Biomimetic Synthesis of Meroterpenoid Natural Products Using Dearomatization Strategies

Thesis submitted for the degree of Doctor of Philosophy

Department of Chemistry

University of Adelaide

Henry P. Pepper

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DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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LIST OF ABBREVIATIONS

AIBN	Azobisizobutyronitrile
aq	Aqueous
ATP	Adenosine Triphosphate
BCG	*Mycobacteria Bovis*
BRSM	Based on Recovered Starting Material
bs	Broad Singlet
CAM	Ceric Ammonium Molybdate
CAN	Ceric Ammonium Nitrate
CA SC5314	*Candia Abicans* SC5314
CD	Circular Dichroism
CoA	Coenzyme A
COSY	Correlated Spectroscopy
cm^{-1}	Wavenumber(s)
d	Doublet
DDT	*para*-Dichlorodiphenyltrichloroethane
DBE	Double Bond Equivalence
DBU	1,8-Diazabicycloundec-7-ene
DDQ	2,3-Dichloro-5,6-Dicyano-1,4-Benzoquinone
DEAD	Diethyl Azodicarboxylate
DHP	3,4-Dihydro-*2H*-pyran

DIBAL-H	Diisobutylaluminium Hydride
DMSO	Dimethyl Sulfoxide
DMF	*N*,*N*-dimethylformamide
dppf	1,1'-Bis(diphenyphosphino)ferrocene
EDDA	Ethylenediaminediacetate
EI	Electron Impact
ESI	Electrospray Ionization
EtOAc	Ethyl Acetate
Grubbs II	Grubbs' Second Generation Catalyst
h	hour(s)
HMBC	Heteronuclear Multiple Bond Connectivity
HMPA	Hexamethylphosphoramide
HMQC	Heteronuclear Multiple Quantum Coherence
HPLC	High Performance Liquid Chromatography
IC_{50}	Half Maximal Inhibitory Concentration
IR	Infrared Spectrum
J	Coupling Constant
KHMDS	Potassium Hexamethyldisilazide
LDA	Lithium Diisopropylamide
m	Multiplet
m/z	Mass Units

MES	2-(*N*-methylmorpholino)-ethanesulfonic Acid
MIC	Minimum Inhibitory Concentration
MOM	Methoxymethyl
mp	Melting Point
MPAP	Monocyclic Polyprenylated Acylphloroglucinol
MRSA	Methicillin Resistant *Staphylococcus Aureus*
MS	Mass Spectrum
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NaHMDS	Sodium Hexamethyldisilazide
NMP	*N*-methyl-2-Pyrrolidine
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
PA01	*Pseudomonas Aeruginosa*
PI3K	Phosphatidylinositol 3-Kinase
PPAP	Polycyclic Polyprenylated Acylphloroglucinol
PP	Pyrophosphate
ppm	Parts Per Million
PPTS	Pyridinium *para*-Toluenesulfonate
p-TsOH	*para*-Toluenesulfonic Acid

q	quartet
R_f	Retention Factor
ROESY	Rotating Frame Nuclear Overhauser Effect Spectroscopy
s	Singlet
SA	*Staphylococcus Aureus*
SAR	Structure Activity Relationship
rt	Room Temperature
t	Triplet
TBS	*tert*-Butyltrimethylsilyl
TBAF	Tetrabutylammonium Fluoride
TES	Triethylsilyl
Tf	Trifluoromethylsulfonate
THC	Tetrahydrocannabinol
THF	Tetrahydrofuran
THN	1,3,6,8-Tetrahydroxynaphthalene
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
UV	Ultraviolet Light
VHPO	Vanadium Dependent Haloperoxidase

ABSTRACT

Synthetic efforts towards various meroterpenoid natural products based on biosynthetic speculation were undertaken in order to gain biosynthetic insight and to develop efficient syntheses of some structurally complex, biologically active compounds.

The first total synthesis of the PPAP natural product garcibracteatone was achieved in four linear steps from phloroglucinol (0.6% overall yield). The key biomimetic synthetic step was an oxidative radical cyclization cascade reaction, where four new carbon-carbon bonds, four new carbocyclic rings and five new stereocentres were formed in the one step.

The first total synthesis of merochlorin A was achieved in five linear steps from methyl-3,5-dimethoxyphenylacetate (6% overall yield). The key biomimetic synthetic step was a [5 + 2] cycloaddition reaction induced be oxidative dearomatization to form the bicyclo[3.2.1]octane core.

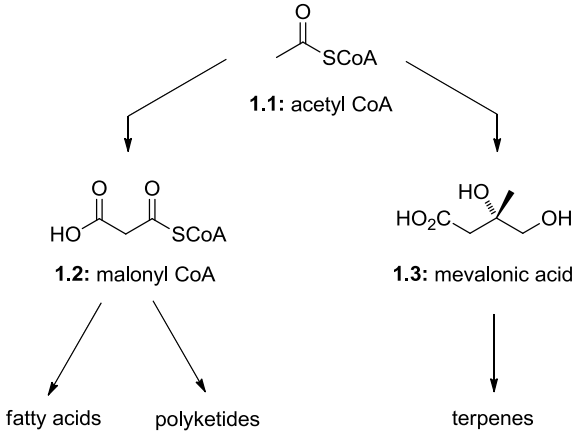
The first total synthesis of the napyradiomycin natural product naphthomevalin was achieved in 11 steps from methyl-3,5-dimethoxyphenylacetate (1.4% overall yield). The key biomimetic synthetic step was a thermal α-ketol rearrangement reaction to form the naphthoquinone core of the napyradiomycins. The synthetic naphthomevalin was additionally converted into A80915G *via* a biomimetic S_N2 epoxidation reaction, and into napyradiomycin A1 *via* a chemoenzymatic reaction.

CHAPTER 1

Thesis Introduction

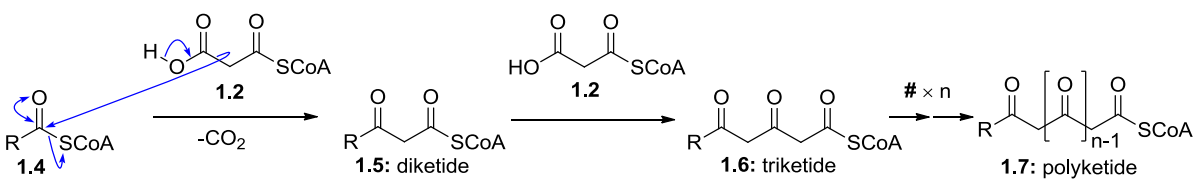
1.1 Meroterpenoid Natural Products

The organic compounds which make up life are divided into two distinct classes: primary metabolites and secondary metabolites. Primary metabolism is responsible for the compounds essential for the existence of life, including nucleic acids, proteins, carbohydrates and lipids. Secondary metabolism produces compounds which are non-essential for the general existence of life, but do play specific roles in the organism which produces them.



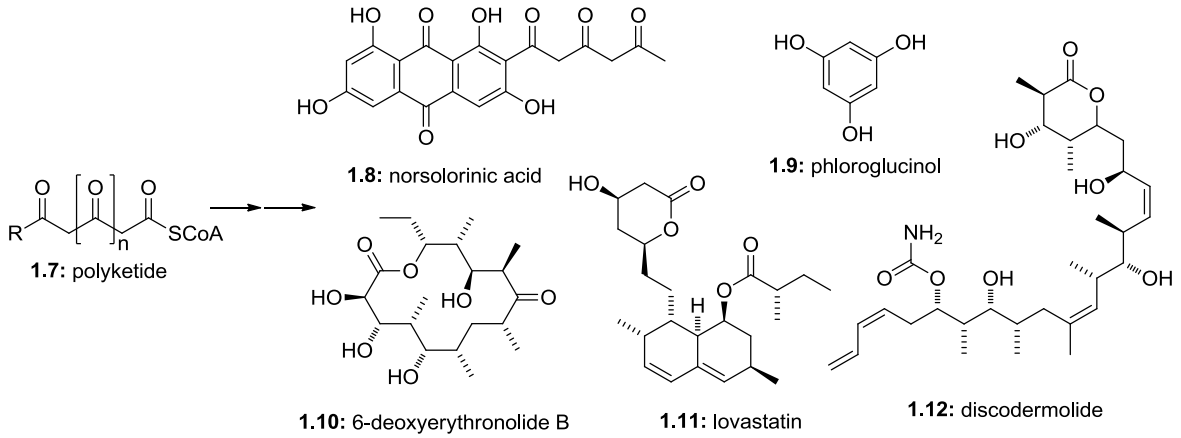
Scheme 1.1: Biosynthesis of three different natural product classes from acetyl CoA

Secondary metabolites include alkaloids, polyketides and terpenes; such compounds are commonly referred to as natural products. The same fundamental biosynthetic building blocks which are essential for primary metabolism are also responsible for the production of secondary metabolites. Alkaloids, for instance, are nitrogen containing natural products which are biosynthesized from otherwise essential amino acids. Acetyl coenzyme A (**1.1**), a vital molecule in the citric acid cycle (a fundamental process occurring in all aerobic organisms), is also the key starting point for the biosynthesis of both polyketides and terpenes (**scheme 1.1**). Malonyl CoA (**1.2**) is produced by the biotin carboxylation of acetyl CoA (**1.1**), catalyzed by acetyl CoA carboxylase.



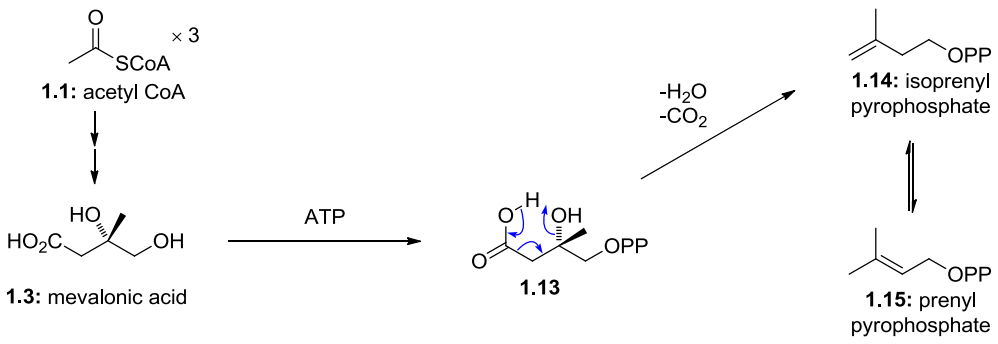
Scheme 1.2: Biosynthesis of linear polyketides[1]

Repeated condensation and decarboxylation of malonyl CoA units gives rise to diketides, (**1.5**), triketides (**1.6**) and further to polyketides (**1.7**) of different lengths (**scheme 1.2**). The linear polyketides can cyclize to form highly oxygenated aromatic natural products such as phloroglucinol (**1.9**) and norsolorinic acid (**1.8**).[1] Alternatively, reduction and elimination reactions can occur resulting in a wide variety of functional groups, including alcohols, alkenes and saturated hydrocarbons, forming the huge structural variety of polyketide natural products observed in nature (**scheme 1.3**). Many polyketide natural products have potent biological activities. Lovastatin (**1.11**), for example, is a drug currently used clinically in the treatment of dyslipidemia.[2]



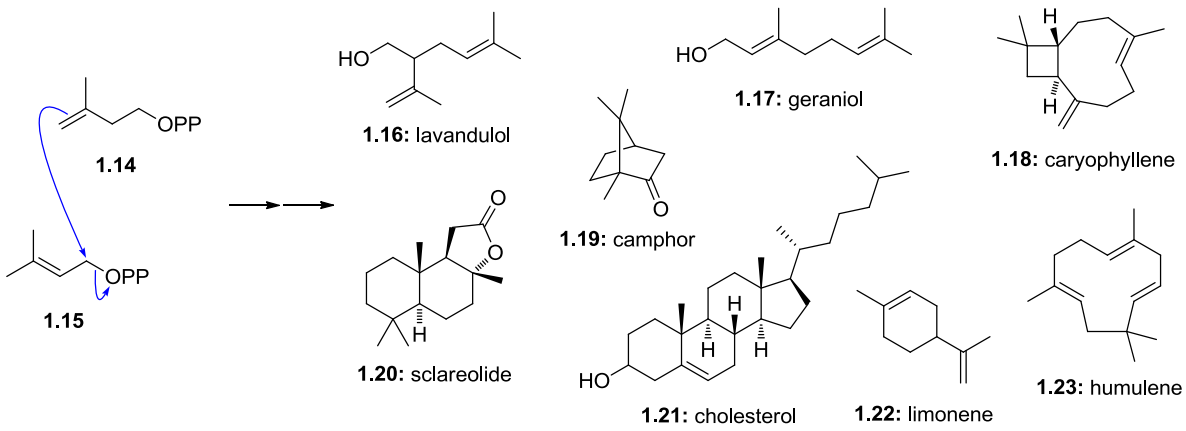
Scheme 1.3: Example polyketide natural products[2-5]

Terpenes are natural products made up of repeating 5-carbon isoprene units, and are biosynthesized from isoprenyl pyrophosphate (**1.14**) and prenyl phosphate (**1.15**). These two 5-carbon building blocks are produced in organisms from the concerted elimination of H_2O and CO_2 from mevalonic acid (**1.3**), which is biosynthesized from three molecules of acetyl-CoA (**scheme 1.4**).[6]



Scheme 1.4: Biosynthesis of the terpene building blocks *via* the mevalonate pathway[6]

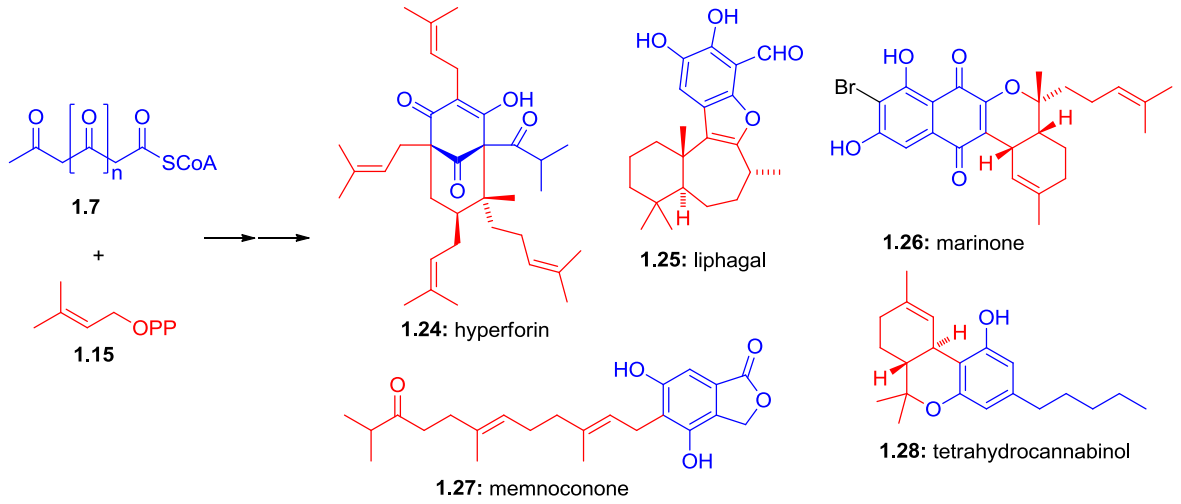
While the biosynthesis of isoprenyl pyrophosphate (**1.14**) and prenyl phosphate (**1.15**) occurs *via* this mevalonate biosynthetic pathway in the majority of nature, there also exists an alternate non-mevalonate pathway to these two building blocks.[7,8] The non-mevalonate pathway of terpene biosynthesis is relevant in certain species of plants, protozoa, and bacteria.[9] The union of combinations of isoprenyl pyrophosphate (**1.14**) and/or prenyl pyrophosphate (**1.15**) units *via* electrophilic reactions results in the formation of 10-carbon monoterpenes, 15-carbon sesquiterpenes, 20-carbon diterpenes and even higher molecular weight compounds. Linear terpenes can then undergo electrophilic cyclization, producing wide varieties of cyclic structures (**scheme 1.5**). Many compounds biosynthesized *via* this pathway contain oxygen in their chemical structure; such compounds are referred to as terpenoids, while hydrocarbon derivatives are referred to as simply terpenes.



Scheme 1.5: Example terpene and terpenoid natural products

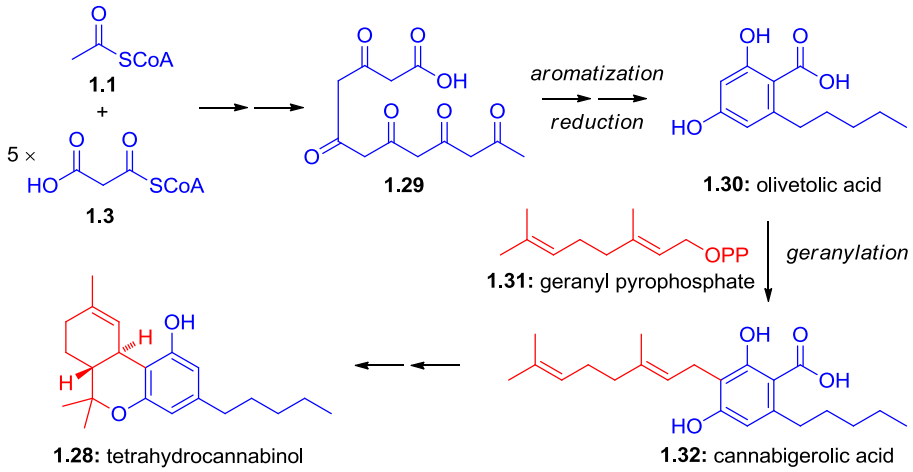
Terpene and terpenoid natural products are very abundant in plants; monoterpenes in particular are responsible for many of the flavours and fragrances found in plants. Common examples include geraniol (**1.17**) (found in roses and geraniums), lavandulol (**1.16**) (found in lavender), and limonene (**1.22**) (found in citrus fruits).[6] Polycyclic steroid compounds such as cholesterol (**1.21**) are also biosynthesized from the same mevalonate pathway as the simpler terpenes and terpenoids.

Meroterpenoid is the name given to natural products which have mixed biosynthetic origin, derived partially from the mevalonate terpene biosynthetic pathway and partially from the polyketide biosynthetic pathway.[10] Most meroterpenoids observed in nature contain aromatic units derived from the cyclization of fully oxidized linear polyketides as part of their chemical structure.



Scheme 1.6: Example meroterpenoid natural products (blue = polyketide derived fragment, red = terpene derived fragment)[11-14]

The highly oxygenated aromatic rings are activated with respect to electrophilic aromatic substitution, and undergo alkylation with terpene building blocks such as prenyl pyrophosphate (**1.15**) catalyzed by prenyltransferase enzymes, resulting in these mixed origin natural products.[15] Meroterpenoids have been identified in many natural sources, but are most common in marine organisms, as well as species of plants and fungi.[16] Some examples of identified meroterpenoid natural products include the presumed active ingredient in St. Johns wort, hyperforin (**1.24**),[17] the marine sponge derived PI3K inhibitor liphagal (**1.25**),[12] and the fungal metabolite memnococone (**1.27**).[14]



Scheme 1.7: Simplified biosynthesis of tetrahydrocannabinol, a meroterpenoid natural product (blue = polyketide derived fragment, red = terpene derived fragment)[18]

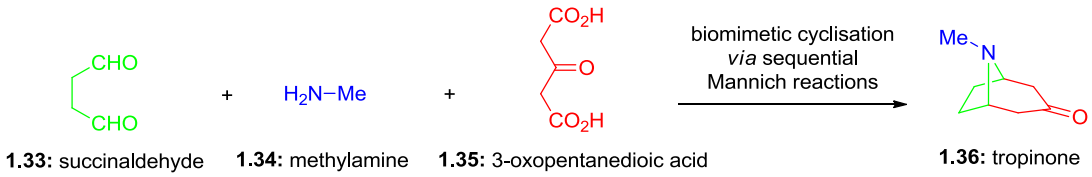
The cannabinoid and meroterpenoid natural product tetrahydrocannabinol (**1.28**) is famous as the major psychoactive constituent of cannabis.[19] THC has many known medicinal benefits: it has been shown to aid in the treatment of certain neurological diseases, and to help alleviate the symptoms of patients suffering from AIDs and undergoing chemotherapy.[20] The biosynthetic origin of THC starting from the simple terpene and polyketide building blocks, is briefly illustrated in **scheme 1.7**. Condensation of one molecule of acetyl CoA (**1.1**) and five molecules of malonyl CoA (**1.3**) would form the linear triketide (**1.29**), which undergoes cyclization and reduction to give the aromatic ring and hydrocarbon chain of olivetolic acid (**1.30**). Alkylation with geranyl pyrophosphate (**1.31**) then occurs at the nucleophilic aromatic ring to yield cannabigerolic acid (**1.32**).[18] THC (**1.28**) is biosynthesized from cannabigerolic acid *via* a sequence of oxidation, cyclization and decarboxylation events. This example illustrates how meroterpenoid natural products arise from the union of these two distinct biosynthetic pathways.

1.2 Biomimetic Synthesis of Natural Products

The isolation of newly discovered natural products still makes a major contribution to developing new drugs, despite the rise of more modern drug discovery methods such as combinatorial chemistry and rational design.[21] A study in 2011 had found that 47% of new approved drugs in the past 30 years are natural products or synthetically derived analogues of natural products.[22] Many natural products can only be isolated in minute quantities from the source, in which case farming and isolation of the compound from the natural source is impractical. Chemical synthesis is often required in order to provide the quantities needed for clinical trials.

With the continued requirement for natural products as candidates for new and more powerful drugs, there is an even greater need to develop efficient syntheses of complex molecules. One strategy that can be utilized in the synthesis of a natural product is to mimic key step(s) from its proposed biosynthesis. This approach is known as biomimetic synthesis.[23] Heathcock stated on the subject of biomimetic synthesis that, ‘‘*The basic assumption of this approach is that Nature is the quintessential process development chemist. We think that the molecular frameworks of most natural products arise by intrinsically favourable chemical pathways – favourable enough that the skeleton could have arisen by a non-enzymatic reaction in the primitive organism. If a molecule produced in this purely*

chemical manner was beneficial to the organism, enzymes would have evolved to facilitate the production of this useful material''.[24] The term biomimetic synthesis was coined in 1973 by Breslow,[25] but the first reported example was Robinson's historical synthesis of tropinone (**1.36**) in 1917.[26] This involved sequential Mannich reactions which mirror how tropinone is formed in nature, generating high molecular complexity quickly from just three simple starting materials (**scheme 1.8**).[26,27]



Scheme 1.8: Robinson's biomimetic synthesis of tropinone[26]

The biosynthetic origin of the molecule in question does not necessarily need to be well studied or understood for biomimetic synthesis to be undertaken. It is common practice to hypothesize about how nature might piece together simple biosynthetic building blocks such as amino acids, acetyl CoA (**1.1**) and prenyl pyrophosphate (**1.15**) to construct a complex three-dimensional structure *via* intricate cascade reactions. If the proposed biomimetic reactions are found to proceed efficiently when performed in the laboratory, this can provide some insight that a similar process may be occurring in the organism. Such biomimetic synthetic studies can act to complement biosynthetic studies, further benefiting the understanding of how nature constructs complex molecules.

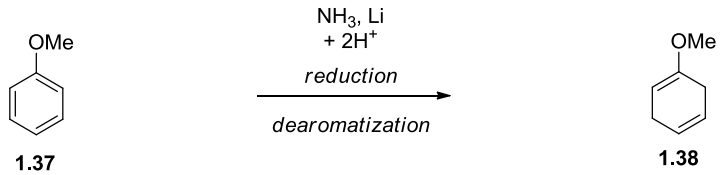
There are potentially many other advantages to utilizing a biomimetic approach. Biosyntheses often involve cascade reactions where structural complexity is generated quickly, and successfully mimicking such steps in the laboratory can save the need for additional synthetic steps.[23] Nature does not utilize protecting groups, so taking inspiration from the biosynthesis can lead to a synthetic plan minimizing the use of protecting groups, hence saving steps otherwise required to introduce and remove them. In many cases in nature, a single intermediate is synthetically modified to form a variety of natural products. This can inspire a "diversity oriented synthesis" to a whole family of natural products. Thinking about how nature constructs molecules may also inspire the development of new reaction methodologies, which could be used for broader utility.[25]

Of course, biomimetic synthesis is not a universally effective approach and should only be applied to suitable cases. Processes which have evolved to be under strict enzymatic control

should be avoided; while those that appear to be predisposed to form a specific product are ideal candidates. Natural products that are heavily oxidized by cytochrome-P450 and similar enzymes, for example, generally cannot be synthesized with full functionality using a biomimetic approach with the currently available synthetic methods.[25] Nevertheless, when paired with other modern methods, biomimetic synthesis is an invaluable tool to aid in solving future synthetic problems of ever increasing complexity

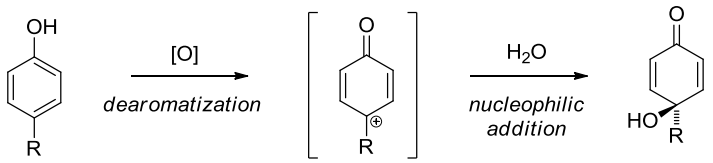
1.3 Dearomatization Strategies in Organic Synthesis

The stability of aromatic structures has caused them to be widely distributed throughout nature. The abundance of the aromatic group is rivaled by its synthetic utility, which includes but is not limited to aromatic substitution reactions, and suitability as substrates in sp^2 based cross coupling reactions. Perhaps one of the most flexible and intriguing processes aromatic compounds undergo is dearomatization.[28-30] Such processes typically result in the formation of reactive intermediates which can be exploited for useful transformations as such carbon-carbon bond formation, carbon-heteroatom bond formation, cycloadditions and cascade reactions.[28] The products of dearomatization often have widely different reactivity than the aromatic parent compound; thus further increasing potential reaction pathways.



Scheme 1.9: Example of dearomatization induced by reduction

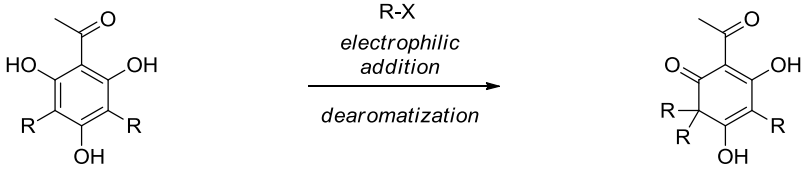
Dearomatization reactions can be loosely classified based on the process that induces the dearomatization. Dearomatization can be achieved under reductive conditions, which typically involves the formal addition of one or more molecules of H_2 across the aromatic ring. A commonly employed example is the Birch reduction, where solvated electrons produced by the dissolution of alkali metals in liquid NH_3 act as the reducing agent, typically resulting in the formation of diene structures such as **1.38** (**scheme 1.9**).[28] Reduction of aromatic rings can also be achieved by typical catalytic hydrogenation methods, provided high enough pressures and temperatures are employed.



1.39 **1.40** **1.41**

Scheme 1.10: Example of dearomatization induced by reduction

Dearomatization induced by oxidation is most commonly practiced with phenolic compounds, but reactions are also prominent with heterocyclic compounds including furans, benzofurans and indoles.[28,31] Many laboratory reagents have been developed for the purpose of phenolic oxidation; some reliable oxidants include hypervalent iodine reagents such as $PhI(OAc)_2$,[29] lead (IV) compounds such as $Pb(OAc)_4$,[32,33] and quinone based oxidants such as DDQ. Examples utilizing electrochemistry for the purpose of oxidative dearomatization have also been reported.[34,35] Treatment of phenols such as **1.39** with a suitable oxidant typically results in formation of a dearomatized phenoxonium ion such as **1.40**, followed by nucleophilic addition at the *ortho* or *para* postion, forming a new carbon-carbon or carbon-heteroatom bond and a new stereogenic centre. Substitution will occur at the position which better stabilizes a carbocation. If the reaction is performed with 1,2-diphenols or 1,4-diphenols in the presence of H_2O, *ortho*-quinones and *para*-quinones can be isolated respectively.



1.42 **1.43**

Scheme 1.11: Example of dearomatization induced by electrophilic addition

It is possible for certain phenol compounds to undergo dearomatization under electrophilic addition conditions analogous to the reaction of enolates. Such reactions result in a new quaternary centre and lock the ring into the non-aromatic ketone tautomer (**scheme 1.11**). While this type of reaction is not common to all phenols, it is known to be a reliable reaction in highly oxygenated acylphloroglucinol type compounds such as **1.42**, and has been utilized in several successful total syntheses.[36,37]

Reductive dearomatization processes exist in nature and the benzene reductase enzymes which catalyze these reactions have been identified in species of anaerobic bacteria.[38] The dearomatization of phenols is an extremely relevant process in the biosynthesis of many natural products.[39,40] Phenols are common functional groups in natural products, arising from the polyketide and shikimate biosynthetic pathway, and many natural products contain structural features which presumably originate from dearomatization processes of phenols (**figure 1.1**).[11,39-41] Such biosynthetic processes have inspired some elegant biomimetic syntheses.[42]

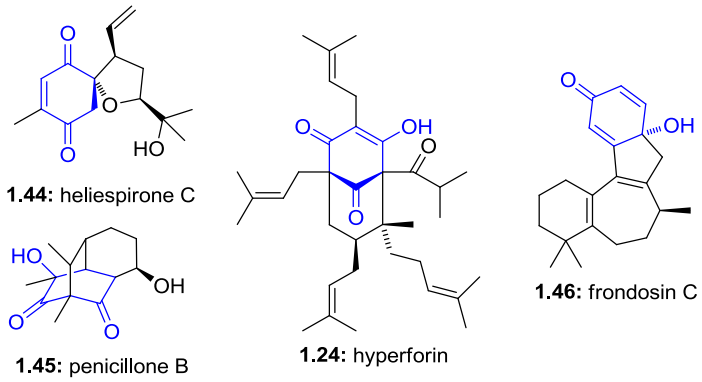
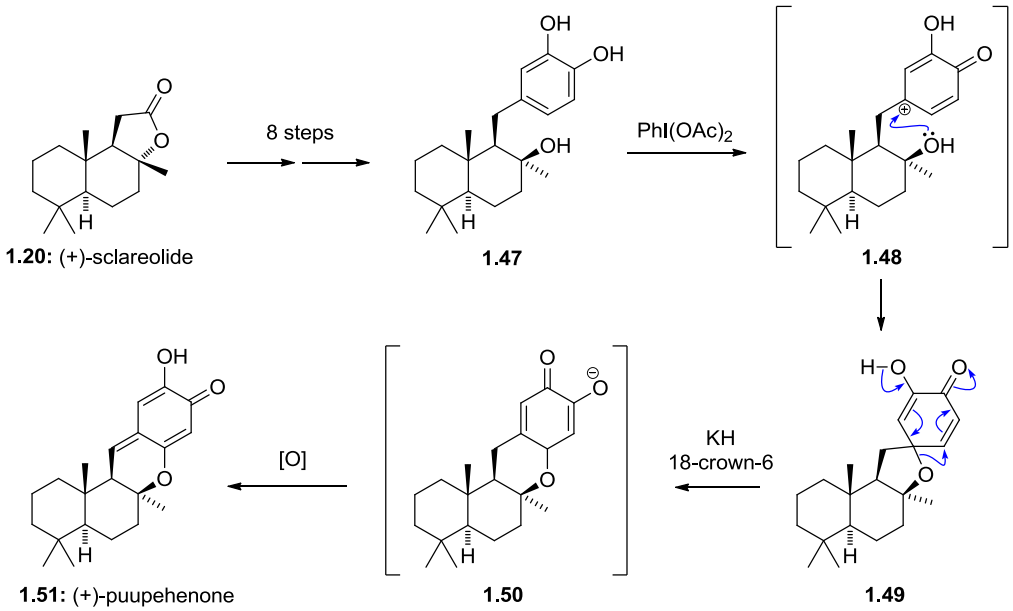


Figure 1.1: Example natural products that presumably originate from dearomatization processes (dearomatized fragments are highlighted in blue)[11,39-41]



Scheme 1.12: 2002 synthesis of (+)-puupehenone by Quideau *et al.*[43]

The total synthesis of the marine derived sesquiterpenoid natural product (+)-puupehenone (**1.51**) by Quideau *et al.* in 2002 utilized a dearomatization reaction as a key step.[43] The chiral pool starting material (+)-sclareolide (**1.20**) was converted into the key intermediate **1.47** in eight synthetic operations. When treated with $PhI(OAc)_2$, **1.47** underwent dearomatization and subsequent spirocyclization of the resultant phenoxonium ion with the proximate alcohol. Under basic conditions, **1.49** then underwent a 1,2-oxyalkyl shift to give the fused tetracyclic ring system **1.50**, which oxidized *in situ* to the natural product (+)-puupehenone (**1.51**). This example illustrates the effectiveness of oxidative dearomatization of phenols as applied to the formation of new rings, and also how the reactivity of the resultant dearomatized structures can be exploited for unique transformations.

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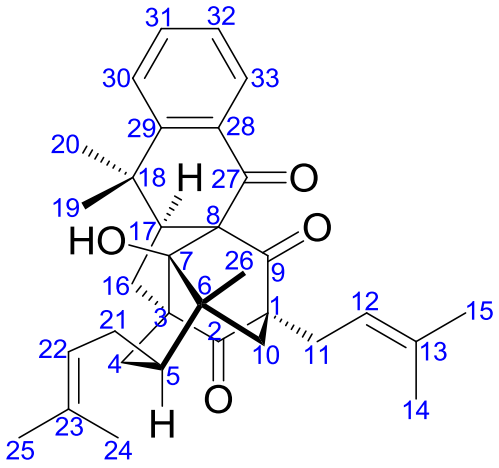
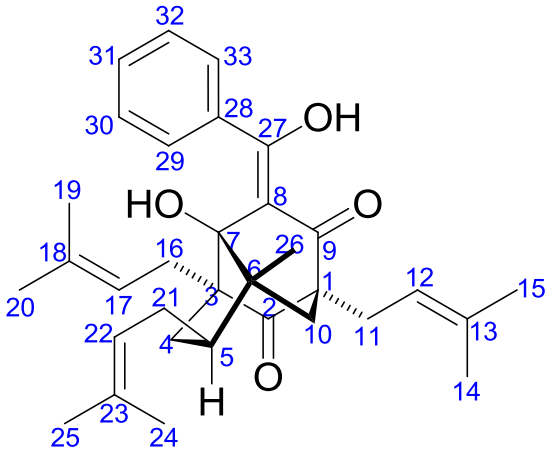
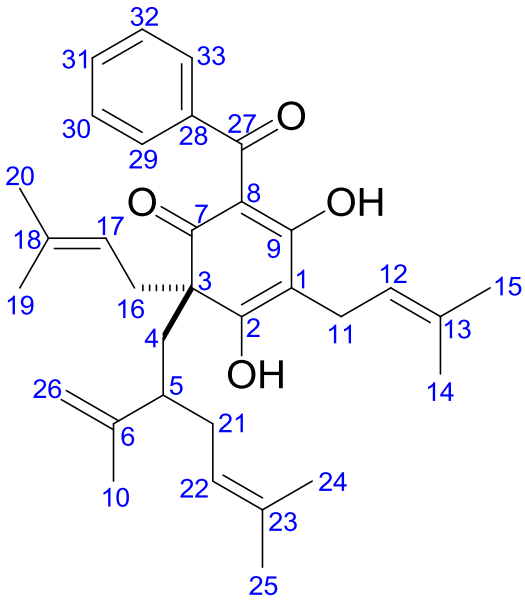
CHAPTER 2

Biomimetic Synthesis of Garcibracteatone





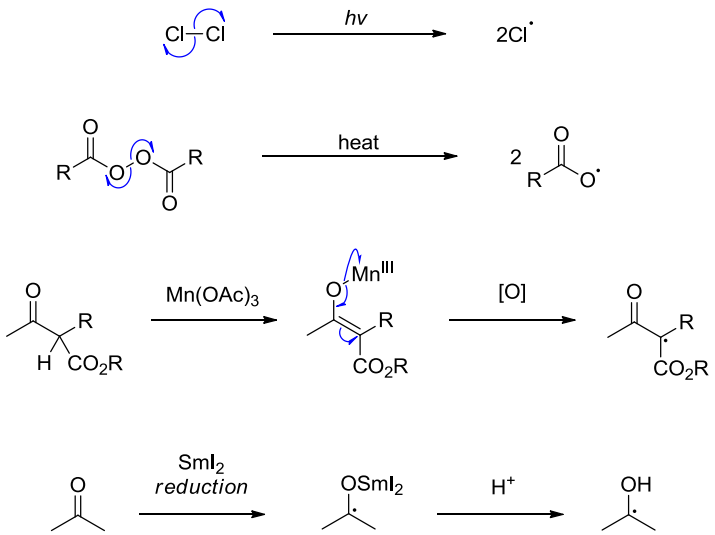


Carbon atoms of PPAP compounds and related synthetic intermediates will be referred to numerically as per these diagrams for the length of this chapter.

2.1 Introduction

2.1.1 Radical Cyclization Reactions in Organic Synthesis

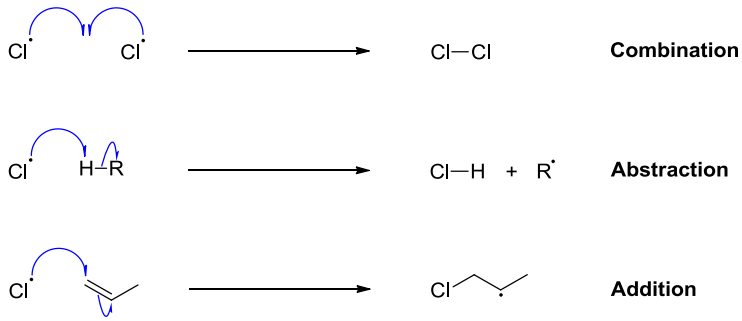
While underutilized relative to the more conventional ionic based reactions, radical reactions, which involve uncharged species with an unpaired electron, have a noteworthy place in organic synthesis. Despite their high reactivity, radicals can be exploited to induce a variety of synthetically useful transformations in organic compounds, which include but are not limited to the formation of new carbon-carbon bonds. The reactivity of radicals is often predictable and their chemistry is compatible with a wide range of functional groups without the need for protecting groups.[1]



Scheme 2.1: Methods of radical initiation[1]

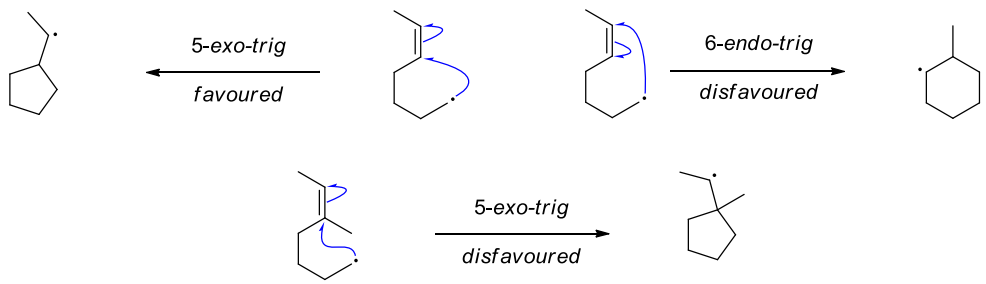
Synthetically useful radical reactions involve three types of steps: initiation, propagation, and termination. The initiation of radicals can be achieved by several different methods. The thermal or photochemical homolytic cleavage of weak bonds has historically been the most conventional method of radical generation in the laboratory. For example, chlorine gas dissociates into chlorine atoms in the presence of light and diacylperoxides decompose to acyloxy radicals on heating (**scheme 2.1**).[1] Radicals produced in this way can then initiate the desired synthetically useful chain reactions. Alternatively, radicals can be produced by single electron oxidation of an appropriate substrate using a suitable oxidizing agent. The oxidation of 1,3-dicarbonyl compounds to stabilized enolic radical using $Mn(OAc)_3$, CAN, Fe (III)

salts, or hypervalent iodine reagents is a well documented process (**scheme 2.1**).[2] Radical processes initiated by oxidation usually terminate by further oxidation of the radical to a carbocation by either the same oxidant responsible for radical initiation, or by the addition of a co-oxidant. Another commonly employed radical generation method in organic synthesis is the reduction of carbonyl compounds with reagents such as SmI_2 resulting in the formation of carbinol radicals (**scheme 2.1**).[3]



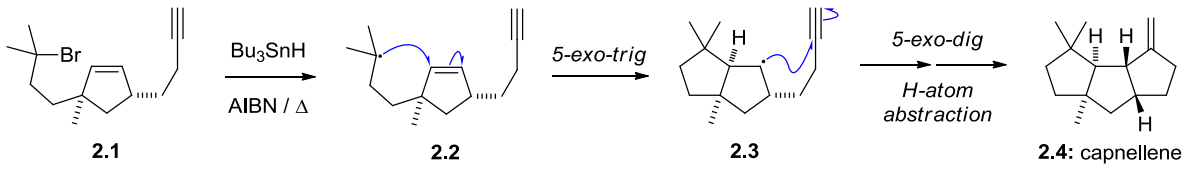
Scheme 2.2: Reactions of radicals[1]

Reactions of radicals can be classified into three main types: combination, abstraction and addition (**scheme 2.2**).[1] Radical combination events are generally not useful synthetically because radicals are only present in low concentrations; however, because such processes destroy radicals, combination is important as a termination step in chain reactions. Radical abstraction results in the cleavage of a single bond and formation of a new radical. Abstraction generally occurs at the weakest available single bond such as carbon-halogen bonds. The organotin reagent Bu_3SnH is a common additive in radical reactions to encourage hydrogen abstraction by cleavage of the weak Sn-H bond. Radical addition reactions are the most useful of the three reaction types synthetically. Radicals readily add to multiple bonds such as alkenes, alkynes or even molecular oxygen, resulting in the formation of a new bond. This process is particularly important for the formation of new carbon-carbon bonds.



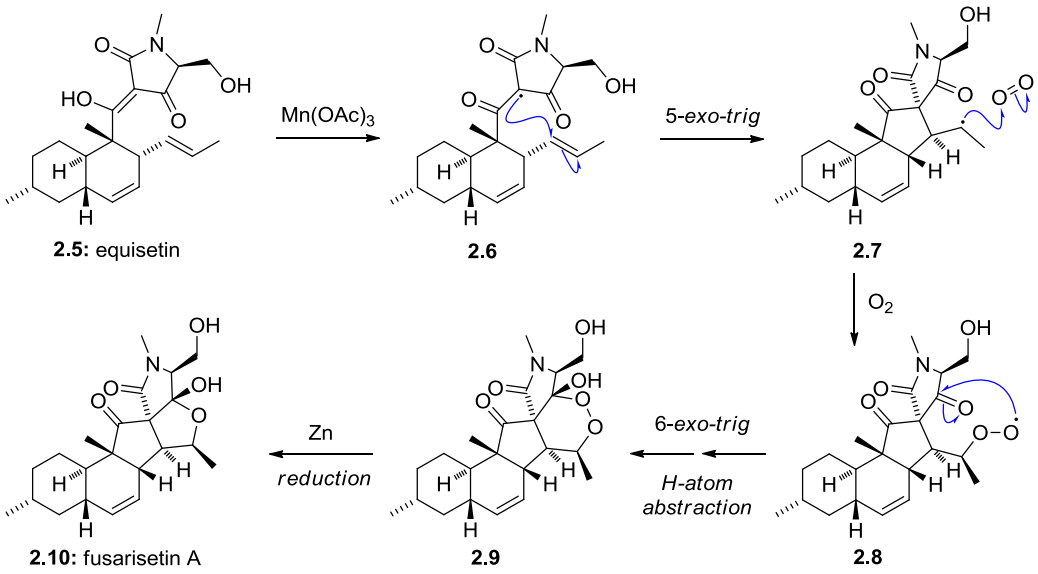
Scheme 2.3: Beckwith's guidelines for regiochemistry in radical cyclizations[4]

The synthetic scope of radical addition in an intermolecular sense in limited, as the double bond of the radical trap must be activated with an electron withdrawing group and must be present in high excess. However, the requirements are much less stringent in an intramolecular sense, and such reactions are therefore much more reliable. Intramolecular radical addition reactions are termed "radical cyclizations" and are an important method in organic synthetic chemistry for the construction of new rings. Baldwin's rules for ring closure, along with the naming convention introduced by Baldwin to classify the different cyclization modes of ionic reactions are generally applicable to radical cyclizations.[5,6] Radical cyclizations in particular have been studied in greater detail by Beckwith, who developed rules for the regiochemical as well as stereochemical outcomes of radical cyclization reactions, concerning the stereoelectronic and steric influences.[7] Based on his research, Beckwith concluded that radical cyclization reactions under kinetic control occur preferentially in the *exo* mode. Beckwith also concluded that radical addition is disfavoured at the more substituted position of a double bond (**scheme 2.3**).[4]



Scheme 2.4: Key radical cyclization step in the synthesis of capnellene by Curran *et al.*[8]

With an understanding of the favourability of cyclization modes and the selectivity of radical reactions, the outcomes of radical cyclization processes can be predictable. It is therefore possible to design starting materials to precisely define the bonds that will form and break during the reaction.[2] This can allow complex polycyclic compounds to be constructed quickly from a relatively simple precursor by exploiting a radical cyclization cascade reaction. A classic example of the exploitation of the predictability of these reactions is the synthesis of capnellene (**2.4**) by Curran *et al.* (**scheme 2.4**). Reduction of alkyl bromide **2.1** with Bu_3SnH generated the radical **2.2,** which underwent a cascade of radical cyclizations to yield capnellene (**2.4**).[9] Radical reactions are relevant processes in biosynthesis, and radical cyclization cascade reactions involved in the biosynthesis of natural products are often thought to not be under strict enzymatic control, as the precursor is predisposed toward the chemical change. Such biosynthetic processes are therefore attractive targets for biomimetic synthesis.



Scheme 2.5: Key biomimetic radical cyclization step in the synthesis of fusarisetin A[10]

In 2012, Gao *et al.* effectively utilized biomimetic radical chemistry toward the synthesis of the polycyclic fungal metabolite fusarisetin A (**2.10**).[10] The presumed biosynthetic precursor to fusarisetin and co-isolated natural product equisetin (**2.5**) was prepared in 11 steps from citronellal. Treatment of the synthetic equisetin with $Mn(OAc)_3$ under aerobic conditions presumably resulted in oxidation to the stabilized diketo radical **2.6**, which underwent a radical cyclization cascade process involving incorporation of oxygen resulting in the peroxide intermediate **2.9**. A final reduction step gave the natural product fusarisetin A (**2.10**). This cascade process was proposed to mirror the biosynthesis of fusarisetin A (**2.10**) from equisetin (**2.5**),[11] and its successful execution in the laboratory demonstrated a highly efficient method to construct the intricate polycyclic ring system of this natural product.

2.1.2 Polycyclic Polyprenylated Acylphloroglucinol Natural Products

Polycyclic polyprenylated acylphloroglucinols (PPAPs) are a large group of meroterpenoid natural products isolated primarily from plants of the *Clusiaceae* and *Hypericaceae* families.[12,13] Many PPAPs have been shown to exhibit potent biological activities. Hyperforin (**2.12**), for example, is the main active ingredient in St. Johns wort and has antidepressant properties.[14-19] Garcinol (**2.11**) is a potent antibiotic with activity against MRSA comparable to that of vancomycin, as well as strong anti-tumor activity against human leukemia HL-60 cells.[20] Most PPAPs feature a highly oxygenated, densely substituted bicyclo[3.3.1]nonane core adorned with prenyl and/or geranyl side-chains.

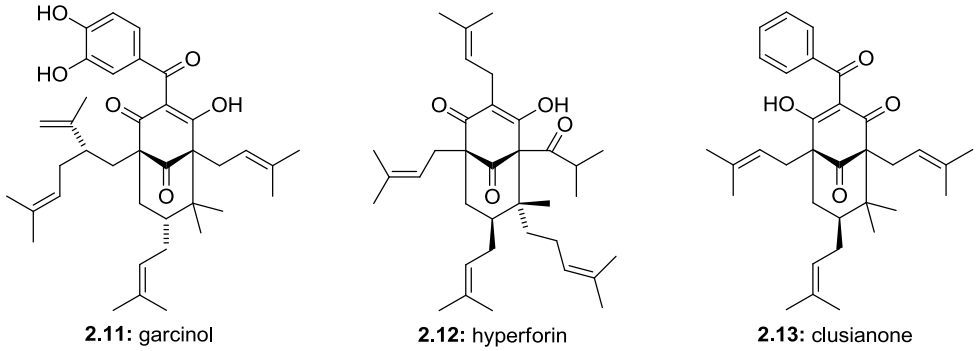
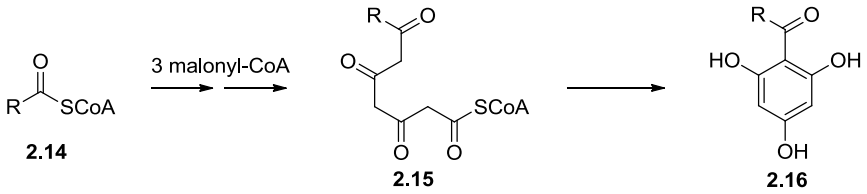


Figure 2.1: Example PPAP natural products[14,20,21]

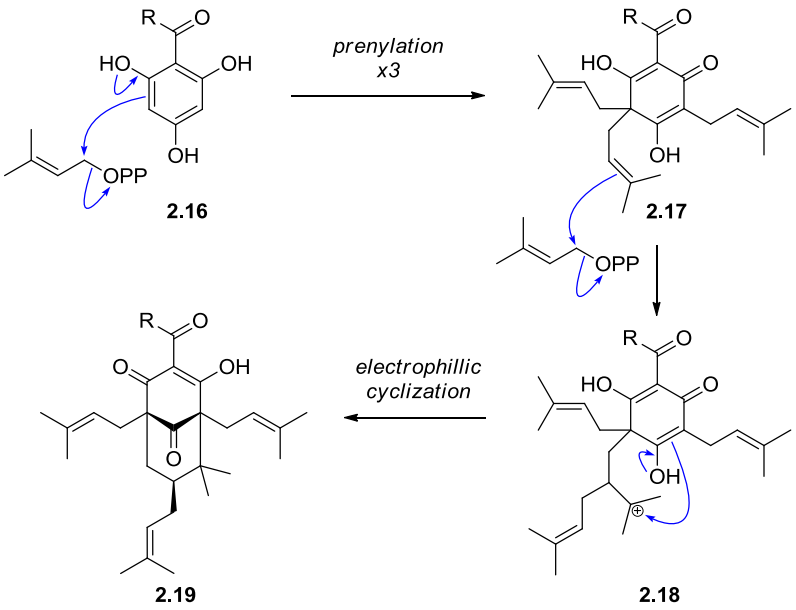
2.1.3 Biosynthesis of Polycyclic Polyprenylated Acylphloroglucinols

Biosynthetically, PPAPs are derived from the simpler monocyclic polyprenylated acylphloroglucinols (MPAPs) which are in turn derived from acylphloroglucinols.[13] Biosynthesis of acylphloroglucinols occur through the polyketide biosynthetic pathway, involving condensation of one acyl-CoA (**2.14**) and three malonyl-CoA units followed by cyclization of the tetraketide product **2.15** to yield acylphloroglucinols **2.16** (**scheme 2.6**).[13]



Scheme 2.6: Biosynthesis of acylphloroglucinols[13]

Prenylation or geranylation occurs through enzyme catalyzed addition of prenyl or geranyl pyrophosphate. Reaction of one of the prenyl or geranyl side-chains with prenyl pyrophosphate would then generate the carbocation (**2.18**), which could cyclize with the dearomatized acylphloroglucinol core to generate the bicyclo[3.3.1]nonane-2,4,9-trione structure (**2.19**) common to most PPAPs (**scheme 2.7**).[13] Alkylation of different terpene substituents and at different positions on the phloroglucinol ring gives rise to the wide variety of PPAP natural products observed.

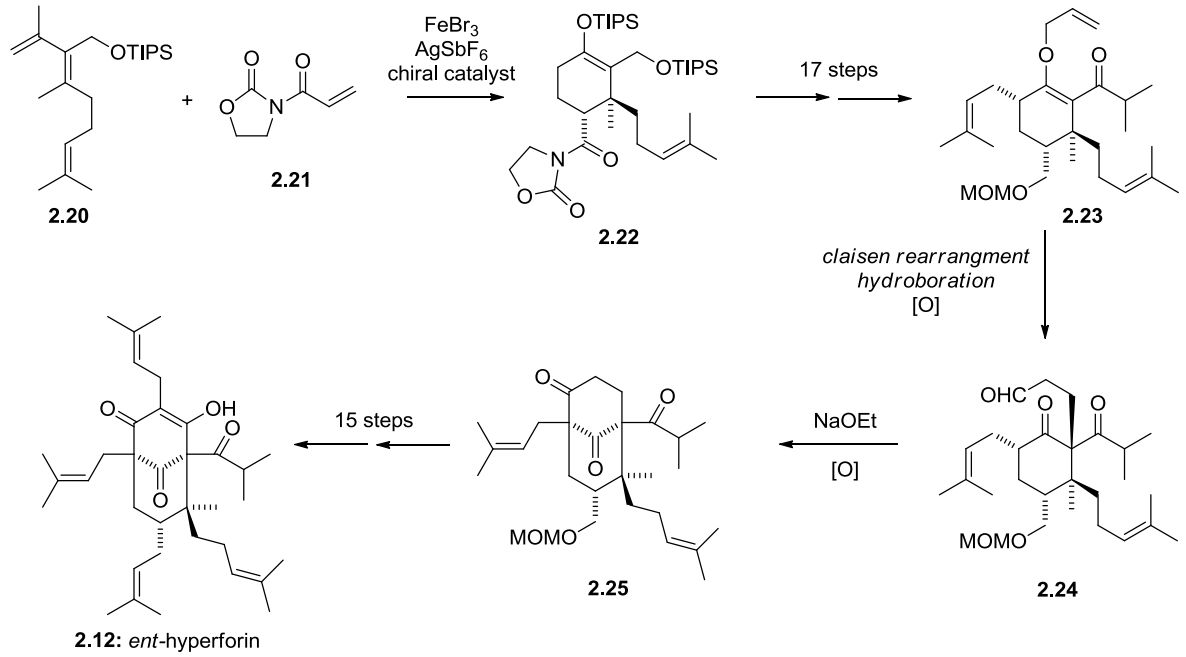


Scheme 2.7: Biosynthesis of PPAPs from MPAPs[13]

2.1.4 Previous Synthetic Work Targeting PPAP Natural Products

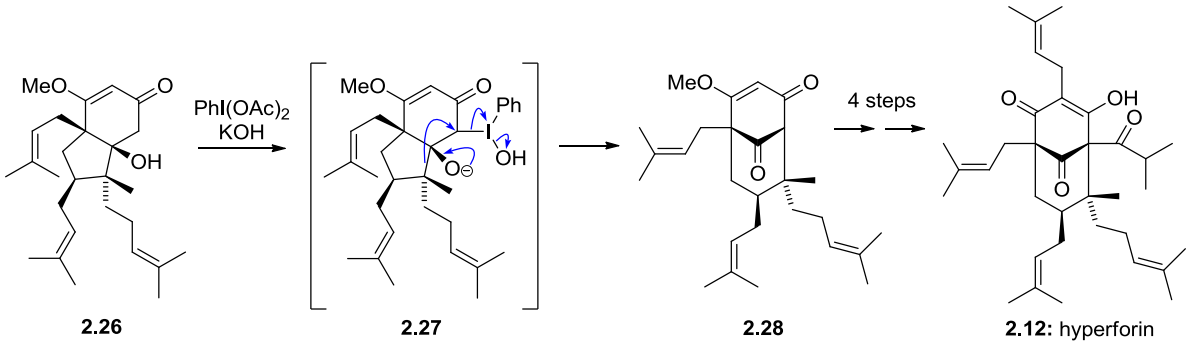
The vast number of family members, potent biologically activity and intriguing chemical structures have made PPAPs highly attractive targets for chemists interested in complex natural product synthesis. The area of PPAP synthesis is so extensive that three reviews on the subject have been recently published.[13,22,23] The bicyclo[3.3.1]nonane core common to most PPAPs, which contains two quaternary stereogenic centres, has proven to be a great challenge to synthetic chemists. This difficult to access structural feature has led to the development of many inventive strategies and techniques for its synthesis; hence, a multitude of research exists in the literature detailing work in this area.[24-54] However, many of these methodologies have yet to be applied to total syntheses. An example of a successful strategy is the use of an Effenberger cyclization reaction to construct this key framework.[55] This approach was first introduced by Stoltz *et al.* in 2002[56] and has since been applied to several successful total syntheses of PPAP natural products.[57-62] Several other approaches have also led to the completion of impressive total syntheses.[63-70]

The most historically famous PPAP natural product, hyperforin (**2.12**), has also been proven to be one of the most challenging synthetic targets. After its structure elucidation in 1975, the first total synthesis of this natural product was not completed until 2010. This feat was achieved by Shibasaki *et al.*, who reported a catalytic asymmetric synthesis of *ent*-hyperforin.[71,72]



Scheme 2.8: 2010 enantioselective synthesis of *ent*-hyperforin by Shibasaki *et al.*[71,72]

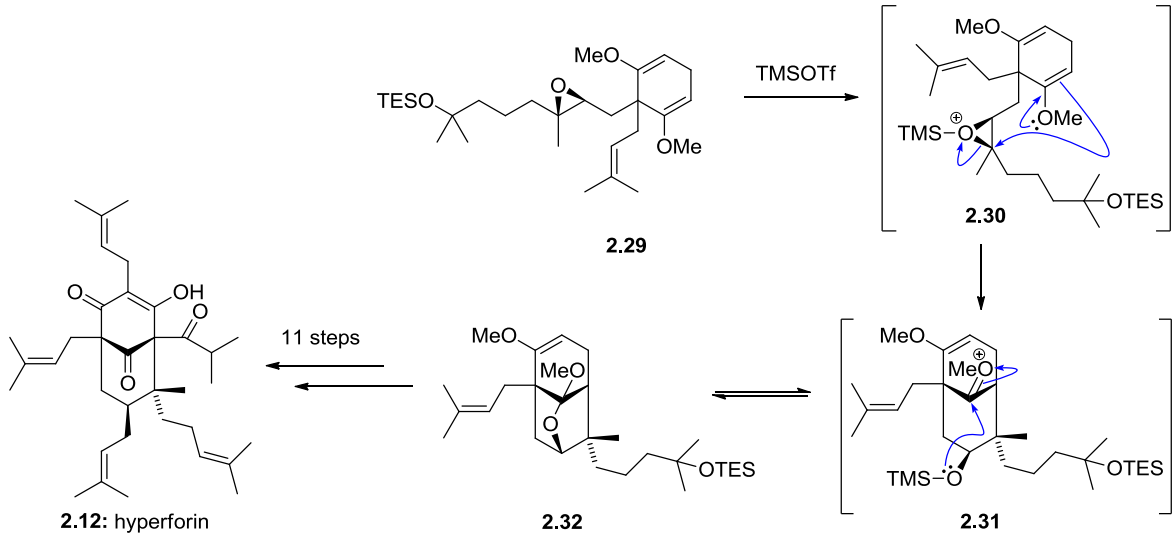
The first key construction step of the synthesis was an asymmetric Diels-Alder reaction forming **2.22**, establishing the first 6-membered ring of the molecule in a high degree of diastereoselectivity and enantioselectivity. 17 steps were then required to introduce the isopropyl, prenyl and allyl groups to give **2.23**. A combination of Clasien rearrangement and intramolecular aldol reactions effectively installed the two quaternary centres of the bicyclo[3.3.1]nonane core stereoselectively. The total synthesis of *ent*-hyperforin was then completed in 15 steps from **2.25**. The sheer number of protecting group manipulations and functional group interconversions that were required to complete this synthesis is a good demonstration of the difficulty involved with PPAP natural product synthesis.



Scheme 2.9: 2015 synthesis of hyperforin by Maimone *et al.*[73]

Since the first total synthesis of this historical target was completed, a number of other total syntheses of hyperforin (**2.12**) have been reported. Recently in 2015, Maimone *et al.* reported

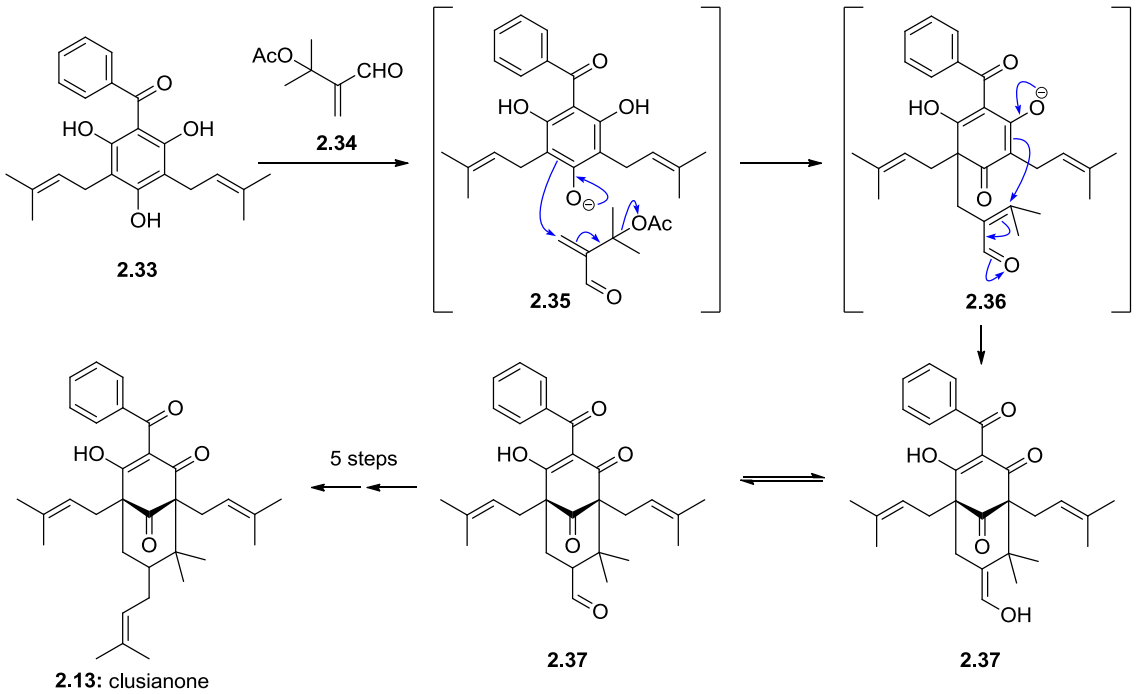
a very concise synthesis of racemic hyperforin utilizing a unique strategy.[73] 6-5 fused bicycle **2.26** was accessed in five steps from 2-methylcyclopent-2-enone, which underwent hypervalent iodine induced ring expansion to the bicyclo[3.3.1]nonane ring skeleton of hyperforin. **2.28** was then converted into hyperforin (**2.12**) in just four synthetic operations.



Scheme 2.10: 2012 enantioselective synthesis of hyperforin by Shair *et al.*[74]

Attempts to apply a biomimetic approach to the synthesis of PPAPs involving cationic cyclizations of MPAP type compounds (**scheme 2.7**) have been largely unsuccessful. The success of these key cyclization reactions are hindered by many potential chemoselectivity issues, with different *O* and *C* cyclization events possible between the phloroglucinol core and multiple terpene side chains. Many reported applications of this approach did not produce the desired cyclization mode to yield the bicyclo[3.3.1]nonane ring structure.[75,76] For the most part, successful cyclizations have only been reported in systems lacking the full functionality of the natural products.[58,67] Shair *et al.* utilized a strategy loosely based on biosynthetic understanding to good effect during their 2012 enantioselective total synthesis of hyperforin (**2.12**).[74] Shair envisioned that a similar bond disconnection to the electrophilic cyclizations of PPAPs during the biosynthesis could be applicable to the total synthesis, given the right substrate prior to cyclization. Hence, the bicyclo[3.3.1]nonane core of hyperforin was constructed *via* a Lewis acid catalyzed epoxide ring opening cyclization cascade reaction of chiral epoxide **2.29**. 11 step conversion of **2.32** into hyperforin (**2.12**) then followed, with one step involving a difficult bridgehead acylation reaction to install the third and final quaternary centre of the molecule.

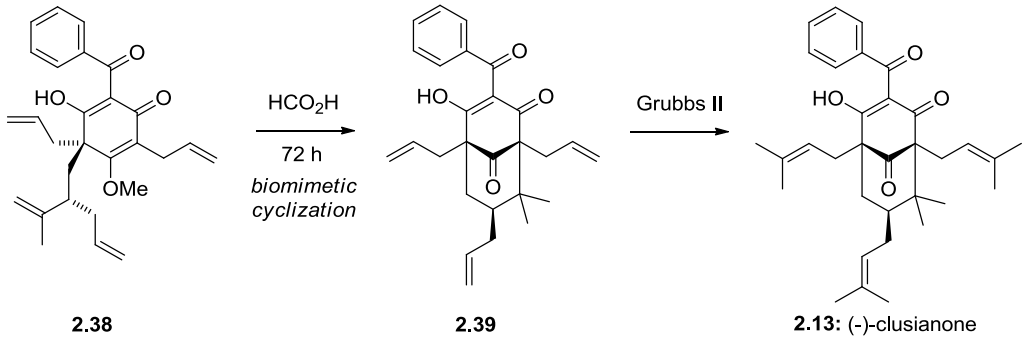
Perhaps one of the closest examples of a successful biomimetic approach to a PPAP natural product is the synthesis of clusianone (**2.13**) by Porco *et al*. in 2007.[77] Porco is the pioneer of utilizing dearomatization strategies to PPAP synthesis, taking advantage of the fact that di-*C*-alkylated acylphloroglucinol compounds such as **2.33** readily undergo dearomatization under alkylation conditions. Alkylative dearomatization of **2.33** with *α,β*-unsaturated aldehyde **2.34**, followed by intramolecular Michael addition, furnished the bicyclo[3.3.1]nonane ring structure of clusianone in a single cascade process. A four step conversion from **2.37** then established the full functionality of clusianone (**2.13**). Using the double Michael acceptor **2.34** as the electrophile paired with a dearomatization strategy was an ingenious solution to achieve this cyclization reaction on such a functionalized system lacking protecting groups. Porco *et al.* also applied a similar methodology to syntheses of the PPAP natural products hyperibone K,[78] Plukenetione A[79] and 7-*epi*-nemorosone.[80]



Scheme 2.11: 2007 synthesis of clusianone by Porco *et al*.[77]

Very recently, Porco *et al.* were able to achieve an alternate total synthesis of clusianone (**2.13**) utilizing a biomimetic cationic cyclization.[81] The trialkylated acylphloroglucinol compound **2.38**, obtained *via* the established dearomatization strategy was treated with various Brønsted and Lewis acids in the hopes of yielding the desired bicyclic compound **2.39**. Many different cyclic compounds were isolated under the ~70 different conditions trialed, however, only when the reaction was performed in neat HCO_2H was the

bicyclo[3.3.1]nonane compound **2.39** observed. **2.39** was then converted into clusianone (**2.13**) through a final cross metathesis reaction.



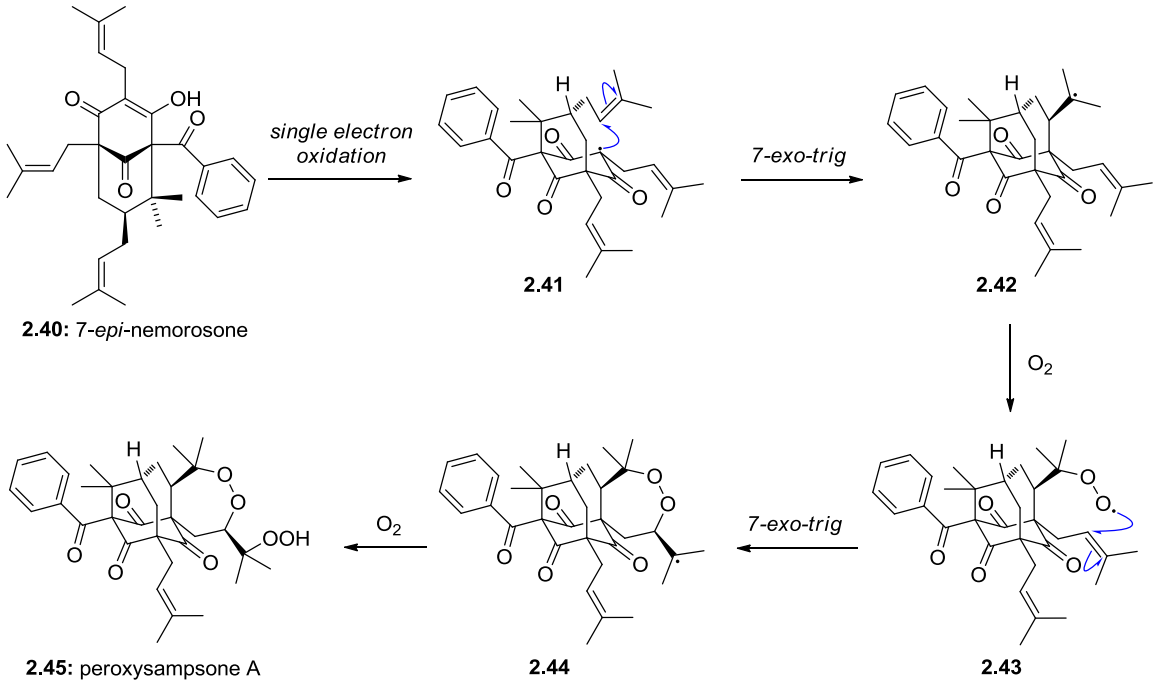
Scheme 2.12: 2014 synthesis of (-)-clusianone by Porco *et al.*[81]

This synthesis was the first report of this biomimetic synthetic strategy being successfully applied to the fully functionalized system. While impressive, the number of years it took before this feat was achieved and that only one of many conditions trialed was successful in inducing this transformation demonstrates the difficulties associated with the biomimetic synthesis of PPAPs.

2.1.5 Radical Cyclizations in PPAP Biosynthesis and Biomimetic Synthesis

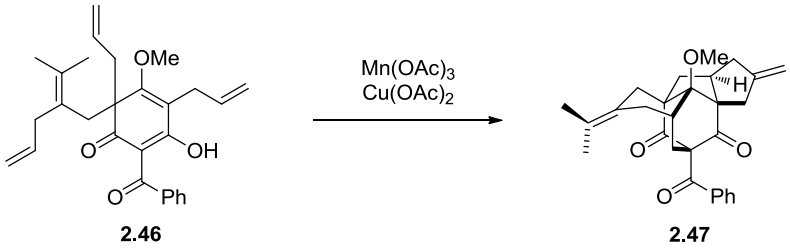
While the biosynthesis of PPAPs containing the more common bicyclo[3.3.1]nonane core involves cationic cyclizations, it is proposed that some of the more complex PPAP skeletons arise in nature from radical cyclization processes. For example, the additional rings and peroxide bond of peroxysampsone A (**2.45**) presumably originate from radical cyclizations of 7-*epi*-nemorosone (**scheme 2.13**).[82] The highly conjugated and densely oxygenated acylphloroglucinol core of PPAPs is primed for the formation of stabilized α-diketo radicals *via* single electron oxidation processes. The biomimetic synthesis of PPAP natural products based on a radical pathway is theoretically more synthetically feasible than an ionic pathway due to the selectivity and predictability of intramolecular radical reactions.

In 2009, Porco *et al.* took their established dearomatization strategy to the synthesis of PPAP compounds and coupled it with oxidative radical cyclization chemistry. This methodology resulted in the synthesis of a small library of PPAP type analogues, some containing intriguing bicyclo[2.2.2]octadione cores (**scheme 2.14**).[83]



Scheme 2.13: Proposed biosynthesis of peroxysampsone A *via* a radical cyclization cascade process

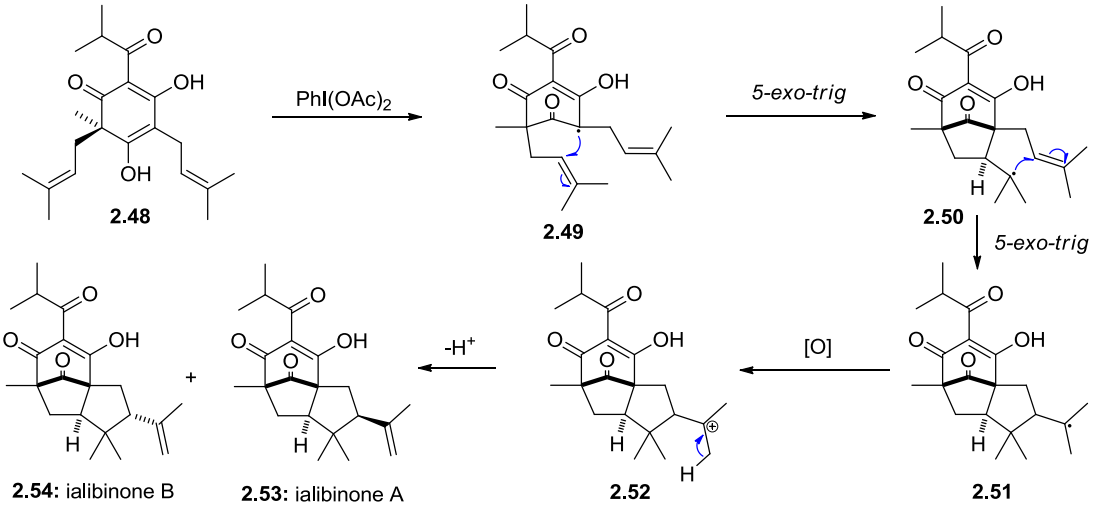
These complex molecular architectures were all produced in a single step from a simple, monocyclic precursor *via* a radical cyclization cascade reaction. It was noteworthy that most of the reactions reported only gave a single product, even though several reactive groups were present. This demonstrated the inherent selectivity of these radical cyclization reactions towards the synthesis of PPAP type structures.



Scheme 2.14: Oxidative radical cyclization reaction example by Porco *et al.*[83]

In 2010, George *et al.* reported a total synthesis of the PPAP natural products ialibinones A (**2.53**) and B (**2.54**) *via* a radical cyclization approach based on biosynthetic speculation.[84] Synthesis began by accessing dearomatized acylphloroglucinol **2.48** in three steps from phloroglucinol. Treatment of **2.48** with $PhI(OAc)_2$ then yielded a mixture of ialibinones A (**2.53**) and B (**2.54**), which were seperable by HPLC. Presumably this cascade process

involved single electron oxidation of **2.48** to give the stabalized diketo radical **2.49**, which underwent a sequence of two consecutive 5-*exo-trig* radical cyclizations followed by oxidation to the carbocation and loss of a proton to yield ialibinones A (**2.53**) and B (**2.54**), mirroring the proposed biosynthesis (**scheme 2.15**).



Scheme 2.15: 2010 biomimetic synthesis of ialibinones A and B by George *et al.*[84]

This work was the first reported biomimetic total synthesis of a PPAP natural product utilizing a radical cyclization approach. A nearly identical route to ialibinones A and B was later reported by Simpkins *et al.* using $Mn(OAc)_3$ as the oxidant.[85] These examples demonstrated oxidative radical cyclizations to be a very powerful approach to quickly generate the required molecular complexity of PPAP natural products.

2.1.6 Garcibracteatone and Nemorosonol

In 2005, garcibracteatone (**2.55**), a highly complex PPAP natural product containing a compact hexacyclic ring system and seven stereocentres, was isolated from the bark of *Garcinia bracteata*.[86] Garcibracteatone was co-isolated with the previously reported compound nemorosonol (**2.56**), which contains a tricyclo-[4.3.1.0]-decane core analogous to that of garcibracteatone.[86-88] The structure of garcibracteatone (**2.55**) was elucidated on the basis of 2D NMR studies. Its relative stereochemistry was not rigorously determined, but was predicted to be as shown in **figure 2.2** by comparison with nemorosonol (**2.56**). The postulated common precursor weddellianone A (**2.57**) had been previously isolated from *Clusia weddelliana,* although its relative stereochemistry was not determined.[89]

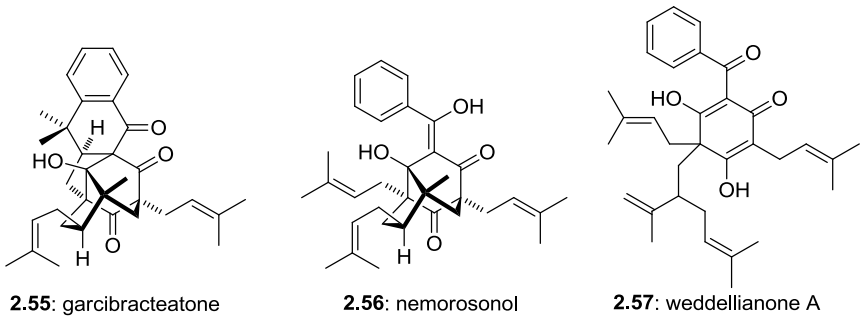
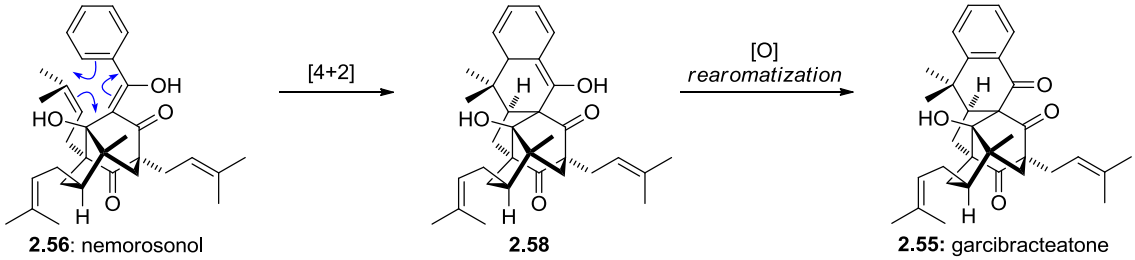


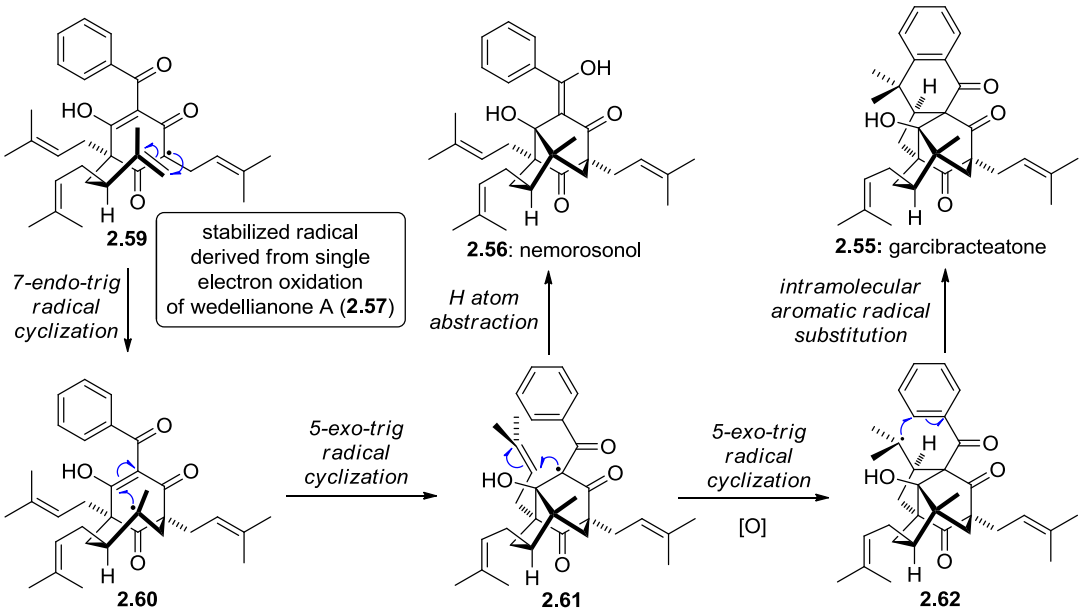
Figure 2.2: PPAP natural products of interest[86,87,89]

2.1.7 Proposed Biosynthesis of Garcibracteatone and Nemorosonol



Scheme 2.16: Original proposed biosynthesis of garcibracteatone from nemorosonol[86]

Sevénet *et al.* proposed a biosynthetic link between garcibracteatone (**2.55**) and nemorosonol (**2.56**) *via* an intramolecular Diels-Alder reaction between the benzophenone and the prenyl side chain of nemorosonol, followed by oxidation of the resultant diene (**scheme 2.16**).[86]

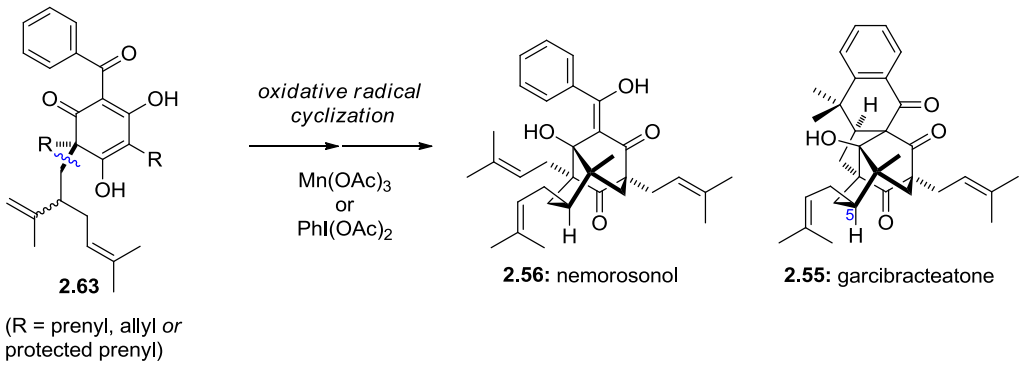


Scheme 2.17: Our proposed biosynthesis of garcibracteatone and nemorosonol

We, however, propose an alternative biosynthesis of garcibracteatone and nemorosonol from weddellianone A *via* a series of highly selective predisposed radical cyclizations (**scheme 17**). Oxidation of weddellianone A (**2.57**) would result in the formation of stabilized radical **2.59,** which might undergo a 7-*endo-trig* cyclization with the pendant lavandulyl sidechain to give the tertiary radical **2.60**. A subsequent 5-*exo-trig* radical cyclization with the phloroglucinol core would give the diketo radical **2.61**, which could abstract a hydrogen atom from a suitable donor to form nemorosonol (**2.56**). Alternatively, **2.61** could undergo a second 5-exo-trig cyclization onto the C-3 prenyl group to give tertiary radical **2.62**. Garcibracteatone (**2.55**) could then be formed from **2.62** *via* a final intramolecular aromatic radical substitution reaction.

2.1.8 Project Aims

The objective of this research was to attempt to synthesize garcibracteatone (**2.55**) and/or nemorosonol (**2.56**) *via* our proposed biomimetic radical cyclization cascade pathway (**scheme 2.17**). In order to test this, we planned to synthesize a weddellianone A type intermediate such as **2.63** and subject it to oxidative radical cyclization conditions, which should hopefully induce the desired cascade process.



Scheme 2.18: Proposed research: synthesis of garcibracteatone and/or nemorosonol *via* radical cyclization cascade reaction

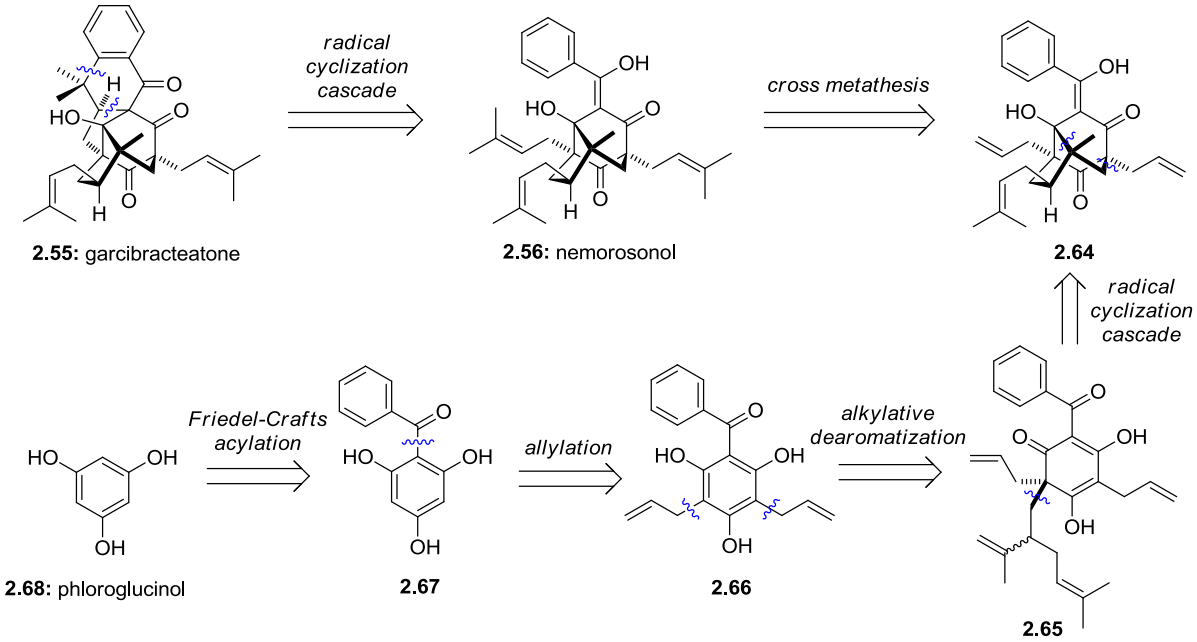
The ideal outcome would be to yield garcibracteatone and/or nemorosonol in one highly selective radical cyclization cascade process from weddellianone A (**2.57**) (R = prenyl). If this direct approach was found to be unfeasible, a more step-wise approach could be a plausible alternative, employing the use of a less functionalized starting intermediate (R = allyl or protected prenyl). This more step-wise approach would first yield nemorosonol,

which could hopefully be converted into garcibracteatone *via* a second radical cyclization cascade reaction. If successful, this should lead to a highly concise synthesis of these very complex PPAP natural products, which at this point in time had yet to be synthesized. Formation of either of these natural products *via* radical cyclization synthetically in the lab would strongly suggest that a similar process occurs in the biosynthesis, while also expanding the area of biomimetic radical cyclization chemistry. Total synthesis may also uncover currently unknown structural information about garcibracteatone (**2.55**) and nemorosonol (**2.56**) such as the relative stereochemistry at C-5 of garcibracteatone and the absolute stereochemistry of both natural products.

2.2 Results and Discussion

2.2.1 Retrosynthetic Analysis of Garcibracteatone and Nemorosonol

Our intended approach towards garcibracteatone (**2.55**) and nemorosonol (**2.56**) was to use the well established dearomatization strategy employed in such successful PPAP syntheses as the synthesis of ialibinones A (**2.53**) and B (**2.54**) by George *et al.*,[84] as well as the synthesis of clusianone (**2.13**) by Porco *et al* (**scheme 2.11**).[77] This would involve using phloroglucinol as the starting material and converting it to the desired intermediate *via* successive alkylation processes (**scheme 2.19**). We at first hypothesized that it may be too ambitious to attempt the oxidative dearomatization cascade reaction on a fully functionalized weddellianone A[89] type intermediate, and that it may be more reasonable to pursue a more step-wise strategy.



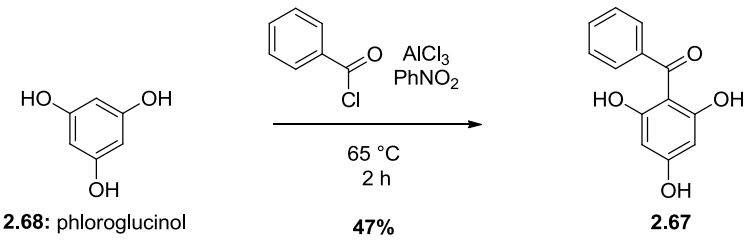
Scheme 2.19: Retrosynthetic analysis of garcibracteatone and nemorosonol

With this in mind, we decided to initially pursue the synthesis using allyl groups in place of the natural prenyl substituents, which were predicted to be less reactive towards radical addition due to the formation of a less stable secondary radical intermediate. In theory, the use of these less reactive groups could promote the 7-*endo-trig* cyclization process to occur first in the cascade process as required, and also promote termination of the cascade reaction by hydrogen abstraction to yield the nemorosonol skeleton **2.64** rather than further

cyclization. After synthesis of **2.64**, the allyl groups could potentially be converted into prenyl groups *via* a cross metathesis reaction to yield nemorosonol (**2.56**). This late stage allyl to prenyl conversion is a well documented and widely successful reaction in PPAP synthesis.[65,67,71,79,80] Nemorosonol (**2.56**) could then hopefully be converted into garcibracteatone (**2.55**) *via* a second and final radical cyclization cascade process involving 5-*exo*-*trig*, and subsequent aromatic radical substitution events.

2.2.2 Synthesis of Allylated Model System

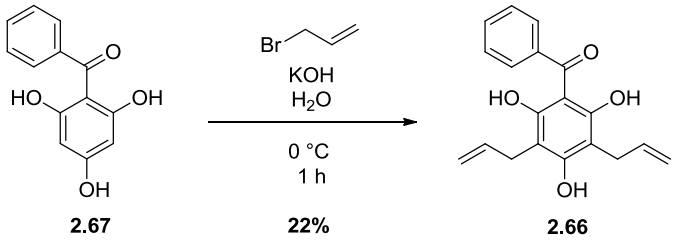
The first reaction was the Friedel-Crafts acylation of phloroglucinol (**2.68**) with benzoyl chloride. Some commercial samples of phloroglucinol came as the dihydrate which was undesired for this reaction; in these cases, the phloroglucinol dihydrate could be converted to anhydrous phloroglucinol by boiling the compound in PhMe. Literature Friedel-Crafts conditions using $AlCl_3$ as the Lewis acid in $PhNO_2$ solvent yielded the desired benzoyl phloroglucinol **2.67** in consistently modest yields.[90] The use of excessive amounts of $AlCl_3$ and the high boiling point $PhNO_2$ made the work up procedure for this reaction difficult; however, this reaction could still be run routinely and reliably on a 10 g scale to yield the quantities of **2.67** required.



Scheme 2.20: Friedel-Crafts acylation of phloroglucinol[90]

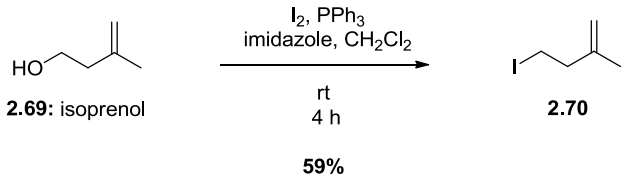
The direct alkylation of alkyl halides to electron rich aromatic ring systems under basic conditions is known to be low yielding and unselective. This is primarily due to competing alkylative dearomatization processes, which occur at comparable rates.[84] The use of a polar protic solvent was necessary to discourage potential *O*-alkylation processes and to therefore maximize desired *C*-alkylation. Following a similar procedure to Porco *et al.*,[77] the desired diallylated acylphloroglucinol was obtained in 22% yield. TLC analysis showed formation of many products indicating the reaction was indeed unselective as expected. Although the yield

was low, enough of **2.66** could be obtained from this reaction to satisfactorily test the applicability of the allyl system in the later oxidative radical cyclization steps.



Scheme 2.21: Diallylation of **2.67**

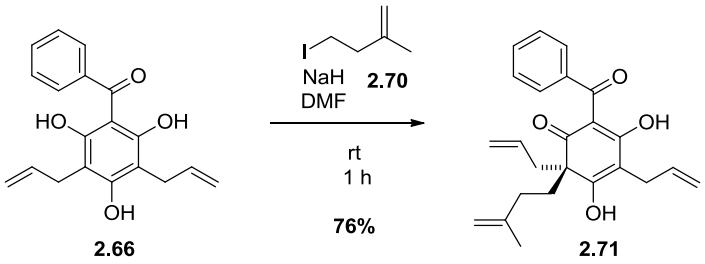
It was planned to introduce the lavandulyl side chain of weddellianone A (**2.57**) *via* alkylative dearomatization with lavandulyl iodide. Unfortunately, we had difficulties sourcing the required lavandulol at this point in time. As an adequate substitute, an isoprenyl group was used in place of lavandulyl during early testing. In either case, the initial 7-*endo-trig* radical addition process should in theory be identical.



Scheme 2.22: Iodination of isoprenol[91]

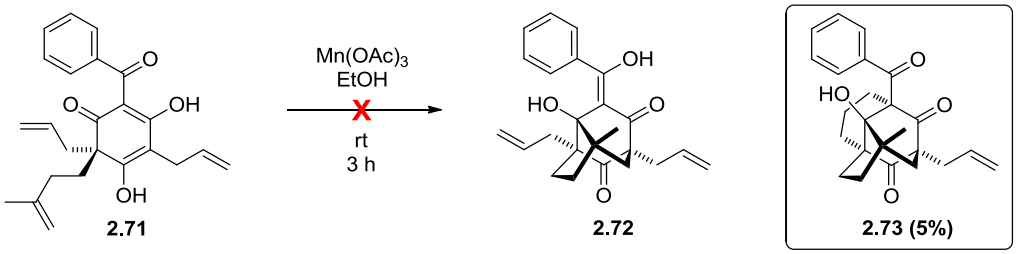
The use of an isoprenyl group would also simplify the stereochemistry of the obtained products, as one less pair of stereoisomers could potentially form in comparison to alkylation with lavandulyl iodide. This would allow simplification of isolation and characterization of the future intermediates, which was desirable for the early testing phases. The required isoprenyl iodide (**2.70**) was obtained by iodination of isoprenol (**2.69**) under standard conditions followed by purification by distillation.[91]

Alklyative dearomatization of **2.66** with isoprenyl iodide (**2.70**) and NaH in DMF proceeded smoothly to give the simplified weddellianone A analogue **2.71**. In spite of the use of an unactivated alkyl iodide, this reaction was very rapid, demonstrating the high propensity of acylphloroglucinols towards dearomatization. The product isolated was not rigorously characterized as the NMR spectra showed a complex mixture, indicating it existed as three different tautomeric forms.



Scheme 2.23: Alkylative dearomatization of **2.66** with isoprenyl iodide

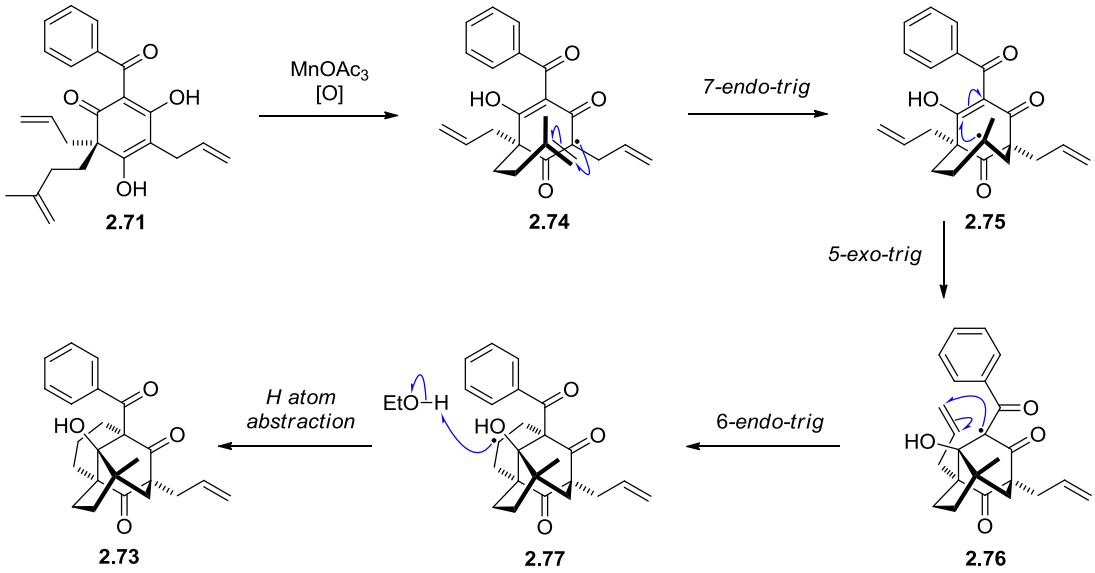
With **2.71** in hand the first key radical cyclization reaction could be investigated. **2.71** was treated with $Mn(OAc)_3$ as the single electron oxidant and TLC analysis of the formed mixture showed a single product that was abundant enough to be isolated.[2] The yield obtained from this process was very low, but repeating the reaction on a larger scale allowed a satisfactory quantity of the product to be obtained for characterization purposes.



Scheme 2.24: $Mn(OAc)_3$ mediated oxidative radical cyclization

First interpretation of the ^1H NMR data showed that this compound was no longer a mixture of tautomers and instead showed a single set of peaks. The IR spectra showed a similar pattern of carbonyl stretches to that reported for garcibracteatone,[86] indicating the molecule was locked into a similar triketone structure. The other immediately obvious feature in the ^1H NMR spectrum was that the sp^2 signals for the isoprenyl group and one of the allyl groups were absent, indicating reactions had taken place at these sites. After extensive analysis of 2D NMR data, we assigned the structure to be the pentacyclic structure **2.73** (**scheme 2.24**). Our proposed mechanism for the formation of **2.73** is shown in **scheme 2.25**. After single electron oxidation to the stabilized radical **2.74**, formation of this product presumably involved 7-*endo-trig* radical cyclization with the isoprenyl side chain as the first cyclization step to give tertiary radical **2.76**, followed by 5-*exo-trig* cyclization with the phloroglucinol core. The radical **2.76** apparently did not react with the solvent as proposed, but instead underwent a

subsequent 6-*endo-trig* radical cyclization with the allyl group to give the secondary radical **2.77**, which then presumably abstracted a hydrogen atom from the solvent to give **2.73**.

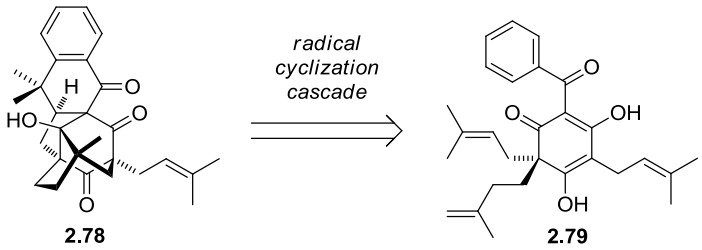


Scheme 2.25: Proposed mechanism for the formation of **2.73**

The reaction was also trialed using AcOH as the solvent to see if hydrogen atom abstraction would occur at an earlier point; however, the result was the same. While this reaction did not produce the intended product and the resultant product **2.73** was a dead end with respect to total synthesis, it uncovered some encouraging information. This result showed that the first two cyclization events we had proposed are possible and proceed in the correct order under standard conditions. The fact that a third cyclization event was observed lends precedent to the possibility of performing the entire cascade reaction to give garcibracteatone (**2.55**) in the one pot, given the correct substrate.

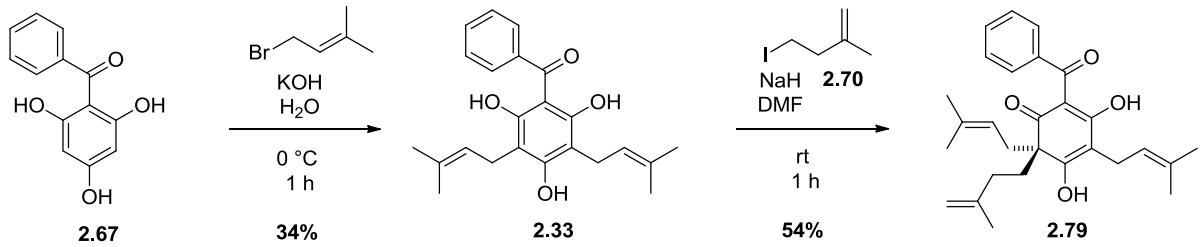
2.2.3 Synthesis of Prenylated Model System

With good precedent from our first radical cyclization attempt, the next objective chosen was to synthesize the diprenylated intermediate **2.79** and attempt to convert it into the garcibracteatone analogue **2.78** in a single radical cyclization cascade process (**scheme 2.26**). Synthesis of **2.79** could be achieved using a modification of the already established conditions for the synthesis of **2.71**. If this reaction was found to be successful, the total synthesis of garcibracteatone (**2.55**) could then be pursued by substitution of the isoprenyl group with a lavandulyl chain.



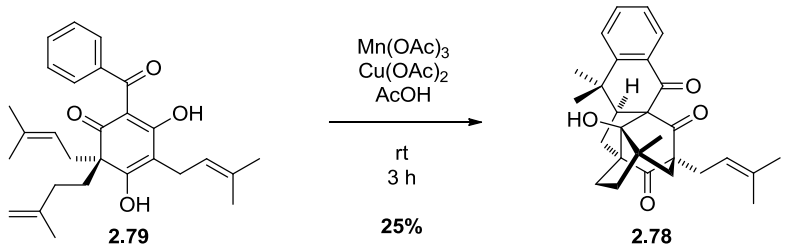
Scheme 2.26: Next objective: synthesis of garcibracteatone analogue **2.78** *via* radical cyclization cascade reaction

Diprenylation of acylphloroglucinol **2.67** under literature conditions gave the diprenylated acylphloroglucinol **2.33** in 34% yield.[77] Alkylative dearomatization with isoprenyl iodide (**2.70**) was similarly effective on the diprenylated system to yield the desired radical cyclization precursor **2.79**. As expected, weddellianone A analogue **2.79** was also shown to exist as a mixture of tautomers by ^{1}H NMR and was therefore not rigorously characterized.



Scheme 2.27: Synthesis of weddellianone A analogue **2.79**[77]

With **2.79** in hand the radical cyclization reaction could be attempted. The ideal outcome for this reaction would be for all radical cyclization events to occur in the one reaction vessel and result in the synthesis of garcibracteatone analogue **2.78**. For this reaction, $Cu(OAc)_2$ was added as a co oxidant to hopefully discourage termination of the radical chain by hydrogen atom abstraction and promote termination by oxidation to the carbocation. The use of the $Mn(OAc)_3/Cu(OAc)_2$ oxidation system has been widely explored in the literature for radical cyclization reactions.[2,83,85] Treatment of weddellianone A analogue **2.79** with these conditions produced a single isolatable product. Similar to the previously attempted radical cyclization reaction (**scheme 2.24**), first glance at the data for this product showed the formed product was a single tautomer, presumably a triketone, and that reactions had taken place at the isoprenyl group and only one prenyl group. Comparison of the ^{1}H and ^{13}C NMR data of this product to the literature data for natural garcibracteatone[86] showed promising agreement, and analysis of 2D NMR also supported the proposed structure **2.78**.



Scheme 2.28: Synthesis of garcibracteatone analogue **2.78** by oxidative radical cyclization

As the product was a crystalline solid, we attempted to grow crystals suitable for X-ray crystallographic analysis, which would confirm the proposed structure. It was found to be a good substrate for crystallization, and quality crystals could easily be grown from heptane. X-ray crystallography then confirmed the structure to be the proposed garcibracteatone analogue **2.78** (**figure 2.3**).

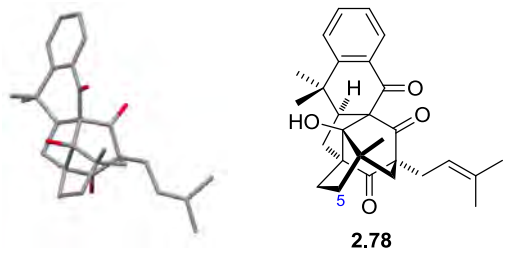


Figure 2.3: X-ray crystal structure of garcibracteatone analogue

We believe the mechanism for the formation of **2.78** is as we proposed for the biosynthesis of garcibracteatone (**scheme 2.17**). The result from this reaction was significant as four new carbon-carbon bonds, four new carbocyclic rings and five new stereocentres were formed in a single cascade reaction with complete control of relative stereochemistry; the high degree of molecular complexity that was generated in this single reaction compensated for the low yield of 25%. The synthesized garcibracteatone analogue **2.78** closely resembled the natural product, missing only the C-5 prenyl group. With this result, we were confident that our established route could be modified to complete the total synthesis of garcibracteatone (**2.55**).

2.2.4 Total Synthesis of (±)-Garcibracteatone

With the success of the model system lending excellent precedent, our attention turned to the total synthesis of garcibracteatone (**2.55**). The difference was that a lavandulyl side chain would need to be installed during the alkylative dearomatization reaction, which required the

iodide derived from lavandulol (**2.80**). A point to keep in mind was that incorporation of the lavandulyl group into these molecules would add an additional stereocentre, resulting in the formation of pairs of diastereoisomers, complicating characterization and purification.

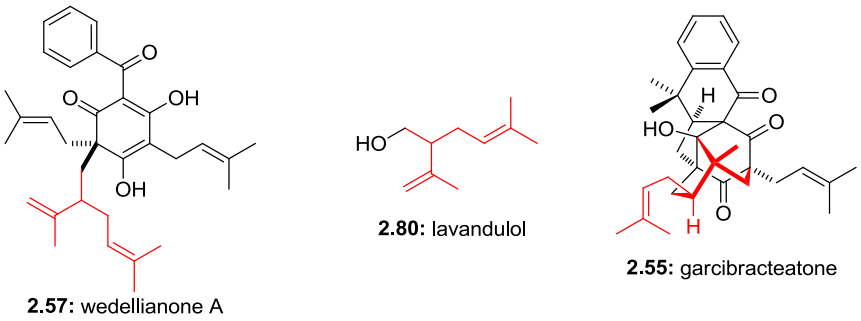
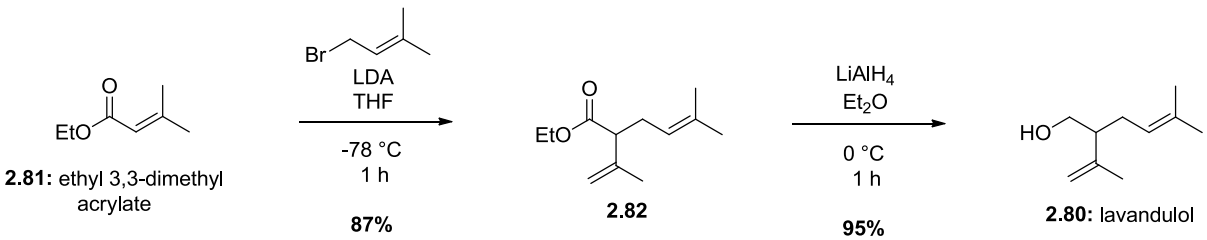


Figure 2.4: Garcibracteatone and weddellianone A each contain a lavandulyl moeity

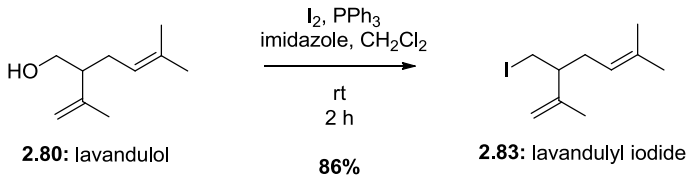
It was eventually concluded that sourcing lavandulol (**2.80**) from commercial suppliers in a reasonable quantity was not possible; hence, we looked into synthesizing it. There were several reported total syntheses of racemic lavandulol in the literature, however many of these employed the use of dated methods,[92-95] and others were simply using lavandulol as a natural product target to test their specific methodology rather than aiming to develop a practical synthesis.[96-99] Ideally, we desired a route to lavandulol that was short, scalable and high yielding. After much consideration, we hypothesized a novel route to lavandulol from inexpensive commercial starting materials in two steps. Prenyl bromide was added to a THF solution of Ethyl 3,3-dimethyl acrylate (**3.81**) after deprotonation with LDA at low temperature.[100]



Scheme 2.29: Synthesis of lavandulol

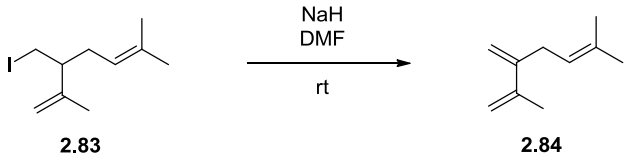
Deprotonation of this compound resulted in concomitant migration of the double bond from the *α-β* position to the *β-γ* position, which after alkylation resulted in the β-γ unsaturated ester **2.82**. Reductive cleavage of **2.82** with $LiAlH_4$ then yielded lavandulol (**2.80**). Both of these reactions were very easy to perform, reliable and high yielding (83% over the two steps).

This represented a practical synthesis of lavandulol, which we believe is superior to existing methods. The required lavandulyl iodide (**2.83**) was then obtained by iodination of lavandulol (**2.80**) under standard conditions.[75]



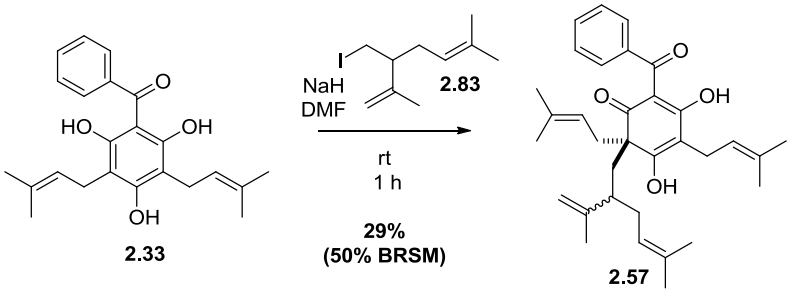
Scheme 2.30: Iodination of lavandulol

Early attempts to perform the alkylative dearomatization reaction with lavandulyl iodide under the previously successful conditions led to disappointing results. Very little or none of the desired compound was isolated, with **2.33** being recovered unreacted. Lavandulyl iodide (**2.83**) was unable to be recovered, indicating it had reacted in some way under the conditions. Isolation of the triene compound **2.84** from the reaction mixture confirmed that an elimination side reaction was taking place.



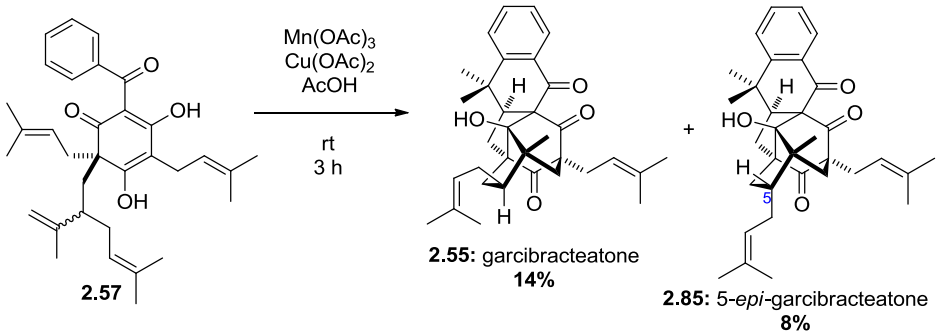
Scheme 2.31: Undesired side reaction: elimination of lavandulyl iodide

This elimination observation was unfortunate, but not unexpected. Lavandulyl iodide (**2.83**) is an unactivated electrophile and the increased conjugation present in the elimination product **2.84** may help favour elimination to occur over substitution. Attempts to alternatively convert lavandulol into the corresponding triflate resulted in instantaneous elimination under the triflation conditions,[83] so efforts were concentrated on the iodide. It was found that the yield of the desired product could be increased by using a large excess of the iodide **2.83**. By using around six equivalents of both **2.83** and base, reasonable conversions of around 29% could be achieved along with 21% recovered starting material. These reaction conditions were not ideal as large amounts of lavandulol (which needed to be synthesized) were consumed to obtain only a modest amount of product. It was therefore worth investigating this elimination vs. substitution problem to hopefully improve the practicality of this reaction.



Scheme 2.32: Alkylative dearomatization of **2.33** with lavandulyl iodide

The use of weaker bases such as K_2CO_3 resulted in no product, while the use of the stronger base LDA also gave no product. Performing the reaction at either a lower temperature or a higher temperature resulted in lower yield. Interestingly, putting either NaH or **2.83** in excess relative to each other resulted in lower yields and the best results were obtained when they were in equal mole ratios. Attempting to alkylate lavandulyl iodide (**2.83**) to other nucleophiles such as dimedone to test its electrophilicity only resulted in elimination, reinforcing its poor ability to perform in substitution reactions. We concluded that lavandulyl iodide was simply too poor of an electrophile for substitution to achieve a better result and that it was fortunate that this reaction would proceed at least to some extent. It was noteworthy that the one instance of lavandulyl iodide (**2.83**) being used in the literature was also for an alkylative dearomatization reaction of an acylphloroglucinol system, a testament to how robust this type of alkylative dearomatization reaction is.[75]



Scheme 2.33: Synthesis of garcibracteatone and 5-*epi*-garcibracteateone by oxidative radical cyclization of **2.57**

After settling on reaction conditions, enough of the dearomatization product **2.57** could be produced to proceed with the key radical cyclization reaction. The NMR spectrum of **2.57**

was even more complex than that of the previously isolated dearomatization products as it was now an expected mixture of tautomers and diastereoisomers. One of the diastereoisomers of **2.57** is the natural product weddellianone A;[89] however, the mixture could not be separated by conventional flash chromatography. The mixture **2.57** was treated under the same successful oxidative radical conditions using $Mn(OAc)_3$ and $Cu(OAc)_2$ that yielded the garcibracteatone analogue **2.78**. TLC analysis showed formation of two major products very close together on the plate and of similar R_f to the previously isolated garcibracteatone analogue. Fortunately, the two products were surprisingly easy to separate by flash chromatography, and pure samples of each could be isolated. The NMR data of each product was compared to the literature data for garcibracteatone.[86] The data of the higher R_f compound was found to match with the literature data for garcibracteatone, thus confirming the total synthesis had been successfully completed.[89] The ^1H NMR of the lower R_f compound was similar to garcibracteatone and was predicted to be its C-5 epimer. To obtain higher purity samples for analysis and also to obtain X-ray quality crystals, the higher R_f compound and the lower R_f compound were recrystallized from MeOH and heptane respectively.

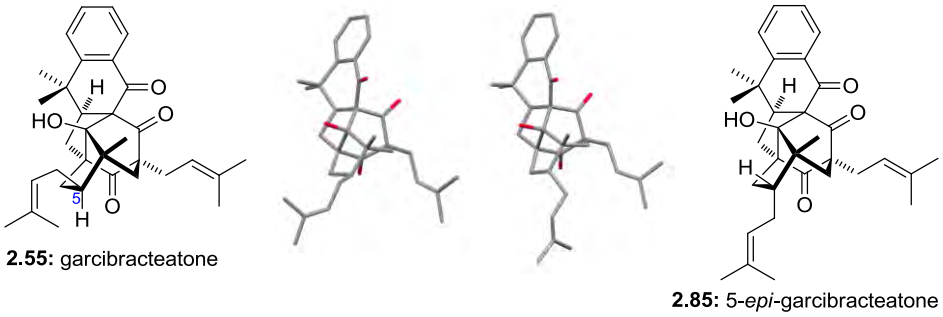


Figure 2.5: X-ray crystal structure of garcibracteatone and 5-*epi*-garcibracteateone

X-ray crystallographic analysis of the crystals confirmed the structure of the higher R_f compound to be garcibracteatone (**2.55**), as reported, and the structure of the lower R_f compound to be 5-*epi*-garcibracteatone (**2.85**) (**figure 2.5**). In addition to the completion of the first total synthesis, being the first to determine its X-ray crystal structure we were able to confirm the relative stereochemistry at C-5 of garcibracteatone (**2.55**) to be as it was predicted in the isolation paper. We believe the success of this reaction demonstrates the power of radical cyclization chemistry, along with the use of biosynthetic speculation as applied to the rapid generation of molecular complexity. The efficiency and inherent

selectivity of this reaction strongly suggests that a similar process is involved in the biosynthesis of the natural product. It is difficult to imagine how else the ornate garcibracteatone structure could be accessed, either synthetically or biosynthetically.

2.2.5 Structural Reassignment of Doitunggarcinones A and B

Not long after we completed our synthesis of garcibracteatone, Laphookhieo *et al.* reported the isolation of two new PPAP natural products, doitunggarcinone A (**2.86**) and doitunggarcinone B (**2.87**).[101] These two compounds were proposed to be structurally similar isomers of nemorosonol (**2.56**) and garcibracteatone (**2.55**), differing only in the position of the C-23 double bond and the relative stereochemistry at C-5.

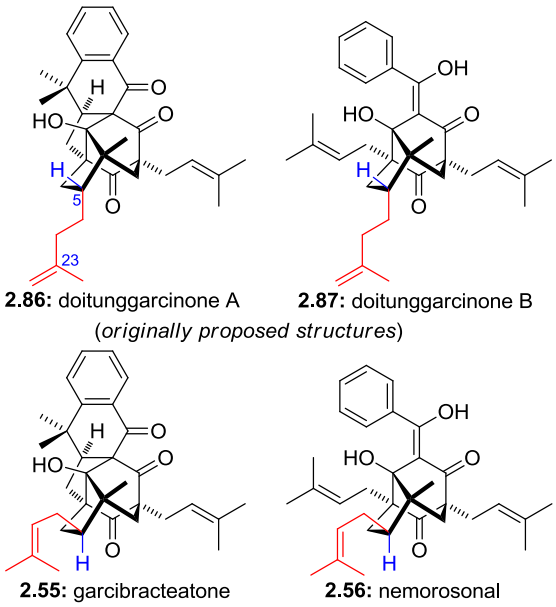


Figure 2.6: The recently discovered natural products doitunggarcinone A and doitunggarcinone B and comparison of their originally proposed structures with garcibracteatone and nemorosonol.[101]

However, upon careful inspection of the reported NMR data and comparison to our synthetic samples, we had reason to believe that Laphookhieo had incorrectly assigned the relative stereochemistry at C-5 of doitunggarcinone A (**2.86**) and B (**2.87**). Careful analysis of the side-by-side NMR comparison of doitunggarcinone A with each of our synthetic compounds showed a clear similarity with garcibracteatone (**2.55**), but likeness was more distant when compared to 5-*epi*-garcibracteatone (**2.56**) (**figure 2.7, table 2.1 and table 2.2**)

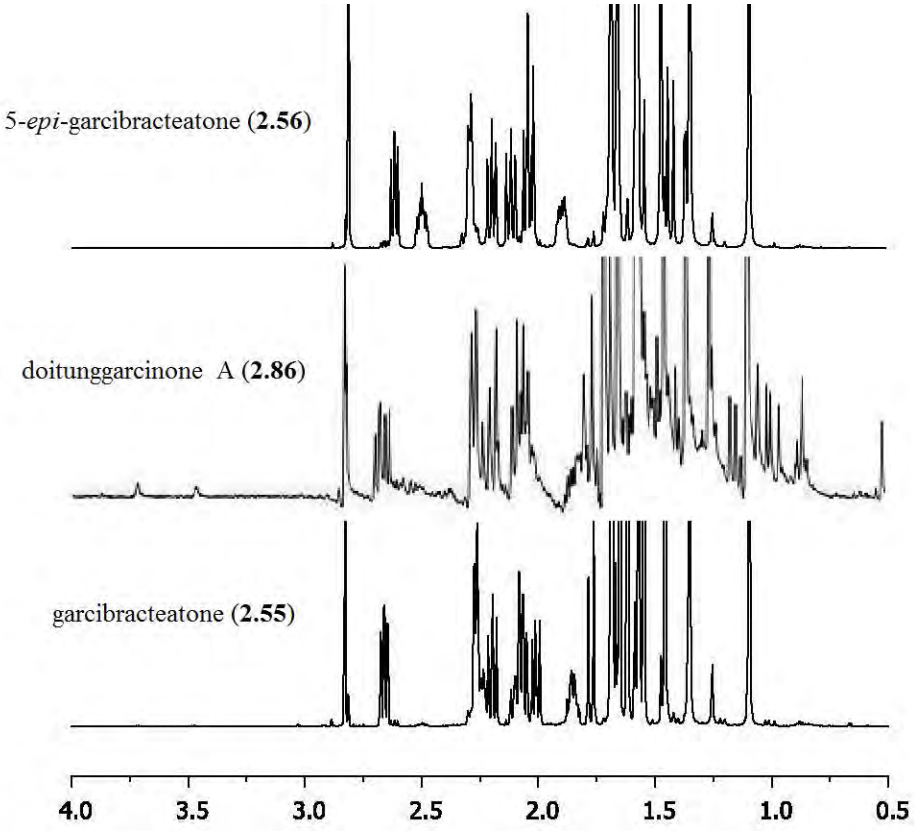


Figure 2.7: Comparison of the 4.0 – 0.5 ppm region of the ^{1}H NMR spectra of natural doitunggarcinone A (middle spectrum), synthetic garcibracteatone and synthetic 5-*epi*-garcibracteatone

Table 2.1: ^{1}H NMR data comparison of synthetic garcibracteatone (**2.55**) and 5-*epi*-garcibracteatone (**2.85**), and natural nemorosonol (**2.56**), doitunggarcinone A (**2.86**), doitunggarcinone B (**2.87**)[86,87,101]

	2.56	**2.55**	**2.85**	**2.86**	**2.87**
1	63.6	63.2	63.0	63.1	63.3
2	209.4	213.3	213.4	213.2	210.8
3	62.8	70.2	71.0	70.2	62.6
4	40.4	32.5	30.2	32.5	40.2
5	48.7	56.9	52.5	56.4	47.8
6	47.3	47.5	42.5	41.5	47.4
7	83.9	91.8	91.8	91.7	83.4
8	109.8	69.2	69.1	69.2	109.5
9	199.1	203.3	203.3	203.1	198.9
10	46.4	47.5	35.1	47.4	46.5
11	25.7	25.1	24.8	25.1	24.9
12	120.2	118.8	119.0	118.7	119.3
13	133.5	134.3	134.6	134.3	133.5
14	26.2	25.9	25.8	25.8	26.0
15	18.0	17.9	17.9	17.8	17.9

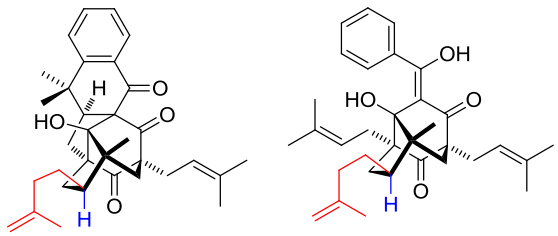
16	29.9	29.0	31.1	29.0	29.5
17	120.4	56.8	56.2	56.8	119.8
18	133.1	37.1	37.2	37.2	133.9
19	26.1	26.2	26.2	26.1	17.8
20	17.7	29.8	29.8	29.7	26.0
21	35.5	33.0	29.5	32.7	32.8
22	123.8	122.9	122.8	36.4	36.3
23	131.5	132.4	132.6	145.6	145.7
24	25.8	25.8	25.9	110.0	109.8
25	17.9	18.0	17.8	22.5	22.5
26	19.1	18.4	22.8	18.4	19.3
27	174.9	200.3	200.2	200.2	174.8
28	135.3	136.4	136.3	136.4	134.8
29	128.3	150.2	150.2	150.3	127.9
30	130.2	123.5	123.5	123.5	128.0
31	128.3	133.6	133.7	133.6	130.4
32	130.2	126.9	126.9	126.9	128.0
33	128.3	126.6	126.4	126.4	127.9

Table 2.2: ^{13}C NMR data comparison of synthetic garcibracteatone (**2.55**) and 5-*epi*-garcibracteatone (**2.85**), and natural nemorosonol (**2.56**), doitunggarcinone A (**2.86**), doitunggarcinone B (**2.87**)[86,87,101]

	2.56	**2.55**	**2.85**	**2.86**	**2.87**
1					
2					
3					
4	2.05 m 1.56 m	2.01 dd *J* = 11.8, 7.9 1.56 m	2.12 dd *J* = 12.3,10.9 1.35 m	2.05 m 1.60 m	1.97 m 1.50 m
5	1.57 m	1.85 m	2.50 m	1.81 m	1.63 m
6					
7					
8					
9					
10	1.56 m 1.48 m	1.77 d *J* = 13.9 1.68 d *J* = 13.8	2.03 d *J* = 14.2 1.43 d *J* = 14.5	1.81 m 1.60 m	1.68 m 1.55 m
11	2.92 m 2.88 m	2.27 d *J* = 7.3	2.29 d *J* = 8.0	2.26 m	2.45 m 2.16 m
12	5.59 m	5.01 t *J* = 7.2	5.02 t *J* = 7.2	5.04 t *J* = 7.2	5.17 m
13					
14	1.71 s	1.65 s	1.66 s	1.65 s	1.64 s
15	1.64 s	1.57 s	1.58 s	1.55 s	1.51 s
16	2.61 m 2.18 m	2.20 dd *J* = 11.3, 10.1 2.07 m	1.9 m 1.68 m	2.20 m 2.06 m	2.45 m 2.16 m
17	5.15 m	2.66 dd *J* = 9.8, 7.8	2.62 dd *J* = 9.8, 7.7	2.66 m	4.92 m
18					
19	1.54 m	1.35 s	1.35 s	1.35 s	1.64 s
20	1.40 m	1.10 s	1.10 s	1.08 s	1.71 s

21	2.10 m 2.08 m	2.24 m 2.05 dd *J* = 11.5, 7.8	2.2 dd J = 11.2, 10.1 2.05 t *J* = 9.5	2.20 m 2.06 m	2.16 m 1.97 m
22	4.95 m	5.04 t *J* = 7.2	5.11 t *J* = 7.2	2.05 m 1.81 m	1.97 m 1.79 m
23					
24	1.63 s	1.68 s	1.69 s	4.70 brs 4.66 brs	4.66 brs 4.62 brs
25	1.49 m	1.62 s	1.58 s	1.71 s	1.67
26	0.90 m	1.46 s	1.47 s	1.45 s	1.15
27					
28					
29	7.04 m				7.47 m
30	7.47 m	7.35 d *J* = 7.6	7.35 d *J* = 7.8	7.34 m 7.38 m	7.44 m
31	7.04 m	7.54 td *J* = 7.6, 1.4	7.54 td *J* = 7.6, 1.4	7.54 dt *J* = 7.6, 0.8	7.47 m
32	7.47 m	7.36 t *J* = 7.6	7.36 t *J* = 7.6	7.34-7.38 m	7.44 m
33	7.04 m	7.69 dd *J* = 7.6, 1.3	7.70 dd *J* = 7.6, 1.2	7.69 d *J* = 7.6	7.47 m
OH	2.0 s 16.0 s	2.83 s	2.81 s	2.82 s	5.08 s 15.32 s

We were certain that our stereochemical assignment of garcibracteatone was correct as we had the crystal structures of both epimers; hence the stereochemical assignment of doitunggarcinone A reported by Laphookhieo *et al.* was incorrect. This NMR comparison of synthetic compounds and related natural products allowed us to confidently reassign the structures of doitunggarcinones A and B to be **2.88** and **2.89** respectively, matching the C-5 stereochemistry of garcibracteatone (**2.55**) and nemorosonol (**2.56**) (**figure 2.8**).

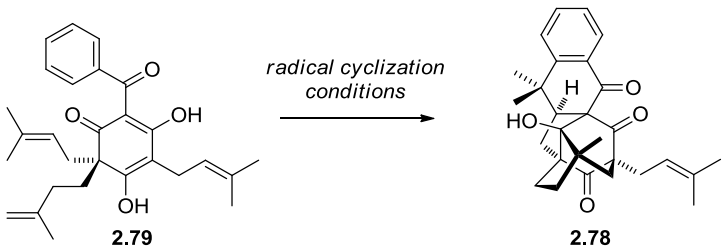


2.88: doitunggarcinone A **2.89:** doitunggarcinone B

Figure 2.8: Reassigned structures of doitunggarcinone A and doitunggarcinone B[102]

A total synthesis of doitunggarcinone A (**2.88**) was completed in 2013 by Stephen Tulip, an Honours student in our research group, using our established garcibracteatone methodology.[103]

2.2.6 Attempted Optimization of Radical Cyclization Cascade Reaction



2.79 **2.78**

Scheme 2.34: Attempted optimization of radical cyclization cascade reaction

Even though the biomimetic radical cyclization cascade reaction was a success in yielding garcibracteatone (**2.55**) under standard conditions, the isolated yield was low so it was in our interest to try to optimize the reaction. It was also hoped that screening other oxidation reagents and conditions could uncover additional information about the reaction. We were also very interested in the possibility observing nemorosonol type intermediates under different reaction conditions. The model system (isoprenyl in place of lavandulyl) was used for testing as the substrates were easier to prepare and the formation of only one diasteroisomer simplified purification and isolation.

Table 2.3: Attempted optimization conditions of radical cyclization cascade reaction

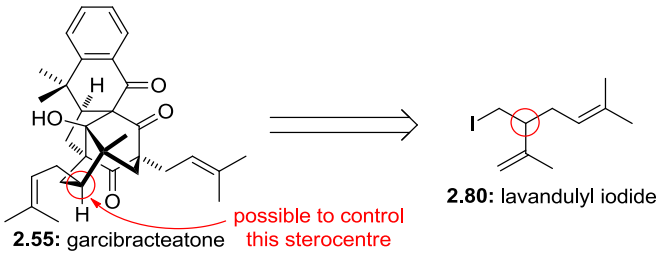
Reagent	Solvent	Time	Temperature	Result
$Mn(OAc)_3 + Cu(OAc)_2$	AcOH	3 h	rt	**2.78** (25%)
$PhI(OAc)_2$	THF	1 h	rt	unknown product
CAN	EtOH	1 h	rt	decomposition
$Fe(CN)_6K_3$	EtOH	3 h	65 °C	decomposition
Fremy's salt	EtOH	16 h	65 °C	no reaction
$Mn(OAc)_3$	AcOH	3 h	rt	**2.78** (16%)
$Mn(OAc)_3 + Cu(OAc)_2$	EtOH	3 h	rt	**2.78** (23%)
$Mn(OAc)_3 + Cu(OAc)_2$	AcOH	3 h	65 °C	**2.78** (24%)
$Mn(OAc)_3 + Cu(OAc)_2$	EtOH	3 h	0 °C	**2.78** (23%)
$Mn(OAc)_3 + Cu(OAc)_2$	AcOH	30 min	rt	**2.78** (22%)
$Mn(OAc)_3 + Cu(OAc)_2$	AcOH	16 h	rt	**2.78** (24%)

Attempts to perform the reaction using other oxidants failed as use of CAN or $Fe(CN)_6K_3$ resulted in decomposition and Fremy's salt resulted in no reaction. Use of $PhI(OAc)_2$ under similar conditions to the synthesis of ialibinones A (**2.53**) and B (**2.54**) by George *et al.*[84] gave the formation of a new compound. The product isolated from the $PhI(OAc)_2$ reaction proved to be too difficult to characterize as it existed as a mixture of tautomers, although by

rough analysis of the complicated ^{1}H NMR spectrum, it was clear that this product was unlike nemorosonol (**2.56**). When using the $Mn(OAc)_3/Cu(OAc)_2$ oxidation system, the modification of temperature, time or solvent seemed to be largely irrelevant to the product yield. The formation of the product **2.78** was also mostly unaffected by absence of $Cu(OAc)_2$, albeit in a slightly lowered yield. Unfortunately, the oxidative radical cyclization reaction optimization effort was overall unsuccessful, and not much was gained from this exercise.

2.2.7 Total Synthesis of (-)-Garcibracteatone

Sèvenet *et al.* who originally published the isolation and characterization of garcibracteatone (**2.55**) were unable to determine its absolute stereochemistry.[86] The natural product was determined to have an optical rotation value of $[\alpha]_D^{25}$ = -1.0 (c 1.00, $CHCl_3$), which is unusually low for a molecule with seven stereocentres. A rotation value of -1 is arguably within experimental error as polarimetry is an inherently unreliable technique and minor chiral impurities can have a major impact on the result; hence, it was arguable whether garcibracteatone existed as one enantiomer in nature or was in fact racemic. Because the absolute stereochemistry of the natural product remained unknown, this was an opportunity for us to add this piece of information to the literature. This could be possible by modifying our current racemic synthesis to an enantiopure synthesis that incorporated starting materials of known configuration. If we could achieve this, the absolute stereochemistry of garcibracteatone (**2.55**) could be determined by measuring the optical rotation of our synthetic sample and comparing it to the literature value.

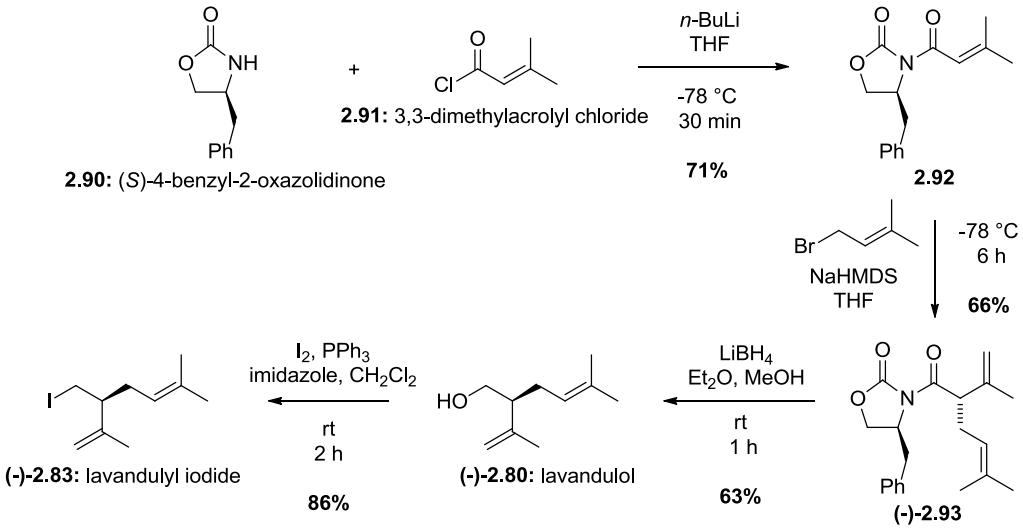


Scheme 2.35: Proposed strategy for the enantiopure synthesis of garcibracteatone

In order to synthesize a single enantiomer of a molecule containing multiple stereocentres, the configuration of at least one stereocentre needs to be controlled. Fortunately, in our currently establish methodology there was one stereocentre which was hypothetically simple to control; the one present in the lavandulyl side chain (**scheme 2.35**). The objective was to

therefore synthesize lavandulyl iodide (**2.80**) in enantiopure form; the rest of the synthesis need not be modified.

Consulting the literature revealed several reported total syntheses of enantiopure lavandulol (**2.80**). Approaches ranged from the use of chiral auxillaries,[104] the use of chiral pool compounds as the starting material,[105,106] enzymatic resolution of racemic lavandulol,[107] and chiral catalysis.[108] After consideration of each of these options, we decided to incorporate a chiral auxilliary approach, as it would essentially be a modification of our already established synthesis of racemic lavandulol. The phenylalanine derived oxazolidinone auxiliary **2.90**[109] was chosen instead of the imidazolidin-2-one auxiliary used in the literature synthesis[104] due to availability. This change would also add some new, albeit trivial, synthetic steps to the literature.

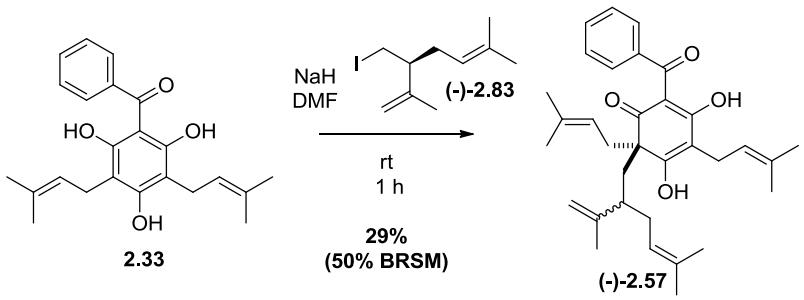


Scheme 2.36: Synthesis of (-)-lavandulol *via* a chiral auxiliary strategy

The first step was the simple union of the Evans auxiliary (*S*)-4-benzyl-2-oxazolidinone (**2.90**) to 3,3-dimethylacroyl chloride[110] (**2.91**) to yield **2.92**, which would serve as the substrate for asymmetric alkylation. Under literature conditions, treatment of the auxiliary with *n*-BuLi at low temperatures followed by addition of the acid chloride produced the desired product **2.92** in reasonable yield of 71% after purification by recrystallization.[111] Early attempts of the asymmetric alkylation of **2.92** with LDA and prenyl bromide gave poor results, with undesirable diastereomeric ratios of the product **2.93**. This was found to be a very slow reaction and attempts to speed up the reaction by warming to above -78 °C would result in poor stereoselectivity. After performing this reaction several times, a satisfactory diastereomeric ratio of 15 : 1, as calculated from the ^{1}H NMR spectrum, was achieved. Using

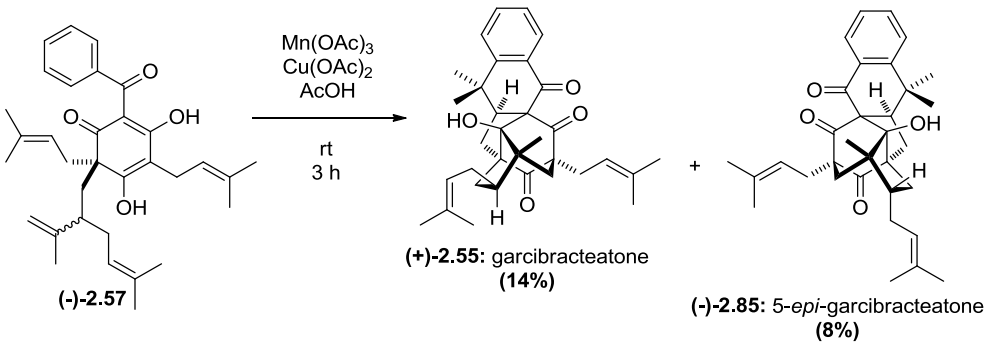
NaHMDS as the base, as well as keeping the temperature at -78 °C for the entire reaction duration, was found to be optimal to achieve a desirable diastereoselectivity of **(-)-2.93**.

The reductive cleavage of the auxiliary to give (-)-lavandulol (**2.80**) was found to be more difficult than expected. Early attempts gave low yields of around 50%, so several different reducing agents were screened in the hope of improving this. Of the reagents trialed, $LiBH_4$ was found to give the best results, increasing the yield to 63% which was still lower than expected for such a simple transformation. With the establishment of the asymmetric alkylation and the reductive cleavage of the auxiliary, this completed our synthesis of (-)-lavandulol (**2.80**). This route was ultimately not very practical due to the low yields, unreliable diastereoselectivity and the inherent atom inefficiency of a chiral auxiliary approach. Despite this, it still proved to be adequate to produce the quantities of (-)-lavandulol required for this project.



Scheme 2.37: Alkylative dearomatization of **2.33** with (-)-lavandulyl iodide

With the produced (-)-lavandulol (**2.80**), the iodination, alkylative dearomatization and oxidative radical cyclization reactions were performed in sequence under identical conditions to the racemic synthesis. This yielded a mixture of enantiomerically enriched garcibracteatone (**2.55**) and the epimer of its enantiomer (**2.85**) (**scheme 2.38**).



Scheme 2.38: Synthesis of (+)-garcibracteatone and (-)-5-*epi*-garcibracteateone

Optical rotation analysis of our synthetic sample revealed an $[\alpha]_D^{25}$ value of +2.0 in $CHCl_3$ with a concentration of 1.0 g/dm. The natural product had a reported $[\alpha]_D^{25}$ value of -1.0 under the same conditions. The comparable low value that we recorded for our synthetic sample supported the hypothesis that garcibracteatone was in fact a single enantiomer in nature. An $[\alpha]_D^{25}$ value of +2.0 for our synthetic sample suggested we had made the opposite enantiomer of the natural product and therefore the absolute stereochemistry of garcibracteatone was opposite to what we had synthesized. However, because both optical rotation values were so low, it could still be argued that these results were within experimental error. We therefore thought it was still necessary to obtain further evidence before we could confidently assign the absolute stereochemistry.

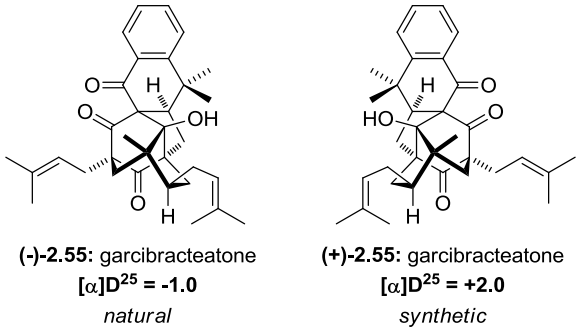


Figure 2.9: Comparison of the optical rotation of natural and synthetic garcibracteatone

The other experimental technique we considered was to perform chiral HPLC analysis, although in order for this to be effective we needed to acquire a sample of natural garcibracteatone (**2.55**) to use as a reference. Fortunately, after contacting Sèvenet *et al.* (the chemists who reported the isolation of garcibracteatone) they were able to send us a small sample of the natural product, which we could use for the analysis. Chiral HPLC analysis was performed by Yuji Nakano at Monash University as the required facilities were not available at the University of Adelaide. Three chiral HPLC traces of garcibracteatone (**2.55**) samples were performed; one of our synthetic racemic sample (**figure 2.11**), one of our synthetic enantiomerically enriched sample (**figure 2.12**), and one of the natural sample (**figure 2.10**). The trace of our racemic sample showed a peak with a retention time of around six minutes and one of around 12 minutes. The trace of our enantiomerically enriched sample also showed both of these peaks; however the ration was about 22 : 1 in favour of the six minute peak by integration. This further confirmed that we had achieved a good enantioselectivity during our synthesis. The trace of the natural sample only contained a peak at 12 minutes and

by comparison to the other traces, this was definitive proof that we had indeed synthesized the opposite enantiomer of the natural product. This result reinforced the conclusions from the polarimetry experiment.

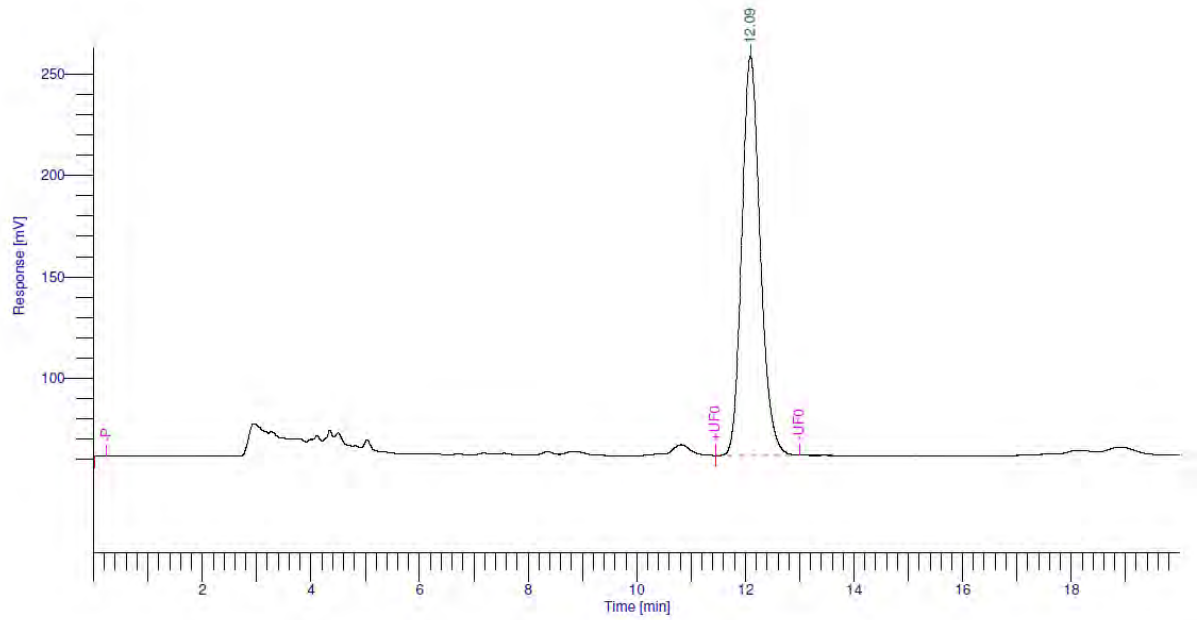


Figure 2.10: HPLC trace of natural (-)-garcibracteatone (**2.55**)

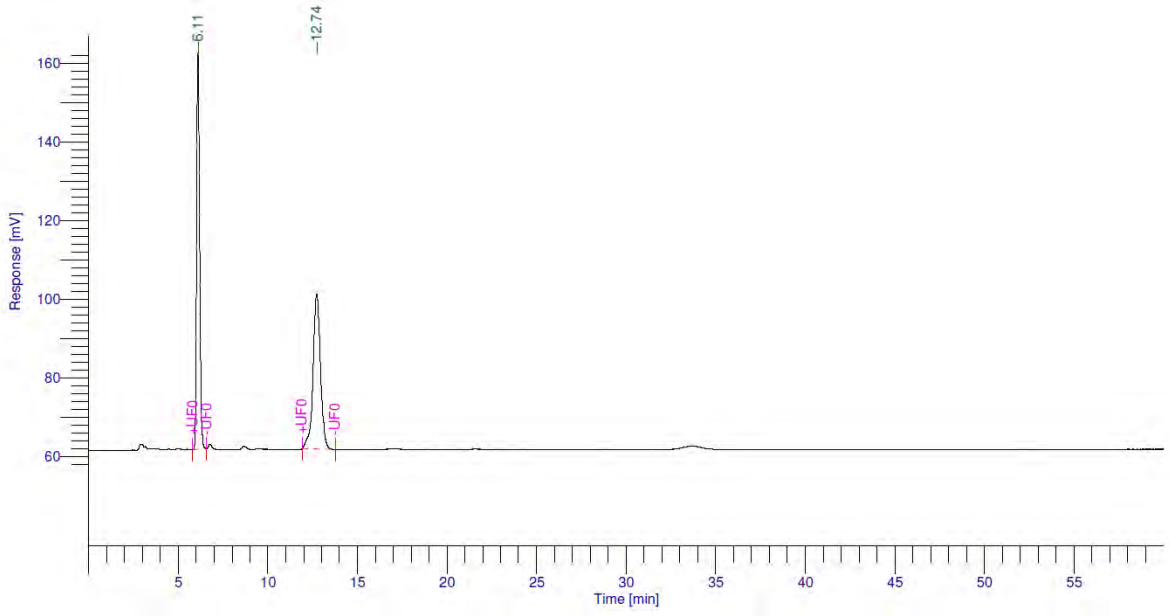


Figure 2.11: HPLC trace of synthetic (±)-garcibracteatone (**2.55**)

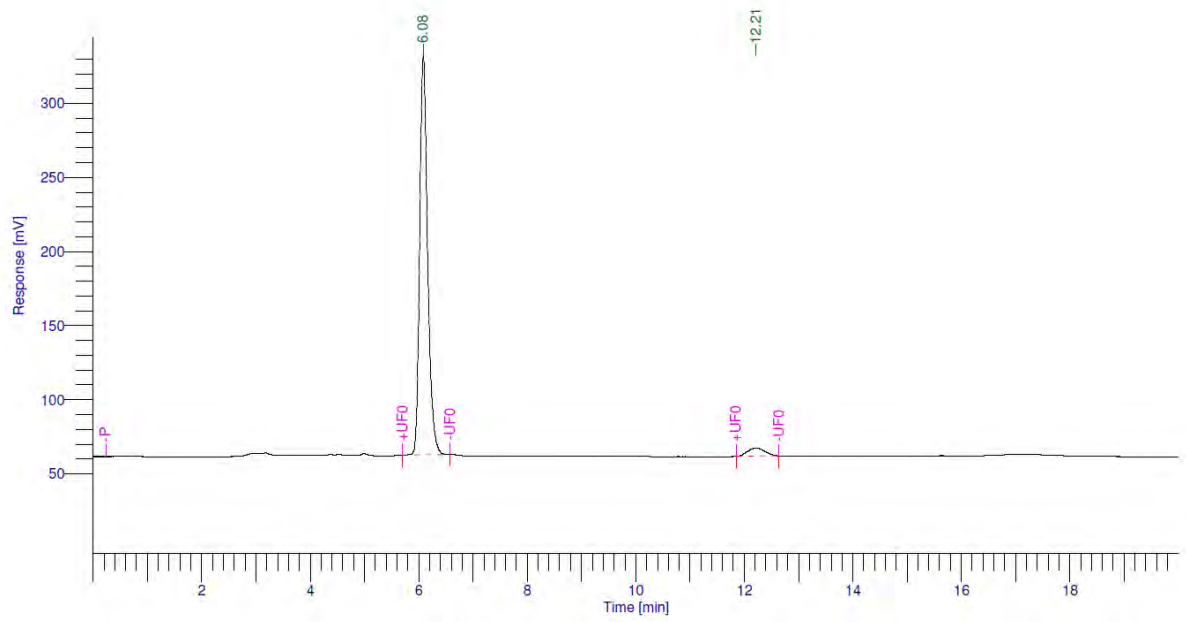
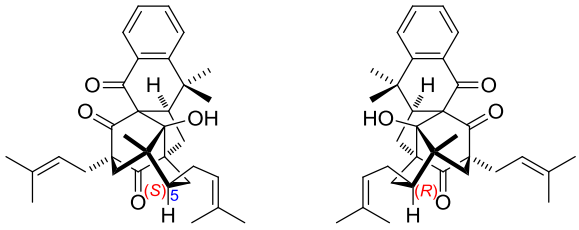


Figure 2.12: HPLC trace of synthetic (+)-garcibracteatone (**2.55**)



(-)-2.55: garcibracteatone
natural

(+)-2.55: garcibracteatone
synthetic

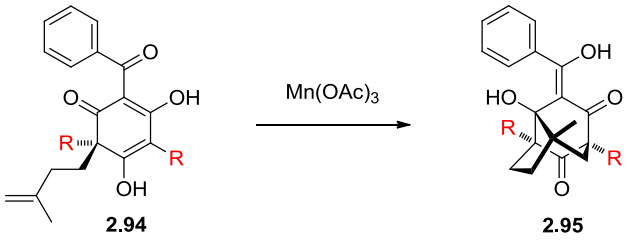
Figure 2.13: Absolute stereochemistry of garcibracteatone

Because the absolute configuration of the auxiliary used was known, the configuration of the lavandulol we synthesized was also known and therefore the C-5 stereocentre of our synthetic garcibracteatone was *R* configuration. After confirming that our synthetic sample was the opposite enantiomer of the natural product, this confirmed that the C-5 stereocentre of garcibracteatone was *S* configuration. Therefore we had successfully assigned the absolute configuration of garcibracteatone (**2.55**) to be as shown in **figure 2.13**.

2.2.8 Attempted Synthesis of Nemorosonol

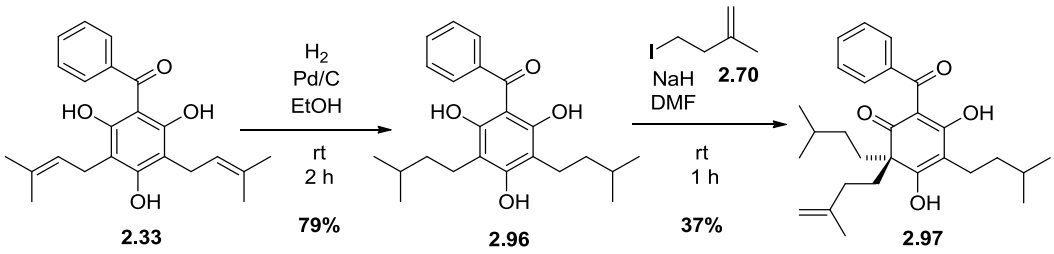
Currently all of our radical cyclization attempts had only yielded garcibracteatone like products and no formation of nemorosonol[87] like products had been observed. Despite

garcibracteatone (**2.55**) being the more structurally impressive molecule and its total synthesis already had fulfilled many of our goals; it was still worth investigating the synthesis of nemorosonol (**2.56**). In order to obtain the nemorosonol skeleton from a radical cyclization process, the cascade would need to terminate after the first two cyclization events had occurred.



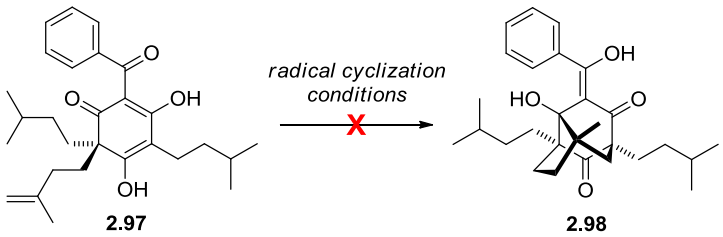
Scheme 2.39: Theoretical synthesis of nemorosonol ring skeleton (R = unreactive group)

In theory, this could be achieved by only having one reactive alkene group present in the molecule prior to cyclization (**scheme 2.39**), making it impossible for subsequent cyclization events to take place. After consideration, the simplest way to test this was to hydrogenate the already available diprenylated acylphloroglucinol intermediate **2.33**, which would convert the prenyl groups into unreactive isopentyl groups. If this approach was successful in yielding the nemorosonol skeleton, performing the synthesis with masked groups, which could be later converted into the natural prenyl groups, could then be pursued.



Scheme 2.40: Synthesis of the diisopenyl intermediates

Early attempts at the hydrogenation of **2.33** under standard conditions gave low yield of the desired hydrogenation product **2.96**. Another major product was isolated from this reaction which was determined to be a derivative of **2.96** where the benzoyl group was replaced with a hydrogen atom, presumably originating from a hydrogenolysis process. Increased care in monitoring this reaction by TLC and shortening the reaction time led to acceptable yields of **2.96**. Alkylative dearomatization of **2.96** with isoprenyl iodide (**2.70**) under our established conditions then yielded the substrate required to test the key radical cyclization reaction **2.97**.



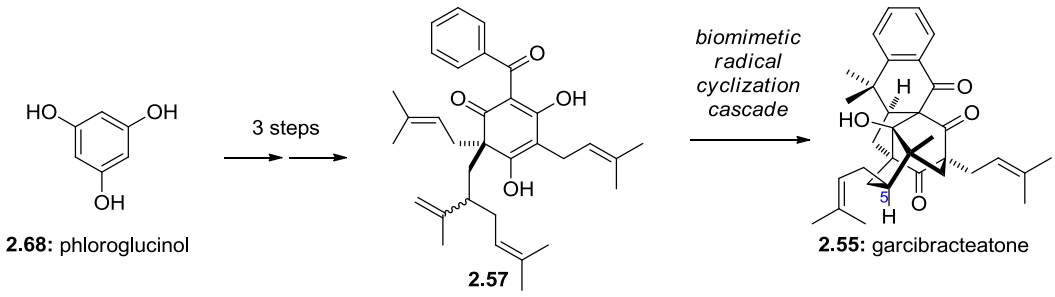
Scheme 2.41: Attempts to synthesize simplified nemorosonol analogue **2.98**

Unfortunately, all attempts to yield the nemorosonol analogue **2.98** under radical cyclization conditions failed, with no isolatable products being formed and only complex mixtures or decomposition observed. Many similar reagents and conditions shown in **table 2.3** were trialed for this process with no success. Performing the reaction in the absence of $Cu(OAc)_2$ to help promote termination by hydrogen abstraction rather than oxidation was ineffective. Additives such as thiophenol, added with the intention of being a good hydrogen atom donor to promote termination by hydrogen abstraction, also did not alter the outcome.

Unfortunately, no analogues containing the nemorosonol ring system were synthesized. Presumably, termination by hydrogen atom abstraction was a relatively slow step and it was more favorable for the radical intermediate to follow decomposition pathways.

2.3 Conclusions

The first total synthesis of the PPAP natural product garcibracteatone (**2.55**) was achieved in four linear steps from phloroglucinol (**2.68**) (0.6% overall yield). The synthesis features eight carbon-carbon bond forming events in four steps, and the use of protecting groups in avoided. The key biomimetic oxidative radical cyclization cascade reaction was found to be an impressive method for the construction of the highly complex polycyclic structure of garcibracteatone, with four new carbon-carbon bonds, four new carbocyclic rings and five new stereocentres formed in a single synthetic operation. The success of this strategy highlights the power of biomimetic synthesis as applied to the rapid generation of molecular complexity. The efficiency and inherent selectivity of the radical cascade reaction strongly suggests that a similar process is involved in the biosynthesis of the natural product. No formation of nemorosonol (**2.56**) or nemorosonol-like analogues were ever observed under the attempted oxidative radical cyclization conditions.



Scheme 2.42: Summary of the biomimetic total synthesis of garcibracteatone

Synthesis of garcibracteatone (**2.55**) along with its C-5 epimer (**2.85**), and X-ray crystallographic analysis of both compounds allowed the unambiguous determination of the relative stereochemistry at C-5 of garcibracteatone to be as predicted in the isolation paper by comparison of the NMR data.[86] Using the same data, we were able to confidently reassign the relative stereochemistry at C-5 of doitunggarcinone A (**2.88**) and B (**2.89**) to match that of garcibracteatone and nemorosonol.

Our synthetic efforts towards garcibracteatone resulted in two novel syntheses of lavandulyl iodide (**2.80**), one racemic and one enantioselective. These syntheses allow easy access to an electrophilic derivative of this naturally occurring terpene moiety, and in future could be used for broader utility.

Alkylative dearomatization with (-)-lavandulyl iodide **(2.80)** ultimately allowed the synthesis of (+)-garcibracteatone (**2.55**) and (-)-5-*epi*-garcibracteatone (**2.85**). Chiral HPLC comparison of synthetic (+)-garcibracteatone with a natural sample of garcibracteatone allowed the unambiguous determination of the absolute stereochemistry of the natural product.

In future, a similar biomimetic radical cyclization approach could be applied to the synthesis of the related natural products hyperuralones A and B[112] and other PPAPs of presumably radical biosynthetic origin such as peroxysampsone A (**2.45**) (**scheme 2.13**).[82]

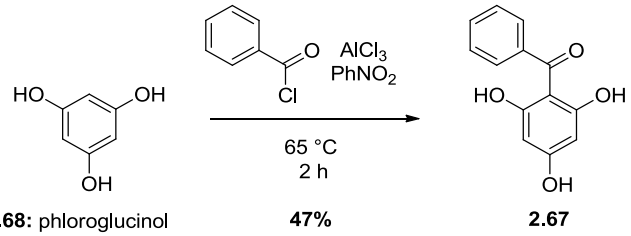
2.4 Experimentals

2.4.1 General Methods

All chemicals used were purchased from commercial suppliers and used as received. 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 Merck aluminium sheets silica gel 60 F255. Visualization was aided by viewing under a UV lamp and staining with ceric ammonium molybdate stain followed by heating. All R_f values were rounded to the nearest 0.01. Flash chromatography was performed using Davasil (40-63 micron) grade silica gel. Melting points were recorded on a Stanford Research Systems Digimelt digital melting point apparatus and are uncorrected. Infrared spectra were recorded using a Perkin Elmer Spectrum BX FT-IR system spectrometer as the neat compounds. High field NMR was recorded using a Varian Inova-6000 spectrometer (^{1}H at 600 MHz, ^{13}C at 150 MHz). Solvents used for spectra were chloroform 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 chloroform (δ 77.0). Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet and (m) multiplet. All J values were rounded to the nearest 0.1 Hz. ESI high resolution mass spectra were recorded using an LTQ Orbitrap XL ETD (Thermo Fisher Scientific Inc., MA).

2.4.2 Experimental Procedures

phenyl(2,4,6-trihydroxyphenyl)methanone (2.67)[90]



2.68: phloroglucinol **47%** **2.67**

To a suspension of anhydrous phloroglucinol (**2.68**) (11.5 g, 91.2 mmol) in $PhNO_2$ (90 mL), $AlCl_3$ (48.6 g, 365 mmol) was added in three portions at rt. The reaction mixture was stirred at rt for 30 min. Benzoyl chloride (11.7 mL, 100 mmol) was added, and the mixture was heated at 65 °C for 2 h. The reaction mixture was then cooled to rt before being quenched by pouring onto ice water and extracted with EtOAc (3 x 100 mL). The product was then extracted into 2 M NaOH solution (2 x 150 mL). The aqueous extracts were neutralized with conc. HCl, and the product extracted back into EtOAc (3 x 100 mL). The combined organics were washed sequentially with H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 4:1 → 2:1 gradient elution) to give phenyl(2,4,6-trihydroxyphenyl)methanone (**2.67**) (9.80 g, 47%) as a yellow solid.

R_f = 0.10 (petrol/EtOAc, 2:1)

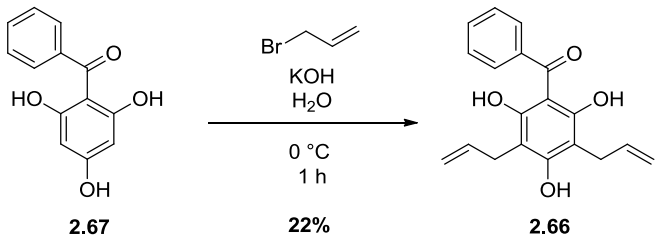
Mp = 164-167 °C

IR (neat): 3363, 1638, 1594, 1286, 1151, 1056, 818, 697 cm^{-1}

^{1}H NMR (600 MHz, acetone-*d6*) δ 10.15 (br s, 3H), 7.57 (d, *J* = 7.2 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 7.2 Hz, 2H), 5.95 (s, 2H).

^{13}C NMR (150 MHz, acetone-*d6*) δ 199.5, 165.2, 163.6, 142.3, 131.3, 128.6, 128.0, 104.9, 95.6.

(3,5-diallyl-2,4,6-trihydroxyphenyl)(phenyl)methanone (2.66)



2.67 **2.66**

To a solution of **2.67** (2.29 g, 9.95 mmol) in H_2O (20 mL), KOH (1.12 g, 19.9 mmol) was added at 0 °C. Allyl bromide (1.71 mL, 19.9 mmol) was then added drop wise over 20 min. The reaction mixture was warmed to rt and stirred for a further 1 h. The mixture was acidified with 1 M HCl solution (10 mL) and then extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 8:1 as eluent) to give (3,5-diallyl-2,4,6-trihydroxyphenyl)(phenyl)methanone (**2.66**) (691 mg, 22%) as a yellow solid.

R_f = 0.29 (petrol/EtOAc, 4:1)

Mp = 83-85 °C

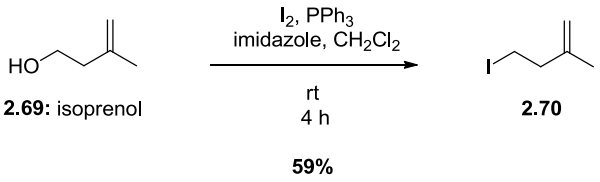
IR (neat): 3468, 3234, 2926, 1620, 1590, 1560, 1205, 1106, 911, 697 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.64 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 5.98 (s, 1H), 6.00 – 5.92 (m, 2H), 5.15 (dq, *J* = 26.7, 1.6 Hz, 2H), 5.13 (dq, *J* = 19.6, 1.6 Hz, 2H), 3.41 (t, *J* = 1.6 Hz, 2H), 3.40 (t, *J* = 1.6 Hz, 2H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 197.9, 161.0, 158.0, 139.9, 136.1, 132.2, 129.2, 127.8, 116.0, 104.6, 27.0.

HRMS (ESI): calculated for $C_{19}H_{19}O_4$ 311.1278 $[M+H]^+$, found 311.1278.

isoprenyl iodide (2.70)[91]



2.69: isoprenol

2.70

59%

To a solution of PPh_3 (22.0 g, 83.9 mmol) and imidazole (5.72 g, 83.9 mmol) in CH_2Cl_2 (200 mL), I_2 (21.3 g, 83.9 mmol) was added at 0 °C. After 15 min, isoprenol (**2.69**) (8.11 mL, 79.9 mmol) was added drop wise at 0 °C. The reaction mixture was stirred at rt for 4 h. The reaction mixture was concentrated *in vacuo*, and the residue diluted with hexanes and filtered through celite. The filtrate was concentrated *in vacuo*. The residue was distilled under reduced pressure (45 °C, 15 torr) to yield isoprenyl iodide (**2.70**) (9.20 g, 59%) as a pale orange oil.

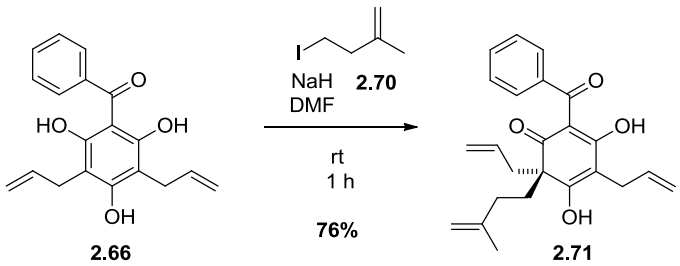
R_f = 0.68 (neat petrol)

IR (neat): 2969, 1650, 1445, 1233, 1170, 893 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.86 (s, 1H), 4.76 (s, 1H), 3.26 (t, *J* = 7.8 Hz, 2H), 2.59 (t, *J* = 7.8 Hz, 2H), 1.74 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 143.9, 112.3, 41.9, 21.7, 3.5.

4,6-diallyl-2-benzoyl-3,5-dihydroxy-6-(3-methylbut-3-en-1-yl)cyclohexa-2,4-dienone (2.71)



To a solution of **2.66** (400 mg, 1.29 mmol) in anhydrous DMF (8 mL), NaH (60% dispersion in mineral oil, (155 mg, 3.87 mmol) was added at rt. The mixture was stirred at rt for 5 min before isoprenyl iodide (**2.70**) (502 mg, 2.56 mmol) was added at rt. The reaction mixture was stirred at rt for 1h. The mixture was quenched with 1 M HCl solution (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organics were washed sequentially with H_2O (2 x 30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 6:1 →4:1 gradient elution) to give 4,6-diallyl-2-benzoyl-3,5-dihydroxy-6-(3-methylbut-3-en-1-yl)cyclohexa-2,4-dienone (**2.71**) (371 mg, 76%) as a yellow solid.

R_f = 0.14 (petrol/EtOAc, 4:1)

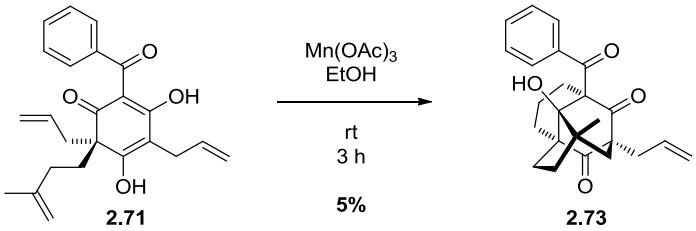
Mp = 97 - 101 °C

IR (neat): 3167, 2878, 1648, 1198, 890, 696 cm^{-1}

NMR spectra showed a complex mixture of tautomers.

HRMS (ESI): calculated for $C_{24}H_{27}O_4$ 379.1904$[M+H]^+$, found 379.1907.

7-allyl-5a-benzoyl-2a1-hydroxy-8a-methyloctahydro-1H-2a,7-methanoacenaphthylene-6,9(2H)-dione (2.73)



To a solution of $Mn(OAc)_3(H_2O)_2$ (212 mg, 0.790 mmol) in degassed EtOH (1 mL), **2.71** (150 mg, 0.396 mmol) in degassed EtOH (6 mL) was added at rt. The reaction mixture was stirred at rt for 3 h. The mixture was quenched with H_2O (15 mL) and was extracted with EtOAc (3 x 20 mL). The combined organics were washed sequentially with H_2O (30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 10:1 as eluent) to give 7-allyl-5a-benzoyl-2a1-hydroxy-8a-methyloctahydro-1H-2a,7-methanoacenaphthylene-6,9(2H)-dione (**2.73**) (7 mg, 5%) as a white crystalline solid.

R_f = 0.35 (petrol/EtOAc, 4:1)

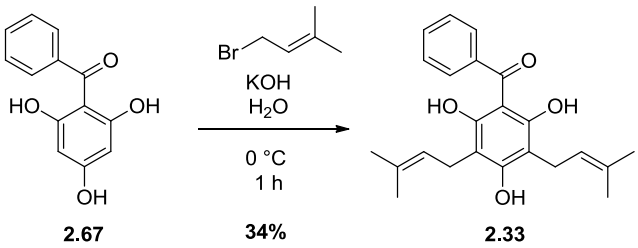
Mp = 115-117 °C

IR (neat): 3528, 2932, 1736, 1707, 1650, 1243, 1072, 914, 689 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 2H), 5.71 (m, 1H), 5.09 (d, *J* = 4.1 Hz, 1H), 5.06 (s, 1H), 4.71 (s, 1H), 2.57 (dd, *J* = 14.4, 7.0 Hz, 1H), 2.39 – 2.30 (m, 2H), 2.28 (ddd, *J* = 12.7, 4.3, 2.2 Hz, 1H), 1.97 (m, 3H), 1.86 (td, *J* = 12.1, 6.7 Hz, 1H), 1.74 (ddd, *J* = 12.5, 9.5, 3.1 Hz, 1H), 1.58 (t, *J* = 7.1 Hz, 1H), 1.56 – 1.54 (m, 1H), 1.54 – 1.51 (m, 1H), 1.43 (ddd, *J* = 13.5, 9.5, 6.7 Hz, 1H), 1.18 (s, 3H), 0.95 – 0.82 (m, 1H).
^{13}C NMR (150 MHz, $CDCl_3$) δ 210.8, 207.2, 204.6, 137.9, 133.4, 132.1, 128.3, 127.9, 118.7, 80.6, 66.5, 65.7, 62.8, 43.3, 40.5, 39.0, 35.5, 31.3, 30.6, 28.0, 23.3, 19.8.

HRMS (ESI): calculated for $C_{24}H_{27}O_4$ 379.1904 $[M+H]^+$, found 379.1901.

phenyl(2,4,6-trihydroxy-3,5-bis(3-methylbut-2-en-1-yl)phenyl)methanone (2.33)[77]



2.67 **34%** **2.33**

To a solution of **2.67** (10.0 g, 43.4 mmol) in H_2O (80 mL), KOH (4.89 g, 86.9 mmol) was added at 0 °C. Prenyl bromide (10.0 mL, 86.9 mmol) was then added drop wise over 20 min at 0 °C. The reaction mixture stirred at 0 °C for a further 1 h. The reaction mixture was acidified with 1 M HCl solution (40 mL) and then extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 20:1 → 10:1 gradient elution) to give phenyl(2,4,6-trihydroxy-3,5-bis(3-methylbut-2-en-1-yl)phenyl)methanone (**2.33**) (5.35 g, 34%) as a yellow solid.

R_f = 0.45 (petrol/EtOAc, 4:1)

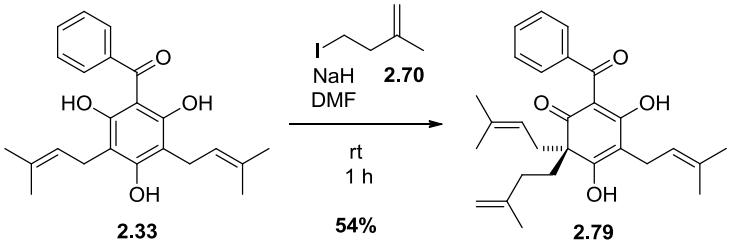
Mp = 76 - 82 °C

IR (neat): 3360, 2912, 1618, 1560, 1427, 1325, 1098, 694 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.91 (s, 2H), 7.65 – 7.62 (m, 2H), 7.59 – 7.55 (m, 1H), 7.52 – 7.48 (m, 2H), 6.35 (s, 1H), 5.22 (t, *J* = 7.1 Hz, 2H), 3.34 (d, *J* = 7.0 Hz, 4H), 1.78 (s, 6H), 1.74 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 198.0, 161.0, 157.6, 140.3, 135.0, 132.0, 129.0, 127.9, 121.8, 106.3, 104.5, 25.8, 21.8, 17.9.

2-benzoyl-3,5-dihydroxy-4,6-bis(3-methylbut-2-en-1-yl)-6-(3-methylbut-3-en-1-yl)cyclohexa-2,4-dienone (2.79)



To a solution of **2.33** (454 mg, 1.24 mmol) in anhydrous DMF (5 mL), NaH (60% dispersion in mineral oil, 149 mg, 3.72 mmol) was added at rt. The mixture was stirred at rt for 5 min. isoprenyl iodide (**2.70**) (0.29 mL, 2.48 mmol) was then added at rt. The reaction mixture was stirred at rt for 1 h. The mixture was quenched with 1 M HCl solution (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organics were washed sequentially with H_2O (2 x 30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/ EtOAc, 6:1 →4:1 gradient elution) to give 2-benzoyl-3,5-dihydroxy-4,6-bis(3-methylbut-2-en-1-yl)-6-(3-methylbut-3-en-1-yl)cyclohexa-2,4-dienone (**2.79**) (293 mg, 54%) as a viscous yellow oil.

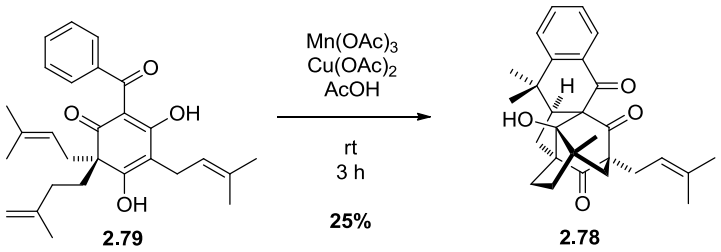
R_f = 0.23 (petrol/EtOAc, 4:1)

IR (neat): 2914, 1647, 1446, 1370, 1186, 693 cm^{-1}

NMR spectra showed a complex mixture of tautomers.

HRMS (ESI): calculated for $C_{28}H_{35}O_4$ 435.2530 $[M+H]^+$, found 435.2528.

2a1-hydroxy-4,4,12a-trimethyl-11-(3-methylbut-2-en-1-yl)-3,3a,4,11,12,12a-hexahydro-1H-2a,11 methanocyclopenta[3,4]indeno[1,7a-b]naphthalene-9,10,13(2H,2a1H)-trione (2.78)



To a solution of $Mn(OAc)_3(H_2O)_2$ (252 mg, 0.94 mmol) and $Cu(OAc)_2(H_2O)$ (86 mg, 0.45 mmol) in degassed AcOH (2 mL), **2.79** (195 mg, 0.45 mmol) in degassed AcOH (8 mL) was added at rt. The reaction mixture was stirred at rt for 3 h. The mixture was quenched with H_2O (15 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were washed sequentially with H_2O (30 mL), *sat*. $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 10:1 as eluent) to give 2a1-hydroxy-4,4,12a-trimethyl-11-(3-methylbut-2-en-1-yl)-3,3a,4,11,12,12a-hexahydro-1H-2a,11 methanocyclopenta[3,4]indeno[1,7a-b]naphthalene-9,10,13(2H,2a1H)-trione (**2.78**) (50mg, 25%) as a white crystalline solid.

R_f = 0.42 (petrol/EtOAc, 4:1)

Mp = 204-206 °C

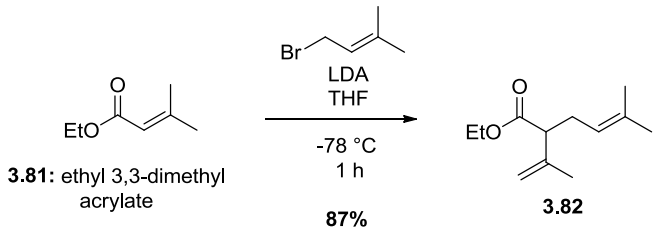
IR (neat): 3468, 2949, 1736, 1707, 1663, 1599, 1118, 765 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 7.6, 1.3 Hz 1H), 7.54 (td, *J* = 7.6, 1.3 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 5.05 (t, *J* = 7.2 Hz, 1H), 2.85 (s, 1H), 2.68 (dd, *J* = 9.8, 7.7 Hz, 1H), 2.37 (t, *J* = 12.1 Hz, 1H), 2.28 (d, *J* = 7.3 Hz, 2H), 2.26 – 2.23 (m, 1H), 2.06 (dd, *J* = 11.5, 7.7 Hz, 1H), 1.98 – 1.93 (m, 1H), 1.82 – 1.71 (m, 2H), 1.78 (d, *J* =13.9 Hz, 1H), 1.68 (d, *J* = 13.9 Hz, 1H), 1.65 (s, 3H), 1.57 (s, 3H), 1.49 (s, 3H), 1.36 (s, 3H), 1.11 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 213.4, 203.4, 200.2, 150.3, 136.3, 134.3, 133.7, 126.9, 126.4, 123.5, 118.8, 90.9, 72.8, 68.5, 63.1, 57.0, 46.0, 44.7, 39.5, 37.2, 29.9, 29.0, 26.2, 25.9, 25.1, 24.5, 22.9, 17.9.

HRMS (ESI): calculated for $C_{28}H_{33}O_4$ 433.2373$[M+H]^+$, found 433.2372.

ethyl 5-methyl-2-(prop-1-en-2-yl)hex-4-enoate (3.82)[100]



To a solution of LDA (2.0 M in heptane, 46.8 mL, 93.6 mmol) in anhydrous THF (80 mL), ethyl 3,3-dimethyl acrylate (**3.81**) (10.0 g, 78 mmol) in anhydrous THF (12 mL) was added drop wise at -78 °C. The mixture was stirred at -78 °C for 15 min. Prenyl bromide (9.90 mL, 85.8 mmol) was then added at -78 °C. The reaction mixture was stirred for a further 1 h before gradual warming to rt. The mixture was quenched with *sat*. NH_4Cl solution (100 mL) and extracted with Et_2O (3 x 100 mL). The combined organics were washed with brine (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 20:1 as eluent) to give ethyl 5-methyl-2-(prop-1-en-2-yl)hex-4-enoate (**3.82**) (13.3 g, 87%) as a colourless oil.

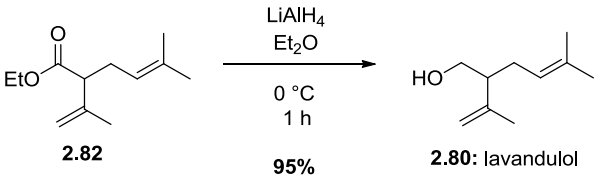
R_f = 0.65 (petrol/EtOAc, 4:1).

