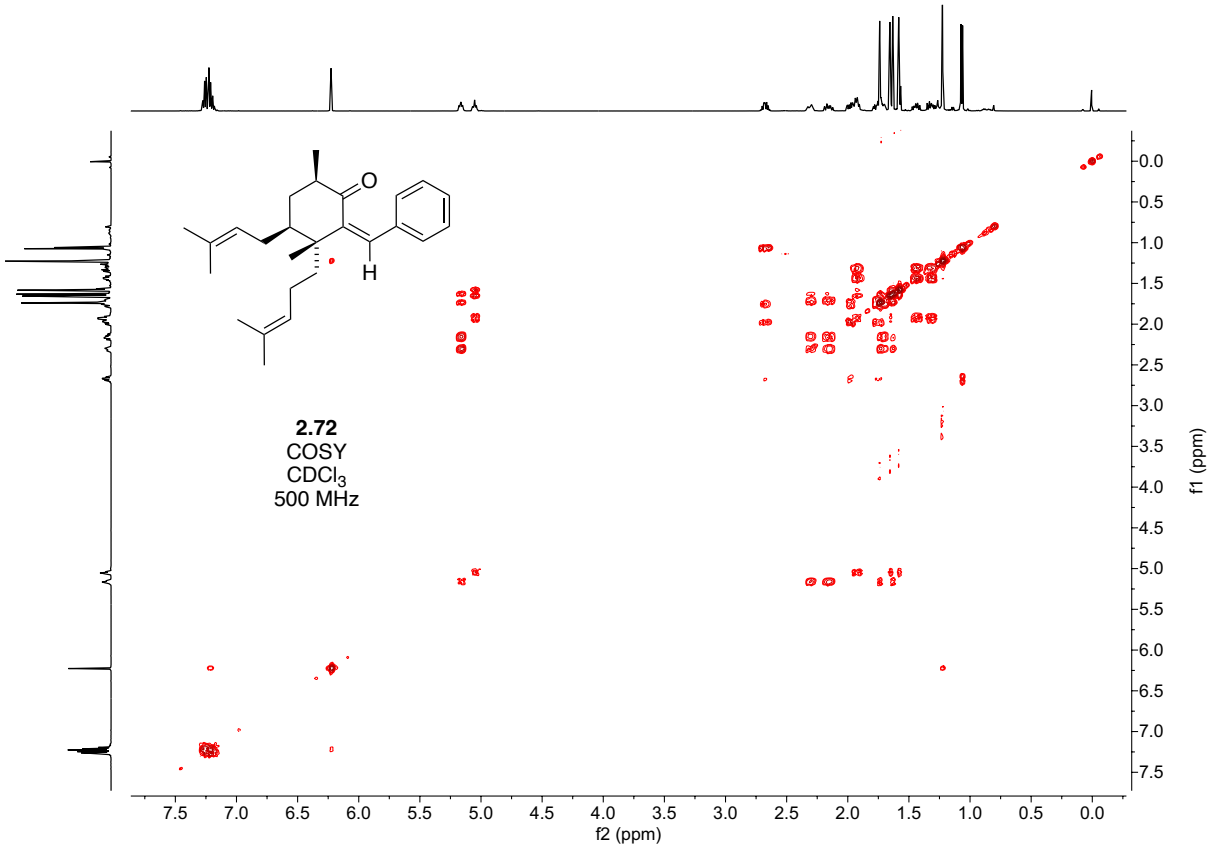


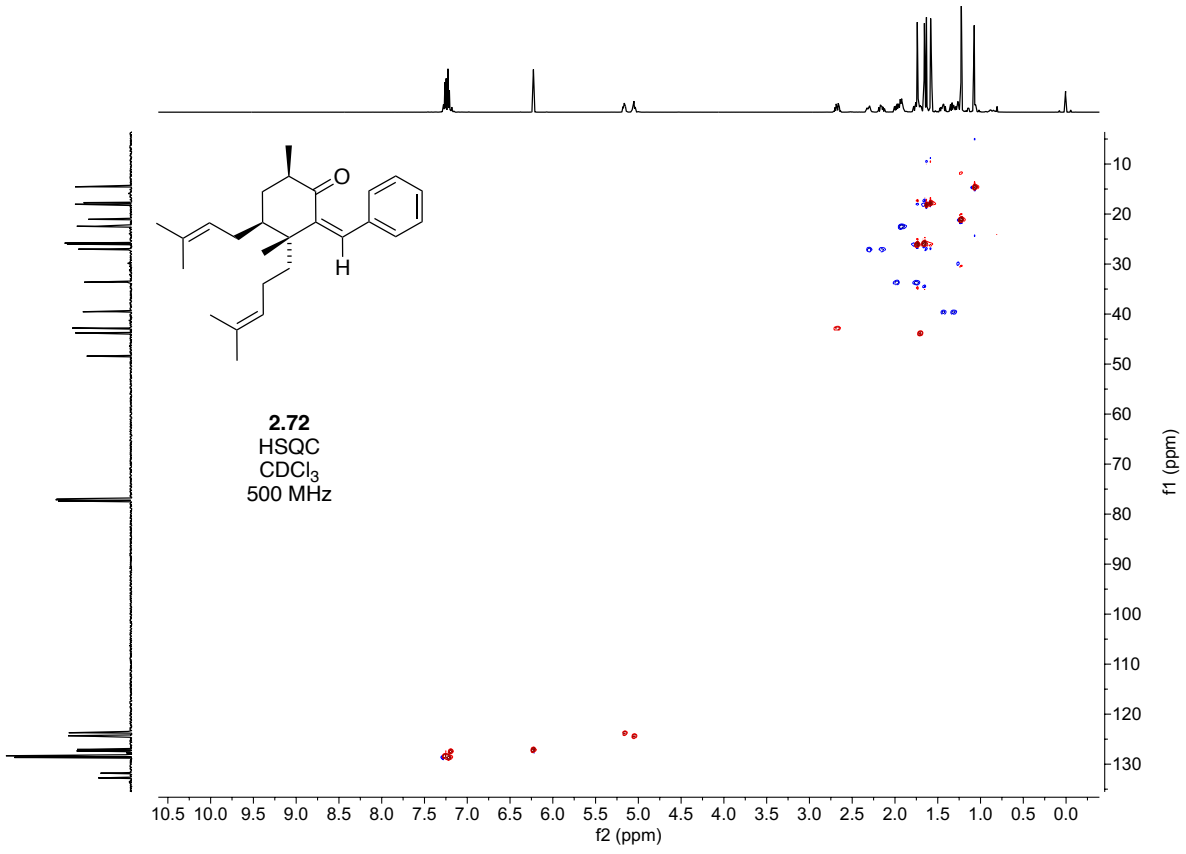
2.72
^{1}H NMR
$CDCl_3$
500 MHz

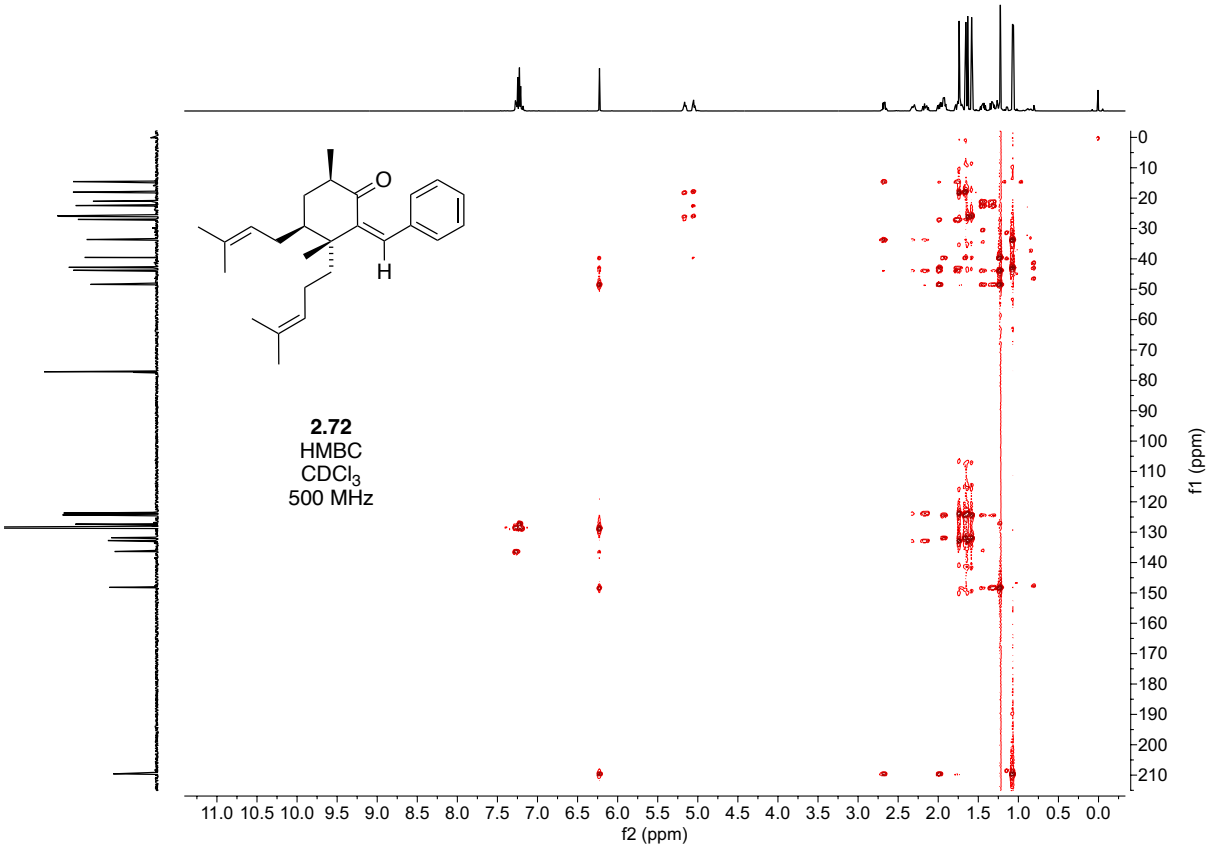


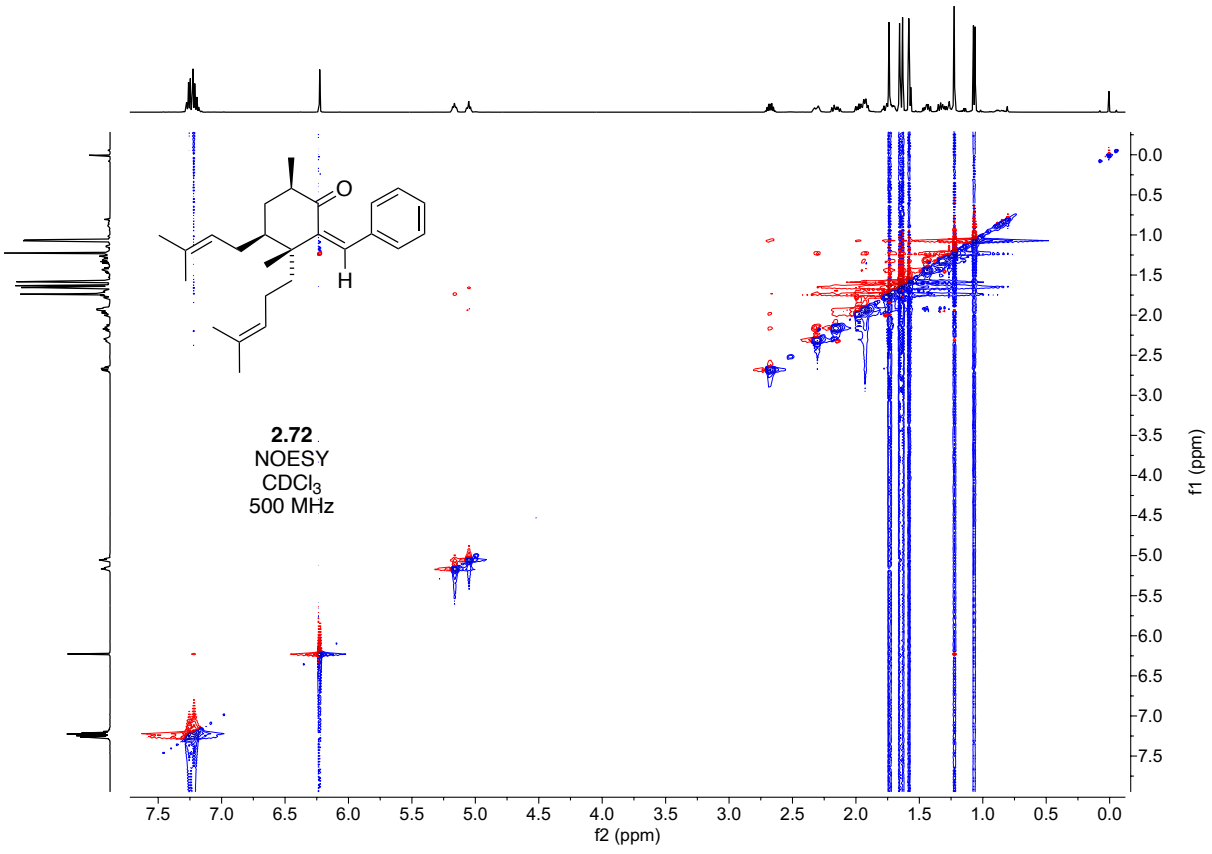
2.72
^{13}C NMR
$CDCl_3$
125 MHz

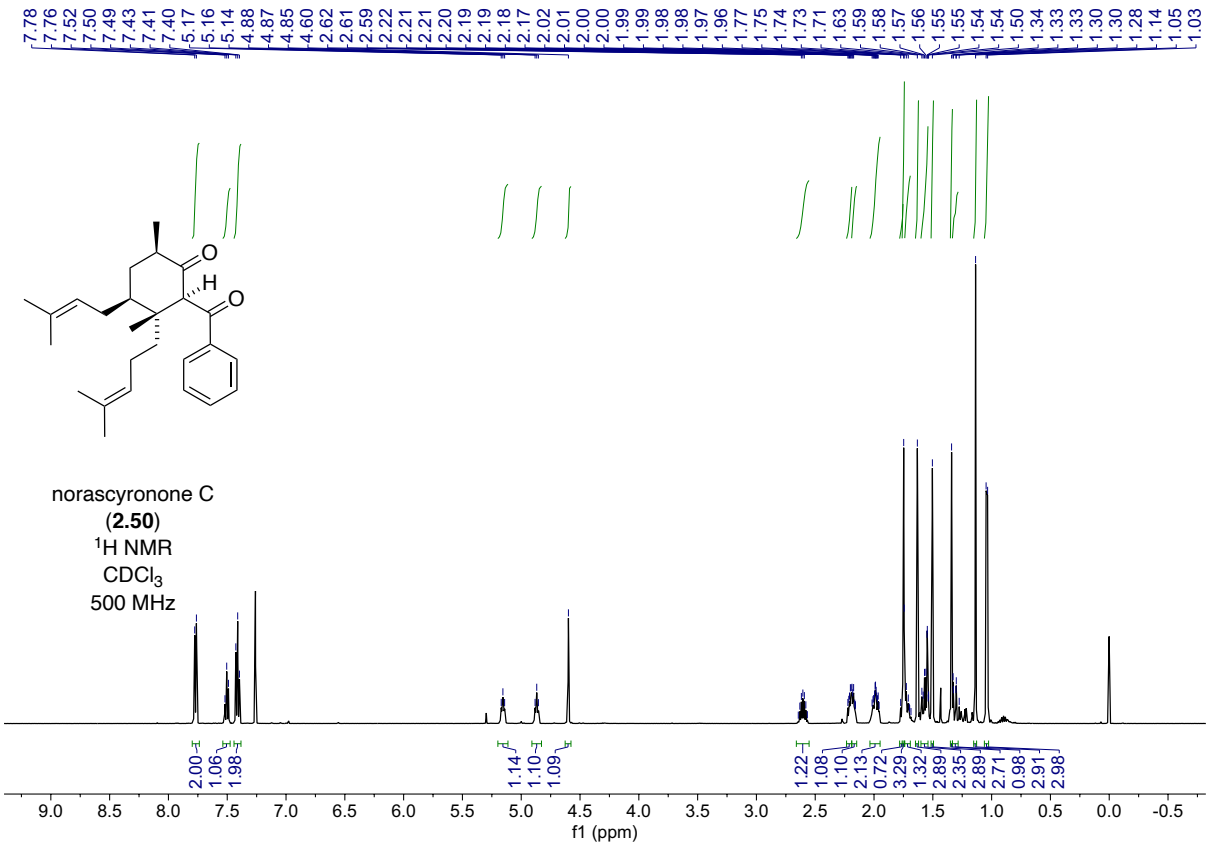


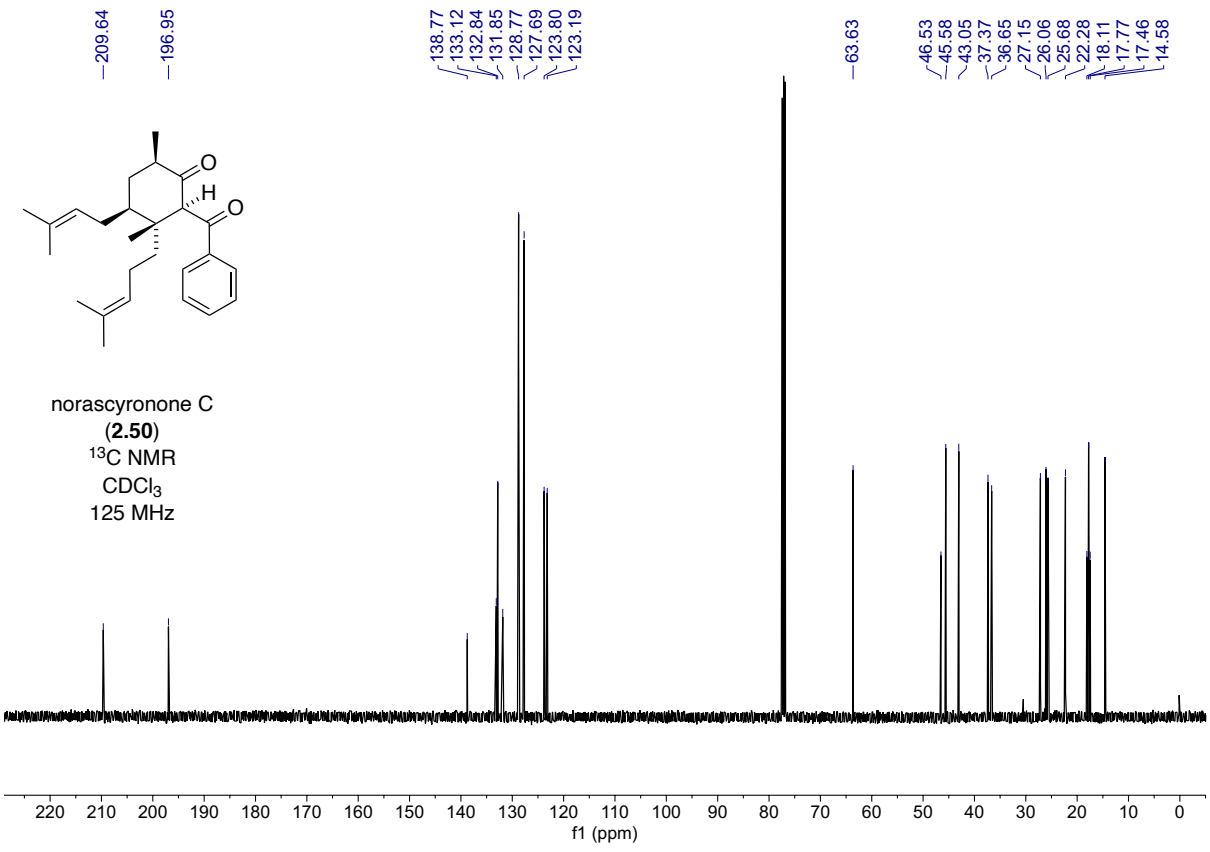

O
H
2.72
COSY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

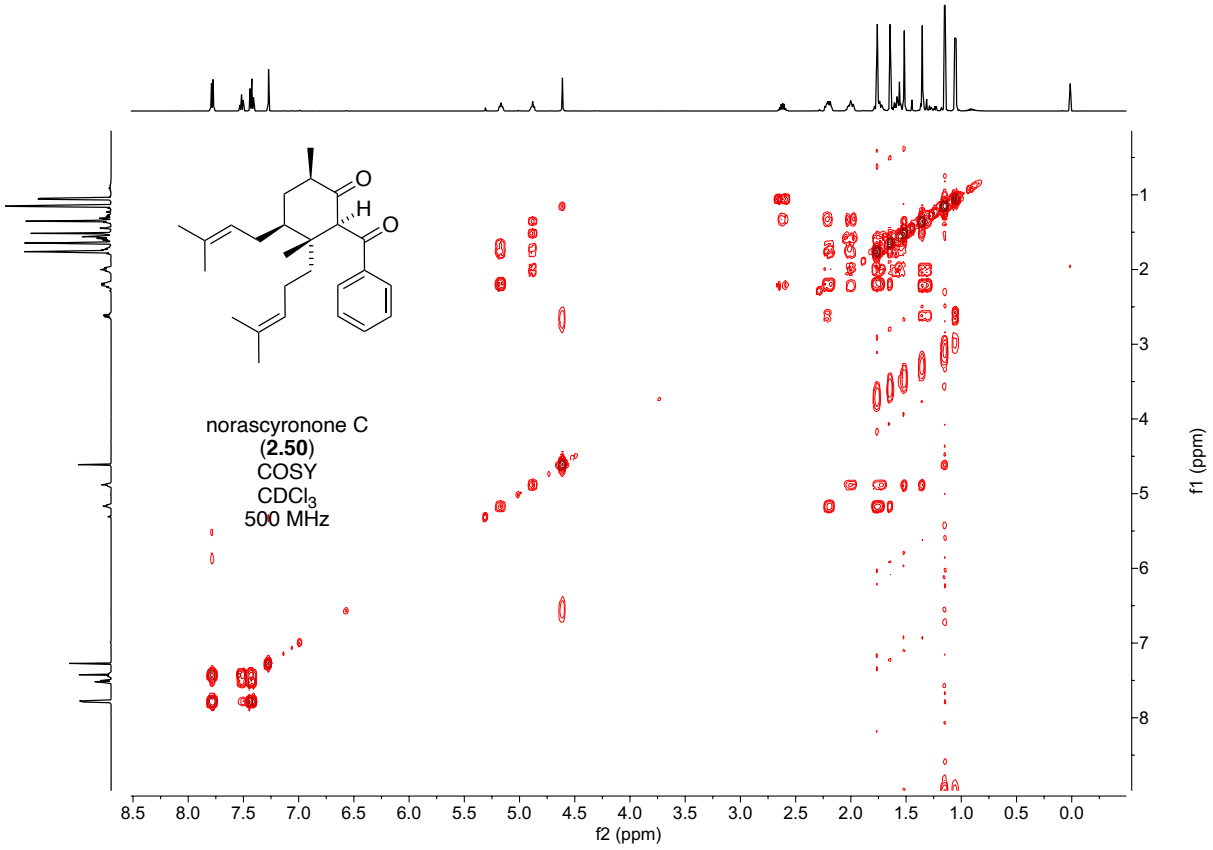

O
H
2.72
HSQC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

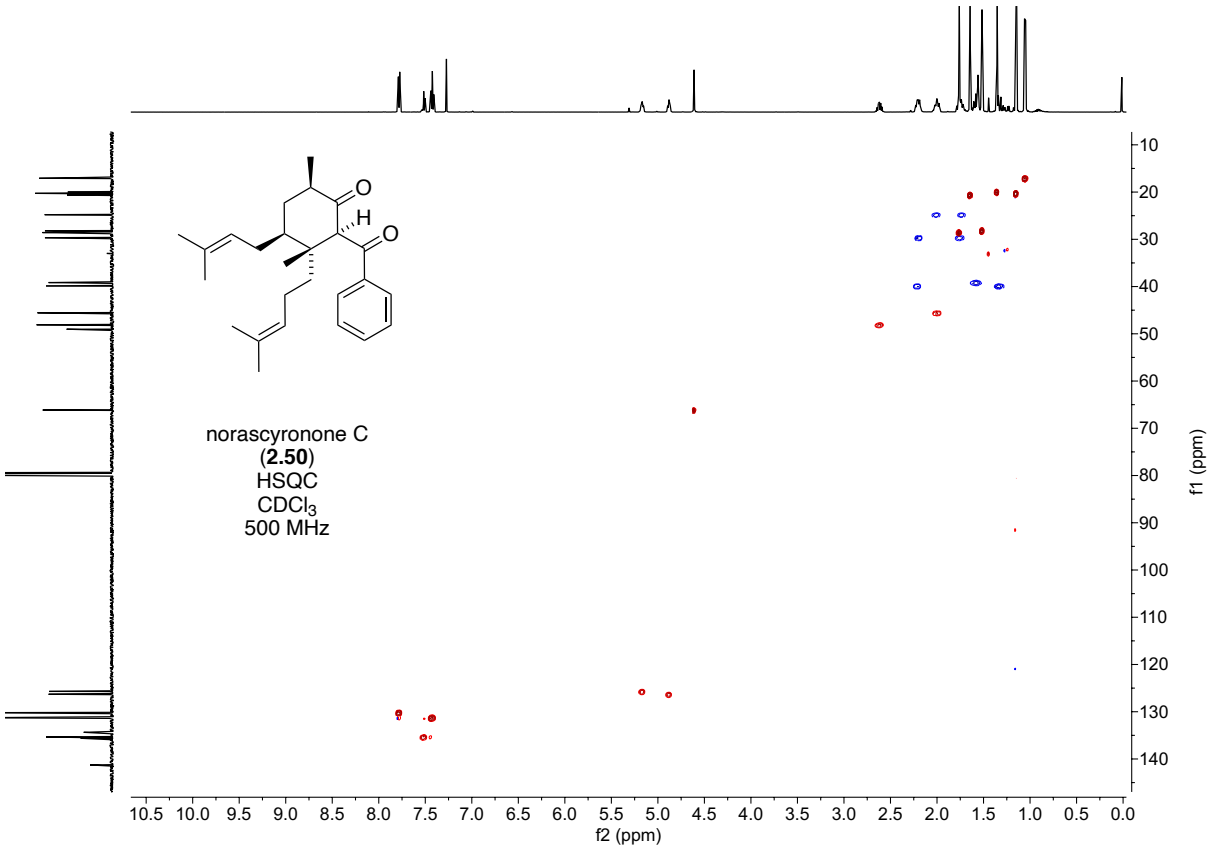

O
H
2.72
HMBC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

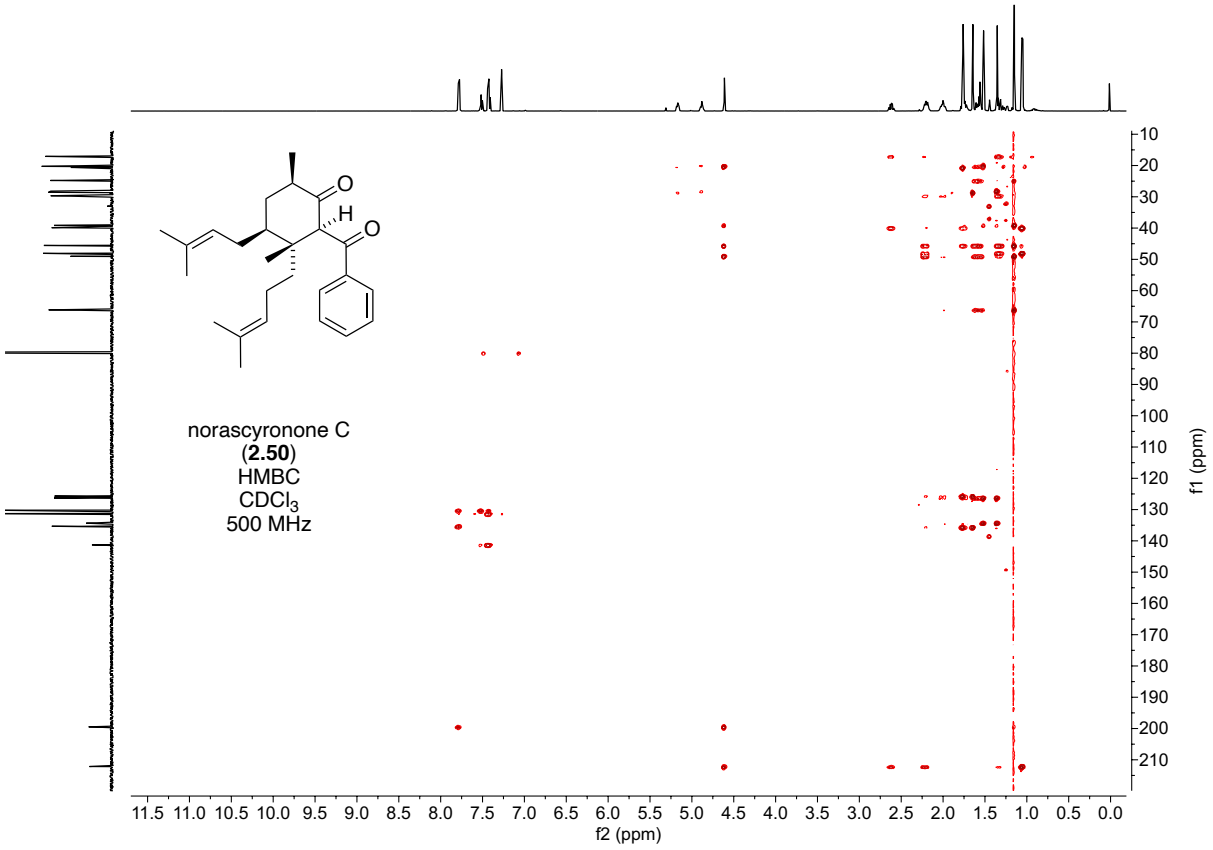

O
H
2.72
NOESY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

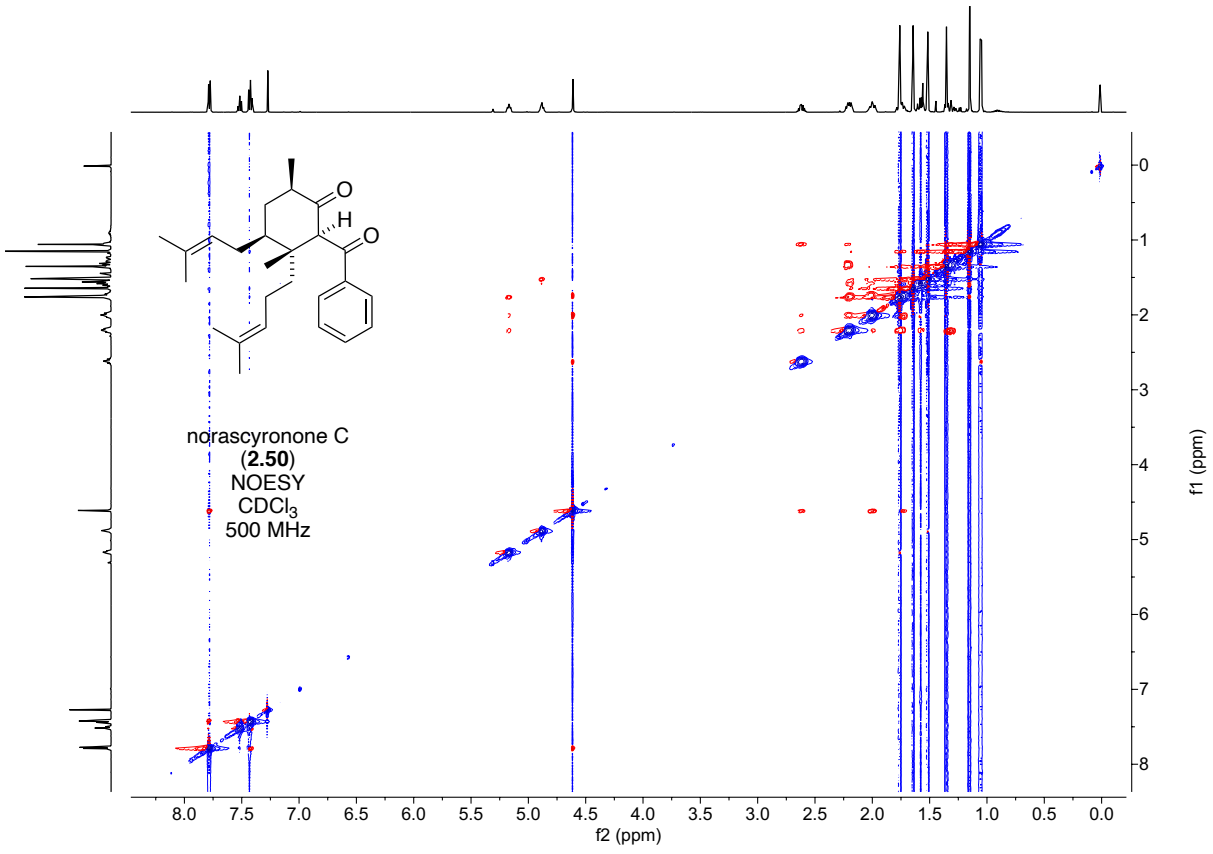

norascyronone C
(2.50)
1H NMR
CDCl3
500 MHz
f1 (ppm)

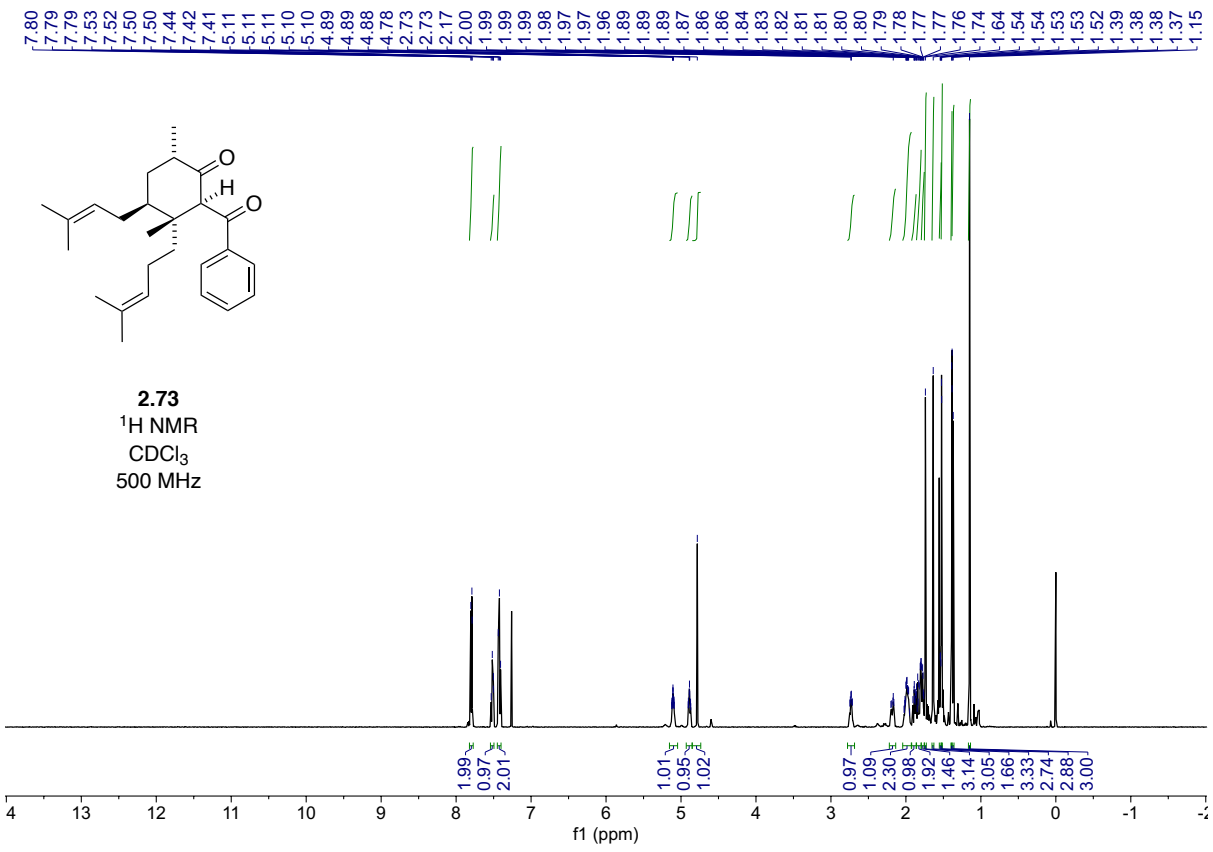

norascyronone C
(2.50)
13C NMR
CDCl3
125 MHz
f1 (ppm)

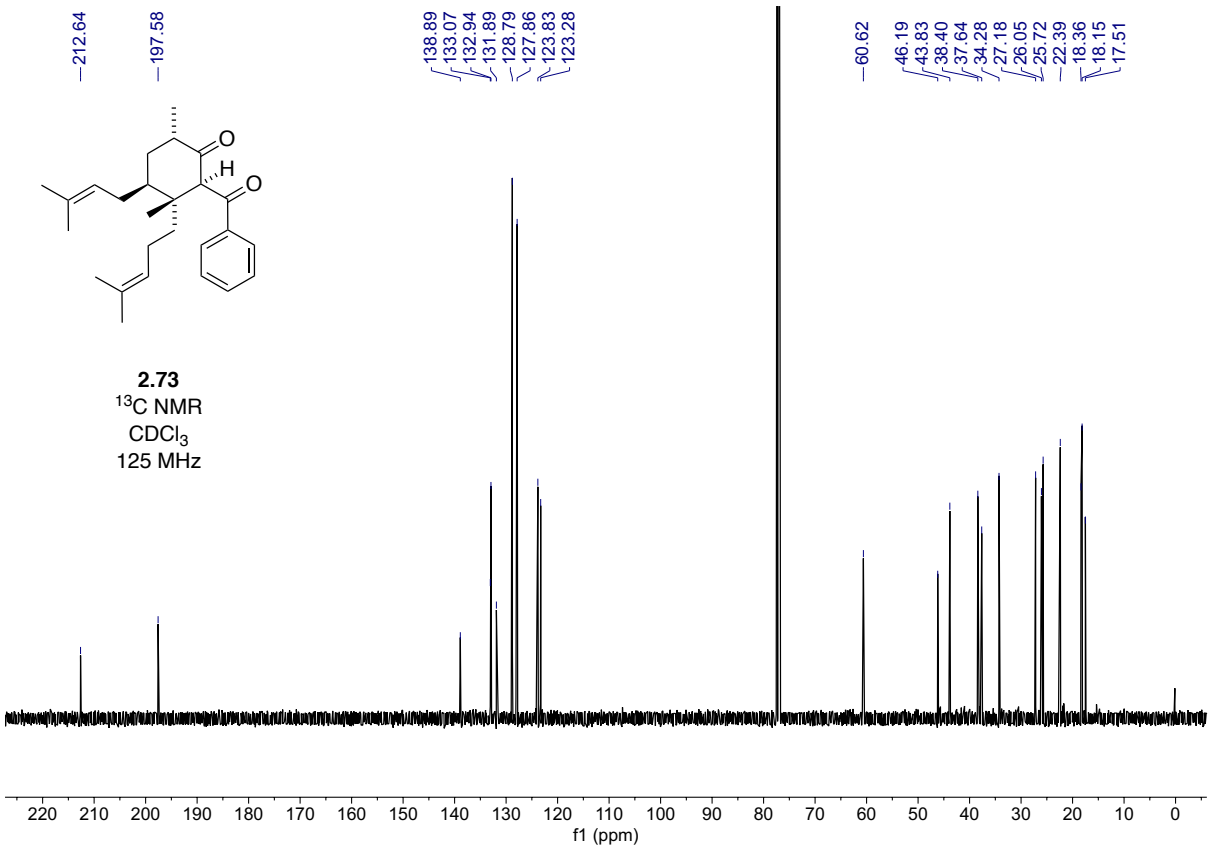

norascyronone C
(2.50)
COSY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

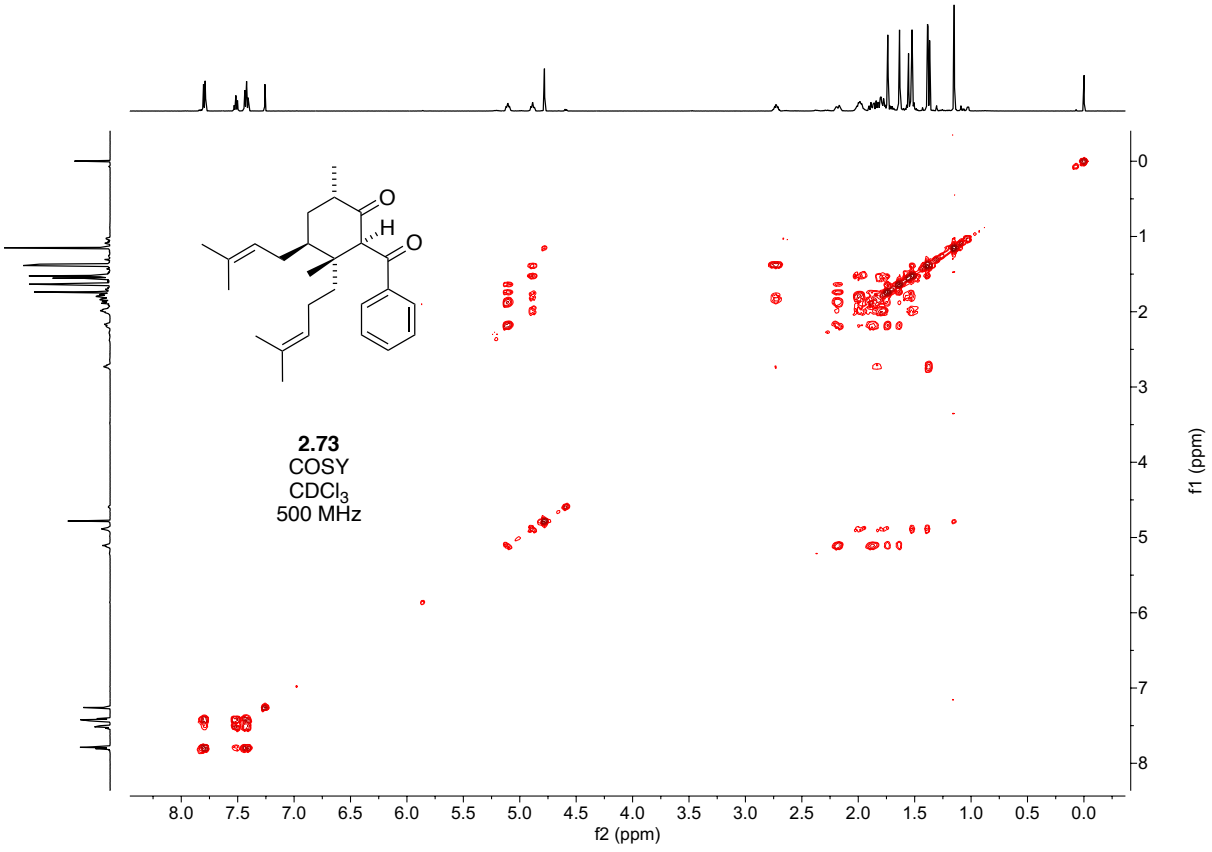

norascyronone C
(2.50)
HSQC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

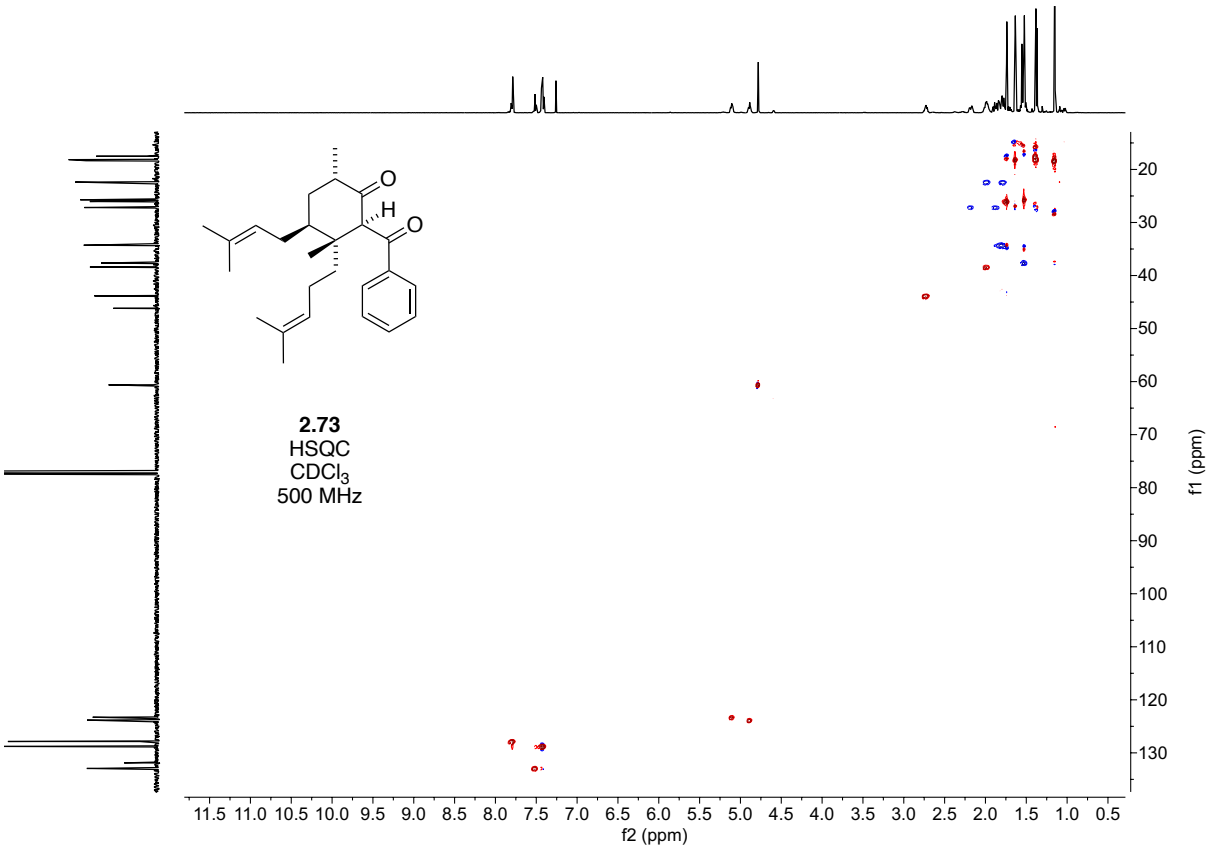

norascyronone C
(2.50)
HMBC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

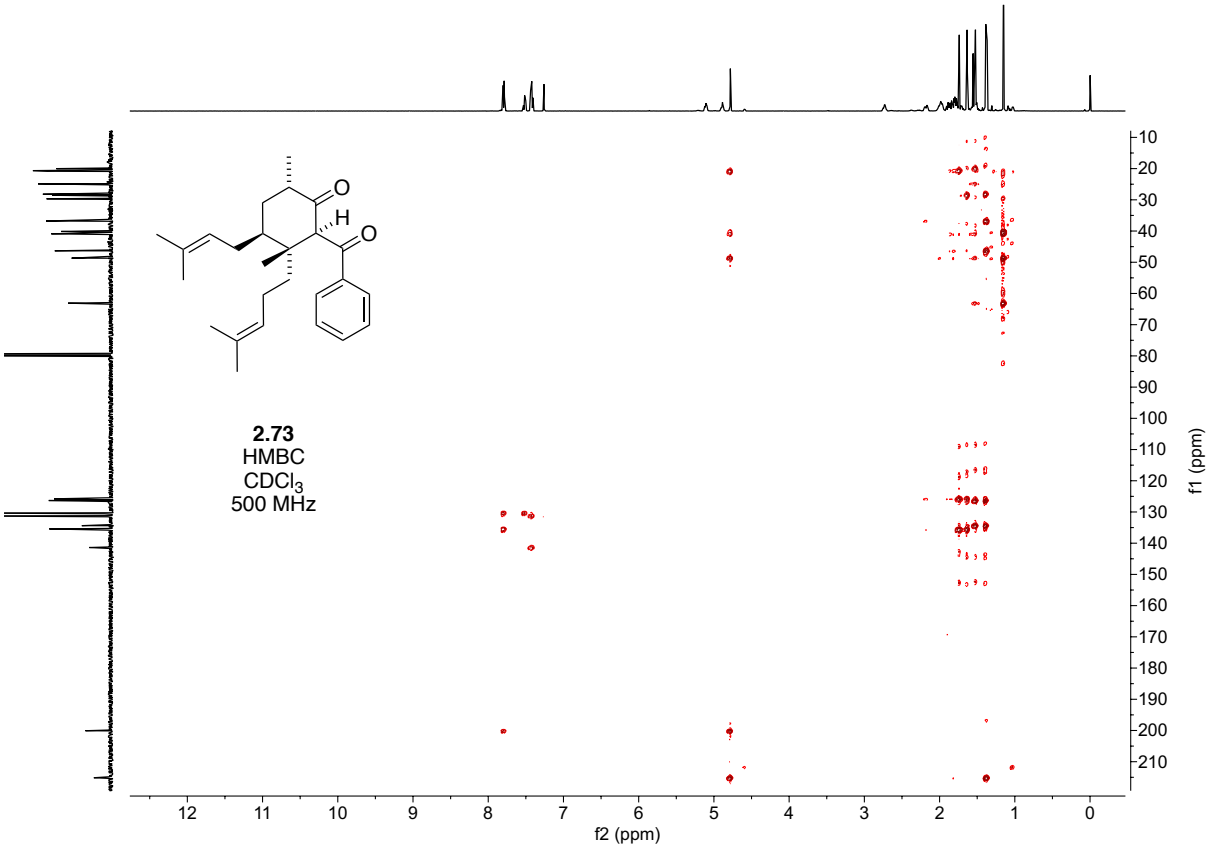

norascyronone C
(2.50)
NOESY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

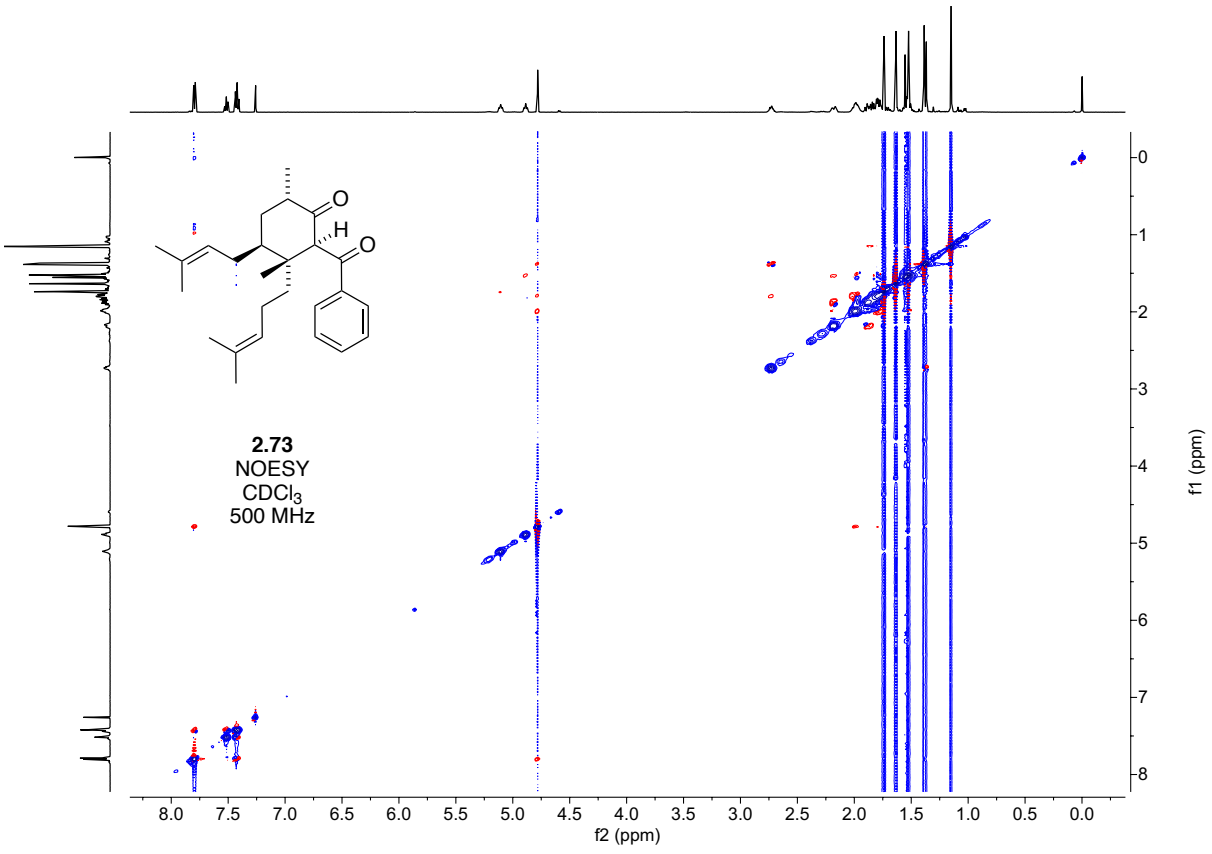

7.80 7.79 7.79 7.53 7.52 7.50 7.50 7.44 7.42 7.41 5.11 5.11 5.10 5.10 4.89 4.89 4.88 4.78 2.73 2.73 2.17 2.00 1.99 1.99 1.99 1.98 1.97 1.97 1.96 1.89 1.89 1.89 1.87 1.86 1.86 1.84 1.83 1.82 1.81 1.81 1.80 1.80 1.79 1.78 1.77 1.77 1.76 1.74 1.64 1.54 1.54 1.53 1.53 1.52 1.39 1.38 1.38 1.37 1.15
O
H
O
2.73
1H NMR
CDCl3
500 MHz
1.99 0.97 2.01 1.01 0.95 1.02 0.97 1.09 2.30 0.98 1.92 1.46 3.14 3.05 1.66 3.33 2.74 2.88 3.00
f1 (ppm)

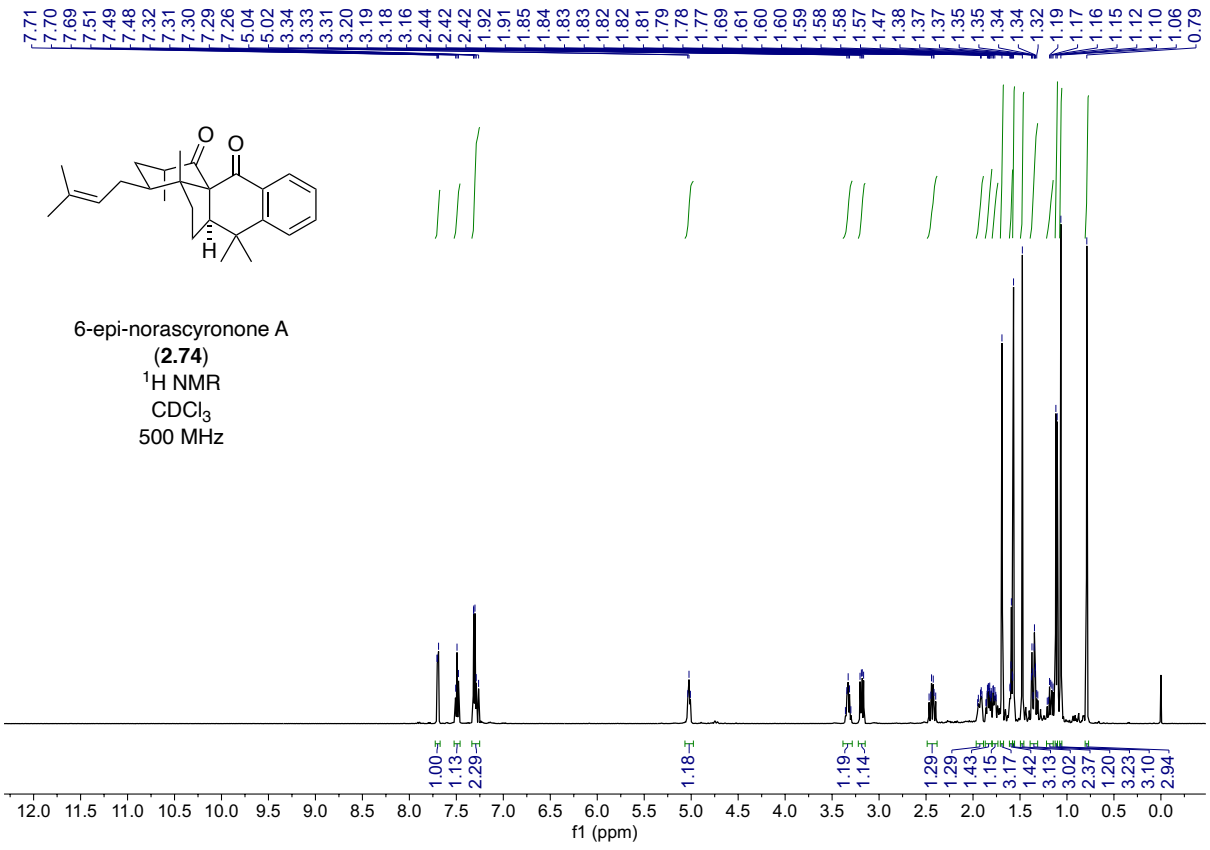

212.64 197.58 138.89 133.07 132.94 131.89 128.79 127.86 123.83 123.28 60.62 46.19 43.83 38.40 37.64 34.28 27.18 26.05 25.72 22.39 18.36 18.15 17.51
O
H
O
2.73
13C NMR
CDCl3
125 MHz
f1 (ppm)


O
H
O
2.73
COSY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

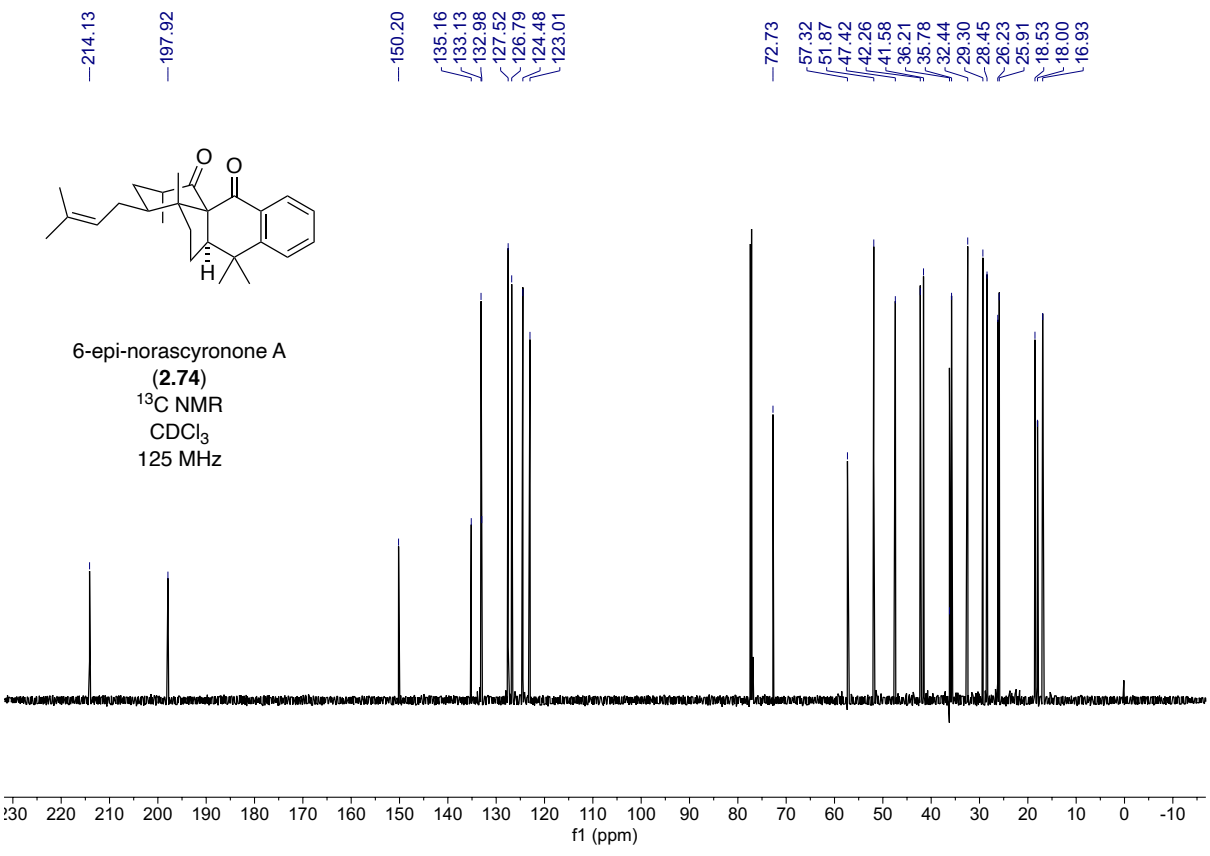

O
H
O
2.73
HSQC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)


O
H
O
2.73
HMBC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

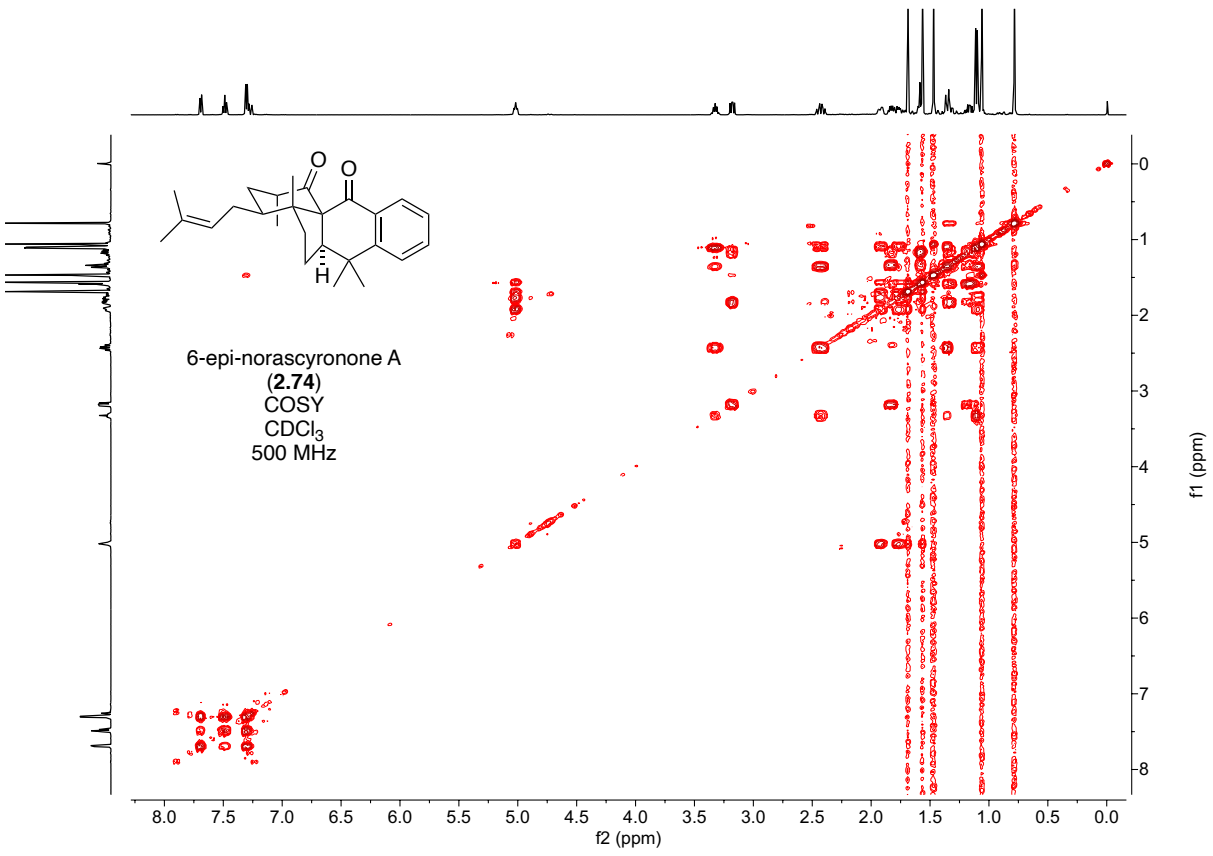

O
H
O
2.73
NOESY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

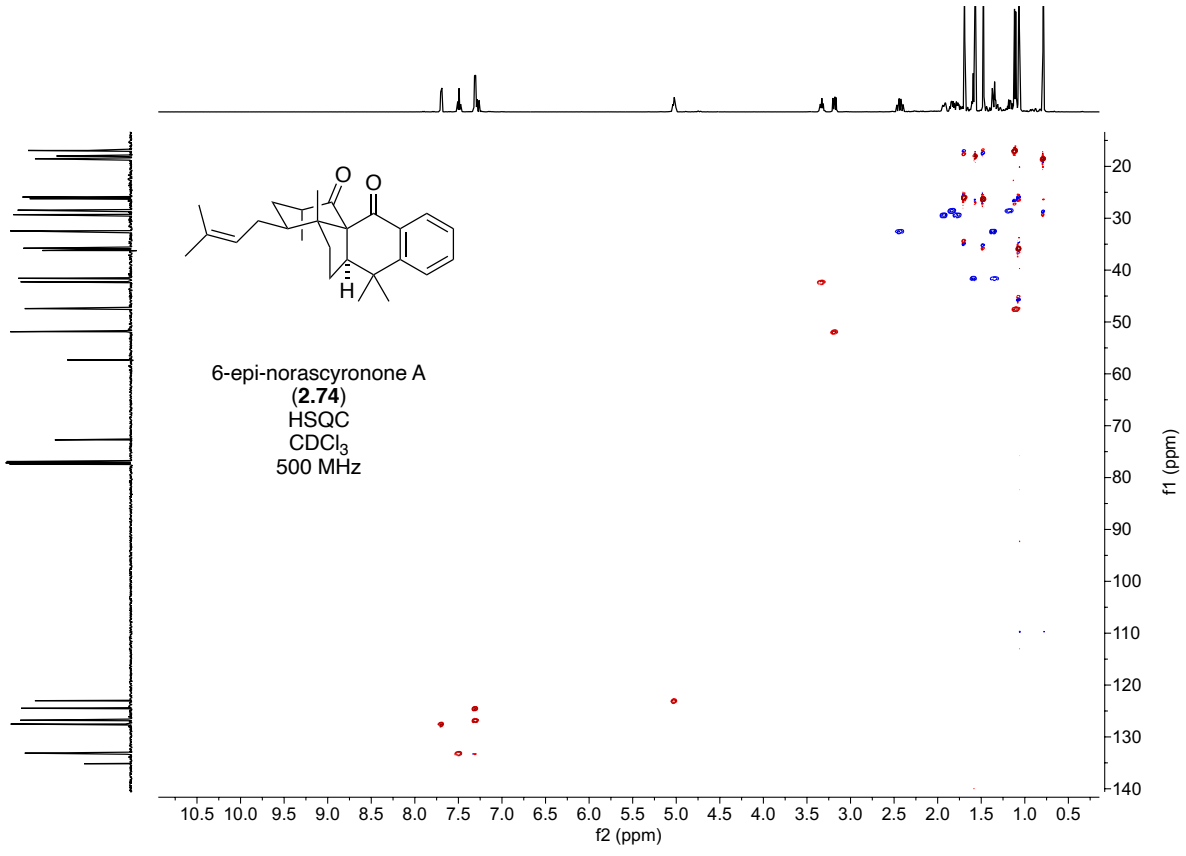


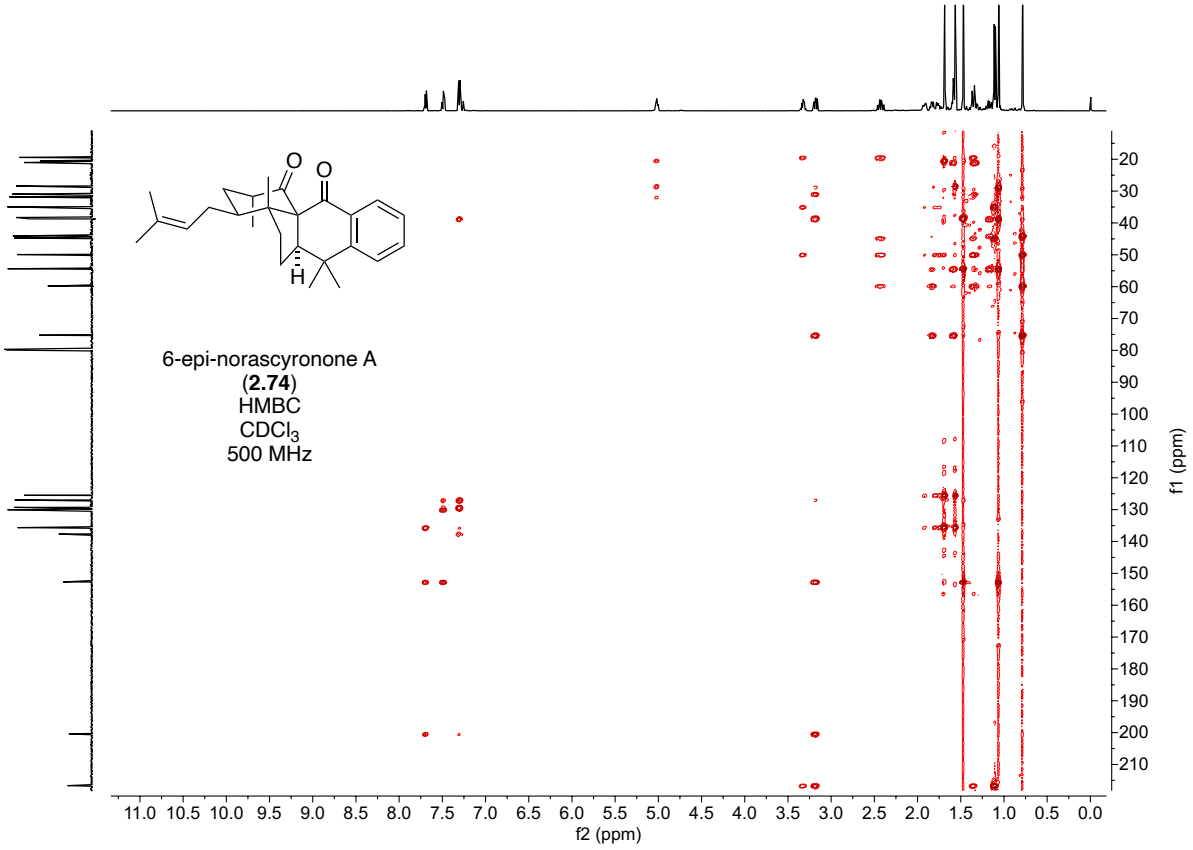
6-epi-norascyronone A
(**2.74**)
^{1}H NMR
$CDCl_3$
500 MHz

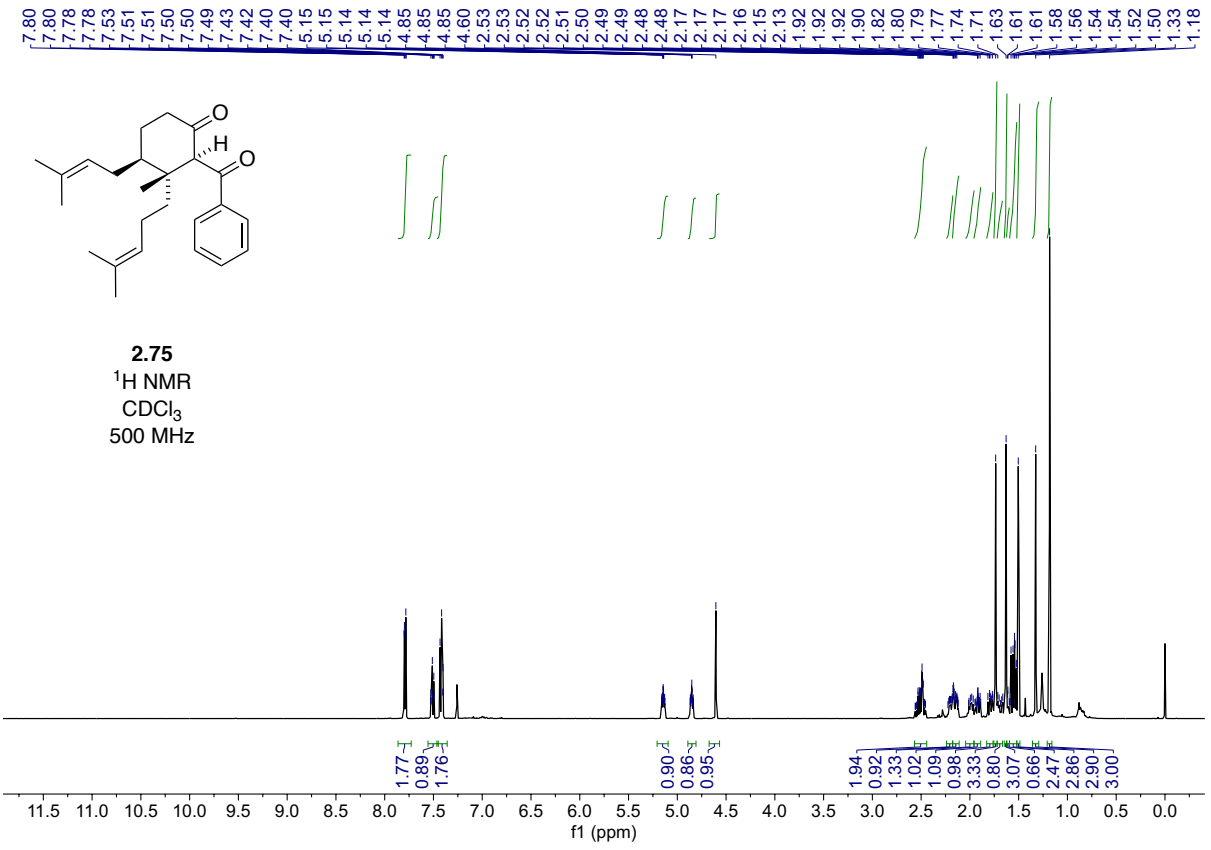


6-epi-norascyronone A
(**2.74**)
^{13}C NMR
$CDCl_3$
125 MHz

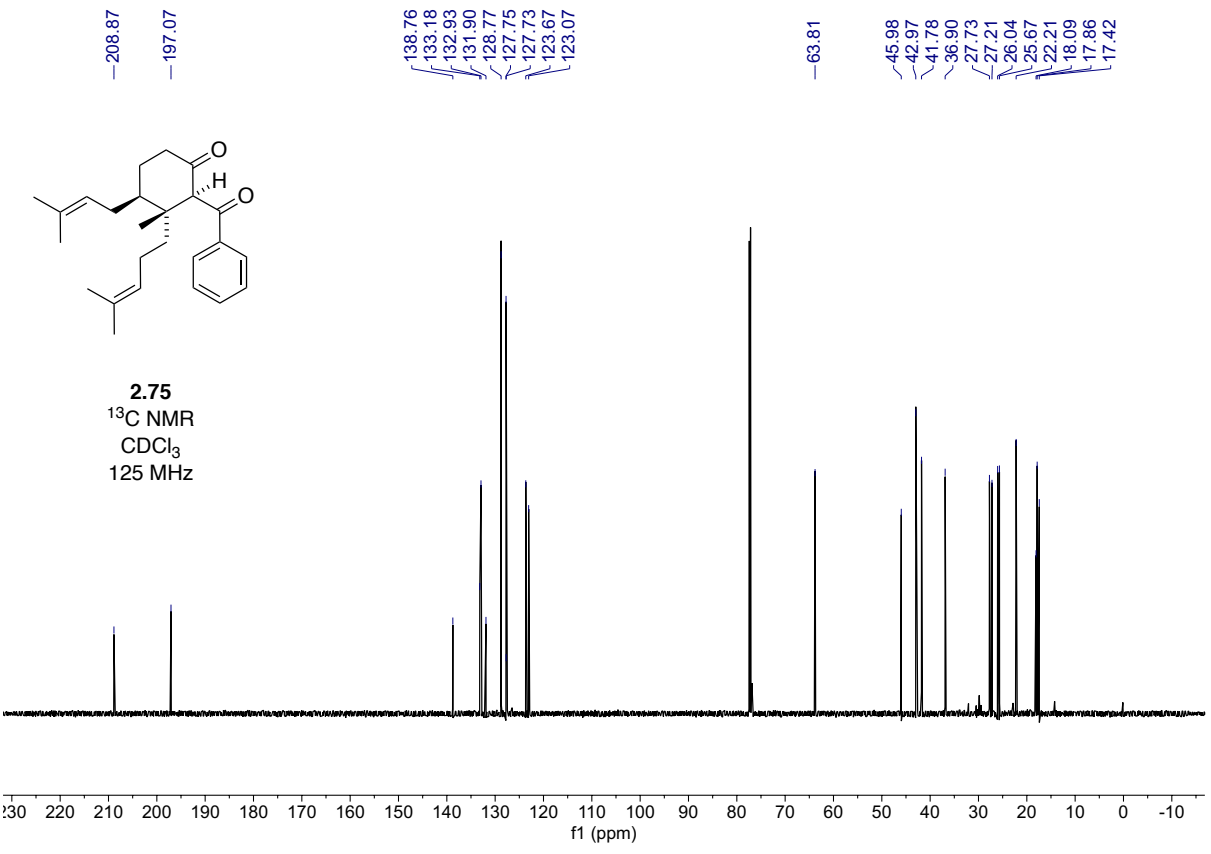

6-epi-norascyronone A
(2.74)
COSY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)


6-epi-norascyronone A
(2.74)
HSQC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

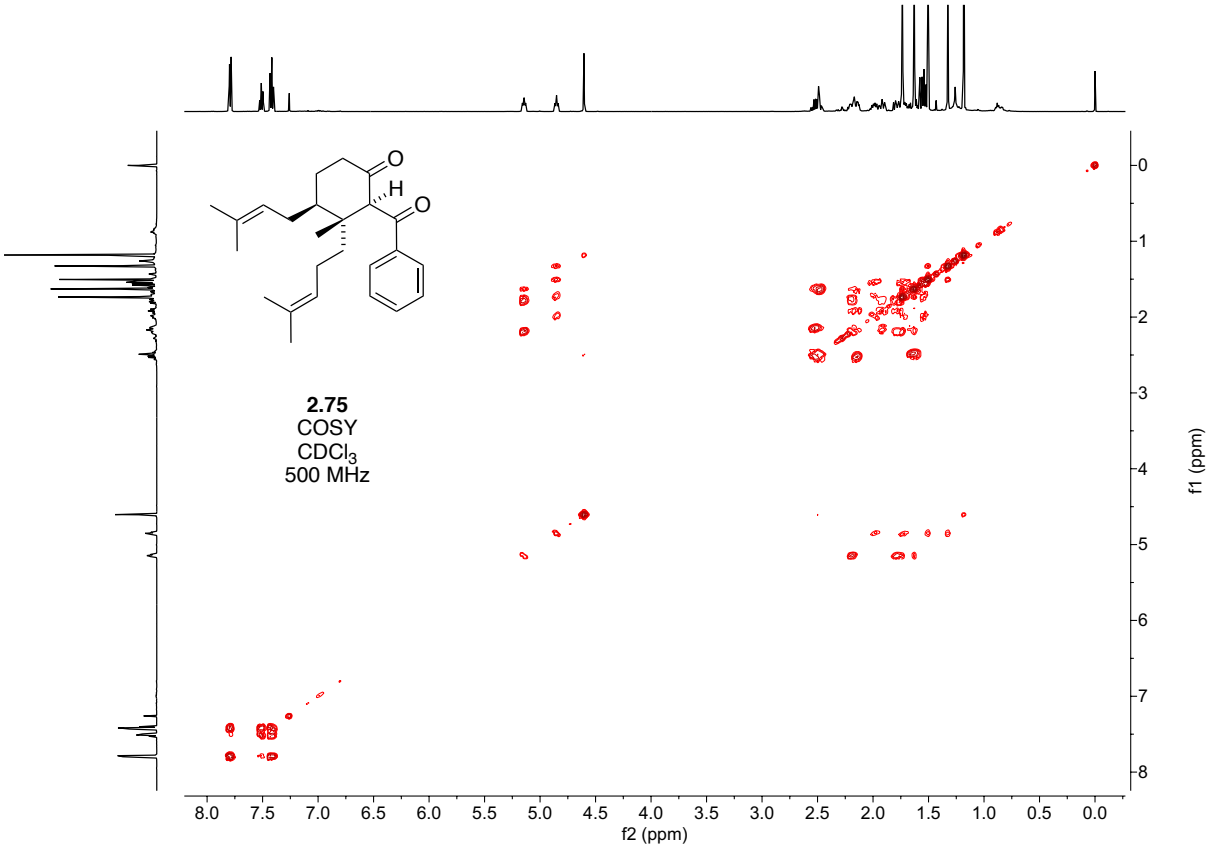

O
O
H
6-epi-norascyronone A
(2.74)
HMBC
CDCl3
500 MHz
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f2 (ppm)
20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210
f1 (ppm)

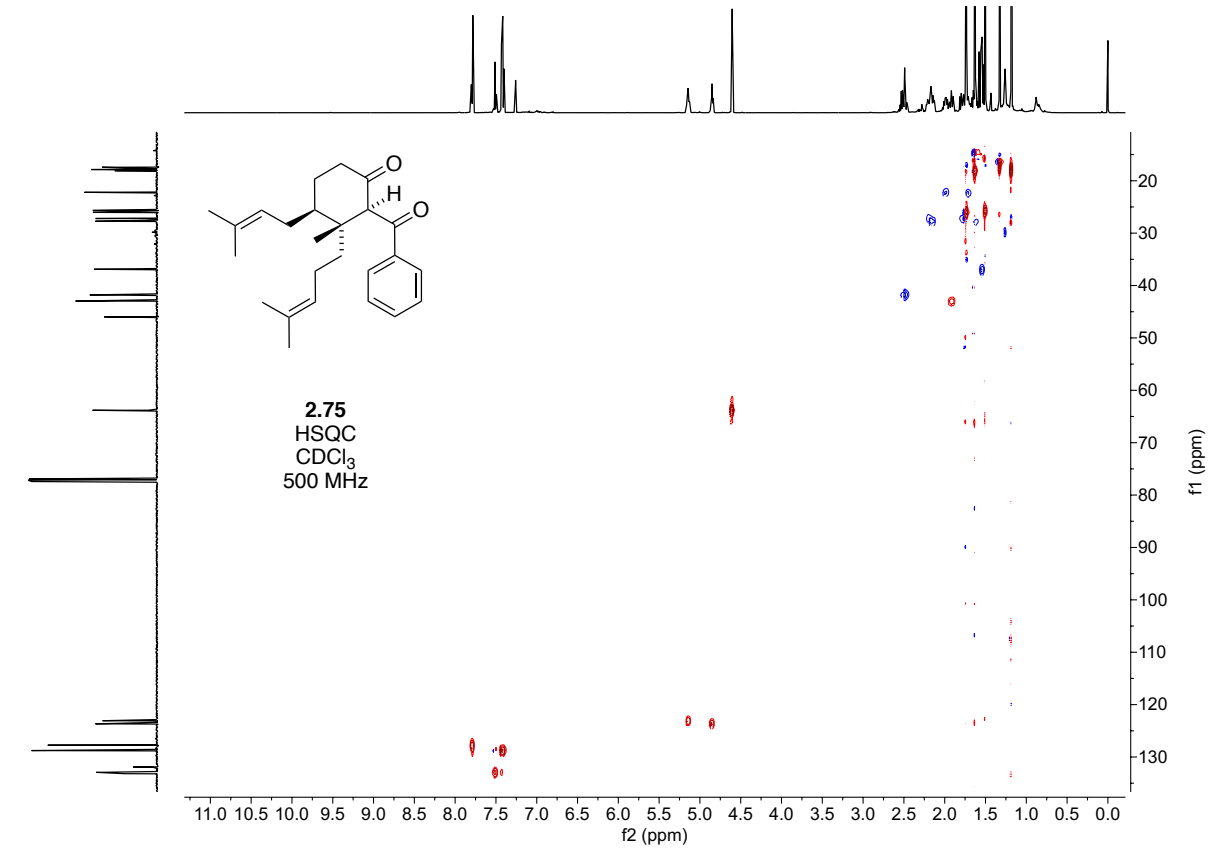


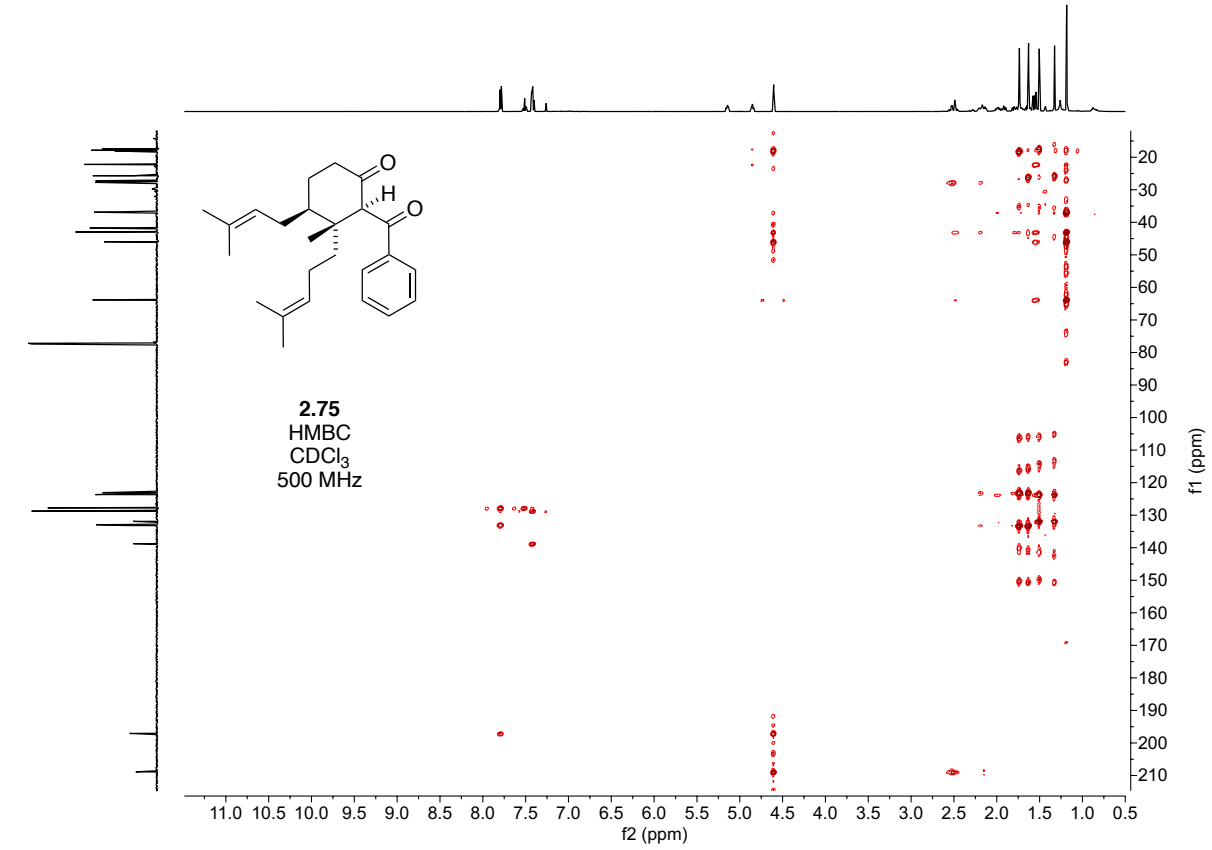
2.75
^{1}H NMR
$CDCl_3$
500 MHz

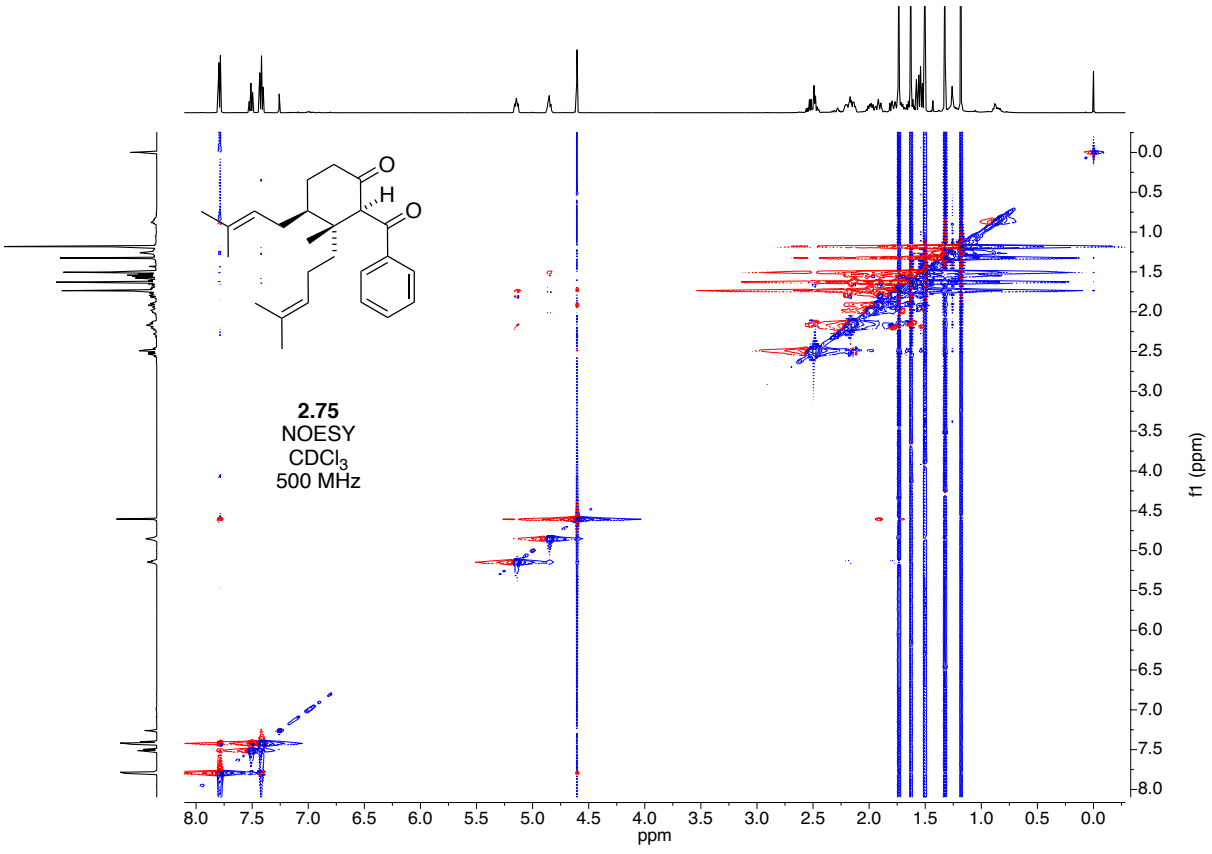


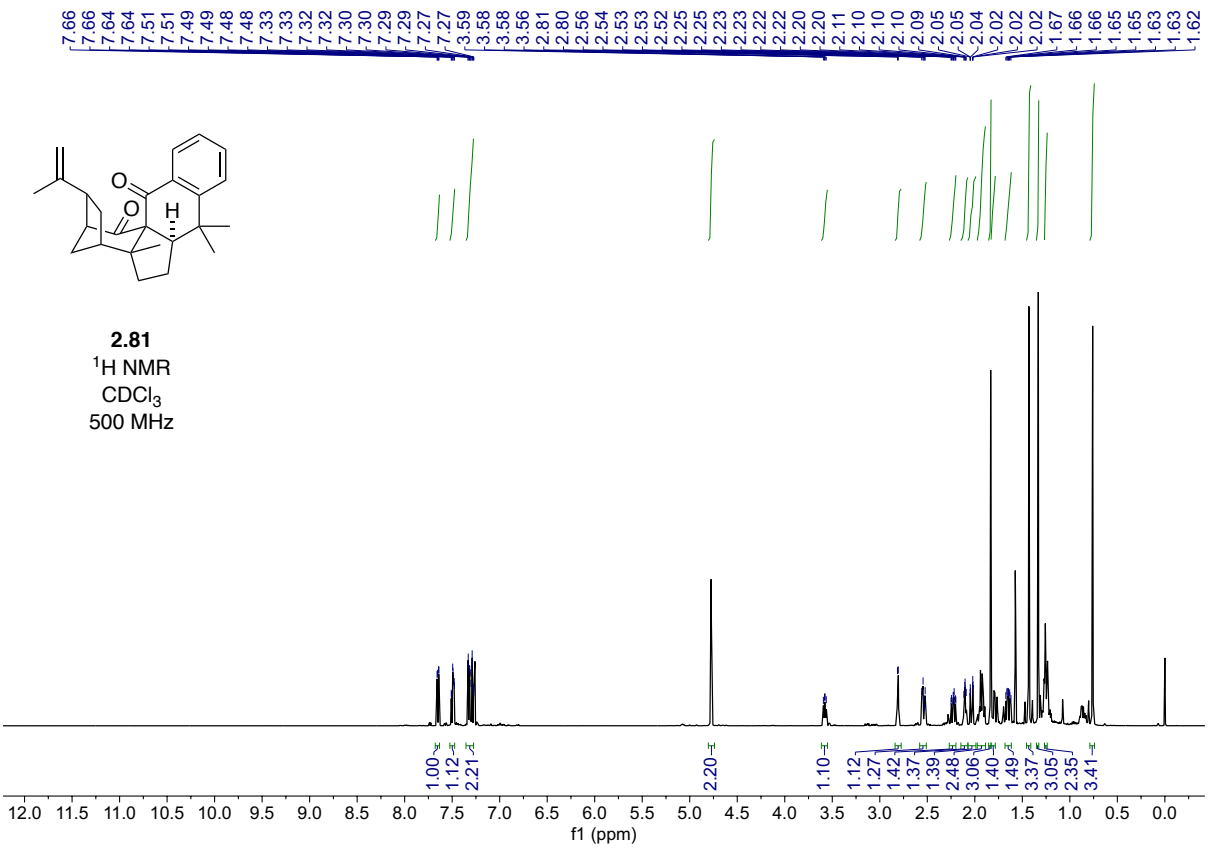
2.75
^{13}C NMR
$CDCl_3$
125 MHz

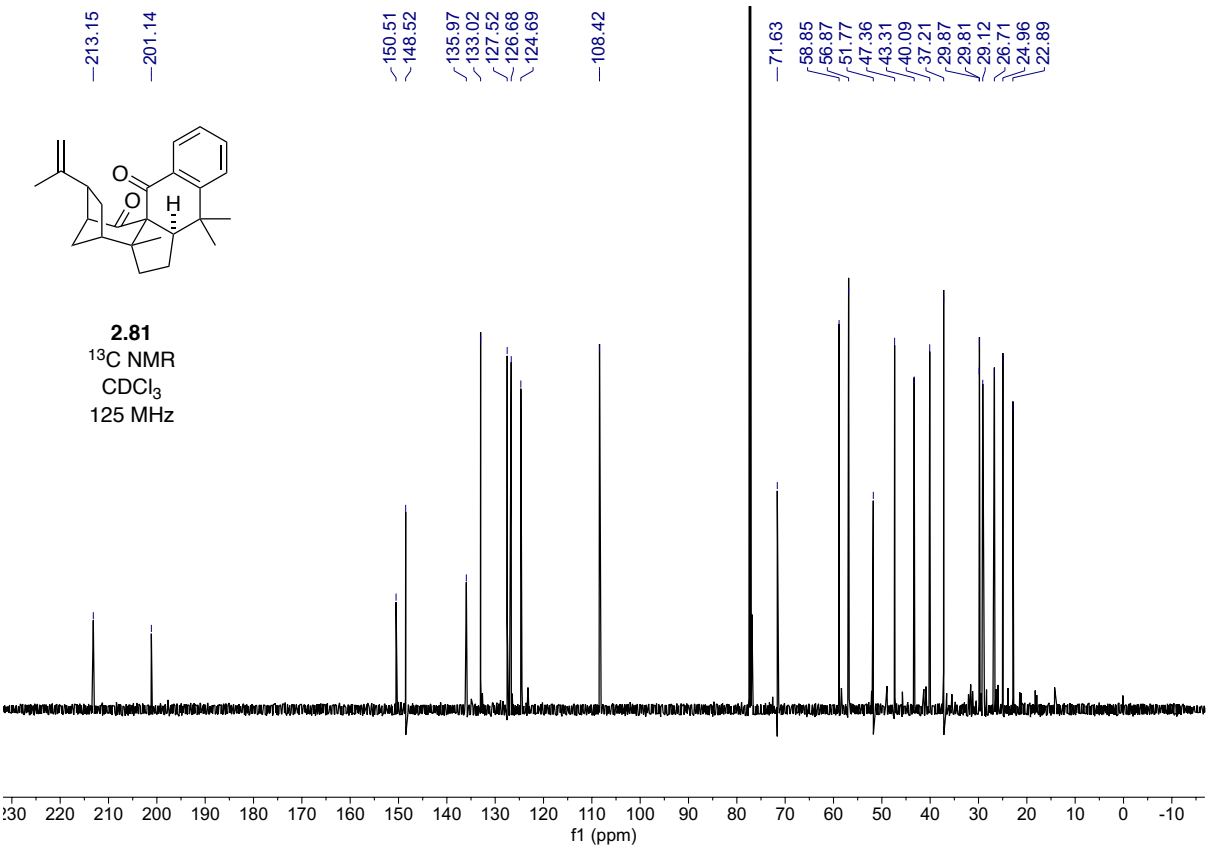

O
H
O
2.75
COSY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

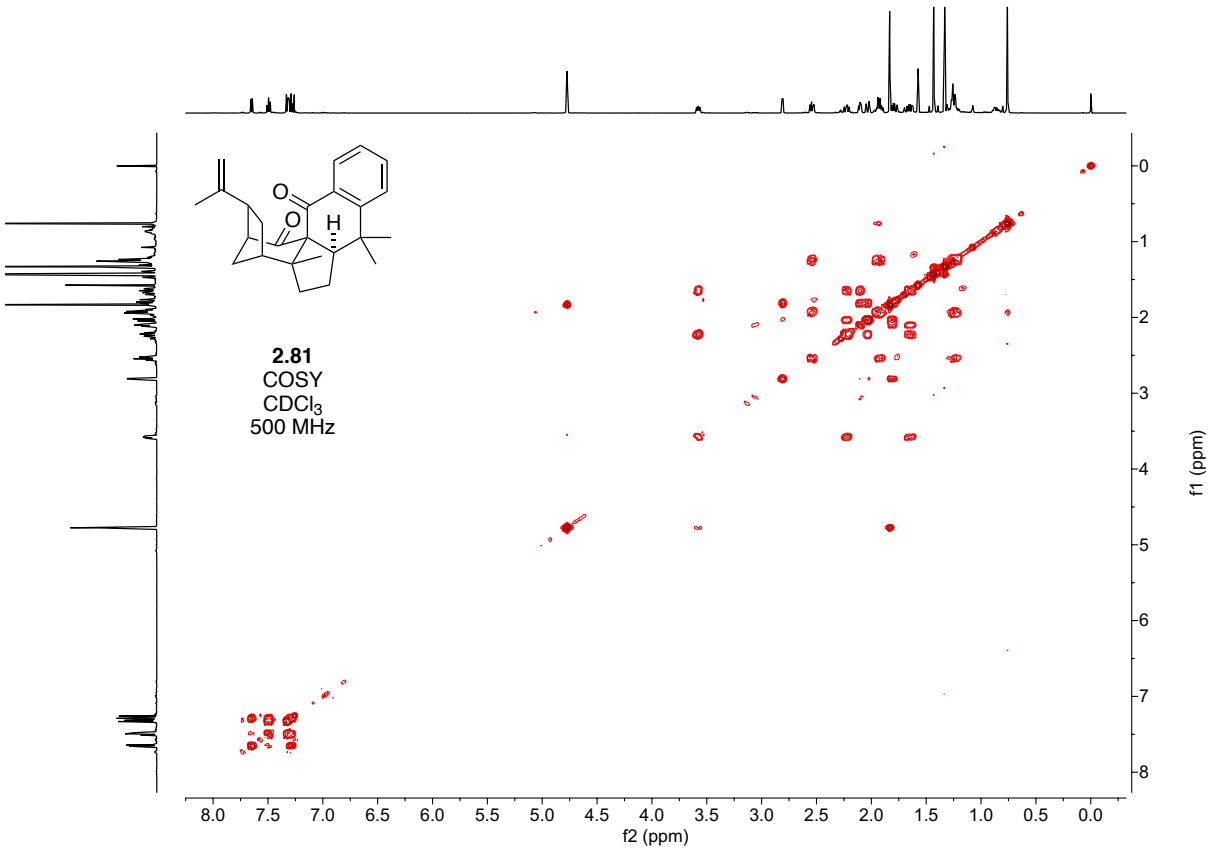

O
H
O
2.75
HSQC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

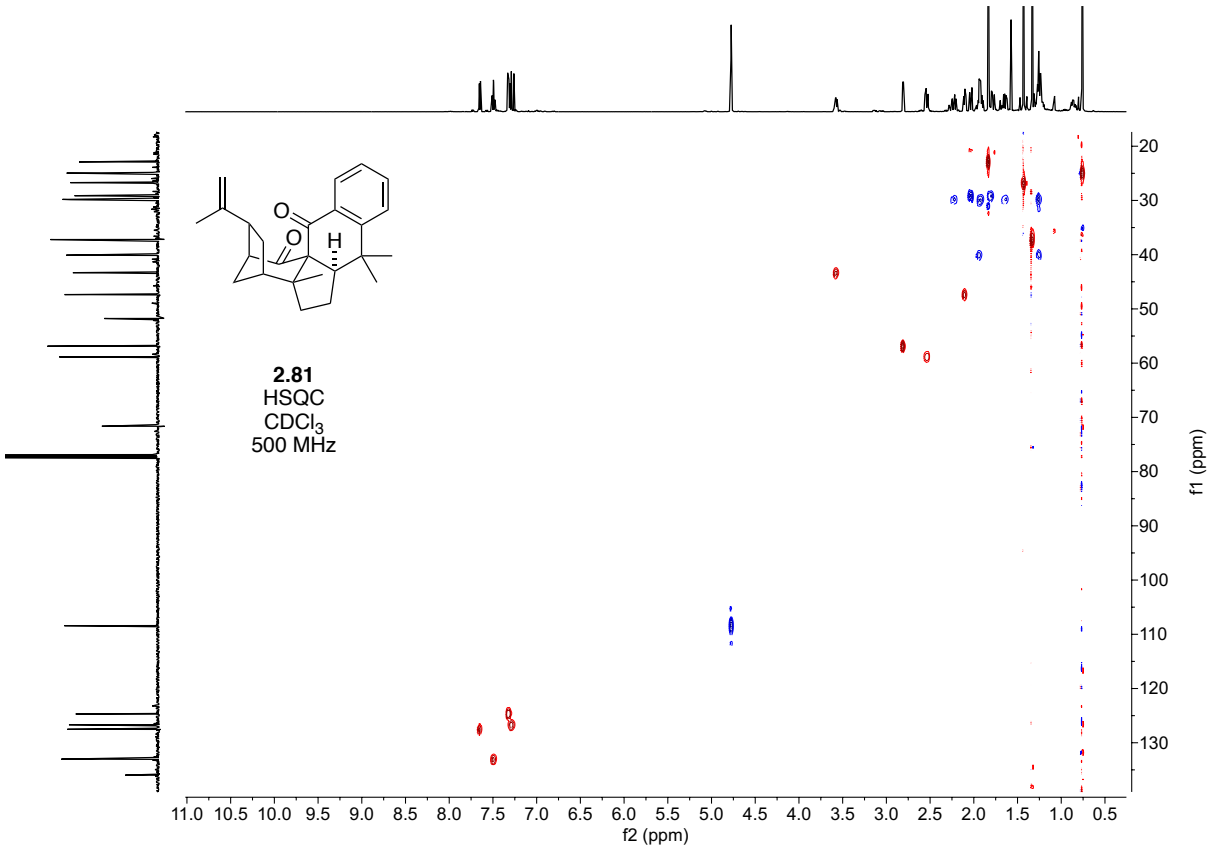

O
H
O
2.75
HMBC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

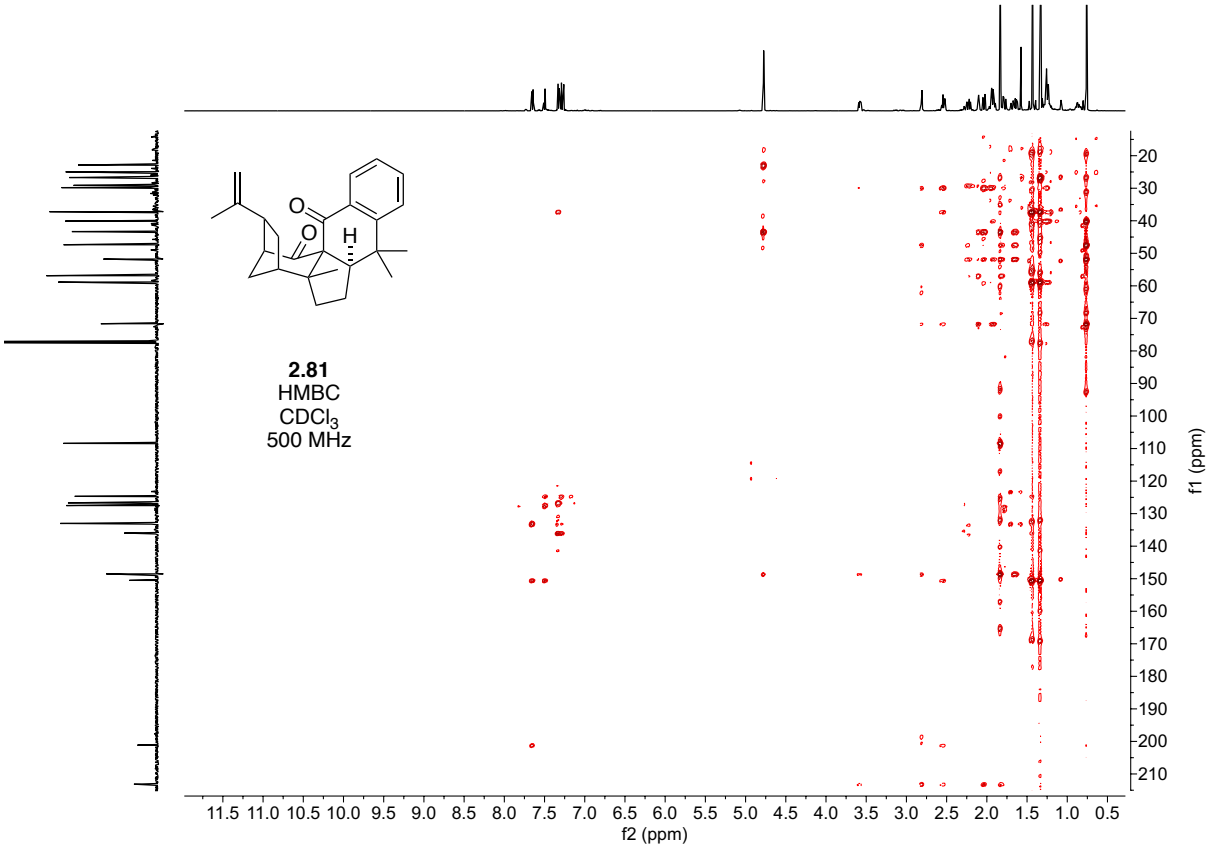

O
H
O
2.75
NOESY
CDCl3
500 MHz
ppm
f1 (ppm)

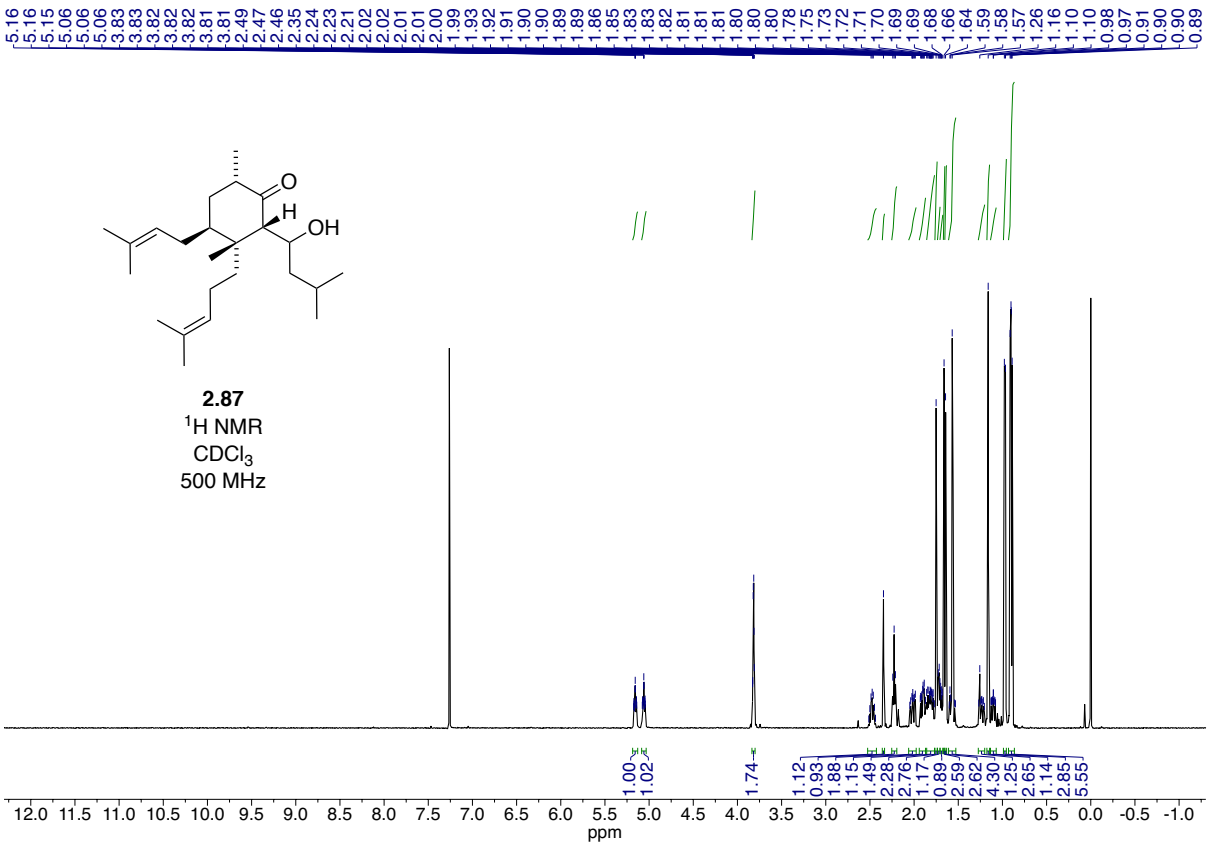

7.66 7.66 7.64 7.64 7.51 7.51 7.49 7.49 7.48 7.48 7.33 7.32 7.32 7.30 7.30 7.29 7.29 7.27 7.27 3.59 3.58 3.58 3.56 2.81 2.80 2.56 2.54 2.53 2.53 2.52 2.25 2.25 2.23 2.23 2.22 2.22 2.20 2.20 2.11 2.10 2.10 2.10 2.09 2.05 2.05 2.04 2.02 2.02 2.02 1.67 1.66 1.66 1.65 1.65 1.63 1.63 1.62
O
O
H
2.81
1H NMR
CDCl3
500 MHz
1.00 1.12 2.21 2.20 1.10 1.12 1.27 1.42 1.37 1.39 2.48 3.06 1.40 1.49 3.37 3.05 2.35 3.41
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

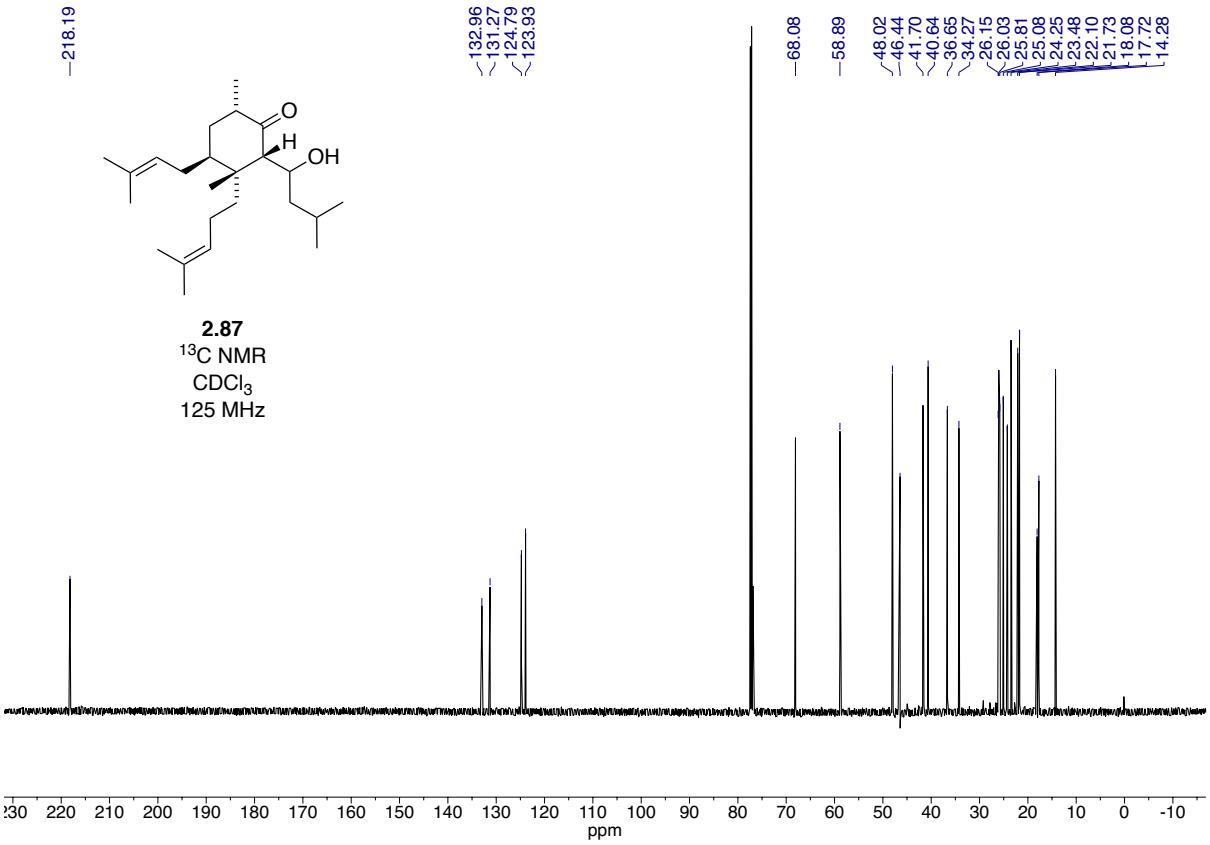

213.15 201.14 150.51 148.52 135.97 133.02 127.52 126.68 124.69 108.42 71.63 58.85 56.87 51.77 47.36 43.31 40.09 37.21 29.87 29.81 29.12 26.71 24.96 22.89
O
O
H
2.81
13C NMR
CDCl3
125 MHz
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

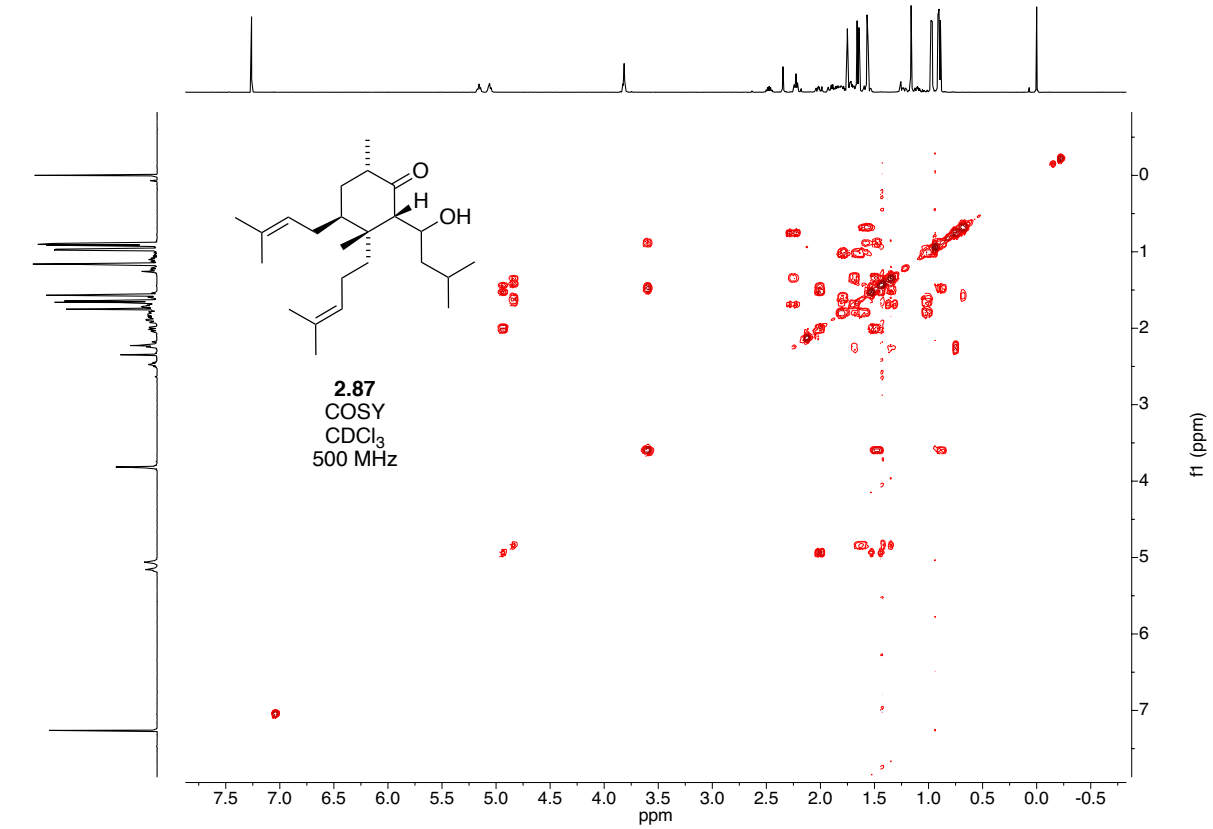

O
O
H
2.81
COSY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

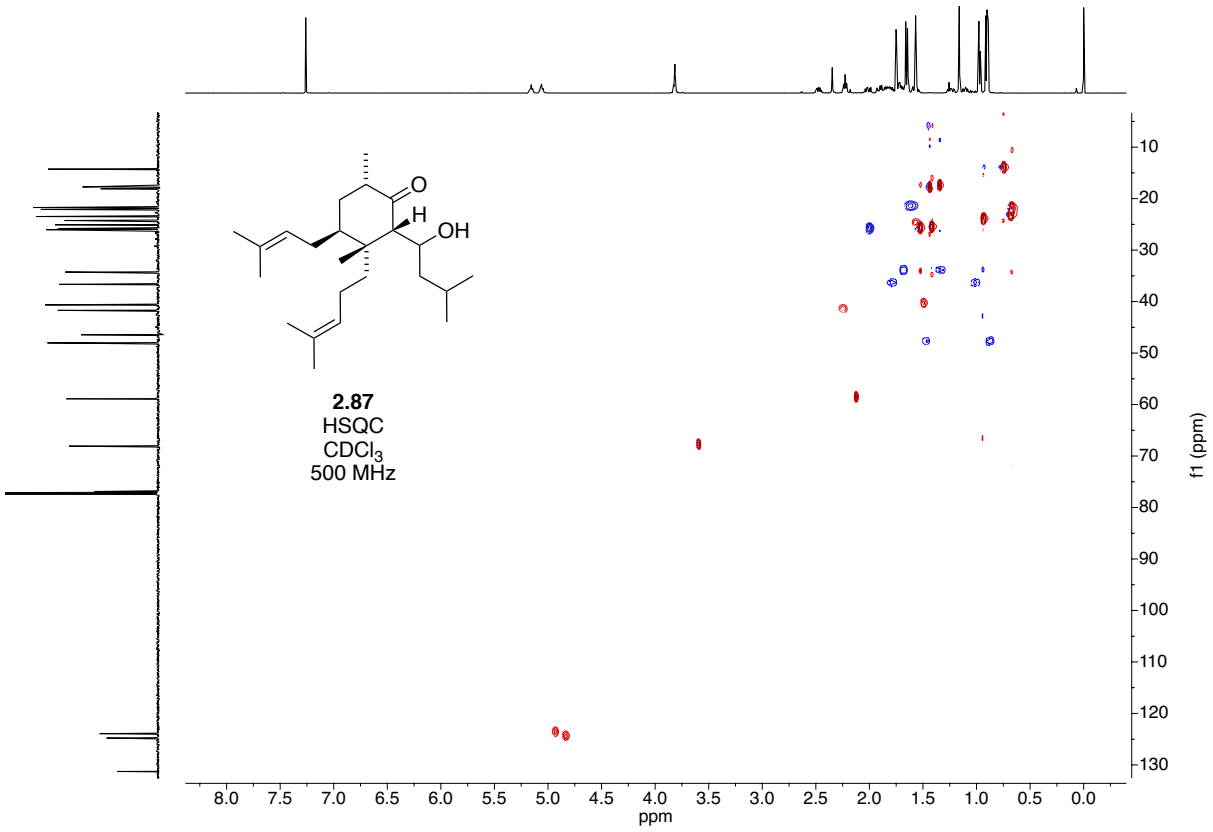

O
O
H
2.81
HSQC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

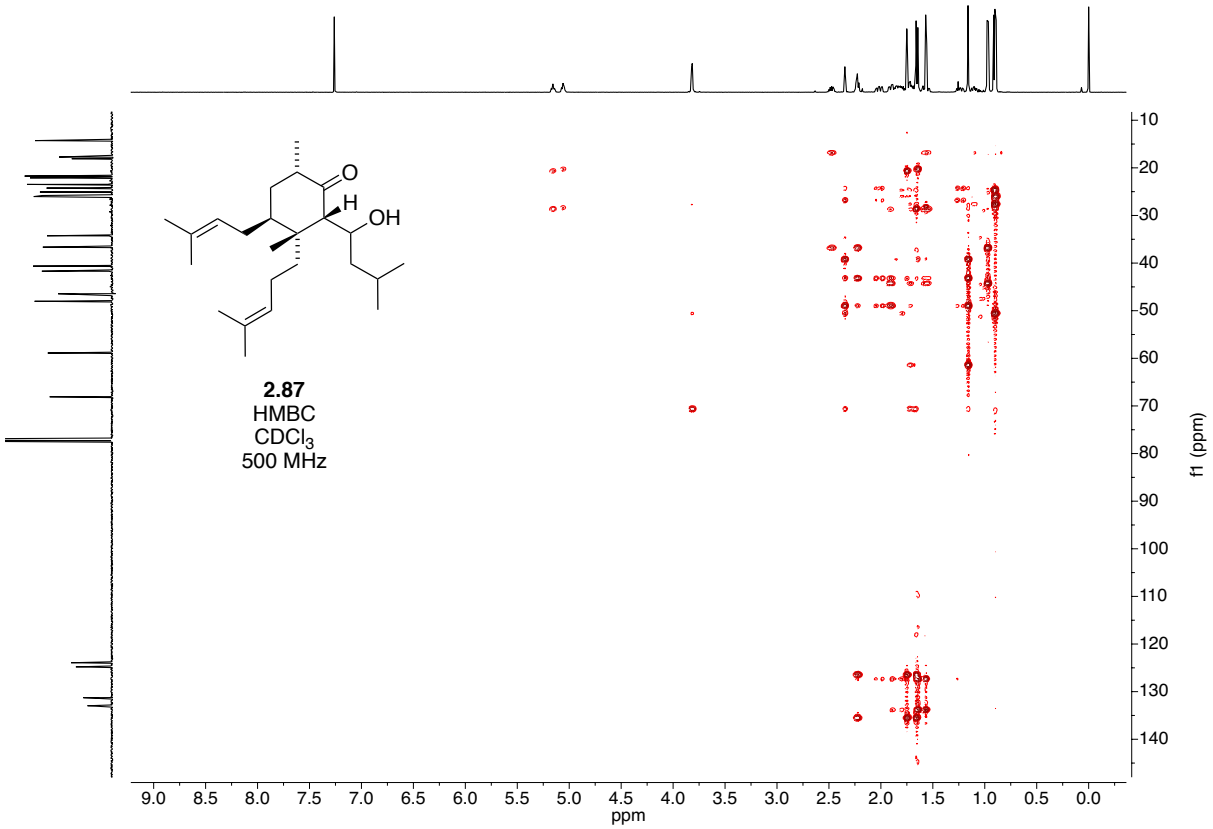

O
O
H
2.81
HMBC
CDCl3
500 MHz
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f2 (ppm)
20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210
f1 (ppm)

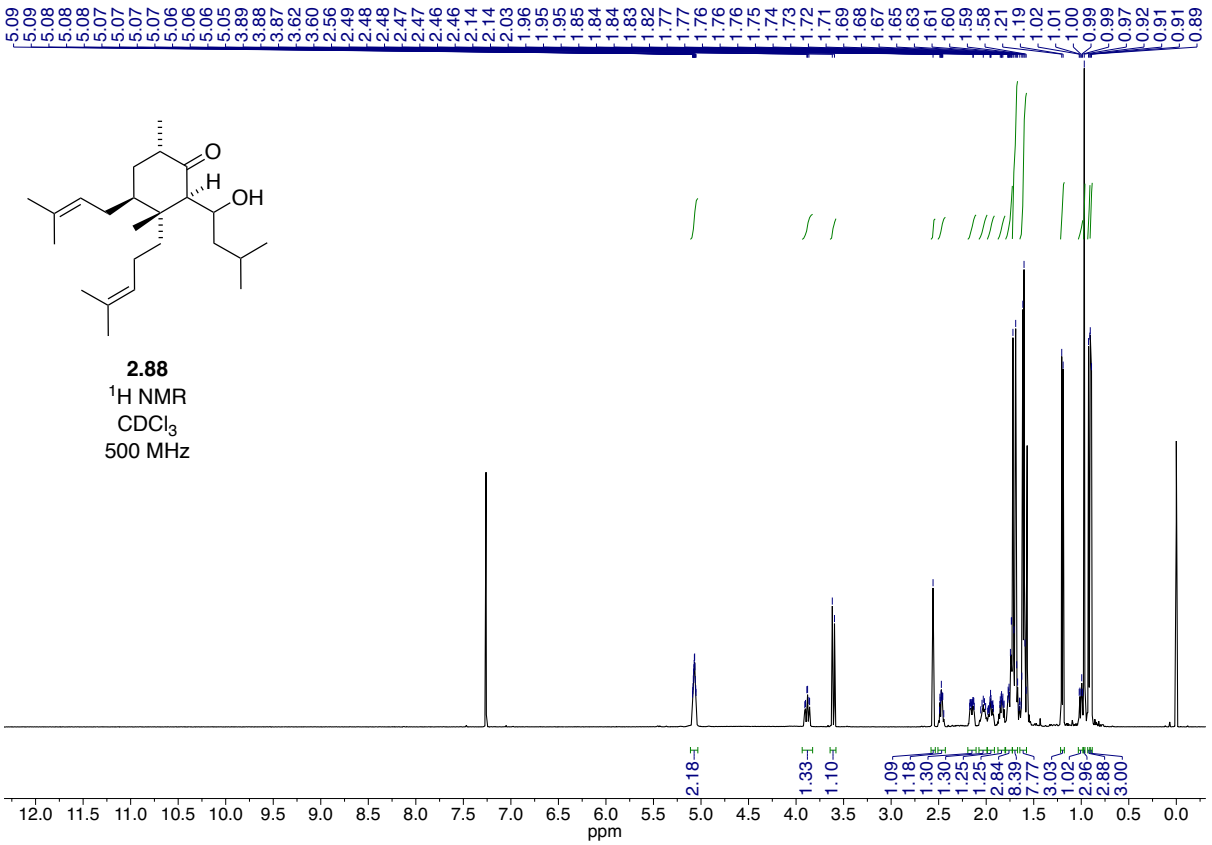

O
H
OH
2.87
1H NMR
CDCl3
500 MHz
ppm

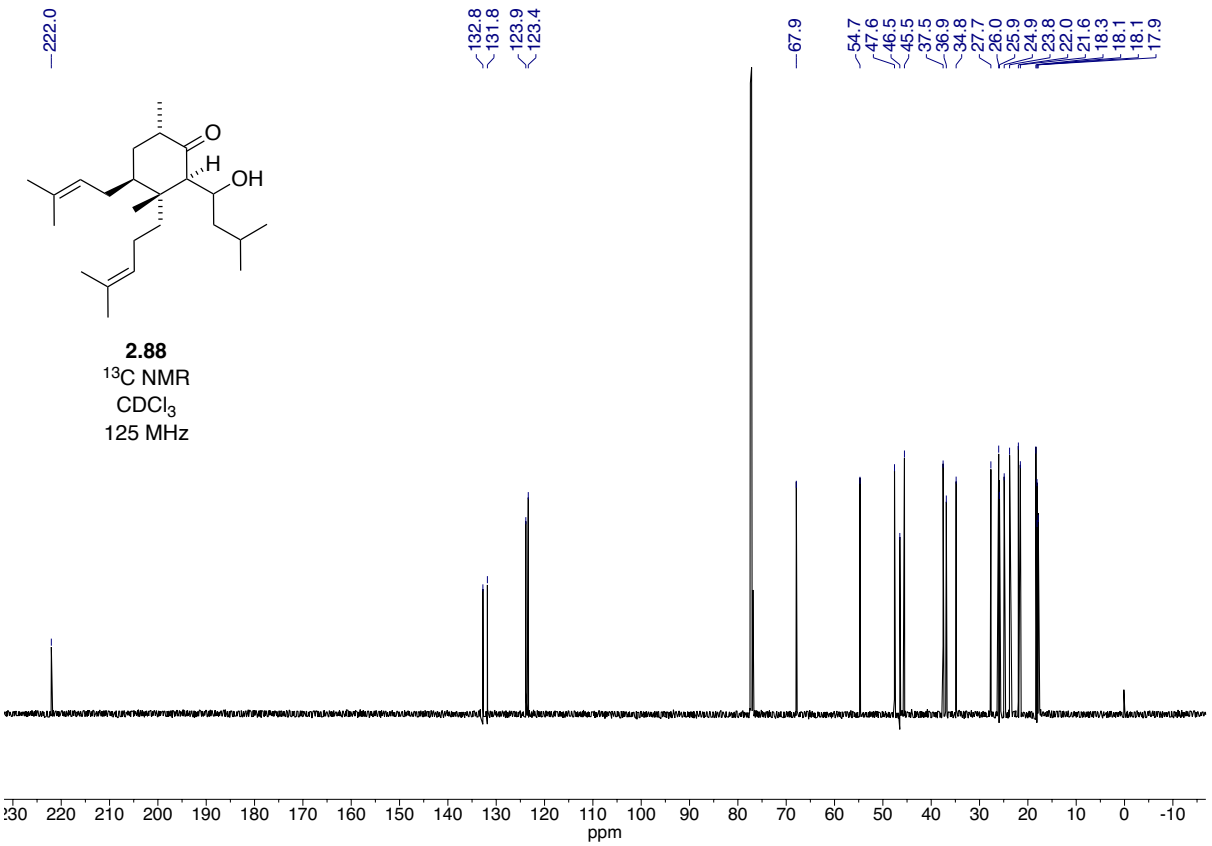

O
H
OH
2.87
13C NMR
CDCl3
125 MHz
ppm

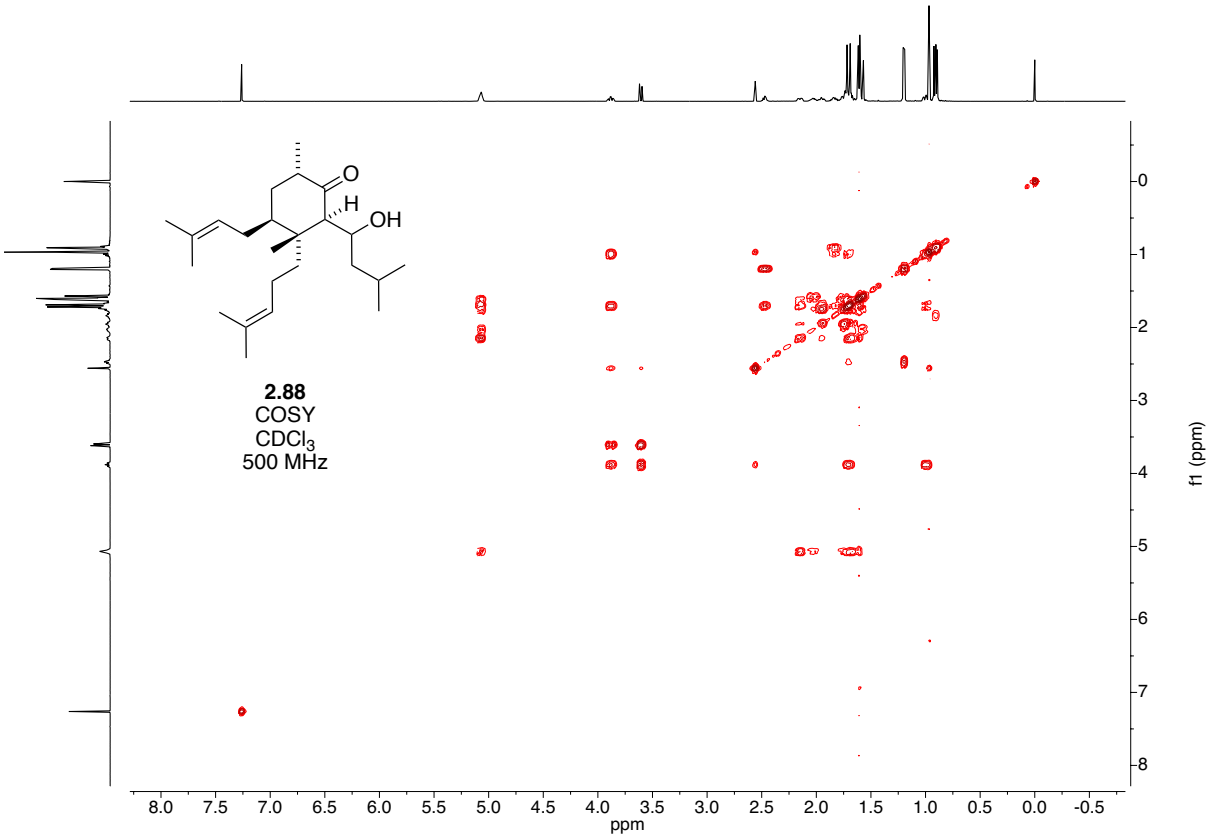

O
H
OH
2.87
COSY
CDCl3
500 MHz
f1 (ppm)
ppm

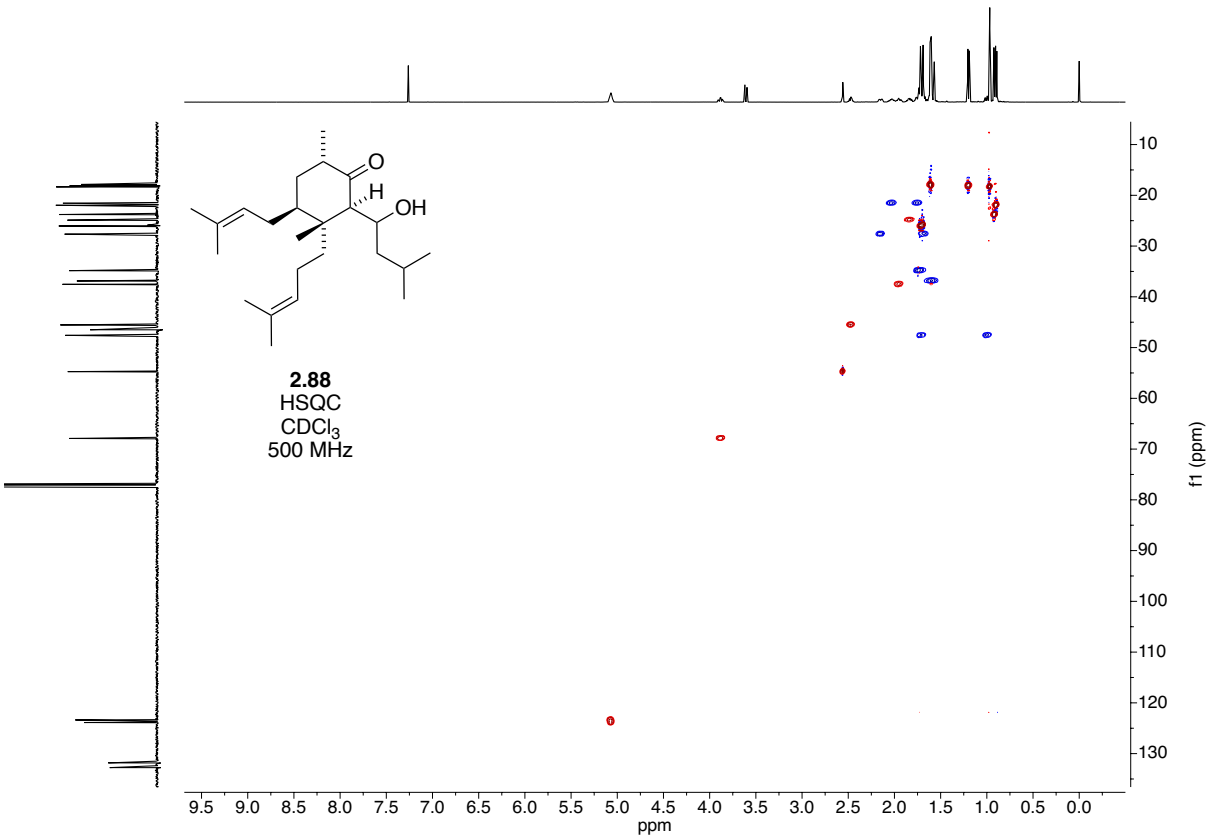

O
H
OH
2.87
HSQC
CDCl3
500 MHz
f1 (ppm)
ppm

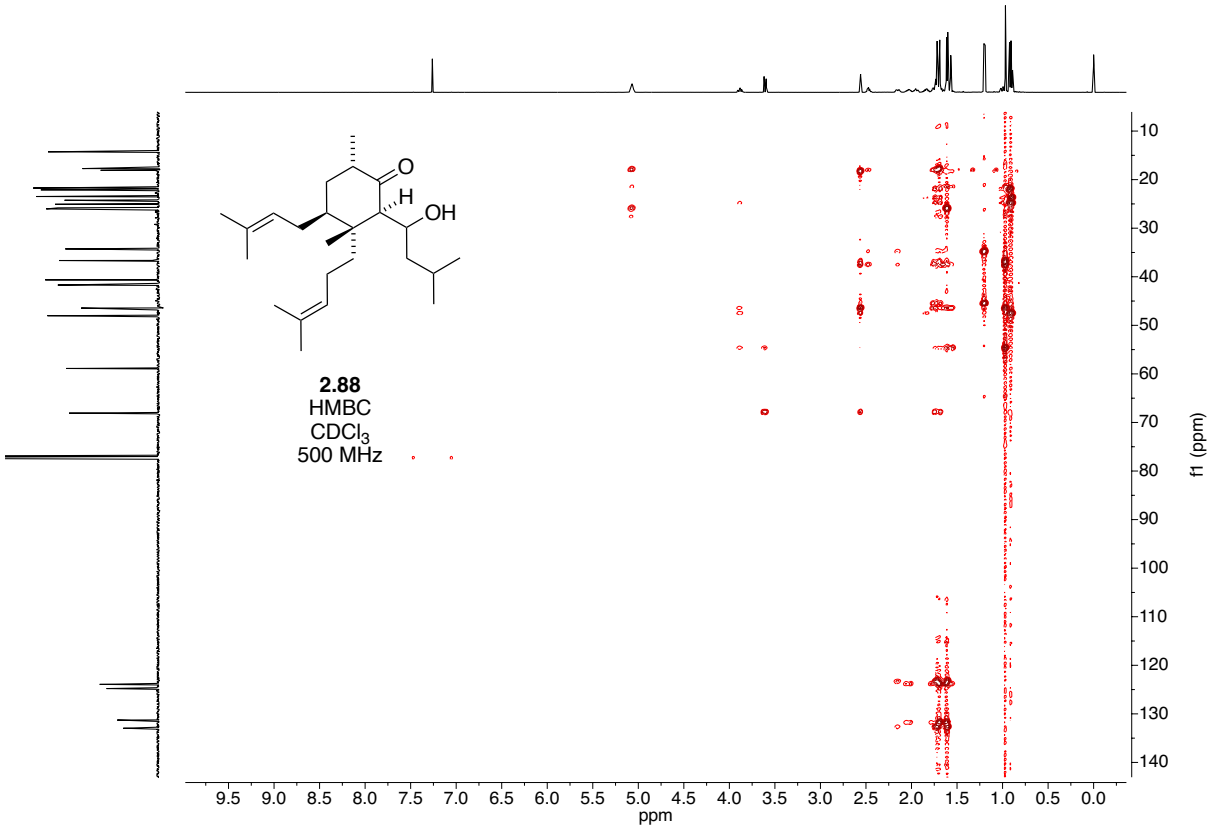

O
H
OH
2.87
HMBC
CDCl3
500 MHz
f1 (ppm)
ppm

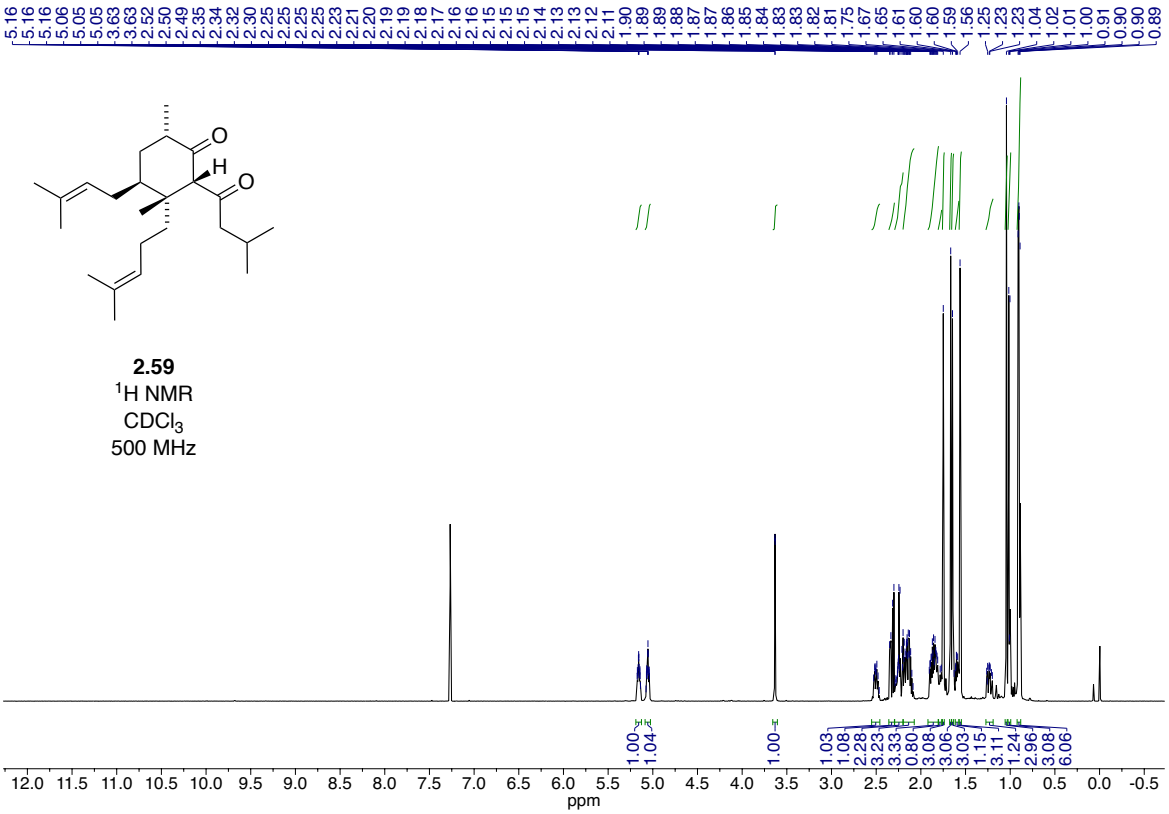

O
H
OH
2.88
1H NMR
CDCl3
500 MHz
ppm

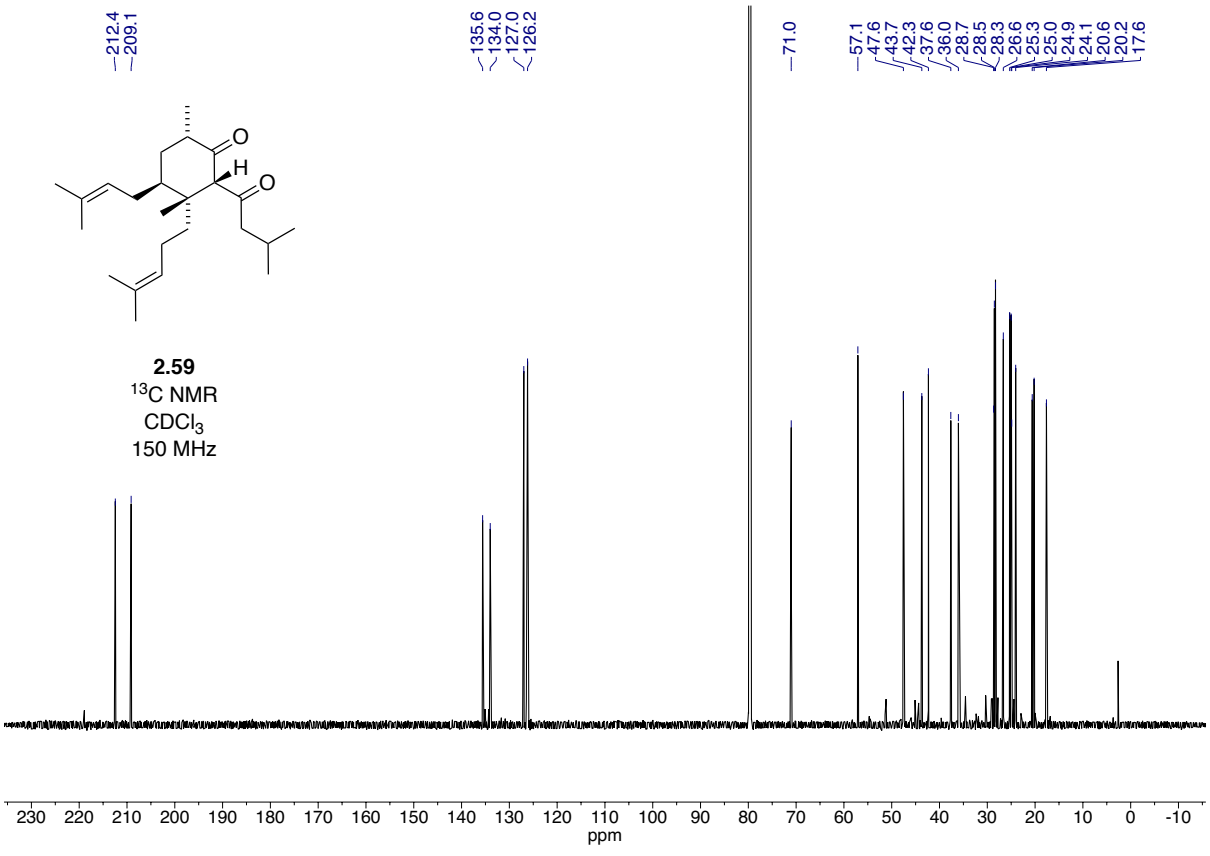

O
H
OH
2.88
13C NMR
CDCl3
125 MHz
ppm

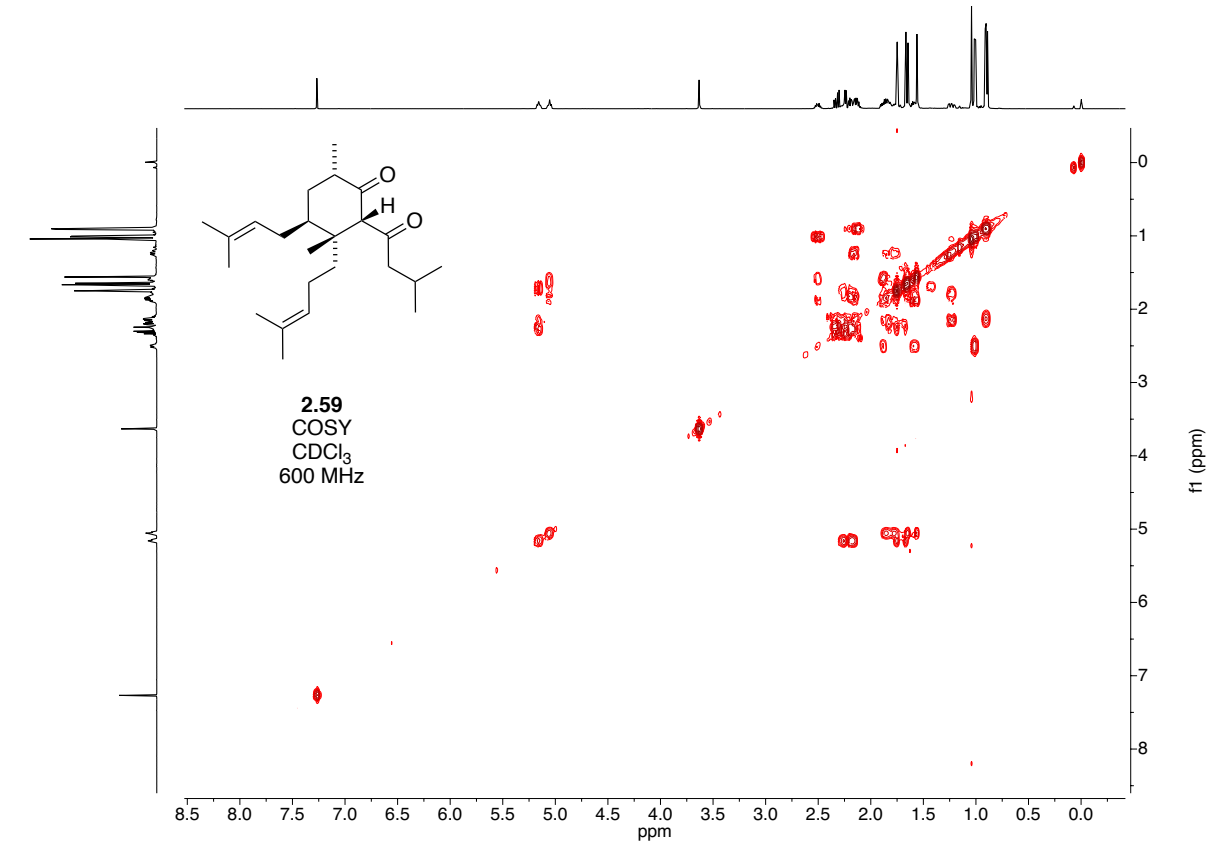

O
H
OH
2.88
COSY
CDCl3
500 MHz
f1 (ppm)
ppm

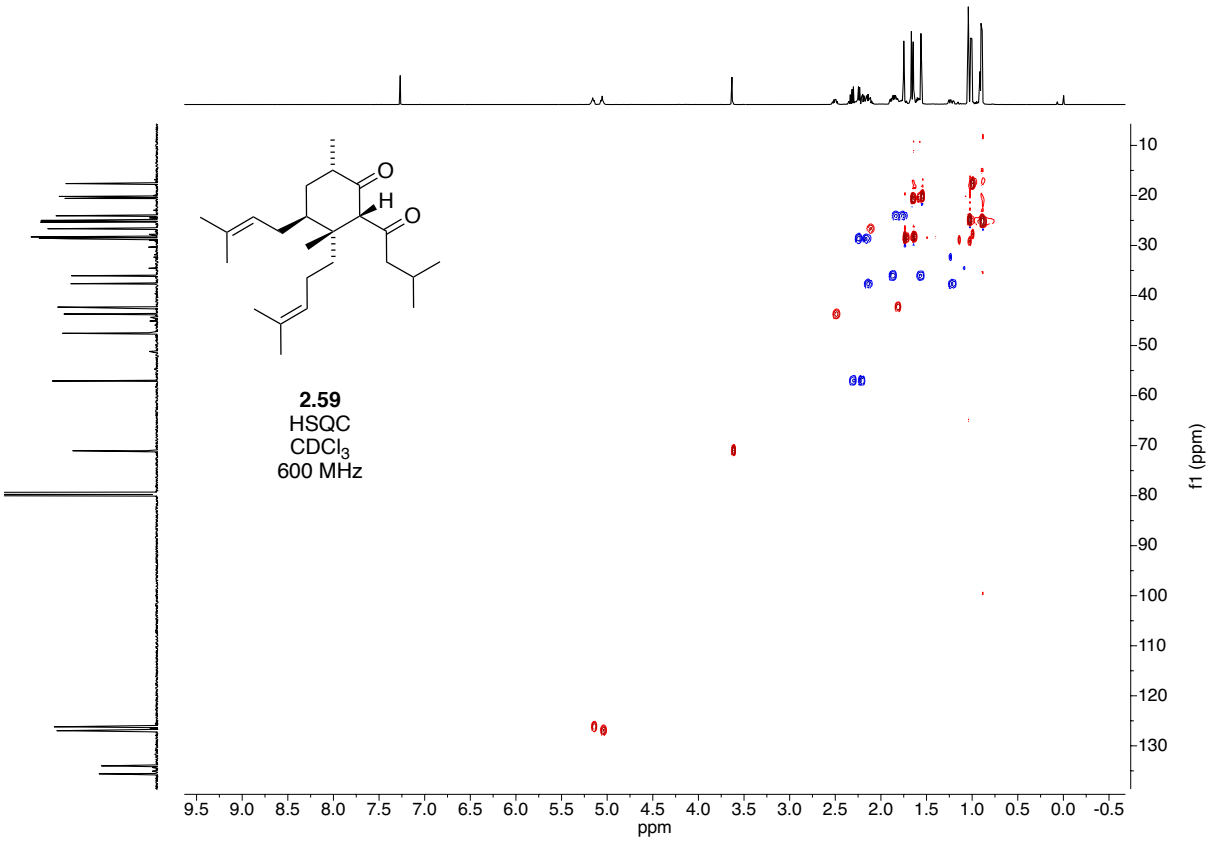

O
H
OH
2.88
HSQC
CDCl3
500 MHz
f1 (ppm)
ppm

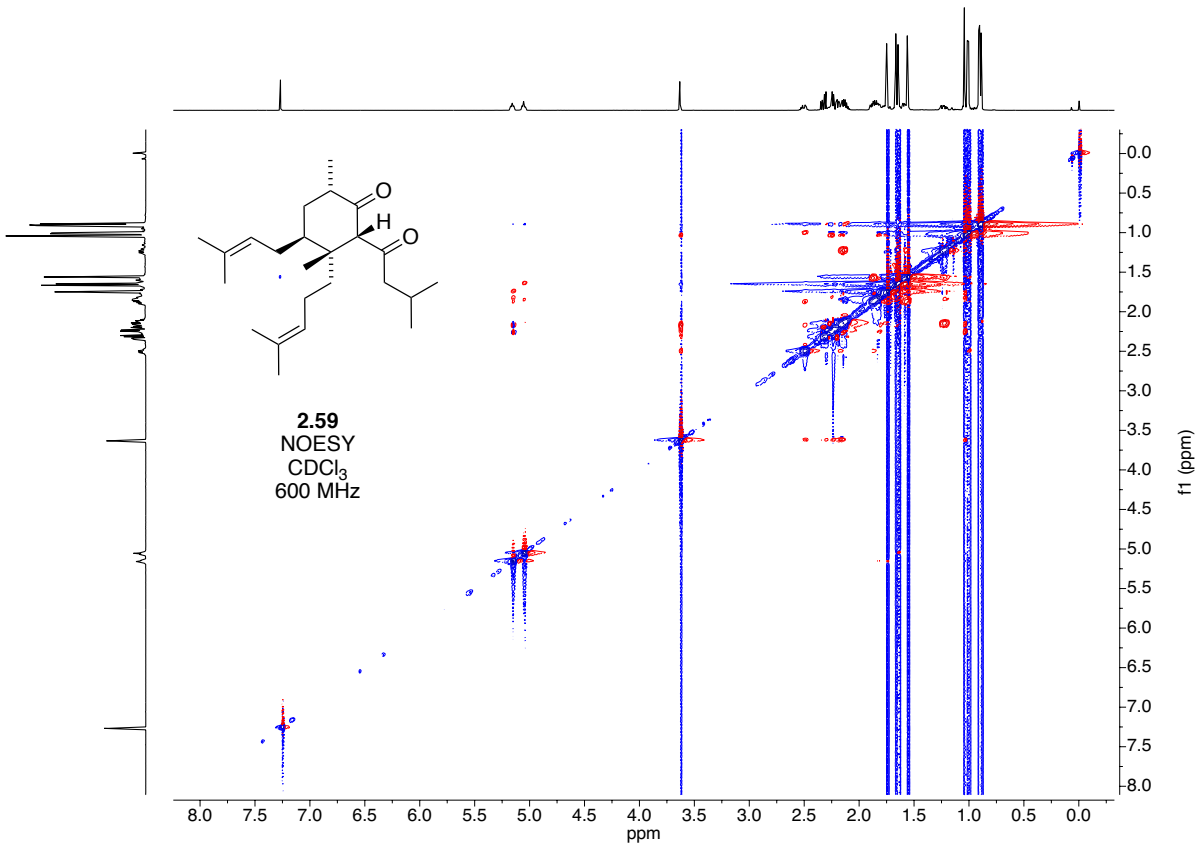

O
H
OH
2.88
HMBC
CDCl3
500 MHz
ppm
f1 (ppm)

