

Investigations into the Divergent, Biogenically Inspired Synthesis of Structurally Related Natural Products

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by

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Abstract

Natural products are pivotal in the development of new pharmaceutical agents as they may possess novel mechanisms of actions, inherent to their structural framework. Such intriguing metabolites are of interest to various fields of research, such as pharmacology, biochemistry and total synthetic chemistry. Perhaps the most compelling synthetic method is found with the biomimetic approach, which in addition to affording the natural product of interest in an efficient manner, such strategies may also offer insight into a given metabolite's biosynthetic origins. This thesis will detail our investigations into the biogenic origins of two structural related families of natural products via a biomimetic total synthetic approach.

The total synthesis of the structurally related marine natural products from *Aka coralliphaga*, has been achieved via a biogenically inspired divergent approach. This divergent strategy detailed siphonodictyal B as the biogenic precursor to liphagal, corallidictyals A – D and siphonodictyals B1 – B3. We report the successful total synthesis and stereochemical reassignment of siphonodictyal B, in accordance with our proposal. Additionally, the total synthesis of liphagal and the corallidictyals A – D was achieved directly from our confirmed reassigned configuration of siphonodictyal B. We propose these transformations of siphonodictyal B to liphagal and the corallidictyals, detailed within this work, are representative of biosynthetic reactions that occur within the host organism, *Aka coralliphaga*.

Progress towards the biogenically inspired, total synthesis of virgatolide B has been made. Our method sought to afford virgatolide B via a hetero-Diels-Alder reaction between a *Z*-exocyclic enol ether dienophile and an *o*-QM, generated *in situ* from an analogue of pestaphthalide A. Synthesis of the key biogenic precursors, that would in our opinion be representative of those that may occur in nature, was achieved. However, upon investigating various thermal and basic conditions, synthesis of virgatolide B could not be achieved. Despite our failed attempts at synthesising virgatolide B, we still assert that the virgatolides A – C are biosynthesised in nature via a divergent, [4 + 2] cycloaddition of an appropriate *Z*-exocyclic enol ether with an *o*-QM derived from either of the co-isolated pestaphthalides A or B.

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.

I give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

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06/06/2019

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Abbreviations

Abbreviation	Full Name
°C	degrees Celsius
¹³ C NMR	carbon nuclear magnetic resonance
¹ H NMR	proton nuclear magnetic resonance
Ac	Acetyl
AcOH	acetic acid
AIBN	azobisisobutyronitrile
aq.	aqueous
atm	Atmosphere
Bn	Benzyl
br	Broad
Bu	butyl
Bz	benzoyl
c	concentration for specific rotation measurements
CAN	ceric ammonium nitrate
cm ⁻¹	Wavenumbers
conc	Concentrated
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
DBU	1,8-diazobicycloundec-7-ene
DCC	<i>N,N</i> -dicyclohexylcarbodiimide
DEAD	diethylazodicarboxylate
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
<i>N,N</i> -DMA	dimethylacetamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
EI	electron impact
<i>ent</i>	Enantiomer
<i>epi</i>	Epimer

equiv	Equivalents
Et	Ethyl
Et ₃ N	Triethylamine
Et ₂ O	diethyl ether
ESI	electrospray ionisation
EtOAc	ethyl acetate
g	grams
h	hours
HMPA	hexamethylphosphoramide
HMBC	heteronuclear multiple bond correlation spectroscopy
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation spectroscopy
Hz	Hertz
hν	light
<i>i</i> -Pr	isopropyl
<i>i</i> -Pr ₂ NH	diisopropylamine
IR	infrared
<i>J</i>	coupling constant
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
LiTMP	lithium tetramethylpiperidide
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
<i>m</i> -QM	<i>m</i> -quinone methide
Me	methyl
MHz	megahertz
Min	minutes
Mp	melting point
<i>n</i> -Bu	<i>n</i> -butyl
<i>n</i> -BuLi	<i>n</i> -butyllithium
nm	nanometre
NMO	<i>N</i> -methylmorpholine

NMR	nuclear magnetic resonance
NOESY	nuclear overhauser effect spectroscopy
Nu	nucleophile
<i>o</i> -QM	<i>ortho</i> -quinone methide
<i>p</i> -QM	<i>para</i> -quinone methide
<i>p</i> -TsOH	<i>para</i> -toluenesulfonic acid
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate (Cornforth reagent)
Ph	phenyl
PhMe	toluene
PIDA	phenyliodine diacetate ((diacetoxy)iodobenzene)
PIFA	phenyliodine di(trifluoroacetate) (di(trifluoroacetoxy))iodobenzene)
ppm	parts per million
PPTS	pyridinium <i>p</i> -toluenesulfonate
R _f	retention factor
rt	room temperature
S _N 2	substitution nucleophilic bimolecular
TBAI	tetra- <i>N</i> -butylammonium iodide
TBS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
TES	triethylsilyl
TFA	trifluoroacetic acid
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyranyl (THP ether)
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	<i>para</i> -toluenesulfonyl (tosyl)

CHAPTER 1

Introduction

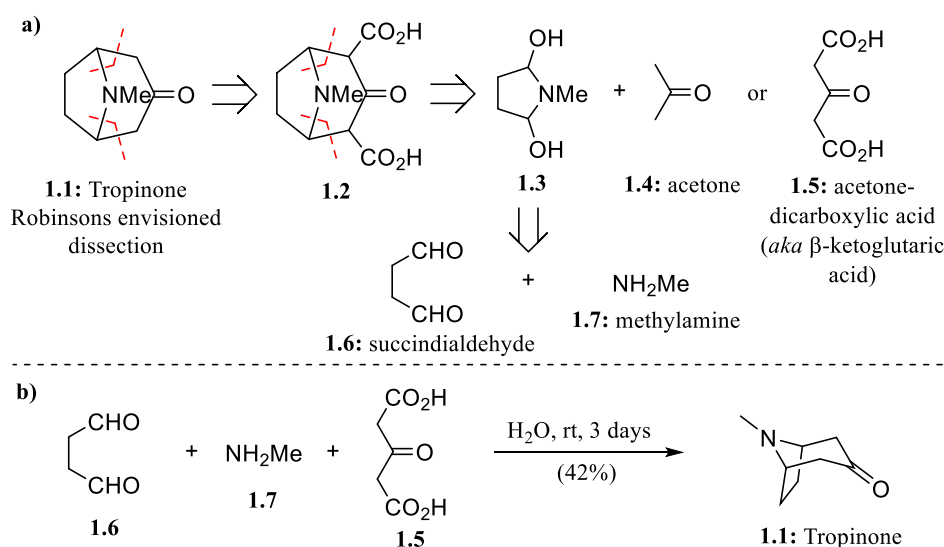
1.1 Natural Products and Their Influence on Modern Medicine

Pharmacologically active natural products, strictly defined as secondary metabolites that are not essential to the functioning of primary metabolic processes (structural proteins, energy production, etc.), have been employed in the treatment of various ailments such as pain, fever and infections since recorded history.^[1-3] The discovery of new natural products in the advancement of medicinal chemistry is essential, as demonstrated in the ten year period of 2000 to 2010, where 50% of small molecule drugs brought to the market were either derived, inspired or were themselves natural products.^[4] However, given a large proportion of natural products are used as drugs themselves, artificial access to a given metabolite is necessary to mitigate any detrimental impact to the host organism due to over-harvesting, as demonstrated by the extinction of the ancient therapeutic herb, *Silphium*. The disappearance of *Silphium* from the historical record around the second century BCE, serves to highlight the danger of unsustainable harvesting practices of naturally sourced medicines. *Silphium* was thought to be an ancient species of giant fennel, native to a small region in north Africa. The herb was extensively sought after by the ancient Greeks and Romans, due to its reported utility in the treatment of fever, pain and as a contraceptive.^[5-7] *Silphium* quickly became absent from the proceeding historical record due to unsustainable harvesting practices, perpetuated by an ever increasing demand on the black market, in conjunction with its impossible cultivation.^[6] The apparent extinction of *Silphium* demonstrates the requirement for the investigation of not only the specific bioactive constituents of a given natural medicine, but also to gain sustainable access to the desired bioactive components, either by synthetic means or cultivation.^[6,7]

1.2 The Biomimetic Approach

Today, there are an abundance of methods for gaining artificial access to natural products within and outside the field of organic chemistry. To this day the most common method of artificially accessing natural products is via a *total synthetic* approach, that seeks to synthesise the desired product by any method available to the chemist.^[8,9] Traditional synthetic approaches generally employ the use of protecting groups, and as a consequence require multiple functional group manipulations, typically resulting in a large number of linear synthetic transformational events. However, the development of chiral catalysts in the past few decades has led to the development of a new expanded *tool-box* of reactions. Such

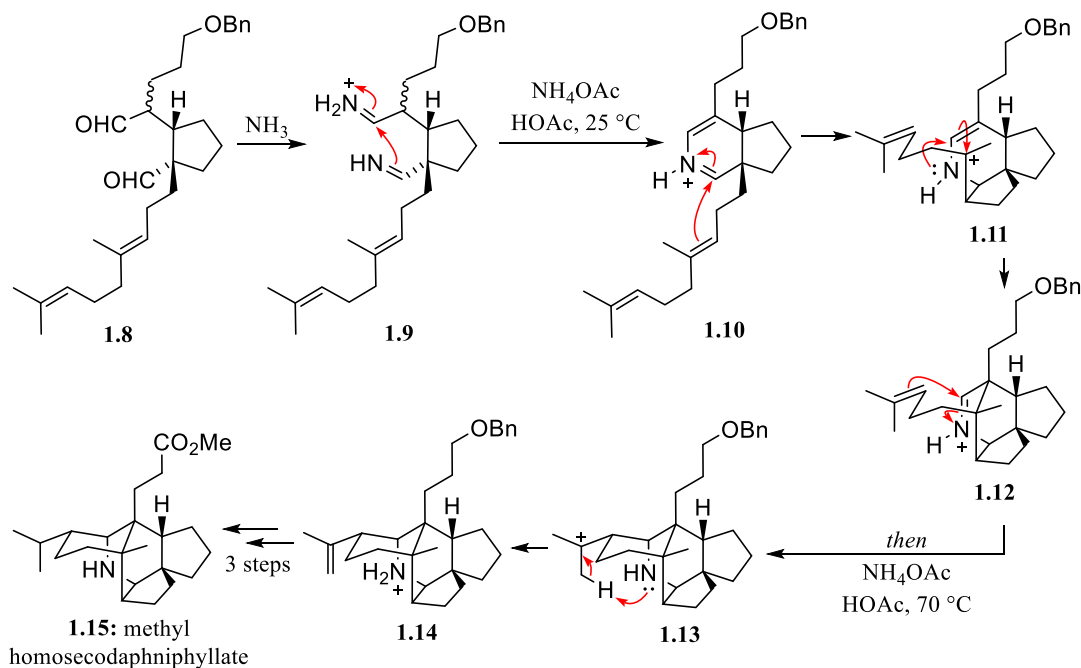
advancements have led to the regio- and stereoselectivity optimisation of standard synthetic protocols.^[10–13] However, as the vast majority of metabolic processes in nature are mediated by enzymes, many of these biosynthetic reactions do not have a direct equivalent in the laboratory.^[14,15] Enzymes can induce non-spontaneous transformations of seemingly unreactive substrates by lowering the energy of activation associated with said process. However, if a given reaction of a particular species is spontaneous, then enzymes may facilitate and control said spontaneous transformations, directing them to a particular end product to prevent formation of various inutile by-products.^[14–16] Based on this premise, the artificial synthesis of certain natural products may be accessible to chemists through less traditional methods, by imitating ‘spontaneous’ reaction sequences and events that may be representative of that which occurs in nature.^[16] This *biomimetic* method of approaching the synthesis of natural products, was first formalised by the organic chemist, Sir Robert Robinson.^[17]



Scheme 1.1: Sir Robert Robinson’s non-traditional method of approaching the synthesis of natural products, 1917. **a)** original dissection and retro-synthetic analysis of tropinone (**1.1** – **1.7**). **b)** one-pot, total synthesis of tropinone (**1.1**).^[17]

In his original 1917 paper, Robinson envisioned that tropinone (**1.1**) could be accessed, first by dissecting the alkaloid based upon its points of symmetry, which he concluded could be reduced to acetone (**1.4**), methylamine (**1.7**) and succindialdehyde (**1.6**) (scheme 1.1). Robinson successfully synthesised tropinone (**1.1**) via a one-pot condensation of acetone (**1.4**), methylamine (**1.7**) and succindialdehyde (**1.6**). However, due to poor yields, Robinson substituted acetone (**1.4**) for acetone dicarboxylate (**1.5**), which afforded tropinone (**1.1**) in a respectable yield of 42%. Based on his successful one-pot synthesis of tropinone (**1.1**),

Robinson asserted that this method of deconstruction would lead to any desired natural product in the most efficient manner possible.

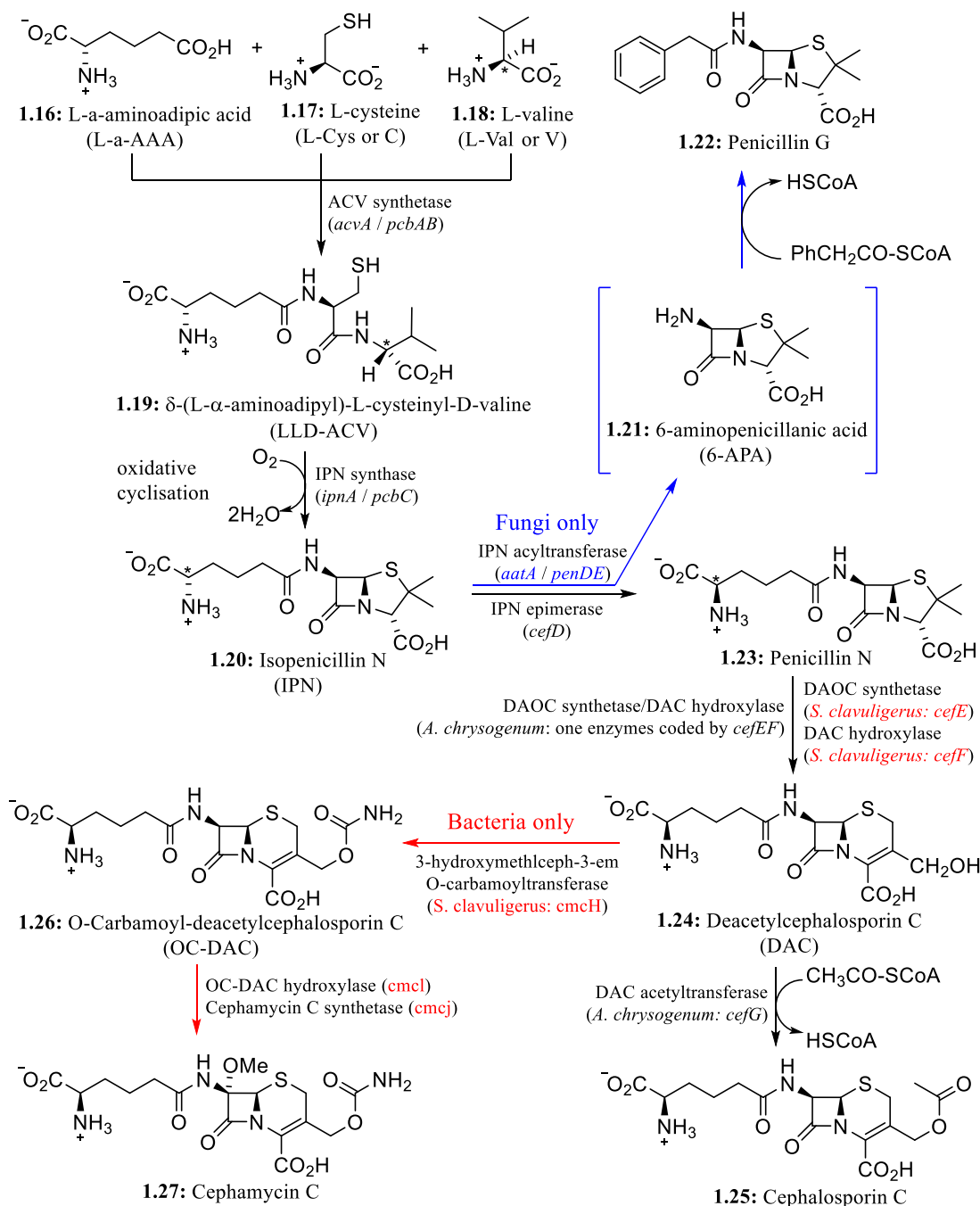


Scheme 1.2: Heathcock's biogenically inspired total synthesis of the complex *Daphniphyllum* alkaloid, methyl homosecodaphniphyllate (**1.15**), via a one-pot, three-step cascade sequence.^[14,18]

This alternative method of approaching the synthesis of both simple and complex natural products represents a lens through which to view and frame a retro-synthetic problem. The underlying premise is one where nature would be expected to synthesise any product via the *path of least resistance* and that such a pathway would be relatively favourable. If a spontaneously arising compound conferred a substantial benefit to the host organism, its production might then come under enzymatic control. Such an assumption would be expected to apply chiefly to secondary metabolites, as they are beneficial, but not crucial to the survival of the host organism. As summarised by Heathcock,^[14] “*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 nonenzymic reaction in the primitive organism.*” Under this premise, any secondary metabolite should be accessible to the chemist by attempting to imitate the speculated reaction sequences from biologically relevant precursors, without the need to employ specialised enzymes.

1.3 Natural Product or Artefact? – The Role of Selective Pressures on the Evolution of Biosynthetic Pathways

This brief review seeks to highlight the impact of selective pressures on various biosynthetic pathways in nature and serves to instil context for our work in relation to the current state of the biomimetic total synthetic field.

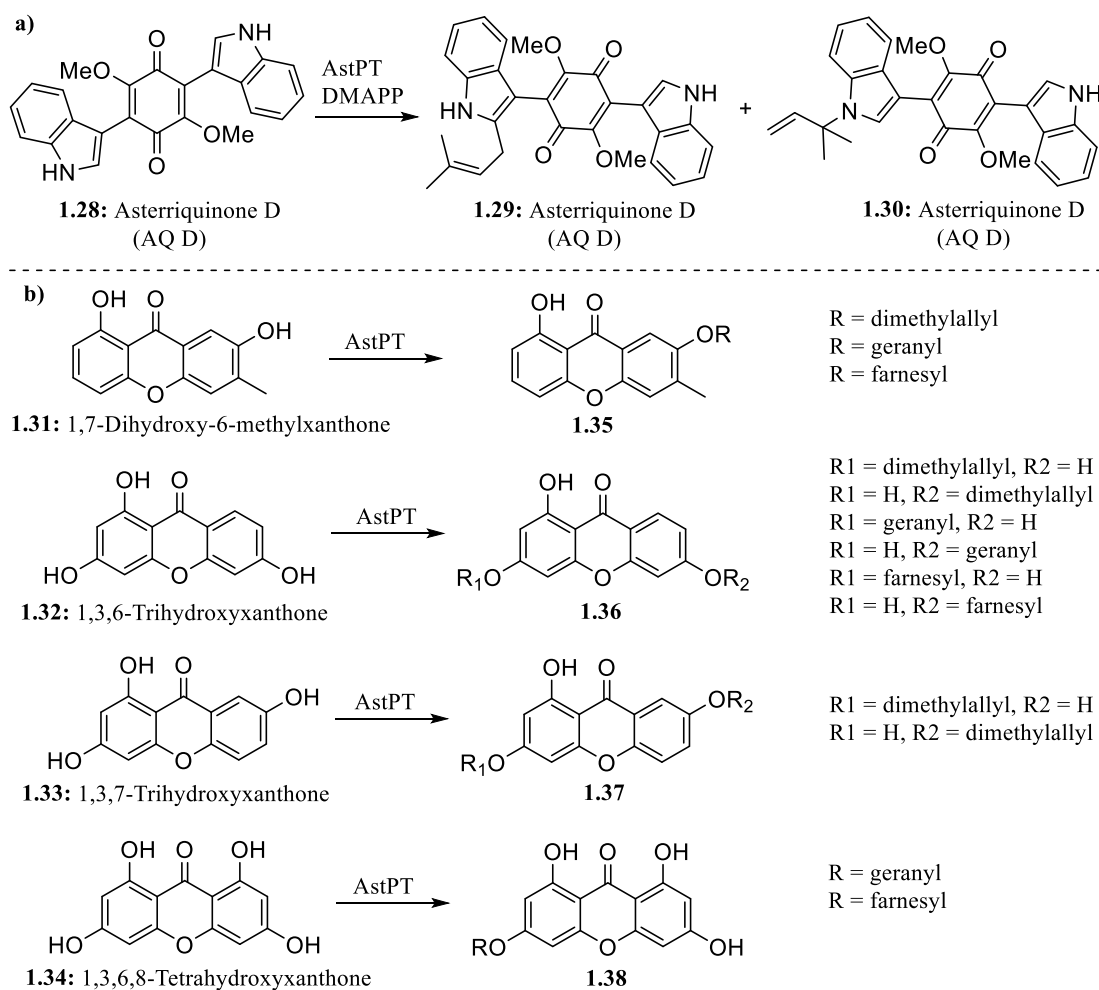


Scheme 1.3: Biosynthetic pathways for the related β -lactam antibiotics, penicillins (**1.22:** fungi only), cephalosporins (**1.25:** both fungi and bacteria) and cephamycins (**1.27:** bacteria only), diverging from IPN (**1.20**), highlighting the shared evolutionary ancestry between certain species of bacteria and fungi.^[19,20]

As previously discussed, natural products belong to the class of secondary metabolites that are not crucial to the primary metabolic processes of the host, and hence, are not all necessarily bioactive. The degree to which a secondary metabolite's biosynthesis is regulated may be inferred by the specificity of its *target function*, which would emerge as a consequence of an applied selective pressure. Therefore, we may gain insight into a given natural product's biosynthetic pathway, i.e. enzymatic or spontaneous, by assessing its bioactivity.

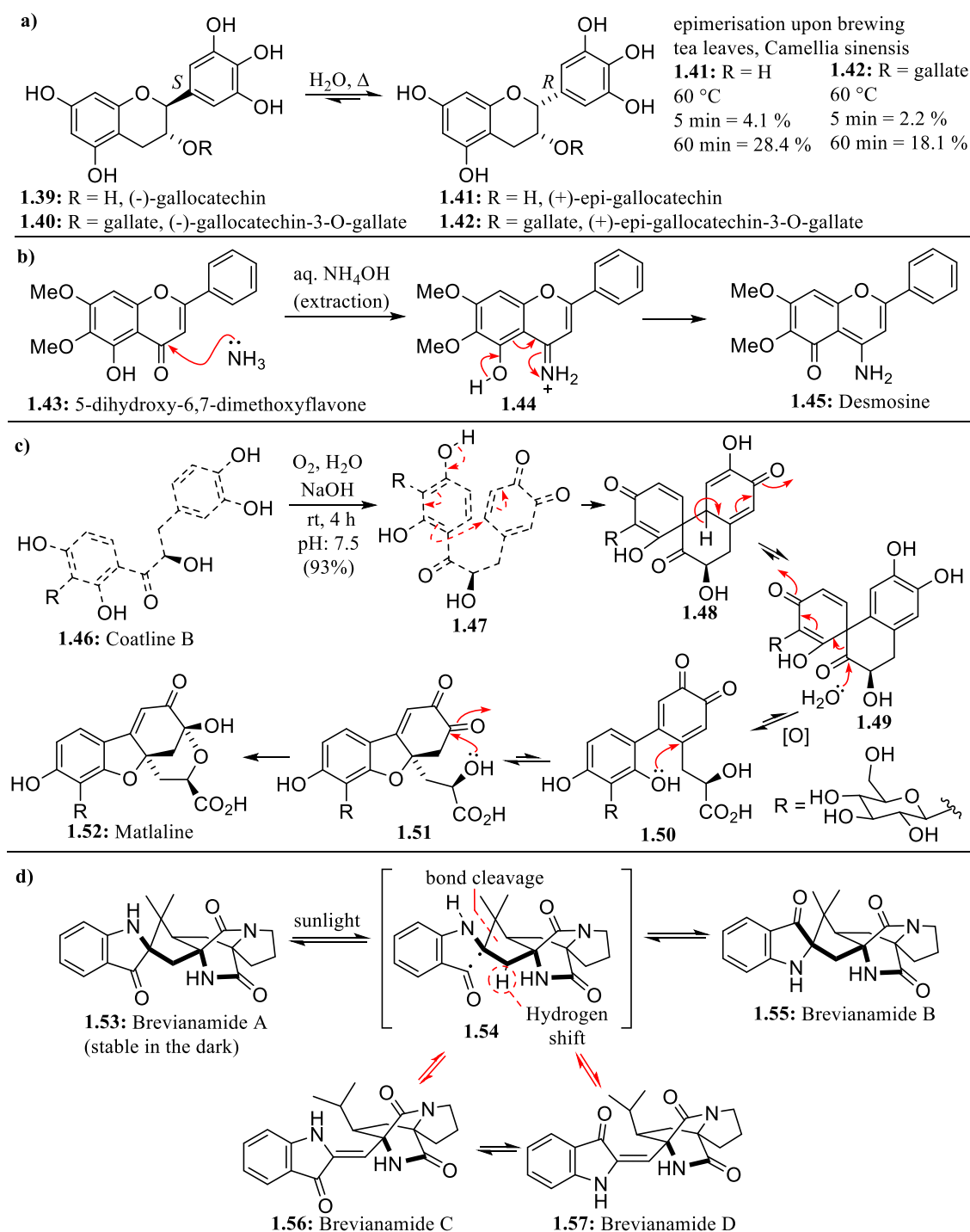
The biosynthesis of the penicillins (**1.22**: fungi only), cephalosporins (**1.25**: both fungi and bacteria) and cephamycins (**1.27**: bacteria only) are examples of antibiotic natural products that are tightly regulated at every biosynthetic level in nature, through a series of substrate specific enzymes (scheme 1.3).^[19–23] The first two biosynthetic steps for the β -lactams are conserved and diverge from their shared biosynthetic intermediate, isopenicillin N (**1.20**: IPN) (scheme 1.3). The biosynthesis of β -lactams demonstrates how a family of related natural products may emerge in multiple species that do not appear to share a recent evolutionary ancestor, and yet share a biosynthetic intermediate (IPN: **1.20**). Penicillins, cephalosporins, and other naturally occurring β -lactam antibiotics, are examples of natural products that have evolved to combat foreign, encroaching bacterial species via a target specific mode of action, and thereby directly serve an *evolutionary purpose*.^[21,24–26] Thus, such a case demonstrates the potential capacity of a strong selective pressure in conserving an emergent, enzymatically regulated biosynthetic pathway.

In contrast to the β -lactams and other highly regulated biosynthetic routes, natural products may be biosynthesised via more promiscuous enzymes that are tolerant of various substrates, and thus, would afford a wide array of secondary metabolites.^[27–29] Cytochrome P450's and prenylation transferase's, such as AstPT (scheme 1.4), are examples of promiscuous enzymes that facilitate simple transformations of a wide range of substrates. An obvious advantage for nature to evolve promiscuous enzymes is to grant access to a wide variety of differing metabolites that may be advantageous to the host, while also preserving resources. If a few metabolites that had emerged from this broader spectrum approach provided a significant competitive advantage, nature could then further evolve dedicated substrate-specific enzymes to govern their biosynthesis. Such a method may serve as an evolutionary *screening* for potentially beneficial natural products.



Scheme 1.4: Investigations into the substrate tolerance and regioselectivity of the promiscuous prenylating enzyme, AstPT.^[30] **a).** AstPT only accepts dimethylallyl diphosphate (DMAPP) for the non-selective alkylation of Asterriquinone D (**1.28:** AQ D). **b).** Investigations into the regioselective alkylation of various xanthenes (**1.31 – 1.34**) with either DMAPP, geranyl diphosphate (GPP) or farnesyl diphosphate (FPP) (**1.35 – 1.38**).

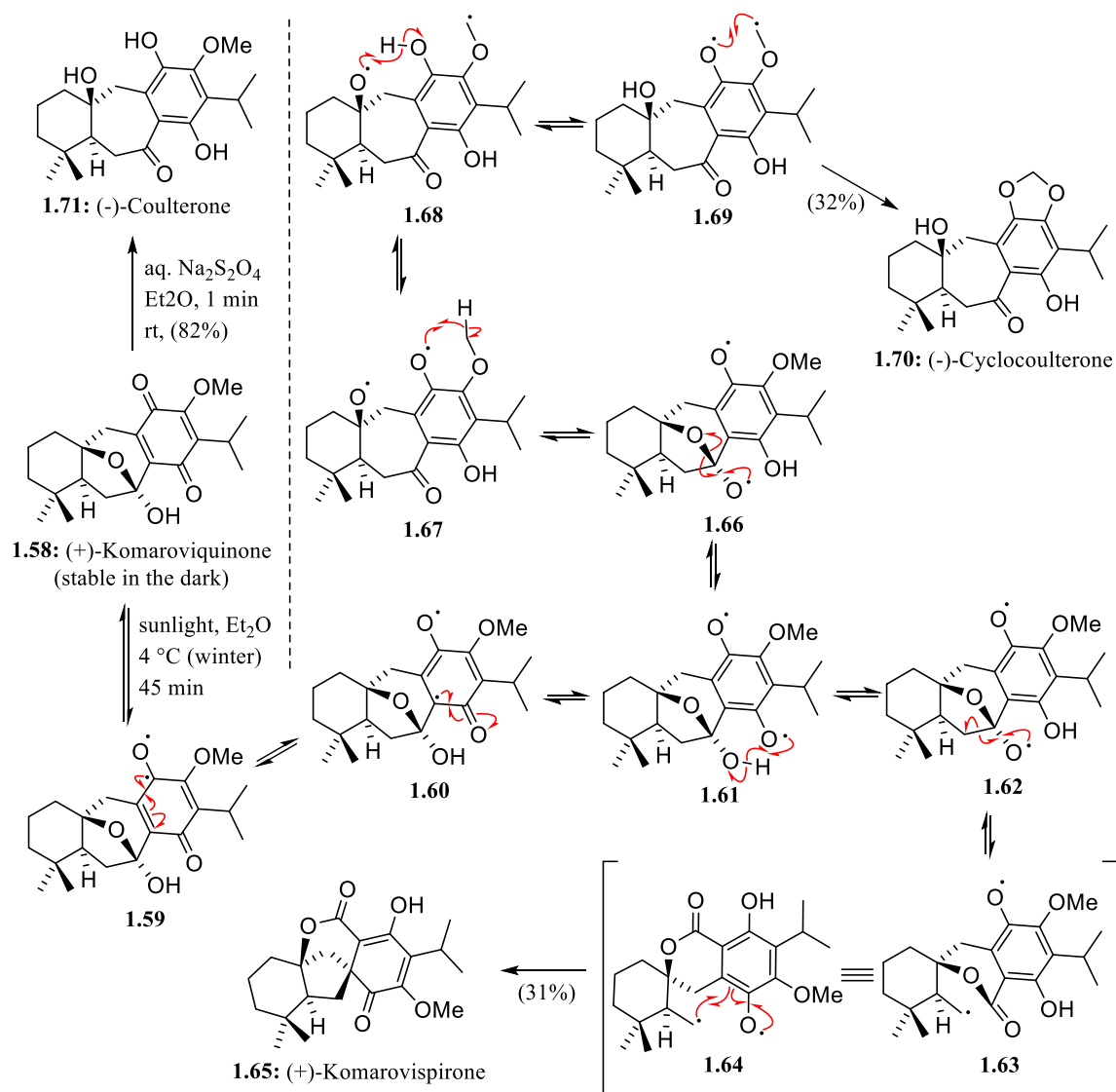
Artefactual products of isolation are indistinguishable from natural products, which have emerged spontaneously upon the exposure of a given biogenic precursor to environmental conditions. Examples of artefacts vary from unnatural epimers of natural products, such as the thermal isomerisation of the (-)-gallocatechins (**1.39 & 1.40**) upon brewing the tea of *camellia sinensis* (scheme 1.5),^[31,32] to various nucleophilic & electrophilic substitutions of reactive functional groups, as discovered for the isolation of the alkaloid artefact desmosine (**1.45**) (scheme 1.5).^[32,33] Additionally, natural products have been found to undergo spontaneous rearrangement upon exposure to mild environmental conditions, to afford artefactual complex molecular frameworks. The conversion of the natural product coatline B (**1.46**) to the previously proposed natural product Matlaline (**1.52**), demonstrates the complexity of molecular systems that can be afforded under mild environmental conditions (scheme 1.5).^[34,35]



Scheme 1.5: Examples of suspected artefacts of isolation: **a)** epimerisation of (-)-catechins (**1.39** & **1.40**) from *camellia sinensis*.^[31,32] **b)** Formation of the alkaloid artefact desmosine (**1.45**).^[32,33] **c)** The spontaneous oxidative rearrangement of coatline B (**1.46**).^[34,35] **d)** Proposed formation of the artefacts brevianamide B – C (**1.55** – **1.57**) from brevianamide A (**1.53**), *Penicillium brevi-compactum*.^[32,36]

As it may not be immediately obvious which isolated metabolites are true natural products, and those which may be artefacts, it is necessary to not only consider the conditions required to generate a suspected artefactual product, but also the environment in which the host organism has evolved. For example, the metabolites brevianamide A – D (**1.53**, **1.55** – **1.57**) were initially isolated from the fungus *Penicillium brevi-compactum*, however, when the

fungus was extracted in low light conditions, only brevianamide A (**1.53**) was isolated (scheme 1.5).^[32,36] Therefore, we can infer from the outcome of the isolation conditions employed and speculations regarding the habitat of the host, that brevianamides B – D (**1.55** – **1.57**) are most likely artefacts that formed via the photolytic cleavage of brevianamide A (**1.53**), as fungi are non-photosynthetic organisms that do not thrive under exposure to sunlight. For a more detailed review on artefactual products, see Champy^[32], Pettus^[34], and Capon^[37].

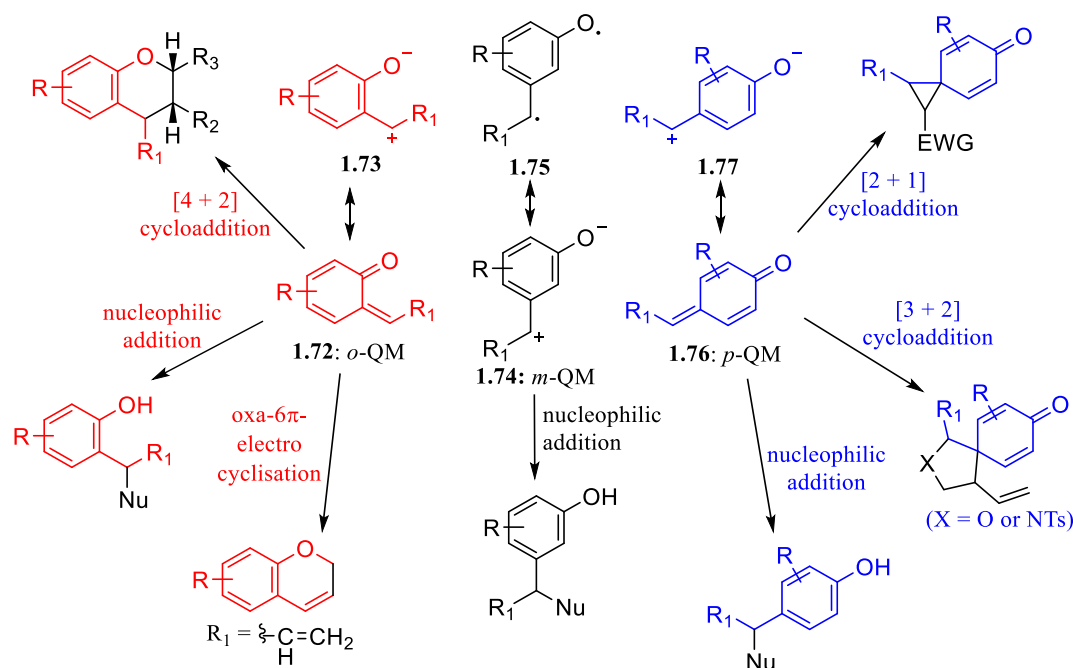


Scheme 1.6: Isolated *non-enzymatically* biosynthesised natural products from the shrub *Dracocephalum komarovi*, and the mild, *biomimetic* photo-catalysed formation of (-)- (+)-komarospirone (**1.65**) and cyclocoulterone (**1.70**) from (+)-komaroviquinone (**1.58**), and the rapid formation of (-)-coulterone (**1.71**) under mild reductive conditions.^[32,38,39]

Natural products that may be biosynthesised through non-enzymatically mediated processes would be akin to artefactual products that have instead, emerged within the host cell.^[32,38,40–42] The natural products from the highland shrub *Dracocephalum komarovi* (**1.58**, **1.65**, **1.70**

& **1.71**), are examples of metabolites that may have formed in nature under non-enzymatic pathways (scheme 1.6).^[32,38,39] Recently, (+)-komarovspirone (**1.65**) and (-)-cyclocoulerone (**1.70**) were found to form upon exposure of (+)-komaroviquinone (**1.58**) to sunlight in Et₂O at 4 °C, which the authors argued, was representative of the cold, winter conditions of the shrub's native mountainous habitat.^[38] In addition, under mild reductive conditions, (-)-coulerone (**1.71**) was rapidly acquired from (+)-komaroviquinone (**1.58**), indicating that either metabolite may be the others biosynthetic precursor, afforded spontaneously under REDOX conditions. The metabolites (+)-komarovspirone (**1.65**) and (-)-cyclocoulerone (**1.70**) may not be artefactual, but rather natural products that have emerged within the host plant, as indicated by their biomimetic, sunlight initiated transformation from (+)-komaroviquinone (**1.58**).^[38]

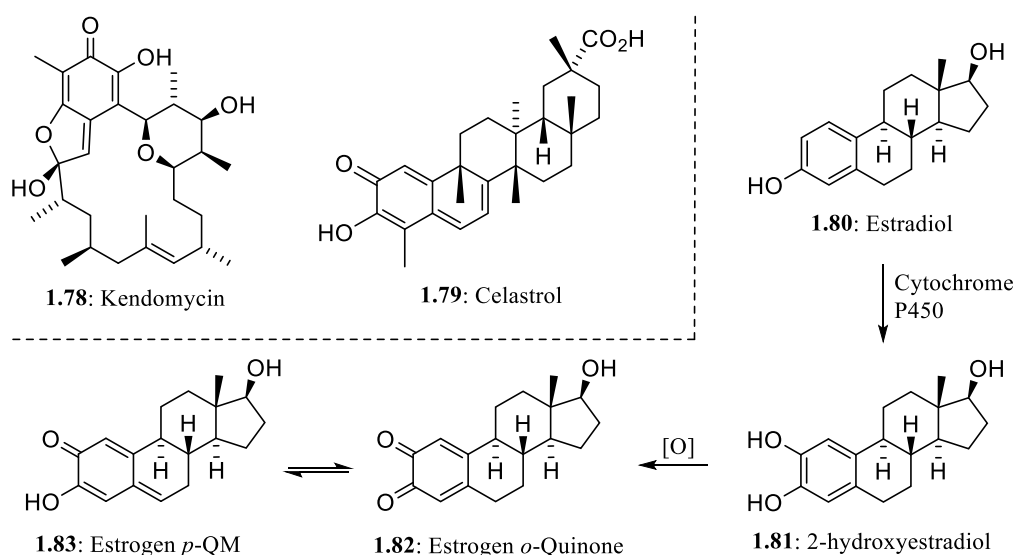
1.3.1 Quinone Methides as Reactive Intermediates in Nature



Scheme 1.7: Various reaction pathways for *ortho*-(**1.72**),^[43–45] *meta*-(**1.74**),^[46–49] and *para*-QMs (**1.76**).^[50–57]

Quinone methides are highly reactive species that have become of great interest to chemists as viable substrates in a wide range of synthetic transformations. Additionally, quinone methide species have been proposed to act as reactive biosynthetic precursors and intermediates in nature (scheme 1.7).^[44,45,57–60] However, the synthetic scope of QMs has generally been focused around *ortho*-(**1.72**) and *para*-QMs (**1.76**),^[74–76,78,85–91] as *meta*-QMs (**1.74**) are generally difficult to generate, short lived species, with limited synthetic application.^[46–49] Of the three isomeric species, *para*-QMs (**1.76**) are the most stable of the

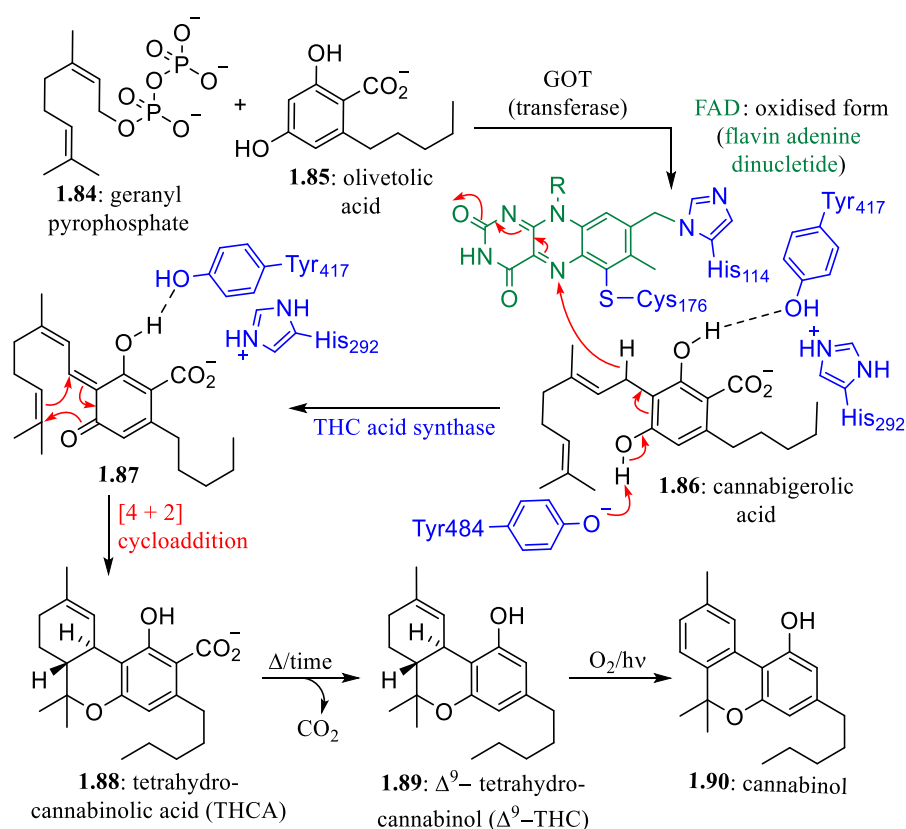
family, with an extensive history as viable Michael acceptors, and as stable natural products themselves (schemes 1.7 & 1.8).^[45,57,60–62] *p*-QM natural products, such as kendomycin (**1.78**) and celastrol (**1.79**), have gained attention due to their broad spectrum of bioactivities, which range from anti-inflammatory and anti-carcinogenic properties to novel antibiotic activity against drug resistant pathogenic bacteria (MSRA).^[61–66] Alternatively, endogenous hormones, such as estradiol (**1.80**) have been found to undergo auto-oxidation and isomerisation to the cytotoxic estrogen *o*-quinone **1.82** and estrogenic *p*-QM **1.83** metabolites within the body (scheme 1.8). Both estrogenic *o*-quinone **1.82** and *p*-QM **1.83** are known carcinogens, which were demonstrated to undergo nucleophilic attack from DNA, elucidating one of the primary carcinogenic mechanisms of action for estrogen and other related endogenous/exogenous hormones (scheme 1.8).^[61,67–71]



Scheme 1.8: Examples of pharmacologically active *p*-QM natural products, kendomycin (**1.78**) & celastrol (**1.79**).^[61,62,64,72] Metabolism of estradiol (**1.80**) to the cytotoxic estrogenic *p*-QM **1.83**.^[61,69,73]

Although stable *o*-QMs have rarely been isolated,^[74,75] their presence has been directly implicated in the biosynthesis of various natural products, such as the cannabinoids from the psychoactive plant, *cannabis sativa*.^[76–78] Δ^9 -Tetrahydrocannabinol (**1.89**: Δ^9 -THC) and other cannabinoids have been found to possess both pronounced psychoactive and cytotoxic bioactive profiles (scheme 1.9). The intriguing psychoactive, pain relieving and cytotoxic properties of the cannabinoids has led to growing interest into the therapeutic effects of these drugs and their biosynthetic origin.^[76–79] Upon enzymatic formation of the biosynthetic intermediate cannabigerolic acid (**1.86**),^[80] THC acid synthase was discovered to induce an intramolecular hetero-Diels-Alder cyclisation of the oxidatively generated *o*-QM **1.87** (scheme 1.9).^[78,80–83] Over time, the afforded tetrahydrocannabinolic acid (THCA)

spontaneously degrades to the bioactive cytotoxic/psychoactive, artefactual metabolite Δ^9 -THC (**1.89**), which further undergoes oxidation to the less psychoactive product cannabinol (**1.90**). THC acid synthase was shown to not exhibit any catalytic activity towards decarboxylated substrates, highlighting the conserved nature for the biosynthesis of the cannabinolic acids. As all the cannabinoids are cytotoxic, they were found to be stored within vesicles, and are released upon cell damage as a primary chemical defence mechanism for the host plant.^[82] The biosynthesis of Δ^9 -THC (**1.89**) and other the cannabinoids demonstrates the importance of *o*-QMs in nature as viable biosynthetic species that grants nature access to a wide array of varying molecular frameworks.



Scheme 1.9: Biosynthetic pathway of cannabinoids (**1.88** – **1.90**) via an enzyme facilitated [4 + 2] cycloaddition of cannabigerolic acid *o*-QM (**1.87**). Geranyl-pyrophosphate-olivetolic acid geranyltransferase = GOT. ^[78,80–83]

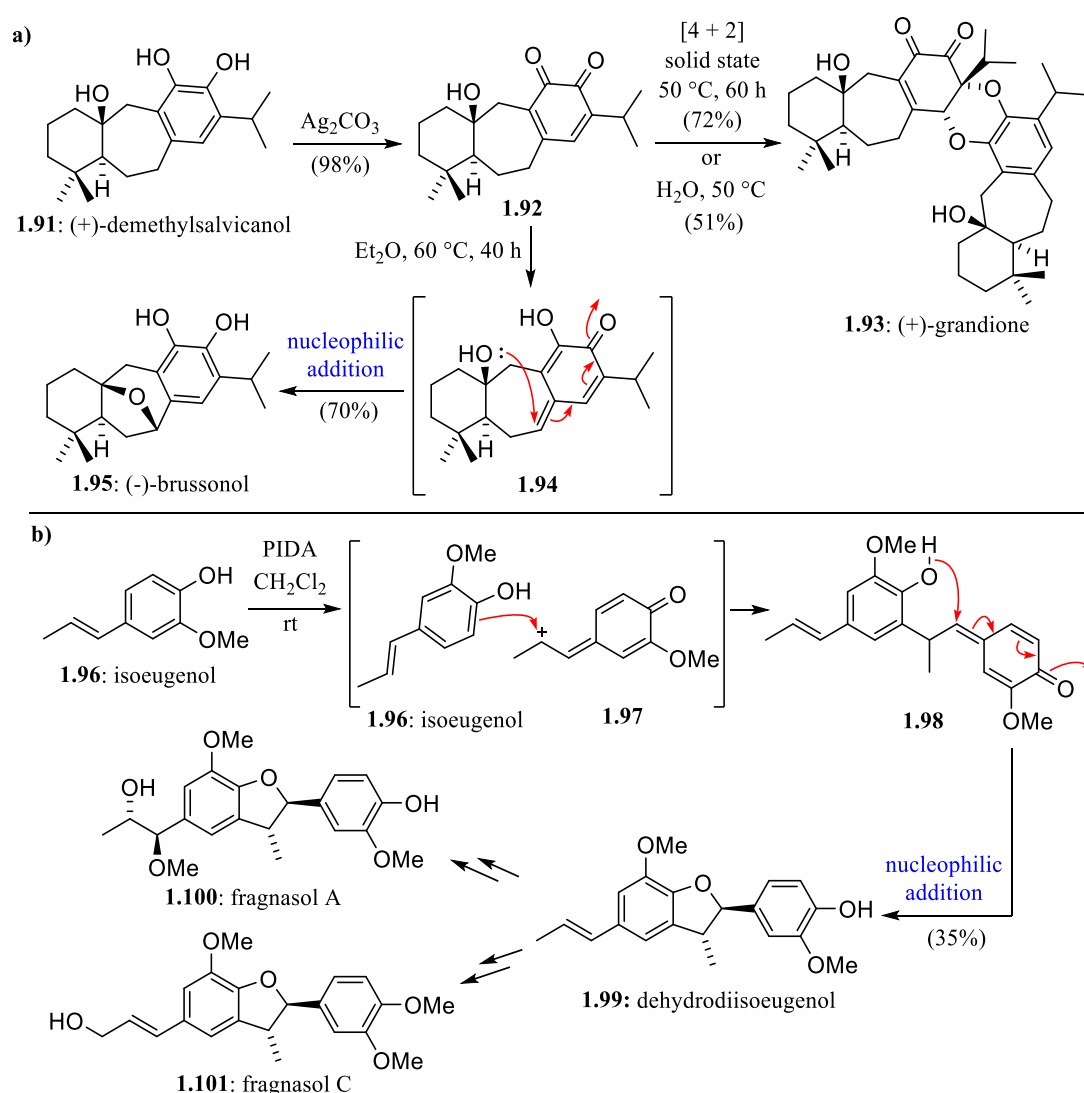
1.3.2 Scope

Our work is focused upon the growing advances in uncovering the biosynthetic routes of natural products through biogenically inspired synthetic methods, specifically centred around the employment of quinone methides as reactive intermediates in the synthesis of heterocyclic natural products. As only a few select examples will be discussed here, several

reviews have been published by Bray,^[43] Scheidt,^[45] and Spivey,^[84] which detail the wide scope of utility of *o*-QMs in natural product chemistry.

1.3.3 Spontaneous, Biomimetic Cyclisation and Cascade Reactions Involving *para*- and *ortho*-Quinone Methide as Biogenic Intermediates

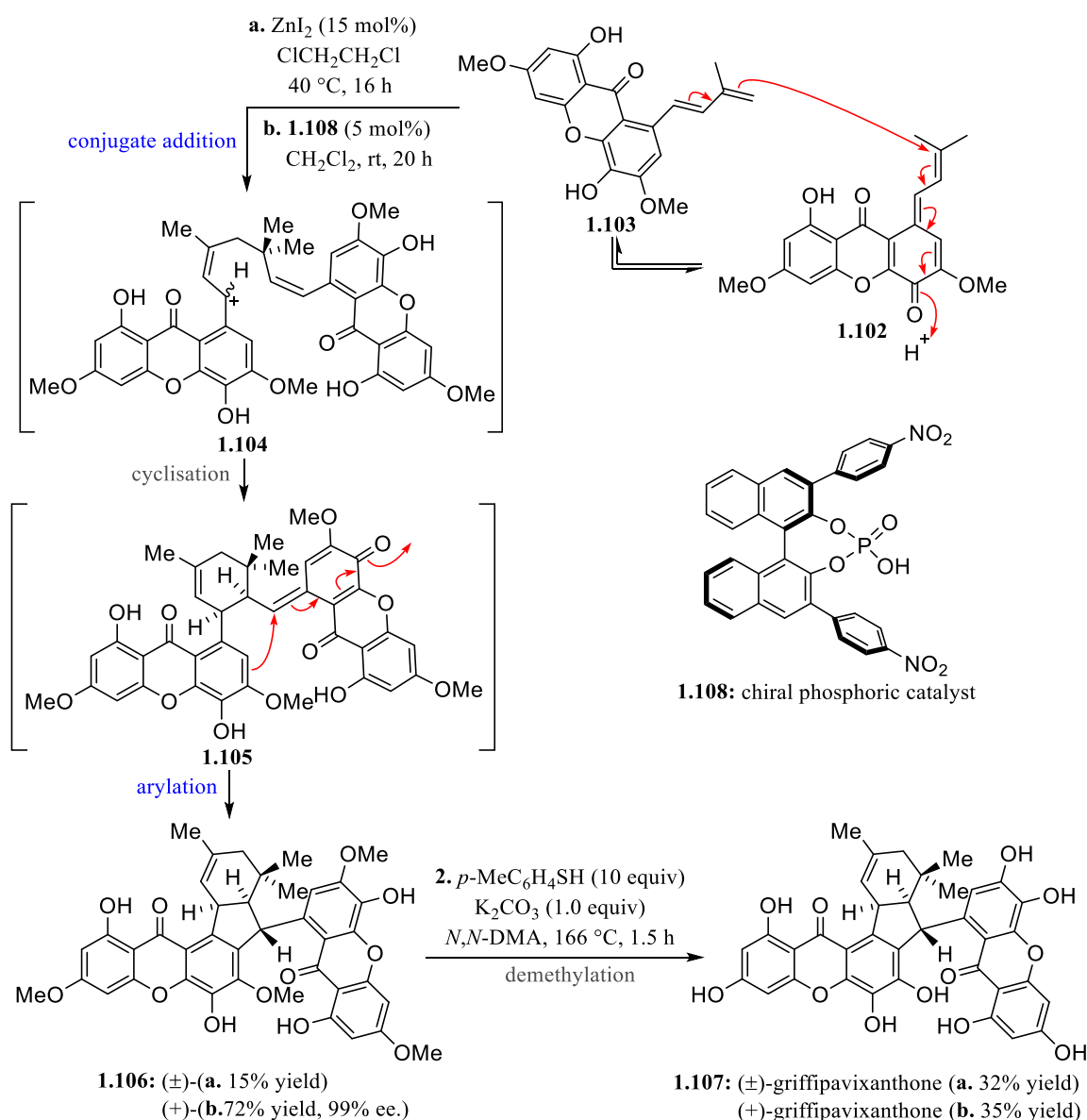
The use of *p*-QMs in both total and biogenically inspired syntheses has been largely limited to 1,6-conjugate Michael additions, which generally allow for limited, yet controlled reactions. Upon their formation, *p*-QMs have been demonstrated to undergo spontaneous 1,6-conjugate additions with various nucleophilic substrates, the most notable of which are intramolecular cyclisations to afford heterocycles.



Scheme 1.10: Examples of *para*-QMs as reactive species that undergo spontaneous transformations; **a)** Majetich's synthesis of (+)-grandione (**1.93**) and the unexpected ring closure of generated *p*-QM **1.94** to give (-)-brussonol (**1.95**).^[34,85] **b)** Antus's synthesis of fragnasols A (**1.100**) and C (**1.101**) from dehydrodiisoeugenol (**1.99**) via an oxidative cascade reaction (**1.96 – 1.99**).^[34,86]

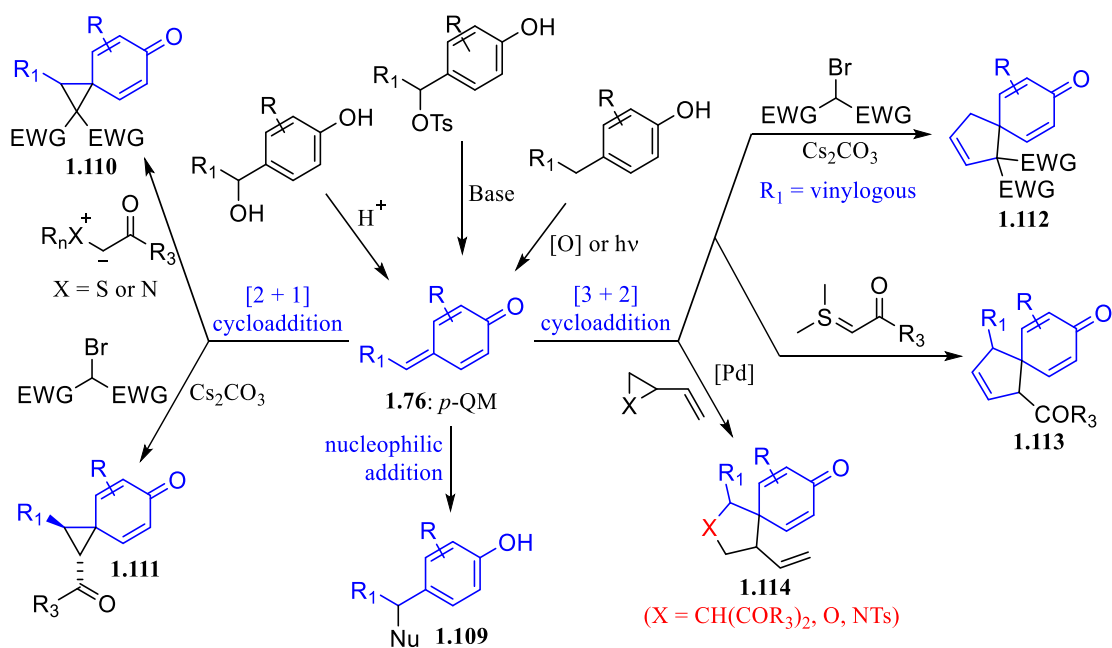
Upon investigating the biogenically inspired synthesis of (+)-grandione (**1.93**), Majetich and co-workers found that oxidation of (+)-demethylsalvicanol (**1.91**) led to the formation of the ring fused heterocyclic natural product, (-)-brussonol (**1.95**) (scheme 1.10 – a).^[85] (-)-Brussonol (**1.95**) was presumed to have formed upon isomerisation of the *in situ* generated *ortho*-quinone **1.92** to *p*-QM **1.94**, which underwent nucleophilic attack to afford the ring fused 5,6-oxa-heterocycle moiety. The formation of dehydrodiisoeugenol (**1.99**) and the subsequent synthesis of fragnasols A (**1.100**) & C (**1.101**) by Antus *et al.*,^[86] provides insight into the biosynthetic pathway of these simple heterocycles in nature (scheme 1.10 – b). The heterocyclic scaffold for the fragnasols was installed early in their synthetic route via an oxidative cascade reaction of isoeugenol (**1.96**) with *p*-QM **1.97** to afford dehydrodiisoeugenol (**1.99**). Analogously to Antus's synthetic route, dehydrodiisoeugenol (**1.99**) could serve as a biosynthetic intermediate in nature, providing the heterocyclic scaffold for the fragnasols A (**1.100**) & C (**1.101**) early in their biosynthesis (scheme 1.10).

Porco Jr and co-workers published two alternative, acid catalysed protocols for the seemingly complex dimeric natural product, griffipavixanthone (**1.107**), from the *p*-QM tetrahydroxyxanthone **1.102** (scheme 1.11). The first method detailed a Lewis acid catalysed dimerization (**1.104**) of isomerised xanthone **1.103** with *p*-QM **1.102** via a Michael addition, which was proposed to undergo an intramolecular cyclisation (**1.104**) and arylation (**1.105**) to afford the desired griffipavixanthone scaffold (**1.106**) (scheme 1.11 – a).^[87] Porco Jr published an alternative method, using a chiral phosphoric acid catalyst (**1.108**), which was found to induce a dimerization via a conjugate addition of **1.103** to *p*-QM **1.102**, followed by cyclisation (**1.104**) and arylation of the *in situ* *p*-QM dimer **1.105** to almost exclusively afford the *syn*-(+)-isomer scaffold **1.106** (scheme 1.11 – b).^[88] Proceeding from the chiral catalytic dimerization, demethylation of *syn*-(+)-**1.106** was found to exclusively afford the natural isomer, (+)-griffipavixanthone (**1.107**). Porco Jr's biogenically inspired method provides evidence for the existence of a substrate specific *p*-QM xanthone **1.102** dimerizing enzyme, which if true, indicates that (+)-griffipavixanthone (**1.107**) may possess undiscovered target specific, bioactive properties, having emerged as a consequence of an unknown selective pressure.



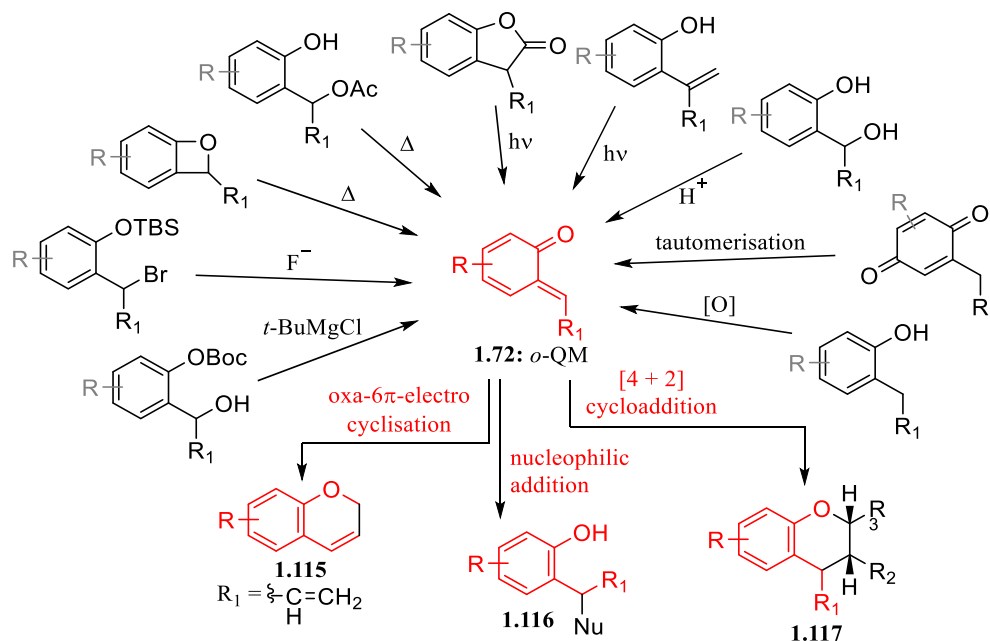
Scheme 1.11: Synthesis of (+)-griffipavixanthone (**1.107**) from *p*-QM **1.102** by Porco Jr *et al.* Comparison of a one-pot, acid catalysed transformation of *p*-QM **1.102** to the cyclised tetrahydroxyxanthone **1.106** with either; **a.** ZnI₂,^[87] or **b.** chiral phosphoric acid catalyst **1.108**.^[88]

The vast majority of biomimetic, and total synthetic methods involving *p*-QMs have either revolved around their employment as substrates in 1,6 conjugate additions (**1.109**), or as end products themselves (schemes 1.7, 1.10 – 1.12). Recently, interest in developing and widening the scope of novel *p*-QM reactions has been expanding beyond the already well-known 1,6-conjugate additions to both metal and non-metal catalysed [2 + 1] (**1.110** & **1.111**) and [3 + 2] (**1.112** – **1.114**) cycloadditions (scheme 1.12).^[50–57] This developing field of unique transformations could prove relevant to biomimetic synthesis, as we may yet discover that nature has evolved enzymes which can induce such cycloaddition reactions.



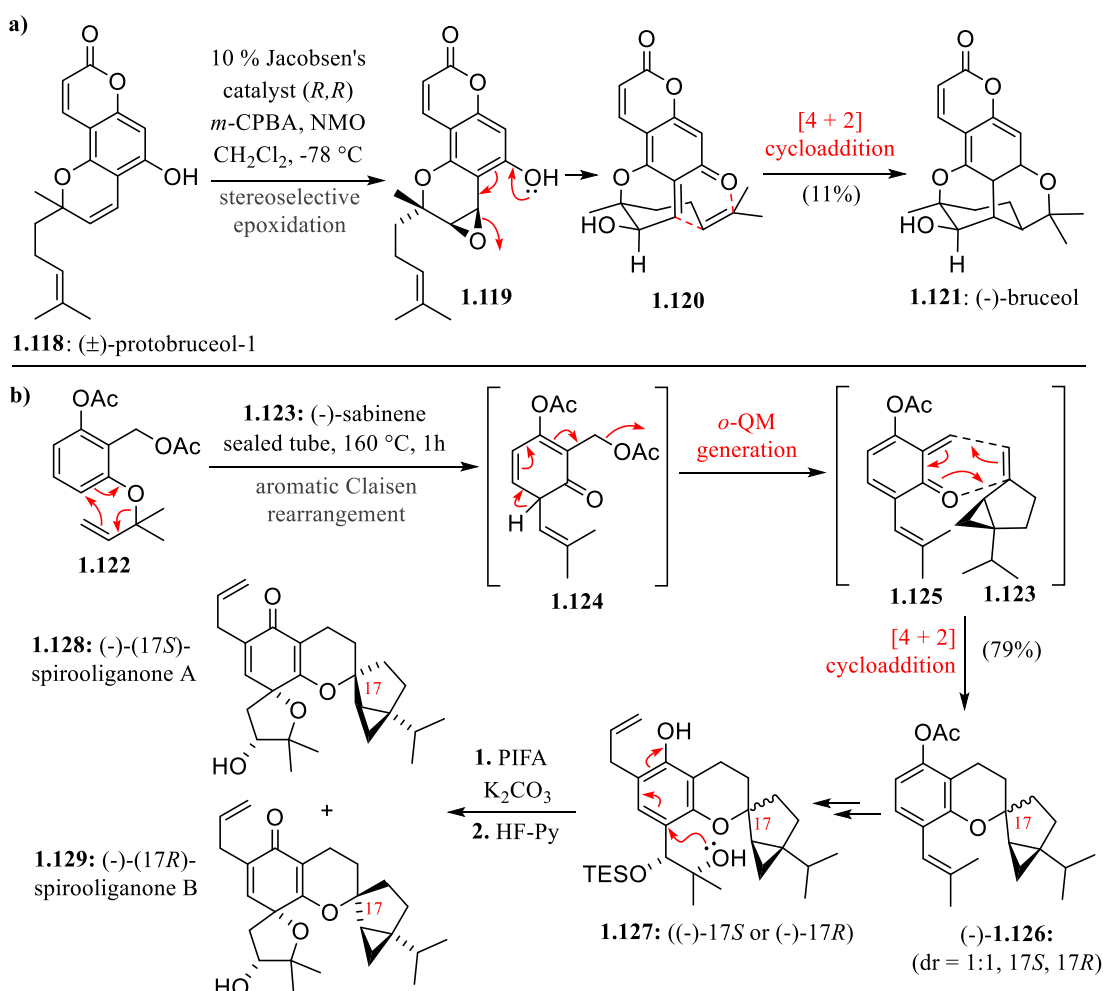
Scheme 1.12: Examples of viable reactions, highlighting the emerging diverse utility of *p*-QMs (1.76), from 1,6 nucleophilic additions to novel [2 + 1] and [3 + 2] cycloadditions.^[50–57]

o-QM species are seldom isolated as stable species, and are more widely known for their ability to undergo electrocyclisations, serve as dienes in cycloadditions, and as Michael acceptors, making them the most versatile of the three isomeric quinone methide species (scheme 1.13).^[43,44,59,84,89]



Scheme 1.13: Various methods of generating *o*-QMs (1.72) and examples of their synthetic utility available to both chemist and nature alike.^[43,44,59,84,89]

The propensity for *in situ* generated *o*-QMs to undergo spontaneous cyclisation reactions, as demonstrated by the biomimetic synthesis of (-)-bruceol (**1.121**) and the spiroooliganones ((-)-(17*S*)-**1.128**: A & (-)-(17*R*)-**1.129**: B),^[90,91] demonstrates the validity for the occurrence of these efficient transformations in nature (scheme 1.14). George's biomimetic method grants significant insight into the possible biosynthesis of (-)-bruceol (**1.121**), without the necessary requirement of substrate specific enzymes, despite its seemingly complex carbon framework (scheme 1.14 - a).^[90] In nature, the epoxidation event of protobruceol (**1.118**) may be catalysed by a promiscuous cytochrome P450 enzyme, analogous to the substrate preferences of Jacobsen's catalyst. However, the spontaneous proceeding epoxide ring opening (**1.119**), and intramolecular cyclisation of *o*-QM **1.120** would not need to be enzymatically mediated, and rather, the stereoconfiguration of the generated epoxide (**1.119**) would dictate the stereochemical outcome of the [4 + 2] cycloaddition.^[90]

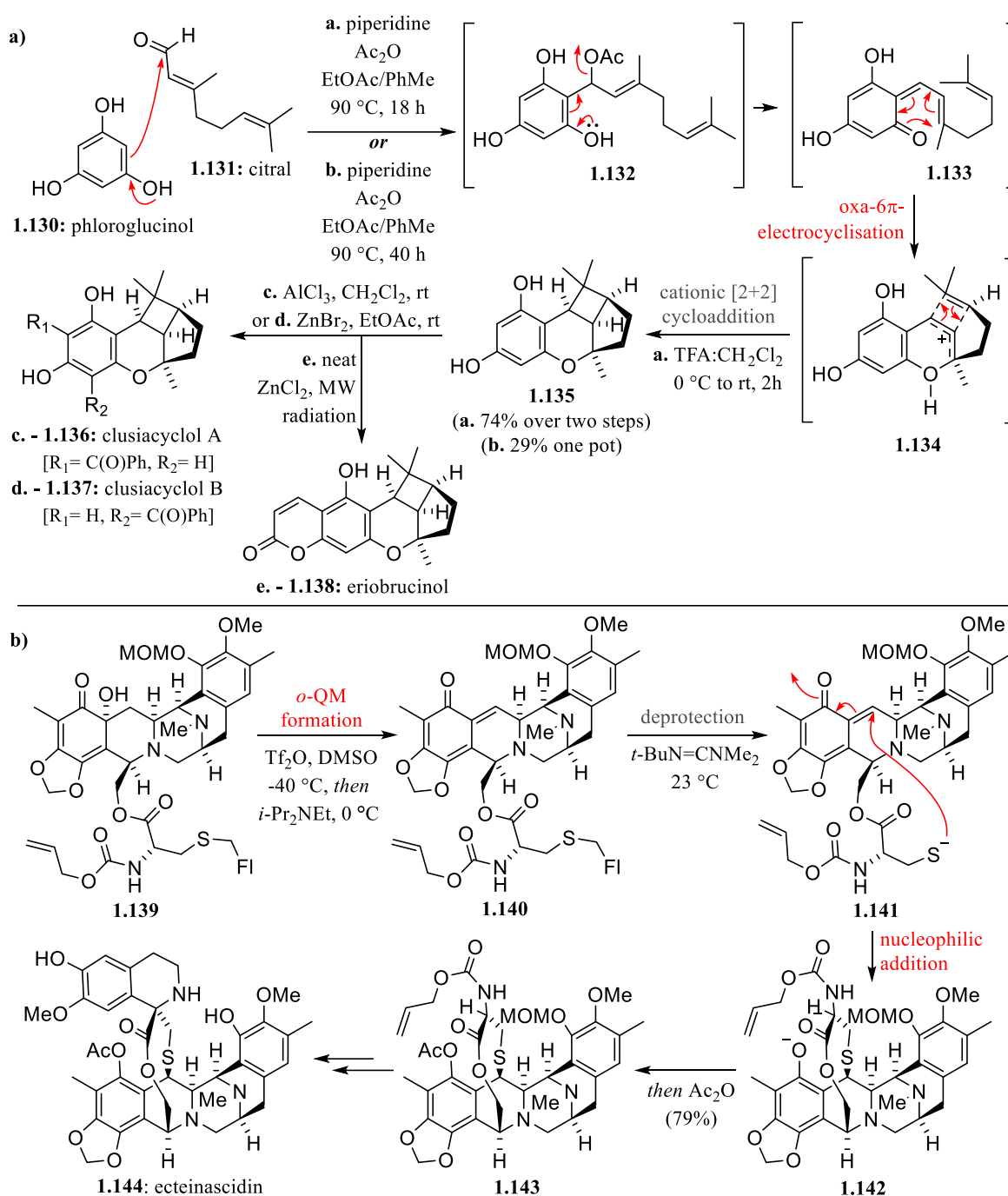


Scheme 1.14: a) George's biogenically inspired synthesis of (-)-bruceol (**1.121**) via a one-pot epoxidation and a subsequent intramolecular [4 + 2] cycloaddition from an *in situ* generated *o*-QM **1.120**.^[90] b) Tong's synthesis of (-)-(17*S*)-spiroooliganone A (**1.128**) and (-)-(17*R*)-spiroooliganones B (**1.129**), with the characteristic spirocycle afforded via a hetero-Diels-Alder reaction of (-)-sabinene (**1.123**) and *o*-QM **1.125**, generated upon an aromatic Claisen rearrangement (**1.122**).^[91]

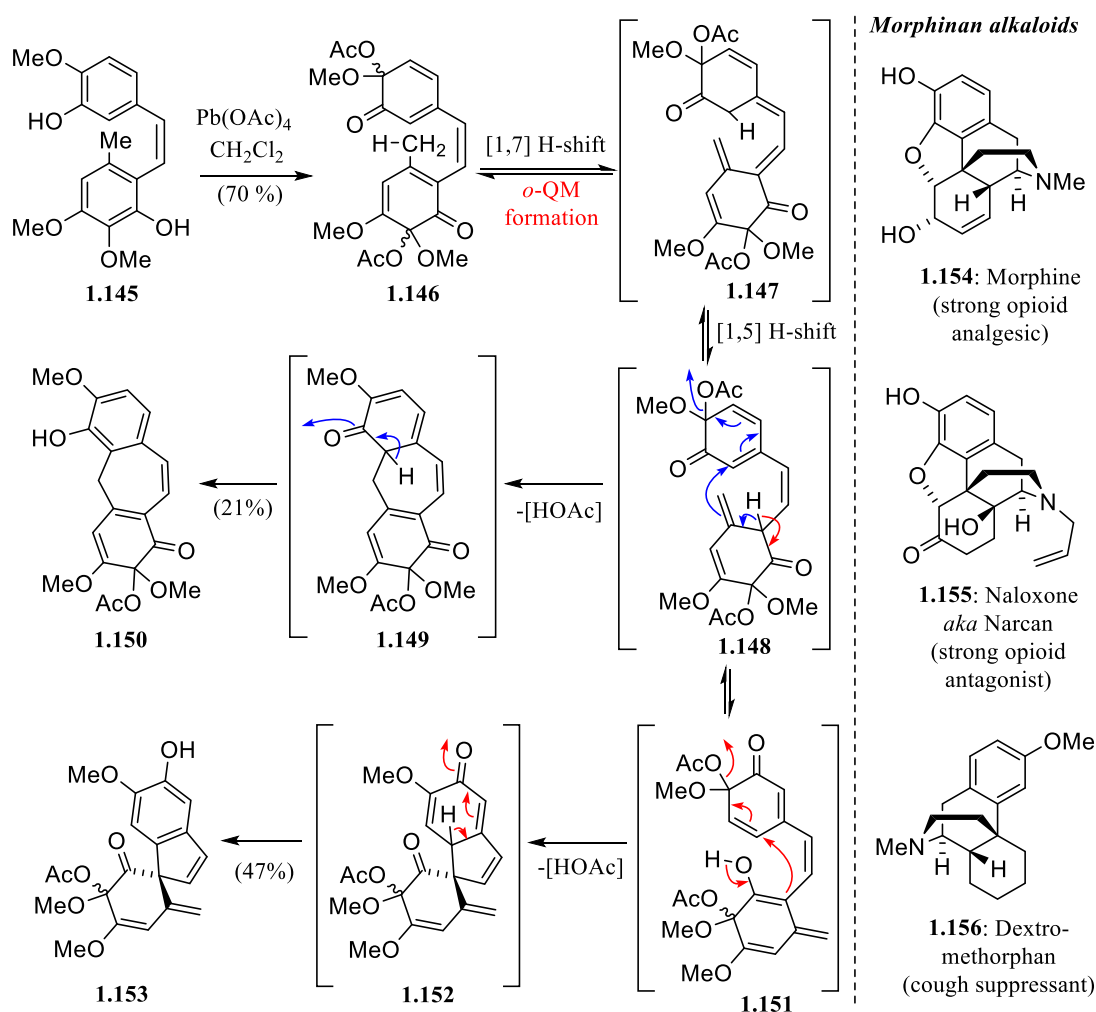
The synthesis of spirooliganones (-)-(17*S*)-A (**1.128**) and (-)-(17*R*)-B (**1.129**), by Tong *et al.*, demonstrates the efficiency of the consecutive reaction sequences that give rise to complex molecular frameworks, highlighting the impressive reaction economy that can be achieved with *o*-QM species (scheme 1.14, b).^[91] Upon heating the reactants in a sealed tube, **1.122** was found to have undergone an aromatic Claisen rearrangement (**1.122** to **1.124**) to *o*-QM **1.125**, which subsequently led to a hetero-Diels-Alder reaction with (-)-sabinene (**1.123**) to exclusively afford the desired regioisomers **1.126** in a 1:1 diastereomeric ratio. Finally, spirooliganones (-)-(17*S*)-A (**1.128**) and (-)-(17*R*)-B (**1.129**) were afforded upon subjecting each diastereomer **1.127** (either (-)-(17*S*) or (-)-(17*R*)) to PIFA, which led to a phenolic oxidative dearomatisation/spirocyclisation, and a subsequent silyl deprotection afforded the desired natural products. Tong's synthesis of the natural C17 spirocyclic diastereomers, spirooliganones (-)-(17*S*)-A (**1.128**) and (-)-(17*R*)-B (**1.129**), provides evidence for their likely emergence in nature, either through non-enzymatic means, or via promiscuous enzymes.

Hsung's biogenically inspired synthesis of clusiacyclol A (**1.136**), B (**1.137**) and eriobrucinol (**1.138**), details an impressive one-pot cascade sequence that affords the shared characteristic tetracyclic carbon scaffold.^[92] The key cascade reaction was initiated upon condensation of phloroglucinol (**1.130**) with citral (**1.131**). The *in situ* coupled triphenol **1.132** was found to undergo a subsequent oxa-6 π -electrocyclisation (**1.133**) via an *o*-QM intermediate. Upon isolation of the afforded chromane **1.134**, addition of TFA:CH₂Cl₂ led to the desired tetracyclic system **1.135**, in good yield (scheme 1.15 – a, **a.**). Alternatively, the *in situ* chromane **1.134** was found to undergo a cationic [2 + 2] cycloaddition upon heating the reaction mixture for a total of 40 hours (scheme 1.15 – a, **b.**). Finally, the afforded tetracycle **1.135** was acylated to give the related natural products, clusiacyclols A (**c.** - **1.136**), B (**d.** - **1.137**), and eriobrucinol (**e.** - **1.138**) (scheme 1.15 – a). Hsung's biogenically inspired route represents a divergent, economical method, which capitalizes upon a spontaneous cascade sequence (**1.130** – **1.133**) to generate a reactive *o*-QM intermediate (**1.133**). Few examples exist of *o*-QMs partaking in nucleophilic additions, which may be attributed to their highly reactive nature and propensity to react with the bases required to generate enolates and other nucleophilic substrates. Corey's synthesis of ecteinascidin (**1.144**) describes a one-pot formation of the macrocyclic moiety via a base facilitated elimination of alcohol **1.139**, to generate *o*-QM **1.140** *in situ* (scheme 1.15 – b). In the same pot, *o*-QM **1.140** underwent a nucleophilic attack (**1.141**) from the deprotected anionic sulphide moiety to install the characteristic macrocyclic system of ecteinascidin (**1.142**). Both Hsung's and Corey's biomimetic methods are examples of how reactive *o*-QM species may be employed to rapidly afford complex molecular frameworks via the formation of new

heterocyclic and macrocyclic systems alike. Such examples of ring forming transformations may represent an economical method for nature to generate a variety of complex natural products.^[43,93,94]



Scheme 1.15: **a)** Hsung's biogenically inspired synthesis of clusiacyclopentane **A** (**1.136**), **B** (**1.137**) and eriobrucinol (**1.138**) via a one-pot, coupling, *o*-QM **1.133** formation, followed by an *oxa-6 π* -electrocyclisation and a successive cationic [2 + 2] cycloaddition to afford the desired tetracyclic scaffold.^[92] **b)** Corey's total synthesis of ecteinascidin (**1.144**) via a one-pot, *in situ* generated *o*-QM **1.140**, followed by deprotection and nucleophilic attack of the generated thiolate anion to *o*-QM **1.141**.^[43,94] Fl = 9-fluorenyl.



Scheme 1.16: Feldman's incidental cyclisation cascade reaction, involving two consecutive hydrogen shifts (**1.146** – **1.148**) via an *o*-QM intermediate **1.147**.^[95]

Although *o*-QMs have found use in cycloadditions, electrocyclisations, and to lesser degree as Michael acceptors, their involvement in sigmatropic hydrogen and alkyl shifts is scarce in natural product synthesis outside of a few examples. While investigating 6π -electrocyclisations of substituted *Z*-stilbene, Feldman observed the formation of two unexpected tricyclic compounds **1.150** and **1.153** (scheme 1.16).^[95] Upon the oxidation of *Z*-stilbene **1.145**, Feldman proposed that the afforded bis(*ortho*-quinone monoketal) **1.146** would undergo a 6π -electrocyclisation to give a 6,6,6-fused tricyclic scaffold, characteristic of morphinan alkaloids (**1.154** – **1.156**). However, upon heating bis(*ortho*-quinone monoketal) **1.146** in benzene under reflux, the ring fused 6,7,6-tricyclic and spirocyclic ketones **1.150** and **1.153** were isolated. The tricyclic (**1.150**) and spirocyclic (**1.153**) scaffolds were hypothesised to have formed via a [1,7]-sigmatropic hydrogen shift to generated *o*-QM **1.147**, which underwent a consecutive [1,5]-sigmatropic hydrogen shift. The postulated *in situ* methide **1.148** was postulated to undergo one of two competing electrocyclization pathways, (**1.148** – **1.149**) and (**1.148** to **1.151** then **1.152**), which would

afford either 6,7,6-tricyclic ketone **1.150** or spirocyclic ketone **1.153**. Such transformational pathways may be viable biosynthetic route to complex tricyclic ring systems, and hence, may become a subject of focus in the near future.

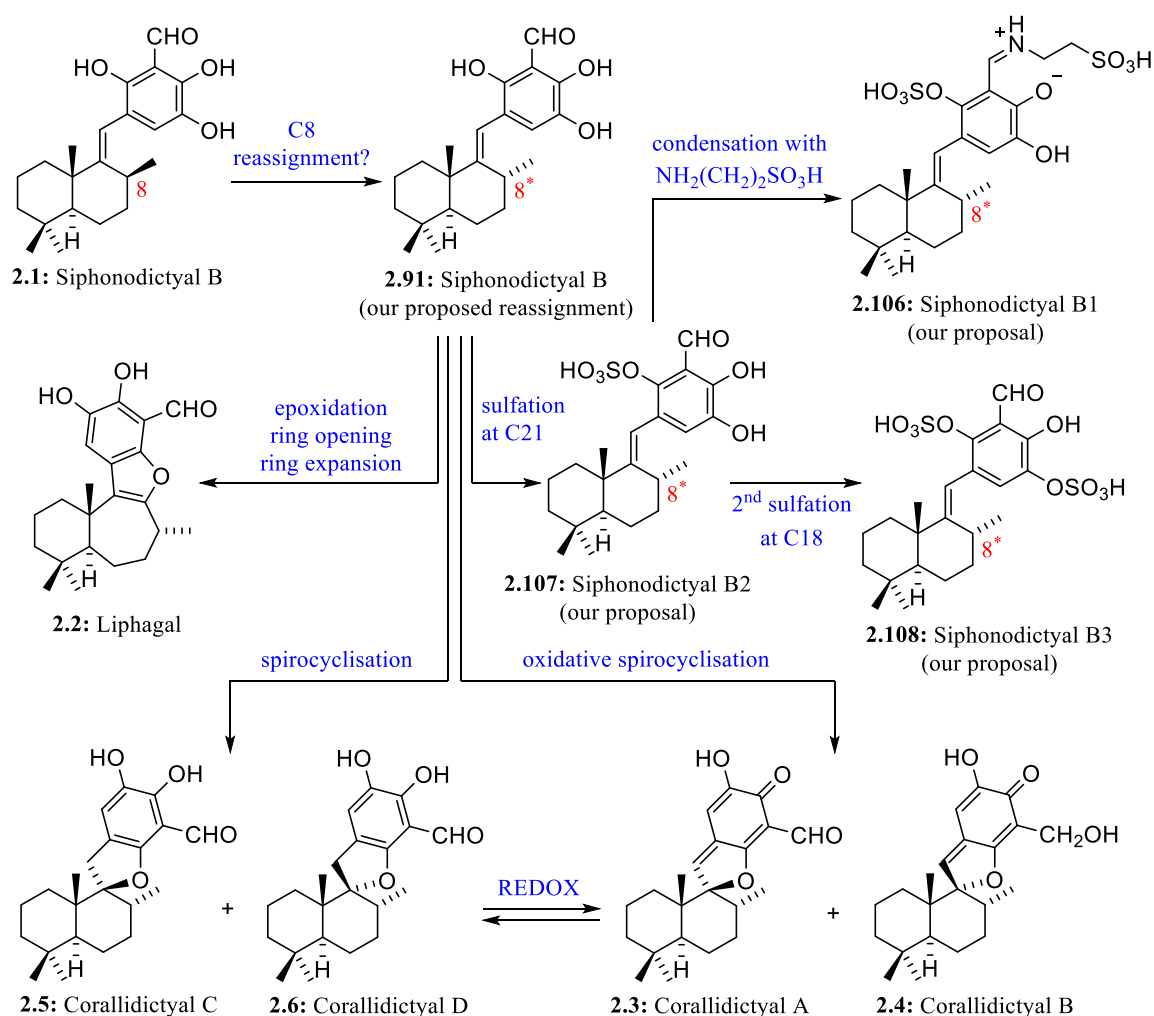
1.3.4 Outlook

This short review has sought to outline the current state and limitation of the biomimetic total synthetic field, while also highlighting the diverse utility of quinone methides as reactive intermediates in nature. Additionally, the analysis of such successful biomimetic synthetic methods may not just afford insight into the biosynthetic origins of such natural products, but also to elucidate the degree to which these processes are regulated in nature, and as such, the selective pressures under which these metabolites have emerged under.

1.4 Project Aims

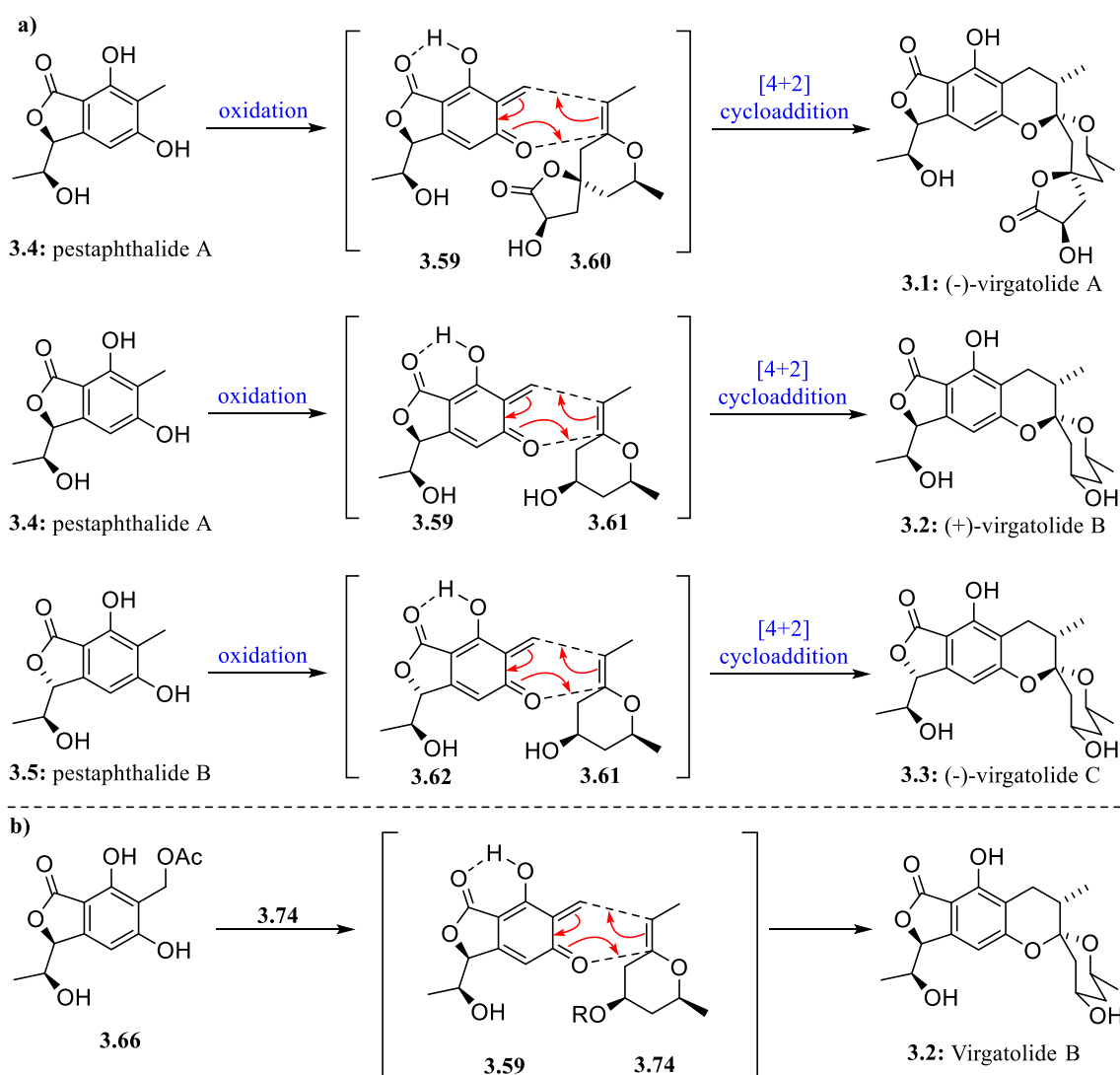
We set out to biomimetically synthesise a series of complex natural products that appeared to diverge from a shared biosynthetic intermediate. In addition to accessing the target natural products in an efficient manner, we also sought to gain insight into the biogenic origins of these two families of related metabolites.

Chapter 2: details our synthetic approach towards the seemingly related marine natural products from *Aka coralliphaga*. Investigations into the biogenically inspired synthesis of liphagal (**2.2**) and the corallidictyals A – D (**2.3** – **2.6**) from our proposed reassignment of siphonodictyal B **2.91** will be discussed (scheme 1.17). Additionally, our method will detail the stereochemical reassignment of the siphonodictyal natural sulfonate esters, B1 – B3, from **2.7** – **2.9** to **2.106** – **2.108** respectively. Finally, analysis of the seemingly divergent biosynthetic origin of the family of meroterpenoids will be explored, in an attempt to elucidate the biogenic origins of these complex natural products.



Scheme 1.17: Our biogenically inspired proposal for the synthesis and stereochemical reassignment of the related marine natural products from *Aka coralliphaga*.

Chapter 3: will detail our investigation into the synthesis of virgatolide B (**3.2**) via a biogenically inspired [4 + 2] cycloaddition pathway involving *o*-QM intermediate **3.59** (scheme 1.18). Our proposed biosynthetic pathway applies to the family of virgatolides (**3.1** – **3.3**), which would diverge from the proposed commonly shared biogenic precursor and co-isolated natural products, pestaphthalides A (**3.4**) and B (**3.5**). Our method sought to gain synthetic access to the intriguing 6,6-spiroketal natural product via a novel hetero-Diels-Alder reaction between an *in situ* generated *o*-QM intermediate (**3.59**) and a *Z*-exocyclic enol ether (**3.74**). Additionally, we were intent on unveiling the biosynthetic origins of this family of novel spiroketal natural products.



Scheme 1.18: a): Our biosynthetic proposal for virgatolides A – C (**3.1** – **3.3**) and **b):** our proposed, biogenically inspired synthesis of virgatolide B (**3.2**) via a hetero-Diels-Alder reaction of *Z*-exocyclic enol ether **3.74** and pestaphthalide A analogue **3.66**.