IR (neat): 2976, 1733, 1647, 1179, 1150, 895 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.03 (t, *J* = 7.1 Hz, 1H), 4.91 – 4.86 (m, 2H), 4.13 (qd, *J* = 7.1, 1.8 Hz, 2H), 3.01 (t, *J* = 7.7 Hz, 1H), 2.51 (dt, *J* = 15.1, 7.8 Hz, 1H), 2.26 (dt, *J* = 14.3, 7.0 Hz, 1H), 1.76 (s, 3H), 1.68 (s, 3H), 1.62 (d, *J* = 11.5 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 173.5, 142.5, 133.4, 121.2, 113.4, 60.4, 53.3, 29.0, 25.7, 20.5, 17.8, 14.2.

lavandulol (2.80)



To a solution of $LiAlH_4$ (5.60 g, 148 mmol) in Et_2O (200 mL), **2.82** (13.2 g, 67.5 mmol) in Et_2O (60 mL) was added drop wise over 20 min at 0 °C. The reaction mixture was warmed to rt and stirred for 1 h. The mixture was then cooled to 0 °C, quenched by careful drop wise addition of H_2O (5.6 mL) and stirred at rt for 5 min. 15% NaOH solution (5.6 mL) was added and the mixture was stirred at rt for a further 5 min before H_2O (16.8 mL) was added. The mixture was filtered, rinsing thoroughly with Et_2O and the filtrate was concentrated *in vacuo* to yield lavandulol (**2.80**) (9.90 g, 95%) as a colourless oil which was used in the next step without further purification.

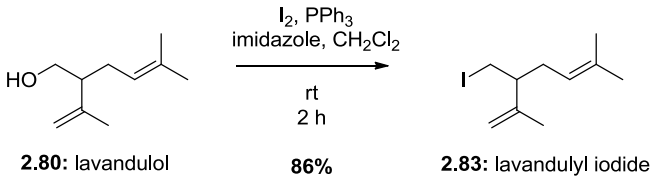
R_f = 0.39 (petrol/EtOAc, 4:1)

IR (neat): 3351, 2916, 1646, 1440, 1376, 1038, 888 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.08 (t, *J* =7.2, 1H), 4.94 – 4.91 (m, 1H), 4.82 (d, *J* = 0.6 Hz, 1H), 3.57 (dt, *J* = 11.3, 5.8 Hz, 1H), 3.50 (dt, *J* =8.7, 3 Hz, 1H) 2.28 (qd, *J* = 7.6, 5.2 Hz, 1H), 2.11 (dt, *J* = 14.6, 7.3 Hz, 1H), 2.04 (dt, *J* = 14.6, 7.1 Hz, 1H), 1.70 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H), 1.43 (t, *J* = 5.3 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 145.4, 132.7, 122.0, 113.1, 63.6, 49.9, 28.4, 25.7, 19.5, 17.8.

lavandulyl iodide (2.83)



2.80: lavandulol **86%** **2.83:** lavandulyl iodide

To a solution of PPh_3 (18.5 g, 70.6 mmol) and imidazole (4.80 g, 70.6 mmol) in CH_2Cl_2 (200 mL), I_2 (17.9 g, 70.6 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 15 min. **2.80** (9.90 mL, 64.2 mmol) in CH_2Cl_2 (30 mL) was then added drop wise at 0 °C. The reaction mixture was stirred at rt for 2 h. The mixture was quenched with $Na_2S_2O_3$ solution (36 g in 200 mL of H_2O) and stirred at rt for 10 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (200 mL). The combined organics were washed with brine (200 mL), dried over anhy,drous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (neat petrol as eluent) to give lavandulyl iodide (**2.83**) (14,6 g, 86%) as a pale orange oil.

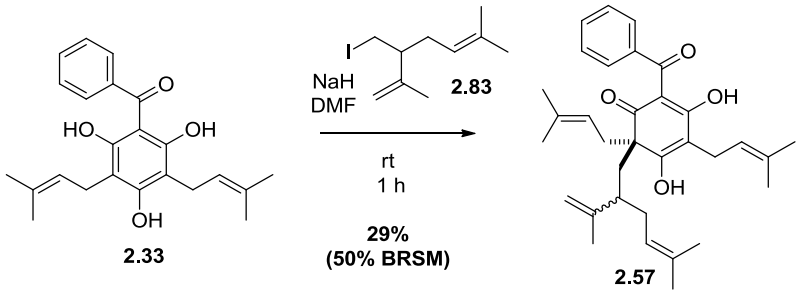
R_f = 0.70 (neat petrol)

IR (neat): 2968, 2913, 1647, 1439, 1375, 1187, 893 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.03 (tt, *J* = 7.9, 1.3 Hz, 1H), 4.91 – 4.89 (m, 1H), 4.75 (s, 1H), 3.28 (dd, *J* = 9.8, 5.8 Hz, 1H), 3.19 (dd, *J* = 9.8, 7.7 Hz, 1H), 2.29 (dt,*J* = 14.3, 7.1, 1H), 2.24 (dt, *J* = 14.3, 7.1 Hz, 1H), 2.11 (dt, *J* = 14.3, 7.0 Hz, 1H), 1.69 (s, 3H), 1.68 (s, 3H), 1.63 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 145.5, 133.4, 121.5, 112.8, 49.4, 39.9, 25.8, 19.3, 18.0, 11.3.

2-benzoyl-3,5-dihydroxy-6-(5-methyl-2-(prop-1-en-2-yl)hex-4-en-1-yl)-4,6-bis(3-methylbut-2-en-1-yl)cyclohexa-2,4-dienone (2.57)



To a solution of **2.33** (616 mg, 1.68 mmol) in anhydrous DMF (12 mL), NaH (242 mg, 10.1 mmol) was added at rt. The mixture was stirred at rt for 10 min. **2.83** (2.66 g, 10.1 mmol) in anhydrous DMF (2 mL) was then added at rt. The reaction mixture was stirred at rt for 1 h. The mixture was quenched with 1 M HCl solution (15 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were washed sequentially with H_2O (2 x 30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 50:1 →15:1 gradient elution) to give 2-benzoyl-3,5-dihydroxy-6-(5-methyl-2-(prop-1-en-2-yl)hex-4-en-1-yl)-4,6-bis(3-methylbut-2-en-1-yl)cyclohexa-2,4-dienone (**2.57**) (242 mg, 29%) as a viscous yellow oil along with recovered starting material (129 mg, 21%).

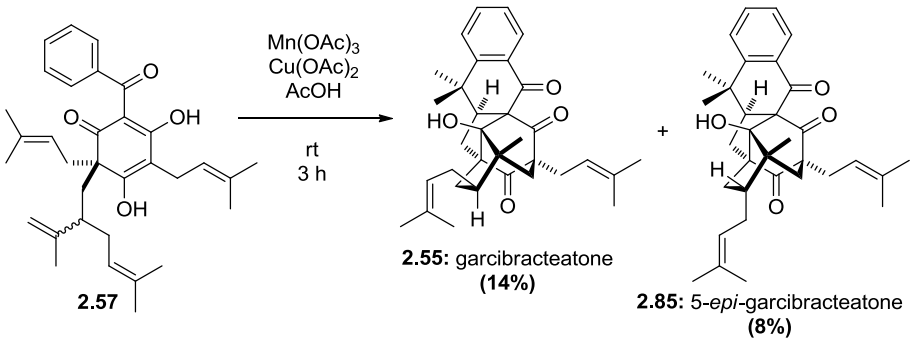
R_f = 0.42 (petrol/EtOAc, 4:1)

IR (neat): 3278, 2914, 1645, 1445, 1182, 695 cm^{-1}

NMR showed a complex mixture of tautomers and diasteroisomers.

HRMS (ESI): calculated for $C_{33}H_{43}O_4$ 503.3156 $[M+H]^+$, found 503.3149.

Garcibracteatone (2.55) and 5-*epi*-garcibracteatone (2.85)



To a solution of $Mn(OAc)_3(H_2O)_2$ (457 mg, 1.70 mmol) and $Cu(OAc)_2(H_2O)$ (154 mg, 0.81 mmol) in degassed AcOH (2 mL), **2.57** (408 mg, 0.81 mmol) in degassed AcOH (12 mL) was added at rt. The reaction mixture was stirred at rt for 3 h. The mixture was quenched with H_2O (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organics were washed sequentially with H_2O (50 mL), *sat*. $NaHCO_3$ solution (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/ EtOAc, 20:1 →15:1 gradient elution) to give garcibracteatone **(2.55)** (56mg, 14%) as a white crystalline solid.

R_f= 0.62 (petrol/EtOAc, 4:1)

Mp = 196-199 °C

IR (neat): 3468, 2977, 1736, 1706, 1665, 1601, 1450, 1260, 1111, 765, cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.54 (td, *J* = 7.6, 1.4 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 5.04(t,*J* = 7.2 Hz, 1H), 5.01 (t, *J* =7.2 Hz, 1H), 2.83 (s, 1H), 2.66 (dd, *J* = 9.9, 7.8 Hz, 1H), 2.30 – 2.23 (m, 1H), 2.27 (d, *J* = 7.3 Hz, 1H), 2.20 (dd, *J* = 11.3, 10.1 Hz, 1H), 2.12 -2.05 (m, 1H), 2.07 (dd, *J* = 11.5, 7.8 Hz, 1H), 2.01 (dd, *J* = 11.8, 7.9 Hz, 1H), 1.89 – 1.82 (m, 1H), 1.77 (d, *J* = 13.9 Hz, 1H), 1.68 (d, *J* = 13.8 Hz, 1H), 1.68 (s, 3H), 1.65 (s, 3H), 1.62 (s, 3H), 1.59-1.55 (m, 1H), 1.57 (s, 3H), 1.55 (s, 1H), 1.46 (s, 3H), 1.35 (s, 3H), 1.10 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 213.3, 203.3, 200.3, 150.2, 136.4, 134.3, 133.6, 132.4, 126.9, 126.4, 123.5, 122.9, 118.8, 91.8, 70.2, 69.2, 63.2, 56.9, 56.8, 47.5, 41.5, 37.1, 33.0, 32.5, 29.8, 29.0, 26.2, 25.9, 25.8, 25.1, 18.4, 18.0, 17.9.

HRMS (ESI): calculated for $C_{33}H_{41}O_4$ 501.2999$[M+H]^+$, found 501.3002.

Further elution gave 5-*epi*-garcibracteatone (**2.85**) (31mg, 8%) as a white crystalline solid.

R_f = 0.58 (petrol/EtOAc, 4:1)

Mp = 212-216 °C

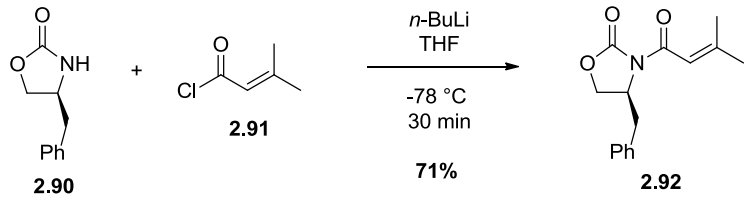
IR (neat): 3487, 2964, 1735, 1706, 1666, 1598, 1455, 1298, 1107, 760 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.54 (td, *J* = 7.6, 1.4 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 5.11 (t, *J* = 7.3 Hz, 1H), 5.02 (t, *J* = 6.9 Hz, 1H), 2.81 (s, 1H), 2.62 (dd, *J* = 9.8, 7.7 Hz, 1H), 2.53 - 2.47 (m, 1H), 2.33 – 2.26 (m, 1H), 2.29 (d, *J* = 8.0 Hz, 1H), 2.20 (dd, *J* = 11.2, 10.1 Hz, 1H), 2.12 (dd, *J* = 12.3, 10.9 Hz, 1H), 2.05 (t, *J* = 9.5 Hz, 1H), 2.03 (d, *J* = 14.2 Hz, 1H), 1.93 – 1.87 (m, 1H), 1.72 – 1.65 (m, 1H), 1.69 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H), 1.58 (s, 3H), 1.47 (s, 3H), 1.43 (d, *J* = 14.5 Hz, 1H), 1.38 - 1.34 (m, 1H), 1.35 (s, 3H), 1.10 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 213.4, 203.3, 200.2, 150.2, 136.3, 134.6, 133.7, 132.6, 126.9, 126.4, 123.5, 122.8, 119.0, 91.8, 71.0, 69.1, 63.0, 56.2, 52.5, 42.5, 37.2, 35.1, 31.1, 30.2, 29.8, 29.5, 26.2, 25.9, 25.8, 24.8, 22.8, 17.9, 17.8.

HRMS (ESI): calculated for $C_{33}H_{41}O_4$ 501.2999 $[M+H]^+$, found 501.3018.

(*S*)-4-benzyl-3-(3-methylbut-2-enoyl)oxazolidin-2-one (2.92)[111]



To a solution of **2.90** (13.4 g, 75.6 mmol) in THF (120 ml), *n*-BuLi (2.5 M in hexanes, 32.4 mL, 80.9 mmol) was added at -78 °C. The mixture was stirred at -78 °C for 5 min before **2.91** (9.59 g, 80.9 mmol) was added at -78 °C. The reaction mixture was stirred a -78 °C for 5 min before slow warming to rt over 30 min. The mixture was quenched with *sat*. NH_4Cl solution (5 mL), concentrated *in vacuo*, and the residue was dissolved in CH_2Cl_2 (150 mL) and hexanes (150 mL). The solution was washed sequentially with *sat*. $NaHCO_3$ solution (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was recrystallized from hexanes/EtOAc (4 crops) to yield pure (*S*)-4-benzyl-3-(3-methylbut-2-enoyl)oxazolidin-2-one (**2.92**) (13.0 g, 71%) as a white crystalline solid.

R_f = 0.28 (petrol/EtOAc, 4:1)

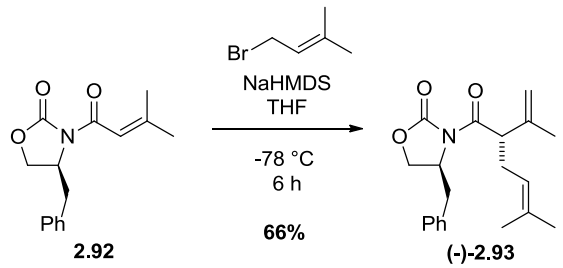
Mp = 79 – 81 °C

IR (neat): 2958, 1779, 1759, 1674, 1625, 1382, 1350, 1254, 1183, 1048, 1001, 851, 712 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.3 Hz, 3H), 7.30 – 7.21 (m, 3H), 6.98 – 6.94 (m, 1H), 4.76 – 4.69 (m, 1H), 4.17 (dd, *J* = 15.2, 7.6 Hz, 1H), 4.14 (dd, *J* = 9.0, 3.1 Hz, 1H), 3.35 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.78 (dd, *J* = 13.4, 9.7 Hz, 1H), 2.23 (d, *J* = 1.0 Hz, 3H), 2.01 (d, *J* = 0.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 159.5, 153.4, 135.6, 129.5, 128.9, 127.2, 115.9, 65.9, 55.2, 38.1, 28.1, 21.4.

(*S*)-4-benzyl-3-((*S*)-5-methyl-2-(prop-1-en-2-yl)hex-4-enoyl)oxazolidin-2-one (2.93)



2.92 **(-)-2.93**

To a solution of **2.92** (9.31 g, 35.9 mmol) in THF (100 mL), NaHMDS (1.0 M solution in THF, 39.5 mL, 39.5 mmol) was added at -78 °C. The mixture was stirred at -78 °C for 1 h before addition of prenyl bromide (8.30 mL, 71.8 mmol) drop wise at -78 °C. The resultant mixture was stirred at -78 °C for 6 h. The mixture was quenched with *sat*. NH_4Cl solution (100 mL) and extracted with Et_2O (3 x 100 mL). The combined organics were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 10:1 as eluent) to give (*S*)-4-benzyl-3-((*S*)-5-methyl-2-(prop-1-en-2-yl)hex-4-enoyl)oxazolidin-2-one (**2.93**) (7.78 g, 66%) as a colourless oil.

R_f = 0.40 (petrol/EtOAc, 4:1)

IR (neat): 2919, 1775, 1697, 1206, 701 cm^{-1}

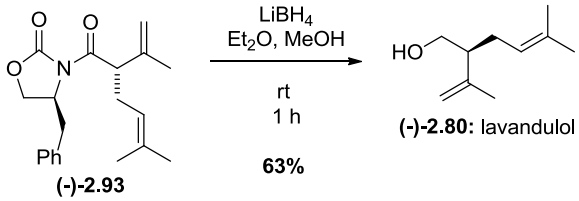
$[\alpha]_D^{25}$ = (c 1.0, $CHCl_3$) -102.6°

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.3 Hz, 2H), 7.29 – 7.25 (m, 1H), 7.21 (d, *J* = 7.0 Hz, 2H), 5.14 (t, *J* = 7.2 Hz, 1H), 4.89 (d, *J* = 7.7 Hz, 2H), 4.69 – 4.63 (m, 1H), 4.47 (dd, *J* = 9.0, 5.8 Hz, 1H), 4.17 – 4.11 (m, 2H), 3.22 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.78 (dd, *J* = 13.5, 9.3 Hz, 1H), 2.62 (dt, *J* = 15.8, 8.3 Hz, 1H), 2.36 – 2.29 (m, 1H), 1.83 (s, 3H), 1.70 (s, 3H), 1.67 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 173.3, 153.0, 143.1, 135.3, 133.8, 129.4, 128.9, 127.3, 121.4, 113.4, 65.7, 55.5, 50.3, 37.8, 29.8, 25.8, 21.3, 17.8.

HRMS (ESI): calculated for $C_{20}H_{26}NO_3$ 328.1907 $[M+H]^+$, found 328.1907.

(-)-lavandulol (2.80)



To a solution of **(-)-2.93** (3.26 g, 9.98 mmol) in Et_2O (30 mL) and MeOH (0.53 mL, 12.9 mmol), $LiBH_4$ (283 mg, 12.9 mmol) was added at 0 °C. The resultant mixture was stirred at rt for 1 h. The mixture was quenched with *sat*. NH_4Cl solution (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organics were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 6:1 as eluent) to give (-)-lavandulol (**2.80**) (975 mg, 63%) as a colourless oil.

R_f= 0.40 (petrol/EtOAc, 4:1)

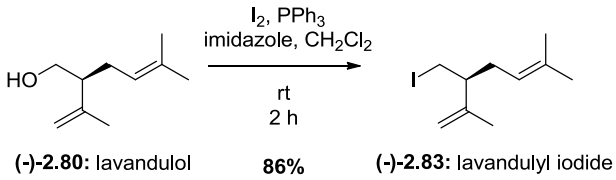
IR (neat): 3351, 2916, 1646, 1440, 1376, 1038, 888 cm^{-1}

$[\alpha]_D^{25}$ = (c 1.0, $CHCl_3$) -2.0°

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.08 (t,*J* =7.2, 1.2 Hz, 1H), 4.94 – 4.91 (m, 1H), 4.82 (d, *J* = 0.6 Hz, 1H), 3.57 (dt, *J* = 11.3, 5.8 Hz, 1H), 3.50 (dt, *J* =8.7, 3 Hz, 1H) 2.28 (qd, *J* = 7.6, 5.2 Hz, 1H), 2.11 (dt, *J* = 14.6, 7.3 Hz, 1H), 2.04 (dt, *J* = 14.6, 7.1 Hz, 1H), 1.70 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H), 1.43 (t, *J* = 5.3 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 145.4, 132.7, 122.0, 113.1, 63.6, 49.9, 28.4, 25.7, 19.5, 17.8.

(-)-lavandulyl iodide (2.83)



(-)-2.80: lavandulol **86%** **(-)-2.83:** lavandulyl iodide

To a solution of PPh_3 (3.68 g, 14.0 mmol) and imidazole (954 mg, 14.0 mmol) in CH_2Cl_2 (70 mL), I_2 (3.56 g, 1.40 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 15 min. **(-)-2.80** (2.06 mL, 13.4 mmol) in CH_2Cl_2 (10 mL) was then added drop wise at 0 °C. The reaction mixture was stirred at rt for 2 h. The mixture was quenched with $Na_2S_2O_3$ solution (18 g in 100 mL of H_2O) and stirred at rt for 10 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organics were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (neat petrol as eluent) to give (-)-lavandulyl iodide **(2.83)** (2.70 g, 77%) as a pale orange oil.

R_f = 0.70 (neat petrol)

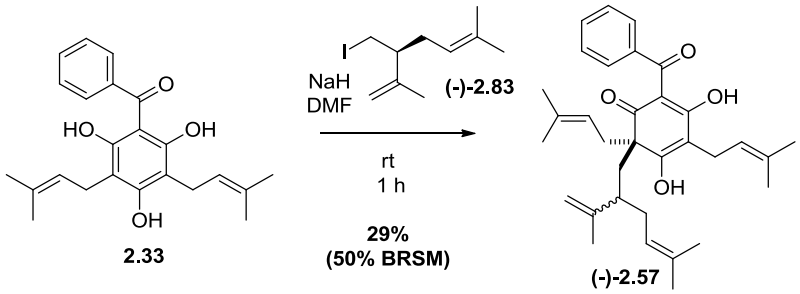
IR (neat): 2968, 2913, 1647, 1439, 1375, 1187, 893 cm^{-1}

$[\alpha]_D^{25}$ = (c 1.0, $CHCl_3$) -1.8°

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.03 (tt, *J* = 7.9, 1.3 Hz, 1H), 4.91 – 4.89 (m, 1H), 4.75 (s, 1H), 3.28 (dd, *J* = 9.8, 5.8 Hz, 1H), 3.19 (dd, *J* = 9.8, 7.7 Hz, 1H), 2.29 (dt,*J* = 14.3, 7.1, 1H), 2.24 (dt, *J* = 14.3, 7.1 Hz, 1H), 2.11 (dt, *J* = 14.3, 7.0 Hz, 1H), 1.69 (s, 3H), 1.68 (s, 3H), 1.63 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 145.5, 133.4, 121.5, 112.8, 49.4, 39.9, 25.8, 19.3, 18.0, 11.3.

4-benzoyl-5-hydroxy-6-((*R*)-5-methyl-2-(prop-1-en-2-yl)hex-4-en-1-yl)-2,6-bis(3-methylbut-2-en-1-yl)cyclohex-4-ene-1,3-dione (2.57)



To a solution of **2.33** (620 mg, 1.70 mmol) in anhydrous DMF (12 mL), NaH (164 mg, 10.2 mmol) was added at rt. The mixture was stirred at rt for 10 min. **(-)-2.83** (2.70 g, 10.2 mmol) in anhydrous DMF (2 mL) was then added at rt. The reaction mixture was stirred at rt for 1h. The mixture was quenched with 1M HCl solution (15 mL) and extracted with EtOAc (3x 20 mL). The combined organics were washed sequentially with H_2O (2 x 30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 50:1 → 15:1 gradient elution) to give 4-benzoyl-5-hydroxy-6-((*R*)-5-methyl-2-(prop-1-en-2-yl)hex-4-en-1-yl)-2,6-bis(3-methylbut-2-en-1-yl)cyclohex-4-ene-1,3-dione (**2.57**) (252 mg, 29%) as a viscous yellow oil along with recovered starting material (130 mg, 21%).

R_f = 0.42 (petrol/EtOAc, 4:1)

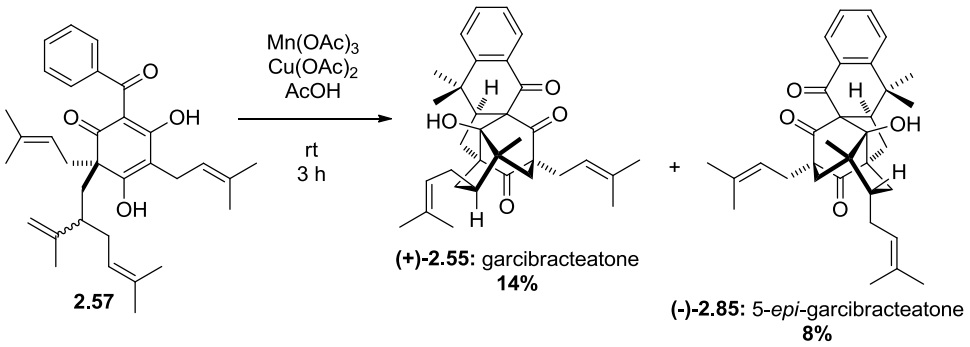
IR (neat): 3278, 2914, 1645, 1445, 1182, 695 cm^{-1}

$[\alpha]_D^{25}$ = (c 1.0, $CHCl_3$) -7.8°

NMR showed a complex mixture of tautomers and diasteroisomers.

HRMS (ESI): calculated for $C_{33}H_{43}O_4$ 503.3156 $[M+H]^+$, found 503.3149.

(+)-garcibracteatone (2.55) and (-)-5-epi-garcibracteatone (2.85)



To a solution of $Mn(OAc)_3(H_2O)_2$ (280 mg, 1.04 mmol) and $Cu(OAc)_2(H_2O)$ (95 mg, 0.497 mmol) in degassed AcOH (2 mL), **2.57** (250 mg, 0.497 mmol) in degassed AcOH (8 mL) was added at rt. The reaction mixture was stirred at rt for 3 h. The mixture was quenched with H_2O (15 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were washed sequentially with H_2O (30 mL), *sat*. $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 20:1 → 15:1 gradient elution) to give (+)-garcibracteatone (**2.55**) (36 mg, 14%) as a white crystalline solid.

R_f = 0.62 (petrol/EtOAc, 4:1)

Mp = 196 - 199 °C

IR (neat): 3468, 2977, 1736, 1706, 1665, 1601, 1450, 1260, 1111, 765 cm^{-1}

$[\alpha]_D^{25}$ = (c 1.0, $CHCl_3$) +2.0°

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.54 (td, *J* = 7.6, 1.4 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 5.04(t,*J* = 7.2 Hz, 1H), 5.01 (t, *J* =7.2 Hz, 1H), 2.83 (s, 1H), 2.66 (dd, *J* = 9.9, 7.8 Hz, 1H), 2.30 – 2.23 (m, 1H), 2.27 (d, *J* = 7.3 Hz, 1H), 2.20 (dd, *J* = 11.3, 10.1 Hz, 1H), 2.12 -2.05 (m, 1H), 2.07 (dd, *J* = 11.5, 7.8 Hz, 1H), 2.01 (dd, *J* = 11.8, 7.9 Hz, 1H), 1.89 – 1.82 (m, 1H), 1.77 (d, *J* = 13.9 Hz, 1H), 1.68 (d, *J* = 13.8 Hz, 1H), 1.68 (s, 3H), 1.65 (s, 3H), 1.62 (s, 3H), 1.59-1.55 (m, 1H), 1.57 (s, 3H), 1.55 (s, 1H), 1.46 (s, 3H), 1.35 (s, 3H), 1.10 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 213.3, 203.3, 200.3, 150.2, 136.4, 134.3, 133.6, 132.4, 126.9, 126.4, 123.5, 122.9, 118.8, 91.8, 70.2, 69.2, 63.2, 56.9, 56.8, 47.5, 41.5, 37.1, 33.0, 32.5, 29.8, 29.0, 26.2, 25.9, 25.8, 25.1, 18.4, 18.0, 17.9.

HRMS (ESI): calculated for $C_{33}H_{41}O_4$ 501.2999 $[M+H]^+$, found 501.3002.

Further elution gave (-)-5-*epi*-garcibracteatone (**2.85**) (21mg, 8%) as a white crystalline solid.

R_f = 0.58 (petrol/EtOAc, 4:1)

Mp = 212-216 °C

IR (neat): 3487, 2964, 1735, 1706, 1666, 1598, 1455, 1298, 1107, 760 cm^{-1}

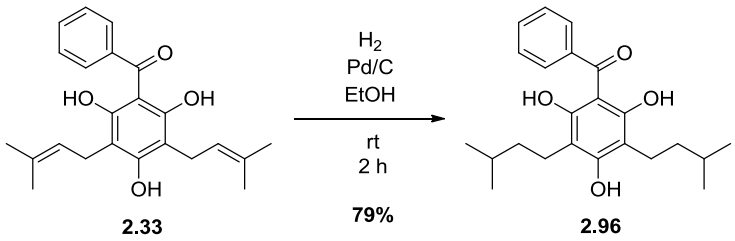
$[\alpha]_D^{25}$ = (c 1.0, $CHCl_3$) -34.1°

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.54 (td, *J* = 7.6, 1.4 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 5.11 (t, *J* = 7.3 Hz, 1H), 5.02 (t, *J* = 6.9 Hz, 1H), 2.81 (s, 1H), 2.62 (dd, *J* = 9.8, 7.7 Hz, 1H), 2.53 - 2.47 (m, 1H), 2.33 – 2.26 (m, 1H), 2.29 (d, *J* = 8.0 Hz, 1H), 2.20 (dd, *J* = 11.2, 10.1 Hz, 1H), 2.12 (dd, *J* = 12.3, 10.9 Hz, 1H), 2.05 (t, *J* = 9.5 Hz, 1H), 2.03 (d, *J* = 14.2 Hz, 1H), 1.93 – 1.87 (m, 1H), 1.72 – 1.65 (m, 1H), 1.69 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H), 1.58 (s, 3H), 1.47 (s, 3H), 1.43 (d, *J* = 14.5 Hz, 1H), 1.38 - 1.34 (m, 1H), 1.35 (s, 3H), 1.10 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 213.4, 203.3, 200.2, 150.2, 136.3, 134.6, 133.7, 132.6, 126.9, 126.4, 123.5, 122.8, 119.0, 91.8, 71.0, 69.1, 63.0, 56.2, 52.5, 42.5, 37.2, 35.1, 31.1, 30.2, 29.8, 29.5, 26.2, 25.9, 25.8, 24.8, 22.8, 17.9, 17.8.

HRMS (ESI): calculated for $C_{33}H_{41}O_4$ 501.2999 $[M+H]^+$, found 501.3018.

phenyl(2,4,6-trihydroxy-3,5-diisopentylphenyl)methanone (2.96)



To a solution of **2.33** (1.20 g, 3.27 mmol) in EtOH (40 mL), Pd/C (50 mg) was added at rt. The flask was evacuated three times and placed under an atmosphere of H_2. The reaction mixture was stirred at rt for 2 h. The mixture was filtered through celite and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 6:1 as eluent) to give phenyl(2,4,6-trihydroxy-3,5-diisopentylphenyl)methanone (**2.96**) (950 mg, 79%) as a yellow crystalline solid.

R_f = 0.49 (petrol/EtOAc, 4:1)

IR (neat): 3505, 2949, 1621, 1561, 1314, 1191, 1092, 926, 698 cm^{-1}

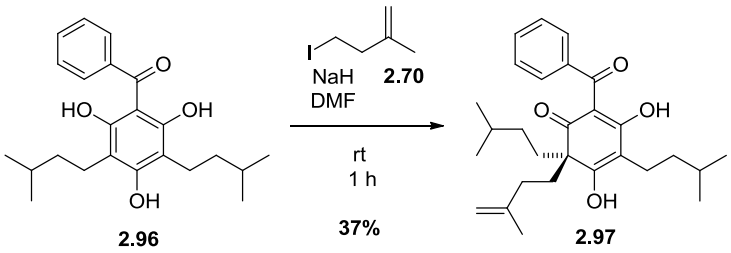
Mp = 82 - 83 °C

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.64 (d, *J* = 7.1 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 5.40 (s, 1H), 2.54 (dt, *J* = 14.7, 6.0 Hz, 4H), 1.65 – 1.55 (m, 2H), 1.40 – 1.34 (m, 4H), 0.95 (s, 3H), 0.94 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 197.6, 159.6, 157.4, 139.9, 132.3, 129.4, 127.8, 107.8, 104.4, 38.1, 28.2, 22.5, 20.7.

HRMS (ESI): calculated for $C_{23}H_{31}O_4$ 371.2217 $[M+H]^+$, found 371.2221.

2-benzoyl-3,5-dihydroxy-4,6-diisopentyl-6-(3-methylbut-3-en-1-yl)cyclohexa-2,4-dienone (2.97)



To a solution of **2.96** (409 mg, 1.10 mmol) in anhydrous DMF (10 mL), NaH (80 mg, 3.3 mmol) was added at rt. The mixture was stirred at rt for 5 min before **2.70** (0.26 mL, 2.20 mmol) was then added at rt. The reaction mixture was stirred at rt for 1h. The mixture was quenched with 1M HCl solution (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organics were washed sequentially with H_2O (2 x 30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 8:1 gradient elution) to give 2-benzoyl-3,5-dihydroxy-4,6-diisopentyl-6-(3-methylbut-3-en-1-yl)cyclohexa-2,4-dienone (**2.97**) (177 mg, 37%) as an off white solid.

R_f = 0.28 (petrol/EtOAc, 4:1)

Mp = 116 - 119 °C

IR (neat): 3187, 2956, 1646, 1447, 1207, 1171, 692 cm^{-1}

NMR spectra showed a complex mixture of tautomers.

HRMS (ESI): calculated for $C_{28}H_{39}O_4$ 439.2843 $[M+H]^+$, found 439.2847.

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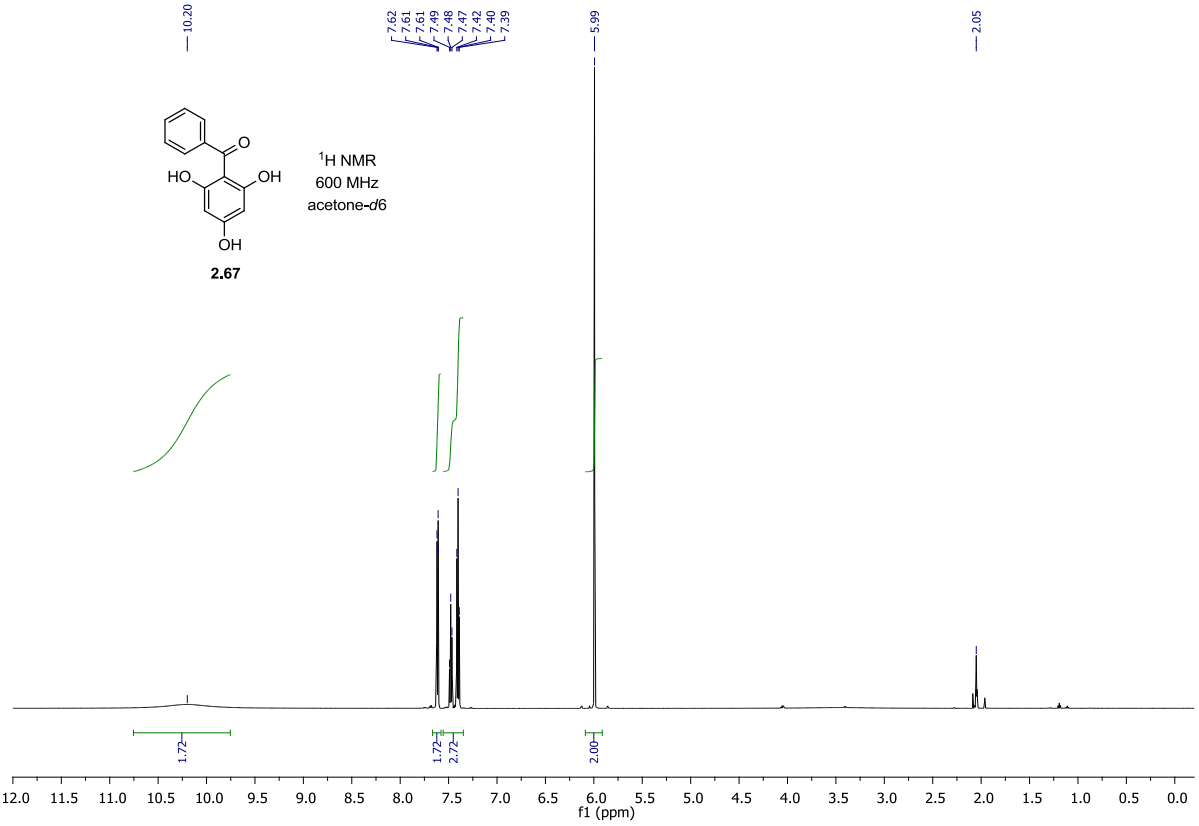
Appendix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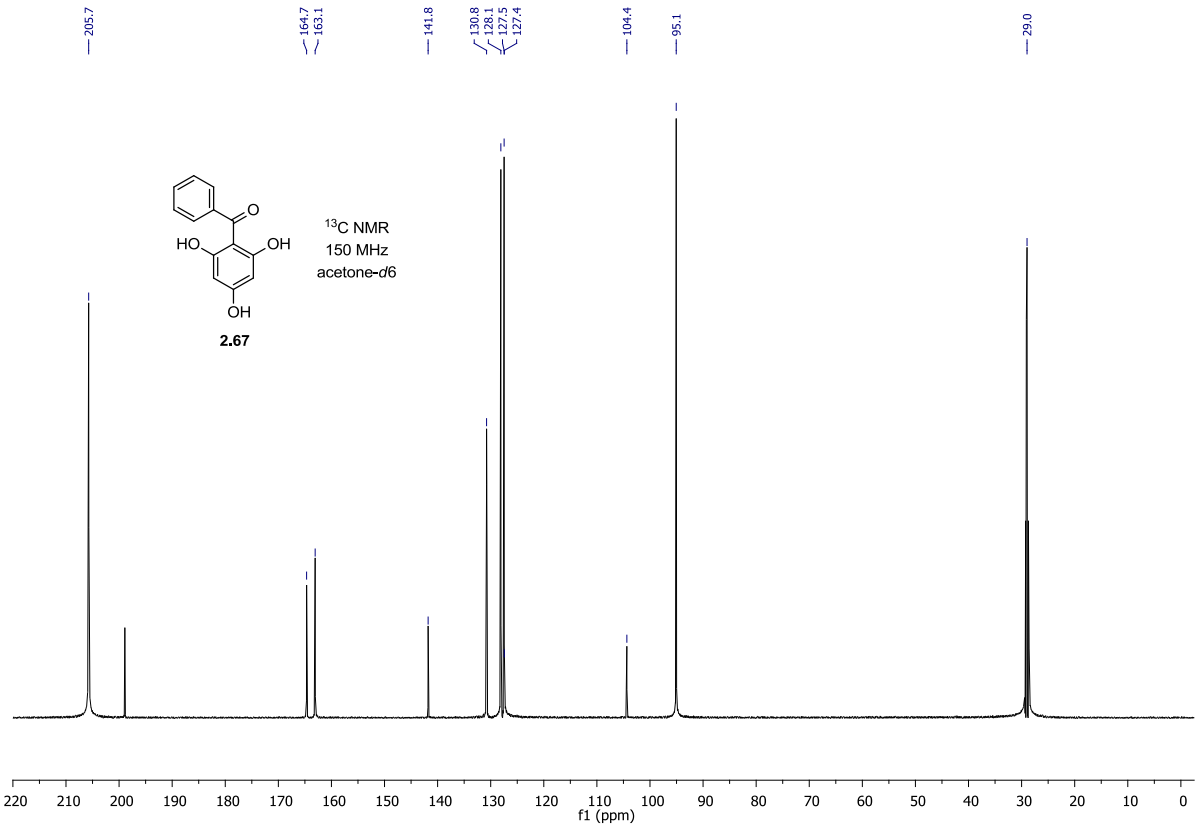
7.62
7.61
7.61
7.49
7.48
7.47
7.42
7.40
7.39
5.99
2.05
HO
OH
OH
O
2.67
^{1}H NMR
600 MHz
acetone-d6
1.72
1.72
2.72
2.00
f1 (ppm)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164.7
163.1
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127.4
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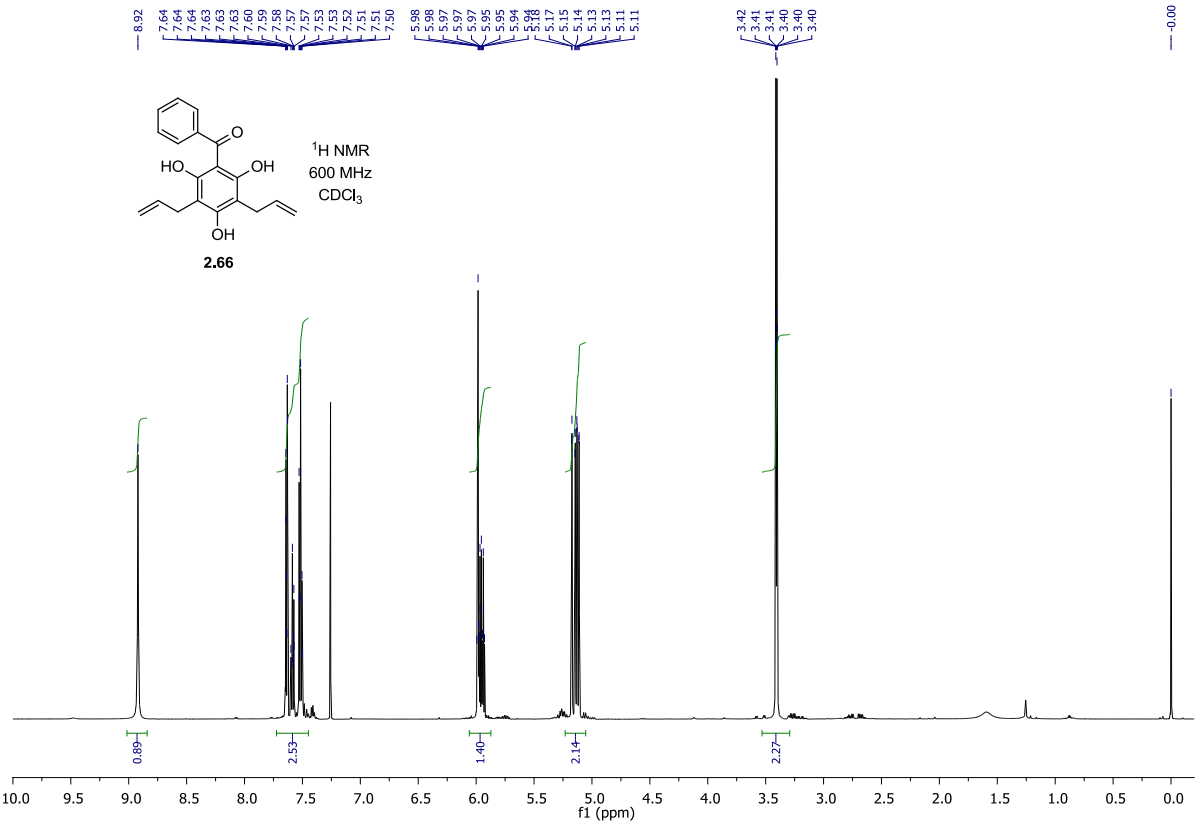
95.1
29.0
HO
OH
OH
O
2.67
^{13}C NMR
150 MHz
acetone-d6
f1 (ppm)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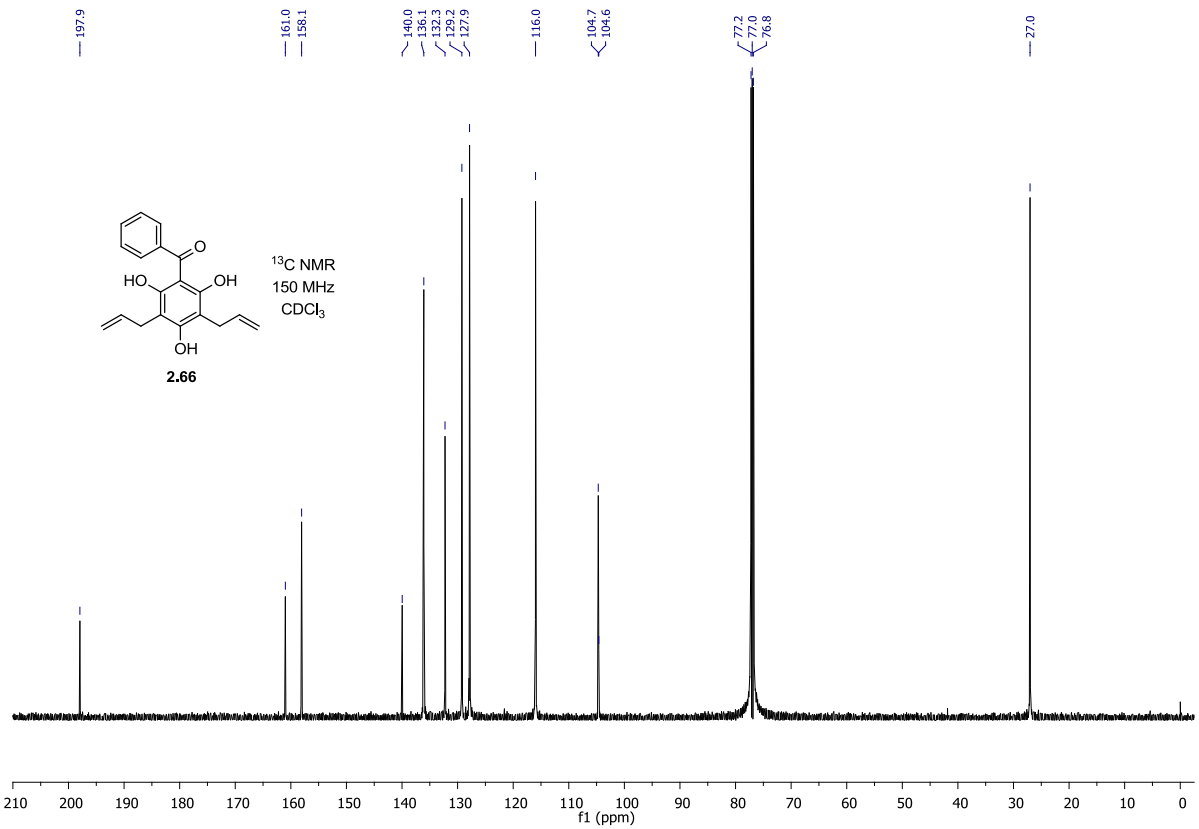
7.64
7.64
7.64
7.63
7.63
7.63
7.60
7.59
7.58
7.57
7.57
7.53
7.52
7.51
7.51
7.50
5.98
5.98
5.97
5.97
5.97
5.95
5.95
5.94
5.18
5.17
5.15
5.14
5.13
5.13
5.11
5.11
3.42
3.41
3.41
3.40
3.40
3.40
-0.00
O
HO
OH
OH
2.66
1H NMR
600 MHz
CDCl3
0.89
2.53
1.40
2.14
2.27
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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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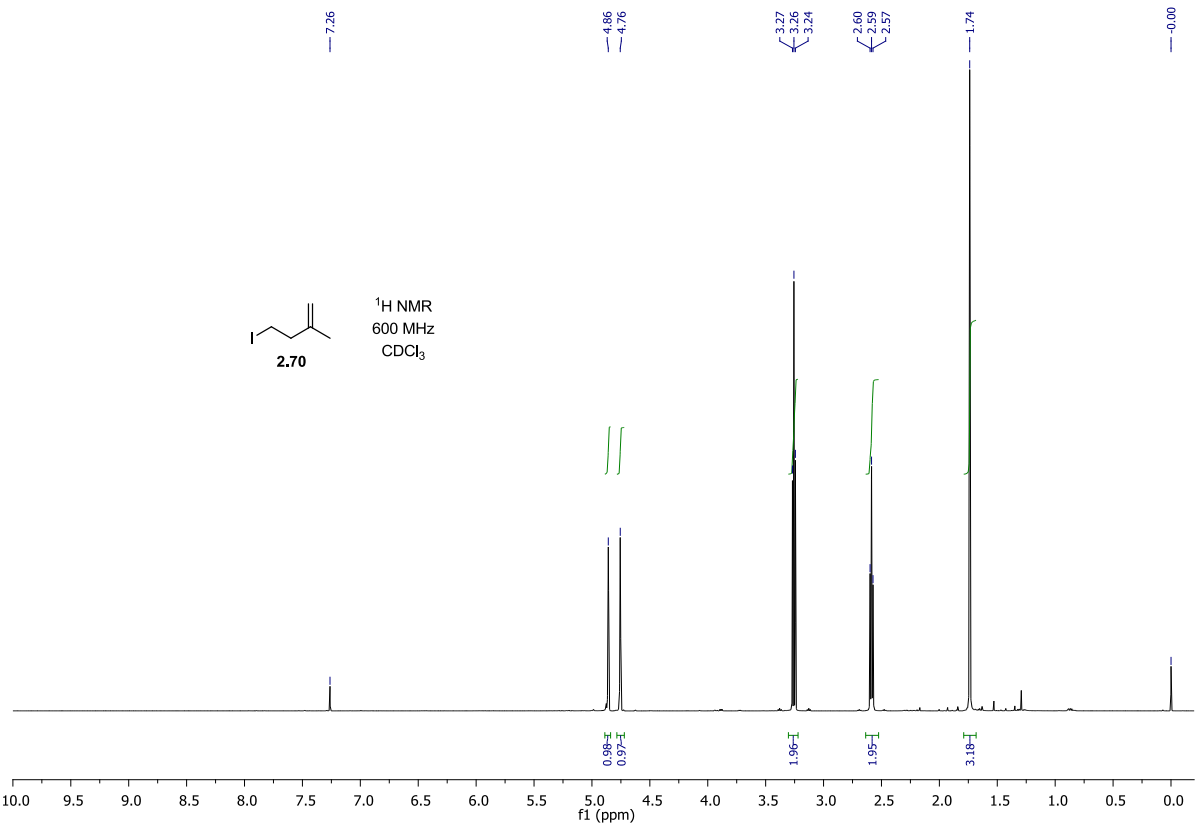
161.0
158.1
140.0
136.1
132.3
129.2
127.9
116.0
104.7
104.6
77.2
77.0
76.8
27.0
O
HO
OH
OH
2.66
13C NMR
150 MHz
CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



2.70

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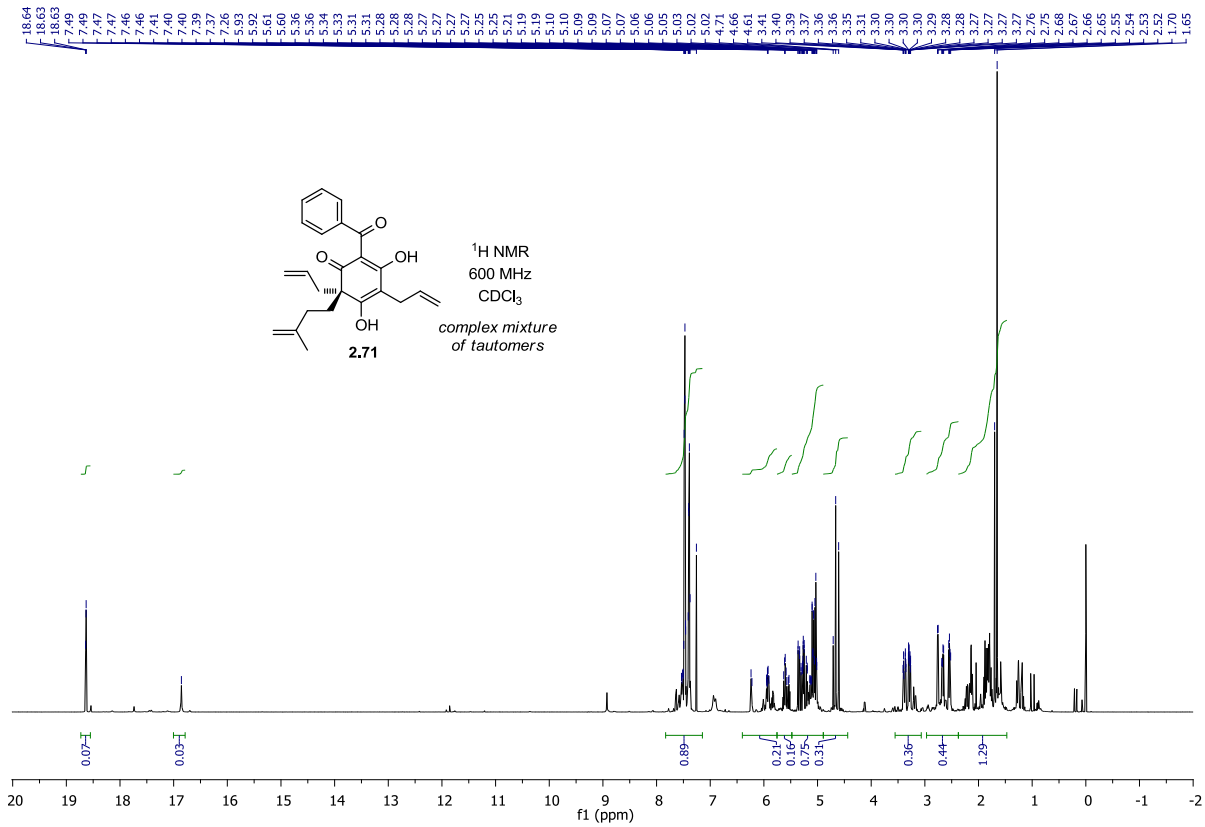
600 MHz
$CDCl_3$

2.70

^{13}C NMR
150 MHz
$CDCl_3$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O
OH
OH
2.71
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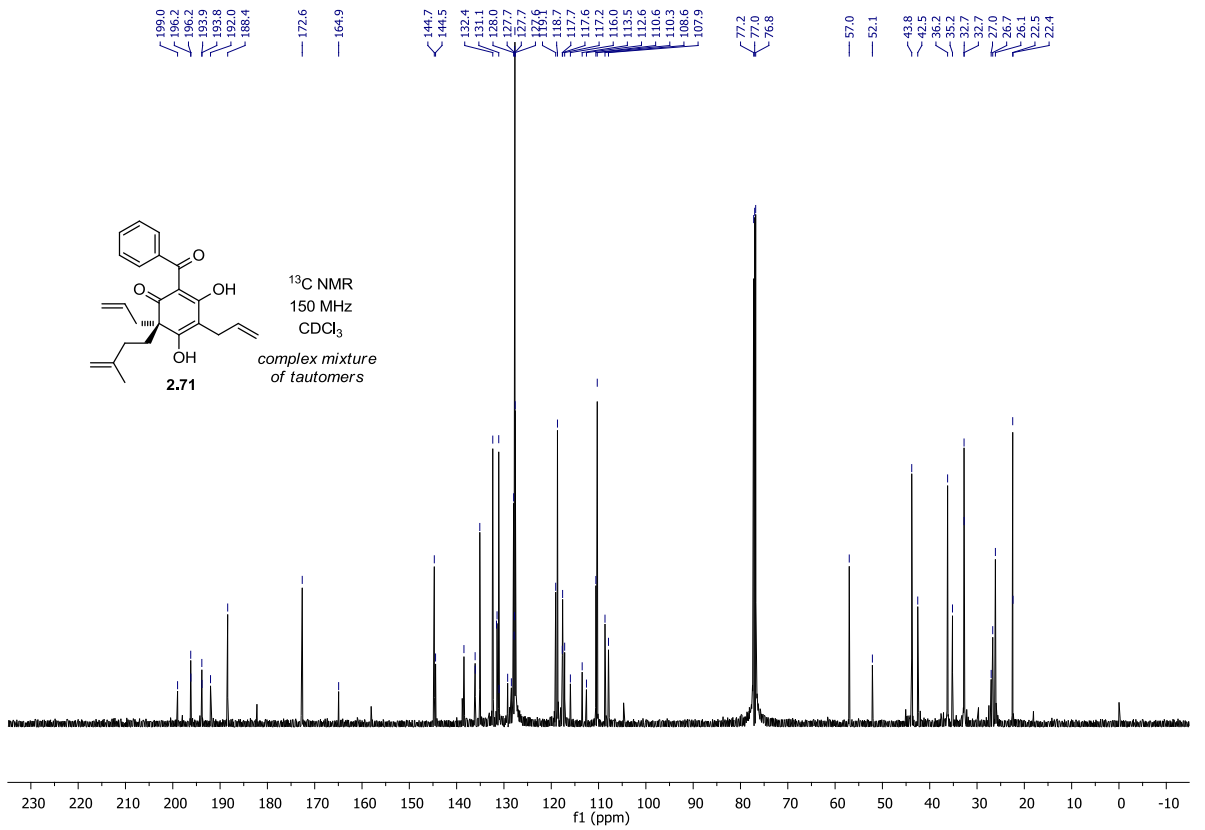
600 MHz
$CDCl_3$
complex mixture
of tautomers
f1 (ppm)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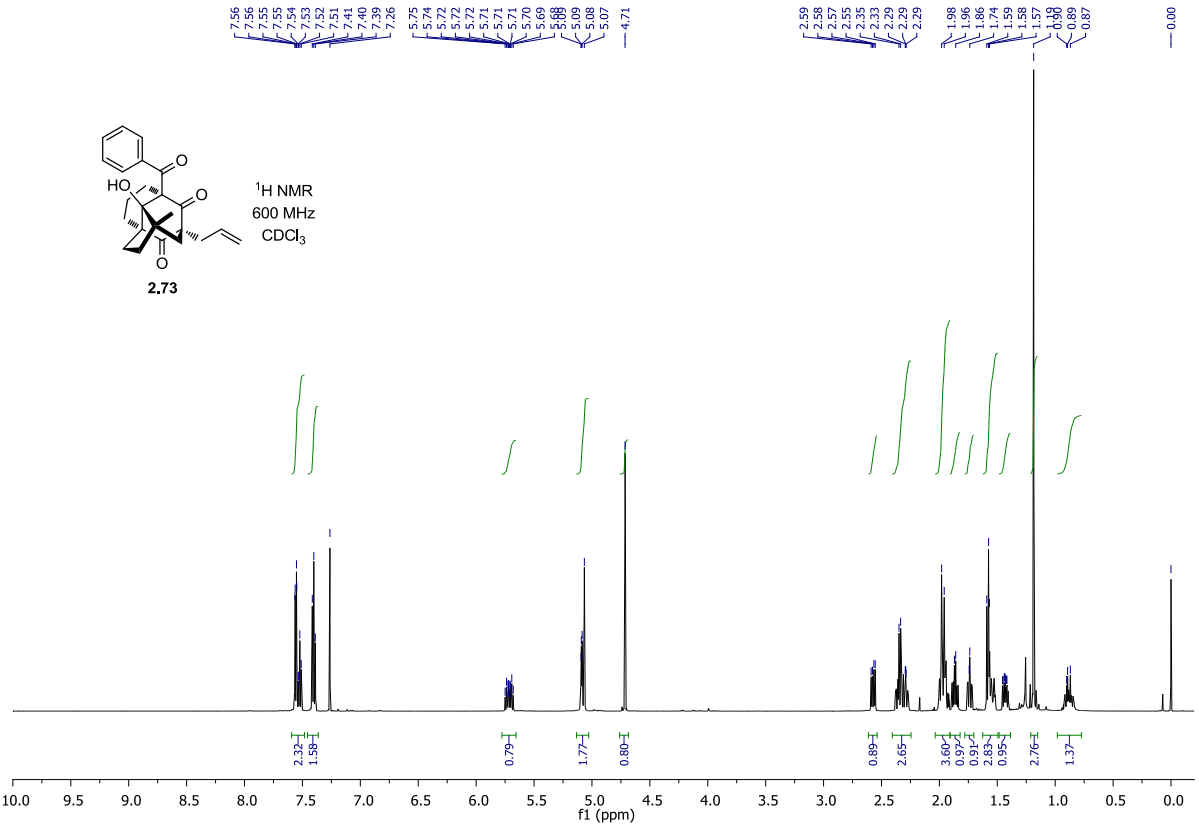
O
OH
OH
2.71
^{13}C NMR
150 MHz
$CDCl_3$
complex mixture
of tautomers
f1 (ppm)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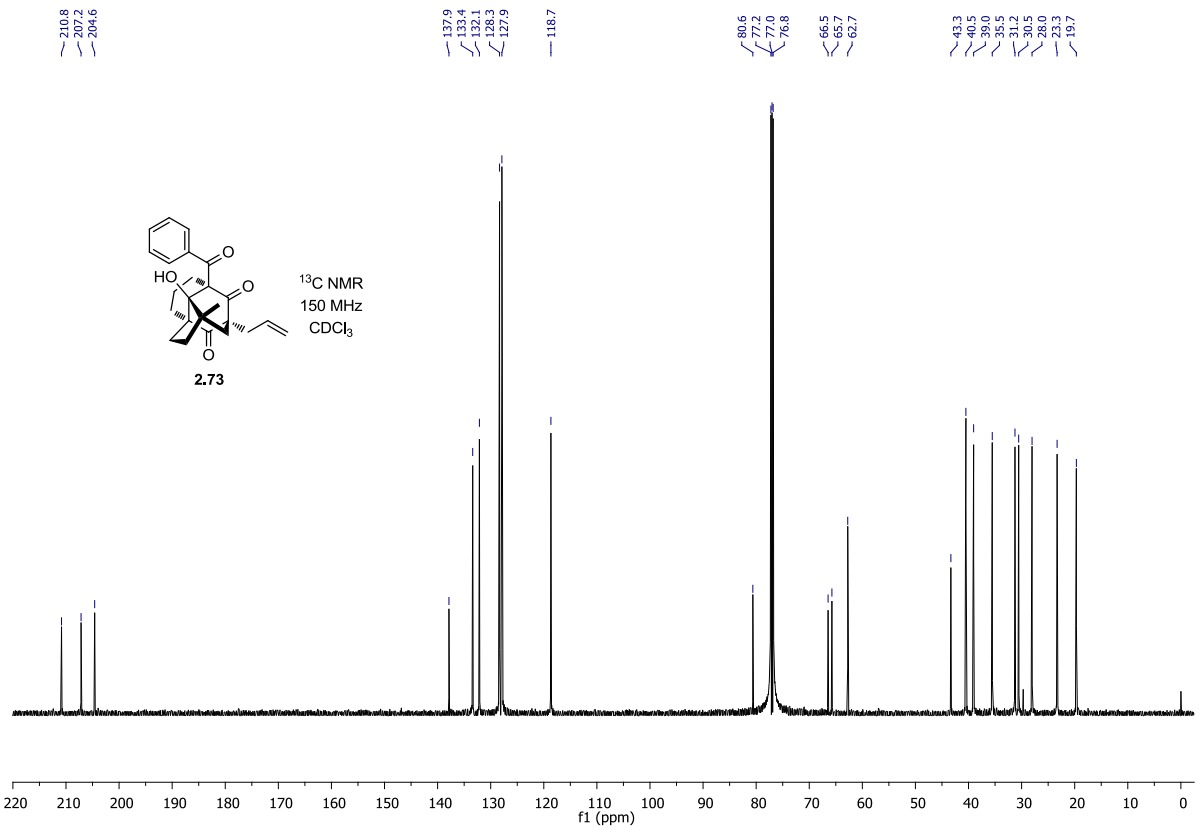
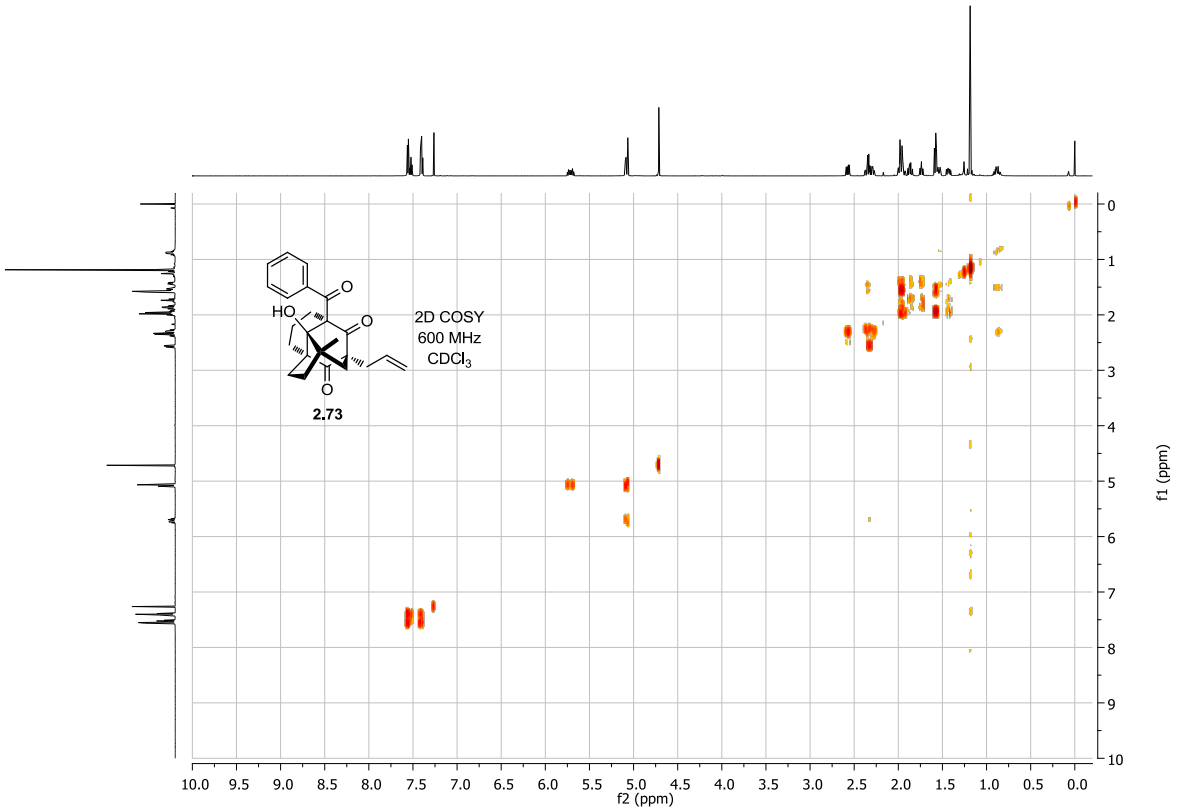
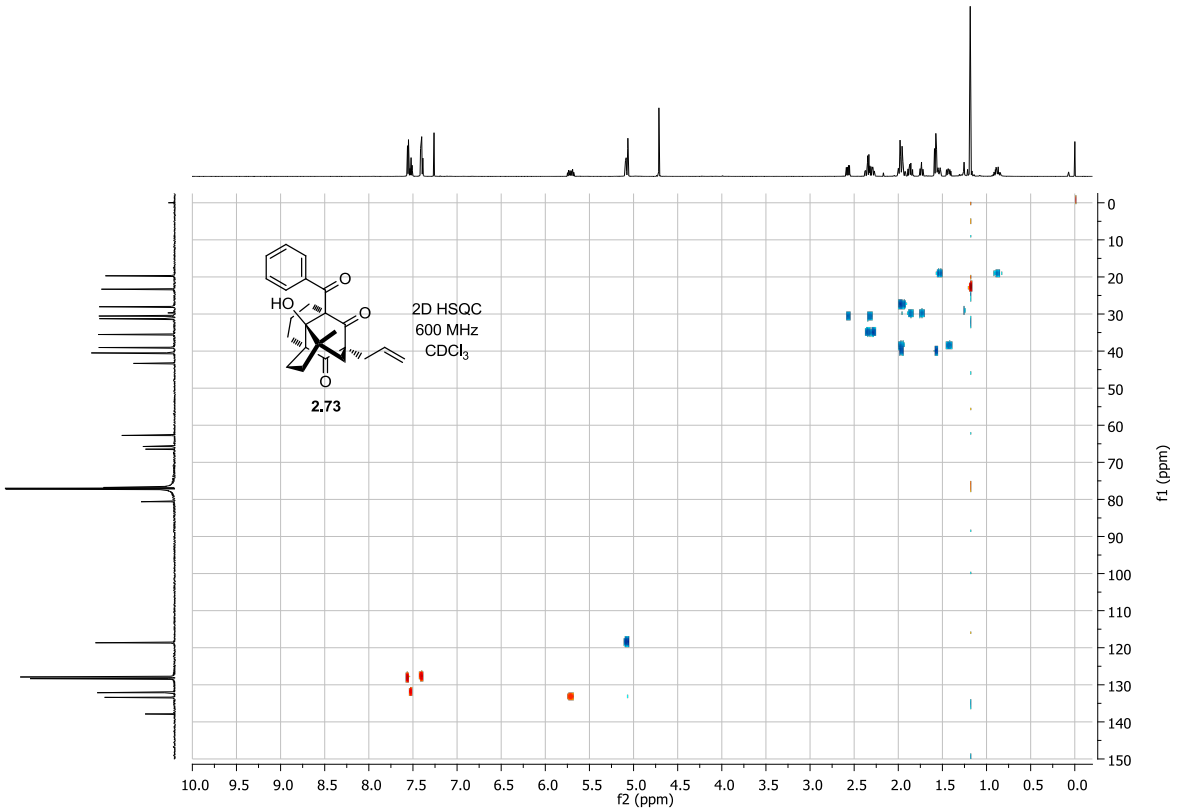
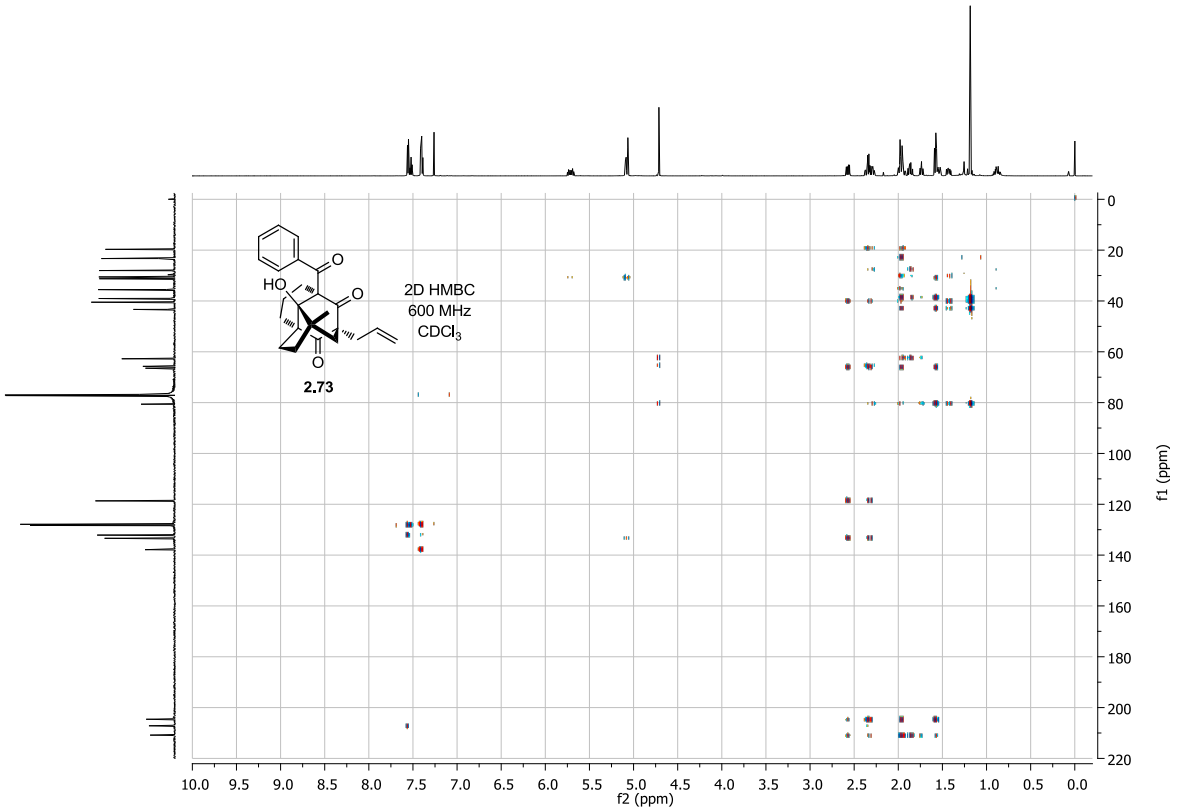
O
O
O
2.73
^{1}H NMR
600 MHz
$CDCl_3$
f1 (ppm)


HO
O
O
O
2.73
^{13}C NMR
150 MHz
$CDCl_3$
f1 (ppm)


HO
O
O
O
2.73
2D COSY
600 MHz
CDCl3
f2 (ppm)
f1 (ppm)


HO
O
O
O
2.73
2D HSQC
600 MHz
CDCl3
f2 (ppm)
f1 (ppm)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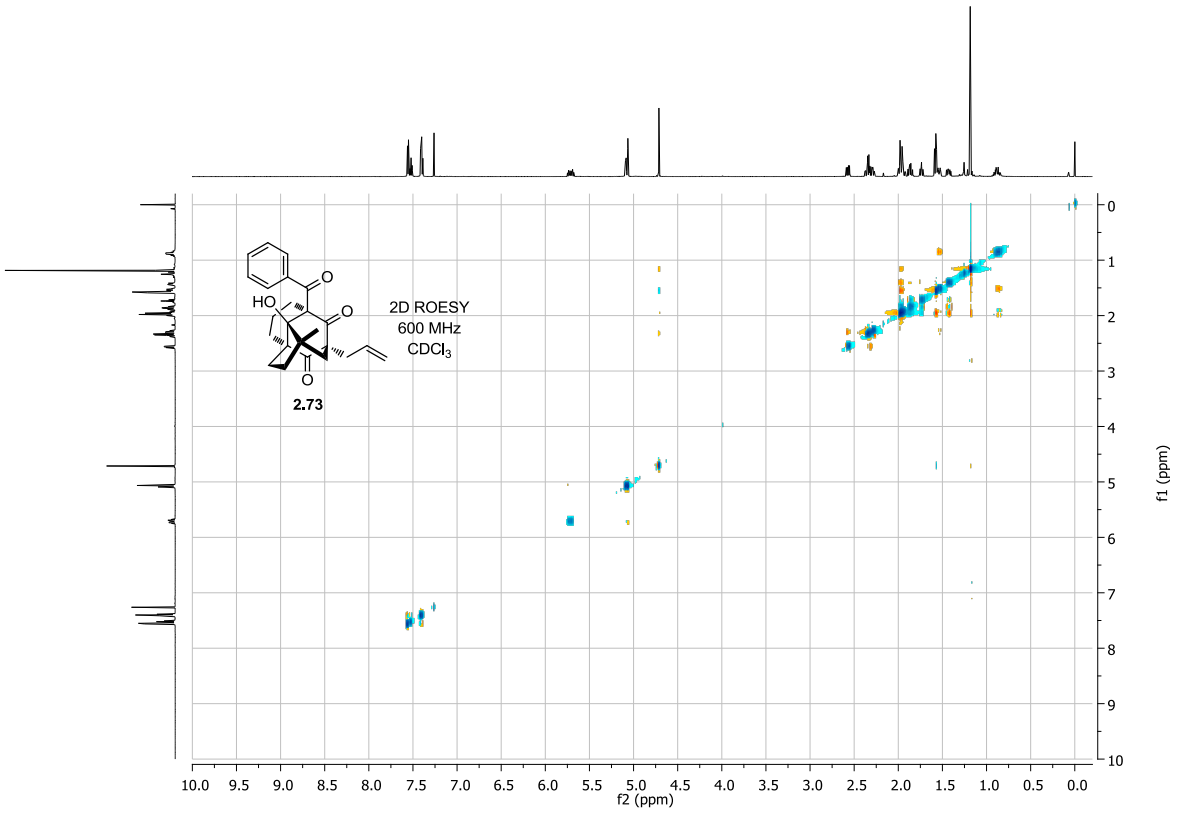
O
O
O
2.73
2D HMBC
600 MHz
CDCl3
f2 (ppm)
f1 (ppm)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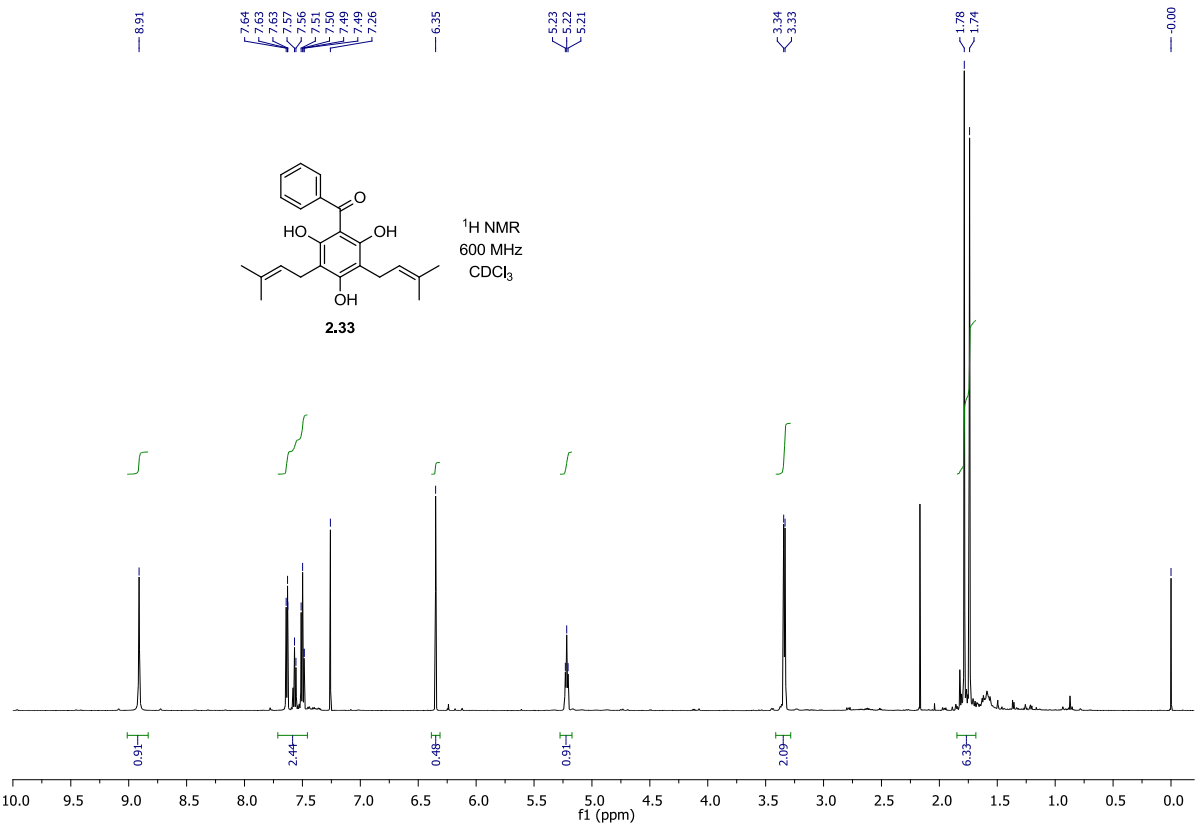
O
O
O
2.73
2D ROESY
600 MHz
CDCl3
f2 (ppm)
f1 (ppm)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7.63
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7.56
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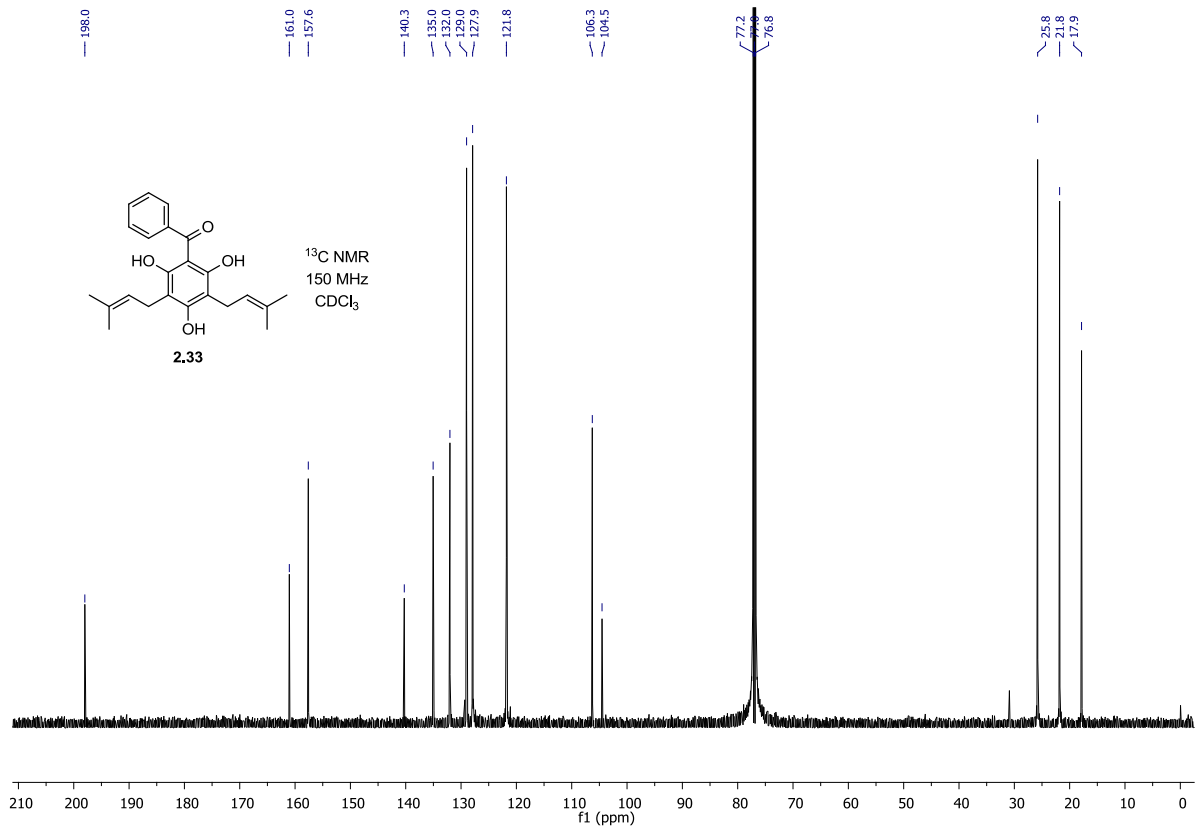
7.50
7.49
7.49
7.26
6.35
5.23
5.22
5.21
3.34
3.33
1.78
1.74
0.00
O
HO
OH
OH
2.33
1H NMR
600 MHz
CDCl3
0.91
2.44
0.48
0.91
2.09
6.33
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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157.6
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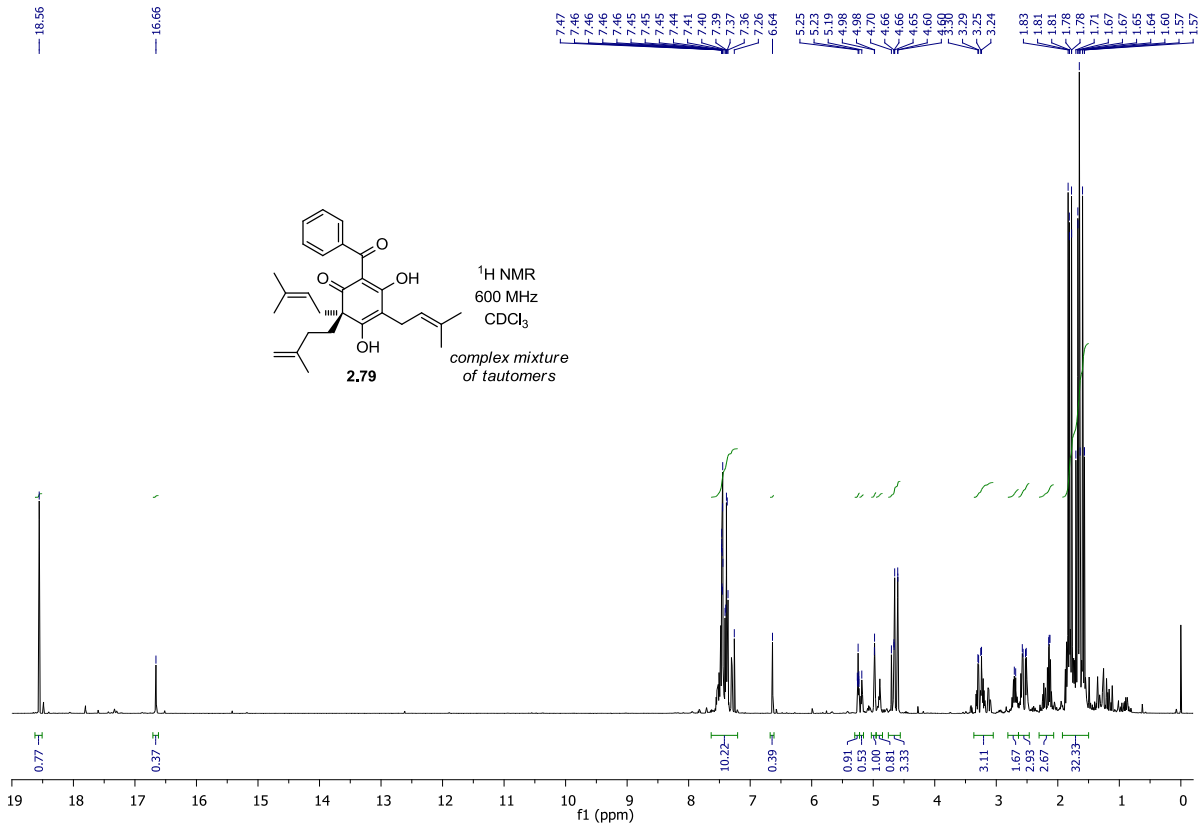
135.0
132.0
129.0
127.9
121.8
106.3
104.5
77.2
77.0
76.8
25.8
21.8
17.9
O
HO
OH
OH
2.33
13C NMR
150 MHz
CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.40
7.39
7.37
7.36
7.26
6.64
5.25
5.23
5.19
4.98
4.98
4.70
4.66
4.66
4.65
4.60
3.30
3.29
3.25
3.24
1.83
1.81
1.81
1.78
1.78
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O
O
OH
OH
2.79
1H NMR
600 MHz
CDCl3
complex mixture
of tautomers
0.77
0.37
10.22
0.39
0.91
0.53
1.00
0.81
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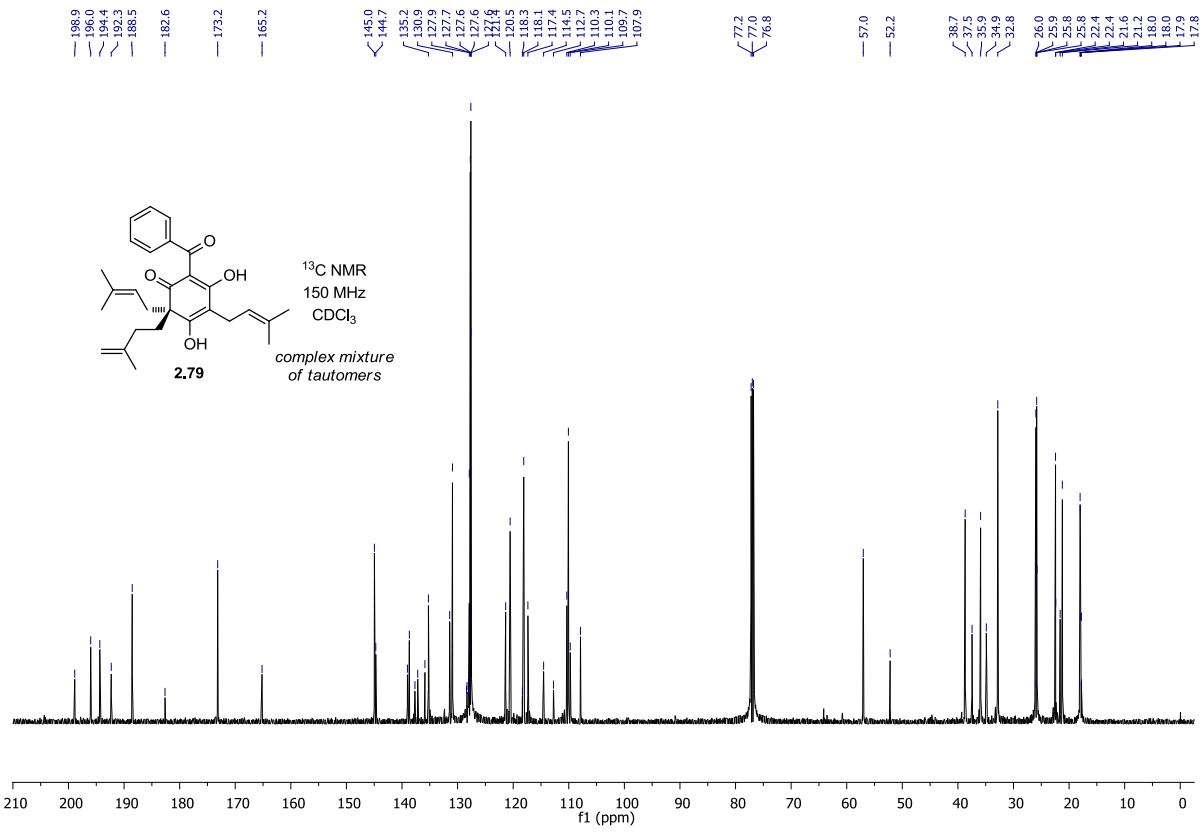
1.67
2.93
2.67
32.33
19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
f1 (ppm)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135.2
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127.9
127.7
127.6
127.6
121.5
118.3
118.1
117.4
114.5
112.7
110.3
110.1
109.7
107.9
77.2
77.0
76.8
57.0
52.2
38.7
37.5
35.9
34.9
32.8
26.0
25.9
25.8
25.8
22.4
22.4
21.6
21.2
18.0
18.0
17.9
17.8
O
O
OH
OH
2.79
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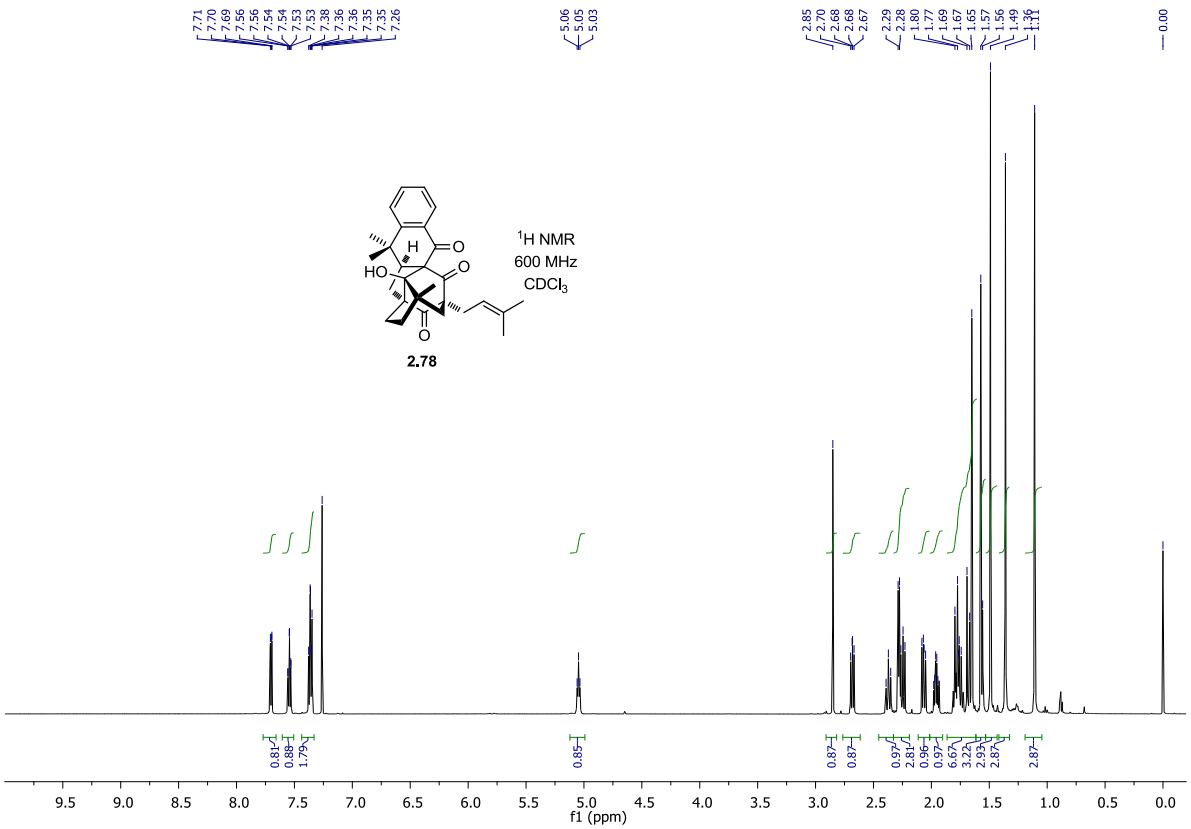
150 MHz
CDCl3
complex mixture
of tautomers
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.53
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7.38
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7.36
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7.35
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5.03
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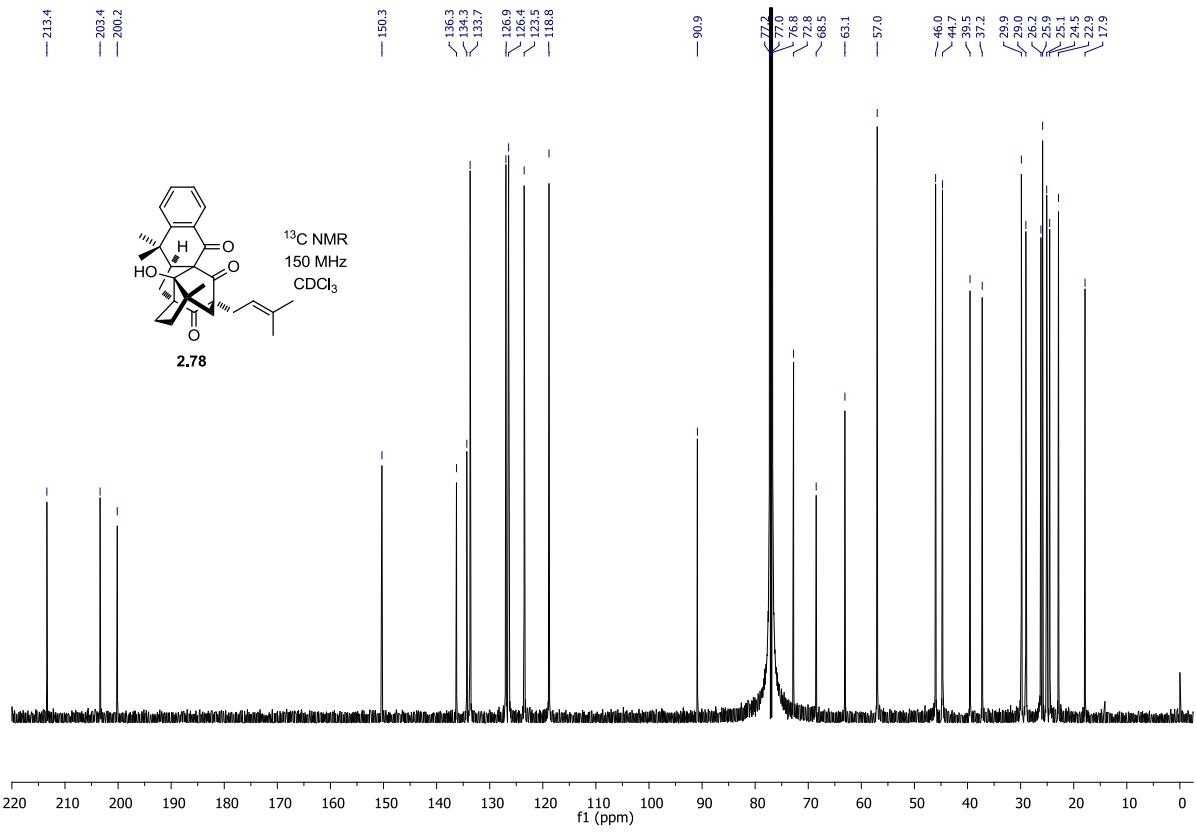
0.87
0.87
0.97
2.81
0.96
0.97
6.67
3.22
2.95
2.87
2.87
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
^{1}H NMR
600 MHz
$CDCl_3$
2.78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118.8
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77.0
76.8
72.8
68.5
63.1
57.0
46.0
44.7
39.5
37.2
29.9
29.0
26.2
25.9
25.1
24.5
22.9
17.9
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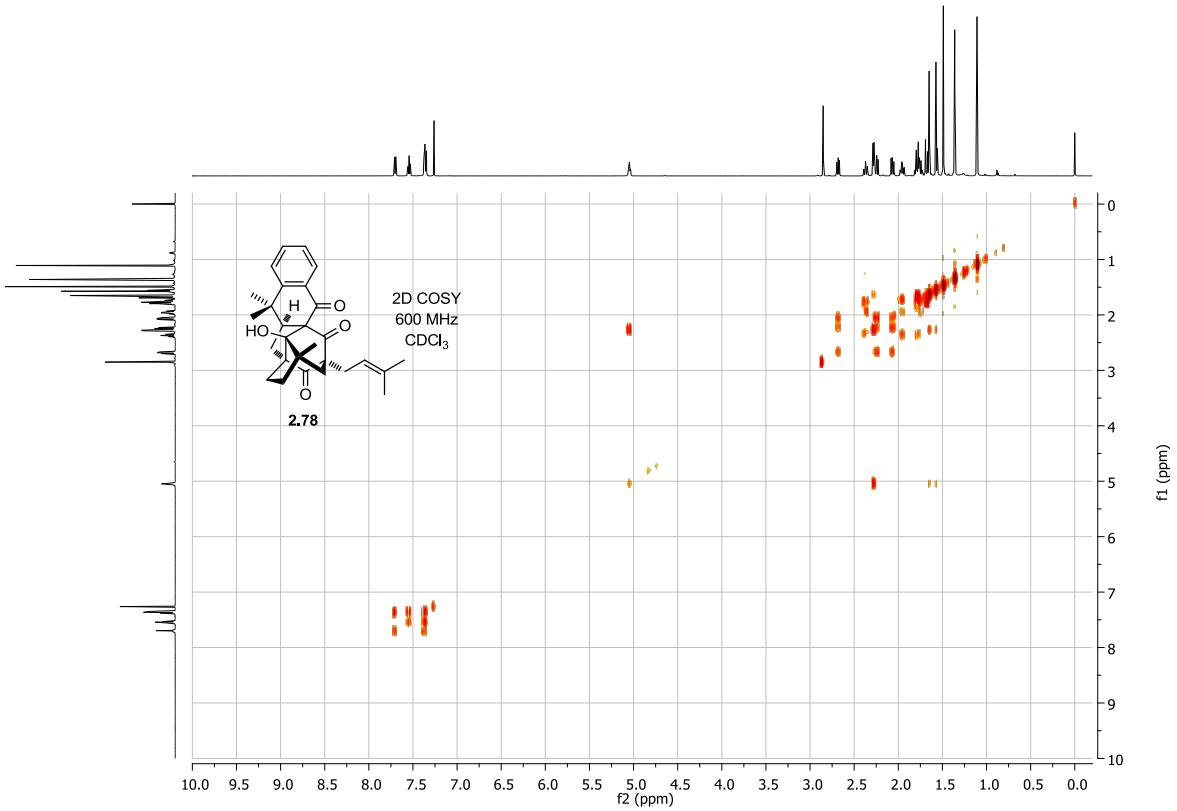
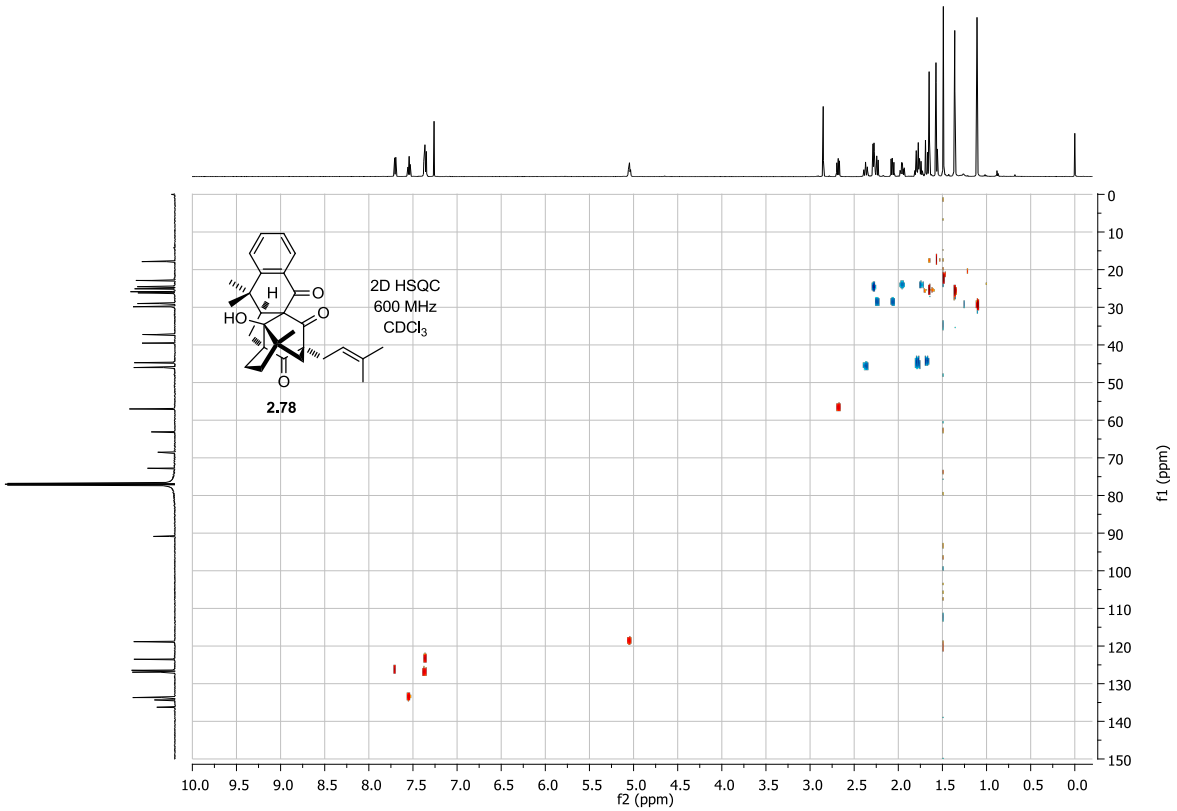
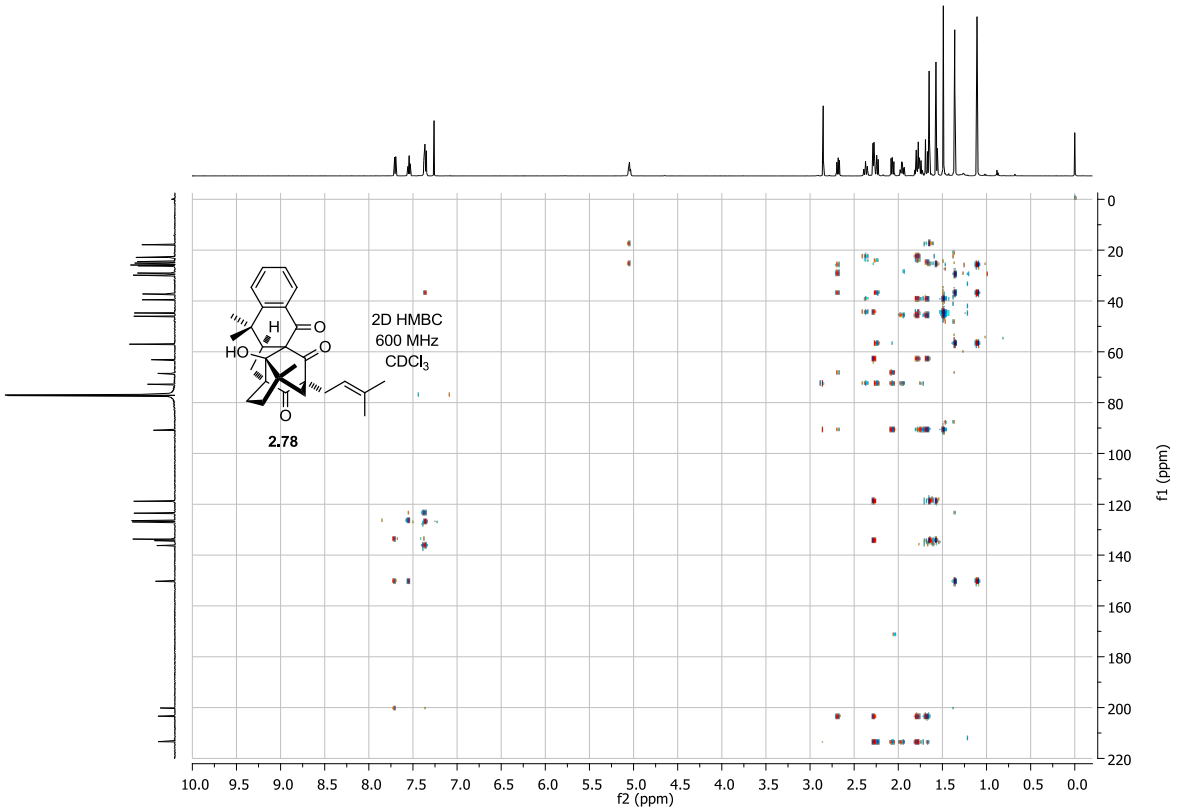
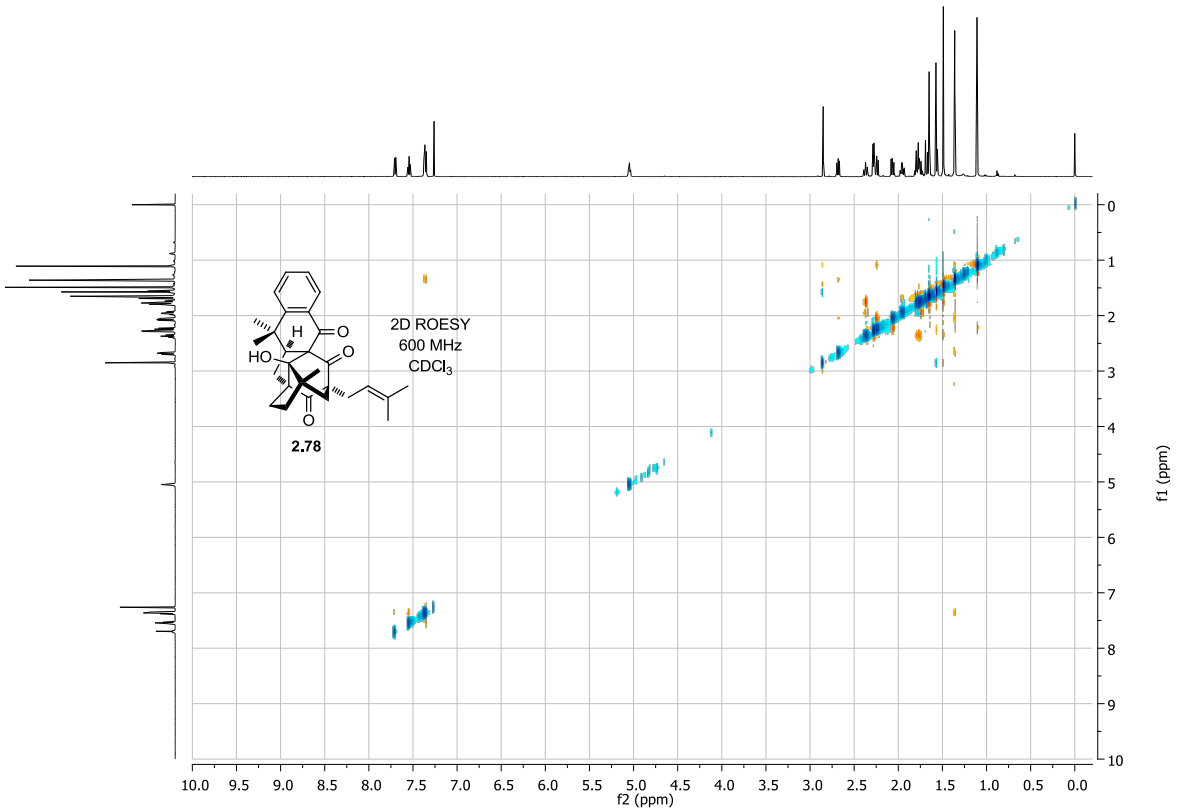
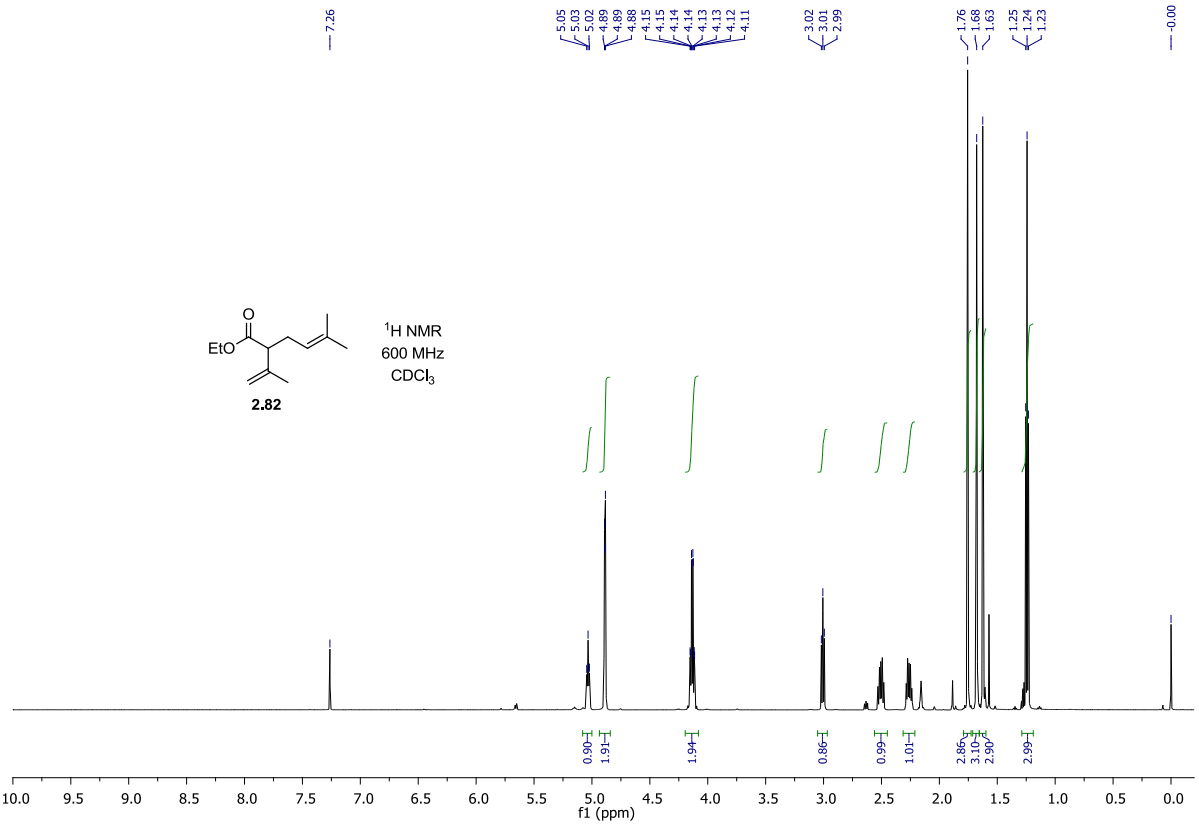
f1 (ppm)
^{13}C NMR
150 MHz
$CDCl_3$
2.78

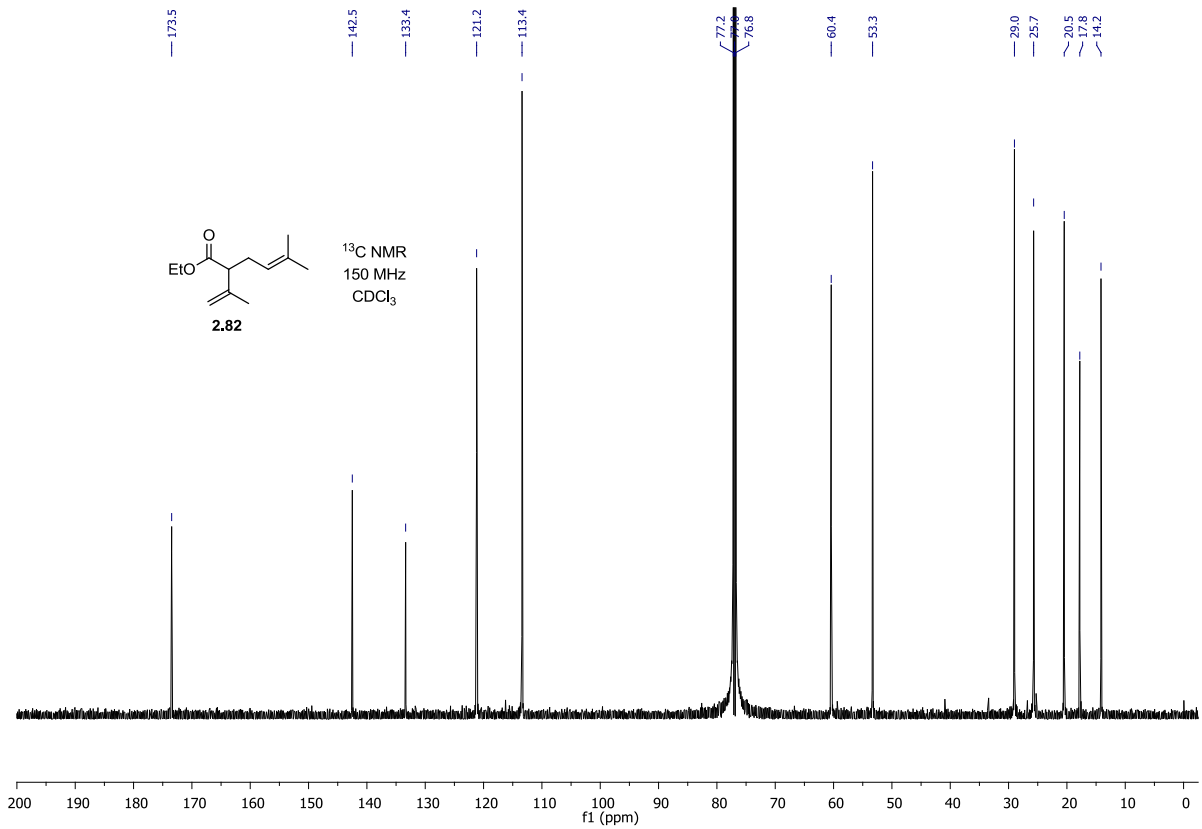

2D COSY
600 MHz
$CDCl_3$
2.78
f2 (ppm)
f1 (ppm)

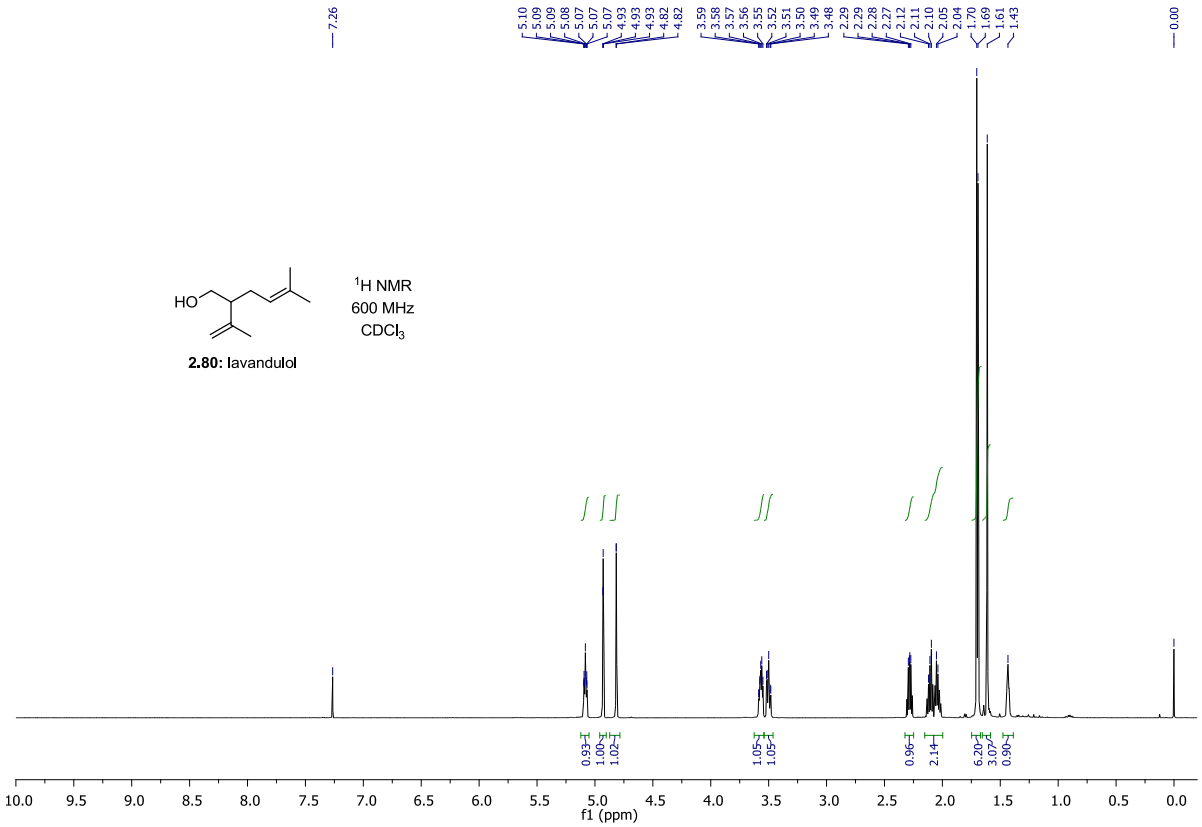

2D HSQC
600 MHz
$CDCl_3$
2.78
f2 (ppm)
f1 (ppm)

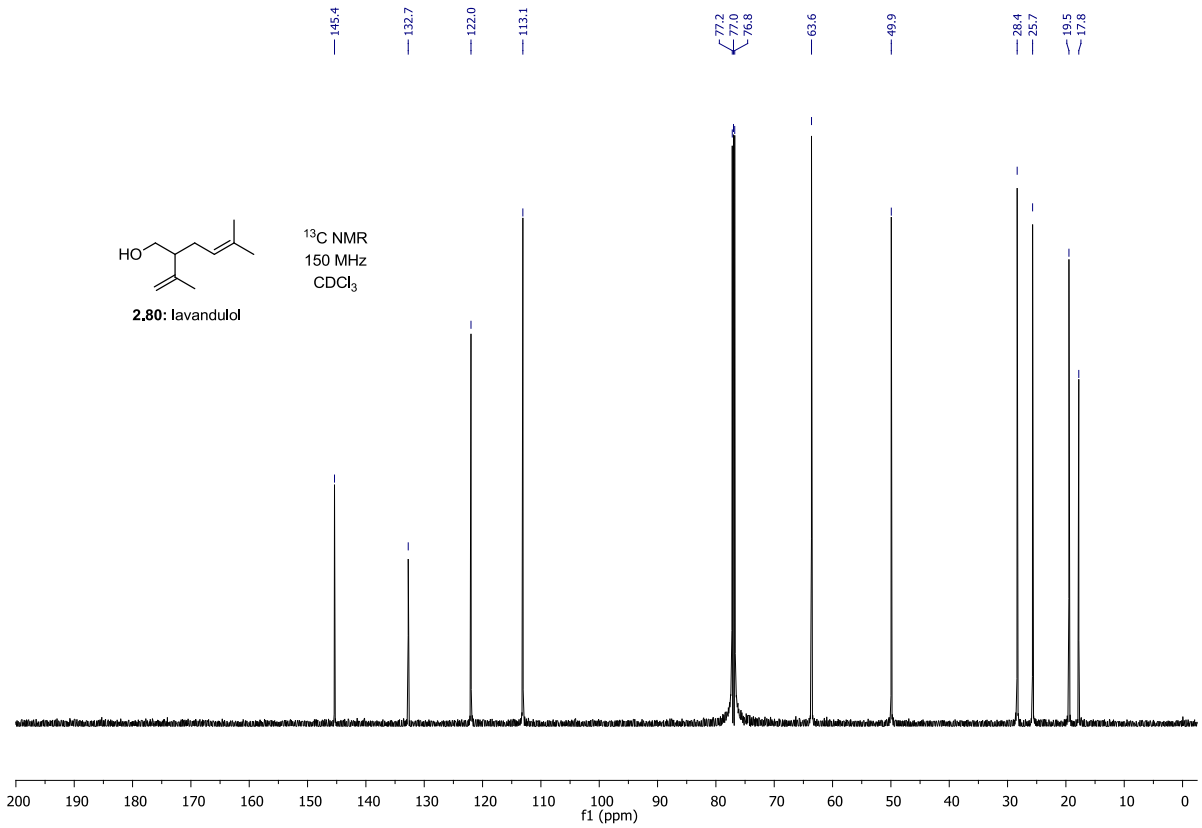

2D HMBC
600 MHz
CDCl3
2.78
f2 (ppm)
f1 (ppm)

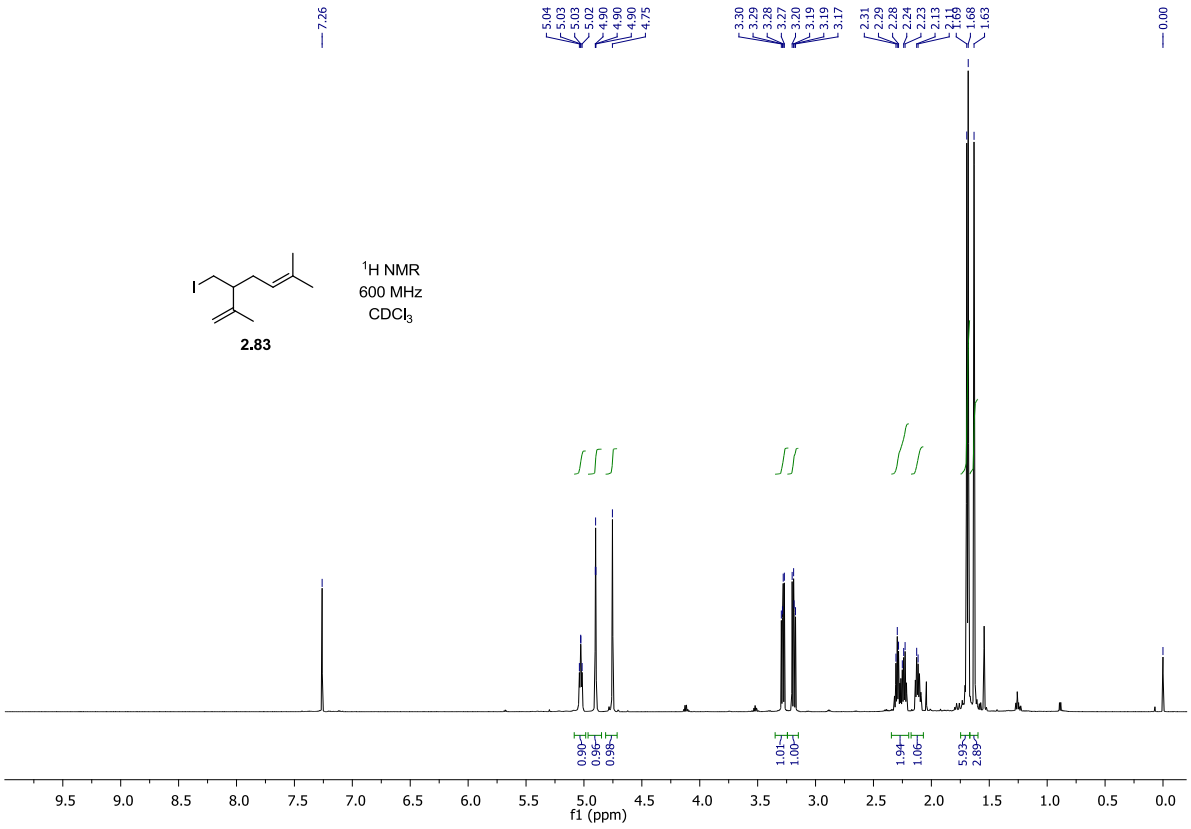

2D ROESY
600 MHz
CDCl3
2.78
f2 (ppm)
f1 (ppm)

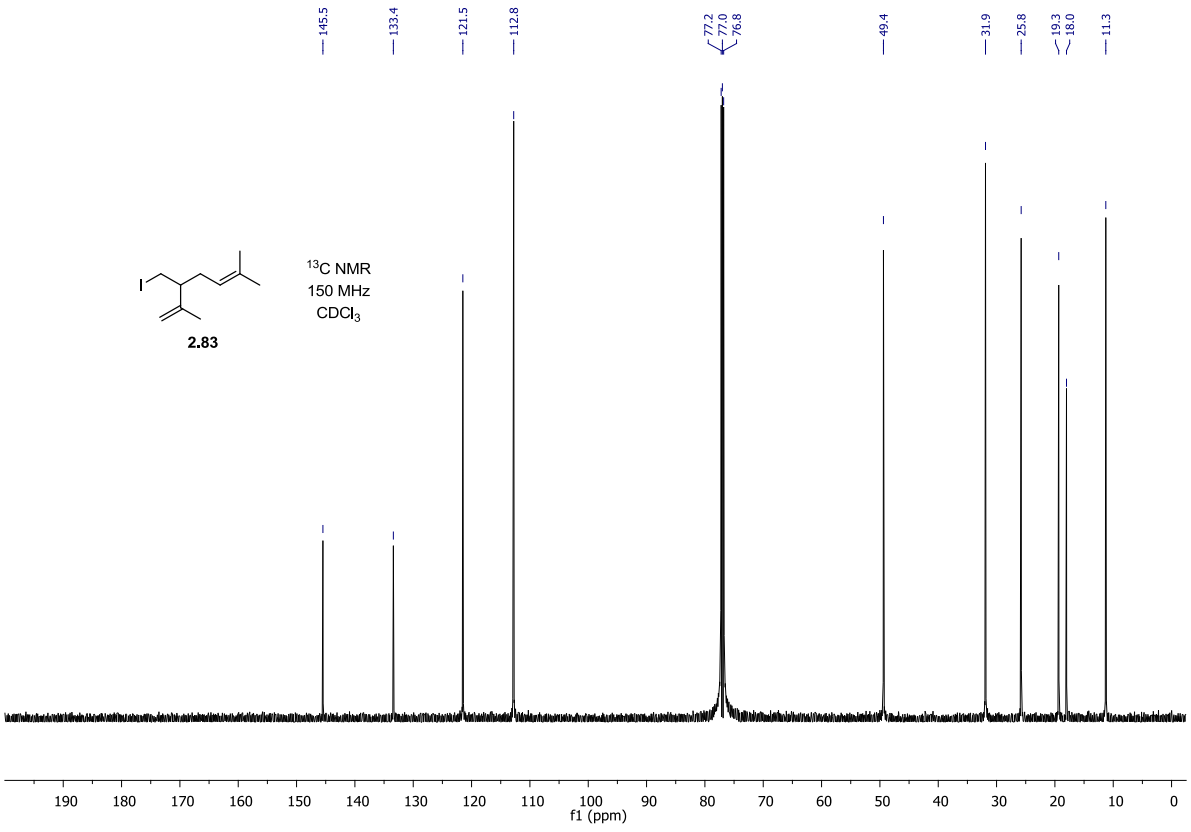

7.26
5.05
5.03
5.02
4.89
4.89
4.88
4.15
4.15
4.14
4.14
4.13
4.13
4.12
4.11
3.02
3.01
2.99
1.76
1.68
1.63
1.25
1.24
1.23
0.00
O
EtO
2.82
1H NMR
600 MHz
CDCl3
0.90
1.91
1.94
0.86
0.99
1.01
2.86
3.10
2.90
2.99
f1 (ppm)

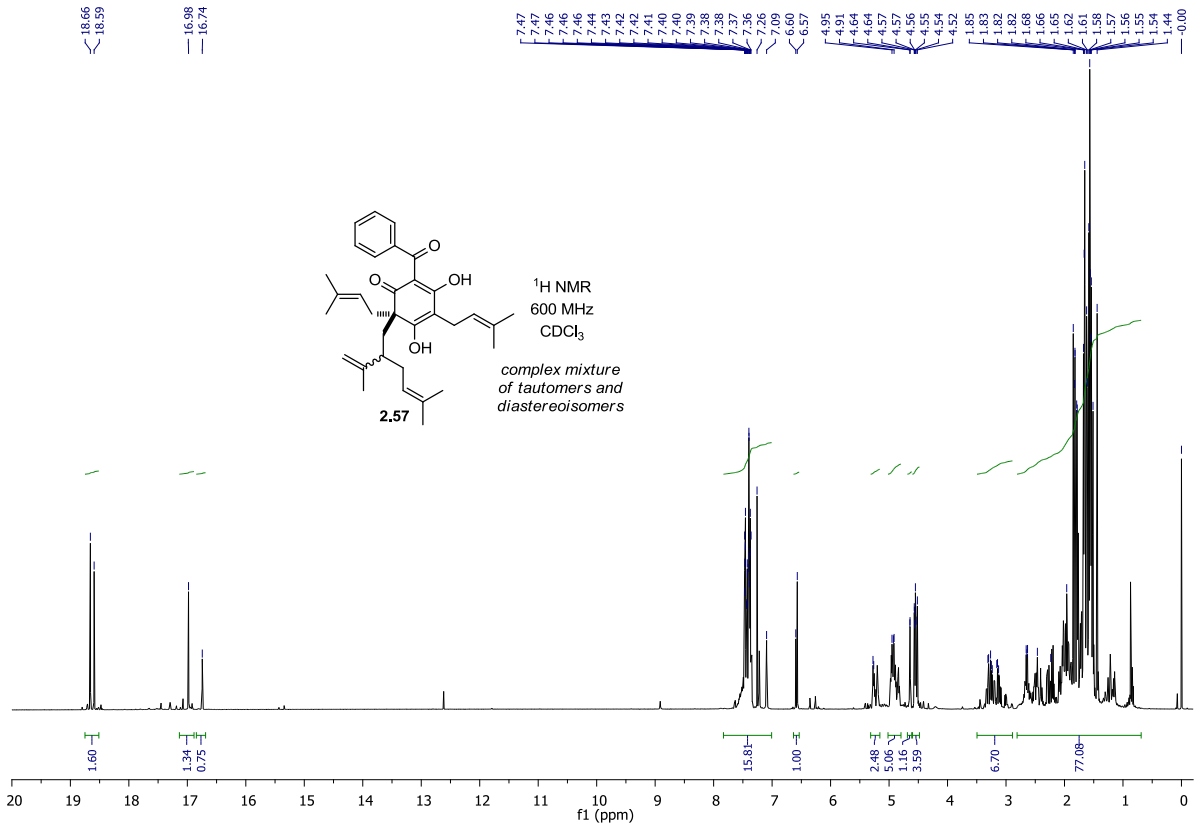

173.5
142.5
133.4
121.2
113.4
77.2
76.8
60.4
53.3
29.0
25.7
20.5
17.8
14.2
O
EtO
2.82
13C NMR
150 MHz
CDCl3
f1 (ppm)

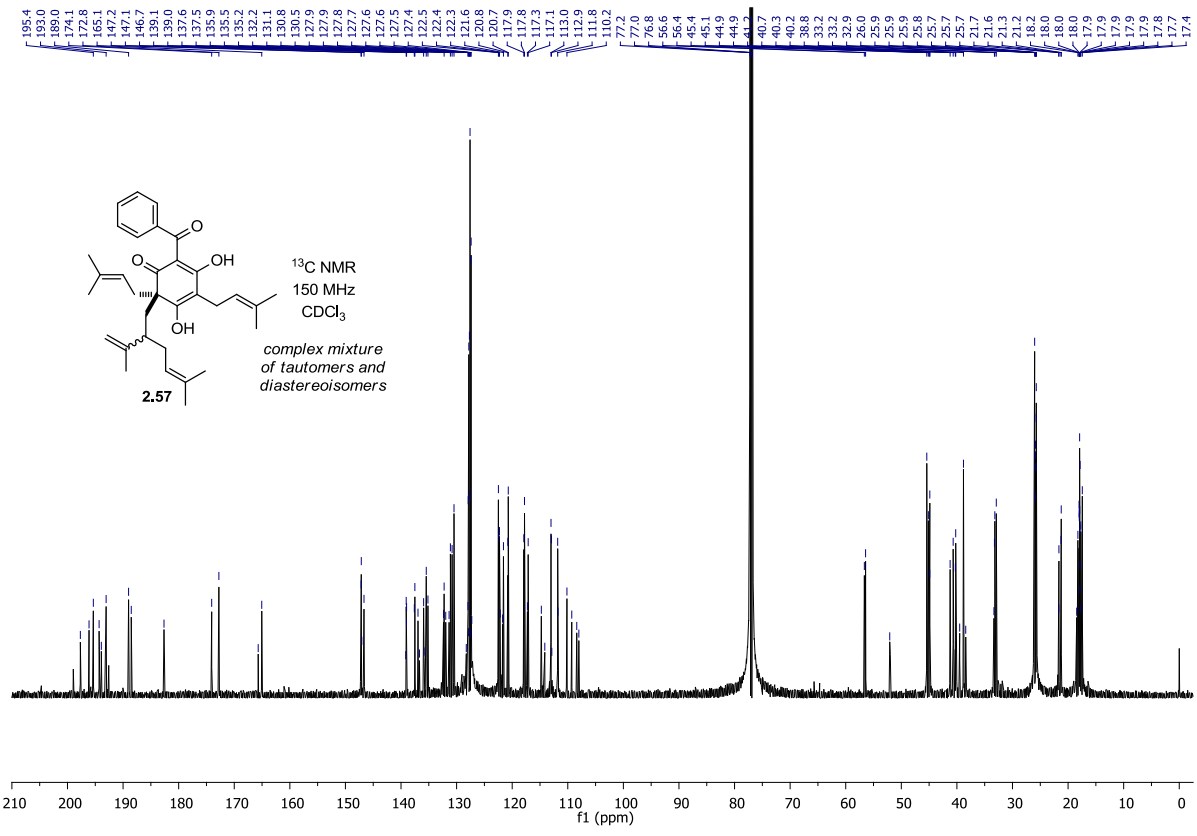

HO
2.80: lavandulol
^{1}H NMR
600 MHz
$CDCl_3$
7.26
5.10 5.09 5.09 5.08 5.07 5.07 5.07 4.93 4.93 4.93 4.82 4.82
3.59 3.58 3.57 3.56 3.55 3.52 3.51 3.50 3.49 3.48
2.29 2.29 2.28 2.27 2.12 2.11 2.10 2.05 2.04
1.70 1.69 1.61 1.43
0.00
0.93 1.00 1.02 1.05 1.05 0.96 2.14 6.20 3.07 0.90
10.0 9.5 9.0 8.5 8.0 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)

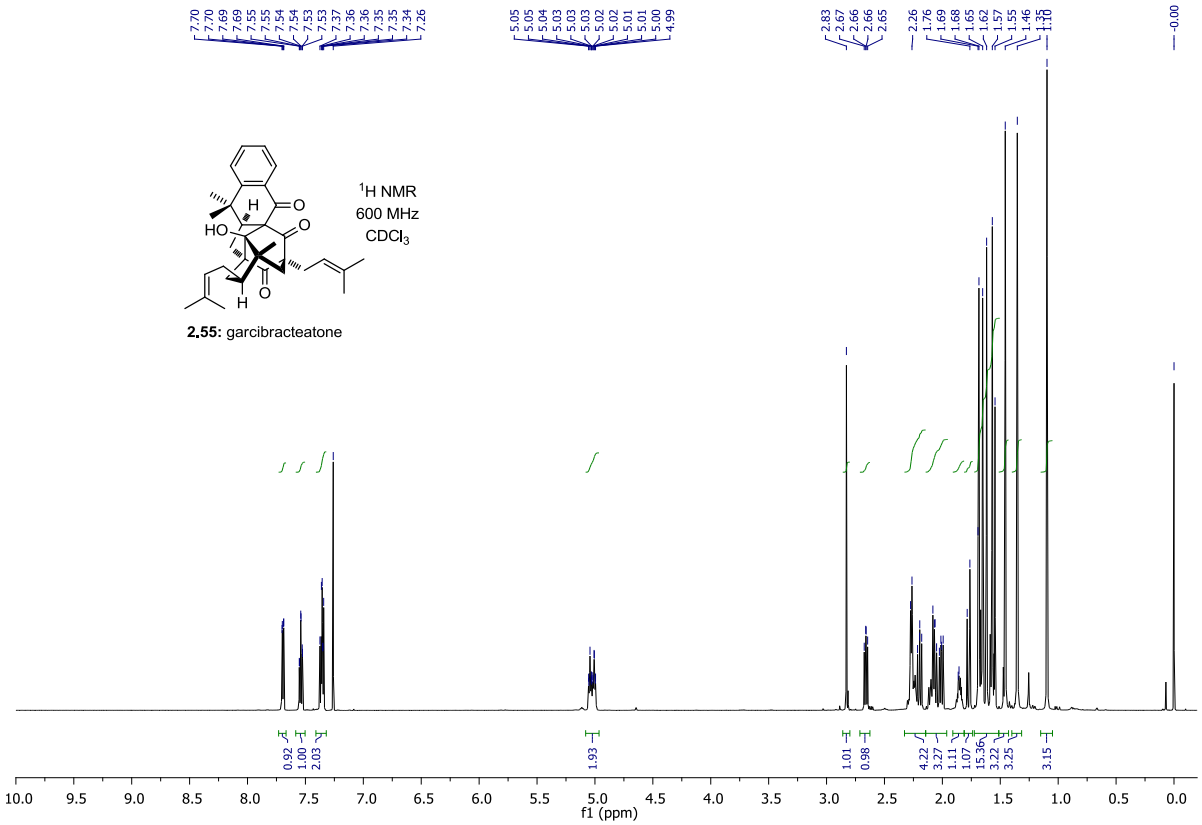

HO
2.80: lavandulol
^{13}C NMR
150 MHz
$CDCl_3$
145.4
132.7
122.0
113.1
77.2
77.0
76.8
63.6
49.9
28.4
25.7
19.5
17.8
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.26
5.04
5.03
5.03
5.02
4.90
4.90
4.90
4.75
3.30
3.29
3.28
3.27
3.20
3.19
3.19
3.17
2.31
2.29
2.28
2.24
2.23
2.13
2.11
1.69
1.68
1.63
0.00
0.90
0.96
0.98
1.01
1.00
1.94
1.06
5.93
2.89
I
2.83
^{1}H NMR
600 MHz
$CDCl_3$
f1 (ppm)

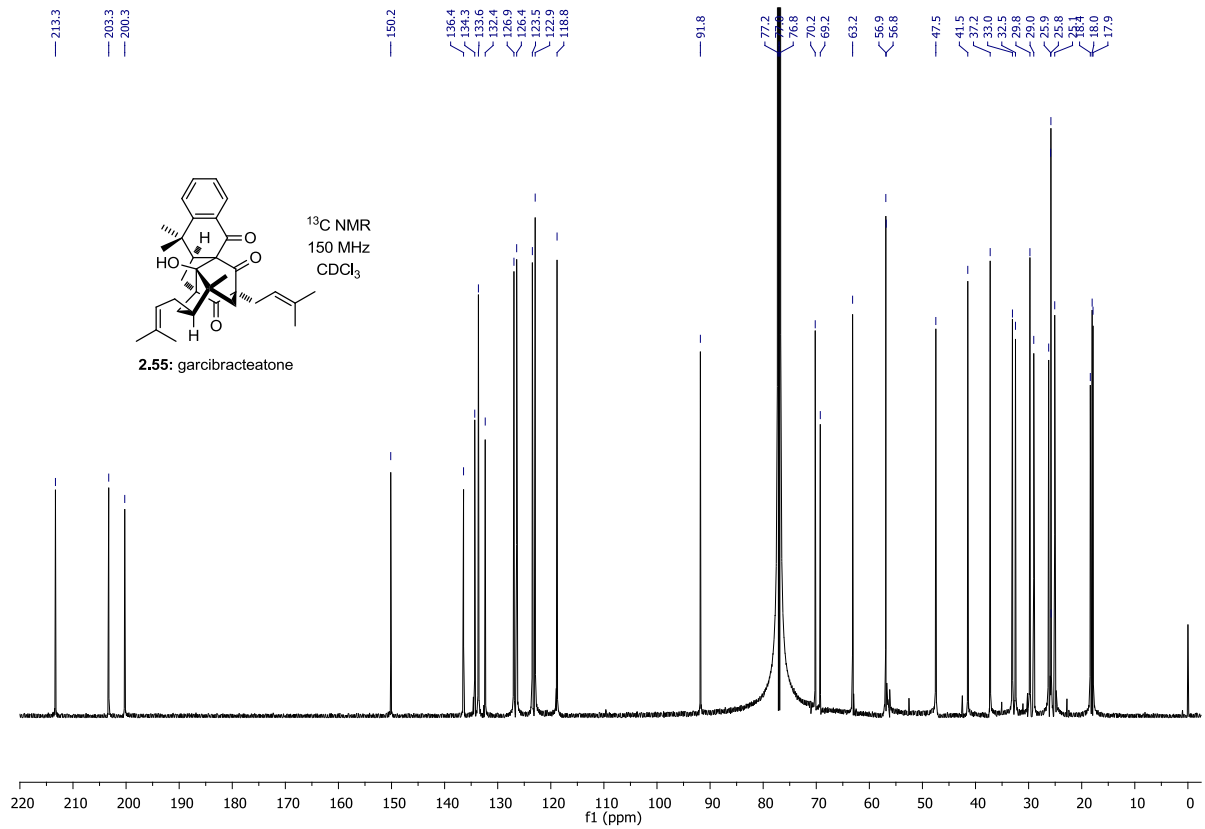

145.5
133.4
121.5
112.8
77.2
77.0
76.8
49.4
31.9
25.8
19.3
18.0
11.3
I
2.83
^{13}C NMR
150 MHz
$CDCl_3$
f1 (ppm)


18.66
18.59
16.98
16.74
7.47
7.47
7.46
7.46
7.46
7.44
7.43
7.42
7.42
7.41
7.40
7.40
7.39
7.38
7.38
7.37
7.36
7.26
7.09
6.60
6.57
4.95
4.91
4.64
4.64
4.57
4.57
4.56
4.55
4.54
4.52
1.85
1.83
1.82
1.82
1.68
1.66
1.65
1.62
1.61
1.58
1.57
1.56
1.55
1.54
1.44
0.00
O
O
OH
OH
2.57
1H NMR
600 MHz
CDCl3
complex mixture
of tautomers and
diastereoisomers
1.60
1.34
0.75
15.81
1.00
2.48
5.06
1.16
3.59
6.70
77.08
20
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

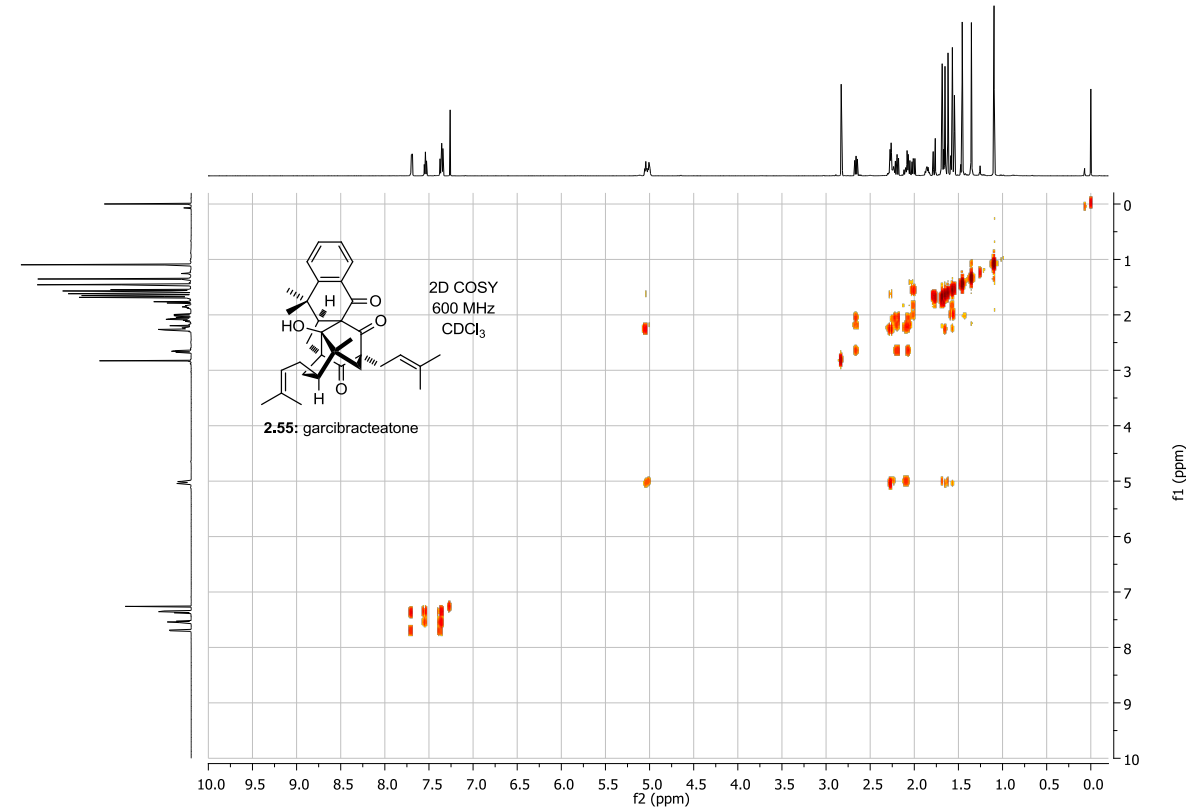

195.4
193.0
189.0
174.1
172.8
165.1
147.2
147.1
146.7
139.1
139.0
137.6
137.5
135.9
135.5
135.2
132.2
131.1
130.8
130.5
127.9
127.9
127.8
127.7
127.6
127.6
127.5
127.4
122.5
122.4
122.3
121.6
120.8
120.7
117.9
117.8
117.3
117.1
113.0
112.9
111.8
110.2
77.2
77.0
76.8
56.6
56.4
45.4
45.1
44.9
44.9
41.2
40.7
40.3
40.2
38.8
33.2
33.2
32.9
26.0
25.9
25.9
25.9
25.8
25.7
25.7
25.7
21.7
21.6
21.3
21.2
18.2
18.0
18.0
18.0
17.9
17.9
17.9
17.9
17.9
17.8
17.7
17.4
O
O
OH
OH
2.57
13C NMR
150 MHz
CDCl3
complex mixture
of tautomers and
diastereoisomers
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

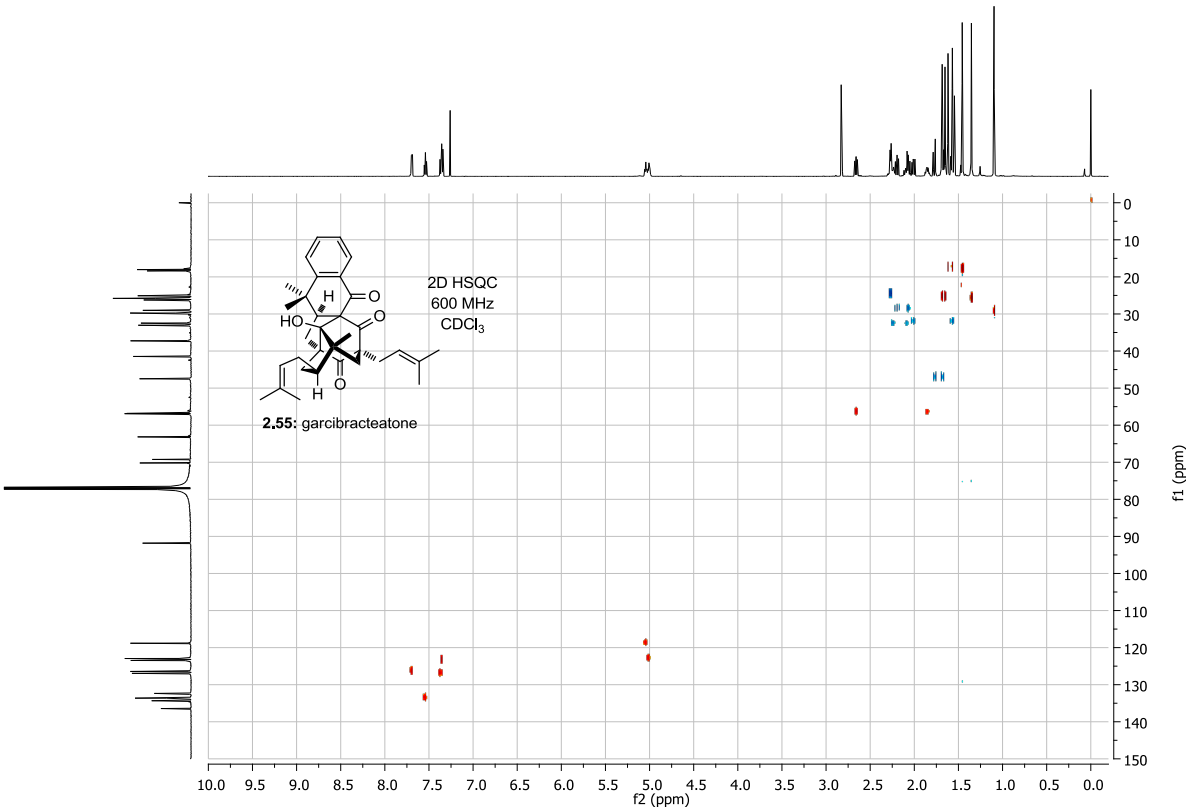


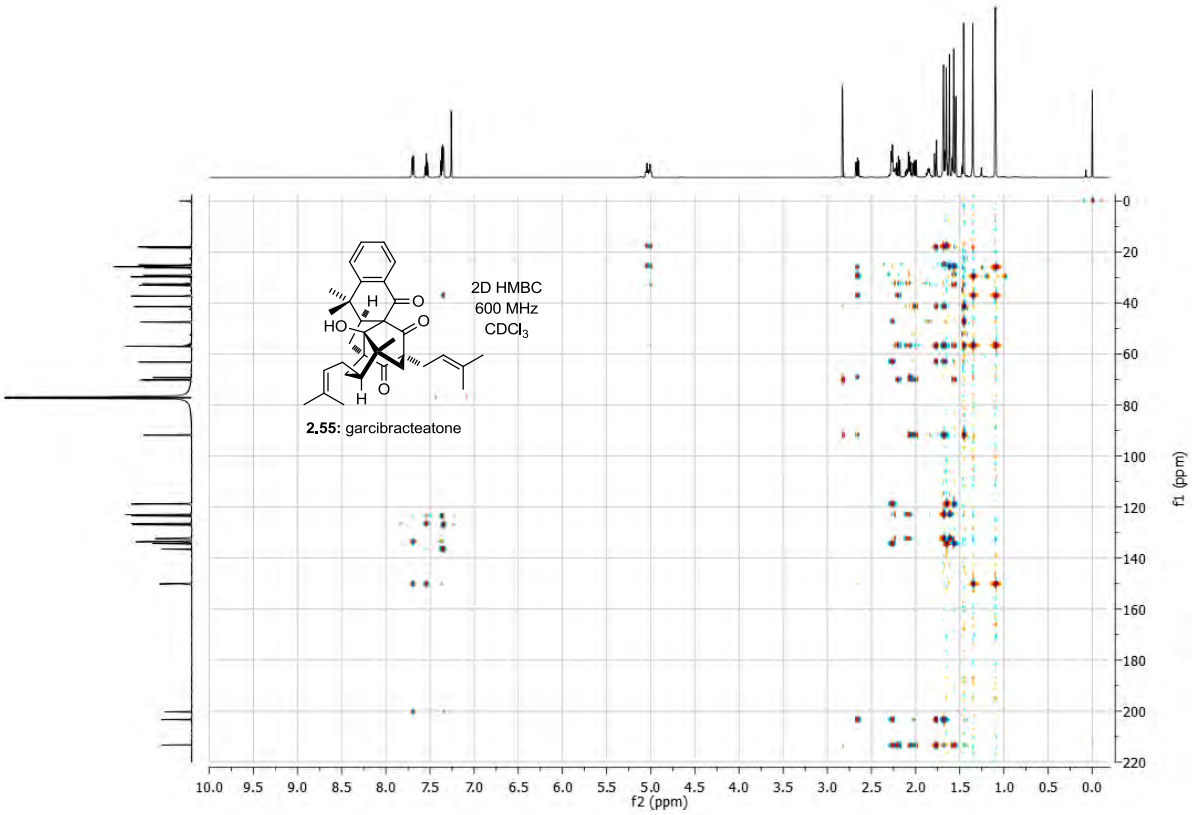
2,55: garcibracteatone

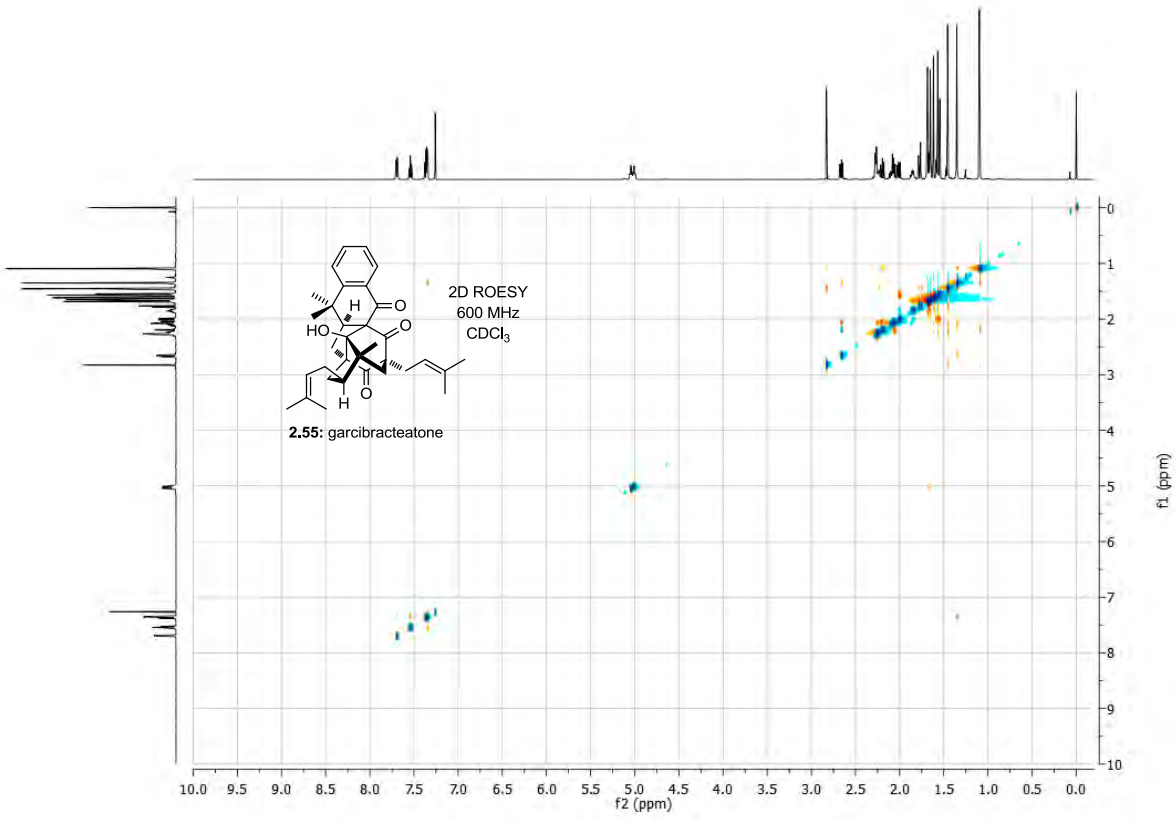


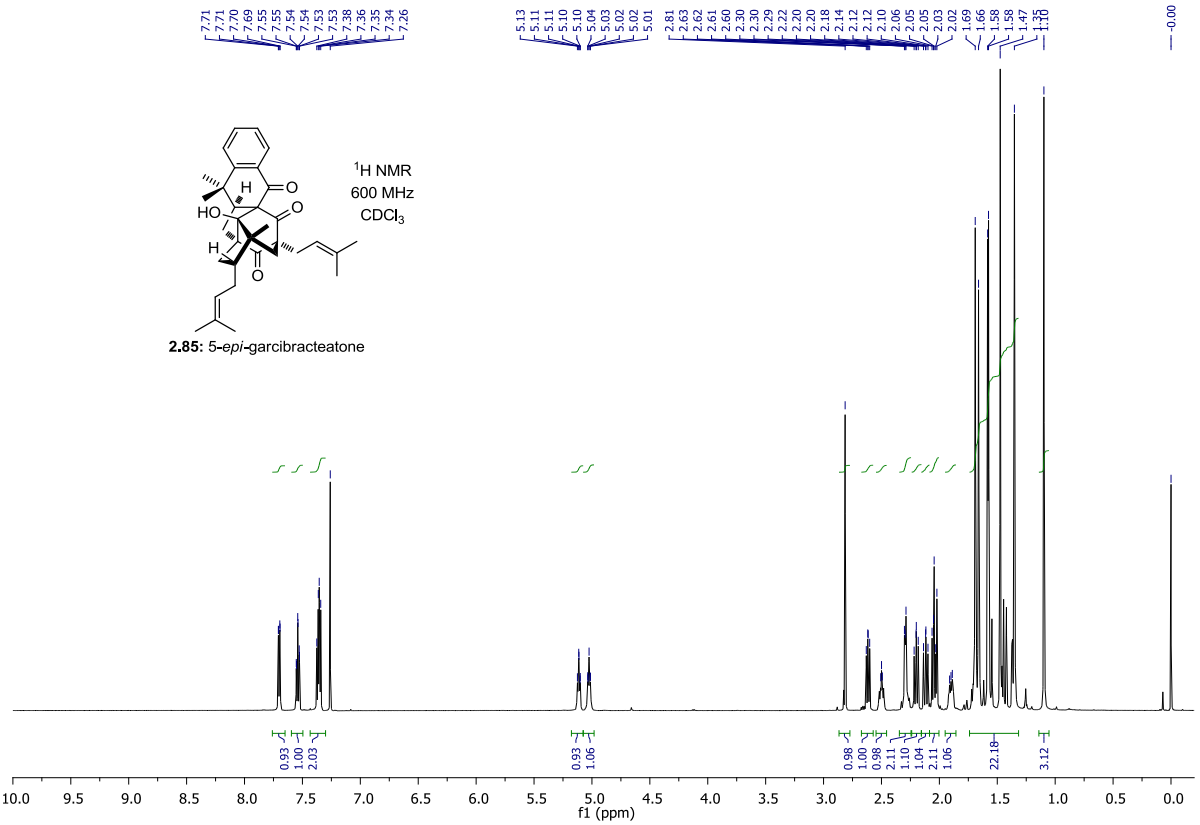
2.55: garcibracteatone


2D COSY
600 MHz
CDCl3
2.55: garcibracteatone
f2 (ppm)
f1 (ppm)

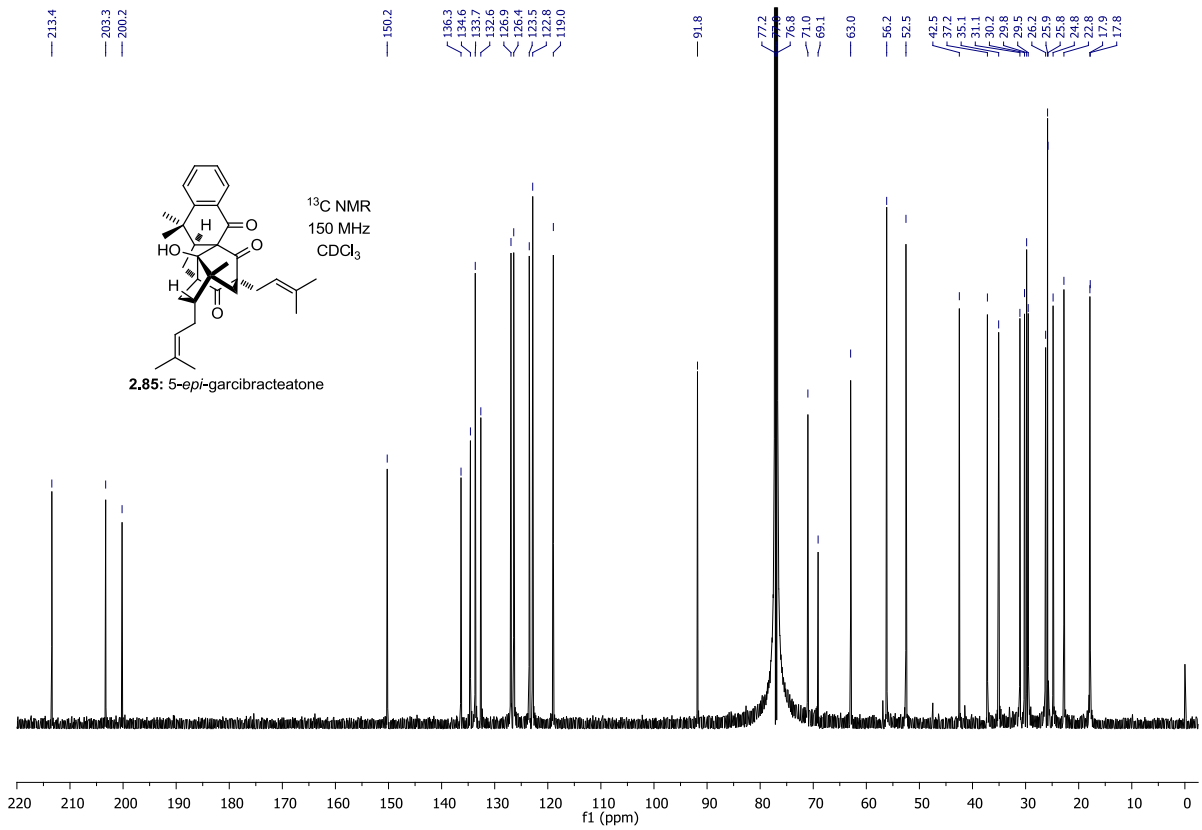

2D HSQC
600 MHz
CDCl3
2.55: garcibracteatone
f2 (ppm)
f1 (ppm)


2D HMBC
600 MHz
CDCl3
2.55: garcibracteatone
f2 (ppm)
f1 (ppm)

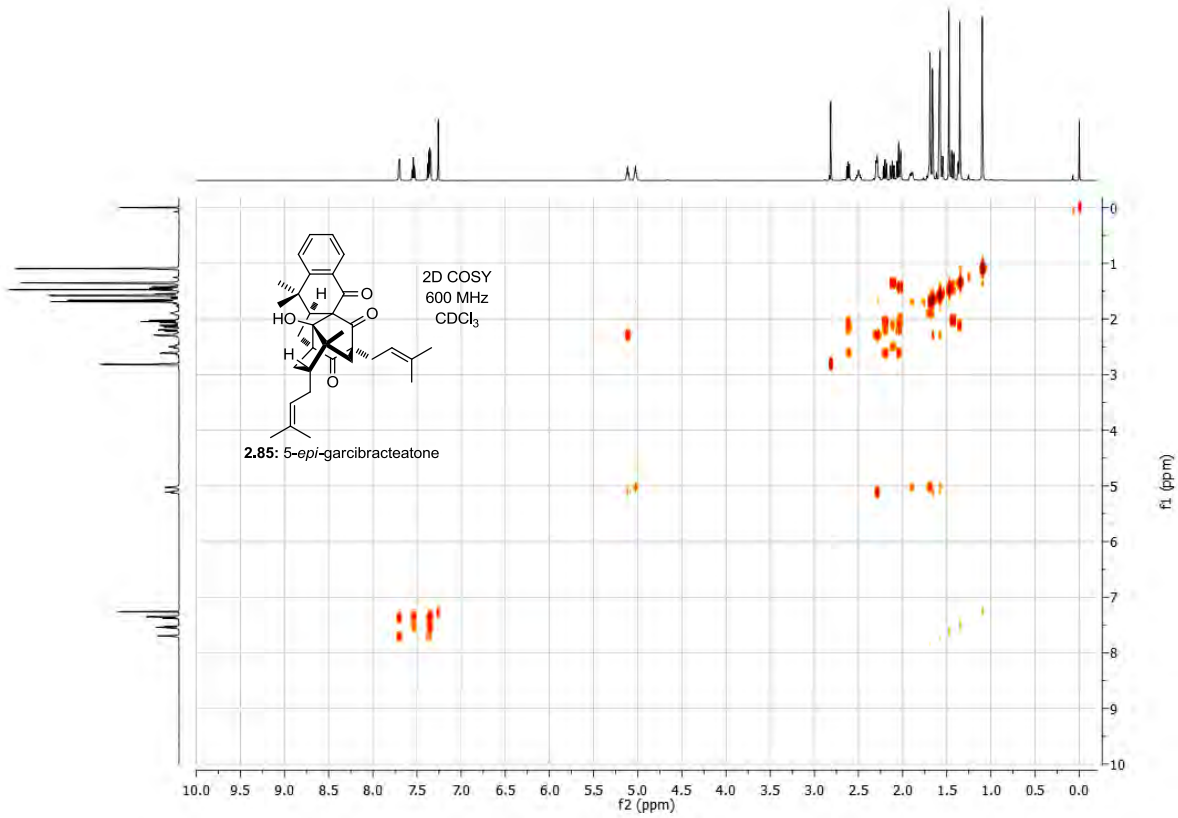

2D ROESY
600 MHz
CDCl3
2.55: garcibracteatone
f2 (ppm)
f1 (ppm)

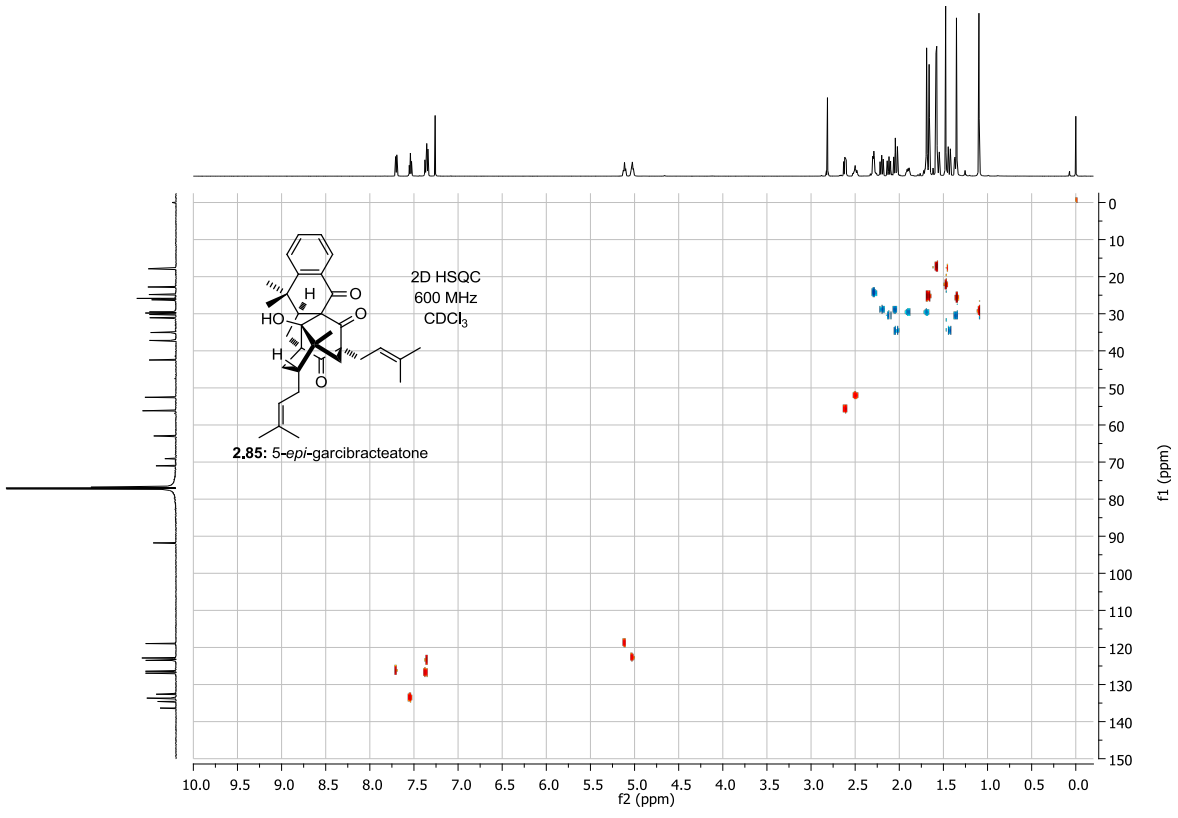


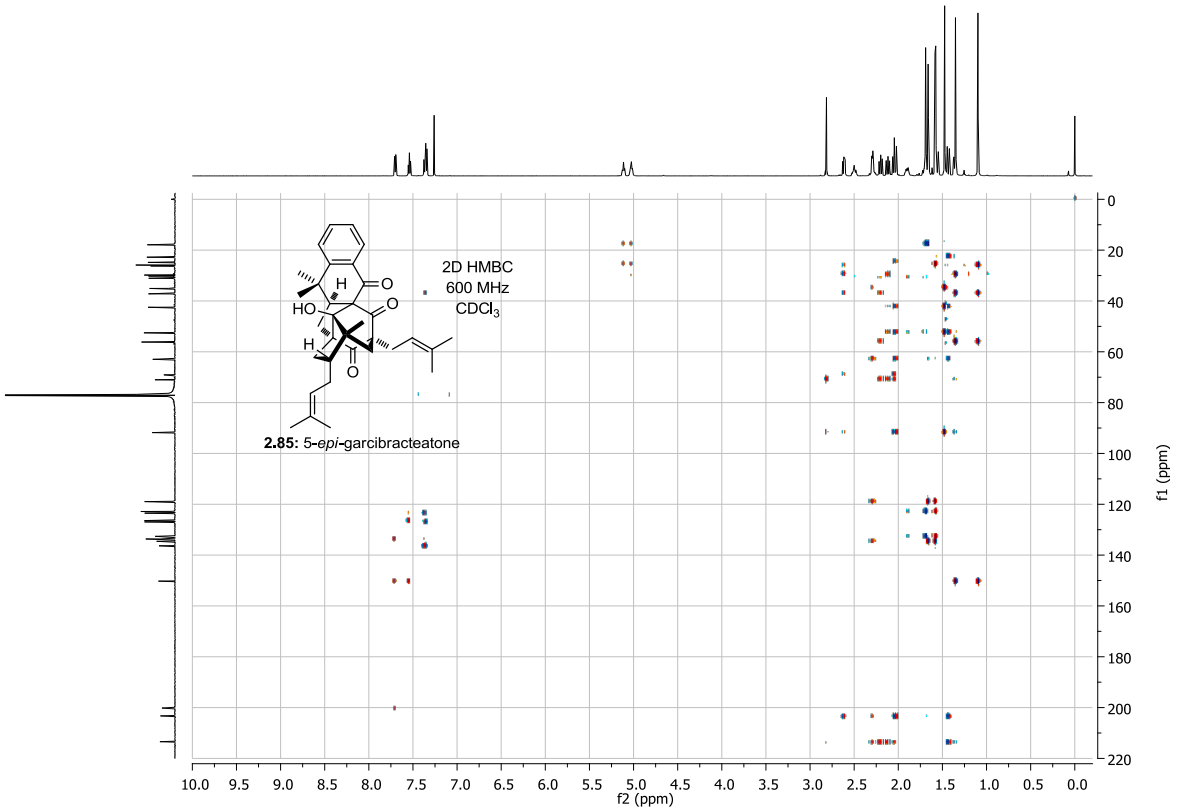
2.85: 5-*epi*-garcibracteatone

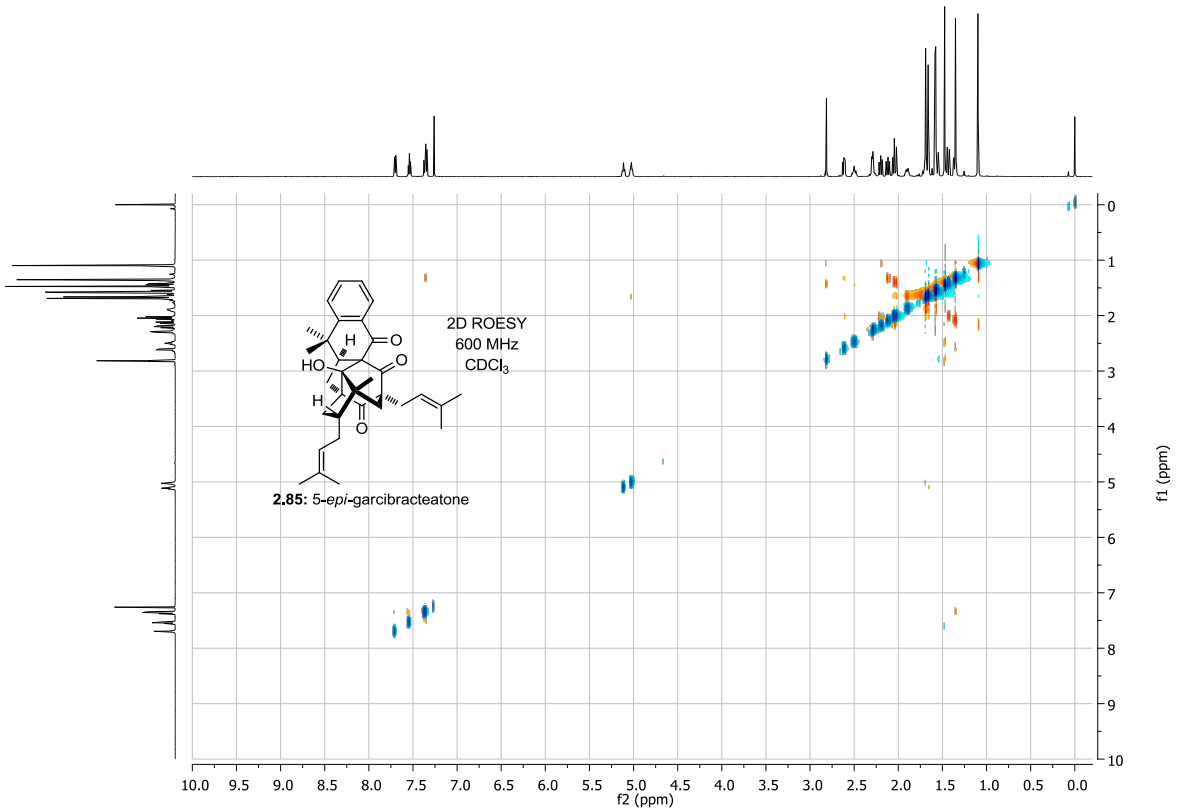


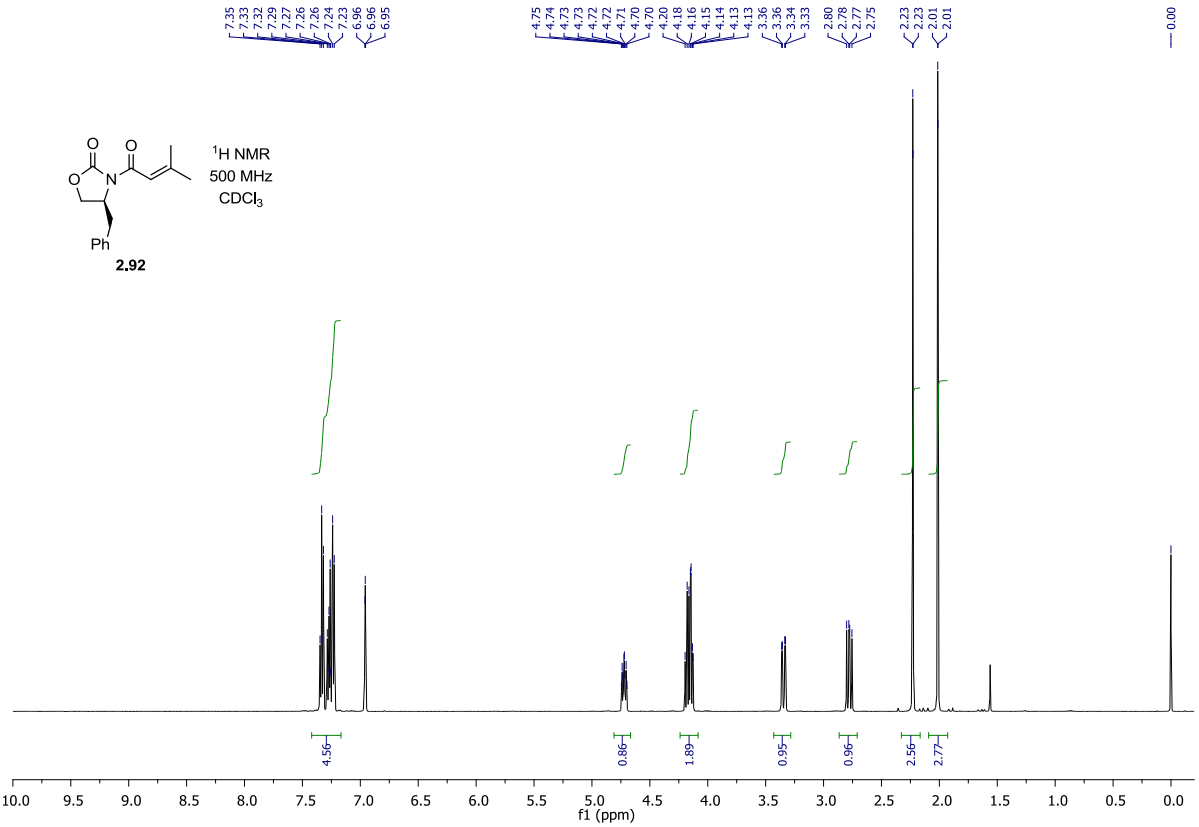
2.85: 5-*epi*-garcibracteatone

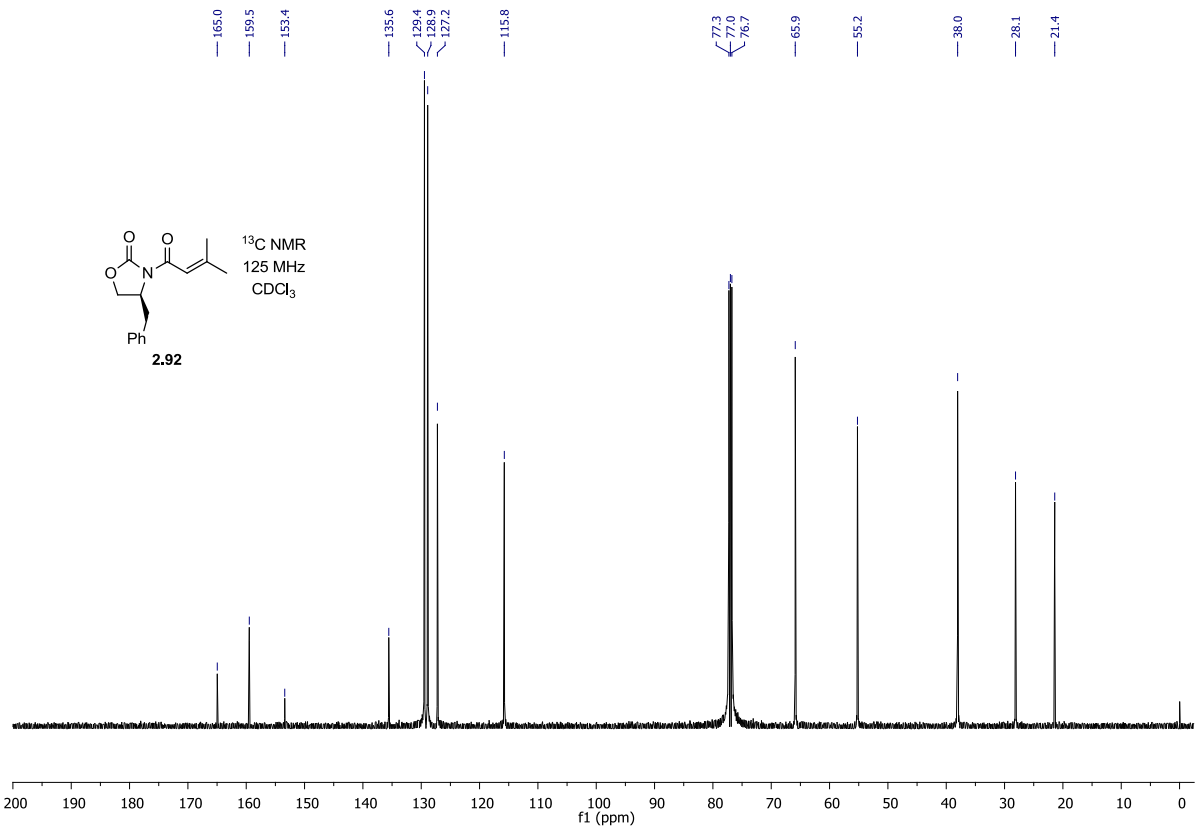

2D COSY
600 MHz
CDCl3
2.85: 5-epi-garcibracteatone
f2 (ppm)
f1 (ppm)