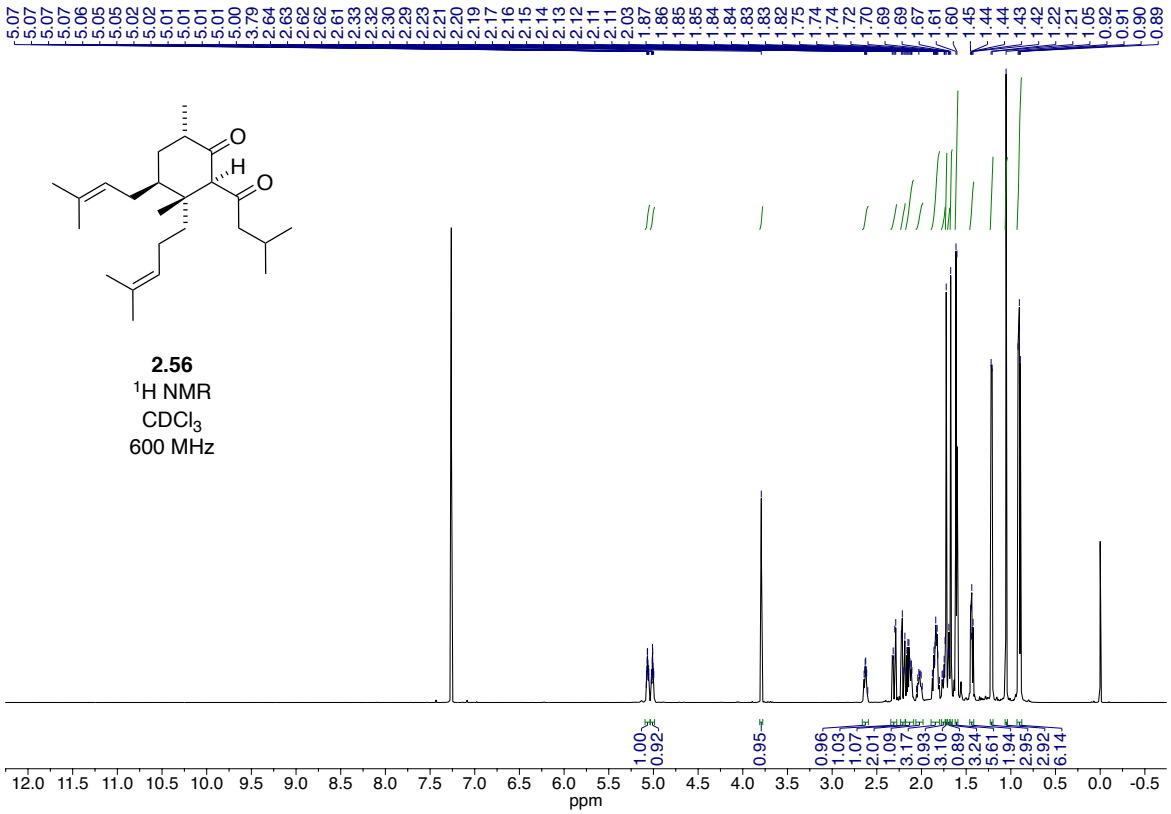

5.16 5.16 5.06 5.05 5.05 3.63 2.52 2.50 2.49 2.35 2.34 2.32 2.30 2.25 2.25 2.25 2.25 2.23 2.21 2.20 2.19 2.19 2.18 2.17 2.16 2.16 2.15 2.15 2.14 2.13 2.12 2.11 1.90 1.89 1.89 1.88 1.87 1.87 1.86 1.85 1.84 1.83 1.83 1.82 1.81 1.75 1.67 1.65 1.61 1.60 1.60 1.59 1.56 1.25 1.23 1.23 1.04 1.02 1.01 1.00 0.91 0.90 0.90 0.89
O
H
O
2.59
1H NMR
CDCl3
500 MHz
1.00 1.04 1.00 1.03 1.08 2.28 3.23 3.33 0.80 3.08 3.06 3.03 1.15 3.11 1.24 2.96 3.08 6.06
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

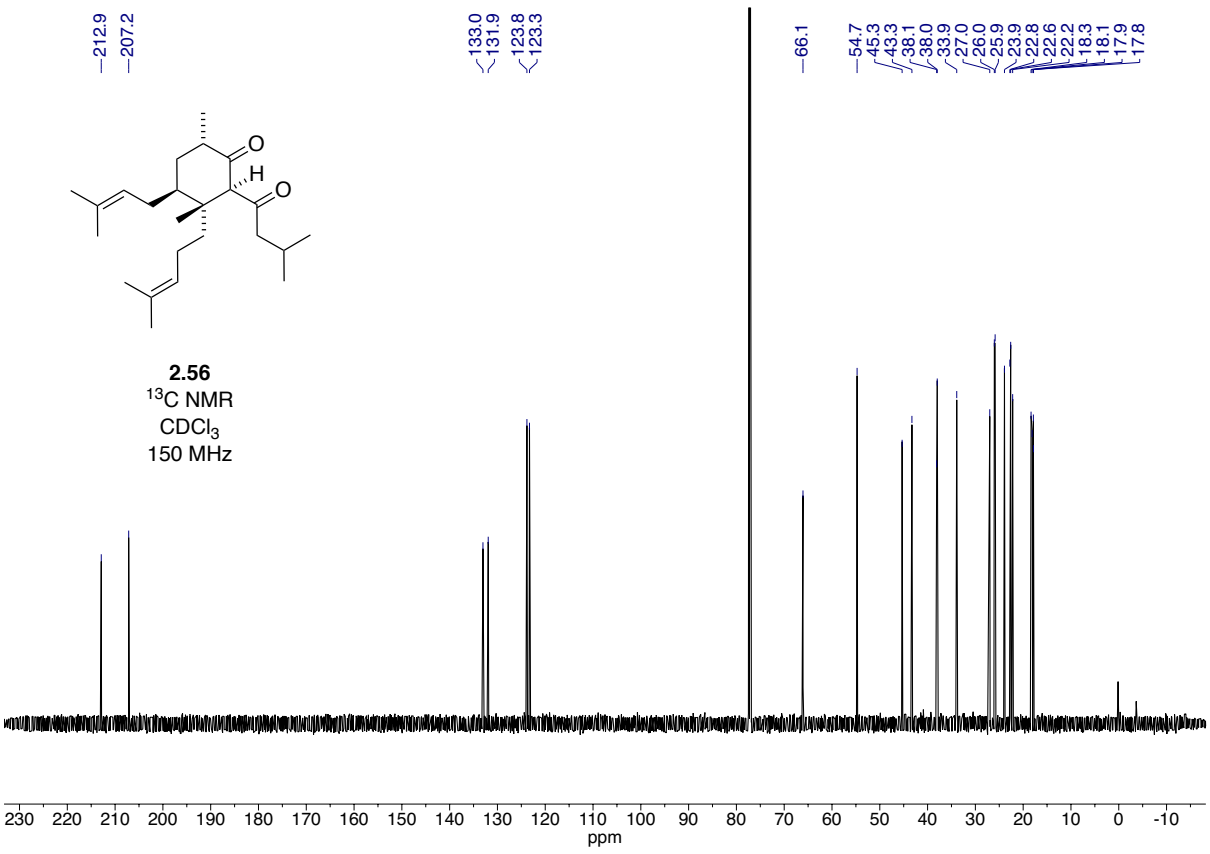

212.4 209.1
135.6 134.0 127.0 126.2
71.0
57.1 47.6 43.7 42.3 37.6 36.0 28.7 28.5 28.3 26.6 25.3 25.0 24.9 24.1 20.6 20.2 17.6
O
H
O
2.59
13C NMR
CDCl3
150 MHz
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

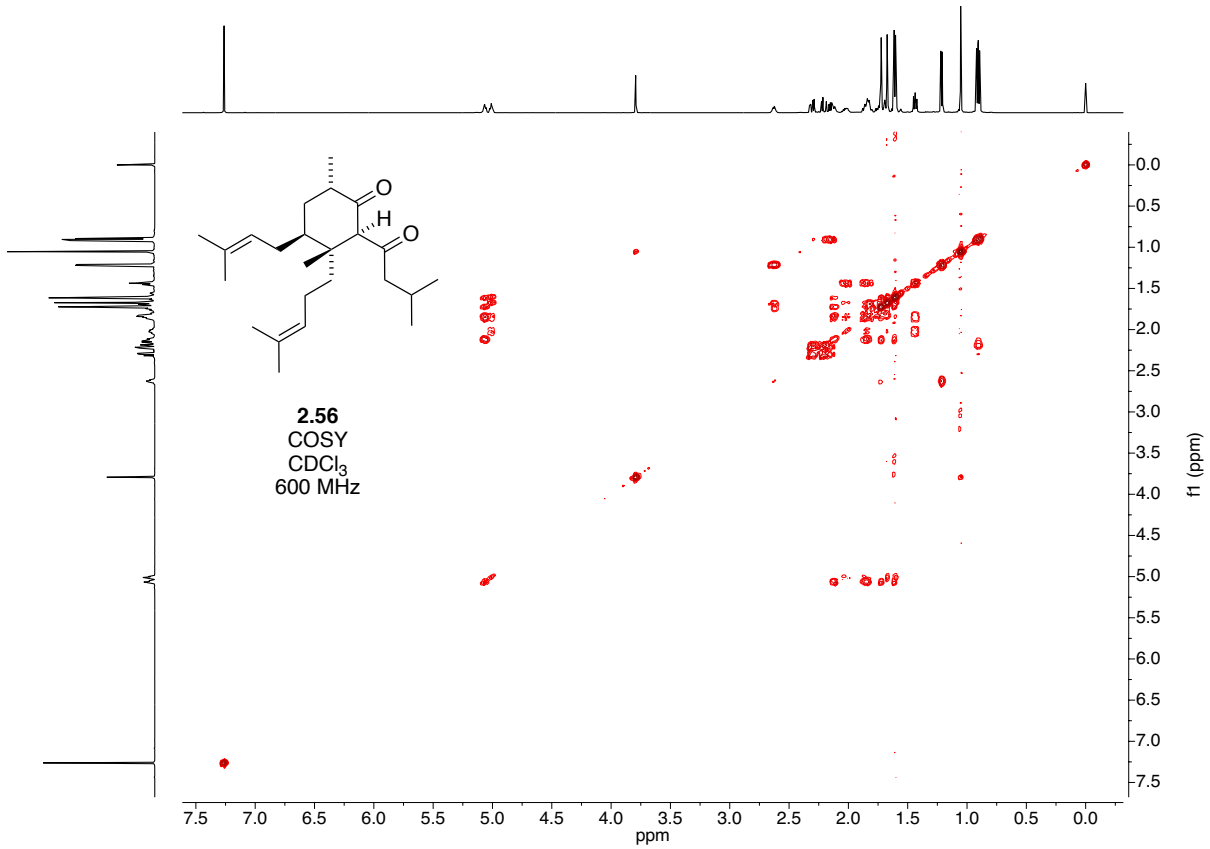

O
H
O
2.59
COSY
CDCl3
600 MHz
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm
0 1 2 3 4 5 6 7 8
f1 (ppm)

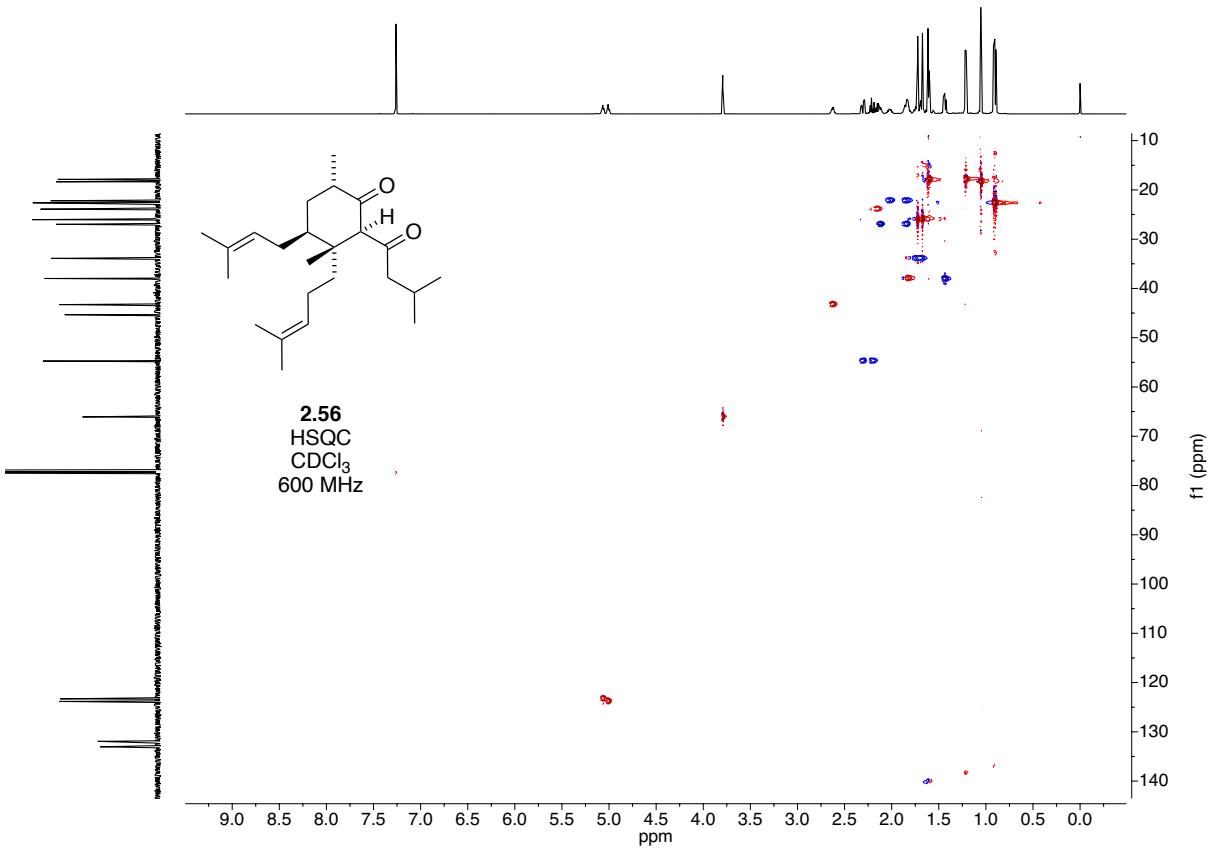

O
H
O
2.59
HSQC
CDCl3
600 MHz
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm
10 20 30 40 50 60 70 80 90 100 110 120 130
f1 (ppm)

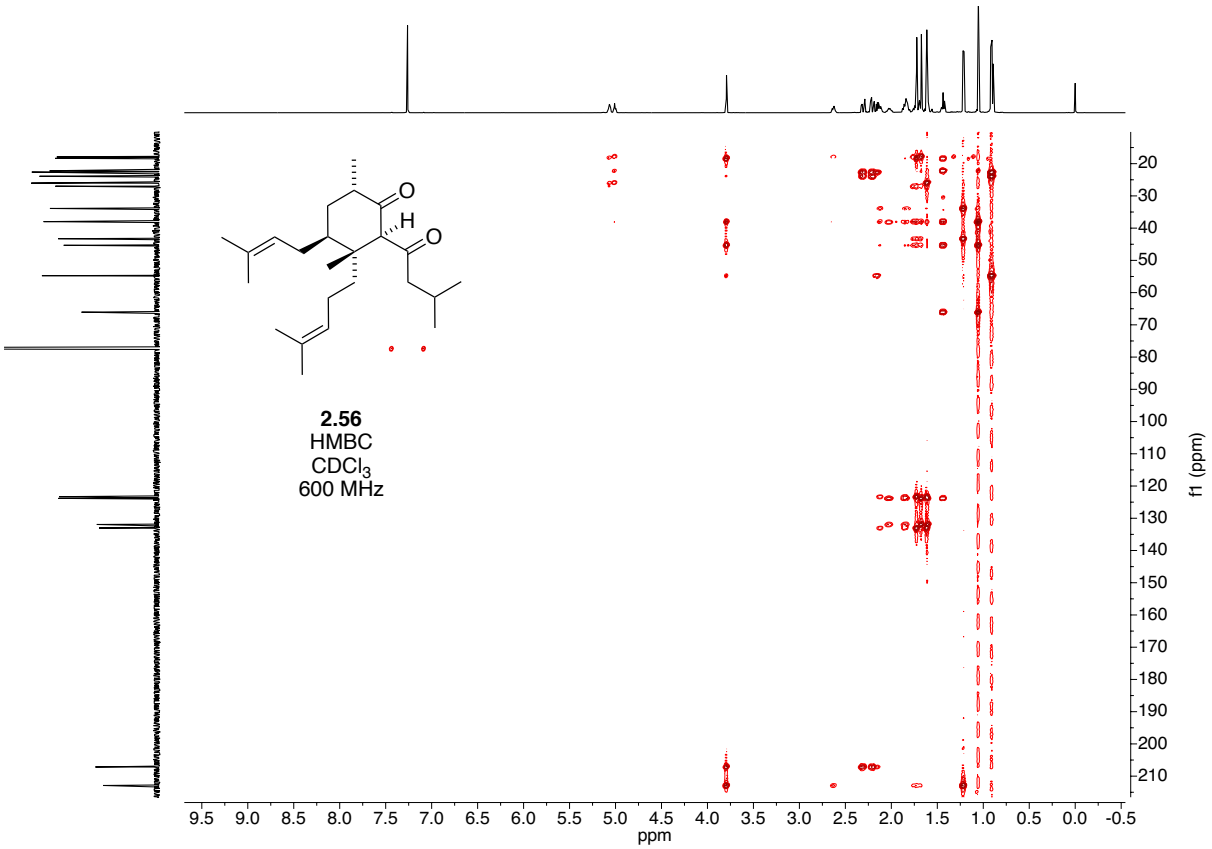

O
H
O
2.59
NOESY
CDCl3
600 MHz
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0
f1 (ppm)

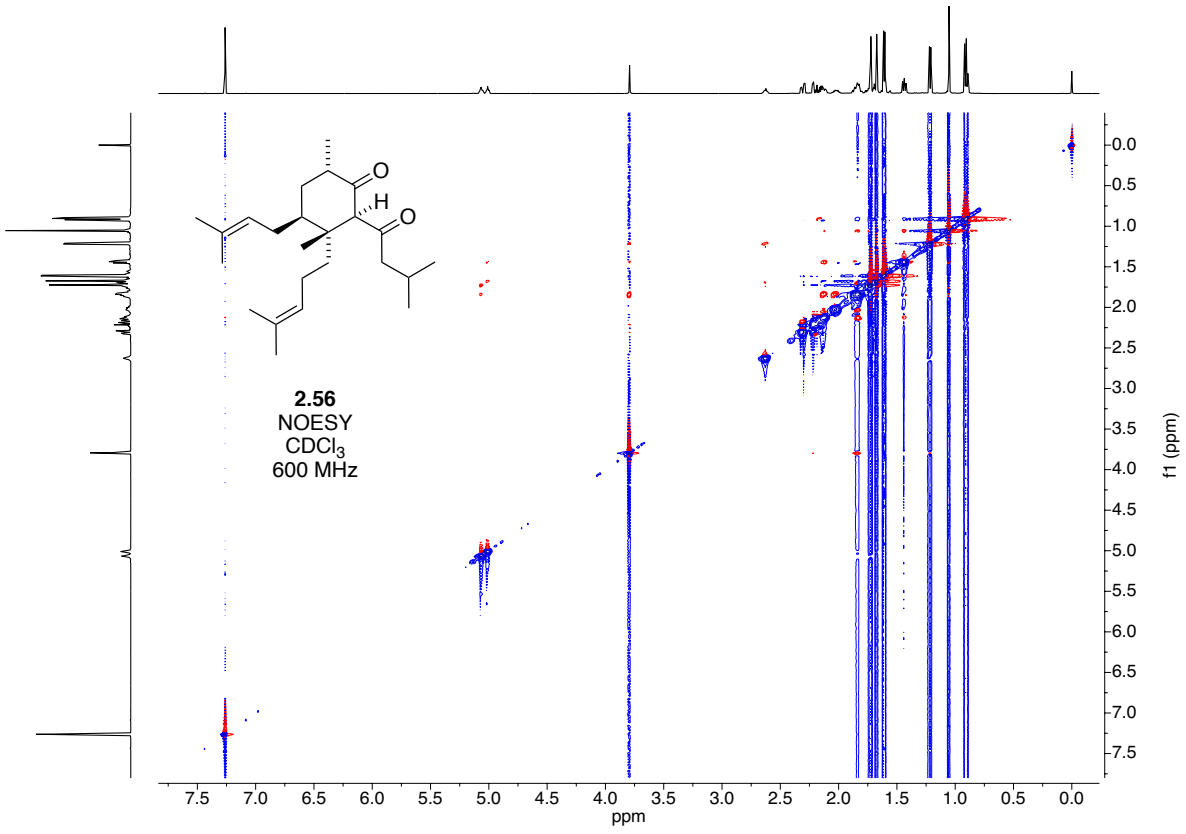

O
H
O
2.56
1H NMR
CDCl3
600 MHz
ppm

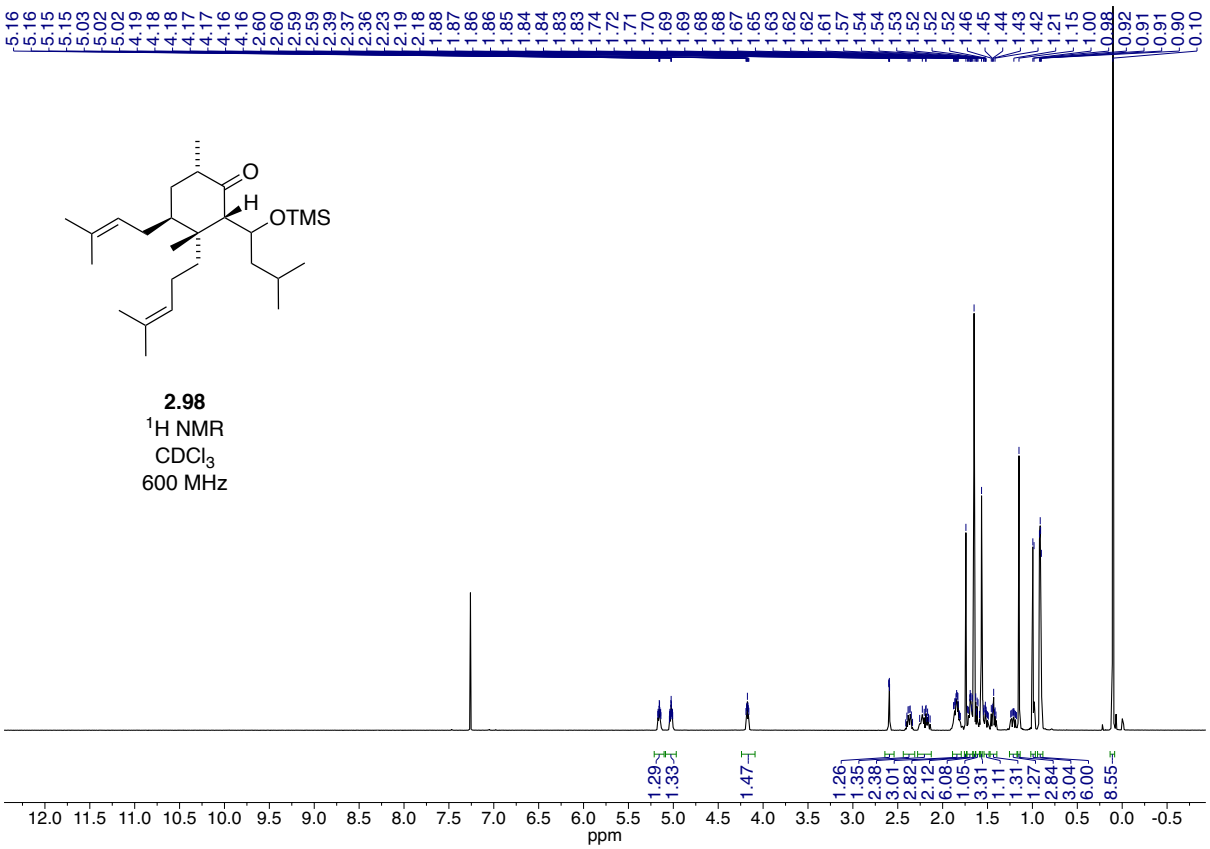

O
H
O
2.56
13C NMR
CDCl3
150 MHz
ppm


O
H
O
2.56
COSY
CDCl3
600 MHz
f1 (ppm)
ppm

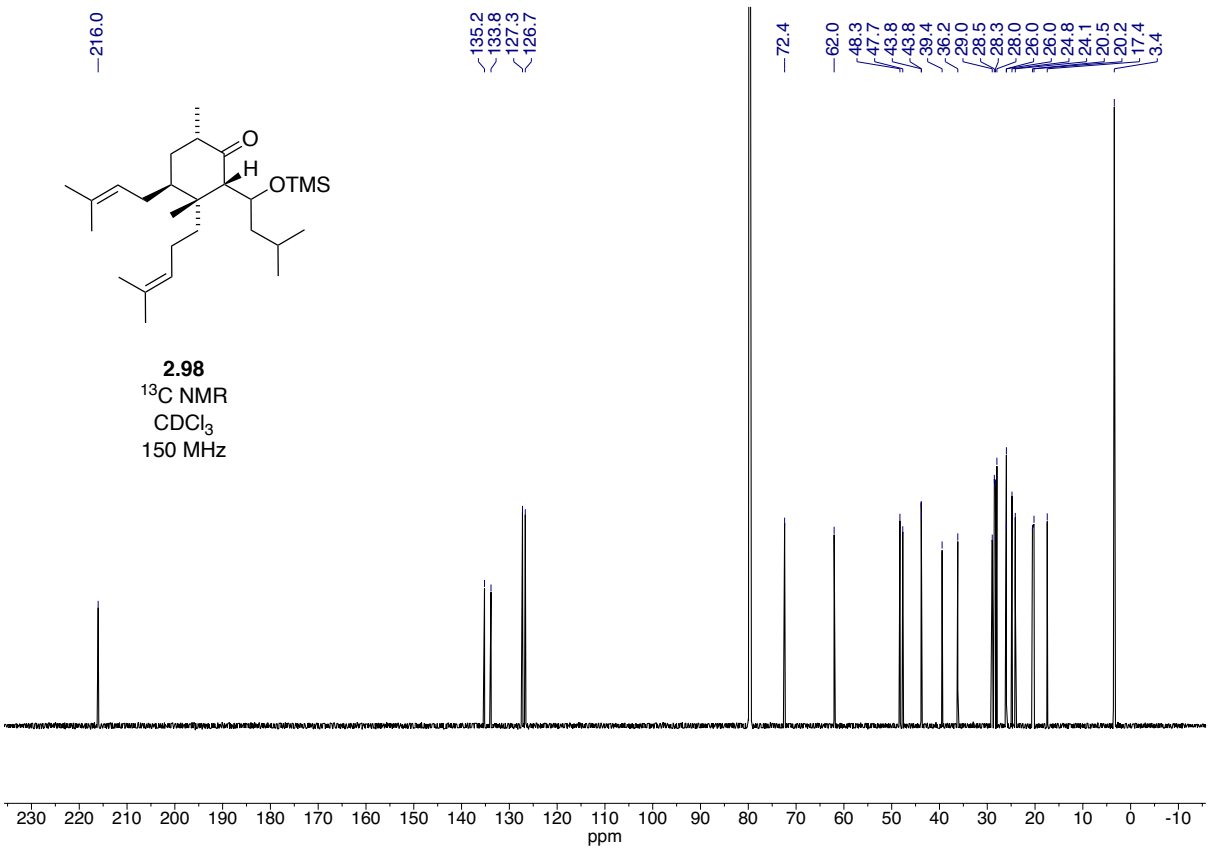

O
H
O
2.56
HSQC
CDCl3
600 MHz
f1 (ppm)
ppm


O
H
O
2.56
HMBC
CDCl3
600 MHz
f1 (ppm)
ppm

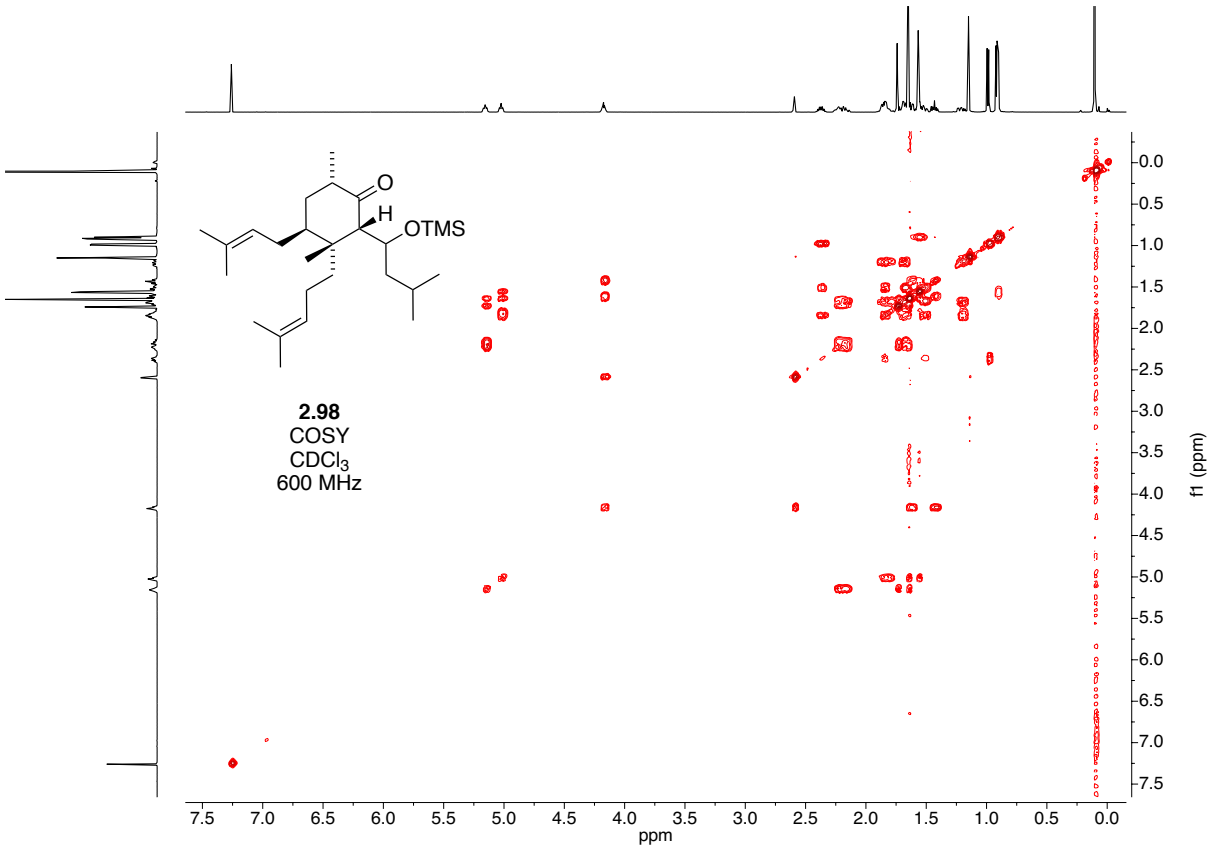

O
H
O
2.56
NOESY
CDCl3
600 MHz
f1 (ppm)
ppm

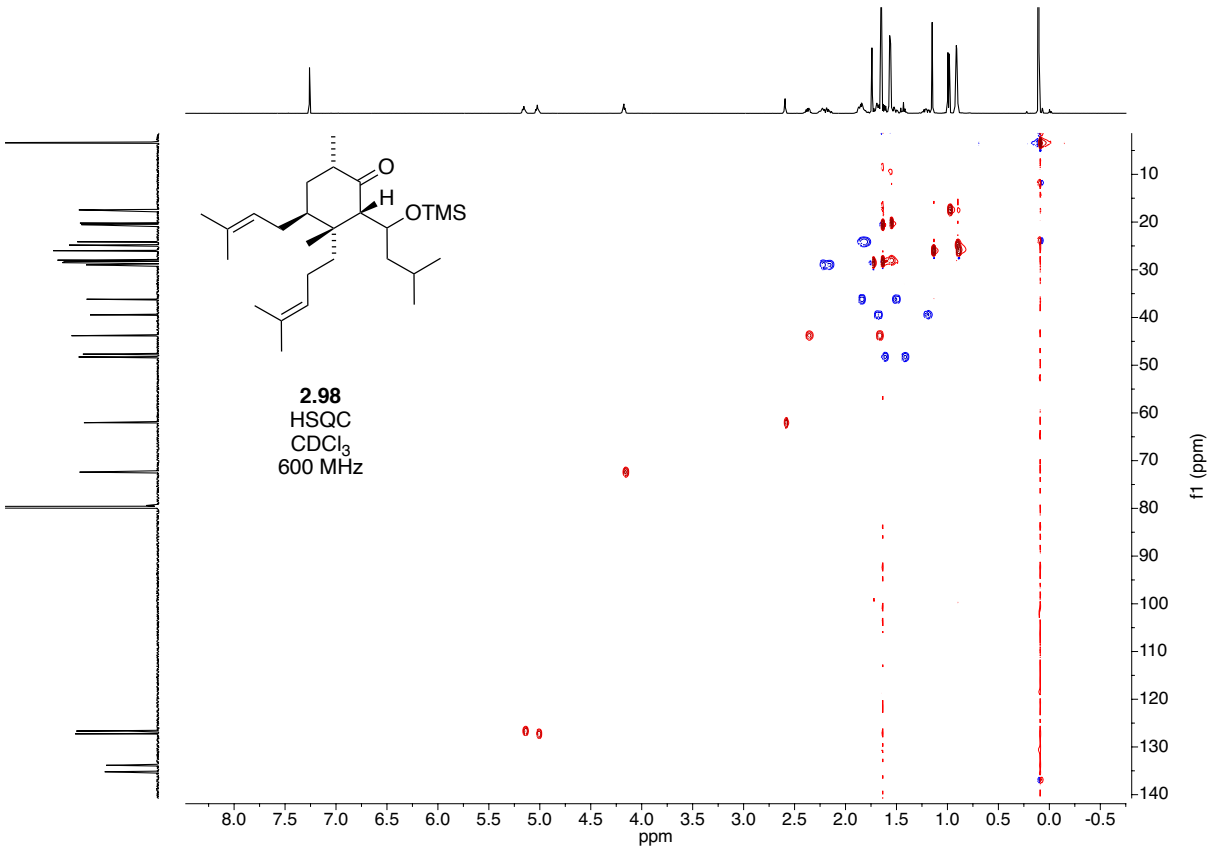


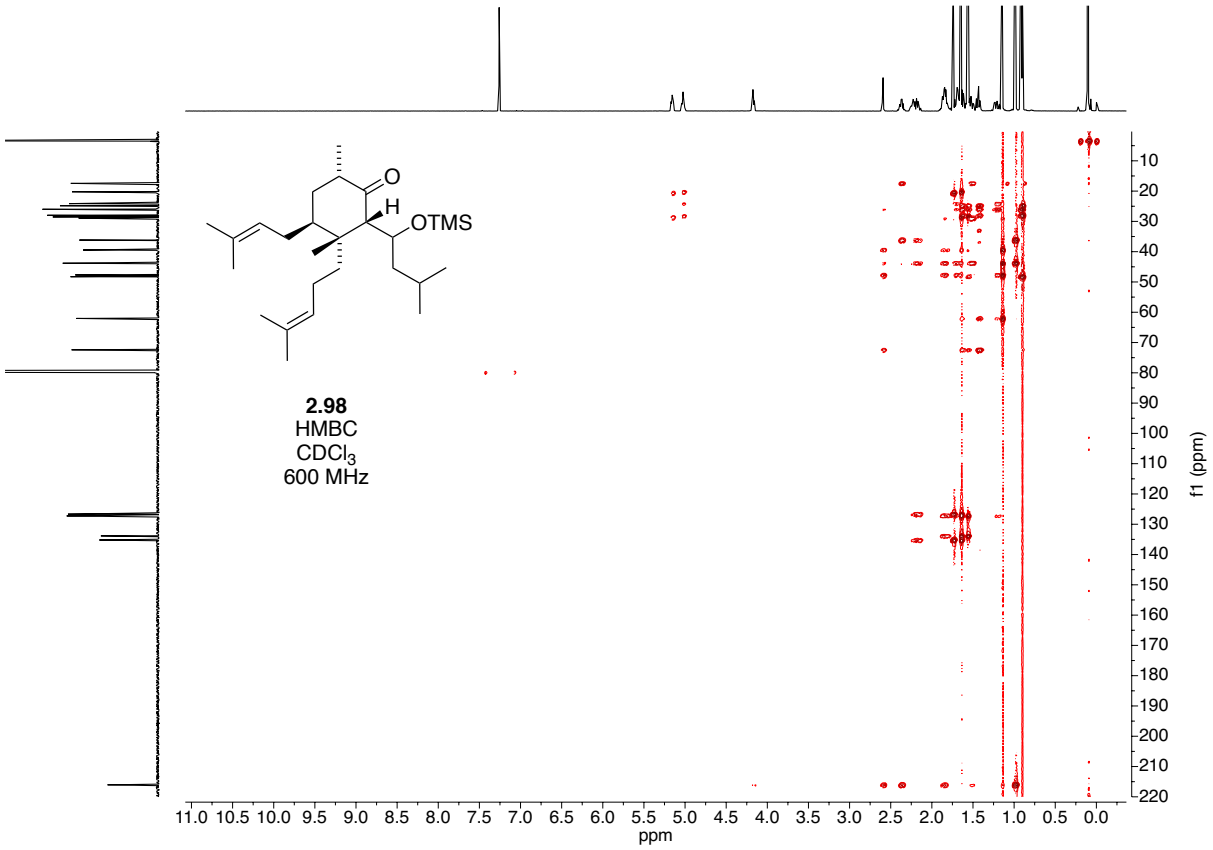
2.98
^{1}H NMR
$CDCl_3$
600 MHz

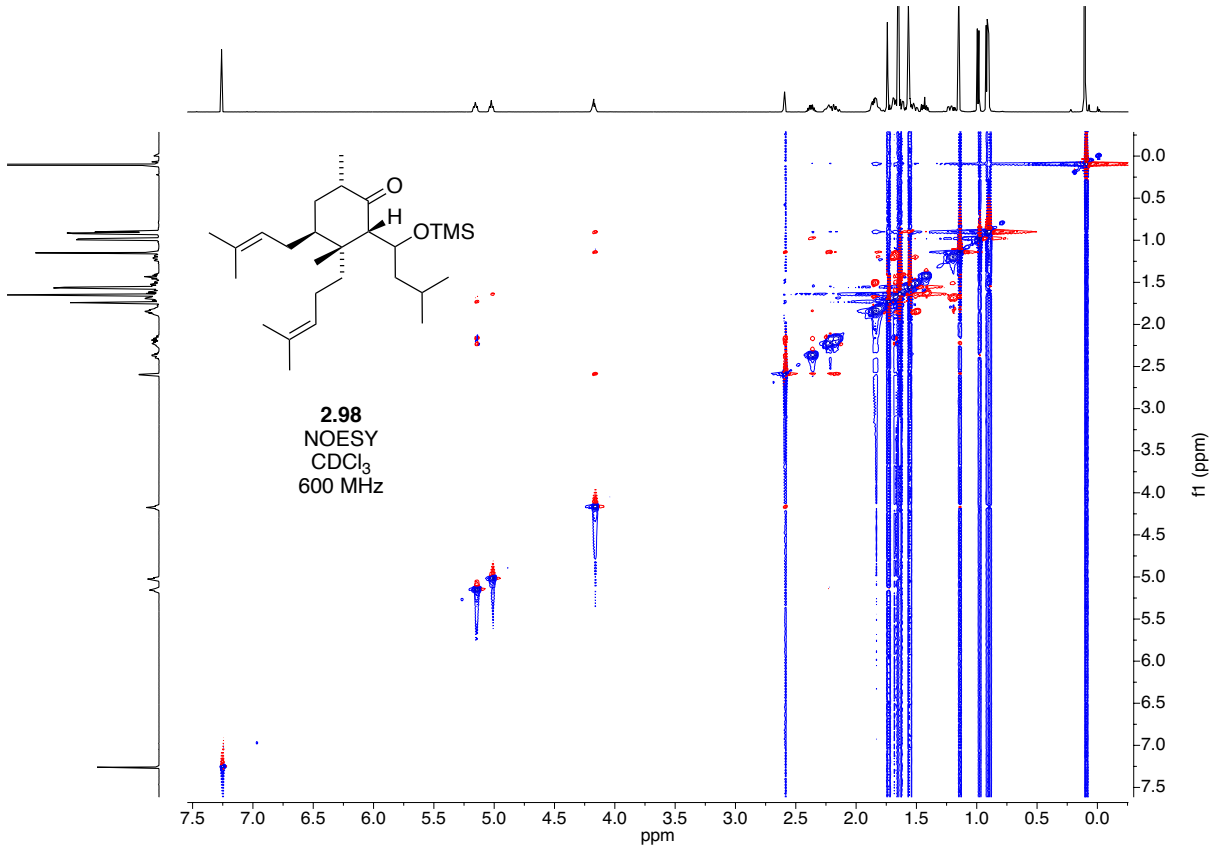


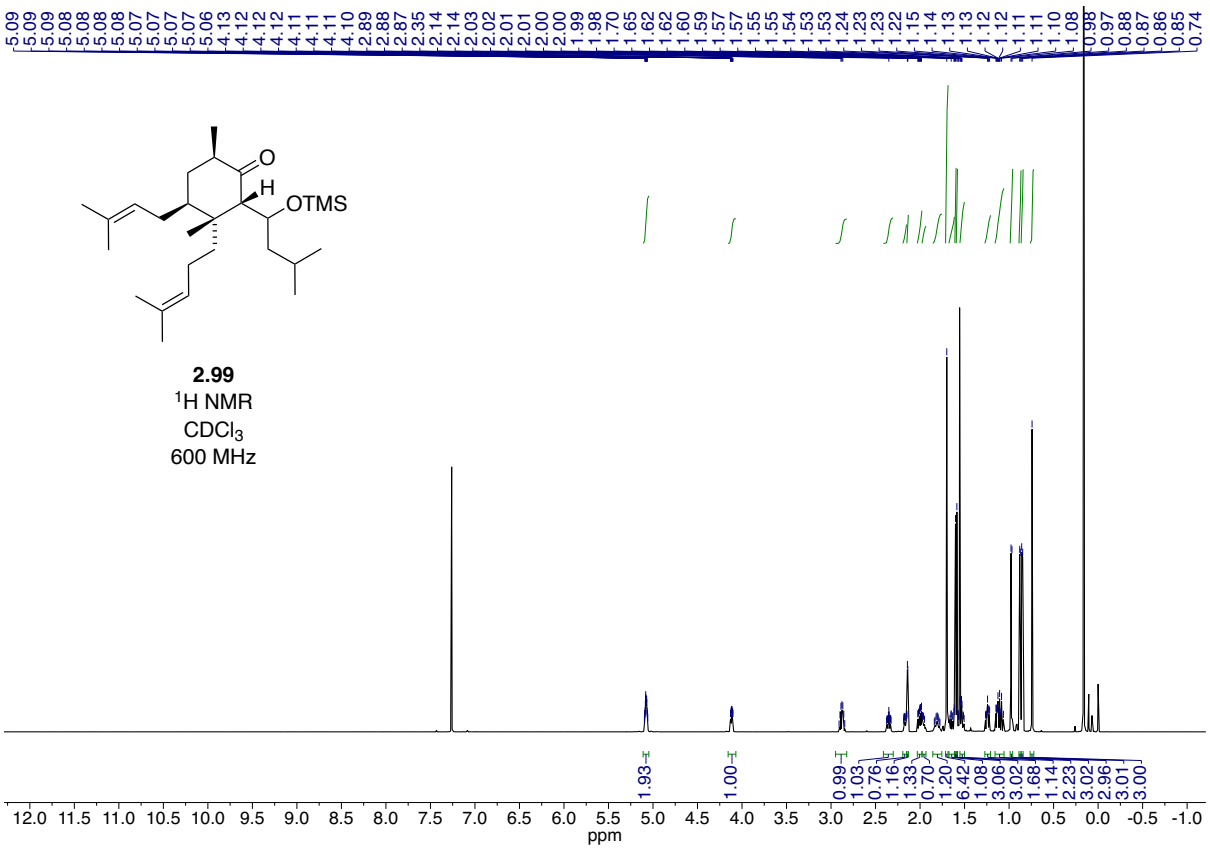
2.98
^{13}C NMR
$CDCl_3$
150 MHz

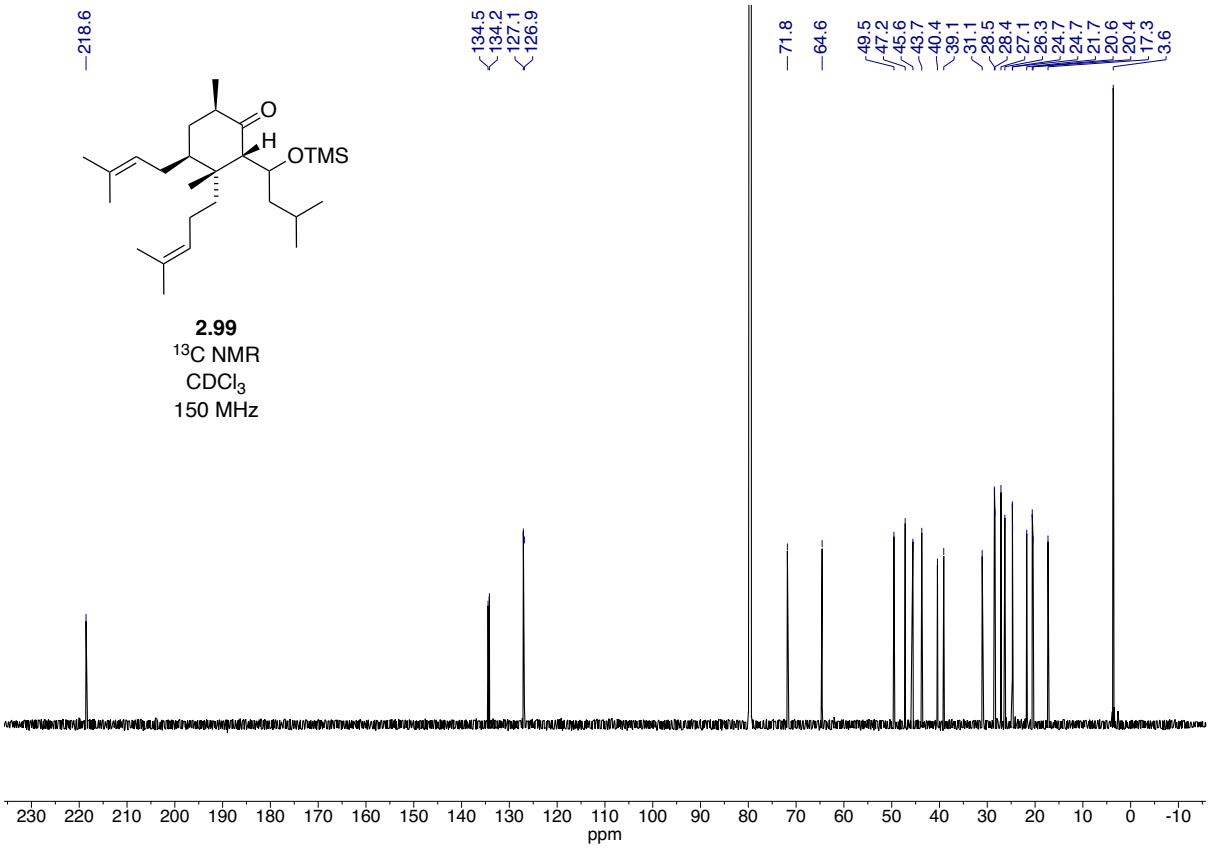

O
H
OTMS
2.98
COSY
CDCl3
600 MHz
ppm
f1 (ppm)

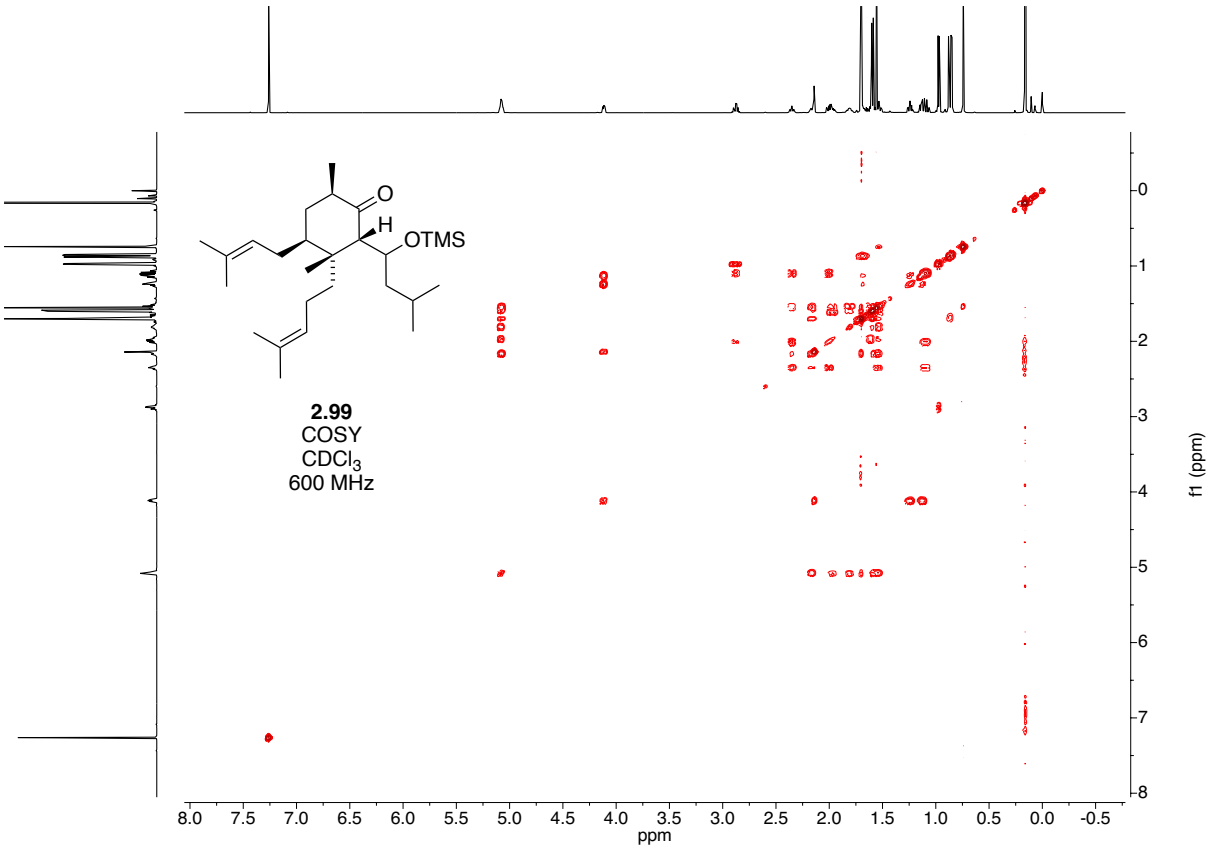

O
H
OTMS
2.98
HSQC
CDCl3
600 MHz
ppm
f1 (ppm)

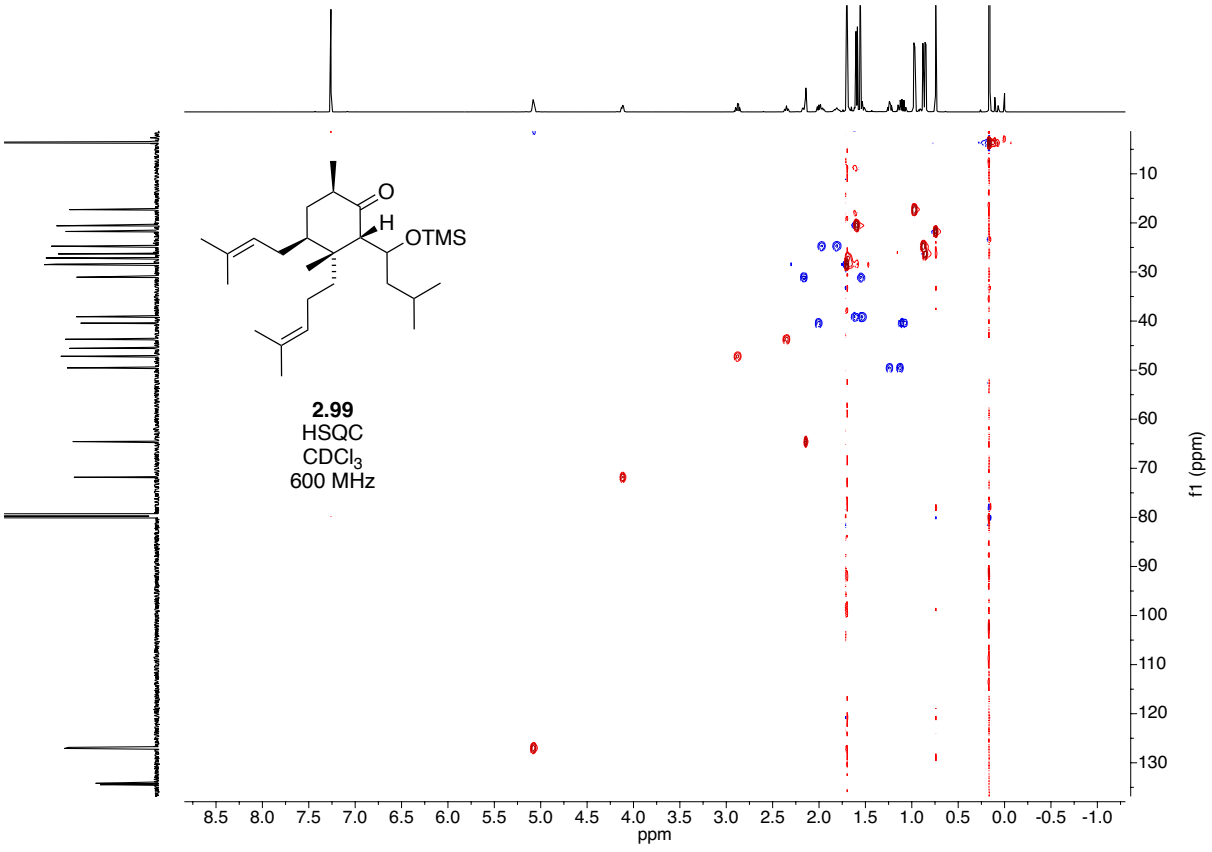

O
H
OTMS
2.98
HMBC
CDCl3
600 MHz
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220
f1 (ppm)

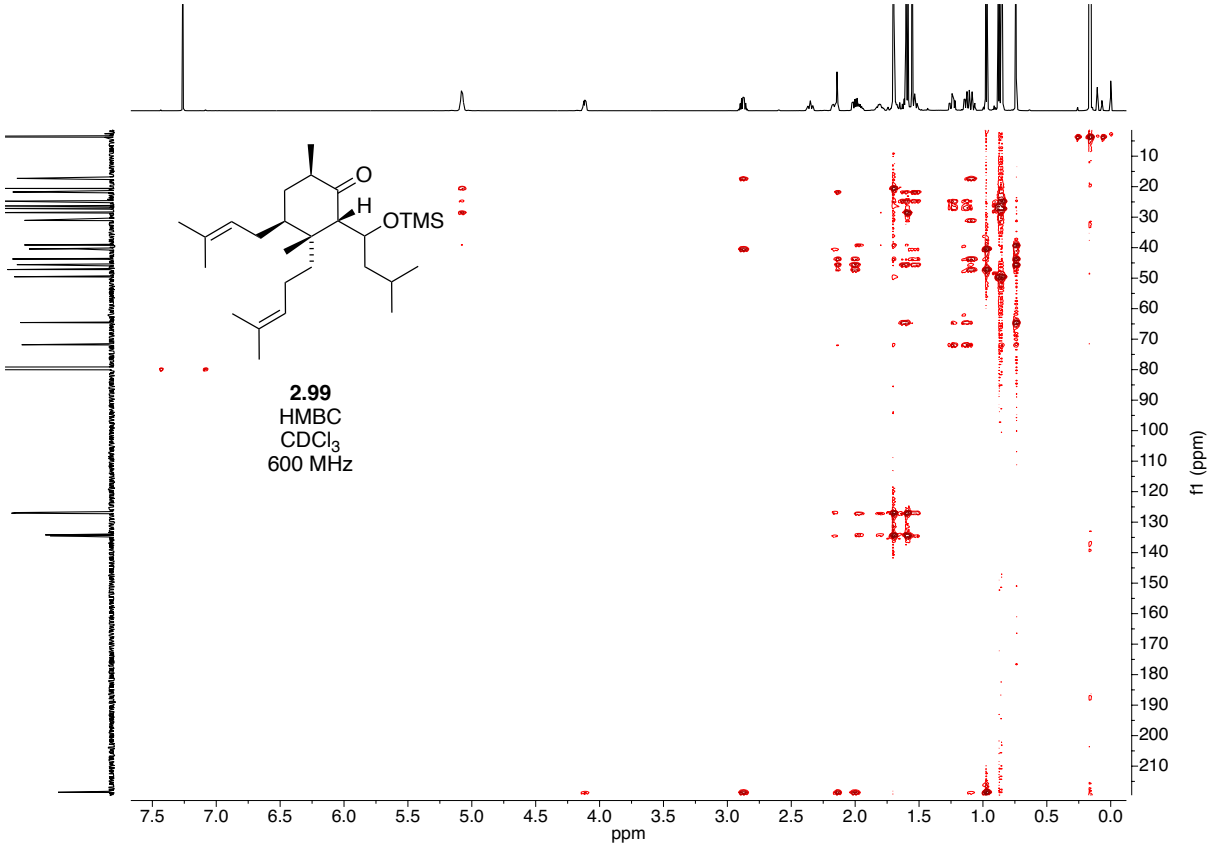

O
H
OTMS
2.98
NOESY
CDCl3
600 MHz
ppm
f1 (ppm)

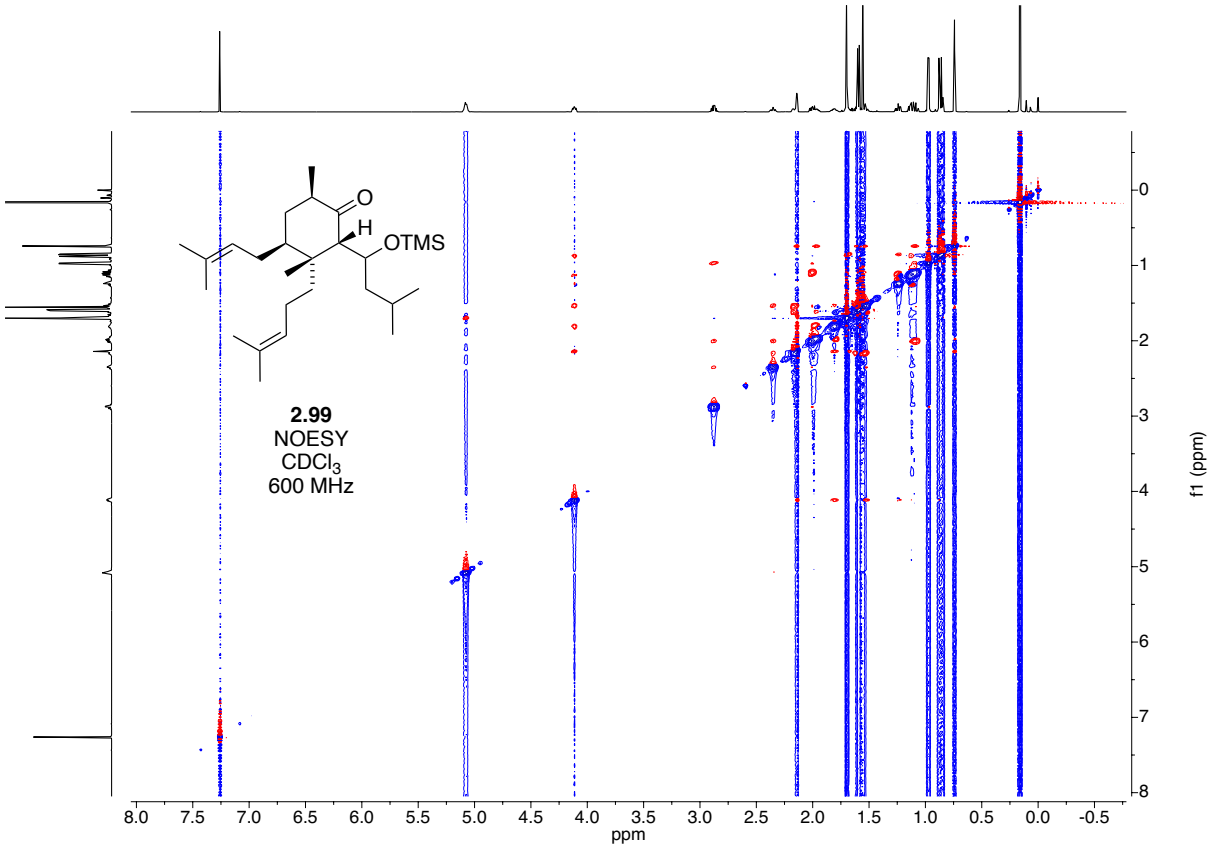

O
H
OTMS
2.99
1H NMR
CDCl3
600 MHz
ppm

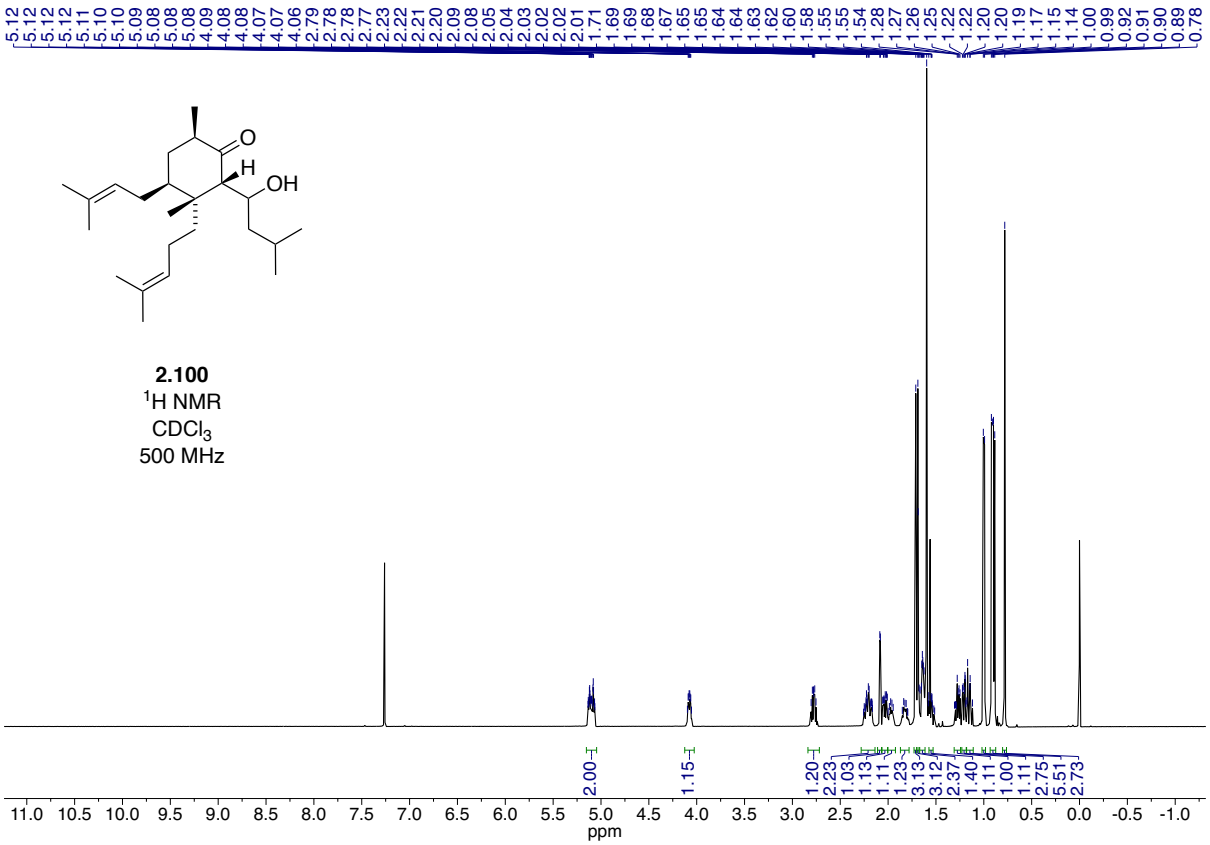

O
H
OTMS
2.99
13C NMR
CDCl3
150 MHz
ppm

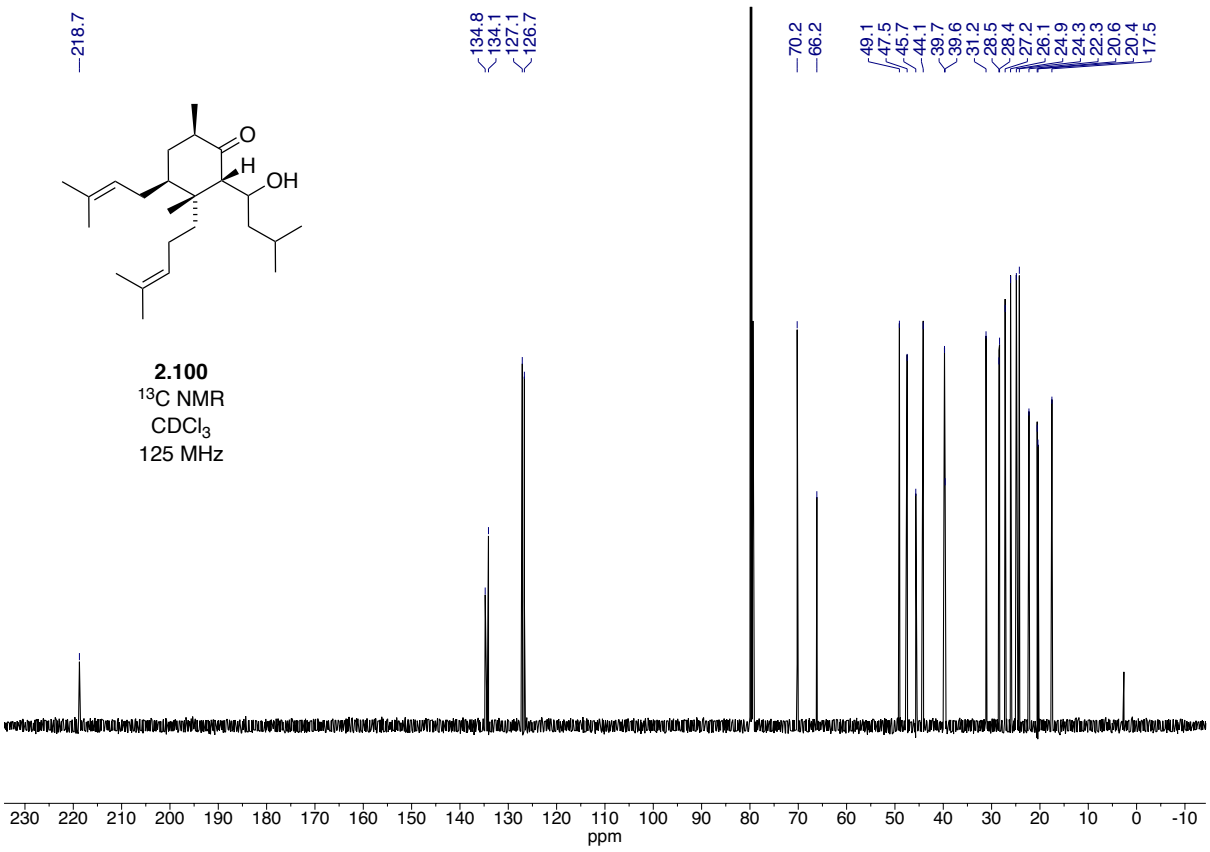

O
H
OTMS
2.99
COSY
CDCl3
600 MHz
f1 (ppm)
ppm

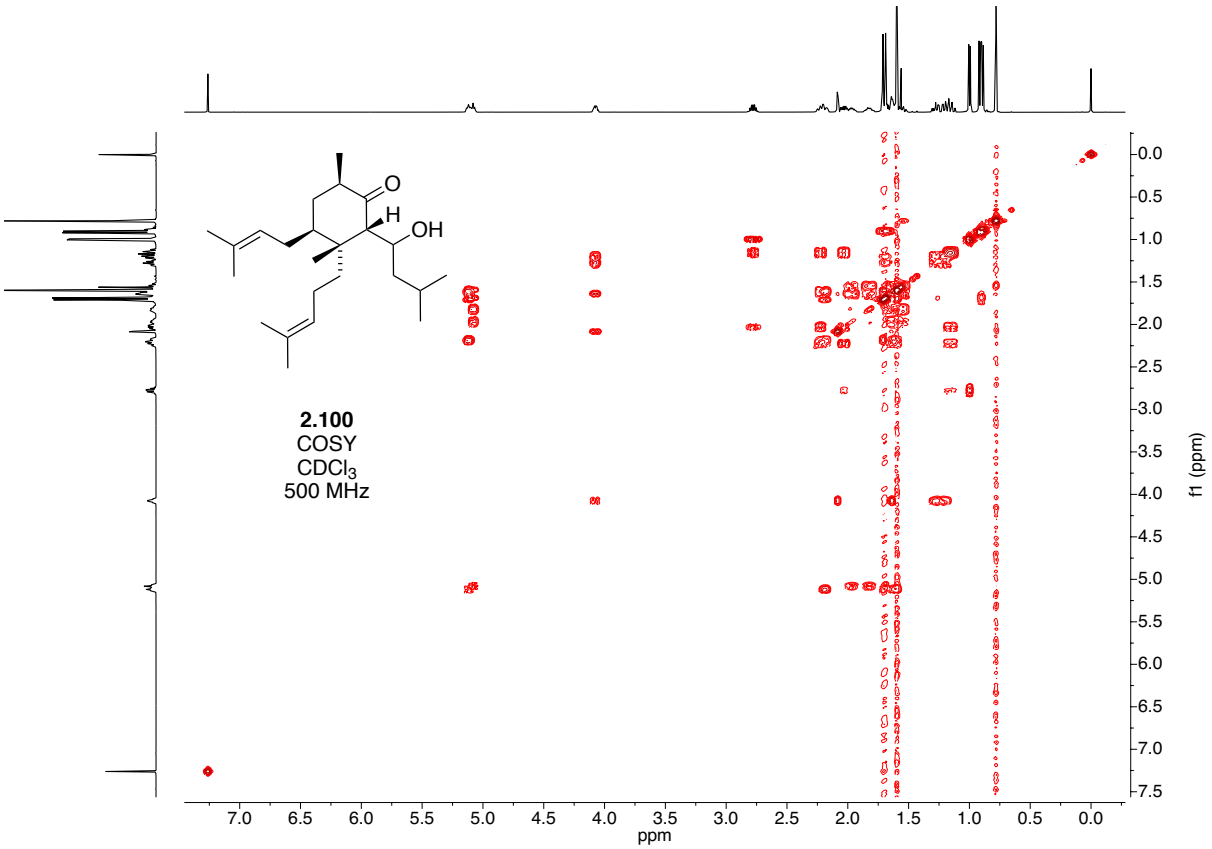

O
H
OTMS
2.99
HSQC
CDCl3
600 MHz
f1 (ppm)
ppm

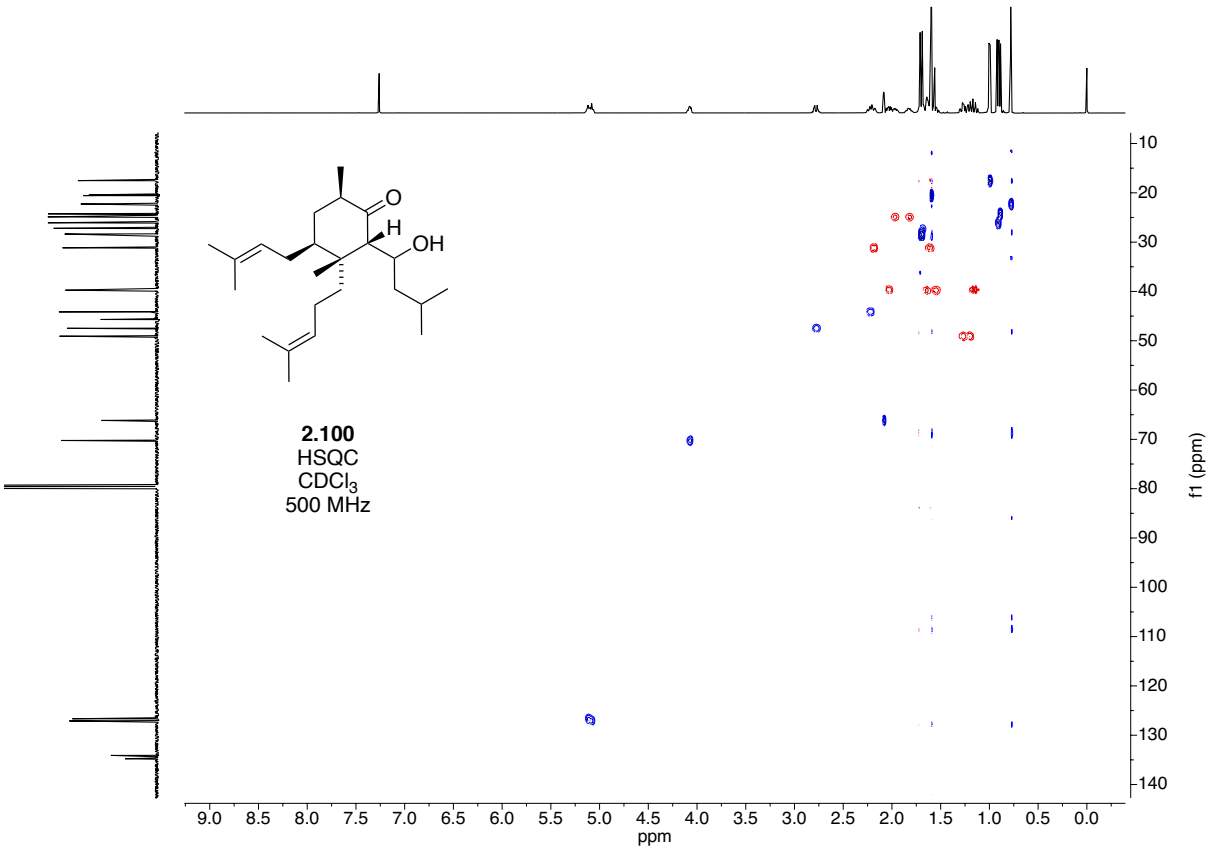

O
H
OTMS
2.99
HMBC
CDCl3
600 MHz
ppm
f1 (ppm)

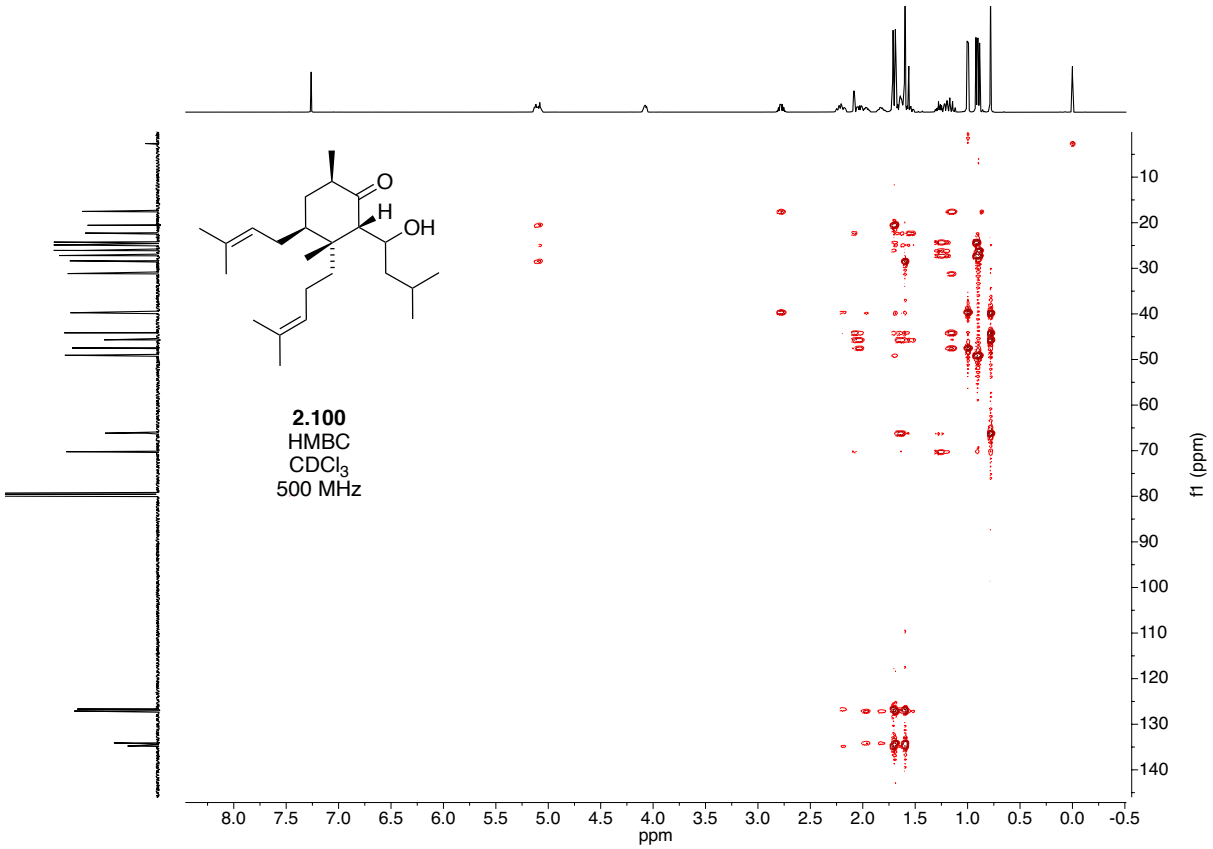

O
H
OTMS
2.99
NOESY
CDCl3
600 MHz
ppm
f1 (ppm)

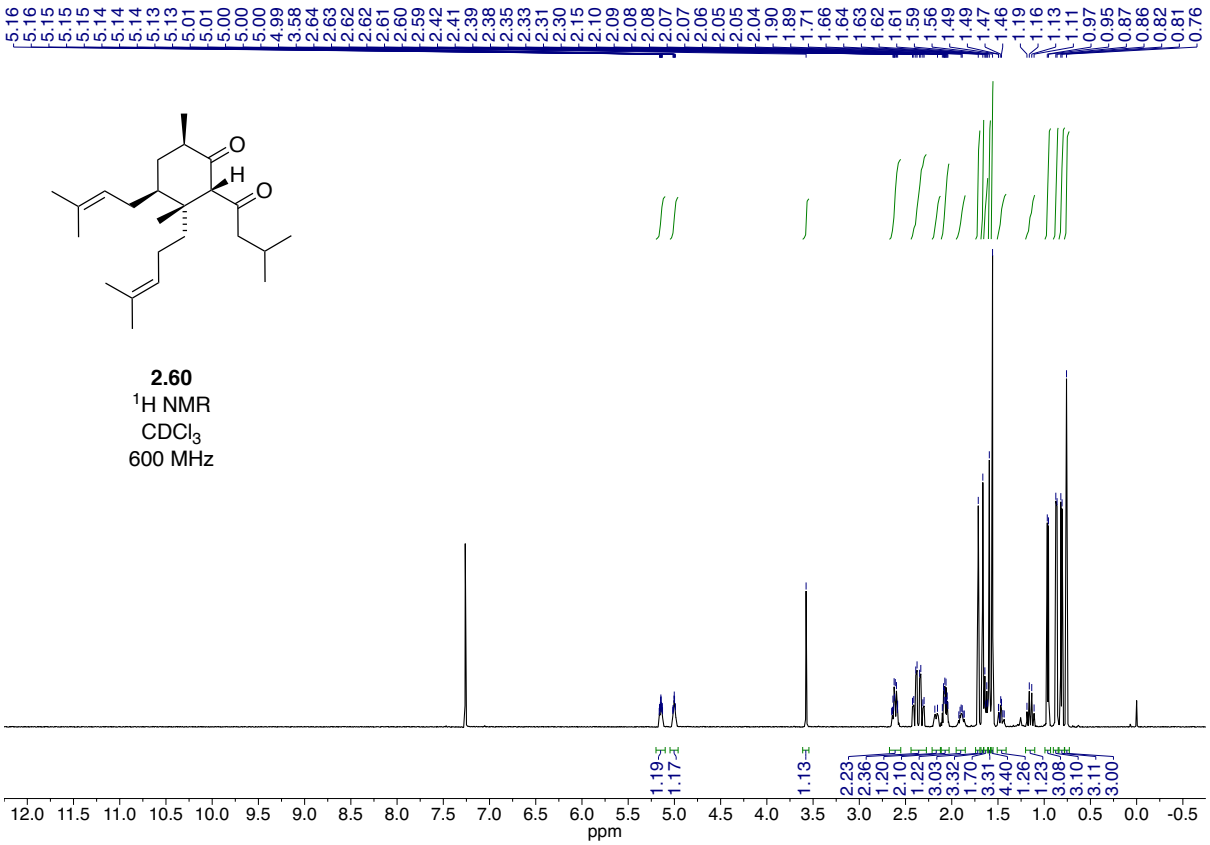

O
H
OH
2.100
1H NMR
CDCl3
500 MHz
ppm


O
H
OH
2.100
13C NMR
CDCl3
125 MHz
ppm

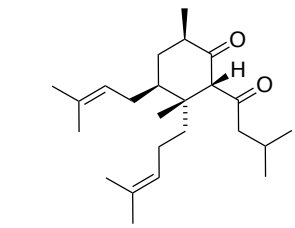

O
H
OH
2.100
COSY
CDCl3
500 MHz
ppm
f1 (ppm)


O
H
OH
2.100
HSQC
CDCl3
500 MHz
ppm
f1 (ppm)

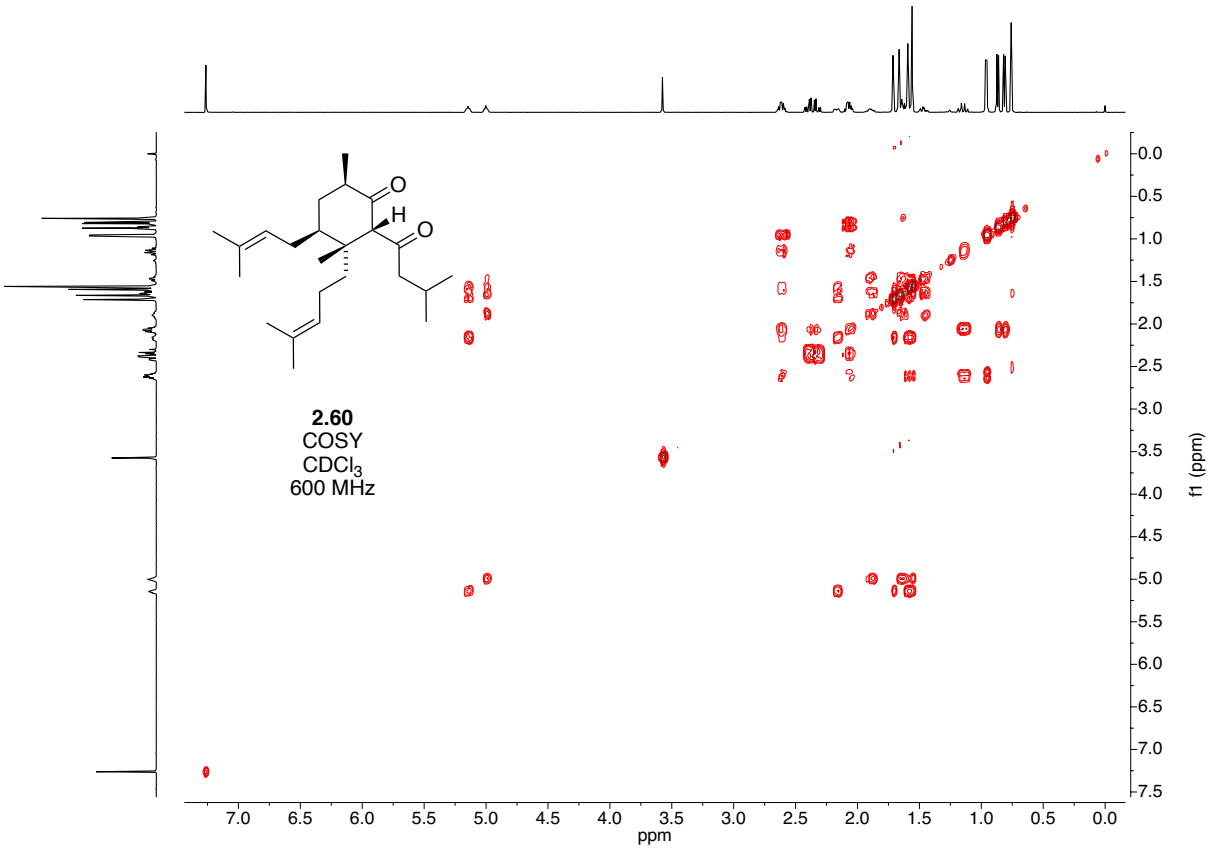

O
H
OH
2.100
HMBC
CDCl3
500 MHz
f1 (ppm)
ppm

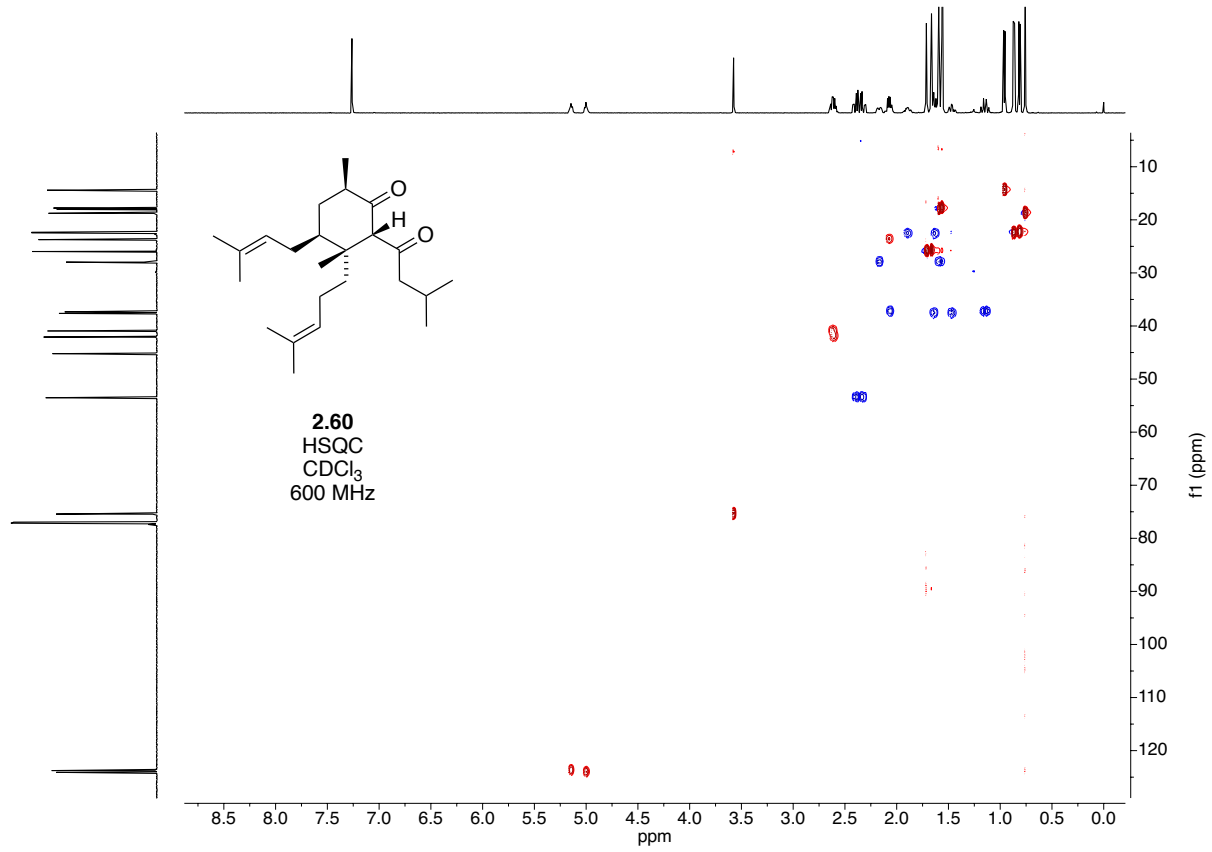


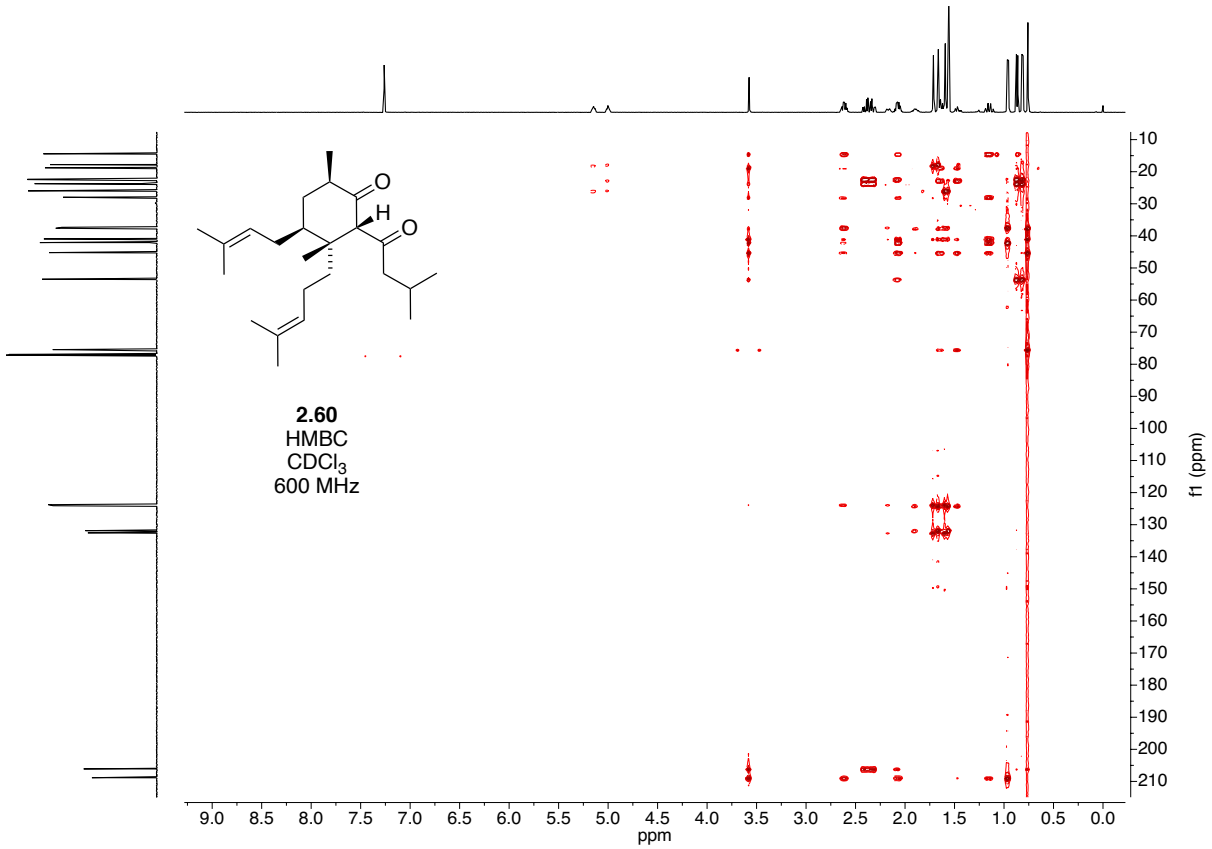
2.60
^{1}H NMR
$CDCl_3$
600 MHz

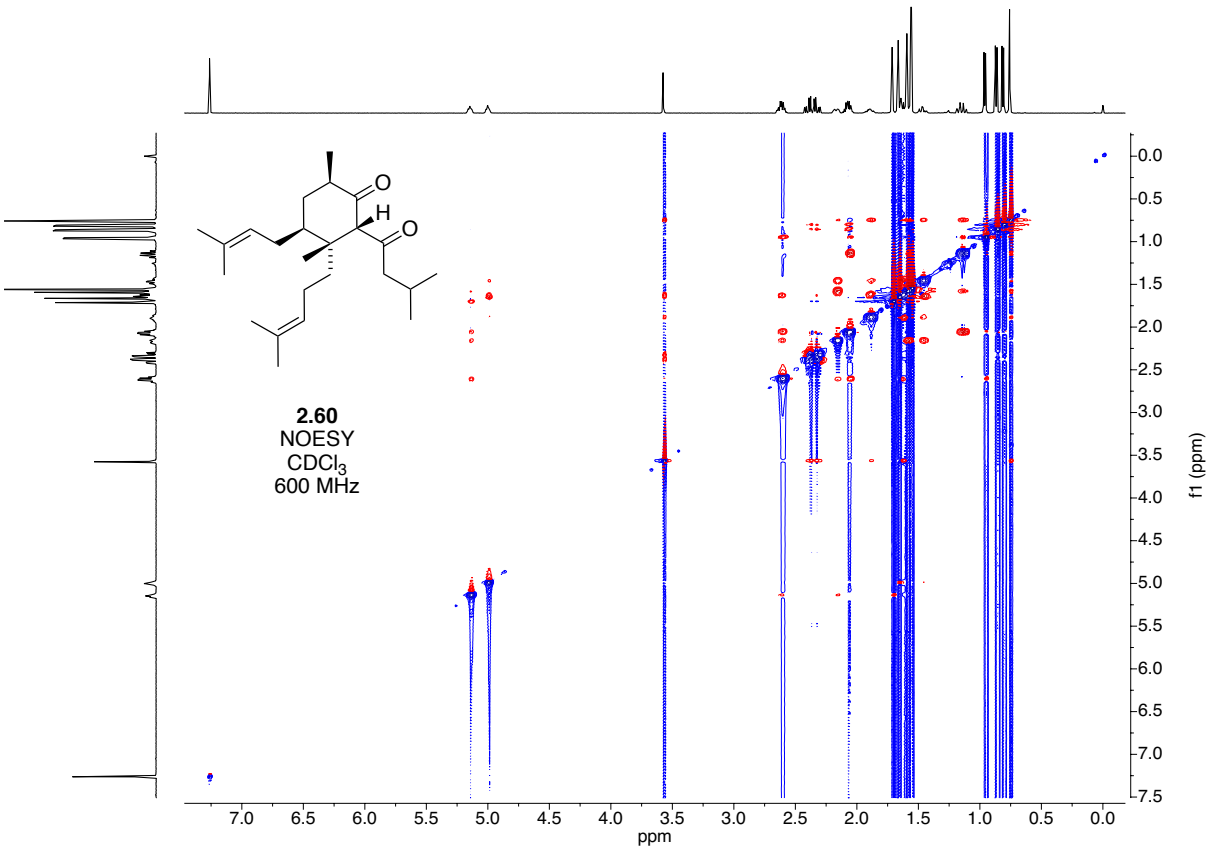


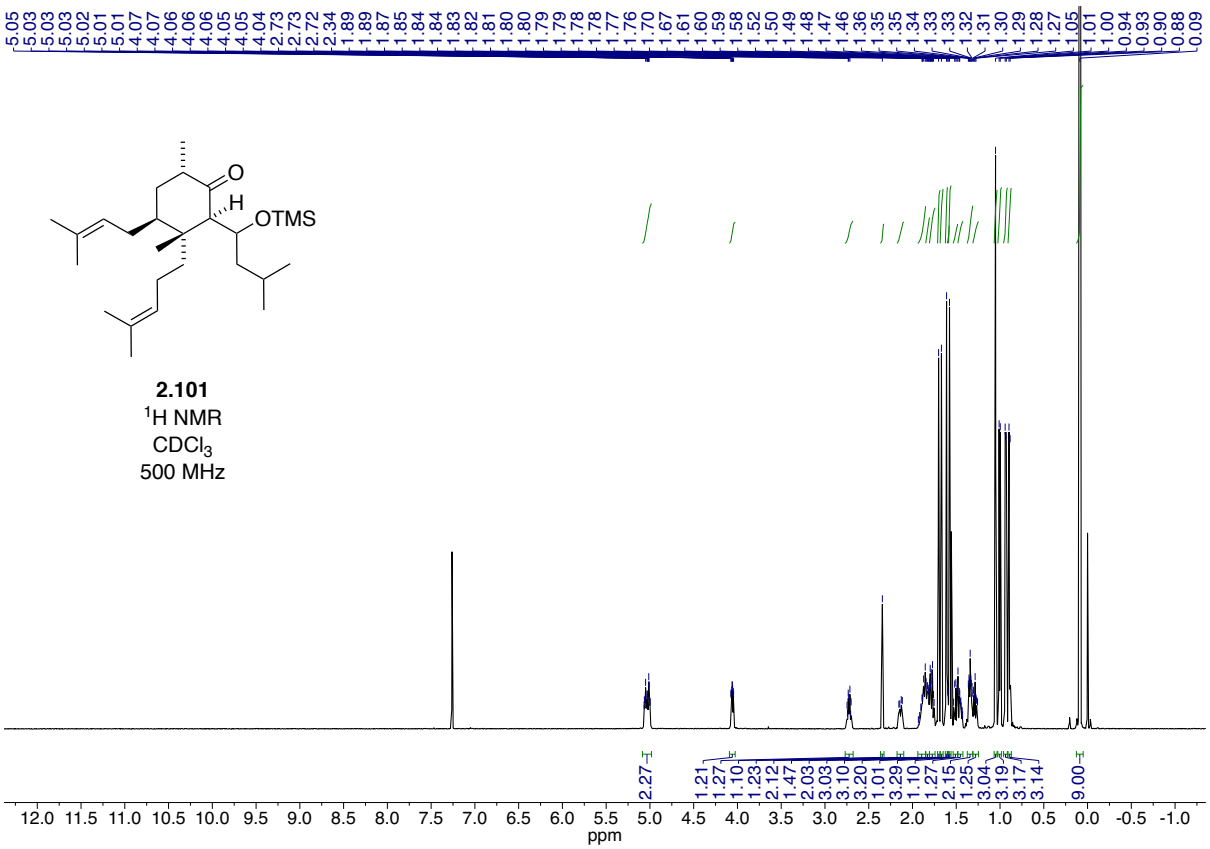
2.60
^{13}C NMR
$CDCl_3$
150 MHz

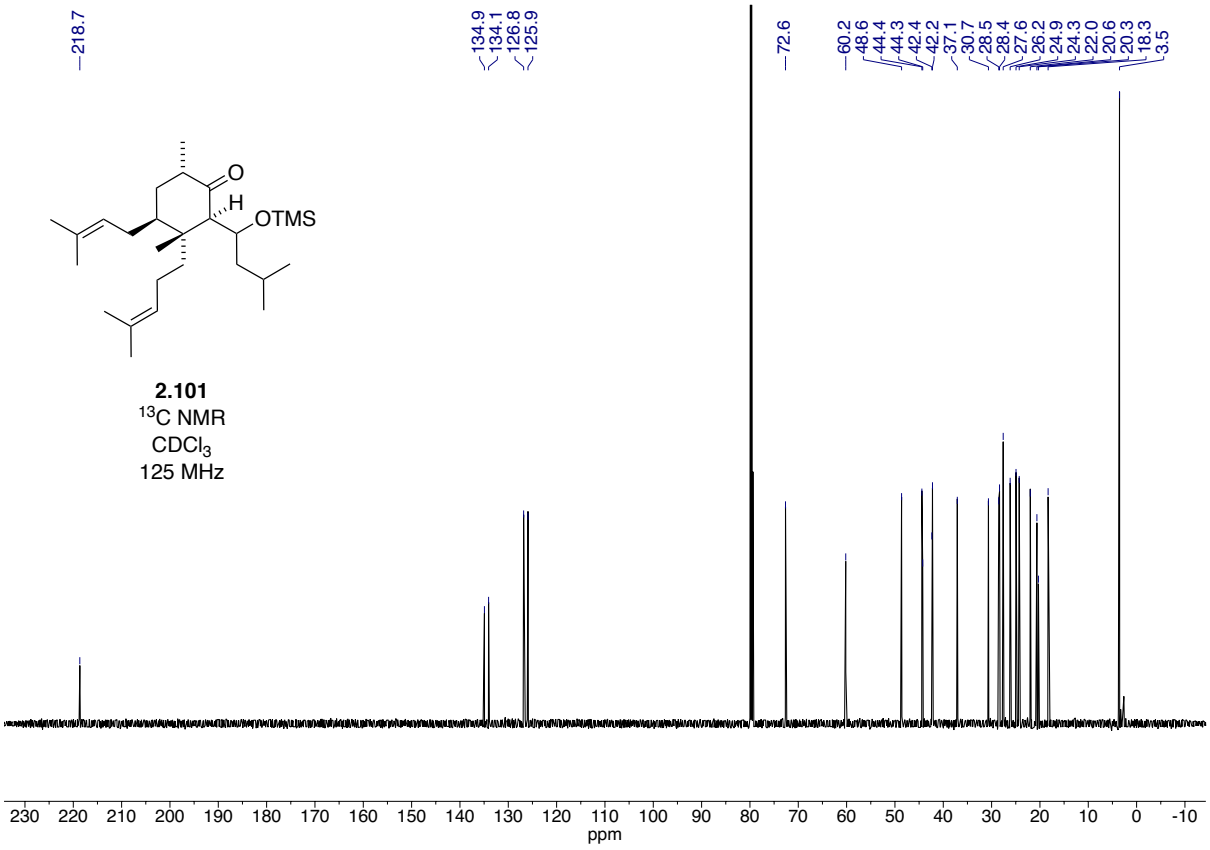

O
H
O
2.60
COSY
CDCl3
600 MHz
ppm
f1 (ppm)

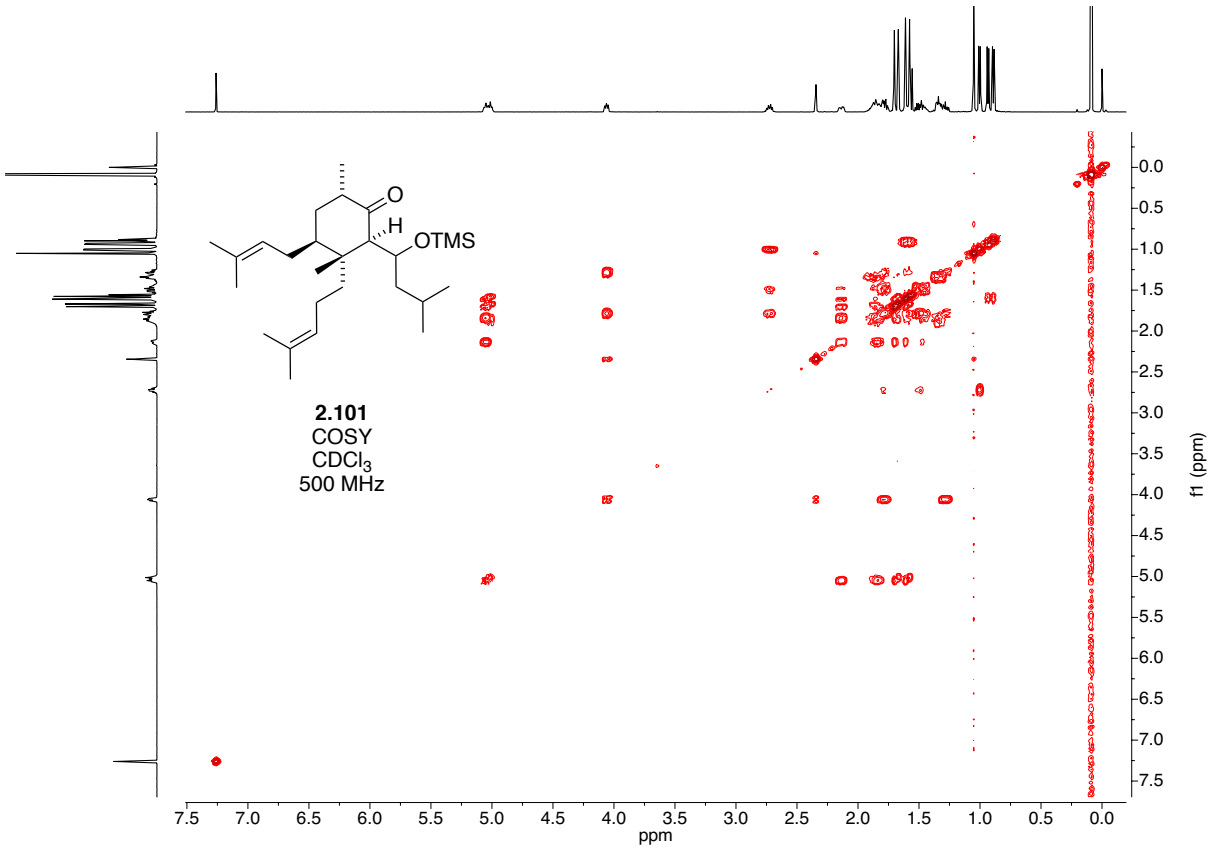

O
H
O
2.60
HSQC
CDCl3
600 MHz
ppm
f1 (ppm)

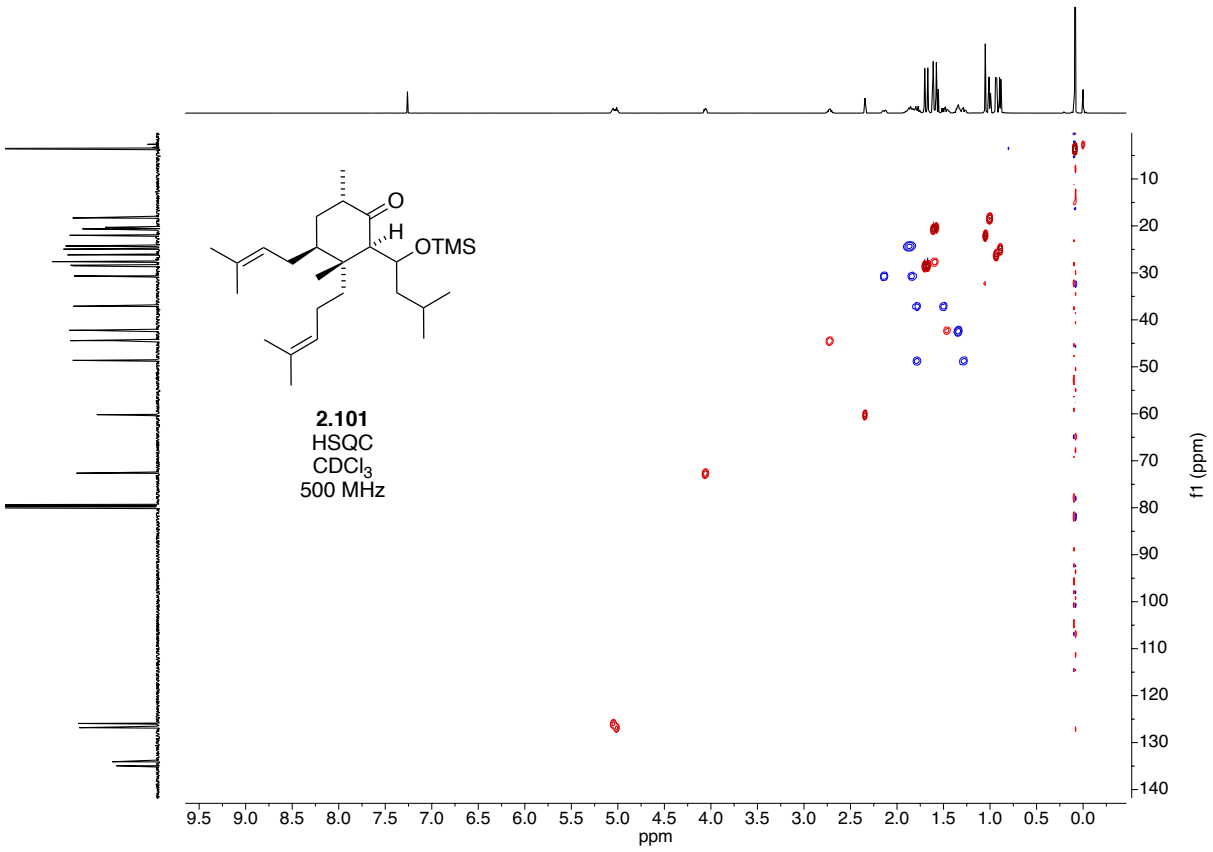

O
H
O
2.60
HMBC
CDCl3
600 MHz
ppm
f1 (ppm)

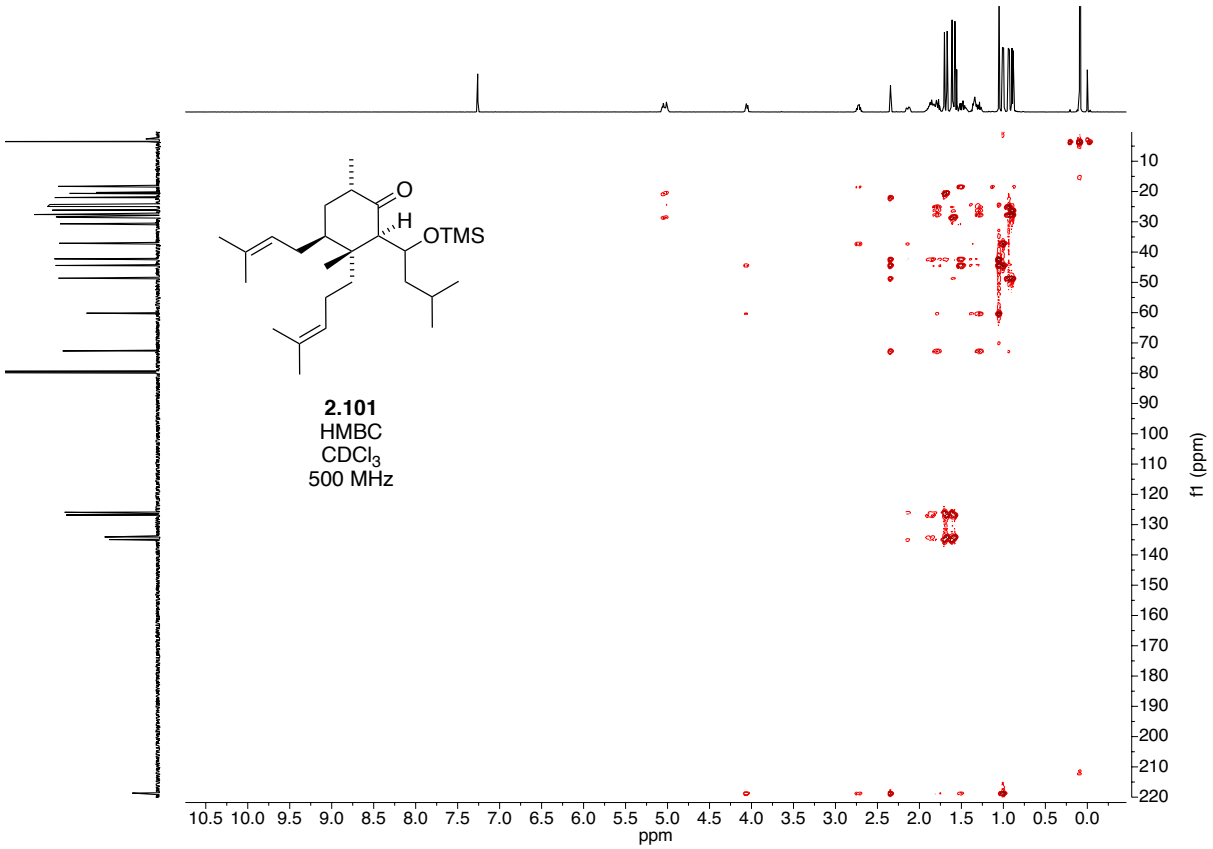

O
H
O
2.60
NOESY
CDCl3
600 MHz
ppm
f1 (ppm)

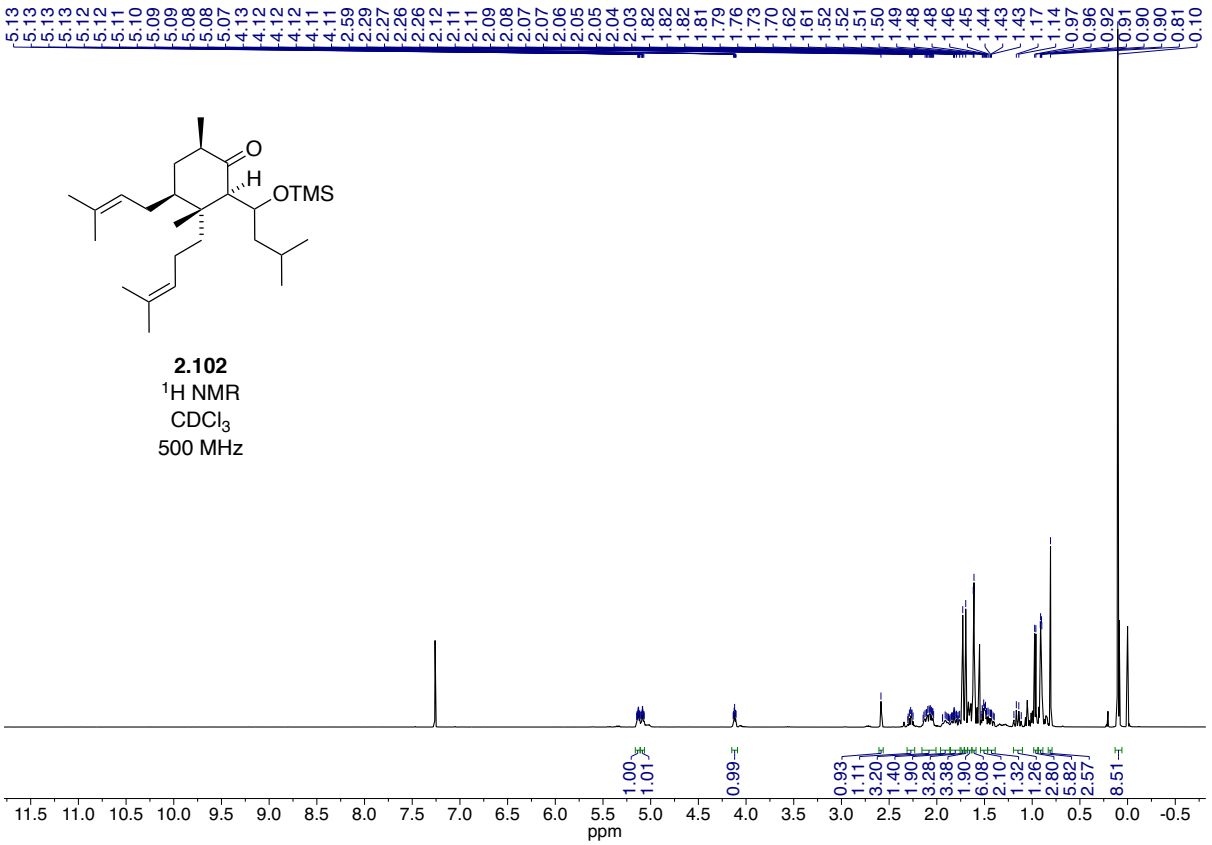

O
H
OTMS
2.101
1H NMR
CDCl3
500 MHz
ppm


O
H
OTMS
2.101
13C NMR
CDCl3
125 MHz
ppm

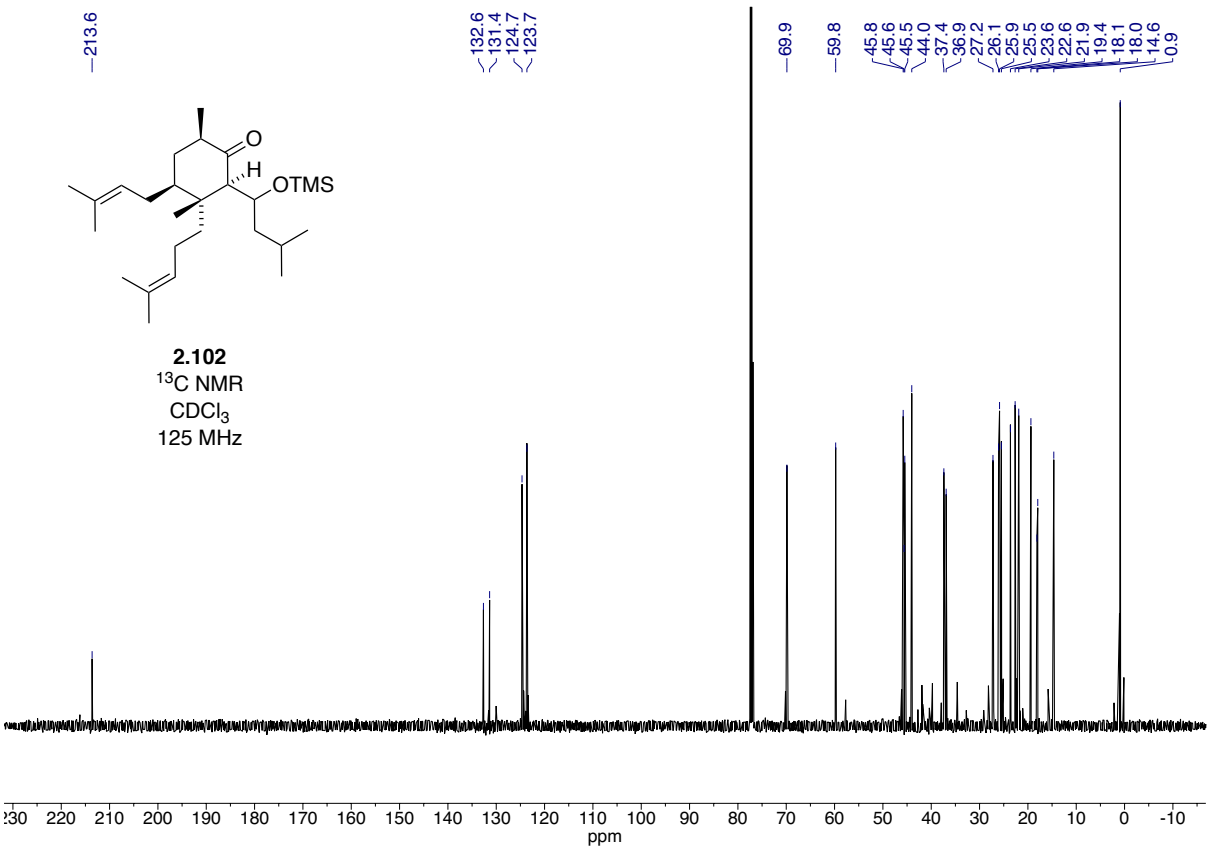

O
H
OTMS
2.101
COSY
CDCl3
500 MHz
ppm
f1 (ppm)


O
H
OTMS
2.101
HSQC
CDCl3
500 MHz
ppm
f1 (ppm)

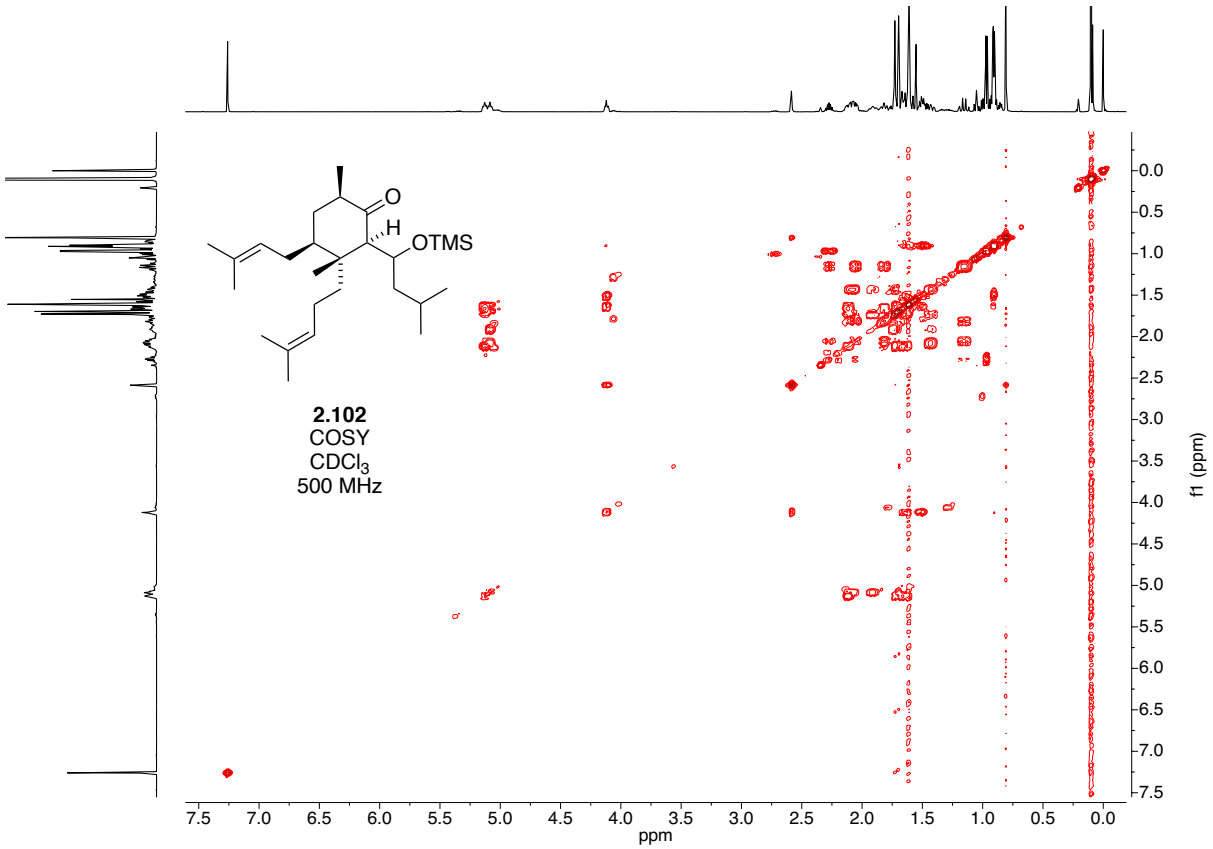

O
H
OTMS
2.101
HMBC
CDCl3
500 MHz
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220
f1 (ppm)

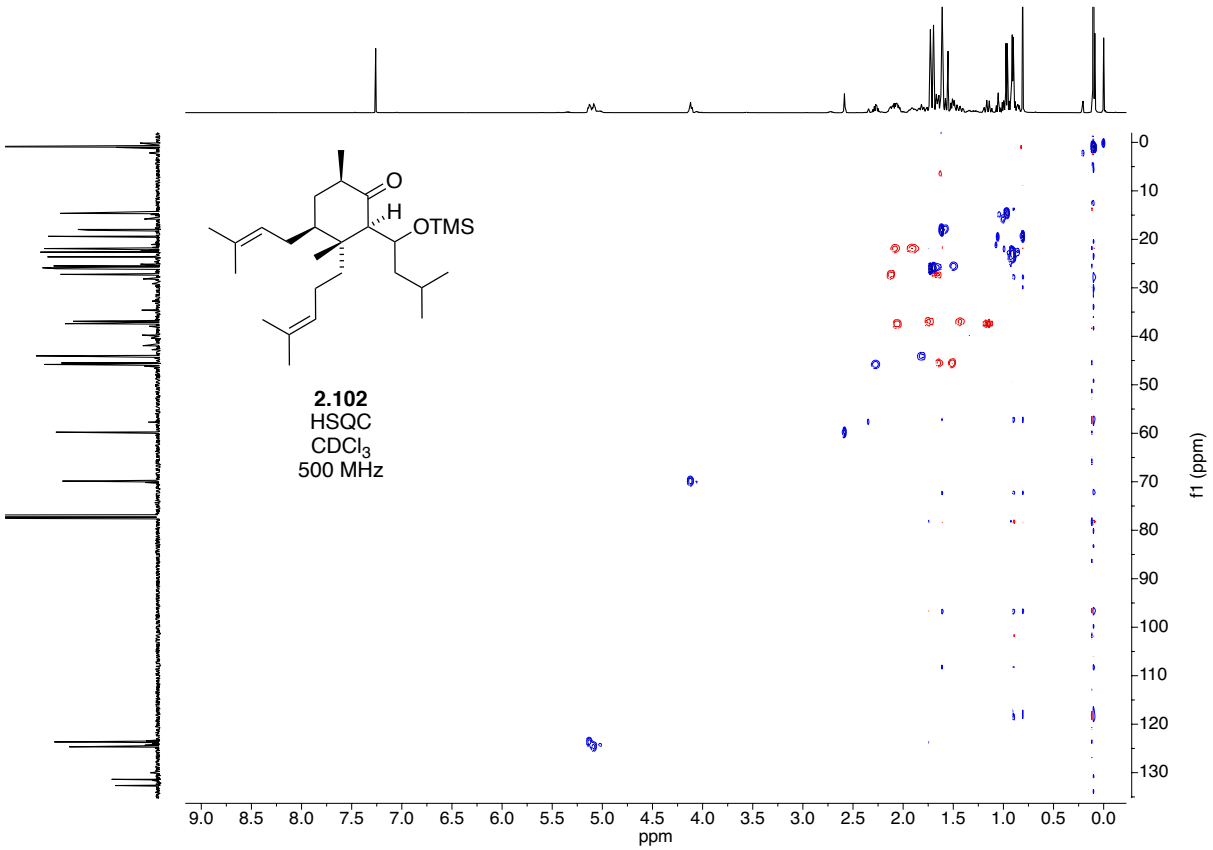


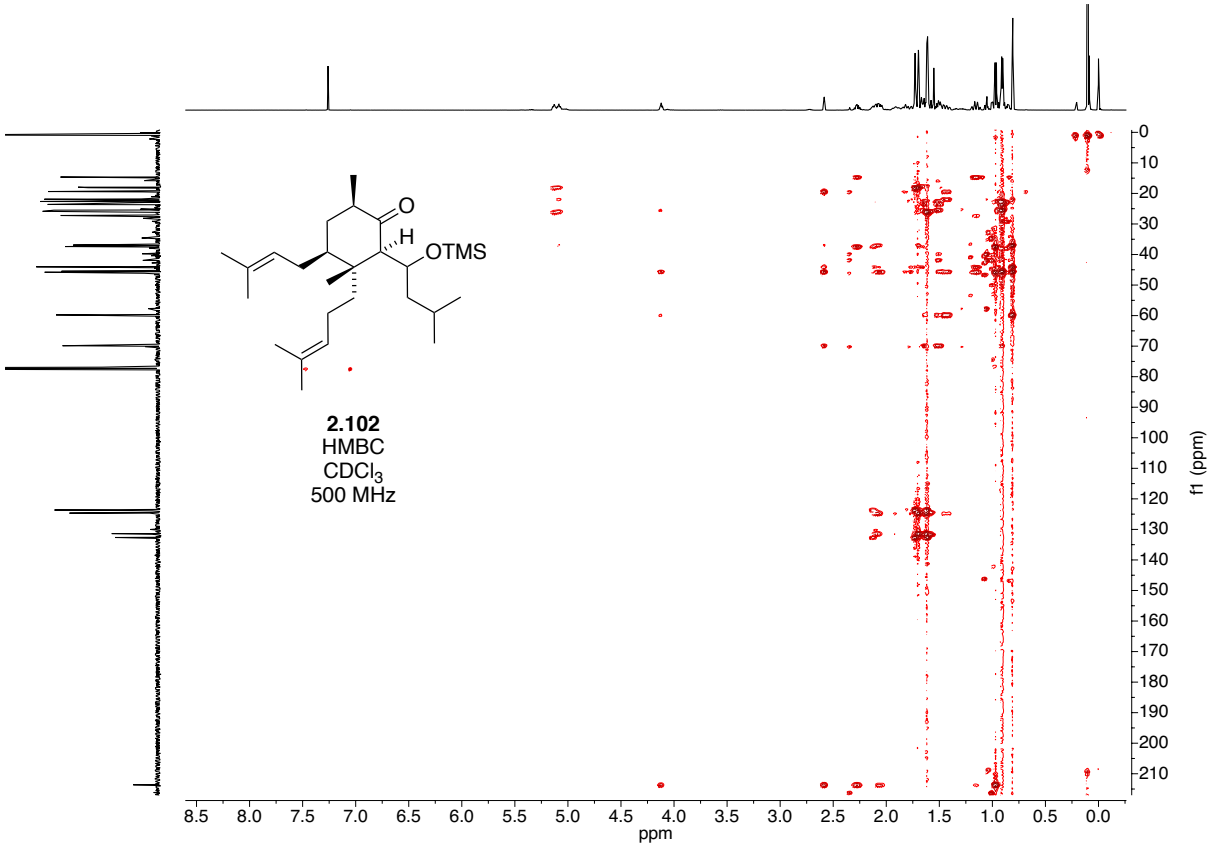
2.102
^{1}H NMR
$CDCl_3$
500 MHz

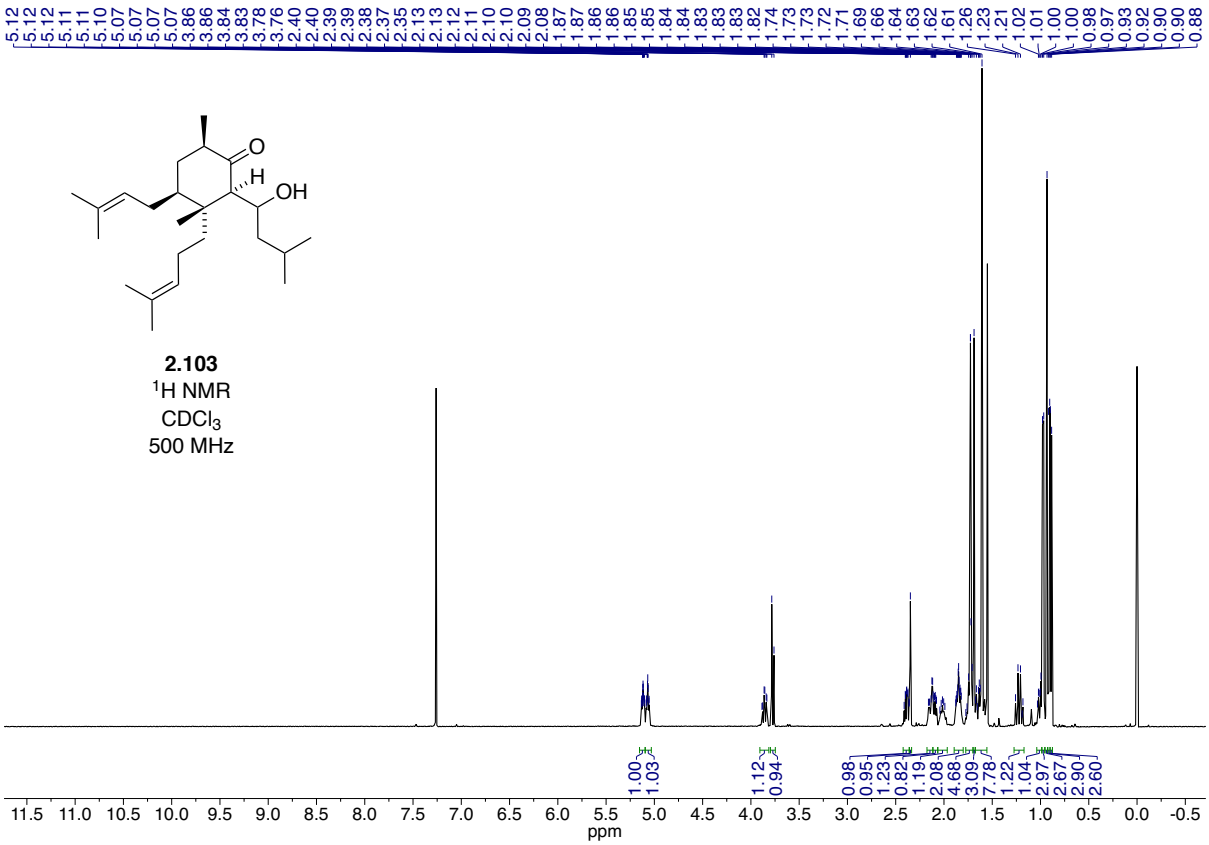


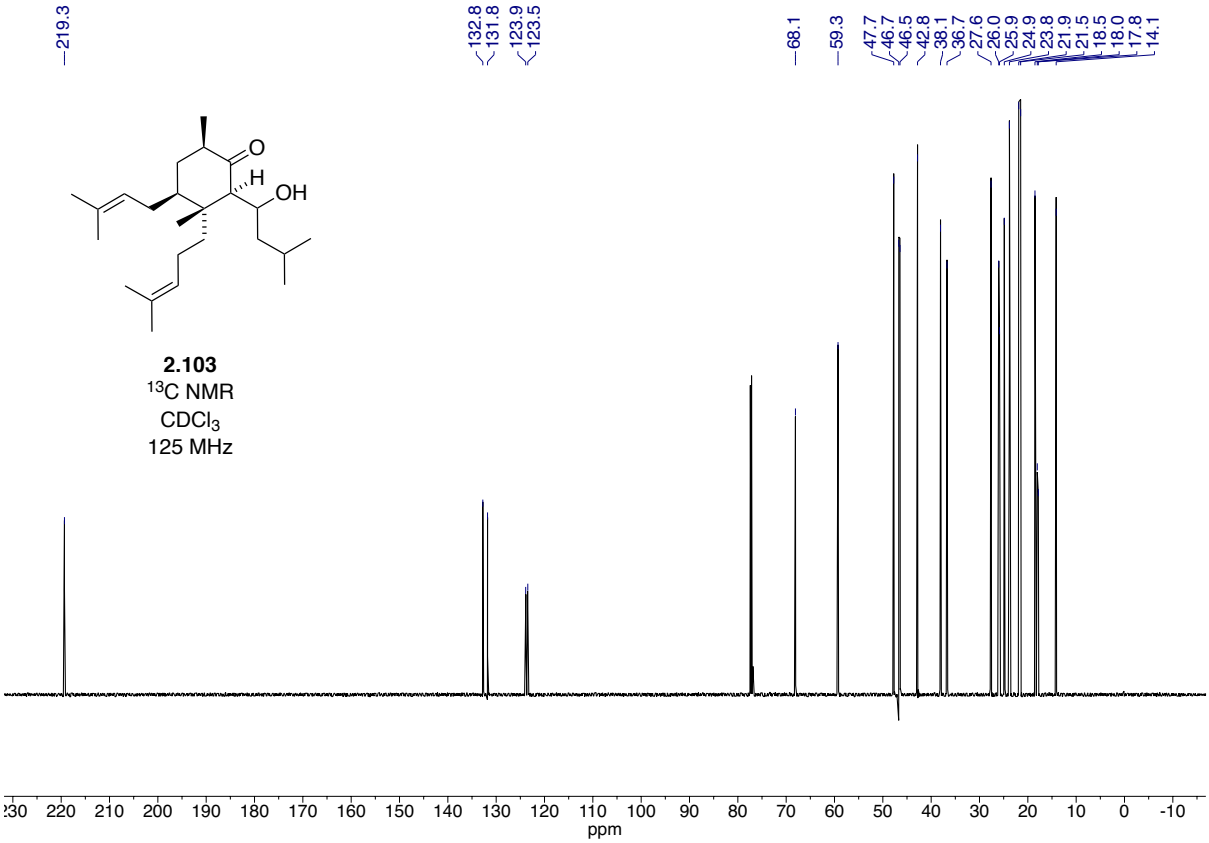
2.102
^{13}C NMR
$CDCl_3$
125 MHz

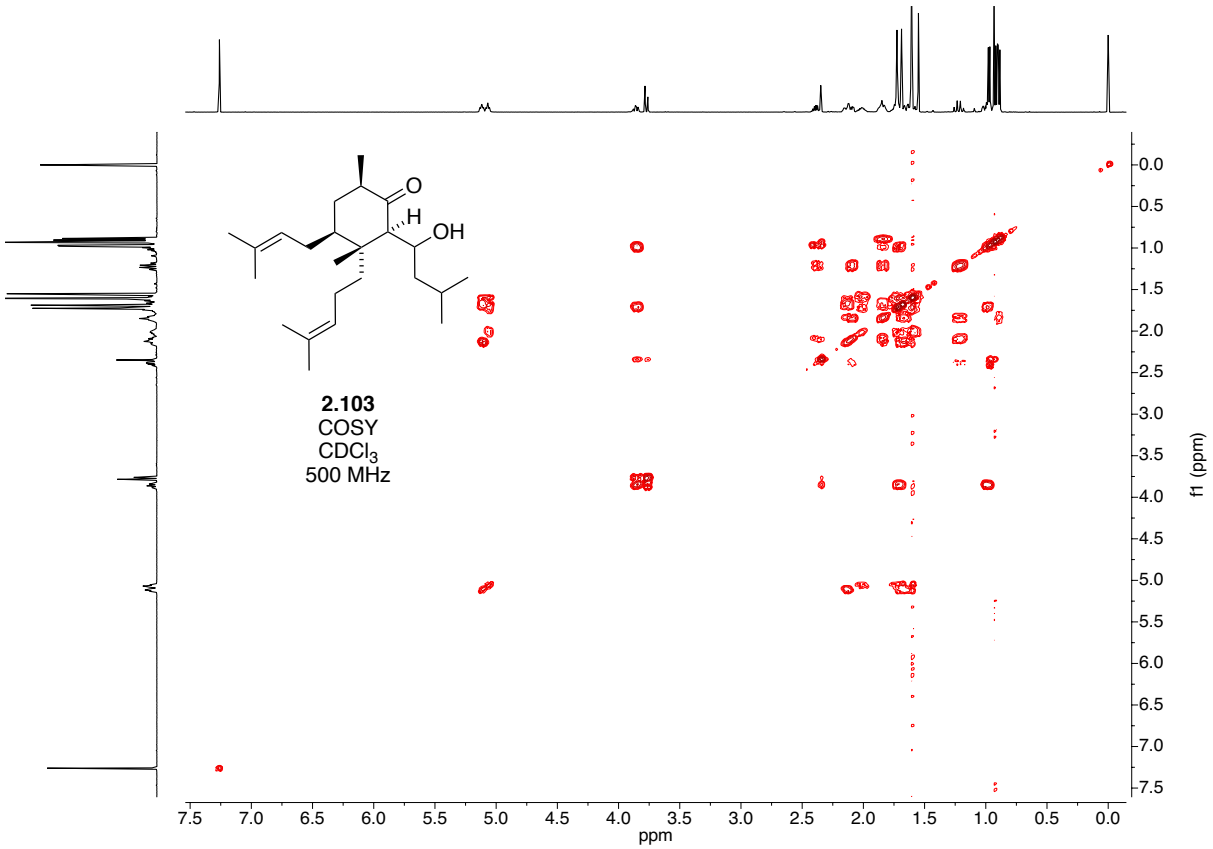

O
H
OTMS
2.102
COSY
CDCl3
500 MHz
ppm
f1 (ppm)