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CHAPTER 2

The Divergent, Biogenically Inspired Synthesis of Structurally Related Marine Natural Products from *Aka coralliphaga*

2.1 Isolation of Meroterpenoids from *Aka coralliphaga*

Aka coralliphaga (previously named both *Siphonodictyon coralliphagum* and *Aka coralliphagum*) is a burrowing sea sponge found off the coast of the Caribbean in coral reefs.^[96] *Aka coralliphaga* was found to be rich in bioactive meroterpenoids, most of which share conserved carbon skeletons.^[96–100] Meroterpenoid natural products are secondary metabolites, derived from terpene subunits, that possess two fused six membered ring systems (figure 2.1). To date, most of the meroterpenoids isolated from *Aka coralliphaga* have been shown to exhibit a broad spectrum of bioactivity: from anti-bacterial properties observed in siphonodictyal B (**2.1**) and corallidictyals A – D (**2.3 – 2.6**), to PI3 kinase inhibitory activity found with liphagal (**2.2**) and corallidictyals A (**2.3**) & B (**2.3**).^[96–100] Siphonodictyal B (**2.1**) was the first meroterpenoid to be discovered by Faulkner *et al* in 1981,^[97,98] and Andersen isolated the suspected biogenically related metabolite liphagal (**2.2**) in 2006.^[99] The corallidictyals A (**2.3**) & B (**2.3**) were first isolated by Westly *et al*, in 1994.^[100] Finally, Köck isolated and identified both families of the siphonodictyals B, B1 – B3 (**2.1, 2.7 – 2.9**), and the corallidictyals A – D (**2.3 – 2.6**) In the 2007.^[96]

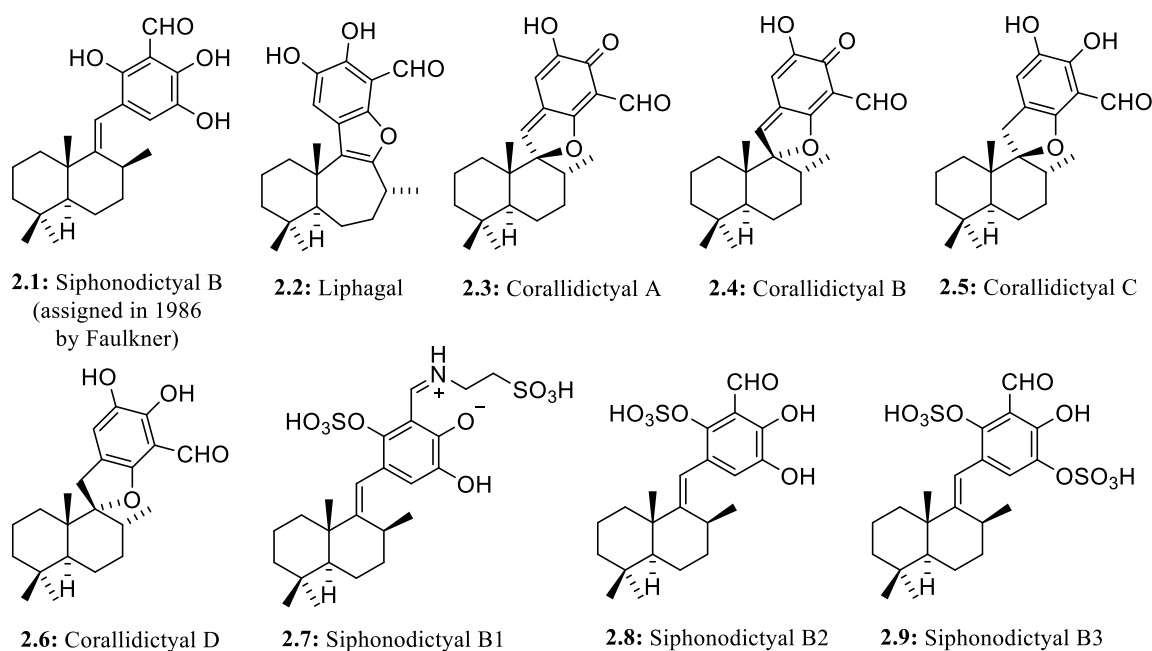
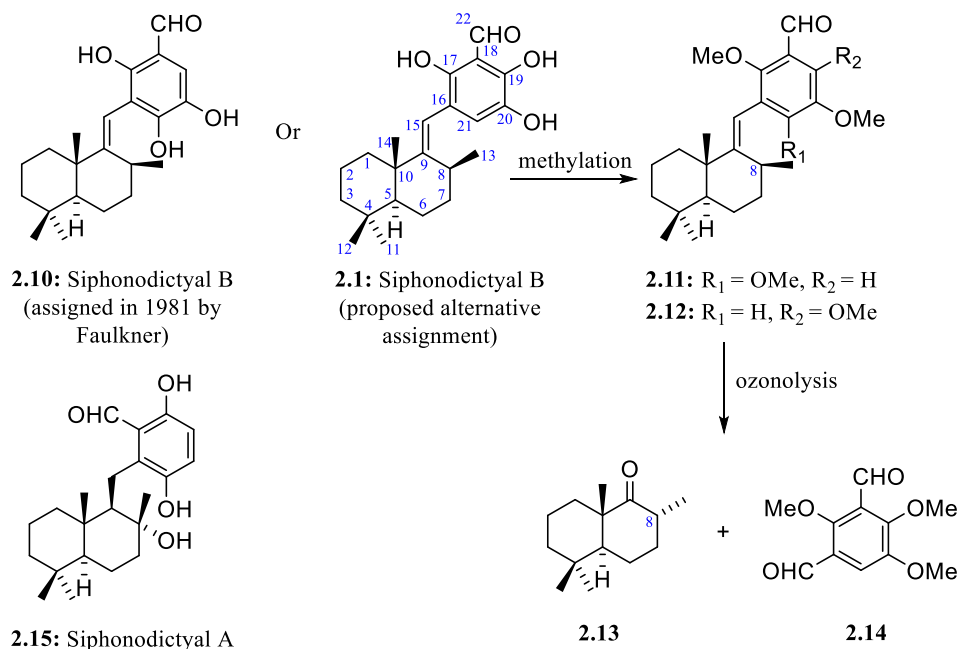


Figure 2.1: Isolated meroterpenoid natural products from the sea sponge *Aka coralliphaga*.^[96–100]

2.2 Previous Structural Assignments and the Proposed Biosynthetic Origins of Siphonodictyal B & Liphagal

2.2.1 First Assignment of Siphonodictyal B by Faulkner *et al* 1981

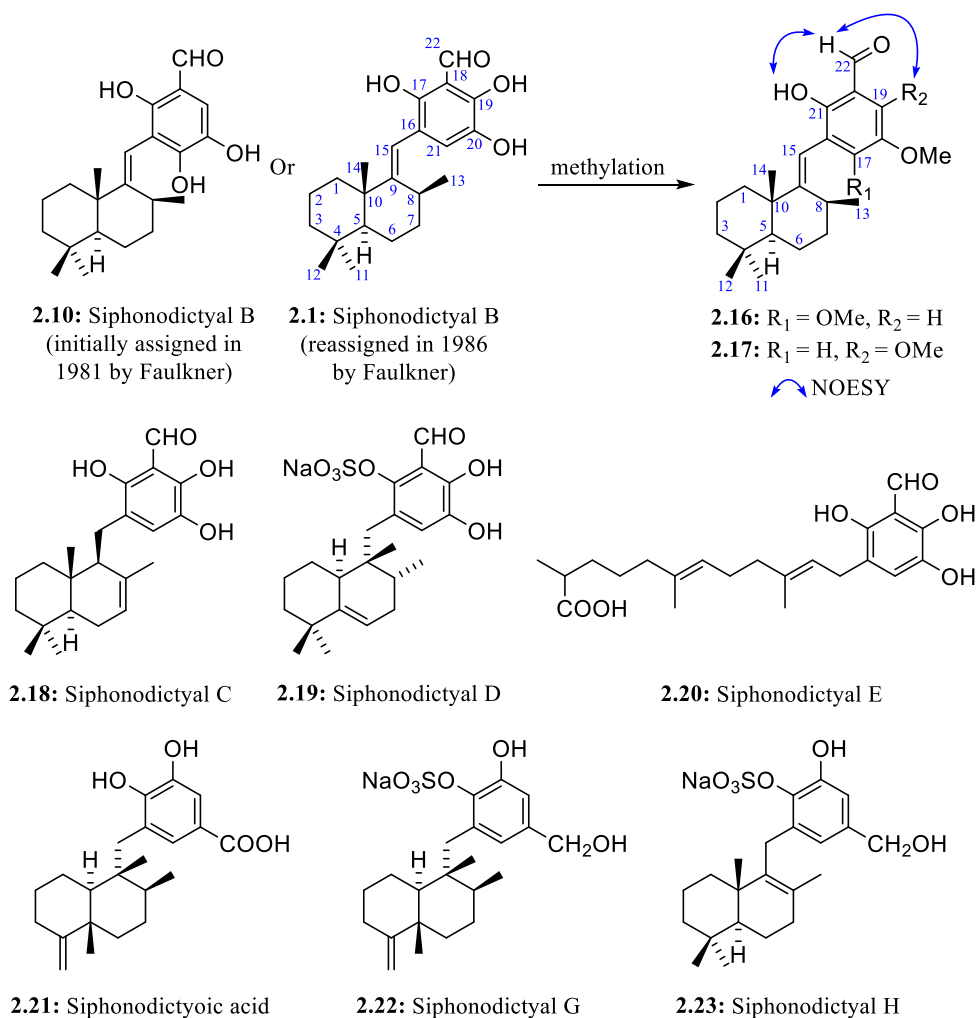


Scheme 2.1: Structural assignment of siphonodictyal B, isolated with siphonodictyal A from the sea sponge *Aka coralliphaga* (*Siphonodictyon coralliphagum*) by Faulkner *et al*, 1981.^[97]

Siphonodictyal A (**2.15**) and siphonodictyal B (**2.10** or **2.1**) were first isolated as a complex mixture of secondary metabolites from *Aka coralliphagum* (*Siphonodictyon coralliphagum*) by Faulkner *et al* in 1981 (scheme 2.1).^[97] Of the two meroterpenoids, siphonodictyal B exhibited strong antimicrobial activity against the bacterium, *Staphylococcus aureus*, whereas siphonodictyal A (**2.15**) failed to demonstrate any notable growth inhibitory properties.^[97] Structural elucidation of siphonodictyal B proved difficult, and consequently, Faulkner proposed two candidate structures, **2.10** or **2.1**, upon analysis of trimethoxy ether derivatives, **2.11** or **2.12**, following methylation of the natural sample. Ozonolysis, followed by quenching the lysed methylated meroterpenoid under reductive conditions gave ketone **2.13** and aryl dialdehyde **2.14**, which was proposed to be acquired from either **2.11** or **2.12**. The stereoconfiguration of the C8 methyl substituent was determined via a ¹H NMR decoupling experiment of the unknown trimethoxy derivative (either **2.11** or **2.12**). Irradiation of the methyl signal, at δ 0.90 ppm, caused the multiplet at δ 2.65 ppm to collapse into a doublet of doublets, with coupling constants of 6 and 2 Hz. Faulkner claimed the observed coupling constants were consistent with that of equatorial protons, projecting from

a saturated six-membered ring system in a chair conformation. Upon repeating the same decoupling experiment for ketone **2.13**, the coupling constants were found to be 6 and 12 Hz. Faulkner proposed that during ozonolysis and the reductive quenching protocol, the afforded ketone had isomerised exclusively to the predicted, more stable configuration **2.13** (scheme 2.1). As aryl dialdehyde **2.14** gave no relevant information regarding the regio-configuration of its parent compound, either **2.11** or **2.12**, a series of substituted aryl compounds were synthesised to build a library of ^1H and ^{13}C NMR pattern peaks. The afforded library of NMR spectral patterns was used as reference for the assignment of the aromatic phenolic moiety of siphonodictyal B. Thus, Faulkner determined that structure **2.10**, by comparison with the synthesised library of substituted methylated phenols, was the configuration of siphonodictyal B.

2.2.2 Reassignment of Siphonodictyal B by Faulkner *et al* 1986



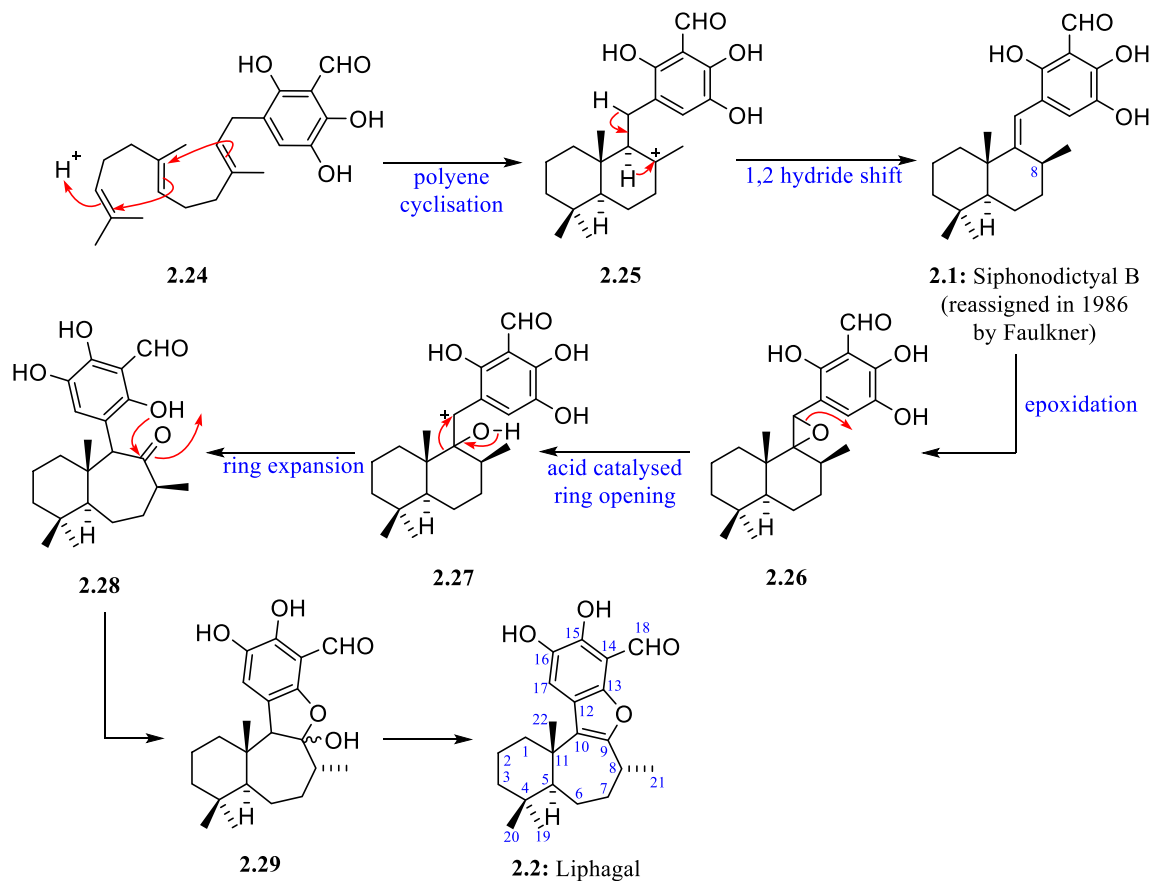
Scheme 2.2: Structural reassignment of siphonodictyal B, isolated with new meroterpenoids, siphonodictyals C – H (**2.18** – **2.23**), from the sea sponge *Aka coralliphagum* (*Siphonodictyon coralliphagum*) by Faulkner *et al*, 1986.

In 1986, Faulkner published a second article detailing the isolation and characterisation of new, structurally related meroterpenoids, siphonodictyals C – H (**2.18** – **2.23**), from *Aka coralliphaga* (*Siphonodictyon coralliphagum*). Within the same article, Faulkner and Sullivan re-examined their previous assignment of siphonodictyal B, which at the time, was assigned as structure **2.10** (scheme 2.2).^[98] Faulkner conceded that prediction of the aromatic proton signals was too crude to accurately assign the regio-configuration of the aromatic substituent of siphonodictyal B. With newly isolated samples, siphonodictyal B was dimethylated, to afford either **2.16** or **2.17**. Faulkner identified two NOESY correlations of the C22 aldehyde proton at δ 10.9 ppm with the C21 phenolic proton at δ 11.42 ppm, and the aliphatic C19 methoxy protons at δ 3.99 ppm. Irradiation of the C17 aromatic proton signal at δ 7.01 ppm caused an increase in intensity of the C15 olefinic proton at δ 6.13 ppm, and the second C18 aliphatic methoxy protons at δ 3.83 ppm; highlighting the proximity if all three protons to one another (scheme 2.2). From these NOESY studies, Faulkner concluded that the structure of the dimethoxy derivative must be **2.17**, and therefore, **2.1** was reassigned as the true structure of siphonodictyal B.

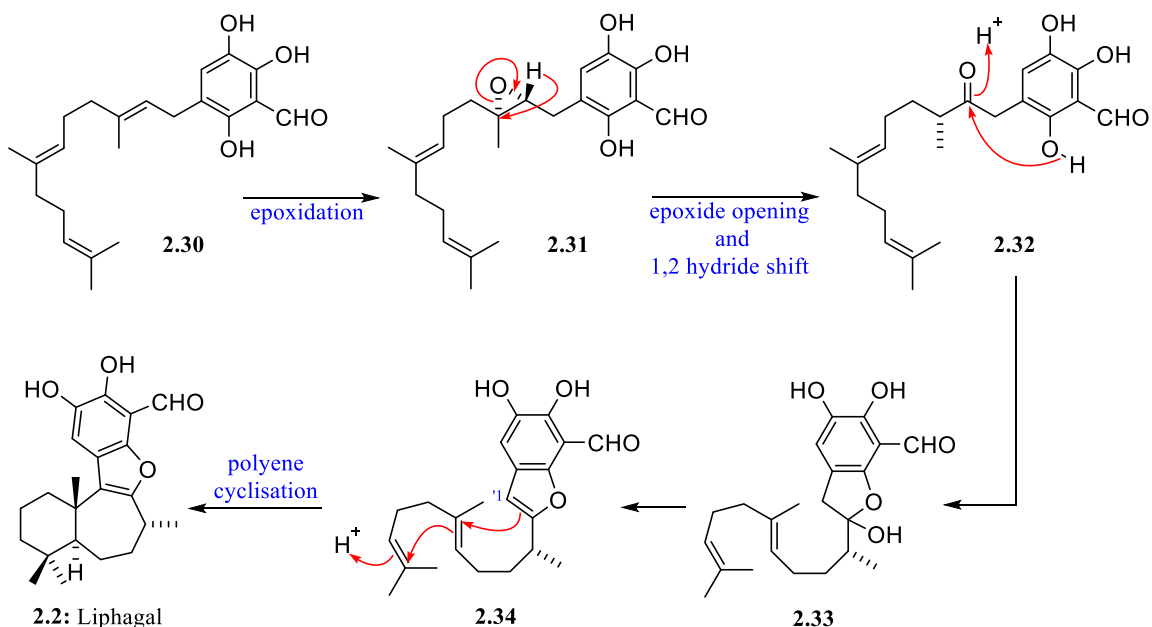
2.2.3 Isolation and Biosynthetic Proposal of Liphagal by Andersen *et al*

In 2006, Andersen isolated the meroterpenoid liphagal (**2.2**) (figure 2.1) from the same sea sponge, *Aka coralliphaga*, that Faulkner had previously isolated the siphonodictyals from (scheme 2.1 and 2.2).^[97–99] Andersen argued that liphagal (**2.2**) possessed structural similarities to siphonodictyal B (**2.1**) as indicated by NMR analysis, and consequently concluded that they may share a biosynthetic precursor. Andersen proposed two possible biosynthetic pathways for liphagal (**2.2**). The first route, *pathway A*, detailed the initial synthesis of siphonodictyal B (**2.1**) via a polyene cyclisation (**2.24**) and a subsequent 1,2-hydride shift (**2.25**) (scheme 2.3). Upon ring opening of the theorised siphonodictyal B epoxide **2.26**, a cationic initiated ring expansion and cyclisation cascade sequence would afford liphagal (**2.2**) in nature. Andersen's alternative biosynthetic *pathway B* detailed the biosynthesis of the liphagal framework via preformation of a benzofuran moiety (**2.34**). The heterocyclic oxygen of the theorised benzofuran intermediate **2.34** was envisioned to introduce significant electron density at C'1 **2.34**, which could facilitate a polyene cyclisation to obtain liphagal (**2.2**).

Pathway A



Pathway B



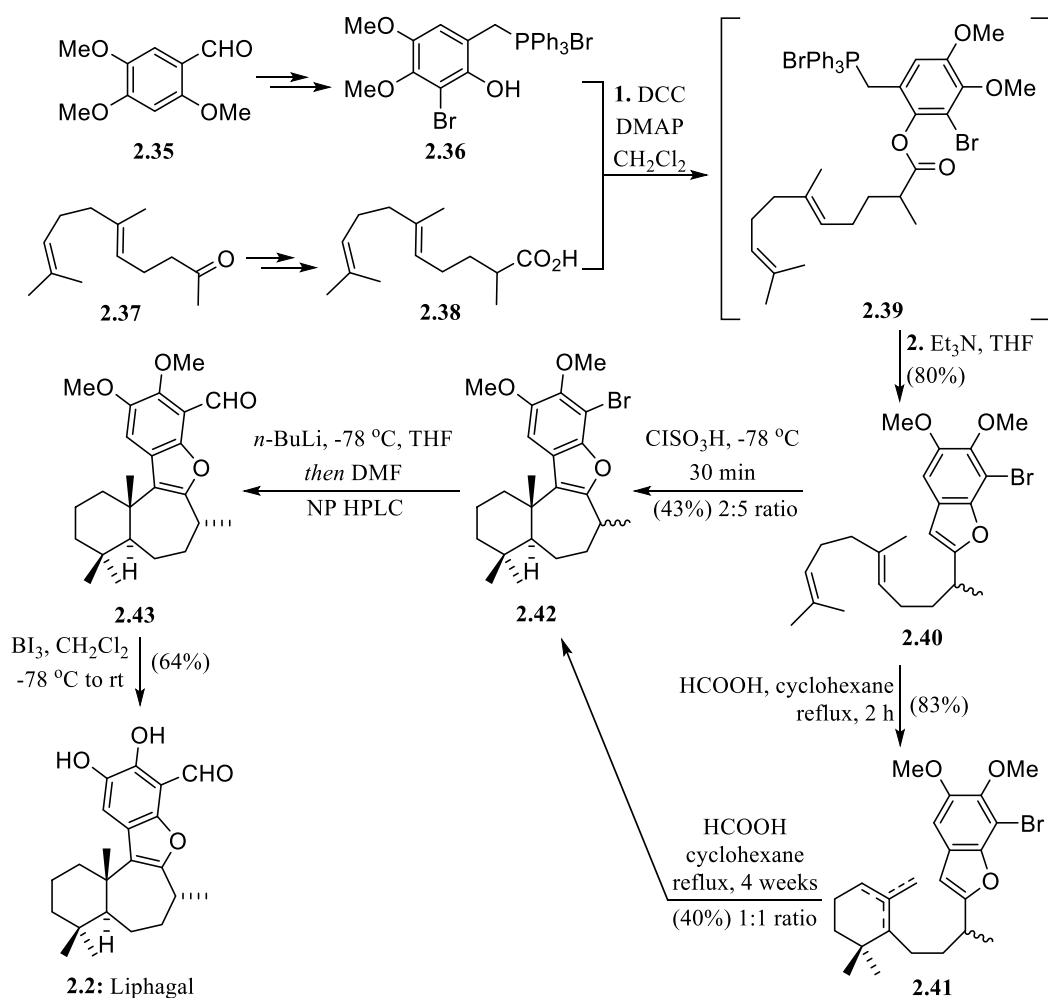
Scheme 2.3: Biosynthetic *pathway A* (top), proposed by Andersen, which details siphonodictyal B (2.1) as a biosynthetic precursor to liphagal (2.2). Alternative biosynthetic *pathway B* (bottom), proposed by Andersen, which details preformation of the benzofuran moiety 2.34, in the biosynthesis of liphagal (2.2).^[99]

2.3 Reported Biogenically Inspired Synthetic Methods for Liphagal, Siphonodictyal B & Corallidictyal D

At the time we were preparing our proposal (2014), there were eight reported syntheses of liphagal (**2.2**), four of which were biogenically inspired.^[101–104] Throughout the literature, the reported biogenically inspired syntheses of liphagal (**2.2**) were in accordance with one of the two biosynthetic pathways proposed by Anderson. Reported biogenically inspired syntheses based on Andersen's *pathway A*, detailed the preformation of a siphonodictyal B (**2.1**) backbone, which served as a scaffold for the synthesis of liphagal (**2.2**). Our proposal was fundamentally inspired by Andersen's *pathway A*. Alternatively, two reported total syntheses of liphagal (**2.2**), were in alignment with Andersen's *pathway B*, where the key biogenic step detailed an acid catalysed polyene cyclisation to afford the liphagane skeleton.

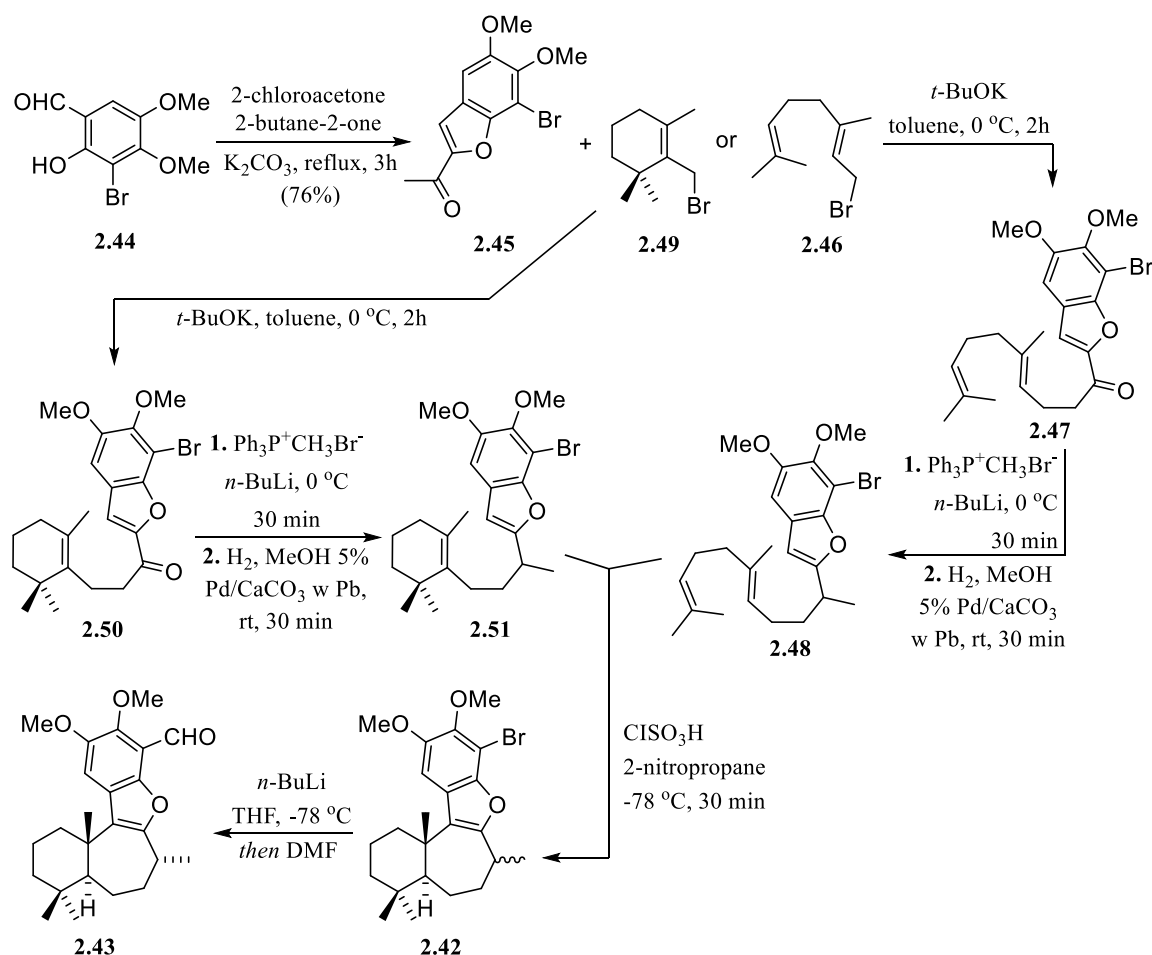
2.3.1 Literature Syntheses in Agreement with Anderson's Biosynthetic Pathway B

Within the same isolation article, Andersen reported the successful biogenically inspired synthesis of liphagal (**2.2**) in accordance with *pathway B* (scheme 2.4).^[99] Andersen's biogenically inspired method served, not only to provide significant validity for *pathway B*'s legitimacy as a biosynthetic pathway occurring in nature, but also to confirm the structural assignment of liphagal (**2.2**). Andersen's synthetic approach detailed the preformation of benzofuran **2.40**, which would serve to facilitate a polyene cyclisation directed by the heterocyclic oxygen, to afford the liphagane scaffold **2.42**. The key benzofuran polyene **2.40** was acquired via a one-pot, two-step ester coupling of aryl-Wittig salt **2.36** with carboxylic acid **2.38**, followed by a base catalysed intramolecular Wittig olefination of the *in situ* generated ester **2.39** (scheme 2.4). The key biomimetic polyene cyclisation was attempted upon heating **2.40** at reflux, in formic acid and cyclohexane. However, after 2 hours, only one six-membered ring had undergone cyclisation (**2.41**), and only after heating the reaction mixture for a further 4 weeks was the desired liphagane scaffold **2.42** afforded. Alternatively, cyclisation could be achieved within a reasonable time period by subjecting polyene **2.40** to chlorosulfonic acid in nitropropane to give **2.42**. Finally, formylation, purification via HPLC, and demethylation of **2.43** furnished liphagal (**2.2**). Although Andersen's biomimetic polyene cyclisation does grant validity to the proposed biosynthetic *pathway B*, the extremely slow rate of reaction under relatively mild acidic conditions (**2.40** to **2.41**, then **2.42**) highlights the unfavourable nature of the reaction.



Scheme 2.4: Andersen's polyene cyclisation *pathway B* biomimetic synthesis of liphagal (**2.2**).^[99]

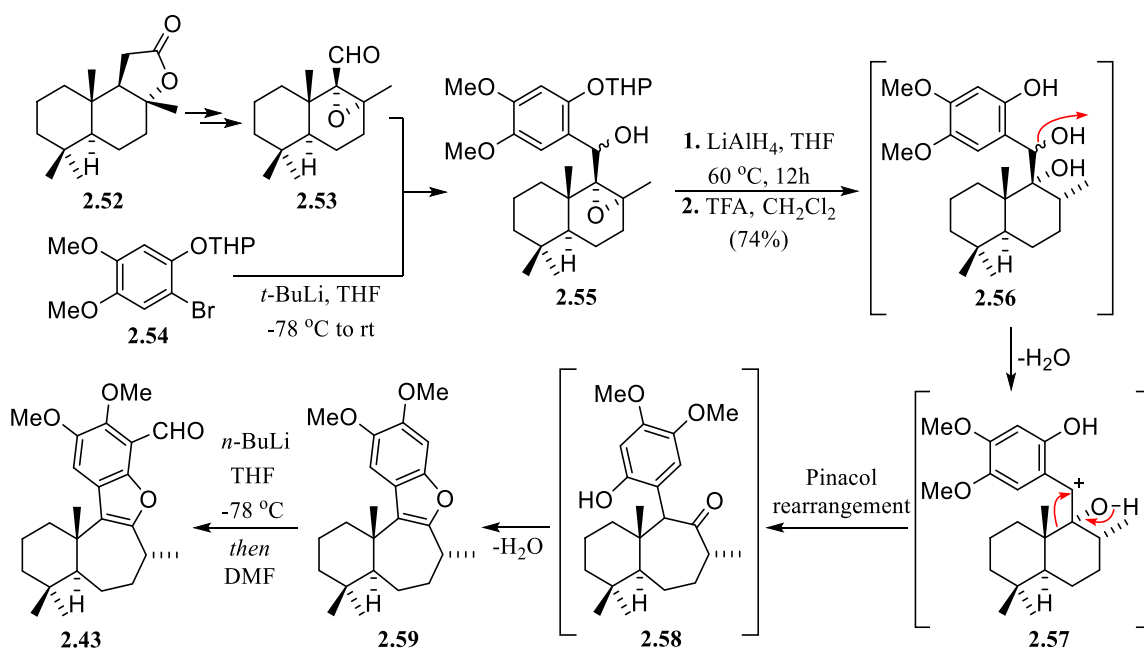
Further validity of Andersen's liphagal (**2.2**) proposal came with Mehta's biogenically inspired acid catalysed polyene cyclisation (scheme 2.5),^[105] inspired by biosynthetic *pathway B*. Mehta's approach mirrored Andersen's polyene pathway, while also investigated a preformed cycloalkene system. Benzofuran **2.45** was coupled with either geranyl bromide (**2.46**) or cyclogeranyl bromide **2.49** to give polyene **2.48** and cycloalkene **2.51** respectively. Both **2.47** and **2.50** were independently methylated via a Wittig olefination and selective hydrogenation, employing a lead poisoned palladium/ $CaCO_3$ catalyst, to afford **2.48** and **2.51** respectively. Geranyl benzofuranal bromide **2.48** was subjected to Andersen's optimised chosulfonic acid and 2-nitropropane conditions, which led to a polyene cyclisation, directed by the electron rich benzofuranal oxygen, to furnish the liphagane skeleton **2.42** in an unfavourable 1:2.5 epimeric ratio. Similarly, cyclogeranyl benzofuranal bromide **2.51** was cyclised under identical conditions, to afford **2.42** in the same unfavourable, 1:2.5 epimeric ratio. Finally, formylation and separation of the epimers gave methoxy liphagal precursor **2.43**, which concluded Mehta's formal biogenically inspired, *pathway B* synthesis of liphagal (**2.2**).



Scheme 2.5: Mehta's *pathway B* inspired biomimetic formal synthesis of liphagal (**2.2**).^[105]

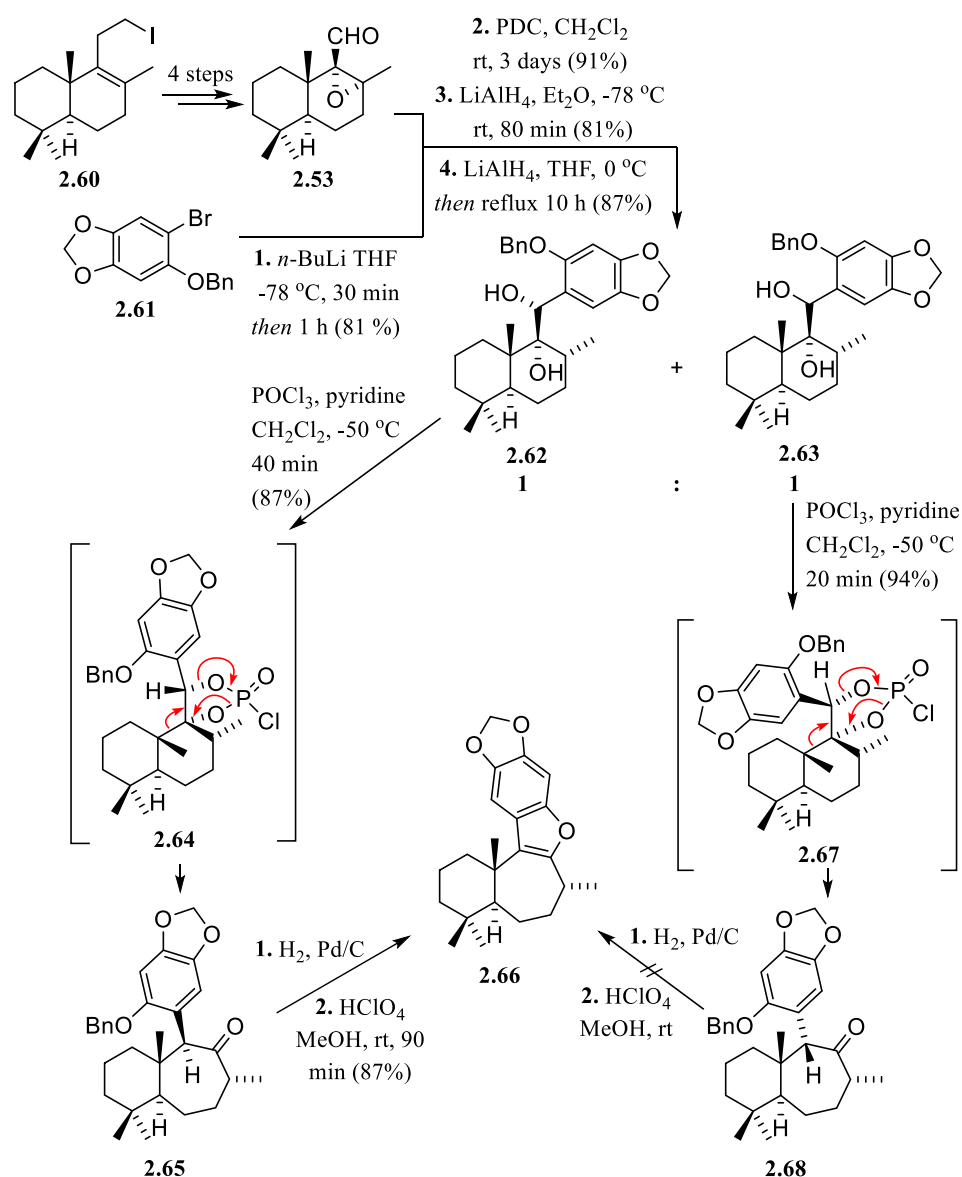
2.3.2 Literature Syntheses in Agreement with Anderson's Biosynthetic Pathway A

Baldwin and George reported a *pathway A* biogenically inspired formal synthesis of liphagal (**2.2**), founded in generating aromatic diol **2.56**, which was postulated to undergo a pinacol-like rearrangement to afford the liphagane scaffold **2.59** (scheme 2.6).^[106] Epoxy aldehyde **2.53** was coupled with aryl bromide **2.54** via a lithiation-bromide exchange with *t*-BuLi, to yield **2.55**. The afforded epoxy benzyl alcohol **2.55** was reduced, and the resulting crude diol was subjected to trifluoroacetic acid to facilitate a Pinacol-like cascade reaction (**2.56** – **2.58**). Upon THP deprotection of **2.55**, protonation of the afforded benzylic alcohol (**2.56**) was proposed to induce a ring expansion (**2.57** – **2.58**) via benzylic carbocation **2.57**. Following ring expansion (**2.58**), the theorised ketone intermediate **2.58** was suspected to proceed to the liphagane scaffold **2.59** via hemiacetal formation and dehydration. Finally, formylation of **2.59** concluded Baldwin and George's biogenically inspired formal synthesis of liphagal (**2.2**), highlighting the plausibility for the existence of *pathway A* in nature, in contrast to Andersen's and Mehta's polyene cyclisation methods.



Scheme 2.6: Baldwin and George's *pathway A* inspired biomimetic formal synthesis of liphagal (**2.2**), via a one-pot Pinacol-like rearrangement and subsequent ring expansion.^[106]

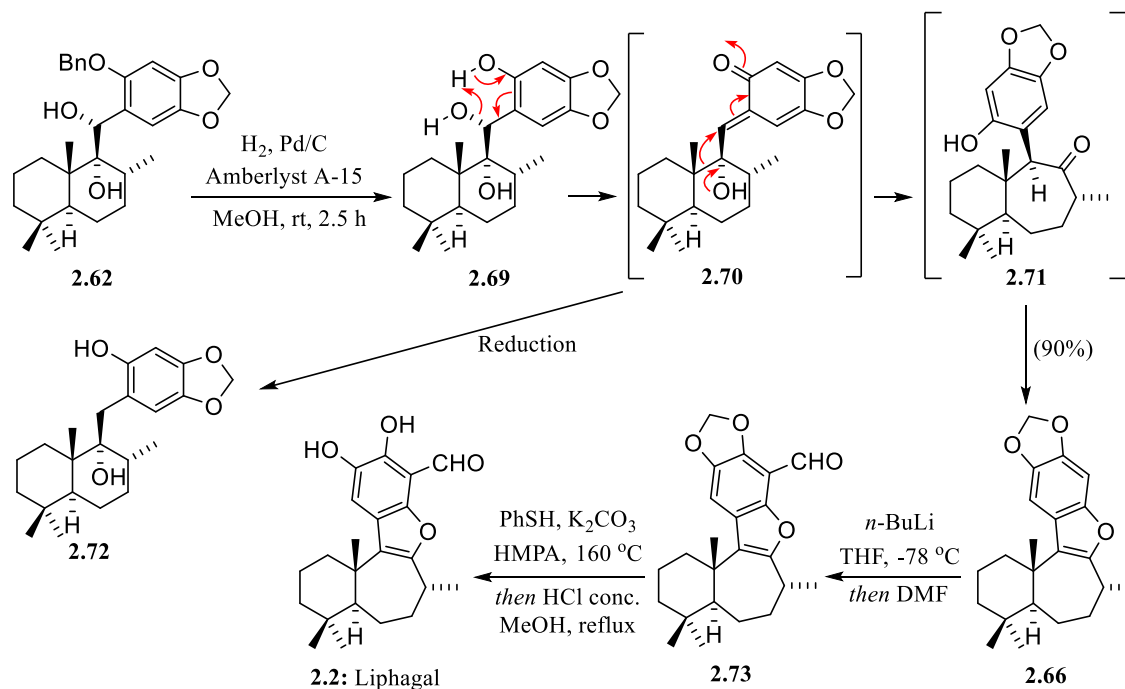
Inspired by Andersen's proposed biosynthetic *pathway A*, Alvarez-Manzaneda's biomimetic approach sought to initiate a one-pot, pinacol-like rearrangement, ring expansion, and intramolecular cyclisation to afford the liphagane skeleton **2.66** (scheme 2.7 and 2.8).^[107] The starting point of Alvarez-Manzaneda's route detailed coupling of epoxide **2.53** with aryl bromide **2.61**, followed by PDC facilitated oxidation and subsequent reduction with LiAlH_4 to obtain the desired diol, as a mixture of diastereomers **2.62** and **2.63** (scheme 2.7). Both diastereomers **2.62** & **2.63**, were separated, and individually subjected to POCl_3 in pyridine, which led to a Pinacol-like rearrangement and ring expansion (**2.64** & **2.67**) to give ketones **2.65** & **2.68** respectively. However, upon benzyl ether cleavage, via hydrogenation and subsequent treatment with perchloric acid, only ketone **2.65** was shown to undergo cyclisation to the liphagane tetracyclic skeleton **2.66**. Despite investigating various acidic conditions, Alvarez-Manzaneda failed to cyclise ketone **2.68** to **2.66** in any appreciable quantity.



Scheme 2.7: Alvarez-Manzaneda's *pathway A* inspired biomimetic synthesis of liphagal (**2.2**), via a PO_3Cl facilitated Pinacol-like rearrangement and subsequent ring expansion.^[107]

Alvarez-Manzaneda explored an alternative cyclisation route by subjecting **2.62** to a one-pot hydrogenation, in the presence of Amberlyst A15, which initiated a cascade reaction to afford liphagane skeleton **2.66**, via the proposed ring expanded ketone intermediate **2.71** (scheme 2.8). While optimising the reaction conditions, phenol **2.72** was isolated upon increasing the hydrogen pressure, while simultaneously decreasing the relative load of Amberlyst A15 to **2.62**. Based on the emergence of phenol **2.72**, Alvarez-Manzaneda proposed that the intermediate preceding the ring expansion was likely to be an *o*-QM (**2.70**), rather than a benzylic carbocation, which could be reduced upon a reduction in catalyst loading, in accordance with observations (scheme 2.8). Tetracycle **2.66** was formylated to **2.73** and demethenylated to concluded Alvarez-Manzaneda's biogenically inspired total

synthesis of liphagal (**2.2**), providing additional validity for the occurrence of biosynthetic *pathway A* in nature.



Scheme 2.8: Alvarez-Manzaneda's *pathway A* inspired biomimetic synthesis of liphagal (**2.2**), one-pot cascade Pinacol-like rearrangement via a proposed *ortho*quinone methide intermediate (**2.70**).^[107]

2.3.3 Isolation and Synthesis of the Structurally Related Meroterpenoids from *Aka coralliphaga*

Corallidictyals A (**2.3**) & B (**2.4**) were first isolated by Westly and co-workers from *Aka coralliphagum*, as an inseparable mixture in a 3:7 ratio respectively (figure 2.2).^[100] Westly postulated that corallidictyals A (**2.3**) & B (**2.4**) were conceivably interconverting in solution, by ring opening of the spirocycle via the phenolic oxygen. Westly heated an isolated sample of **2.3** & **2.4** at $100\text{ }^\circ\text{C}$ in DMSO-d_6 , so to observe evidence for interconversion of corallidictyals A (**2.3**) & B (**2.4**). However, the ratio of corallidictyals A (**2.3**) & B (**2.4**) did not change upon heating the samples, as observed by ^1H NMR analysis. In an attempt to generate the hypothesised phenolic anion, following a potential ring opening of the spirocycle moiety, NaOD was added to a sample of corallidictyals A (**2.3**) and B (**2.4**). However, no change in the ratio of spirocycles was observed, consistent with previous thermal isomerisation attempts. Thus, Westly concluded that corallidictyals A (**2.3**) and B (**2.4**) were in fact distinct, non-interchangeable spirocycles. Interestingly, the mixture of

natural products were found to be selective, mild inhibitors of protein kinase C, which has been identified as a broad yet viable target in treatment of malignant tumours.^[100]

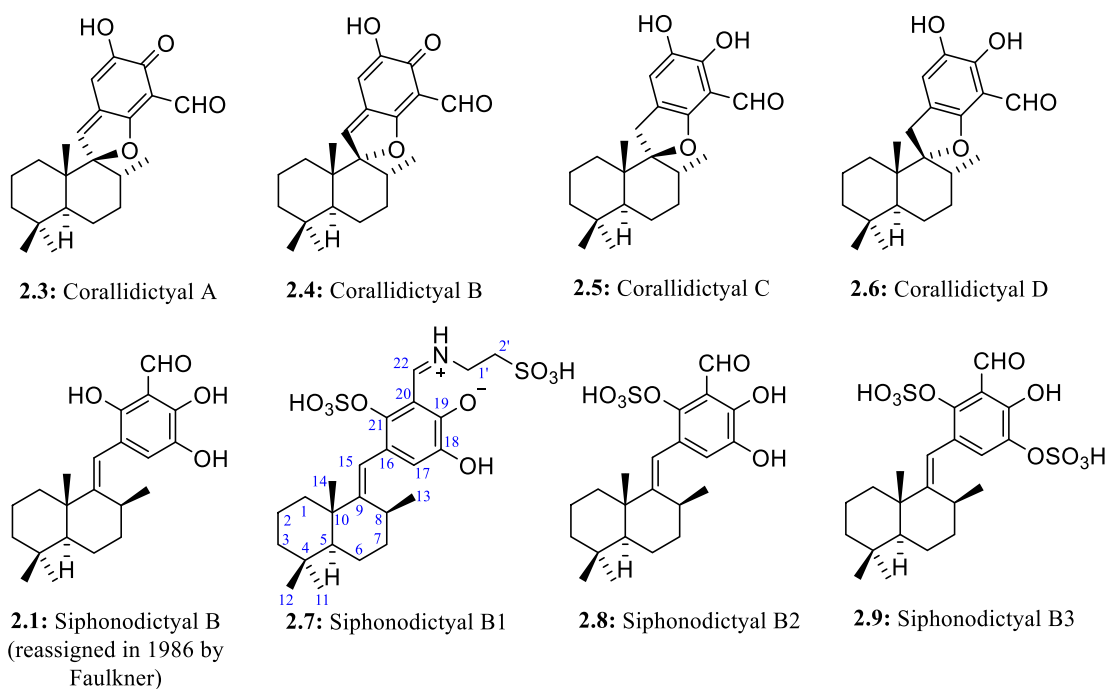


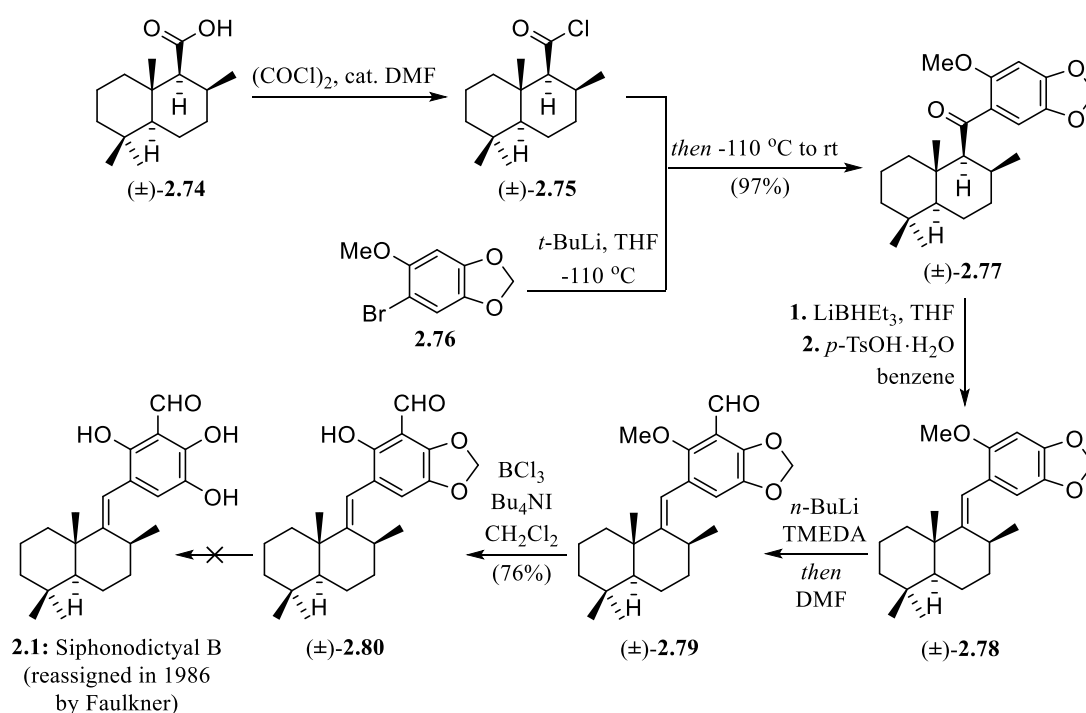
Figure 2.2: Isolation of corallidictyals A – D (2.3 – 2.6), and siphonodictyal B (2.1) and related siphonodictyal B analogues, B1 (2.7), B2 (2.8), B3 (2.9), isolated from the sea sponge *Aka coralliphagum* (*Siphonodictyon coralliphagum*)^[96,100]

In 2007, Köck *et al* isolated a series of meroterpenoids from *Aka coralliphagum*, all of which showed strong structural resemblance to siphonodictyal B (2.1) (figure 2.2).^[96] Siphonodictyal B2 (2.8) and B3 (2.9) were determined to be mono- and di-sulfate esters of siphonodictyal B (2.1) respectively. Siphonodictyal B1 (2.7) was found to be a mono-sulfate ester, akin to siphonodictyal B2 (2.8), which possessed a taurine iminium moiety in place of the aryl aldehyde at C22. Additionally, the previously undiscovered corallidictyals C (2.5) and D (2.6) were isolated, which upon NMR analysis, were revealed to be reduced analogues of the co-isolated corallidictyals A (2.3) and B (2.4). Köck found that the sulfated siphonodictyal B isomers (2.7 – 2.9) had little, to no antimicrobial activity, unlike siphonodictyal B (2.1). However, corallidictyals A – D (2.3 – 2.6) showed notable antimicrobial activity (gram -/+ bacteria, yeast and pathogenic fungi), while also displaying strong cytotoxic activity against L929 mouse fibroblast cell lines. The seemingly cytotoxic properties of corallidictyals A (2.3) & B (2.4) appears to be most likely due to the *p*-QM, aryl aldehyde and phenolic moieties. Although, the corallidictyals C (2.5) & D (2.4) lack the hypothetically cytotoxic *p*-QM moiety, they may readily undergo oxidation, which in tandem with the aldehyde substituent, could be the source of their cytotoxic properties. Thus,

the putative reactive moieties of corallidictyals and siphonodictyals may elucidate the meroterpenoids seemingly broad spectrum, non-selective cytotoxic mechanism of action.

2.3.4 Literature Syntheses of Siphonodictyal B and Corallidictyal D

At the time of our proposal formulation (2014), there was one reported attempted synthesis of siphonodictyal B (**2.1**).

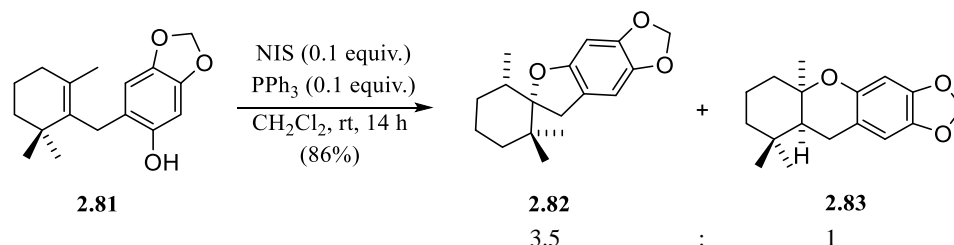


Scheme 2.9: Attempted synthesis of siphonodictyal B (**2.1**) by Seifert *et al.*^[108]

Seifert *et al* were the first to report an attempted synthesis of siphonodictyal B (**2.1**), which detailed a coupling approach of a lithiated aryl bromide (**2.76**) with an acyl chloride (**2.75**) to obtain the desired siphonodictyal scaffold (**2.77**) (scheme 2.9).^[108] (±)-Drimanic acid (**2.74**) served as a starting point in Seifert's route, which could be readily converted to the acyl chloride **2.75** upon treatment with oxalyl chloride and a catalytic quantity of DMF. Upon investigating a suitable aryl bromide coupling partner, large protecting groups, such as benzyloxy, were found to considerably decrease the coupling yields. Therefore **2.76** was chosen as a suitable aryl coupling partner due to the small size of protecting groups, which ensured the siphonodictyal scaffold (**2.77**) could be afforded in good yield. The afforded ketone **2.77**, which was subsequently reduced, and the resulting benzyl alcohol was eliminated to give the desired aryl alkene **2.78**. *ortho*-Lithiation of **2.78**, followed by quenching with DMF gave aryl aldehyde **2.79**, and deprotection of the methoxy protecting group gave the demethylated precursor **2.80**. However, despite investigating a wide variety of strong Lewis and Brønsted acids, the methylenedioxy protecting group proved too

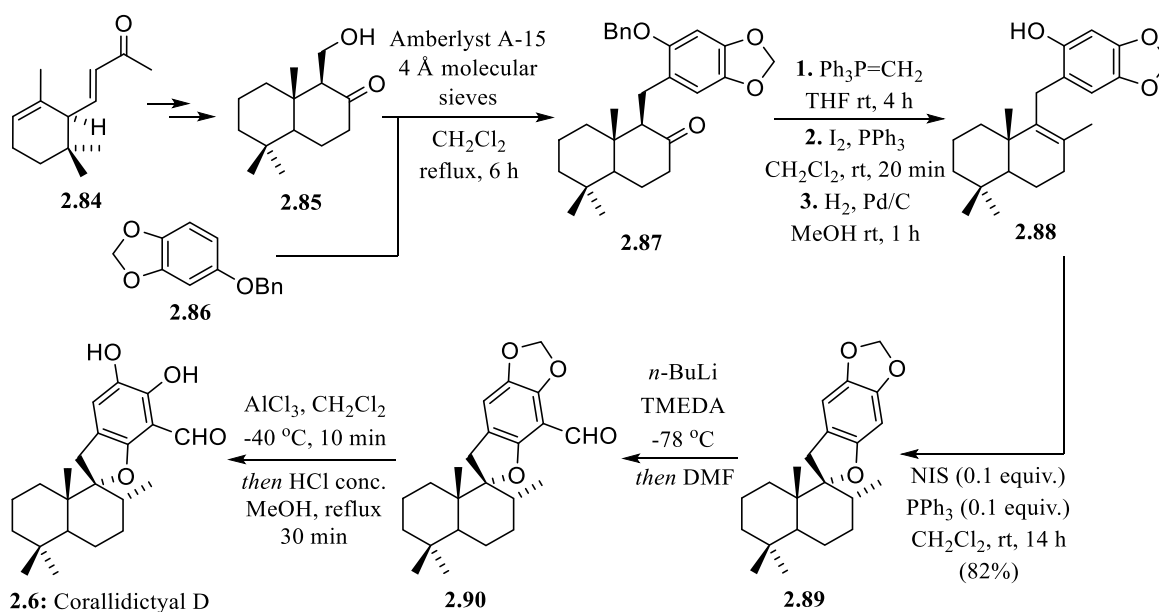
resistant to be removed, which concluded Seifert's attempted synthesis of siphonodictyal B (**2.1**).

At the time of preparation of our proposal (2014), there was one reported total synthesis of corallidictyal D (**2.6**).



Scheme 2.10: Novel spirocyclisation via NIS and PPh₃ by Alvarez-Manzaneda *et al.*^[109]

Alvarez-Manzaneda *et al* reported the first total synthesis of corallidictyal D (**2.6**) in 2013, via a catalytic spirocyclisation with catalytic *N*-iodosuccinimide and triphenylphosphine. The key spirocyclisation step was modeled on a simplified *o*-(β -cyclogeranyl) phenol **2.81** system, to afford the spirocycle **2.82** and tetracycle **2.83** (scheme 2.10).^[109]



Scheme 2.11: Total synthesis of corallidictyal D (**2.6**) by Alvarez-Manzaneda *et al.*^[109]

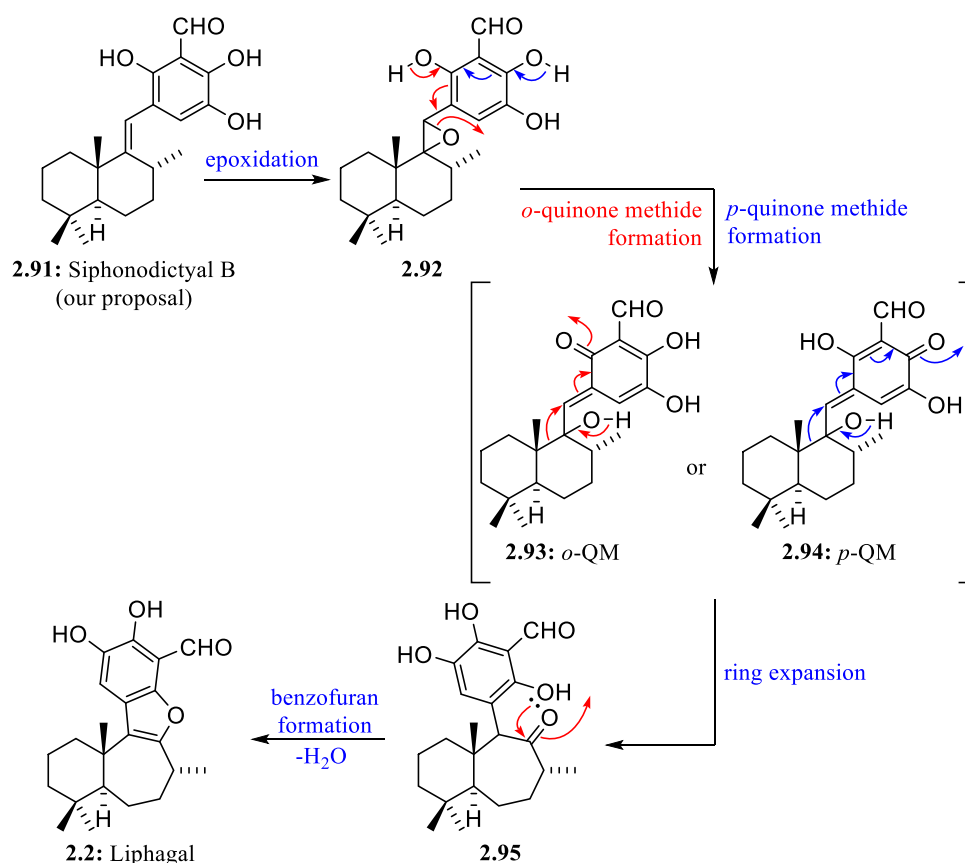
Starting from α -ionone (**2.84**), hydroxy ketone **2.85** was synthesised over 5 steps, followed by arylation with protected ether **2.86** in the presence of the cationic resin, Amberlyst (A-15) (scheme 2.11). The afforded coupled ketone **2.87** was subjected to Wittig olefinic methenylation, followed by alkene isomerisation and selective hydrogenation to furnish the key desired phenol **2.88**. Phenol **2.88** was subjected to Alvarez-Manzaneda's optimised spirocyclisation conditions with catalytic *N*-iodosuccinimide and triphenylphosphine to afford corallidictyal D skeleton **2.89**, as the exclusive isomer. Alvarez-Manzaneda

speculated that in order to achieve exclusive stereoselectivity, the mechanism must involve an *anti*-facial, concerted attack of the *endo*-alkene **2.88**, thereby, precluding the formation of a carbocation intermediate. **2.89** was subjected to *ortho*-lithiation and quenching with DMF to install the aryl aldehyde moiety. Finally, aryl aldehyde **2.90** was demethenylated with AlCl₃, and upon addition of a methanolic solution of HCl, enantiopure corallidictyal D (**2.6**) was afforded (scheme 2.11).

2.4 Our Divergent Biosynthetic Proposal

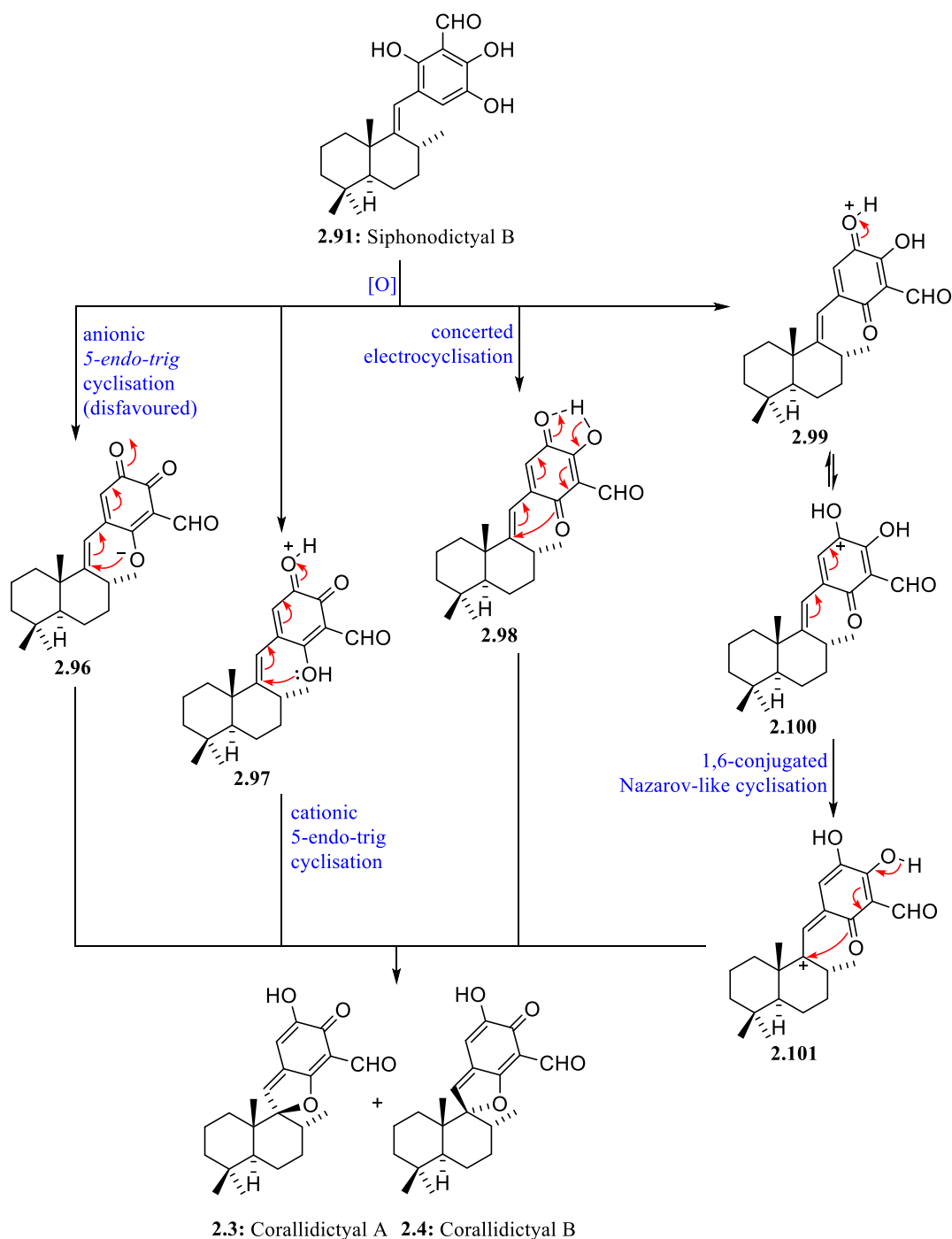
We propose that 8-*epi*-siphonodictyal B (**2.91**), which is the C8 epimer of Faulkner's assignment (**2.1**), is the true configuration of siphonodictyal B. Additionally, we hypothesise that under a divergent biosynthetic pathway, our proposed reassigned configuration of siphonodictyal B (**2.91**) is the biogenic precursor to liphagal (**2.2**), 8-*epi*-siphonodictyals B1 - B3 (**2.106** – **2.108**) and corallidictyals A - D (**2.3** - **2.6**), all of which consequently possess a singular biological origin in nature (scheme 2.15). The proposed biosynthetic *pathway A* to liphagal (**2.2**) from siphonodictyal B (**2.1**), as proposed by Andersen *et al* (scheme 2.3), does appear plausible with the exception of the a C8 epimerisation event.^[99] Our scepticism towards Andersen's proposed epimerisation event is founded in the unlikelihood that the shared C8 stereoconfiguration between liphagal (**2.2**) and the corallidictyals A - D (**2.3** - **2.6**) (which were assigned independently of one another) is purely coincidental.^[96,99,100] Furthermore, the stereochemical assignment of siphonodictyals B1 - B3 (**2.7** – **2.9**) was based upon NMR studies and in accordance to the configuration of siphonodictyal B (**2.1**) postulated by Faulkner. Thus, the C8 stereochemical configuration of siphonodictyal B (**2.1**) and siphonodictyals B1 - B3 (**2.7** – **2.9**) was not re-examined by Köck (figure 2.1 or 2.2).^[96] As no C8 epimers of siphonodictyal B (**2.1**), liphagal (**2.2**) and corallidictyals A - D (**2.3** - **2.6**) have been isolated from natural samples to date, and if we assume Andersen's *pathway A* to be valid, then the proposed epimerisation event must be catalysed by dedicated substrate-specific enzyme/s in order for *pathway A* to be plausible. The requirement of substrate-specific enzymes would introduce unnecessary complexity and further convolute a given biosynthetic pathway. Therefore, the introduction of substrate-specific enzymes would appear to only waste resources if the end products did not provide a specific advantage to the host. A divergent biosynthetic pathway would be favoured over multiple linear biosynthetic pathways that would give rise to liphagal (**2.2**) and the corallidictyals A - D (**2.3** – **2.6**), as the latter route would require multiple enzymes, resulting in a more convoluted pathway to the meroterpenoids than appears necessary.

A divergent, non-enzymatically mediated biosynthetic pathway would appear to be the simplest explanation and would satisfy the minimalist concept defined by *Occam's razor* (or *Ockham's razor*), where upon two differing explanations, the proposal that requires the least necessary assumptions is presumed to be the correct one. Simply stated, if there is no selective pressure to create multiple pathways for say 'X' natural products, in preference to a singular pathway that can diverge to give the same number of 'X' natural products, then the likelihood of multiple biosynthetic pathways emerging is improbable. Thus, the introduction of epimerisation enzymes and multiple discrete biosynthetic pathways for seemingly related natural products appears to overly convolute the biosynthetic origins of this family of meroterpenoids. Faulkner's assignment of siphonodictyal B (**2.1**), regarding the C8 methyl substituent, requires that Anderson's proposed *pathway A* to liphagal (**2.2**) be unnecessarily convoluted. Therefore, a potential miss-assignment of the C8 methyl substituent of siphonodictyal B (**2.1**) by Faulkner, would appear to resolve the proposed obstacles acknowledged by Andersen without the introduction of specific epimerisation enzymes into the biosynthetic pathway to liphagal (**2.2**).



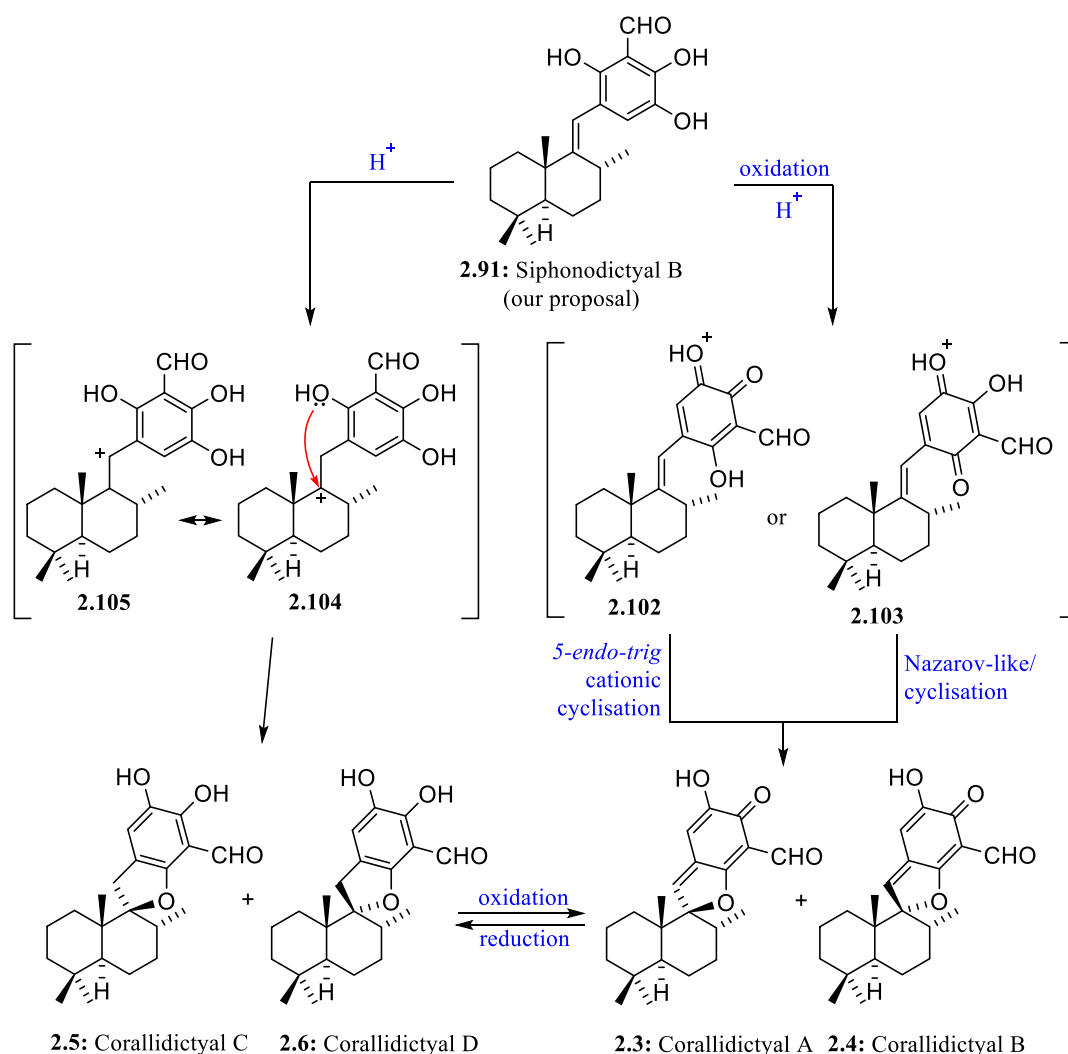
Scheme 2.12: Our *pathway A* inspired biosynthetic proposal for liphagal (**2.2**) from our proposed reassigned siphonodictyal B **2.91** via an *o*-QM **2.93** or a *p*-QM **2.94**.

In regard to the biosynthesis of liphagal (**2.2**), we propose that the theoretical ring expansion, as detailed in Andersen's *pathway A* proposal (scheme 2.3), may proceed by either *o*-QM **2.93** or *p*-QM **2.94**. Both *o*-QM **2.93** or *p*-QM **2.94** may serve as more favourable intermediates than the proposed benzylic carbocation **2.27** following the theorised epoxide ring opening event (**2.92**) (scheme 2.12).^[44,60,84,110] Conceivably, corallidictyals A – D (**2.3** – **2.6**) could be accessed from siphonodictyal B **2.91** directly. Furthermore, the family of corallidictyals A B (**2.3** – **2.4**) may also be derived in nature from corallidictyals C & D (**2.5** & **2.6**) and *vice versa*, via REDOX reactions (scheme 2.13 and 2.14).



Scheme 2.13: Our biosynthetic proposal for corallidictyals A & B (**2.3** & **2.4**).

We hypothesise that corallidictyals A & B (**2.3** & **2.4**) could be accessed in nature via the oxidation of siphonidictyal B **2.91** to either *ortho*-quinone (**2.96** or **2.97**) or *para*-quinone (**2.98** or **2.99**) (scheme 2.13). The proposed *ortho*-quinone **2.96** may be envisioned to undergo an anionic *5-endo-trig* cyclisation to afford corallidictyals A & B (**2.3** & **2.4**). However, anionic *5-endo-trig* cyclisations are disfavoured according to Baldwin's rules, and hence, if such a route to corallidictyals A & B (**2.3** & **2.4**) does occur, it may proceed if no other alternative reaction pathway is available.^[111,112] Although Baldwin's rules are stated to apply beyond radical and nucleophilic ring closures to both homolytic and cationic processes, exceptions to these conjugate cationic *5-endo-trig* cyclisations have been extensively reported throughout the literature.^[11,113–115] Therefore, Baldwin's rules do not appear to apply in their entirety to cationic species, which Baldwin does acknowledge, leaving us to speculate that a *5-endo-trig* spirocyclisation of the protonated oxygenic moiety of quinone **2.97**, may in fact be a viable mechanism for the biosynthesis of corallidictyals A & B (**2.3** & **2.4**) in nature.



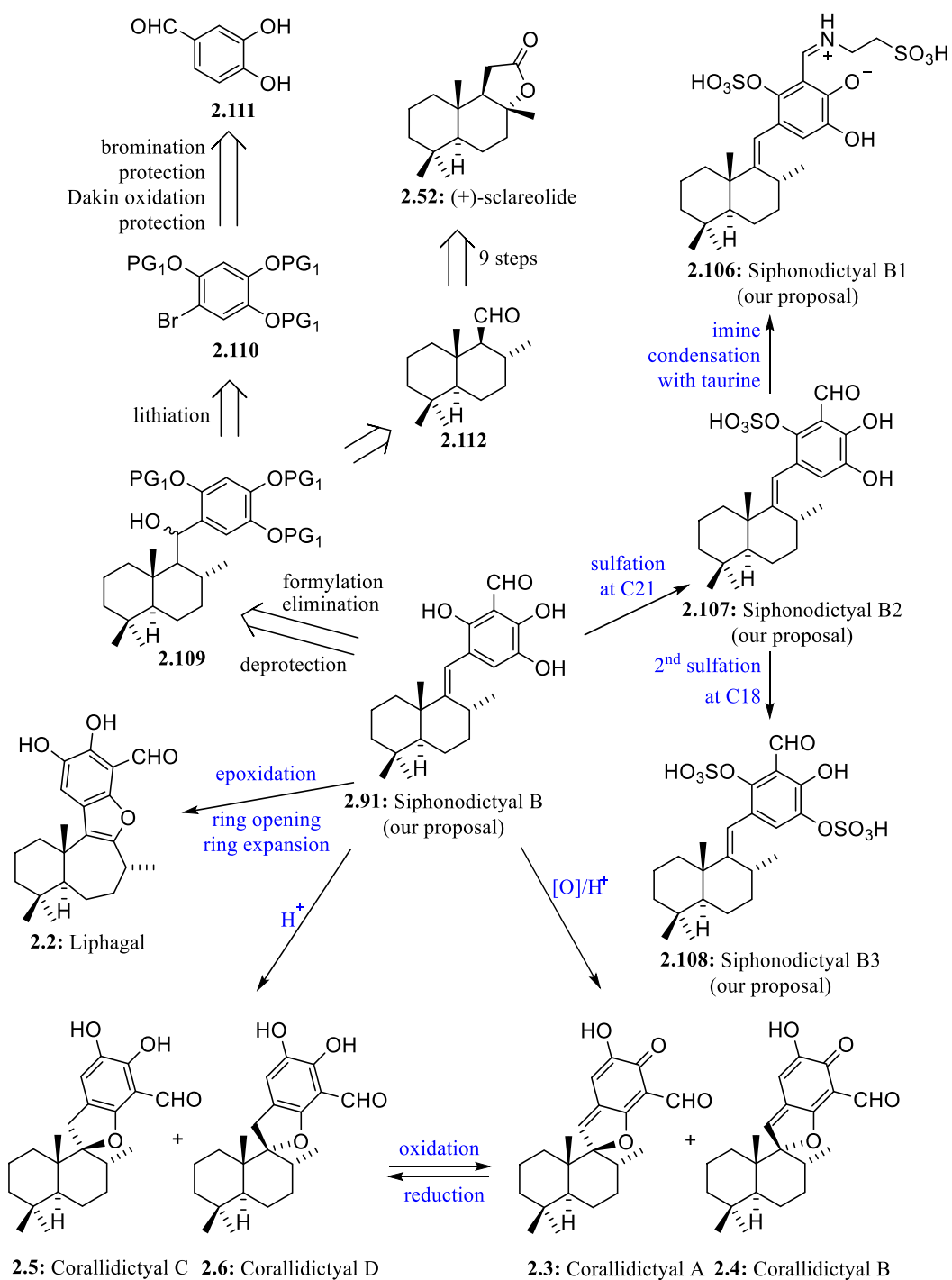
Scheme 2.14: Our biosynthetic proposal for corallidictyals A – B (**2.3** – **2.6**).

Plausible alternative oxidative pathways to corallidictyals A & B (**2.3** & **2.4**) may proceed via a *para*-quinone intermediate (**2.98** or **2.99**), where a concerted electrocyclization (**2.98**) or a step-wise cyclisation akin to a Nazarov reaction may occur (**2.99** to **2.101**) (scheme 2.13).^[116,117] Corallidictyals C & D (**2.5** & **2.6**) may be acquired directly from siphonodictyal B **2.91** by either a Brønsted or Lewis acid mediated cyclisation via trapping of tertiary carbocation **2.104** by the phenolic oxygen (scheme 2.14). Finally, we propose that under mild REDOX conditions, such as those found within cells, corallidictyals A & B (**2.3** & **2.4**) may be reversibly oxidised to corallidictyals C & D (**2.5** & **2.6**) and back to **2.3** & **2.4** under reductive conditions.

2.4.1 Retro-Synthetic Analysis

As we have proposed that the true stereoconfiguration of siphonodictyal B is **2.91** and not **2.1**, our proposal must also involve the reassignment of siphonodictyals B1 - B3 **2.7** – **2.9** to **2.106** – **2.108** in accordance with our hypothesis (scheme 2.15). Biosynthesis of 8-*epi*-siphonodictyals B1 - B3 (**2.106** – **2.108**), as through the lens of our proposal, can be envisioned by a selective sulfonation at C21, resulting in siphonodictyal B2 **2.107**, while an additional sulfonation at C18 would yield siphonodictyal B3 **2.108**. As siphonodictyal B1 **2.106** possesses an imine sulfonic acid moiety at C22, its biosynthesis in nature may proceed via an imine condensation of siphonodictyal B2 **2.107** with 2-aminoethanesulfonic acid, a ubiquitous biological substrate known colloquially as ‘taurine’ (scheme 2.15).

We set out to synthesise our proposed reassigned C8 epimeric configuration of siphonodictyal B **2.91** and upon its acquisition, to compare the characterisation data to that of the natural sample isolated by Faulkner (scheme 2.15).^[97,98] Upon the anticipated successful synthesis and reassignment of siphonodictyal B **2.91**, we sought to investigate our divergent biogenically inspired hypothesis, by synthesising liphagal (**2.2**), corallidictyals A – D (**2.3** – **2.6**) and siphonodictyals B1 – B3 (**2.106** – **2.108**) from siphonodictyal B **2.91** (scheme 2.15). Retrosynthetic analysis of siphonodictyal B **2.91** led us to envision direct access through a sequential elimination, formylation and global deprotection, from benzyl alcohol **2.109**. The most direct route to benzyl alcohol **2.109** appeared to be through an aryl lithiated coupling of aryl bromide **2.110** with aldehyde **2.112**, where aryl bromide **2.110** could be accessed from 2,3-dihydroxybenzaldehyde **2.111**, and aldehyde **2.112** could be synthesised from (+)-sclareolide **2.52** (scheme 2.15).



Scheme 2.15: Retrosynthetic analysis of our proposed reassignment of siphonodictyal B **2.91**, and the naturally derived analogues, siphonodictyal B1 – B3 (**2.106** – **2.108**), under our divergent synthetic proposal for meroterpenoids from *Aka coralliphagum*.

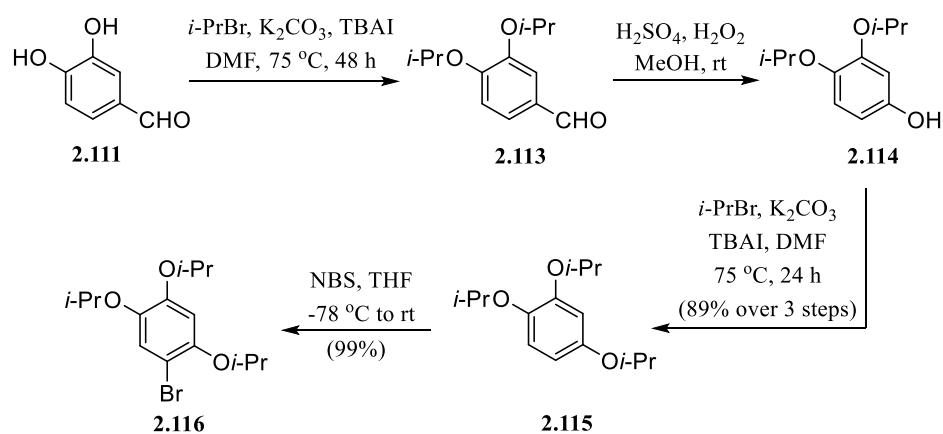
2.5 Pursuit of Siphonodictyal B

Our priority was to synthesis the siphonodictyal B epimer **2.91** in accordance with our proposal (scheme 2.15), by way of a convergent approach; we sought to synthesise and couple the globally protected aryl bromide **2.110** with aldehyde **2.112** via a bromide-lithium exchange to obtain benzyl alcohol **2.109**.

2.5.1 Synthesis of Aryl Bromide 2.116

We set out to synthesise an aryl bromide that could be globally deprotected, so as to minimise functional group manipulations. Any protecting group chosen would need to be resistant to a variety of harsh conditions, while also labile enough to be removed under relatively mild conditions, as the foreseen conjugated alkene moiety of siphonodictyal B **2.91** was expected to be sensitive to strong acidic conditions. Benzyl ether protecting groups were not chosen as they were predicted to have been too difficult to remove under hydrogenating conditions in the presence of the conjugated alkenyl moiety. Additionally, benzyl ether protecting groups had previously introduced issues during bromide-lithium couplings as observed by Seifert in the attempted to synthesise siphonodictyal B (**2.1**), most likely due to unfavourable steric interactions.^[108] For these reasons, *iso*-propoxy ether protecting groups were chosen as they are more labile in comparison to methoxy ethers, while still possessing a good degree of stability under a large array of harsh conditions.^[106]

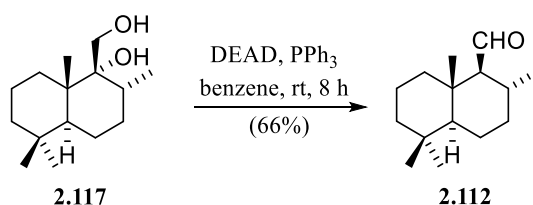
2,3-dihydroxybenzaldehyde (**2.111**) was chosen as our starting point in the synthesis of aryl bromide coupling partner **2.116** (scheme 2.16). Di-protection of **2.111** with 2-bromopropane, in the presence of tetrabutylammonium iodide, gave di-*iso*-propoxy ether benzaldehyde **2.113**, and was of sufficient purity to be used without further purification following an extensive workup.^[118] Oxidation of protected aldehyde **2.113** to phenol **2.114** was achieved following an acidic Dakin oxidation procedure,^[118,119] again, of sufficient purity without the need for a formal purification procedure. Next, protection of phenol **2.114** was achieved with 2-bromopropane and TBAI in DMF to afford the globally protected aryl tris-*iso*-propoxy ether **2.115** in a yield of 89% over 3 steps from 2,3-dihydroxybenzaldehyde (**2.111**). Finally, treatment of tris-*iso*-propoxy ether **2.115** with NBS in THF at -78 °C, followed by warming to room temperature gave the desired protected aryl bromide **2.116** as a single regioisomer.^[120] With the desired aryl bromide **2.116** in hand, we turned our attention to synthesising the aldehyde coupling precursor **2.112**.



Scheme 2.16: Synthesis of aryl bromide **2.116**.^[118–120]

2.5.2 Synthesis of Aldehyde **2.112**

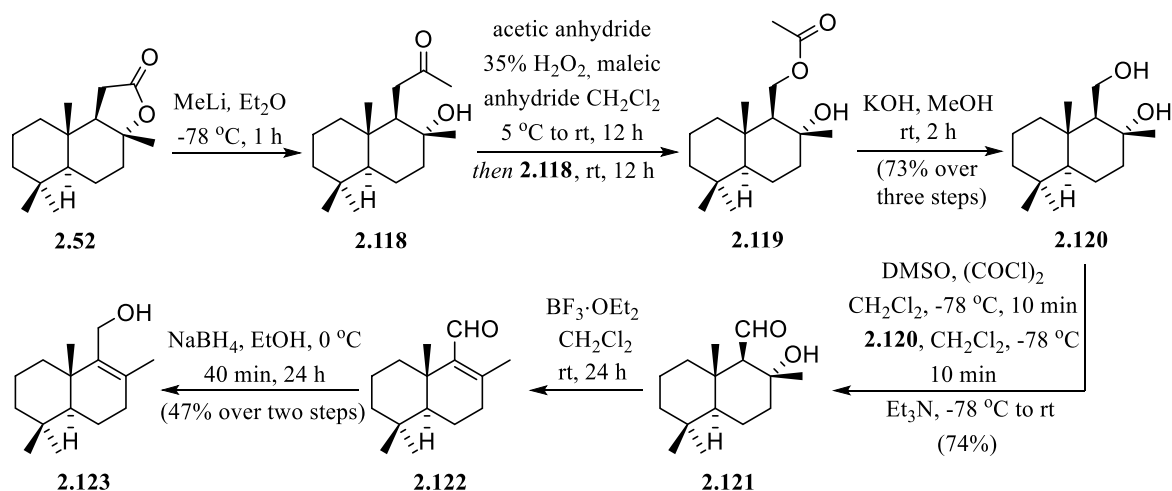
Our synthetic route to aldehyde **2.112** was based upon a methodology paper by Barrero and Alvarez-Manzaneda *et al*, which investigated the conversion of 1,2-diols to carbonyl compounds under Mitsunobu conditions (scheme 2.17).^[121] Specifically, what caught our attention was the conversion of a 1,2-diol sesquiterpene **2.117** to our desired aldehyde **2.112**. Access to the necessary diol **2.117** was foreseen via a reduction of a literature epoxide, following a series of well-established literature procedures.^[106,122–124]



Scheme 2.17: Preparation of carbonyls from 1,2-diols via Mitsunobu conditions, by Barrero *et al*.^[121]

(+)-Sclareolide **2.52** represented the starting point in our pursuit of aldehyde **2.112**, as an enantiopure, relatively cheap and accessible starting material (scheme 2.18). Following a modified three-step protocol to diol **2.120**, discovered by Kuchkova and refined by Sudhakarrao, treatment of (+)-sclareolide **2.52** with MeLi gave ketone **2.118** via alkylation of the lactone moiety.^[122,123] **2.118** was subsequently oxidised under Baeyer-Villiger conditions to yield the acetate **2.119** and then subjected to basic hydrolysis to afford diol **2.120** in a yield of 73% over 3 steps.^[122,123] In order to eliminate the tertiary alcohol to obtain the quaternary alkene **2.123**, oxidation of the primary alcohol of **2.120** to aldehyde **2.121** was required to direct the proceeding elimination, which was achieved under Swern oxidative conditions. The newly formed aldehyde moiety of **2.121** was found to direct the subsequent $\text{BF}_3 \cdot \text{OEt}_2$ mediated elimination, to the conjugated alkenyl-aldehyde **2.122**.

Finally, **2.122** was reduced to alcohol **2.123**, in preparation of the Sharpless epoxidation (scheme 2.18).^[124]

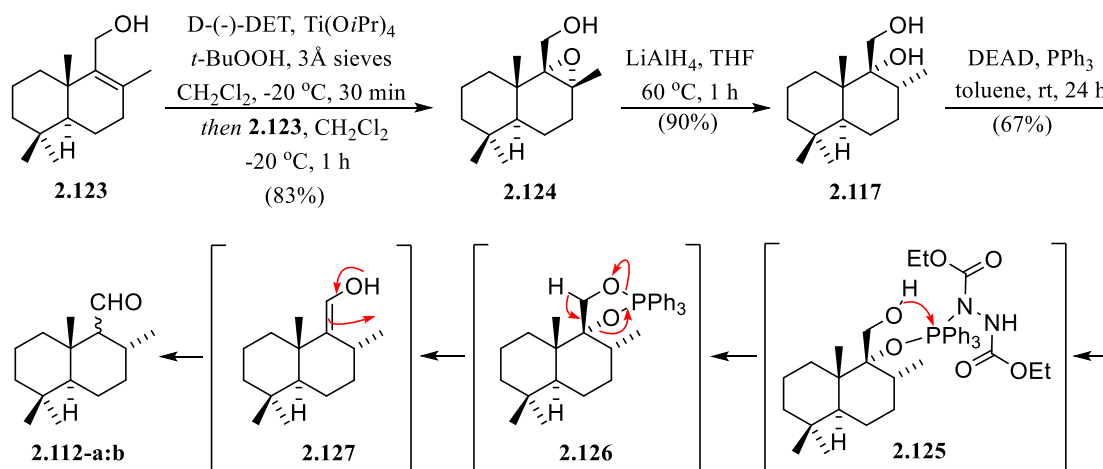


Scheme 2.18: Synthesis of aldehyde coupling precursor **2.112**.^[122–124]

In pursuit of 1,2-diol **2.117**, Sharpless stereoselective epoxidation with the chiral unnatural ligand, D-(-)-diethyl tartrate, gave the desired epoxide **2.124** (scheme 2.19).^[125,126] The stereoconfiguration of epoxide **2.124** was verified by comparison of the obtained spectroscopic data with that of the reported literature spectra, without any notable formation of the undesired stereoisomer. Finally, reduction with LiAlH₄ in THF while heating afforded 1,2-diol **2.117** in good yield, allowing us to proceed in the investigation of Barrero's Mitsunobu-like facilitated rearrangement of diol **2.117** to the desired aldehyde **2.112**.

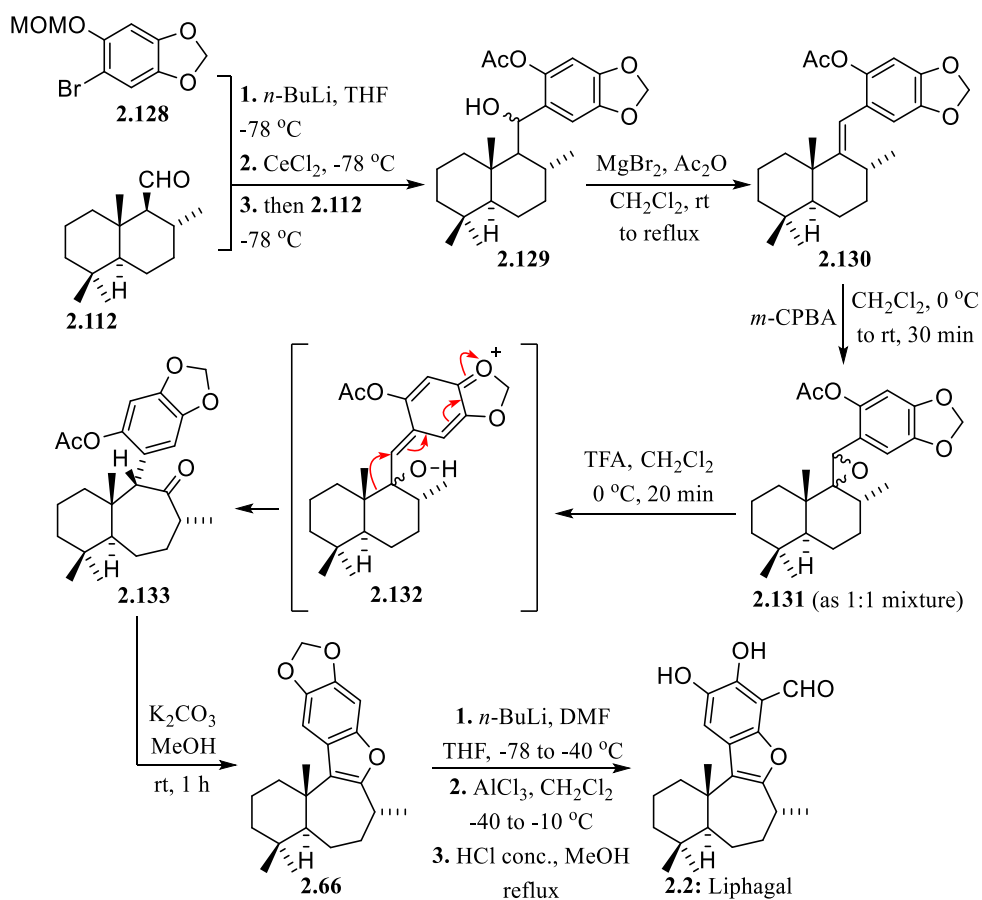
Upon treatment of 1,2-diol **2.117** with diethyl azodicarboxylate (DEAD) and PPh₃, under standard Mitsunobu's conditions, the desired aldehyde was isolated as a pair of stereoisomers **2.112-a:b**, and not as a single diastereomer as reported by Barrero *et al* (scheme 2.19).^[121] Following the hypothesised formation of intermediate **2.125**, the proposed spontaneous rearrangement of **2.126** may have afforded enol ether **2.127**. The proposed *in situ* enol ether **2.127** could then undergo tautomerization to the more stable aldehyde **2.112**, thereby rationalising the observed loss of stereochemical information inherent to diol **2.117**. The loss of stereochemical information was not regarded an issue, as the anticipated coupling of aldehyde **2.112-a:b** with aryl bromide **2.116** and subsequent elimination would afford the desired siphonodictyal B **2.91** carbon skeleton, as envisioned. However, increasing the reaction scale to obtain synthetically useful quantities of aldehyde epimers **2.112-a:b** proved unexpectedly difficult, as multiple tedious workups were required due to the formation of an insoluble gum-like by-product, which resulted in unacceptable product loss. As unresolvable difficulties encountered from Barrero's

Mitsunobu diol rearrangement resulted in the failure to obtain synthetically useful quantities of aldehyde **2.112-a:b**, we set out to synthesise aldehyde **2.112** via an alternative route.