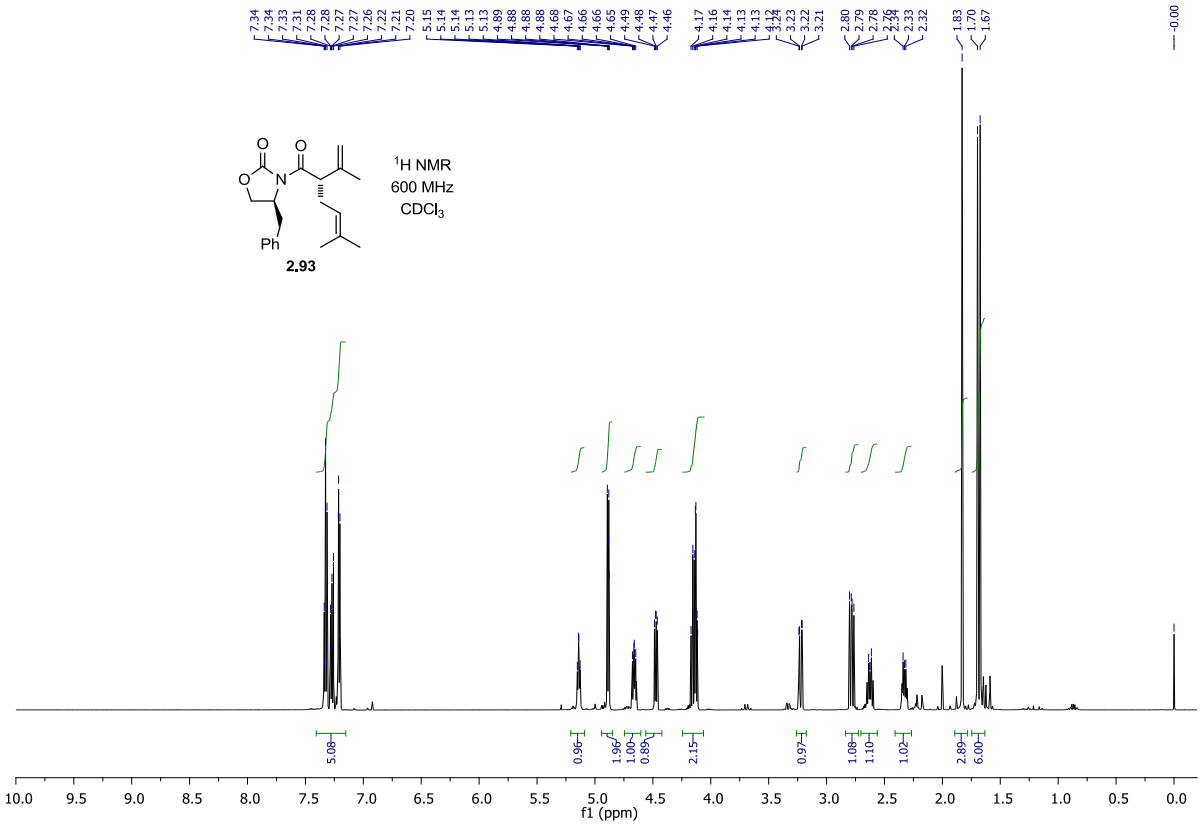

2D HSQC
600 MHz
CDCl3
2.85: 5-epi-garcibracteatone
f2 (ppm)
f1 (ppm)


2D HMBC
600 MHz
$CDCl_3$
2.85: 5-*epi*-garcibracteatone
f2 (ppm)
f1 (ppm)


2D ROESY
600 MHz
$CDCl_3$
2.85: 5-*epi*-garcibracteatone
f2 (ppm)
f1 (ppm)


7.35
7.33
7.32
7.29
7.27
7.26
7.26
7.24
7.23
6.96
6.96
6.95
4.75
4.74
4.73
4.73
4.72
4.72
4.71
4.70
4.70
4.20
4.18
4.16
4.15
4.14
4.13
4.13
3.36
3.36
3.34
3.33
2.80
2.78
2.77
2.75
2.23
2.23
2.01
2.01
0.00
O
O
O
N
Ph
2.92
1H NMR
500 MHz
CDCl3
4.56
0.86
1.89
0.95
0.96
2.56
2.77
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


165.0
159.5
153.4
135.6
129.4
128.9
127.2
115.8
77.3
77.0
76.7
65.9
55.2
38.0
28.1
21.4
O
O
O
N
Ph
2.92
13C NMR
125 MHz
CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.34
7.34
7.33
7.31
7.28
7.28
7.27
7.27
7.26
7.22
7.21
7.20
5.15
5.14
5.14
5.13
5.13
4.89
4.88
4.88
4.88
4.68
4.67
4.66
4.66
4.65
4.49
4.48
4.47
4.46
4.17
4.16
4.14
4.13
4.13
3.24
3.23
3.22
3.21
2.80
2.79
2.78
2.76
2.34
2.33
2.32
1.83
1.70
1.67
0.00
O
O
O
N
Ph
2.93
1H NMR
600 MHz
CDCl3
5.08
0.96
1.96
1.00
0.89
2.15
0.97
1.08
1.10
1.02
2.89
6.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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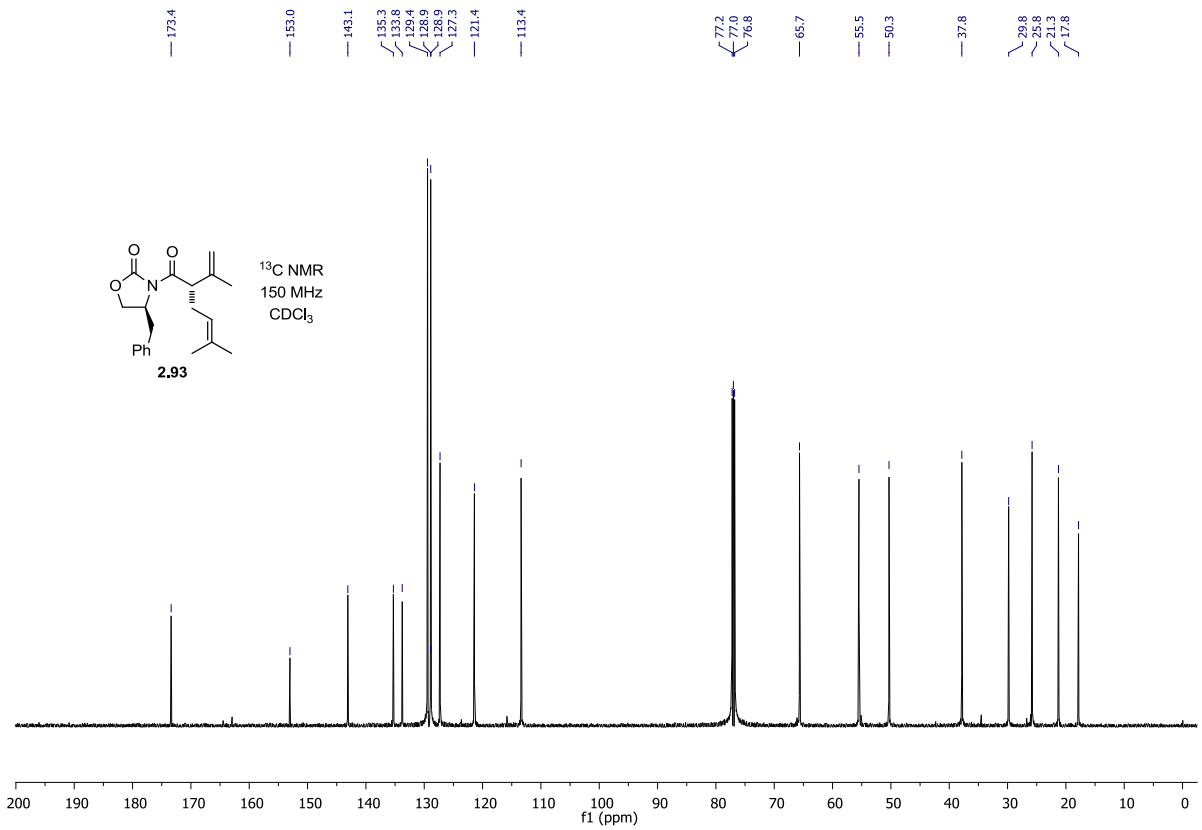
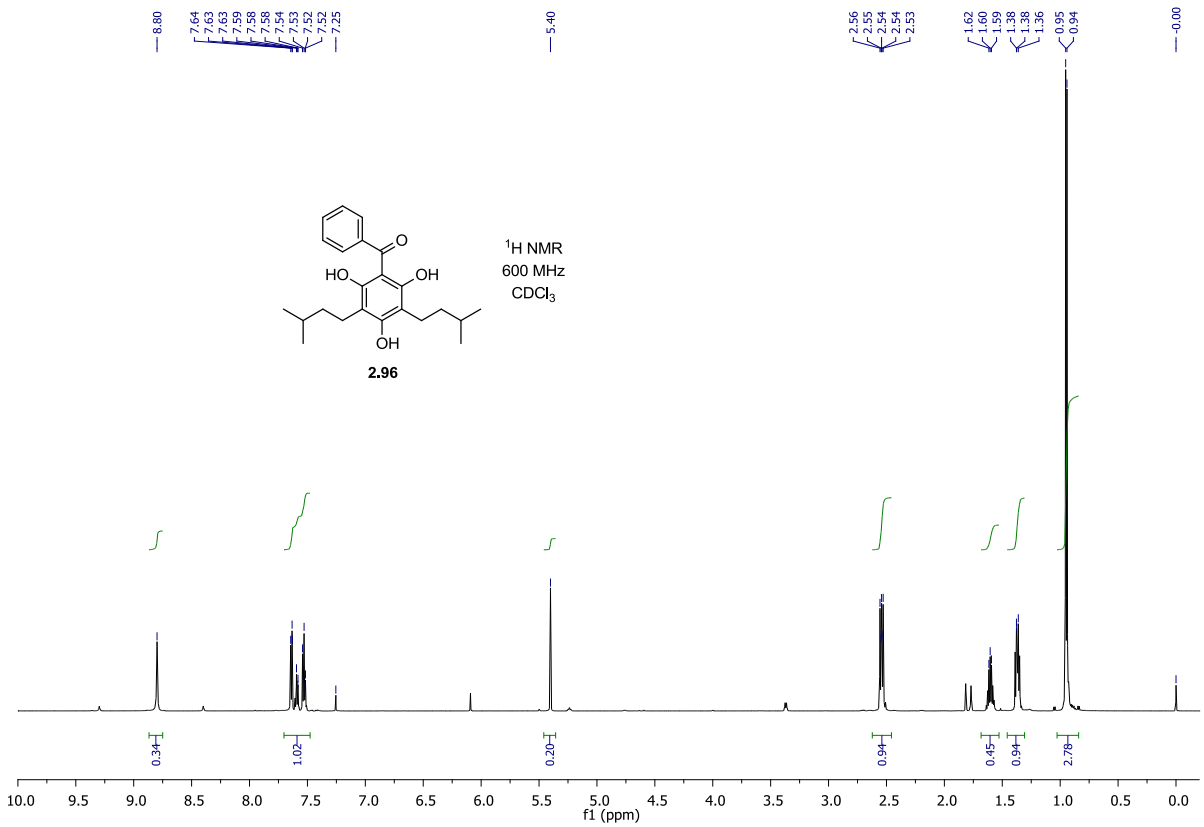
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


173.4
153.0
143.1
135.3
133.8
129.4
128.9
128.9
127.3
121.4
113.4
77.2
77.0
76.8
65.7
55.5
50.3
37.8
29.8
25.8
21.3
17.8
O
O
O
N
Ph
2.93
13C NMR
150 MHz
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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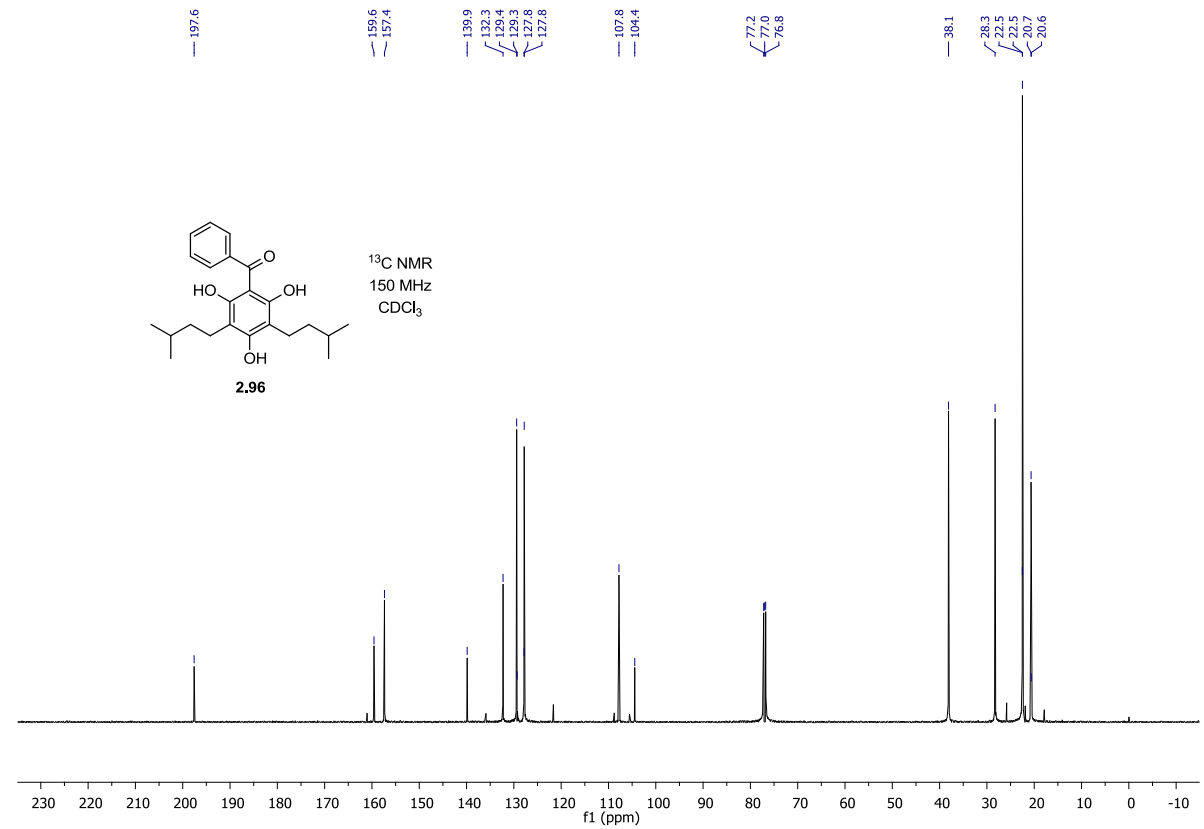
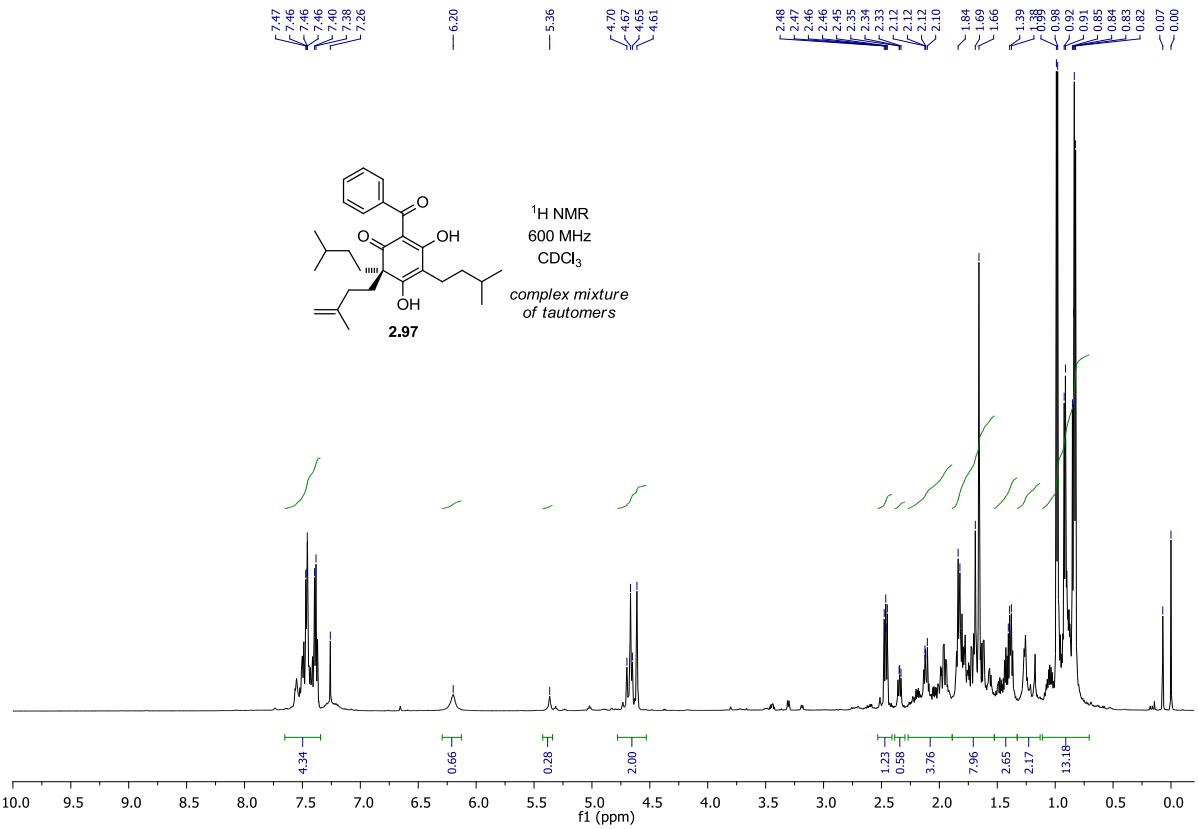
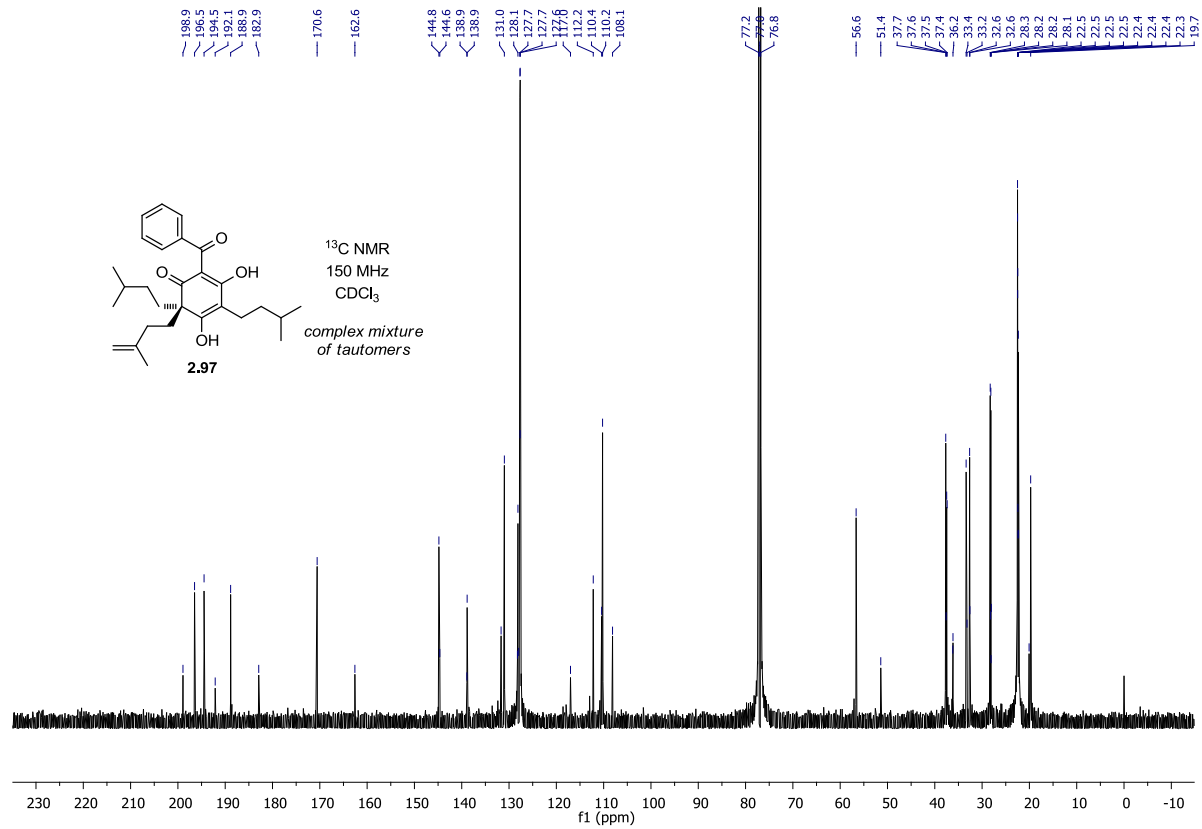
7.64
7.63
7.63
7.59
7.58
7.58
7.54
7.53
7.52
7.52
7.25
5.40
2.56
2.55
2.54
2.54
2.53
1.62
1.60
1.59
1.38
1.38
1.36
0.95
0.94
-0.00
HO
OH
OH
O
2.96
1H NMR
600 MHz
CDCl3
0.34
1.02
0.20
0.94
0.45
0.94
2.78
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


197.6
159.6
157.4
139.9
132.3
129.4
129.3
127.8
127.8
107.8
104.4
77.2
77.0
76.8
38.1
28.3
22.5
22.5
20.7
20.6
HO
OH
OH
O
2.96
13C NMR
150 MHz
CDCl3
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
OH
OH
2.97
^{1}H NMR
600 MHz
$CDCl_3$
complex mixture
of tautomers
f1 (ppm)


O
O
OH
OH
2.97
^{13}C NMR
150 MHz
$CDCl_3$
complex mixture
of tautomers
f1 (ppm)

Crystal data for 2.78, garcibracteatone (2.55) and 5-*epi*-garcibracteatone (2.85)

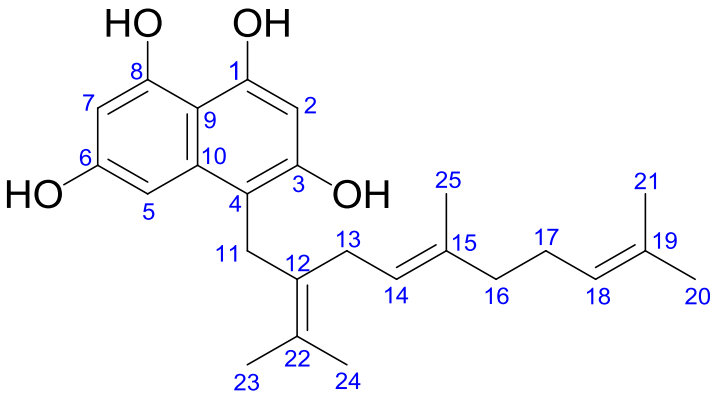
Compound	**2.78**
Empirical formula	$C_{28}H_{32}O_4$
Formula weight	432.55
Crystal system	monoclinic
Space group	P -1
a (Å)	7.5132(4)
b (Å)	12.0010(9)
c (Å)	13.3750(9)
α (°)	78.084(6)
β (°)	79.260(5)
γ (°)	73.336(6)
Volume ($Å^3$)	1119.98
Z	2
R-Factor %	5.22

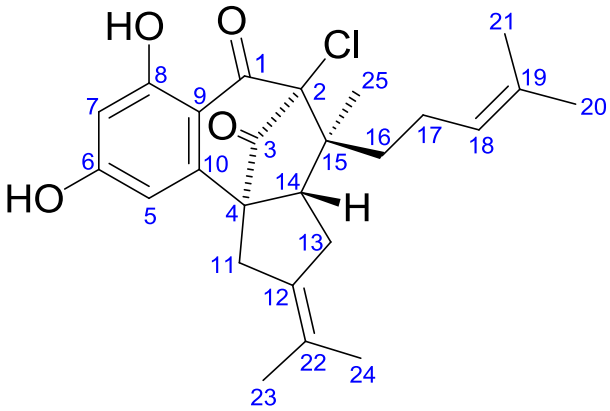
Compound	**garcibracteatone (2.55)**
Empirical formula	$C_{33}H_{40}O_4$
Formula weight	500.65
Crystal system	monoclinic
Space group	$P2_1/c$
a (Å)	15.2492(4)
b (Å)	7.6175(2)
c (Å)	23.1871(6)
α (°)	90
β (°)	91.092(2)
γ (°)	90
Volume ($Å^3$)	2692.94
Z	4
R-Factor %	5.1

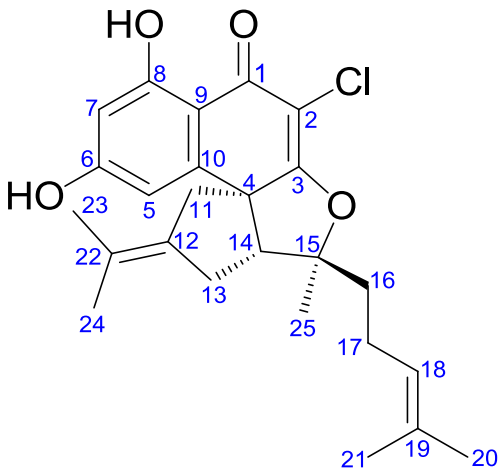
Compound	**5-*epi*-garcibracteatone(2.85)**
Empirical formula	$C_{33}H_{40}O_4$
Formula weight	500.65
Crystal system	monoclinic
Space group	C2/*c*
a (Å)	21.9005(8)
b (Å)	11.9505(4)
c (Å)	21.1324(9)
α (°)	90
β (°)	104.066(4)
γ (°)	90
Volume ($Å^3$)	5365.0
Z	8
R-Factor %	5.25

CHAPTER 3

Biomimetic Synthesis of Merochlorin A







Carbon atoms of merochlorins and related synthetic intermediates will be referred to numerically as per these diagrams for the length of this chapter.

3.1 Introduction

3.1.1 Halogenated Natural Products

Once considered to be rare in nature, the number of known natural products containing at least one halogen atom in their structure was reported to be over 5000 in 2015.[1] A wide structural diversity of halogenated compounds are observed in nature, ranging from nucleosides, peptides, lipids, terpenoids, polyketides and alkaloids.[2] While natural products containing halogens have been isolated from terrestrial plants, fungi and bacteria, the majority of organohalogen natural products are marine in origin.[2]

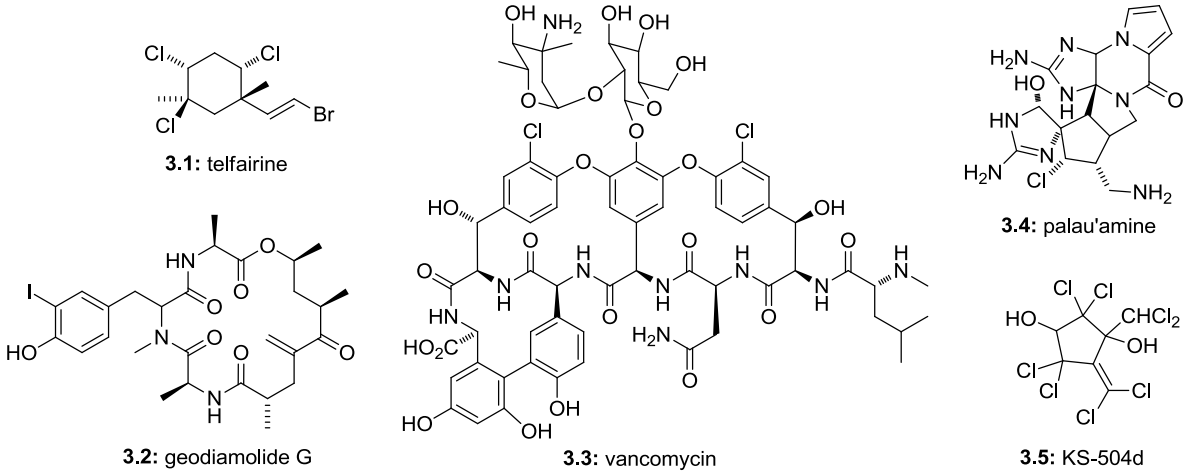
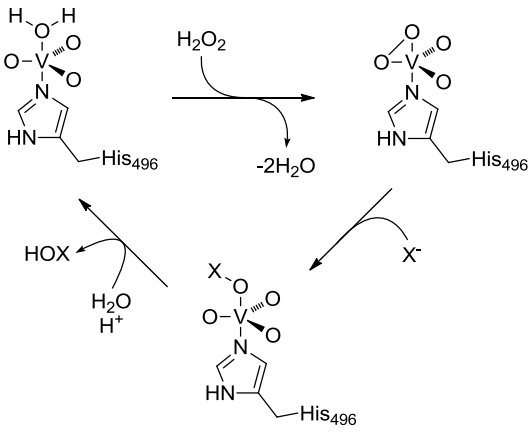


Figure 3.1: Example organohalogen natural products[3-7]

Many organohalogen natural products have potent biological activities and have had wide applications. The glycopeptide natural product vancomycin (**3.3**) produced by the soil bacterium *Amycolatopsis orientalis* is a potent antibiotic which has been used to treat life threatening infections for over 40 years.[3] Along with synthetic compounds such as DDT, many natural organohalogen have insecticidal properties such as the monoterpene telfairin (**3.1**), derived from the marie algae *Plocamium telfairine*.[4] The wide variety of fascinating chemical structures and potent activities of organohalogen natural products make them attractive targets for chemical synthesis.

3.1.2 Vanadium-Dependant Haloperoxidases: Nature's Halogenation Catalysts

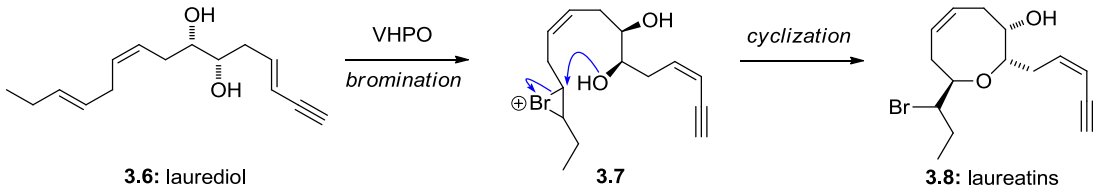
With the discovery of new halogenated natural products, the enzymes responsible for the incorporation of halogen atoms into their structures have also been discovered. Haem haloperoxidases, non-haem iron halogenases and non-metallo haloperoxidases such as flavin dependent halogenases are some examples of such enzymes, which and have been found to catalyze halogenation reactions in a wide variety of organisms.[8] One class of halogenating enzymes are the vanadium-dependant haloperoxidases (VHPO).[9] With an average concentration of 35-50 nM, vanadium is the second most abundant transition metal in the ocean; hence VHPOs are particularly relevant in marine organisms and have been identified in species of marine bacteria, fungi and seaweed.[9] The vanadate centre in the active site of these enzymes is responsible for the oxidation of halides to reactive hypohalous acids with hydrogen peroxide.



Scheme 3.1: Catalytic cycle of VHPOs (X = Cl, Br or I)[9]

The catalytic cycle (**scheme 3.1**) shows that H_2O_2 coordinates to the vanadium centre *via* Lewis acid/base interactions, which activates the peroxide through charge separation towards nucleophilic attack from a halide ion. Protonation of the resultant hypohalite species with H_2O then generates the reactive hypohalous acid. Hypohalous acids (HOX) are chemically equivalent to electrophilic halogen (X^+) and react with nucleophilic sites in organic compounds, such as alkenes and aromatic rings, to generate the wide variety of halogenated natural products that are observed. In the absence of a suitable organic substrate, the HOX quickly reacts with another molecule of H_2O_2 to form oxygen; hence, substrates must be

bound in the active site for halogenation to occur, resulting in the high degree of substrate specificity and stereoselectivity. VHPOs are classified by the most electronegative halide which is readily oxidized; therefore, vanadium-dependent chloroperoxidases are able to oxidize chloride, bromide and iodide while vanadium-dependent bromoperoxidases are only able to oxidize bromide and iodide.[10] The mechanism of these enzymes does not involve change in oxidation state of the vanadium centre; hence, there is no risk of oxidative inactivation during turnover for these catalysts. This fact makes VHPOs attractive for use in synthetic applications as biocatalysts, and some successful examples of chemoenzymatic transformations of small organic compounds using VHPOs have been reported.[11]

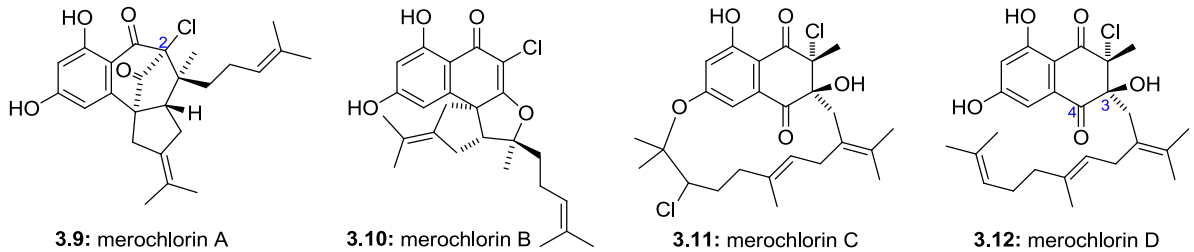


3.6: laurediol **3.7** **3.8:** laureatins

Scheme 3.2: Biosynthesis of laurendiol to laureatins *via* VHPO catalyzed bromonium cyclization[12]

A well understood example of a biosynthetic transformation catalyzed by a VHPO is the conversion of laurediol (**3.6**) into laureatins (**3.8**).[13] VHPO catalyzed alkene bromination of laurediol results in bromonium cyclization with the alcohol group to generate the 8-membered cycloether of laureatins.[12] The reaction takes place in the active site of the enzyme, resulting in the high degree of regioselectivity and diastereoselectivity observed.

3.1.3 Merochlorins A-D: Cyclic Chlorinated Marine Meroterpenoids

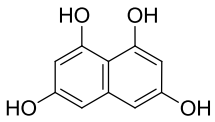


3.9: merochlorin A **3.10:** merochlorin B **3.11:** merochlorin C **3.12:** merochlorin D

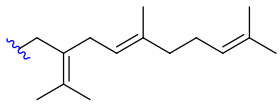
Figure 3.2: Merochlorin natural products[14]

In 2012, a family of four new chlorinated meroterpenoid natural products merochlorins A-D (**3.9-3.12**) were isolated from *Streptomyces* sp. Strain CHN-189[15] collected from a marine

sediment near Oceanside, California.[14] Merochlorins A (**3.9**) and B (**3.10**) were found to have potent antibiotic activities, with MIC values in the range of 2-4 μM against clinically relevant MRSA strains. Merochlorin C (**3.11**) and D (**3.12**) showed weak antibiotic activity.[14,16] The chemical structures of the merochlorins were elucidated by 2D NMR spectroscopy experiments. A crystal structure of a methylated and acetylated derivative of merochlorin A (**3.9**) was solved, resulting in the unambiguous determination of its absolute stereochemistry to be as shown (**figure 3.2**).[14]



3.13: 1,3,6,8-tetrahydroxynaphthalene



3.14: isosesquilavandulyl

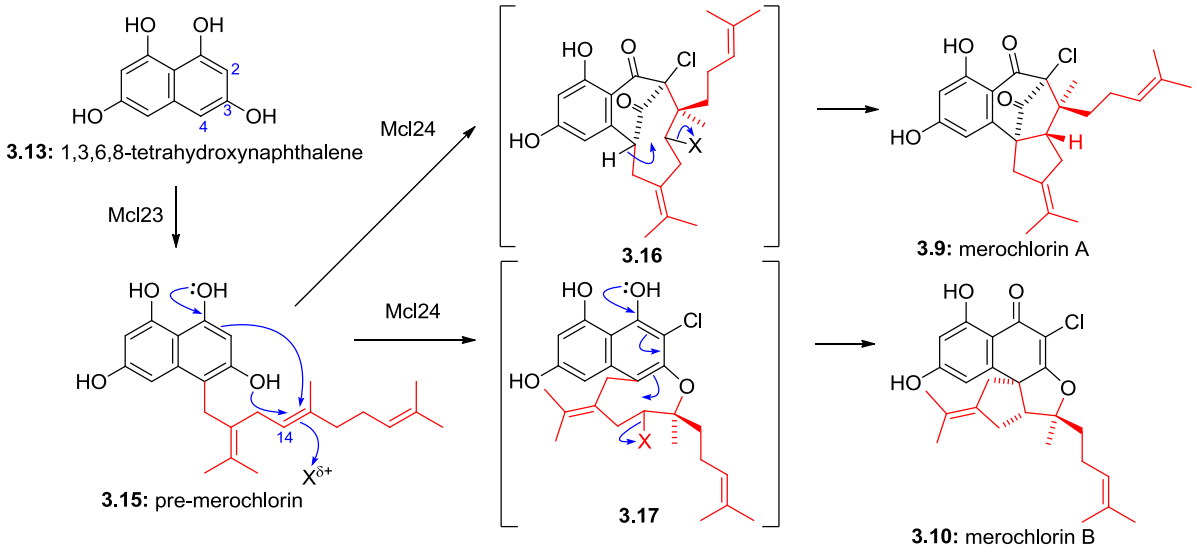
Figure 3.3: Biosynthetic fragments which make up the merochlorins

Structurally, the merochlorins are each fundamentally made up of a 1,3,6,8-tetrahydroxynaphthalene (**3.13**) derived polyketide fragment, and the same 15-carbon isosesquilavandulyl (**3.14**) terpene moiety. Merochlorin A (**3.9**) and B (**3.10**) are structural isomers of each other. The bicyclo[3.2.1]octane ring structure of merochlorin A and the 6-6-5 fused ring system of merochlorin B are the result of unique cyclization reactions between the terpene sidechain and the tetrahydroxynaphthalene core. Merochlorin C (**3.11**) and D (**3.12**) each contain naphthoquinone skeletons, with the substitution of the terpene side chain being at the C-3 position in contrast to the C-4 position like in merochlorins A and B. The C-2 chlorine atom common to all four members suggests the involvement of halogenating enzymes in their biosynthesis. The macrocyclic structure of merochlorin C (**3.11**) is also the probable result of chloronium cyclization induced by a halogenating enzyme. The potent antibiotic activity and intriguing tetracyclic ring structures of merochlorin A and B make them attractive targets for total synthesis.

3.1.4 Proposed Biosynthesis of Merochlorins A and B

In addition to the isolation and characterization of the merochlorins, Moore *et al.* reported a thorough investigation into the genome responsible for merochlorin production, sequenced from the CNH-189 bacterium. Their investigations revealed several genes corresponding to enzymes responsible for merochlorin production. Three genes in particular were found to be

necessary for the production of merochlorins A and B: a THN synthase (Mcl17), an aromatic prenyl transferase (Mcl23) and a vanadium-dependent haloperoxidase (Mcl24). Based on these observations, Moore *et al.* tentatively proposed a biosynthetic origin for the merochlorins (**scheme 3.3**).[14]

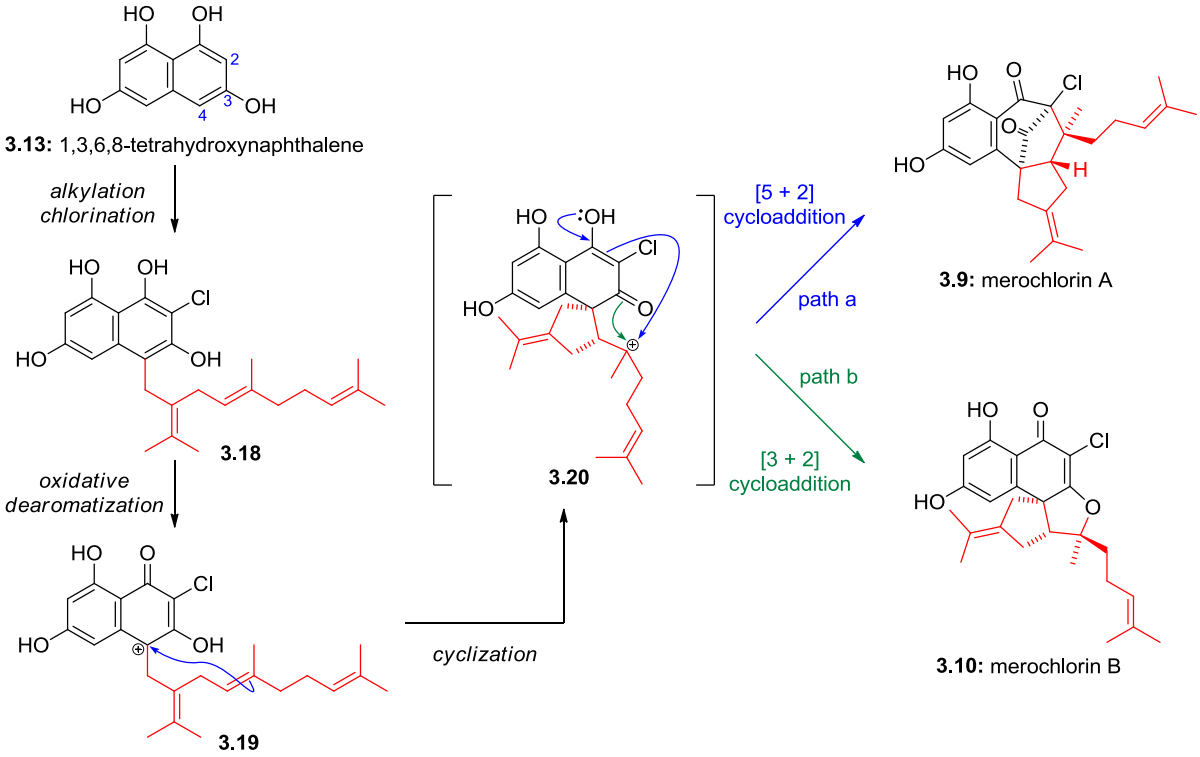


Scheme 3.3: Originally proposed biosynthesis of merochlorins A and B (X = O or Cl)

Knowing that the Mcl17 gene is necessary for merochlorin production confirmed THN (**3.13**) to be a biosynthetic intermediate. THN is presumably alkylated at the C-4 position by Mcl23 to give pre-merochlorin (**3.15**). It was then proposed that the VHPO Mcl24 is responsible for both the incorporation of chlorine at the C-2 position as well as oxidation of the C-14 alkene. Chloronium cyclization or alternatively epoxide cyclization at either the C-2 or the C-3 oxygen atom would yield merochlorin A (**3.9**) or merochlorin B (**3.10**), respectively. These cyclization cascade events were proposed to occur through the eight-membered ring intermediates **3.16** and **3.17**.[14]

The cyclization mechanism proposed by Moore *et al.* for the biosynthesis of merochlorin A and B was by their own admission highly speculative; we herein propose an alternative which we believe is more synthetically reasonable. We are in agreement that Mcl23 and Mcl24 are responsible for alkylation at the C-4 position and chlorination at the C-2 position. We then propose that oxidative dearomatization of **3.18** would generate the reactive phenoxonium ion **3.19** which could cyclize *via* a [5 + 2] cycloaddition to give **3.9**, or *via* a [3 + 2] cycloaddition to give **3.10**. These cycloadditions are presumably step-wise in mechanism. In nature the oxidative dearomatization event could perhaps be catalyzed by the putative iron-sulfur cluster

containing protein encoded by Mcl30,[14] or alternatively could be catalyzed by the same VHPO Mcl24 responsible for chlorination.



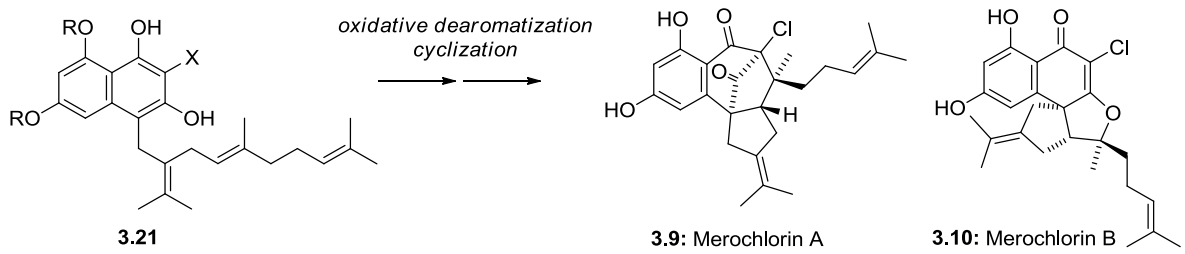
Scheme 3.4: Our proposed biosynthesis of merochlorins A and B

Similar [5 + 2] cycloadditions have previously been proposed to occur in the biosynthesis of other natural products,[17,18] however we believe our suggested pathway to merochlorin A to be the first biosynthetic proposal of an intramolecular [5 + 2] cycloaddition directly initiated by oxidative dearomatization.

3.1.5 Project Aims

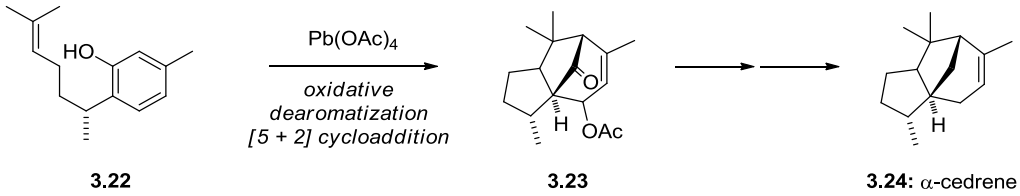
We aimed to test our proposal for the biosynthesis of merochlorins A (**3.9**) and B (**3.10**) involving cyclization events induced by oxidative dearomatization by testing the feasibility of these processes synthetically. Preparation of an intermediate such as **3.21** and subsequently subjecting it to oxidative dearomatization conditions would hopefully result in the tetracyclic ring skeletons of merochlorins A (**3.9**) and/or B (**3.10**). If successful, the total synthesis of these natural products could then be pursued. This approach should lead to a concise synthesis of these unique meroterpenoid natural products, which at this point in time had yet

to be synthesized. Formation of either of these natural products *via* oxidative dearomatization-induced cyclization in the lab would give strong insight that a similar process occurs in their biosynthesis.



Scheme 3.5: Proposed research: biomimetic synthesis of merochlorin A and B *via* biomimetic cyclization reactions induced by oxidative dearomatization (X = H or Cl)

Literature precedent for an oxidative dearomatization process directly inducing a cycloaddition is limited; however, a related example was reported by Pettus *et al.* in 2010. Oxidative dearomatization with $Pb(OAc)_4$ of the phenol **3.22** was found to result in formation of the tricyclic product **3.23** *via* [5 +2] cycloaddition of the aromatic core with the alkene side chain. A two step modification of **3.23** completed the total synthesis of the sesquiterpene natural product α-cedrene (**3.24**).[19] This successful example gave good precedent that our proposed biomimetic reaction may be feasible under similar conditions.



Scheme 3.6: Synthesis of α-cedrene by Pettus *et al.* involving an oxidative dearomatization-induced [5 + 2] cycloaddition[19]

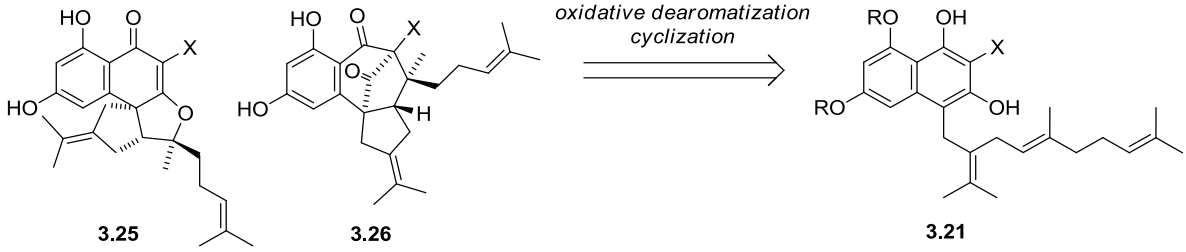
The required key synthetic intermediate **3.21** is made up of a THN fragment and an isosesquilavandulyl fragment. The synthesis of THN compounds was limited in the literature at the time of starting this project and the synthesis of isosesquilavandulyl compounds was completely unexplored. This research would require the exploration of these areas of synthetic chemistry, resulting in the addition of new methods to the literature. As both meochlorins A (**3.9**) and B (**3.10**) have shown to display strong antibiotic activity, the development of a practical total synthesis would be invaluable in the further exploration of

these compounds as potential antibiotics. Our developed synthetic method should be applicable for the synthesis of merochlorin analogues which could be used to investigate the SARs of these compounds.

3.2 Results and Discussion

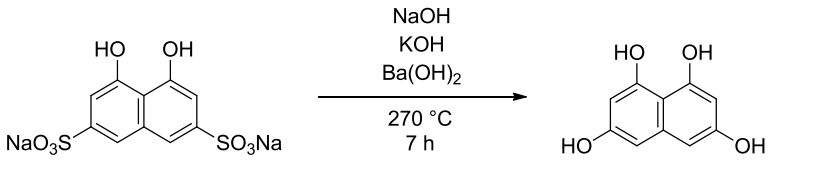
3.2.1 Initial Retrosynthesis of Merochlorins A and B

In order to test our proposed cyclization reactions to yield the skeletons of merochlorin A and/or merochlorin B, an intermediate such as **3.21** needed to be synthesized. The pre-merochlorin like intermediate **3.21** is made up of a polyketide derived THN fragment and a terpene derived isosesquilavandulyl chain; therefore, syntheses of both fragments would need to be developed.



Scheme 3.7: Retrosynthetic analysis of merochlorin A and merochlorin B (X = H or Cl)

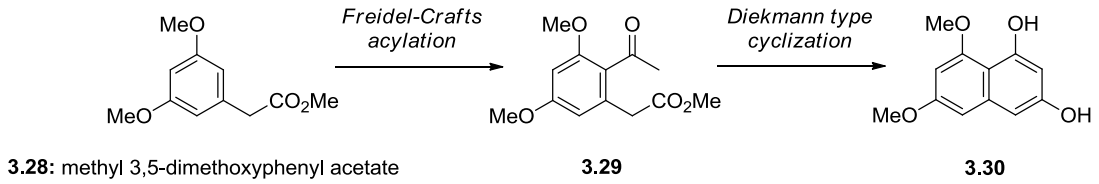
THN (**3.13**) itself is not commercially available, presumably due to its instability to air. There were several reports in the literature of the synthesis of THN from commercially available chromotropic acid disodium salt (**3.27**) *via* a technically challenging alkali fusion process, involving molten NaOH (**scheme 3.8**).[20-23] This was an undesirable option as the equipment needed to perform this alkali fusion reaction safely and reliably was not available, and we also hypothesized that use of a partially protected intermediate would be a more reasonable starting point than THN itself.



Scheme 3.8: Literature synthesis of THN from chromotropic acid disodium salt[20-23]

The only other literature option for the synthesis of THN compounds was the method employed by Barrow *et al.*[24,25] and other research groups,[26,27] which was to form the second

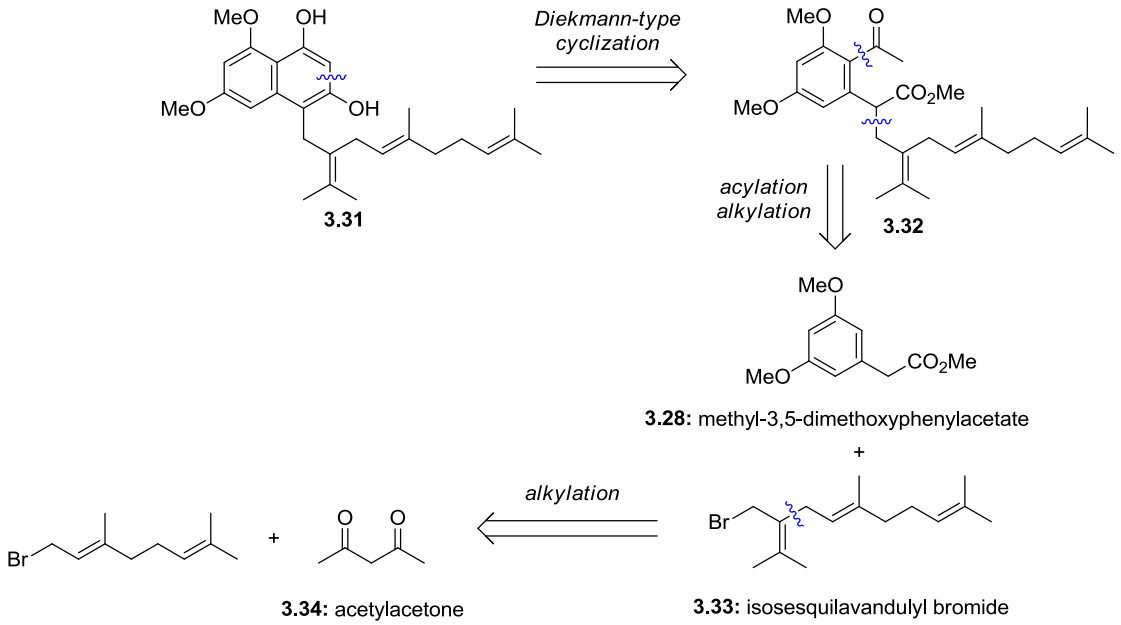
fused aromatic ring *via* a Dieckmann type condensation between an aryl methyl ketone and an ester (**scheme 3.9**).



3.28: methyl 3,5-dimethoxyphenyl acetate **3.29** **3.30**

Scheme 3.9: Literature synthetic approach to 1,3-dihydroxy-6,8-dimethoxynaphthalene[25]

With this approach in mind, we hypothesized a plausible retrosynthesis of **3.21** which would involve α-alkylation of an ester with isosesquilavandulyl bromide **3.33** along with the Dieckmann strategy to yield the THN moeity (**scheme 3.10**). Bromide **3.33** could be derived from acetylacetone (**3.34**) and geranyl bromide by modification of a previously reported synthesis of isolavandulyl bromide.[28] We opted to conduct this work with non-chlorinated intermediates to start with in order to simplify the synthesis. Investigations of the most practical point to introduce the required chlorine atom would be undertaken following the success of the cyclization reaction on the non-chlorinated system.



3.31 **3.32**

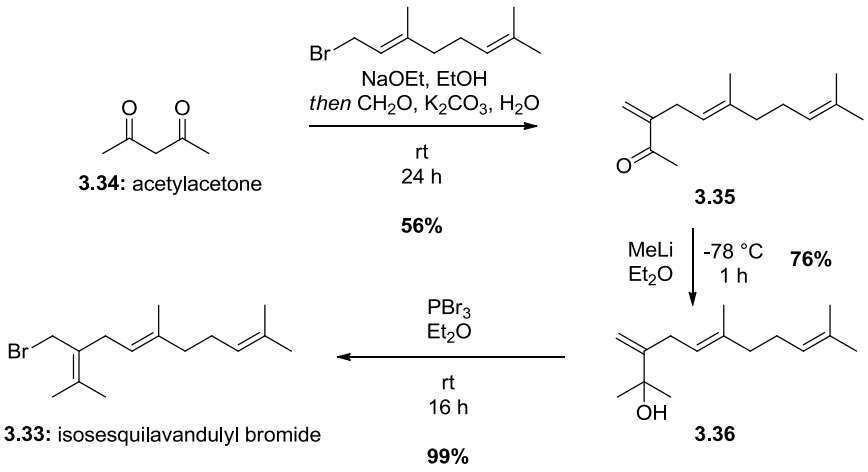
3.28: methyl-3,5-dimethoxyphenylacetate

3.34: acetylacetone **3.33:** isosesquilavandulyl bromide

Scheme 3.10: Retrosynthetic analysis of key intermediate **3.31**

The first target was the terpene derived fragment, which required the synthesis of the previously unreported isosesquilavandulyl bromide (**3.33**). Following the procedure of

Plietker *et al.*, the α-β-unsaturated ketone **3.35** was synthesized in one pot from acteylacetone (**3.34**), geranyl bromide and formaldehyde under basic conditions.[29] This operation involved two successive reactions: the mono alkylation of acetylacetone with geranyl bromide, followed by aldol reaction which induces deacylation with formaldehyde. This deacylating aldol-type α-methylenation process is presumably analogous in mechanism to the Horner-Wadsworth-Emmons olefination.[30] Purification of **3.35** was found to be challenging as its boiling point was slightly too high for distillation to be practical using the available apparatus. Therefore, purification needed to be performed by a difficult flash column which limited the production scale to no more than 10 g of acetylacetone (**3.34**).

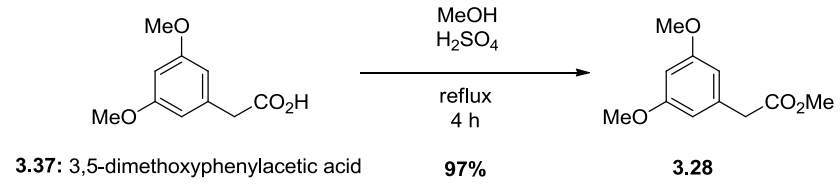


Scheme 3.11: Synthesis of isosesquilavandulyl bromide

1,2-addition of MeLi to the ketone of **3.35** at -78 °C then yielded the tertiary alcohol **3.36**. As long as the starting material **3.35** had been purified adequately, this reaction was straightforward, reliable and proceeded in good yield of 76%. Finally, *β*-bromination of the *α,β*-unsaturated alcohol **3.36** with PBr_3 gave the allylic bromide **3.33** with a concomitant migration of the double bond to the internal position.[28] The isosesquilavandulyl bromide **3.33** was found to be unstable to light and samples would turn dark over time. Interestingly, it was also found to be highly unstable to SiO_2 as attempts to purify by flash chromatography resulted in rapid decomposition. Therefore, **3.33** was routinely used immediately after aqueous workup without further purification.

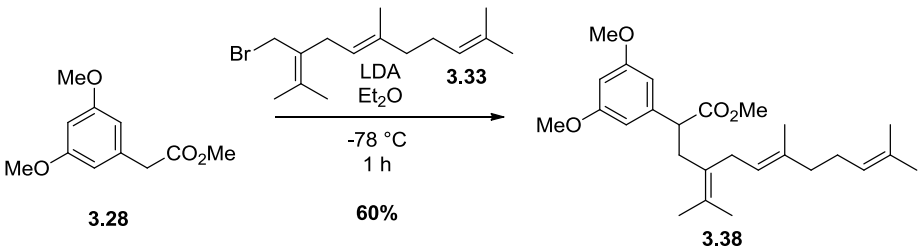
Methyl-3,5-dimethoxyphenylacetic acid (**3.28**), the chosen starting material for the polyketide derived fragment, was not commercially available in reasonable quantities. We found the most practical way to access this compound was to purchase the inexpensive 3,5-dimethoxyphenylacetic acid (**3.37**) and convert it into **3.28** *via* a simple Fischer esterification

procedure, with refluxing MeOH and catalytic H_2SO_4, which proceeded in near quantitative yield (**scheme 3.12**).[31]



Scheme 3.12: Esterification of 3,5-dimethoxyphenylacetic acid[31]

With methyl-3,5-dimethoxyphenylacetate (**3.28**) and isosesquilavandulyl bromide (**3.33**) in hand, we first attempted the union between the two fragments. Under standard conditions using LDA to form the enolate from the ester at low temperature, alkylation proceeded smoothly at the desired position in 60% yield (**scheme 3.13**).

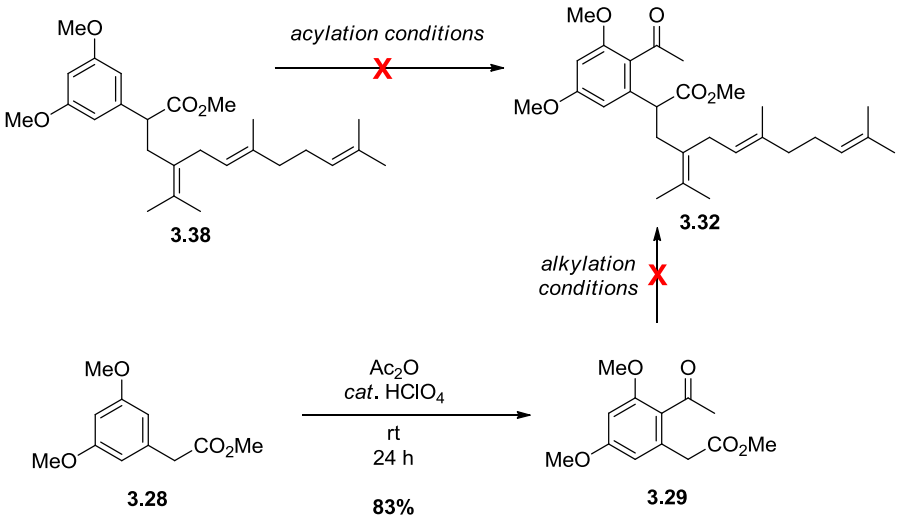


Scheme 3.13: α-Alkylation of methyl-3,5-dimethoxyphenylacetate

The plan next was to install an acetyl group on the aromatic ring of **3.38** to form **3.32**, which is primed for Dieckmann-type cyclization. The Friedel-Crafts acylation conditions reported by Barrow *et al.* using Ac_2O with catalytic $HClO_4$ led to undesirable results.[24] The acidic conditions provided were found to quickly cause side reactions with the alkene groups present in the terpene side chain. Other Friedel-Crafts conditions trialed using Lewis acids led to similar outcomes. Attempting this transformation using other methods such as the Vilsmeier-Haack reaction were also unsuccessful.[32]

The next logical step was to reverse the sequence of operations, performing the Friedel-Crafts reaction before alkylation. Hence, Friedel-Crafts acylation of methyl-3,5-dimethoxyphenylacetate (**3.28**) with Ac_2O and catalytic $HClO_4$ gave the acylated compound **3.29** in 83% yield.[24] Perhaps unsurprisingly, attempts to selectively alkylate **3.39** failed to yield the desired product. The presence of the second enolizable carbonyl group complicated the reaction, and would result in cyclization rather than the desired alkylation. Several bases

were screened, and care was taken control the equivalency of reagents added to maximize the formation of the thermodynamic enolate, with no success.

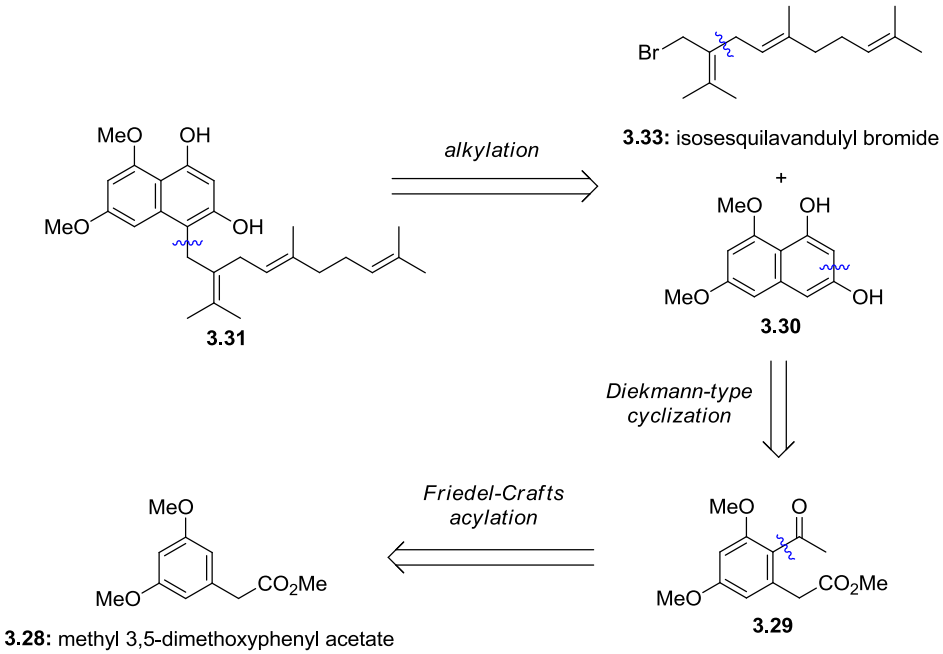


Scheme 3.14: Unsuccessful attempts to synthesize **3.32**[24]

3.2.2 Synthesis of Di-*O*-Methyl Deschloro Merochlorin A

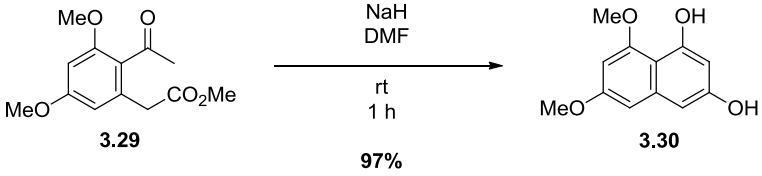
It was clear that our original retrosynthetic analysis as presented contained too many chemoselectivity issues to be viable. We contemplated the possibility of pursuing a more step-wise modification of the route, which would minimize potential selectivity issues. This would involve alkylation of an inert sidechain, which could be transformed into the desired isosesquilavandulyl chain at a later step. Another option would be to protect the aromatic acyl group prior to the alkylation reaction. However, both of these approaches would significantly lengthen the synthesis and we decided to first investigate alternative retrosyntheses which would hopefully entirely avoid chemoselectivity issues.

We then considered the possibility of direct alkylation of a THN type intermediate (**scheme 3.51**). Such a transformation could be thought to be accessible *via* a Pd(0) catalyzed process such as a Stille reation or a Tsuji-Trost type reaction.[33] However, we were more interested in the possibility of direct alkylation using the alkyl bromide under basic conditions, analogous to our previous work with phloroglucinol-type compounds.[34] Consultation of the literature showed that electrophilic aromatic substitution processes performed on similar intermediates were selective for the 4 position. This was good precedent that our enolate-type alkylation process would be similarly selective.[35]



Scheme 3.15: Second generation retrosynthetic analysis of **3.31**

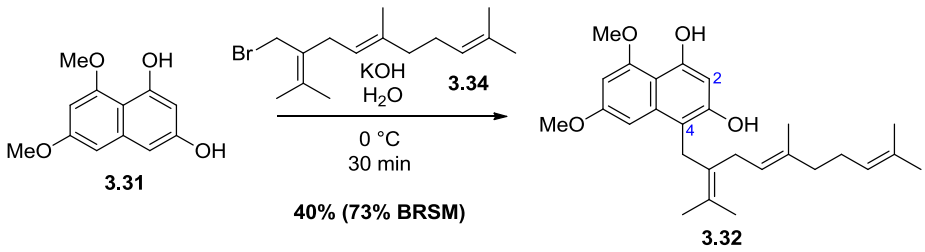
Under the conditions of Barrow *et al.*, aromatization of the aromatic ketone **3.29** *via* Dieckmann type cyclization proceeded in near quantitative yield using NaH in DMF.[24] This reaction was very simple to perform and was reliable and scalable, confirming the aromatization approach to be a practical method to access THN type intermediates.



Scheme 3.16: Aromatization reaction *via* Dieckmann type cyclization[24]

Following similar conditions to our PPAP work,[34] THN **3.30** was treated with KOH in H_2O followed by addition of isosesquilavandulyl **3.32**. TLC analysis showed rapid formation of new products and after isolation, ^{1}H NMR analysis confirmed alkylation had occurred on the aromatic ring. The higher R_f compound contained twice as many signals corresponding to terpene type fragments than the lower R_f compound in the ^{1}H NMR spectrum, and was assumed to be the product of alkylation at both the C-2 and C-4 positions. The data for the lower R_f product was promising, but it was necessary to systematically confirm alkylation had occurred at the desired C-4 postion. 2D NMR analysis, careful examination of the

chemical shifts of the aromatic protons and comparison to similar literature structures agreed that the isolated product was **3.32** as required.[24,35]



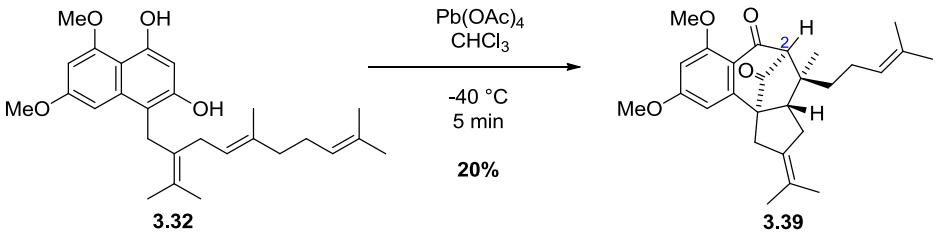
Scheme 3.17: Selective alkylation of **3.31**

By careful control of the amount of base and bromide added, we were able to increase the isolated yield of **3.32** to 40% with 33% starting material being recovered. Attempts to drive this reaction further to completion by addition of more reagents would result in formation of the unwanted dialkylation side product. We were surprised to find that the NMR spectra of **3.32** showed two sets of peaks with almost identical chemical shift in a ratio of ~3 : 1. Repurification of this product did not change this ratio. We hypothesized that a double bond isomerization event could have occurred resulting in a mixture of *E/Z* isomers. However, at this point in time we decided to move forward with the mixture rather than attempting to solve this puzzling observation.

With the key merochlorin precursor compound **3.32** in our possession, it was time to attempt the biomimetic oxidative cyclization reactions. Probably the most similar reaction example in the literature was a [5 + 2] cycloaddition process induced by oxidative dearomatization of different phenol compounds by Pettus *et al.*,[19] who reported $Pb(OAc)_4$ to be the most effective oxidant for the transformations they were interested in (**scheme 3.6**).

With this in mind, we set at to follow the procedure of Pettus *et al.* involving the use of $Pb(OAc)_4$ in $CHCl_3$ using our substrate.[19] The $Pb(OAc)_4$ was freshly recrystallized from AcOH prior to use. The reaction was run in a dilute solution of $CHCl_3$, the concentration presumably being important to minimize potential incorporation of AcOH into the molecule from the acetate ligands *via* a Wessely oxidation process.[36,37] Addition of 1.05 equivalents of $Pb(OAc)_4$ at -40 °C quickly resulted in the complete consumption of the starting material and the formation of new products as observed by TLC analysis. The major product from this reaction was isolated in 20% yield. NMR analysis of the pure product showed that the phenol protons were no longer present, and there were two carbonyl groups present and that one of the alkenes had reacted. These observations, along with the presence of the presumed C-2

bridgehead proton singlet at δ 3.22 and the characteristic pattern of multiplets, lead us to propose we had successfully made the [5 + 2] cycloaddition product **3.39**. This hypothesis was confirmed by analysis of 2D NMR data and comparison to the literature data of merochlorin A.[14]



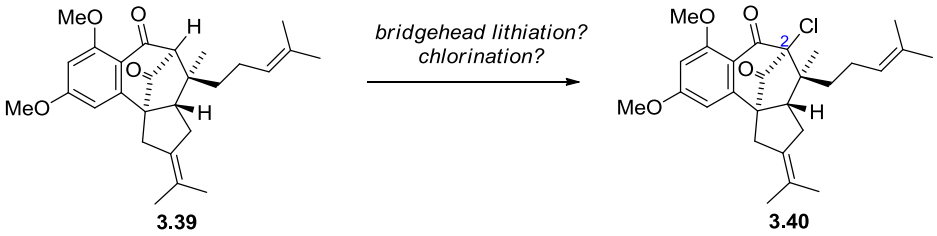
3.32 **3.39**

Scheme 3.18: Oxidative dearomatization cyclization cascade reaction

This result was extremely significant for both our biosynthetic proposal for the merochlorins and our goal of completing the total synthesis of merochlorin A (**3.9**). Still, this work would have greater impact and would lead to further opportunities if we were additionally able to observe the [3 + 2] cycloadditon product. We attempted to isolate the other minor products from this reaction but were unable to obtain pure samples of any of them for conclusive characterization. Despite this, we were able to confirm the absence of any products containing the merochlorin B ring system by analysis of the NMRs of the crude mixtures. We screened some alternative oxidation procedures to explore the effect on yield and product outcome. Hypervalent iodine oxidants such as $PhI(OAc)_2$ and $PhI(OCOCF_3)_2$ gave an identical product mixture to the $Pb(OAc)_4$ procedure, and the [5 +2] cycloaddition product was able to be isolated in similar, albeit slightly worse, yield.[38] However, these reactions were much slower and more difficult to drive to completion. The effect of fluorinated solvents such as CF_3CH_2OH, commonly employed in procedures using these reagents, was inconsequential relative to more traditional solvents such as CH_2Cl_2. Other oxidants trialed, such as DDQ or CAN resulted in decomposition of the starting material.

3.2.3 Introduction of Chlorine

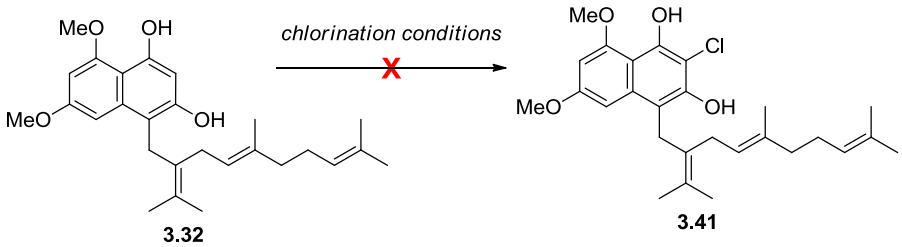
With our newly developed oxidative dearomatization reaction solely forming the [5 + 2] cycloaddition product, we set our next objective to the total synthesis of merochlorin A (**3.9**). In comparison to the natural product, our intermediate **3.39** was only missing the C-2 chlorine atom and the free phenols.



Scheme 3.19: Theoretical bridgehead chlorination reaction

Introduction of a chlorine atom into the C-2 position of **3.39** was theoretically problematic as it would require reaction at the bridgehead position. Such a reaction is typically forbidden by Bredt's rule, which states that the formation of a double bond, carbanion, carbocation or radical is not possible at a bridgehead position, unless the rings are large enough.[39] The bicyclo[3.2.1]octanone bridged ring system of **3.39** was likely too small for reaction to be possible, although there was some literature precedent for similar processes occurring.[40-43] Treatment of **3.39** with strong bases followed by quenching with D_2O resulted in isolation of the unaltered starting material, indicating no bridgehead deprotonation was occurring. With this reaction proving to be impossible as expected, we looked towards chlorination at an earlier point in the synthesis.

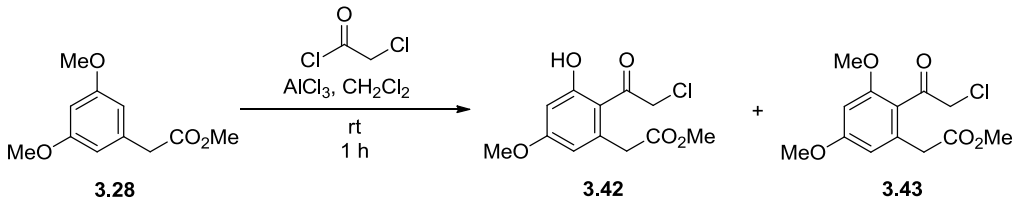
The next point of consideration was chlorination at the previous intermediate in the sequence, the alkylation product **3.32**. Reactions were trialed using either NCS or SO_2Cl_2 as the chlorinating agents. Several conditions were screened involving the presence or absence of various bases, and different temperatures, but unfortunately the desired product **3.41** was never observed. Either no reaction or overchlorination was the outcome, indicating that selective chlorination of this particular compound was a challenging task, and was unlikely to be feasible.



Scheme 3.20: Unsuccessful selective chlorination attempts

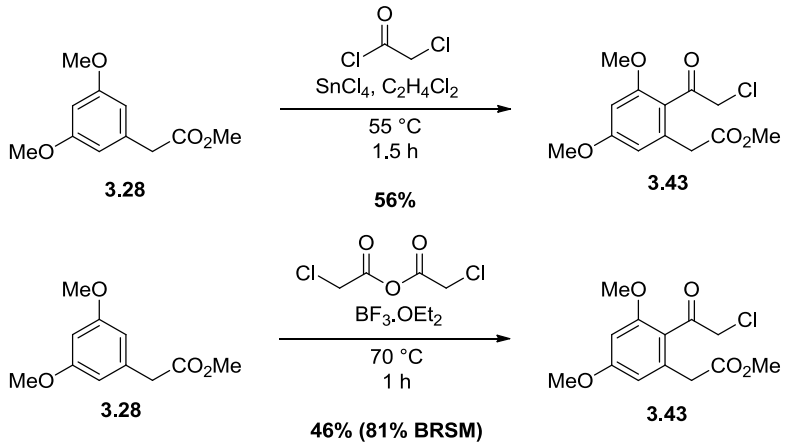
As chlorination of the THN compound **3.31** would likely be selective for the undesired C-4 position, we instead contemplated the possibility of introducing the chlorine atom during the

Friedel-Crafts reaction. The literature revealed that direct installation of a chloroacetyl group onto and aromatic ring *via* a Friedel-Crafts reaction using chloracetyl chloride or alternatively a Houben-Hoesch reaction using chloroacetonitrile was indeed possible.[44,45]



Scheme 3.21: Friedel-Crafts acylation with $AlCl_3$ and chloroacetyl chloride

Standard Friedel-Crafts conditions using chloroacetyl chloride with $AlCl_3$ were first trialed; the TLC of this reaction revealed the formation of multiple products. After isolation and analysis of the NMR spectrum, we determined chloroacetates **3.42** and **3.43** to be the major products of this reaction. The presence of these products confirmed that the chloroacetyl group was successfully being incorporated into the molecule; however, a significant amount of the *ortho* methyl ether was being cleaved in the process. It was evident that this side reaction was occurring too fast to be controlled, so we presumably needed to use a milder Lewis acid. The use of $TiCl_4$ or $SnCl_4$ as the Lewis acid was found to be similarly effective to $AlCl_3$ at promoting Friedel-Crafts acylation but with the complete absence of any undesired deprotection side reactions.



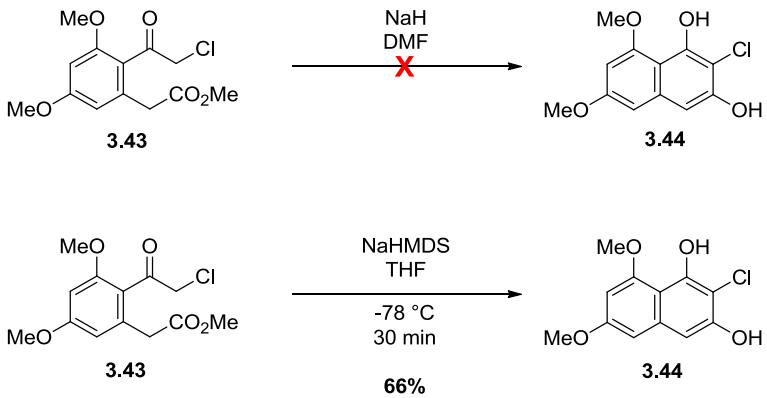
Scheme 3.22: Introdution of chloroacetyl group *via* Friedel-Crafts acylation

While both $TiCl_4$ and $SnCl_4$ were trialed for further reaction optimization, the choice overall did not have much effect on product yield. While our initial procedure of performing the

reaction at room temperature in CH_2Cl_2 yielded the desired product, it was impossible to drive to completion no matter how long it was left stirring, or how many equivalents of Lewis acid or chloroacetyl chloride were added. While the unreacted starting material could be easily recovered and we could achieve a reasonable result of around 40% yield with 40% recovered starting material, this reaction was still worth investigating further. We determined that by changing the solvent to the higher boiling point $C_2H_4Cl_2$ and warming the reaction mixture up to just 55 °C would result in a much shorter reaction time and allow the reaction to reach completion in a modest yield of 56%. The reaction was also trialed using chloroacetic anhydride as the electrophile. We were able to achieve limited conversion into the desired product with analogous conditions to previous (**scheme 3.14**) using catalytic $HClO_4$ if the temperature was elevated. Reaction with chloroacetic anhydride could be improved by changing the acid to $BF_3.OEt_2$ resulting in a reasonable conversion of 46%. While the chloroacetyl chloride reaction was the preferable procedure for scale up, the use of chloroacetic anhydride was perhaps more novel and involved the use of less toxic reagents.

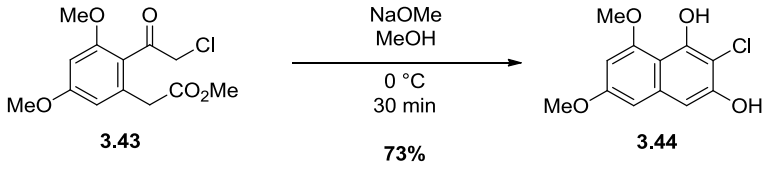
3.2.4 Synthesis of Di-*O*-Methyl Merochlorin A

With ample quantities of the chloroacetate **3.43** available we were set to proceed with the seemingly straightforward task of repeating the aromatization, alkylation and cyclization reactions on the chlorinated system. Early testing proved the aromatization reaction to be problematic, as our previously successful conditions of NaH in DMF lead to decomposition of this substrate (**scheme 3.23**). Assuming milder conditions were required, we opted to use the hindered amide base NaHMDS at -78 °C. These conditions were successful in producing the desired aromatized compound **3.44** in 66% yield.



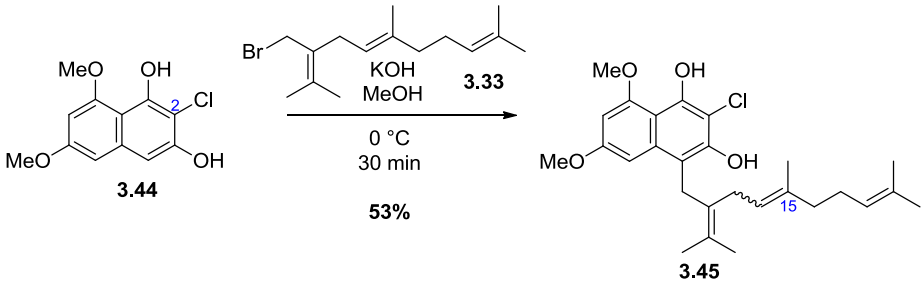
Scheme 3.23: Early attempts at the aromatization reaction on the chlorinated system

However, yields were found to fluctuate when this reaction was repeated and it was difficult to drive to completion. Subtle alterations to the reaction conditions, such as a longer reaction time or warmer temperature would lead to quick decomposition. Desiring a more robust reaction, we discovered that the use of a polar protic solvent was the key to avoiding unwanted side reactions. Performing the reaction with NaOMe as the base in MeOH at 0 °C resulted in a respectable yield of 73% with no risk of decomposition. It was unclear why such a subtle change had such a dramatic effect on the outcome; one possible explanation might be that the use of a polar protic solvent discourages potential S_N2 side reactions.



Scheme 3.24: Base induced aromatization

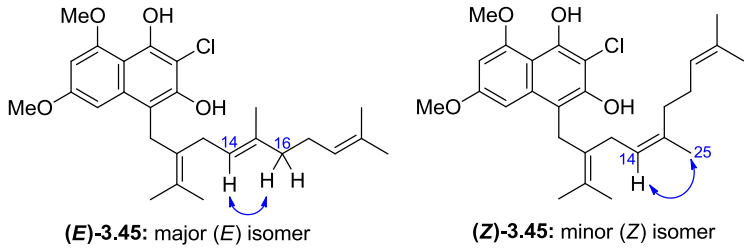
Initial attempts to perform the alkylation reaction on the chlorinated substrate under the same conditions as previous resulted in no reaction, and starting material was recovered. Fortunately, this problem was easily resolved by changing the solvent to MeOH, achieving full conversion and a yield of the desired product of 53%. The unreactivity of this particular substrate in H_2O could be explained as a simple solubility issue. This reaction was found to be far more robust than on the non-chlorinated system, giving a higher yield. This improvement was an obvious result of the chlorine atom blocking undesired alkylation from occurring at the C-2 position, which was previously the cause of some difficulties.



Scheme 3.25: Alkylation of **3.44**

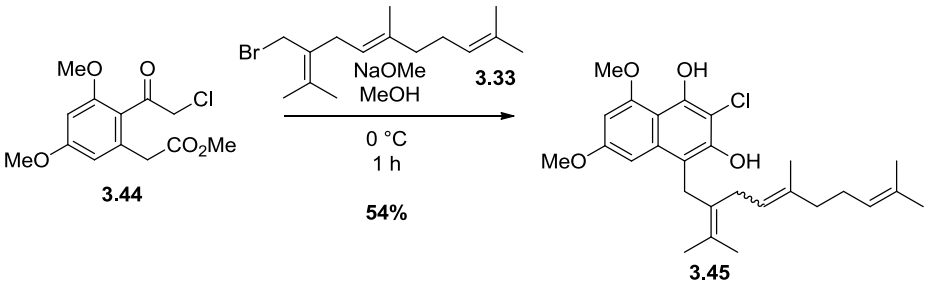
As observed with the non-chlorinated intermediate **3.32**, the product of this reaction also existed as an inseparable mixture of two nearly identical compounds, which we predicted to

be likely explained by *E/Z* isomerization of the C-15 alkene. This hypothesis was investigated with 2D NOESY NMR studies. Careful analysis of the spectrum revealed that the less abundant H-9 proton signal (δ 4.88 t) showed a cross peak with the C-25 methyl group (δ 1.49 s). This cross peak was not observed in the more abundant set of peaks, and instead a cross peak was present between the H-9 proton (δ 4.88 t) and the H-16 protons (δ 1.77 m).



Scheme 3.26: 2D NOESY study of **3.45** (arrow indicates an observed cross peak observed between those protons)

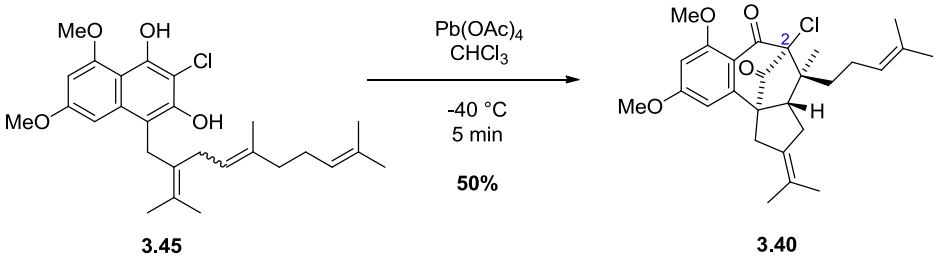
This evidence allowed us to confidently conclude that **3.45** indeed existed as a mixture of *E*/*Z* isomers, with the *E* being the more abundant isomer in a ratio of approximately 3 : 1. As the starting material we were using was the pure *E* isomer, this was a puzzling observation as clearly an isomerization event was occurring. Presumably, some sort of reversible side reaction was taking place at the C-15 alkene under the alkylation conditions, resulting in the observed isomerization.



Scheme 3.27: One pot alkylation/aromatization reaction

As our developed aromatization and alkylation reactions took place under very similar reaction conditions and precise control of reagent amounts was not necessary, we hypothesized that the two processes could effectively be performed in one pot. To test this, we trialed an alkylation reaction with the chloroacetate compound **3.44**, and added **3.33** to the reaction mixture when aromatization had reached completion by TLC analysis. This was an

immediate success and we were able to obtain the desired product **3.45** in 54% yield, with no sacrifice of purity. Overall this two reaction one pot procedure was found to be higher yielding, more reliable and much easier to perform than then two step alternative. This operation formed two key carbon-carbon bonds in one step, and deleted a synthetic step to further shorten our already concise synthetic route. The product obtained from these one pot reaction conditions also existed as a 3 : 1 mixture of *E*/*Z* isomers.



3.45 **3.40**

Scheme 3.28: Oxidative dearomatization cyclization cascade reaction

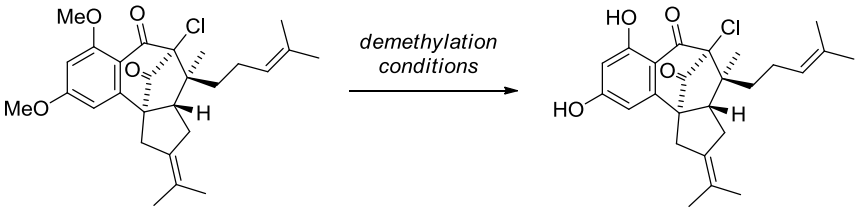
We were hopeful that the oxidative dearomatization cyclization reaction would proceed similarly to the non-chlorinated system, and that the presence of the C-2 chlorine atom would not affect the sterics or electronics of the molecule in a way which may impede cyclization. Subjection of **3.45** to our previously established conditions resulted in quick consumption of starting material and a familiar looking product pattern by TLC analysis. The major product was isolated in a very reasonable yield of 50%. The NMR of the product was very similar to the non-chlorinated merochlorin A analogue **3.39** previously synthesized, but was missing the diagnostic C-2 proton signal that was present in the ^{1}H NMR of **3.39**. The data showed good agreement with the literature data for merochlorin A.[14] Based primarily on this NMR data comparison, we could confidently assign the structure of the isolated compound to be the [5 + 2] cycloaddition product **3.40** as expected.

This cascade reaction formed two carbon-carbon bonds, two rings, and four contiguous stereocentres (two of which are all-carbon quaternary centres) in a single step. We believe this transformation mirrors the biosynthesis of merochlorin A (**3.9**) and that the success of this reaction in the laboratory lends support to our proposal. Although there are a few other examples of biomimetic [5 + 2] cycloadditions in natural product synthesis,[46-48] we believe this is the first example that is directly initiated by oxidative dearomatization. The formation of a single diasteroisomer from a 3:1 mixture of *E*/*Z* is consistent with the reaction being step-wise, proceeding *via* a tertiary carbocation as we proposed.

As with the non-chlorinated system, we did not observe the formation of any merochlorin B like products from this reaction. This perhaps indicated that the phenoxonium ion derived from **3.45** is predisposed to form the [5 + 2] cycloaddition product under non-enzymatic conditions.

3.2.5 Total Synthesis of Merochlorin A

With the successful synthesis of di-*O*-methyl merochlorin A (**3.40**), a final deprotection step would complete the total synthesis of merochlorin A. However, the cleavage of aromatic methyl ethers is known to be a difficult transformation and typically requires the use of strong Lewis acids.[49] This choice of protecting group was extremely practical in the early steps of the synthesis as the already protected starting material was commercially available, and the methoxy group was evidently inert to all of our reaction conditions. In the likely scenario that our molecule could not tolerate the harsh conditions required to cleave off both protecting groups, we were prepared to repeat the synthesis with a new protecting group strategy.



3.40 **3.9:** Merochlorin A

Scheme 3.29: Demethylation reaction attempts

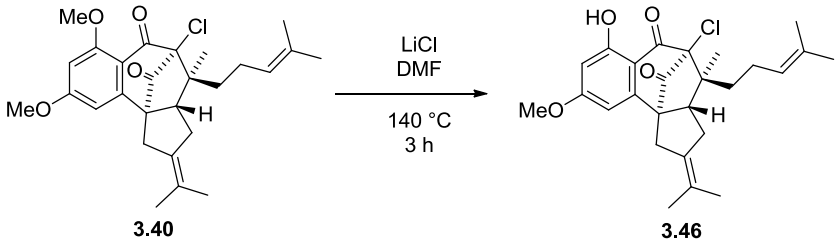
The conventional method for the cleavage of aryl methyl ethers is by the use of BBr_3, so this was a logical reagent to start with, despite the potential risk of side reactions. Unsurprisingly, treatment of **3.40** with BBr_3 at room temperature in CH_2Cl_2 resulted in mixtures of products resulting from reaction at the double bonds. Deprotection of the *ortho* methyl group was also occurring to some extent under these conditions but it was evident that the undesired side reactions at the alkenes were too fast to be avoided. Similar products were observed when $AlCl_3$ was used.

Table 3.1: Conditions trailed for the demethylation of **3.40**

Reagent	Solvent	Time	Temperature	Result
BBr_3	CH_2Cl_2	30 min	rt	side reactions

$AlCl_3$	$C_2H_4Cl_2$	30 min	80 °C	side reactions
$AlCl_3$	CH_2Cl_2	30 min	rt	side reactions
AlI_3, NBu_4I, phloroglcinol[50]	PhH	30 min	rt	side reactions
PhSH, K_2CO_3[51]	NMP	1 h	150 °C	decomposition
PhSH, *n*-BuLi[52]	HMPA, PhMe	1 h	150 °C	decomposition
NaCN[53]	DMF	1 h	130 °C	decomposition
LiCl	DMF	3 h	130 °C	demethylation only
LiI	DMF	3 h	130 °C	demethylation only

Discouragingly, consultation of the literature revealed very few examples of methyl ether cleavage reactions occurring on a molecule containing at least one alkene group in its chemical structure. One relevant example reported a successful demethylation using AlI_3 and NBu_4I with phloroglucinol as a scavenger for iodine.[50] Applying these reaction conditions to our compound led to similar results to the other strong Lewis acids trialed. It was becoming clear that the standard strong Lewis acidic conditions were not applicable to our system and alternatives needed to be considered. The use of thiolate anions as nucleophiles in methyl ether cleavage reactions has been shown to be successful on some apparently sensitive substrates.[52,54] However, reported reactions always required high temperatures (upwards of 150 °C) for demethylation to occur, and it was uncertain whether our molecule could withstand these conditions. Two conditions were trialed involving the use of thiolate anions derived from thiophenol (**table 3.1**);[51,52] however, these just led to quick decomposition of the starting material, indicating that thiolate based conditions were incompatible.



3.40 3.46

Scheme 3.30: Monodemethylation with LiCl

At this point it was necessary to explore some more unconventional methods. We considered Krapcho demethylation conditions, a reaction more commonly used for the demethylation of methyl esters which involves the use of LiCl in a polar aprotic solvent at high temperatures.[55,56] To our delight, heating **4.30** at 140 °C in DMF in the presence of LiCl yielded the monodemethylation product **3.46** cleanly, in reasonable conversion. As this was the sole encouraging result from our experimentation, we decided to pursue the optimization

of these conditions. Our investigation also found LiI to be equally effective in this transformation, but because the choice between these two reagents made no noticeable difference to the reaction outcome, we generally used the more conventional LiCl.

Attempts were made to induce the subsequent second demethylation by increasing the reaction time. We were able to isolate trace amounts of merochlorin A (**3.9**). However, leaving the reaction for even longer periods led to lower combined yields, poor product purity and eventually complete decomposition. Increasing the reaction temperature with the use of higher boiling point solvents such as HMPA or collidine resulted in decomposition. Heating with microwave irradiation did not appear to change the outcome of the reaction.

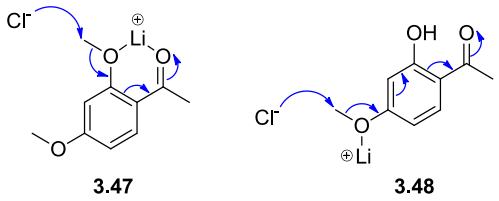
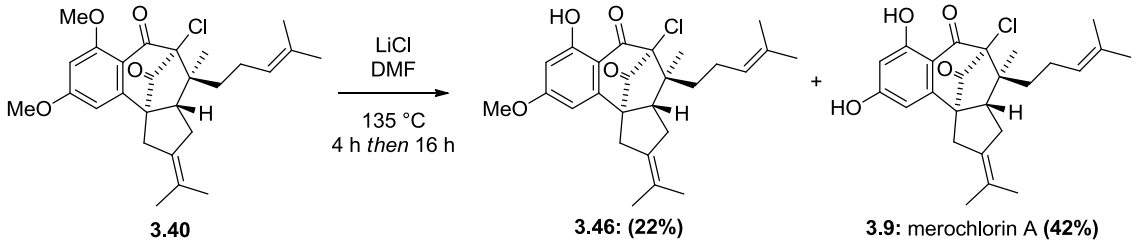


Figure 3.4: Mechanistic rationalization of demethylation reaction with LiCl

The apparent relative ease of demethylation of the *ortho* methoxy group relative to the *para* on our system could be explained mechanistically (**figure 3.4**). Lewis acid/base interactions of the lithium cation to the *ortho* methoxy group is enhanced by additional coordination to the proximate Lewis basic carbonyl group, hence increasing the relative reactivity of the *ortho* methoxy group towards S_N2 attack. This mechanism also explains how reactivity at both the *ortho* and *para* positions is increased by the presence of the carbonyl group which acts as an electron sink.



Scheme 3.31: Two step demethylation sequence with LiCl

Our trials concluded 135 °C to be the optimal temperature for reasonable reaction rate and product purity; however, we still could not obtain much of the natural product when starting from **3.40**. We were happy to discover that by subjection of the same conditions to *O*-

methylmerochlorin A **3.46** overnight, merochlorin A was yielded in greater than 50% conversion. Applying this result, we developed an optimal procedure for the demethylation of **3.40**, which involved heating it in LiCl and DMF for four hours, performing an aqueous workup and then subjecting the crude residue to the same reaction conditions overnight (**scheme 3.31**). Using this method, we could obtain pure merochlorin A (**3.9**) in a satisfactory yield of 42% along with 22% of **3.46**. The demethylation reaction being superior when performed over two steps could perhaps be explained by the presence of the phenolate ion formed after the initial demethylation inhibiting the reactivity of the system. Acidification by aqueous workup liberates the neutral phenol compound, which is presumably more reactive towards S_N2 substitution. An attempt to perform demethylation of **3.40** under these conditions, with the addition of one equivalent of AcOH with the intent of acidifying the phenolate *in situ* was unsuccessful, and did not change the outcome of the reaction.

The ^{13}C NMR data of our synthetic merochlorin A matched with the literature data for the natural product. Strangely, the ^{1}H NMR data for our synthetic sample was consistently ~0.08 ppm higher for all peaks when compared to the literature.[14] This was most plausibly explained by a simple referencing error by the isolation chemists.

Table 3.2: NMR data comparison of synthetic merochlorin A with natural merochlorin A[14]

	natural merochlorin A (DMSO-d_6)		synthetic merochlorin A (DMSO-d_6)	
	^{13}C	^{1}H	^{13}C	^{1}H
1	193.2		193.0	
2	91.3		91.0	
3	200.1		199.8	
4	61.5		61.3	
5	103.7	6.38, d *J* = 2.0	103.3	6.46, d *J* = 2.0
6	166.5		166.6	
7	102.1	6.16, d *J* = 2.0	101.8	6.28, d *J* = 2.0
8	165.4		165.8	
9	109.8		109.6	
10	150.5		150.3	
11	29.3	2.87, d *J* = 13.0 2.65, d *J* = 13.0	29.0	2.95, d *J* = 15.2 2.73, d *J* = 15.2
12	132.1		132.4	
13	31.9	2.36, dd *J* = 14.0, 4.0 2.33, dd *J* = 14.0, 9.4	31.9	2.45 – 2.38 m
14	58.8	2.24, dd *J* = 9.4, 4.0	58.1	2.33, dd *J* = 9.1, 4.2
15	45.3		45.1	
16	39.2	1.14, q *J* = 6.0 1.40, dt *J* = 14.8, 4.8	39.4	1.20, dt, *J* = 13.2, 4.9 1.47, dt, *J* = 13.2, 4.9

17	22.8	2.03, m 1.75, m	22.6	2.10, m 1.83, m
18	124.2	4.92, t *J* = 6.5	124.3	5.01, t *J* = 7.1
19	131.6		131.6	
20	26.1	1.53, s	25.8	1.61, s
21	18.1	1.45, s	17.9	1.54, s
22	123.1		123.0	
23	20.9	1.56, s	21.0	1.63, s
24	21.1	1.65, s	21.3	1.73, s
25	16.5	0.81, s	16.5	0.88, s
OH		11.9, s		12.00 s, 11.35 s

As conclusive proof we had synthesized merochlorin A (**3.9**), and as the correct diastereoisomer, we were able to acquire an X-ray crystal structure of our synthetic sample, using crystals acquired by recrystallization from heptane (**figure 3.5**). This demonstrated the first crystal structure obtained for the natural product as the original isolation reported only X-ray crystallographic data for a synthetically modified merochlorin A derivative.[14]

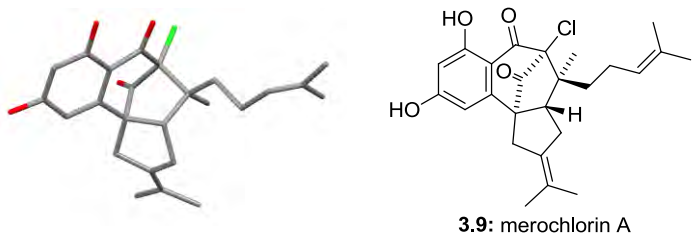


Figure 3.5: X-ray crystal structure of our synthetic merochlorin A

3.2.6 Synthesis of Merochlorin A Analogues

Our developed synthetic route towards merochlorin A (**3.9**) was very concise, requiring only five linear steps starting from methyl-3,5-dimethoxyphenylacetate (**3.28**), or alternatively six linear steps from acetylacetone (**3.34**) and geranyl bromide. In addition, we believed the convergent nature of the synthesis made it applicable to the synthesis of analogues for the purpose of biological testing and SAR studies. As previously mentioned, merochlorin A (**3.9**) has been shown to exhibit potent antibiotic activity,[14,16] and is therefore a potential candidate as a lead compound for the development of new antibiotics. Hence, we were interested in synthesizing some merochlorin A analogues to demonstrate the applicability of our synthetic route for this purpose.

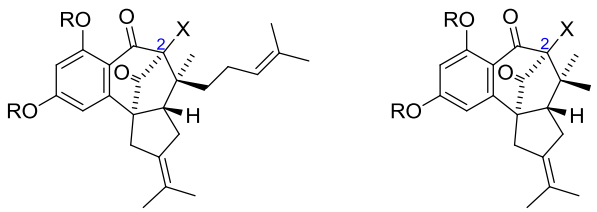
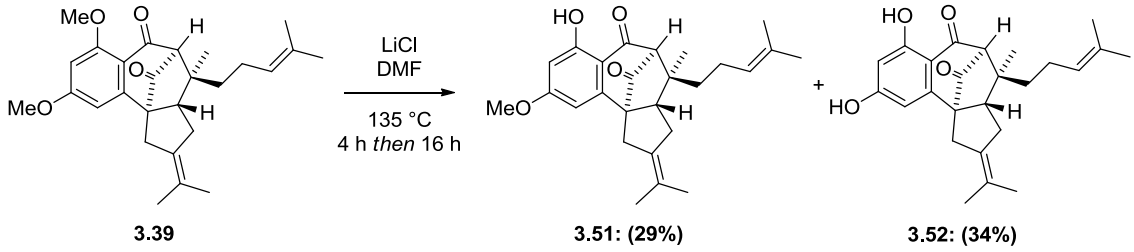


Figure 3.6: Merochlorin A analogue targets (R = Me or H, X = Cl or H)

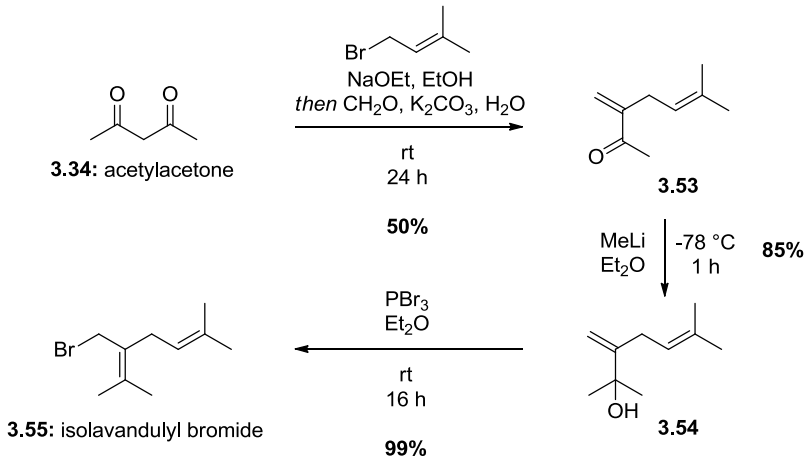
Our plan was to synthesize 11 easily accessible analogues (12 including merochlorin A itself) which would focus on parts of the molecule which were easily modified *via* our chemistry, and could provide valuable information as part of a SAR study. The parts of the molecule of interest were the identity of the oxygen substituents on the aromatic ring (OH or OMe), the substituent at C-2 (H or Cl) and the length of the terpene fragment (whether it is derived from the 15 carbon isosesquilavandulyl (**3.14**) chain or the 10 carbon isolavandulyl chain).

The methyl protected merochlorin A intermediates **3.39** and **3.40** were already in our possession which were worth testing in antibiotic assays. The next step was to synthesize analogues **3.51** and **3.52**, which could be obtained by the demethylation of the di-*O*-methyldeschloro merochlorin A **3.39** which we had already synthesized (**scheme 3.32**). Thankfully, our established demethylation conditions were found to be equally effective on the non-chlorinated system, yielding adequate quantities of merochlorin A analogues **3.51** and **3.52** for characterization and biological testing.



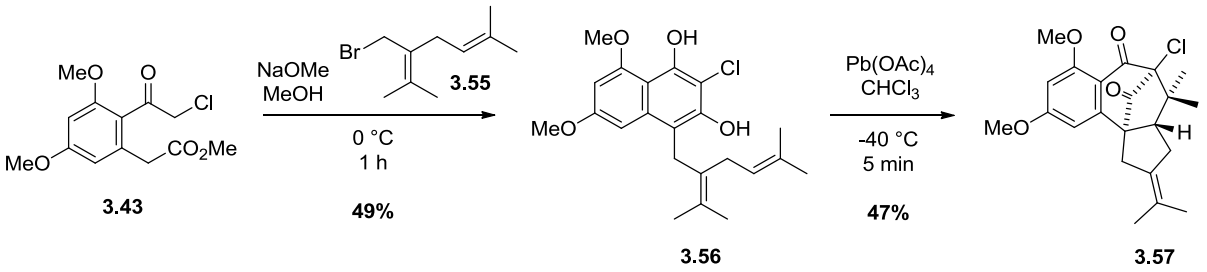
Scheme 3.32: Two step demethylation sequence with LiCl

In addition to supplying useful biological information, successful synthesis of the isolavandulyl derived analogues would demonstrate broader utility of our oxidative dearomatization cyclization reaction. Starting from acetylacetone (**3.34**) and prenyl bromide, isolavandulyl bromide (**3.55**) was synthesized in three steps following the procedures of Marazano *et al.* (**scheme 3.33**)., in analogous operations to our previous synthesis of isosesquilavandulyl bromide (**3.33**).[28]

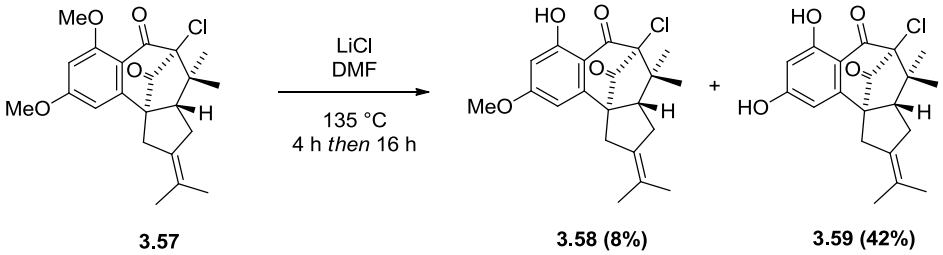


Scheme 3.33: Synthesis of isolavandulyl bromide **3.55**[28]

With no modification to our established reaction conditions, both the one pot alkylation/aromatization reaction using lavandulyl bromide (**3.55**) as the electrophile and the oxidative dearomatization cyclization reaction were successful in yielding the simplified dimethyl merochlorin A analogue **3.57** (**scheme 3.34**). Demethylation of **3.57** then yielded the mono methyl and fully deprotected analogues **3.58** and **3.59** respectively.

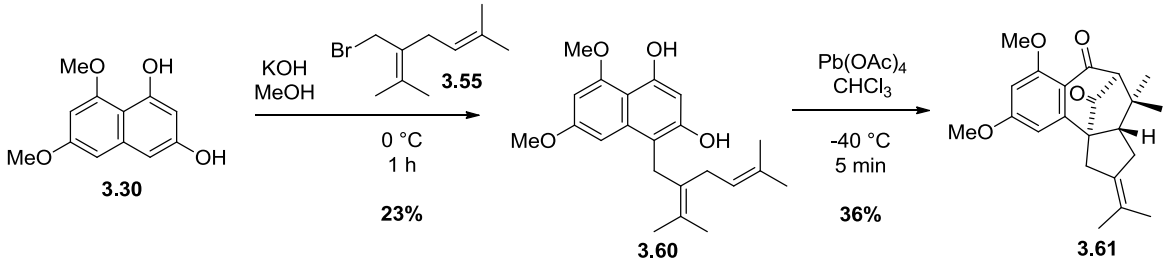


Scheme 3.34: Synthesis of simplified dimethyl merochlorin A analogue **3.57** (these reactions were carried out by undergraduate student Ben Fawcett under my direct supervision)

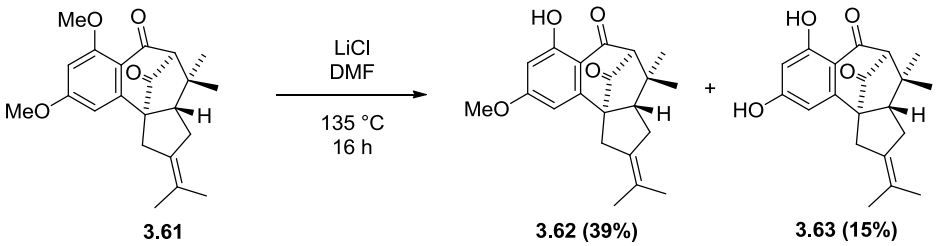


Scheme 3.35: Synthesis of simplified merochlorin A analogues **3.58** and **3.59** (these reactions were carried out by undergraduate student Ben Fawcett under my direct supervision)

It was still necessary to resort to the longer, more step-wise approach to the synthesis of the non-chlorinated analogues **3.61**, **3.62** and **3.63**. Utilizing the same conditions used for the preparation of di-*O*-methyldeschloro merochlorin A **3.39** proved effective in yielding the simplified analohue **3.61**. Demethylation of **3.61** under our established conditions then gave the final two analogues **3.62** and **3.63**.



Scheme 3.36: Synthesis of simplified dimethyl merochlorin A analogue **3.61**



Scheme 3.37: Synthesis of simplified merochlorin A analogues **3.62** and **3.63**

3.2.7 Biological Testing of Merochlorin Analogues

We sent our 12 synthetic samples (including merochlorin A) to Prof. Lixin Zhang at the Institute of Microbiology, Chinese Acadamy of Sciences for biological testing. *In vitro* antibiotic assays were performed against a variety of clinically relevant targets: methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus aureus* (SA), *Candia abicans* SC5314 (CA SC5314), *Pseudomonas aeruginosa* (PA01), and *Mycobacteria bovis* (BCG).

Table 3.3: Results from antibacterial assays of our merochlorin analogues (MIC values in μg/mL)

Compound	MRSA	SA	CA SC5314	PA01	BCG
3.40	>100	>100	>100	>100	>40
3.46	>100	>100	>100	>100	>40
3.9 merochlorin A	6.25	6.25	>100	>100	>40

3.39	>100	>100	>100	>100	>40
3.51	>100	>100	>100	>100	>40
3.52	1.56	1.56	>100	>100	>40
3.57	>100	>100	>100	>100	>40
3.58	>100	>100	>100	>100	>40
3.59	3.13	6.25	>100	>100	>40
3.61	>100	>100	>100	>100	>40
3.62	>100	>100	>100	>100	>40
3.63	6.25	12.5	>100	>100	>40
Postive control	vancomycin 1.0	vancomycin 1.0	ketoconazole 0.016	ciprofloxacin 0.39	isoniazi 0.05

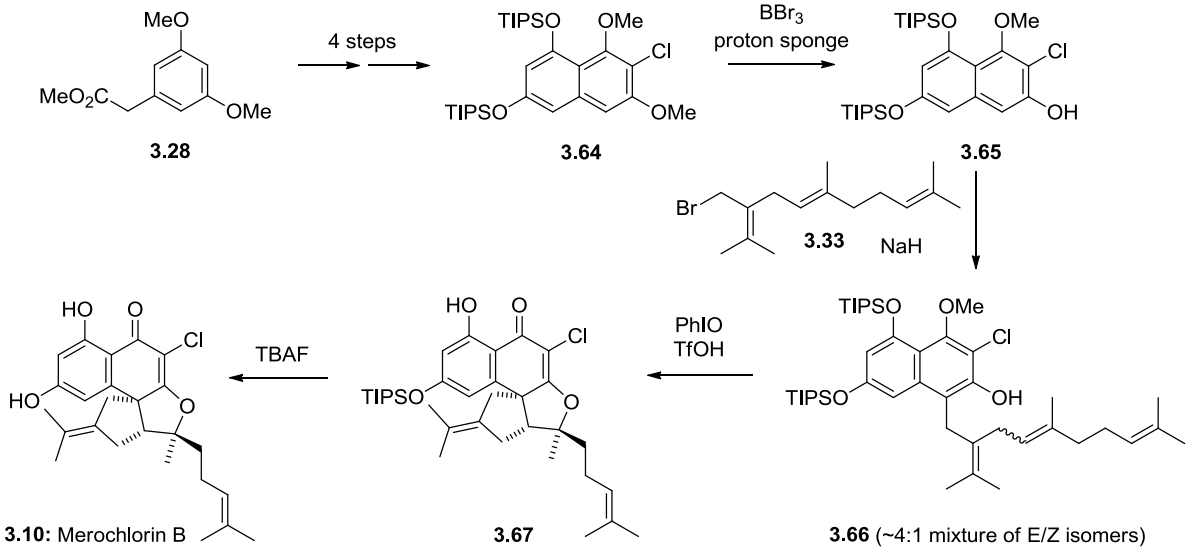
The results from the antibacterial assays (**table 3.3**) showed that positive results were obtained for four of our compounds against MRSA and SA bacterial strains. The MIC value for our synthetic merochlorin A (**3.9**) against MRSA was found to be 6.25 μg/mL, whereas the value for the natural product was reported to be 2-4 μg/mL.[14,16] It is important to note that unlike the natural product, our synthetic samples were racemic; hence, we should expect MIC values to be double that of enantiopure samples, assuming the opposite enantiomer has negligible activity. Taking this into account, we successfully reproduced the positive result recorded by the isolation chemists.

Taking a look at the results for our synthetic analogues, there were some clear, consistent correlations which could be made. All of the methylated analogues lost all activity, which indicates the presence of the two free phenols at these positions on the aromatic ring is vital for activity. However, it is possible that solubility issues when performing the experiments could be the cause of this. All of the diphenol compounds displayed potent levels of activity. This indicated that the longer terpene chain and the C-2 chlorine atom are not important for activity. In fact, the analogue with the highest level of activity was **3.52**, where the only difference between it and merochlorin A (**3.9**) is replacement of the C-2 chlorine atom with a hydrogen atom. Overall, even though these results were very preliminary, we were still able to obtain some intriguing results and correlations which could be built upon in future.

3.2.8 Subsequent Literature Research on the Merochlorins

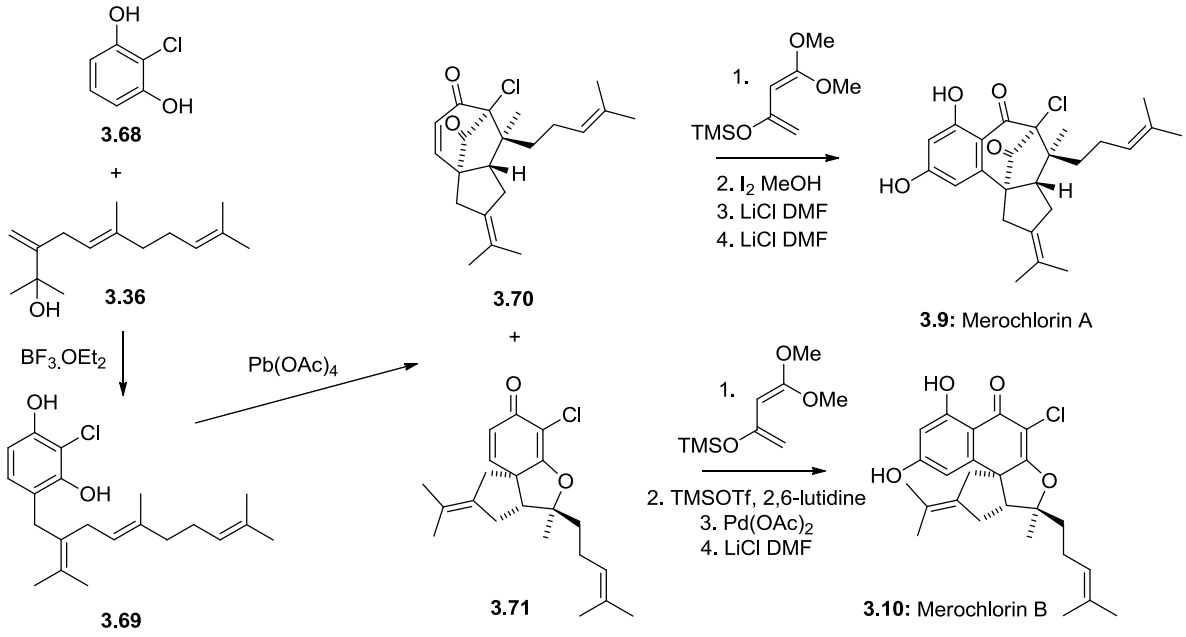
After publishing our synthesis of merochlorin A (**3.9**),[57] several other research groups published work on the merochlorin family of natural products. Much of this work was particularly relevant to our research and is worthy of discussion. Trauner *et al.* had an identical idea regarding the synthesis of merochlorins A (**3.9**) and B (**3.10**), and published

their synthesis in early 2014.[58] The key intermediate **3.66** was prepared in six linear steps from methyl-3,5-dimethoxyacetate (**3.28**) in 28% overall yield. The approach the Trauner group used for the synthesis of this cyclization precursor was similar to ours; however, their method was three steps longer and utilized a different pattern of protecting groups.



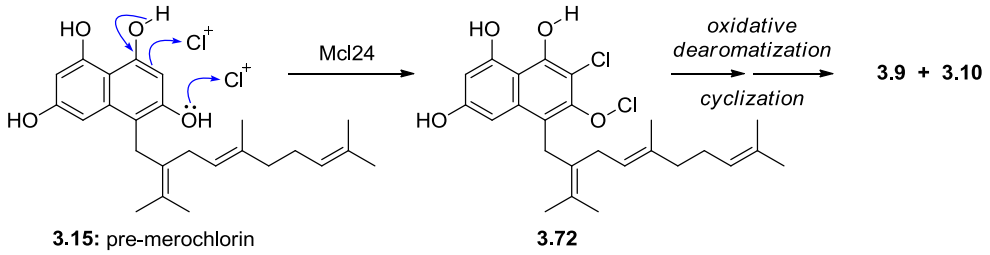
Scheme 3.38: 2014 synthesis of merochlorin B by Trauner *et al.*[58]

They similarly observed isomerization of the terpene chain resulting in a 4 : 1 mixture of *E/Z* isomers from the base induced alkylation conditions. The oxidative dearomatization cyclization cascade reaction was found to be difficult using **3.66** as the substrate, and only the exotic hypervalent iodine reagent PhI(OH)Tf (prepared *in situ* from PhIO and TfOH) led to successful cyclization. Interestingly, in contrast to our synthesis, only the [3 +2] cycloaddition product was observed, which led to the total synthesis of merochlorin B (**3.10**). Trauner *et al.* rationalized this observation by hypothesizing that the presence of the methyl ether protecting group increased the relative nucleophilicity of the carbonyl, thus favouring the [3 + 2]-pathway.[58] Comparison between our total synthesis of merochlorin A and Trauner's synthesis of merochlorin B provides an excellent example of how subtle changes in the substrate for a biomimetic cascade reaction can dramatically change the favoured product. The same oxidative dearomatization approach toward merochlorins A and B was additionally employed by Tang *et al.*, who recently published their total synthesis in 2015.[59] The use of the monocyclic intermediate **3.69** was employed for the oxidative dearomatization cyclization reaction, avoiding early synthesis of the THN moiety in favour of a late stage introduction of the aromatic ring *via* a Diels-Alder reaction (**scheme 3.39).**



Scheme 3.39: 2015 synthesis of merochlorin A and B by Tang *et al.*[59]

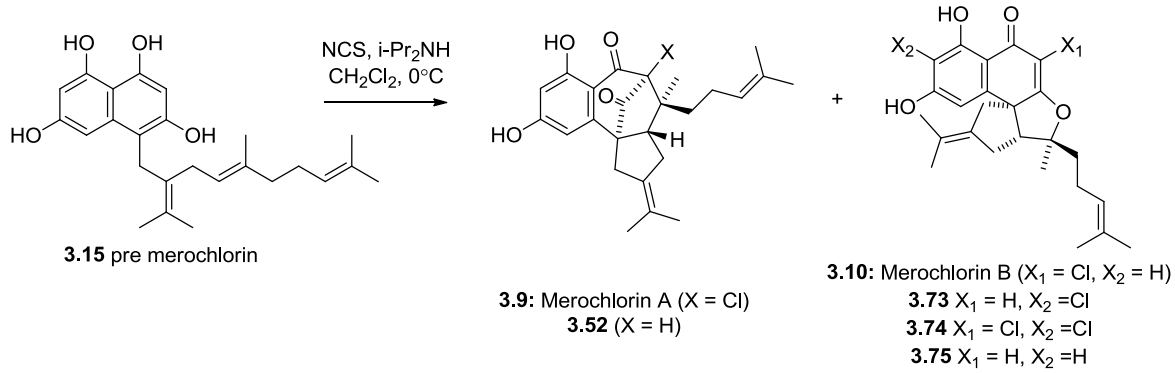
The approach by Tang was noteworthy as it ultimately resulted in the synthesis of both merochlorin A (**3.9**) and B (**3.10**), as both the [5+2] and [3+2] cycloaddition products were observed from the same oxidative dearomatization conditions. This example further demonstrates how changes in the substrate affect the outcome of this biomimetic reaction.



Scheme 3.40: Mcl24 catalyzed biosynthetic conversion of pre-merochlorin into merochlorins A and B[60]

Moore *et al.*, the chemists responsible for the isolation of the merochlorins, have had a continued interest in the biosynthetic origins of these natural products and have since reported further studies. Much of the recent work had reinforced what they had previously proposed; in addition, they were able to confirm pre-merochlorin (**3.15**) to be a biosynthetic intermediate and that the VHPO Mcl24 is the sole enzyme responsible for its conversion into merochlorin A (**3.9**) and B (**3.10**).[60] Their biosynthetic work, along with the synthetic work performed by Trauner *et al.* and us, convinced them to reconsider their proposal for the

cyclization events responsible in the biosynthesis of merochlorins A and B to involve oxidative dearomatization. Because the Mcl24 enzyme is responsible for both chlorination and oxidative dearomatization, presumably some form of electrophilic chlorine is responsible for inducing oxidative dearomatization, perhaps by the formation of an aromatic hypochlorite such as **3.72** (**scheme 3.40**).

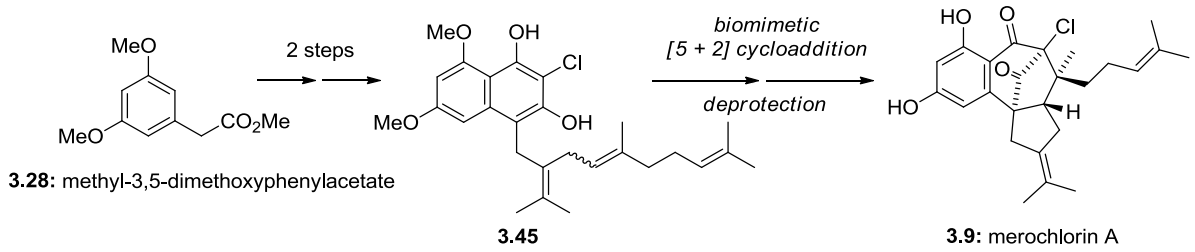


Scheme 3.41: 2014 synthesis of merochlorin A and B compounds by Moore *et al.*[61]

Additionally, Moore *et al.* were interested in the possibility of mimicking the action of the Mcl24 enzyme synthetically using conventional laboratory reagents in order to gain further insight into the mechanism of the conversion of pre-merochlorin (**3.15**) into **3.9** and **3.10**. Hence, they treated synthetic pre-merochlorin (**3.15**) with a variety of different chlorinating conditions to see if they could observe either the [5+2] cycloaddition or [3+2] cycloaddition. Pleasingly, they found that utilizing a combination of NCS in the presence of diisoproylamine resulted in the formation of a mixture of six merochlorin A and B type compounds with differing chlorine substitution (**scheme 3.41**).[61] The presence of an amine base was found to be crucial for the success of this reaction, and the formation of a reactive chloroamine intermediate was proposed to be responsible. This chlorinating system presumably mimics the action of the enzyme, and the diisopropylamine additive is analogous to the lysine residue in the active site. Interestingly, each of the new compounds produced from this reaction were confirmed to be trace products present in the merochlorin producing strain *Streptomyces* sp. CNH-189 by HPLC comparison.[61] The deschloro merochlorin A compound **3.52** was the same compound we were able to synthesize during our synthetic work (**scheme 3.32**). While low yielding and unselective, the conversion of pre-merochlorin (**3.15**) into six merochlorin natural products gives good insight into merochlorin biosynthesis, and could perhaps be considered an example of "biomimetic diversity orientated synthesis".

3.3 Conclusions

The first total synthesis of merochlorin A (**3.9**) was achieved in five linear steps from methyl-3,5-dimethoxyphenylacetate (**3.28**) (6% overall yield). The key biomimetic [5 + 2] cycloaddition reaction induced by oxidative dearomatization was found to be a highly effective method to generate the bicyclo[3.2.1]octane core of the natural product in a single operation. We believe that the success of this approach strongly suggests that a similar process is involved in the biosynthesis of merochlorin A (**3.9**). Our biosynthetic speculation has additionally been supported by the recent enzymatic studies by Moore *et al.* who, based on their results, believe that a VHPO enzyme is responsible for oxidative dearomatization during biosynthesis.



Scheme 3.42: Summary of the biomimetic total synthesis of merochlorin A

The overall synthetic strategy of our final route is based on our proposed biosynthesis, and includes a sequence of aromatization, alkylation, and oxidative cyclization reactions. The one pot alkylation/aromatization reaction which forms two key carbon-carbon bonds was found to be a concise method for the synthesis of highly functionalized naphthalene derivatives. The final demethylation reaction was found to be challenging, but we found eventual success in utilizing Krapcho demethylation conditions. This successful demethylation allowed the commercially available **3.28** to be used as the starting material, thus allowing for a simplified and short synthesis.

Taking advantage of the concise and adaptable nature of this methodology, we were able to efficiently synthesize 11 additional merochlorin analogues. Subjecting these analogues and our synthetic merochlorin A (**3.9**) to antimicrobial assays gave access to some early SAR correlations. In future, this methodology could be applied to the synthesis of even more

analogues for biological testing in order to better understand the antibiotic activity of merochlorin A.

The merochlorin B (**3.10**) structure was found to be inaccessible *via* this methodology with the substrates we used during testing. The merochlorin B ring system was however proven be accessible *via* an oxidative dearomatization strategy during the work of Trauner *et al.* and Tang *et al*., given the right substrate

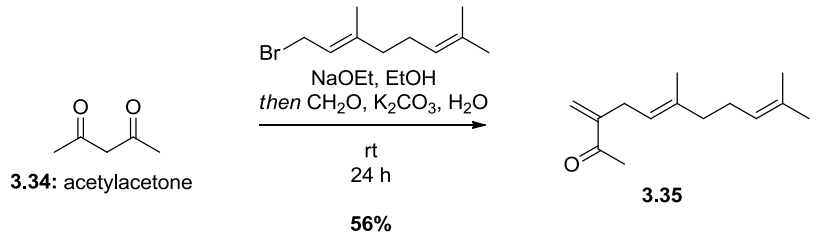
3.4 Experimentals

3.4.1 General Methods

All chemicals used were purchased from commercial suppliers and used as received, except for $Pb(OAc)_4$ which was recrystallized from glacial acetic acid prior to use. 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 Merck aluminium sheets silica gel 60 F255. Visualization was aided by viewing under a UV lamp and staining with ceric ammonium molybdate stain followed by heating. All R_f values were rounded to the nearest 0.01. Flash chromatography was performed using Davasil (40-63 micron) grade silica gel. Melting points were recorded on a Stanford Research Systems Digimelt digital melting point apparatus and are uncorrected. Infrared spectra were recorded using a Perkin Elmer Spectrum BX FT-IR system spectrometer as the neat compounds. High field NMR was recorded using a Varian Inova-6000 spectrometer (^1H at 600 MHz, ^{13}C at 150 MHz). Solvents used for spectra were chloroform unless otherwise specified. ^1H 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 chloroform (δ 77.0). Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet and (m) multiplet. All *J* values were rounded to the nearest 0.1 Hz. High resolution EI mass spectra were recorded on a VG Autospec mass spectrometer operating at 70 eV. High resolution ESI mass spectra were obtained on a LTQ Orbitrap XL ETD (Thermo Fisher Scientific) mass spectrometer by the Adelaide Proteomics Centre.

3.4.2 Experimental Procedures

(*E*)-6,10-dimethyl-3-methyleneundeca-5,9-dien-2-one (3.35)[29]



To a solution of acetylacetone (**3.34**) (10.0 g, 100 mmol) in EtOH (80 mL), NaH (60% dispersion in mineral oil, 4.4 g, 110 mmol) was added portion wise at 0 °C. The mixture was stirred at 0 °C for 10 min. Geranyl bromide (28.0 g, 130 mmol) was then added at 0 °C. The mixture was stirred at rt for 6 h. The mixture was then diluted with H_2O (200 mL) followed by successive addition of formaldehyde (37% in H_2O, 30 mL) and K_2CO_3 (27.6 g, 200 mmol). The resultant mixture was stirred at rt for 36 h. The mixture was diluted with H_2O (100 mL) and extracted with Et_2O (3x 200 mL). The combined organics were washed with brine (300 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/ EtOAc, 30:1) to give (*E*)-6,10-dimethyl-3-methyleneundeca-5,9-dien-2-one (**3.35**) (11.6 g, 56%) as a colourless oil.

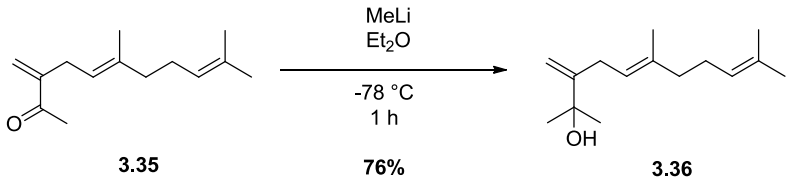
R_f = 0.60 (petrol/EtOAc, 4:1)

IR (neat): 2916, 1679, 1626, 1437, 1363, 1118 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.00 (s, 1H), 5.75 (s, 1H), 5.14 (t, *J* = 7.2 Hz, 1H), 5.09 (t, *J* = 6.6 Hz, 1H), 2.95 (d, *J* = 7.3 Hz, 2H), 2.34 (s, 3H), 2.11 – 2.02 (m, 4H), 1.68 (s, 3H), 1.60 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 199.7, 148.0, 137.6, 131.4, 124.7, 124.2, 120.6, 39.7, 28.7, 26.5, 25.9, 25.7, 17.6, 15.82.

(*E*)-2,6,10-trimethyl-3-methyleneundeca-5,9-dien-2-ol (3.36)



3.35 **76%** **3.36**

To a solution of **3.35** (11.6, 56.2 mmol) in Et_2O (150 mL), MeLi (1.6 M in Et_2O, 70.0 mL, 112 mmol) was added drop wise at -78 °C. The mixture was stirred at -78 °C for 1 h before slow warming to rt. The mixture was quenched with *sat*. NH_4Cl solution (200 mL) and extracted with Et_2O (2 x 200 mL). The combined organics were washed with brine (300 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/ EtOAc, 8:1) to give (*E*)-2,6,10-trimethyl-3-methyleneundeca-5,9-dien-2-ol (**3.36**) (9.50 g, 76%) as a colourless oil.

R_f = 0.44 (petrol/EtOAc, 4:1)

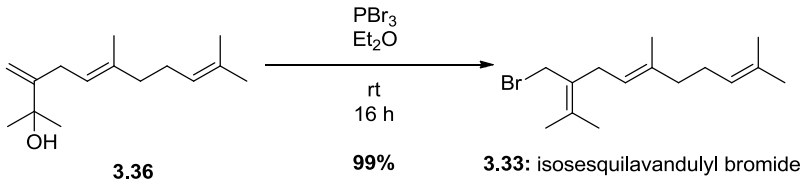
IR (neat): 3376, 2974, 2916, 1443, 1376, 961, 903 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.21 (t, *J* = 7.2 Hz, 1H), 5.10 (t, *J* = 7.2 Hz, 1H), 5.07 (s, 1H), 4.80 (s, 1H), 2.81 (d, *J* = 7.3 Hz, 2H), 2.13 – 2.09 (m, 2H), 2.06 – 2.04 (m, 2H), 1.68 (s, 3H), 1.61 (s, 3H), 1.61 (s, 3H), 1.50 (s, 1H), 1.37 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 155.1, 136.6, 131.5, 124.3, 122.6, 107.9, 73.4, 39.7, 30.3, 29.3, 26.6, 25.7, 17.7, 15.8.

HRMS (ESI): calculated for $C_{15}H_{26}O$ 245.1881 $[M+Na]^+$, found 245.1880.

(*E*)-3-(bromomethyl)-2,6,10-trimethylundeca-2,5,9-triene (3.33)



To a solution of **3.36** (3.80 g, 17.0 mmol) in Et_2O (100 mL), pyridine (0.270 mL, 3.40 mmol) and PBr_3 (1.60 mL, 17.0 mmol) were added successively at rt. The mixture was stirred at rt for 16 h. The mixture was diluted with Et_2O (100 mL) and washed successively with *sat*. NH_4Cl solution (100 mL), H_2O (100 mL) and brine (100 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give (*E*)-3-(bromomethyl)-2,6,10-trimethylundeca-2,5,9-triene (**3.33**) (4.80 g, 99%) as a pale brown oil which was used in the next step without further purification.

R_f = 0.62 (neat petrol)

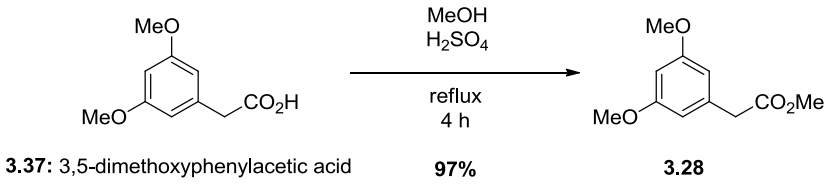
IR (neat): 2916, 1679, 1626, 1437, 1363, 1118 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.07 (t, *J* = 7.5 Hz, 1H), 5.03 (t, *J* = 7.2 Hz, 1H), 4.05 (s, 2H), 2.89 (d, *J* = 7.0 Hz, 2H), 2.11 – 1.98 (m, 4H), 1.78 (s, 3H), 1.74 (s, 3H), 1.69 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 136.5, 133.7, 131.4, 129.0, 124.2, 122.0, 39.8, 34.8, 29.5, 26.6, 25.7, 21.0, 20.5, 17.7, 16.1.

HRMS (EI): calculated for $C_{15}H_{25}Br$ 286.1119 $[M]^{+\bullet}$, found 286.1115.

Methyl-3,5-dimethoxyphenylacetate (3.28)[31]



3.37: 3,5-dimethoxyphenylacetic acid **97%** **3.28**

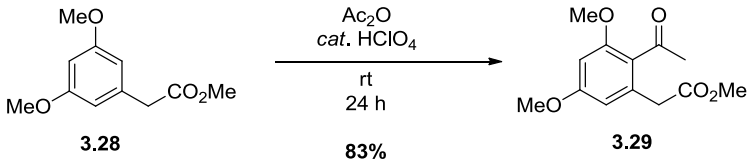
To a solution of 3,5-dimethoxyphenylacetic acid (**3.37**) (25.0 g, 127 mmol) in MeOH (350 mL), H_2SO_4 (0.2 mL) was added at rt. The reaction mixture was heated at reflux for 4 h. The mixture was cooled to rt before Na_2CO_3 (10 g) was added. The mixture was filtere filtered through celite and concentrated *in vacuo*. The residue was dissolved in Et_2O (200 mL) and H_2O (200 mL). The layers were separated and the aqueous phase was extracted with Et_2O (200 mL). The combined organics were washed with brine (300 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield methyl-3,5-dimethoxyphenylacetate (**3.28**) (25.9 g, 97%) as a colourless oil.

R_f = 0.29 (petrol/EtOAc, 4:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (d, *J* = 2.2 Hz, 2H), 6.39 (t, *J* = 2.2 Hz, 1H), 3.79 (s, 6H), 3.71 (s, 3H), 3.57 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 160.8, 136.0, 107.3, 99.2, 55.3, 52.1, 41.4.

methyl 2-(2-acetyl-3,5-dimethoxyphenyl)acetate (3.29)[24]



To a solution of methyl-3,5-dimethoxyphenylacetate (**3.28**) (12.6 g, 60.0 mmol) in Ac_2O (50.0 mL), 70% $HClO_4$ (0.2 mL) was added at rt. The mixture was stirred at rt for 24 h before being diluted with Et_2O (200 mL), followed by the addition of Na_2CO_3 (20.0 g). The resultant mixture was filtered through celite and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/ EtOAc, 4:1 → 2:1 gradient elution) to give methyl 2-(2-acetyl-3,5-dimethoxyphenyl)acetate (**3.29**) (12.6 g, 83%) as a pale yellow solid.

R_f = 0.29 (petrol/EtOAc, 2:1)

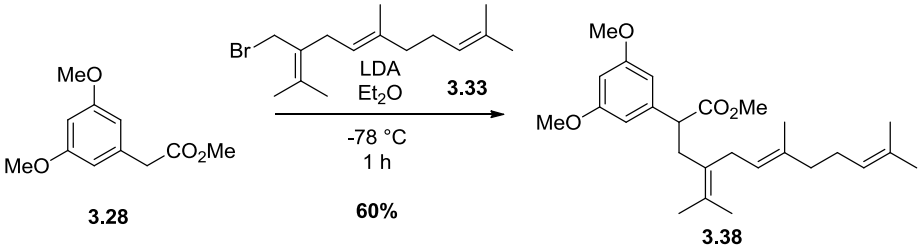
Mp = 58 – 60 °C

IR (neat): 2950, 2842, 1718, 1666, 1593, 1578, 1196, 1160, 843 cm^{-1}

^{1}H NMR (600 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).

^{13}C NMR (150 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.

(*E*)-methyl 2-(3,5-dimethoxyphenyl)-7,11-dimethyl-4-(propan-2-ylidene)dodeca-6,10-dienoate (3.38)



To a solution of *i*Pr_2NEt (0.13 mL, 0.92 mmol) in THF (3 mL), *n*-BuLi (2.5 M in hexanes, 0.37 mL, 0.92 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 30 min before cooling to -78 °C. **3.28** (150 mg, 0.765 mmol) was then added at -78 °C and the mixture was stirred at -78 °C for 30 min. **3.33** (350 mg, 1.23 mmol) was then added at -78 °C and the reaction mixture was stirred at -78 °C for a further 30 min, followed by slow warming to rt over 30 min. The mixture was quenched with *sat*. NH_4Cl solution (8 mL) and extracted with Et_2O (3 x 5 mL). The combined organics were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/ EtOAc, 50:1 → 20:1 gradient elution) to give (*E*)-methyl 2-(3,5-dimethoxyphenyl)-7,11-dimethyl-4-(propan-2-ylidene)dodeca-6,10-dienoate (**3.38**) (188 mg, 60%) as a colourless oil.

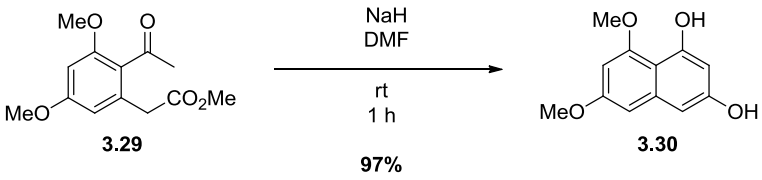
R_f = 0.51 (petrol/EtOAc, 4:1)

IR (neat): 3450, 2930, 1736, 1595, 1459, 1430, 1205, 1155, 1064, 833, 691 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.47 (d, *J* = 2.2 Hz, 2H), 6.35 (t, *J* = 2.2 Hz, 1H), 5.07 (t, *J* = 6.9 Hz, 1H), 4.98 (t, *J* = 6.8 Hz, 1H), 3.77 (s, 6H), 3.64 (s, 3H), 3.63 (dd, *J* = 15.1, 7.8 Hz, 1H), 2.82 (dd, *J* = 13.7, 8.1 Hz, 1H), 2.72 (dd, *J* = 15.1, 6.6 Hz, 1H), 2.61 (dd, *J* = 15.1, 7.2 Hz, 1H), 2.42 (dd, *J* = 13.8, 7.0 Hz, 1H), 2.10 – 1.94 (m, 4H), 1.65 (s, 3H), 1.63 (s, 6H), 1.58 (s, 6H).

^{1}H NMR (125MHz, $CDCl_3$) δ 174.2, 160.7, 141.6, 135.0, 131.3, 128.4, 127.9, 124.3, 123.0, 106.1, 99.1, 55.3, 51.9, 50.6, 39.8, 36.4, 30.9, 26.7, 25.7, 20.6, 20.5, 17.7, 16.1.

1,3-dihydroxy-6,8-dimethoxynaphthalene (3.30)[24]



To a solution of **3.29** (11.27 g, 44.7 mmol) in DMF (140 mL), NaH (60% in mineral oil, 3.57 g, 89 mmol) was added portion wise at rt. The mixture was stirred at rt for 1h. The mixture was then quenched with 1 M HCl (200 mL) and extracted with EtOAc (4 x 150 mL). The combined organics were washed with brine (3 x 200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/ EtOAc, 2:1 as eluent) to give1,3-dihydroxy-6,8-dimethoxynaphthalene (**3.30**) (9.56 g, 97%) as a pale brown solid.

R_f = 0.24 (petrol/EtOAc, 2:1)

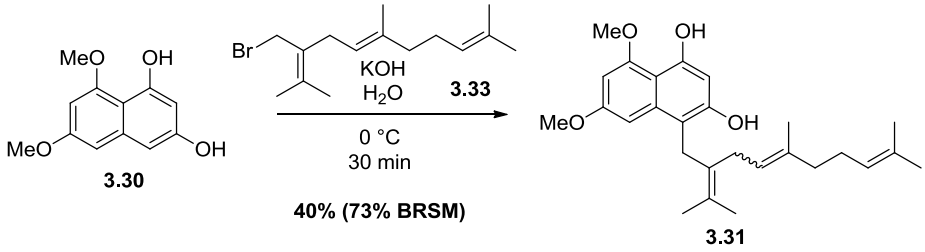
Mp =119 – 122 °C

IR (neat): 3401, 2939, 1634, 1600, 1384, 1205, 1126, 835 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.21 (s, 1H), 6.54 (d, *J* = 1.5 Hz, 1H), 6.52 (s, 1H), 6.35 (d, *J* = 1.5 Hz, 1H), 6.28 (s, 1H), 5.46 (s, 1H), 3.97 (s, 3H), 3.84 (s, 3H).

^{13}C NMR (150 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.

1,3-dihydroxy-4-(5,9-dimethyl-2-(propan-2-ylidene)deca-4,8-dien-1-yl)-6,8-dimethoxynaphthalene (3.31)



To a solution of **3.30** (4.43 g, 20.1 mmol) in MeOH (60 mL), KOH (1.13 g, 20.1 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 10 min before bromide **3.33** (7.70 g, 27.0 mmol) was added at 0 °C. The reaction mixture was stirred at 0 °C for a further 30 min before diluting with H_2O (120 mL) and quenching with 1 M HCl (40 mL).The mixture was extracted with EtOAc (4 x 150 mL), and the combined organics were washed with brine (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 8:1 as eluent) to give 1,3-dihydroxy-4-(5,9-dimethyl-2-(propan-2-ylidene)deca-4,8-dien-1-yl)-6,8-dimethoxynaphthalene (3:1 mixture of *E*/*Z* isomers) (**3.31**) (3.4 g, 40%) as a dark red oil along with recovered **3.30** (1.49 g, 33%).

R_f = 0.30 (petrol/EtOAc, 4:1)

IR (neat): 3403, 2914, 1623, 1455, 1381, 1147, 731 cm^{-1}

NMR data for major (*E*)-isomer:

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.22 (s, 1H), 6.75 (s, 2H), 6.36 (s, 1H), 6.33 (s, 1H), 5.86 (s, 1H), 5.05 (t, *J* = 6.9 Hz, 1H), 4.94 (t, *J* = 6.5 Hz, 1H), 4.00 (s, 3H), 3.84 (s, 3H), 3.67 (s, 2H), 2.60 (d, *J* = 6.1 Hz, 2H), 1.99 (s, 3H), 1.89 – 1.84 (m, 2H), 1.78 – 1.73 (m, 2H), 1.79 (s, 3H), 1.67 (s, 3H), 1.58 (s, 3H), 1.30 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 158.0, 157.8, 154.9, 154.5, 137.5, 136.0, 131.3, 131.2, 127.5, 124.3, 122.6, 107.7, 106.5, 100.2, 95.9, 94.9, 56.0, 55.1, 39.6, 29.5, 28.6, 26.5, 25.6, 20.8, 20.7, 17.6, 16.0

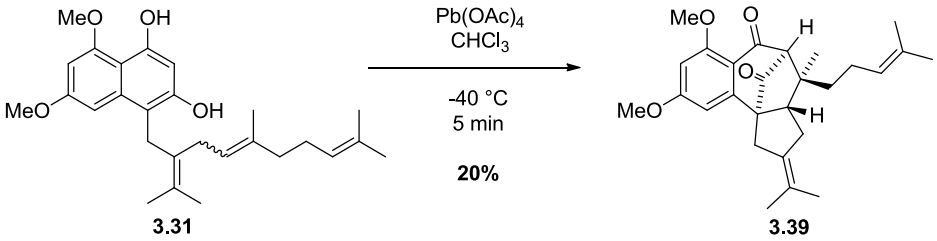
NMR data for major (*Z*)-isomer:

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.23 (s, 1H), 6.75 (s, 2H), 6.36 (s, 1H), 6.33 (s, 1H), 5.88 (s, 1H), 4.98 (t, *J* = 6.9 Hz, 1H), 4.93 (t, *J* = 6.5 Hz, 1H), 4.00 (s, 3H), 3.84 (s, 3H), 3.68 (s, 2H), 2.60 (d, *J* = 6.1 Hz, 2H), 1.98 (s, 3H), 1.89 – 1.84 (m, 2H), 1.78 – 1.73 (m, 2H), 1.61 (s, 3H), 1.59 (s, 3H), 1.47 (s, 3H), 1.30 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 158.0, 157.8, 155.0, 154.5, 137.4, 136.3, 131.4, 131.2, 127.6, 124.2, 123.4, 107.6, 106.6, 100.2, 95.9, 95.0, 56.0, 56.1, 31.8, 29.2, 28.5, 26.2, 25.6, 23.3, 20.8, 20.7, 17.4.

HRMS (EI): calculated for $C_{27}H_{36}O_4$ 424.2614 $[M]^{+\bullet}$, found 424.2612.

di-*O*-methyldeschloro merochlorin A (3.39)



To a solution of **3.31** (317 mg, 0.750 mmol) in $CHCl_3$ (40 mL), $Pb(OAc)_4$ (348 mg, 0.780 mmol) was added portion wise at -40 °C. The reaction mixture was stirred at -40 °C for 5 min before gradual warming to rt. The mixture was filtered through a short pad of SiO_2 and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/ EtOAc, 3:1 as eluent) to give di-*O*-methyldeschloro merochlorin A (**3.39**) (65 mg, 20%) as a white solid.

R_f = 0.28 (petrol/EtOAc, 2:1)

Mp = 123 – 125 °C

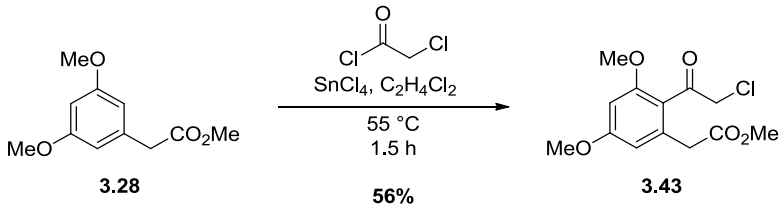
IR (neat): 2918, 1755, 1665, 1594, 1330, 1204, 1164 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.53 (s, 1H), 6.40 (s, 1H), 5.03 (t, J = 6.9 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.22 (s, 1H), 3.11 (d, J = 15.2 Hz, 1H), 2.65 (d, J = 15.2 Hz, 1H), 2.39 – 2.27 (m, 2H), 2.25 (dd, J = 9.6, 4.0 Hz, 1H), 2.18 – 2.09 (m, 1H), 1.92 – 1.83 (m, 1H), 1.78 (s, 3H), 1.65 (s, 3H), 1.63 (s, 3H), 1.61-1.58 (m, 1H), 1.57 (s, 3H), 1.29 (td, J = 12.8, 4.6 Hz, 1H), 0.93 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 204.9, 192.4, 164.6, 163.6, 152.6, 132.6, 131.4, 124.1, 123.0, 115.5, 99.9, 97.0, 77.6, 64.2, 58.7, 56.1, 55.5, 40.7, 40.2, 30.9, 29.2, 25.6, 23.1, 21.0, 20.7, 20.4, 17.6.

HRMS (ESI): calculated for$C_{27}H_{35}O_4$423.2535 $[M+H]^+$, found 423.2515.

methyl 2-(2-(2-chloroacetyl)-3,5-dimethoxyphenyl)acetate (3.43)



To a solution of **3.28** (1.41 g, 6.71 mmol) in $C_2H_4Cl_2$ (15 mL), $SnCl_4$ (3.50 mL, 30.3 mmol) was added drop wise rt. The mixture was stirred at rt for 10 min before chloroacetyl chloride (2.33 mL, 26.9 mmol) was added at rt. The resultant mixture was heated to 55 °C and stirred for 1.5 h. The mixture was cooled to rt, quenched carefully with 1 M HCl (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were washed with *sat*. $NaHCO_3$ solution (2 x 100 mL), H_2O (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/ EtOAc, 3:1 as eluent) to give methyl 2-(2-(2-chloroacetyl)-3,5-dimethoxyphenyl)acetate (**3.43**) (1.07 g, 56%) as a white solid.

R_f = 0.30 (petrol/EtOAc, 2:1)

Mp = 82 – 84 °C

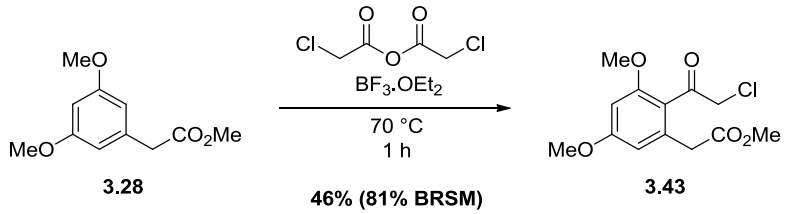
IR (neat): 2940, 1733, 1692, 1601, 1425, 1324, 1148 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.42 (d, *J* = 2.2 Hz, 1H), 6.39 (d, *J* = 2.2 Hz, 1H), 4.65 (s, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.72 (s, 2H), 3.68 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 196.3, 171.5, 162.5, 159.7, 136.6, 119.9, 109.0, 97.4, 55.8, 55.5, 52.1, 50.4, 39.1.

HRMS (ESI): calculated for $C_{13}H_{15}O_5ClNa$ 309.0506 $[M+Na]^+$, found 309.0505.

methyl 2-(2-(2-chloroacetyl)-3,5-dimethoxyphenyl)acetate (3.43)



A mixture of **3.28** (14.1 g, 67.1 mmol) and chloroacetic anhydride (68.7 g, 402 mmol) were heated at 70 °C. BF_3OEt_2 (16.6 mL, 134 mmol) was added at 70 °C, and the mixture was stirred at 70 °C for 1 h. The mixture was cooled, quenched with 1 M HCl (150 mL) and extracted with EtOAc (3 x 100 mL). The combined organics were washed sequentially with *sat*. $NaHCO_3$ solution (2 x 200 mL), H_2O (200 mL) and brine (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/ EtOAc, 3:1 as eluent) to give methyl 2-(2-(2-chloroacetyl)-3,5-dimethoxyphenyl)acetate (**3.43**) (8.78 g, 46%) as a white solid along with recovered starting material (4.90 g, 35%).

R_f= 0.30 (petrol/EtOAc, 2:1)

Mp =82-84 °C

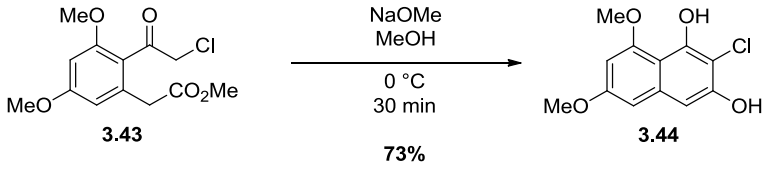
IR (neat):2940, 1733, 1692, 1601, 1425, 1324, 1148 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.42 (d, *J* = 2.2 Hz, 1H), 6.39 (d, *J* = 2.2 Hz, 1H), 4.65 (s, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.72 (s, 2H), 3.68 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 196.3, 171.5, 162.5, 159.7, 136.6, 119.9, 109.0, 97.4, 55.8, 55.5, 52.1, 50.4, 39.1.

HRMS (ESI): calculated for $C_{13}H_{15}O_5ClNa$ 309.0506 $[M+Na]^+$, found 309.0505.

1,3-dihydroxy-2-chloro-6,8-dimethoxynaphthalene (3.44)



To a suspension of **3.43** (1.05 g, 3.66 mmol) in MeOH (60 mL), NaH (60% in mineral oil, 3.66 g, 9.15 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 30 minutes. The mixture was quenched with 1 M HCl (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 2:1 as eluent) to give 1,3-dihydroxy-2-chloro-6,8-dimethoxynaphthalene (**3.44**) (680 mg, 73%) as a white solid.

R_f = 0.26 (petrol/EtOAc, 2:1)

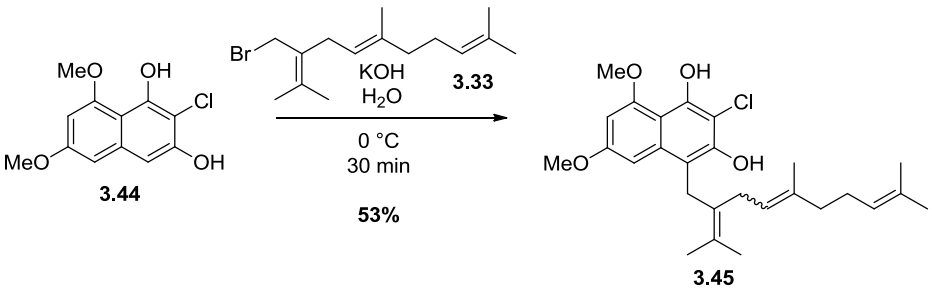
Mp = 148 - 151°C

IR (neat): 3321, 2943, 1613, 1370, 1210, 1159, 1051, 833 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.75 (s, 1H), 6.79 (s, 1H), 6.55 (d, *J* = 2.2 Hz, 1H), 6.33 (d, *J* = 2.2 Hz, 1H), 5.73 (s, 1H), 4.01 (s, 3H), 3.86 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 158.4, 156.6, 150.9, 150.8, 135.9, 106.0, 103.4, 101.3, 98.5, 96.5, 56.2, 55.3.

1,3-dihydroxy-2-chloro-4-(5,9-dimethyl-2-(propan-2-ylidene)deca-4,8-dien-1-yl)-6,8-dimethoxynaphthalene (3:1 mixture of E/Z isomers) (3.45)



To a solution of **3.44** (239 mg, 0.94 mmol) in MeOH (15 mL), KOH (105 mg, 1.88 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 10 min before **3.33** (400 mg, 1.4 mmol) was added at 0 °C. The reaction mixture was stirred at 0 °C for a further 30 min before dilution with H_2O (20 mL) and quenched with 1 M HCl (5 mL).The mixture was extracted with EtOAc (4 x 40 mL) and the combined organics were washed with brine (80 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/ EtOAc, 15:1 → 10:1 gradient elution) to give alkylation 1,3-dihydroxy-2-chloro-4-(5,9-dimethyl-2-(propan-2-ylidene)deca-4,8-dien-1-yl)-6,8-dimethoxynaphthalene (3:1 mixture of E/Z isomers) (**3.45**) (431 mg, 53%) as a pale yellow solid.

R_f = 0.44 (petrol/EtOAc, 4:1)

Mp = 95 - 97 °C

IR (neat): 3486, 3339, 2919, 1620, 1597, 1380, 1257, 1154 cm^{-1}

NMR data for major (*E*)-isomer:

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.80 (s, 1H), 6.74 (d, *J* = 2.2 Hz, 1H), 6.35 (d, *J* = 2.2 Hz, 1H), 6.01 (s, 1H), 5.01 (t, *J* = 6.9 Hz, 1H), 4.79 (t, *J* = 6.1 Hz, 1H), 4.00 (s, 3H), 3.82 (s, 3H), 3.78 (s, 2H), 2.51 (d, *J* = 6.5 Hz, 2H), 1.99 (s, 3H), 1.89 – 1.80 (m, 2H), 1.77 – 1.75 (m, 2H), 1.74 (s, 3H), 1.66 (s, 3H), 1.56 (s, 3H), 1.28 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 158.0, 156.9, 149.1, 149.1, 135.6, 134.1, 131.1, 131.0, 125.6, 124.5, 123.0, 109.7, 106.1, 103.7, 96.3, 96.0, 56.3, 55.2, 39.6, 29.5, 28.9, 26.5, 25.7, 20.8, 20.7, 17.6, 15.8.

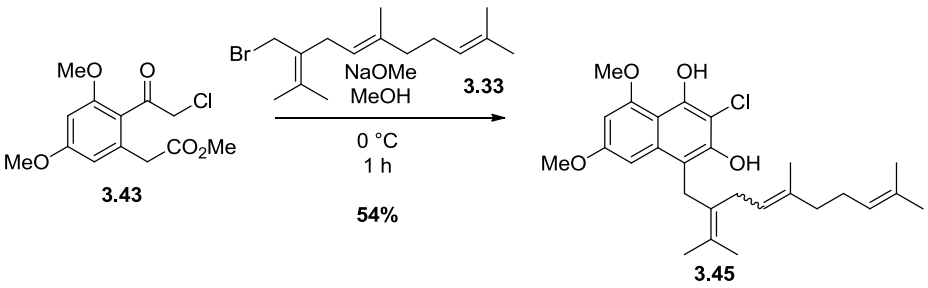
NMR data for minor (*Z*)-isomer:

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.81 (s, 1H), 6.74 (d, *J* = 2.2 Hz, 1H), 6.35 (d, *J* = 2.2 Hz, 1H), 6.03 (s, 1H), 4.96 (t, *J* = 6.9 Hz, 1H), 4.88 (t, *J* = 6.1 Hz, 1H), 4.01 (s, 3H), 3.82 (s, 3H), 3.78 (s, 2H), 2.51 (d, *J* = 6.5 Hz, 2H), 1.97 (s, 3H), 1.89 – 1.80 (m, 2H), 1.77 – 1.75 (m, 2H), 1.61 (s, 3H), 1.53 (s, 3H), 1.49 (s, 3H), 1.28 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 158.0, 157.0, 149.2, 149.2, 135.5, 134.6, 131.3, 131.0, 125.7, 124.4, 123.8, 109.7, 106.1, 103.7, 96.3, 96.0, 56.3, 55.2, 31.8, 29.1, 28.7, 26.3, 25.6, 23.3, 20.8, 20.8, 17.5.

HRMS (EI): calculated for $C_{27}H_{35}O_4Cl$ 458.2224 $[M]^{+\bullet}$, found 458.2226.

1,3-dihydroxy-2-chloro-4-(5,9-dimethyl-2-(propan-2-ylidene)deca-4,8-dien-1-yl)-6,8-dimethoxynaphthalene (3:1 mixture of E/Z isomers) (3.45)



To a suspension of **3.43** (3.80 g, 13.2 mmol) in MeOH (150 mL), NaOMe (2.10 g, 40.0 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 30 minutes before **3.33** (4.8 g, 17.2 mmol) was added. The resultant mixture was stirred for a further 20 mins before it was diluted with H_2O (120 mL) and quenched with 1 M HCl (30 mL). The mixture was extracted with EtOAc (4 x 150 mL), and the combined organics were washed with brine (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/ EtOAc, 15:1 → 10:1 gradient elution) to give 1,3-dihydroxy-2-chloro-4-(5,9-dimethyl-2-(propan-2-ylidene)deca-4,8-dien-1-yl)-6,8-dimethoxynaphthalene (3:1 mixture of E/Z isomers) (**3.45**) (3.25 g, 54%) as a pale yellow solid.

R_f = 0.44 (petrol/EtOAc, 4:1)

Mp = 95 - 97 °C

IR (neat): 3486, 3339, 2919, 1620, 1597, 1380, 1257, 1154 cm^{-1}

NMR data for major (*E*)-isomer:

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.80 (s, 1H), 6.74 (d, *J* = 2.2 Hz, 1H), 6.35 (d, *J* = 2.2 Hz, 1H), 6.01 (s, 1H), 5.01 (t, *J* = 6.9 Hz, 1H), 4.79 (t, *J* = 6.1 Hz, 1H), 4.00 (s, 3H), 3.82 (s, 3H), 3.78 (s, 2H), 2.51 (d, *J* = 6.5 Hz, 2H), 1.99 (s, 3H), 1.89 – 1.80 (m, 2H), 1.77 – 1.75 (m, 2H), 1.74 (s, 3H), 1.66 (s, 3H), 1.56 (s, 3H), 1.28 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 158.0, 156.9, 149.1, 149.1, 135.6, 134.1, 131.1, 131.0, 125.6, 124.5, 123.0, 109.7, 106.1, 103.7, 96.3, 96.0, 56.3, 55.2, 39.6, 29.5, 28.9, 26.5, 25.7, 20.8, 20.7, 17.6, 15.8.

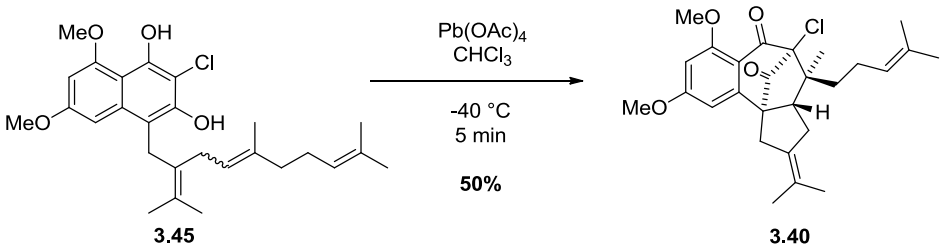
NMR data for minor (*Z*)-isomer:

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.81 (s, 1H), 6.74 (d, *J* = 2.2 Hz, 1H), 6.35 (d, *J* = 2.2 Hz, 1H), 6.03 (s, 1H), 4.96 (t, *J* = 6.9 Hz, 1H), 4.88 (t, *J* = 6.1 Hz, 1H), 4.01 (s, 3H), 3.82 (s, 3H), 3.78 (s, 2H), 2.51 (d, *J* = 6.5 Hz, 2H), 1.97 (s, 3H), 1.89 – 1.80 (m, 2H), 1.77 – 1.75 (m, 2H), 1.61 (s, 3H), 1.53 (s, 3H), 1.49 (s, 3H), 1.28 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 158.0, 157.0, 149.2, 149.2, 135.5, 134.6, 131.3, 131.0, 125.7, 124.4, 123.8, 109.7, 106.1, 103.7, 96.3, 96.0, 56.3, 55.2, 31.8, 29.1, 28.7, 26.3, 25.6, 23.3, 20.8, 20.8, 17.5.

HRMS (EI): calculated for $C_{27}H_{35}O_4Cl$ 458.2224 $[M]^{+\bullet}$, found 458.2226.

di-*O*-methyl merochlorin A (3.40)



3.45 **3.40**

To a solution of **3.45** (1.89 g, 4.10 mmol) in $CHCl_3$ (300 mL), $Pb(OAc)_4$ (1.90 g, 4.32 mmol) was added portion wise at -40 °C. The reaction mixture was stirred at -40 °C for 5 min before gradual warming to rt. The mixture was filtered through a short pad of SiO_2 and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 3:1 as eluent) to give di-*O*-methyl merochlorin A (**3.40**) (938 mg, 50%) as a white solid.

R_f = 0.29 (petrol/EtOAc, 2:1)

Mp = 99 – 101 °C

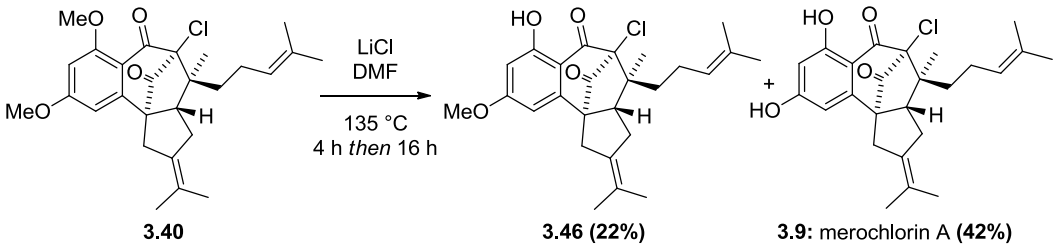
IR (neat): 2916, 1766, 1688, 1601, 1564, 1329, 1205 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.52 (d, *J* = 1.9 Hz, 1H), 6.41 (d, *J* = 2.0 Hz, 1H), 5.02 (t, *J* = 7.0 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.17 (d, *J* = 15.2 Hz, 1H), 2.76 (d, *J* = 15.3 Hz, 1H), 2.47 (d, *J* = 15.1 Hz, 1H), 2.43 – 2.36 (m, 1H), 2.34 (dd, *J* = 9.7, 2.9 Hz, 1H), 2.17 – 2.10 (m, 1H), 1.89 – 1.81 (m, 1H), 1.78 (s, 3H), 1.75 – 1.68 (m, 1H), 1.66 (s, 3H), 1.63 (s, 3H), 1.57 (s, 3H), 1.34 – 1.27 (m, 1H), 0.93 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 200.5, 187.2, 165.1, 164.0, 151.6, 131.6, 131.6, 123.9, 123.7, 114.8, 99.9, 97.1, 91.0, 61.2, 58.9, 56.2, 55.6, 44.2, 38.4, 32.0, 29.7, 25.6, 22.8, 21.1, 20.8, 17.6, 16.0.

HRMS (ESI): calculated for $C_{27}H_{33}O_4ClNa$ 479.1965 $[M+Na]^+$, found 479.1972.

***O*-methyl merochlorin A (3.40) and merochlorin A (3.9)**



3.40 **3.46 (22%)** **3.9:** merochlorin A **(42%)**

3.40 (307 mg, 0.672 mmol) and LiCl (424 mg, 10.0 mmol) were dissolved in DMF (7 mL). The mixture was heated to 135 °C and stirred for 4 h. The mixture was cooled, quenched with 1 M HCl (20 mL) and then extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (3 x 20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. LiCl (424 mg, 10.0 mmol) and DMF (7 mL) were added to the residue and the mixture was heated to 135 °C and stirred overnight. The mixture was cooled, quenched with 1 M HCl (20 mL) and then extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (3 x 20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/ EtOAc, 10:1 → 4:1 gradient elution) to give *O*-methyl merochlorin A (**3.40**) (64 mg, 22%) as a white solid.

R_f = 0.54 (petrol/EtOAc, 4:1)

Mp = 110 – 111 °C

IR (neat): 2915, 1771, 1619, 1576, 1381, 1204, 966 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 12.32 (d, *J* = 6.0 Hz, 1H), 6.43 (d, *J* = 2.0 Hz, 1H), 6.36 (d, *J* = 2.2 Hz, 1H), 5.00 (t, *J* = 6.9 Hz, 1H), 3.86 (s, 3H), 3.14 (d, *J* = 15.4 Hz, 1H), 2.71 (d, *J* = 15.4 Hz, 1H), 2.46 - 2.37 (m,2H),2.32 (dd, *J* = 9.5, 4.2 Hz, 1H), 2.16 – 2.10 (m,1H), 1.89 – 1.81 (m, 1H), 1.78 (s, 3H), 1.68 (dt, 12.0, 5.0 Hz, 1H), 1.65 (s, 6H), 1.58 (s, 3H), 1.23 (dt, 12.0, 5.0 Hz, 1H), 0.98 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 199.2, 194.2, 166.7, 166.5, 149.6, 132.2, 131.4, 124.0, 123.4, 110.7, 102.4, 99.1, 90.5, 61.3, 58.6, 55.9, 45.2, 39.4, 31.9, 29.0, 25.6, 22.7, 21.1, 20.8, 17.6, 16.6.

HRMS (ESI): calculated for $C_{26}H_{30}O_4Cl$ 441.1833 $[M-H]^-$, found 441.1832.

Further elution gave merochlorin A (**3.9**) (123 mg, 42%) as a white solid.

R_f = 0.39 (petrol/EtOAc, 2:1)

Mp = 63 - 65 °C

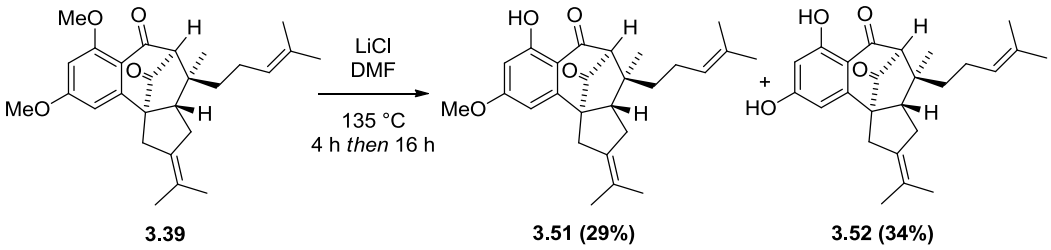
IR (neat): 3450, 2916, 1776, 1619, 1595, 1448, 1149, 845 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 12.23 (s,1H), 6.39 (d, *J* = 2.1 Hz, 1H), 6.31 (d, *J* = 1.9 Hz, 1H),6.12 (s, 1H), 4.99 (t, *J* = 6.9 Hz, 1H), 3.13 (d, *J* = 15.4 Hz, 1H), 2.69 (d, *J* = 15.4 Hz, 1H), 2.46 – 2.37 (m, 2H), 2.33 (dd, *J* = 9.5, 4.1 Hz, 1H), 2.17 – 2.09 (m, 1H), 1.90 – 1.79 (m, 1H), 1.76 (s, 3H), 1.68 (dt, 12.0, 5.0 Hz, 1H), 1.65 (s, 6H), 1.58 (s, 3H), 1.23 (dt, 12.0, 5.0 Hz, 1H),0.98 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 199.5, 194.2, 166.2, 163.6, 150.6, 132.3, 131.3, 124.1, 123.4, 111.0, 102.3, 102.1, 90.6, 61.4, 58.6, 45.2, 39.4, 31.9, 29.0, 25.6, 22.7, 21.1, 20.8, 17.7, 16.6.

HRMS (ESI): calculated for $C_{25}H_{28}O_4Cl$ 427.1676 $[M-H]^-$, found 427.1662.

_O_-methyldeschlorin merochlorin A (3.51) and deschloro merochlorin A (3.52)



3.39 **3.51 (29%)** **3.52 (34%)**

3.39 (195 mg, 0.461 mmol) and LiCl (293 mg, 6.92 mmol) were dissolved in DMF (5 mL). The mixture was heated to 135 °C and stirred for 4 h. The mixture was cooled, quenched with 1 M HCl (20 mL) and then extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (3 x 20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. LiCl (293 mg, 6.92 mmol) and DMF (5 mL) were added to the residue and the mixture was heated to 135 °C and stirred overnight. The mixture was cooled, quenched with 1 M HCl (20 mL) and then extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (3 x 20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/ EtOAc, 5:1 as eluent) to give *O*-methyldeschlorin merochlorin A (**3.51**) (54 mg, 29%) as a white solid.

R_f = 0.49 (petrol/EtOAc, 4:1)

Mp = 130-135 °C

IR (neat): 2909, 1755, 1611, 1429, 1348, 1203, 971, 820, cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 12.62 (s, 1H), 6.43 (d, *J* = 2.1 Hz, 1H), 6.34 (d, *J* = 2.1 Hz, 1H), 5.02 (t, *J* = 7.0 Hz, 1H), 3.85 (s, 3H), 3.26 (s, 1H), 3.08 (d, *J* = 15.4 Hz, 1H), 2.61 (d, *J* = 15.3 Hz, 1H), 2.37 – 2.29 (m, 2H), 2.22 (dd, *J* = 9.2, 5.3 Hz, 1H), 2.19 – 2.09 (m, 1H), 1.95 – 1.84 (m, 1H), 1.77 (s, 3H), 1.65 (s, 3H), 1.65 (s, 3H), 1.60 (s, 3H), 1.51 (td, *J* = 12.0, 4.8 Hz, 1H), 1.29 (td, *J* = 12.0, 4.8 Hz, 1H), 0.97 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 204.0, 199.5, 166.3, 166.2, 150.5, 132.5, 132.0, 123.6, 123.4, 111.3, 102.2, 98.9, 75.6, 64.2, 58.5, 55.7, 41.4, 41.3, 30.7, 28.5, 25.7, 23.1, 21.1, 20.8, 20.7, 17.6.

Further elution gave deschloro merochlorin A (**3.52**) (62 mg, 34%) as a white solid.

R_f = 0.25 (petrol/EtOAc, 2:1)

Mp = 76 – 80 °C

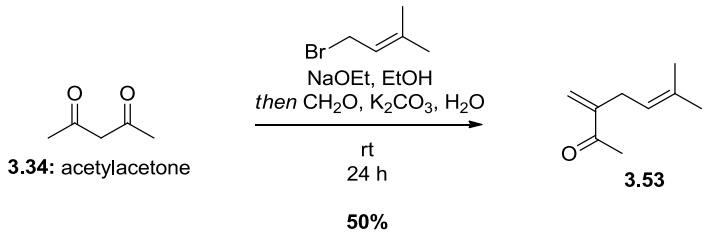
IR (neat): 3340, 2916, 1761, 1623, 1451, 1160, 1037, 754 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 12.54 (s, 1H), 6.38 (d, *J* = 1.8 Hz, 1H), 6.28 (d, *J* = 1.8 Hz, 1H), 5.01 (t, *J* = 7.0 Hz, 1H), 3.27 (s, 1H), 3.08 (d, *J* = 15.4 Hz, 1H), 2.59 (d, *J* = 15.4 Hz, 1H), 2.38 – 2.30 (m, 2H), 2.23 (dd, *J* = 9.1, 5.4 Hz, 1H), 2.18 – 2.09 (m, 1H), 1.95 – 1.84 (m, 1H), 1.77 (s, 3H), 1.65 (s, 3H), 1.65 (s, 3H), 1.59 (s, 3H), 1.52 (dt, *J* = 12.0, 4.8 Hz, 1H), 1.29 (dt, *J* = 12.0, 4.8 Hz, 1H), 0.98 (s, Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 204.0, 199.5, 165.9, 162.9, 151.5, 132.4, 132.0, 123.6, 123.5, 111.6, 110.8, 102.1, 101.8, 75.6, 64.3, 58.5, 41.4, 41.3, 30.7, 28.6, 25.7, 23.1, 21.1, 20.8, 17.6.

HRMS (ESI): calculated for $C_{25}H_{29}O_4$ 393.2071 $[M-H]^-$, found 393.2070.