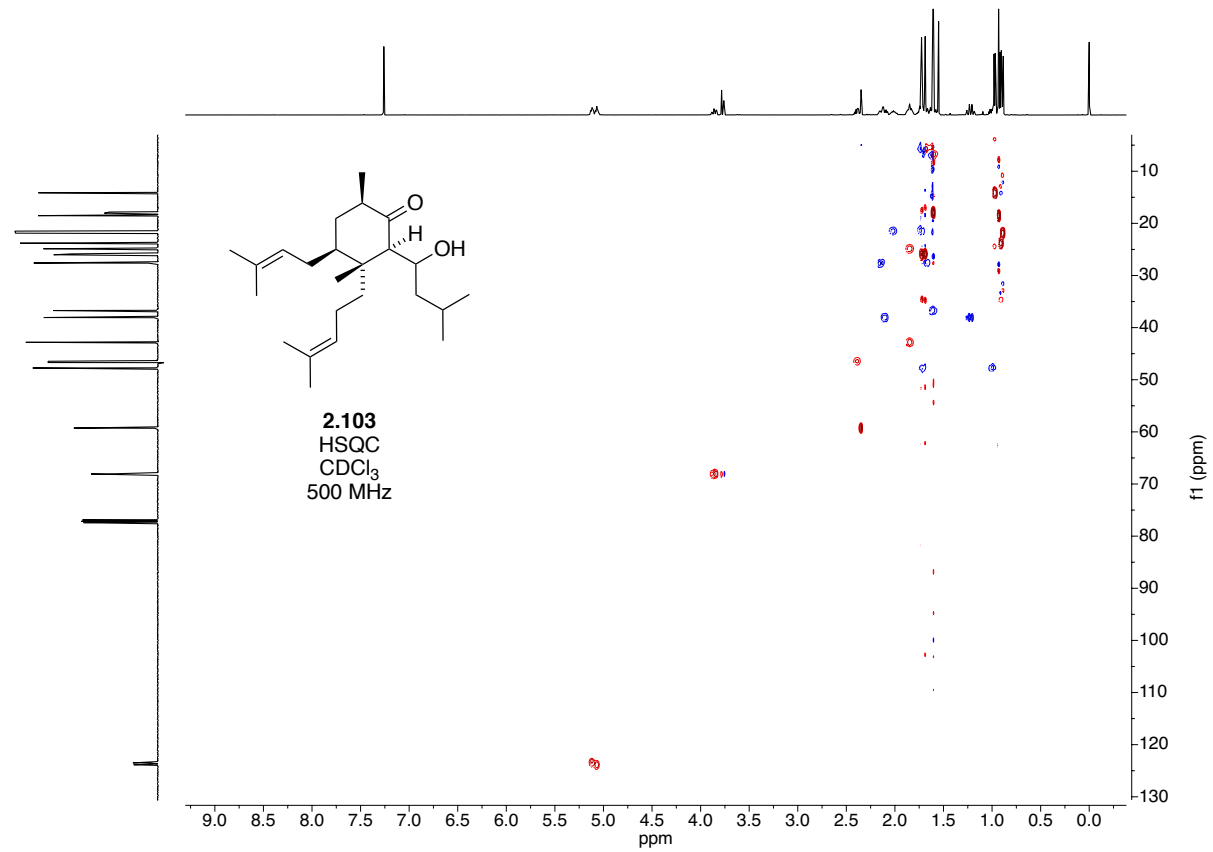

O
H
OTMS
2.102
HSQC
CDCl3
500 MHz
ppm
f1 (ppm)

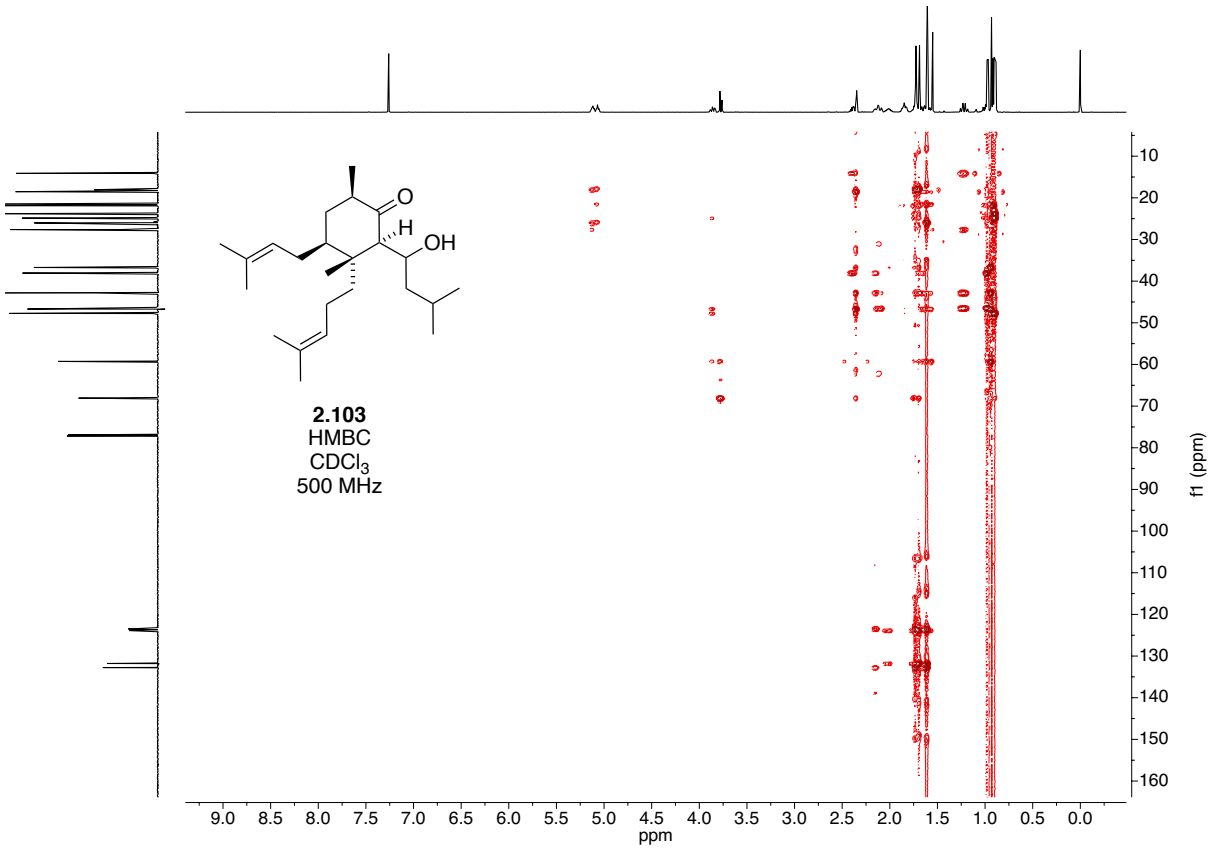

O
H
OTMS
2.102
HMBC
CDCl3
500 MHz
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210
f1 (ppm)

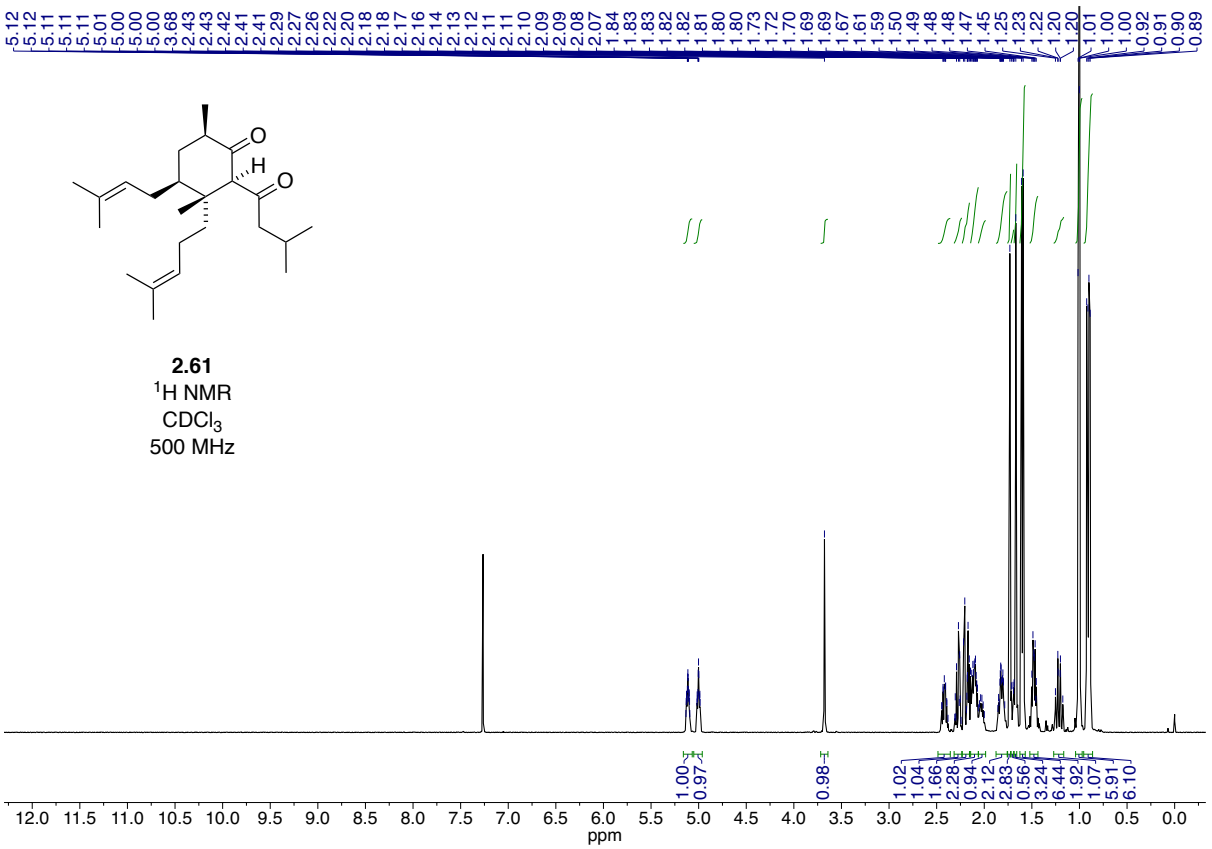

O
H
OH
2.103
1H NMR
CDCl3
500 MHz
ppm

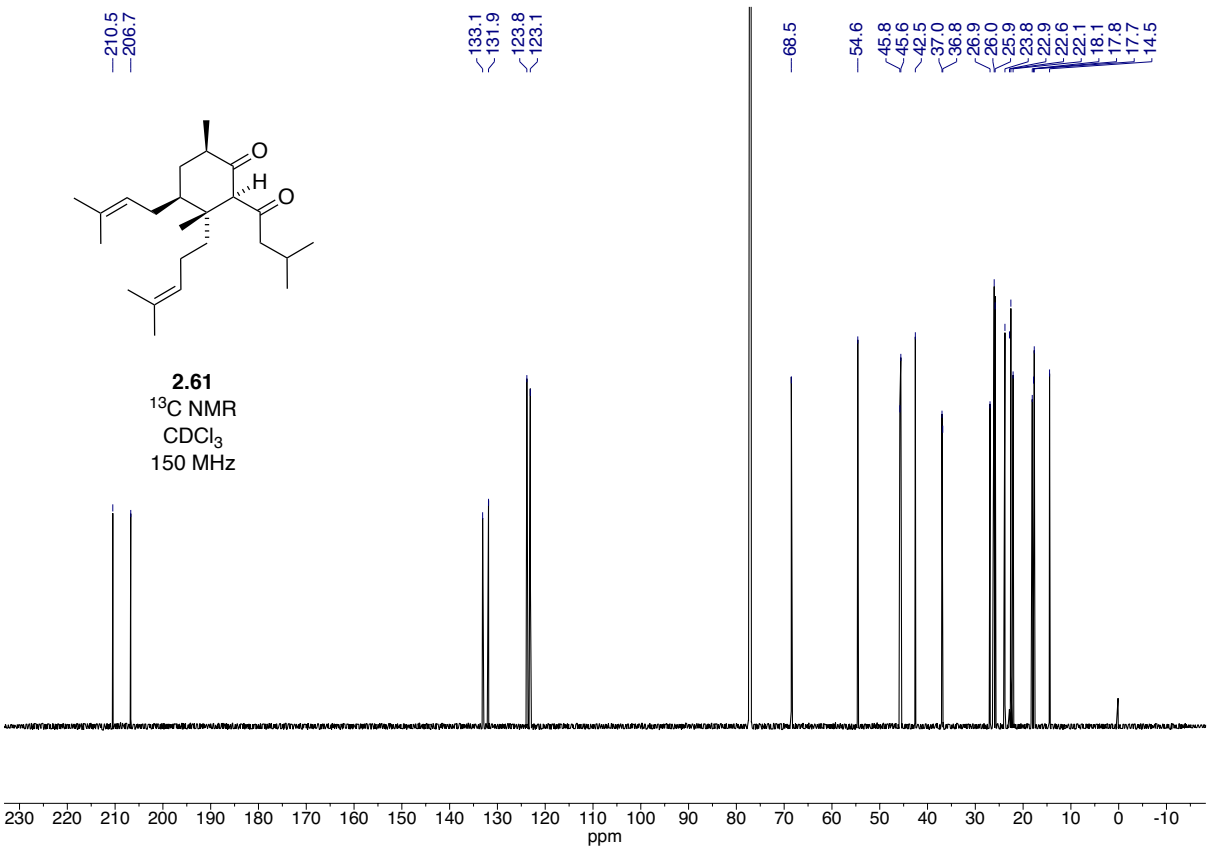

O
H
OH
2.103
13C NMR
CDCl3
125 MHz
ppm

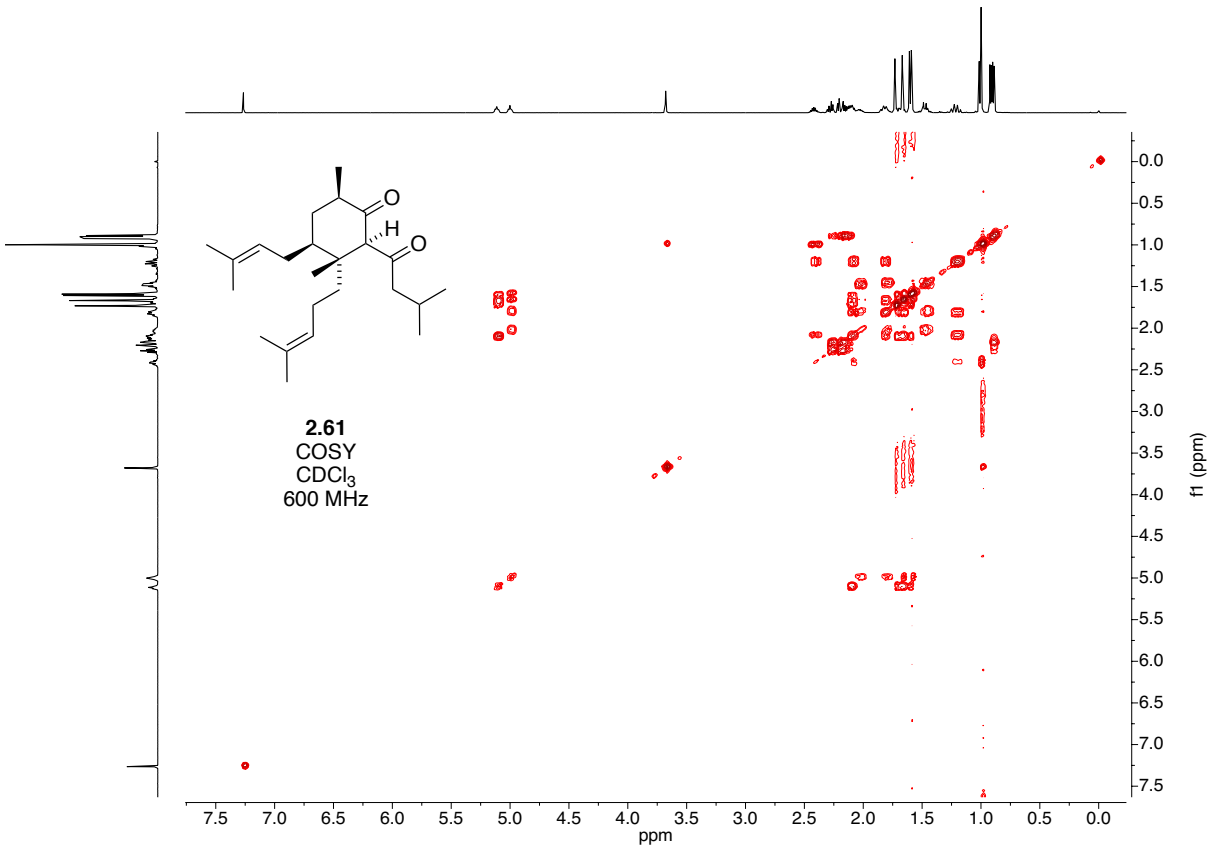

O
H
OH
2.103
COSY
CDCl3
500 MHz
ppm
f1 (ppm)

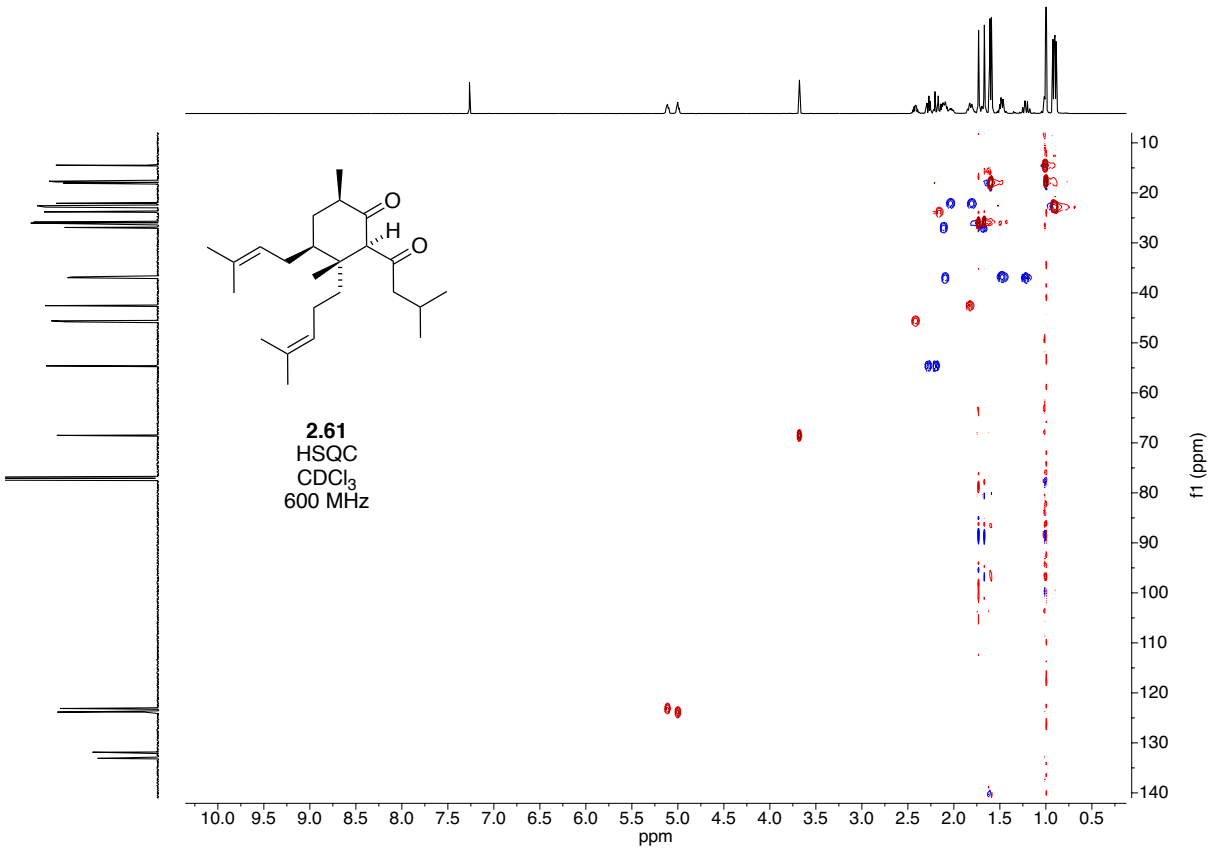

O
H
OH
2.103
HSQC
CDCl3
500 MHz
ppm
f1 (ppm)

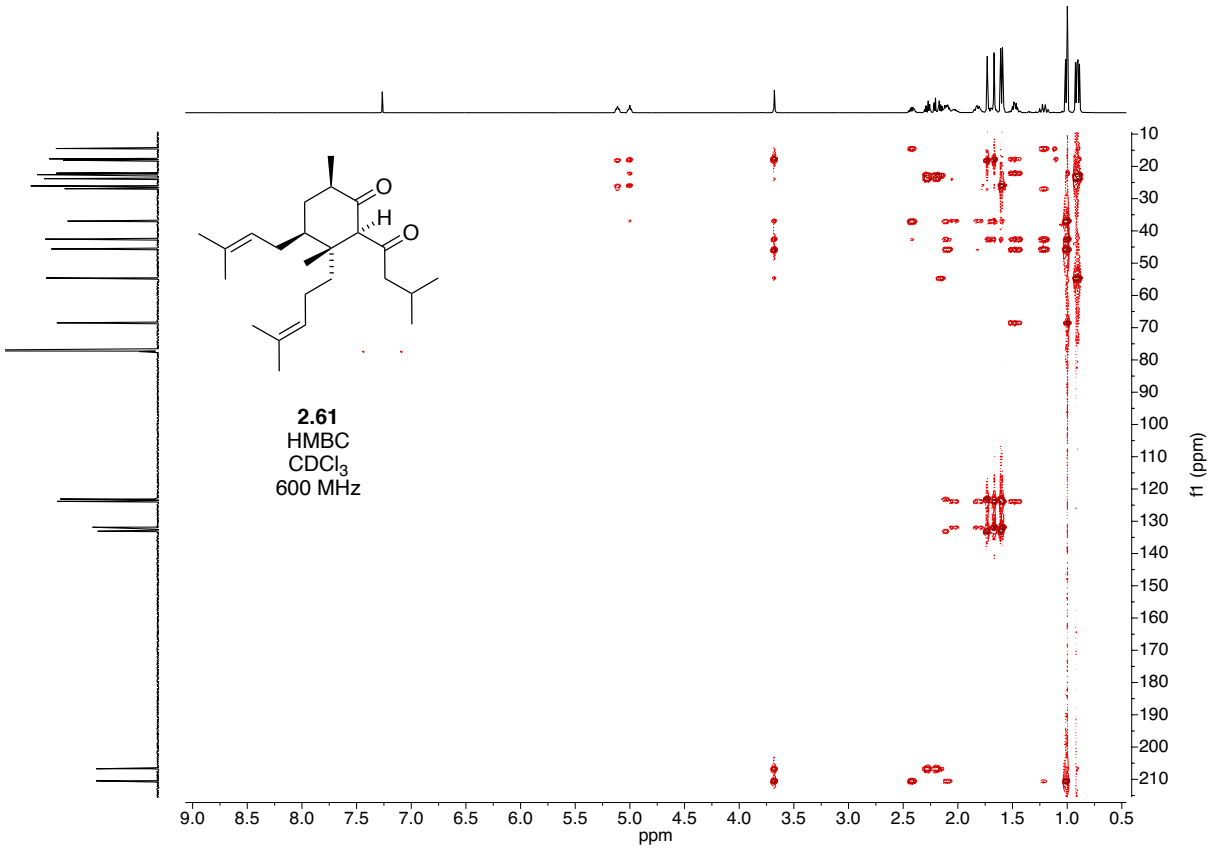

O
H
OH
2.103
HMBC
CDCl3
500 MHz
ppm
f1 (ppm)

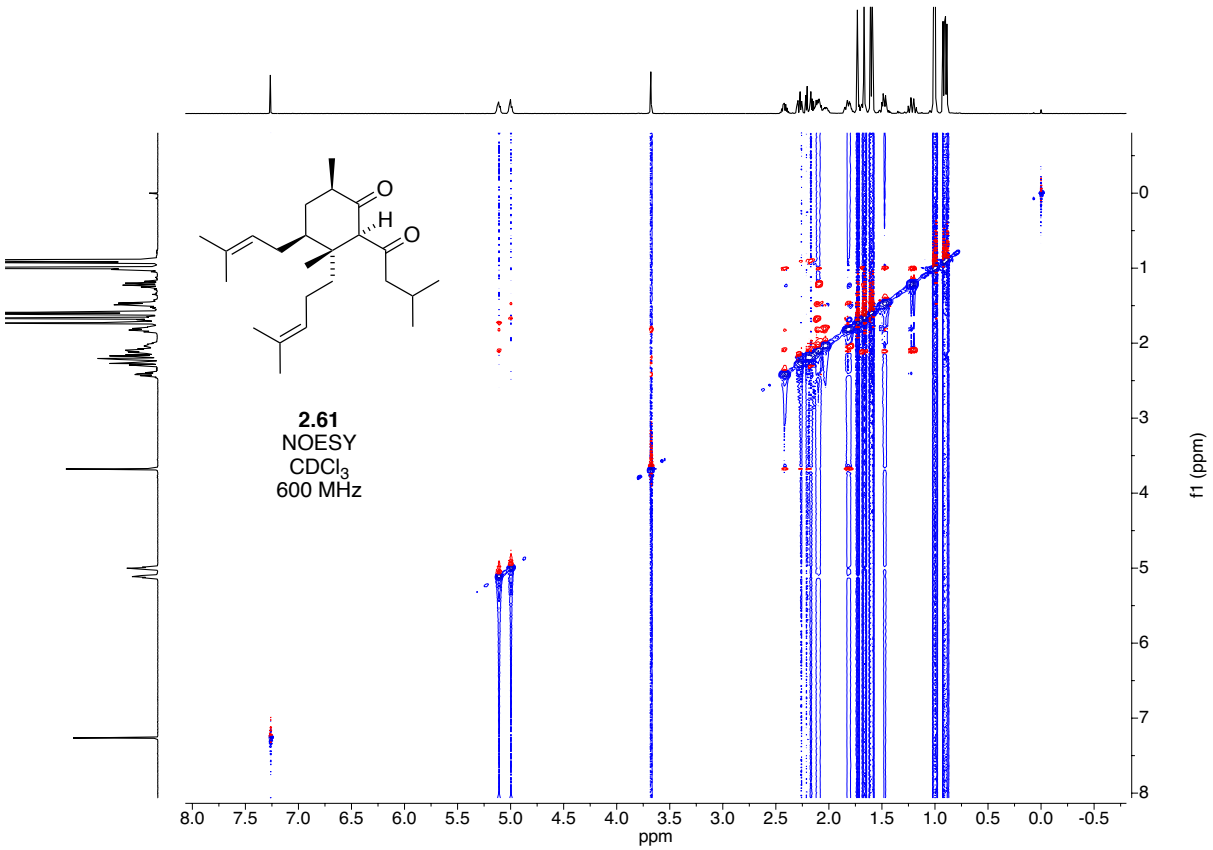

O
H
O
2.61
1H NMR
CDCl3
500 MHz
ppm

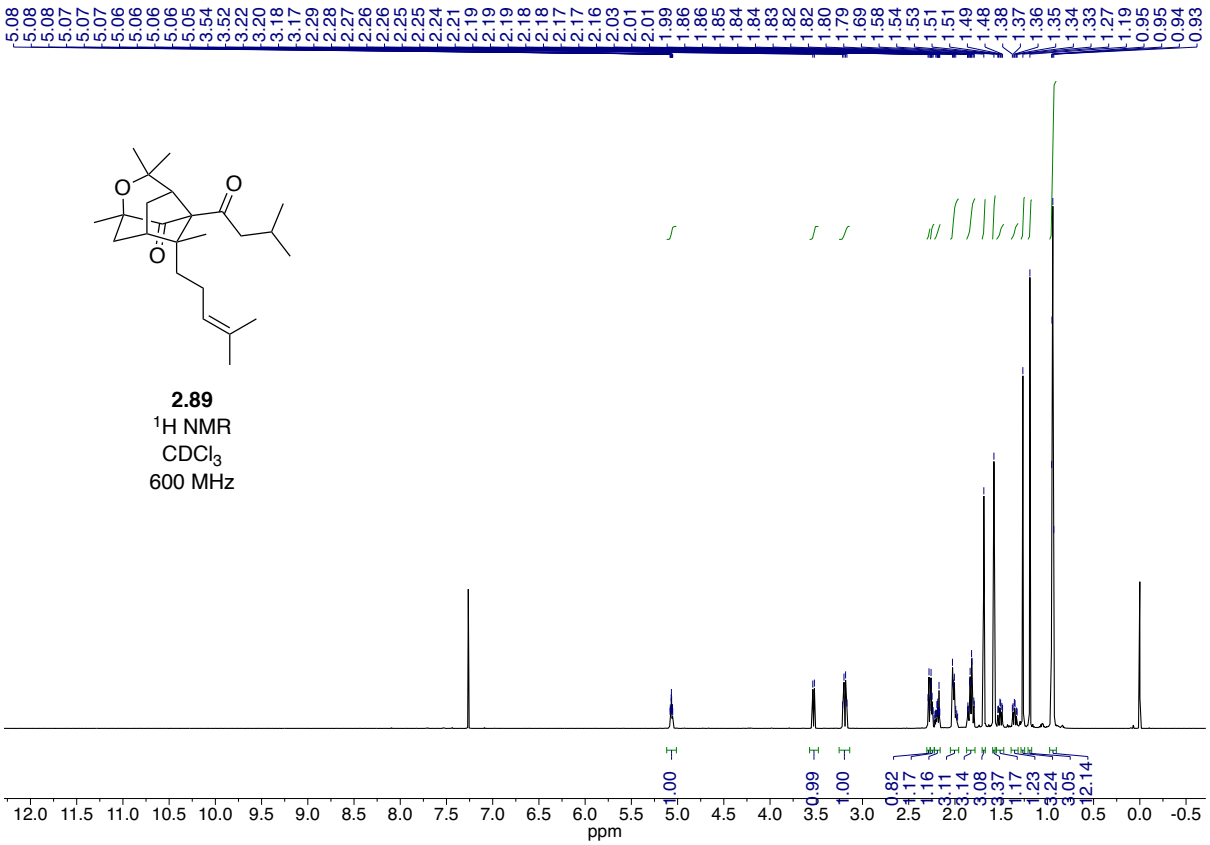

O
H
O
2.61
13C NMR
CDCl3
150 MHz
ppm

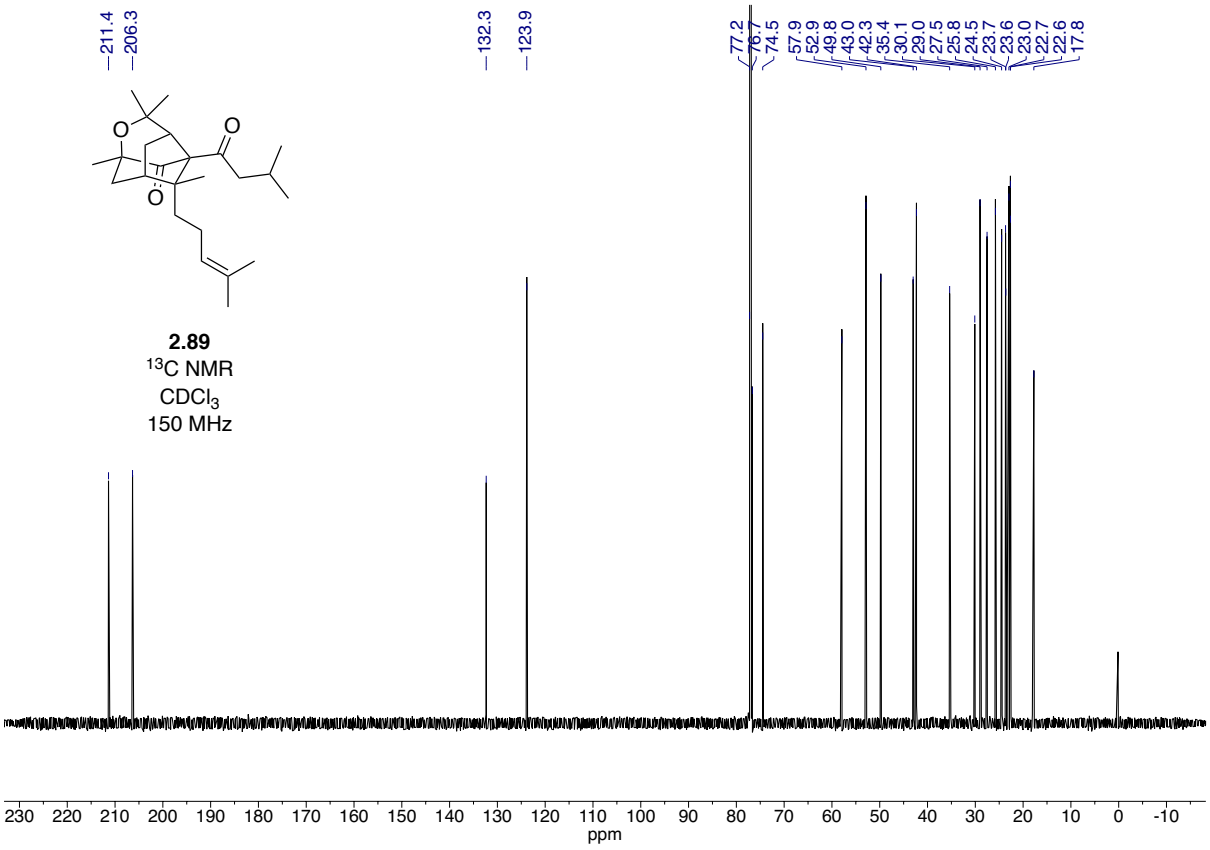

O
H
O
2.61
COSY
CDCl3
600 MHz
ppm
f1 (ppm)

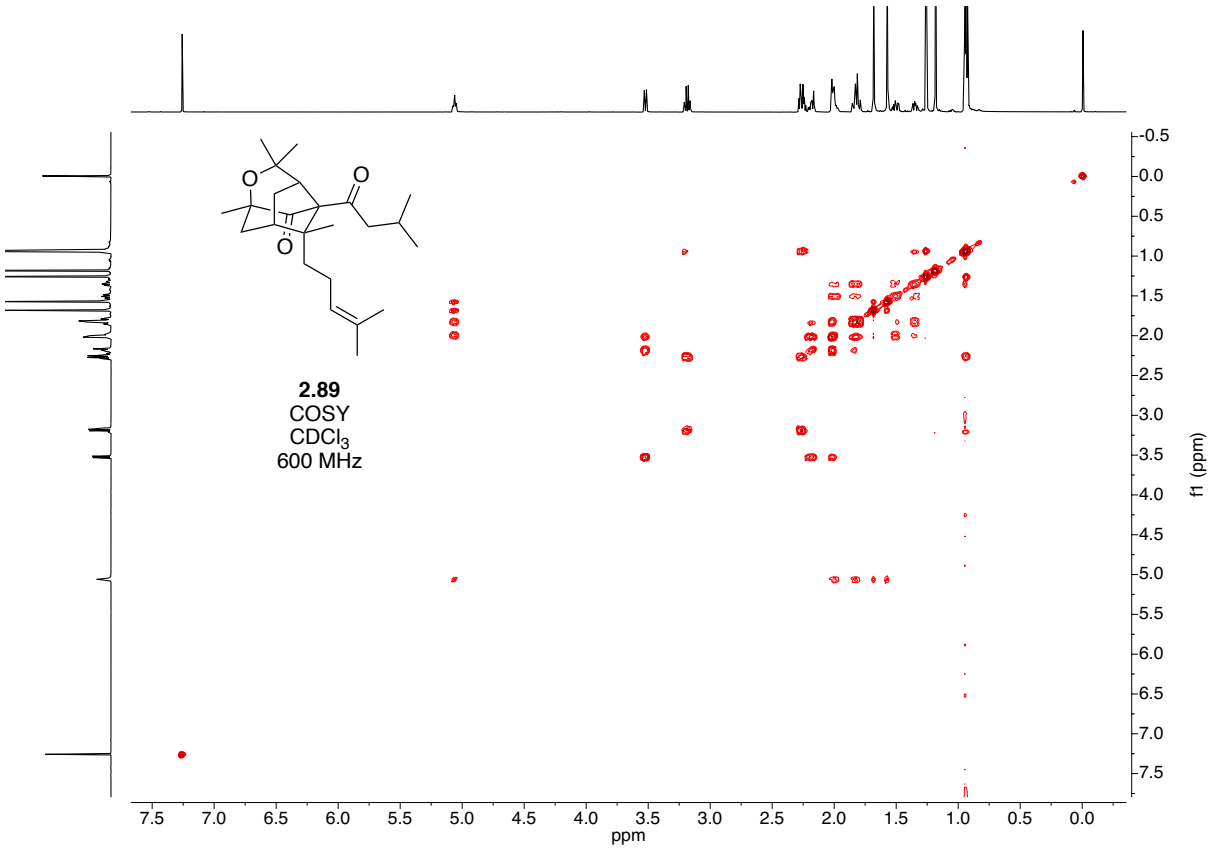

O
H
O
2.61
HSQC
CDCl3
600 MHz
ppm
f1 (ppm)

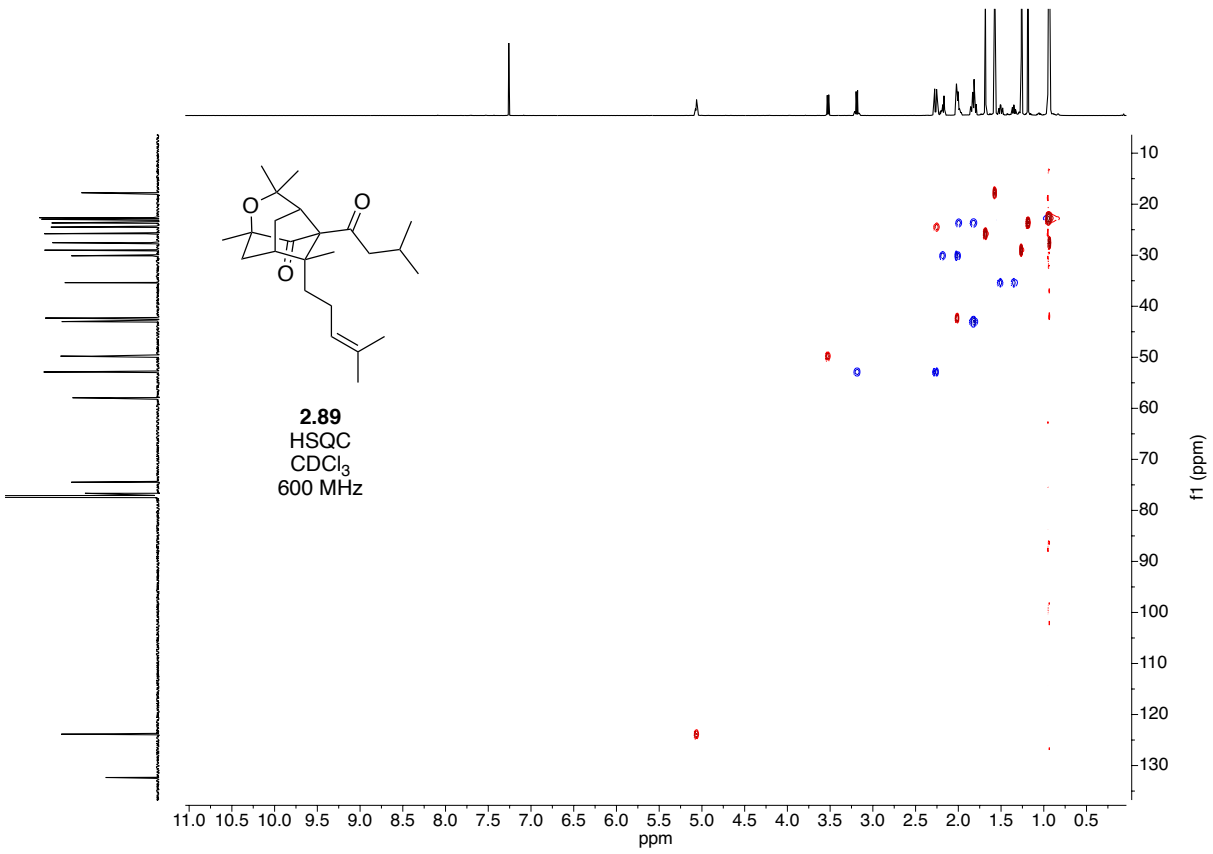

O
H
O
2.61
HMBC
CDCl3
600 MHz
f1 (ppm)
ppm

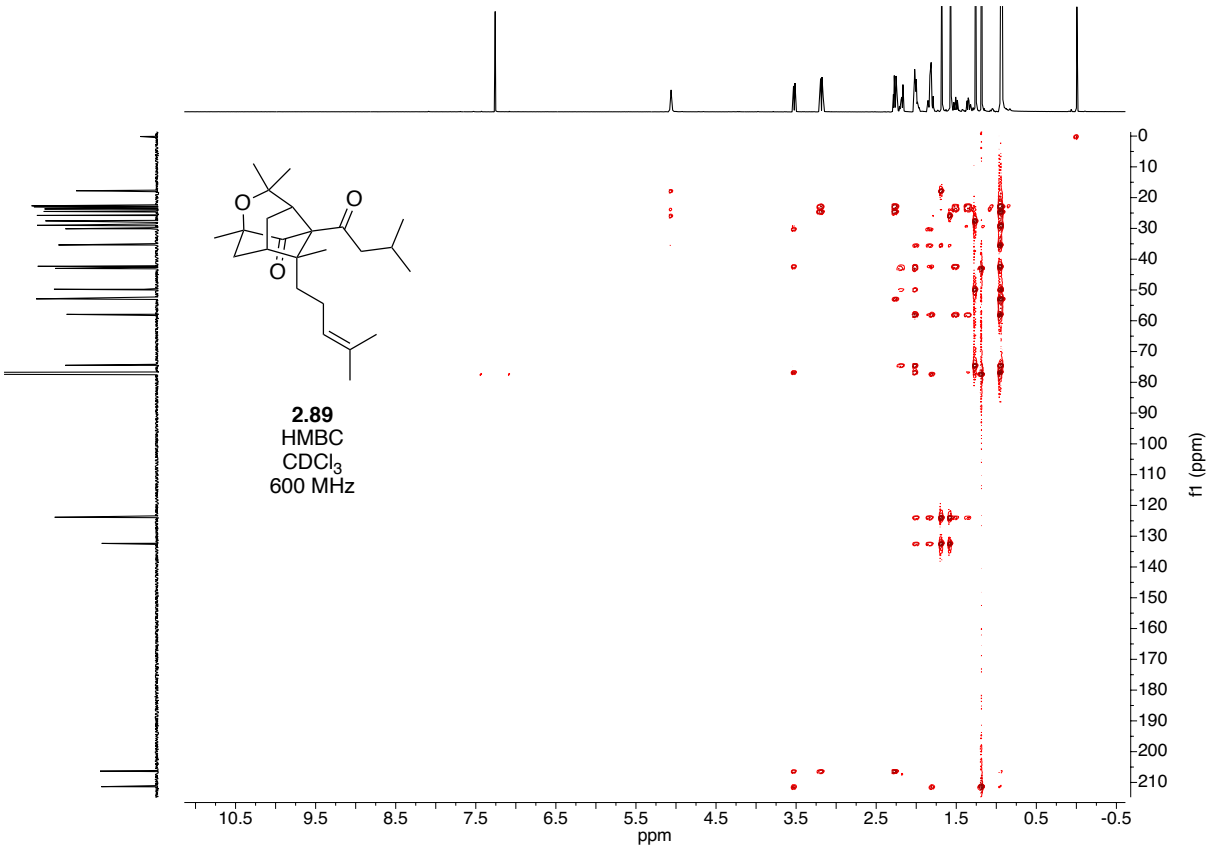

O
H
O
2.61
NOESY
CDCl3
600 MHz
f1 (ppm)
ppm

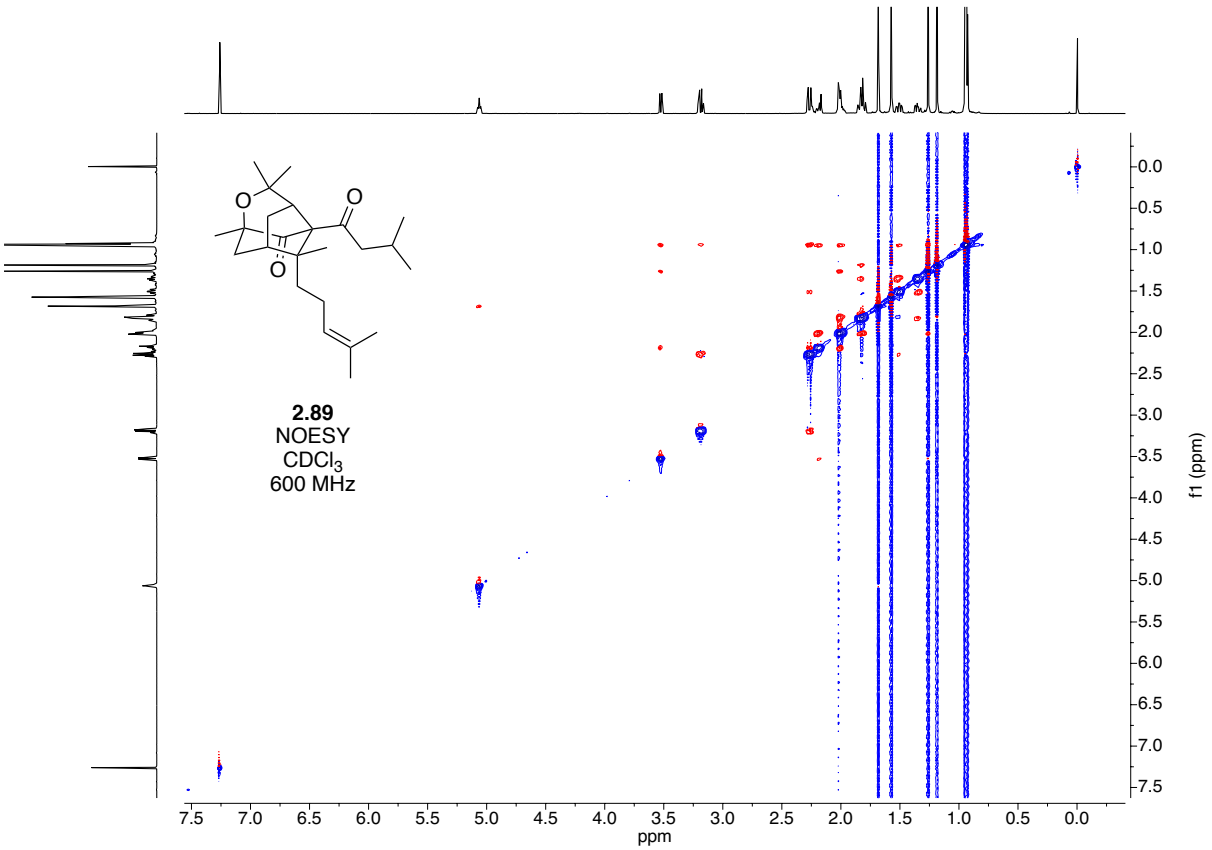

5.08 5.08 5.08 5.07 5.07 5.07 5.06 5.06 5.06 5.06 5.05 3.54 3.52 3.22 3.20 3.18 3.17 2.29 2.28 2.27 2.26 2.26 2.25 2.25 2.24 2.21 2.19 2.19 2.19 2.18 2.18 2.17 2.17 2.16 2.03 2.01 2.01 1.99 1.86 1.86 1.85 1.84 1.84 1.83 1.82 1.82 1.80 1.79 1.69 1.58 1.54 1.53 1.51 1.51 1.49 1.48 1.38 1.37 1.36 1.35 1.34 1.33 1.27 1.19 0.95 0.95 0.94 0.93
O
O
O
2.89
1H NMR
CDCl3
600 MHz
1.00 0.99 1.00 0.82 1.17 1.16 3.11 3.14 3.08 3.37 1.17 1.23 3.24 3.05 12.14
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

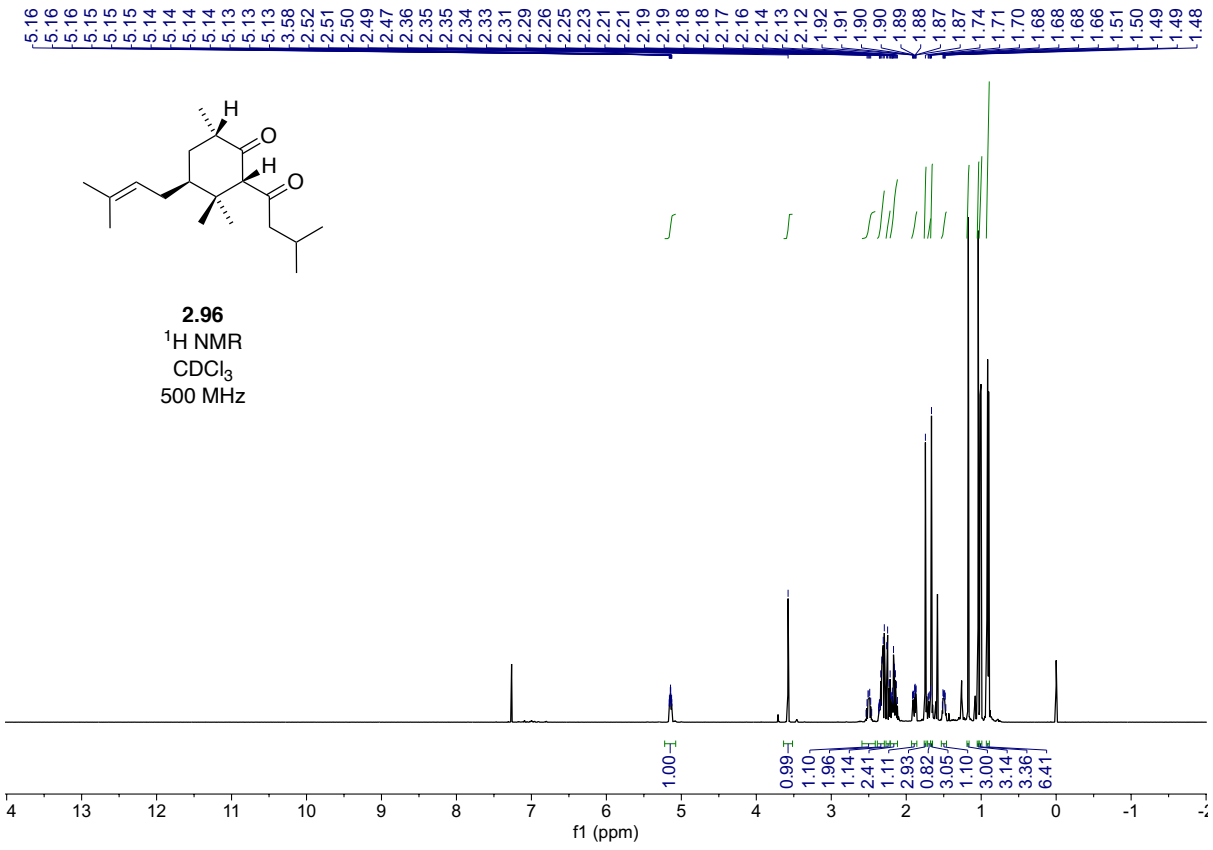

211.4 206.3 132.3 123.9 77.2 76.7 74.5 57.9 52.9 49.8 43.0 42.3 35.4 30.1 29.0 27.5 25.8 24.5 23.7 23.6 23.0 22.7 22.6 17.8
O
O
O
2.89
13C NMR
CDCl3
150 MHz
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

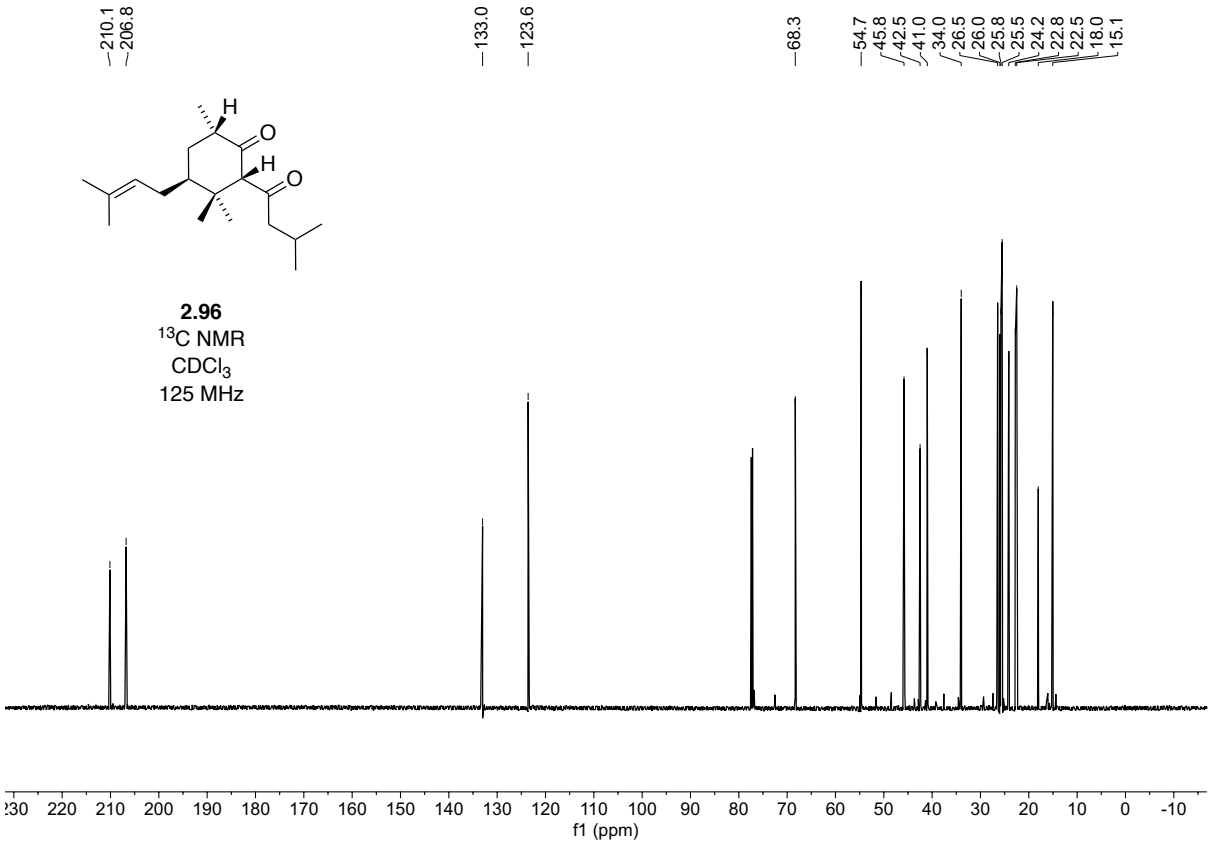

O
O
O
2.89
COSY
CDCl3
600 MHz
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm
-0.5 0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5
f1 (ppm)

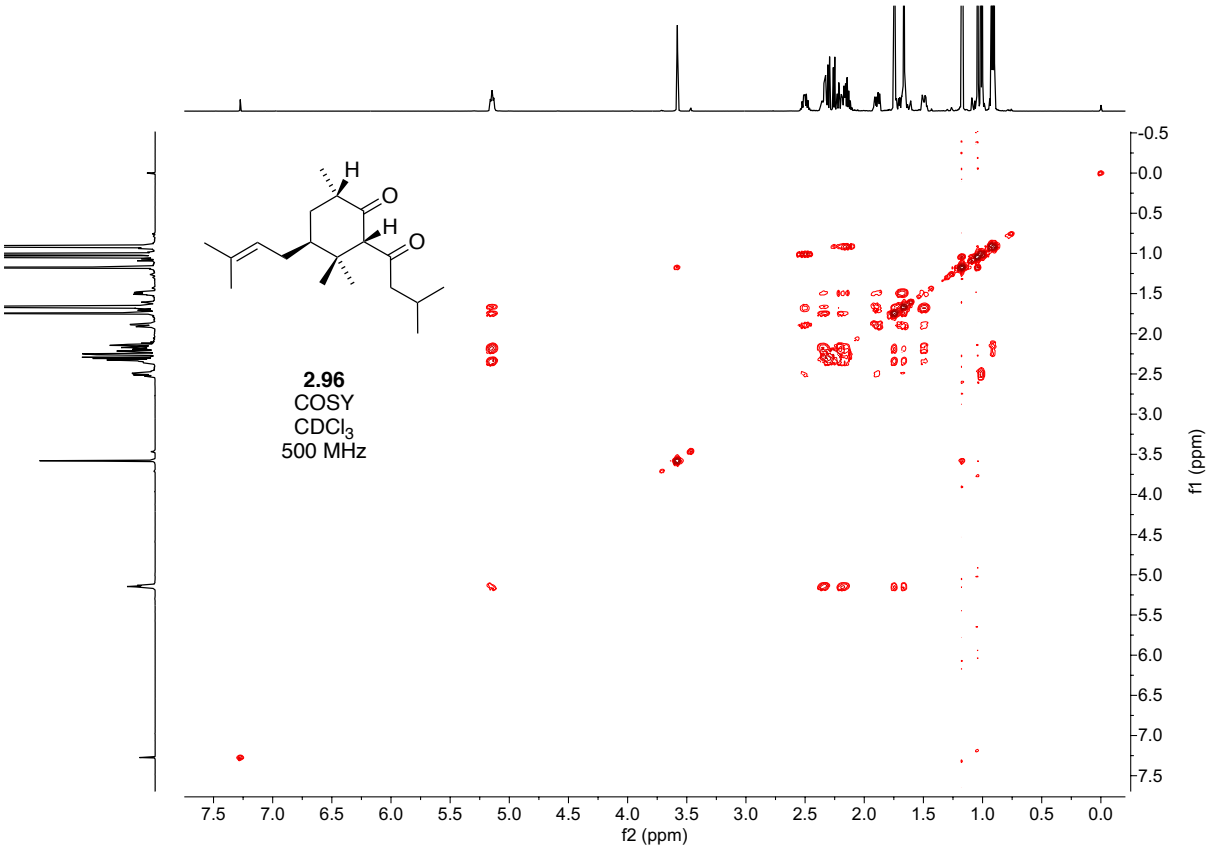

O
O
O
2.89
HSQC
CDCl3
600 MHz
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm
10 20 30 40 50 60 70 80 90 100 110 120 130
f1 (ppm)

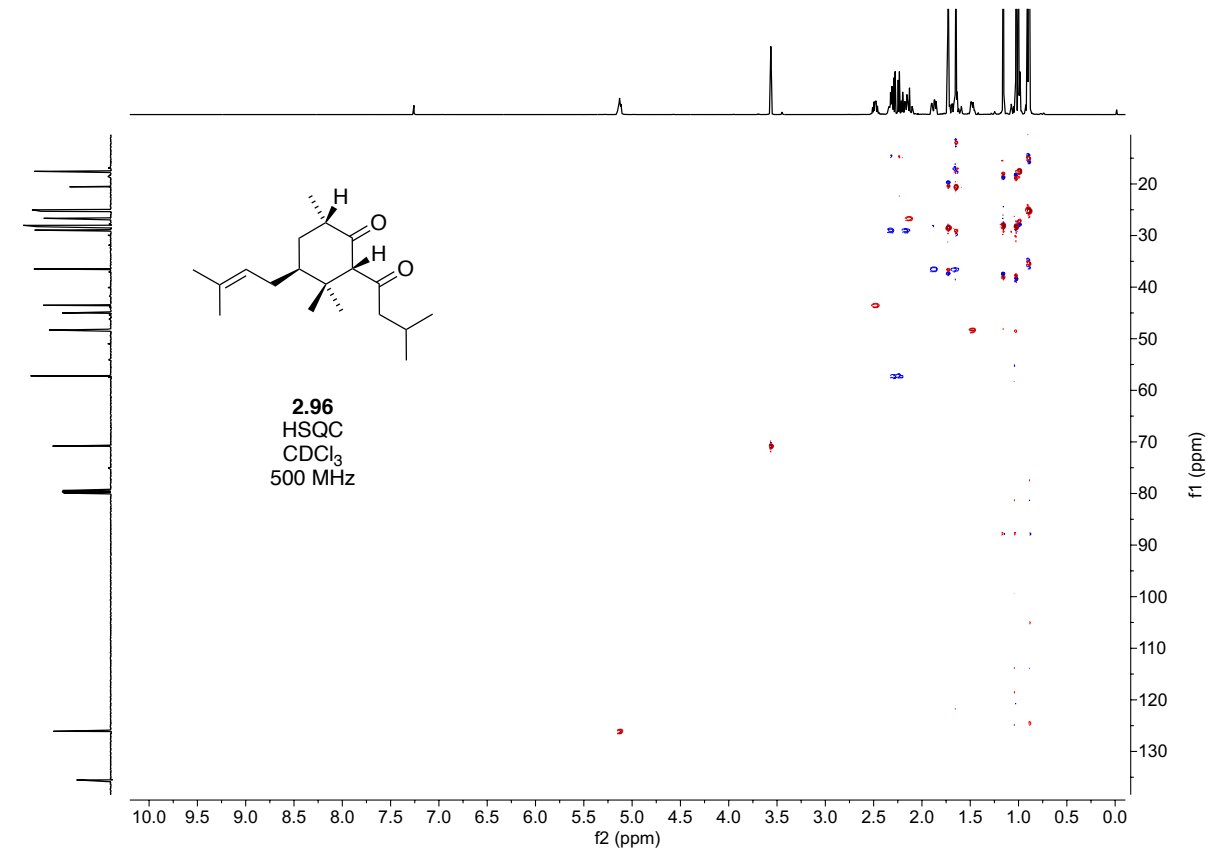

O
O
O
2.89
HMBC
CDCl3
600 MHz
f1 (ppm)
ppm

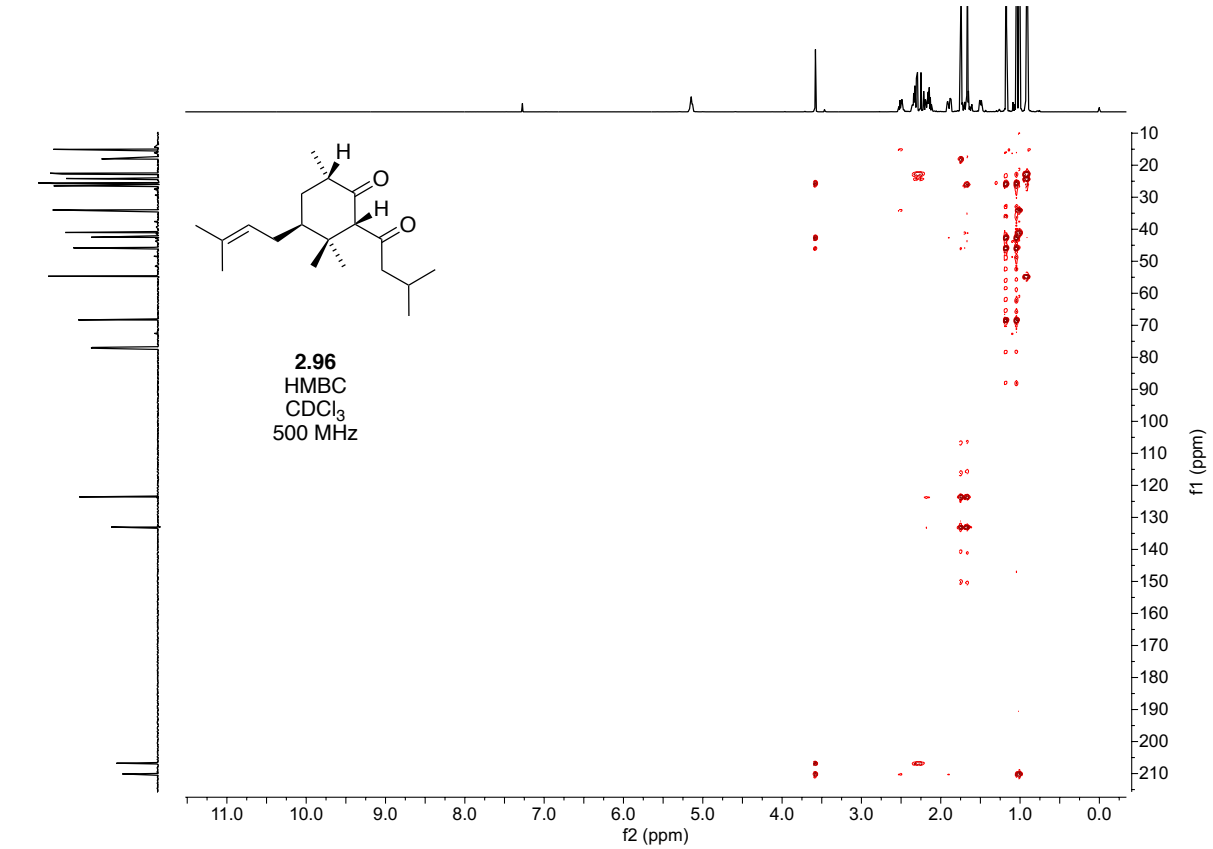

O
O
O
2.89
NOESY
CDCl3
600 MHz
f1 (ppm)
ppm

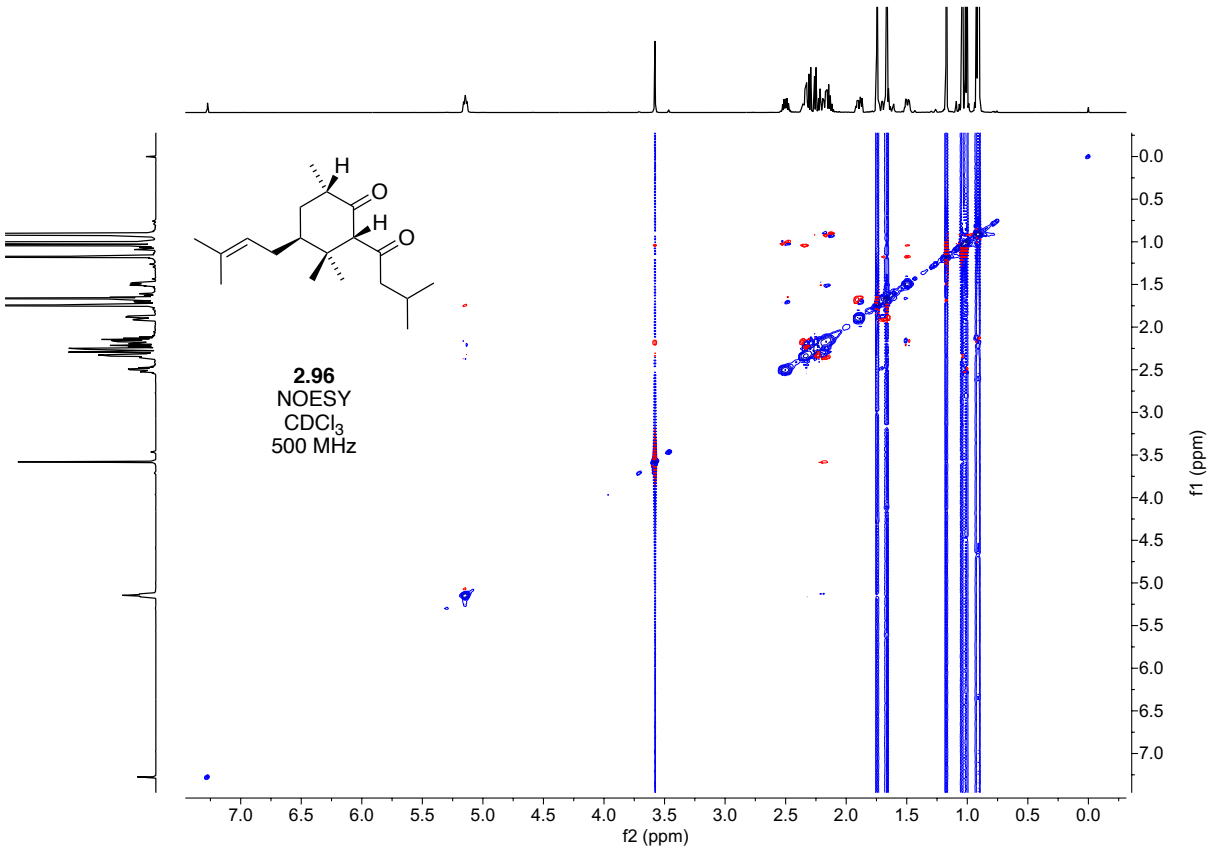

5.16 5.16 5.16 5.15 5.15 5.15 5.14 5.14 5.14 5.14 5.13 5.13 5.13 3.58 2.52 2.51 2.50 2.49 2.47 2.36 2.35 2.35 2.34 2.33 2.31 2.29 2.26 2.25 2.23 2.21 2.21 2.19 2.19 2.18 2.18 2.17 2.16 2.14 2.13 2.12 1.92 1.91 1.90 1.90 1.89 1.88 1.87 1.87 1.74 1.71 1.70 1.68 1.68 1.68 1.66 1.51 1.50 1.49 1.49 1.48
H
O
H
O
2.96
1H NMR
CDCl3
500 MHz
1.00 0.99 1.10 1.96 1.14 2.41 1.11 2.93 0.82 3.05 1.10 3.00 3.14 3.36 6.41
f1 (ppm)

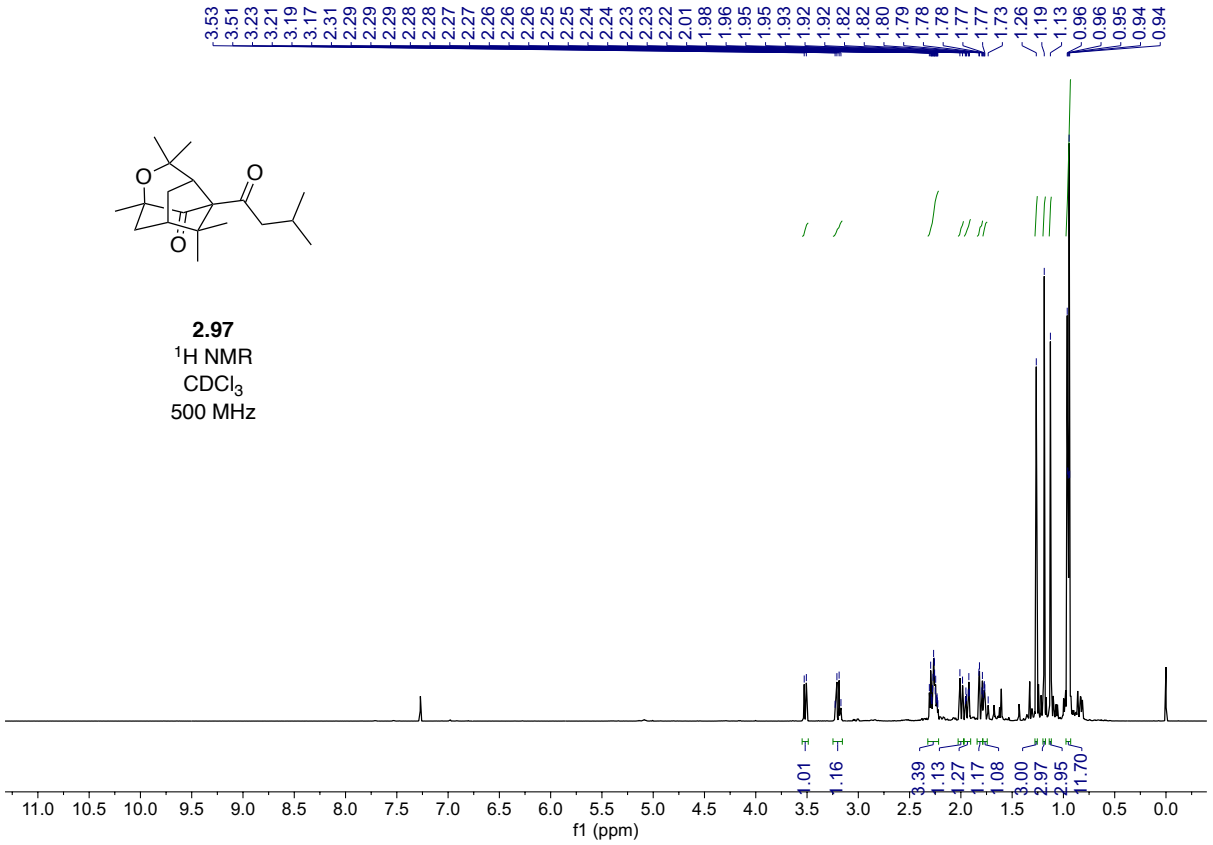

210.1
206.8
133.0
123.6
68.3
54.7
45.8
42.5
41.0
34.0
26.5
26.0
25.8
25.5
24.2
22.8
22.5
18.0
15.1
H
O
H
O
2.96
13C NMR
CDCl3
125 MHz
f1 (ppm)


H
O
H
O
2.96
COSY
CDCl3
500 MHz
f1 (ppm)
f2 (ppm)

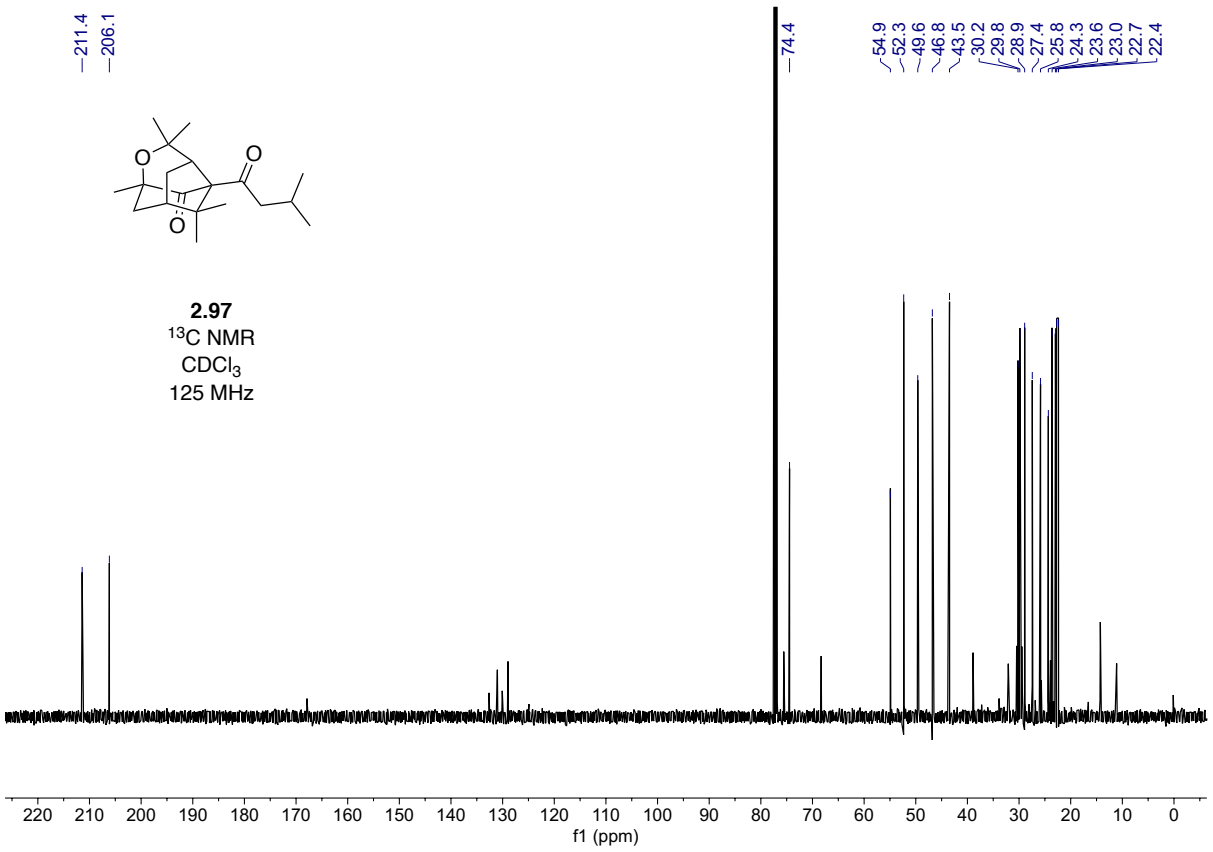

H
O
H
O
2.96
HSQC
CDCl3
500 MHz
f1 (ppm)
f2 (ppm)


H
O
H
O
2.96
HMBC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

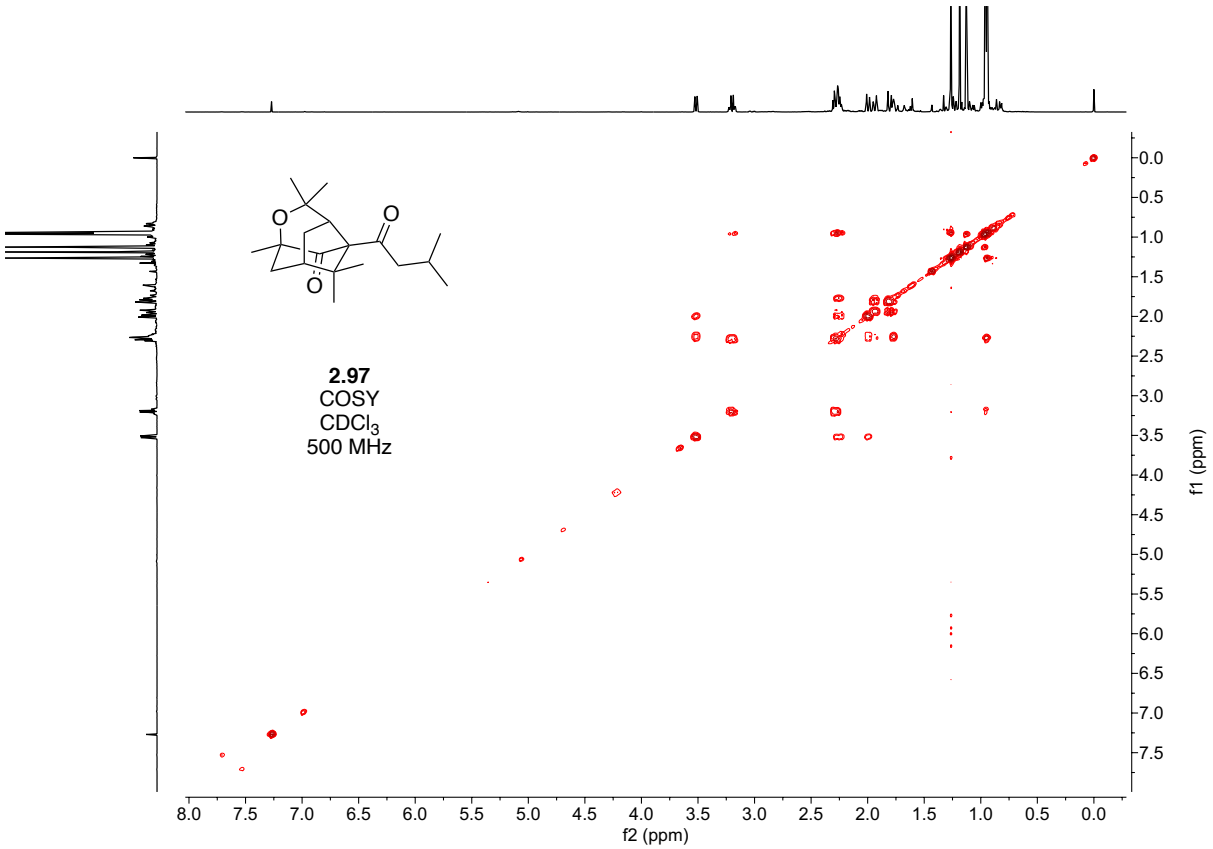

H
O
H
O
2.96
NOESY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

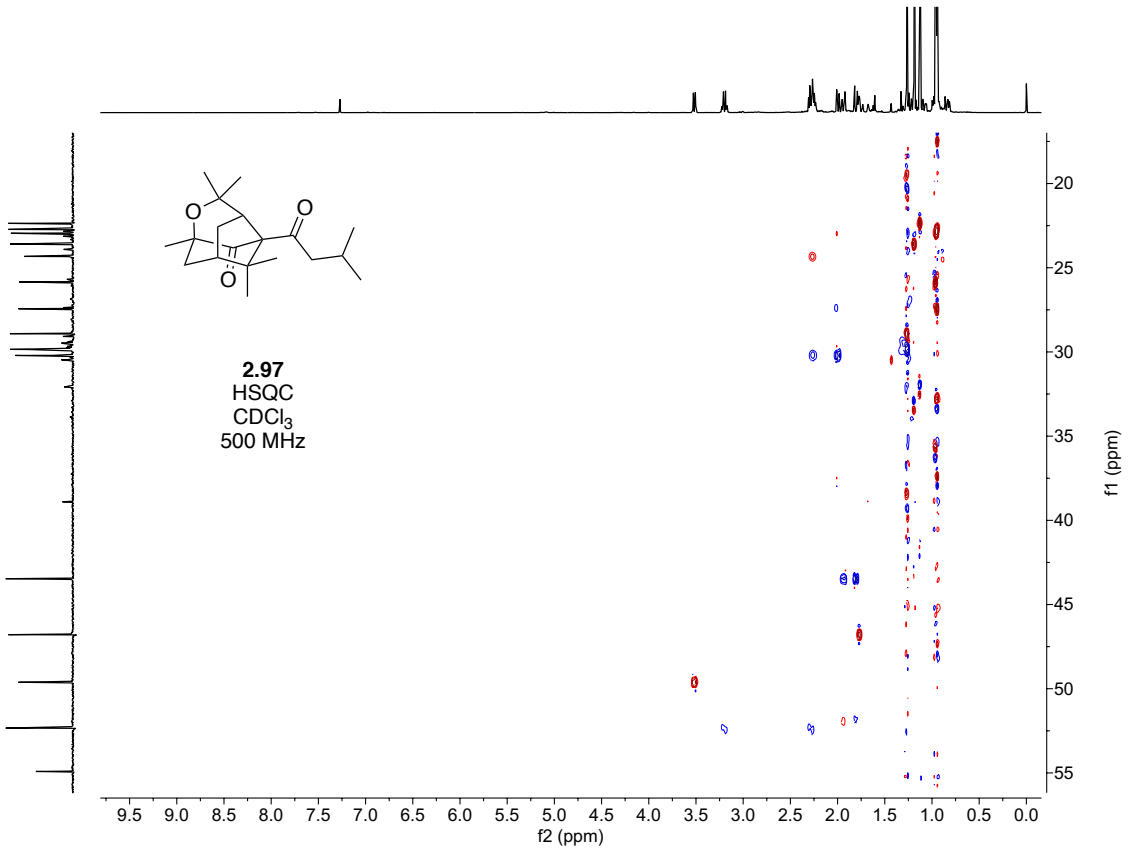


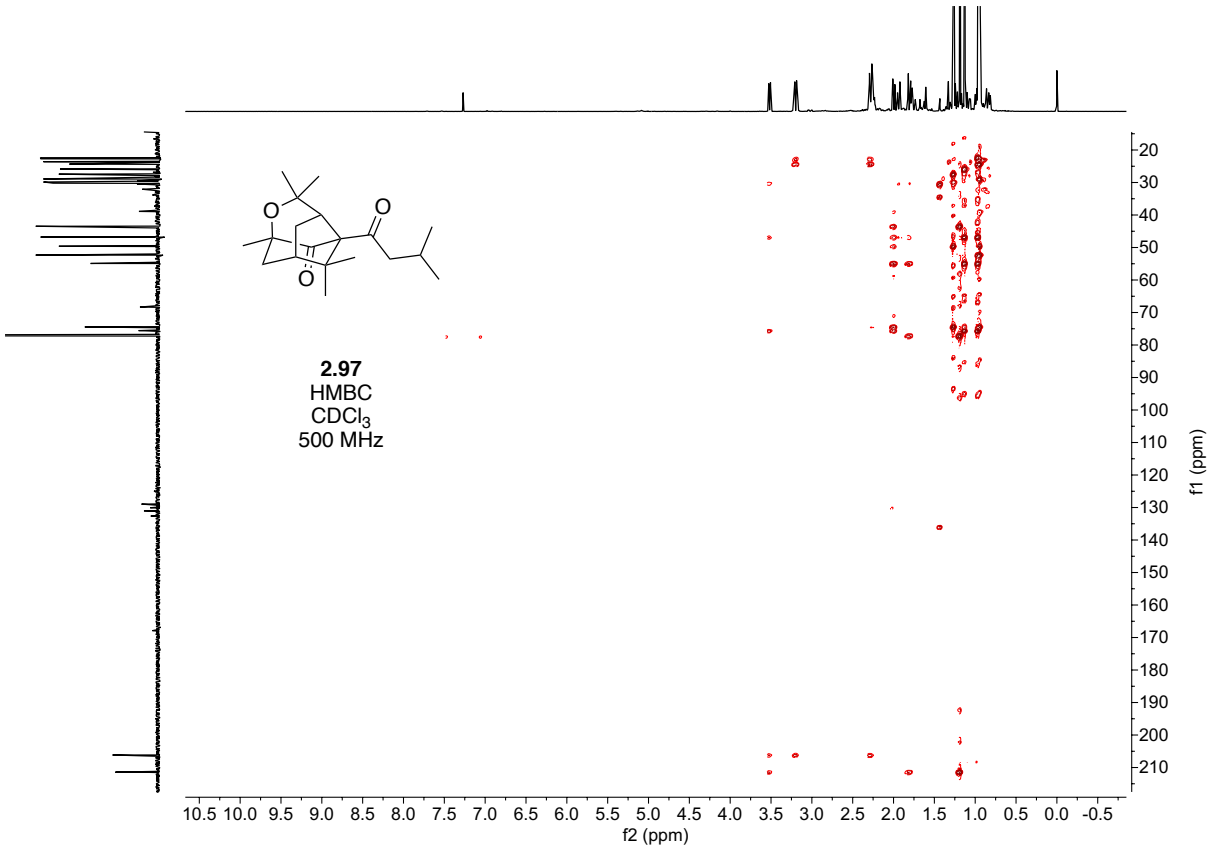
2.97
^{1}H NMR
$CDCl_3$
500 MHz

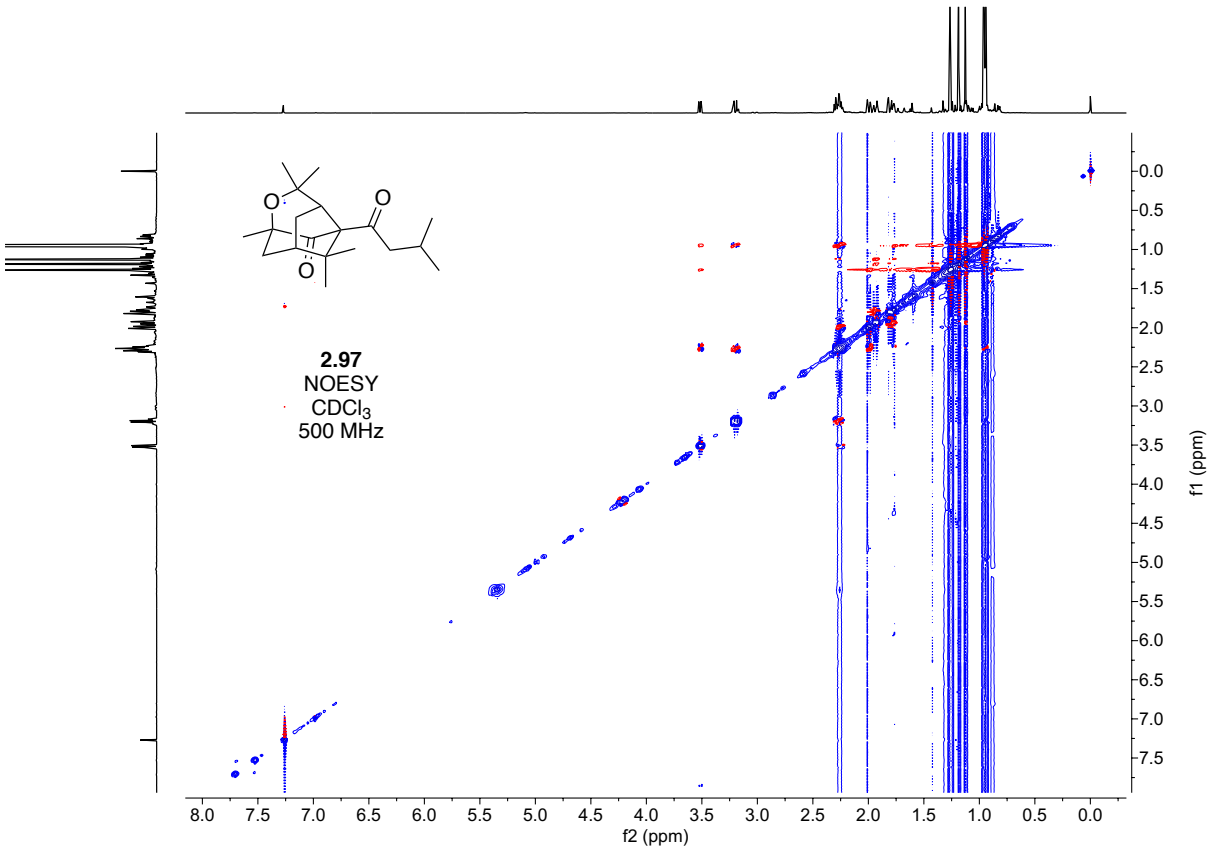


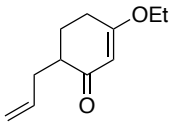
2.97
^{13}C NMR
$CDCl_3$
125 MHz


O
O
O
2.97
COSY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

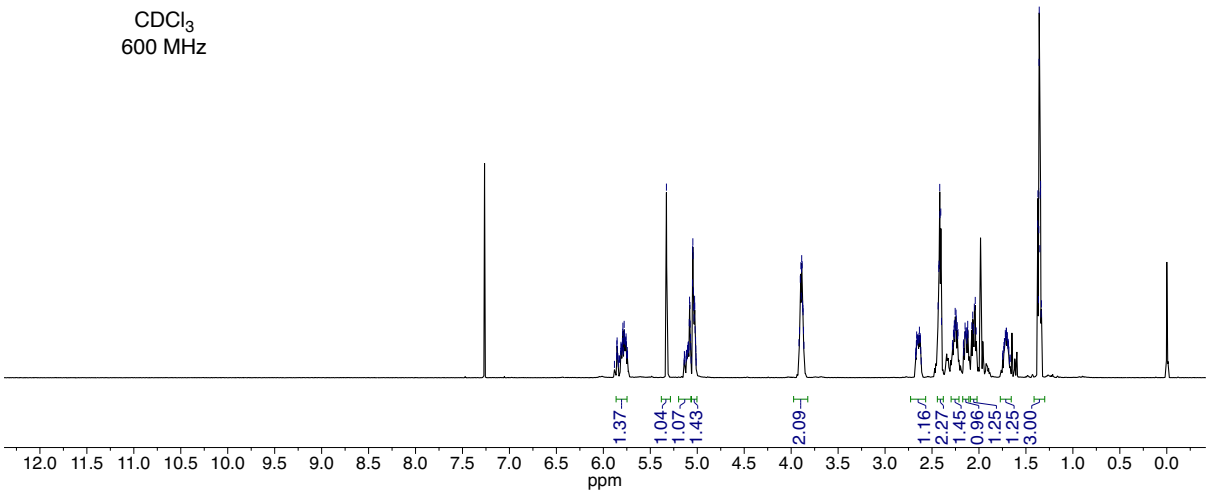

O
O
O
2.97
HSQC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

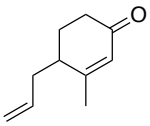

2.97
HMBC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)


2.97
NOESY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

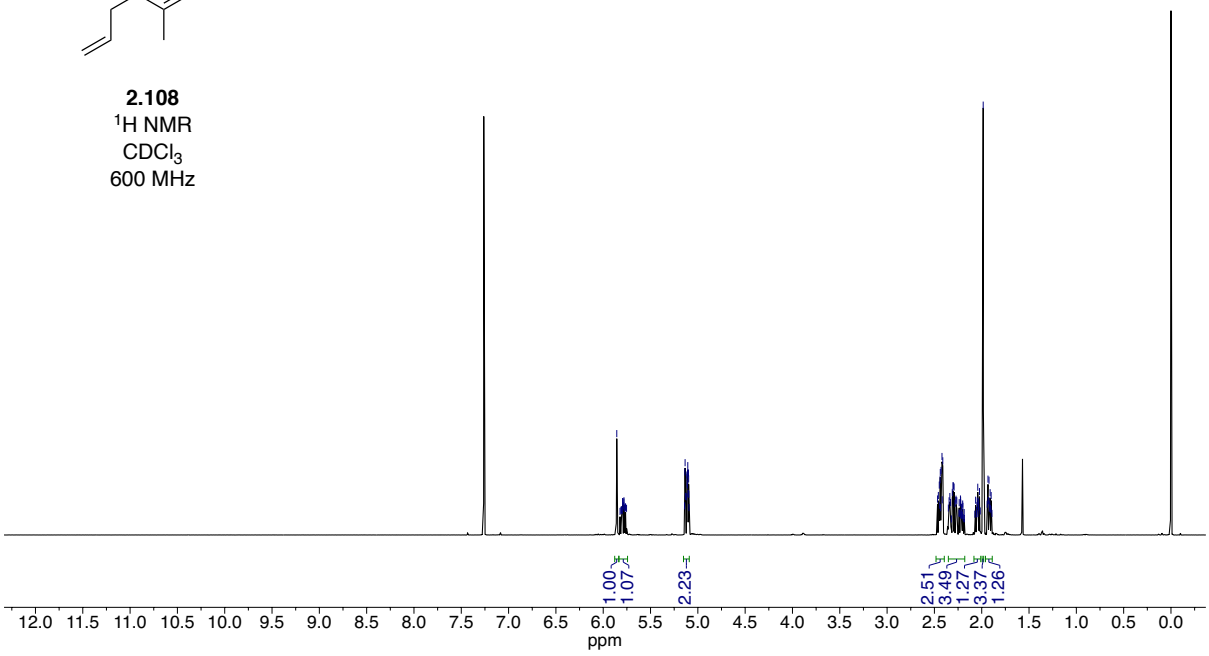


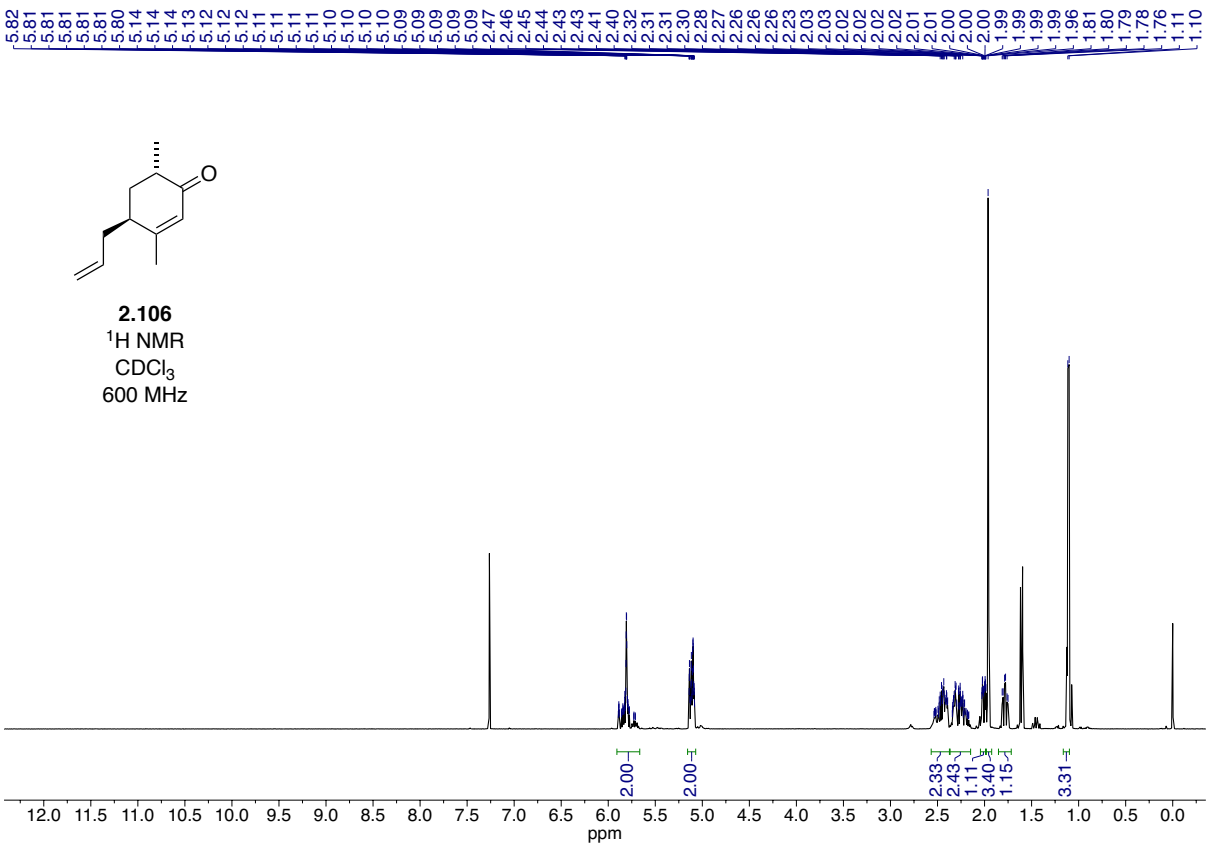
2.107
^{1}H NMR
$CDCl_3$
600 MHz

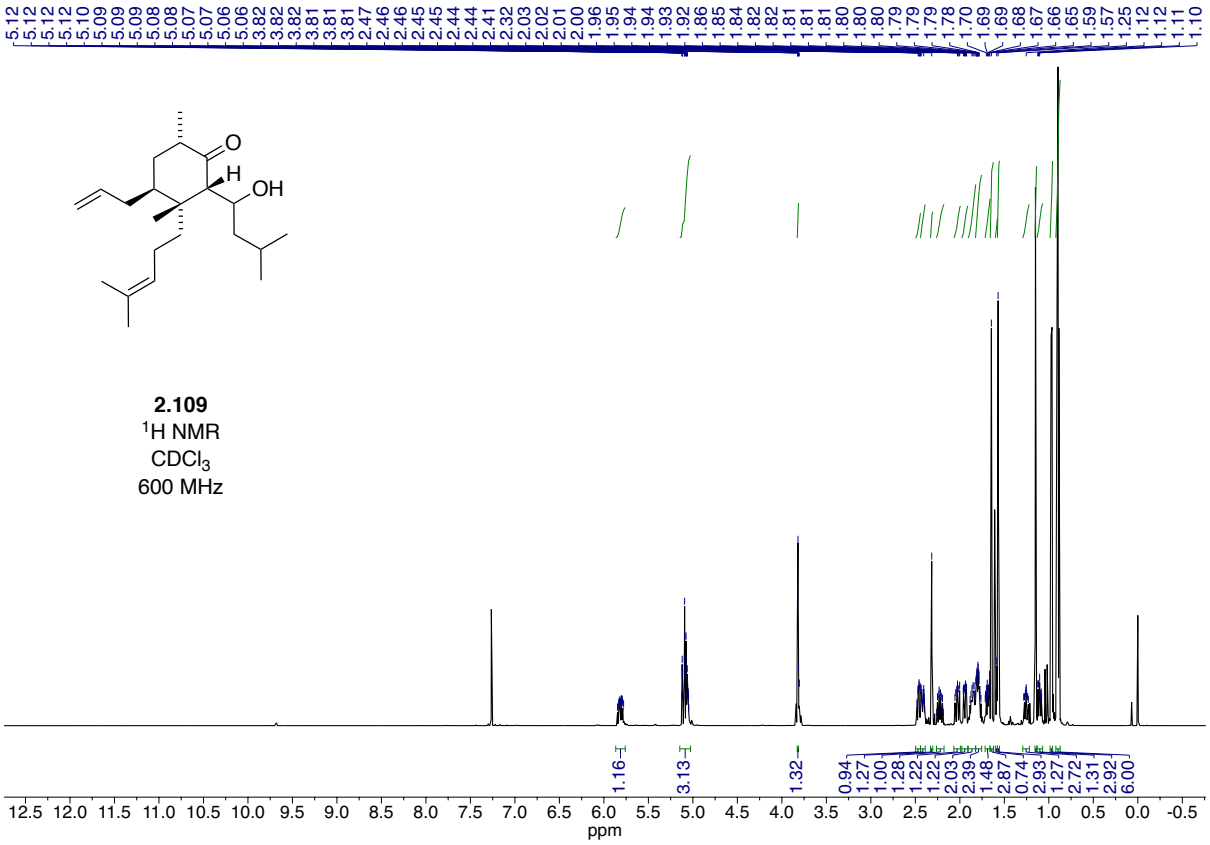


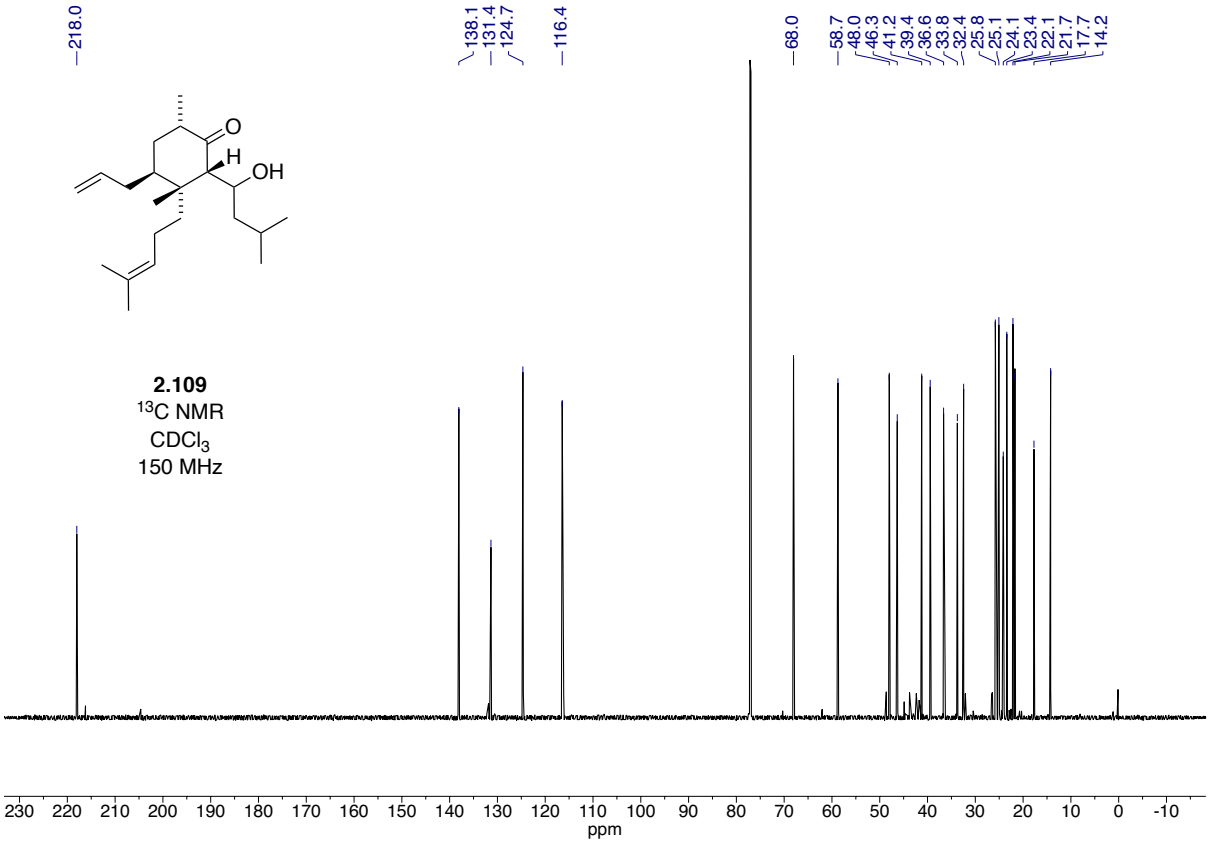


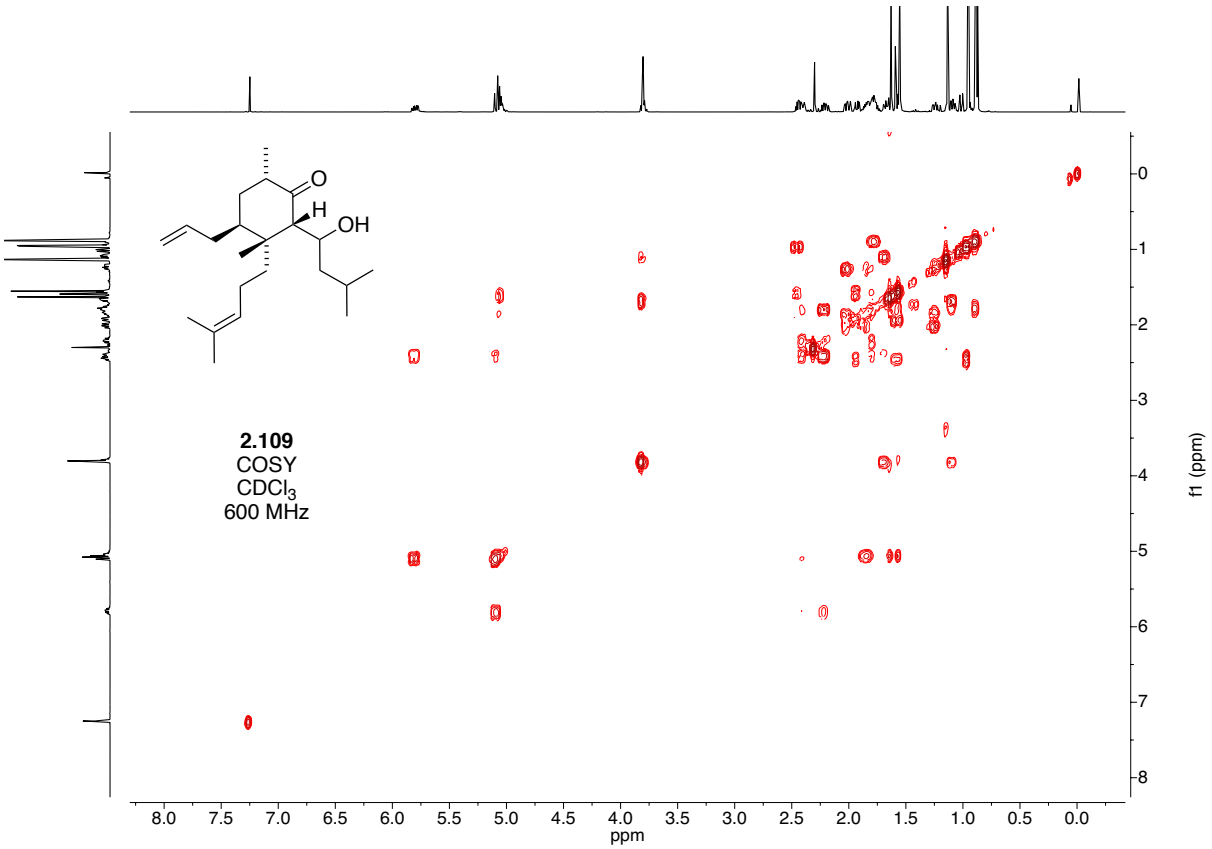
2.108
^{1}H NMR
$CDCl_3$
600 MHz

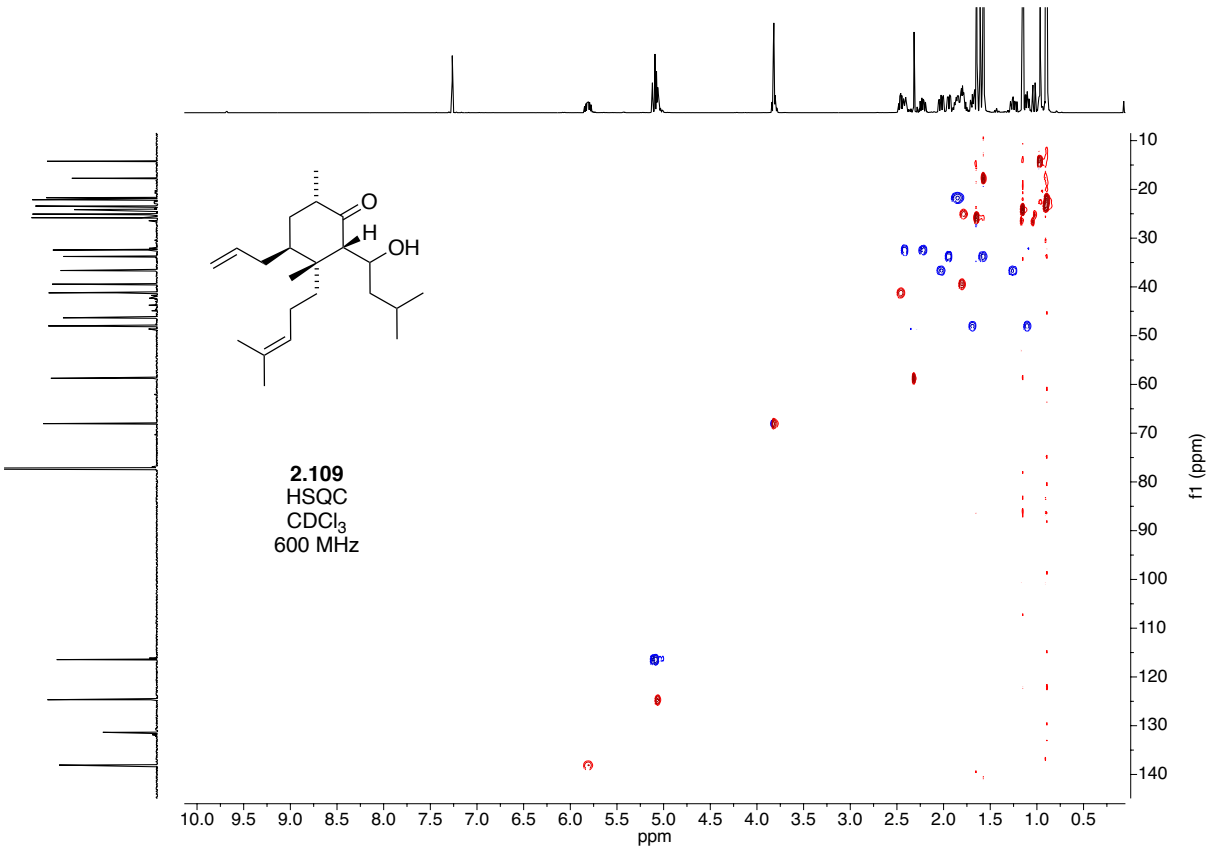


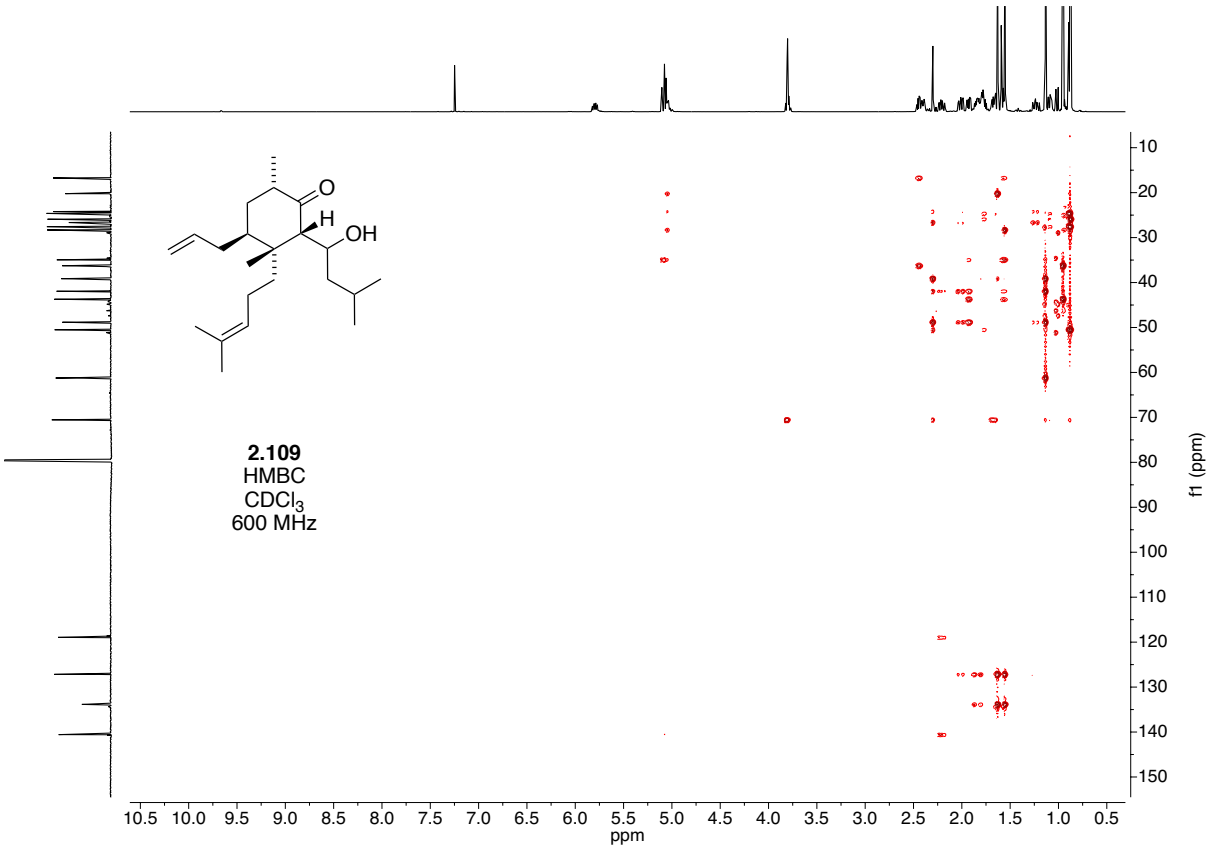

5.82 5.81 5.81 5.81 5.81 5.80 5.14 5.14 5.13 5.12 5.12 5.11 5.11 5.11 5.10 5.10 5.10 5.09 5.09 5.09 5.09 5.09 2.47 2.46 2.45 2.44 2.43 2.43 2.41 2.40 2.32 2.31 2.31 2.30 2.28 2.27 2.26 2.26 2.26 2.23 2.03 2.02 2.02 2.02 2.02 2.01 2.01 2.00 2.00 2.00 1.99 1.99 1.99 1.99 1.96 1.81 1.80 1.79 1.78 1.76 1.11 1.10
O
2.106
1H NMR
CDCl3
600 MHz
2.00
2.00
2.33
2.43
1.11
3.40
1.15
3.31
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

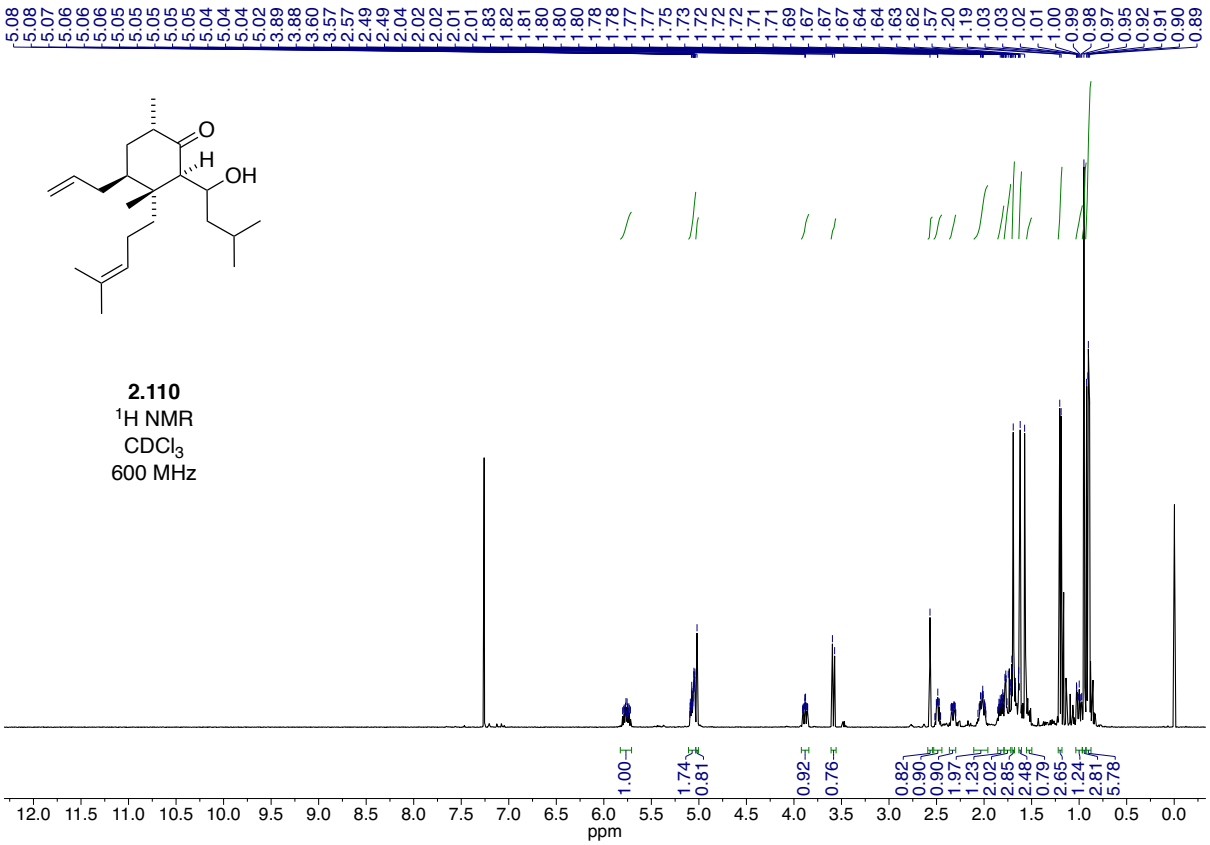

O
H
OH
2.109
1H NMR
CDCl3
600 MHz
ppm

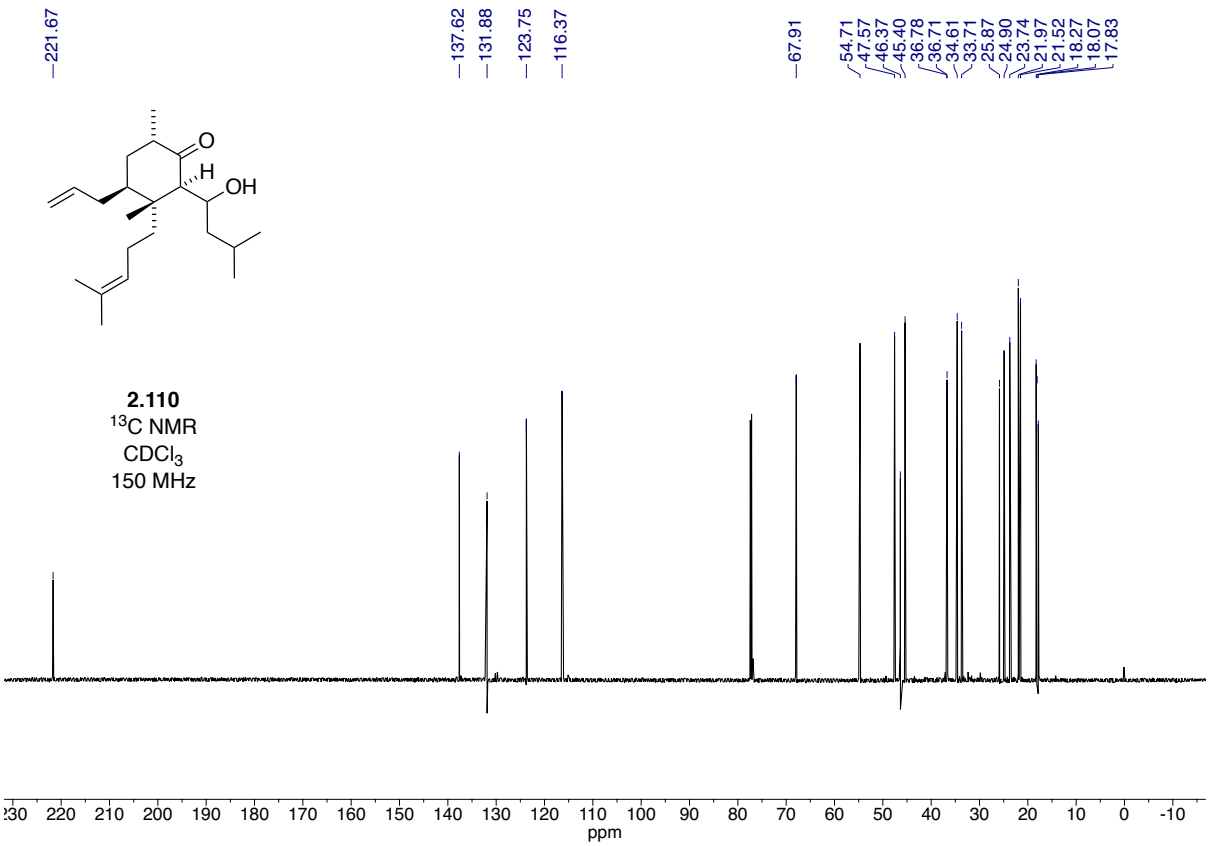

O
H
OH
2.109
13C NMR
CDCl3
150 MHz
ppm

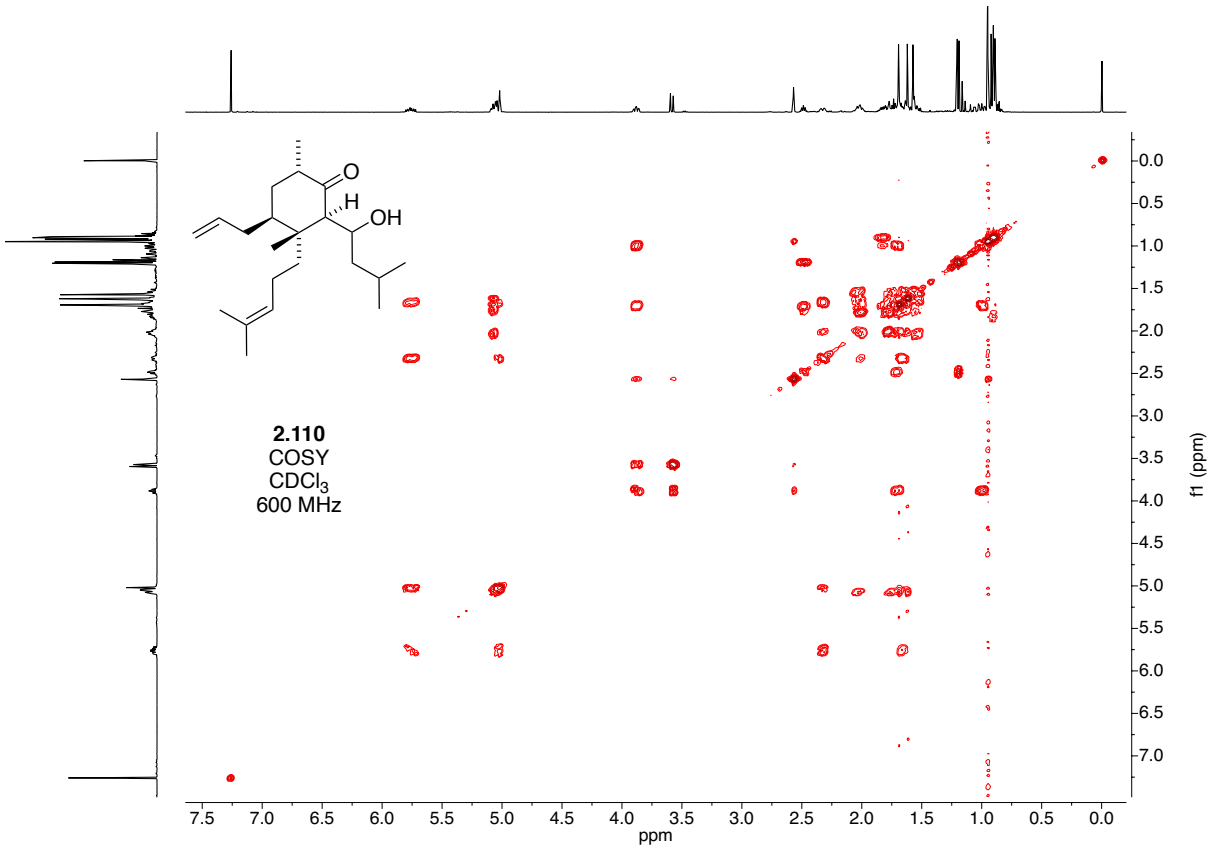

O
H
OH
2.109
COSY
CDCl3
600 MHz
f1 (ppm)
ppm

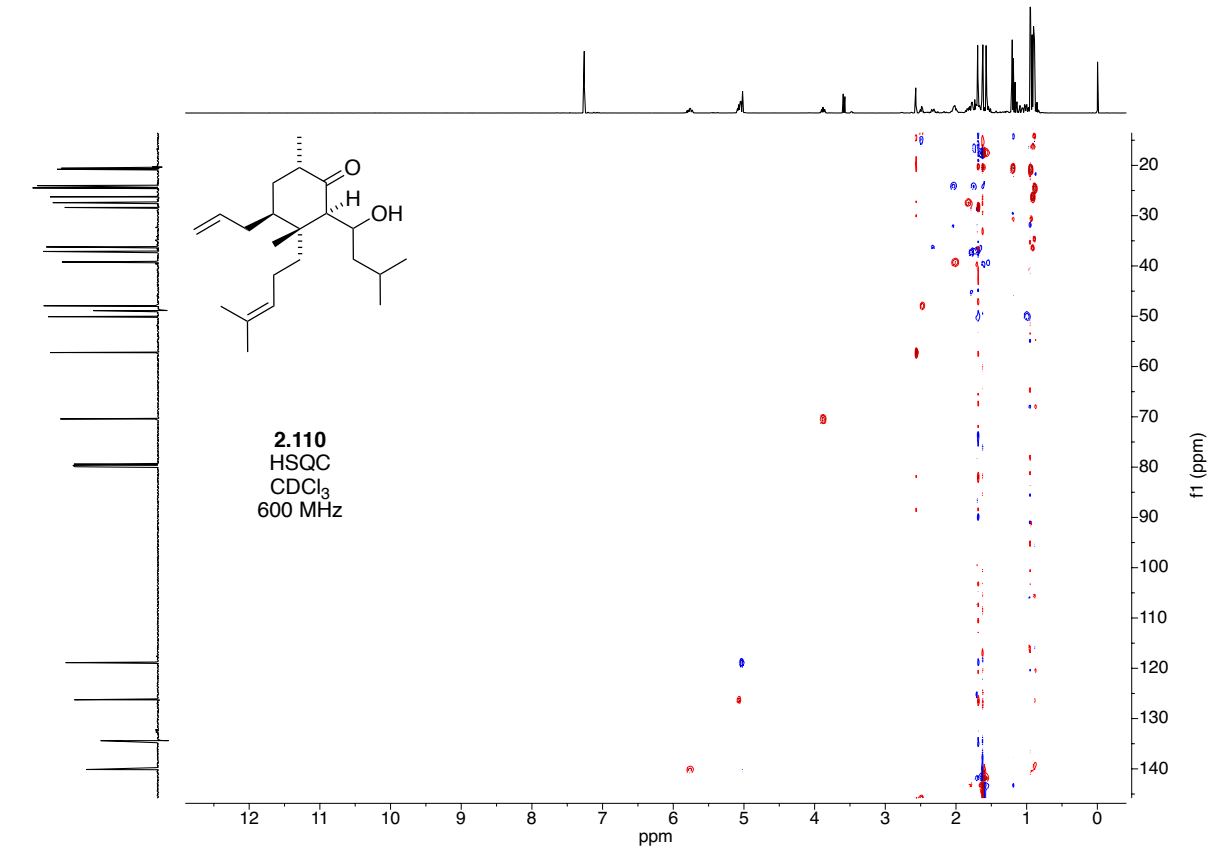

O
H
OH
2.109
HSQC
CDCl3
600 MHz
f1 (ppm)
ppm

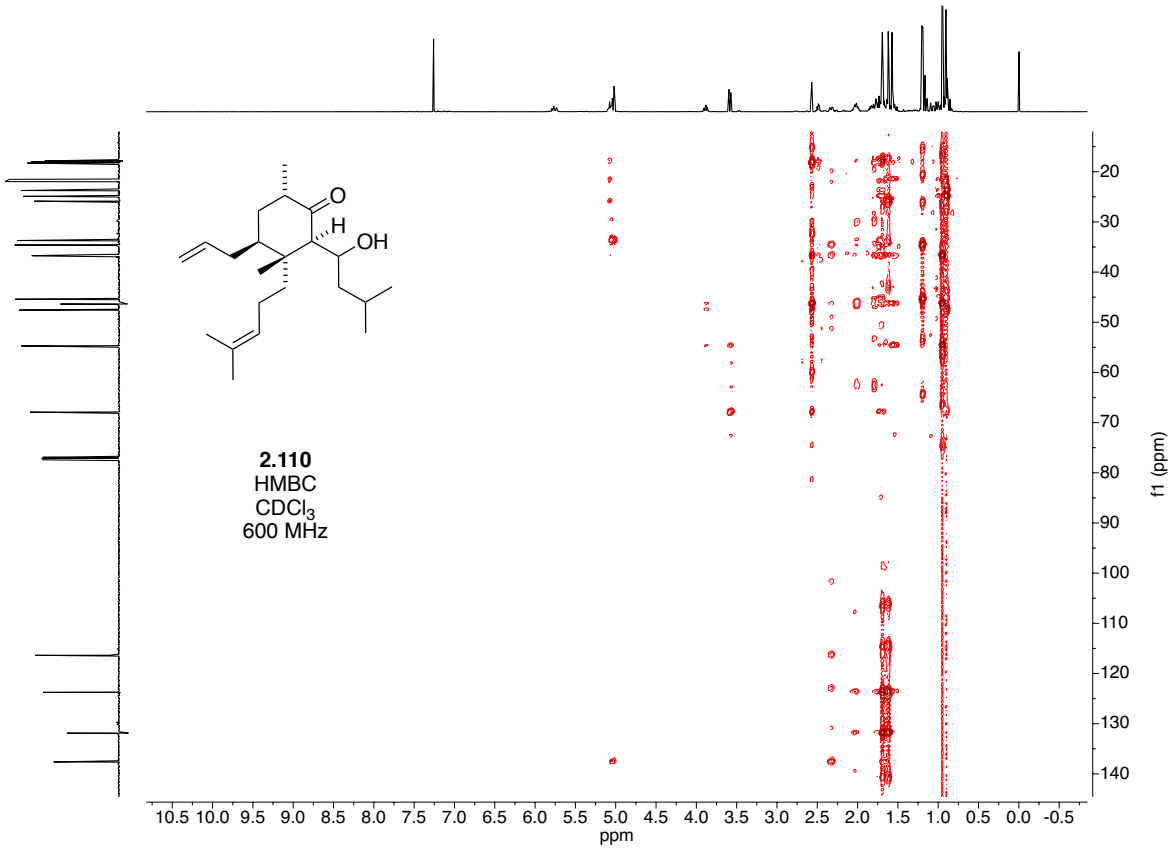

O
H
OH
2.109
HMBC
CDCl3
600 MHz
ppm
f1 (ppm)

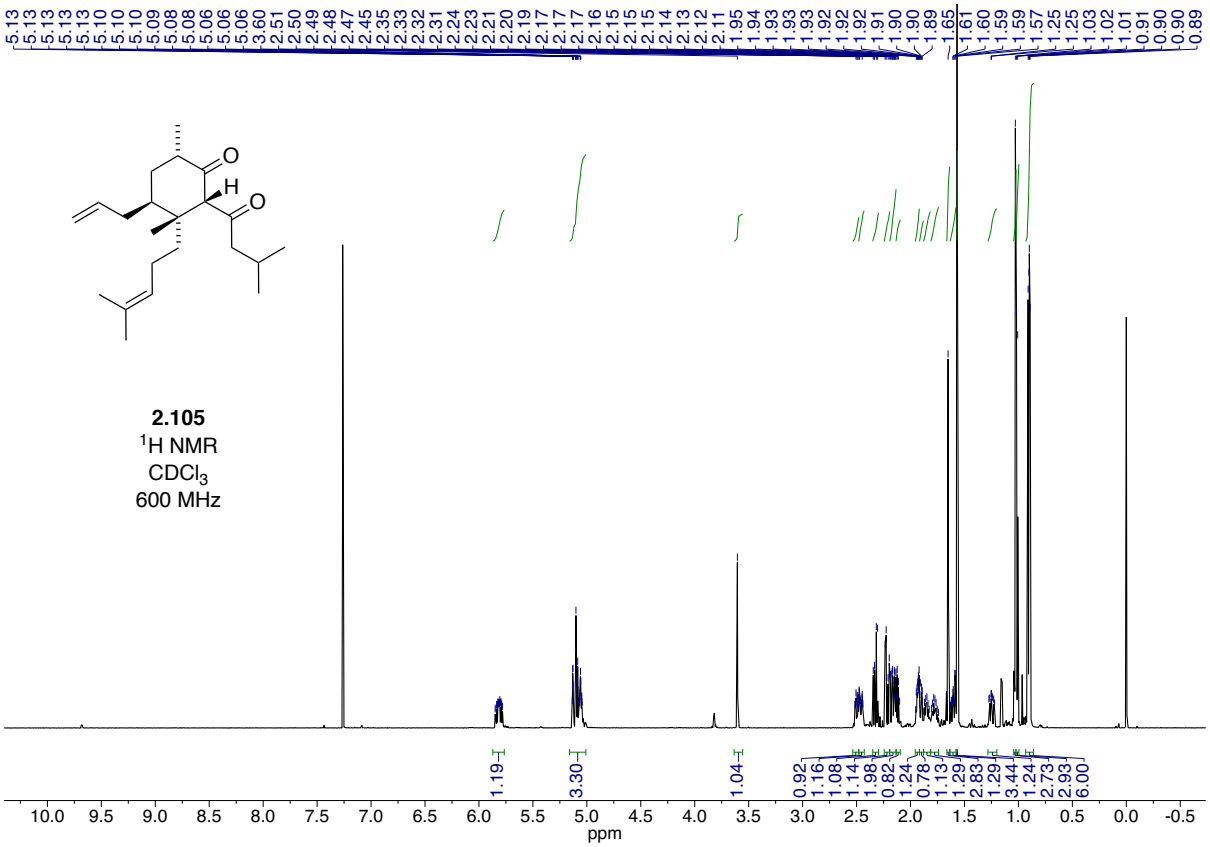

O
H
OH
2.110
1H NMR
CDCl3
600 MHz
ppm

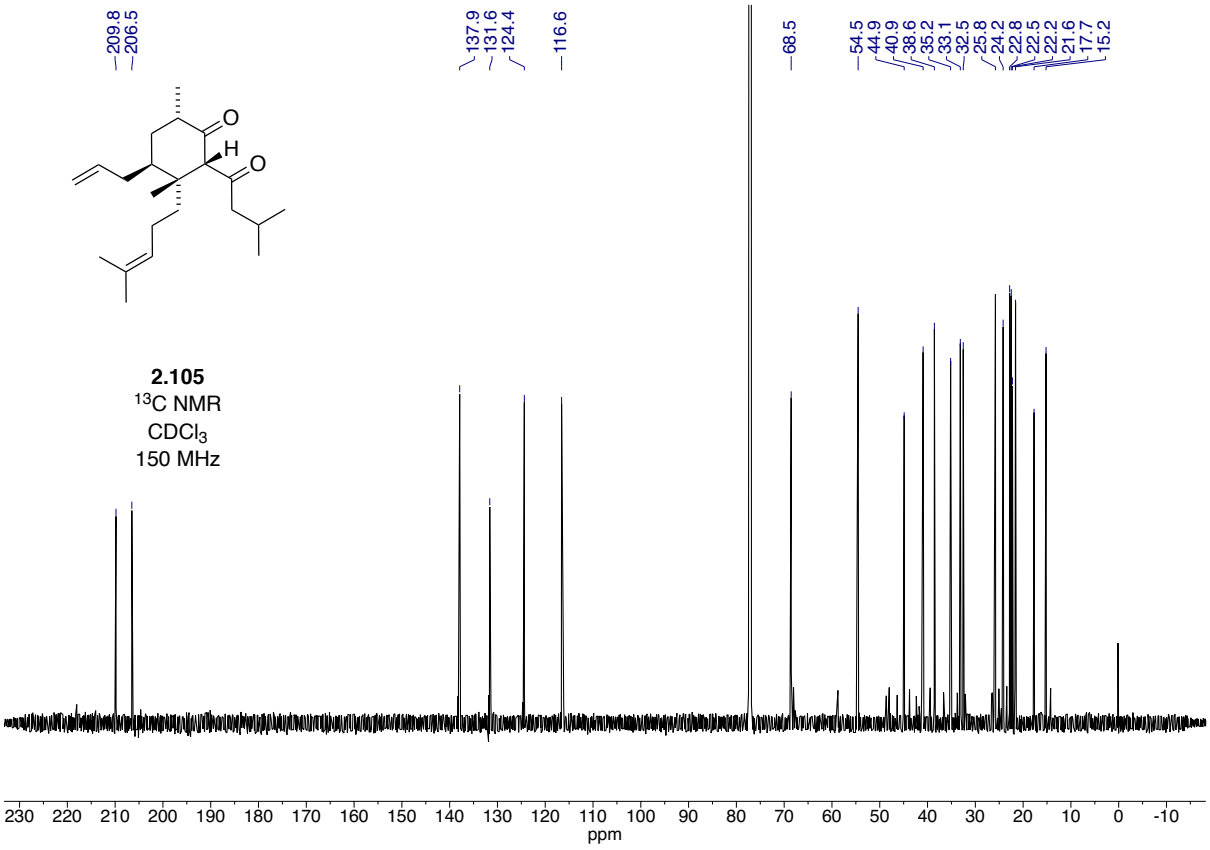

O
H
OH
2.110
13C NMR
CDCl3
150 MHz
ppm

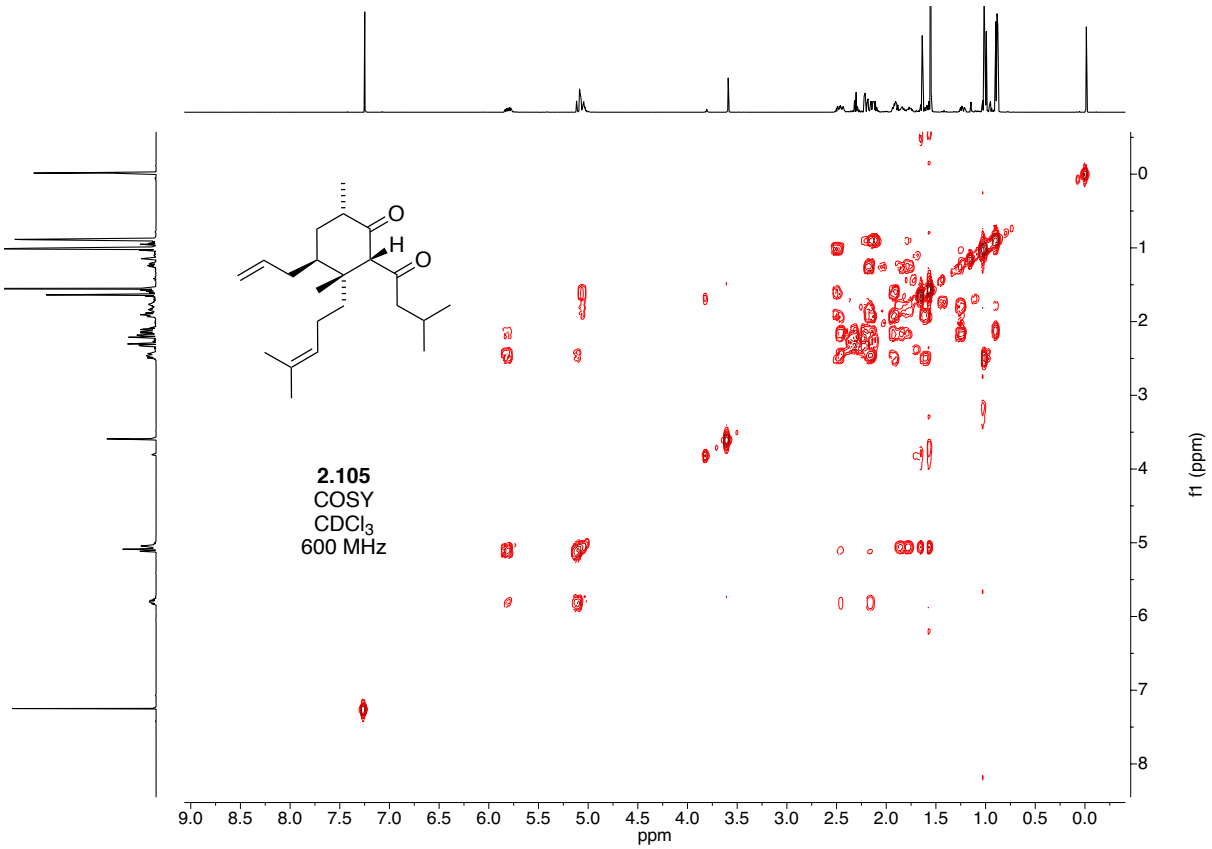

O
H
OH
2.110
COSY
CDCl3
600 MHz
ppm
f1 (ppm)

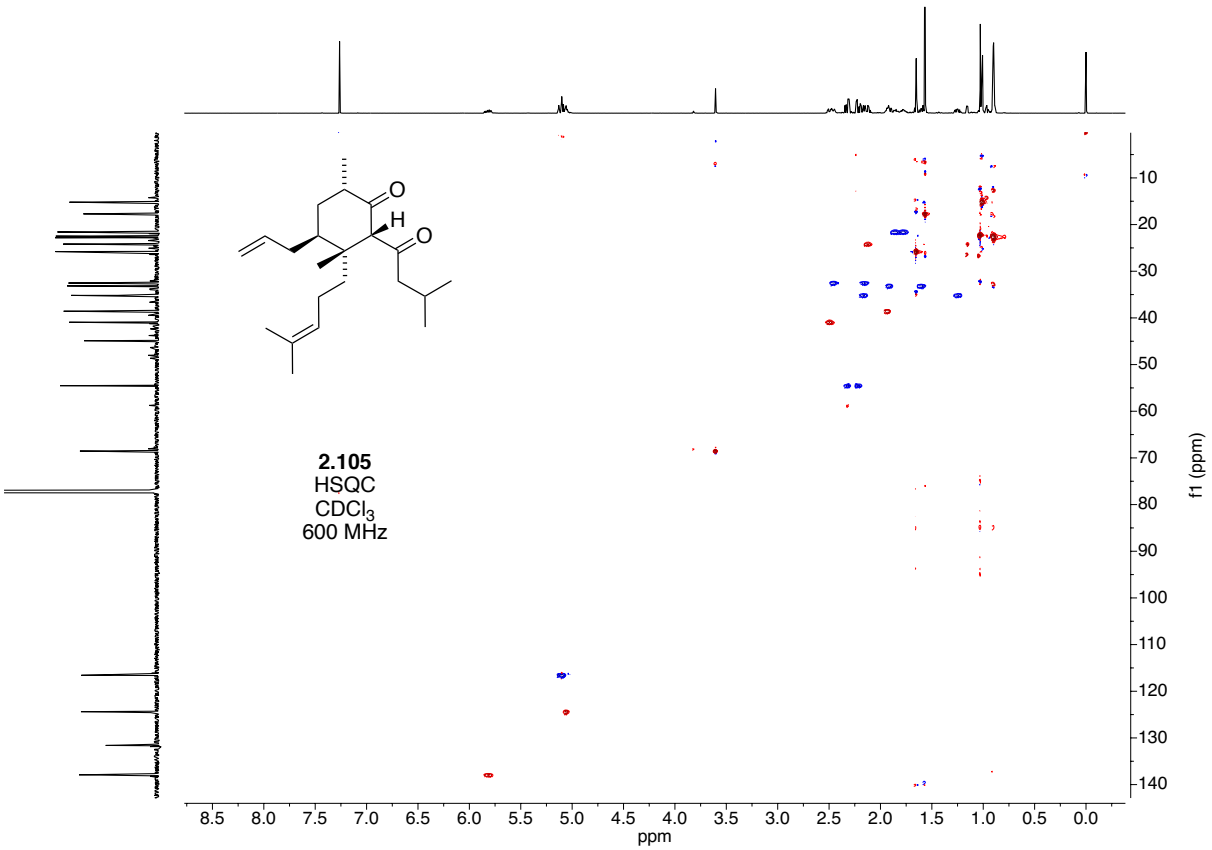

O
H
OH
2.110
HSQC
CDCl3
600 MHz
ppm
f1 (ppm)

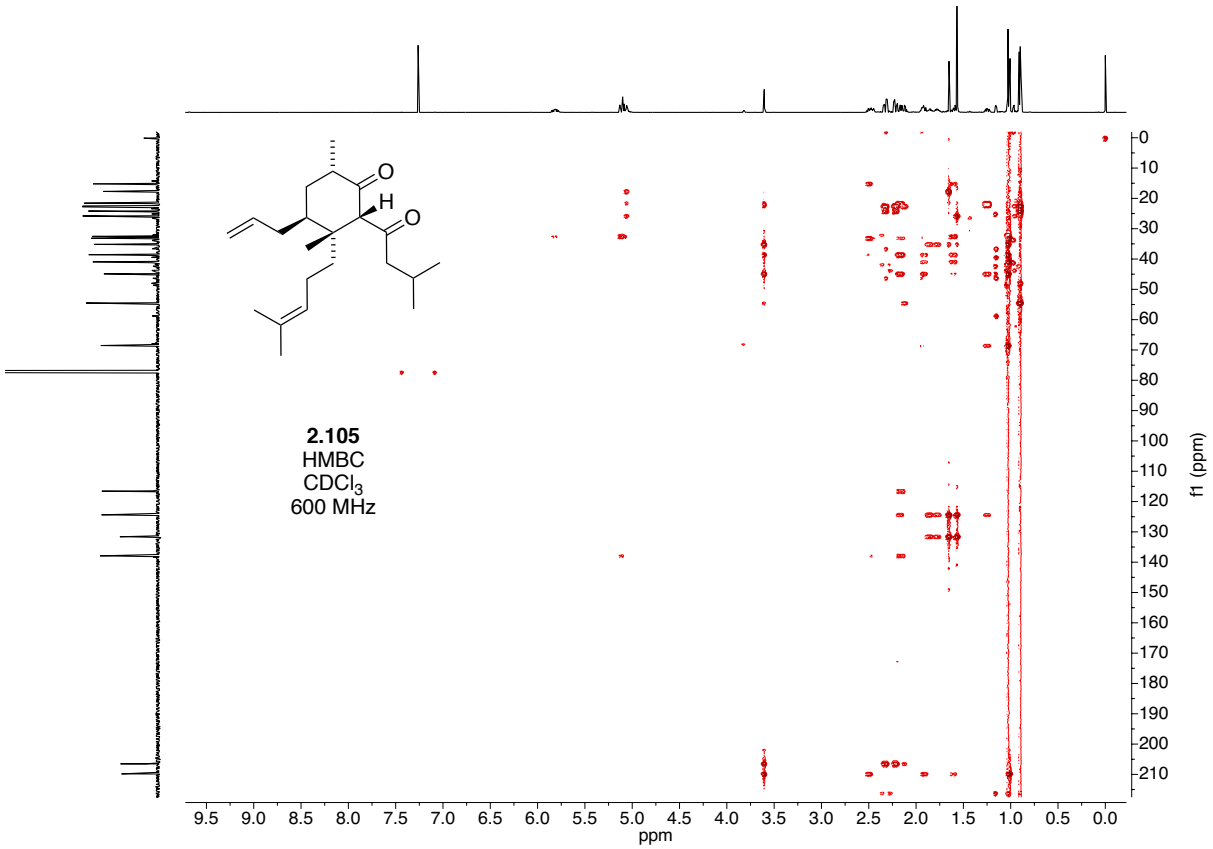

O
H
OH
2.110
HMBC
CDCl3
600 MHz
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm
20 30 40 50 60 70 80 90 100 110 120 130 140
f1 (ppm)