Scheme 2.19: Synthesis of aldehyde epimers **2.112-a:b** via Mitsunobu conditions.^[121,125,126]

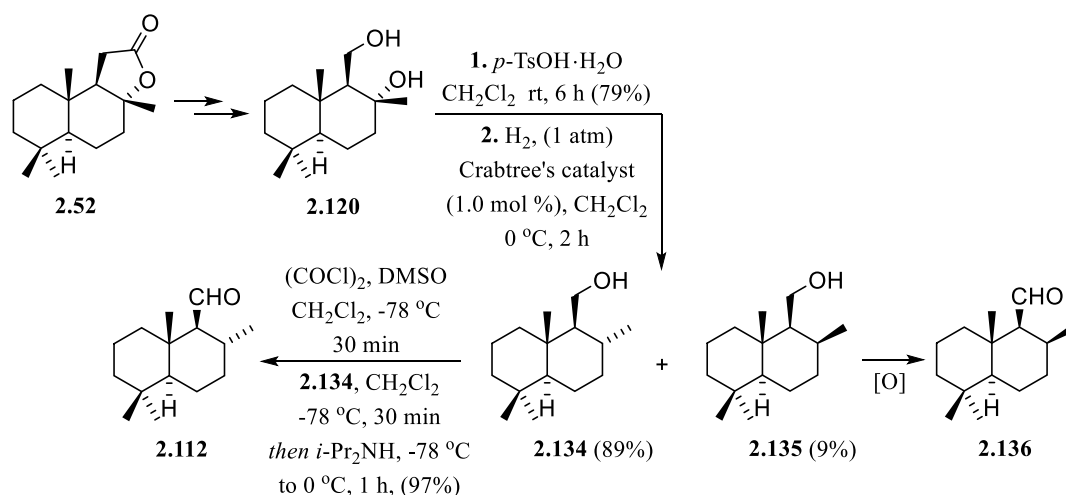
2.5.3 Katoh's Biogenically Inspired Synthesis of Liphagal – Synthesis of Aldehyde **2.112**



Scheme 2.20: Biogenic inspired total synthesis of liphagal (**2.2**) by Katoh *et al.*^[127]

During the synthesis of our target coupling precursor aldehyde **2.112**, Katoh *et al* published a total synthesis of liphagal, which was claimed to be biogenically inspired by Andersen's biosynthetic *pathway A* proposal (scheme 2.20).^[99,127] Katoh's route was akin to our own proposal for the biogenic synthesis of liphagal (**2.2**) from siphonodictyal B (**2.1**). However, the route did not involve the total synthesis of siphonodictyal B (**2.1**) itself, and instead, involved the epoxidation of a protected substrate that possessed the siphonodictyal B scaffold **2.130**, to afford epoxide **2.131** as a racemic mixture of diastereomers. On isolation of epoxide **2.131** (**1:1** – dr), Katoh subjected the mixture **2.131** (**1:1** – dr) to TFA in CH₂Cl₂, which led to an acid catalysed, biogenically inspired ring expansion (**2.132**) to obtain ketone **2.133**. Subsequent acetate hydrolysis of ketone **2.133** led to a spontaneous intramolecular cyclisation to afford the benzofuran moiety, furnishing liphagane skeleton **2.83**. Finally, formylation and deprotection of the methylene protecting group concluded Katoh's stereoselective total synthesis of liphagal (**2.2**).

Of particular interest to us was Katoh's route to obtain aldehyde **2.112** (scheme 2.21); as our previously explored pathway to **2.112-a:b** proved unnecessarily convoluted due to issues regarding reaction scaling of the Misunobu-like diol rearrangement. Additionally, our route detailed a longer linear sequence to obtain aldehyde **2.112** from (+)-sclereolide (**2.52**) (8 steps). Comparatively, Katoh's synthetic route appeared simpler, with fewer synthetic steps (6 steps from (+)-sclereolide **2.52**) and appeared to be scalable. Additionally, Katoh's method granted access to alcohol epimer **2.135**,^[127] which could be oxidised to aldehyde **2.136**, and serve as a coupling precursor in the synthesis of siphonodictyal B (**2.1**), in accordance with Faulkner's assignment.^[97,98]



Scheme 2.21: Synthesis of aldehyde coupling precursor **2.112**, by Katoh *et al*^[127]

2.5.4 Alternative Synthetic Route to Aldehydes **2.112** and **2.136**

With significant difficulties inherent to our synthetic route to aldehyde **2.112** via Barrero's Mitsunobu-like rearrangement of diol **2.117**,^[121] we sought to mirror Katoh's synthetic route to aldehyde **2.112**.^[127] Thus, as Katoh's synthesis would grant access to both alcohol **2.135**, was of interest to us as **2.135** could be oxidised to aldehyde **2.136**, potentially granting access to siphonodictyal B (**2.1**), in accordance with Faulkner's assignment.^[97,98] Thus, synthesising both C8 epimers of siphonodictyal B, **2.1** and **2.91**, would allow us to either confirm our hypothesis, or resolve any ambiguity in regards to the natural products stereoconfiguration.

Upon mirroring Katoh's published protocol, synthesis of endo-alkenyl-alcohol **2.137** via an acid catalysed elimination of diol **2.120** was found to be scalable without any considerable loss of yield (table 2.1),^[127] and could be achieved in relatively good purity without the need for a formal purification protocol. Following the synthesis of the endo-alkenyl-alcohol **2.137**, hydrogenation conditions were investigated in order to gain access to both alcohol epimers, **2.134** and **2.135**. Investigation into suitable catalysts commenced with 10 % palladium on carbon (Pd/C) in MeOH. However, despite trialling varying solvents, both alcohols (**2.134** and **2.135**) were obtained in unusually low yields (entries 1 and 2, table 2.1). Upon trailing hydrogenation conditions with 10% Pd/C, a relatively non-polar mixture of by-products was observed to form as the major product. ¹H NMR and ¹³C NMR analysis of the isolated unknown polar by-product revealed the presence of multiple alkane signals and a single alkenyl proton. Based on the limited data available, it appeared that the primary alcohol of **2.137** had undergone reduction, despite the mild conditions (room temperature and H₂ supplied via a breathable bladder). All hydrogenation conditions with 10% Pd/C consistently afforded the partially hydrogenated, inseparable mixture of unfunctionalized alkane/alkenyl sesquiterpenes as the major products (entries 1 and 2, table 2.1).

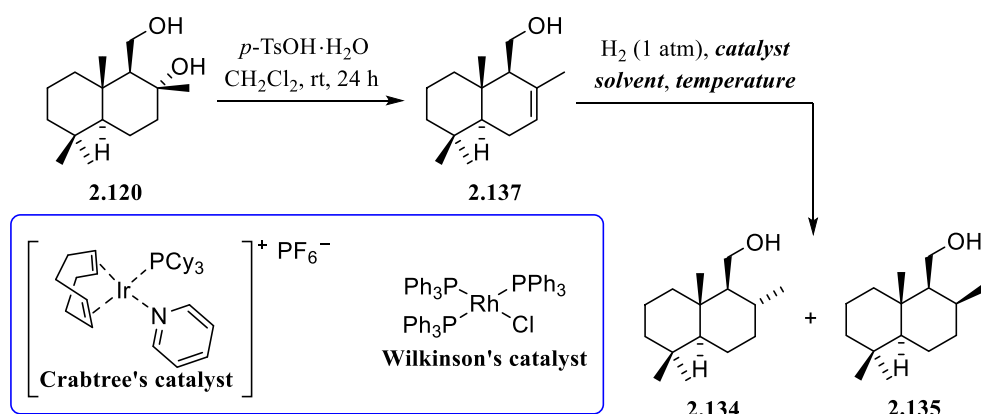
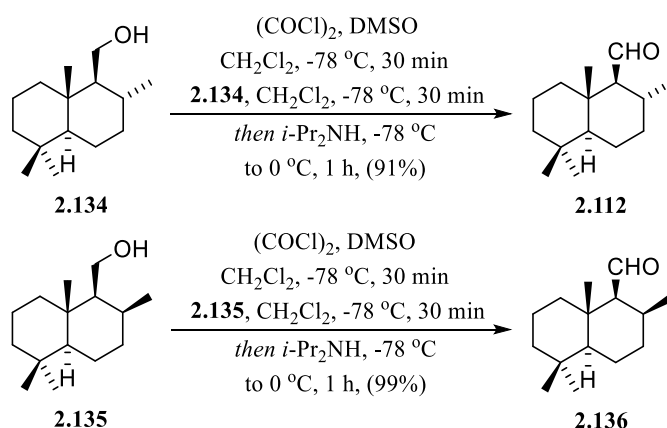


Table 2.1: Acid catalysed elimination, and screening of hydrogenation conditions for the synthesis of alcohols **2.134** and **2.135**.^[127]

Entry	Catalyst (mol %)	Conditions	Outcome
1	10wt % Pd/C (10)	MeOH, 0 °C, 6 h	2.134 (9%), 2.135 (14%) complex mixture
2	10wt % Pd/C (10)	CH ₂ Cl ₂ , 0 °C, 8 h	2.134 (7%), 2.135 (12%) complex mixture
3	Crabtree's catalyst (1.0)	CH ₂ Cl ₂ , 0 °C, 24 h	slow/incomplete reaction
4	Crabtree's catalyst (1.0)	CH ₂ Cl ₂ , -10 °C, 8 h	2.134 (64%), 2.135 (4%)
5	Wilkinson's catalyst (5.0)	CH ₂ Cl ₂ , rt, 24 h	2.134 (89%), 2.135 (7%)

Changing from the previously employed 10 % Pd/C to Crabtree's catalyst, Katoh's reported yields could not be replicated. Additionally, despite mirroring the same reaction preparative method, where the solvent was degassed with argon, sonicated and evacuated to remove all traces of O₂, the reduction of alcohol **2.137** could not be pushed to completion (entry 3, table 2.1).^[127] Upon analysis of the literature, Crabtree's catalyst has been shown to undergo spontaneous self-dimerization at room temperature,^[128,129] and is reported to be particularly sensitive to acidic impurities. With this in mind, alkenyl-alcohol **2.137** was purified prior to the attempted catalytic reduction at reduced temperatures, in an attempt to remove any potential contaminating *p*-TsOH. Additionally, the gradual periodical addition of Crabtree's catalyst every two hours has been suggested to help mitigate inactivation of the iridium catalyst via dimerization. However, despite these additional precautions, the complete reduction of alcohol **2.137** could not be achieved (entries 3 and 4, table 2.1). Finally, our investigation of hydrogenating catalysts led us to the more robust Wilkinson's catalyst, which successfully reduced the crude alkenyl-alcohol **2.137** at room temperature to afford both alcohols, **2.134** and **2.135** (entry 5, table 2.1), in comparable selectivity and yield with Katoh's Crabtree's reduction (scheme 2.21). With both alcohols **2.134** and **2.135** at hand, oxidation to the desired aldehydes **2.112** and **2.136** was realised following Katoh's Swern

conditions (scheme 2.22).^[127] With a simple, yet robust synthetic route, granting access to both aldehydes **2.112** and **2.136**, we set out to synthesise both C8 epimers of siphonodictyal B (**2.1** and **2.91**).

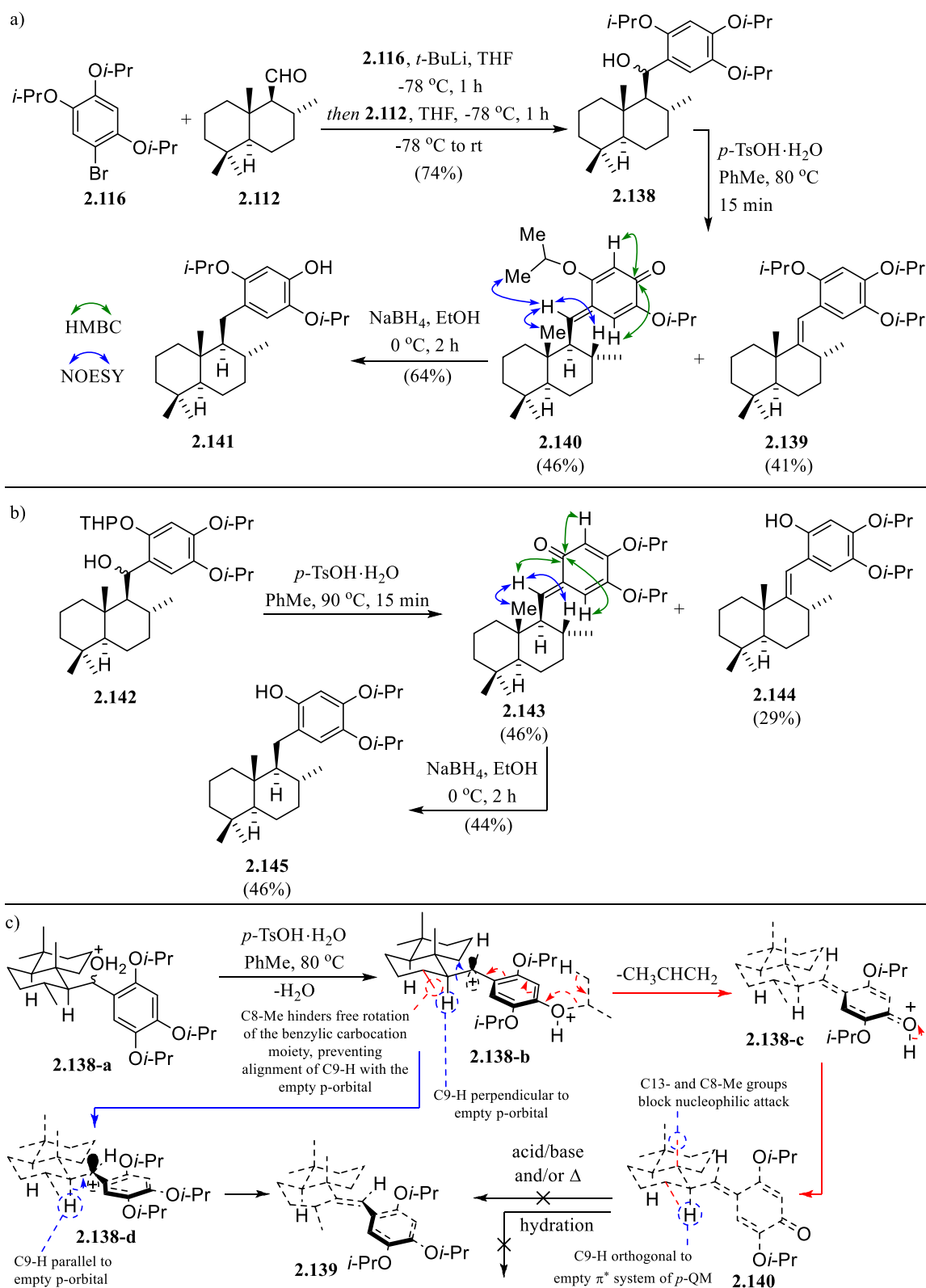


Scheme 2.22: Swern oxidation of alcohols **2.134** and **2.135** to the desired aldehydes **2.112** and **2.136**, respectively.^[127]

2.5.5 Synthesis of Siphonodictyal B **2.91**, in Accordance with Our Proposed C8 Reassignment

With access to both aldehydes **2.112** and **2.136**, we set out to synthesise siphonodictyal B **2.91** in accordance with our proposed C8 epimeric reassignment. Synthetic access to siphonodictyal B (**2.91**), as depicted in our retrosynthetic analysis (scheme 2.15), was envisioned through coupling of aldehyde **2.112** with aryl bromide **2.116** via halogen-lithium exchange.^[130] **2.116** was subjected to a cooled solution of *t*-BuLi in THF, followed by addition of **2.112** to afford benzyl alcohol **2.138**, as a single stereoisomer (scheme 2.23). The absolute stereo-configuration of **2.138** at the hydroxy benzyl moiety was not determined.

Elimination of benzyl alcohol **2.138**, by treatment with *p*-TsOH in toluene gave alkene **2.139**, albeit in a lower yield than anticipated due to the unexpected formation of polar by-product **2.140**. The identity of **2.140** was found to be a *p*-QM as indicated upon comparison to the fortuitously afforded *o*-QM isomer **2.143**, following the attempted synthesis of an analogous model system for liphagal (**2.2**) by a member of our group (scheme 2.23 – b). NOESY and HMBC NMR correlations elucidated the identity of both isomers, which was confirmed upon the subsequent reduction of both quinone methide isomers, **2.140** and **2.143**, to their corresponding phenols, **2.141** and **2.145** respectively (scheme 2.23).



Scheme 2.23: a). Coupling of aryl bromide **2.116** with aldehyde **2.112** and a subsequent elimination of benzyl alcohol **2.138** to afford alkene **2.139**, alongside undesired *p*-QM **2.140**. b) Kuan's and George's synthesis of *o*-QM **2.143**. c) proposed mechanistic rationale for the competing elimination pathways of benzyl alcohol **2.138**, affording alkene **2.139** and *p*-QM **2.140**.

The formation of *o*-QM **2.143**, as observed for Kuan's system (scheme 2.23 – b), was not observed under any explored acid catalysed elimination conditions for our tri-*iso*-proxy ether

system **2.138**. *p*-QM **2.140** was found to be stable under elevated thermal conditions and was observed to slowly decompose at a sustained temperature of 140 °C, in toluene within a sealed tube. Additionally, *p*-QM **2.140** appeared inert to strong non-nucleophilic acids (TFA, *p*-TsOH), and bases (NaH, NEt₃) as a solution of refluxing toluene. Therefore, *p*-QM **2.140** was determined to not be interchangeable with alkene **2.139**, nor could it undergo rehydration to afford a benzyl alcohol. Various elimination conditions were investigated in an attempt to minimise the formation of the undesired *p*-QM by-product **2.140** (table 2.2). Trialling elimination conditions of **2.138** with *p*-TsOH at room temperature marginally decreased the formation of alkene **2.139**, and consequently, led to an increase in the yield of *p*-QM **2.140** (entry 2, table 2.2). Despite reducing the molar equivalents of *p*-TsOH and reducing the temperature protocol, the generation of the undesired *p*-QM **2.140** could not be mitigated (entry 3, table 2.2). Employing the milder acid, pyridinium *p*-toluenesulfonate, under thermal conditions significantly reduced the formation of **2.140** and afforded alkene **2.139** in an acceptable yield of 52%, while additionally affording starting benzyl alcohol **2.138** (entry 4, table 2.2). Finally, generation of *p*-QM **2.140** was almost entirely negated upon elimination of **2.138** via phosphoryl chloride in pyridine,^[131,132] which gave alkene **2.139** and recovered benzyl alcohol **2.138** in acceptable yields (entry 5, table 2.2).

We suspect that the observed formation of the undesired *p*-QM **2.140** from benzyl alcohol **2.138**, may be due to the equatorially projecting C8-methyl substituent potentially restricting free rotation of the benzylic carbocation moiety of **2.138-b**. If such a restriction of rotation occurred, then the necessary alignment of the C9-H with the empty *p*-orbital of the benzylic carbocation (**2.138-b**) may have been considerably less favourable, impeding the desired formation of alkene **2.139** (scheme 2.23-c). Thus, in the presence of a strong acid, the formation of *p*-QM **2.140** from benzylic carbocation **2.138-b** appeared to be comparatively favourable as the desired C9-H elimination pathway (**2.138-b** to **2.138-c**). The formation of **2.140** was drastically reduced upon changing from more acidic conditions, to employing phosphorus oxychloride in pyridine, which seemingly validated our rationale regarding the effect of strong acids on the formation of *p*-QM **2.140** (entry 5, table 2.2). Additionally, as the *p*-QM **2.140** could not be isomerised back to the desired alkene **2.139** under any acidic, basic or thermal conditions, we similarly suspect, that the C8-Me substituent inhibited free rotation of the *p*-QM moiety, preventing the necessary alignment of the C9-H with the antibonding π^* system of **2.140** (scheme 2.23-c). In regards to the attempted hydration of *p*-QM **2.140**, if the C8- and C13-Me substituents did in fact introduce notable steric occupancy around both the *p*-orbital of benzylic carbocation **2.138-b** and the methide antibonding π^* system of *p*-QM **2.140**, then hydration of *p*-QM **2.140** via the nucleophilic attack of

hydroxide would prove unsurprisingly difficult. Lastly, the reduction of *p*-QM **2.140** with NaBH₄ to afford phenol **2.141**, appears to contradict our previous assertion regarding the C8- and C13-Me substituents shielding the methide moiety of **2.140** from nucleophilic attack. Although it has been observed that NaBH₄ is able to reduce organometallic species via a single electron transfer mechanism,^[133–135] no such electron transfer mechanisms have been observed for organic systems, and rather, NaBH₄ acts as a source of nucleophilic hydride.^[136–139] Therefore, although somewhat unfavourable, we would rationalise that NaBH₄ could approach the methide moiety of **2.140** on the opposite face to the C13-Me substituent in order to minimise unfavourable steric shielding effects surrounding the methide moiety (scheme 2.23-c). Such a backside attack would be expected to suffer steric congestion, which appears to be reflected in the modest yields obtained for the reduction of both QMs **2.140** and **2.143**.

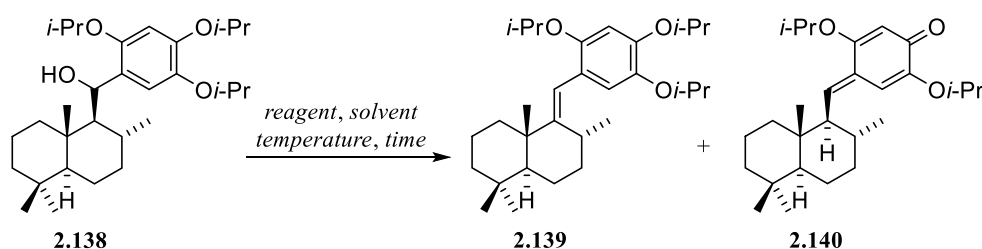
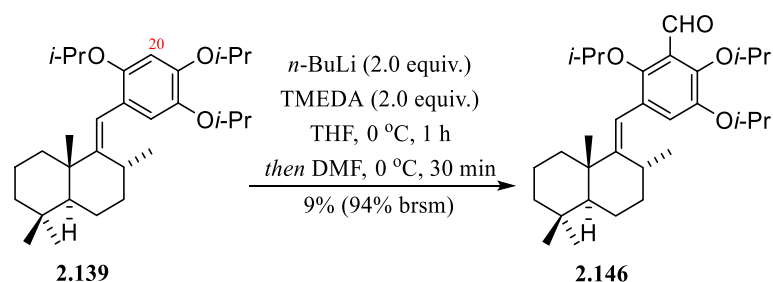


Table 2.2: Screening elimination conditions for alkene **2.139** from benzyl alcohol **2.138**.

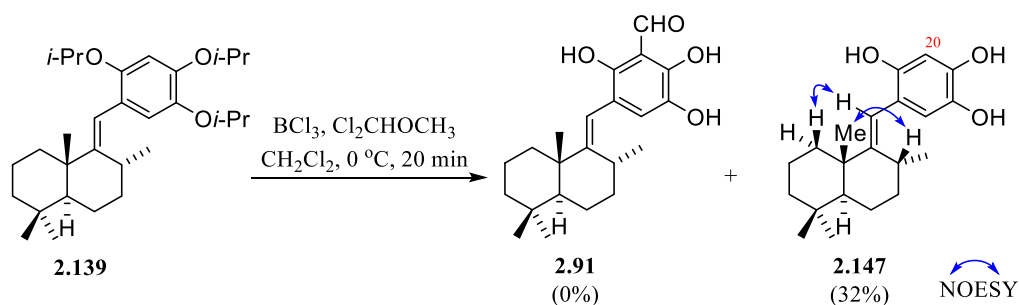
Entry	Catalyst/Reagent (mol eq)	Conditions	Alkene (2.139)	<i>p</i> -QM (2.140)
1	<i>p</i> -TsOH (0.1)	PhMe, 80 °C, 15 min	41%	46%
2	<i>p</i> -TsOH (1)	PhMe, rt, 3 h	36%	57%
3	<i>p</i> -TsOH (0.1)	PhMe, rt, 5 h	38%	52%
4	PPTS (0.1)	PhMe, 80 °C, 30 min	53% (82% brsm)	12%
5	POCl ₃ (1.5)	Pyridine, 80 °C, 1 h	54% (90% brsm)	6%

Following elimination of benzyl alcohol **2.138**, *ortho*-directed lithiation and subsequent formylation of alkene **2.139** was attempted via addition of two equivalents of *n*-BuLi and tetramethylethylenediamine (TMEDA) (scheme 2.24).^[140] Upon purification, following quenching of the *ortho*-lithiated mixture with DMF, the majority of the isolated product was found to be starting alkene **2.139**, and only minor quantities of the desired aryl aldehyde **2.146** was acquired (scheme 2.24). We suspect that the *iso*-propoxy protecting groups of alkene **2.139** may have introduced significant steric hindrance at C20, preventing an *ortho*-directed lithiation event from proceeding. As the yields of the desired aryl aldehyde **2.146** were unacceptably poor under the protocol explored, we chose to investigate an alternative formylation method.



Scheme 2.24: Attempted formylation of alkene **2.139** via an *ortho*-directed lithiation with $n\text{-BuLi}$ (2.0 equivalents) and TMEDA.

The first alternative formylation protocol considered was a Rieche formylation.^[140] The one-pot, Lewis acid mediated protocol could potentially install the desired aryl aldehyde moiety and remove the *iso*-propoxy protecting groups via addition of dichloromethyl methyl ether ($\text{Cl}_2\text{CHOCH}_3$) and BCl_3 , to potentially afford siphonodictyal B **2.91**, in accordance with our proposed reassigned configuration. However, despite attempting to tweak temperature protocols and Lewis acid addition rates/concentrations, the formation of the desired formylated/deprotected product **2.91** was not observed, and only **2.147** was isolated upon quenching the reaction mixture (scheme 2.25).



Scheme 2.25: Failed one-pot, deprotection and formylation of alkene **2.139**, affording nor-formyl siphonodictyal B **2.147**.

With the Rieche formylation failing to afford siphonodictyal B **2.91**, an *ortho*-directed lithium mediated formylation was revisited (table 2.3). By increasing the molar equivalents of $n\text{-BuLi}$ to five, while maintaining the equivalents of TMEDA at two, alkene **2.139** was successfully formylated to afford the desired aryl aldehyde **2.146** in good yield based upon recovered starting material **2.139**. Additional molar equivalents of $n\text{-BuLi}$, upwards of eight, led to decomposition of the starting material and resulted in the isolation of an undesired mixture of products, which appeared to have undergone a second formylation at C17. Upon addition of DMF to the reaction mixture, quenching the mixture within five minutes was required and could not be heated above 0 °C, otherwise decomposition would ensue. **2.146** could be accessed in synthetically useful quantities by recycling recovered starting alkene **2.139** through several *ortho*-directed lithiation mediated formylations.

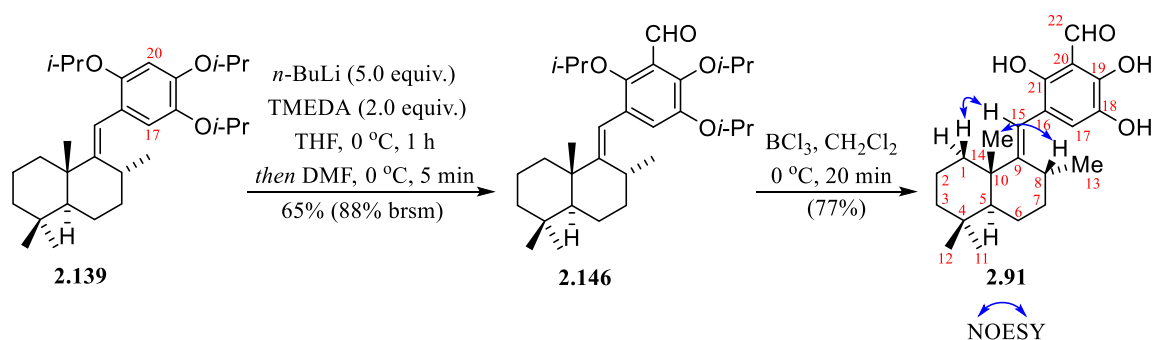


Table 2.3: Formylation of alkene **2.139** (via 5 equivalents of *n*-BuLi), followed by deprotection of aryl aldehyde **2.146** to afford siphonodictyal B **2.91**. **Below:** Comparison of Köck's reported ^1H & ^{13}C NMR spectra with our acquired data.^[96]

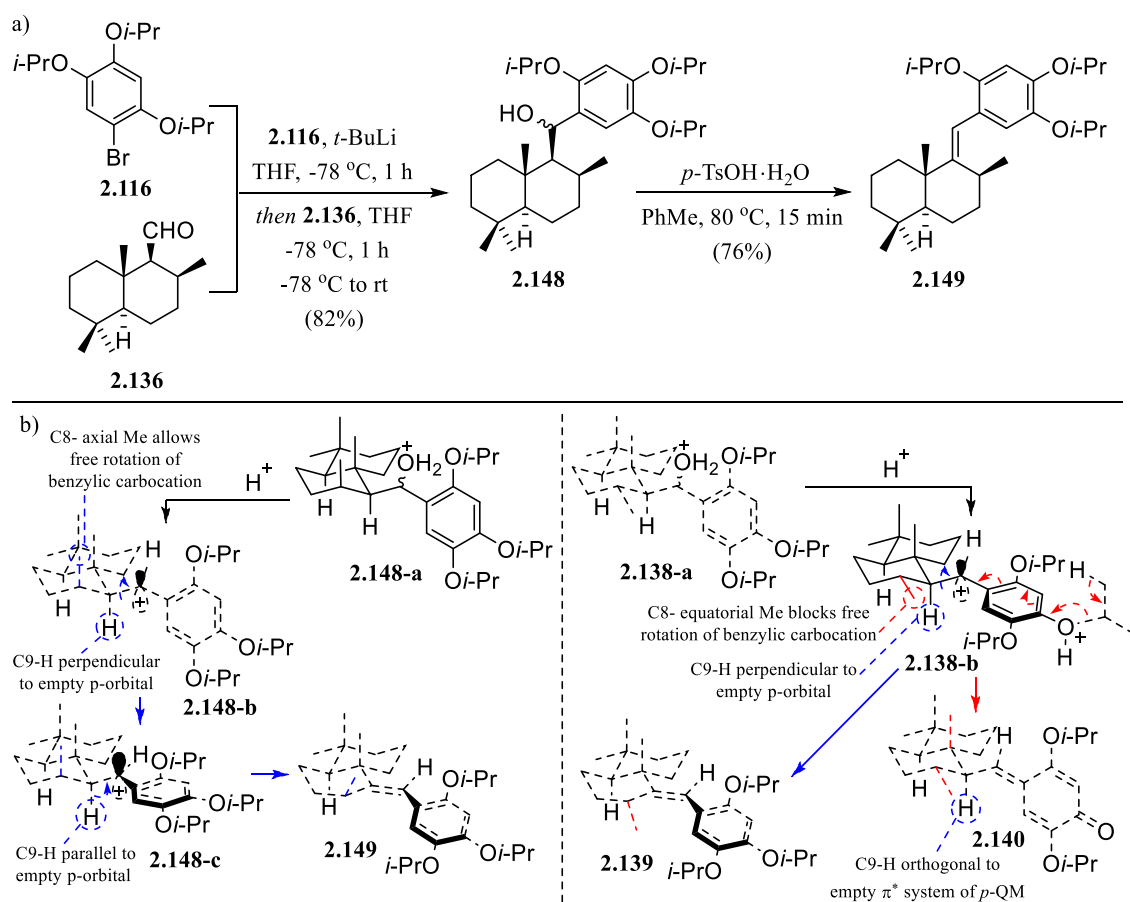
Assignment	Köck ^1H NMR	This work, ^1H NMR 500 MHz	Köck ^{13}C NMR	This work, ^{13}C NMR, 125 MHz
C-1	1.78, 1.40	1.79-1.27 (overlapped m)	39.1	39.1
C-2	1.63, 1.49	1.79-1.27 (overlapped m)	19.0	19.0
C-3	1.38, 1.16	1.79-1.27 (overlapped m)	41.9	41.9
C-4	-	-	33.0	33.0
C-5	1.30	1.79-1.27 (overlapped m)	49.0	49.1
C-6	1.71, 1.49	1.79-1.27 (overlapped m)	19.4	19.4
C-7	1.72, 1.34	1.79-1.27 (overlapped m)	31.2	31.2
C-8	2.62	2.62 (m)	31.7	31.8
C-9	-	-	157.0	157.0
C-10	-	-	40.3	40.4
C-11	0.89	0.88 (s)	21.4	21.5
C-12	0.86	0.85 (s)	33.6	33.6
C-13	0.89	0.87 (d, $J = 7.0$ Hz)	21.9	21.9
C-14	1.12	1.12 (s)	22.9	22.9
C-15	6.04	6.03 (s)	113.4	113.4
C-16	-	-	116.6	116.6
C-17	6.85	6.84 (s)	126.2	126.2
C-18	10.03 (OH)	10.03 (s)	136.1	136.1
C-19	9.00 (OH)	9.02 (s)	147.8	147.8
C-20	-	-	110.2	110.2
C-21	10.90 (OH)	10.91 (s)	151.2	151.3
C-22	10.26	10.25 (s)	194.8	194.8

All spectra run in DMSO- d_6

Finally, our proposed reassigned configuration of siphonodictyal B, **2.91**, was acquired upon addition of BCl_3 to a cooled solution of aldehyde **2.146** in CH_2Cl_2 (table 2.3). The Lewis acid mediated deprotection was quenched after 20 minutes, in order to mitigate the formation of seemingly decomposed by-products. Upon purification, **2.91** was observed to rapidly decompose on contact with SiO_2 , and consequently, was rapidly flushed through SiO_2 via flash column chromatography immediately upon quenching the reaction mixture. NMR analysis and comparison of our sample **2.91** matched perfectly with Köck's reported spectral data (table 2.3). However, Faulkner had only reported a few select ^1H NMR spectral peaks, none of which matched with our acquired proton spectra for **2.91**. Therefore, we set out to synthesise (**2.1**), in accordance with Faulkner's assignment to confirm our hypothesised reassigned configuration of siphonodictyal B.

2.5.6 Total Synthesis of Siphonodictyal B **2.1**, In Accordance with Faulkner's Configuration

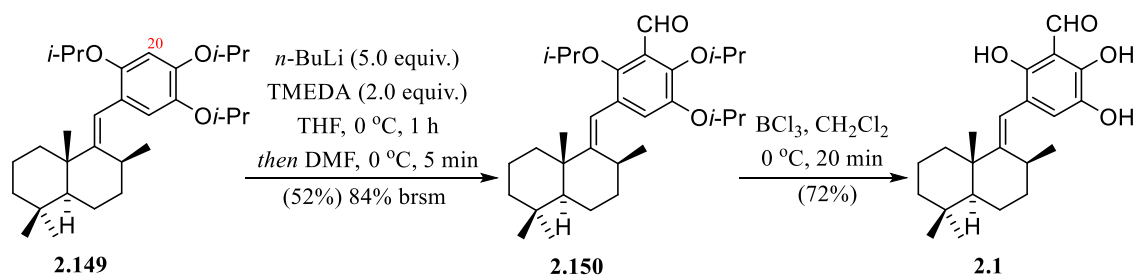
With synthesis of our proposed reassigned configuration of siphonodictyal B **2.91** complete, we set out to synthesise siphonodictyal B (**2.1**) in accordance with Faulkner's assignment to determine the true configuration of the natural product. Following our previously explored lithium-halogen exchange coupling conditions, aryl bromide **2.116** was subjected to *t*-BuLi in THF, followed by addition of aldehyde **2.136**, which afforded benzyl alcohol **2.148** in good yield as a mixture of epimers (scheme 2.26-a). Investigation into elimination conditions for benzyl alcohol **2.148** commenced with the previously explored elimination conditions with *p*-TsOH in toluene. Interestingly, alkene **2.149** was isolated as the major product and despite mirroring the same elimination conditions that afforded both alkene **2.139** and *p*-QM **2.140** from benzyl alcohol **2.138**, formation of the anticipated equivalent *p*-QM was not observed. As we had previously asserted, the formation of *p*-QM **2.140** via acid catalysed elimination of benzyl alcohol **2.138** was most likely due to the C8-Me substituent projecting equatorially, which could consequently restrict the necessary free rotation of the generated benzylic cation (**2.138-b**) required for the elimination of C9-H (scheme 2.23-c & 2.26-b). This rationale appears to be supported by the clean elimination of benzyl alcohol **2.148** to the desired alkene **3.149** (scheme 2.26). Thus, from the comparison of these reaction outcomes, it is incontestable that the configuration of the C8-Me substituent is the most prominent factor in determining the elimination pathway of these meroterpenoid benzyl alcohols (**2.138** and **2.148**).



Scheme 2.26: a) Coupling of aryl bromide **2.116** with aldehyde **2.136**, and subsequent elimination of benzyl alcohol **2.148** to give alkene **2.149**. b) proposed comparison for the elimination mechanistic pathways of benzyl alcohol **2.138-a** and **2.148-a**.

With access to alkene **2.149**, we set out to install the aldehyde moiety under the same previously optimised *ortho*-directed lithiation conditions investigated for the synthesis of siphonodictyal B **2.91** (table 2.3). Formylation of alkene **2.149**, with five and two molar equivalents of *n*-BuLi and TMEDA respectively, gave aldehyde **2.150** in reasonable consistent yields (scheme 2.27). As was performed previously, the recovered starting alkene **2.149** was cycled through multiple formylation reactions to acquire synthetically useful quantities of aldehyde **2.150**. Finally, aryl aldehyde **2.150** was deprotected via the same previously explored BCl₃ conditions for the synthesis of siphonodictyal B **2.91**, which was quenched after 20 minutes to afford siphonodictyal B (**2.1**), in accordance with Faulkner's assigned configuration (scheme 2.27). As observed for the isolation of **2.91** (table 2.3), Faulkner's siphonodictyal B (**2.1**) was found to readily decompose on contact with SiO₂, and hence, was rapidly flushed through SiO₂ via flash column chromatography to minimise any loss of product (scheme 2.27). NMR analysis confirmed the expected structure of siphonodictyal B (**2.1**). However, both the ¹H and ¹³C NMR of our synthesised sample of

2.1 did not match the spectral data reported by Köck, nor did Faulkner's select few ^1H NMR natural sample peaks match any peaks of our synthesised sample (**2.1**).



Scheme 2.27: *ortho*-Lithiation, formylation of alkene **2.149** (via 5 equivalents of $n\text{-BuLi}$), followed by Lewis acid mediated deprotection of aryl aldehyde **2.150**, afforded Faulkner's assigned configuration of siphonodictyal B (**2.1**).

2.5.7 Elucidation of the True Configuration of Siphonodictyal B

In Faulkner's original isolation paper, the isolated sample of siphonodictyal B was subjected to methylation experiments, and the resulting methyl ether product **2.12** was further characterised by NMR studies. Thus, in an effort to elucidate the true structural and stereoconfiguration of Faulkner's isolated natural sample, we set out to synthesise both trimethoxy ether derivatives of our synthetically acquired siphonodictyal B epimers, **2.91** and **2.1**. Both synthetic siphonodictyal B epimer samples, **2.91** and **2.1**, were methylated under identical conditions with MeI , to afford **2.151** and **2.12** respectively (table 2.4). Comparison of the ^1H and ^{13}C NMR data revealed that methylated siphonodictyal B derivative **2.151** perfectly matched that of Faulkner's methylated sample. Thus, from these methylation experiments, we are confident in concluding that the true configuration of siphonodictyal B is in fact **2.91**, in direct accordance with our proposed reassignment (table 2.4).

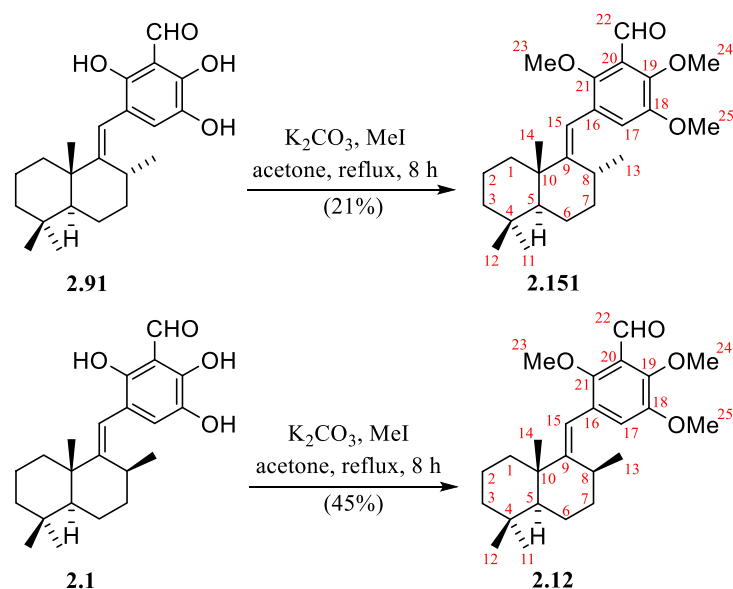


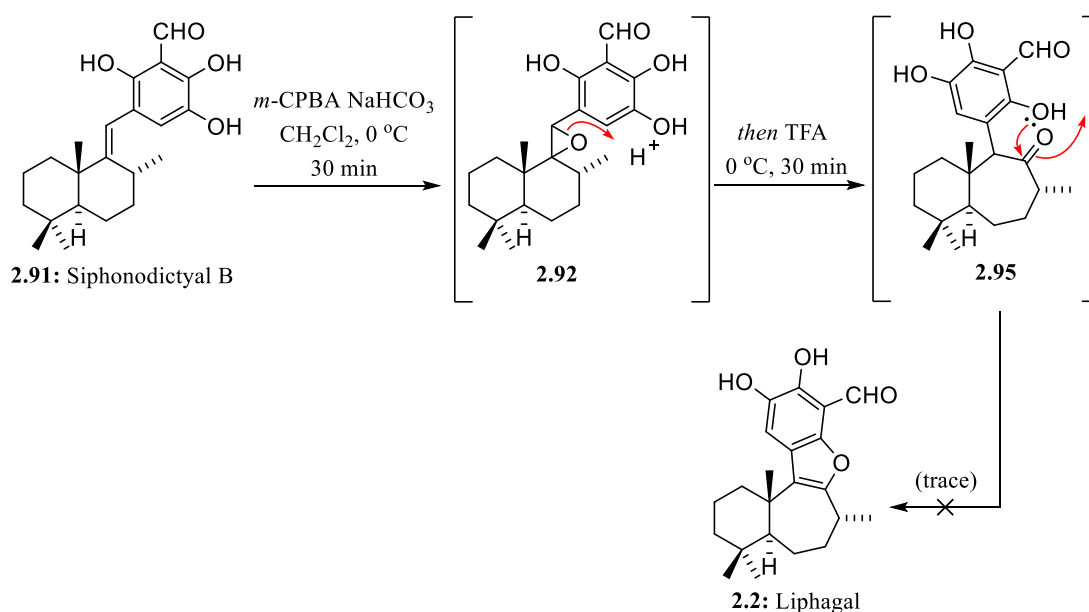
Table 2.4: Methylation of both siphonodictyal B epimers **2.1** and **2.91**, affording **2.151** and **2.12**.

Below: Comparison of Faulkner's reported ^1H NMR spectra of **2.12** with our afforded epimers **2.151** and **2.12**.

Assignment	Faulkner 2.12	This work, 2.91 (500 MHz)	This work, 2.12 (500 MHz)
H-1	not reported	1.86 – 1.24 (m, 2H)	1.83 – 1.42 (m, 2H)
H-2	not reported	1.86 – 1.24 (m, 2H)	1.83 – 1.42 (m, 2H)
H-3	not reported	1.86 – 1.24 (m, 2H)	1.27 – 1.25 (m, 1H), 1.83 – 1.42 (m, 1H)
H-5	not reported	1.86 – 1.24 (m, 1H)	0.99 (d, $J = 11.0$ Hz, 1H)
H-6	not reported	1.86 – 1.24 (m, 2H)	1.83 – 1.42 (m, 2H)
H-7	not reported	1.86 – 1.24 (m, 2H)	1.83 – 1.42 (m, 2H)
H-8	2.65 (m, 1 H)	2.66 (m, 1H)	2.96 (quintet, $J = 6.7$ Hz, 1H)
H-11	0.91 (s, 3 H)	0.91 (s, 3H)	0.92 (s, 3H)
H-12	0.89 (s, 3 H)	0.89 (s, 3H)	0.90 (s, 3H)
H-13	0.90 (d, 3 H, $J = 7$ Hz)	0.90 (d, $J = 6.5$ Hz, 3H)	1.28 (d, $J = 7.5$ Hz, 3H)
H-14	1.19 (s, 3 H)	1.19 (s, 3H)	1.23 (s, 3H)
H-15	6.21 (s, 1 H)	6.21 (s, 1H)	6.21 (s, 1H)
H-17	6.91 (s, 1 H)	6.91 (s, 1H)	6.95 (s, 1H)
H-22	10.40 (s, 1 H)	10.40 (s, 1H)	10.43 (s, 1H)
H-23	3.91 (s, 3 H)	3.91 (s, 3H)	3.93 (s, 3H)
H-24	3.85 (s, 3 H)	3.85 (s, 3H)	3.86 (s, 3H)
H-25	3.72 (s, 3 H)	3.72 (s, 3H)	3.74 (s, 3H)

2.6 Biogenically Inspired Synthesis of Liphagal from Siphonodictyal B

With access to siphonodictyal B (**2.91**), we set out to synthesise liphagal (**2.2**) via our *pathway A* inspired proposal (scheme 2.12). We sought to directly synthesise liphagal (**2.2**) from siphonodictyal B (**2.91**) via a one-pot, epoxidation and subsequent acid catalysed transformation. In our opinion, a successful one-pot transformation would provide significant evidence towards our biosynthetic proposal, being that, we believe siphonodictyal B (**2.91**) is indeed the biogenic precursor to liphagal (**2.2**), and the other structurally related meroterpenoids (**2.3 – 2.6**, **2.106 – 2.108**) (scheme 2.15).



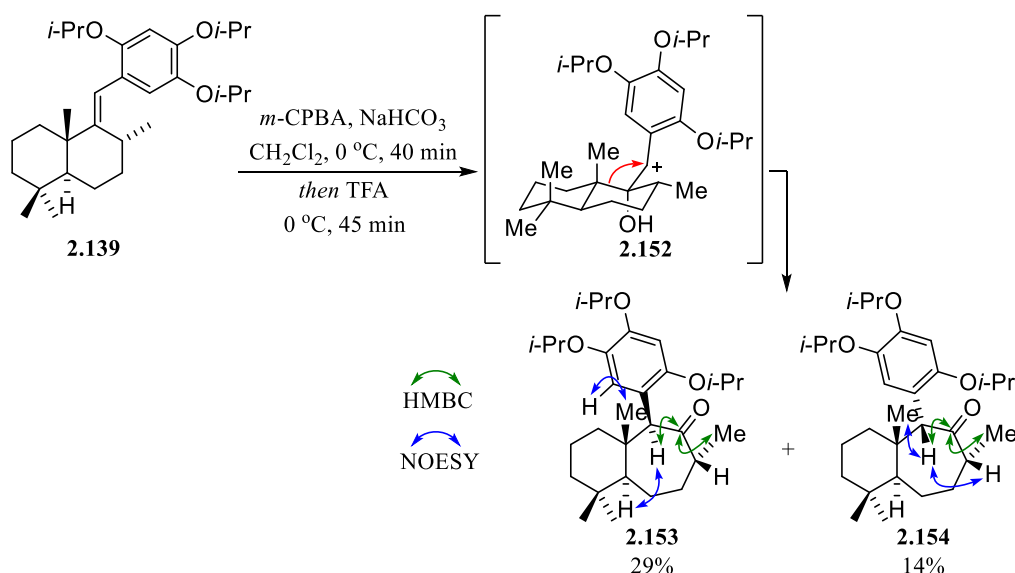
Scheme 2.28: Attempted one-pot biogenic transformation of siphonodictyal B (**2.91**) to liphagal (**2.2**).

The starting point of our investigation into the synthesis of liphagal (**2.2**) commenced with a two-step protocol investigated for a model system by a member of our group. Siphonodictyal B (**2.91**) was subjected to a mixture of *m*-CPBA and NaHCO₃ in CH₂Cl₂ at 0 °C (scheme 2.28). The epoxidation procedure was monitored by TLC, which revealed the formation of a minor faint polar spot. However, upon addition of TFA to the epoxidized reaction mixture, no new developing products were observed by TLC analysis, which was confirmed upon purification of the reaction mixture. An isolated minor fraction revealed trace spectral peaks that corresponded to liphagal (**2.2**), as elucidated by ¹H NMR analysis of the complex mixture. Efforts to isolate the anticipated *in situ* siphonodictyal epoxide **2.92** were fruitless, as the crude mixture appeared to readily degrade upon contact with SiO₂, leading us to speculate that the proposed epoxide was unstable and could not be isolated. In

addition to the predicted inherent instability of epoxide **2.92**, the aromatic aldehyde moiety of siphonodictyal B (**2.91**) and its epoxidized derivative **2.92** may have been susceptible to oxidation upon addition of *m*-CPBA. Exploring alternative solvent systems, such as THF and dioxane, failed to yield liphagal (**2.2**) in any isolatable quantity. Only conditions employing THF afforded a series of complex fractions, that upon purification were revealed to possess trace spectral peaks characteristic of liphagal (**2.2**), as highlighted by ¹H NMR analysis (scheme 2.28).

2.6.1 Investigation into a Simplified Liphagal System

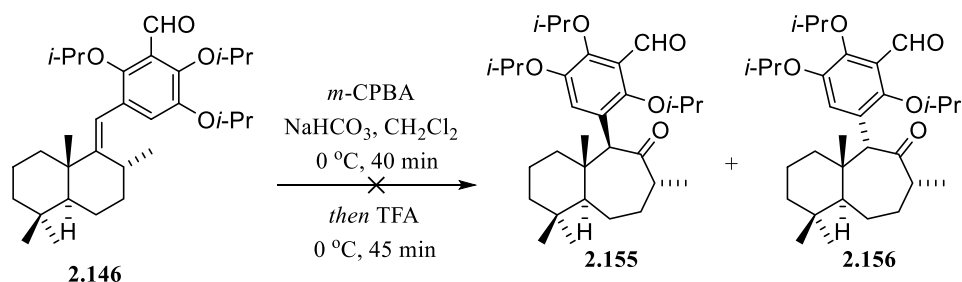
As the aromatic aldehyde moiety of siphonodictyal B (**2.91**) was suspected to undergo degradation during the epoxidation event, we set out to trial our one-pot, oxidative-acidic conditions on a simpler system. Alkene **2.139** was chosen as a simplified model system on which to trial our one-pot *m*-CPBA/TFA conditions. Subjecting alkene **2.139** to a mixture of *m*-CPBA and NaHCO₃ in CH₂Cl₂, followed by the subsequent addition of TFA afforded ring expanded ketones **2.153** and **2.154**, that were separated and characterised by NMR analysis (scheme 2.29). Examination of the NOESY spectra elucidated that ketones **2.153** and **2.154** were in fact epimers of one another, consistently isolated in a 2:1 ratio in favour of **2.153**.



Scheme 2.29: Model investigation of a one-pot, epoxidation and acid catalysed biogenic transformation of siphonodictyal B precursor **2.139** to ring expanded ketones **2.153** and **2.154**.

As **2.153** and **2.154** are benzylic ketones, one would expect that under acidic conditions, such as those employed, ketones **2.153** and **2.154** could freely interchange with one another via an acid facilitated keto-enol tautomerisation (scheme 2.29). Hence, the simplest

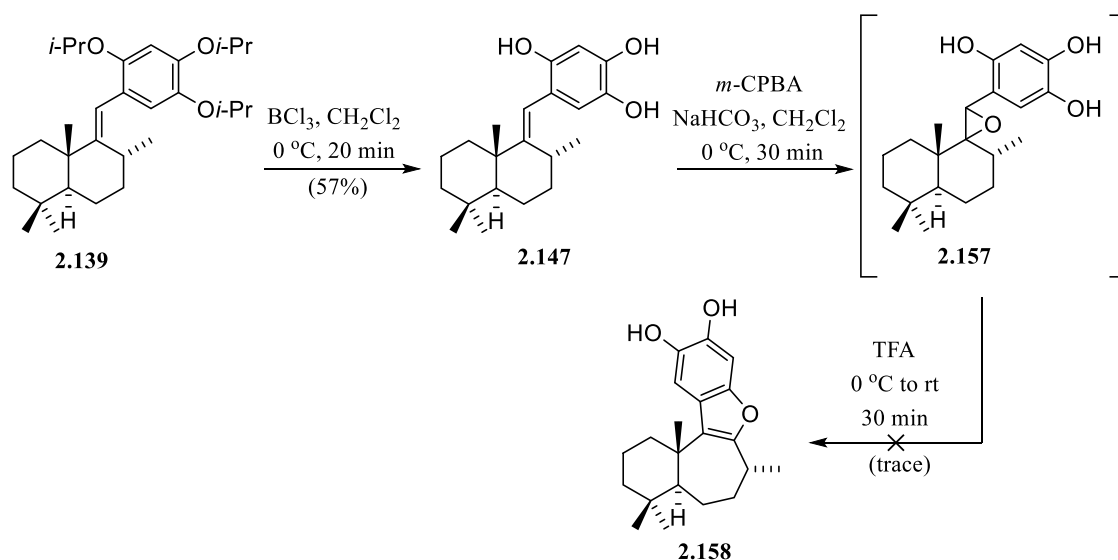
explanation for the consistently isolated 2:1 ratio observed for **2.153** and **2.154** respectively, would be a non-equivalent population equilibrium in favour of **2.153**, presumably driven by steric strain attributed to the large substituted aromatic moiety. However, both Katoh's and Alvarez-Manzaneda's reported syntheses of liphagal (**2.2**) contradict this rationale. Katoh *et al* synthesised an analogous ring expanded ketone (**2.133**) as a single diastereomer under almost identical conditions to our own, employing *m*-CPBA and TFA (scheme 2.20).^[127] Similarly, Alvarez-Manzaneda reported the isolation of two diastereomeric diols, **2.62** and **2.63**, which upon treatment with phosphorus oxychloride in pyridine, afforded the ring expanded benzylic ketones **2.65** and **2.68** (scheme 2.7).^[107] Ring expanded ketone **2.65** was observed to undergo cyclisation to **2.66** via a one-pot hydrogenation (H₂ and Pd/C), and subsequent acidification with perchloric acid in MeOH. In contrast, under the same conditions, the desired cyclised liphagal scaffold **2.66** could only be isolated in trace quantities from ketone **2.68**, alongside an unresolvable mixture of products. Despite investigating various acidic and basic conditions, Alvarez-Manzaneda concluded that ketone **2.68** could not be isomerised to its epimer **2.65**. Given that benzylic ketones **2.65** and **2.68**, which are analogous to our own, were not found to readily undergo keto-enol tautomerisation under either acidic or basic conditions, we would argue that the 2:1 ratio observed for our ketone system (**2.153** and **2.154**) is most likely not due to an acid catalysed *in situ* epimerisation of the benzylic moiety. Therefore, we suspect that the observed preference for the formation of ring expanded ketone **2.153** over **2.154** is most likely due to the differing sterically strained nature of the two envisioned competing benzylic carbocation intermediates. We predict that the more favourable carbocation intermediate **2.152** would possess the benzylic carbocation substituent projecting equatorially from the sesquiterpene six-membered ring system, and the less favourable competing carbocation with the bulky tri-*iso*-proxy phenyl moiety projecting in an axial fashion (scheme 2.29). The former (**2.152**) would represent the more stable carbocation of the two competing intermediates due to the minimisation of unfavourable steric interactions. Thus, benzylic carbocation intermediate **2.152** would in theory give rise to ketone **2.153** as the major product, and the more sterically strained axial benzylic carbocation intermediate would afford **2.154** (scheme 2.29).



Scheme 2.30: Attempted ring expansion of aldehyde **3.146** via one-pot, epoxidative/acidic conditions.

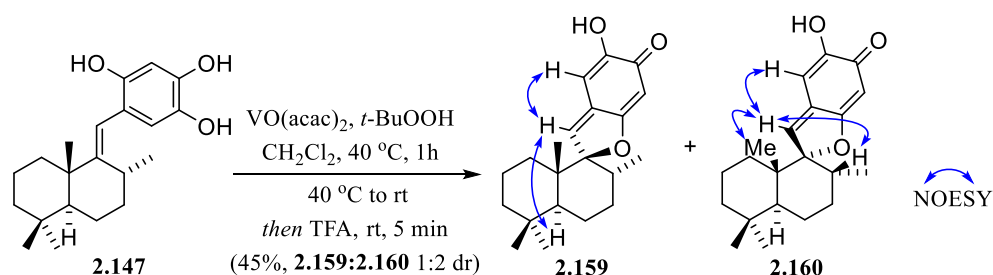
Following the successful ring expansion of alkene **2.139**, we set out to determine whether the aryl aldehyde moiety of the siphonodictyal-meroterpenoid system was susceptible to oxidation/decomposition under our investigated one-pot, epoxidative/acidic conditions, in the pursuit of liphagal (**2.2**) from siphonodictyal B (**2.91**). As suspected, under the same successful conditions for the ring expansion of **2.139**, no discernible product was observed to form during both the epoxidation and acid catalysed procedures, as determined by TLC analysis (scheme 2.30). Upon quenching the reaction mixture, only a mixture of seemingly decomposed unidentifiable by-products were isolated following column chromatography.

Given that the conditions explored thus far failed to epoxidise and transform both siphonodictyal B (**2.91**) and the protected aldehyde **2.146** to their respective products, yet were able to afford ring expanded ketones **2.153** & **2.154** from alkene **2.139**, we suspected that the aryl aldehyde moiety of the siphonodictyal system was susceptible to oxidation upon addition of *m*-CPBA. Although the aryl aldehyde moiety appeared to undergo degradation, as evident by the failed transformation of aldehyde **3.146**, it was unclear whether the phenolic oxygens were also impeding the reaction events from proceeding. Therefore, we set out to acquire the previously, yet accidentally synthesised deprotected alkene **2.147**, which was isolated upon investigating Reiche formylation conditions (scheme 2.25). **2.139** was deprotected via addition of BCl_3 to afford **2.147** (scheme 2.31). However, the transformation of acquired analogue **2.147** to the liphagal analogue **2.158** was found to be unsuccessful under Kuan's one-pot protocol.



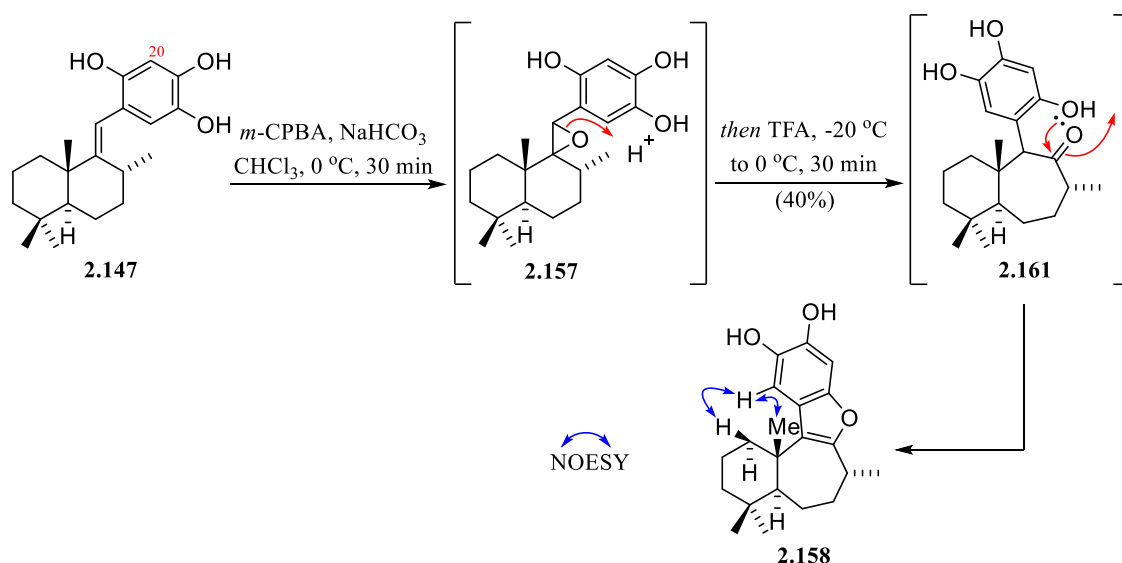
Scheme 2.31: Synthesis of model **2.147** and investigation into our groups one-pot, epoxidative/acidic protocol.

In light of this observation, we set out to investigate an epoxidation procedure developed by Alessandra Lattanzi, which detailed a $\text{VO}(\text{acac})_2$ catalysed epoxidation with *t*-BuOOH (scheme 2.31).^[141] However, upon purification, a mixture of spirocycles **2.159** and **2.160** were isolated, and no anticipated liphagal analogue **2.158** was observed to have formed. Comprehensive NMR analysis revealed the identity of the isolated spirocycles as analogues of corallidictyals A (**2.3**) and B (**2.4**) (Figures 2.1 and 2.2). In addition, spirocycles **2.159** and **2.160** were isolated in a 1:2 ratio respectively, analogous to the 3:7 ratio that was observed upon isolation of corallidictyals A (**2.3**) & B (**2.4**) by Westly.^[100] However, efforts to acquire **2.159** and **2.160** in significant quantities under the same vanadium oxide epoxidation conditions proved difficult. (scheme 2.32). As the $\text{VO}(\text{acac})_2$ was added in a 10% molar equivalence relative to **2.147**, we suspect that the vanadium oxide complex directly oxidised the siphonodictyal B analogue **2.147**. Evidence for our claim stems from the emergence of a less polar spot upon TLC analysis, which coincided with a deep red colour change of the reaction mixture upon addition of $\text{VO}(\text{acac})_2$, preceding the inclusion of *t*-BuOOH. Thus, assuming $\text{VO}(\text{acac})_2$ directly oxidised the siphonodictyal B analogue **2.147** to either an *ortho*- or a *para*-quinone, then cyclisation to spirocycles **2.159** and **2.160** may have ensued upon addition of TFA (scheme 2.32), akin to our proposal for the biosynthesis of corallidictyals A (**2.3**) and B (**2.4**) (scheme 2.13 and 2.14).



Scheme 2.32: Synthesis of spirocycles **2.159** & **2.160** in the attempted one-pot, VO(acac)₂ catalysed epoxidative/acidic biogenic transformation of siphonodictyal B analogue **2.147**.

As the one-pot, VO(acac)₂ facilitated epoxidation/TFA conditions failed to afford the anticipated liphagal analogue **2.158**, we returned to our previously explored *m*-CPBA/TFA conditions to investigate various solvent and temperature protocols. Changing solvent system from CH₂Cl₂ to CHCl₃ was found to afford the desired analogue **2.158**, albeit in a yield of 19% (scheme 2.33). Yields were further improved by optimising the temperature protocol while employing chloroform as the solvent system. TFA was added to the reaction mixture at -20 °C and was gradually warmed to 0 °C, which gave liphagal analogue **2.158** in a yield of 40% (scheme 2.33).



Scheme 2.33: Successful model investigation of a one-pot, epoxidation and acid catalysed biogenic transformation of **2.147** to **2.158**.

2.6.2 Synthesis of Liphagal (2.2) from Siphonodictyal B (2.91)

Given the successful formation of **2.158** from siphonodictyal B analogue **2.147**, we suspected that the aryl aldehyde moiety of siphonodictyal B (**2.91**) was responsible for impeding the epoxidation event upon the addition of *m*-CPBA. Conditions employing CH₂Cl₂ that were cooled to 0 °C or colder during the epoxidation protocol led to the isolation

of liphagal (**2.2**) in trace quantities, as indicated by key characteristic spectral peaks by ^1H NMR analysis (entries 1 and 2, table 2.5). In contrast, temperatures above $0\text{ }^\circ\text{C}$ during the epoxidation of siphonodictyal B (**2.91**) solely afforded decomposition by-products (entry 5, table 2.3). Next, CH_2Cl_2 was substituted for CHCl_3 , as explored in our previously successful model system (scheme 2.33). We also sought to determine the significance of the NaHCO_3 buffering agent for the epoxidation event. Both epoxidation protocols employing the solvent CHCl_3 , with or without the addition of NaHCO_3 , afforded liphagal (**2.2**) from siphonodictyal B (**2.91**) in similarly poor yields. Characterisation data of our synthetic sample of liphagal (**2.2**) was found to match perfectly to that of Andersen's reported synthetic and natural samples (entries 5 and 6, table 2.5). Although both protocols employing CHCl_3 gave rise to liphagal (**2.2**), conditions with NaHCO_3 led to slightly greater yields (entry 5, table 2.5). We suspect NaHCO_3 marginally improved yields by buffering against free protons, liberated upon the formation of *m*-chlorobenzoic acid from *m*-CPBA during the epoxidation of siphonodictyal B (**2.91**).

Further optimisation of the acid catalysed ring expansion/cascade protocol was investigated by trialling varying temperature conditions preceding the addition of TFA, following the epoxidation of siphonodictyal B (**2.91**). Mirroring the same temperature protocol explored for the synthesis of the model liphagal analogue **2.158** (scheme 2.33), liphagal (**2.2**) was obtained in an improved yield of 16% upon cooling the reaction mixture to $-20\text{ }^\circ\text{C}$ preceding the addition of TFA, and then warmed to $0\text{ }^\circ\text{C}$ before being quenched (entry 7, table 2.5). Interestingly, for the previously explored model system under the same temperature protocol, liphagal analogue **2.158** was acquired in a yield of 40% (scheme 2.33), compared to 16% for the synthesis of liphagal (**2.2**) from siphonodictyal B (**2.91**) (entry 7, table 2.5). As the model system explored differs only by the existence of the aryl aldehyde substituent at C20, then it would seem reasonable to conclude that the discrepancy in the isolated yield of liphagal (**2.2**), compared to liphagal model **2.158**, is most likely due to the aryl aldehyde moiety, which we suspect, is susceptible to an oxidative attack from *m*-CPBA, akin to a Dakin oxidation. Further optimisation led to an improved temperature protocol, where upon the addition of TFA, the reaction mixture was gradually warmed from $-20\text{ }^\circ\text{C}$ to room temperature and was stirred for 2 hours to afford liphagal (**2.2**) in a yield of 26% (entry 8, table 2.5). Additional attempts to modify the TFA and corresponding temperature protocols failed to improve yields of liphagal (**2.2**), which led us to investigate alternative chlorinated solvents. CHCl_3 was substituted for CCl_4 , and following the same previously optimised temperature protocol, liphagal (**2.2**) was isolated in a significantly improved yield of 42% (entry 9, table 2.5). Yields could not be improved following the exploration of other various

chlorinated solvents ($\text{Cl}_2\text{CHCHCl}_2$) and as such, our investigation into the synthesis of liphagal (**2.2**) from siphonodictyal B (**2.91**) could not be further optimised.

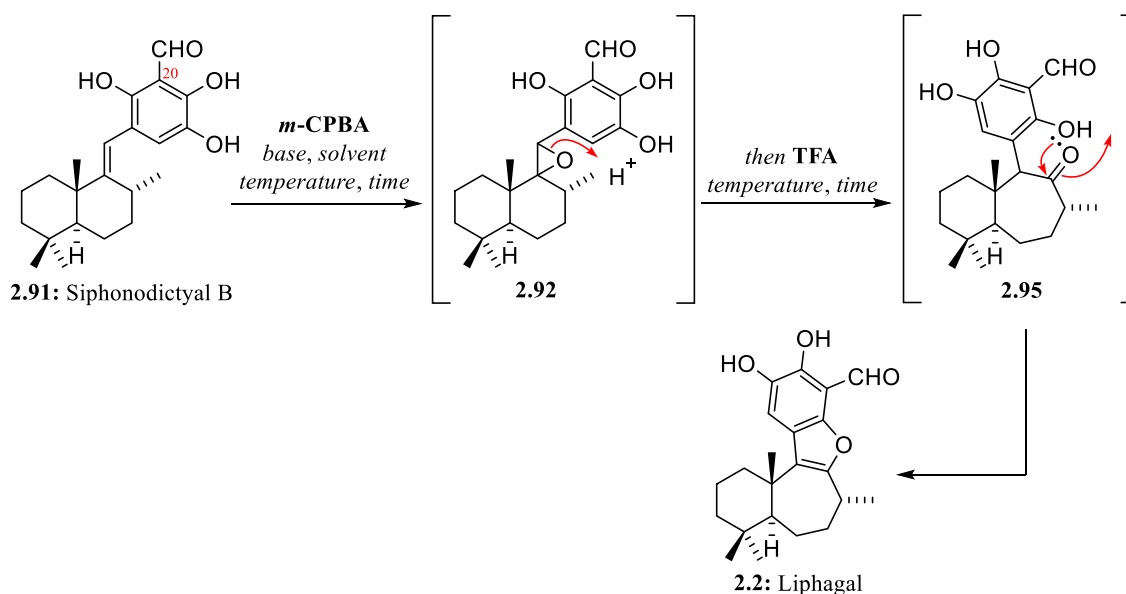
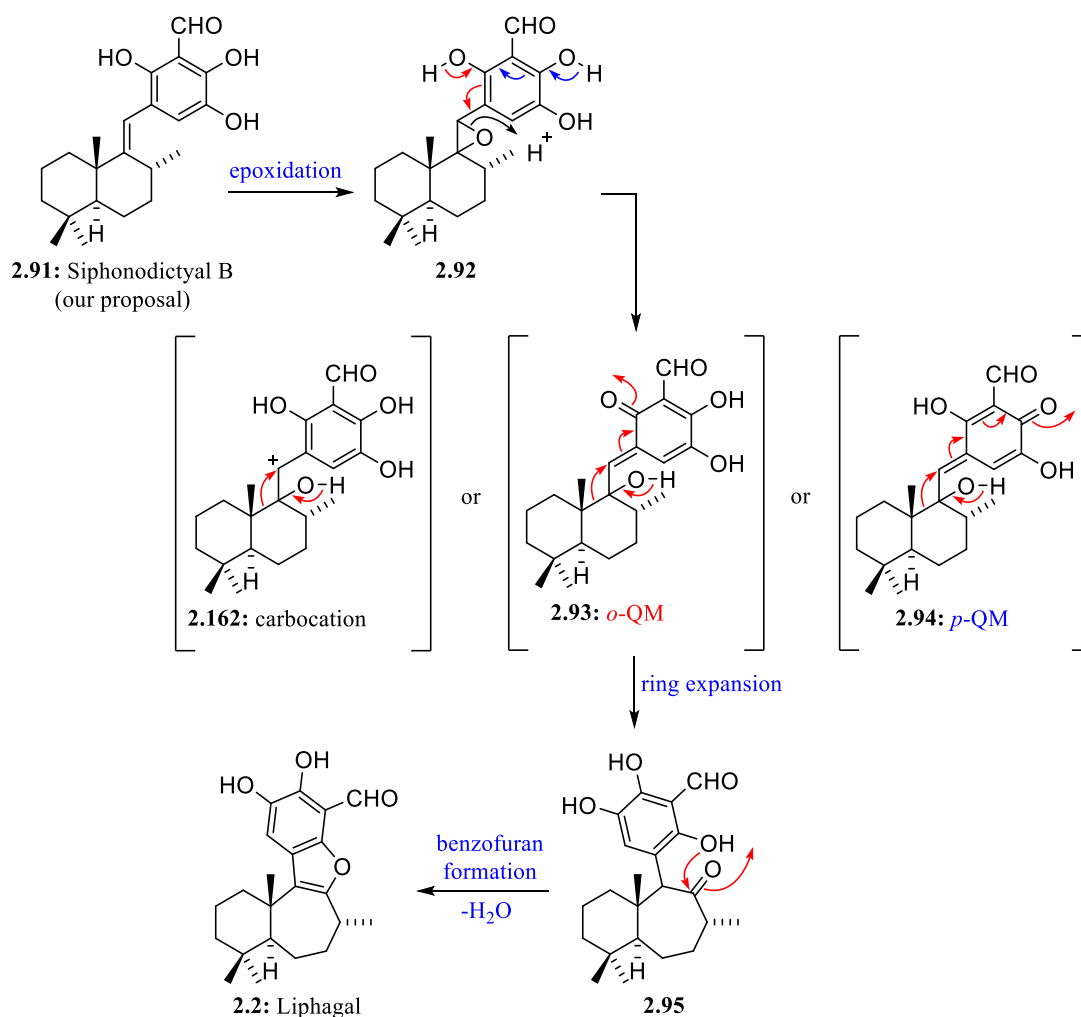


Table 2.5: Investigation of our one-pot, biogenic synthesis of liphagal (**2.2**).

Entry	Solvent/Base	Conditions for epoxidation	Conditions for the addition of TFA	Yield of Liphagal (2.2)
1	$\text{CH}_2\text{Cl}_2/$ NaHCO_3	$-10\text{ }^\circ\text{C}$, 1 h	$-20\text{ }^\circ\text{C}$, 1 h	trace
2	$\text{CH}_2\text{Cl}_2/$ NaHCO_3	$0\text{ }^\circ\text{C}$, 1 h	$-20\text{ }^\circ\text{C}$, 1 h	trace
3	$\text{CH}_2\text{Cl}_2/$ NaHCO_3	$10\text{ }^\circ\text{C}$, 1 h	$-20\text{ }^\circ\text{C}$, 1 h	decomposition
4	THF/ NaHCO_3	$0\text{ }^\circ\text{C}$, 1 h	$-20\text{ }^\circ\text{C}$, 1 h	trace
5	$\text{CHCl}_3/$ NaHCO_3	$0\text{ }^\circ\text{C}$, 1 h	$-20\text{ }^\circ\text{C}$, 1 h	10%
6	CHCl_3	$0\text{ }^\circ\text{C}$, 1 h	$-20\text{ }^\circ\text{C}$, 1 h	8%
7	$\text{CHCl}_3/$ NaHCO_3	$0\text{ }^\circ\text{C}$, 1 h	$-20\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$, 20 min then $0\text{ }^\circ\text{C}$, 1 h	16%
8	$\text{CHCl}_3/$ NaHCO_3	$0\text{ }^\circ\text{C}$, 1 h	$0\text{ }^\circ\text{C}$ to rt, 30 min then rt, 2 h	26%
9	$\text{CCl}_4/$ NaHCO_3	$0\text{ }^\circ\text{C}$, 1 h	$0\text{ }^\circ\text{C}$ to rt, 30 min then rt, 2 h	42%

2.6.3 Speculation into the Biogenically Inspired Transformation of Siphonodictyal B to Liphagal



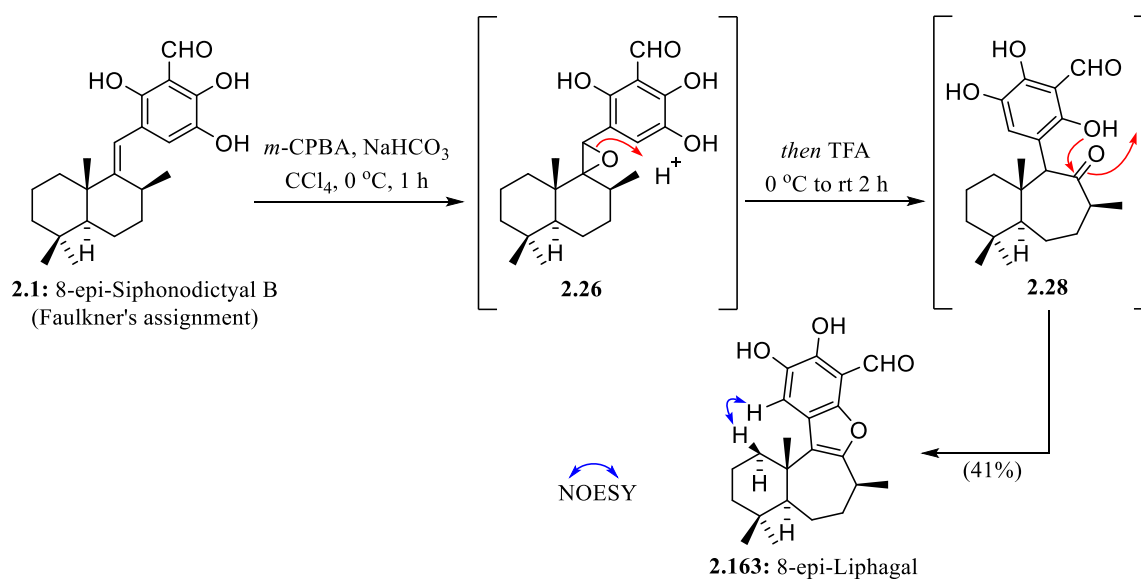
Scheme 2.34: Possible mechanistic pathways for our biomimetic synthesis of liphagal (**2.2**).

As proposed, there are three possible competing intermediates, carbocation **2.162**, *o*-QM **2.93** and *p*-QM **2.94**, that may arise following the acid catalysed ring opening of epoxide **2.92**. All three possible intermediates would be expected to give rise to ring expanded ketone **2.95** and consequently, liphagal (**2.2**) (scheme 2.34). Given that *o*-QMs (**2.93**) or *p*-QMs (**2.94**) do not exist as charged species, but rather, are in equilibrium with their tautomeric Zwitterionic species, they may prove to be more stable alternatives to carbocation intermediate **2.162**. Therefore, of the three possible intermediates following ring opening of epoxide **2.92**, the quinone methides, *o*-QM **2.93** and *p*-QM **2.94**, may be favoured alternative intermediates over carbocation **2.162**. Additionally, *p*-QM **2.94** would be expected to possess a lower energetic barrier of formation (E_a) and hence, would represent the more stable intermediate relative to *o*-QM **2.93**, as indicated by the exclusive emergence of the *p*-QM **2.140** upon the attempted elimination of benzyl alcohol **2.138** (scheme 2.23). Therefore,

given that the emergence of both quinone methide intermediates (**2.93** & **2.94**) is possible, we would expect that the ring expansion event would proceed via *p*-QM **2.94**, and not *o*-QM **2.93** (scheme 2.34).

2.6.4 Biomimetic Synthesis of 8-*epi*-Liphagal (**2.163**) from 8-*epi*-Siphonodictyal B (**2.1**)

Continuing from our successful one-pot transformation of siphonodictyal B (**2.91**) to liphagal (**2.2**), we sought to investigate an analogous one-pot transformation of Faulkner's erroneously assigned 8-*epi*-siphonodictyal B (**2.1**) to 8-*epi*-liphagal (**2.163**). As there was no evidence for the formation of 8-*epi*-liphagal (**2.163**) from siphonodictyal B (**2.91**), we were intent on determining if an epimerisation event at the C8 position could occur during a one-pot transformation of 8-*epi*-siphonodictyal B (**2.1**). Therefore, we set out to synthesise 8-*epi*-liphagal (**2.163**) from Faulkner's erroneously assigned configuration of 8-*epi*-siphonodictyal B (**2.1**) to confirm that a non-enzymatically mediated epimerisation could not occur under our employed oxidative/acidic conditions (scheme 2.35). Following our previously optimised protocol (entry 9, table 2.5), 8-*epi*-siphonodictyal B (**2.1**) was epoxidized, the mixture was cooled to -20 °C preceding the addition of TFA, and the resultant mixture was gradually warmed to afford 8-*epi*-liphagal (**2.163**) in a yield of 41% (scheme 2.35). As suspected, evidence for an epimerisation event was not observed as indicated by the lack of liphagal (**2.2**) present within any of the fractions isolated upon purification.



Scheme 2.35: biomimetic transformation of 8-*epi*-siphonodictyal B (**2.1**) to 8-*epi*-liphagal (**2.163**).

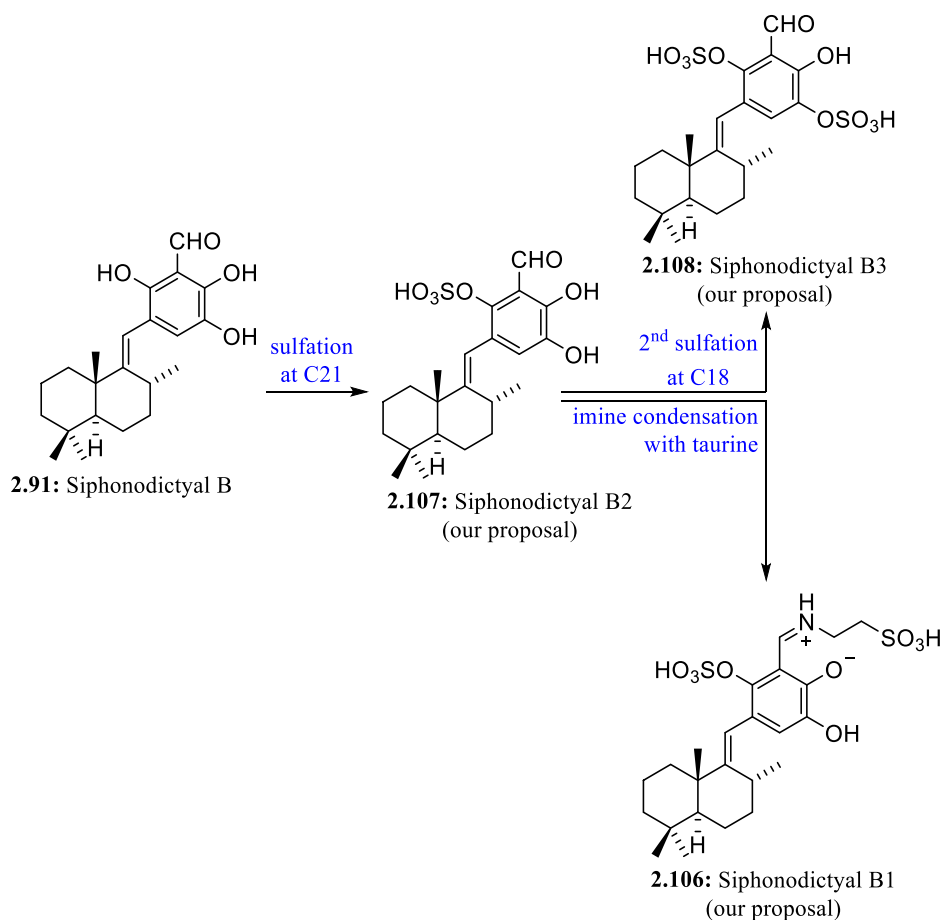
As suspected, there was no evidence for the simultaneous emergence of both liphagal C8 epimers, **2.2** & **2.163**, arising from either siphonodictyal B (**2.91**) or 8-*epi*-siphonodictyal B

(**2.1**) during the investigated one-pot biomimetic reactions (table 2.5 or scheme 2.35). Therefore, we can confidently conclude that under our non-enzymatic conditions, a C8 epimerisation event does not occur. Based on these experiments, it would be reasonable to assume that the possibility of a non-enzymatic epimerisation event occurring in nature during the biosynthesis of liphagal (**2.2**) from siphonodictyal B (**2.91**), is highly unlikely. As of the writing of this literature, liphagal (**2.2**) does not appear to target any specific system or fulfil a necessary biological role, i.e. strong anti-bacterial activity etc. (*Aka coralliphaga*). Therefore, liphagal (**2.2**) does not appear to provide any specific benefit, and does not appear to be crucial to the survival of the host organism, unlike the contrasting example of the family of penicillin producing fungi, *Penicillium*.^[24] Hence, if the above premises are true, and there is no clear selective pressure for the emergence of liphagal (**2.2**), then we must conclude that the likelihood for the evolution of dedicated substrate-specific enzymes that would closely regulate the biosynthesis of liphagal (**2.2**) is remote. Based on this rationale, theorising the existence of specific epimerising enzymes, under Andersen's biosynthetic *pathway A*, introduces unnecessary complexity to a metabolic system, while also leading to unfavourable resource management issues for the host organism. However, it would appear plausible that the epoxidation event of siphonodictyal B (**2.91**) may be mediated by more promiscuous cytochrome P450 enzymes. The resultant siphonodictyal B epoxide **2.92** most likely undergoes a non-enzymatic, spontaneous ring opening and cascade sequence to afford liphagal (**2.2**) in nature.

2.7 Synthetic Investigation of Siphonodictyals B1 – B3

Following the successful biogenically inspired synthesis of liphagal (**2.2**), we set out to synthesise the series of naturally occurring sulphated siphonodictyal B (**2.91**) analogues, siphonodictyals B1 – B3, **2.106** – **2.108**, in accordance with our proposal (scheme 2.15), following the successful stereochemical reassignment of siphonodictyal B (tables 2.3 & 2.4). Synthetic access to the sulfated siphonodictyals was envisioned by an initial sulfation of siphonodictyal B (**2.91**) at C21 to give siphonodictyal B2 **2.107**, with a second subsequent sulfation at C18 to afford siphonodictyal B3 **2.108**. Siphonodictyal B1 **2.106** could be potentially accessed via an imine condensation of siphonodictyal B2 **2.107** with 2-aminoethanesulfonic acid (scheme 2.36). However, a regioselective sulfation at C21, and another successive sulfation at C18, would prove difficult under non-enzymatically mediated methods. Nonetheless, we set out to acquire siphonodictyal B2 **2.107** & B3 **2.108** via sulfation of siphonodictyal B (**2.91**) in a non-selective manner, then given the anticipated

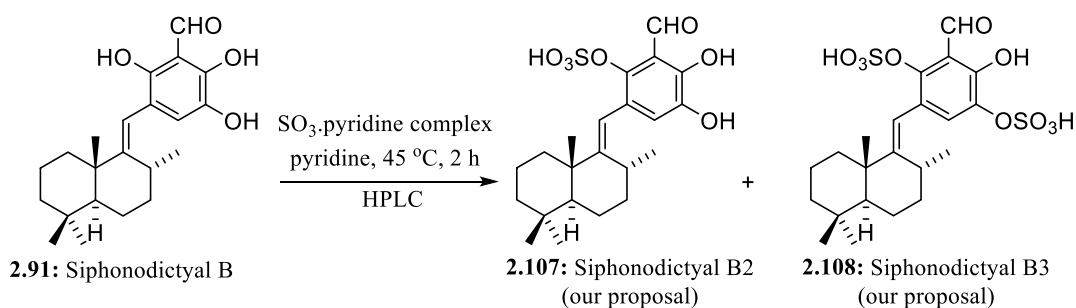
success of the sulfation procedure, to attempt the synthesis of siphonodictyal B1 **2.106** by an imine condensation of **2.107** and 2-aminoethanesulfonic acid.



Scheme 2.36: Biosynthesis of siphonodictyals B1 – B3 (**2.106** – **2.108**) from siphonodictyal B (**2.91**), in accordance with our proposed stereochemical reassignment.

The search of mild conditions throughout the literature for the sulfation of phenolic alcohols, that would also be compatible with the sensitive alkenyl moiety of siphonodictyal B (**2.91**), appeared to be limited to only a handful of sulfating agents. A procedure by Wolfenden for acquiring sulfated phenolic esters detailed the use of commercially available SO₃.pyridine in a pyridine solution with a given phenol.^[142] Following Wolfenden's protocol,^[142] siphonodictyal B (**2.91**) was heated as a mixture with SO₃.pyridine in pyridine, and was stirred for two hours (scheme 2.37). As the sulfated siphonodictyal B derivatives were expected to be water soluble, the solvent was removed under reduced pressure following the addition of sodium bicarbonate, before loading the crude mixture onto a HPLC column and eluting with a MeCN:H₂O solvent gradient. Given that the crude sulfated mixture was loaded directly onto the HPLC column, we chose not to use Köck's MeCN/NH₄OAc gradient mixture, due to concerns of blocking eluent flow.^[96] Instead, a MeCN/H₂O eluent gradient was chosen to minimise potential precipitation of any salts and non-polar by-products

introduced upon loading the crude mixture onto the column (table 2.6). The acquired retention times for our unknown sulfated reaction mixture were compared to those reported by Köck for the elution of siphonodictyals B2 (**2.107**) and B3 (**2.108**) via HPLC-MS. However, comparison of our acquired retention times proved difficult due to the variance in our HPLC method, column length and type, as well as the composition of the crude reaction mixture itself. However, speculation into the comparison of Köck's method, and our own, hinted as the potential identity of the acquired fractions (table 2.6).



Scheme 2.37: Attempted synthesis of siphonodictyals B2 and B3, **2.107** and **2.108**, from siphonodictyal B (**2.91**).

Upon the attempted purification of the reaction mixture, the first peak eluted appeared to solely possess water soluble impurities that did not display any characteristic spectral peaks of either the desired sulfated products or siphonodictyal B (**2.91**), as indicated by NMR analysis (peak 1, table 2.6). We suspect that the second and third peaks to elute contained di- (peak 2, table 2.6) and mono-sulfated (peak 3, table 2.6) products of siphonodictyal B (**2.91**) respectively, given their relatively similar retention times for the elution of siphonodictyals B3 (**2.108**) (peak 6, table 2.6) and B2 (**2.107**) (peak 7, table 2.6) as reported by Köck.^[96] Upon analysis of the freeze dried samples, the second (peak 2, table 2.6) and third (peak 3, table 2.6) eluted fractions were only found to possess a few key identifiable ¹H NMR peaks that were characteristic of siphonodictyals B3 (**2.108**) and B2 (**2.107**) respectively. Both the proceeding eluted fractions (peaks 4 & 5, table 2.6) were found to be unidentifiable complex mixtures, with the fifth (peak 5, table 2.6) fraction possessing a few key ¹H NMR spectral peaks that were characteristic of siphonodictyal B (**2.91**). Despite all attempts to optimise Wolfenden's SO₃.pyridine and pyridine conditions,^[142] we were unable to obtain both siphonodictyal B2 (**2.107**) & B3 (**2.108**) and as such, the synthesis of siphonodictyal B1 (**2.106**) could not be attempted. Based on the above results, we predict that the biosynthesis of the sulfated siphonodictyal B meroterpenoids, **2.106** – **2.108**, may be facilitated by either regioselective or promiscuous enzymes in nature.

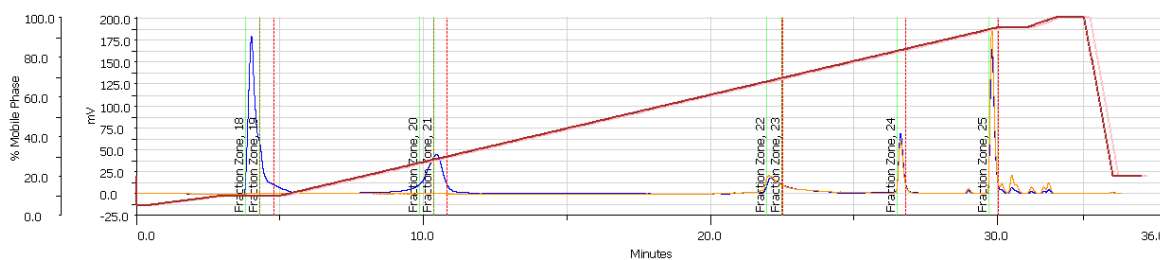


Table 2.6: Above. Our HPLC trace for the attempted synthesis of siphonodictyals B1 **2.107** and B2 **2.108**. **Below.** Comparison of HPLC elution rates of Köck's^[96] reported isolation of siphonodictyals B2 (**2.107**) and B3 (**2.108**) against our unknown fractions (below).