6-methyl-3-methylenehept-5-en-2-one (3.53)[28]



To a solution of acetylacetone (**3.34**) (13.5 g,135 mmol) in EtOH (90 mL), NaH (60% dispersion in mineral oil, 5.94 g, 149 mmol) was added portion wise at 0 °C. The mixture was stirred at 0 °C for 10 min. Prenyl bromide (18.7 mL, 162 mmol) was then added at 0 °C. The mixture was stirred at rt overnight. The mixture was then diluted with H_2O (200 mL), followed by successive addition of paraformaldehyde (20.0 g, 675 mmol) and K_2CO_3 (37.0 g, 138 mmol). The resultant mixture was stirred at rt for a further 24 h. The mixture was diluted with H_2O (100 mL) and extracted with Et_2O (3x 200 mL). The combined organics were washed with brine (300 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was distilled under reduced pressure (80 °C, 15 torr) to give 6-methyl-3-methylenehept-5-en-2-one (**3.53**) (9.43 g, 50%) as a colourless oil.

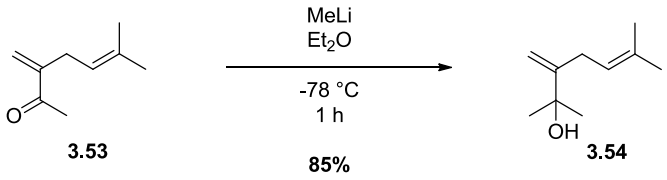
R_f = 0.33 (petrol/EtOAc, 10:1)

IR (neat): 2917, 1678, 1432, 1364, 1121, 944, 843 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (s, 1H), 5.75 (s, 1H), 5.14 (t, *J* = 7.3 Hz, 1H), 2.95 (d, *J* = 7.3 Hz, 2H), 2.35 (s, 3H), 1.74 (s, 3H), 1.62 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7, 148.1, 134.0 124.8, 120.7, 28.9, 25.9, 25.7, 17.6.

2,6-dimethyl-3-methylenehept-5-en-2-ol (3.54)[28]



3.53 **3.54**

To a solution of **3.53** (3.00 g, 21.7 mmol) in Et_2O (50 mL), MeLi (1.5 M in Et_2O, 28.9 mL, 43.4 mmol) was added drop wise at -78 °C. The mixture was stirred at -78 °C for 1 h before slow warming to rt. The mixture was quenched with *sat*. NH_4Cl solution (100 mL) and extracted with Et_2O (2 x 100 mL). The combined organics were washed with brine (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give 2,6-dimethyl-3-methylenehept-5-en-2-ol (**3.54**) (2.84 g, 85%) as a colourless oil.

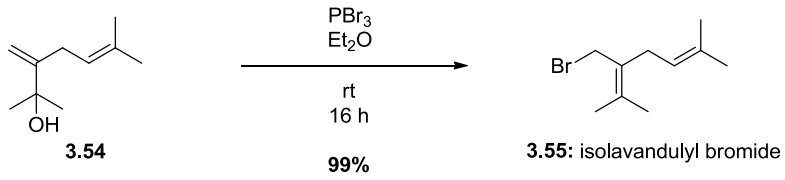
R_f = 0.37 (petrol/EtOAc, 4:1)

IR (neat): 3379, 2975, 1637, 1440, 1376, 1136, 961, 902 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (t, *J* = 7.2 Hz, 1H), 5.09 (d, *J* = 1.2 Hz, 1H), 4.79 (d, *J* = 1.2 Hz, 1H), 2.81 (d, *J* = 7.2 Hz, 2H), 1.75 (s, 3H), 1.63 (s, 3H), 1.51 (s, 1H), 1.37 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 133.0, 122.6, 107.9, 73.4, 30.3, 29.3, 25.7, 17.6.

isolavandulyl bromide (3.55)[28]



3.54 **3.55:** isolavandulyl bromide

To a solution of **3.54** (2.84 g, 18.4 mmol) in Et_2O (100 mL), pyridine (0.15 mL, 1.8 mmol) and PBr_3 (0.87 mL, 9.2 mmol) were added successively at rt. The mixture was stirred at rt for 1 h. The mixture was diluted with Et_2O (100 mL), and washed successively with *sat*. NH_4Cl solution (100 mL), H_2O (100 mL) and brine (100 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give isolavandulyl bromide (**3.55**) (3.95 g, 99%) as a pale brown oil which was used in the next step without further purification.

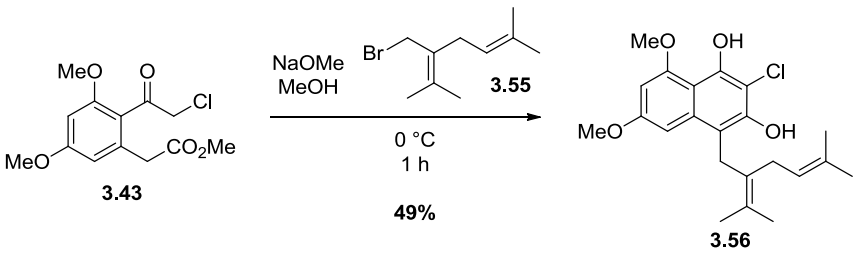
R_f = 0.70 (petrol/EtOAc, 10:1)

IR (neat): 3396, 2924, 1443, 1370, 1200, 988 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04 (t, *J* = 7.3 Hz, 1H), 4.06 (s, 2H), 2.89 (d, *J* = 7.2 Hz, 2H), 1.79 (s, 3H), 1.75 (s, 3H), 1.72 (s, 6H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 133.7, 132.8, 128.9, 121.9, 46.1, 34.9, 34.1, 29.6, 25.7, 20.7.

2-chloro-6,8-dimethoxy-4-(5-methyl-2-(propan-2-ylidene)hex-4-en-1-yl)naphthalene-1,3-diol (3.56)



To a solution of **3.43** (3.53 g, 12.3 mmol) in MeOH (100 mL), NaOMe (2.00 g, 37.0 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 30 min before **3.55** (3.48 g, 16.0 mmol) was added. The reaction mixture was stirred at 0 °C for a further 30 min. The mixture was diluted with H_2O (100 mL), quenched with 1 M HCl (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine (150 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/ EtOAc, 15:1 → 10:1 gradient elution) to give 2-chloro-6,8-dimethoxy-4-(5-methyl-2-(propan-2-ylidene)hex-4-en-1-yl)naphthalene-1,3-diol (**3.56**) (2.36g, 49%) as a pale yellow solid.

R_f = 0.37 (petrol/EtOAc, 4:1)

Mp = 173 – 175 °C

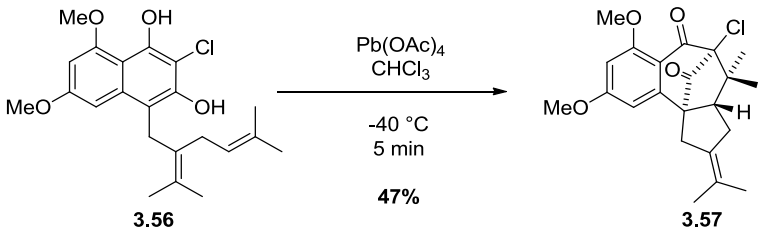
IR (neat): 3503, 3331, 2912, 1620, 1597, 1380, 1256, 1154, 936, 818, 722 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.83 (s, 1H), 6.75 (d, *J* = 2.1 Hz, 1H), 6.37 (d, *J* = 2.1 Hz, 1H), 6.04 (s, 1H), 4.85 (t, *J* = 6.7 Hz, 1H), 4.03 (s, 3H), 3.84 (s, 3H), 3.79 (s, 2H), 2.50 (d, *J* = 6.6 Hz, 2H), 1.99 (s, 3H), 1.75 (s, 3H), 1.52 (s, 3H), 1.30 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 156.9, 149.2, 149.1, 135.5, 130.9, 130.6, 125.7, 123.3, 109.7, 106.1, 103.7, 96.3, 96.0, 56.3, 55.2, 29.5, 28.7, 25.6, 20.8, 20.7, 17.4.

HRMS (ESI): calculated for $C_{22}H_{26}ClO_4$ 389.1525 $[M-H]^-$, found 389.1522.

5-chloro-7,9-dimethoxy-4,4-dimethyl-2-(propan-2-ylidene)-3,3a,4,5-tetrahydro-1H-5,10b-methanobenzo[e]azulene-6,11(2H)-dione (3.57)



3.56 3.57

To a solution of **3.56** (1.33 g, 34.0 mmol) in $CHCl_3$ (300 mL), $Pb(OAc)_4$ (1.58 g, 35.7 mmol) was added portion wise at -40 °C. The reaction mixture was stirred at -40 °C for 5 min before gradual warming to rt. The mixture was filtered through a short pad of SiO_2 and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/ EtOAc, 3:1) to give 2-chloro-6,8-dimethoxy-4-(5-methyl-2-(propan-2-ylidene)hex-4-en-1-yl)naphthalene-1,3-diol (**3.57**) (614 mg, 47%) as a white solid.

R_f = 0.17 (petrol/EtOAc, 2:1)

Mp = 190 – 194 °C

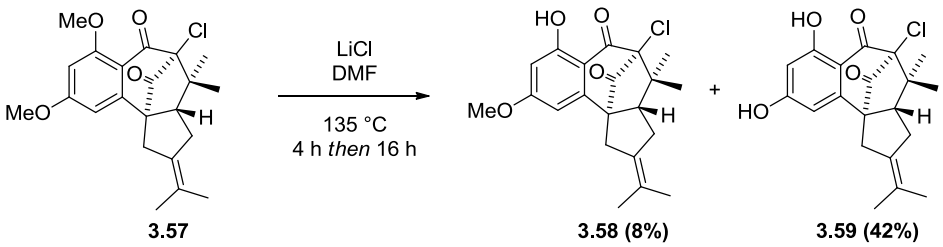
IR (neat): 2986, 1768, 1682, 1600, 1565, 1452, 1204, 1159, 727 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.53 (d, *J* = 1.9 Hz, 1H), 6.41 (d, *J* = 1.9 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.21 (d, *J* = 15.2 Hz, 1H), 2.75 (d, *J* = 15.2 Hz, 1H), 2.54 – 2.45 (m, 1H), 2.39 – 2.30 (m, 2H), 1.78 (s, 3H), 1.66 (s, 3H), 1.14 (s, 3H), 0.90 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.7, 187.8, 165.1, 163.8, 151.4, 131.6, 123.8, 114.9, 100.0, 97.1, 89.7, 61.3, 60.0, 56.2, 55.7, 41.7, 30.7, 29.7, 24.1, 21.1, 20.8, 19.6.

HRMS (ESI): calculated for $C_{22}H_{25}ClO_4Na$ 411.1339 $[M+Na]^+$, found 411.1335.

5-chloro-7-hydroxy-9-methoxy-4,4-dimethyl-2-(propan-2-ylidene)-3,3a,4,5-tetrahydro-1H-5,10b-methanobenzo[e]azulene-6,11(2H)-dione (3.58) and 5-chloro-7,9-dihydroxy-4,4-dimethyl-2-(propan-2-ylidene)-3,3a,4,5-tetrahydro-1H-5,10b-methanobenzo[e]azulene-6,11(2H)-dione (3.59)



3.57 **3.58 (8%)** **3.59 (42%)**

3.57 (459 mg, 1.18 mmol) and LiCl (750 mg, 17.7 mmol) were dissolved in DMF (12 mL). The mixture was heated to 135 °C and stirred for 4 h. The mixture was cooled, quenched with 1 M HCl (40 mL) and then extracted with EtOAc (3 x 40 mL). The combined organics were washed with brine (3 x 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. LiCl (750 mg, 17.7 mmol) and DMF (12 mL) were added to the residue and the mixture was heated to 135 °C and stirred overnight. The mixture was cooled, quenched with 1 M HCl (40 mL) and then extracted with EtOAc (3 x 40 mL). The combined organics were washed with brine (3 x 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/ EtOAc, 10:1 → 4:1gradient elution) to give 5-chloro-7-hydroxy-9-methoxy-4,4-dimethyl-2-(propan-2-ylidene)-3,3a,4,5-tetrahydro-1H-5,10b-methanobenzo[e]azulene-6,11(2H)-dione (**3.58**) (36 mg, 8%) as a white solid.

R_f = 0.48 (petrol/EtOAc, 4:1)

Mp = 164 – 167 °C

IR (neat): 2911, 1773, 1620, 1577, 1432, 1380, 1295, 1201, 1158, 912, 835, 729 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 12.24 (s, 1H), 6.44 (d, *J* = 2.2 Hz, 1H), 6.36 (d, *J* = 2.2 Hz, 1H), 3.87 (s, 3H), 3.16 (d, *J* = 15.4 Hz, 1H), 2.71 (d, *J* = 15.4 Hz, 1H), 2.48 – 2.44 (m, 1H), 2.39 -2.32 (m, 1H), 1.77 (s, 3H), 1.65 (s, 3H), 1.14 (s, 3H), 0.96 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.4, 194.5, 166.7, 166.4, 149.6, 131.4, 124.1, 110.8, 102.5, 99.1, 89.7, 61.6, 59.7, 55.9, 42.4, 30.7, 29.0, 25.2, 21.1, 20.8, 20.3.

HRMS (ESI): calculated for $C_{21}H_{23}O_4ClNa$ 397.1183 $[M+Na]^+$, found 397.1170.

Further elution gave 5-chloro-7,9-dihydroxy-4,4-dimethyl-2-(propan-2-ylidene)-3,3a,4,5-tetrahydro-1H-5,10b-methanobenzo[e]azulene-6,11(2H)-dione (**3.59**) (177 mg, 42%) as a white solid.

R_f = 0.16 (petrol/EtOAc, 4:1)

Mp = 247 – 255 °C

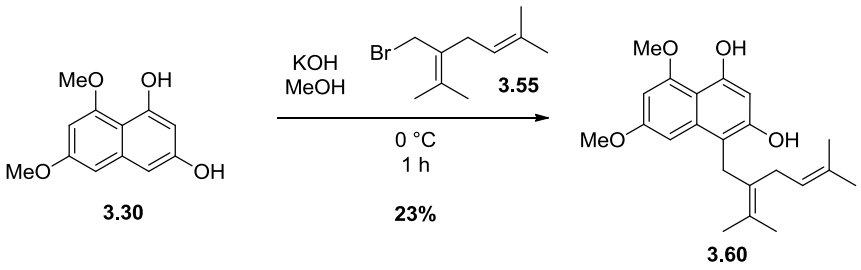
IR (neat): 3354, 2978, 1775, 1628, 1606, 1585, 1451, 1283, 1152, 848, 703 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 12.16 (s, 1H), 6.40 (d, *J* = 2.0 Hz, 1H), 6.31 (d, *J* = 2.0 Hz, 1H), 6.00 (s, 1H), 3.16 (d, *J* = 15.5 Hz, 1H), 2.69 (d, *J* = 15.4 Hz, 1H), 2.50 – 2.44 (m, 1H), 2.40 – 2.32 (m, 2H), 1.77 (s, 3H), 1.65 (s, 3H), 1.14 (s, 3H), 0.96 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 194.6, 166.1, 163.3, 150.6, 131.3, 124.2, 111.2, 102.4, 102.1, 89.7, 61.6, 59.8, 42.4, 30.8, 29.1, 25.2, 21.1, 20.9, 20.3.

HRMS (ESI): calculated for $C_{20}H_{20}ClO_4$ 359.1056 $[M-H]^-$, found 359.1055.

6,8-dimethoxy-4-(5-methyl-2-(propan-2-ylidene)hex-4-en-1-yl)naphthalene-1,3-diol (3.60)



To a solution of **3.30** (2.57 g, 11.7 mmol) in MeOH (40 mL), KOH (654 mg, 11.7 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 10 min before **3.55** (3.80 g, 17.5 mmol) was added at 0 °C. The reaction mixture was stirred at 0 °C for a further 30 min before it was diluted with H_2O (80 mL) and quenched with 1 M HCl (25 mL).The mixture was extracted with EtOAc (4 x 100 mL), and the combined organics were washed with brine (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/ EtOAc, 15:1 → 8:1 gradient elution) to give 6,8-dimethoxy-4-(5-methyl-2-(propan-2-ylidene)hex-4-en-1-yl)naphthalene-1,3-diol (**3.60**) (1.43 g, 34%) as a dark red oil along with recovered **3.30** (590 mg, 23%).

R_f = 0.23 (petrol/EtOAc, 4:1)

Mp = 144 – 149 °C

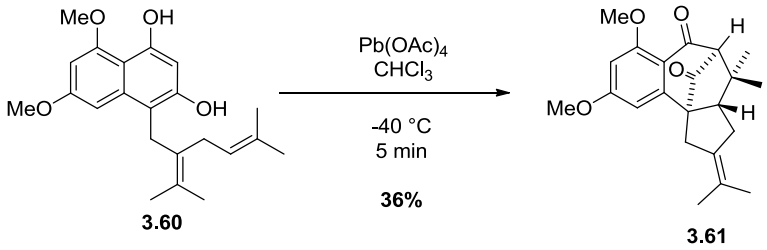
IR (neat): 3411, 3347, 2909, 1644, 1625, 1602, 1454, 1377, 1306, 1150, 1026, 933, 818, 720 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (s, 1H), 6.76 (d, *J* = 2.1 Hz, 1H), 6.37 (s, 1H), 6.34 (d, *J* = 2.1 Hz, 1H), 5.87 (s, 1H), 4.97 (t, *J* = 6.8 Hz, 1H), 4.01 (s, 3H), 3.86 (s, 3H), 3.69 (s, 2H), 2.60 (d, *J* = 6.7 Hz, 2H), 2.00 (s, 3H), 1.81 (s, 3H), 1.61 (s, 3H), 1.29 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 157.8, 155.0, 154.5, 137.5, 132.6, 131.1, 127.6, 122.8, 107.8, 106.6, 100.2, 95.9, 95.0, 56.1, 55.1, 29.5, 28.5, 25.7, 20.8, 20.7, 17.6.

HRMS (ESI): calculated for $C_{22}H_{28}O_4Na$ 379.1885 $[M+Na]^+$, found 379.1873.

7,9-dimethoxy-4,4-dimethyl-2-(propan-2-ylidene)-3,3a,4,5-tetrahydro-1H-5,10b-methanobenzo[e]azulene-6,11(2H)-dione (3.61)



To a solution of **3.60** (1.21 mg, 3.39 mmol) in $CHCl_3$ (200 mL), $Pb(OAc)_4$ (1.58 g, 3.56 mmol) was added portion wise at -40 °C. The reaction mixture was stirred at -40 °C for 5 min before gradual warming to rt. The mixture was filtered through a short pad of $SiO_2$and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 3:1 → 2:1 gradient elution) to give (3aS,5S,10bS)-7,9-dimethoxy-4,4-dimethyl-2-(propan-2-ylidene)-3,3a,4,5-tetrahydro-1H-5,10b-methanobenzo[e]azulene-6,11(2H)-dione (**3.61**) (422 mg, 36%) as a white solid.

R_f = 0.12 (petrol/EtOAc, 2:1)

Mp = 174 – 178 °C

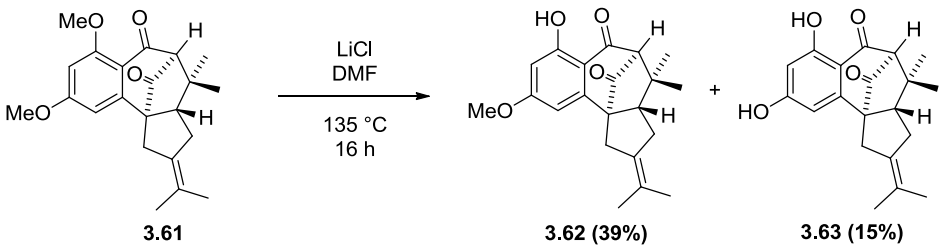
IR (neat): 2910, 1751, 1666, 1599, 1568, 1452, 1212, 1165, 1062, 846, 671 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55 (d, *J* = 1.7 Hz, 1H), 6.41 (d, *J* = 1.7 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.15 (s, 1H), 3.13 (d, *J* = 15.5 Hz, 1H), 2.66 (d, *J* = 15.5 Hz, 1H), 2.42 – 2.28 (m, 2H), 2.25 (dd, *J* = 9.6, 4.3 Hz, 1H), 1.78 (s, 3H), 1.65 (s, 3H), 1.14 (s, 3H), 0.96 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2, 192.9, 164.7, 163.6, 152.6, 132.5, 123.1, 115.4, 100.1, 97.0, 77.7, 64.8, 59.3, 56.2, 55.5, 37.0, 30.2, 29.4, 27.4, 24.5, 21.1, 20.8.

HRMS (ESI): calculated for $C_{22}H_{27}O_4$ 355.1909 $[M+H]^+$, found 355.1907.

7-hydroxy-9-methoxy-4,4-dimethyl-2-(propan-2-ylidene)-3,3a,4,5-tetrahydro-1H-5,10b-methanobenzo[e]azulene-6,11(2H)-dione (3.62) and 7,9-dihydroxy-4,4-dimethyl-2-(propan-2-ylidene)-3,3a,4,5-tetrahydro-1H-5,10b-methanobenzo[e]azulene-6,11(2H)-dione (3.63)



3.61 **3.62 (39%)** **3.63 (15%)**

3.61 (399 mg, 1.80 mmol) and LiCl (701 mg, 16.5 mmol) were dissolved in DMF (8 mL). The mixture was heated to 135 °C and stirred overnight. The mixture was cooled, quenched with 1 M HCl (20 mL) and then extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (3 x 20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/ EtOAc, 10:1 → 4:1 gradient elution) to give 7-hydroxy-9-methoxy-4,4-dimethyl-2-(propan-2-ylidene)-3,3a,4,5-tetrahydro-1H-5,10b-methanobenzo[e]azulene-6,11(2H)-dione (**3.62**) (147 mg, 39%) as a white solid.

R_f = 0.48 (petrol/EtOAc, 4:1)

Mp = 158 – 162 °C

IR (neat): 2961, 1757, 1615, 1563, 1294, 1198, 1158, 963, 835, 742, 572 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 12.56 (s, 1H), 6.44 (d, *J* = 2.1 Hz, 1H), 6.34 (d, *J* = 2.1 Hz, 1H), 3.85 (s, 3H), 3.18 (s, 1H), 3.08 (d, *J* = 15.5 Hz, 1H), 2.63 (d, *J* = 15.5 Hz, 1H), 2.37 – 2.31 (m, 2H), 2.23 (dd, *J* = 8.5, 6.4 Hz, 1H), 1.77 (s, 3H), 1.65 (s, 3H), 1.14 (s, 3H), 1.01 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 199.7, 166.3, 166.1, 150.3, 132.2, 123.4, 111.1, 102.4, 98.9, 75.8, 64.8, 58.9, 55.7, 37.9, 30.2, 28.7, 27.7, 24.9, 21.0, 20.8.

HRMS (ESI): calculated for $C_{21}H_{25}O_4$ 341.1753 $[M+H]^+$, found 341.1737.

Further elution gave 7,9-dihydroxy-4,4-dimethyl-2-(propan-2-ylidene)-3,3a,4,5-tetrahydro-1H-5,10b-methanobenzo[e]azulene-6,11(2H)-dione (**3.63**) (56 mg, 15%) as a white solid.

R_f = 0.24 (petrol/EtOAc, 4:1)

Mp = 219 – 225 °C

IR (neat): 3372, 2962, 1754, 1625, 1583, 1459, 1188, 1013, 860, 767, 642, 561 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 12.48 (s, 1H), 6.41 (d, *J* = 2.2 Hz, 1H), 6.29 (d, *J* = 2.2 Hz, 1H), 3.19 (s, 1H), 3.09 (t, *J* = 13.6 Hz, 1H), 2.61 (d, *J* = 15.7 Hz, 1H), 2.41 – 2.30 (m, 2H), 2.24 (dd, *J* = 8.3, 6.7 Hz, 1H), 2.21 (s, 1H), 1.76 (s, 3H), 1.65 (s, 3H), 1.14 (s, 3H), 1.01 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4, 199.8, 165.9, 163.2, 151.3, 132.1, 123.5, 111.4, 102.4, 101.8, 75.8, 64.9, 58.9, 37.9, 30.2, 28.7, 27.7, 24.9, 21.0, 20.8.

HRMS (ESI): calculated for $C_{20}H_{21}O_4$ 325.1445 $[M-H]^-$, found 325.1446.

References

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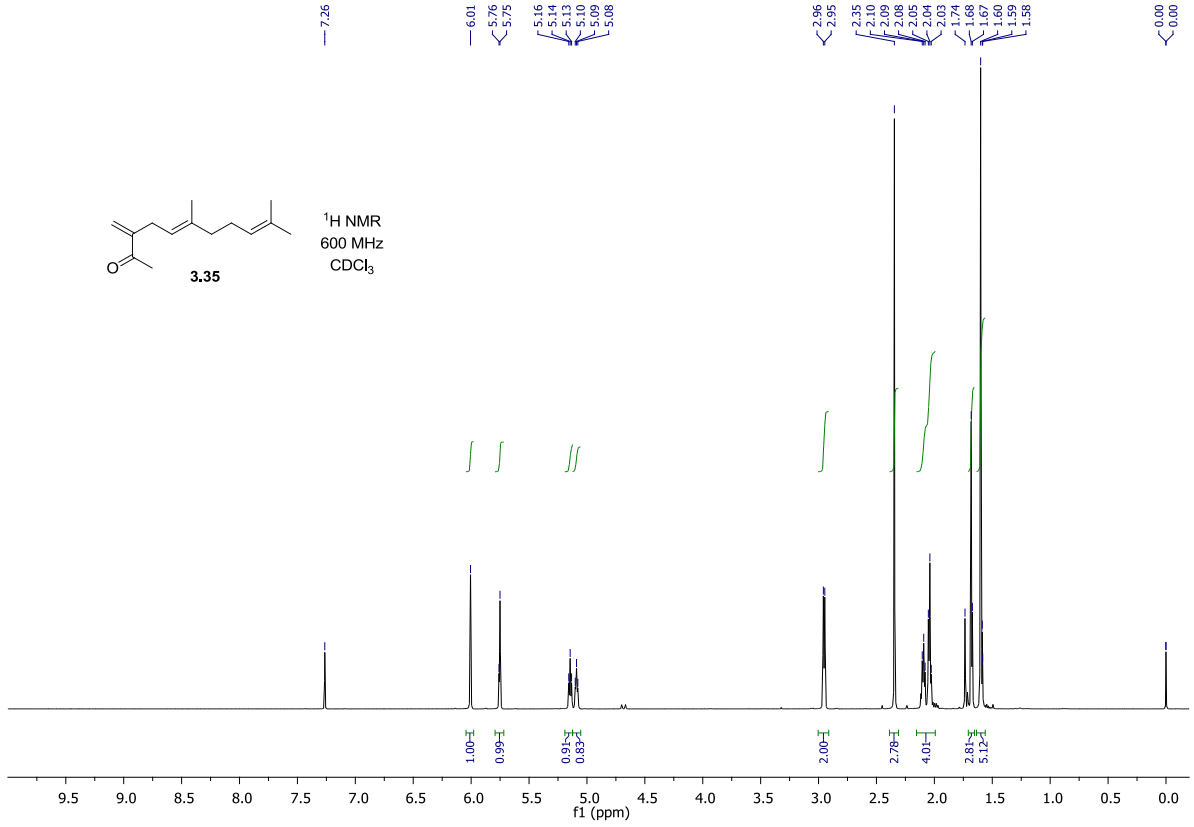
Appendix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2.09
2.08
2.05
2.04
2.03
1.74
1.68
1.67
1.60
1.59
1.58
0.00
0.00
1.00
0.99
0.91
0.83
2.00
2.78
4.01
2.81
5.12
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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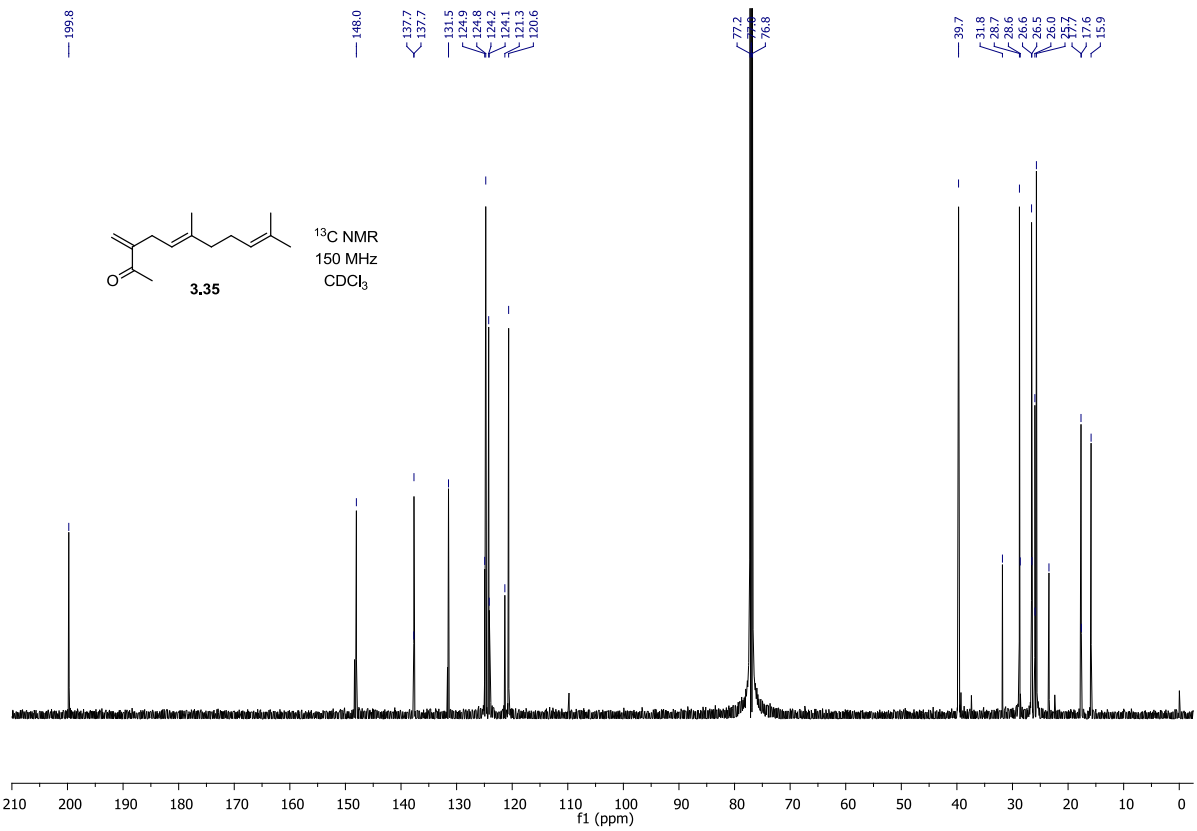
1H NMR
600 MHz
CDCl3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121.3
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77.2
77.0
76.8
39.7
31.8
28.7
28.6
26.6
26.5
26.0
25.7
17.7
17.6
15.9
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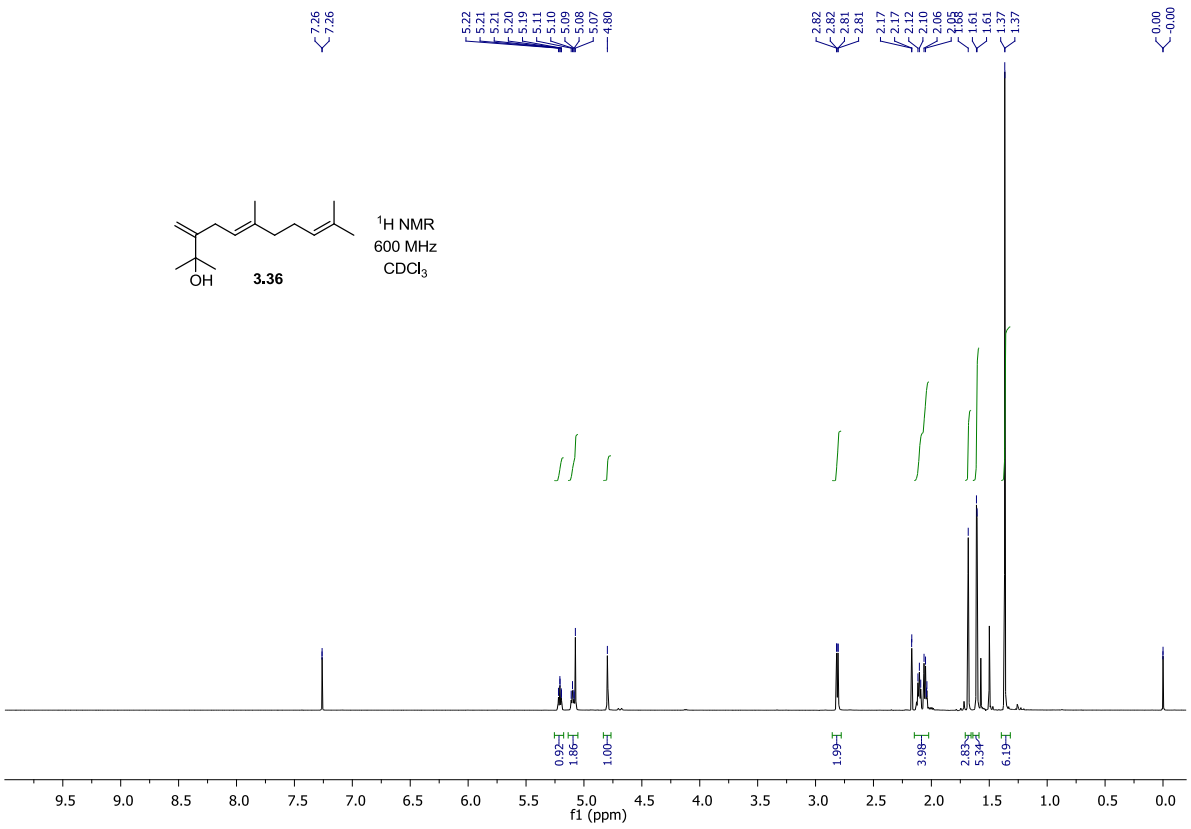
3.35
13C NMR
150 MHz
CDCl3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5.20
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5.11
5.10
5.09
5.08
5.07
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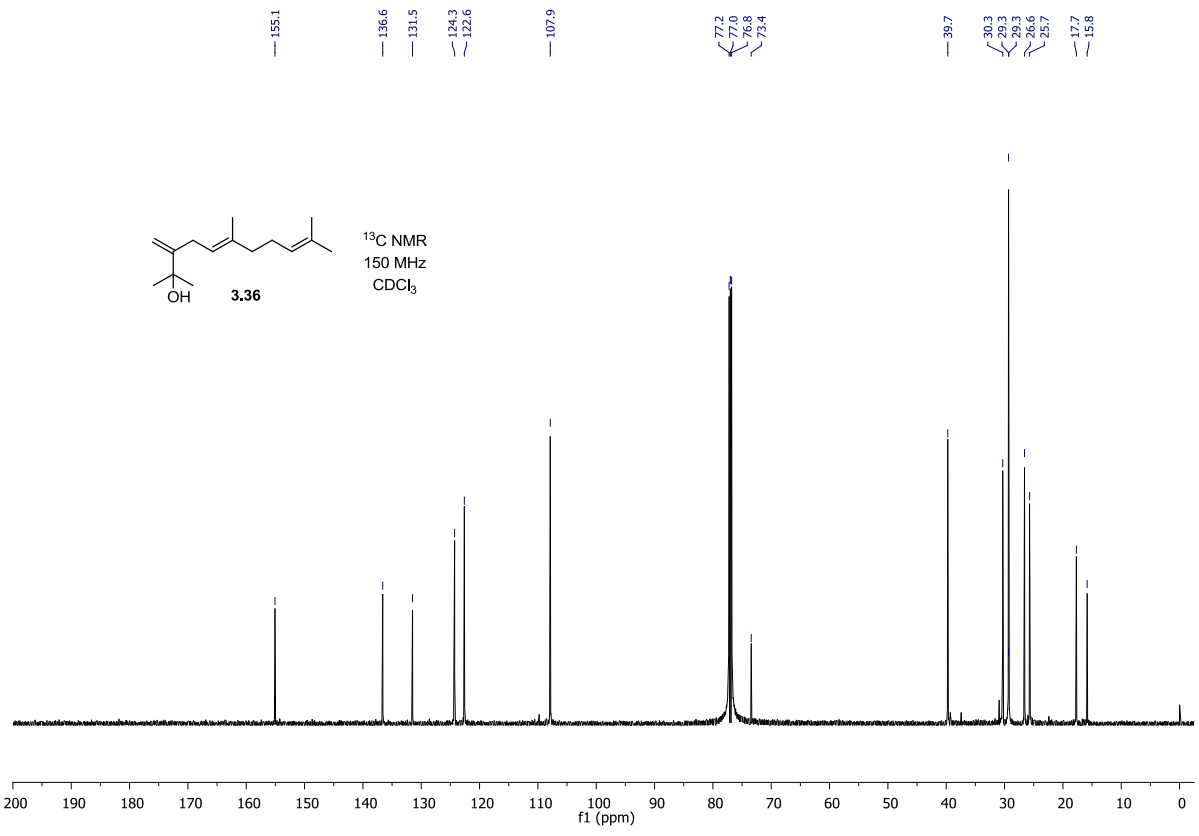
2.82
2.82
2.81
2.81
2.17
2.17
2.12
2.10
2.06
1.68
1.61
1.61
1.37
1.37
0.00
-0.00
OH
3.36
^{1}H NMR
600 MHz
$CDCl_3$
0.92
1.86
1.00
1.99
3.98
2.83
5.34
6.19
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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73.4
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30.3
29.3
29.3
26.6
25.7
17.7
15.8
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^{13}C NMR
150 MHz
$CDCl_3$
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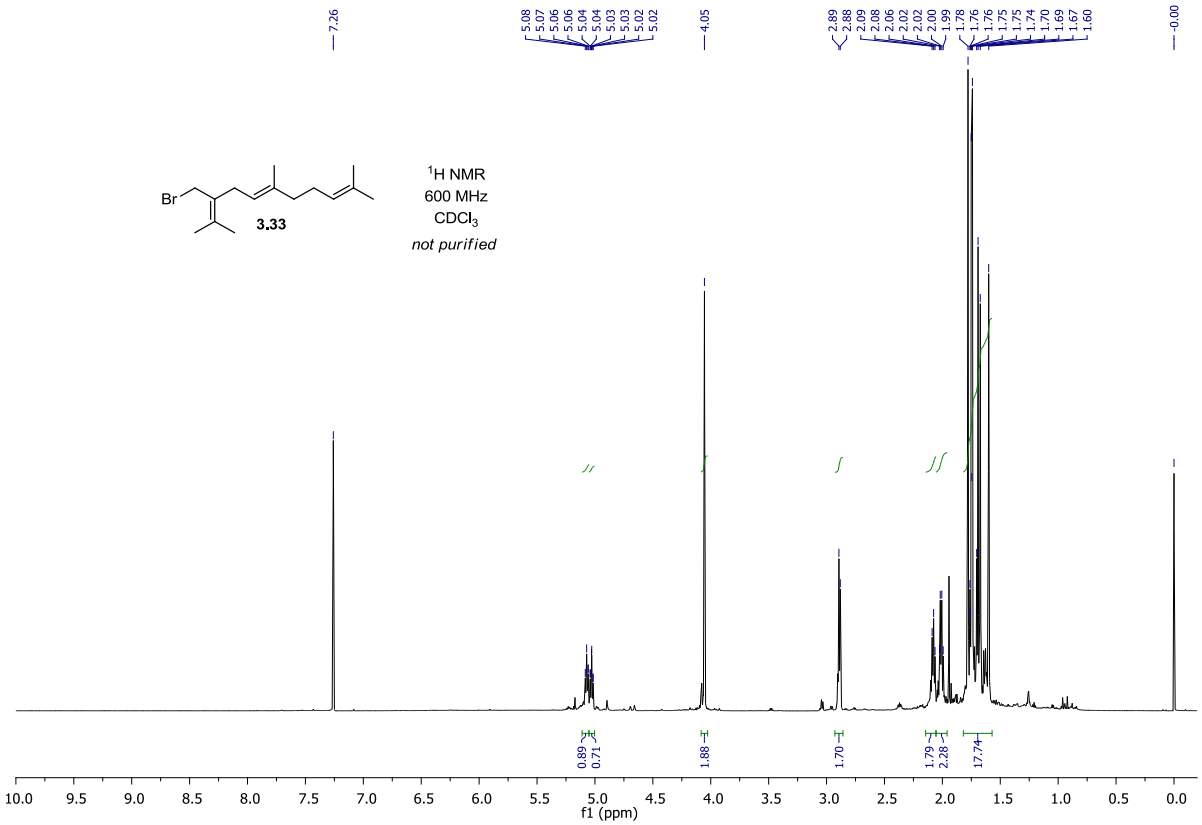
f1 (ppm)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2.08
2.06
2.02
2.02
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1.75
1.75
1.74
1.70
1.69
1.67
1.60
0.00
Br
3.33
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CDCl3
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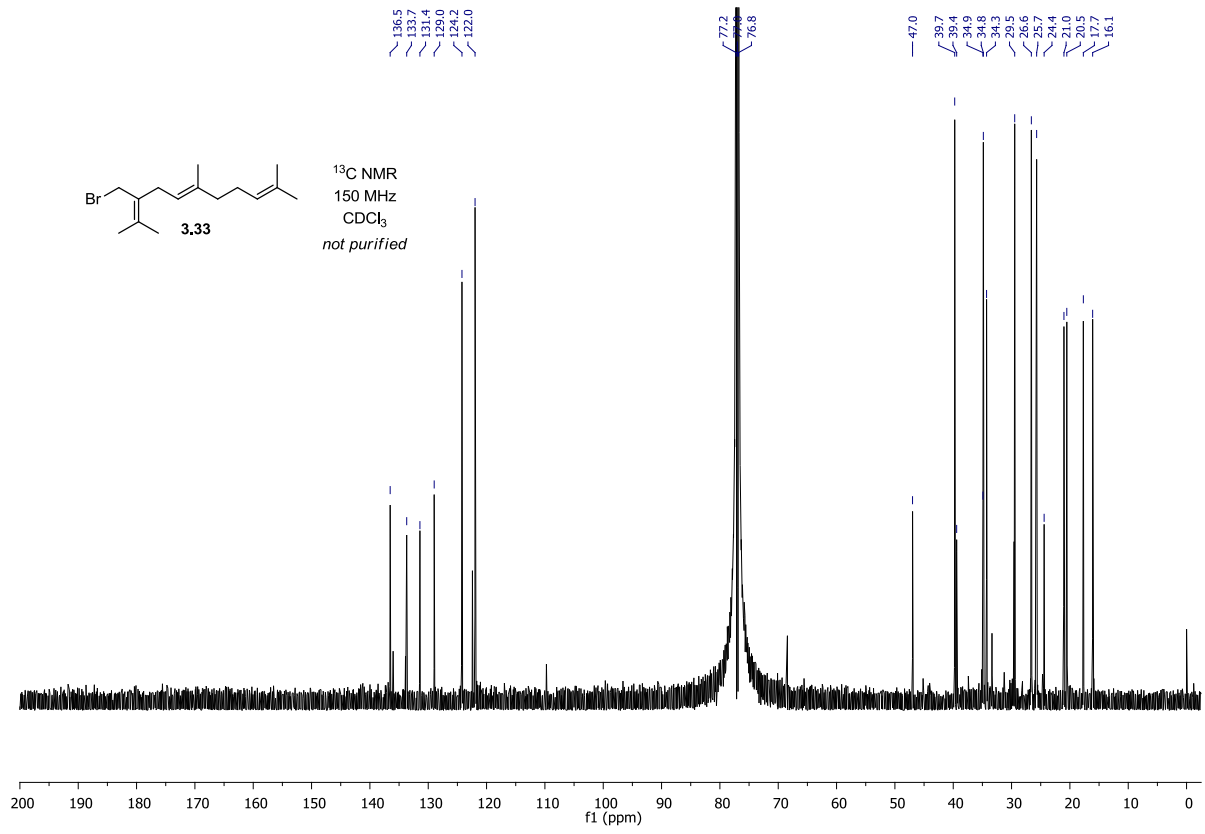
17.74
f1 (ppm)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34.8
34.3
29.5
26.6
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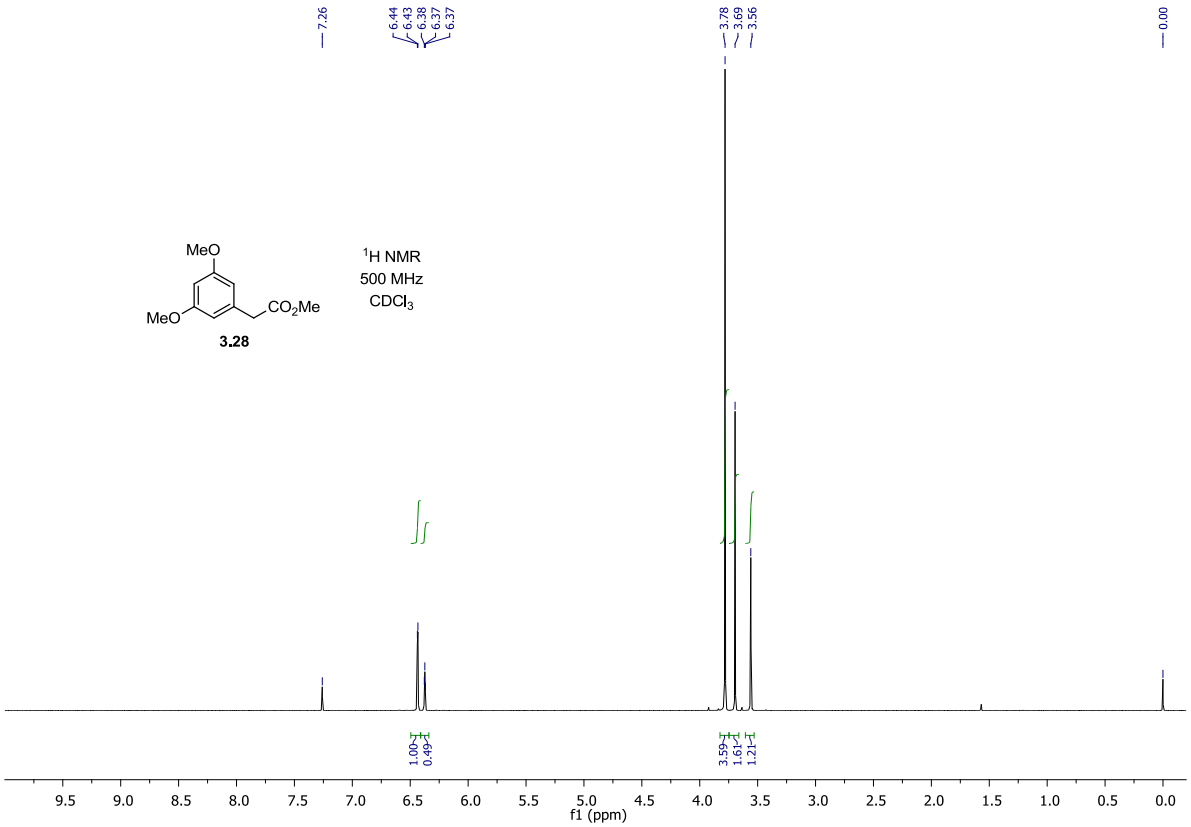
CDCl3
not purified
f1 (ppm)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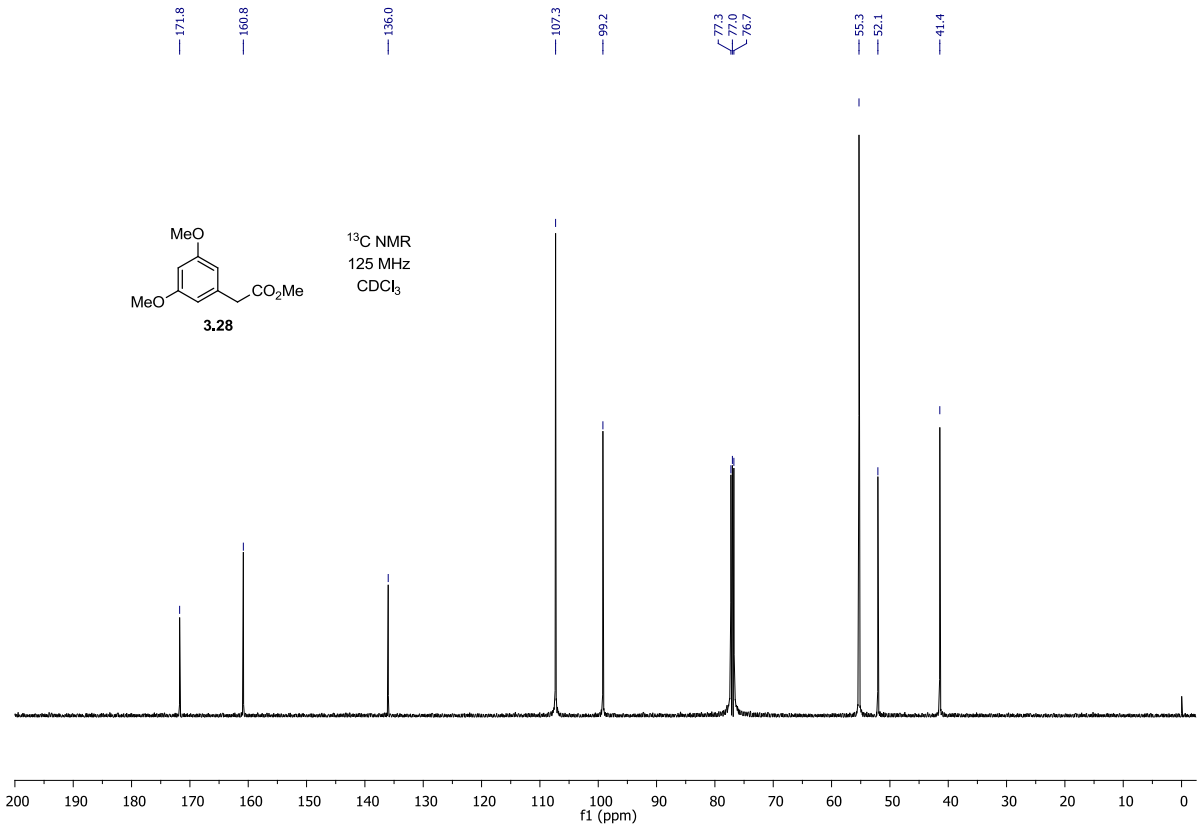
f1 (ppm)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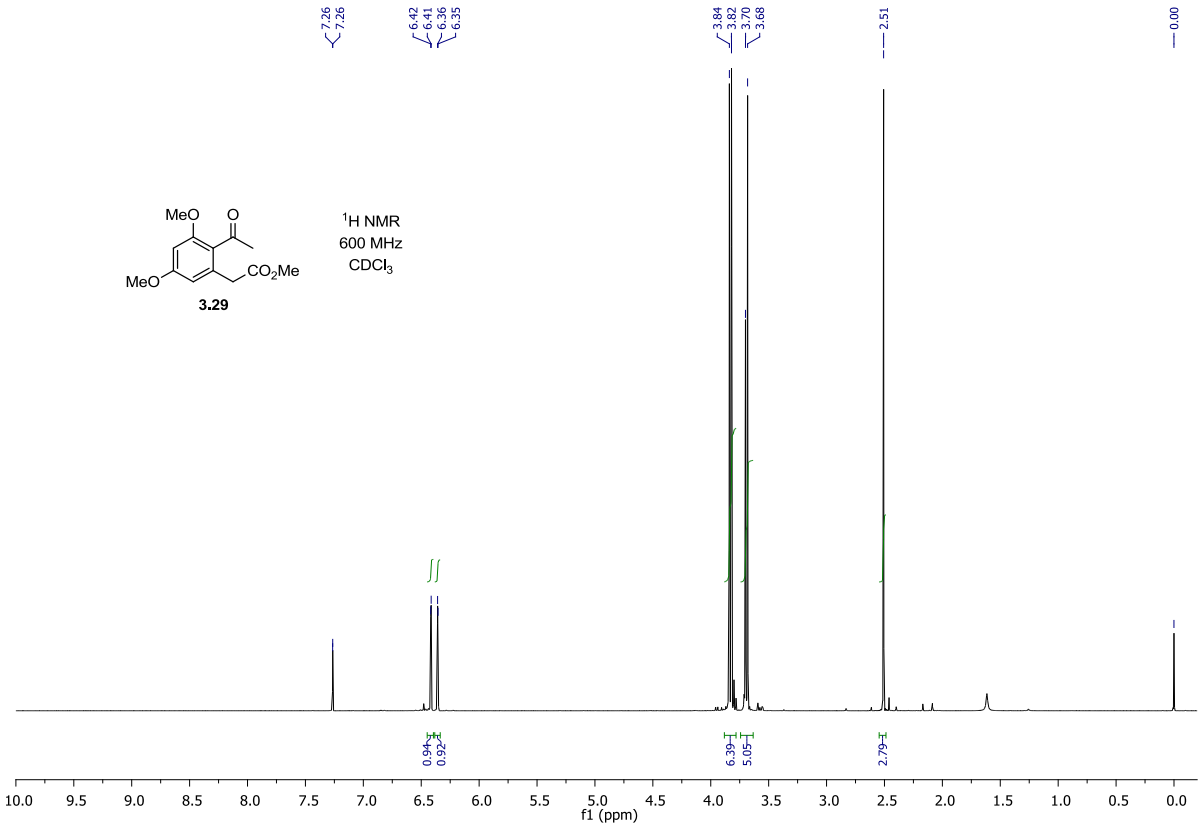
CDCl3
f1 (ppm)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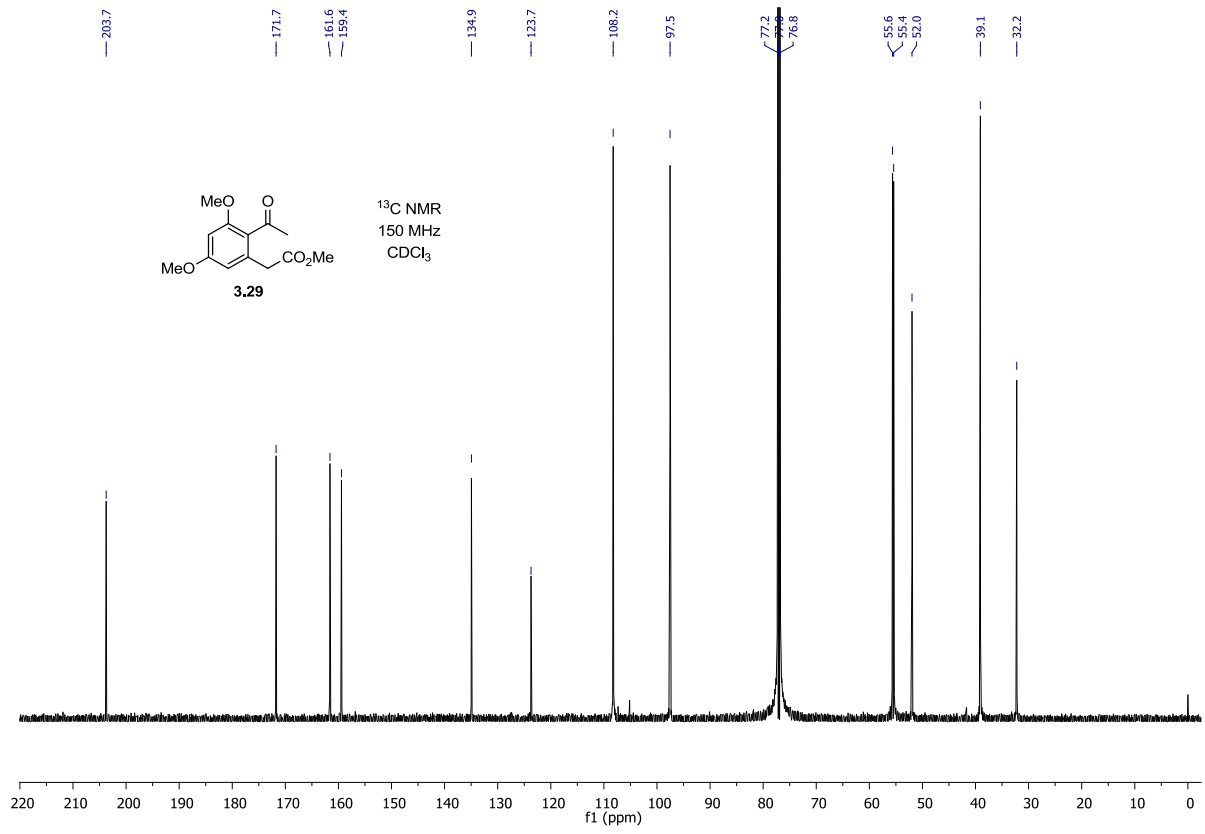
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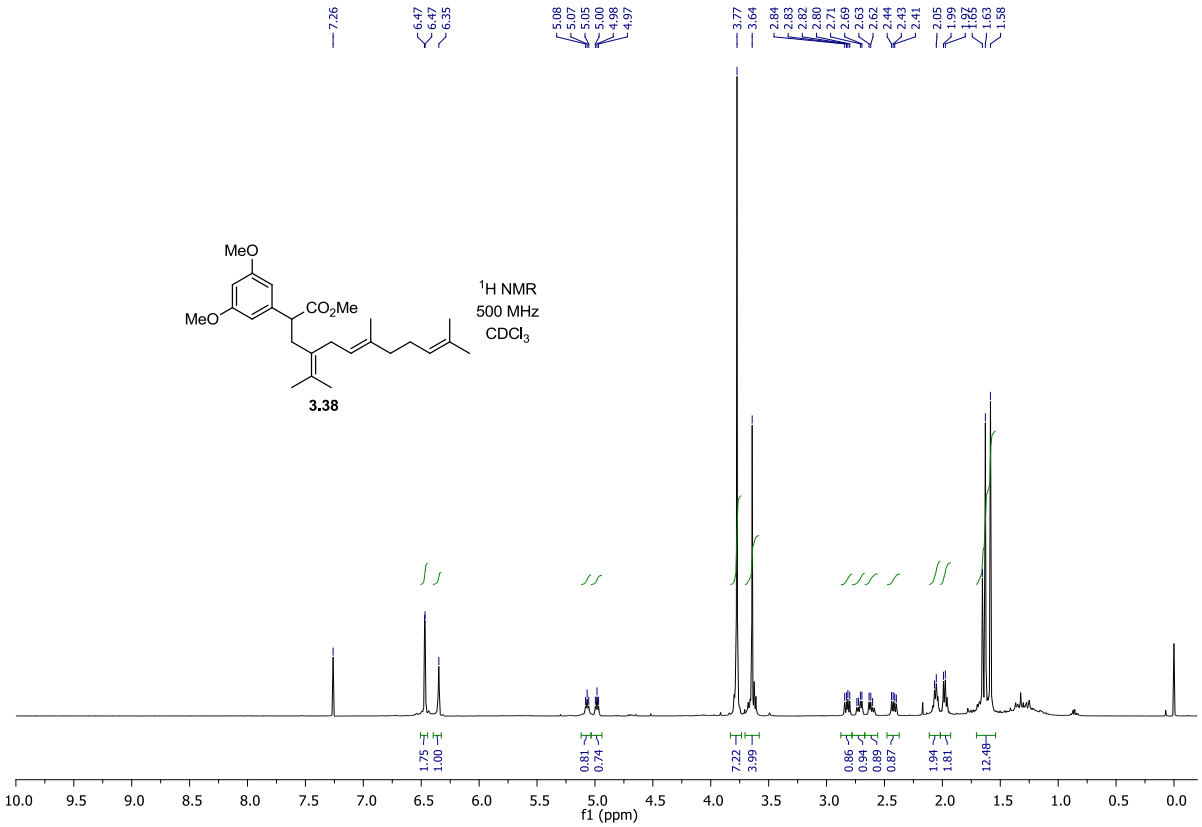
3.29
13C NMR
150 MHz
CDCl3
f1 (ppm)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1.65
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MeO
MeO
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1H NMR
500 MHz
CDCl3
3.38
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0.81
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7.22
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1.94
1.81
12.48
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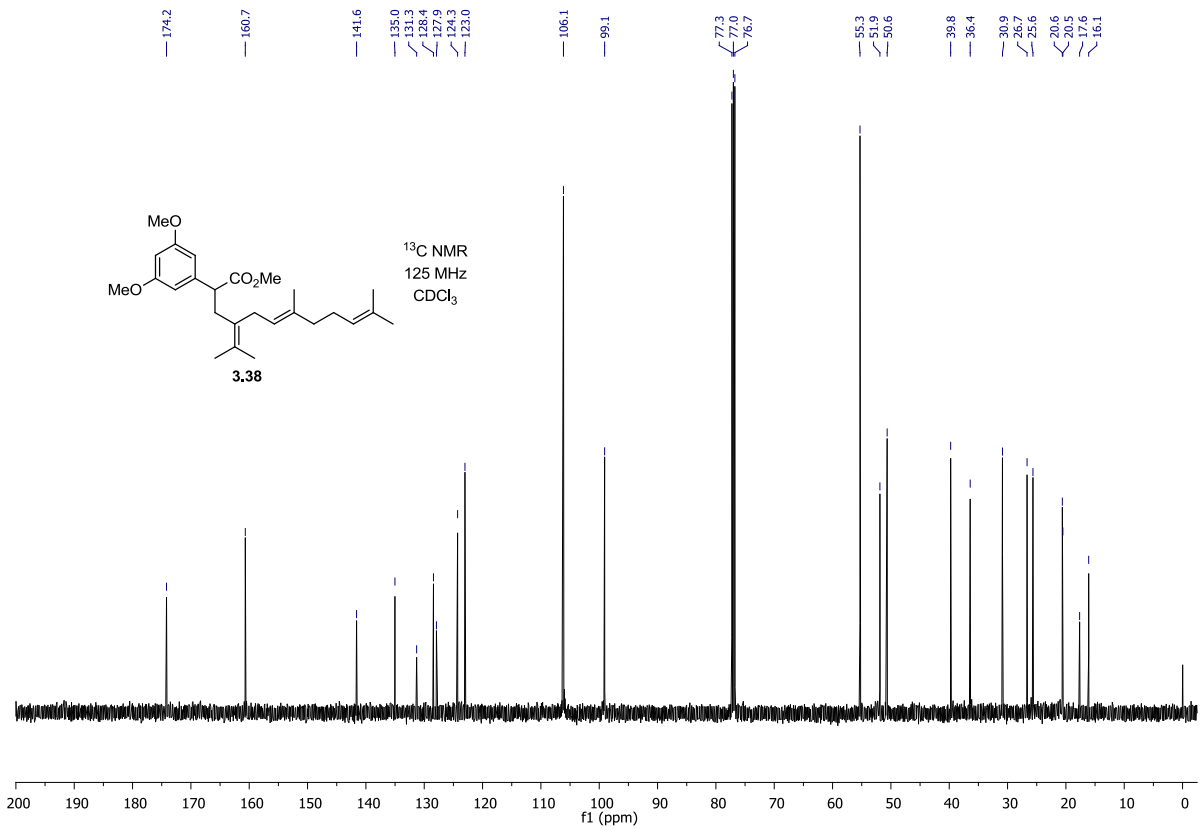
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106.1
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77.3
77.0
76.7
55.3
51.9
50.6
39.8
36.4
30.9
26.7
25.6
20.6
20.5
17.6
16.1
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125 MHz
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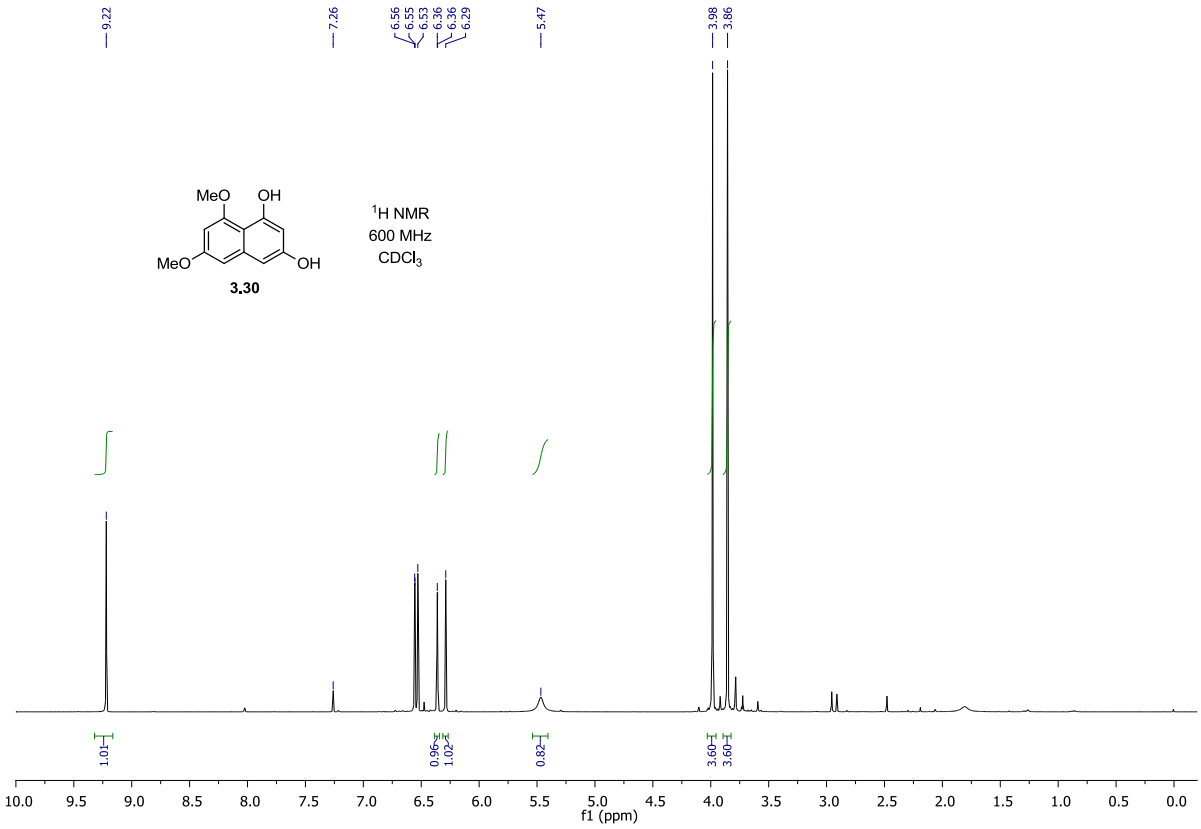
f1 (ppm)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OH
MeO
OH
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^{1}H NMR
600 MHz
$CDCl_3$
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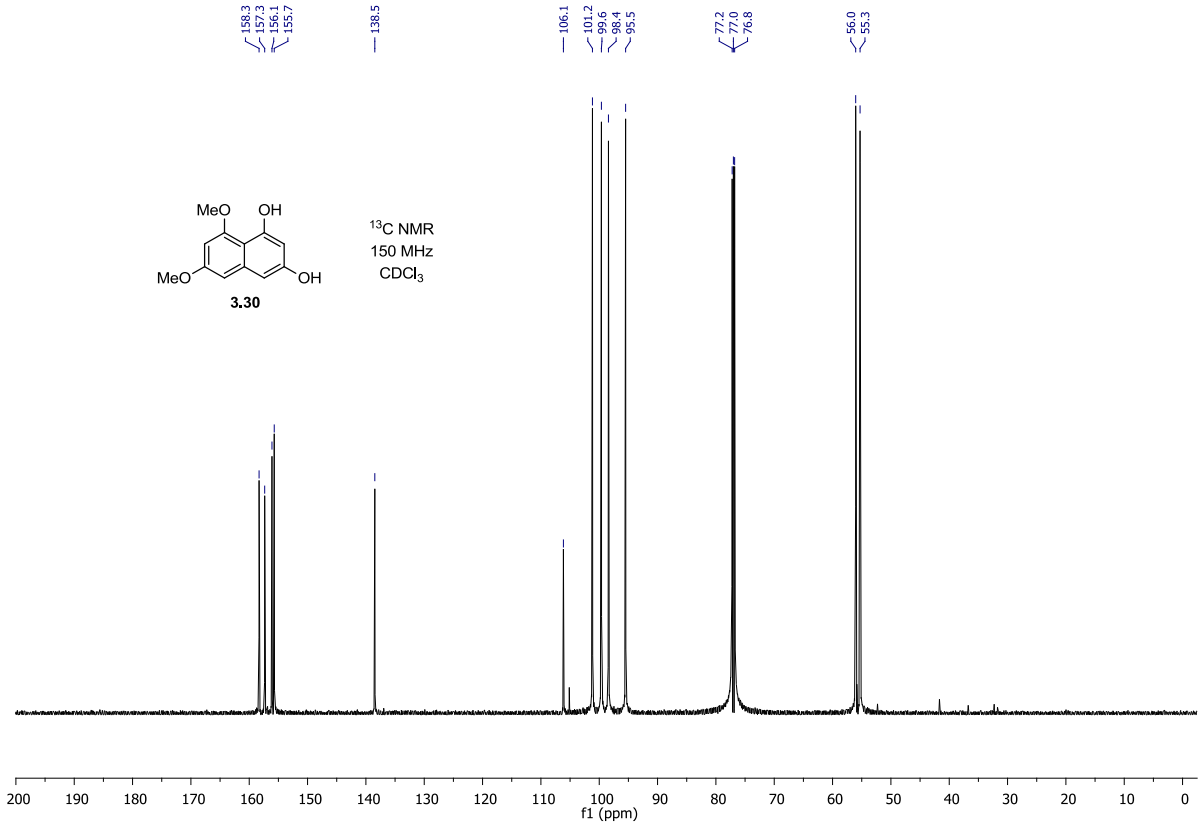
1.02
0.82
3.60
3.60
f1 (ppm)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OH
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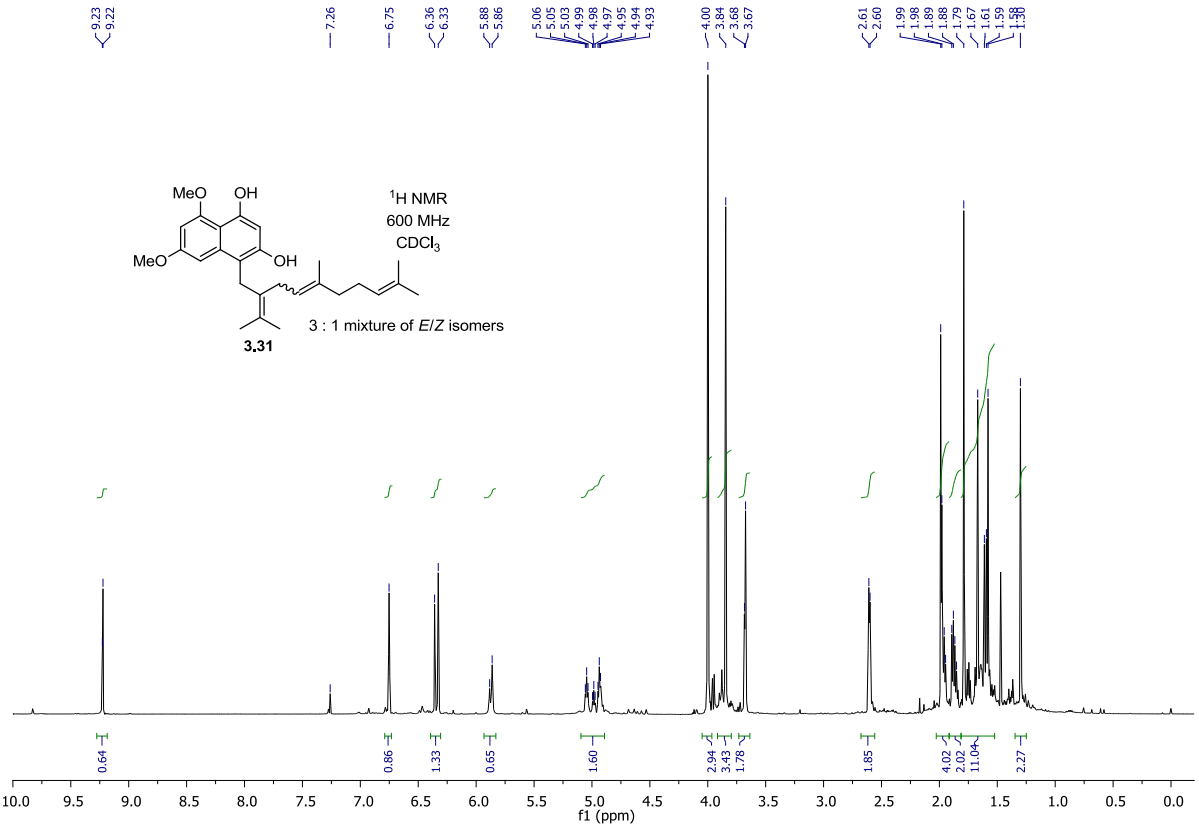
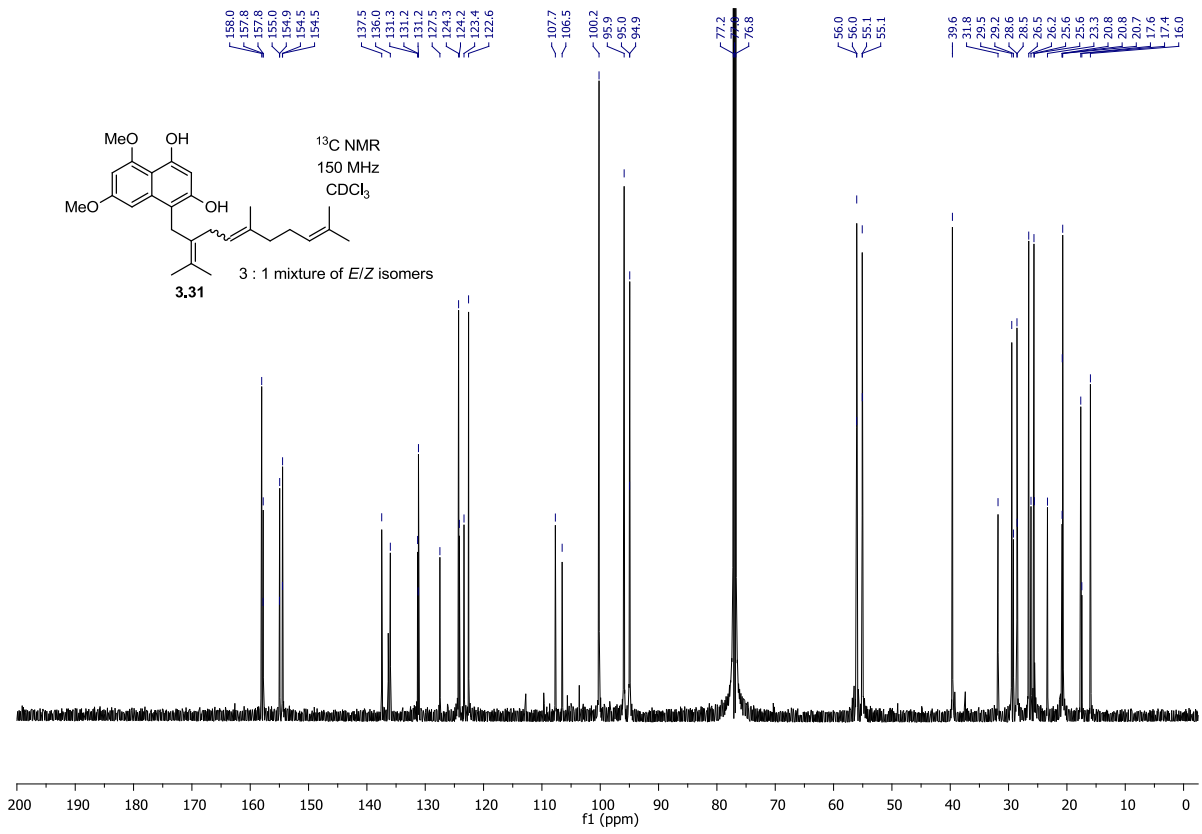
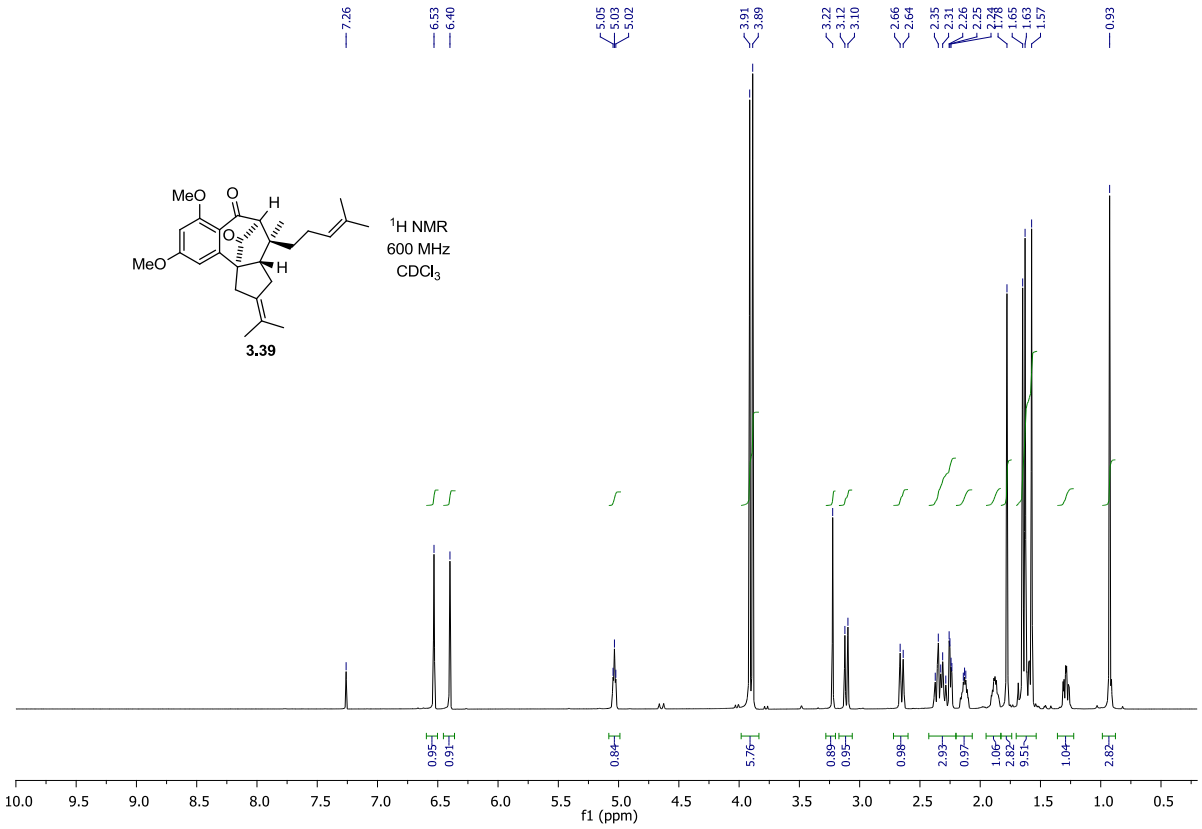
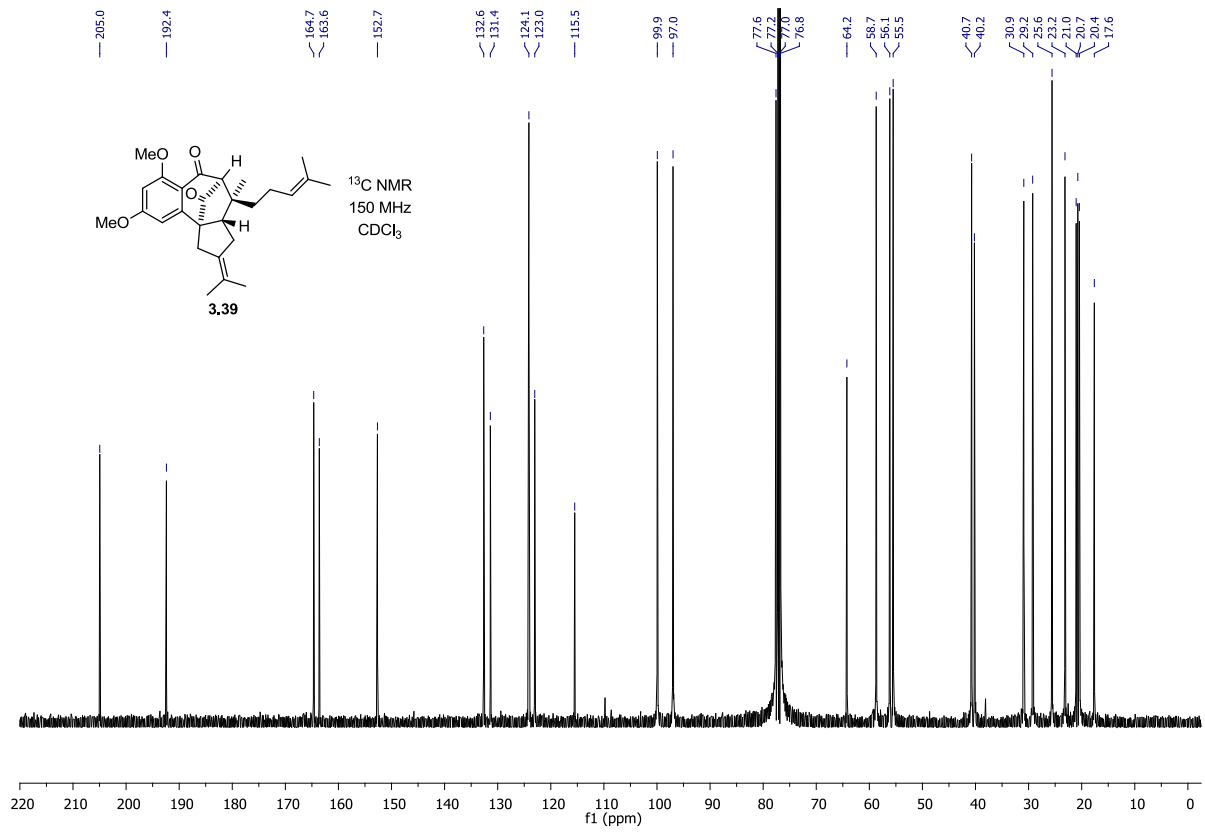
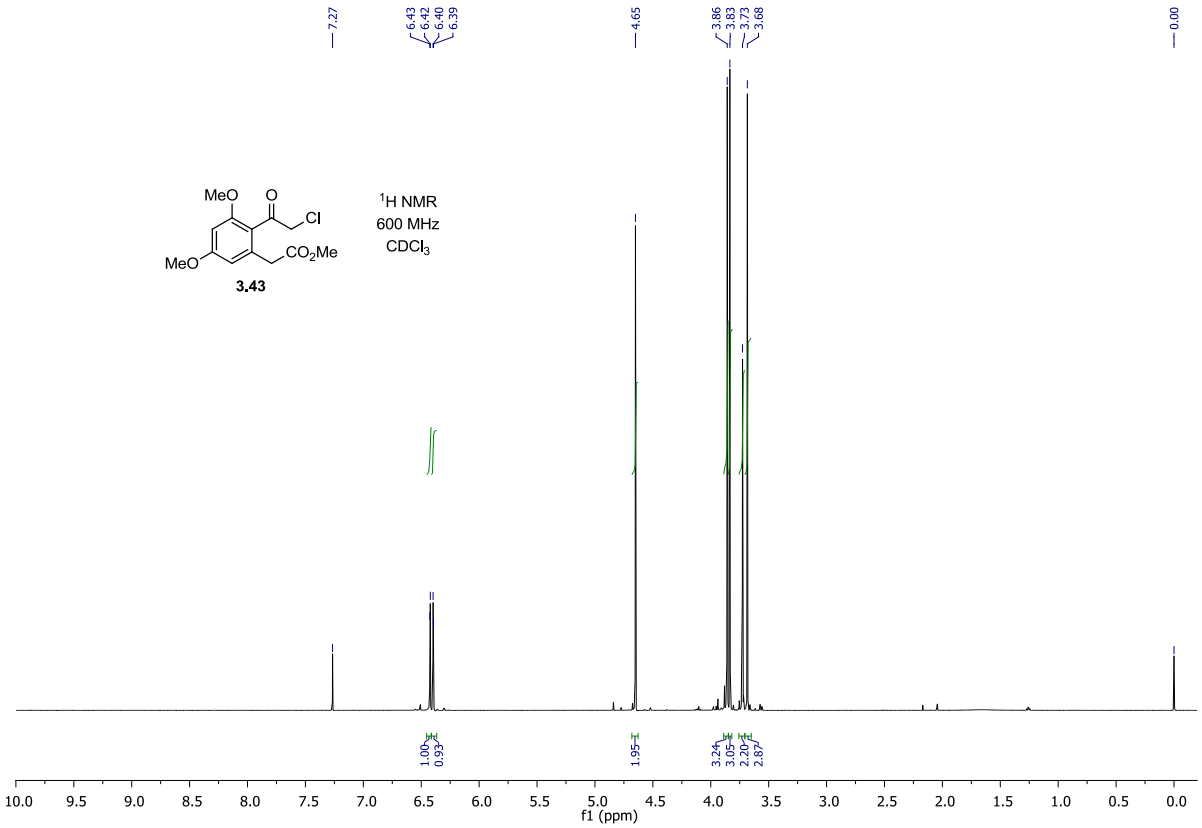
OH
3.30
^{13}C NMR
150 MHz
$CDCl_3$
f1 (ppm)

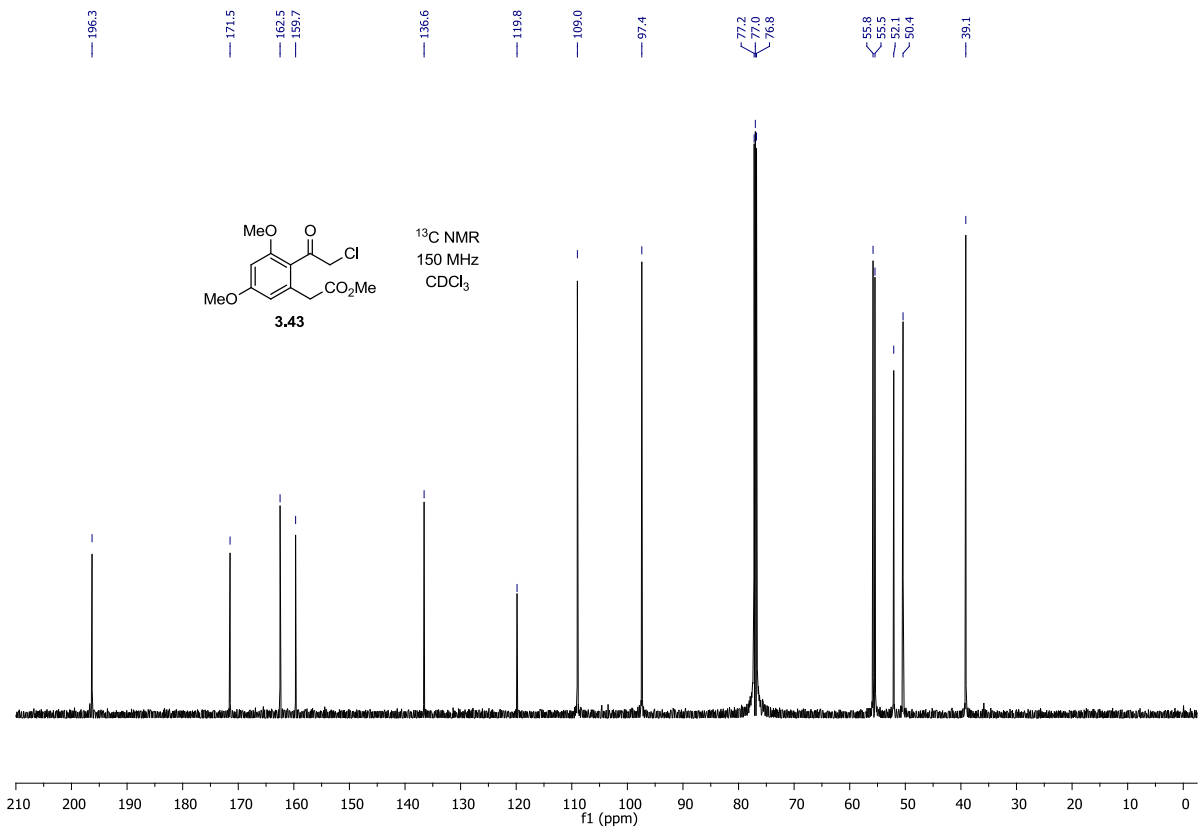

MeO
OH
MeO
OH
^{1}H NMR
600 MHz
$CDCl_3$
3 : 1 mixture of *E*/*Z* isomers
3.31
f1 (ppm)

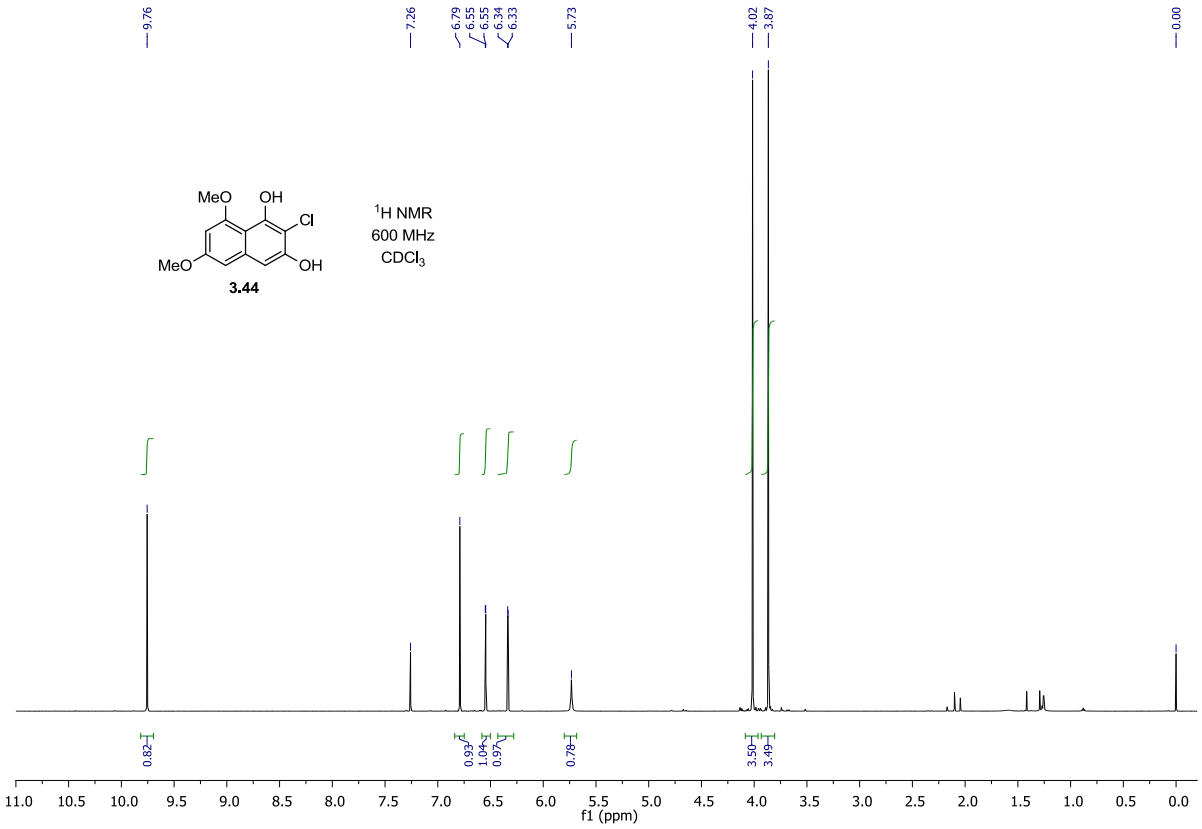

MeO
OH
MeO
OH
^{13}C NMR
150 MHz
$CDCl_3$
3 : 1 mixture of *E*/*Z* isomers
3.31
f1 (ppm)

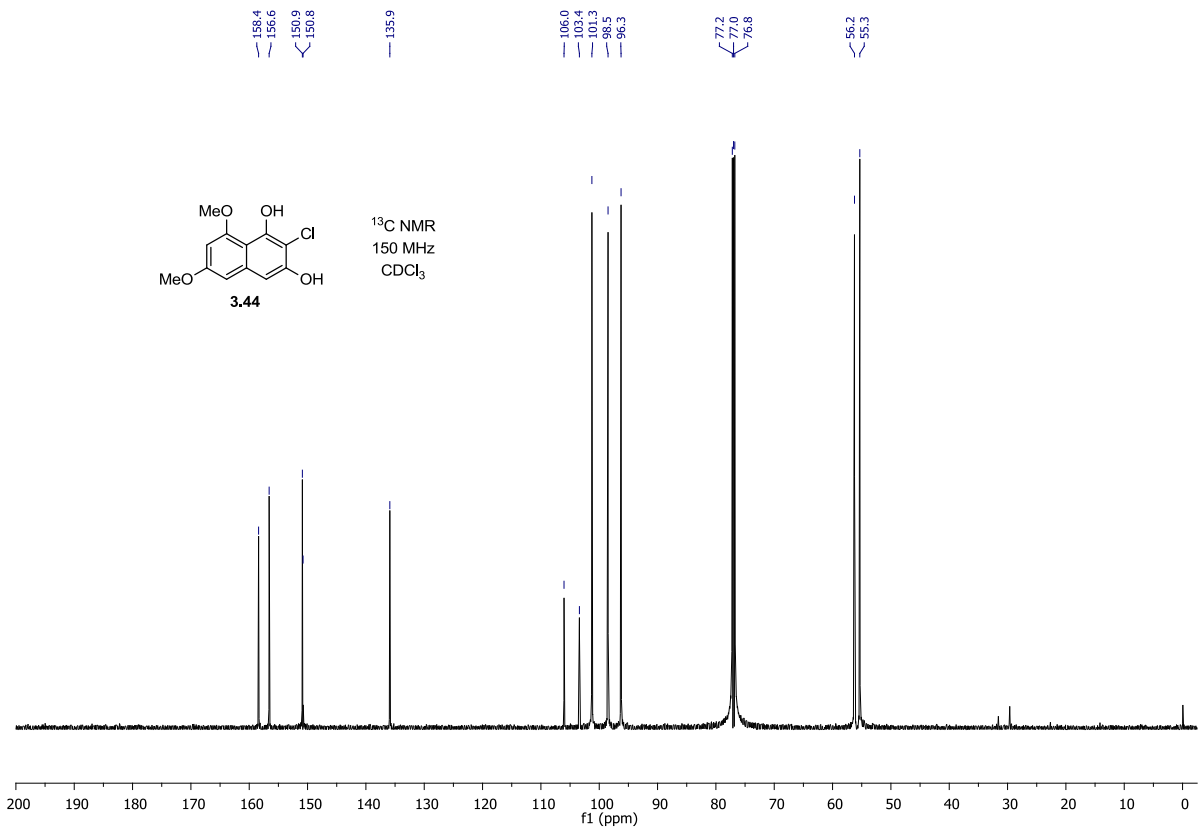

7.26
6.53
6.40
5.05
5.03
5.02
3.91
3.89
3.22
3.12
3.10
2.66
2.64
2.35
2.31
2.26
2.25
1.65
1.63
1.57
0.93
MeO
O
H
O
MeO
H
3.39
1H NMR
600 MHz
CDCl3
0.95
0.91
0.84
5.76
0.89
0.95
0.98
2.93
0.97
1.06
2.82
9.51
1.04
2.82
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

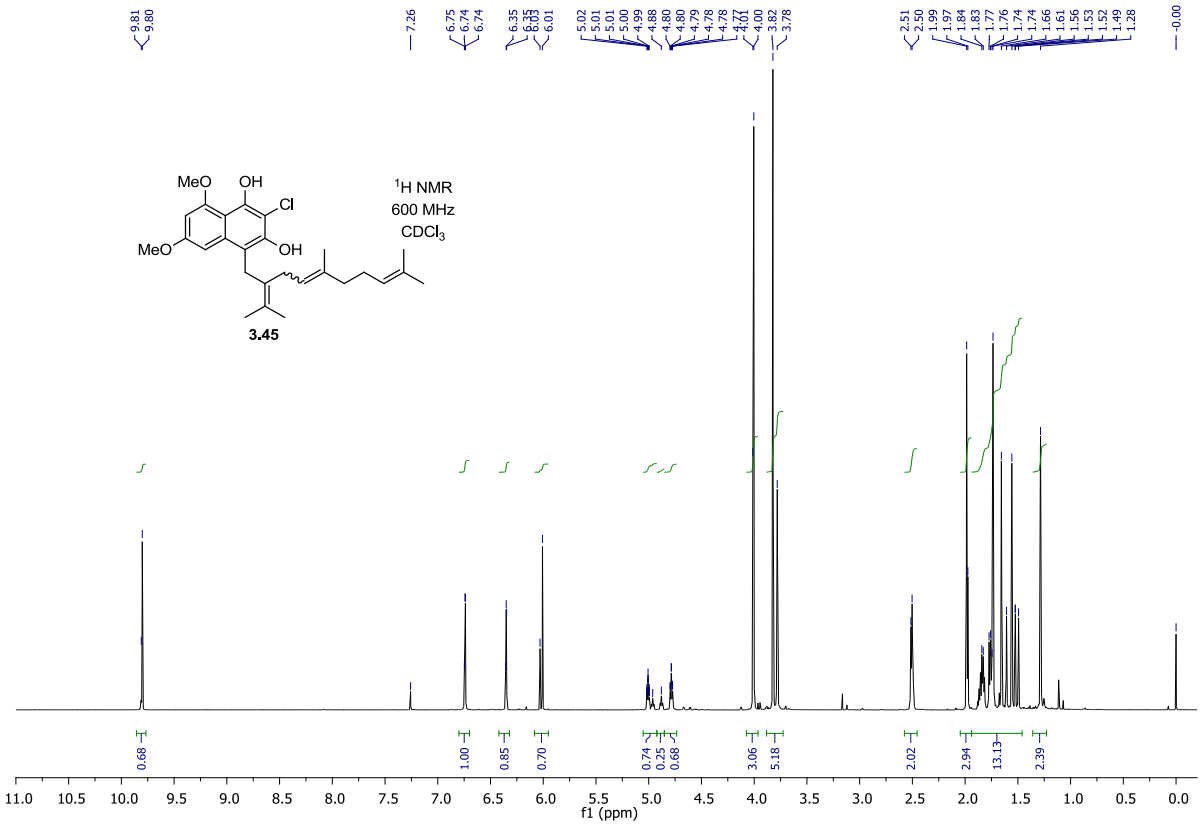

205.0
192.4
164.7
163.6
152.7
132.6
131.4
124.1
123.0
115.5
99.9
97.0
77.6
77.2
77.0
76.8
64.2
58.7
56.1
55.5
40.7
40.2
30.9
29.2
25.6
23.2
21.0
20.7
20.4
17.6
MeO
O
H
O
MeO
H
3.39
13C NMR
150 MHz
CDCl3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

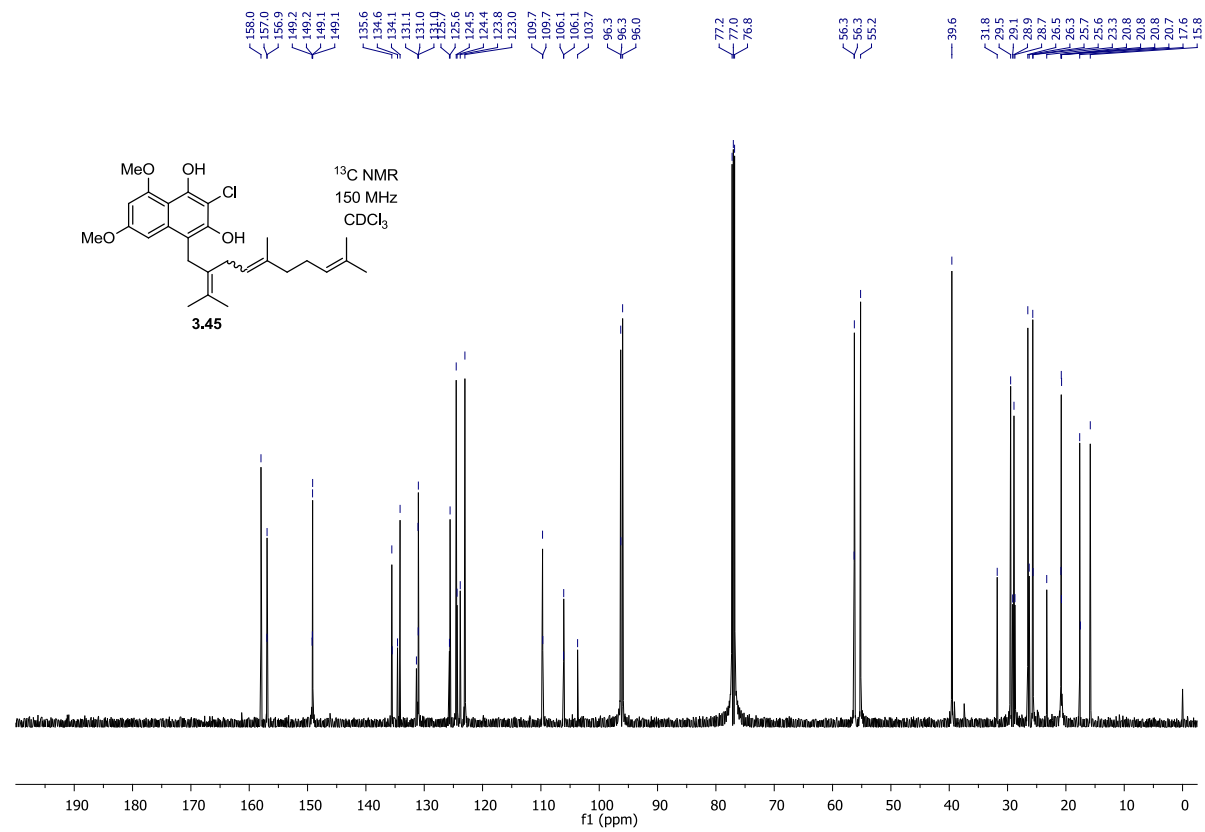

7.27
6.43
6.42
6.40
6.39
4.65
3.86
3.83
3.73
3.68
0.00
MeO
O
Cl
MeO
CO2Me
3.43
1H NMR
600 MHz
CDCl3
1.00
0.93
1.95
3.24
3.05
2.20
2.87
f1 (ppm)

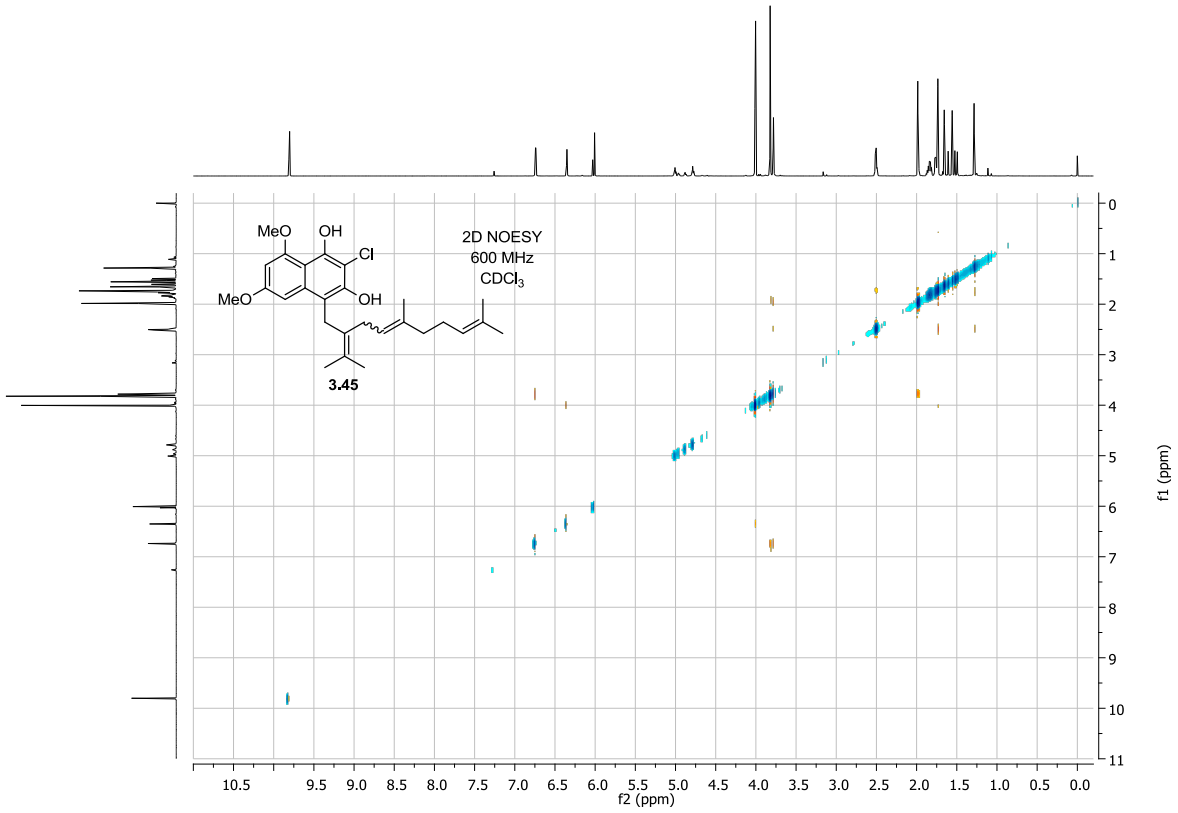

196.3
171.5
162.5
159.7
136.6
119.8
109.0
97.4
77.2
77.0
76.8
55.8
55.5
52.1
50.4
39.1
MeO
O
Cl
MeO
CO2Me
3.43
13C NMR
150 MHz
CDCl3
f1 (ppm)

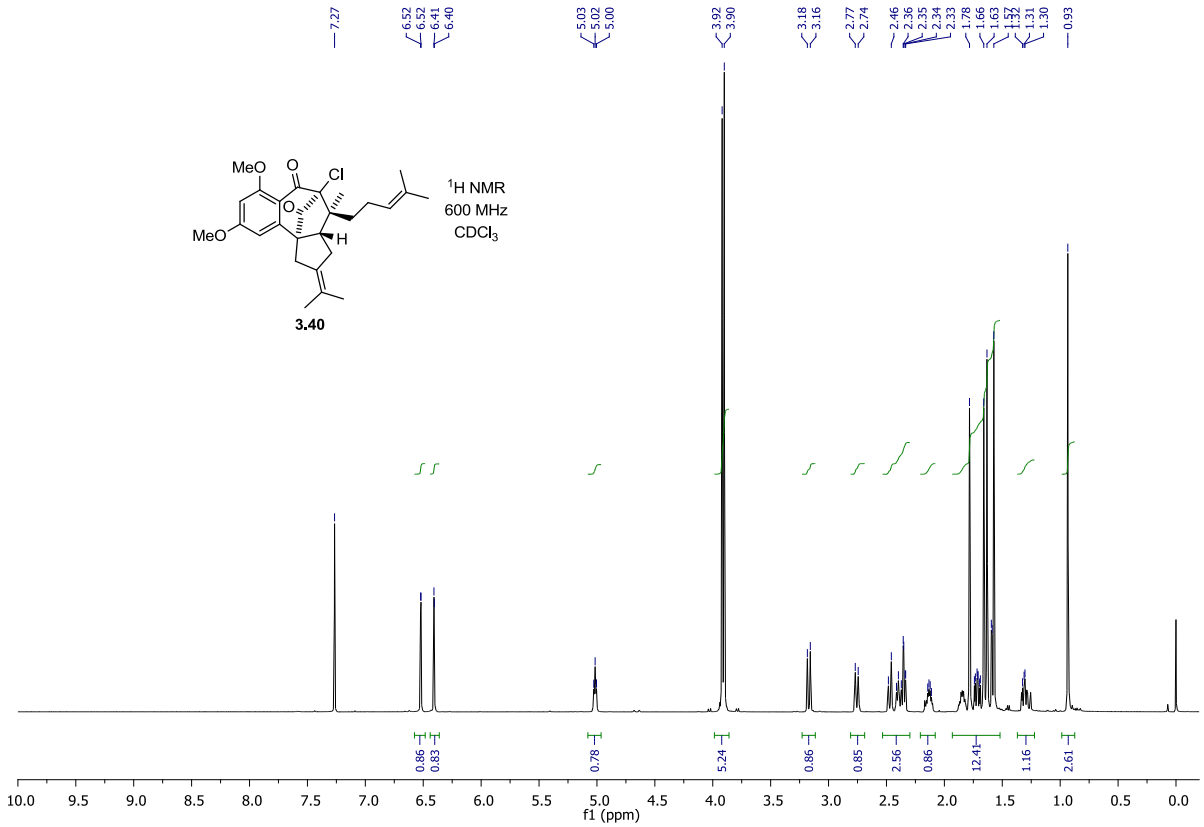

9.76
7.26
6.79
6.55
6.55
6.34
6.33
5.73
4.02
3.87
0.00
MeO
OH
Cl
MeO
OH
3.44
1H NMR
600 MHz
CDCl3
0.82
0.93
1.04
0.97
0.78
3.50
3.49
f1 (ppm)

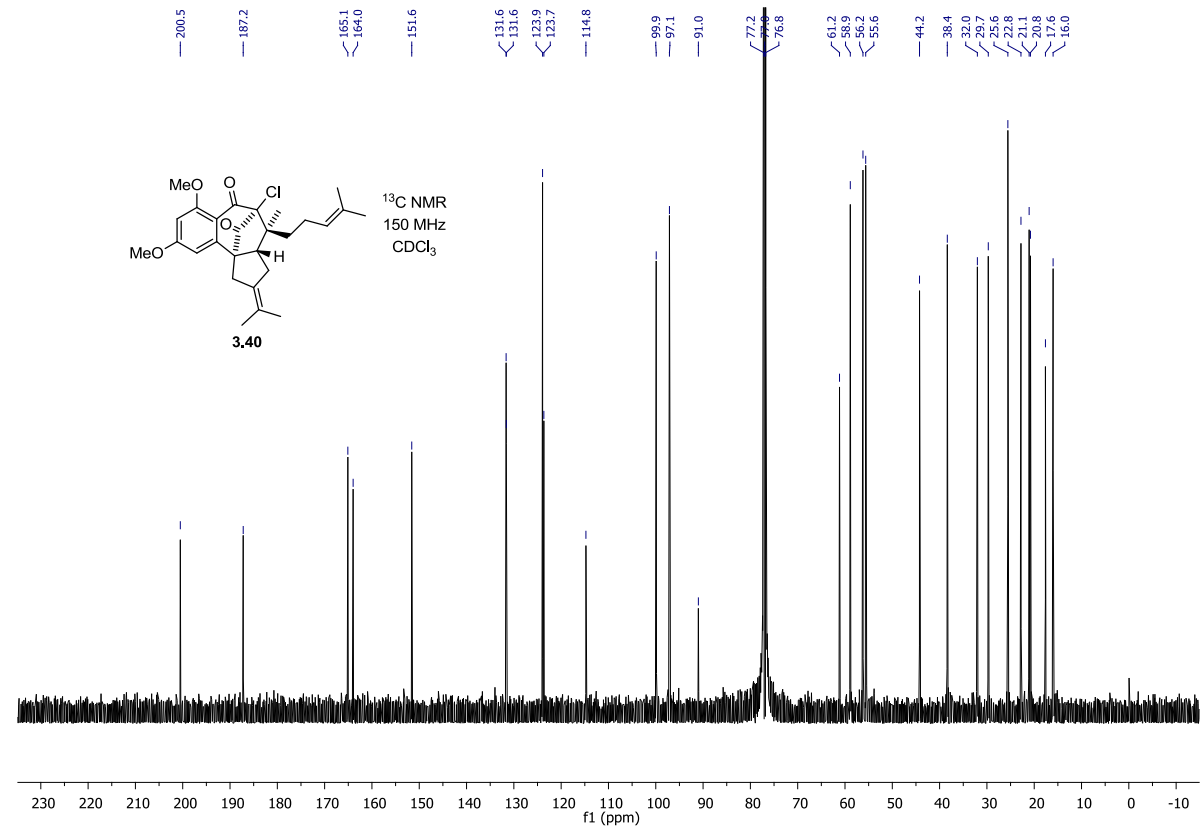

158.4
156.6
150.9
150.8
135.9
106.0
103.4
101.3
98.5
96.3
77.2
77.0
76.8
56.2
55.3
MeO
OH
Cl
MeO
OH
3.44
13C NMR
150 MHz
CDCl3
f1 (ppm)

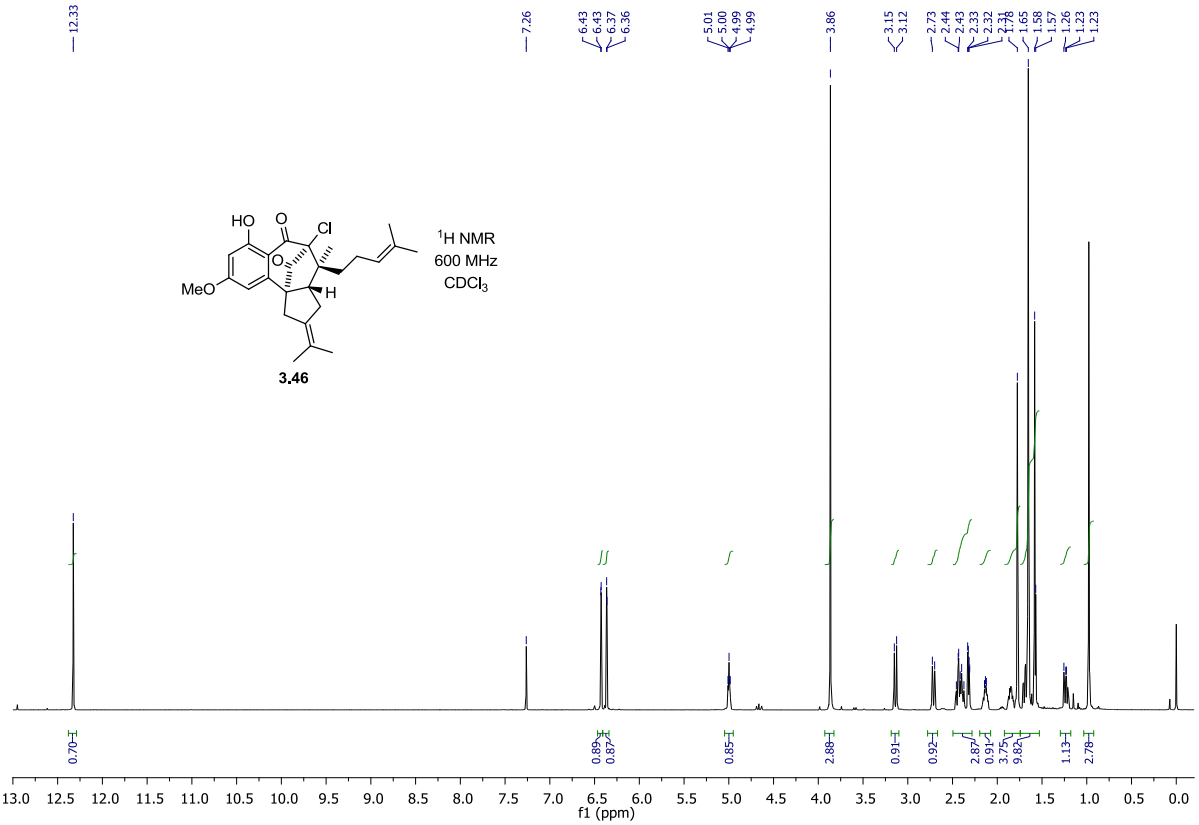

MeO
OH
Cl
MeO
OH
3.45
^{1}H NMR
600 MHz
$CDCl_3$
f1 (ppm)

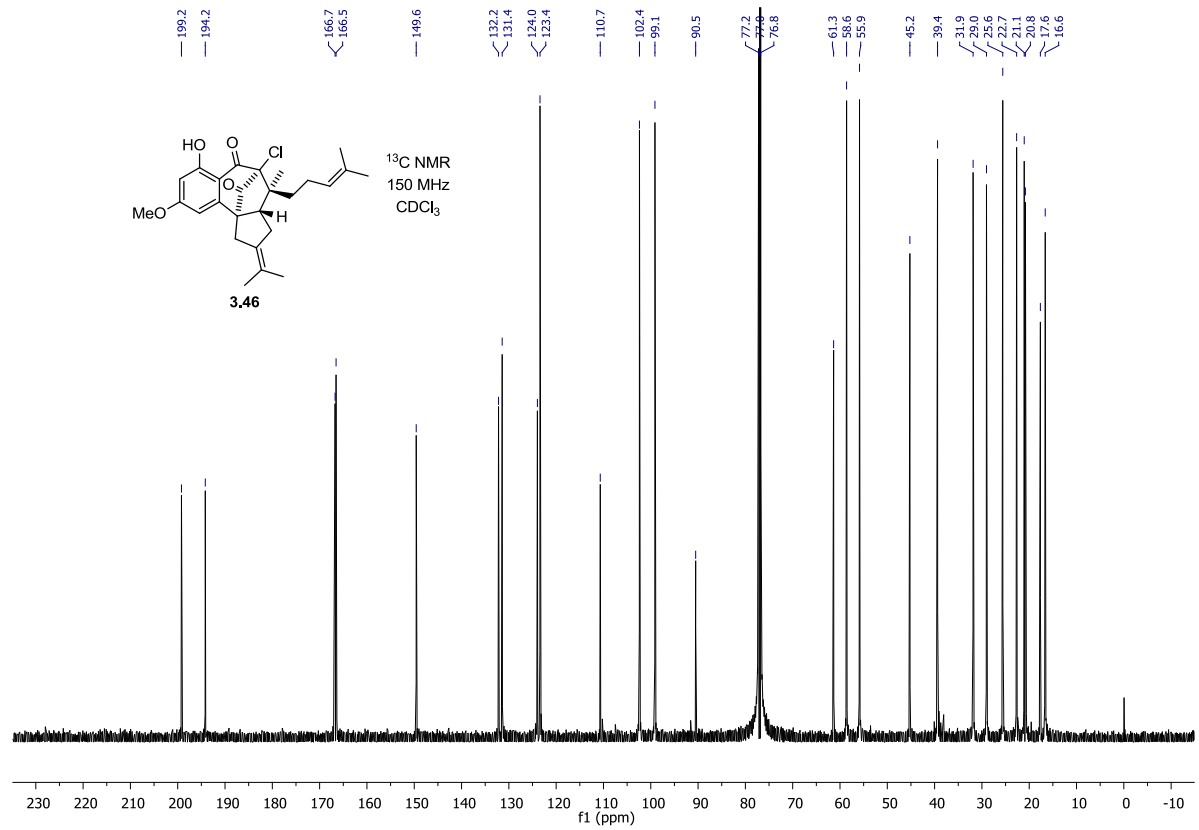

MeO
OH
Cl
MeO
OH
3.45
^{13}C NMR
150 MHz
$CDCl_3$
f1 (ppm)

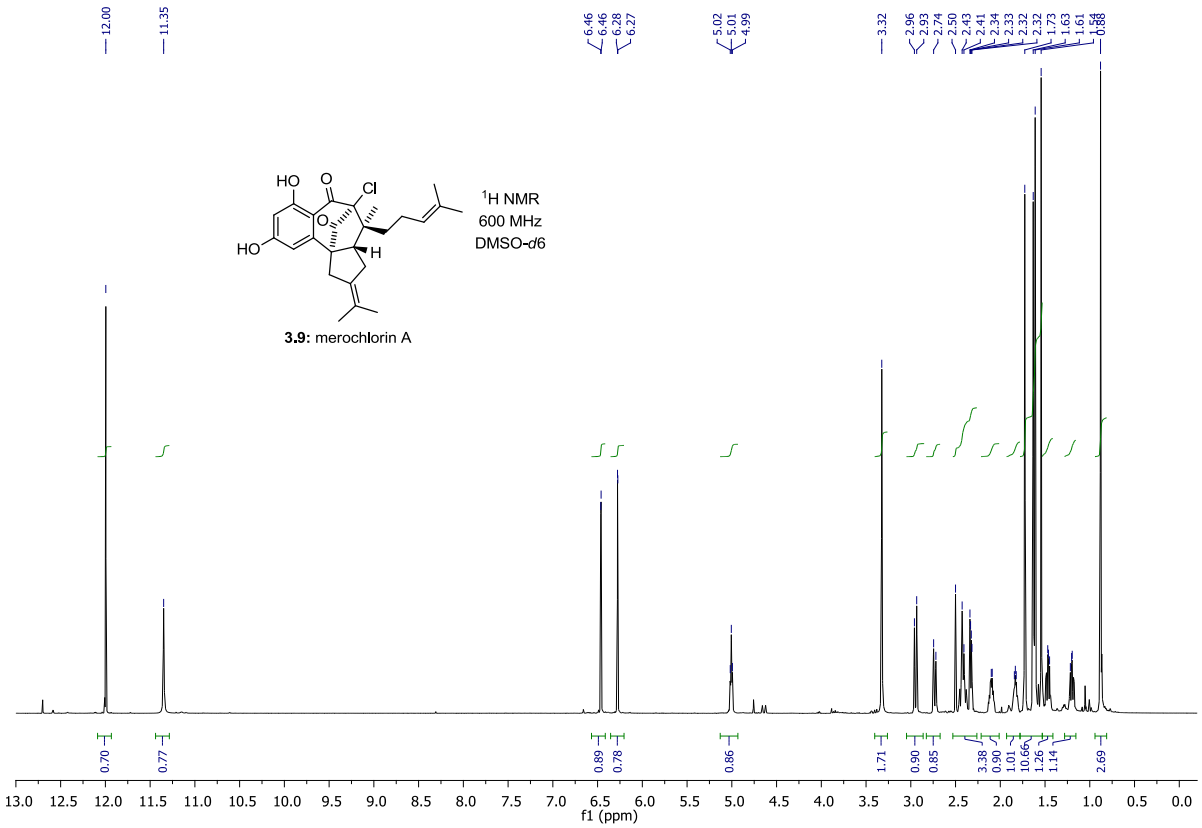

MeO
OH
Cl
MeO
OH
3.45
2D NOESY
600 MHz
CDCl3
f2 (ppm)
f1 (ppm)

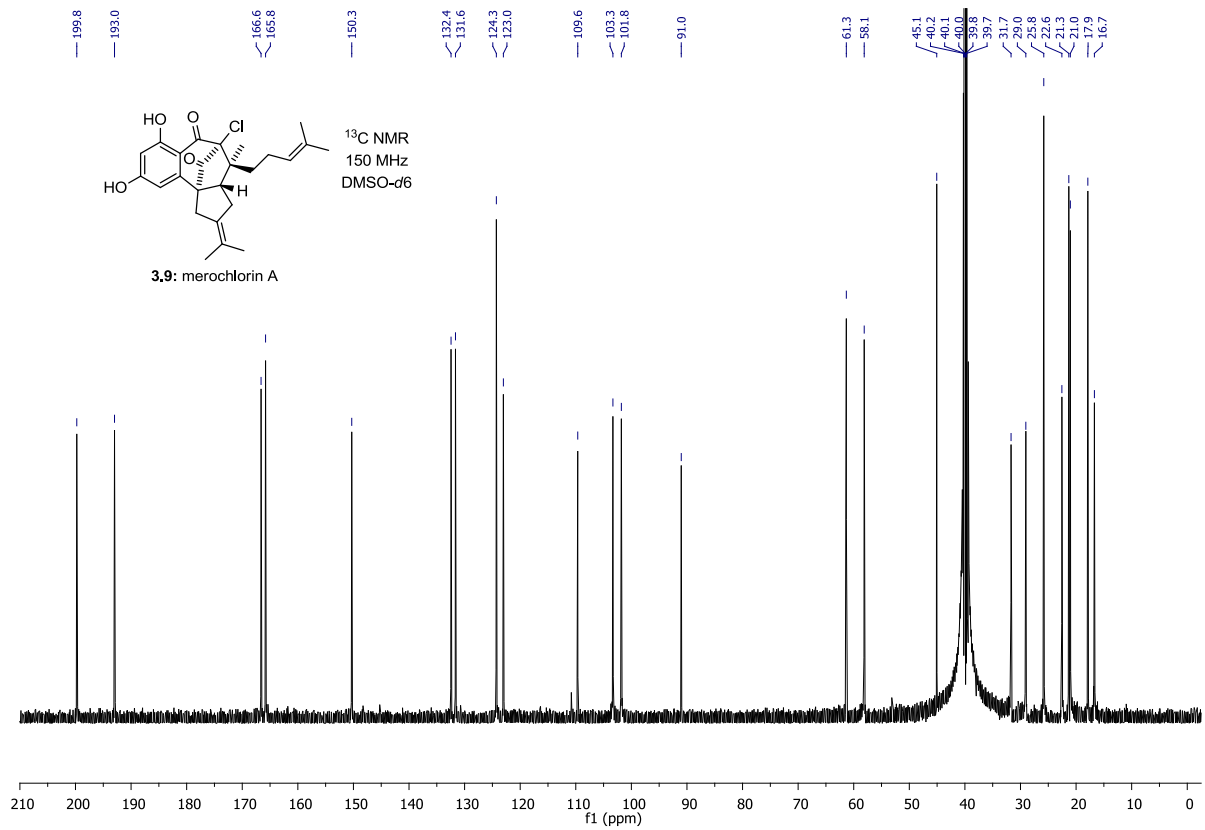

7.27
6.52
6.52
6.41
6.40
5.03
5.02
5.00
3.92
3.90
3.18
3.16
2.77
2.74
2.46
2.36
2.35
2.34
2.33
1.78
1.66
1.63
1.32
1.31
1.30
0.93
MeO
O
Cl
O
MeO
H
3.40
^{1}H NMR
600 MHz
$CDCl_3$
0.86
0.83
0.78
5.24
0.86
0.85
2.56
0.86
12.41
1.16
2.61
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

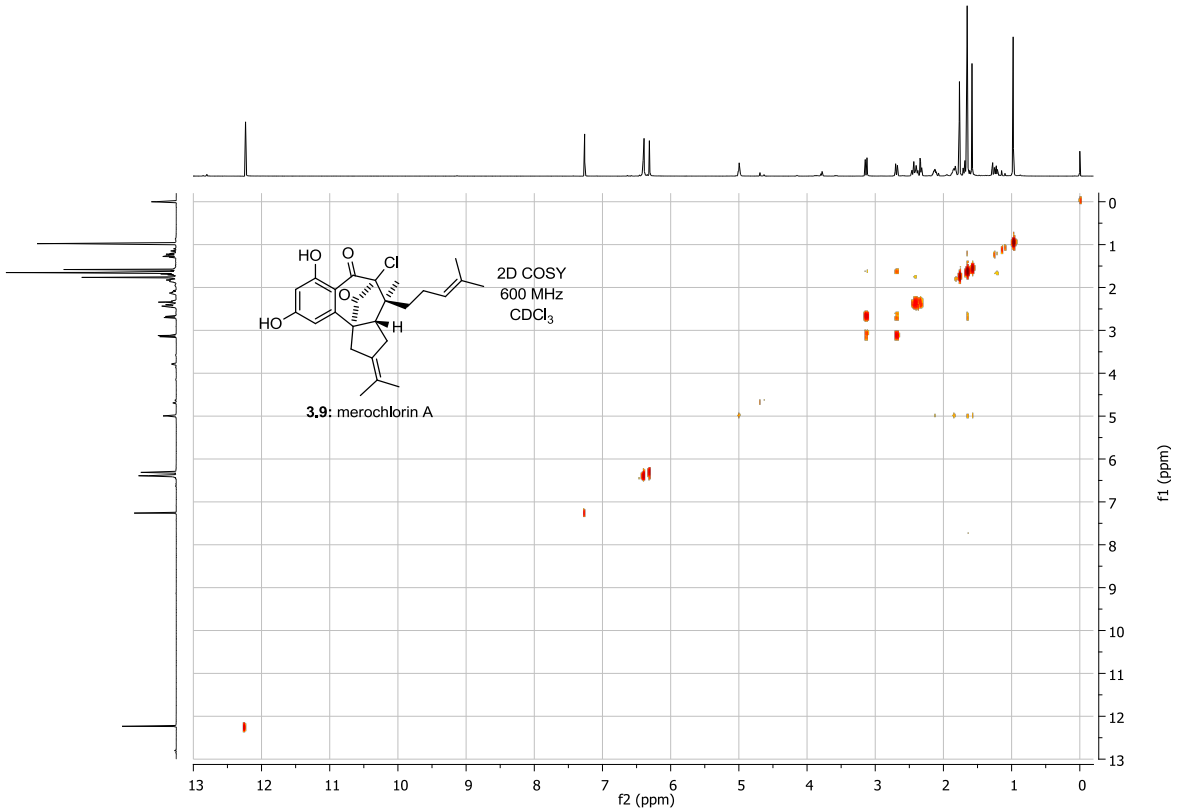

200.5
187.2
165.1
164.0
151.6
131.6
131.6
123.9
123.7
114.8
99.9
97.1
91.0
77.2
77.0
76.8
61.2
58.9
56.2
55.6
44.2
38.4
32.0
29.7
25.6
22.8
21.1
20.8
17.6
16.0
MeO
O
Cl
O
MeO
H
3.40
^{13}C NMR
150 MHz
$CDCl_3$
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

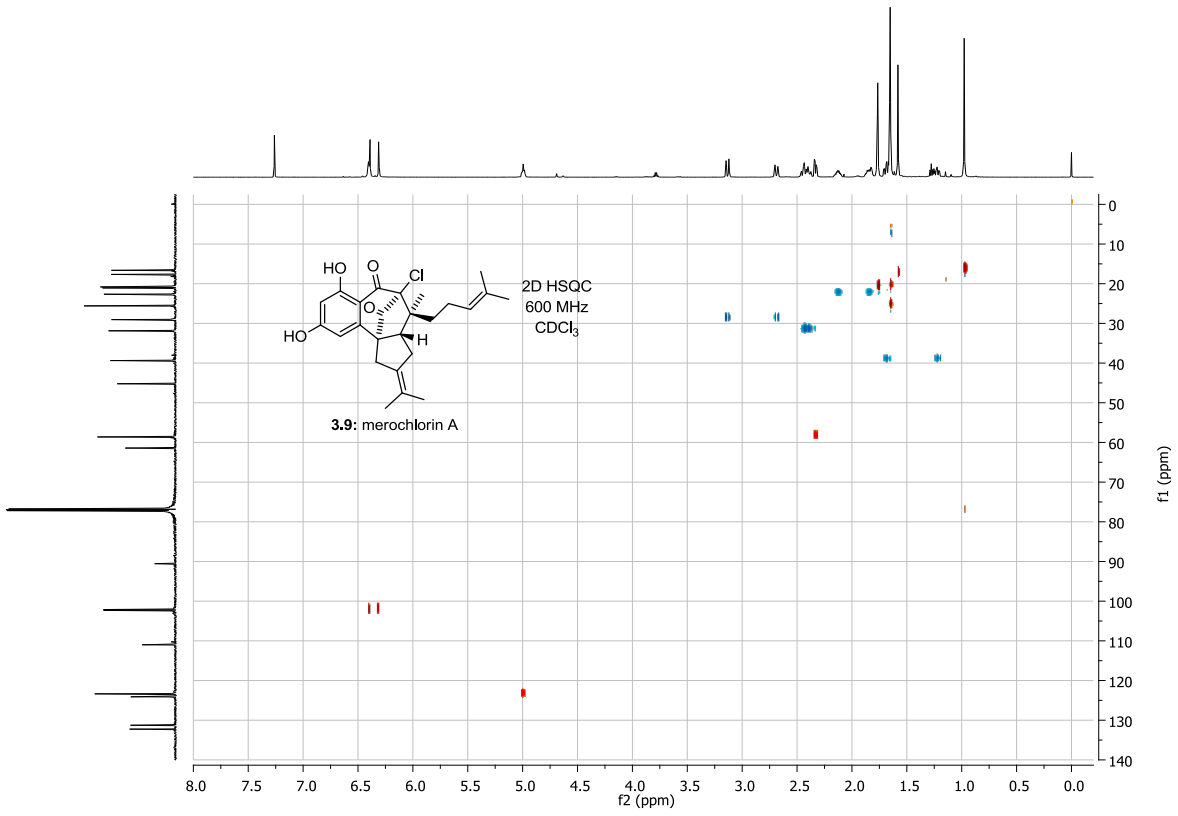

12.33
7.26
6.43
6.43
6.37
6.36
5.01
5.00
4.99
4.99
3.86
3.15
3.12
2.73
2.44
2.43
2.33
2.32
1.65
1.58
1.57
1.26
1.23
1.23
HO
O
Cl
O
MeO
H
3.46
^{1}H NMR
600 MHz
$CDCl_3$
0.70
0.89
0.87
0.85
2.88
0.91
0.92
2.87
0.91
3.75
9.82
1.13
2.78
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

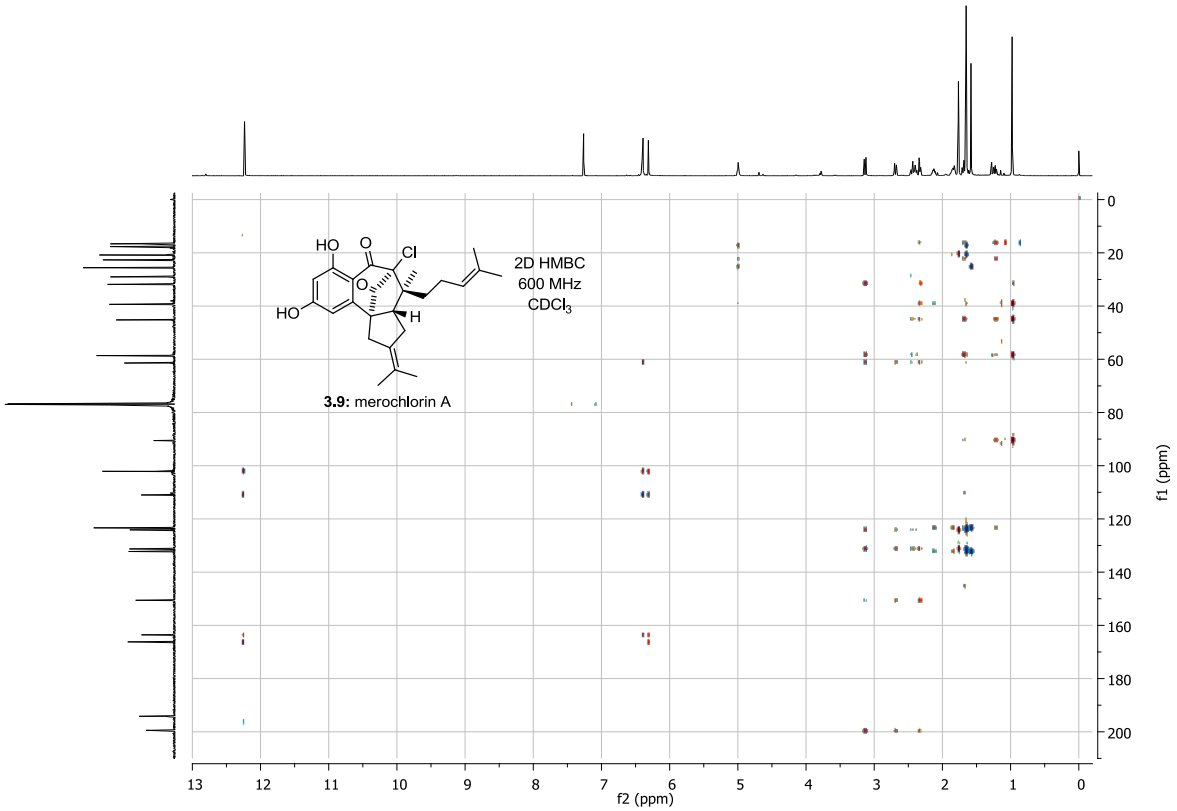

199.2
194.2
166.7
166.5
149.6
132.2
131.4
124.0
123.4
110.7
102.4
99.1
90.5
77.2
77.0
76.8
61.3
58.6
55.9
45.2
39.4
31.9
29.0
25.6
22.7
21.1
20.8
17.6
16.6
HO
O
Cl
O
MeO
H
3.46
^{13}C NMR
150 MHz
$CDCl_3$
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

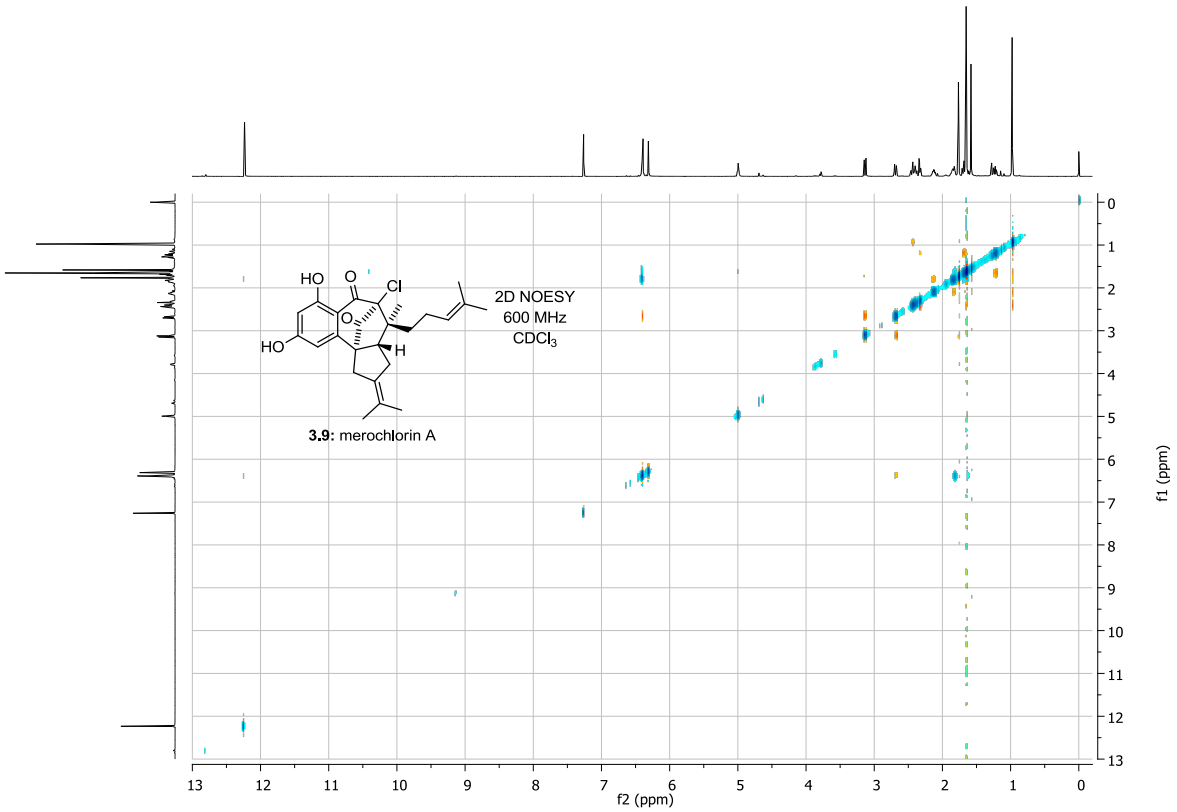

12.00
11.35
6.46
6.46
6.28
6.27
5.02
5.01
4.99
3.32
2.96
2.93
2.74
2.50
2.43
2.41
2.34
2.33
2.32
2.32
1.73
1.63
1.61
0.88
HO
O
Cl
O
HO
H
1H NMR
600 MHz
DMSO-d6
3.9: merochlorin A
0.70
0.77
0.89
0.78
0.86
1.71
0.90
0.85
3.38
0.90
1.01
10.66
1.26
1.14
2.69
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

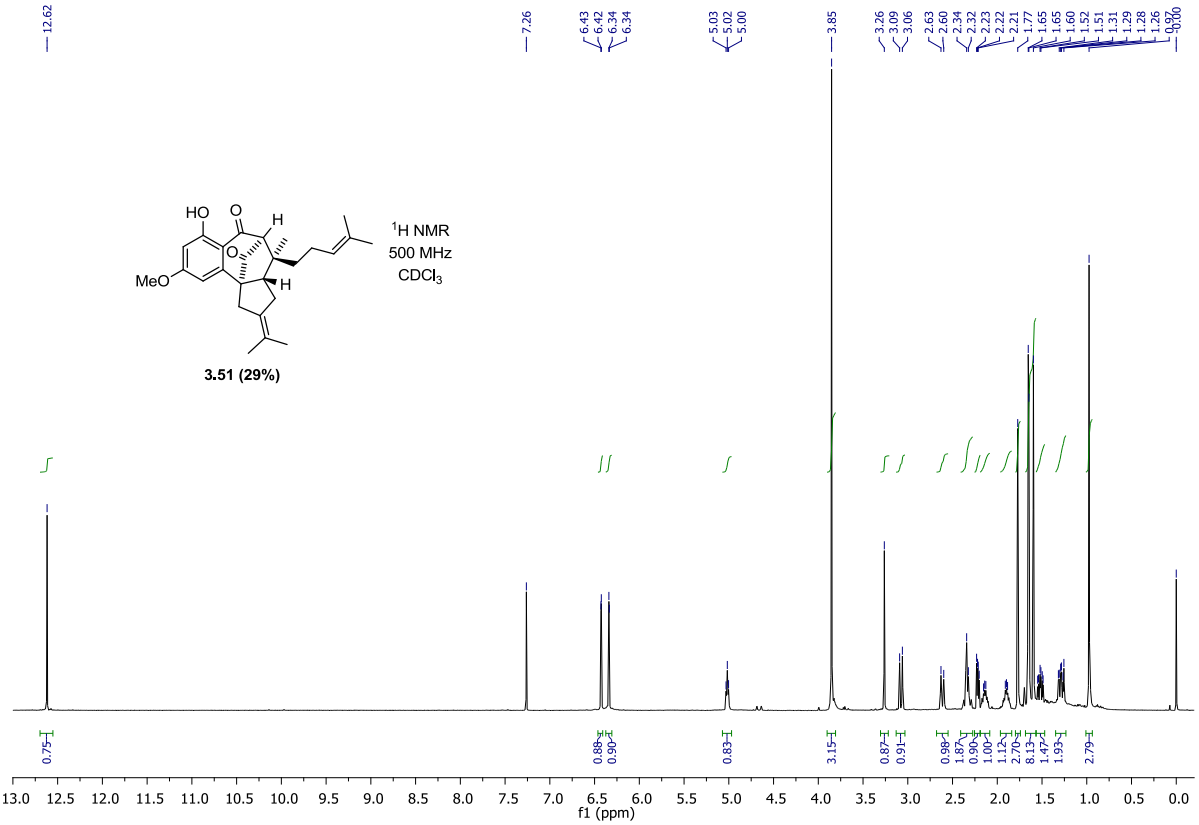

199.8
193.0
166.6
165.8
150.3
132.4
131.6
124.3
123.0
109.6
103.3
101.8
91.0
61.3
58.1
45.1
40.2
40.1
40.0
39.8
39.7
31.7
29.0
25.8
22.6
21.3
21.0
17.9
16.7
HO
O
Cl
O
HO
H
13C NMR
150 MHz
DMSO-d6
3.9: merochlorin A
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

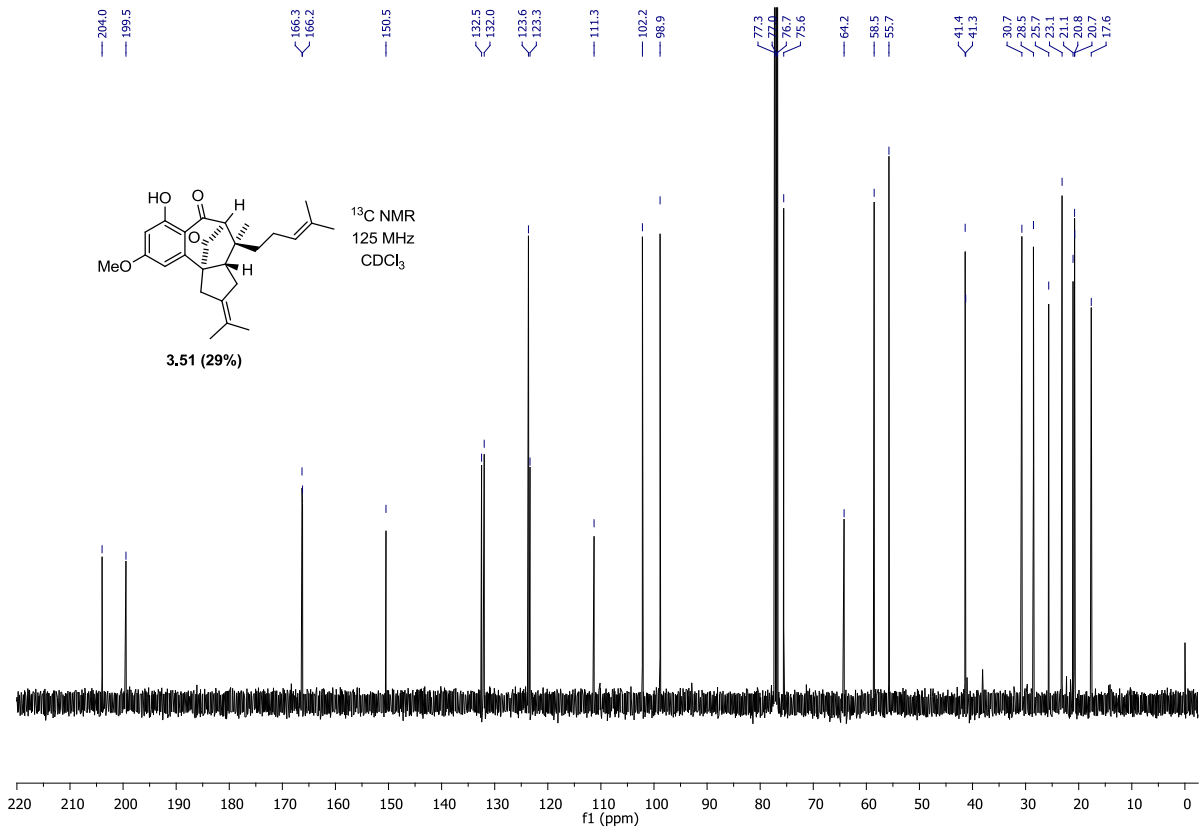

HO
O
Cl
O
HO
H
2D COSY
600 MHz
CDCl3
3.9: merochlorin A
f2 (ppm)
f1 (ppm)

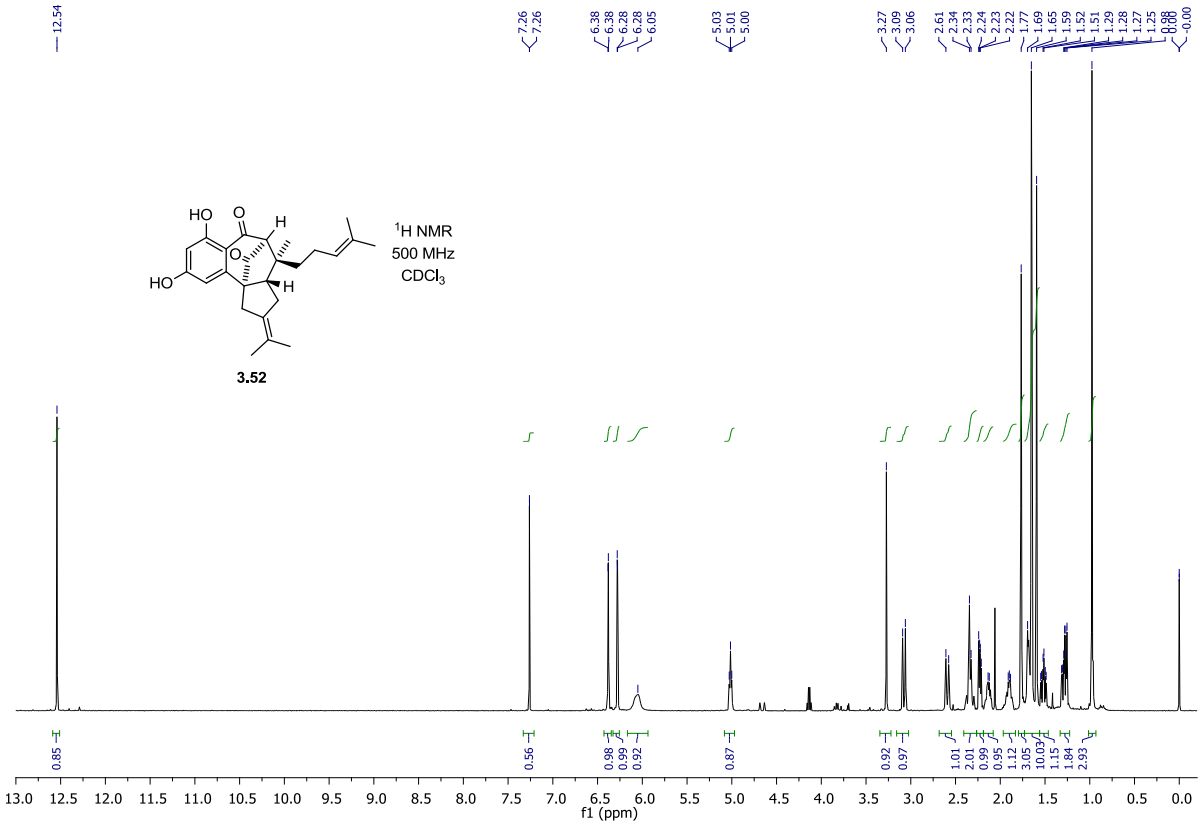

HO
O
Cl
O
HO
H
2D HSQC
600 MHz
CDCl3
3.9: merochlorin A
f2 (ppm)
f1 (ppm)

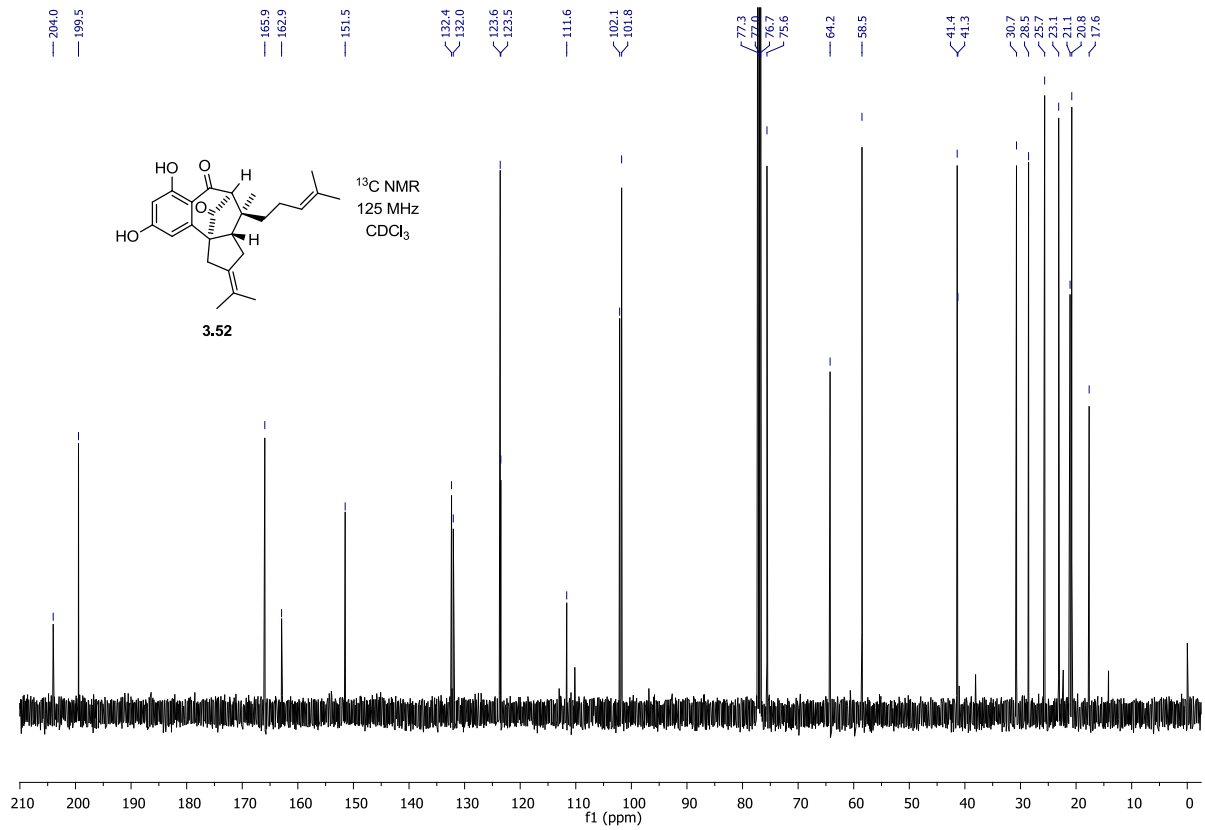

HO
O
Cl
O
HO
H
2D HMBC
600 MHz
CDCl3
3.9: merochlorin A
f2 (ppm)
f1 (ppm)

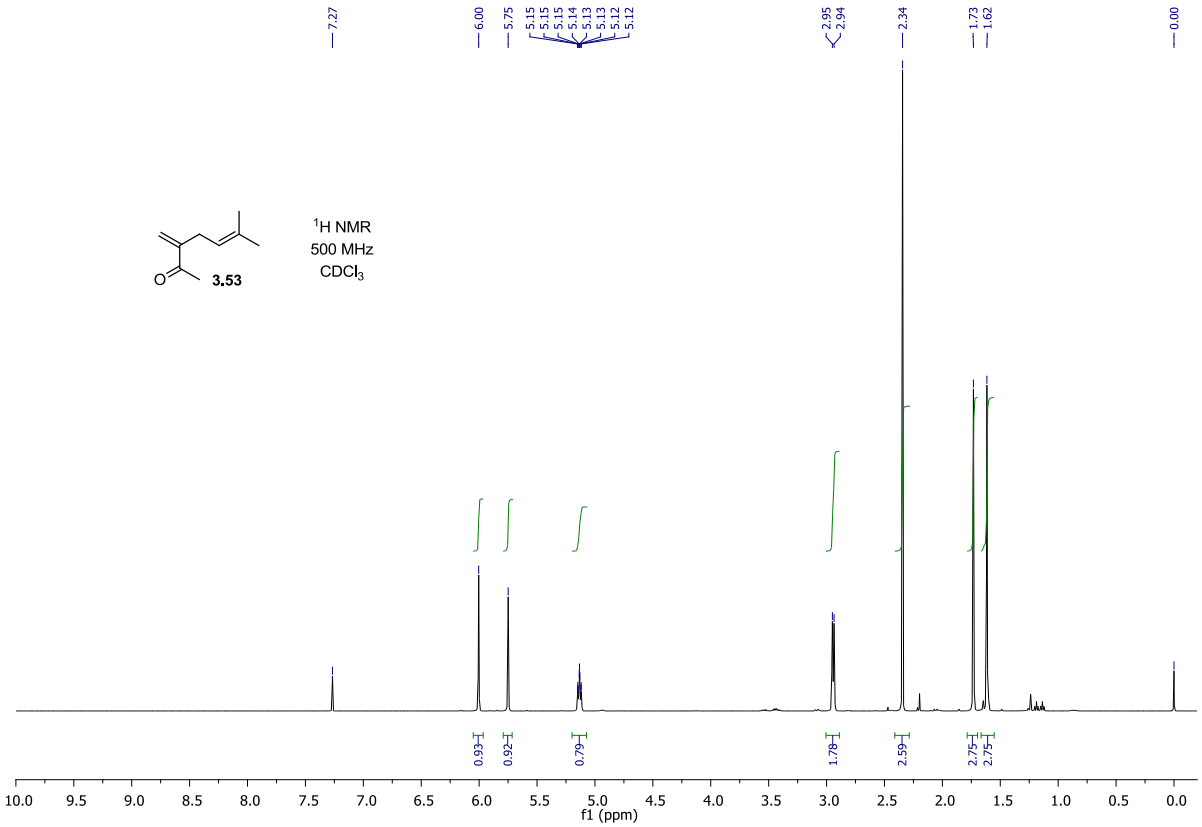

HO
O
Cl
O
HO
H
2D NOESY
600 MHz
CDCl3
3.9: merochlorin A
f2 (ppm)
f1 (ppm)

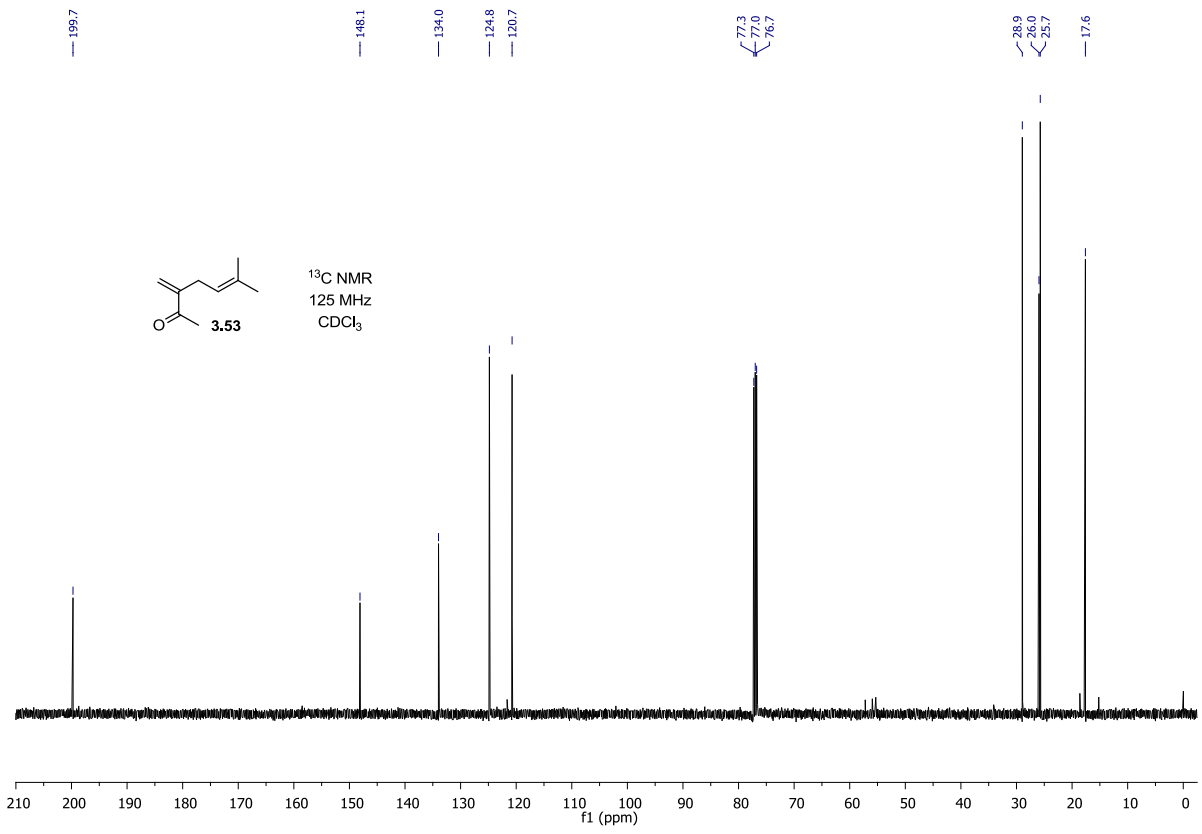

12.62
7.26
6.43
6.42
6.34
6.34
5.03
5.02
5.00
3.85
3.26
3.09
3.06
2.63
2.60
2.34
2.32
2.23
2.22
2.21
1.77
1.65
1.60
1.52
1.51
1.31
1.29
1.28
1.26
0.07
0.00
HO
O
H
O
MeO
H
1H NMR
500 MHz
CDCl3
3.51 (29%)
0.75
0.88
0.90
0.83
3.15
0.87
0.91
0.99
1.87
0.90
1.00
1.12
2.70
8.13
1.47
1.93
2.79
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

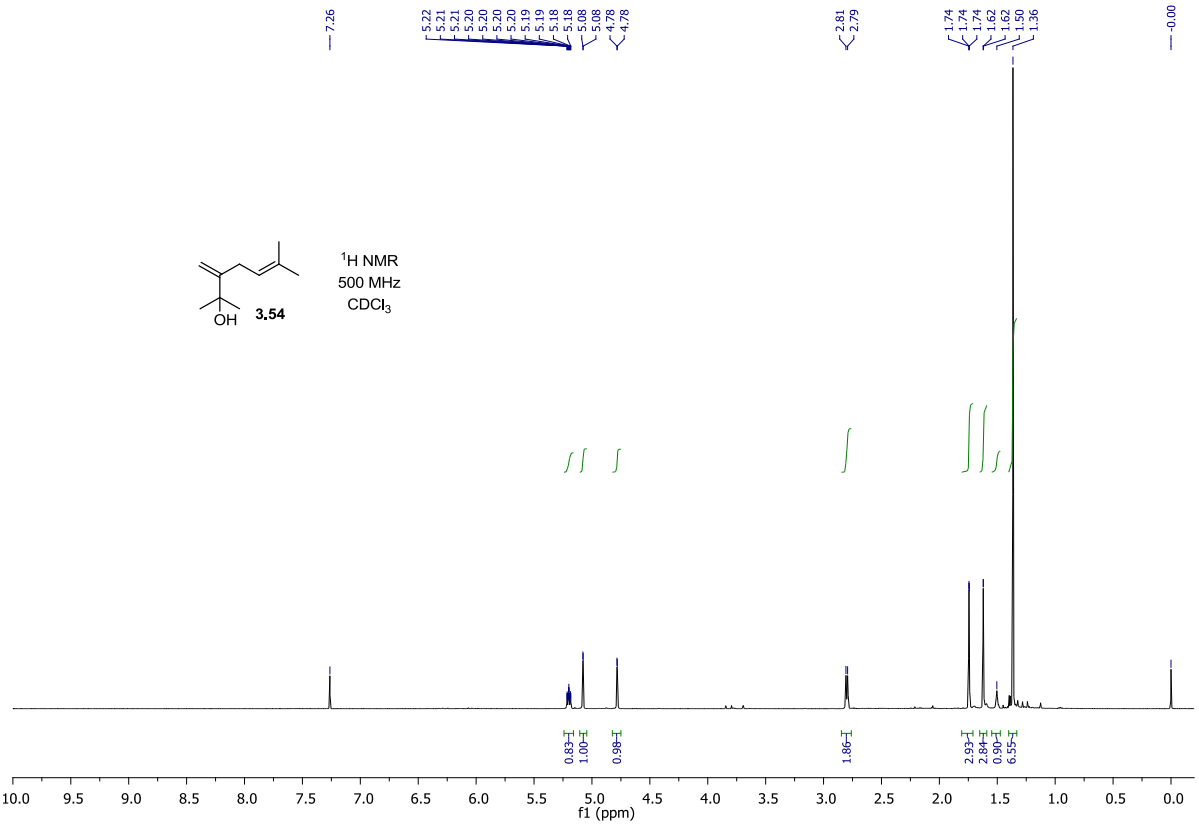

204.0
199.5
166.3
166.2
150.5
132.5
132.0
123.6
123.3
111.3
102.2
98.9
77.3
77.0
76.7
75.6
64.2
58.5
55.7
41.4
41.3
30.7
28.5
25.7
23.1
21.1
20.8
20.7
17.6
HO
O
H
O
MeO
H
13C NMR
125 MHz
CDCl3
3.51 (29%)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

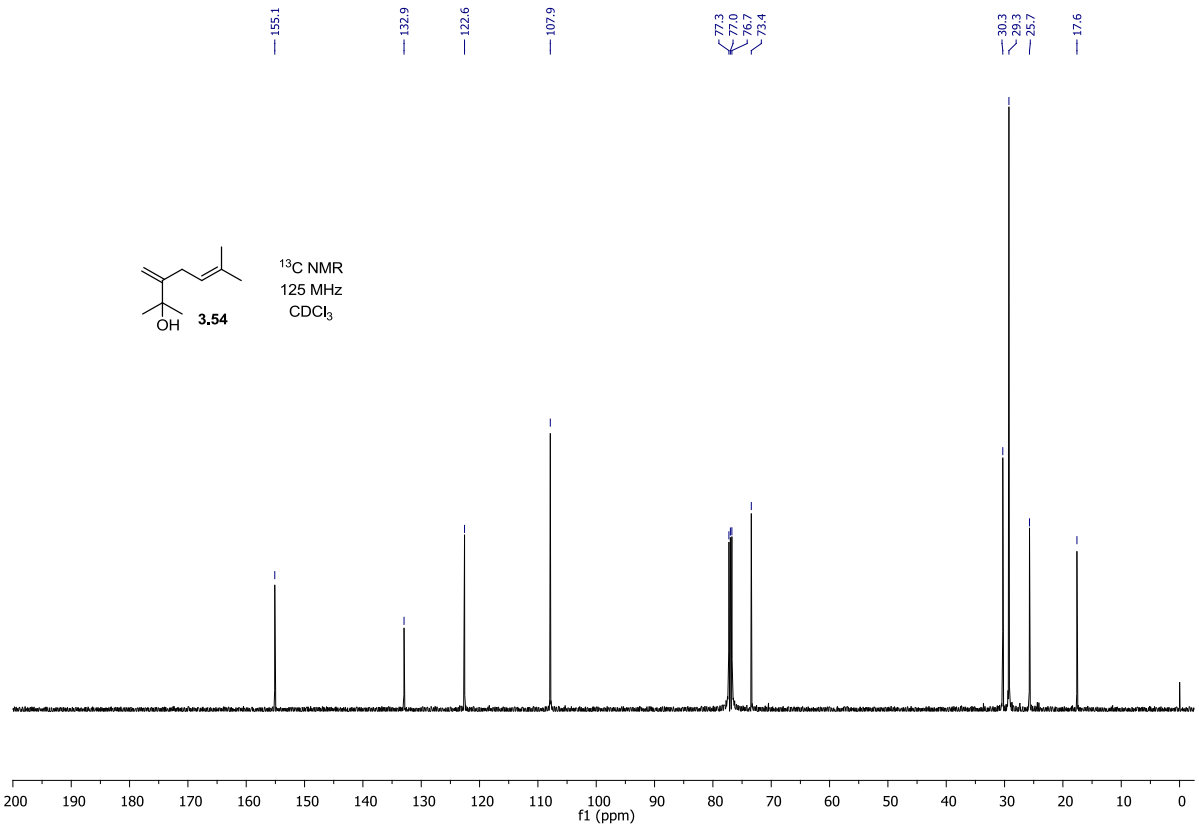

12.54
7.26
7.26
6.38
6.38
6.28
6.28
6.05
5.03
5.01
5.00
3.27
3.09
3.06
2.61
2.34
2.33
2.24
2.23
2.22
1.77
1.69
1.65
1.59
1.52
1.51
1.29
1.28
1.27
1.25
0.88
0.00
-0.00
HO
O
H
O
HO
H
1H NMR
500 MHz
CDCl3
3.52
0.85
0.56
0.98
0.99
0.92
0.87
0.92
0.97
1.01
2.01
0.99
0.95
1.12
3.05
10.03
1.15
1.84
2.93
f1 (ppm)

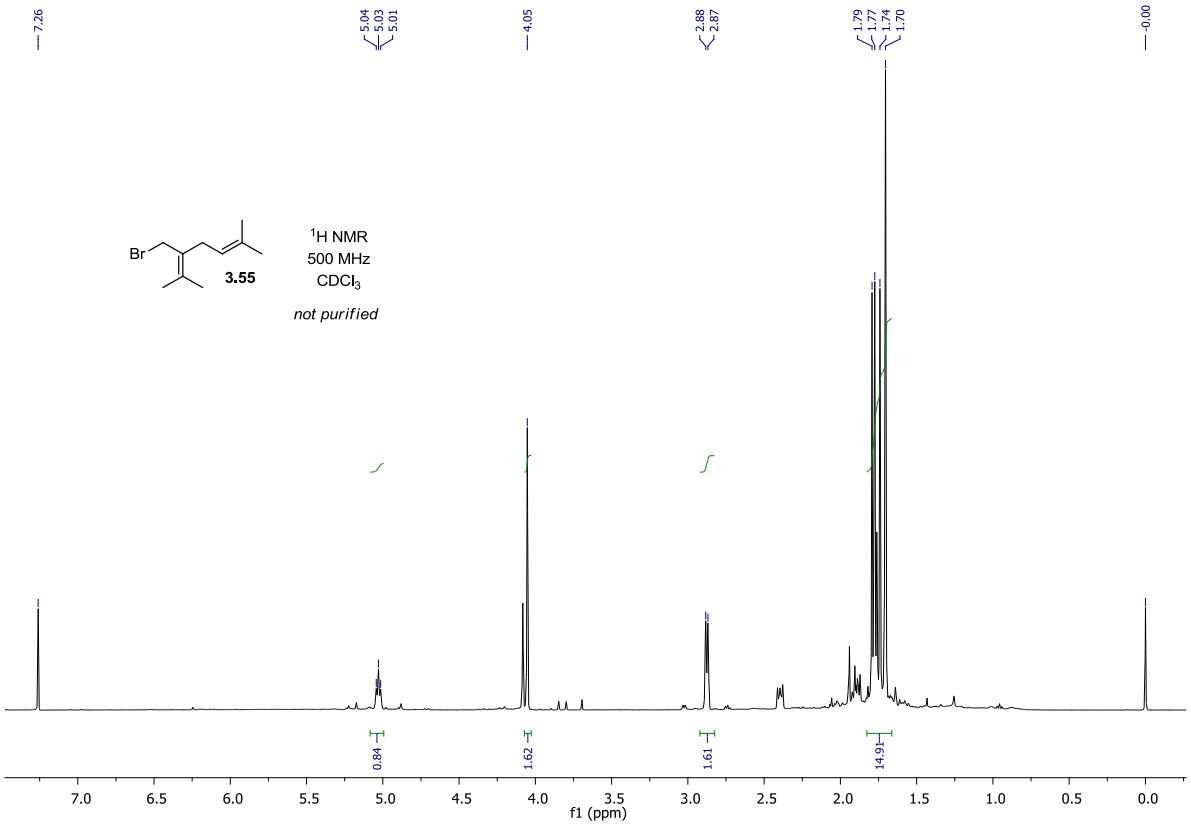

204.0
199.5
165.9
162.9
151.5
132.4
132.0
123.6
123.5
111.6
102.1
101.8
77.3
77.0
76.7
75.6
64.2
58.5
41.4
41.3
30.7
28.5
25.7
23.1
21.1
20.8
17.6
HO
O
H
O
HO
H
13C NMR
125 MHz
CDCl3
3.52
f1 (ppm)

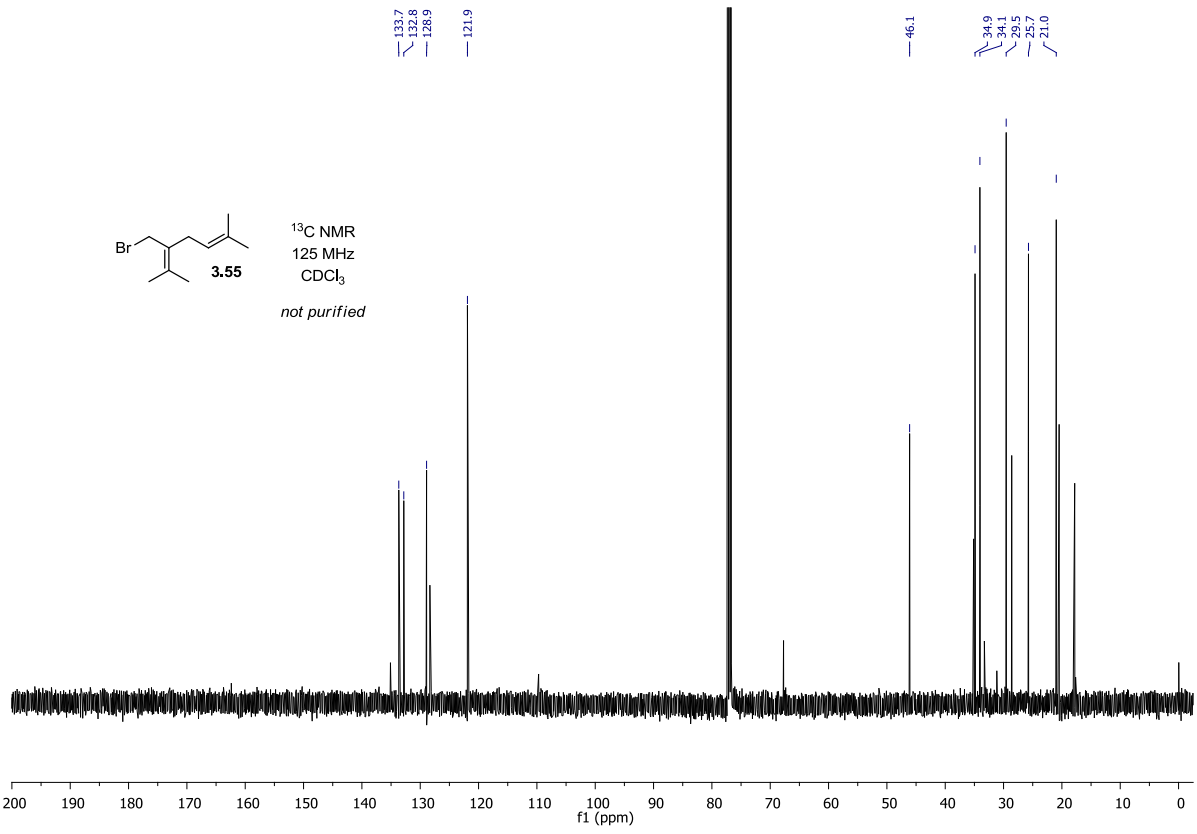

7.27
6.00
5.75
5.15
5.15
5.15
5.14
5.13
5.13
5.12
5.12
2.95
2.94
2.34
1.73
1.62
0.00
0.93
0.92
0.79
1.78
2.59
2.75
2.75
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
3.53
^{1}H NMR
500 MHz
$CDCl_3$

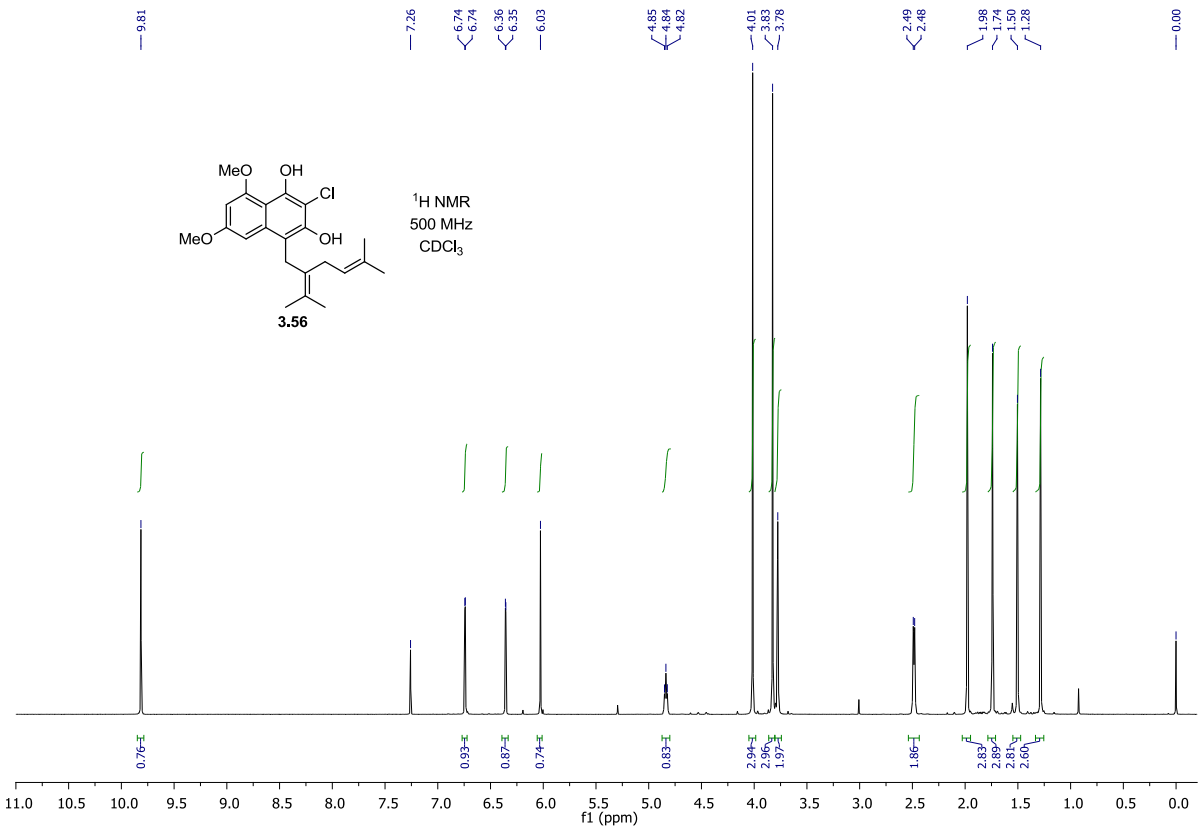

199.7
148.1
134.0
124.8
120.7
77.3
77.0
76.7
28.9
26.0
25.7
17.6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)
3.53
^{13}C NMR
125 MHz
$CDCl_3$