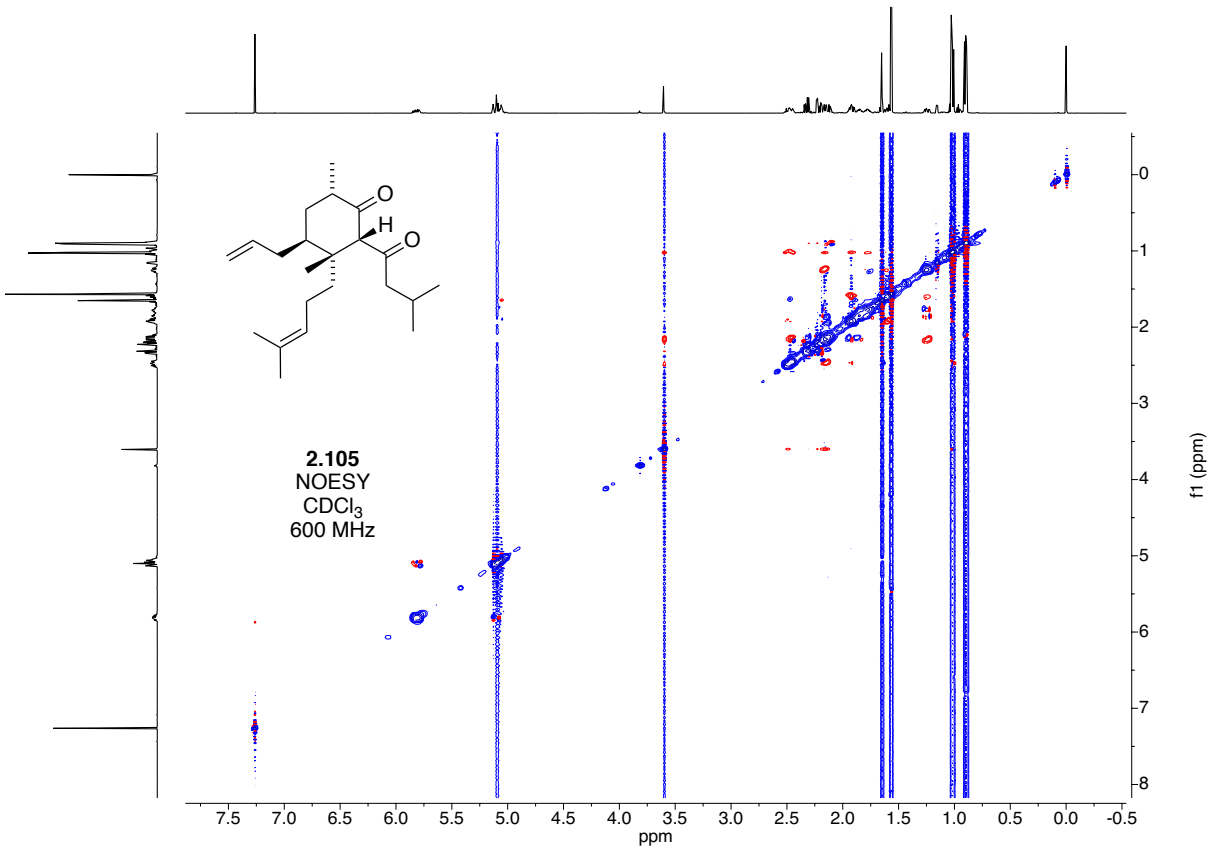

2.105
1H NMR
CDCl3
600 MHz
ppm

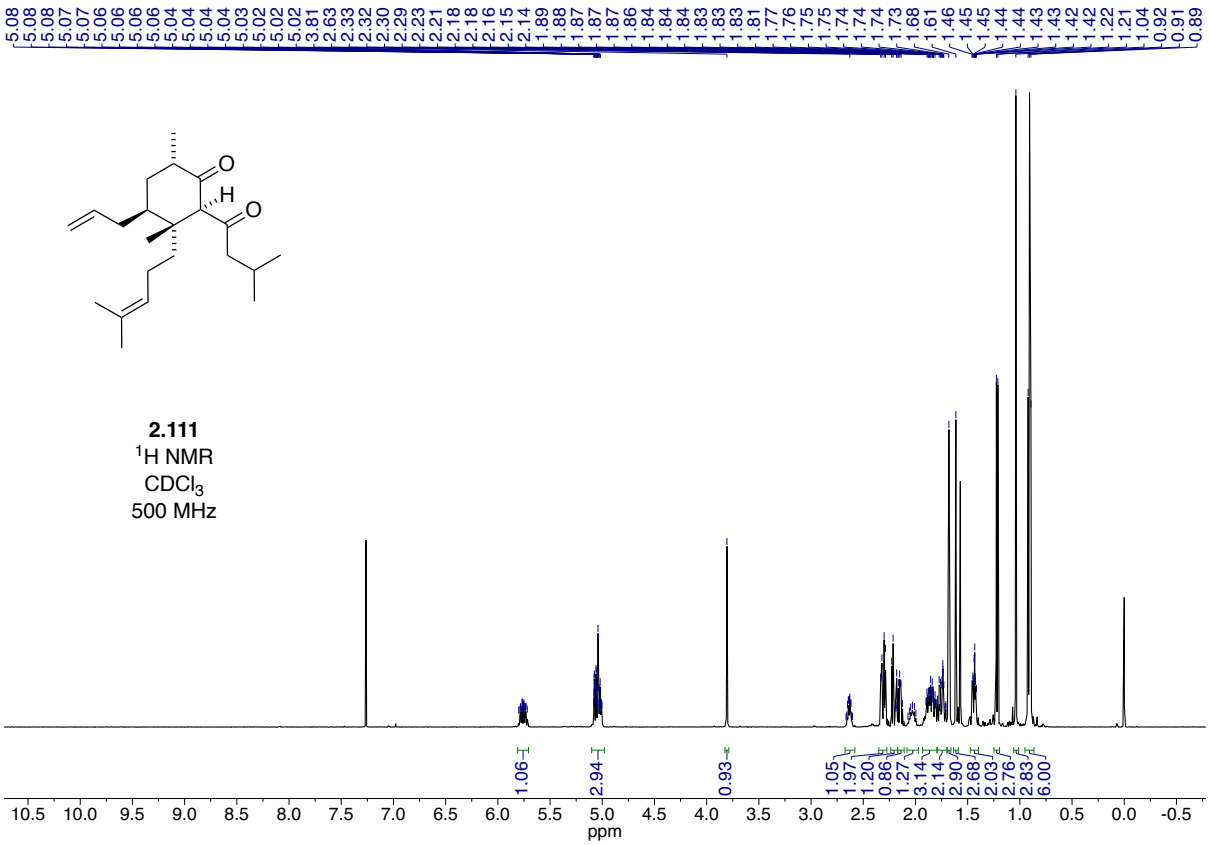

2.105
13C NMR
CDCl3
150 MHz
ppm

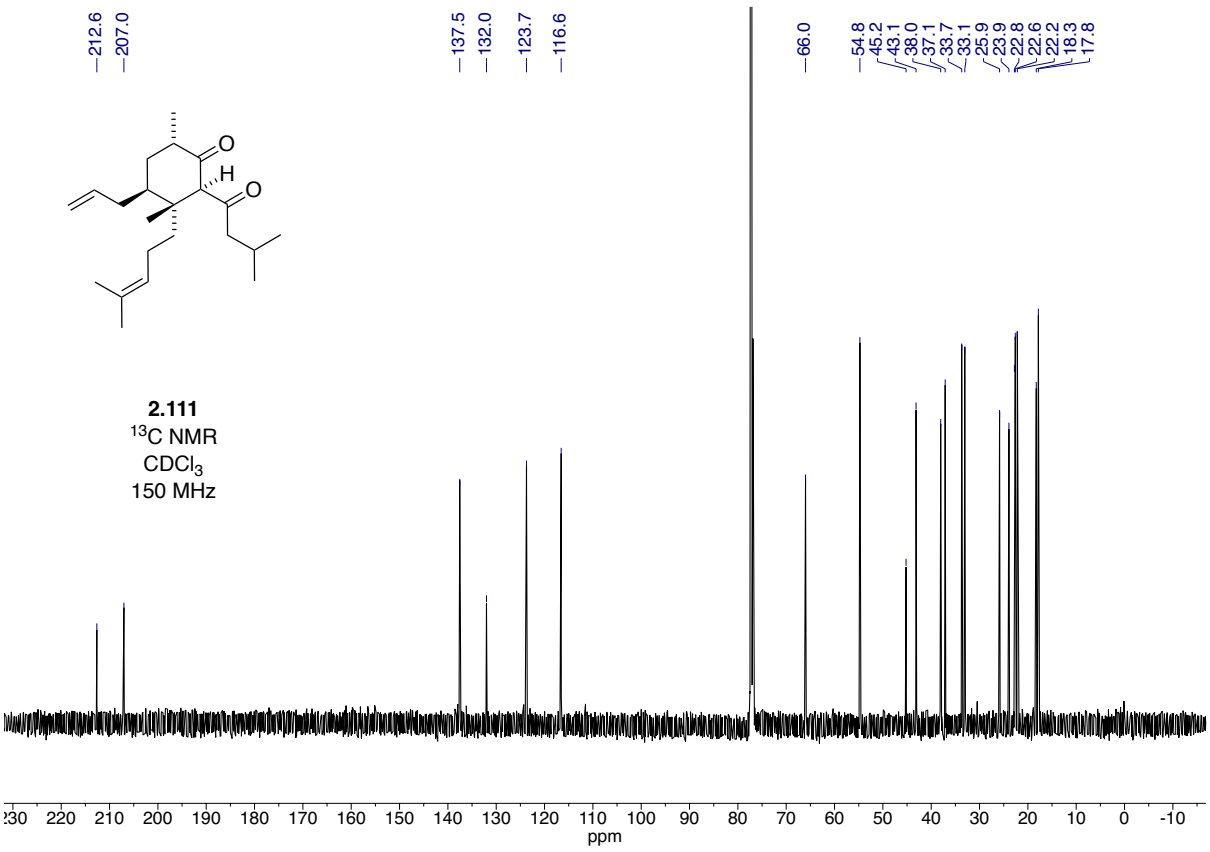

O
H
O
2.105
COSY
CDCl3
600 MHz
f1 (ppm)
ppm

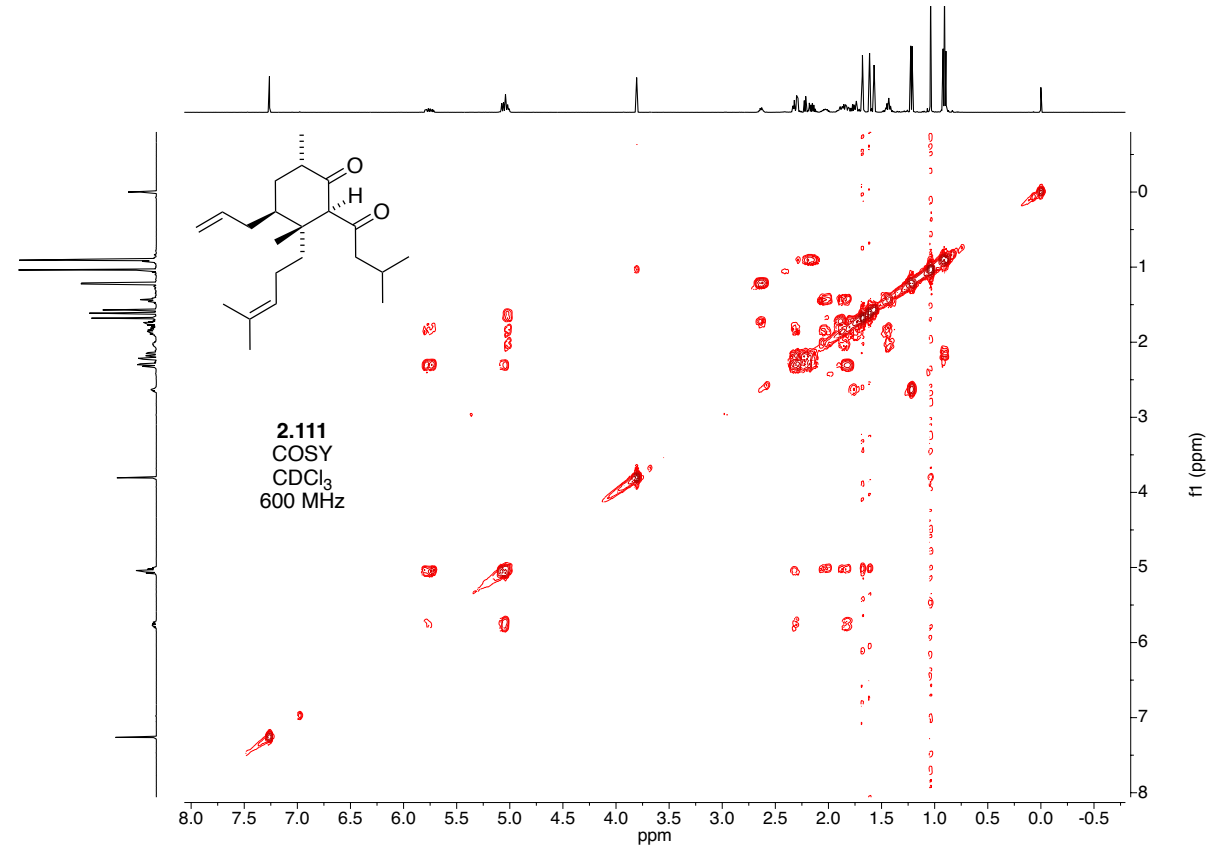

O
H
O
2.105
HSQC
CDCl3
600 MHz
f1 (ppm)
ppm

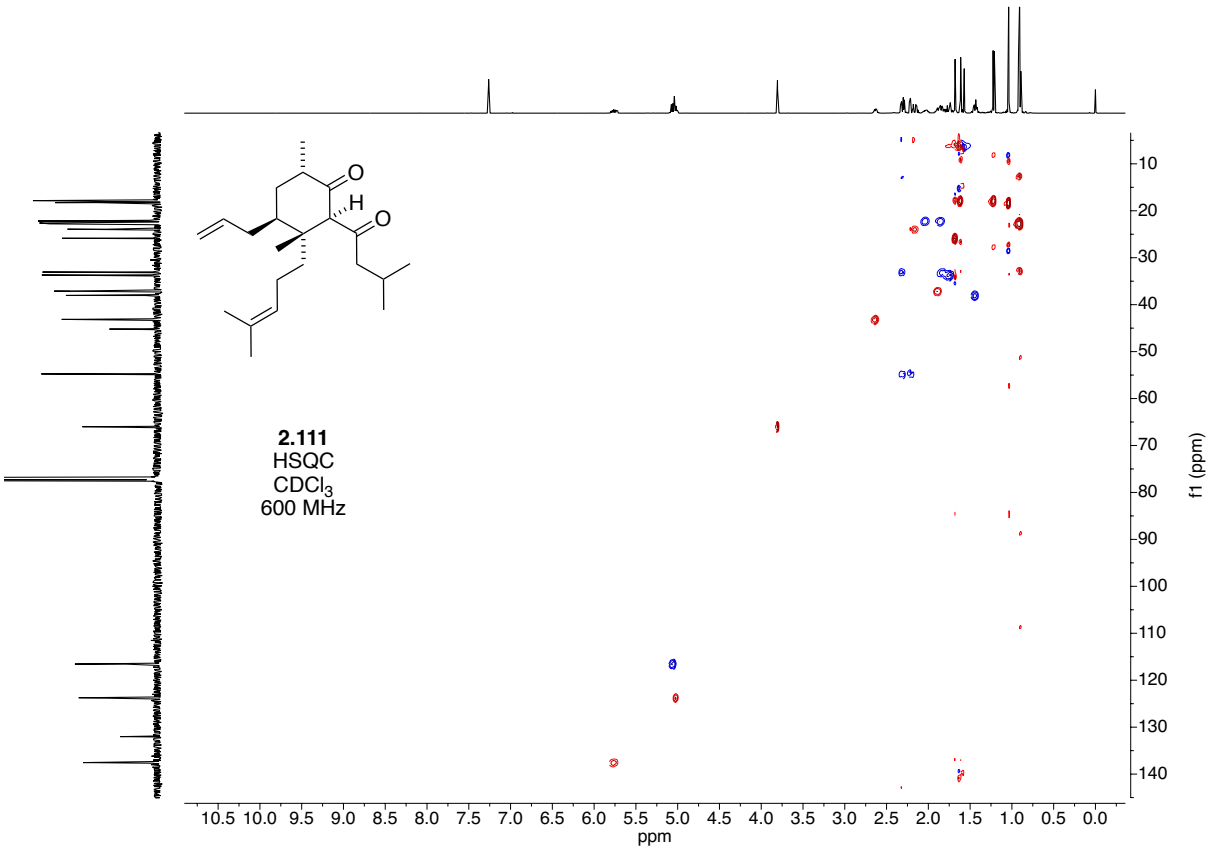

O
H
O
2.105
HMBC
CDCl3
600 MHz
f1 (ppm)
ppm

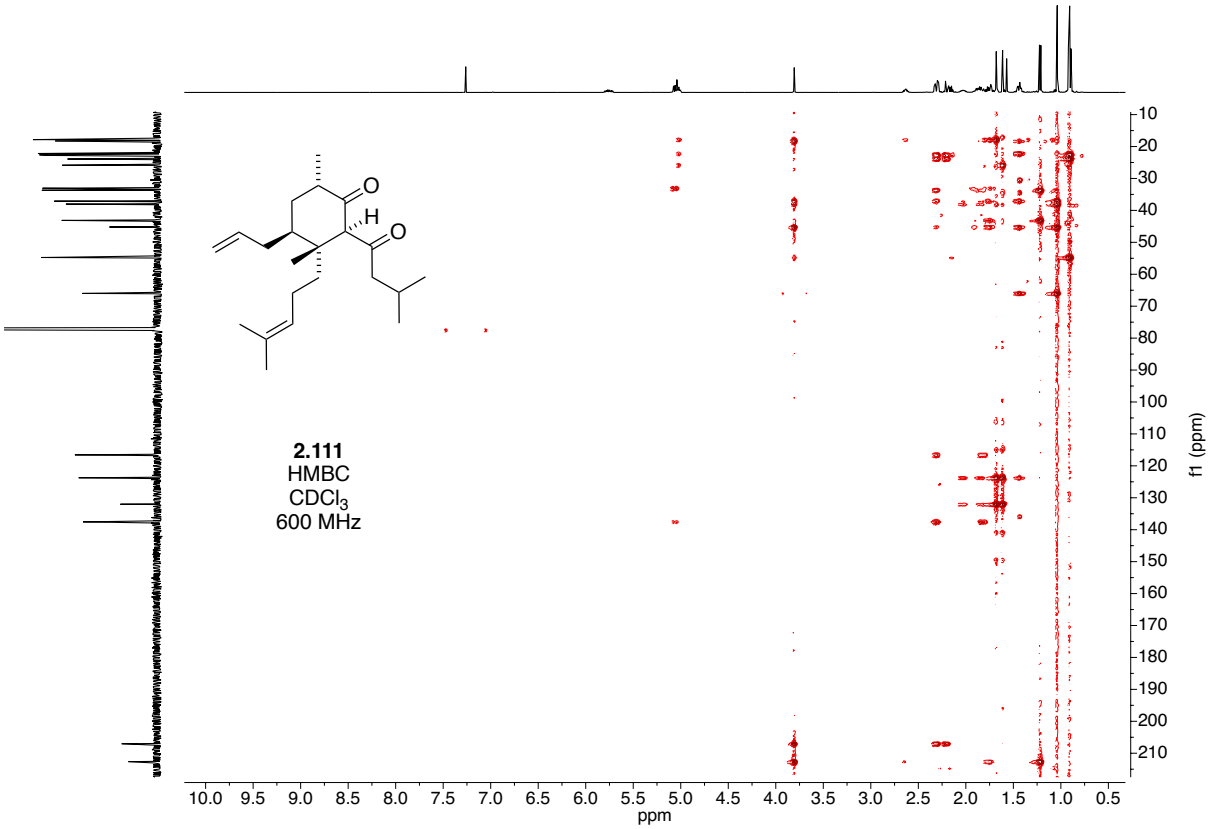

O
H
O
2.105
NOESY
CDCl3
600 MHz
f1 (ppm)
ppm

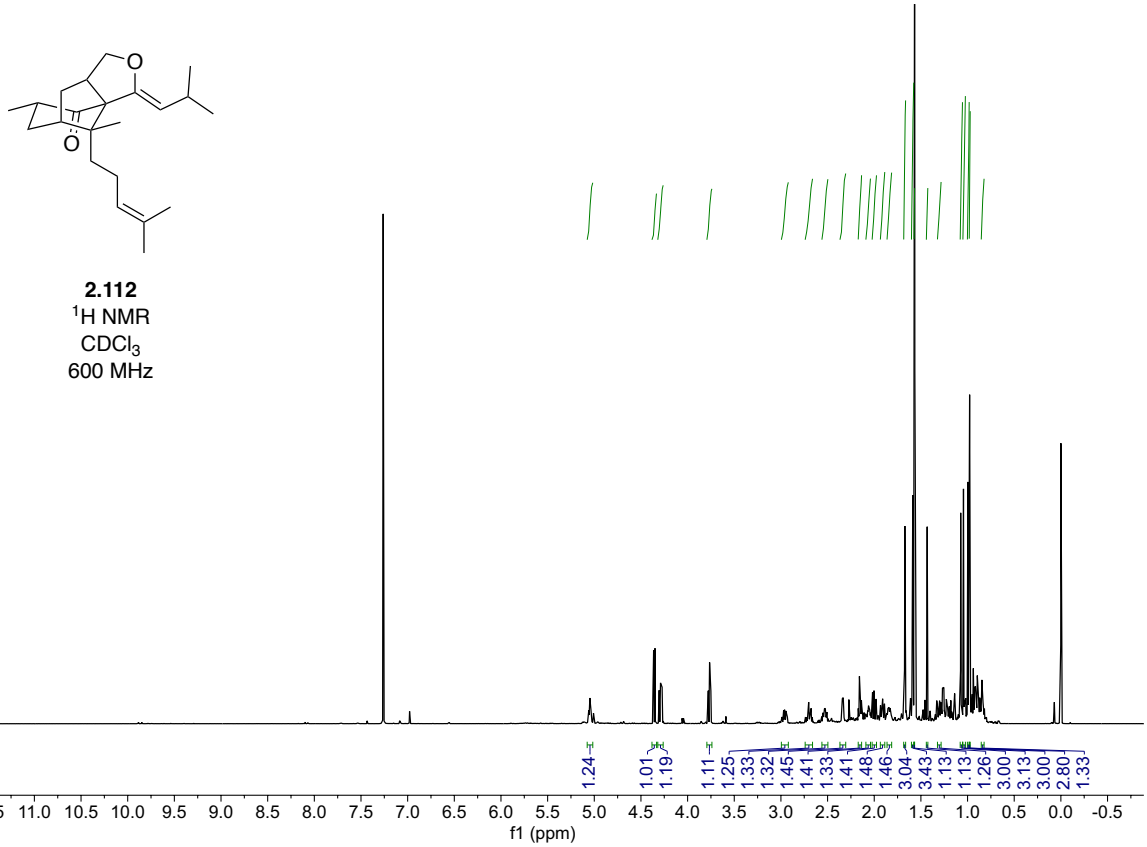

5.08 5.08 5.08 5.07 5.07 5.06 5.06 5.06 5.04 5.04 5.04 5.04 5.03 5.02 5.02 5.02 3.81 2.63 2.33 2.32 2.30 2.29 2.23 2.21 2.18 2.18 2.16 2.15 2.14 1.89 1.88 1.87 1.87 1.87 1.86 1.84 1.84 1.84 1.83 1.83 1.83 1.81 1.77 1.76 1.75 1.75 1.74 1.74 1.74 1.73 1.68 1.61 1.46 1.45 1.45 1.44 1.44 1.43 1.43 1.42 1.42 1.22 1.21 1.04 0.92 0.91 0.89
O
H
O
2.111
1H NMR
CDCl3
500 MHz
1.06
2.94
0.93
1.05
1.97
1.20
0.86
1.27
3.14
2.14
2.90
2.68
2.03
2.76
2.83
6.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

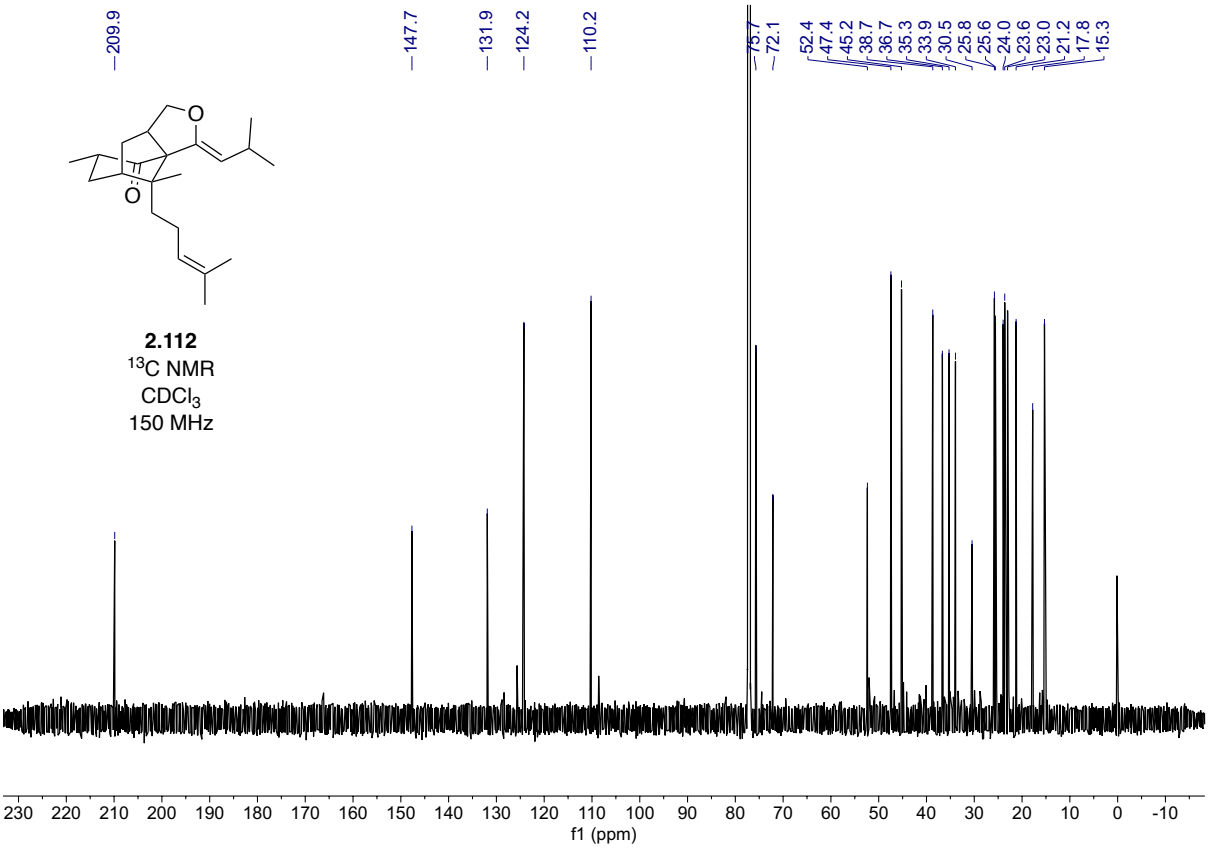

212.6
207.0
137.5
132.0
123.7
116.6
66.0
54.8
45.2
43.1
38.0
37.1
33.7
33.1
25.9
23.9
22.8
22.6
22.2
18.3
17.8
O
H
O
2.111
13C NMR
CDCl3
150 MHz
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

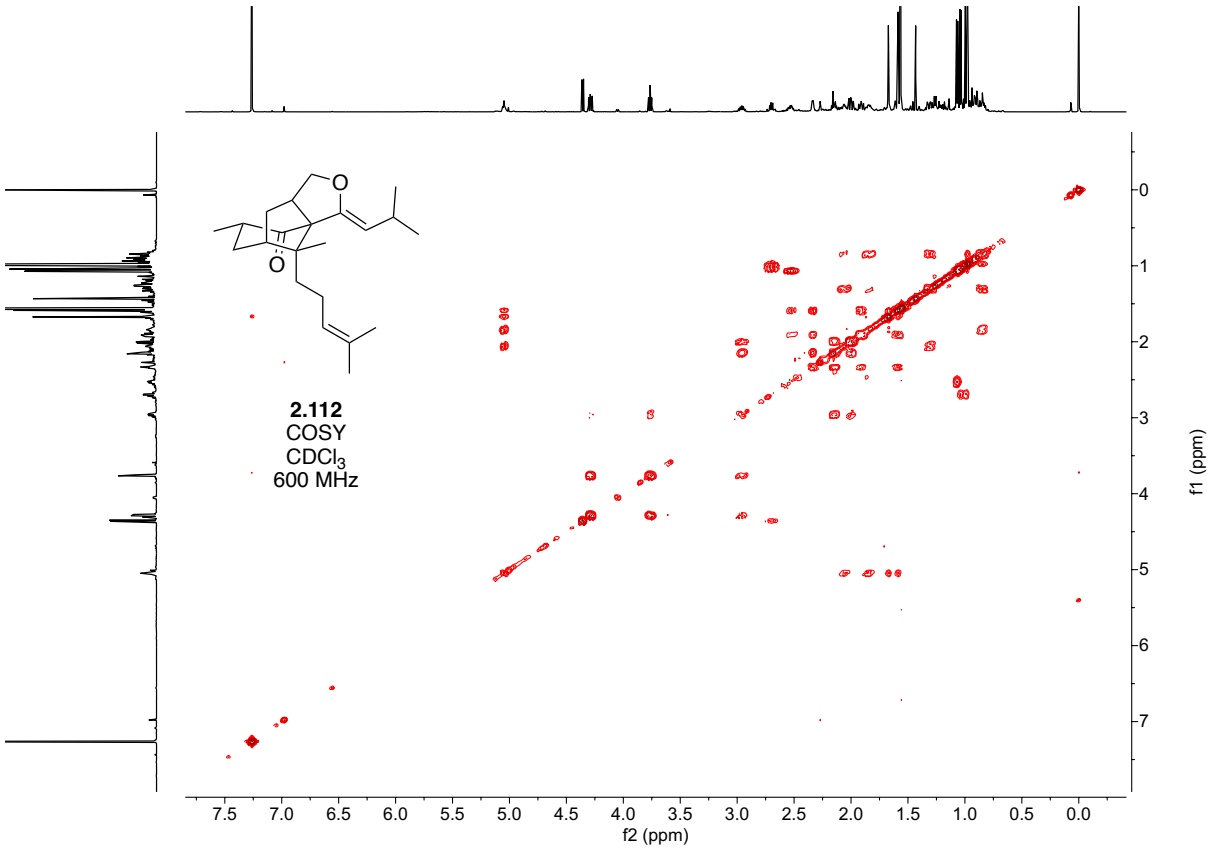

O
H
O
2.111
COSY
CDCl3
600 MHz
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm
0 1 2 3 4 5 6 7 8
f1 (ppm)

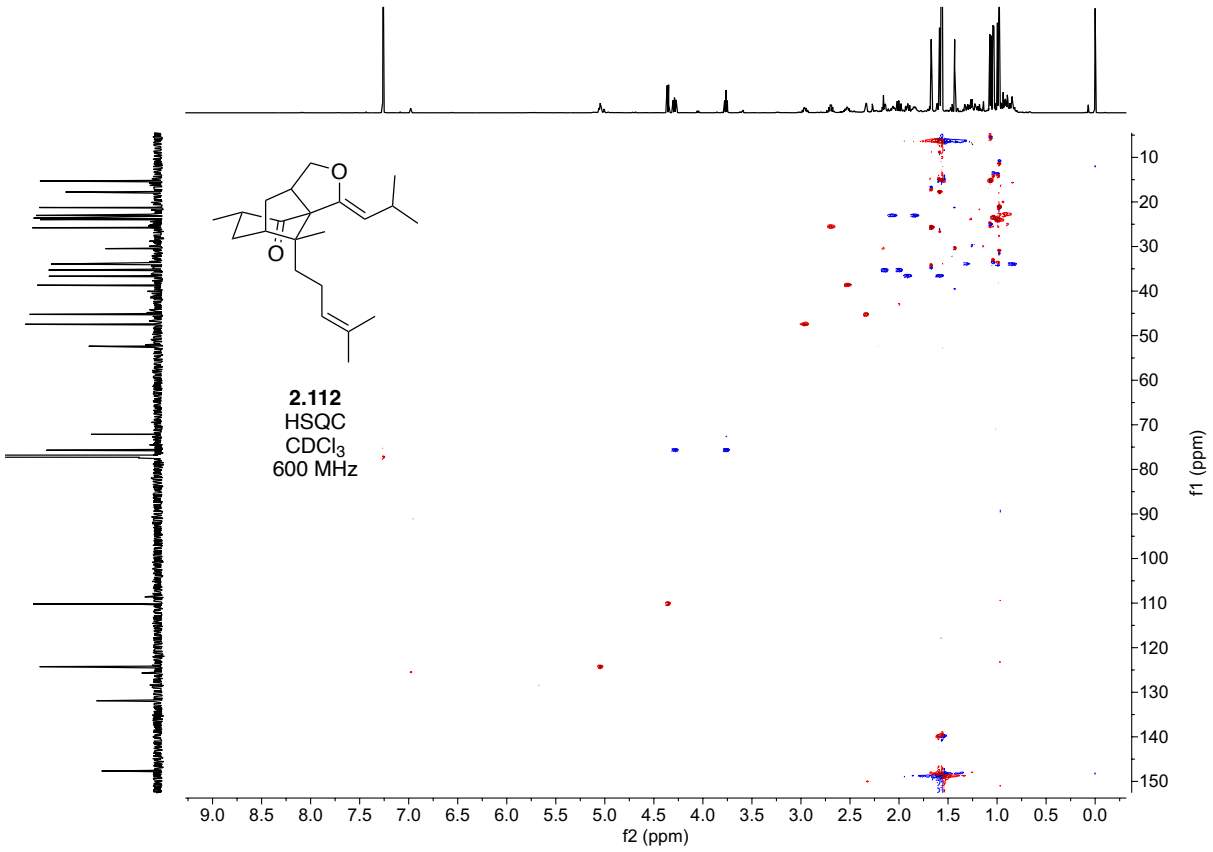

O
H
O
2.111
HSQC
CDCl3
600 MHz
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm
10 20 30 40 50 60 70 80 90 100 110 120 130 140
f1 (ppm)

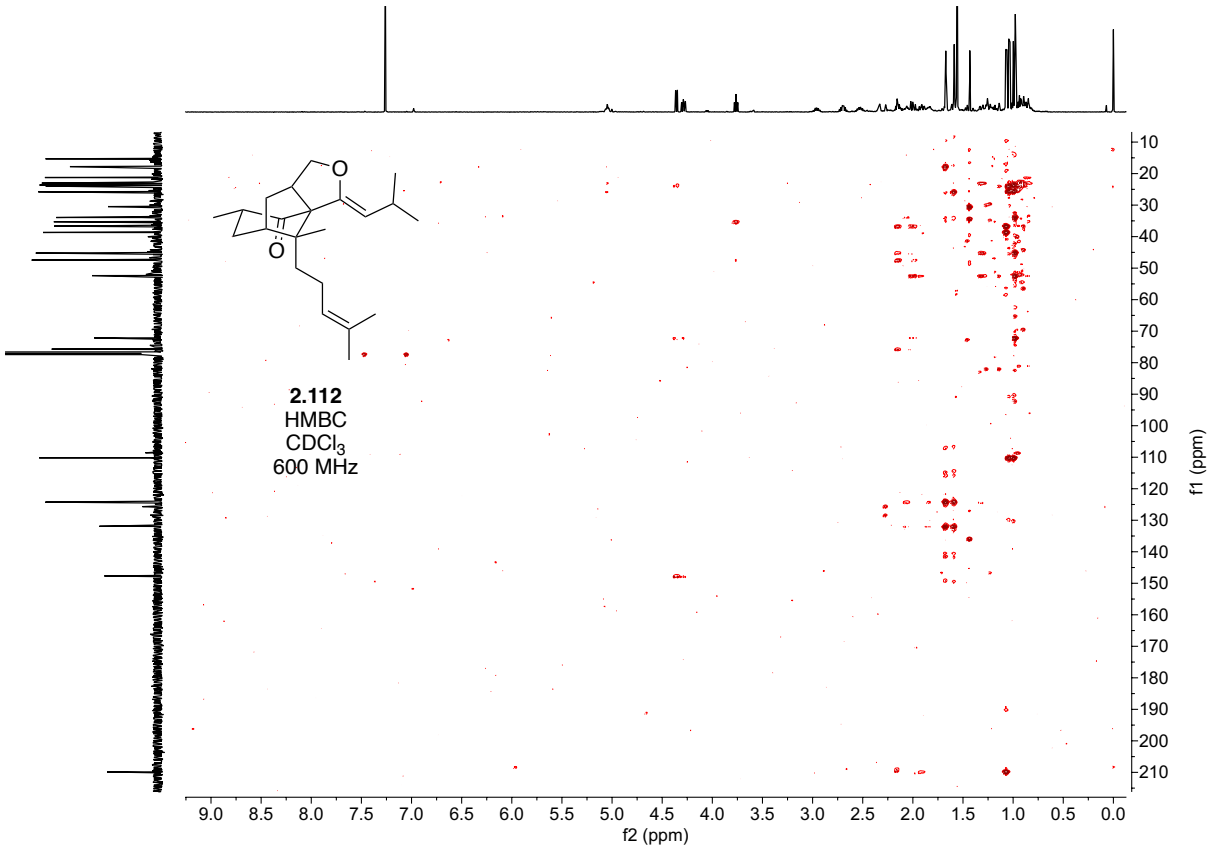

O
H
O
2.111
HMBC
CDCl3
600 MHz
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210
f1 (ppm)

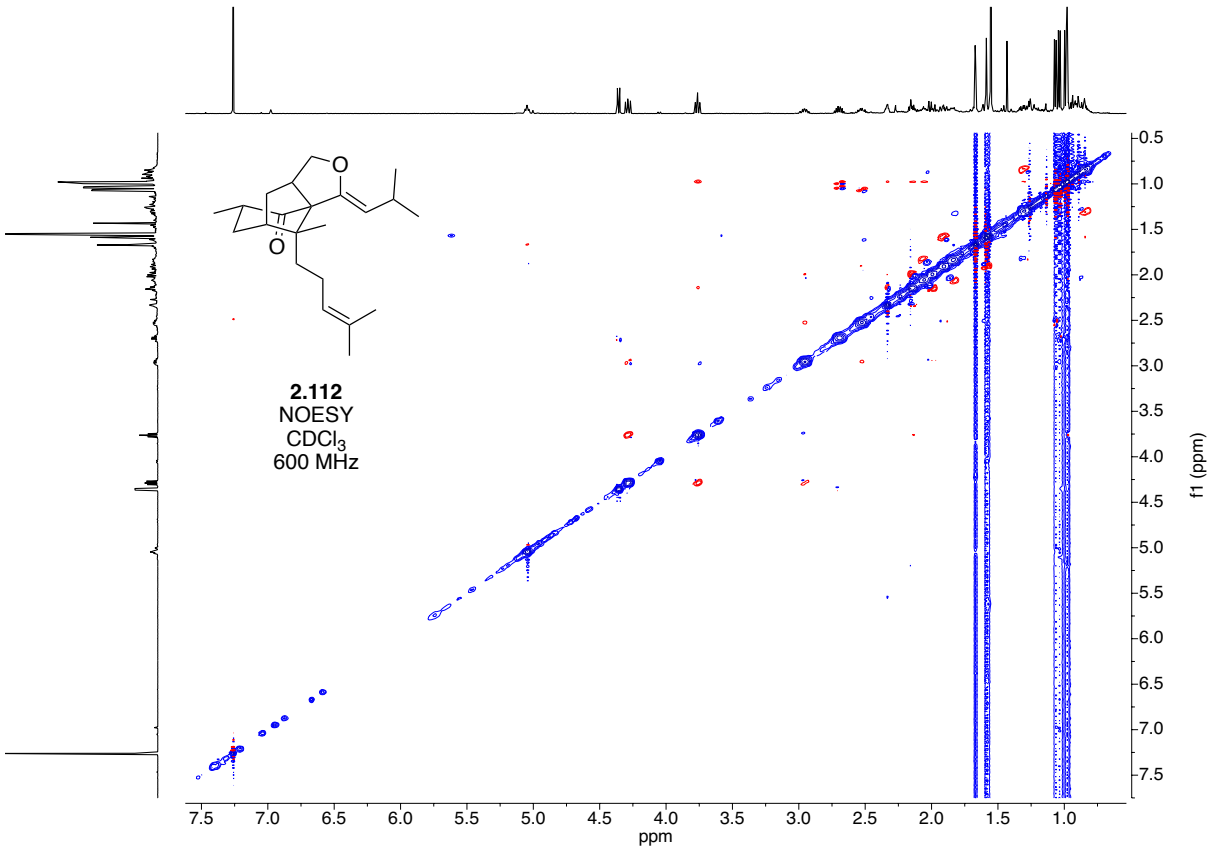

O
O
2.112
1H NMR
CDCl3
600 MHz
1.24
1.01
1.19
1.11
1.25
1.33
1.32
1.45
1.41
1.33
1.41
1.48
1.46
3.04
3.43
1.13
1.13
1.26
3.00
3.13
3.00
2.80
1.33
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

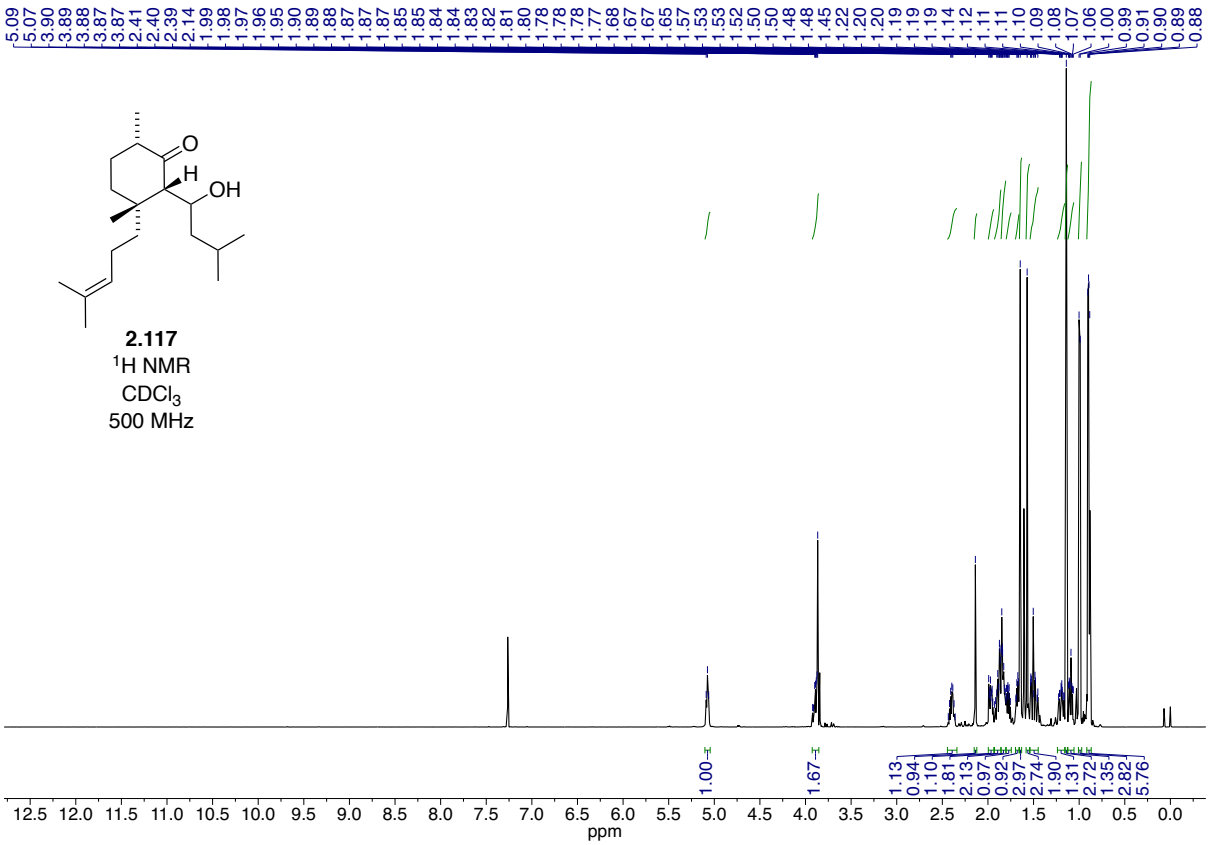

209.9
147.7
131.9
124.2
110.2
75.7
72.1
52.4
47.4
45.2
38.7
36.7
35.3
33.9
30.5
25.8
25.6
24.0
23.6
23.0
21.2
17.8
15.3
O
O
2.112
13C NMR
CDCl3
150 MHz
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

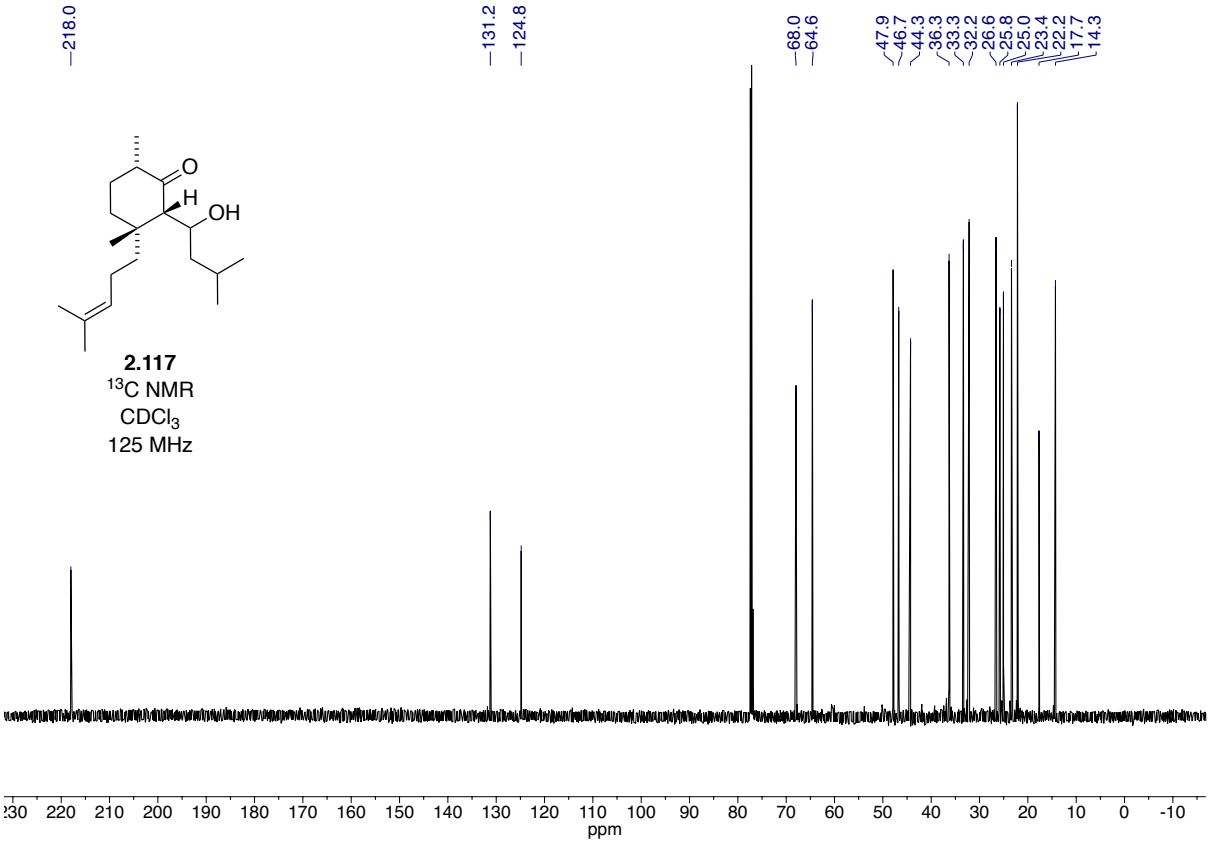

O
O
2.112
COSY
CDCl3
600 MHz
f2 (ppm)
f1 (ppm)

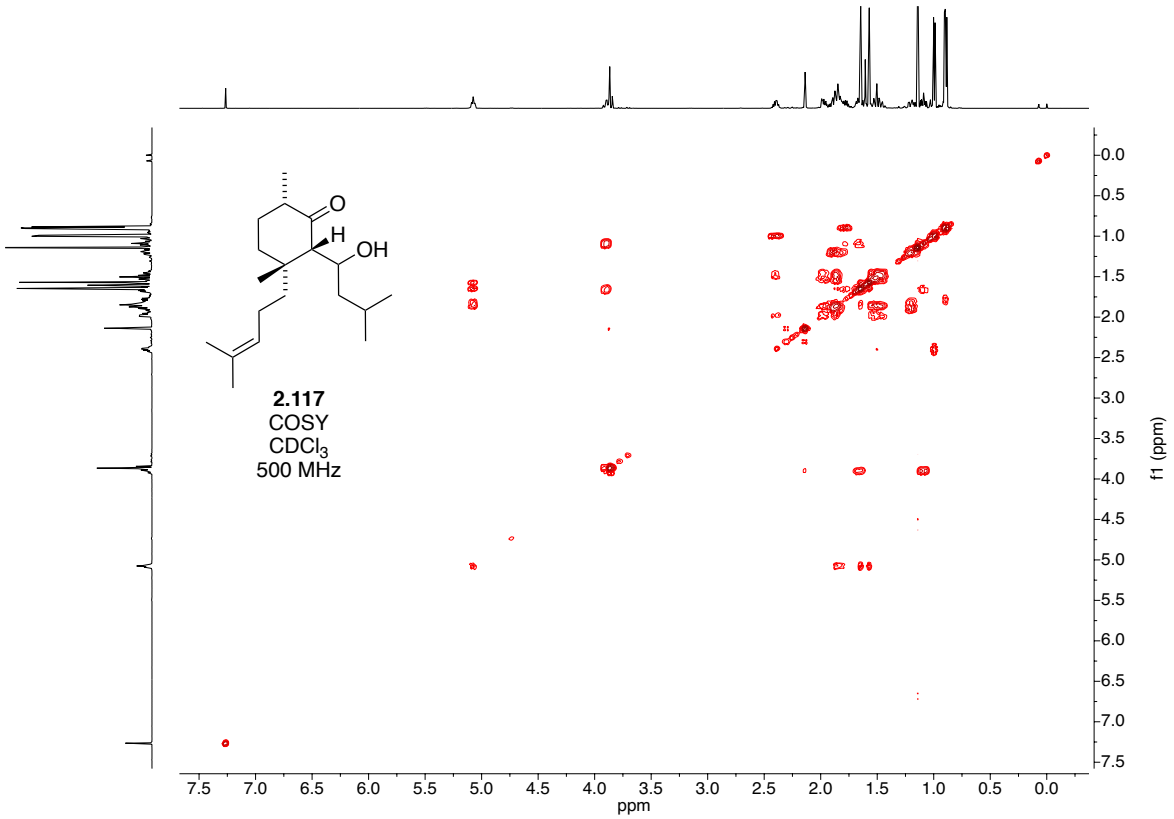

O
O
2.112
HSQC
CDCl3
600 MHz
f2 (ppm)
f1 (ppm)

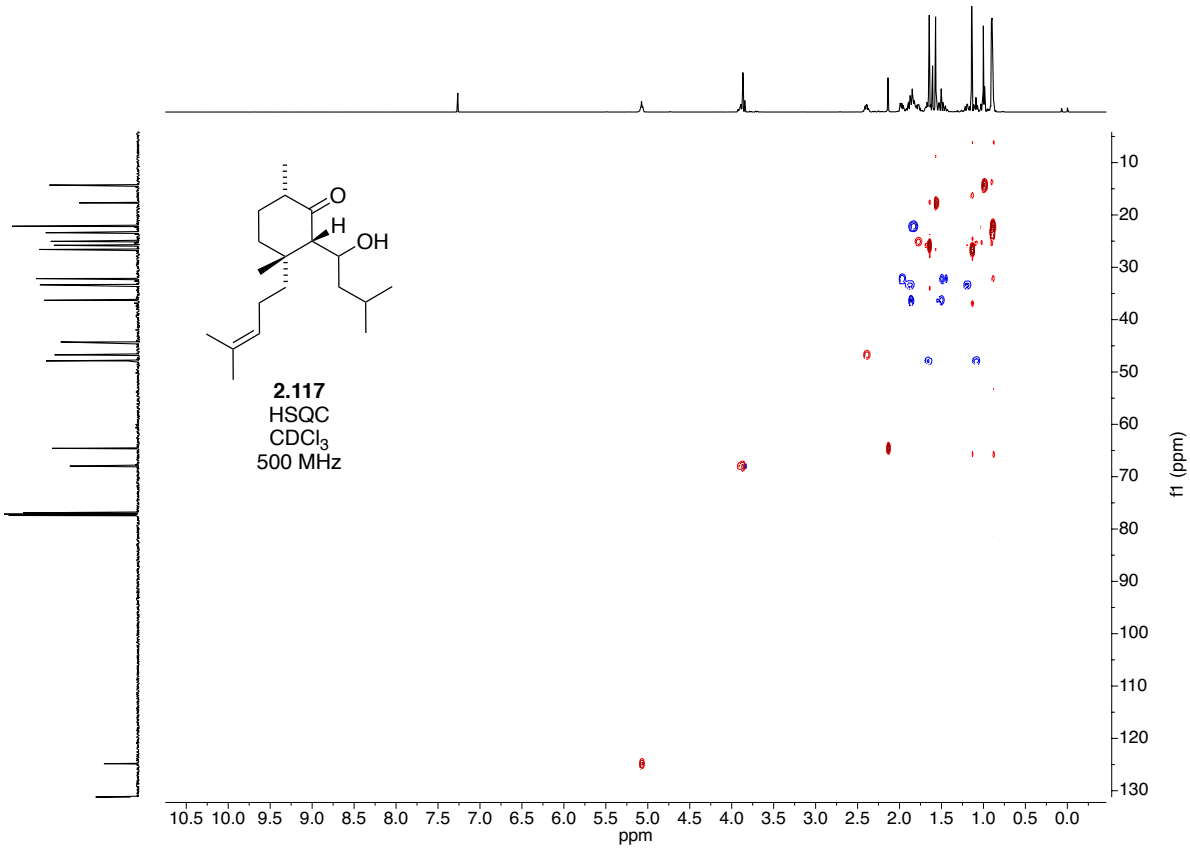

O
O
2.112
HMBC
CDCl3
600 MHz
f2 (ppm)
f1 (ppm)

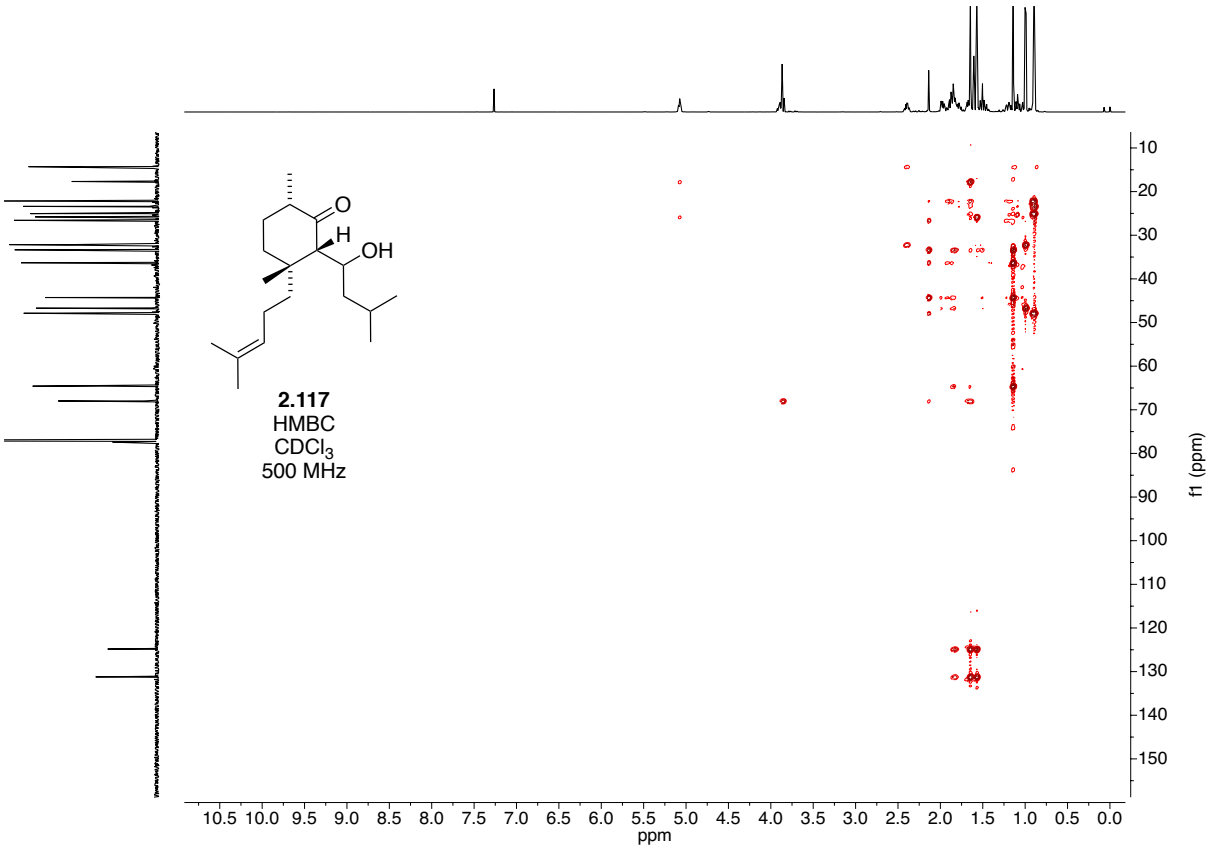

O
O
2.112
NOESY
CDCl3
600 MHz
ppm
f1 (ppm)

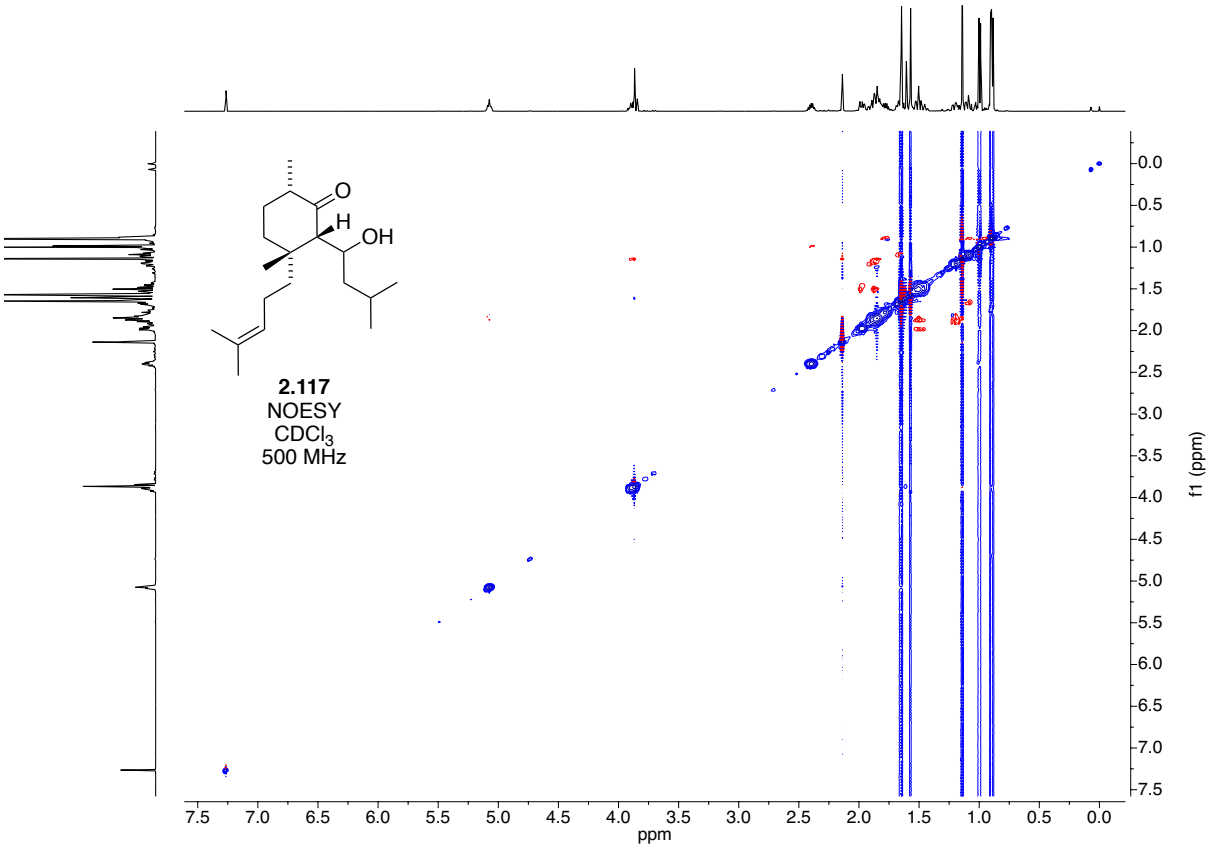

O
H
OH
2.117
1H NMR
CDCl3
500 MHz
ppm

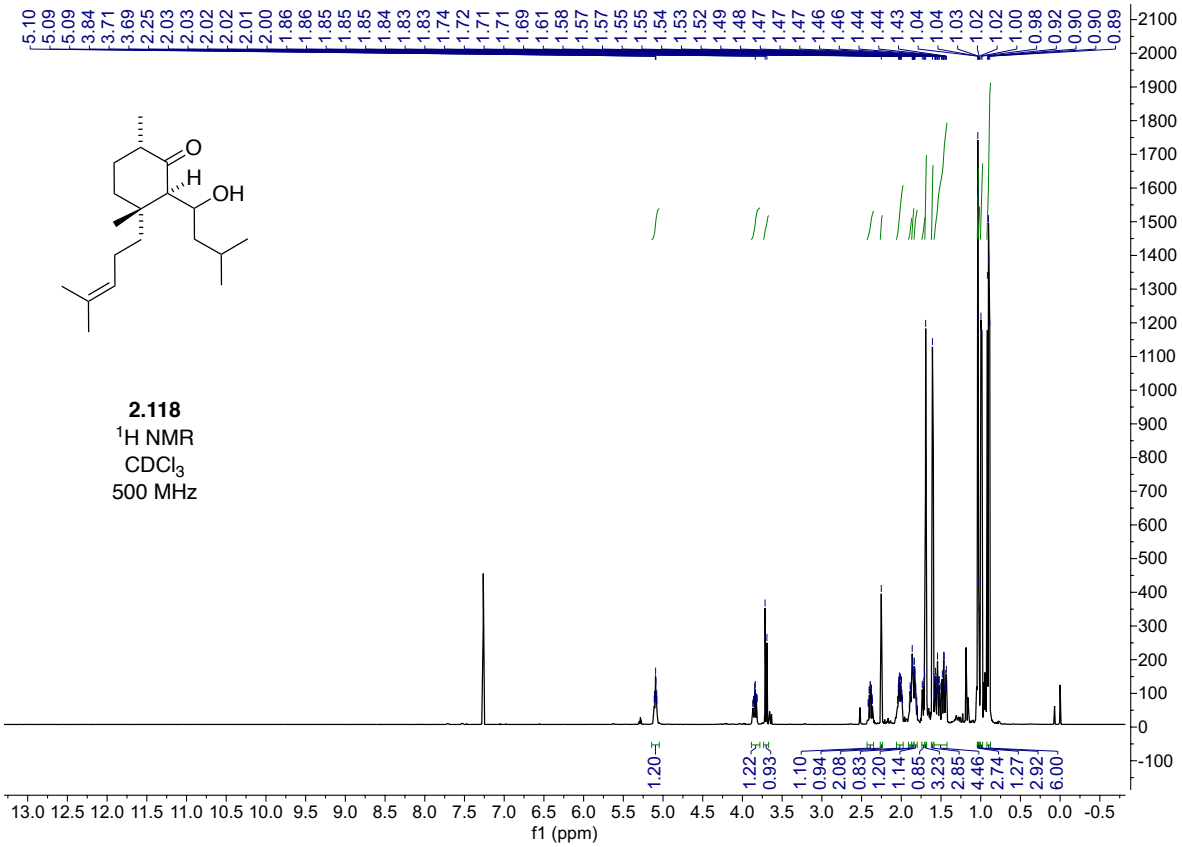

O
H
OH
2.117
13C NMR
CDCl3
125 MHz
ppm

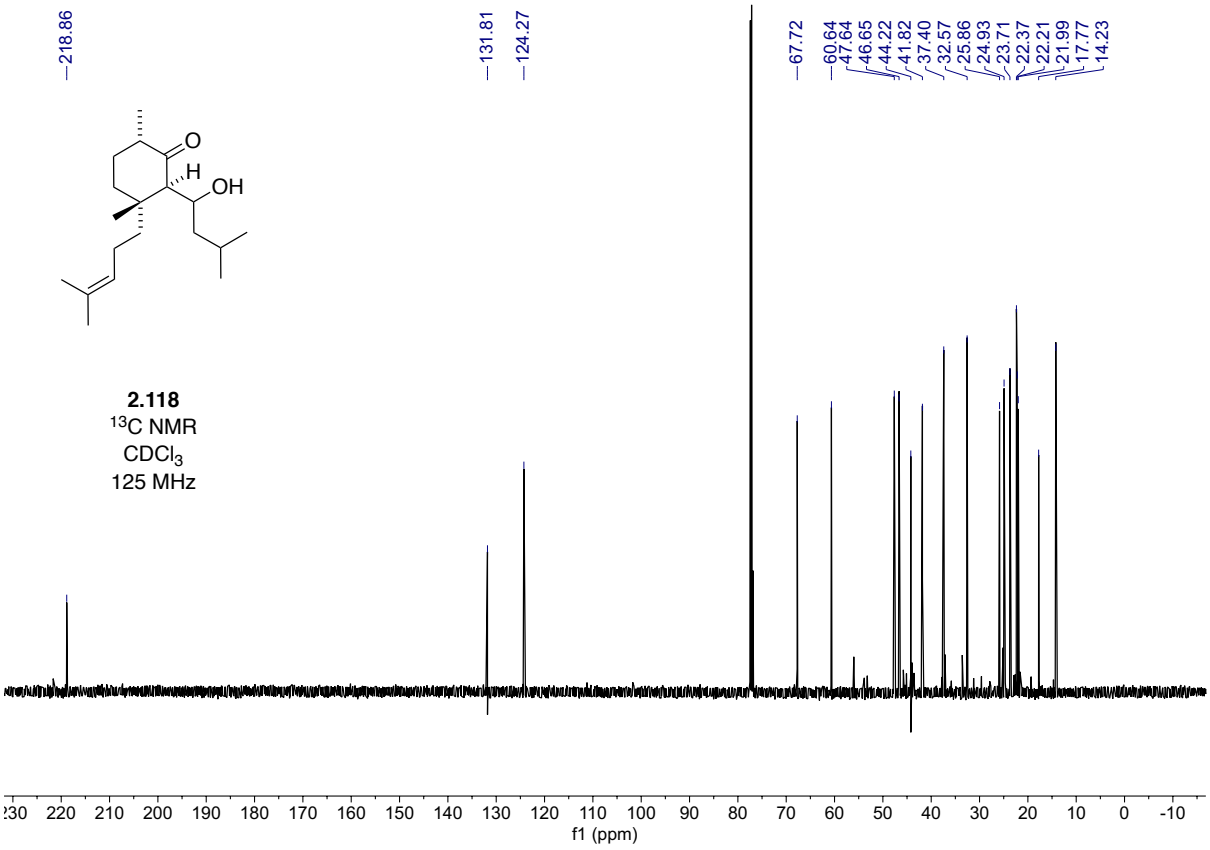

O
H
OH
2.117
COSY
CDCl3
500 MHz
ppm
f1 (ppm)

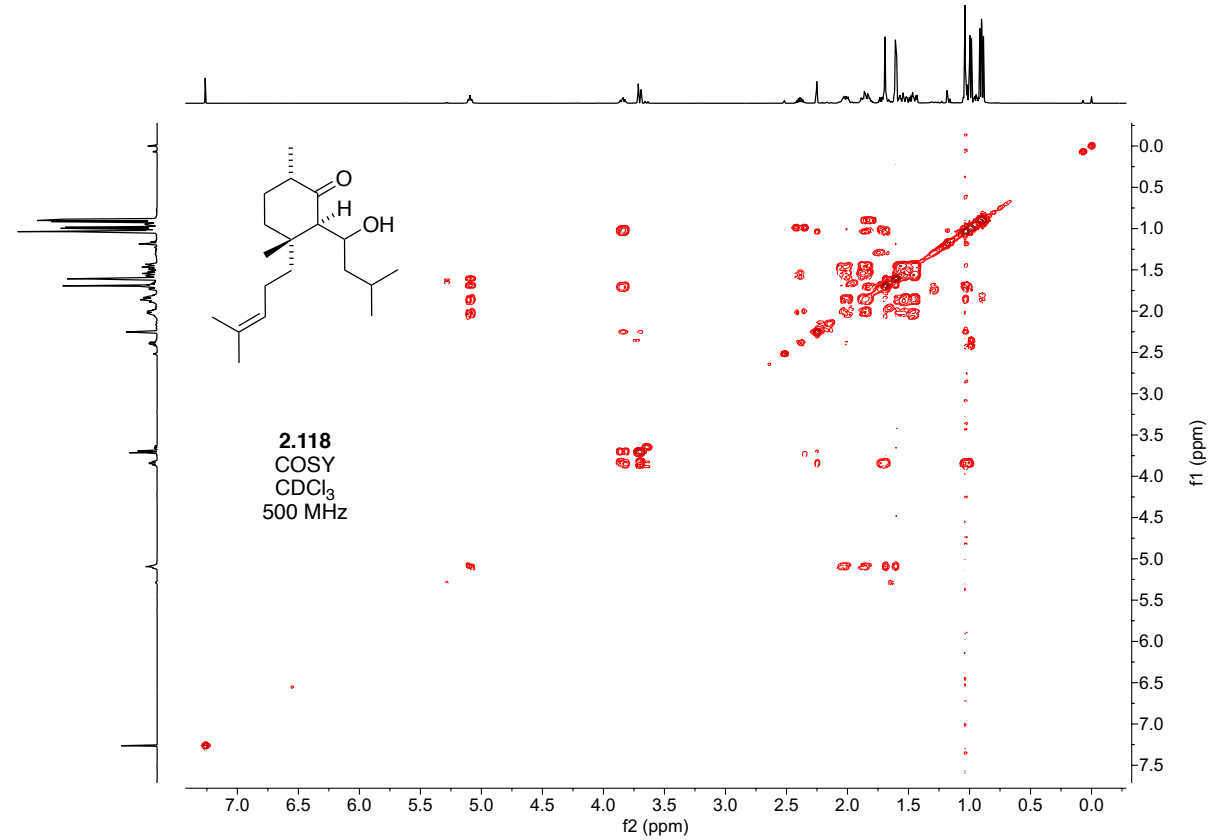

O
H
OH
2.117
HSQC
CDCl3
500 MHz
ppm
f1 (ppm)

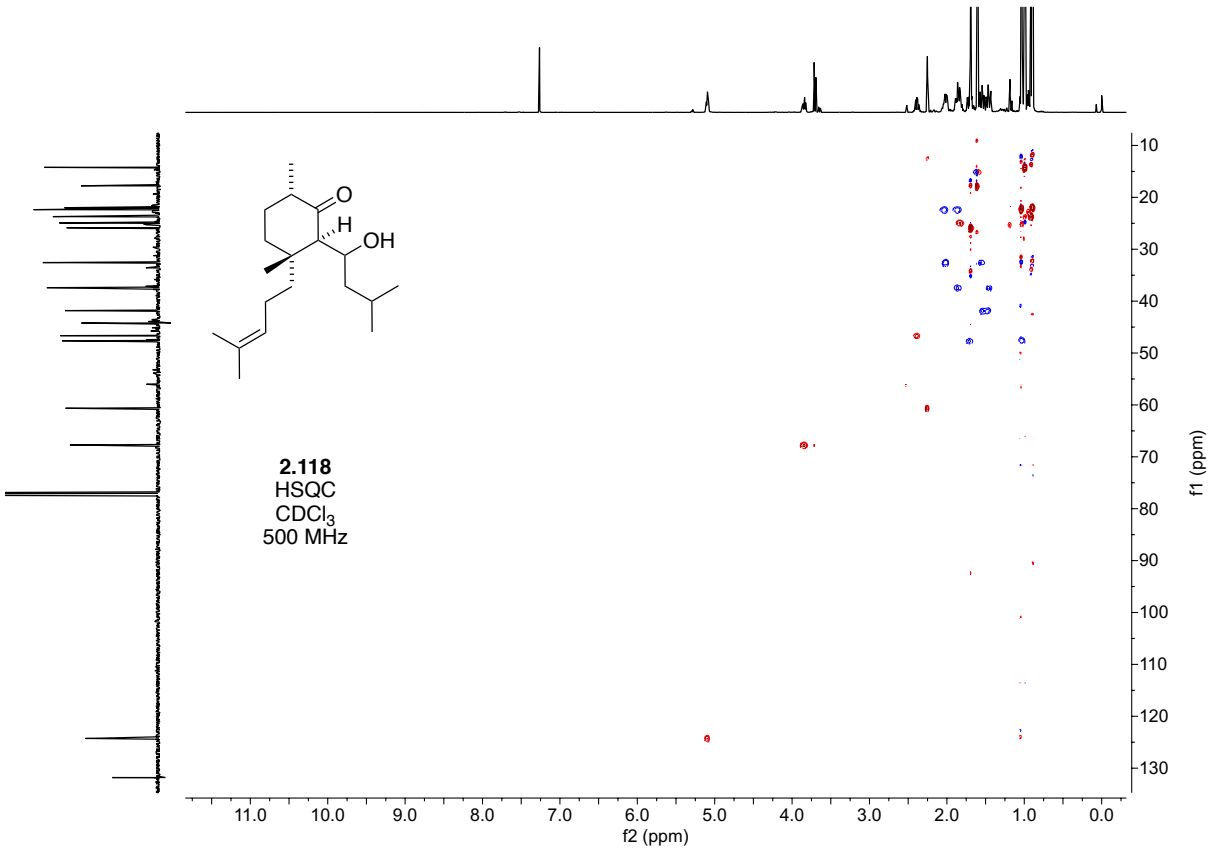

O
H
OH
2.117
HMBC
CDCl3
500 MHz
f1 (ppm)
ppm

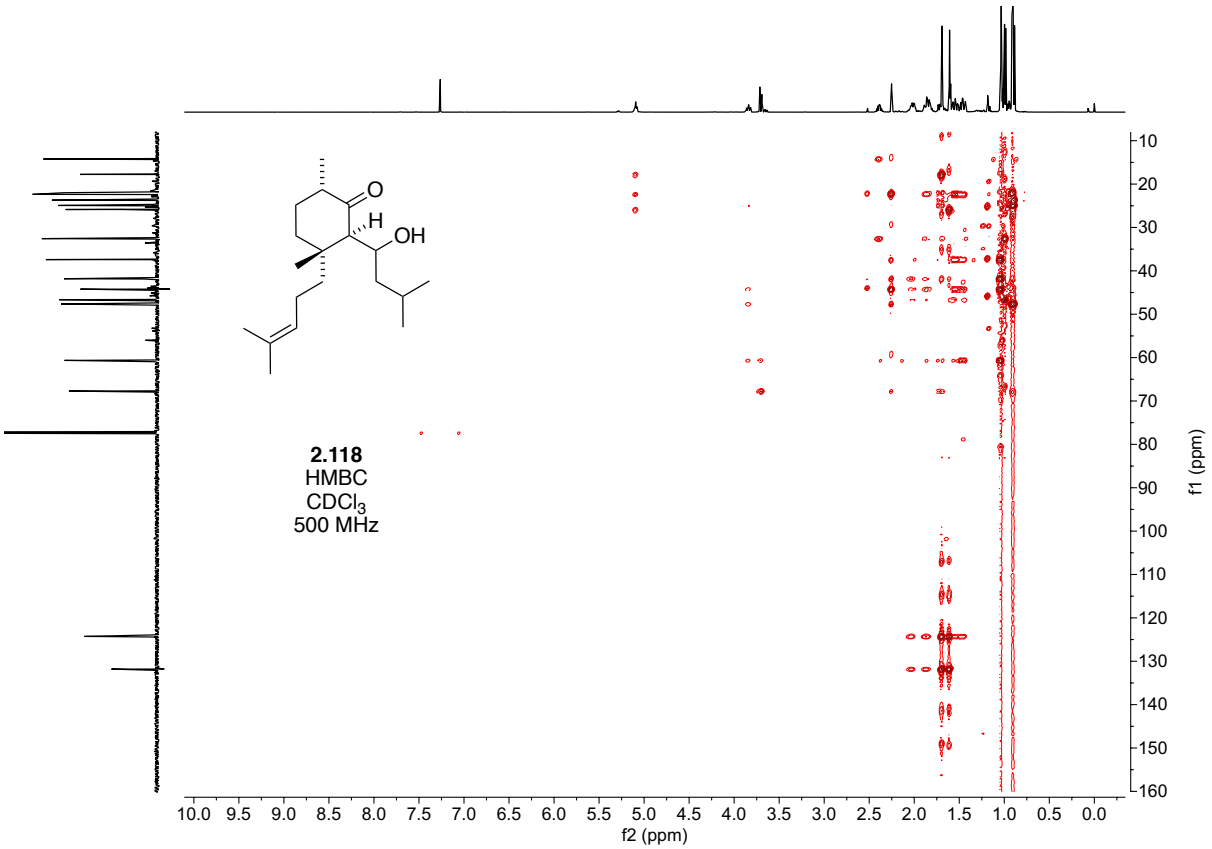

O
H
OH
2.117
NOESY
CDCl3
500 MHz
f1 (ppm)
ppm

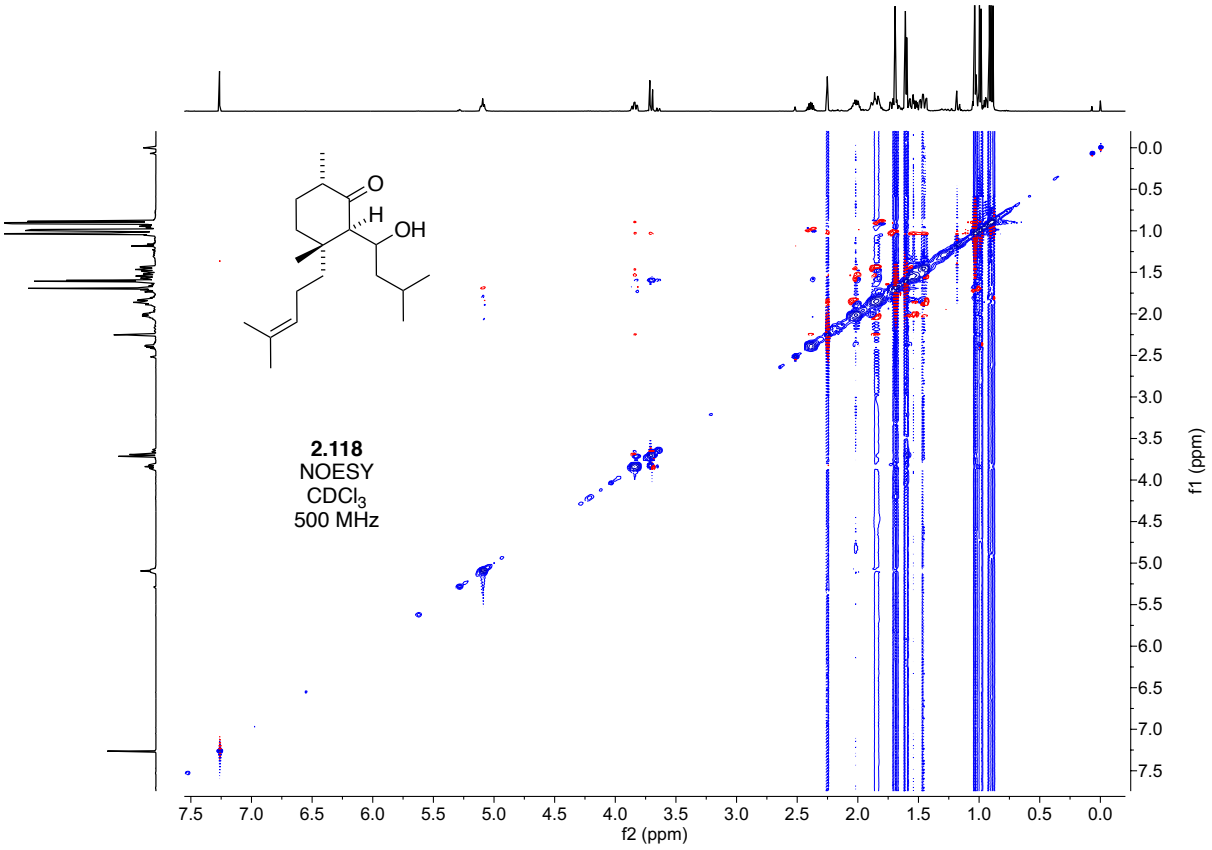

O
H
OH
2.118
1H NMR
CDCl3
500 MHz
f1 (ppm)

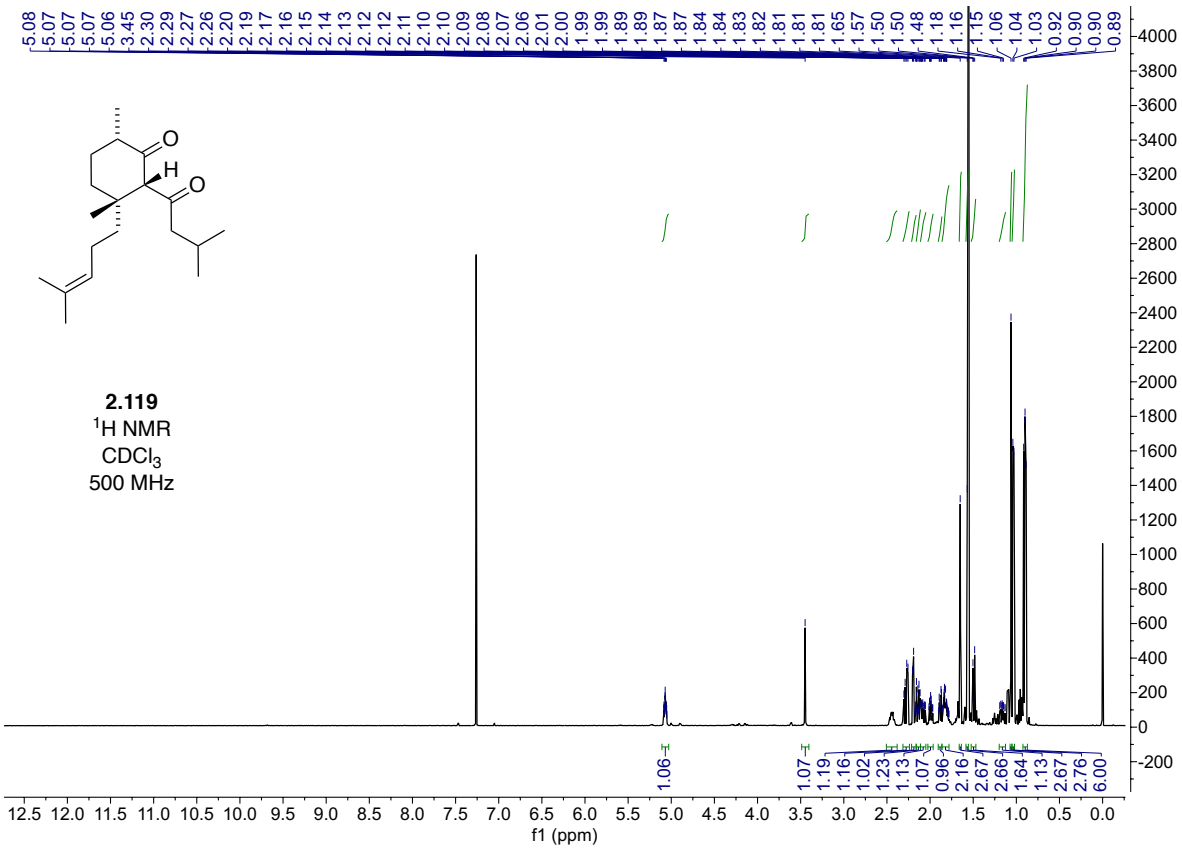

218.86
131.81
124.27
67.72
60.64
47.64
46.65
44.22
41.82
37.40
32.57
25.86
24.93
23.71
22.37
22.21
21.99
17.77
14.23
O
H
OH
2.118
13C NMR
CDCl3
125 MHz
f1 (ppm)

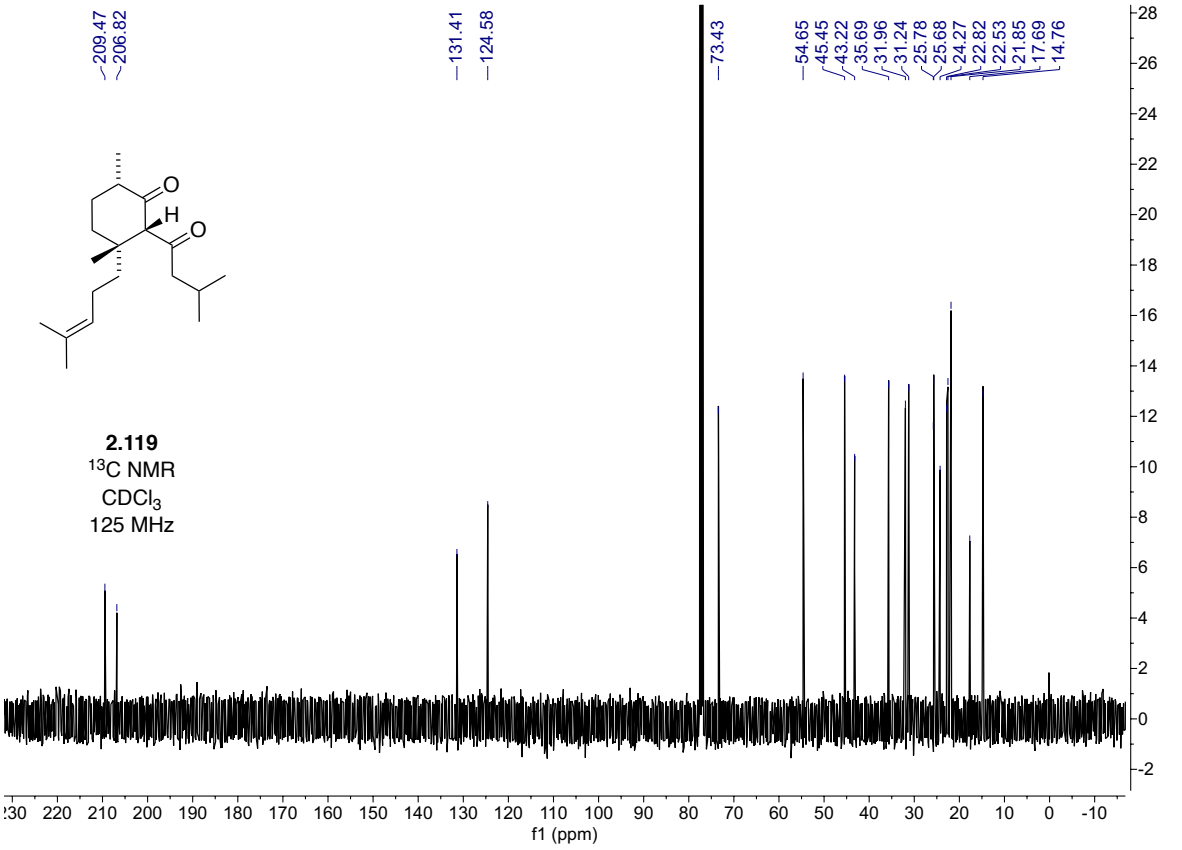

O
H
OH
2.118
COSY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

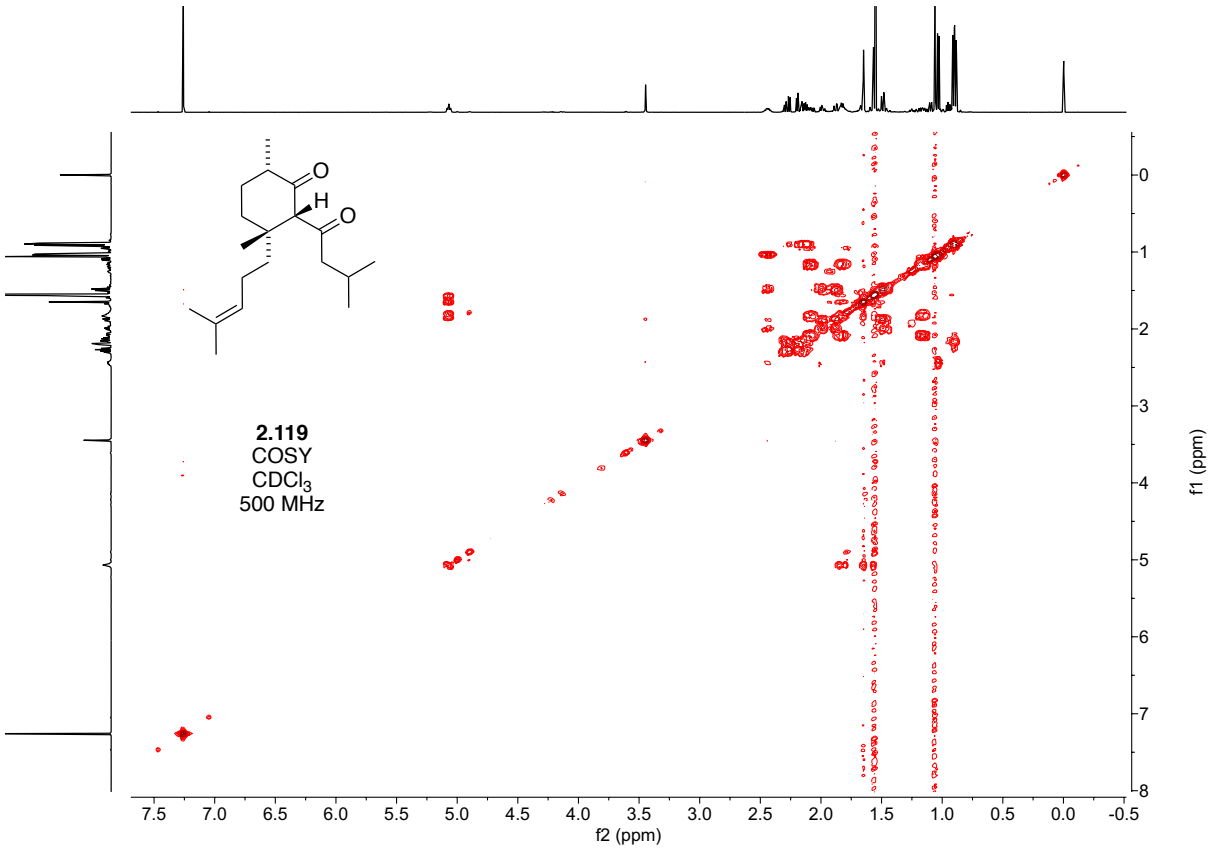

O
H
OH
2.118
HSQC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

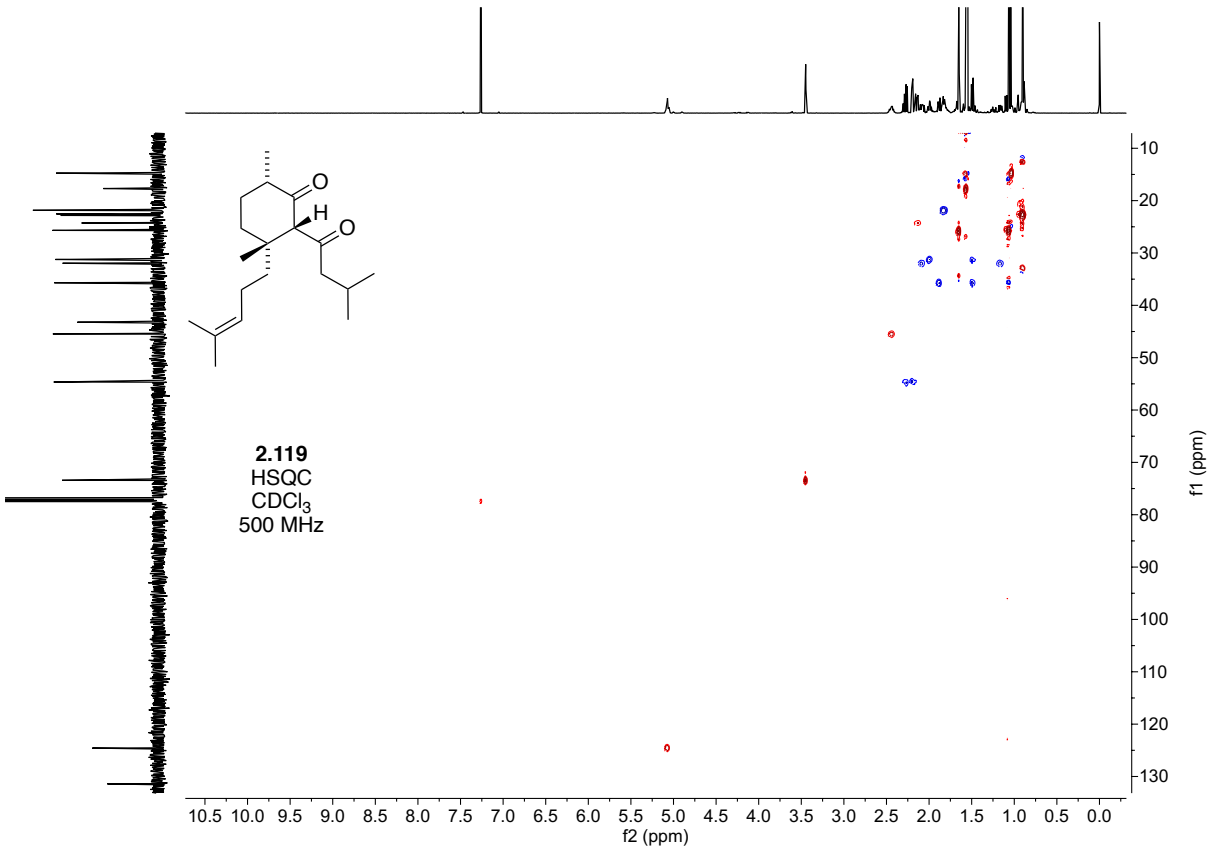

O
H
OH
2.118
HMBC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

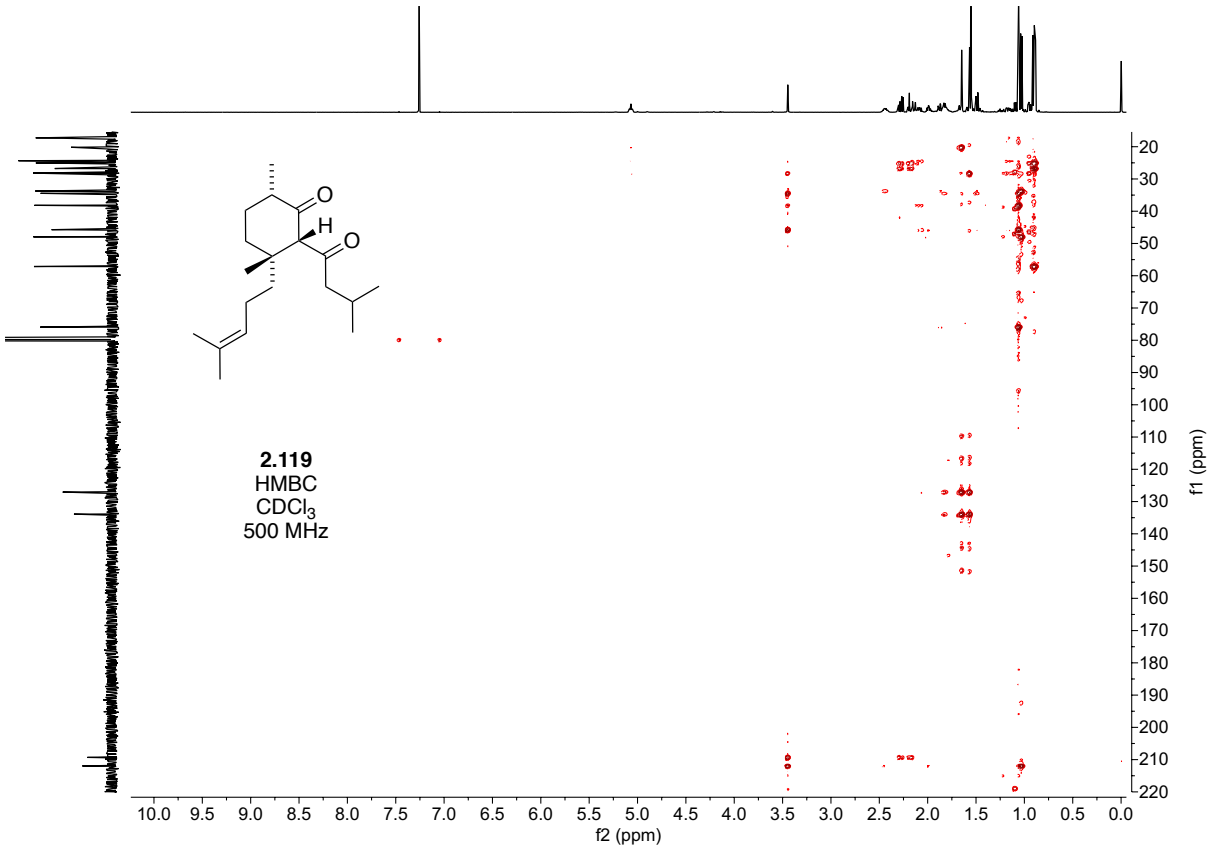

O
H
OH
2.118
NOESY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

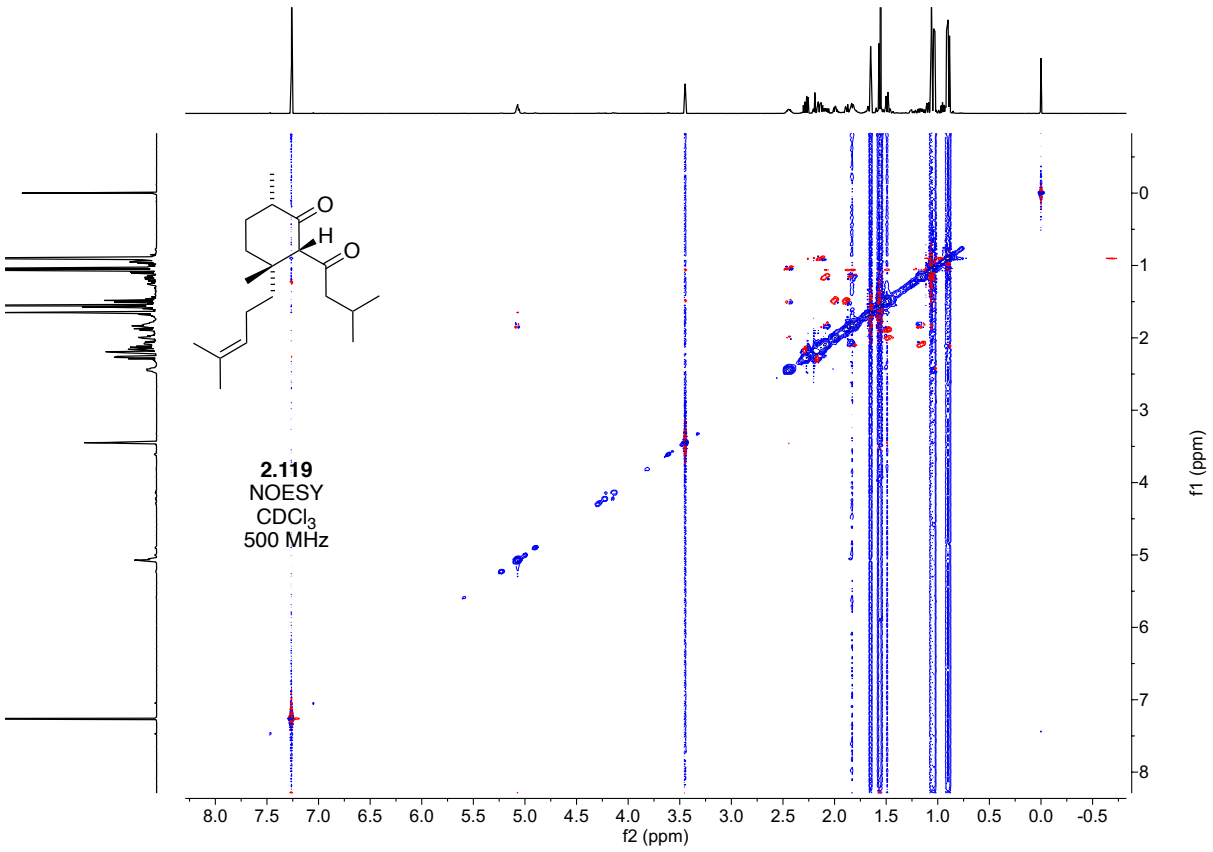

2.119
1H NMR
CDCl3
500 MHz
f1 (ppm)

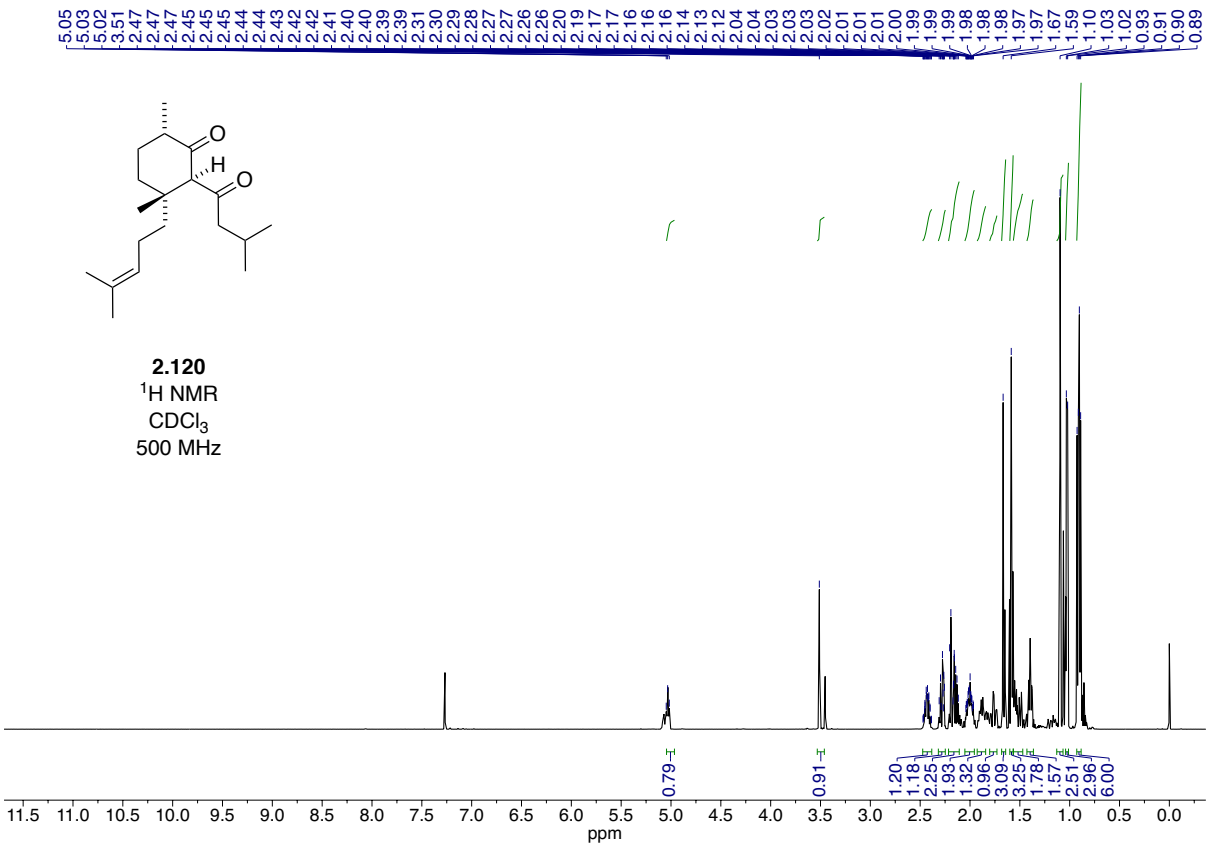

2.119
13C NMR
CDCl3
125 MHz
f1 (ppm)

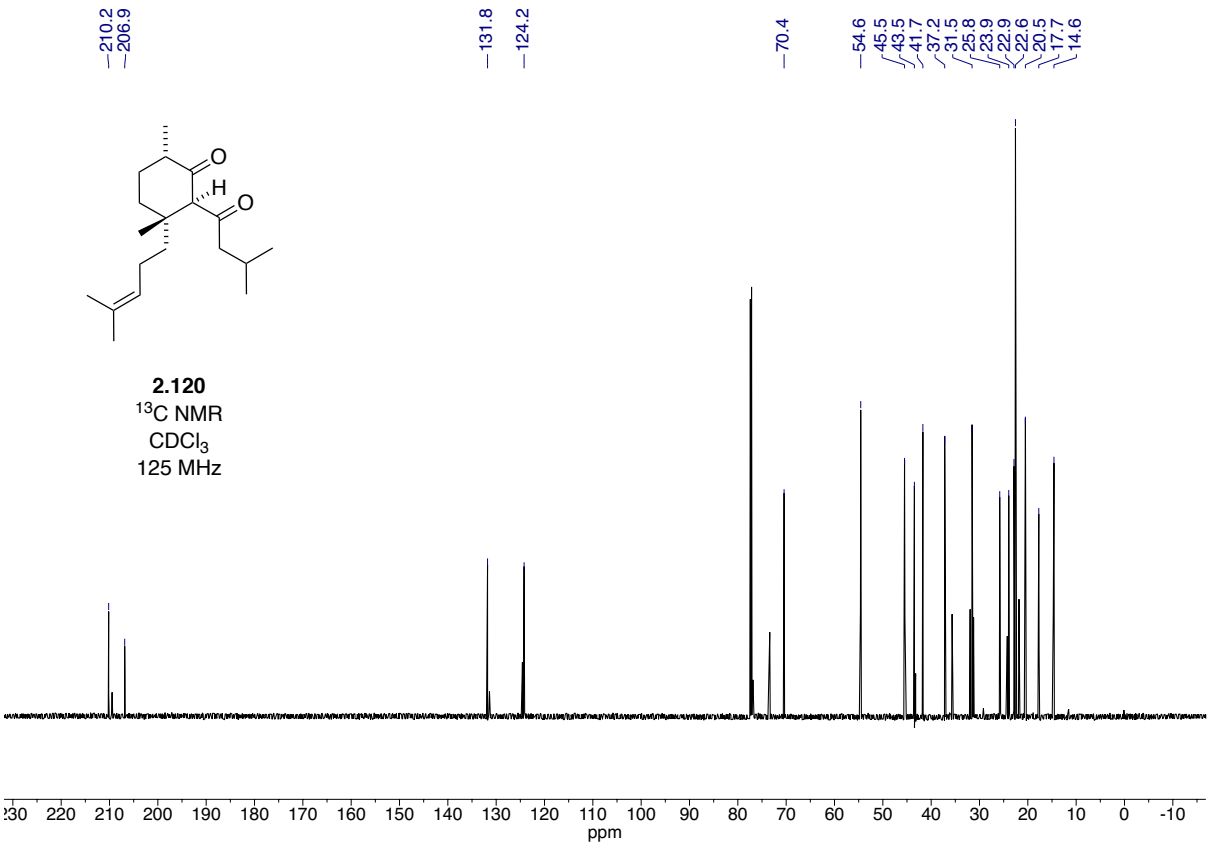

O
H
O
2.119
COSY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

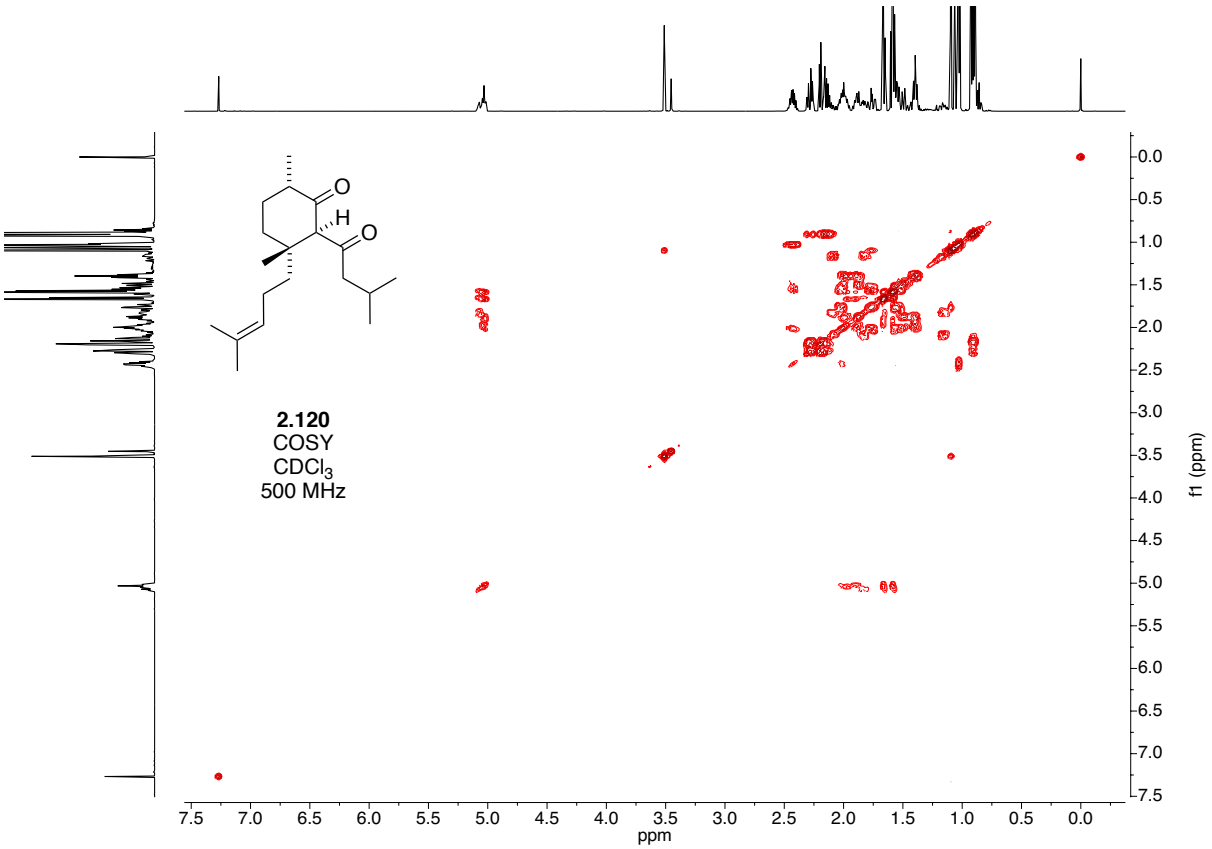

O
H
O
2.119
HSQC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

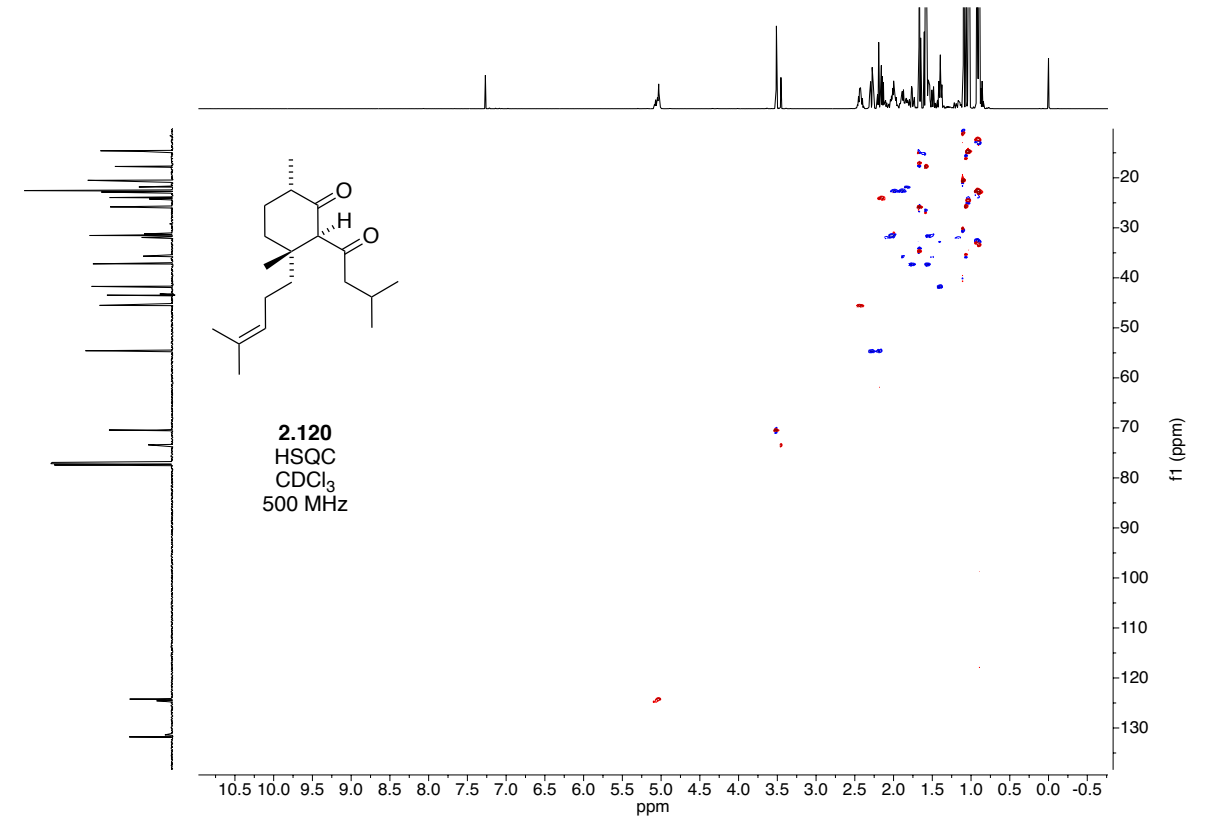

2.119
HMBC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

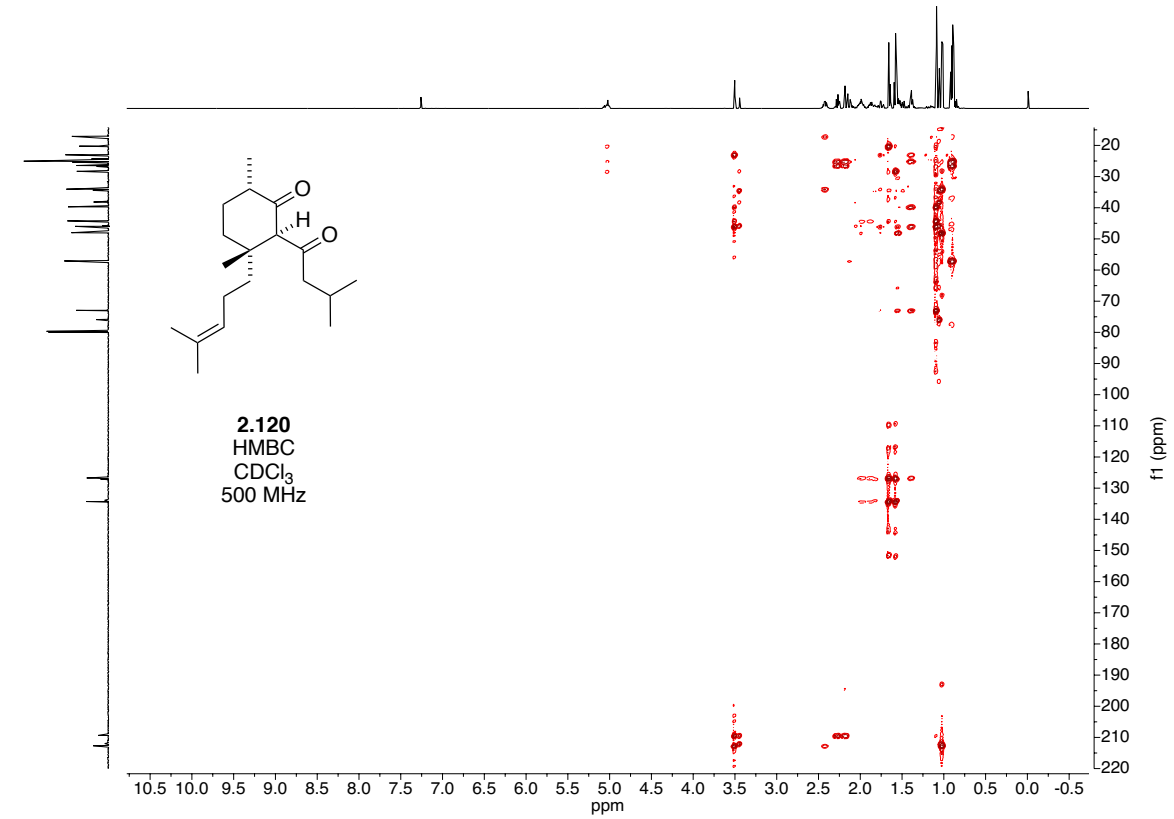

2.119
NOESY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

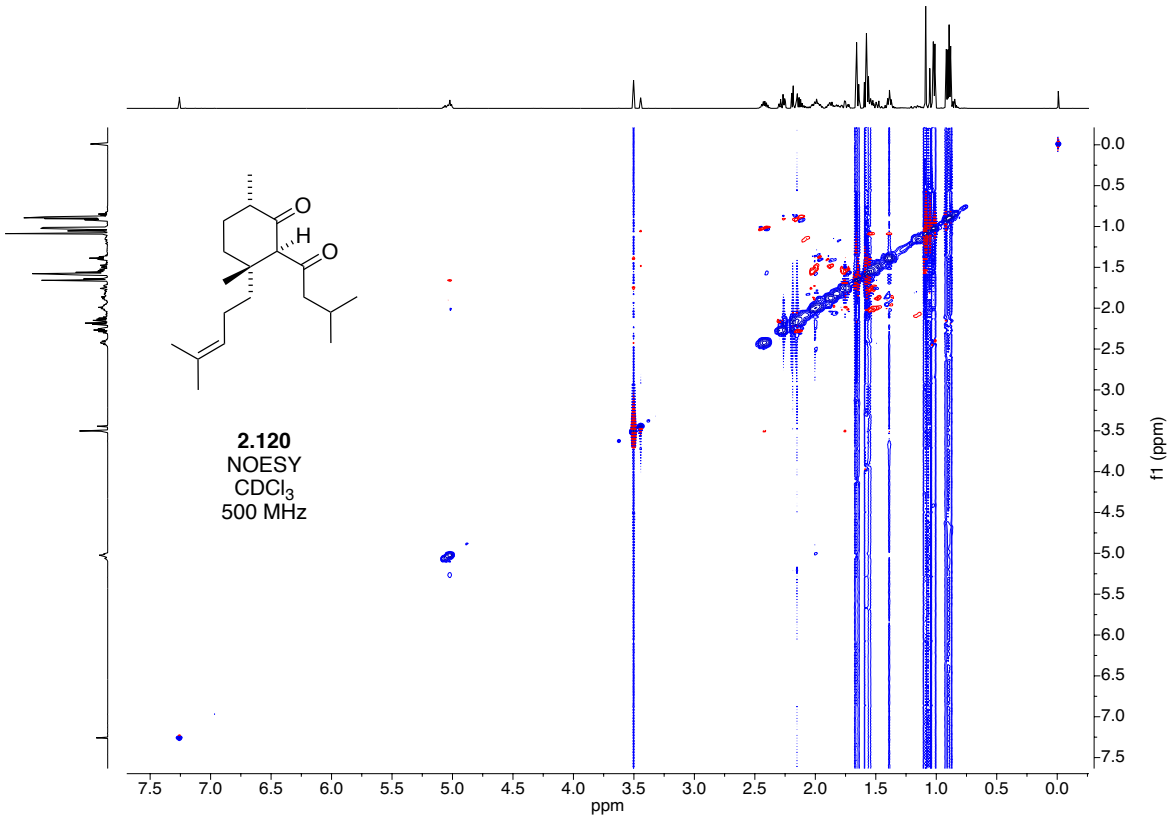

5.05 5.03 5.02 3.51 2.47 2.47 2.47 2.45 2.45 2.44 2.44 2.43 2.42 2.42 2.41 2.40 2.40 2.39 2.39 2.31 2.30 2.29 2.28 2.27 2.27 2.26 2.26 2.20 2.19 2.17 2.17 2.16 2.16 2.16 2.14 2.13 2.12 2.04 2.04 2.03 2.03 2.03 2.02 2.01 2.01 2.00 1.99 1.99 1.99 1.98 1.98 1.98 1.97 1.97 1.67 1.59 1.10 1.03 1.02 0.93 0.91 0.90 0.89
O
H
O
2.120
1H NMR
CDCl3
500 MHz
0.79 0.91 1.20 1.18 2.25 1.93 1.32 0.96 3.09 3.25 1.78 1.57 2.51 2.96 6.00
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

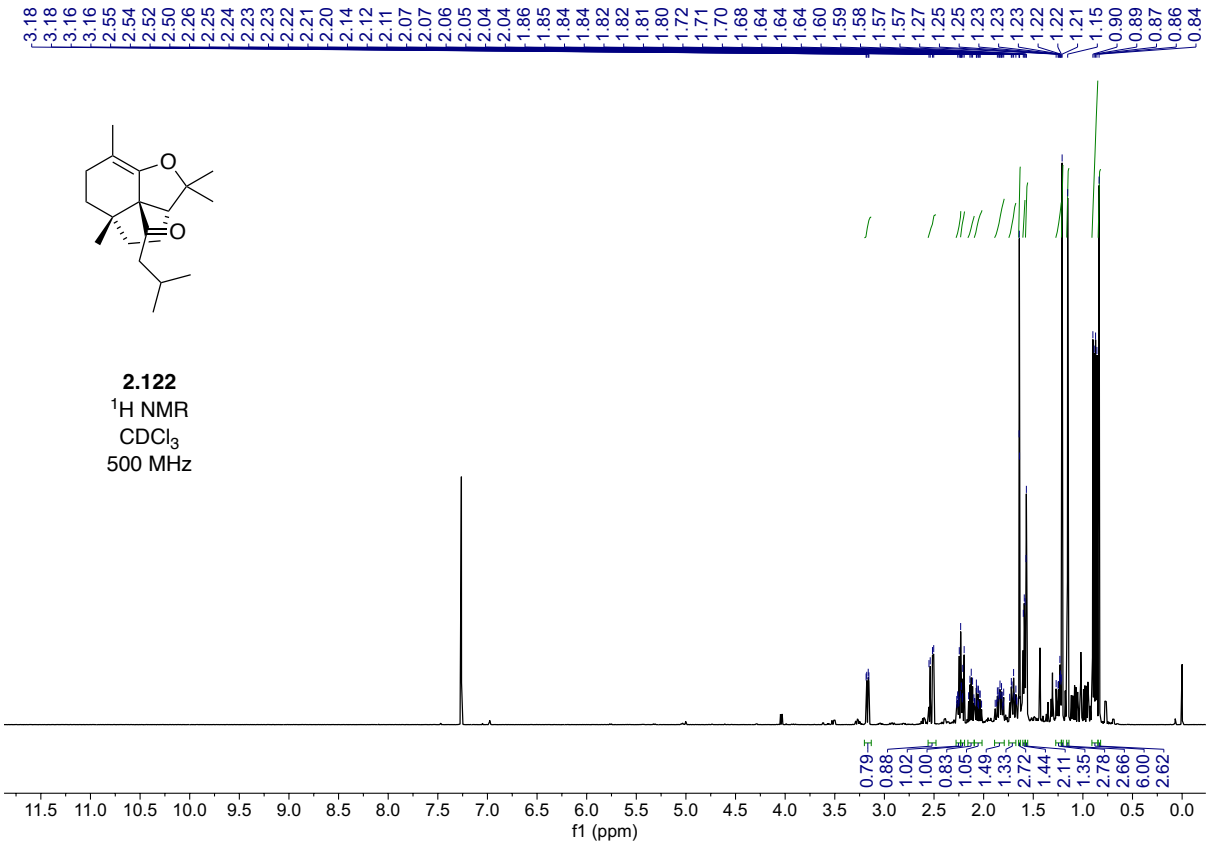

210.2 206.9 131.8 124.2 70.4 54.6 45.5 43.5 41.7 37.2 31.5 25.8 23.9 22.9 22.6 20.5 17.7 14.6
O
H
O
2.120
13C NMR
CDCl3
125 MHz
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

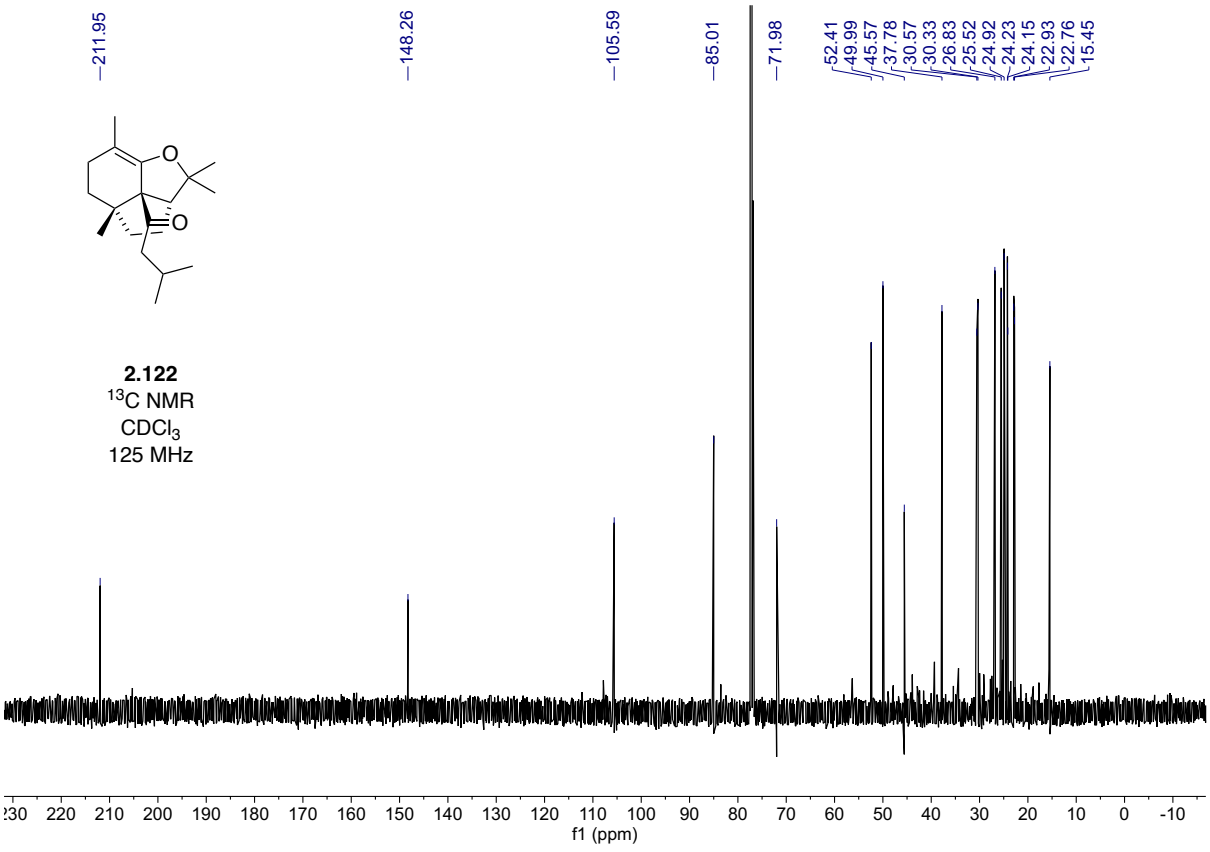

O
H
O
2.120
COSY
CDCl3
500 MHz
ppm
f1 (ppm)

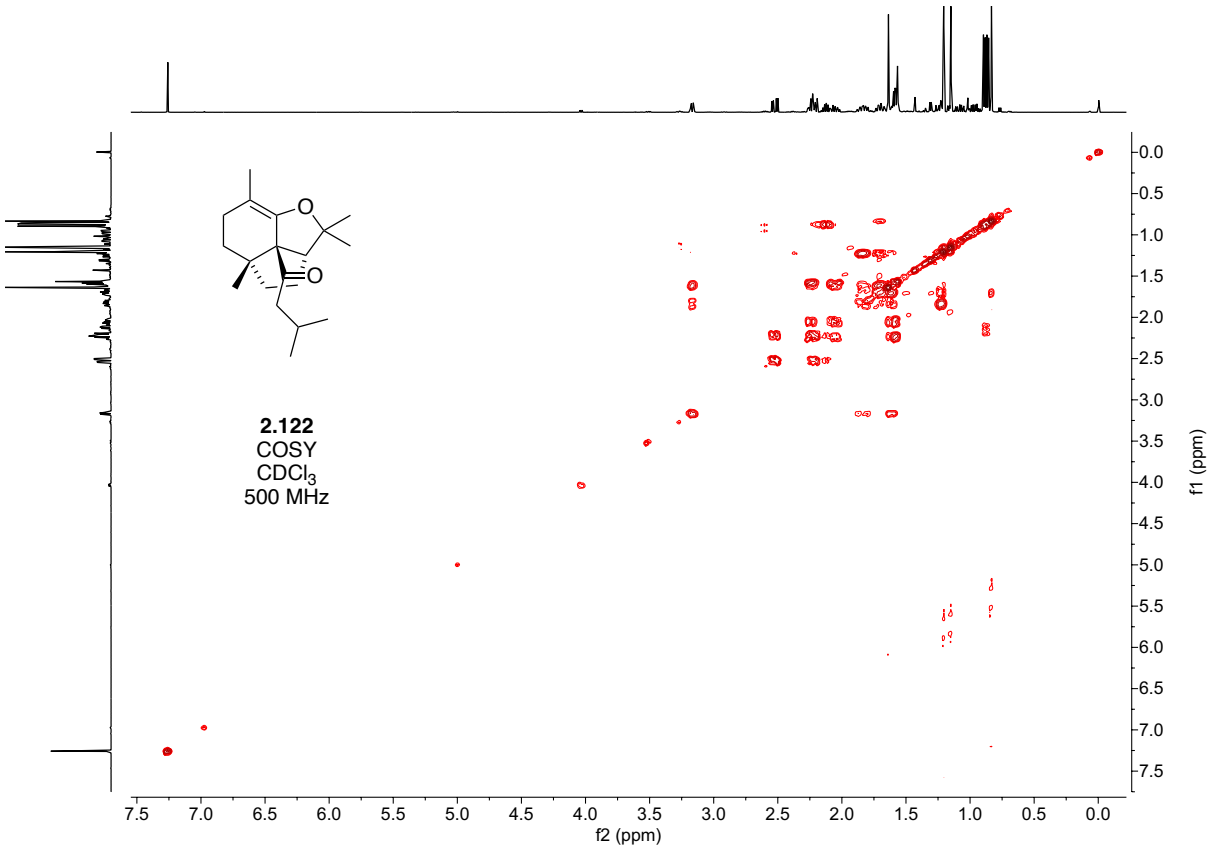

O
H
O
2.120
HSQC
CDCl3
500 MHz
ppm
f1 (ppm)

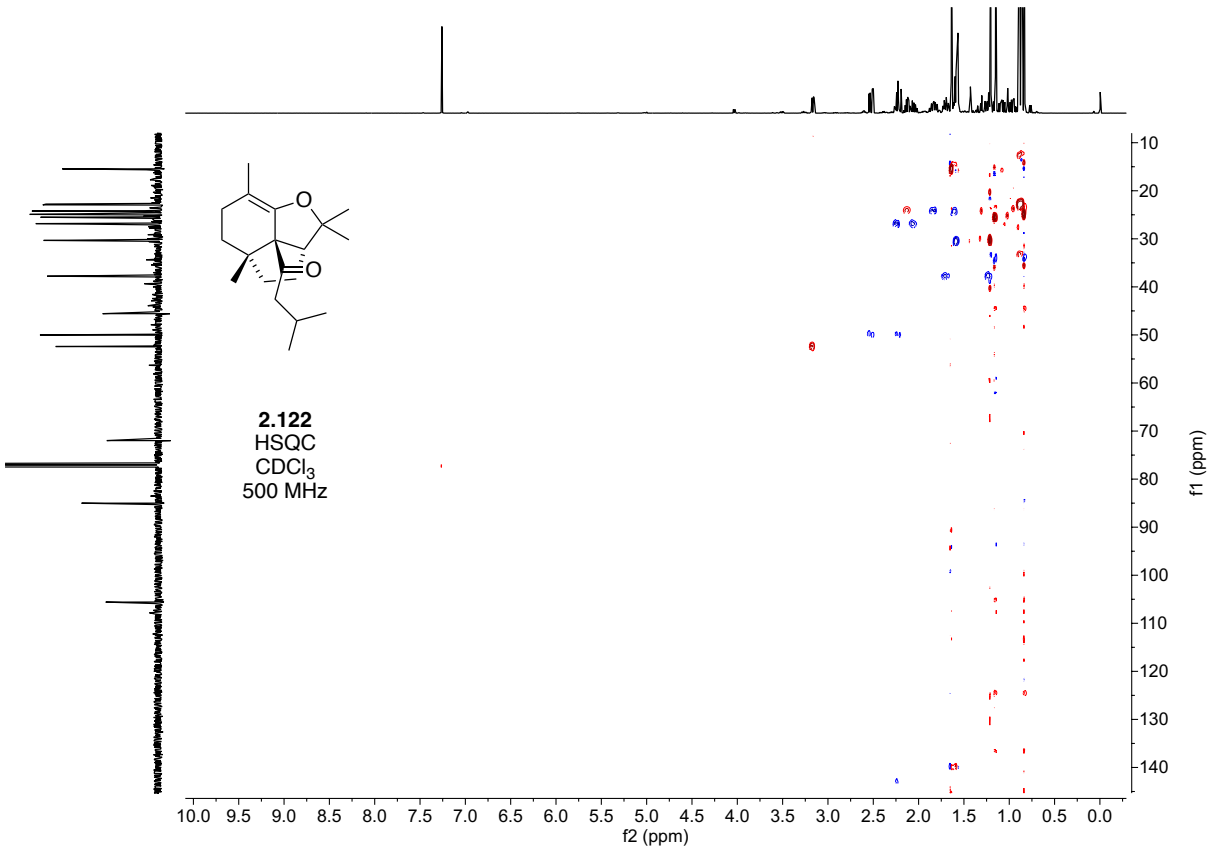

O
H
O
2.120
HMBC
CDCl3
500 MHz
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm
20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220
f1 (ppm)

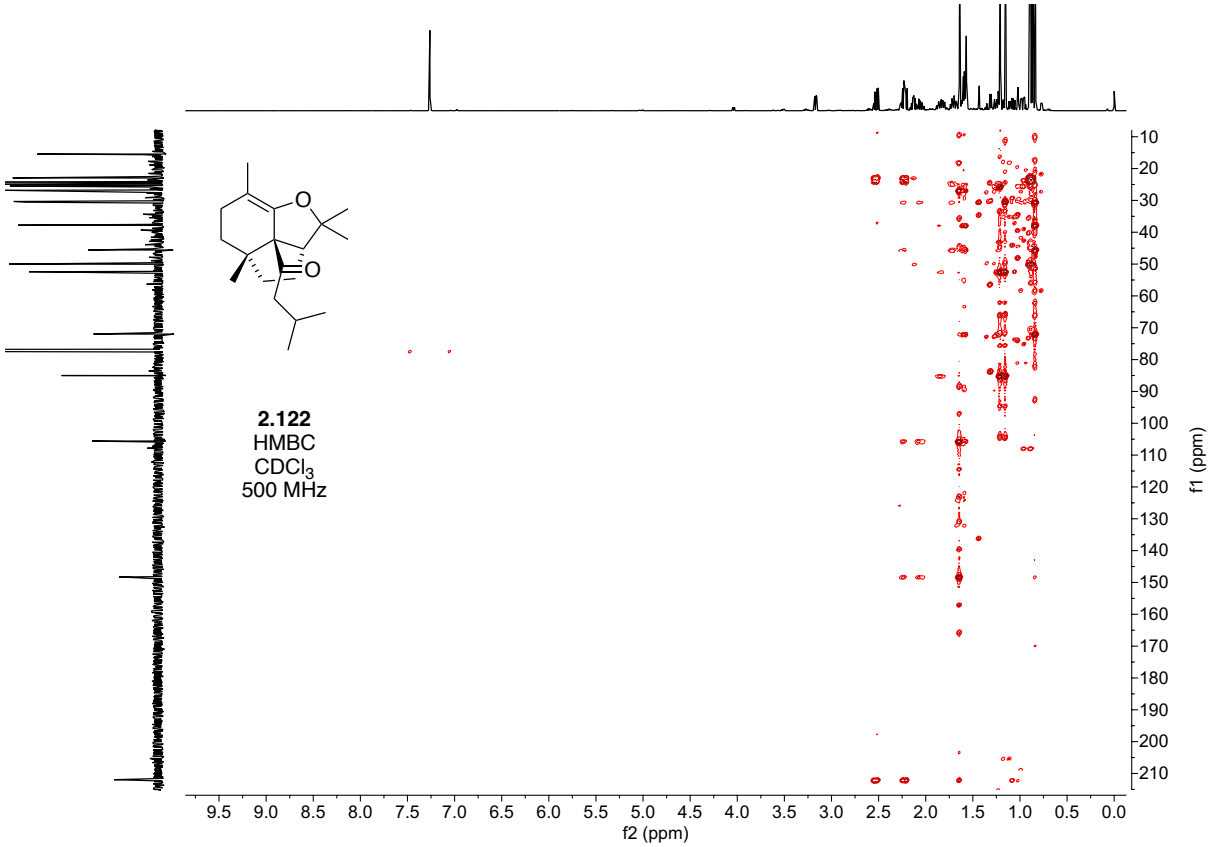

O
H
O
2.120
NOESY
CDCl3
500 MHz
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5
f1 (ppm)

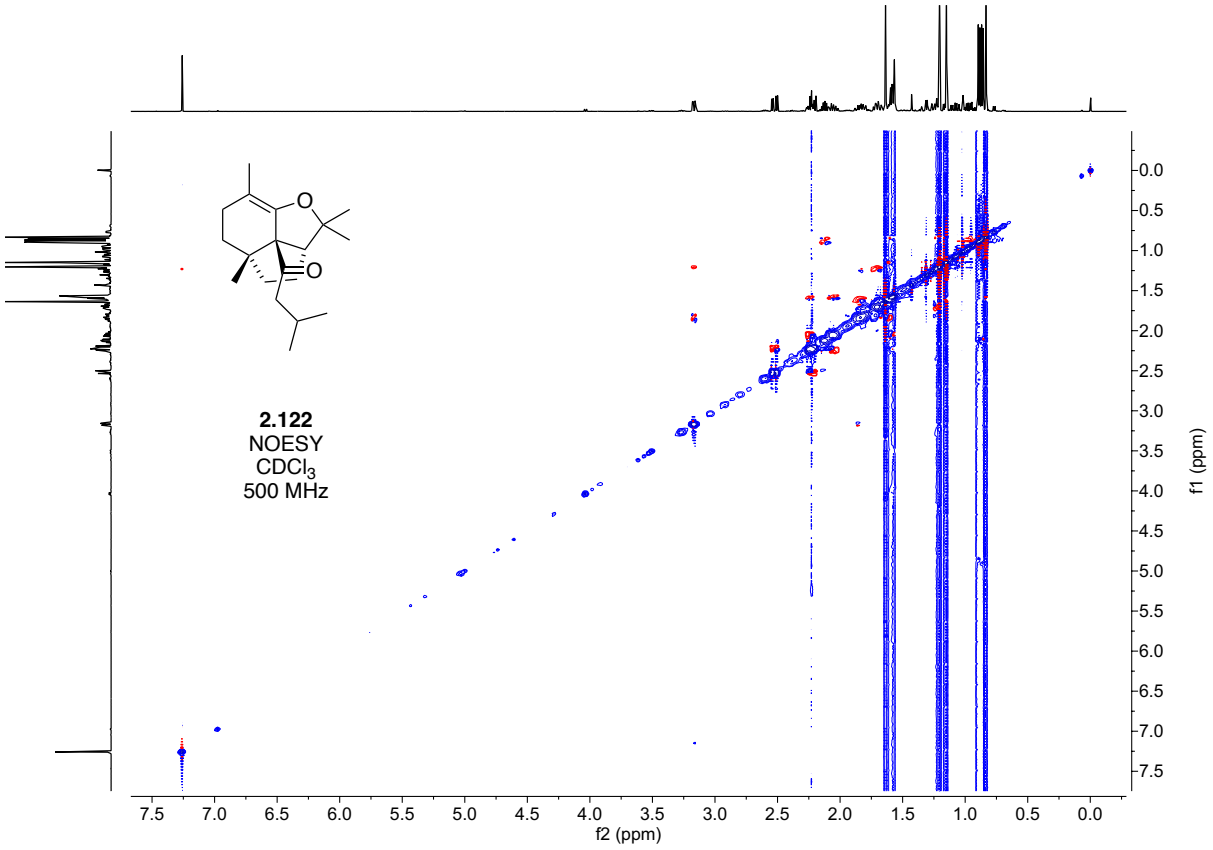

3.18 3.18 3.16 3.16 2.55 2.54 2.52 2.50 2.26 2.25 2.24 2.23 2.23 2.22 2.21 2.20 2.14 2.12 2.11 2.07 2.07 2.06 2.05 2.04 2.04 1.86 1.85 1.84 1.84 1.82 1.82 1.81 1.80 1.72 1.71 1.70 1.68 1.64 1.64 1.64 1.60 1.59 1.58 1.57 1.57 1.27 1.25 1.25 1.23 1.23 1.23 1.22 1.22 1.21 1.15 0.90 0.89 0.87 0.86 0.84
O
O
2.122
1H NMR
CDCl3
500 MHz
0.79 0.88 1.02 1.00 0.83 1.05 1.49 1.33 2.72 1.44 2.11 1.35 2.78 2.66 6.00 2.62
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

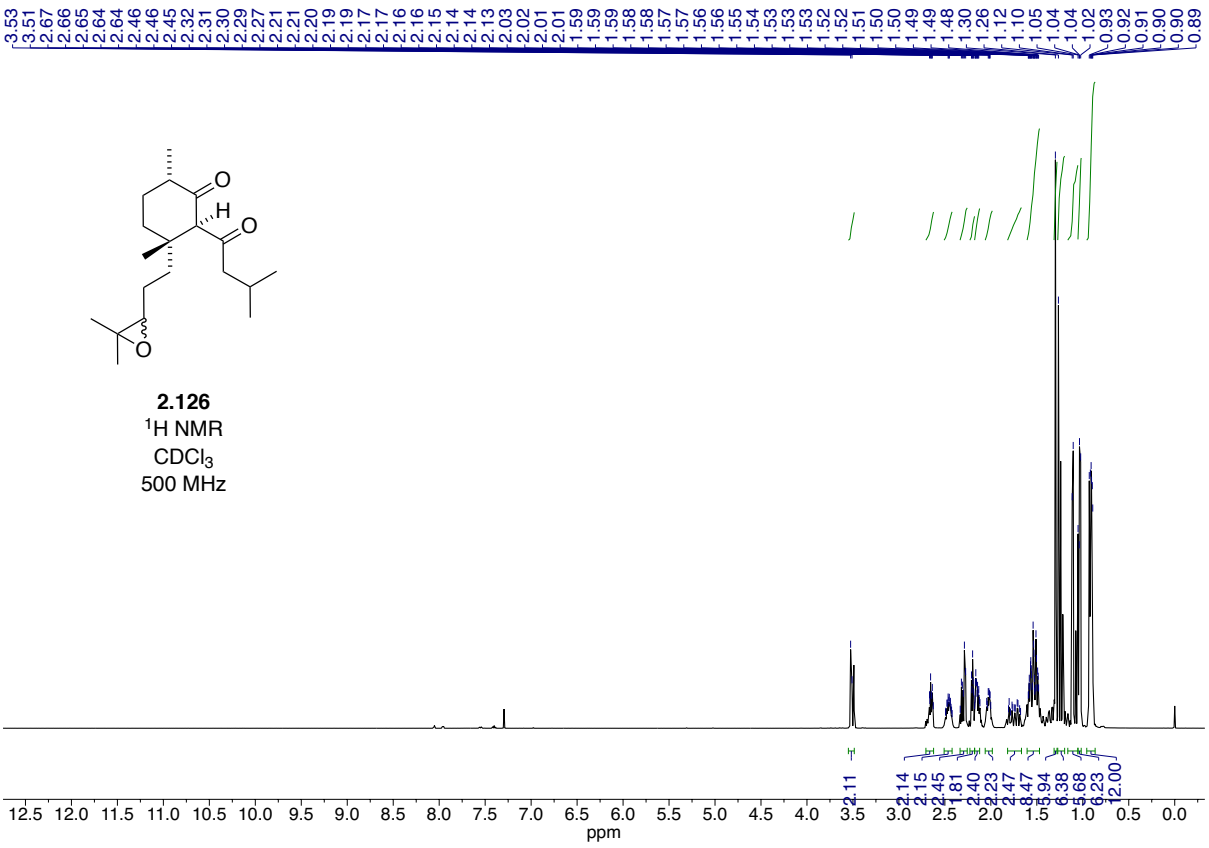

211.95 148.26 105.59 85.01 71.98 52.41 49.99 45.57 37.78 30.57 30.33 26.83 25.52 24.92 24.23 24.15 22.93 22.76 15.45
O
O
2.122
13C NMR
CDCl3
125 MHz
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
O
2.122
COSY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

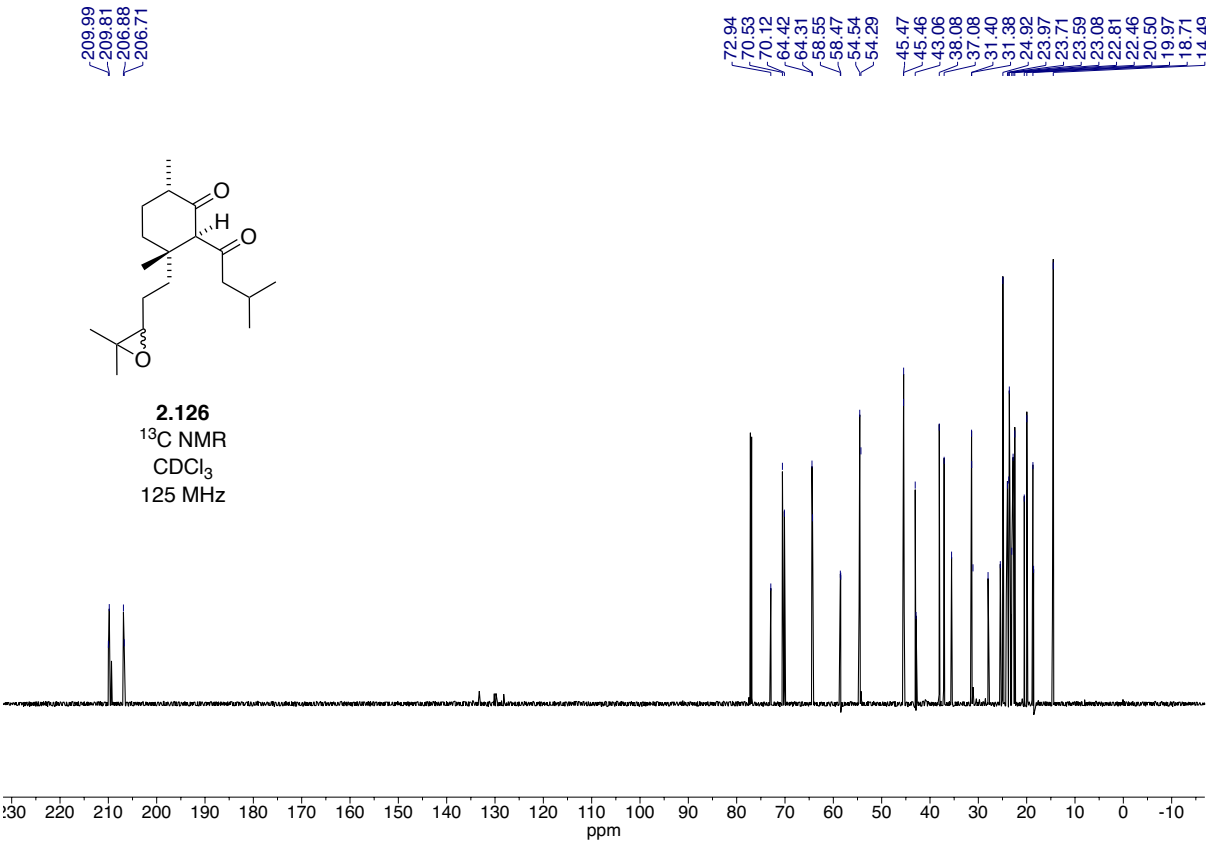

O
O
2.122
HSQC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)