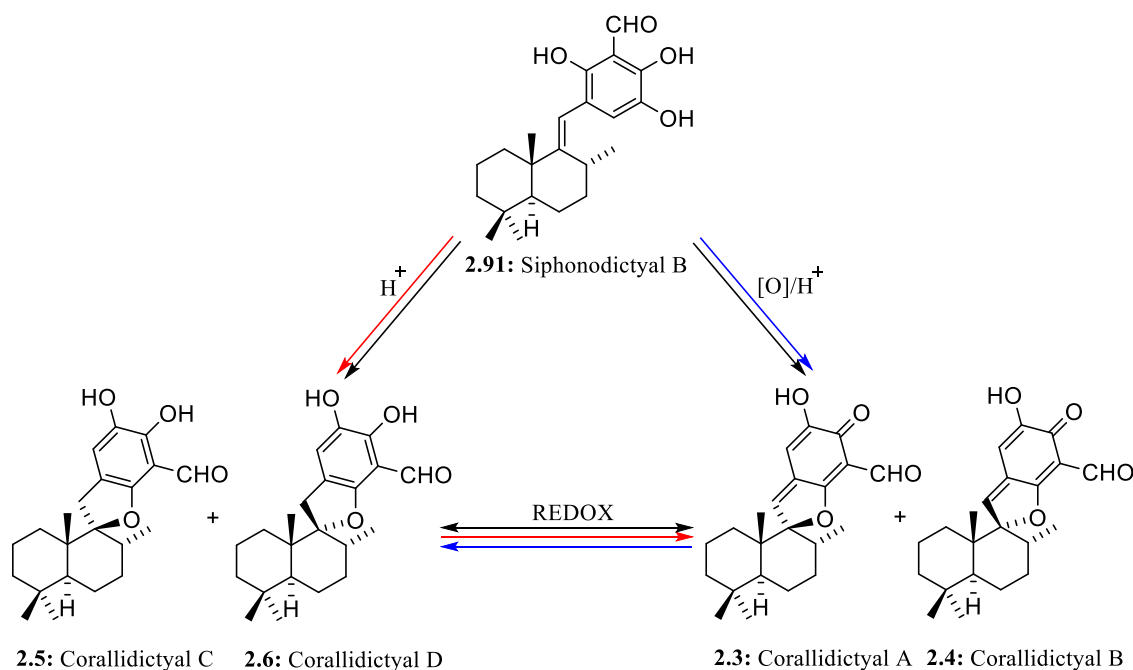
<i>Peak/Compound</i>	<i>Author</i>	<i>Elution time</i>	<i>Eluent ratio</i>
1	this work	3.9 minutes	10% MeCN/90% H ₂ O
2	this work	10.5 minutes	30% MeCN/70% H ₂ O
3	this work	22.0 minutes	65% MeCN/35% H ₂ O
4	this work	26.7 minutes	82% MeCN/18% H ₂ O
5	this work	29.8 minutes	97% MeCN/3% H ₂ O
6 (Siphonodictyal B3: 2.108)	Köck <i>et al</i>	11.9 minutes	20% MeCN/80% NH ₄ OAc
7 (Siphonodictyal B2: 2.107)	Köck <i>et al</i>	17.1 minutes	20% MeCN/80% NH ₄ OAc

Köck *et al* HPLC protocol: HPLC-MS analyses were performed with an Agilent 1100, HPLC system and a Bruker Daltonics microTOFLC mass spectrometer. Separation was achieved by a Waters XTerra RP18 column (3.0×150mm, 3.5 μm), applying a MeCN/NH₄OAc (5 mM in water) gradient (0 min: 20% MeCN/80% NH₄OAc; 30 min: 100% MeCN/0% NH₄OAc; 35 min: 100% MeCN/0% NH₄OAc).^[96] Our HPLC protocol: HPLC analyses was performed with a Gilson GX-Prep HPLC system, equipped with a Phenomenex C18 column (250×21.2 mm), applying a MeCN/H₂O gradient (0 min: 5% MeCN/95% H₂O; 3 min: 10% MeCN/90% H₂O; 5 min to 30 min: 10% MeCN/90% H₂O to 90% MeCN/10% H₂O).

Upon the attempted purification of the reaction mixture, the first peak eluted appeared to solely possess water soluble impurities that did not display any characteristic spectral peaks of either the desired sulfated products or siphonodictyal B (**2.91**), as indicated by NMR analysis (peak 1, table 2.6). We suspect that the second and third peaks to elute contained di- (peak 2, table 2.6) and mono-sulfated (peak 3, table 2.6) products of siphonodictyal B (**2.91**) respectively, given their relatively similar retention times for the elution of siphonodictyals B3 (**2.108**) (peak 6, table 2.6) and B2 (**2.107**) (peak 7, table 2.6) as reported by Köck.^[96] Upon analysis of the freeze dried samples, the second (peak 2, table 2.6) and third (peak 3, table 2.6) eluted fractions were only found to possess a few key identifiable ¹H NMR peaks that were characteristic of siphonodictyals B3 (**2.108**) and B2 (**2.107**) respectively. Both the preceding eluted fractions (peaks 4 & 5, table 2.6) were found to be unidentifiable complex mixtures, with the fifth (peak 5, table 2.6) fraction possessing a few key ¹H NMR spectral peaks that were characteristic of siphonodictyal B (**2.91**). Despite all attempts to optimise Wolfenden's SO₃.pyridine and pyridine conditions,^[142] we were unable to obtain both siphonodictyal B2 (**2.107**) & B3 (**2.108**) and as such, the synthesis of

siphonodictyal B1 (**2.106**) could not be attempted. Based on the above results, we predict that the biosynthesis of the sulfated siphonodictyal B meroterpenoids, **2.106** – **2.108**, may be facilitated by either regioselective or promiscuous enzymes in nature.

2.8 Investigation into the Biomimetic Synthesis and Biosynthetic Origins of Corallidictyals A – D



Scheme 2.38: Our proposed biosynthetic origin of the corallidictyals A – D (**2.3** – **2.6**). Black arrows: proposed access to corallidictyals A (**2.3**) & B (**2.4**) and C (**2.5**) & D (**2.6**) by interconversion through REDOX conditions and from siphonodictyal B (**2.91**). Red arrows: corallidictyals C (**2.5**) & D (**2.6**) accessed exclusively from A (**2.3**) & B (**2.4**), which in turn are formed from siphonodictyal B (**2.91**). Blue arrows: corallidictyals A (**2.3**) & B (**2.4**) accessed exclusively from C (**2.5**) & D (**2.6**), which in turn are formed from siphonodictyal B (**2.91**).

With the successful conversion of siphonodictyal B (**2.91**) to liphagal (**2.2**) (table 2.5), we set out to investigate and further validate our divergent biosynthetic proposal by synthesising corallidictyals A – D (**2.3** – **2.6**) directly from siphonodictyal B (**2.91**). As stated in our proposal (schemes 2.13 – 2.15), we hypothesise that the corallidictyals A – D (**2.3** – **2.6**) are derived from siphonodictyal B (**2.91**) in nature. Here it is worth noting that as both sets of corallidictyals A (**2.3**) & B (**2.4**) and C (**2.5**) & D (**2.6**) can conceivably be interchanged with one another under REDOX conditions, and that each set may be accessed from siphonodictyal B (**2.91**) directly, then biosynthetic access to each set of corallidictyals in nature appears unclear. Thus, we sought to determine whether both sets of corallidictyals A

(**2.3**) & B (**2.4**) and C (**2.5**) & D (**2.6**) could be acquired from siphonodictyal B (**2.91**) directly, or whether one set, derived from **2.91**, may give rise to the other via REDOX conditions (scheme 2.38).

2.8.1 Investigation into the Biomimetic Synthesis of Corallidictyals A – D (**2.3** – **2.6**) from Siphonodictyal B (**2.91**)

Investigation into the synthesis of corallidictyals A (**2.3**) & B (**2.4**) was envisioned by an initial oxidation of siphonodictyal B (**2.91**), followed by addition of a Brønsted acid, in an attempt to induce a spirocyclisation event via either of the hypothesised *ortho*- or *para*-quinone intermediates, **2.102** or **2.103** (scheme 2.14). DDQ was the first oxidising agent considered, which upon addition to siphonodictyal B (**2.91**), immediately led to unidentifiable decomposition by-products (entry 1, table 2.7). As DDQ appeared to be too strong of an oxidising agent, Ag₂O was investigated as a milder alternative. However, before TFA could be added, the reaction mixture appeared to undergo considerable visual decomposition (entry 2, table 2.7). Upon ¹H NMR analysis of the major fraction isolated, a key spectral peaks that were characteristic of corallidictyals A (**2.3**) & B (**2.4**) were observed as an inseparable mixture with siphonodictyal B (**2.91**).

Following the apparent spontaneous formation of corallidictyals A (**2.3**) & B (**2.4**) with Ag₂O, our proposal regarding the requirement of an acid to facilitate the key spirocyclisation event, from either **2.102** or **2.103**, appeared incorrect (entry 2, table 2.7). However, Ag₂O was suspected to be too inherently basic, which may have led to the decomposition of siphonodictyal B (**2.91**). Therefore, the mild oxidant Ag₂CO₃ was added to a mixture of siphonodictyal B (**2.91**) and CeliteTM in benzene in accordance with a standard Fétizon oxidation protocol (entry 3, table 2.7).^[143] Despite the absence for the development of a new R_f value upon TLC analysis, the crude reaction mixture was filtered through CeliteTM to reveal corallidictyals A (**2.3**) & B (**2.4**) as the exclusive products, in a 1 : 2 ratio respectively, similarly to the 3:7 ratio reported by Westly^[100] (entry 3, table 2.7). Thus, in contrast to our previous proposal (scheme 2.13), the spirocyclisation event, following the oxidation of siphonodictyal B (**2.91**), was confirmed to occur spontaneously and did not require the addition of an acid to catalyse the formation of corallidictyals A (**2.3**) & B (**2.4**). Ag₂O was revisited as an oxidising agent, where it replaced Ag₂CO₃ in the Fétizon oxidation,^[143] to determine whether the oxidation of siphonodictyal B (**2.91**) to corallidictyals A (**2.3**) & B (**2.4**) could occur under more basic conditions. Oxidation with Ag₂O led to the isolation of

corallidictyals A (**2.3**) & B (**2.4**) in a 1:2 ratio respectively, consistent with that observed previously (entry 3, table 2.7), albeit in a notably lower yield (entry 4, table 2.7).

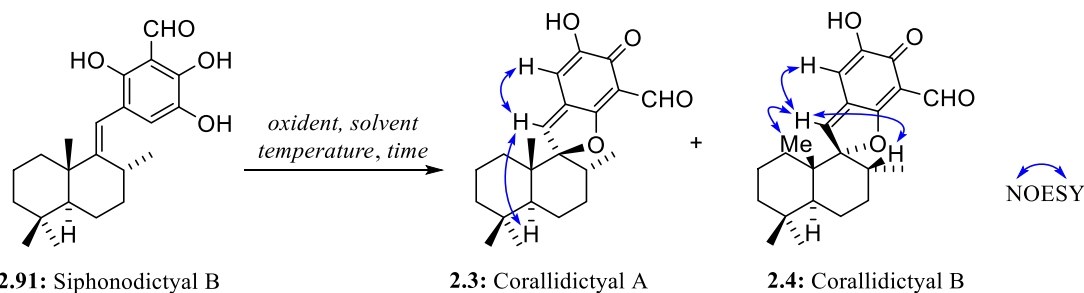


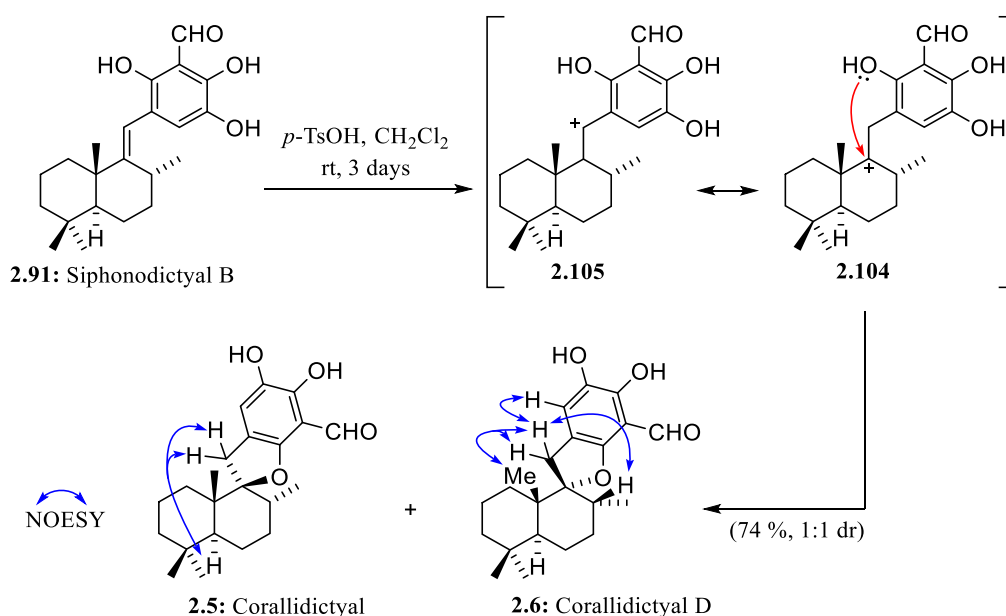
Table 2.7: Investigation for the biogenically inspired synthesis corallidictyals A (**2.3**) & B (**2.4**), from siphonodictyal B (**2.91**).

Entry	Oxidant	Solvent	Conditions	Outcome/Yield
1	DDQ	CH ₂ Cl ₂	0 °C, 30 min	Decomposition
2	Ag ₂ O	CH ₂ Cl ₂	rt, 60 min	Inseparable product with 2.91 and decomposition
3	Ag ₂ CO ₃ /Celite™	Benzene	rt, 90 min	88 % of 2.3 & 2.4 in a 1 : 2 ratio
4	Ag ₂ O/Celite™	Benzene	rt, 90 min	51 % of 2.3 & 2.4 in a 1 : 2 ratio
5	Chloranil	CH ₂ Cl ₂	rt, 24 h	62 % of 2.3 & 2.4 in a 1 : 2 ratio
6	O ₂	MeOH	rt, 8 days	29 % of 2.3 & 2.4 in a 1 : 2 ratio

Following the exploration of silver reagents for the oxidation of siphonodictyal B (**2.91**), we set out to determine whether weaker oxidants under neutral pH conditions could afford corallidictyals A (**2.3**) & B (**2.4**). Chloranil in CH₂Cl₂ led to the acquisition of corallidictyals A (**2.3**) & B (**2.4**) in a yield of 62 %, in the same previously observed diastereomeric ratio of 1:2 respectively (entry 5, table 2.7). We suspect the significantly slower reaction rate observed upon the addition of chloranil, was primarily attributed to the mild nature of the oxidant. However, it is conceivable that either slightly acidic or basic conditions may influence the rate of reaction, consequently accelerating the formation of corallidictyals A (**2.3**) & B (**2.4**) from siphonodictyal B (**2.91**).

All of the oxidants trialled so far, possess an oxidative potential that may be observed within typical biological oxidative limits. Therefore, biological oxidants, such as NAD⁺ or NADP⁺, may possess a sufficient oxidative potential to initiate a spontaneous oxidation event of siphonodictyal B (**2.91**), that may not require enzymatic mediation. Thus, we set out to investigate whether such a transformation from siphonodictyal B (**2.91**) could take place under mild environmental oxidative conditions. Investigation into the mildest oxidative conditions necessary for transformation, may indicate whether the corallidictyals A (**2.3**) &

B (**2.4**) are exclusively biosynthesised within the host organism, or if they may also be afforded upon exposure of siphonodictyal B (**2.91**) to environmental conditions. For these reasons, a freshly synthesised sample of siphonodictyal B (**2.91**) in MeOH was subjected to an atmosphere of pure O₂ via a breathable bladder. The resultant solution was stirred at room temperature for eight days to afford corallidictyals A (**2.3**) & B (**2.4**) in the same previously observed ratio of 1:2 respectively, albeit in poor yield (entry 6, table 2.7). Comparatively, efforts to oxidise siphonodictyal B (**2.91**) in the presence of air at room temperature in the dark, either in a solution of MeOH or neat, failed to yield any observable quantities of corallidictyals A (**2.3**) & B (**2.4**). After fourteen days exposed to air, both neat and methanolic solvated samples were mostly comprised of siphonodictyal B (**2.91**), alongside some minor unidentifiable decomposition by-products. Additionally, stirring siphonodictyal B (**2.91**) over SiO₂ rapidly lead to decomposition, and no characteristic peaks corresponding to corallidictyals A (**2.3**) & B (**2.4**) were observed. Based on these experiments, there appears to be significant limitations under which the corallidictyals A (**2.3**) & B (**2.4**) may be afforded from siphonodictyal B (**2.91**) upon exposure to O₂. Therefore, we predict corallidictyals A (**2.3**) & B (**2.4**) are formed primarily within the host organism via non-enzymatic or promiscuous enzymatic pathways. However, we also acknowledge that to a lesser degree, siphonodictyal B (**2.91**) may undergo oxidation outside the host cell to afford corallidictyals A (**2.3**) & B (**2.4**).



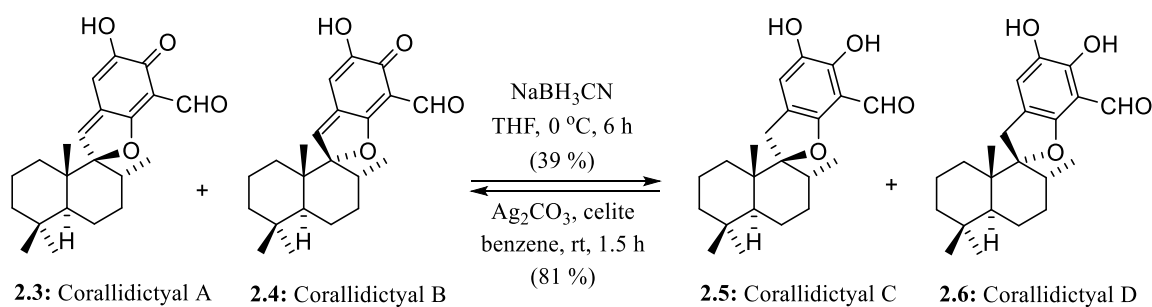
Scheme 2.39: Synthesis of corallidictyals C (**2.5**) & D (**2.6**) via an acid catalysed spirocyclisation of siphonodictyal B (**2.91**).

Next, we were interested in determining whether corallidictyals C (**2.5**) & D (**2.6**) could be accessed from siphonodictyal B (**2.91**) via an acid catalysed spirocyclisation. Investigation

into acidic conditions commenced upon subjecting siphonodictyal B (**2.91**) to a solution of *p*-TsOH in CH₂Cl₂, at room temperature and the reaction was monitored by TLC analysis (scheme 2.39). The reaction was quenched after three days following the disappearance of siphonodictyal B (**2.91**) to afford corallidictyals C (**2.5**) & D (**2.6**) in an equal relative diastereomeric ratio. The slow reaction rate observed for acid catalysed spirocyclisation of siphonodictyal B (**2.91**) was most likely due to an unfavourable equilibrium of the two competing carbocation transition states, **2.105** & **2.104**, in favour of the aromatic stabilised benzylic carbocation **2.105**. Given that corallidictyals C (**2.5**) & D (**2.6**) were the only products isolated under acid catalysed conditions, the proposed benzylic carbocation **2.105** does not appear to lead to a product endpoint. Comparatively, the tertiary carbocation **2.104** would be expected to afford the desired spirocycles, and thus, such an unfavourable equilibrium would introduce a mechanistic bottleneck in the synthesis of corallidictyals C (**2.5**) & D (**2.6**) from siphonodictyal B (**2.91**) (scheme 2.39).

2.8.2 Investigation into the Interconversion of Corallidictyals A (**2.3**) & B (**2.4**) with C (**2.5**) & D (**2.6**)

Following the synthesis of corallidictyals A – D (**2.3** – **2.6**) directly from siphonodictyal B (**2.91**), we set out to observe whether the corallidictyals A (**2.3**) & B (**2.4**) and C (**2.5**) & D (**2.6**) were interconvertible with one another under mild REDOX conditions. Investigation into such transformations would potentially allow us to gain biosynthetic insight into the origin of these meroterpenoids in nature. First, we set out to reduce corallidictyals A (**2.3**) & B (**2.4**) to C (**2.5**) & D (**2.6**) with a mild reducing agent. NaBH₃CN was chosen due to its mild reduction potential, which may be representative of biologically relevant reducing agents such as NADH. A mixture of corallidictyals A (**2.3**) & B (**2.4**), as a 1:2 diastereomeric ratio respectively, was subjected to a cooled solution of NaBH₃CN in THF. Upon purification of the quenched reaction mixture, corallidictyals C (**2.5**) & D (**2.6**) were isolated in the same conserved 1:2 ratio respectively (scheme 2.40). Next, the oxidation of the isolated mixture of corallidictyals C (**2.5**) & D (**2.6**) was attempted to obtain corallidictyals A (**2.3**) & B (**2.4**). Under the previously successful Fétizon oxidative conditions employed (entry 3, table 2.7), corallidictyals C (**2.5**) & D (**2.6**), as a 1:2 ratio respectively, was subjected to a mixture of Ag₂CO₃ and CeliteTM in benzene (scheme 2.40). Corallidictyals A (**2.3**) & B (**2.4**) were isolated in the same conserved 1:2 diastereomeric ratio respectively. We propose that the mild oxidative conditions investigated may be representative of mild biologically relevant oxidants found in nature.

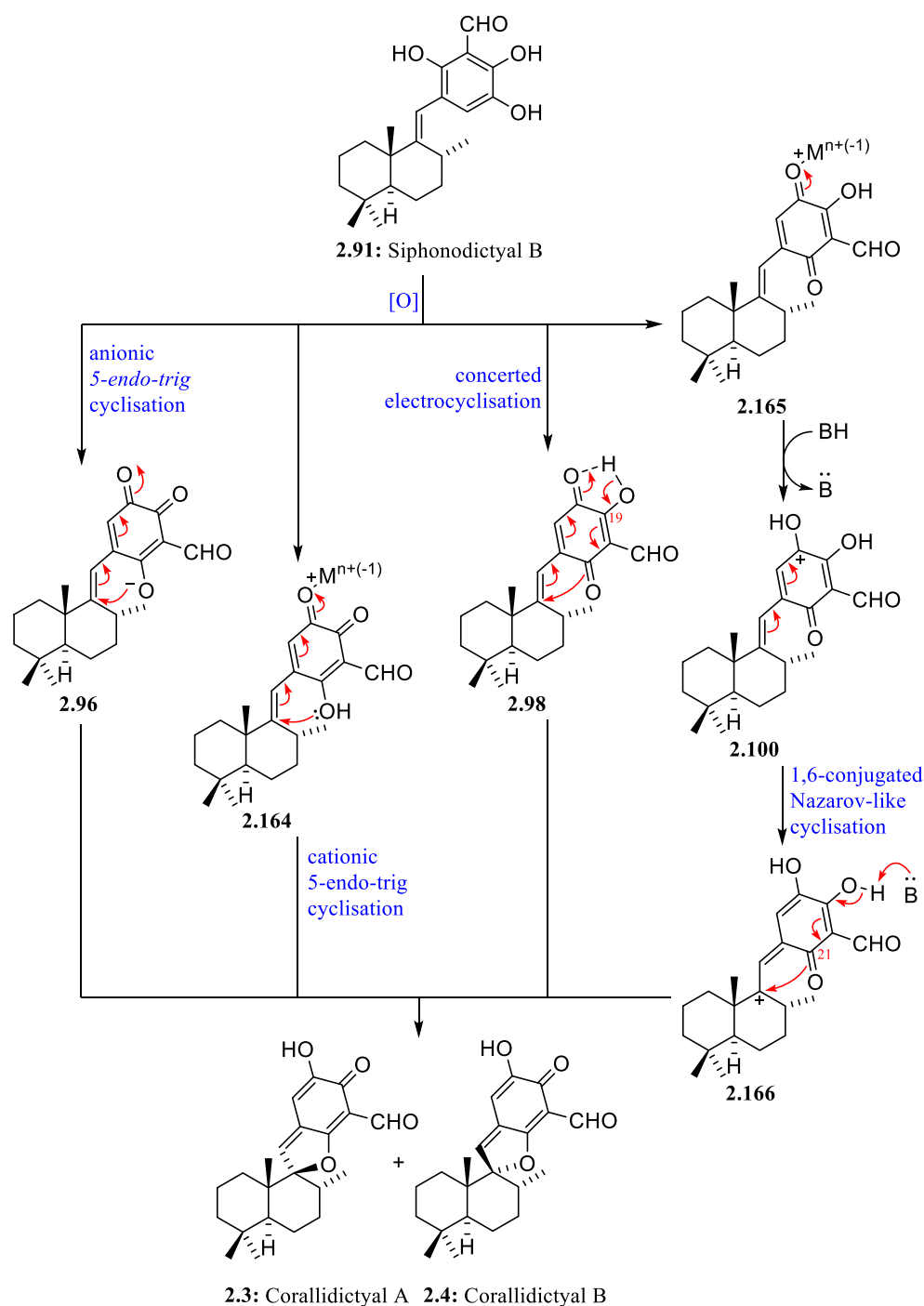


Scheme 2.40: Biogenically inspired interconversion of the corallidictyals A – D (2.3 – 2.6), under REDOX conditions.

2.8.3 Biosynthetic Speculation into the Origins of the Corallidictyals

Our initial proposal involved the presence of a Brønsted or Lewis acid, that could facilitate the spirocyclisation of either of the predicted quinone intermediates **2.102** or **2.103** (scheme 2.14). Under the previously described proposal, each plausible cyclisation pathway (**2.97**, **2.98**, **2.99** – **2.101**) was proposed to proceed via pronation of the oxygenic quinone moiety following the oxidation of siphonodictyal B (**2.91**), with exception of an anionic *5-endo-trig* cyclisation (**2.96**) (schemes 2.13).

Westly reported that the isolated corallidictyals A (**2.3**) & B (**2.4**) could not interconvert via ring opening of the spirocycle oxygen moiety, under either thermal or base facilitated conditions. Therefore, we may reasonably assume that the formation of the corallidictyals A (**2.3**) & B (**2.4**) from siphonodictyal B (**2.91**) is under kinetic control, and thus, Baldwin's rules would appear to apply in their entirety. Given that the above assumptions are true, then in the absence of an acidic catalyst, spirocyclisation of *ortho*-quinone **2.96** via an anionic *5-endo-trig* cyclisation would be disfavoured according to Baldwin's rules.^[111–114] The oxidatively induced spirocyclisation of siphonodictyal B (**2.91**) on addition of silver oxidants (Ag_2CO_3 & Ag_2O) occurred rapidly, and as such, indicates the unlikelihood that corallidictyals A (**2.3**) & B (**2.4**) form via an anionic *5-exo-trig* cyclisation from **2.96** (scheme 2.41). Therefore, given the rapid rate of reaction of siphonodictyal B (**2.91**) upon addition of silver oxidants, we propose that in the presence of a metal cation (Ag^+ , or $\text{Mg}^{2+}/\text{Ca}^{2+}$ for biological systems), an oxygenic *ortho*-quinone cation intermediate **2.164** may be generated, which could proceed to the corallidictyals A (**2.3**) & B (**2.4**) via a conjugate cationic *5-endo-trig* spirocyclisation (scheme 2.41). Alternatively, the previously described route in our initial proposal would detail an oxidative concerted spirocyclisation of from *para*-quinone **2.98** (scheme 2.13 and scheme 2.41).



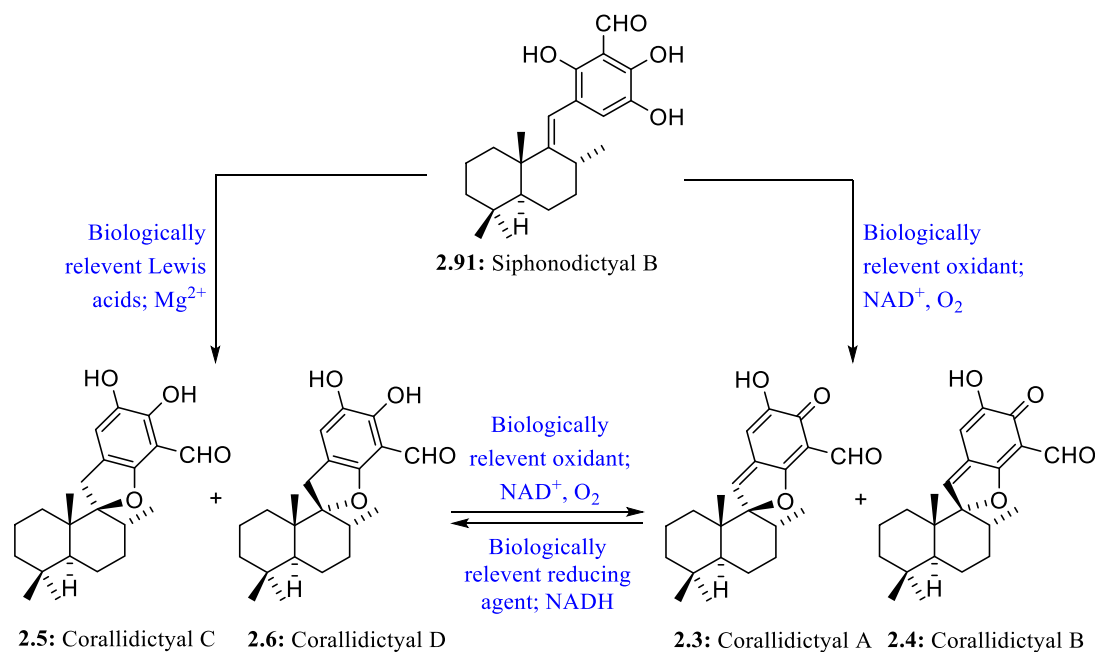
Scheme 2.41: Revised proposal for the biogenically inspired, oxidative spirocyclisation mechanism of siphonodictyal B (**2.91**) to corallidictyals A (**2.3**) & B (**2.4**). $M^{n+(-1)}$ = biological metal ion, i.e. Mg^{2+} , BH = weak conjugate acid, i.e. H_2CO_3 .

The last plausible pathway was envisioned to proceed through a step-wise cyclisation mechanism, akin to a conjugated Nazarov cyclisation (**2.165** to **2.100** then **2.166**), which conceivably, could be mediated by a metal cation (Ag^+ , Mg^{2+} , Ca^{2+} etc.) coordinating to the proposed *para*-quinone **2.165** (scheme 2.41). The tertiary carbocation intermediate **2.166** could undergo nucleophilic attack from the conjugated carbonyl oxygen at C21 (**2.166**), where the driving force for spirocyclisation is formation of the comparatively stable quinone

methide entity, to afford corallidictyals A (**2.3**) & B (**2.4**) (scheme 2.41). The concerted electrocyclization route (**2.98**) would be expected to proceed spontaneously, and independently of any counter ion (Ag^+ or CO_3^{2-}). On the other hand, we predict that the proposed 1,6-conjugate Nazarov-like spirocyclisation route (**2.165** to **2.100** then **2.166**) would depend upon the presence of a coordinating cation. Under our proposed competing pathways (scheme 2.41), the strength of the oxidant employed would not be the sole determining factor in the rate of formation for the corallidictyals A (**2.3**) & B (**2.4**). Both the oxidative potential of the oxidant and the availability of cationic species (Ag^+ , Mg^{2+} , Ca^{2+} etc.) would be expected to determine the rate of reaction of siphonodictyal B (**2.91**). Therefore, if more than one oxidative mechanism was possible, then we would expect the reaction rate to be determined by the most favourable reaction pathway available to siphonodictyal B (**2.91**). Thus, if the non-metal oxidant conditions explored limited the number of permitted favourable reaction pathways available to siphonodictyal B (**2.91**), then we would expect a mechanistic bottleneck to ensue, which may account for the observed discrepancy in reaction rates for silver oxidants (entries 3 and 4, table 2.7) compared to non-metal oxidants (entries 5 and 6, table 2.7).

Following our successful investigation into the synthesis of the corallidictyals A – D (**2.3** – **2.6**) directly from siphonodictyal B (**2.91**) and through interconversion of each set via REDOX conditions, the biosynthetic origins of the corallidictyals appears considerably convoluted. In contrast to the natural sample's reported molar ratio of 2:3 respectively,^[96] corallidictyals C (**2.5**) & D (**2.6**) were afforded in an equal diastereomeric ratio under our acid catalysed spirocyclisation conditions (scheme 2.39). Additionally, the reaction rate for the acid catalysed spirocyclisation of siphonodictyal B (**2.91**) was drastically slower than the rate of reduction of corallidictyals A (**2.3**) & B (**2.4**) (schemes 2.39 & 2.40). Comparatively, both the Ag_2CO_3 and Ag_2O mediated oxidative spirocyclisation reactions of siphonodictyal B (**2.91**) afforded corallidictyals A (**2.3**) & B (**2.4**) (entries 3 & 4, table 2.7) in a relative ratio of 1:2 respectively, analogous with the natural sample's isolated ratio of 3:7 respectively, as reported by Westly.^[100] Moreover, the oxidative spirocyclisation of siphonodictyal B (**2.91**) was high yielding, occurred rapidly, and did not afford any undesired by-products, indicating the overwhelming favourability of the oxidation reaction pathway. Based on these observations, we predict that the corallidictyals C (**2.5**) & D (**2.6**) are accessed in nature via the reduction of corallidictyals A (**2.3**) & B (**2.4**), which in turn are accessed directly from siphonodictyal B (**2.91**) (scheme 2.42). However, it does appear plausible that a portion of corallidictyals C (**2.5**) & D (**2.6**) may also be accessed directly from siphonodictyal B (**2.91**)

by a Lewis acid mediated spirocyclisation in nature. As such, we predict that corallidictyals C (2.5) & D (2.6) are primarily derived via the reduction of corallidictyals A (2.3) & B (2.4) in nature, and to a lesser degree, are directly afforded upon spirocyclisation of siphonodictyal B (2.91).^[96]



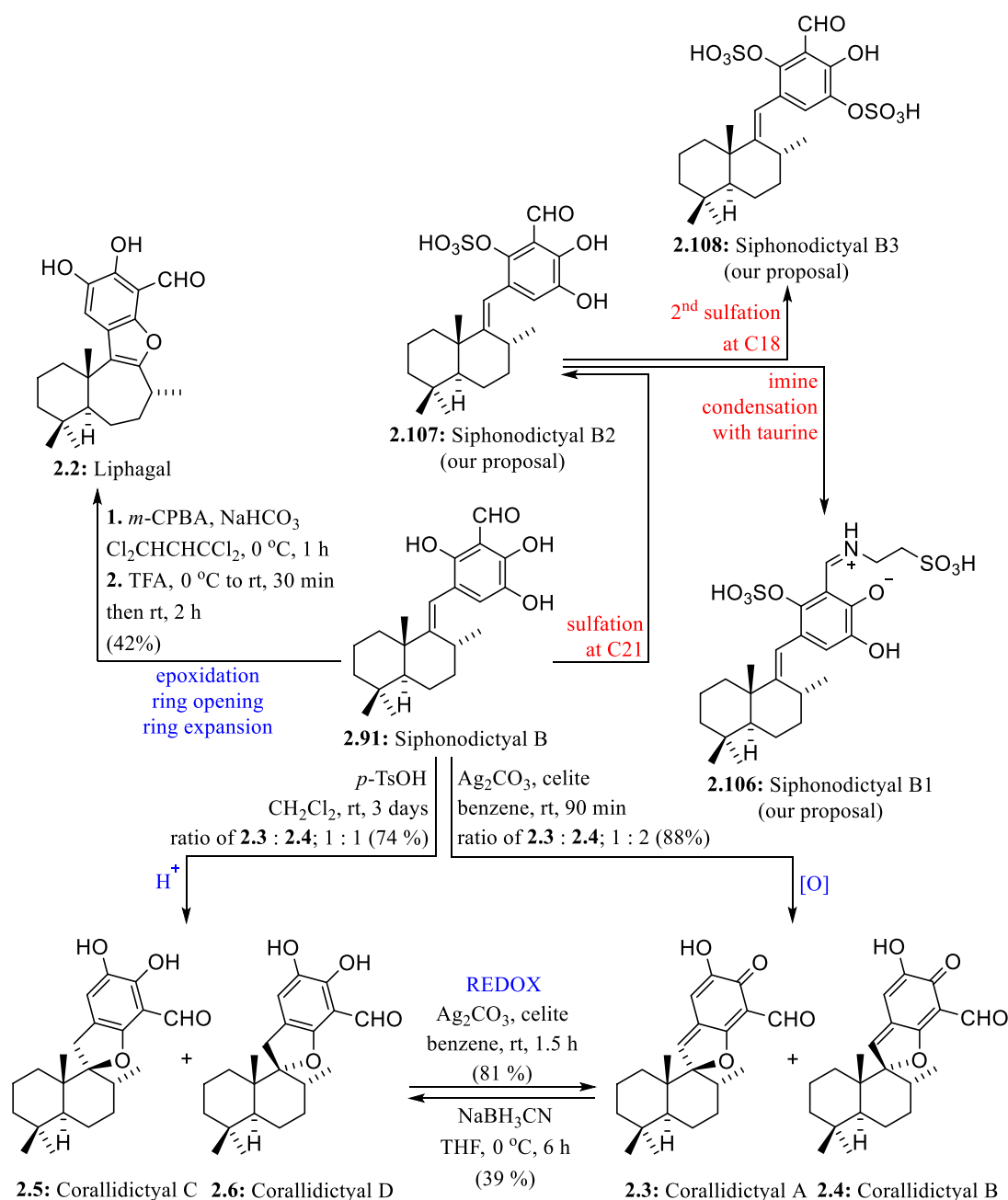
Scheme 2.42: Speculation for the biosynthetic origin of the corallidictyals A – D (2.3 – 2.6) from siphonodictyal B (2.91).

Finally, overwhelming evidence indicates that the corallidictyals A (2.3) & B (2.4) are biosynthetically derived via the direct oxidation of siphonodictyal B (2.91). However, the mechanism, as well as the oxidant source, whether biological or environmental, is somewhat less clear. The previously reported screening of oxidative conditions (table 2.7), revealed that siphonodictyal B (2.91) was capable of undergoing oxidation under an atmosphere of pure O_2 (entry 6, table 2.7) to give corallidictyals A (2.3) & B (2.4), albeit in poor yields and requiring drastically longer reaction times compared to silver oxidants (entries 3 & 4, table 2.7). Given that there were significant limitations inherent to the auto-oxidation of siphonodictyal B (2.91) in the presence of O_2 , we propose that the vast majority of corallidictyals A (2.3) & B (2.4) are formed within the host organism, and that a measurable minority of product may be afforded as an artefact of isolation. Within the cell, we envision that corallidictyals A (2.3) & B (2.4) could spontaneously form upon exposure of siphonodictyal B (2.91) to biological oxidants (NAD^+), or via catalysis from a non-substrate specific, promiscuous enzyme.

2.9 Summary and Biogenic Analysis of our Synthetic Investigations for the Family of Related Meroterpenoid Natural Products from *Aka coralliphaga*

To summarise this work, we have, for the first time, successfully synthesised, and reassigned the stereoconfiguration of siphonodictyal B (**2.91**) (tables 2.3 & 2.4). In addition, we have synthesised and consequently, proven that Faulkner's assigned configuration of 8-*epi*-siphonodictyal B **2.1**, is in fact not the true stereoconfiguration of the siphonodictyal B (scheme 2.27 & table 2.4). Following the successful reassignment of siphonodictyal B (**2.91**), we embarked upon the investigation of our divergent, biosynthetic proposal, which states that siphonodictyal B (**2.91**) is the biogenic precursor to liphagal (**2.2**), the corallidictyals A – D (**2.3** – **2.6**), and the siphonodictyals B1 – B3 (**2.106** – **2.108**) (scheme 2.43). Our successful biogenically inspired one-pot, two-step epoxidation and acid catalysed cascade transformation demonstrated that siphonodictyal B (**2.91**), in accordance with our reassigned stereoconfiguration, is a viable biogenic precursor to liphagal (**2.2**) (table 2.5). Additionally, the epoxidation and acid catalysed transformation of Faulkner's erroneously assigned configuration of 8-*epi*-siphonodictyal B **2.1** did not afford liphagal (**2.2**), and instead afforded the unnatural epimer, 8-*epi*-liphagal **2.163**, as predicted (scheme 2.35). The biogenic conversions of siphonodictyal B (**2.91**) and its epimer **2.1** to liphagal (**2.2**) and **2.157** respectively, confirmed our prediction that a non-enzymatic facilitated epimerisation event did not occur under the epoxidative/acidic conditions investigated.

The synthesis of siphonodictyals B1 – B3 (**2.106** – **2.108**) from siphonodictyal B (**2.91**) was investigated in an attempt to confirm our proposed stereochemical reassignment of the siphonodictyal B meroterpenoids (**2.91**, **2.106** – **2.108**) (scheme 2.43). However, all attempts to selectively install sulfonate esters at the C21 and C18 phenolic moieties of siphonodictyal B (**2.91**) failed to afford any isolatable desired products (**2.107** and **2.108**) (scheme 2.37 and table 2.6). ¹H NMR analysis of the eluted second (peak 2, table 2.6) and third (peak 3, table 2.6) fractions revealed that the complex mixtures contained characteristic peaks of siphonodictyal B3 (**2.108**) and B2 (**2.107**) respectively. Due to the inability to resolve these selective sulfonation issues, the attempted synthesis of siphonodictyals B1 – B3 (**2.106** – **2.108**) was not further pursued. Continued investigation into the potential stereochemical reassignment of siphonodictyals B1 – B3 (**2.106** – **2.108**) would require installation of the sulfonate esters by a selective means, either with milder reagents or perhaps via enzymatically catalysed means.



Scheme 2.43: Summary of the biogenically inspired total synthesis of liphagal (**2.2**), and the corallidictyals A – D (**2.3** – **2.6**) from siphonodictyals B (**2.91**), in accordance with our divergent biogenic proposal for the related meroterpenoid natural products isolated from *Aka coralliphaga*.

Finally, we have demonstrated that the corallidictyals A – D (**2.3** – **2.6**) can be accessed directly from siphonodictyals B (**2.91**) in one step, according to our biosynthetic proposal (table 2.7 and scheme 2.39). Additionally, we have successfully interconverted corallidictyals A (**2.3**) & B (**2.4**) with C (**2.5**) & D (**2.6**) under mild REDOX conditions (scheme 2.40), which may be representative of biologically relevant conditions present within the host organism, *Aka coralliphaga*. Based on our investigation into the biosynthetic origin of the corallidictyals, we assert that within the host organism, corallidictyals C (**2.5**) & D (**2.6**) are most likely derived from corallidictyals A (**2.3**) & B (**2.4**) under reductive

conditions, which are in turn afforded via an oxidative spirocyclisation of siphonodictyal B (**2.91**) (scheme 2.43).

As of the writing of this work, the known meroterpenoids derived from *Aka coralliphaga* possess mild to moderate non-selective bioactivity, such as anti-microbial and PI3 kinase inhibitory properties.^[96–100] However, siphonodictyal B (**2.91**), siphonodictyals B1 – B3 (**2.106 – 2.108**), liphagal (**2.2**), and corallidictyals A – D (**2.3 – 2.6**) do not appear to target any specific system or threat, which indicates the absence of a notable selective pressure that would specifically afford these meroterpenoids in nature. Without an apparent determining selective pressure, the likelihood for the emergence of substrate-specific enzymes, dedicated to catalysing the biosynthesis of the siphonodictyals (**2.91**, **2.106 – 2.108**), corallidictyals (**2.3 – 2.6**) and liphagal (**2.2**), appears remote. Biosynthetic pathways governed and closely regulated by highly selective, efficient enzymes would only emerge given that the products of the metabolic process in question, directly pertain to the survival of the host organism. Therefore, without the presence of an existentially driven selective pressure, it would be reasonable to assume that the biosynthesis of the meroterpenoids in question are not regulated by substrate specific enzymes. Based upon our biogenically inspired synthetic investigations, we assert that siphonodictyal B (**2.91**) is the biogenic precursor to siphonodictyals B1 – B3 (**2.106 – 2.108**), liphagal (**2.2**), and corallidictyals A – D (**2.3 – 2.6**) (scheme 2.43).

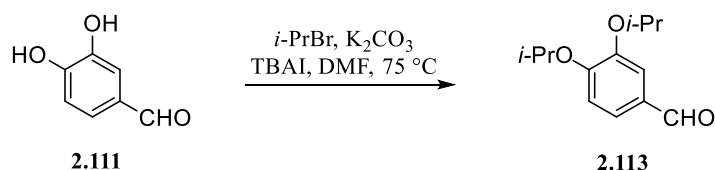
2.10 Experimental

2.10.1 General Experimental

All commercially obtained chemicals were used without further purification. Solvents stated as dry, were either collected from a solvent purification system (THF or DMF) or distilled under an atmosphere of nitrogen and stored over 3Å molecular sieves. Thin-layer chromatography (TLC) was conducted on Merck silica gel 60 F₂₅₄ aluminium sheets and visualised under a UV lamp or with ceric ammonium molybdate (CAM), vanillin or potassium permanganate staining followed by heated. All R_f values are rounded to the nearest 0.01. Davisil 43-60 micron chromatographic silica media was used for flash chromatography. ¹H and ¹³C NMR spectra were either recorded on an Agilent 500 spectrometer (¹H at 500 MHz, ¹³C at 125 MHz) or on an Agilent spectrometer with a 600 MHz Oxford magnet, with a cryoprobe (¹H at 600 MHz, ¹³C at 150 MHz) in CDCl₃ as the solvent, unless specified. ¹H and ¹³C chemical shifts are reported in ppm relative to TMS (δ 0.0). All *J* values were quoted to the nearest 0.1 Hz. Multiplicities are reported as (br) Broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (qnt) quintet, (sext) sextet, (hept) heptet and (m) multiplet. IR spectra were recorded on a Perkin-Elmer Fourier-Transform Infrared (FT-IR) spectrometer on a nickel-selenide crystal as neat compounds. High resolution mass spectra were obtained on an Agilent ESI high resolution mass spectrometer. Melting points were recorded on a Reichert electrothermal melting point apparatus and are uncorrected. Optical rotations were obtained on an Anton Paar MCP 100 Polarimeter in CHCl₃.

2.10.2 Experimental Procedures

3,4-Diisopropoxybenzaldehyde **2.113**^[118]



to a solution of 3,4-dihydroxybenzaldehyde **2.111** (2.00 g, 14.48 mmol) in DMF (30 mL) was added potassium carbonate (6.00 g, 43.4 mmol), 2-bromopropane (4.10 mL, 43.4 mmol) and TBAI (0.54 g, 1.49 mmol). The reaction mixture was stirred at 75 °C for 48 h, followed by cooling to room temperature. The reaction mixture was diluted with Et₂O (100 mL) and water (50 mL). The organic phase was separated, and the aqueous phase was extracted with Et₂O (3 × 50 mL). The organic extracts were combined then dried over MgSO₄ and concentrated *in vacuo* to give crude 3,4-diisopropoxybenzaldehyde **2.113** (2.97 g) as a brown oil, which was used in the next step without further purification.

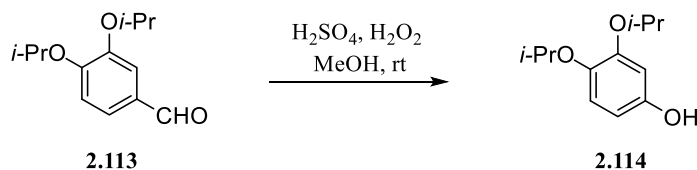
R_f = 0.70 (2:1 Petrol:EtOAc)

¹H NMR (600 MHz, CDCl₃): δ 9.83 (s, 1H), 7.45 – 7.43 (m, 2H), 6.99 (d, *J* = 8.7 Hz, 1H), 4.64 (hept, *J* = 6.1 Hz, 1H), 4.53 (hept, *J* = 6.1 Hz, 1H), 1.39 (d, *J* = 6.1 Hz, 6H), 1.36 (d, *J* = 6.1 Hz, 6H).

¹³C NMR (150 MHz, CDCl₃): δ 190.9, 155.0, 149.0, 130.1, 126.4, 116.2, 114.9, 72.5, 71.8, 22.1, 22.0.

Data for **2.113** matched that which had been previously reported.

3,4-Diisopropoxyphenol **2.114**^[118,119]



To a solution of 3,4-diisopropoxybenzaldehyde **2.113** (2.97 g, 13.35 mmol) in MeOH (55 mL) at room temperature, was added conc. H₂SO₄ (0.60 mL, 10.68 mmol) dropwise. 30% aqueous H₂O₂ solution (10.6 mL, 102.8 mmol) was then added in one portion and the resulting reaction mixture was stirred at room temperature for 6 h. Upon completion, the reaction mixture was quenched with saturated NaHCO₃ solution (10 mL) and extracted with CH₂Cl₂ (3 × 75 mL). The combined organics were dried over MgSO₄ and concentrated *in vacuo* to give crude 3,4-diisopropoxyphenol **2.114** as a brown gum (3.04 g). Product was used without purification.

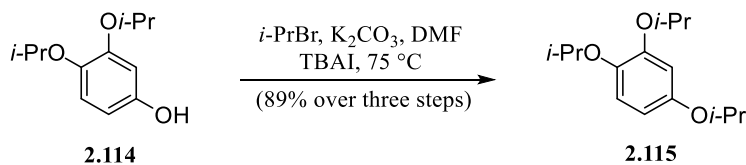
R_f = 0.35 (4:1 Petrol:EtOAc)

¹H NMR (600 MHz, CDCl₃): δ 6.79 (d, *J* = 8.5 Hz, 1H), 6.45 (d, *J* = 2.9 Hz, 1H), 6.31 (dd, *J* = 8.5, 2.9 Hz, 1H), 4.59 (d, *J* = 4.6 Hz, 1H), 4.46 (hept, *J* = 6.1 Hz, 1H), 4.28 (hept, *J* = 6.1 Hz, 1H), 1.33 (d, *J* = 6.1 Hz, 6H), 1.28 (d, *J* = 6.1 Hz, 6H).

¹³C NMR (150 MHz, CDCl₃): δ 151.1, 150.7, 142.6, 121.2, 107.0, 105.0, 73.7, 71.5, 22.3, 22.2.

Data for **2.114** matched that which had been previously reported.

1,2,4-Triisopropoxybenzene **2.115**^[118]



To a solution of 3,4-diisopropoxyphenol **2.114** (10.5 g, 49.9 mmol) in DMF (150 mL) was added K₂CO₃ (15.6 g, 113 mmol), 2-bromopropane (10.6 mL, 113 mmol) and TBAI (1.40 g, 3.79 mmol). The reaction mixture was stirred at 75 °C for 24 h, followed by cooling to room temperature. The reaction mixture was diluted with Et₂O (150 mL) and water (150 mL). The organic phase was separated, and the aqueous phase was extracted with Et₂O (3 × 150 mL). The organic extracts were combined and washed with water (150 mL) and brine (150 mL), dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 4:1) to give 1,2,4-triisopropoxybenzene **2.115** as a yellow oil (11.2 g, 89%).

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

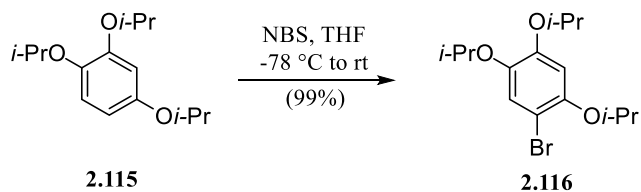
IR (neat): 2975, 2931, 1734, 1606, 1584, 1499, 1466, 1453, 1421, 1382, 1371, 1335, 1300, 1257, 1214, 1181, 1163, 1109 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 6.82 (d, *J* = 8.7 Hz, 1H), 6.49 (s, 1H), 6.39 (d, *J* = 8.7 Hz, 1H), 4.50 – 4.40 (m, 2H), 4.30 (qnt, *J* = 6.1 Hz, 1H). 1.33 – 1.28 (m, 18H).

¹³C NMR (125 MHz, CDCl₃): δ 153.4, 150.5, 142.8, 120.7, 107.5, 106.7, 73.5, 71.6, 70.5, 22.3, 22.22, 22.15.

Data for **2.115** matched that which had been previously reported.

1-Bromo 2,4,5-triisopropoxybenzene **2.116**^[120]



A solution of 1,2,4-triisopropoxybenzene **2.115** (11.2 g, 44.4 mmol) in THF (220 mL) was cooled to -78 °C. NBS (7.90 g, 44.4 mmol) was added portion wise over 5 min at -78 °C, and the resultant mixture was stirred at this temperature for 15 min. The reaction mixture was allowed to warm to room temperature and the solvent was removed *in vacuo*. The residue was diluted with EtOAc (200 mL) and filtered through a pad of neutral alumina, followed by concentrating *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 4:1) to give 1-bromo-2,4,5-triisopropoxybenzene **2.116** as a yellow oil (14.6 g, 99%).

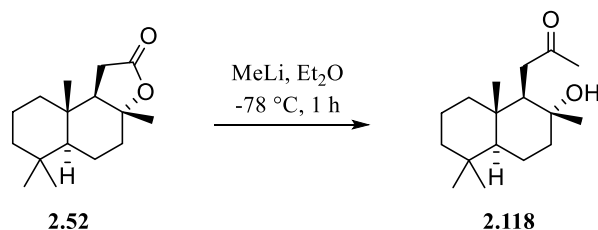
Rf = 0.58 (petrol/EtOAc, 4:1)

IR (neat): 2975, 2931, 1594, 1569, 1486, 1467, 1382, 1372, 1333, 1307, 1254, 1198, 1182, 1163, 1137, 1106, 1025 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 7.08 (s, 1H), 6.57 (s, 1H), 4.47 – 4.32 (m, 3H), 1.35 (d, J = 6.1 Hz, 6H), 1.31 (d, J = 6.4 Hz, 6H), 1.30 (d, J = 6.4 Hz, 6H).

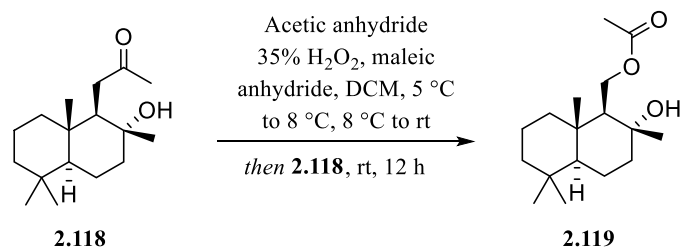
¹³C NMR (125 MHz, CDCl₃): δ 153.4, 150.5, 142.8, 120.7, 107.5, 106.7, 73.5, 71.6, 70.5, 22.3, 22.22, 22.15.

Data for **2.116** matched that which had been previously reported.

Ketone 2.118^[122,123]

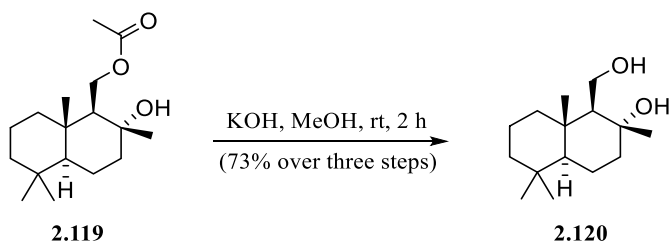
To a solution of (+)-sclareolide **2.52** (10.0 g, 39.9 mmol) in Et₂O (150 mL) at -78 °C, was added a solution of MeLi (1.5 M in Et₂O, 50 mL, 75 mmol). The resulting reaction mixture was stirred at -78 °C for 1 h, before the mixture was quenched with 10% aqueous sulfuric acid solution (50 mL). The mixture was extracted with Et₂O (2 × 100 mL), and the organic phase was washed sequentially with saturated aqueous NaHCO₃ (150 mL), water (150 mL), brine (100 mL). The organic extracts were dried over MgSO₄ and concentrated *in vacuo* to give crude ketone **2.118** as a colourless oil (9.98 g). Crude product was used without purification.

R_f = 0.19 (petrol/EtOAc, 3:1)

Acetate 2.119^[122,123]

To a solution of acetic anhydride (50 mL, 529 mmol) in CH₂Cl₂ (70 mL) at 5 °C, was added 35% aqueous H₂O₂ solution (50 mL, 75 mmol). The mixture was stirred at 5 °C for 1 h, then maleic anhydride (30 g, 306 mmol) was added in three portions over 20 min at 8 °C and stirred at this temperature for a further 1 h. The reaction mixture was warmed to room temperature and stirred for 1 h, before crude ketone **2.118** (9.98 g, 37.6 mmol) in CH₂Cl₂ (40 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 12 h. The mixture was diluted with CH₂Cl₂ (200 mL) and extracted. The organic phase was sequentially washed with water (200 mL), saturated aqueous NaHCO₃ solution (2 × 100 mL), brine (100 mL). Extracts were dried over MgSO₄ and concentrated *in vacuo* to give crude acetate **2.119** as a colourless oil (13.95 g). Crude product was used without purification.

R_f = 0.27 (petrol/EtOAc, 3:1)

Diol 2.120^[122,123]

To a solution of crude ester **2.119** (13.95 g, 37.6 mmol) in MeOH (150 mL) at room temperature, was added KOH (10.2 g, 182 mmol). The resulting reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with Et₂O (150 mL) and extracted. The organic phase was sequentially washed with water (2 × 100 mL), brine (100 mL) and the organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 3:1) to give pure diol **2.120** as a white solid (7.6 g, 73% over 3 steps).

R_f = 0.08 (petrol/EtOAc, 3:1)

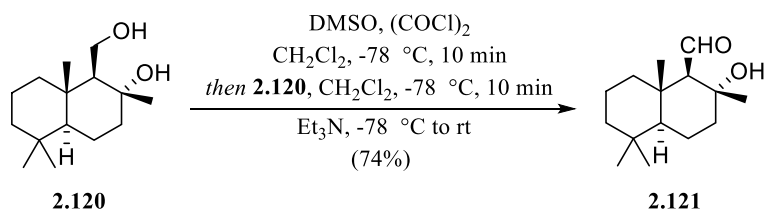
IR (neat): 3310, 2918, 1458, 1381, 1048 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 3.91 (d, *J* = 7.0 Hz, 2H), 3.58 (br s, 1H), 3.21 (br s, 1H), 1.88 (dt, *J* = 12.0, 3.0 Hz, 1H), 1.75 – 1.37 (m, 6H), 1.34 (s, 3H), 1.31 – 1.06 (m, 4H), 0.97 (dd, *J* = 12.2, 2.0 Hz, 1H), 0.88 (s, 3H), 0.79 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 75.1, 61.1, 60.5, 55.9, 44.4, 41.7, 40.0, 37.5, 33.6, 33.3, 24.3, 21.6, 20.2, 18.6, 16.0.

Data for **2.120** matched that which had been previously reported.

Hydroxy aldehyde **2.121**^[126]



To a solution of DMSO (1.67 mL, 27.71 mmol) in CH₂Cl₂ (22 mL) at -78 °C, was added (COCl)₂ (1.2 mL, 13.86 mmol) and the resulting mixture was stirred for 10 min. Diol **2.120** (1 g, 4.16 mmol) in CH₂Cl₂ (22 mL) was added to the mixture and was stirred at -78 °C for a further 10 min. Triethylamine (6.36 mL, 46.18 mmol) was added dropwise to the mixture, which was then warmed to room temperature. The mixture was quenched with water (50 mL) and extracted with CH₂Cl₂ (3 × 80 mL). The organic extracts were combined, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 5:1) to give pure hydroxy aldehyde **2.121** as a colourless solid (730 mg, 74%).

R_f = 0.34 (petrol/EtOAc, 2:1)

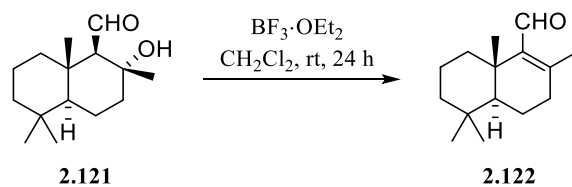
IR (neat): 3441, 2929, 1715, 1467, 1096 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 10.03 (s, 1H), 3.11 (br s, 1H), 2.08 (s, 1H), 2.00 – 1.94 (m, 1H), 1.82 (dt, *J* = 13.0 Hz, *J* = 3.0 Hz, 1H), 1.73 – 1.67 (m, 1H), 1.54 – 1.43 (m, 3H), 1.38 (s, 3H), 1.36 – 1.20 (m, 3H), 1.12 (s, 3H), 0.97 (dd, *J* = 12.0 Hz, *J* = 2.0 Hz, 1H), 0.90 (s, 3H), 0.83 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 208.2, 72.8, 71.3, 55.2, 42.7, 41.6, 39.8, 37.3, 33.3, 33.2, 25.3, 21.4, 19.9, 18.2, 17.6.

Data for **2.121** matched that which had been previously reported.

endo*-Alkenyl aldehyde **2.122*^[126]

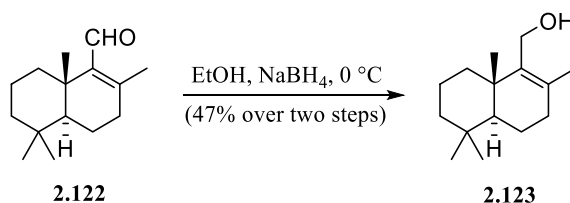


To a solution of hydroxy aldehyde **2.121** (4.5 g, 18.88 mmol) in CH_2Cl_2 (120 mL) at room temperature, was added $\text{BF}_3 \cdot \text{OEt}_2$ (4.66 mL, 37.79 mmol) and the resulting mixture was stirred for 24 h. The mixture was quenched with saturated aqueous NaHCO_3 solution (125 mL) and extracted with CH_2Cl_2 (50 mL). The organic extracts were dried over MgSO_4 and concentrated *in vacuo* to give crude *endo*-alkenyl aldehyde **2.122** as a colourless impure solid (3.97 g). Crude product was used without purification.

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

$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 10.04 (s, 1H), 2.57 – 2.54 (m, 1H), 2.28 – 2.25 (m, 2H), 2.03 (s, 3H), 1.73 – 1.59 (m, 2H), 1.49 – 1.41 (m, 3H), 1.18 (s, 3H), 1.10 – 0.91 (s, 3H), 0.90 (s, 3H), 0.86 (s, 3H).

endo-Alkene alcohol 2.123^[126]



To a solution of aldehyde-alkene **2.122** (3.97 g, 18.02 mmol) in EtOH (90 mL) at 0 °C, was added NaBH₄ (1.35 g, 35.69 mmol) and the resulting mixture was stirred for 40 min. The mixture was quenched with 10% aqueous H₂SO₄ solution (70 mL) and extracted with Et₂O (3 × 100 mL) and sequentially washed with saturated aqueous NaHCO₃ solution (150 mL), water (150 mL), brine (150 mL). The organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 15:1 then 4:1) to give pure *endo*-alkene alcohol **2.123** as a colourless solid (1.88 g, 47% over two steps).

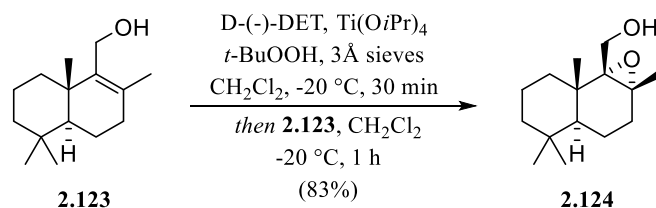
R_f = 0.37 (petrol/EtOAc, 4:1)

¹H NMR (500 MHz, CDCl₃): δ 4.20 (dd, *J* = 13.2 Hz, *J* = 3.2 Hz, 1H), 4.04 (dd, *J* = 13.2 Hz, *J* = 3.2 Hz, 1H), 2.17 – 2.01 (m, 2H), 1.91 – 1.88 (m, 1H), 1.72 (s, 3H), 1.70 – 1.62 (m, 2H), 1.54 – 1.38 (m, 3H), 1.25 (td, *J* = 12.9 Hz, *J* = 3.8 Hz, 1H), 1.18 (dd, *J* = 13.4 Hz, *J* = 4.2 Hz, 1H), 1.14 (dd, *J* = 12.5 Hz, *J* = 1.7 Hz, 1H), 0.97 (s, 3H), 0.89 (s, 3H), 0.84 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 141.0, 132.4, 58.3, 51.7, 41.7, 38.1, 36.8, 33.7, 33.26, 33.25, 21.6, 20.7, 19.3, 19.0, 18.9.

Data for **2.123** matched that which had been previously reported.

Epoxy alcohol **2.124**^[126]



To a mixture of 3Å (15 g) and D-(-)-diethyl tartrate (0.39 ml, 2.25 mmol) in CH₂Cl₂ (15 mL) at -20 °C, was added Ti(O*i*-Pr)₄ (0.68 mL, 2.25 mmol) and the resulting mixture was stirred for 10 min. *t*-BuOOH (5.5 M in decane, 1.63 mL, 8.99 mmol) was added dropwise to the reaction mixture and was stirred for 30 min at -20 °C. *endo*-alkene alcohol **2.123** (1.0 g, 4.496 mmol) in CH₂Cl₂ (12.5 mL) was added to the reaction mixture and was stirred at -20 °C for 1 h. The reaction was quenched with 30% aqueous NaOH solution (1 mL) and diluted with Et₂O (50 mL) and was filtered through a pad of Celite™, diluted with Et₂O (50 mL) and sequentially washed with water (50 mL), brine (50 mL). The organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 8:1) to give pure epoxy alcohol **2.124** as a colourless solid (890 mg, 83%).

R_f = 0.44 (petrol/EtOAc, 2:1)

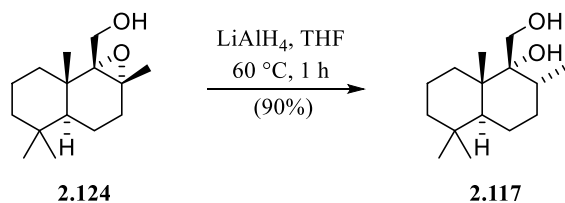
IR (neat): 3412, 2928, 1463, 1373, 1023 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 3.88 (dd, *J* = 10.7 Hz, *J* = 6.4 Hz, 1H), 3.55 (dd, *J* = 12.5, *J* = 3.2 Hz, 1H), 2.04 – 1.92 (m, 2H), 1.86 – 1.78 (m, 2H), 1.61 – 1.50 (m, 2H), 1.42 – 1.33 (m, 4H), 1.30 (s, 3H), 1.28 – 1.23 (m, 1H), 1.17 (td, *J* = 13.2, 5.1 Hz, 1H), 0.97 (s, 3H), 0.84 (s, 3H), 0.81 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 71.2, 64.5, 56.9, 43.2, 41.4, 37.1, 33.9, 33.5, 32.9, 29.4, 21.5, 21.4, 18.3, 17.1, 16.2.

Data for **2.124** matched that which had been previously reported.

1,2-Diol **2.117**^[106]



To a solution of alcohol-epoxide **2.124** (1.64 g, 6.88 mmol) in tetrahydrofuran (120 mL) at room temperature, was added a LiAlH_4 solution (2 M in THF, 13.8 mL, 27.6 mmol) and the reaction mixture was heated at $60\text{ }^\circ\text{C}$ for 1 h while stirred. The reaction mixture was cooled to room temperature before being placed on an ice bath and quenched with ethanol (15 mL) and 1M aqueous HCl (20 mL). The mixture was extracted with EtOAc ($2 \times 200\text{ mL}$) and the extracts were sequentially washed with water ($2 \times 150\text{ mL}$), and brine (50 mL). The organic extracts were dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (petrol/EtOAc, 10:1) to give pure 1,2-diol **2.117** as a white solid (1.5 g, 90%).

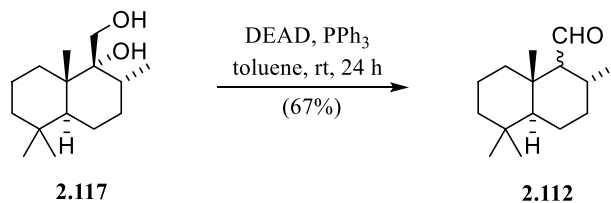
$R_f = 0.48$ (petrol/EtOAc, 2:1)

$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 3.73 (dd, $J = 10.9\text{ Hz}$, $J = 4.5\text{ Hz}$, 1H), 3.50 (dd, $J = 10.9$, $J = 5.3\text{ Hz}$, 1H), 2.35 (br s, 1H), 1.80 – 1.74 (m, 2H), 1.58 – 1.55 (m, 2H), 1.49 – 1.45 (m, 3H), 1.38 – 1.29 (m, 3H), 1.21 – 1.16 (m, 2H), 0.90 (d, $J = 6.7\text{ Hz}$, 3H), 0.88 (s, 6H), 0.83 (s, 3H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 75.5, 63.6, 46.4, 42.0, 41.7, 35.6, 33.6, 33.3, 31.9, 31.3, 22.1, 21.7, 18.6, 16.4, 15.6.

Data for **2.117** matched that which had been previously reported.

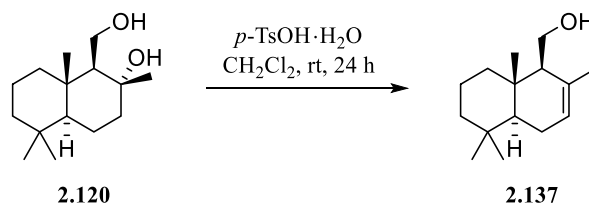
Aldehyde **2.112**^[121]



To a solution of triphenylphosphine (177 mg, 0.675 mmol) in toluene (2.5 mL) at room temperature, was added diethyl azodicarboxylate (1.31 mL, 0.675 mmol) and the reaction mixture was stirred at this temperature for 15 min. 1,2-diol **2.117** (50 mg, 0.225 mmol) in toluene (1.5 mL) was added to the reaction mixture and the resulting mixture was stirred at room temperature for 24 h. The mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 30:1) to give aldehyde **2.112** as a colourless oil (33.5 mg, 67%), which was a mixture of diastereomers and was used without purification.

R_f = 0.70 (petrol/EtOAc, 4:1)

Alkenyl alcohol **2.137**^[144]



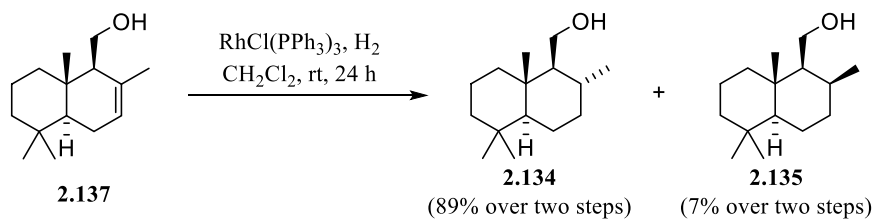
To a solution of diol **2.120** (2.67 g, 11.1 mmol) in CH_2Cl_2 (110 mL) at room temperature, was added $p\text{-TsOH}\cdot\text{H}_2\text{O}$ (2.11 g, 11.1 mmol) and the reaction mixture was stirred at this temperature for 24 h. The mixture was quenched with saturated aqueous NaHCO_3 solution (80 mL) and extracted with CH_2Cl_2 (3×100 mL). The organic extracts were dried over MgSO_4 and concentrated *in vacuo* to give crude alkenyl alcohol **2.137** as a colourless oil (2.40 g). Product was used without purification.

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

Data for **2.137** matched that which had been previously reported.

$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 5.54 (br s, 1H), 3.85 (dd, $J = 2.1$ Hz, $J = 11.45$ Hz, 1H), 3.78 – 3.72 (m, 1H), 2.02 – 1.40 (m, 4H), 1.78 (s, 3H), 1.68 – 1.40 (m, 3H), 1.30 – 1.04 (m, 4H), 0.89 (s, 3H), 0.86 (s, 6H).

Alcohols 2.134 and 2.135



To a de-gassed solution of alkenyl alcohol **2.137** (1.5 g, 6.746 mmol) in CH_2Cl_2 (120 mL) at room temperature, was added Wilkinson's catalyst (300 mg, 0.324 mmol), followed by subjecting the reaction vessel to an atmosphere of hydrogen via a breathable bladder and the reaction mixture was stirred at room temperature for 24 h. The mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on SiO_2 (petrol/EtOAc, 30:1) to give alcohol **2.134** as a white solid (1.35 g, 89% over two steps) and alcohol **2.135** as a white solid (110 mg, 7% over two steps).

Partial data for alcohol **2.134**:

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

$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 3.79 (d, $J = 11.4$ Hz, 1H), 3.63 (d, $J = 11.2$ Hz, 1H), 2.17 (br s, 1H), 1.89 – 1.86 (m, 1H), 1.81 – 1.77 (m, 1H), 1.64 – 1.59 (m, 2H), 1.47 – 1.37 (m, 2H), 1.33 – 1.25 (m, 1H), 3.79 (d, $J = 3.5$ Hz, 1H), 1.18 – 1.11 (m, 1H), 1.06 – 1.00 (m, 3H), 0.97 (d, $J = 6.4$ Hz, 3H), 0.87 (s, 3H), 0.84 (s, 3H), 0.81 (s, 3H), 0.68 – 0.66 (m, 1H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 61.9, 60.7, 55.0, 42.1, 39.4, 37.6, 36.8, 33.6, 33.3, 30.8, 21.9, 21.8, 21.0, 18.8, 15.6.

Partial data for alcohol **2.135**:

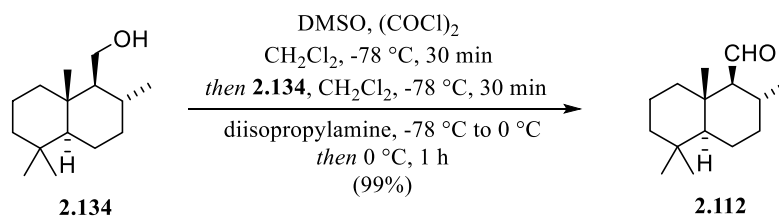
$R_f = 0.37$ (petrol/EtOAc, 4:1).

$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 3.86 (dd, $J = 10.6$ Hz, $J = 4.6$ Hz, 1H), 3.59 (t, $J = 9.9$ Hz, 1H), 2.17 – 2.04 (m, 1H), 1.69 – 1.36 (m, 11H), 1.16 (td, $J = 14.2$ Hz, $J = 4.5$ Hz, 1H), 1.01 (td, $J = 12.9$ Hz, $J = 3.2$ Hz, 1H), 0.96 (d, $J = 7.6$ Hz, 3H), 0.86 (s, 6H), 0.81 (s, 3H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 61.0, 56.5, 55.7, 42.0, 39.9, 37.6, 34.5, 33.6, 33.3, 28.5, 21.6, 18.4, 17.5, 17.1, 15.6.

Data for **2.135** matched that which had been previously reported.

Aldehyde **2.112** epimers^[144]



To a solution of (COCl)₂ (0.44 mL, 5.24 mmol) in CH₂Cl₂ (17.5 mL) at -78 °C, was added DMSO (0.622 mL, 9.41 mmol) and the resulting mixture was stirred for 30 min. Alcohol **2.134** (819 mg, 3.59 mmol) in CH₂Cl₂ (17.5 mL) was added to the mixture and was stirred at -78 °C for a further 30 min. Diisopropylamine (3.5 mL, 19.78 mmol) was added dropwise to the mixture, which was then warmed to 0 °C. The mixture was stirred at 0 °C for 1 h then quenched with water (50 mL) and extracted with CH₂Cl₂ (3 × 80 mL). The organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 30:1) to give pure aldehyde **2.112** as a colourless solid (792 mg, 99%).

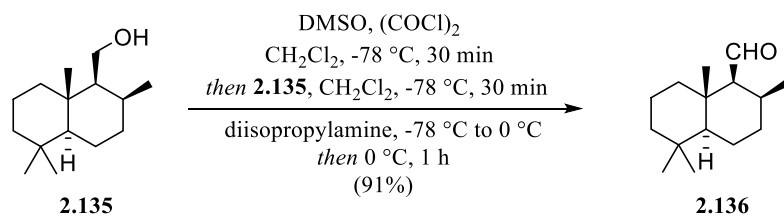
R_f = 0.70 (petrol/EtOAc, 4:1)

¹H NMR (500 MHz, CDCl₃): δ 9.69 (dd, *J* = 4.9 Hz, 1H), 2.09 (septet, *J* = 5.7 Hz, 1H), 1.91 – 1.88 (m, 1H), 1.63 – 1.50 (m, 4H), 1.42 – 1.35 (m, 3H), 1.28 – 1.19 (m, 3H), 1.09 (s, 3H), 0.99 (qd, *J* = 12.6 Hz, *J* = 4.4 Hz, 1H), 0.86 (s, 3H), 0.84 (s, 3H), 0.79 (d, *J* = 6.4 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 207.8, 70.3, 54.2, 41.9, 40.2, 38.2, 35.5, 33.5, 33.3, 27.5, 21.8, 21.6, 20.7, 18.3, 16.0.

Data for **2.112** matched that which had been previously reported.

Aldehyde 2.136



To a solution of (COCl)₂ (0.53 ml, 6.36 mmol) in CH₂Cl₂ (21 mL) at -78 °C, was added DMSO (0.76 mL, 11.49 mmol) and the resulting mixture was stirred for 30 min. Alcohol **2.135** (0.984 g, 4.39 mmol) in CH₂Cl₂ (21 mL) was added to the mixture and was stirred at -78 °C for a further 30 min. Diisopropylamine (4.3 mL, 24.3 mmol) was added dropwise to the mixture, which was then warmed to 0 °C. The mixture was stirred at 0 °C for 1 h then quenched with water (60 mL) and extracted with CH₂Cl₂ (3 × 120 mL). The organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 30:1) to give pure aldehyde **2.136** as a colourless solid (889 mg, 91%).

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

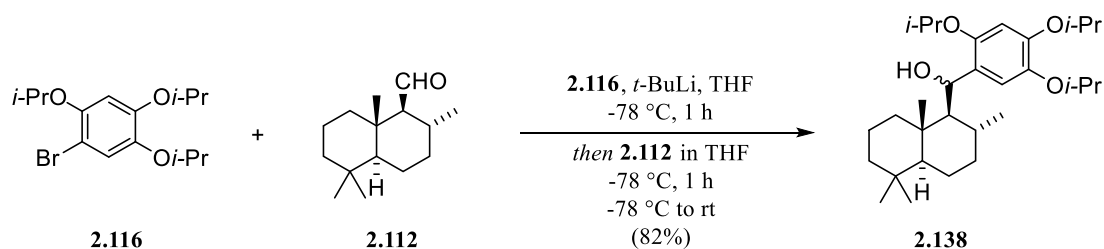
[α]_D²⁵ = +12.6° (c 0.24, CHCl₃)

IR (neat): 2924, 2842, 2854, 1713, 1458, 1387, 1112 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 9.88 (s, 1H), 2.40 – 2.38 (m, 1H), 1.98 – 1.96 (m, 2H) 1.69 – 1.26 (m, 12H) 1.18 (s, 1H), 1.04 (d, *J* = 7.2 Hz, 3H), 0.87 (s, 3H), 0.85 (m, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 206.6, 65.6, 55.7, 41.9, 39.7, 37.1, 34.2, 33.4, 33.2, 29.9, 21.5, 18.0, 18.0, 17.3, 17.2.

Benzyl alcohol **2.138**



To a solution of aryl bromide **2.116** (2.12 g, 6.40 mmol) in anhydrous THF (12 mL), *t*-BuLi (1.0 M in pentane, 5.76 mL, 5.76 mmol) was added dropwise at -78 °C. The reaction mixture was stirred at this temperature for 1 h. A solution of aldehyde **2.112** (710 mg, 3.19 mmol) in anhydrous THF (12 mL) was then added dropwise over 10 min at -78 °C. The reaction mixture was stirred at -78 °C for a further 1 h, and then allowed to warm to room temperature. The reaction mixture was quenched with saturated aqueous NH₄Cl solution (40 mL) and extracted with Et₂O (2 × 100 mL). The combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 10:1) to give benzyl alcohol **2.138** as a white solid (1.12 g, 74%).

R_f = 0.46 (petrol/EtOAc, 10:1)

$[\alpha]_{\text{D}}^{25} = +7.9^\circ$ (c 0.63, CHCl₃)

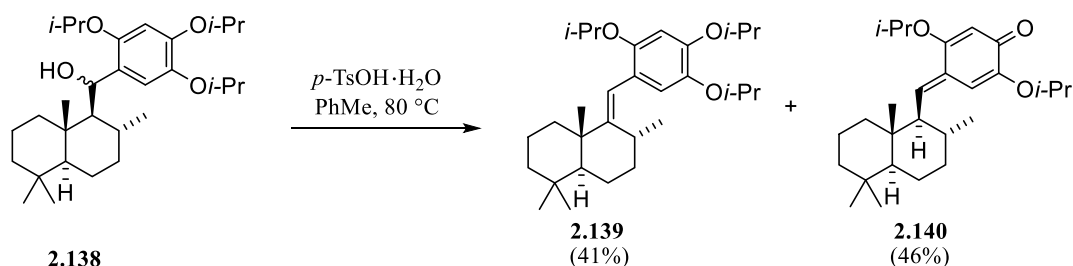
IR (neat): 3476, 2974, 2931, 1608, 1496, 1382, 1188 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 7.03 (s, 1H), 6.47 (s, 1H), 5.26 (d, *J* = 4.0 Hz, 1H), 4.53 (septet, *J* = 6.1 Hz, 1H), 4.47 (septet, *J* = 6.1 Hz, 1H), 4.34 (septet, *J* = 6.1 Hz, 1H), 2.86 (d, *J* = 4.0 Hz, 1H), 2.01 – 1.87 (m, 2H), 1.78 – 1.74 (m, 1H), 1.69 – 1.55 (m, 2H), 1.50 – 1.35 (m, 4H), 1.36 (d, *J* = 6.7 Hz, 3H), 1.35 (d, *J* = 6.7 Hz, 3H), 1.31 (d, *J* = 6.2 Hz, 3H), 1.31 (d, *J* = 6.2 Hz, 3H), 1.28 (d, *J* = 6.0 Hz, 3H), 1.27 (d, *J* = 6.0 Hz, 3H), 1.19 – 1.00 (m, 3H), 1.11 (s, 3H), 0.92 – 0.89 (m, 1H), 0.87 (m, 3H), 0.85 (s, 3H), 0.78 (d, *J* = 6.4 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 149.7, 148.2, 141.9, 128.9, 120.3, 105.1, 73.3, 72.3, 70.9, 67.4, 58.7, 55.3, 42.3, 39.7, 38.9, 37.8, 33.8, 33.5, 28.7, 23.2, 22.4, 22.31, 22.29, 22.27, 22.1, 21.9, 19.0, 15.3.

HRMS (ESI): calculated for C₃₀H₃₀O₄Na 497.3607 [M+Na]⁺, found 497.3621

Alkene 2.139 and *para*-QM 2.140



To a solution of benzyl alcohol **2.138** (300 mg, 0.632 mmol) in PhMe (24 mL) was added *p*-TsOH·H₂O (12 mg, 63.2 μmol) at room temperature. The reaction mixture was heated to 80 °C for 15 min and the reaction mixture was cooled to room temperature. The reaction mixture was quenched with saturated aqueous NaHCO₃ solution (100 mL) and extracted with EtOAc (2 × 150 mL). The combined organic extracts were sequentially washed with water (100 mL), brine (100 mL), dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 10:1) to give alkene **2.139** as a colourless oil (115 mg, 41%). Further purification lead to isolation of a *para*-QM **2.140** by-product (119 mg, 46%).

Data for **alkene 2.139**:

R_f = 0.50 (petrol/EtOAc, 10:1)

[α]_D²⁵ = -67.9° (c 0.75, CHCl₃)

IR (neat): 2972, 2929, 2867, 1603, 1567, 1493, 1465, 1400, 1371, 1333, 1310, 1189 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 6.70 (s, 1H), 6.46 (s, 1H), 6.17 (s, 1H), 4.45 (septet, *J* = 6.1 Hz, 1H), 4.34 (septet, *J* = 6.1 Hz, 1H), 4.26 (septet, *J* = 6.1 Hz, 1H), 2.68 – 2.64 (m, 1H), 1.86 – 1.64 (m, 5H), 1.55 – 1.33 (m, 7H), 1.30 (d, *J* = 6.1 Hz, 6H), 1.29 (d, *J* = 6.1 Hz, 6H), 1.25 (d, *J* = 6.1 Hz, 3H), 1.25 (d, *J* = 6.1 Hz, 3H), 1.20 (dd, *J* = 13.4 Hz, *J* = 13.3 Hz, 1H), 1.17 (s, 3H), 0.91 (s, 3H), 0.90 (d, *J* = 7.1 Hz, 3H), 0.88 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 156.5, 150.2, 147.8, 142.9, 125.0, 122.0, 115.6, 108.8, 73.0, 72.11, 72.07, 49.5, 42.5, 40.74, 40.73, 39.9, 34.0, 33.3, 32.3, 31.6, 23.1, 22.414, 22.408, 22.39, 22.30, 22.25, 22.1, 21.7, 19.9, 19.6.

HRMS (ESI): calculated for C₃₀H₄₈O₃ 479.3501 [M+Na]⁺, found 479.3503

Data for *para*-QM 2.140:

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

$[\alpha]_D^{25} = -25^\circ$ (c 0.2, CHCl₃)

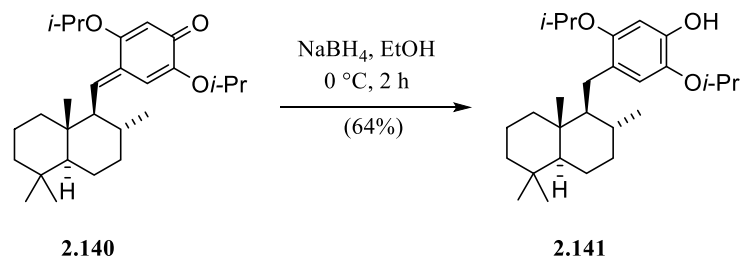
IR (neat): 3253, 2924, 2867, 1626, 1575, 14.54, 1370, 1186, 1106 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 6.74 (d, $J = 11.6$ Hz, 1H), 6.37 (s, 1H), 5.72 (s, 1H), 4.46 (septet, $J = 6.0$ Hz, 2H), 1.92 – 1.84 (m, 2H), 1.76 – 1.41 (m, 6H), 1.36 (d, $J = 6.1$ Hz, 6H), 1.32 (d, $J = 6.0$, 3H), 1.31 (d, $J = 6.0$, 3H), 1.24 – 1.02 (m, 4H), 0.99 (s, 3H), 0.92 (m, 1H), 0.88 (s, 3H), 0.84 (s, 3H), 0.67 (d, $J = 6.5$, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 183.1, 161.6, 148.7, 144.6, 129.4, 106.8, 103.8, 71.0, 69.9, 57.9, 54.9, 42.1, 41.4, 39.2, 36.1, 33.50, 33.47, 32.1, 22.0, 21.7, 21.63, 21.56, 21.49, 21.47, 21.1, 18.6, 15.1.

HRMS (ESI): calculated for C₂₇H₄₂O₃Na 359.2217 [M+Na]⁺, found 359.2210

para-Phenol **2.141**



To a solution of *p*-QM **2.140** (200 mg, 0.483 mmol) in ethanol (20 mL) at 0 °C, was added NaBH₄ (27.4 mg, 0.724 mmol). The resulting reaction mixture was stirred at 0 °C for 2 h. The mixture was extracted with ethyl acetate (150 ml) and sequentially washed with 1M HCl solution (10 ml), water (2 × 50 ml), and brine (50 ml). The organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 8:1) to give *para*-phenol **2.141** (128 mg, 64%).

$R_f = 0.77$ (petrol/EtOAc, 1:2)

¹H NMR (500 MHz, CDCl₃): δ 6.75 (s, 1H), 6.48 (s, 1H), 5.50 (br s, 1H), 4.42 (hept, $J = 6.1$ Hz, 1H), 4.37 (hept, $J = 6.1$ Hz, 1H), 2.57 (dd, $J = 15.8$ Hz, $J = 3.0$ Hz, 1H), 2.39 (dd, $J = 15.8$ Hz, $J = 6.2$ Hz, 1H), 1.82 – 1.80 (m, 1H), 1.74 – 1.71 (m, 1H), 1.59 – 1.36 (m, 5H), 1.33 (d, $J = 6.1$ Hz, 6H), 1.32 (d, $J = 6.1$ Hz, 3H), 1.31 (d, $J = 6.1$ Hz, 3H), 1.30 – 1.26 (m, 1H), 1.18 – 0.95 (m, 3H), 0.90 (s, 3H), 0.89 – 0.86 (m, 2H), 0.87 (s, 3H), 0.84 (s, 3H), 0.73 (d, $J = 6.4$ Hz, 3H).

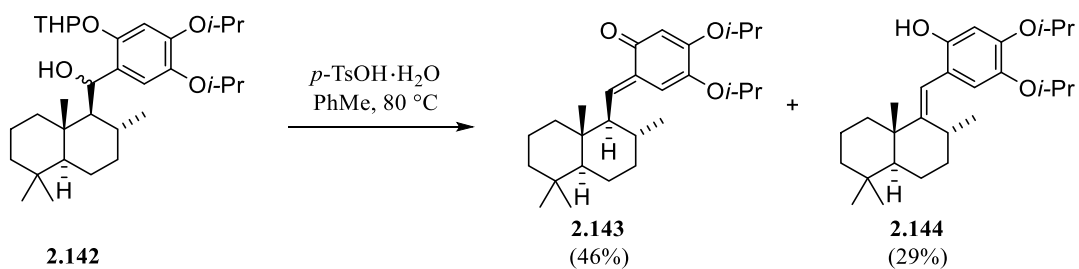
¹³C NMR (125 MHz, CDCl₃): δ 149.7, 144.8, 137.7, 125.3, 116.8, 101.5, 73.0, 70.7, 58.4, 55.5, 42.3, 39.6, 38.6, 37.4, 35.0, 33.61, 33.4, 27.0, 22.34, 22.33, 22.30, 22.28, 21.99, 21.98, 21.5, 18.9, 14.4.

$[\alpha]_D^{25} = -5.6^\circ$ (c 0.9, CHCl₃)

IR (neat): 3541, 2973, 2930, 2843, 1599, 1504, 1185 cm⁻¹

HRMS (ESI): calculated for C₂₇H₄₄O₃ 415.3218 [M-H]⁻, found 415.3210

ortho-QM **2.143**



To a solution of THP protected alkene **2.142** (123 mg, 0.24 mmol) in PhMe (4 mL) was added *p*-TsOH·H₂O (5 mg, 23.7 μmol) at room temperature. The reaction mixture was heated to 90 °C for 15 min and the reaction mixture was cooled to room temperature. The mixture was quenched with saturated aqueous NaHCO₃ solution (10 mL) and extracted with Et₂O (3 × 10 mL). The combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (gradient elution, petrol/EtOAc, 5:1 → 3:1) to give *ortho*-QM **2.143** as a yellow film (45.5 mg, 46%).

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

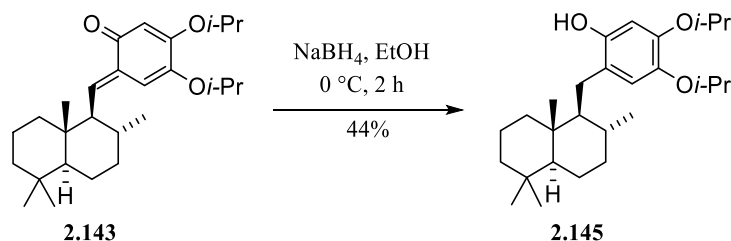
¹H NMR (500 MHz, CDCl₃): δ 7.05 (d, *J* = 11.0 Hz, 1H), 6.17 (s, 1H), 5.71 (s, 1H), 4.48 (hept, *J* = 6.1 Hz, 1H), 4.35 (hept, *J* = 6.1 Hz, 1H), 1.91 – 1.86 (m, 1H), 1.83 (t, *J* = 11.0 Hz, 1H), 1.79 – 1.71 (m, 1H), 1.67 – 1.48 (m, 2H), 1.52–1.49 (m, 1H), 1.43 – 1.30 (m, 4H), 1.36 (d, *J* = 6.1 Hz, 6H), 1.34 (d, *J* = 6.1 Hz, 6H), 1.18 – 1.00 (m, 2H), 1.03 (s, 3H), 0.93 (dd, *J* = 12.5, 2.2 Hz, 1H), 0.88 (s, 3H), 0.84 (s, 3H), 0.66 (d, *J* = 6.2 Hz, 3H)

¹³C NMR (125 MHz, CDCl₃): δ 184.3, 164.4, 149.4, 146.0, 133.6, 106.8, 104.8, 71.58, 71.57, 58.1, 54.9, 42.2, 41.3, 39.3, 36.2, 33.6, 33.5, 31.8, 22.0, 21.7, 21.7, 21.6, 21.6, 21.47, 21.44, 18.7, 15.2.

IR (neat): 2925, 2853, 1650, 1619, 1561, 1455, 1425, 1372, 1229 cm⁻¹

HRMS (ESI): calculated for C₂₇H₄₃O₃ 415.3212 [M+H]⁺, found 415.3219.

ortho-Phenol 2.145



To a solution of *ortho*-QM **2.143** (45 mg, 0.0185 mmol) in ethanol (4 mL) at 0 °C, was added NaBH₄ (6.2 mg, 0.164 mmol). The resulting reaction mixture was stirred at 0 °C for 2 h. The mixture was extracted with ethyl acetate (40 ml) and sequentially washed with 1M HCl solution (2 ml), water (2 × 20 ml), and brine (10 ml). Extracts were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 8:1) to give *ortho*-phenol **2.145** (20 mg, 44%).

R_f = 0.76 (petrol/EtOAc, 1:2)

[α]_D²⁵ = -6.7° (c 0.5, CHCl₃).

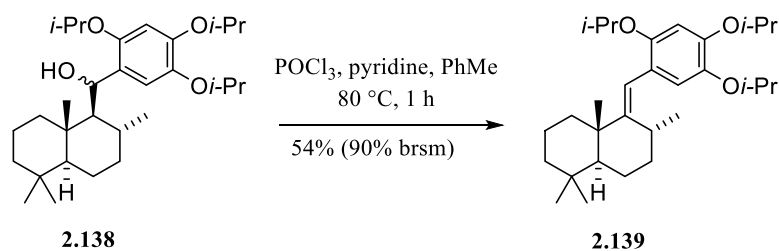
IR (neat): 3378, 2973, 2930, 2844, 1616, 1514, 1190 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ 6.77 (s, 1H), 6.35 (s, 1H), 4.51 (br s, 1H), 4.42 (hept, *J* = 6.1 Hz, 1H), 4.30 (hept, *J* = 6.1 Hz, 1H), 2.58 (dd, *J* = 15.8 Hz, *J* = 2.2 Hz, 1H), 2.25 (dd, *J* = 15.8 Hz, *J* = 6.5 Hz, 1H), 1.82 – 1.79 (m, 1H), 1.73 – 1.70 (m, 1H), 1.58 – 1.25 (m, 6H), 1.30 (d, *J* = 6.1 Hz, 6H), 1.28 (d, *J* = 6.1 Hz, 6H), 1.22 – 1.13 (m, 2H), 1.04 – 0.90 (m, 3H), 0.90 (s, 3H), 0.87 (s, 3H), 0.83 (s, 3H), 0.72 (d, *J* = 6.5 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 147.8, 142.1, 122.5, 122.3, 105.4, 73.6, 71.7, 57.4, 55.3, 39.5, 38.6, 42.1, 37.2, 35.2, 33.6, 33.4, 27.3, 22.32, 22.25, 22.21, 21.94, 21.93, 21.4, 18.9, 14.3.