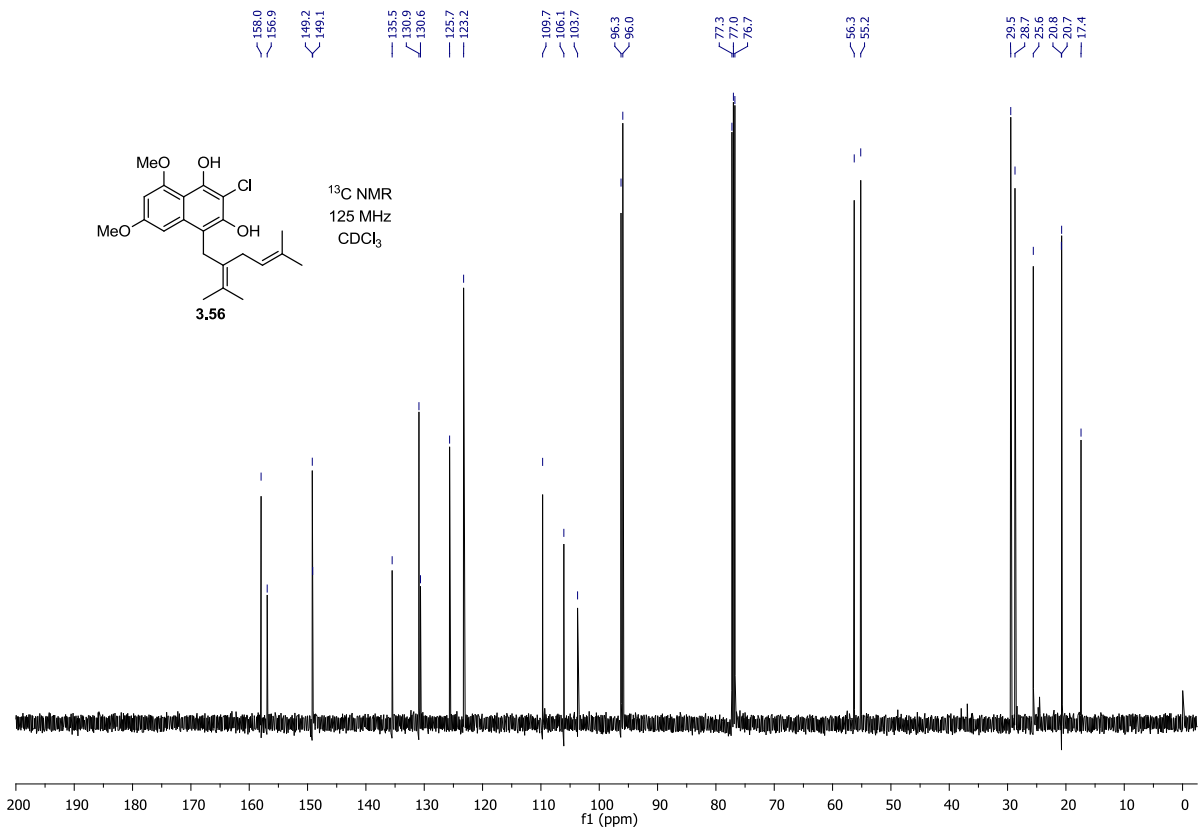

7.26
5.22
5.21
5.21
5.20
5.20
5.20
5.20
5.19
5.19
5.18
5.08
5.08
4.78
4.78
2.81
2.79
1.74
1.74
1.74
1.62
1.62
1.50
1.36
0.00
OH
3.54
1H NMR
500 MHz
CDCl3
0.83
1.00
0.98
1.86
2.93
2.84
0.90
6.55
f1 (ppm)

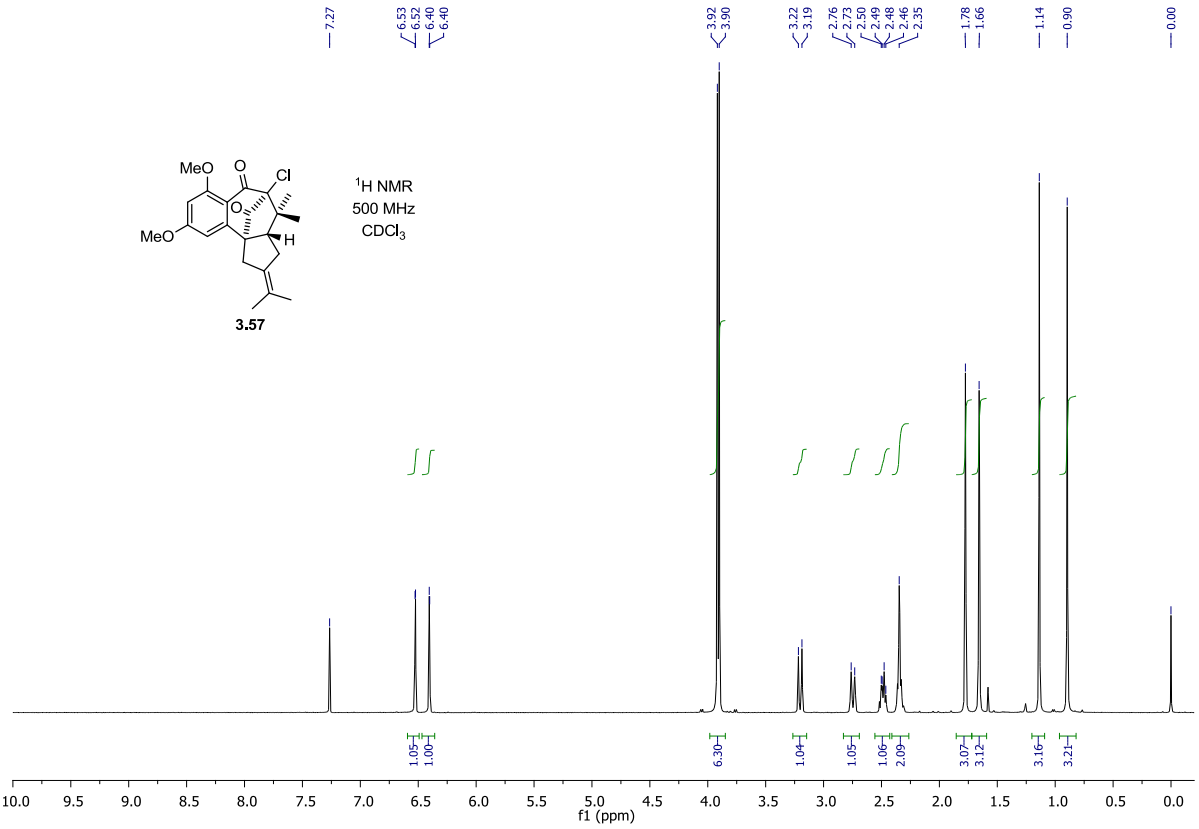

155.1
132.9
122.6
107.9
77.3
77.0
76.7
73.4
30.3
29.3
25.7
17.6
OH
3.54
13C NMR
125 MHz
CDCl3
f1 (ppm)

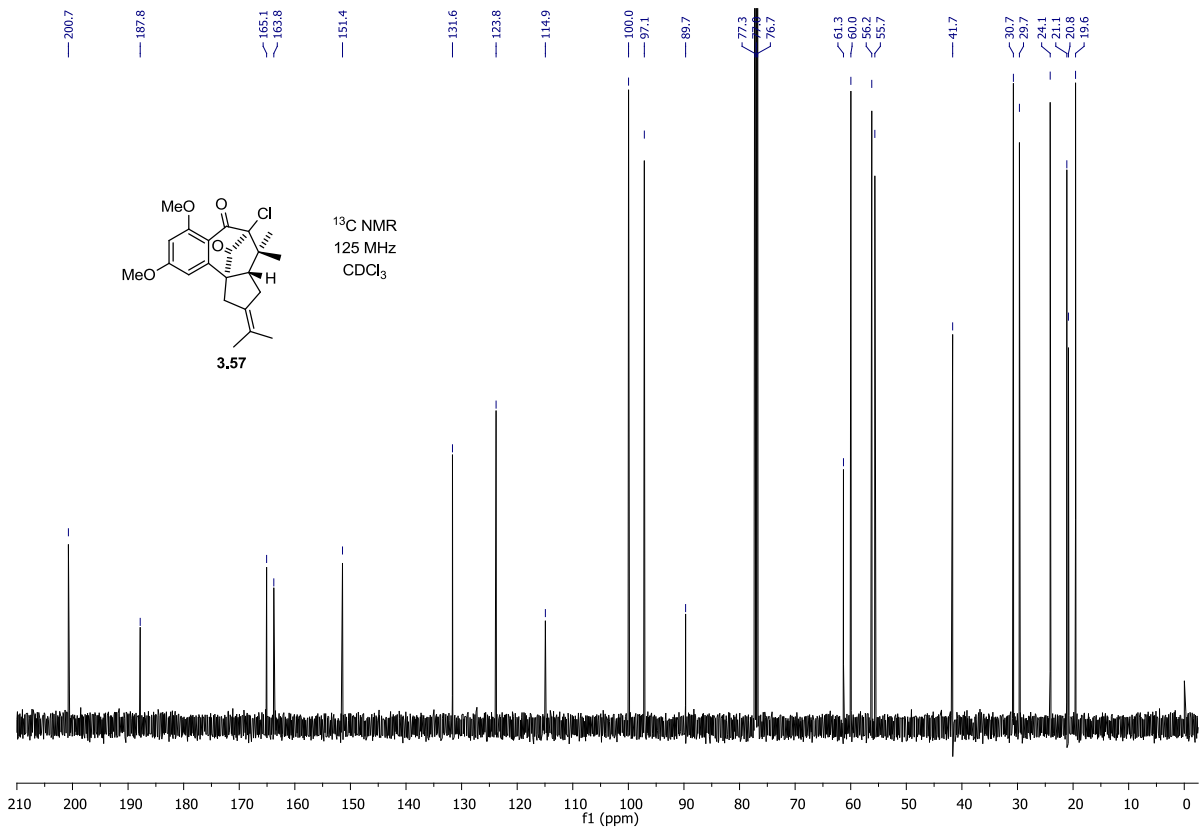

7.26
5.04
5.03
5.01
4.05
2.88
2.87
1.79
1.77
1.74
1.70
0.00
Br
3.55
^{1}H NMR
500 MHz
$CDCl_3$
not purified
0.84
1.62
1.61
14.91
f1 (ppm)

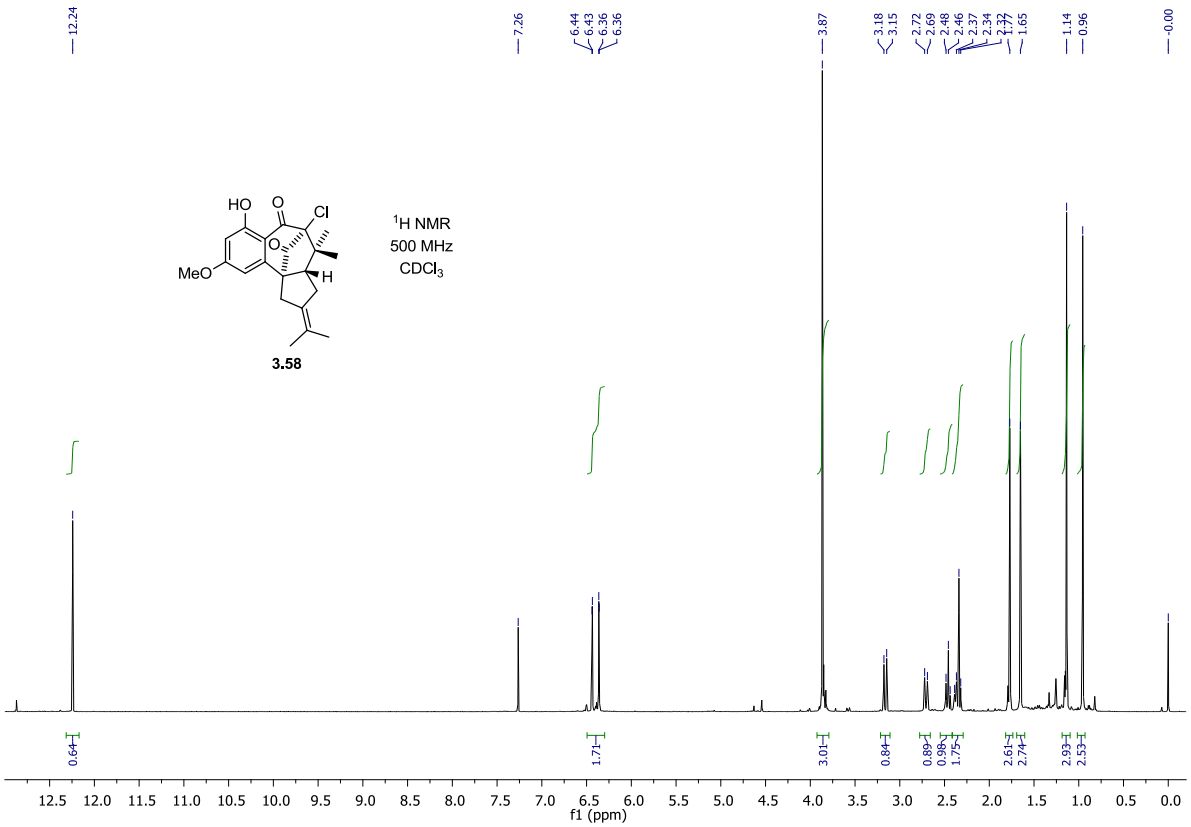

133.7
132.8
128.9
121.9
46.1
34.9
34.1
29.5
25.7
21.0
Br
3.55
^{13}C NMR
125 MHz
$CDCl_3$
not purified
f1 (ppm)

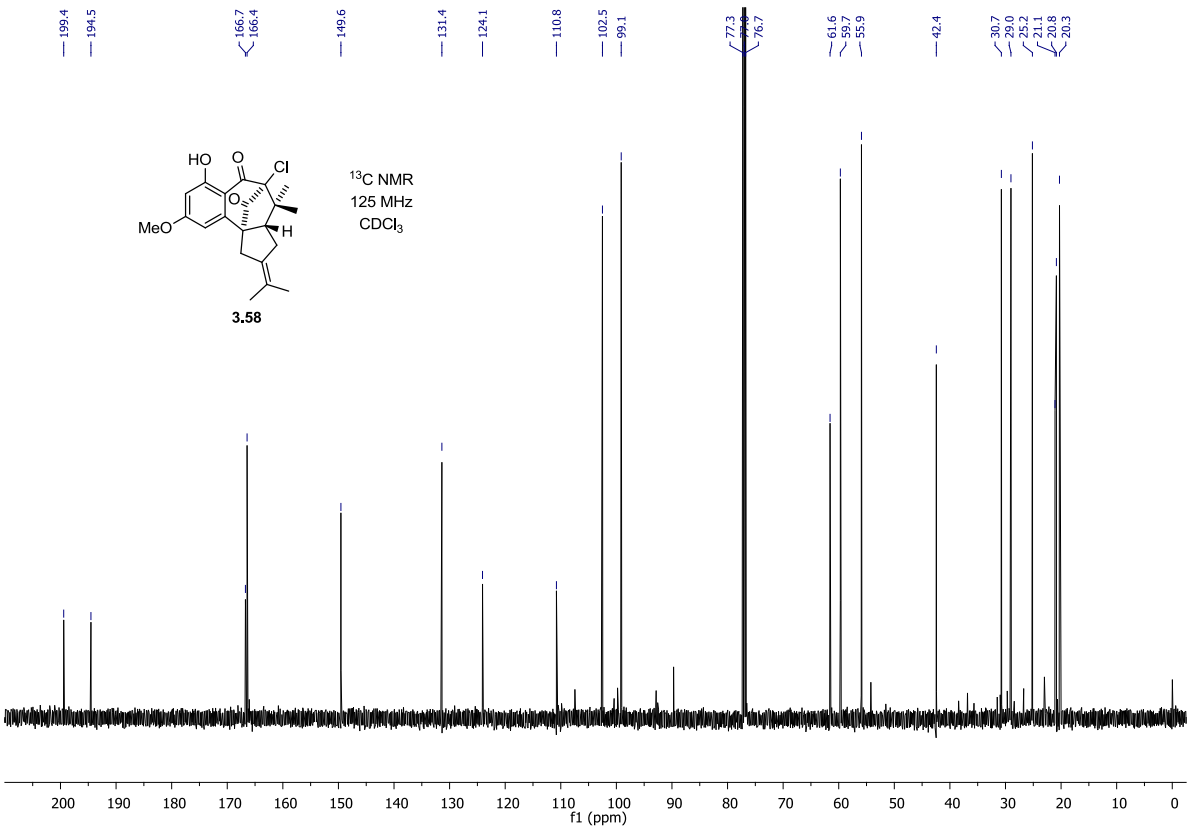

9.81
7.26
6.74
6.74
6.36
6.35
6.03
4.85
4.84
4.82
4.01
3.83
3.78
2.49
2.48
1.98
1.74
1.50
1.28
0.00
MeO
OH
Cl
MeO
OH
3.56
1H NMR
500 MHz
CDCl3
0.76
0.93
0.87
0.74
0.83
2.94
2.96
1.97
1.86
2.83
2.89
2.81
2.60
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

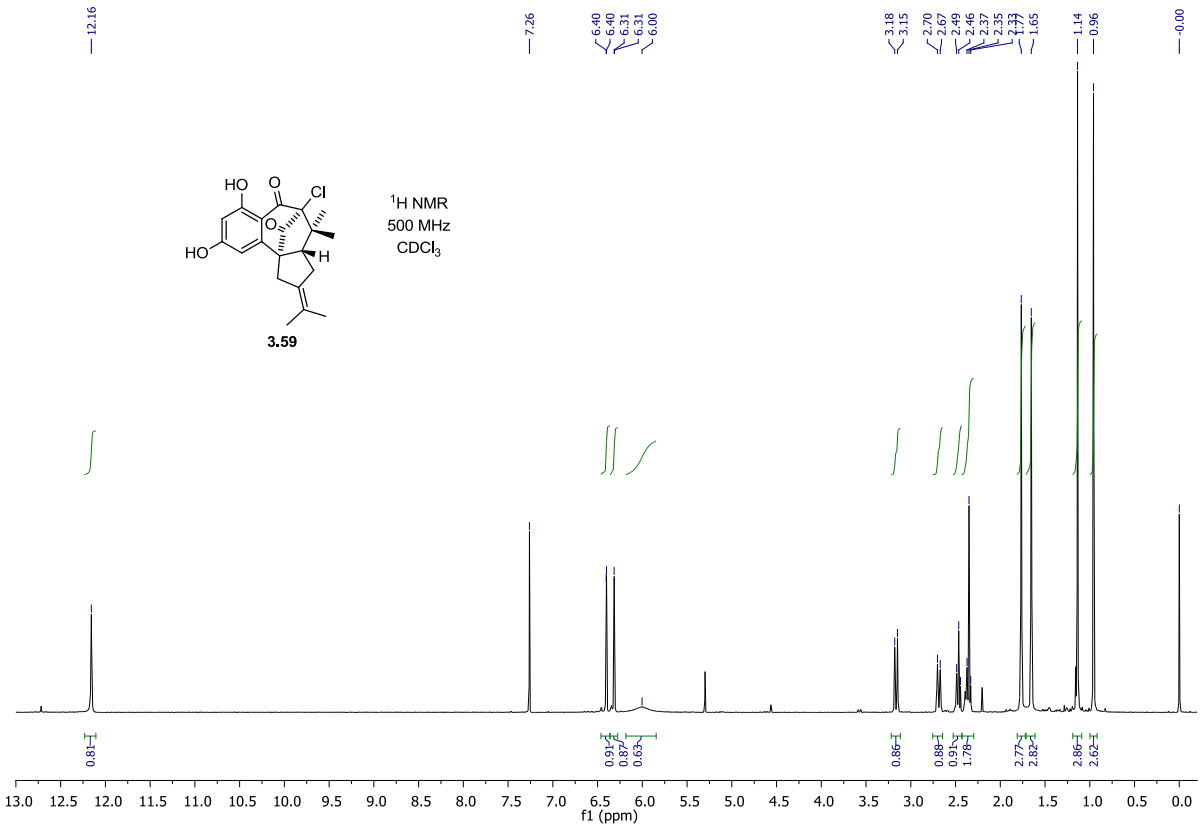

158.0
156.9
149.2
149.1
135.5
130.9
130.6
125.7
123.2
109.7
106.1
103.7
96.3
96.0
77.3
77.0
76.7
56.3
55.2
29.5
28.7
25.6
20.8
20.7
17.4
MeO
OH
Cl
MeO
OH
3.56
13C NMR
125 MHz
CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

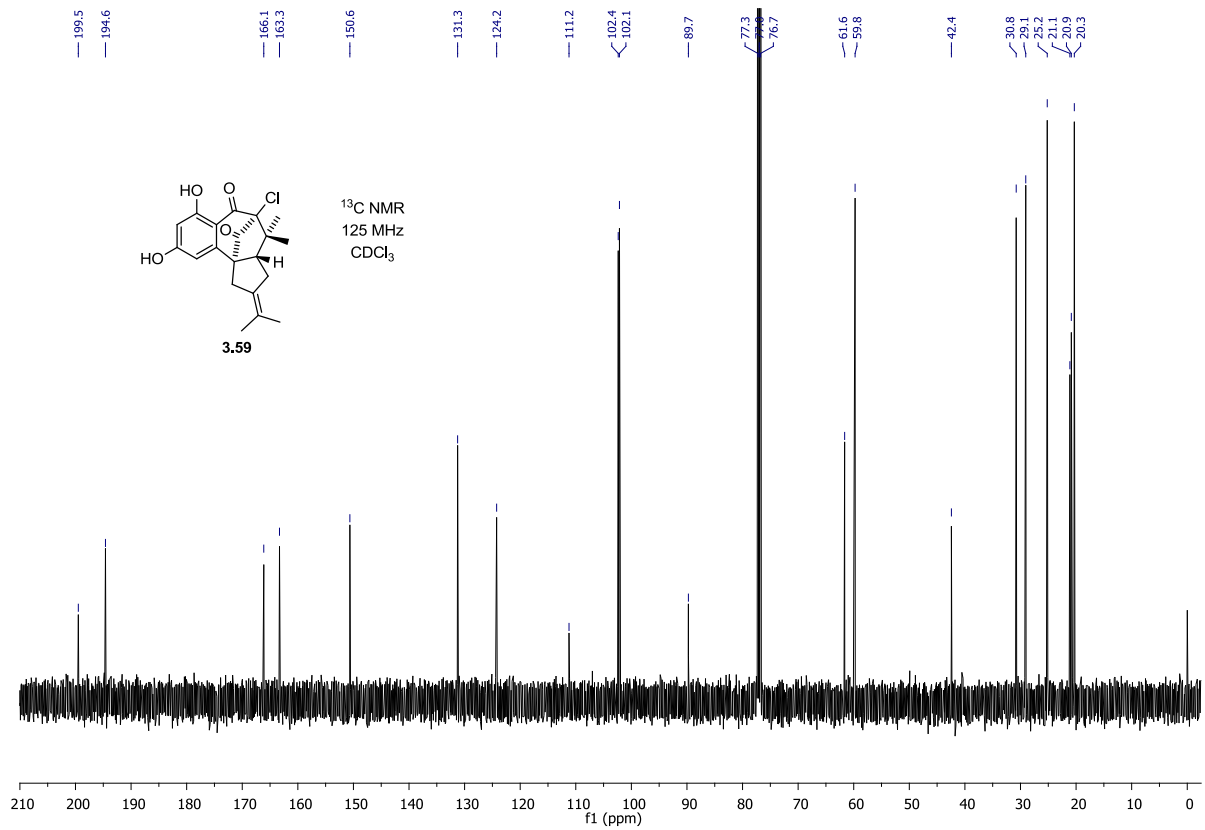

MeO
O
Cl
O
MeO
H
3.57
^{1}H NMR
500 MHz
$CDCl_3$
7.27
6.53
6.52
6.40
6.40
3.92
3.90
3.22
3.19
2.76
2.73
2.50
2.49
2.48
2.46
2.35
1.78
1.66
1.14
0.90
0.00
1.05
1.00
6.30
1.04
1.05
1.06
2.09
3.07
3.12
3.16
3.21
f1 (ppm)

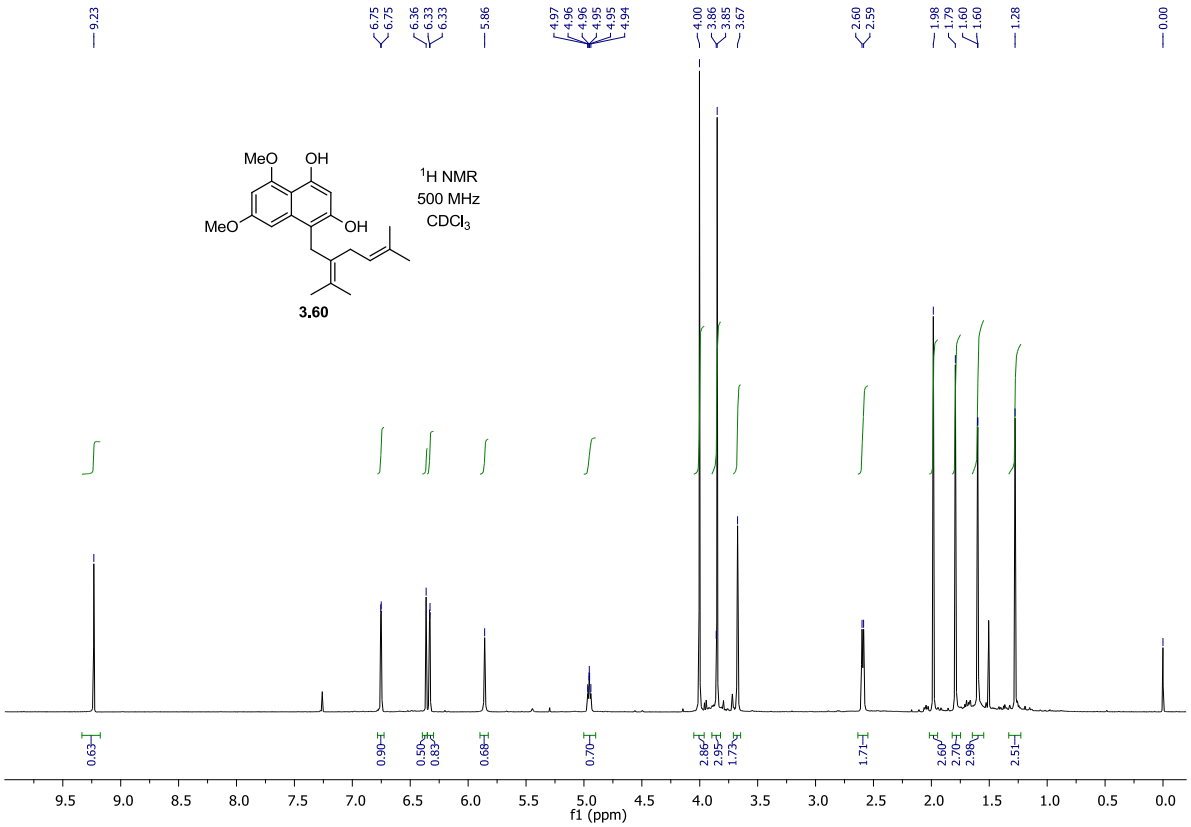

MeO
O
Cl
O
MeO
H
3.57
^{13}C NMR
125 MHz
$CDCl_3$
200.7
187.8
165.1
163.8
151.4
131.6
123.8
114.9
100.0
97.1
89.7
77.3
77.0
76.7
61.3
60.0
56.2
55.7
41.7
30.7
29.7
24.1
21.1
20.8
19.6
f1 (ppm)

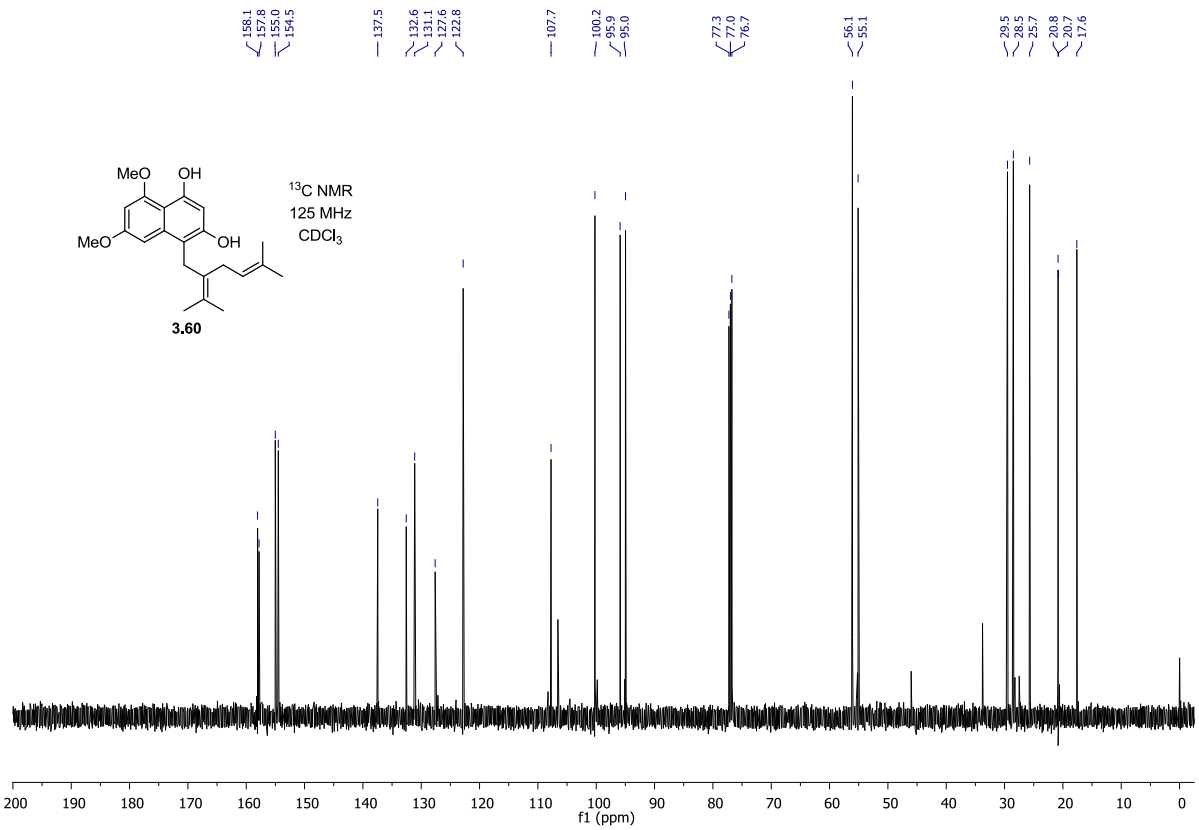

12.24
7.26
6.44
6.43
6.36
6.36
3.87
3.18
3.15
2.72
2.69
2.48
2.46
2.37
2.34
1.77
1.65
1.14
0.96
-0.00
HO
O
Cl
O
MeO
H
3.58
^{1}H NMR
500 MHz
$CDCl_3$
0.64
1.71
3.01
0.84
0.89
0.98
1.75
2.61
2.74
2.93
2.53
f1 (ppm)


199.4
194.5
166.7
166.4
149.6
131.4
124.1
110.8
102.5
99.1
77.3
77.0
76.7
61.6
59.7
55.9
42.4
30.7
29.0
25.2
21.1
20.8
20.3
HO
O
Cl
O
MeO
H
3.58
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)


12.16
7.26
6.40
6.40
6.31
6.31
6.00
3.18
3.15
2.70
2.67
2.49
2.46
2.37
2.35
2.33
1.77
1.65
1.14
0.96
-0.00
HO
O
Cl
HO
O
H
3.59
^{1}H NMR
500 MHz
$CDCl_3$
0.81
0.91
0.87
0.63
0.86
0.88
0.91
1.78
2.77
2.82
2.86
2.62
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


199.5
194.6
166.1
163.3
150.6
131.3
124.2
111.2
102.4
102.1
89.7
77.3
76.7
61.6
59.8
42.4
30.8
29.1
25.2
21.1
20.9
20.3
HO
O
Cl
HO
O
H
3.59
^{13}C NMR
125 MHz
$CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


9.23
6.75
6.75
6.36
6.33
6.33
5.86
4.97
4.96
4.96
4.95
4.95
4.94
4.00
3.86
3.85
3.67
2.60
2.59
1.98
1.79
1.60
1.60
1.28
0.00
MeO
OH
MeO
OH
1H NMR
500 MHz
CDCl3
3.60
0.63
0.90
0.50
0.83
0.68
0.70
2.86
2.95
1.73
1.71
2.60
2.70
2.98
2.51
f1 (ppm)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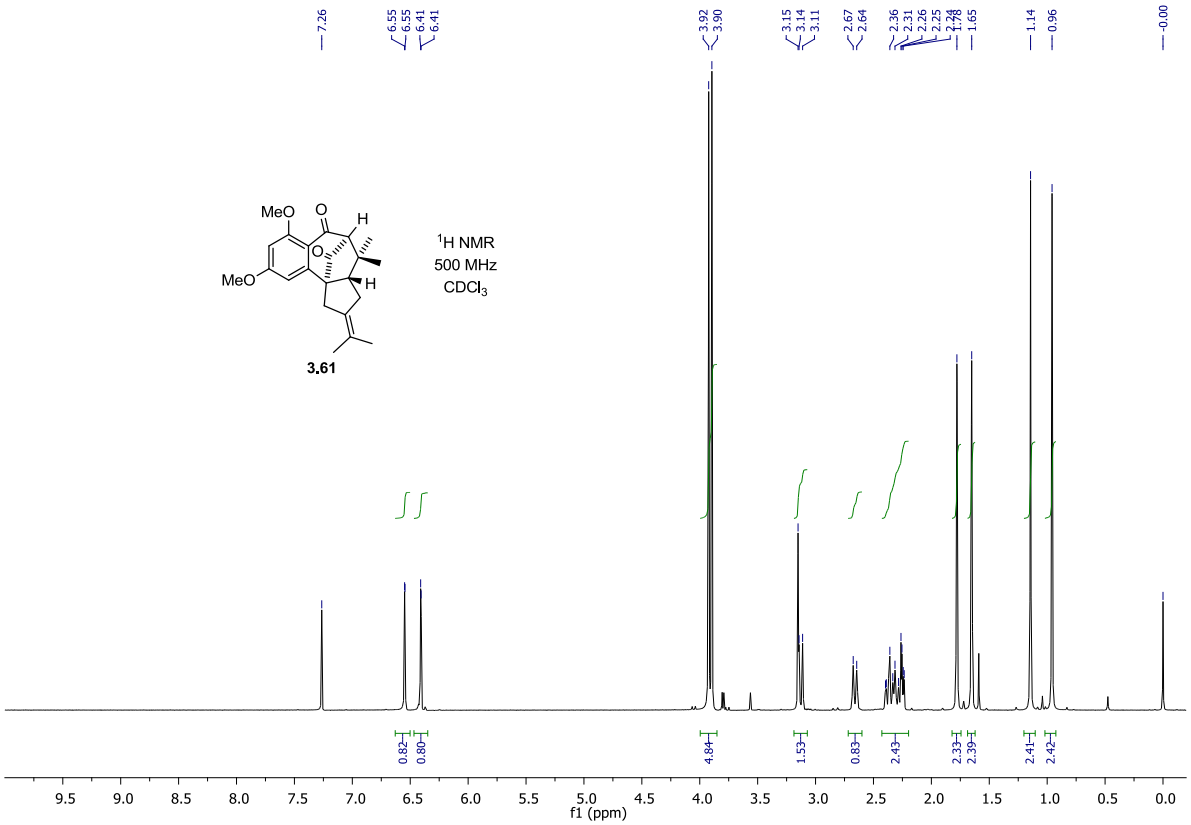
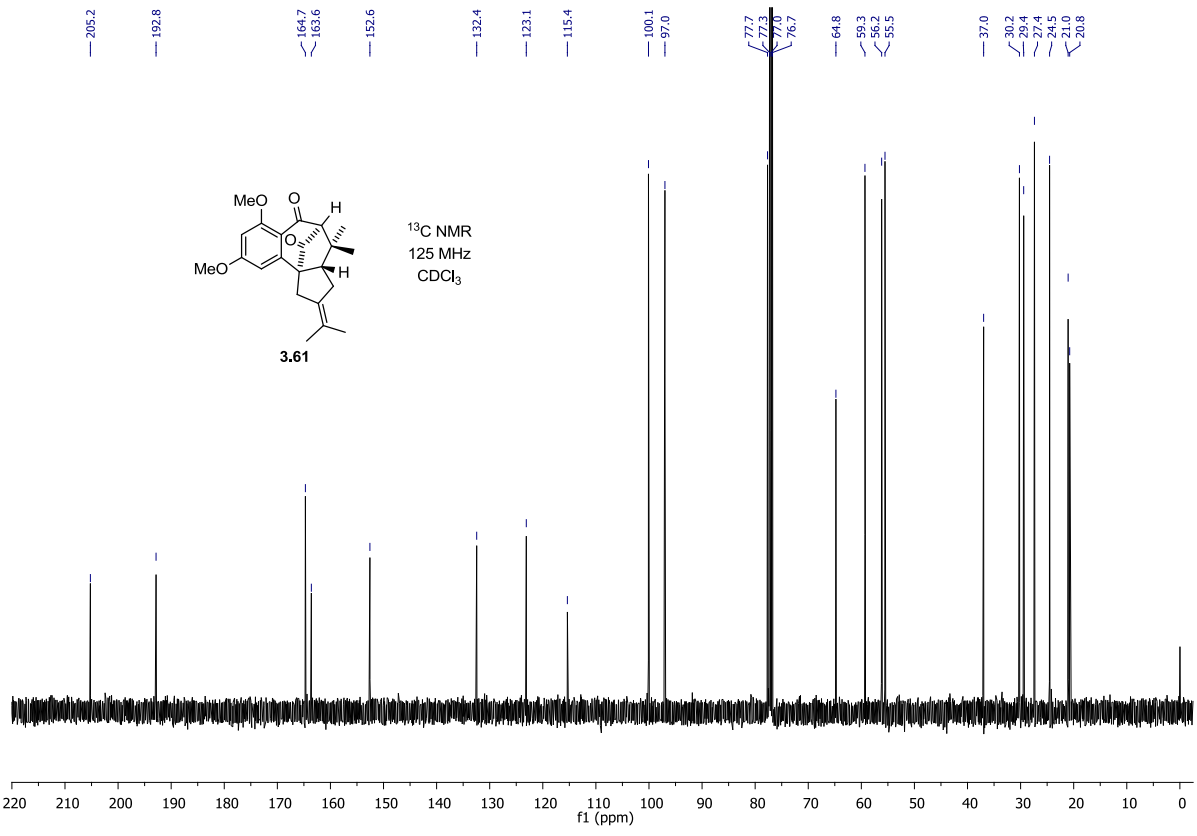
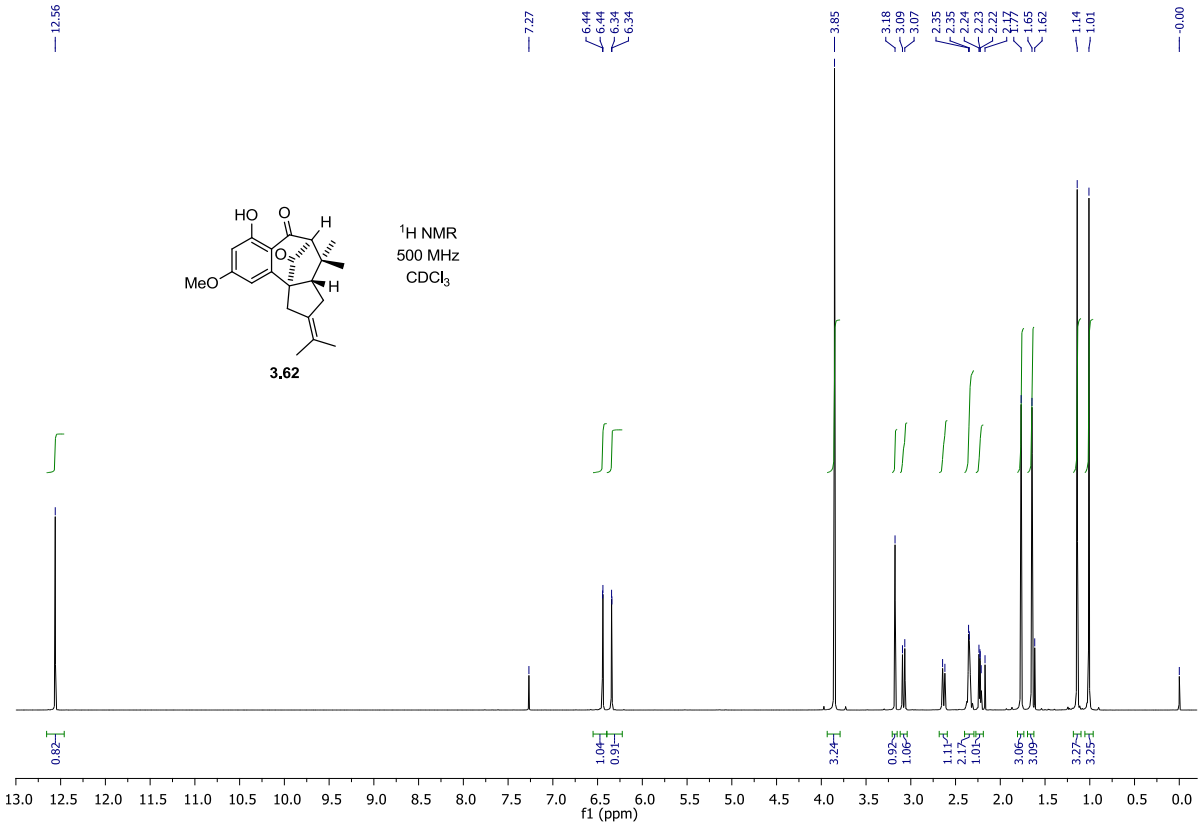
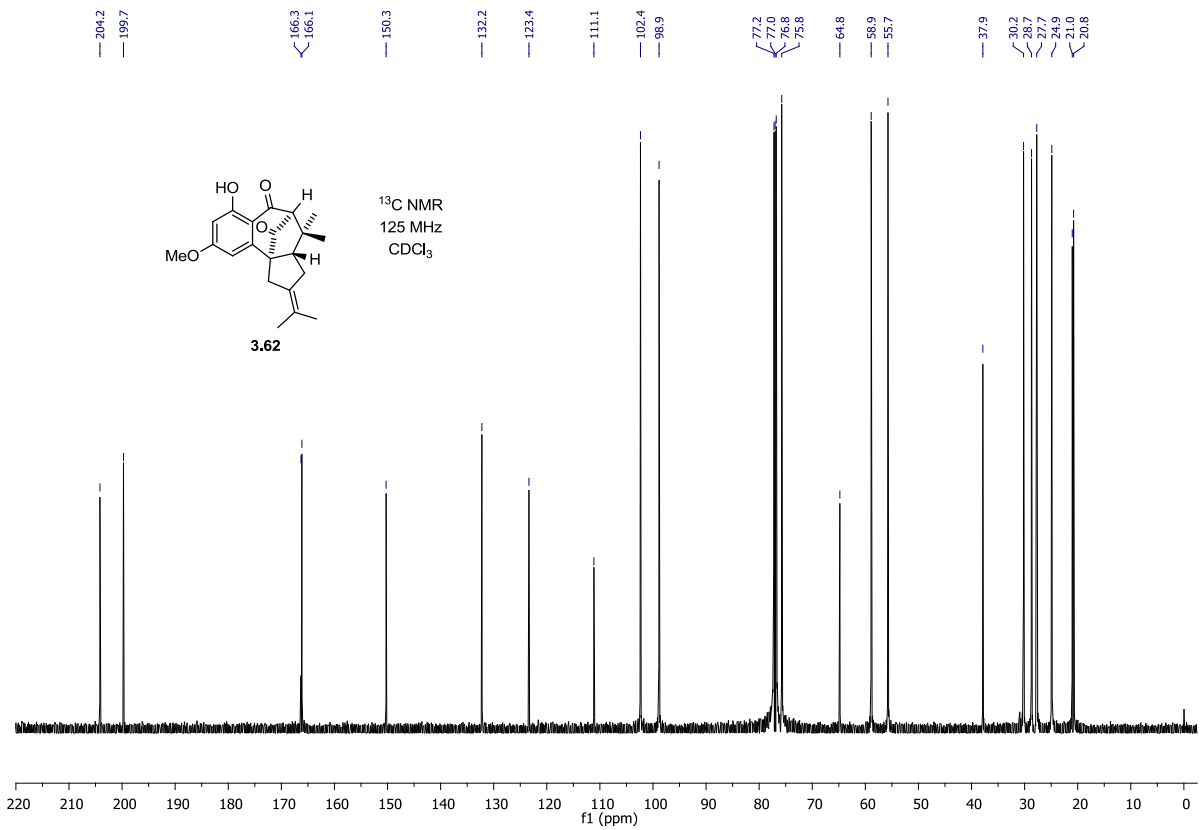
157.8
155.0
154.5
137.5
132.6
131.1
127.6
122.8
107.7
100.2
95.9
95.0
77.3
77.0
76.7
56.1
55.1
29.5
28.5
25.7
20.8
20.7
17.6
MeO
OH
MeO
OH
13C NMR
125 MHz
CDCl3
3.60
f1 (ppm)


7.26
6.55
6.55
6.41
6.41
3.92
3.90
3.15
3.14
3.11
2.67
2.64
2.36
2.31
2.26
2.25
1.65
1.14
0.96
0.00
MeO
O
H
O
MeO
H
3.61
^{1}H NMR
500 MHz
$CDCl_3$
0.82
0.80
4.84
1.53
0.83
2.43
2.33
2.39
2.41
2.42
f1 (ppm)

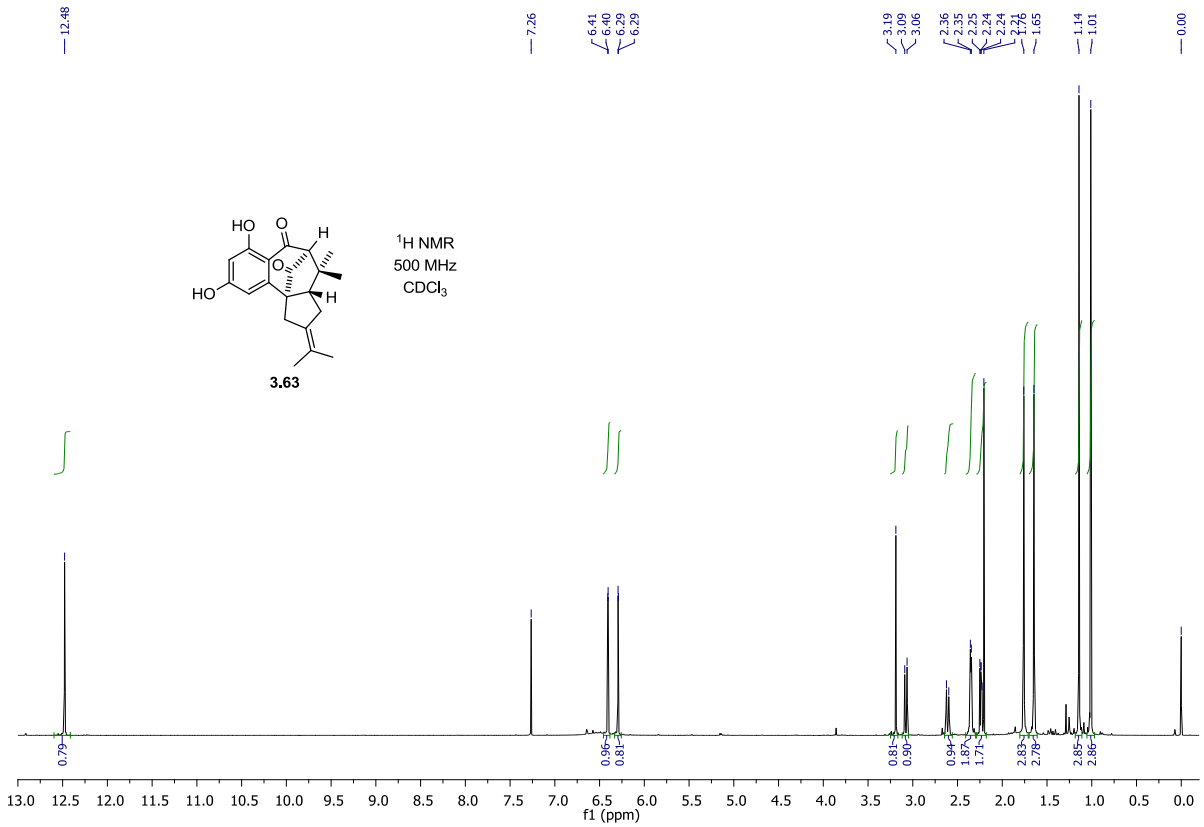

205.2
192.8
164.7
163.6
152.6
132.4
123.1
115.4
100.1
97.0
77.7
77.3
77.0
76.7
64.8
59.3
56.2
55.5
37.0
30.2
29.4
27.4
24.5
21.0
20.8
MeO
O
H
O
MeO
H
3.61
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

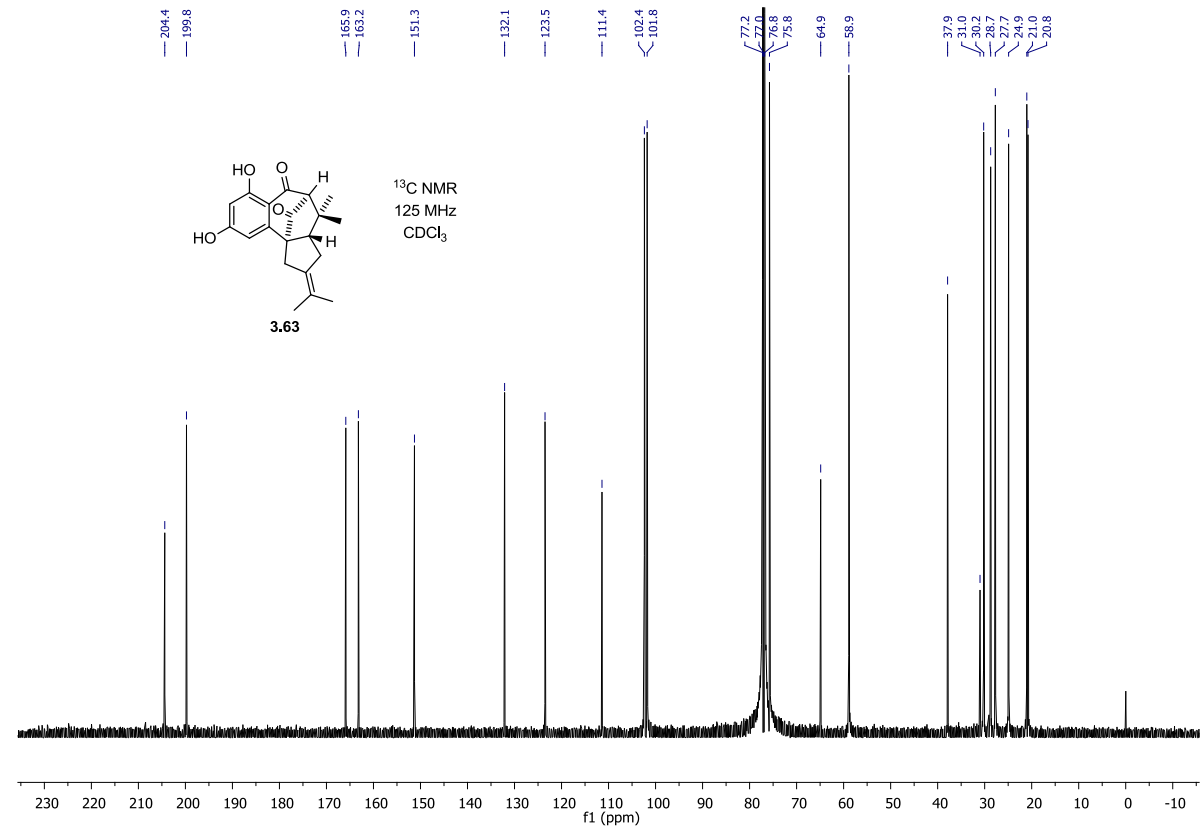

12.56
7.27
6.44
6.44
6.34
6.34
3.85
3.18
3.09
3.07
2.35
2.35
2.24
2.23
2.22
1.65
1.62
1.14
1.01
-0.00
HO
O
H
O
MeO
H
^{1}H NMR
500 MHz
$CDCl_3$
0.82
1.04
0.91
3.24
0.92
1.06
1.11
2.17
1.01
3.06
3.09
3.27
3.25
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

3.62


204.2
199.7
166.3
166.1
150.3
132.2
123.4
111.1
102.4
98.9
77.2
77.0
76.8
75.8
64.8
58.9
55.7
37.9
30.2
28.7
27.7
24.9
21.0
20.8
HO
O
H
O
MeO
H
^{13}C NMR
125 MHz
$CDCl_3$
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

3.62


12.48
7.26
6.41
6.40
6.29
6.29
3.19
3.09
3.06
2.36
2.35
2.25
2.24
2.24
2.21
1.76
1.65
1.14
1.01
0.00
HO
O
H
HO
O
H
3.63
^{1}H NMR
500 MHz
$CDCl_3$
0.79
0.96
0.81
0.81
0.90
0.94
1.87
1.71
2.83
2.78
2.85
2.86
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

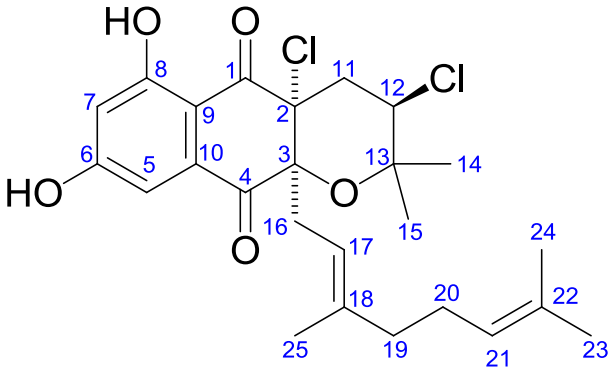

204.4
199.8
165.9
163.2
151.3
132.1
123.5
111.4
102.4
101.8
77.2
77.0
76.8
75.8
64.9
58.9
37.9
31.0
30.2
28.7
27.7
24.9
21.0
20.8
HO
O
H
HO
O
H
3.63
^{13}C NMR
125 MHz
$CDCl_3$
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

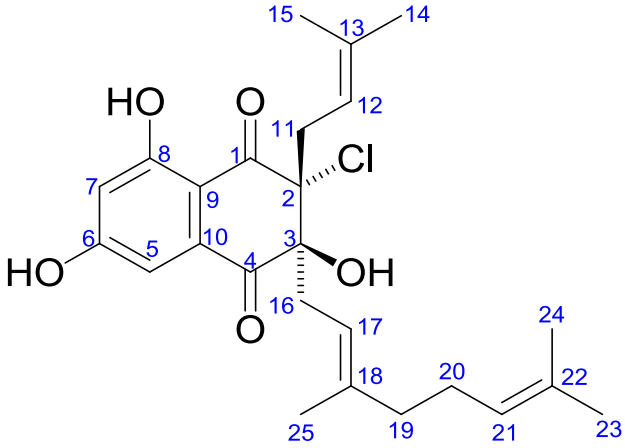
Crystal data for merochlorin A (3.9)

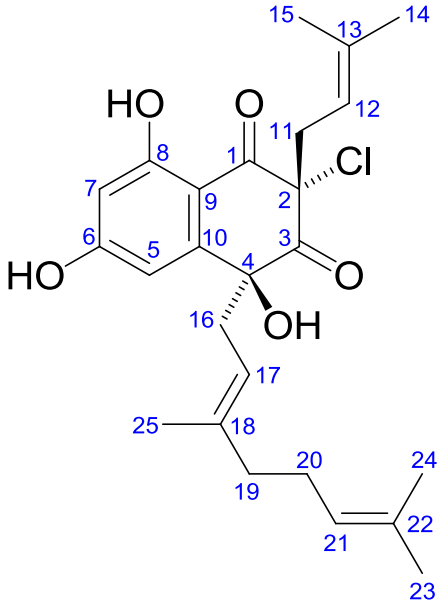
Compound	merochlorin A **(3.9)**
Empirical formula	$C_{25}H_{29}ClO_4$
Formula weight	428.95
Crystal system	monoclinic
Space group	P -1
a (Å)	8.2445(6)
b (Å)	9.3051(5)
c (Å)	15.4428(15)
α (°)	101.261(6)
β (°)	95.594(7)
γ (°)	109.334(6)
Volume ($Å^3$)	1079.42
Z	2
R-Factor %	6.14

CHAPTER 4

Biomimetic Synthesis of Napyradiomycin Natural Products





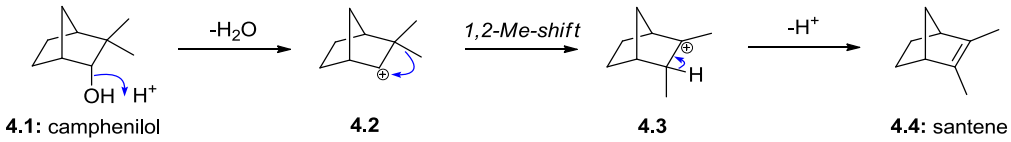


Carbon atoms of napyradiomycin compounds and related synthetic intermediates will be referred to numerically as per these diagrams for the length of this chapter.

4.1 Introduction

4.1.1 The α-Ketol Rearrangement

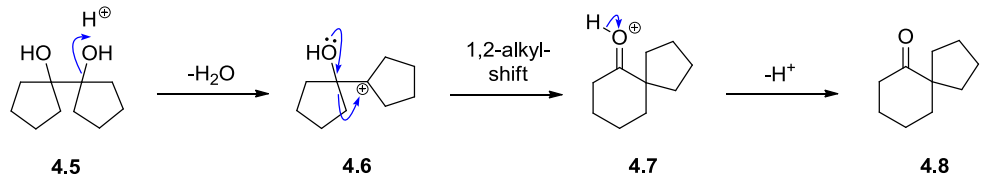
1,2-Rearrangements are a class of organic reactions where a substituent moves from one atom to an adjacent atom in the same molecule, usually proceeding *via* a reactive intermediate. This type of reaction has proven to be an invaluable tool in the total synthesis of complex molecules and is relevant in the biosynthesis of many naturally occurring compounds.



Scheme 4.1: Wagner-Meerwein rearrangement[1]

Many 1,2-rearrangments are induced by carbocation intermediates. Of these, the most important reaction is the Wagner-Meerwein rearrangement (**scheme 4.1**).[1] Carbocations rearrange predictably by hydride or alkyl shifts in order to become more stable, especially in cases where alternate processes such as S_N1 or E1 reactions are not possible. The Wagner-Meerwein rearrangement is important in the biosynthesis of certain steroid and terpenoid natural products such as the fragrance compound santene (**4.4**).[2]

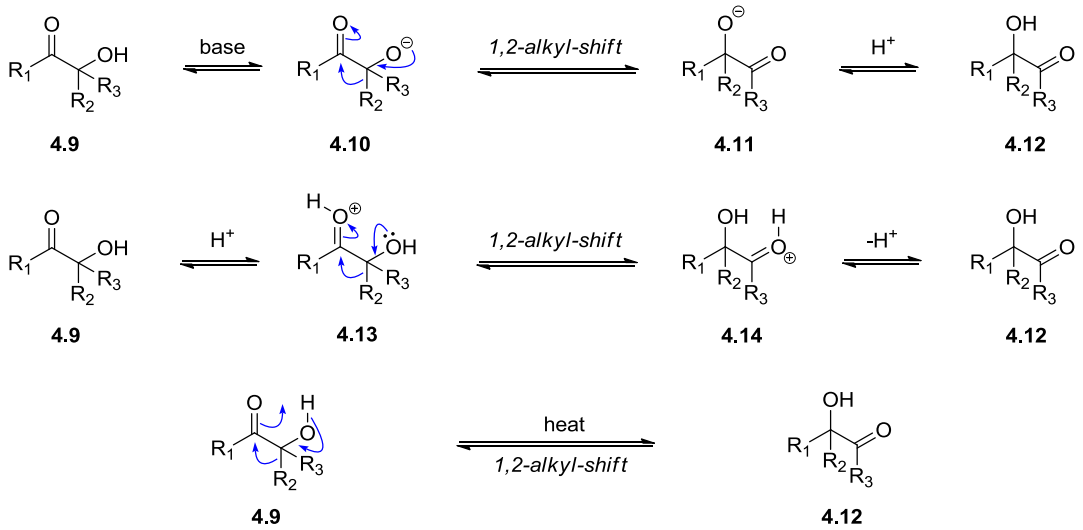
Another well known example is the pinacol rearrangement, in which 1,2-diols such as **4.5** undergo a 1,2-alkyl shift and subsequent formation of a ketone under acidic conditions, proceeding through a carbocation intermediate (**scheme 4.2**).[3] This reaction can be useful even with already stable carbocations, as rearrangement allows further stabilization by the adjacent oxygen atom.



Scheme 4.2: Pinacol rearrangement[3]

The α-ketol rearrangement (also known as the α-hydroxy ketone rearrangement) is the 1,2-rearrangement of an α-hydroxy carbonyl compound resulting in an isomeric product.[4] This

reaction is typically achieved synthetically by treating suitable substrates with base, acid or heat. While rearrangements involving α-ketols are most common, rearrangements of α-hydroxy aldehydes and α-hydroxy imines also exist and follow the same mechanism. Mechanistically, this reaction proceeds differently depending on what conditions are used (**scheme 4.3**); however, in all cases alkyl shift and ketone formation occur simultaneously. The α-ketol rearrangement is a reversible process, and this is an important fact when designing a synthetically useful step.

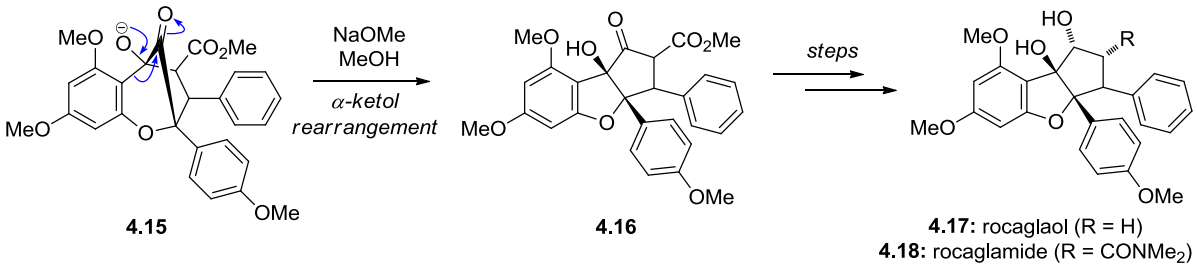


Scheme 4.3: The α-ketol rearrangement[4]

Reactions are run under thermodynamic control and, generally, there must be a considerable thermodynamic energy difference between the two isomers for the chemical equilibrium to lie far to the right and hence achieve a reasonable yield. This can limit the synthetic utility of the α-ketol rearrangement, but knowledge of this reaction can be exploited by designing syntheses where the desired isomer is significantly more thermodynamically stable than the starting material. This can be achieved by utilizing a ring expansion reaction of a cyclopropane or cyclobutane as the alkyl shift event, overall resulting in an overall reduction of ring strain. The desired isomer containing increased conjugation or decreased levels of steric interactions relative to the starting compound can also increase reaction success.

In the synthesis of the rocoglamide natural products by Porco *et al.* in 2006, an α-ketol rearrangement played a pivotal role.[5,6] The bridged bicyclic α-ketol intermediate **4.15**, conveniently constructed *via* an enantioselective [3 + 2] dipolar photocycloaddition reaction, underwent ring contraction as a result of α-ketol rearrangement under basic conditions, forming the 6-5-5 fused tricyclic core of the rocoglamides (**scheme 4.4**). This approach was

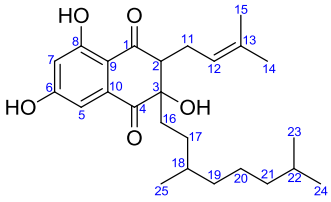
suggested to be biomimetic, as a similar process had been proposed for the biosynthesis. From the key intermediate **4.15**, Porco *et al.* were able to complete the total synthesis of both rocaglaol (**4.17**) and rocoglamide (**4.18**).[6]



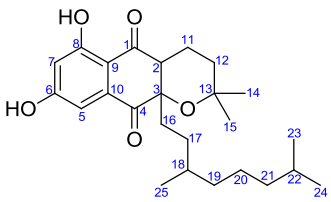
Scheme 4.4: Key α-ketol rearrangement step in the 2006 synthesis of rocoglaol and rocoglamide by Porco *et al.*[5,6]

4.1.2 Napyradiomycin Natural Products

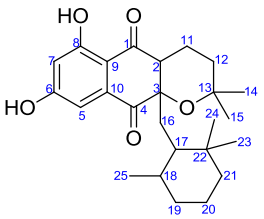
The napyradiomycins are a large family (55 currently reported) of naphthoquinone meroterpenoid natural products isolated from actinobacteria. They are characterized by their unique polycyclic frameworks and distinct halogenation patterns, and are structurally related to the marinone,[7,8] naphterpin[9,10] and merochlorin[11] families. All napyradiomycins contain halogen atoms in their chemical structure or are biosynthetically derived from halogenated intermediates, with VHPO enzymes being responsible for halogen incorporation during their biosynthesis.



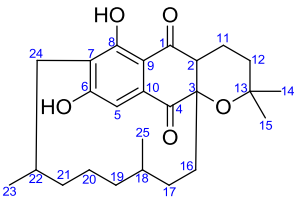
4.19: Type O napyradiomycins



4.20: Type A napyradiomycins



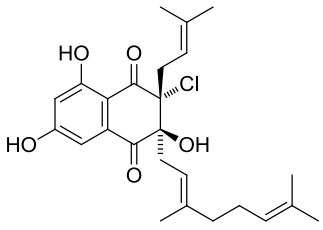
4.21: Type B napyradiomycins



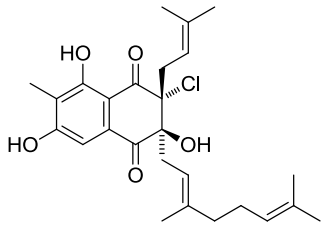
4.22: Type C napyradiomycins

Figure 4.1: General structure of napyradiomycins[12]

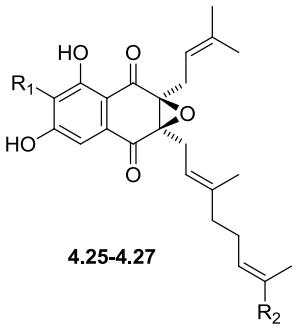
The general napyradiomycin structure consists of a naphthoquinone skeleton with an oxygen atom and a geranyl substituent bonded to C-3 and a prenyl group bonded to C-2 (**4.19**-**4.22**). The degree of cyclization of the two terpene substituents divides the napyradiomycins into four different classes (**figure 4.1**).[12] While napyradiomycins of the general structure **4.20**, **4.21** and **4.22** have previously been classified into appropriately named classes, napyradiomycins of the general structure **4.19** have not been given a title and we herein propose that such compounds be referred to as type O napyradiomycins. Type O napyradiomycins **(4.19)** are the most biosynthetically fundamental members, where both terpene substituents remain uncyclized and are generally bicyclic structures. In type A napyradiomycins (**4.20**), the prenyl group is cyclized onto the C-3 oxygen atom in a tetrahydropyran ring and the geranyl substituent is uncyclized. In addition to the cyclized prenyl group, type B napyradiomycins (**4.21**) have an additional 6-membered ring resulting from cyclization of the geranyl group. The final class is the type C napyradiomycins (**4.22**), in which the geranyl substituent has instead cyclized with the aromatic ring at the C-7 position, giving a 14-membered macrocycle.



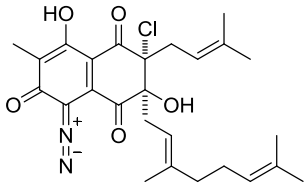
4.23: naphthomevalin



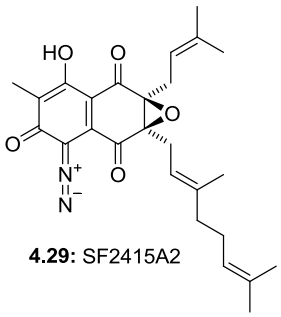
4.24: SF2415B1



4.25-4.27



4.28: SF2415A1

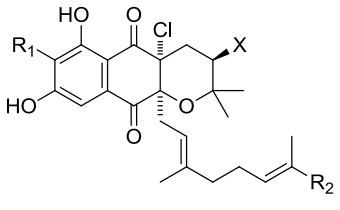


4.29: SF2415A2

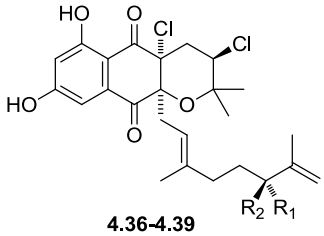
Table 4.1: Type O napyradiomycins

no.	groups	name	source
4.23		naphthomevalin[13]	*Streptomyces sp.*Gő 28
4.24		SF2415B1[15]	*Streptomyces aculeolatus*
4.25	R_1 = H; R_2 = Me	A80915G[16]	*Streptomyces aculeolatus* A80915
4.26	R_1 = H; R_2 = CO_2H	A80915G-23-acid[17]	*Streptomyces* sp. MS239
4.27	R_1 = Me; R_2 = Me	SF2415B2[15]	*Streptomyces aculeolatus*
4.28		SF2415A1[15]	*Streptomyces aculeolatus*
4.29		SF2415A2[15]	*Streptomyces aculeolatus*

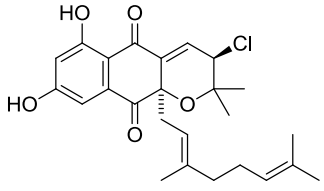
The relatively structurally simple type O napyradiomycins naphthomevalin (**4.23**)[13] and SF2415B1(**4.24**)[14,15] are the presumed biosynthetic precursors to many of the other napyradiomycins. The C-7 methyl group common to SF2415B1 and many other type A, B and O napyradiomycins is presumably introduced at an earlier point in the biosynthesis; hence, SF2415B1 (**4.24**) is commonly invoked as an intermediate in the biosynthesis of the C-7 methylated napyradiomycins, while naphthomevalin (**4.23**) is invoked as an intermediate in the biosynthesis of the other napyradiomycins. Naphthomevalin (**4.23**) was first isolated in 1991 from the culture broth of Streptomyces sp. Strain Gő 28 collected in Strathgordon, Tasmania.[13] It has since, in several instances, been co-isolated with other napyradiomycins.[18,19] The relative stereochemistry of naphthomevalin of the chlorine atom at C-2 relative to the hydroxyl group at C-3 was determined to be *trans*-configuration by successful conversion of the natural product to the epoxide derivative A80915G (**4.25**) under alkaline conditions. Additionally, the absolute stereochemistry of naphthomevalin was determined to be (2*S*, 3*R*) on the basis of CD spectroscopy studies.[13] Two epoxide derivatives of naphthomevalin have currently been discovered: A80915G (**4.25**), isolated in 1989 from *Streptomyces aculeolatus* A80915;[16] and A80915G-23-acid, (**4.26**) isolated in 2008 from *Streptomyces* sp. MS239.[17] SF2415B1 (**4.24**) and SF2415B2 (**4.27**) were co-isolated in 1987 from *Streptomyces aculeolatus* along with their diazo derivatives SF2415A1 (**4.28**) and SF2415A2 (**4.29**).[15] This intriguing α-diazoketone structure common to **4.28** and **4.29** isalso seen in several type A and B napyradiomycins.[20]



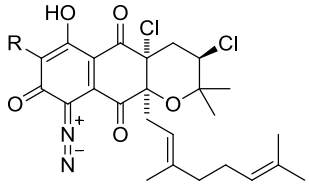
4.30-4.35



4.36-4.39



4.40

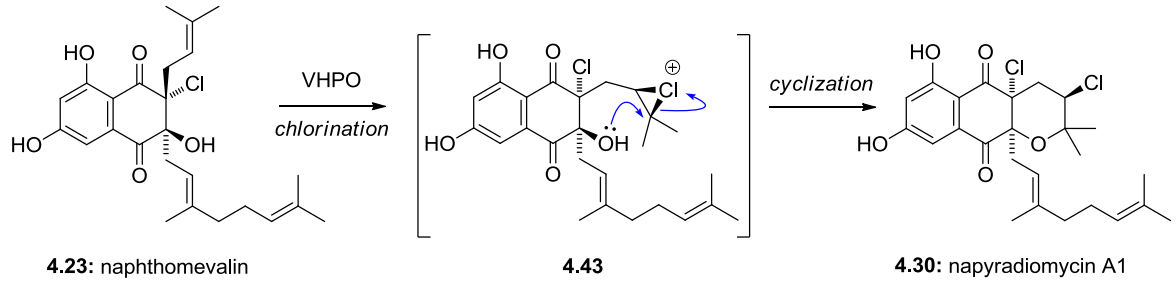


4.41-4.42

Table 4.2: Type A napyradiomycins

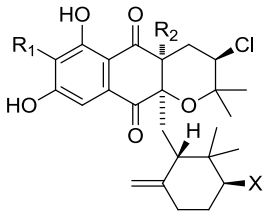
no.	groups	name	source
4.30	R_1 = H, R_2 = Me, X = Cl	napyradiomycin A1[12]	*Chaniarubra* MG802AF1
4.31	R_1 = H, R_2 = CHO, X = Cl	23-oxonapyradiomycin A1[21]	*Strepomycesantimycoticus* NT17
4.32	R_1 = H, R_2 = CH_2OH, X = Cl	23-hydroxynapyradiomycin A1[21]	*Strepomycesantimycoticus* NT17
4.33	R_1 = H, R_2 = Me, X = Br	12-dechloro-12-bromonapyradiomycin A1[19]	*Streptomyces* SCSIO 10428
4.34	R_1 = Me, R_2 = Me, X = Cl	SF2415B3[15]	*Streptomyces aculeolatus*
4.35	R_1 = Me, R_2 = Me, X = Br	CNQ525.538[22]	*Streptomyces*CNQ-525
4.36	R_1 = H, R_2 = H	napyradiomycin A2[23]	*Chaniarubra* MG802-AFI
4.37	R_1 = OH, R_2 = H	napyradiomycin A2a[21]	*Strepomycesantimycoticus* NT17
4.38	R_1 = H, R_2 = OH	napyradiomycin A2b[21]	*Strepomycesantimycoticus* NT17
4.39	R_1, R_2 = =O	21-oxonapyradiomycin A2[21]	*Strepomycesantimycoticus* NT17
4.40		2-dechloro-11-dehydronapyradiomycin A1[19]	*Streptomyces* SCSIO 10428
4.41	R = Me	SF2415A3[15]	*Streptomyces aculeolatus*
4.42	R = H	7-demethyl SF2415A3[21]	*Strepomycesantimycoticus* NT17

Napyradiomycin A1 (**4.30**), along with five other co-isolated type B and C napyradiomycins, were the first reported members, isolated in 1986 from *Chaniarubra* MG802AF1.[12] It has been proposed that chloronium cyclizations of type O napyradiomycins such as naphthomevalin (**4.23**) catalyzed by VHPO enzymes are responsible for the tetrahydropyran ring of the type A napyradiomycins (**scheme 4.5**).[24] The existence of these cyclization reactions as biosynthetic processes has been well studied, and some of the enzymes responsible have been identified and used to catalyze similar reactions in the laboratory.[25]

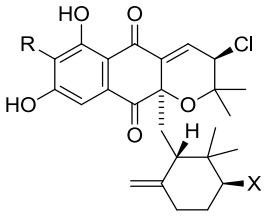


Scheme 4.5: Biosynthesis of type A napyradiomycins[24]

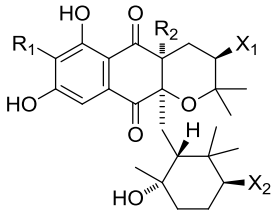
Many of the 13 currently reported type A napyradiomycins are structurally simple modifications of the napyradiomycin A1 skeleton, such as the A2 napyradiomycins **4.36-4.39**.[21,23] **4.33** was isolated in 2013 from *Streptomyces* SCSIO 10428 and identified as the 12-bromo analogue of napyradiomycin A1.[19] The bromine atoms present in **4.33**, **4.35**[22] along with several type B napyradiomycins are the presumed result of bromonium cyclizations catalyzed by VHPOs, rather than the more common chlorination.



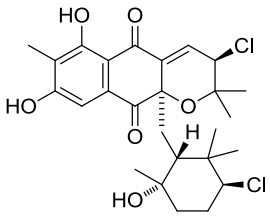
4.44-4.47



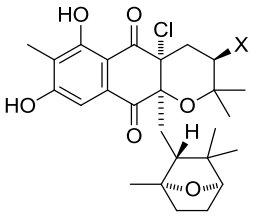
4.48-4.50



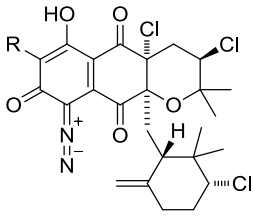
4.51-4.57



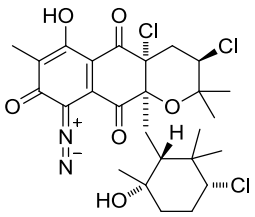
4.58



4.59-4.60



4.61-6.62



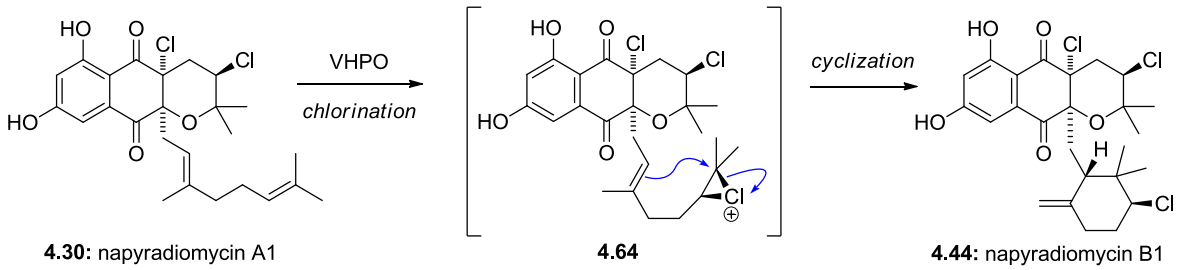
4.63

Table 4.3: Type B napyradiomycins

no.	groups	name	source
4.44	R_1 = H, R_2 = Cl, X = Cl	napyradiomycin B1[12]	*Chaniarubra* MG802AF1
4.45	R_1 = Me, R_2 = Cl, X = Cl	A80915A[16]	*Streptomyces aculeolatus* A80915
4.46	R_1 = H, R_2 = Cl, X = Br	napyradiomycin B3[12]	*Chaniarubra* MG802AF1
4.47	R_1 = Me, R_2 = H, X = Cl	2-dechloroA80915A[18]	*Streptomyces sp.* M18_3
4.48	R = H, X = Cl	napyradiomycin B2[12]	*Chaniarubra* MG802AF1
4.49	R = Me, X = Cl	2-dechloro-11-dehydroA80915A[26]	*Streptomyces* CNQ-525
4.50	R = H, X = Br	2-dechloro-11-dehydronapyradiomycin B3[27]	*Streptomyces* CNQ-329
4.51	R_1 = H, R_2 = Cl, X_1 =Cl, X_2 = Cl	napyradiomycin B4[23]	*Chainiarubra* MG802AFI
4.52	R_1 = Me, R_2 = Cl, X_1 = Cl, X_2 = Cl	A80915C[16]	*Streptomyces aculeolatus* A80915
4.53	R_1 = H, R_2 = H, X_1 = Cl, X_2 = Cl	2-dechloronapyradiomycin B4[27]	*Streptomyces* CNQ-329
4.54	R_1 = Me, R_2 = H,	CNQ525.512[22]	*Streptomyces* CNQ-525

	X_1 = Cl, X_2 = Cl		
4.55	R_1 = H, R_2 = OH, X_1 = Cl, X_2 = Cl	2-dechloro-2-hydroxynapyradiomycin B4[28]	N/A
4.56	R_1 = Me, R_2 = OH, X_1 = Cl, X_2 = Cl	2-dechloro-2-hydroxyA80915C[24]	*Streptomyces* CNQ-525
4.57	R_1 = Me, R_2 = H, X_1 = Br, X_2 = Br	CNQ525.600[22]	*Streptomyces* CNQ-525
4.58		CNQ525.510A[22]	*Streptomyces* CNQ-525
4.59	X = Cl	CNQ525.510B[29]	*Streptomyces* CNQ-525
4.60	X = Br	CNQ525.554[22]	*Streptomyces* CNQ-525
4.61	R = Me	A80915B[16]	*Streptomyces aculeolatus* A80915
4.62	R = H	7-demethyl A80915B[21]	*Strepomycesantimycoticus* NT17
4.63		A80915D[16]	*Streptomyces aculeolatus* A80915

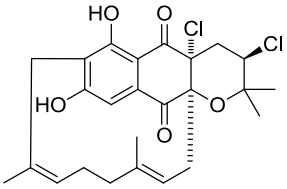
With many more potential sites for structural diversity, it is no surprise that the type B napyradiomycin category contains the most members, with 20 currently reported. Further chloronium cyclizations of the geranyl chain of the type A napyradiomycins result in the characteristic 6-membered ring of the type B napyradiomycins (**scheme 4.6**). It has been proposed that unique VHPO enzymes are responsible for these different cyclization reactions.[24]



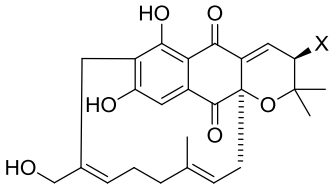
Scheme 4.6: Biosynthesis of type B napyradiomycins[24]

Napyradiomycin B1 (**4.44**), B2 (**4.48**) and B3 (**4.46**) were the first type B napyradiomycins reported, co-isolated in 1986 along with napyradiomycin A1 (**4.30**) from *Chaniarubra* MG802AF1.[12] Napyradiomycin B2 (**4.48**),[12] along with napyradiomycin B4 (**4.51**) which was later isolated in 1987 from the same strain,[23] and A80915C (**4.52**)[30] have had their absolute configurations determined experimentally to be (3*R*, 4*R*, 12*R*) by X-ray crystallographic analysis. This result matches the absolute stereochemistry reported for that of naphthomevalin (**4.23**) and this has led to the current assumption that all napyradiomycins

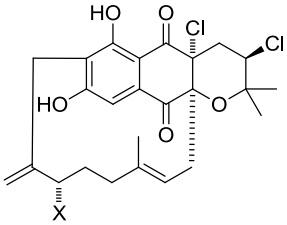
have the same configuration. CNQ525.501B (**4.59**) and CNQ525.554 (**4.60**), isolated in 2013 from *Streptomyces* CNQ-525 are structurally unique in the fact that they are pentacyclic.[22] The additional bridged cycloether ring is the obvious result of intramolecular S_N2 substitution of the C-21 halogen atom with the C-18 hydroxyl group during biosynthesis.



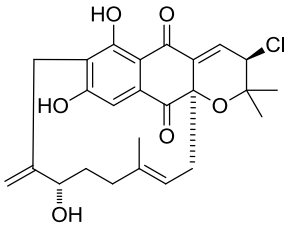
4.65: napyradiomycin C1



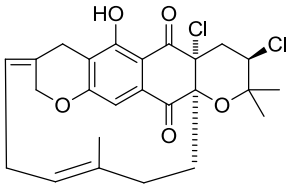
4.66-4.67



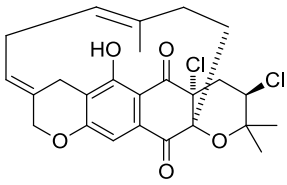
4.68-4.69



4.70



4.71: napyradiomycin SR

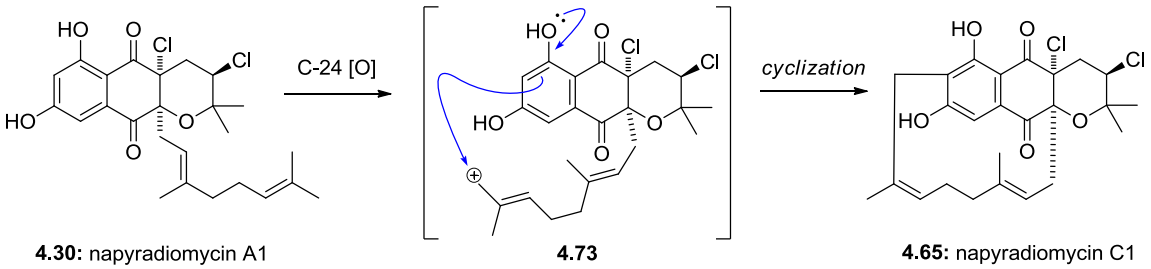


4.72

Table 4.4: Type C napyradiomycins

no.	groups	name	source
4.65		napyradiomycin C1[12]	*Chaniarubra* MG802AF1
4.66	X = Cl	2-dechloro-11-dehydro-23-hydroxynapyradiomycin C1[27]	*Streptomyces* CNQ-329
4.67	X = OH	2-dechloro-11-dehydro-12-dechloro-12-hydroxy-23-hydroxynapyradiomycin C1[27]	*Streptomyces* CNQ-329
4.68	X = Cl	napyradiomycin C2[12]	*Chaniarubra* MG802AF1
4.69	X = OH	21-dechloro-21-hydroxynapyradiomycin C2[21]	*Strepomycesantimycoticus* NT17
4.70		2-dechloro-11-dehydro-21-dechloro-21-hydroxynapyradiomycin C2[27]	*Streptomyces* CNQ-329
4.71		napyradiomycin SR[21]	*Strepomycesantimycoticus* NT17
4.72		16-(*E*)-napyradiomycin SR[27]	*Streptomyces* CNQ-329

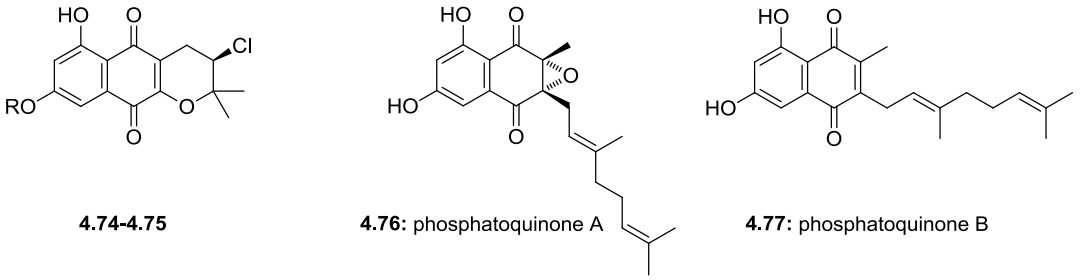
There are currently eight type C napyradiomycin natural products identified, characterized by their intriguing macrocyclic structures. Their biosynthesis presumably involves some oxidation event at the C-24 position of certain type A napyradiomycins, ultimately resulting in the formation of a carbocation such as **4.73**, which could be imagined to undergo cyclization with the proximate aromatic ring, resulting in the 14-membered macrocycle (**scheme 4.7**).



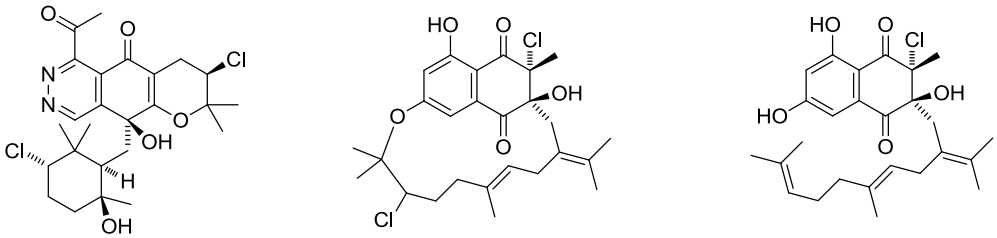
4.30: napyradiomycin A1 **4.73** **4.65:** napyradiomycin C1

Scheme 4.7: Biosynthesis of type C napyradiomycins

The first type C napyradiomycins were also discovered during the same investigation which unveiled the first type A and B napyradiomycins, with napyradiomycin C1 (**4.65**) and C2 (**4.68**) being isolated in 1986 from *Chaniarubra* MG802AF1 along with napyradiomycins A1, B1, B2 and B3.[12] Napyradiomycin SR (strained ring) (**4.71**), which was isolated in 2008 from *Strepomycesantimycoticus* NT17, is an interesting case as unlike the other type C napyradiomycins it contains a strained pentacyclic structure.[21] The additional tetrahydropyrano ring fused to the naphthoquinone of napyradiomycin SR (**4.71**) presumably originates *via* oxidation at the C-23 position followed by phenol cyclization. In 2013, the C-16 isomer of napyradiomycin SR **4.72** was isolated from *Streptomyces* CNQ-329 along with three other type C napyradiomycins **4.66**, **4.67** and **4.70**.[27]



4.74-4.75 **4.76:** phosphatoquinone A **4.77:** phosphatoquinone B



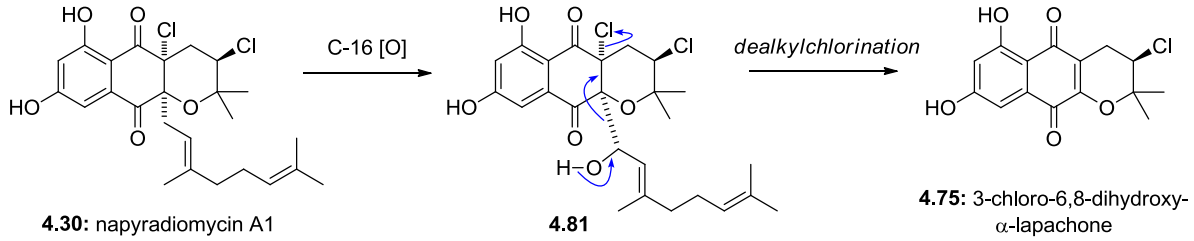
4.78: azamerone **4.79:** merochlorin C **4.80:** merochlorin D

Table 4.5: Miscellaneous napyradiomycins

no.	groups	name	source
4.74	R = Me	3-chloro-6-hydroxy-8-methoxy-α-lapachone[21]	*Strepomycesantimycoticus* NT17
4.75	R = H	3-chloro-6,8-dihydroxy-α-lapachone[19]	*Streptomyces* SCSIO 10428

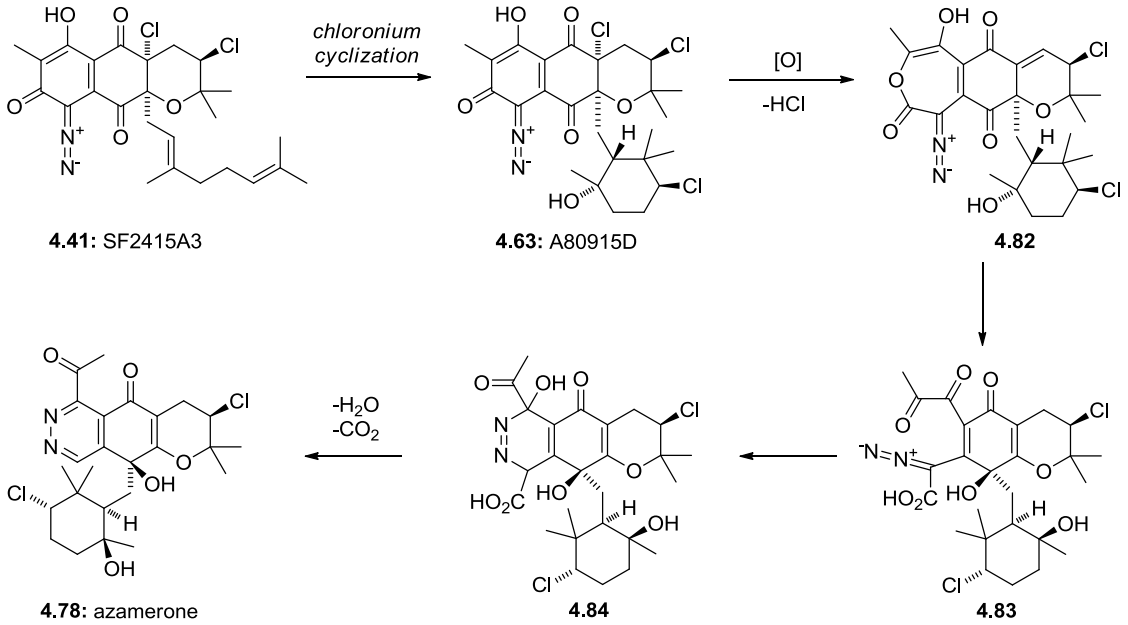
4.76		Phosphatoquinone A[31]	*Streptomyces sp.* TA-0363
4.77		Phosphatoquinone B[31]	*Streptomyces sp.* TA-0363
4.78	-	Azamerone[32,33]	*Strepomyces*CNQ766
4.79	-	Merochlorin C[11]	CNH-189
4.80	-	Merochlorin D[11]	CNH-189

There are currently seven compounds which do not fit into any of the four classes (**figure 4.1**) but that we still believe should be considered members of the napyradiomycin family (**table 4.5**). Each of these compounds shares similar biosynthetic origins and have also been isolated from *Streptomyces* bacteria. 3-Chloro-6-hydroxy-8-methoxy-α-lapachone[21] (**4.74**) and 3-chloro-6,8-dihydroxy-α-lapachone[19] (**4.75**) were isolated from *Strepomycesantimycoticus* NT17 in 2008 and *Streptomyces* SCSIO 10428 in 2013 respectively, and both were co-isolated with napyradiomycin natural products. While **4.74** and **4.75** lack the geranyl group of the napyradiomycins, they presumably still share the same biosynthetic pathway as type A napyradiomycins. Oxidation at the C-16 position of napyradiomycin A1 followed by dealkylchlorination of **4.81** is a currently speculative but plausible biosynthesis of 3-chloro-6,8-dihydroxy-α-lapachone (**4.75**) (**scheme 4.8**).



Scheme 4.8: Proposed biosynthesis of 3-chloro-6,8-dihydroxy-α-lapachone

A seemingly related natural product azamerone (**4.78**) was isolated from *Strepomyces* CNQ766 in 2006. While the unique pyridazine ring structure of azamerone makes its link between the other napyradiomycins unclear at first glance, a plausible biosynthesis from the α-diazoketone napyradiomycin A80915D (**4.63**) involving an oxidative rearrangement has been proposed (**scheme 4.9**).[32] In 2005, Moore et al. studied the biosynthesis of azamerone (**4.78**) in detail and confirmed SF2415A3 (**4.41**) to be a biosynthetic intermediate towards azamerone by labeling studies.[33]



Scheme 4.9: Proposed biosynthesis of azamerone[33]

The epoxide natural product phosphatoquinone A (**4.76**) along with the achiral phosphatoquinone B (**4.77**) were isolated from *Streptomyces sp.* TA-0363 in 1999.[31] The phosphatoquinones are closely related to type O napyradiomycins; however, the C-2 position is substituted with a methyl group instead of a prenyl group. Interestingly, by comparison of the CD spectra, phosphatoquinone A (**4.76**) was found to have the opposite absolute stereochemistry to naphthomevalin (**4.23**). Merochlorins C (**4.79**) and D (**4.80**) are also clearly closely related, with merochlorin D differing from naphthomevalin only by the alkyl substituents at C-2 and C-3; methyl and isosesquilavandulyl instead of prenyl and geranyl respectively.[11]

4.1.3 Biological Activity of Napyradiomycins

Napyradiomycins are most notable for their antibiotic activity and most isolated napyradiomycins have been tested in antimicrobial assays. Napyradiomycins are biologically active against Gram positive bacteria but have been repeatedly shown to be ineffective against Gram negative bacteria. Reported antibiotic activity for napyradiomycins against varying strains of *Staphylococcus* bacteria is summarized in **table 4.6**.

Naphthomevalin (**4.23**) has shown to possess good activity against various strains of Gram positive bacteria in the range of ~1-2 μg/mL.[19] Interestingly, the epoxide compound A80915G (**4.25**) and the diazoketone derivatives SF2415A1 (**4.28**) and SF2415A2 (**4.29**)

were reported to share comparable antibiotic activity to naphthomevalin. A80915G-23-acid (**4.26**) was found to be inactive and is the only O-type napyradiomycin to have no antibacterial activity.[17] Napyradiomycin A1 (**4.30**) has been shown to possess good antibacterial activity in similar potency to that of naphthomevalin. The 12-bromo analogue of napyradiomycin A1 **4.33** exhibits greater potency than napyradiomycin A1 and has the highest activity of the type A napyradiomycins, inhibiting the growth of *Staphylococcus aureus* ATCC 29213 in the range of 0.5 μg/mL. The type A napyradiomycins containing additional oxidation at the C-23 position of the geranyl side chain **4.31** and **4.32** display markedly reduced activity; this observation is analogous to the relative reduced activity of **4.26**.

Table 4.6: Selected antimicrobial activities of napyradiomycins against *Staphylococcus aureus* (the shown values are representative of the compounds activity against other similar test microorganisms – the napyradiomycins not listed have yet to be tested in assays)

Natural Product	**Test microorganism**	**MIC (μg/mL)**
naphthomevalin (**4.23**)	*Staphylococcus aureus* ATCC 29213	1[19]
A80915G (**4.25**)	*Staphylococcus aureus* V41	4[16]
A80915G-23-acid (**4.26**)	*Staphylococcus aureus* 209P JC-1	>64[17]
SF2415B1 (**4.24**)	*Staphylococcus aureus* 209P JC-1	1.56[14]
SF2415B2 (**4.27**)	*Staphylococcus aureus* 209P JC-1	6.25[14]
SF2415A1 (**4.28**)	*Staphylococcus aureus* 209P JC-1	3.13[14]
SF2415A2 (**4.29**)	*Staphylococcus aureus* 209P JC-1	3.13[14]
napyradiomycin A1 (**4.30**)	*Staphylococcus aureus* FDA 209P	1.56[34]
23-oxonapyradiomycin A1 (**4.31**)	*Staphylococcus aureus* ATCC 29213	23[19]
23-hydroxynapyradiomycin A1 (**4.32**)	*Staphylococcus aureus* 209P JC-1	>16
2-dechloro-11-dehydronapyradiomycin A1 (**4.40**)	*Staphylococcus aureus* ATCC 29213	4[19]
12-dechloro-12-bromonapyradiomycin A1 (**4.33**)	*Staphylococcus aureus* ATCC 29213	0.5[19]
SF2415B3 (**4.34**)	*Staphylococcus aureus* 209P JC-1	1.56[14]
SF2415A3 (**4.41**)	*Staphylococcus aureus* 209P JC-1	0.78[14]
7-demethyl SF2415A3 (**4.42**)	*Staphylococcus aureus* 209P JC-1	2[21]
napyradiomycin B1 (**4.44**)	*Staphylococcus aureus* FDA 209P	1.56[34]
napyradiomycin B2 (**4.48**)	*Staphylococcus aureus* FDA 209P	6.25[34]
napyradiomycin B3 (**4.46**)	*Staphylococcus aureus* FDA 209P	0.78[34]
2-dechloro-11-dehydronapyradiomycin B3 (**4.50**)	MRSA	>64[27]
napyradiomycin B4 (**4.51**)	MRSA	32[27]
2-dechloronapyradiomycin B4 (**4.53**)	MRSA	>64[27]
A80915A (**4.45**)	*Staphylococcus aureus* V41	1[16]

2-dechloro-11-dehydroA80915A (**4.49**)	MRSA	1.95[26]
A80915C (**4.52**)	*Staphylococcus aureus* V41	>128[16]
CNQ525.510A (**4.58**)	MRSA	15.6[26]
CNQ525.512 (**4.54**)	MRSA	1.95[26]
A80915B (**4.61**)	*Staphylococcus aureus* V41	0.06[16]
7-demethyl A80915B (**4.62**)	*Staphylococcus aureus* 209P JC-1	3.7[21]
A80915D (**4.63**)	*Staphylococcus aureus* V41	0.25[16]
napyradiomycin C1 (**4.65**)	*Staphylococcus aureus* FDA 209P	12.5[34]
2-dechloro-11-dehydro-23-hydroxynapyradiomycin C1 (**4.66**)	MRSA	16[27]
2-dechloro-11-dehydro-12-dechloro-12-hydroxy-23-hydroxynapyradiomycin C1 (**4.67**)	MRSA	64[27]
napyradiomycin C2 (**4.68**)	*Staphylococcus aureus* FDA 209P	25[34]
2-dechloro-11-dehydro-21-dechloro-21-hydroxynapyradiomycin C2 (**4.70**)	MRSA	>64[27]
napyradiomycin SR (**4.71**)	*Staphylococcus aureus* ATCC 29213	>128[19]
16-(*E*)-napyradiomycin SR (**4.72**)	MRSA	>64[27]
Vancomycin (control)	MRSA	1

The type B napyradiomycin class encompasses some of the most biologically active members; hence, compounds of this type may show the most promise as potential antibiotics. Most type B napyradiomycins have shown antibiotic activity comparable to or greater than that of napyradiomycin A1 (**4.30**). One of the more active is napyradiomycin B3 (**4.46**), which is the C-21 bromo analogue of napyradiomycin B1. The diazoketone type B napyradiomycin derivatives have proven to be some of the most active members; for example both **4.61** and **4.63** inhibit the growth of *Staphylococcus aureus* in the sub micromolar range. All type C napyradiomycins that have currently been tested display considerably lower antibacterial activity compared to the other classes.

With extensive antibacterial assay data available for this diverse array of structural variations, SAR correlations for the napyradiomycins have been interpreted. The fact that type O, A and B napyradiomycins all share comparable activity despite vastly different molecular shape strongly indicates that the naphthoquinone moiety common to all of these natural products is fundamental for activity. Whether the molecule lacks the C-7 methyl group or not does not appear to be important for activity, as otherwise identical compounds differing only in the substituent at this position all have comparable activity. Compounds which are elimination products of the C-2 chlorine atom have noticeably reduced activity than the corresponding C-2 chlorinated derivatives, whereas substitution at this position with H or OH has less impact, indicating the C-2 stereocentre has importance. There is a noticeable correlation with the type

B napyradiomycins suggesting the methylenecyclohexene derivatives are more active than the otherwise sp^3 hydroxylated analogues. Brominated derivatives are consistently more active than the corresponding chlorinated compounds. Perhaps one of the more surprising observations is that the diazoketone functionality has little impact on activity of type A and O napyradiomycins, despite this structural change directly affecting the electronics of the napyradiomycin core.

A study by Hensler *et al.* in 2011 examined the bactericidal kinetics of A80915A (**4.45**) and A80915B (**4.61**) in detail and discovered the two natural products to have similar activity and kinetics.[35] These results indicated that the diazoketone derivative A80915B (**4.61**) had the same mode of antimicrobial action as A80915A (**4.45**). The same study also showed that **4.45** and **4.61** possess rapid bactericidal kinetics, even greater than that of vancomycin.[35] Unfortunately, in the cases where it has been tested, the antibacterial activity of napyradiomycins has been found to greatly decrease in the presence of blood serum. Production of synthetic analogues which retain activity in the presence of serum may be necessary to access viable lead compounds for use as potential new antibiotics.

In addition to the impressive antibiotic properties of the napyradiomycins, their cytotoxicities have also been extensively researched and many napyradiomyincs have been shown to possess significant anti-cancer activity. Cytotoxicity of napyradiomycins has been explored against various cancer cell lines, the most common being HCT-116 colon carcinoma. Reported cytoxicity data for napyradiomycins against varying cancer cell lines is summarized in **table 4.7**. In general, the SAR correlations observed for the cytoxicity of napyradiomycins is comparable to that observed for their antibiotic activities. For example, type C napyradiomycins have relatively low cytotoxicites, and brominated derivatives of type A and B napyradiomycins have shown greater activity than the corresponding chlorinated ones. Similar trends to these have been observed in antibacterial assays.

Table 4.7: Cytotoxicities of napyradiomycins against selected cancer cell lines

Natural Product	Test Cancer Cell Line	IC_{50} (µg/mL)
naphthomevalin (**4.23**)	SF-268	29.6[19]
napyradiomycin A1 (**4.30**)	SF-268 L-1210	18.5[19] 2.7[34]
23-oxonapyradiomycin A1 (**4.31**)	SF-268	132.7[19]
2-dechloro-11-dehydronapyradiomycin A1 (**4.40**)	SF-268	22.8[19]
12-dechloro-12-bromonapyradiomycin A1 (**4.33**)	SF-268	11.5[19]

CNQ525.538 (**4.35**)	HCT-116	6[22]
napyradiomycin B1 (**4.44**)	SF-268 HCT-116 L-1210	11.1[19] 2[22] 2.2[34]
napyradiomycin B2 (**4.48**)	HCT-116	3.18[27]
napyradiomycin B3 (**4.46**)	SF-268 HCT-116	15.3[19] 0.19[27]
2-dechloro-11-dehydronapyradiomycin B3 (**4.50**)	HCT-116	4.8[27]
napyradiomycin B4 (**4.51**)	HCT-116	1.41[27]
2-dechloronapyradiomycin B4 (**4.53**)	HCT-116	9.4[27]
A80915A (**4.45**)	HCT-116	1.84[26]
A80915C (**4.52**)	HCT-116	15[22]
CNQ525.510A (**4.58**)	HCT-116	0.97[26]
CNQ525.512 (**4.54**)	HCT-116	2.40[26]
CNQ525.600 (**4.57**)	HCT-116	49[22]
CNQ525.510B (**4.59**)	HCT-116	17[22]
CNQ525.554 (**4.60**)	HCT-116	>100[22]
A80915B (**4.61**)	HCT-116	<1[22]
A80915D (**4.63**)	HCT-116	<1[22]
napyradiomycin C1 (**4.65**)	L-1210	9.2[34]
2-dechloro-11-dehydro-23-hydroxynapyradiomycin C1 (**4.66**)	HCT-116	4.19[27]
2-dechloro-11-dehydro-12-dechloro-12-hydroxy-23-hydroxynapyradiomycin C1 (**4.67**)	HCT-116	>20[27]
2-dechloro-11-dehydro-21-dechloro-21-hydroxynapyradiomycin C2 (**4.70**)	HCT-116	>20[27]
napyradiomycin SR (**4.71**)	SF-268	98.1[19]
16-(*E*)-napyradiomycin SR (**4.72**)	HCT-116	16.1[27]
cisplatin (control)	SF-268	7.3
etoposide (control)	HCT-116	1

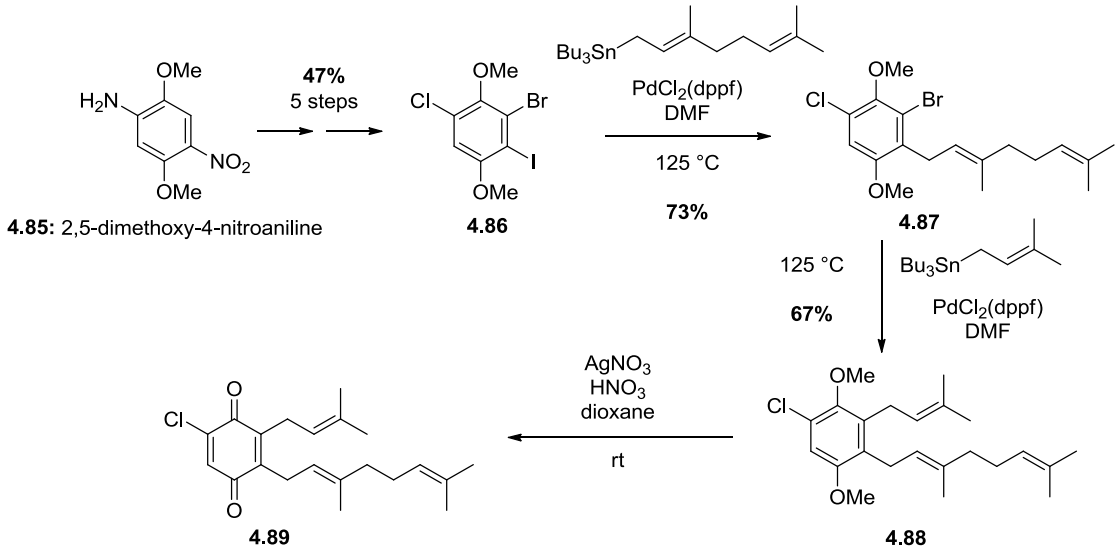
The only diazoketone derivatives which have currently been tested in cytotoxicity assays are A80915B (**4.61**) and A80915D (**4.63**), and these two compounds display the highest activity of all the napyradiomycins, with IC_{50} values against HCT-116 in the sub-micromolar range.[22] Because the presence of the diazo group evidently has a greater impact on cytotoxicity, it has been proposed that non-diazo derivates may be more suitable lead compounds as potential antibiotics due to decreased side effects.[35]

There have been a number of studies exploring the mechanism of action to account for the biological activity of napyradiomycins. Fenical *et al.* hypothesized that these molecules may act as Michael acceptors in biological systems due to the level of conjugation present in the naphthoquinone core. Alternatively, napyradiomycins may be binding to a specific protein target.[22] If the former were the case, napyradiomycins would be expected to cause broad,

nonspecific cellular damage. If the latter were true, napyradiomycins would be more attractive targets as anti-cancer agents. Fenical concluded that due to the wide effect on activity resulting from structural variance, napyradiomycins must be binding to a specific protein target. Additionally, using fluorescence-activated cell sorting methods, they discovered that the cytotoxicity of napyradiomycins is attributed to their ability to induce apoptosis in cancer cells, a desirable trait for potential anti-cancer drugs. In a later publication, Fenical *et al.* determined the specific target of napyradiomycins to nGrp94, a heat shock protein found within the endoplasmic reticulum of mammalian cells.[29] In 1993, Hori *et al.* discovered that napyradiomycins A1 (**4.30**) and B1 (**4.41**) inhibited estrogen-receptor binding in mammalian cells in the range of 4.2 μg/mL and 0.352 μg/mL respectively, and were confirmed to act as antagonists.[36] Interested in the inhibition of mitochondrial complexes, Yamamoto *et al.* showed napyradiomycin A1 (**4.30**) effectively inhibits mitochondrial transport in cancer cells.[37] The combined results of these studies demonstrate that several different modes of action likely contribute to the cytotoxicity of napyradiomycins.

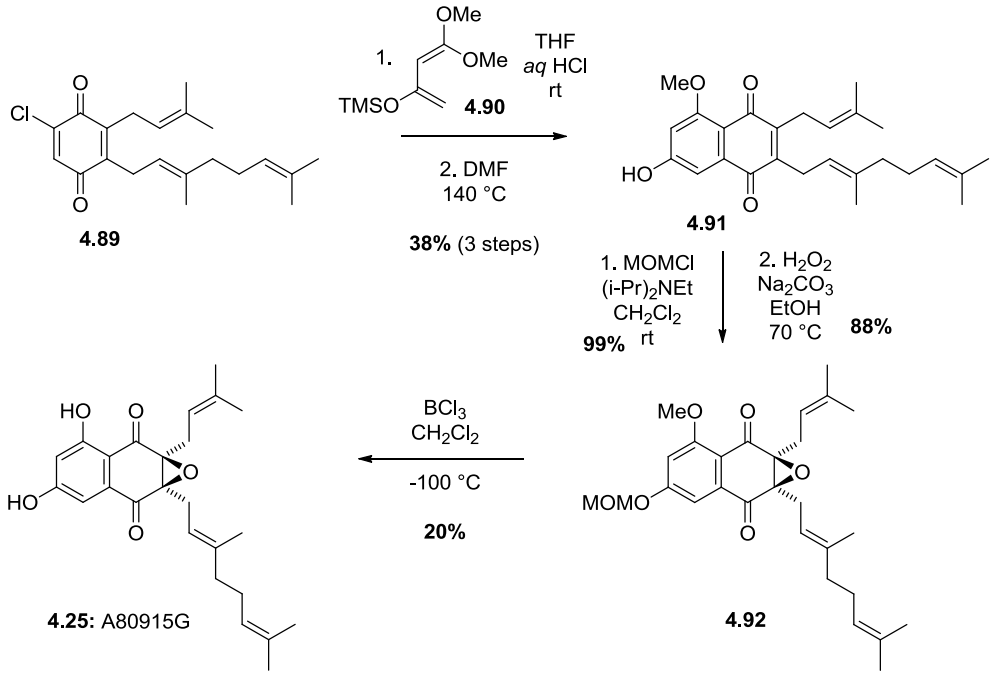
4.1.4 Previous Synthetic Work Targeting Napyradiomycins

Despite the size of the family, their intriguing chemical structures and potent biological activities, very little synthetic work has been performed on the napyradiomycins. Napyradiomycin synthesis has proven to be a challenging task; to date there have only been three reported total syntheses of napyradiomycin natural products, and no other synthetic progress has been published. The first reported total synthesis of a napyradiomycin natural product was the synthesis of A80915G (**4.25**) by Nakata *et al.* in 1999.[38] Nakata envisioned the naphthoquinone core of A80915G could be formed *via* a Diels-Alder reaction and that sequential Stille reactions would be suitable to install the prenyl and geranyl substituents. Execution of their strategy required the trihalogenated protected hydroquinone **4.86**, which was prepared in five steps from 2,5-dimethoxy-4-nitroaniline **4.85**. After extensive optimization of the reaction conditions, Pd-catalyzed Stille cross-coupling with geranyl tributyltin could be controlled to occur exclusively at the C-I bond. Prenylation using prenyl tributyltin under similar conditions was then subsequently selective for the C-Br bond, furnishing the prenylated and geranylated intermediate **4.88**. Oxidation with $AgNO_3$ gave the quinone **4.89** which was immediately taken on to the key Diels-Alder reaction step without further purification.



Scheme 4.10: 1999 synthesis of A80915G by Nakata *et al.*[38]

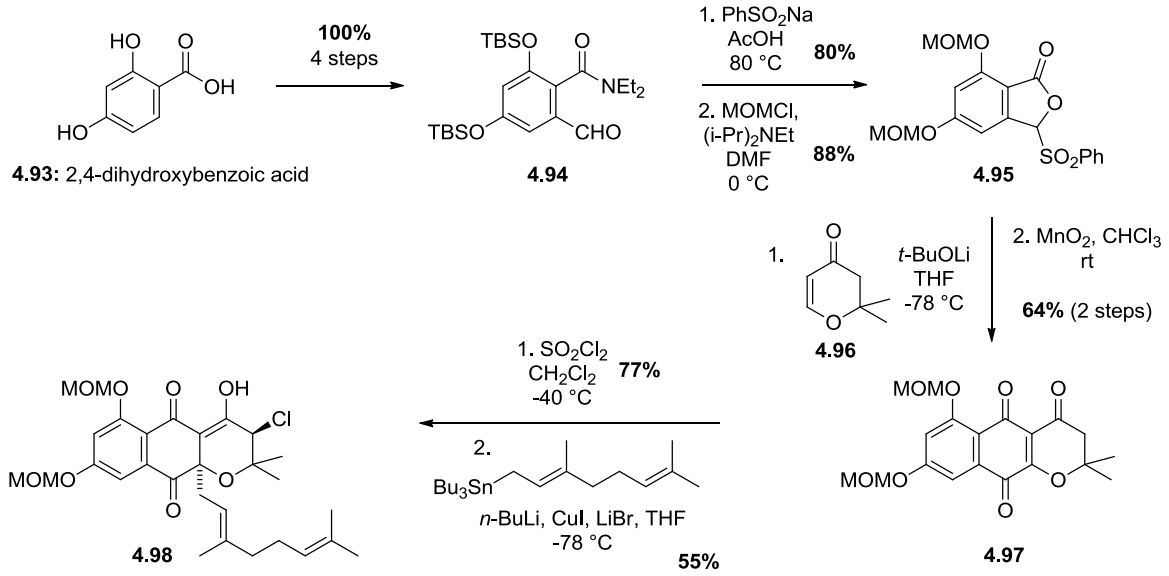
Several differently protected dienes were trialed for the Diels-Alder reaction, but only **4.90** resulted in successful cycloaddition and formation of the desired product **4.91**. The total synthesis of A80915G (**4.25**) was completed after a series of protecting group manipulations and oxidation with H_2O_2 under alkaline conditions to install the epoxide.



Scheme 4.11: 1999 synthesis of A80915G by Nakata *et al.*[38]

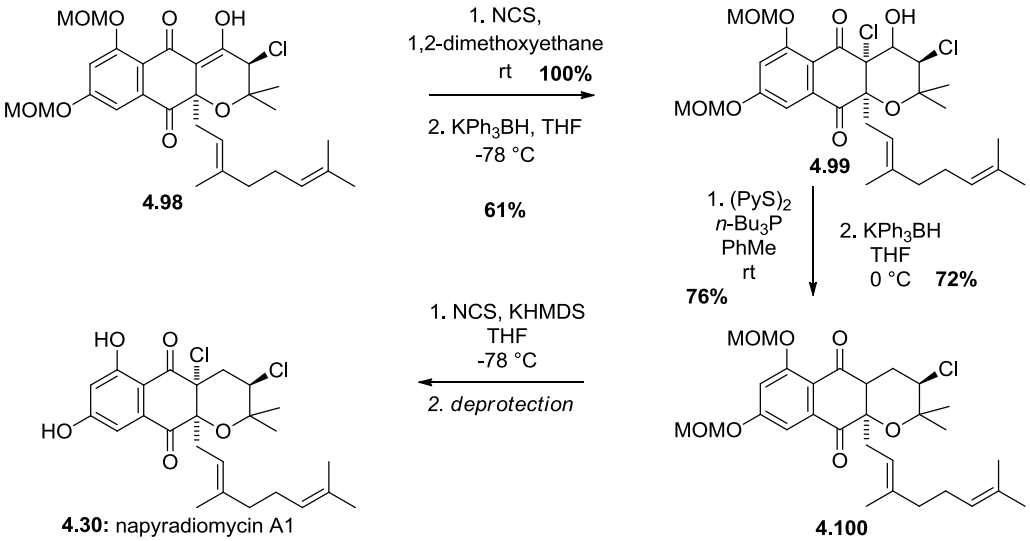
Compared to the type O napyradiomycin A80915G (**4.25**), napyradiomycin A1 (**4.30**) is a more intimidating synthetic target, with its additional chlorine atoms and stereogenic centres.

Tatsuta *et al.* were up to this task, and they completed the first total synthesis of napyradiomycin A1 (**4.30**) in 2002.[39] Synthesis began with the quantitative four step conversion of 2,4-dihydroxybenzoic acid (**4.93**) into aldehyde **4.94**. Lactonization with $PhSO_2Na$ followed by reprotection of the phenols with MOMCl gave the key intermediate **4.95** required for the crucial Michael-Diekmann cascade reaction. This cyclization process was achieved by deprotonation of **4.95** with *t*-BuOLi followed by addition of the Michael acceptor **4.96**.



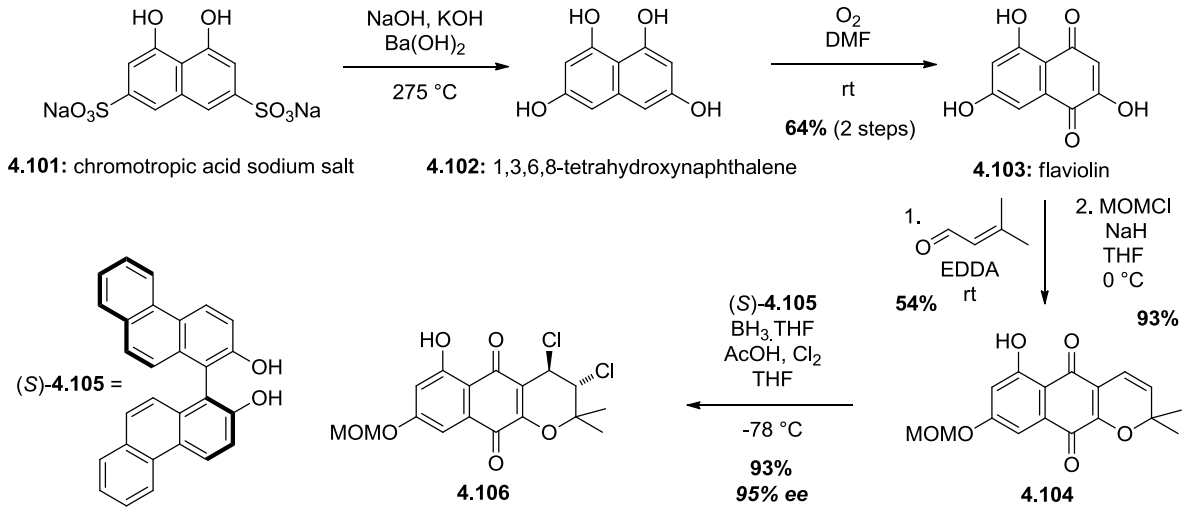
Scheme 4.12: 2002 synthesis of Napyradiomycin A1 by Tatsuta *et al.*[39]

Oxidation of the resultant hydroquinone with MnO_2 gave the naphthoquinone **4.97**. This proved to be a unique and effective method to access the naphthoquinone core of the napyradiomycins efficiently. The first chlorine atom of the molecule was introduced by α-chlorination with SO_2Cl_2 under neutral conditions with no stereochemical control. The geranyl chain was installed by Michael addition of geranyllithium, generated *in situ* by transmetallation of geranyl tributyltin. Geranylation occurred on the opposite face to the chlorine atom, resulting in the formation of **4.98** in good diastereoselectivity. Selective deoxygenation at the C-11 position to yield **4.100** was found to be achievable *via* a four step protocol where more direct methods failed. Finally, the C-2 chlorine atom was successfully installed by treatment of **4.100** with KHMDS and NCS; the first total synthesis of napyradiomycin A1 (**4.30**) was completed following a final MOM deprotection step.



Scheme 4.13: 2002 synthesis of Napyradiomycin A1 by Tatsuta *et al.*[39]

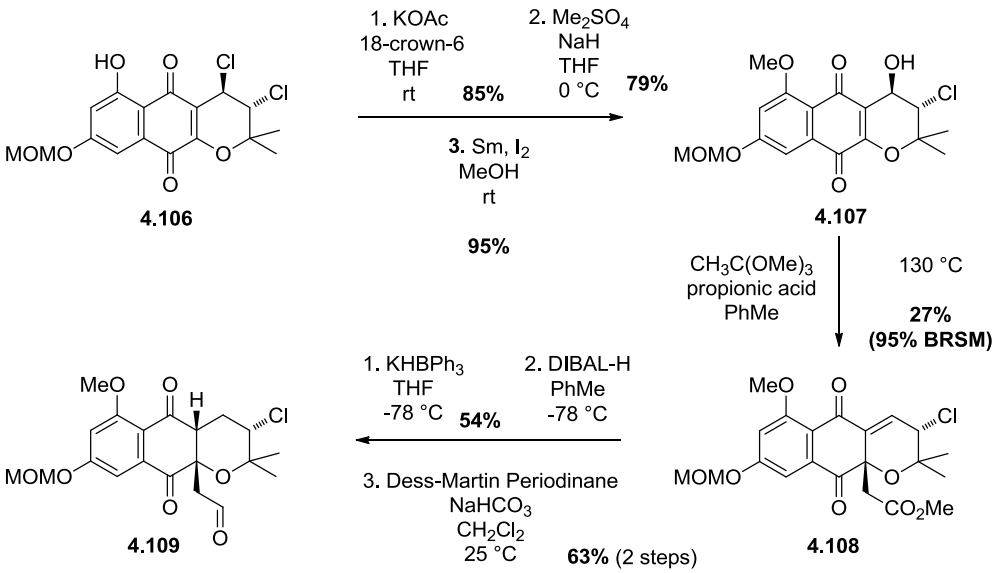
Seven years later, in 2009, Snyder *et al.* reported the first enantioselective synthesis of napyradiomycin A1 (**4.30**), taking advantage of new advances in asymmetric chemistry.[40] Choosing a more biomimetic option for the starting material, synthesis began with 1,3,6,8-tetrahydroxynapthalene (**4.102**), which was accessed *via* alkali fusion of commercially available chromotropic acid sodium salt (**4.101**). THN (**4.102**) was converted to flaviolin (**4.103**) by oxidation in air at room temperature, establishing the naphthoquinone core early in the synthesis.



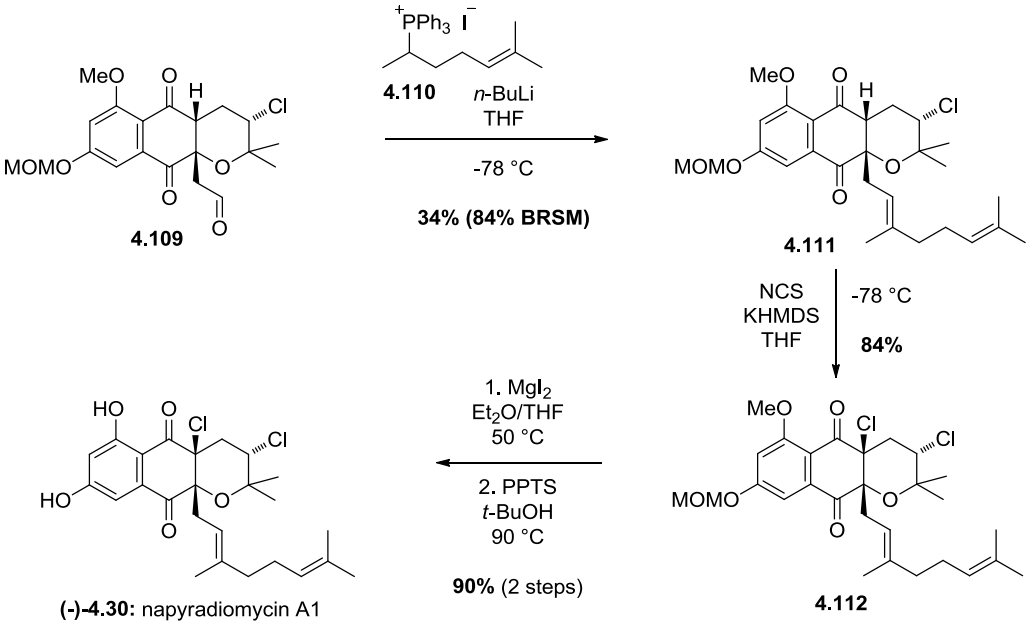
Scheme 4.14: 2009 synthesis of (-)-Napyradiomycin A1 by Snyder *et al.*[40]

Alkylation and subsequent 6π-electrocyclization with 3-methylcrotonaldehyde and EDDA followed by selective MOM protection of the non-hydrogen bonded phenol yielded the

tricyclic compound **4.104**. Asymmetric chlorination of the isolated double bond of **4.104** was then achieved with Cl_2, BH_3.THF and AcOH in the presence of the chiral ligand (*S*)-**4.105**. This key reaction installed the C-12 chlorine atom of napyradiomycin A1 in excellent yield and enantioselectivity.



Scheme 4.15: 2009 total synthesis of (-)-Napyradiomycin A1 by Snyder *et al.*[40]



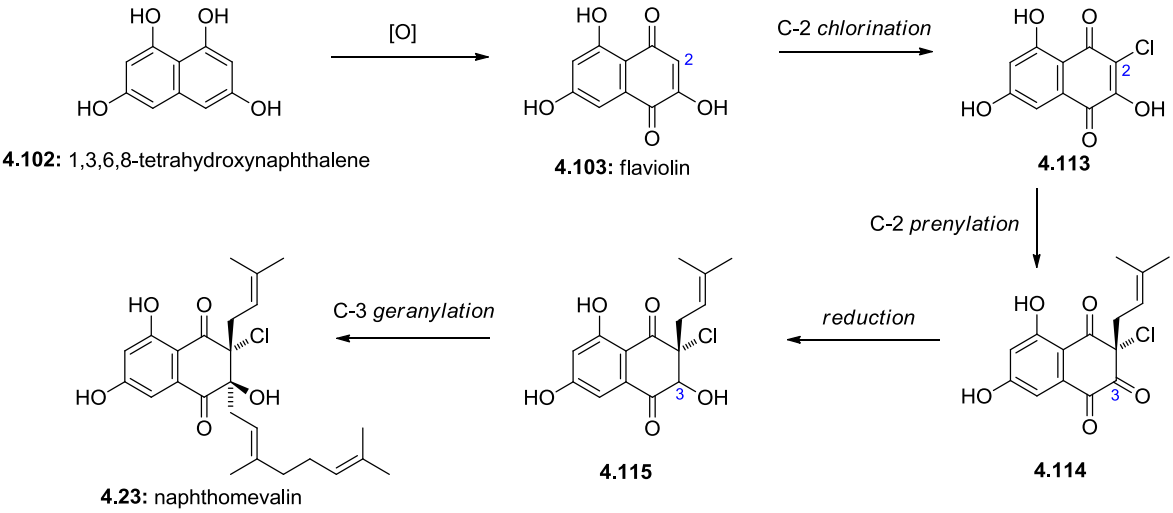
Scheme 4.16: 2009 synthesis of (-)-Napyradiomycin A1 by Snyder *et al.*[40]

A series of functional group conversions then yielded **4.107**, which underwent acid catalyzed Johnson-Claisen rearrangement in the presence of excess $CH_3C(OMe)_3$ to generate ester

4.108 with the desired stereochemistry. After obtaining aldehyde **4.109** in three steps from **4.108** *via* straightforward functional group interconversions, it underwent Wittig olefination with the ylide derived from **4.110** to install the geranyl side chain. C-2 chlorination was performed under identical conditions to the Tatsuta synthesis to yield **4.112**. Finally, sequential deprotection reactions yielded (-)-napyradiomycin A1 (**4.30**).

4.1.5 Proposed Biosynthesis of Naphthomevalin

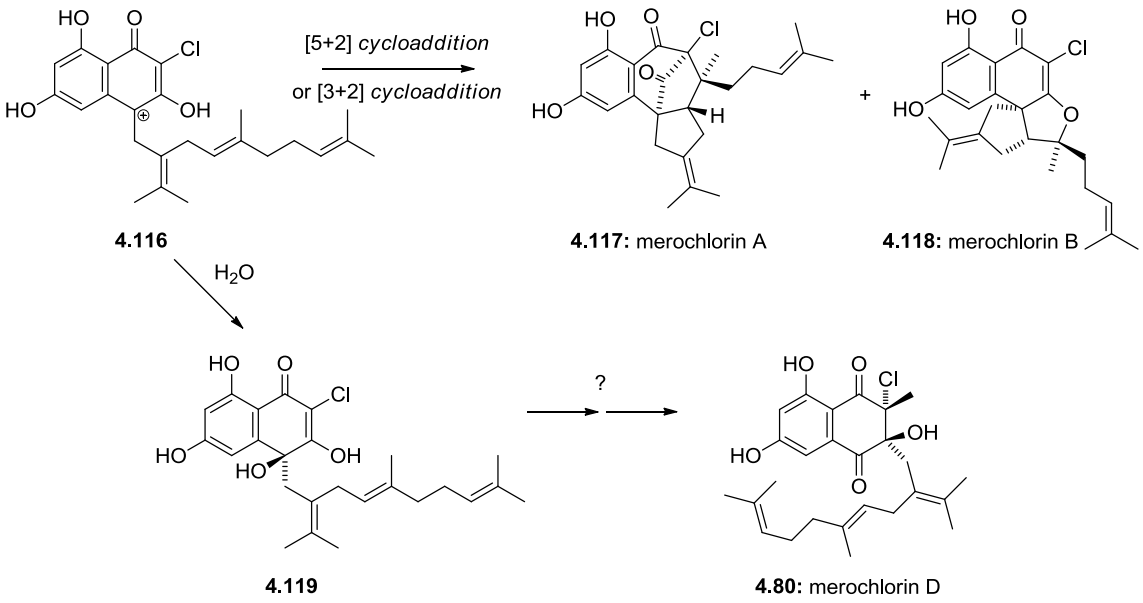
While the biosynthetic origins of the additional rings found in the more complex napyradiomycins are the obvious result of VHPO catalysis, the origin of the naphthoquinone skeleton, common to all napyradiomycins, is less clear. Previous labeling studies have indicated THN (**4.102**) to be the polyketide biosynthetic precursor to the napyradiomycins.[41] Flaviolin (**4.103**) has previously been postulated as a biosynthetic intermediate,[24,42-45] a known natural product that is formed by the facile oxidation of THN in air.[46] Invoking flaviolin as biosynthetic intermediate is a seemingly logical proposal due to the superficial resemblance between flaviolin and the napyradiomycin core. It has been proposed that chlorination and prenylation at the C-2 position of flaviolin (**4.103**) in either order could yield the triketone **4.114**. Reduction of the C-3 carbonyl group would then need to occur followed by geranylation at the same position to yield naphthomevalin (**scheme 4.17**).[24]



Scheme 4.17: Previously proposed biosynthesis of naphthomevalin[24]

This proposal is currently speculative, and currently little evidence has so far been uncovered to support it. Furthermore, there are some intrinsic problems with the plausibility of this

biosynthesis. The oxidation of THN (**4.102**) to flaviolin (**4.103**) is effectively an over-oxidation in the context of napyradiomycin biosynthesis, requiring the additional reduction step to reach the correct oxidation state. Furthermore, the C-3 position of **4.115** is deactivated with respect to electrophilic attack; hence the necessary geranylation process would be unfavorable. These problems encouraged us to consider an alternate biosynthesis of the napyradiomycins which would involve oxidative dearomatization as a key step.

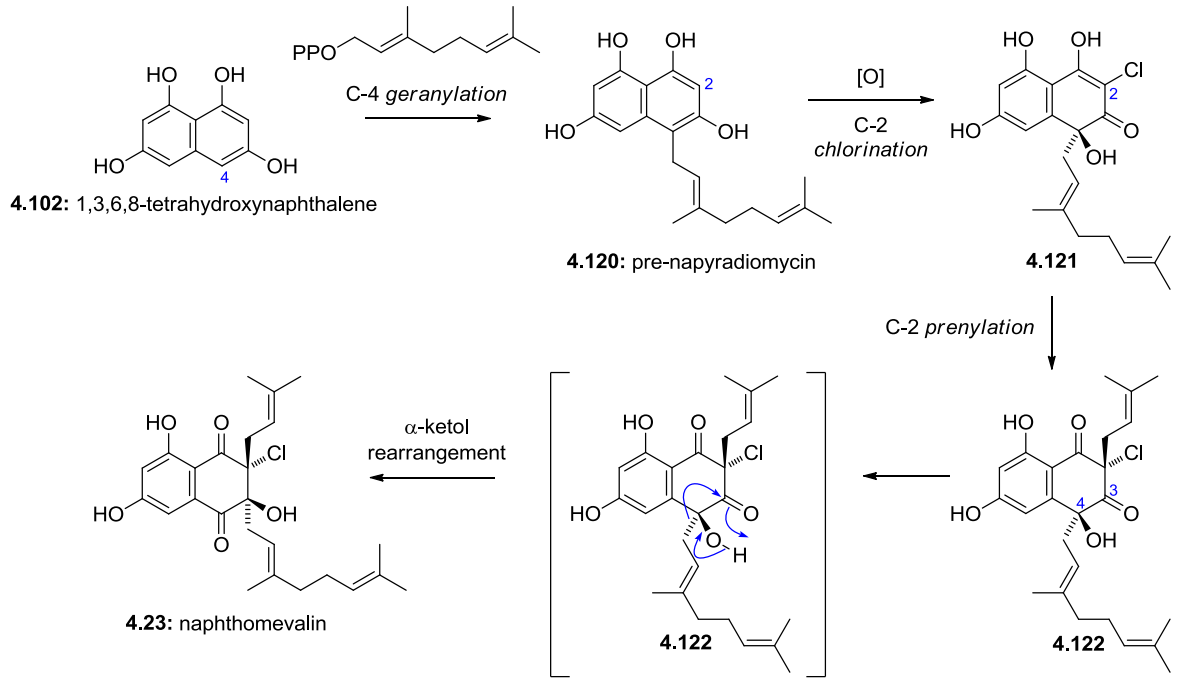


Scheme 4.18: Possible biosynthetic pathway to merochlorin D *via* the same oxidative dearomatization process involved in the formation of merochlorin A and B

Our work on the biomimetic synthesis of merochlorin A[47] led us to consider the possibility that the same dearomatization process which induces the cycloaddition reactions to form merochlorins A (**4.177**) and B (**4.118**) is also involved in the biosynthesis of merochlorins C (**4.79**) and D (**4.80**). The reactive phenoxonium ion **4.116** resulting from dearomatization could alternatively undergo quenching with H_2O to yield the tertiary alcohol **4.119** (**scheme 4.18**). **4.119** is in the same oxidation state as the napyradiomycins, and could be a potential biosynthetic precursor to merochlorin D (**4.80**). This hypothesis does not contradict current knowledge about merochlorin biosynthesis and would invoke a common advanced intermediate in the biosynthesis of the four currently characterized merochlorin natural products.

Expanding on this hypothesis, we propose a biosynthetic origin for naphthomevalin and hence, the entire napyradiomycin family. THN (**4.102**) would first undergo geranylation at

the nucleophilic C-4 position to yield **4.120**, which is structurally similar to the known biosynthetic merochlorin precursor pre-merochlorin.[11] Oxidative dearomatization and reaction of the resultant phenoxonium ion with H_2O would give the tertiary alcohol, which could be chlorinated at the C-2 position to give **4.121**.

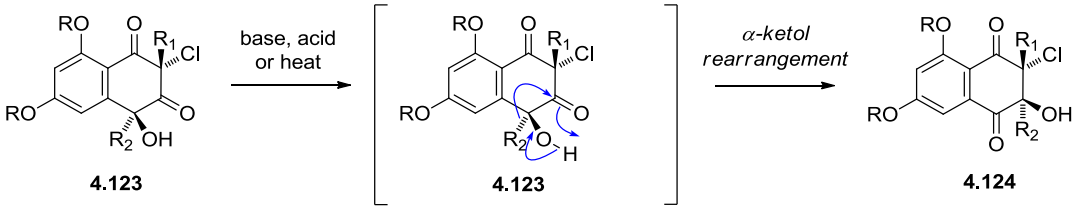


Scheme 4.19: Our proposed biosynthesis of naphthomevalin

As a VHPO is now known to catalyze the oxidative dearomatization process in the merochlorin biosynthesis,[48] it is possible that both the dearomatization and chlorination processes are catalyzed simultaneously by the same enzyme. Prenylation at the C-2 position would then yield the key 1,3-diketone intermediate **4.122**. We then propose that **4.122** undergoes an α-ketol rearrangement, resulting in the 1,2-shift of the geranyl substituent from the C-4 position to the C-3 position, generating the naphthoquinone skeleton common to all napyradiomycins. This process may or may not be enzyme catalyzed. While the 1,2-migration of a long alkyl chain is an unusual biosynthetic hypothesis, a related example was recently reported by Müller *et al.*, who proposed a biosynthesis for the Aurachin family of natural products involving enzyme catalyzed 1,2-migration of a farnesyl substituent *via* retro-[2,3]-Wittig rearrangement and subsequent Claisen rearrangement processes.[49,50]

4.1.6 Project Aims

The primary objective of this research was to challenge our biosynthetic proposal for the napyradiomycins by synthetically attempting this unprecedented α-ketol rearrangement. To achieve this, an intermediate such as **4.123** would be prepared and should hopefully undergo 1,2-shift to the naphthoquinone skeleton **4.124** when subjected to base, acid or heat (**scheme 4.20**).



Scheme 4.20: Proposed key biomimetic synthetic step: α-ketol rearrangement (R_1 = prenyl or methyl, R_2 = prenyl, geranyl or isosesquilavandulyl)

A range of different R_1 and R_2 substituents would be sufficient for testing purposes. While natural products such as merochlorin D (**4.80**) and phosphatoquinone A (**4.76**) would be suitable synthetic targets for testing, the natural product of greatest interest was naphthomevalin (**4.23**). Naphthomevalin is the presumed biosynthetic precursor to many other napyradiomycins and is therefore of significance; it should also be one of the easiest targets to synthesize.

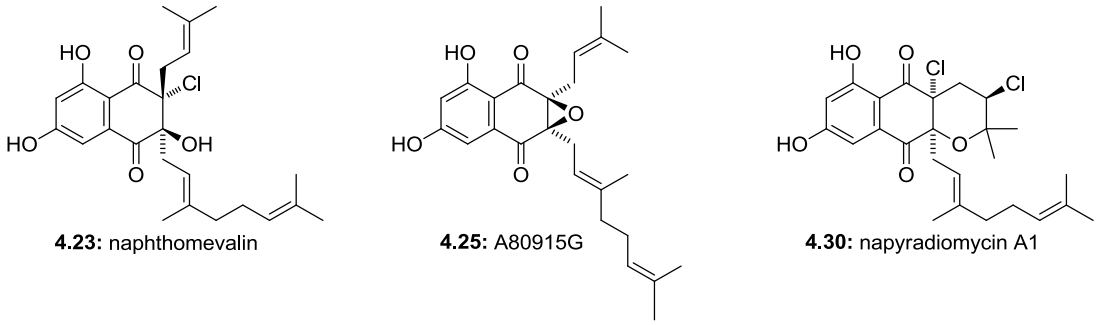


Figure 4.2: Primary natural product targets

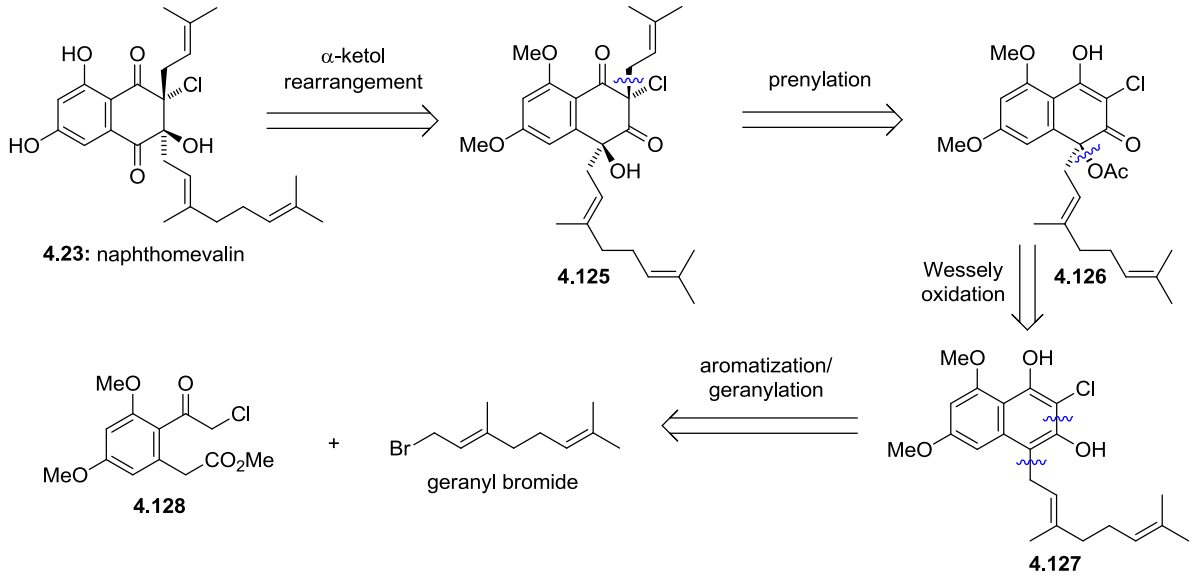
If the proposed biomimetic α-ketol rearrangement is found to be possible, the total synthesis of naphthomevalin (**4.23**) will then be pursued. With naphthomevalin in hand, we could then explore its conversion into A80915G (**4.25**), or even some of the more complex napyradiomycins such as napyradiomycin A1 (**4.30**). The success of this α-ketol

rearrangement would strongly suggest that a similar process occurs in nature, and may contribute to a paradigm shift in the biosynthesis and biomimetic synthesis of napyradiomycin natural products. It should also hopefully result in the development of unique and efficient methods to access some of these useful, biologically active natural products synthetically.

4.2 Results and Discussion

4.2.1 Retrosynthetic Analysis of Naphthomevalin

Much of the methodology we had developed for the synthesis of THN intermediates during our work on the merochlorins would be applicable to our plan for napyradiomycin natural products.[47] An α-ketol rearrangement of an intermediate such as **4.125** should yield naphthomevalin (**4.23**) in an analogous process to our proposed biosynthesis.



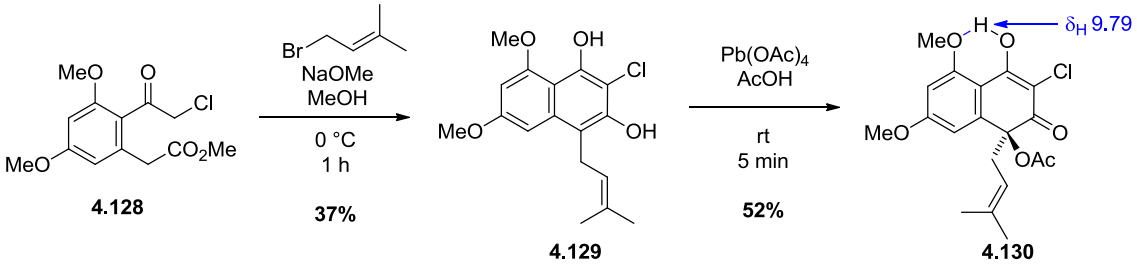
Scheme 4.21: Retrosynthetic analysis of naphthomevalin

Wessely oxidation of the THN intermediate **4.127** would allow access to the required dearomatized ring system with the correct number of oxygen atoms. **4.127** would be easily accessed *via* our established one pot aromatization/alkylation protocol using geranyl bromide as the electrophile. Methyl ethers would be the continued protecting group of choice as they were found to be convenient and effective during our merochlorin synthesis.

4.2.2 Model System Synthesis

We opted to begin with the synthesis of a model system, substituting the natural geranyl or isosesquilavandulyl side chains of naphthomevalin or merochlorin D, respectively, for a prenyl group. This change would simplify characterization of the intermediates, and involve the use of more readily available reagents but would still allow for adequate testing of our

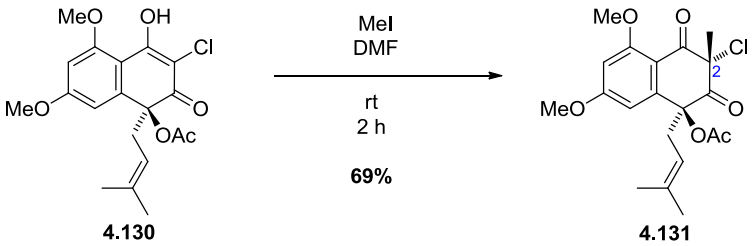
proposed reactions. Aromatization of chloroacetate **4.128** followed by alkylation with prenyl bromide gave the desired alkylation product **4.129** with similar effectiveness to the isosesquilavandulyl system.[47] However, purification by flash chromatography was found to be more difficult with this reaction, to the point of being completely impractical. We discovered an effective purification alternative in simply triturating the crude product with cold MeOH. Doing this, we could obtain a far higher purity of **4.129** than any other purification method and it was a simple and economical procedure to perform.



Scheme 4.22: Synthesis of dearomatization product **4.130**

We hypothesized that applying our previous oxidative dearomatization conditions using $Pb(OAc)_4$ to **4.129** should induce Wessely oxidation,[51,52] and thus result in the incorporation of AcOH to yield the tertiary acetate **4.130**.[47] Wessely oxidation should be the preferred pathway as a cyclization event of a phenoxonium intermediate with the prenyl side chain would be disfavoured as the ring generated would be small, and too strained. AcOH was used as the solvent for this reaction to maximize the concentration of the nucleophile to hopefully increase the rate of the desired pathway. As expected, these conditions quickly yielded the Wessely oxidation product **4.130** in 52% yield. ^{1}H NMR of this compound suggested the presence of only one tautomer: the enol form, as drawn (**scheme 4.22**). The presence of intramolecular hydrogen bonding, as indicated by the high chemical shift (δ 9.79) of the enol proton, is likely responsible for the stability of this particular tautomeric form.

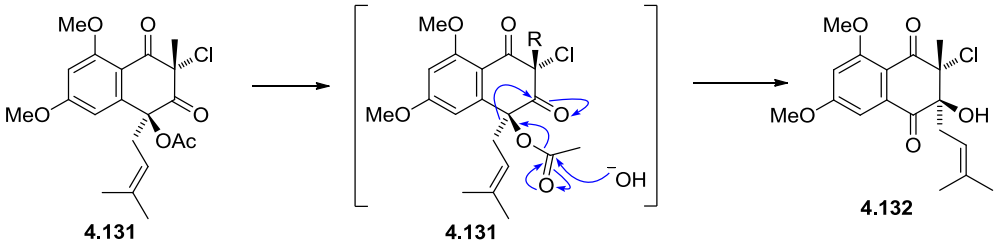
We next wanted to introduce a new alkyl group into the molecule, which could be achieved by simple alkylation of the α-chloroenol of **4.130**. A methyl group was chosen for this purpose, which would be adequate for our simplified system. A methyl group at the C-2 position is common to merochlorins C (**4.79**) and D (**4.80**),[11] as well as the phosphatoquinone natural products (**4.76**-**4.77**).[31] The α-chloroenol of **4.130** was evidently less acidic than expected, as bases such as DBU or *t*-BuOK failed to induce reaction to occur with MeI, indicating complete deprotonation was not occurring.



4.130 4.131

Scheme 4.23: *C*-Methylation of α-chloroenol

Some success with methylation was found by using NaH in THF, however a significant amount of the methyl ether formed by an *O*-alkylation side reaction was additionally observed. This problem was solved by switching the solvent to DMF; under these conditions the reaction exclusively formed the C-alkylation product **4.131**. The amount of base needed to be carefully controlled as an excess would result in increased decomposition of the product. **4.131** was isolated as a single diastereoisomer, as indicated by the ^{1}H NMR spectrum. At this point the relative stereochemistry was not rigorously determined but was predicted to be as show, (**scheme 4.131**) as alkylation presumably occurs on the opposite face of the cyclohexane ring to the prenyl group.

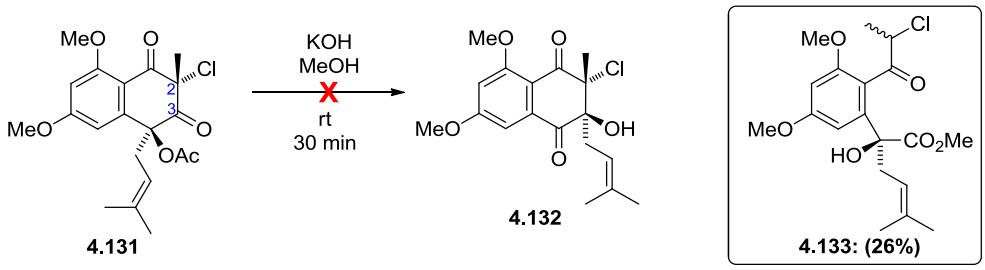


4.131 4.131 4.132

Scheme 4.24: Base induced α-ketol rearrangement proposal

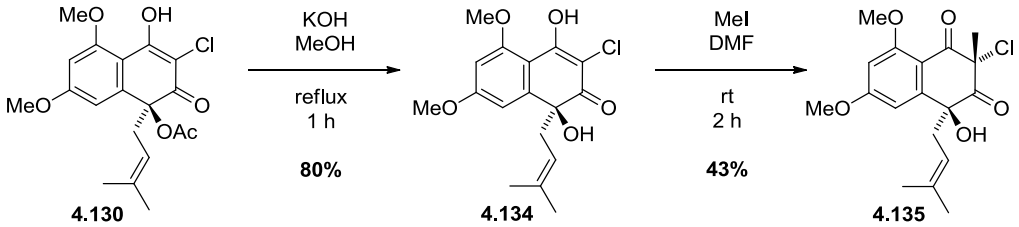
One of the most common methods to induce an α-ketol rearrangement is formation of the alkoxide under basic conditions.[4] With this in mind, a logical proposal was to induce α-ketol rearrangement subsequent to hydrolysis of the acetate, as represented by the mechanism in **scheme 4.24**. Treatment of **4.131** with KOH in MeOH resulted in a mixture of products by TLC analysis; none of the isolated compounds resembled the desired product **4.132** by ^{1}H NMR analysis. By interpretation of the data, the structure of the most abundant product was determined to be **4.133**, which was isolated as a mixture of two diastereoisomers. This product presumably originates *via* a fragmentation process, involving cleavage of the C-2 - C-3 bond induced by nucleophilic attack of methoxide onto the C-3 carbonyl group. Performing this reaction using K_2CO_3 in place of KOH gave identical results. Judging by

how quickly the formation of **4.133** occurred under seemingly mild conditions, the substrate **4.131** was too unstable towards nucleophilic base for selective ester hydrolysis to be possible. This result also helped explain why the product **4.131** formed was unstable to the previous methylation reaction conditions.



Scheme 4.25: Failed base induced α-ketol rearrangement reaction

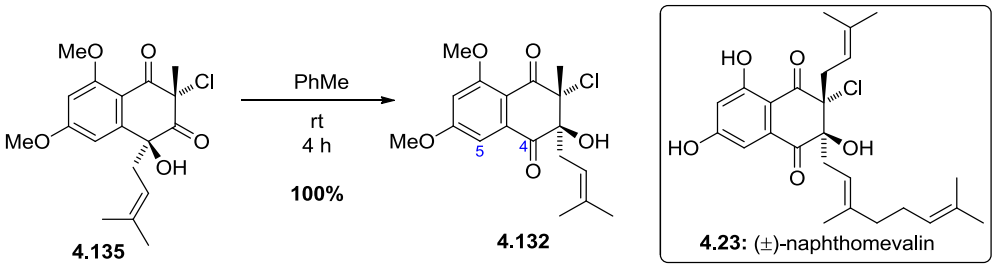
Hopeful it would be a more suitable substrate for ester hydrolysis, we attempted hydrolysis on **4.130**, the previous intermediate in sequence. Treatment of **4.130** with KOH in MeOH at reflux cleanly yielded the ester hydrolysis product **4.134** in 80% yield. No matter how long the product was heated under these conditions, no α-ketol rearrangement was observed. This lack of rearrangement was not discouraging as the enol compounds were predicted to be less reactive towards α-ketol rearrangement than the corresponding 1,3-diketones due to increased stabilization of the carbonyl group.



Scheme 4.26: Synthesis of α-ketol rearrangement precursor compound

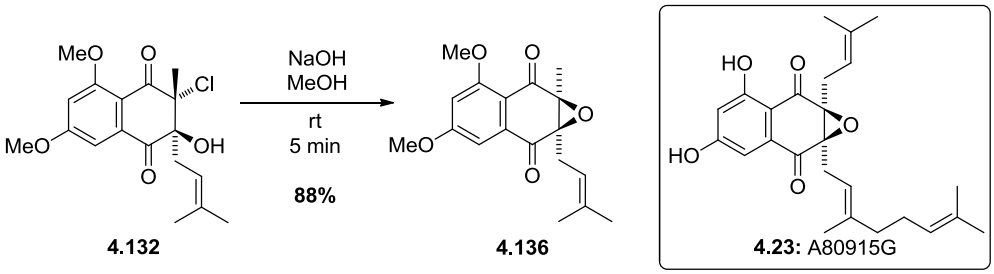
Methylation of **4.134** was theoretically more problematic than **4.130** due the presence of an additional acidic group. Despite this, the same conditions used for the methylation of **4.130** proved to be effective and yielded the compound required to test α-ketol rearrangement **4.135**. This reaction was unfortunately slower, lower yielding and more difficult to drive to completion than the reaction of the acetate protected substrate. **4.135** was also found to be unstable to the reaction conditions if excessive use of base was added, so this needed to be carefully controlled.

With **4.135** in hand, tests towards the key α-ketol rearrangement reaction could begin. Based on our recent observations of the reactivity of these 1,3-diketone compounds, we were doubtful that basic conditions would be suitable. The few basic conditions screened for the rearrangement of **4.135** resulted in the formation of fragmentation products such as **4.133** or no reaction at all. The use of the Lewis acid $BF_3.OEt_2$ or the Brønsted acid *p*-TsOH also failed to promote any reaction at all. The application of thermal conditions towards α-ketol rearrangements had been well documented in the literature and was certainly an option worth exploring.[4] This typically involves heating the compound of interest in a solvent to induce rearrangement. We chose PhMe as the solvent as it has a suitably high boiling point and non-polar solvents are known to be effective for concerted processes.



Scheme 4.27: Thermal induced α-ketol rearrangement to form naphthomevalin analogue

Heating **4.135** in PhMe at reflux led to complete consumption of the starting material and clean, quantitative formation of a marginally lower R_f compound in four hours. ^{1}H NMR analysis of this new product showed an identical pattern of peaks to the starting material, differing only in chemical shift. At an early glance, this NMR was extremely encouraging as it was exactly what would be expected if only the α-ketol rearrangement had occurred, and it was difficult to envisage what else might have happened. The most dramatic chemical shift difference was seen in the aromatic protons, which were shifted downfield from δ 6.87 and 6.47 ppm in the starting material, to 7.12 and 6.80 ppm in the product respectively. Rearrangement to a naphthoquinone skeleton would explain this observation as the electron withdrawing carbonyl group would now be in the *ortho*/*para* position on the ring relative to the two aromatic protons, hence deshielding these positions. Although 2D NMR was a largely ineffective technique during this project, as these compounds have many DBEs and relatively few protons, we were still able to observe a diagnostic ^3J HMBC correlation between the C-5 proton and the C-4 carbonyl group in the product. This cross peak was not observed in the starting material.



Scheme 4.28: S_N2 epoxidation reaction to form A80915G analogue

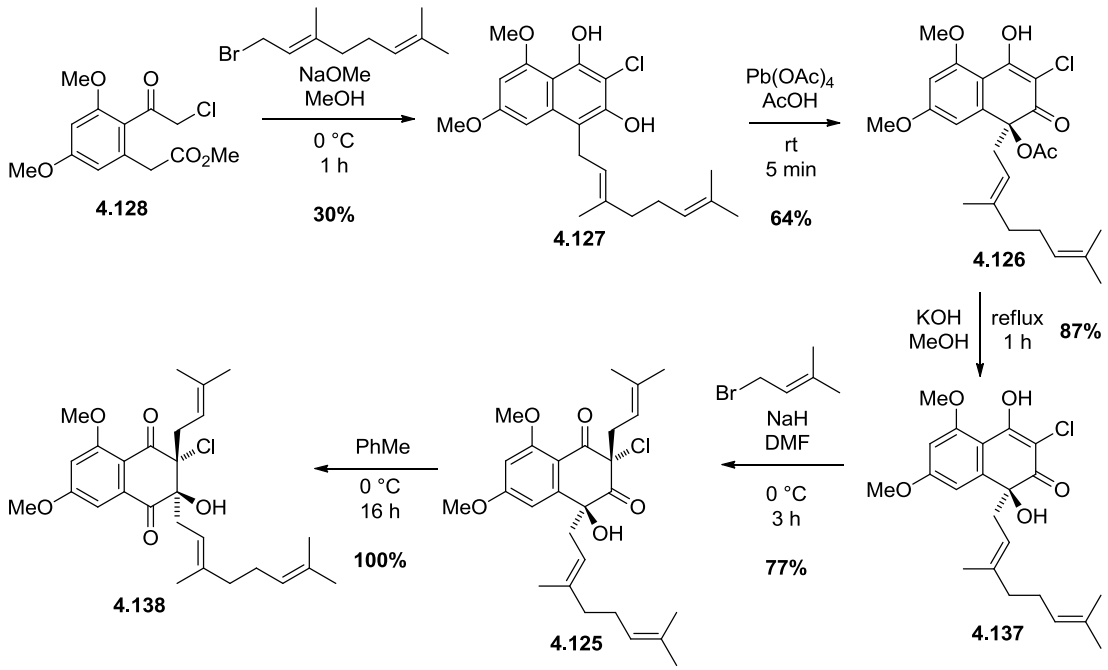
Based on our data analysis, we were able to confidently assign the structure of the isolated compound as the α-ketol rearrangement product **4.132**. Additionally, we were able to obtain further evidence by successfully repeating the epoxidation reaction performed on naphthomevalin reported in its isolation paper.[13] Treatment of **4.132** with NaOH in MeOH cleanly induced epoxidation to yield the A80915G analogue **4.136**, spectroscopically determined by the loss of the OH peak in the ^{1}H NMR and the characteristic up field shift of the C-2 and C-3 carbon peaks. The success of this reaction also confirmed the relative stereochemistry of the alkyl substituents to be *trans* to each other, as this S_N2 process could not occur otherwise.

The success of this reaction demonstrated the first application of an α-ketol rearrangement to form the naphthoquinone skeleton of the napyradiomycins. The proven feasibility of this approach now opened up the possibility of the synthesis of many napyradiomycin natural products using this methodology. This also gave strong support to our proposal that these natural products biosynthetically originate from a similar rearrangement process, rather than the commonly proposed flaviolin (**4.103**) intermediacy.

4.2.3 Synthesis of Di-*O*-Methyl Naphthomevalin

Following the success of the model system, the route could be adapted to the synthesis of naphthomevalin (**4.23**) by simply changing the electrophiles used during the alkylation reactions. Applying our aromatization/alkylation procedure to form the geranylated intermediate **4.127** with geranyl bromide gave a comparable result to the prenylation reaction. Again, in comparison to the isosesquilavandulylation reaction, **4.127** was isolated in lower yield and was more difficult to purify by flash chromatography. Fortunately, our MeOH trituration procedure used for the purification of **4.129** was also applicable to this system and allowed the isolation of **4.127** in good purity. Wessely oxidation of **4.127** with $Pb(OAc)_4$ in AcOH then proceeded smoothly to yield the acetate **4.126**. We discovered that **4.126** could

also be adequately purified by simple MeOH trituration, thus deleting another flash chromatography purification from this synthetic route. Using this procedure, we were able to obtain higher yields of **4.126** with no sacrifice of purity. The high polarity of **4.126** was evidently responsible for the difficulties experienced with flash chromatography purification. Acetate hydrolysis of **4.126** with KOH in MeOH at reflux then yielded the tertiary alcohol **4.137**, which was routinely taken onto the next step without further purification.



Scheme 4.29: Synthesis of di-*O*-methyl naphthomevalin

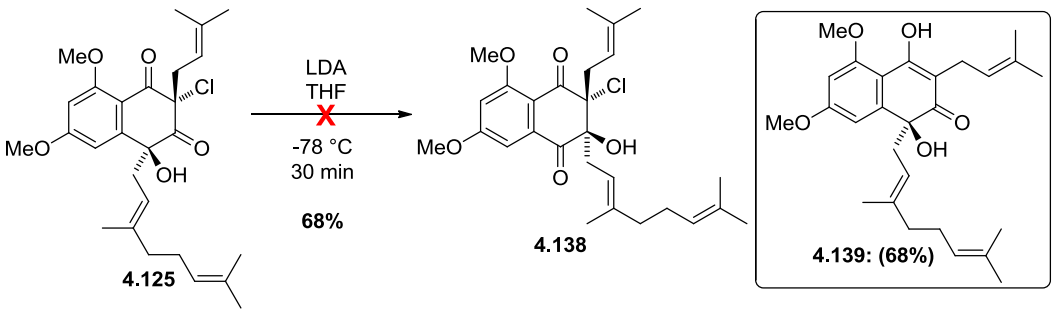
The conditions used for the chloroenol methylation in our model system were also found to be effective for the prenylation. As prenyl bromide is an activated nucleophile in comparison to MeI, this reaction was found to be faster and higher yielding than the methylation reaction. However, as a result of this, unfortunately lower diastereoselectivity was observed when the reaction was conducted at room temperature. Changing the reaction temperature to 0 °C solved this problem, and acceptable diastereomeric ratios of 10 : 1 for the desired isomer by ^{1}H NMR analysis could be achieved.

Applying our established α-ketol rearrangement conditions, a solution of **4.138** in PhMe was heated at reflux, resulting in clean, quantitative conversion to a higher R_f compound. The changes in the NMR data between the isolated product and the starting material were analogous to that of the model system, confirming that α-ketol rearrangement had occurred. We believe this to be the first report of an α-ketol rearrangement inducing the 1,2-shift of a

geranyl substituent. Additionally, we believe this to be the first instance of a 1,2-shift of any carbon chain this long being induced by an α-ketol rearrangement; most examples reported involve either methyl shifts or ring contraction/expansion events.[4]

Upon experimentation with this reaction, some interesting details were uncovered. The reaction was determined to be scale dependent; while reactions performed on <50 mg scales would reach completion in a few hours, scales much larger needed to be left overnight. We typically left this reaction heating at reflux overnight to ensure complete consumption of the starting material. No negative effects resulting from a longer reaction time were observed. TLC and ^{1}H NMR analysis of the reaction showed that the *cis* diastereoisomer of **4.125** was inert towards α-ketol rearrangement under these conditions. This could be explained with a steric argument, as the theoretical rearranged product would have two bulky alkyl substituents close to each other, and this isomer would likely be of higher energy than the starting material.

Being interested in the effect of solvent on this α-ketol rearrangement, we performed an extensive exploration of different solvents. We found that the reaction would proceed, at least to some extent, in many different solvents, including both polar and non-polar. No other reaction products were observed during any of these tests. We were surprised to find that a consistent trend based on polarity, boiling point (and hence reaction temperature) or any other properties was not clear based on our results. Furthermore, other than our established method of PhMe reflux, no other reaction conditions provided were able to reproducibly drive the reaction to completion, no matter how long the reaction was left for. Presumably, in refluxing PhMe the position of the equilibrium lies far to the right, and this is not the case for the other conditions trialed. While not much could be taken from this study, we could tentatively say overall that non-polar solvents are more effective for this transformation than polar solvents, and that PhMe is optimal, followed by hexanes.

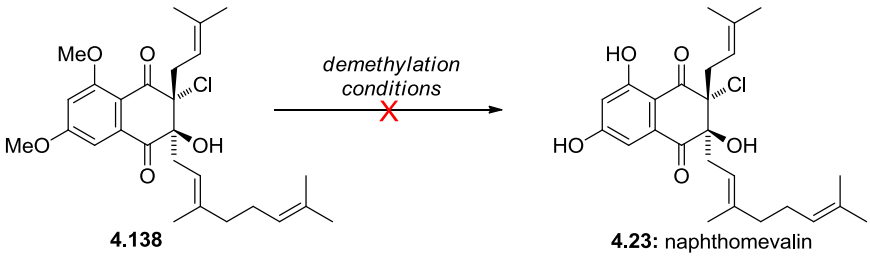


Scheme 4.30: Unexpected dechlorination reaction

Other attempts were made to induce α-ketol rearrangement in **4.125** under basic conditions with no success. An interesting side reaction, however, was observed when **4.125** was treated with LDA in THF at low temperatures, resulting in what we believed was the dechlorination product **4.139** in 68% yield. Formation of this product could be imagined to involve nucleophilic attack of LDA on the chlorine atom, analogous to a deprotonation process. However, this is speculative in the absence of any further mechanistic studies. The use of a strong amide base was found to be necessary; this process would not occur if diisopropylamine was used in place of LDA.

4.2.4 Investigation into the Total Synthesis of Naphthomevalin *via* Methyl Ether Protecting Group Strategy

With di-*O*-methyl naphthomevalin (**4.138**) in hand, only a single deprotection reaction remained to complete the total synthesis of naphthomevalin (**4.23**). The task ahead was a difficult demethylation reaction of a sensitive substrate containing alkene groups. As we were able to solve a very similar problem in the final step of our merochlorin A total synthesis utilizing a Krapcho type demethylation procedure,[53,54] we were optimistic that the same reaction conditions would prove effective here.[47] To our dismay, heating **4.138** in DMF in the presence of LiCl, as per our merochlorin A demethylation reaction, led to quick decomposition of the starting material.

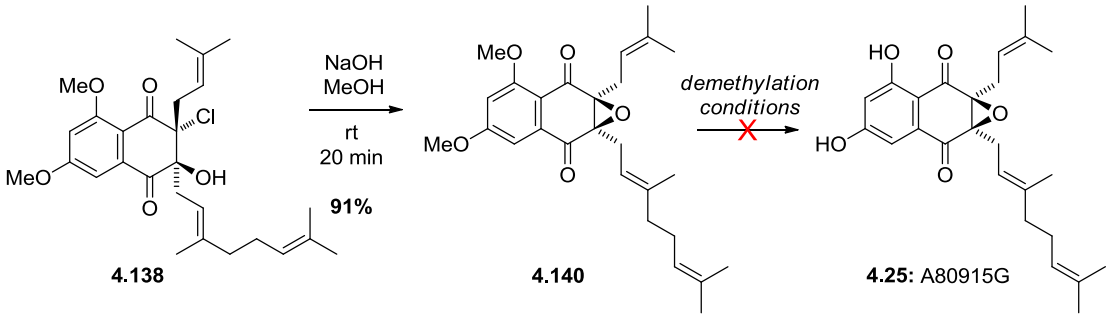


4.138 **4.23**: naphthomevalin

Scheme 4.31: Unsuccessful demethylation of **4.138**

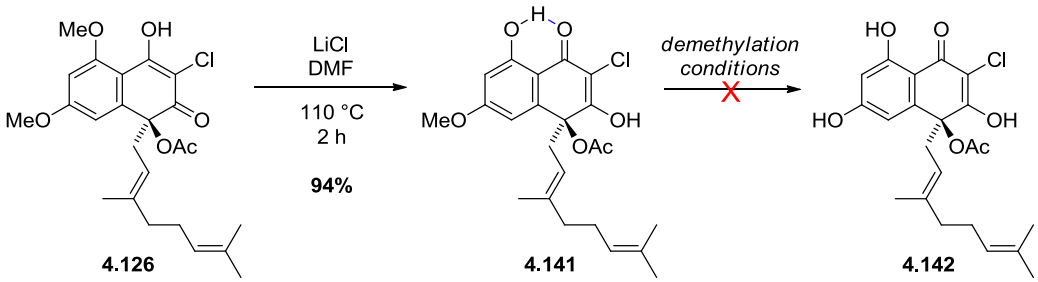
Decomposition occurred even at much lower temperatures than would be required for demethylation to occur. This was discouraging as these conditions were the most likely to yield a successful result. This failed reaction indicated this substrate was too sensitive for demethylation to be possible. Forced to explore alternative conditions, we tried using conventional strong Lewis acids like BBr_3 and $AlCl_3$ which unsurprisingly led to undesired reactions at the alkenes. The use of thiolates led to quick decomposition.

Di-*O*-methyl naphthomevalin (**4.138**) was converted to di-*O*-methyl A80915G (**4.140**) *via* S_N2 epoxidation with NaOH in MeOH. While these conditions were chosen as they were the literature procedure, we found that essentially any base/solvent combination was effective at inducing this transformation including, but not limited to, TBAF in THF. **4.140** was also observed as a minor byproduct during attempts to demethylate **4.138** with LiCl. Demethylation attempts were performed on **4.140** in the hopes of obtaining A80915G (**4.25**); unfortunately this substrate was found to be no more stable to demethylation conditions than **4.138**.



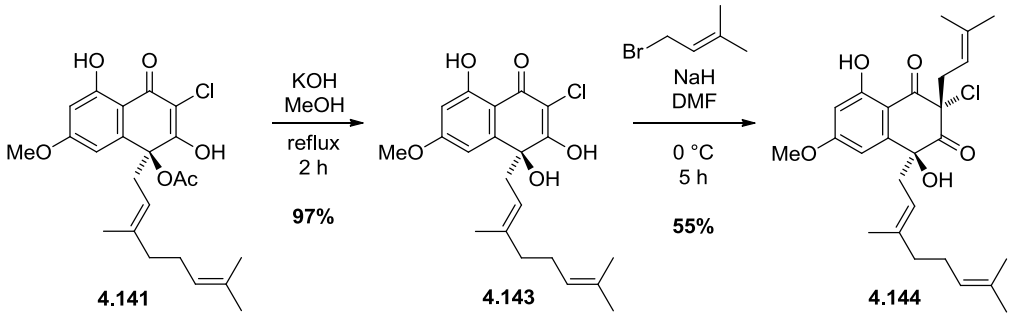
Scheme 4.32: Synthesis of di-*O*-methyl A80915G and failed demethylation attempts

At this point it was becoming increasingly more likely that we would have to repeat the synthesis with a new protecting group strategy in order to yield the desired natural products. Before embarking on this new task, it was worth investigating the possibility of demethylation at an earlier point in the synthesis. After experimentation, it was discovered that partial demethylation of the acetate intermediate **4.126** could be achieved relatively easily using Krapcho demethylation conditions to yield the mono-*O*-methyl intermediate **4.141**. However, no matter how long the reaction was left heating for or how high the temperature provided, we could not achieve conversion of **4.141** into the diphenol **4.142**.



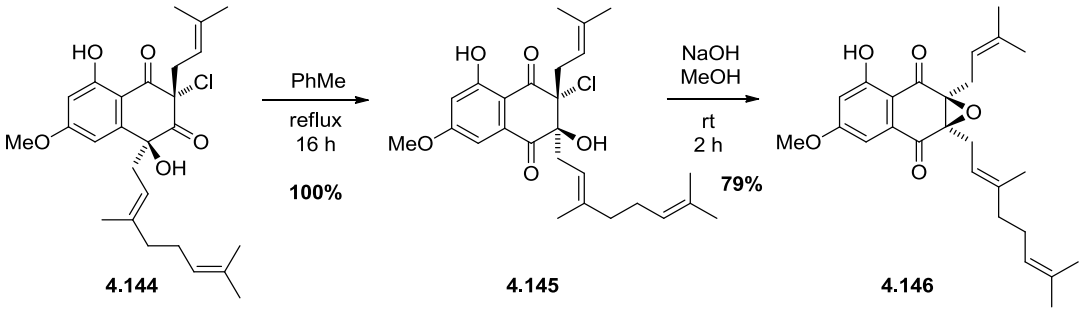
Scheme 4.33: Partial demethylation of **4.126**

The NMR data of **4.141** implied it existed as a single tautomer, but the opposite enol form to that of the starting material (**scheme 4.33**). This indicated that the intramolecular hydrogen bonding stabilization is stronger in the form that is drawn, relative to the alternative enol form. **4.141**, along with its hydrolysis product **4.143**, were found to be more polar (R_f = 0.08 in 8:1 CH_2Cl_2/MeOH) in comparison to other intermediates in this project, making them impractical to purify by chromatography.



Scheme 4.34: Synthesis of mono-methylated intermediate **4.144**

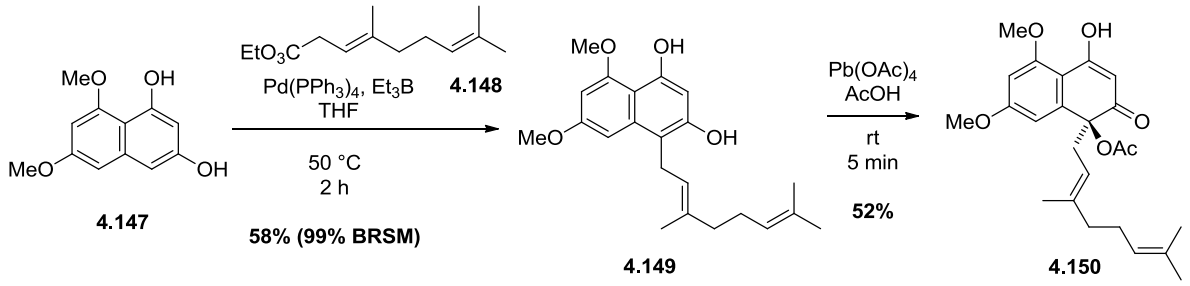
We took **4.141** on to the rest of the steps in sequence with the intention of testing the reactivity of the mono-methylated intermediates towards demethylation (**scheme 4.34**). All of our established reaction conditions were found to be applicable to the mono-methylated system, allowing the synthesis of *O*-methyl naphthomevalin **4.145** and *O*-methyl A80915G **4.144**. Prenylation of the α-chloroenol **4.143** was found to occur at a slower rate than the dimethylated system. However, despite the presence of the extra acidic functional group, this reaction still proceeded cleanly.



Scheme 4.35: Synthesis of *O*-methyl naphthomevalin **4.145** and *O*-methyl A80915G **4.146**

In comparison to the dimethylated system, α-ketol rearrangement of **4.144** appeared to occur at a faster rate based on experimental observation. We devised a competition experiment

which would further confirm this, by running a reaction using a mixture of 30 mg each of both **4.138** and **4.144**. The reaction mixture was concentrated after 45 min of heating at reflux in PhMe and the product mixture was subjected to ^{1}H NMR analysis. The concentration of the compounds present in the mixture was determined by comparison of the integration values of the relevant peaks in the ^{1}H NMR spectrum. The starting material to product ratio was determined to be 1.6 : 1 for the dimethylated system, and 1 : 2.4 for the mono-methylated system. This confirmed the suspected increased reaction rate of the mono-methylated system relative to the dimethylated system. Unfortunately, none of the compounds shown in **scheme 4.34** or **scheme 4.35** were found to be suitable substrates for successful demethylation, making **4.145** the closest structure to naphthomevalin we were able to access using this route.

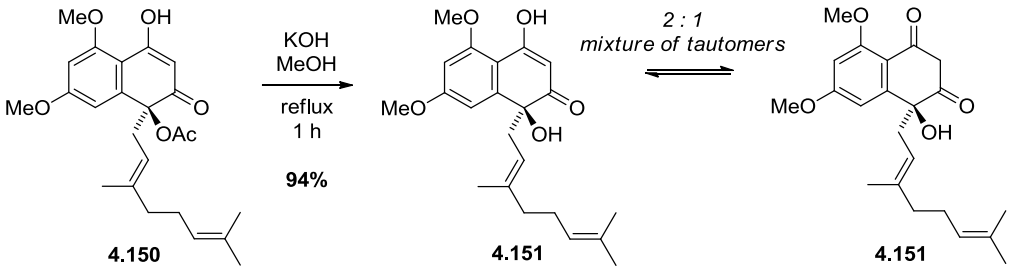


Scheme 4.36: Pd(0) catalyzed geranylation[48,55]

We remained hesitant to begin repeating the synthesis with a new protecting group strategy as it was a daunting task, so we continued to explore the current methyl ether strategy. We contemplated the possibility of later stage introduction of the chlorine atom, which would allow testing of deprotection reactions on the non-chlorinated intermediates. This would also result in the synthesis of a larger library of substrates on which to test the α-ketol rearrangement reaction, which could provide more information on the scope and limitations of this reaction.