2.122
HMBC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

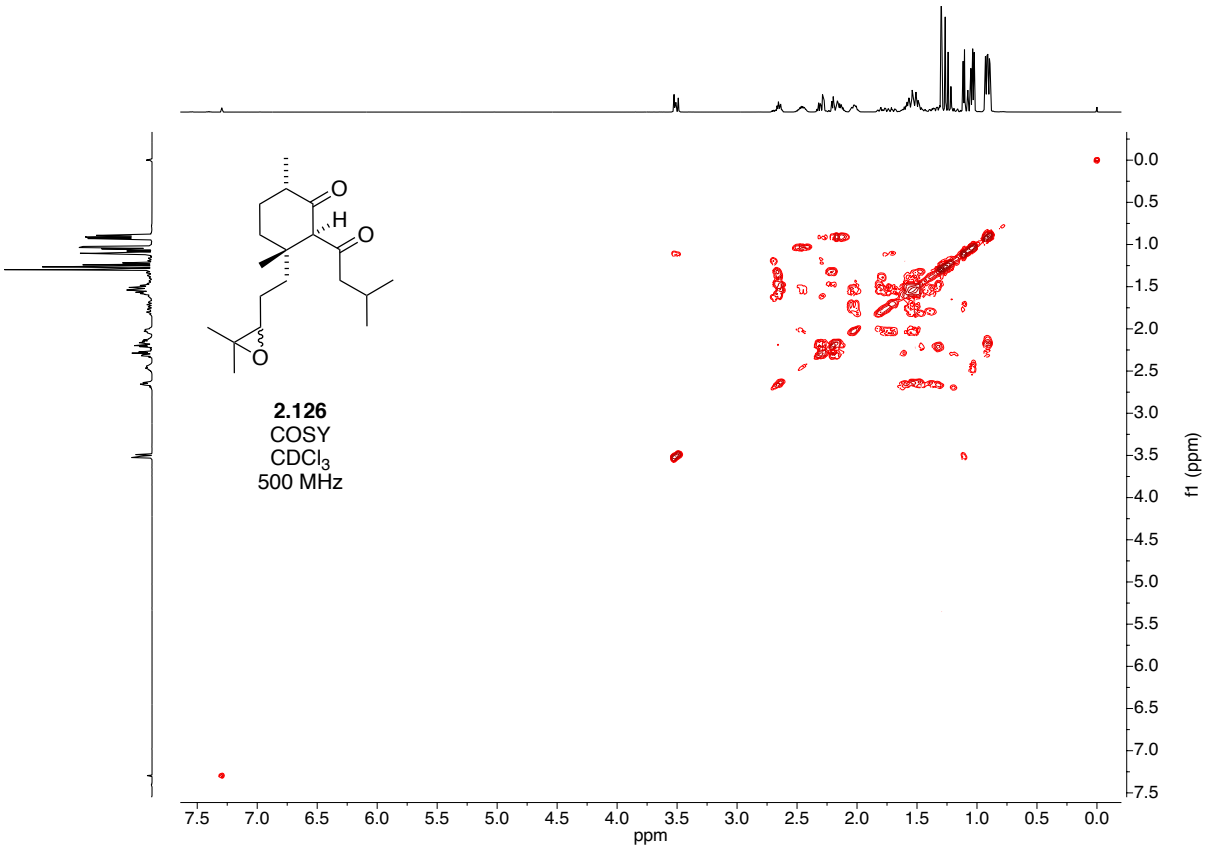

2.122
NOESY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)

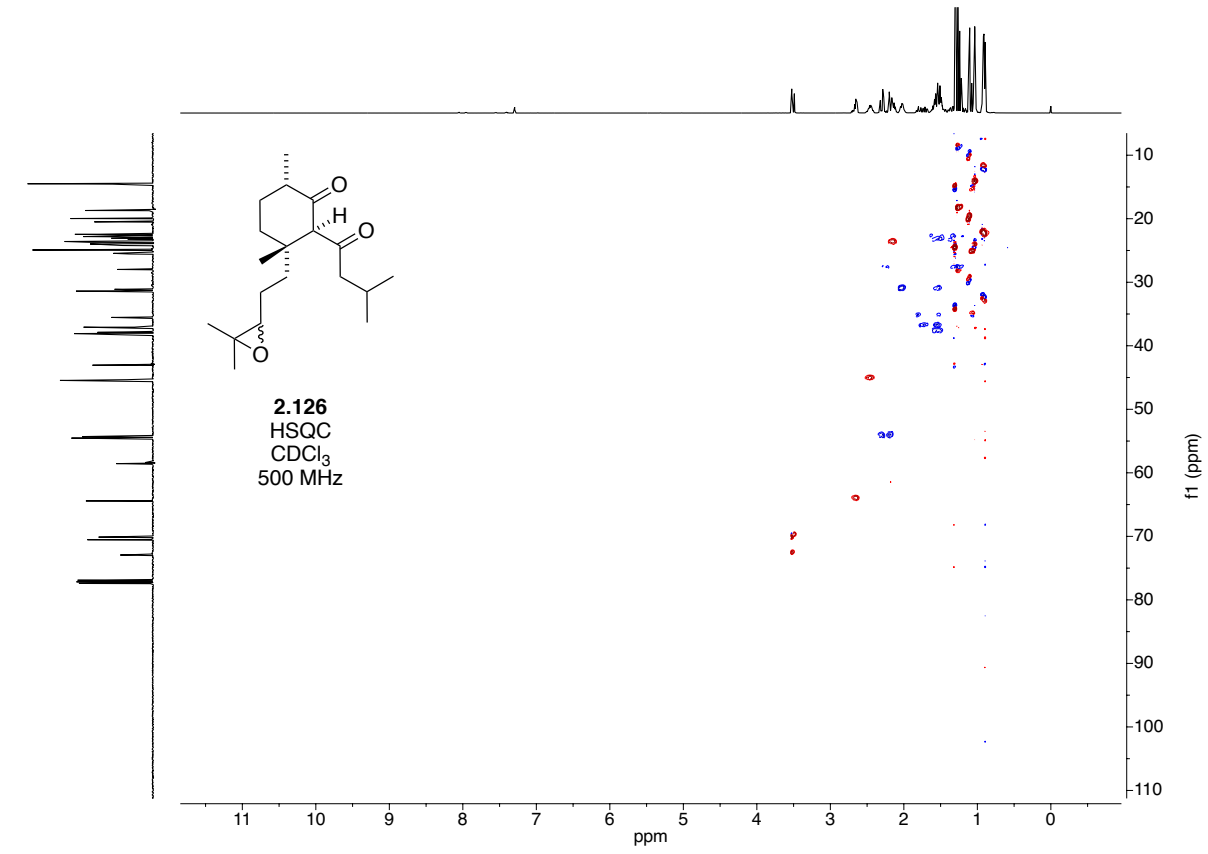


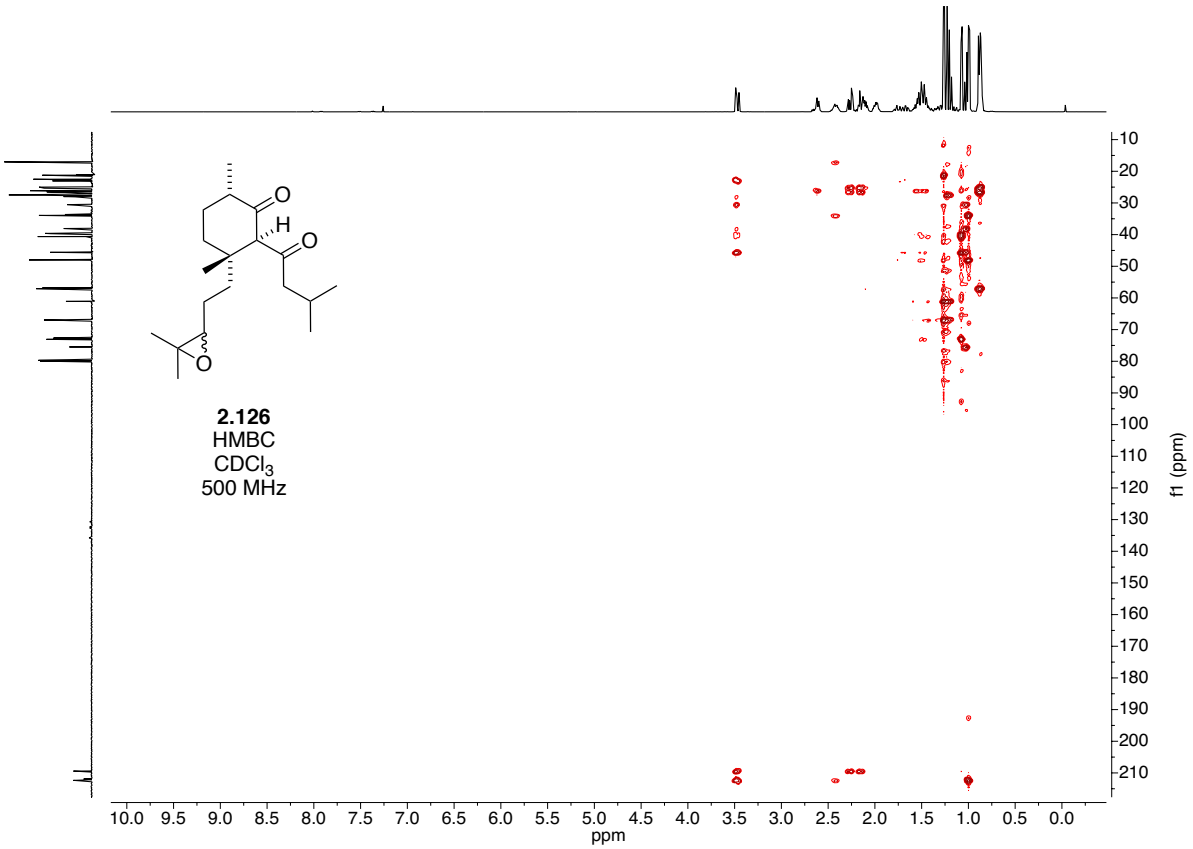
2.126
^{1}H NMR
$CDCl_3$
500 MHz

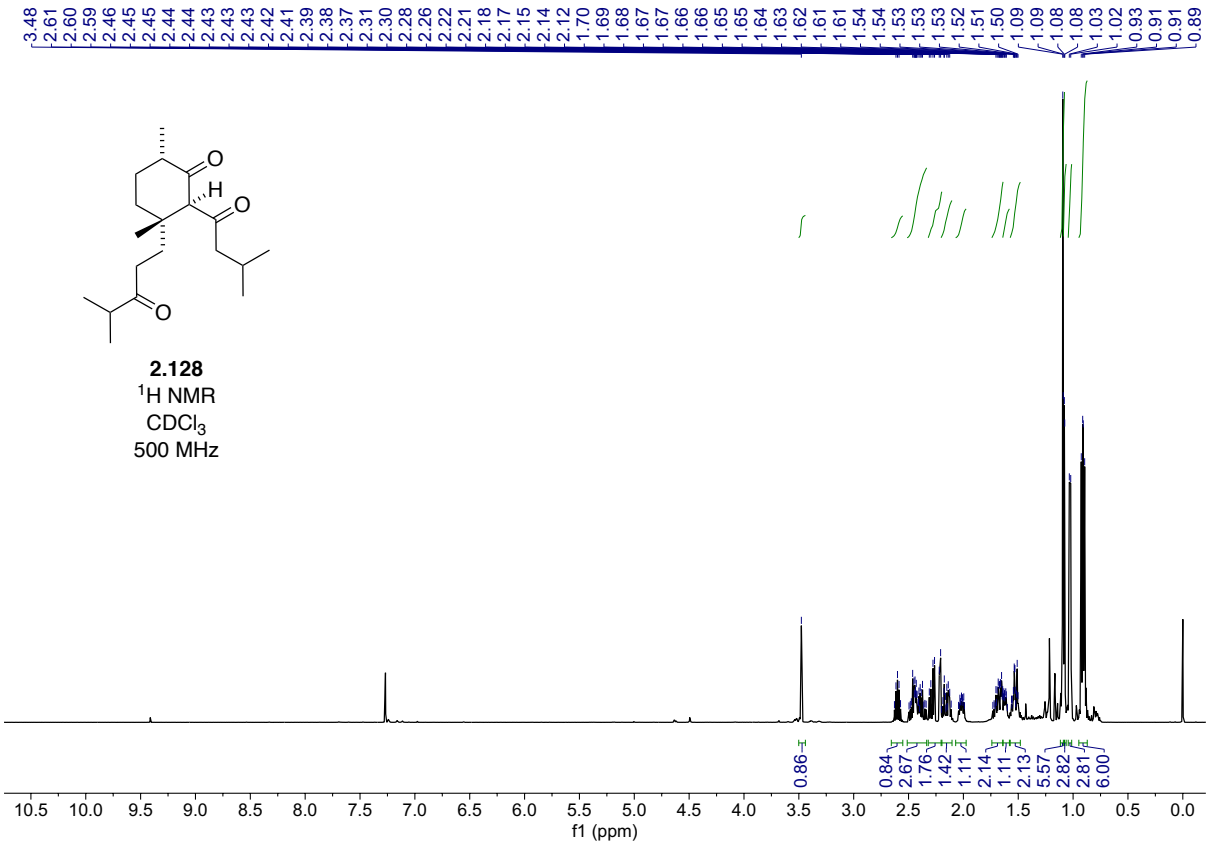


2.126
^{13}C NMR
$CDCl_3$
125 MHz

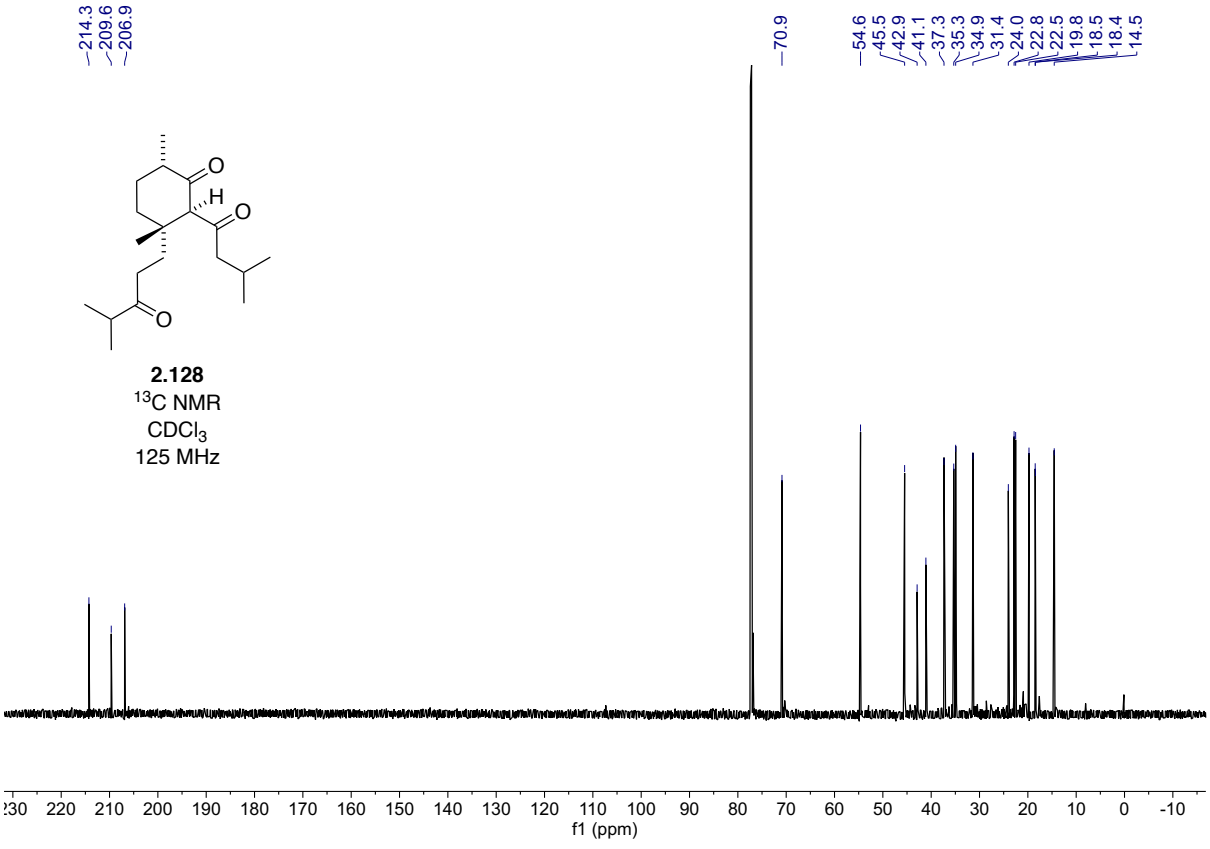

O
H
O
O
2.126
COSY
CDCl3
500 MHz
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5
f1 (ppm)


O
H
O
O
2.126
HSQC
CDCl3
500 MHz
11 10 9 8 7 6 5 4 3 2 1 0
ppm
10 20 30 40 50 60 70 80 90 100 110
f1 (ppm)

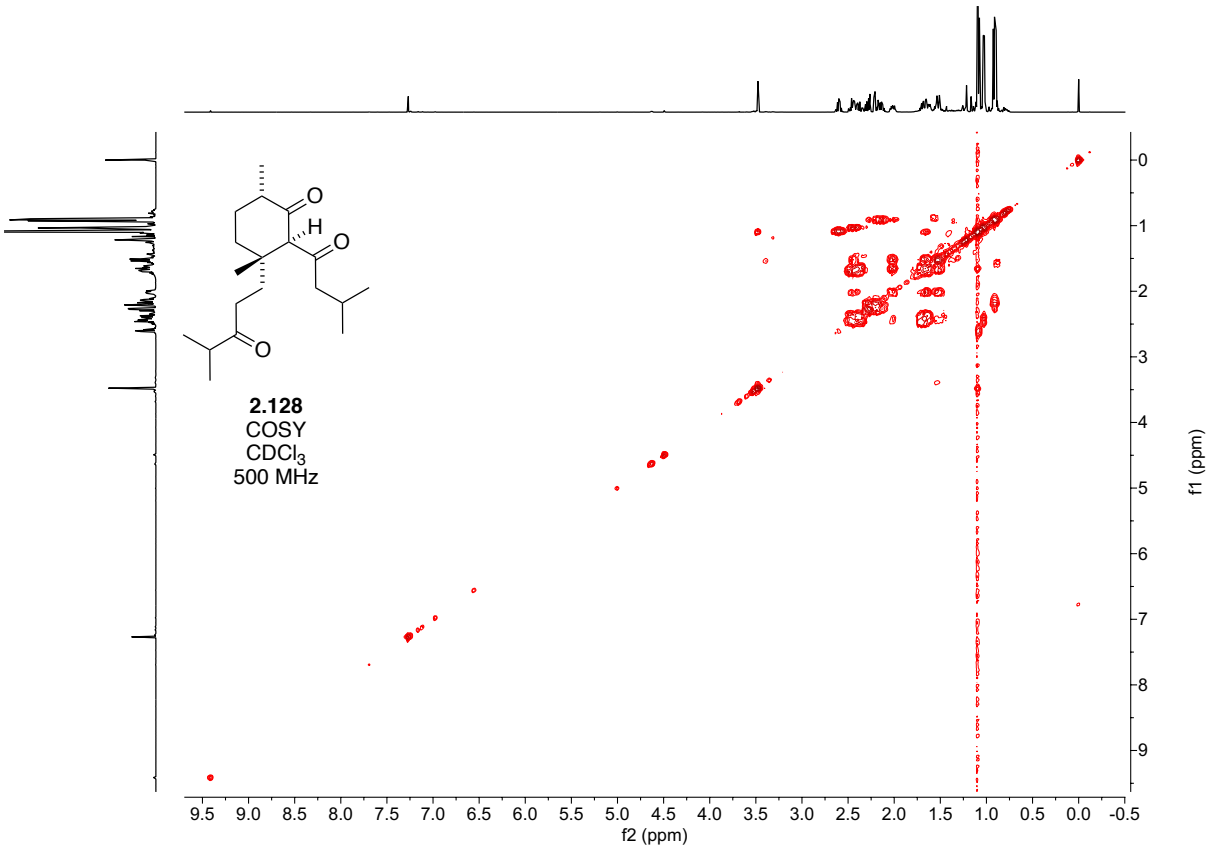

O
H
O
O
2.126
HMBC
CDCl3
500 MHz
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210
f1 (ppm)

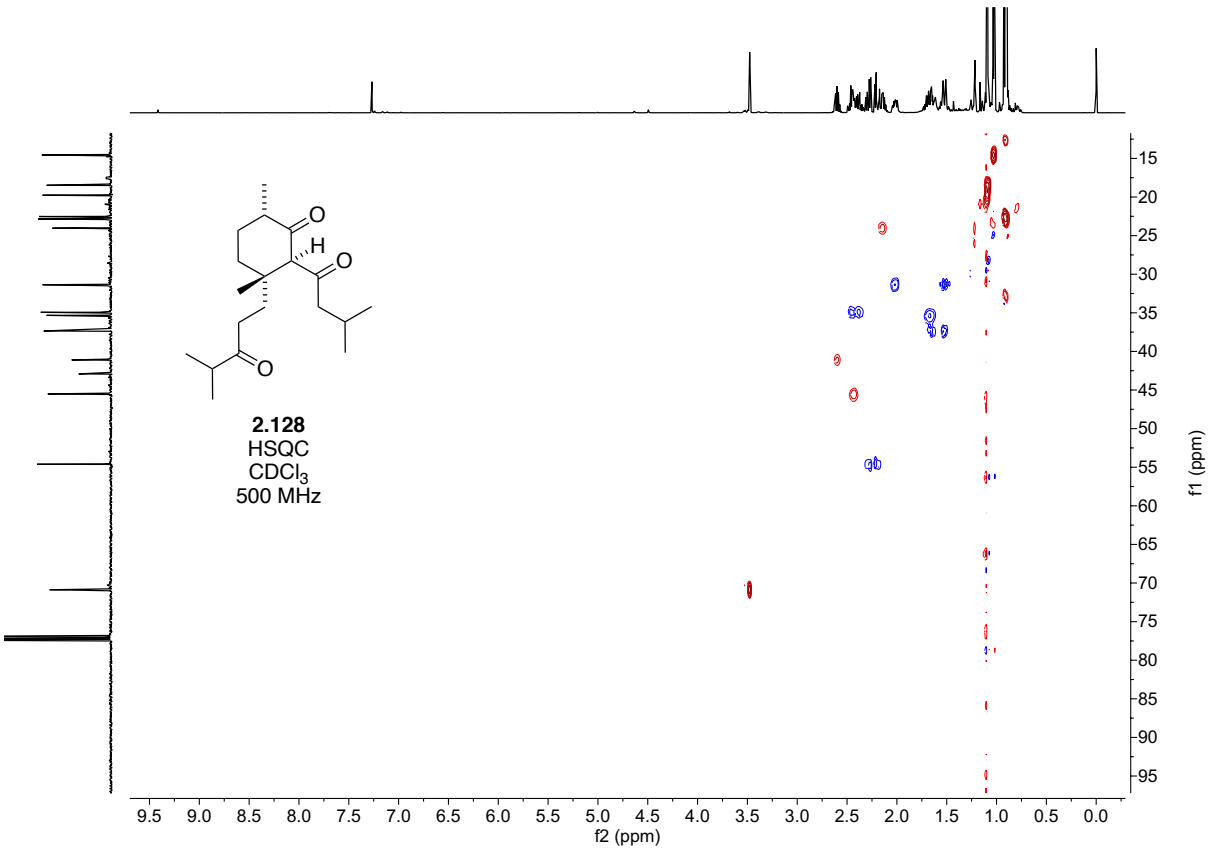


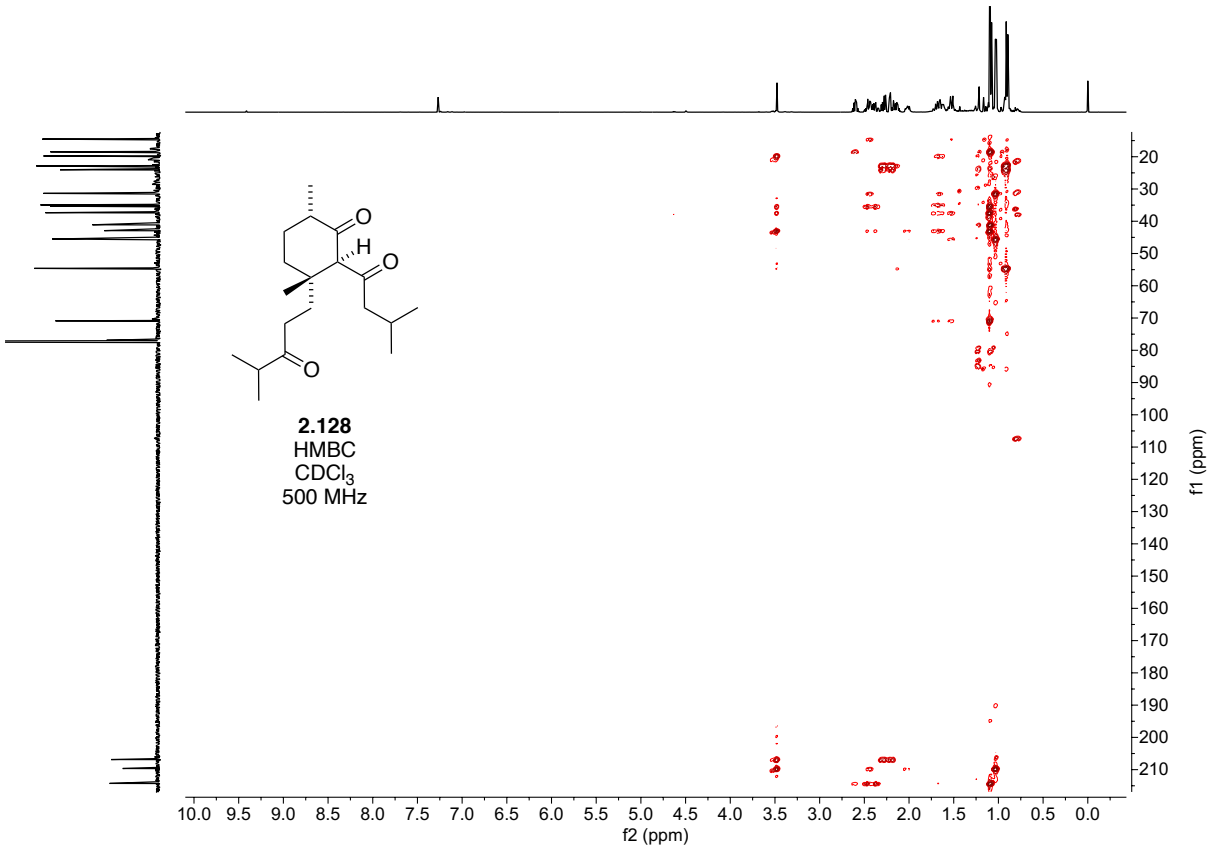
2.128
^{1}H NMR
$CDCl_3$
500 MHz



2.128
^{13}C NMR
$CDCl_3$
125 MHz


O
H
O
O
2.128
COSY
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)


O
H
O
O
2.128
HSQC
CDCl3
500 MHz
f2 (ppm)
f1 (ppm)


O
H
O
O
2.128
HMBC
CDCl3
500 MHz
f1 (ppm)
f2 (ppm)

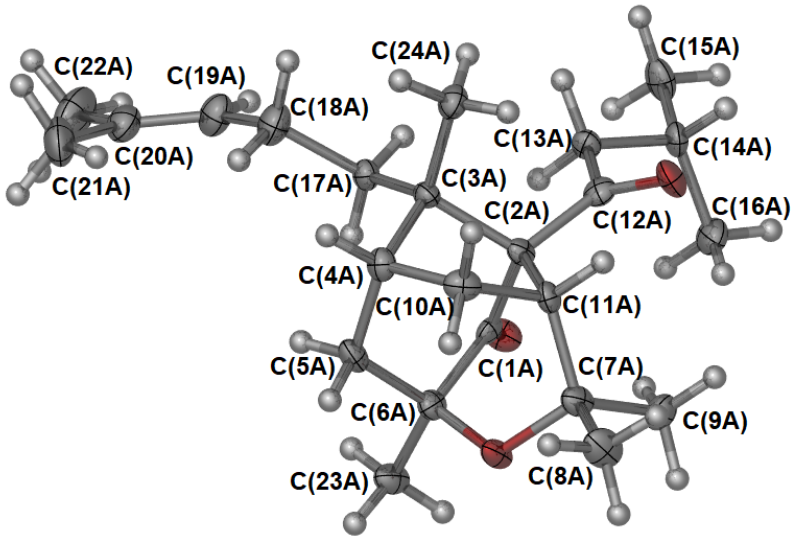
2.6.2 Single Crystal X-ray Crystallography

A single crystal was mounted in Paratone-N oil on a MiTeGen micromount. X-ray diffraction data were collected at 150(2) K on an Oxford X-calibur single crystal diffractometer using Mo Kα radiation.[1] The data set was corrected for absorption using a multi-scan method, and the structure solved by direct methods (SHELXS)[2] and refined by full-matrix least squares on F2 by SHELXL,[3] interfaced through the programs X-Seed (version 4)[4] and Olex2.[5] All non-hydrogen atoms were refined anisotropically and hydrogen atoms were included as invariants at geometrically estimated positions, unless specified otherwise. The sample is a mixture of enantiomers with two molecules in the asymmetric unit (Z' = 2). Table 2.7 lists the X-ray experimental data and refinement parameters for the crystal structures. Perspective views of the structure of **2.89** is shown in Figure 2.10.

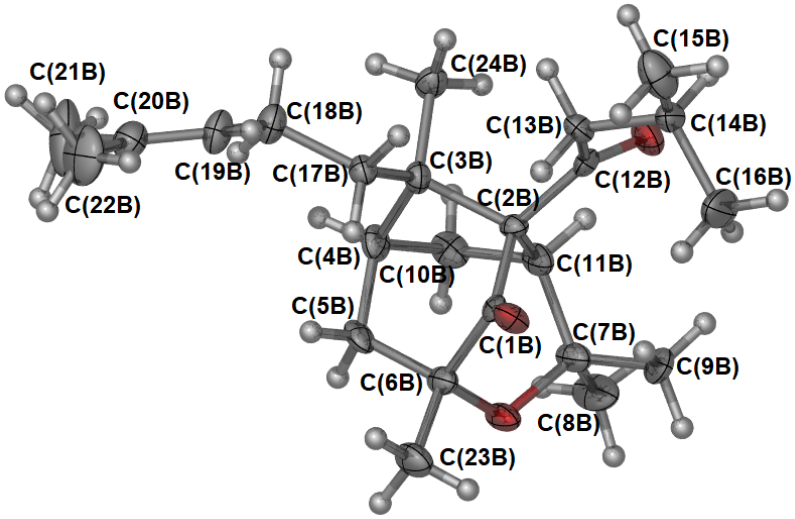
Table 2.7: X-ray experimental data for 2.89

Compound	**2.89**
Empirical formula	$C_{24}H_{38}NO_3$
Formula weight	374.54
Crystal system	monoclinic
Space group	$P2_1$
a (Å)	8.0166(6)
b (Å)	13.7076(12)
c (Å)	19.863(2)
α (°)	90

β (°)	92.008(8)
γ (°)	90
Volume (Å^3)	2181.4(3)
Z	4 (Z' = 2)
Density (calc.) (Mg/m^3)	1.140
Absorption coefficient (mm^{-1})	0.073
F(000)	824.0
Crystal size (mm^3)	0.28 × 0.18 × 0.02
2θ range for data collection (º)	6.838 to 57.008
Reflections collected	18221
Observed reflections [*R*(*int*)]	8856 [R_{int} = 0.0903]
Data/restraints/parameters	8856/1/503
Goodness-of-fit on F2	0.927
R_1 [I>2σ(I)]	0.0689
wR_2 (all data)	0.0995
Largest diff. peak and hole (e.Å^{-3})	0.24/-0.25
Flack parameter	-0.8(10)



(a)



(b)

Figure 2.10: Perspective views of two molecules in the asymmetric unit (a, b) of 2.89. Carbon – grey, hydrogen – white, oxygen – red, chlorine – yellow.

References

[1] CrysAlisPro 1.171.38.43d (Rigaku Oxford Diffraction, **2015**).

[2] (a) Sheldrick, G. M. A short history of SHELX. Acta Crystallogr. A Found. Adv. 2008, 64, 112-122. (b) Sheldrick, G. M. SHELXT - Integrated space-group and crystal-structure determination. Acta Crystallogr. A Found. Adv. 2015, 71, 3-8.

[3] Sheldrick, G. M. Crystal structure refinement with SHELXL. Acta. Crystallogr. C Struct. Chem. 2015, 71, 3-8.

[4] Barbour, L. J. X-Seed - A software tool for supramolecular crystallography. J. Supramol. Chem. 2001, 1, 189-191.

[5] Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. OLEX2: a complete structure solution, refinement and analysis program. J. Appl. Cryst. 2009, 42, 339-341.

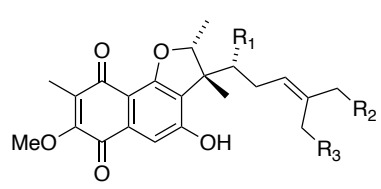
Chapter Three

Progress Towards the Biomimetic Synthesis of Furaquinocins A to H and Neomarinone

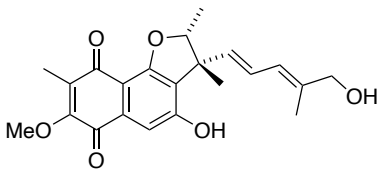
3.1 Introduction

3.1.1 Isolation of Furaquinocins A to H and Neomarinone

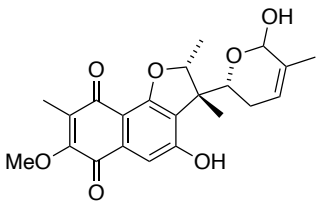
In 1989, two new meroterpenoid natural products furaquinocins A (**3.01**) and B (**3.02**) were isolated from the fermentation broth of *Streptomyces* sp. KO-3988 by Omura (Figure 3.1).[1] Both natural products exhibit strong cytotoxic properties against HeLa S3 and B16 melanoma cells *in vitro* at concentrations of 3.1 and 1.6 µg/mL, respectively.[1] One year later, in 1990, six more furaquinocins C to H (**3.03** to **3.08**) were isolated from the same fermentation broth.[2] All new members of the furaquinocin family also show moderate to high cytotoxic properties against HeLa S3 and B16 melanoma cells with furaquinocin H (**3.08**) being the most potent at 0.22 µg/mL. The chemical structures of all furaquinocins were elucidated by extensive 2D NMR spectroscopy experiments. In 1992, the absolute stereochemistry of furaquinocin A (**3.01**) was confirmed by single-crystal X-ray analysis.[3]



Furaquinocin	R_1	R_2	R_3
A (**3.01**)	OH	H	OH
B (**3.02**)	OH	OH	H
C (**3.03**)	H	H	H
D (**3.04**)	OH	H	H
F (**3.06**)	H	OH	H
H (**3.08**)	OH	OH	OH



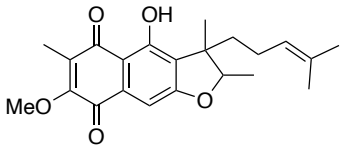
Furaquinocin E
(**3.05**)



Furaquinocin G
(**3.07**)

Figure 3.1: Structures of Furaquinocins A to H (3.01 to 3.08).

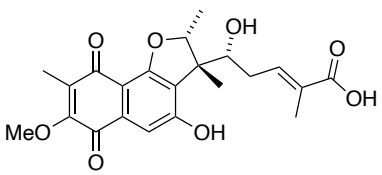
Furanonaphthoquinone I (**3.09**) was isolated from *Steptomyces cinnamonensis* ATCC 15413 in 1991 (Figure 3.2).[4] With the dihydrobenzofuran ring closed at the C-3 hydroxyl group, it is a regioisomer of furaquinocin C (**3.03**). The absolute and relative stereochemistry has not been determined.



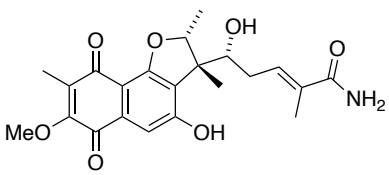
furanonaphthoquinone I
(**3.09**)

Figure 3.2: Structure of furanonaphthoquinone I (3.09).

Two more related natural products, furaquinocin I (**3.10**) and J (**3.11**) were isolated in 2011 from a genetically-engineered strain of *Streptomyces reveromyceticus* SN-593 (Figure 3.3).[5] The main structural difference to all other furaquinocins is the type of residue attached to the side chain; to be precise, a carboxyl group for furaquinocin I (**3.10**) and a carboxamide group for furaquinocin J (**3.11**).



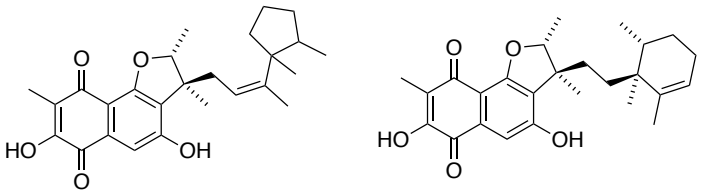
furaquinocin I
(**3.10**)



furaquinocin J
(**3.11**)

Figure 3.3: Structures of furaquinocin I (3.10) and J (3.11).

Neomarinone (**3.12**) was first isolated from marine actinomycete bacteria by Hardt *et al.* in 2000 and its originally proposed structure was revised in 2003 by Moore (Figure 3.4).[6,7]

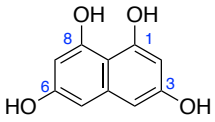


Originally proposed structure of neomarinone (**3.12**) by Fenical in 2000.

Revised structure of neomarinone (**3.12**) by Moore in 2003.

Figure 3.4: Originally proposed structure by Fenical and revised structure of neomarinone (3.12) by Moore.[6,7]

Structurally, the furaquinocins and neomarinone contain a highly functionalised naphthoquinone core with different oxidation pattern on the isoprenoid sidechain. Early labelling studies revealed that the naphthoquinone moiety is biosynthetically derived from the symmetrical precursor 1,3,6,8-tetrahydroxynaphthalene (THN, **3.13**) (Figure 3.5).



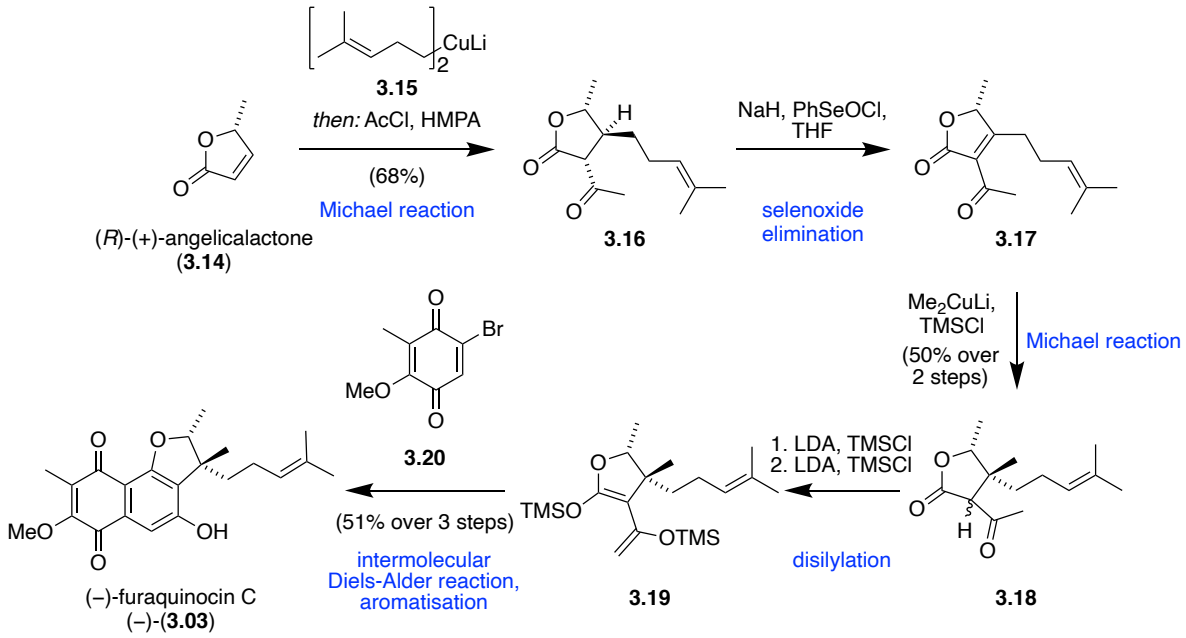
1,3,6,8-tetrahydroxynaphthalene (THN, **3.13**)

Figure 3.5: Structure of biosynthetic precursor molecule, THN (3.13).

3.1.2 Previous Work on Furaquinocins A to H and Neomarinone

Several total syntheses of members of the furaquinocin family and neomarinone have been published so far. The first total synthesis of (–)-furaquinocin C ((–)-**3.03**) was achieved in only six steps by Smith and co-workers in 1995 (Scheme 3.1).[8] Starting from (*R*)-(+)-angelicalactone (**3.14**), conjugate addition of Gilman reagent **3.15** (derived from homoprenyl

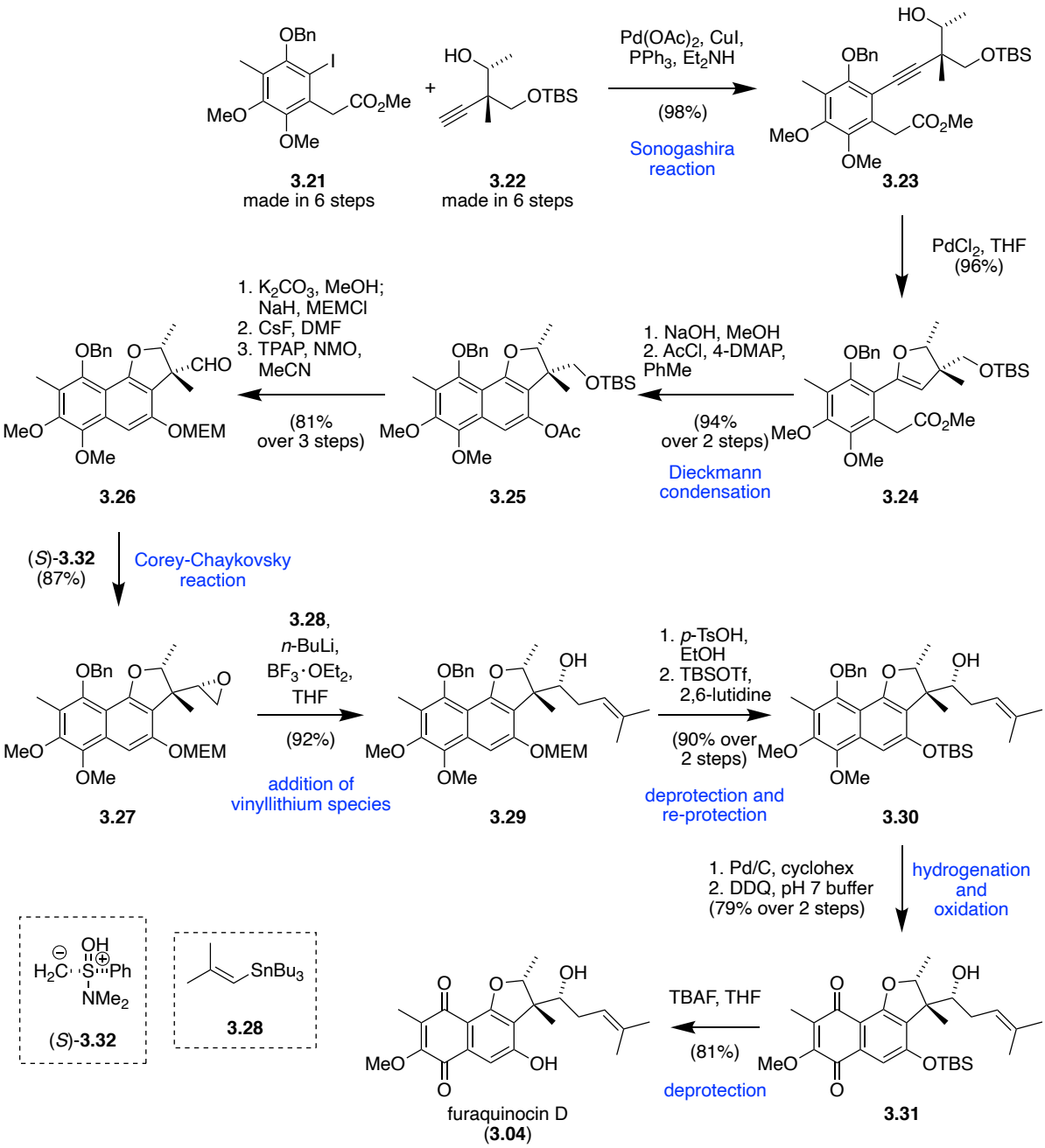
iodide) and trapping of the resultant enolate with acetyl chloride afforded lactone **3.16**. Selenoxide elimination gave unsaturated lactone **3.17** which was the substrate for the second 1,4-addition with lithium dimethyl copper to obtain diketone **3.18**. Disilylation afforded Brassard-type diene **3.19** in 2 steps. Intermolecular Diels-Alder cycloaddition with bromoquinone **3.20** gave (–)-furaquinocin C ((–)-(**3.03**)) in 51% yield.



Scheme 3.1: Total synthesis of (–)-furaquinocin C ((–)-(3.03) by Smith III and co-workers in 1995.[8]

In 1998, the total syntheses of furaquinocins A (**3.01**), B (**3.02**), D (**3.04**) and H (**3.08**) were published by Suzuki and co-workers (Scheme 3.2).[9] Aromatic fragment **3.21** was synthesised in 5 steps and (+)-alkyne **3.22** was prepared in enantiomerically pure form in 6 steps. Both fragments were coupled in a Sonogashira cross coupling reaction to afford alkyne **3.23**. Next, the dihydrofuran moiety of **3.24** was installed in a palladium-catalysed coupling reaction. Then, saponification of the ester **3.24** formed the sodium carboxylate which was immediately treated with acetyl chloride and DMAP to furnish the core of the furaquinocins of **3.25** in a Dieckmann condensation. From there, the group started working on the remaining task which was to

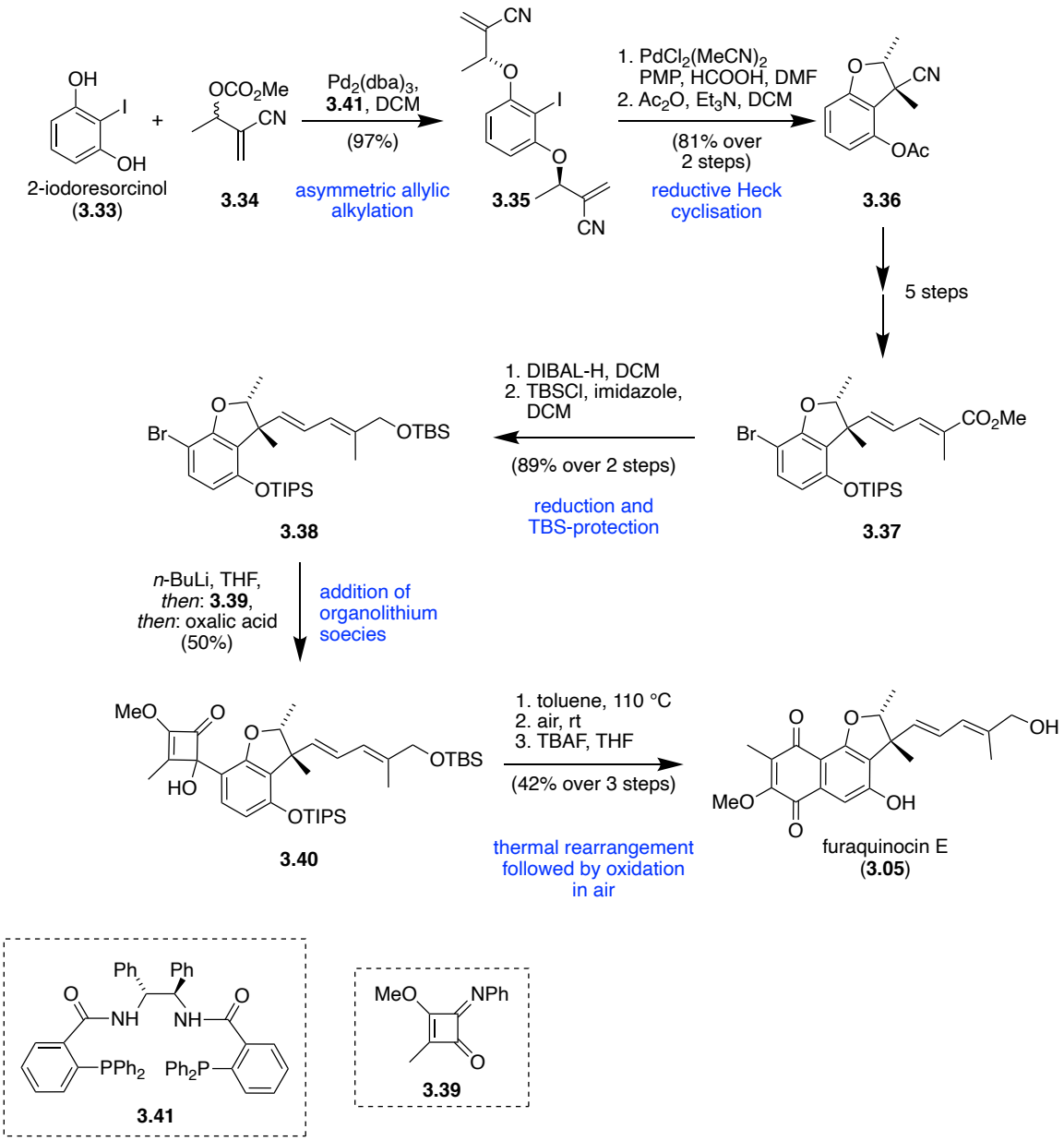
construct the side chain while controlling the third stereogenic centre. Acetate **3.25** was converted to aldehyde **3.26** in three steps, including exchanging the acetyl for a MEM protecting group, deprotection of the hydroxyl group and Ley-Griffith oxidation to the aldehyde. Formation of the epoxide **3.27** through a Corey-Chaykovsky reaction gave the precursor to all furaquinocins with the desired stereochemistry.



Scheme 3.2: Total synthesis of furaquinocin D (3.04) by Suzuki in 1998.

Tin-lithium exchange and addition of the generated vinyl lithium species **3.28** to epoxide **3.27** gave alcohol **3.29**. Removal of protecting groups and oxidation of the THN core to the corresponding naphthoquinone core afforded furaquinocin D (**3.04**) in 5 more steps. Ring opening of epoxide **3.27** with different vinystannanes gave access to furaquinocins A (**3.01**), B (**3.02**) and H (**3.08**).

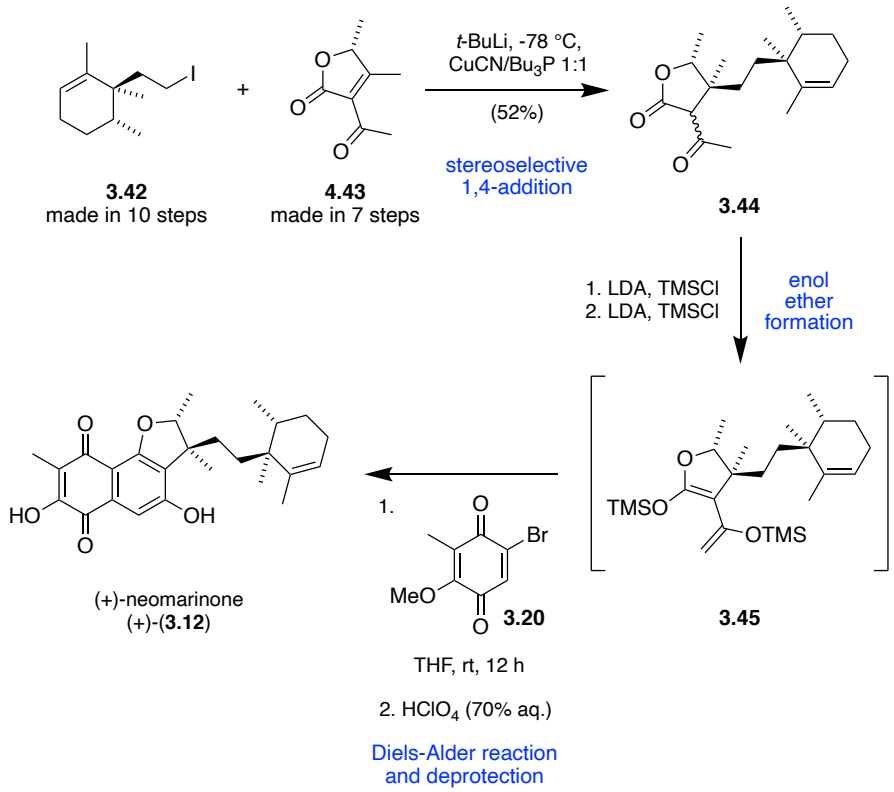
In 2002 and 2003, total syntheses of furaquinocins A (**3.01**), B (**3.02**) and E (**3.05**) were reported by Trost and co-workers (Scheme 3.3).[10,11] The total synthesis of furaquinocin E (**3.05**) commenced with constructing the furaquinocin core with the desired absolute and relative stereochemistry in two Pd-catalysed steps (Scheme 3.3). Tsuji-Trost allylation of 2-iodoresorcinol (**3.33**) with allylic carbonate **3.34** in the presence of asymmetric ligand **3.41** gave **3.35** which was immediately followed by a reductive Heck cyclisation to give intermediate **3.36**. Five more steps from dihydrobenzofuran **3.36** were necessary to install the side chain of **3.37**, including a Horner-Wadsworth-Emmons reaction. Reduction of the ester **3.37** and protection of the resulting hydroxyl group with TBSCl gave compound **3.38**. Lithium-halogen exchange and 1,2-addition to squaric acid derivative **3.39** followed by hydrolysis of the resulting imine gave access to intermediate **3.40**. Key step of the synthesis was the subsequent thermal rearrangement of **3.40** and oxidation under exposure of air gave silyl protected furaquinocin E (**3.05**) which was easily deprotected with TBAF in THF. Furthermore, the group also completed the total syntheses of furaquinocins A (**3.01**) and B (**3.02**) (syntheses not shown).[10]



Scheme 3.3: Total synthesis of furaquinocin E (3.05).[10,11]

In 2009, the first total synthesis of (+)-neomarinone ((+)-**3.12**) was reported by Sarandeses and Sestelo (Scheme 3.4).[12] The first key step in the total synthesis was the stereoselective 1,4-addition of the mixed Gilman reagent derived from iodide **3.42** to unsaturated lactone **3.43** in 52% yield. In this step the highly functionalised side chain of neomarinone (**3.12**) was installed with the desired absolute and relative stereochemistry. Diketone **3.44** was sequentially treated with LDA and TMSCl to form the corresponding Brassard-type diene **3.45** which was used

directly in the next step without isolation. Bromoquinone **3.20** was added to the reaction at room temperature and, after 12 h, methyl neomarinone was afforded. Methyl ether hydrolysis with $HClO_4$ completed the total synthesis of (+)-neomarinone ((+)-**3.12**).



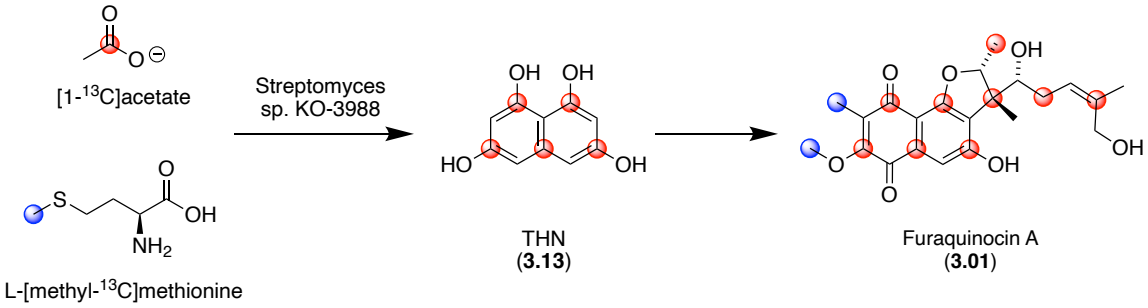
Scheme 3.4: Total synthesis of (+)-neomarinone ((+)-3.12) by Sarandeses and Sestelo.[12]

All these examples are impressive feats of natural product synthesis, but they do not reflect how these natural products are synthesised in nature.

3.1.3 Proposed Biosynthesis of Furaquinocins A to H and Neomarinone

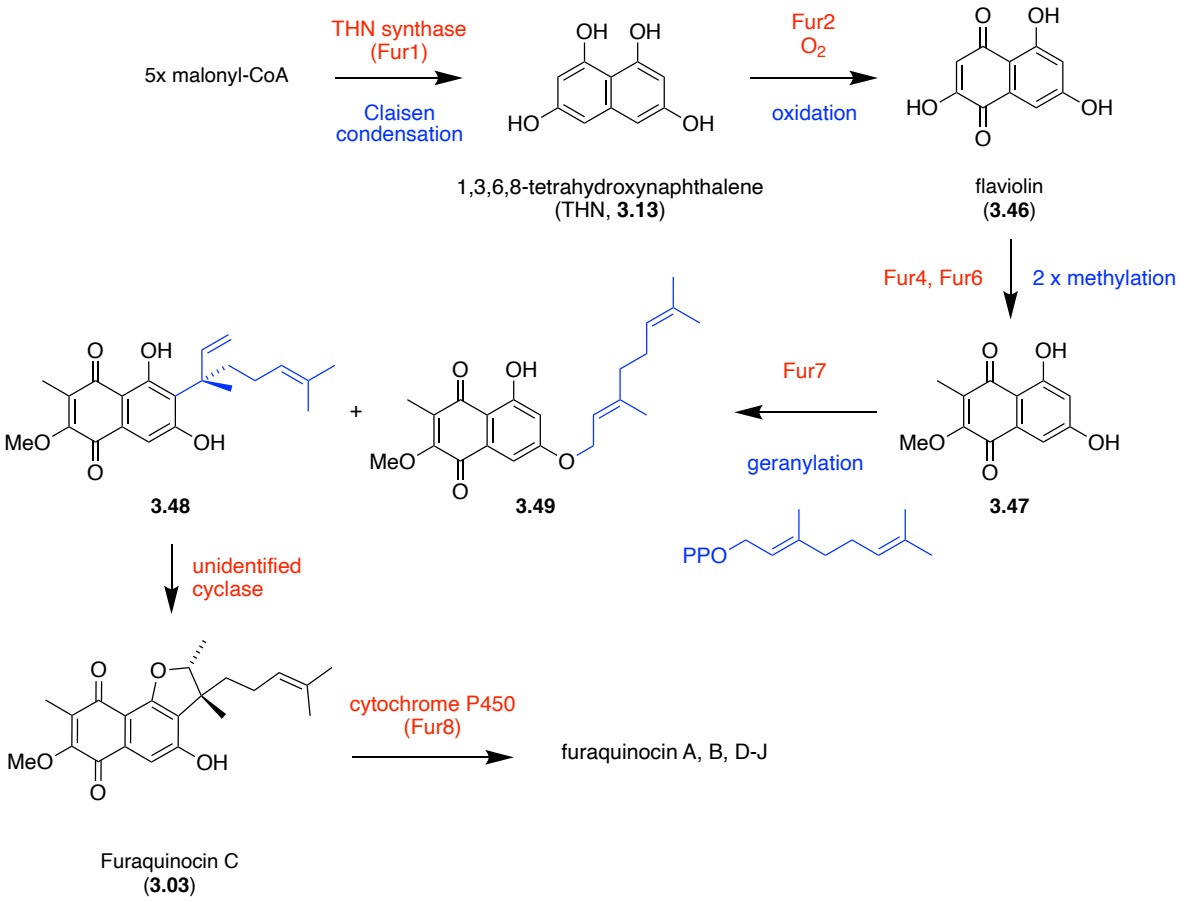
The biosynthetic pathways of the furaquinocin natural product family were first elucidated by Omura and co-workers *via* ^{13}C-labelling studies.[13] By conducting feeding experiments with [1-^{13}C]acetate and L-[methyl-^{13}C]-methionine, the group was able to prove that the 20 carbons

forming the polyketide unit are derived from acetate and the remaining two carbons are from methionine (Scheme 3.5). The highly oxidised polyketide moiety is derived from the symmetric precursor THN (**3.13**).[13]



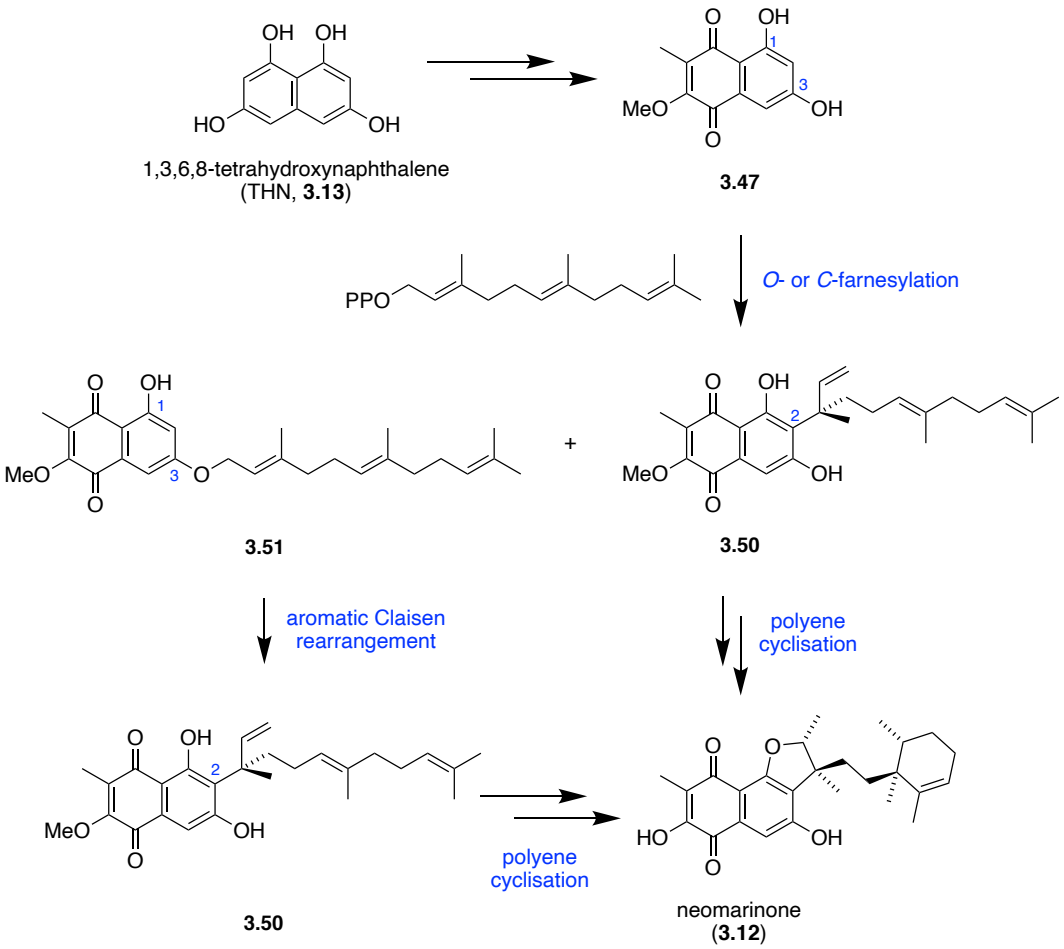
Scheme 3.5: Labelling pattern of furaquinocin A (3.01) from [1-^{13}C]acetate and L-[methyl-^{13}C]methionine.[13]

In 2006, the Dairi group proposed the biosynthesis of the furaquinocins by cloning and identifying the biosynthetic gene cluster of furaquinocin A (**3.01**).[14] Alongside the putative THN synthase (*fur1*), the group identified key genes, such as C-methytransferase (*fur4*), *O*-methyltransferase (*fur6*), prenyltransferase (*fur7*) and cytochrome P450 enzyme (*fur8*). In 2010, Kuzuyama and co-workers shed some more light onto the biosynthesis of the furaquinocin family.[15] With this information in hand, the proposed biosynthesis is described in Scheme 3.6. It was predicted that monooxygenase *fur2* catalyses the oxidation of the THN core (**3.13**) to flaviolin (**3.46**). *C*- and *O*-methylation of flaviolin generates **3.47**. Following this, alkylation in the presence of prenyltransferase *fur7* and geranyl pyrophosphate (GPP) gave two products, *C*-prenylated **3.48** and *O*-prenylated **3.49** in a 10:1 ratio. Although this result might indicate that *O*-prenylated **3.49** is a biosynthetic precursor to reverse prenylated **3.48**, the required Claisen rearrangement has not yet been successfully promoted *in vitro*. Reverse prenylated **3.48** undergoes cyclisation to furaquinocin C (**3.03**), which could then be further oxidised to give access to other members of the furaquinocin family.



Scheme 3.6: Proposed biosynthesis of the furaquinocin natural products.

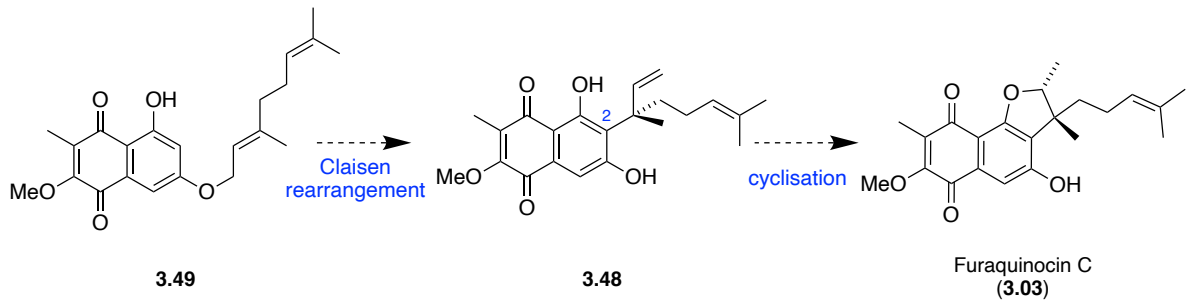
After revising the structure of neomarinone (**3.12**), Moore and co-workers proposed a biosynthesis of the natural product that involved *C*-prenylation of the C-2 position or, alternatively, *O*-prenylation of the C-1 or C-3 hydroxyl groups followed by Claisen rearrangement to intermediate **3.50** (Scheme 3.7).[7] From there, proton-assisted cyclisation and methyl migration of the side chain would form the cyclohexene moiety of neomarinone (**3.12**).



Scheme 3.7: Proposed biosynthetic pathway of neomarinone (3.12) by Moore and co-workers.[7,16]

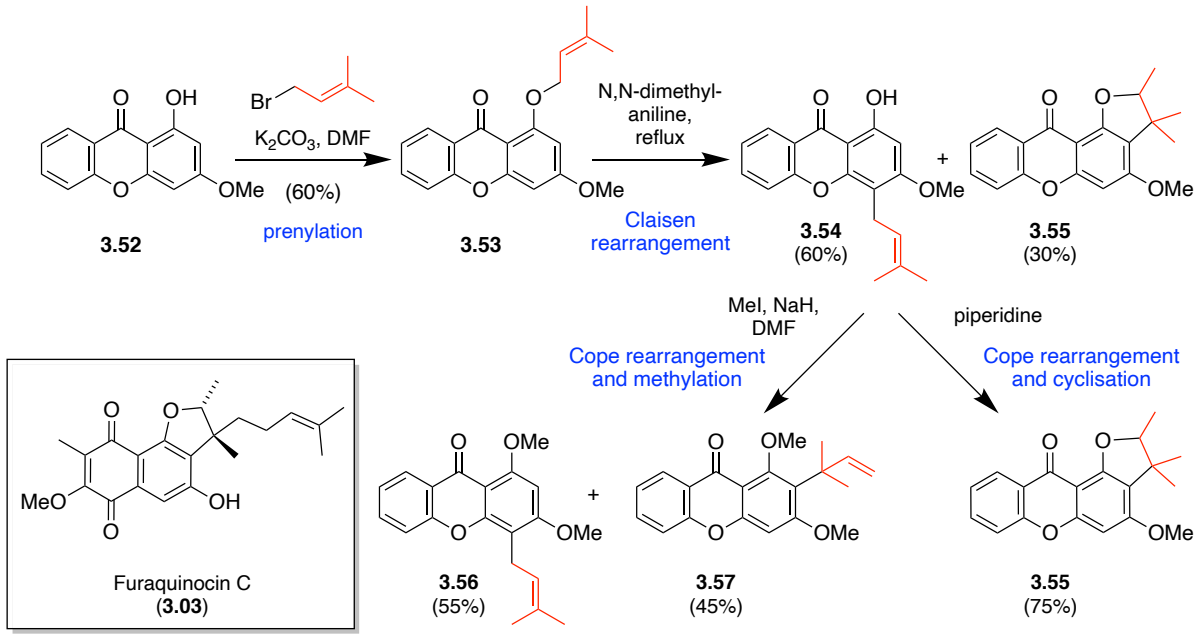
3.1.4 Examples of Claisen/Cope Rearrangement Reactions

We were really intrigued by the biosynthetic proposals involving an aromatic Claisen rearrangement. Hence, the key step of our biomimetic proposal is the Claisen rearrangement of *O*-prenylated flaviolin **3.49** to **3.48** and subsequent cyclisation to furaquinocin C (**3.03**) (Scheme 3.8).



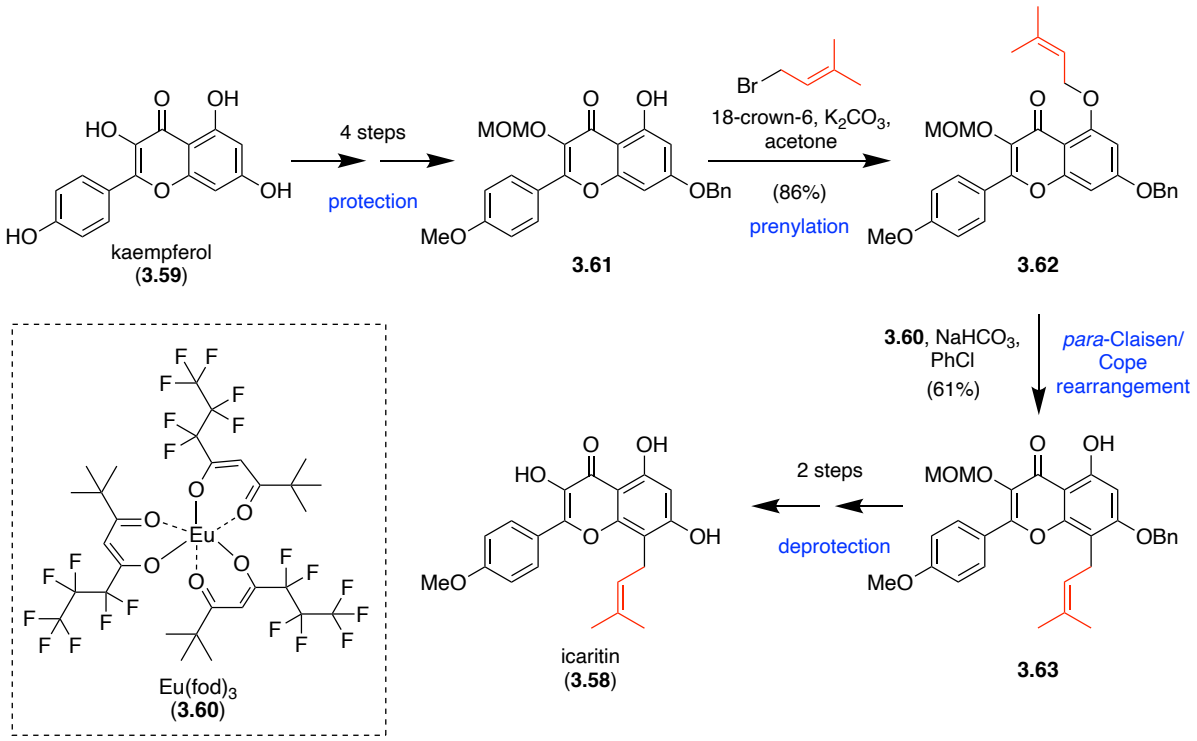
Scheme 3.8: Proposed Claisen rearrangement and cyclisation of intermediate 3.49 to form furaquinocin C (3.03).

There are numerous examples in literature where aromatic Claisen rearrangements on similar systems have been achieved.[17–20] During the work on the total synthesis of morellin, Rao and co-workers observed an unusual Cope rearrangement of one of their intermediates.[17,18] Their synthesis, pictured in Scheme 3.9, commenced with *O*-prenylation of xanthone **3.52** followed by Claisen rearrangement of **3.53** in *N*,*N*-dimethylaniline (DMA). The rearrangement afforded amongst the desired *para*-rearrangement product **3.54** another side product in 30% yield which was identified as the *ortho*-rearrangement and cyclisation product **3.55**. Intriguingly, the undesired side product **3.55** shows the dihydrobenzofuran moiety of the furaquinocin natural products. When the group tried to methylate the free hydroxyl group of **3.54** with iodomethane and sodium hydride in DMF, as well as forming the desired dimethylated intermediate **3.56** in 55% yield, the remaining starting material underwent Cope rearrangement to intermediate **3.57** in 45% yield. Furthermore, treatment of **3.54** with the base piperidine promoted Cope rearrangement and immediate cyclisation of the obtained intermediate to **3.55** in 75% yield.



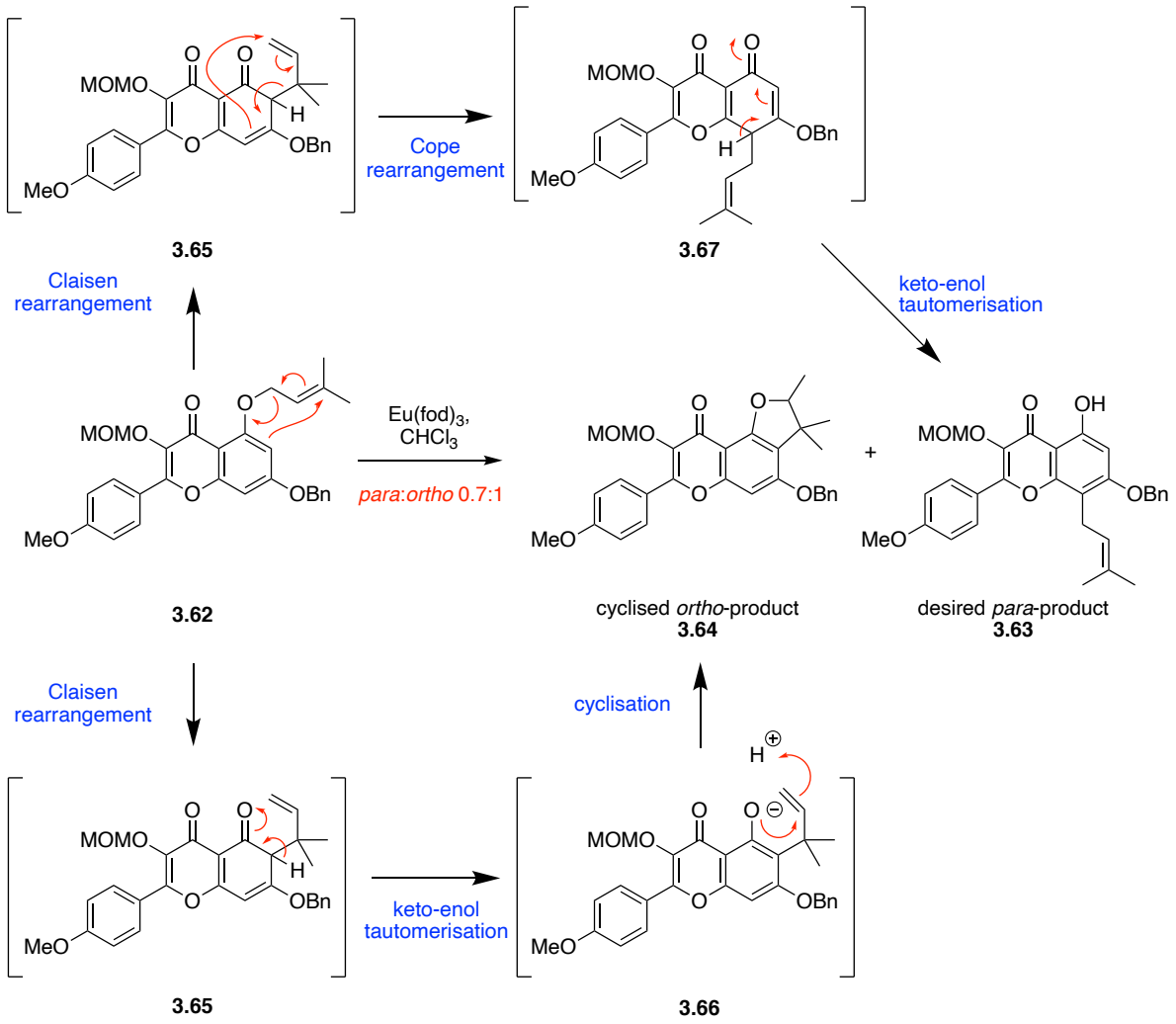
Scheme 3.9: Observed Claisen/ Cope rearrangements during the work on the total synthesis of morellin by Rao and co-workers.[17,18]

In 2015, Zhang and co-workers reported the semisynthesis of the icaritin (**3.58**) from kaempferol (**3.59**).[19] The key step of their synthesis was a *para*-Claisen/Cope rearrangement which was catalysed by a common ^{1}H NMR shift reagent, tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)-europium (Eu(fod)$_3$, **3.60**) (Scheme 3.10). Three of the four free hydroxyl groups of kaempferol (**3.59**) were selectively protected in the first four steps of the synthesis to give intermediate **3.61**. The remaining hydroxyl group was prenylated to form key step precursor **3.62**. Upon heating in the presence of Eu(fod)$_3$ (**3.60**) and $NaHCO_3$ in chlorobenzene, *para*-Claisen/Cope rearrangement occurred giving desired product **3.63** in 61% yield. Finally, two deprotection steps followed to yield natural product icaritin (**3.58**) in an overall yield of 23% over 11 steps.



Scheme 3.10: Semisynthesis of icaritin (3.58) from kaempferol (3.59) via Claisen/Cope-rearrangement of *O*-prenylated intermediate 3.62 to 3.63.[19]

During optimisation of their key Claisen/Cope rearrangement reaction, the group faced challenges with the regioselectivity of *ortho*- and *para*-rearranged products. Interestingly, they reported that in their earlier attempts they obtained the cyclised version of *ortho*-rearranged product in a ratio of 0.7 to 1 in favour of side product **3.64** (Scheme 3.11). Mechanistically speaking, the group proposed that *ortho*-Claisen rearrangement gave intermediate **3.65** which would rearomatise by keto-enol tautomerisation to **3.66**. Cyclisation of the hydroxyl group with the reverse prenyl chain double bond would form the dihydrobenzofuran moiety of cyclised side product **3.64**. Alternatively, **3.65** could undergo Cope rearrangement to intermediate **3.67** which could then rearomatise through keto-enol tautomerisation to the desired *para*-rearrangement product **3.63**.



Scheme 3.11: Proposed mechanism of undesired side product formation by Zhang et al.[19]

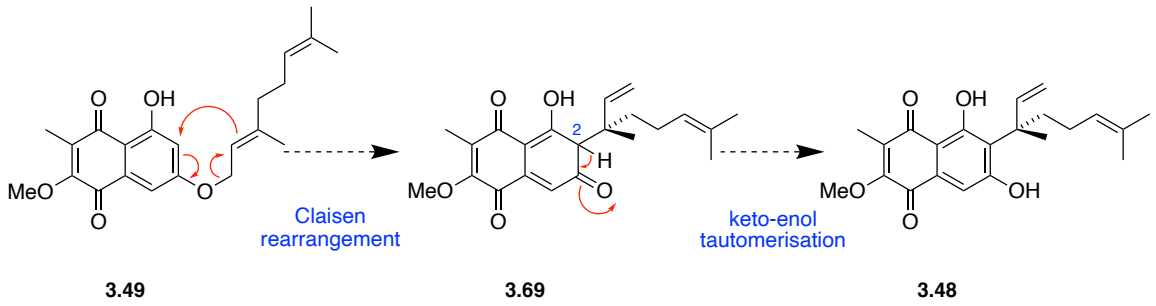
Again, the obtained dihydrobenzofuran moiety of the side product **3.64** is the motif we were interested in. These reported results seemed promising as to the possibility of performing the desired key step on our system.

3.1.5 Project Aims

The main objective of this project was to gain insight into the biosynthesis of the furaquinocin and neomarinone natural products. To achieve this, we desired to investigate the reactivity of

the oxidised flaviolin system **3.49** and the non-oxidised THN intermediates **3.67** and **3.68** (Figure 3.6) in regard to our proposed key step. If successful, we could apply this newly developed methodology to a biomimetic total synthesis of members of the furaquinocin and neomarinone natural product family.

First, we planned to synthesise *O*-geranylated flaviolin analogue **3.49**. Ideally, **3.49** would undergo aromatic Claisen rearrangement to the C-2 position followed by keto-enol tautomerisation to give rearranged intermediate **3.48** (Scheme 3.12).

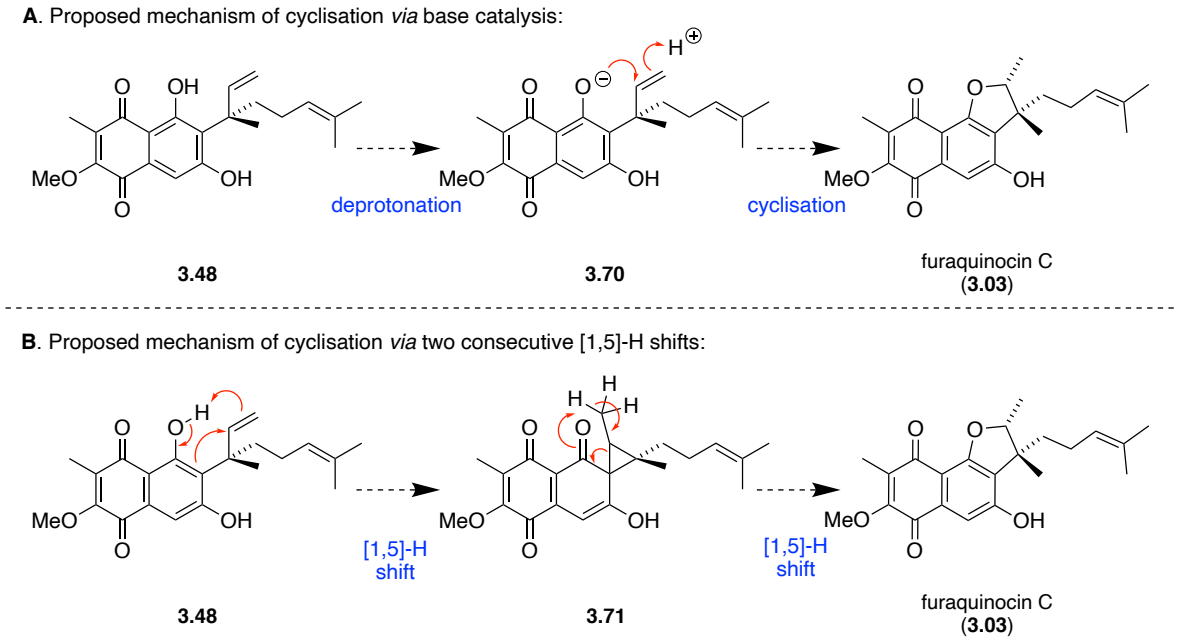


3.49 **3.69** **3.48**

Scheme 3.12: Proposed key aromatic Claisen rearrangement of *O*-geranylated flaviolin analogue 3.49 to 3.48.

After successful Claisen rearrangement, our next aim would be to perform the required cyclisation to the natural product furaquinocin C (**3.03**). Two possible pathways could give the desired dihydrobenzofuran moiety (Scheme 3.13). The first pathway would go analogous to the proposed cyclisation mechanism by Zhang and co-workers (Scheme 3.13, **A**).[19] Deprotonation of the phenol would give anionic intermediate **3.70** which could attack the double bond forming cyclised natural product furaquinocin C (**3.03**). In 2012, Novak and co-workers suggested an alternative pathway for the cyclisation of such compounds *via* two consecutive [1,5]-H shifts (Scheme 3.13, **B**).[21] The first hydrogen shift would give

cyclopropane intermediate **3.71** which could then undergo another hydrogen shift to form natural product furaquinocin C (**3.03**).



Scheme 3.13: A. Proposed cyclisation mechanism *via* base catalysis.[19] B. Proposed mechanism *via* two [1,5]-H shifts.[21]

Furthermore, we wanted to attempt Claisen or Cope rearrangement on the non-oxidised THN intermediates **3.67** and **3.68** to investigate the selectivity and likelihood of the desired rearrangement on the reduced system as well. Oxidation to the quinone and C-7 methylation could be performed afterwards.

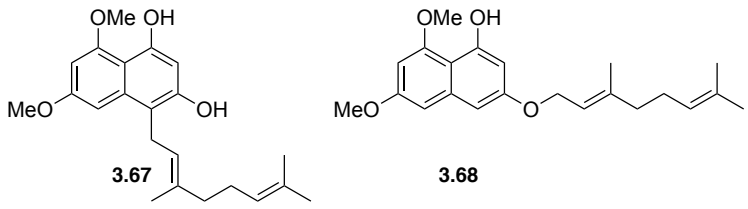


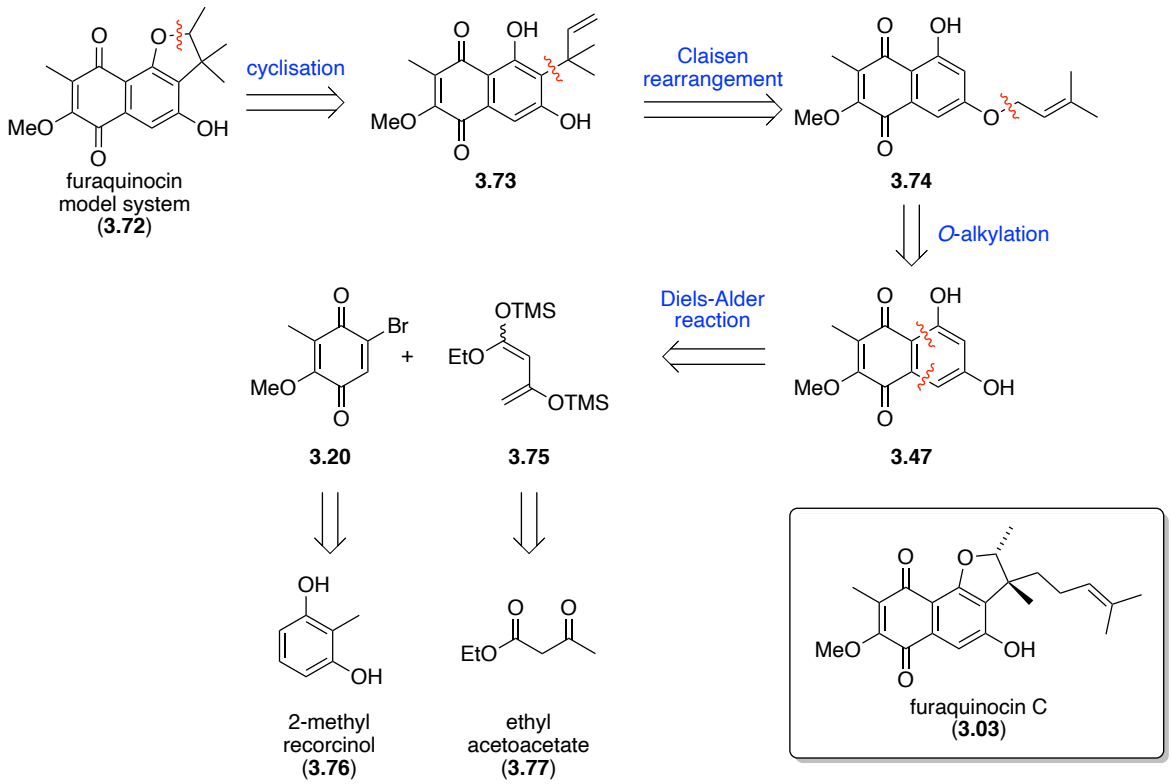
Figure 3.6: THN based target molecules 3.67 and 3.68.

If successful, it would be desirable to selectively oxidise the side chain of furaquinocin C (**3.03**) to access other members of the furaquinocin family.

3.2 Results and Discussion

3.2.1 Retrosynthetic Analysis of the Furaquinocin Model System

Our first synthetic strategy commenced by examining the alkylation and subsequent Claisen rearrangement on the oxidised flaviolin system. For simplicity, we decided to use a similar model system **3.72**, substituting the geranyl side chain of the natural products with a smaller prenyl group (Scheme 3.14). The advantage of this simpler model system is that the characterisation of the intermediates and the desired products would be easier by spectroscopic methods. It also minimises the chance of side reaction, such as unwanted cyclisations or *E*/*Z* isomerisations.

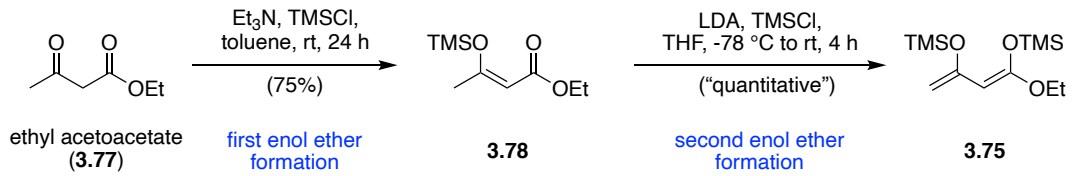


Scheme 3.14: Retrosynthetic analysis of furaquinocin model system 3.72 from the simpler precursor molecules, 2-methyl resorcinol (3.76) and ethyl acetoacetate (3.77).

As shown in our retrosynthesis in Scheme 3.14, we envisaged that the tricyclic core of the furaquinocin model system **3.72** could be installed through cyclisation of intermediate **3.73**. The reverse prenylated precursor **3.73** could be obtained by Claisen rearrangement of *O*-prenylated naphthoquinone **3.74** which was envisioned to be obtained by prenylation of naphthoquinone **3.47**. Intermolecular Diels-Alder reaction of bromoquinone **3.20** and diene **3.75** using conditions previously reported by Trost and co-workers would afford desired intermediate **3.47**.[10] Bromoquinone **3.20** could be synthesised from commercially available 2-methyl resorcinol (**3.76**) in three steps following literature-known procedures.[22–24] The Brassard-type diene **3.75** could be easily accessed within two steps from ethyl acetoacetate (**3.77**) also following known methodologies.[25]

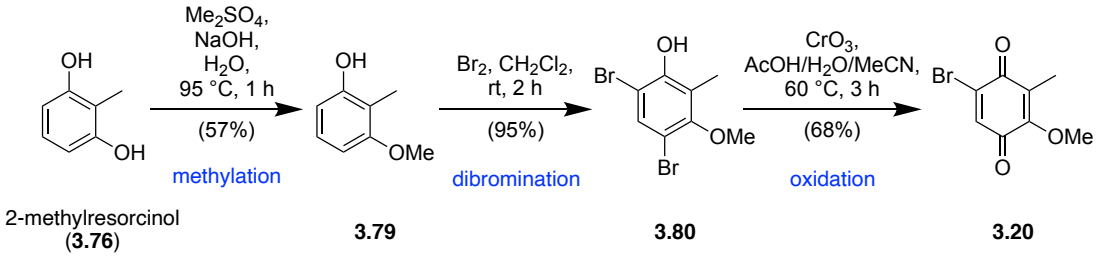
3.2.2 Synthesis of the Naphthoquinone Core

Our forward synthesis, shown in Scheme 3.15, started with preparing TMS-protected enol ether **3.75** which was achieved in excellent yields following a two-step procedure by Wagner *et al.* from 2015.[25] Firstly, commercially available ethyl acetoacetate (**3.77**) was transformed into its mono-TMS-protected analogue **3.78** with trimethylsilyl chloride (TMSCl) and triethylamine in 75% yield. The product was purified by distillation. A second treatment of **3.78** with LDA and TMSCl yielded diene **3.75** in quantitative yields (Scheme 3.15). The diene **3.75** was used without further purification as it was found to be unstable at elevated temperatures and distillation was not possible. The ^{1}H NMR data matched the reported spectroscopic data confirming the success of the synthesis.[25]



Scheme 3.15: Synthesis of TMS-protected diene 3.75 in two steps following a literature procedure by Wagner and co-workers.[25]

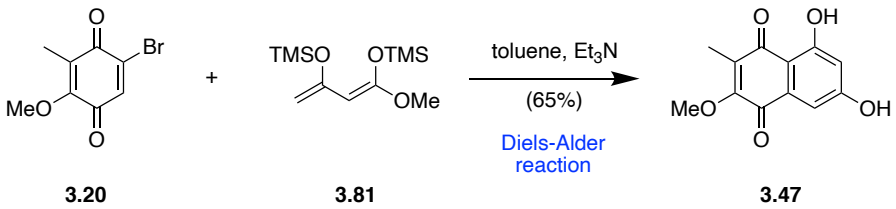
The second building block of the intermolecular Diels-Alder reaction was synthesised in three steps from commercially available 2-methylresorcinol (**3.76**) following known procedures.[22–24] First, **3.76** was mono-*O*-methylated with dimethylsulfate to afford **3.79** (Scheme 3.16).[22] The competing methylation of the second hydroxyl group began prior to full consumption of the starting material which resulted in the modest yields averaging around 57%. Dibromination with molecular bromine afforded bromophenol **3.80** in almost quantitative yields. Finally, chromium-mediated oxidation of bromophenol **3.80** gave the desired bromoquinone **3.20** in 68% yield. Comparison of the obtained ^{1}H NMR data with the reported literature confirmed the success of the synthesis.[23,24]



Scheme 3.16: Synthesis of bromoquinone 3.20 in three steps from 2-methylresorcinol (3.76).[22–24]

Next, we attempted the Diels-Alder reaction of bromoquinone **3.20** with diene **3.75**. The successful Diels-Alder reaction of bromoquinone **3.20** with methoxy analogue **3.81** had

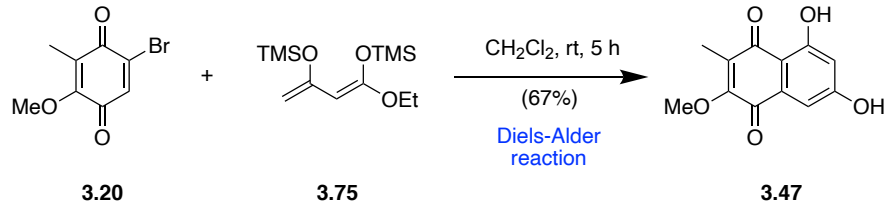
previously been reported in good yields by the Trost group (Scheme 3.17).[10] The reaction was carried out in toluene with addition of Et_3N as base.



3.20 **3.81** **3.47**

Scheme 3.17: Diels-Alder reaction of bromoquinone 3.20 and diene 3.81 reported by Trost *et al.*[10]

With this example in mind, we decided to try these reaction conditions with our diene **3.75**. Unfortunately, the reported result was not reproducible in our hands. After various attempts to optimise the Diels-Alder reaction by changing variables such as temperature, time, solvents, and equivalents, we finally found that omitting the base and using dichloromethane instead of toluene afforded the best conversion giving the desired product in 67% yield (Scheme 3.18).



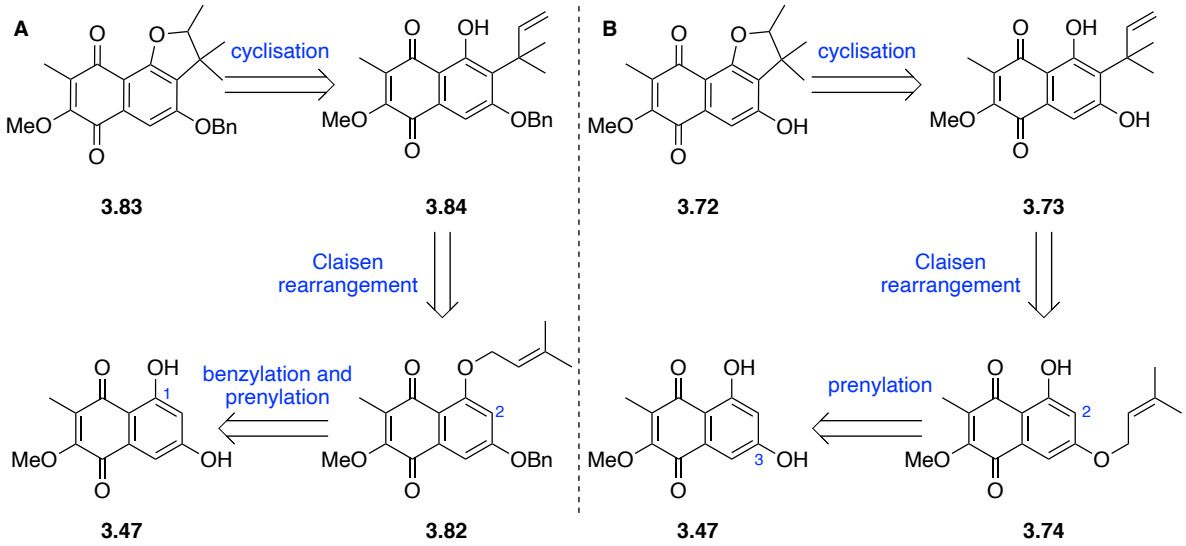
3.20 **3.75** **3.47**

Scheme 3.18: Diels-Alder reaction of bromoquinone 3.20 and diene 3.75 in 67% yield.

With good quantities of naphthoquinone **3.47** in hand, we were now in a position to test our proposed Claisen rearrangement and cyclisation reaction.

3.2.3 Attempted Claisen Rearrangement and Cyclisation Reaction of Benzylated Naphthoquinone 3.82

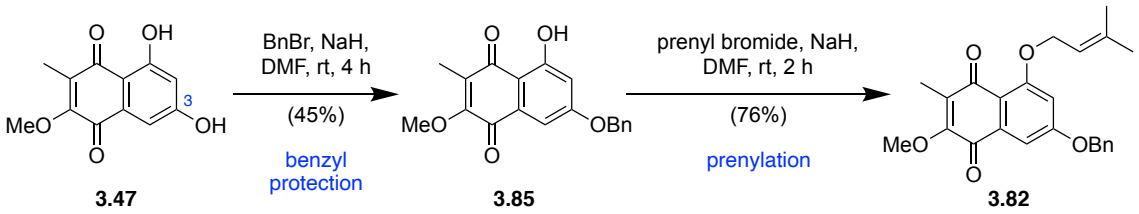
Following the optimisation of the Diels-Alder reaction, we drew our attention to the next part in our synthesis. Naphthoquinone **3.47** offers two possible positions for the *O*-prenylation, the C-1 hydroxyl group (Scheme 3.19, path **A**) and the C-3 hydroxyl group (Scheme 3.19, path **B**). We decided to investigate pathway **A** first. It was envisioned that benzyl-protected natural product analogue **3.83** could be afforded by cyclisation of intermediate **3.84**. Precursor **3.84** could be obtained by Claisen rearrangement of *O*-prenylated naphthoquinone **3.82**. Prenylated naphthoquinone **3.82** was proposed to be synthesised from Diels-Alder product **3.47** through hydroxyl group protection with benzyl bromide, followed by *O*-prenylation with prenyl bromide.



Scheme 3.19: A. Retrosynthetic analysis of benzyl-protected flaviolin 3.83. B. Retrosynthetic analysis of unprotected flaviolin 3.72.

Alternatively, shown in path **B**, furaquinocin C analogue **3.72** could be obtained *via* cyclisation of rearranged intermediate **3.73**. **3.73** would be obtained from Claisen rearrangement of *O*-prenylated **3.74**, and **3.74** would be easily accessed through prenylation of the C-3 hydroxyl group of **3.47**.

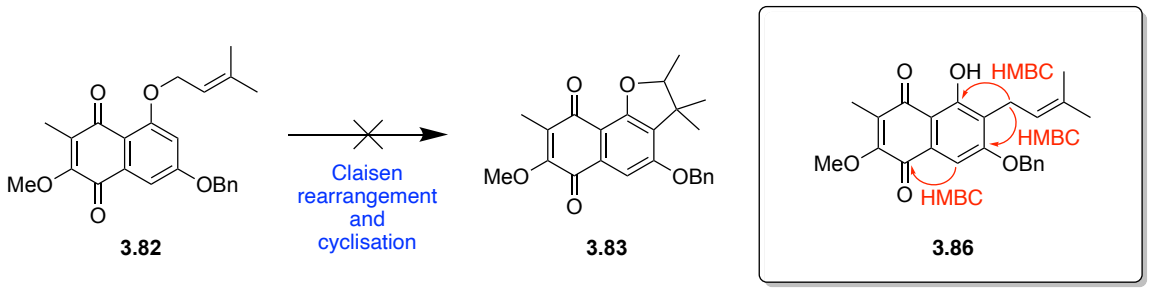
Based on literature research, we believed that protection of the more reactive hydroxyl group would help to direct the Claisen rearrangement in the preferred C-2 position. Consequently, the C-3 hydroxyl group of naphthoquinone **3.47** was protected with benzyl bromide yielding benzyl protected intermediate **3.85** in 45% yield. The product was then *O*-prenylated with prenyl bromide and sodium hydride in 76% yield to afford the desired rearrangement precursor **3.82** (Scheme 3.20).



Scheme 3.20: Benzylation and prenylation of naphthoquinone 3.47.

With the rearrangement precursor in hand, the Claisen rearrangement and subsequent cyclisation reaction was investigated. The trialled conditions are summarised in Table 3.1.

Table 3.1: Trialled reaction conditions for Claisen rearrangement and cyclisation of precursor 3.82.

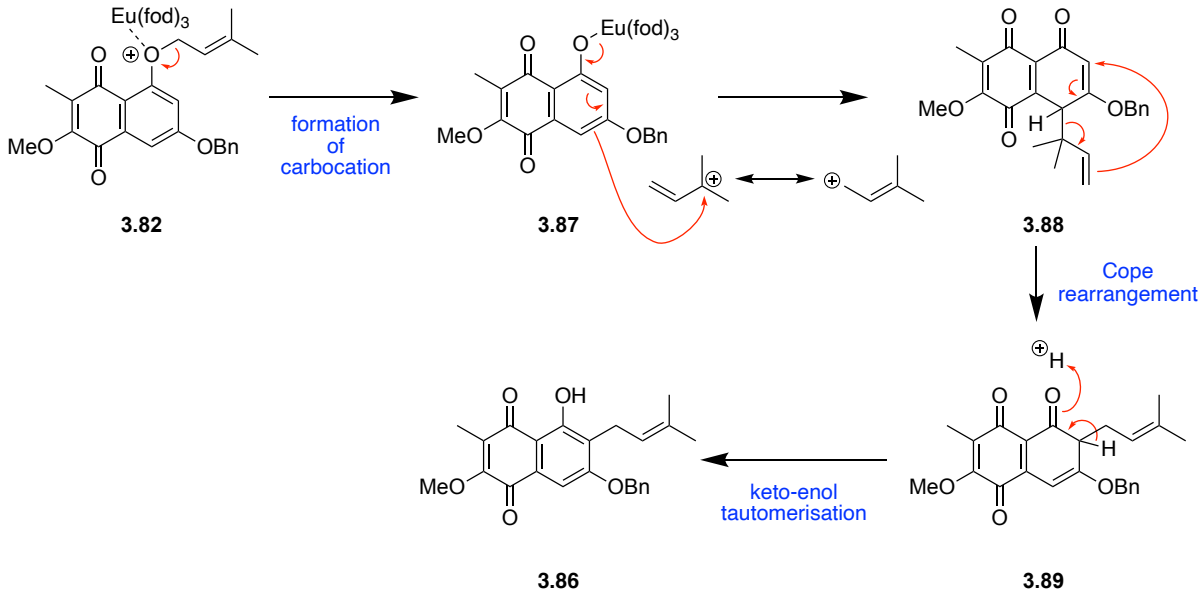


Entry	Reagent	Solvent	Conditons	Result[#]
1	$Eu(fod)_3$	$CHCl_3$	60 °C, 2 days	n.r.
2	$Eu(fod)_3$	toluene	85 °C, 4 h	*ortho*-rearrangement product **3.86** (6%), phenol **3.85** (8%) and decomposition
3	-	DMA	reflux, 30 min	phenol **3.85** and decomposition
4	NaOAc	Ac_2O	reflux, o.n.	slow decomposition

[#]Unless otherwise specified, results were indicated by TLC analysis. All percentage yields are isolated yields after standard workup and purification by flash column chromatography on silica gel; o.n. overnight, s.m. starting material, DMA *N*,*N*-dimethylaniline.

As $Eu(fod)_3$ has shown to be a reliable reagent in promoting Claisen/Cope rearrangements of similar systems, in the first three entries we trialled this reagent with different solvents and temperatures. Zhang *et al.* successfully isolated the *ortho*-rearrangement and cyclisation product when stirring their substrate in chloroform at 60 °C for 24 hours.[19] Al-Maharik and Botting also reported the successful rearrangement of acetylated and *O*-prenylated genistein with $Eu(fod)_3$ using the same conditions.[26] However, when using these reaction conditions on our system even under prolonged reaction time, no reaction occurred (entry 1). Changing the solvent from chloroform to toluene and heating the reaction mixture to 60 °C formed two new compounds which were isolated and characterised by ^{1}H NMR spectroscopy (entry 2). One compound was identified as the deprenylated starting material **3.85** in 8% yield. The second compound was identified as the *ortho*-rearrangement product **3.86** in 6% yield. ^{1}H NMR

analysis showed that the OH-signal at 12.58 ppm reappeared which indicates that the prenyl group is not attached to the hydroxyl group anymore. The spectra also showed only one aromatic proton singlet at 7.23 ppm. The prenyl group peaks are still visible with a significant upfield shift of the prenyl CH_2 group from 4.63 ppm to 3.45 ppm indicating the connection to a carbon atom rather than an oxygen. Key HMBC correlations (shown in red) strongly suggest the attachment of the prenyl group at the C-2 position. We proposed the following mechanism (Scheme 3.21).



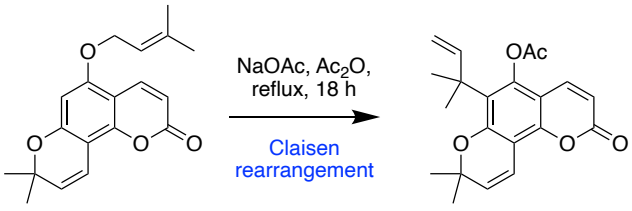
Scheme 3.21: Proposed mechanism of side product 3.86 formation *via* the formation of a dimethylallyl carbocation followed by nucleophilic attack and a Cope rearrangement.

The Lewis-acidic $Eu(fod)_3$ coordinates to the prenylated oxygen and, upon heating, promotes the formation of a dimethylallyl carbocation. Intermediate **3.87** then reacts with the cationic species to form intermediate **3.88** which readily undergoes Cope rearrangement to **3.89**. Finally, keto-enol tautomerisation re-introduces aromaticity and gives *ortho*-rearrangement product **3.86**. Surprisingly, this system shows unprecedented reactivity by favouring *ortho*-rearrangement over *para*-rearrangement.

We increased the reaction time to 18 h under the same conditions to see if we could increase the yield of side product **3.86**, however, TLC analysis indicated the same product distribution along with a fair amount of decomposition.

Raghavan and co-workers reported the successful Claisen-rearrangement of various prenylated xanthones in *N*,*N*-dimethylaniline (DMA) at temperatures up to 200 °C (see section 3.1.4).[17,18] When naphthoquinone **3.82** was heated at reflux in DMA for 30 min, we did not observe rearrangement of the prenyl side chain. Instead, the reaction conditions mostly led to decomposition of the starting material as well as the formation of a small amount of deprenylated compound **3.85** (entry 3). Heating **3.82** at reflux overnight led to full decomposition of the starting material.

In 1983, Murray and Jorge reported the efficient and short synthesis of nordentatin.[30] A key step of this synthesis is the Claisen rearrangement of prenyl ether **3.90** to rearranged intermediate **3.91** which exhibits a reverse prenyl chain (Scheme 3.22).[30]



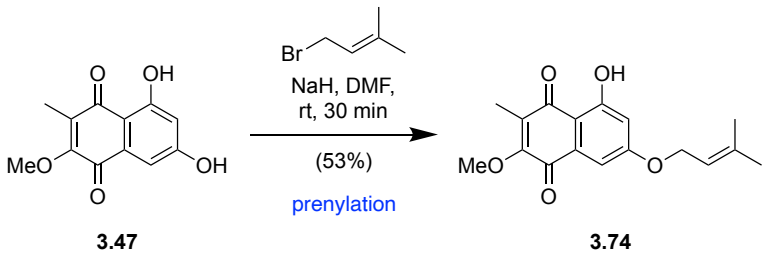
3.90 **3.91**

Scheme 3.22: Performed Claisen rearrangement by Murray and Jorge in 1983.[30]

These rearrangement conditions were tried on benzylated naphthoquinone **3.82** (entry 4). However, slow decomposition of the starting material was observed under these conditions.

3.2.4 Attempted Claisen Rearrangement and Cyclisation of Unprotected Naphthoquinone 3.74 and Total Synthesis of Fumaquinone

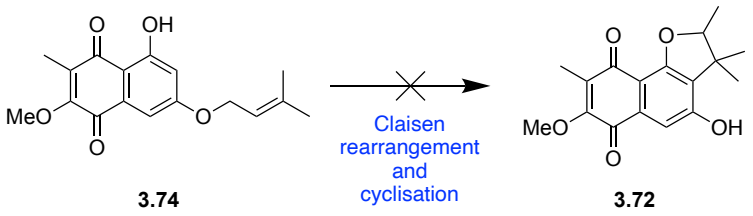
As the previous pathway did not seem to be successful, we thought that the bulky protecting group might be in the way and prevent the Claisen rearrangement from taking place. Therefore, the rearrangement was trialled on the unprotected system. For that, naphthoquinone **3.47** was prenylated with prenyl bromide and sodium hydride to give *O*-prenylated **3.74** in 53% yield (Scheme 3.23).



Scheme 3.23: Prenylation of unprotected naphthoquinone 3.47.

With prenylated naphthoquinone **3.74** in hand, we first investigated the desired Claisen rearrangement under thermal and basic reaction conditions. The trialled conditions are summarised in Table 3.2.

Table 3.2: Attempted thermal and/or basic Claisen rearrangement and cyclisation conditions of naphthoquinone 3.74.



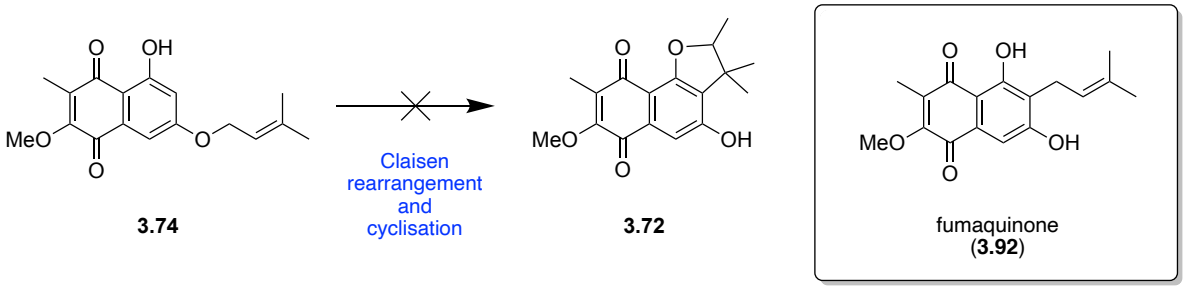
Entry	Reagent	Solvent	Conditons	Yield[#]
1	-	H_2O	reflux, o.n.	n.r.
2	-	toluene	reflux, o.n.	n.r.
3	-	xylene	reflux, o.n.	decomposition
4	-	DMF	reflux, o.n.	decomposition
5	-	piperidine	rt, o.n.	decomposition
6	NaH	DMF	rt, 3 h	n.r.
7	NaH	DMF	50 °C, o.n.	decomposition
8	-	DMA	100 °C, o.n.	n.r.

[#]All results were indicated by TLC analysis. rt room temperature, o.n. overnight, n.r. no reaction.

When refluxing the starting material in water or toluene overnight no reaction occurred (entries 1 and 2). Changing to solvents with higher boiling points like xylene and DMF led to decomposition of the starting material (entries 3 and 4). When the rearrangement was performed with the base piperidine as solvent at room temperature, decomposition of the starting material was observed (entry 5). In entry 6, the rearrangement was attempted with sodium hydride in DMF at room temperature which did not lead to any reaction after 3 h. When increasing the temperature to 50 °C, the starting material started to degrade (entry 7). In entry 8, the starting material was heated at 100 °C in DMA as a basic solvent which did not lead to the formation of any new species.

As application of heat and/or basic reagents were not successful in promoting the desired Claisen rearrangement, we moved on to screening reaction conditions with $Eu(fod)_3$ as rearrangement reagent. The conditions are summarised in Table 3.3.

Table 3.3: Trialled reaction conditions for Claisen-rearrangement and cyclisation of naphthoquinone 3.74.

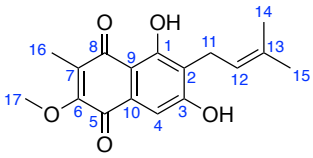


Entry	Reagent	Solvent	Conditons	Yield[#]
1	$Eu(fod)_3$, $NaHCO_3$	$CHCl_3$	reflux, o.n.	n.r.[*]
2	$Eu(fod)_3$, $NaHCO_3$	PhCl	85 °C, o.n.	r.s.m., deprenylation and fumaquinone (**3.92**, 43%)
3	$Eu(fod)_3$, $NaHCO_3$	toluene	85 °C, o.n.	n.r.[*]
4	$Eu(fod)_3$, $NaHCO_3$	benzene	reflux, o.n.	n.r.[*]
5	$Eu(fod)_3$, $NaHCO_3$	1,2-dichloroethane	reflux, o.n.	n.r.[*]
6	$Eu(fod)_3$, $NaHCO_3$	1,2-dichlorobenzene	170 °C, o.n.	decomposition[*]

[#]Percentage yields are isolated yields after aqueous workup and purification by flash column chromatography on silica gel; [*]Indicated by TLC analysis; r.s.m. recovered starting material, n.r. no reaction, o.n. overnight.

Once again, we decided to perform a comprehensive screening of various chlorinated and unchlorinated solvents in combination with $Eu(fod)_3$ on prenylated naphthoquinone **3.74**. In the first entry, the starting material was refluxed in chloroform for 24 h which did not promote any reaction. When the reaction was performed in chlorobenzene at 85 °C, one of the compounds was easily identified as the deprenylated naphthoquinone **3.47**. The other compound, however, was more interesting. From the ^{1}H NMR data it was obvious that the prenyl side chain has maintained a normal (non-reversed) configuration. However, the upfield shift of the prenyl CH_2 group from 4.57 ppm to 3.39 ppm indicated that the prenyl group is now attached to a carbon atom. When comparing the acquired spectroscopic data to literature, we found that the ^{1}H NMR data of the natural product fumaquinone (**3.92**) matched our acquired ^{1}H NMR data perfectly.[31,32] A comparison of ^{1}H and ^{13}C NMR data for both the natural and synthetic fumaquinone (**3.92**) is summarised in Table 3.4.

Table 3.4: Comparison of ^{1}H and ^{13}C NMR data of natural and synthetic fumaquinone (3.92) in acetone-d_6.

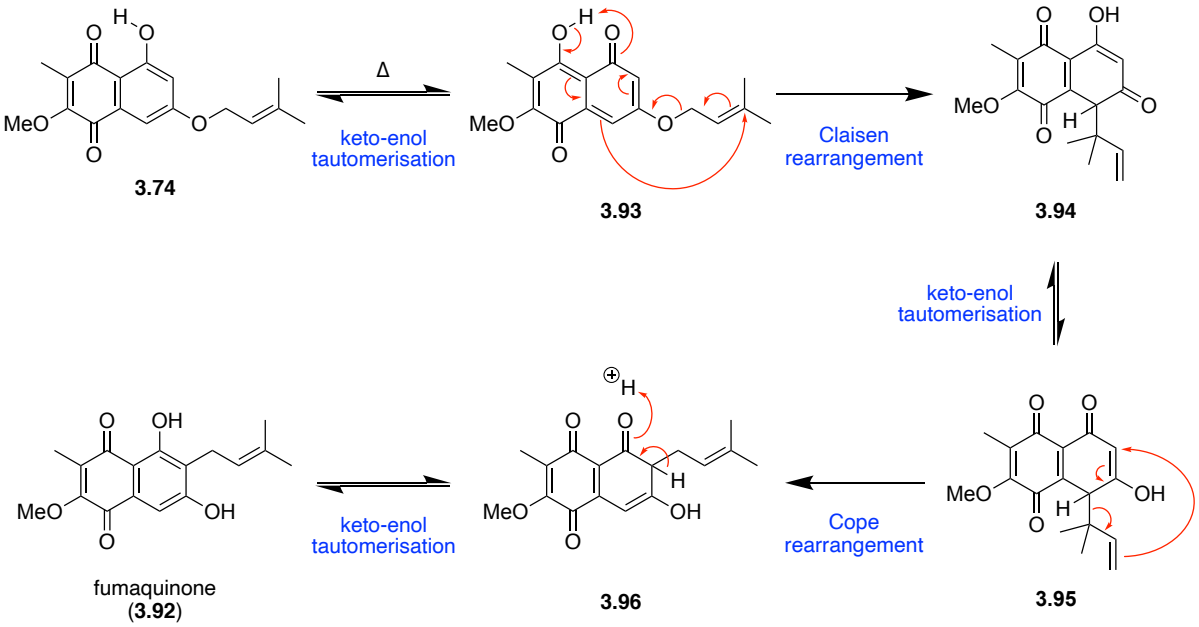


Position	^{1}H NMR data of natural 3.92 400 MHz[32]	^{1}H NMR data of synthetic 3.92 500 MHz	^{13}C NMR data of natural 3.92 100 MHz[32]	^{13}C NMR data of synthetic 3.92 125 MHz
1	-	-	162.2	163.9
2	-	-	122.3	124.0
3	-	-	161.9	160.6
4	7.13 (s, 1H)	7.13 (s, 1H)	108.2	109.8
5	-	-	181.0	182.8
6	-	-	158.9	160.6
7	-	-	131.6	133.4
8	-	-	191.0	192.8
9	-	-	109.1	110.8
10	-	-	131.7	133.5
11	3.39 (d, 7.4, 2H)	3.39 (d, 7.2, 2H)	22.7	24.4
12	5.23 (t, 7.2, 1H)	5.24 (t, 7.4, 1H)	122.0	123.7
13	-	-	132.7	134.4
14	1.78 (s, 3H)	1.78 (s, 3H)	18.0	19.7
15	1.65 (s, 3H)	1.65 (s, 3H)	25.9	27.6
16	1.99 (s, 3H)	2.00 (s, 3H)	8.8	10.5
17	4.07 (s, 3H)	4.08 (s, 3H)	61.3	63.0
6-OH	9.78 (s, 1H)	9.79 (brs, 1H)	-	-
8-OH	12.80 (s, 1H)	12.82 (s, 1H)	-	-

*Signals are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constants, integration).

Mechanistically, we propose that, upon heating, the fumaquinone system undergoes keto-enol tautomerisation to form intermediate **3.93** which is in equilibrium with enol **3.74** (Scheme 3.24). Claisen rearrangement of the prenyl group of naphthoquinone **3.93** forms reverse prenylated **3.94** which can tautomerise to give **3.95**. Cope rearrangement of the reverse prenyl chain of **3.95** forms intermediate **3.96**. **3.96** subsequently tautomerises to give the natural product fumaquinone (**3.92**).

We speculate that the regioselectivity of the first Claisen rearrangement is due to the initial keto-enol tautomerisation of **3.74** to **3.94**.

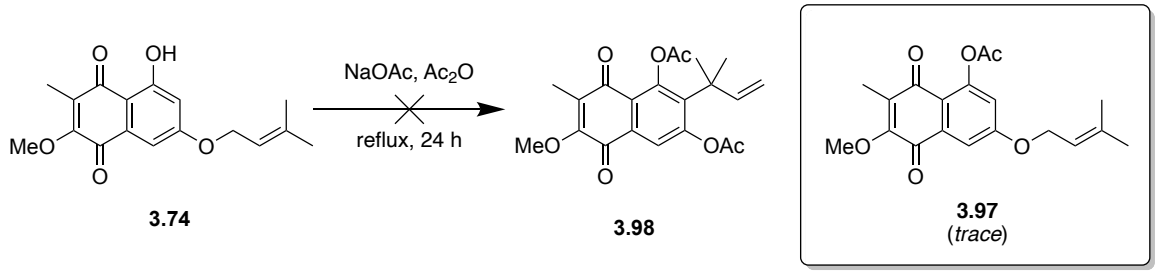


Scheme 3.24: Proposed mechanism of consecutive Claisen and Cope rearrangements to form natural product fumaquinone (3.92) from *O*-prenylated precursor 3.74.

In entry 3 and 4 of Table 3.3, the Claisen rearrangement was trialled with the non-chlorinated solvents toluene and benzene at 85 °C and reflux temperature, respectively. In both cases, no reaction occurred. Refluxing the starting material in 1,2-dichloroethane overnight did not lead

to any reaction. Lastly, when heating the starting material in 1,2-dichlorobenzene at 170 °C, the starting material decomposed (entry 6).

We also attempted Claisen rearrangement with NaOAc in refluxing Ac_2O following the procedure by Murray and Jorge as described before (Scheme 3.25).[30] TLC analysis of the reaction mixture indicated mostly decomposition of the starting material along with a very faint spot. The new compound was subsequently isolated. Interpretation of the ^1H NMR data indicated that the starting material did not undergo desired Claisen rearrangement. Instead, the C-1 hydroxyl group was acetylated forming intermediate **3.97** in trace amounts.



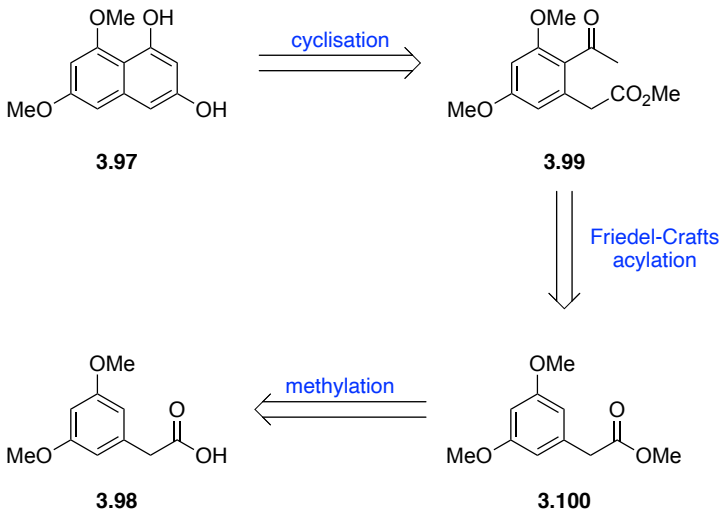
3.74 **3.98** **3.97** (*trace*)

Scheme 3.25: Attempted rearrangement reaction with NaOAc and Ac_2O following a procedure by Murray and Jorge.

3.2.5 Synthesis of prenylated THN precursors

Looking at the proposed biosynthesis of the furaquinocins and neomarinone we decided that an alternative pathway to investigate was prenylation and rearrangement of the non-oxidised THN. Although, from a biosynthetic point of view, it is strongly suggested that prenylation takes place after oxidation of the THN to the flaviolin core, we were eager to investigate if the desired Claisen or Cope rearrangement could be promoted on the THN system. We speculated that a more electron-rich system would facilitate the desired rearrangement at the C-2 position and, therefore, circumvent the previously discussed regioselectivity problem associated with the quinone moiety.

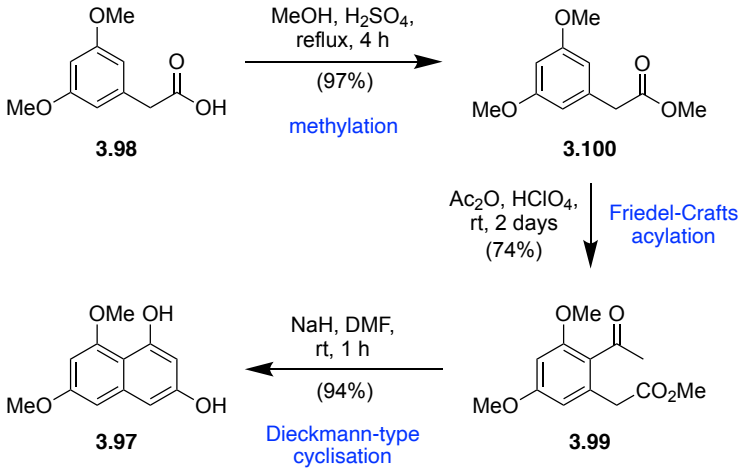
In our retrosynthetic analysis (Scheme 3.26), it was envisioned that methyl protected THN **3.97** could be synthesised from commercially available acid **3.98** following a well-established procedure in our group.[33,34] THN analogue **3.97** would be synthesised in good yields by cyclisation of precursor **3.99**. Friedel-Crafts acylation of ester **3.100** would give **3.99**. Ester **3.100** could be obtained via simple esterification of acid **3.98**.



3.97 **3.99** **3.98** **3.100**

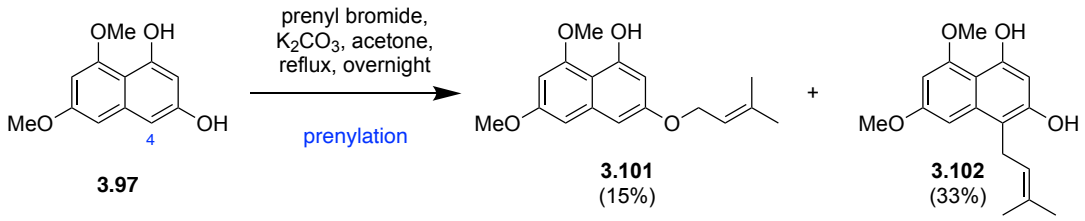
Scheme 3.26: Retrosynthetic analysis of THN 3.97.

Following the described forward synthesis in Scheme 3.27, commercially available 3,5-dimethoxy phenylacetic acid (**3.98**) was esterified with methanol and sulfuric acid in almost quantitative yields.[33,34] The obtained ester **3.100** was then subjected to a Friedel-Crafts acylation with acetic anhydride to generate cyclisation precursor **3.99** in 74% yield. Dieckmann-type condensation between the ketone moiety and the ester afforded methyl protected THN **3.97** in excellent yields.



Scheme 3.27: Forward synthesis of methylated THN 3.97.

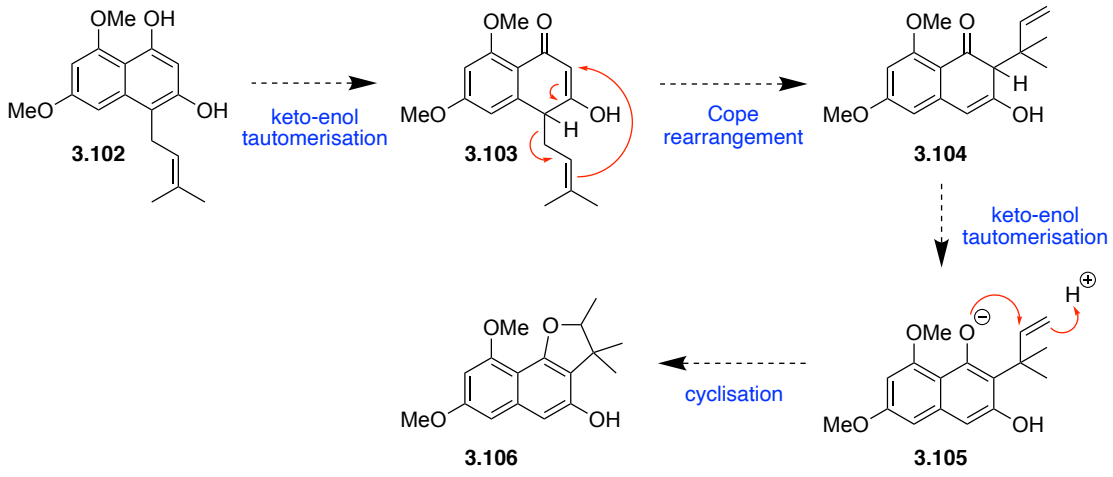
The obtained THN **3.97** was then taken on to the prenylation reaction (Scheme 3.28). Heating the substrate **3.97** at reflux overnight with prenyl bromide and potassium carbonate afforded 15% of the *O*-prenylated product **3.101** and 33% of the *C*-prenylated product **3.102** along with a diprenylated species (not shown) and unreacted starting material. Interestingly, *C*-prenylation always took place in C-4 position. We did not mind obtaining both products in this reaction as we were interested in attempting rearrangement conditions on both prenylated intermediates.



Scheme 3.28: Prenylation of THN 3.97 with prenyl bromide.

3.2.6 Attempted Cope Rearrangement of *C*-prenylated THN

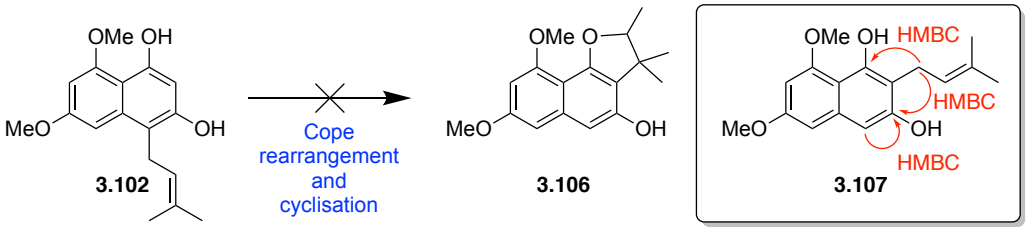
With both prenylated precursors in hand, we decided to first investigate the Cope rearrangement of *C*-prenylated THN **3.102**. Our proposed mechanism described in Scheme 3.29 commences with keto-enol tautomerisation of THN **3.102** to enone **3.103** which would then undergo Cope rearrangement to intermediate **3.104**. The system would tautomerise again to re-install aromaticity of the ring to form intermediate **3.105**. Cyclisation of intermediate **3.105** would afford dihydrobenzofuran **3.106**.



Scheme 3.29: Proposed reaction mechanism for Cope rearrangement and subsequent cyclisation reaction of *C*-prenylated THN 3.102.

With the proposed mechanism in mind, we subjected *C*-prenylated THN **3.102** to different rearrangement conditions listed in Table 3.5.

Table 3.5: Reaction conditions for Cope rearrangement and cyclisation reaction

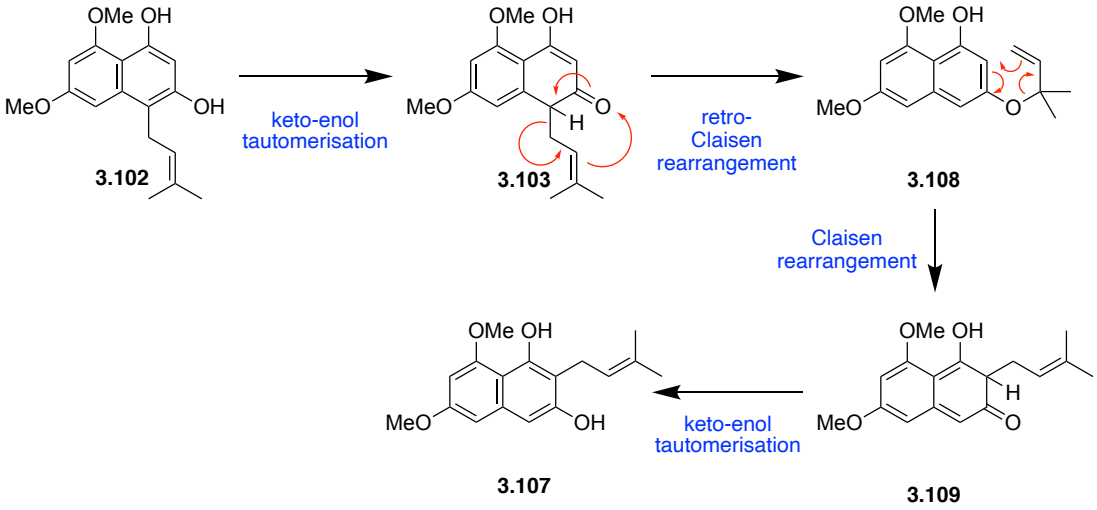


Entry	Reaction Conditions	Yield
1	H_2O, reflux, 24 h	no reaction*
2	DMF, reflux, 24 h	decomposition*
3	piperidine, H_2O, reflux, 48 h	no reaction*
4	pyridine, H_2O, reflux, 48 h	no reaction*
5	$Eu(fod)_3$, $NaHCO_3$, $CHCl_3$, reflux, 24 h	no reaction*
6	$Eu(fod)_3$, $NaHCO_3$, PhCl, 85 °C, 24 h	**3.107** (27%)

*Unless otherwise specified, all outcomes are indicated by TLC and/or crude ^1H NMR analysis. All percentage yields are isolated yields after purification by flash column chromatography on silica gel.

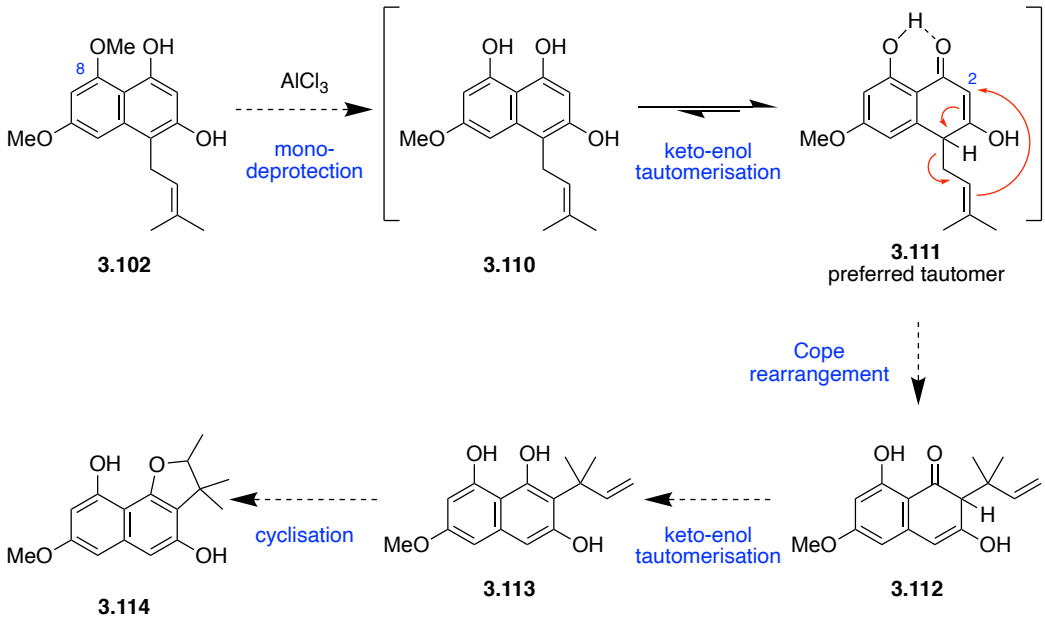
In the first two entries, the main interest was to investigate if Cope rearrangement and cyclisation could be promoted by applying heat to the system. When refluxing the substrate **3.102** in H_2O for 24 hours (entry 1), the starting material did not react at all. Refluxing substrate **3.102** in DMF for a prolonged period led to decomposition of the *C*-prenylated THN **3.102** (entry 2). We decided to explore if addition of a base would induce rearrangement and cyclisation. In entry 3, substrate **3.102** was refluxed for 48 hours in H_2O with addition of piperidine as a base which did not lead to any reaction. In entry 4, the reaction was repeated with pyridine as a base but again the starting material did not react. Next, we turned our focus towards reaction conditions with $Eu(fod)_3$ and sodium bicarbonate. Heating the starting

material **3.102** at reflux in chloroform for 24 h did not form any compound (entry 5). When heating the substrate **3.102** in chlorobenzene as solvent at 85 °C for 24 h (entry 6), TLC analysis indicated the formation of a new compound with a lower R_f value than the starting material. Aqueous workup and purification by flash column chromatography allowed us to isolate the new compound and analyse it by spectroscopic methods. Key HMBC correlations indicate that the prenyl group moved from the C-4 to the C-2 position. We propose **3.102** undergoes keto-enol tautomerisation to intermediate **3.103** which can then form **3.108** in a retro-Claisen rearrangement (Scheme 3.30). A second Claisen rearrangement of **3.108** affords **3.109** which rearomatises to **3.107** *via* keto-enol tautomerisation.



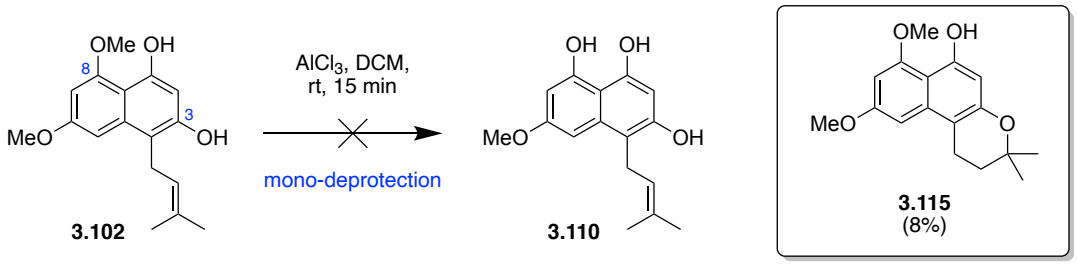
Scheme 3.30: Proposed mechanism of 3.102 to 3.107 *via* two consecutive Claisen rearrangements.

In a last attempt on the *C*-prenylated THN system, we decided to try to mono-deprotect the methyl ether on C-8. We assumed that intramolecular hydrogen bonds between the resulting free hydroxyl group and the C-1 carbonyl group would force the equilibrium towards the desired keto-enol tautomer **3.111** (Scheme 3.31). This tautomer is required for a successful Cope rearrangement in C-2 position. Keto-enol tautomerisation and cyclisation of the side chain would then afford the desired dihydrobenzofuran moiety of **3.106**.



Scheme 3.31: Proposed rearrangement and cyclisation mechanism of mono-deprotected THN 3.111.

We first attempted the mono-deprotection of the C-8 hydroxyl group with BBr_3 which led to degradation of the starting material. Variation of equivalents, concentration, reaction time and temperature did not change the outcome of the reaction. Next, we treated *C*-prenylated THN **3.102** with aluminium(III) chloride as we had good experiences in our group with this deprotection method.[35] However, instead of promoting the deprotection, the Lewis acid mediated cyclisation of the prenyl group with the C-3 hydroxyl group to give chromane **3.115** in 8% yield (Scheme 3.32). We believe that the Lewis acid and adventitious water form the Brønsted acid HCl, which can protonate the olefin forming a tertiary carbocation as an intermediate. Following this, the lone pair of the oxygen of the hydroxyl group attacks the carbocation to close the ring, giving the product **3.115** after a final deprotonation step.

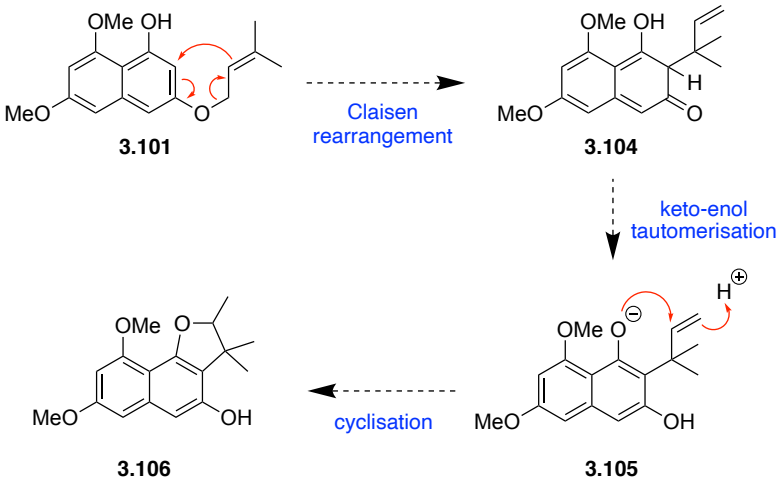


Scheme 3.32: Attempted deprotection led to cyclisation of side chain to form 3.115.

All trialled reaction conditions with *C*-prenylated intermediate **3.102** were unsuccessful, hence, we decided to investigate rearrangement and cyclisation of *O*-prenylated THN precursor **3.101** next.

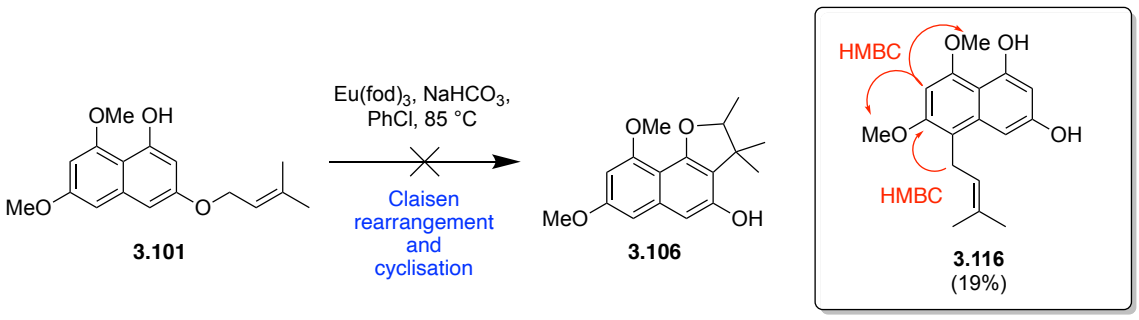
3.2.7 Attempted Claisen Rearrangement of *O*-Prenylated THN

As *C*-prenylated THN **3.102** was found to show undesired reactivity towards rearrangement conditions, we decided to turn our focus to the *O*-prenylated analogue **3.101**. In our proposed reaction mechanism to form natural product analogue **3.106** (Scheme 3.33), the first step would involve Claisen rearrangement of *O*-prenylated THN **3.101** to intermediate **3.104** which then could undergo keto-enol tautomerisation to **3.105**. Cyclisation of the enolate could then hopefully form the desired dihydrobenzofuran **3.106**.



Scheme 3.33: Proposed mechanism of Claisen rearrangement and cyclisation of *O*-prenylated THN 3.101.

The first reaction condition to provoke desired Claisen rearrangement we tried was $Eu(fod)_3$ as reagent with $NaHCO_3$ in chlorobenzene at 85 °C (Scheme 3.34). The same conditions gave an interesting side product when used on the *C*-prenylated intermediate **3.102**. Hence, we were interested to see what would happen to *O*-prenylated intermediate **3.101**. TLC analysis of the formed mixture showed a new spot along with residual starting material.



Scheme 3.34: Attempted Claisen rearrangement and cyclisation with *O*-prenylated THN precursor 3.101 and isolation of side product 3.116.

First interpretation of the ^1H NMR data showed that the new compound isolated from the reaction mixture showed the same pattern of signals as the C-4 prenylated THN intermediate

3.102 (Figure 3.7). Hence, we were quite certain that the prenyl chain remained in its normal (non-reversed) configuration. However, the signals did not match the known C-4 prenylated intermediate **3.102**. The ^{1}H NMR of the new side product clearly shows two OH singlets at 9.42 ppm and 4.92 ppm. Furthermore, three distinctive aromatic CH peaks are visible; two doublets at 6.67 ppm and 6.37 ppm as well as a singlet at 6.46 ppm.

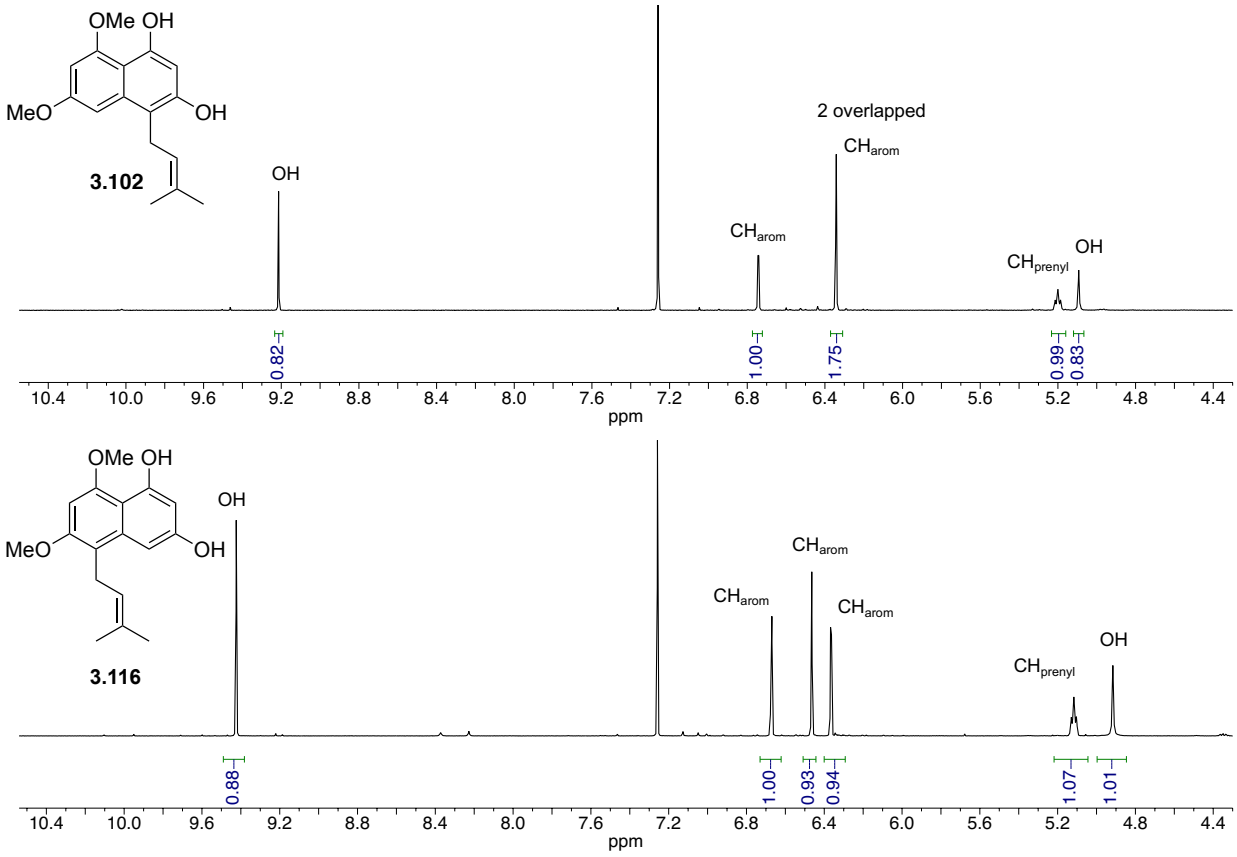
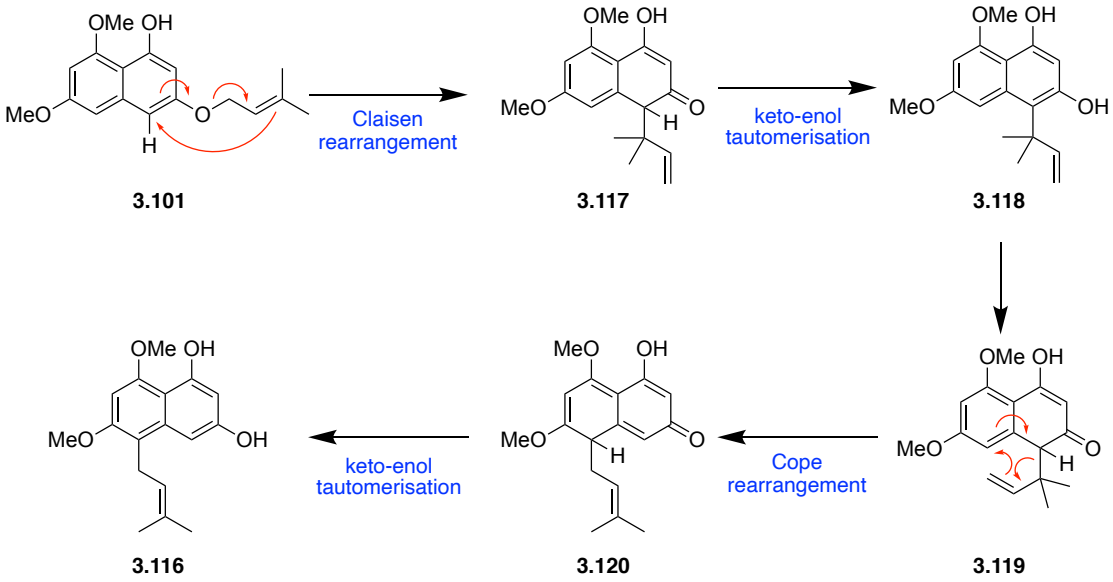


Figure 3.7: Comparison of the 10 ppm to 5 ppm region of ^{1}H NMR spectra of C-4 prenylated THN 3.102 and new isolated side product 3.116.

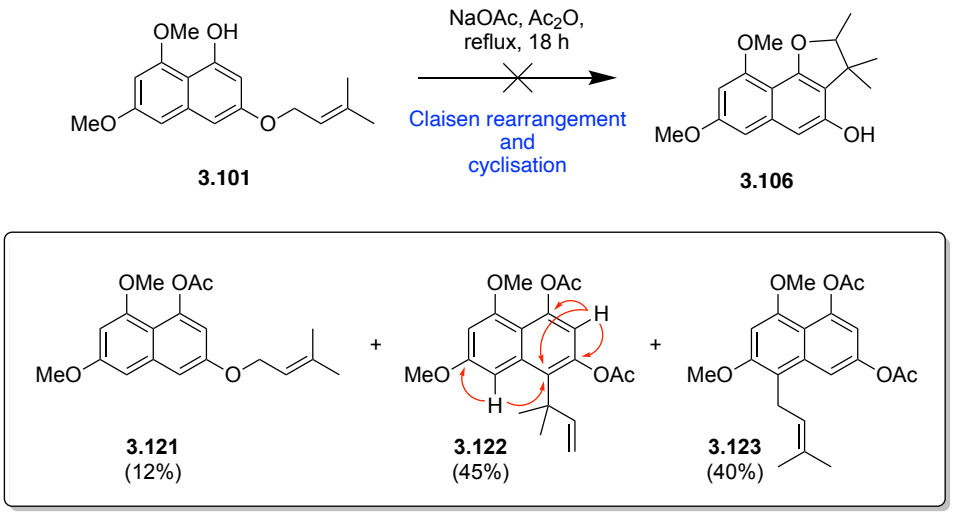
Careful analysis of the obtained ^{1}H, ^{13}C and 2D NMR data led us to the conclusion that the prenyl chain was now attached to the C-5 position of the THN core. There is a strong correlation between the methoxy groups and the aromatic C-H singlet indicating that the side chain is attached to the left-hand side of the molecule (see HMBC correlations in red). Our

proposed mechanism for the formation of **3.116** is shown in Scheme 3.35. Claisen rearrangement of *O*-prenylated THN **3.101** presumably gives intermediate **3.117** which tautomerises to intermediate **3.118** with the reverse prenyl chain in C-4 position. The reaction did not terminate at this point but underwent a subsequent Cope rearrangement and keto-enol tautomerisation to give rearranged THN **3.116**.