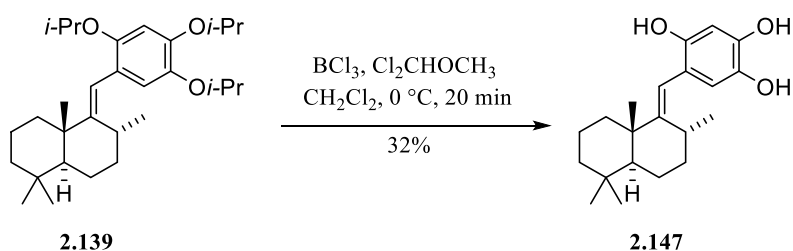
HRMS (ESI): calculated for C₂₇H₄₄O₃ 415.3218 [M-H]⁻, found 415.3210

Alkene 2.139



To a solution of benzyl alcohol **2.138** (1.15 g, 2.42 mmol) in dry PhMe (50 mL) and pyridine (3.80 mL, 47.0 mmol), was added POCl_3 (0.68 mL, 7.30 mmol) at room temperature. The reaction mixture was heated to $80\text{ }^\circ\text{C}$ for 1 h and allowed to cool to room temperature. The mixture was quenched with saturated aqueous NaHCO_3 solution (100 mL) and extracted with Et_2O ($3 \times 100\text{ mL}$). The combined organic extracts were sequentially washed with water ($3 \times 100\text{ mL}$), brine (50 mL), dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (petrol/EtOAc, 10:1) to give alkene **2.139** as a colourless oil (600 mg, 54%). Further elution gave recovered benzyl alcohol **2.138** (410 mg, 36%).

Triphenol **2.147**



To a solution of alkene **2.139** (36 mg, 0.081 mmol) and dichloromethyl methyl ether (0.011 mL, 0.11 mmol) in anhydrous CH_2Cl_2 (2 mL) at $0\text{ }^\circ\text{C}$, was added BCl_3 (1.0 M in CH_2Cl_2 , 0.5 mL, 0.5 mmol) dropwise. The reaction mixture was stirred at $0\text{ }^\circ\text{C}$ for 20 min, then quenched with saturated aqueous NaHCO_3 solution (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (petrol/EtOAc, 4:1) to give triphenol **2.147** as an amorphous, yellow film (8.6 mg, 32%).

$R_f = 0.41$ (petrol/EtOAc, 4:1)

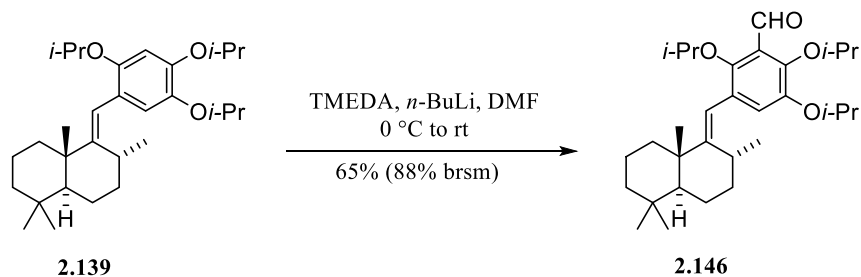
MP: product begin to decompose at $76\text{ }^\circ\text{C}$

$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 6.52 (s, 1H), 6.44 (s, 1H), 5.97 (s, 1H), 5.21 (br s, 1H), 4.76 (br s, 1H), 4.66 (br s, 1H), 2.61 – 2.55 (m, 1H), 1.76 – 1.05 (m, 11H), 1.17 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H), 0.77 (d, $J = 6.9\text{ Hz}$, 3H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 164.1, 146.7, 143.3, 136.3, 118.2, 116.3, 111.0, 101.9, 52.1, 42.3, 41.7, 39.2, 34.6, 34.1, 33.8, 33.2, 22.7, 21.7, 21.10, 21.08, 19.5.

HRMS (ESI): calculated for $\text{C}_{21}\text{H}_{30}\text{O}_3$, 329.2122 $[\text{M}-\text{H}]^-$, found 329.1232

Aryl aldehyde **2.146**



To a solution of alkene **2.139** (600 mg, 1.31 mmol) in anhydrous THF (22 mL) and TMEDA (0.34 mL, 2.27 mmol) at 0 °C, was added *n*-BuLi (2.0 M in hexanes, 3.25 mL, 6.50 mmol) dropwise. The resultant mixture was stirred at 0 °C for 1 h. DMF (1.0 mL, 12.9 mmol) was then added dropwise, and the reaction mixture was allowed to stir for 5 min. The reaction was quenched with saturated aqueous NH₄Cl solution (40 mL) and extracted with Et₂O (2 × 100 mL). The combined organic extracts were washed with water (3 × 100 mL), brine (2 × 100 mL), dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 30:1) to give aryl aldehyde **2.146** as a colourless oil (410 mg, 65%). Further elution gave recovered alkene **2.139** (140 mg, 23%).

R_f = 0.31 (petrol/EtOAc, 10:1)

[α]_D²⁵ = +9.6° (c 0.50, CHCl₃)

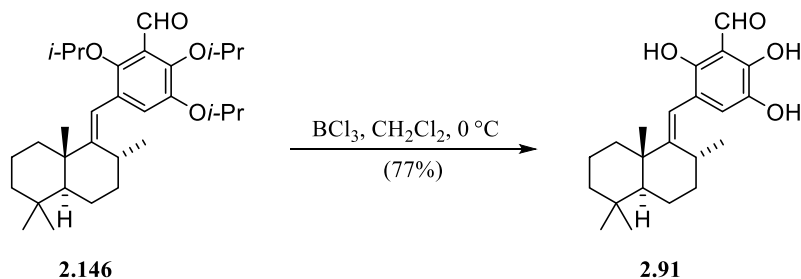
IR (neat): 2973, 2928, 2870, 1696, 1565, 1498, 1453, 1381, 1371, 1332, 1306, 1252, 1224, 1201, 1106, 1028 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 10.43 (s, 1H), 6.90 (s, 1H), 6.19 (s, 1H), 4.58 (septet, *J* = 6.2 Hz, 1H), 4.47 (septet, *J* = 6.0 Hz, 1H), 4.31 (septet, *J* = 6.2 Hz, 1H), 2.68 – 2.62 (m, 1H), 1.82 – 1.69 (m, 4H), 1.61 – 1.33 (m, 7H), 1.31 (d, *J* = 6.0 Hz, 6H), 1.29 (d, *J* = 6.0 Hz, 3H), 1.27 (d, *J* = 6.0 Hz, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.17 (s, 3H), 0.91 (s, 3H), 0.89 (s, 3H), 0.87 (d, *J* = 7.2 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 191.3, 157.3, 150.9, 148.7, 146.0, 130.0, 125.9, 125.7, 115.2, 76.2, 75.6, 72.3, 50.5, 42.4, 41.1, 39.7, 34.0, 33.3, 32.82, 32.79, 22.5, 22.34, 22.29, 22.24, 22.21, 21.99, 21.95, 21.71, 20.4, 19.6.

HRMS (ESI): calculated for C₃₁H₄₈O₄Na 507.3450 [M+H]⁺, found 507.3456

Siphonodictyal B 2.91



To a solution of aryl aldehyde **2.146** (350 mg, 0.72 mmol) in anhydrous CH_2Cl_2 (12 mL) at 0°C , was added BCl_3 (1.0 M in CH_2Cl_2 , 3.60 mL, 3.60 mmol) dropwise. The reaction mixture was stirred at 0°C for 20 min, then quenched with saturated aqueous NaHCO_3 solution (40 ml) and extracted with CH_2Cl_2 (3×40 mL). The combined organic extracts were dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (petrol/EtOAc, 8:1) to give siphonodictyal B **2.91** as an amorphous yellow solid (200 mg, 77%).

$R_f = 0.31$ (petrol/EtOAc, 2:1)

MP: product begin to decompose at 80°C

$[\alpha]_D^{25} = -61.2^\circ$ (c 0.67, CHCl_3)

IR (neat): 3430, 3128, 2926, 1637, 1617, 1453, 1254 cm^{-1}

$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 11.46 (s, 1H), 10.31 (s, 1H), 6.84 (s, 1H), 5.92 (s, 1H), 5.43 (s, 1H), 5.13 (s, 1H), 2.59 (m, 1H), 1.83 – 1.14 (m, 11H), 1.18 (s, 3H), 0.91 (s, 3H), 0.88 (s, 3H), 0.77 (d, $J = 7.0$ Hz, 3H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 194.5, 165.8, 148.5, 147.6, 136.9, 123.7, 116.7, 109.4, 109.1, 52.4, 42.3, 41.9, 39.2, 34.8, 34.2, 33.9, 33.2, 22.6, 21.7, 21.2, 21.1, 19.4.

$^1\text{H NMR}$ (500 MHz, CD_3OD): δ 10.34 (s, 1H), 6.81 (s, 1H), 6.05 (s, 1H), 2.65 (m, 1H), 1.84 – 1.21 (m, 11H), 1.19 (s, 3H), 0.93 (s, 3H), 0.89 (s, 3H), 0.87 (d, $J = 7.1$ Hz, 3H).

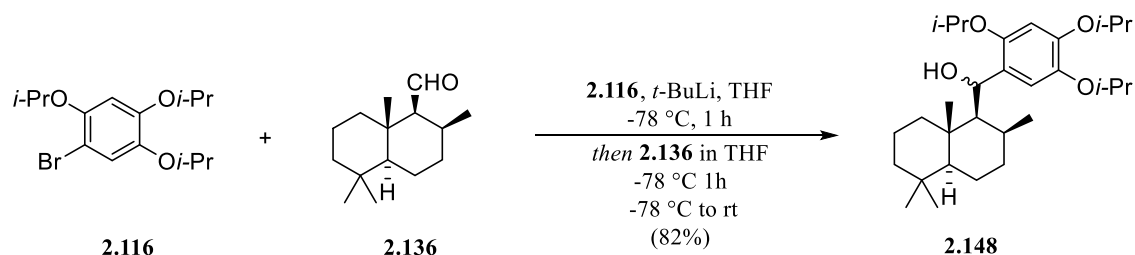
$^{13}\text{C NMR}$ (125 MHz, CD_3OD): δ 195.9, 159.8, 152.9, 149.5, 137.3, 127.6, 119.0, 114.4, 111.5, 51.8, 43.6, 42.2, 40.6, 34.9, 34.2, 34.1, 33.7, 23.2, 22.4, 22.1, 21.6, 20.6.

$^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ 10.91 (s, 1H), 10.25 (s, 1H), 10.03 (s, 1H), 9.02 (s, 1H), 6.84 (s, 1H), 6.03 (s, 1H), 2.62 (m, 1H), 1.79 – 1.62 (m, 4H), 1.51 – 1.48 (m, 2H), 1.39 – 1.27 (s, 5H), 1.12 (s, 3H), 0.88 (s, 3H), 0.87 (d, $J = 7.0$ Hz, 3H), 0.85 (s, 3H).

¹³C NMR (125 MHz, DMSO-d₆): δ 194.8, 157.0, 151.3, 147.8, 136.1, 126.2, 116.6, 113.4, 110.2, 49.1, 41.9, 40.4, 39.1, 33.6, 33.0, 31.8, 31.2, 22.9, 21.9, 21.5, 19.4, 19.0.

HRMS (ESI): calculated for C₂₂H₂₉O₄ 357.2071 [M-H]⁻, found 357.2067

Benzyl alcohol **2.148**



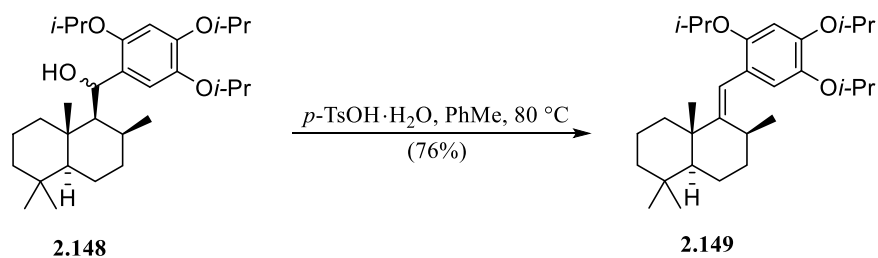
To a solution of aryl bromide **2.116** (2.80 g, 8.45 mmol) in anhydrous THF (15 mL), *t*-BuLi (1.0 M in pentane, 7.80 mL, 7.80 mmol) was added dropwise at -78 °C and the reaction mixture was stirred at this temperature for 1 h. A solution of aldehyde **2.136** (900 mg, 4.05 mmol) in anhydrous THF (15 mL) was then added dropwise over 10 min at -78 °C. The reaction mixture was stirred at -78 °C for a further 1 h, and then allowed to warm to room temperature. The reaction mixture was quenched with saturated aqueous NH₄Cl solution (50 mL) and extracted with Et₂O (2 × 100 mL). The combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 10:1) to give benzyl alcohol **2.148** as a white solid (1.58 g, 82%). ¹H NMR showed a mixture of two diastereoisomers, therefore **2.148** was not fully characterized.

R_f = 0.53 (petrol/EtOAc, 10:1)

IR (neat): 2973, 2929, 1591, 1493, 1361, 1190 cm⁻¹

HRMS (EI): calculated for C₃₀H₄₈O₃ 456.3603 [M-H₂O]⁺, found 456.3615

Alkene 2.149



To a solution of benzyl alcohol **2.148** (1.58 g, 3.33 mmol) in PhMe (50 mL) was added *p*-TsOH·H₂O (63 mg, 0.33 mmol) at room temperature. The reaction mixture was heated at 80 °C for 15 min, followed by cooling to room temperature. The reaction mixture was then quenched with saturated aqueous NaHCO₃ solution (100 mL) and extracted with EtOAc (2 × 150 mL). The combined organic extracts were sequentially washed with water (100 mL), brine (100 mL), dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 10:1) to give alkene **2.149** as a colourless oil (1.15 g, 76%).

Data for **2.149**:

R_f = 0.56 (petrol/EtOAc, 10:1)

[α]_D²⁵ = +56.0° (c 0.24, CHCl₃)

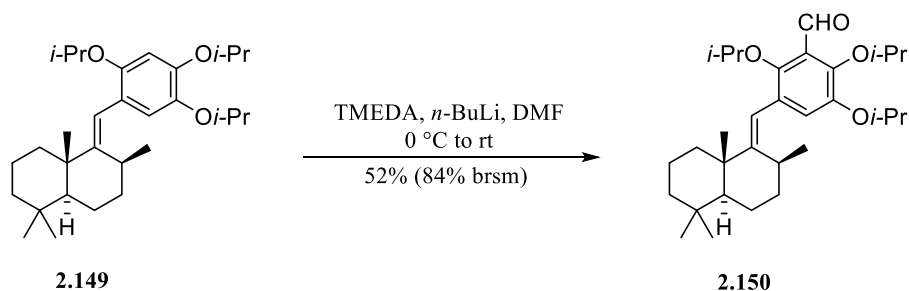
IR (neat): 2972, 2929, 2867, 1603, 1567, 1493, 1465, 1400, 1371, 1333, 1310, 1189 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 6.73 (s, 1H), 6.51 (s, 1H), 6.16 (s, 1H), 4.45 (septet, *J* = 6.1 Hz, 1H), 4.33 (septet, *J* = 6.1 Hz, 1H), 4.22 (septet, *J* = 6.1 Hz, 1H), 3.03 (m, 1H), 1.81 – 1.60 (m, 3H), 1.54 – 1.40 (m, 7H), 1.32 (d, *J* = 6.0 Hz, 3H), 1.30 (d, *J* = 6.3 Hz, 3H) 1.30 (d, *J* = 6.1 Hz, 3H), 1.28 (m, 3H), 1.27 (d, *J* = 6.1 Hz, 3H), 1.25 (d, *J* = 6.0 Hz, 3H), 1.23 (d, *J* = 7.5 Hz, 3H), 1.19 (s, 3H), 0.99 (dd, *J* = 11.8 Hz, *J* = 11.9 Hz, 1H), 0.89 (s, 3H), 0.88 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 155.3, 150.7, 147.8, 143.3, 124.5, 121.0, 115.7, 109.5, 73.1, 72.9, 72.2, 54.8, 42.3, 40.9, 38.7, 34.1, 34.0, 33.5, 30.8, 22.8, 22.6, 22.5, 22.40, 22.35, 22.30, 22.28, 22.25, 21.8, 19.0, 17.9.

HRMS (EI): calculated for C₃₀H₄₈O₃ 456.3603 [M]⁺, found 456.3600

Aldehyde 2.150



To a solution of alkene **2.149** (1.15 g, 2.52 mmol) in anhydrous THF (42 mL) and TMEDA (0.76 mL, 5.07 mmol) at 0 °C, was added *n*-BuLi (2.0 M in hexanes, 6.30 mL, 12.6 mmol) dropwise. The resultant mixture was stirred at 0 °C for 1 h. DMF (2.0 mL, 25.8 mmol) was then added dropwise, and the reaction mixture was allowed to stir for 5 min. The reaction was quenched with saturated aqueous NH₄Cl solution (70 mL) and extracted with Et₂O (2 × 200 mL). The combined organic extracts were washed with water (3 × 200 mL), brine (2 × 200 mL), dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 30:1) to give aldehyde **2.150** as a colourless oil (628 mg, 52%). Further purification gave recovered alkene **2.149** (368 mg, 32%).

R_f = 0.47 (petrol/EtOAc, 10:1)

[α]_D²⁵ = -53.0° (c 0.8, CHCl₃)

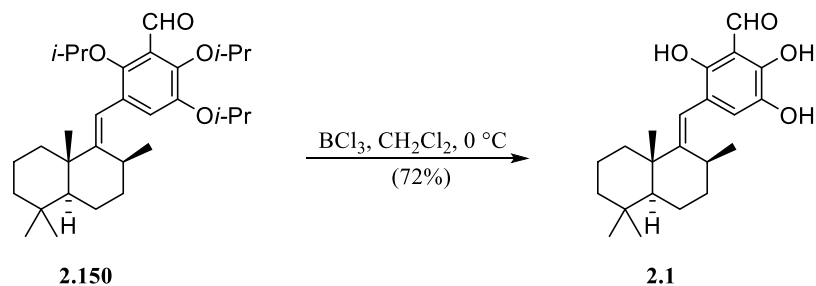
IR (neat): 2973, 2928, 2870, 1696, 1565, 1498, 1453, 1381, 1371, 1332, 1306, 1252, 1224, 1201, 1106, 1028 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 10.44 (s, 1H), 6.93 (s, 1H), 6.19 (s, 1H), 4.59 (septet, *J* = 6.2 Hz, 1H), 4.46 (septet, *J* = 6.0 Hz, 1H), 4.23 (septet, *J* = 6.2 Hz, 1H), 2.99 (m, 1H), 1.81 – 1.40 (m, 11H), 1.33 (d, *J* = 6.0 Hz, 6H), 1.30 (d, *J* = 6.2 Hz, 3H), 1.28 (d, *J* = 6.1 Hz, 3H), 1.25 (d, *J* = 6.8 Hz, 6H), 1.25 (d, *J* = 6.8 Hz, 3H), 1.22 (d, *J* = 8.0 Hz, 3H), 1.20 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 191.2, 156.3, 151.2, 148.8, 146.4, 129.3, 125.8, 124.5, 116.0, 76.7, 76.3, 72.1, 54.9, 42.3, 41.1, 38.7, 34.1, 34.0, 33.5, 31.2, 22.7, 22.37, 22.35, 22.27, 22.25, 22.0, 21.8, 18.9, 17.8.

HRMS (ESI): calculated for C₃₁H₄₉O₄ 485.3631 [M+H]⁺, found 485.3636

8-*epi*-Siphonodictyal B 2.1



To a solution of aldehyde **2.150** (173 mg, 0.357 mmol) in anhydrous CH_2Cl_2 (6 mL) at $0\text{ }^\circ\text{C}$, was added BCl_3 (1.0 M in CH_2Cl_2 , 1.80 mL, 1.80 mmol) dropwise. The reaction mixture was stirred at $0\text{ }^\circ\text{C}$ for 20 min, then quenched with saturated aqueous NaHCO_3 solution (20 ml) and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (petrol/EtOAc, 8:1) to give 8-*epi*-siphonodictyal B **2.1** as an amorphous yellow solid (93 mg, 72 %).

$R_f = 0.32$ (petrol/EtOAc, 2:1)

MP: product begin to decompose at $80\text{ }^\circ\text{C}$

$[\alpha]_D^{25} = +5.3^\circ$ (c 0.75, CHCl_3)

IR (neat): 3331, 2923, 2854, 1642, 1603, 1453, 1261 cm^{-1}

^1H NMR (500 MHz, CDCl_3): δ 11.35 (s, 1H), 10.33 (s, 1H), 6.84 (s, 1H), 5.85 (s, 1H), 5.55 (s, 1H), 5.09 (s, 1H), 2.72 (m, 1H), 1.86 – 1.58 (m, 7H), 1.54 – 1.41 (m, 4H), 1.22 (s, 3H), 1.11 (d, $J = 7.5$ Hz, 3H), 0.91 (s, 6H).

^{13}C NMR (125 MHz, CDCl_3): δ 194.5, 165.94, 148.7, 147.6, 137.1, 123.5, 115.6, 110.7, 109.3, 55.1, 42.0, 41.3, 38.8, 34.2, 34.0, 33.4, 31.7, 22.7, 22.5, 21.8, 18.8, 17.8.

^1H NMR (500 MHz, CD_3OD): δ 10.38 (s, 1H), 6.90 (s, 1H), 6.08 (s, 1H), 2.97 (quintet, $J = 6.7$ Hz, 1H), 1.83 – 1.29 (m, 11H), 1.25 (d, $J = 6.4$ Hz, 3H), 1.25 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H).

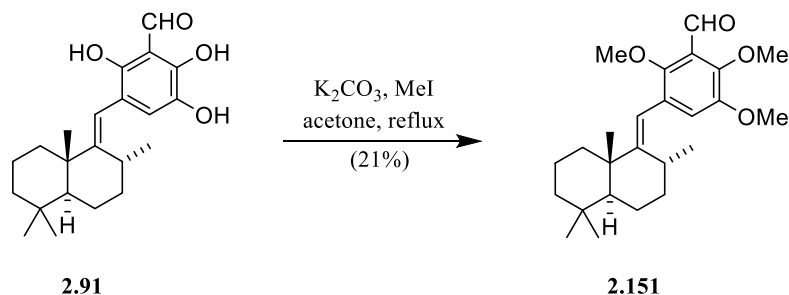
^{13}C NMR (125 MHz, CD_3OD): δ 195.9, 158.5, 153.5, 149.6, 137.5, 126.9, 118.0, 114.9, 111.7, 55.9, 43.3, 42.1, 39.7, 35.2, 34.9, 33.9, 32.4, 23.3, 23.24, 22.23, 19.9, 19.0.

^1H NMR (500 MHz, $\text{DMSO-}d_6$): δ 11.01 (s, 1H), 10.26 (s, 1H), 10.07 (s, 1H), 9.11 (s, 1H), 6.91 (s, 1H), 6.01 (s, 1H), 3.35 (quintet, $J = 6.9$ Hz, 1H), 1.73 – 1.39 (m, 11H), 1.22 (d, $J = 7.4$ Hz, 3H), 1.15 (s, 3H), 0.86 (s, 3H), 0.86 (s, 3H).

¹³C NMR (125 MHz, DMSO-d₆): 194.8, 155.5, 151.8, 148.0, 136.3, 125.5, 115.6, 113.3, 110.4, 54.2, 41.7, 40.5, 38.1, 33.7, 33.6, 33.2, 30.5, 22.7, 22.4, 21.6, 18.4, 17.4.

HRMS (ESI): calculated for C₂₂H₃₁O₄ 359.2217 [M+H]⁺, found 359.2210

Methoxy-siphonodictyal B **2.151**



To a solution of siphonodictyal B **2.91** (15 mg, 0.042 mmol) and K₂CO₃ (75 mg, 0.54 mmol) in dry acetone (10 mL) at room temperature, was added MeI (0.30 mL, 4.82 mmol). The reaction mixture was heated at reflux for 8 h, then allowed to cool to room temperature and quenched with 1 M aqueous HCl solution (10 mL). The mixture was extracted with Et₂O (30 mL), followed by washing with water (30 mL) and brine (20 mL) before being dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 10:1) to give methoxy-siphonodictyal B **2.151** as a colourless oil (3.5 mg, 21%).

R_f = 0.50 (petrol/EtOAc, 4:1)

[α]_D²⁵ = -129.6° (c 0.28, CHCl₃)

IR (neat): 2928, 2868, 1695, 1476, 1388, 1228 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 10.40 (s, 1H), 6.91 (s, 1H), 6.21 (s, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 3.72 (s, 3H), 2.66 (m, 1H), 1.86 – 1.24 (m, 11H), 1.19 (s, 3H), 0.91 (s, 3H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 3H).

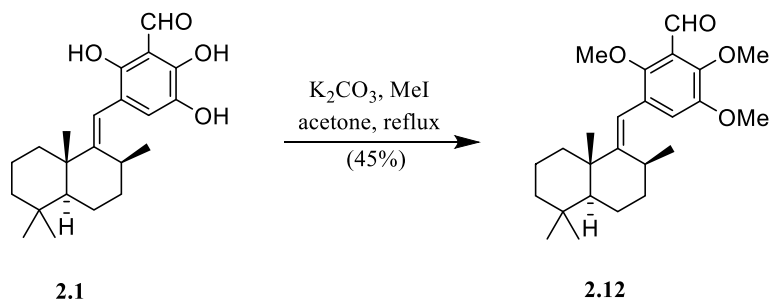
¹³C NMR (125 MHz, CDCl₃): δ 190.3, 158.7, 152.0, 149.4, 148.3, 130.4, 123.5, 120.6, 114.0, 62.1, 61.6, 56.5, 50.1, 42.4, 41.0, 39.7, 34.0, 33.2, 32.7, 32.4, 22.8, 22.2, 21.7, 20.2, 19.5.

¹H NMR (500 MHz, C₆D₆): δ 10.60 (s, 1H), 6.82 (s, 1H), 6.31 (s, 1H), 3.74 (s, 3H), 3.61 (s, 3H), 3.29 (s, 3H), 2.63 (m, 1H), 1.79 (m, 1H), 1.73 – 1.27 (m, 10H), 1.15 (s, 3H), 0.97 (d, *J* = 7.1 Hz, 3H), 0.89 (s, 3H), 0.88 (s, 3H).

¹³C NMR (125 MHz, C₆D₆): δ 189.3, 158.4, 152.3, 150.4, 148.9, 130.5, 125.1, 120.4, 114.9, 61.8, 61.7, 56.1, 50.7, 42.7, 41.3, 40.0, 34.1, 33.5, 33.2, 32.9, 22.9, 22.4, 21.9, 20.6, 19.9

HRMS (ESI): calculated for C₂₅H₃₆O₄Na 423.2511 [M+Na]⁺, found 423.2505

Methoxy-8-*epi*-siphonodictyal B 2.12



To a solution of 8-*epi*-siphonodictyal B **2.1** (10 mg, 0.028 mmol) and K_2CO_3 (50 mg, 0.362 mmol) in dry acetone (10 mL) at room temperature, was added MeI (0.10 mL, 1.61 mmol). The reaction mixture was heated at reflux for 8 h, then allowed to cool to room temperature and quenched with 1 M HCl solution (10 mL). The mixture was extracted with Et_2O (30 mL), followed by washing with water (30 mL) and brine (20 mL) before being dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (petrol/ $EtOAc$, 10:1) to give methoxy-8-*epi*-siphonodictyal B **2.12** as a colourless oil (5 mg, 45%).

$R_f = 0.70$ (petrol/ $EtOAc$, 4:1)

$[\alpha]_D^{25} = +100.0^\circ$ (c 0.16, $CHCl_3$)

IR (neat): 2942, 2853, 1674, 1566, 1498, 1371, 1234 cm^{-1}

1H NMR (500 MHz, $CDCl_3$): δ 10.43 (s, 1H), 6.95 (s, 1H), 6.21 (s, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 3.74 (s, 3H), 2.96 (quintet, $J = 6.7$ Hz, 1H), 1.83 – 1.44 (m, 9H), 1.28 (d, $J = 7.5$ Hz, 3H), 1.27 – 1.25 (m, 1H), 1.23 (s, 3H), 0.99 (d, $J = 11.0$ Hz, 1H), 0.92 (s, 3H), 0.90 (s, 3H).

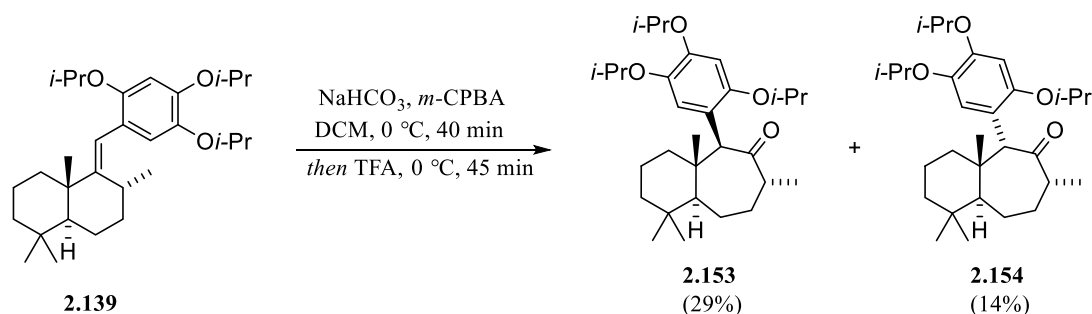
^{13}C NMR (125 MHz, $CDCl_3$): δ 190.2, 157.9, 152.7, 149.4, 148.6, 129.4, 123.7, 119.9, 114.5, 62.1, 56.4, 54.9, 42.1, 41.0, 38.7, 34.1, 34.0, 33.4, 31.2, 29.7, 22.8, 22.4, 21.9, 18.9, 17.8.

1H NMR (500 MHz, C_6D_6): 10.60 (s, 1H), 6.84 (s, 1H), 6.36 (s, 1H), 3.74 (s, 3H), 3.62 (s, 3H), 3.33 (s, 3H), 3.01 (m, 1H), 1.78 – 1.26 (m, 11H), 1.19 (s, 3H), 1.18 (d, $J = 7$ Hz, 3H), 0.89 (s, 3H), 0.88 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6): δ 189.2, 157.6, 153.1, 150.3, 149.2, 129.5, 125.4, 119.8, 115.6, 62.0, 61.7, 56.0, 55.3, 42.5, 41.3, 39.1, 34.5, 34.2, 33.6, 31.7, 22.9, 22.7, 22.1, 19.3, 18.2.

HRMS (ESI): calculated for $C_{25}H_{36}O_4Na$ 423.2506 $[M+Na]^+$, found 423.2511

Ring expansion ketones 2.153 & 2.154



To a solution of alkene **2.139** (33.7 mg, 0.0738 mmol) and NaHCO_3 (9.4 mg, 0.154 mmol) in CH_2Cl_2 (5 mL) at 0 °C, was added *m*-CPBA (21.0 mg, 0.1217 mmol) in one portion. The resulting reaction mixture was stirred at 0 °C for 40 mins. TFA (0.03 ml, 5.13 mmol) was added dropwise to the reaction mixture, and was stirred at 0 °C for a further 40 min. The reaction mixture was quenched with saturated aqueous Na_2CO_3 solution (10ml), followed by extraction with EtOAc (100ml). The organic extracts were sequentially washed with water (25 mL), brine (10 mL), dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (petrol/EtOAc, 10:1) to give ketones **2.153** (10 mg, 29%) and **2.154** (5 mg, 14%) as white, gum-wax like solids.

Ring expanded ketone 2.153

$R_f = 0.39$ (petrol/EtOAc, 10:1)

IR (neat): 2972, 2927, 2868, 1703, 1606, 1498, 1370 cm^{-1}

^1H NMR (500 MHz, CDCl_3): δ 7.42 (s, 1H), 6.43 (s, 1H), 4.70 (s, 1H), 4.45 (sep, $J = 6.1$ Hz, 1H), 4.37 (sep, $J = 5.6$ Hz, 2H), 2.43 – 2.39 (m, 1H), 2.08 – 2.02 (m, 1H) 1.98 – 1.94 (m, 1H), 1.53 – 0.85 (m, 9H), 1.37 (d, $J = 6.0$ Hz, 3H), 1.33 – 1.26 (m, 9H), 1.30 (d, $J = 6.6$ Hz, 6H), 1.03 (d, $J = 7.1$ Hz, 3H), 0.99 (s, 3H), 0.96 (s, 3H), 0.79 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3): δ 216.0, 150.1, 147.7, 142.2, 122.7, 121.0, 105.2, 72.7, 72.3, 70.7, 62.6, 53.0, 49.8, 42.2, 41.3, 38.2, 35.2, 34.2 29.7, 24.6, 22.56, 22.50, 22.45, 22.42, 22.34, 22.33, 21.8, 19.5, 19.1, 17.5.

$[\alpha]_D^{25} = -88.2^\circ$ (c 0.5, CHCl_3)

HRMS (ESI): calculated for $\text{C}_{30}\text{H}_{48}\text{O}_4$ 473.3625 $[\text{M}+\text{H}]^+$, found 473.3624

Ring expanded ketone 2.154

R_f = 0.45 (petrol/EtOAc, 10:1)

IR (neat): 2971, 2928, 2870, 1708, 1606, 1499, 1371 cm⁻¹

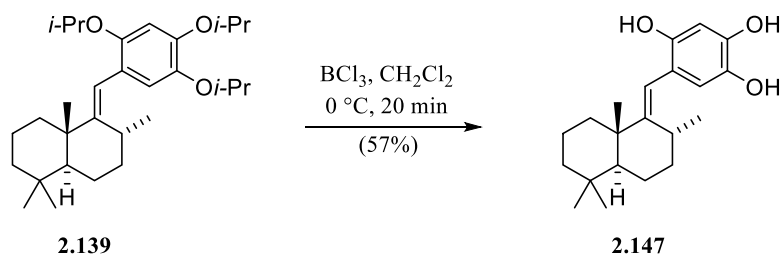
¹H NMR (500 MHz, CDCl₃): δ 7.59 (s, 1H), 6.44 (s, 1H), 4.75 (s, 1H), 4.45 (sep, *J* = 6.0 Hz, 1H), 4.37 (sep, *J* = 6.0 Hz, 2H), 2.70 – 2.63 (m, 1H), 2.23 – 2.19 (m, 1H), 1.79 – 0.84 (m, 10H), 1.34 – 1.26 (m, 18H), 0.95 (d, *J* = 6.2 Hz, 3H), 0.86 (s, 3H), 0.85 (s, 3H), 0.84 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 215.3, 150.8, 147.9, 142.0, 123.3, 117.6, 105.0, 72.6, 72.5, 70.7, 55.9, 54.1, 49.4, 41.3, 41.2, 37.1, 33.6, 32.9, 22.70, 22.54, 22.46, 22.41, 22.35, 22.32, 22.21, 21.7, 20.1, 19.0, 16.1.

HRMS (ESI): calculated for C₃₀H₄₈O₄ 473.3625 [M+H]⁺, found 473.3634.

[α]_D²⁵ = +39.2° (c 0.25, CHCl₃)

Triphenol **2.147**



To a solution of alkene **2.139** (266 mg, 0.582 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C, was added BCl_3 (1.0 M in CH_2Cl_2 , 1.9 ml, 1.9 mmol) dropwise. The reaction mixture was stirred at 0 °C for 20 min, then quenched with saturated aqueous NaHCO_3 solution (16 ml) and extracted with CH_2Cl_2 (3 \times 50 mL). The combined organic extracts were dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (petrol/EtOAc, 4:1) to give triphenol **2.147** as an amorphous, yellow solid (110 mg, 57%).

R_f = 0.41 (petrol/EtOAc, 4:1)

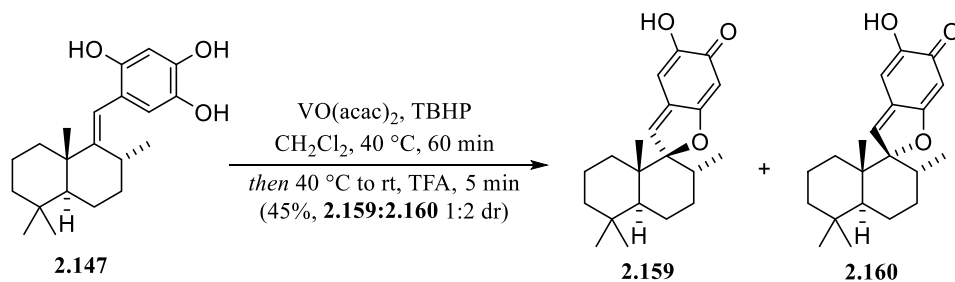
MP: product begin to decompose at 76 °C

^1H NMR (500 MHz, CDCl_3): δ 6.52 (s, 1H), 6.44 (s, 1H), 5.97 (s, 1H), 5.21 (br s, 1H), 4.76 (br s, 1H), 4.66 (br s, 1H), 2.61 – 2.55 (m, 1H), 1.76 – 1.05 (m, 11H), 1.17 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H), 0.77 (d, J = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3): δ 164.1, 146.7, 143.3, 136.3, 118.2, 116.3, 111.0, 101.9, 52.1, 42.3, 41.7, 39.2, 34.6, 34.1, 33.8, 33.2, 22.7, 21.7, 21.10, 21.08, 19.5.

HRMS (ESI): calculated for $\text{C}_{21}\text{H}_{30}\text{O}_3$, 329.2122 $[\text{M}-\text{H}]^-$, found 329.1232

Spirocycles 2.159 & 2.160



To a solution of triphenol **2.147** (20.0 mg, 0.0605 mmol) in CH_2Cl_2 (4 mL) at 40 °C, was added $\text{VO}(\text{acac})_2$ (1.6 mg, 0.00605 mmol) and *t*-BuOOH (5.0 M in decane, 0.03 mL, 0.15 mmol). The resulting reaction mixture was stirred at 40 °C for 60 min, before the mixture was cooled to room temperature. TFA (0.05 mL, 0.653 mmol) was added to the reaction mixture, and was stirred at room temperature for 5 min before being quenched with saturated aqueous NaHCO_3 solution (2 mL). The mixture was extracted with ethyl acetate (50 mL), and the organic phase was washed sequentially with water (2 × 50 mL), brine (20 mL). Extracts were dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (petrol/EtOAc, 8:1) to give the product as a brown solid, spirocycles **2.159** & **2.160** a mixture of diastereoisomers in a 1:2 ratio respectively (9.0 mg, 45%).

$R_f = 0.21$ (petrol/EtOAc, 2:1)

NMR data for spirocycle **2.159**;

$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 7.41 (br s, 1H), 7.21 (s, 1H), 6.36 (s, 1H), 5.91 (s, 1H), 2.49 – 2.41 (m, 1H), 1.94 – 1.91 (m, 1H), 1.78 – 1.70 (m, 1H), 1.58 – 1.19 (m, 9H), 1.25 (s, 3H), 0.92 (s, 3H), 0.88 (s, 3H), 0.55 (d, $J = 6.5$ Hz, 3H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 181.7, 175.4, 150.7, 143.3, 131.5, 108.8, 96.7, 95.5, 51.9, 44.2, 41.8, 35.51, 33.70, 33.48, 33.35, 29.7, 21.86, 21.54, 18.3, 16.2, 15.5.

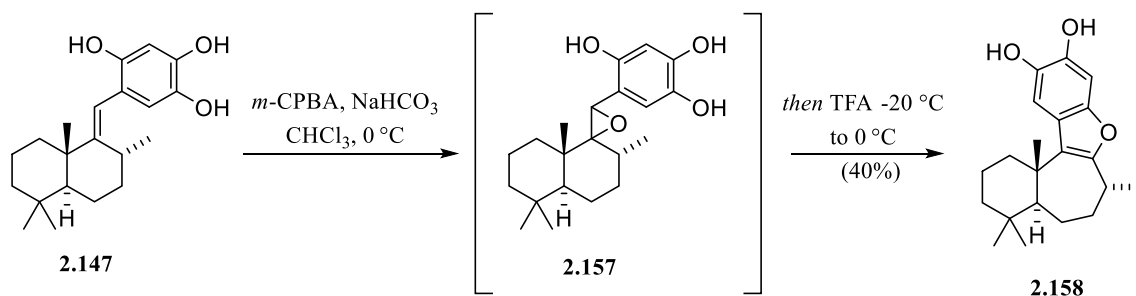
NMR data for spirocycle **2.160**;

$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 7.41 (br s, 1H), 6.96 (s, 1H), 6.31 (s, 1H), 5.98 (s, 1H), 2.34 – 2.27 (m, 1H), 1.78 – 1.70 (m, 2H), 1.64 – 1.62 (m, 1H), 1.58 – 0.93 (m, 8H), 1.21 (s, 3H), 0.93 (s, 3H), 0.86 (s, 3H), 0.56 (d, $J = 6.6$ Hz, 3H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 181.7, 175.4, 150.7, 145.5, 131.3, 107.1, 96.6, 95.7, 47.3, 43.5, 41.4, 34.0, 33.68, 33.29, 32.7, 32.1, 21.90, 21.46, 19.0, 18.2, 15.6.

HRMS (ESI): calculated for $\text{C}_{21}\text{H}_{28}\text{O}_3$, 329.2111 $[\text{M}+\text{H}]^+$, found 329.2115

Analogue 2.158



To a solution of triphenol **2.147** (35.0 mg, 0.1059 mmol) and NaHCO₃ (15.2 mg, 0.181 mmol) in CHCl₃ (4 mL) at 0 °C, was added *m*-CPBA (28.5 mg, 0.165 mmol) in one portion. The resulting reaction mixture was stirred at 0 °C for 30 min, before cooling the mixture to -20 °C. TFA (0.1 mL, 1.307 mmol) was added dropwise to the reaction mixture at -20 °C, followed by slowly warming the mixture to 0 °C, over 30 min. The reaction was quenched with saturated aqueous NaHCO₃ solution (10 mL) and extracted with Et₂O (2 × 30 mL). The organic extracts were washed sequentially with water (2 × 50 mL), brine (30 mL). Extracts were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 8:1) to give liphagal analogue **2.158** as yellow solid (13.8 mg, 40%).

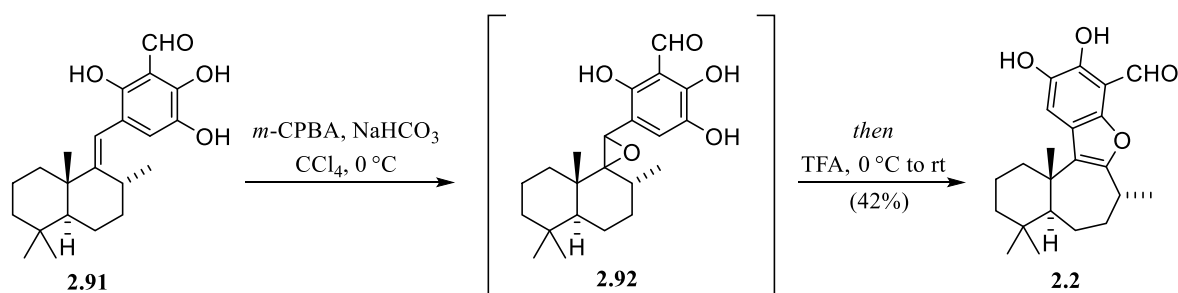
R_f = 0.43 (petrol/EtOAc, 2:1)

¹H NMR (500 MHz, CDCl₃): δ 7.20 (s, 1H), 6.90 (s, 1H), 5.33 (br s, 1H), 5.01 (br s, 1H), 3.17 – 3.13 (m, 1H), 2.57 – 2.54 (m, 1H), 2.16 – 2.13 (m, 1H), 1.84 – 1.17 (m, 9H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.34 (s, 3H), 0.97 (s, 3H), 0.94 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 156.1, 148.4, 140.8, 138.8, 125.1, 121.4, 108.1, 97.7, 53.6, 42.0, 40.2, 34.8, 33.6, 33.3, 33.2, 29.7, 24.2, 22.0, 21.8, 20.1, 18.8.

HRMS (ESI): calculated for C₂₁H₂₈O₃, 329.2111 [M+H]⁺, found 329.2074

Liphagal 2.2



To a solution of siphonodictyal B **2.91** (20 mg, 0.056 mmol) and NaHCO₃ (8 mg, 0.095 mmol) in CCl₄ (2 mL) at 0 °C, was added *m*-CPBA (14 mg, 0.062 mmol) in one portion and the resulting mixture was stirred at 0 °C for 1 h. TFA (0.04 mL, 0.52 mmol) was then added dropwise, and the reaction mixture was allowed to slowly warm to room temperature over 30 min, and stirred for a further 2 h. The mixture was quenched with saturated aqueous NaHCO₃ solution (20 mL) and extracted with Et₂O (2 × 50 mL). The combined organic extracts were sequentially washed with water (50 mL), brine (50 mL) then dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 8:1) to give liphagal **2.2** as a yellow solid (8.3 mg, 42%).

$R_f = 0.45$ (petrol/EtOAc, 10:1)

$[\alpha]_D^{25} = +22.6$ (c 0.50, CHCl₃), lit. $[\alpha]_D^{25} = +25.99$ (c 0.072, CHCl₃)

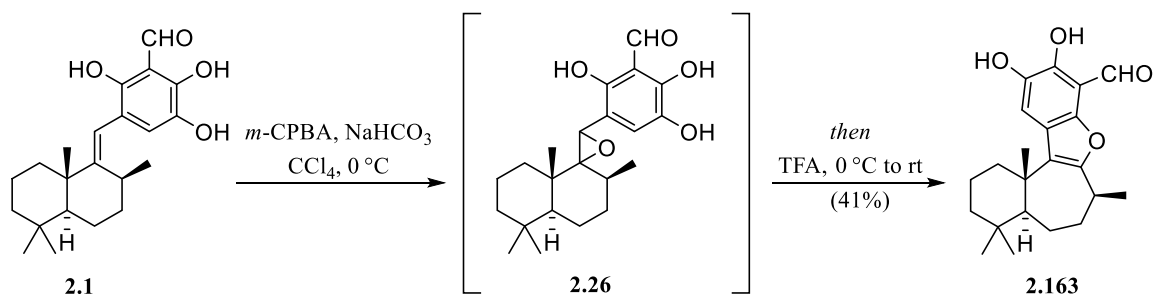
IR (neat): 3417, 2930, 2868, 1654, 1455, 1389, 1328, 1301 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 11.24 (s, 1H), 10.44 (s, 1H), 7.55 (s, 1H), 5.32 (s, 1H), 3.21 (sextet, *J* = 7.0 Hz, 1H), 2.54 (m, 1H), 2.18 (m, 1H), 1.87 (m, 1H), 1.71 (m, 1H), 1.64 – 1.45 (m, 6H), 1.43 (d, *J* = 7.0 Hz, 3H), 1.35 (s, 3H), 1.25 (ddd, *J* = 13.0, 13.0, 3.0 Hz, 1H), 0.98 (s, 3H), 0.95 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 192.6, 156.7, 148.2, 145.5, 139.6, 125.7, 120.5, 116.2, 106.5, 53.9, 42.1, 40.5, 39.7, 35.4, 35.0, 33.9, 33.5, 24.4, 22.2, 21.9, 20.4, 19.0.

HRMS (ESI): calculated for C₂₂H₂₉O₄ 357.2066 [M+H]⁺, found 357.2060

8-*epi*-Liphagal **2.163**



To a solution of 8-*epi*-siphonodictyal B **2.1** (27 mg, 0.075 mmol) and NaHCO₃ (11 mg, 0.13 mmol) in CCl₄ (1 mL) at 0 °C, was added *m*-CPBA (17 mg, 0.075 mmol) in one portion and the resulting mixture was stirred at 0 °C for 1 h. TFA (0.10 mL, 1.31 mmol) was then added dropwise, and the reaction mixture was allowed to warm to room temperature over 30 min, and stirred for a further 2 h. The mixture was quenched with saturated aqueous NaHCO₃ solution (20 mL) and extracted with Et₂O (2 × 30 mL). The combined organic extracts were sequentially washed with water (50 mL), brine (50 mL) then dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 8:1) to give 8-*epi*-liphagal **2.163** as a yellow solid (11 mg, 41%).

R_f = 0.60 (petrol/EtOAc, 2:1)

[α]_D²⁵ = +86.4 (c 0.22, CHCl₃)

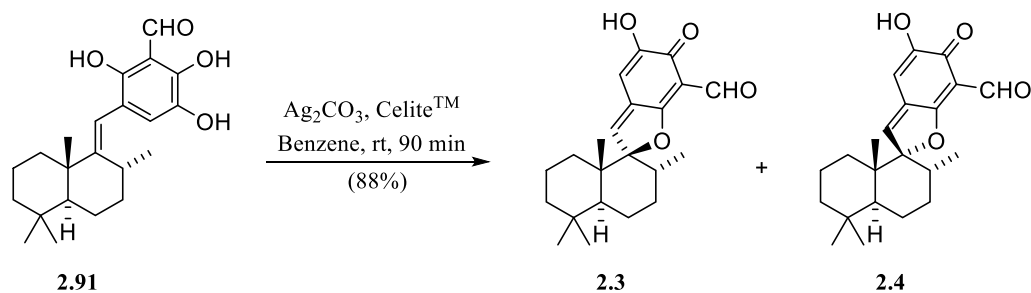
IR (neat): 3374, 2927, 2866, 1652, 1454, 1330, 1300, 1188 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 11.24 (s, 1H), 10.46 (s, 1H), 7.51 (s, 1H), 5.34 (s, 1H), 3.33 – 3.29 (m, 1H), 2.53 – 2.50 (m, 1H), 2.06 – 1.65 (m, 8H), 1.52 – 1.42 (m, 2H), 1.39 (s, 3H), 1.37 (d, *J* = 6.9 Hz, 3H), 1.00 (s, 3H), 0.97 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 192.4, 155.3, 147.7, 145.3, 139.5, 124.9, 120.4, 115.5, 106.4, 50.4, 42.0, 40.2, 39.2, 35.9, 34.6, 33.8, 31.1, 22.8, 22.3, 20.4, 18.8, 18.7.

HRMS (ESI): calculated for C₂₂H₂₇O₄ 355.1915 [M-H]⁻, found 355.1916

Corallidictyals A (2.3) and B (2.4)



To a solution of siphonodictyal B **2.91** (7.0 mg, 0.0195 mmol) in benzene (6 mL) at room temperature, was added Ag_2CO_3 (21.5 mg, 0.0780 mmol) and Celite™ (50 mg). The resulting reaction mixture was stirred at room temperature for 90 min. The mixture was diluted with diethyl ether (50 ml), filtered through a pad of Celite™ and concentrated *in vacuo* to give a brown solid, corallidictyals A **2.3** and B **2.4** as a mixture of diastereoisomers in a 1:2 ratio respectively (6.1 mg, 88%).

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

NMR data for corallidictyal A **2.3**;

$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 10.26 (s, 1H), 7.50 (s, 1H), 7.41 (br s, 1H), 6.48 (s, 1H), 2.65 – 2.60 (m, 1H), 2.02 – 0.81 (m, 10H), 1.35 (s, 3H), 1.24 (d, $J = 4.75$ Hz, 1H), 0.93 (s, 3H), 0.90 (s, 3H), 0.54 (d, $J = 6.6$ Hz, 3H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 186.6, 180.3, 175.8, 150.31, 147.8, 131.7, 113.1, 107.72, 98.4, 52.3, 44.9, 41.7, 35.5, 33.8, 33.7, 33.51, 33.48, 29.7, 21.87, 21.49, 16.4, 15.5.

NMR data for corallidictyal B **2.4**;

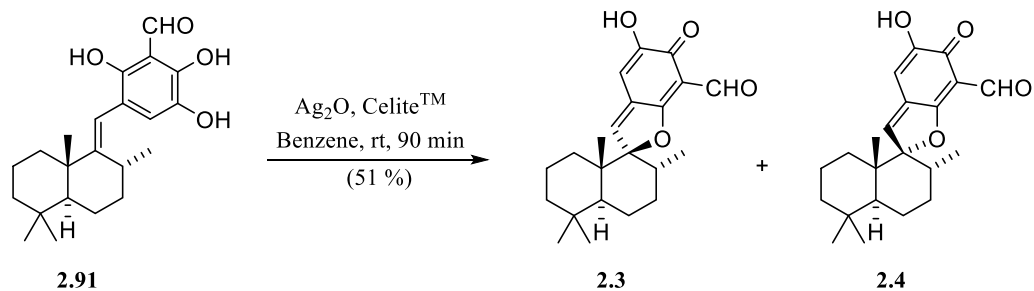
$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 10.30 (s, 1H), 7.41 (br s, 1H), 7.24 (s, 1H), 6.43 (s, 1H), 2.45 – 2.39 (m, 1H), 1.83 – 0.81 (m, 10H), 1.74 (dd, $J = 2.3, 12.75$ Hz, 1H), 1.27 (s, 3H), 0.95 (s, 3H), 0.87 (s, 3H), 0.55 (d, $J = 6.5$ Hz, 3H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 186.2, 180.0, 177.0, 150.26, 149.8, 130.8, 111.2, 107.68, 98.2, 47.3, 44.0, 41.2, 34.2, 33.7, 33.31, 33.30, 32.0, 30.4, 21.89, 21.47, 19.4, 15.6.

IR (neat): 3322, 2927, 2856, 1692, 1643, 1598, 1566 cm^{-1}

HRMS (ESI): calculated for $\text{C}_{22}\text{H}_{28}\text{O}_4$, 355.1915 $[\text{M}-\text{H}]^-$, found 355.1911

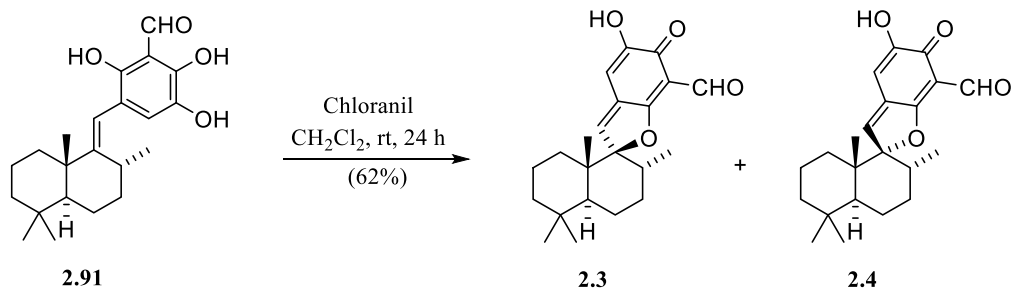
Corallidictyals A (2.3) and B (2.4)



To a solution of siphonodictyal B **2.91** (10.0 mg, 0.0279 mmol) in benzene (8 mL) at room temperature, was added Ag_2O (12.9 mg, 0.056 mmol) and CeliteTM (50 mg). The resulting reaction mixture was stirred at room temperature for 90 min. The mixture was diluted with diethyl ether (50 ml), filtered through a pad of CeliteTM and concentrated *in vacuo* to give a brown solid, corallidictyals A **2.3** and B **2.4** as a mixture of diastereoisomers in a 1:2 ratio respectively (5.1 mg, 51%).

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

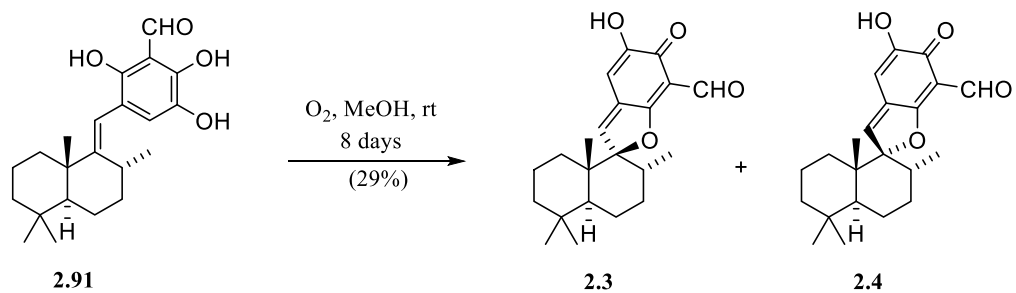
Corallidictyals A (2.3) and B (2.4)



To a solution of siphonodictyal B **2.91** (10.0 mg, 0.0279 mmol) in CH₂Cl₂ (6 mL) at room temperature, was added chloranil (73.0 mg, 0.297 mmol). The resulting reaction mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on SiO₂ (petrol/ethyl acetate, 8:1) to give a yellow solid, corallidictyals A **2.3** and B **2.4** as a mixture of diastereoisomers in a 1:2 ratio respectively (6.2 mg, 62%).

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

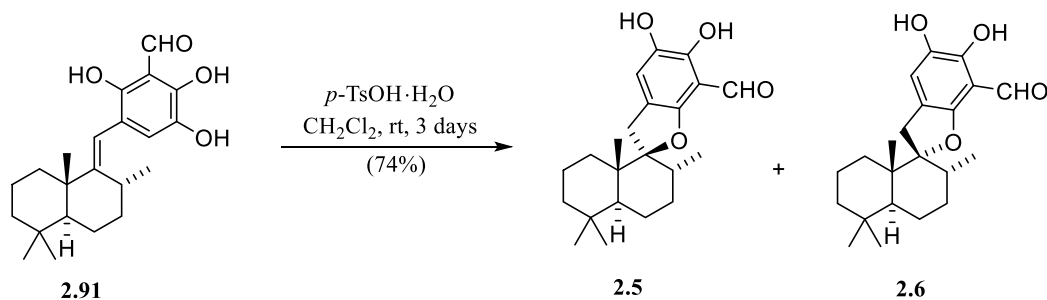
Corallidictyals A (2.3) and B (2.4)



A solution of Siphonodictyal B **2.91** (55.8 mg, 0.156 mmol) in MeOH (30 mL) at room temperature was stirred under an atmosphere of pure oxygen via a breathable bladder. The solution was stirred at room temperature for 8 days, followed by concentration *in vacuo* and purified by flash column chromatography on SiO₂ (petrol/ethyl acetate, 4:1) to give an inseparable mixture of corallidictyals A **2.3** and B **2.4** in a ratio of 1:2 ratio respectively as a light brown solid (16.3 mg, 29 %).

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

Corallidictyals C (2.5) and D (2.6)



To a solution of siphonodictyal B **2.91** (7 mg, 0.0195 mmol) in CH₂Cl₂ (10 mL) at room temperature, was added p -TsOH·H₂O (5.2 mg, 0.0302 mmol) in one portion. The resulting reaction mixture was stirred at room temperature under a nitrogen atmosphere for 3 days. The mixture was extracted with diethyl ether (50 ml) and the combined organic extracts were sequentially washed with aqueous Na₂CO₃ solution (10 ml), water (25 mL), brine (10 mL), dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/diethyl ether, 3:1) to give corallidictyal C **2.5**, corallidictyal D **2.6** and an unknown isomer as an inseparable mixture in a ratio of 1:1:0.5 respectively, as a yellow solid (5.2 mg, 74%).

R_f = 0.75 (petrol/EtOAc, 1:1)

NMR data for corallidictyal C **2.5**;

¹H NMR (500 MHz, DMSO-*d*₆): δ 10.53 (br s, 1H), 10.08 (s, 1H), 8.66 (br s, 1H), 6.94 (s, 1H), 3.05 (d, J = 16.6 Hz, 1H), 2.85 (d, J = 16.6 Hz, 1H), 2.22 – 2.15 (m, 1H), 1.63 – 1.00 (m, 10H), 1.13 (s, 3H), 1.04 (dd, J = 3.1 Hz, J = 12.5 Hz, 1H), 0.85 (s, 3H), 0.82 (s, 3H), 0.68 (d, J = 6.6 Hz, 3H).

¹³C NMR (125 MHz, DMSO-*d*₆): δ 191.7, 155.0, 147.0, 137.3, 120.6, 117.2, 106.14, 99.8, 47.1, 43.0, 41.2, 34.6, 33.17, 32.6, 30.5, 30.3, 29.1, 21.5, 20.7, 17.7, 15.0, 14.6.

¹H NMR (500 MHz, CDCl₃): δ 11.10 (br s, 1H), 10.13 (s, 1H), 6.96 (s, 1H), 5.01 (br s, 1H), 3.07 (d, J = 16.3 Hz, 1H), 2.88 (d, J = 16.3 Hz, 1H), 2.30 – 2.23 (m, 1H), 1.71 – 0.99 (m, 10 H), 1.17 (s, 3H), 1.04 – 1.00 (m, 1H), 0.88 (s, 3H), 0.86 (s, 3H), 0.74 (d, J = 6.4 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ, 192.87, 156.5, 146.10, 136.7, 119.3, 118.0, 105.6, 100.9, 48.1, 42.5, 35.1, 33.47, 33.3, 33.0, 31.2, 30.9, 21.6, 21.2, 18.1, 15.3, 14.9.

NMR data for corallidictyal D 2.6;

¹H NMR (500 MHz, DMSO-d₆): δ 10.53 (br s, 1H), 10.14 (s, 1H), 8.66 (br s, 1H), 6.90 (s, 1H), 3.09 (d, *J* = 16.3 Hz, 1H), 2.71 (d, *J* = 16.3 Hz, 1H), 1.81 – 1.74 (m, 1H), 1.61 – 1.07 (m, 10H), 1.60 – 1.55 (m, 1H), 0.92 (s, 3H), 0.88 (s, 3H), 0.83 (s, 3H), 0.66 (d, *J* = 6.6 Hz, 3H).

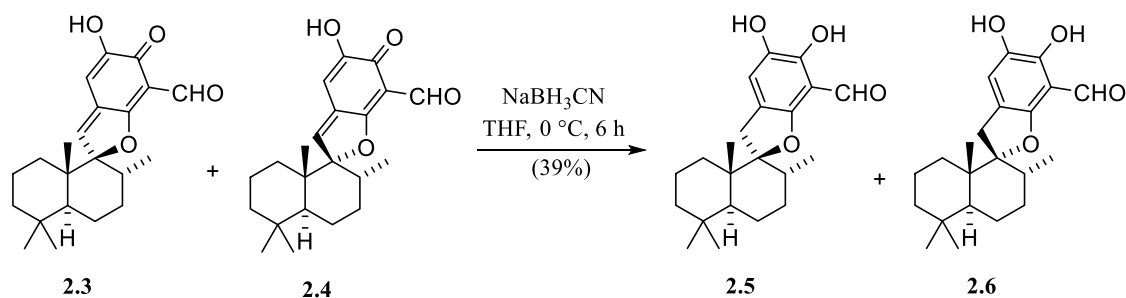
¹³C NMR (125 MHz, DMSO-d₆): δ 192.0, 155.7, 146.9, 137.4, 120.7, 116.8, 106.06, 98.2, 46.1, 42.0, 41.3, 36.4, 33.23, 32.9, 32.8, 30.70, 30.68, 21.7, 20.9, 17.8, 15.7, 15.5.

¹H NMR (500 MHz, CDCl₃): δ 11.08 (br s, 1H), 10.20 (s, 1H), 6.93 (s, 1H), 5.01 (br s, 1H), 3.15 (d, *J* = 16.0 Hz, 1H), 2.73 (d, *J* = 16.0 Hz, 1H), 1.82 – 1.75 (m, 1H), 1.70 – 0.99 (m, 10), 1.50 – 1.44 (m, 1H), 0.97 (s, 3H), 0.91 (s, 3H), 0.85 (s, 3H), 0.73 (d, *J* = 6.4 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 192.91, 156.9, 146.10, 136.8, 119.3, 117.4, 105.7, 99.3, 46.8, 41.9, 41.7, 37.1, 33.50, 33.4, 31.3, 31.1, 29.8, 21.9, 21.4, 18.2, 16.2, 15.6.

HRMS (ESI): calculated for C₂₂H₃₀O₄ 357.2071 [M-H]⁻, found 357.2068

Corallidictyals C (2.5) and D (2.6)



To a solution of a mixture of corallidictyals A **2.3** and B **2.4** (50 mg, 0.140 mmol) in THF (20 mL) at 0 °C, was added sodium cyanoborohydride (48.5 mg, 0.772 mmol). The resulting reaction mixture was stirred at 0 °C under a nitrogen atmosphere for 6 h and upon completion the mixture was extracted with diethyl ether (100 ml). The combined organic extracts were sequentially washed with water (50 mL), brine (25 mL) then dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/diethyl ether, 3:1) to give a yellow solid, corallidictyals C **2.5** and D **2.6** as a mixture of diastereoisomers in a 1:2 ratio respectively (19.8 mg, 39%).

$R_f = 0.75$ (petrol/EtOAc, 1:1)

NMR data for corallidictyals C **2.5**;

¹H NMR (500 MHz, DMSO-*d*₆): δ 10.53 (br s, 1H), 10.08 (s, 1H), 8.66 (br s, 1H), 6.94 (s, 1H), 3.05 (d, $J = 16.6$ Hz, 1H), 2.85 (d, $J = 16.6$ Hz, 1H), 2.22 – 2.15 (m, 1H), 1.63 – 1.00 (m, 10H), 1.12 (s, 3H), 1.04 (dd, $J = 3.1$ Hz, $J = 12.5$ Hz, 1H), 0.85 (s, 3H), 0.82 (s, 3H), 0.68 (d, $J = 6.7$ Hz, 3H).

¹³C NMR (125 MHz, DMSO-*d*₆): δ 191.7, 155.0, 147.0, 137.3, 120.6, 117.2, 106.14, 99.8, 47.1, 43.0, 41.2, 34.6, 33.17, 32.6, 30.5, 30.3, 29.1, 21.5, 20.7, 17.7, 15.0, 14.6.

¹H NMR (500 MHz, CDCl₃): δ 11.10 (br s, 1H), 10.13 (s, 1H), 6.96 (s, 1H), 5.04 (br s, 1H), 3.07 (d, $J = 16.3$ Hz, 1H), 2.88 (d, $J = 16.3$ Hz, 1H), 2.30 – 2.23 (m, 1H), 1.70 – 0.99 (m, 10 H), 1.17 (s, 3H), 1.01 (dd, $J = 3.3$ Hz, $J = 13.0$ Hz, 1H), 0.88 (s, 3H), 0.86 (s, 3H), 0.74 (d, $J = 6.4$ Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ , 192.87, 156.5, 146.10, 136.7, 119.3, 118.0, 105.6, 100.9, 48.1, 42.5, 35.1, 33.47, 33.3, 33.0, 31.2, 30.9, 21.6, 21.2, 18.1, 15.3, 14.9.

NMR data for corallidictyal D 2.6;

¹H NMR (500 MHz, DMSO-d₆): δ 10.53 (br s, 1H), 10.14 (s, 1H), 8.66 (br s, 1H), 6.90 (s, 1H), 3.09 (d, *J* = 16.3 Hz, 1H), 2.71 (d, *J* = 16.3 Hz, 1H), 1.81 – 1.74 (m, 1H), 1.61 – 1.07 (m, 10H), 1.60 – 1.55 (m, 1H), 0.92 (s, 3H), 0.88 (s, 3H), 0.82 (s, 3H), 0.66 (d, *J* = 6.7 Hz, 3H).

¹³C NMR (125 MHz, DMSO-d₆): δ 192.0, 155.7, 146.9, 137.4, 120.7, 116.8, 106.06, 98.2, 46.1, 42.0, 41.3, 36.4, 33.23, 32.9, 32.8, 30.70, 30.68, 21.7, 20.9, 17.8, 15.7, 15.5.

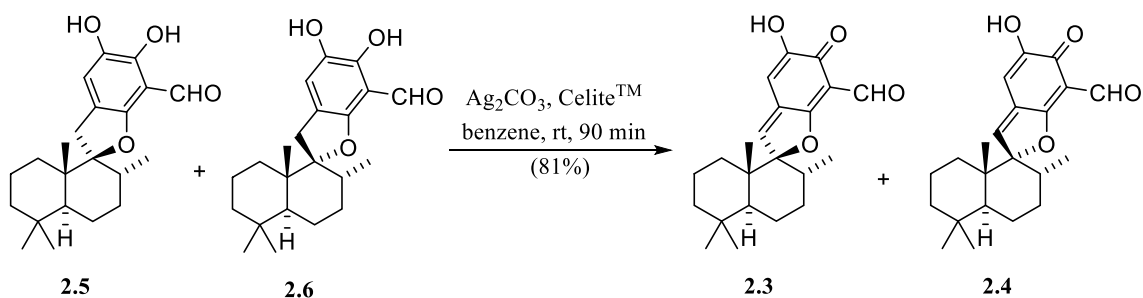
¹H NMR (500 MHz, CDCl₃): δ 11.09 (br s, 1H), 10.20 (s, 1H), 6.93 (s, 1H), 5.04 (br s, 1H), 3.15 (d, *J* = 16.0 Hz, 1H), 2.73 (d, *J* = 16.0 Hz, 1H), 1.82 – 1.75 (m, 1H), 1.70 – 0.99 (m, 10 H), 1.48 (dd, *J* = 4.0 Hz, *J* = 12.9 Hz, 1H), 0.96 (s, 3H), 0.91 (s, 3H), 0.85 (s, 3H), 0.74 (d, *J* = 6.4 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 192.91, 156.9, 146.10, 136.8, 119.4, 117.4, 105.7, 99.3, 46.8, 41.9, 41.7, 37.1, 33.50, 33.4, 31.3, 31.1, 29.8, 21.9, 21.4, 18.2, 16.2, 15.6.

IR (neat): 3340, 2922, 2852, 1732, 1651, 1575, 1466 cm⁻¹

HRMS (ESI): calculated for C₂₂H₃₀O₄ 357.2071 [M-H]⁻, found 357.2078

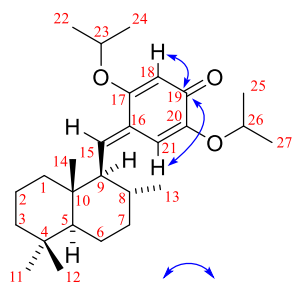
Corallidictyals A (2.3) and B (2.4) from C (2.5) and D (2.6)



To a solution of to a mixture of corallidictyals C **2.5** and D **2.6** in a 1 : 2 ratio respectively (10 mg, 0.0279 mmol) in benzene (3 mL) at room temperature, was added Ag_2CO_3 (30.8 mg, 0.112 mmol) and CeliteTM (50 mg). The resulting reaction mixture was stirred at room temperature for 90 min. The mixture was diluted with diethyl ether (50 ml), filtered through a pad of CeliteTM and concentrated *in vacuo* to give a brown solid, corallidictyals A **2.3** and B as a mixture of diastereoisomers in a 1:2 ratio respectively (8.1 mg, 81%).

$R_f = 0.18$ (petrol/EtOAc, 1:2)

2.10.3 Characterisation Tables of ^1H and ^{13}C data



2.140: *p*-QM HMBC

Table 2.8: *p*-QM 2.140 assignment

Assignment	^{13}C NMR, CDCl_3 125 MHz	^1H NMR, 500 MHz, CDCl_3	COSY	HMBC C \rightarrow H
C-1	42.2	1.42 – 1.31 (m, 1H), 1.20 – 1.02 (m, 1H)	-	-
C-2	18.7	1.54 – 1.45 (m, 1H), 1.42 – 1.31 (m, 1H)	-	-
C-3	41.4	1.42 – 1.31 (m, 1H), 0.90 – 0.87 (m, 1H)	-	-
C-4	33.5	-	-	-
C-5	54.9	0.94 (dd, $J = 12.6, 2.4$ Hz, 1H)	-	$\rightarrow 9, 14$
C-6	21.1	1.65 – 1.62 (m, 1H), 1.42 – 1.31 (m, 1H)	-	-
C-7	36.2	1.92 – 1.88 (m, 1H), 1.20 – 1.02 (m, 1H)	-	$\rightarrow 9, 13$
C-8	32.1	1.76 – 1.68 (m, 1H)	$\rightarrow 9, 13$	$\rightarrow 7, 9, 13, 15$
C-9	58.0	1.90 (t, $J = 11.0$ Hz, 1H)	$\rightarrow 8, 15$	$\rightarrow 13, 14, 15,$ 21
C-10	39.3	-	-	$\rightarrow 9, 14, 15$
C-11	33.6	0.88 (s, 3H)	-	-
C-12	22.1	0.84 (s, 3H)	-	-
C-13	21.5*	0.67 (d, $J = 6.5$ Hz, 3H)	$\rightarrow 8$	$\rightarrow 6, 7, 9$
C-14	15.1	0.99 (s, 3H)	$\rightarrow 9$	$\rightarrow 1, 5, 9$
C-15	144.7	6.74 (d, $J = 11.6$ Hz, 1H)	$\rightarrow 9, 21$	$\rightarrow 9, 21$
C-16	161.6	-	-	$\rightarrow 15, 18, 21$
C-17	129.4	-	-	$\rightarrow 9, 15, 18,$ 21
C-18	103.8	5.72 (s, 1H)	-	-
C-19	183.1	-	-	$\rightarrow 18, 21$
C-20	148.8	-	-	$\rightarrow 18, 21$
C-21	106.9	6.37 (s, 1H)	$\rightarrow 15$	$\rightarrow 15$
C-22	21.5*	1.36 (d, $J = 6.1$ Hz, 3H)	$\rightarrow 23$	-
C-23	70.0**	4.46 (hept, $J = 5.7$ Hz, 1H)	$\rightarrow 22, 24$	-
C-24	21.6*	1.36 (d, $J = 6.1$ Hz, 3H)	$\rightarrow 23$	-
C-25	21.5*	1.32 (d, $J = 6.00$ Hz, 3H)	$\rightarrow 26$	-
C-26	71.0**	4.46 (hept, $J = 5.7$ Hz, 1H)	$\rightarrow 25, 27$	-
C-27	21.7*	1.32 (d, $J = 6.00$ Hz, 3H)	$\rightarrow 26$	-

*, ** - These assignments are interchangeable.

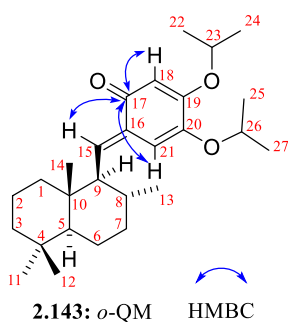
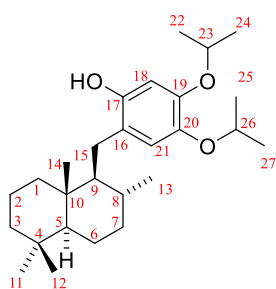


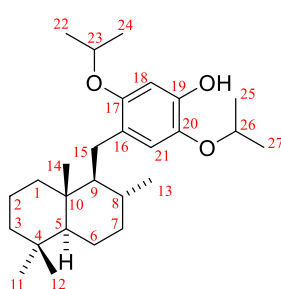
Table 2.9: *o*-QM 2.143 assignment

Assignment	¹³ C NMR, CDCl ₃ 150 MHz	¹ H NMR, 600 MHz, CDCl ₃	COSY	HMBC C → H
C-1	41.3	1.43 – 1.30 (m, 1H), 0.94 – 0.91 (m, 1H)	-	-
C-2	18.7	1.52 – 1.48 (m, 1H), 1.43 – 1.30 (m, 1H)	-	-
C-3	42.2	1.43 – 1.30 (m, 1H), 1.18 – 1.12 (m, 1H)	-	-
C-4	33.5	-	-	-
C-5	54.9	0.93 (dd, <i>J</i> = 12.5, 2.19 Hz, 1H)	-	→ 9, 14
C-6	21.6**	1.67 – 1.62 (m, 1H), 1.43 – 1.30 (m, 1H)	-	-
C-7	36.2	1.91 – 1.82 (m, 1H), 1.09 – 1.00 (m, 1H)	-	→ 9, 13
C-8	31.8	1.79 – 1.71 (m, 1H)	→ 13	→ 7, 9, 13, 15
C-9	58.1	1.83 (t, <i>J</i> = 11.0 Hz, 1H)	→ 13, 15	→ 13, 14, 15
C-10	39.3	-	-	→ 9, 14, 15
C-11	33.6	0.88 (s, 3H)	-	-
C-12	22.0	0.84 (s, 3H)	-	-
C-13	21.7**	0.66 (d, <i>J</i> = 6.2 Hz, 3H)	→ 8, 9	→ 6, 7, 9
C-14	15.2	1.03 (s, 3H)	→ 8, 9	→ 1, 5, 9
C-15	149.3	7.05 (d, <i>J</i> = 11.0 Hz, 1H)	→ 9, 21	→ 9, 18, 21
C-16	133.6	-	-	→ 9, 15, 18
C-17	184.3	-	-	→ 15, 18, 21
C-18	104.8	5.71 (s, 1H)	-	-
C-19	164.4	-	-	→ 18, 21, 23
C-20	146.0	-	-	→ 18, 21, 26
C-21	106.8	6.17 (s, 1H)	→ 15	→ 15, 18
C-22	21.7**	1.36 (d, <i>J</i> = 6.1 Hz, 3H)	→ 23	-
C-23	71.57*	4.48 (hept, <i>J</i> = 6.1 Hz, 1H)	→ 22, 24	-
C-24	21.6**	1.36 (d, <i>J</i> = 6.1 Hz, 3H)	→ 23	-
C-25	21.46**	1.34 (d, <i>J</i> = 6.1 Hz, 3H)	→ 26	-
C-26	71.56*	4.35 (hept, <i>J</i> = 6.1 Hz, 1H)	→ 25, 27	-
C-27	21.44**	1.34 (d, <i>J</i> = 6.1 Hz, 3H)	→ 26	-

* - These assignments are interchangeable.



2.145: *o*-phenol



2.141: *p*-phenol

Table 2.10: ^1H NMR comparison of *ortho*-phenol **2.145** and *para*-phenol **2.141**

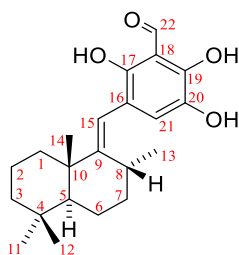
Assignment	2.145: <i>ortho</i> -phenol 500 MHz, CDCl_3	2.141: <i>para</i> -phenol 500 MHz, CDCl_3
H-1	1.82 – 1.79 (m, 1H), 0.94 – 0.90 (overlapped m, 1H)	1.82 – 1.80 (m, 1H), 0.89 – 0.86 (overlapped m, 1H)
H-2	1.58 – 1.52 (overlapped m, 1H), 1.43 – 1.37 (overlapped m, 1H)	1.59 – 1.52 (overlapped m, 1H), 1.39 – 1.36 (overlapped m, 1H)
H-3	1.40 – 1.33 (overlapped m, 1H), 1.22 – 1.13 (overlapped m, 1H)	1.39 – 1.36 (overlapped m, 1H), 1.18 – 1.05 (overlapped m, 1H)
H-5	0.94 – 0.90 (overlapped m, 1H)	0.89 – 0.86 (overlapped m, 1H)
H-6	1.58 – 1.52 (overlapped m, 1H), 1.33 – 1.25 (overlapped m, 1H)	1.59 – 1.52 (overlapped m, 1H), 1.30 – 1.26 (overlapped m, 1H)
H-7	1.73 – 1.70 (m, 1H), 1.04 – 0.94 (m, 1H)	1.74 – 1.71 (m, 1H), 1.03 – 0.95 (m, 1H)
H-8	1.52 – 1.43 (m, 1H)	1.51 – 1.43 (m, 1H)
H-9	1.22 – 1.13 (overlapped m, 1H)	1.18 – 1.05 (overlapped m, 1H)
H-11	0.87 (s, 3H)	0.87 (s, 3H)
H-12	0.83 (s, 3H)	0.84 (s, 3H)
H-13	0.72 (d, $J = 6.5$ Hz, 3H)	0.73 (d, $J = 6.4$ Hz, 3H)
H-14	0.90 (s, 3H)	0.90 (s, 3H)
H-15a, H-15b	2.58 (dd, $J = 15.8$ Hz, $J = 2.2$ Hz, 1H), 2.25 (dd, $J = 15.8$ Hz, $J = 6.5$ Hz, 1H)	2.57 (dd, $J = 15.8$ Hz, $J = 3.0$ Hz, 1H), 2.39 (dd, $J = 15.8$ Hz, $J = 6.2$ Hz, 1H)
H-17(-OH)	4.51 (br s, 1H)	-
H-18	6.35 (s, 1H)	6.48 (s, 1H)
H-19(-OH)	-	5.50 (br s, 1H)
H-21	6.77 (s, 1H)	6.75 (s, 1H)
H-23	4.30 (hept, $J = 6.1$ Hz, 1H)	4.37 (hept, $J = 6.1$ Hz, 1H)
H-26	4.42 (hept, $J = 6.1$ Hz, 1H)	4.42 (hept, $J = 6.1$ Hz, 1H)
H-22, H-24	1.28 (d, $J = 6.1$ Hz, 6H)	1.32 (d, $J = 6.1$ Hz, 3H), 1.31 (d, $J = 6.1$ Hz, 1H)
H-25, H-27	1.30 (d, $J = 6.1$ Hz, 6H)	1.33 (d, $J = 6.1$ Hz, 6H)

Table 2.11: ^{13}C NMR comparison of *ortho*-phenol **2.145** and *para*-phenol **2.141**

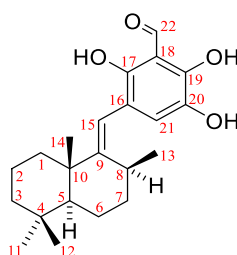
Assignment	2.145: <i>ortho</i>-phenol 125 MHz, CDCl_3	2.141: <i>para</i>-phenol 125 MHz, CDCl_3
C-1	39.5	39.6
C-2	18.9	18.9
C-3	42.1	42.3
C-4	33.4	33.4
C-5	55.3	55.5
C-6	21.93*	21.98*
C-7	37.2	37.4
C-8	35.2	35.0
C-9	57.4	58.4
C-10	38.6	38.6
C-11	33.6	33.6
C-12	21.94*	21.99*
C-13	21.4	21.5
C-14	14.3	14.4
C-15	27.3	27.0
C-16	122.5***	125.3
C-17	122.3	149.7
C-18	105.4	101.5
C-19	142.1	144.8
C-20	147.8	137.7
C-21	122.5***	116.8
C-23	73.6	70.7
C-26	71.7	73.0
C-22, C-24	22.32 (overlapped)	22.30**, 22.28**
C-25, C-27	22.25**, 22.21**	22.34**, 22.33**

*, ** - These chemical shift assignments are interchangeable. *** peaks overlap

Siphonodictyal B carbon numbering in accordance to Köck^[96]:



2.91: Siphonodictyal B
(our proposed reassignment)



2.1: Siphonodictyal B
(Faulkner's assignment)

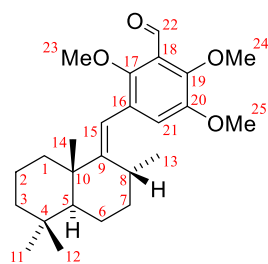
Table 2.12: Comparison of the ¹H NMR spectrum of natural siphonodictyal B isolated by Köck^[96] and our synthetic sample.

Assignment	Köck, DMSO- <i>d</i> ₆	This work, 2.91 DMSO- <i>d</i> ₆ , 500 MHz	This work, 2.1 DMSO- <i>d</i> ₆ , 500 MHz
H-1a, H-1b	1.78, 1.40	1.79-1.27 (overlapped m)	1.73 – 1.39(overlapped m)
H-2a, H-2b	1.63, 1.49	1.79-1.27 (overlapped m)	1.73 – 1.39(overlapped m)
H-3a, H-3b	1.38, 1.16	1.79-1.27 (overlapped m)	1.73 – 1.39(overlapped m)
H-5	1.30	1.79-1.27 (overlapped m)	1.73 – 1.39(overlapped m)
H-6a, H-6b	1.71, 1.49	1.79-1.27 (overlapped m)	1.73 – 1.39 (overlapped m)
H-7a, H-7b	1.72, 1.34	1.79-1.27 (overlapped m)	1.73 – 1.39 (overlapped m)
H-8	2.62	2.62 (m)	3.35 (quintet, <i>J</i> = 6.9 Hz)
Me-11	0.89	0.88 (s)	0.86 (s)
Me-12	0.86	0.85 (s)	0.86 (s)
Me-13	0.89	0.87 (d, <i>J</i> = 7.0 Hz)	1.22 (d, <i>J</i> = 7.4 Hz)
Me-14	1.12	1.12 (s)	1.15 (s)
H-15	6.04	6.03 (s)	6.01 (s)
H-17	6.85	6.84 (s)	6.91 (s)
22-CHO	10.26	10.25 (s)	10.26 (s)
18-OH	10.03	10.03 (br s)	10.07 (br s)
19-OH	9.00	9.02 (br s)	9.11 (br s)
21-OH	10.90	10.91 (br s)	11.01 (br s)

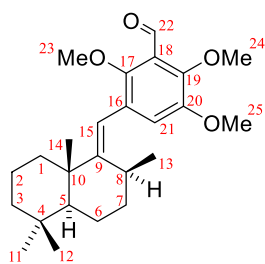
Table 2.13: Comparison of the ^{13}C NMR spectra of natural siphonodictyal B isolated by Köck^[96] and our synthetic sample.

Assignment	Köck CDCl_3	This work 2.91 CDCl_3 125 MHz	This work 2.1 CDCl_3 125 MHz	Köck $\text{DMSO-}d_6$	This work 2.91 $\text{DMSO-}d_6$ 125 MHz	This work 2.1 $\text{DMSO-}d_6$ 125 MHz
C-1	39.2	39.2	38.8	39.1	39.1	38.1
C-2	19.4	19.4	17.8	19.0	19.0	17.4
C-3	42.2	42.2	42.0	41.9	41.9	41.7
C-4	34.1	34.1	34.0	33.0	33.0	33.2*
C-5	52.4	52.4	55.1	49.0	49.1	54.2
C-6	21.7	21.7	18.8	19.4	19.4	18.4
C-7	34.8	34.7	33.4*	31.2	31.2	30.5
C-8	33.9	33.9	34.2*	31.7	31.8	33.7*
C-9	165.8	165.8	165.9	157.0	157.0	155.5
C-10	41.9	41.9	41.3	40.3	40.4	40.5
C-11	33.2	33.2	31.7*	33.6	33.6	33.6*
C-12	21.2	21.2	22.5**	21.4	21.5	21.6**
C-13	21.1	21.1	21.8**	21.9	21.9	22.4**
C-14	22.5	22.6	22.7**	22.9	22.9	22.7**
C-15	109.3	109.4	110.7	113.4	113.4	113.3
C-16	116.6	116.6	115.6	116.6	116.6	115.6
C-17	123.6	123.7	123.5	126.2	126.2	125.5
C-18	136.9	136.9	137.1	136.1	136.1	136.3
C-19	147.5	147.5	147.6	147.8	147.8	148.0
C-20	109.0	109.0	109.3	110.2	110.2	110.4
C-21	148.4	148.5	148.7	151.2	151.3	151.8
C-22	194.5	194.5	194.5	194.8	194.8	194.8

*, ** - These chemical shift assignments are interchangeable.



2.151: tris-methoxy-siphonodictyal B



2.12: tris-methoxy-siphonodictyal B
(Faulkner's assignment)

Table 2.14: Comparison of the ^1H NMR spectra of our synthetic methylated siphonodictyal B epimers (**2.91** & **2.1**) with Faulkner's^[97] artificially methylated natural sample.

Assignment	Faulkner methoxy- siphonodictyal B CDCl_3	This work 2.151: methoxy- siphonodictyal B CDCl_3 , 500 MHz	This work 2.12: methoxy- siphonodictyal B CDCl_3 , 500 MHz
H-1a, H-1b	not reported	1.86 – 1.24 (m, 2H)	1.83 – 1.42 (m, 2H)
H-2a, H-2b	not reported	1.86 – 1.24 (m, 2H)	1.83 – 1.42 (m, 2H)
H-3a, H-3b	not reported	1.86 – 1.24 (m, 2H)	1.27 – 1.25 (m, 1H), 1.83 – 1.42 (m, 1H)
H-5	not reported	1.86 – 1.24 (m, 1H)	0.99 (d, $J = 11.0$ Hz, 1H)
H-6a, H-6b	not reported	1.86 – 1.24 (m, 2H)	1.83 – 1.42 (m, 2H)
H-7a, H-7b	not reported	1.86 – 1.24 (m, 2H)	1.83 – 1.42 (m, 2H)
H-8	2.65 (m, 1 H)	2.66 (m, 1H)	2.96 (quintet, $J = 6.7$ Hz, 1H)
Me-11	0.91 (s, 3 H)	0.91 (s, 3H)	0.92 (s, 3H)
Me-12	0.89 (s, 3 H)	0.89 (s, 3H)	0.90 (s, 3H)
Me-13	0.90 (d, 3 H, $J = 7$ Hz)	0.90 (d, $J = 6.5$ Hz, 3H)	1.28 (d, $J = 7.5$ Hz, 3H)
Me-14	1.19 (s, 3 H)	1.19 (s, 3H)	1.23 (s, 3H)
H-15	6.21 (s, 1 H)	6.21 (s, 1H)	6.21 (s, 1H)
H-17	6.91 (s, 1 H)	6.91 (s, 1H)	6.95 (s, 1H)
22-CHO	10.40 (s, 1 H)	10.40 (s, 1H)	10.43 (s, 1H)
23-OMe	3.91 (s, 3 H)	3.91 (s, 3H)	3.93 (s, 3H)
24-OMe	3.85 (s, 3 H)	3.85 (s, 3H)	3.86 (s, 3H)
25-OMe	3.72 (s, 3 H)	3.72 (s, 3H)	3.74 (s, 3H)

Table 2.15: Comparison of the ^{13}C NMR spectra of our synthetic methylated siphonodictyal B epimers, **2.91** & **2.1**, with Faulkner's^[97] artificially methylated natural sample.

Assignment	Faulkner methoxy– siphonodictyal B Benzene- <i>d</i> ₆ , 125 MHz	This work 2.151: methoxy- siphonodictyal B Benzene- <i>d</i> ₆ , 125 MHz	This work 2.12: methoxy- siphonodictyal B Benzene- <i>d</i> ₆ , 125 MHz
C-1	40.0	40.0	39.1
C-2	20.5**	20.6**	18.2
C-3	42.7	42.7	42.5
C-4	34.1	34.1	34.2
C-5	42.4	61.8	62.0
C-6	19.9**	19.9**	19.3
C-7	33.1	33.2	33.6
C-8	32.7	32.9	31.7
C-9	158.3 (s)	158.4	157.6
C-10	41.3	41.3	41.3
C-11	33.4	33.5	34.5
C-12	22.9	22.9	22.1*
C-13	21.9*	21.9*	22.7*
C-14	22.4*	22.4*	22.9*
C-15	114.9 (d)	114.9	115.6
C-16	130.4 (s)	130.5	129.5
C-17	120.5 (d)	120.4	119.8
C-18	148.9 (s)	148.9	149.2
C-19	150.3 (s)	150.4	150.3
C-20	125.0 (s)	125.1	125.4
C-21	152.3 (s)	152.3	153.1
C-22	189.1 (s)	189.3	189.2
C-23	61.6 (q)	61.7	61.7
C-24	56.1 (q)	56.1	56.0
C-25	50.5 (q)	50.7	55.3

*, ** - These chemical shift assignments are interchangeable.

Ring expanded Ketones 2.153 and 2.154

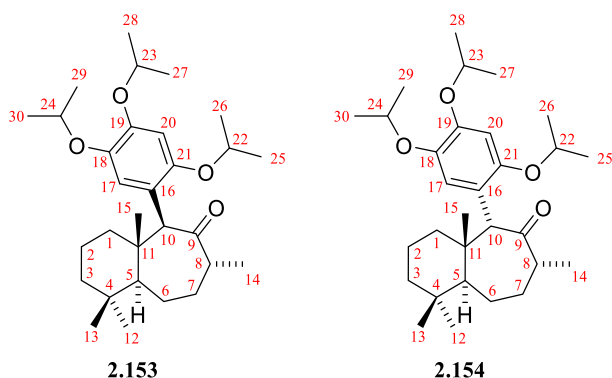


Table 2.16: ^1H NMR comparison of ring expanded ketones

Assignment	2.153 500 MHz, CDCl_3	2.154 500 MHz, CDCl_3
H-1	0.94 – 0.85 (overlapped m, 2H)	1.55 – 1.42 (overlapped m, 1H), 1.19 – 1.03 (overlapped m, 1H)
H-2	1.53 – 1.39 (overlapped m, 1H), 1.23 – 1.15 (overlapped m, 1H)	1.55 – 1.42 (overlapped m, 1H), 1.34 – 1.26 (overlapped m, 1H)
H-3	1.37 – 1.26 (overlapped m, 1H), 1.23 – 1.15 (overlapped m, 1H)	1.34 – 1.26 (overlapped m, 1H), 1.19 – 1.03 (overlapped m, 1H)
H-5	1.37 – 1.26 (overlapped m, 1H)	0.88 – 0.84 (overlapped m, 1H)
H-6	1.98 – 1.94 (m, 1H), 1.23 – 1.15 (overlapped m, 1H)	1.79 – 1.69 (overlapped m, 1H), 1.79 – 1.69 (overlapped m, 1H)
H-7	2.08 – 2.02 (m, 1H), 1.53 – 1.39 (overlapped m, 1H)	2.23 – 2.19 (overlapped m, 1H), 1.19 – 1.03 (overlapped m, 1H).
H-8	2.43 – 2.39 (m, 1H)	2.70 – 2.63 (m, 1H)
H-10	4.70 (s, 1H)	4.75 (s, 1H)
H-12	0.79 (s, 3H)	0.84 (s, 3H)
H-13	0.96 (s, 3H)	0.86 (s, 3H)
H-14	1.03 (d, $J = 7.1$ Hz, 3H)	0.95 (d, $J = 6.2$ Hz, 3H)
H-15	0.99 (s, 3H)	0.86 (s, 3H)
H-17	7.42 (s, 1H)	7.59 (s, 1H)
H-19	6.43 (s, 1H)	6.44 (s, 1H)
H-22	4.37 (sep, $J = 5.6$ Hz, 1H)	4.37 (sep, $J = 6.0$ Hz, 1H),
H-23	4.45 (sep, $J = 6.1$ Hz, 1H)	4.45 (sep, $J = 6.0$ Hz, 1H)
H-24	4.37 (sep, $J = 5.6$ Hz, 1H)	4.37 (sep, $J = 6.0$ Hz, 1H),
H-25, H-26	*1.37 (d, $J = 6.0$ Hz, 3H), *1.30 (d, $J = 6.6$ Hz, 3H)	1.35 – 1.29 (overlapped m, 6H)
H-27, H-28	*1.33 – 1.26 (m, 6H)	1.35 – 1.29 (overlapped m, 6H)
H-29, H-30	*1.33 – 1.26 (m, 3H), *1.30 (d, $J = 6.6$ Hz, 3H)	1.35 – 1.29 (overlapped m, 6H)

* - These chemical shift assignments are interchangeable.