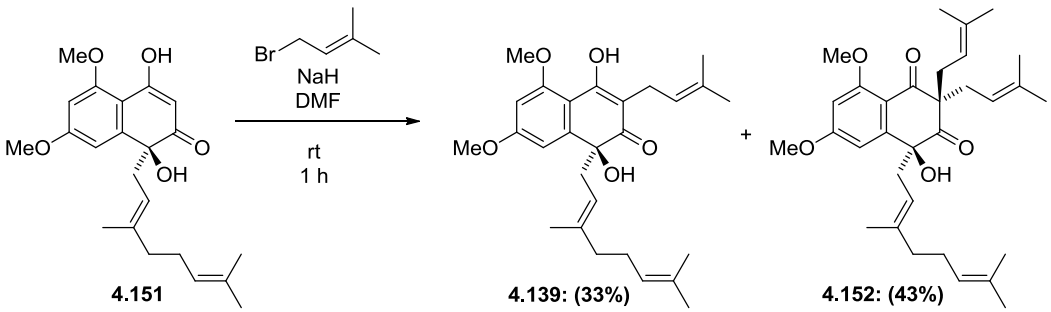
As we discovered during our work on the merochlorins, alkylation of the non-chlorinated THN intermediate was lower yielding, unselective and difficult to control.[47] As we found analogous problems with the geranylation reaction under basic conditions, we opted to change our approach to the Pd(0) catalyzed alkylation with Et_3B (**scheme 4.36**), which had been previously employed in synthetic work towards the merochlorins by Moore *et al.*[48,55] Ethyl geranyl carbonate (**4.148**) was prepared in one step from geraniol and ethyl chloroformate.[56] While this reaction was more successful than using basic conditions, we found it to be impossible to drive to completion and a significant amount of starting material

was recovered. Changes in each of the reaction variables, including time, temperature, amount/ratios of reagents and catalytic loading were explored to try and find what was limiting this reaction; however no impact on the reaction outcome was observed. Unable to optimize this reaction, we were forced to settle with these conditions. The reaction was routinely left heating at 50 °C for two hours before quenching. While a good yield of **4.149** based on recovered starting material could be obtained, it was unfortunate that material needed to be recycled repetitively through a process involving expensive reagents, making this reaction not particulary practical. Wessely oxidation of **4.149** was possible by utilizing our established reaction conditions; however, we had some difficulty in reproducing an adequate yield for this Wessely oxidation reaction in contrast to the chlorinated system, which was more reliable.



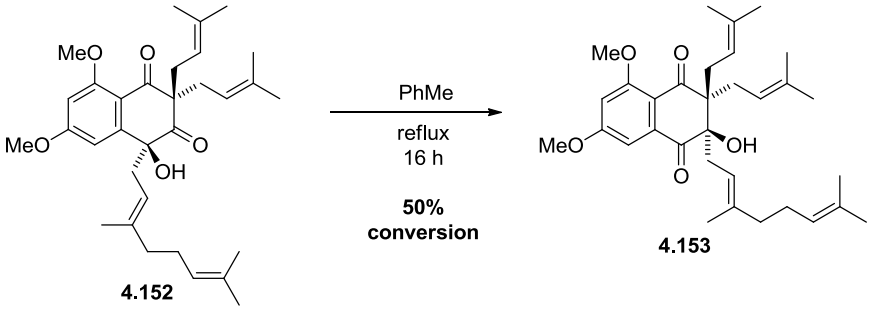
Scheme 4.37: Synthesis of dearomatized intermediate **4.151**

Interestingly, the hydrolysis product **4.151** was found to exist as a 2 : 1 mixture of tautomers by ^{1}H NMR analysis, with the enol form pictured being the most abundant followed by the diketone form (**scheme 4.37**). The presence of the diketone was revealed by the characteristic pair of doublets around δ 3.5 in the ^{1}H NMR spectrum. This tautomeric form was never observed in any of the chlorinated intermediates, indicating that the presence of the chlorine atom must increase the relative stability of the enol forms.



Scheme 4.38: Diprenylation of **4.151**

We were interested in investigating what effect the presence of two alkyl substituents at the C-2 position would have on the α-ketol rearrangement, in contrast to one alkyl and one chloride. To obtain a substrate required for testing, we performed a prenylation reaction on **4.151** using prenyl bromide and NaH in DMF. In addition to the desired diprenylated intermediate **4.152**, we also obtained a quantity of the mono prenylation product **4.139**. The spectroscopic data of **4.139** was found to match that of the previously isolated product (**scheme 4.30**), further confirming dechlorination had occurred under those reaction conditions.

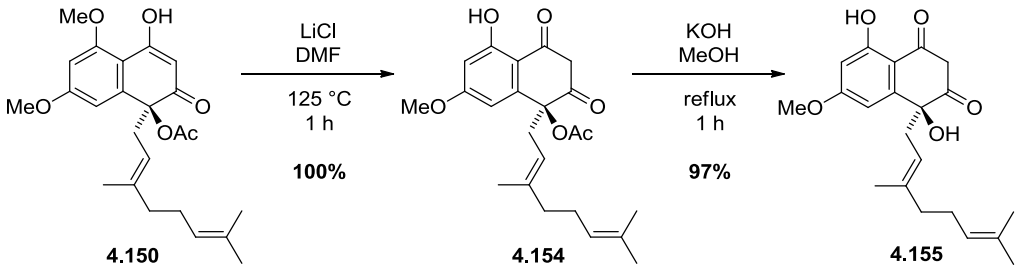


Scheme 4.39: α-ketol rearrangement of diprenylated intermediate

Heating a solution of **4.152** in PhMe at reflux slowly yielded a 1 : 1 mixture of a new product and the starting material. The starting material and the product were too similar in R_f to achieve any separation by flash chromatography, but by comparing the crude NMR to previously successful α-ketol rearrangement products, we were confident in assigning the structure of the product to be **4.153**. No matter how long this reaction was left for, a greater conversion could not be achieved. The position of the equilibrium under these conditions was evidently halfway between the two isomers; hence, at 50% conversion, the rates of the forward and backward reactions were equal. The fact that α-ketol rearrangement would occur at least to some extent on this more sterically hindered system was an interesting observation, and further expanded the known scope of this reaction. The steric clash between the *cis* prenyl group and the geranyl chain in **4.153** is likely responsible for a smaller difference in thermodynamic stability between the starting material and product, resulting in the difference in position of the equilibrium.

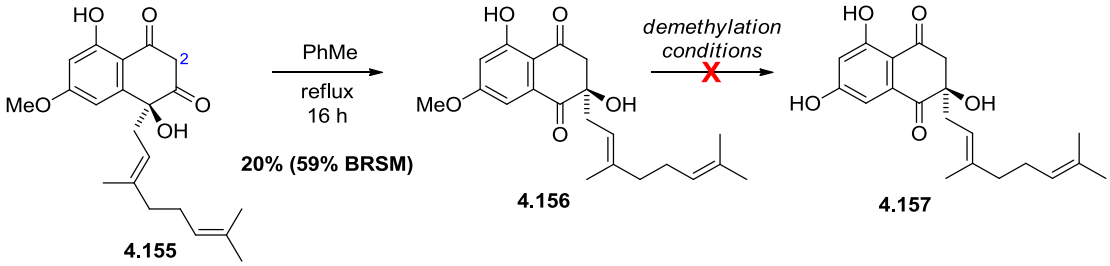
Demethylation of **4.150** with LiCl in DMF proceeded quickly to yield **4.154** but, similar to previous reactions, demethylation of the second methoxy group was found to be impossible. ^{1}H NMR showed that **4.154**, along with the hydrolysis product **4.155**, existed predominantly

as the diketone tautomer. This subtle difference in tautomeric abundance evidently did not affect the success of demethylation.



Scheme 4.40: Synthesis of monodemethylated products

With our experimentation so far, only compounds containing an sp^3 C-2 carbon atom had shown reactivity toward α-ketol rearrangement. Of the synthesized intermediates which were not fully substituted at the C-2 position, only **4.155** existed as the diketone which contains an sp^3 C-2 carbon atom as the more abundant tautomeric form. Therefore, we hypothesized that **4.155** may be more reactive towards α-ketol rearrangement than the previously isolated compounds which predominately exist as the enol tautomer.



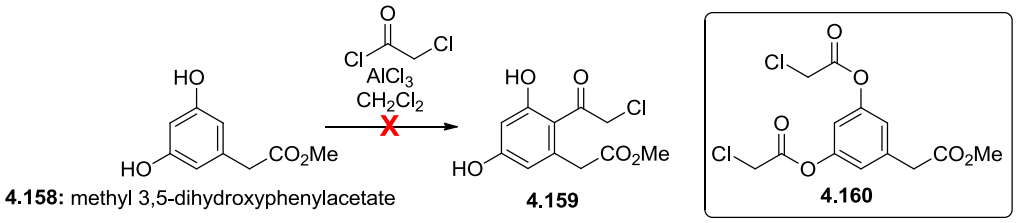
Scheme 4.41: α-ketol rearrangement

As predicted, **4.155** did show some reactivity, and we were able to isolate 20% of the rearrangement product **4.156** along with 39% recovered starting material under our now standard conditions of refluxing PhMe. A greater conversion could not be achieved, indicating the system had reached equilibrium at this point. In contrast, the dimethylated intermediate **4.150** was completely unreactive. As the new product **4.156** was now locked into the 1,4-diketone form, it was possible this structural change could cause it to be more reactive towards demethylation. This was unfortunately not the case and a similar result was observed as the attempted demethylation of **4.150**. Nevertheless, the successful formation of

4.156, albeit in low yield, was an interesting observation and proved that this α-ketol rearrangement reaction had fewer limitations.

4.2.5 Exploration of Alternative Protecting Group Strategies

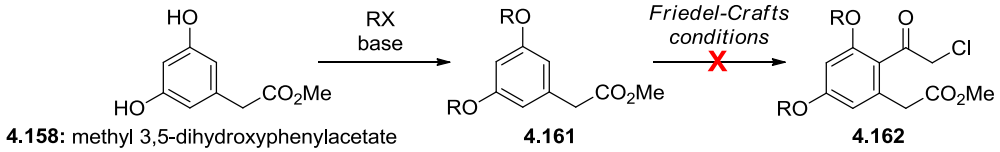
With the exhaustion of options for the demethylation approach, it became necessary to explore alternative protecting group strategies. At first glance, the most apparent problem with modifying our current synthetic route with new protecting groups was the installation of the chloroacetyl substituent *via* Friedel-Crafts acylation, which required the use of a strong Lewis acid. No commonly used phenol protecting groups, other than the currently employed methyl ethers, would be likely to stay intact under these reaction conditions. As previously discussed, we even experienced some problems with undesired deprotection of methyl ethers during the Friedel-Crafts reaction. Attempting to avoid these inevitable issues, we performed Friedel-Crafts acylation of unprotected methyl 3,5-dihydroxyphenylacetate (**4.158**), in the hope of installing the new protecting groups in the subsequent step. However, we were unable to observe any Friedel-Crafts products at all, and diester **4.160** was the major product formed in this reaction. This indicated that protection of the phenols was indeed necessary for successful installation of the chloroacetyl group.



Scheme 4.42: Unsuccessful Friedel-Crafts acylation of unprotected starting material

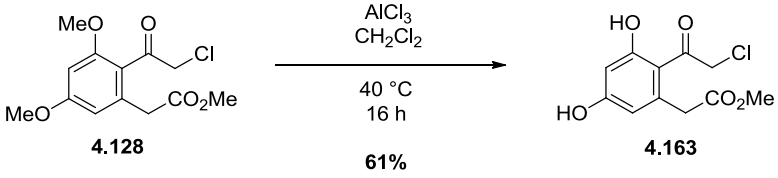
Trivial syntheses of some protected intermediates **4.161** were then performed to try and determine which protecting groups might be suitable. Benzyl, allyl and TIPS groups were tested as these were hypothesized to be the most likely candidates to stay intact during the Friedel-Crafts reaction. Unfortunately, each of these protecting groups were found to be unsuitable, as partial or complete deprotection was observed under the Friedel-Crafts conditions. Different conditions were screened, including different Lewis acids and Brønsted acids, different temperatures and the use of chloracetyl chloride or chloroacetic anhydride as the electrophile with no success. With the most promising of the commonly used protecting groups proving to be incompatible, we now had to consider the option of looking into more

exotic protecting groups which may withstand the conditions. We considered *p*-nitrobenzyl and 3,5-dichlorobenzyl, as the electron withdrawing substituents on the aromatic ring are known to make the benzyl group less reactive towards nucleophilic attack.[57] However we did not believe these protecting groups would be applicable to this synthesis as they would probably be too difficult to remove during the final step, likely requiring the use of hydrogenolysis.



Scheme 4.43: Unsuccessful Friedel-Crafts reaction attempts with differently protected substrates (R = benzyl, allyl or TIPS)

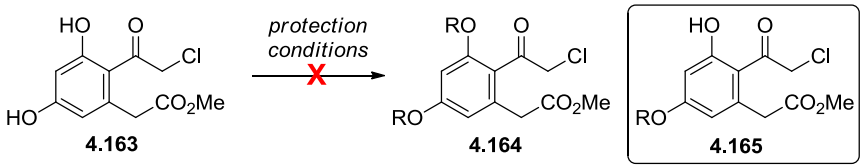
Convinced that methyl ether protecting groups were necessary for the success of the Friedel-Crafts reaction, the new plan was to deprotect the chloroacetate **4.128**, followed by reprotection with new protecting groups. Demethylation of **4.128** with $AlCl_3$ in CH_2Cl_2 was found to be a reliable way to yield the diphenol **4.163**. As with previous demethylation reactions, cleavage of the *ortho* methoxy group was found to be much faster relative to the *para* position. Gentle warming of the reaction mixture to 40 °C as opposed to running it at room temperature was found to have a significant impact on the rate of reaction, which would then reliably reach completion overnight.



Scheme 4.44: Demethylation with $AlCl_3$

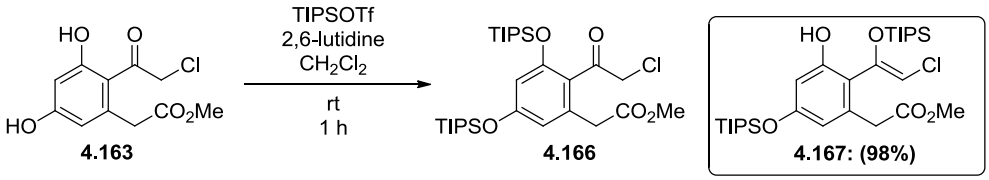
Unexpectedly, phenol protection **4.163** was found to be extremely challenging. Treatment of **4.163** with three equivalents of both TBSCl and imidazole in CH_2Cl_2 would cleanly yield the monoprotection product **4.165** (R = TBS), but with no reaction occurring at the *ortho* hydroxyl group. Desperate for reactivity, the solvent was changed to DMF and the reaction mixture was heated at 100 °C overnight, with no success. Attempts to alternatively protect **4.163** with benzyl, allyl or MOM ethers under basic conditions led to identical results; no

reaction would occur at the *ortho* position. Thinking the issue may lie with the basic conditions used, an attempt to protect with THP under standard acid catalysis conditions using DHP with PPTS in CH_2Cl_2 was investigated.[57] However, the result was no different than with basic conditions. As an alternative, benzyl ether protection was attempted using Mitsunobu conditions (BnOH, DEAD and PPh_3) which was ultimately unsuccessful.[58]



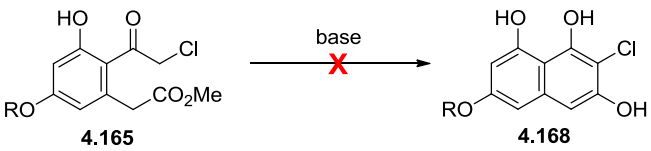
Scheme 4.45: Unsuccessful diprotection of **4.163** (R = benzyl, allyl, TBS, THP or MOM)

As an excellent demonstration of the inherent unreactivity of the *ortho* phenol, silyl enol ether **4.167** was isolated as the sole product of the reaction of **4.163** with TIPSOTf and 2,6-lutidine. The formation of this product made it apparent that even the acetate was more reactive than the phenol, further reinforcing the fact that the desired diprotection was not possible.



Scheme 4.46: Attempted triisopropylsilyl protection of **4.163**

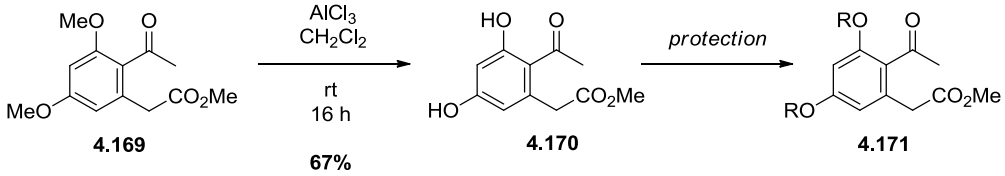
In the hope that one of these monoprotected intermediates could ultimately be useful to us, we went ahead with the aromatization reaction. However, when the mono THP or TBS protected intermediates **4.165** were treated with NaOMe or NaH, no reaction occurred. Increasing the reaction temperature did not assist cyclization; the only process that was observed after an extended period was slow deprotection.



Scheme 4.47: Aromatization failed to proceed on the mono-protected system

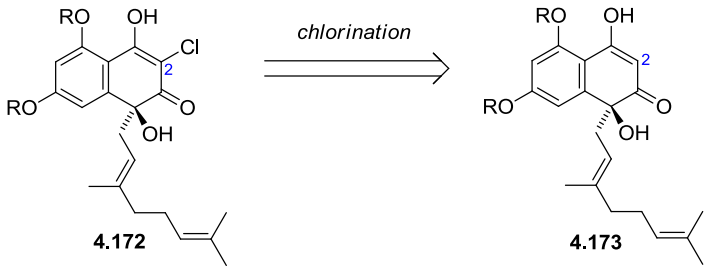
It was now evident that both phenol groups needed to be protected for the aromatization reaction to proceed. The presence of the acidic phenol group was presumably responsible for lack of reactivity, as cyclization would require the formation of the dianion.

Puzzled by the failure of the diprotection reaction on the chloroacetate substrate, we speculated whether this reaction would perform any better in the absence of the chlorine atom. In order to test this, **4.170** was obtained by demethylation of previously obtained **4.169** with $AlCl_3$ in CH_2Cl_2. In comparison to the chloroacetate, demethylation of this substrate occurred at a faster rate. Gentle heating was not required and full deprotection could be achieved by stirring at room temperature overnight.



Scheme 4.48: Demethylation and subsequent protection of **4.169 (**R = benzyl, allyl or THP)

Again, we trialed the phenol protection reaction with benzyl, allyl and THP as the protecting groups. The result this time was remarkably different to the chlorinated system: diprotection occurred with each of these protecting groups under standard conditions, producing **4.171** in good yield. Clearly the presence of the chlorine atom was having a negative influence on the nucleophilicity of the *ortho* phenol, as the reaction proceeded well in its absence. One possible explanation is that the increased acidity of the chloroacetate group relative to the acetate was causing deprotonation of the acetate, instead of at the phenol as required.



Scheme 4.49: Proposed later stage chlorination strategy

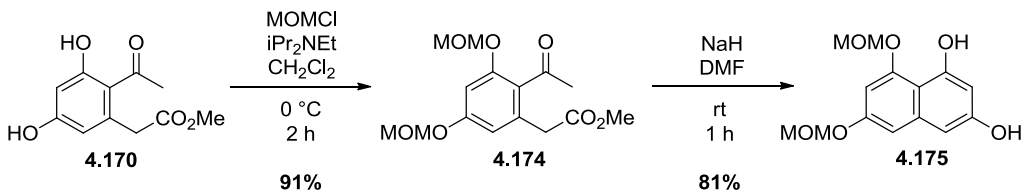
With no other alternatives available, we were forced to pursue this route which would ultimately require later stage installation of the C-2 chlorine atom. As attempted chlorination of **4.171** with NCS or SO_2Cl_2 under acid or base catalysis failed to be selective for the desired

position, we hypothesized that the most logical point to introduce the chlorine atom in order to achieve site selectivity would be the dearomatized intermediate following the Wessely oxidation. Chlorination should be achievable by treating **4.172** with an electrophilic chlorine source, in an analogous process to prenylation at the C-2 position. It was important that the chlorination be performed earlier in sequence to the prenylation in order for the correct stereochemistry to be achieved.

4.2.6 Methoxy Methyl Ether Protecting Group Strategy

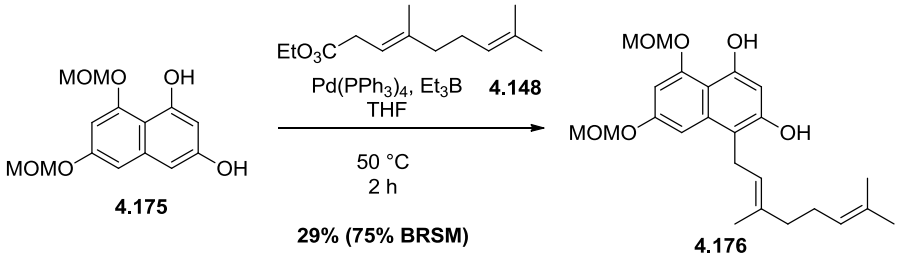
We were now confronted with a difficult decision, namely the choice of protecting group in which to pursue the rest of the synthesis with. This was highly important, as an inadequate choice would lead to a great deal of wasted time and resources, as several steps would need to be performed before the eventual outcome would be known. The two most important factors of consideration for protecting group choice were compatibility with the conditions used in the later steps in the synthesis, and ease of removal. Silyl ethers such as TBS or TIPS would likely not survive the hydroxide conditions needed for the later ester hydrolysis. The conditions necessary to cleave a benzyl ether protecting group, commonly requiring either hydrogenolysis or Lewis acid, would be incompatible with our substrate due to the multiple alkenes present in the structure.

The two reported literature syntheses of napyradiomycin A1 (**4.30**),[39,40] as well as the synthesis of A80915G (**4.25**),[38] all employed the use of MOM ether groups for phenol protection, and in each case were able to successfully deprotect them as the final step in the syntheses (**schemes 4.11**, **4.13** and **4.16**). The application of MOM ethers to our synthesis should guarantee that the final deprotection reaction is possible, based on this excellent precedent being performed on very similar substrates. MOM ethers are known to be stable to most conditions other than acidic hydrolysis, so we had good confidence in their compatibility with the rest of the steps in our synthetic route.



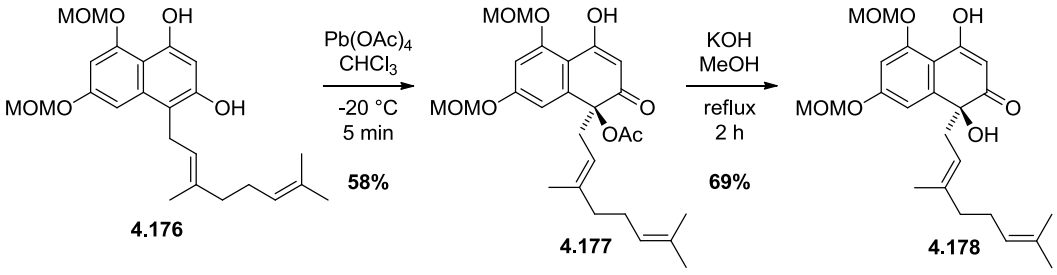
Scheme 4.50: Synthesis of di-MOM protected THN

Di-MOM protection of **4.170** proceeded smoothly under standard conditions of MOMCl and iPr_2NEt in CH_2Cl_2. The addition of at least three equivalents of MOMCl was found to be necessary to drive this reaction all the way to completion. Base induced aromatization by Diekmann-type cyclization of **4.174** with NaH in DMF then yielded the di-MOM protected THN **4.175**. While acidification of the reaction mixture during the workup procedure was important during this reaction for the generation of the phenols from their sodium salts, care had to be taken, as reckless over acidification would lead to unwanted MOM ether hydrolysis products. This was a relevant point for many steps later in the synthesis, as the acidity of the enol intermediates required an acidic workup step to ensure isolation of the neutral compounds.



Scheme 4.51: Pd(0) catalyzed geranylation[48,55]

All of the same issues we previously had with the geranylation of THN compounds were found to apply to the MOM protected system, except the reaction was even lower yielding when performed under basic conditions, making the palladium catalyzed reaction the only practical option. Again, this reaction failed to reach a desirable conversion. The starting material needed to be recycled through the alkylation reaction several times for desirable amounts of the geranylated THN **4.176** to be obtained.



Scheme 4.52: Synthesis of dearomatized MOM protected intermediates

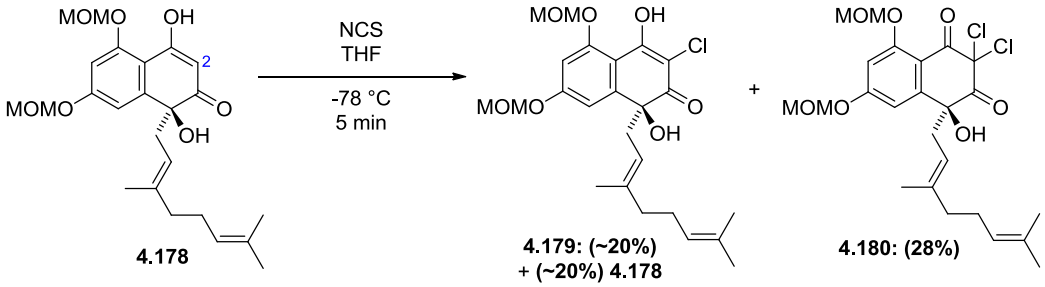
During the following two steps we began experiencing problems as a result of the new protecting group strategy. Treatment of **4.176** with $Pb(OAc)_4$ in AcOH would yield the

desired Wesseley oxidation product **4.177**, however we experienced variable yields in the range of ~20-60%. Thinking the acidic solvent used may be the issue led us to discover that this reaction could just as effectively be performed in $CHCl_3$, relying solely on the ligands from the $Pb(OAc)_4$ reagent as the nucleophile source. The change to a lower freezing point solvent additionally allowed the reaction to be performed at a decreased temperature. Unfortunately, these changes did not make a noticeable impact on the outcome of this reaction, as yields obtained with this solvent change were still variable.

The new protecting groups were unfortunately found to be not entirely compatible with our established acetate hydrolysis conditions. Initially, we were only able to obtain the desired product **4.178** in ~40% yield, with some deprotection of the *ortho*-MOM ether being responsible for the low yield. Logically, the deprotection side reaction could potentially be avoided by performing the reaction under milder conditions, but running this reaction at elevated temperature was found to be necessary. Using K_2CO_3 in place of KOH gave identical results. It was established that our original conditions of KOH in MeOH at reflux temperatures were still optimal for this reaction. This was another reaction that was found to be unreliable, and our best result of 69% was not consistently reproducible using the same conditions. To make matters worse, it was discovered that the two dearomatized intermediates **4.177** and **4.178** were unstable, and would undergo decomposition when stored at -20 °C for extended periods. Care had to be taken to perform these reactions immediately after each other to avoid decomposition. The inherent instability of these products was likely partly responsible for the variable yields we were experiencing. Despite these less than ideal results, we were still able to obtain acceptable quantities of tertiary alcohol **4.178** for further experimentation.

4.2.7 Late Stage Introduction of Chlorine

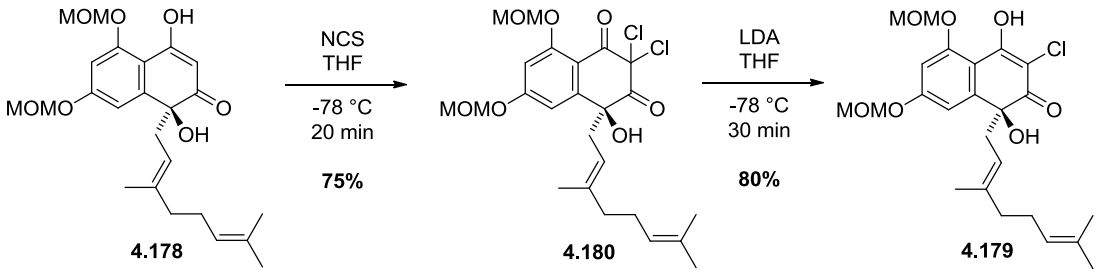
4.178 was presumed to be the best stage for the introduction of chlorine, as the enol structure should ensure the C-2 position is the most reactive site in the molecule. However, addition of NCS to **4.178** at -78 °C resulted in formation of the dichlorination product **4.180** in addition to the desired monochloride **4.179**. Other than this, the reaction was clean and chlorination was not occurring at any other sites. Controlling this reaction to prevent dichlorination was found to be impossible. The product of the first chlorination event was expected to be more reactive than the starting material due to the presence of an additional electron withdrawing group, resulting in the difficulties in controlling this reaction.



Scheme 4.53: Unselective chlorination of **4.178**

Because the starting material was reactive enough to react under neutral conditions at -78 °C, the potential for optimization was unlikely. The best result for this reaction we were able to achieve was a ~1 : 1 : 1 mixture of starting material **4.178** to chloride **4.179** to dichloride **4.180** with addition of 1.0 equivalents of NCS; any additional NCS added would just result in an exponential increase in unwanted dichlorination. What made this reaction even more impractical was the impossibility of achieving any separation from the unreacted starting material **4.178** and **4.179** using conventional flash chromatography, making it an ineffective method for the acquisition of pure quantities of **4.179** for further use.

Thankfully, we were able to devise an intelligent compromise which could potentially access the required α-chloro enol **4.179** in pure form, for the price of an additional synthetic operation. We thought back to the dechlorination of **4.125** we observed as an unexpected side reaction using LDA (**scheme 4.30**). Based on this, the plan was oxidation of **4.178** to the dichloride followed by reductive dechlorination using LDA to give **4.179**. Hypothetically, these two reactions should be overall much higher yielding than our current monochlorination procedure.

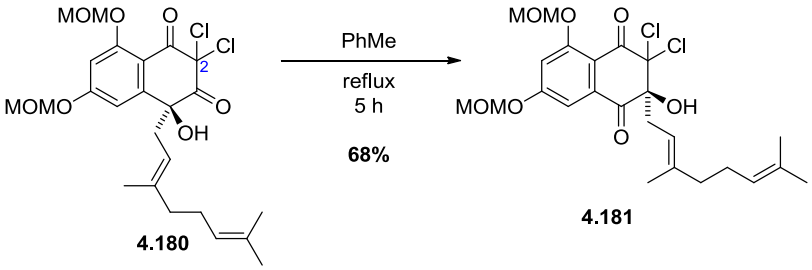


Scheme 4.54: Dichlorination followed by dechlorination

Dichlorination of **4.178** proceeded in good yield with the addition of two equivalents of NCS at -78 °C. We found that if addition of NCS was performed too rapidly, or the reaction

temperature was increased, a small amount of an unknown impurity (that would be later identified) with identical R_f to the product would form, contaminating the sample. Hence, care had to be taken when performing this reaction to avoid this issue.

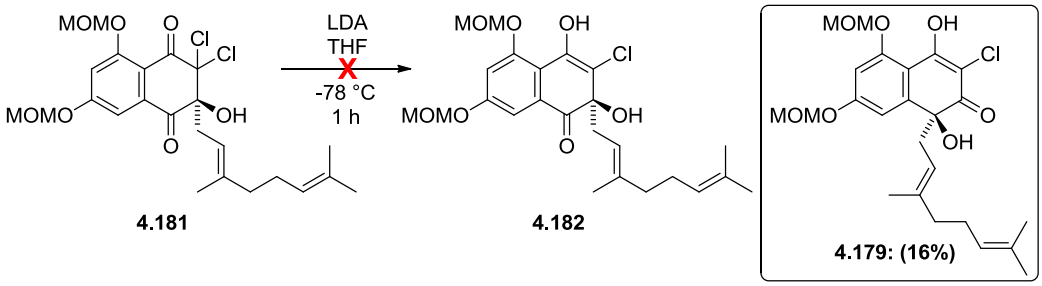
Remarkably, treatment of the dichloride **4.180** with LDA at -78 °C resulted in the sole formation of a product with an identical R_f to previously isolated **4.179** by TLC analysis, and its identity was confirmed by ^{1}H NMR analysis. As yields of around 80% could be reliably obtained for the dechlorination, this was a very pleasing result which allowed the access of **4.179** in two very simple to perform operations from **4.180**. We found that the use of four equivalents of LDA was optimal for the dechlorination; the reaction was difficult to drive to completion if less was used. The explanation for this in part could be that the acidic tertiary alcohol present in **4.180** is responsible for quenching one equivalent of base. In contrast to the non-chlorinated enol **4.178**, **4.179** was found to be perfectly stable under standard conditions, indicating the presence of the chlorine atom had a positive effect on the stability of these compounds.



Scheme 4.55: α-Ketol rearrangement of dichloride **4.180**

As the dichloride **4.180** was locked into the 1,3-diketone form due to full substitution at the C-2 position, we expected it to be reactive toward α-ketol rearrangement. Hence, **4.180** was heated at reflux in PhMe for five hours, resulting in clean conversion to the α-ketol rearrangement product **4.181**. We had reason to believe the dichloride to be more reactive toward α-ketol rearrangement than the prenylated substrate, as this reaction was found to occur to some extent at room temperature. A sample of **4.180** left at room temperature in a solution of $CDCl_3$ would reach equilibrium at 50% conversion to **4.181** in 48 hours. This increased reactivity could be rationalized by the decreased steric bulk and increase in electron withdrawing potential of the dichloride moiety. Interestingly, the rearranged compound **4.181** was discovered to be the same compound as the impurity that was sometimes observed during the dichlorination reaction (**scheme 4.54**). We were unsure as to how this product was

forming to a small extent under these reaction conditions, as attempts to purposely induce α-ketol rearrangement using NCS failed to achieve the same result.

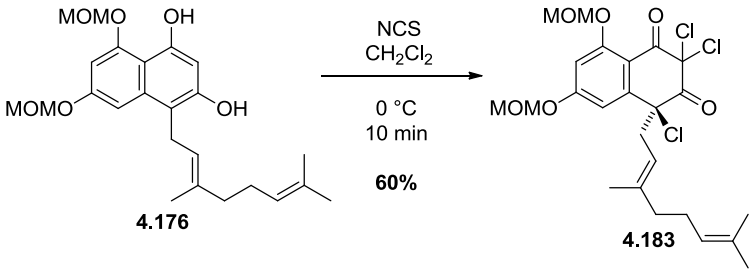


Scheme 4.56: Dechlorination conditions on 1,4-diketone unexpectedly resulted in retro rearrangement

We were interested to test whether the 1,4-diketone **4.181** would behave in the same way as the 1,3-diketone structures when treated with LDA. This reaction was found to proceed poorly when performed with **4.181**, as starting material was consumed only very slowly and multiple minor byproducts were formed (as observed by TLC analysis). In 16% yield, we were able to isolate a compound which had an R_f value similar to what we were expecting based on previous experience. We were surprised to find that the NMR data for the isolated compound matched that of the previously isolated chloroenol **4.179**. The existence of this product in the reaction mixture could only be explained by the occurrence of a retro α-ketol rearrangement process. This was the major product from the reaction; no other compounds were abundant enough to be isolated and no other intermediate products were observed on the TLC plate during the reaction process. This indicated that the retro α-ketol rearrangement process was very fast and hence occurring almost instantly following dechlorination. When full substitution is not present at the C-2 position, the 1,3-diketone is expected to be more stable than the 1,4-diketone form, as it can exist as a stable enol. The thermodynamic driving force to reform the 1,3-diketone must be strong enough for the retro α-ketol rearrangement to occur rapidly under these conditions. This observation also helps further explain the evident unreactivity toward α-ketol rearrangement of the compounds not containing full C-2 substitution.

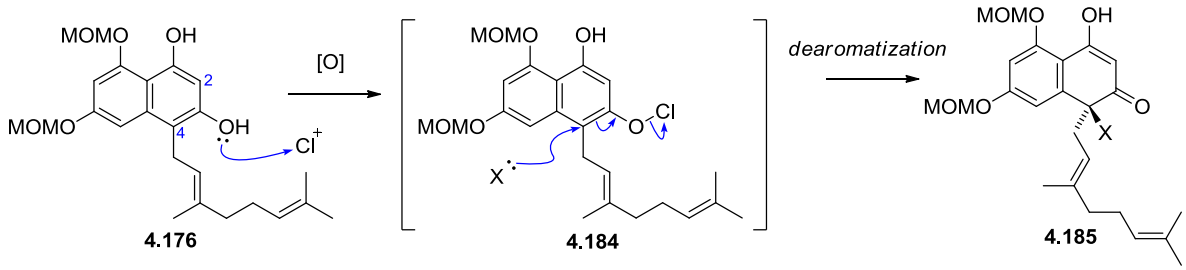
Our new synthetic route toward naphthomevalin was already looking considerably longer than our previous methyl ether protected strategy. In addition, we were experiencing issues with low yields, unreliable procedures and unstable intermediates. It was worth trying to optimize the route by looking into alternative options, as well as potential alteration of the

sequence of operations. One intriguing, potentially useful process we happened to observe during testing was that treatment of the geranylated THN **4.176** with NCS resulted in dearomatization and formation of the trichloride **4.183**. This was the sole product of the reaction, and addition of any less than three equivalents of NCS would result in a mixture of **4.183** and unreacted starting material.



Scheme 4.57: Trichlorination of geranylated THN **4.176**

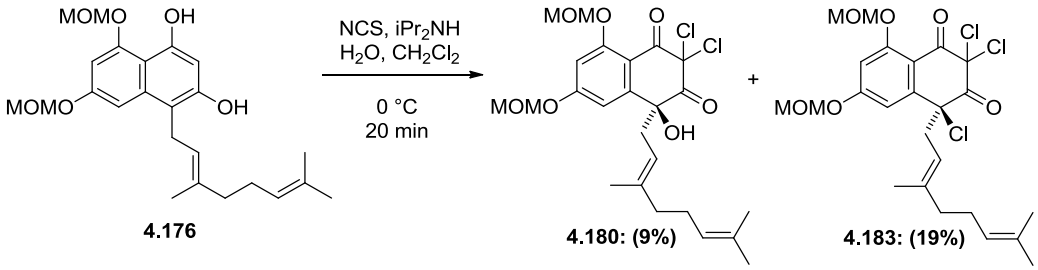
4.183 is structurally similar and exists in the same oxidation state as our later intermediate **4.180**. Hence, we contemplated the possibility of **4.183**, or alternatively the adoption of a similar process for its formation, being useful towards the synthesis of naphthomevalin. With this result in mind, we hypothesized a reaction which would allow access to **4.180** in one step from the geranylation product **4.176**. This idea was likely too ambitious to work in practice, but because it could potentially delete two synthetic operations from our sequence, including currently unreliable reactions involving unstable intermediates, it was worth investigation. Chlorination at the C-4 position of **4.176** presumably occurs through a hypochlorite intermediate such as **4.184** which is attacked by chloride to yield the dearomatized compound **4.185** (X = Cl). We hypothesized that it may be possible for reaction of **4.184** with an alternative nucleophile, in this case H_2O, to yield the alternative oxidation product **4.185** (X = OH).



Scheme 4.58: Mechanistic rationalization of oxidation reaction (X = Cl or OH)

Astonishingly, we were able to produce a positive result based on this proposal. Treatment of **4.176** with NCS in the presence of *i*-Pr_2NH and H_2O in CH_2Cl_2 generated the trichloride

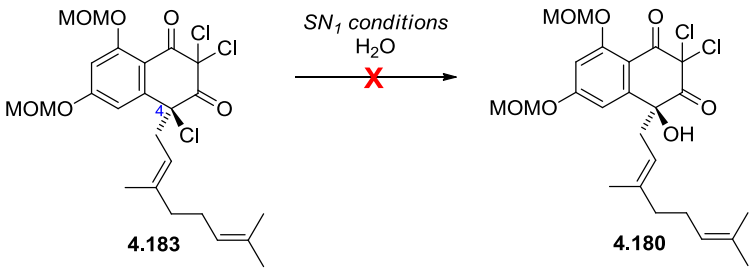
4.183 along with a small amount of the desired tertiary alcohol **4.180** (**scheme 4.59**).[59] The NMR data of **4.180** isolated from this reaction matched that of our previously isolated sample. This result was extremely encouraging, proving this process was indeed possible and could potentially result in the streamlining of our synthesis, provided it could be optimized.



Scheme 4.59: Trioxidation of geranylated THN **4.176**

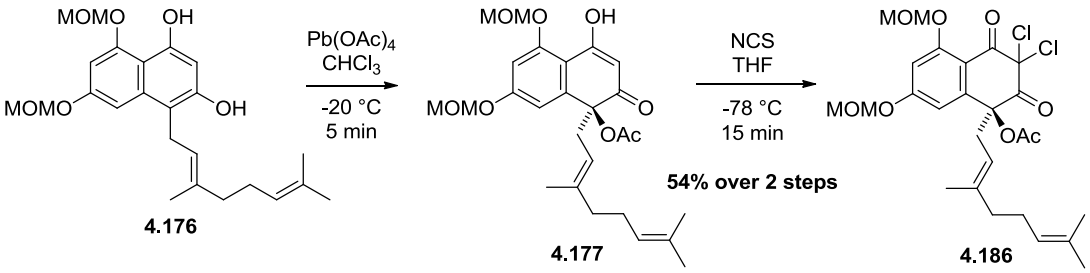
We performed an extensive reaction screening process, altering variables such as solvent (use of the water miscible solvents MeCN and DMF), reaction temperature, addition rates of reagents and the presence or absence of iPr_2NH. However, in all cases other than the aforementioned conditions, negligible quantities of the tertiary alcohol **4.180** were observed. It was hypothesized that the addition of a scavenging reagent for chloride ions may increase the yield of the tertiary alcohol, by limiting the amount of chloride responsible for the formation of the undesired product. Hence, we trialed the reaction using Ag(I) salts such as $AgBF_4$ and $AgNO_3$ as additives; however, these did not alter the outcome and only trichlorination was observed. Discouragingly, we had difficulties reproducing our original successful result (**scheme 4.59**). These results indicated that this reaction would unfortunately not be a practical asset to our synthesis, and that it would still be better to perform this transformation over multiple steps. The difficulty in obtaining the tertiary alcohol **4.180** by this process could be explained by the reaction with chloride being much faster relative to the reaction with H_2O, and was not possible to control.

Trichloride **4.183** could be obtained in reasonable yield and was a stable compound, so it was worth investigating its conversion into tertiary alcohol **4.180**. This transformation could be imagined to be achieved *via* S_N1 substitution of the C-4 chlorine atom with H_2O. This was perhaps unlikely to work in practice; it is uncommon for chloride to act as a leaving group in S_N1 reactions, and formation of a carbocation adjacent to a carbonyl group is generally unfavourable.



Scheme 4.60: Unsuccessful attempts at S_N1 process

Simply heating **4.183** at reflux in H_2O gave no reaction. The use of Ag(I) salts such as $AgBF_4$, AgF and $AgNO_3$ was trialed in order to aid the leaving of chloride; however, heating a mixture of **4.183** in the presence of H_2O and one of these salts would result in either no reaction or decomposition. We promptly decided that the trichloride **4.183** would not be synthetically useful to us, and that it would still be necessary to install the C-4 oxygen atom *via* Wessely oxidation.

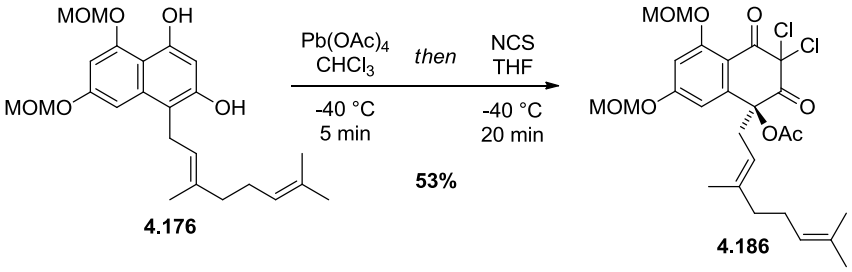


Scheme 4.61: Alternate reaction sequence to yield **4.186**

Alteration of the sequence of operations was of interest to potentially increase the overall yield of our synthesis. We tried performing the dichlorination reaction before the hydrolysis in sequence, which was found to proceed well to yield **4.186**. It was at this point that we found we could achieve more reliable results from the Wessely oxidation procedure if we took the crude material onto the next step without purification by flash chromatography. As we knew that **4.177** was an unstable compound, it was unlikely to be completely stable to chromatography, which could help explain the previous low yields. The chlorination was a sufficiently robust process that it would work reliably using less than pure **4.177**. Already with this simple sequence change we had obtained overall higher yields than previous and increased reaction reliability.

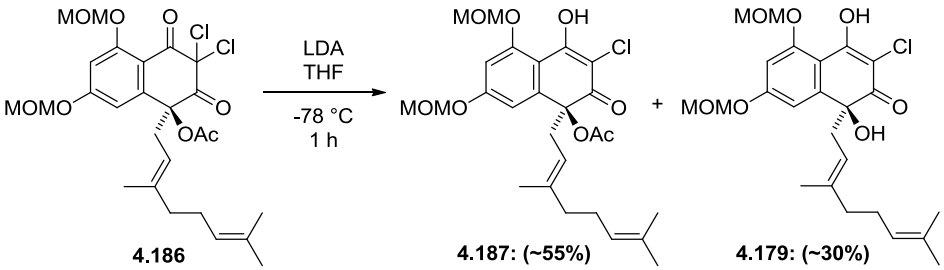
As the chlorination reaction was such a simple and robust procedure, we hypothesized it may be possible to perform the Wessely oxidation and the chlorination in the same pot. Hence,

4.176 was treated with $Pb(OAc)_4$ in $CHCl_3$ and -40 °C, followed by addition of NCS at -40 °C. These conditions resulted in the isolation of the desired product **4.186** in 53% yield. There was no sacrifice in purity by performing the two processes in one pot and purification was no more difficult. This was a pleasing result, as it further shortened our synthetic route and allowed the simplification of the synthesis of **4.186**.



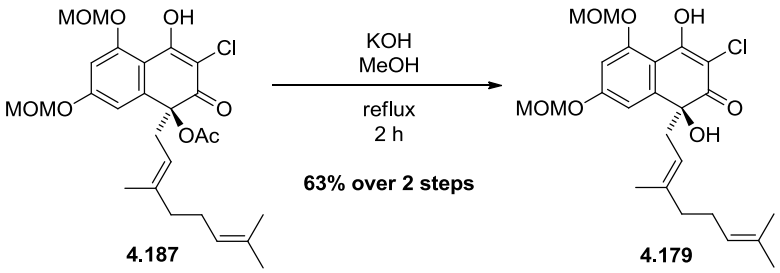
Scheme 4.62: One pot dearomatization/chlorination reaction

While we could now efficiently synthesize the novel intermediate **4.186**, it was still unclear whether it was synthetically useful to us. It was presumably necessary to perform the dechlorination next in sequence before the acetate hydrolysis. This was because, as previously discussed, the 1,3-diketone compounds were found to be highly unstable to hydroxide, whereas the reactions with the enol compounds were more successful. **4.186** was found to be no exception to this. Subjection of **4.186** to our dechlorination conditions using LDA generated a mixture of two products with relatively low R_f. The R_f and NMR data of the higher R_f product was found to match that of the previously isolated tertiary alcohol **4.179**. The lower R_f, more abundant product was determined to be the expected dechlorination product **4.187** by NMR analysis. It was clear that the acetate hydrolysis was occurring to some extent under these reaction conditions, along with the desired dechlorination. Strangely enough, with modification of the reaction time, temperature and amount of LDA added, it was found to be impossible to either drive the acetate hydrolysis to completion, or for it to be avoided entirely. Other than the inconvenience experienced with isolation and characterization, the formation of this mixture of products was not much of a problem. While it was possible to achieve separation between the two products by flash chromatography, albeit with some difficulty due to their similar R_f and high polarity, we generally submitted the mixture to the next step.



Scheme 4.63: Dechlorination and unexpected acetate cleavage

While the hydrolysis reaction of **4.187** was infrequently performed with a pure sample, we generally used the mixture of products obtained from the reaction with LDA. Regardless, the final outcome of the reaction was the same. As discussed, we had difficulties performing this reaction on the non-chlorinated system due to instability of the starting material and the MOM deprotection side reaction (**scheme 4.52**). The α-chloro enol compounds were found to be stable, and we were able to obtain higher yields for the acetate hydrolysis on this system. However, the MOM deprotection side reaction was still a problem here, and while hydrolysis of this system was more reproducible than the non-chlorinated system, it still was not completely reliable and yields fluctuated.

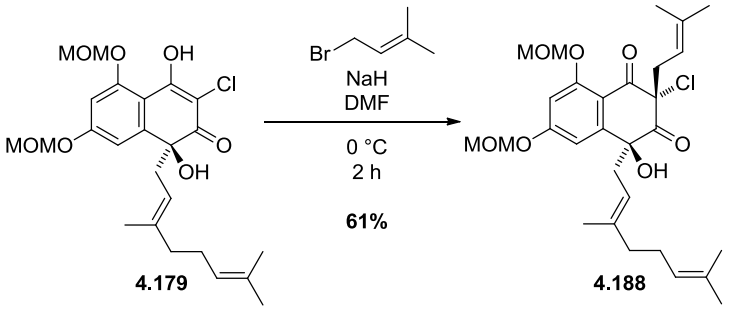


Scheme 4.64: Acetate hydrolysis

We were pleased with these modifications to our synthetic sequence, which yielded the advanced intermediate **4.179** in three steps from geranylated THN **4.176** in 33% overall yield. This was a significant improvement over our old method, which synthesized the same intermediate in four steps in 24% overall yield. This approach also involved the use of more reliable reactions and avoided the isolation of unstable intermediates.

4.2.8 Total Synthesis of Naphthomevalin and A80915G

With access to good quantities of **4.179** finally, we applied our previously established prenylation conditions using prenyl bromide and NaH in DMF to **4.179**, yielding the desired α-ketol rearrangement precursor **4.188**. By keeping the reaction temperature at 0 °C, we were able to achieve a good diastereoselectivity of 10 : 1 of the desired *trans* product.

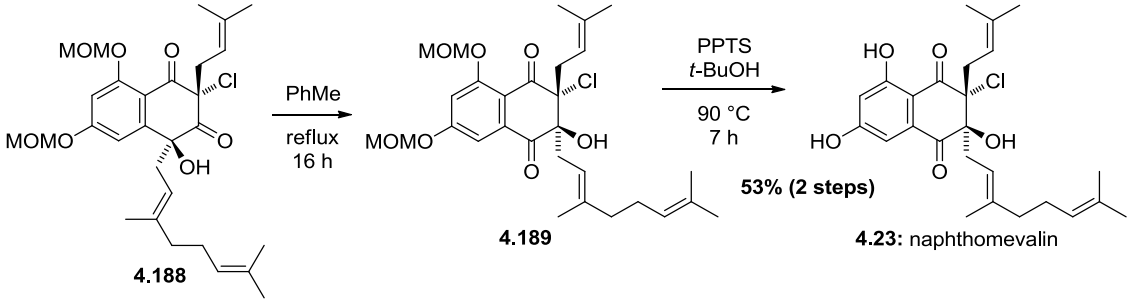


Scheme 4.65: Diastereoselective prenylation

With the successful synthesis of **4.188**, only the α-ketol rearrangement and the final deprotection step remained to complete the total synthesis of naphthomevalin (**4.23**). As the presence or absence of protecting groups was not expected to have an impact on the success of the α-ketol rearrangement, these final two steps could potentially be performed in either order. Thus, we were prepared to test both options to see which would yield more favourable results. Subjecting **4.188** to our standard α-ketol rearrangement conditions of PhMe reflux successfully yielded the desired di-*O*-MOM-naphthomevalin **4.189**. This reaction was not as clean as the dimethyl protected system, and chromatography needed to be performed to remove minor impurities.

With **4.189** in hand we could now start screening MOM deprotection conditions. Standard conditions for MOM deprotection such as aqueous HCl in MeOH or CF_3CO_2H in CH_2Cl_2 were found to be too harsh for our substrate, and resulted in some additional unwanted side reactions at the alkenes. We then moved on to the conditions employed by Snyder *et al*., in their successful synthesis of napyradiomycin A1 (**4.30**).[40] Hence, **4.189** was treated with PPTS in *t*-BuOH and the mixture was heated to 90 °C. TLC analysis showed clean formation of a higher R_f product with consumption of the starting material after one hour of heating, followed by formation of a new product with similar R_f to the starting material with consumption of the first product after around 7 hours. Isolation and NMR analysis of this new product indicated that complete deprotection was successful, with no other unwanted side

reactions occurring to any major extent. We had therefore synthesized naphthomevalin (**4.23**).

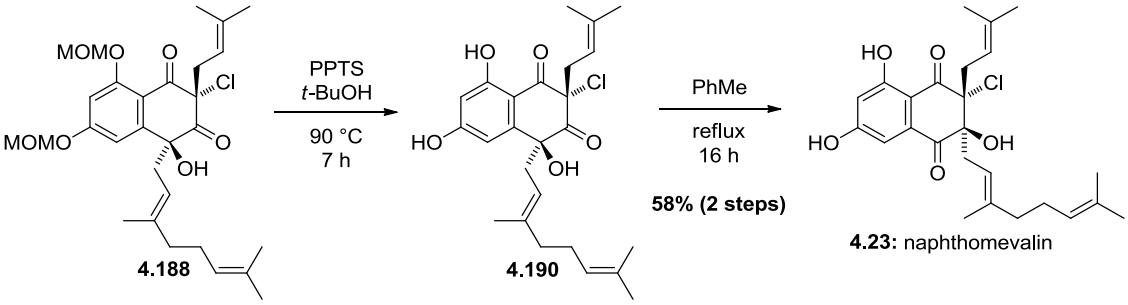


Scheme 4.66: α-Ketol rearrangement followed by deprotection

While we were relieved at finally completing the total synthesis of naphthomevalin (**4.23**), we felt that the yield and purity of the obtained sample could be improved, so we decided to continue optimization of the final two steps. Perhaps unsurprisingly, subjection of **4.189** to Snyder's MOM deprotection conditions of PPTS in *t*-BuOH at 90 °C resulted in some α-ketol rearrangement occurring, along with successful deprotection. Because elevated temperatures were necessary for deprotection to occur using PPTS, the rearrangement side reaction could not be avoided. This was not a major concern, but it did mean that a pure sample of **4.190** could not be isolated in pure form and characterized, as **4.188** and **4.190** both had identical R_f and could not be separated by conventional flash chromatography. It would have been ideal for both the rearrangement and deprotection reactions to occur in the same pot, hence removing a synthetic operation from our sequence. However, α-ketol rearrangement of **4.190** would reach equilibrium at 50% conversion in the alcoholic *t*-BuOH required for the deprotection reaction. Changing the solvent to the higher boiling point *n*-BuOH, and increasing the reaction temperature did not change the result. Further determined to execute the two transformations in one pot, we tried adding an excess amount of PhMe to the reaction mixture after the deprotection had been completed, followed by heating the mixture at reflux overnight. These conditions also failed to drive the α-ketol rearrangement reaction to completion, and also had a negative effect on product purity.

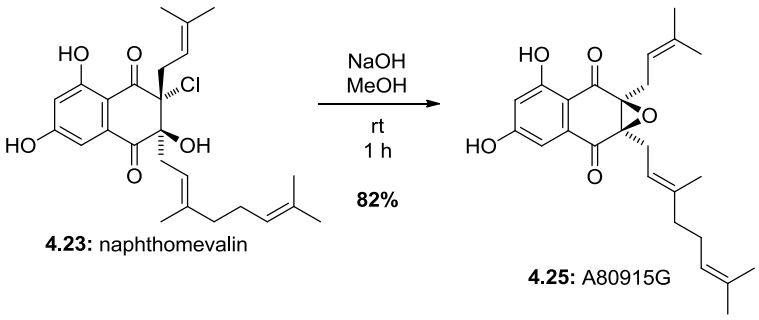
After the disappointing results yielded from attempting the α-ketol rearrangement and deprotection in one pot, we were forced to trial more step-wise procedures to hopefully obtain a more satisfactory result. We attempted removing the *t*-BuOH by rotary evaporation following completion of the deprotection reaction, followed by dissolving the residue in PhMe and heating the mixture at reflux overnight. However, this approach resulted in a

similar outcome as the previously trialed conditions. We tried this again, but additionally performed an aqueous workup after the deprotection had reached completion, hence removing the excess PPTS.



Scheme 4.67: Deprotection followed by α-ketol rearrangement

Performing a workup in between greatly improved the conversion of the α-ketol rearrangement reaction, as well as the purity of the isolated product, indicating the presence of PPTS was having a negative effect. Using this method, we could consistently obtain pure quantities of naphthomevalin (**4.23**) in 58% yield over the two steps (**scheme 4.67**). Following the procedure of Zeeck *et al*., treatment of naphthomevalin with NaOH in MeOH then yielded the epoxide natural product A80915G (**4.25**).[13] This represented the second reported total synthesis of this natural product,[38] but its first biomimetic synthesis.



Scheme 4.68: Synthesis of A80915G by S_N2 epoxidation of naphthomevalin

For comparison purposes, it was unfortunate that the original paper reporting the isolation of A80915G reported no NMR data for the natural product.[16] We were able to compare the NMR data of our synthetic naphthomevalin to the reported literature data of natural naphthomevalin, as well as compare the data for our synthetic A80915G with the limited data of the synthetic sample reported in the same paper (**tables 4.8-4.11**).[13] Zeeck *et al.* only reported selected NMR signals for these compounds, but the spectra of our synthetic samples

agreed with this limited data. In addition, we also compared our spectra to the reported data of the related napyradiomycins SF2415B1 (**4.24**) and SF2415B2 (**4.27**), showing good agreement (**tables 4.8-4.11**).[15]

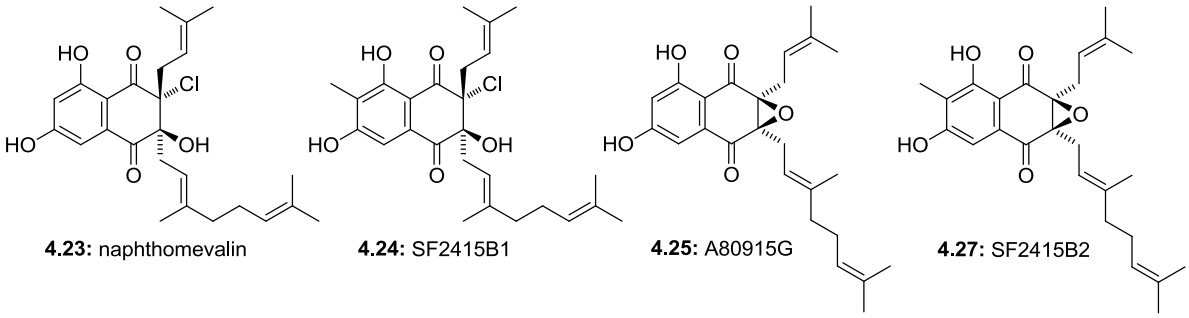


Table 4.8: ^{1}H NMR comparison of natural naphthomevalin (**4.23**), natural SF2415B1 (**4.24**) and synthetic naphthomevalin (**4.23**) in $CDCl_3$

Assignment	Natural naphthomevalin[13]	Natural SF2415B1[15]	Our sample
3-OH	4.15 s	4.14 s	4.18 s
5	7.03 s	7.04 s	7.06 d *J* = 2.0
6-OH	7.16 s	6.66 s	6.81 s
7	6.69 s		6.72 d *J* = 2.0
8-OH	11.94 s	12.28 s	11.96 s
11 a		2.47 dd *J* = 8.0, 14.5	2.51 *J* = 8.0, 14.5
11 b		3.00 dd *J* = 8.0, 14.5	2.99 dd *J* = 8.0, 14.5
12		4.93 t *J* = 8.0	4.93 *J* = 8.0
14		1.58 s	1.59 s
15		1.28 s	1.29 s
16 a		2.27 dd *J* = 8.0, 14.5	2.31 dd *J* = 8.0, 14.5
16 b		2.96 dd *J* = 8.0, 14.5	2.97 dd *J* = 8.0, 14.5
17		4.82 t *J* = 8.0	4.83 *J* = 8.0
19		1.89 m	1.90 m
20		1.95 m	1.96 m
21		5.02 t *J* = 8.0	5.02 *J* = 8.0
23		1.70 s	1.70 s
24		1.57 s	1.56 s
25		1.30 s	1.30 s
26		2.23 s	N/A

Table 4.9: ^{13}C NMR comparison of natural naphthomevalin (**4.23**), natural SF2415B1 (**4.24**) and synthetic naphthomevalin (**4.23**) in $CDCl_3$

Assignment	Natural naphthomevalin[13]	Natural SF2415B1[15]	Our sample
1	195.6	195.5	195.4
2	82.3	83.2	83.0
3	84.4	84.3	84.5
4	196.6	196.8	196.6
5	134.3	130.7	134.3

6	107.3	106.3	107.3
7	163.6	161.4	163.4
8	109.2	119.6	109.2
9	164.7	162.5	164.8
10	110.5	109.7	110.5
11		38.4	38.3
12		116.4	116.5
13		137.9	138.2
14		25.7	25.8
15		17.7	17.7
16		37.3	37.3
17		115.4	115.4
18		141.3	141.5
19		39.7	39.8
20		26.3	26.3
21		123.8	123.8
22		131.7	131.8
23		25.6	25.7
24		17.6	17.7
25		16.1	16.1
26		8.3	N/A

Table 4.10: ^{1}H NMR comparison of synthetic A80915G (**4.25**), natural SF2415B2 (**4.27**) and synthetic A80915G (**4.25**) in $CDCl_3$.

Assignment	**Synthetic A80915G[13]**	**Natural SF2415B2[15]**	**Our sample**
5	7.04 s	7.17 s	7.06 d *J* = 2.0
6-OH	6.28 s	7.55 s	6.36 s
7	6.63 s		6.64 d *J* = 2.0
8-OH	11.82 s	12.15 s	11.83 s
11 a		2.41 dd *J* = 7.0, 15.5	2.42 dd *J* = 7.0, 15.5
11 b		3.26 dd *J* = 7.0, 15.5	3.24 dd *J* = 7.0, 15.5
12		5.15 t *J* = 7.0	5.15 t *J* = 7.0
14		1.71 s	1.72 s
15		1.73 s	1.73 s
16 a		2.53 dd *J* = 7.0, 15.5	2.55 dd *J* = 7.0, 15.5
16 b		3.12 dd *J* = 7.0, 15.5	3.10 dd *J* = 7.0, 15.5
17		5.15 t *J* = 7.0	5.15 t *J* = 7.0
19		2.00 m	2.00 m
20		2.05 m	2.06 m
21		5.05 t *J* = 8.0	5.05 t *J* = 7.0
23		1.63 s	1.64 s
24		1.56 s	1.57 s
25		1.73 s	1.72 s
26		2.15	N/A

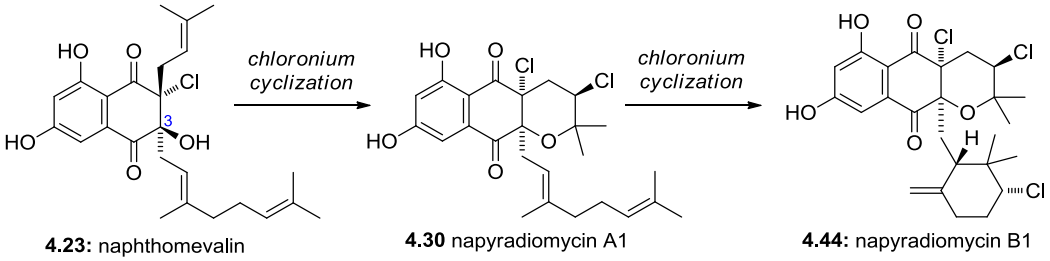
Table 4.11: ^{13}C NMR comparison of synthetic A80915G (**4.25**), natural SF2415B2 (**4.27**) and synthetic A80915G (**4.25**) in $CDCl_3$.

Assignment	Synthetic A80915G[13]	Natural SF2415B2[15]	Our sample
1	191.2	192.0	191.5
2	67.3	67.3	67.4
3	67.6	67.7	67.7
4	195.2	194.9	195.4
5	134.4	130.4	134.3
6	108.0	107.4	108.8
7	163.0	161.4	162.9
8	108.8	119.0	108.8
9	164.6	162.5	164.5
10	109.3	108.4	109.3
11		25.5	25.5
12		116.9	116.9
13		135.1	135.5
14		26.0	25.3
15		18.4	18.2
16		25.7	25.7
17		116.6	116.7
18		138.5	138.9
19		39.5	39.7
20		26.7	26.7
21		123.8	124.0
22		131.2	131.6
23		25.8	25.8
24		17.9	17.7
25		16.8	16.6
26		8.3	N/A

4.2.9 Total Synthesis of (+)-Napyradiomycin A1

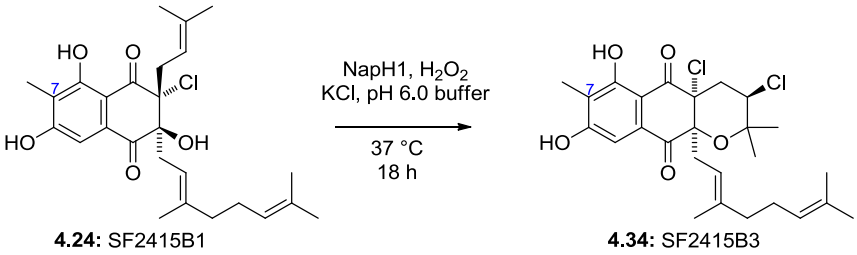
Now that we finally had access to synthetic naphthomevalin, we were of course interested in its biomimetic transformation into some of the more complex, polycyclic napyradiomycin natural products. The next most achievable target was napyradiomycin A1 (**4.30**), which theoretically could be formed by chloronium cyclization of the prenyl group of naphthomevalin with the C-3 alcohol. Similar reactions to this had not been well documented in the literature; such a transformation would theoretically be difficult to perform regioselectively, chemoselectively and stereoselectively with conventional reagents. With low expectations, we attempted reactions synthetically using NCS or SO_2Cl_2. However, we were only able to observe complex mixtures.

The biosynthesis of these natural products from naphthomevalin is known to be catalyzed by VHPO enzymes, which is how nature is able to achieve the necessary selectivity.[25] In general, attempting to apply biomimetic synthesis to reactions that require highly specific enzymes in nature is not recommended. An alternative option of consideration was the possibility of synthesizing napyradiomycin A1 (**4.30**) from our synthetic naphthomevalin (**4.23**) *via* a chemoenzymatic process. This, of course, would require access to the specific enzyme.



Scheme 4.69: Theoretical conversion of naphthomevalin into napyradiomycin A1 and napyradiomycin B1 *via* chloronium cyclizations

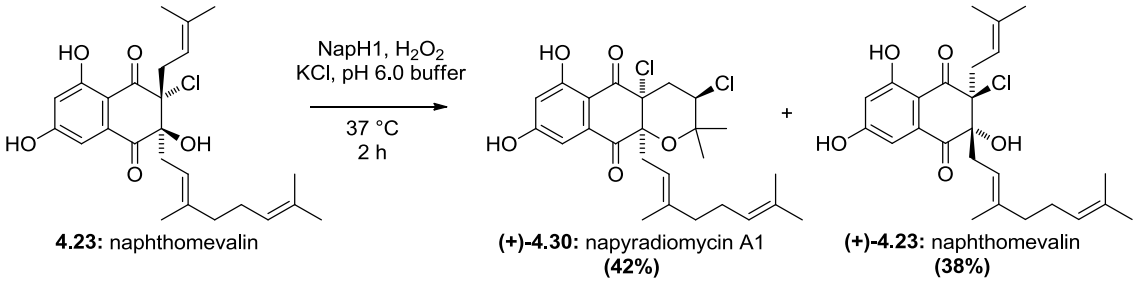
Moore *et al*. had previously published extensive work on these VHPO enzymes, including those responsible for the biosynthesis of napyradiomycins.[11,60] Relevant to our interests, they reported the chemoenzymatic transformation of the natural product SF2415B1 (**4.24**) into SF241B3 (**4.34**) using the NapH1 VHPO enzyme they isolated from Streptomyces sp. CNQ-525 (**scheme 4.70**).[25] This is an analogous reaction to the one we were interested in, as SF2415B1 (**4.24**) and SF2415B3 (**4.34**) are related to naphthomevalin (**4.23**) and napyradiomycin A1 (**4.30**) respectively, differing only in the substituent at C-7.



Scheme 4.70: Literature chemoenzymatic synthesis of SF241B1 from SF241B3[25]

After the Moore research group agreed to collaborate with us, we sent them a sample of our synthetic racemic naphthomevalin. The following work was performed by Dr. Stefan

Diethelm under the supervision of Prof. Bradley Moore; hence, we are unable to comment on the specifics of the isolation of the enzyme, or the procedure of the chemoenzymatic reaction. Stefan subjected our racemic naphthomevalin to their already established conditions of the NapH1 enzyme with H_2O_2 and KCl in pH 6.0 buffer at 37 °C for 18 hours. We were all delighted to find this procedure yielded a mixture of (+)-napyradiomycin A1 (**4.30**) in 42% yield and (+)-naphthomevalin (**4.23**) in 38% yield. This resolution was the result of the chiral environment of the enzyme allowing reaction with only one enantiomer. This reaction was the first reported application of a VHPO enzyme to induce kinetic resolution.



Scheme 4.71: Chemoenzymatic conversion of naphthomevalin to napyradiomycin A1

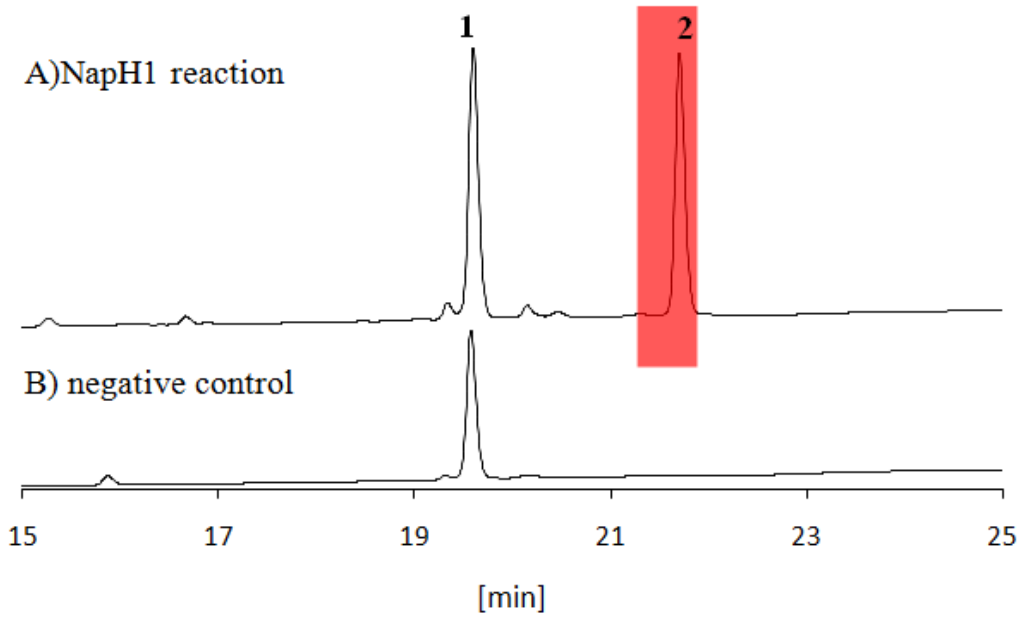


Figure 4.3: HPLC analysis (UV at 254 nm) of the reaction of **4.23** with NapH1 (analytical scale). A) NapH1 reaction after two hours; product peak highlighted in red. B) negative control: no enzyme added.

This was a very pleasing result, and was the first reported synthesis of napyradiomycin A1 (**4.30**) *via* a chemoenzymatic process. This reaction further demonstrates the exquisite selectivity of the NapH1 enzyme, as it adds Cl^+ to one face (the *Re* face) of one alkene (the prenyl group) of one enantiomer ((-)-naphthomevalin) in the cation-π cyclization to form (+)-napyradiomycin A1. It was interesting to discover that the same NapH1 enzyme would react with both SF2415B1 (**4.24**) and naphthomevalin (**4.23**) in the same way. The NMR data of the synthetically obtained (-)-napyradiomycin A1 (**4.30**) was compared to the literature data for natural napyradiomycin A1,[12] as well as the data of the synthetic sample reported by Snyder,[40] and showed good agreement with both (**Tables 4.12 and 4.13**).

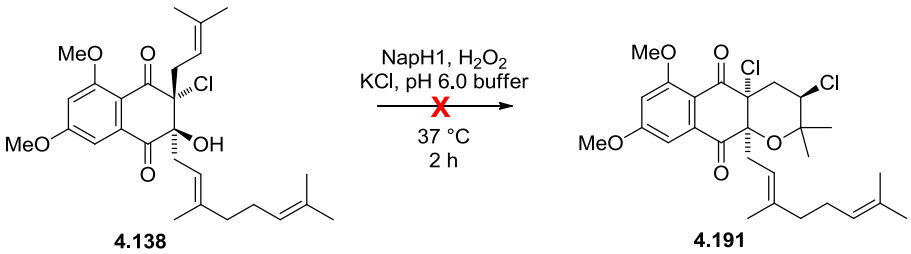
Table 4.12: ^{1}H NMR comparison of natural and synthetic napyradiomycin A1 (**4.30**) in $CDCl_3$

Assignment	Natural Napyradiomycin A1[12]	Synthetic (Snyder)[40]	Our sample
8-OH	11.84 bs	11.83 s	11.83 bs
5	7.22 d *J* = 2.4	7.16 d *J* = 2.5	7.20 d *J* = 2.5
7	6.73 d *J* = 2.4	6.70 d *J* = 2.5	6.73 d *J* = 2.4
6-OH	3.60 bs	5.99 bs	n.d.
21	4.89 bs	4.90 m	4.89 bs
17	4.70 t *J* = 8.0	4.71 t *J* = 8.2	4.72 t *J* = 8.2
12	4.42 dd *J* = 11.2, 4.8	4.42 dd *J* = 11.4, 4.6	4.42 dd *J* = 11.6, 4.4
3	2.70 d *J* = 8.0	2.70 d *J* = 8.4	2.70 d *J* = 8.3
11	2.48 dd *J* = 14.0, 4.8	2.48 dd *J* = 14.4, 4.8	2.48 dd *J* = 14.2, 4.3
11	2.41 dd *J* = 14.0, 11.2	2.41 dd *J* =14.4, 11.2	2.42 dd *J* = 14.2, 11.2
23	1.60 s	1.63 s	1.62 s
19 + 20	1.60 m 4H	1.62 – 1.55 m 4 H	1.64-1.57 m
24	1.52 s	1.50 s	1.51 s
14 or 15	1.50 s	1.50 s	1.50 s
25	1.31 s	1.32 s	1.32 s
14 or 15	1.18 s	1.18 s	1.18 s

Table 4.13: ^{13}C NMR comparison of natural and synthetic napyradiomycin A1 (**4.30**) in $CDCl_3$.

Assignment	Natural Napyradiomycin A1[12]	Synthetic (Snyder)[40]	Our sample
4	196.2	195.7	197.1
1	193.7	193.9	193.8
8	164.8	164.7	164.9
6	163.9	163.1	164.1
18	142.8	142.8	143.1
10	135.3	135.4	135.2
22	131.8	131.7	131.9

21	123.7	123.7	123.8
17	114.9	114.8	114.8
9	110.2	110.4 (HMBC)	110.2
7	109.6	109.4	109.9
5	107.8	107.6	108.2
3	83.6	83.5	83.7
2	79.0	79.0	79.0
13	78.8	78.7	79.0
12	58.8	58.8	58.8
11	42.8	42.7	42.8
16	41.3	41.2	41.5
19	39.8	39.7	39.8
14 or 15	28.8	28.7	28.8
20	26.0	25.9	26.0
23	25.6	25.6	25.8
14 or 15	22.3	22.3	22.4
24	17.5	17.5	17.7
25	16.5	16.4	16.6

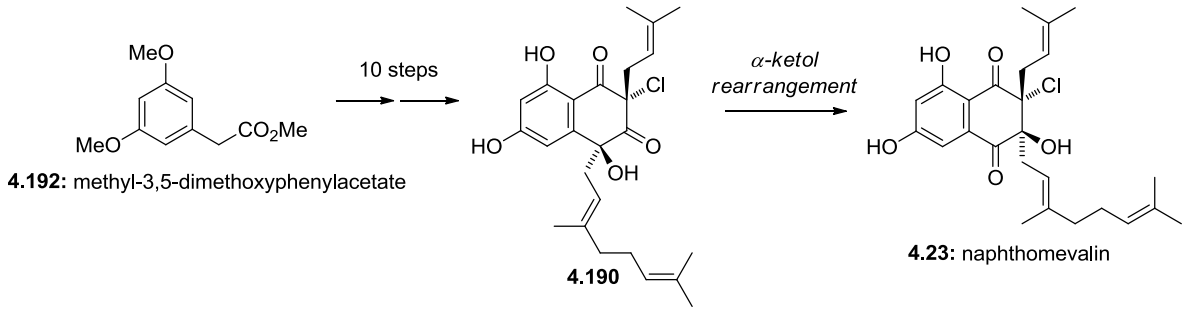


Scheme 4.72: Attempted chemoenzymatic conversion of di-*O*-methyl naphthomevalin to di-*O*-methyl napyradiomycin A1

The chemoenzymatic reaction was additionally trialed using our previously synthesized di-*O*-methyl naphthomevalin (**4.138**), but no reaction was observed (**scheme 4.72**). This failed reaction further demonstrated the substrate specificity of the enzyme, and that the free phenols are necessary.

4.3 Conclusions

The first total synthesis of the napyradiomycin natural product naphthomevalin (**4.23**) was achieved in 11 steps from methyl-3,5-dimethoxyphenylacetate (**4.192**) (1.4% overall yield). Inspired by our proposed biosynthetic pathway, an α-ketol rearrangement involving the 1,2-shift of the geranyl substituent was the key biomimetic synthetic step allowing the synthesis of the naphthoquinone skeleton common to all napyradiomycins by rearrangement of the more synthetically accessible 1,3-diketone structure. Thermal conditions were found to be optimal to induce this transformation; while heating at reflux in PhMe gave the best results, rearrangement was observed at least to some extent at lower temperatures and in different solvents.



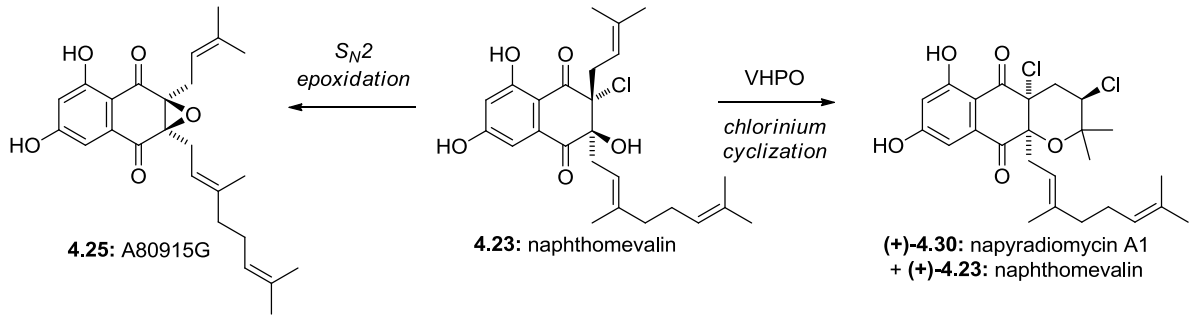
Scheme 4.73: Summary of the biomimetic total synthesis of naphthomevalin

The substrate scope for the α-ketol rearrangement was found to be broad, and successful reactions were observed with many different analogues. However, substrates which were preferentially sp^2 hybridized at the C-2 position were found to resist rearrangement to the naphthoquinone skeleton. The success of this α-ketol rearrangement reaction and the fact that it occurs under mild thermal conditions strongly indicates that a similar process is involved in the biosynthesis of naphthomevalin (**4.23**), and hence we propose it is shared in the biosynthesis of all napyradiomycin natural products. Furthermore, we believe our entire synthetic approach is biomimetic, with geranylation, oxidative dearomatization, chlorination, prenylation and α-ketol rearrangement events all occurring in the same order as our biosynthetic hypothesis (**scheme 4.19**).

Some difficulties were experienced during synthesis, namely with the identification of the optimal phenol protecting groups with which to carry out the synthesis. Di-*O*-methyl naphthomevalin (**4.138**) could be synthesized efficiently in six steps from methyl-3,5-

dimethoxyphenylacetate (**4.192**) (7% overall yield), but final cleavage of the methyl ether protecting groups was found to be impossible. We eventually discovered the use of methoxy methyl ether protecting groups allowed the final deprotection reaction to suceed, and these protecting groups were found to be compatible with each step in our synthesis (albeit with some difficulties).

The deprotected versions of many of the synthetic intermediates in this project may be actual intermediates involved in napyradiomycin biosynthesis and hence could be of use to gain biosynthetic understanding. Possible experiments could include the analysis of HPLC traces of the organic extracts of relevant *Streptomyces* bacteria to identify compound matches, isotopic labeling studies, and further chemoenzymatic studies.



Scheme 4.74: Summary of the total synthesis of A80915G and (+)-napyradiomycin A1

Naphthomevalin (**4.23**) was converted into A80915G (**4.25**) *via* an S_N2 epoxidation reaction, representing the first biomimetic synthesis of this natural product. Racemic naphthomevalin was converted into (+)-napyradiomycin A1 (**4.30**) and (+)-naphthomevalin (**4.23**), and we believe that this combined biomimetic and chemoenzymatic synthetic approach will enable the synthesis of several more members of the napyradiomycin family. In addition, analogues may be synthesized as lead compounds as antibacterial and antitumor agents.

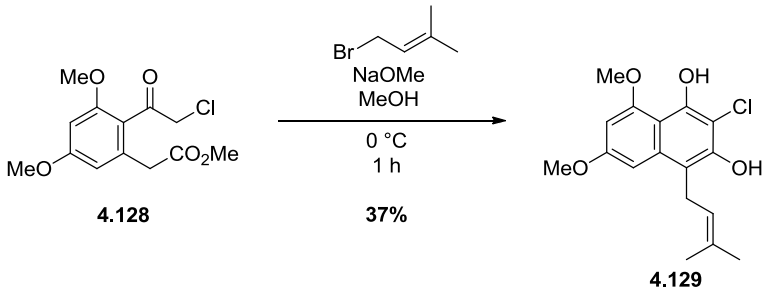
4.4 Experimentals

4.4.1 General Methods

All chemicals used were purchased from commercial suppliers and used as received, except for $Pb(OAc)_4$ which was recrystallized from glacial acetic acid prior to use. 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 Merck aluminium sheets silica gel 60 F255. Visualization was aided by viewing under a UV lamp and staining with ceric ammonium molybdate stain followed by heating. All R_f values were rounded to the nearest 0.01. Flash chromatography was performed using Davasil (40-63 micron) grade silica gel. Melting points were recorded on a Stanford Research Systems Digimelt digital melting point apparatus and are uncorrected. Infrared spectra were recorded using a Perkin Elmer Spectrum BX FT-IR system spectrometer as the neat compounds. High field NMR was recorded using a Varian Inova-6000 spectrometer (^1H at 600 MHz, ^{13}C at 150 MHz). Solvents used for spectra were chloroform unless otherwise specified. ^1H 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 chloroform (δ 77.0). Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet and (m) multiplet. All J values were rounded to the nearest 0.1 Hz. High resolution EI mass spectra were recorded on an Agilent-6230 TOF LC/MS spectrometer.

4.4.2 Experimental Procedures

2-chloro-6,8-dimethoxy-4-(3-methylbut-2-en-1-yl)naphthalene-1,3-diol (4.129)



To a solution of **4.128** (6.76 g, 23.6 mmol) in MeOH (200 mL), NaOMe (3.82 g, 70.8 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 1 h before prenyl bromide (4.08 mL, 35.4 mmol) was added. The reaction mixture was stirred at 0 °C for a further 30 min. The mixture was diluted with H_2O (200 mL), quenched with 1 M HCl (100 mL) and extracted with EtOAc (3 x 150 mL). The combined organics were washed with brine (300 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Trituration of the crude residue with cold MeOH yielded pure 2-chloro-6,8-dimethoxy-4-(3-methylbut-2-en-1-yl)naphthalene-1,3-diol (**4.129**) (2.80g, 37%) as an orange solid.

R_f = 0.54 (petrol/EtOAc, 2:1)

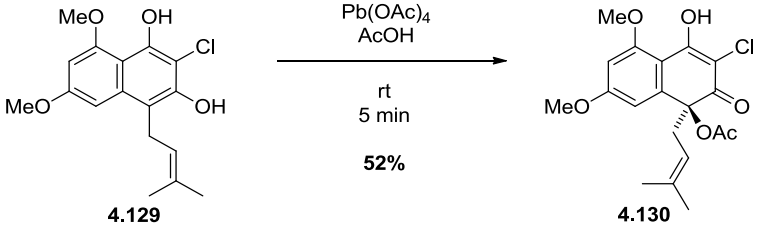
Mp = 175 – 180 °C

IR (neat): 3467, 3301, 2931, 1622, 1594, 1378, 1318, 1257, 1149, 1051, 938, 918, 720 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1H), 6.73 (d, *J* = 2.1 Hz, 1H), 6.37 (d, *J* = 2.1 Hz, 1H), 5.89 (s, 1H), 5.17 (t, *J* = 6.7 Hz, 1H), 4.02 (s, 3H), 3.88 (s, 3H), 3.64 (d, *J* = 6.7 Hz, 2H), 1.88 (s, 3H), 1.70 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 157.2, 149.0, 148.0, 134.6, 131.8, 122.9, 110.9, 106.3, 103.6, 96.1, 96.0, 56.3, 55.3, 25.7, 25.0, 18.0.

3-chloro-4-hydroxy-5,7-dimethoxy-1-(3-methylbut-2-en-1-yl)-2-oxo-1,2-dihydronaphthalen-1-yl acetate (4.130)



4.129 **4.130**

To a solution of **4.129** (2.00 g, 6.20 mmol) in AcOH (75 mL), $Pb(OAc)_4$ (2.88 g, 6.50 mmol) was added at rt. The reaction mixture was stirred at rt for 5 min. The mixture was quenched with *sat*. $NaHCO_3$ solution (150 mL) and extracted with EtOAc (3 x 100 mL). The combined organics were washed sequentially with *sat*. $NaHCO_3$ solution (2 x 200 mL), H_2O (200 mL) and brine (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 2:1 as eluent) to give 3-chloro-4-hydroxy-5,7-dimethoxy-1-(3-methylbut-2-en-1-yl)-2-oxo-1,2-dihydronaphthalen-1-yl acetate (**4.130**) (1.24 g, 52%) as a yellow solid.

R_f = 0.08 (petrol/EtOAc, 2:1)

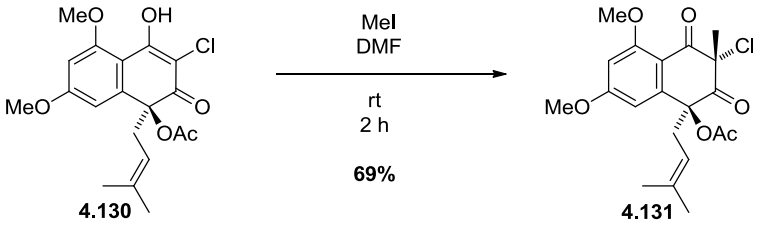
Mp = 197 – 201 °C

IR (neat): 3190, 2967, 1725, 1661, 1620, 1598, 1361, 1337, 1243 1228, 1207,1023, 824, 760 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.49 (s, 1H), 6.60 (d, *J* = 2.3 Hz, 1H), 6.49 (d, *J* = 2.3 Hz, 1H), 4.83 (t, *J* = 7.8 Hz, 1H), 4.05 (s, 3H), 3.85 (s, 3H), 2.69 (dd, *J* = 13.6, 8.4 Hz, 1H), 2.56 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.13 (s, 3H), 1.61 (s, 3H), 1.31 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 198.0, 186.3, 169.5, 164.8, 162.0, 143.5, 139.0, 114.5, 113.5, 101.8, 98.3, 82.0, 56.3, 55.6, 40.6, 25.9, 25.7, 20.6, 17.9.

3-chloro-5,7-dimethoxy-3-methyl-1-(3-methylbut-2-en-1-yl)-2,4-dioxo-1,2,3,4-tetrahydronaphthalen-1-yl acetate (4.131)



To a solution of **4.130** (213 mg, 0.559 mmol) in DMF (6 mL), NaH (20 mg, 0.84 mmol) was added at rt. The mixture was stirred at rt for 30 min before MeI (0.17 mL, 2.8 mmol) was added at rt. The reaction mixture was stirred at rt for a further 2h. The mixture was quenched with 1 M HCl (10 mL), and extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (3 x 20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 4:1 as eluent) to give 3-chloro-5,7-dimethoxy-3-methyl-1-(3-methylbut-2-en-1-yl)-2,4-dioxo-1,2,3,4-tetrahydronaphthalen-1-yl acetate (**4.131**) (153 mg, 69%) as a yellow oil.

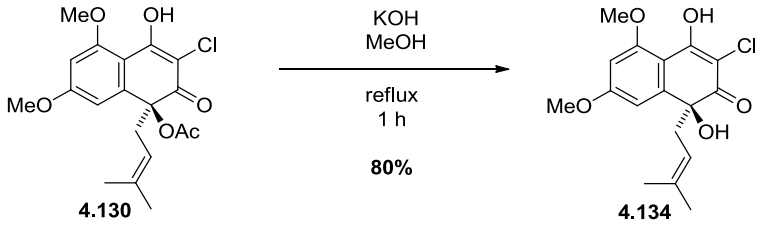
R_f = 0.20 (petrol/EtOAc, 2:1)

IR (neat): 2939, 1737, 1716, 1687, 1598, 1572, 1456, 1337, 1251, 1152, 1062, 968, 827 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.51 (d, *J* = 2.2 Hz, 1H), 6.50 (d, *J* = 2.2 Hz, 1H), 4.94 (t, *J* = 7.7 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 2.95 (dd, *J* = 14.1, 8.2 Hz, 1H), 2.70 (dd, *J* = 14.2, 7.3 Hz, 1H), 2.10 (s, 3H), 1.88 (s, 3H), 1.64 (s, 3H), 1.41 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 198.0, 186.4, 169.5, 164.8, 162.0, 143.5, 139.0, 114.5, 113.5, 101.8, 98.3, 82.0, 71.5, 56.3, 55.56 (s), 40.6, 25.9, 25.7, 20.6, 17.9.

3-chloro-1,4-dihydroxy-5,7-dimethoxy-1-(3-methylbut-2-en-1-yl)naphthalen-2(1H)-one (4.134)



To a solution of **4.130** (1.22 g, 32.0 mmol) in MeOH (30 mL), KOH (719 mg, 12.8 mmol) was added at rt. The reaction mixture was heated at reflux for 1 h. The mixture was cooled, quenched with 1 M HCl (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 2:1 as eluent) to give 3-chloro-1,4-dihydroxy-5,7-dimethoxy-1-(3-methylbut-2-en-1-yl)naphthalen-2(1H)-one (**4.134**) (1.08 g, 80%) as a yellow solid.

R_f = 0.17 (petrol/EtOAc, 2:1)

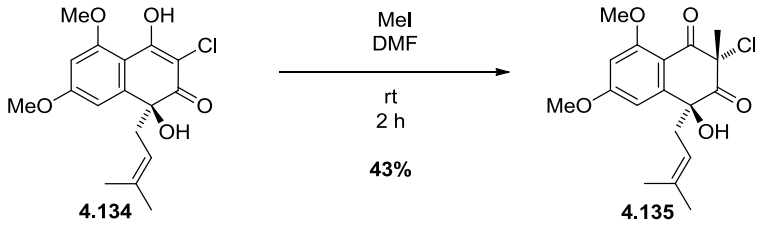
Mp = 123 – 126 °C

IR (neat): 3449, 3184, 2928, 1618, 1588, 1552, 1360, 1332, 1274, 1164, 1008, 838, 702 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ10.56 (s, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 6.50 (d, *J* = 2.4 Hz, 1H), 4.94 (t, *J* = 7.9 Hz, 1H), 4.06 (s, 3H), 3.90 (s, 3H), 2.47 (dd, *J* = 13.7, 7.5 Hz, 1H), 2.40 (dd, *J* = 13.7, 7.5 Hz, 1H), 1.67 (s, 3H), 1.36 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 194.3, 164.1, 162.8, 157.6, 147.3, 137.7, 116.1, 106.0, 104.9, 98.8, 80.1, 57.1, 55.9, 46.3, 25.9, 17.6.

2-chloro-4-hydroxy-6,8-dimethoxy-2-methyl-4-(3-methylbut-2-en-1-yl)naphthalene-1,3(2H,4H)-dione (4.135)



To a solution of **4.134** (158 mg, 46.6 mmol) in DMF (4 mL), NaH (60% in mineral oil, 22 mg, 0.56 mmol) was added at rt. The mixture was stirred at rt for 10 min before MeI (0.05 mL, 0.8 mmol) was added at rt. The reaction mixture was stirred at rt for a further 2 h. The mixture was quenched with 1M HCl (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (3 x 20 mL) dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 4:1 as eluent) to give 2-chloro-4-hydroxy-6,8-dimethoxy-2-methyl-4-(3-methylbut-2-en-1-yl)naphthalene-1,3(2H,4H)-dione (**4.135**) (71 mg, 43%) as a yellow oil.

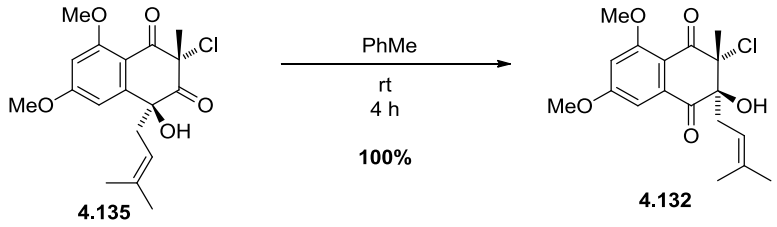
R_f= 0.28 (petrol/EtOAc, 2:1)

IR (neat):3477, 2934, 1736, 1694, 1597, 1572, 1457, 1310, 1200, 1162, 1141, 1053, 961, 730 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (d, *J* = 1.8 Hz, 1H), 6.47 (d, *J* = 1.8 Hz, 1H), 5.03 (t, *J* = 7.2 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 2.67 (dd, *J* = 14.8, 8.4 Hz, 1H), 2.57 (dd, *J* = 14.8, 6.0 Hz, 1H), 1.79 (s, 3H), 1.69 (s, 3H), 1.48 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 201.5, 188.2, 165.7, 161.5, 146.1, 138.1, 115.8, 111.5, 101.5, 99.0, 79.8, 66.7, 56.2, 55.8, 43.3, 25.9, 25.2, 18.2.

3-chloro-2-hydroxy-5,7-dimethoxy-3-methyl-2-(3-methylbut-2-en-1-yl)-2,3-dihydronaphthalene-1,4-dione (4.132)



A solution of **4.135** (29 mg, 0.082 mmol) in PhMe (1 mL) was heated at reflux for 4 h. The solution was cooled and concentrated *in vacuo* to yield 3-chloro-2-hydroxy-5,7-dimethoxy-3-methyl-2-(3-methylbut-2-en-1-yl)-2,3-dihydronaphthalene-1,4-dione (**4.132**) (29 mg, 100%) as a white solid.

R_f = 0.21 (petrol/EtOAc, 2:1)

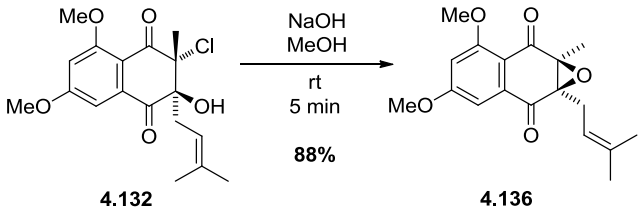
Mp = 105 – 107 °C

IR (neat): 3424, 2927, 1707, 1685, 1592, 1563, 1455, 1319, 1238, 1142, 1058, 955, 783, 724 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, *J* = 2.4 Hz, 1H), 6.80 (d, *J* = 2.4 Hz, 1H), 4.88 (t, *J* = 7.6 Hz, 1H), 4.02 (s, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 2.91 (dd, *J* = 14.8, 7.3 Hz, 1H), 2.30 (dd, *J* = 14.8, 8.0 Hz, 1H), 1.66 (s, 3H), 1.61 (s, 3H), 1.29 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 198.0, 188.0, 165.1, 162.6, 137.3, 135.6, 115.9, 114.6, 105.5, 102.6, 84.2, 81.4, 56.6, 56.1, 36.1, 25.9, 25.4, 17.8.

3,5-dimethoxy-1a-methyl-7a-(3-methylbut-2-en-1-yl)naphtho[2,3-b]oxirene-2,7(1aH,7aH)-dione (4.136)[13]



4.132 **4.136**

To a solution of **4.132** (29 mg, 0.82 mmol) in MeOH (1 mL), NaOH (10 mg, 0.26 mmol) was added at rt. The reaction mixture was stirred at rt for 5 min. The mixture was quenched with 1 M HCl (5 mL) and extracted with EtOAc (3 x 4 mL). The combined organics were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give 3,5-dimethoxy-1a-methyl-7a-(3-methylbut-2-en-1-yl)naphtho[2,3-b]oxirene-2,7(1aH,7aH)-dione (**4.136**) (23 mg, 88%) as a white solid.

R_f = 0.38 (petrol/EtOAc, 2:1)

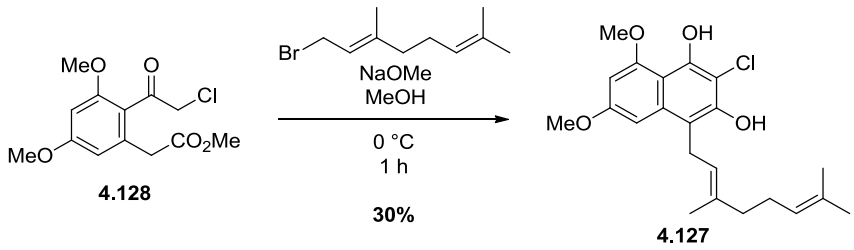
Mp = 103 – 107 °C

IR (neat): 2928, 1681, 1595, 1427, 1339, 1271, 1154, 989, 834, 738 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (d, *J* = 2.3 Hz, 1H), 6.71 (d, *J* = 2.3 Hz, 1H), 5.14 (t, *J* = 7.1 Hz, 1H), 3.90 (s, 3H), 3.90 (s, 3H), 3.05 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.49 (dd, *J* = 15.1, 7.0 Hz, 1H), 1.75 (s, 3H), 1.72 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 193.5, 191.3, 164.5, 160.9, 136.1, 135.3, 116.9, 114.6, 104.7, 102.4, 67.1, 64.9, 56.4, 55.9, 25.8, 25.5, 18.2, 11.9.

(*E*)-2-chloro-4-(3,7-dimethylocta-2,6-dien-1-yl)-6,8-dimethoxynaphthalene-1,3-diol (4.127)



To a suspension of **4.128** (8.0 g, 27.9 mmol) in MeOH (250 mL), NaOMe (6.03 g, 111 mmol) was added at 0 °C. The resultant mixture was stirred at 0 °C for 1 h before addition of geranyl bromide (8.31 mL, 41.8 mmol) at 0 °C. The mixture was stirred at 0 °C for a further 30 mins. The mixture was quenched with 1 M HCl (300 mL) and extracted with EtOAc (150 mL x 4). The combined organics were washed with brine (300 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Trituration of the crude residue with cold MeOH then yielded pure (*E*)-2-chloro-4-(3,7-dimethylocta-2,6-dien-1-yl)-6,8-dimethoxynaphthalene-1,3-diol (**4.127**) (3.23 g, 30%) as a white solid.

R_f = 0.37 (petrol/EtOAc, 4:1)

M.p. = 115 - 117 °C

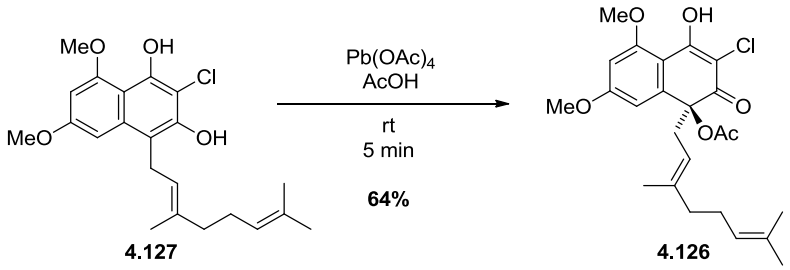
IR (neat): 3490, 3361, 2931, 1618, 1598, 1377, 1257, 1150, 813 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1H), 6.72 (d, *J* = 2.1 Hz, 1H), 6.38 (d, *J* = 2.1 Hz, 1H), 5.89 (s, 1H), 5.16 (t, *J* = 6.6 Hz, 1H), 5.04 (t, *J* = 6.8 Hz, 1H), 4.02 (s, 3H), 3.87 (s, 3H), 3.66 (d, *J* = 6.6 Hz, 2H), 2.08 – 1.98 (m, 4H), 1.87 (s, 3H), 1.61 (s, 3H), 1.55 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 157.1, 149.0, 148.0, 135.4, 134.6, 131.4, 124.1, 122.8, 111.0, 106.2, 103.6, 96.0, 96.1, 56.3, 55.9, 39.7, 26.7, 25.6, 24.9, 17.6, 16.3.

HRMS (ESI): calculated for $C_{22}H_{28}ClO_4$ 391.1676 $[M+H]^+$, found 391.1652.

(*E*)-3-chloro-1-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-5,7-dimethoxy-2-oxo-1,2-dihydronaphthalen-1-yl acetate (4.126)



4.127 **4.126**

To a solution of **4.127** (4.50 g, 11.5 mmol) in AcOH (125 mL), $Pb(OAc)_4$ (5.36 g, 12.1 mmol) was added portion wise at rt. The resultant mixture was stirred at rt for 10 min before H_2O (200 mL) was added. The mixture was cooled to 0 °C and stirred for 15 min. The formed precipitate was isolated under reduced pressure and rinsed sequentially with cold H_2O (2 x 50 mL) and cold MeOH (2 x 50 mL) to yield (*E*)-3-chloro-1-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-5,7-dimethoxy-2-oxo-1,2-dihydronaphthalen-1-yl acetate (**4.126**) (3.30 g, 64%) as a white solid.

R_f = 0.07 (petrol/EtOAc, 1:1)

M.p. = 147 - 150 °C

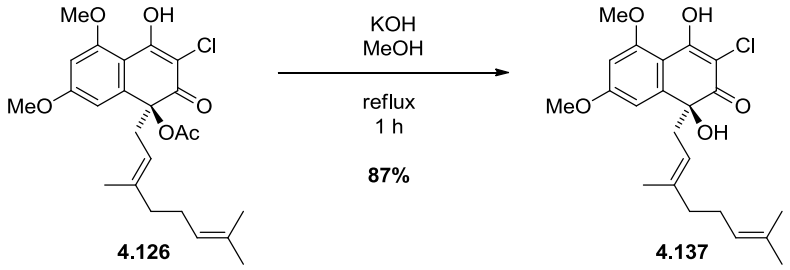
IR (neat): 3193, 2932, 1729, 1662, 1598, 1244, 1029, 859, 824 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.47 (s, 1H), 6.63 (d, *J* = 2.3 Hz, 1H), 6.48 (d, *J* = 2.3 Hz, 1H), 5.02 (t, *J* = 5.9 Hz, 1H), 4.78 (t, *J* = 7.5 Hz, 1H), 4.04 (s, 3H), 3.85 (s, 3H), 2.76 (dd, *J* = 13.3, 8.5 Hz, 1H), 2.57 (dd, *J* = 13.4, 7.3 Hz, 1H), 2.12 (s, 3H), 2.02 – 1.79 (m, 4H), 1.66 (s, 3H), 1.57 (s, 3H), 1.31 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 188.6, 169.0, 162.8, 162.5, 157.4, 145.5, 141.9, 131.6, 124.0, 114.0, 107.6, 104.5, 98.1, 82.3, 57.1, 55.7, 41.3, 39.9, 26.8, 25.6, 20.9, 17.6, 16.0.

HRMS (ESI): calculated for $C_{24}H_{30}ClO_6$ 449.1731 $[M+H]^+$, found 449.1726.

(*E*)-3-chloro-1-(3,7-dimethylocta-2,6-dien-1-yl)-1,4-dihydroxy-5,7-dimethoxynaphthalen-2(1H)-one (4.137)



4.126 **4.137**

To a solution of acetate **4.126** (2.82 g, 6.25 mmol) in MeOH (80 mL), KOH (1.40 g, 25.0 mmol) was added at rt. The resultant mixture was heated at reflux for 1h. The mixture was cooled, quenched with 1M HCl (150 mL) and extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield (*E*)-3-chloro-1-(3,7-dimethylocta-2,6-dien-1-yl)-1,4-dihydroxy-5,7-dimethoxynaphthalen-2(1H)-one (**4.137**) (2.21 g, 87%) as a white solid.

R_f = 0.17 (petrol/EtOAc, 1:1)

M.p. = 58 – 60 °C

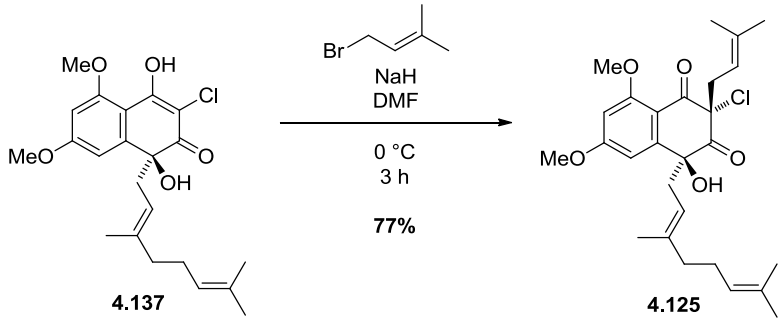
IR (neat): 3490, 3215, 2915, 1620, 1591, 1353, 1160, 1044, 827 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.55 (s, 1H), 6.96 (d, *J* = 2.2 Hz, 1H), 6.49 (d, *J* = 2.1 Hz, 1H), 5.06 (t, *J* = 6.7 Hz, 1H), 4.91 (t, *J* = 7.9 Hz, 1H), 4.04 (s, 3H), 4.00 (s, 1H), 3.89 (s, 3H),2.51 (dd, *J* = 13.5, 8.4 Hz, 1H), 2.43 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.05 – 1.85 (m, 4H), 1.67 (s, 3H), 1.58 (s, 3H), 1.34 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 194.3, 164.2, 162.9, 157.5, 147.2, 141.4, 131.6, 124.1, 115.9, 106.2, 105.0, 104.5, 98.7, 80.0, 57.1, 55.9, 46.4, 39.9, 26.8, 25.6, 17.6, 15.9.

HRMS (ESI): calculated for $C_{22}H_{28}ClO_5$ 407.1625 $[M+H]^+$, found 407.1631.

2-chloro-4-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-6,8-dimethoxy-2-(3-methylbut-2-en-1-yl)naphthalene-1,3(2H,4H)-dione (4.125)



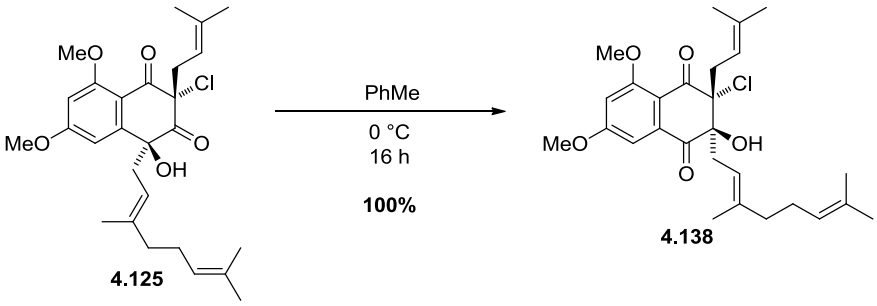
To a solution of **4.137** (153 mg, 0.37 mmol) in anhydrous DMF (5 mL), NaH (60% in mineral oil, 17 mg, 0.41 mmol) was added at rt. The resultant mixture was stirred at rt for 15 mins. The mixture was cooled to 0 °C, and prenyl bromide (0.06 mL, 0.65 mmol) was added. The mixture was stirred at 0 °C for 3 h. The mixture was quenched with 1 M HCl (15 mL) and extracted with EtOAc (3x 15 mL). The combined organics were washed with brine (3x 20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 6:1 → 4:1 gradient elution) to yield pure 2-chloro-4-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-6,8-dimethoxy-2-(3-methylbut-2-en-1-yl)naphthalene-1,3(2H,4H)-dione (**4.125**) (135 mg, 77%) as a colourless oil.

R_f = 0.24 (petrol/EtOAc, 4:1)
IR (neat): 3494, 2916, 1734, 1697, 1598, 1157, 1052 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (d, *J* = 2.3 Hz, 1H), 6.42 (d, *J* = 2.2 Hz, 1H), 5.10 – 4.95 (m, 2H), 4.58 (t, *J* = 7.7 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 1H), 3.85 (s, 3H), 3.03 – 2.88 (m, 2H), 2.64 (dd, *J* = 14.7, 8.4 Hz, 1H), 2.53 (dd, *J* = 14.8, 6.0 Hz, 1H), 2.05 – 1.96 (m, 4H), 1.69 (s, 3H), 1.58 (s, 3H), 1.50 (s, 3H), 1.46 (s, 3H), 1.40 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 201.1, 188.3, 165.2, 160.3, 145.1, 141.6, 137.6, 131.8, 124.0, 115.8, 115.5, 113.9, 101.1, 98.7, 79.9, 69.3, 56.1, 55.7, 43.3, 39.8, 38.2, 26.4, 25.7, 25.6, 17.8, 17.7, 16.5.

HRMS (ESI): calculated for $C_{27}H_{36}ClO_5$ 475.2251 $[M+H]^+$, found 475.2254.

Di-*O*-methyl naphthomevalin (4.138)



A solution of **4.125** (135 mg, 0.284 mmol) in PhMe (3 mL) was heated at reflux for 16 h. The solution was then cooled and concentrated *in vacuo* to yield di-*O*-methyl naphthomevalin (**4.138**) (135 mg, 100%) as a colourless oil.

R_f = 0.17 (petrol/EtOAc, 4:1)

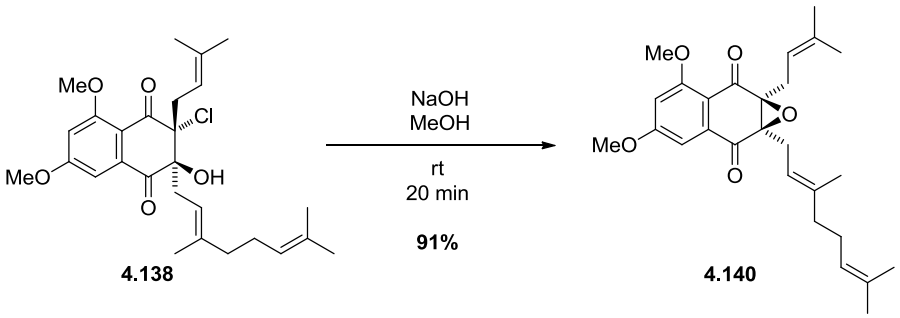
IR (neat): 3480, 3916, 1697, 1594, 1320, 1211, 1160, 1056 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 2.4 Hz, 1H), 6.78 (d, *J* = 2.4 Hz, 1H), 5.04 (t, *J* = 6.7 Hz, 1H), 4.99 (t, *J* = 7.3 Hz, 1H), 4.88 (t, *J* = 7.7 Hz, 1H), 4.04 (s, 1H), 3.94 (s, 3H),3.94 (s, 3H), 2.96 (dt, *J* = 15.8, 8.1 Hz, 2H), 2.40 (dd, *J* = 15.2, 7.6 Hz, 1H), 2.23 (dd, *J* = 14.7, 8.1 Hz, 1H), 2.08 – 1.85 (m, 4H), 1.70 (s, 3H), 1.58 (s, 6H), 1.29 (s, 3H), 1.24 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 187.2, 164.8, 162.1, 140.9, 136.5, 135.4, 131.6, 123.9, 116.8, 116.0, 115.7, 105.5, 102.1, 86.2, 84.5, 56.6, 56.0, 39.8, 37.2, 36.0, 26.4, 25.8, 25.6, 17.7, 17.7, 16.1.

HRMS (ESI): calculated for $C_{27}H_{36}ClO_5$ 475.2251 $[M+H]^+$, found 475.2252.

Di-*O*-methylA80915G (4.140)[13]



To a solution of **4.138** (25 mg, 0.053 mmol) in MeOH (1 mL), NaOH (6 mg, 0.15 mmol) was added at rt. The mixture was stirred at rt for 20 mins. The mixture was quenched with 1M HCl (5 mL) and extracted with EtOAc (3x 5 mL). The combined organics were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield di-*O*-methylA80915G (**4.140**) (21 mg, 91%) as a colourless oil.

R_f = 0.25 (petrol/EtOAc, 4:1)

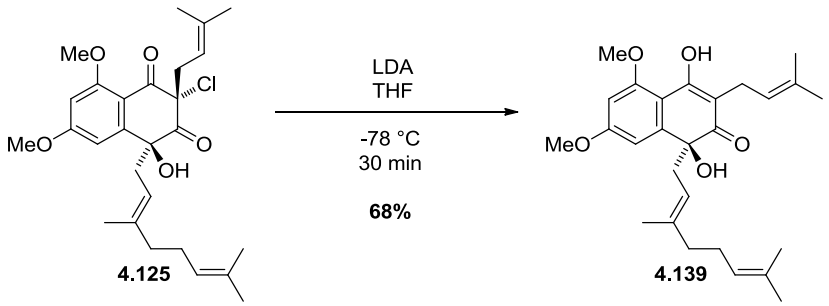
IR (neat): 2917, 1687, 1597, 1327, 1310, 1201, 1157, 829 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (d, *J* = 2.3 Hz, 1H), 6.69 (d, *J* = 2.3 Hz, 1H), 5.21 (t, *J* = 7.5 Hz, 1H), 5.18 (t, *J* = 7.5 Hz, 1H), 5.05 (t, *J* = 7.5 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 2.92 (td, *J* = 15.4, 7.0 Hz, 2H), 2.76 – 2.58 (m, 2H), 2.07 – 1.99 (m, 4H), 1.72 (s, 3H), 1.71 (s, 3H), 1.70 (s, 3H), 1.64 (s, 3H), 1.58 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 193.7, 190.4, 164.4, 161.0, 138.5, 136.1, 134.6, 131.5, 124.0, 117.8, 117.2, 114.8, 104.6, 102.4, 67.6, 67.6, 56.4, 55.8, 39.7, 26.5, 25.8, 25.7, 25.4, 25.3, 18.2, 17.7, 16.5.

HRMS (ESI): calculated for $C_{27}H_{35}O_5$ 439.2485 $[M+H]^+$, found 439.2480.

(*E*)-1-(3,7-dimethylocta-2,6-dien-1-yl)-1,4-dihydroxy-5,7-dimethoxy-3-(3-methylbut-2-en-1-yl)naphthalen-2(1H)-one (4.139)



To a solution of **4.125** (92 mg, 0.19 mmol) in THF (4 mL), LDA solution (2.0 M in THF, 0.24 mL, 0.48 mmol) was added at -78 °C. The resultant mixture was stirred at -78 °C for 30 min before quenching at this temperature with 1M HCl (10 mL). The mixture was extracted with Et_2O (3 x 10 mL) and the combined organics were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 5:1 as eluent) to yield pure (*E*)-1-(3,7-dimethylocta-2,6-dien-1-yl)-1,4-dihydroxy-5,7-dimethoxy-3-(3-methylbut-2-en-1-yl)naphthalen-2(1H)-one (**4.139**) (58 mg, 68%) as a colourless oil.

R_f = 0.21 (petrol/EtOAc, 3:1)

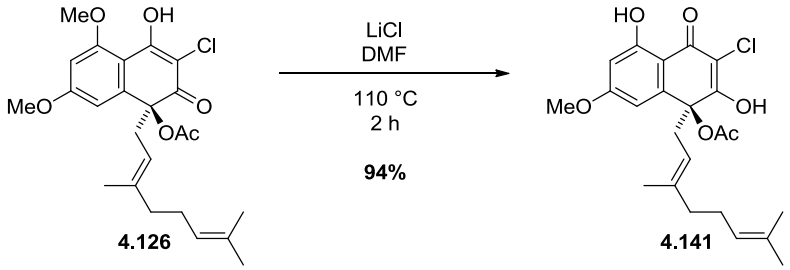
IR (neat): 3440, 3312, 2914, 16.21, 1594, 1566, 1159, 1026, 829 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.95 (s, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 5.16 (t, *J* = 7.1 Hz, 1H), 5.06 (t, *J* = 6.8 Hz, 1H), 4.93 (t, *J* = 7.4 Hz, 1H), 4.17 (s, 1H), 3.99 (s, 3H), 3.87 (s, 3H), 3.18 (dd, *J* = 14.2, 7.2 Hz, 1H), 3.07 (dd, *J* = 14.3, 7.0 Hz, 1H), 2.47 – 2.37 (m, 2H), 2.02 – 1.87 (m, 4H), 1.75 (s, 3H), 1.67 (s, 3H), 1.67 (s, 3H), 1.58 (s, 3H), 1.31 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3, 164.0, 161.8, 157.3, 147.8, 139.7, 131.5, 131.4, 124.2, 122.2, 117.0, 110.8, 107.5, 104.4, 98.5, 78.6, 56.7, 55.7, 46.2, 39.9, 26.8, 25.7, 25.6, 21.5, 17.8, 17.6, 15.9.

HRMS (ESI): calculated for $C_{27}H_{37}O_5$ 441.2641 $[M+H]^+$, found 441.2633.

(*E*)-3-chloro-1-(3,7-dimethylocta-2,6-dien-1-yl)-2,5-dihydroxy-7-methoxy-4-oxo-1,4-dihydronaphthalen-1-yl acetate (4.141)



To a solution of **4.126** (1.14 g, 2.54 mmol) in DMF (16 mL), LiCl (1.00 g, 25.4 mmol) was added at rt. The mixture was heated to 110 °C for 2h. The mixture was cooled, quenched with 1M HCl (30 mL) then extracted with EtOAc (3x 30 mL). The combined organics were washed with brine (3 x 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield (*E*)-3-chloro-1-(3,7-dimethylocta-2,6-dien-1-yl)-2,5-dihydroxy-7-methoxy-4-oxo-1,4-dihydronaphthalen-1-yl acetate (**4.141**) (1.03 g, 94 %) as a brown oil.

R_f = 0.08 (CH_2Cl_2/MeOH, 8:1)

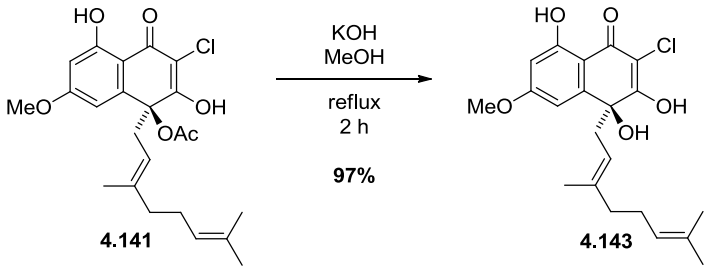
IR (neat): 3210, 2924, 1752, 1595, 1434, 1366, 1162, 1017, 831 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 12.63 (br s, 1H), 6.45 (d, *J* = 2.2 Hz, 1H), 6.37 (d, *J* = 2.2 Hz, 1H), 4.98 (t, *J* = 7.8 Hz, 1H), 4.56 (t, *J* = 7.8 Hz, 1H), 3.81 (s, 3H), 2.94 (dd,*J* = 13.2, 7.1 Hz, 2H), 2.65 (dd, *J* = 13.2, 7.1 Hz, 1H), 2.11 (s, 3H), 1.96 – 1.72 (m, 4H), 1.63 (s, 3H), 1.54 (s, 3H), 1.35 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 181.9, 169.1, 164.7, 163.7, 163.1, 143.4, 142.9, 131.7, 123.8, 113.8, 108.5, 108.1, 103.5, 99.9, 79.2, 55.5, 41.0, 39.8, 26.7, 25.6, 21.0, 17.6, 16.0.

HRMS (ESI): calculated for $C_{23}H_{28}ClO_6$ 435.1574 $[M+H]^+$, found 435.1571.

(*E*)-3-chloro-1-(3,7-dimethylocta-2,6-dien-1-yl)-1,4,5-trihydroxy-7-methoxynaphthalen-2(1H)-one (4.143)



To a solution of **4.141** (990 mg, 2.7 mmol) in MeOH (30 mL), KOH (511 mg, 9.10 mmol) was added at rt. The mixture was heated at reflux for 2h. The mixture was cooled, quenched with 1M HCl (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield (*E*)-3-chloro-1-(3,7-dimethylocta-2,6-dien-1-yl)-1,4,5-trihydroxy-7-methoxynaphthalen-2(1H)-one (**4.143**) (866 mg, 97%) as a brown oil.

R_f = 0.08 (CH_2Cl_2/MeOH, 8:1)

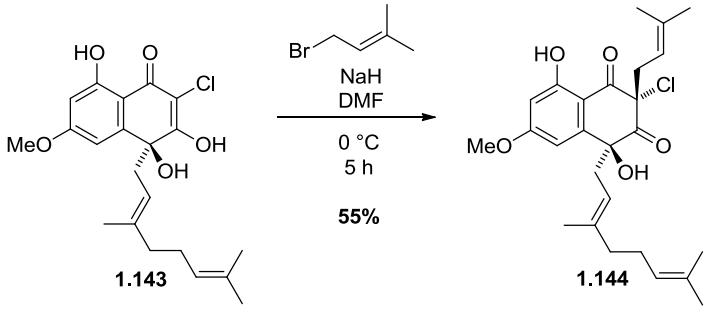
IR (neat): 3315, 2922, 1716, 1595, 1435, 1366, 1275, 1138, 827 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 12.50 (s, 1H), 6.71 (d, *J* = 2.4 Hz, 1H), 6.34 (d, *J* = 2.4 Hz, 1H), 4.95 (t, *J* = 7.5 Hz, 1H), 4.63 (t, *J* = 7.5 Hz, 1H), 3.84 (s, 3H), 2.82 (dd, *J* = 13.3, 8.6 Hz, 1H), 2.54 (dd, *J* = 13.2, 7.3 Hz, 1H), 1.95 – 1.74 (m, 4H), 1.64 (s, 3H), 1.54 (s, 3H), 1.40 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 182.3, 167.1, 165.1, 163.4, 145.0, 142.9, 131.9, 123.7, 115.1, 107.9, 107.7, 104.9, 100.6, 75.0, 55.7, 43.8, 39.8, 26.6, 25.6, 17.6, 16.0.

HRMS (ESI): calculated for $C_{21}H_{24}ClO_5$ 391.1312 $[M-H]^-$, found 391.1314.

2-chloro-4-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)-4,8-dihydroxy-6-methoxy-2-(3-methylbut-2-en-1-yl)naphthalene-1,3(2H,4H)-dione (1.144)



To a solution of **1.143** (1.09 g, 2.77 mmol) in anhydrous DMF (25 mL), NaH (60% in mineral oil, 133 mg, 3.33 mmol) was added at rt. The resultant mixture was stirred at rt for 30 mins. The mixture was cooled to 0 °C and prenyl bromide (0.64 mL, 5.54 mmol) was added. The mixture was stirred at 0 °C for 5 h. The mixture was quenched with 1 M HCl (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine (3 x 100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 20:1 → 15:1 gradient elution) to yield pure 2-chloro-4-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)-4,8-dihydroxy-6-methoxy-2-(3-methylbut-2-en-1-yl)naphthalene-1,3(2H,4H)-dione (**1.144**) (700 mg, 55%) as a white solid.

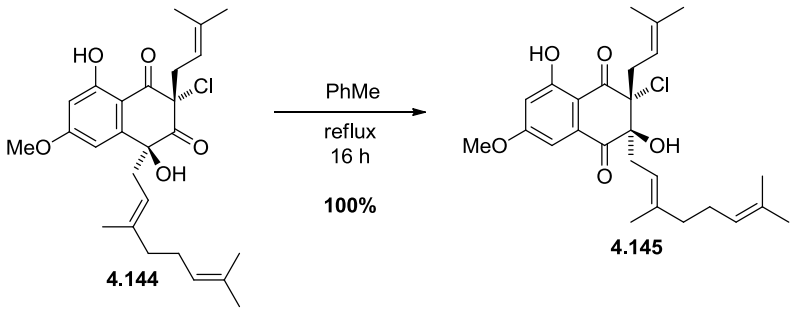
R_f = 0.50 (petrol/EtOAc, 4:1)
M.p. = 72 – 74 °C

IR (neat): 3460, 2917, 1735, 1627, 1358, 1304, 1213, 1163, 973, 811cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 12.07 (s, 1H), 6.80 (d, *J* = 2.5 Hz, 1H), 6.41 (d, *J* = 2.5 Hz, 1H), 5.07 (t, *J* = 6.7 Hz, 1H), 5.02 (t, *J* = 6.9 Hz, 1H), 4.49 (t, *J* = 7.7 Hz, 1H), 3.89 (s, 3H), 3.81 (s, 1H), 3.21 – 3.03 (m, 2H), 2.78 – 2.54 (m, 2H), 2.17 – 1.92 (m, 4H), 1.71 (s, 3H), 1.61 (s, 3H), 1.56 (s, 3H), 1.50 (s, 3H), 1.42 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8, 193.8, 167.8, 165.2, 145.5, 142.4, 138.8, 131.8, 123.9, 115.8, 115.1, 108.9, 105.6, 100.3, 79.3, 64.4, 55.9, 45.5, 39.9, 37.4, 26.4, 25.7, 25.6, 17.9, 17.7, 16.5.

HRMS (ESI): calculated for $C_{26}H_{32}ClO_5$ 459.1938 $[M-H]^-$, found 459.1934.

_O_-methyl naphthomevalin (4.145)



A solution of **4.144** (438 mg, 0.95 mmol) in PhMe (10 mL) was heated at reflux for 1.5 h. The solution was then cooled and concentrated *in vacuo* to yield *O*-methyl naphthomevalin (**4.145**) (438 mg, 100%) as a white solid.

R_f = 0.52 (petrol/EtOAc, 4:1)

M.p. = 61–63 °C

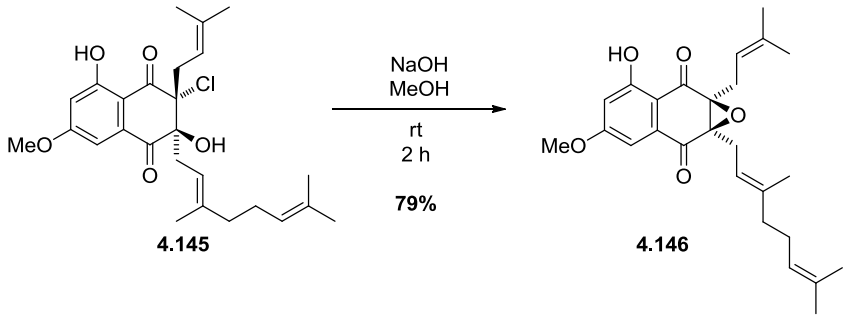
IR (neat): 3481, 2916, 1702, 1642, 1614, 1437, 1383, 1297, 1235, 1164, 756 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 12.02 (s, 1H), 7.08 (d, *J* = 2.5 Hz, 1H), 6.72 (d, *J* = 2.4 Hz, 1H), 5.02 (t, *J* = 6.6 Hz, 1H), 4.93 (t, *J* = 7.5 Hz, 1H), 4.82 (t, *J* = 7.7 Hz, 1H), 4.13 (s, 1H), 3.92 (s, 3H), 2.97 (td, *J* = 14.9, 7.2 Hz, 2H), 2.49 (dd, *J* = 14.9, 8.0 Hz, 1H), 2.28 (dd, *J* = 14.5, 8.3 Hz, 1H), 2.01 – 1.85 (m, 4H), 1.70 (s, 3H), 1.58 (s, 2H), 1.55 (s, 3H), 1.28 (s, 3H), 1.27 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 196.6, 195.4, 166.4, 164.7, 141.1, 138.0, 133.9, 131.7, 123.8, 116.5, 115.6, 110.3, 107.0, 106.5, 84.3, 82.9, 56.2, 39.7, 38.2, 37.2, 26.3, 25.8, 25.6, 17.7, 16.0.

HRMS (ESI): calculated for $C_{26}H_{32}ClO_5$ 459.1938 $[M-H]^-$, found 459.1930

***O*-methylA80915G (4.146)**[13]



To a solution of **4.145** (81 mg, 0.18 mmol) in MeOH (4 mL), NaOH (21 mg, 0.53 mmol) was added at rt. The mixture was stirred at rt for 2 h. The mixture was quenched with 1M HCl (10 mL) and extracted with EtOAc (3x 10 mL). The combined organics were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield *O*-methylA80915G (**4.146**) (60 mg, 79%) as a colourless oil.

R_f = 0.55 (petrol/EtOAc, 4:1)

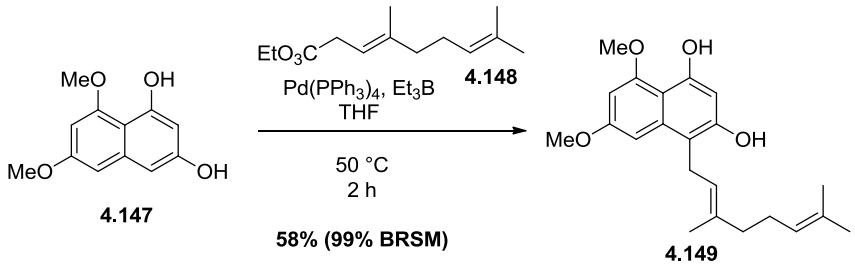
IR (neat): 2916, 1698, 1637, 1614, 1441, 1379, 1315, 1206, 1153, 834, 750 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.83 (s, 1H), 7.09 (d, *J* = 1.0 Hz, 1H), 6.65 (d, *J* = 1.0 Hz, 1H), 5.14 (m, 2H), 5.04 (t, *J* = 7.5 Hz, 1H), 3.87 (s, 3H), 3.23 (dd, *J* = 15.1, 7.0 Hz, 1H), 3.10 (dd, *J* = 15.2, 7.0 Hz, 1H), 2.55 (dd, *J* = 15.2, 6.8 Hz, 1H), 2.42 (dd, *J* = 15.0, 6.3 Hz, 1H), 2.03 (dt, *J* = 14.8, 7.1 Hz, 4H), 1.73 (s, 6H), 1.71(s, 3H), 1.64 (s, 3H), 1.58 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 195.6, 191.1, 166.3, 164.5, 138.8, 135.4, 134.0, 131.5, 124.0, 117.0, 116.91, 109.1, 107.2, 106.6, 67.6, 67.5, 56.0, 39.7, 26.5, 25.8, 25.6, 25.5, 25.3, 18.2, 17.7, 16.5.

HRMS (ESI): calculated for $C_{26}H_{33}O_5$ 425.2328 $[M+H]^+$, found 425.2327.

(*E*)-4-(3,7-dimethylocta-2,6-dien-1-yl)-6,8-dimethoxynaphthalene-1,3-diol (4.149)[48]



A solution of **4.147** (3.0 g, 11.9 mmol), ethyl geranyl carbonate (**4.148**) (4.04, g 17.8 mmol) and $Pd(PPh_3)_4$ (680 mg, 0.59 mmol) in THF (60 mL) was degassed by the bubbling of N_2 gas. Et_3B (1.0 M solution in THF, 17.9 mL, 17.9 mmol) was then added at rt and the mixture was heated at 50 °C for 2 h. The mixture was quenched with saturated NH_4Cl solution (100 mL) and extracted with Et_2O (2 x 75 mL). The combined organics were washed with brine (100 mL) dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 6:1 → 2:1 gradient elution) to yield pure (*E*)-4-(3,7-dimethylocta-2,6-dien-1-yl)-6,8-dimethoxynaphthalene-1,3-diol (**4.149**) (2.49 g, 58%) as a colourless oil, along with starting material (1.22 g, 41%).

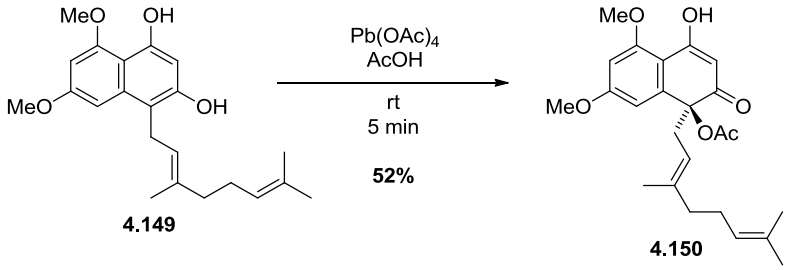
R_f = 0.20 (petrol/EtOAc, 4:1)

IR (neat): 3405, 3358, 2913, 1624, 1602, 1378, 1208, 1145, 1015, 933, 819 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (s, 1H), 6.73 (d, *J* = 2.2 Hz, 1H), 6.36 (s, 1H), 6.34 (d, *J* = 2.1 Hz, 1H), 5.29 (s, 1H), 5.20 (t, *J* = 6.6 Hz, 1H), 5.04 (t, *J* = 6.7 Hz, 1H), 4.00 (s, 3H), 3.87 (s, 3H), 3.58 (d, *J* = 6.6 Hz, 2H), 2.12 – 2.00 (m, 4H), 1.87 (s, 3H), 1.63 (s, 3H), 1.56 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 157.9, 154.3, 153.2, 136.8, 136.5, 131.6, 124.0, 122.9, 109.6, 106.6, 99.9, 95.9, 95.1, 56.1, 55.2, 39.6, 26.6, 25.6, 24.4, 17.7, 16.3.

(*E*)-1-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-5,7-dimethoxy-2-oxo-1,2-dihydronaphthalen-1-yl acetate (4.150)



4.149 **4.150**

To a solution of **4.149** (1.87 g, 5.24 mmol) in AcOH (40 mL), $Pb(OAc)_4$ (2.44 g, 5.50 mmol) was added at rt. The mixture was stirred at rt for 5 min before quenching with saturated $NaHCO_3$ solution (150 mL), and extraction with EtOAc (3 x 75 mL). The combined organics were washed sequentially with saturated $NaHCO_3$ solution (2 x 150 mL), H_2O (150 mL), brine (150 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 2:1 → 1:1 gradient elution) to yield pure (*E*)-1-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-5,7-dimethoxy-2-oxo-1,2-dihydronaphthalen-1-yl acetate (**4.150**) (1.13 g, 52%) as a yellow oil.

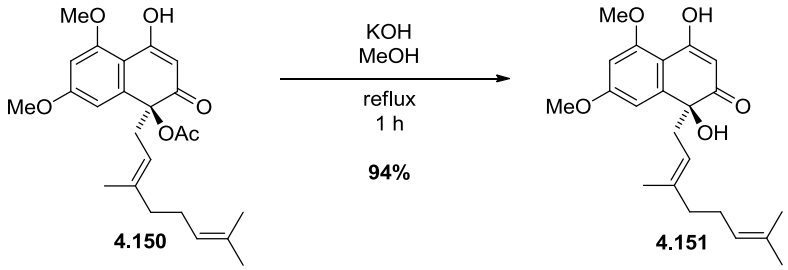
R_f = 0.17 (petrol/EtOAc, 1:1)

IR (neat): 3309, 2924, 1742, 1631, 1596, 1421, 1333, 1207, 1015, 831, 729 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (s, 1H), 6.63 (d, *J* = 2.3 Hz, 1H), 6.46 (d, *J* = 2.3 Hz, 1H), 5.63 (s, 1H), 5.04 (t, *J* = 6.7 Hz, 1H), 4.91 (t, *J* = 7.8 Hz, 1H), 4.01 (s, 3H), 3.85 (s, 3H), 2.70 (dd, *J* = 13.5, 8.1 Hz, 1H), 2.59 (dd, *J* = 13.4, 7.5 Hz, 1H), 2.13 (s, 3H), 1.99 – 1.86 (m, 4H), 1.67 (s, 3H), 1.58 (s, 3H), 1.32 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0, 169.1, 168.1, 162.4, 157.9, 147.4, 140.8, 131.5, 124.1, 115.0, 108.3, 104.5, 102.5, 97.7, 81.9, 56.8, 55.6, 41.0, 39.9, 26.8, 25.6, 21.0, 17.6, 16.0.

(E)-1-(3,7-dimethylocta-2,6-dien-1-yl)-1,4-dihydroxy-5,7-dimethoxynaphthalen-2(1H)-one (4.151)



To a solution of **4.150** (396 mg, 0.953 mmol) in MeOH (12 mL), KOH (214 mg, 3.81 mmol) was added at rt. The mixture was heated at reflux for 2 h. The mixture was cooled, quenched with 1 M HCl (30 mL) and extracted with EtOAc (3 x 15 mL). The combined organics were washed with brine (30 mL) dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield (*E*)-1-(3,7-dimethylocta-2,6-dien-1-yl)-1,4-dihydroxy-5,7-dimethoxynaphthalen-2(1H)-one (**4.151**) (335 mg, 94%) as a yellow oil.

R_f = 0.32 (petrol/EtOAc, 1:1)

IR (neat): 3433, 3309, 2919, 1731, 1626, 1594, 1421, 1282, 1198, 1159, 1045, 830 cm^{-1}

Major tautomer

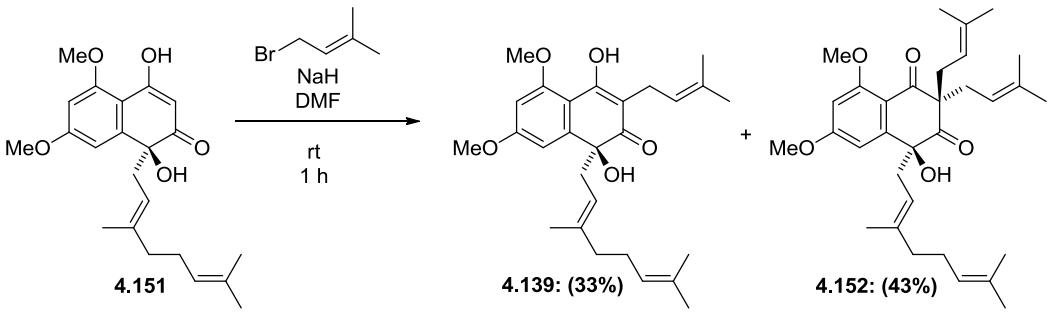
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.85 (s, 1H), 6.96 (d, *J* = 2.4 Hz, 1H), 6.46 (d, *J* = 2.3 Hz, 1H), 5.53 (s, 1H), 5.06 (t, *J* = 7.6 Hz, 1H), 5.00 (t, *J* = 7.8 Hz, 1H), 4.08 (s, 1H), 4.01 (s, 3H), 3.89 (s, 3H), 2.47 (dd, *J* = 13.7, 8.1 Hz, 1H), 2.42 (dd, *J* = 13.7, 7.5 Hz, 1H), 2.06 – 1.90 (m, 4H), 1.68 (s, 3H), 1.58 (s, 3H), 1.34 (s, 3H).

Minor tautomer

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (d, *J* = 2.4 Hz, 1H), 6.46 (d, *J* = 2.1 Hz, 1H), 5.06 (t, *J* = 7.6 Hz, 1H), 5.00 (t, *J* = 7.8 Hz, 1H), 4.16 (s, 1H), 3.91 (s, 3H), 3.91 (s, 3H), 3.64 (d, *J* = 19.7 Hz, 1H), 3.56 (d, *J* = 19.7 Hz, 1H), 2.63 (dd, *J* = 15.1, 6.8 Hz, 1H), 2.57 (dd, *J* = 15.0, 7.7 Hz, 1H), 2.06 – 1.91 (m, 4H), 1.68 (s, 3H), 1.58 (s, 3H), 1.51 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 204.3, 200.8, 188.8, 169.3, 165.4, 162.7, 161.7, 157.9, 149.6, 149.2, 140.6, 140.3, 131.8, 131.5, 124.1, 123.7, 116.8, 116.4, 113.9, 106.9, 104.8, 101.8, 99.3, 98.8, 98.3, 80.5, 79.1, 56.8, 56.2, 55.8, 55.7, 50.5, 45.9, 43.0, 39.9, 39.7, 26.8, 26.3, 25.7, 25.6, 17.7, 17.6, 16.3, 15.9.

(*E*)-4-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-6,8-dimethoxy-2,2-bis(3-methylbut-2-en-1-yl)naphthalene-1,3(2H,4H)-dione (4.152)



To a solution of **4.151** (82 mg, 0.22 mmol) in DMF (4 mL), NaH (60% in mineral oil, 12 mg, 0.30mmol) was added at rt. The mixture was stirred at rt for 20 min before prenyl bromide (0.05 mL, 0.4 mmol) was added at rt. The mixture was stirred at rt for a further 1 h before quenching with 1 M HCl (15 mL) and extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (3 x 15 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 6:1 → 4:1 gradient elution) to yield pure (*E*)-1-(3,7-dimethylocta-2,6-dien-1-yl)-1,4-dihydroxy-5,7-dimethoxy-3-(3-methylbut-2-en-1-yl)naphthalen-2(1H)-one (**4.139**) (32 mg, 33%) as a colourless oil. Further elution gave (*E*)-4-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-6,8-dimethoxy-2,2-bis(3-methylbut-2-en-1-yl)naphthalene-1,3(2H,4H)-dione (**4.152**) (48 mg, 43%) as a colourless oil.

Data for **4.152**

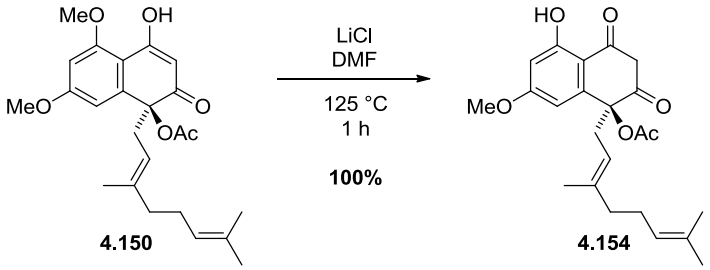
R_f = 0.35 (petrol/EtOAc, 4:1)

IR (neat): 3482, 2915, 1717, 1680, 1599, 1578, 1455, 1199, 1157, 1051, 841 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (d, *J* = 2.3 Hz, 1H), 6.40 (d, *J* = 2.3 Hz, 1H), 5.14 (t, *J* = 7.7 Hz, 1H), 5.04 (t, *J* = 6.8 Hz, 1H), 4.89 (t, *J* = 7.0 Hz, 1H), 4.60 (t, *J* = 7.9 Hz, 1H), 3.98 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.74 (dd, *J* = 14.3, 9.2 Hz, 1H), 2.62 (dd, *J* = 14.3, 6.2 Hz, 1H), 2.50 – 2.33 (m, 3H), 2.23 – 2.15 (dd,*J* = 15.0, 5.7 Hz,1H), 2.04 – 1.90 (m, 4H), 1.67 (s, 3H),1.67 (s, 3H),1.63 (s, 3H), 1.58 (s, 3H), 1.41 (s, 3H),1.41 (s, 3H), 1.39 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 209.9, 195.4, 164.1, 159.8, 145.6, 140.5, 135.3, 134.8, 131.6, 124.0, 119.3, 117.6, 115.9, 115.4, 101.0, 98.2, 79.2, 62.8, 55.9, 55.6, 42.2, 39.9, 38.3, 31.9, 26.6, 26.0, 25.8, 25.6, 18.0, 17.6, 17.5, 16.4.

(*E*)-4-(3,7-dimethylocta-2,6-dien-1-yl)-4,8-dihydroxy-6-methoxynaphthalene-1,3(2H,4H)-dione (4.154)



To a solution of **4.150** (1.86 g, 4.48 mmol) in DMF (35 mL), LiCl (1.9 g, 44.8 mmol) was added at rt. The mixture was heated at 125 °C for 1 h. The mixture was cooled, quenched with 1 M HCl (100 mL) and extracted with EtOAc (3 x 75 mL). The combined organics were washed with brine (3 x 100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield (*E*)-4-(3,7-dimethylocta-2,6-dien-1-yl)-4,8-dihydroxy-6-methoxynaphthalene-1,3(2H,4H)-dione (**4.154**) (1.79 g, 100%) as a brown oil which was used in the next step without further purification.

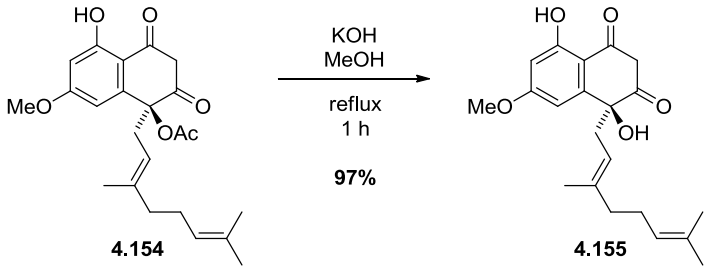
R_f = 0.41 (CH_2Cl_2/MeOH, 8:1)

IR (neat): 2919, 1750, 1639, 1597, 1441, 1369, 1231, 1155, 1019, 843, 731 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 12.70 (s, 1H), 6.50 (d, *J* = 2.4 Hz, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 4.98 (t, *J* = 6.8 Hz, 1H), 4.82 (t, *J* = 7.4 Hz, 1H), 3.86 (s, 3H), 3.73 (d, *J* = 21.0 Hz, 1H), 3.50 (d, *J* = 21.0 Hz, 1H), 2.92 (dd, *J* = 14.0, 6.8 Hz, 1H), 2.65 (dd, *J* = 14.0, 6.8 Hz, 1H), 2.12 (s, 3H), 2.01 – 1.84 (m, 4H), 1.67 (s, 3H), 1.57 (s, 3H), 1.44 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 195.7, 169.3, 166.8, 165.3, 146.1, 142.7, 132.1, 123.5, 114.3, 110.4, 105.0, 99.8, 81.9, 55.7, 51.1, 40.3, 39.7, 26.3, 25.6, 20.6, 17.7, 16.1.

(*E*)-4-(3,7-dimethylocta-2,6-dien-1-yl)-4,8-dihydroxy-6-methoxynaphthalene-1,3(2H,4H)-dione (4.155)



4.154 **4.155**

To a solution of **4.154** (1.78 g, 4.46 mmol) in MeOH (40 mL), KOH (1.0 g, 17.8 mmol) was added at rt. The mixture was heated at reflux for 1 h. The mixture was cooled, quenched with 1 M HCl (100 mL) and extracted with EtOAc (3 x 75 mL). The combined organics were washed with brine (100 mL) dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield (*E*)-4-(3,7-dimethylocta-2,6-dien-1-yl)-4,8-dihydroxy-6-methoxynaphthalene-1,3(2H,4H)-dione (**4.155**) (1.55 mg, 97%) as a yellow oil.

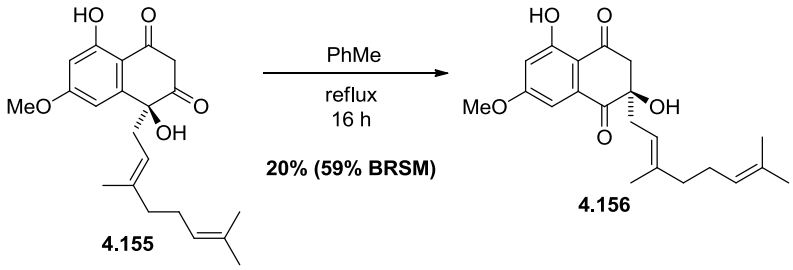
R_f = 0.49 (CH_2Cl_2/MeOH, 8:1)

IR (neat): 3520, 3330, 2917, 2659, 1590, 1478, 1371, 1303, 1159, 1031, 842 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 12.39 (s, 1H), 6.84 (d, *J* = 2.5 Hz, 1H), 6.41 (d, *J* = 2.5 Hz, 1H), 5.03 (t, *J* = 6.8 Hz, 2H), 4.05 (s, 1H), 3.89 (s, 3H), 3.79 (d, *J* = 19.4 Hz, 1H), 3.61 (d, *J* = 19.4 Hz, 1H), 2.65 (dd, *J* = 14.9, 7.1 Hz, 1H), 2.58 (dd, *J* = 14.9, 7.6 Hz, 1H), 2.08 – 1.97 (m, 4H), 1.70 (s, 3H), 1.60 (s, 3H), 1.54 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 203.5, 195.1, 167.3, 165.2, 148.2, 141.1, 131.9, 123.7, 116.1, 109.4, 105.3, 100.5, 80.1, 55.8, 49.5, 43.3, 39.7, 26.3, 25.7, 17.7, 16.4.

(*E*)-2-(3,7-dimethylocta-2,6-dien-1-yl)-2,5-dihydroxy-7-methoxy-2,3-dihydronaphthalene-1,4-dione (4.156)



A solution of **4.155** (1.54 g, 4.27 mmol), in PhMe (30 mL) was heated at reflux for 16 h. The mixture was then cooled and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 10:1 → 2:1 gradient elution) to yield pure (*E*)-2-(3,7-dimethylocta-2,6-dien-1-yl)-2,5-dihydroxy-7-methoxy-2,3-dihydronaphthalene-1,4-dione (**4.156**) (310mg, 20%) as a brown oil, along with starting material (598 mg, 39%).

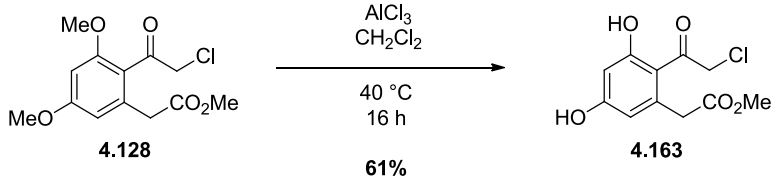
R_f = 0.57 (petrol/EtOAc, 4:1)

IR (neat): 3489, 2915, 1701, 1638, 1614, 1444, 1376, 1292, 1260, 1163, 1064, 972 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 12.30 (s, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 6.70 (d, *J* = 2.3 Hz, 1H), 5.05 (t, *J* = 6.8 Hz, 1H), 4.99 (t, *J* = 7.3 Hz, 1H), 3.92 (s, 3H), 3.85 (s, 1H), 3.24 (d, *J* = 16.9 Hz, 1H), 3.11 (d, *J* = 16.9 Hz, 1H), 2.49 (dd, *J* = 14.3, 8.1 Hz, 1H), 2.39 (dd, *J* = 14.4, 7.3 Hz, 1H), 2.07 – 1.94 (m, 4H), 1.70 (s, 3H), 1.60 (s, 3H), 1.43 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.4, 198.7, 166.3, 164.3, 141.2, 134.6, 131.7, 123.9, 116.1, 112.4, 106.8, 106.5, 77.9, 56.1, 49.3, 39.8, 38.8, 26.3, 25.7, 17.7, 16.2.

methyl 2-(2-(2-chloroacetyl)-3,5-dihydroxyphenyl)acetate (4.163)



To a solution of **4.128** (3.43 g, 12.0 mmol) in CH_2Cl_2 (100 mL), $AlCl_3$ (11.2 g, 83.7 mmol) was added at rt. The reaction mixture was stirred at 40 °C overnight. The mixture was cooled to 0 °C, quenched carefully with 1 M HCl (150 mL), and extracted with EtOAc (3 x 100 mL). The combined organics were washed sequentially with H_2O (150 mL) and brine (150 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Trituration of the crude residue with cold CH_2Cl_2 then yielded methyl 2-(2-(2-chloroacetyl)-3,5-dihydroxyphenyl)acetate (**4.163**) (1.90 g, 61%) as a white solid.

R_f = 0.24 (petrol/EtOAc, 1:1)

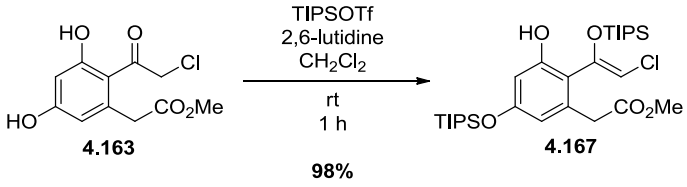
M.p. = 144 – 148 °C

IR (neat): 3072, 2957, 1725, 1663, 1582, 1303, 1277, 1154, 1065, 987, 848, 681 cm^{-1}

^{1}H NMR (500 MHz, acetone-*d6*) δ 9.68 (s, 1H), 6.52 (d, *J* = 1.5 Hz, 1H), 6.45 (d, *J* = 1.5 Hz, 1H), 4.59 (s, 2H), 3.95 (s, 2H), 3.64 (s, 3H).

^{13}C NMR (125 MHz, acetone-*d6*) δ 199.5, 178.9, 172.9, 168.4, 138.7, 115.5, 114.8, 99.9, 77.7, 53.8, 38.1.

methyl 2-(2-(2-chloro-1-((triisopropylsilyl)oxy)vinyl)-3-hydroxy-5-((triisopropylsilyl)oxy)phenyl)acetate (4.167)



To a solution of **4.163** (73 mg, 0.28 mmol) in CH_2Cl_2 (2 mL), TIPSOTf (0.30 mL, 1.1 mmol) and 2,6-lutidine (0.14 mL, 1.3 mmol) were added at rt. The reaction mixture was stirred at rt for 1 h. The mixture was quenched with H_2O (8 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 100:1 as eluent) to yield pure methyl 2-(2-(2-chloro-1-((triisopropylsilyl)oxy)vinyl)-3-hydroxy-5-((triisopropylsilyl)oxy)phenyl)acetate (**4.167**) (156 mg, 98%) as a colourless oil.

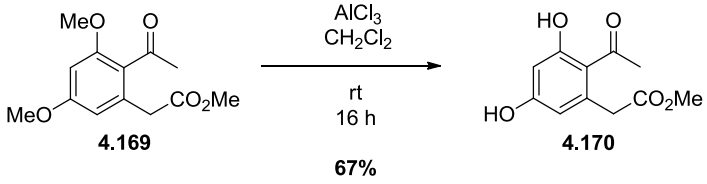
R_f = 0.65 (petrol/EtOAc, 4:1)

IR (neat): 3400, 2945, 2867, 1741, 1610, 1259, 1157, 881 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.78 (d, *J* = 2.0 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 4.06 (s, 2H), 3.66 (s, 3H), 1.35 – 1.22 (m, 6H), 1.13 (d, *J* = 7.4 Hz, 18H), 1.10 (d, *J* = 7.4 Hz, 18H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 154.4, 154.1, 140.2, 127.6, 127.1, 117.5, 116.0, 101.6, 51.8, 36.5, 17.9, 17.9, 12.6, 12.6.

methyl 2-(2-acetyl-3,5-dihydroxyphenyl)acetate (4.170)



To a solution of **4.169** (25.4 g, 100 mmol) in CH_2Cl_2 (500 mL), $AlCl_3$ (66.7 g, 500 mmol) was added at rt. The resultant mixture was stirred at rt for 16 h. The mixture was quenched carefully with 1 M HCl (300 mL) and extracted with EtOAc (3 x 300 mL). The combined organics were washed sequentially with H_2O (500 mL) and brine (500 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Trituration of the crude residue with cold CH_2Cl_2 then yielded pure methyl 2-(2-acetyl-3,5-dihydroxyphenyl)acetate (**4.170**) (15.1 g 67%) as a white solid.

R_f = 0.23 (petrol/EtOAc, 1:1)

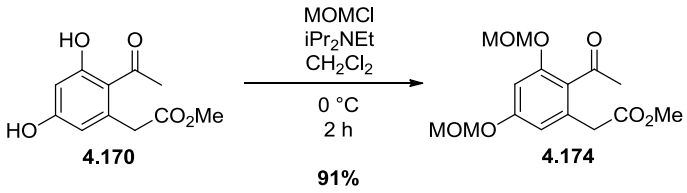
M.p. = 135 – 137 °C

IR (neat): 3179, 1705, 1607, 1574, 1351, 1231, 1167, 1022, 845, 699 cm^{-1}

^{1}H NMR (500 MHz, acetone-*d6*) δ 6.36 (d, *J* = 2.3 Hz, 1H), 6.32 (d, *J* = 2.3 Hz, 1H), 3.79 (s, 2H), 3.63 (s, 3H), 2.51 (s, 3H).

^{13}C NMR (125 MHz, acetone-*d6*) δ 203.5, 172.1, 161.8, 161.5, 137.9, 119.6, 112.4, 102.8, 52.0, 40.5, 32.2.

methyl 2-(2-acetyl-3,5-bis(methoxymethoxy)phenyl)acetate (4.174)



To a suspension of **4.170** (15.0 g, 66.9 mmol) in CH_2Cl_2 (300 mL), MOMCl (15.2 mL, 201 mmol) and *i*Pr_2NEt (35.0 mL, 201 mmol) were added at 0 °C. The mixture was stirred at rt for 2 h. The mixture was quenched with 0.5 M HCl (400 mL) and extracted with CH_2Cl_2 (200 mL). The combined organics were washed with brine (400 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 4:1 as eluent) to yield pure methyl 2-(2-acetyl-3,5-bis(methoxymethoxy)phenyl)acetate (**4.174**) (19.0 g, 91%) as a colourless oil.

R_f = 0.15 (petrol/EtOAc, 3:1)

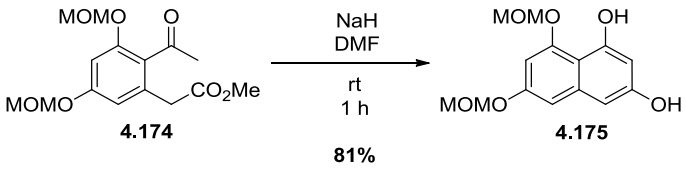
IR (neat): 2954, 1736, 1683, 1602, 1435, 1144, 1020, 997, 922 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (d, *J* = 2.2 Hz, 1H), 6.57 (d, *J* = 2.2 Hz, 1H), 5.19 (s, 2H), 5.16 (s, 2H), 3.69 (s, 2H), 3.68 (s, 3H), 3.48 (s, 3H), 3.47 (s, 3H), 2.54 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 203.8, 171.6, 159.0, 156.6, 134.5, 125.3, 112.1, 102.1, 94.7, 94.3, 56.4, 56.2, 51.9, 38.8, 32.2.

HRMS (ESI): calculated for $C_{13}H_{21}O_7$ 313.1287 $[M+H]^+$, found 313.1276.

6,8-bis(methoxymethoxy)naphthalene-1,3-diol (4.175)



To a solution of **4.174** (12.9 g, 41.3 mmol) in DMF (200 mL), NaH (60% dispersion in mineral oil, 5.87 g, 145 mmol) was added at rt. The mixture was stirred at rt for 1 h. The mixture was quenched with 0.5 M HCl (300 mL) and extracted with EtOAc (4 x 150 mL). The combined organics were washed with brine (4 x 200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 3:1 as eluent) to yield pure 6,8-bis(methoxymethoxy)naphthalene-1,3-diol (**4.175**) (9.36 g, 81%) as a yellow solid.

R_f = 0.11 (petrol/EtOAc, 3:1)

Mp = 93 – 95 °C

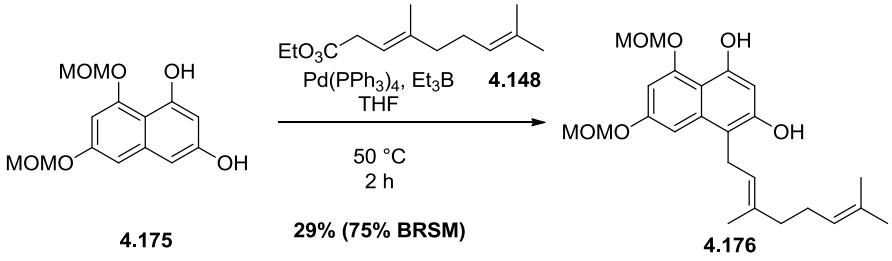
IR (neat): 3331, 1636, 1620, 1605, 1380, 1140, 1031, 905, 836 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (s, 1H), 6.85 (d, *J* = 2.1 Hz, 1H), 6.65 (d, *J* = 2.2 Hz, 1H), 6.56 (d, *J* = 2.4 Hz, 1H), 6.39 (d, *J* = 2.4 Hz, 1H), 5.41 (s, 2H), 5.24 (s, 2H), 5.03 (s, 1H), 3.58 (s, 3H), 3.52 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 155.6, 155.5, 154.8, 138.3, 106.9, 103.2, 101.3, 100.2, 99.2, 95.7, 94.4, 56.9, 56.2.

HRMS (ESI): calculated for $C_{14}H_{17}O_6$ 281.1025 $[M+H]^+$, found 281.1016.

(*E*)-4-(3,7-dimethylocta-2,6-dien-1-yl)-6,8-bis(methoxymethoxy)naphthalene-1,3-diol (4.176)[48]



A solution of **4.175** (7.50 g, 26.7 mmol), ethyl geranyl carbonate (**4.148**) (9.06 g, 40.0 mmol) and $Pd(PPh_3)_4$ (1.56 g, 1.35 mmol) in THF (100 mL) was degassed. Et_3B (1.0 M in THF, 40.0 mL, 40.0 mmol) was then added and the resultant mixture was stirred at 50 °C for 2 h. The mixture was cooled, quenched with *sat*. NH_4Cl solution (100 mL) and extracted with Et_2O (2 x 100 mL). The combined organics were washed with brine (100 mL) dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 5:1 → 3:1 gradient elution) to yield pure (*E*)-4-(3,7-dimethylocta-2,6-dien-1-yl)-6,8-bis(methoxymethoxy)naphthalene-1,3-diol (**4.176**) (3.28 g, 29%) as a brown gum along with recovered starting material (3.46 g, 46%).

R_f = 0.19 (petrol/EtOAc, 3:1)

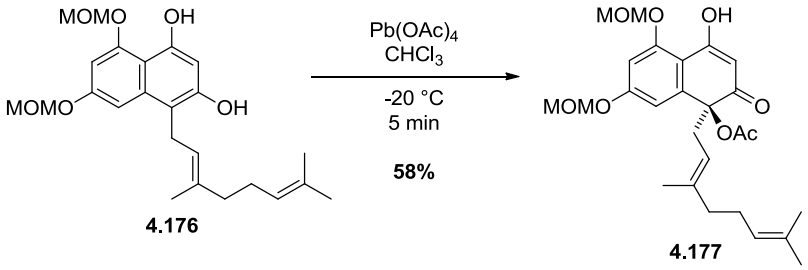
IR (neat): 3378, 2915, 1622, 1602, 1378, 1287, 1138, 1019, 990, 909, 816, cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (s, 1H), 7.08 (d, *J* = 2.1 Hz, 1H), 6.71 (d, *J* = 2.1 Hz, 1H), 6.40 (s, 1H), 5.41 (s, 2H), 5.25 (s, 2H), 5.21 (t, *J* = 6.7 Hz, 1H), 5.06 (t, *J* = 6.8 Hz, 1H), 3.59 (d, J = 6.6 Hz, 1H)3.58 (s, 3H), 3.52 (s, 3H), 2.13 – 1.99 (m, 4H), 1.88 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 155.3, 154.0, 153.3, 137.1, 136.7, 131.7, 124.0, 122.6, 109.7, 107.4, 101.1, 100.5, 98.8, 95.8, 94.6, 56.9, 56.1, 39.7, 26.6, 25.6, 24.5, 17.7, 16.3.

HRMS (ESI): calculated for $C_{24}H_{33}O_6$ 417.2277 $[M+H]^+$, found 417.2268.

(*E*)-1-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-5,7-bis(methoxymethoxy)-2-oxo-1,2-dihydronaphthalen-1-yl acetate (4.177)



4.176 **4.177**

To a solution of **4.176** (2.05 g, 5.04 mmol) in $CHCl_3$ (40 mL), $Pb(OAc)_4$ (2.35 g, 5.30 mmol) was added portion-wise at -20 °C. The mixture was stirred at -20 °C for 5 min before slowly warming to rt. The mixture was filtered through a short pad of SiO_2 and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 2:1 as eluent) to yield pure (*E*)-1-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-5,7-bis(methoxymethoxy)-2-oxo-1,2-dihydronaphthalen-1-yl acetate (**4.177**) (1.40 g, 58%) as a yellow oil.

R_f = 0.22 (petrol/EtOAc, 1:1)

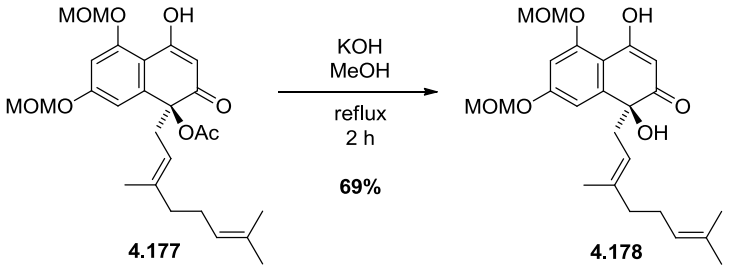
IR (neat): 3316, 2919, 1744, 1634, 1600, 1232, 1149, 1016, 966 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 6.85 (d, *J* = 2.3 Hz, 1H), 6.82 (d, *J* = 2.3 Hz, 1H), 5.66 (s, 1H), 5.36 (s, 2H), 5.19 (d, *J* = 7.0 Hz, 1H), 5.17 (d, *J* = 7.0 Hz, 1H), 5.04 (t, *J* = 6.8 Hz, 1H), 4.92 (t, *J* = 7.4 Hz, 1H), 3.56 (s, 3H), 3.47 (s, 3H), 2.69 (dd, *J* = 13.5, 7.9 Hz, 1H), 2.60 (dd, *J* = 13.5, 7.7 Hz, 1H), 2.13 (s, 3H), 1.98 – 1.85 (m, 4H), 1.67 (s, 3H), 1.57 (s, 3H), 1.31 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 195.1, 169.2, 167.6, 159.9, 155.6, 147.0, 140.8, 131.5, 124.0, 115.0, 109.5, 107.9, 103.0, 102.2, 96.4, 94.3, 81.8, 57.2, 56.4, 40.9, 39.9, 26.8, 25.6, 21.0, 17.6, 15.9.

HRMS (ESI): calculated for $C_{26}H_{35}O_8$ 475.2332 $[M+H]^+$, found 475.2331.

(*E*)-1-(3,7-dimethylocta-2,6-dien-1-yl)-1,4-dihydroxy-5,7-bis(methoxymethoxy)naphthalen-2(1H)-one (4.178)



4.177 4.178

To a solution of **4.177** (1.40 g, 2.95 mmol) in MeOH (40 mL), KOH (662 mg, 11.8 mmol) was added at rt. The mixture was heated at reflux for 2 h. The mixture was cooled, quenched with 0.5 M HCl (50 mL) and extracted with EtOAc (3 x 40 mL). The combined organics were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 2:1 as eluent) to give (*E*)-1-(3,7-dimethylocta-2,6-dien-1-yl)-1,4-dihydroxy-5,7-bis(methoxymethoxy)naphthalen-2(1H)-one (**4.178**) (888 mg, 69%) as a yellow oil.

R_f = 0.33 (petrol/EtOAc, 1:1)

IR (neat): 3440, 3313, 1629, 1597, 1425, 1147, 1015, 964 cm^{-1}

major tautomer (enol)

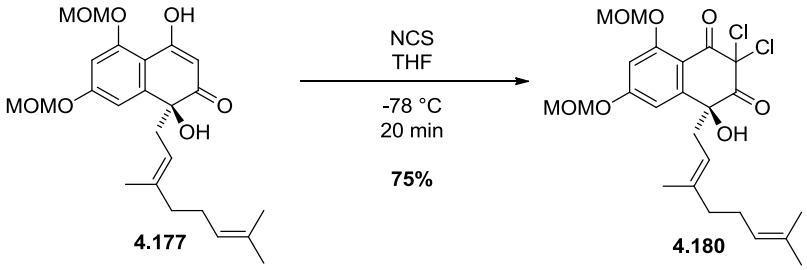
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.14 (d, *J* = 2.0 Hz, 1H), 6.83 (d, *J* = 2.0 Hz, 1H), 5.57 (s, 1H), 5.38 (s, 2H), 5.26 (d, *J* = 5.8 Hz, 1H), 5.21 (d, *J* = 6.8 Hz, 1H), 5.07 (t, *J* = 7.6 Hz, 1H), 5.01 (t, *J* = 7.8 Hz, 1H), 4.02 (s, 1H), 3.56 (s, 3H), 3.49 (s, 3H), 2.51 – 2.41 (m, 2H), 2.07 – 1.90 (m, 4H), 1.68 (s, 3H), 1.59 (s, 3H), 1.35 (s, 3H).

all peaks

^{13}C NMR (125 MHz, $CDCl_3$) δ 204.1, 200.7, 188.8, 168.7, 162.7, 160.1, 159.0, 155.6, 148.8, 148.6, 140.7, 140.3, 131.8, 131.4, 124.1, 123.7, 116.8, 116.4, 109.1, 108.2, 105.9, 103.7, 102.1, 100.0, 96.3, 95.2, 94.2, 94.1, 80.4, 78.9, 57.2, 56.6, 56.5, 56.4, 50.6, 45.8, 43.0, 39.9, 39.7, 26.8, 26.3, 25.6, 25.6, 17.7, 17.6, 16.3, 15.9.

HRMS (ESI): calculated for $C_{34}H_{31}O_7$ 431.2075 $[M-H]^-$, found 431.2081.

(*E*)-2,2-dichloro-4-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-6,8-bis(methoxymethoxy)naphthalene-1,3(2H,4H)-dione (4.180)



To a solution of **4.177** (888 mg, 2.05 mmol) in THF (20 mL), a solution of NCS (548 mg, 4.10 mmol) in THF (20 mL) was added drop wise at -78 °C. The mixture was stirred at -78 °C for 20 min before $Na_2S_2O_3$ (50 mg) was added. The mixture was warmed to rt, filtered through celite and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 6:1 as eluent) to yield pure (*E*)-2,2-dichloro-4-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-6,8-bis(methoxymethoxy)naphthalene-1,3(2H,4H)-dione (**4.180**) (771 mg, 75%) as a colourless oil.

R_f = 0.25 (petrol/EtOAc, 3:1)

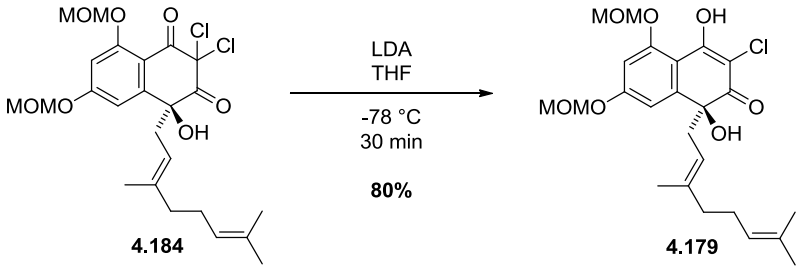
IR (neat): 3464, 2918, 1751, 1715, 1598, 1574, 1296, 1225, 1144, 1019, 923, 796 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (d, *J* = 2.2 Hz, 1H), 6.88 (d, *J* = 2.2 Hz, 1H), 5.33 (d, *J* = 6.8 Hz, 1H), 5.28 (d, *J* = 6.8 Hz, 1H), 5.28 – 5.24 (m, 2H), 5.04 (t, *J* = 6.9 Hz, 1H), 4.99 (t, *J* = 6.9 Hz, 1H), 3.75 (s, 1H), 3.52 (s, 3H), 3.50 (s, 3H), 2.66 (dd, *J* = 14.8, 8.5 Hz, 1H), 2.48 (dd, *J* = 14.8, 6.2 Hz, 1H), 2.09 – 1.97 (m, 4H), 1.71 (s, 3H), 1.60 (s, 3H), 1.47 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0, 178.0, 163.4, 159.3, 144.2, 142.9, 131.9, 123.8, 114.8, 111.9, 105.7, 103.8, 94.8, 94.2, 79.8, 78.8, 56.7, 56.6, 43.1, 39.8, 26.3, 25.7, 17.7, 16.5.

HRMS (ESI): calculated for $C_{24}H_{29}Cl_2O_7$ 499.1296 $[M-H]^-$, found 499.1305.

(*E*)-3-chloro-1-(3,7-dimethylocta-2,6-dien-1-yl)-1,4-dihydroxy-5,7-bis(methoxymethoxy)naphthalen-2(1H)-one (4.179)



To a solution of **4.184** (390 mg, 0.778 mmol) in THF (20 mL), LDA (2.0 M in THF, 1.56 mL, 3.11 mmol) was added at -78 °C. The mixture was stirred at -78 °C for 30 min. The mixture was quenched with 0.5 M HCl (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 2:1 as eluent) to yield pure (*E*)-3-chloro-1-(3,7-dimethylocta-2,6-dien-1-yl)-1,4-dihydroxy-5,7-bis(methoxymethoxy)naphthalen-2(1H)-one (**4.179**) (291 mg, 80%) as a yellow solid.

R_f = 0.19 (petrol/EtOAc, 1:1)

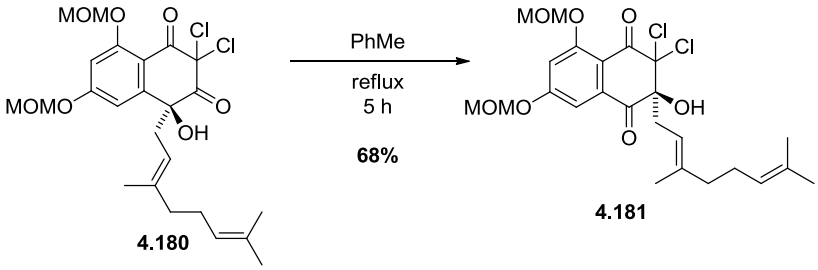
Mp = 66 – 68 °C

IR (neat): 3351, 2924, 1599, 1275, 1148, 1077, 1012, 826 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.60 (s, 1H), 7.15 (d, *J* = 2.3 Hz, 1H), 6.87 (d, *J* = 2.3 Hz, 1H), 5.41 (s, 2H), 5.27 (d, *J* = 6.8 Hz, 1H), 5.21 (d, *J* = 6.9 Hz, 1H), 5.07 (t, *J* = 6.8 Hz, 1H), 4.93 (t, *J* = 7.9 Hz, 1H), 3.96 (s, 1H), 3.58 (s, 3H), 3.49 (s, 3H), 2.52 (dd, *J* = 13.5, 8.3 Hz, 1H), 2.45 (dd, *J* = 13.6, 7.7 Hz, 1H), 2.06 – 1.90 (m, 4H), 1.68 (s, 3H), 1.60 (s, 3H), 1.36 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 194.3, 163.6, 160.3, 155.2, 146.6, 141.3, 131.6, 124.1, 115.9, 109.1, 107.4, 105.2, 102.5, 96.5, 94.3, 79.9, 57.4, 56.5, 46.3, 39.9, 26.8, 25.6, 17.6, 15.9.

HRMS (ESI): calculated for $C_{24}H_{30}ClO_7$ 465.1686 $[M-H]^-$, found 465.1687.

(*E*)-3,3-dichloro-2-(3,7-dimethylocta-2,6-dien-1-yl)-2-hydroxy-5,7-bis(methoxymethoxy)-2,3-dihydronaphthalene-1,4-dione (4.181)



A solution of (**4.180**) (255 mg, 0.509mmol), in PhMe (5 mL) was heated at reflux for 5 h. The mixture was then cooled and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 6:1 as eluent) to yield pure (*E*)-3,3-dichloro-2-(3,7-dimethylocta-2,6-dien-1-yl)-2-hydroxy-5,7-bis(methoxymethoxy)-2,3-dihydronaphthalene-1,4-dione (**4.181**) (169 mg, 66%) as a colourless oil.

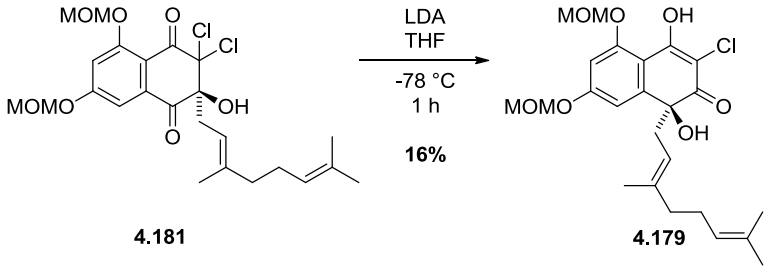
R_f = 0.25 (petrol/EtOAc, 3:1)

IR (neat): 3474, 2916, 1710, 1595, 1316, 1221, 1151, 1025, 958, 915, 802cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ7.33 (d, *J* = 2.4 Hz, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 5.36 (d, *J* = 6.9 Hz, 1H), 5.34 (d, *J* = 6.9 Hz, 1H), 5.31 (d, *J* = 6.9 Hz, 1H), 5.26 (d, *J* = 7.0 Hz, 1H), 5.01 (t, *J* = 6.6 Hz, 1H), 4.91 (t, *J* = 7.4 Hz, 1H), 4.37 (s, 1H), 3.56 (s, 3H), 3.50 (s, 3H), 2.81 (dd, *J* = 14.6, 6.7 Hz, 1H), 2.34 (dd, *J* = 14.5, 8.4 Hz, 1H), 2.03 – 1.86 (m, 4H), 1.70 (s, 3H), 1.58 (s, 3H), 1.25 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ194.3, 179.2, 162.9, 160.9, 141.3, 134.8, 131.8, 123.7, 115.1, 114.1, 110.1, 107.7, 95.3, 94.3, 92.8, 85.5, 56.9, 56.7, 39.7, 35.5, 26.2, 25.6, 17.7, 16.0.

(*E*)-3-chloro-1-(3,7-dimethylocta-2,6-dien-1-yl)-1,4-dihydroxy-5,7-bis(methoxymethoxy)naphthalen-2(1H)-one (4.179)



4.181 **4.179**

To a solution of **4.181** (169 mg, 0.337mmol) in THF (7 mL), LDA (2.0 M in THF, 0.50 mL, 1.0mmol) was added at -78 °C. The mixture was stirred at -78 °C for 1 h. The mixture was quenched with 0.5 M HCl (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 2:1 as eluent) to give (*E*)-3-chloro-1-(3,7-dimethylocta-2,6-dien-1-yl)-1,4-dihydroxy-5,7-bis(methoxymethoxy)naphthalen-2(1H)-one (**4.179**) (26 mg, 16%) as a yellow solid.