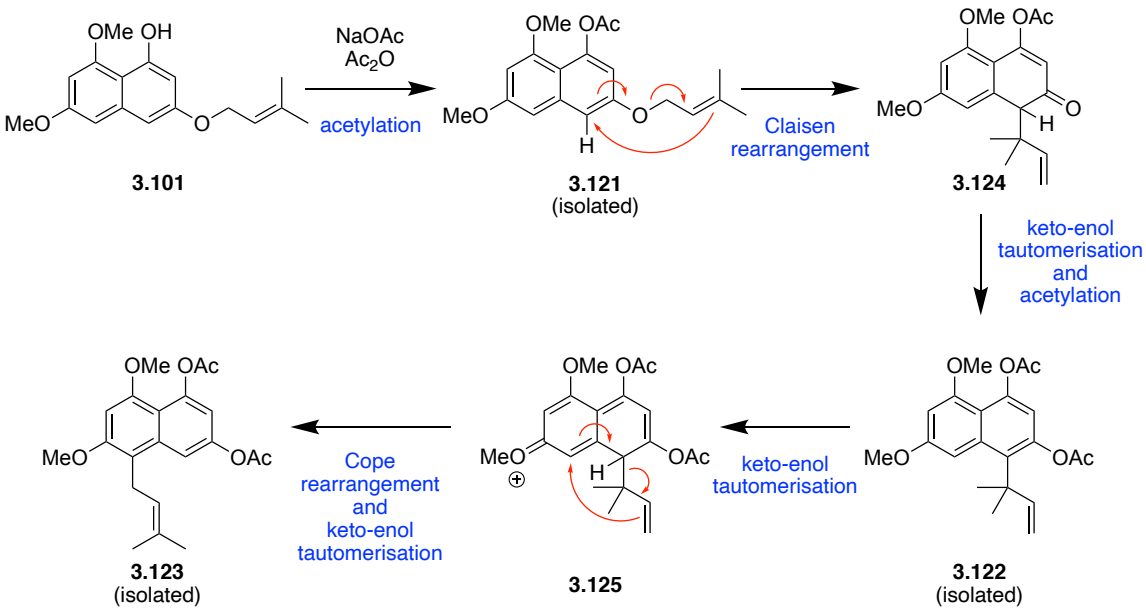
Scheme 3.35: Proposed mechanism for formation of side product 3.115.

Another set of conditions we trialled was the rearrangement promoted by refluxing the starting material in acetic anhydride with sodium acetate gave three compounds (Scheme 3.36).



Scheme 3.36: Attempted rearrangement with NaOAc and Ac_2O gave three new side products 3.121, 3.122 and 3.123, significant HMBC correlations shown in red.

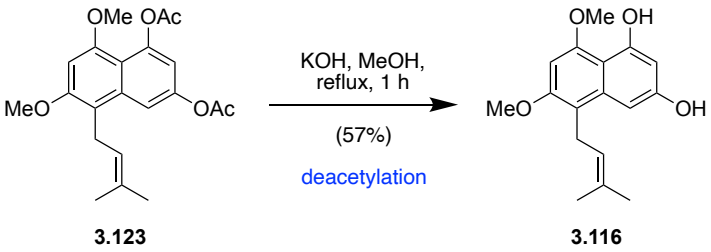
Analysis of the compounds by ^{1}H, ^{13}C and 2D NMR spectroscopy indicated strongly that all three compounds had no free hydroxyl groups. **3.121** had been acetylated once, **3.122** and **3.123** had been acetylated twice. The first compound was easily identified as the acetylated starting material **3.121**. Although the ^{1}H NMR spectra of the second isolated compound showed the desired signals of a reverse prenyl chain, specifically a quartet at 6.34 ppm and two doublets at 5.10 ppm and 5.04 ppm, closer analysis of the acquired data indicated the attachment of the chain to the C-4 instead of the C-2 position (see significant HMBC correlations in red). Analysis of the obtained ^{1}H, ^{13}C and 2D NMR data of the third isolated compound showed attachment of a normal (non-reversed) prenyl group to the C-5 position. Both side products **3.122** and **3.123** showed acetylation on the C-1 and C-3 hydroxyl groups. Based on the structural assignment, we proposed the following mechanism for the formation of all three side products (Scheme 3.37).



Scheme 3.37: Proposed mechanism of Claisen/Cope rearrangement of prenylated THN 3.101 with NaOAc and Ac_2O.

We propose that acetylation of the free C-1 hydroxyl group gives intermediate **3.121**. Claisen rearrangement of the prenyl side chain forms intermediate **3.124** which immediately undergoes keto-enol tautomerisation and acetylation of the newly created free C-3 hydroxyl group to form the second isolated intermediate **3.122**. Under these conditions, **3.122** could undergo another keto-enol tautomerisation to form intermediate **3.125** which subsequently rearranges in a Cope rearrangement attaching the prenyl chain to the C-5 position. After a third keto-enol tautomerisation to re-install aromaticity throughout the ring system, **3.123** was obtained.

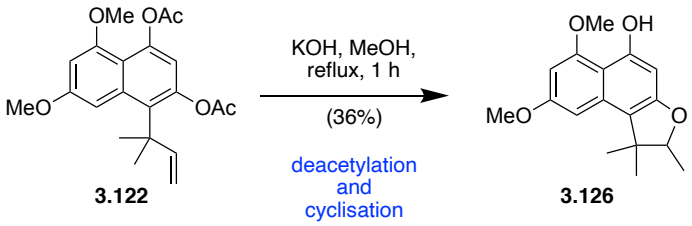
To further confirm the structure of **3.123**, the acetylated side product **3.123** was subjected to deacetylation conditions (potassium hydroxide in refluxing methanol) and the acquired spectroscopic data matched the data obtained for intermediate **3.116** (Scheme 3.38).



3.123 **3.116**

Scheme 3.38: Deacetylation of THN intermediate 3.123 to 3.116 with KOH in refluxing methanol.

We also performed the same deacetylation conditions on intermediate **3.122** to see if the reverse prenyl system would undergo desired cyclisation after removal of the acetate group (Scheme 3.39). To our delight, the reaction did indeed not stop at the deprotection step and the free hydroxyl group cyclised to form the desired dihydrobenzofuran moiety of the furaquinocin natural products in 36% yield. Unfortunately, the obtained product **3.126** was very unstable.

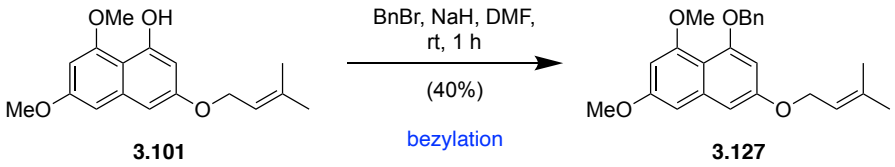


3.122 **3.126**

Scheme 3.39: Deacetylation of intermediate 3.122 with KOH in refluxing methanol.

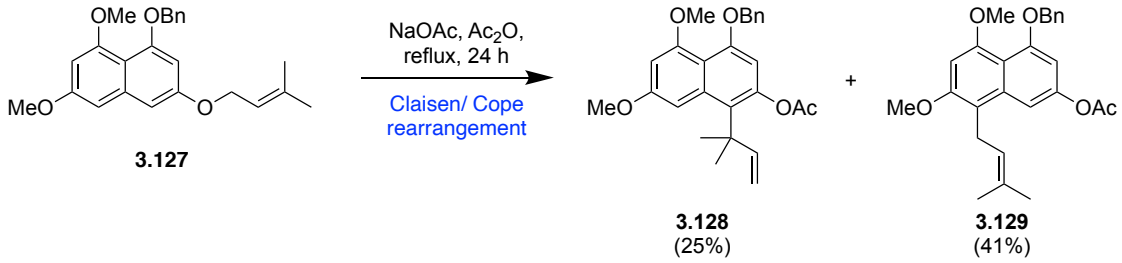
3.2.8 Attempted Claisen Rearrangement of Benzyl protected THN 3.127

Intrigued by the previous rearrangement result using sodium acetate in refluxing acetic anhydride, we decided to protect the free hydroxyl group with benzyl bromide and try the rearrangement conditions again on the protected system. For that, *O*-prenylated THN **3.101** was protected to afford benzylated THN **3.127** in 40% yield (Scheme 3.40).



Scheme 3.40: Benzyl protection of *O*-prenylated THN 3.101 with benzyl bromide.

Next, protected THN **3.127** was subjected to the same rearrangement conditions as the unprotected system (Scheme 3.41). After refluxing the substrate **3.127** for 24 hours, two new spots were visible upon TLC analysis. Aqueous workup and purification by flash column chromatography led us to isolate two new compounds which were analysed by spectroscopic methods. Analogous to the unprotected system **3.101**, the two isolated compounds were **3.128** and **3.129** in 25% and 41% yield, respectively.

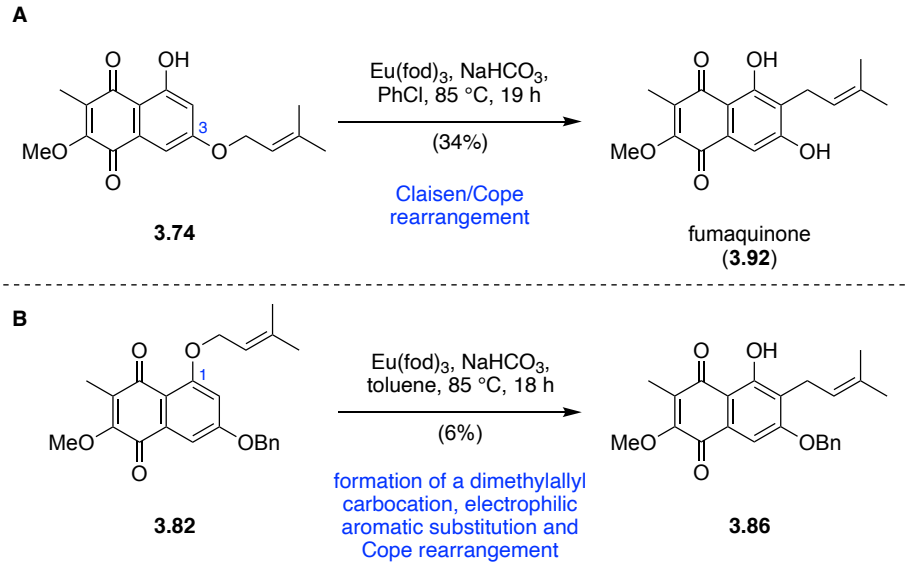


Scheme 3.41: Claisen/Cope rearrangement with NaOAc and Ac_2O.

3.3 Conclusions and Future Directions

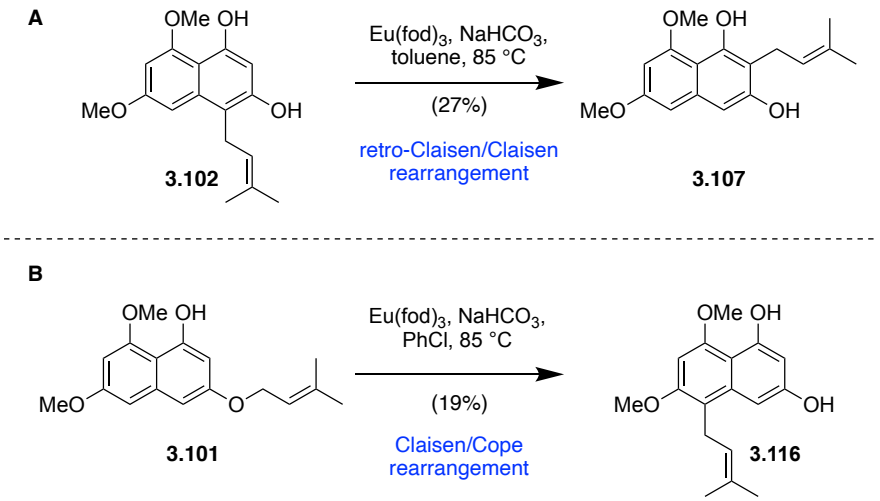
In summary, we have been able to gain significant insight into the reactivity of Claisen/Cope rearrangements of flaviolin and THN systems.

When performing the Claisen rearrangement on C-3 *O*-prenylated flaviolin **3.74**, we successfully synthesised natural product fumaquinone (**3.92**) in 43% yield (Scheme 3.42, **A**). When we performed rearrangement on the C-1 *O*-prenylated flaviolin system **3.82**, benzyl protected fumaquinone (**3.86**) was obtained but in lower yields of 6% (Scheme 3.42, **B**). Mechanistically, the latter reaction showed us some very interesting reactivity as the substrate seemed to prefer to form a dimethylallyl carbocation followed by electrophilic aromatic substitution and Cope rearrangement over undergoing an *ortho*-Claisen rearrangement.



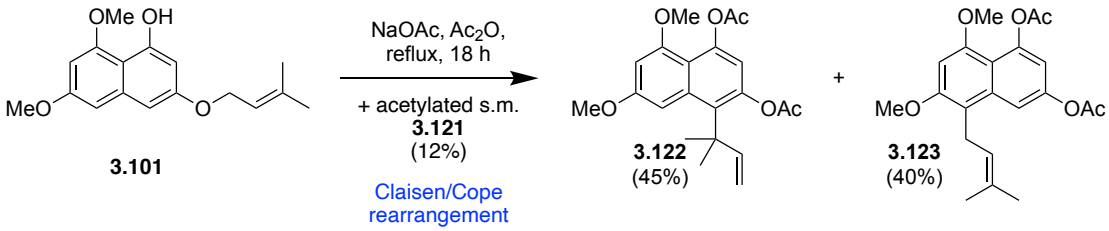
Scheme 3.42: A. Eu(fod)$_3$-catalysed rearrangement on flaviolin analogue 3.74. B. Eu(fod)$_3$-catalysed rearrangement on benzyl protected flaviolin analogue 3.82.

When we moved on to the THN system, we observed some very fascinating reactivity regarding Claisen/Cope rearrangements as well. Although the C-4 prenylated THN **3.102** system was not particularly reactive, we observed retro-Claisen rearrangement followed by Claisen rearrangement to C-2 prenylated THN **3.107** (Scheme 3.43, **A**). Subjecting *O*-prenylated THN **3.101** to the same conditions gave C-5 prenylated THN **3.116** through consecutive Claisen and Cope rearrangements (Scheme 3.43, **B**).



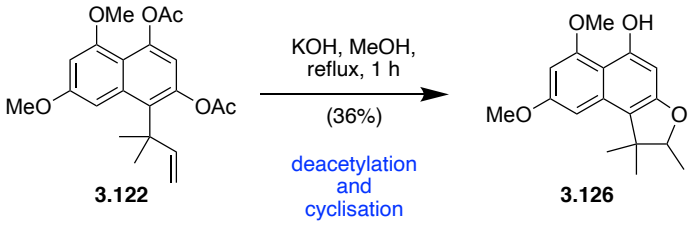
Scheme 3.43: A. Eu(fod)$_3$-promoted rearrangement on *C*-prenylated THN 3.102. B. Eu(fod)$_3$-promoted rearrangement on *O*-prenylated THN 3.101.

We then moved away from europium(III)-promoted rearrangement conditions to NaOAc/Ac_2O (Scheme 3.44). Using these conditions on the *O*-prenylated THN **3.101**, we isolated three new compounds; one of which (**3.122**) showed the desired reversed prenyl chain moiety. Unfortunately, the side chain was attached to the C-4 position (not the C-2 position).



Scheme 3.44: NaOAc/Ac_2O-catalysed rearrangement reaction.

However, to our delight, when we subjected intermediate **3.122** to deacetylation conditions, the free hydroxyl group cyclised to form the desired dihydrobenzofuran moiety of the furaquinocin natural products in 36% yield (Scheme 3.45).



Scheme 3.45: Desired dihydrobenzofuran moiety formation under deacetylation conditions.

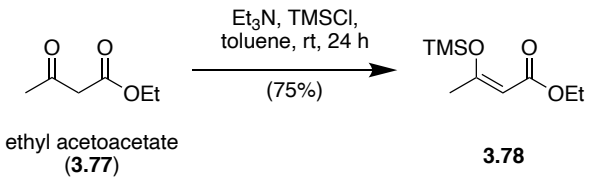
In the future, it would be desirable to perform an even more comprehensive screening of rearrangement reaction conditions to allow rearrangement to go in the desired C-2 position. Based on our previous results, we are confident that cyclisation of the rearranged side chain would then happen spontaneously to give the desired moiety of the furaquinocin and neomarinone natural products.

3.4 Supporting Information

3.4.1 General Methods

All chemicals used were purchased from commercial suppliers and used as received. Unless otherwise stated, all reactions were performed under an inert atmosphere of N_2. All organic extracts were dried over anhydrous magnesium sulfate. Thin layer chromatography was performed using aluminium sheets coated with silica gel F_{254}. Visualisation was aided by viewing under a UV lamp and staining with ceric ammonium molybdate followed by heating. All R_f values were measured to the nearest 0.05. Flash column chromatography was performed using 40-63 micron grade silica gel. Melting points were recorded on a Reichart Thermovar Kofler microscope apparatus and are uncorrected. Infrared spectra were recorded using an FT-IR spectrometer as the neat compounds. High field NMR spectra were recorded using both a 500 MHz spectrometer (^{1}H at 500 MHz, ^{13}C at 125 MHz) and 600 MHz spectrometer (^{1}H at 600 MHz, ^{13}C at 150 MHz) as indicated. The solvent used for spectra was $CDCl_3$ unless otherwise specified. ^{1}H chemical shifts are reported in ppm on the δ-scale relative to TMS (δ 0.0) and ^{13}C NMR are reported in ppm relative to $CDCl_3$ (δ 77.16). Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (quin) quintet, (sext) sextet, (hept) heptet and (m) multiplet. All *J*-values were rounded to the nearest 0.1 Hz. ESI high resolution mass spectra were recorded on an ESI-TOF mass spectrometer.

3.4.2 Experimental Procedures



ethyl acetoacetate (**3.77**)

3.78

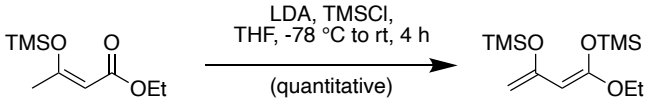
To a solution of ethyl acetoacetate (**3.77**, 20.0 g, 154 mmol, 1 eq.) in toluene (150 mL) was added NEt_3 (25.7 mL, 184 mmol, 1.2 eq.) and TMSCl (23.4 mL, 184 mmol, 1.2 eq.) at room temperature. The reaction mixture was stirred at room temperature for 24 h before it was filtered through a pad of Celite and concentrated *in vacuo*. Purification by distillation (95 °C, 22 mm Hg) afforded **3.78** (23.4 g, 116 mmol, 75%) as a light-yellow oil.

Partial data for **3.78**:

R_f: 0.33 [PE:EtOAc 3:1]

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.12 (s, 1H), 4.11 (q, J = 6.9 Hz, 2H), 2.26 (s, 3H), 1.28 – 1.25 (m, 3H), 0.27 (s, 9H) ppm.

The analytical data match those previously described in the literature.[25]



3.78 **3.75**

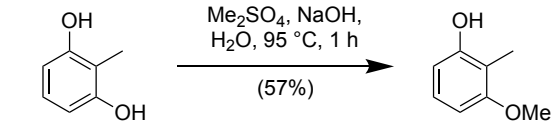
n-BuLi (2M in THF, 17 mL, 34.6 mmol, 1.4 eq.) was added dropwise to a solution of diisopropyl amine (4.8 mL, 34.6 mmol, 1.4 eq.) in THF (50 mL) at 0 °C and stirred for 15 min. Then, the solution was cooled to -78 °C and the trimethylsilyl enol ether **3.78** (5.00 g, 24.7 mmol, 1 eq.) was added dropwise. The reaction mixture was stirred for 1 h at -78 °C before TMSCl (4.4 mL, 34.6 mmol, 1.4 eq.) was added. The mixture was stirred for 2 more hours at -78 °C. After that, the solvent was removed *in vacuo*, the residue was re-dissolved in petrol and filtered through a pad of Celite to afford enol ether **3.75** (6.78 g, 24.7 mmol, quant.) as a dark yellow oil. The crude product was used in the next step without the need for further purification.

Partial data for **3.75**:

R_f: 0.33 [PE:EtOAc 3:1]

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.47 (s, 1H), 4.13 (d, *J* = 1.0 Hz, 1H), 3.91 (s, 1H), 3.77 (q. *J* = 7.0 Hz, 2H), 1.30 (t, *J* = 7.0 Hz, 3H), 0.25 (s, 9H), 0.21 (s, 9H) ppm.

The analytical data match those previously described in the literature.[25]



2-methylresorcinol
(**3.76**)

3.79

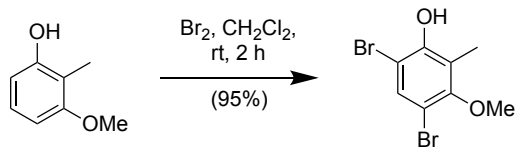
To a solution of 2-methylresorcinol (**3.76**, 10.0 g, 80.6 mmol, 1 eq.) in H_2O (75 mL) was added NaOH (3.87 g, 96.7 mmol, 1.2 eq.). The reaction mixture was heated to 95 °C before Me_2SO_4 (8.4 mL, 88.6 mmol, 1.1 eq.) followed by another load of NaOH (3.87 g, 96.7 mmol, 1.2 eq.) were added. The reaction mixture was stirred at 95 °C for 1 h. The reaction was quenched with 2M aqueous NaOH solution (50 mL) and the aqueous layer was extracted with Et_2O (2 x 75 mL). The organic layer was discarded, and the aqueous layer was carefully acidified with conc. HCl. The acidic aqueous layer was extracted with Et_2O (2 x 75 mL), the combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo*. Purification by flash column chromatography [PE:EtOAc 8:1] afforded methyl phenol **3.79** (6.36 g, 46.0 mmol, 57%) as a pale yellow oil.

Partial data for **3.79**:

R_f: 0.40 [PE:EtOAc 3:1]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.02 (t, *J* = 8.2 Hz, 1H), 6.46 (dd, *J* = 12.9, 8.2 Hz, 2H), 4.80 (s, 1H), 3.81 (s, 3H), 2.12 (s, 3H) ppm.

The analytical data match those previously described in the literature.[24,36]



3.79 **3.80**

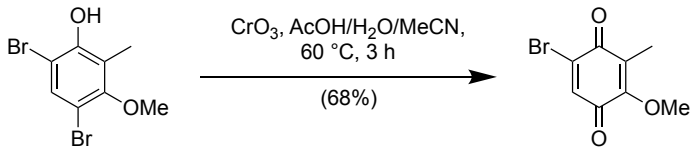
To a solution of methyl phenol **3.79** (2.63 g, 19.0 mmol, 1 eq.) in CH_2Cl_2 (25 mL) was added dropwise a solution of Br_2 (1.96 mL, 38.0 mmol, 2 eq.) in CH_2Cl_2 (25 mL). The reaction mixture was stirred for 2 h at room temperature. Then, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated aqueous sodium thiosulfate solution (2 x 100 mL) and saturated aqueous NaCl solution (2 x 100 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford brominated methyl phenol **3.80** (5.34 g, 18.0 mmol, 95%) as an off-white powder. The crude product was used in the next step without the need for further purification.

Partial data for **3.80**:

R_f: 0.48 [PE:EtOAc 4:1]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (s, 1H), 5.53 (s, 1H), 3.78 (s, 3H), 2.27 (s, 3H) ppm.

The analytical data match those previously described in the literature.[23,24]



3.80 **3.20**

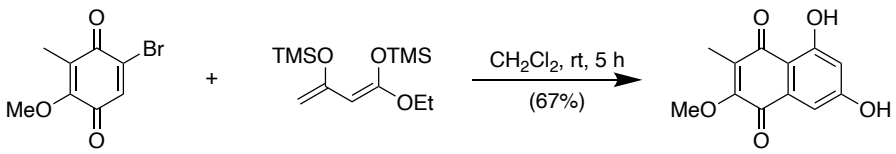
Bromo methyl phenol **3.80** (5.21 g, 17.6 mmol, 1 eq.) was suspended in a 1.5:1:1.5 mixture of AcOH (40 mL), H_2O (27 mL) and MeCN (40 mL). CrO_3 (3.52 g, 35.2 mmol, 2 eq.) dissolved in H_2O (14 mL) was slowly added to the suspension. The reaction mixture was heated at 60 °C for 2 h before it was diluted with saturated aqueous NH_4Cl solution (100 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic layers were washed consecutively with saturated aqueous sodium bicarbonate solution (2 x 50 mL) and saturated aqueous NaCl solution (100 mL). The organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification by flash column chromatography [PE:EtOAc 10:1] afforded bromo quinone **3.20** (2.75 g, 11.9 mmol, 68%) as bright orange needles.

Partial data for **3.20**:

R_f: 0.62 [neat CH_2Cl_2]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.12 (s, 1H), 4.06 (s, 3H), 2.02 (s, 3H) ppm.

The analytical data match those previously described in the literature.[23,24,37]



3.20 **3.75** **3.47**

To a solution of bromoquinone **3.20** (100 mg, 0.433 mmol, 1 eq.) in CH_2Cl_2 (10 mL) was added crude enol ether **3.75** (310 mg, 1.13 mmol, 2.6 eq.) dropwise. The reaction mixture was stirred at room temperature for 5 h. Then, the reaction was quenched with 1M aqueous HCl solution and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with saturated aqueous NaCl solution (50 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography [PE:Et_2O 10:1 → 2:1] to afford naphthoquinone **3.47** (67.5 mg, 0.288 mmol, 67%) as an orange crystalline solid.

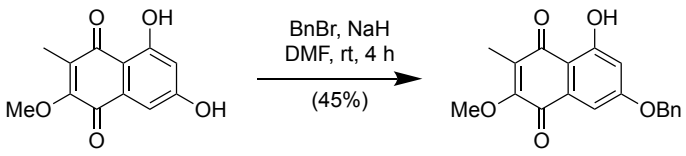
Partial data for **3.47**:

R_f: 0.14 [PE:EtOAc 4:1]

^{1}H NMR (600 MHz, acetone-d_6): δ 12.41 (s, 1H), 7.04 (d, *J* =2.4 Hz, 1H), 6.58 (d, *J* =2.4 Hz, 1H), 4.09 (s, 3H), 2.00 (s, 3H) ppm.

^{13}C NMR (150 MHz, acetone-d_6): δ 190.7, 181.0, 164.8, 164.6, 158.9, 134.6, 131.7, 109.1, 108.7, 108.4, 61.2, 8.7 ppm.

The analytical data match those previously described in the literature.[10]



3.47 **3.85**

To a solution of naphthoquinone **3.47** (170 mg, 0.726 mmol, 1 eq.) in DMF (10 mL) was added NaH (60% dispersion in petroleum ether, 58 mg, 1.45 mmol, 2 eq.) and benzyl bromide (149 mg, 0.872 mmol, 1.2 eq.). The reaction mixture was stirred at room temperature for 4 h. Then, the reaction was quenched with aqueous 1M HCl solution (5 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with saturated aqueous NaCl solution (3 x 50 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography [PE:EtOAc 20:1] to afford the pure benzyl protected naphthoquinone **3.85** (108 mg, 0.332 mmol, 45%) as a yellowish waxy solid.

Data for **3.85**:

R_f: 0.47 [PE:EtOAc 4:1]

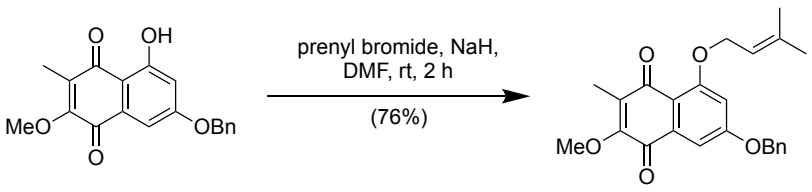
Mp: 124-126 °C

IR (neat): 2981, 1670, 1630, 1600, 1387, 1288, 1186, 1100, 950, 854, 799, 737 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 12.44 (s, 1H), 7.44 – 7.39 (m, 4H), 7.38 – 7.34 (m, 1H), 7.22 (d, *J* = 2.5 Hz, 1H), 6.69 (d, *J* = 2.5 Hz, 1H), 5.15 (s, 2H), 4.10 (s, 3H), 2.06 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 189.9, 180.5, 164.5, 163.7, 158.1, 135.6, 133.2, 131.7, 128.9, 128.6, 127.7, 109.1, 108.4, 107.4, 70.7, 61.2, 8.9 ppm.

HRMS (ESI): calculated for $C_{19}H_{17}O_5$ 325.1071 $[M+H]^+$, found 325.1073.



3.85 **3.82**

To a solution of benzylated naphthoquinone **3.85** (76.2 mg, 0.235 mmol, 1 eq.) in DMF (20 mL) was added NaH (60% dispersion in petroleum ether, 38.0 mg, 0.940 mmol, 4 eq.) and prenyl bromide (140 mg, 0.940 mmol, 4 eq.). The reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with 1M aqueous HCl (10 mL) and diluted with H_2O (10 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with saturated aqueous NaCl solution (3 x 50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography [PE:EtOAc 10:1] to give pure prenylated naphthoquinone **3.82** (70.5 mg, 0.177 mmol, 76%) as a yellow oil.

Data for **3.82**:

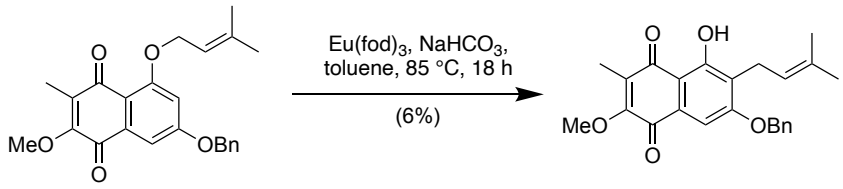
R_f: 0.47 [PE:EtOAc 4:1]

IR (neat): 2981, 2923, 1630, 1592, 1451, 1375, 1291, 1260, 1157, 1104, 1012, 953, 797 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.47 – 7.35 (m, 5H), 7.32 (d, J = 2.4 Hz, 1H), 6.78 (d, J = 2.4 Hz, 1H), 5.57 – 5.52 (m, 1H), 5.18 (s, 2H), 4.63 (d, J = 6.5 Hz, 2H), 4.01 (s, 3H), 2.06 (s, 3H), 1.79 (s, 3H), 1.74 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 184.2, 181.4, 163.2, 160.9, 156.0, 138.4, 135.8, 135.6, 134.4, 128.9, 128.6, 127.8, 119.1, 114.7, 106.4, 104.1, 70.7, 66.6, 60.8, 26.0, 18.5, 9.8 ppm.

HRMS (ESI): calculated for $C_{24}H_{24}NaO_5$ 415.1516 $[M+Na]^+$, found 415.1514.



3.82 **3.86**

To a solution of benzylated naphthoquinone **3.82** (20.0 mg, 0.051 mmol, 1 eq.) in toluene (3 mL) at room temperature, was added $Eu(fod)_3$ (5.0 mg, 0.0051 mmol, 10 mol%). The reaction was stirred at 85 °C for 18 h. Then, the reaction was quenched with 1M aqueous HCl solution (5 mL) and diluted with H_2O (5 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with saturated aqueous NaCl solution (20 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography [PE:EtOAc 20:1 → 5:1] to afford rearranged naphthoquinone **3.86** (1.1 mg, 0.0028 mmol, 6%) as a yellow oil.

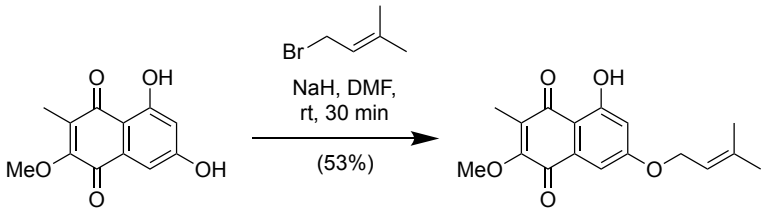
Data for **3.86**:

R_f: 0.50 [PE:EtOAc 4:1]

IR (neat): 3353, 2971, 2924, 1456, 1378, 1160, 1128, 951, 816, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 12.57 (s, 1H), 7.47 – 7.31 (m, 5H), 7.23 (s, 1H), 5.23 (s, 2H), 5.20 (t, *J* = 7.4 Hz, 1H), 4.08 (s, 3H), 3.45 (d, *J* = 7.7 Hz, 2H), 2.05 (s, 3H), 1.69 (s, 2H), 1.66 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 190.5, 180.8, 161.5, 160.7, 158.0, 136.2, 133.0, 131.5, 130.6, 128.9, 128.8, 128.4, 127.5, 124.6, 121.0, 109.6, 103.8, 70.7, 61.2, 26.0, 22.5, 18.0, 8.9 ppm.



3.47 **3.74**

Naphthoquinone **3.47** (187 mg, 0.799 mmol, 1 eq.) was dissolved in DMF (25 mL) and NaH (60% dispersion in petroleum ether, 48.0 mg, 1.20 mmol, 1.5 eq.) and prenyl bromide (150 mg, 0.959 mmol, 1.2 eq.) were added. The reaction was stirred at room temperature for 20 min. Then, the reaction was diluted with H_2O (10 mL) and quenched with 1M aqueous HCl (10 mL) solution. The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic layers were washed with saturated aqueous NaCl solution (3 x 75 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography [PE:EtOAc 15:1 → 5:1] to afford prenylated naphthoquinone **4.74** (129 mg, 0.426 mmol, 53%) as a bright orange solid.

Data for **4.74**:

R_f: 0.56 [PE:EtOAc 4:1]

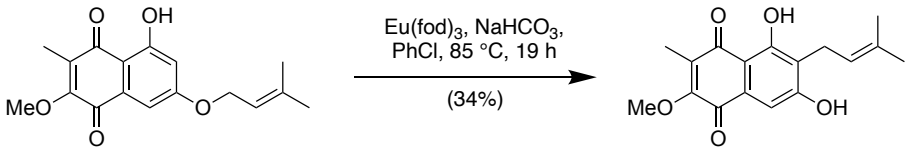
Mp: 121-124 °C

IR (neat): 2950, 1602, 1388, 1287, 1184, 1101, 949, 853, 795 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 12.43 (s, 1H), 7.14 (s, 1H), 6.61 (s, 1H), 5.46 (dddt, *J* = 6.8, 5.4, 2.8, 1.2 Hz, 1H), 4.59 (d, *J* = 6.7 Hz, 2H), 4.09 (s, 3H), 2.06 (s, 3H), 1.81 (s, 3H), 1.76 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 189.9, 180.7, 164.9, 163.7, 158.1, 139.7, 136.5, 133.2, 131.8, 118.5, 108.4, 107.2, 65.8, 61.2, 26.0, 18.4, 8.9 ppm.

HRMS (ESI): calculated for $C_{17}H_{19}O_5$ 303.1227 $[M+H]^+$, found 303.1229.



3.74

fumaquinone
(**3.92**)

To a solution of prenylated naphthoquinone **3.74** (10 mg, 0.033 mmol, 1 eq.) in chlorobenzene (5 mL) at room temperature, were added $Eu(fod)_3$ (3.4 mg, 0.0033 mmol, 10 mol%) and $NaHCO_3$ (3.0 mg, 0.033 mmol, 1 eq.). The reaction was stirred at 85 °C for 19 h. Then, the reaction was quenched with 1M aqueous HCl (10 mL) solution. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with saturated aqueous NaCl solution (20 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography [PE:EtOAc 20:1] to afford fumaquinone (**3.92**, 4.3 mg, 0.014 mmol, 34%) as a bright orange, amorphous solid.

Data for fumaquinone (**3.92**):

R_f: 0.20 [PE:EtOAc 4:1]

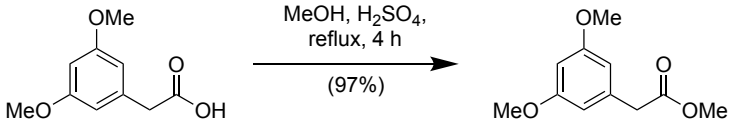
IR (neat): 3401, 2919, 2851, 1660, 1621, 1606, 1285, 1061, 793, 419 cm^{-1}.

^{1}H NMR (500 MHz, acetone-d_6): δ 12.82 (s, 1H), 7.13 (s, 1H), 5.24 (t, J = 7.4 Hz, 1H), 4.08 (s, 3H), 3.39 (d, J = 7.2 Hz, 2H), 2.00 (s, 3H), 1.78 (s, 3H), 1.65 (s, 3H) ppm.

^{13}C NMR (125 MHz, acetone-d_6): δ 192.8, 182.8, 163.9, 160.6, 160.6, 134.4, 133.5, 133.4, 124.0, 123.7, 110.8, 109.8, 63.0, 27.6, 24.4, 19.7, 10.5 ppm.

HRMS (ESI): calculated for $C_{17}H_{19}O_5$ 301.1081 $[M+H]^-$, found 301.1073.

The analytical data match those previously described in the literature.[32]



3.98 **3.100**

To a solution of 3,5-dimethoxyphenyl acetic acid (**3.98**, 25.0 g, 127 mmol, 1 eq.) in MeOH (350 mL) was added a catalytical amount of conc. H_2SO_4 (0.2 mL). The reaction mixture was heated at reflux for 5 h before the reaction was quenched with solid Na_2CO_3. The mixture was filtered through a pad of Celite and the solvent was removed *in vacuo*. The residue was re-dissolved in Et_2O (100 mL) and H_2O (100 mL) and the layers were separated. The aqueous layer was extracted with Et2O (2 x 100 mL) and the combined organic layers were washed with saturated aqueous NaCl solution (200 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude ester **3.100** (26.0 g, 123 mmol, 97%) was used in the next step without the need for further purification.

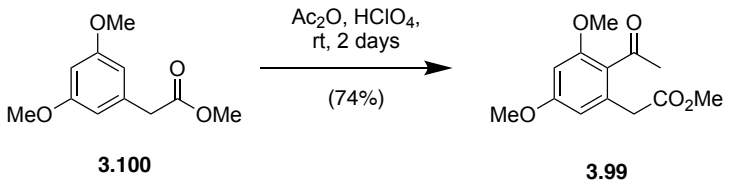
Partial data for **3.100**:

R_f: 0.36 [PE:EtOAc 3:1]

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.43 (d, *J* = 2.2 Hz, 2H), 6.37 (t, *J* = 2.2 Hz, 1H), 3.78 (s, 6H), 3.69 (s, 3H), 3.56 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 160.8, 136.0, 107.3, 99.2, 55.3, 52.1, 41.4 ppm.

The analytical data match those previously described in the literature.[38]



3.100 **3.99**

To a solution of ester **3.100** (12.6 g, 60.0 mmol, 1 eq.) in acetic anhydride (50 mL) was added a catalytical amount of conc. $HClO_4$ (200 µL). The reaction mixture was stirred at room temperature overnight before additional $HClO_4$ (100 µL) was added. The reaction was stirred at room temperature for 2 days. Then, the reaction was quenched with solid Na_2CO_3 and the mixture was filtered through a pad of Celite. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography [PE:EtOAc 4:1 → 2:1] to afford acetate **3.99** (11.2 g, 44.3 mmol, 74%) as a pale yellow solid.

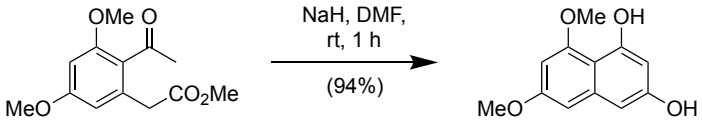
Partial data for **3.99**:

R_f: 0.32 [PE:EtOAc 4:1]

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.42 (d, *J* = 2.2 Hz, 1H), 6.36 (d, *J* = 2.2 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.70 (s, 2H), 3.68 (s, 3H), 2.51 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.7, 171.7, 161.6, 159.4, 135.0, 123.7, 108.3, 97.5, 55.6, 55.4, 52.0, 39.1, 32.2 ppm.

The analytical data match those previously described in the literature.[33]



3.99 **3.97**

To a solution of acetate **3.99** (5.00 g, 19.8 mmol, 1 eq.) in DMF (50 mL) was added NaH (60% dispersion in petroleum ether, 1.59 g, 39.6 mmol, 2 eq.). The reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with 1M aqueous HCl solution (50 mL) and diluted with H_2O (50 mL). The aqueous layer was extracted with EtOAc (3 x 75 mL) and the combined organic layers were washed with saturated aqueous NaCl solution (3 x 100 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography [PE:EtOAc 3:1] to afford THN **3.97** (4.12 g, 18.7 mmol, 94%) as a pale brownish powder.

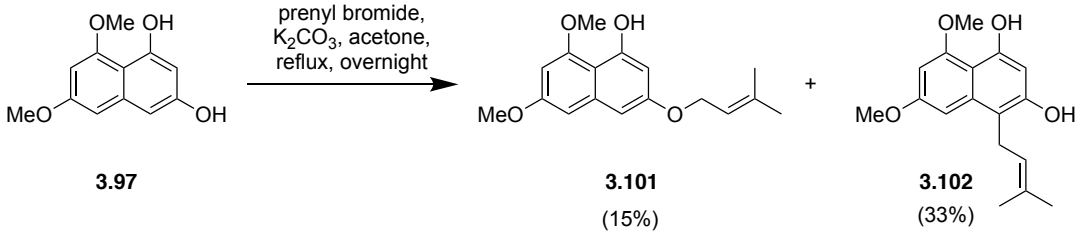
Partial Data for **3.97**:

R_f: 0.20 [PE:EtOAc 3:1]

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.19 (s, 1H), 6.55 (t, *J* = 2.1 Hz, 2H), 6.33 (d, *J* = 2.4 Hz, 1H), 6.30 (d, *J* = 2.1 Hz, 1H), 4.86 (s, 1H), 4.00 (s, 3H), 3.86 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.3, 157.4, 156.1, 155.7, 138.5, 106.1, 101.2, 99.6, 98.4, 95.5, 56.0, 55.3 ppm.

The analytical data match those previously described in the literature.[33]



3.97 **3.101** (15%) **3.102** (33%)

THN **3.97** (500 mg, 2.27 mmol, 1 eq.) was dissolved in acetone (50 mL) and K_2CO_3 (470 mg, 3.41 mmol, 1.5 eq.) and the reaction mixture was stirred for 10 min at room temperature. Then, prenyl bromide (332 µL, 2.72 mmol, 1.2 eq.) was added to the reaction and the mixture was stirred at room temperature overnight. The reaction was quenched with 1M aqueous HCl solution (10 mL) and diluted with H_2O (20 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic layers were washed with saturated aqueous NaCl solution (100 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography [PE:EtOAc 20:1] to afford *O*-prenylated THN **3.101** (63.0 mg, 0.218 mmol, 10%) as white crystals. Further elution [PE:EtOAc 5:1] afforded *C*-prenylated THN **3.102** (152 mg, 0.527 mmol, 23%) as a light brown solid.

Data for *O*-prenylated THN **3.101**:

R_f: 0.45 [PE:EtOAc 3:1]

Mp: 82-85 °C

IR (neat) 3385, 2916, 1635, 1454, 1385, 1207, 1158, 1048, 1023, 829, 767 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.11 (s, 1H), 6.60 (t, *J* = 2.2 Hz, 2H), 6.43 (d, *J* = 2.3 Hz, 1H), 6.31 (d, *J* = 2.1 Hz, 1H), 5.53 (dddd, *J* = 7.7, 6.5, 2.6, 1.3 Hz, 1H), 4.57 (d, *J* = 6.7 Hz, 2H), 4.00 (s, 3H), 3.87 (s, 3H), 1.81 (s, 3H), 1.76 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 158.4, 157.5, 156.0, 138.5, 138.2, 119.9, 106.5, 100.2, 99.5, 99.1, 95.7, 64.9, 56.2, 55.5, 26.0, 18.4 ppm.

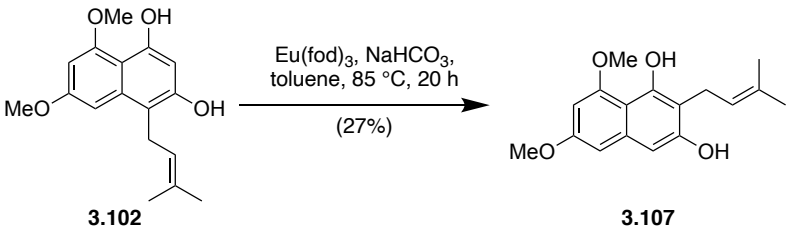
HRMS (ESI): calculated for $C_{17}H_{21}O_4$ 289.1434 $[M+H]^+$, found 289.1435.

Partial data for *C*-prenylated THN **3.102**:

R_f: 0.25 [PE:EtOAc 3:1]

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.21 (s, 1H), 6.74 (d, *J* = 2.1 Hz, 1H), 6.34 (d, *J* = 1.9 Hz, 2H), 5.20 (dddt, *J* = 6.8, 5.4, 2.7, 1.3 Hz, 1H), 5.09 (s, 1H), 4.01 (s, 3H), 3.88 (s, 3H), 3.58 (d, *J* = 6.7 Hz, 2H), 1.88 (s, 3H), 1.74 – 1.71 (s, 3H) ppm.

The analytical data match those previously described in the literature.[39]



3.102 **3.107**

To a solution of *C*-prenylated THN **3.102** (10 mg, 0.035 mmol, 1 eq.) in chlorobenzene (5 mL) at room temperature, were added $Eu(fod)_3$ (3.6 mg, 0.0035 mmol, 10 mol%) and $NaHCO_3$ (2.9 mg, 0.035 mmol, 1 eq.). The reaction was stirred at 85 °C for 20 h. Then, the reaction was quenched with 1M aqueous HCl (10 mL) solution. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with saturated aqueous NaCl solution (20 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography [PE:EtOAc 10:1 → 2:1] to afford rearranged THN **3.107** (2.7 mg, 0.0095 mmol, 27%) as a waxy yellow solid.

Data for **3.107**:

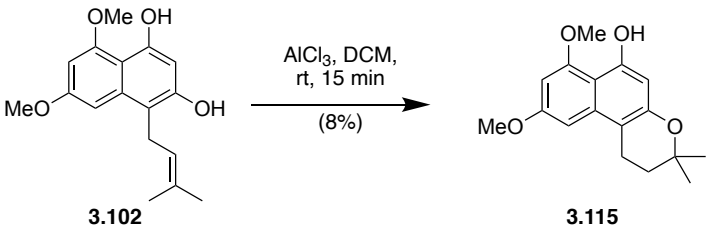
R_f: 0.15 [PE:EtOAc 4:1]

IR (neat): 3351, 2957, 2924, 2853, 1596, 1462, 1321, 1208, 588, 518 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, *J* = 2.5 Hz, 1H), 6.72 (d, *J* = 2.4 Hz, 1H), 6.60 (t, *J* = 1.6 Hz, 1H), 5.20 (t, *J* = 7.3 Hz, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.20 (d, *J* = 7.3 Hz, 2H), 1.77 (s, 3H), 1.66 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): 185.7, 183.9, 164.7, 161.8, 147.6, 137.4, 136.5, 136.2, 118.6, 104.3, 103.6, 56.6, 56.1, 29.9, 27.6, 26.0, 17.9 ppm.

HRMS (ESI): calculated for $C_{17}H_{21}O_4$ 289.1434 $[M+H]^+$, found 289.1415.



3.102 **3.115**

To a solution of prenylated THN **3.102** (107 mg, 0.371 mmol, 1 eq.) in dichloromethane (20 mL) at room temperature, was added $AlCl_3$ (49.0 mg, 0.371 mmol, 1 eq.). The reaction mixture was stirred for 15 min at room temperature before being quenched with 1M aqueous HCl solution (10 mL) and diluted with H_2O (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with saturated aqueous NaCl solution (2 x 40 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography [PE:EtOAc 10:1] to afford cyclised THN **3.115** (8.9 mg, 0.0309 mmol, 8%) as light yellow oil.

Data for **3.115**:

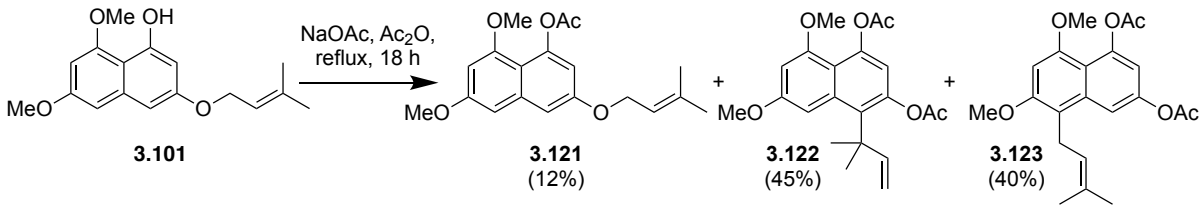
R_f: 0.40 [PE:EtOAc 3:1]

IR (neat) 3396, 2973, 2935, 1617, 1594, 1452, 1386, 1206, 1144, 816 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.07 (s, 1H), 6.64 (d, *J* = 2.1 Hz, 1H), 6.35 (d, *J* = 2.1 Hz, 1H), 6.31 (s, 1H), 4.00 (s, 3H), 3.90 (s, 3H), 2.80 (t, *J* = 6.8 Hz, 2H), 1.92 (t, *J* = 6.8 Hz, 2H), 1.35 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5, 158.0, 154.3, 153.8, 136.6, 106.3, 103.6, 101.1, 101.0, 95.0, 74.1, 56.2, 55.4, 33.1, 26.6, 19.9 ppm.

HRMS (ESI): calculated for $C_{17}H_{21}O_4$ 289.1434 $[M+H]^+$, found 289.1434.



To a solution of *O*-prenylated THN **3.101** (20.3 mg, 0.070 mmol, 1 eq.) in acetic anhydride (3 mL) was added sodium acetate (29.0 mg, 0.352 mmol, 5 eq.). The reaction mixture was heated at reflux for 18 h. Then, the reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was re-dissolved in EtOAc (10 mL) and diluted with saturated aqueous NH_4Cl solution (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl solution (40 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography [PE:EtOAc 20:1] to afford acetylated THN **3.121** (2.80 mg, 0.009 mmol, 12%) as an yellow oil. Further elution afforded rearranged THN **3.122** (10.3 mg, 0.028 mmol, 40%) as a yellow oil and rearranged THN **3.123** (11.8 mg, 0.032 mmol, 45%) as a white solid.

Data for acetylated THN **3.121**:

R_f: 0.44 [PE:EtOAc 3:1]

IR (neat): 2928, 1757, 1627, 1370, 1354, 1210, 1159, 1052, 1019, 833, 774 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.93 (d, *J* = 2.4 Hz, 1H), 6.64 (d, *J* = 2.2 Hz, 1H), 6.61 (d, *J* = 2.5 Hz, 1H), 6.35 (d, *J* = 2.2 Hz, 1H), 5.53 (ddt, *J* = 8.1, 5.4, 1.4 Hz, 1H), 4.58 (d, *J* = 6.8 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 2.33 (s, 3H), 1.81 (s, 3H), 1.76 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 158.9, 157.5, 156.6, 147.8, 138.7, 138.6, 119.5, 109.7, 105.5, 98.6, 98.6, 97.4, 65.1, 56.1, 55.4, 26.0, 21.1, 18.4 ppm.

HRMS (ESI): calculated for $C_{19}H_{23}O_5$ 331.1540 $[M+H]^+$, found 331.1543.

Data for rearranged THN **3.122**:

R_f: 0.31 [PE:EtOAc 3:1]

IR (neat): 2921, 1852, 1758, 1612, 1368, 1199, 1159, 1016, 903, 834, 805 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, *J* = 2.0 Hz, 1H), 6.53 (s, 1H), 6.46 (d, *J* = 2.0 Hz, 1H), 6.34 (dd, *J* = 17.7, 10.7 Hz, 1H), 5.10 (d, *J* = 17.7 Hz, 1H), 5.04 (d, *J* = 10.7 Hz, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 2.31 (s, 3H), 2.28 (s, 3H), 1.68 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 169.9, 157.2, 156.9, 151.5, 147.0, 146.2, 137.1, 130.1, 114.8, 114.6, 109.1, 101.8, 98.6, 56.3, 55.5, 43.2, 30.5, 29.8, 21.7, 21.1 ppm.

HRMS (ESI): calculated for $C_{21}H_{25}O_6$ 373.1646 $[M+H]^+$, found 373.1647.

Data for rearranged THN **3.123**:

R_f: 0.18 [PE:EtOAc 3:1]

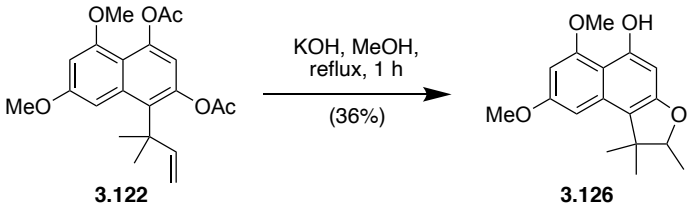
Mp: 132-133 °C

IR (neat): 2981, 1750, 1591, 1359, 1204, 1128, 1022, 896, 822 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, *J* = 2.0 Hz, 1H), 6.77 (d, *J* = 2.0 Hz, 1H), 6.63 (s, 1H), 5.12 (t, *J* = 6.6 Hz, 1H), 3.91 (s, 3H), 3.91 (s, 3H), 3.62 (d, *J* = 6.5 Hz, 2H), 2.34 (s, 3H), 2.32 (s, 3H), 1.83 (s, 3H), 1.67 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 169.2, 155.4, 155.2, 148.6, 147.9, 136.3, 131.8, 123.3, 116.2, 113.4, 113.2, 112.4, 95.8, 56.9, 56.4, 25.8, 24.2, 21.4, 21.1, 18.2 ppm.

HRMS (ESI): calculated for $C_{21}H_{25}O_6$ 373.1646 $[M+H]^+$, found 373.1647.



3.122 **3.126**

To a solution of **3.122** (5.00 mg, 0.014 mmol, 1 eq.) in MeOH (10 mL) was added KOH (4.00 mg, 0.070 mmol, 5 eq.). The reaction mixture was heated at reflux for 1 h before being cooled to room temperature. The reaction was quenched with 1M HCl solution (5 mL) and diluted with H_2O (10 mL). The layers were separated, the aqueous layer was extracted with EtOAc (3 x 15 mL) and the combined organic layers were washed with saturated aqueous NaCl solution (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography [PE:EtOAc 10:1] to afford cyclised THN **3.126** (1.8 mg, 0.005 mmol, 36%) as light yellow oil.

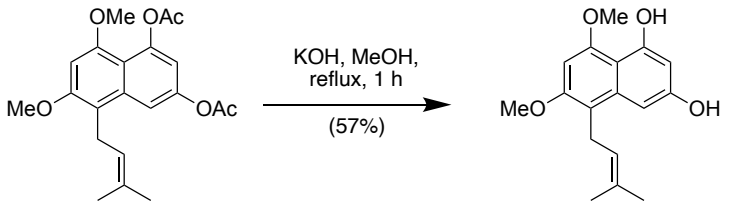
Partial data for **3.126**:

R_f: 0.35 [PE:EtOAc 3:1]

IR (neat): 3397, 2919, 1629, 1462, 1391, 1149, 1064, 1018, 935 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.34 (s, 1H), 6.78 (d, *J* = 2.1 Hz, 1H), 6.35 (s, 1H), 6.29 (d, *J* = 2.1 Hz, 1H), 4.41 (q, *J* = 6.5 Hz, 1H), 4.00 (s, 3H), 3.89 (s, 3H), 1.42 (d, *J* = 6.6 Hz, 3H), 1.25 (s, 6H) ppm.

HRMS (ESI): calculated for $C_{17}H_{21}O_4$ 289.1434 $[M+H]^+$, found 289.1422.



3.123 **3.116**

To a solution of **3.123** (11.0 mg, 0.038 mmol, 1 eq.) in MeOH (4 mL) was added KOH (4.00 mg, 0.076 mmol, 2 eq.). The reaction mixture was heated at reflux for 1 h before being cooled to room temperature. The reaction was quenched with 1M HCl solution (5 mL) and diluted with H_2O (10 mL). The layers were separated, the aqueous layer was extracted with EtOAc (3 x 15 mL) and the combined organic layers were washed with saturated aqueous NaCl solution (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography [PE:EtOAc 3:1] to afford THN **3.116** (6.3 mg, 0.022 mmol, 57%) as light yellow oil.

Data for **3.116**:

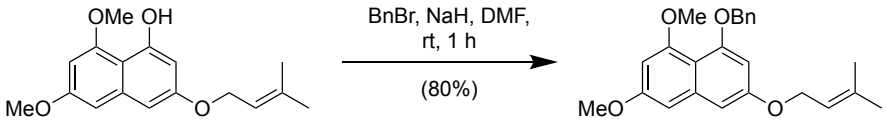
R_f: 0.30 [PE:EtOAc 2:1]

IR (neat): 3380, 2937, 1636, 1612, 1402, 1274, 1212, 1138, 1020, 830 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.42 (s, 1H), 6.67 (d, *J* = 2.3 Hz, 1H), 6.46 (s, 1H), 6.37 (d, *J* = 2.3 Hz, 1H), 5.16 – 5.09 (m, 1H), 4.96 (s, 1H), 4.05 (s, 3H), 3.90 (s, 3H), 3.55 (d, *J* = 6.4 Hz, 2H), 1.84 (s, 3H), 1.67 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.0, 156.2, 155.6, 154.8, 137.1, 131.8, 123.5, 115.7, 106.9, 99.6, 98.3, 92.1, 57.0, 56.3, 25.9, 24.3, 18.2 ppm.

HRMS (ESI): calculated for $C_{17}H_{21}O_4$ 289.1434 $[M+H]^+$, found 289.1441.



3.101 **3.127**

To a solution of *O*-prenylated THN **3.101** (100 mg, 0.347 mmol, 1 eq.) in DMF (10 mL) was added NaH (60% dispersion in petroleum ether, 56.0 mg, 1.39 mmol, 4 eq.) and BnBr (237 mg, 1.39 mmol, 4 eq.). The reaction mixture war stirred at room temperature for 2 h before it was quenched with H_2O and 1M aqueous HCl solution. The aqueous layer was extracted with EtOAc (3 x 15 mL) and the combined organic layers were washed with saturated aqueous NaCl solution (3 x 30 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography [PE:EtOAc 20:1] to afford benzylated THN **3.127** (105 mg, 0.276 mmol, 80%) as an amorphous, yellowish solid.

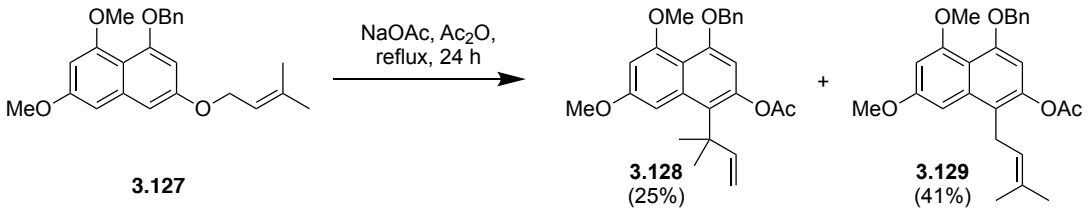
Partial data for benzylated THN **3.127**:

R_f: 0.47 [PE:EtOAc 4:1]

IR (neat): 2933, 1596, 1453, 1390, 1353, 1262, 1163, 1062, 1034, 969, 826, 731 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 – 7.28 (m, 5H), 6.67 (d, *J* = 2.3 Hz, 1H), 6.62 (d, *J* = 2.3 Hz, 1H), 6.48 (d, *J* = 2.3 Hz, 1H), 6.37 (d, *J* = 2.3 Hz, 1H), 5.58 – 5.53 (m, 1H), 5.15 (s, 2H), 4.58 (d, *J* = 6.9 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 1.82 (s, 3H), 1.78 (s, 3H) ppm.

HRMS (ESI): calculated for $C_{24}H_{27}O_4$ 379.1904 $[M+H]^+$, found 379.1903.



3.127

3.128 (25%)

3.129 (41%)

To a suspension of benzylated THN **3.127** (96.0 mg, 0.254 mmol, 1 eq.) in acetic anhydride (20 mL) was added sodium acetate (104 mg, 1.27 mmol, 5 eq.). The reaction mixture was heated at reflux for 24 h. Then, the reaction was cooled to room temperature and saturated aqueous NH_4Cl solution (20 mL) was added. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with saturated aqueous NaCl solution (50 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography [PE:EtOAc 20:1] to afford rearranged THN **3.128** (26.5 mg, 0.063 mmol, 25%) as a yellow oil. Further elution afforded rearranged THN **3.129** (44.1 mg, 0.105 mmol, 41%) as an amorphous, off-white solid.

Partial data for rearranged THN **3.128**:

R_f: 0.38 [PE:EtOAc 4:1]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 – 7.56 (m, 2H), 7.42 – 7.39 (m, 2H), 7.33 – 7.30 (m, 1H), 7.19 (d, *J* = 2.1 Hz, 1H), 6.64 (s, 1H), 6.58 (d, *J* = 2.1 Hz, 1H), 5.15 (s, 2H), 5.15 – 5.13 (m, 1H), 3.91 (s, 3H), 3.91 (s, 3H), 3.61 (d, *J* = 6.6 Hz, 2H), 2.33 (s, 3H), 1.84 (s, 3H), 1.67 (s, 3H) ppm.

IR (neat): 2935, 1756, 1599, 1454, 1342, 1203, 1163, 1066, 1018, 898, 734 cm^{-1}.

HRMS (ESI): calculated for $C_{26}H_{29}O_5$ 421.2010 $[M+H]^+$, found 421.2009.

Partial data for rearranged THN **3.129**:

R_f: 0.33 [PE:EtOAc 4:1]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 – 7.54 (m, 2H), 7.42 – 7.36 (m, 3H), 7.34 – 7.27 (m, 1H), 6.49 (d, *J* = 2.2 Hz, 1H), 6.38 – 6.28 (m, 1H, overlap), 6.33 (s, 1H, overlap) 5.11 (s, 2H), 5.08 (d, *J* = 17.7 Hz, 1H), 5.03 (d, *J* = 10.7 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 2.31 (s, 3H), 1.67 (s, 6H) ppm.

IR (neat): 2981, 1751, 1594, 1369, 1257, 1200, 1145, 1022, 805, 731 cm^{-1}.

HRMS (ESI): calculated for $C_{26}H_{28}O_5$ 421.2010 $[M+H]^+$, found 421.2009.

3.5 References

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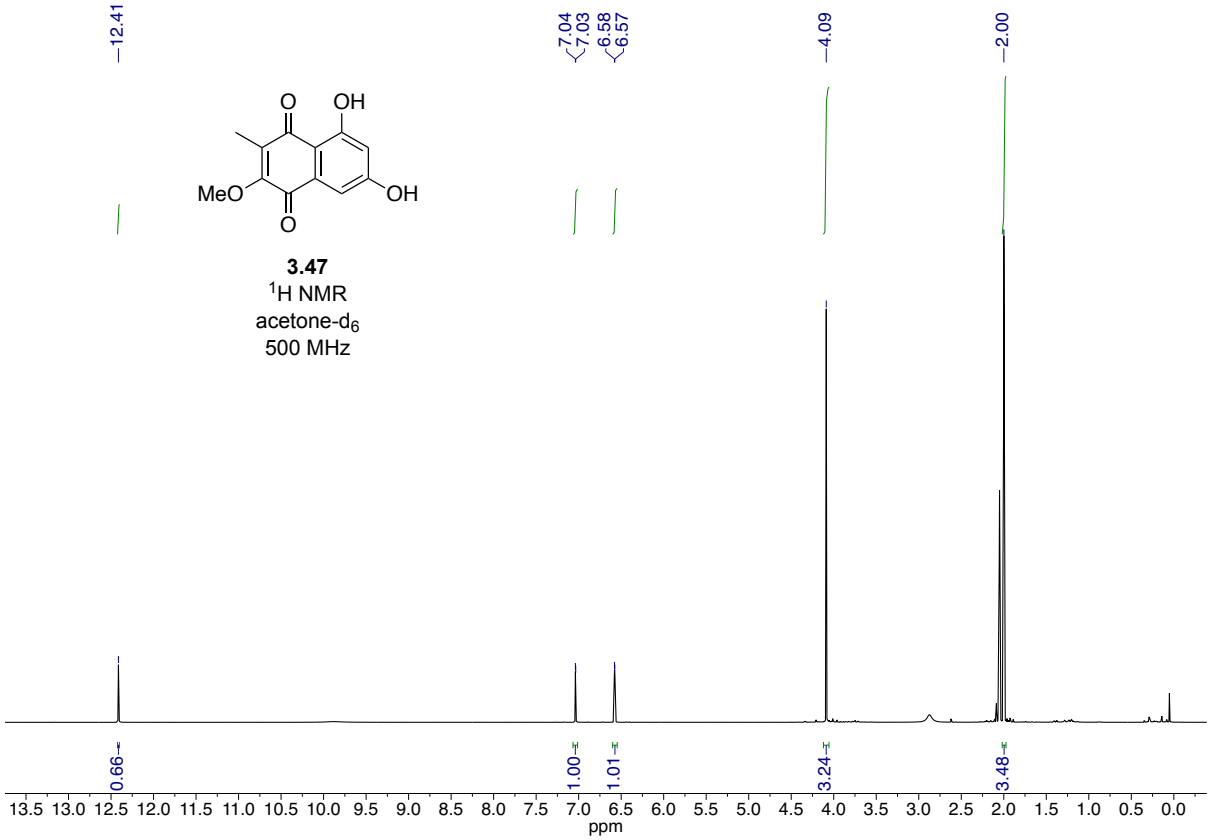
3.6 Appendix

3.6.1 NMR Spectra



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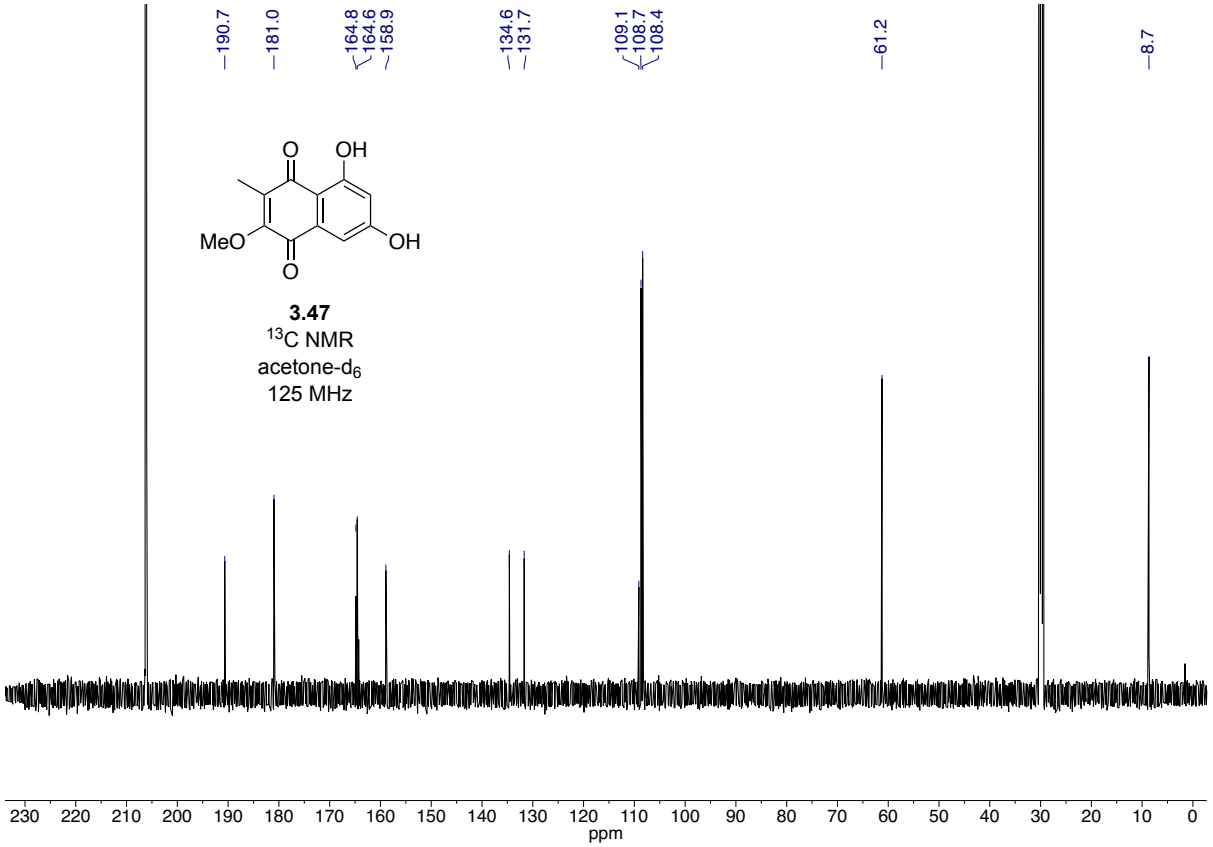
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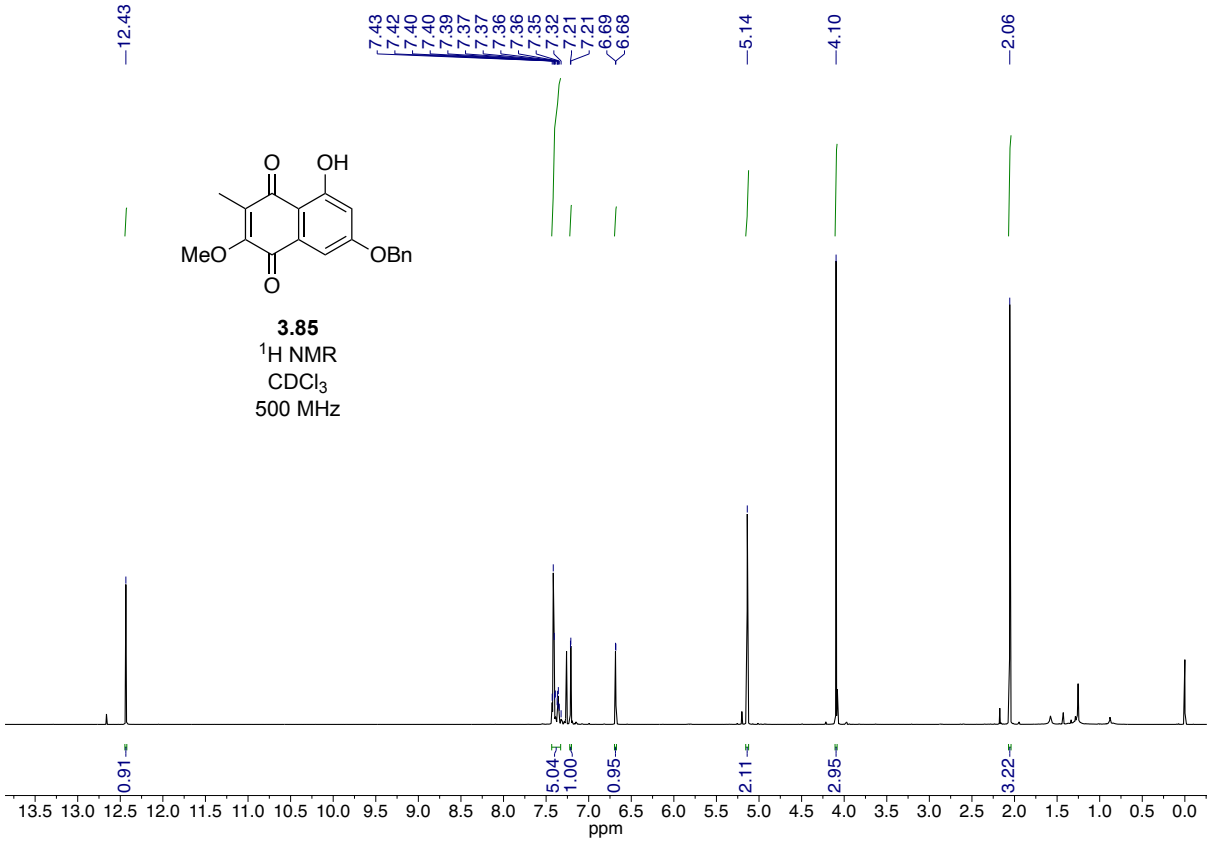
181.0
164.8
164.6
158.9
134.6
131.7
109.1
108.7
108.4
61.2
8.7
O
OH
MeO
OH
O
3.47
13C NMR
acetone-d6
125 MHz
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm



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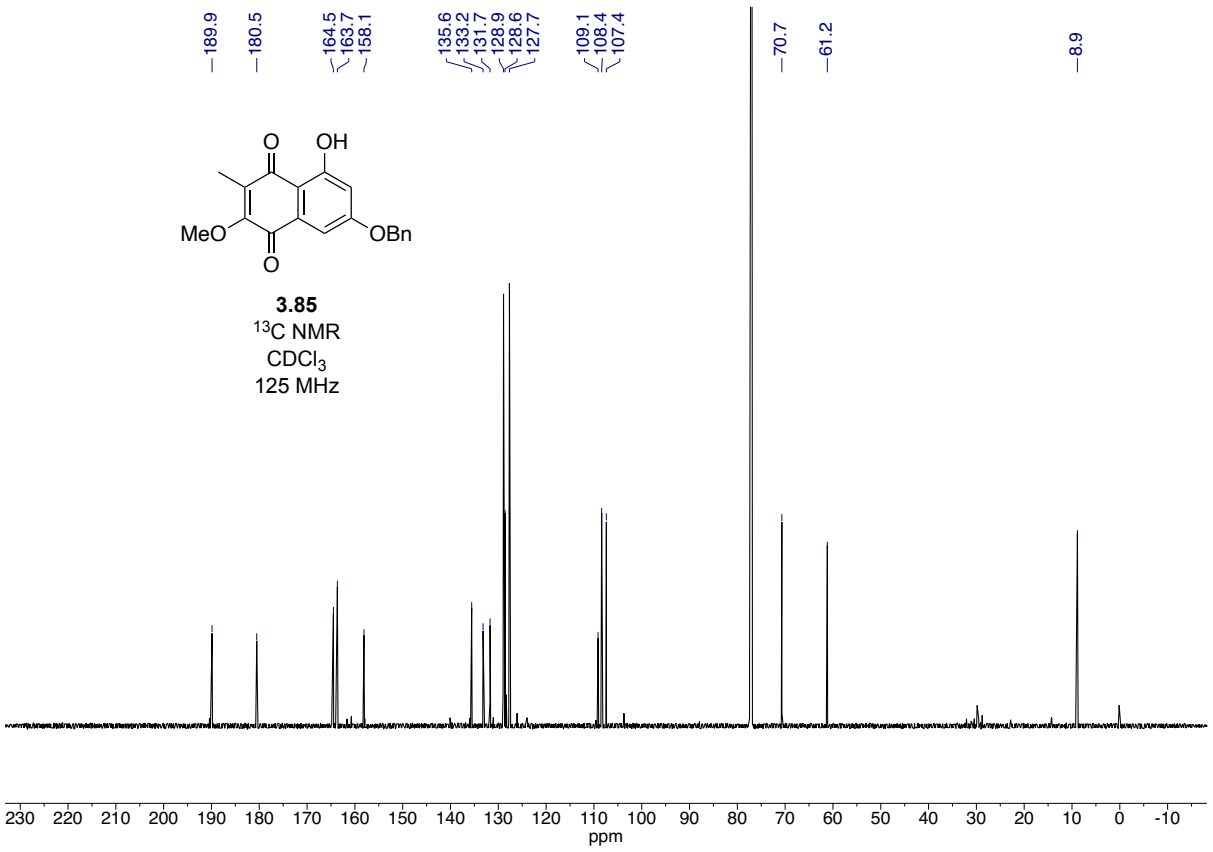
^{1}H NMR
$CDCl_3$
500 MHz



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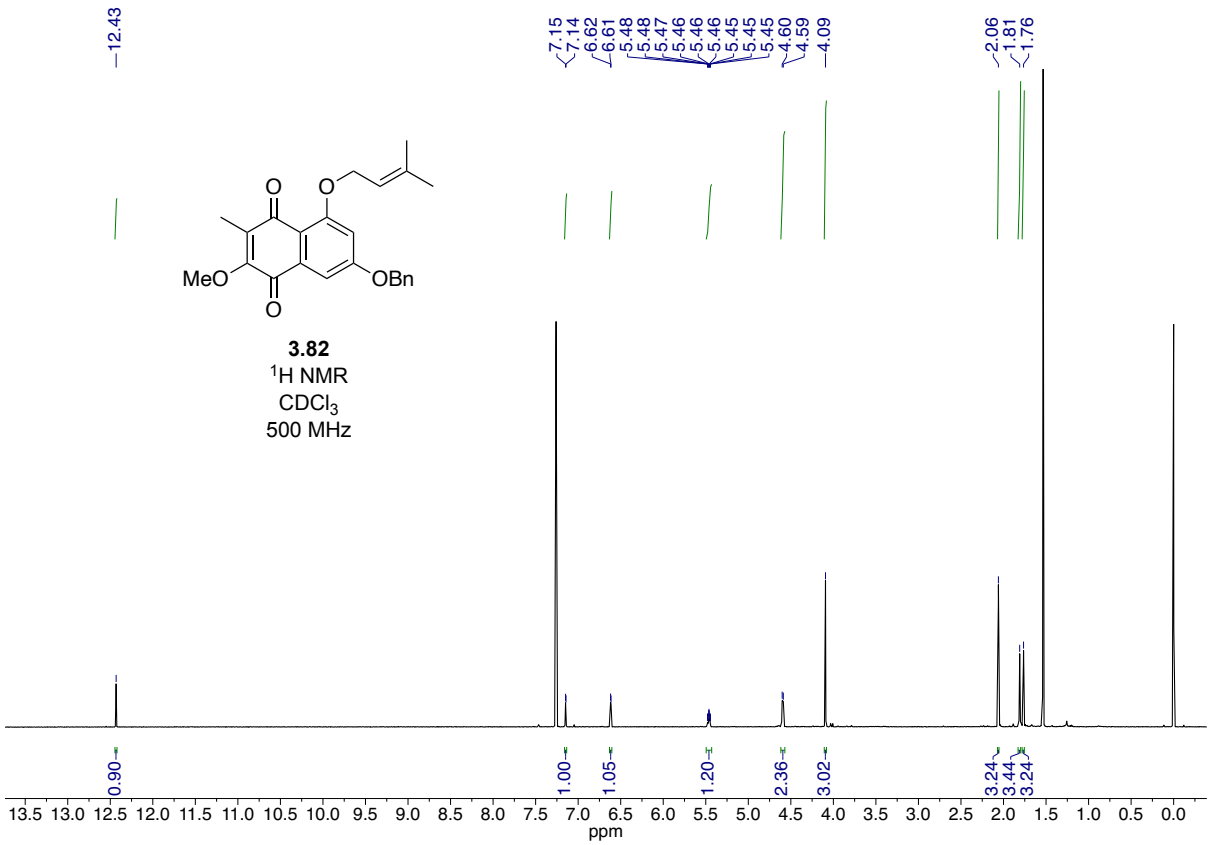
$CDCl_3$
125 MHz



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^{1}H NMR
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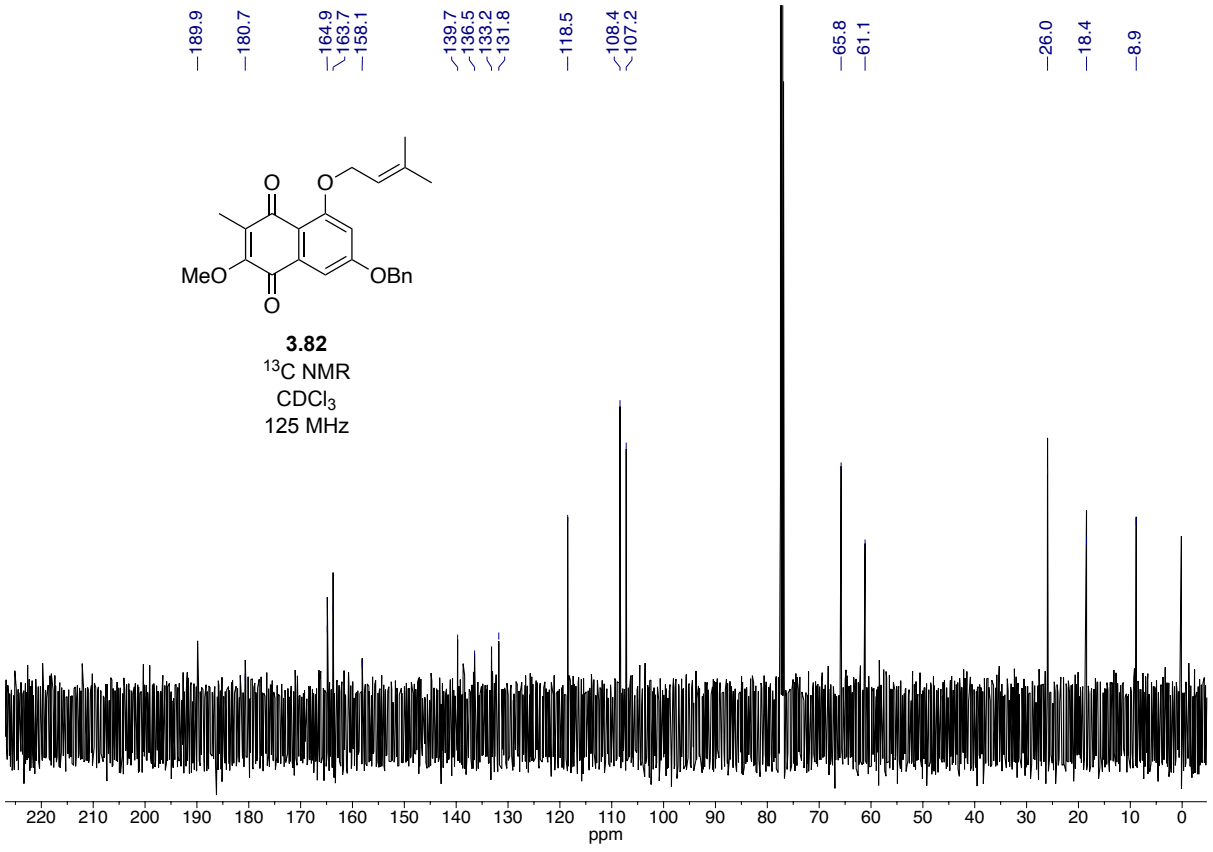
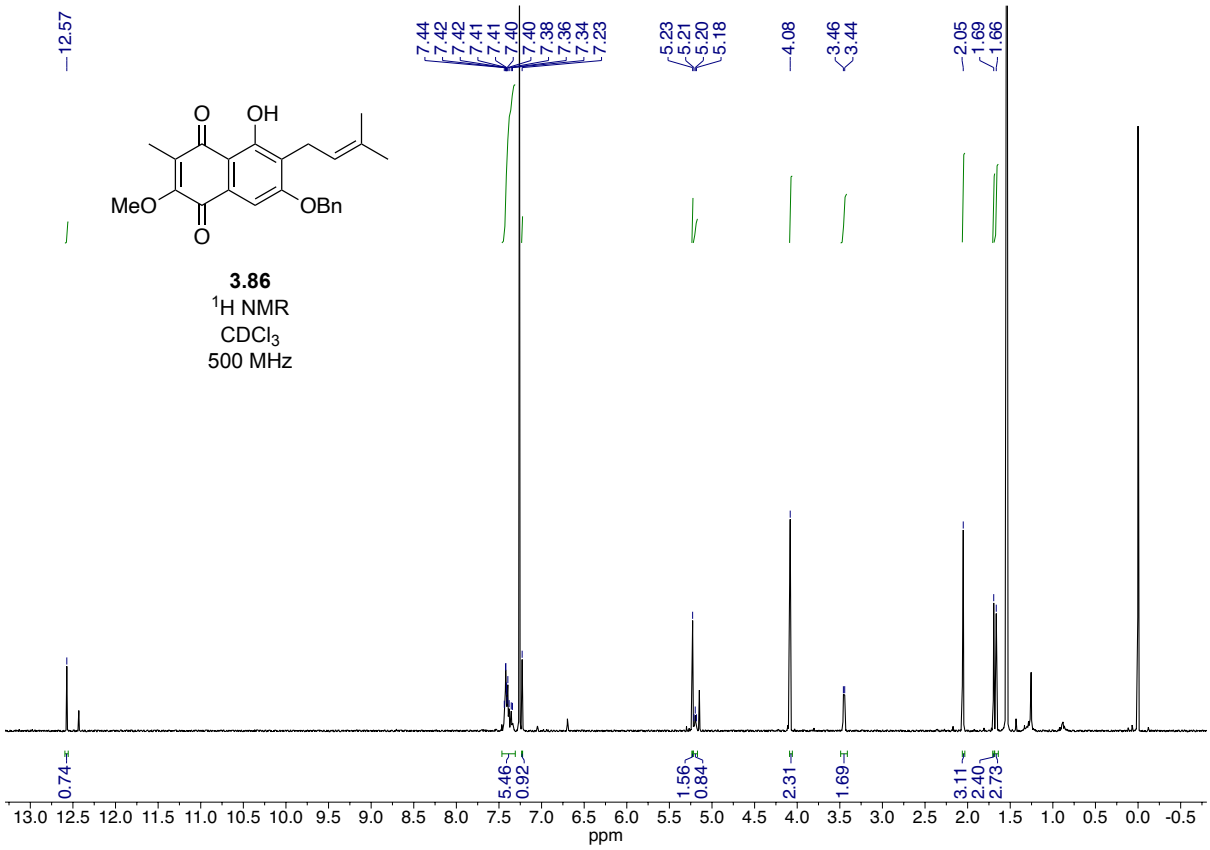


3.82
^{13}C NMR
$CDCl_3$
125 MHz



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^{1}H NMR
$CDCl_3$
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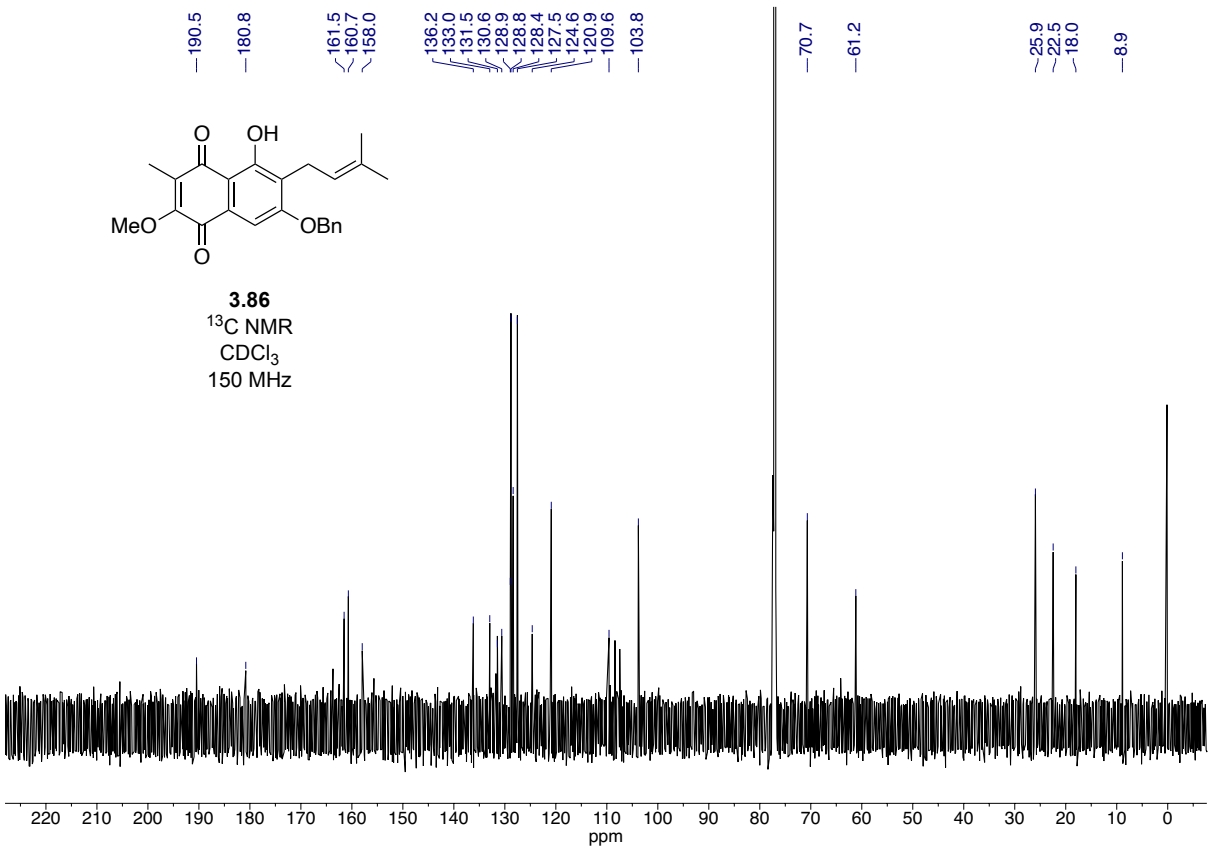

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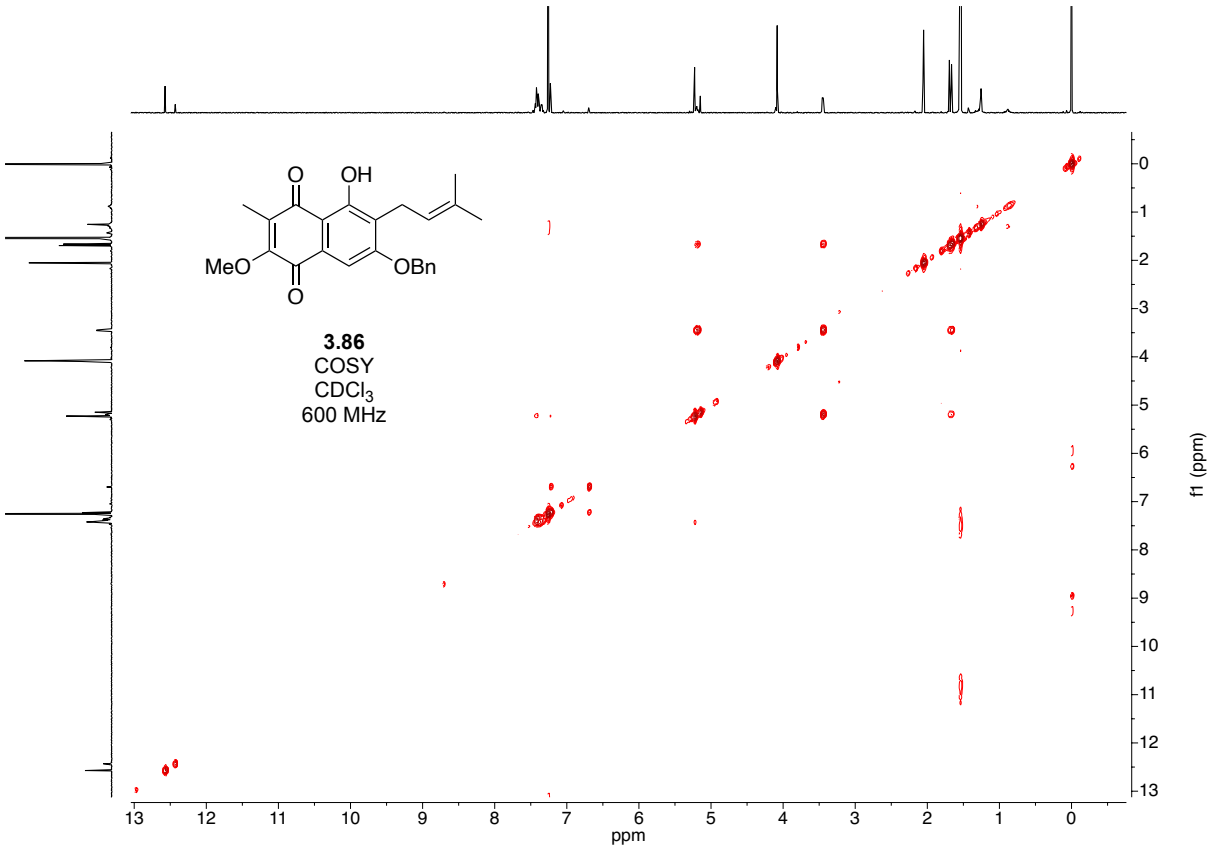
150 MHz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OBn
O
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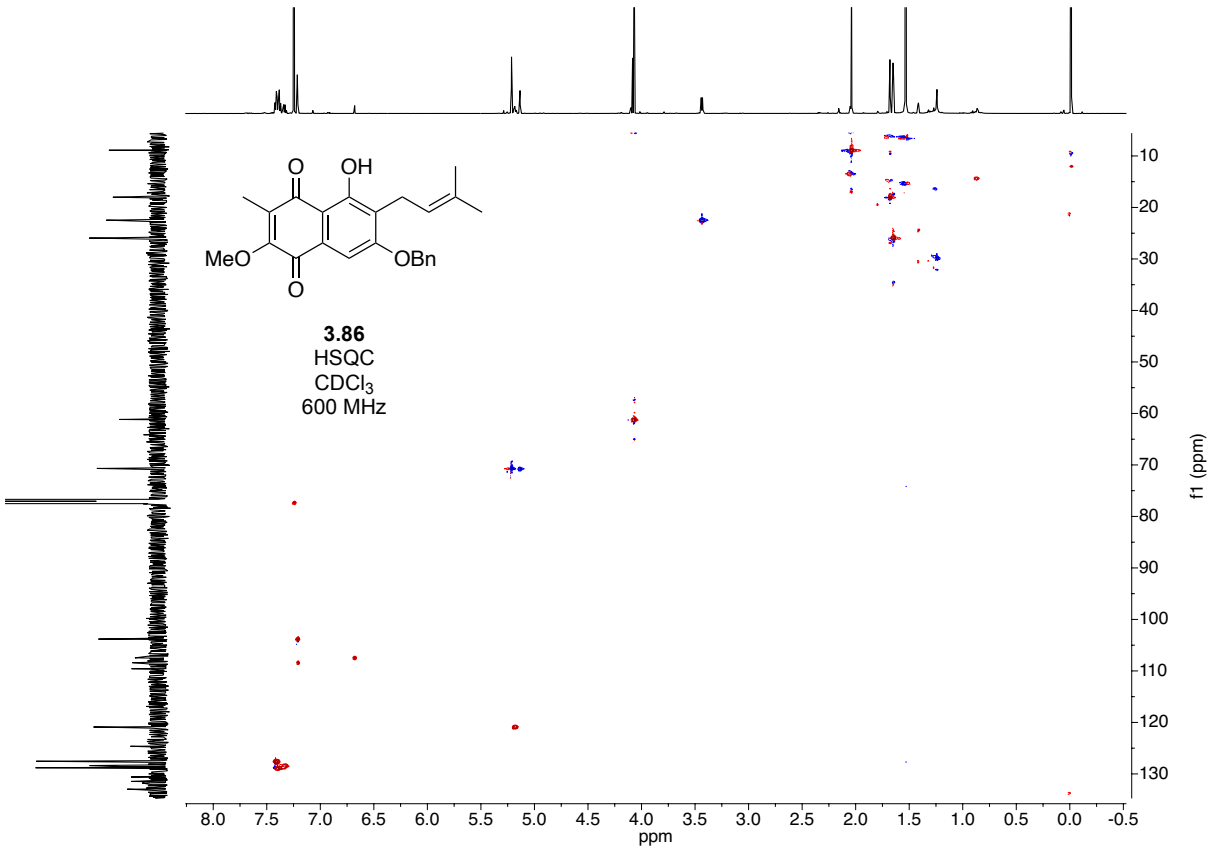
COSY
CDCl3
600 MHz
ppm
f1 (ppm)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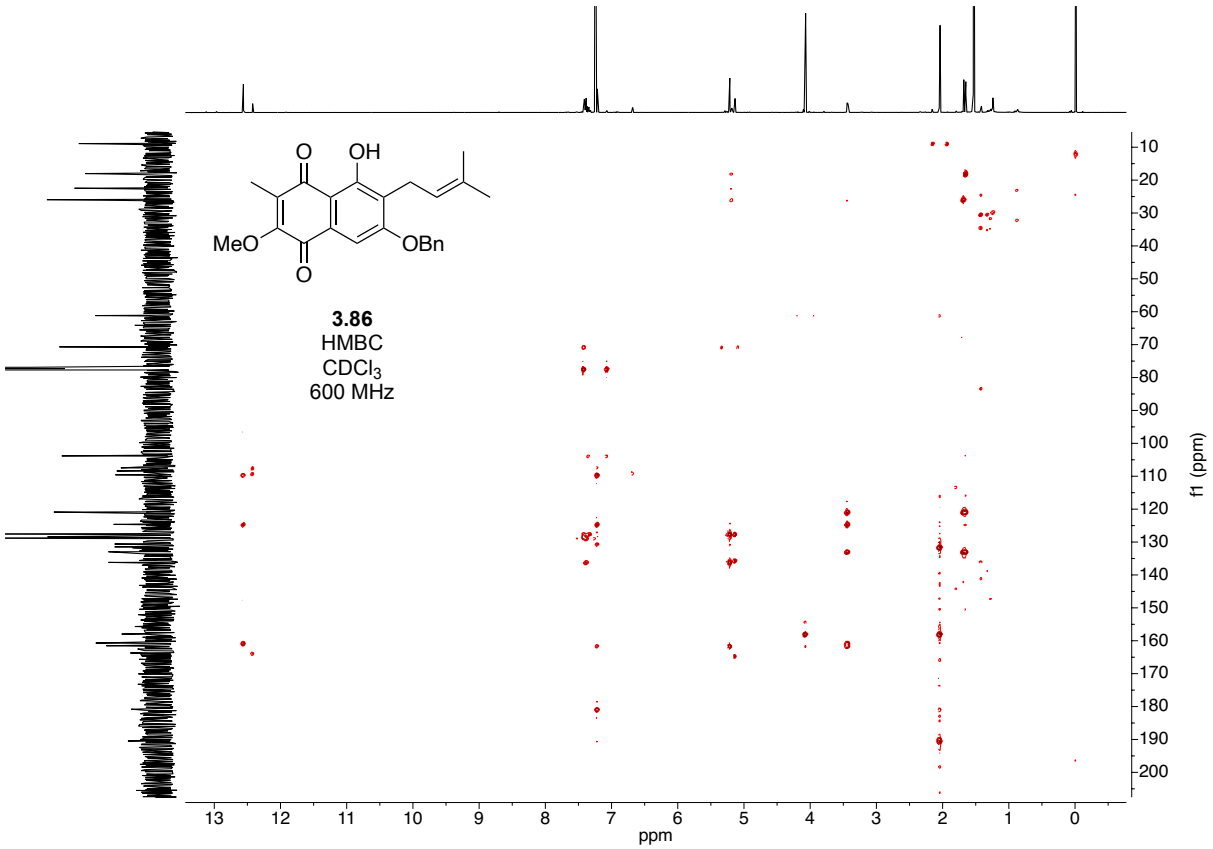
ppm
f1 (ppm)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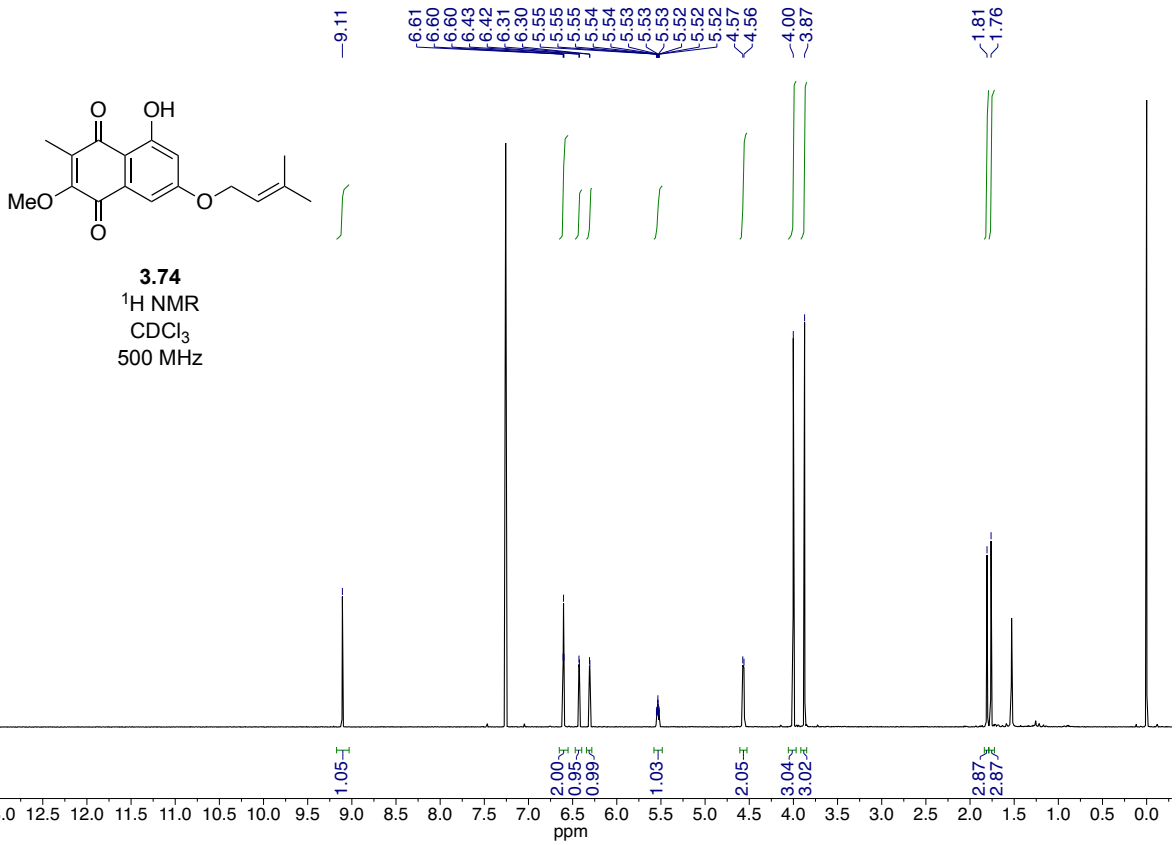
ppm
f1 (ppm)



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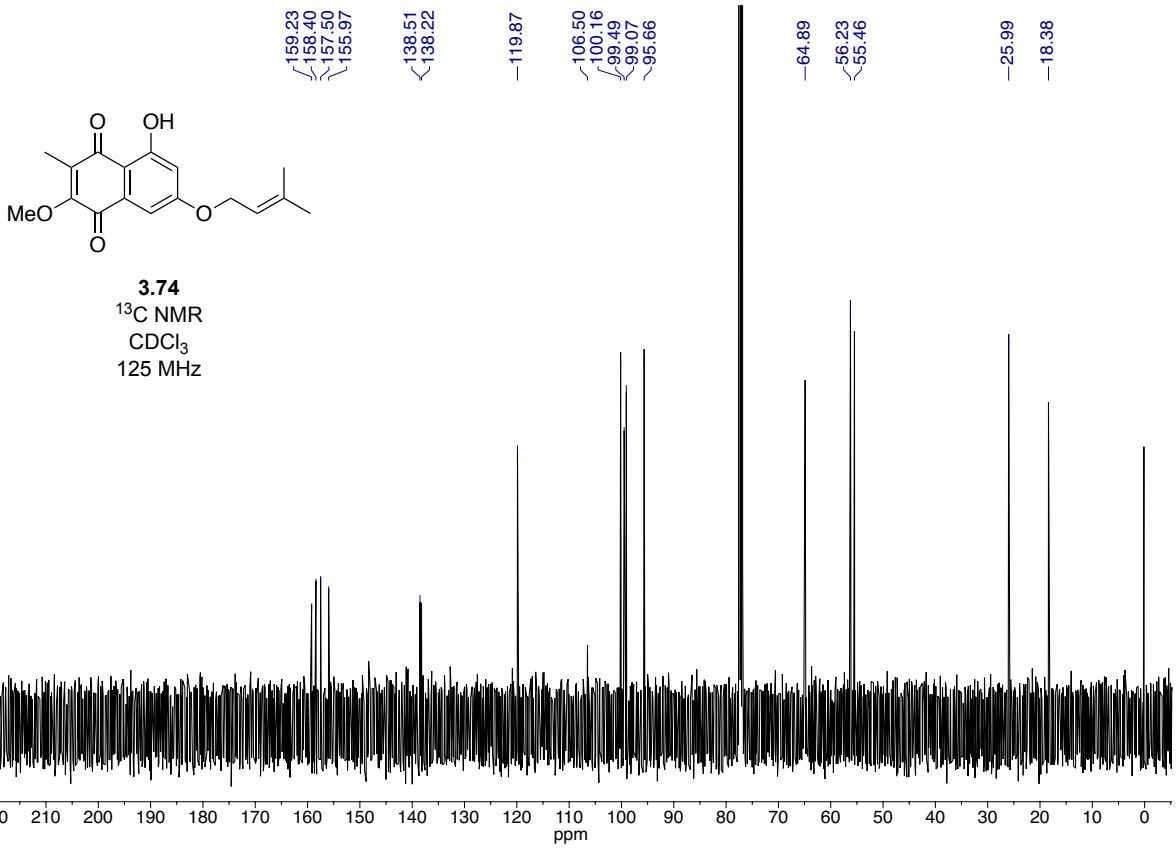

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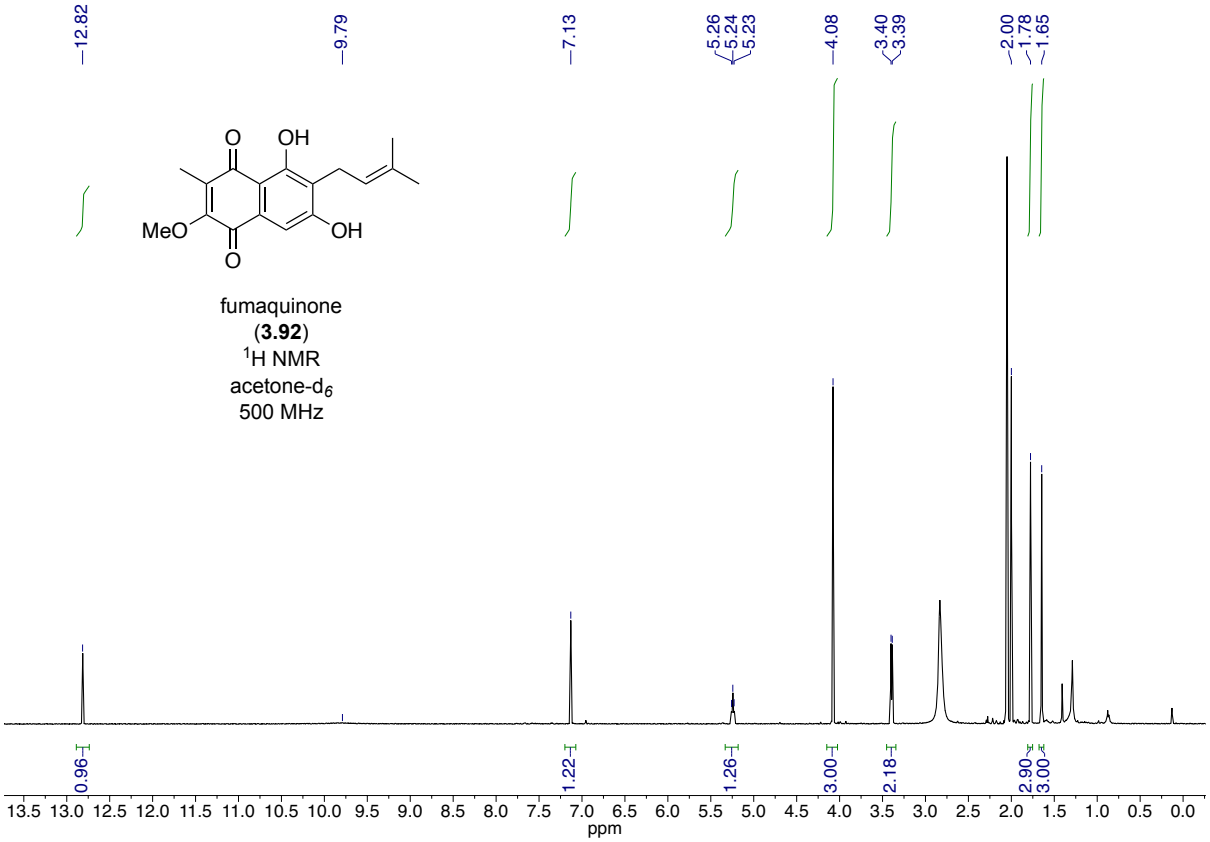
125 MHz



fumaquinone
(**3.92**)
^{1}H NMR
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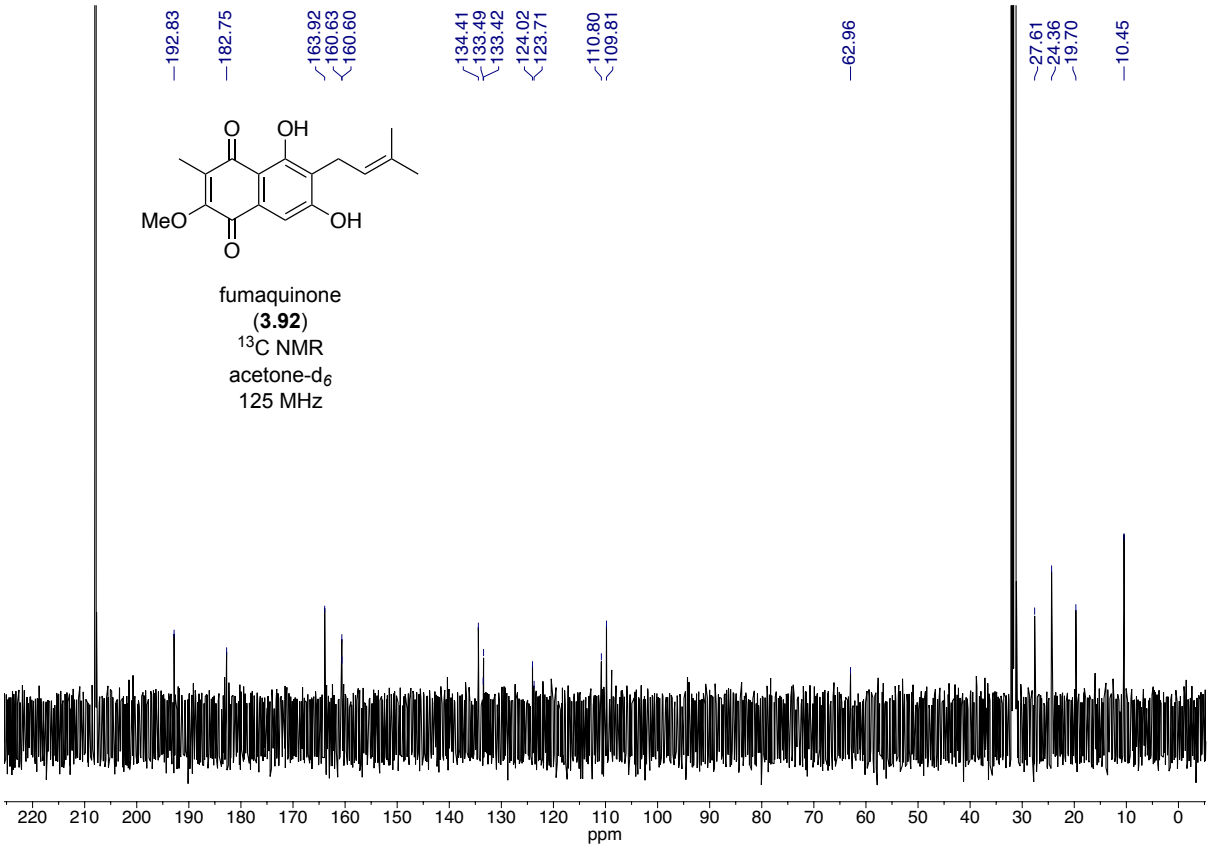
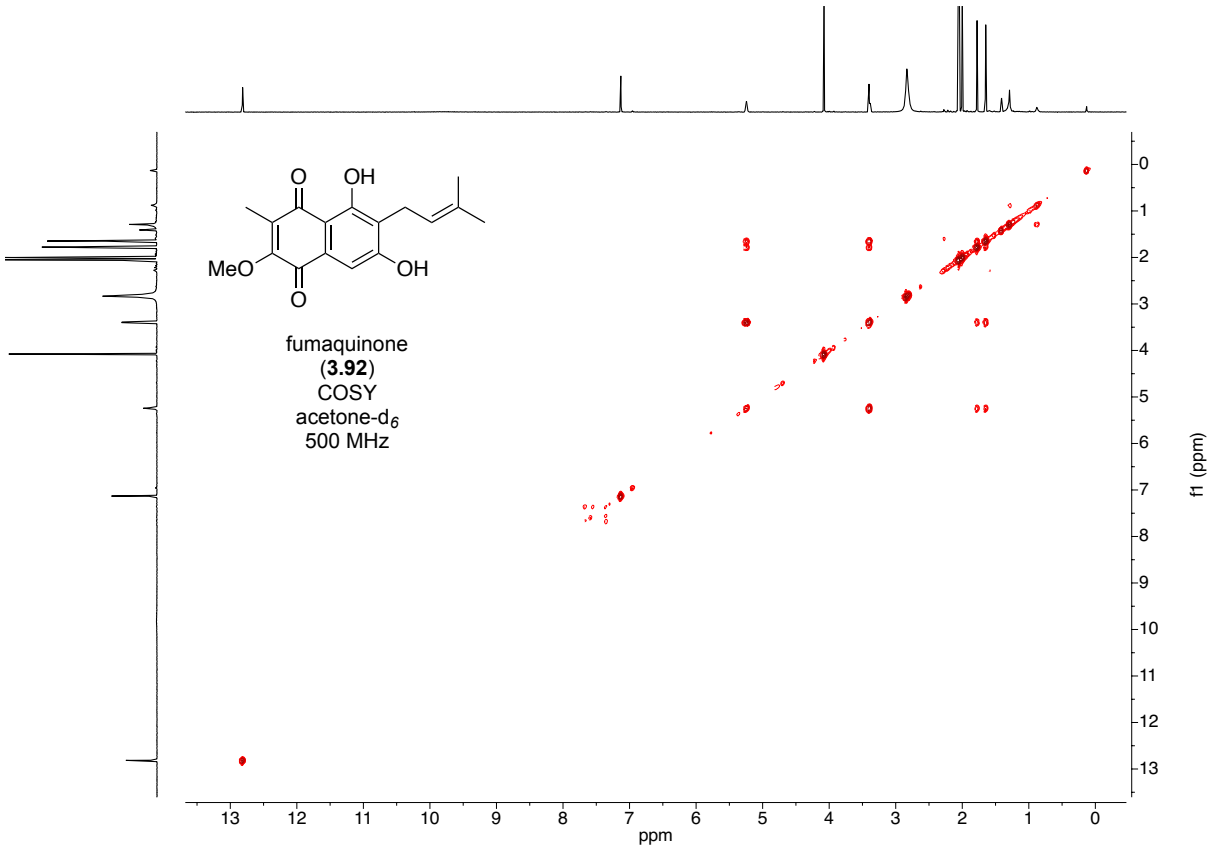
500 MHz



fumaquinone
(**3.92**)
^{13}C NMR
acetone-d_6
125 MHz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OH
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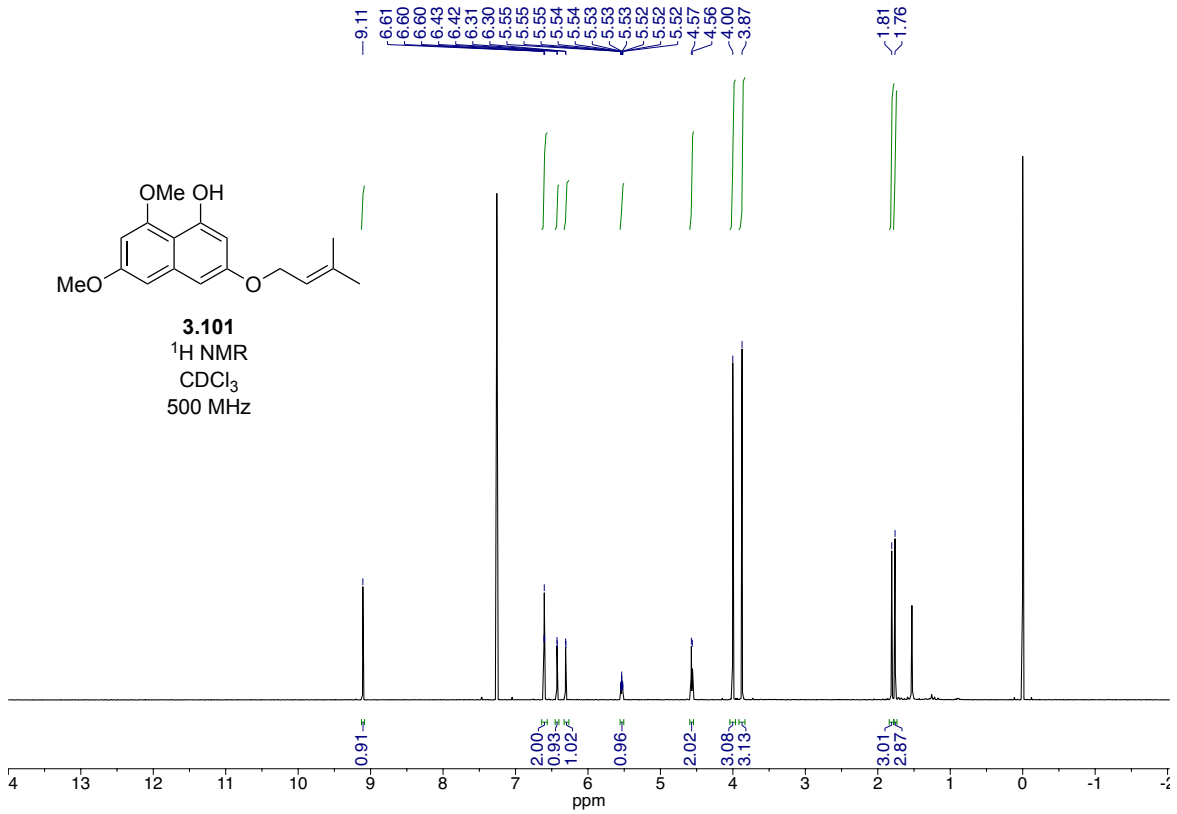
(3.92)
COSY
acetone-d6
500 MHz
ppm
f1 (ppm)



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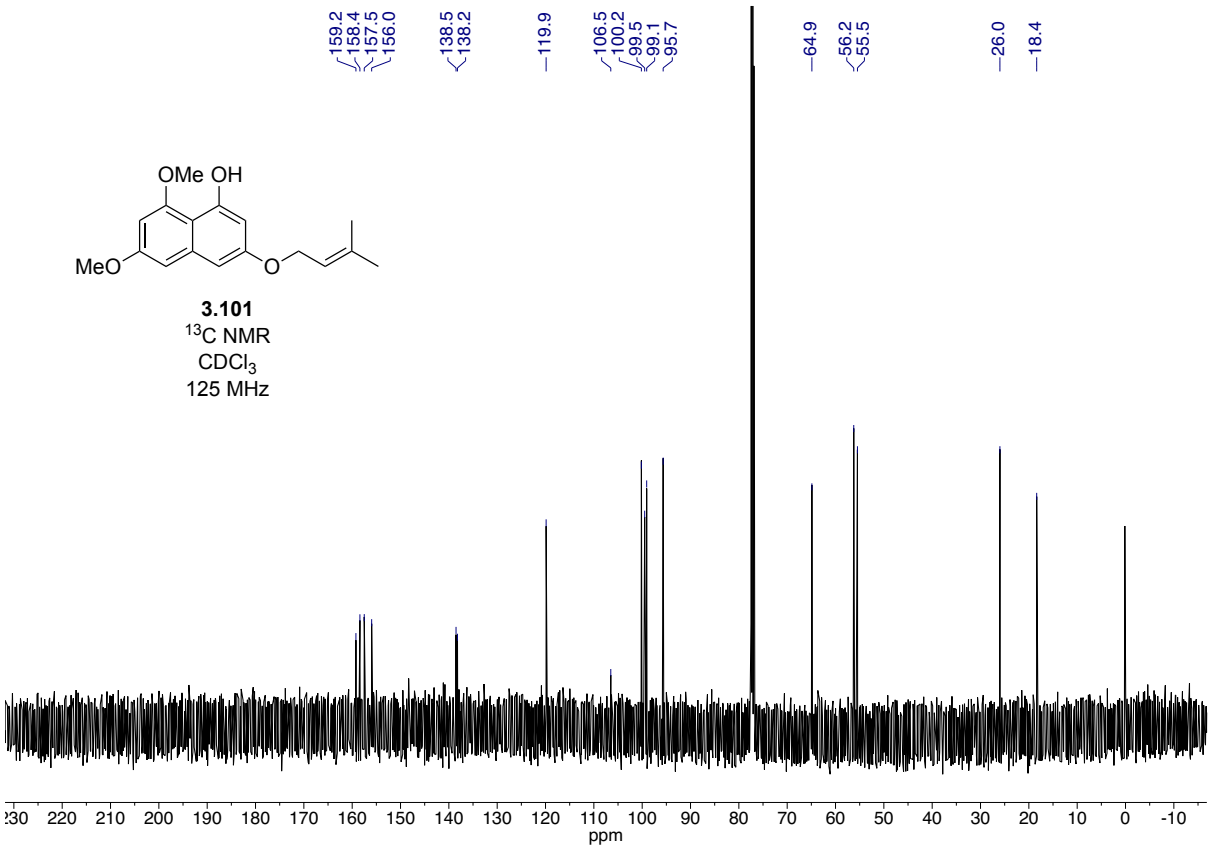

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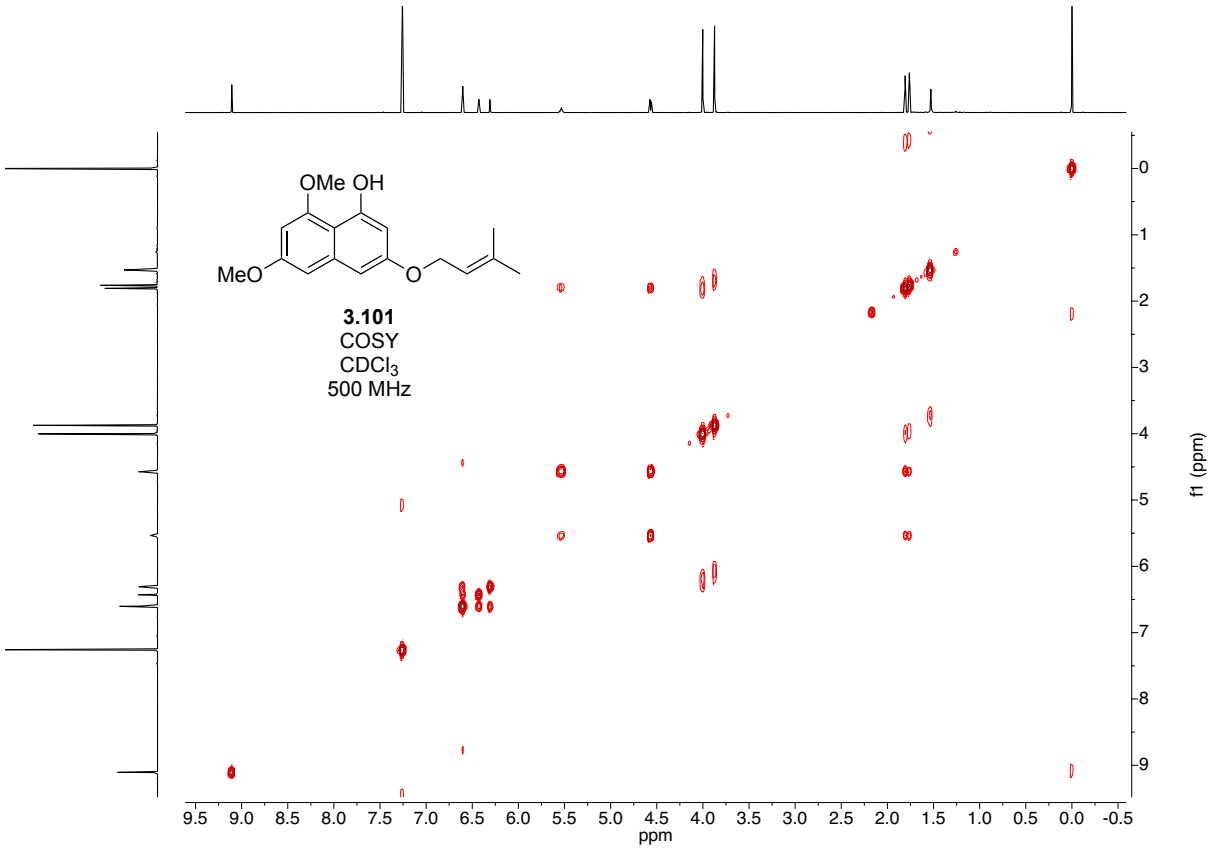
$CDCl_3$
125 MHz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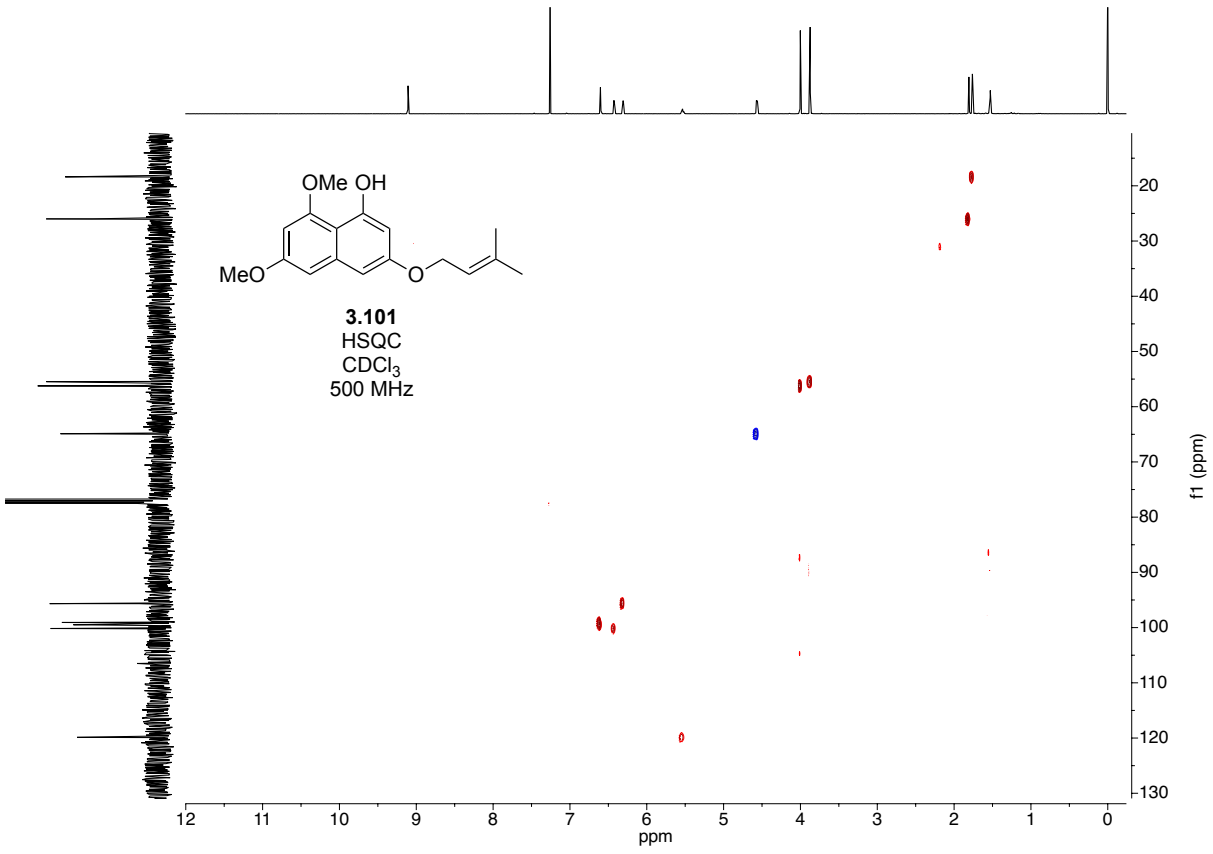
ppm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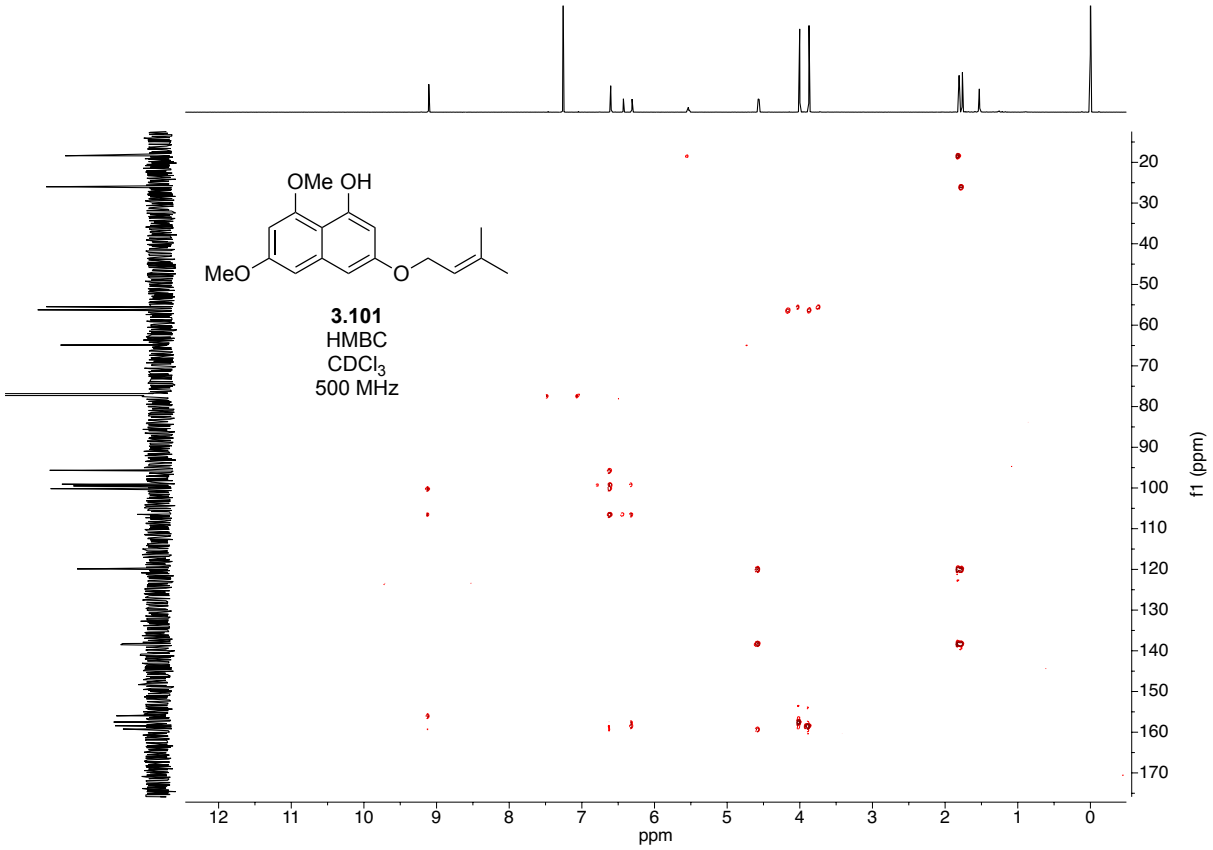
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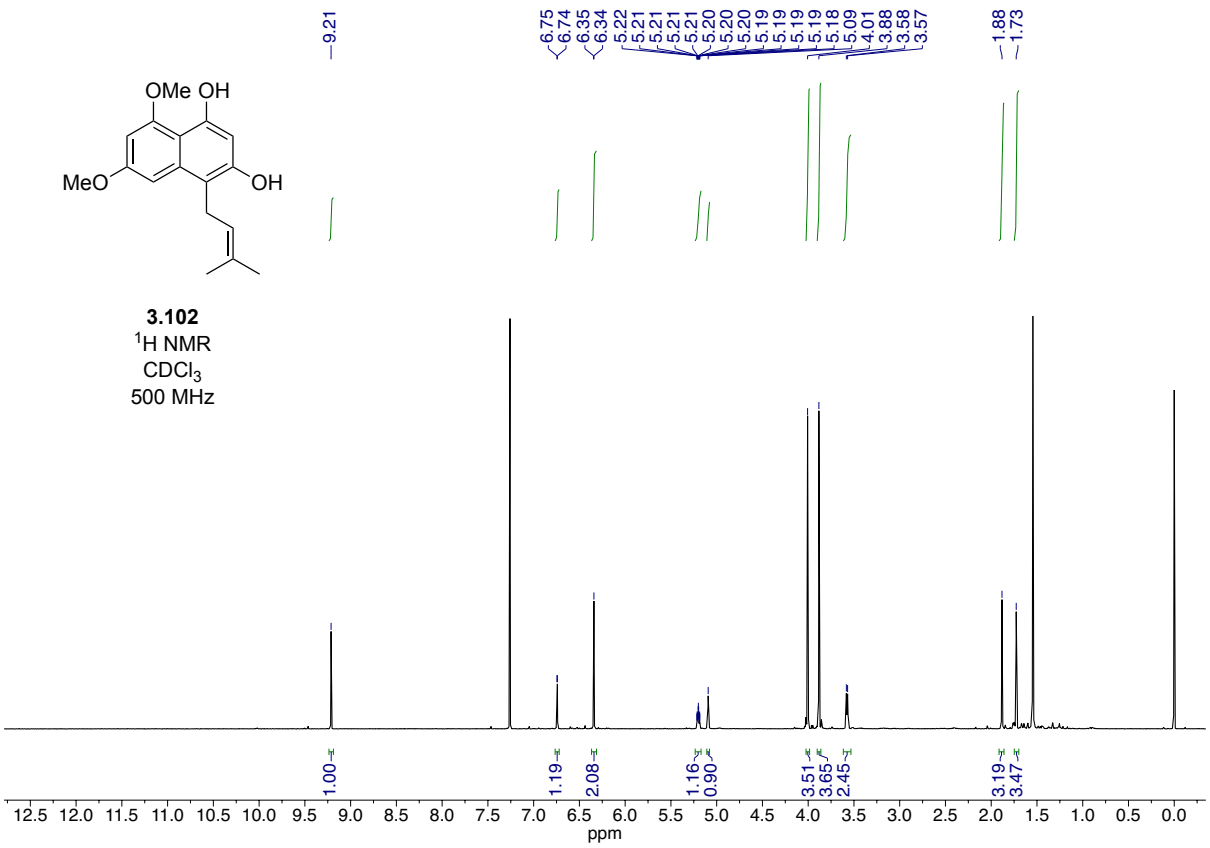
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5.21
5.21
5.21
5.21
5.20
5.20
5.20
5.19
5.19
5.19
5.19
5.18
5.09
4.01
3.88
3.58
3.57
1.88
1.73
1.00
1.19
2.08
1.16
0.90
3.51
3.65
2.45
3.19
3.47
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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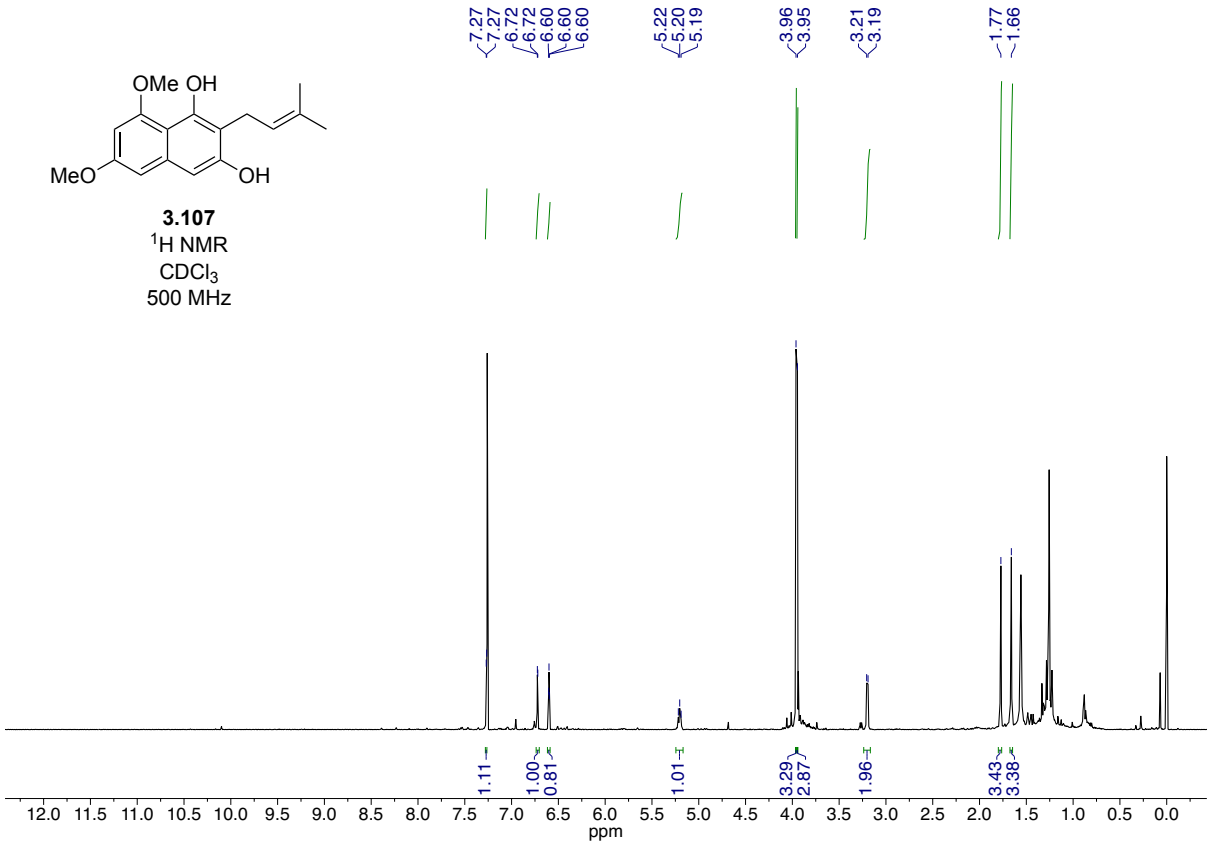
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6.72
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6.60
6.60
5.22
5.20
5.19
3.96
3.95
3.21
3.19
1.77
1.66
1.11
1.00
0.81
1.01
3.29
2.87
1.96
3.43
3.38
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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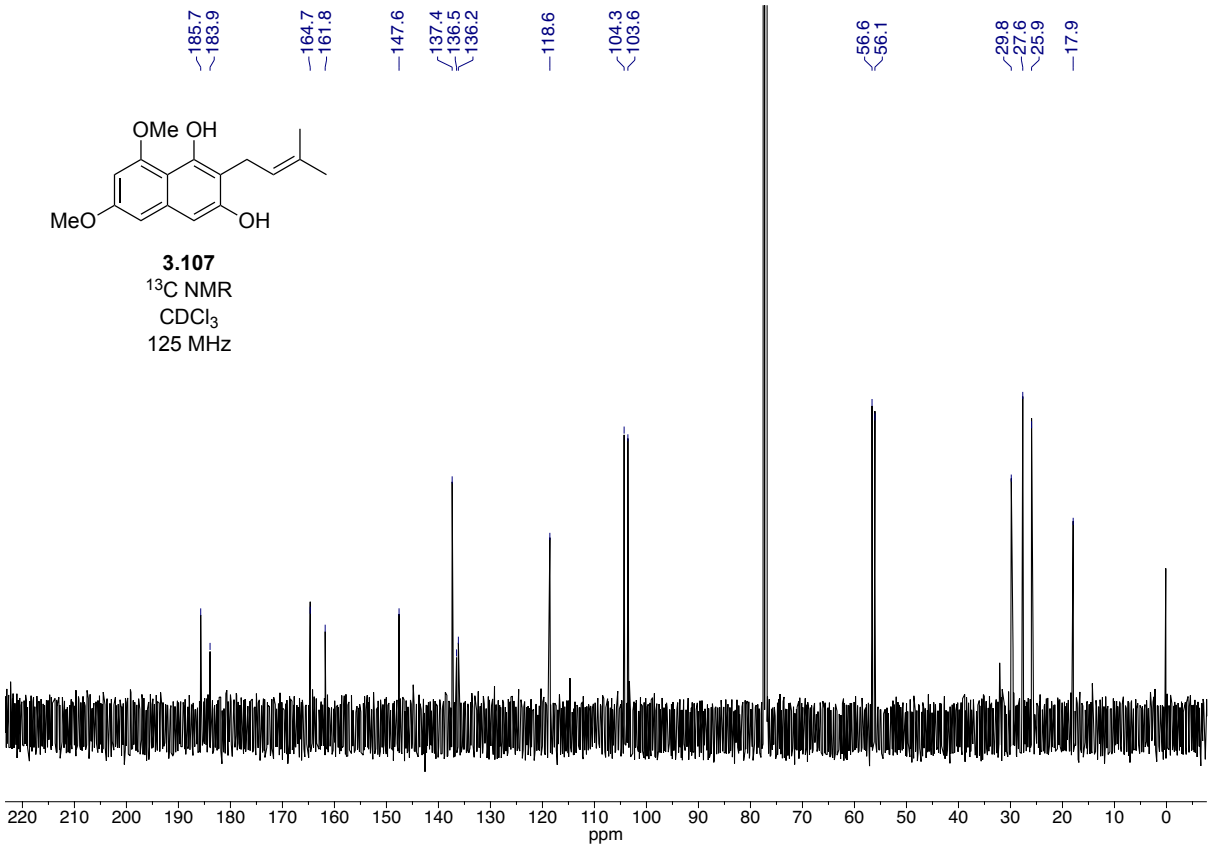
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13C NMR
CDCl3
125 MHz
185.7
183.9
164.7
161.8
147.6
137.4
136.5
136.2
118.6
104.3
103.6
56.6
56.1
29.8
27.6
25.9
17.9
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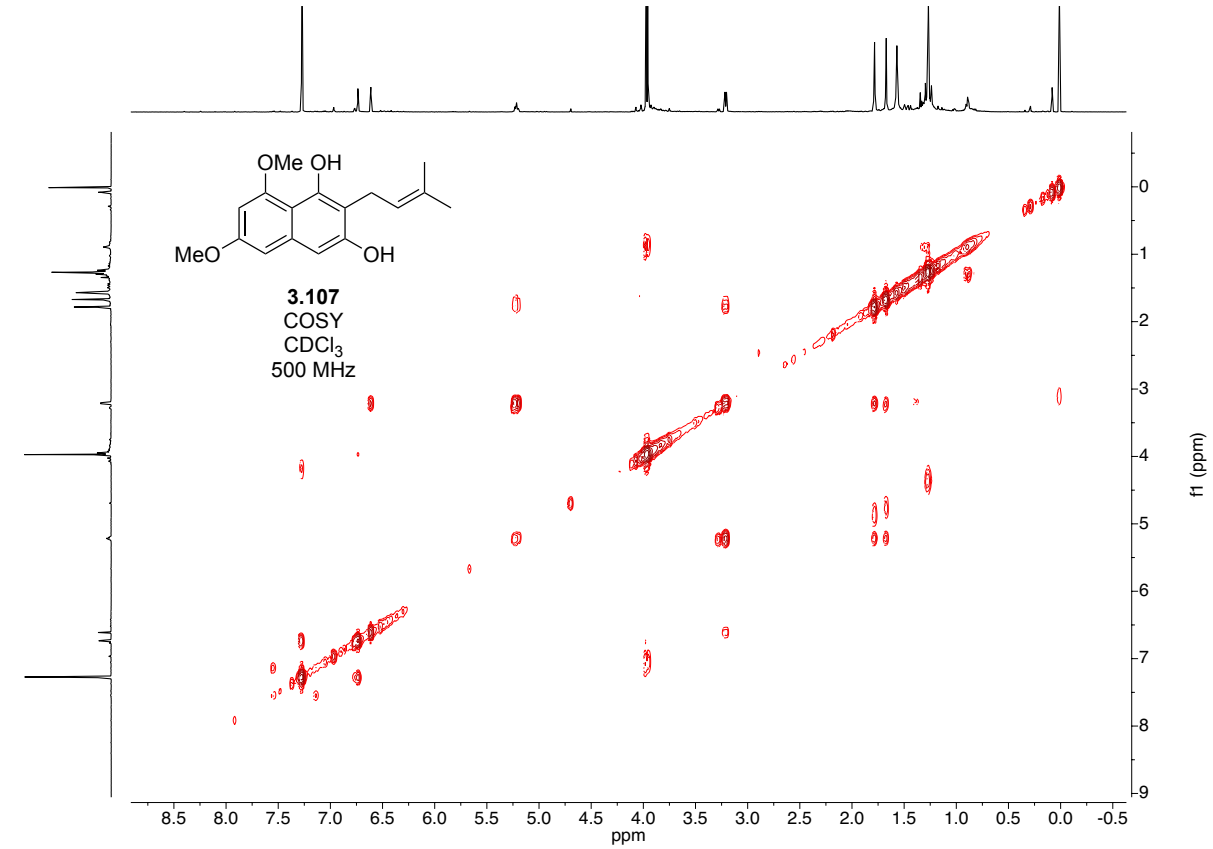
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MeO
OH
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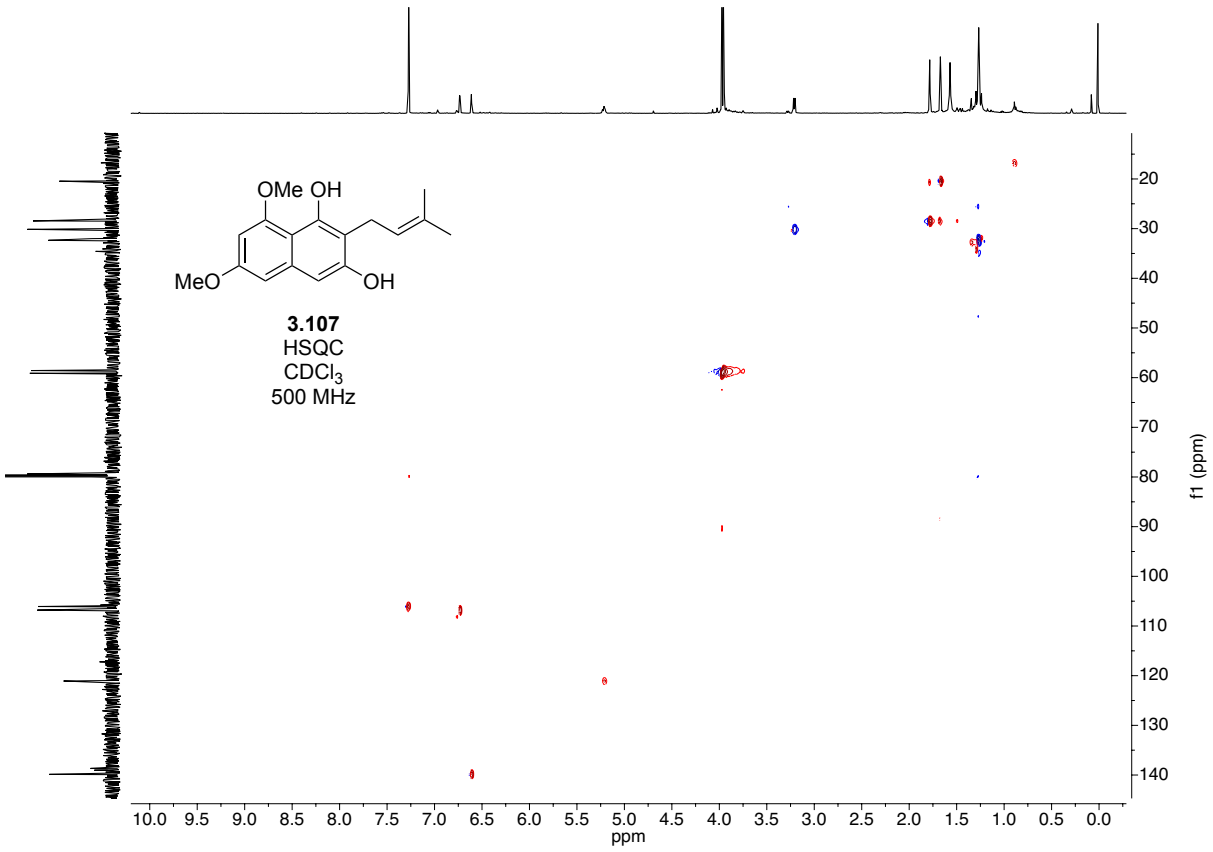
COSY
CDCl3
500 MHz
f1 (ppm)
ppm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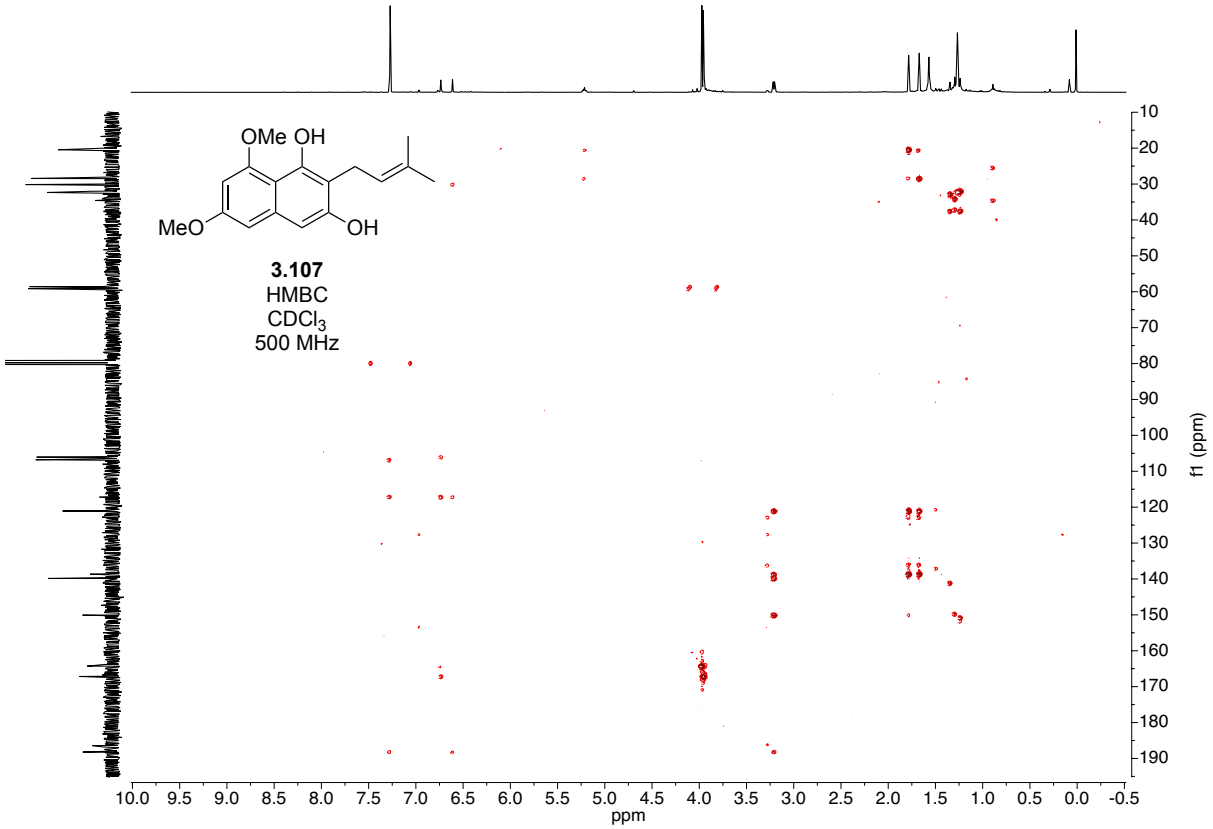
MeO
OH
3.107
HSQC
CDCl3
500 MHz
f1 (ppm)
ppm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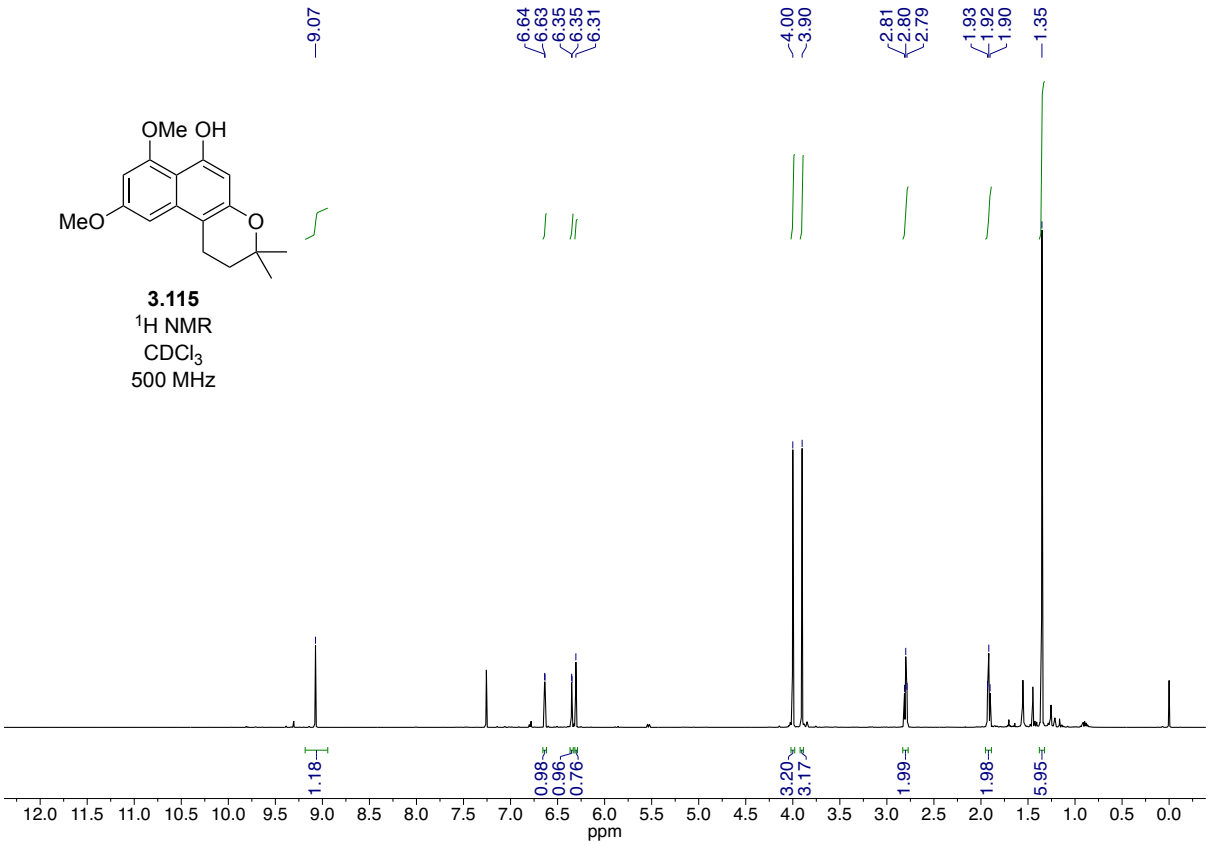
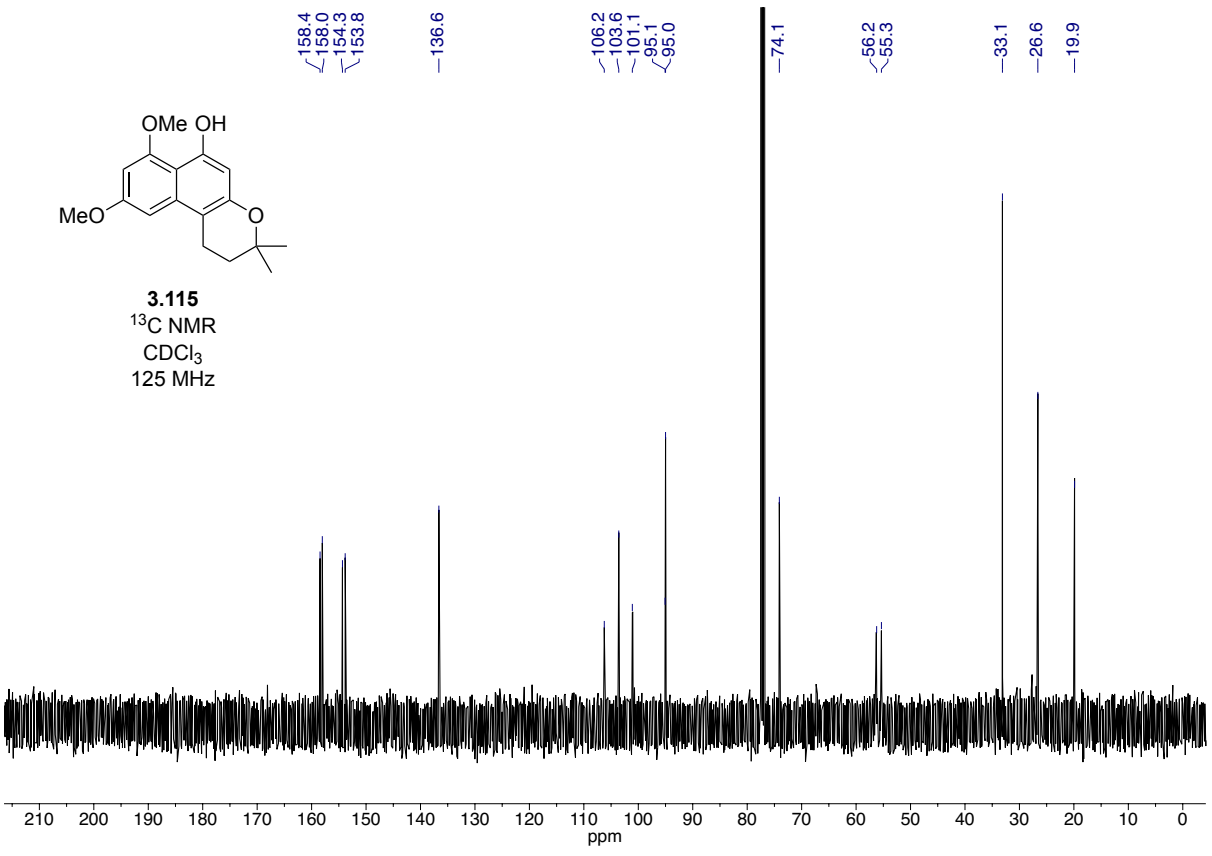
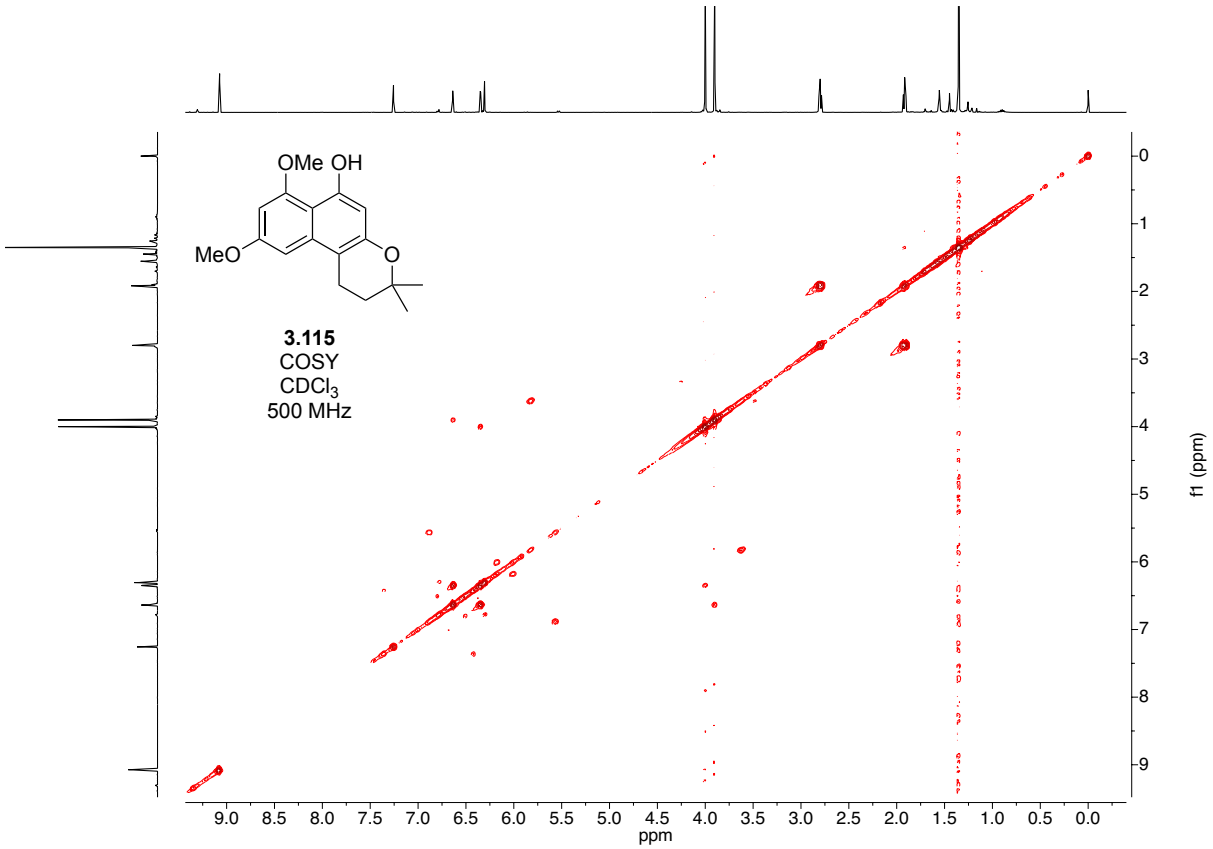
CDCl3
500 MHz
f1 (ppm)
ppm