Table 2.17: ^{13}C NMR comparison of ring expanded ketones

Assignment	2.153 125 MHz, CDCl_3	2.154 125 MHz, CDCl_3
C-1	38.2	33.6
C-2	19.1	19.0
C-3	42.2	41.3
C-4	29.7	35.2
C-5	62.6	55.9
C-6	24.6	22.4
C-7	34.2	37.1
C-8	49.8	49.4
C-9	216.0	215.3
C-10	53.0	54.1
C-11	41.3	41.2
C-12	21.8	21.3
C-13	35.2	32.9
C-14	19.5	16.1
C-15	17.5	20.1
C-16	121.0	117.6
C-17	122.7	123.3
C-18	142.2	142.0
C-19	147.7	147.9
C-20	105.2	105.0
C-21	150.1	150.8
C-22	72.7	72.6
C-23	70.7	70.7
C-24	72.3	72.5
C-25	22.6**	22.7*
C-26	22.5**	22.5*
C-27	22.5**	22.5*
C-28	22.4**	22.4*
C-29	22.3**	22.3*
C-30	22.3**	22.2*

*, ** - These chemical shift assignments are interchangeable.

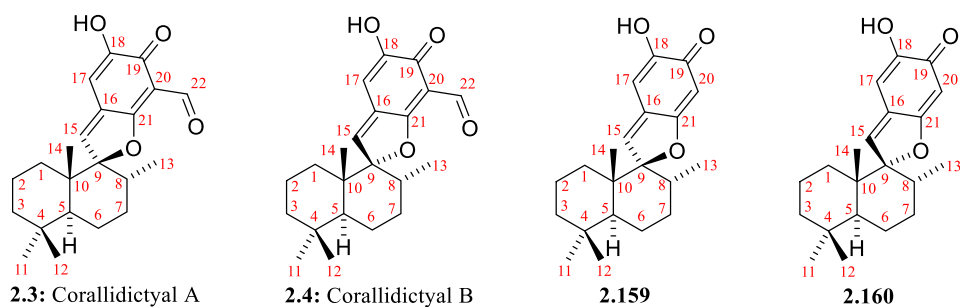


Table 2.18: ^{13}C NMR comparison of corallidictyals A (**2.3**) and B (**2.4**) to synthesised 20-nor-formyl corallidictyal analogues A (**2.159**) and B (**2.160**).

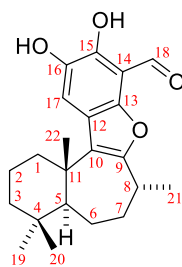
Assignment	This work 2.3: A , CDCl_3 125 MHz	This work 2.4: B , CDCl_3 125 MHz	This work 2.159: A analogue CDCl_3 , 125 MHz	This work 2.160: B analogue CDCl_3 , 125 MHz
1	33.64*	30.32	29.7	32.7
2	18.23	18.18	18.3	18.2
3	41.68	41.19	41.8	41.4
4	33.83*	33.75*	33.70	33.68
5	52.33	47.31	51.9	47.3
6	21.49	21.47	21.54	21.46
7	33.50*	31.96	33.48	32.1
8	35.53	34.20	35.51	34.0
9	113.11	111.15	108.8	107.1
10	44.84	43.96	44.2	43.5
11	33.48*	33.31	33.35	33.29
12	21.87	21.89	21.86	21.90
13	15.53	15.62	15.5	15.6
14	16.44	19.36	16.2	19.0
15	147.80	149.73	143.3	145.5
16	131.68	130.81	131.5	131.3
17	98.40	98.16	96.7	96.6
18	150.24**	150.29**	150.7	150.7
19	180.26	179.97	181.7	181.7
20	107.67***	107.71***	95.5	95.7
21	175.78	177.01	175.4	175.4
22	186.58	186.15	-	-

*, **, *** - These chemical shift assignments are interchangeable.

Table 2.19: ^1H NMR comparison of our synthesised samples of corallidictyals A (**2.3**) and B (**2.4**) to the afforded C20 nor-formyl corallidictyal analogues A (**2.159**) and B (**2.160**).

Assignment	This work 2.3: A , CDCl_3 500 MHz	This work 2.4: B , CDCl_3 500 MHz	This work 2.159: A analogue CDCl_3 , 500 MHz	This work 2.160: B analogue CDCl_3 , 500 MHz
H-1	2.04 – 2.00 (overlapped m, 1H), 0.84 – 0.79 (overlapped m, 1H)	1.48 – 1.41 (overlapped m, 1H), 1.31 – 1.22 (overlapped m, 1H)	1.29 – 1.22 (overlapped m, 2H)	1.10 – 1.04 (overlapped m, 1H), 0.98 – 0.93 (overlapped m, 1H).
H-2	1.49 – 1.40 (overlapped m, 1H), 1.32 – 1.22 (overlapped m, 1H)	1.55 – 1.47 (overlapped m, 1H), 1.38 – 1.33 (overlapped m, 1H)	1.53 – 1.42 (overlapped m, 1H), 1.42 – 1.29 (overlapped m, 1H).	1.53 – 1.42 (overlapped m, 1H), 1.42 – 1.29 (overlapped m, 1H).
H-3	1.48 – 1.42 (overlapped m, 1H), 1.18 – 1.04 (overlapped m, 2H)	1.38 – 1.33 (overlapped m, 1H), 1.19 – 1.11 (overlapped m, 1H)	1.43 – 1.29 (overlapped m, 2H).	1.43 – 1.29 (overlapped m, 2H).
H-5	1.23 (d, $J = 3.6$ Hz, 1H)	1.74 (dd, $J = 2.3,$ 10.5 Hz, 1H)	1.27 – 1.22 (m, 1H)	1.64 – 1.62 (m, 1H)
H-6	1.82 – 1.77 (overlapped m, 1H), 1.65 – 1.48 (overlapped m, 1H)	1.84 – 1.77 (overlapped m, 1H), 1.54 – 1.46 (overlapped m, 1H)	1.78 – 1.70 (overlapped m, 1H), 1.58 – 1.50 (overlapped m, 1H)	1.78 – 1.70 (overlapped m, 1H), 1.50 – 1.34 (overlapped m, 1H)
H-7	2.04 – 2.00 (overlapped m, 1H), 1.30 – 1.20 (overlapped m, 1H)	1.84 – 1.77 (overlapped m, 1H), 1.68 – 1.55 (overlapped m, 1H)	1.94 – 1.91 (m, 1H), 1.22 – 1.19 (overlapped m, 1H)	1.78 – 1.70 (overlapped m, 1H), 1.50 – 1.34 (overlapped m, 1H)
H-8	2.65 – 2.60 (m, 1H)	2.45 – 2.41 (m, 1H)	2.49 – 2.41 (m, 1H)	2.34 – 2.27 (m, 1H)
H-11	0.93 (s, 3H)	0.95 (s, 3H)	0.92 (s, 3H)	0.93 (s, 3H)
H-12	0.90 (s, 3H)	0.87 (s, 3H)	0.88 (s, 3H)	0.86 (s, 3H)
H-13	0.54 (d, $J = 6.6$ Hz, 3H)	0.55 (d, $J = 6.5$ Hz, 3H)	0.55 (d, $J = 6.5$ Hz, 3H)	0.56 (d, $J = 6.6$ Hz, 3H)
H-14	1.35 (s, 3H)	1.27 (s, 3H)	1.25 (s, 3H)	1.21 (s, 3H)
H-15	7.50 (s, 1H)	7.24 (s, 1H)	7.21 (s, 1H)	6.96 (s, 1H)
H-17	6.48 (s, 1H)	6.43 (s, 1H)	6.36 (s, 1H)	6.31 (s, 1H)
18- OH	7.41 (br s, 1H)	7.41 (br s, 1H)	7.41 (br s, 1H)	7.41 (br s, 1H)
H-20	-	-	5.91 (s, 1H)	5.98 (s, 1H)
22-CHO	10.26 (s, 1H)	10.30 (s, 1H)	-	-

Liphagal (**2.2**) carbon numbering (according to Andersen^[99])



2.2: Liphagal

Table 2.20: Comparison of the ¹H NMR spectra of synthetic liphagal (**2.2**) prepared by Andersen,^[99] Stoltz^[101] and this work.

Assignment	Anderson CDCl ₃ , 400 MHz	Stoltz CDCl ₃ , 600 MHz	This work CDCl ₃ , 600 MHz
H-1a, H-1b	2.54 (m), 1.8–1.5 (overlapped m)	2.54 (m), 1.65–1.45 (overlapped m)	2.54 (m), 1.64–1.45 (overlapped m)
H-2a, H-2b	1.8–1.5 (overlapped m)	1.71 (m), 1.65–1.45 (overlapped m)	1.71 (m), 1.64–1.45 (overlapped m)
H-3a, H-3b	1.8–1.5 (overlapped m), 1.25 (m)	1.65–1.45 (overlapped m), 1.25 (ddd, <i>J</i> = 13.3, 13.3, 3.1 Hz)	1.64–1.45 (overlapped m), 1.25 (ddd, <i>J</i> = 13.0, 13.0, 3.0 Hz)
H-5	1.8–1.5 (overlapped m)	1.65–1.45 (overlapped m)	1.64–1.45 (overlapped m)
H-6a, H-6b	1.86 (m), 1.8–1.5 (overlapped m)	1.87 (m), 1.65–1.45 (overlapped m)	1.87 (m), 1.64–1.45 (overlapped m)
H-7a, H-7b	2.17 (m), 1.8–1.5 (overlapped m)	2.18 (dddd, <i>J</i> = 13.1, 6.4, 6.4, 3.5 Hz), 1.65–1.45 (overlapped m)	2.18 (m), 1.64–1.45 (overlapped m)
H-8	3.20 (m)	3.22 (sext, <i>J</i> = 7.0 Hz)	3.21 (sext, <i>J</i> = 7.0 Hz)
15-OH	11.24 (s)	11.24 (s)	11.24 (s)
16-OH	5.32 (br s)	5.30 (s)	5.32 (s)
H-17	7.55 (s)	7.55 (s)	7.55 (s)
18-CHO	10.45 (s)	10.45 (s)	10.44 (s)
Me-19	0.98 (s)	0.98 (s)	0.98 (s)
Me-20	0.95 (s)	0.95 (s)	0.95 (s)
Me-21	1.43 (d, <i>J</i> = 7.0 Hz)	1.43 (d, <i>J</i> = 7.0 Hz)	1.43 (d, <i>J</i> = 7.0 Hz)
Me-22	1.34 (s)	1.35 (s)	1.35 (s)

Note; the ¹H and ¹³C NMR spectra of natural liphagal (**2.2**) were recorded in DMSO-d₆. However, Andersen and co-workers correlated the NMR spectra of their synthetic sample (recorded in CDCl₃ and DMSO-d₆) with that of natural liphagal sample.

Table 2.21: Comparison of the ^{13}C NMR spectra of synthetic liphagal (**2.2**) prepared by Andersen,^[99] Stoltz^[101] and this work.

Assignment	Anderson CDCl ₃ , 100 MHz	Stoltz CDCl ₃ , 150 MHz	This work CDCl ₃ , 600 MHz
C-1	40.4	40.5	40.5
C-2	18.9	19.0	19.0
C-3	42.1	42.1	42.1
C-4	35.0	35.1	35.0
C-5	53.9	54.0	53.9
C-6	24.3	24.4	24.4
C-7	35.3	35.4	35.4
C-8	33.8	33.9	33.9
C-9	156.7	156.7	156.7
C-10	125.7	125.7	125.7
C-11	39.6	39.7	39.7
C-12	120.5	120.5	120.5
C-13	148.1*	148.2*	148.2*
C-14	139.6	139.6	139.6
C-15	145.5*	145.5*	145.5*
C-16	106.4	106.5	106.5
C-17	116.1	116.2	116.2
C-18	192.6	192.7	192.6
C-19	33.5**	33.5**	33.5**
C-20	22.1**	22.2**	22.2**
C-21	21.8	21.9	21.9
C-22	20.4	20.5	20.4

*,** - These chemical shift assignments are interchangeable due to overlap

Corallidictyal A (**2.3**) and B (**2.4**) carbon numbering (according to Köck^[96]):

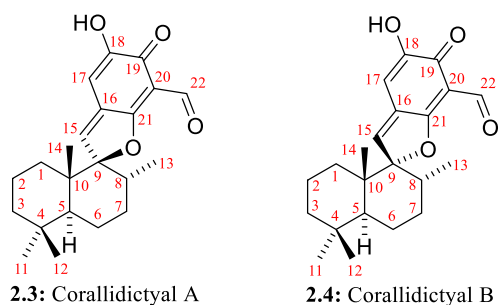


Table 2.22: Comparison of the ¹H NMR spectra of corallidictyals A (**2.3**) and B (**2.4**) Westley^[100] (natural) and this work.

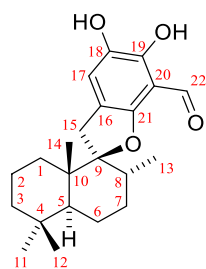
Assignment	Westly 2.3: corallidictyal A CDCl ₃ , 400 MHz	This work 2.3: corallidictyal A CDCl ₃ , 500 MHz	Westly 2.4: corallidictyal B CDCl ₃ , 400 MHz	This work 2.4: corallidictyal B CDCl ₃ , 500 MHz
H-1a, H-1b	2.00-0.80 (m)	2.05 – 1.99 (overlapped m), 1.67 – 0.77 (overlapped m)	2.00 – 0.80 (m)	1.67 – 0.77 (overlapped m)
H-2a, H-2b	2.00-0.80 (m)	1.67 – 0.77 (overlapped m)	2.00-0.80 (m)	1.67 – 0.77 (overlapped m)
H-3a, H-3b	2.00-0.80 (m)	1.67 – 0.77 (overlapped m)	2.00-0.80 (m)	1.67 – 0.77 (overlapped m)
H-5	1.24 (dd, <i>J</i> = 12.0, 2.9 Hz)	1.67 – 0.77 (overlapped m)	1.75 (dd, <i>J</i> = 12.2, 2.7 Hz)	1.83 – 1.73 (overlapped m)
H-6a, H-6b	2.00-0.80 (m)	1.83 – 1.73 (overlapped m)	2.00-0.80 (m)	1.83 – 1.73 (overlapped m), 1.67 – 0.77 (overlapped m)
H-7a, H-7b	2.00-0.80 (m)	2.05 – 1.99 (overlapped m), 1.67 – 0.77 (overlapped m)	2.00-0.80 (m)	1.83 – 1.73 (overlapped m), 1.67 – 0.77 (overlapped m)
H-8	2.61 (m)	2.63 (m, 1H)	2.42 (m)	2.43 (m)
Me-11	0.94 (s)	0.93 (s, 3H)	0.95 (s)	0.95 (s)
Me-12	0.91 (s)	0.91 (s, 3H)	0.88 (s)	0.87 (s)
Me-13	0.55 (d, <i>J</i> = 6.6)	0.54 (d, <i>J</i> = 6.6 Hz, 3H)	0.56 (d, <i>J</i> = 6.6)	0.54 (d, <i>J</i> = 6.5 Hz)
Me-14	1.35 (s)	1.35 (s, 3H)	1.28 (s)	1.27 (s)
H-15	7.50 (s)	7.50 (s, 1H)	7.25 (s)	7.25 (s)
H-17	6.48 (s)	6.48 (s, 1H)	6.43 (s)	6.43 (s)
OH-18	7.40 (br s)	7.42 (br s, 1H)	7.40 (br s)	7.42 (br s)
22-CHO	10.27 (s)	10.26 (s, 1H)	10.31 (s)	10.30 (s)

Table 2.23: Comparison of the ^{13}C NMR spectra of corallidictyals A (**2.3**) and B (**2.4**) Westley^[100] (natural) and this work.

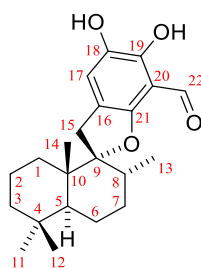
Assignment	Westly 2.3: corallidictyal A CDCl ₃ , 100 MHz	This work 2.3: corallidictyal A CDCl ₃ , 125 MHz	Westly 2.4: corallidictyal B CDCl ₃ , 100 MHz	This work 2.4: corallidictyal B CDCl ₃ , 125 MHz
C-1	41.7-18.2	33.6*	41.2-18.2	32.9
C-2	41.7-18.2	18.23	41.2-18.2	18.18
C-3	41.7-18.2	41.7	41.2-18.2	41.2
C-4	41.7-18.2	33.83*	41.2-18.2	33.75
C-5	52.3	52.3	47.3	47.3
C-6	41.7-18.2	21.48	41.2-18.2	21.45
C-7	41.7-18.2	33.50*	41.2-18.2	32.0
C-8	35.5	35.5	34.2	34.2
C-9	113.1	113.1	111.1	111.2
C-10	44.8	44.8	44.0	44.0
C-11	33.5	33.47*	33.3	33.31
C-12	21.8	21.86	21.9	21.89
C-13	15.5	15.5	15.6	15.6
C-14	16.4	16.4	19.3	19.4
C-15	147.8	147.9	149.7	149.8
C-16	131.7	131.7	130.8	130.8
C-17	98.4	98.5	98.1	98.2
C-18	150.3	150.27	150.3	150.31
C-19	180.3	180.3	180.0	180.0
C-20	107.7	107.68	107.7	107.71
C-21	175.7	175.8	177.0	177.1
C-22	186.6	186.6	186.1	186.2

* - These chemical shift assignments are interchangeable due to overlap

Corallidictyal C (**2.5**) and D (**2.6**) carbon numbering (according to Köck^[96]):



2.5: Corallidictyal C



2.6: Corallidictyal D

Table 2.24: Comparison of the ¹H NMR spectra of corallidictyals C (**2.5**) and D (**2.6**) Köck (natural),^[96] Alvarez-Manzaneda^[109] (synthetic) and this work.

Assignment	Köck 2.5: C DMSO- <i>d</i> ₆	This work 2.5: C DMSO- <i>d</i> ₆ 500 MHz	Köck 2.6: D DMSO- <i>d</i> ₆	This work 2.6: D DMSO- <i>d</i> ₆ 500 MHz	Alvarez- Manzaneda a 2.6: D DMSO- <i>d</i> ₆ 500 MHz
H-1	1.44, 1.16	1.63 – 1.06 (overlapped m)	1.52, 1.30	1.63 – 1.23 (overlapped m)	1.60 – 1.05 (m)
H-2	1.52, 1.34	1.63 – 1.06 (overlapped m)	1.52, 1.34*	1.63 – 1.06 (overlapped m)	1.60 – 1.05 (m)
H-3	1.32, 1.11	1.63 – 1.06 (overlapped m)	1.32, 1.11	1.63 – 1.06 (overlapped m)	1.60–1.05 (m)
H-5	1.05	1.04 (dd, <i>J</i> = 3.1 Hz, <i>J</i> = 12.5 Hz)	1.59	1.63 – 1.23 (overlapped m)	1.60 – 1.05 (m)
H-6	1.48, 1.37	1.63 – 1.06 (overlapped m)	1.57, 1.37	1.63 – 1.06 (overlapped m)	1.60 – 1.05 (m)
H-7	1.63, 1.05	1.63 – 1.06 (overlapped m)	1.52, 1.30*	1.63 – 1.23 (overlapped m)	1.60 – 1.05 (m)
H-8	2.18	2.18 (m)	1.77	1.77 (m)	1.77 (m)
Me-11	0.86	0.85 (s)	0.88	0.88 (s)	0.88 (s)
Me-12	0.83	0.82 (s)	0.82	0.82 (s)	0.82 (s)
Me-13	0.69	0.68 (d, <i>J</i> = 6.7 Hz)	0.67	0.66 (d, <i>J</i> = 6.7 Hz)	0.67 (d, <i>J</i> = 6.5 Hz)
Me-14	1.13	1.12 (s)	0.93	0.92 (s)	0.93 (s)
H-15a, H-15b	3.06, 2.85	3.05 (d, <i>J</i> = 16.6 Hz) 2.85 (d, <i>J</i> = 16.6 Hz)	3.10, 2.71	3.09 (d, <i>J</i> = 16.3 Hz), 2.71 (d, <i>J</i> = 16.3 Hz)	3.10 (d, <i>J</i> = 16.2 Hz), 2.71 (d, <i>J</i> = 16.2 Hz)
H-17	6.94	6.94 (s)	6.91	6.90 (s)	6.90 (s)
OH-18	8.66	8.66 (br s)	8.65	8.66 (br s)	-
OH-19	10.53	10.53 (br s)	10.55	10.53 (br s)	-
22-CHO	10.09	10.08 (s)	10.15	10.14 (s)	10.14 (s)

* - These chemical shift assignments are interchangeable due to overlap

Table 2.25: Comparison of the ^{13}C NMR spectra of corallidictyals C (**2.5**) and D (**2.6**) Köck (natural),^[96] Alvarez-Manzaneda^[109] (synthetic) and this work.

Assignment	Köck 2.5:C DMSO- d_6	This work 2.5: C DMSO- d_6 125 MHz	Köck 2.6:D DMSO- d_6	This work 2.6: D DMSO- d_6 125 MHz	Alvarez- Manzaneda 2.6: D , DMSO- d_6 125 MHz
C-1	30.5	30.5	30.7	30.70*	30.7
C-2	17.7	17.7	17.7	17.8	17.8
C-3	41.2	41.2	41.2	41.3	41.3
C-4	32.6	32.6	32.9	32.9	32.9
C-5	47.1	47.1	46.1	46.1	46.1
C-6	20.6	20.7	20.9	20.9	20.9
C-7	30.2	30.3	30.7	30.68*	30.7
C-8	34.5	34.6	36.4	36.4	36.4
C-9	99.8	99.8	98.2	98.2	98.2
C-10	43.0	43.0	41.9	42.0	42.0
C-11	33.1	33.17	33.2	33.23	33.2
C-12	21.4	21.5	21.7	21.7	21.7
C-13	14.6	14.6	15.4	15.5	15.5
C-14	14.9	15.0	15.7	15.7	15.7
C-15	29.1	29.1	32.8	32.8	32.8
C-16	117.1	117.2	116.8	116.8	116.8
C-17	120.5	120.6	120.6	120.7	120.6
C-18	137.3	137.3	137.4	137.4	137.4
C-19	147.0	147.0	146.9	146.9	146.9
C-20	106.1	106.14	106.1	106.06	106.1
C-21	155.0	155.0	155.7	155.7	155.7
C-22	191.7	191.7	191.9	192.0	191.9

* - These chemical shift assignments are interchangeable due to overlap

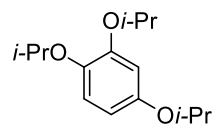
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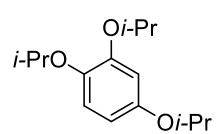
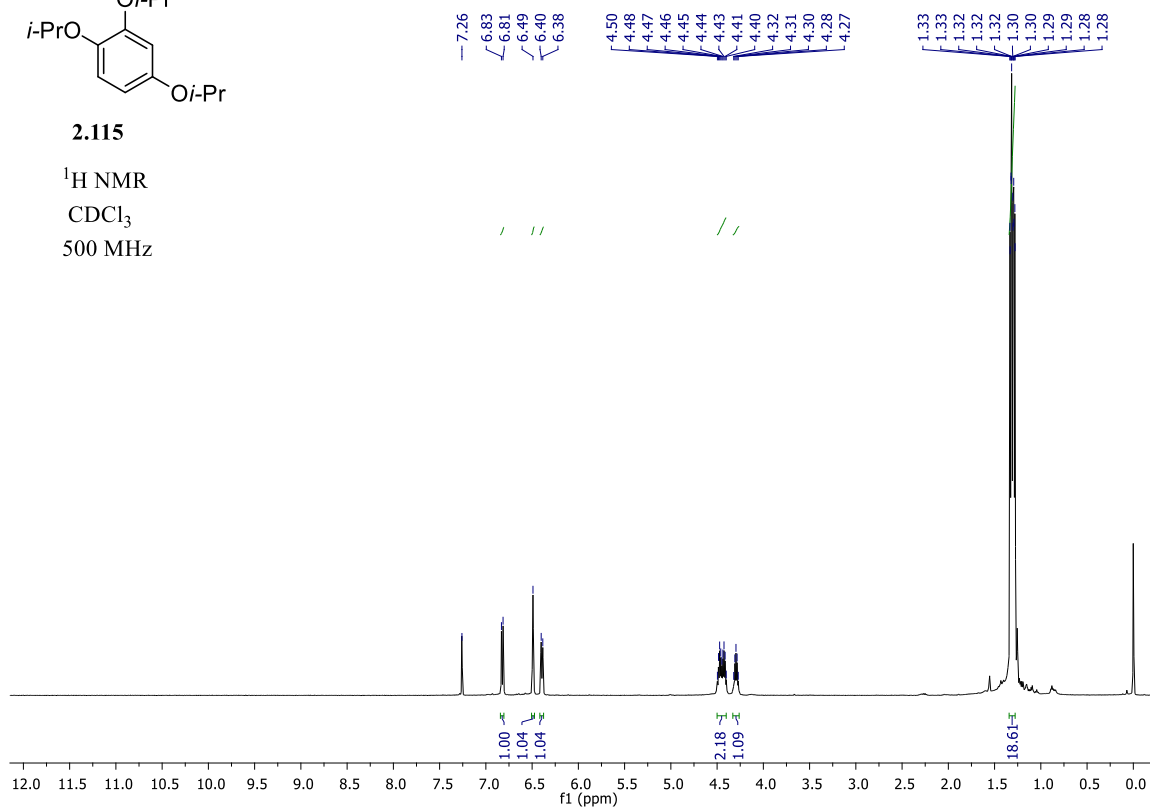
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2.12 NMR Spectra



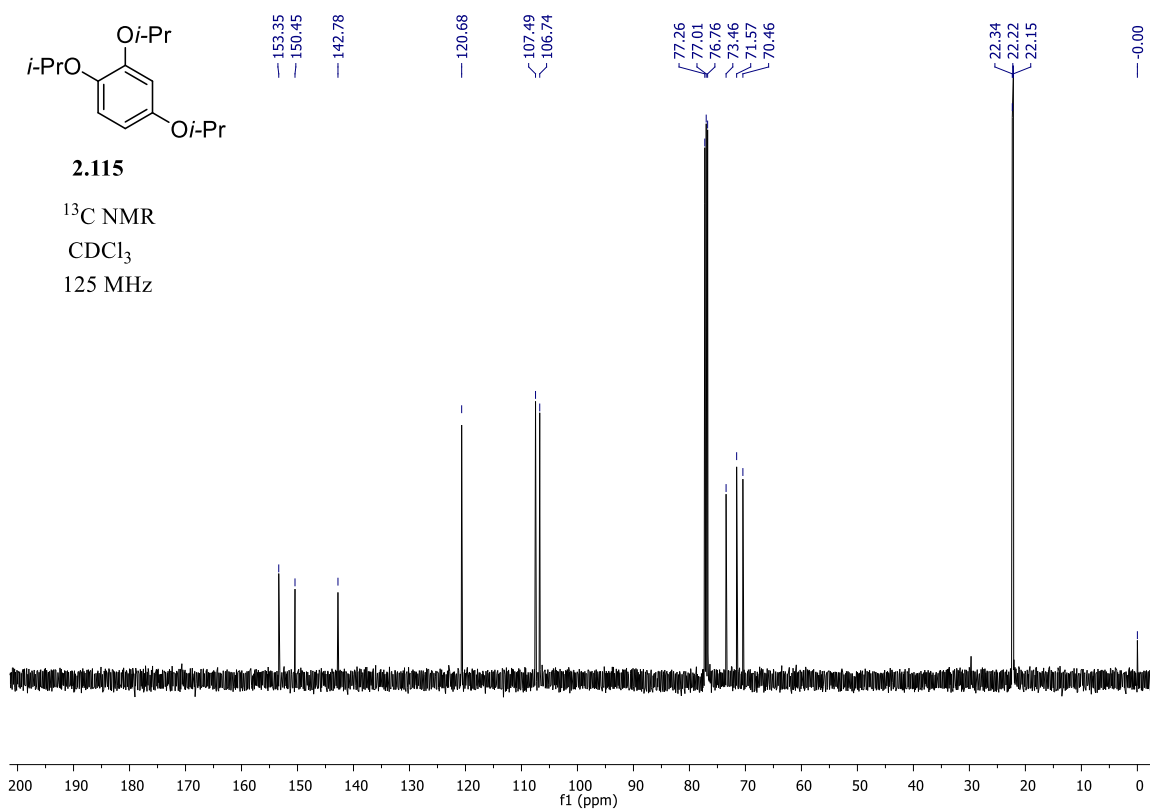
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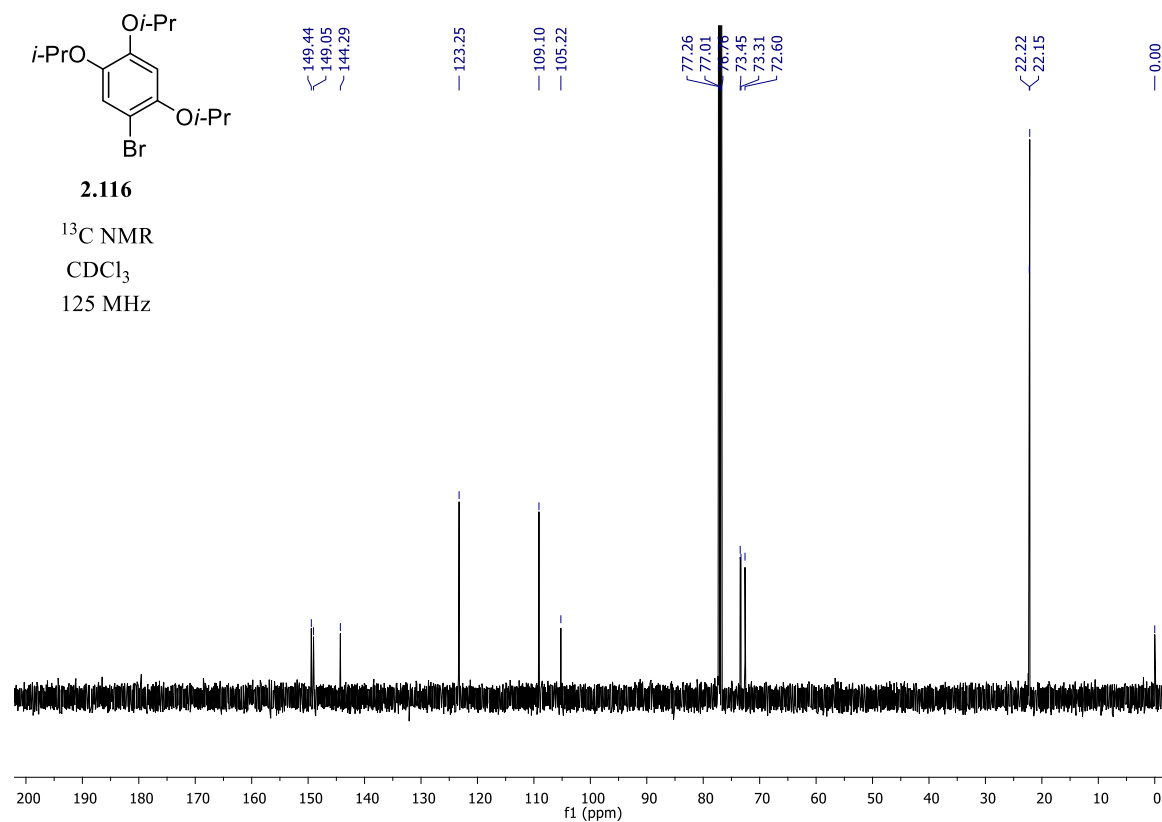
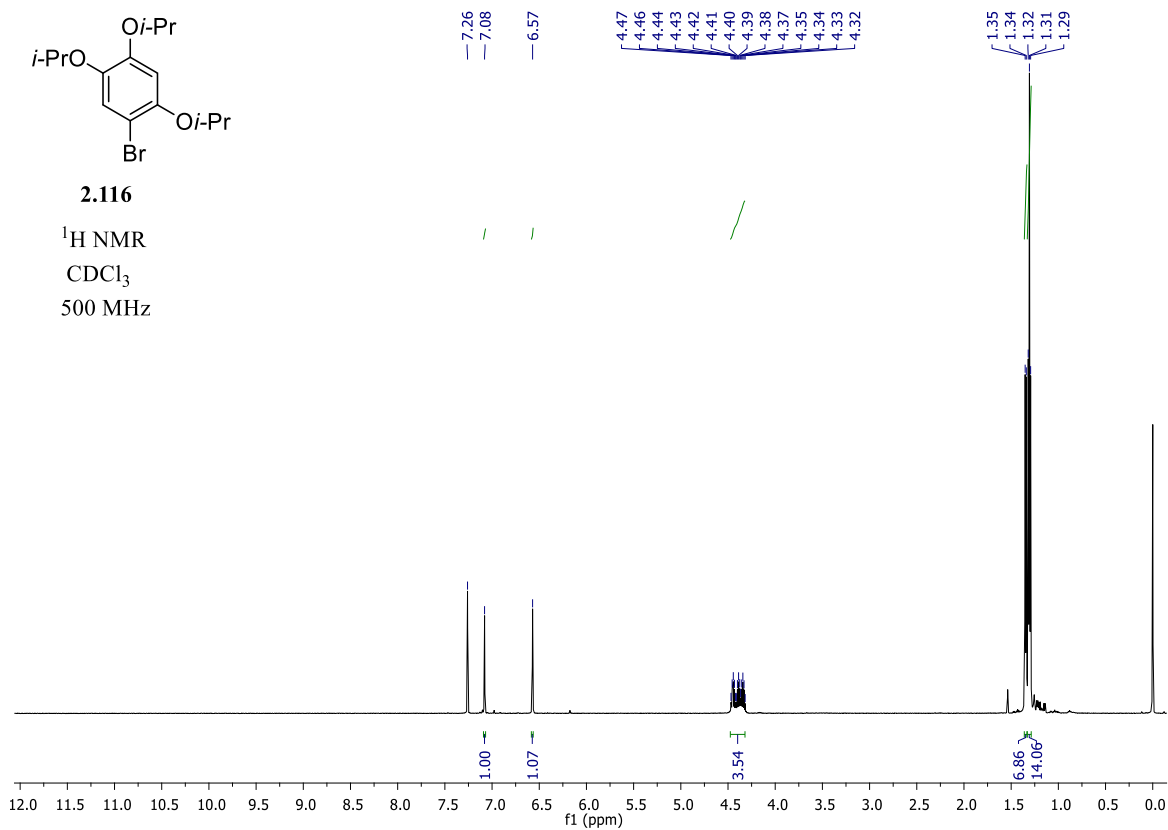
^1H NMR
 CDCl_3
500 MHz

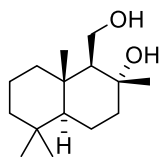


2.115

^{13}C NMR
 CDCl_3
125 MHz





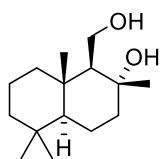
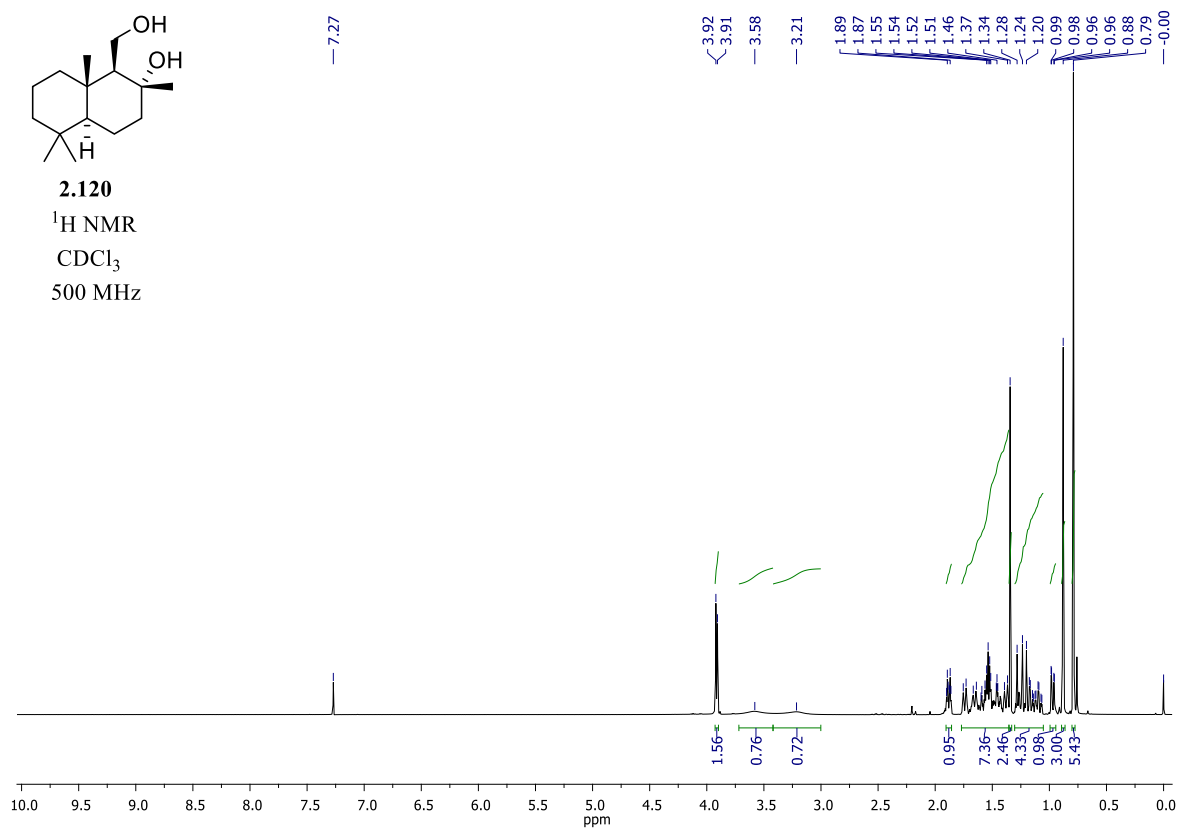


2.120

^1H NMR

CDCl_3

500 MHz

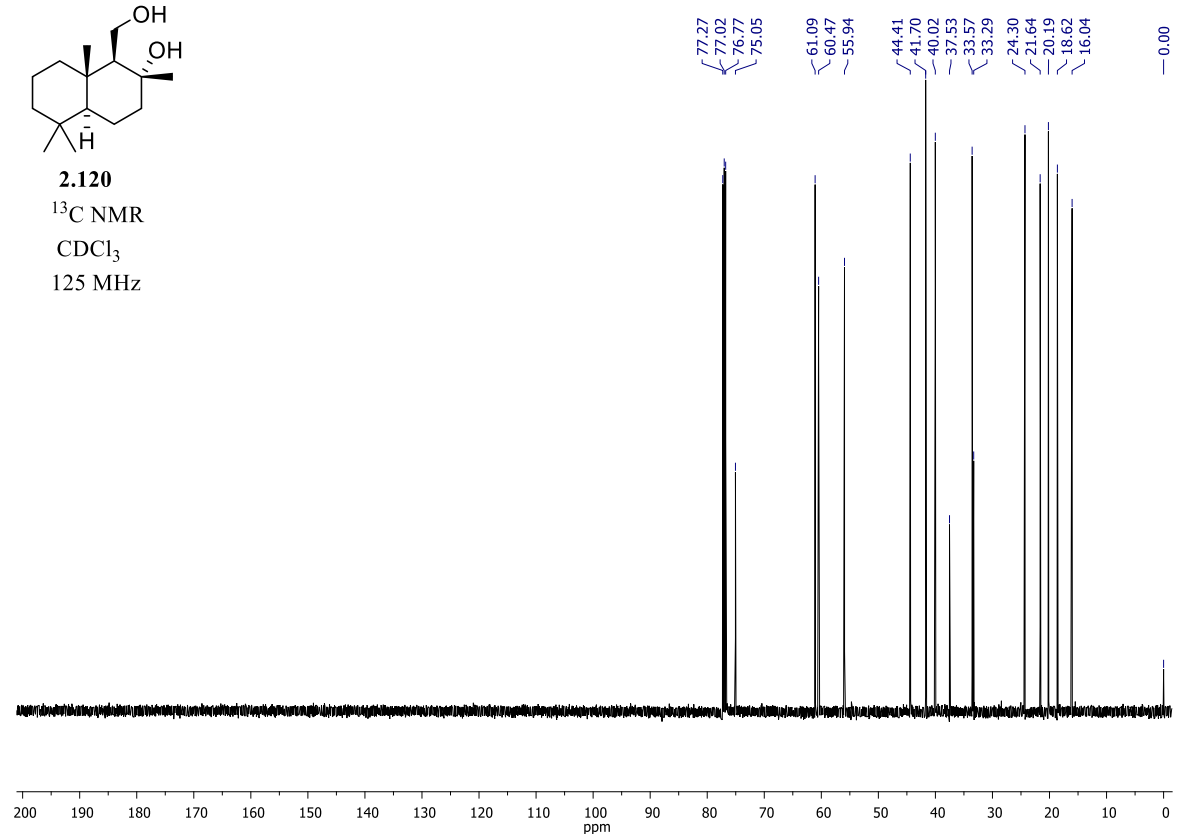


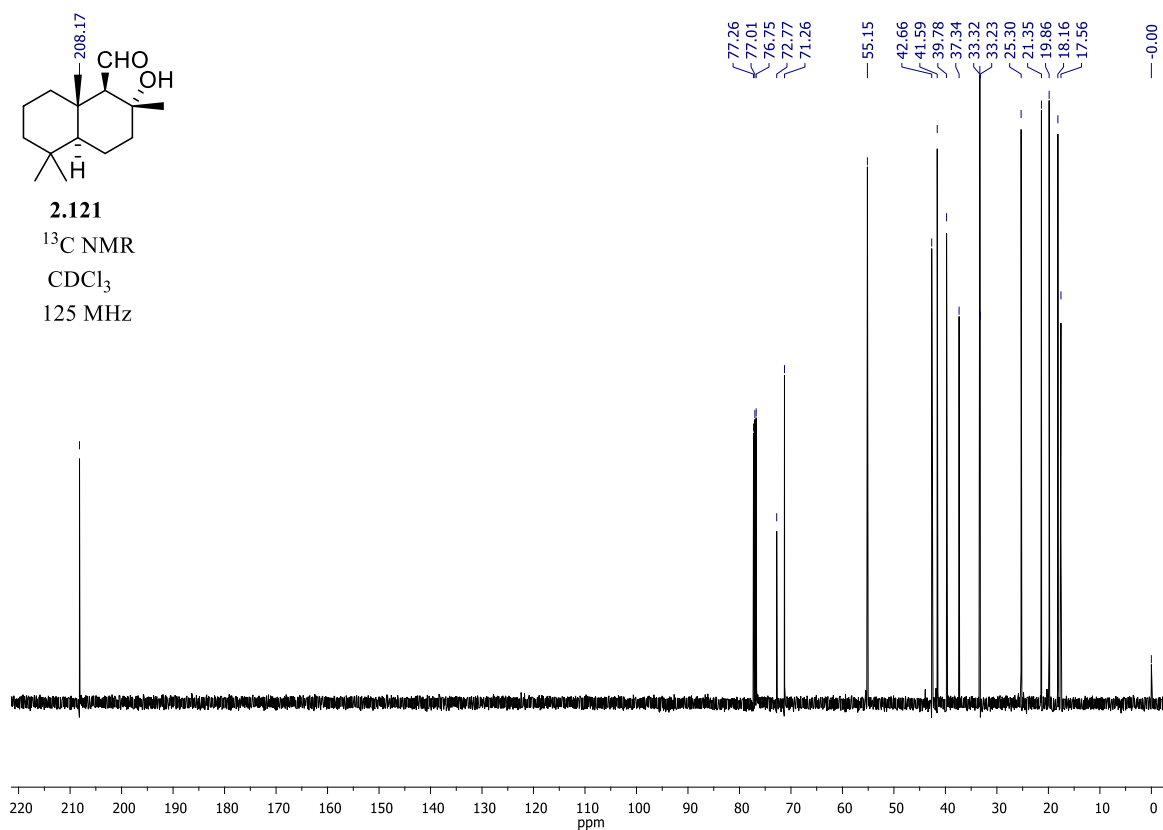
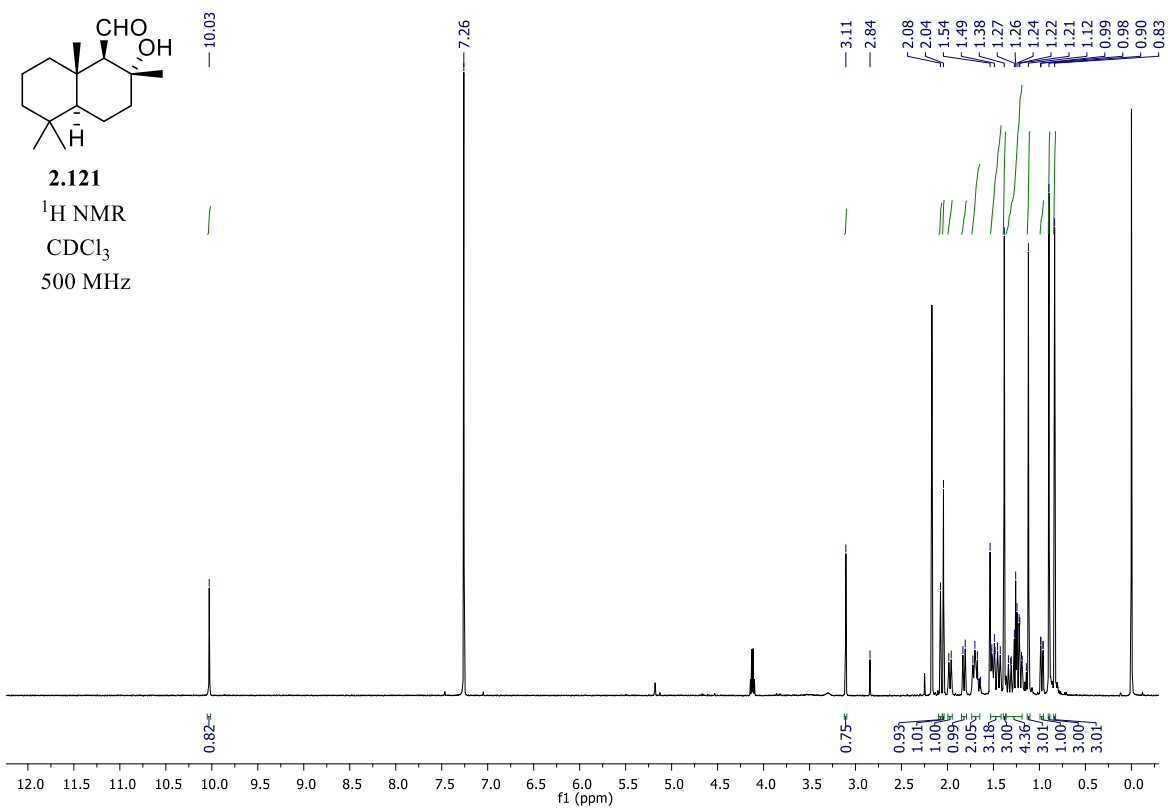
2.120

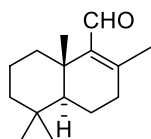
^{13}C NMR

CDCl_3

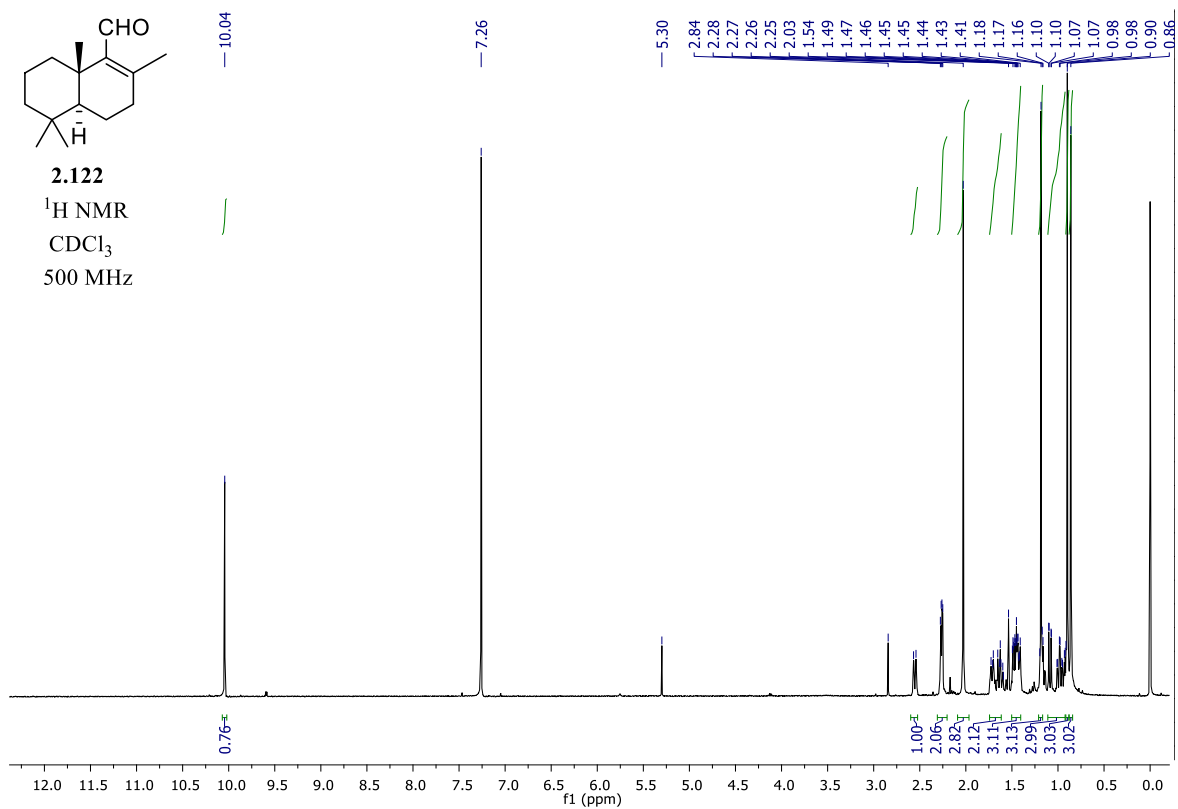
125 MHz

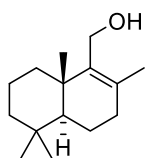




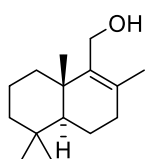
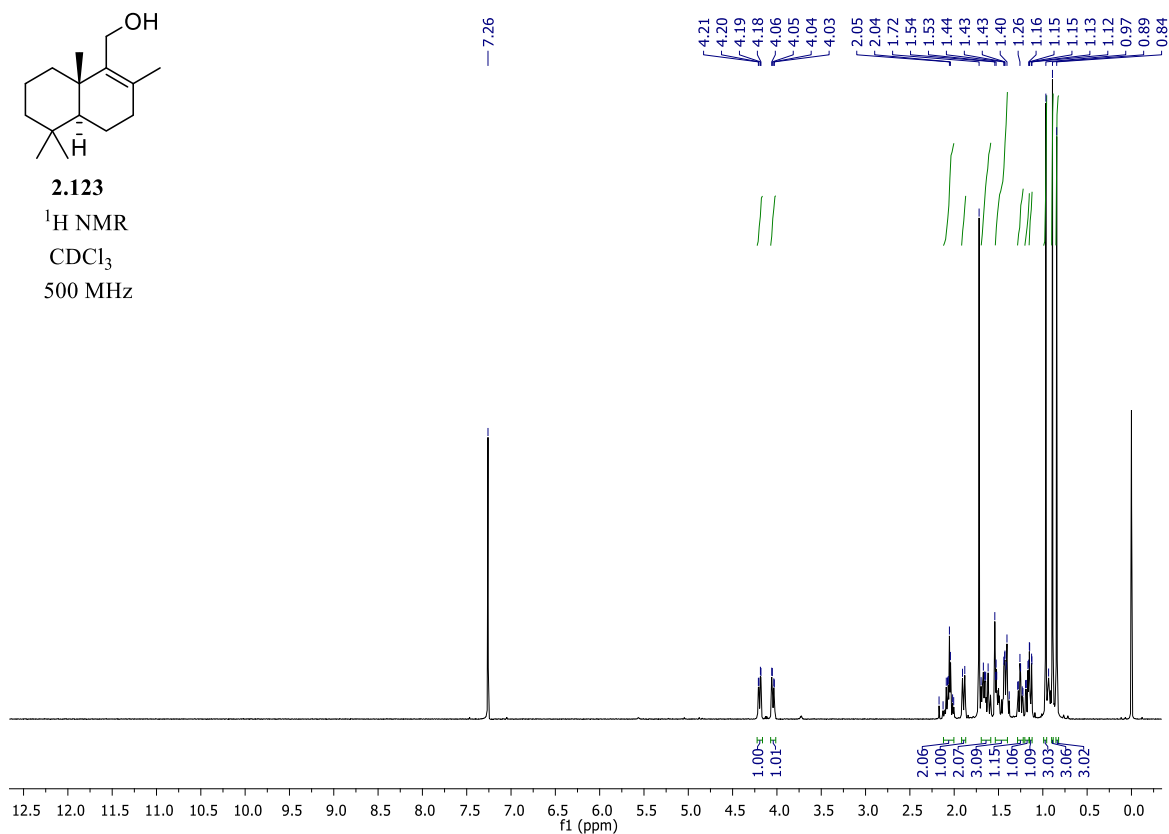


2.122
¹H NMR
CDCl₃
500 MHz

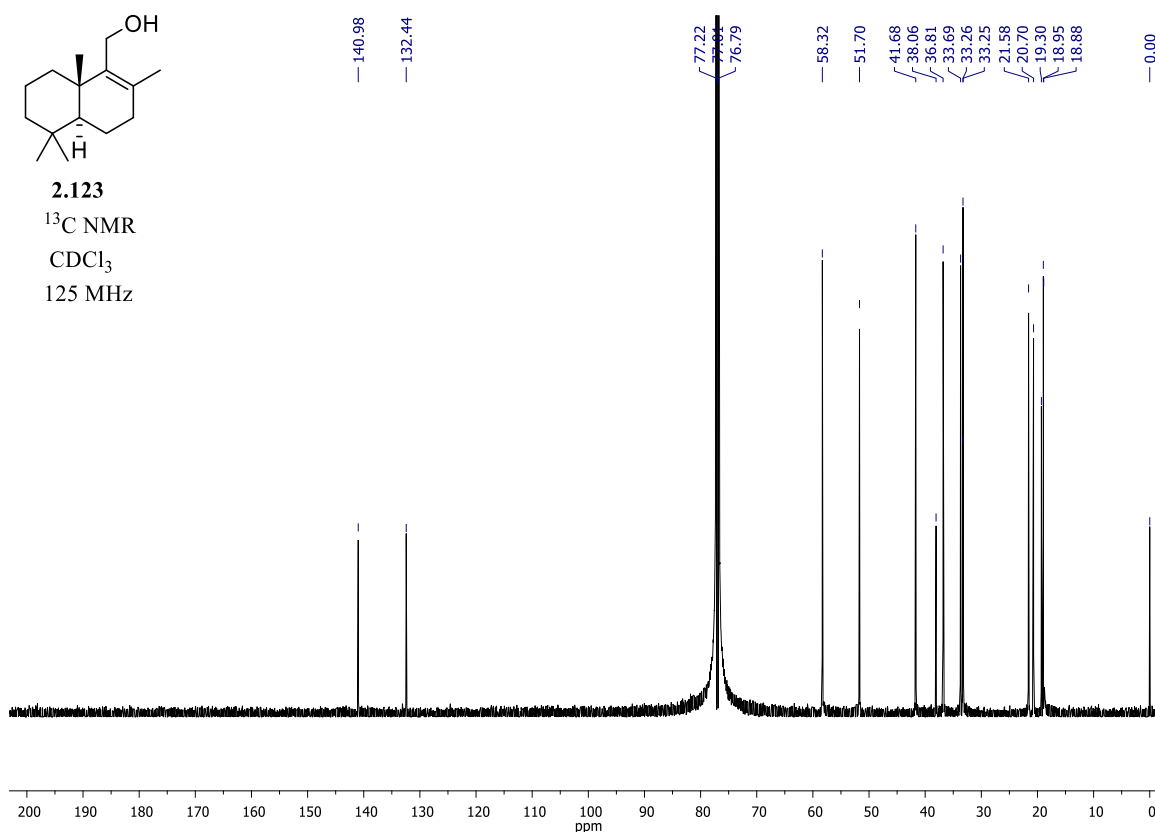


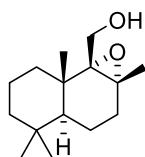


2.123
¹H NMR
 CDCl₃
 500 MHz



2.123
¹³C NMR
 CDCl₃
 125 MHz



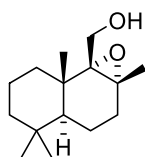
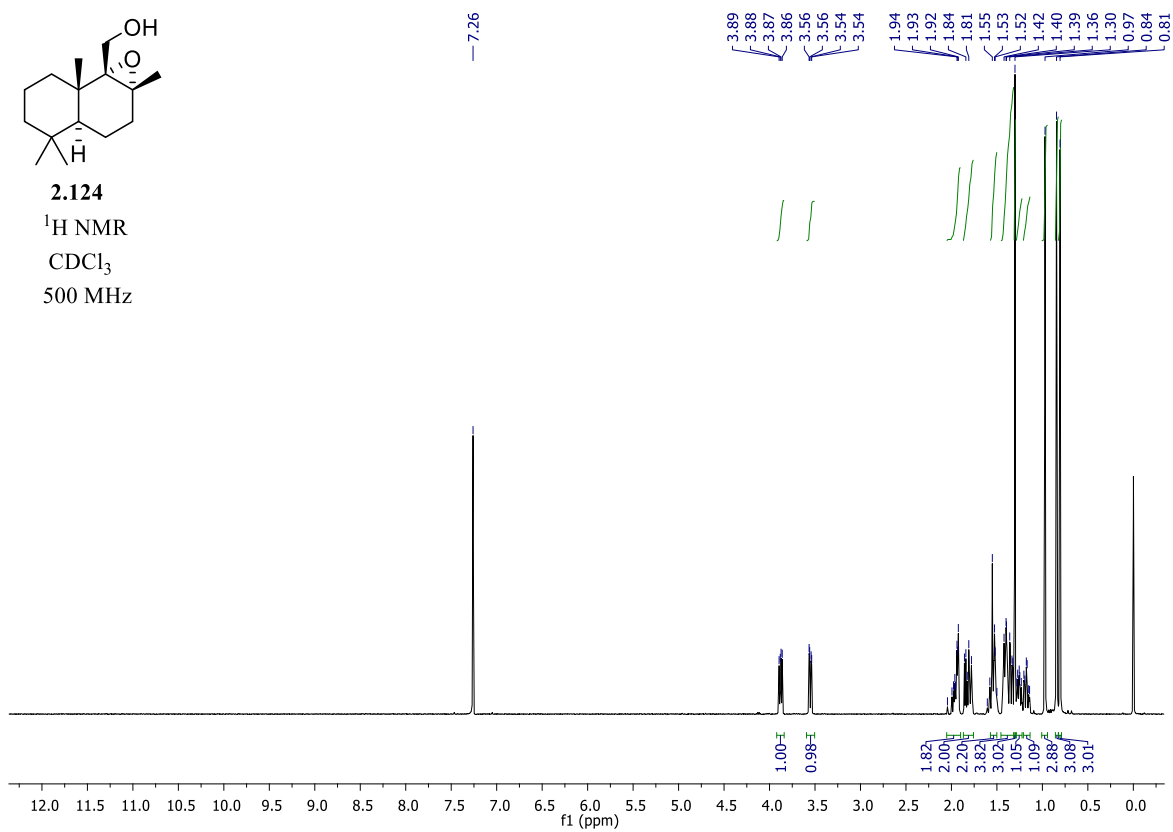


2.124

¹H NMR

CDCl₃

500 MHz

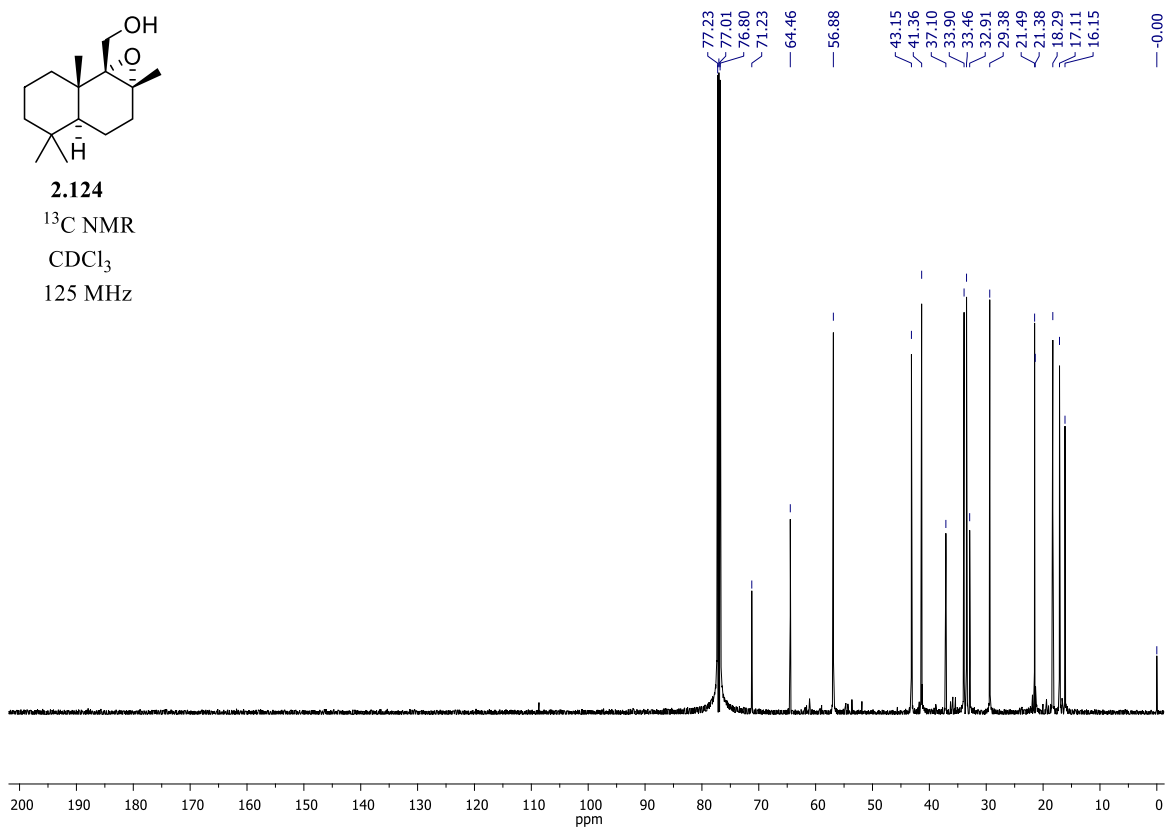


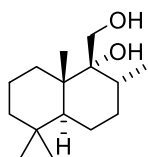
2.124

¹³C NMR

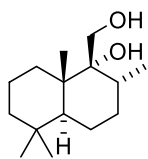
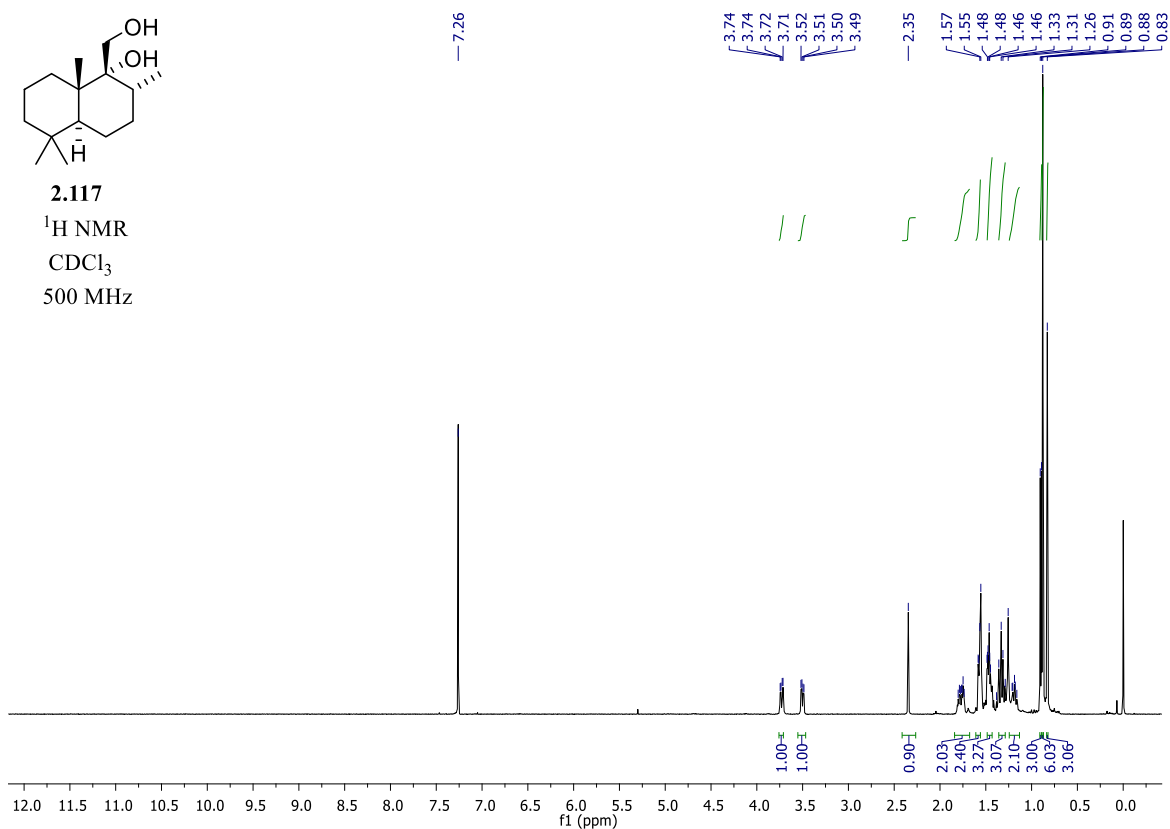
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125 MHz

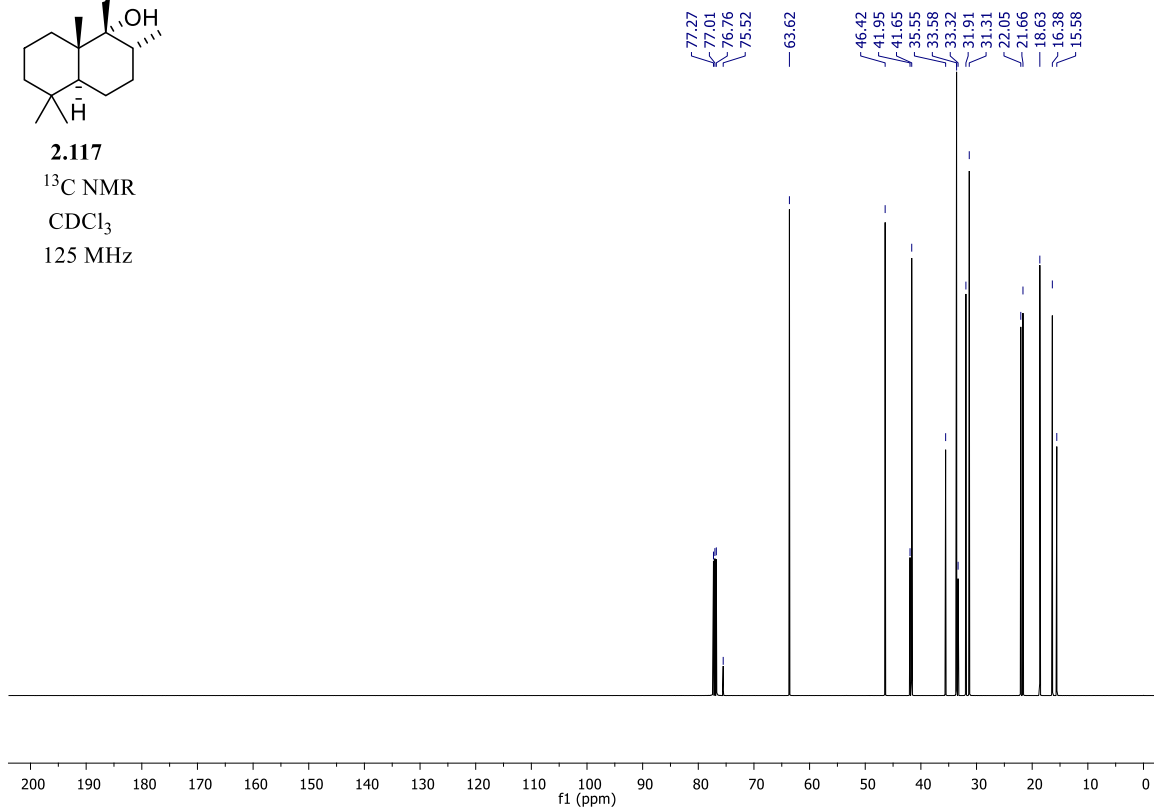


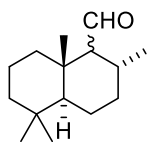


2.117
¹H NMR
 CDCl₃
 500 MHz

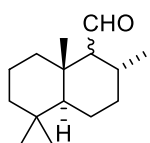
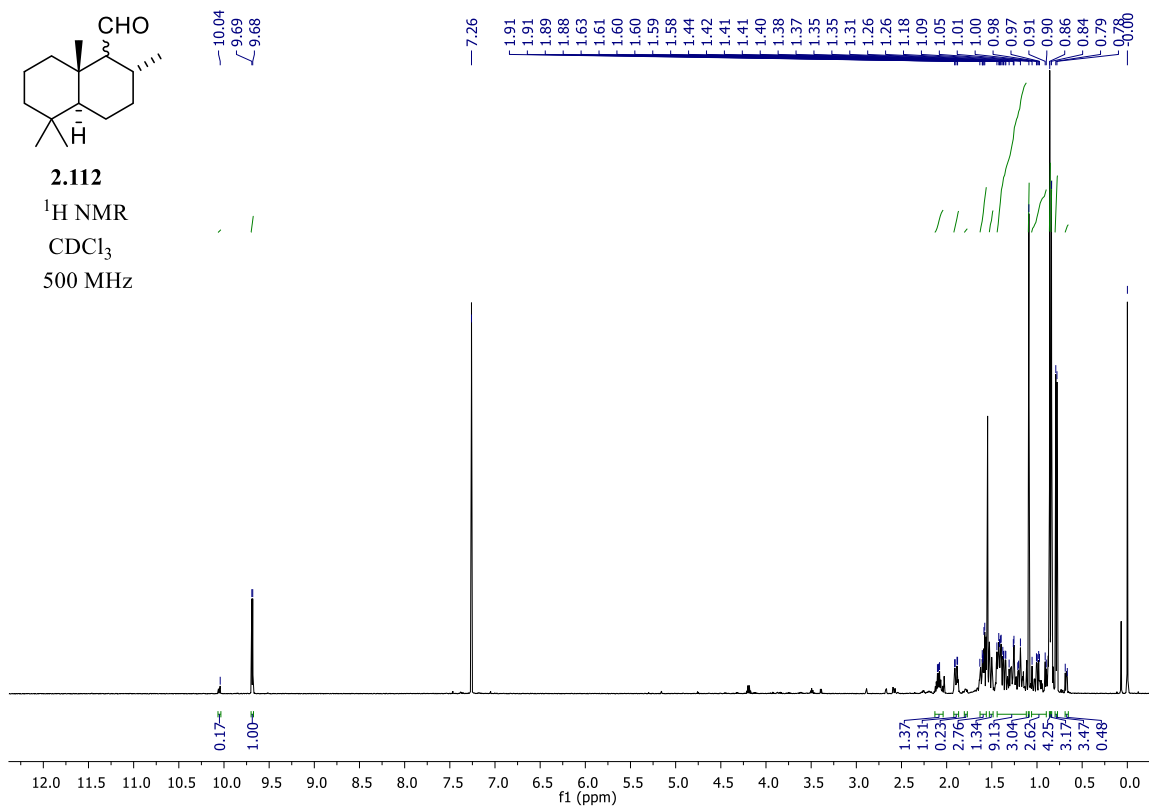


2.117
¹³C NMR
 CDCl₃
 125 MHz

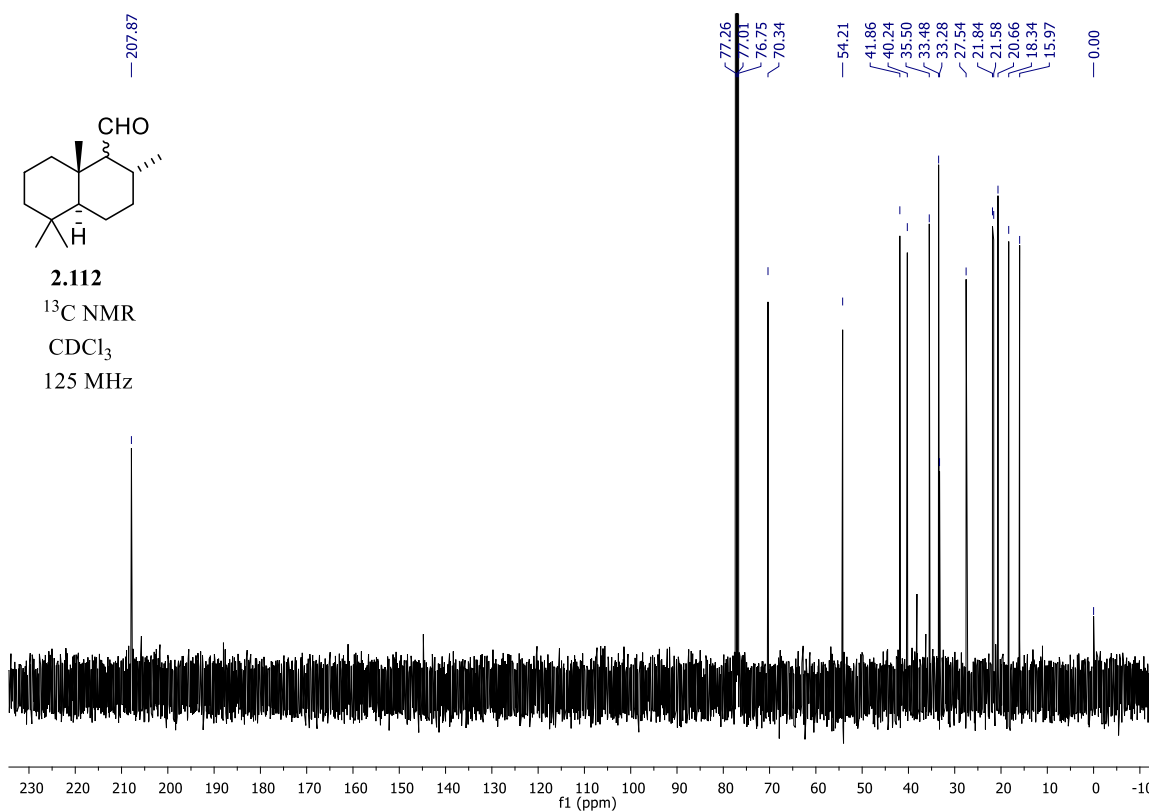


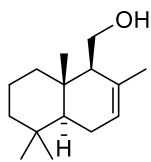


2.112
¹H NMR
 CDCl₃
 500 MHz

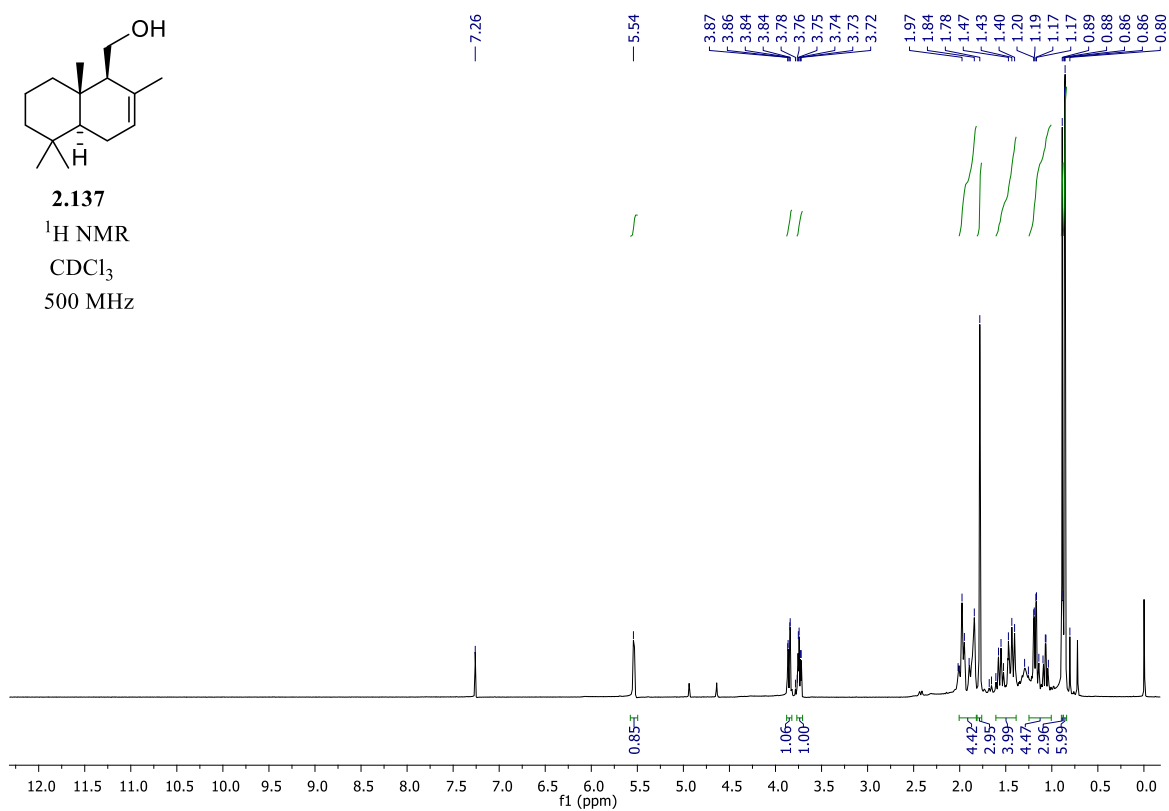


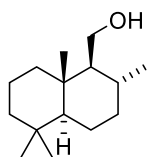
2.112
¹³C NMR
 CDCl₃
 125 MHz



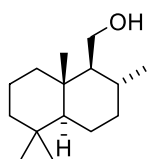
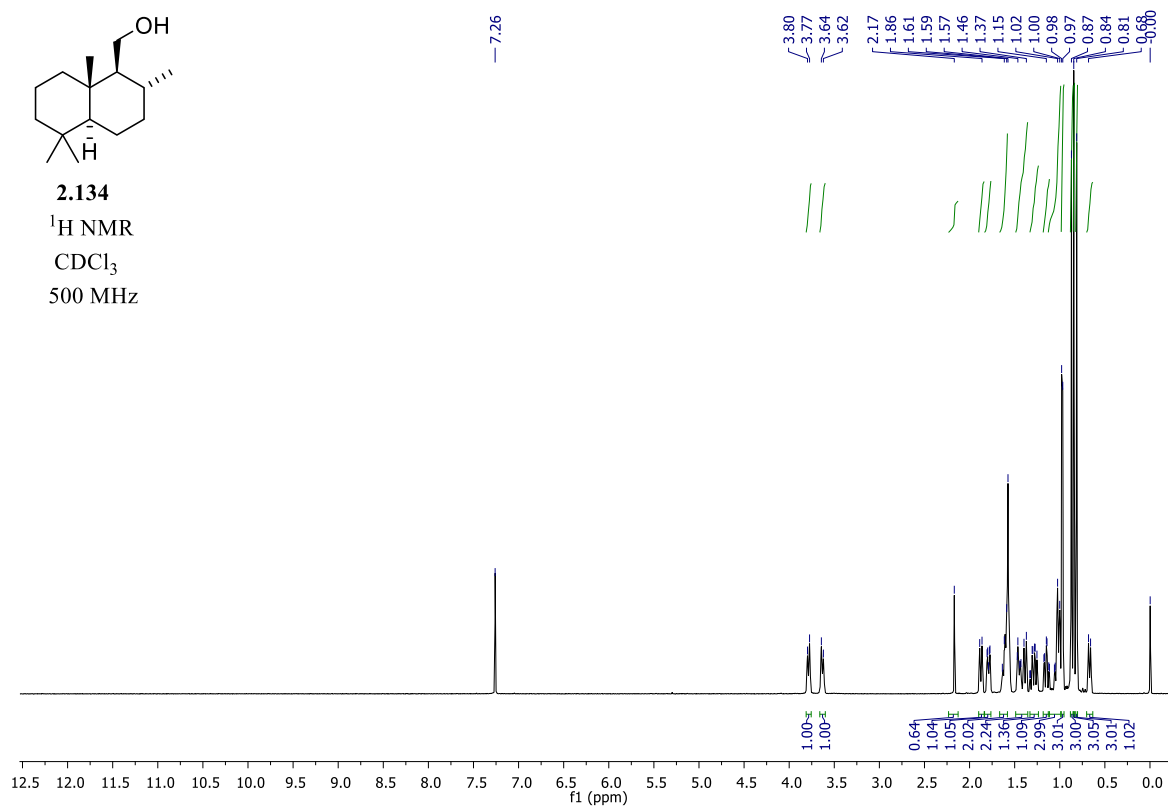


2.137
¹H NMR
CDCl₃
500 MHz

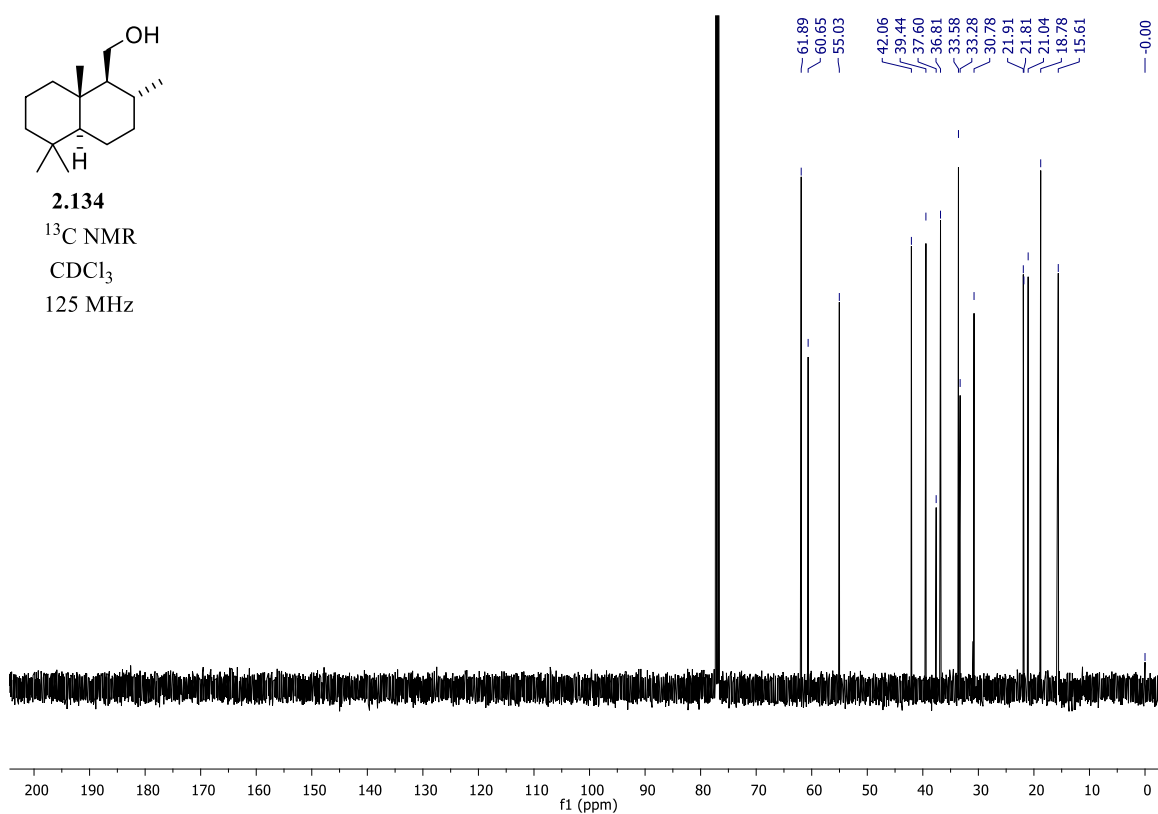


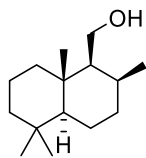


2.134
 ^1H NMR
 CDCl_3
 500 MHz

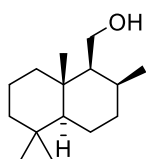
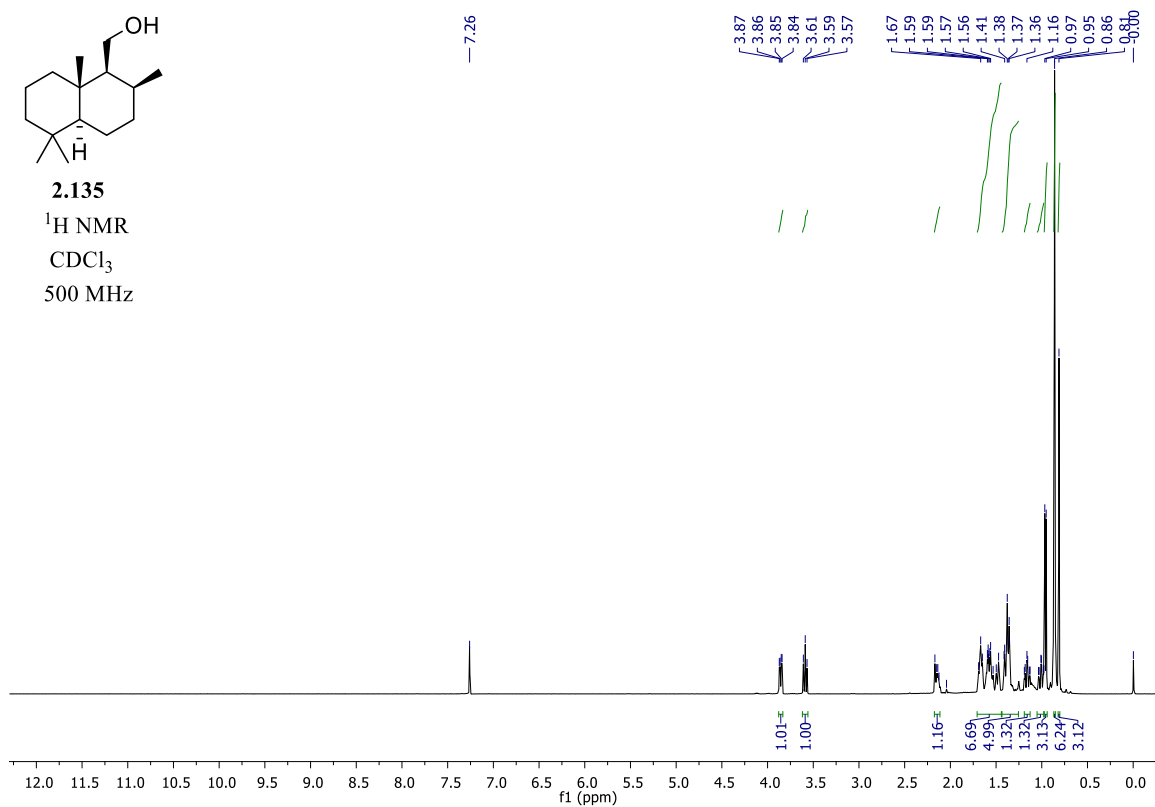