R_f = 0.19 (petrol/EtOAc, 1:1)

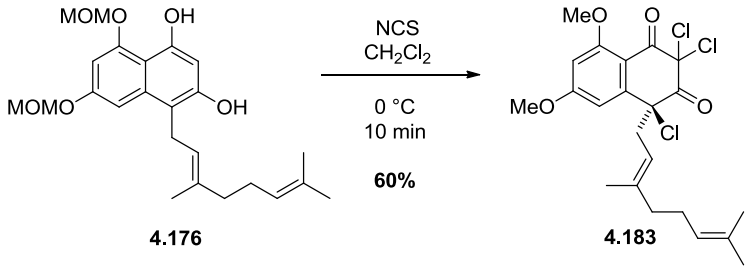
Mp = 66 – 68 °C

IR (neat): 3351, 2924, 1599, 1275, 1148, 1077, 1012, 826 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.60 (s, 1H), 7.15 (d, *J* = 2.3 Hz, 1H), 6.87 (d, *J* = 2.3 Hz, 1H), 5.41 (s, 2H), 5.27 (d, *J* = 6.8 Hz, 1H), 5.21 (d, *J* = 6.9 Hz, 1H), 5.07 (t, *J* = 6.8 Hz, 1H), 4.93 (t, *J* = 7.9 Hz, 1H), 3.96 (s, 1H), 3.58 (s, 3H), 3.49 (s, 3H), 2.52 (dd, *J* = 13.5, 8.3 Hz, 1H), 2.45 (dd, *J* = 13.6, 7.7 Hz, 1H), 2.06 – 1.90 (m, 4H), 1.68 (s, 3H), 1.60 (s, 3H), 1.36 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 194.3, 163.6, 160.3, 155.2, 146.6, 141.3, 131.6, 124.1, 115.9, 109.1, 107.4, 105.2, 102.5, 96.5, 94.3, 79.9, 57.4, 56.5, 46.3, 39.9, 26.8, 25.6, 17.6, 15.9.

HRMS (ESI): calculated for $C_{24}H_{30}ClO_7$ 465.1686 $[M-H]^-$, found 465.1687.

(*E*)-2,2,4-trichloro-4-(3,7-dimethylocta-2,6-dien-1-yl)-6,8-dimethoxynaphthalene-1,3(2H,4H)-dione (4.183)



To a solution of **4.176** (68 mg, 0.17 mmol) in CH_2Cl_2 (4 mL), NCS (74 mg, 0.55 mmol) was added at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. $Na_2S_2O_3$ (5 mg) was added and the mixture was filtered through celite and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 6:1 as eluent) to give (*E*)-2,2,4-trichloro-4-(3,7-dimethylocta-2,6-dien-1-yl)-6,8-dimethoxynaphthalene-1,3(2H,4H)-dione (**4.183**) (52 mg, 60%) as a colourless oil.

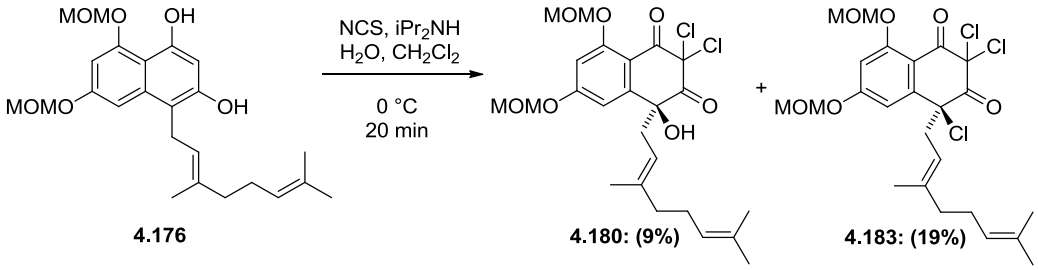
R_f = 0.33 (petrol/EtOAc, 3:1)

IR (neat): 2915, 1756, 1721, 1598, 1574, 1450, 1314, 1147, 975, 920, 822, 732 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$)δ 7.13 (d, *J* = 2.1 Hz, 1H), 6.95 (d, *J* = 2.1 Hz, 1H), 5.30 (s, 1H), 5.28 (d, *J* = 7.0 Hz, 1H), 5.23 (d, *J* = 7.0 Hz, 1H), 4.97 (t, *J* = 6.8 Hz, 1H), 4.70 (t, *J* = 7.1 Hz, 1H), 3.52 (s, 3H), 3.51 (s, 3H), 3.32 (dd, *J* = 14.2, 8.0 Hz, 1H), 2.90 (dd, *J* = 14.2, 6.7 Hz, 1H), 1.97 – 1.84 (m, 4H), 1.64 (s, 3H), 1.56 (s, 3H), 1.48 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 188.6, 178.5, 162.6, 159.0, 143.2, 141.1, 131.7, 123.7, 115.1, 114.0, 108.6, 104.6, 94.9, 94.4, 81.5, 69.5, 56.6, 42.0, 39.7, 26.1, 25.6, 17.6, 16.4.

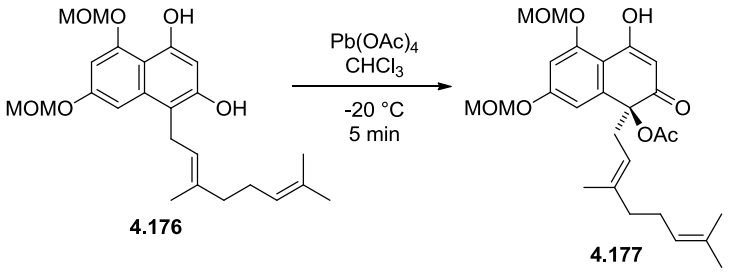
(*E*)-2,2-dichloro-4-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-6,8-bis(methoxymethoxy)naphthalene-1,3(2H,4H)-dione (4.180)



To a solution of **4.176** (70 mg, 0.17 mmol) in CH_2Cl_2 (4 mL), H_2O (0.2 mL) was added at 0 °C. A solution of NCS (81 mg, 0.60 mmol) and iPr_2NH (61 mg, 0.60 mmol) in CH_2Cl_2 (1 mL) was then added at 0 °C. The reaction mixture was stirred at 0 °C for 20 min. The mixture was quenched with 0.5 M HCl (5 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The combined organics were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 7:1 → 6:1 gradient elution) to give (*E*)-2,2-dichloro-4-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-6,8-bis(methoxymethoxy)naphthalene-1,3(2H,4H)-dione (**4.180**) (17 mg, 19%) as a colourless oil. Further elution gave **4.183** (8 mg, 9%) as a colourless oil.

Data of the products matched that of previously isolated

(*E*)-1-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-5,7-bis(methoxymethoxy)-2-oxo-1,2-dihydronaphthalen-1-yl acetate (4.177)



4.176 **4.177**

To a solution of **4.176** (1.49 g, 3.66 mmol) in $CHCl_3$ (30 mL), $Pb(OAc)_4$ (1.71 g, 3.85 mmol) was added portion wise at -20 °C. The mixture was stirred at -20 °C for 5 min before slowly warming to rt. The mixture was filtered through a short pad of SiO_2 and concentrated *in vacuo*. The residue was dissolved in EtOAc (100 mL) and washed sequentially with *sat*. $NaHCO_3$ solution (100 mL), H_2O (100 mL) and brine (100 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield (*E*)-1-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-5,7-bis(methoxymethoxy)-2-oxo-1,2-dihydronaphthalen-1-yl acetate **(4.177)** as a brown oil which was used in the next step without further purification.

R_f = 0.22 (petrol/EtOAc, 1:1)

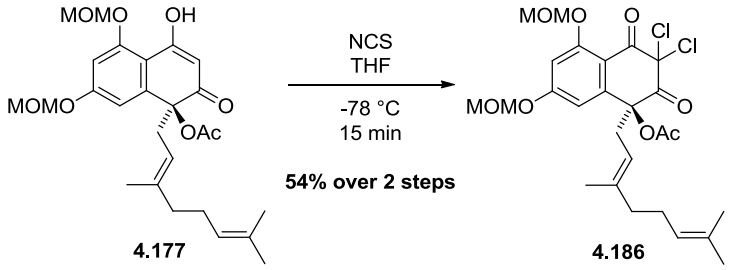
IR (neat): 3316, 2919, 1744, 1634, 1600, 1232, 1149, 1016, 966 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 6.85 (d, *J* = 2.3 Hz, 1H), 6.82 (d, *J* = 2.3 Hz, 1H), 5.66 (s, 1H), 5.36 (s, 2H), 5.19 (d, *J* = 7.0 Hz, 1H), 5.17 (d, *J* = 7.0 Hz, 1H), 5.04 (t, *J* = 6.8 Hz, 1H), 4.92 (t, *J* = 7.4 Hz, 1H), 3.56 (s, 3H), 3.47 (s, 3H), 2.69 (dd, *J* = 13.5, 7.9 Hz, 1H), 2.60 (dd, *J* = 13.5, 7.7 Hz, 1H), 2.13 (s, 3H), 1.98 – 1.85 (m, 4H), 1.67 (s, 3H), 1.57 (s, 3H), 1.31 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 195.1, 169.2, 167.6, 159.9, 155.6, 147.0, 140.8, 131.5, 124.0, 115.0, 109.5, 107.9, 103.0, 102.2, 96.4, 94.3, 81.8, 57.2, 56.4, 40.9, 39.9, 26.8, 25.6, 21.0, 17.6, 15.9.

HRMS (ESI): calculated for $C_{26}H_{35}O_8$ 475.2332 $[M+H]^+$, found 475.2331.

(*E*)-3,3-dichloro-1-(3,7-dimethylocta-2,6-dien-1-yl)-5,7-bis(methoxymethoxy)-2,4-dioxo-1,2,3,4-tetrahydronaphthalen-1-yl acetate (4.186)



4.177 4.186

To a solution of **4.177** (1.58 g, 3.3. mmol) in THF (30 mL), NCS (843 mg, 6.31 mmol) in THF (15 mL) was added drop wise at -78 °C. The mixture was stirred at -78 °C for 15 min. $Na_2S_2O_3$ (30 mg) was added and the mixture was warmed to rt, filtered through celite and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 5:1 as eluent) to give (*E*)-3,3-dichloro-1-(3,7-dimethylocta-2,6-dien-1-yl)-5,7-bis(methoxymethoxy)-2,4-dioxo-1,2,3,4-tetrahydronaphthalen-1-yl acetate (**4.186**) (1.09, 54% over 2 steps) as a colourless oil.

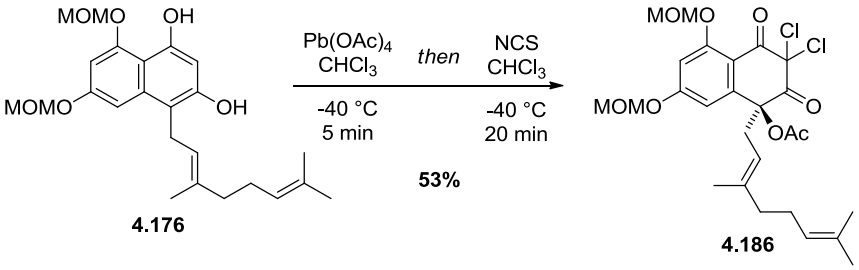
R_f = 0.22 (petrol/EtOAc, 3:1)

IR (neat): 2917,1753, 1719, 1599, 1324, 1225, 1147, 1019, 972, 924 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (d, *J* = 2.2 Hz, 1H), 6.72 (d, *J* = 2.2 Hz, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 5.28 (d, *J* = 6.8 Hz, 1H), 5.23 (d, *J* = 7.0 Hz, 1H), 5.20 (d, *J* = 7.0 Hz, 1H), 5.02 (t, *J* = 6.8 Hz, 1H), 4.92 (t, *J* = 7.3 Hz, 1H), 3.53 (s, 3H), 3.48 (s, 3H), 2.96 (dd, *J* = 14.2, 8.0Hz, 1H), 2.73 (dd, *J* = 14.3, 7.4 Hz, 1H), 2.14 (s, 3H), 2.04 – 1.90 (m, 4H), 1.66 (s, 3H), 1.58 (s, 3H), 1.41 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 190.7, 178.5, 169.2, 162.8, 159.8, 143.4, 141.9, 131.7, 123.8, 113.7, 113.6, 105.4, 104.0, 94.9, 94.4, 82.1, 81.4, 56.7, 56.6, 40.4, 39.8, 26.0, 25.7, 20.4, 17.6, 16.3.

(*E*)-3,3-dichloro-1-(3,7-dimethylocta-2,6-dien-1-yl)-5,7-bis(methoxymethoxy)-2,4-dioxo-1,2,3,4-tetrahydronaphthalen-1-yl acetate (4.186)



To a solution of **4.176** (234 mg, 0.576mmol) in $CHCl_3$ (8 mL), $Pb(OAc)_4$ (268mg, 0.604mmol) was added portion wise at -40 °C. The mixture was stirred at -40 °C for 5 min before NCS (147 mg, 1.04 mmol) was added portion wise at -40 °C. The mixture was stirred at -40 °C for a further 20 min before $Na_2S_2O_3$ (20 mg) was added. The mixture was warmed to rt, filtered through a short pad of SiO_2 and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 5:1 as eluent) to give (*E*)-3,3-dichloro-1-(3,7-dimethylocta-2,6-dien-1-yl)-5,7-bis(methoxymethoxy)-2,4-dioxo-1,2,3,4-tetrahydronaphthalen-1-yl acetate (**4.186**) (166 mg, 53%) as a yellow oil.

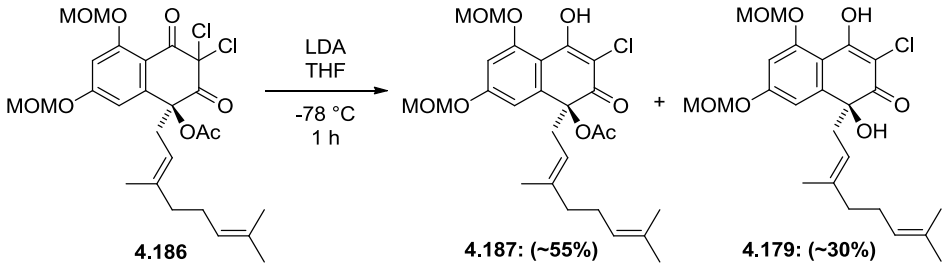
R_f = 0.22 (petrol/EtOAc, 3:1)

IR (neat): 2917, 1753, 1719, 1599, 1324, 1225, 1147, 1019, 972, 924 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (d, *J* = 2.2 Hz, 1H), 6.72 (d, *J* = 2.2 Hz, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 5.28 (d, *J* = 6.8 Hz, 1H), 5.23 (d, *J* = 7.0 Hz, 1H), 5.20 (d, *J* = 7.0 Hz, 1H), 5.02 (t, *J* = 6.8 Hz, 1H), 4.92 (t, *J* = 7.3 Hz, 1H), 3.53 (s, 3H), 3.48 (s, 3H), 2.96 (dd, *J* = 14.2, 8.0Hz, 1H), 2.73 (dd, *J* = 14.3, 7.4 Hz, 1H), 2.14 (s, 3H), 2.04 – 1.90 (m, 4H), 1.66 (s, 3H), 1.58 (s, 3H), 1.41 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 190.7, 178.5, 169.2, 162.8, 159.8, 143.4, 141.9, 131.7, 123.8, 113.7, 113.6, 105.4, 104.0, 94.9, 94.4, 82.1, 81.4, 56.7, 56.6, 40.4, 39.8, 26.0, 25.7, 20.4, 17.6, 16.3.

(*E*)-3-chloro-1-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-5,7-bis(methoxymethoxy)-2-oxo-1,2-dihydronaphthalen-1-yl acetate



To a solution of **4.186** (681 mg, 1.25 mmol) in THF (25 mL), LDA (2.0 M solution in THF, 1.25 mL, 2.50 mmol) was added at -78 °C. The mixture was stirred at -78 °C for 1 h. The mixture was quenched with 0.5 M HCl (30 mL) and extracted with Et_2O (3 x 20 mL). The combined organics were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 2:1 as eluent) to give a 2:1 mixture of (*E*)-3-chloro-1-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-5,7-bis(methoxymethoxy)-2-oxo-1,2-dihydronaphthalen-1-yl acetate (**4.186**) and **4.179** (470 mg combined) as a colourless oil.

R_f = 0.13 (petrol/EtOAc, 1:1)

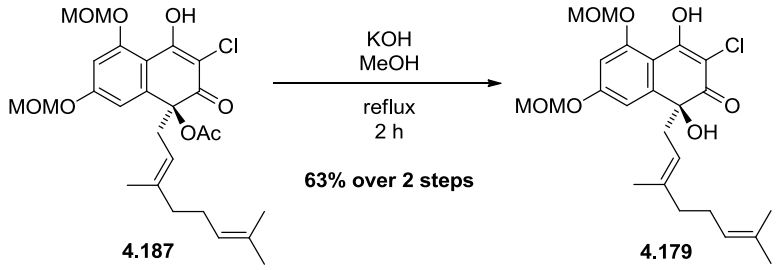
IR (neat): 3265, 2920, 1744, 1668, 1624, 1599, 1368, 1327, 1232, 1153, 1015, 964, 907cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.52 (s, 1H), 6.88 (d, *J* = 2.1 Hz, 1H), 6.83 (d, *J* = 2.0 Hz, 1H), 5.38 (s, 2H), 5.20 (d, *J* = 7.0 Hz, 1H), 5.18 (d, *J* = 6.7 Hz, 1H), 5.03 (t, *J* = 6.1 Hz, 1H), 4.81 (t, *J* = 7.9 Hz, 1H), 3.57 (s, 3H), 3.47 (s, 3H), 2.75 (dd, *J* = 13.3, 8.3 Hz, 1H), 2.60 (dd, *J* = 13.3, 7.7 Hz, 1H), 2.12 (s, 3H), 1.99 – 1.82 (m, 4H), 1.66 (s, 3H), 1.57 (s, 3H), 1.32 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 188.6, 169.1, 162.4, 160.0, 155.2, 145.1, 141.8, 131.6, 124.0, 114.1, 108.7, 108.1, 107.8, 102.5, 96.6, 94.3, 82.2, 57.4, 56.4, 41.3, 39.9, 26.9, 25.6, 20.8, 17.6, 16.0.

HRMS (ESI): calculated for $C_{26}H_{34}ClO_8$ 509.1942 $[M+H]^+$, found 509.1934.

(*E*)-3-chloro-1-(3,7-dimethylocta-2,6-dien-1-yl)-1,4-dihydroxy-5,7-bis(methoxymethoxy)naphthalen-2(1H)-one (4.179)



4.187 4.179

To a solution of **4.187** (470 mg, 0.92 mmol) in MeOH (20 mL), KOH (207 mg, 3.69 mmol) was added at rt. The mixture was heated at reflux for 2 h. The mixture was cooled, quenched with 0.5 M HCl (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 2:1 as eluent) to yield pure (*E*)-3-chloro-1-(3,7-dimethylocta-2,6-dien-1-yl)-1,4-dihydroxy-5,7-bis(methoxymethoxy)naphthalen-2(1H)-one **(4.179)** (313 mg, 62% over 2 steps) as a colourless oil.

R_f = 0.19 (petrol/EtOAc, 1:1)

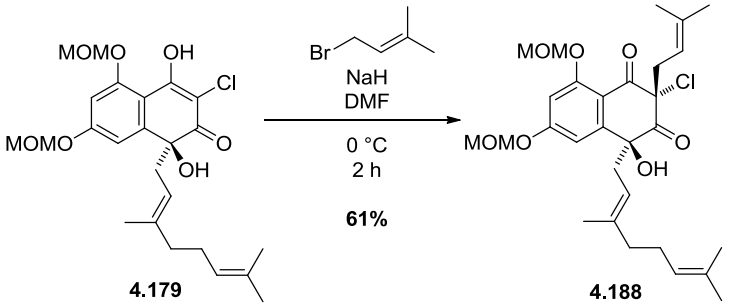
Mp = 66 – 68 °C

IR (neat): 3351, 2924, 1599, 1275, 1148, 1077, 1012, 826 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.60 (s, 1H), 7.15 (d, *J* = 2.3 Hz, 1H), 6.87 (d, *J* = 2.3 Hz, 1H), 5.41 (s, 2H), 5.27 (d, *J* = 6.8 Hz, 1H), 5.21 (d, *J* = 6.9 Hz, 1H), 5.07 (t, *J* = 6.8 Hz, 1H), 4.93 (t, *J* = 7.9 Hz, 1H), 3.96 (s, 1H), 3.58 (s, 3H), 3.49 (s, 3H), 2.52 (dd, *J* = 13.5, 8.3 Hz, 1H), 2.45 (dd, *J* = 13.6, 7.7 Hz, 1H), 2.06 – 1.90 (m, 4H), 1.68 (s, 3H), 1.60 (s, 3H), 1.36 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 194.3, 163.6, 160.3, 155.2, 146.6, 141.3, 131.6, 124.1, 115.9, 109.1, 107.4, 105.2, 102.5, 96.5, 94.3, 79.9, 57.4, 56.5, 46.3, 39.9, 26.8, 25.6, 17.6, 15.9.

HRMS (ESI): calculated for $C_{24}H_{30}ClO_7$ 465.1686 $[M-H]^-$, found 465.1687.

2-chloro-4-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-6,8-bis(methoxymethoxy)-2-(3-methylbut-2-en-1-yl)naphthalene-1,3(2H,4H)-dione (4.188)



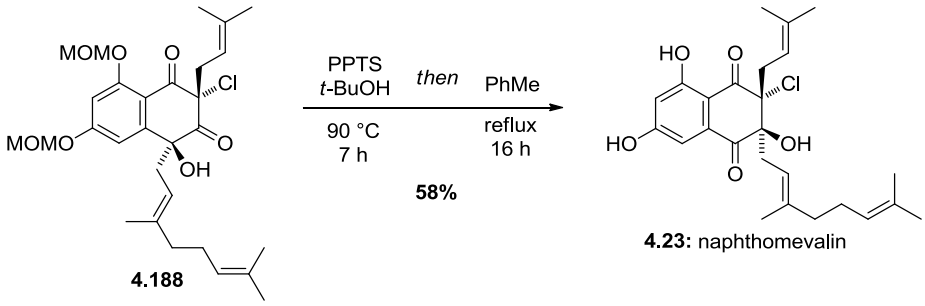
To a solution of **4.179** (413 mg, 0.884 mmol) in DMF (15 mL), NaH (60% dispersion in mineral oil, 39 mg, 0.97 mmol) was added at rt. The mixture was stirred at rt for 20 minutes before cooling to 0 °C. Prenyl bromide (0.15 mL, 1.3 mmol) was added at 0 °C and the mixture was stirred at 0 °C for a further 2 h. The mixture was quenched with 0.5 M HCl (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (3 x 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 7:1 as eluent) to yield pure 2-chloro-4-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-6,8-bis(methoxymethoxy)-2-(3-methylbut-2-en-1-yl)naphthalene-1,3(2H,4H)-dione (**4.188**) (291 mg, 61%) as a yellow oil.

R_f = 0.31 (petrol/EtOAc, 3:1)
IR (neat): 3481, 2915, 1735, 1698, 1599, 1576, 1296, 1224, 1143, 1019, 923, 866 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (d, *J* = 2.3 Hz, 1H), 6.81 (d, *J* = 2.2 Hz, 1H), 5.26 (d, *J* = 6.8 Hz, 1H), 5.24 (s, 2H), 5.23 (d, *J* = 6.7 Hz, 1H), 5.08 – 5.00 (m, 2H), 4.67 (t, *J* = 7.6 Hz, 1H), 3.85 (s, 1H), 3.54 (s, 3H), 3.50 (s, 3H), 3.02 – 2.89 (m, 2H), 2.65 (dd, *J* = 14.7, 8.4 Hz, 1H), 2.53 (dd, *J* = 14.6, 6.1 Hz, 1H), 2.10 – 1.95 (m, 4H), 1.70 (s, 3H), 1.60 (s, 3H), 1.53 (s, 3H), 1.47 (s, 3H), 1.46 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 188.3, 162.6, 157.8, 144.6, 141.7, 137.6, 131.7, 124.0, 115.7, 115.4, 115.3, 105.4, 103.6, 95.2, 94.2, 79.9, 70.0, 56.6, 56.5, 43.3, 39.8, 38.2, 26.4, 25.7, 25.6, 17.9, 17.7, 16.5.

HRMS (ESI): calculated for $C_{29}H_{40}ClO_7$ 535.2463 $[M+H]^+$, found 535.2461.

Naphthomevalin (4.23)



To a solution of **4.188** (65 mg, 0.12 mmol) in *t*-BuOH (3 mL), PPTS (150 mg, 0.597 mmol) was added at rt. The mixture was heated at 90 °C for 7 h before cooling to rt. The mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3 x 8 mL). The combined organics were washed sequentially with H_2O (15 mL) and brine (15 mL) dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then dissolved in PhMe (4 mL) and heated at reflux overnight. The solution was then cooled and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 7:1 as eluent) to yield pure naphthomevalin (**4.23**) (31 mg, 58%) as a colourless oil.

R_f = 0.27 (petrol/EtOAc, 3:1)

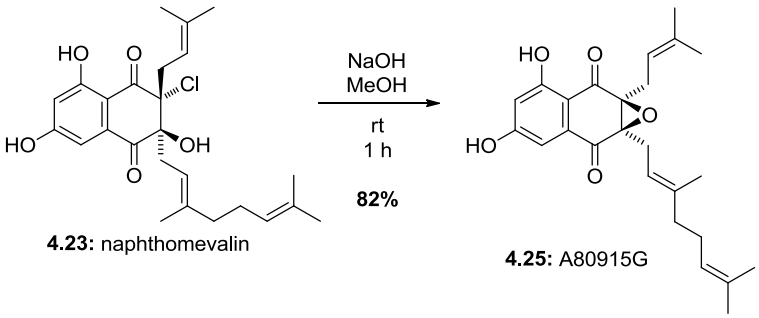
IR (neat): 3349, 2917, 1702, 1614, 1583, 1451, 1237, 1171, 867, 732 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.97 (s, 1H), 7.06 (d, *J* = 2.0 Hz, 1H), 6.81 (s, 1H), 6.73 (d, *J* = 2.0 Hz, 1H), 5.02 (t, *J* = 6.3 Hz, 1H), 4.94 (t, *J* = 7.2 Hz, 1H), 4.84 (t, *J* = 7.6 Hz, 1H), 4.18 (s, 1H), 3.03 – 2.93 (m, 2H), 2.52 (dd, *J* = 14.9, 8.0 Hz, 1H), 2.31 (dd, *J* = 14.6, 8.2 Hz, 1H), 2.03 – 1.85 (m, 4H), 1.71 (s, 3H), 1.59 (s, 3H), 1.57 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 198.1, 167.4, 166.1, 144.1, 140.9, 137.0, 134.4, 126.5, 119.1, 118.1, 113.2, 111.9, 109.9, 87.1, 85.6, 42.4, 41.0, 39.9, 29.0, 28.4, 28.3, 20.4, 20.4, 18.8.

HRMS (ESI): calculated for $C_{25}H_{30}ClO_5$ 445.1787 $[M-H]^-$, found 445.1795.

A80915G (4.25)[13]



To a solution of **4.23** (31 mg, 0.069 mmol) in MeOH (2 mL), NaOH (8 mg, 0.12 mmol) was added at rt. The mixture was stirred at rt for 1 h. The mixture was then quenched with 1 M HCl (7 mL) and extracted with EtOAc (3 x 5 mL). The combined organics were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 8:1 as eluent) to yield pure A80915G **(4.25**) (23 mg, 82%) as a colourless oil.

R_f = 0.44 (petrol/EtOAc, 3:1)

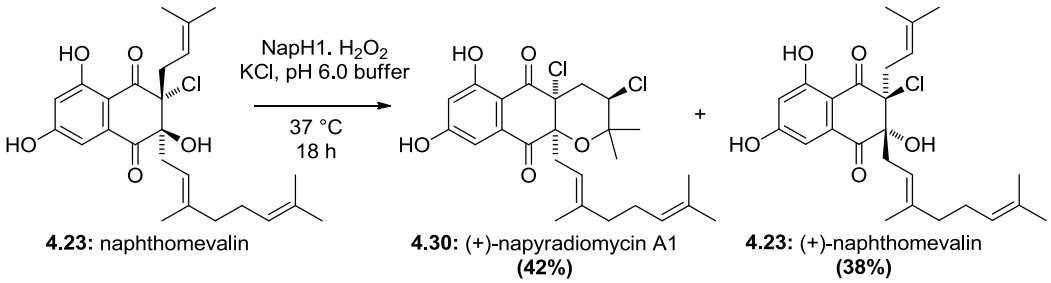
IR (neat): 3412, 2918, 1696, 1638, 1616, 1450, 1378, 1321, 1160 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.82 (s, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.63 (d, *J* = 2.4 Hz, 1H), 6.35 (s, 1H), 5.15 (t, *J* = 7.0 Hz, 1H), 5.15 (t, *J* = 7.0 Hz, 1H), 5.05 (t, *J* = 6.9 Hz, 1H), 3.24 (dd, *J* = 15.3, 7.1 Hz, 1H), 3.10 (dd, *J* = 15.3, 7.0 Hz, 1H), 2.55 (dd, *J* = 15.3, 6.7 Hz, 1H), 2.42 (dd, *J* = 15.3, 6.5 Hz, 1H), 2.10 – 1.95 (m, 4H), 1.73 (s, 3H), 1.72 (s, 3H), 1.72 (s, 3H), 1.64 (s, 3H), 1.57 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 195.4, 191.5, 164.5, 162.9, 139.0, 135.5, 134.3, 131.6, 124.0, 116.9, 116.8, 109.3, 108.8, 108.0, 67.7, 67.4, 39.7, 26.5, 25.8, 25.7, 25.5, 25.3, 18.2, 17.7, 16.6.

HRMS (ESI): calculated for $C_{25}H_{31}O_5$ 411.2171 $[M+H]^+$, found 411.2163.

(+)-napyradiomycin A1 (4.30) and (+)-naphthomevalin (4.23)



4.23: naphthomevalin

4.30: (+)-napyradiomycin A1 **(42%)**

4.23: (+)-naphthomevalin **(38%)**

This procedure was performed by Dr. Stefan Diethelm at the Scripps Institution of Oceanography.

120 mL MES buffer (50 mM MES, pH 6.0) containing KCl (50 mM), Na_3VO_4 (0.3 mM), H_2O_2 (1 mM) and naphthomevalin (**4.23**) (16 mg) was partitioned into 8 polyethylene tubes (15 mL each). To each tube was added NapH1 (200 µg). The reaction was incubated at 37 °C for 18 h. After combining the reaction mixtures, the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed and the residue was filtered through a pad of SiO_2 (eluent: hexanes/EtOAc 4:1). The solvent was evaporated and the residue was further purified by preparative HPLC (PhenomenexSynergi 10µ Hydro- RP 250 x 21 mm column, MeCN/H_2O, 70% MeCN → 100% MeCN. From (±)-naphthomevalin (**4.23)** (16 mg substrate, 0.036 mmol), 7 mg of (+)-napyradiomyin A1 (**4.30**) (0.015 mmol, 42%) and 6 mg (+)-naphthomevalin (**4.23**) (0.013 mmol, 38%) was obtained.

R_f: 0.40 (4:1, hexanes/EtOAc)

$[\alpha]_D^{25}$ = (c 0.70, $CHCl_3$) +38.7°

IR (neat): 2981, 2929, 1655, 1619, 1580, 1460, 1374, 1257, 1075 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.83 (bs, 1H), 7.20 (d, *J* = 2.5 Hz, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 4.89 (bs, 1H), 4.71 (t, *J* = 8.2 Hz, 1H), 4.42 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.70 (d, *J* = 8.3 Hz, 2H), 2.48 (dd, *J* = 14.2, 4.3 Hz, 1H), 2.42 (dd, *J* = 14.2, 11.6 Hz, 1H), 1.64-1.57 (m, 7H), 1.51 (s, 3H), 1.50 (s, 3H), 1.32 (s, 3H), 1.18 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 197.1, 193.8, 164.9, 164.1, 143.1, 135.2, 131.9, 123.8, 114.8, 110.2, 109.9, 108.2, 83.7, 79.0, 79.0, 58.8, 42.8, 41.5, 39.8, 28.8, 26.0, 25.8, 22.4, 17.7, 16.6.

HRMS (ESI): calculated for $C_{25}H_{29}Cl_2O_5$ 479.1398 $[M-H]^-$, found 479.1399.

Naphthomevalin $[\alpha]_D^{25}$ = (c 0.60, $CHCl_3$) +102.1°

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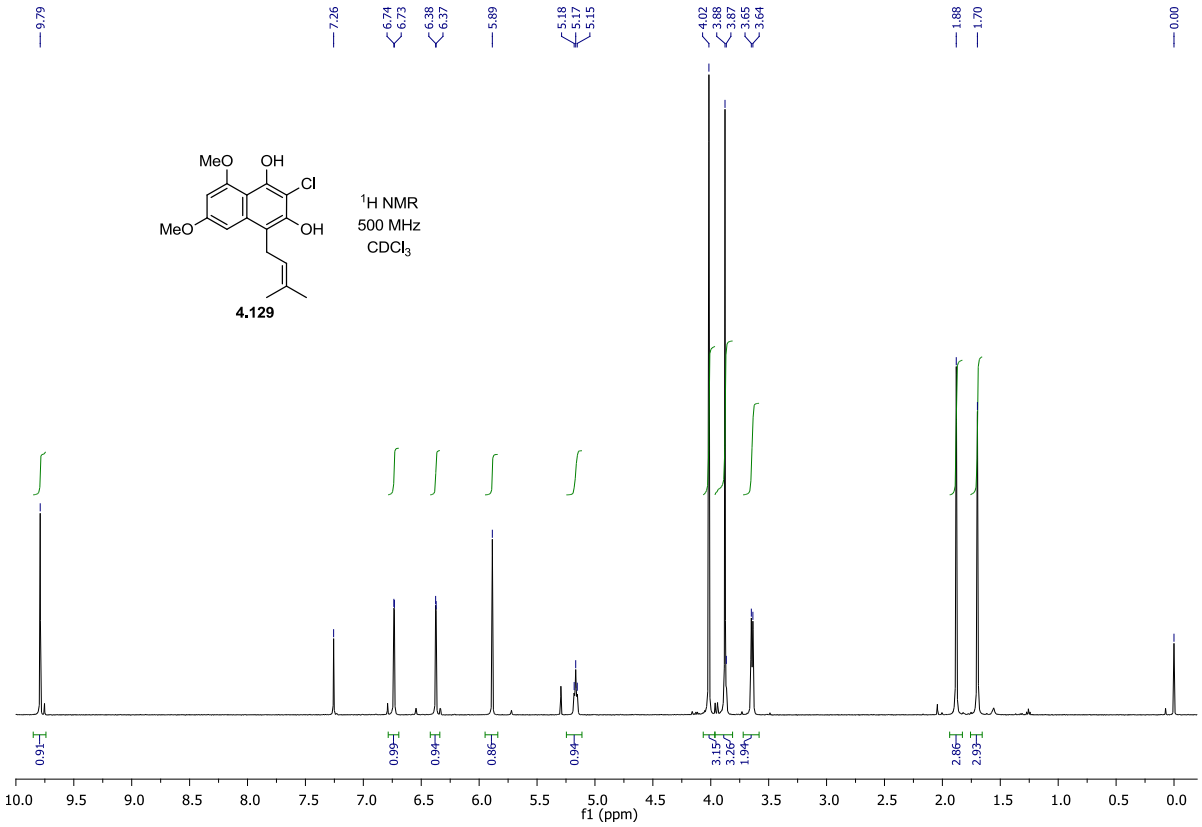
Appendix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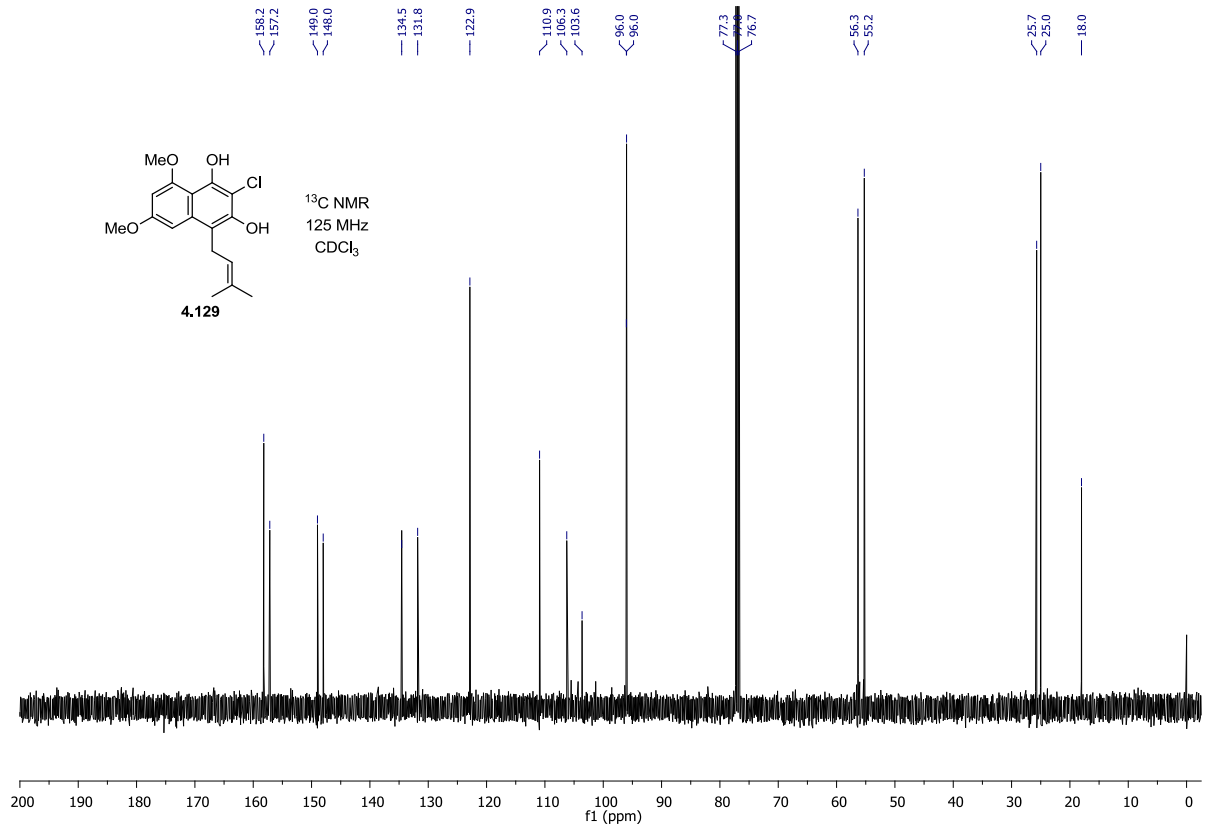
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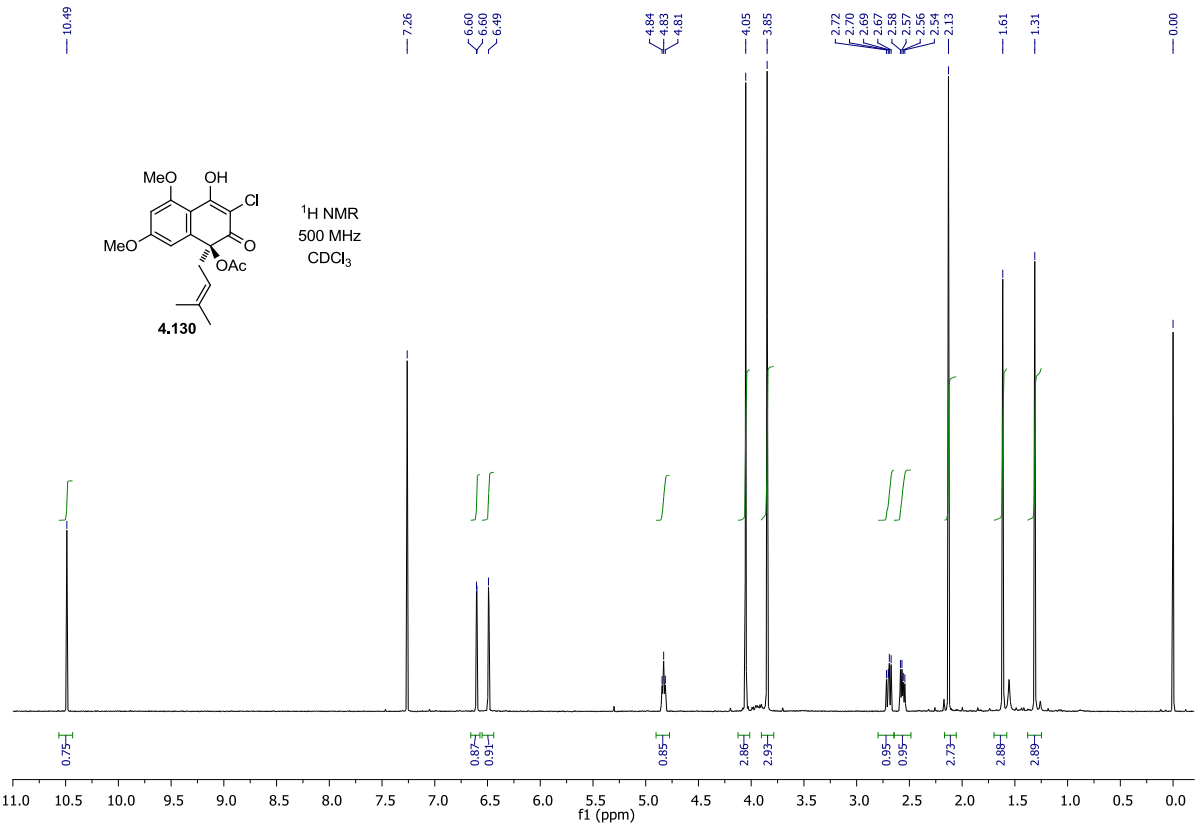
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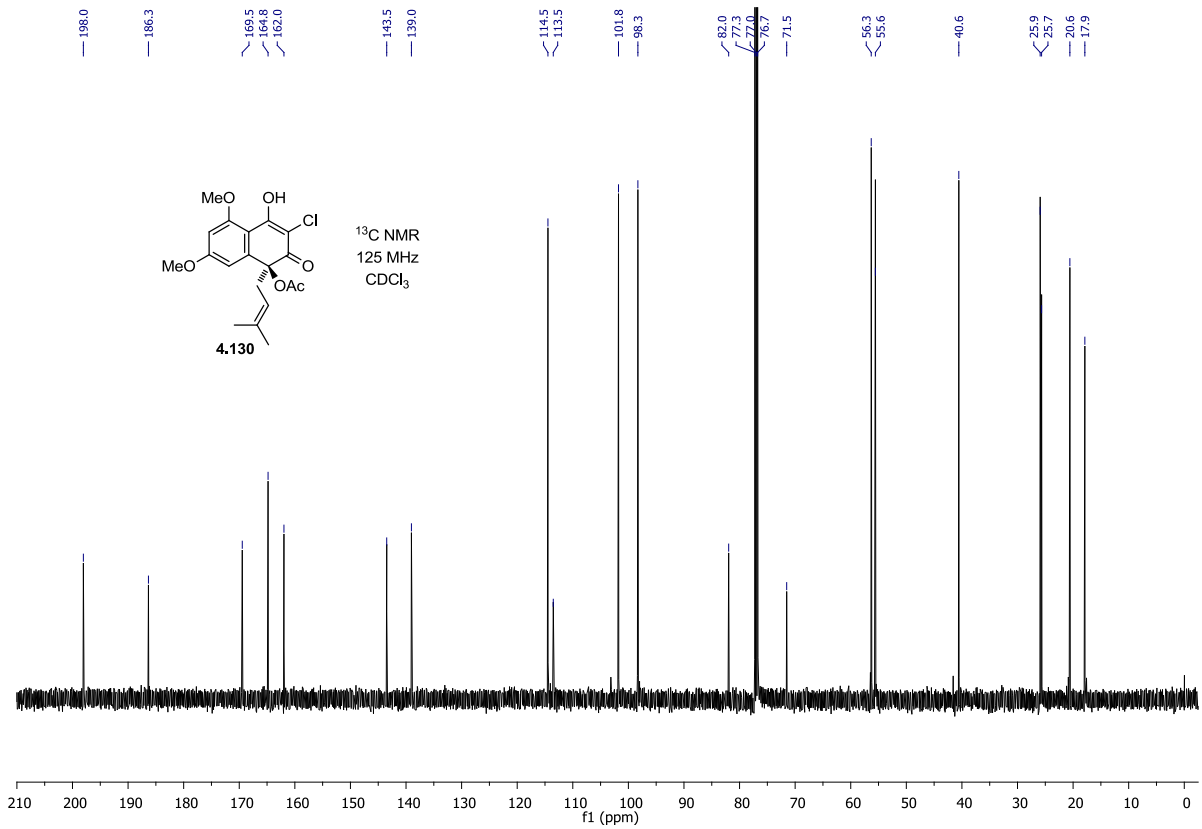
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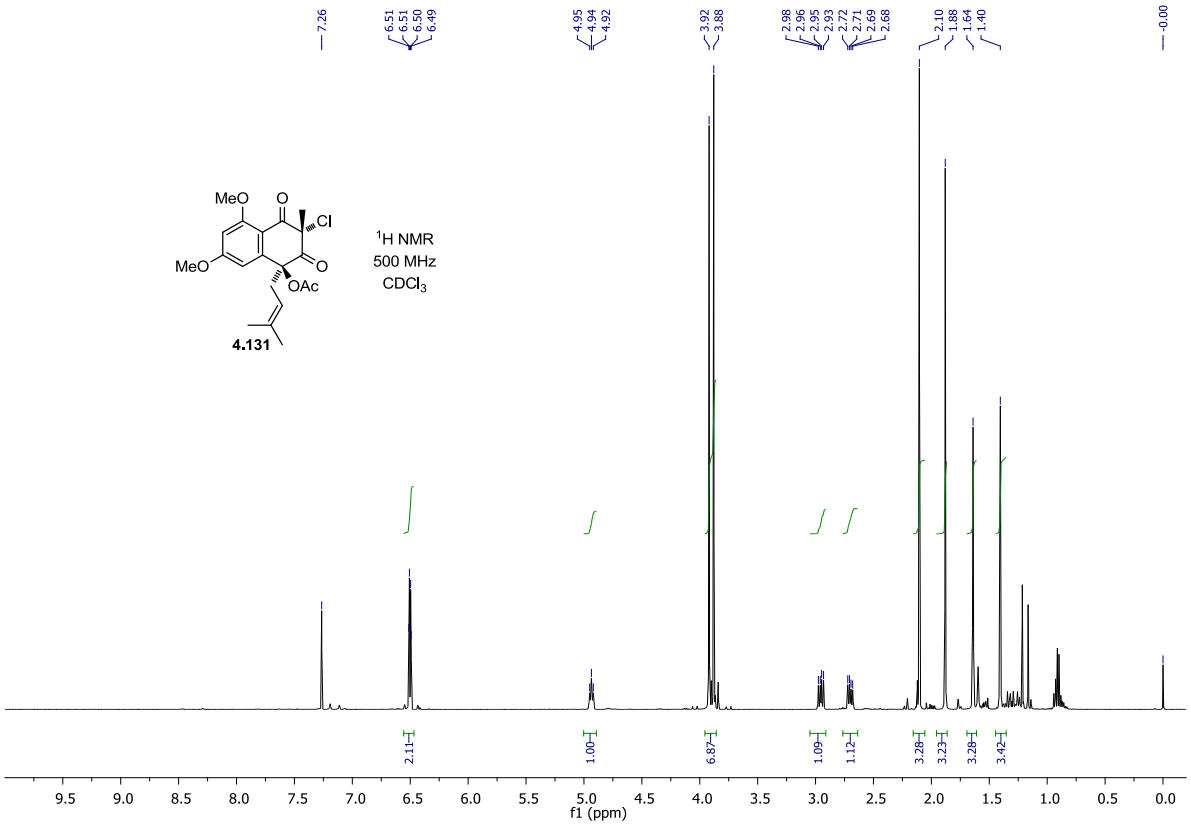
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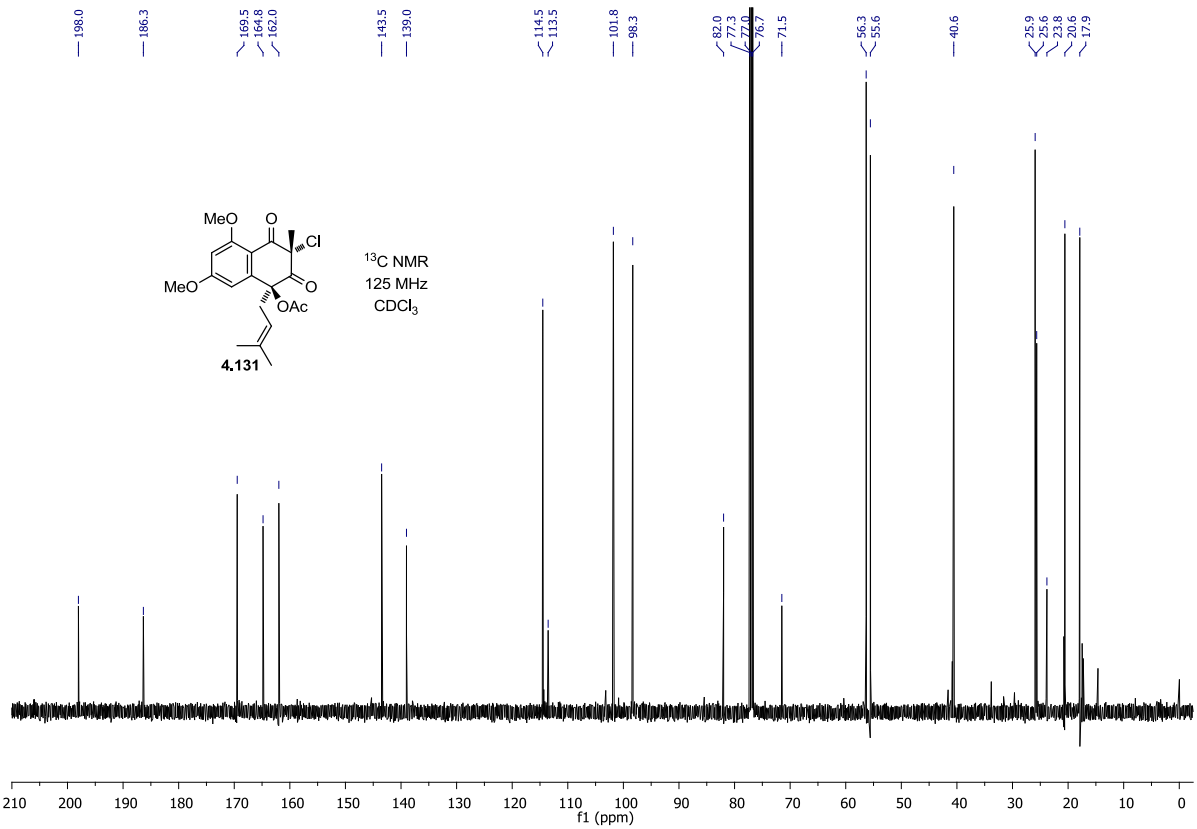
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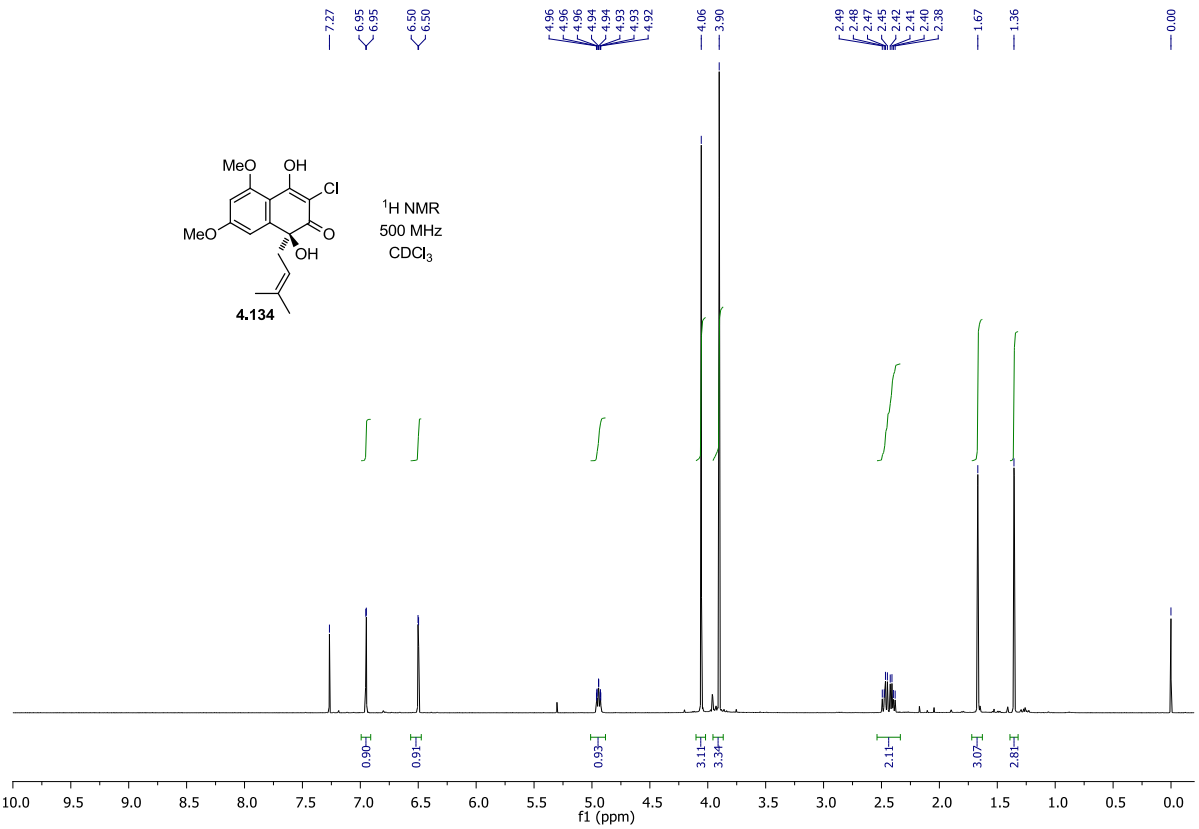
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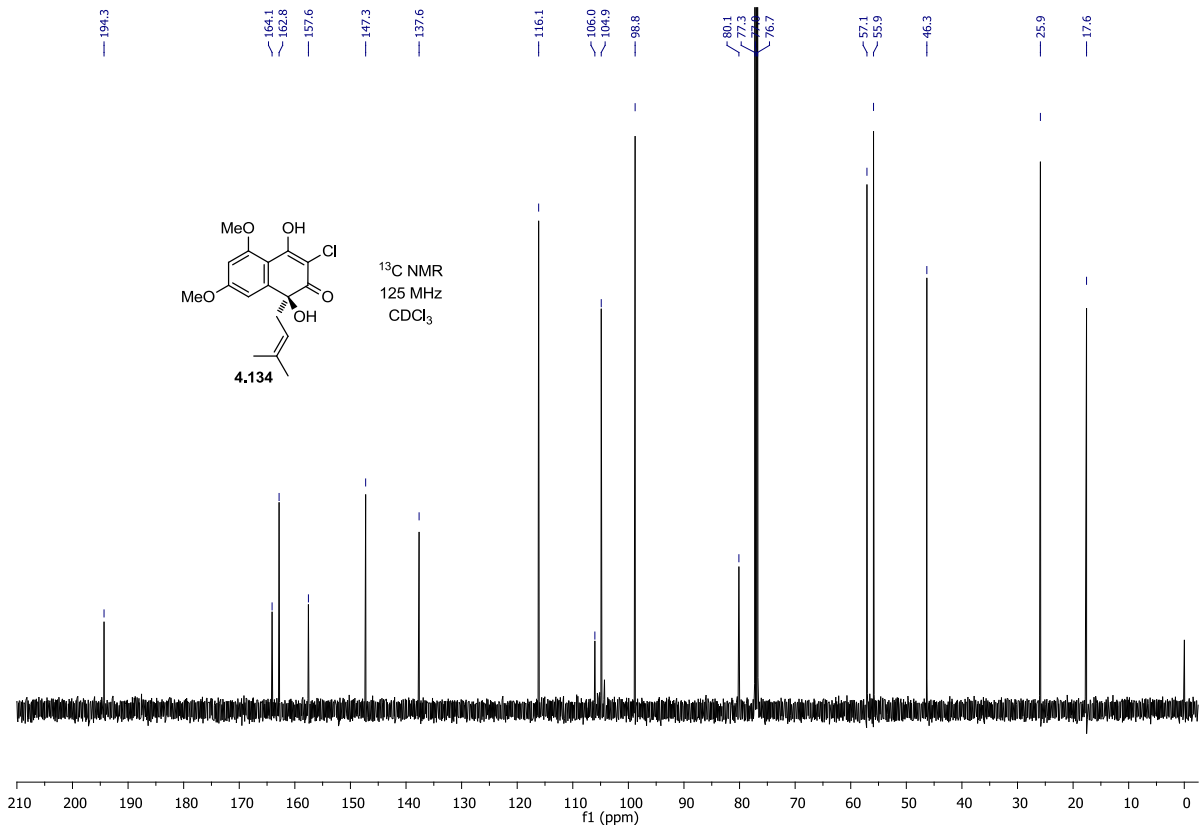
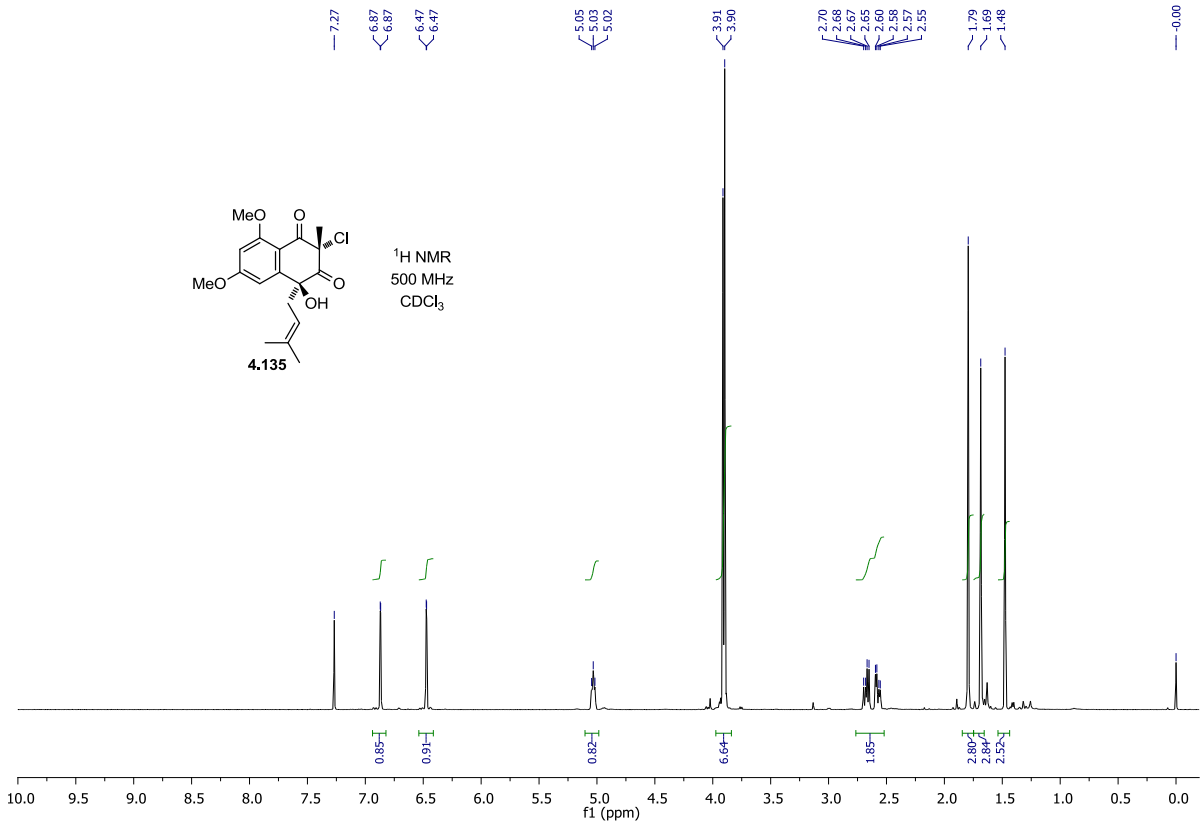
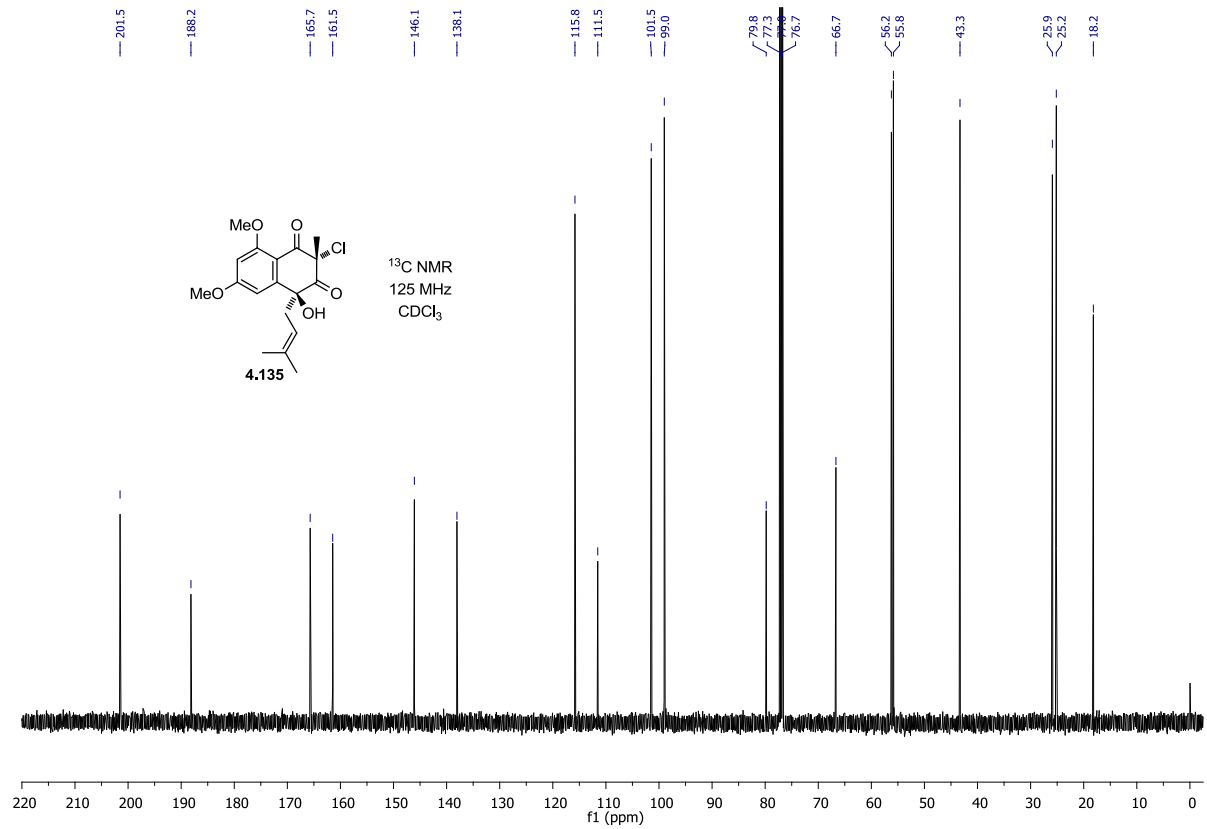
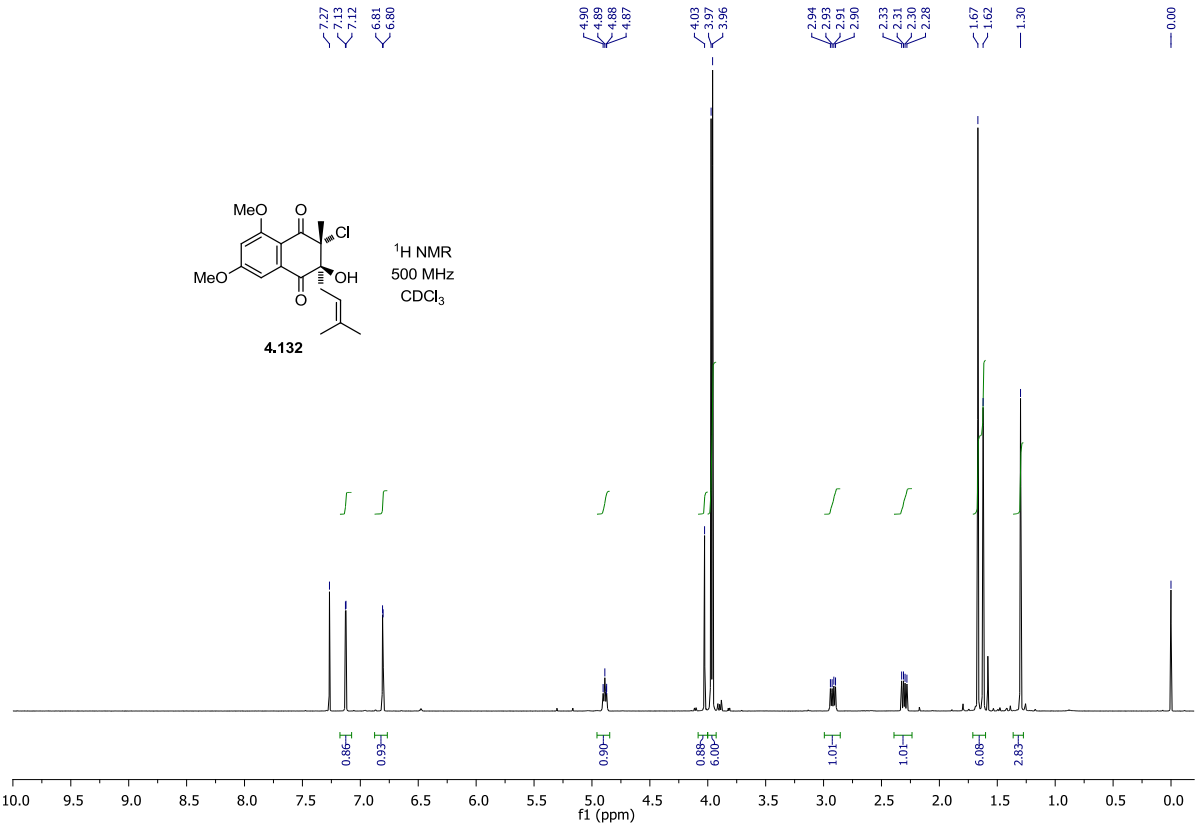
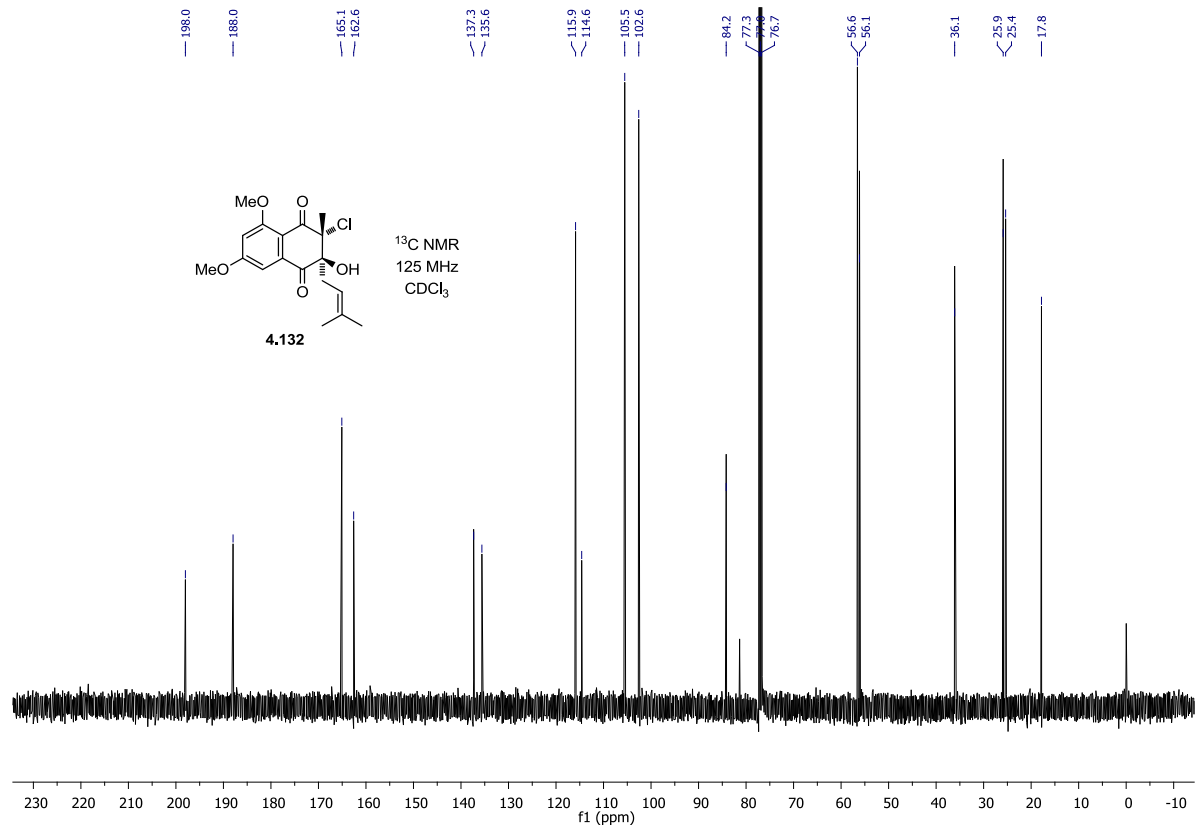
4.94
4.94
4.93
4.93
4.92
4.06
3.90
2.49
2.48
2.47
2.45
2.42
2.41
2.40
2.38
1.67
1.36
0.00
0.90
0.91
0.93
3.11
3.34
2.11
3.07
2.81
f1 (ppm)

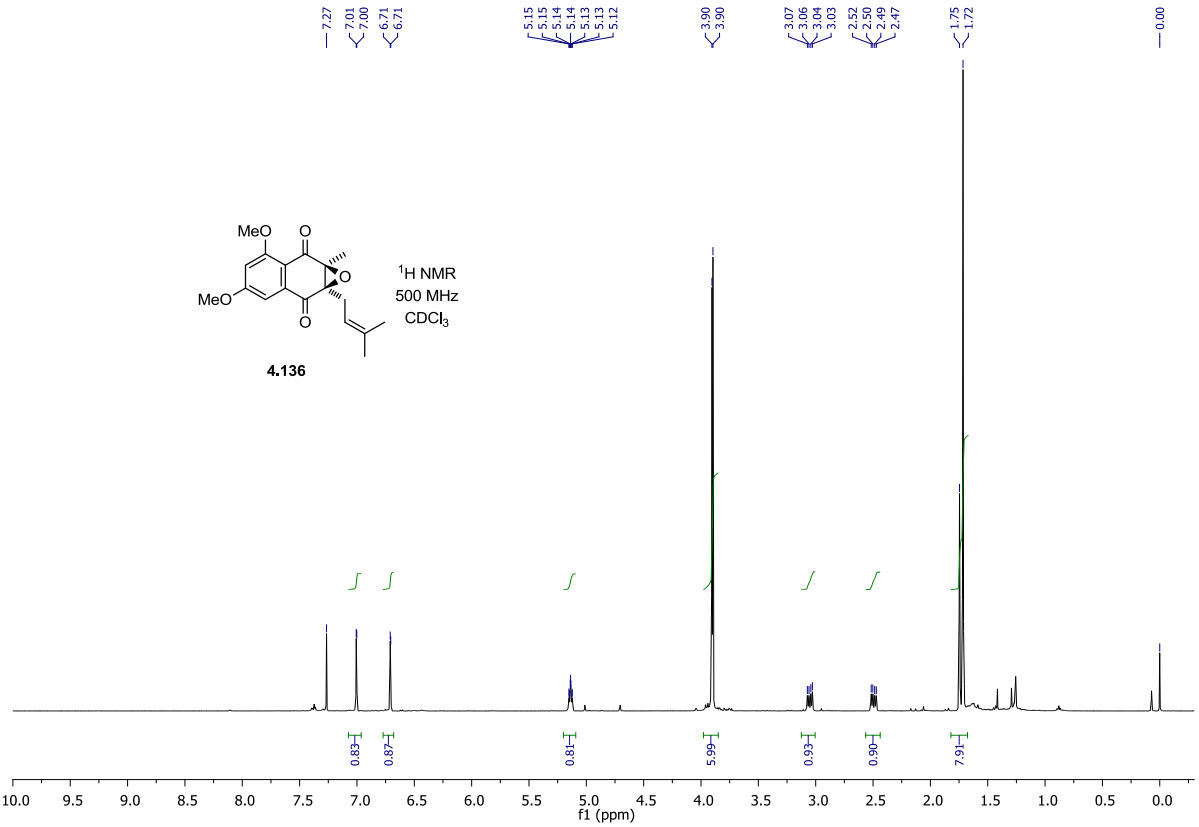

MeO
OH
Cl
MeO
O
OH
4.134
^{13}C NMR
125 MHz
$CDCl_3$
194.3
164.1
162.8
157.6
147.3
137.6
116.1
106.0
104.9
98.8
80.1
77.3
76.7
57.1
55.9
46.3
25.9
17.6
f1 (ppm)

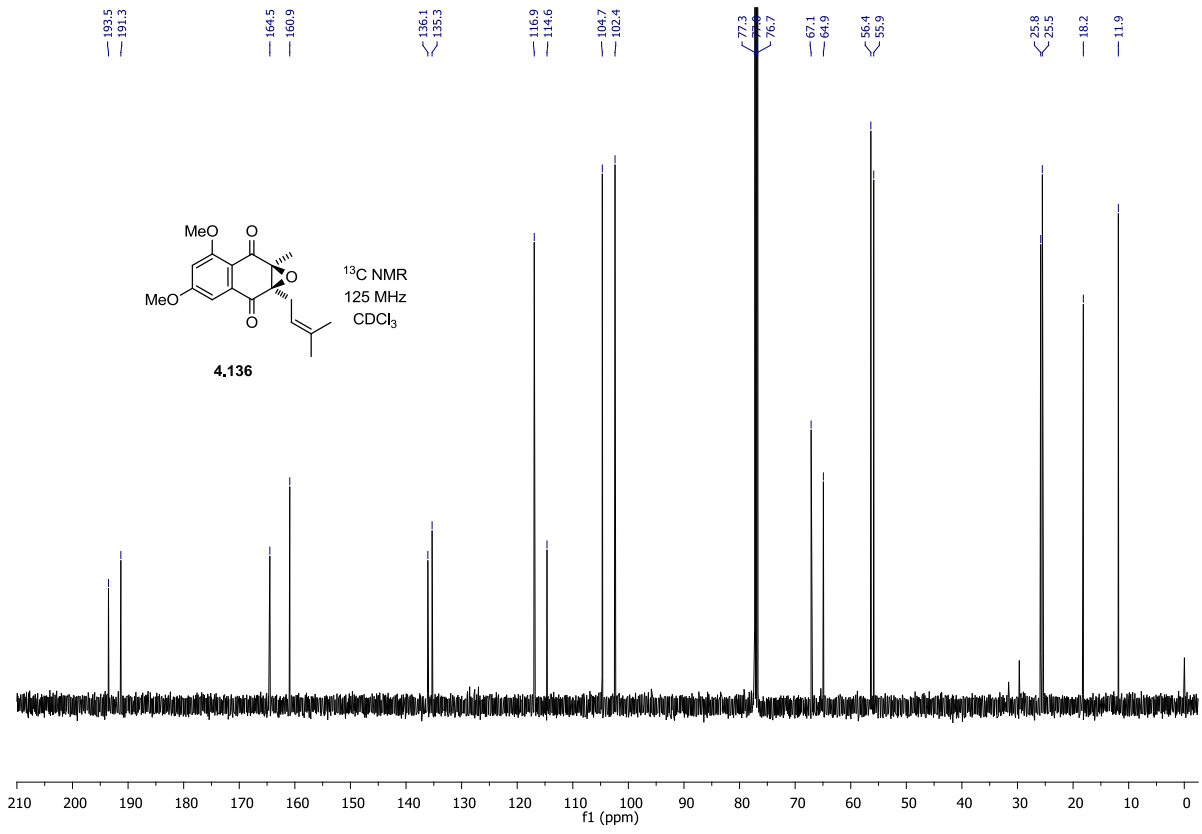

7.27
6.87
6.87
6.47
6.47
5.05
5.03
5.02
3.91
3.90
2.70
2.68
2.67
2.65
2.60
2.58
2.57
2.55
1.79
1.69
1.48
0.00
MeO
O
Cl
MeO
O
OH
4.135
^{1}H NMR
500 MHz
$CDCl_3$
0.85
0.91
0.82
6.64
1.85
2.80
2.84
2.52
f1 (ppm)

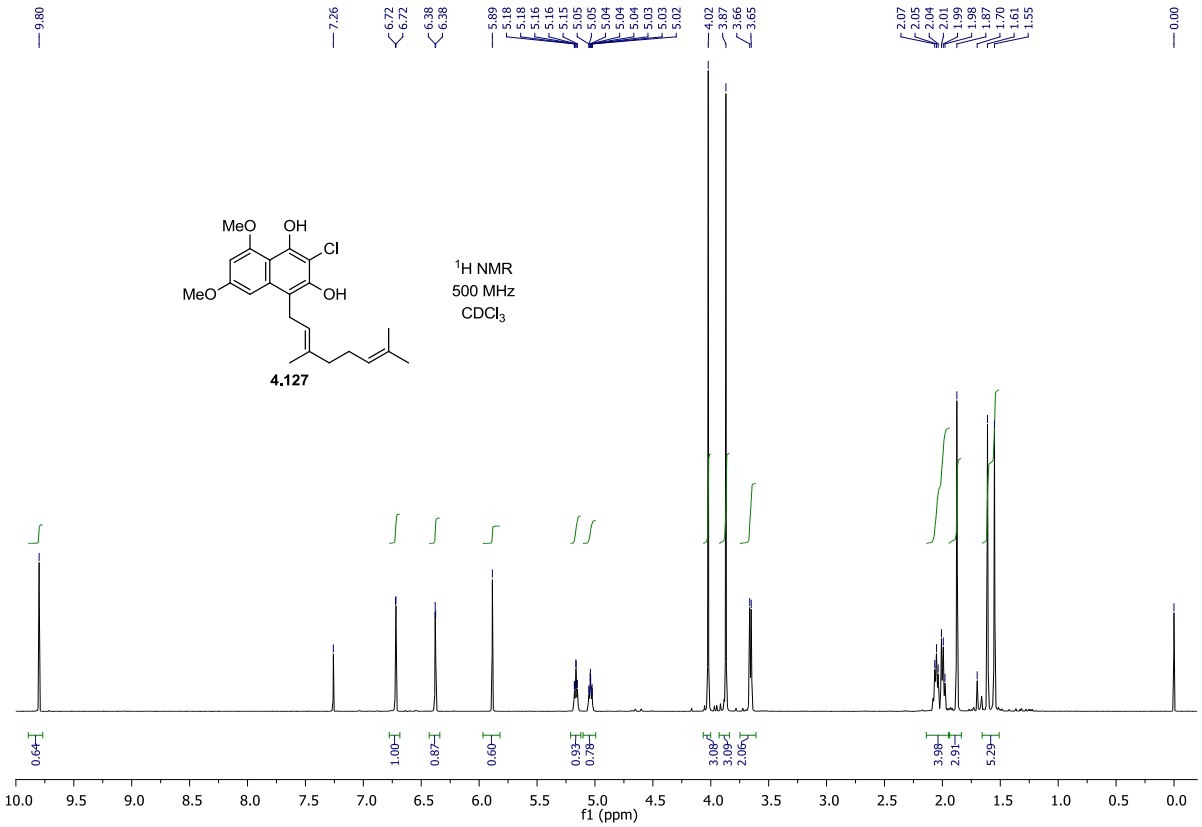

201.5
188.2
165.7
161.5
146.1
138.1
115.8
111.5
101.5
99.0
79.8
77.3
76.7
66.7
56.2
55.8
43.3
25.9
25.2
18.2
MeO
O
Cl
MeO
O
OH
4.135
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

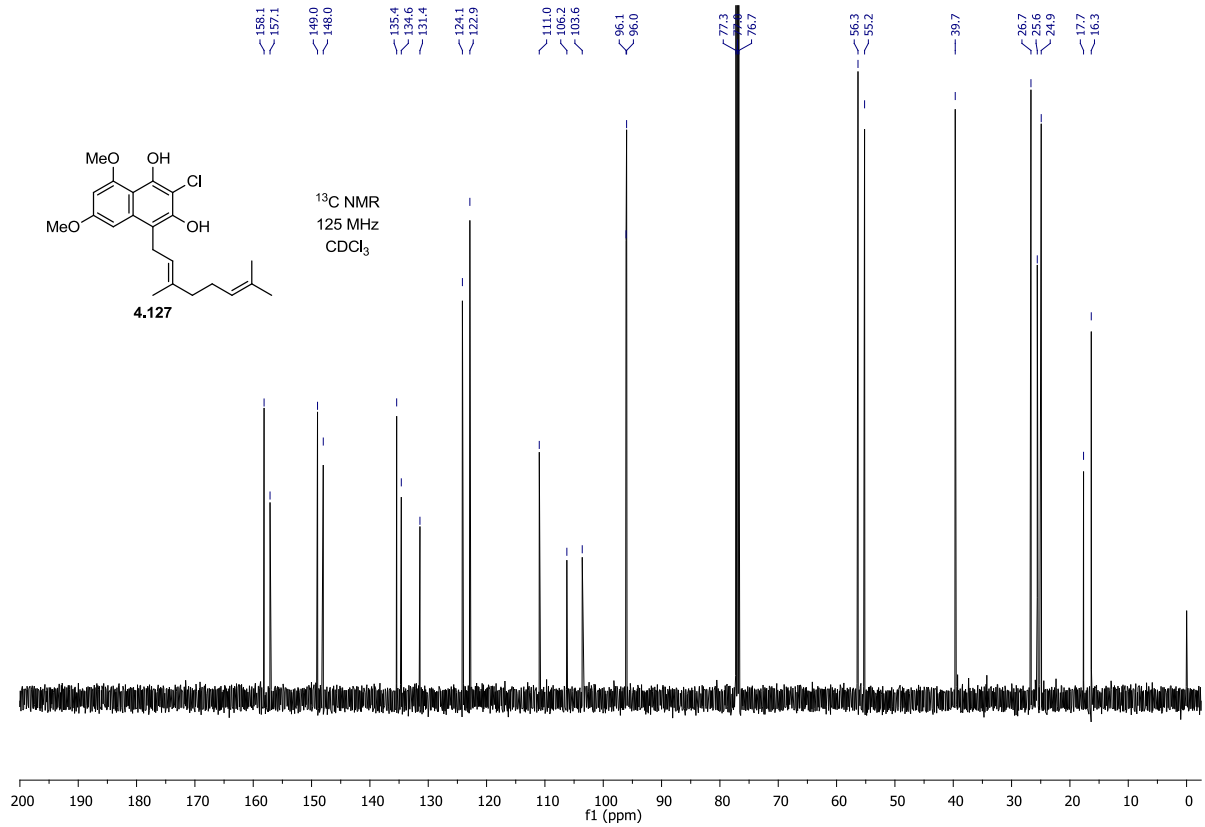

7.27
7.13
7.12
6.81
6.80
4.90
4.89
4.88
4.87
4.03
3.97
3.96
2.94
2.93
2.91
2.90
2.33
2.31
2.30
2.28
1.67
1.62
1.30
0.00
MeO
O
Cl
MeO
OH
O
4.132
^{1}H NMR
500 MHz
$CDCl_3$
0.86
0.93
0.90
0.88
6.00
1.01
1.01
6.08
2.83
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

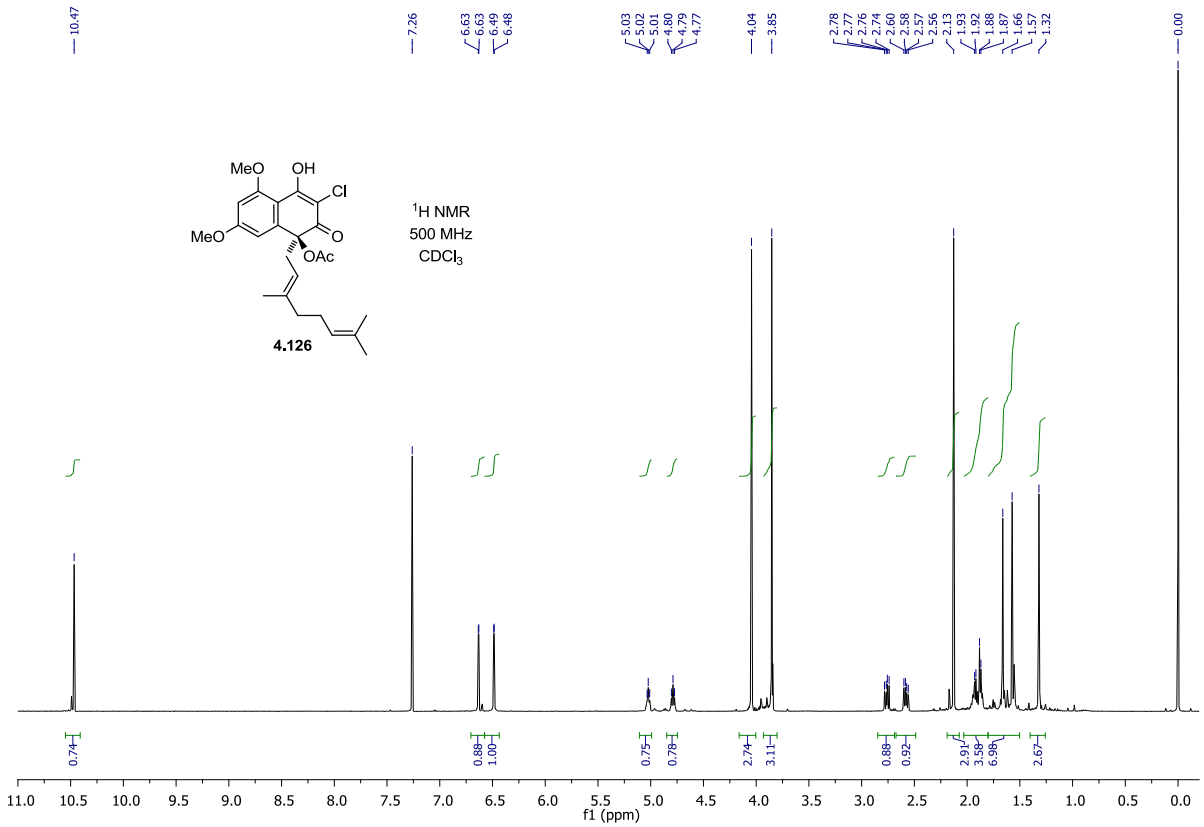

198.0
188.0
165.1
162.6
137.3
135.6
115.9
114.6
105.5
102.6
84.2
77.3
77.0
76.7
56.6
56.1
36.1
25.9
25.4
17.8
MeO
O
Cl
MeO
OH
O
4.132
^{13}C NMR
125 MHz
$CDCl_3$
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

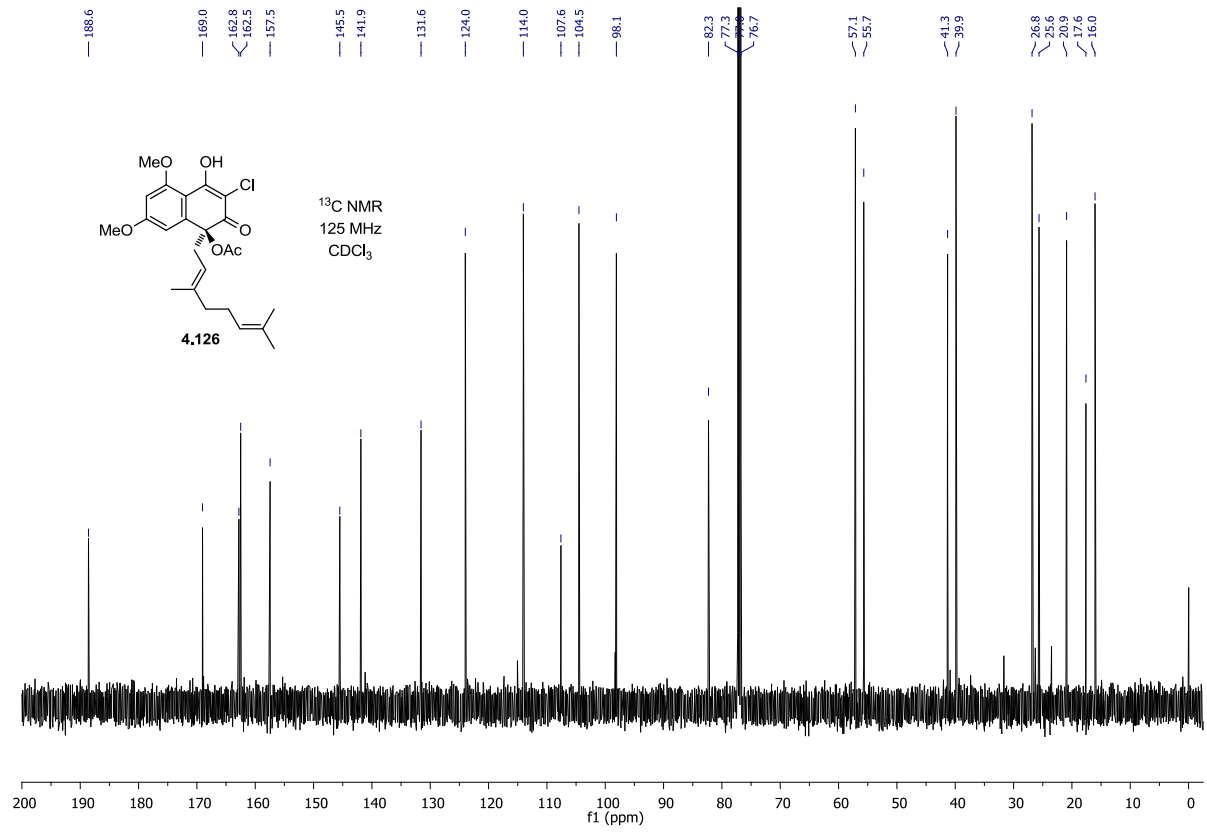

MeO
O
O
MeO
O
^{1}H NMR
500 MHz
$CDCl_3$
4.136
7.27
7.01
7.00
6.71
6.71
5.15
5.15
5.14
5.14
5.13
5.13
5.12
3.90
3.90
3.07
3.06
3.04
3.03
2.52
2.50
2.49
2.47
1.75
1.72
0.00
0.83
0.87
0.81
5.99
0.93
0.90
7.91
f1 (ppm)

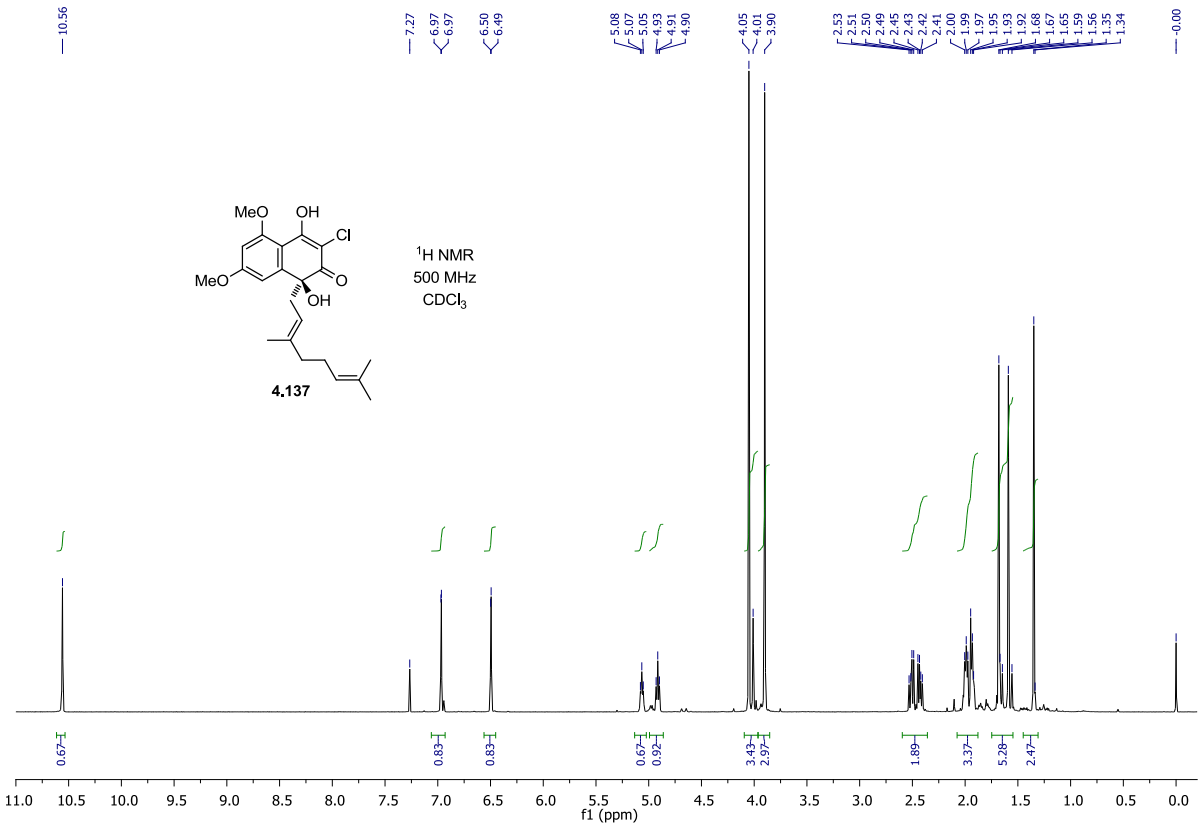

MeO
O
O
MeO
O
^{13}C NMR
125 MHz
$CDCl_3$
4.136
193.5
191.3
164.5
160.9
136.1
135.3
116.9
114.6
104.7
102.4
77.3
76.8
76.7
67.1
64.9
56.4
55.9
25.8
25.5
18.2
11.9
f1 (ppm)

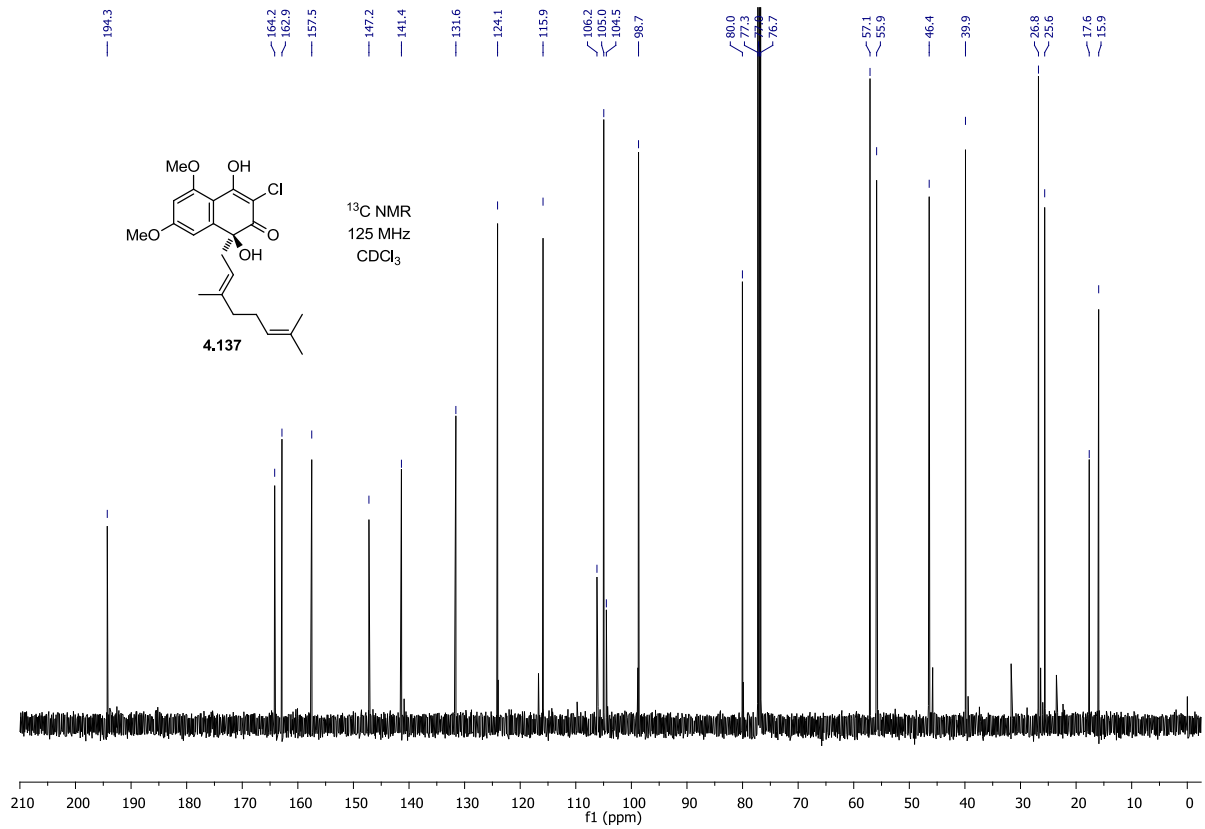

MeO
OH
Cl
MeO
OH
4.127
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

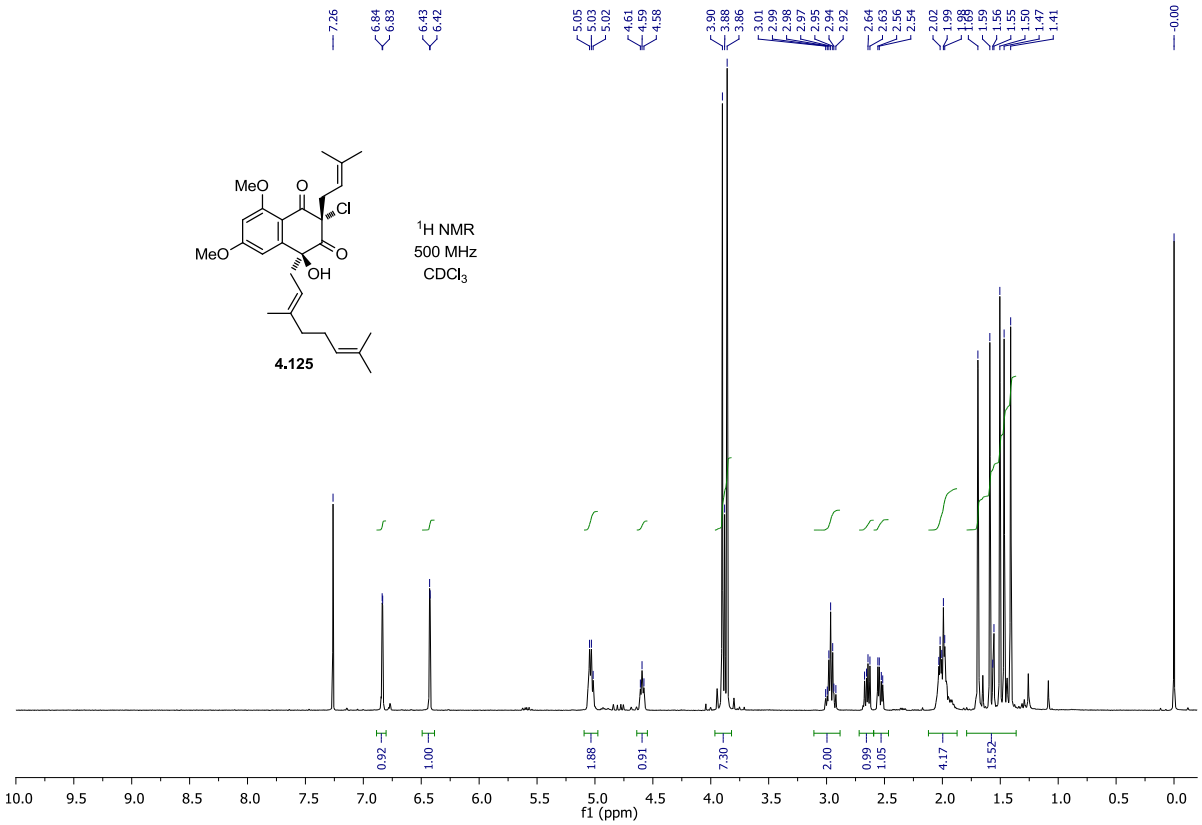

MeO
OH
Cl
MeO
OH
4.127
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

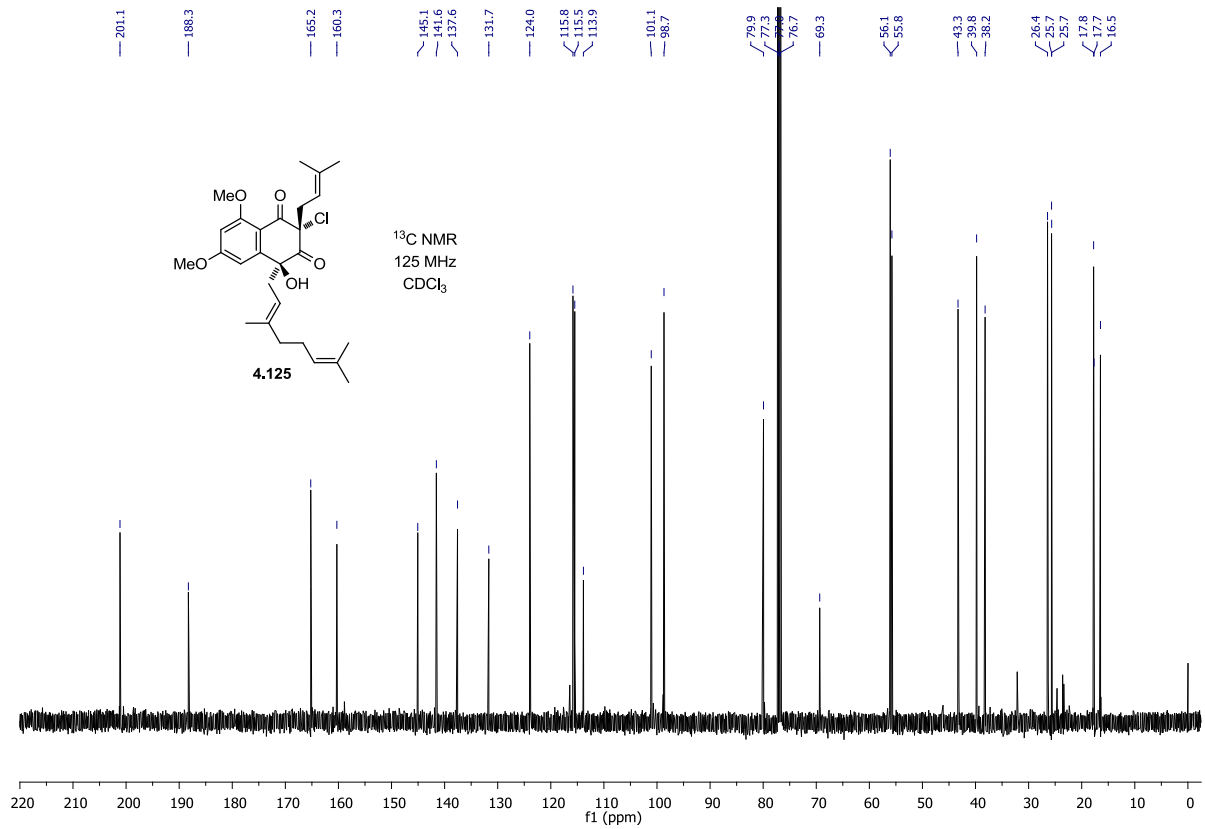

MeO
OH
Cl
MeO
O
OAc
4.126
^{1}H NMR
500 MHz
$CDCl_3$
10.47
7.26
6.63
6.63
6.49
6.48
5.03
5.02
5.01
4.80
4.79
4.77
4.04
3.85
2.78
2.77
2.76
2.74
2.60
2.58
2.57
2.56
2.13
1.93
1.92
1.88
1.87
1.66
1.57
1.32
0.00
0.74
0.88
1.00
0.75
0.78
2.74
3.11
0.88
0.92
2.91
3.38
6.98
2.67
f1 (ppm)

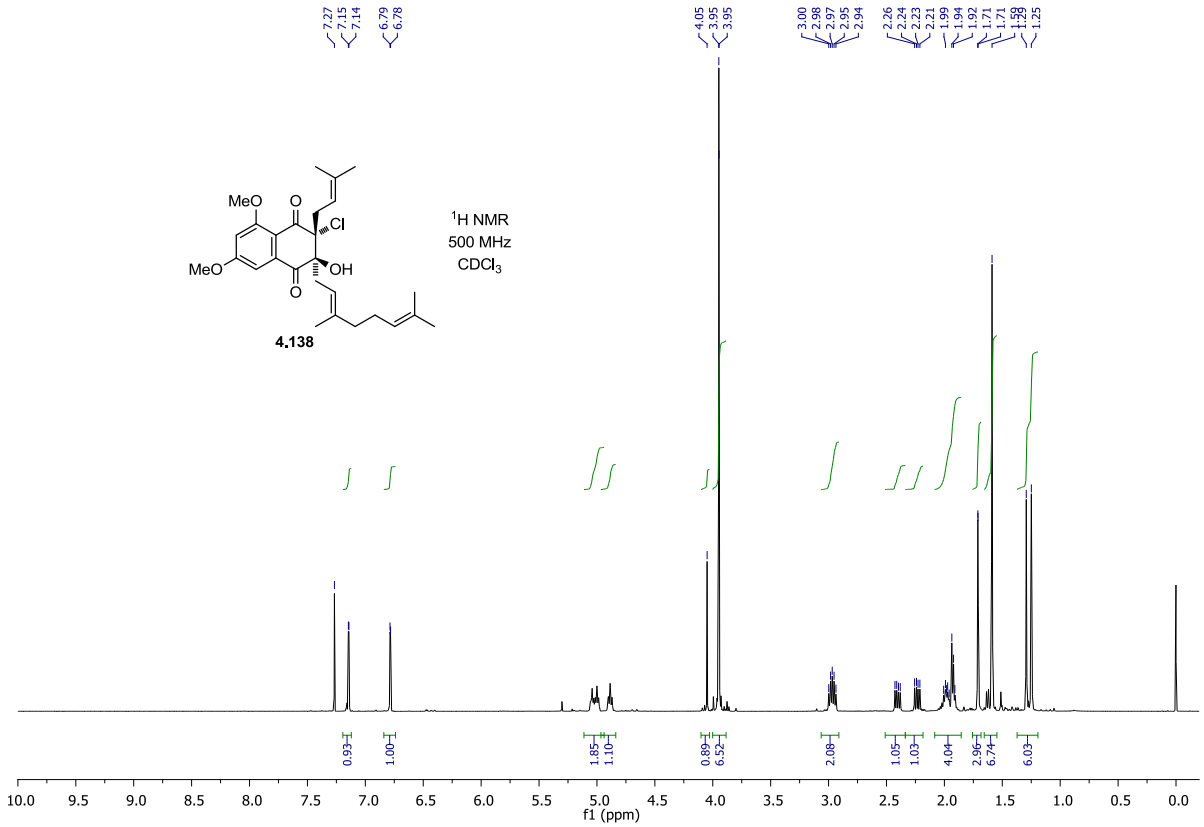

MeO
OH
Cl
MeO
O
OAc
4.126
^{13}C NMR
125 MHz
$CDCl_3$
188.6
169.0
162.8
162.5
157.5
145.5
141.9
131.6
124.0
114.0
107.6
104.5
98.1
82.3
77.3
76.8
76.7
57.1
55.7
41.3
39.9
26.8
25.6
20.9
17.6
16.0
f1 (ppm)

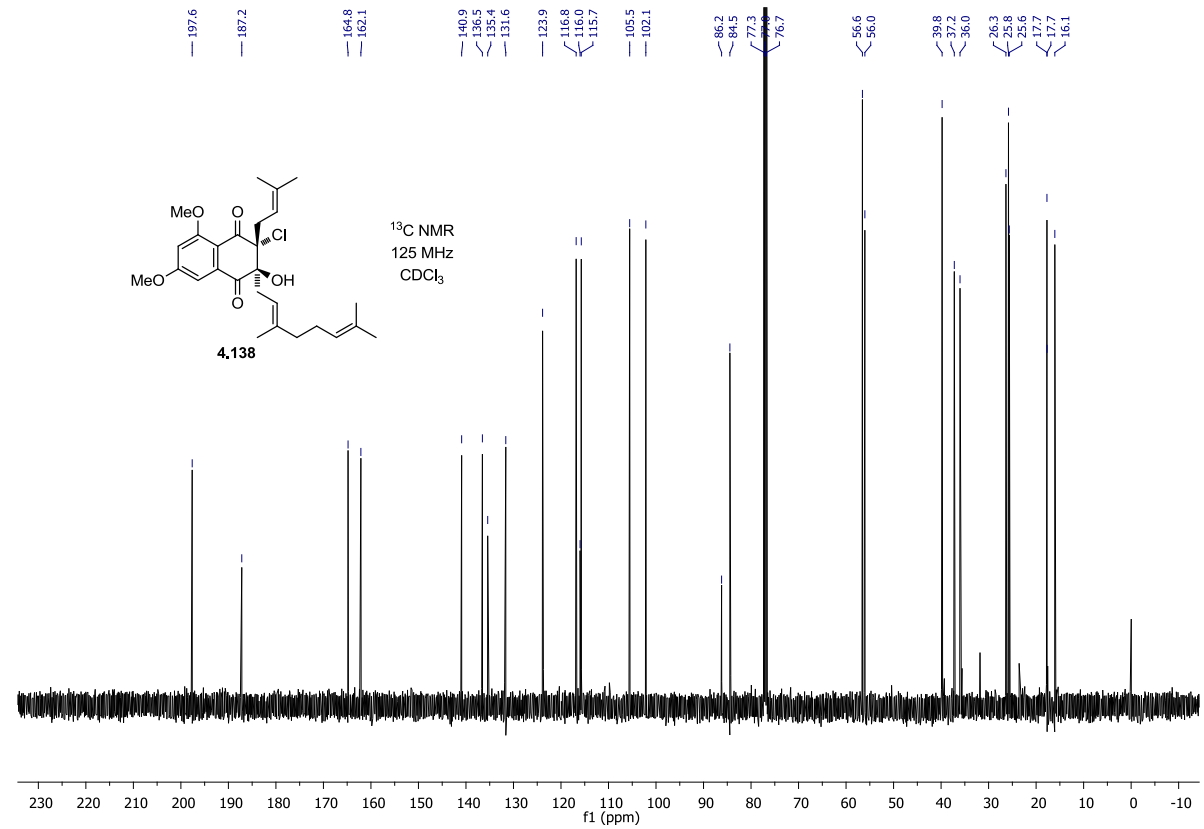

MeO
OH
Cl
MeO
O
OH
4.137
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

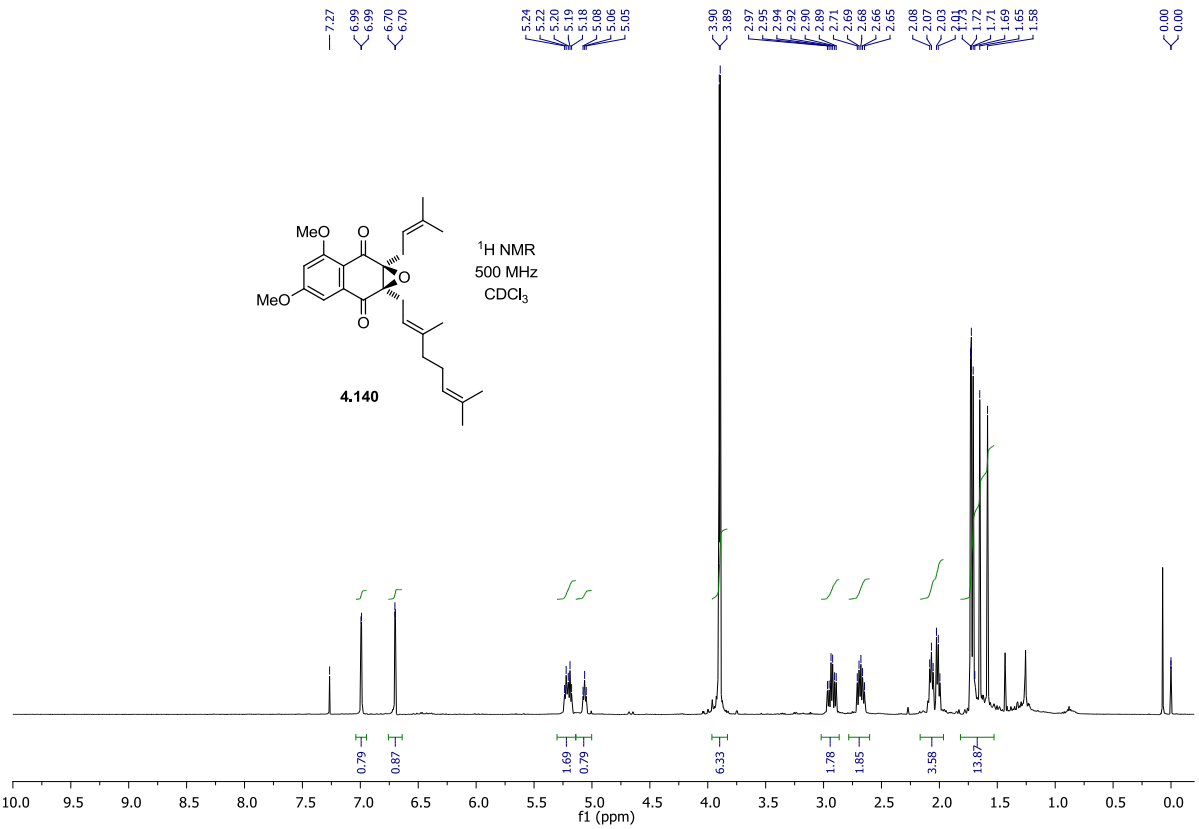

MeO
OH
Cl
MeO
O
OH
4.137
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

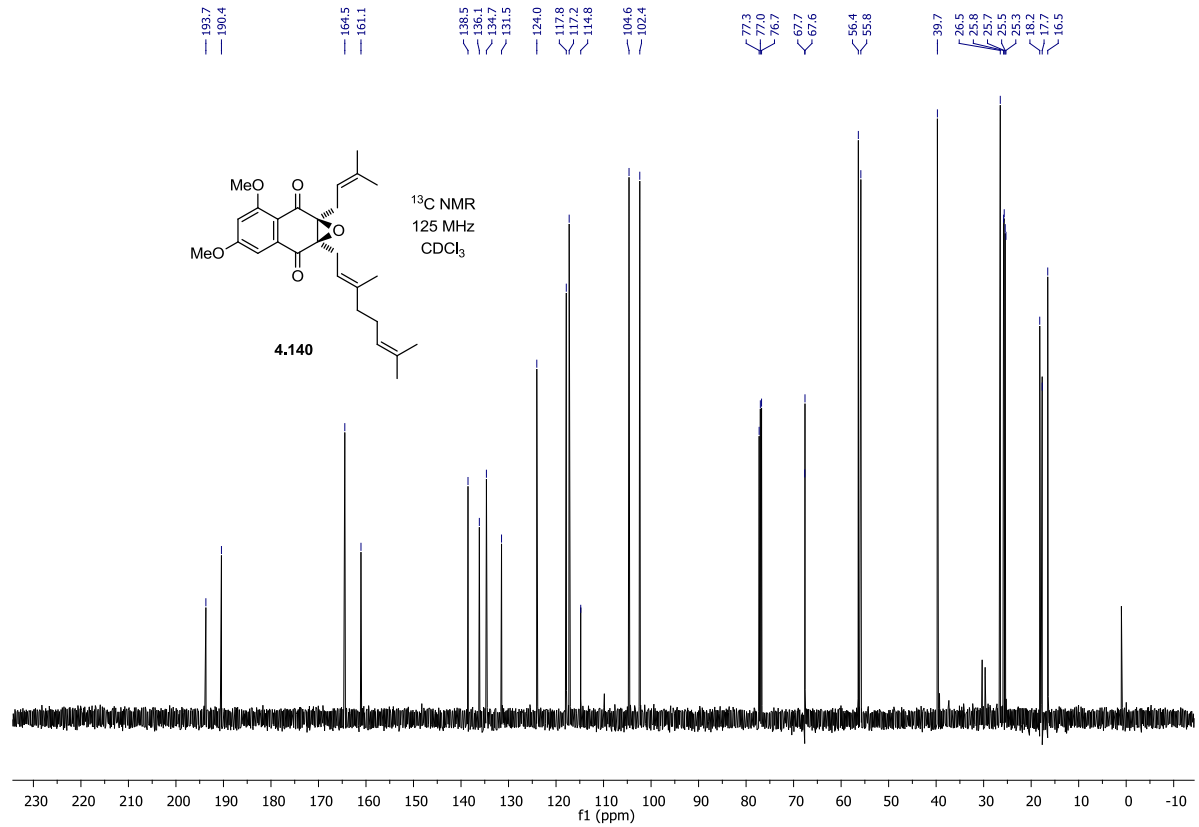

MeO
O
Cl
MeO
O
OH
4.125
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

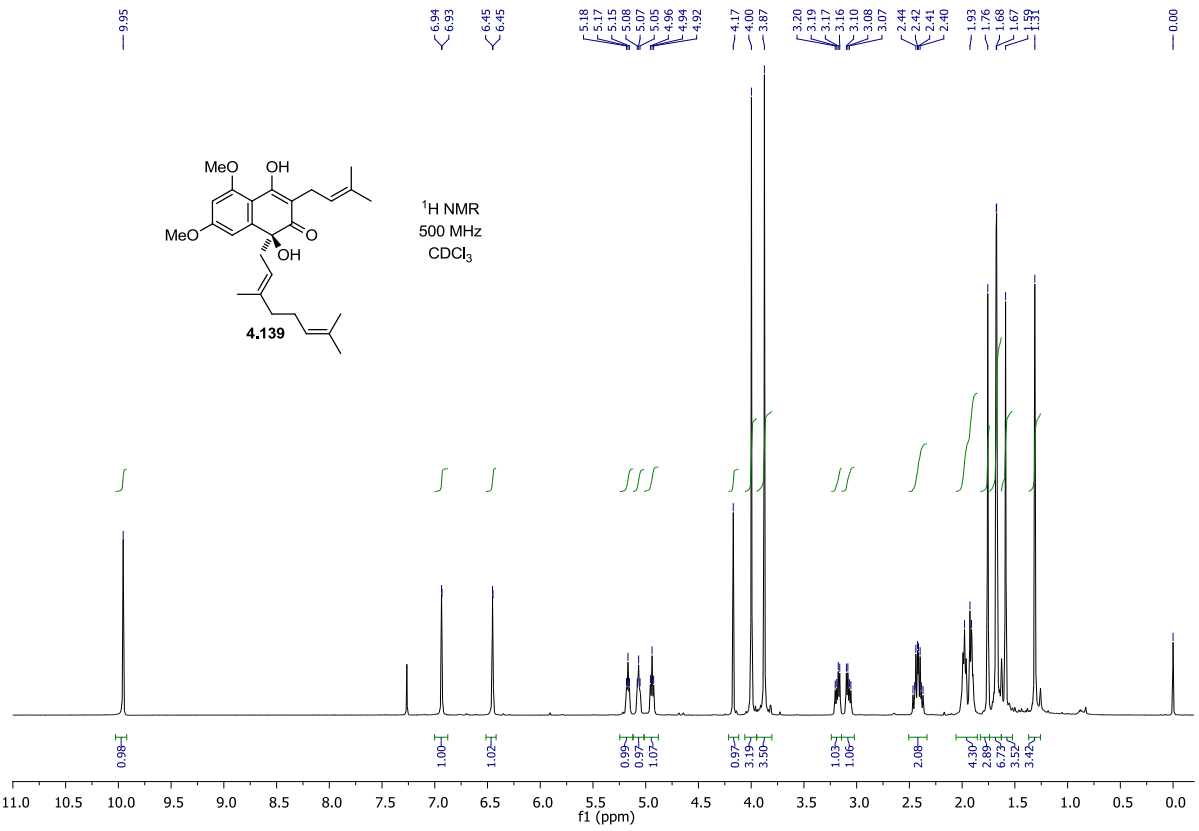

MeO
O
Cl
MeO
O
OH
4.125
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

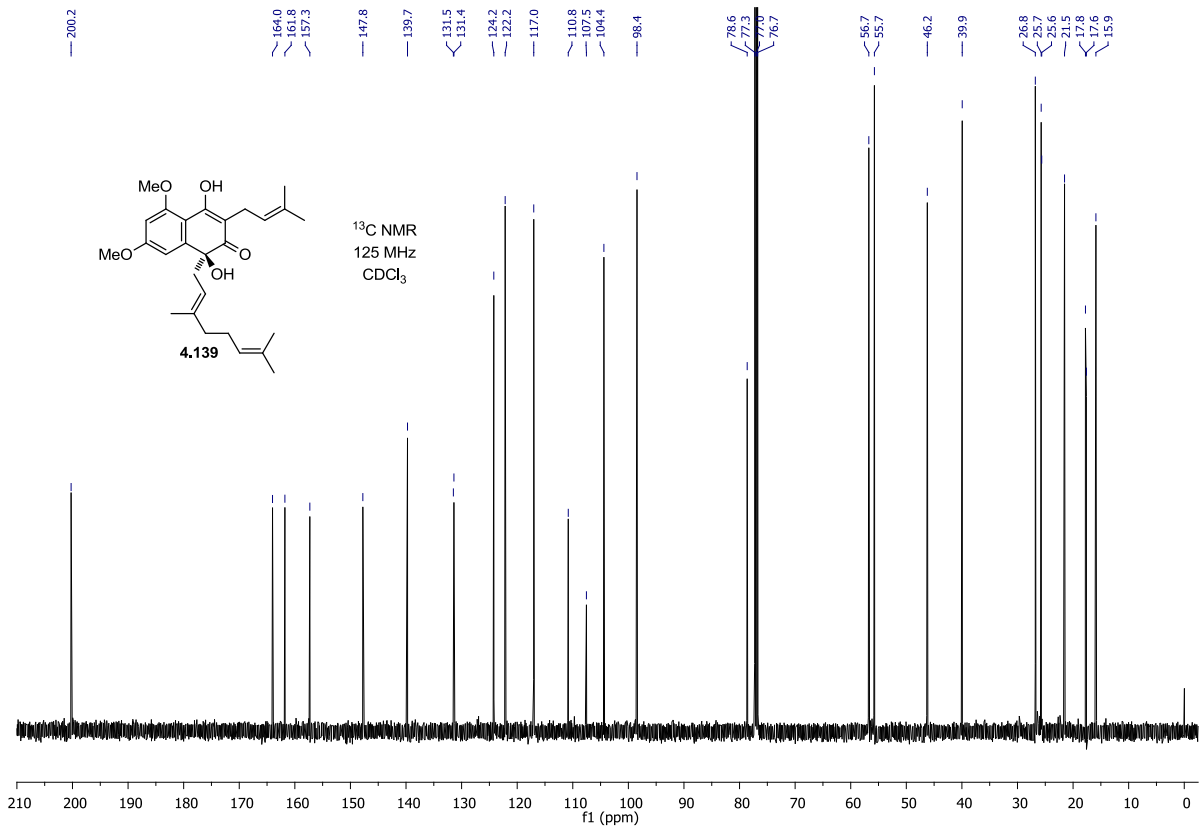

MeO
O
Cl
MeO
OH
O
4.138
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

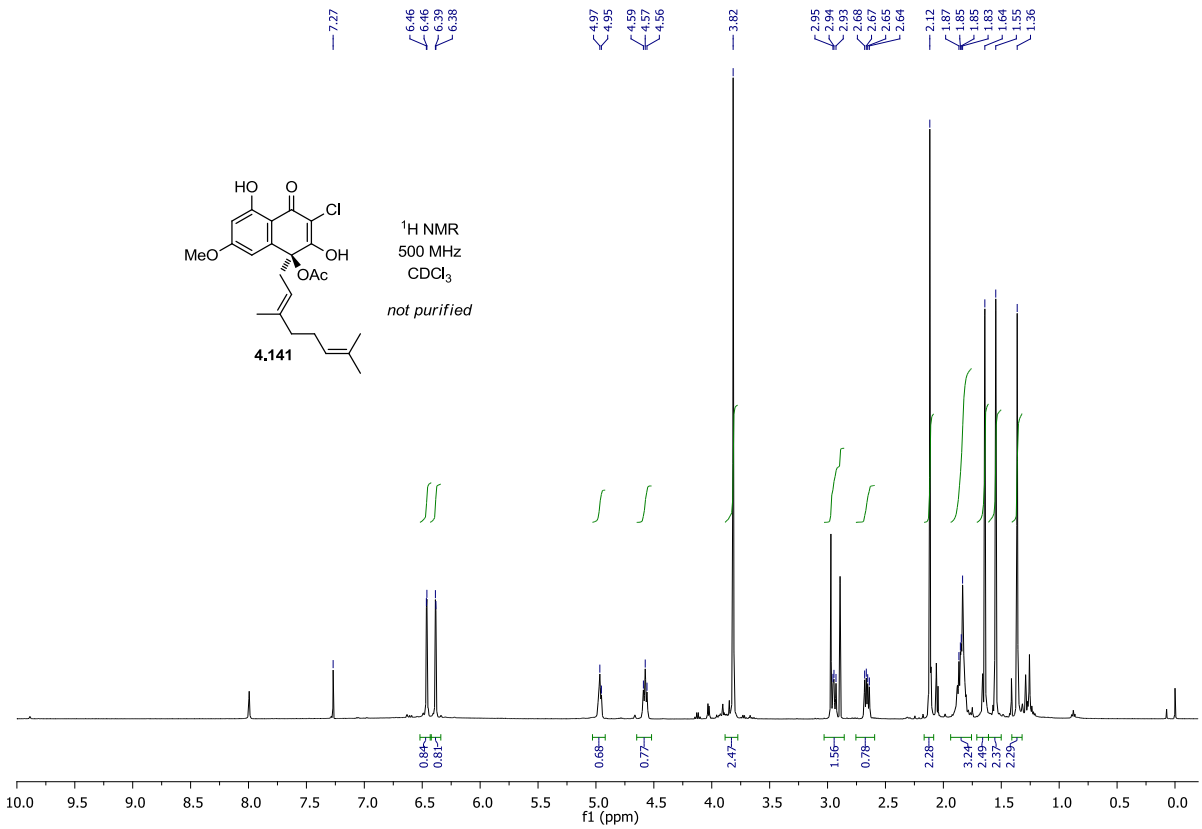

MeO
O
Cl
MeO
OH
O
4.138
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

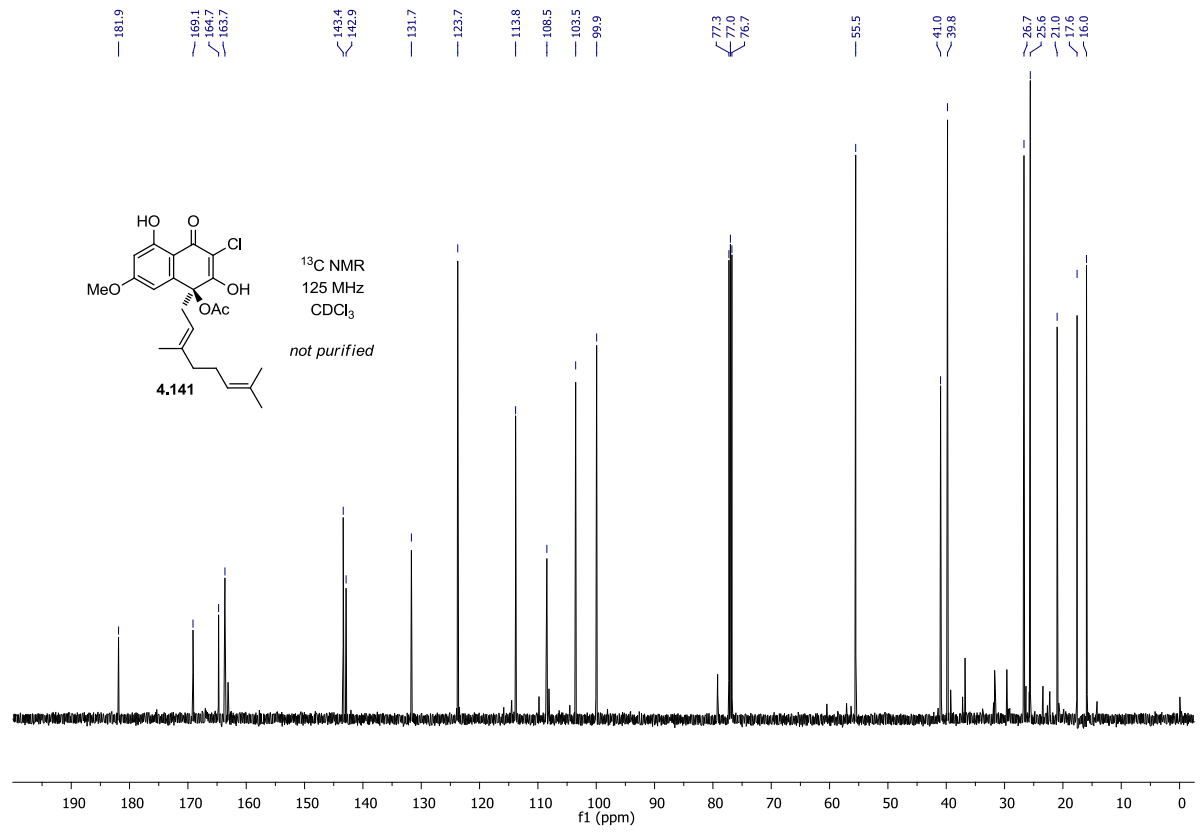

MeO
MeO
O
O
O
O
4.140
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

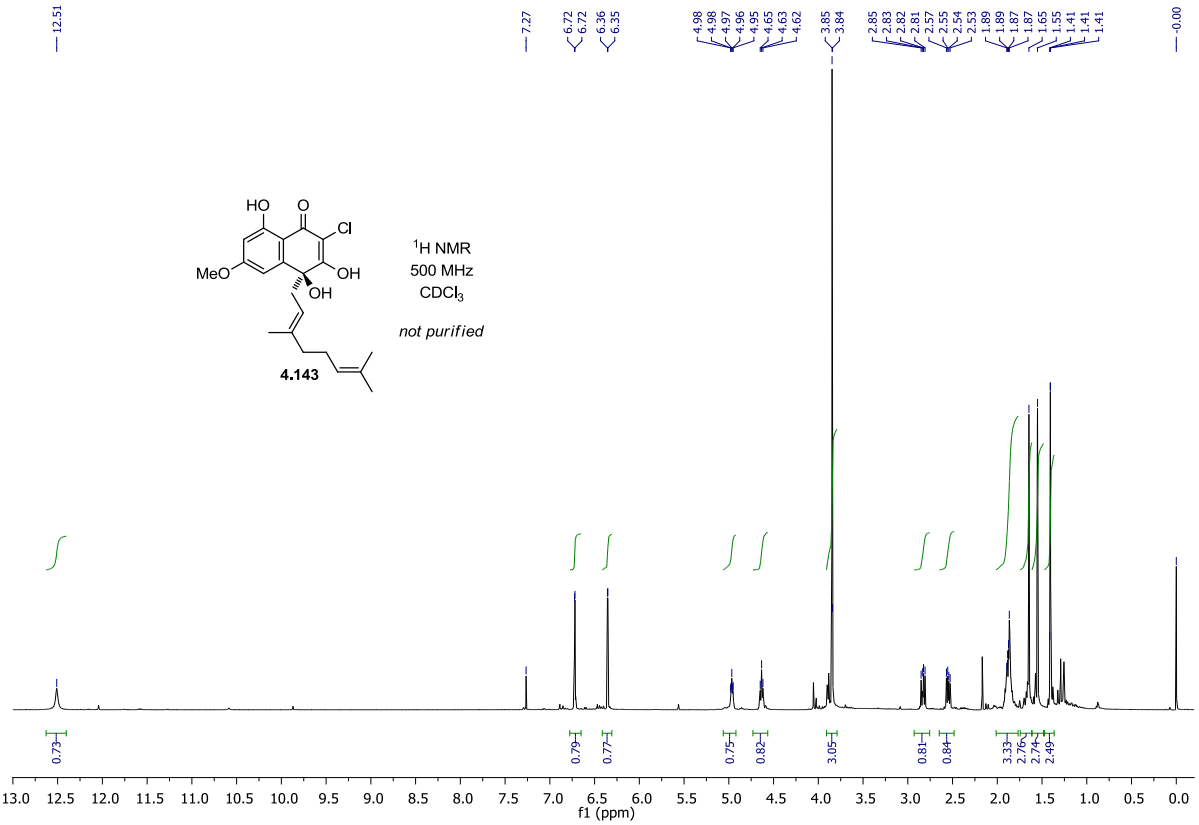

MeO
MeO
O
O
O
O
4.140
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

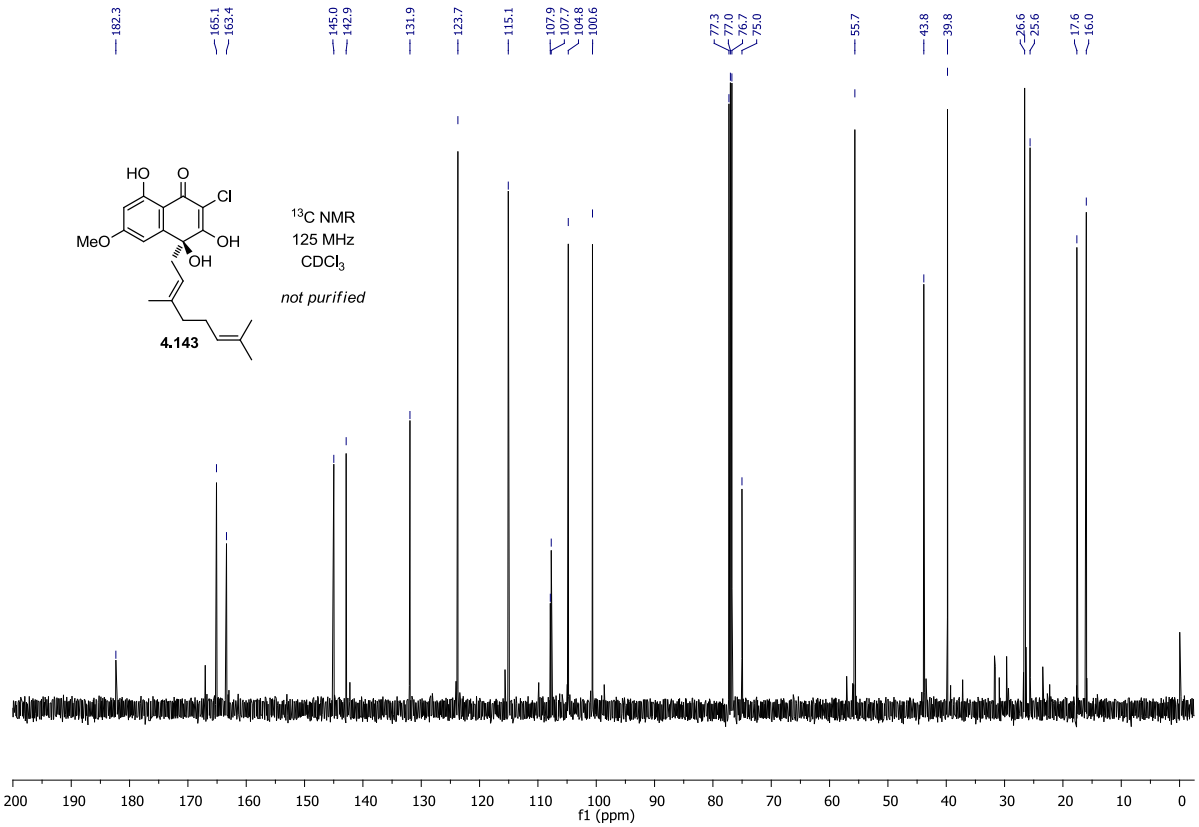

MeO
OH
MeO
O
OH
4.139
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

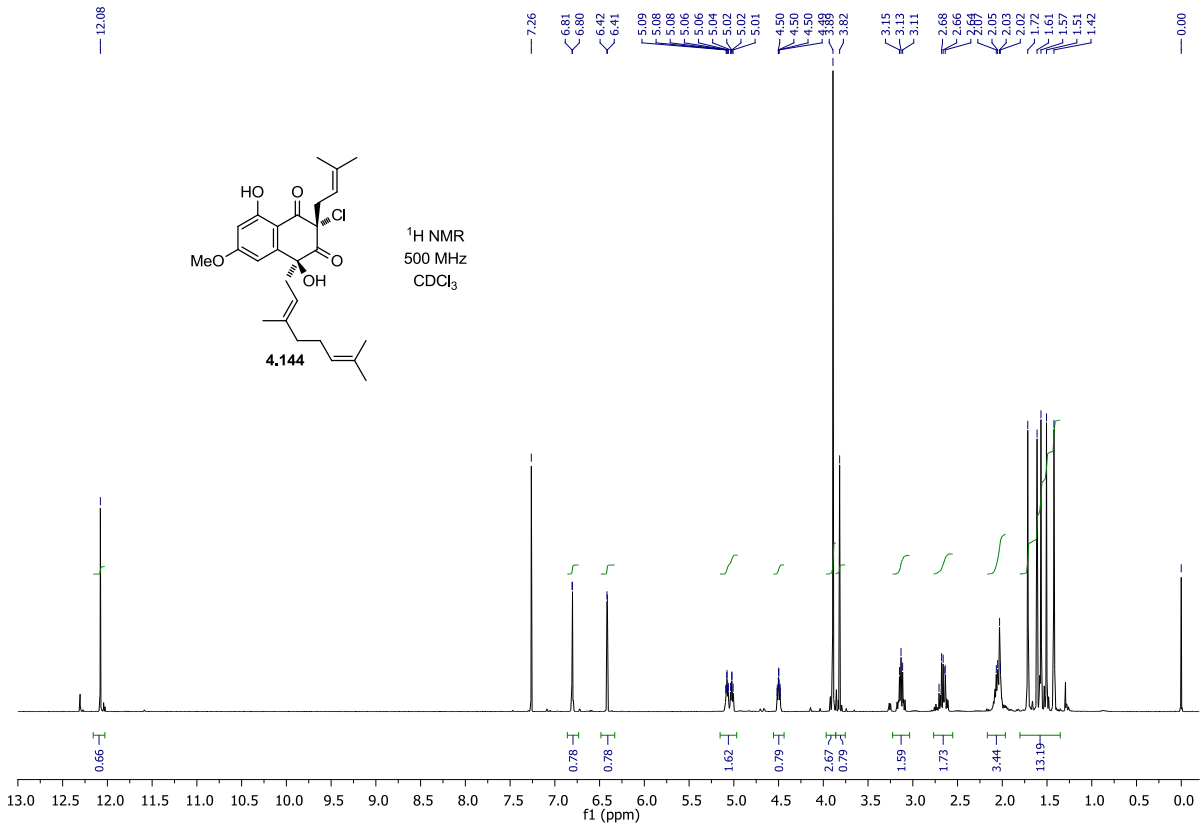

MeO
OH
MeO
O
OH
4.139
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

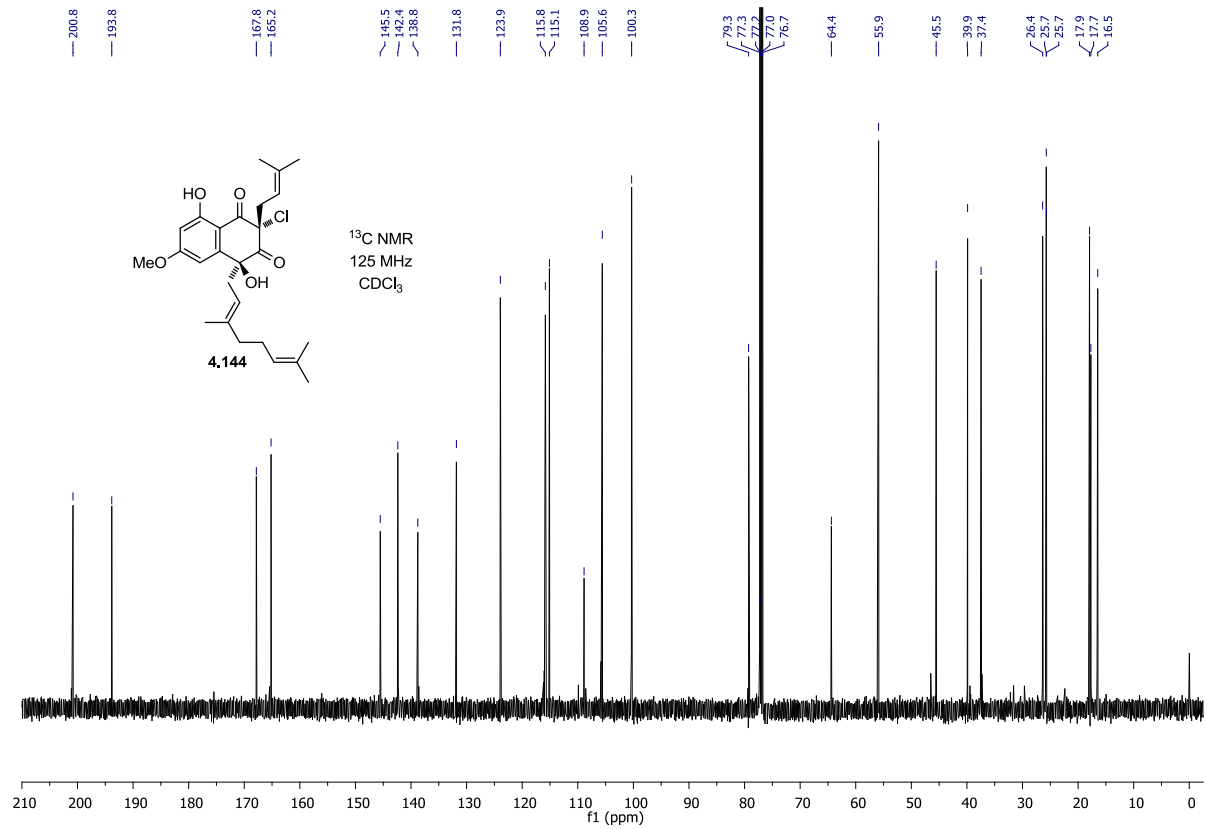

7.27
6.46
6.46
6.39
6.38
4.97
4.95
4.59
4.57
4.56
3.82
2.95
2.94
2.93
2.68
2.67
2.65
2.64
2.12
1.87
1.85
1.85
1.83
1.64
1.55
1.36
HO
O
Cl
MeO
OH
OAc
4.141
1H NMR
500 MHz
CDCl3
not purified
0.84
0.81
0.68
0.77
2.47
1.56
0.78
2.28
3.24
2.49
2.37
2.29
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

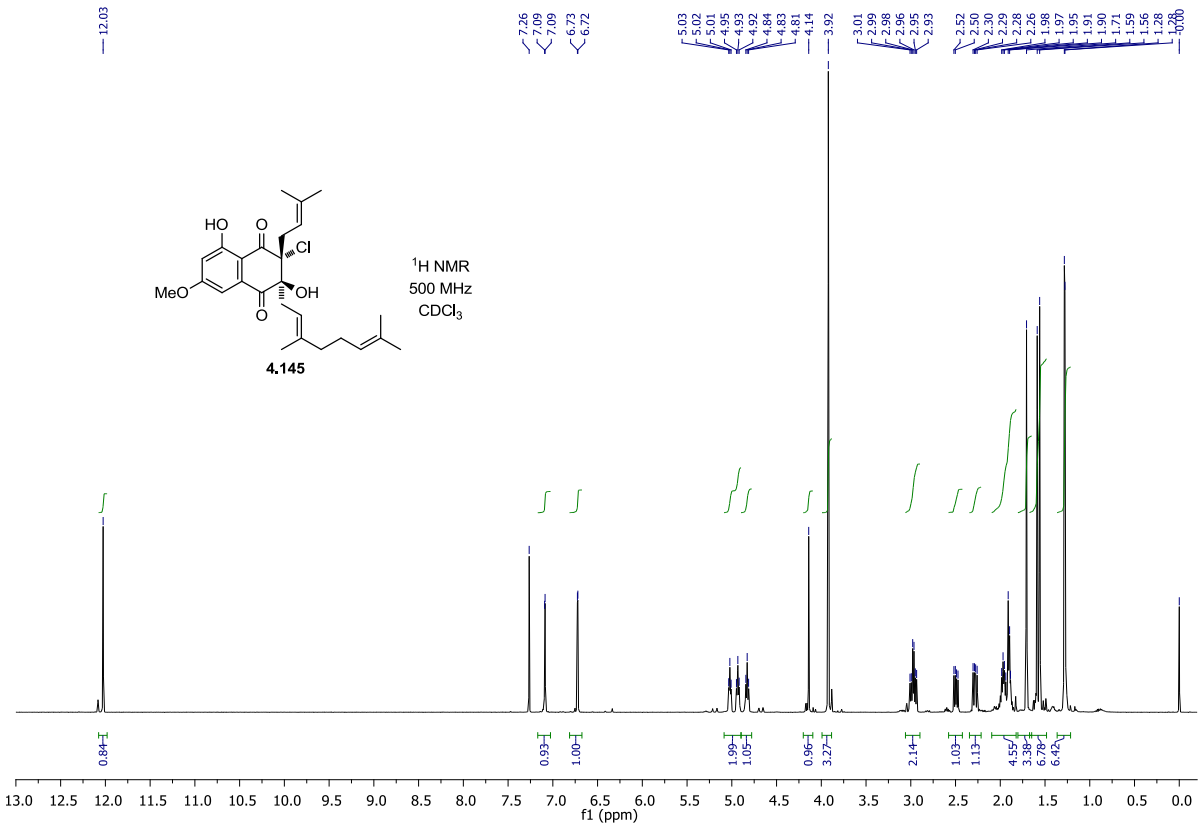

181.9
169.1
164.7
163.7
143.4
142.9
131.7
123.7
113.8
108.5
103.5
99.9
77.3
77.0
76.7
55.5
41.0
39.8
26.7
25.6
21.0
17.6
16.0
HO
O
Cl
MeO
OH
OAc
4.141
13C NMR
125 MHz
CDCl3
not purified
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

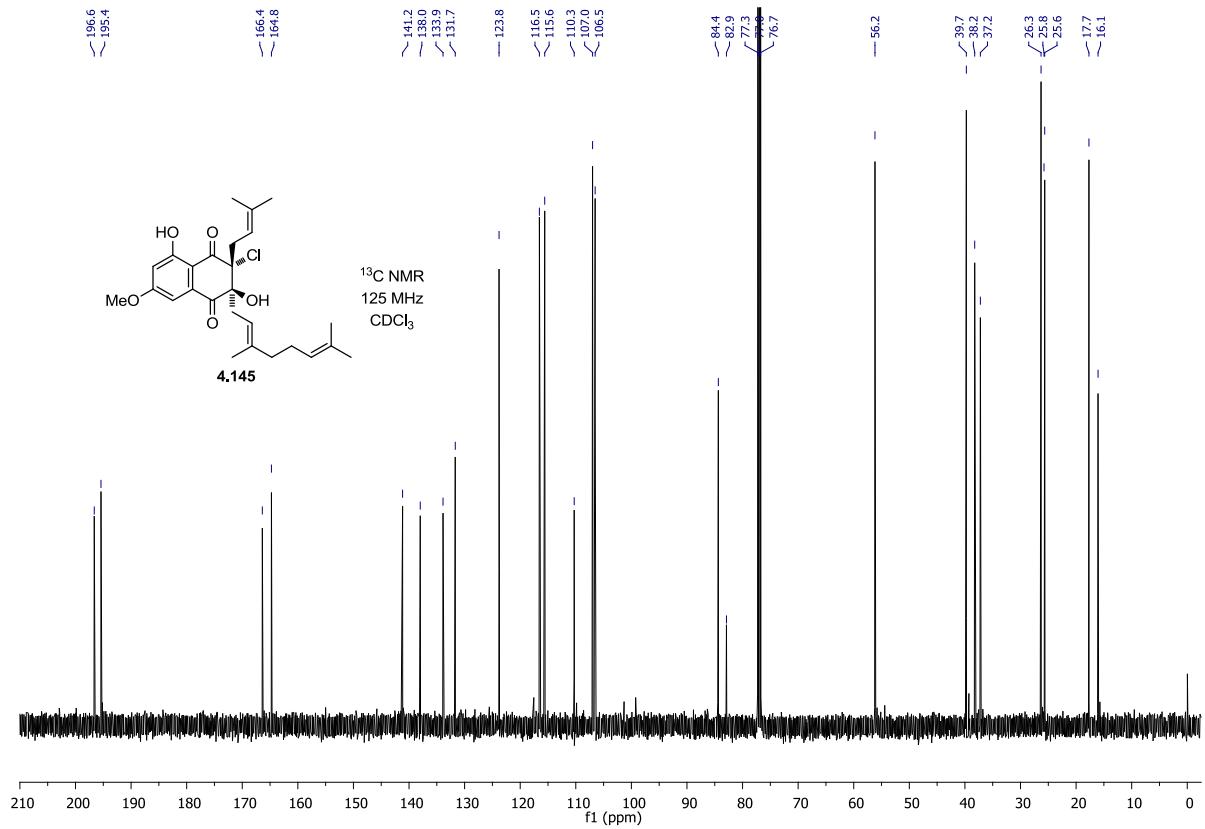

HO
O
Cl
MeO
OH
OH
4.143
^{1}H NMR
500 MHz
$CDCl_3$
not purified
f1 (ppm)

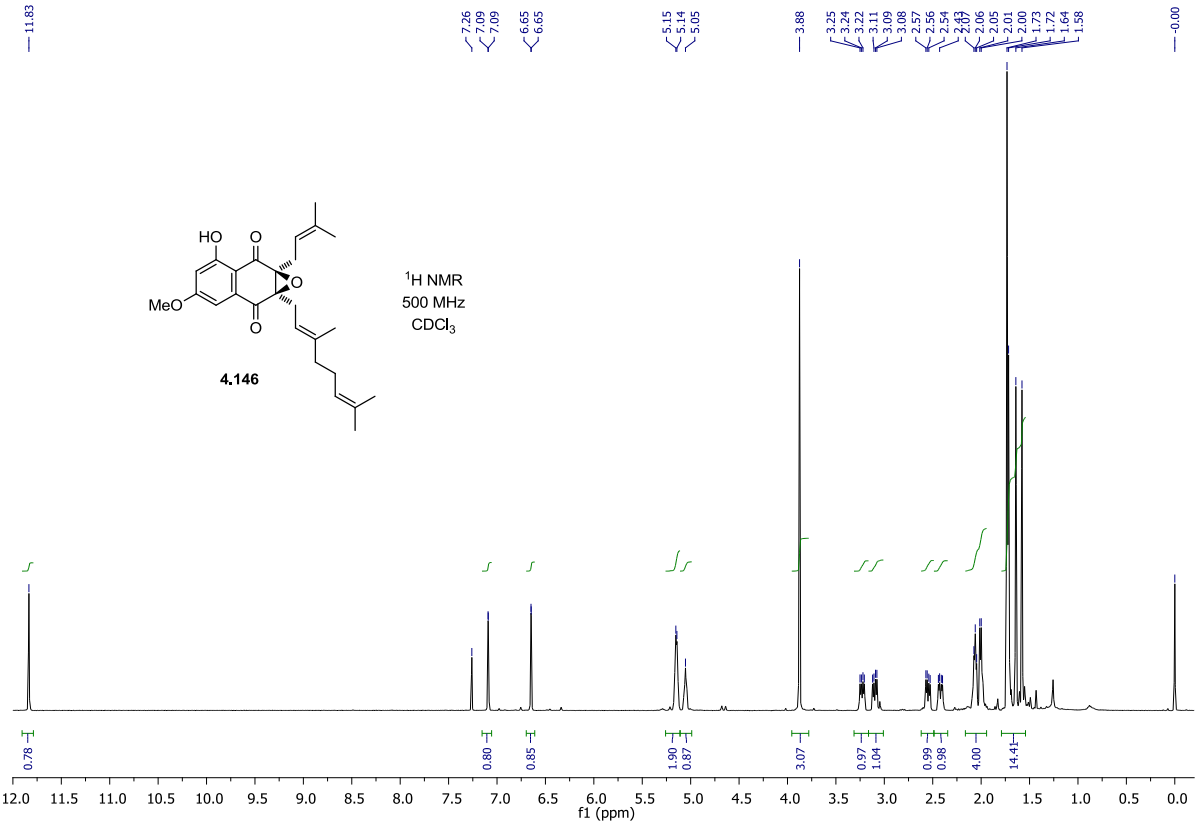

HO
O
Cl
MeO
OH
OH
4.143
^{13}C NMR
125 MHz
$CDCl_3$
not purified
f1 (ppm)

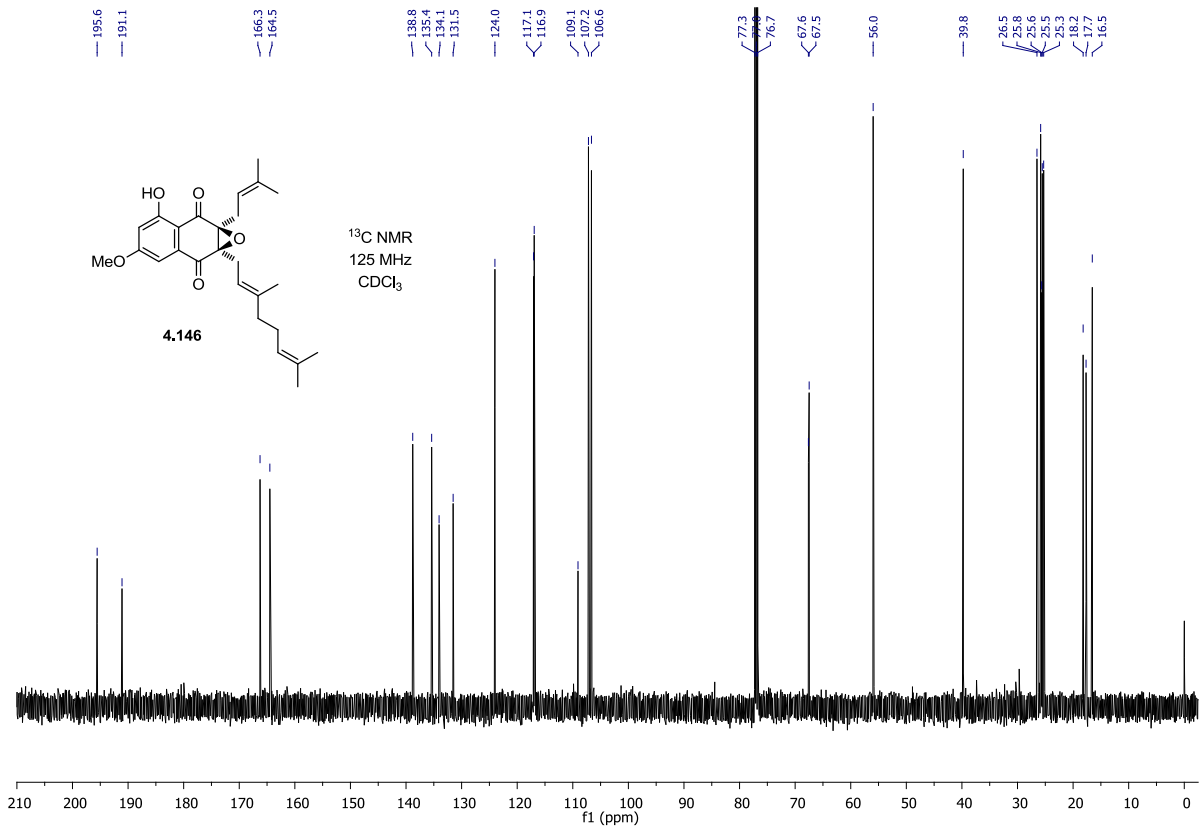

HO
O
Cl
MeO
O
OH
4.144
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

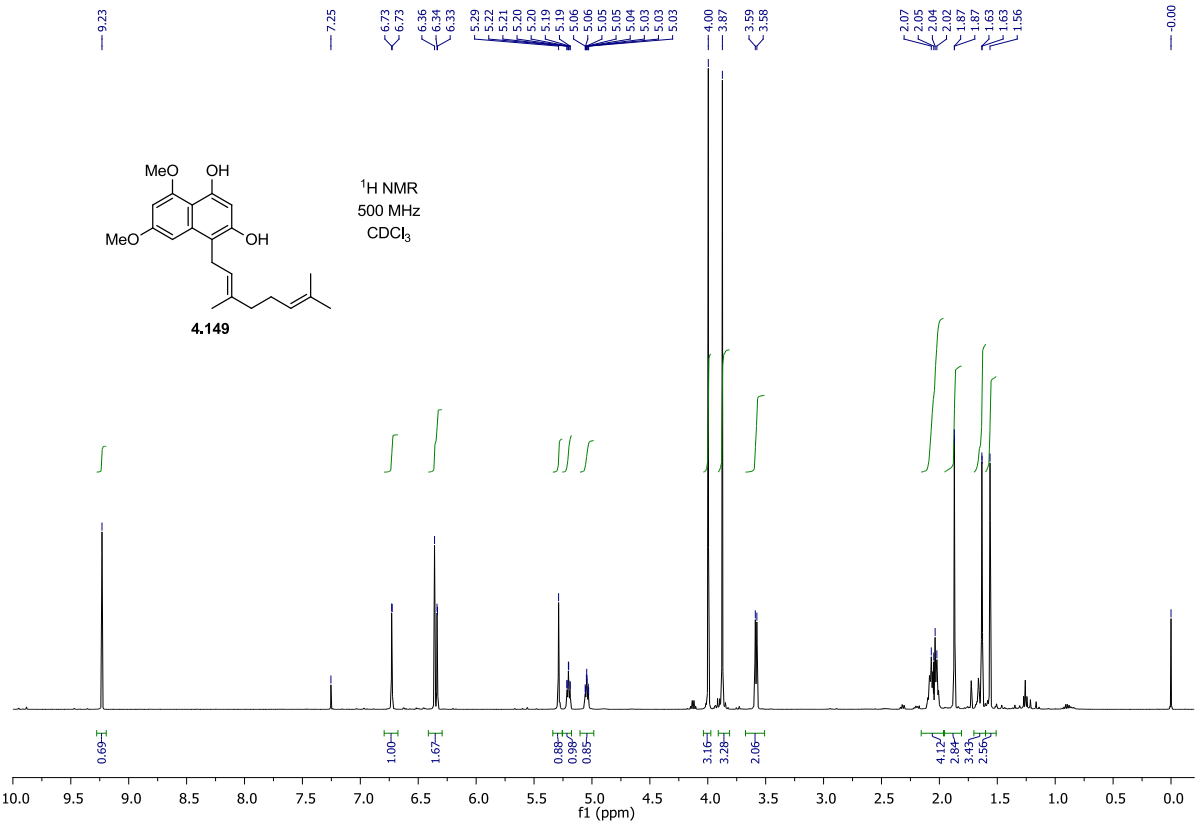

HO
O
Cl
MeO
O
OH
4.144
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

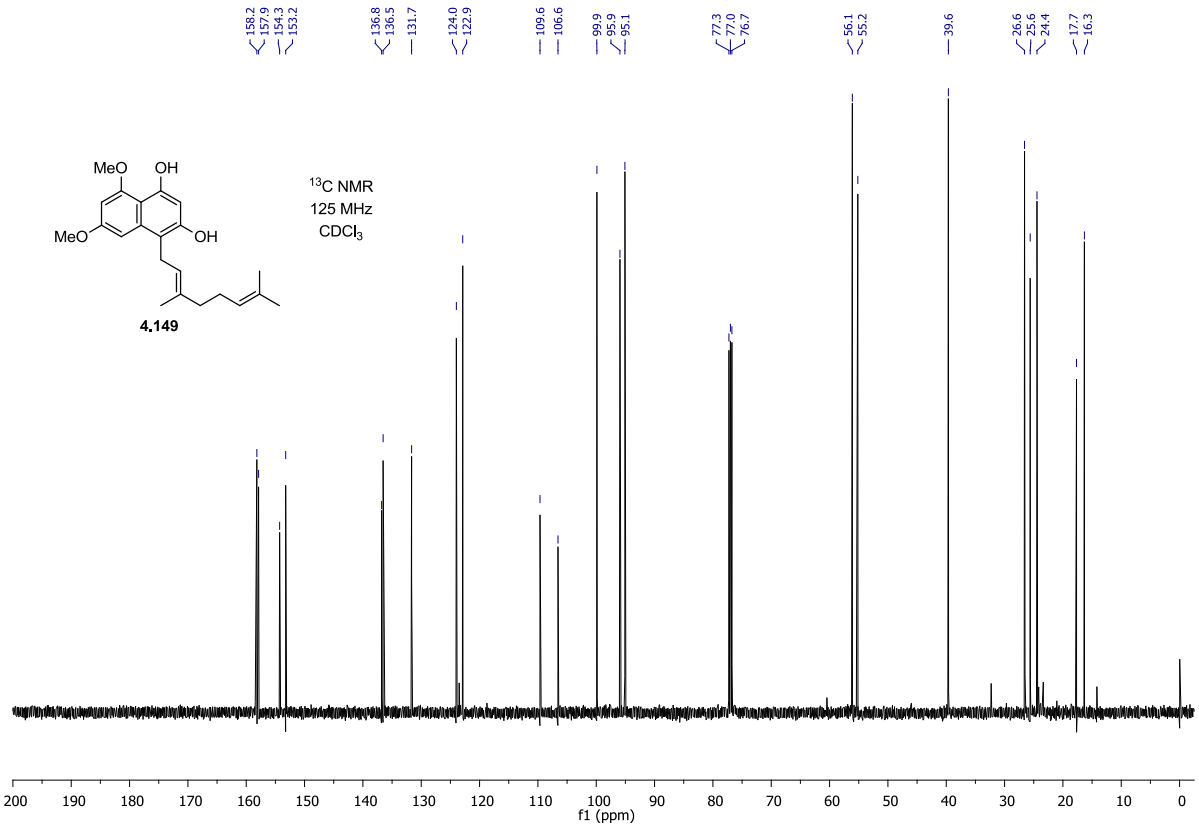

HO
O
Cl
MeO
OH
O
4.145
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

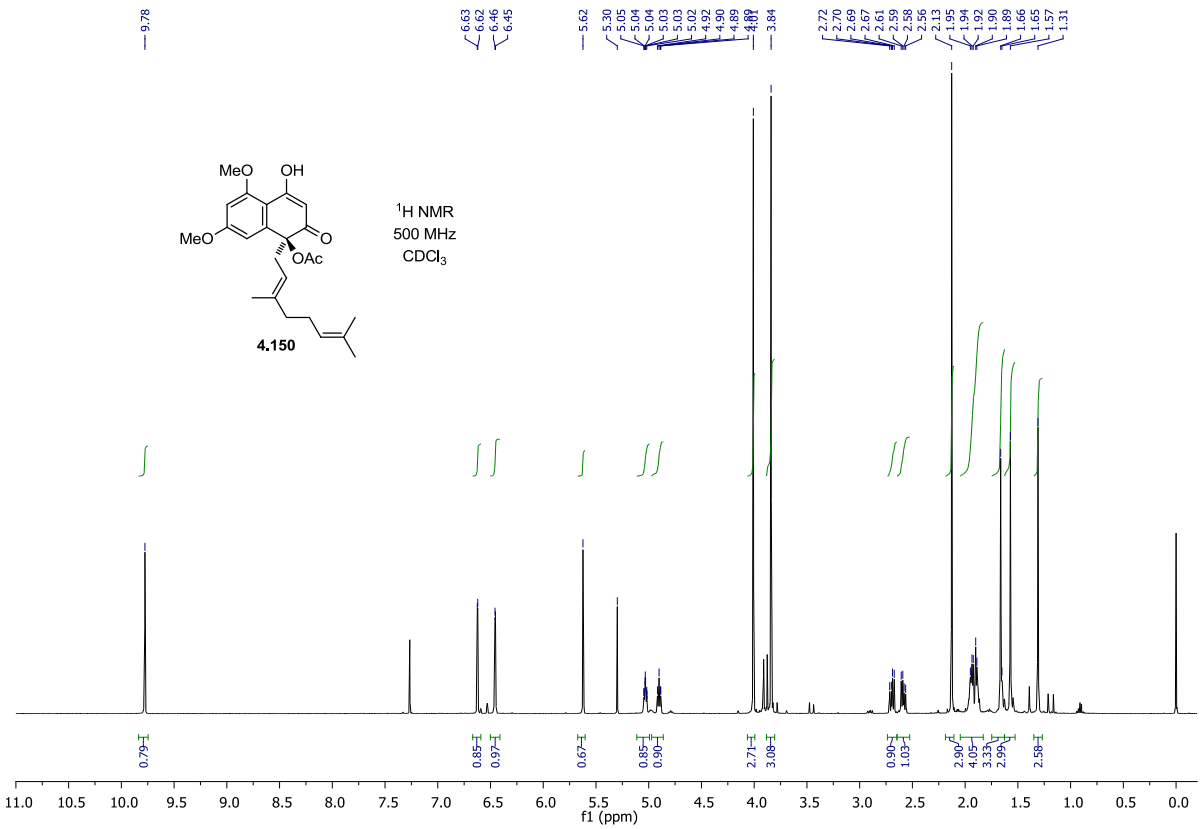

HO
O
Cl
MeO
OH
O
4.145
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

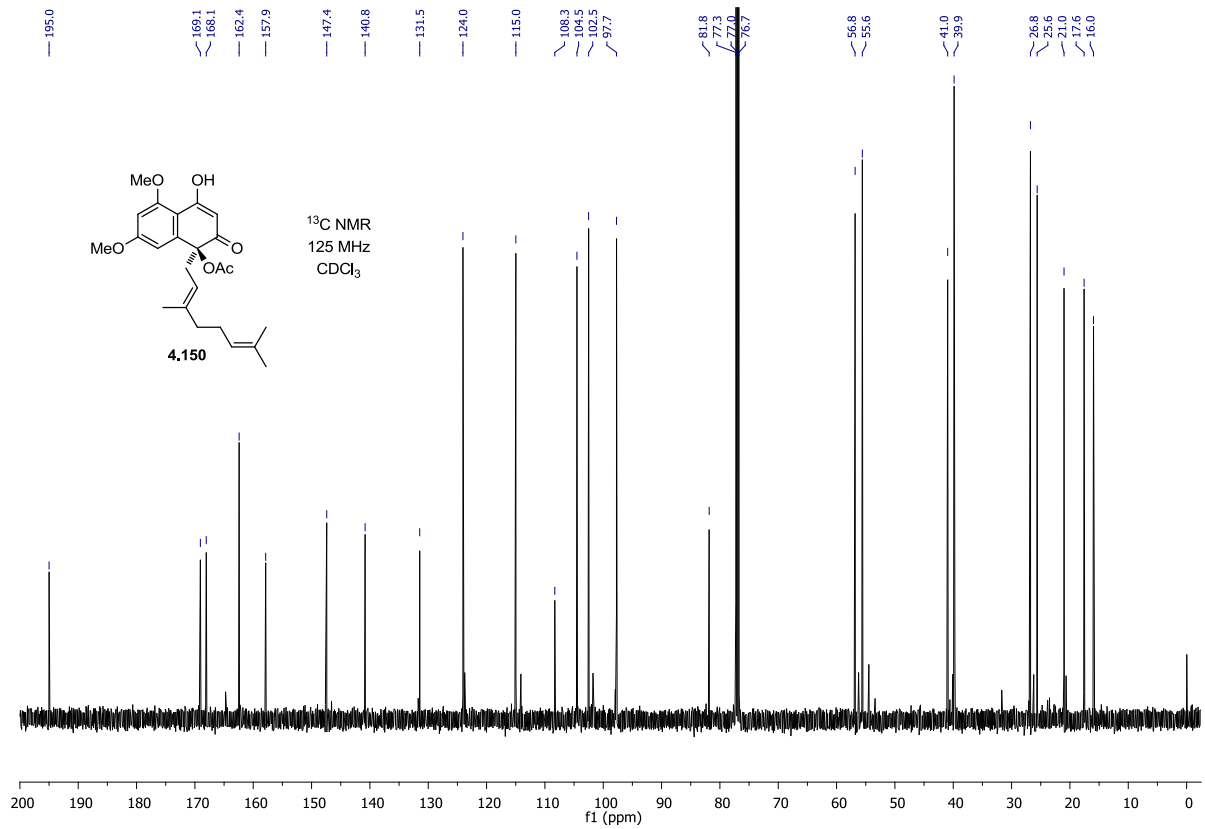

HO
O
MeO
O
O
4.146
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

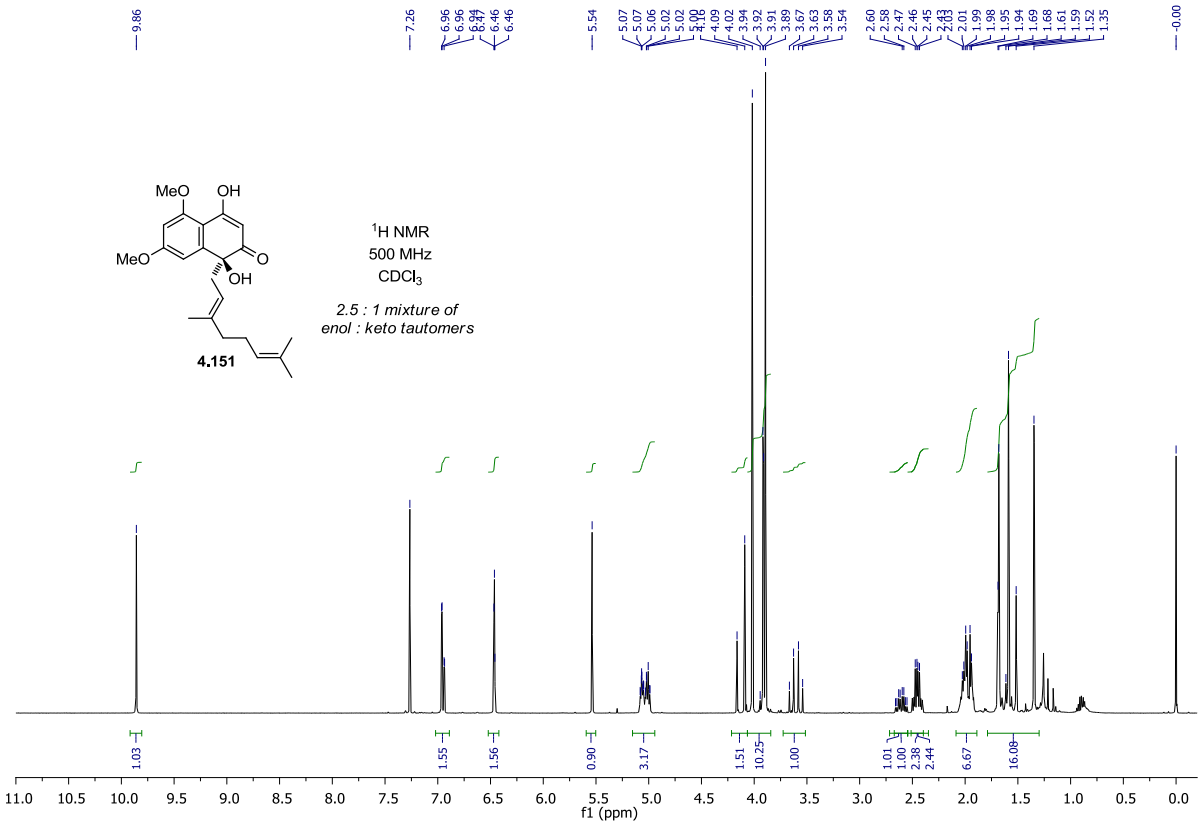

HO
O
MeO
O
O
4.146
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

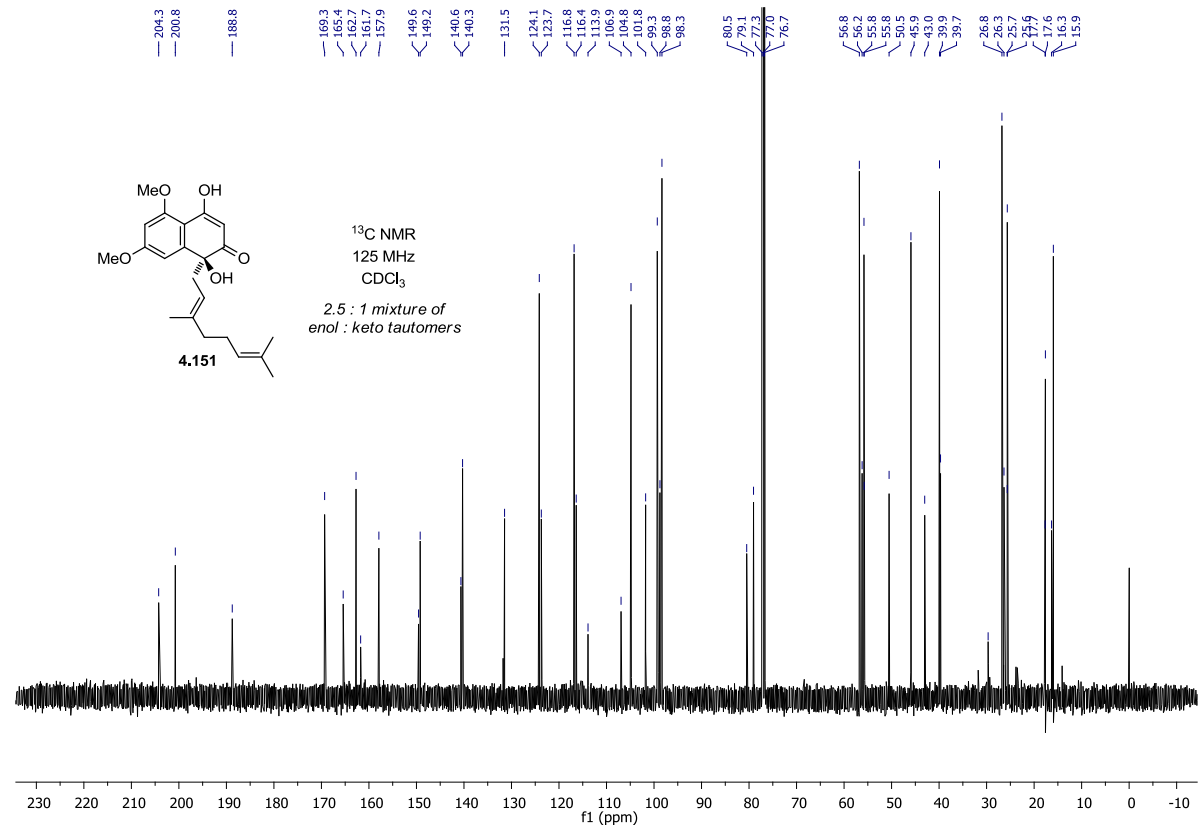

MeO
OH
MeO
OH
4.149
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

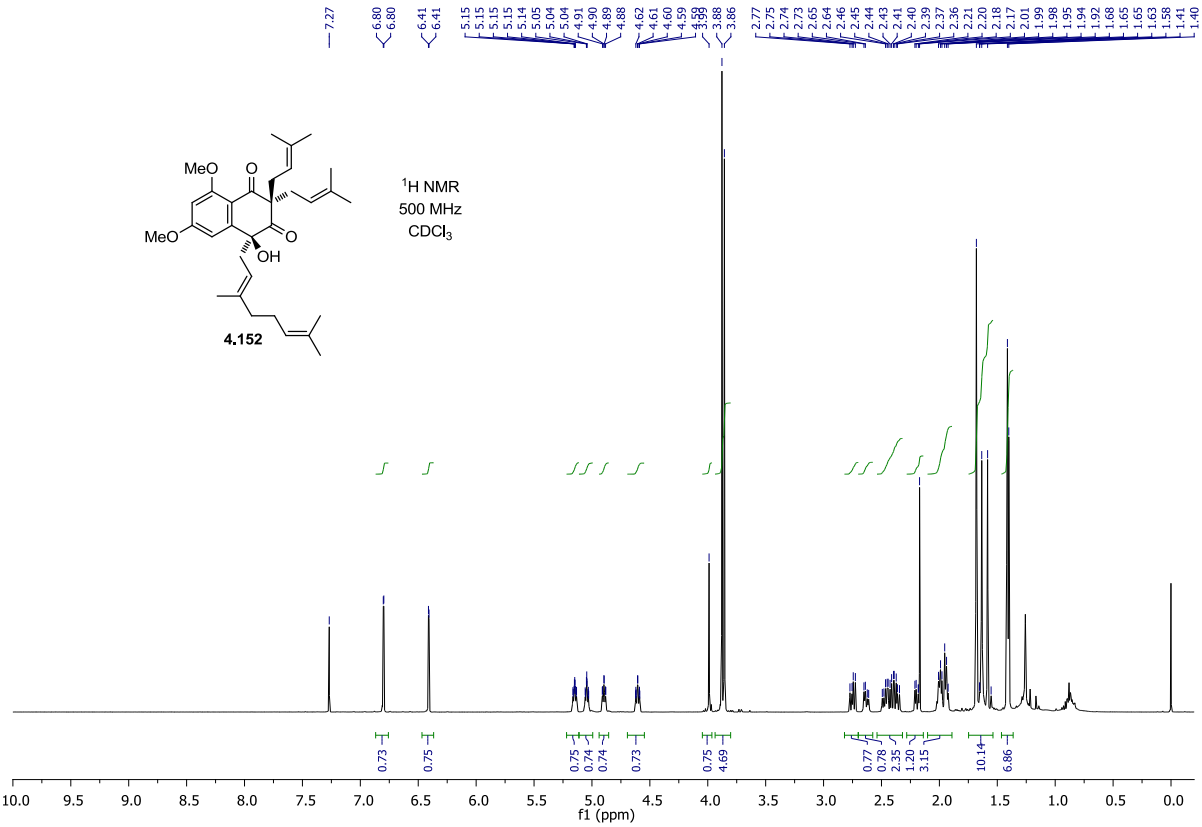

MeO
OH
MeO
OH
4.149
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

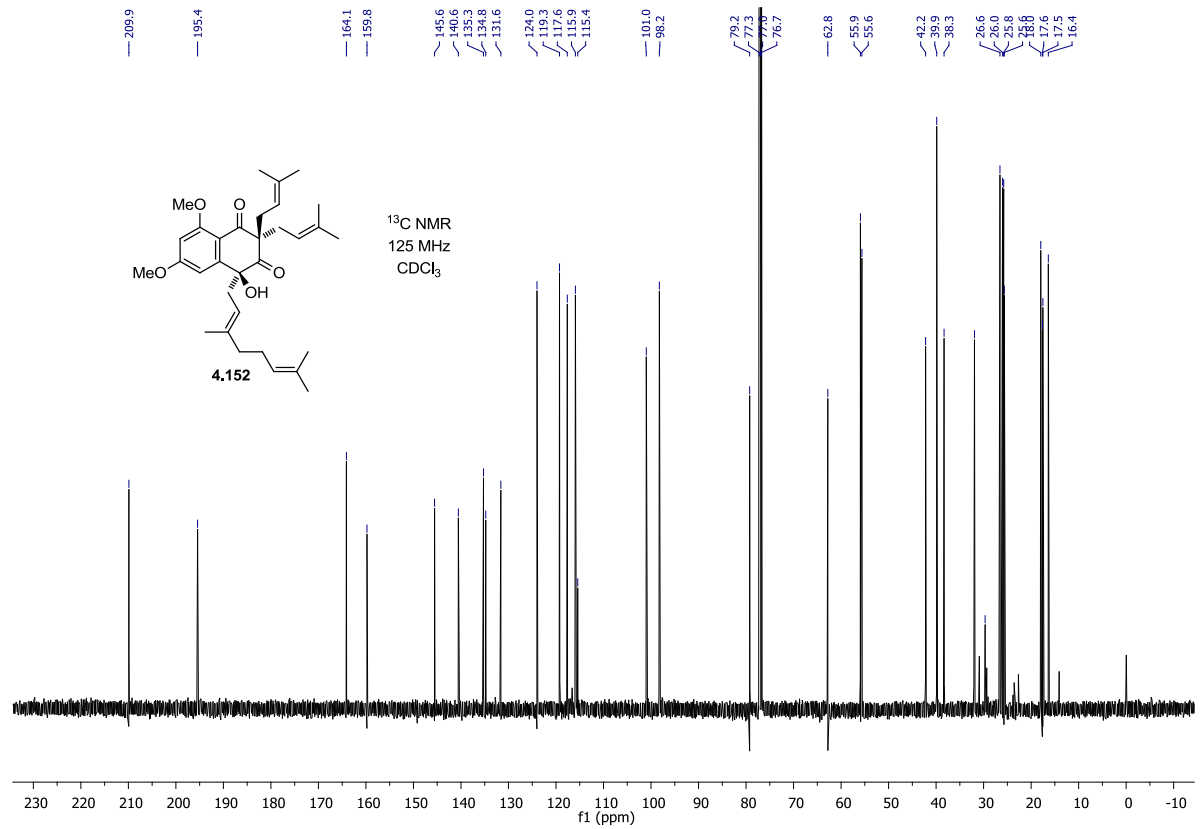

MeO
OH
MeO
O
OAc
4.150
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

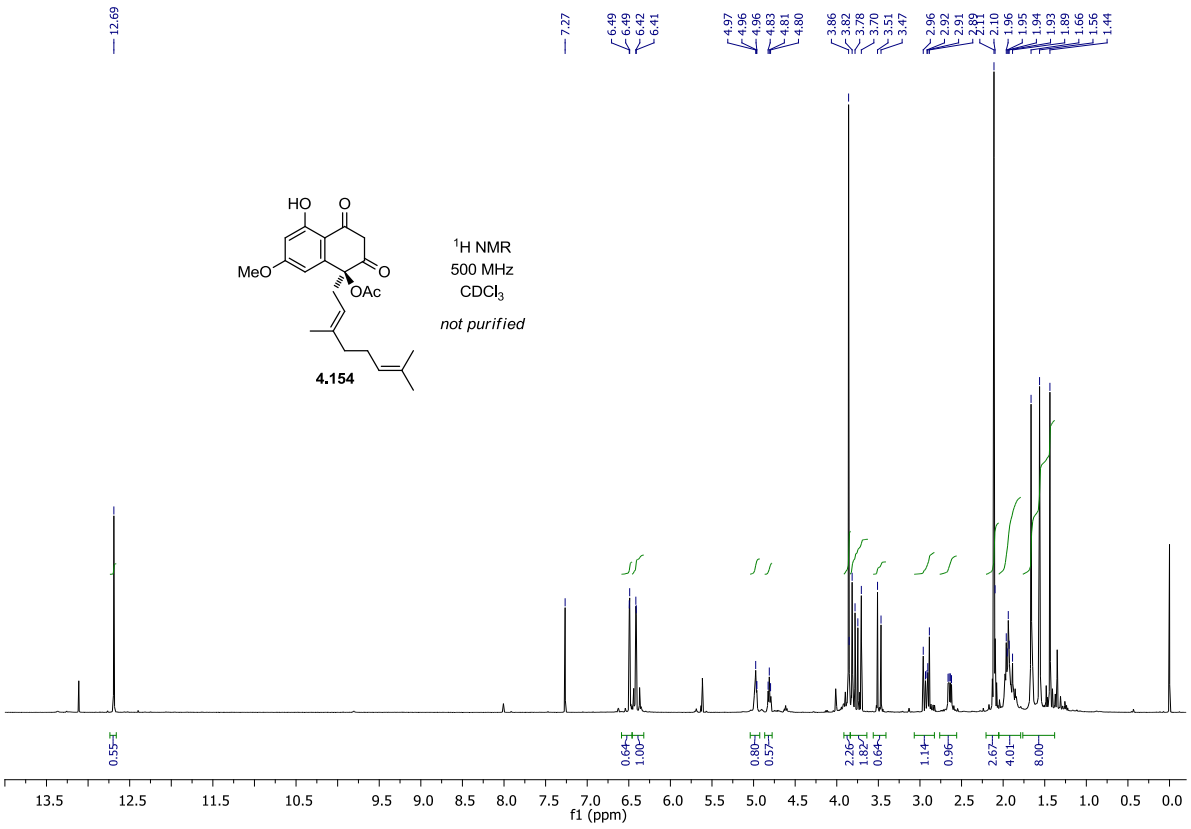

MeO
OH
MeO
O
OAc
4.150
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

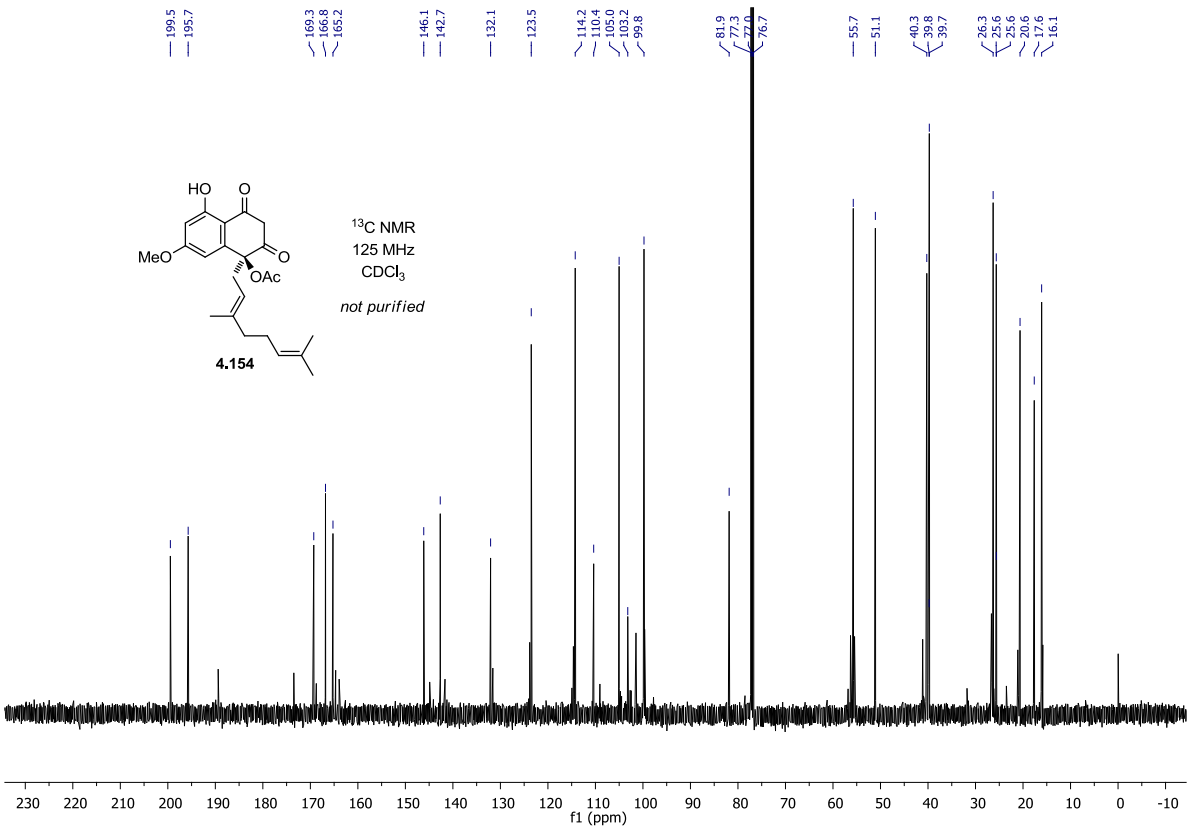

MeO
OH
MeO
O
OH
4.151
1H NMR
500 MHz
CDCl3
2.5 : 1 mixture of
enol : keto tautomers
f1 (ppm)