3.115
^{1}H NMR
$CDCl_3$
500 MHz



3.115
^{13}C NMR
$CDCl_3$
125 MHz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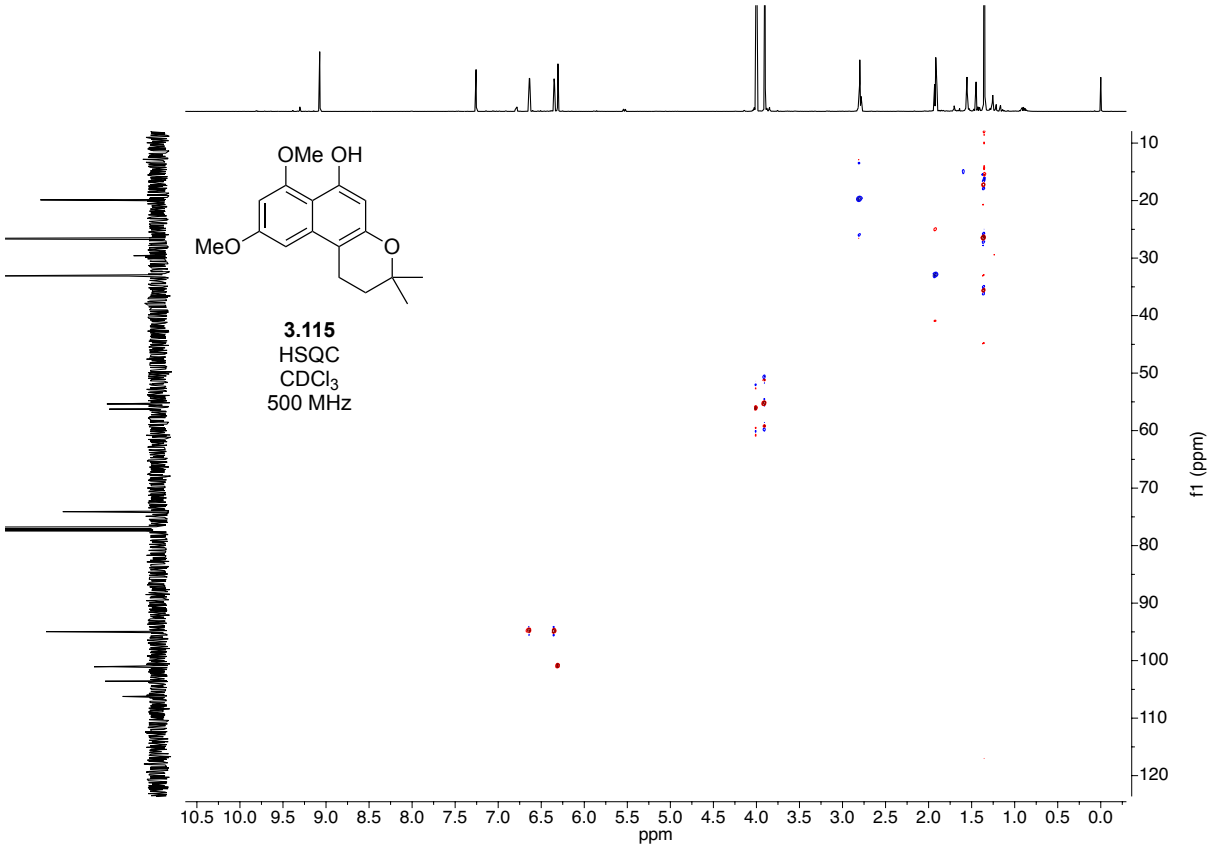
MeO
O
3.115
COSY
CDCl3
500 MHz
f1 (ppm)
ppm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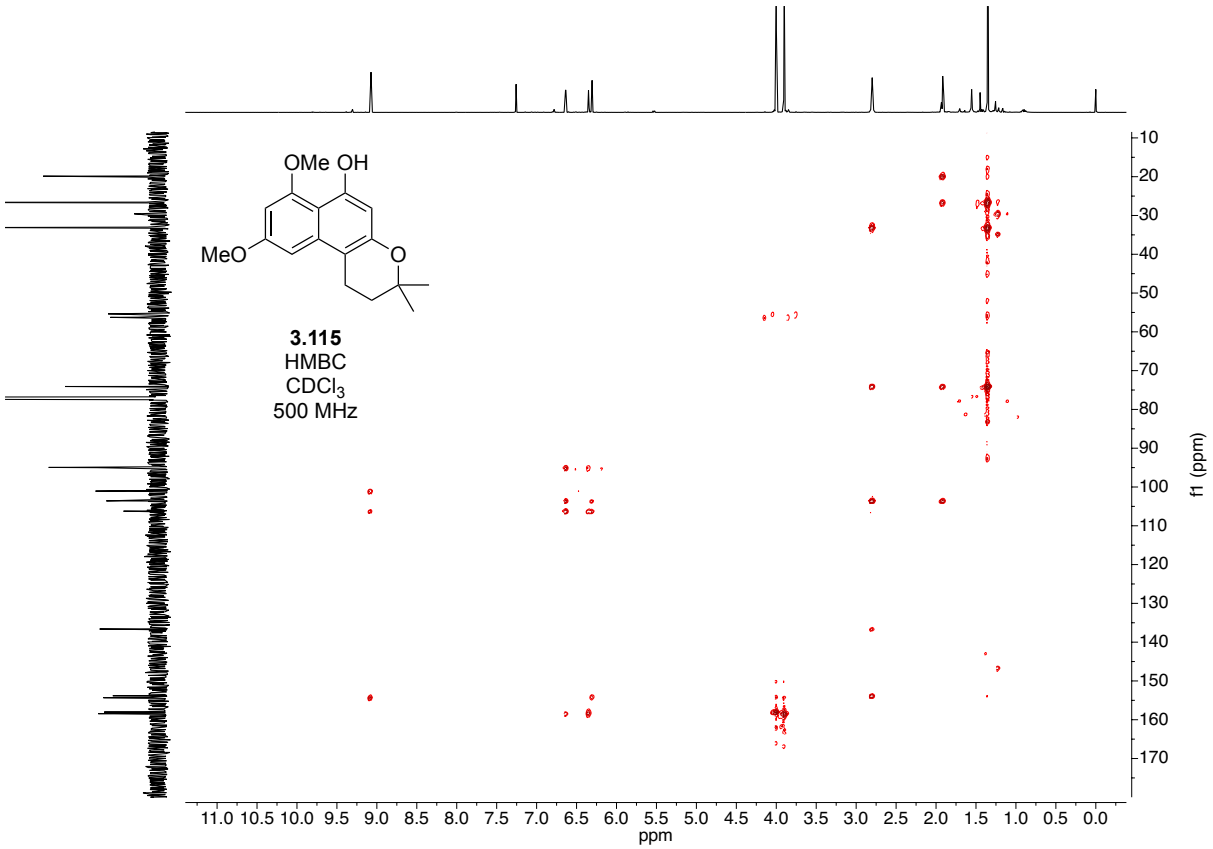
MeO
O
3.115
HSQC
CDCl3
500 MHz
f1 (ppm)
ppm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MeO
O
3.115
HMBC
CDCl3
500 MHz
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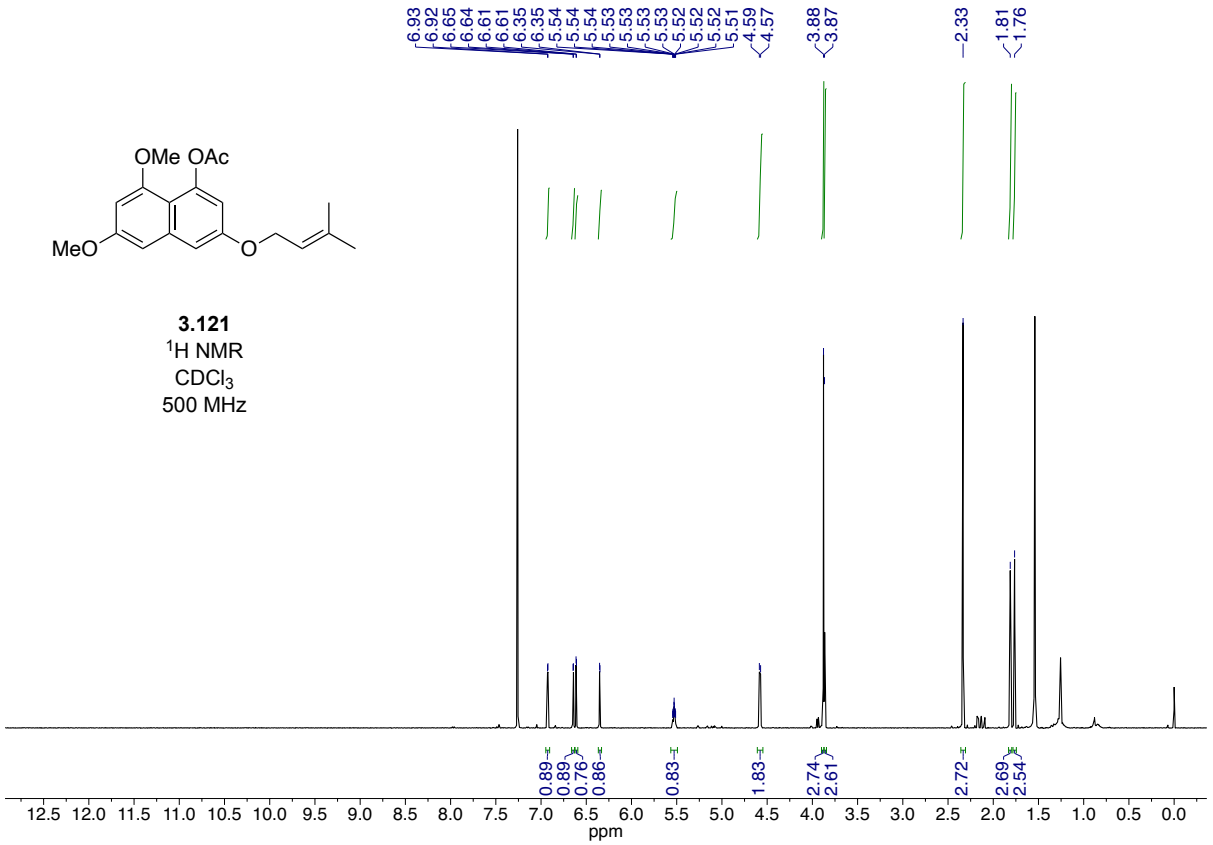
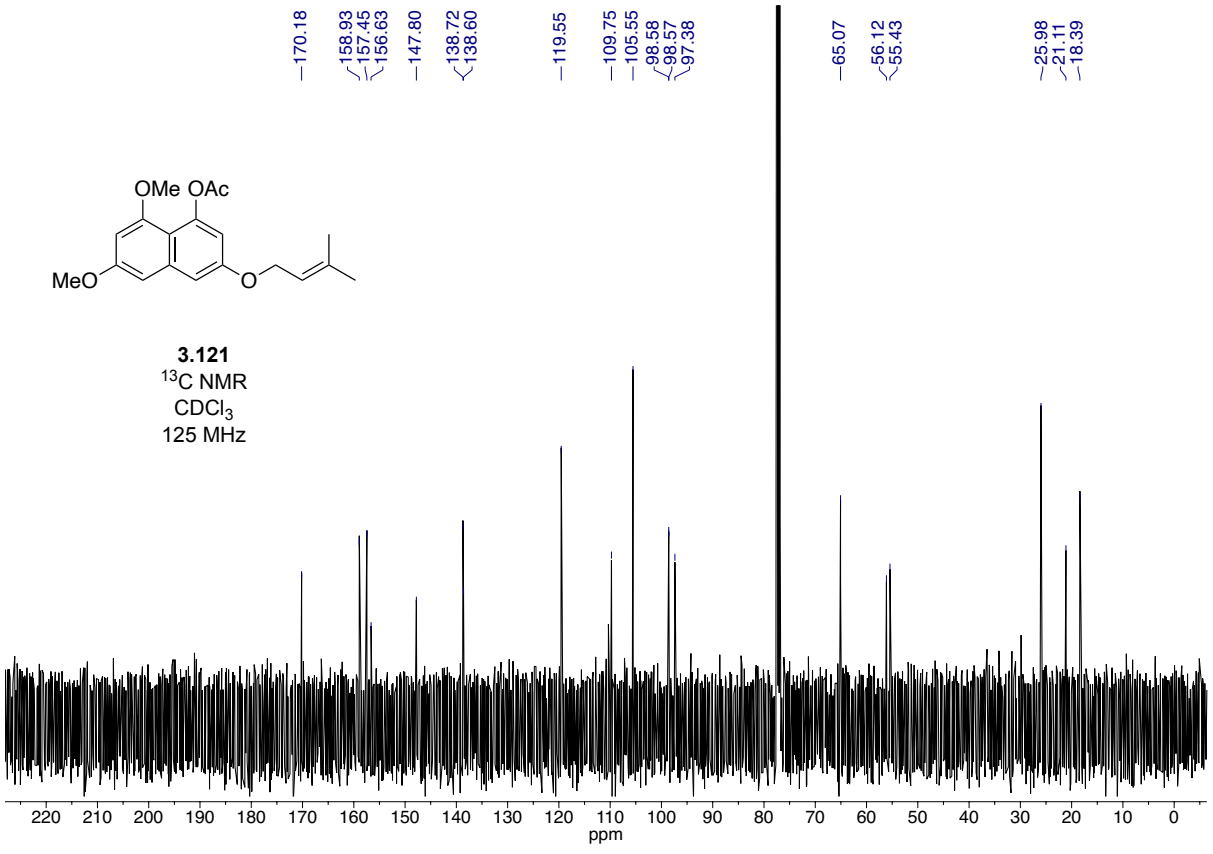
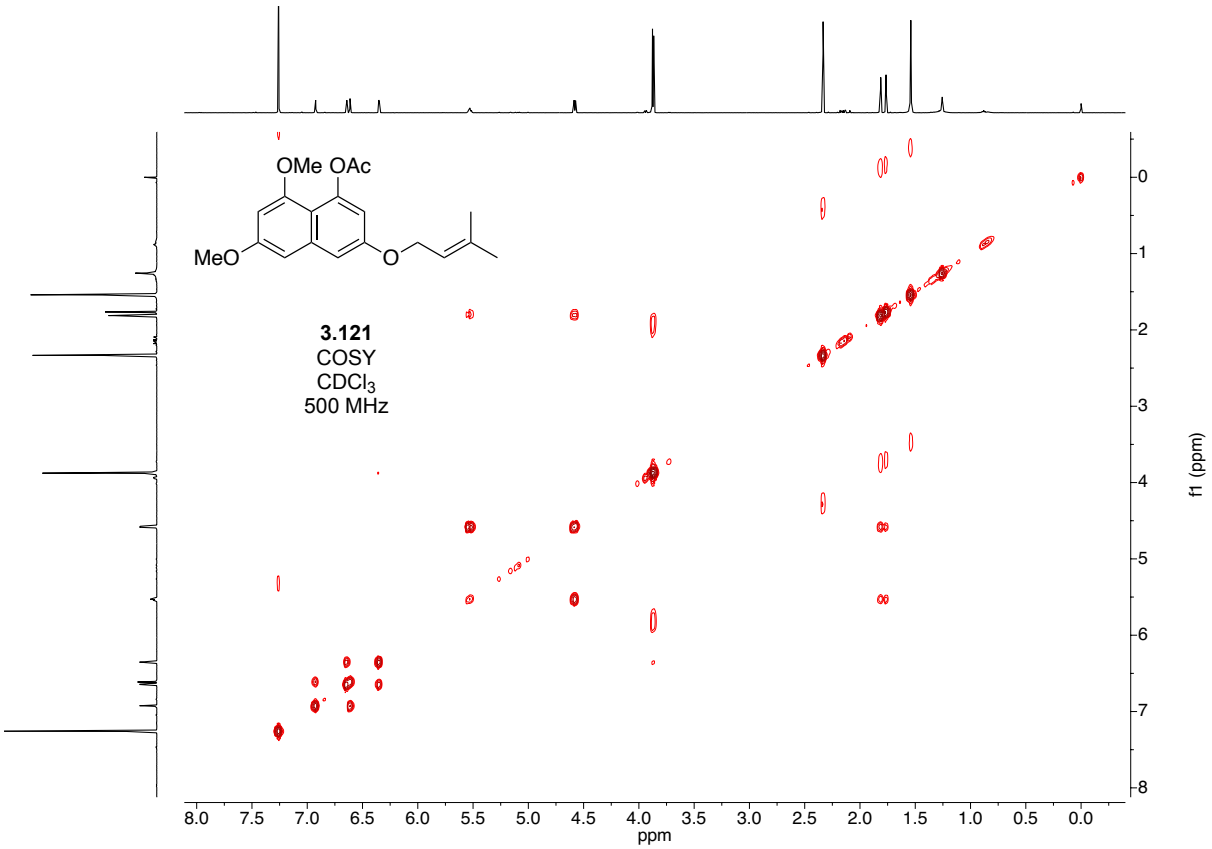
ppm
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170
f1 (ppm)



3.121
^{1}H NMR
$CDCl_3$
500 MHz



3.121
^{13}C NMR
$CDCl_3$
125 MHz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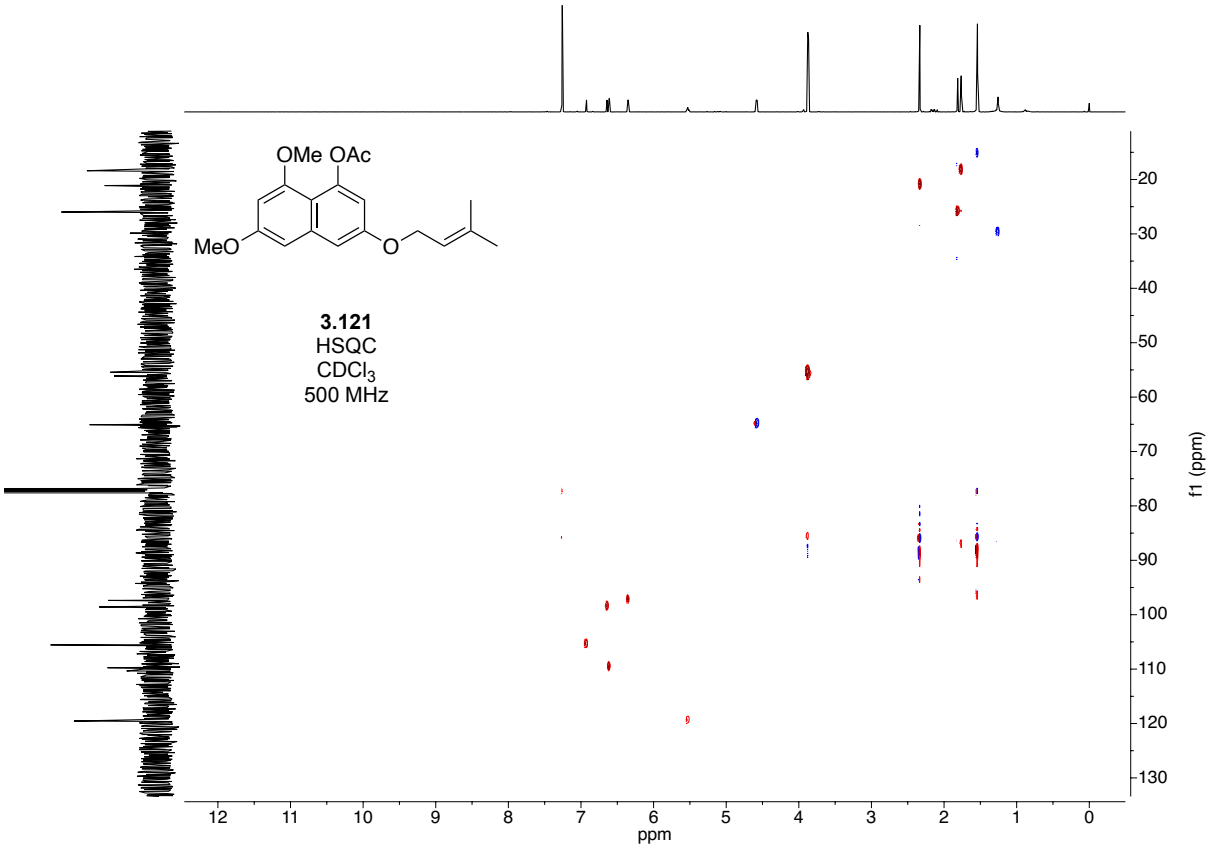
MeO
O
3.121
COSY
CDCl3
500 MHz
f1 (ppm)
ppm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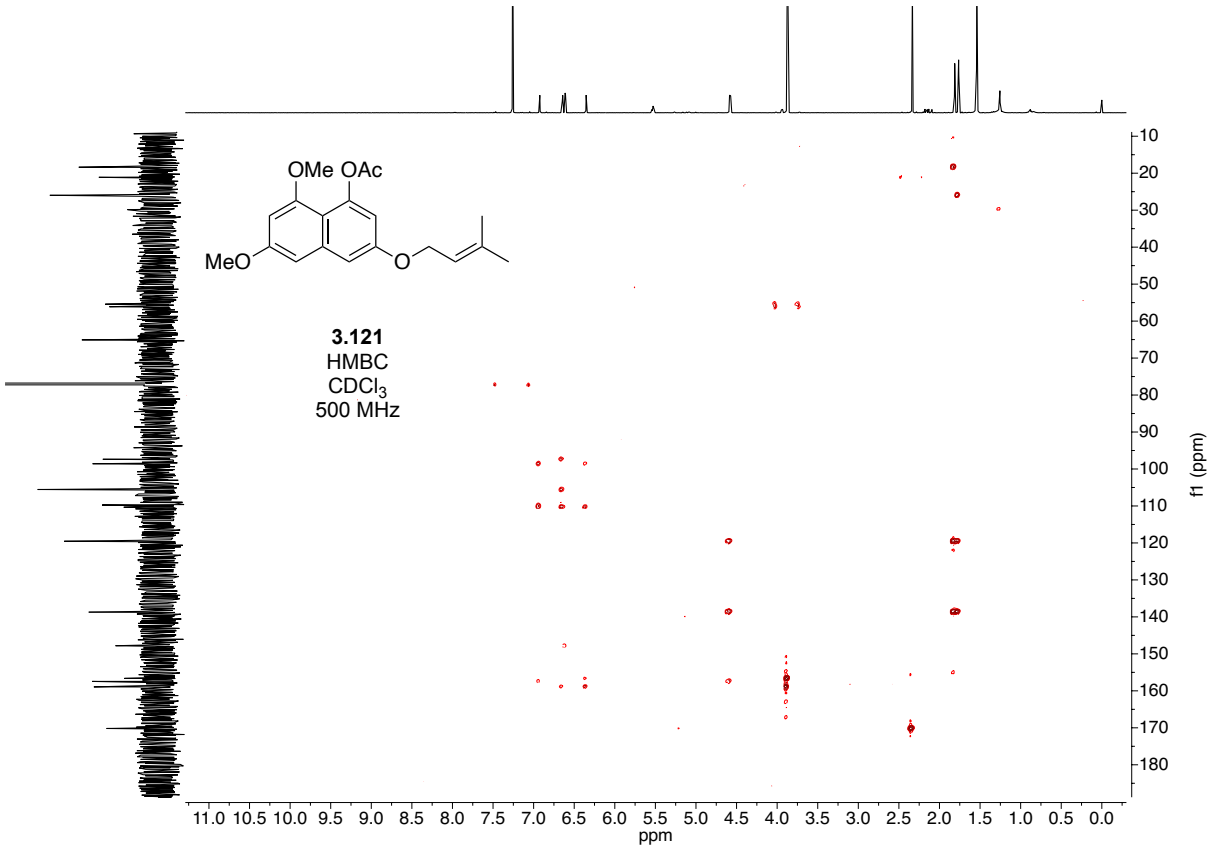
MeO
O
3.121
HSQC
CDCl3
500 MHz
f1 (ppm)
ppm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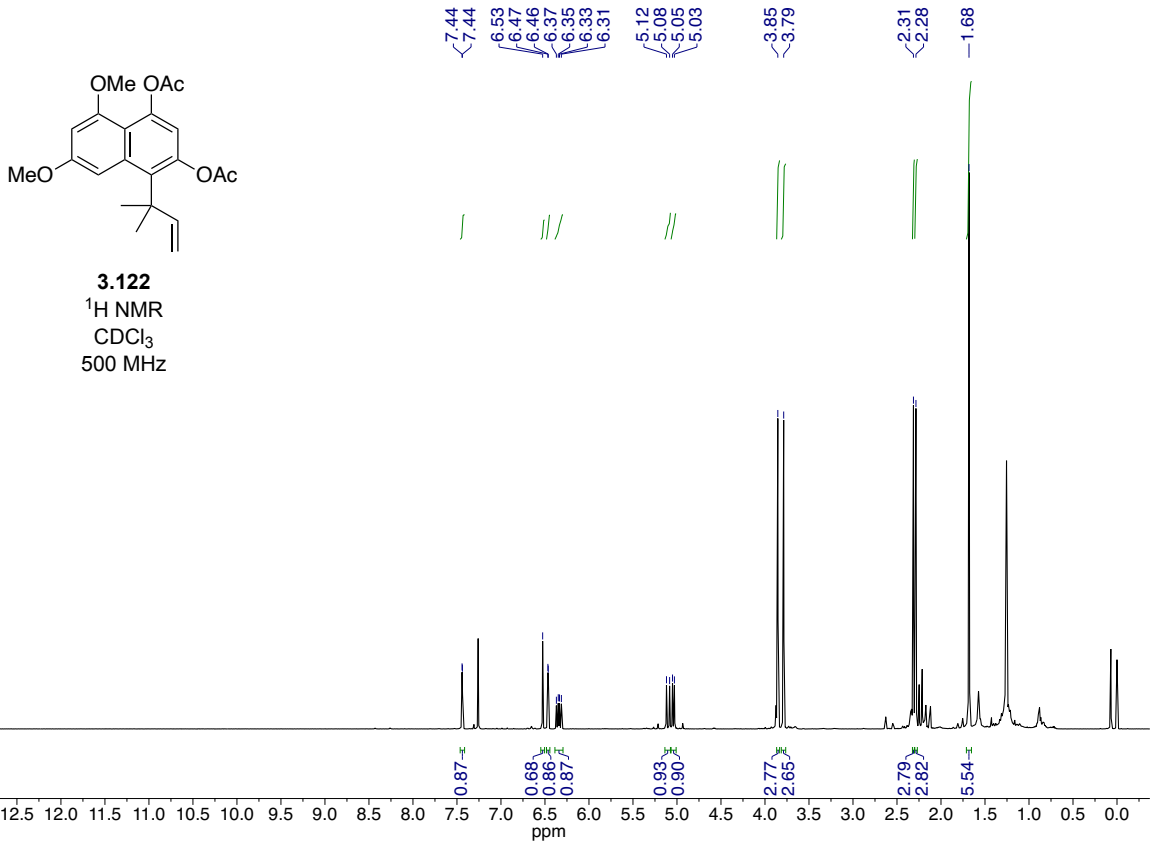
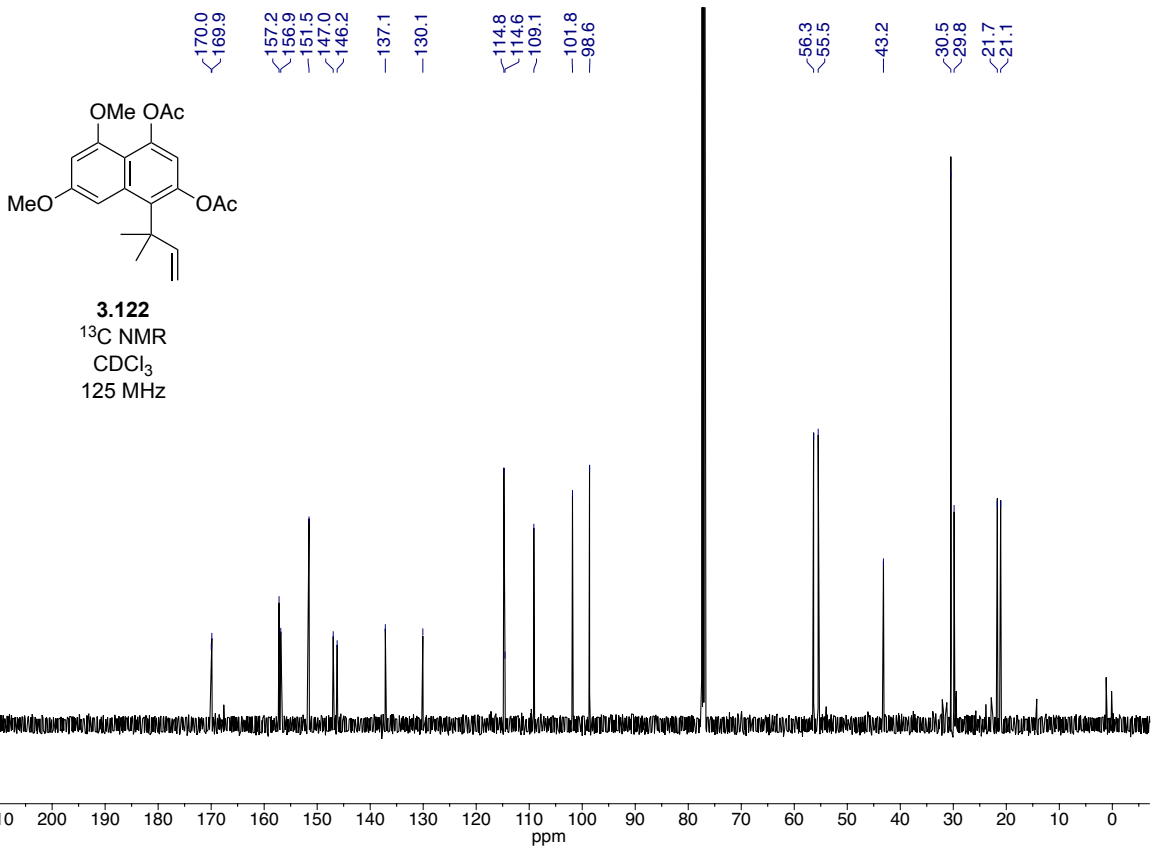
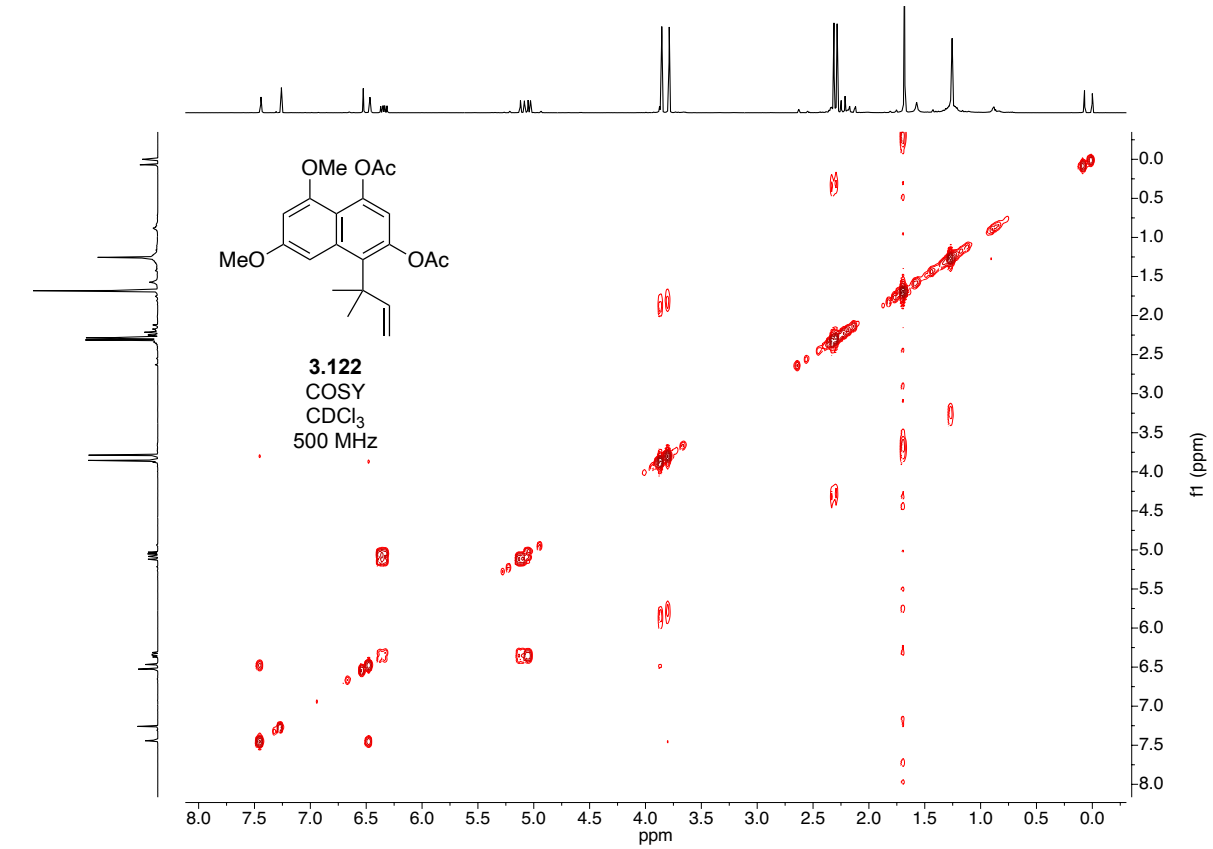
MeO
O
3.121
HMBC
CDCl3
500 MHz
f1 (ppm)
ppm



3.122
^{1}H NMR
$CDCl_3$
500 MHz



3.122
^{13}C NMR
$CDCl_3$
125 MHz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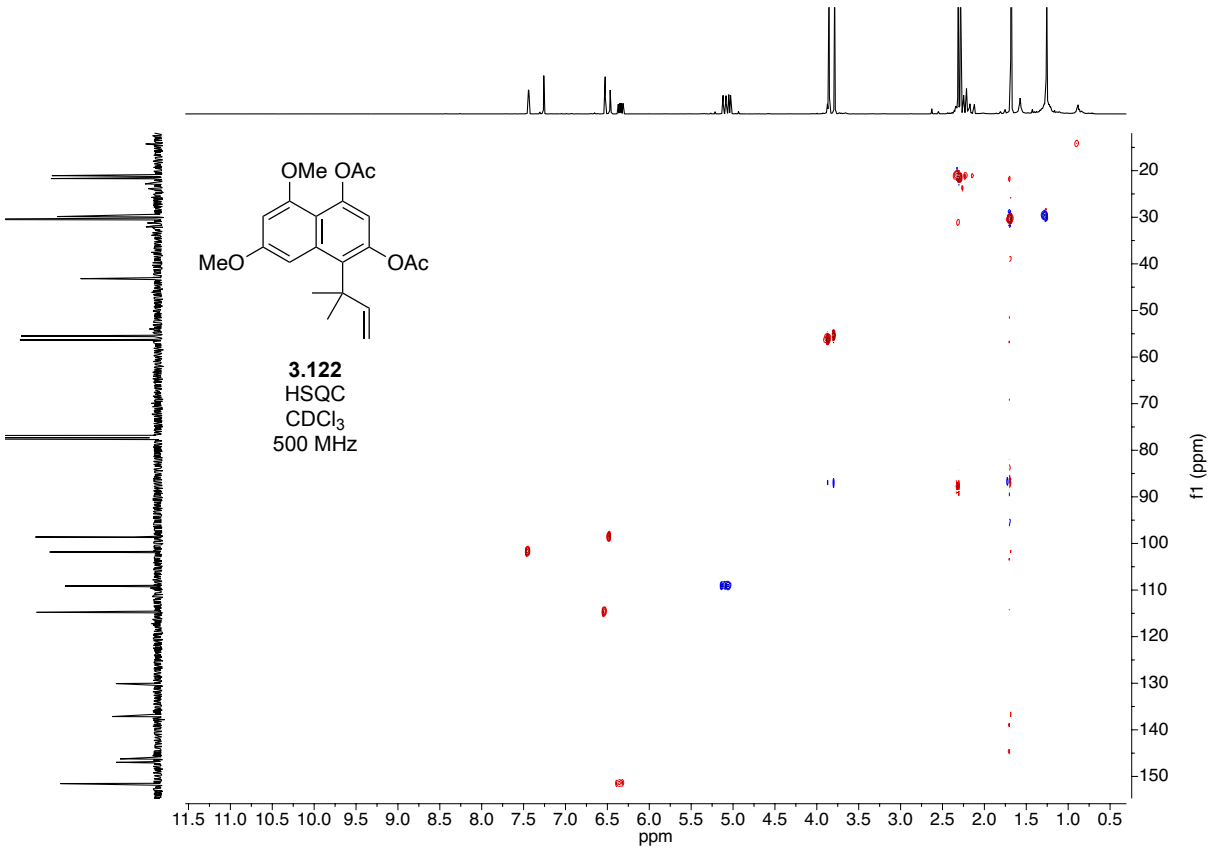
MeO
OAc
3.122
COSY
CDCl3
500 MHz
f1 (ppm)
ppm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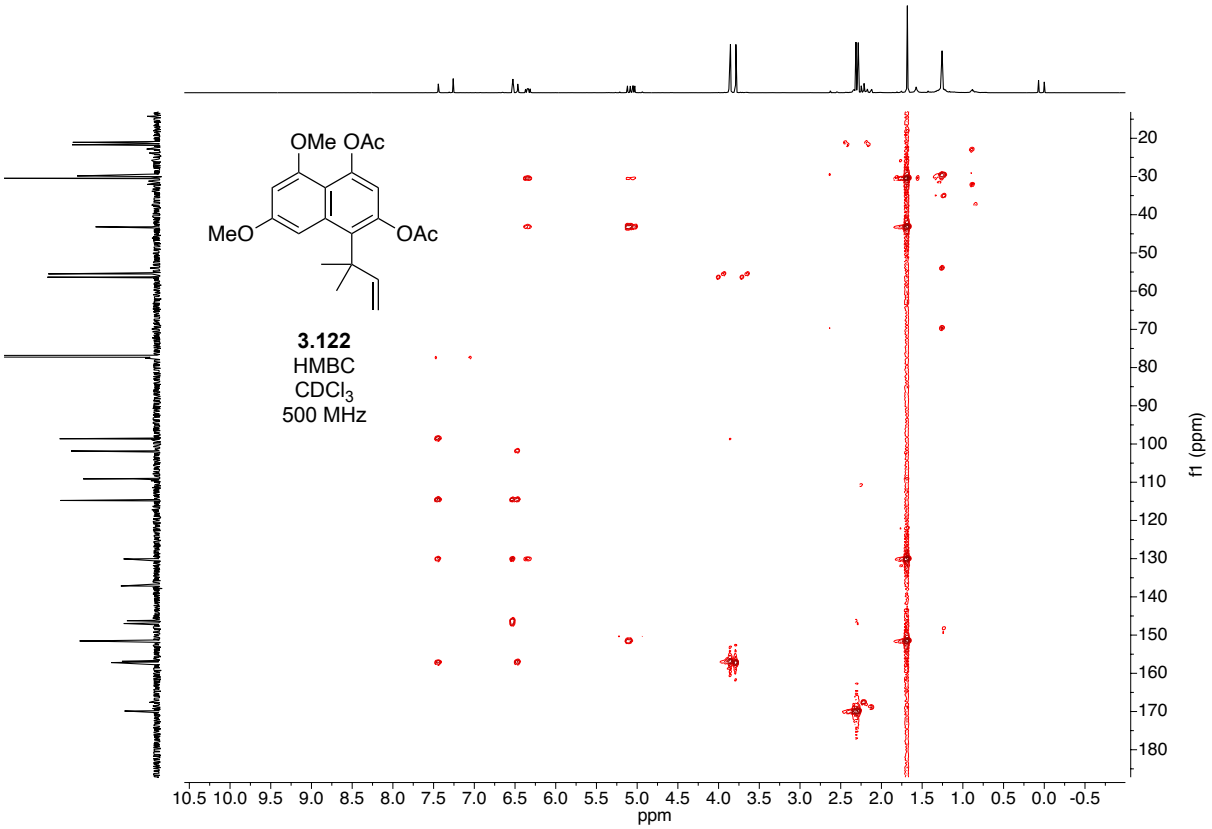
MeO
OAc
3.122
HSQC
CDCl3
500 MHz
f1 (ppm)
ppm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MeO
OAc
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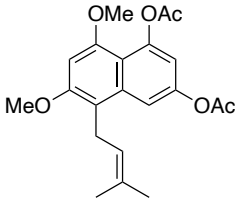
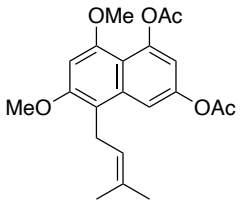
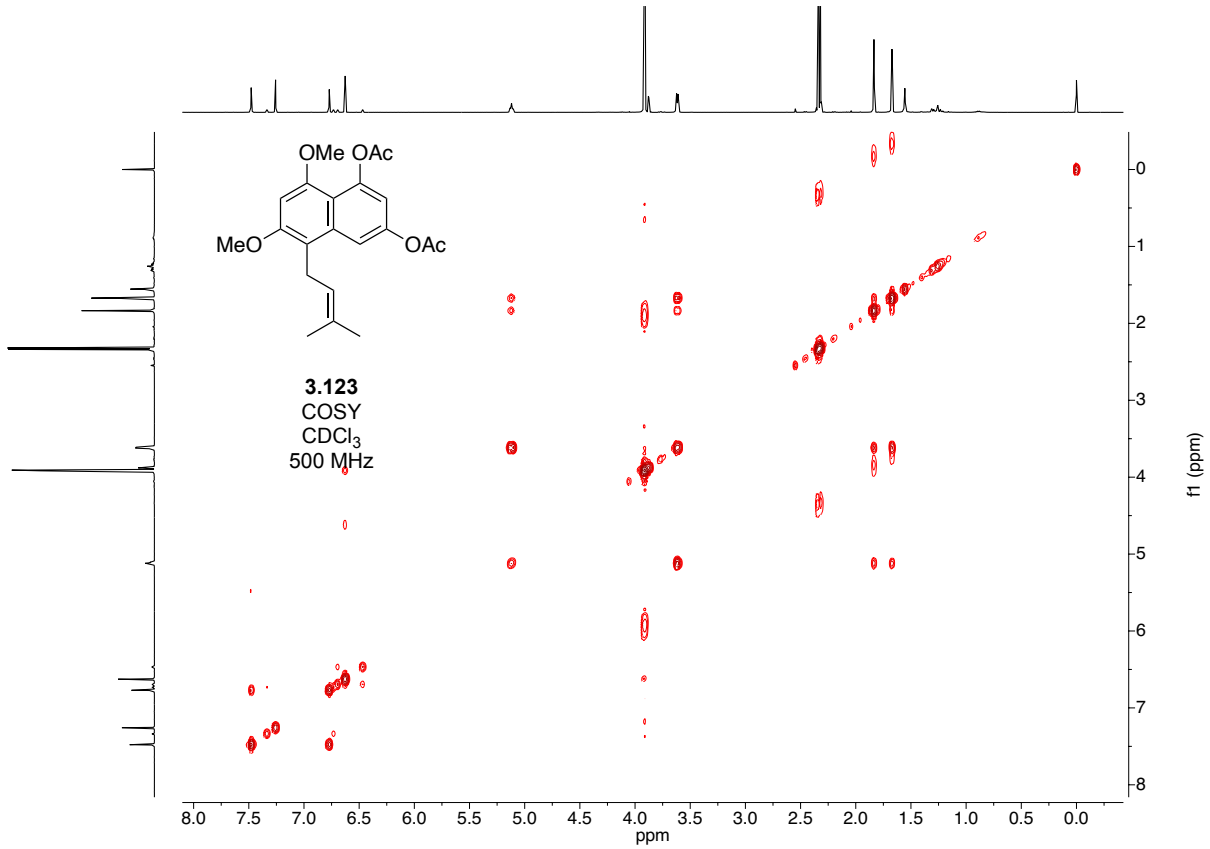
HMBC
CDCl3
500 MHz
f1 (ppm)
ppm

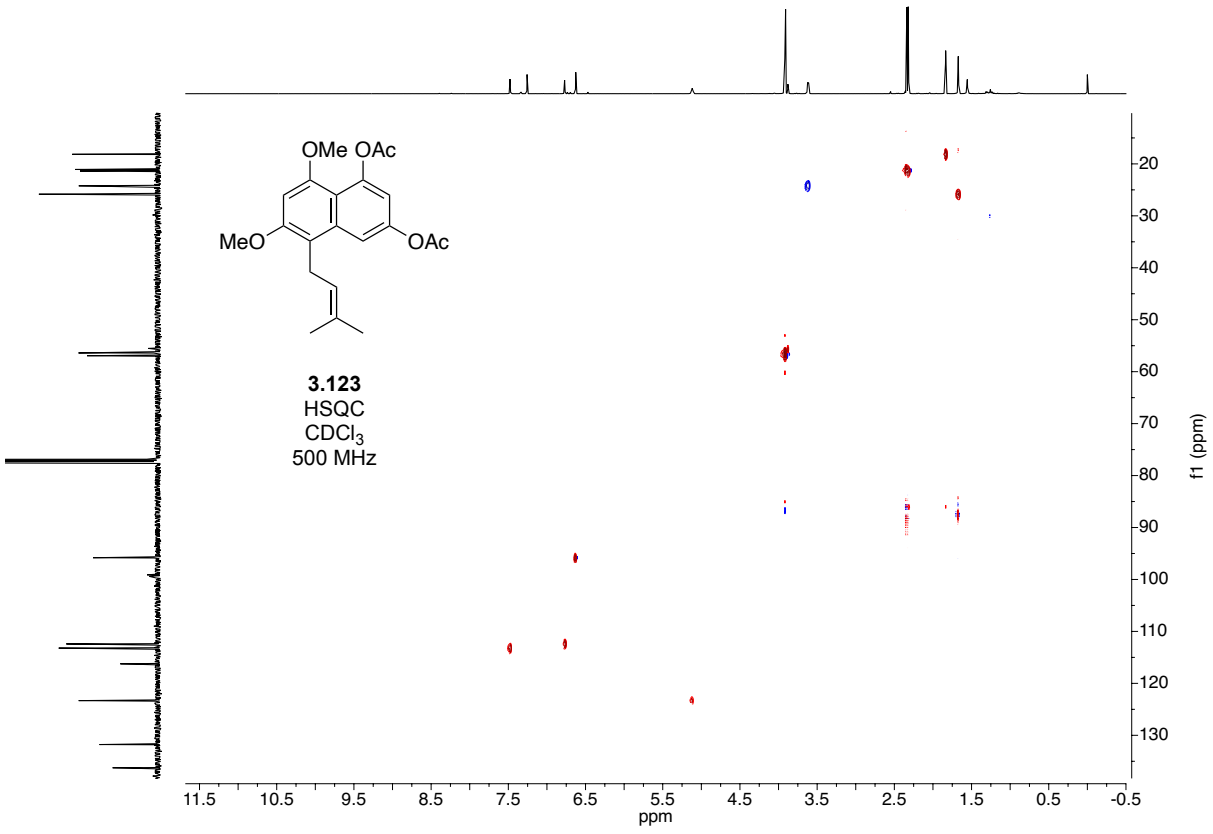


3.123
^{1}H NMR
$CDCl_3$
500 MHz



3.123
^{13}C NMR
$CDCl_3$
125 MHz


OMe OAc
MeO
OAc
3.123
COSY
CDCl3
500 MHz
f1 (ppm)
ppm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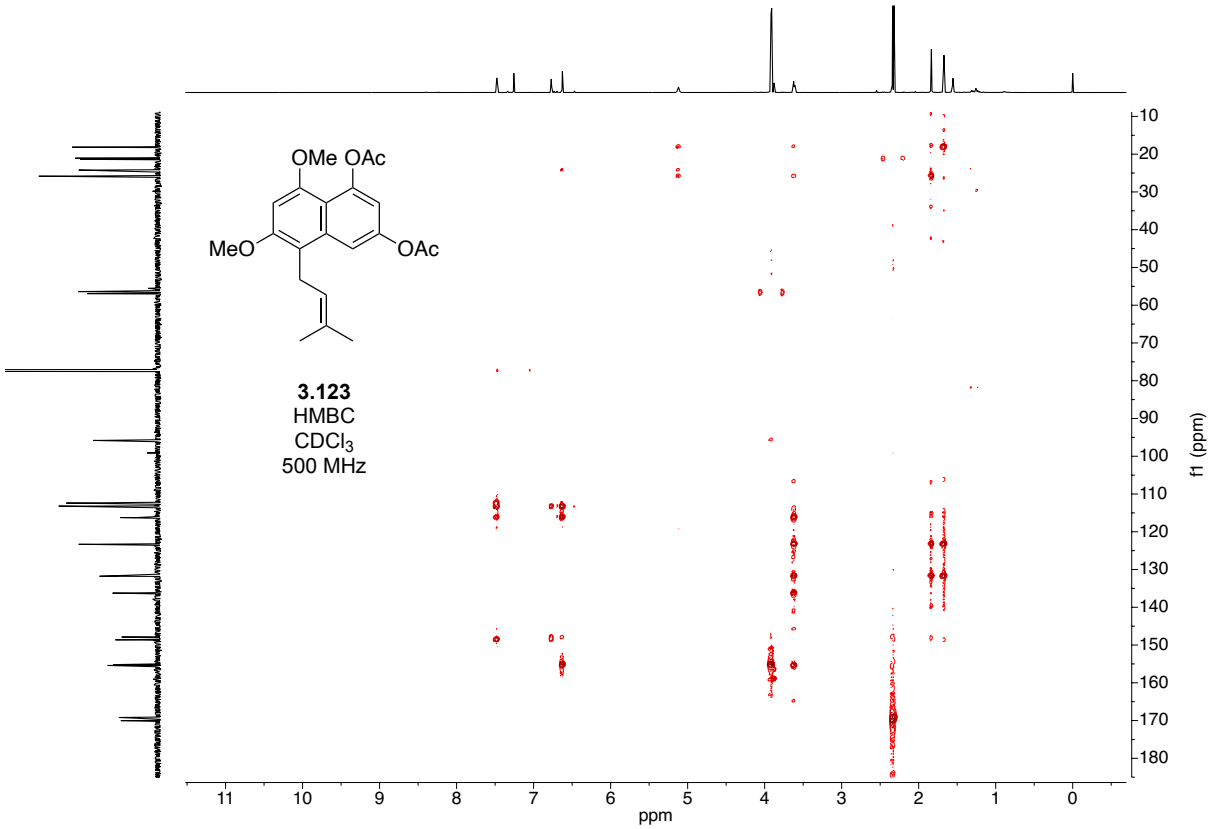
MeO
OAc
3.123
HSQC
CDCl3
500 MHz
f1 (ppm)
ppm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OAc
3.123
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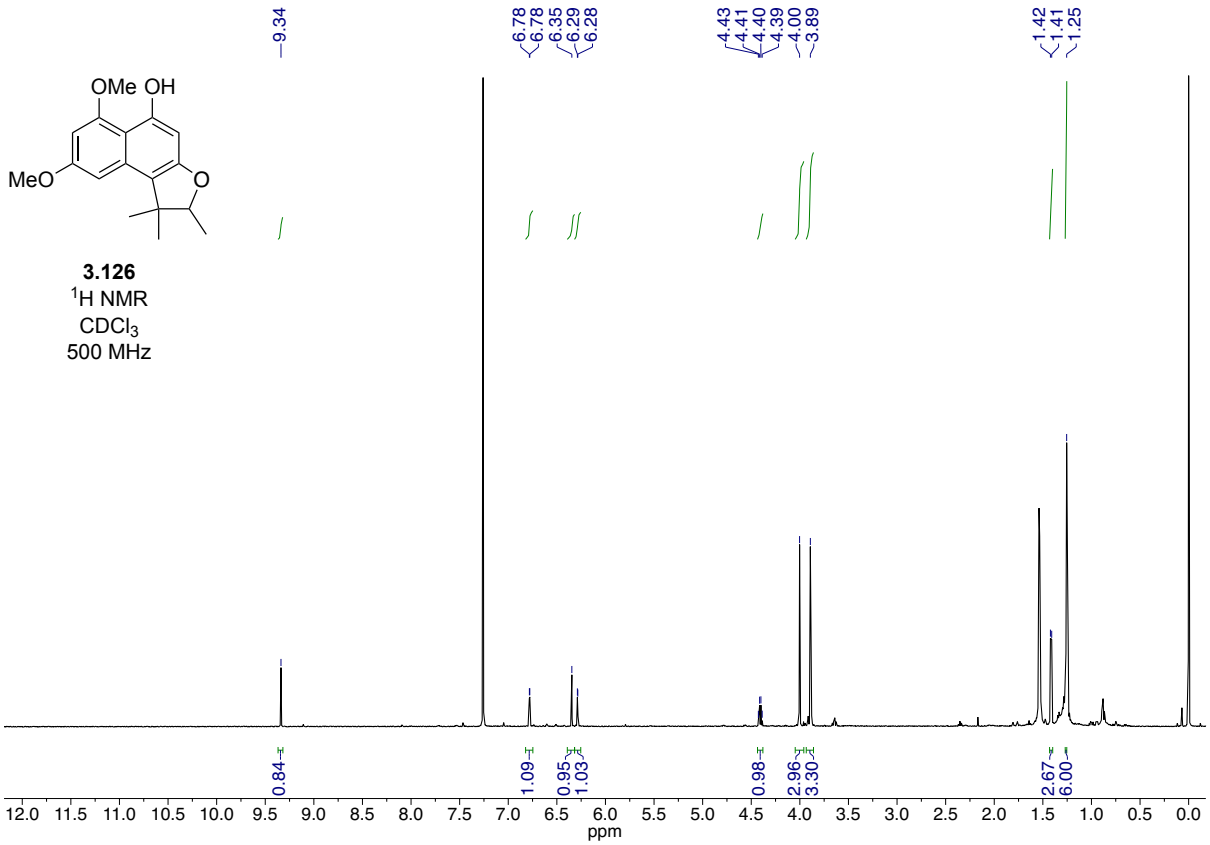
CDCl3
500 MHz
ppm
f1 (ppm)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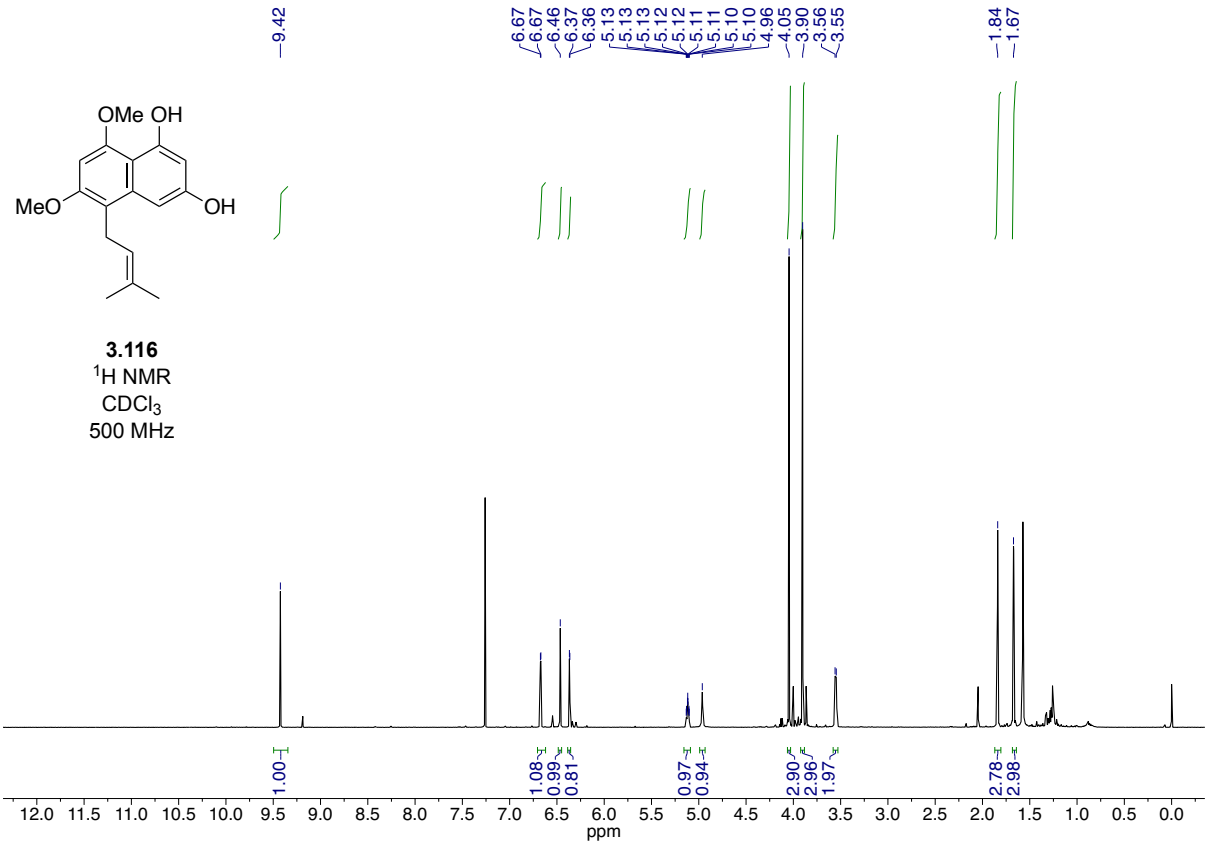
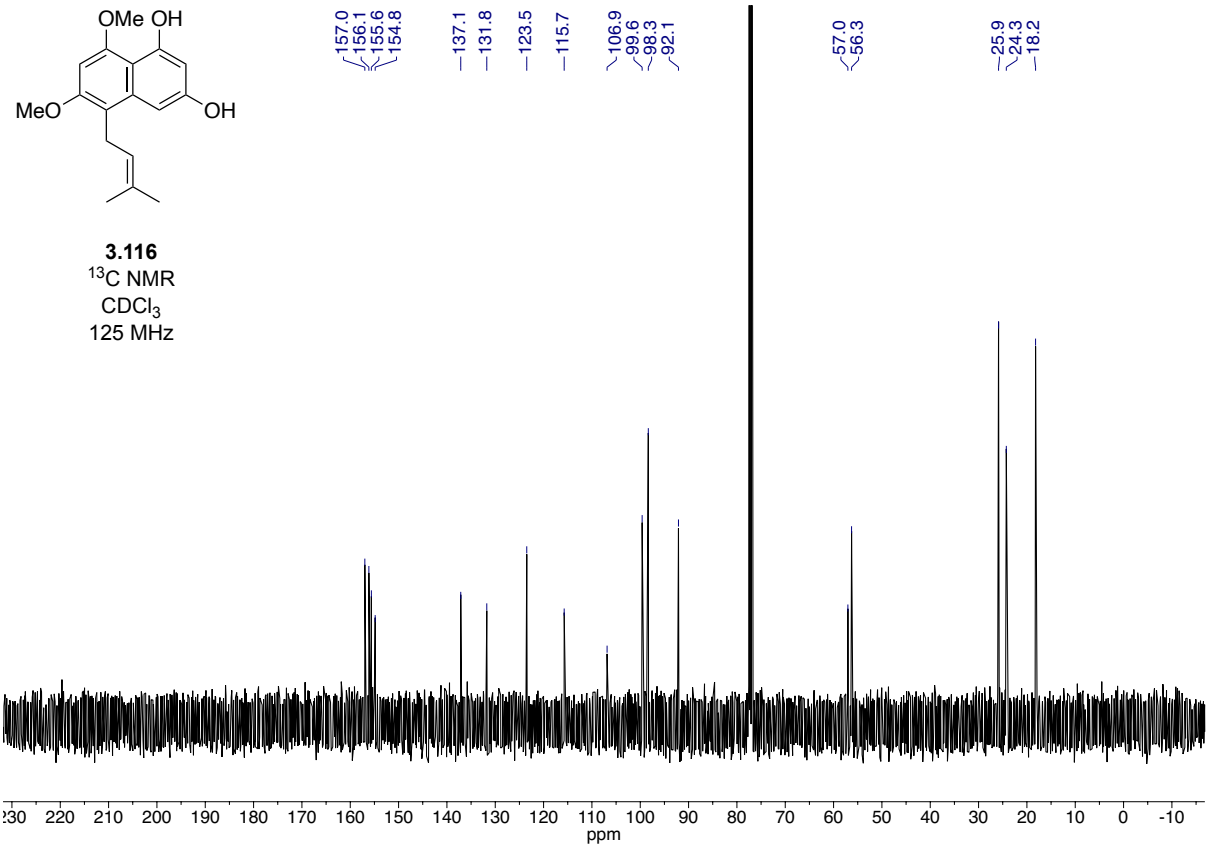
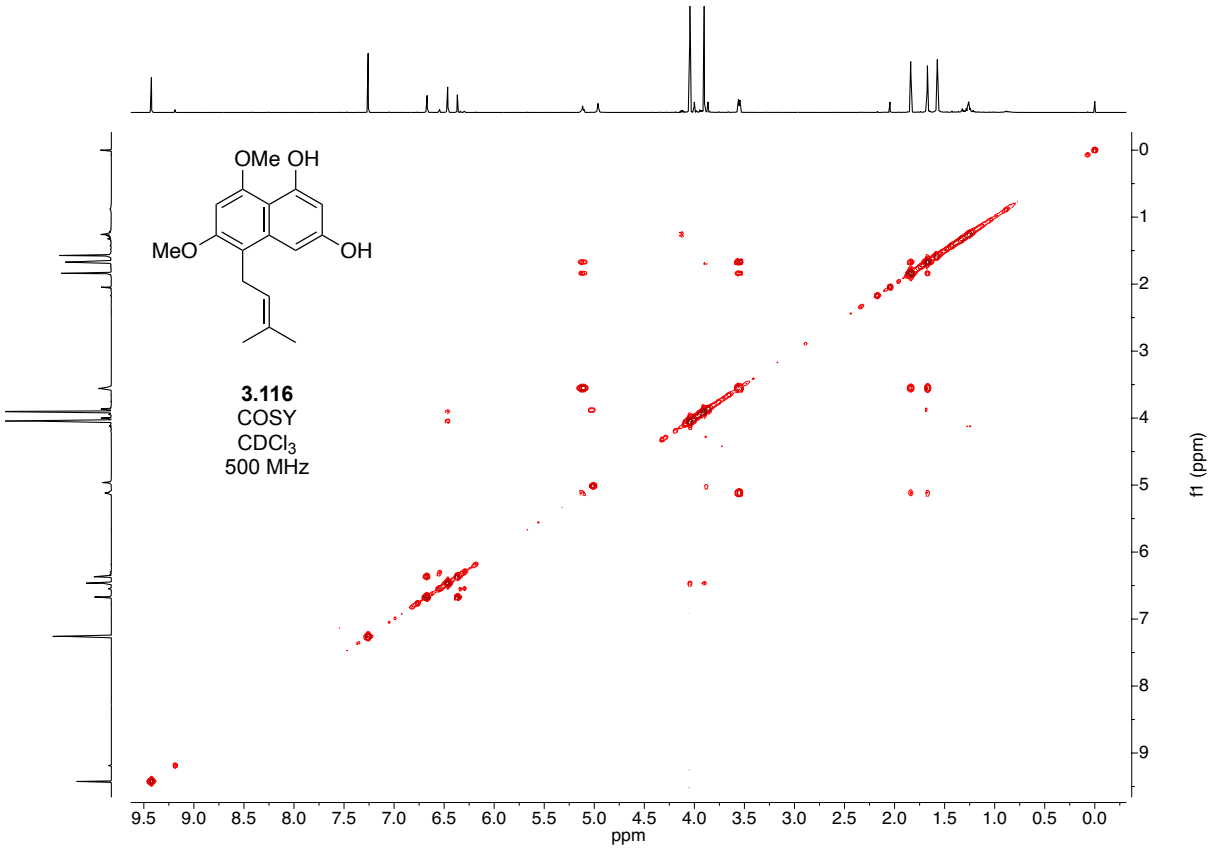
MeO
O
3.126
1H NMR
CDCl3
500 MHz
9.34
6.78
6.78
6.35
6.29
6.28
4.43
4.41
4.40
4.39
4.00
3.89
1.42
1.41
1.25
0.84
1.09
0.95
1.03
0.98
2.96
3.30
2.67
6.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

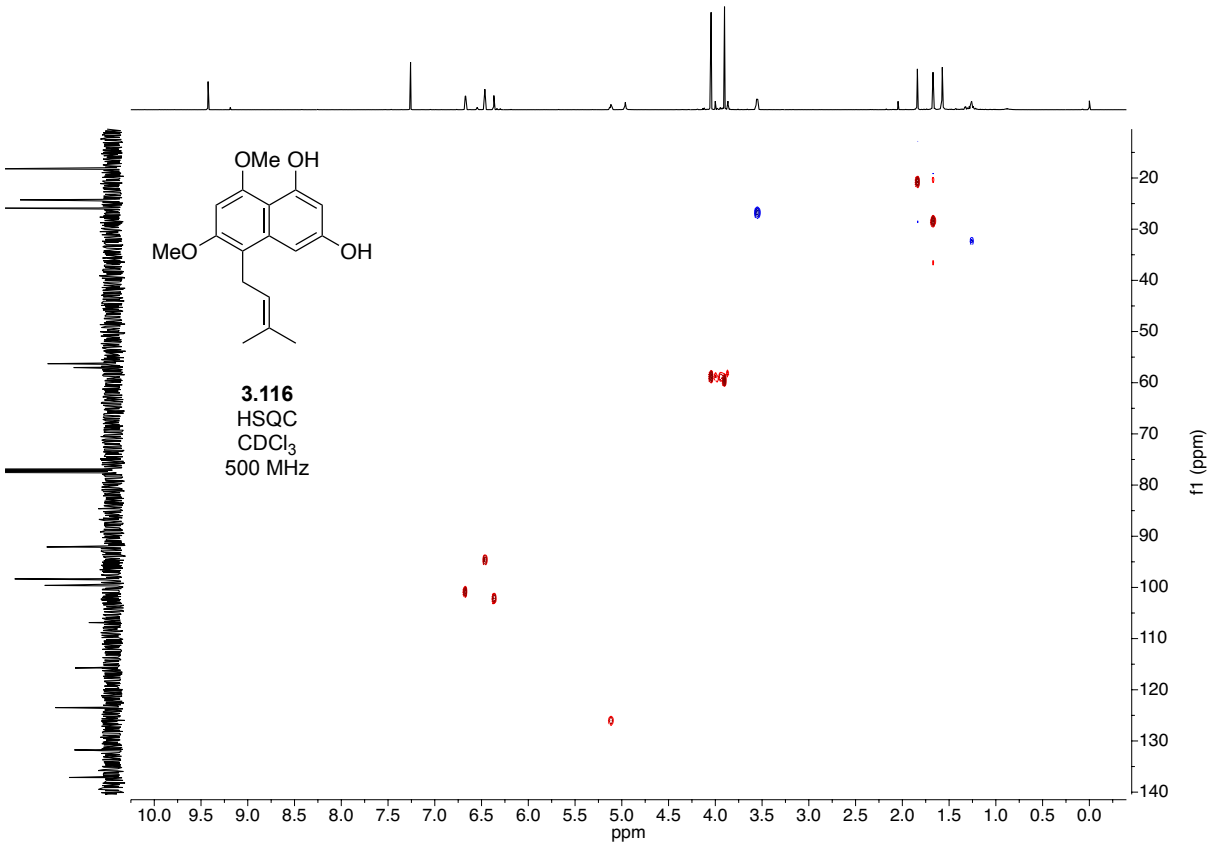


3.116
^{1}H NMR
$CDCl_3$
500 MHz



3.116
^{13}C NMR
$CDCl_3$
125 MHz


OMe OH
MeO
OH
3.116
COSY
CDCl3
500 MHz
f1 (ppm)
ppm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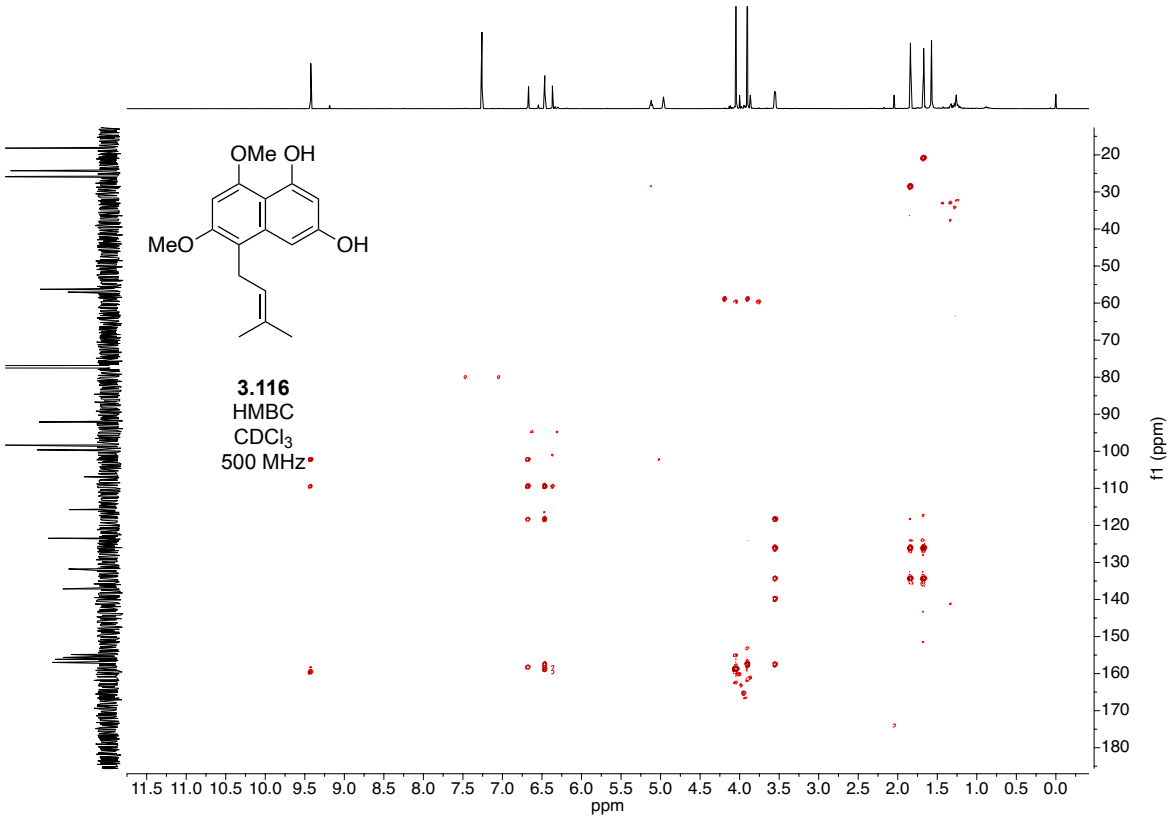
MeO
OH
3.116
HSQC
CDCl3
500 MHz
f1 (ppm)
ppm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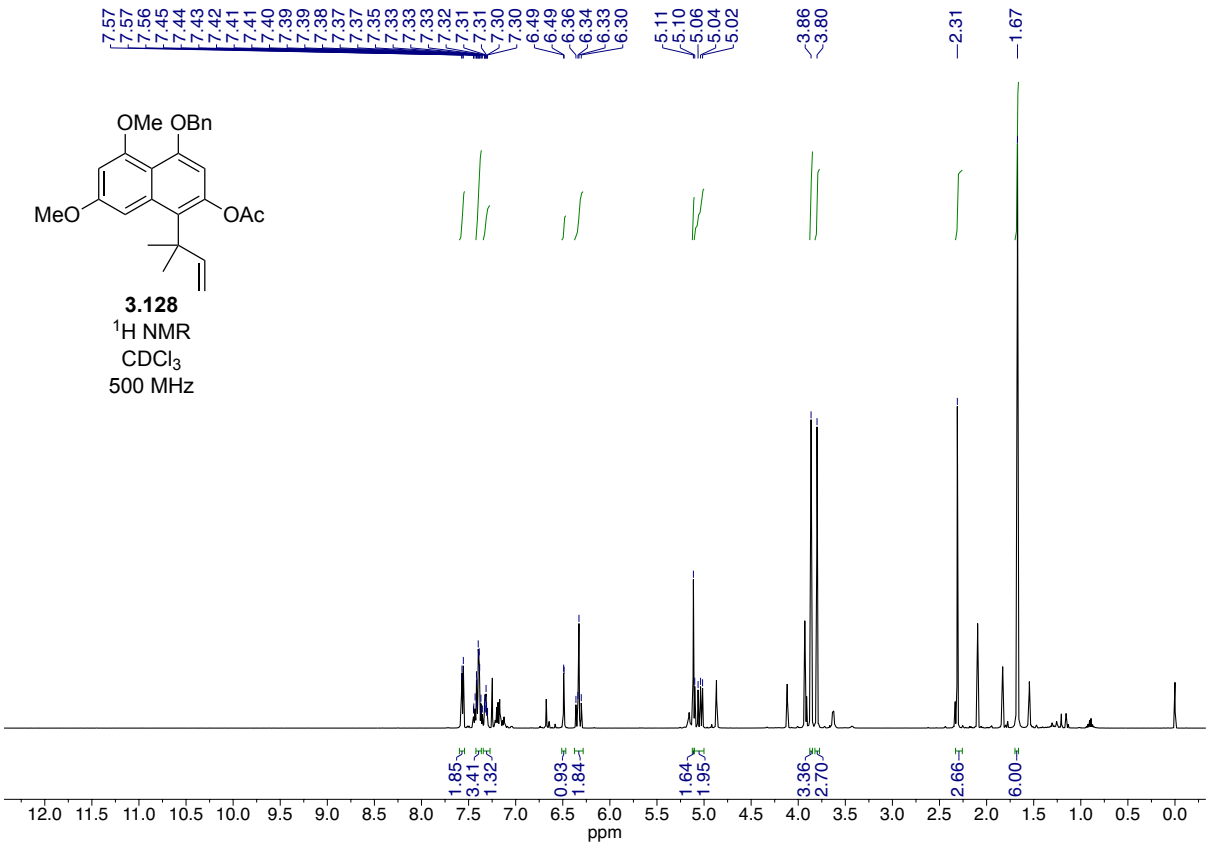
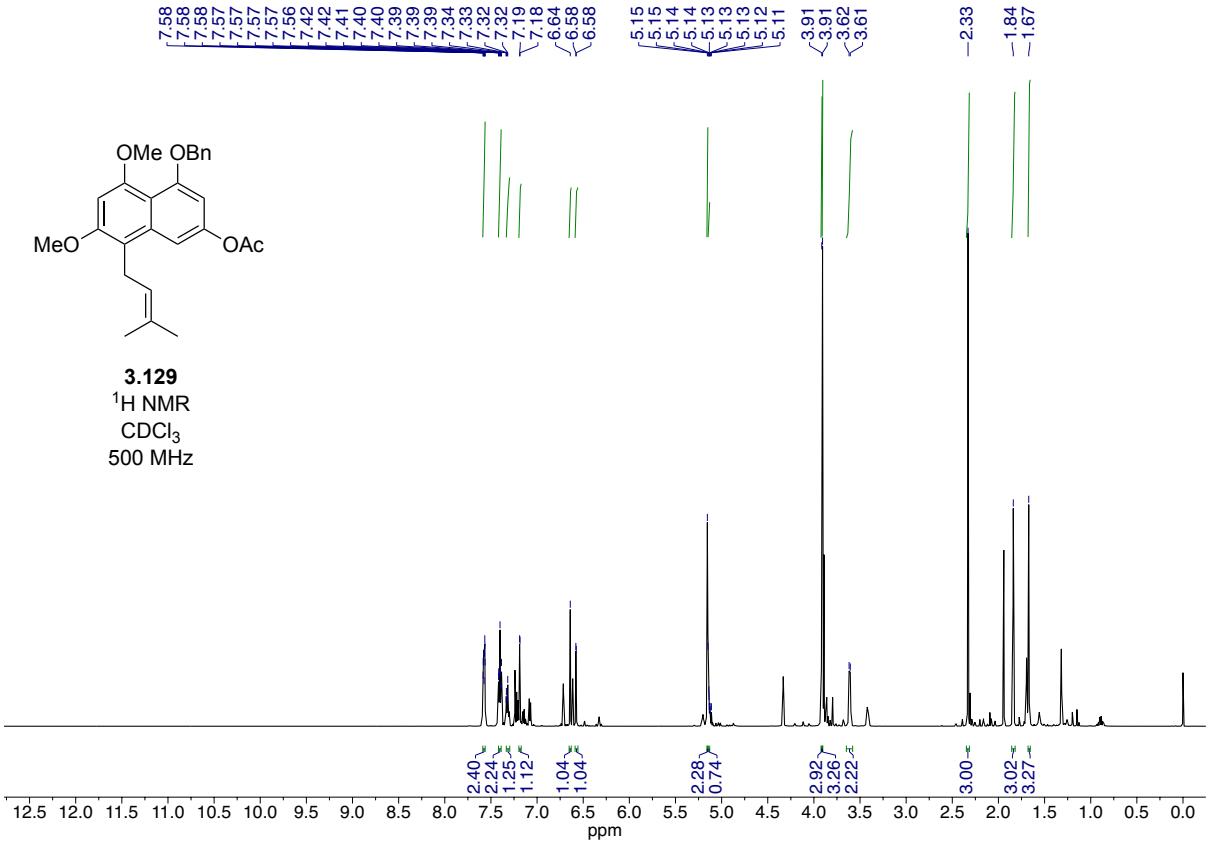
MeO
OH
3.116
HMBC
CDCl3
500 MHz
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm
20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180
f1 (ppm)


OMe OBn
MeO
OAc
3.128
1H NMR
CDCl3
500 MHz
ppm


OMe OBn
MeO
OAc
3.129
1H NMR
CDCl3
500 MHz
ppm

Chapter Four

Progress Towards the Biomimetic Synthesis of Furobinordentatin, Furobiclausarin and Other Related Natural Products

4.1 Introduction

4.1.1 The Coumarin Natural Products Nordentatin, Dentatin and Clausarin

Coumarin natural products are a class of natural compounds that is ubiquitous in nature and is attributed a large range of pharmacological activities.[1] Nordentatin (**4.01**) and dentatin (**4.02**) were first isolated in 1967 from the root bark of *Clausena dentata* (Willd.) R. and S (Figure 4.1).[2] The originally proposed angular structures of nordentatin (**4.01**) and dentatin (**4.02**) were revised in 1970.[3–5] In 1973, Mowat and Murray were able to confirm the revised structure by synthesis.[6]

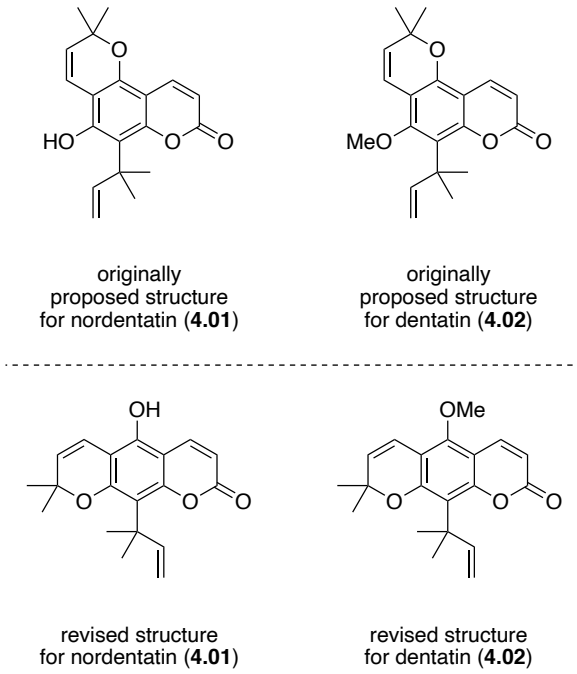
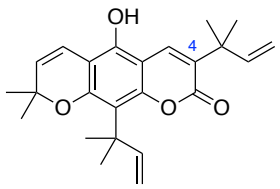


Figure 4.1: Originally proposed and revised structures of nordentatin (4.01) and dentatin (4.02).

Clausarin (**4.03**) was isolated in 1977 from the roots of the citrus plant *Clausena pentaphylla* roots (Figure 4.2).[7] Structurally, it is very similar to nordentatin with an additional reverse prenyl chain on C-4 position.



clausarin
(4.03)

Figure 4.2: Structure of clausarin (4.03).

Nordentatin (**4.01**) and clausarin (**4.03**) have been traditionally used as folk medicine to treat various diseases, such as viral hepatitis, cough, asthma, fever and headache.[8,9] Newer studies showed that both natural products exhibited significant cytotoxic activity against several human cancer cell lines.[10–12] Nordentatin (**4.01**) also exhibited strong suppressive properties on hepatitis B virus surface antigen production in human hepatoma cells.[8]

4.1.2 Isolation of Furobinordentatin and Furobiclausarin

In 1994, the isolation of novel dimeric coumarins furobinordentatin (**4.04**) and furobiclausarin (**4.05**) was reported by the Furukawa group (Figure 4.3).[13,14] Furobinordentatin (**4.04**) was isolated from the root of *Citrus yuko* (Rutaceae). Its structure was firstly assigned by spectroscopic methods and could then be confirmed by single crystal X-ray analysis. The molecule is a dimer of two nordentatin (**4.01**) units. Interestingly, the connecting tetrahydrofuran ring shows a *cis* relationship of three of its protons.[13]

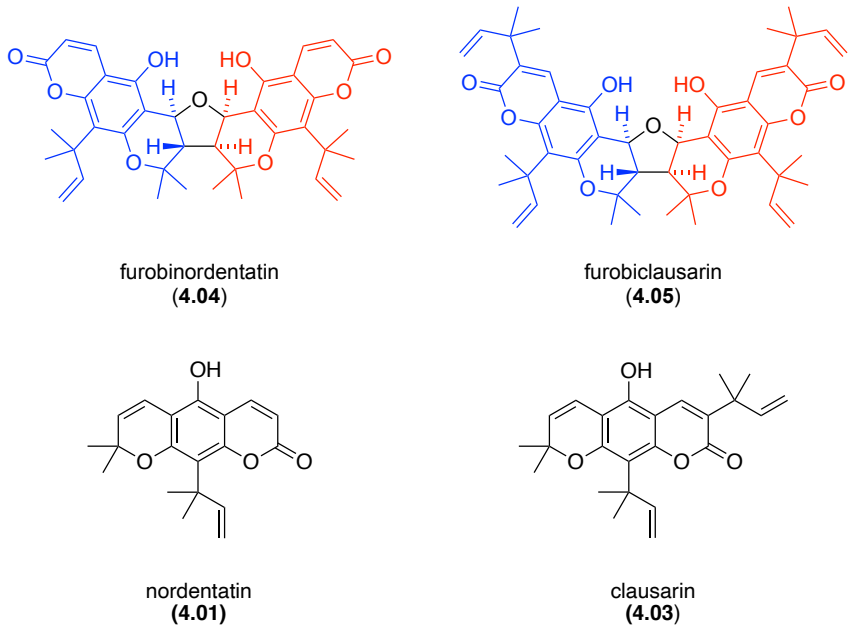


Figure 4.3: Structures of novel pyranocoumarin dimers furbinordentatin (4.04) and furobiclausarin (4.05) and the monomers nordentatin (4.01) and clausarin (4.03).

Furobiclausarin (**4.05**) was isolated in the same year from *Citrus hassaku*.[14] The structure of furobiclausarin (**4.05**) was elucidated by spectroscopic methods. It was assigned to be a dimer of two clausarin (**4.03**) units connected by a tetrahydrofuran ring. The relative configurations of the protons in the tetrahydrofuran moiety were assigned on the basis of *J*-values and NOE experiments.[14] As both, furobinordentatin (**4.04**) and furobiclausarin (**4.05**) do not show any optical rotation, it was suggested that they might be either formed without participation of enzymes or as isolation artifacts.[14]

4.1.3 Isolation of Isolation of Claudimerines-A and -B

In 1996, two more pyranocoumarin dimers claudimerin-A (**4.06**) and claudimerin-B (**4.07**) were isolated from *Citrus hassaku* (Rutaceae) (Figure 4.4).[15]

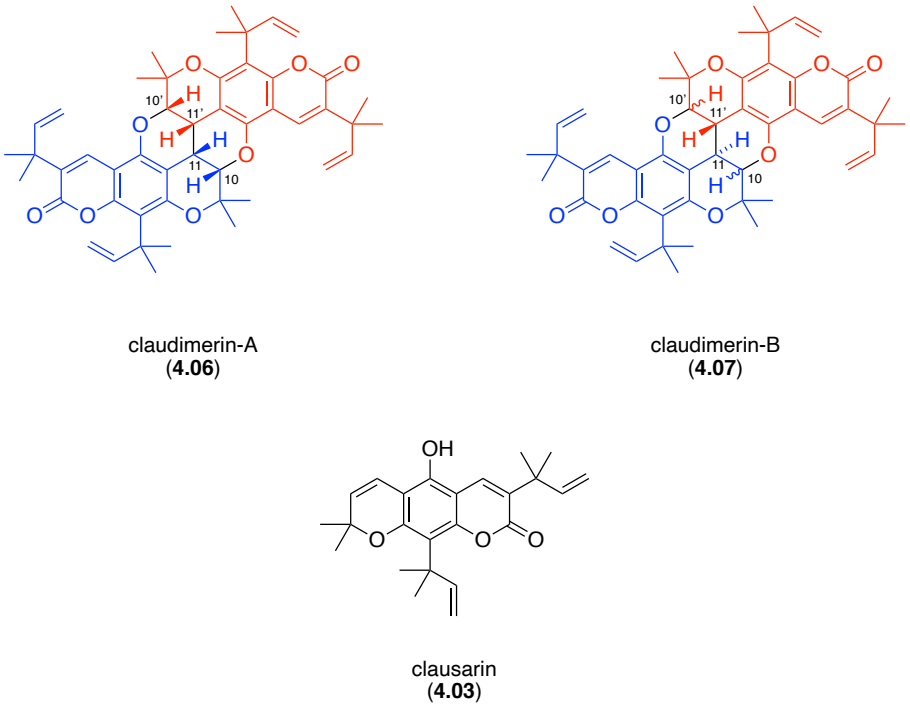


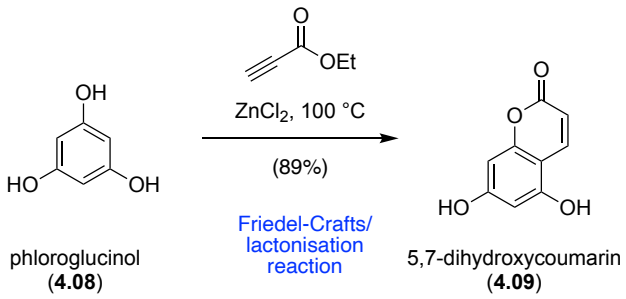
Figure 4.4: Structures of pyranocoumarin dimers claudimerin-A (4.06) and claudimerin-B (4.07) and the monomer clausarin (4.03).

The structure of claudimerin-A (**4.06**) was firstly elucidated by spectroscopic methods and later confirmed by single crystal X-ray analysis. The interesting feature is a pyranopyran ring connecting two clausarin (**4.03**) units. Claudimerin-B (**4.07**) was assigned by spectroscopic methods based on the assignment of claudimerin-A (**4.06**). The main difference was the coupling constants of H-10 and H-11. In claudimerin-A (**4.06**), the *J*-values indicated a *cis*-configuration whereas the *J*-values of claudimerin-B (**4.07**) were much higher indicating a *cis*/*trans* orientation between the four protons. From the NOE experiments, it remained unclear whether claudimerin-B (**4.07**) showed a *trans-trans-trans* or a *cis-trans-trans* configuration at the connection.[15] Both claudimerin-A (**4.06**) and claudimerin-B (**4.07**) lack optical activity which leaves the assumption they might be isolation artifacts or are formed in the plant cells without the participation of enzymes.

4.1.4 Previous Work on the Synthesis of Nordentatin and Clausarin

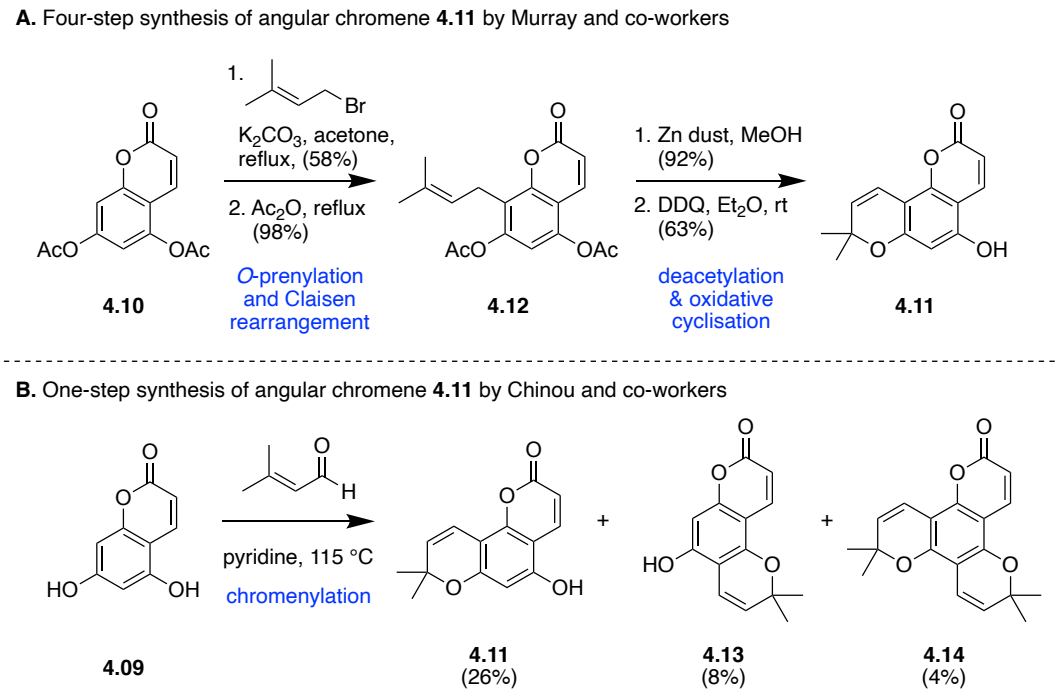
Neither of the dimeric natural products **4.04** to **4.07** have been synthesised to date. However, several syntheses of the monomeric units, nordentatin (**4.01**) and clausarin (**4.03**), have been published so far.

The first step of the synthesis, the tandem Friedel-Crafts/lactonization reaction of phloroglucinol (**4.08**) with ethyl propiolate, was reported by Kaufman and Kelly in 1965 (Scheme 4.1).[16]



Scheme 4.1: Synthesis of 5,7-dihydroxycoumarin (4.09) from phloroglucinol (4.08) by Kaufman and Kelly.[16]

Murray and co-workers reported the transformation of acetylated coumarin **4.10** to angular chromene **4.11** in four steps in their total synthesis of several coumarin natural products (Scheme 4.2, **A.**).[17,18] Acetylated coumarin was *O*-prenylated in 58% yield with prenyl bromide and potassium carbonate at reflux. The intermediate readily underwent Claisen rearrangement in acetic anhydride at reflux to give *para*-rearrangement product **4.12** in almost quantitative yields. Deacetylation with zinc dust in methanol and oxidative cyclisation gave angular chromene **4.11** in good yields.

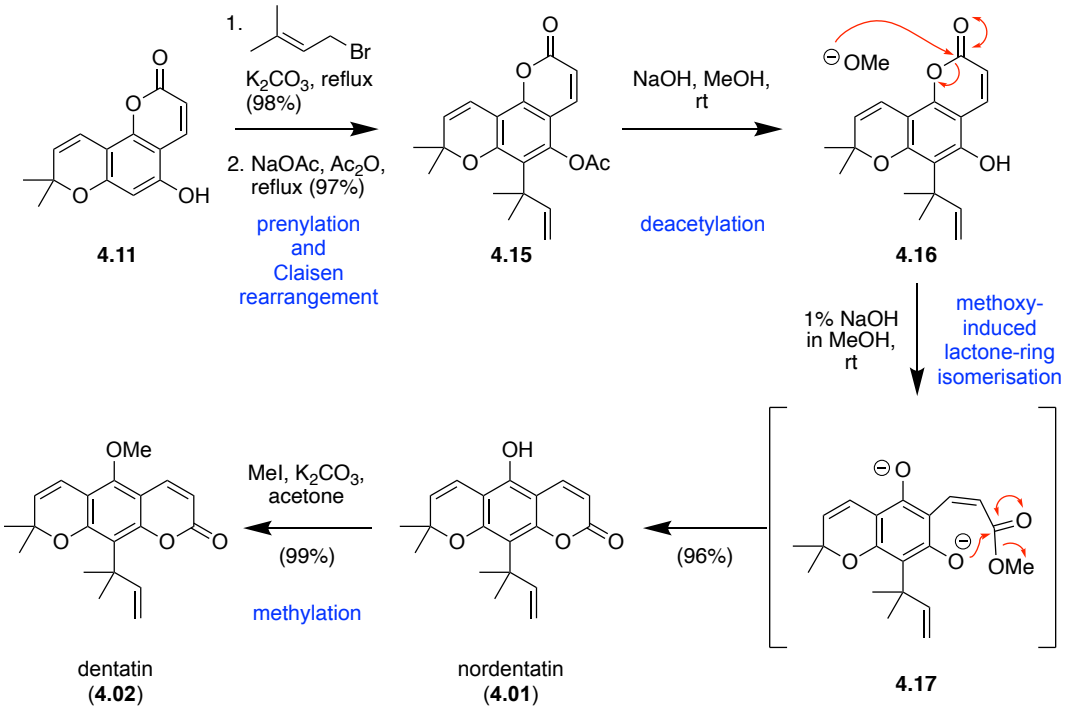


Scheme 4.2: A. Four-step synthesis of chromene 4.11 by Murray and co-workers.[17,18] B. One-step procedure by Chinou and co-workers.[19]

More recently in 2005, a one-step procedure from 5,7-dihydroxycoumarin (**4.09**) to chromene **4.11** was reported by Chinou and co-workers (Scheme 4.2, **B.**).[19] The group performed chromenylation of dihydroxycoumarin **4.09** with 3-methyl-2-butenal in pyridine at 115 °C affording desired chromene in 26% yield alongside linear chromene **4.13** and dichromenylated compound **4.14**. Although the yield of this reaction was modest, this procedure minimised the step count to one.

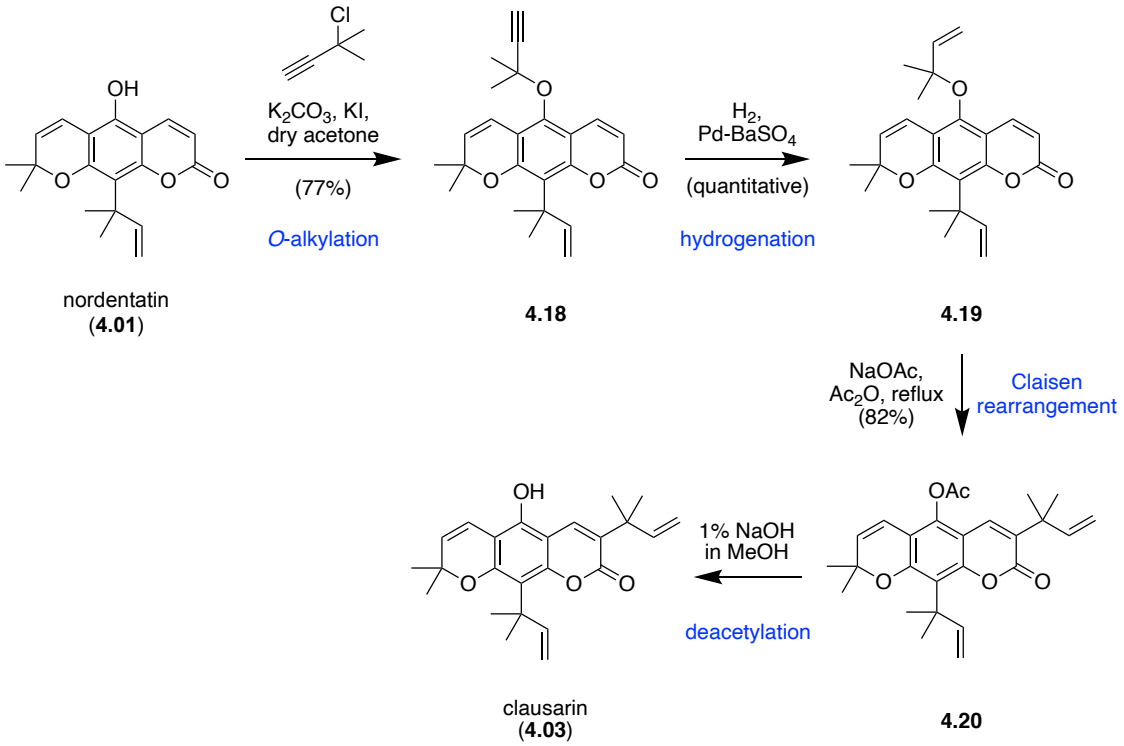
Building on the synthesis of chromene **4.11**, the first total synthesis of nordentatin (**4.01**) and dentatin (**4.02**) was published in 1983 by Murray and co-workers (Scheme 4.3).[17,20] First, chromene **4.11** was *O*-prenylated with prenyl bromide and potassium carbonate at reflux. The intermediate underwent Claisen rearrangement to *ortho*-rearrangement product **4.15** in the presence of NaOAc and acetic anhydride. Deacetylation with sodium hydroxide in methanol

gave hydroxy compound **4.16** which could then undergo lactone-ring isomerisation through intermediate **4.17** to afford nordentatin (**4.01**) in excellent yields. *O*-methylation of nordentatin (**4.01**) with iodomethane gave dentatin (**4.02**) in quantitative yields.



Scheme 4.3: Synthesis of nordentatin (4.01) and dentatin (4.02) from 4.11 by Murray and Jorge.

In the same paper, Murray and co-workers also reported the synthesis of clausarin (**4.03**) from nordentatin (**4.01**) (Scheme 4.4). Nordentatin (**4.01**) was alkylated with 3-chloro-3-methylbut-1-yne to give ether **4.18** which was partially hydrogenated in the following step *via* a Rosenmund reduction. Reverse prenylated **4.19** then underwent Claisen rearrangement to acetylated clausarin **4.20**. Deprotection in 1% NaOH in methanol gave the natural product clausarin (**4.03**). The group did not report a yield for the last step.



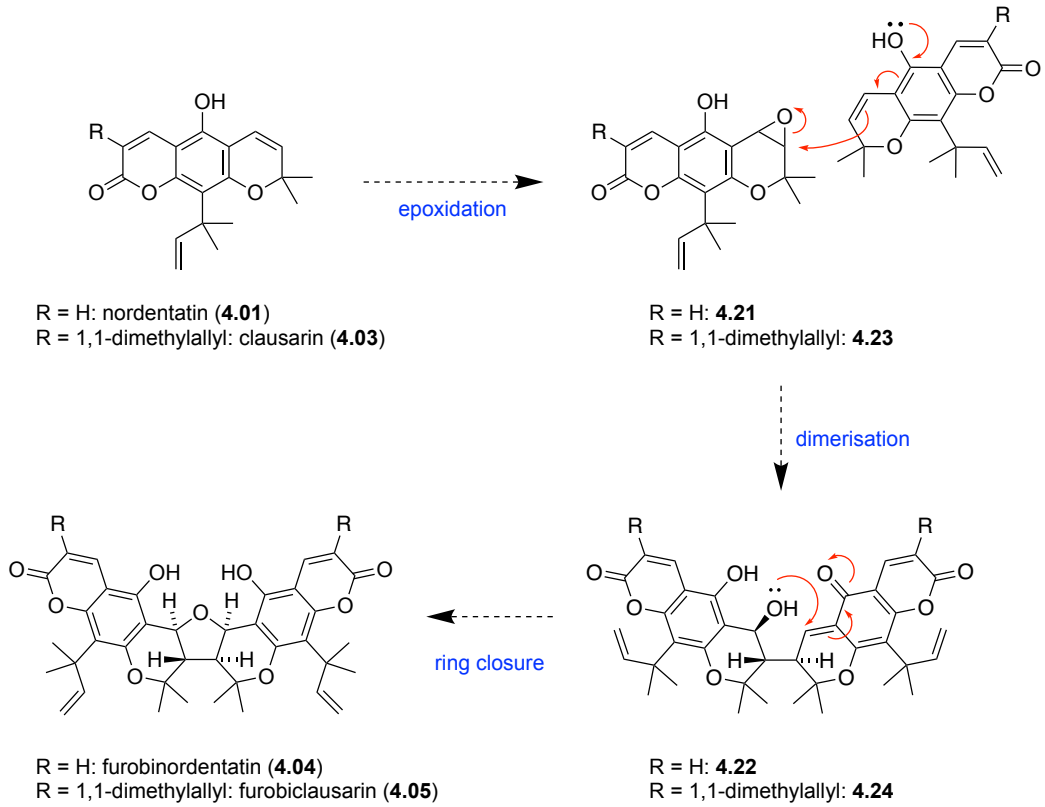
Scheme 4.4: Total synthesis of clausarin (4.03) from nordentatin (4.01) in 5 steps by Murray and co-workers.

4.1.5 Proposed Biosynthesis of the Dimeric Natural Products Furobinordentatin and Furobiclausarin

We propose that there are two possible pathways in nature to form the dimeric natural products; one going *via* epoxidation of the chromene double bond and the other one going *via* a radical pathway.

Our proposed epoxidation mechanism (shown in Scheme 4.5) commences with epoxidation of the chromene double bond of nordentatin (**4.01**) to **4.21** which is immediately followed by nucleophilic attack of a second nordentatin (**4.01**) unit to form dimeric *ortho*-quinone methide intermediate **4.22**. We believe that the attack would take place in the less electrophilic position

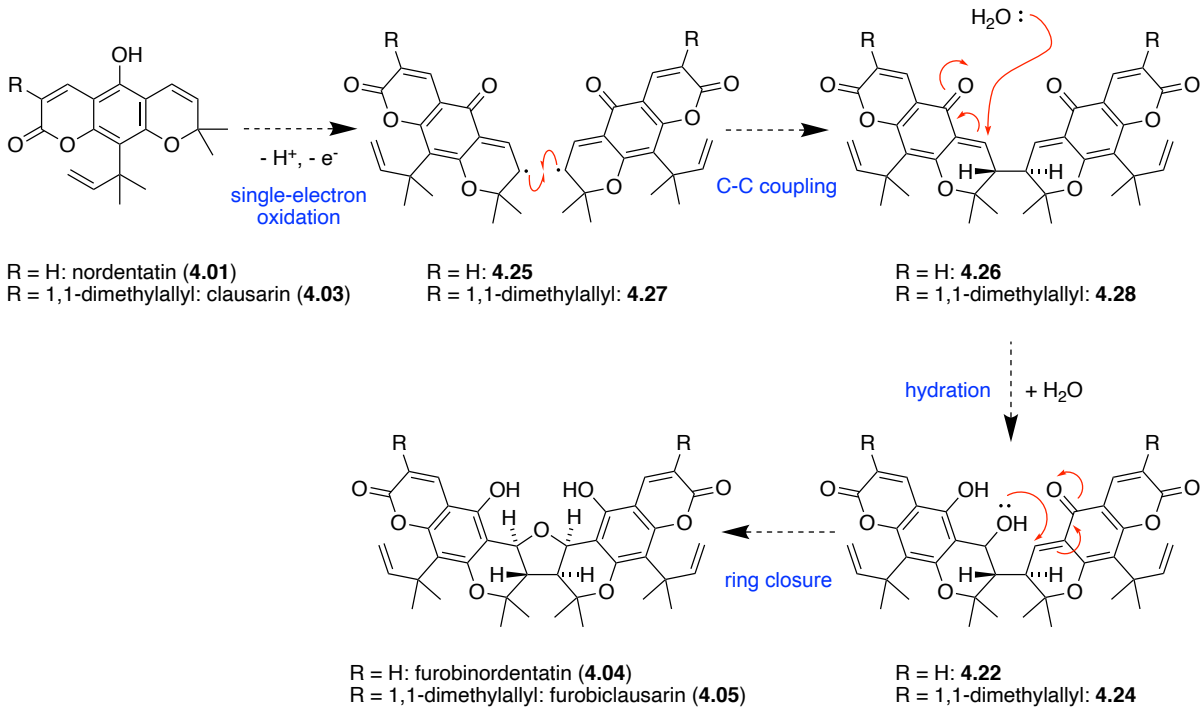
of the epoxide as it is sterically more accessible. The C-1 hydroxyl group could then attack the Michael system forming the desired tetrahydrofuran connection of furobinordentatin (**4.04**). Analogous to the dimerisation of nordentatin would be the dimerisation of clausarin (**4.03**) to furobiclausarin (**4.05**) (Scheme 4.5).



Scheme 4.5: Proposed mechanism of the formation of furobinordentatin (4.04) and furobiclausarin (4.05) through the epoxide pathway.

An alternative biosynthetic pathway would go through a radical mechanism (Scheme 4.6). Single-electron oxidation of nordentatin (**4.01**) would give highly persistent radical species **4.25** which could then undergo C-C coupling with another radical. Nucleophilic attack of water on the Michael system would form the same *ortho*-quinone methide intermediate **4.22** as in the former pathway. **4.22** could cyclise forming the tetrahydrofuran moiety of furobinordentatin

(**4.04**). The mechanism for the formation of furobiclausarin (**4.05**) from clausarin (**4.03**) would follow the same pathway.

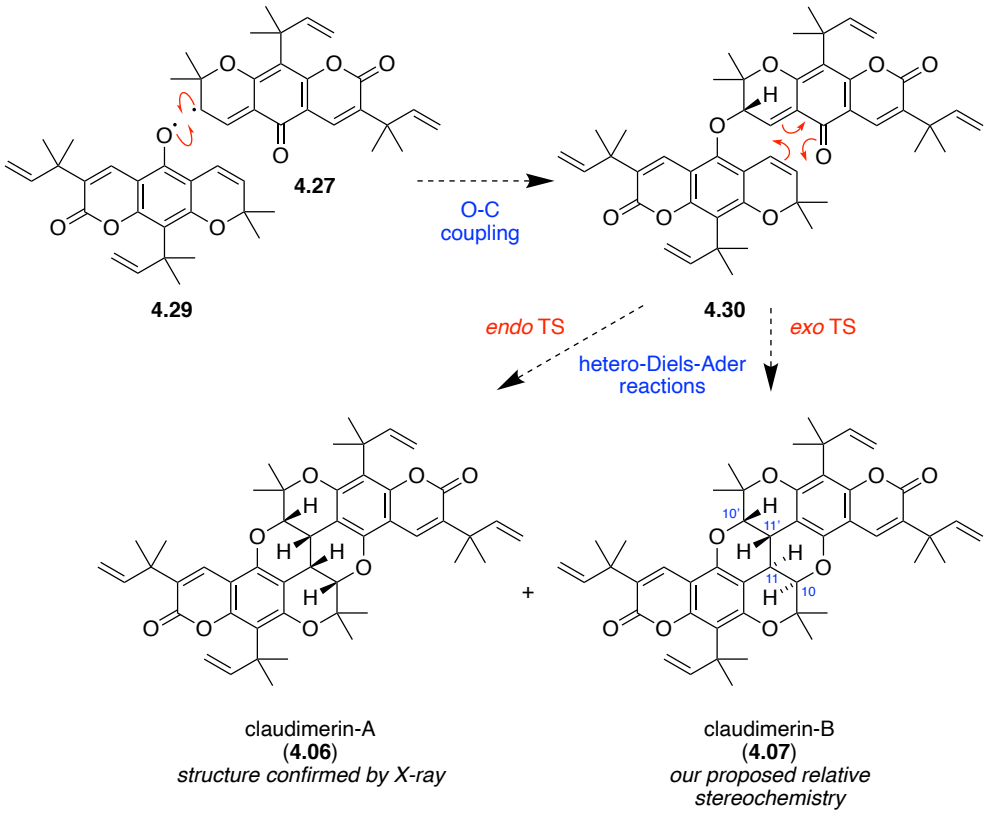


Scheme 4.6: Radical mechanism for dimerisation of nordentatin (4.01) and clausarin (4.03) to furobinordentatin (4.04) and furobiclausarin (4.05), respectively.

4.1.6 Proposed Biosynthesis of the Dimeric Natural Products Claudimerines-A and -B

Similar to the second proposed biosynthetic pathway of furobinordentatin (**4.04**) and furobiclausarin (**4.05**), we believe that single-electron oxidation of clausarin (**4.03**) would give the two radical species **4.27** and **4.29** which are in resonance with each other (Scheme 4.7). They could undergo O-C coupling to intermediate **4.30**. Intramolecular *hetero*-Diels-Alder reaction of the *ortho*-quinone methide with the chromene alkene gives claudimerines-A (**4.06**)

and -B (**4.07**). Based on the two possible transition states, we propose the relative stereochemistry of H-10 and H-10' of claudimerin-B (**4.07**) to be down and up, respectively.

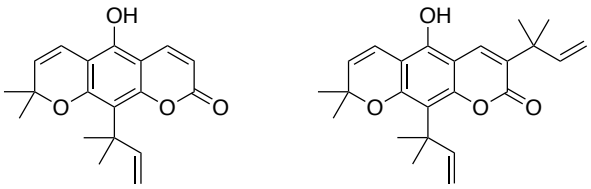


Scheme 4.7: Proposed dimerisation of clausarin to claudimerines-A (4.06) and -B (4.07) and our putative assignment of H-10 and H-10'.

4.1.7 Project Aims

The primary objective of this project was to develop a biomimetic total synthesis of the dimeric natural products, furobinordentatin (**4.04**), furobiclausarin (**4.05**) and claudimerines-A (**4.06**) and -B (**4.07**).

To achieve this, it was desirable to synthesise the monomers nordentatin (**4.01**) and clausarin (**4.03**) (Figure 4.5), and investigate oxidative dimerisation reactions.



nordentatin
(**4.01**)

clausarin
(**4.03**)

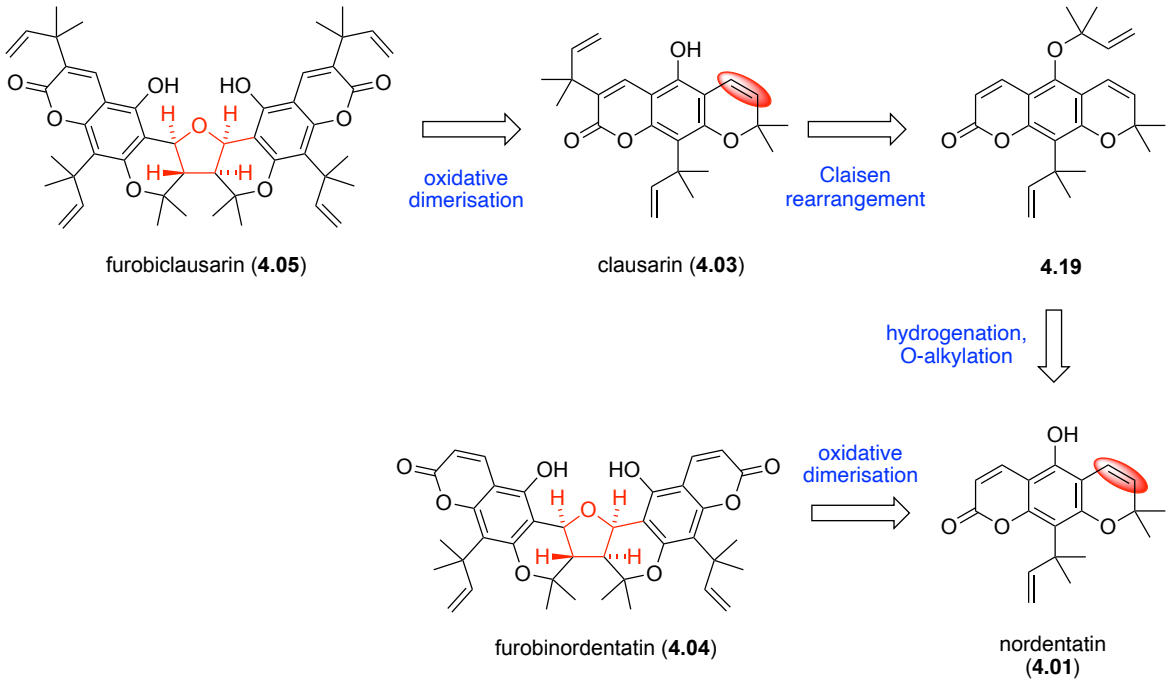
Figure 4.5: Synthetic targets nordentatin (4.01) and clausarin (4.03).

We were curious to explore the reactivity of both monomers under epoxidation and radical oxidation conditions. Ideally, one of the pathways would lead to the formation of the dimeric natural products furobinordentatin (**4.04**), furobiclausarin (**4.05**) and/or claudimerines-A (**4.06**) and -B (**4.07**).

4.2 Results and Discussion

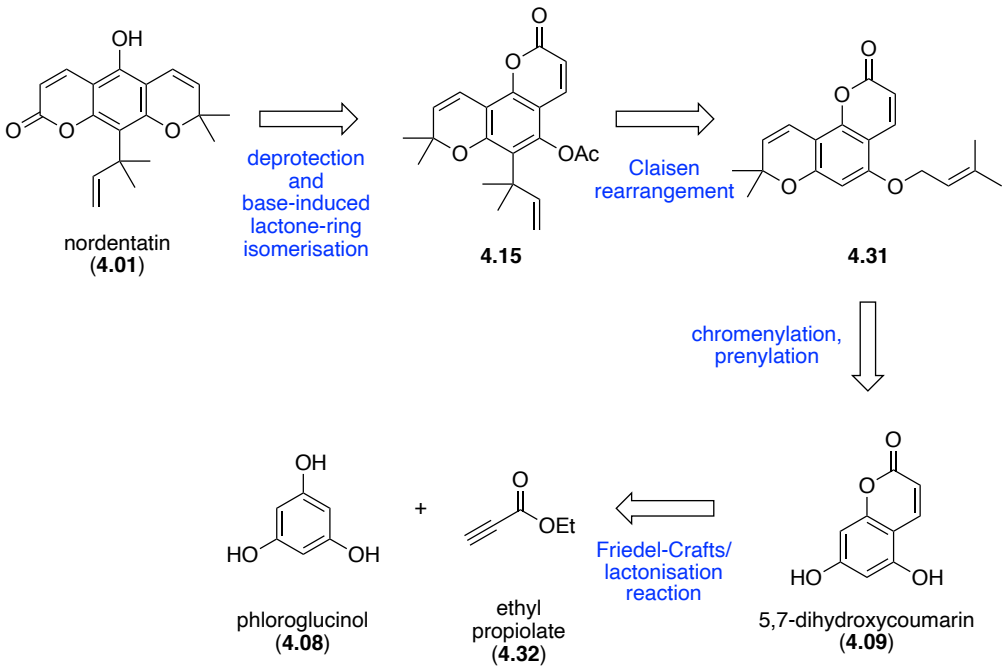
4.2.1 Retrosynthetic Analysis of Furobinordentatin and Furobiclausarin

Furobinordentatin (**4.04**) and furobiclausarin (**4.05**) are both unique examples of pyranocoumarin dimers, hence, there is only little literature precedents for the synthesis of such compounds. Looking at the connecting tetrahydrofuran moiety (shown in red), we devised our retrosynthetic analysis for both natural products (Scheme 4.8). Key step of our synthesis would be the oxidative dimerisation of nordentatin (**4.01**) and clausarin (**4.03**) to furobinordentatin (**4.04**) and furobiclausarin (**4.05**), respectively. We envisaged that we could selectively oxidise the chromene alkene of one monomer unit (**4.01** or **4.03**) and promote dimerisation with another unit.



Scheme 4.8: Retrosynthetic analysis of the bicoumarins, furobinordentatin (4.04) and furobiclausarin (4.05).

Both monomers, clausarin (**4.03**) and nordentatin (**4.01**), have been synthesised in the past by Murray and Jorge.[20,21] It was envisioned that clausarin (**4.03**) could be obtained from **4.19** *via* two consecutive Claisen rearrangements. **4.19** could be synthesised *via* *O*-alkylation of nordentatin (**4.01**) with 3-chloro-3-methylbut-1-yne and partial hydrogenation of the triple bond with Rosenmund's catalyst. The biosynthetic precursor nordentatin (**4.01**) could be prepared following literature-known procedures (Scheme 4.9).[16,20,21]

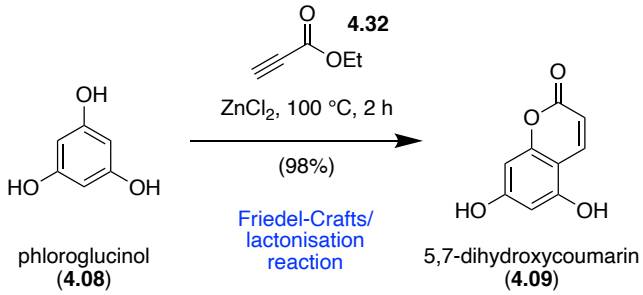


Scheme 4.9: Retrosynthetic analysis of nordentatin (4.01).

First, nordentatin (**4.01**) could be made from **4.15** by deprotection of the acetate and methoxide-mediated lactone rearrangement. Claisen rearrangement of *O*-prenylated **4.31** would give **4.15**. Chromenylation and *O*-prenylation of 5,7-dihydroxycoumarin (**4.09**) would yield **4.31**. Intermediate 5,7-dihydroxycoumarin (**4.09**) could be easily accessed from readily available phloroglucinol (**4.08**) following a procedure by Kaufman and Kelly.[16]

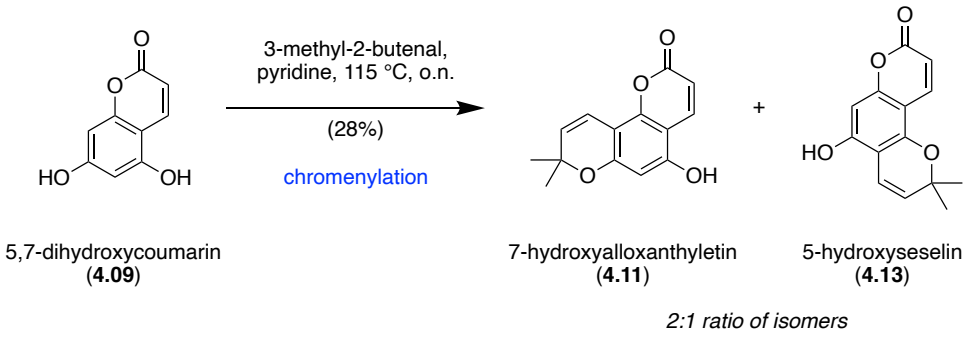
4.2.2 Synthesis of Nordentatin

The first step in the synthesis of nordentatin (**4.01**) was the formation of 5,7-dihydroxycoumarin (**4.09**) by condensation of commercially available phloroglucinol (**4.08**) with ethyl propiolate (**4.32**) in almost quantitative yields following a procedure from 1965 (Scheme 4.10).[16]



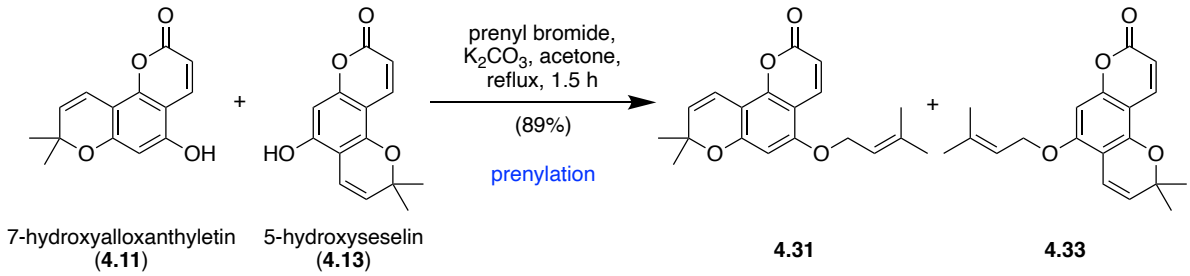
Scheme 4.10: Synthesis of 5,7-dihydroxycoumarin (4.09) from phloroglucinol (4.08) and ethyl propiolate (4.32) in 98% yield.

The following step was the chromenylation of 5,7-dihydroxycoumarin (**4.09**) with 3-methyl-2-butenal (Scheme 4.11). As previously reported in literature both possible chromenylation products, 7-hydroxyalloxanthyletin (**4.11**) and 5-hydroxyseselin (**4.13**), as well as the dialkylated product (not shown) were formed during this reaction which resulted in the relative modest yields of the desired compound.[20,22] Although both chromenylation products **4.11** and **4.13** could be separated and isolated by flash column chromatography their very similar R_f values caused it to be an extremely difficult separation. Fortunately, we discovered that it did not affect the overall yields of the following steps if we carried through the mixture of isomers instead of isolating the desired chromene **4.11**.



Scheme 4.11: Chromenylation of 5,7-dihydroxycoumarin (4.09) with 3-methyl-2-butenal.

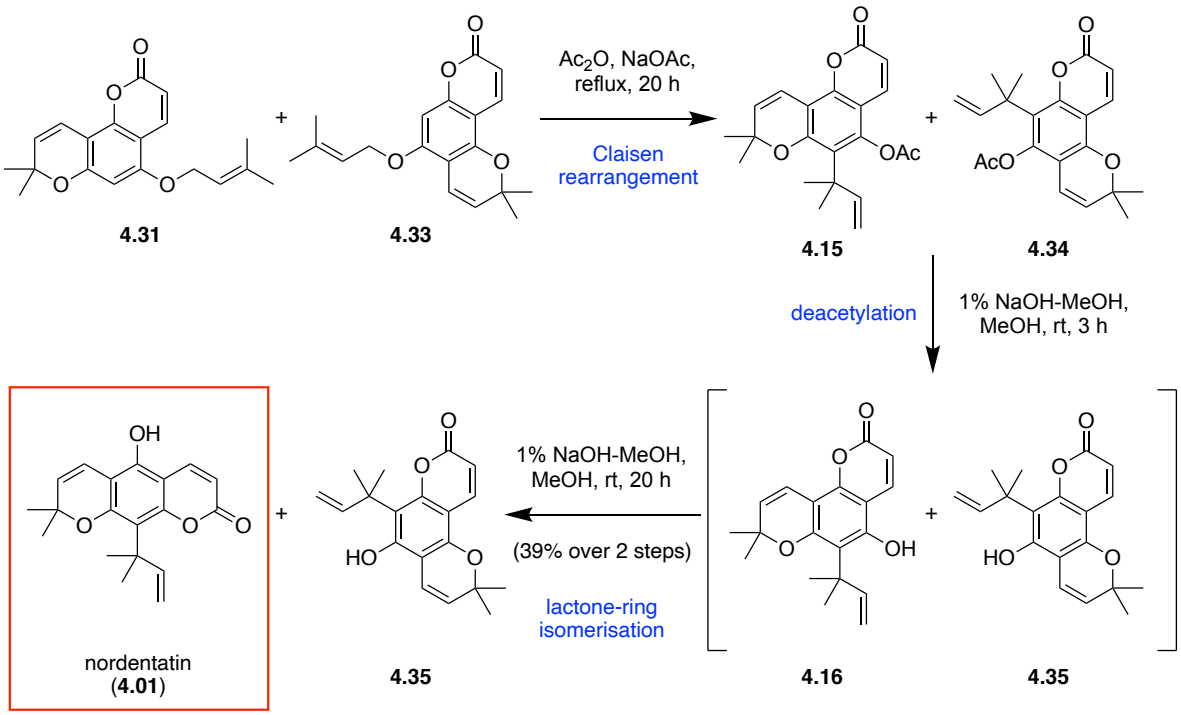
Prenylation of the isomeric mixture (**4.11** and **4.13**) with prenyl bromide gave the two prenylated pyranocoumarins **4.31** and **4.33** in 89% yield (Scheme 4.12). Again, the mixture was taken through to the next step without separating the two chromenes.



Scheme 4.12: Prenylation of the chromene mixture (4.11 and 4.13) in 89% yield.

Next, the mixture of isomers was heated at reflux with sodium acetate in acetic anhydride for 24 h to give both acetylated intermediates **4.15** and **4.34** through Claisen rearrangement of the prenyl side chain (Scheme 4.13). The reaction mixture was filtered, the solvent was removed *in vacuo* and the crude reaction mixture was used in the following step without the need for further purification. Subjecting the crude acetylated compounds **4.15** and **4.34** to sodium hydroxide in methanol led, first, to deacetylated intermediates **4.16** and **4.35**. Then, the angular chromene **4.16**, spontaneously, underwent methoxide-mediated lactone-ring isomerisation to the thermodynamically more stable isomer nordentatin (**4.01**). As the linear chromene **4.35** was

not able to perform the same rearrangement, it remained as the deacetylated intermediate **4.35**. In this step, the R_f values of the two compounds were different enough to allow quick and effective separation by flash column chromatography on silica gel. The desired compound nordentatin (**4.01**) was yielded in 39% over 2 steps. The undesired side product **4.35** was not isolated.



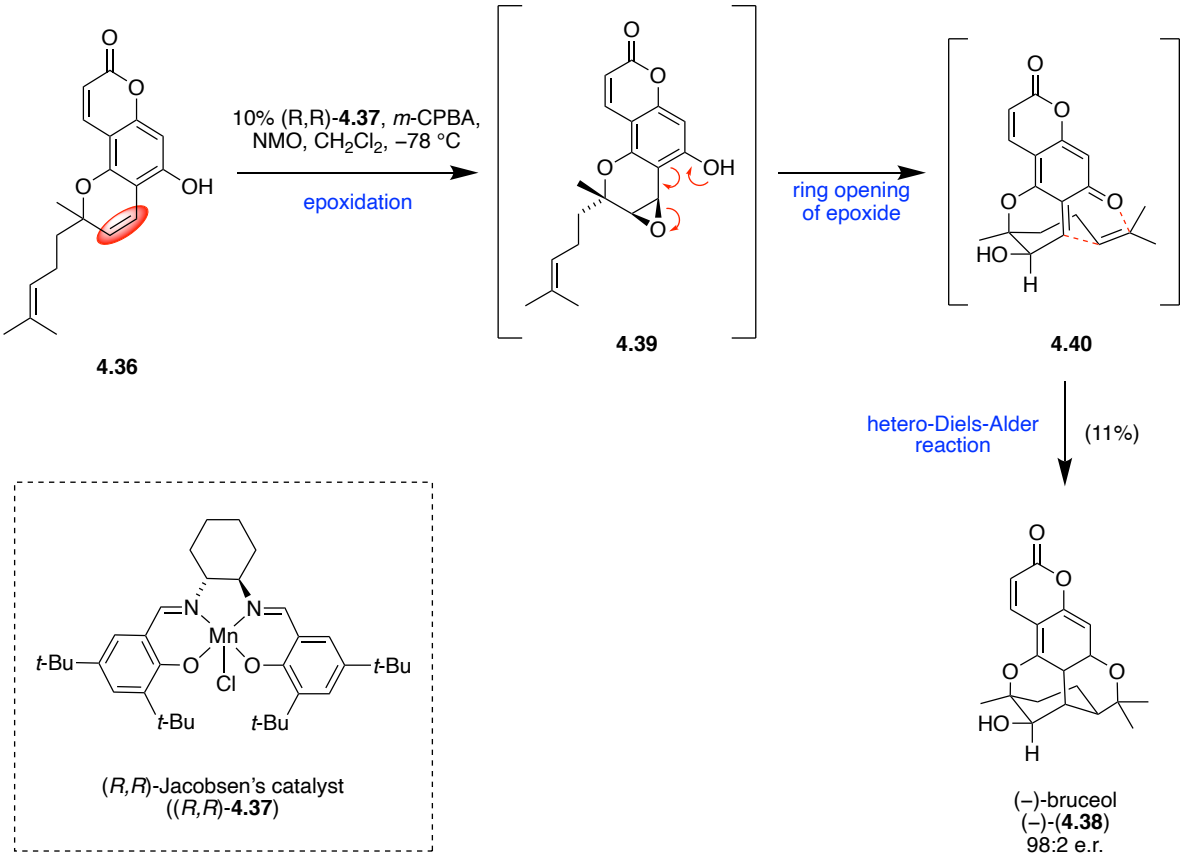
Scheme 4.13: Synthesis of nordentatin (4.01) in 39% yield over two steps.

With good quantities of nordentatin (**4.01**) in hand, we started to investigate the oxidative dimerisation reaction.

4.2.3 Attempted Oxidative Dimerisation *via* Epoxidation of Nordentatin

The first oxidation pathway we were intrigued to investigate was the dimerisation *via* epoxidation of one nordentatin (**4.01**) unit. When searching for suitable epoxidation conditions,

we were aware that the system showed three alkenes that could potentially react. Hence, it was essential to choose the right epoxidation agent. In 2019, our group reported the selective epoxidation of a chromene alkene of a similar system **4.36** with *m*-CPBA and Jacobsen's catalyst (**4.37**) (Scheme 4.14).[23] In the biomimetic total synthesis of bruceol (**4.38**), chromene **4.36** was selectively epoxidized to intermediate **4.39** which immediately ring opened and underwent a hetero-Diels-Alder reaction to form the natural product (–)-bruceol (**4.38**).

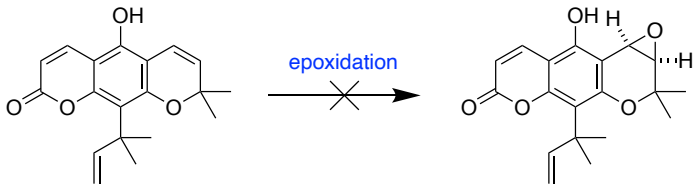


Scheme 4.14: Epoxidation of 4.36 with (*R,R*)-Jacobsen's catalyst and *m*-CPBA in the biomimetic total synthesis of (–)-bruceol (4.38).[23]

Jacobsen-type catalysts are known for their selectivity for electron rich *cis*-alkenes.[24,25] Hence, we were optimistic that we could use these conditions to selectively epoxidise the

chromene alkene unit while leaving the other double bonds untouched. Our attempted epoxidations are summarised in Table 4.1.

Table 4.1: Attempted epoxidation with *m*-CPBA.



nordentatin (**4.01**) **4.21**

Entry	Oxidant	Reaction conditions	Outcome
1	*m*-CPBA, (*R*,*R*)-Jacobsen's cat. (**4.37**), NMO	CH_2Cl_2, –78 °C, 50 min	complex mixture of compounds
2	*m*-CPBA	CH_2Cl_2, 0 °C, 2 h	no reaction
3	*m*-CPBA	CH_2Cl_2, rt, 3 h	residual s.m., complex mixture of compounds
4	*m*-CPBA	CH_2Cl_2, rt, o.n.	decomposition

*Unless otherwise specified, the outcome was determined by TLC analysis, rt room temperature, o.n. overnight, s.m. starting material.

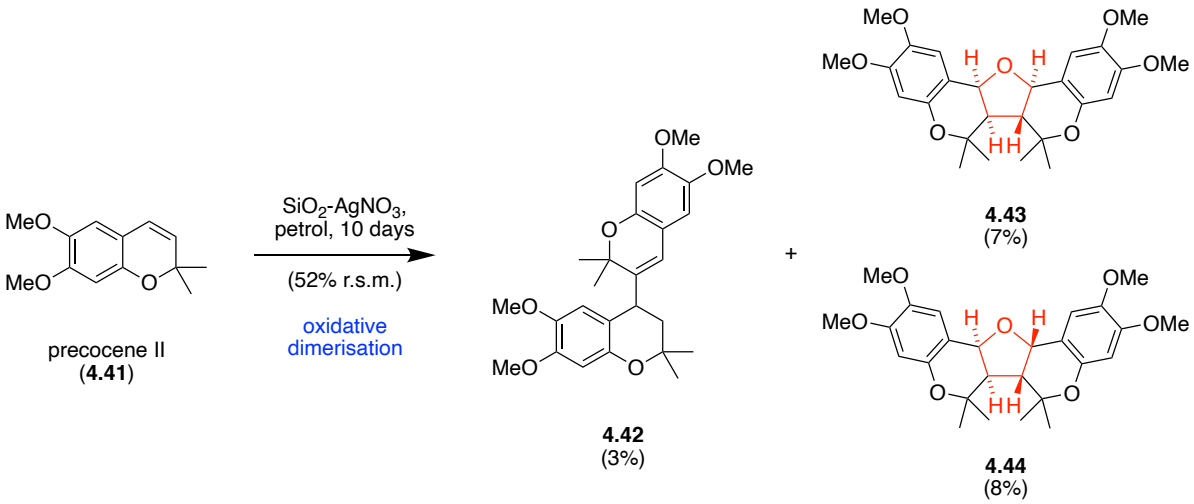
Unfortunately, when exposing nordentatin (**4.01**) to *m*-CPBA and (*R*,*R*)-Jacobsen's catalyst (**4.37**), TLC analysis showed one big streak from the baseline containing several more visible spots. Although we attempted to isolate these compounds by flash column chromatography, it was impossible to identify distinct species; even after several attempts of the reaction and different solvent systems for the purification (entry 1). Next, we attempted the epoxidation reaction with *m*-CPBA alone, as one of the impurities we struggled to remove from the reaction mixture was the remaining catalyst. Hence, nordentatin (**4.01**) was treated with the peroxide in CH_2Cl_2 at 0 °C for 2 h but no reaction occurred (entry 2). When we repeated the reaction with *m*-CPBA at room temperature, TLC analysis indicated the formation of a complex mixture of

compounds (entry 3). After purification by flash column chromatography, we were able to isolate one spot that, upon ^{1}H NMR analysis, showed an inseparable 1:1 mixture of two compounds. Even though the chemical shift and the coupling constants of one of these compounds seemed promising and indicated the formation of the desired epoxide, we were not able to purify the compound or increase the yield any further. In a last attempt, we left the reaction stirring in CH_2Cl_2 at room temperature overnight which led to full decomposition of the starting material (entry 4).

Due to the poor yield and inseparable impurities, we decided that this synthetic pathway was not viable. Hence, we shifted our focus towards other ways to achieve the desired dimerisation reaction.