2.134
 ^{13}C NMR
 CDCl_3
 125 MHz

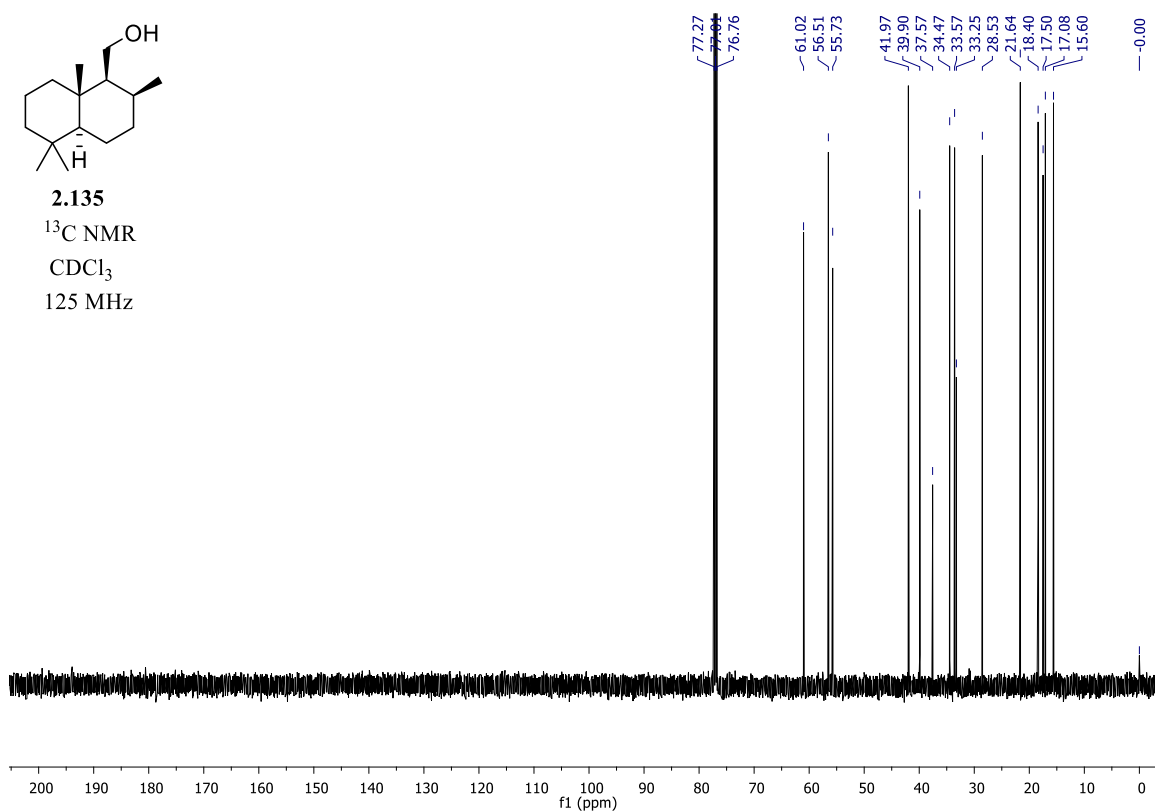


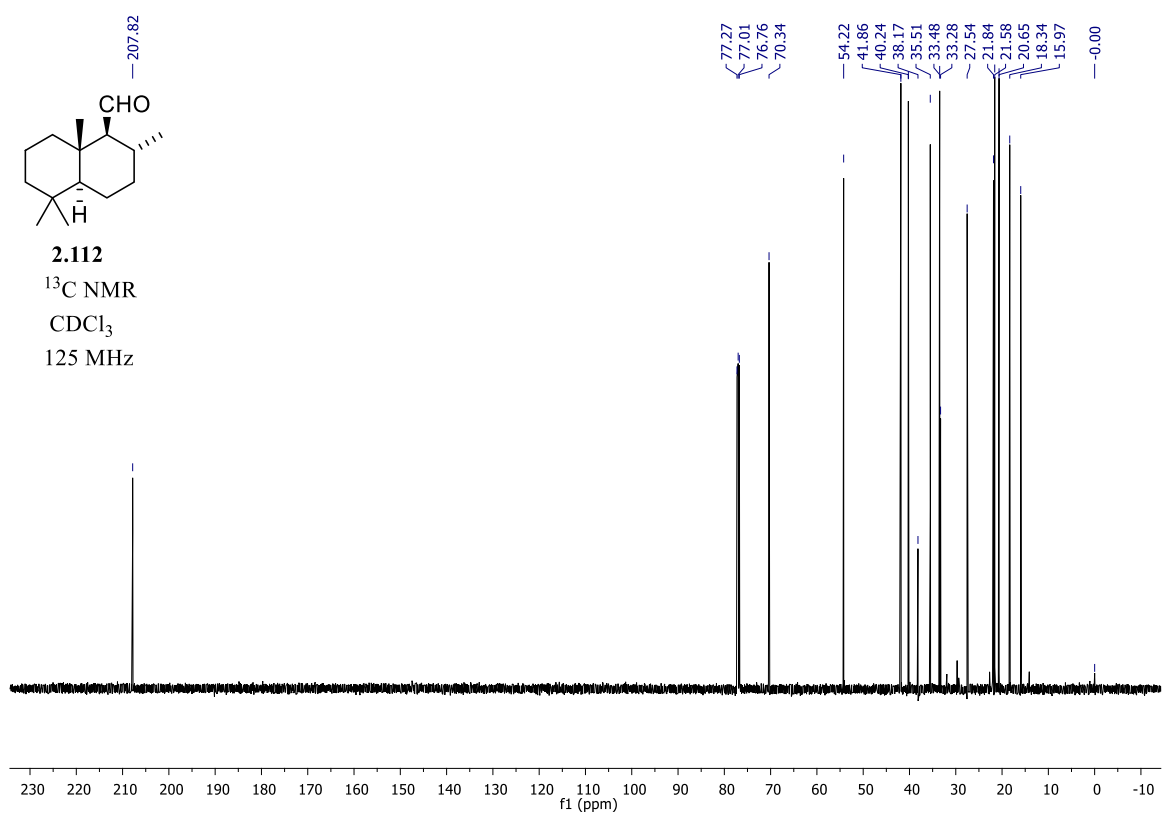
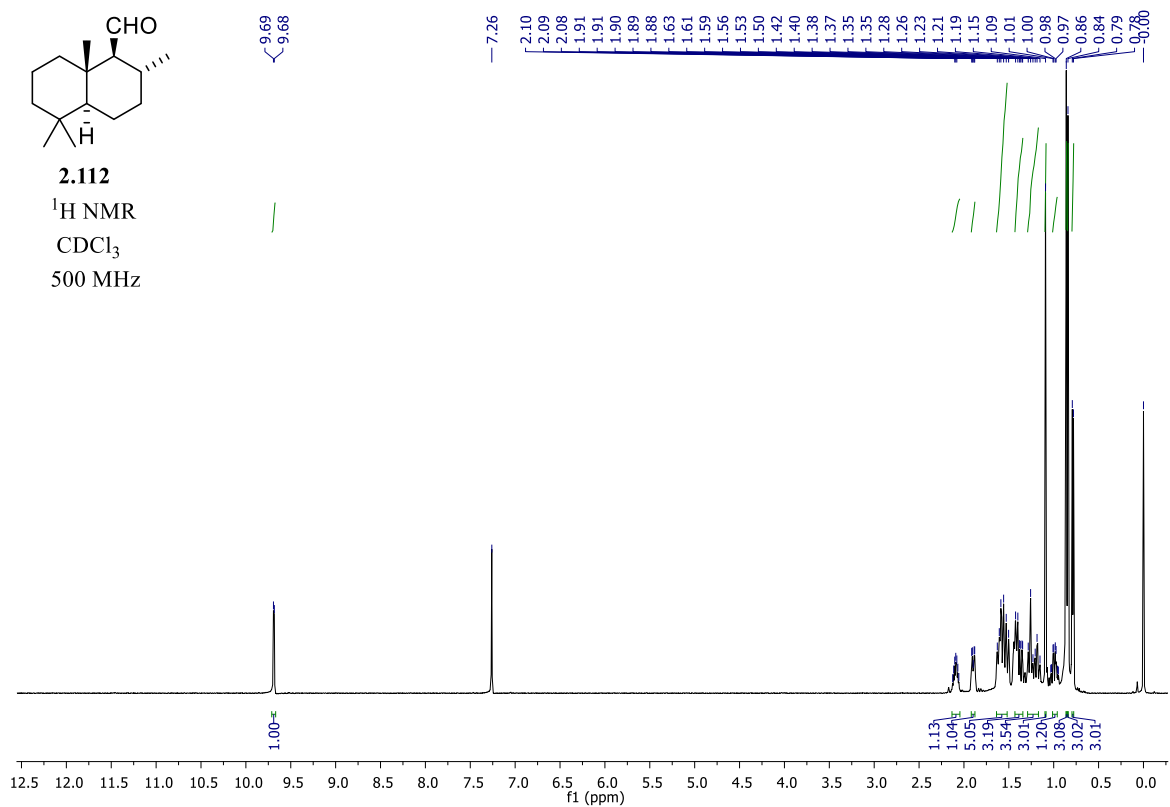


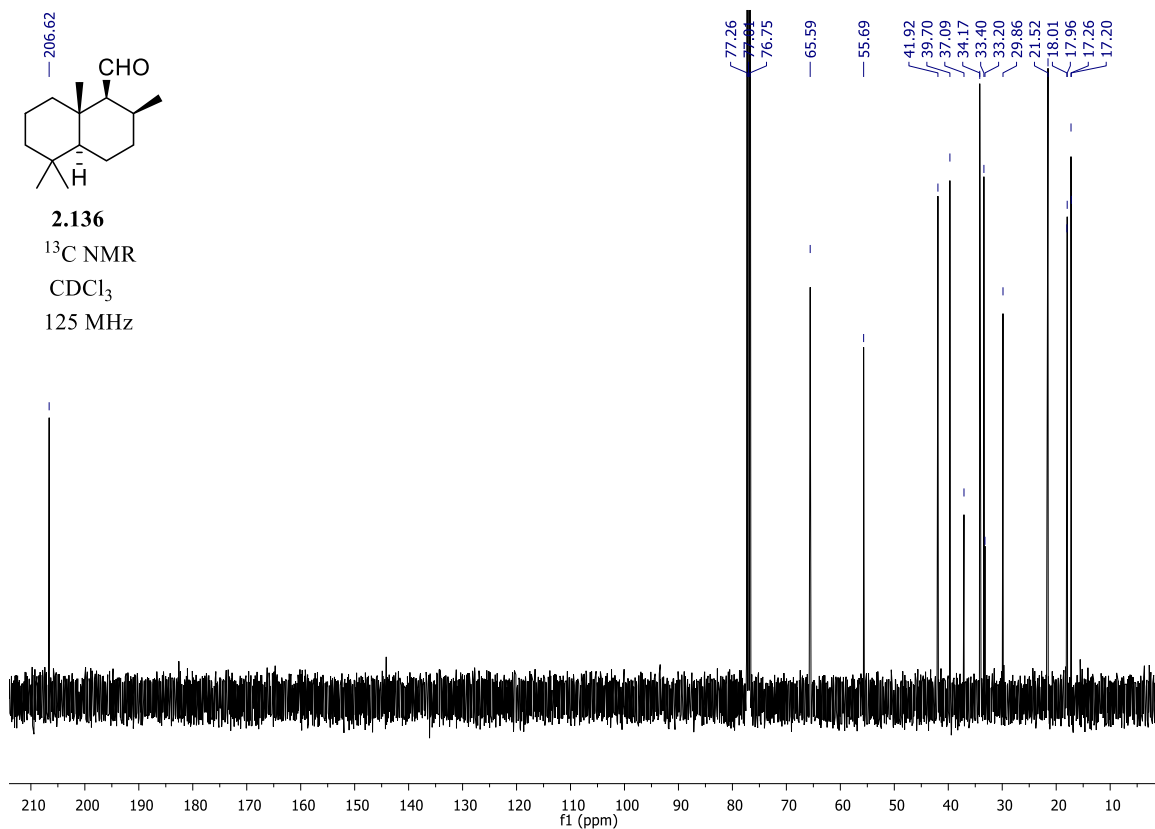
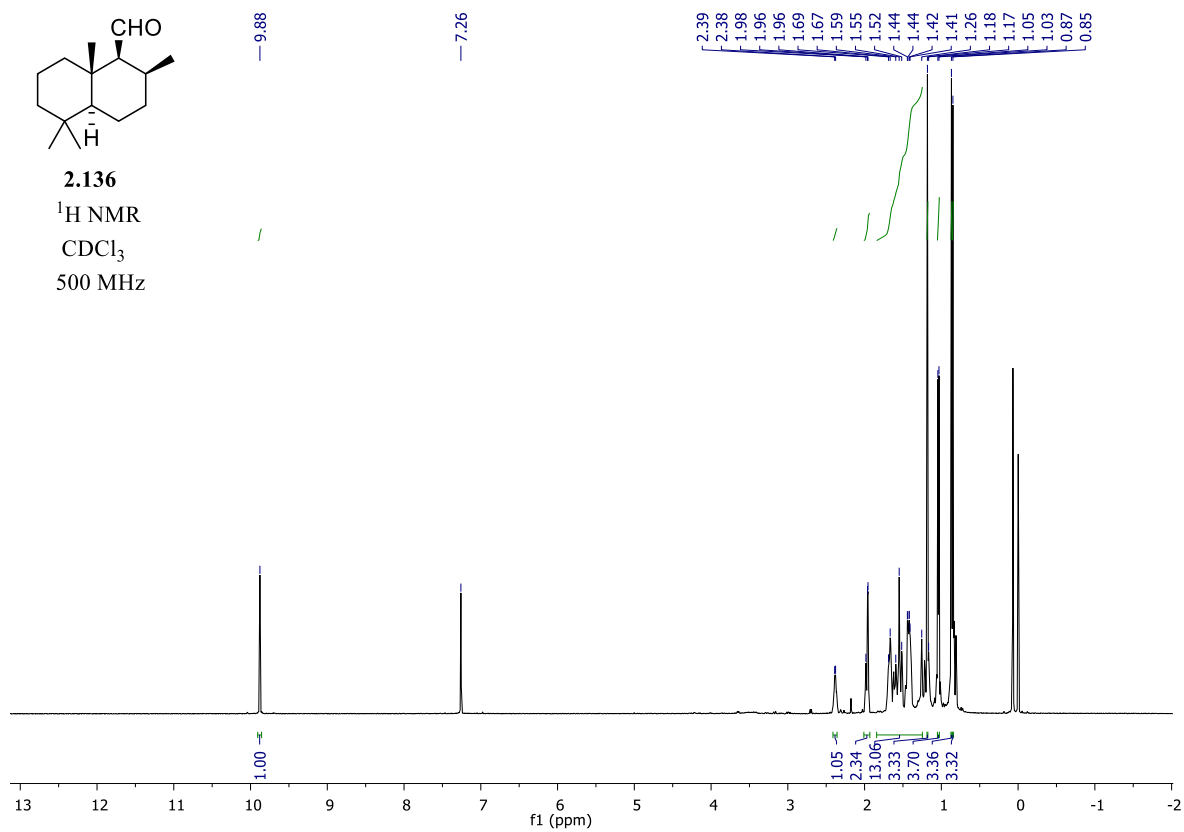
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 500 MHz

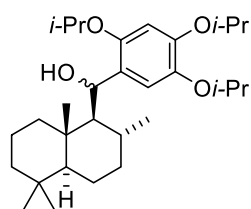


2.135
¹³C NMR
 CDCl₃
 125 MHz







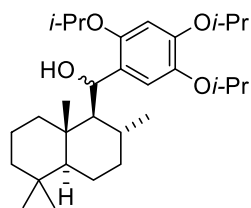
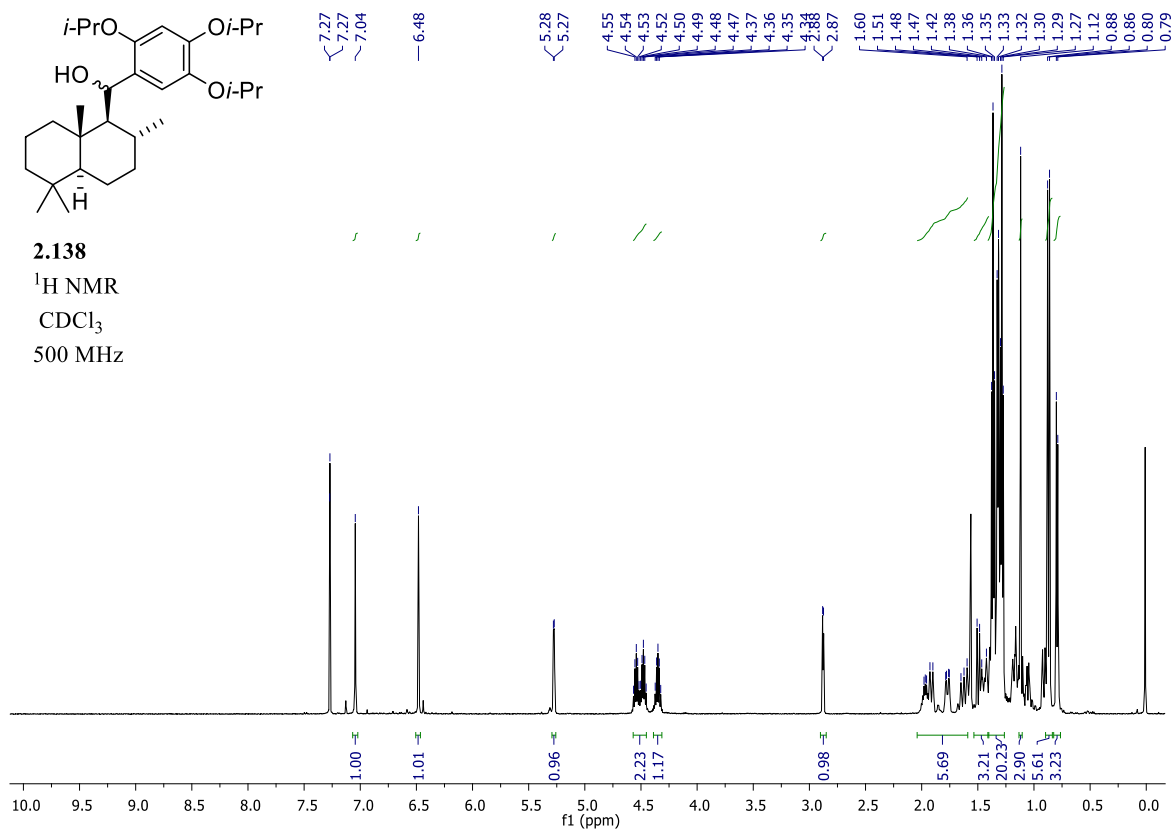


2.138

^1H NMR

CDCl_3

500 MHz

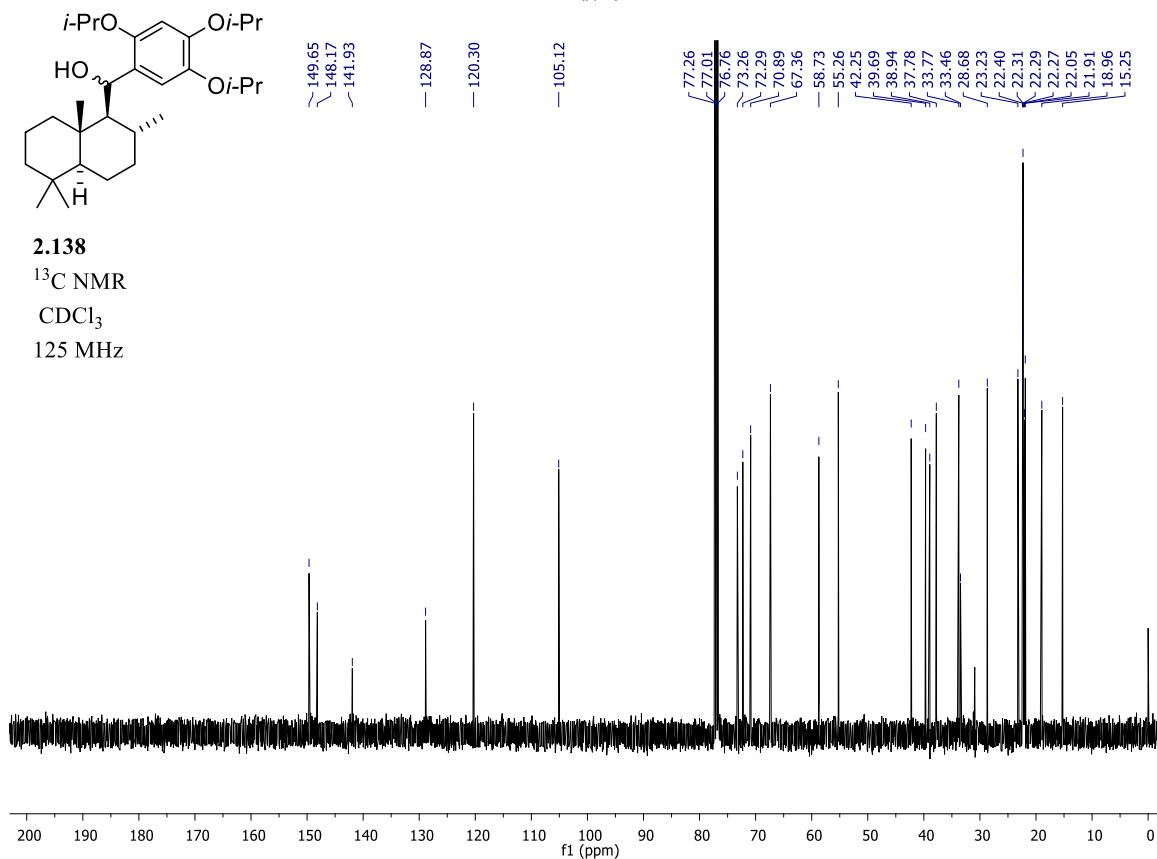


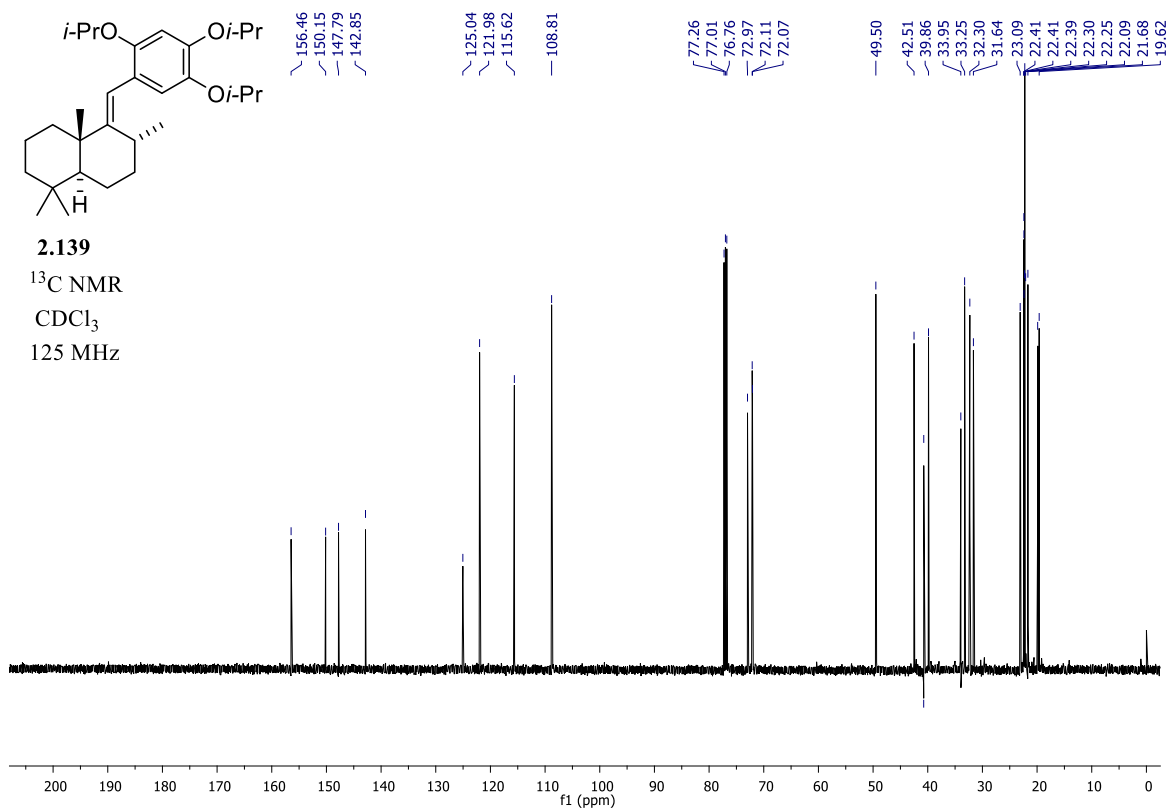
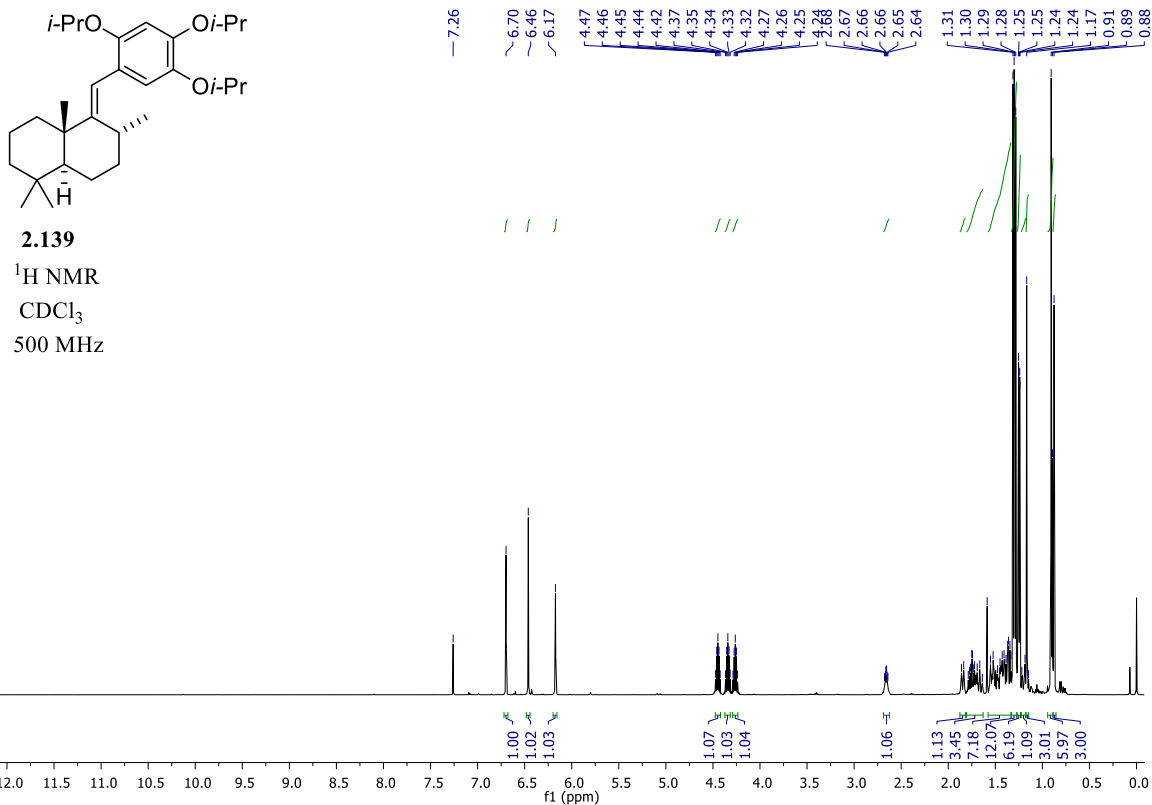
2.138

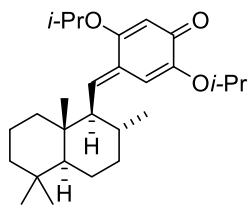
^{13}C NMR

CDCl_3

125 MHz





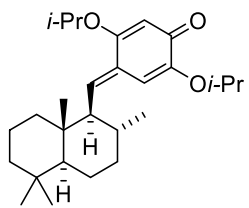
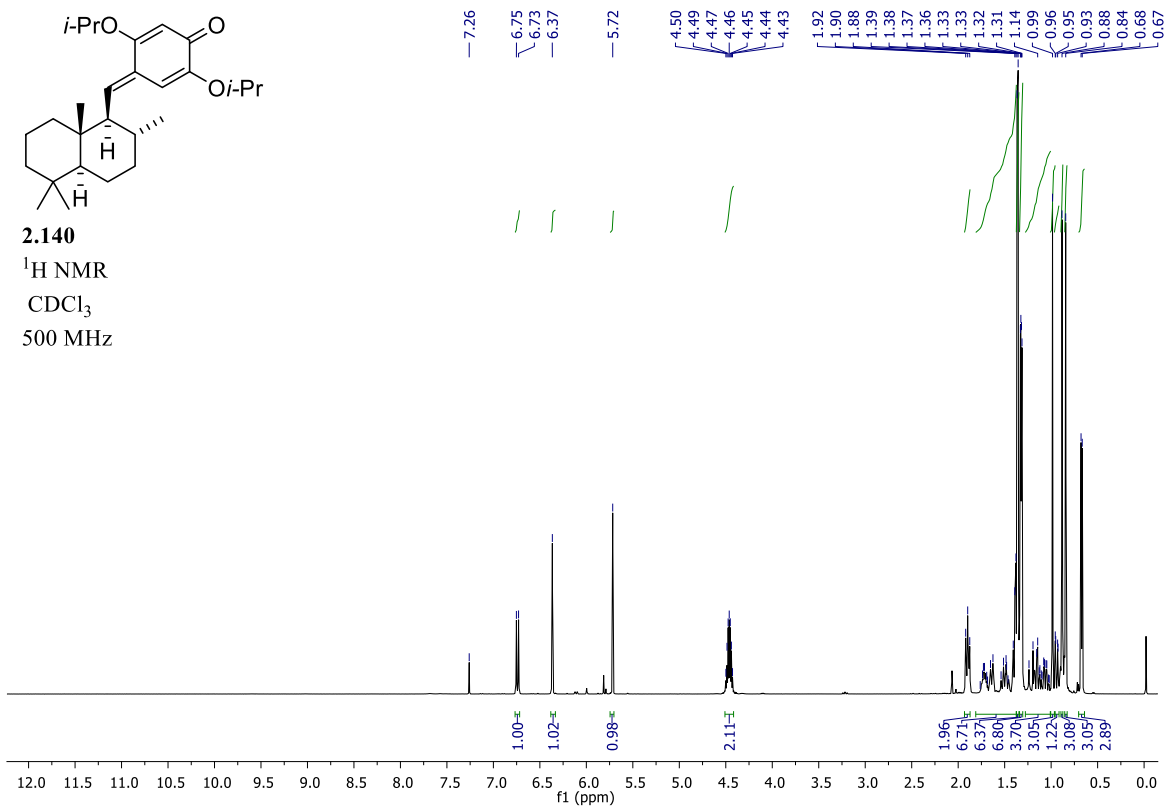


2.140

^1H NMR

CDCl_3

500 MHz

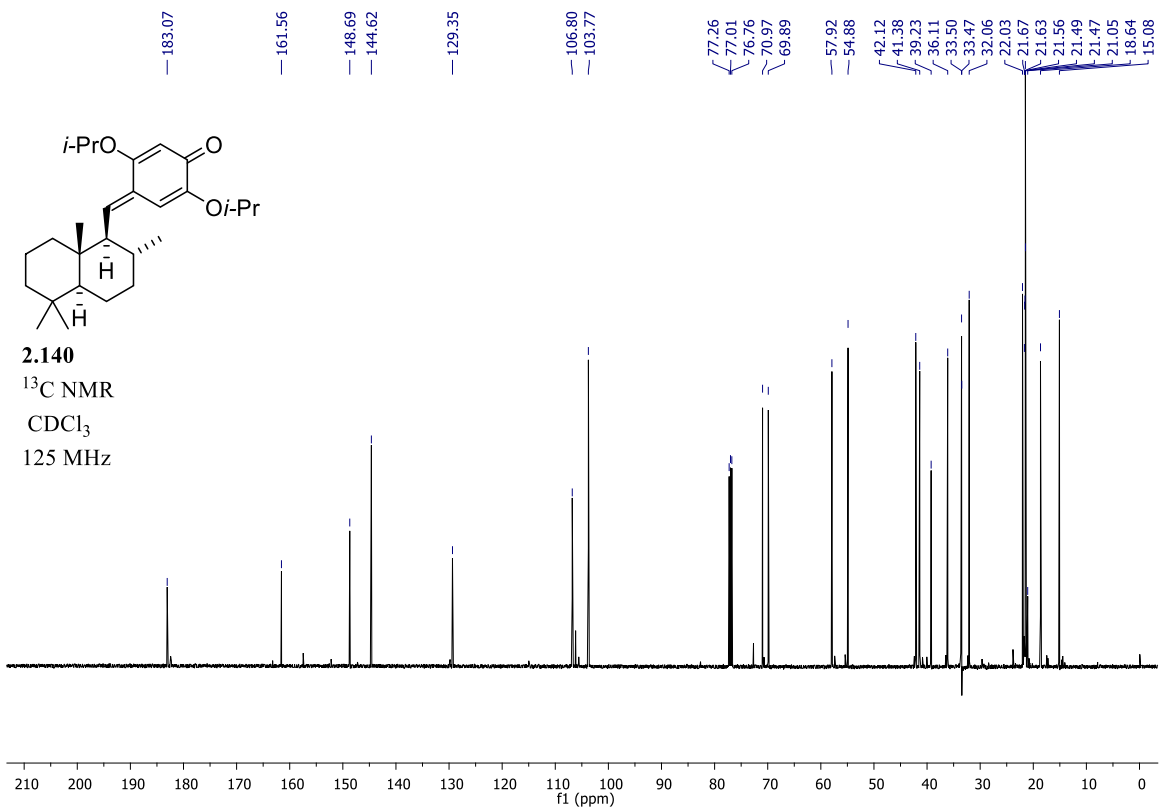


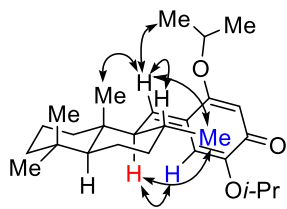
2.140

^{13}C NMR

CDCl_3

125 MHz



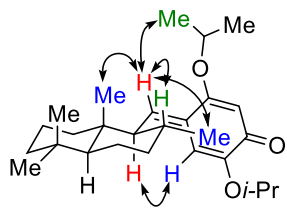
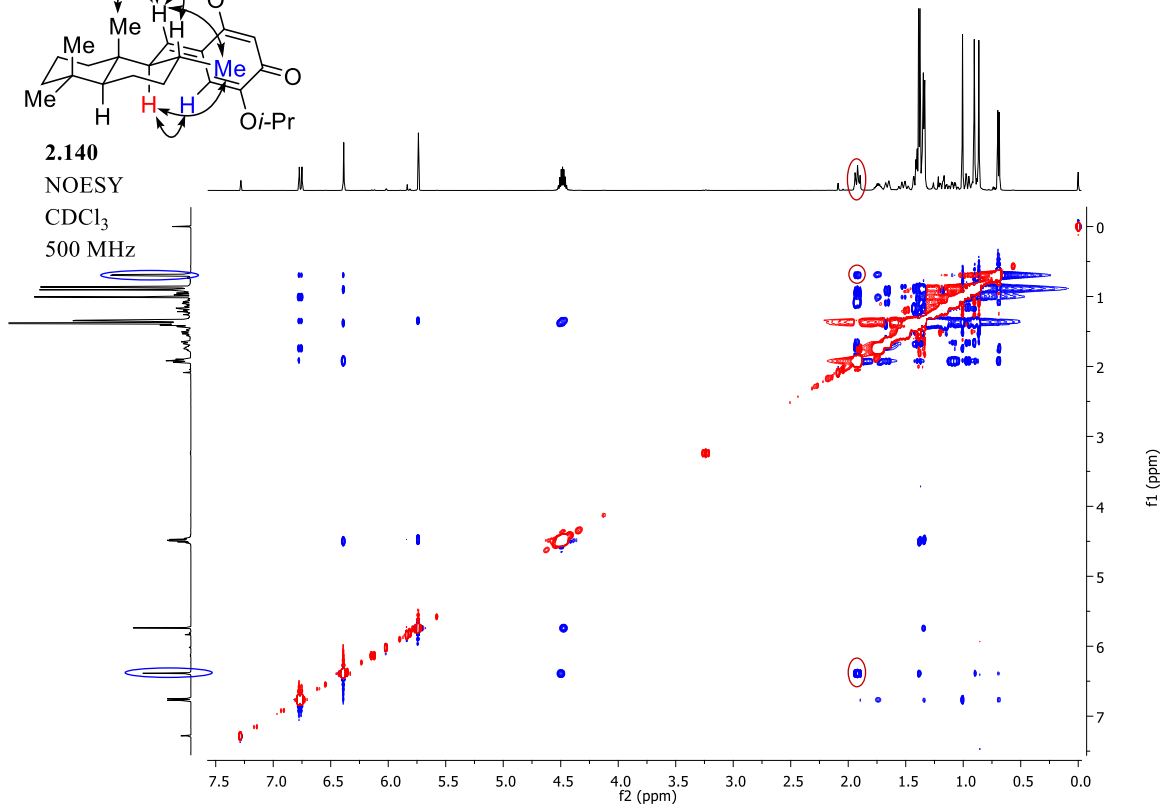


2.140

NOESY

CDCl₃

500 MHz

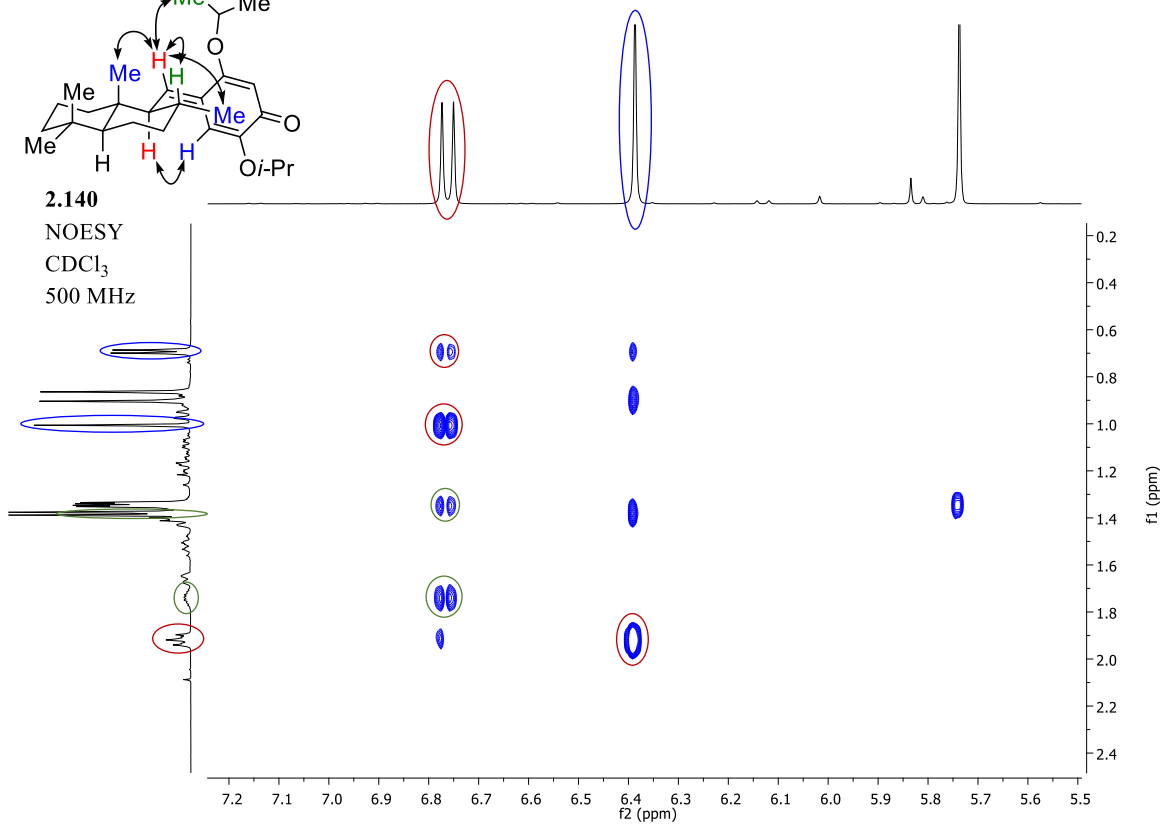


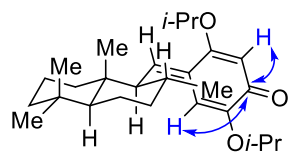
2.140

NOESY

CDCl₃

500 MHz



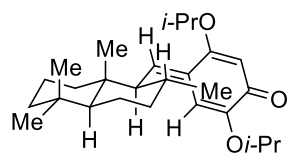
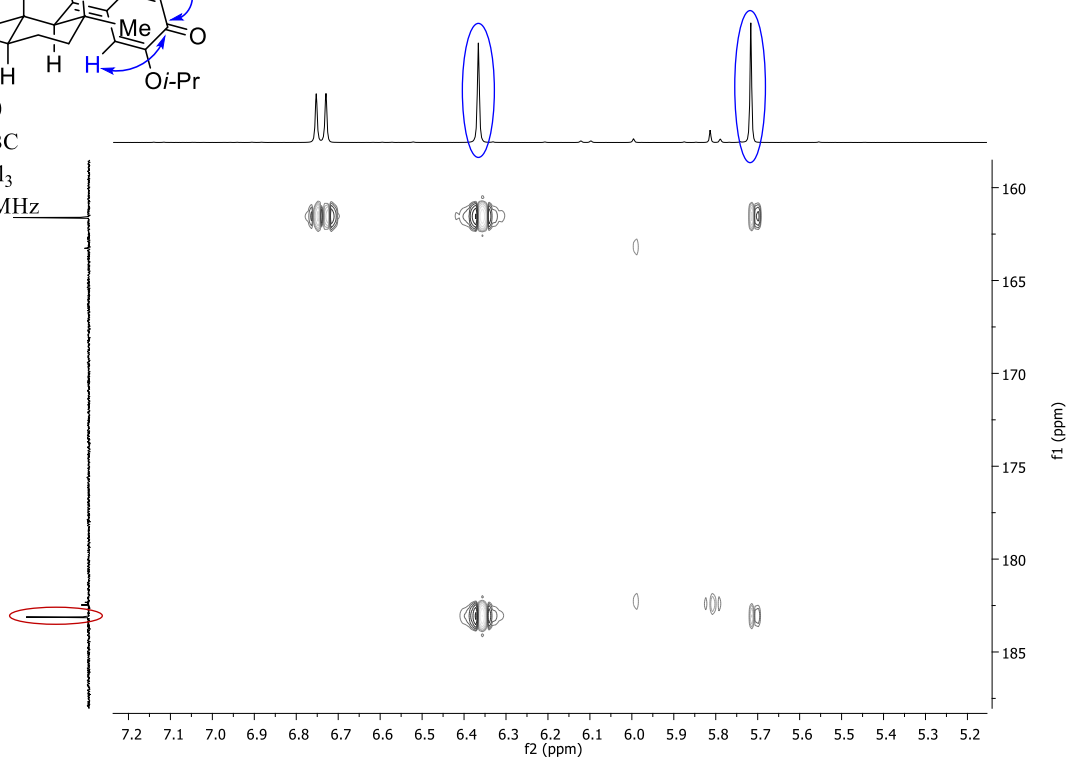


2.140

HMBC

CDCl₃

500 MHz

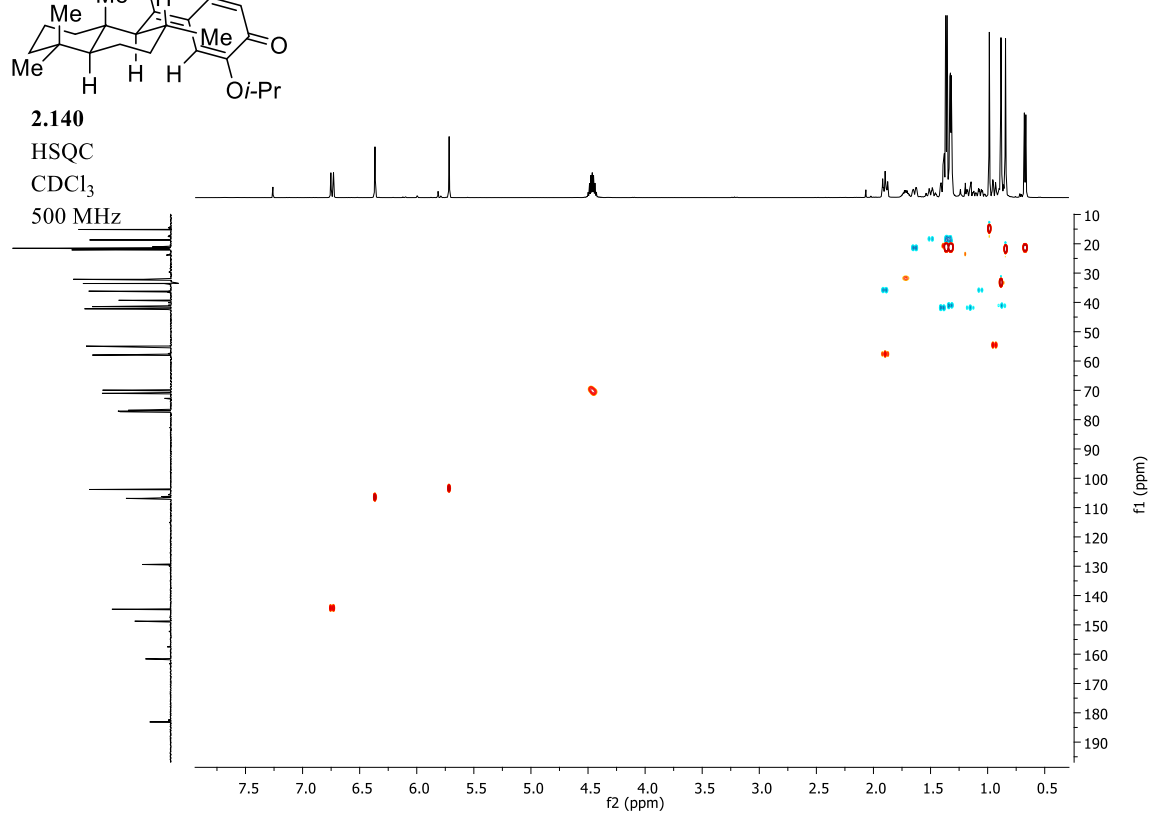


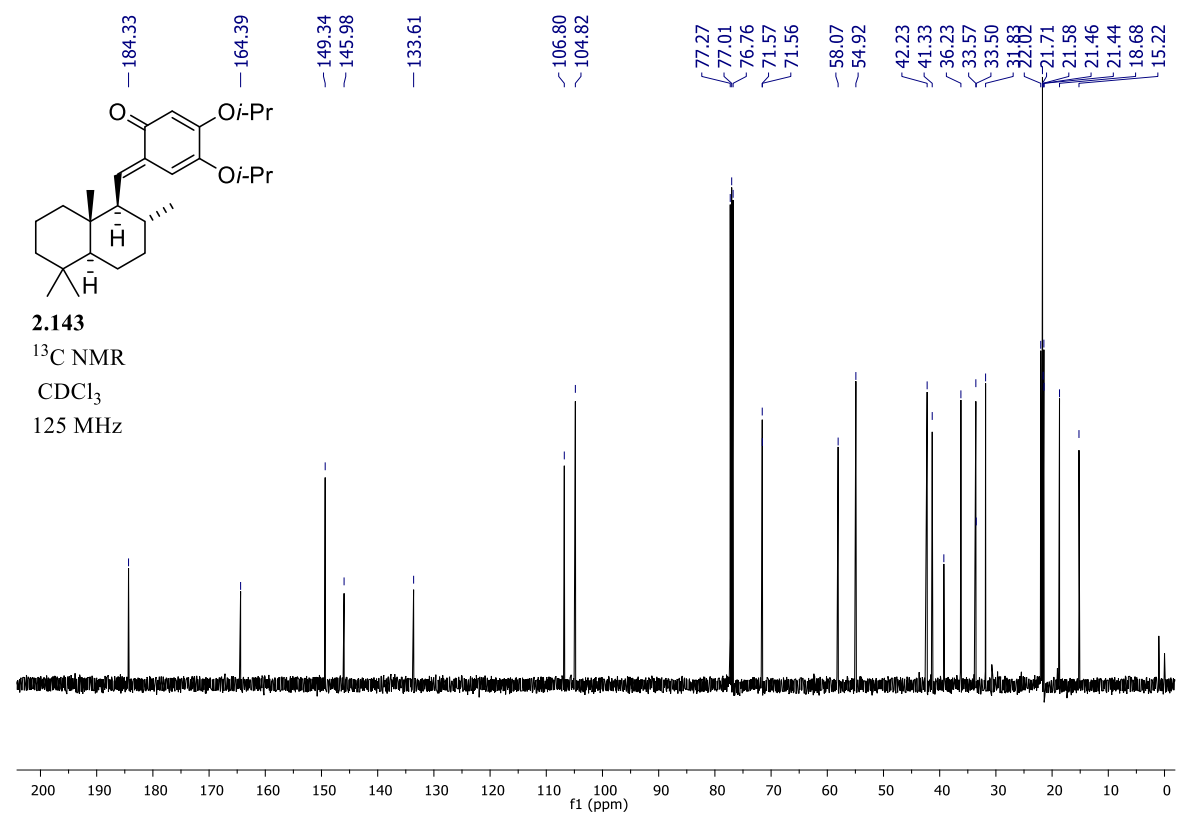
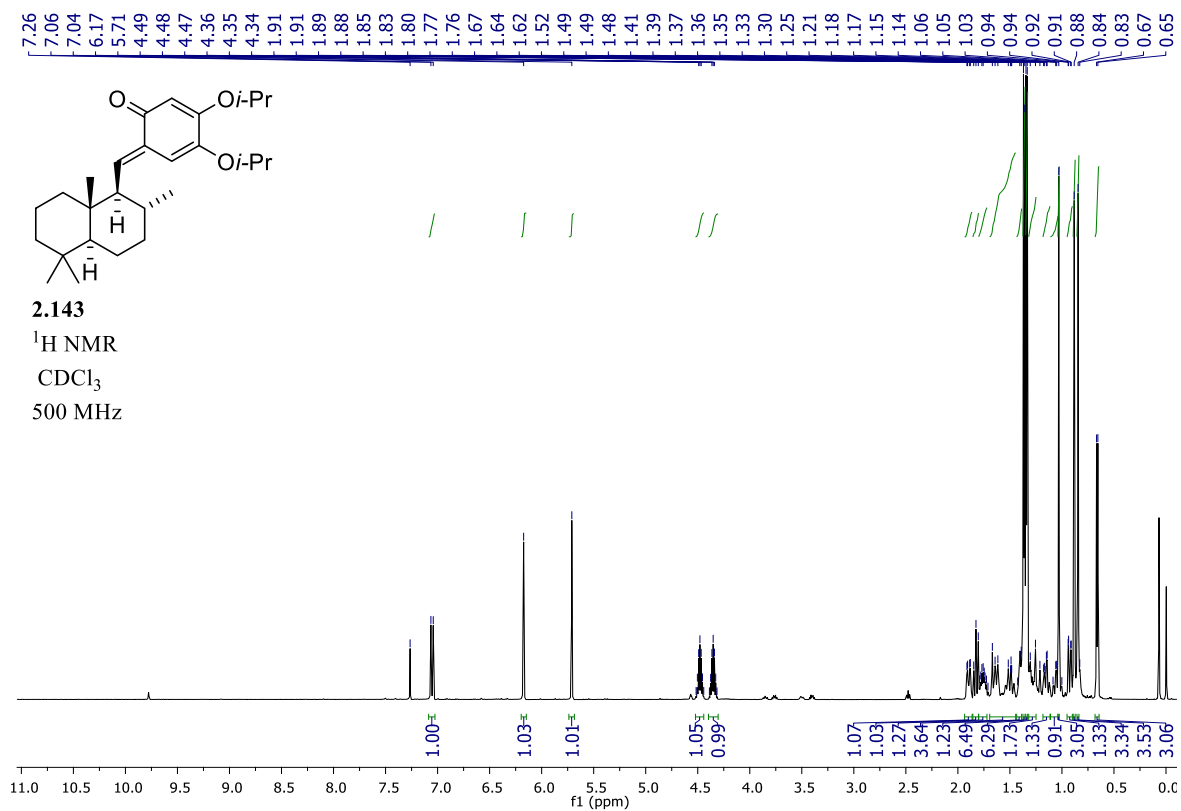
2.140

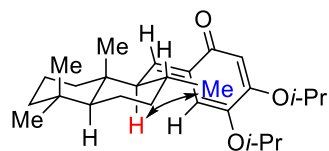
HSQC

CDCl₃

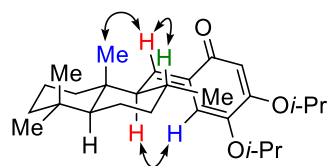
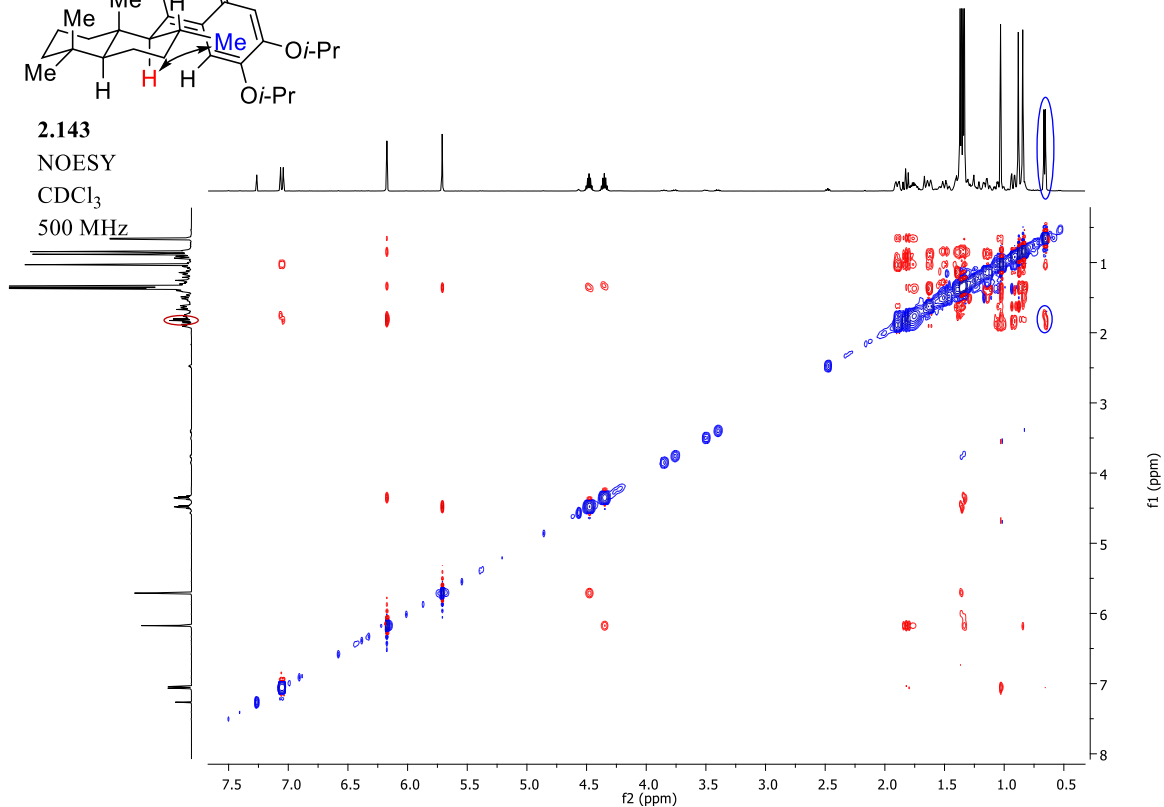
500 MHz



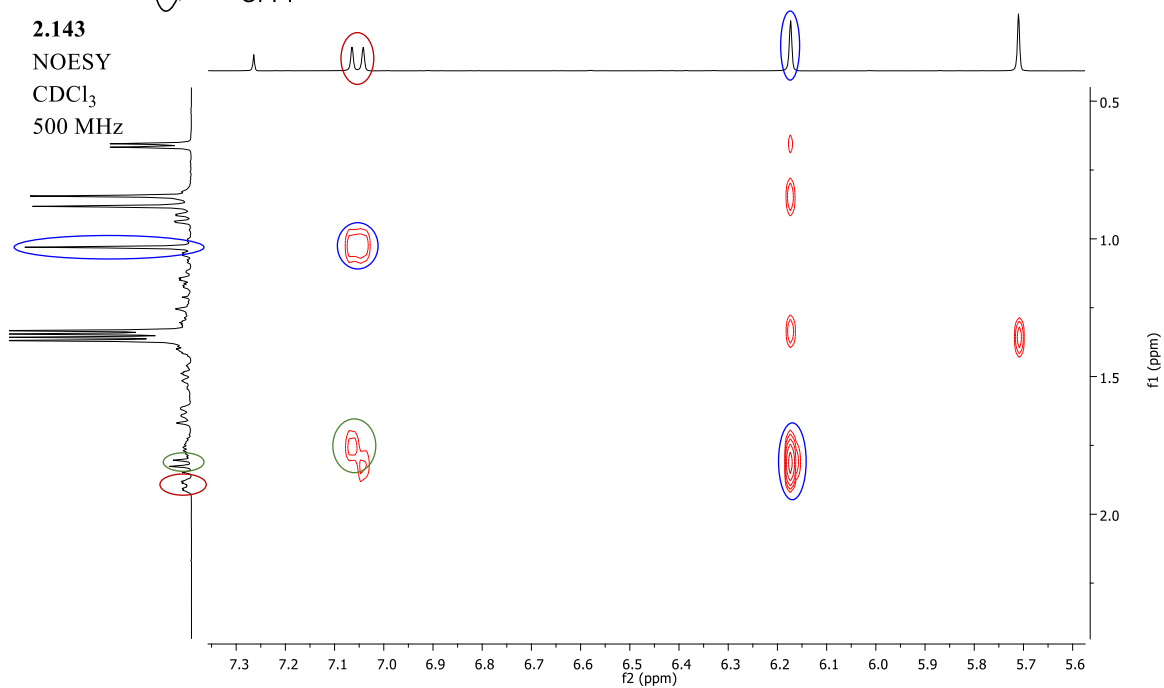


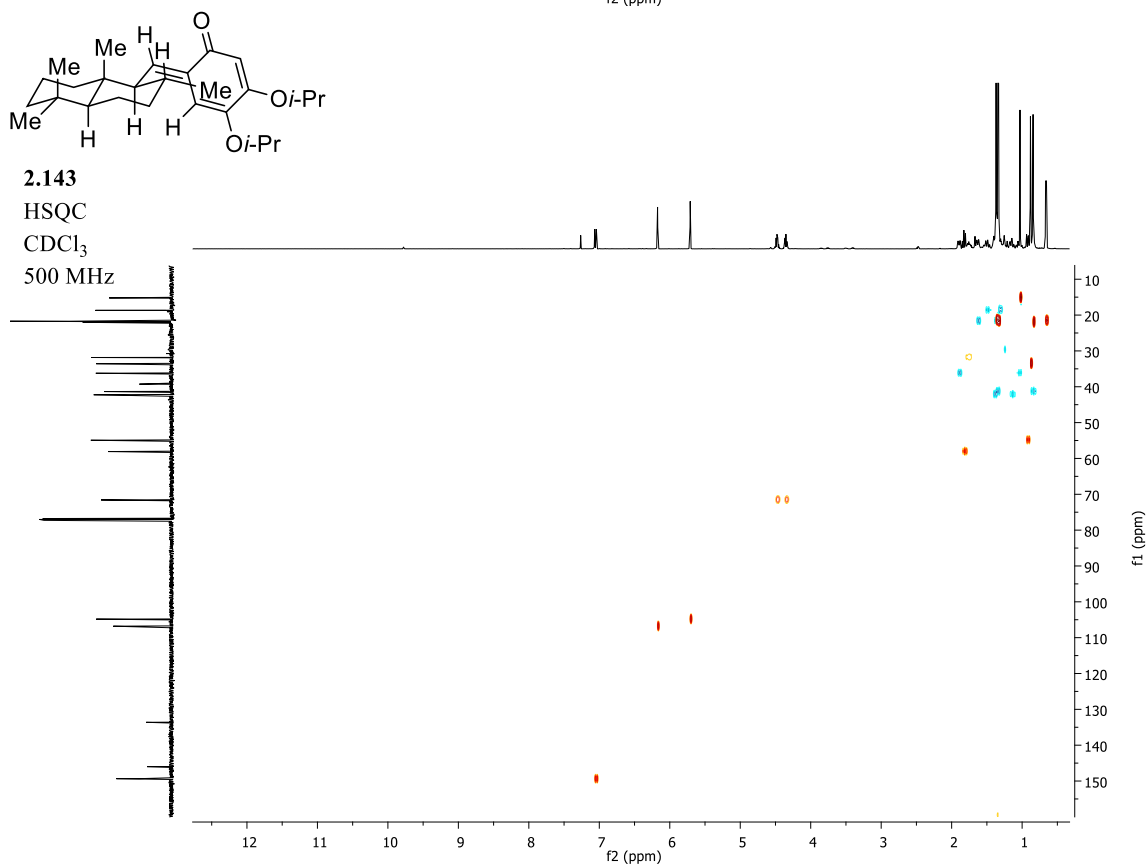
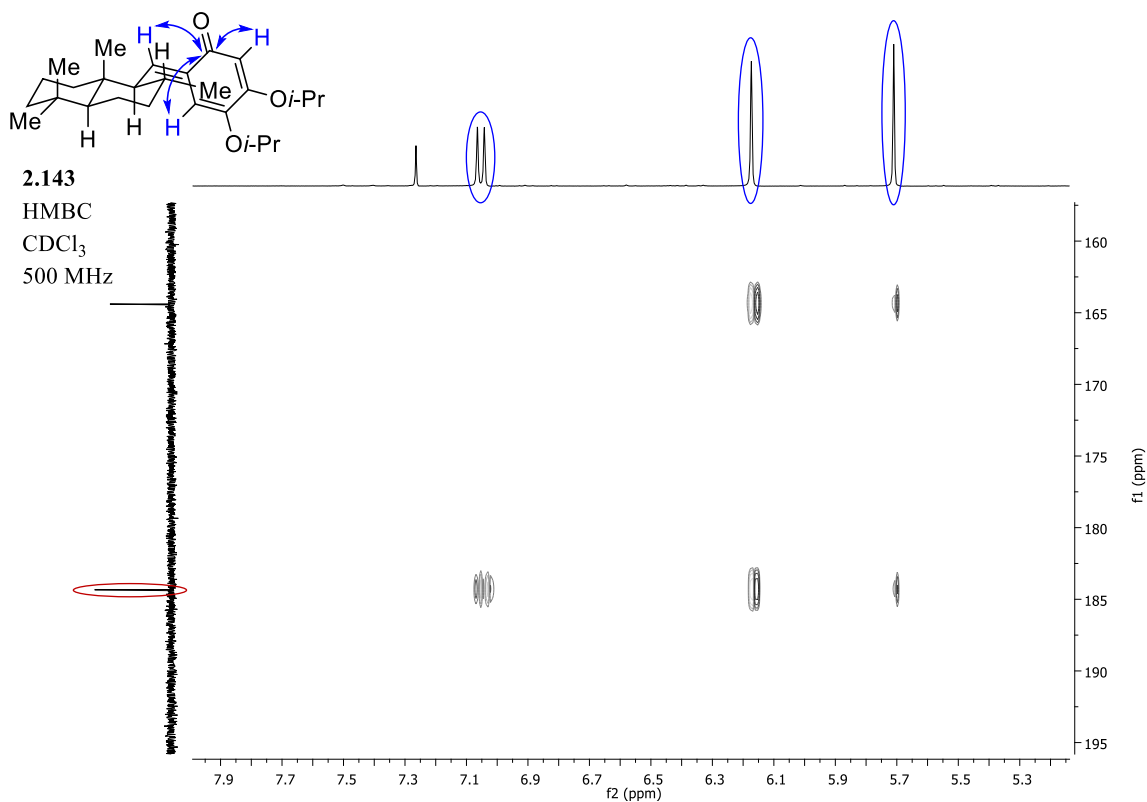


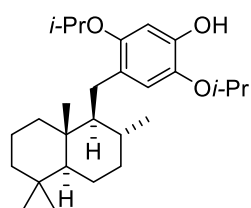
2.143
NOESY
CDCl₃
500 MHz



2.143
NOESY
CDCl₃
500 MHz





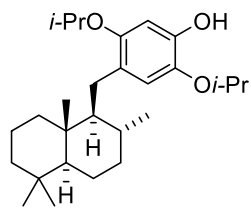
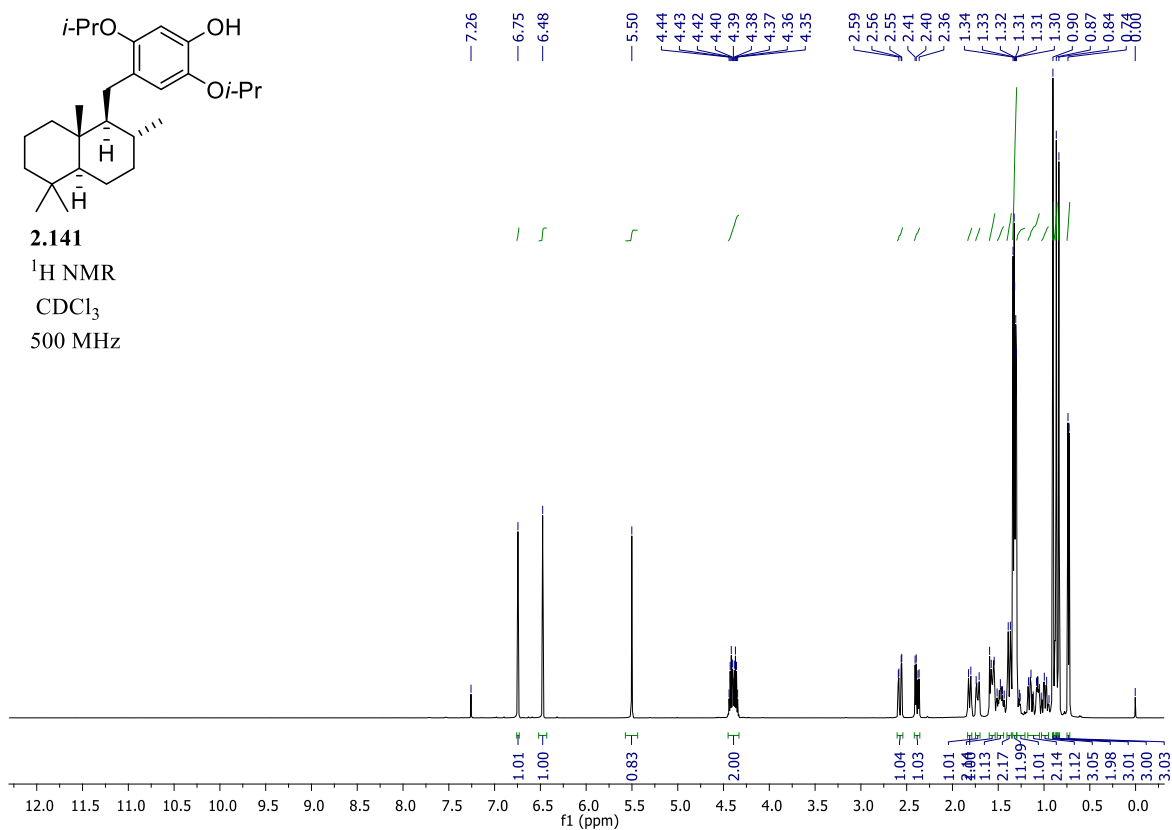


2.141

¹H NMR

CDCl₃

500 MHz

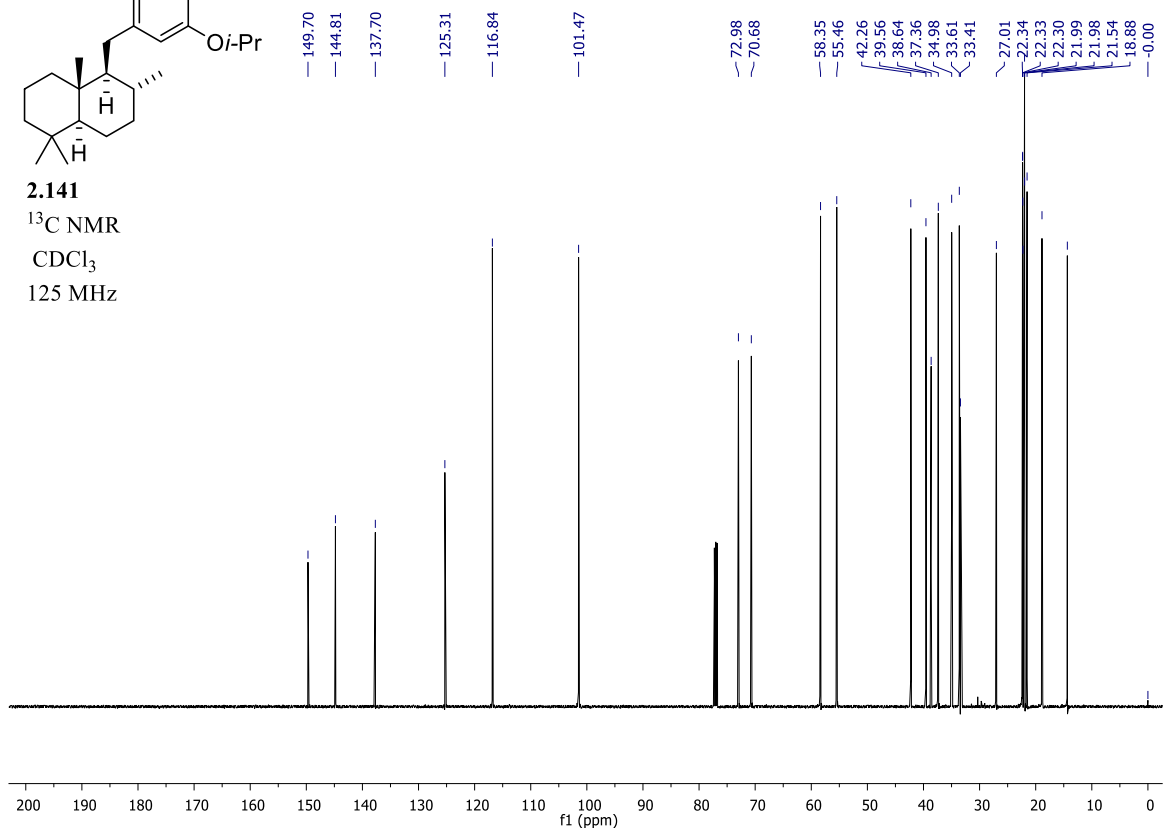


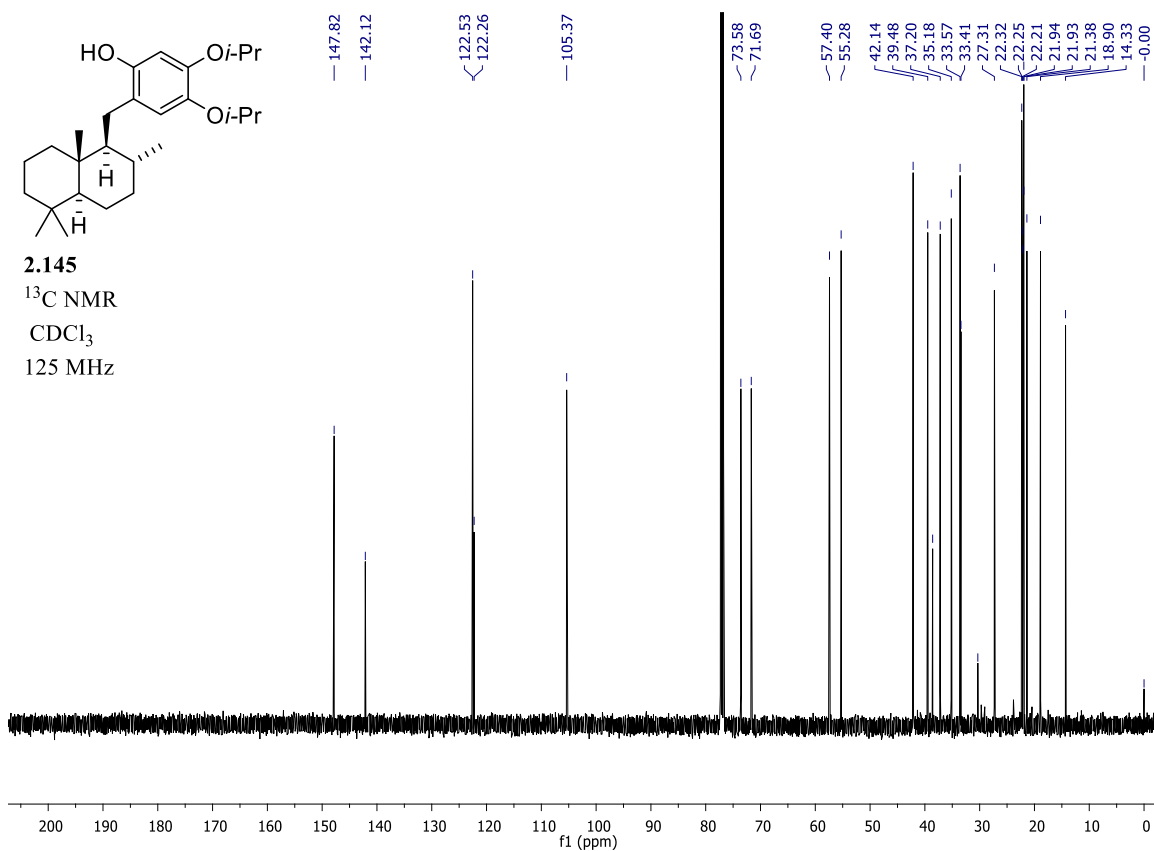
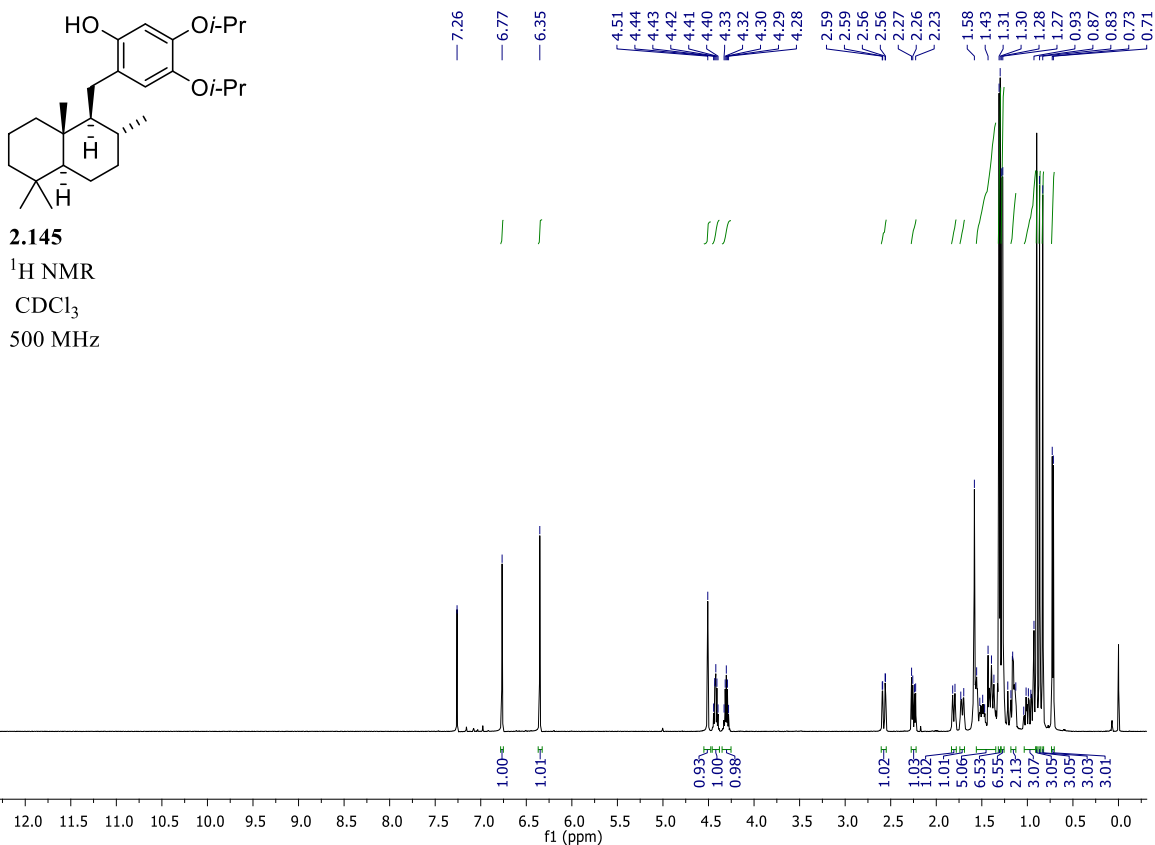
2.141

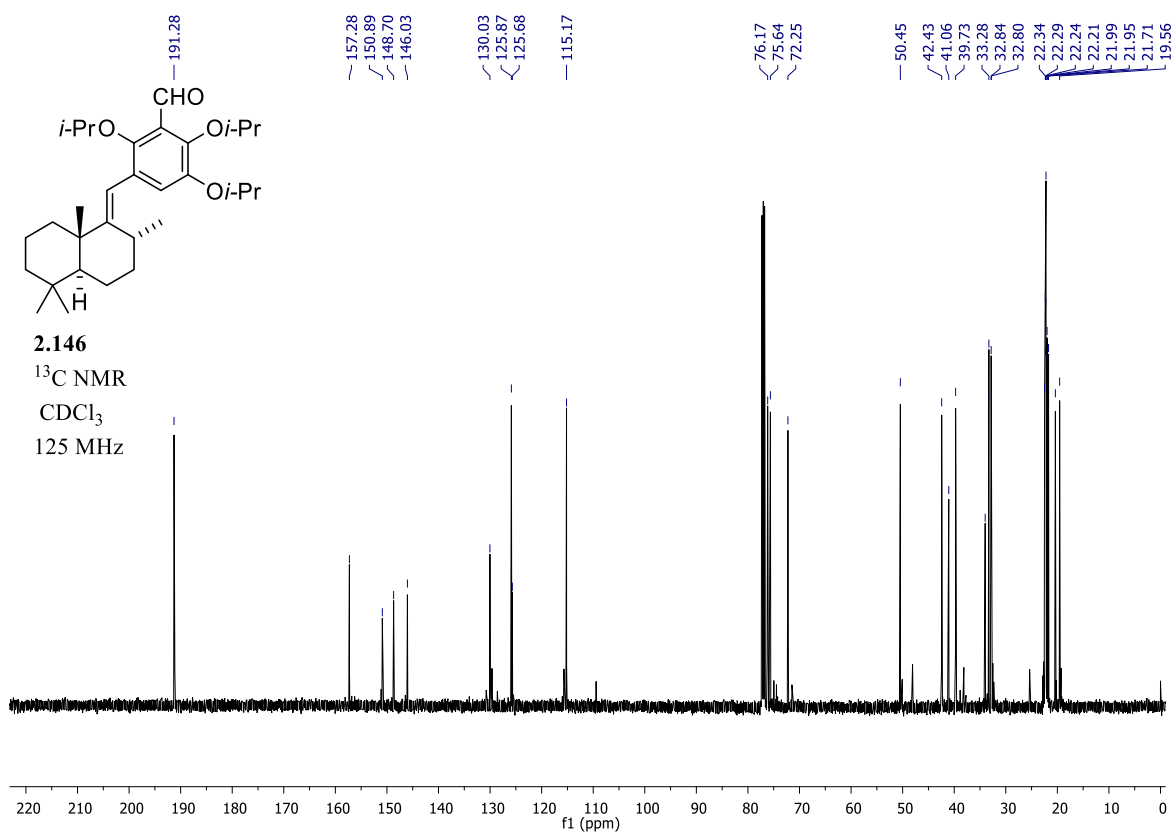
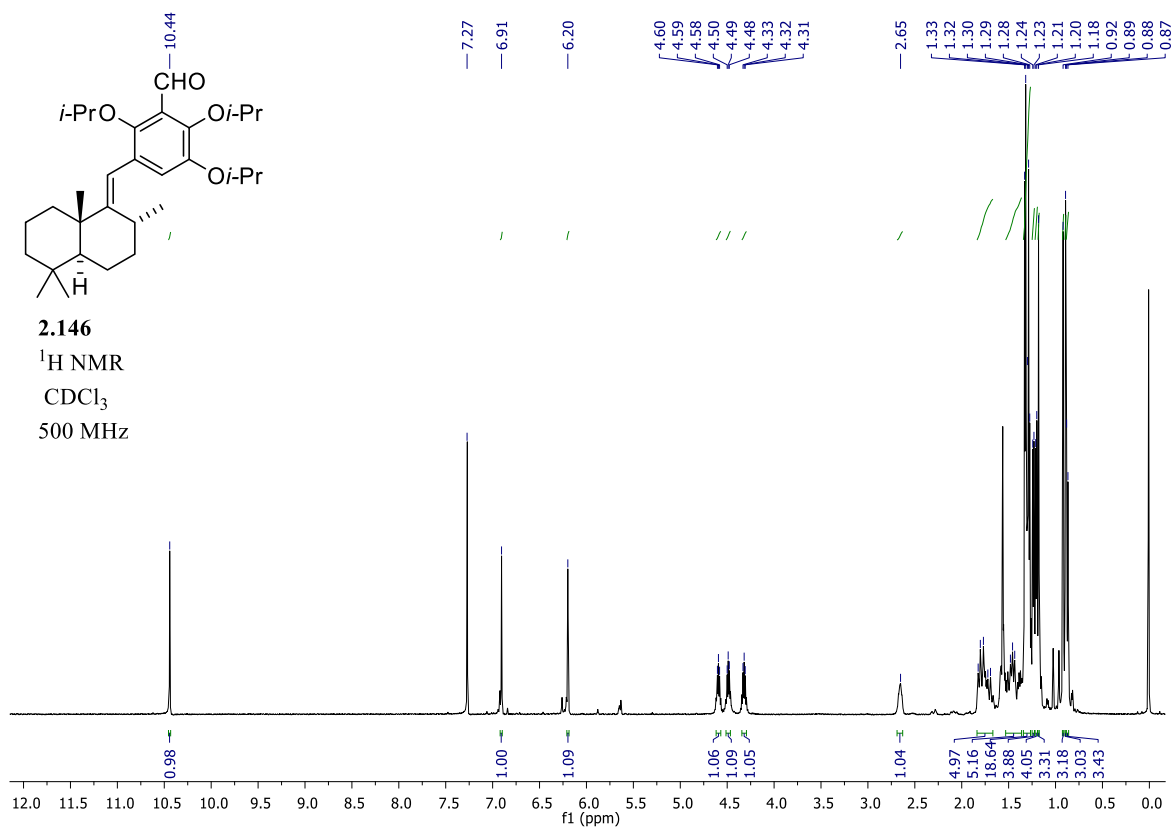
¹³C NMR

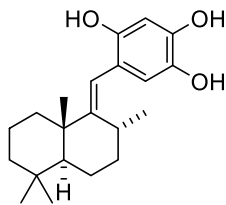
CDCl₃

125 MHz

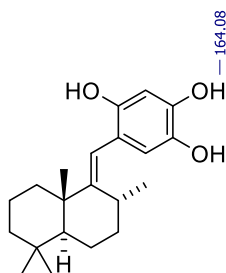
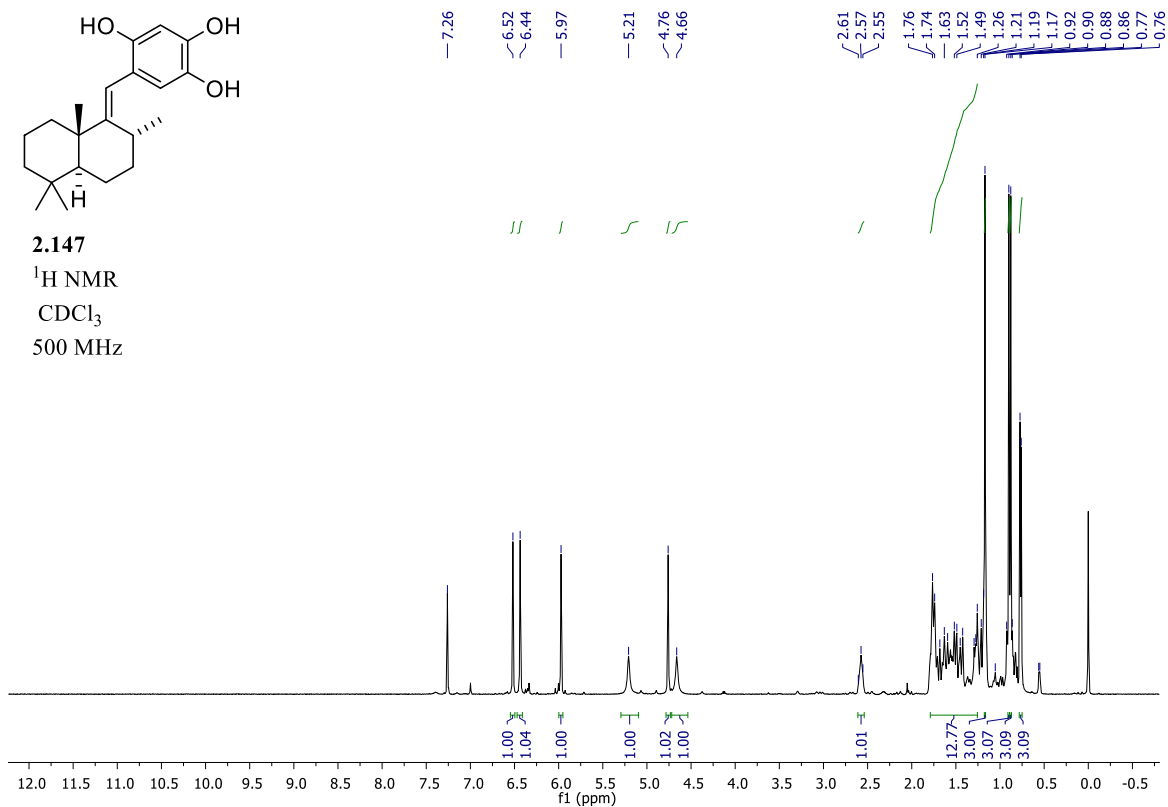




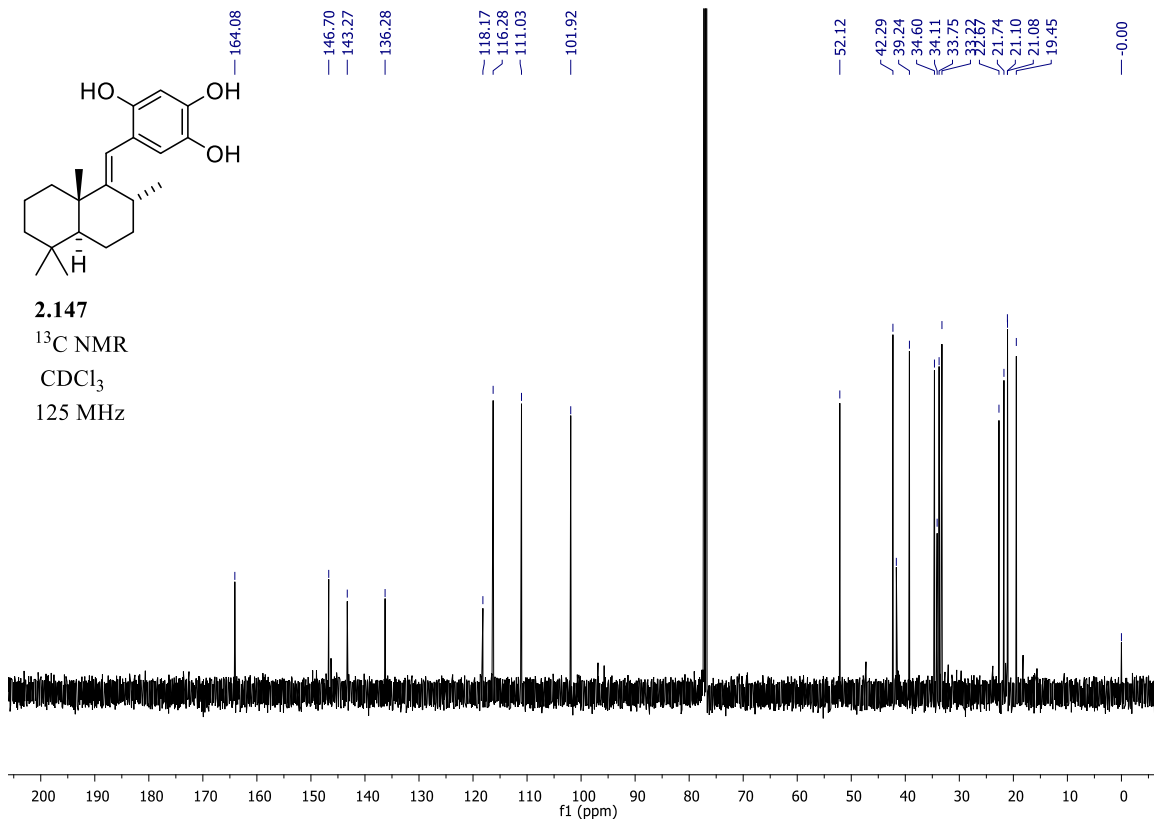


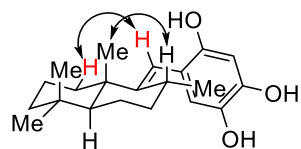


2.147
 ^1H NMR
 CDCl_3
 500 MHz

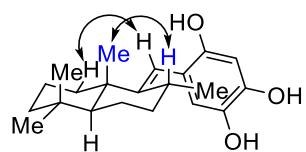
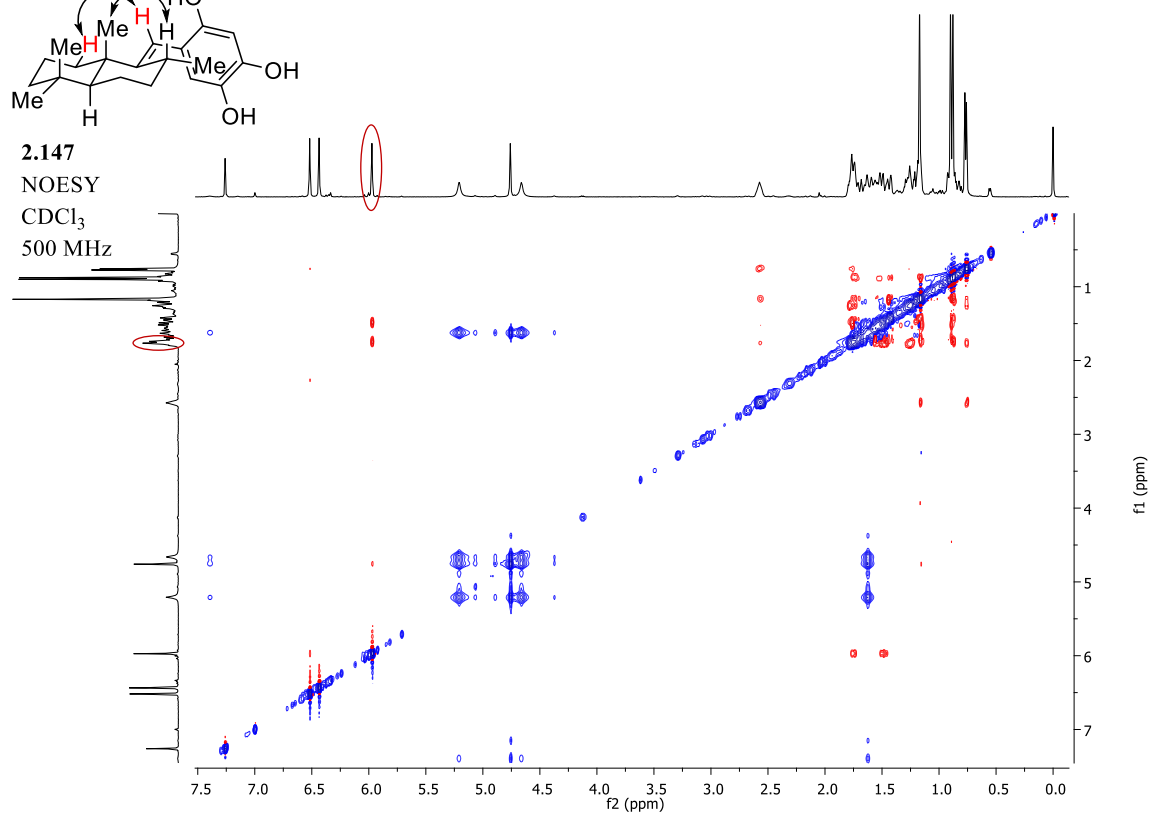


2.147
 ^{13}C NMR
 CDCl_3
 125 MHz

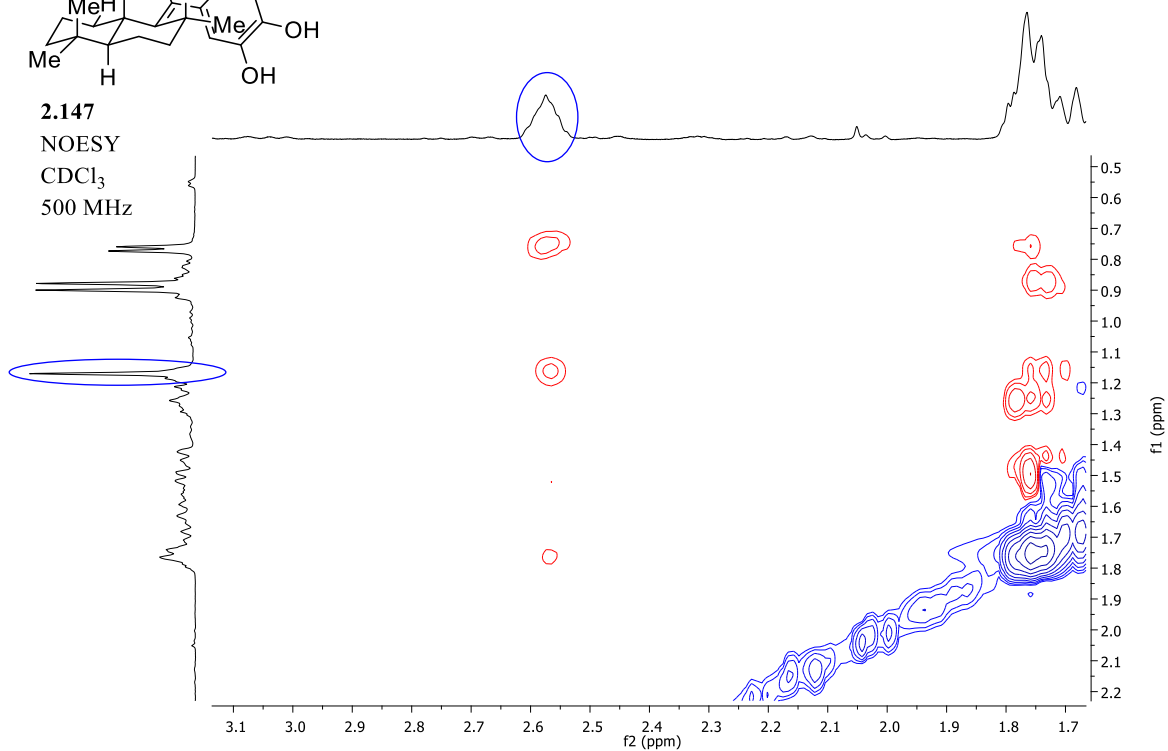


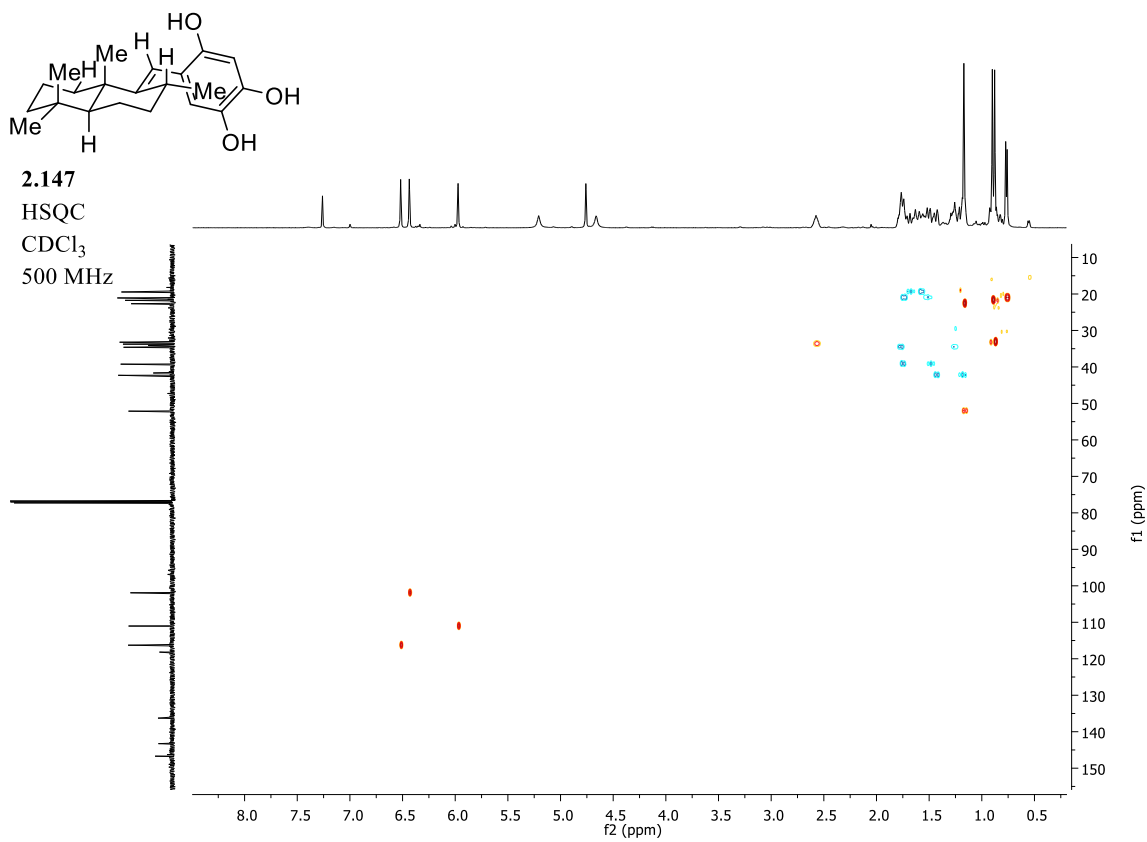
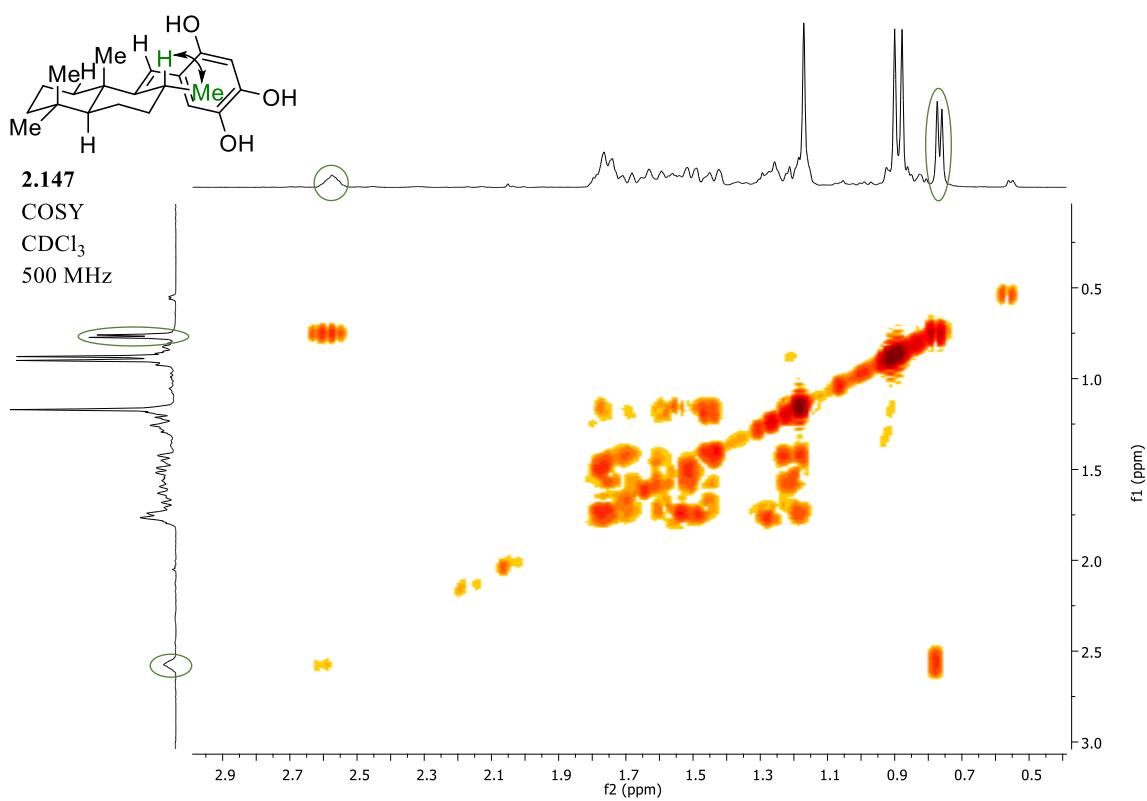