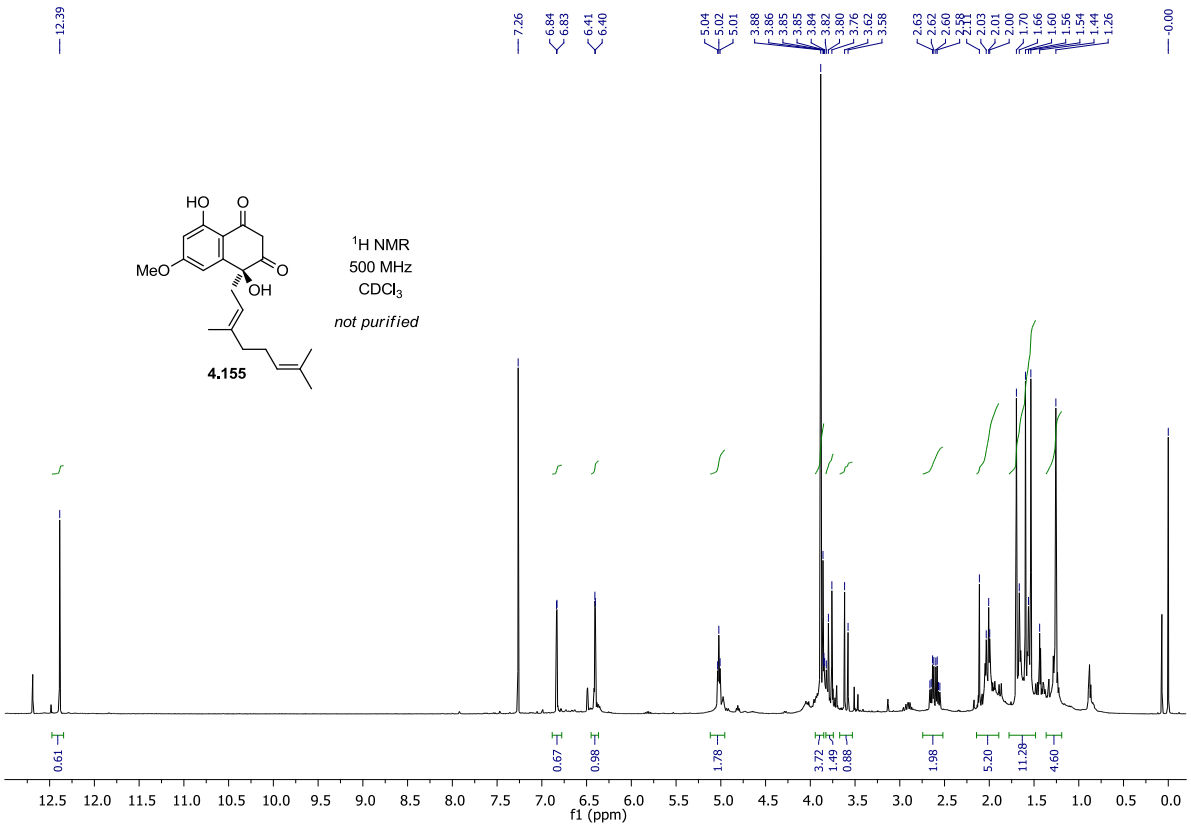

MeO
OH
MeO
O
OH
4.151
13C NMR
125 MHz
CDCl3
2.5 : 1 mixture of
enol : keto tautomers
f1 (ppm)

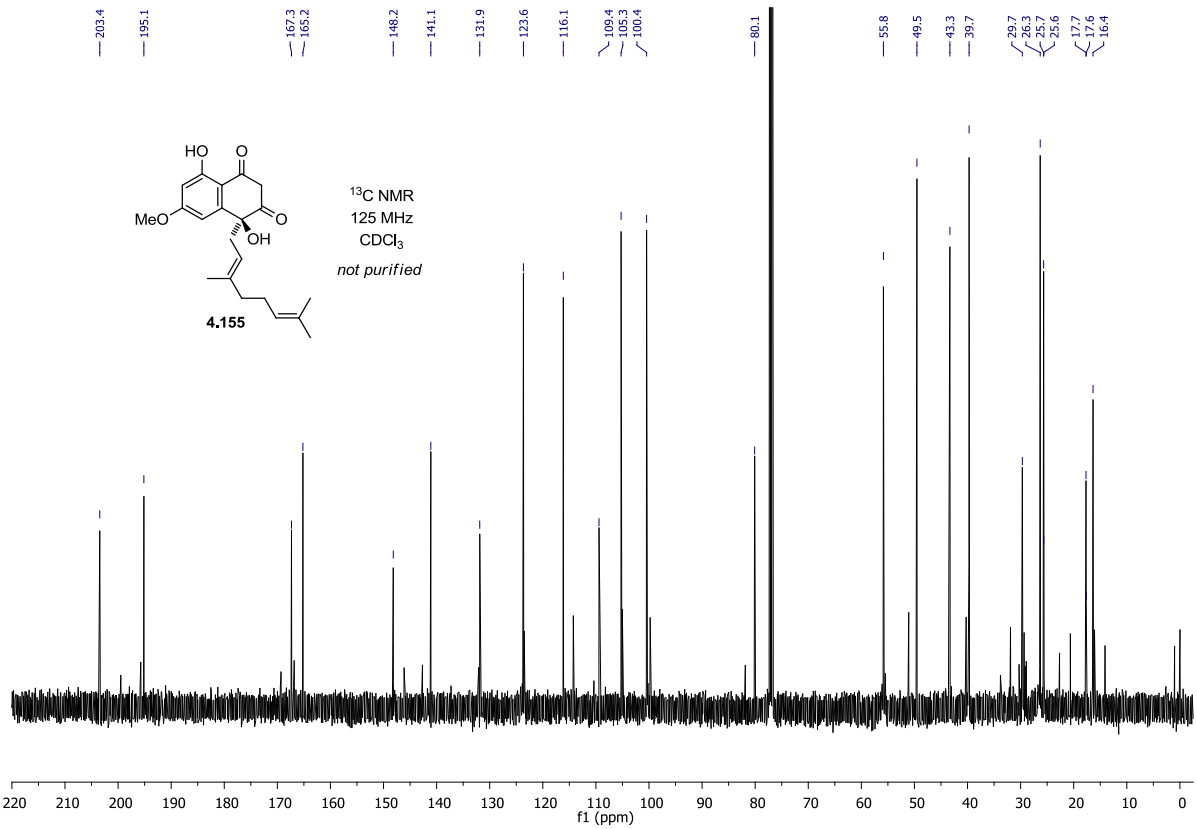

MeO
O
MeO
O
OH
4.152
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

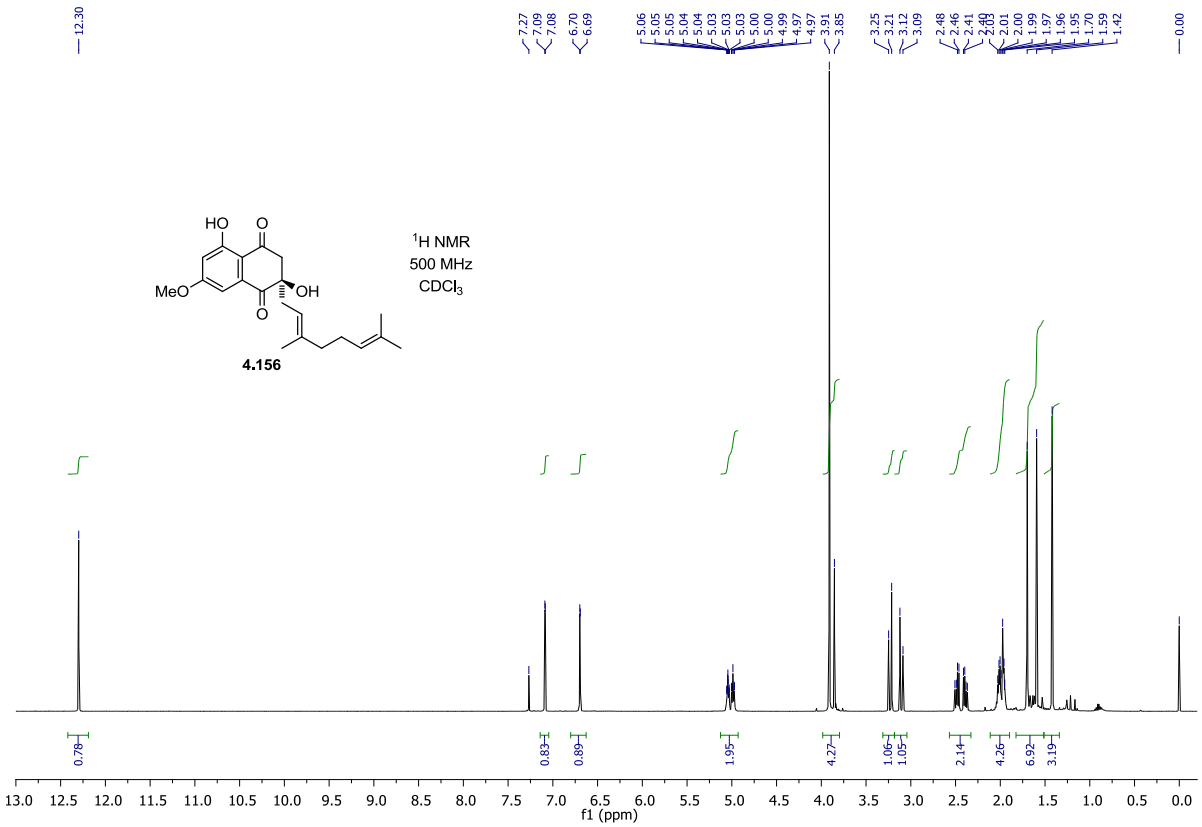

MeO
O
MeO
O
OH
4.152
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

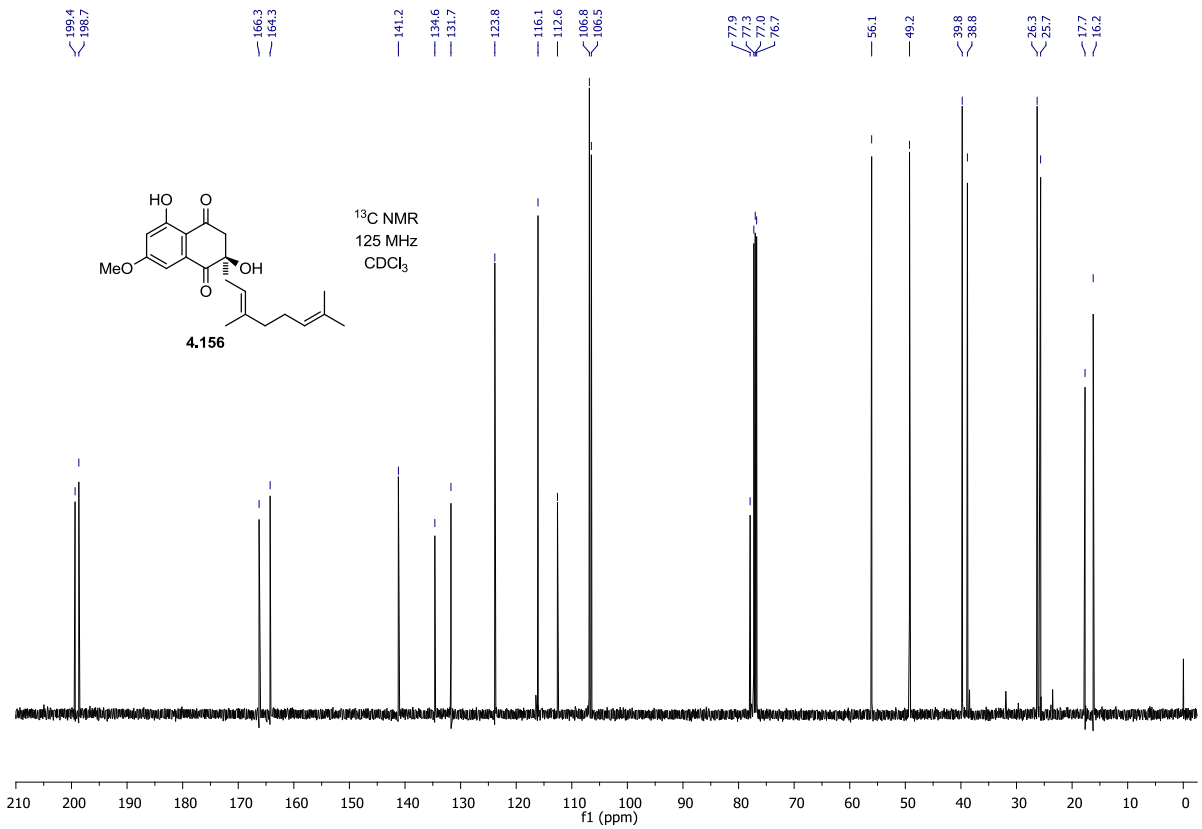

HO
O
MeO
O
OAc
4.154
^{1}H NMR
500 MHz
$CDCl_3$
not purified
f1 (ppm)

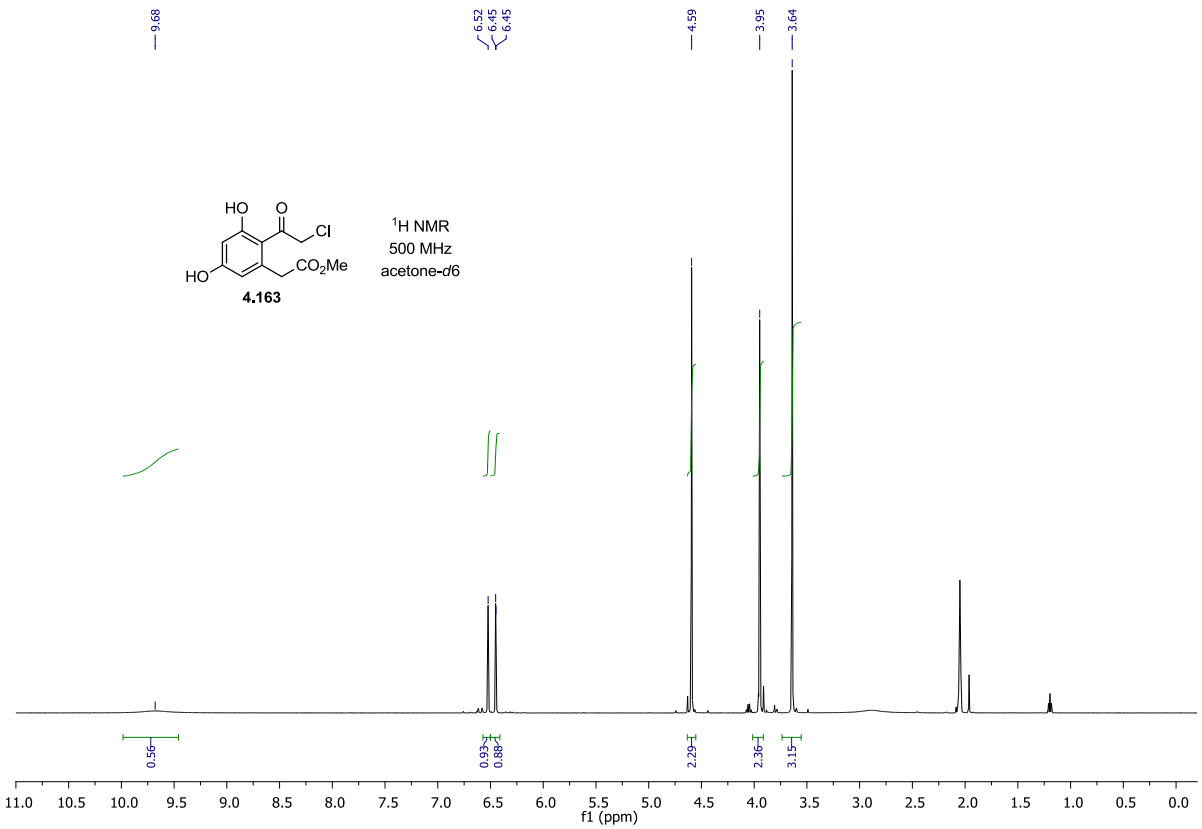

HO
O
MeO
O
OAc
4.154
^{13}C NMR
125 MHz
$CDCl_3$
not purified
f1 (ppm)

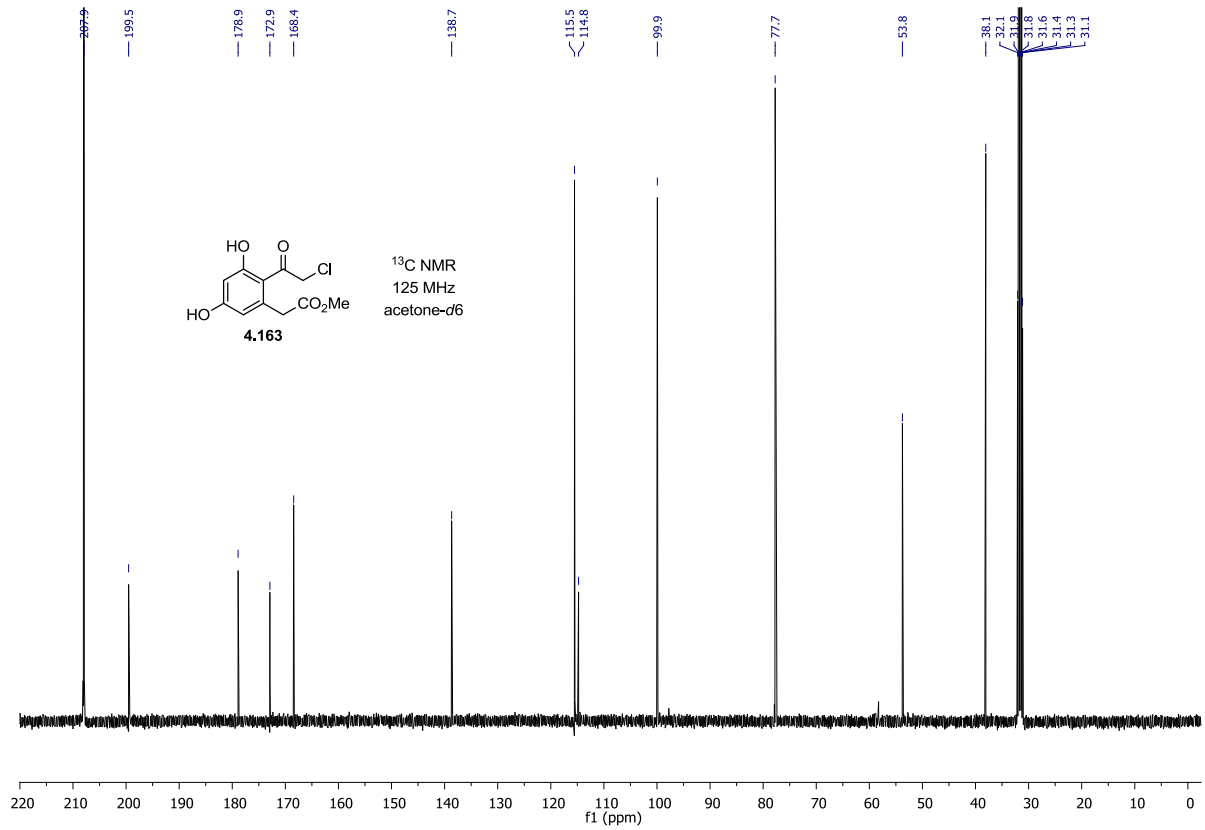

HO
O
MeO
O
OH
4.155
^{1}H NMR
500 MHz
$CDCl_3$
not purified
f1 (ppm)

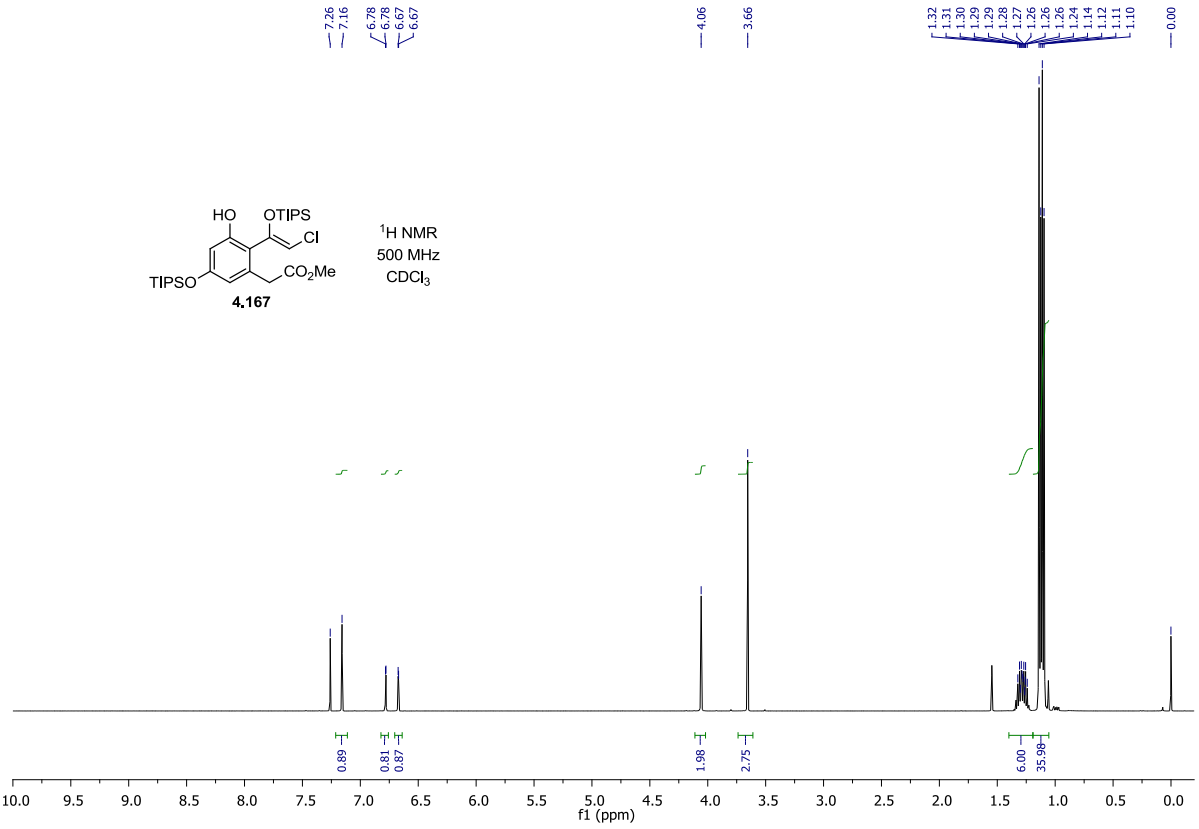

HO
O
MeO
O
OH
4.155
^{13}C NMR
125 MHz
$CDCl_3$
not purified
f1 (ppm)

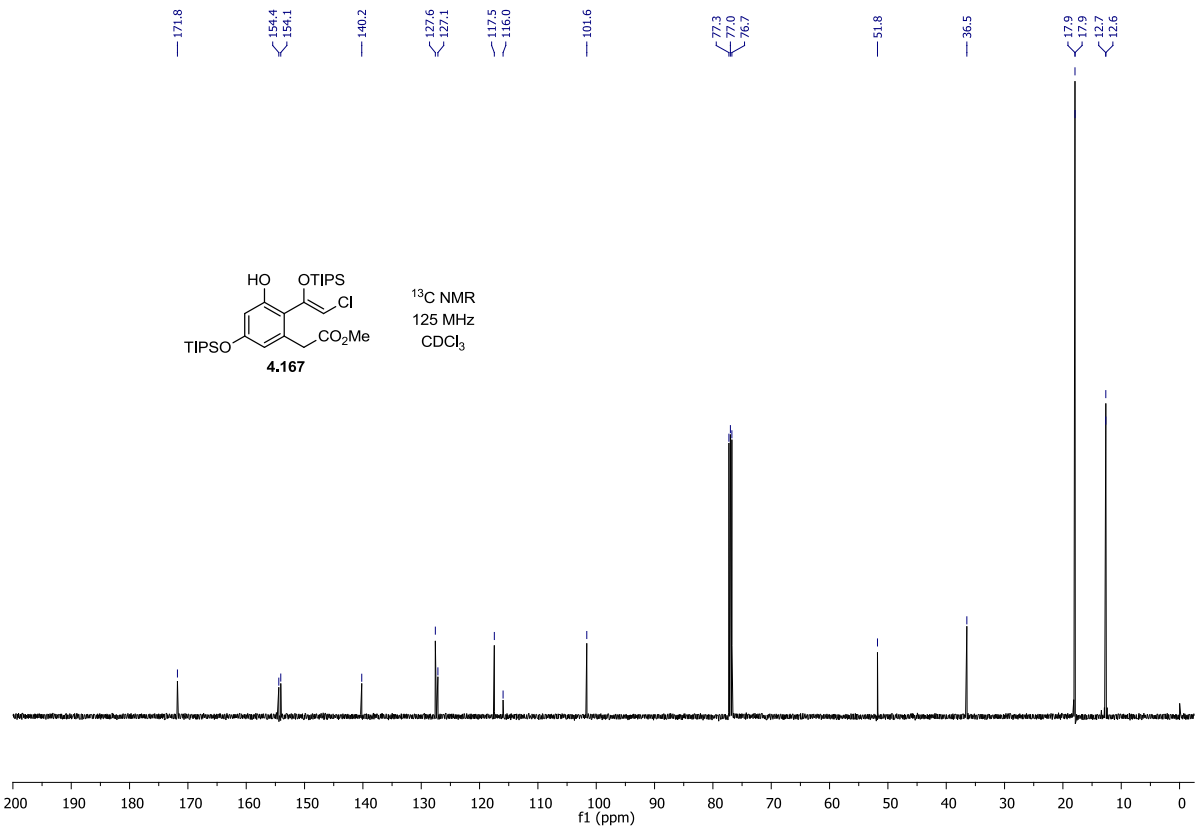

HO
O
MeO
OH
O
4.156
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

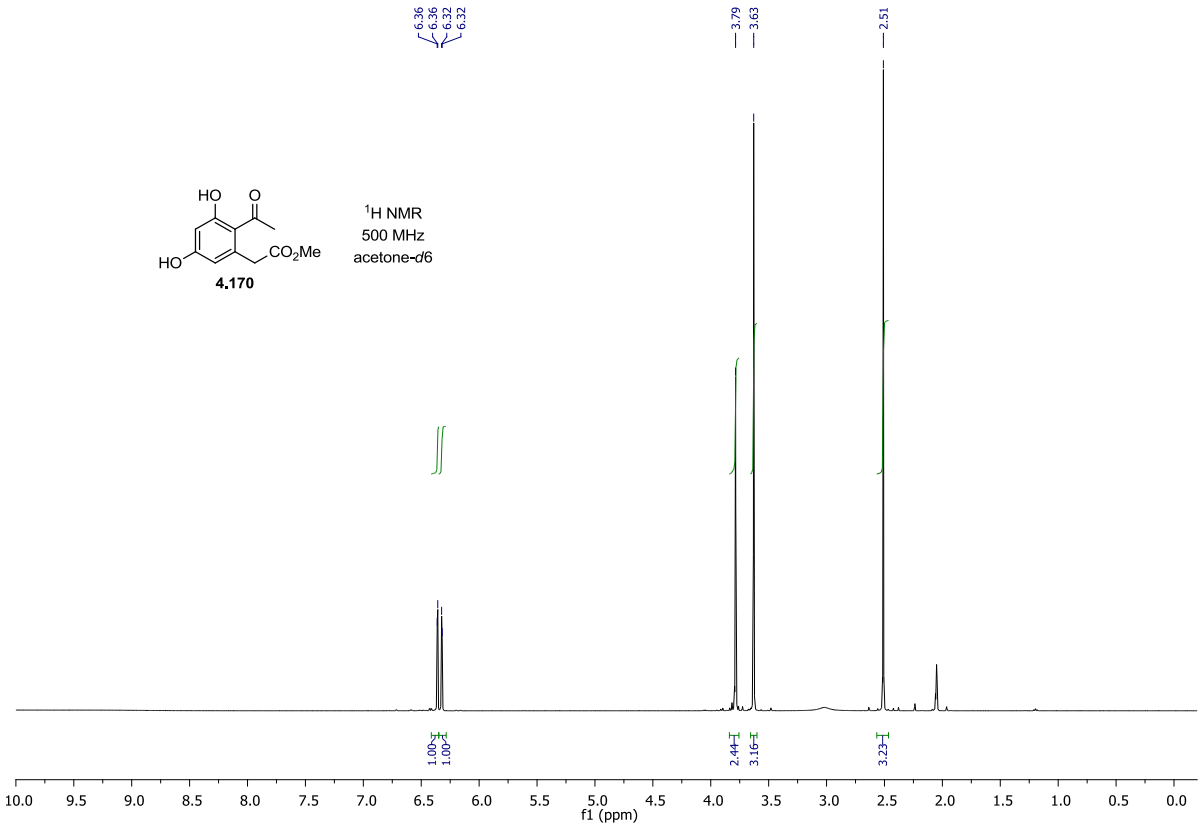

HO
O
MeO
OH
O
4.156
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

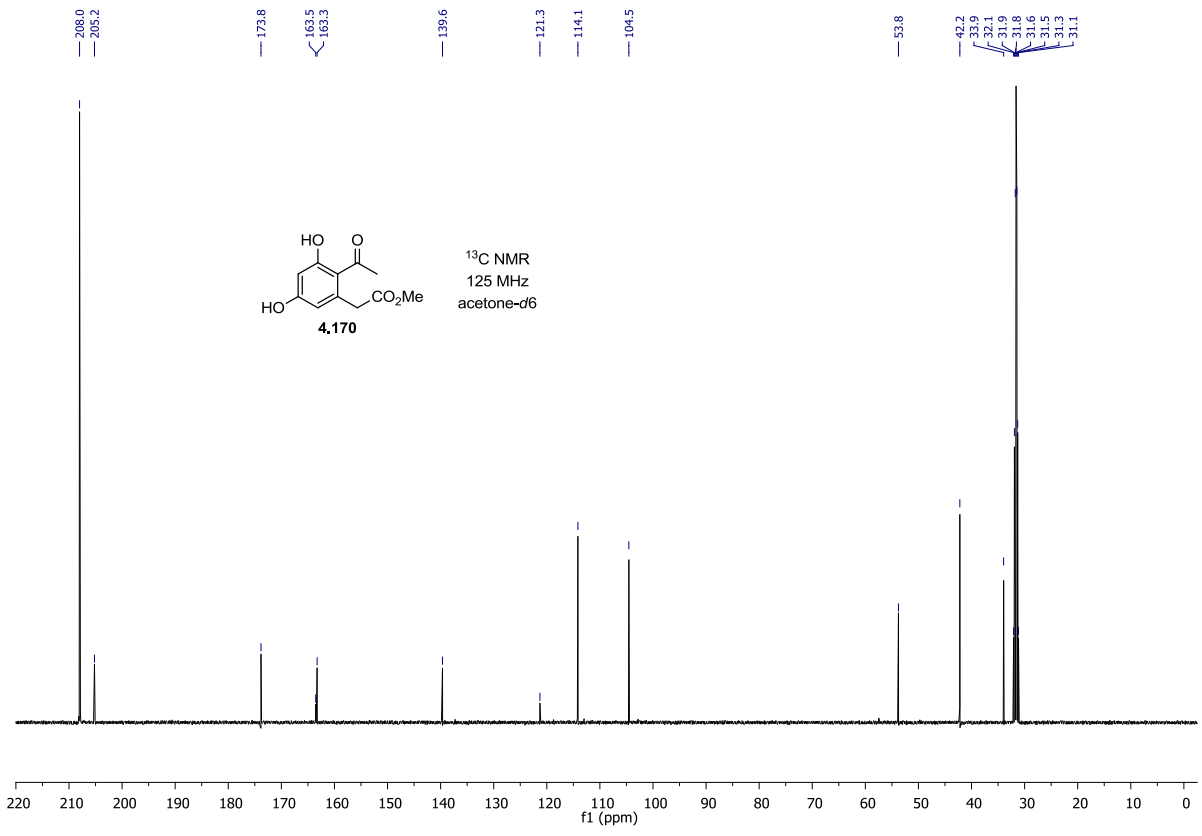

9.68
6.52
6.45
6.45
4.59
3.95
3.64
HO
O
Cl
CO2Me
HO
4.163
1H NMR
500 MHz
acetone-d6
0.56
0.93
0.88
2.29
2.36
3.15
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

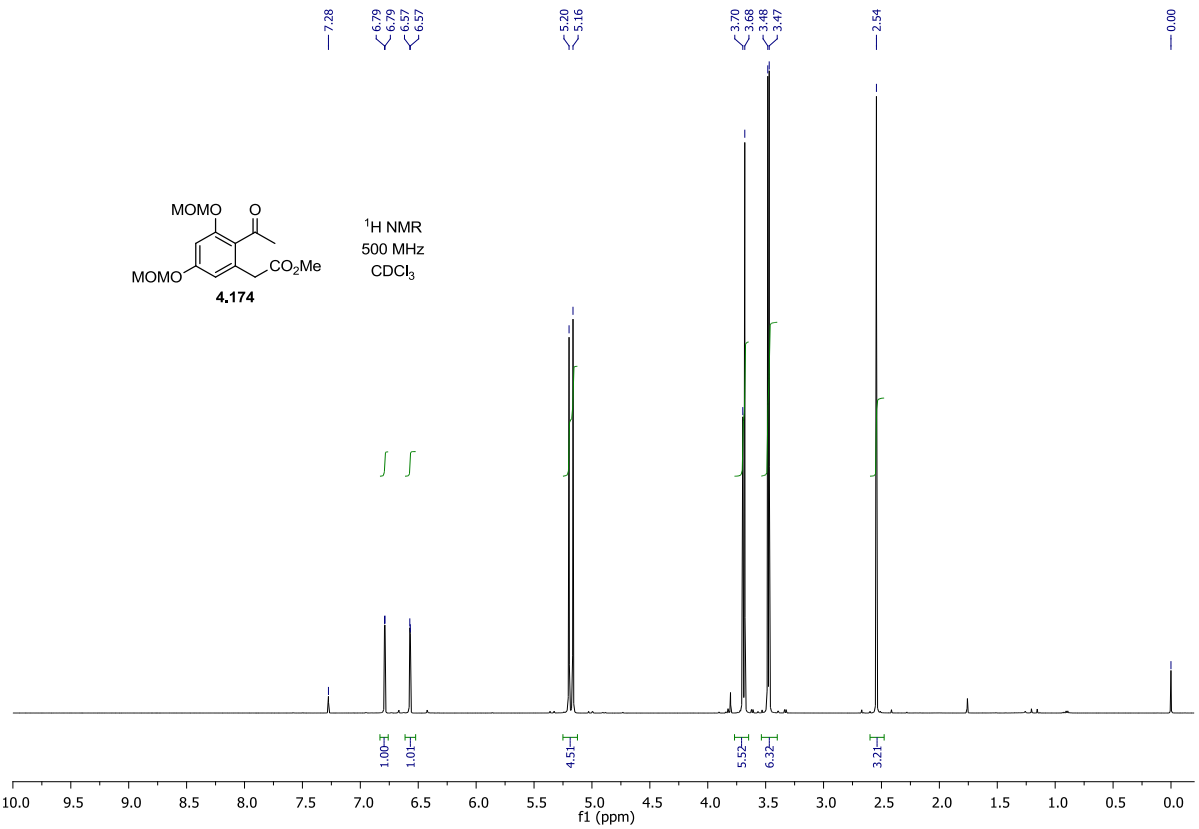

207.9
199.5
178.9
172.9
168.4
138.7
115.5
114.8
99.9
77.7
53.8
38.1
32.1
31.9
31.8
31.6
31.4
31.3
31.1
HO
O
Cl
CO2Me
HO
4.163
13C NMR
125 MHz
acetone-d6
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

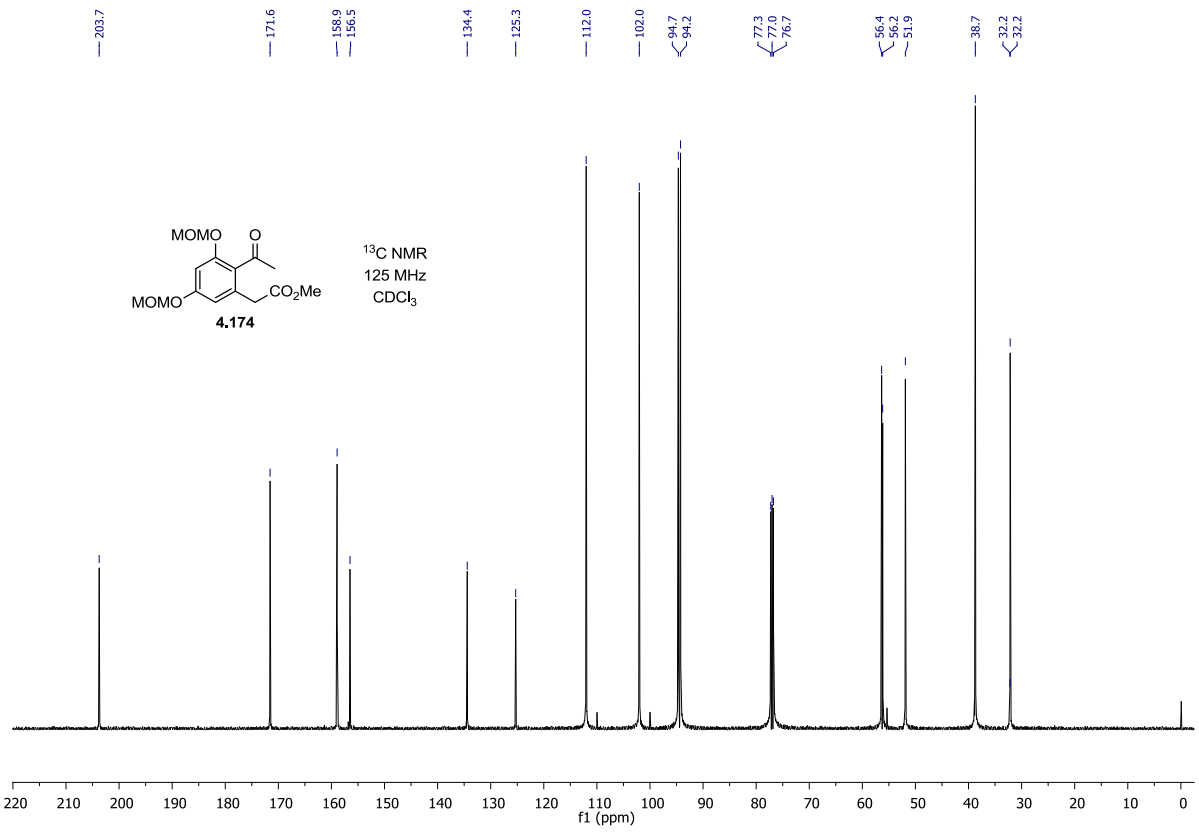

HO
OTIPS
Cl
CO2Me
TIPSO
4.167
1H NMR
500 MHz
CDCl3
7.26
7.16
6.78
6.78
6.67
6.67
4.06
3.66
1.32
1.31
1.30
1.29
1.29
1.28
1.27
1.26
1.26
1.26
1.24
1.14
1.12
1.11
1.10
0.00
0.89
0.81
0.87
1.98
2.75
6.00
35.98
f1 (ppm)

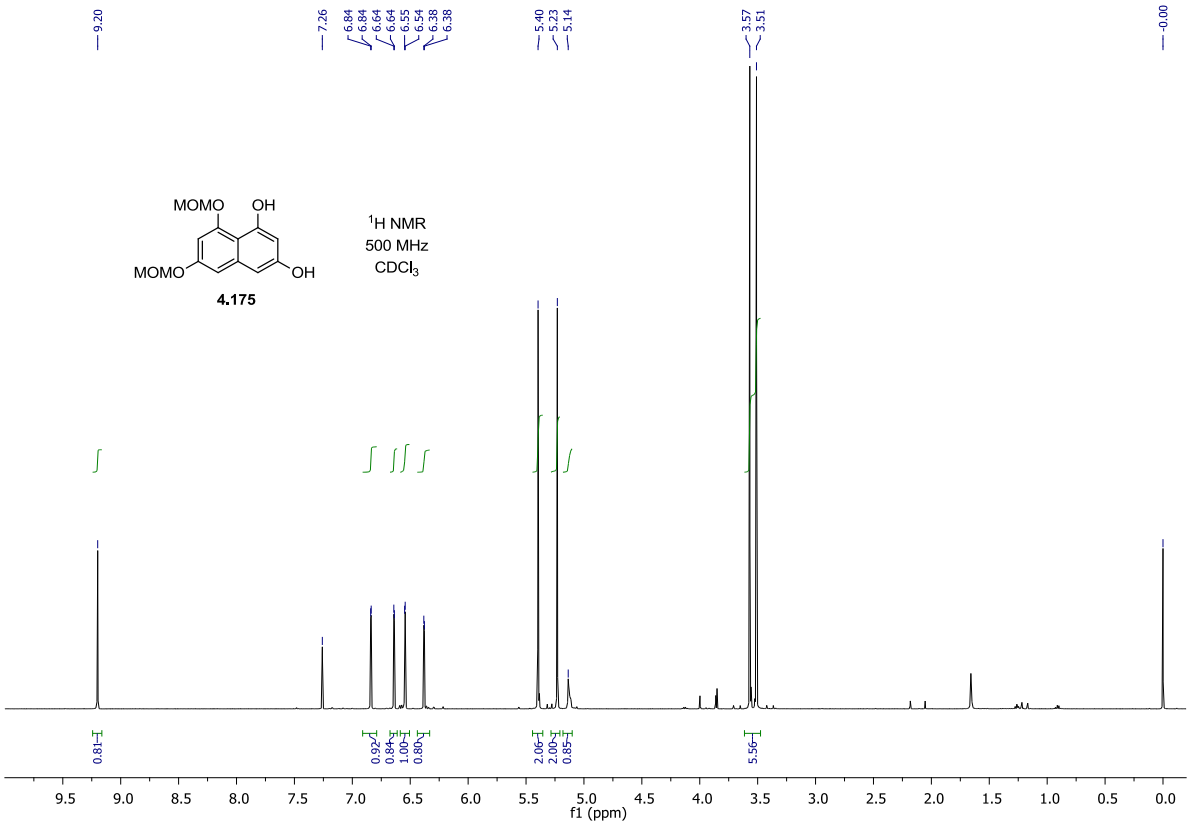

HO
OTIPS
Cl
CO2Me
TIPSO
4.167
13C NMR
125 MHz
CDCl3
171.8
154.4
154.1
140.2
127.6
127.1
117.5
116.0
101.6
77.3
77.0
76.7
51.8
36.5
17.9
17.9
12.7
12.6
f1 (ppm)

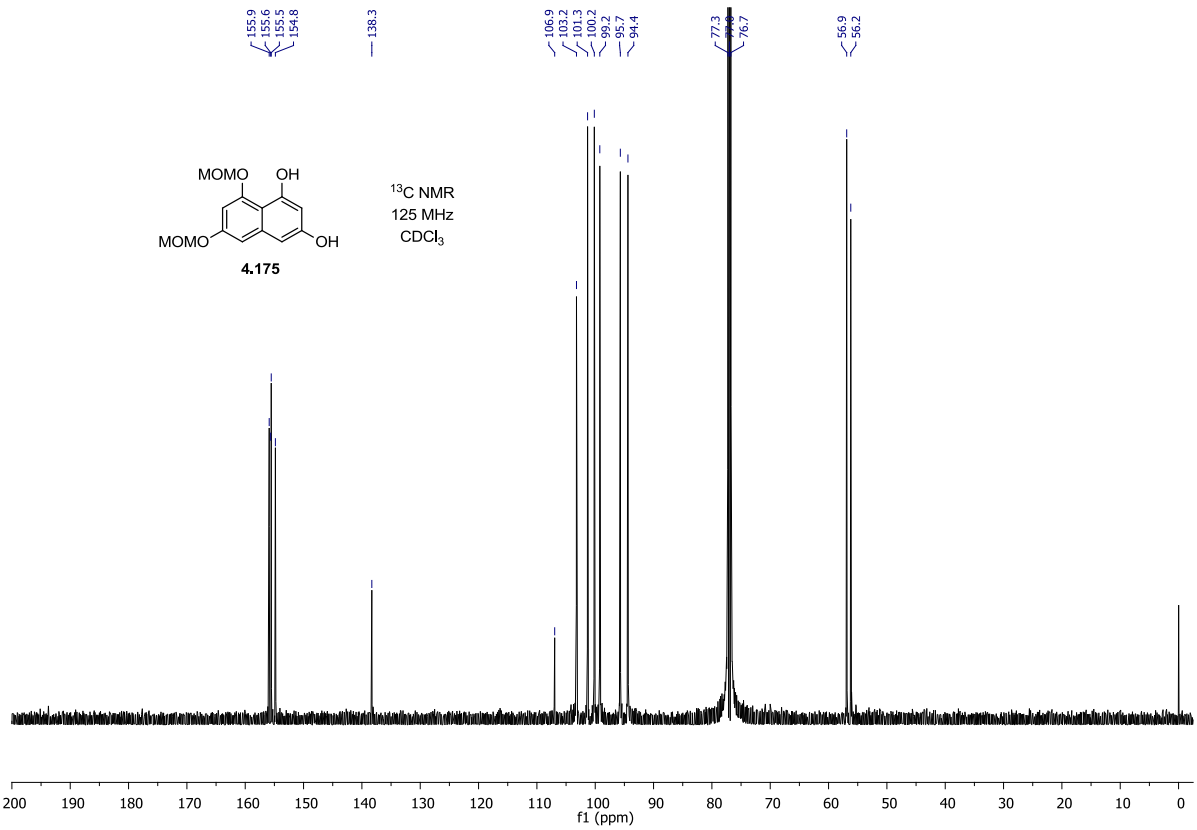

6.36
6.36
6.32
6.32
3.79
3.63
2.51
HO
O
HO
CO2Me
4.170
1H NMR
500 MHz
acetone-d6
1.00
1.00
2.44
3.16
3.23
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

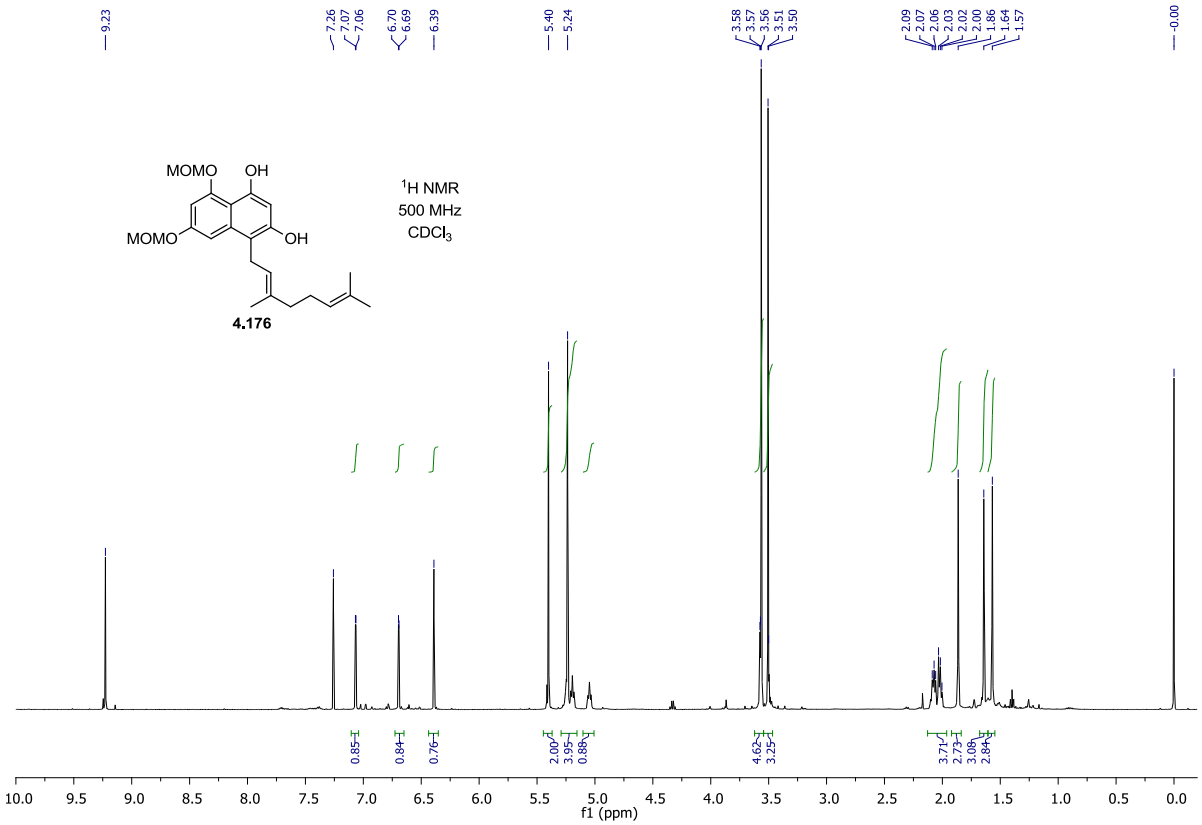

208.0
205.2
173.8
163.5
163.3
139.6
121.3
114.1
104.5
53.8
42.2
33.9
32.1
31.9
31.8
31.6
31.5
31.3
31.1
HO
O
HO
CO2Me
4.170
13C NMR
125 MHz
acetone-d6
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

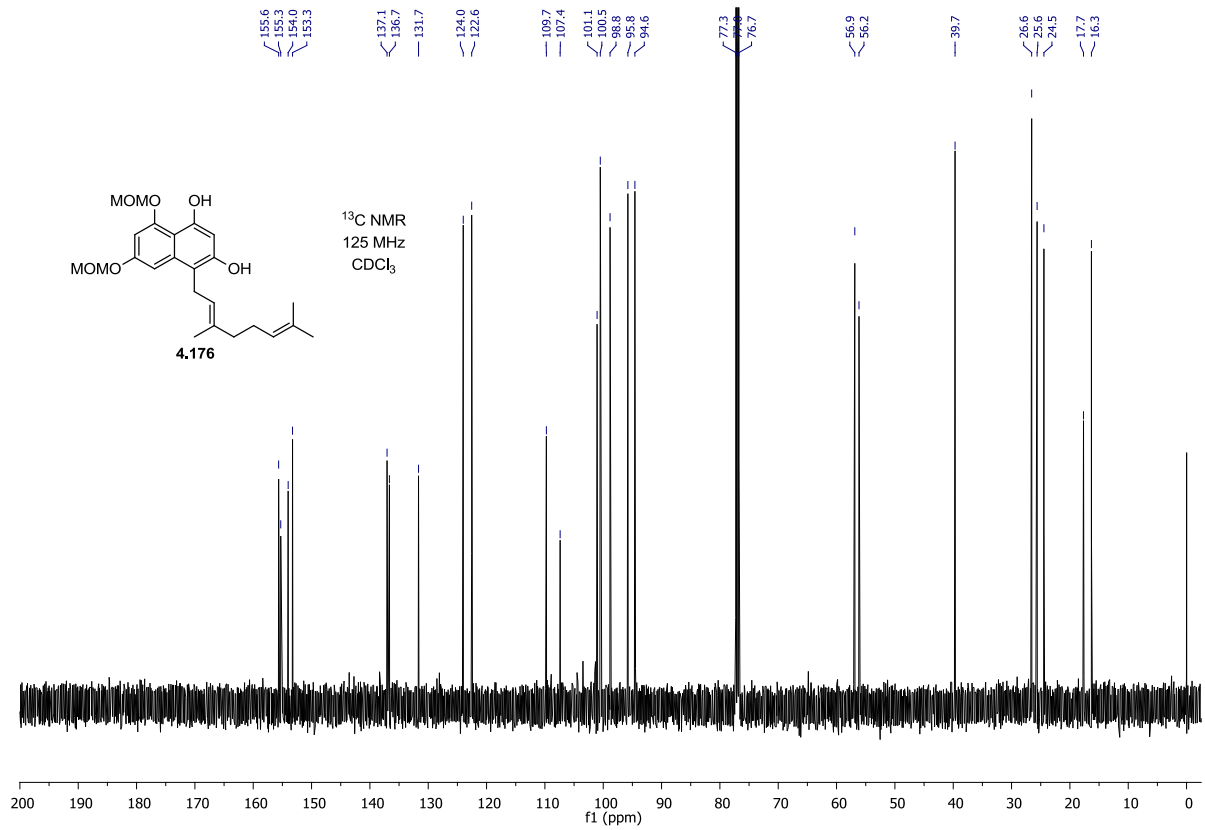

MOMO
O
MOMO
CO2Me
4.174
1H NMR
500 MHz
CDCl3
7.28
6.79
6.79
6.57
6.57
5.20
5.16
3.70
3.68
3.48
3.47
2.54
0.00
1.00
1.01
4.51
5.52
6.32
3.21
f1 (ppm)

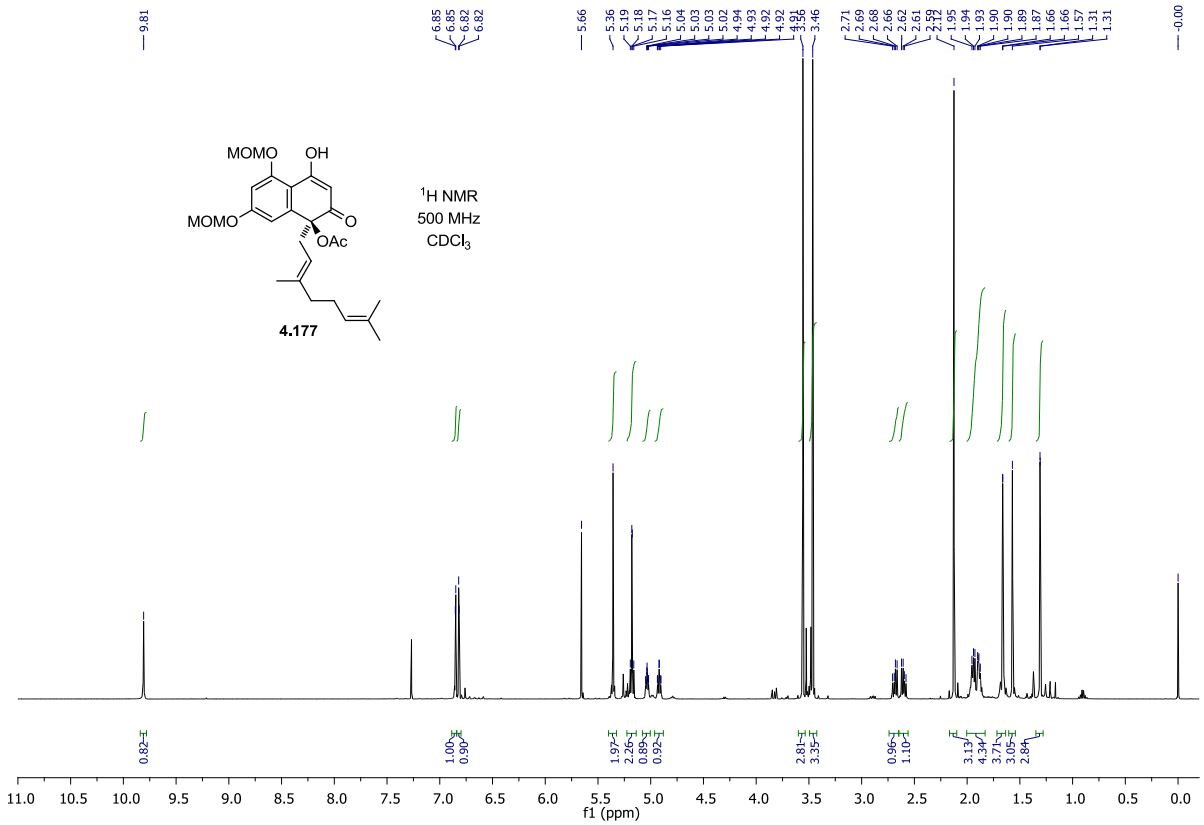

MOMO
O
MOMO
CO2Me
4.174
13C NMR
125 MHz
CDCl3
203.7
171.6
158.9
156.5
134.4
125.3
112.0
102.0
94.7
94.2
77.3
77.0
76.7
56.4
56.2
51.9
38.7
32.2
32.2
f1 (ppm)

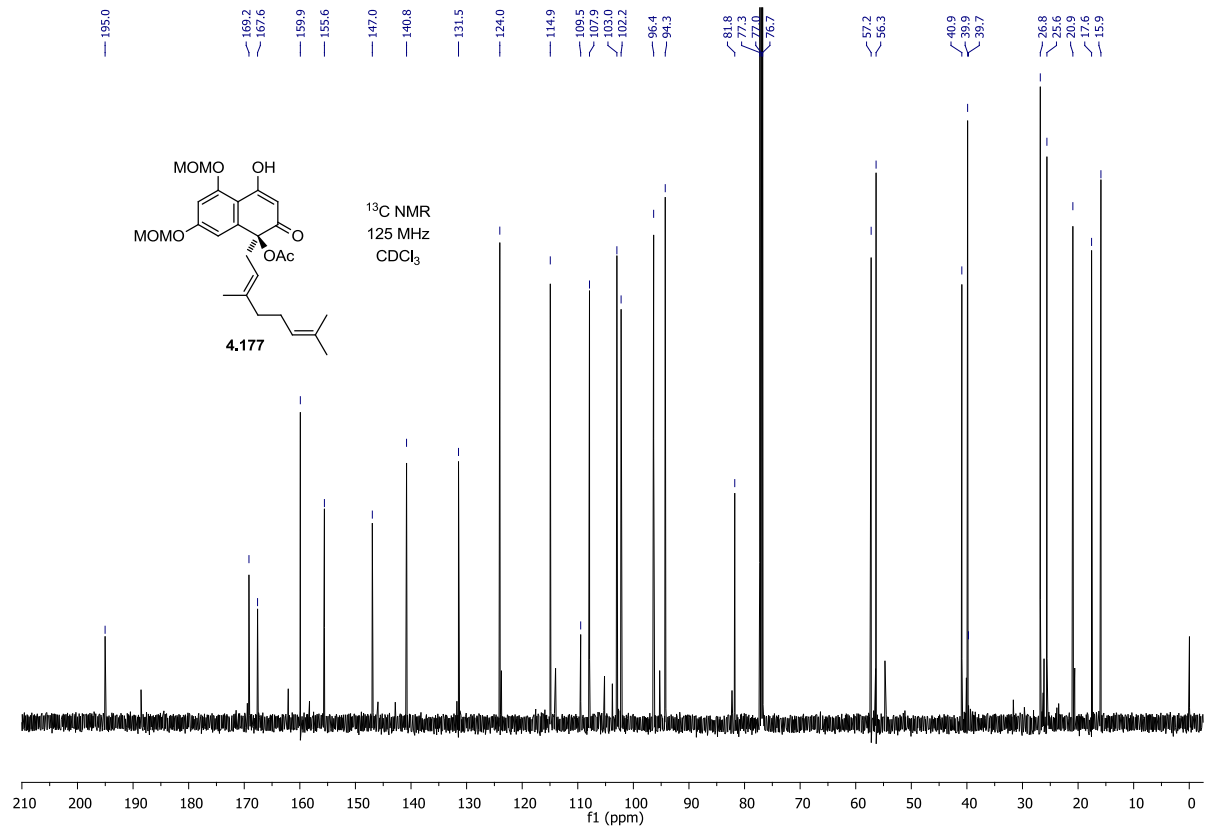

9.20
7.26
6.84
6.84
6.64
6.64
6.55
6.54
6.38
6.38
5.40
5.23
5.14
3.57
3.51
0.00
MOMO
OH
MOMO
OH
4.175
1H NMR
500 MHz
CDCl3
0.81
0.92
0.84
1.06
0.80
2.06
2.00
0.85
5.56
f1 (ppm)

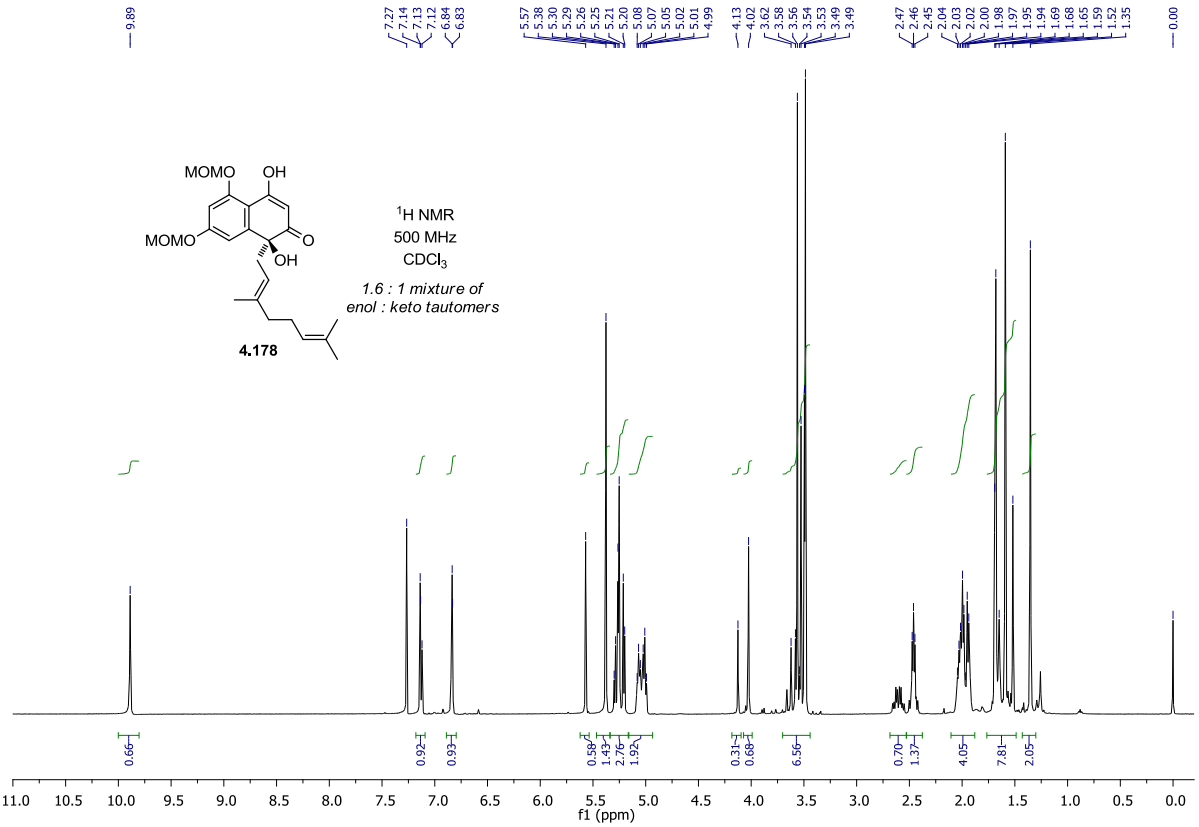

155.9
155.6
155.5
154.8
138.3
106.9
103.2
101.3
100.2
99.2
95.7
94.4
77.3
76.8
76.7
56.9
56.2
MOMO
OH
MOMO
OH
4.175
13C NMR
125 MHz
CDCl3
f1 (ppm)

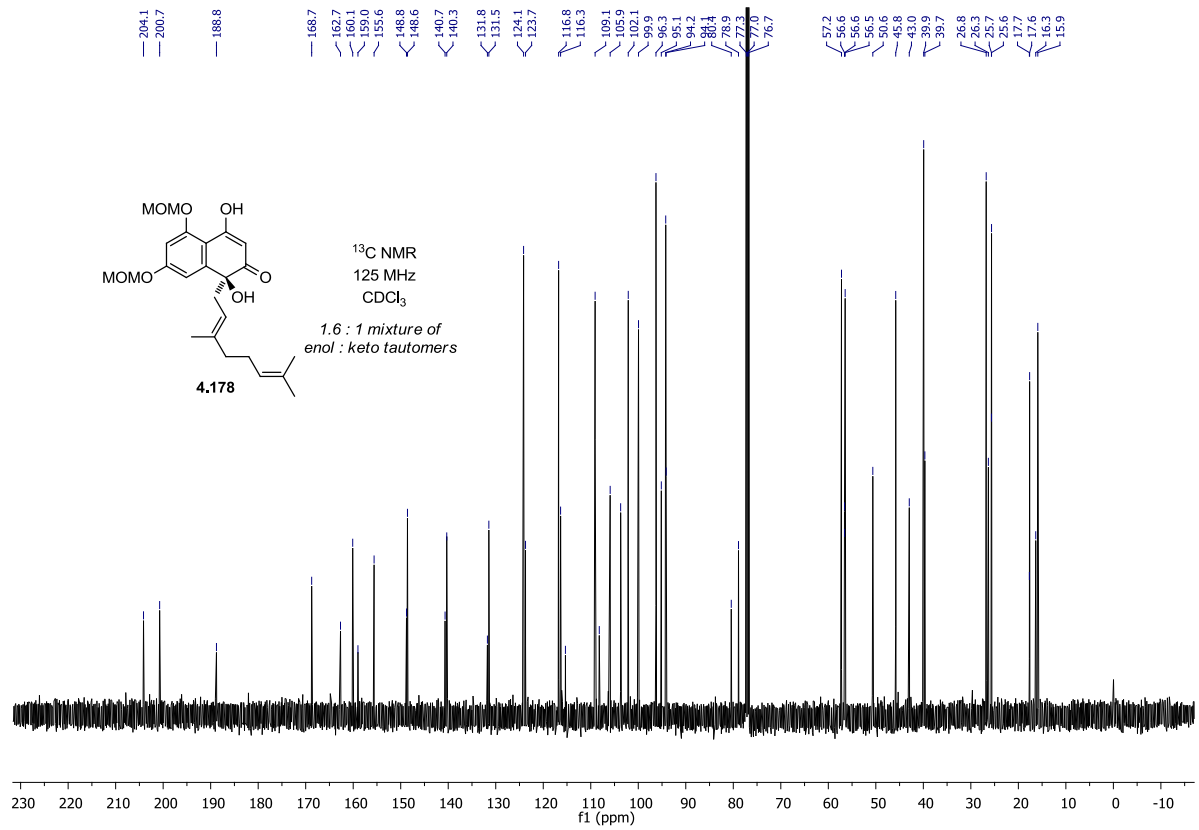

MOMO
OH
MOMO
OH
4.176
^{1}H NMR
500 MHz
$CDCl_3$
9.23
7.26
7.07
7.06
6.70
6.69
6.39
5.40
5.24
3.58
3.57
3.56
3.51
3.50
2.09
2.07
2.06
2.03
2.02
2.00
1.86
1.64
1.57
0.00
0.85
0.84
0.76
2.00
3.95
0.88
4.62
3.25
3.71
2.73
3.08
2.84
f1 (ppm)

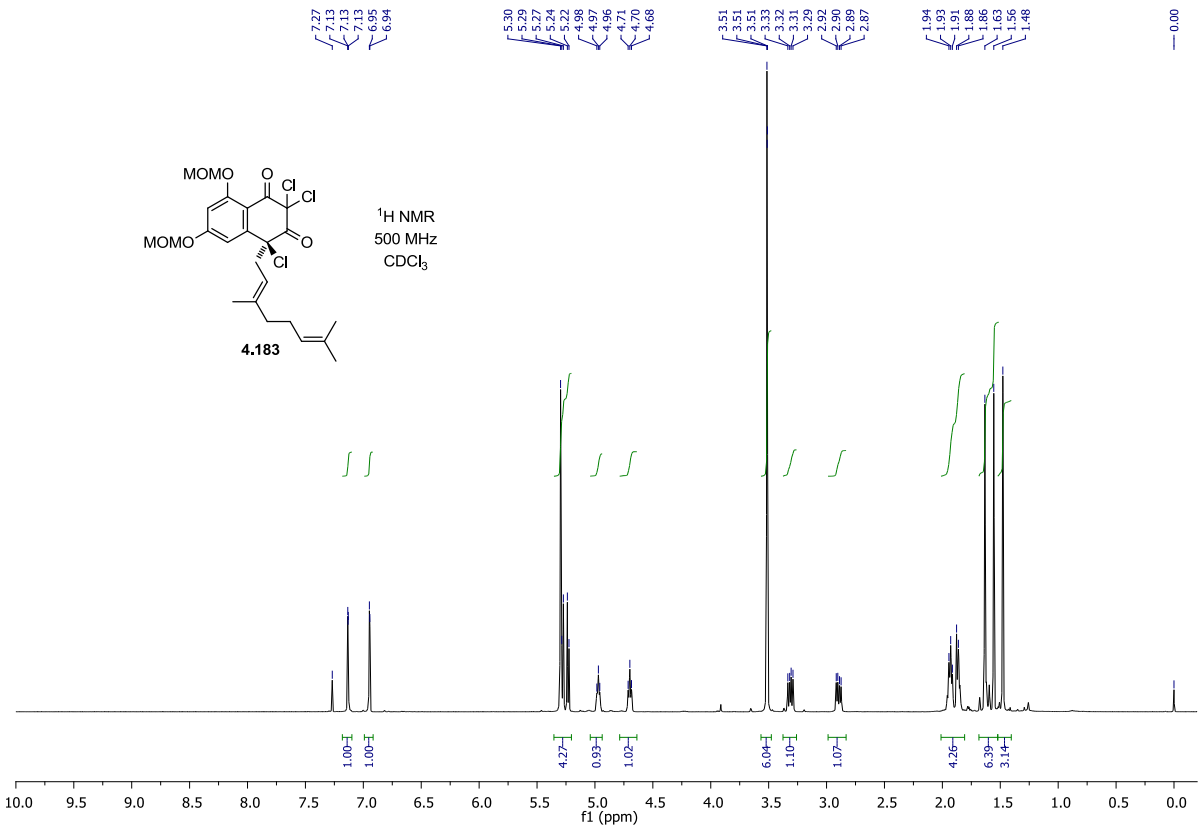

MOMO
OH
MOMO
OH
4.176
^{13}C NMR
125 MHz
$CDCl_3$
155.6
155.3
154.0
153.3
137.1
136.7
131.7
124.0
122.6
109.7
107.4
101.1
100.5
98.8
95.8
94.6
77.3
77.0
76.7
56.9
56.2
39.7
26.6
25.6
24.5
17.7
16.3
f1 (ppm)

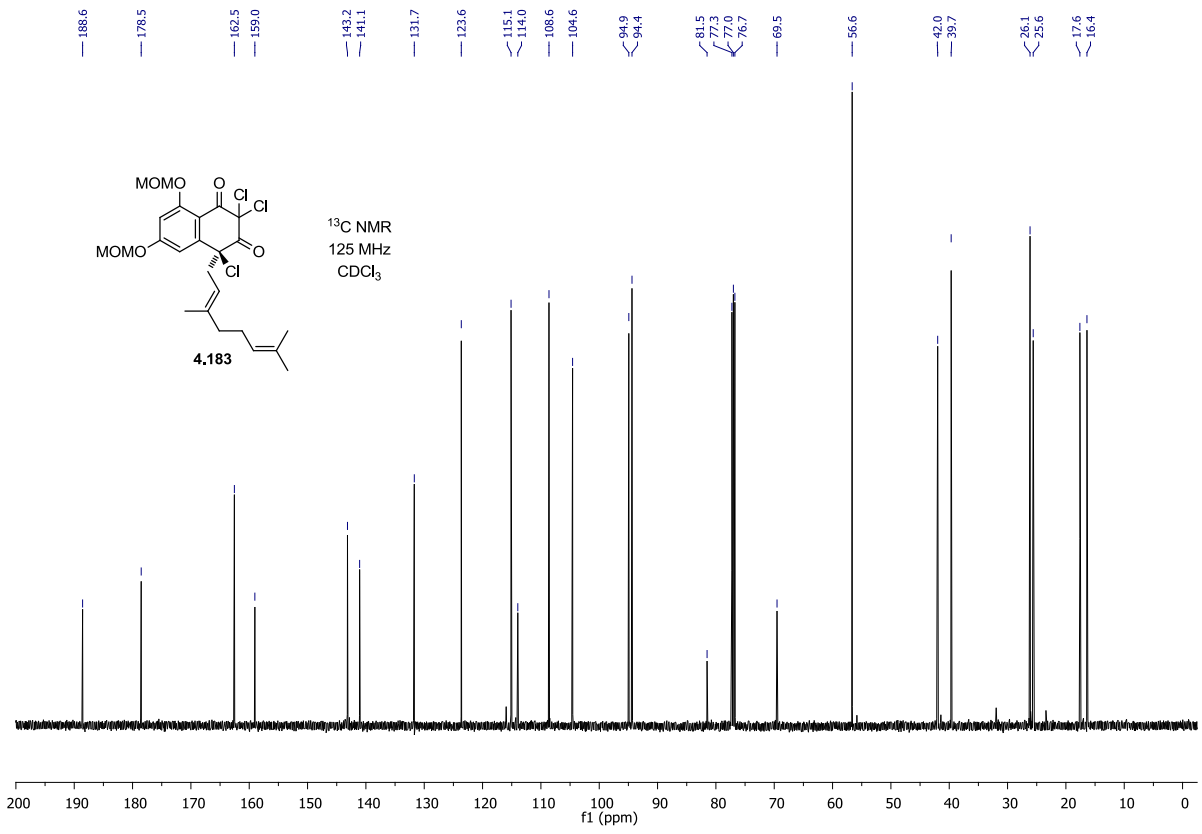

MOMO
OH
MOMO
O
OAc
4.177
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

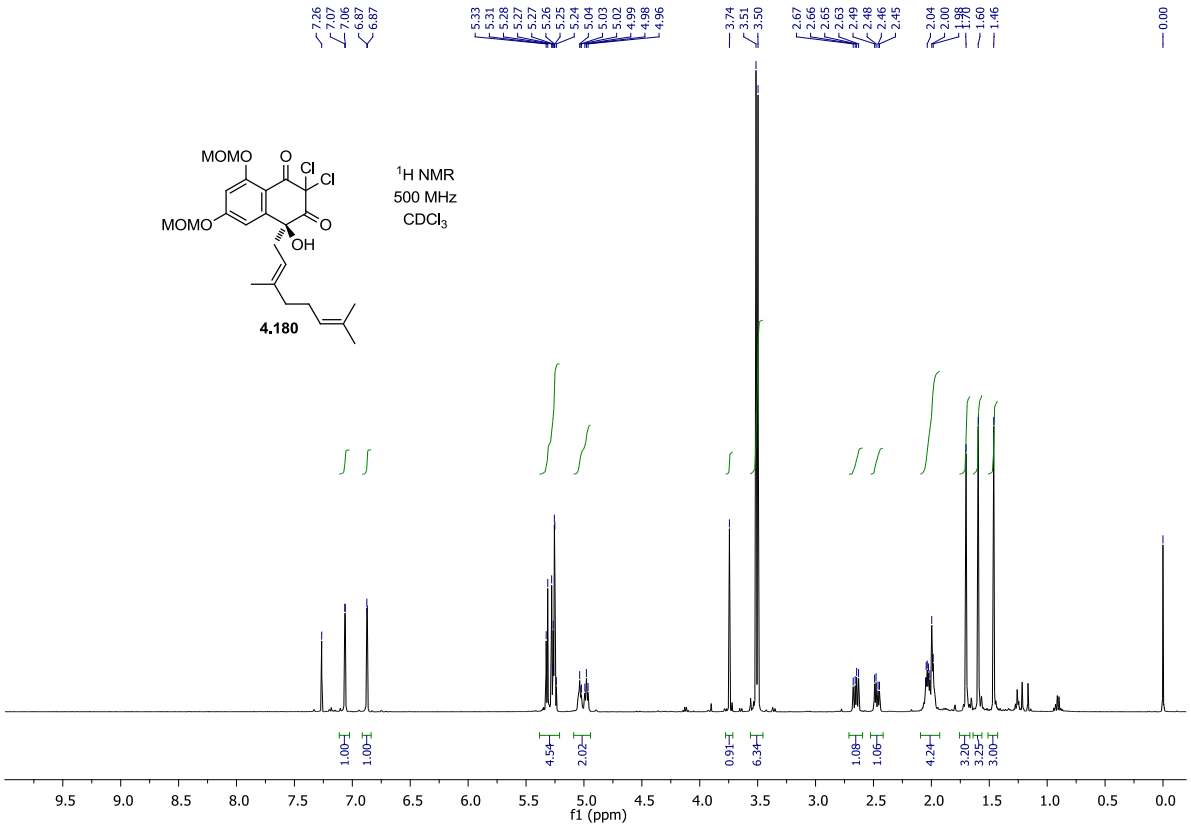

MOMO
OH
MOMO
O
OAc
4.177
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

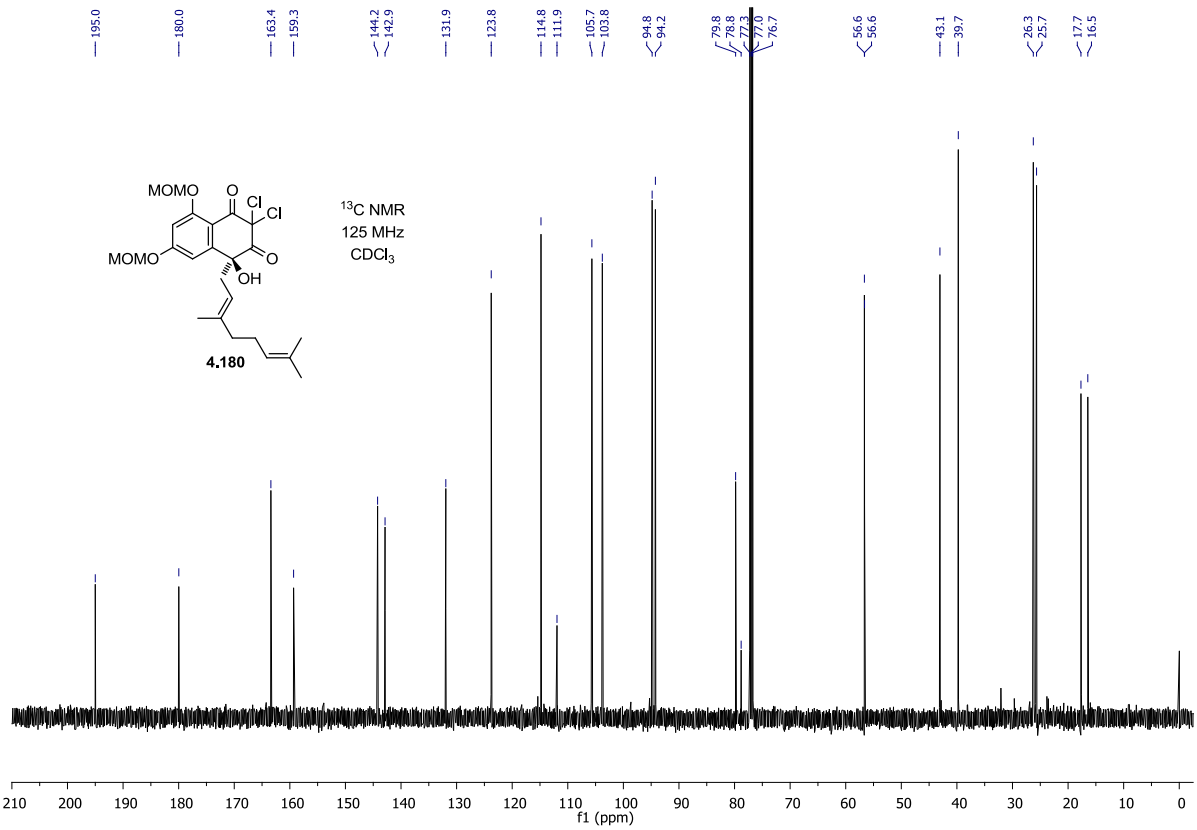

MOMO
OH
MOMO
O
OH
4.178
^{1}H NMR
500 MHz
$CDCl_3$
1.6 : 1 mixture of
enol : keto tautomers
f1 (ppm)

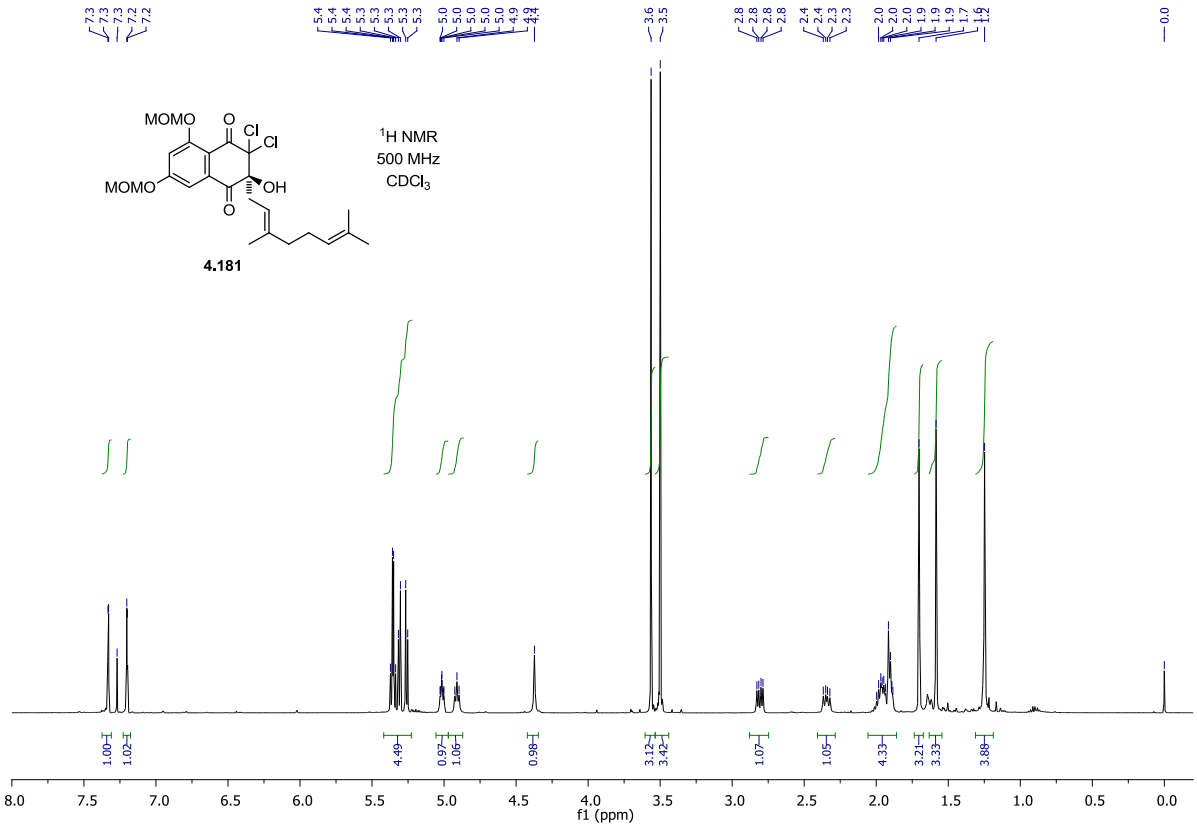

MOMO
OH
MOMO
O
OH
4.178
^{13}C NMR
125 MHz
$CDCl_3$
1.6 : 1 mixture of
enol : keto tautomers
f1 (ppm)

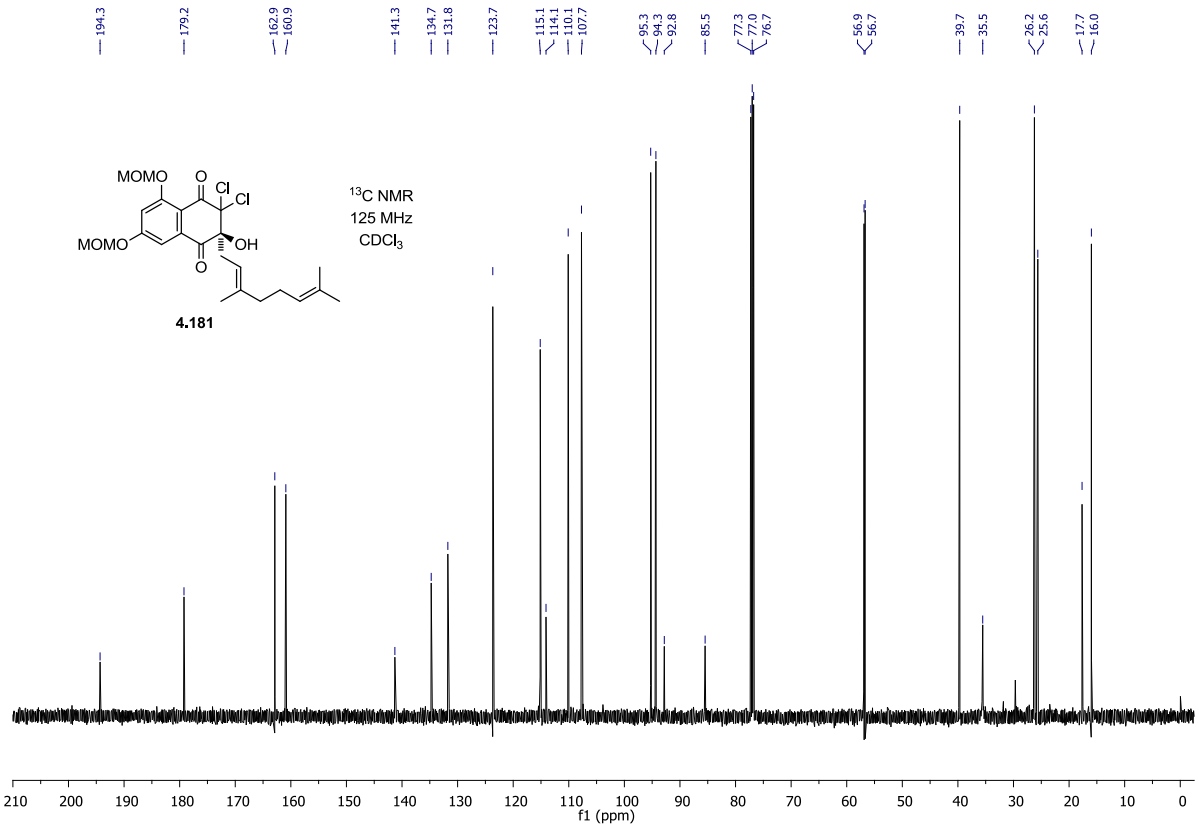

MOMO
O
Cl
Cl
MOMO
O
Cl
4.183
1H NMR
500 MHz
CDCl3
f1 (ppm)

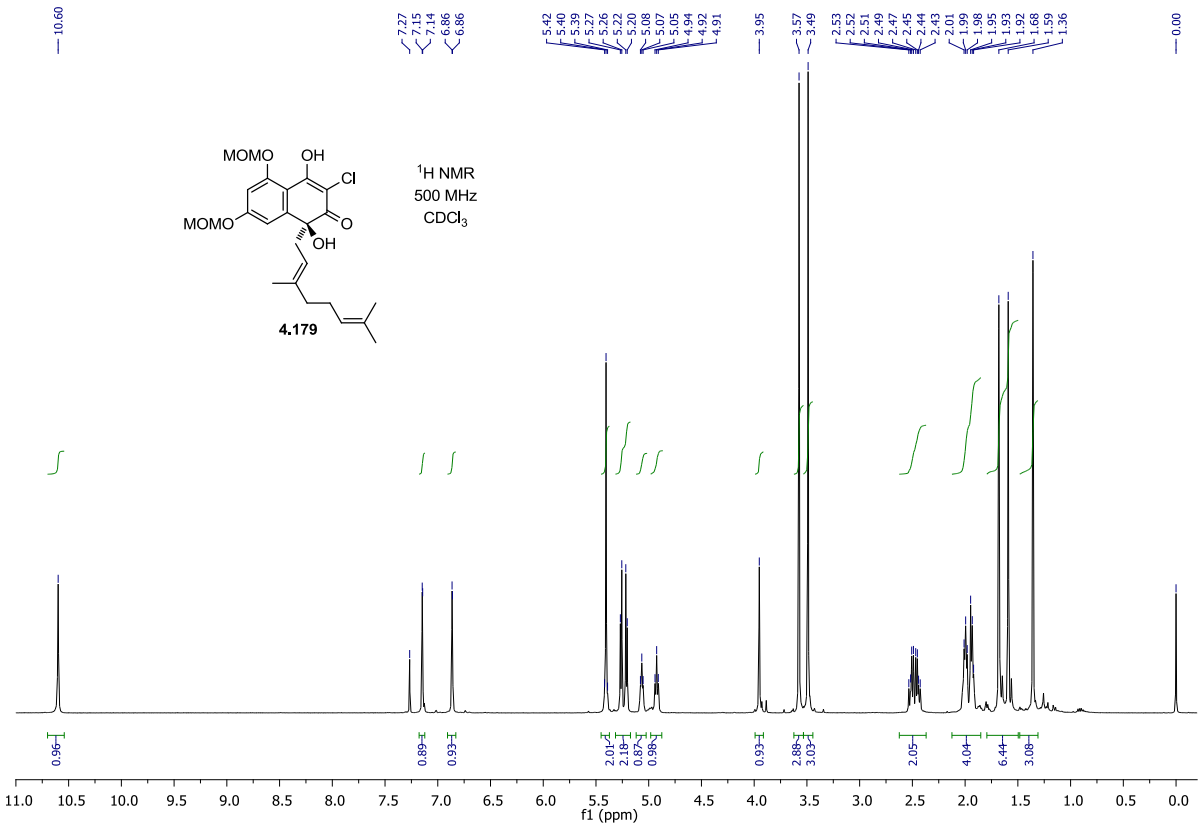

MOMO
O
Cl
Cl
MOMO
O
Cl
4.183
13C NMR
125 MHz
CDCl3
f1 (ppm)

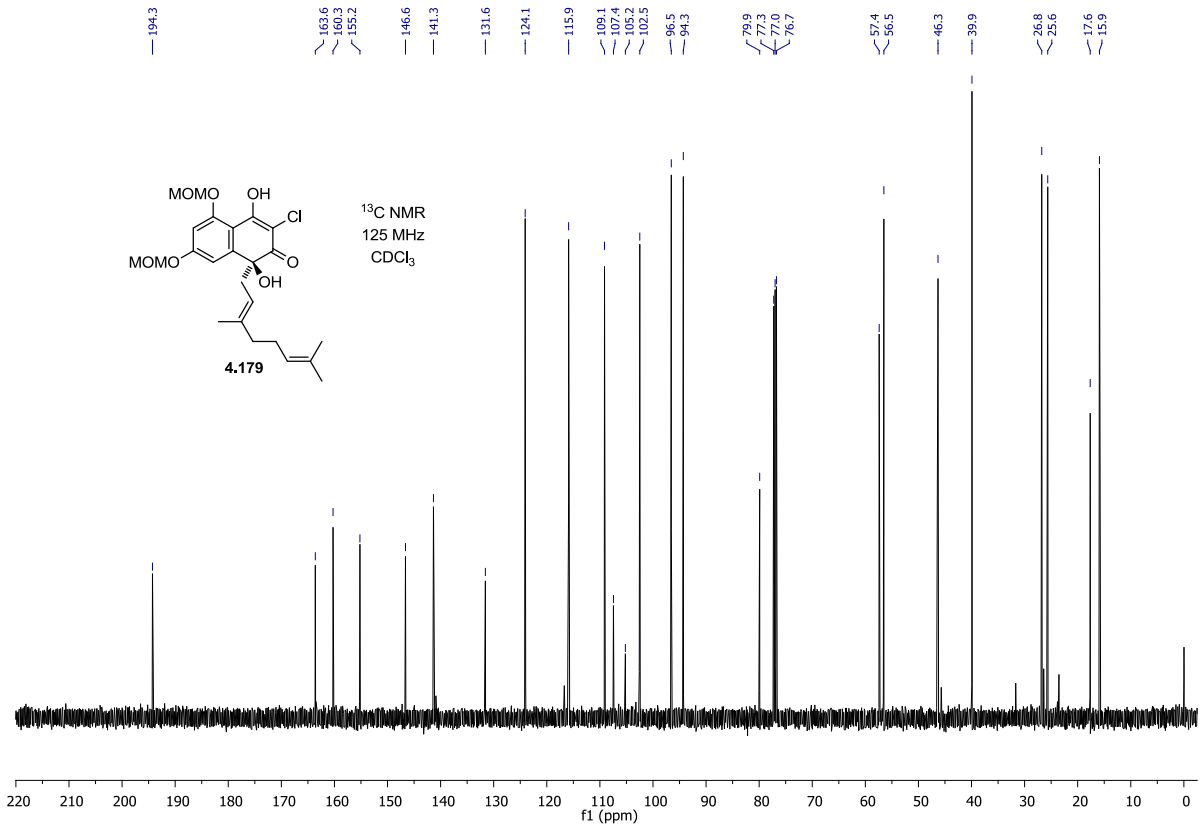

MOMO
O
Cl
Cl
MOMO
O
OH
4.180
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

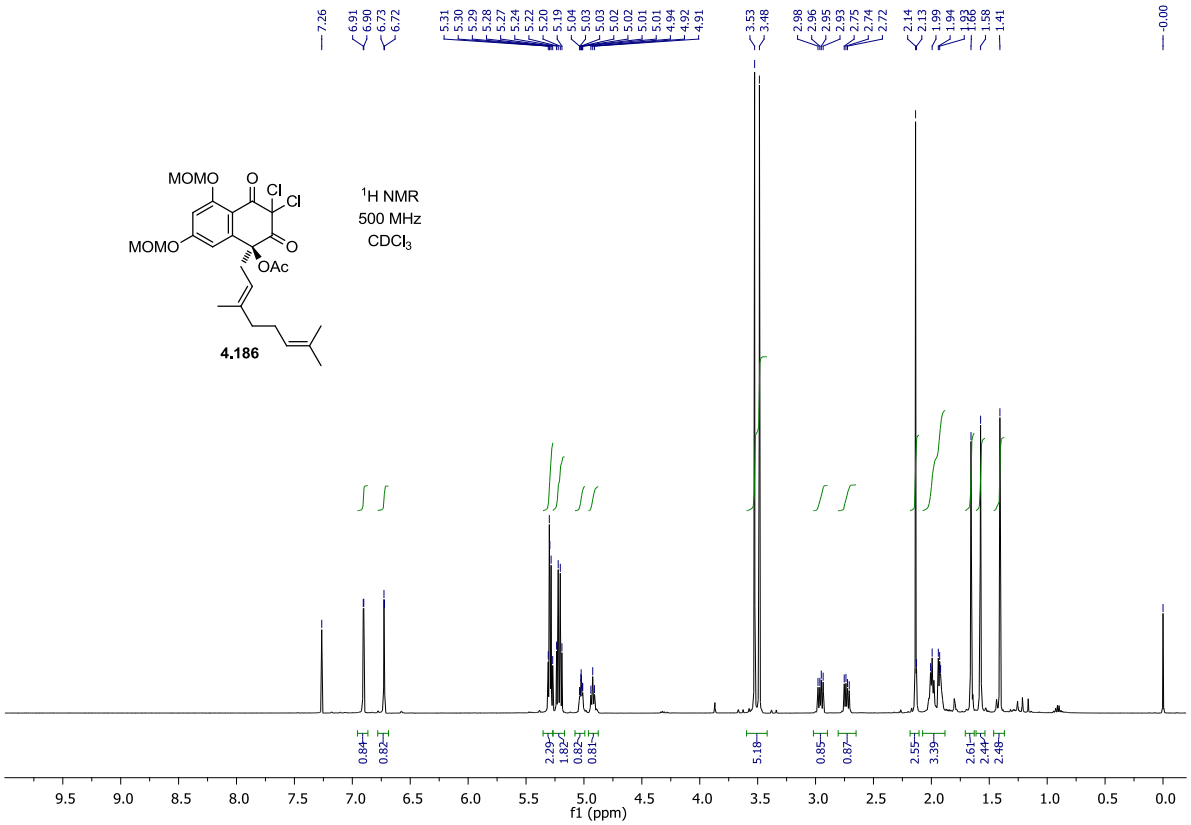

MOMO
O
Cl
Cl
MOMO
O
OH
4.180
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

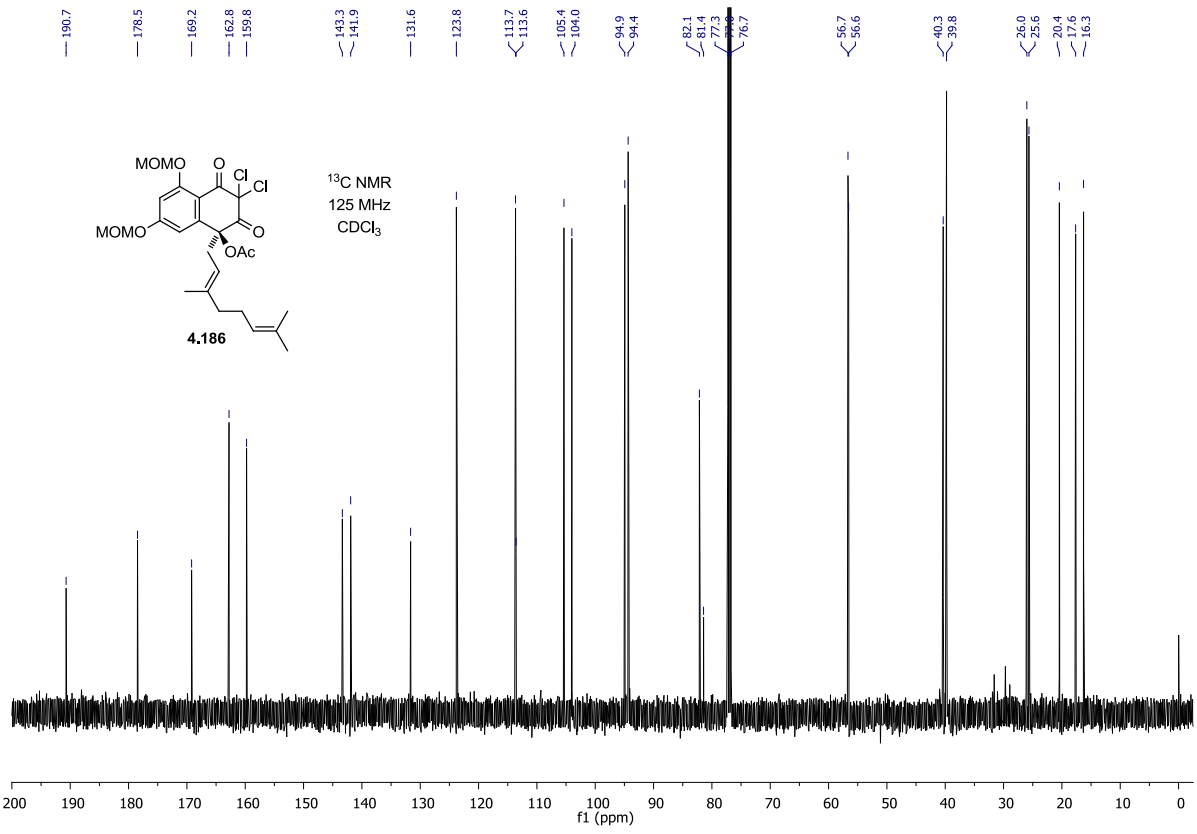

MOMO
O
Cl
Cl
MOMO
OH
O
4.181
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

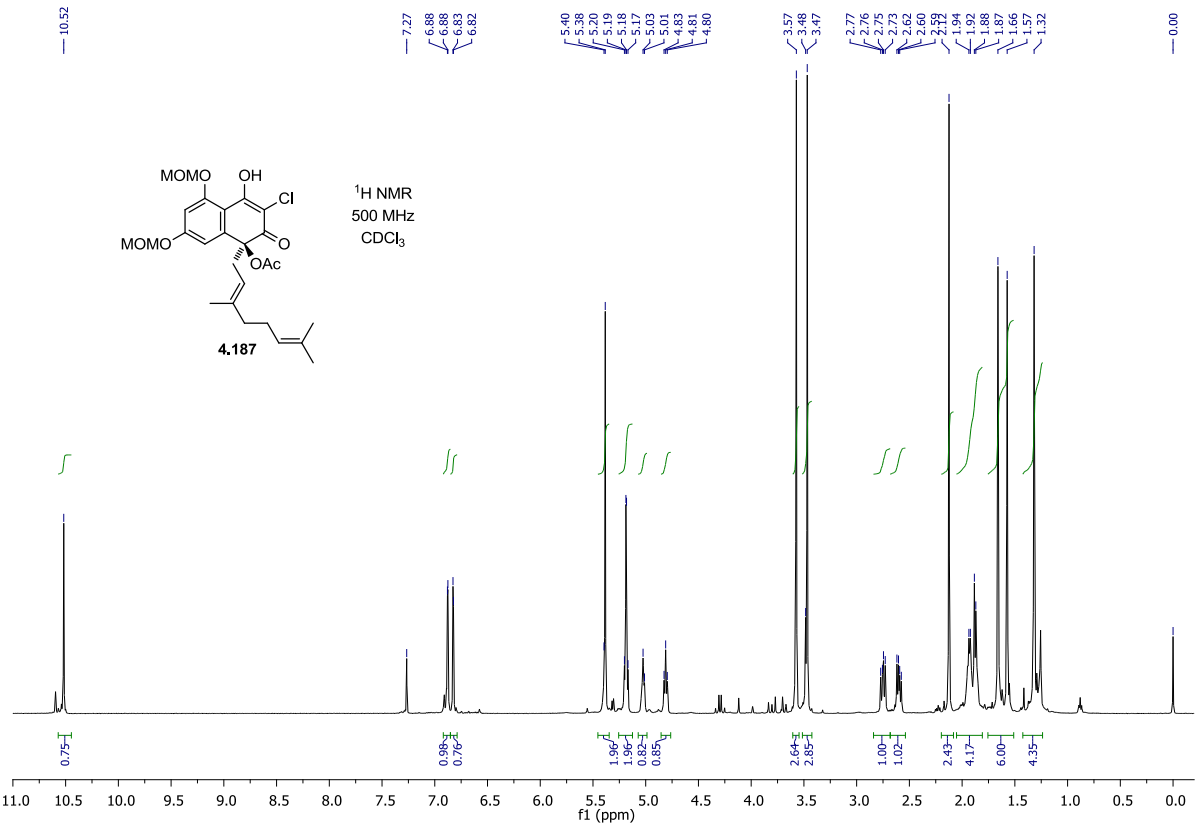

MOMO
O
Cl
Cl
MOMO
OH
O
4.181
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

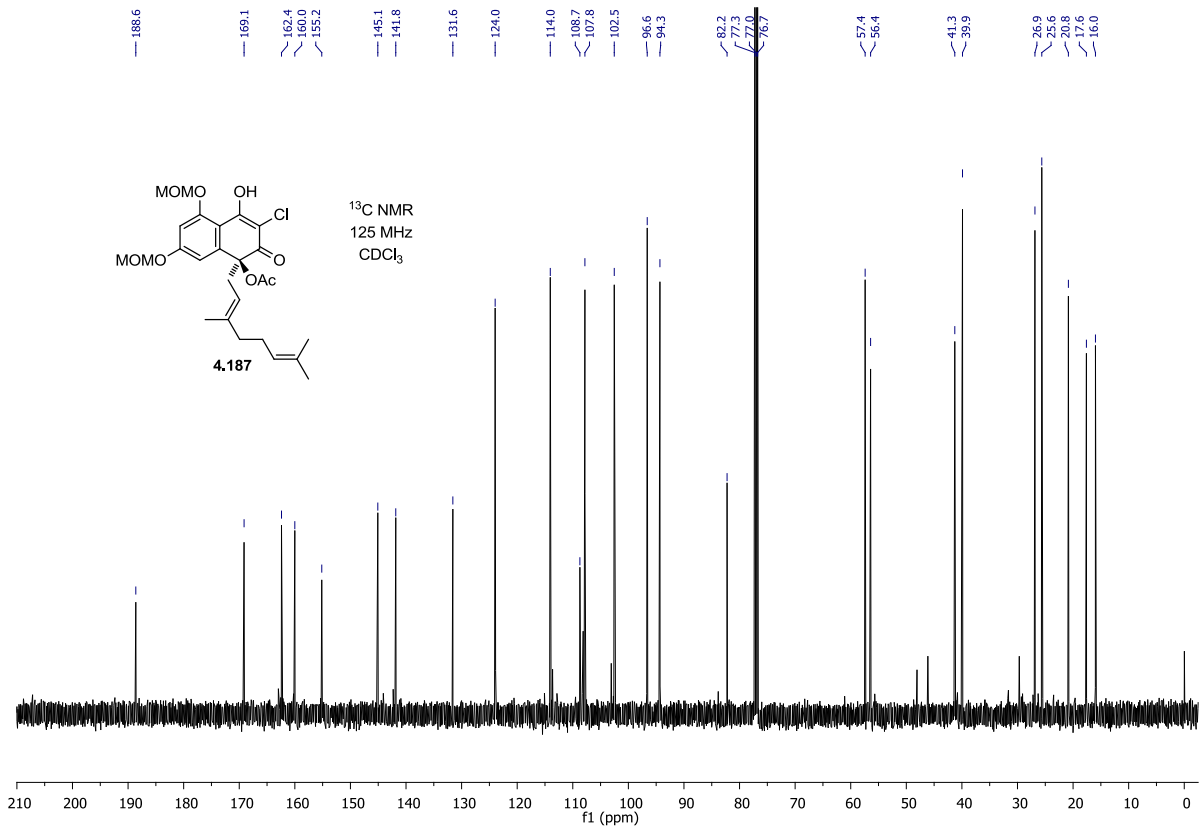

MOMO
OH
Cl
MOMO
O
OH
4.179
1H NMR
500 MHz
CDCl3
f1 (ppm)

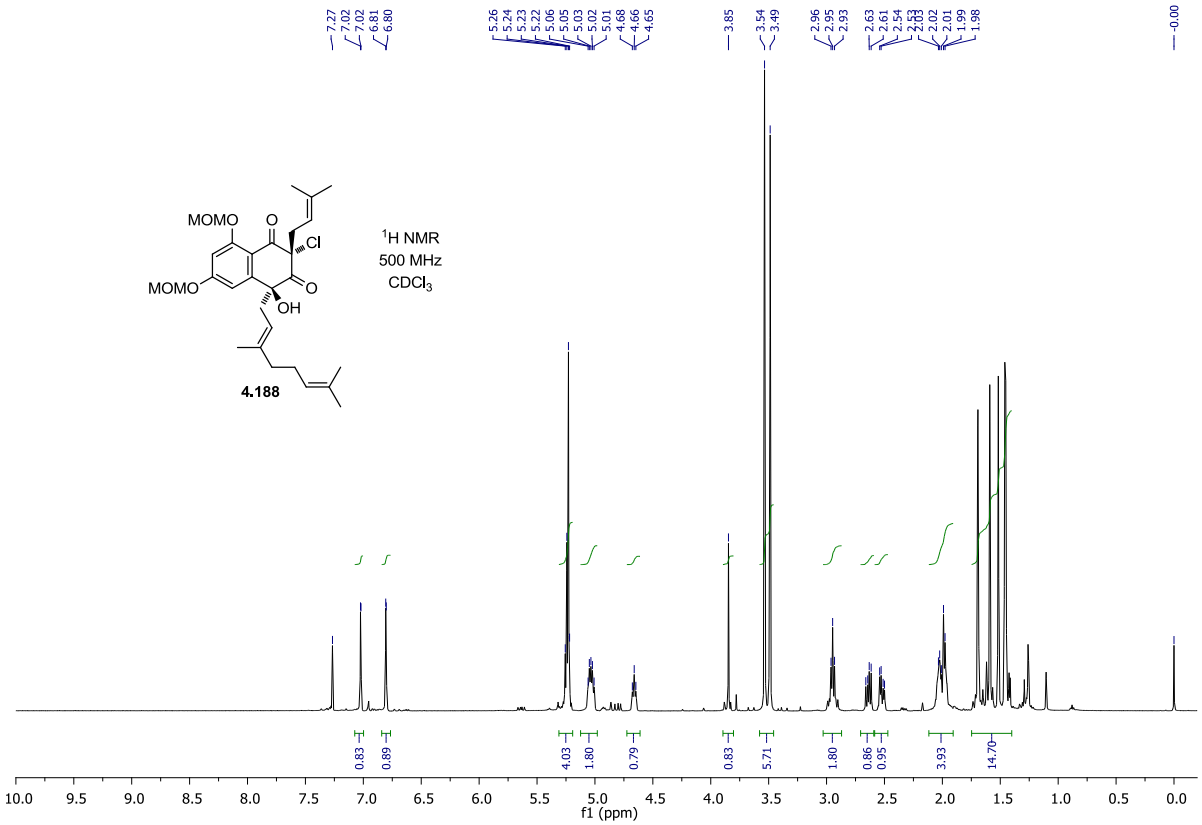

MOMO
OH
Cl
MOMO
O
OH
4.179
13C NMR
125 MHz
CDCl3
f1 (ppm)

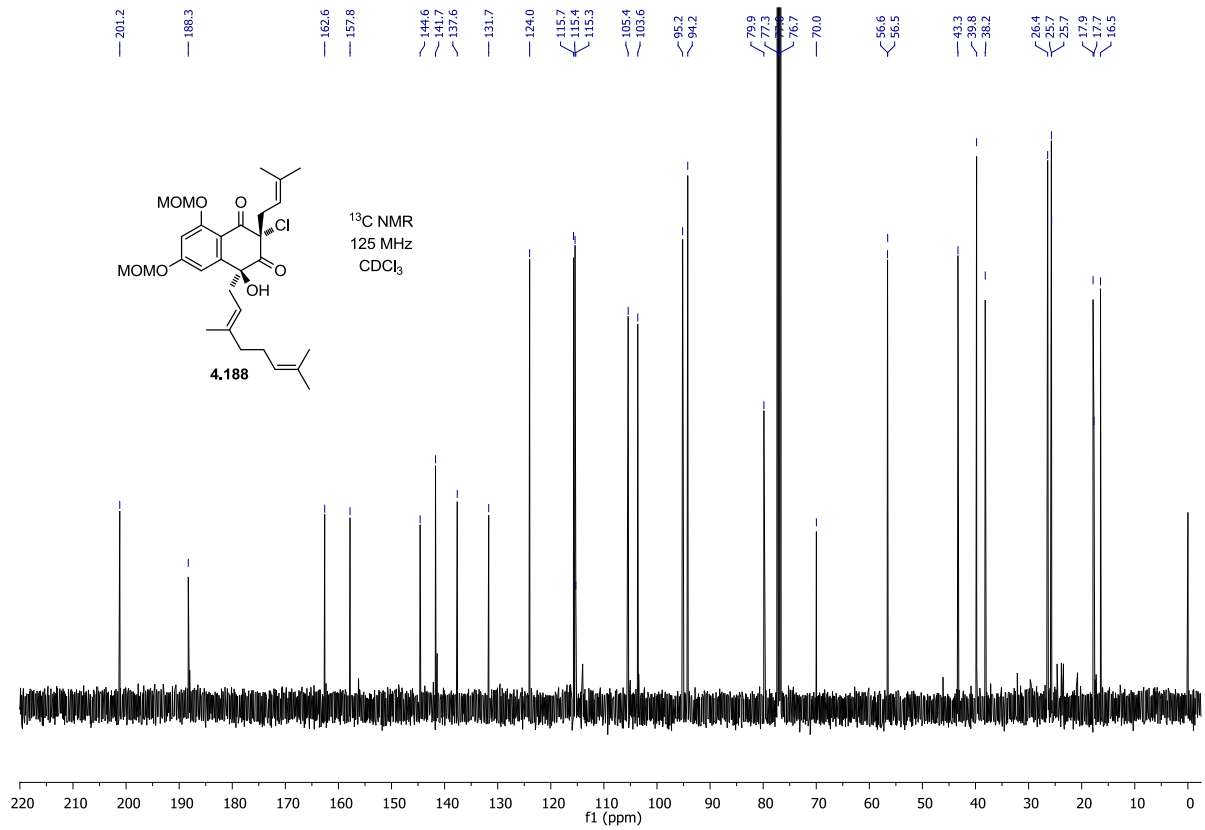

MOMO
O
Cl
Cl
MOMO
O
OAc
4.186
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

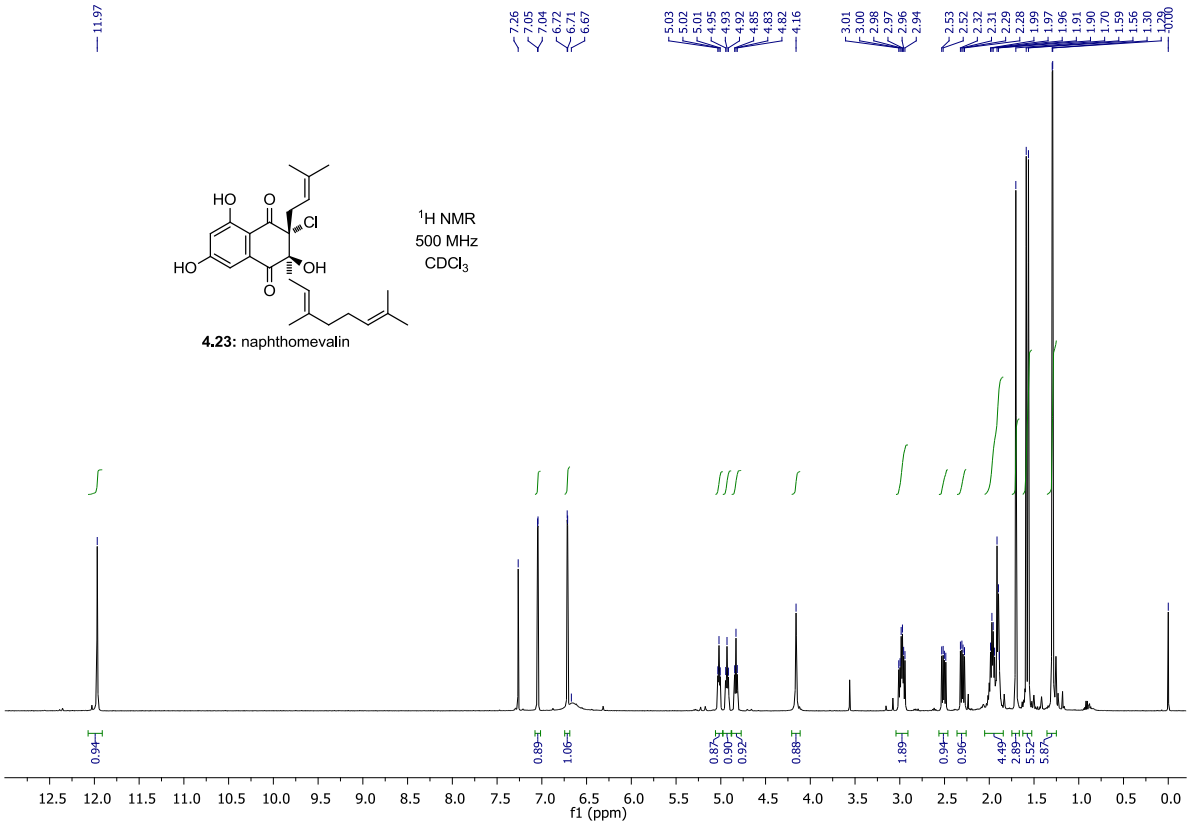

MOMO
O
Cl
Cl
MOMO
O
OAc
4.186
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

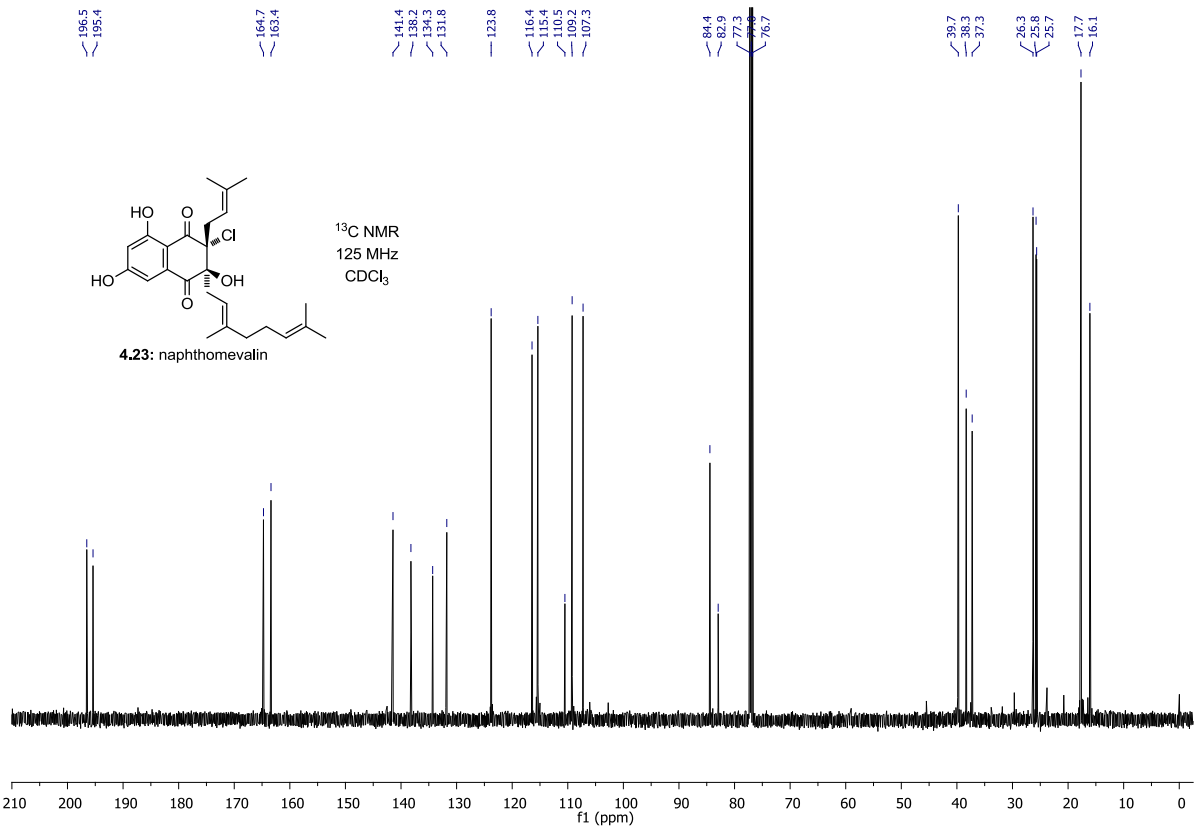

MOMO
OH
Cl
MOMO
O
OAc
4.187
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

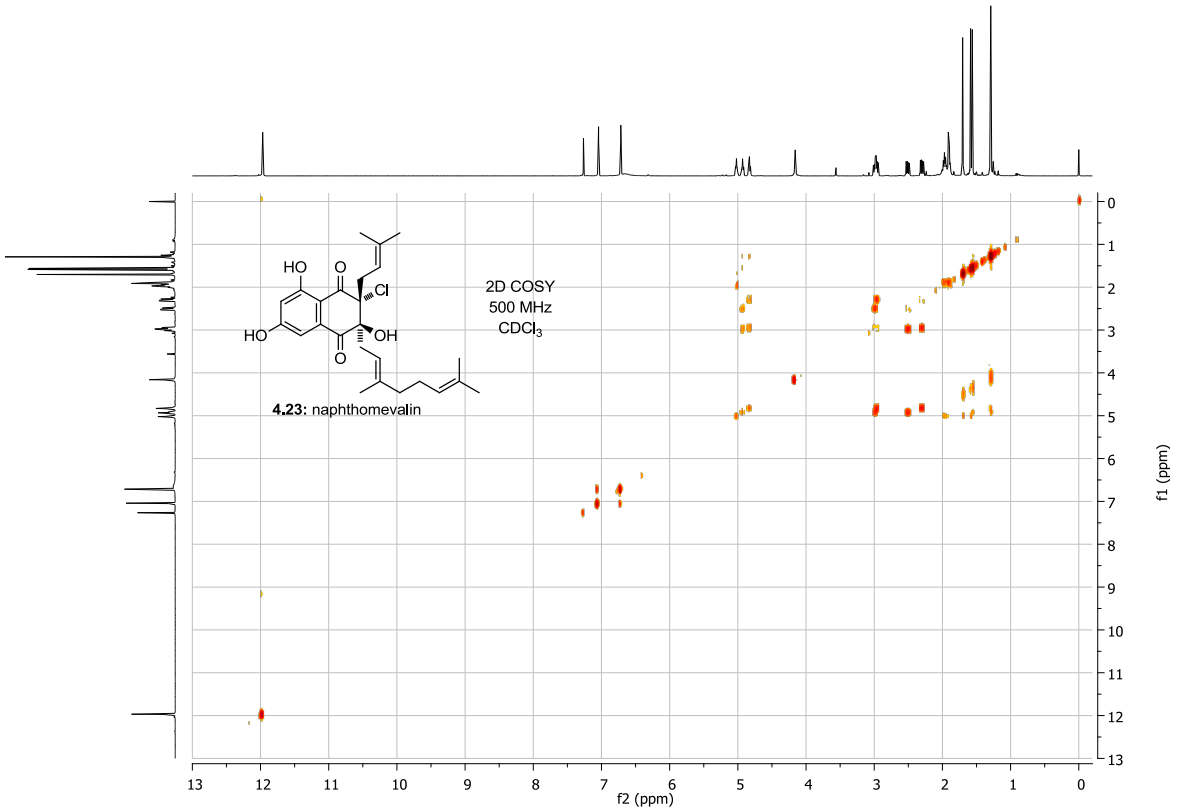

MOMO
OH
Cl
MOMO
O
OAc
4.187
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

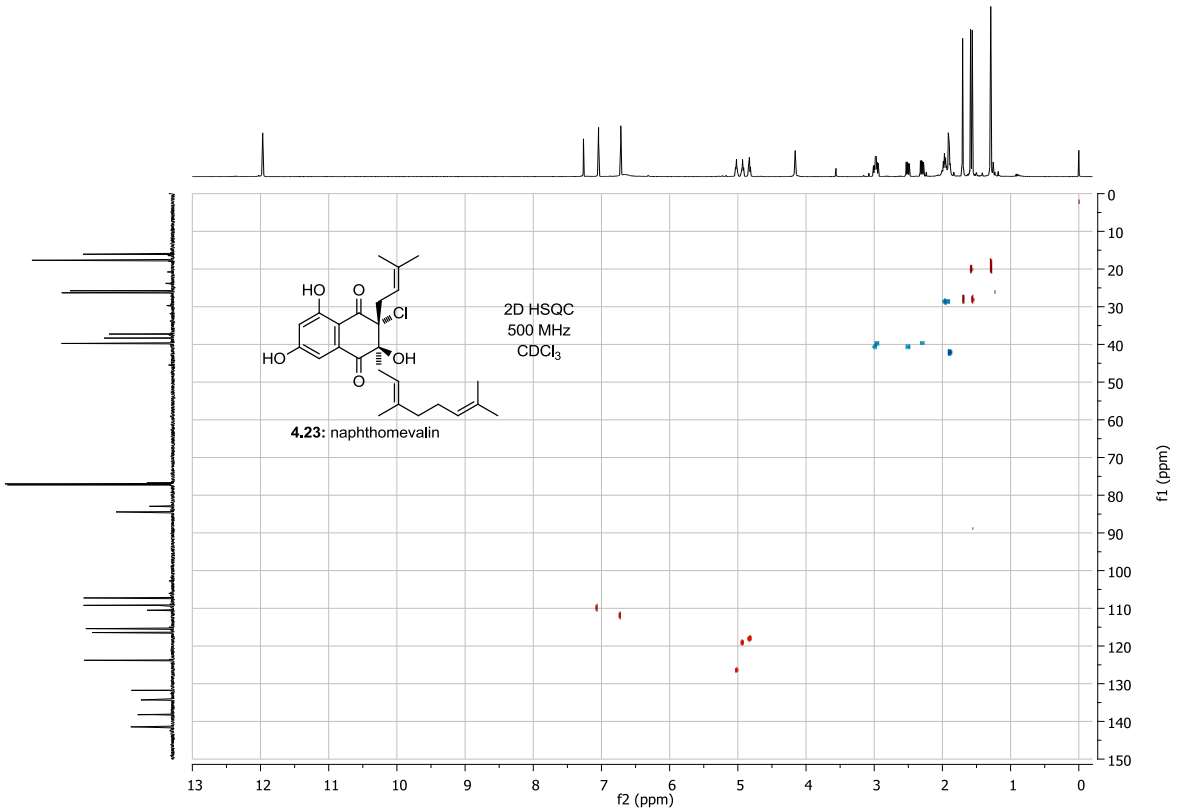

MOMO
O
Cl
MOMO
O
OH
4.188
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

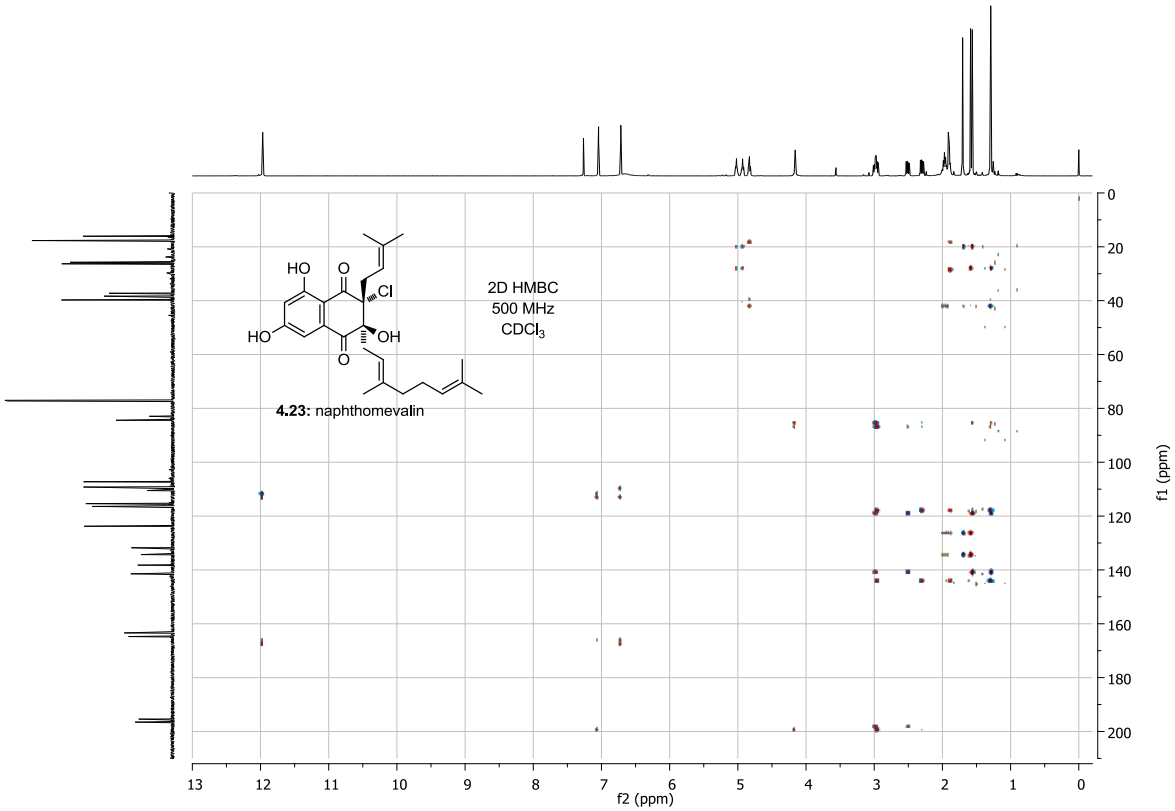

MOMO
O
Cl
MOMO
O
OH
4.188
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

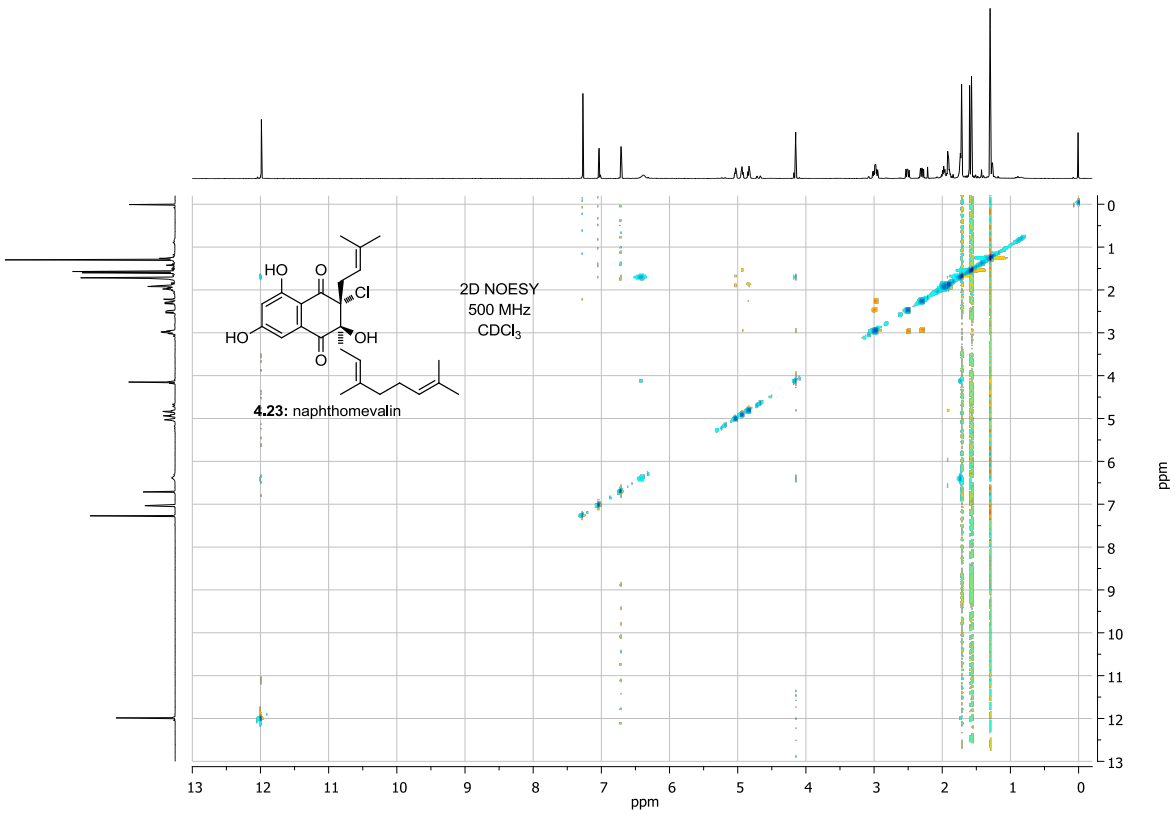

HO
O
Cl
HO
OH
O
4.23: naphthomevalin
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

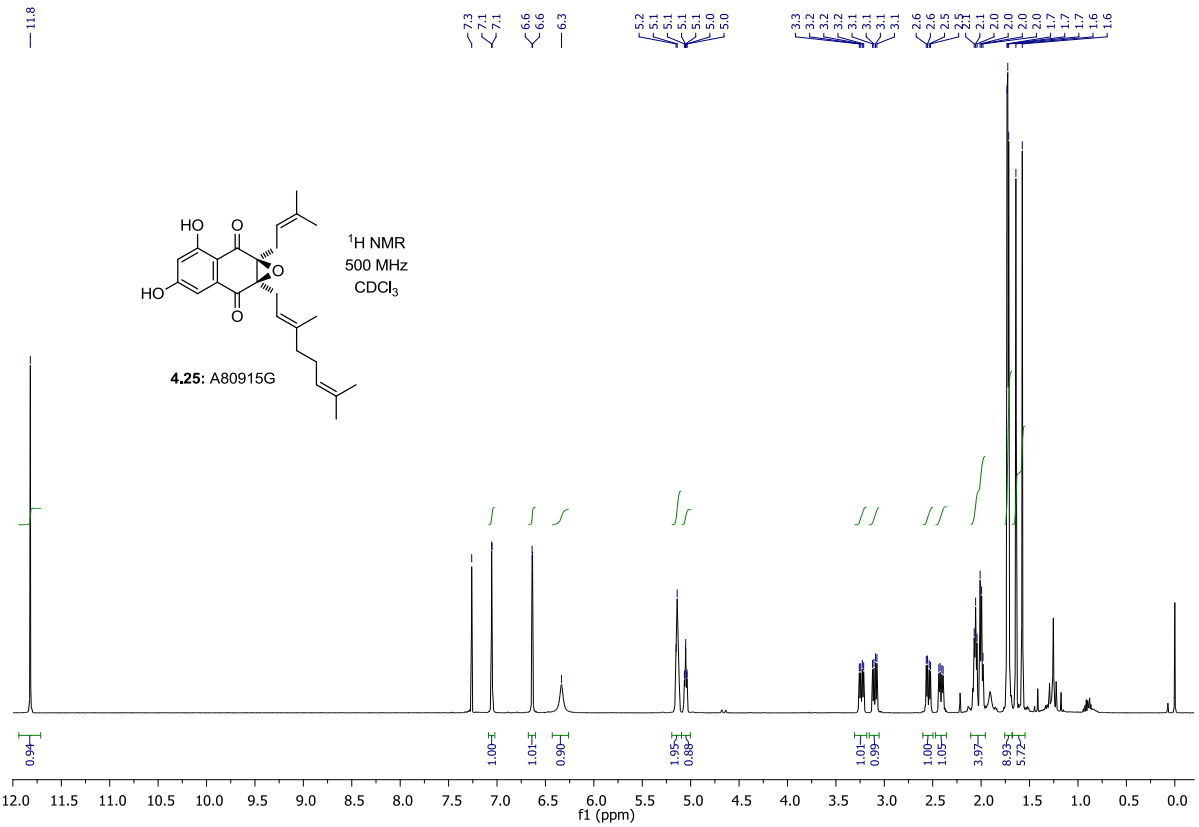

HO
O
Cl
HO
OH
O
4.23: naphthomevalin
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

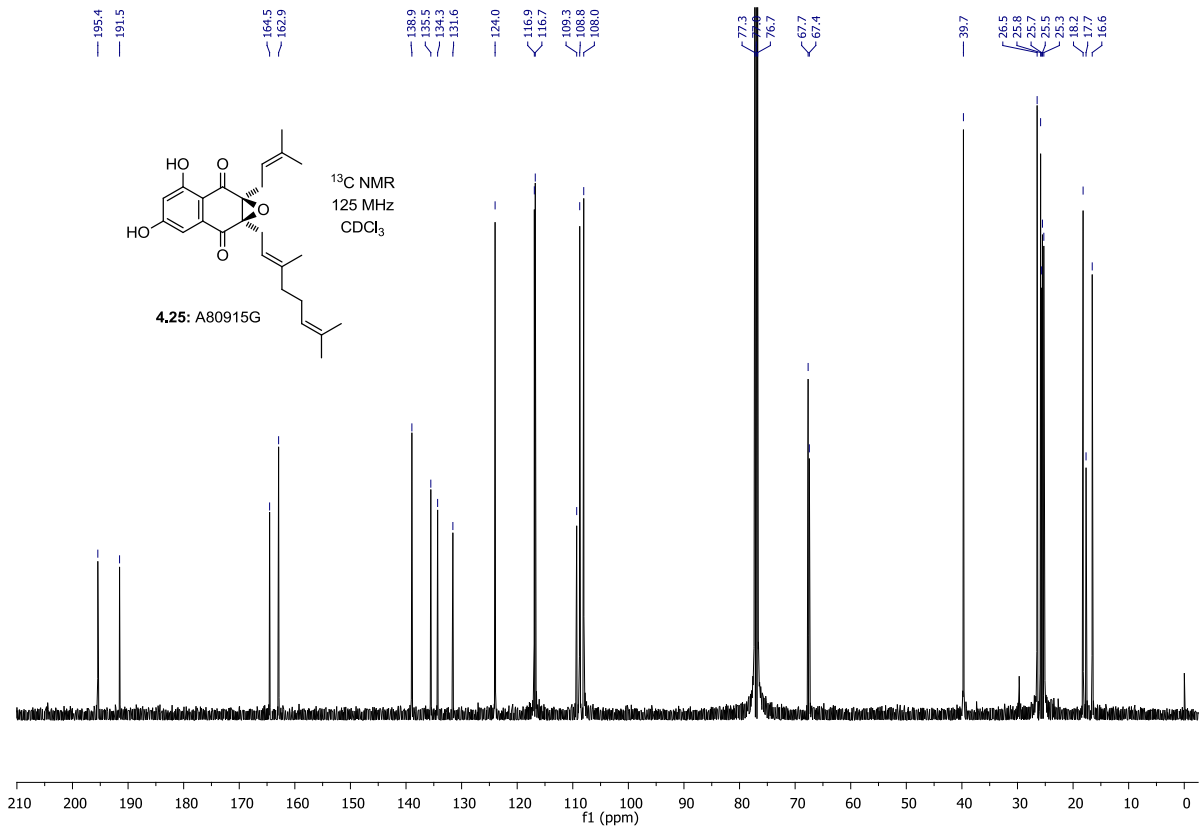

HO
O
Cl
HO
OH
O
4.23: naphthomevalin
2D COSY
500 MHz
CDCl3
f2 (ppm)
f1 (ppm)

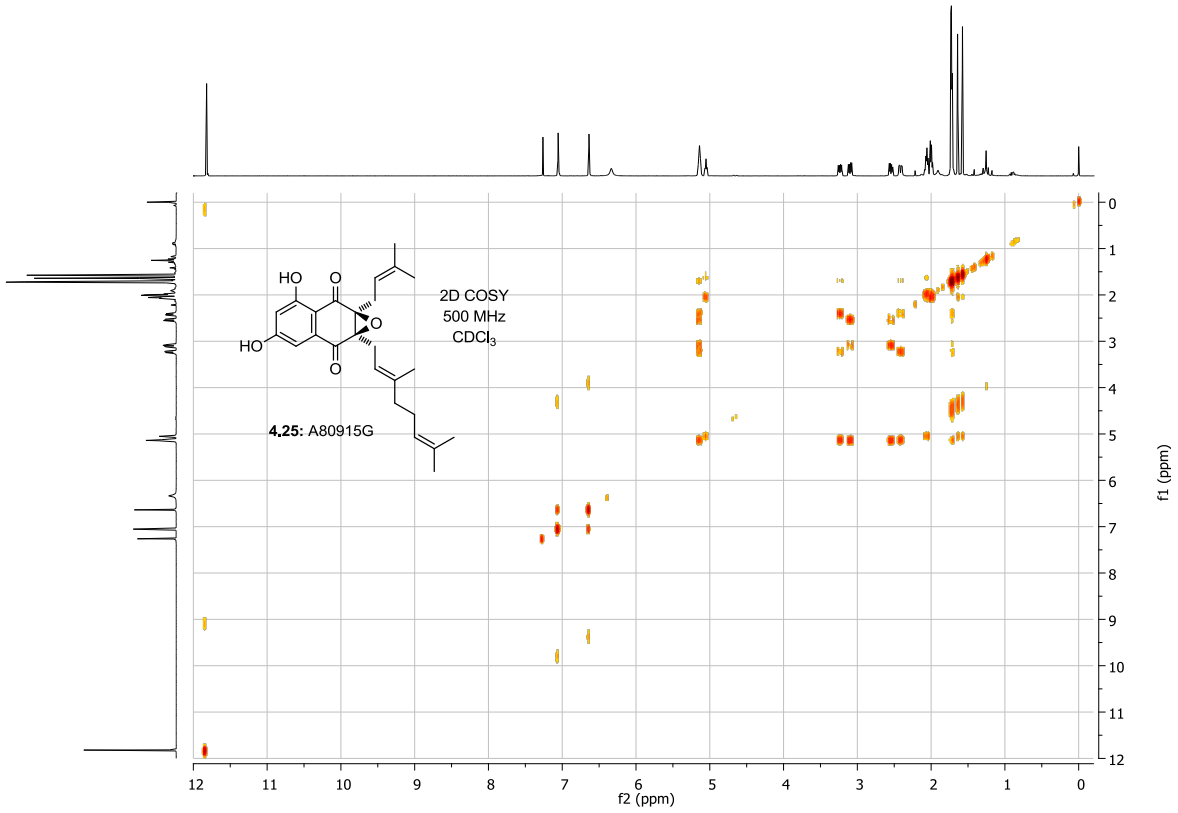

HO
O
Cl
HO
OH
O
4.23: naphthomevalin
2D HSQC
500 MHz
CDCl3
f2 (ppm)
f1 (ppm)

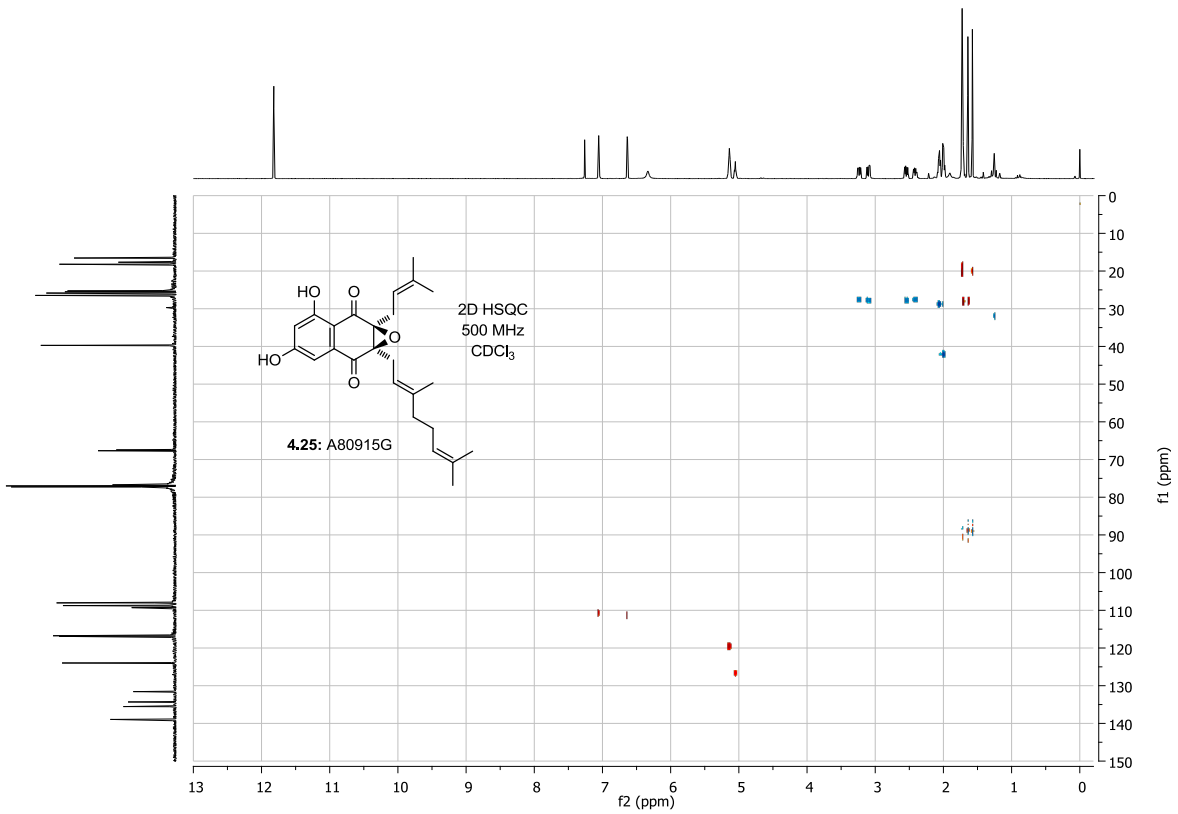

HO
O
Cl
HO
OH
O
4.23: naphthomevalin
2D HMBC
500 MHz
CDCl3
f2 (ppm)
f1 (ppm)

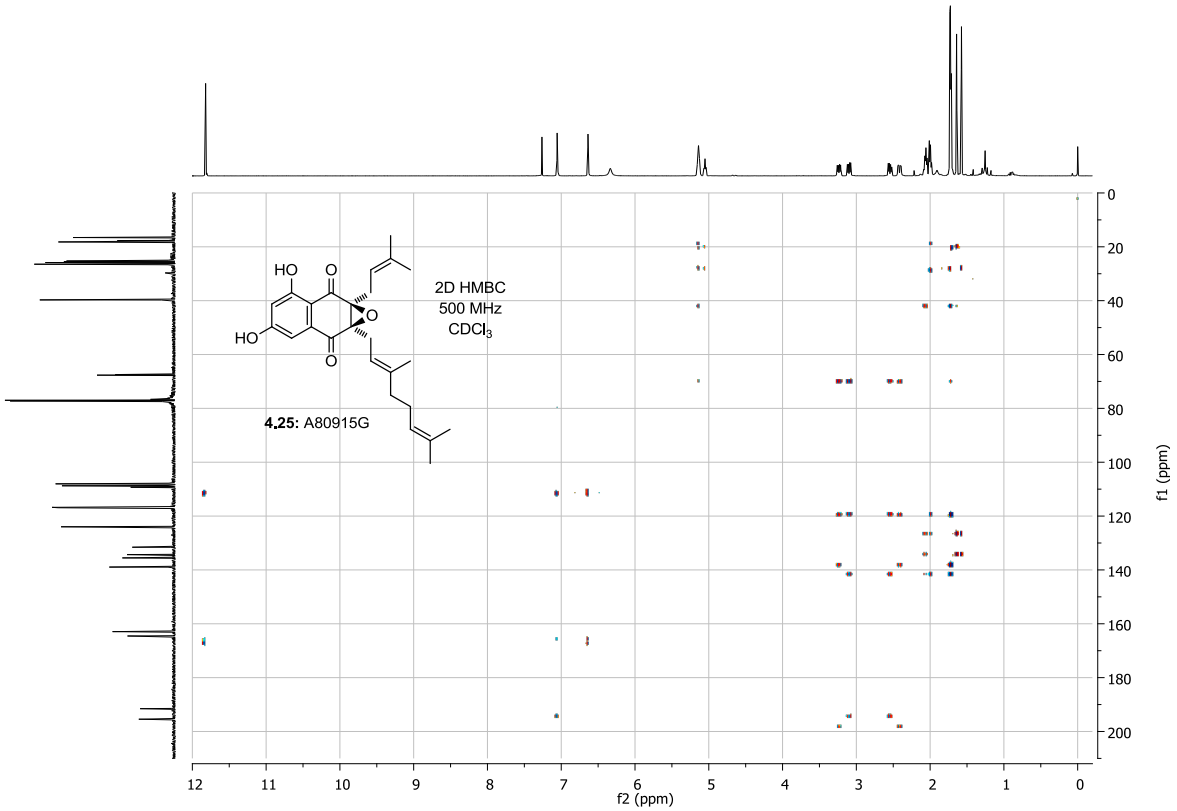

HO
O
Cl
HO
OH
O
4.23: naphthomevalin
2D NOESY
500 MHz
CDCl3
ppm
ppm

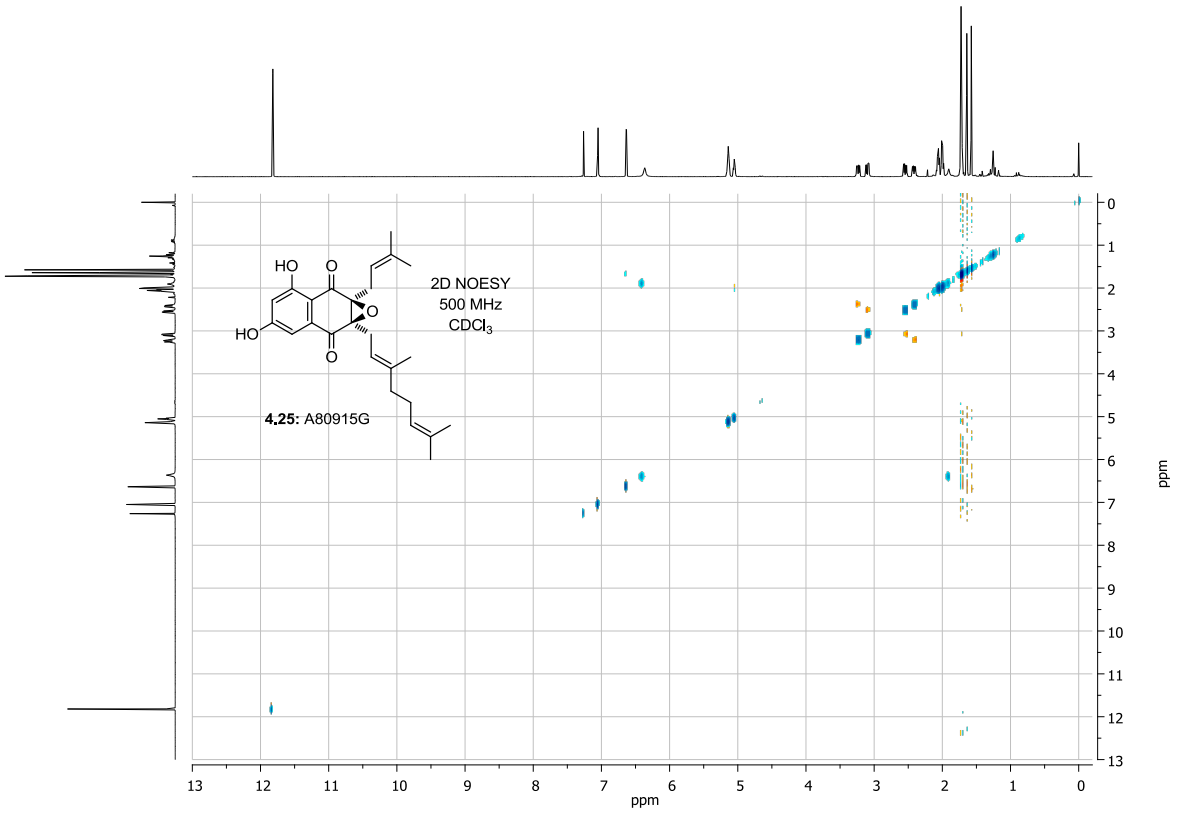

HO
O
HO
O
O
^{1}H NMR
500 MHz
$CDCl_3$
4.25: A80915G
f1 (ppm)

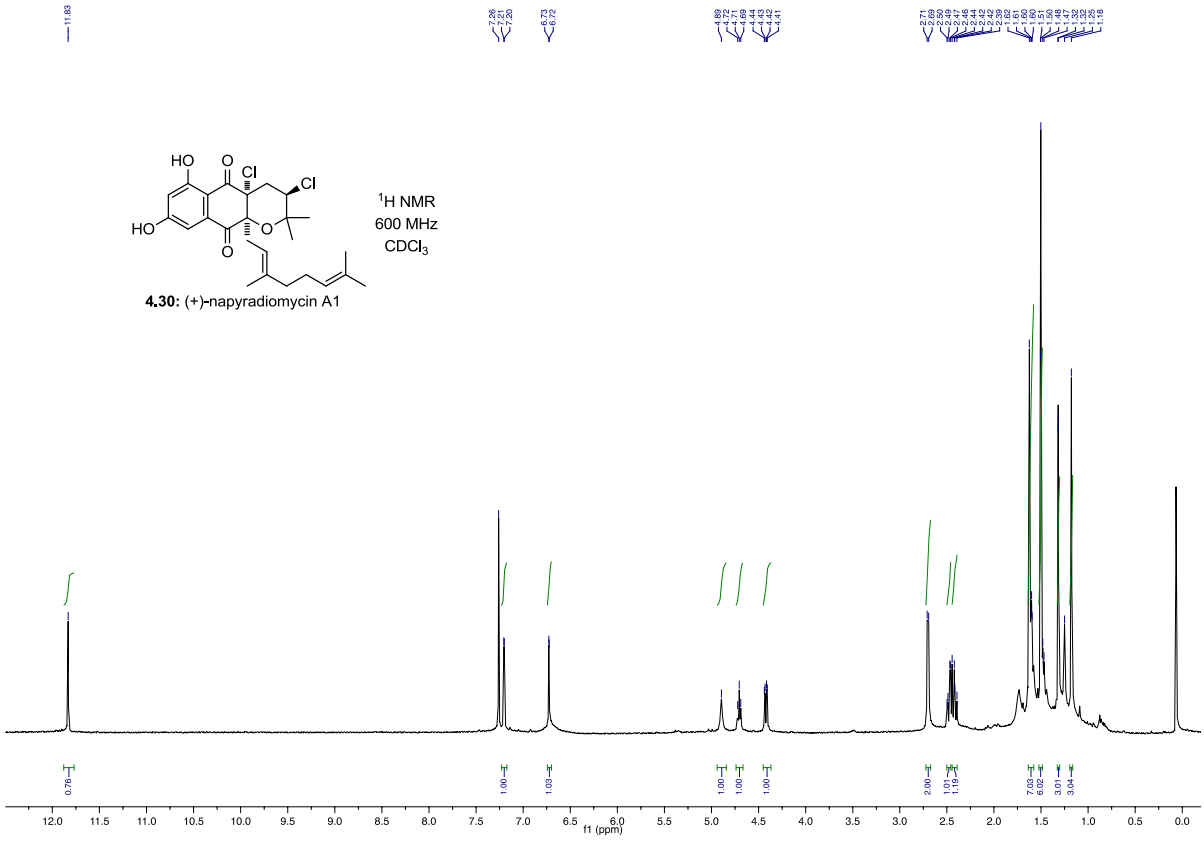

HO
O
HO
O
O
^{13}C NMR
125 MHz
$CDCl_3$
4.25: A80915G
f1 (ppm)

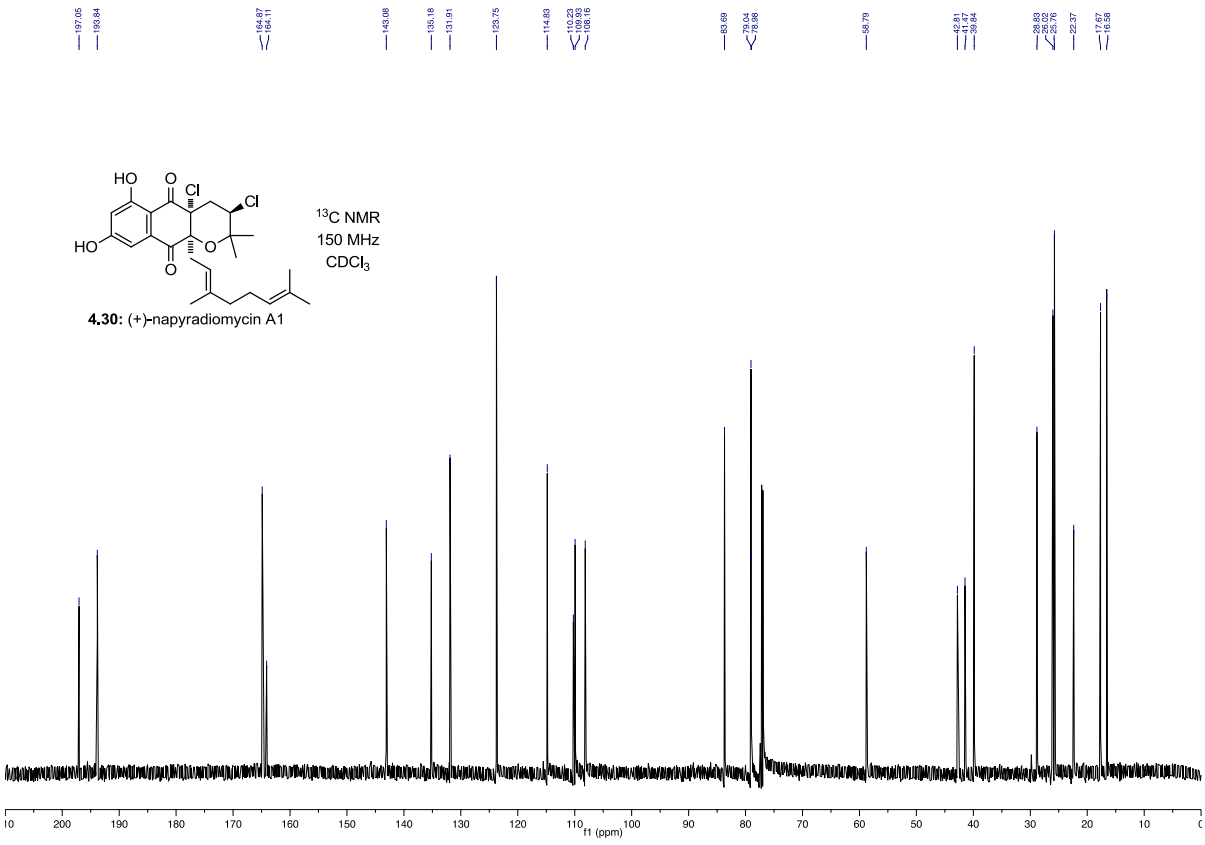

HO
O
HO
O
O
2D COSY
500 MHz
CDCl3
4.25: A80915G
f2 (ppm)
f1 (ppm)

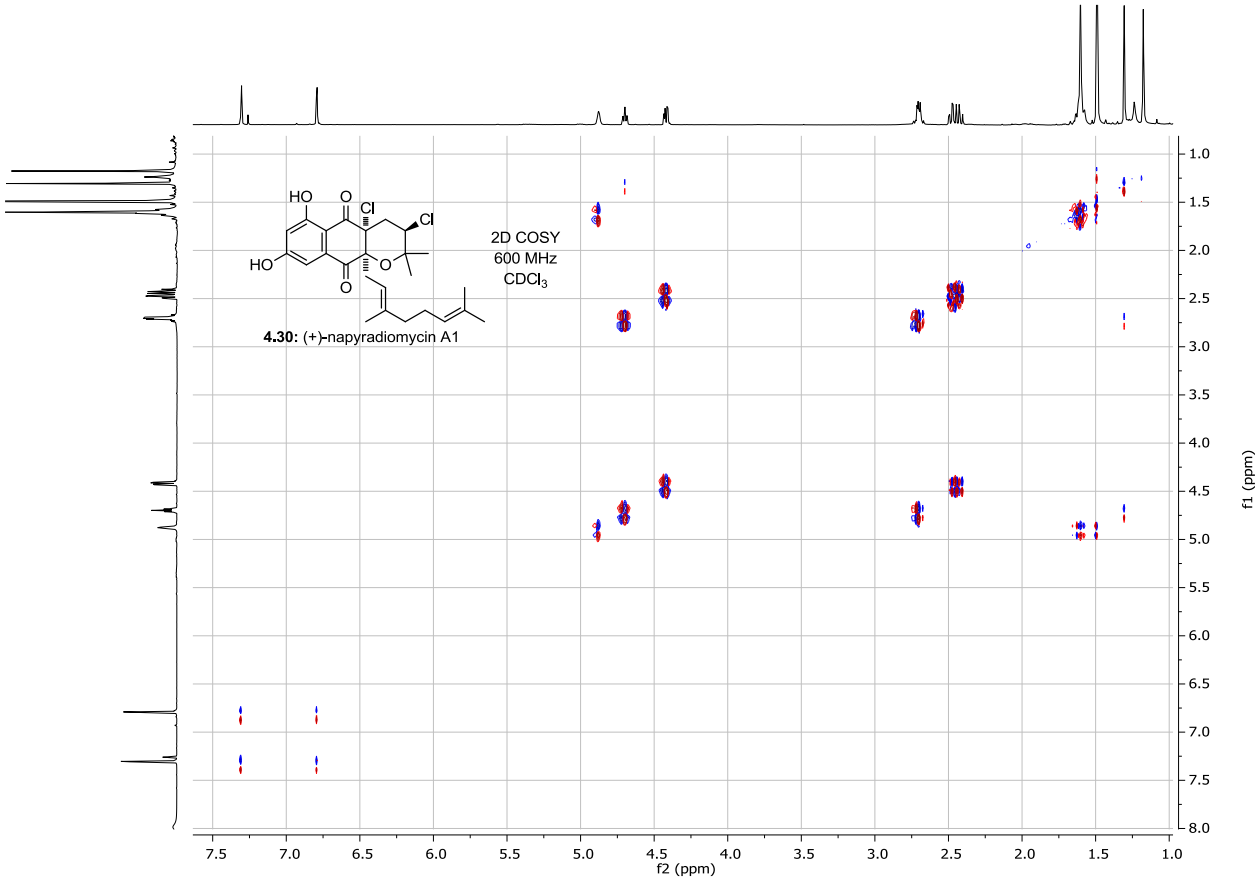

HO
O
HO
O
O
2D HSQC
500 MHz
CDCl3
4.25: A80915G
f2 (ppm)
f1 (ppm)

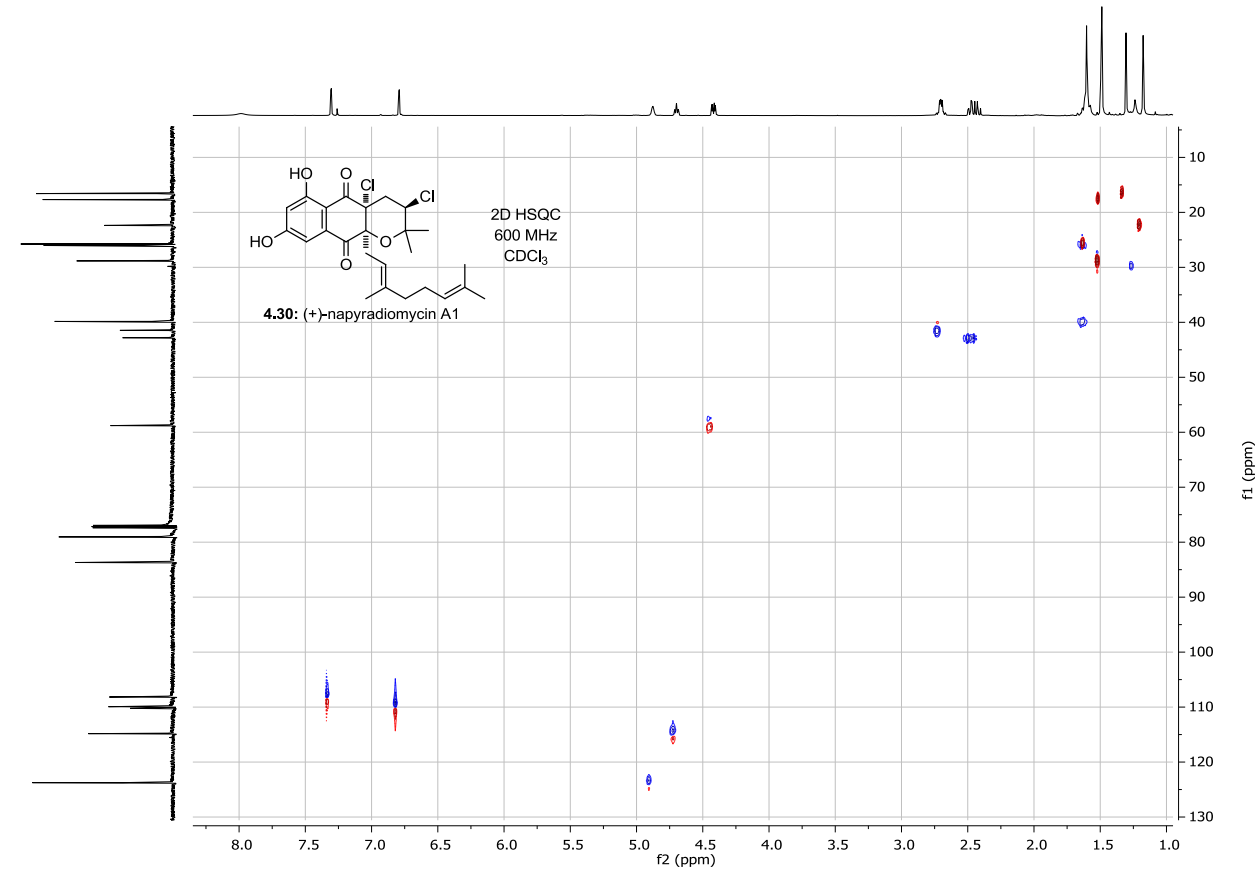

HO
O
HO
O
O
2D HMBC
500 MHz
CDCl3
4,25: A80915G
f2 (ppm)
f1 (ppm)

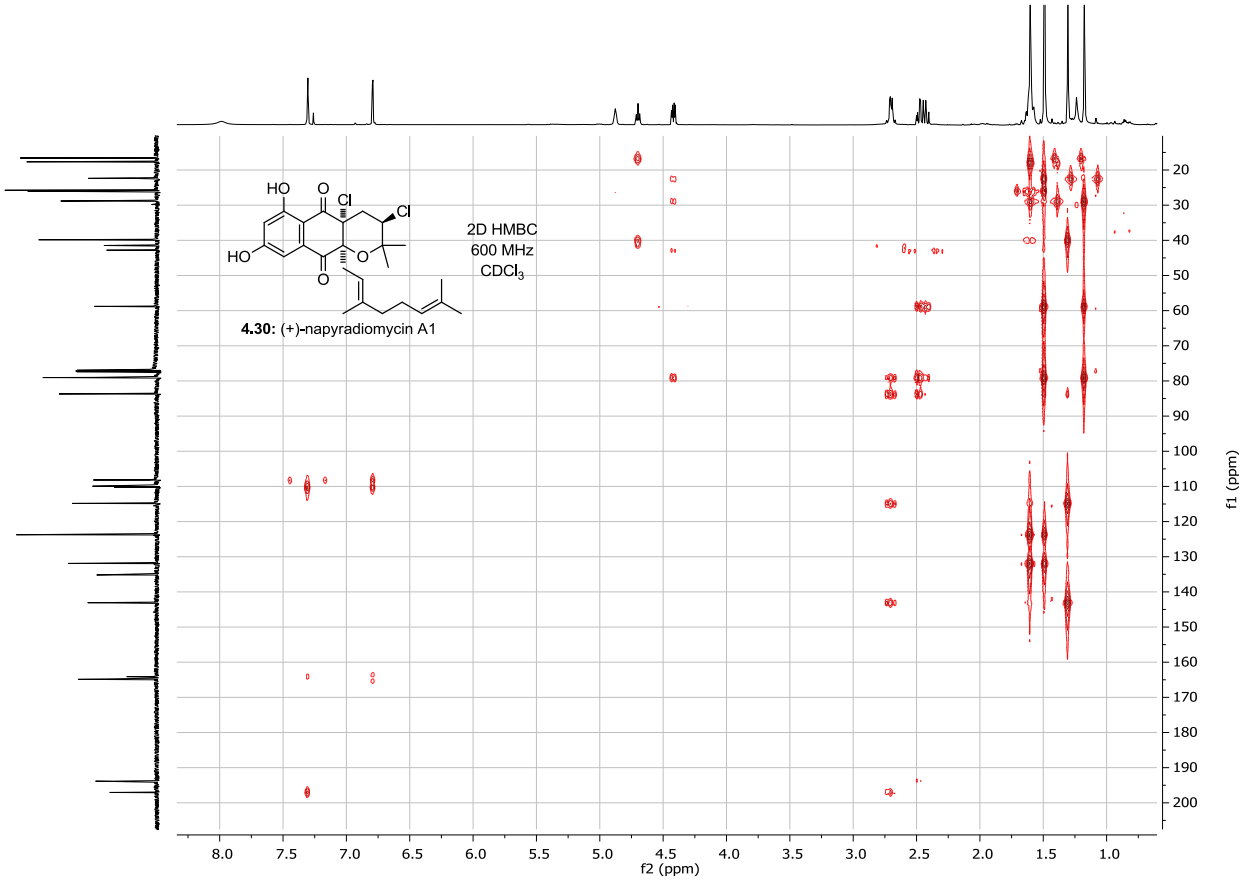

HO
O
HO
O
O
2D NOESY
500 MHz
CDCl3
4,25: A80915G
ppm
ppm


HO
O
Cl
Cl
HO
O
O
4.30: (+)-napyradiomycin A1
1H NMR
600 MHz
CDCl3
f1 (ppm)


HO
O
Cl
Cl
HO
O
O
4.30: (+)-napyradiomycin A1
13C NMR
150 MHz
CDCl3
f1 (ppm)


HO
O
Cl
Cl
HO
O
O
2D COSY
600 MHz
CDCl3
4.30: (+)-napyradiomycin A1
f2 (ppm)
f1 (ppm)


HO
O
Cl
Cl
HO
O
O
2D HSQC
600 MHz
CDCl3
4.30: (+)-napyradiomycin A1
f2 (ppm)
f1 (ppm)


HO
O
Cl
Cl
HO
O
O
2D HMBC
600 MHz
CDCl3
4.30: (+)-napyradiomycin A1
f2 (ppm)
f1 (ppm)