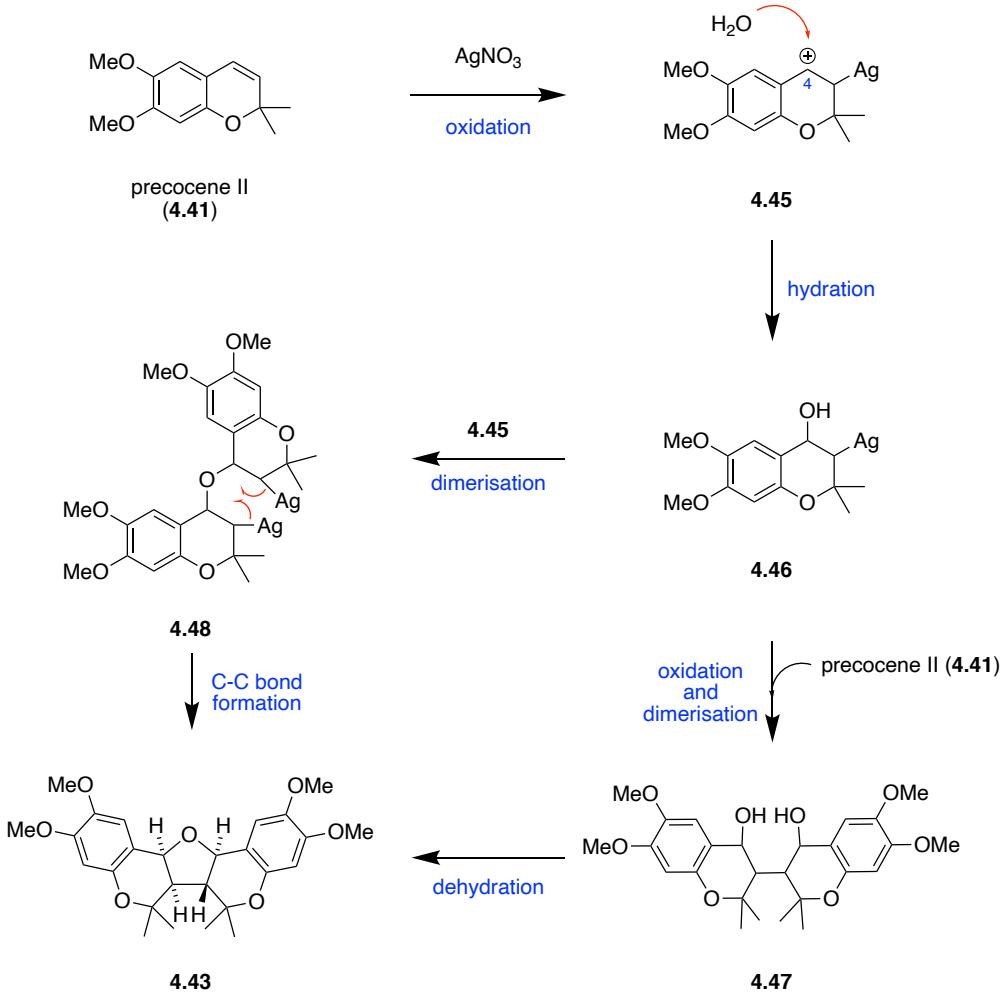
4.2.4 Attempted Oxidative Dimerisation of Nordentatin with $AgNO_3$ and $FeCl_3$

In 1983, Fraga and co-workers reported the unintended isolation of three novel dimerisation products of precocene II (**4.41**) (Scheme 4.15).[26] These dimeric products, two of them containing a tetrahydrofuran ring, were formed while the group attempted to purify the monomer, precocene II (**4.41**), *via* flash column chromatography on silica gel impregnated with 20% silver(I) nitrate. The group was able to obtain the same experimental results by using iron(III) chloride.[27,28]



Scheme 4.15: Formation of dimeric compounds 4.42, 4.43 and 4.44 from precocene II (4.41) with silver nitrate and silica gel by Fraga and co-workers.[26]

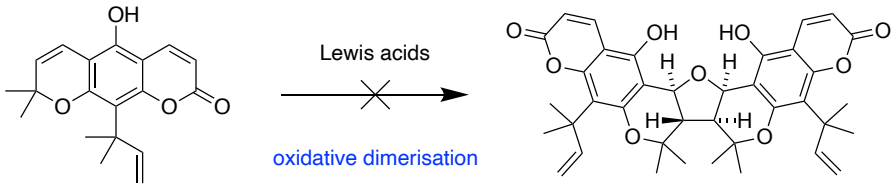
The group proposed the following mechanism (Scheme 4.16): Precocene II (**4.41**) first forms a complex with the Lewis acid, $AgNO_3$, generating a benzylic carbocation at the C-4 position (intermediate **4.45**). The cation acts as an electrophile, either being attacked by another precocene II (**4.41**) molecule (pathway not shown) or being attacked by water to form organometallic species **4.46**. It was then proposed that intermediate **4.46** either undergoes a second single electron oxidation followed by dimerisation with another precocene II (**4.41**) unit to form **4.47**. Dehydration gives desired dimer **4.43**. Alternatively, organometallic species **4.46** reacts with another carbocation **4.45** to form intermediate **4.48** which forms a new C-C bond after losing silver.



Scheme 4.16: Proposed mechanism of Lewis acid-mediated dimerisation reaction of precocene II (4.41) by Fraga *et al.*[26]

These results seemed very promising as the reported system shows striking similarities to our target molecule including the right relative stereochemistry on the tetrahydrofuran moiety. The attempted dimerisation conditions are listed in Table 4.2.

Table 4.2: Attempted dimerisation reaction with silver(I) nitrate and iron(III) chloride.



nordentatin (**4.01**) furobinordentatin (**4.04**)

Entry	Oxidant	Reaction conditions[#]	Outcome[*]
1	20% $AgNO_3$ in silica	petrol, rt, 10 days	no reaction
2	20% $AgNO_3$ in silica	petrol, 40 °C, 2 days	no reaction
3	20% $AgNO_3$ in silica	toluene, reflux, 1 h	slow decomposition
4	$FeCl_3$	acetic acid, rt, 4.5 h	undesired oxidation on reversed prenyl chain
5	$FeCl_3$	acetic anhydride, rt, 3 h	undesired oxidation on reversed prenyl chain
6	$FeCl_3$ (10 mol%), DDQ (1.2 eq.)	toluene, rt, o.n.	undesired oxidation on reversed prenyl chain

[*]Unless otherwise specified outcomes are indicated by TLC analysis, [#]rt room temperature, o.n. overnight.

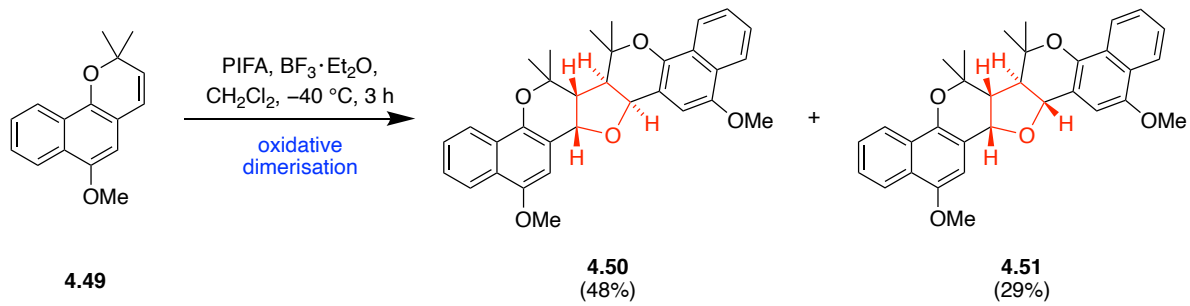
Firstly, the reaction conditions reported by Fraga and co-workers with 20% silver nitrate impregnated silica in petrol were attempted (entry 1). After leaving the reaction mixture for 10 days, no reaction was observed. As a second attempt (entry 2), the reaction mixture was heated at 40 °C for 2 days. Again, TLC analysis only showed starting material. When heating the reaction mixture to reflux temperature in toluene, the starting material nordentatin (**4.01**) started to decompose within 1 h without indicating the formation of any new species (entry 3). The following three entries summarise our attempted oxidative dimerisation with iron(III) chloride. In entry 4, nordentatin (**4.01**) was treated with iron(III) chloride in acetic acid at room temperature. After 4.5 h, TLC analysis indicated the formation of a new compound which was consequently isolated and purified by flash column chromatography on silica gel.

Unfortunately, analysis by ^{1}H NMR spectroscopy indicated that oxidation occurred on the prenyl side chain rather than on the chromene unit of nordentatin (**4.01**). As this was an undesired outcome, the side product was not further assigned. The same result was observed when subjecting nordentatin (**4.01**) to iron(III) chloride in acetic anhydride (entry 5). As a third attempt, nordentatin (**4.01**) was reacted with a catalytic amount of iron(III) chloride and a small excess of DDQ (entry 6) following a procedure by Huang and co-workers.[29] Again, only oxidation on the prenyl side chain was observed. We speculate that the Lewis acid $FeCl_3$ and adventitious water form the Brønsted acid HCl which protonates the side chain olefin forming a carbocation. Following this, water can attack the carbocation leading to the observed oxidation on the side chain in entries 4 to 6.

Neither silver(I) nitrate nor iron(III) chloride successfully promoted the desired dimerisation of nordentatin (**4.01**), hence, we again consulted literature for other reagents to try.

4.2.5 Attempted Oxidative Dimerisation of Nordentatin with Hypervalent Iodine Reagents

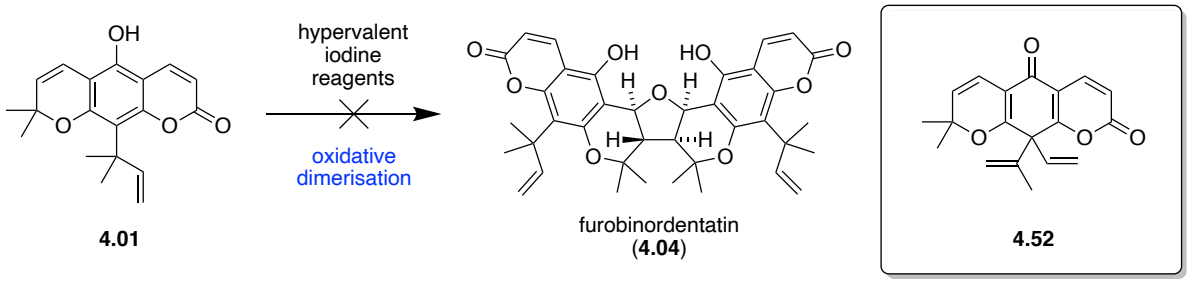
Hypervalent iodine reagents like phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis(trifluoroacetate) (PIFA) belong to another group of oxidants which showed promising results with similar systems. In 2012, Copp and co-workers reported the dimerisation reaction of **4.49** to **4.50** and **4.51** with PIFA and boron trifluoride diethyl etherate in 48% and 29% yield, respectively (Scheme 4.17).[30] Again, the same relative stereochemistry on the tetrahydrofuran ring was obtained as required in our system.



Scheme 4.17: Syntheses of furanopyran dimers 4.50 and 4.51 by Cadelis *et al.*[30]

All screened reaction conditions with hypervalent iodine reagents are outlined in Table 4.3.

Table 4.3: Attempted oxidative dimerisation reaction with hypervalent iodine reagents.

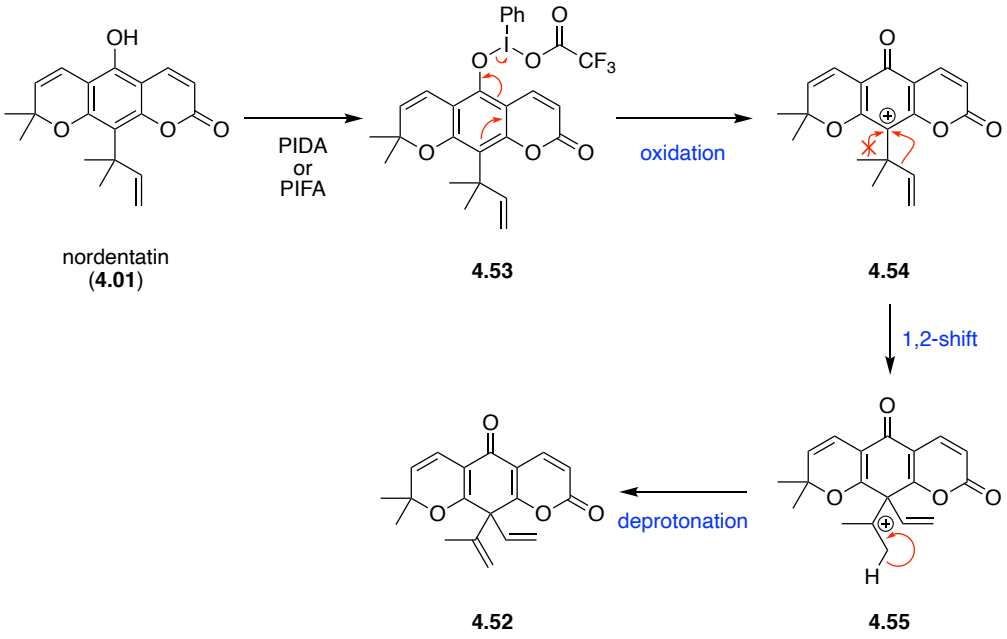


Entry	Oxidant	Reaction conditions	Outcome[#]
1	PIDA (1 eq.), TEMPO	THF, rt, 30 min	decomposition
2	PIDA (1 eq.)	THF, rt, 3 h	decomposition
3	PIDA (10 mol%)	HFIP, 0 °C to rt, 3 days	residual s.m. (not recovered) and **4.52** (14%)[*]
4	PIFA, $BF_3 \cdot Et_2O$	CH_2Cl_2, 0 °C, 4 h	**4.52** (7%)[*]

[#]Unless otherwise specified reaction outcomes were indicated by TLC. [*]All percentage yields are isolated yields after standard work up and purification by flash column chromatography on silica gel, s.m. starting material, rt room temperature.

Firstly, nordentatin (**4.01**) was subjected to PIDA and TEMPO in THF at room temperature which led to decomposition of the starting material within 30 min (entry 1). In the second entry, nordentatin (**4.01**) was reacted with PIDA in THF at room temperature without adding TEMPO. TLC analysis after 30 min indicated slow degradation of the starting material; full

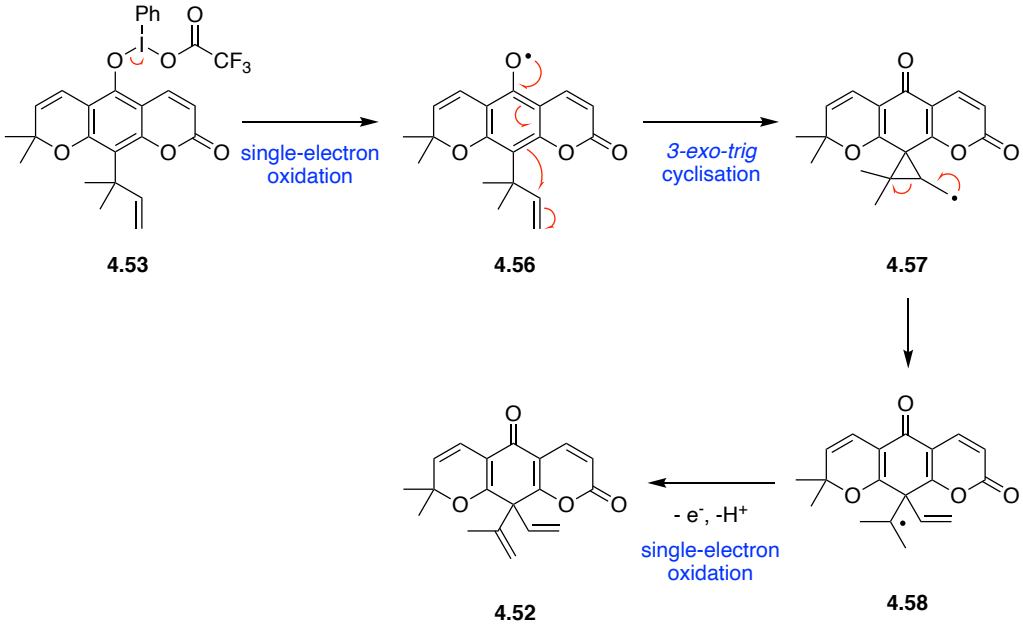
decomposition was observed after 3 h at room temperature. In entry 3, nordentatin (**4.01**) was treated with 10 mol% PIDA in hexafluoroisopropanol (HFIP) at 0 °C. The reaction mixture was slowly allowed to warm to room temperature.[31] After 3 days, TLC analysis showed a new spot with a higher R_f value, alongside remaining starting material. Thorough analysis by spectroscopic methods indicated that the new compound featured two terminal alkenes; one being at 5.36 ppm and 5.10 ppm and the other one showing at 5.33 ppm and 5.23 ppm. In entry 4, the reaction was carried out with PIFA and boron trifluoride diethyl etherate in CH_2Cl_2 at 0 °C which led to the same side product formation in 7% yield. We proposed two plausible mechanisms for the formation of side product **4.52** (Scheme 4.18 and Scheme 4.19).



Scheme 4.18: Proposed mechanism of side product formation.

Oxidation with PIDA or PIFA forms cationic species **4.54** which could, then, either undergo a 1,2-shift of the methyl or the vinyl group. In accordance with the higher migratory aptitude of alkenyl groups over alkyl groups, only the rearrangement of the vinyl is observed forming cationic intermediate **4.55**. Deprotonation gives side product **4.52**. Alternatively, we suggest

the mechanism could go *via* a radical pathway where single-electron oxidation generates radical species **4.56** (Scheme 4.19). 3-exo-trig cyclisation gives intermediate **4.57** which ring opens to **4.58**. Another single-electron oxidation gives side product **4.52**.



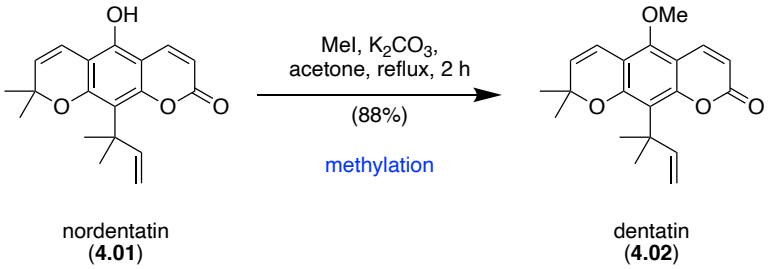
Scheme 4.19: Alternative mechanism for side product formation *via* a radical pathway.

As harsher oxidants led to degradation of the starting material, nordentatin (**4.01**), we thought that methylating the hydroxyl group would make the starting material less prone to decomposition.

4.2.6 *O*-Methylation of Nordentatin to Dentatin

As the oxidative dimerisation reaction with nordentatin (**4.01**) remained unsuccessful, we turned our focus to its methylated analogue, dentatin (**4.02**), which we thought would be more stable under harsher oxidation conditions. The isolation chemists also reported spectroscopic data for the methylated version of furobinordentatin (**4.04**).[13] Hence, we knew we could easily

confirm the success of the dimerisation reaction. Following a literature procedure, *O*-methylation of nordentatin (**4.01**) worked smoothly with iodomethane and potassium carbonate in acetone at reflux affording dentatin (**4.02**) in 88% yield (Scheme 4.20).[8]

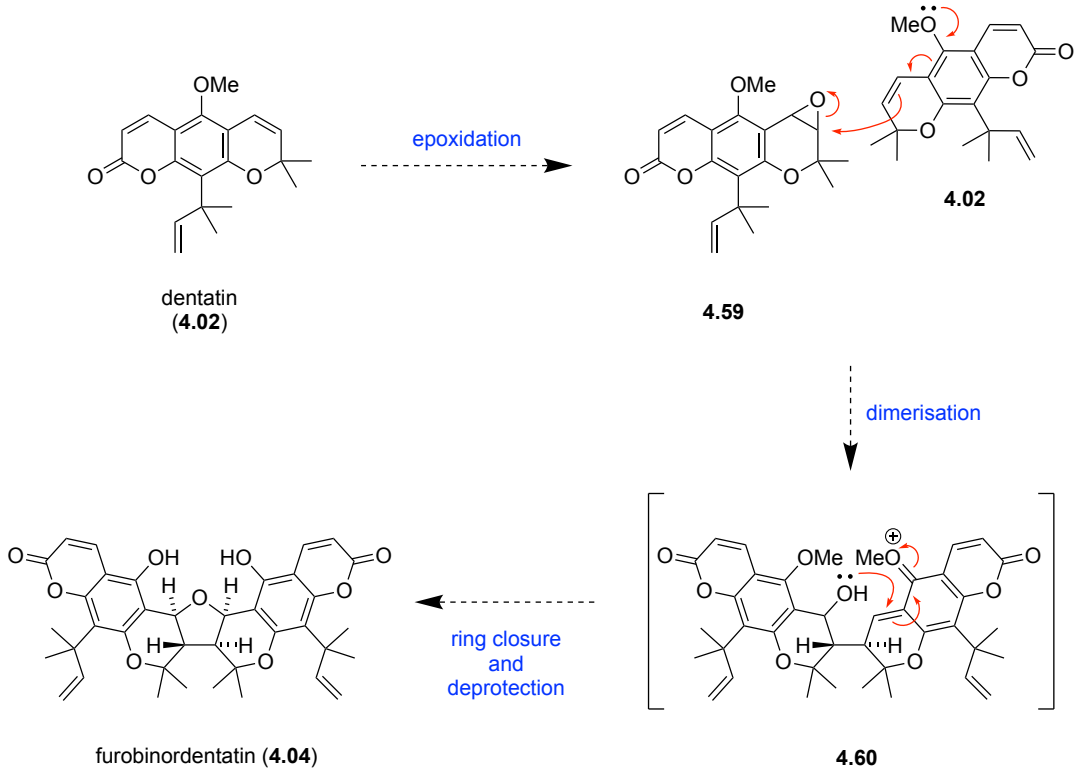


Scheme 4.20: *O*-methylation of hydroxyl group of nordentatin (4.01) with iodomethane and potassium carbonate.[8]

With dentatin (**4.02**) in good quantities in our hands, we started investigating the oxidative dimerisation reaction.

4.2.7 Attempted Oxidative Dimerisation Reaction of Dentatin *via* Epoxidation

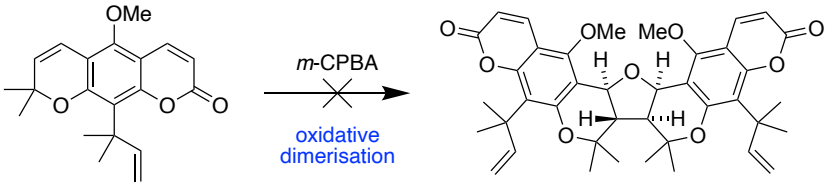
The first pathway we wanted to investigate was the epoxidation reaction of the chromene alkene. When we performed this reaction on nordentatin (**4.01**), the conditions did not allow us to isolate a distinctive species, however, we were hopeful for a different outcome on the dentatin scaffold. Analogous to the proposed dimerisation of nordentatin (**4.01**), we proposed that dentatin (**4.02**) would be first epoxidised on the chromene alkene followed by nucleophilic attack of another unoxidised unit of dentatin (**4.02**). Ring closure and deprotection of the dimethyl ether of furobinordentatin would give the desired natural product dimer (**4.04**) (Scheme 4.21).



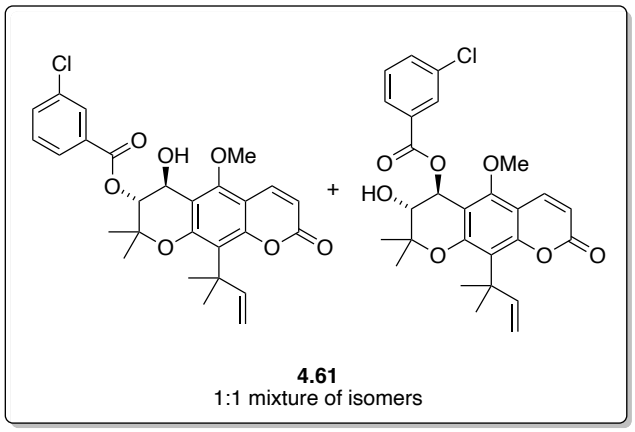
Scheme 4.21: Proposed mechanism for oxidative dimerisation reaction of dentatin *via* the epoxidation pathway.

With this proposal in mind, we decided to first try reaction epoxidation conditions with *m*-CPBA and Jacobsen's catalyst (**4.36**). All attempted oxidative dimerisation reactions are summarised in Table 4.4.

Table 4.4: Attempted oxidative dimerisation reaction with dentatin (4.02) using *m*-CPBA.



4.02 **4.62**



4.61
1:1 mixture of isomers

Entry	Oxidant	Reaction conditions	Outcome*
1	(*S,S*)-Jacobsen's cat (**4.36**), *m*-CPBA, NMO	CH_2Cl_2, –78 °C, 50 min	r.s.m.[#] (26%), **4.61** (47%)
2	*m*-CPBA	CH_2Cl_2, rt, 3 h	residual s.m. (not recovered), **4.61** (17%)
3	*m*-CPBA	benzene, rt, o.n.	**4.61** (89%)

*Unless otherwise specified all percentage yields are after purification by column chromatography on silica gel, #r.s.m. recovered starting material, s.m. starting material, rt room temperature, o.n. overnight.

When we exposed dentatin (**4.02**) to (*S,S*)-Jacobsen's catalyst, *m*-CPBA and NMO in CH_2Cl_2 at –78 °C for 50 min (following the same procedure as with nordentatin (**4.01**)), a new compound was isolated alongside unreacted starting material (entry 1). Analysis by spectroscopic methods indicated that, instead of formation of the desired epoxide, a 1:1 mixture of the two isomeric esters **4.61** was obtained. Even after various attempts to stop the reaction at the epoxidation stage by changing variables such as reaction time, temperature and omitting the catalyst (entry 2), the reaction always led to the same 1:1 mixture of **4.61** in varying yields.

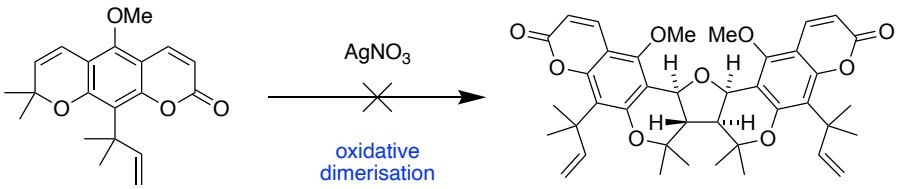
However, an increase in yield to 89% was observed when we changed the solvent from dichloromethane to benzene and left the reaction stirring overnight at room temperature.

Unfortunately, all attempts to hydrolyse the ester with potassium hydroxide in refluxing methanol led to degradation of the starting material.

4.2.8 Attempted Oxidative Dimerisation of Dentatin with Silver Nitrate

Again, we performed several attempts to promote the dimerisation reaction of dentatin (**4.02**) to methylated furobinordentatin (**4.62**) with silver(I) nitrate. The screened reaction conditions are outlined in Table 4.5.

Table 4.5: Attempted oxidative dimerisation reaction with silver(I) nitrate.



4.02 **4.62**

Entry	Oxidant	Reaction conditions	Outcome*
1	20% $AgNO_3$-silica	acetone, rt, o.n.	no reaction
2	20% $AgNO_3$-silica	petrol, rt, 5 days	no reaction
3	20% $AgNO_3$-silica	toluene, reflux, o.n.	slow decomposition

*Unless otherwise specified all outcomes are indicated by TLC analysis. rt room temperature, o.n. overnight.

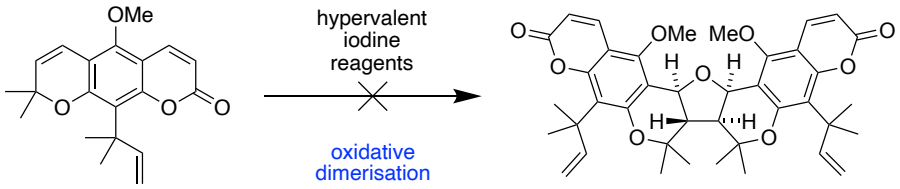
Firstly, dentatin (**4.02**) was stirred in acetone with 20% silver nitrate impregnated silica at room temperature overnight. No reaction was observed under these conditions. The same reaction was repeated with petrol instead of acetone as solvent following the procedure by Fraga and

co-workers (entry 2).[26] Again, no reaction occurred after 5 days at room temperature. When heating dentatin (**4.02**) at reflux in toluene overnight, TLC analysis indicated slow decomposition of the starting material.

4.2.9 Attempted Oxidative Dimerisation of Dentatin with Hypervalent Iodine Reagents

We were interested to see how dentatin (**4.02**) would behave when subjected to hypervalent iodine reagents as these conditions led to the formation of an interesting side product **4.52** when used on nordentatin (**4.01**). As the free hydroxyl group of nordentatin (**4.01**) took part in the formation of the side product we were hoping for a different outcome when performing the same conditions on the methylated system. All attempted oxidative dimerisation reactions are summarised in Table 4.6.

Table 4.6: Attempted oxidative dimerisation with hypervalent iodine reagents.



4.02 **4.62**

Entry	Oxidant	Reaction conditions	Outcome*
1	PIFA, $BF_3 \cdot OEt_2$	CH_2Cl_2, –70 to –10 °C, 3 h	RSM[#] (58%) and slow decomposition
2	PIFA, $BF_3 \cdot OEt_2$	CH_2Cl_2, rt, 5 h	slow decomposition
3	PIDA, TEMPO	THF, 0 °C to rt, o.n.	no reaction

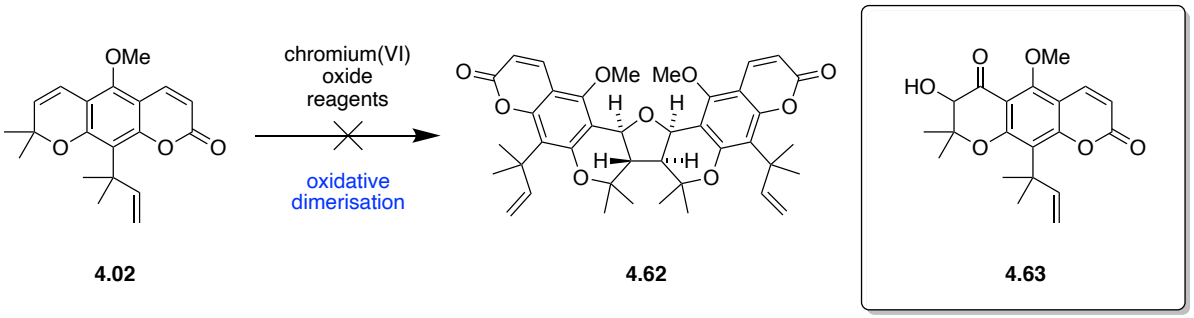
[#]All yields are isolated yields after purification by flash column chromatography on silica gel, *outcomes were indicated by TLC analysis unless otherwise specified, rt room temperature, o.n. overnight.

First, oxidative dimerisation reaction was attempted with PIFA and boron trifluoride diethyl etherate at low temperatures for 3 h (entry 1). No reaction was observed under these conditions, only slow degradation of the starting material. When we extended the reaction time and elevated the temperature, TLC analysis indicated slow decomposition of the starting material (entry 2). Attempts to perform the reaction with PIDA and TEMPO instead resulted in no reaction even after leaving the reaction overnight (entry 3).

4.2.10 Attempted Oxidative Dimerisation of Dentatin with Chromium(VI) Oxidants

As dentatin (**4.02**) seemed to be less reactive than nordentatin (**4.01**), we were eager to try harsher oxidation conditions, such as chromium(VI) reagents, to promote desired oxidative dimerisation. In 1986, Fraga and Garcia reported the successful dimerisation of precocene II with Jones reagent and chromium(VI) oxide in water.[32] All attempted dimerisation reactions are summarised in Table 4.7.

Table 4.7: Attempted oxidative dimerisation of dentatin (4.02) with chromium(VI) reagents.



4.02 **4.62** **4.63**

Entry	Oxidant	Reaction conditions	Outcome
1	CrO_3, silica	acetone, rt, o.n.	r.s.m. (23%), **4.63** (12%)
2	CrO_3, silica	acetone, rt, 2 days	decomposition*
3	Jones reagent	acetone, 0 °C to rt, o.n.	r.s.m. (52%), **4.63** (9%)
4	PCC	CH_2Cl_2, rt, 4 h	residual starting material (not recovered), **4.63** (*trace*)*

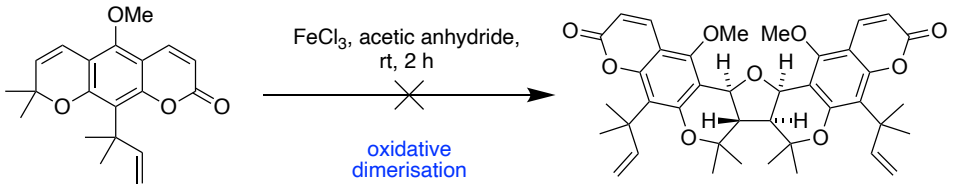
#All yields are isolated yields after standard work up and purification by flash column chromatography on silica gel, *indicated by TLC analysis, rt room temperature, o.n. overnight.

Firstly, oxidation conditions reported by Fraga and Garcia were attempted (entries 1 and 2).[32] When treating dentatin (**4.02**) with chromium(VI) oxide and silica in acetone at room temperature, TLC analysis indicated the formation of a new compound alongside unreacted starting material. Analysis by spectroscopic methods showed the disappearance of the chromene proton peaks which seemed promising. However, a closer look at the new proton signals at 4.31 ppm and 3.92 ppm as well as the new carbonyl carbon signal at 194.8 ppm led us to the structural assignment of **4.63**. We propose that the chromene alkene is first dihydroxylated, followed by a second oxidation to form ketone **4.63**. Attempts to increase the formation of the side product by extending reaction times led to decomposition of the starting material (entry 2). The same side product **4.63** was formed when changing to Jones reagent in 9% yield. (entry 3). When using pyridinium chlorochromate as the oxidant, TLC analysis indicated the formation of trace amounts of side product **4.63** after 4 h. Again, our substrate

did not undergo the desired oxidative dimerisation reaction which led us to consult the literature once more.

4.2.11 Other Attempted Oxidative Dimerisation Reactions

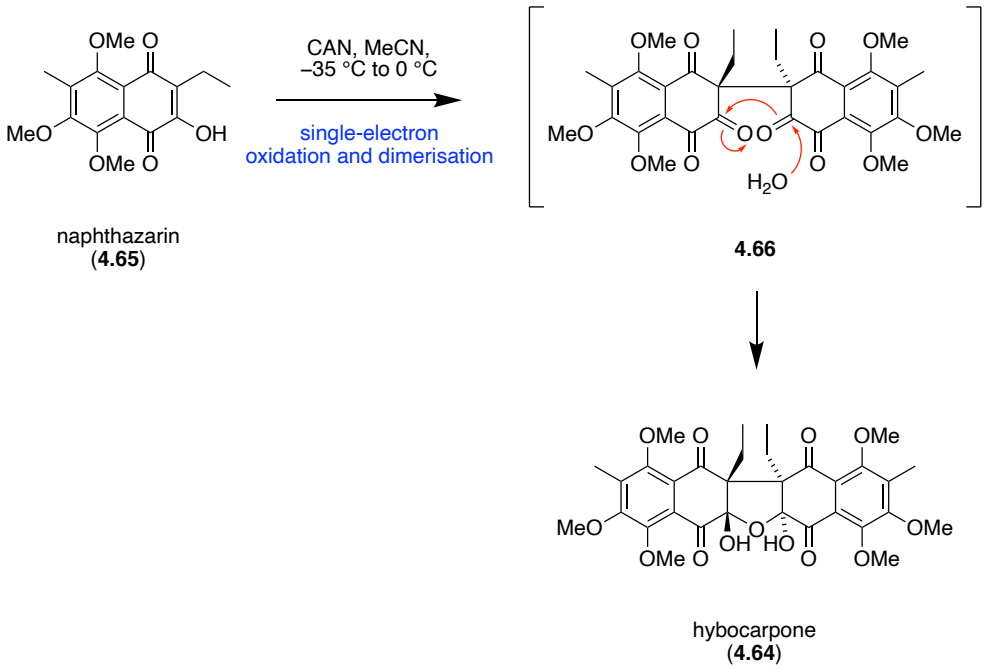
Another reaction condition we wanted to try was the oxidation with iron(III) chloride. Somewhat unsurprisingly, when we attempted the oxidative dimerisation reaction with $FeCl_3$ in acetic anhydride, we observed undesired oxidation on the prenyl alkene (Scheme 4.22). This was consistent with our findings on the nordentatin system. As this was undesired reactivity, the side product was not further characterised.



4.02 **4.62**

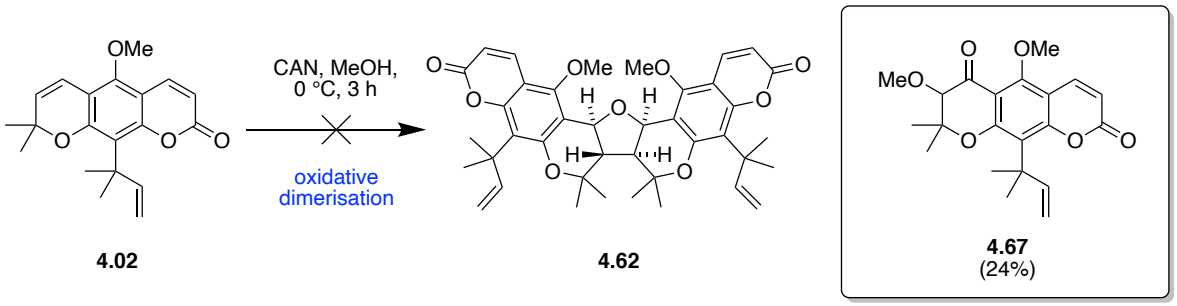
Scheme 4.22: Attempted oxidation with iron(III) chloride.

Lastly, another strong single-electron oxidant we were curious to try was cerium(IV) ammonium nitrate (CAN). In 2001, Nicolaou and Gray reported the successful total synthesis of hybocarpone (**4.64**). Their key step was a dimerisation-hydration cascade of naphthazarin (**4.65**) initiated by a single-electron oxidation with CAN (Scheme 4.23).[33]



Scheme 4.23: Proposed mechanism for dimerisation of naphthazarin (4.65) *via* a single-electron oxidation with CAN by Nicolaou and Gray.[33]

We first performed the reaction following the literature conditions with no success. TLC analysis showed only starting material even after leaving the reaction at room temperature for 2 days. As a second attempt, we changed the solvent from acetonitrile to methanol (Scheme 4.24). After 3 h at 0 °C, a new compound had formed which was subsequently isolated and characterised by spectroscopic methods. The compound was assigned the structure of **4.67**, showing a characteristic carbonyl signal at 191.0 ppm in the ^{13}C NMR spectrum and an additional methoxy peak at 3.59 ppm in the ^{1}H NMR spectrum. HRMS and IR spectroscopy supported this structural assignment.



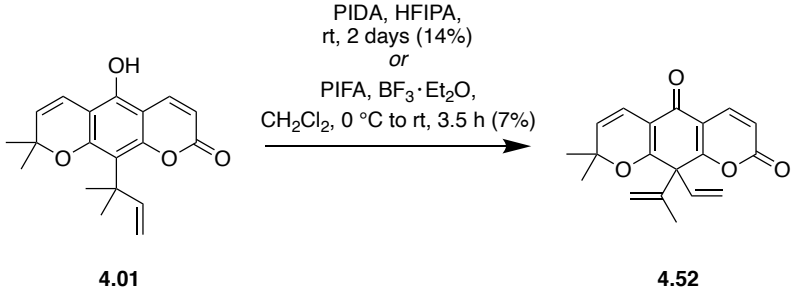
Scheme 4.24: Attempted oxidation with ceric ammonium nitrate (CAN).

Further investigations into the oxidative dimerisation of nordentatin (**4.01**) and dentatin (**4.02**) are currently underway.

4.3 Conclusion and Future Directions

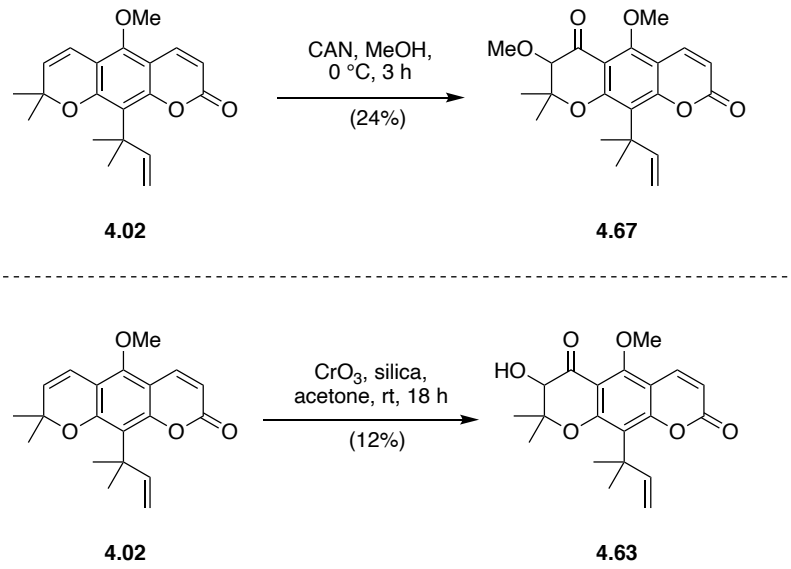
In summary, we have been able to gain significant insight into the reactivity for both compounds, nordentatin (**4.01**) and dentatin (**4.02**), in regard to oxidation conditions. Several oxidation conditions led to new and previously unreported compounds.

Treatment of nordentatin (**4.01**) with hypervalent iodine reagents, such as PIDA and PIFA, formed side product **4.52** which shows a unique scaffold with two terminal alkenes (Scheme 4.25).



Scheme 4.25: Oxidation of nordentatin (4.01) with hypervalent iodine reagents.

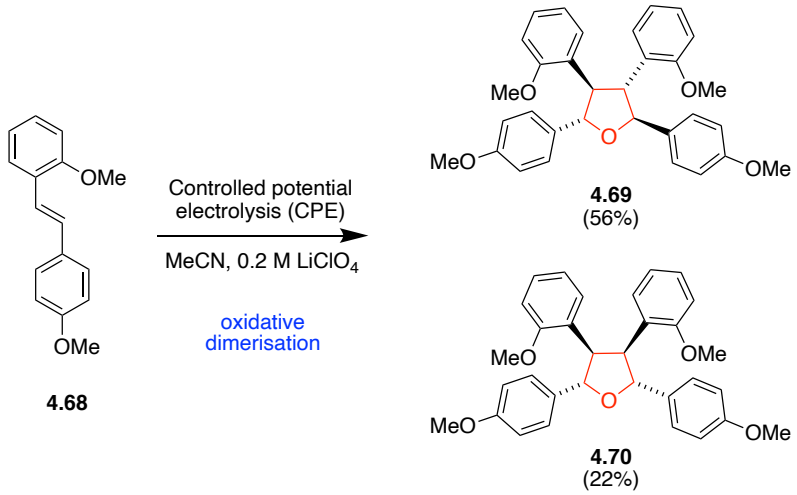
When we performed oxidation of dentatin (**4.02**) with CAN or chromium(VI) oxide, two structurally very similar compounds, **4.67** and **4.63**, were formed. Both compounds went through oxidation on the chromene alkene only differing in the methyl ether protecting group (Scheme 4.26). Both compounds were assigned by thorough analysis of the spectroscopic data. However, it would be desirable in the future to remove the methoxy protecting groups on both compounds and confirm that the products are identical.



Scheme 4.26: Oxidation of dentatin (4.02) with CAN and chromium(VI) oxide.

Further oxidative dimerisation studies are required in the future. It would be desirable to utilise electrochemistry as a tool to achieve the desired oxidative dimerisation. Our group recently purchased the ElectraSyn 2.0 which offers an exciting, new method to perform radical dimerisation reactions. Compared to traditional oxidation methods, electrochemical oxidation techniques often tolerate a larger range of functional groups, proceed under milder conditions, such as lower temperatures and pressures, and allow shorter reaction times. They are also considered to be more environmentally friendly and sustainable.[34]

One example would be the successful dimerisation of 4,2'-dimethoxystilbene (**4.68**) through anodic oxidation to dimers **4.69** and **4.70** by Kam and co-workers (Scheme 4.27).[35,36] Both dimerisation products show the desired tetrahydrofuran moiety as connection of the two monomeric units.



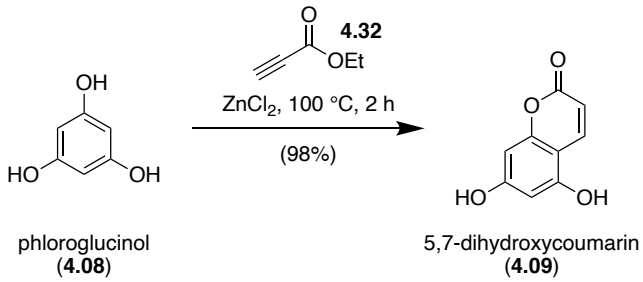
Scheme 4.27: Anodic oxidation of 4,2'-dimethoxystilbene (4.68) to form dimeric products 4.69 and 4.70 by Kam and co-workers.

4.4 Supporting Information

4.4.1 General Methods

All chemicals used were purchased from commercial suppliers and used as received. Unless otherwise stated, all reactions were performed under an inert atmosphere of N_2. All organic extracts were dried over anhydrous magnesium sulfate. Thin layer chromatography was performed using aluminium sheets coated with silica gel F_{254}. Visualisation was aided by viewing under a UV lamp and staining with ceric ammonium molybdate followed by heating. All R_f values were measured to the nearest 0.05. Flash column chromatography was performed using 40-63 micron grade silica gel. Melting points were recorded on a Reichart Thermovar Kofler microscope apparatus and are uncorrected. Infrared spectra were recorded using an FT-IR spectrometer as the neat compounds. High field NMR spectra were recorded using both a 500 MHz spectrometer (^{1}H at 500 MHz, ^{13}C at 125 MHz) and 600 MHz spectrometer (^{1}H at 600 MHz, ^{13}C at 150 MHz) as indicated. The solvent used for spectra was $CDCl_3$ unless otherwise specified. ^{1}H chemical shifts are reported in ppm on the δ-scale relative to TMS (δ 0.0) and ^{13}C NMR are reported in ppm relative to $CDCl_3$ (δ 77.16). Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (quin) quintet, (sext) sextet, (hept) heptet and (m) multiplet. All *J*-values were rounded to the nearest 0.1 Hz. ESI high resolution mass spectra were recorded on an ESI-TOF mass spectrometer.

4.4.2 Experimental Procedures



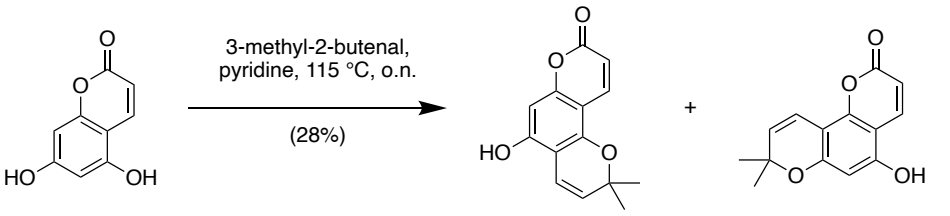
phloroglucinol (**4.08**) — 5,7-dihydroxycoumarin (**4.09**)

A mixture of phloroglucinol (**4.08**, 20.0 g, 159 mmol, 1 eq.), zinc chloride (10.8 g, 79.5 mmol, 0.5 eq.) and ethyl propiolate (**4.32**, 24.6 g, 238 mmol, 1.5 eq.) was heated at reflux for 1 h. The reflux condenser was removed, and the reaction mixture was heated for another hour until no solvent remained. The reaction mixture was quenched with 10% aqueous HCl solution (100 mL) and filtered. The crude product was washed with boiling water to afford 5,7-dihydroxycoumarin (**4.09**, 28.2 g, 159 mmol, quant.) as an orange-brown powder.

Partial data for 5,7-dihydroxycoumarin (**4.09**):

^{1}H NMR (500 MHz, DMSO-d_6): δ =10.63 (s, 1H), 10.34 (s, 1H), 7.95 (d, J = 9.6 Hz, 1H), 6.26 (d, J = 1.9 Hz, 1H), 6.18 (d, J = 2.0 Hz, 1H), 6.03 (d, J = 9.6 Hz, 1H). ppm.

The analytical data match those previously described in the literature.[16]



5,7-dihydroxycoumarin (**4.09**) | 5-hydroxyseselin (**4.13**) | 7-hydroxyalloxanthyletin (**4.11**)

To a suspension of 5,7-dihydroxycoumarin (**4.09**, 10.0 g, 56.1 mmol, 1 eq.) in pyridine (10 mL) was added 3-methyl-2-butenal (7.5 mL, 78.6 mmol, 1.4 eq.). The reaction mixture was heated at reflux overnight. The reaction mixture was purified by flash column chromatography [PE:EtOAc 10:1 → 2:1]. A second purification by flash column chromatography [8:1 → 2:1] afforded pure 5-hydroxyseselin (**4.13**) and 7-hydroxyalloxanthyletin (**4.11**) as a 2:1 mixture (2.42 g, 9.91 mmol, 18%).

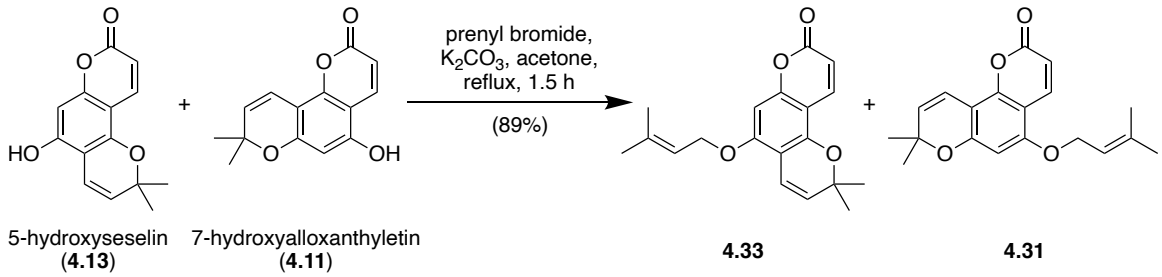
Partial data of 5-hydroxyseselin (**4.13**):

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.00 (d, J = 9.6 Hz, 1H), 6.78 (d, J = 10.0 Hz, 1H), 6.20 (s, 1H), 6.15 (d, J = 9.6 Hz, 1H), 5.57 (d, J = 10.0 Hz, 1H), 1.44 (s, 6H) ppm.

Partial data of 7-hydroxyalloxanthyletin (**4.11**):

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98 (d, J = 9.5 Hz, 1H), 6.63 (d, J = 10.0 Hz, 1H), 6.43 (s, 1H), 6.15 (d, J = 9.6 Hz, 1H), 5.58 (d, J = 10.0 Hz, 1H), 1.48 (s, 6H) ppm.

The analytical data match those previously described in the literature.[19]



A mixture of 5-hydroxyseselin (**4.13**) and 7-hydroxyalloxanthyletin (**4.11**) (2.42 g, 9.90 mmol, 1 eq.) was dissolved in acetone (50 mL). To that solution, K_2CO_3 (4.10 g, 29.7 mmol, 3 eq.) and prenyl bromide (1.37 mL, 11.9 mmol, 1.2 eq.) were added and the reaction mixture was heated at reflux for 1.5 h. Then, the reaction was quenched with 1M aqueous HCl solution (50 mL) and the aqueous layer was extracted with EtOAc (3 x 70 mL). The combined organic layers were washed with saturated aqueous NaCl solution (100 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo*. Purification by flash column chromatography [PE:EtOAc 10:1] afforded a mixture of **4.33** and **4.31** (2.76 g, 8.84 mmol, 89%) as a yellow oil.

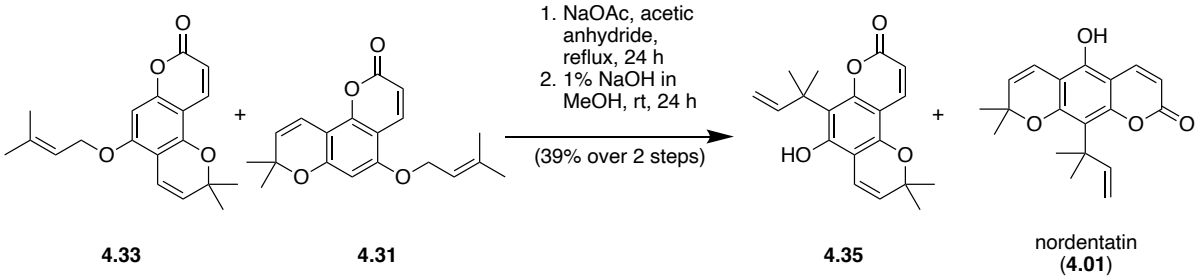
Partial data **4.33**:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98 (d, J = 9.6 Hz, 1H), 6.80 (d, J = 10.0 Hz, 1H), 6.24 (s, 1H), 6.11 (d, J = 9.6 Hz, 1H), 5.57 (d, J = 10.0 Hz, 1H), 5.51 – 5.47 (m, 1H), 4.57 (d, J = 6.8 Hz, 2H), 1.81 (s, 3H), 1.74 (s, 3H), 1.46 (s, 6H) ppm.

Partial data of **4.31**:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (d, J = 9.6 Hz, 1H), 6.64 (d, J = 10.0 Hz, 1H), 6.35 (s, 1H), 6.14 (d, J = 9.6 Hz, 1H), 5.53 (d, J = 10.0 Hz, 1H), 5.47 – 5.43 (m, 1H), 4.55 (d, J = 6.6 Hz, 2H), 1.80 (s, 3H), 1.76 (s, 3H), 1.46 (s, 6H) ppm.

The analytical data match those previously described in the literature.[10]



4.33 **4.31** **4.35** nordentatin (**4.01**)

To a solution of prenylated chromenes **4.33** and **4.31** (4.80 g, 15.4 mmol, 1 eq.) in acetic anhydride (185 mL) was added NaOAc (5.00 g, 61.0 mmol, 4 eq.). The reaction mixture was heated at reflux for 24 h. Then, the reaction mixture was filtered through a pad of Celite and washed thoroughly with EtOAc. The filtrate was concentrated *in vacuo* and the crude product was dissolved in a pre-made solution of 1% NaOH in MeOH (100 mL). The reaction mixture was stirred at room temperature for 24 h before it was quenched with 1M aqueous HCl solution (50 mL). The organic solvent was removed *in vacuo* and the remaining aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with saturated aqueous NaCl solution (100 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography [PE:EtOAc 10:1 → 2:1] to afford pure nordentatin (**4.01**, 1.86 g, 5.95 mmol, 39% over 2 steps) as yellow powder. Side product **4.35** was not isolated.

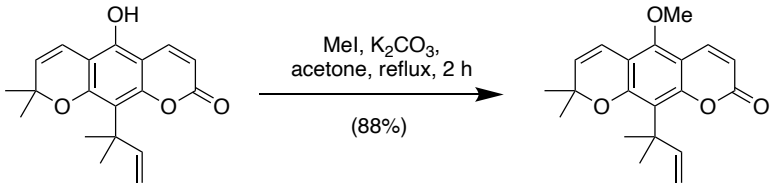
Partial data for nordentatin (**4.01**):

R_f: 0.25 [PE:EtOAc 1:1]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.99 (d, J = 9.6 Hz, 1H), 6.47 (d, J = 9.9 Hz, 1H), 6.30 (dd, J = 17.4, 10.6 Hz, 1H), 6.16 (d, J = 9.6 Hz, 1H), 5.72 (d, J = 9.9 Hz, 1H), 5.40 (s, 1H), 4.94 (dd, J = 17.4, 1.1 Hz, 1H), 4.88 (dd, J = 10.6, 1.1 Hz, 1H), 1.66 (s, 6H), 1.46 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.3, 156.0, 154.4, 150.2, 146.5, 139.0, 130.3, 116.5, 114.9, 110.7, 108.2, 106.0, 103.9, 77.2, 41.2, 29.7, 27.4 ppm.

The analytical data match those previously described in the literature.[10,12,22]



nordentatin (**4.01**) dentatin (**4.02**)

To a solution of nordentatin (**4.01**, 1.86 g, 5.95 mmol, 1 eq.) in acetone (50 mL) at room temperature were added K_2CO_3 (4.94 g, 35.7 mmol, 6 eq.) and iodomethane (740 µL, 11.9 mmol, 2 eq.). The reaction mixture was heated at reflux for 2 h before being allowed to cool to room temperature. The solution was quenched with 1M HCl solution (25 mL) and diluted with H_2O (25 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with saturated aqueous NaCl solution (75 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on SiO_2 [PE:EtOAc 8:1 → 1:1] to afford pure dentatin (**4.02**, 1.73 g, 5.30 mmol, 89%) as a light yellow waxy solid.

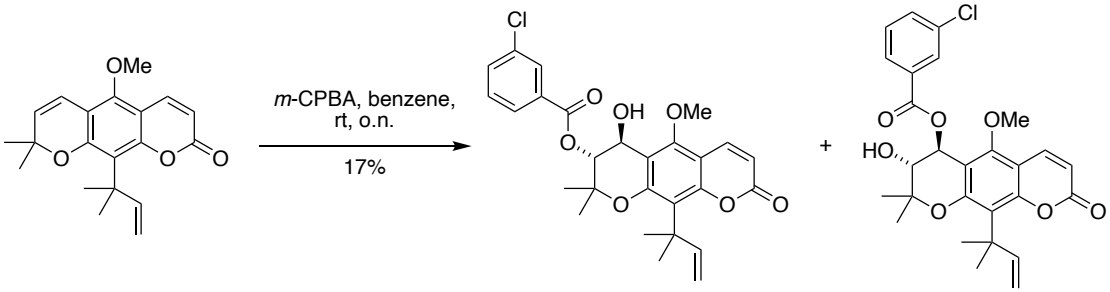
Partial data for dentatin (**4.02**):

R_f: 0.60 [PE:EtOAc 1:1]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, *J* = 9.6 Hz, 1H), 6.57 (d, *J* = 9.9 Hz, 1H), 6.31 (dd, *J* = 17.4, 10.6 Hz, 1H), 6.19 (d, *J* = 9.6 Hz, 1H), 5.69 (d, *J* = 9.9 Hz, 1H), 4.94 (d, *J* = 17.4 Hz, 1H), 4.88 (d, *J* = 10.6 Hz, 1H), 3.83 (s, 3H), 1.66 (s, 6H), 1.45 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.9, 156.2, 154.1, 151.4, 150.0, 139.1, 130.5, 119.4, 116.5, 111.9, 108.3, 107.7, 77.5, 63.6, 41.3, 29.6, 27.7 ppm.

The analytical data match those previously described in the literature.[10]



dentatin
(**4.02**)

4.61
1:1 mixture of isomers

To a solution of dentatin (**4.02**, 20 mg, 0.059 mmol, 1 eq.) in benzene (8 mL) at room temperature was added *m*-CPBA (122 mg, 0.129 mmol, 2.2 eq.). The reaction mixture was stirred at room temperature overnight. The solution was quenched with saturated aqueous NH_4Cl solution (5 mL) and diluted with H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (2 x 20 mL) and saturated aqueous NaCl solution (20 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography [PE:EtOAc 4:1] to afford **4.61** (26 mg, 0.052 mmol, 89%) in an inseparable 1:1 mixture of isomers.

Data for **4.61** in a 1:1 mixture of isomers:

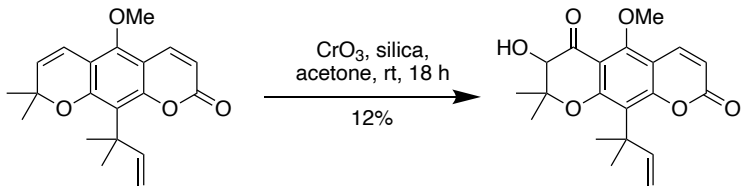
R_f: 0.10 [3:1 PE:EtOAc]

IR (neat): 3443, 2982, 1717, 1670, 1587, 1387, 1250, 1125, 828, 732 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (dt, *J* = 3.9, 1.9 Hz, 2H), 7.95 – 7.90 (m, 2H), 7.80 (d, *J* = 9.7 Hz, 1H), 7.79 (d, *J* = 9.7 Hz, 1H), 7.59 – 7.53 (m, 2H), 7.39 (t, *J* = 7.9 Hz, 2H), 6.57 (d, *J* = 5.0 Hz, 1H), 6.34 – 6.26 (m, 2H, overlapped), 6.28 (d, *J* = 4.6 Hz, 1H, overlapped), 6.22 (dd, *J* = 9.7, 4.1 Hz, 1H), 4.96 (d, *J* = 17.4 Hz, 2H), 4.91 (dt, *J* = 10.6, 1.3 Hz, 2H), 4.08 (d, *J* = 5.0 Hz, 1H), 3.91 (d, *J* = 4.6 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 1.72 (s, 3H), 1.71 (s, 3H), 1.70 (s, 3H), 1.67 (s, 3H), 1.53 (s, 3H), 1.52 (s, 3H), 1.48 (s, 3H), 1.42 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3, 165.7, 160.4, 156.3, 156.2, 156.2, 155.0, 154.8, 150.0, 149.9, 138.8, 138.8, 135.0, 134.9, 133.7, 133.6, 131.5, 131.5, 130.1, 130.2, 130.0, 130.0, 128.1, 128.1, 79.2, 78.6, 73.3, 71.9, 69.8, 65.3, 63.8, 63.7, 41.7, 41.8, 30.0, 29.6, 29.6, 29.1, 26.5, 24.8, 21.4, 20.4 ppm.

HRMS (ESI): calculated for $C_{27}H_{27}ClNaO_7$ 521.1338 $[M+Na]^+$, found 521.1336.



dentatin
(**4.02**)

4.63

To a solution of dentatin (**4.02**, 50 mg, 0.153 mmol, 1 eq.) in acetone (10 mL) at room temperature was added chromium(VI) oxide (8.0 mg, 0.084 mmol, 0.55 eq.) in acetone (5 mL). The reaction mixture was stirred at room temperature for 18 h. Then, another portion of chromium(VI) oxide (15 mg, 0.153 mmol, 1 eq.) was added to the reaction. The mixture was stirred for another 1.5 h at room temperature before being quenched with saturated aqueous $Na_2S_2O_3$ solution (15 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with saturated aqueous NaCl solution (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 5:1] to yield **4.63** (6.7 mg, 0.019 mmol, 12%) as a yellow oil.

Data for **4.63**:

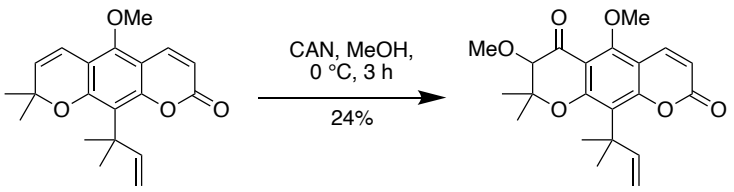
R_f: 0.10 [4:1 PE:EtOAc]

IR (neat): 3456, 2982, 1738, 1695, 1570, 1375, 1214, 1162, 1117, 1093, 723 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, *J* = 9.8 Hz, 1H), 6.26 (d, *J* = 9.7 Hz, 1H), 6.23 (dd, *J* = 17.4, 10.6 Hz, 1H), 4.94 (d, *J* = 17.5 Hz, 1H), 4.90 (d, *J* = 10.6 Hz, 1H), 4.31 (d, *J* = 2.3 Hz, 1H), 3.95 (s, 3H), 3.92 (d, *J* = 2.5 Hz, 1H), 1.69 (s, 3H), 1.66 (s, 3H), 1.65 (s, 3H), 1.22 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 194.9, 164.1, 162.0, 160.9, 159.5, 152.0, 141.4, 122.7, 115.7, 112.9, 111.6, 111.3, 86.9, 79.2, 66.6, 44.1, 32.5, 31.4, 29.3, 19.9 ppm.

HRMS (ESI): calculated for $C_{20}H_{23}O_6$ 359.1489 $[M+H]^+$, found 359.1490.



dentatin (**4.02**)

4.67

To a solution of dentatin (**4.02**, 31 mg, 0.095 mmol, 1 eq.) in MeOH (5 mL) at 0 °C was added ceric ammonium nitrate (CAN) (62 mg, 0.114 mmol, 1.2 eq.). The reaction mixture allowed to slowly warm to room temperature over a period of 3 h. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl solution (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 [PE:Et_2O 4:1] to yield **4.67** (8.5 mg, 0.023 mmol, 24%) as a yellowish oil.

Data for **4.67**:

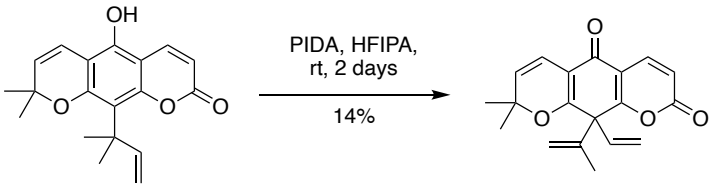
R_f: 0.30 [3:1 PE:EtOAc]

IR (neat): 2982, 1733, 1711, 1569, 1433, 1371, 1165, 1083, 831, 605 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, *J* = 9.7 Hz, 1H), 6.24 (d, *J* = 9.7 Hz, 1H), 6.22 (dd, *J* = 17.5, 10.6 Hz, 1H), 4.93 (d, *J* = 17.4 Hz, 1H), 4.89 (d, *J* = 10.6 Hz, 1H), 3.96 (s, 3H), 3.62 (s, 1H), 3.59 (s, 3H), 1.67 (s, 3H), 1.66 (s, 3H), 1.50 (s, 3H), 1.38 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 191.0, 161.3, 159.8, 157.8, 157.2, 149.7, 139.2, 119.6, 112.8, 111.2, 108.9, 108.5, 85.2, 82.6, 64.1, 60.3, 41.5, 29.6, 29.3, 25.0, 20.2 ppm.

HRMS (ESI): calculated for $C_{21}H_{25}O_6$ 373.1646 $[M+H]^+$, found 373.1646.



nordentatin (**4.01**)

4.52

To a solution of nordentatin (**4.01**, 25.6 mg, 0.082 mmol, 1 eq.) in HFIPA (5 mL) at 0 °C was added PIDA (3.0 mg, 0.0082 mmol, 0.1 eq.). The reaction mixture was stirred at room temperature for 2 days. The reaction was quenched with 1M HCl solution (15 mL) and diluted with H_2O (15 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with saturated aqueous NaCl solution (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography [PE:EtOAc 9:1 → 5:1] to afford pure **4.52** (3.6 mg, 0.012 mmol, 14%) as a light orange waxy solid.

Data for **4.52**:

R_f = 0.50 [2:1 PE:EtOAc]

IR (neat): 2976, 2929, 1751, 1657, 1427, 1348, 1125, 959 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, *J* = 9.6 Hz, 1H), 6.55 (d, *J* = 10.0 Hz, 1H), 6.31 (d, *J* = 9.6 Hz, 1H), 6.25 (dd, *J* = 17.6, 10.6 Hz, 1H), 5.38 (dd, *J* = 20.1, 10.3 Hz, 2H), 5.33 (s, 1H), 5.23 (s, 1H), 5.10 (d, *J* = 17.6 Hz, 1H), 1.63 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 178.5, 168.3, 166.3, 160.1, 140.1, 140.1, 135.2, 124.7, 118.9, 118.5, 115.3, 114.6, 113.5, 109.6, 81.0, 57.2, 28.7, 28.6, 19.9 ppm.

HRMS (ESI): calculated for $C_{20}H_{19}O_4$ 311.1278 $[M+H]^+$, found 311.1280.

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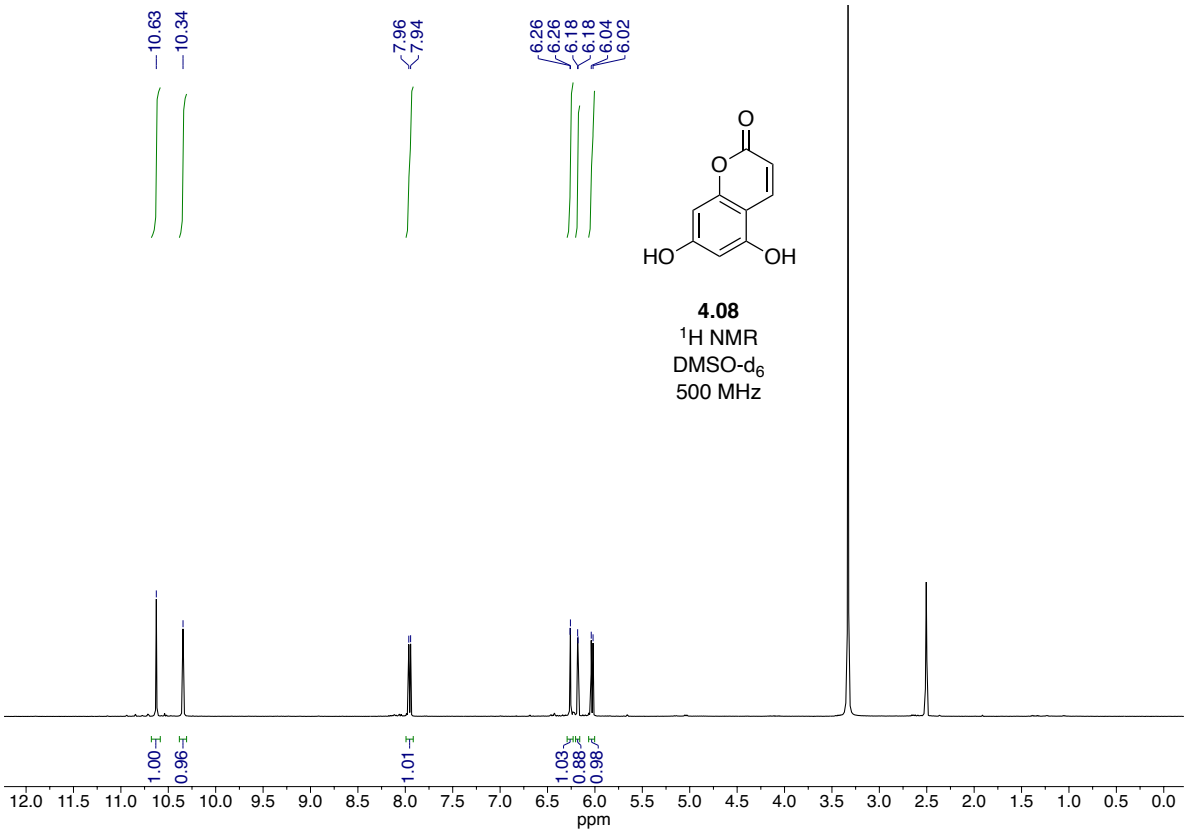
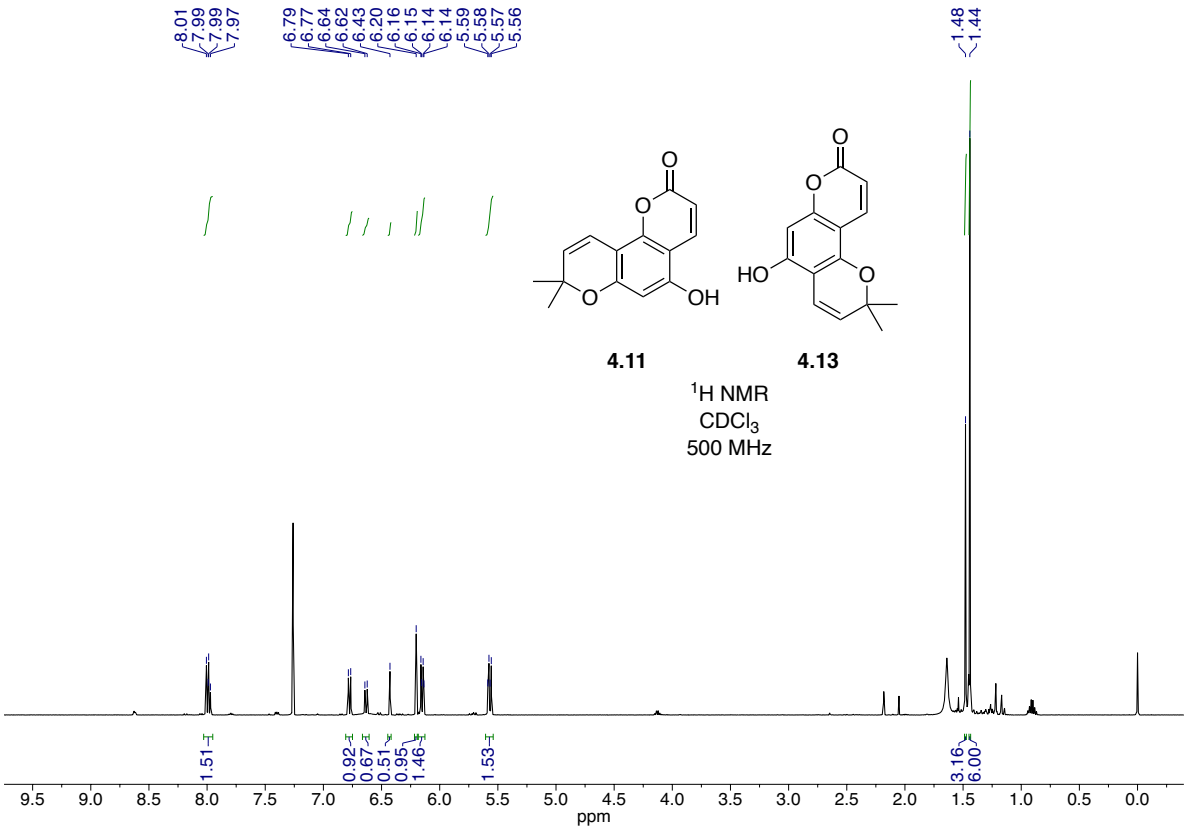
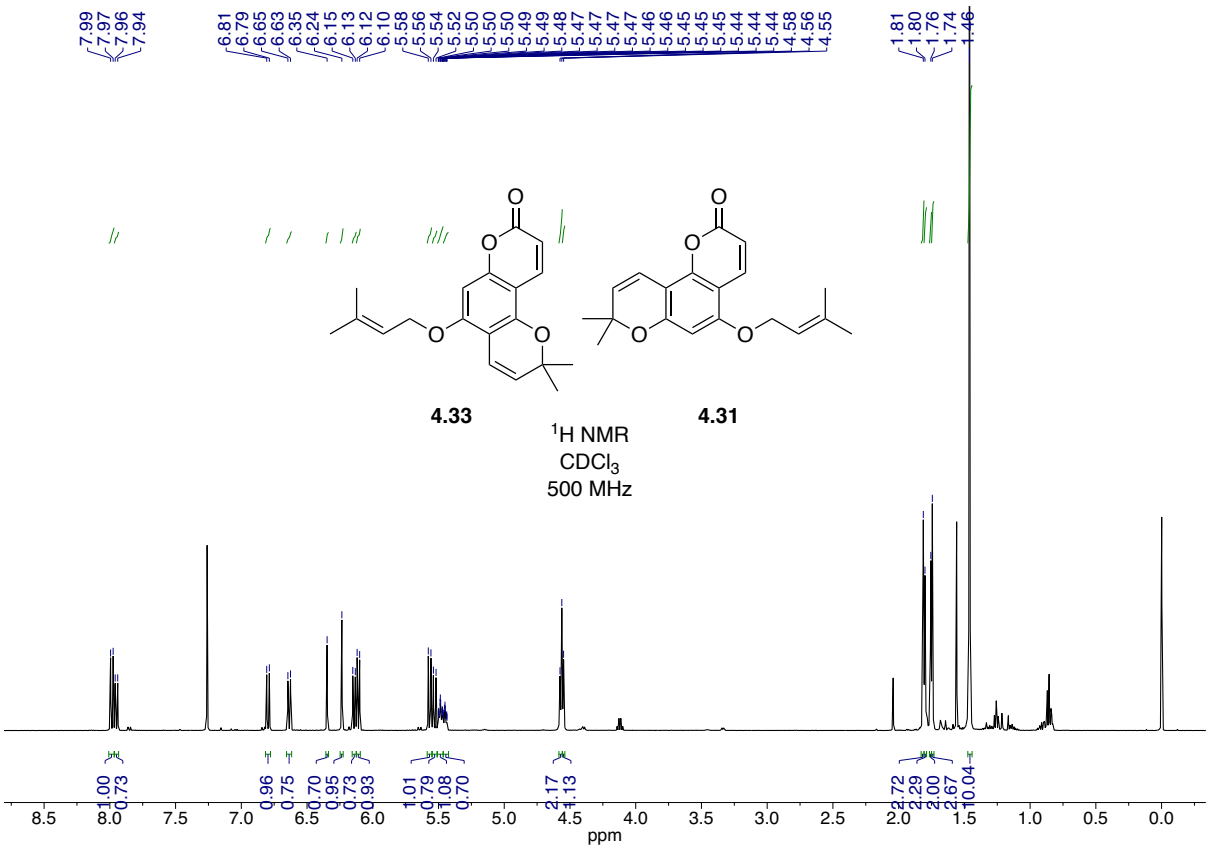
4.5.1 NMR Spectra



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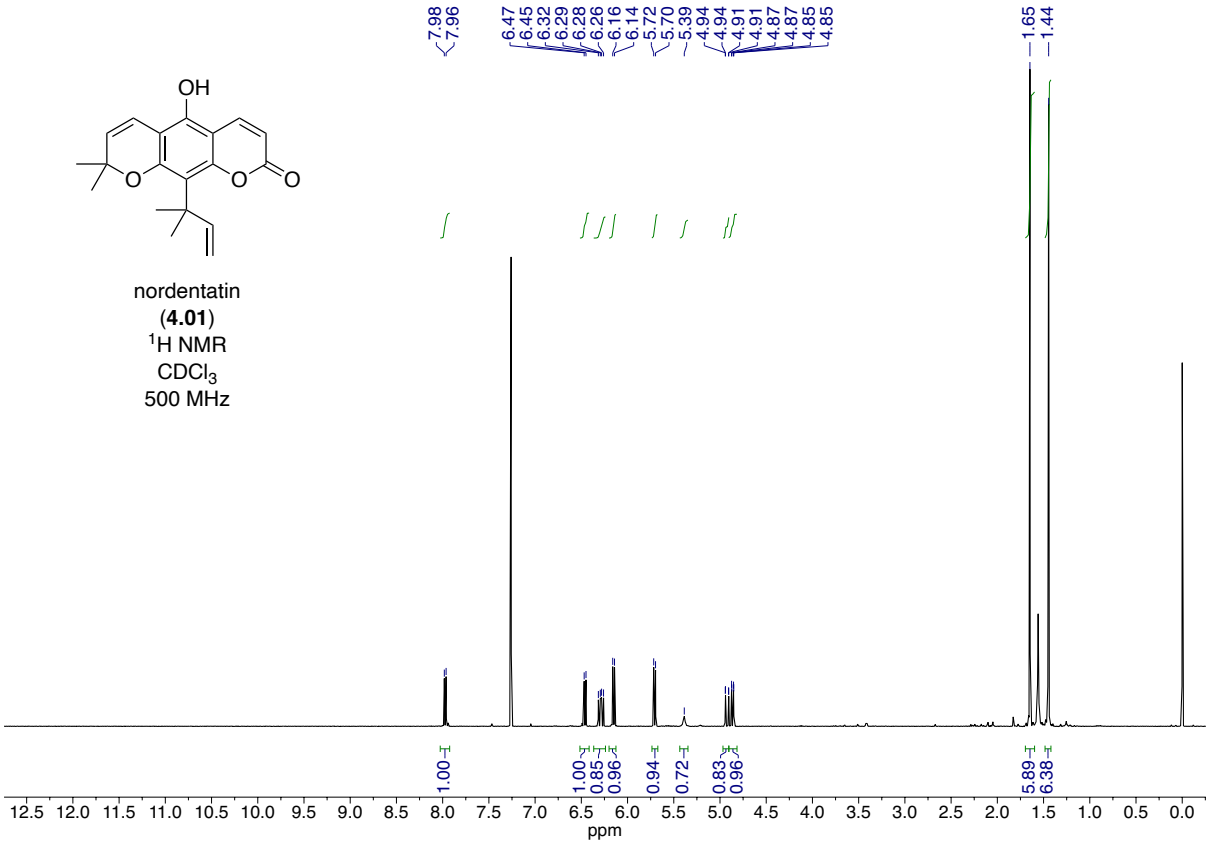
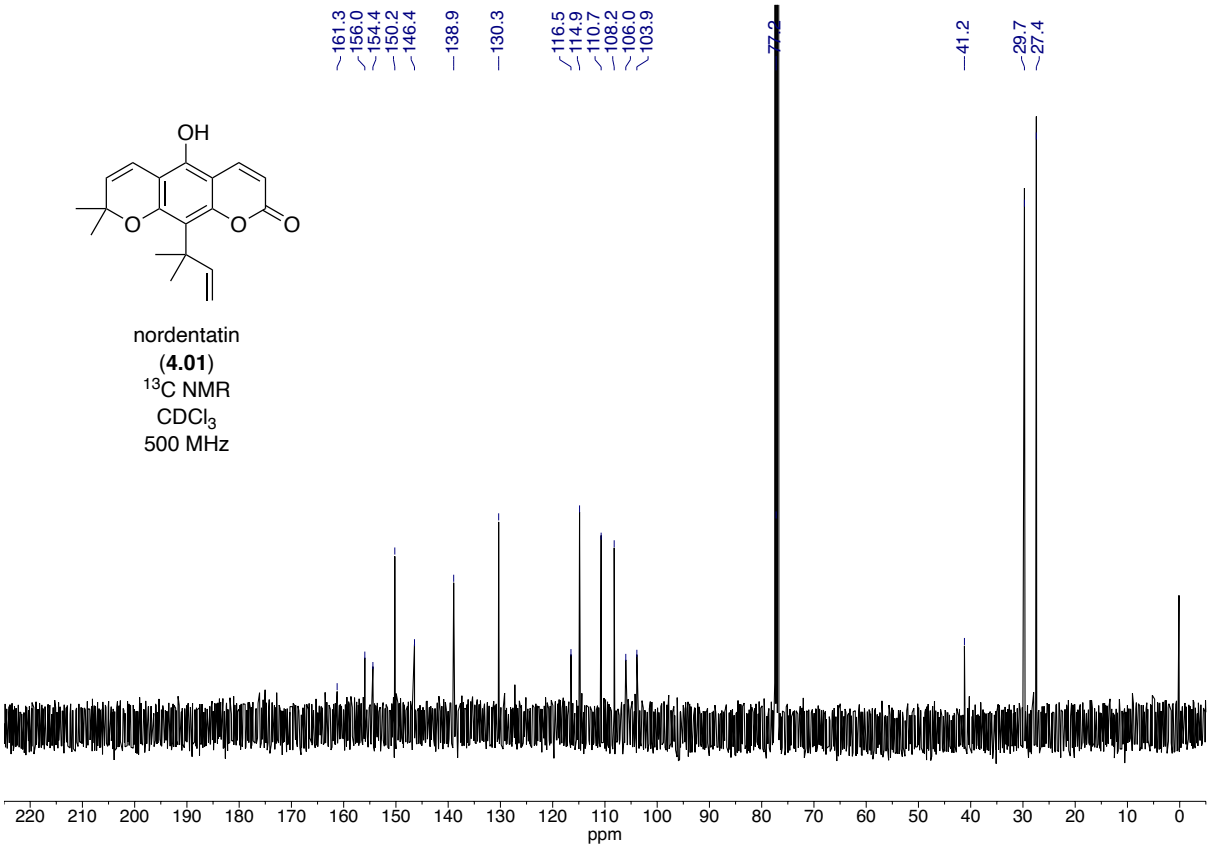
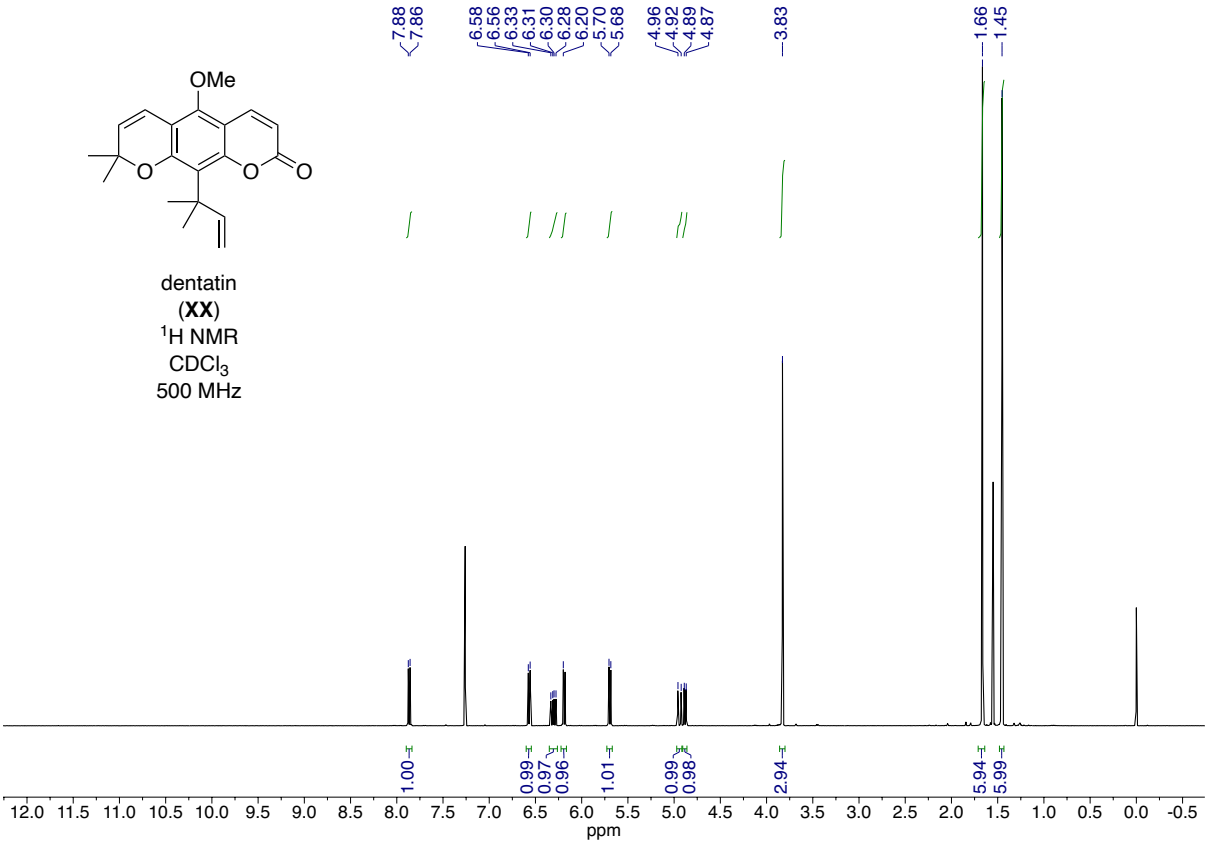
7.97
7.96
7.94
6.81
6.79
6.65
6.63
6.35
6.24
6.15
6.13
6.12
6.10
5.58
5.56
5.54
5.52
5.50
5.50
5.50
5.49
5.49
5.48
5.47
5.47
5.47
5.47
5.46
5.46
5.45
5.45
5.45
5.44
5.44
5.44
4.58
4.56
4.55
1.81
1.80
1.76
1.74
1.46
4.33
4.31
1H NMR
CDCl3
500 MHz
1.00
0.73
0.96
0.75
0.70
0.95
0.73
0.93
1.01
0.79
1.08
0.70
2.17
1.13
2.72
2.29
2.00
2.67
10.04
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm



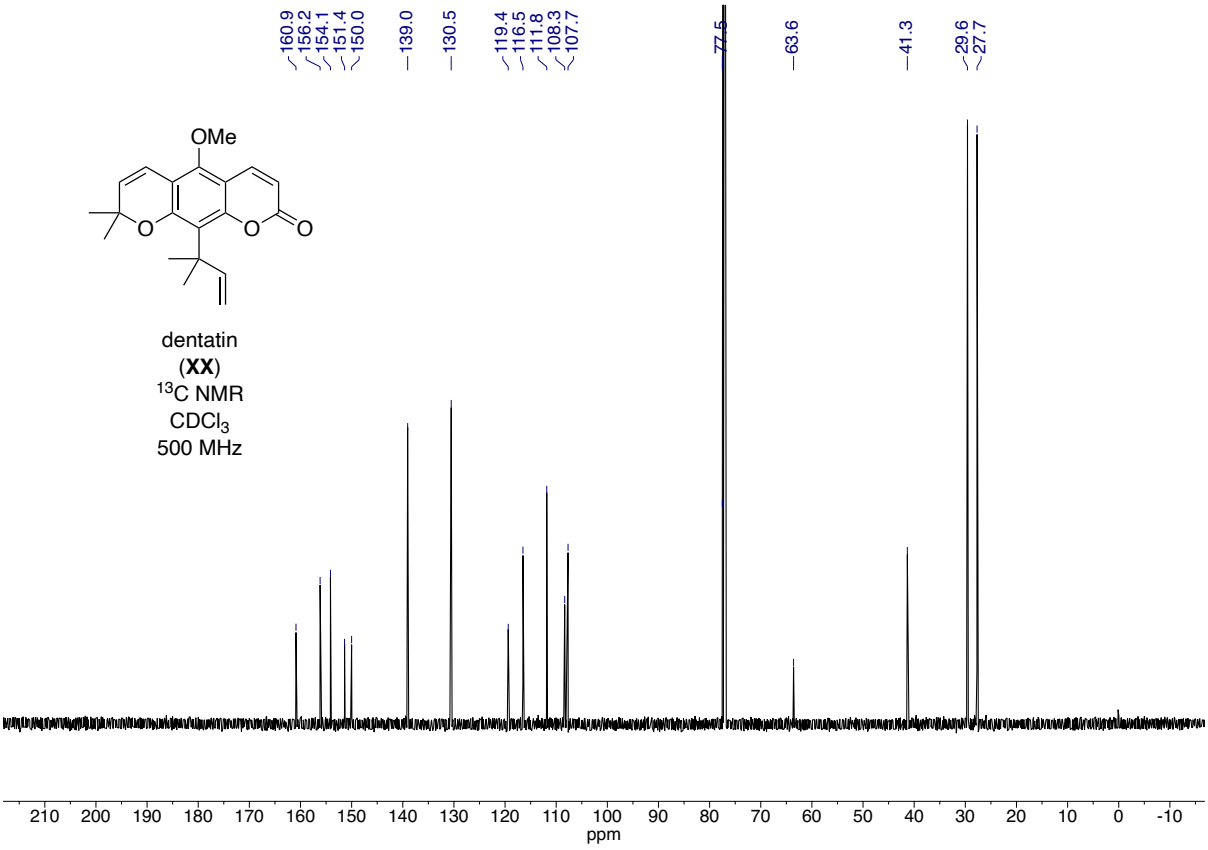
nordentatin
(**4.01**)
^{1}H NMR
$CDCl_3$
500 MHz



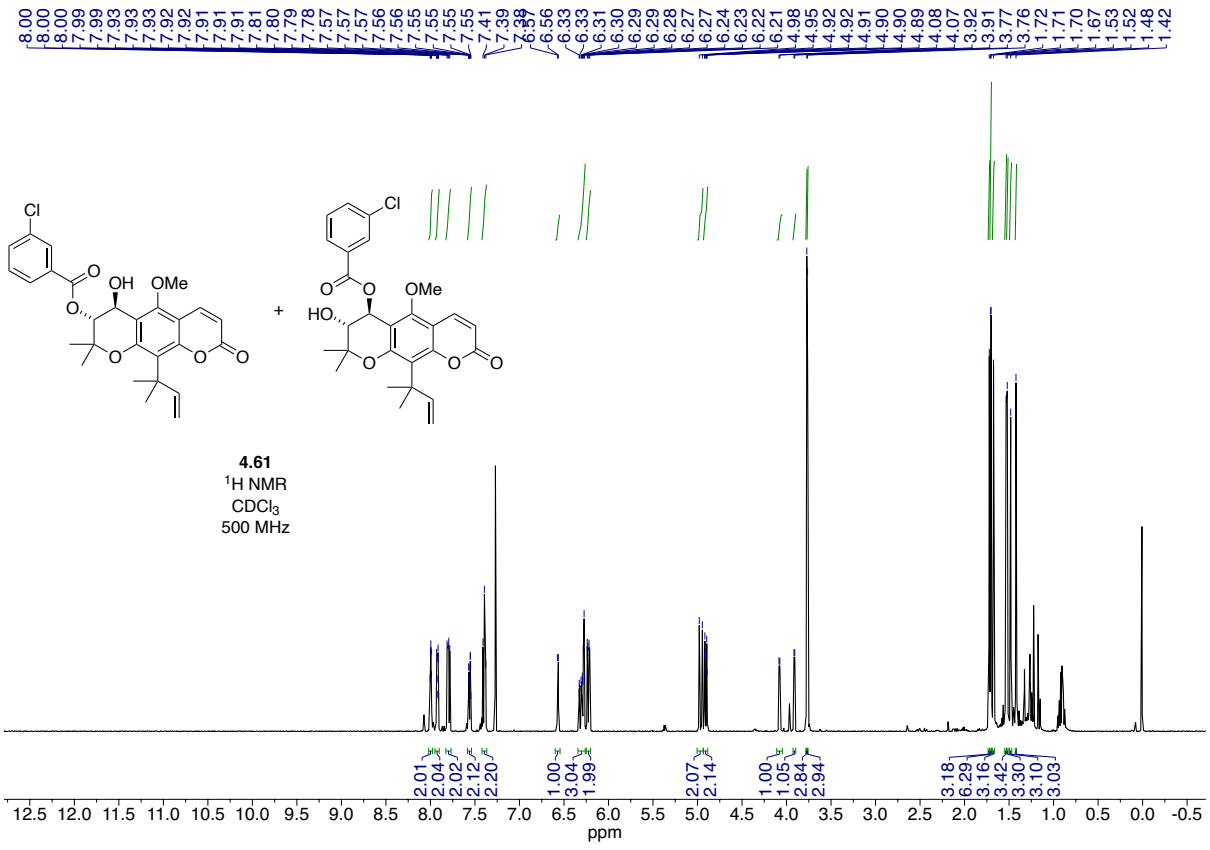
nordentatin
(**4.01**)
^{13}C NMR
$CDCl_3$
500 MHz



dentatin
(**XX**)
^{1}H NMR
$CDCl_3$
500 MHz



dentatin
(**XX**)
^{13}C NMR
$CDCl_3$
500 MHz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O
HO
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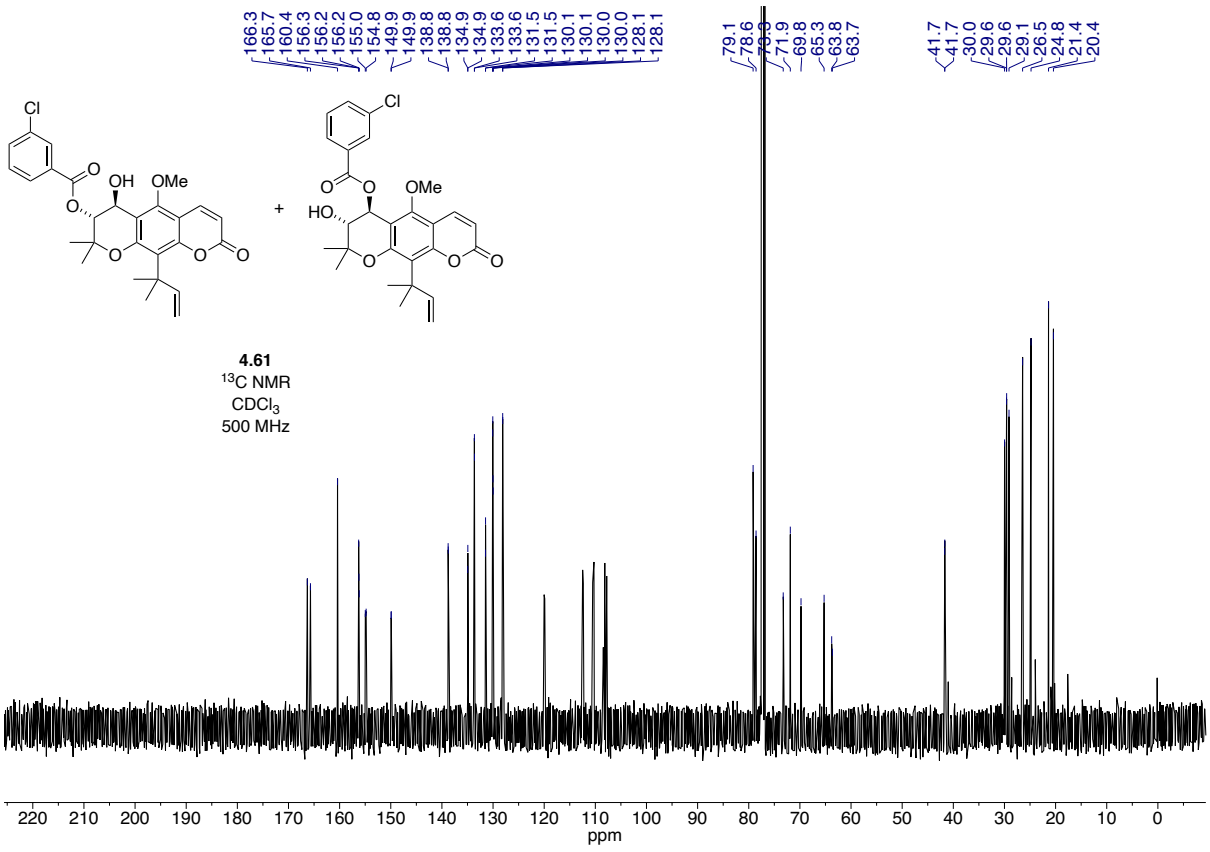
^{1}H NMR
$CDCl_3$
500 MHz
ppm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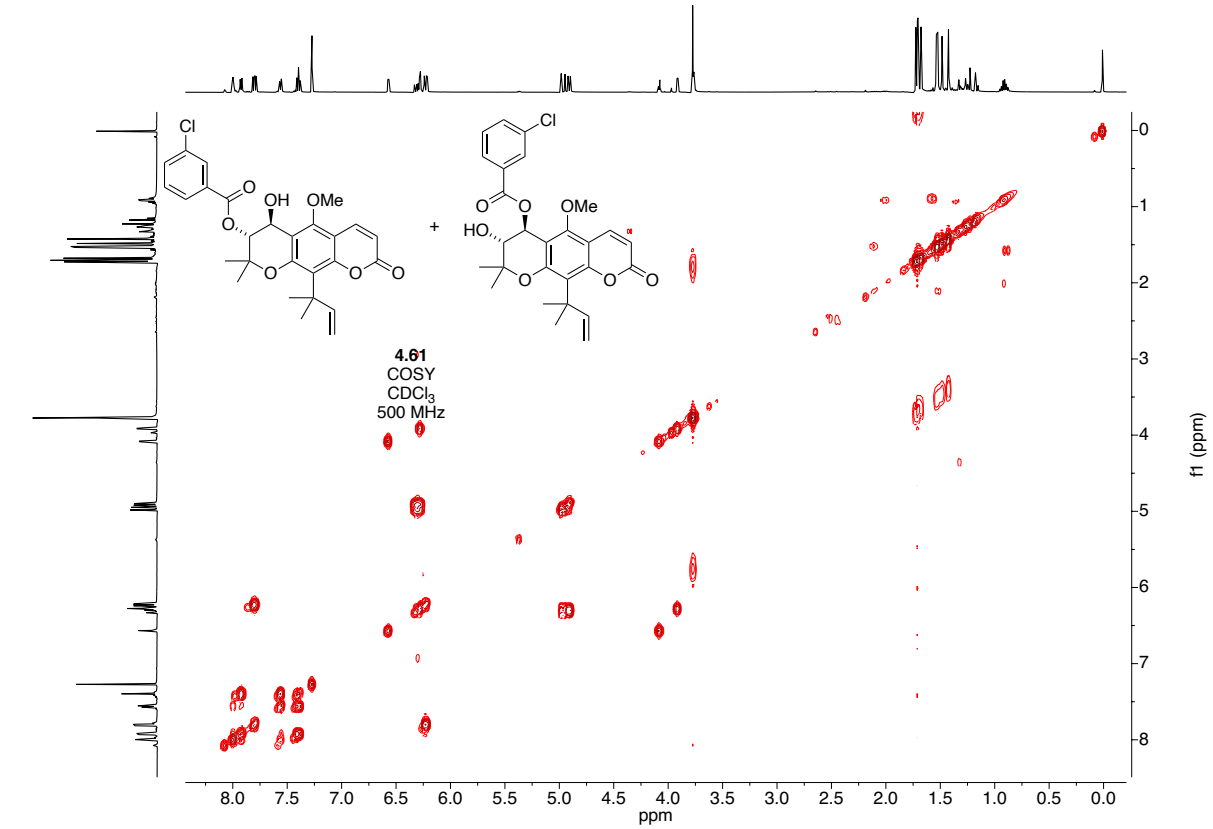
OMe
O
HO
4.61
^{13}C NMR
$CDCl_3$
500 MHz
ppm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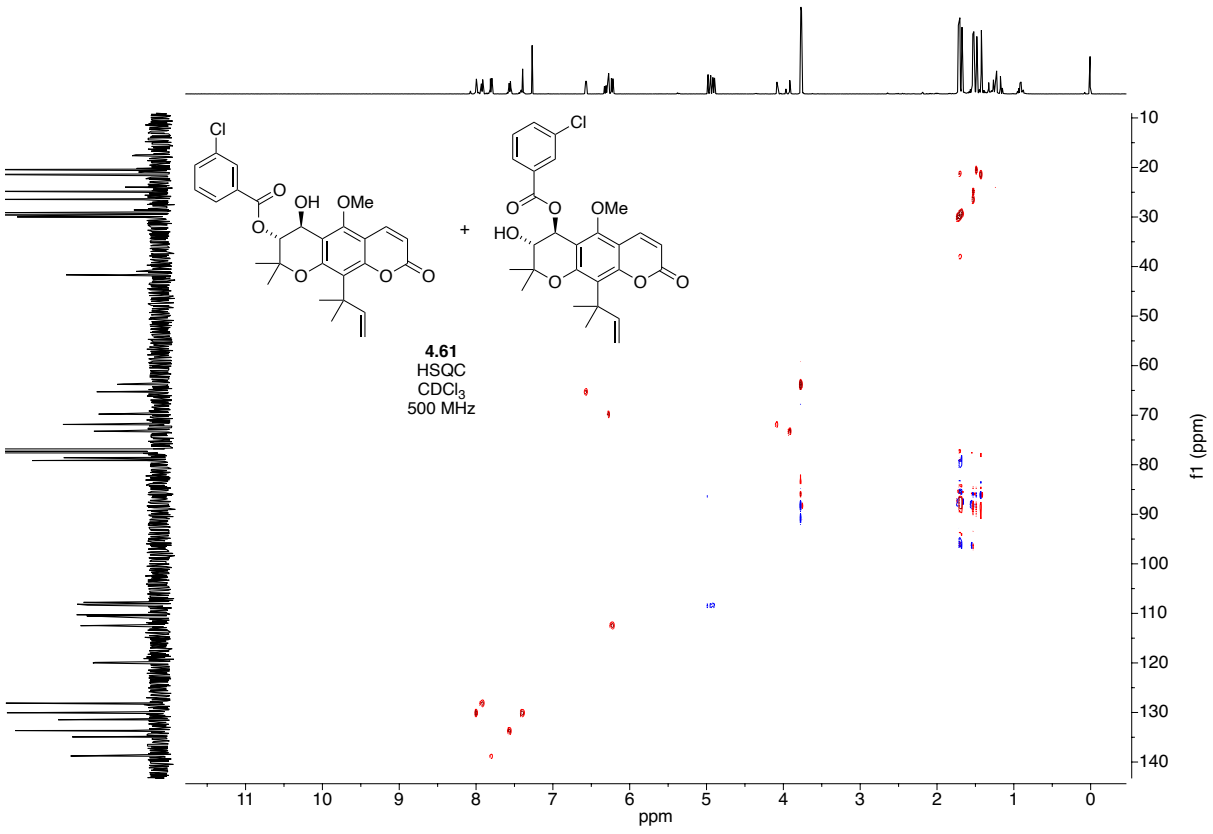
OH
OMe
HO
4.61
COSY
CDCl3
500 MHz
f1 (ppm)
ppm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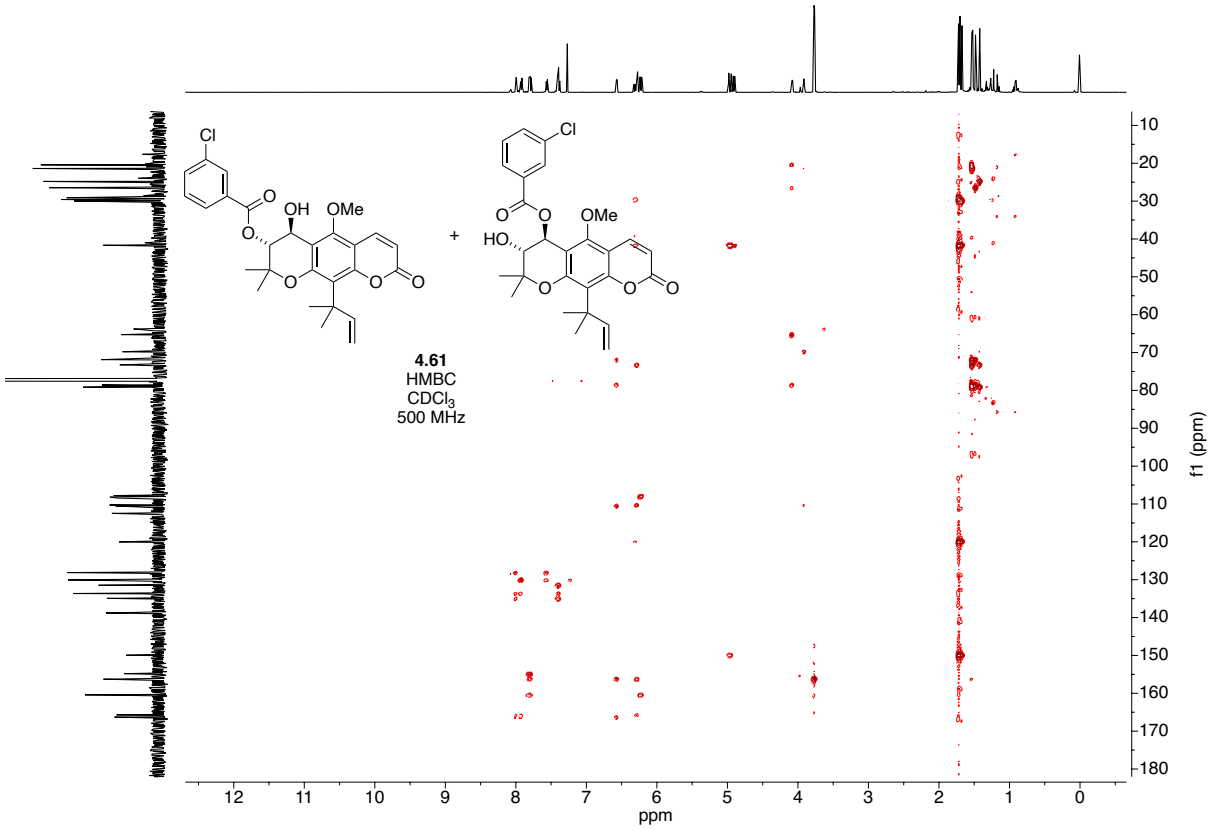
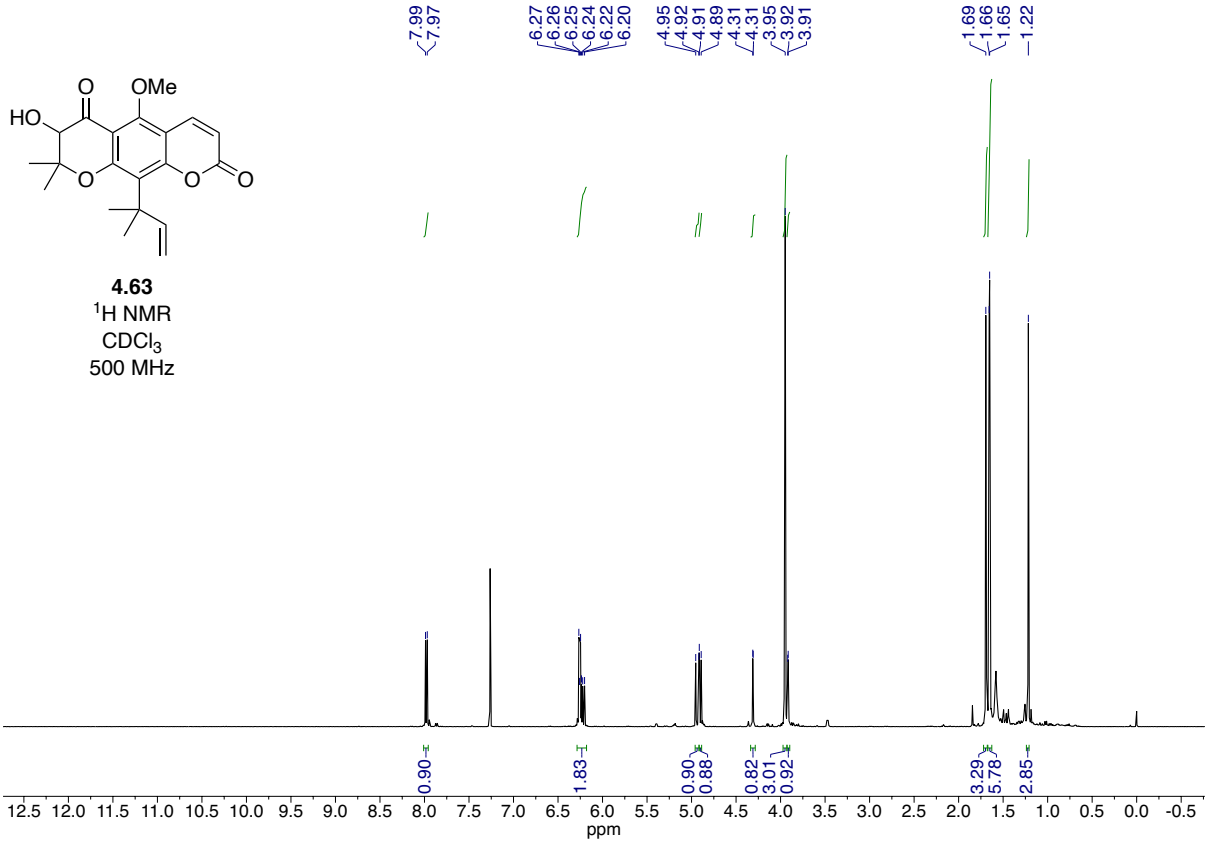
OH
OMe
HO
4.61
HSQC
CDCl3
500 MHz
f1 (ppm)
ppm


Cl
OH
OMe
O
O
O
O
O
+
Cl
HO
OMe
O
O
O
O
O
4.61
HMBC
CDCl3
500 MHz
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)



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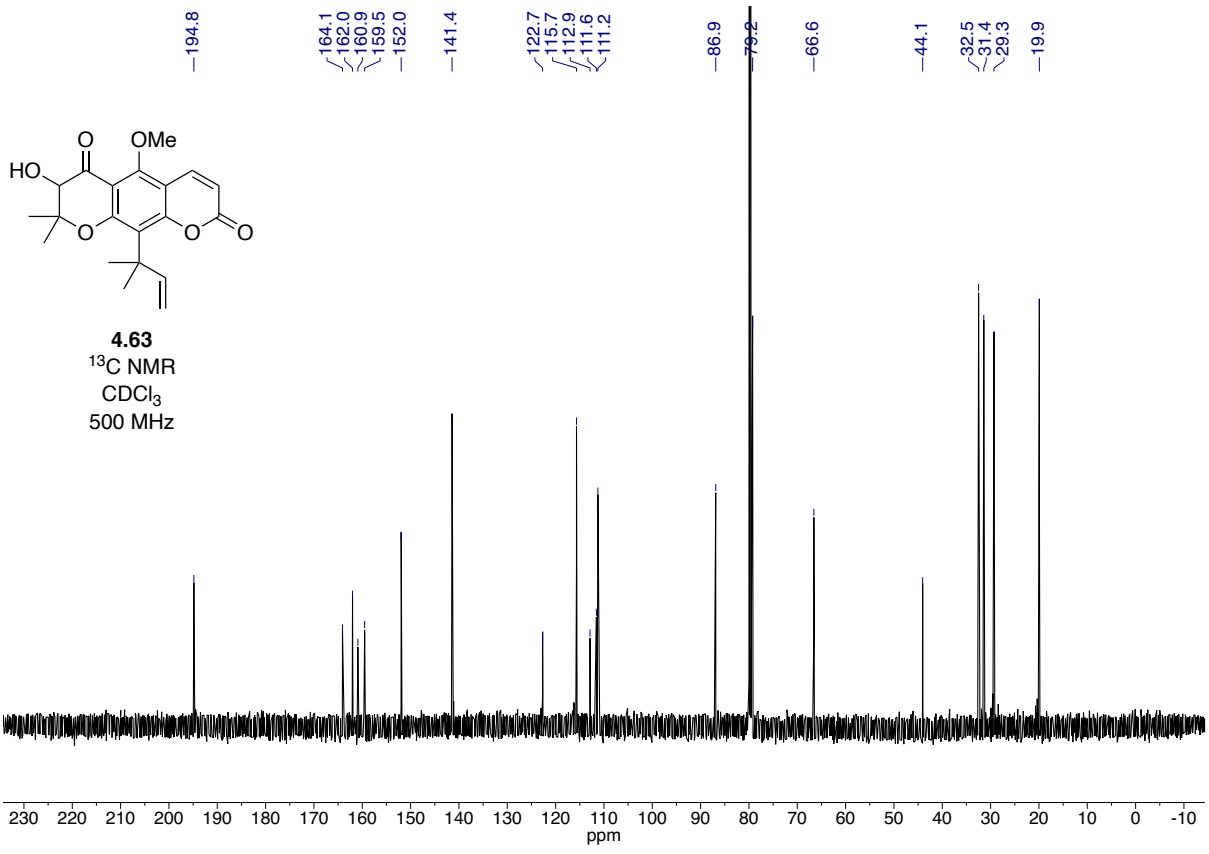

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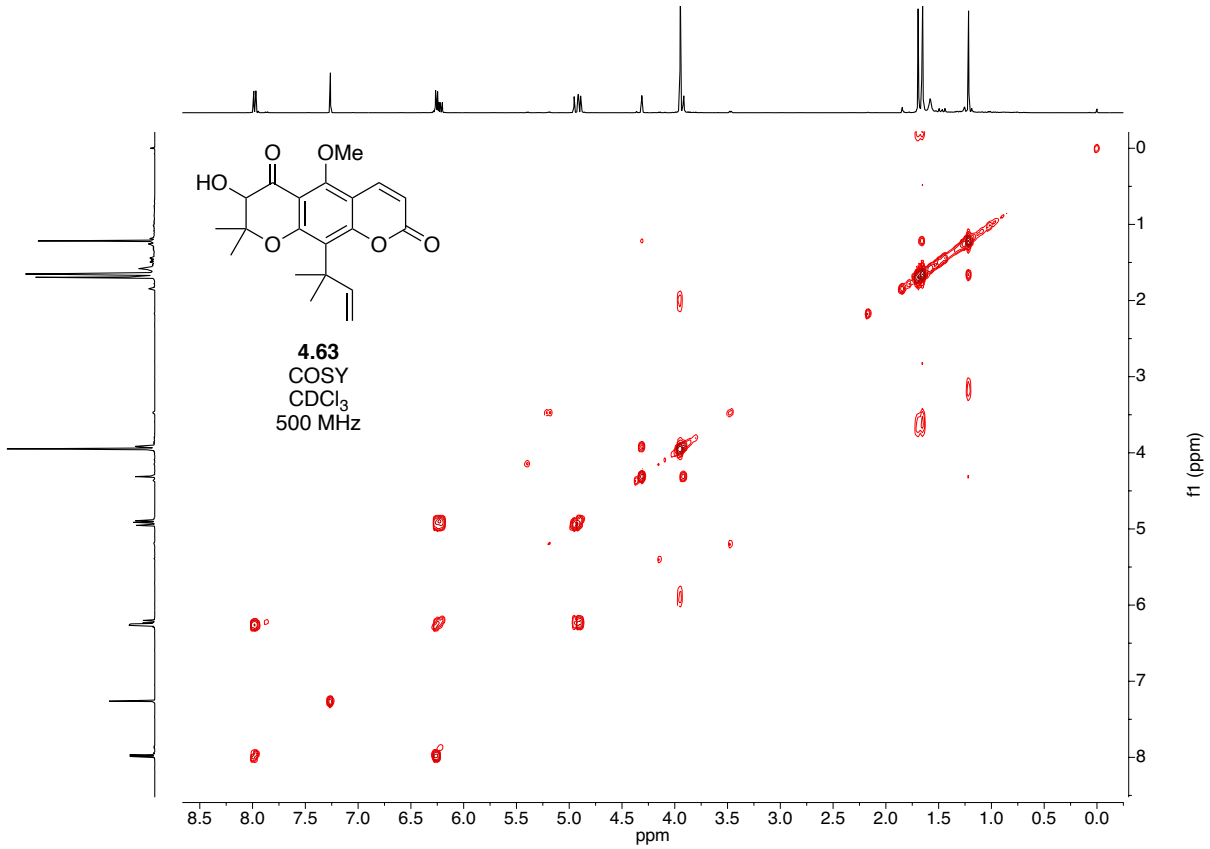
^{13}C NMR
$CDCl_3$
500 MHz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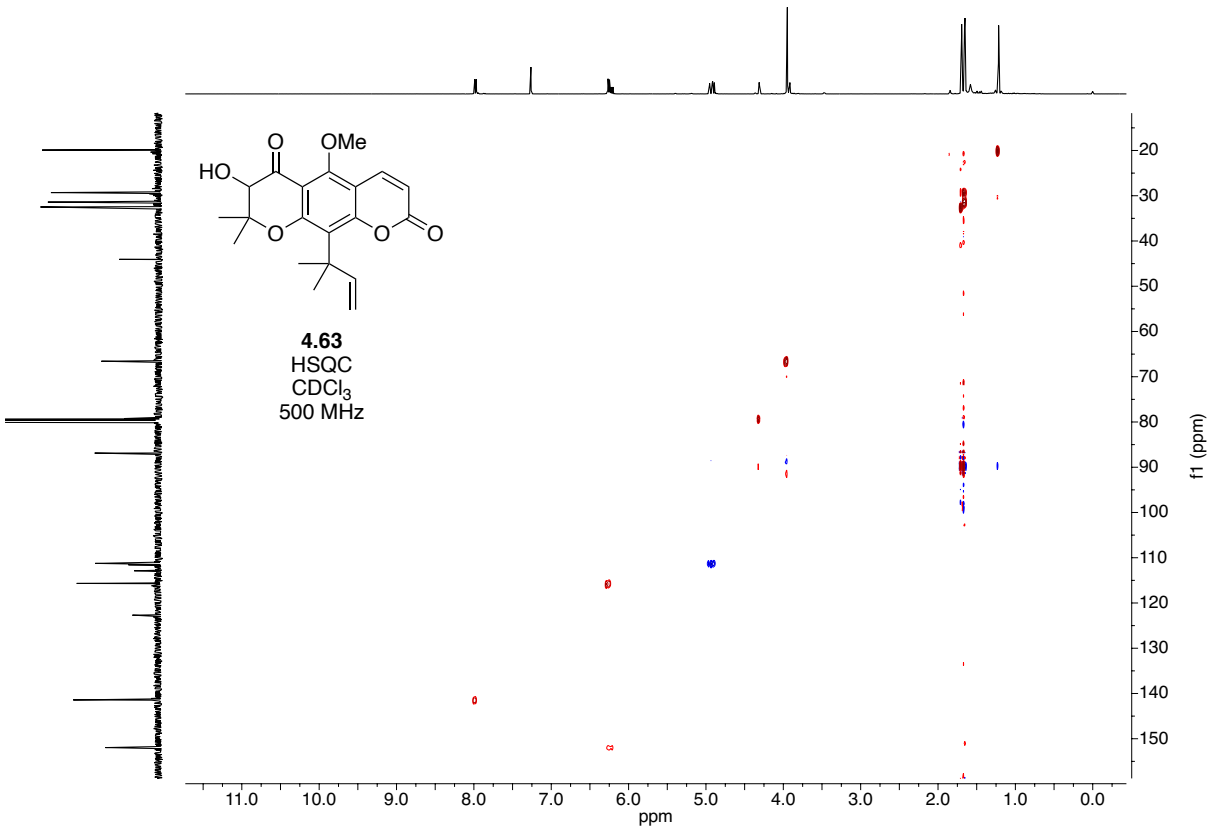
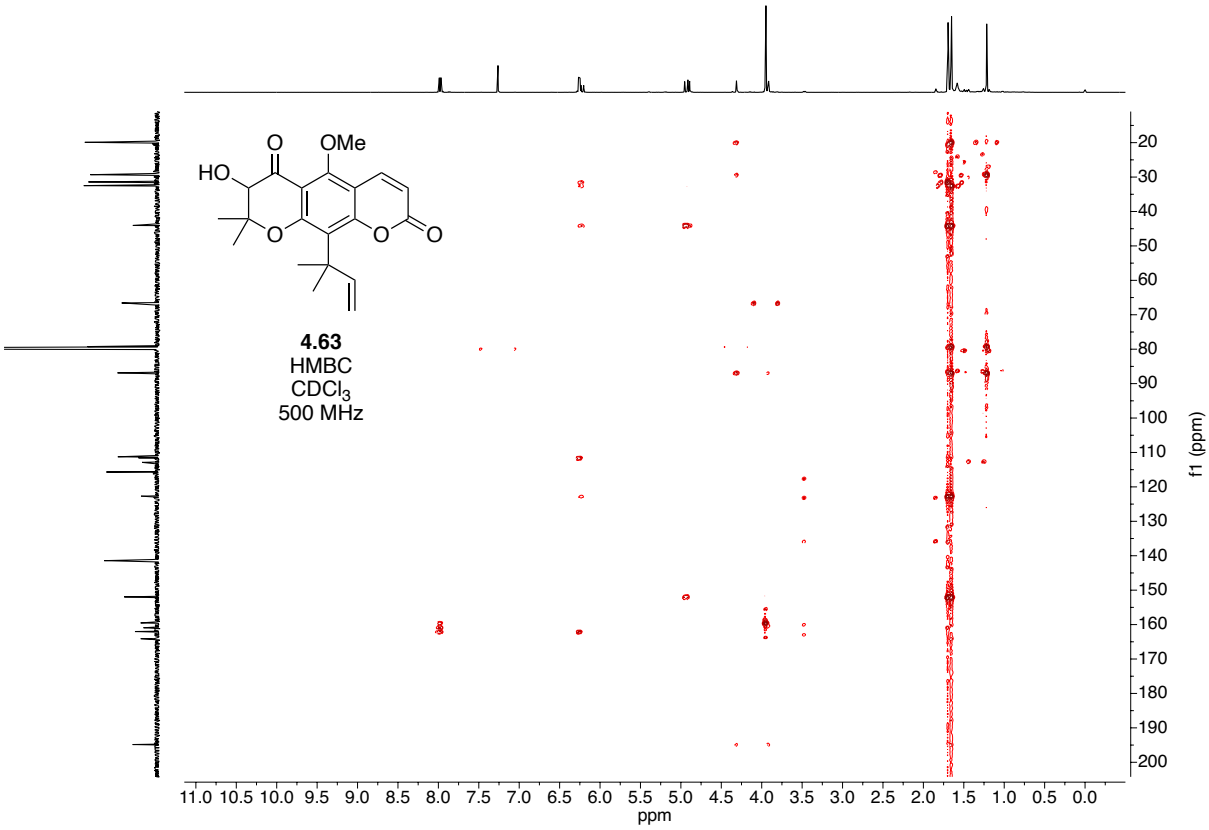
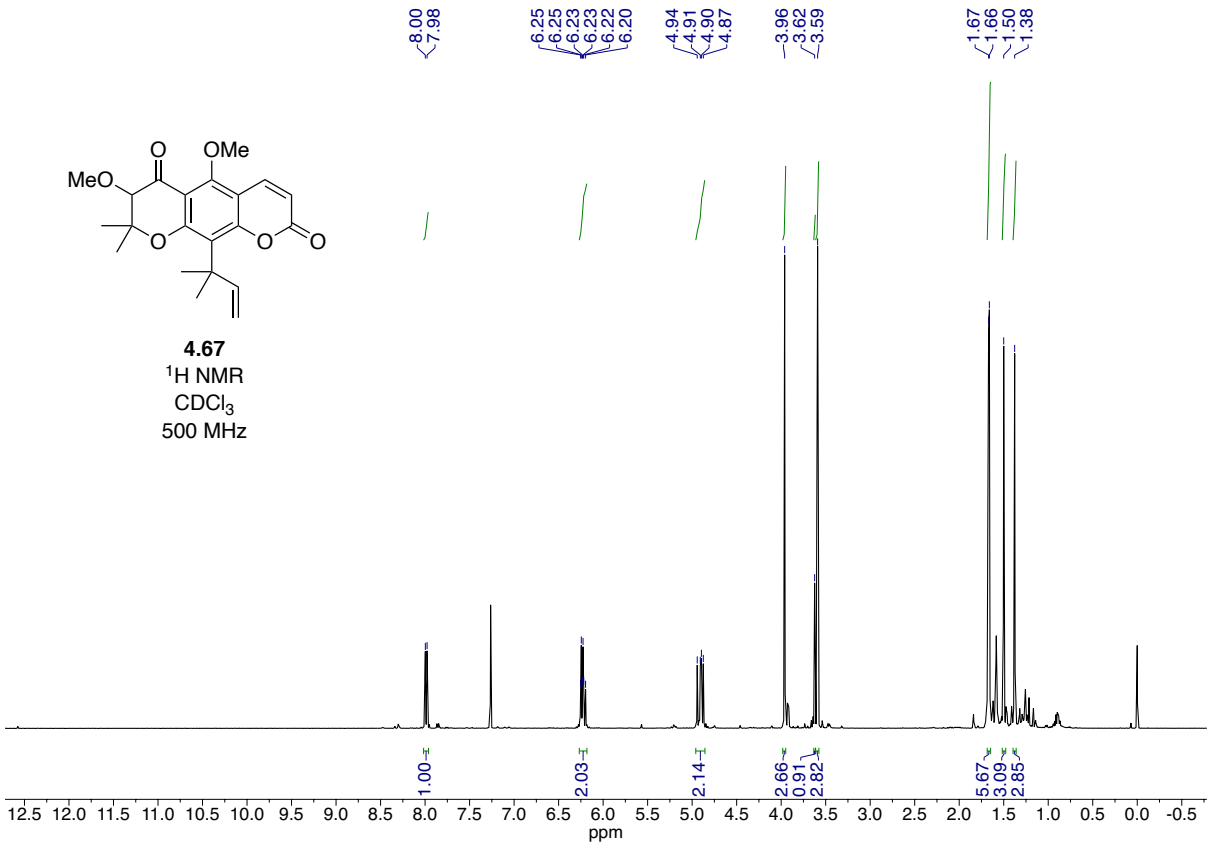
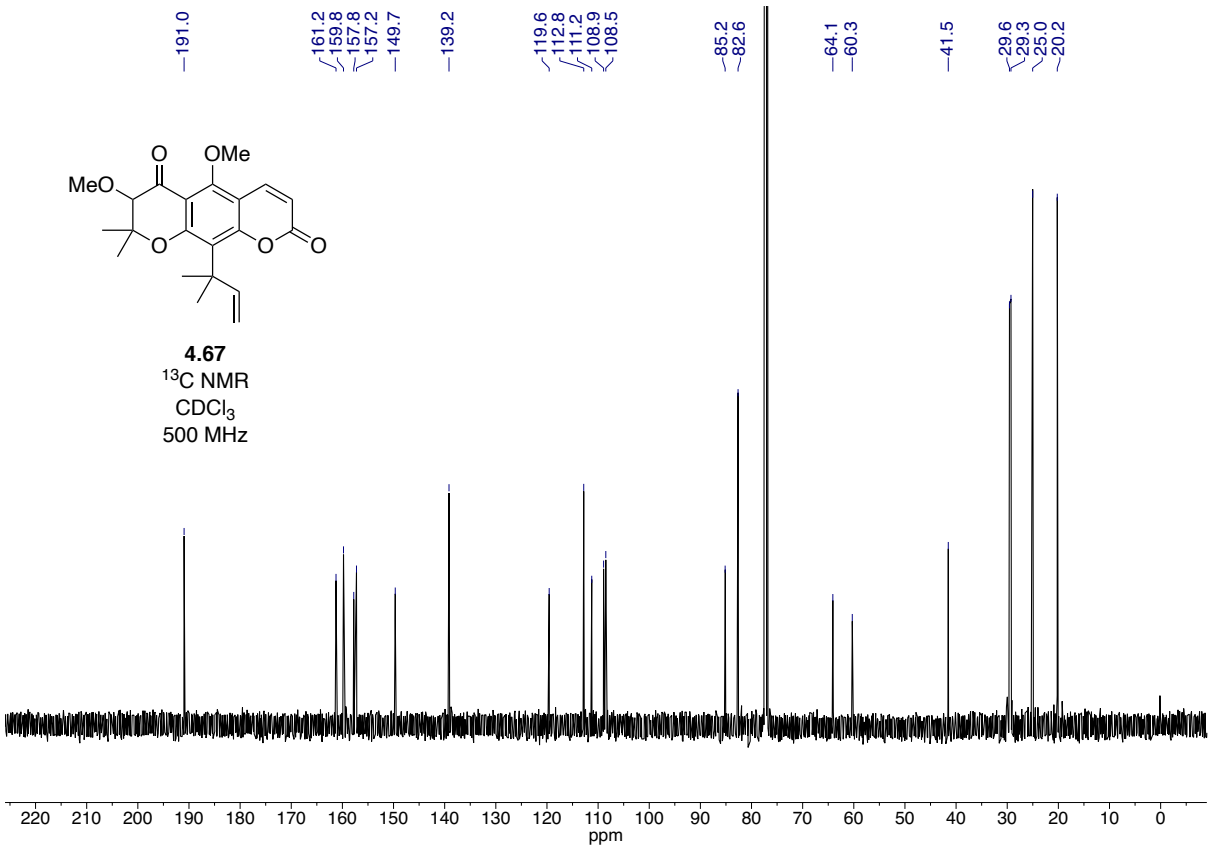
O
OMe
O
O
O
4.63
COSY
CDCl3
500 MHz
f1 (ppm)
ppm


HO
O
OMe
O
O
O
4.63
HSQC
CDCl3
500 MHz
f1 (ppm)
ppm


HO
O
OMe
O
O
O
4.63
HMBC
CDCl3
500 MHz
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm
20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200
f1 (ppm)



4.67
^{1}H NMR
$CDCl_3$
500 MHz



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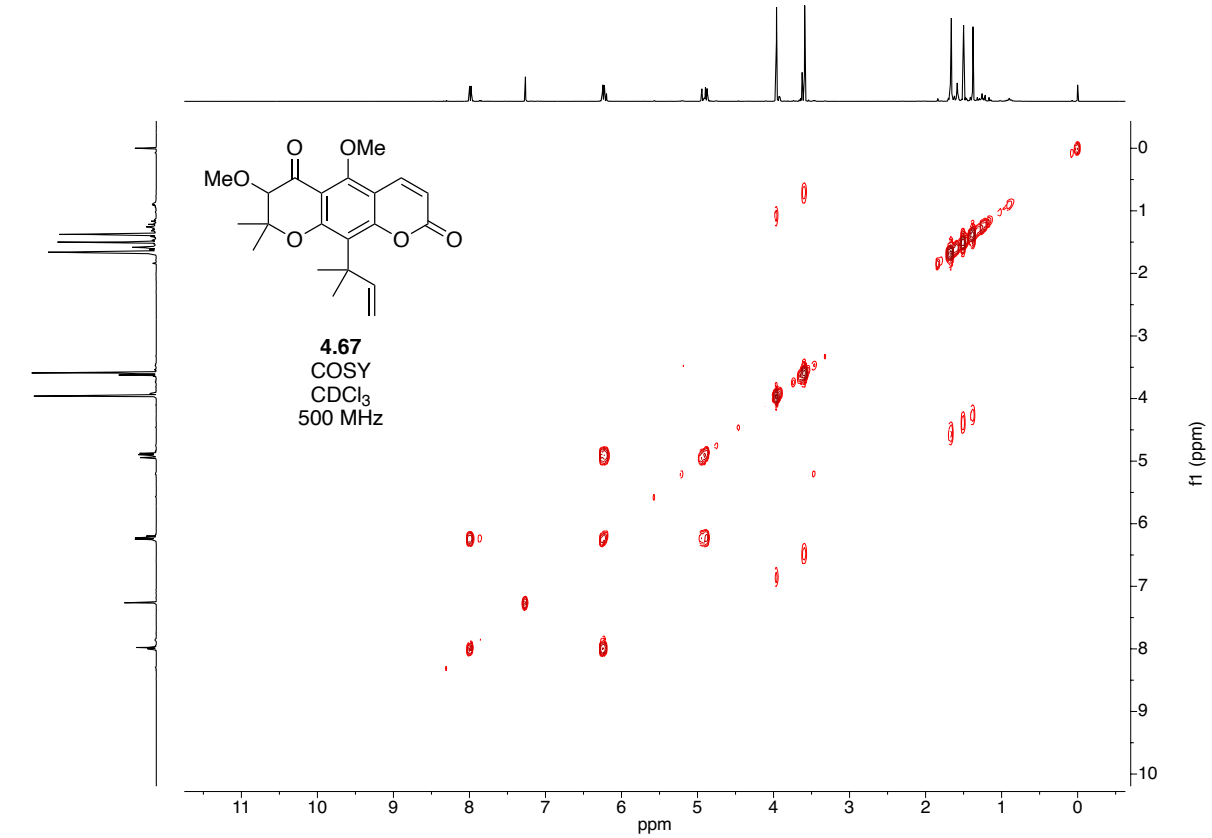
^{13}C NMR
$CDCl_3$
500 MHz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OMe
O
O
O
O
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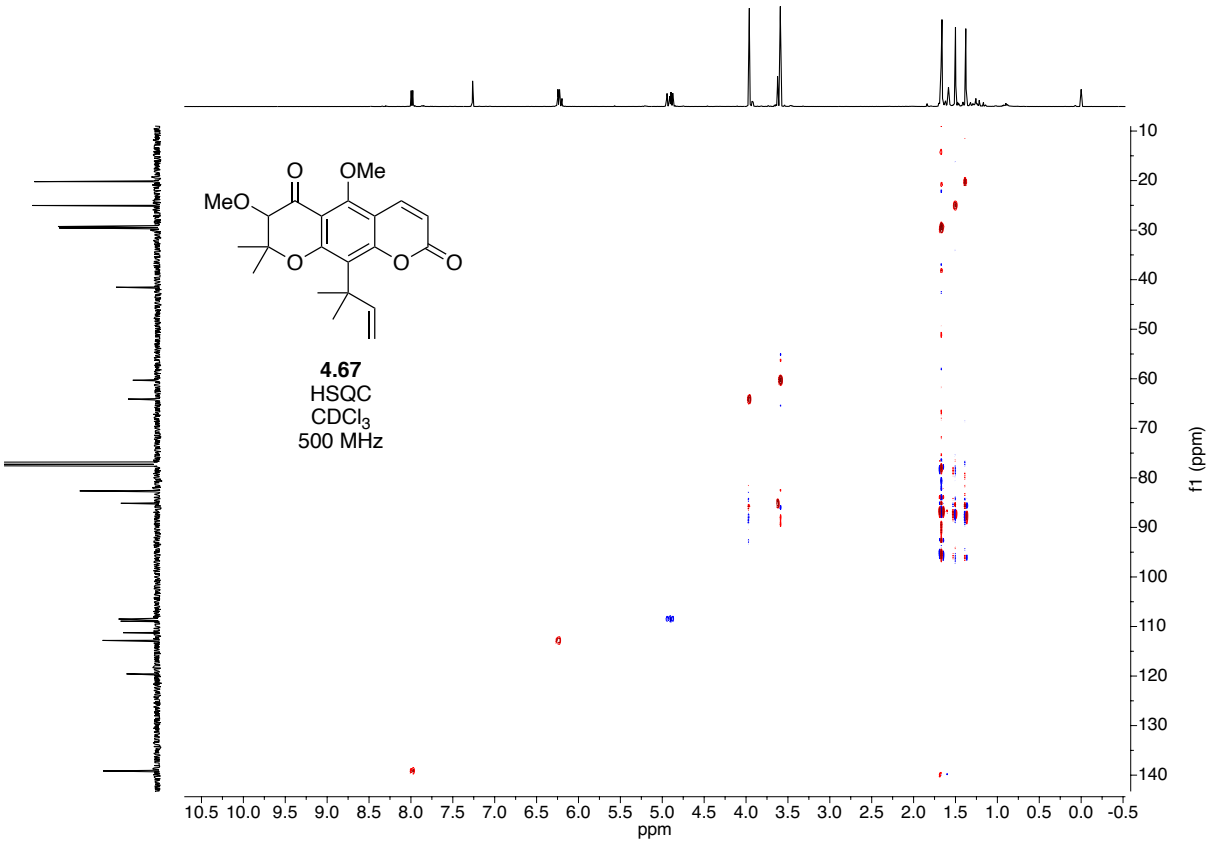
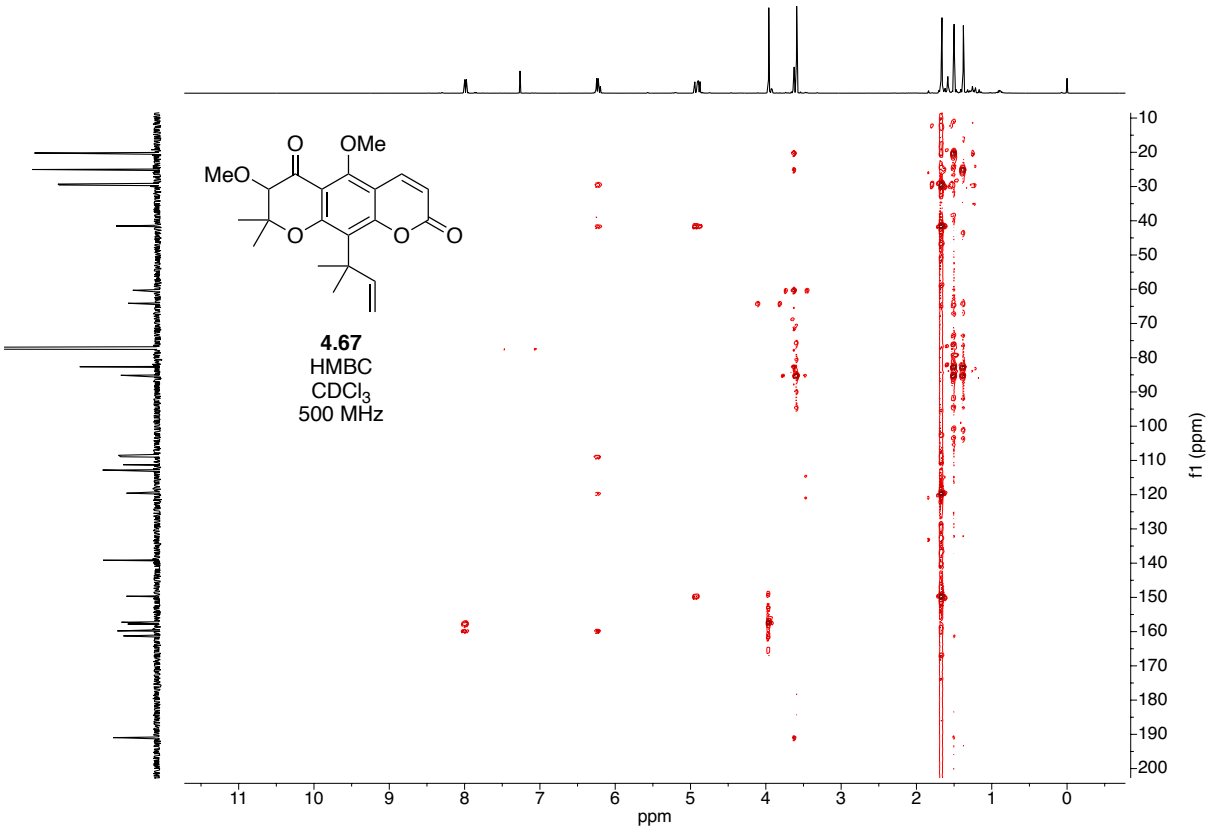
COSY
CDCl3
500 MHz
ppm
f1 (ppm)


MeO
OMe
O
O
O
O
4.67
HSQC
CDCl3
500 MHz
ppm
f1 (ppm)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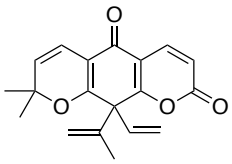
OMe
MeO
O
O
O
4.67
HMBC
CDCl3
500 MHz
f1 (ppm)
ppm



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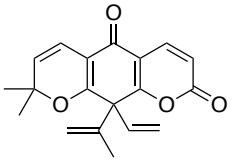

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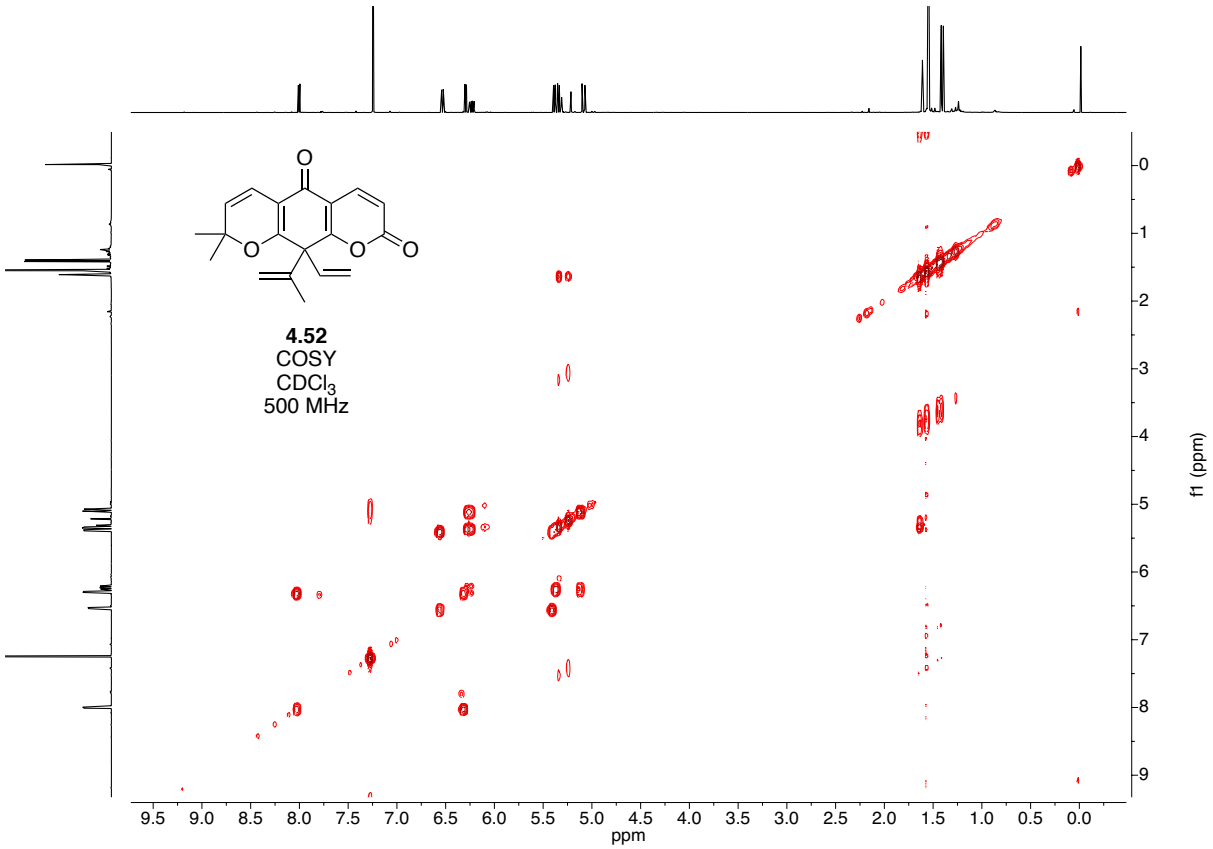
500 MHz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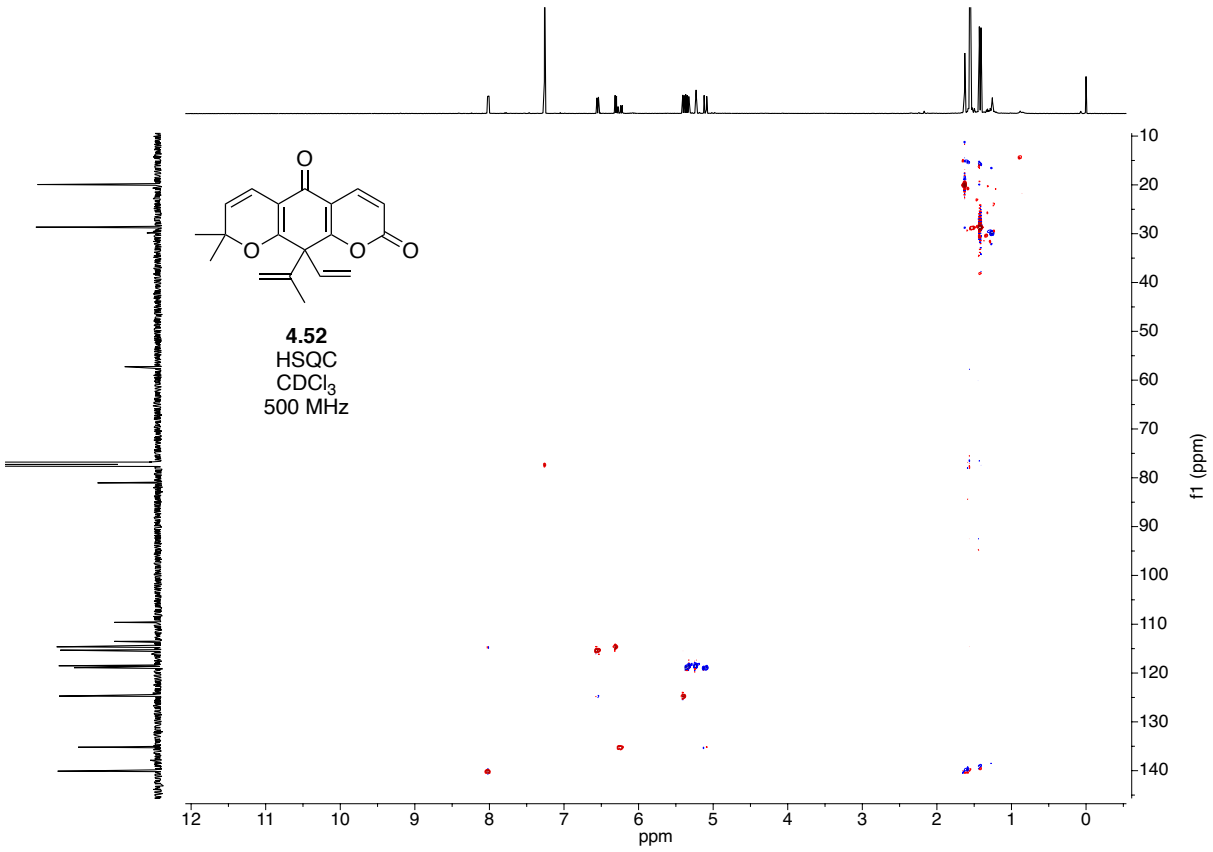
ppm
f1 (ppm)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ppm
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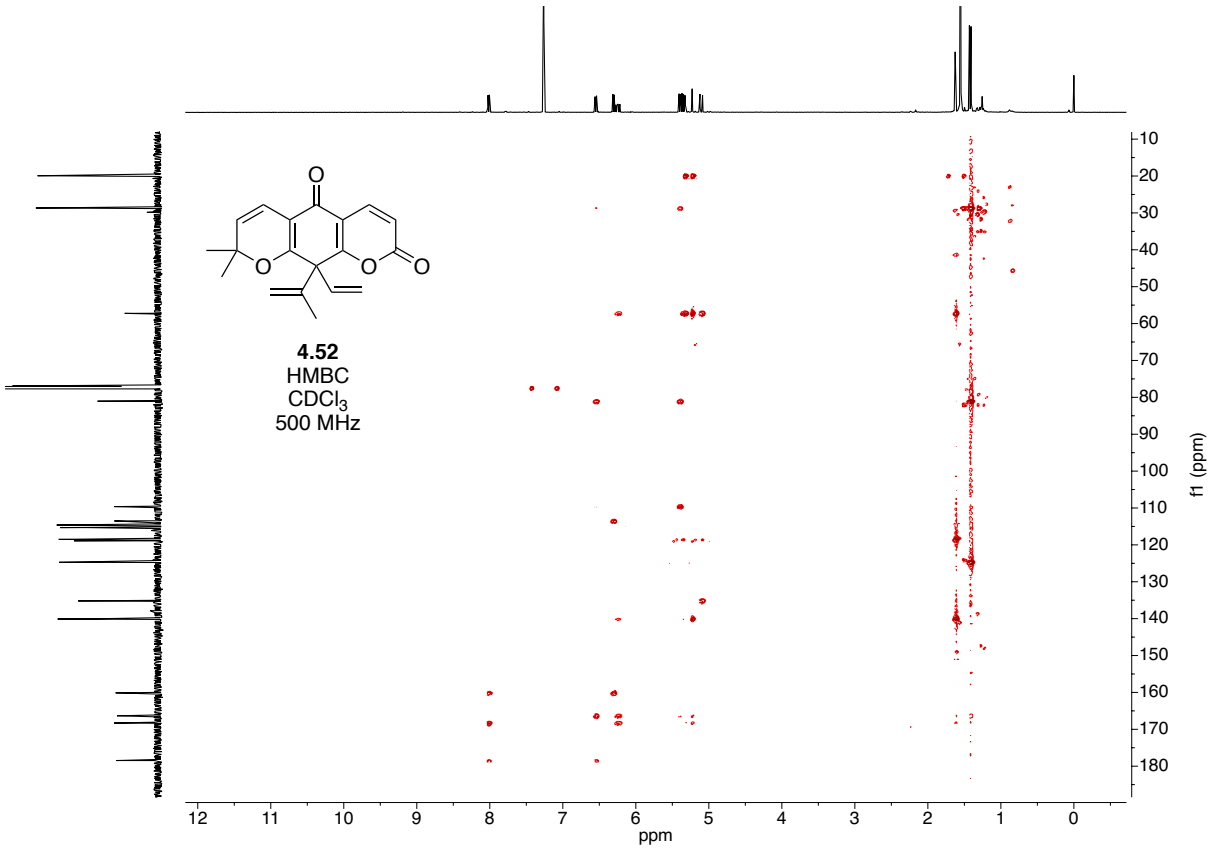
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HMBC
CDCl3
500 MHz
ppm
f1 (ppm)