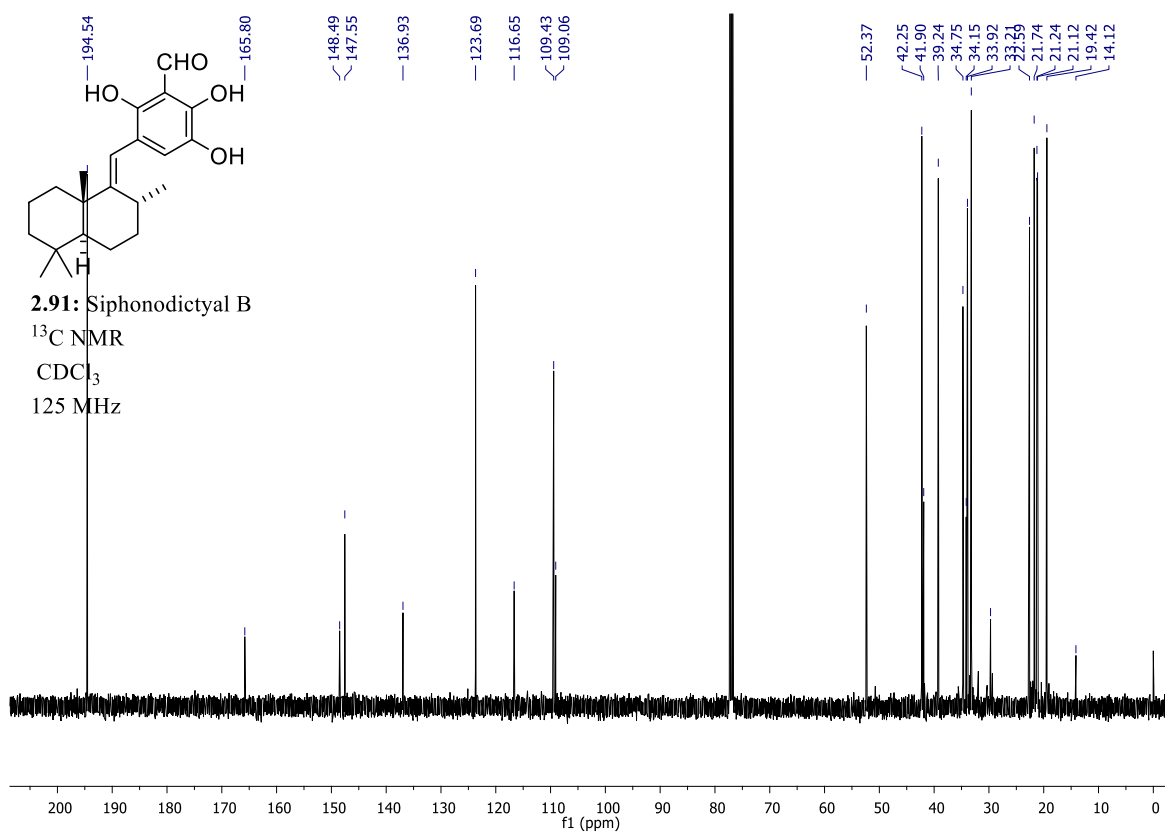
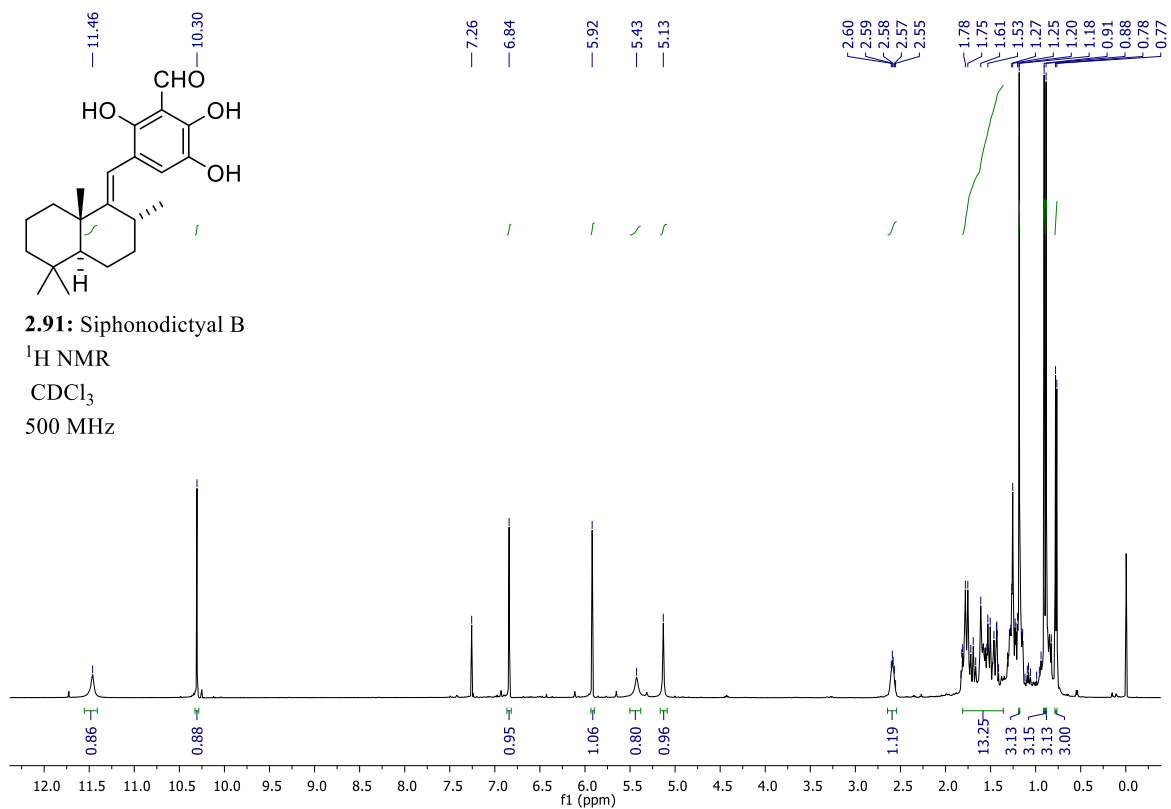
2.147
NOESY
CDCl₃
500 MHz

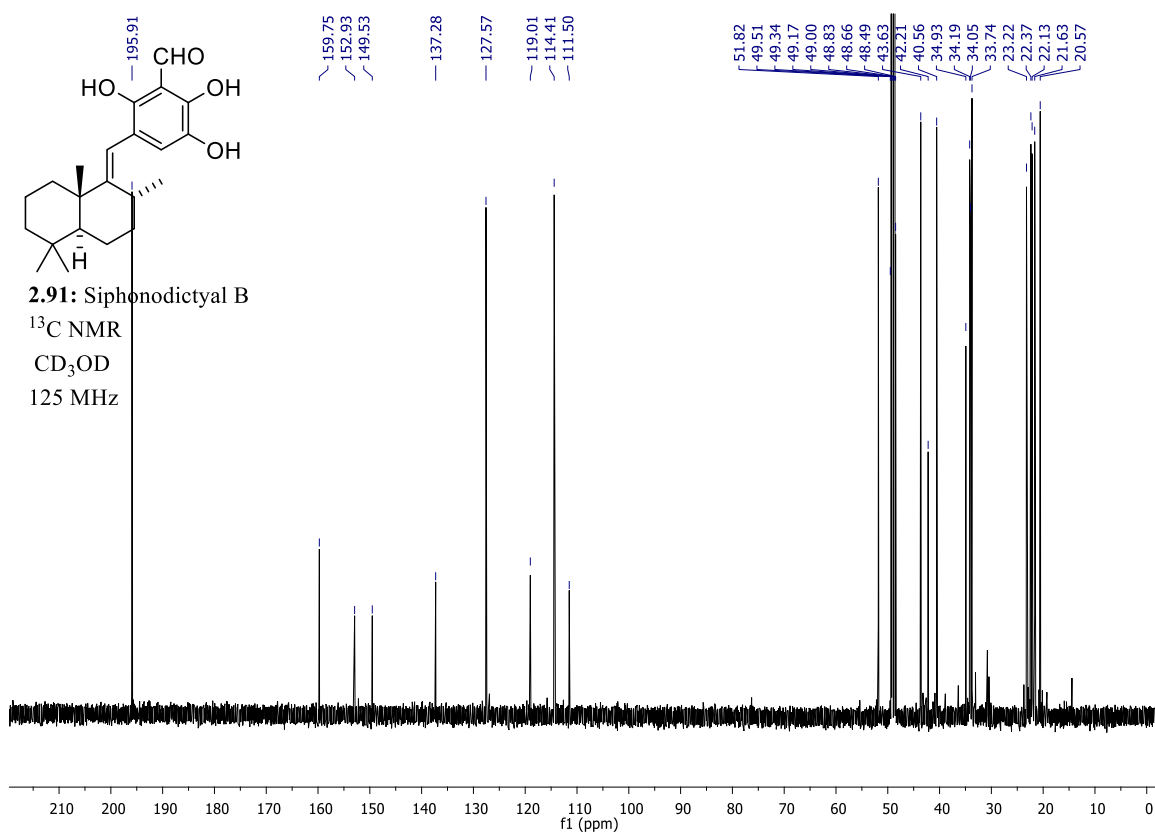
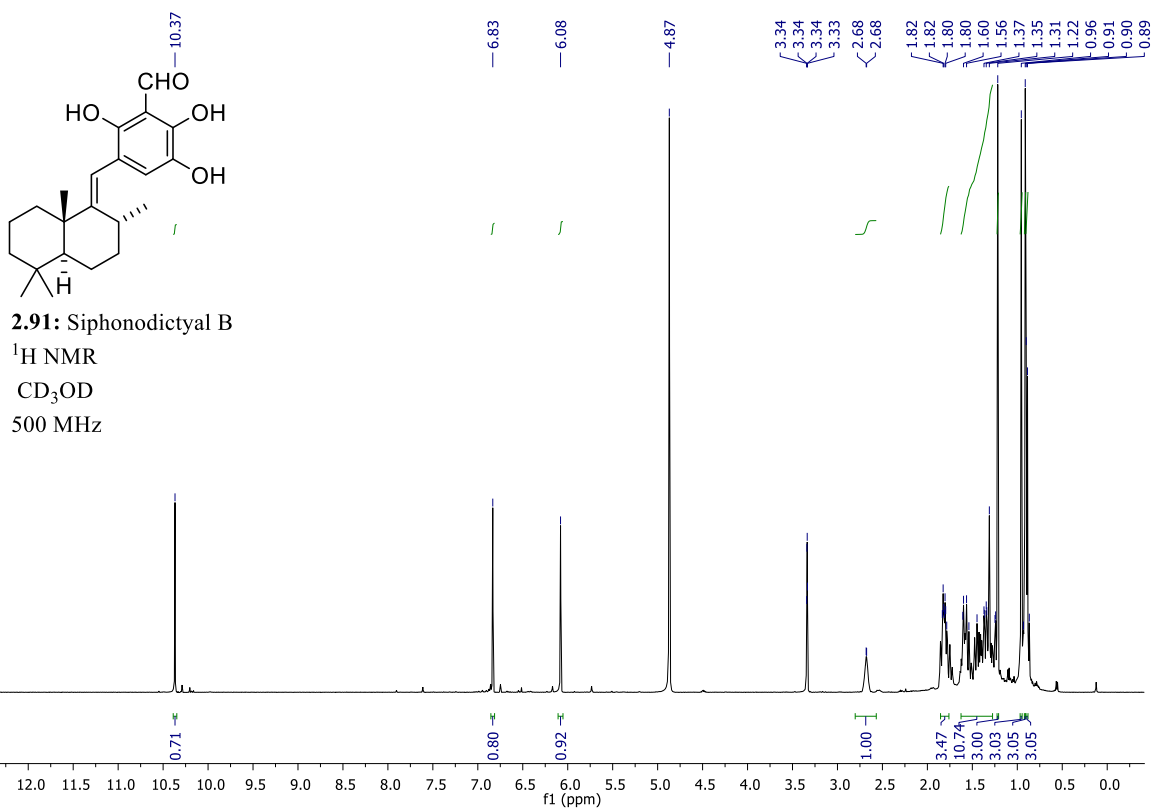


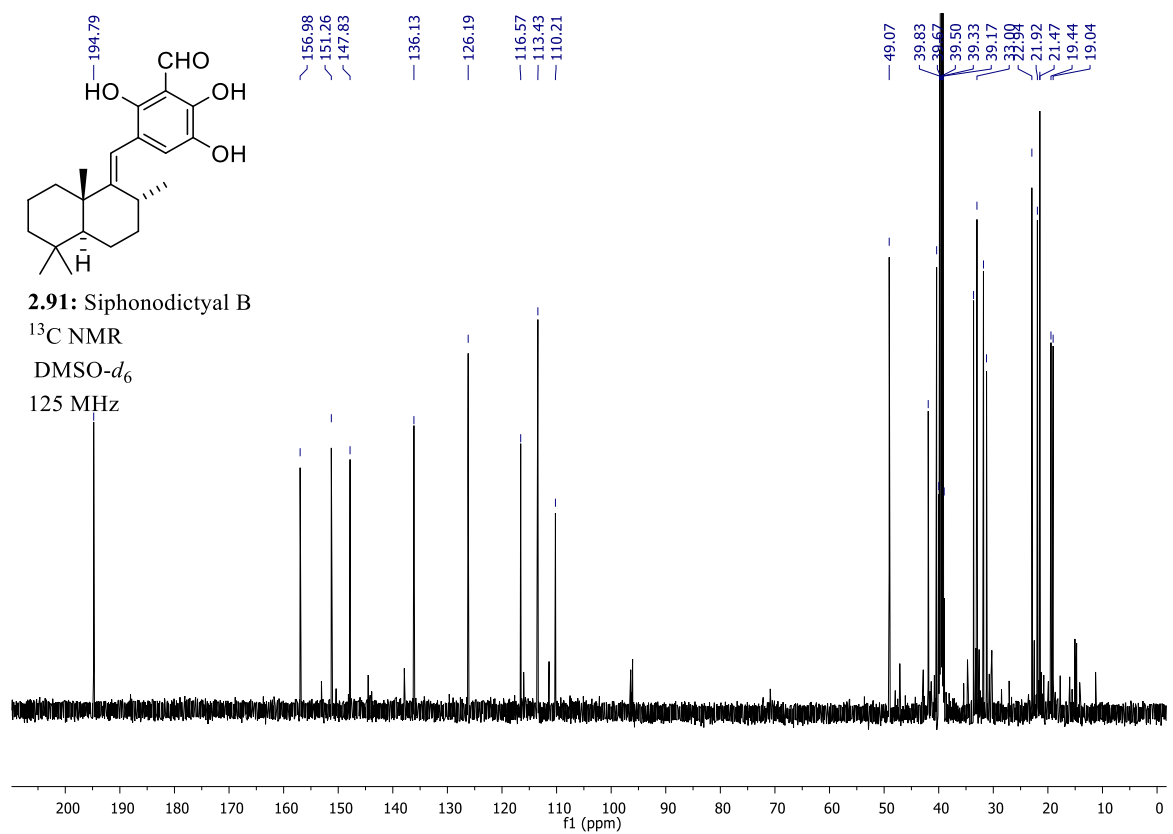
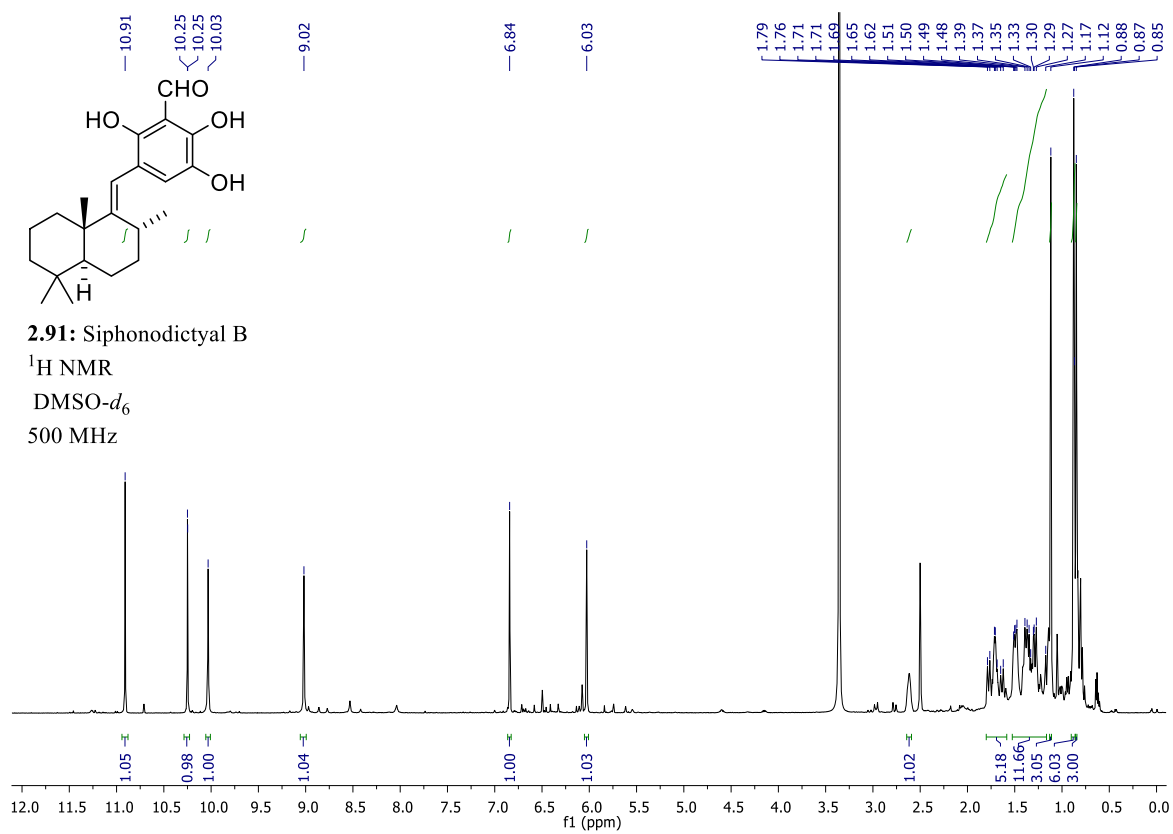
2.147
NOESY
CDCl₃
500 MHz

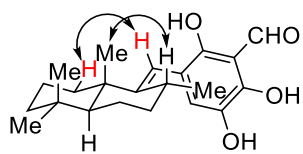




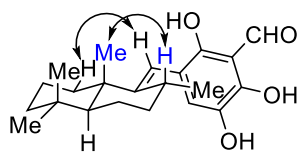
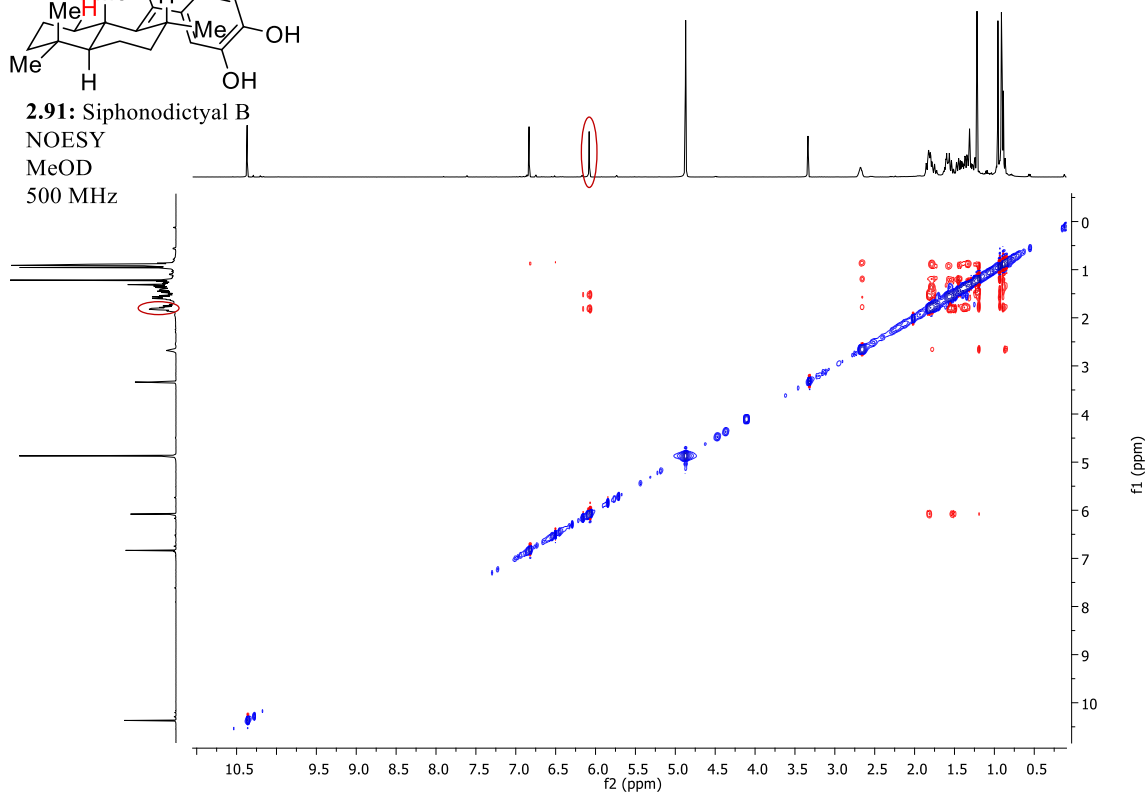




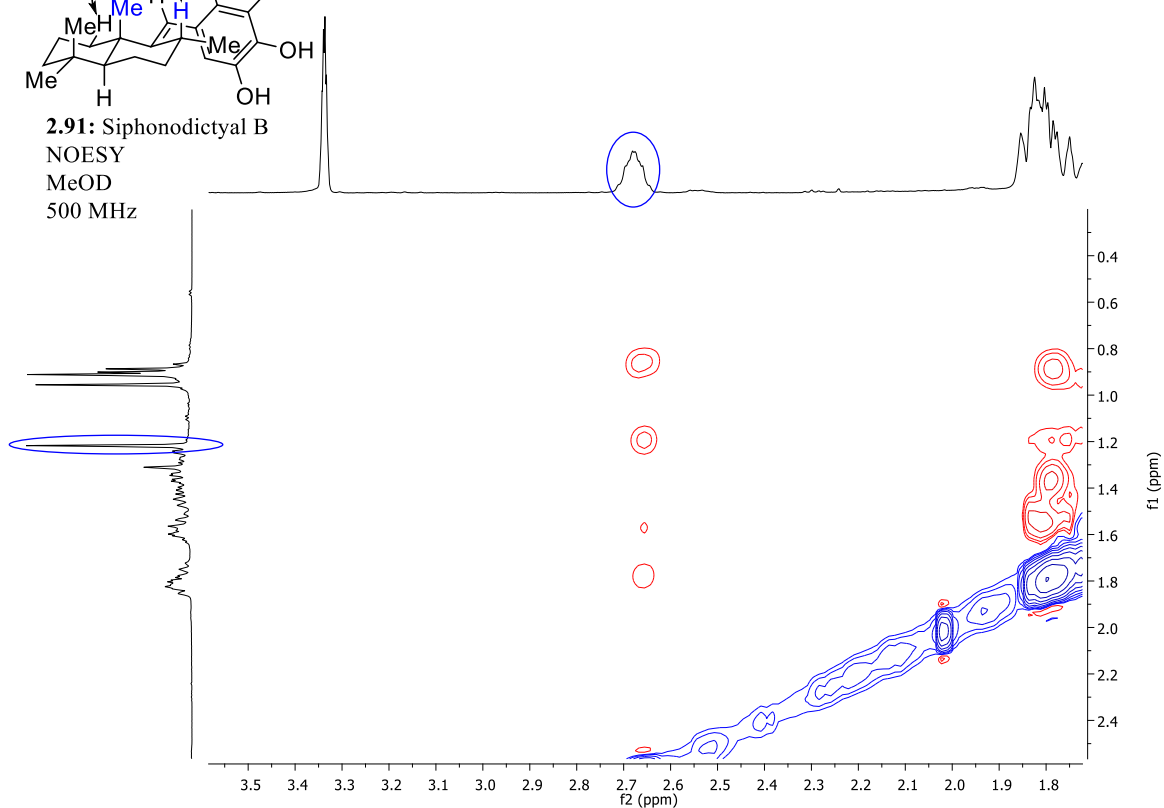


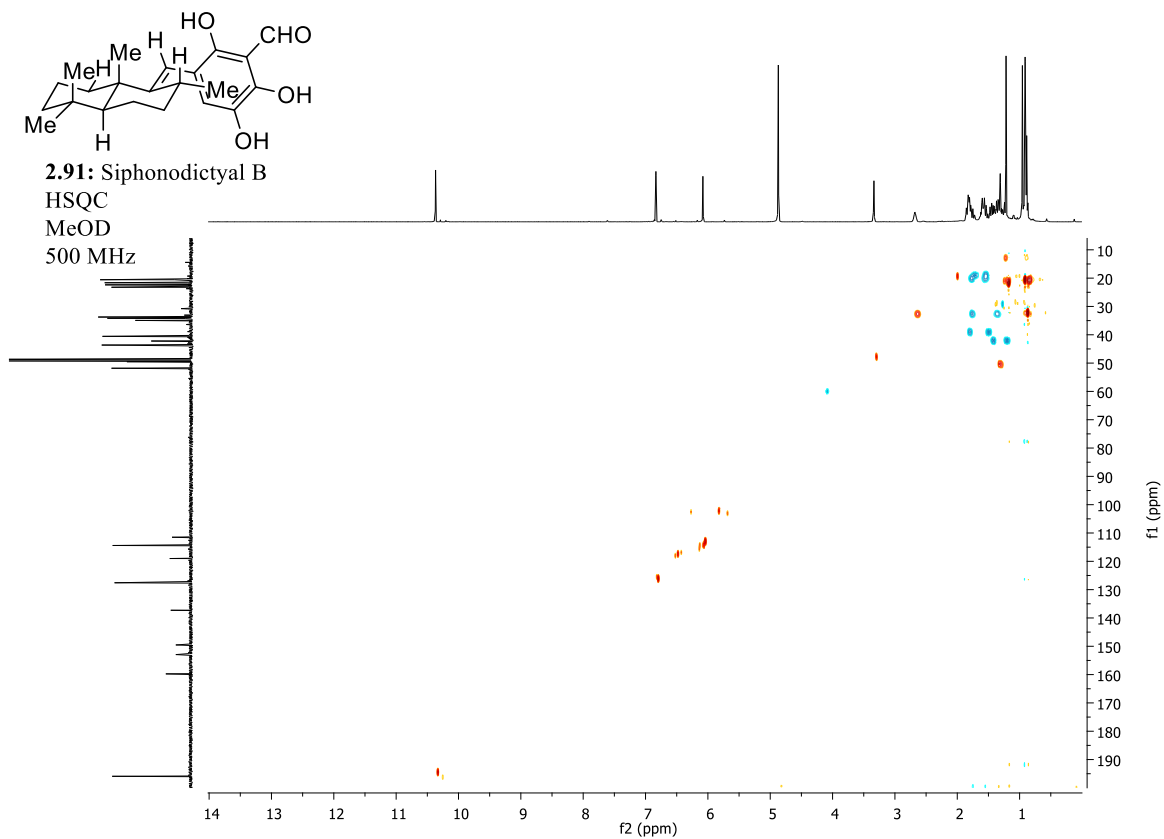
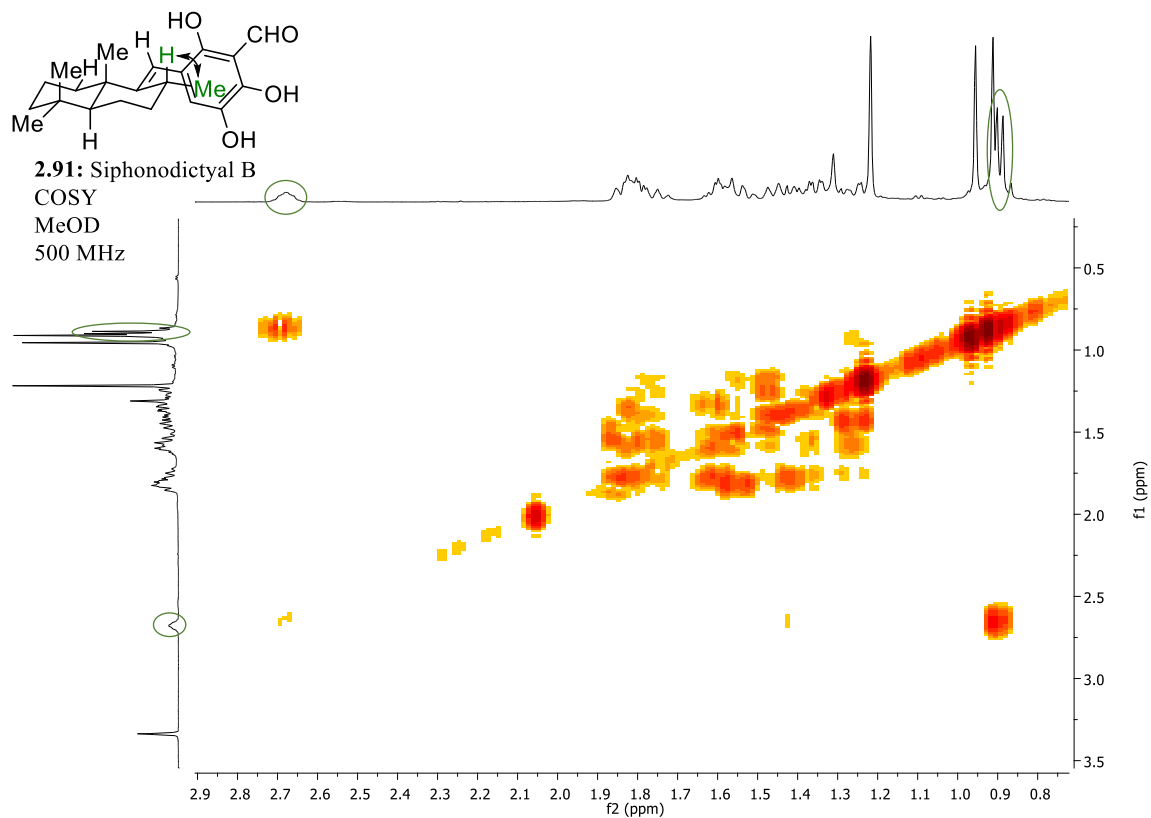


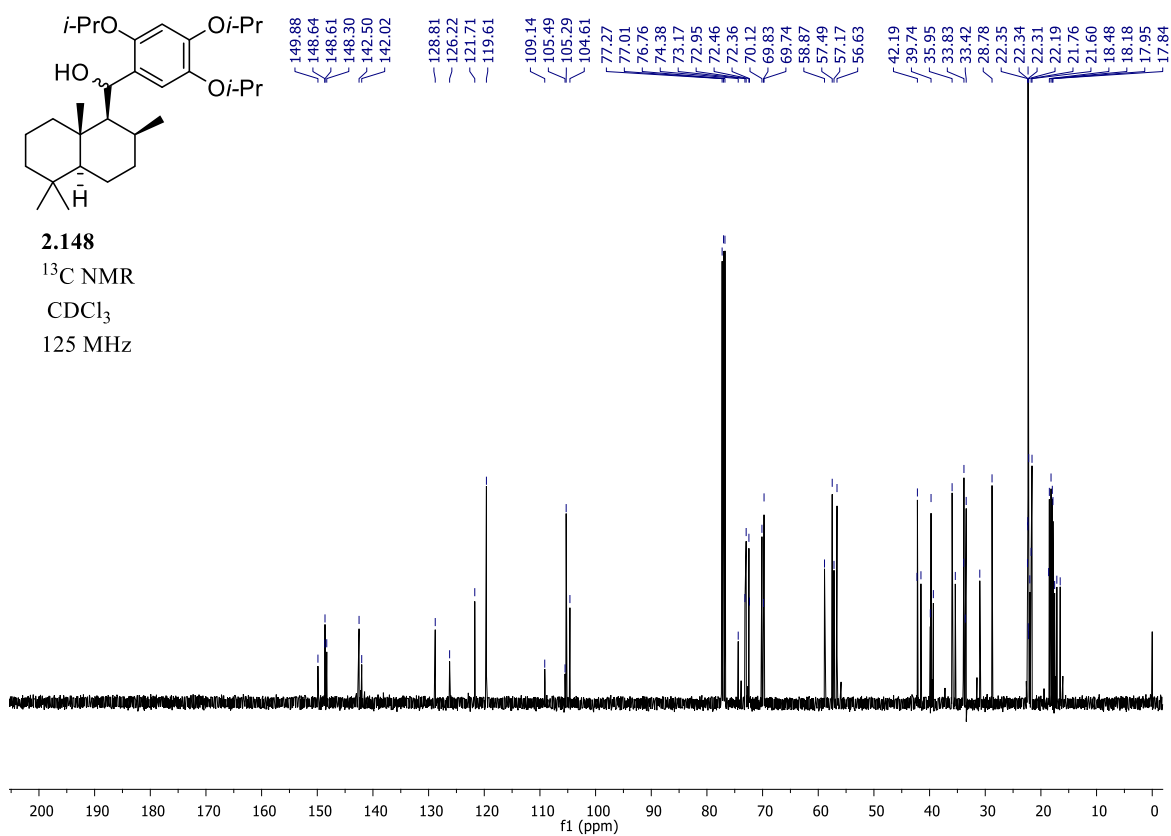
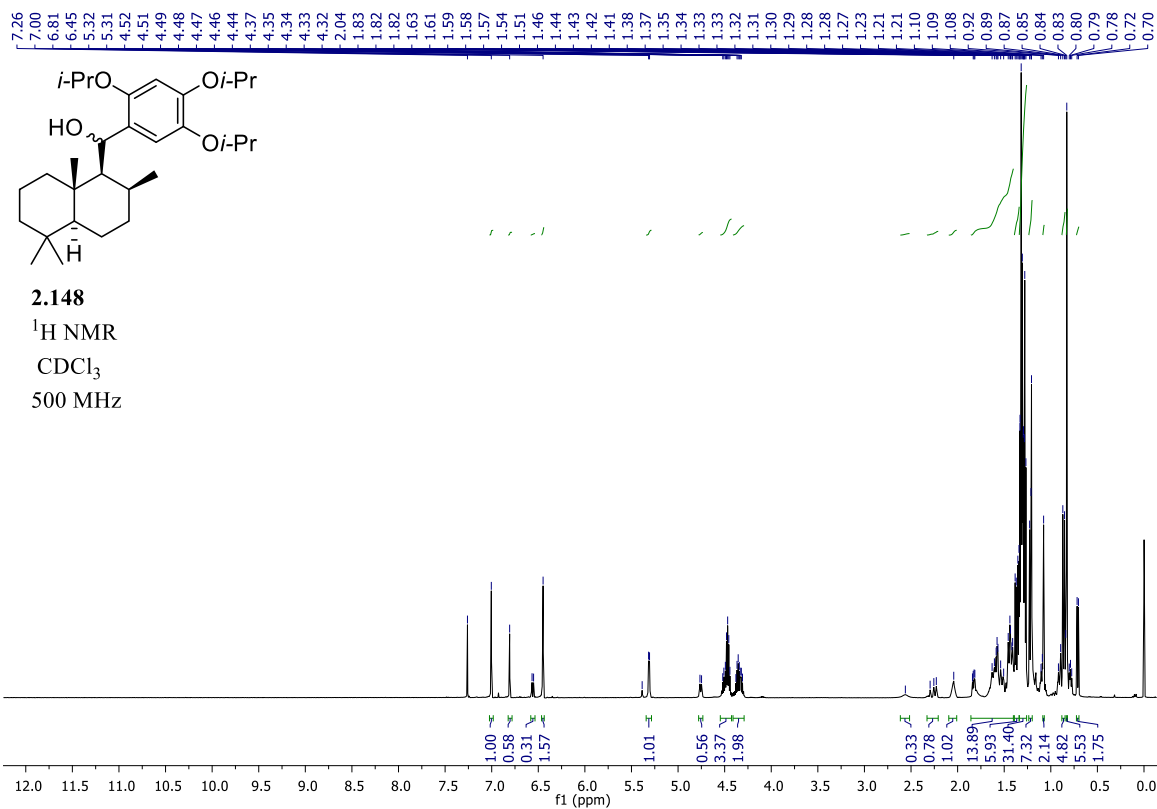
2.91: Siphonodictyal B
NOESY
MeOD
500 MHz

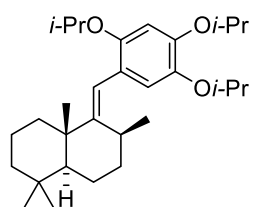


2.91: Siphonodictyal B
NOESY
MeOD
500 MHz

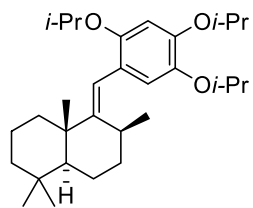
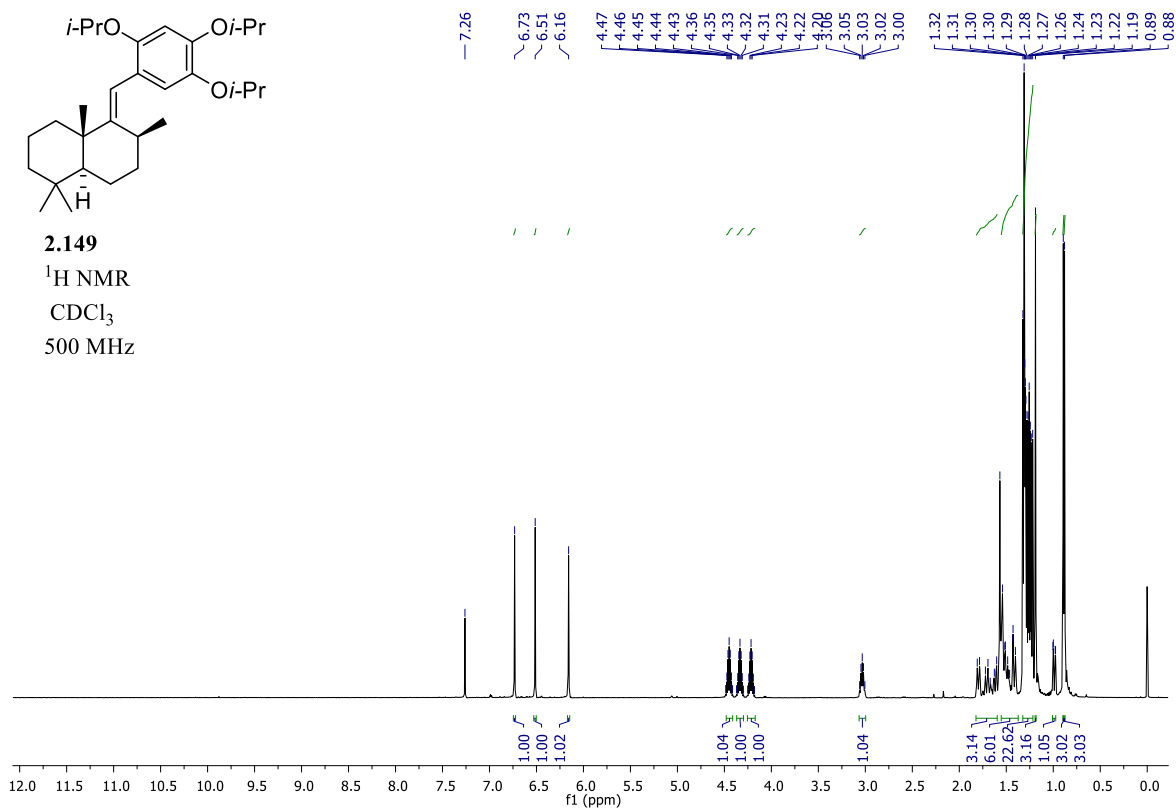




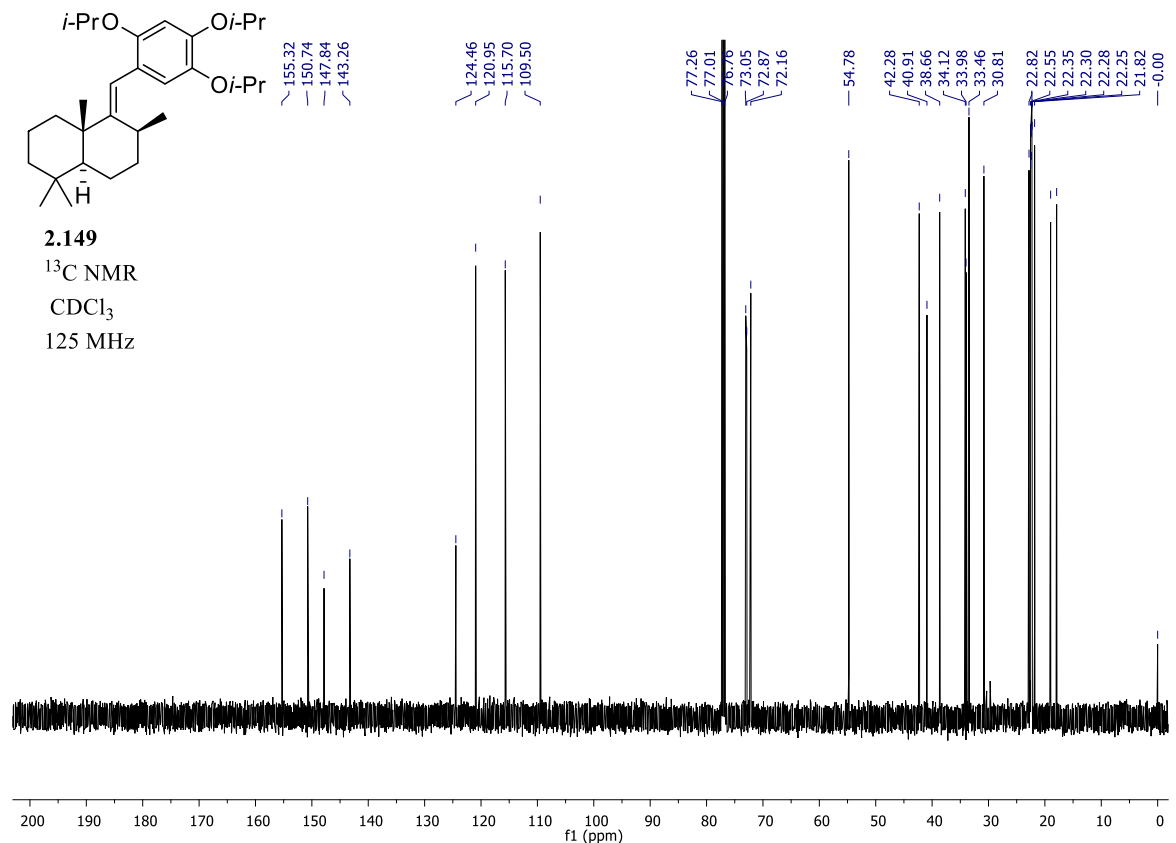


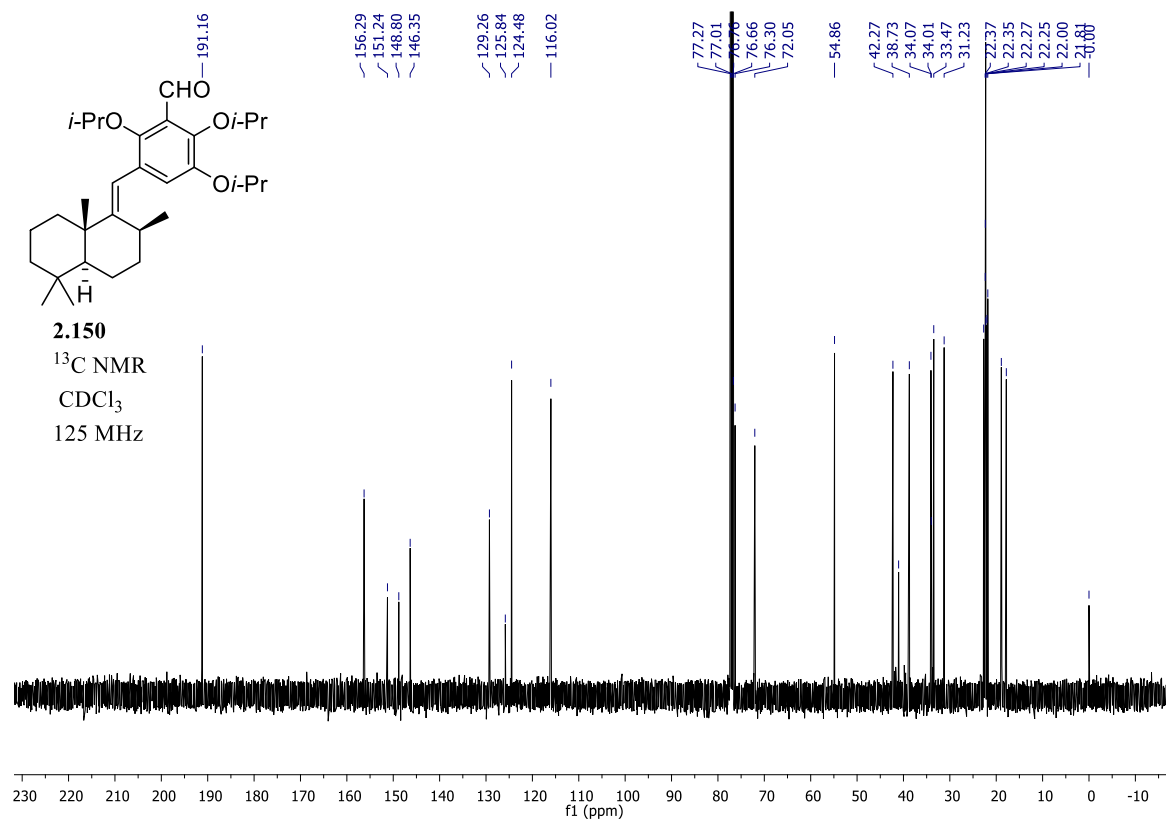
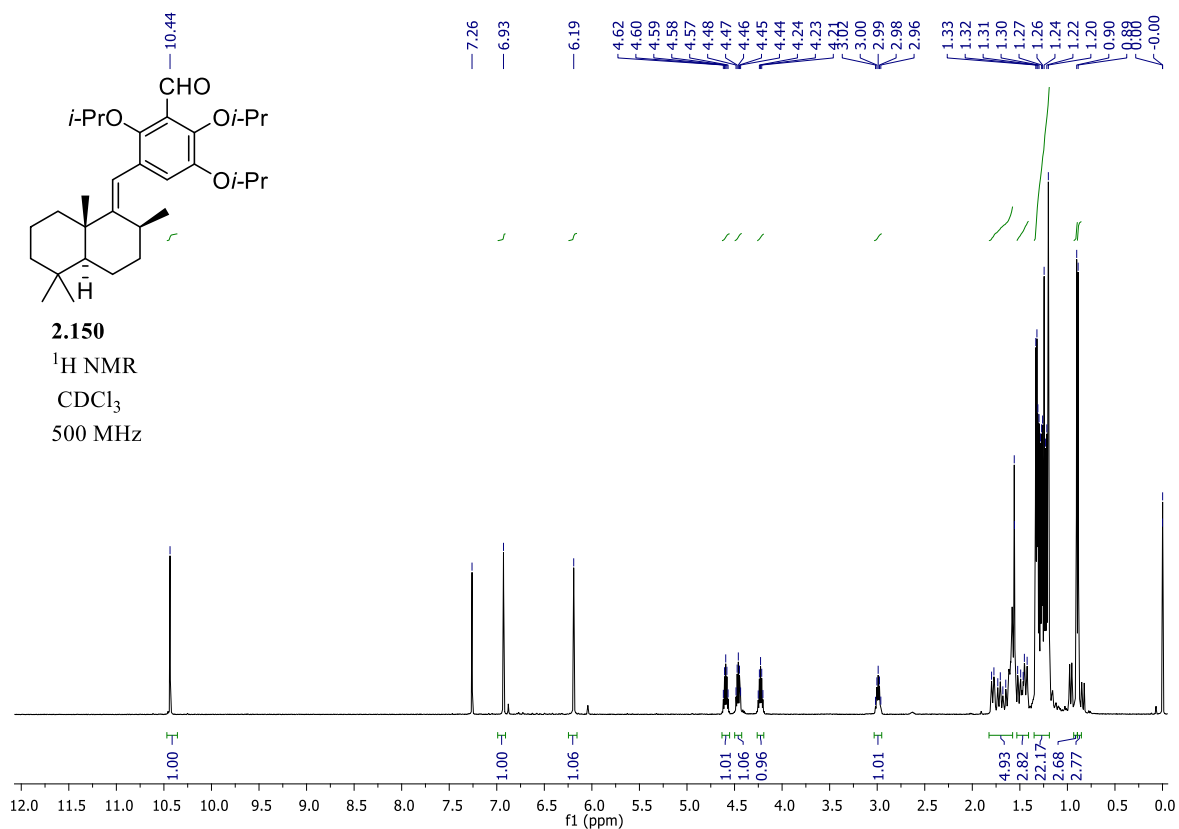


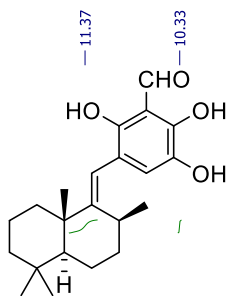
2.149
¹H NMR
 CDCl₃
 500 MHz



2.149
¹³C NMR
 CDCl₃
 125 MHz





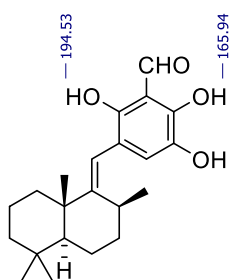
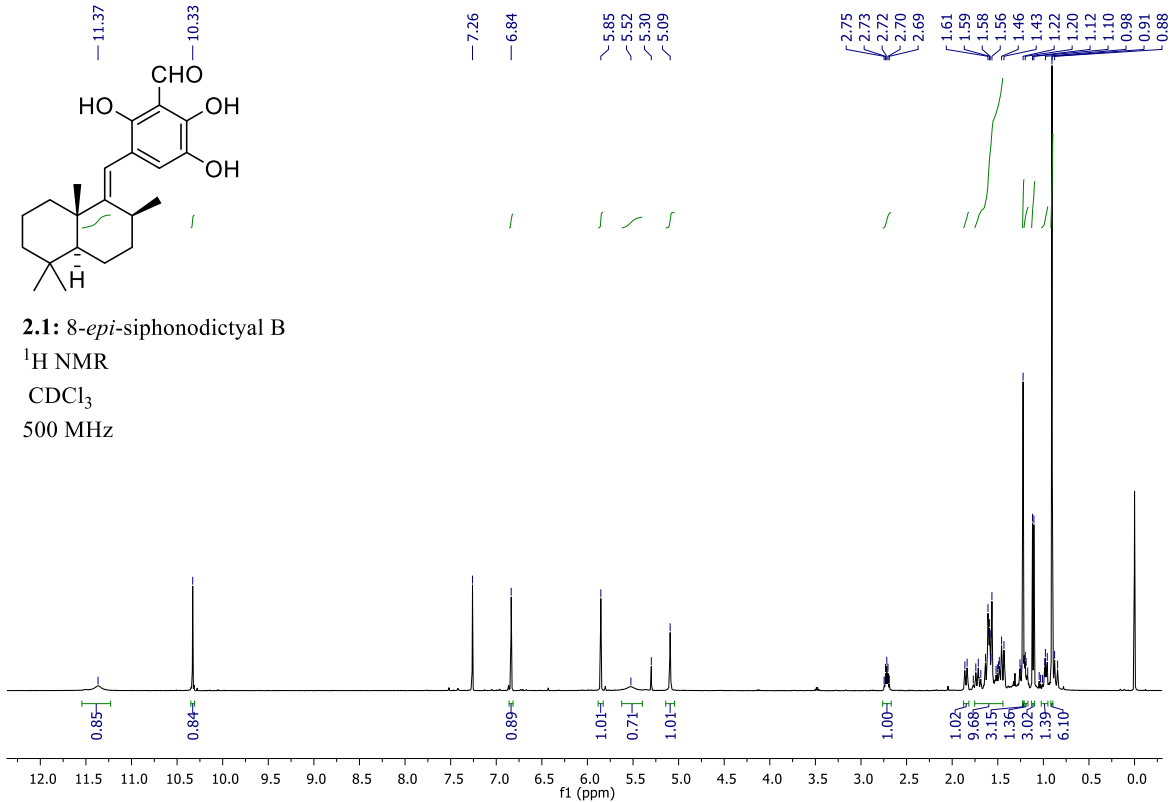


2.1: 8-*epi*-siphonodictyal B

^1H NMR

CDCl_3

500 MHz

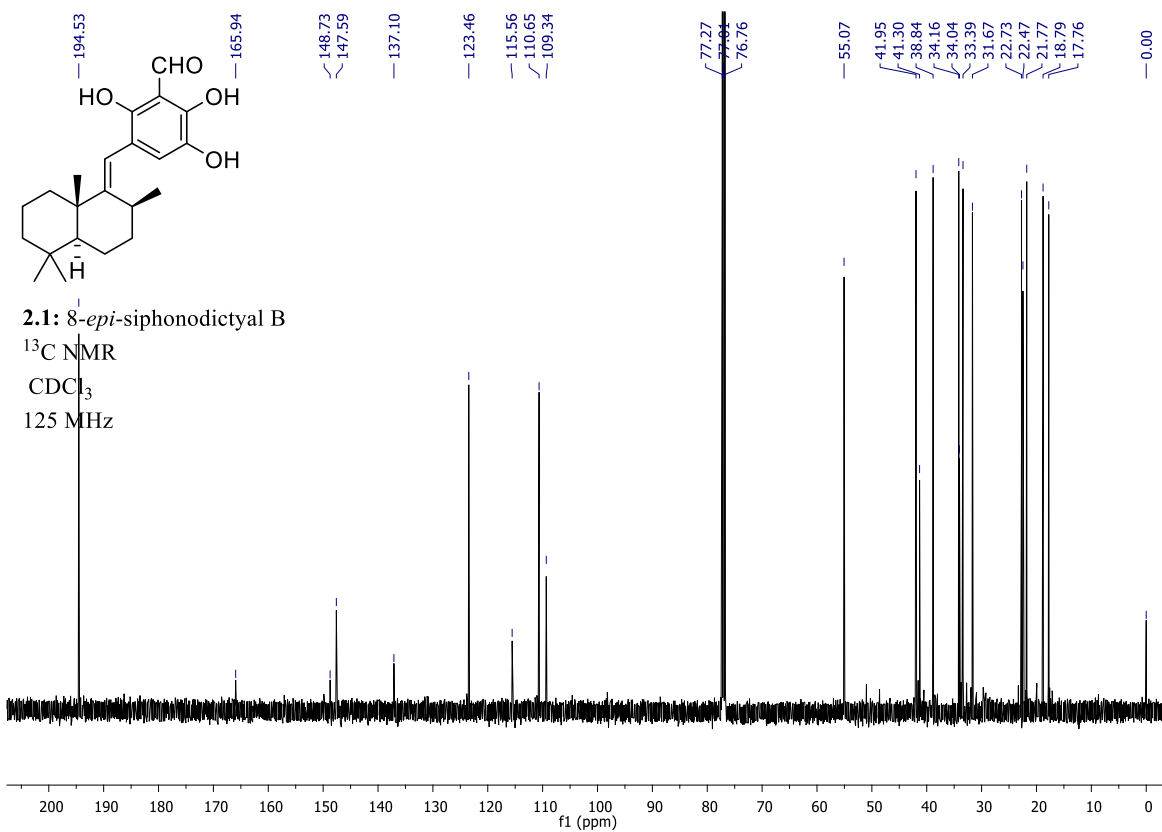


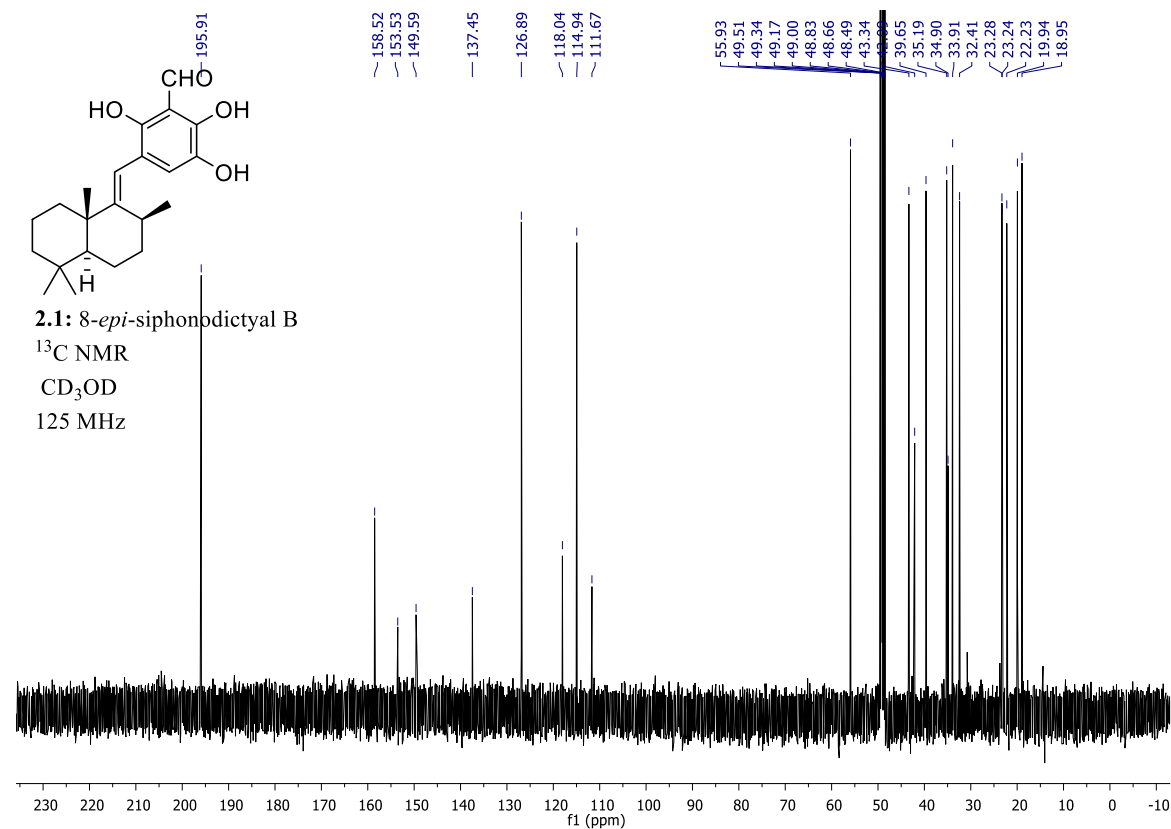
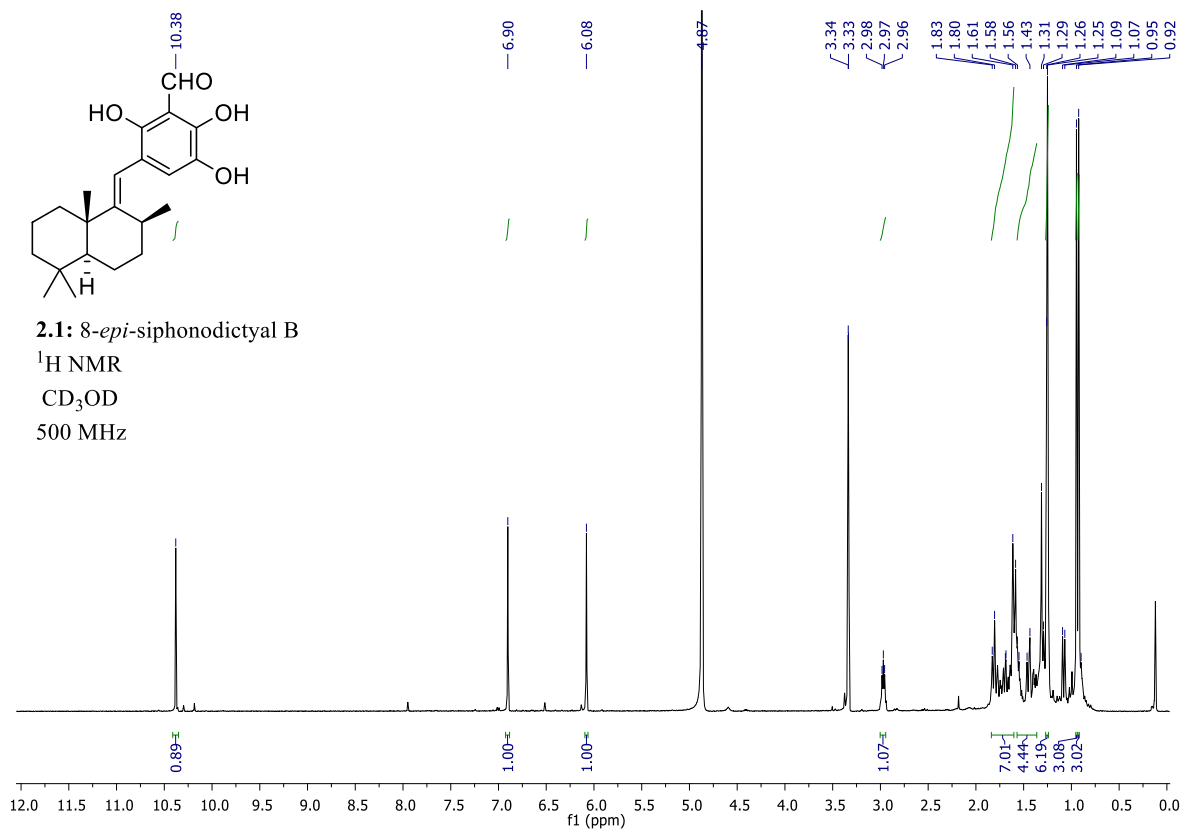
2.1: 8-*epi*-siphonodictyal B

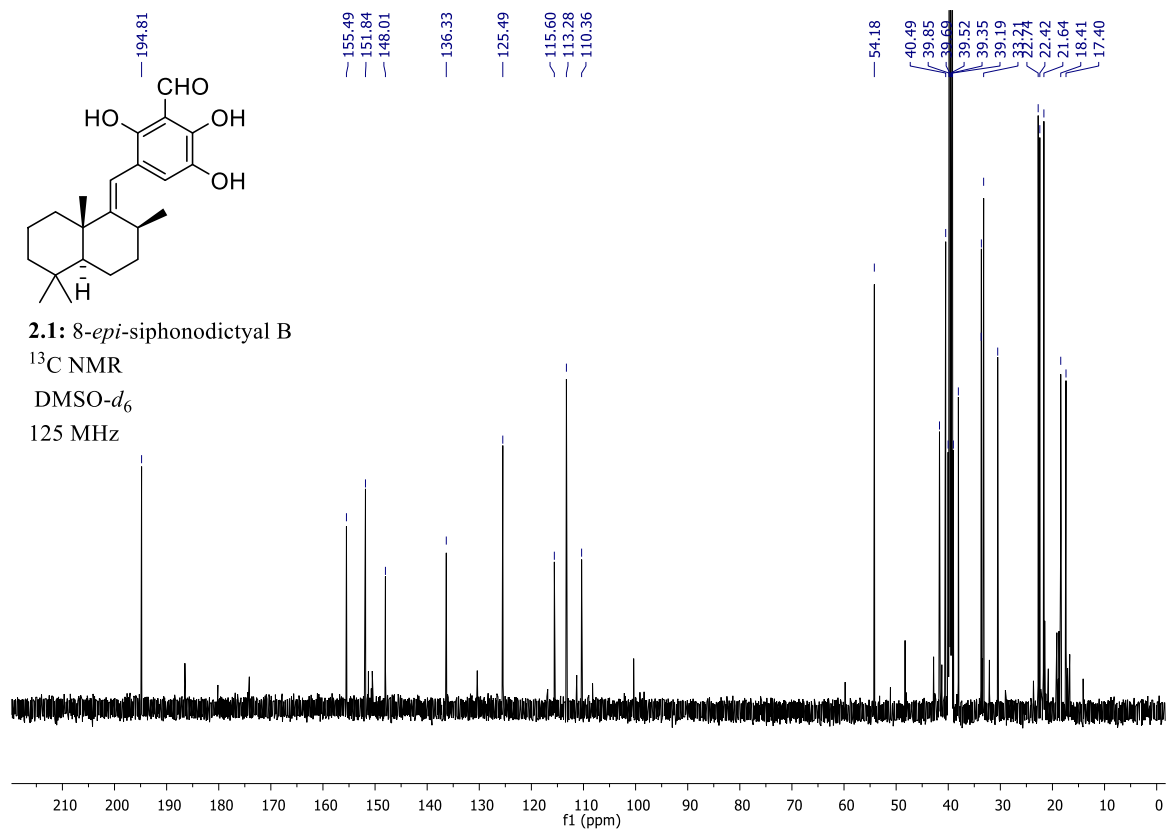
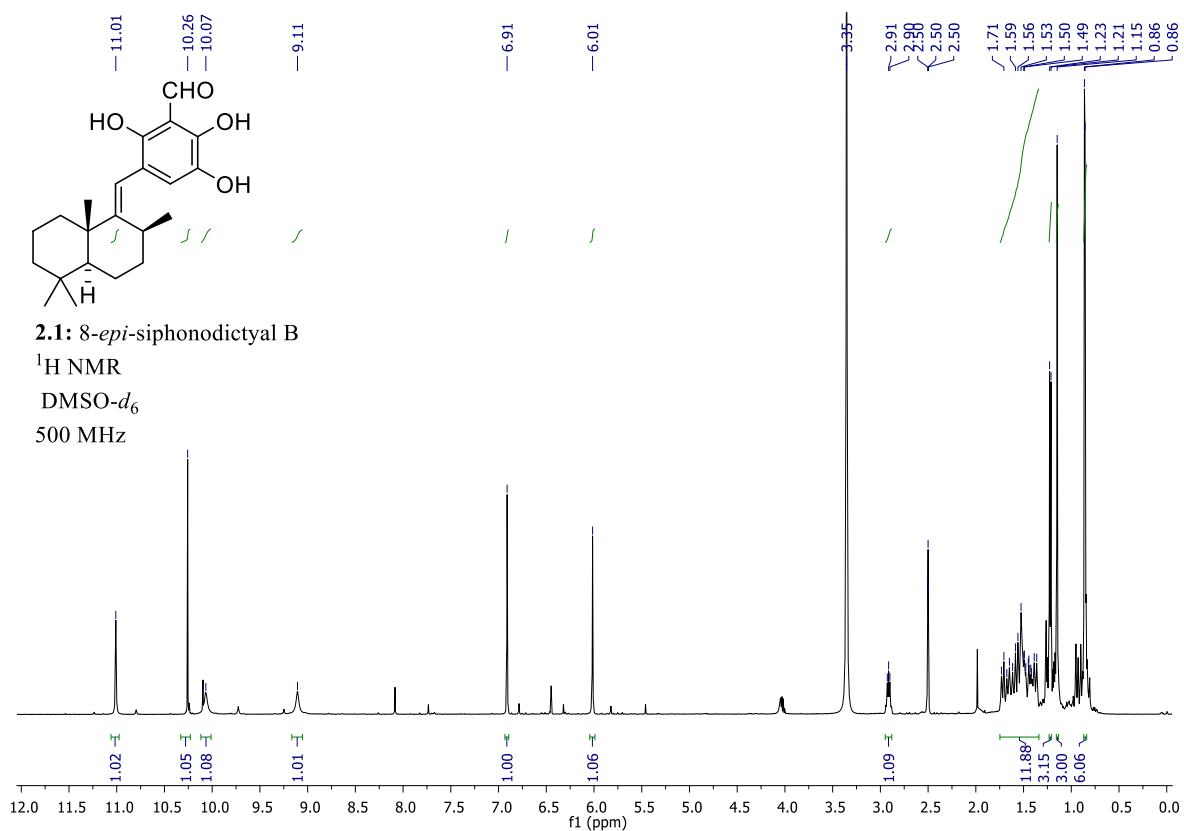
^{13}C NMR

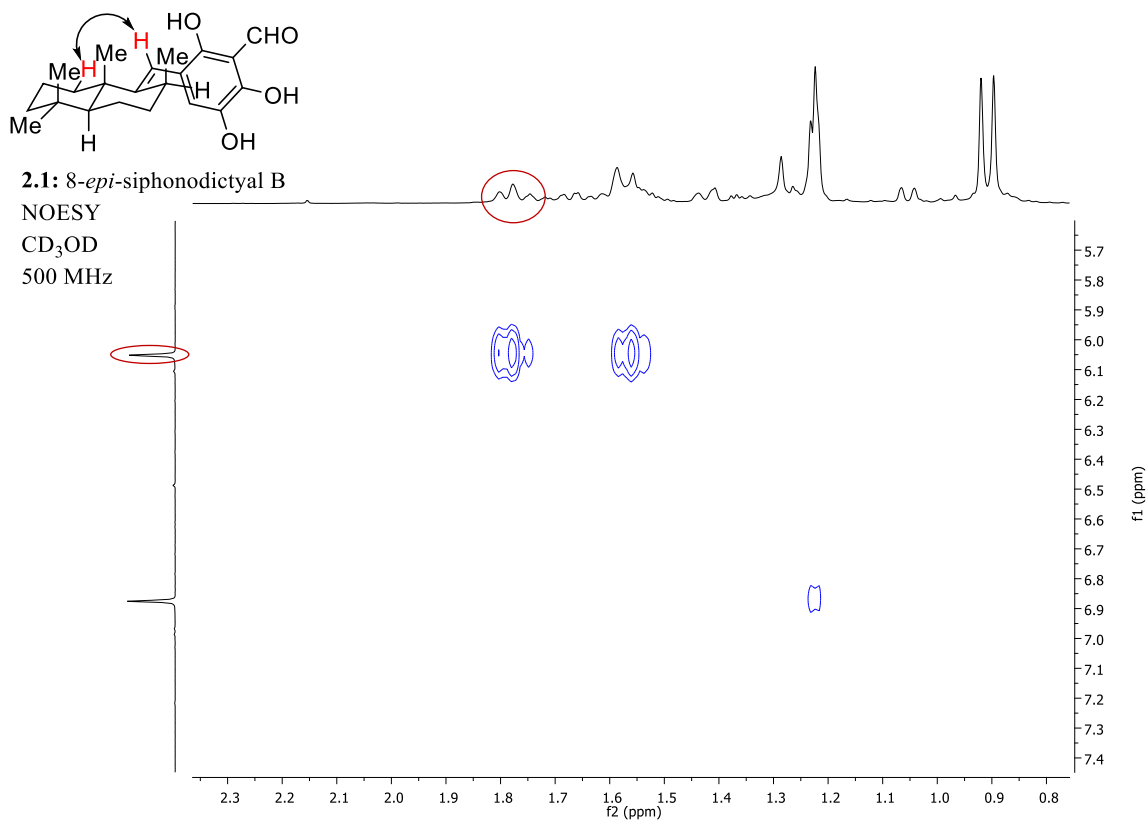
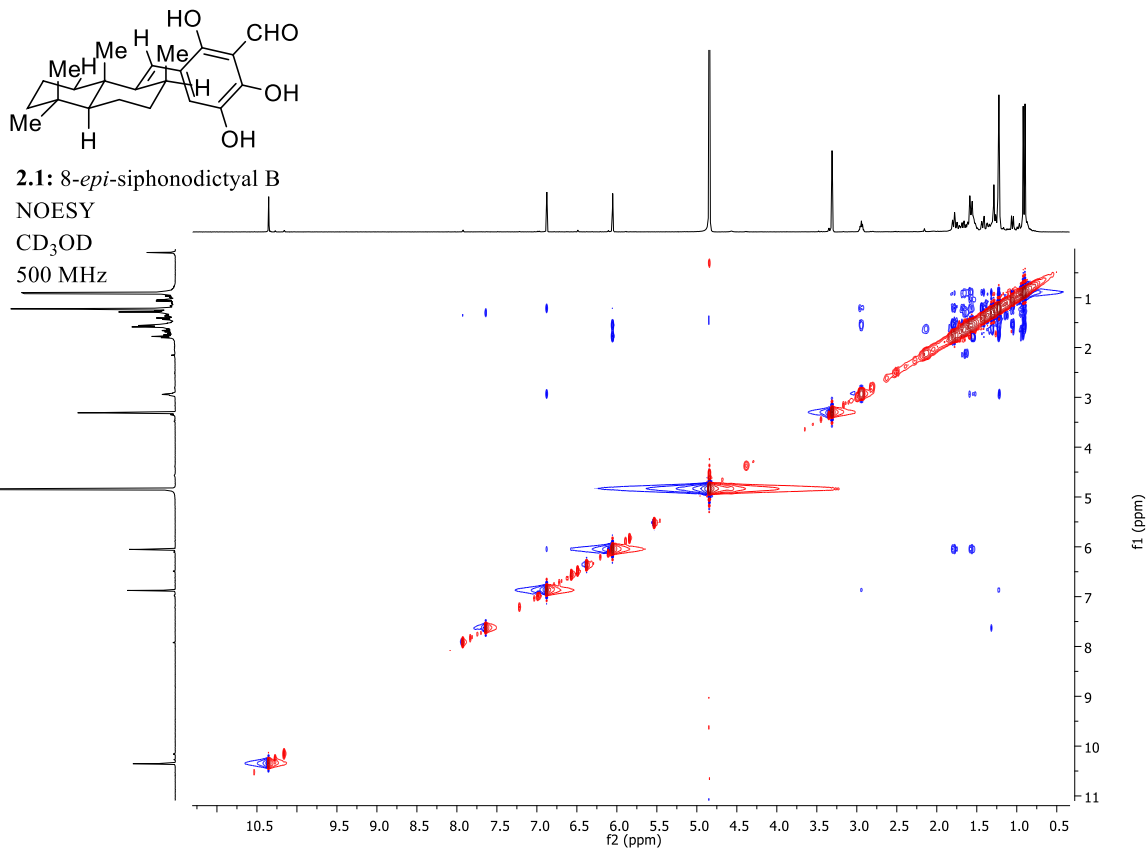
CDCl_3

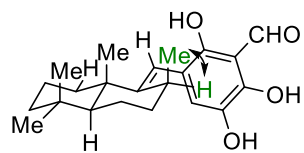
125 MHz









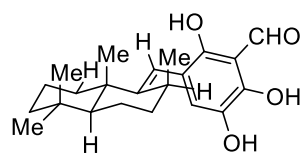
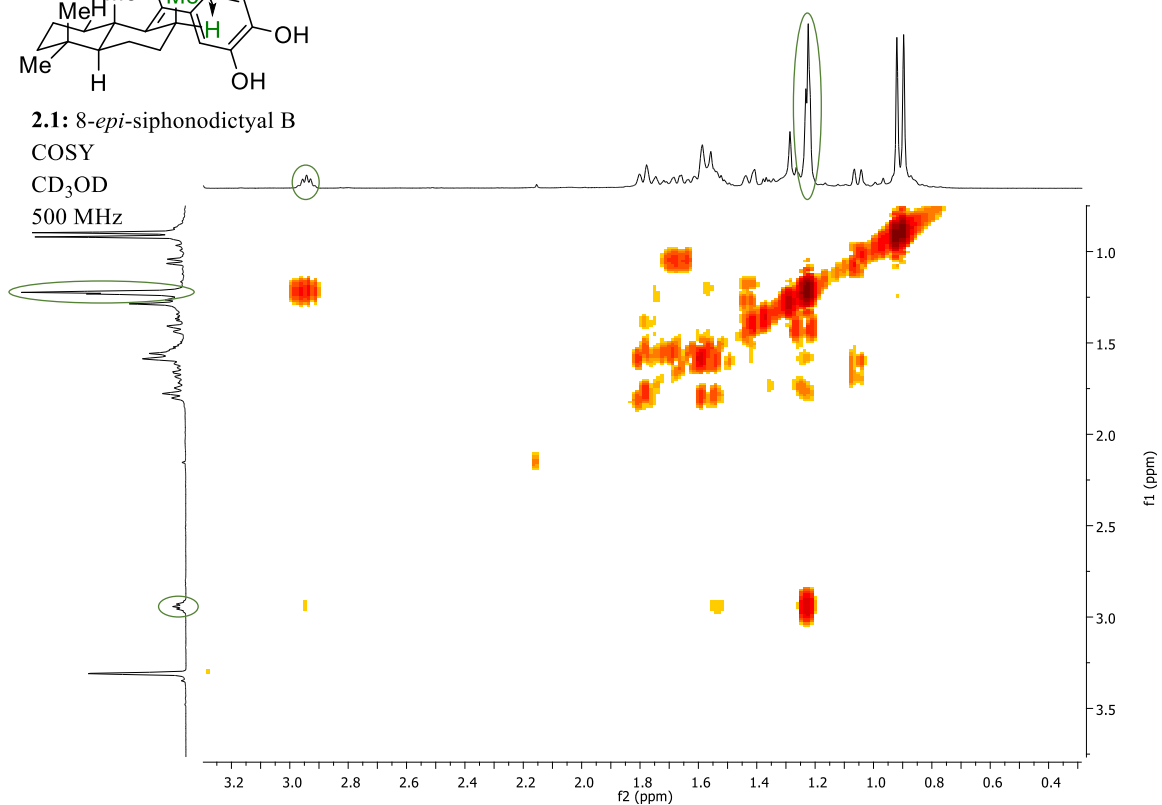


2.1: 8-*epi*-siphonodictyal B

COSY

CD₃OD

500 MHz

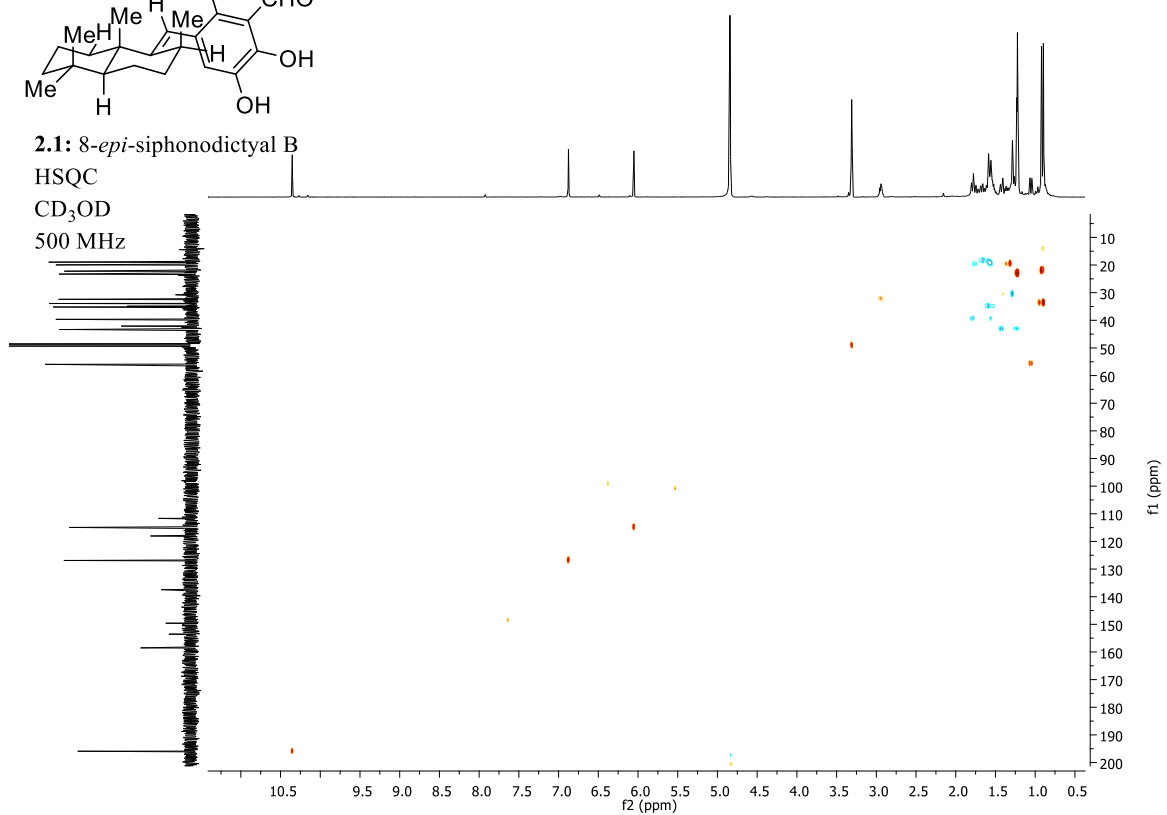


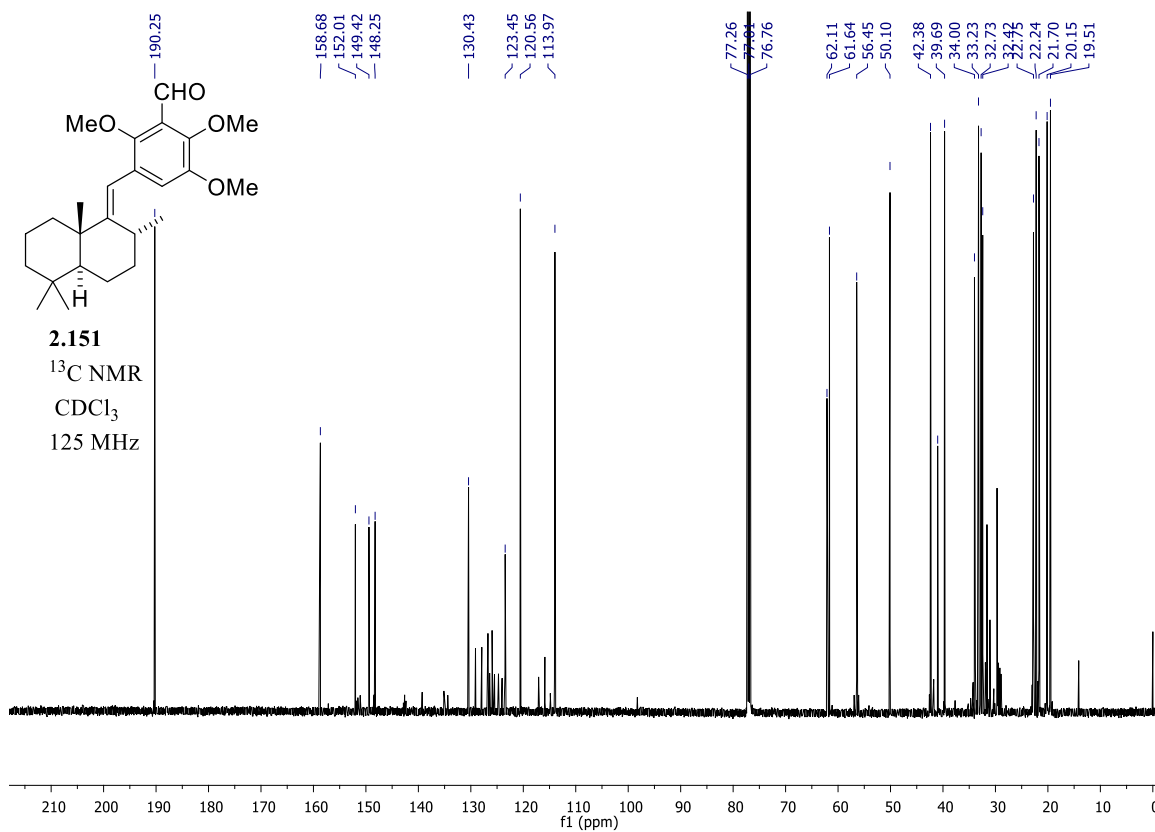
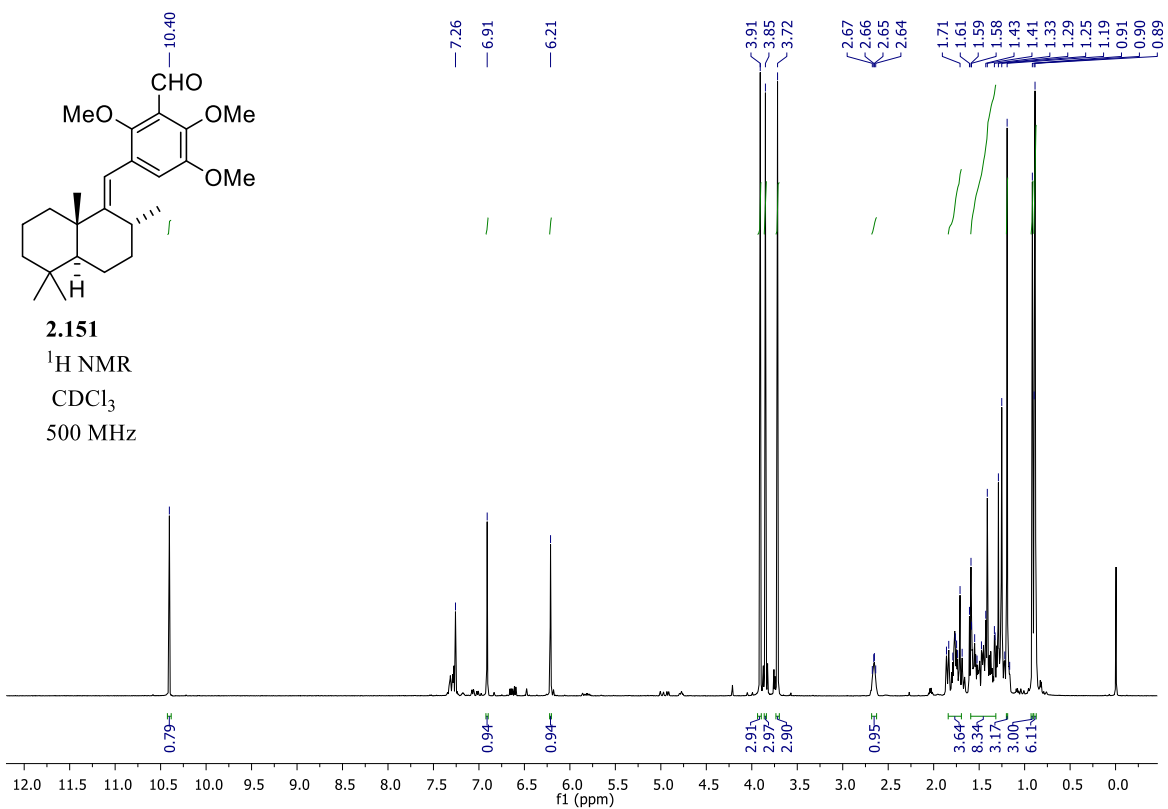
2.1: 8-*epi*-siphonodictyal B

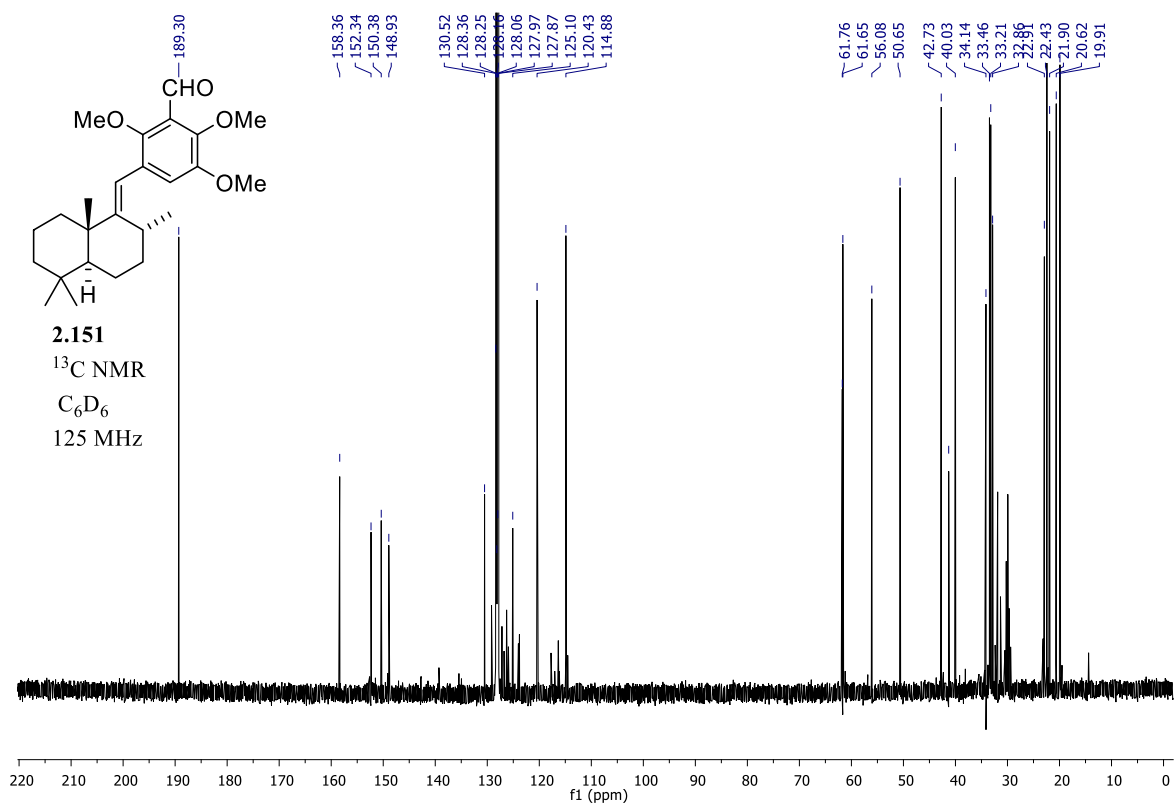
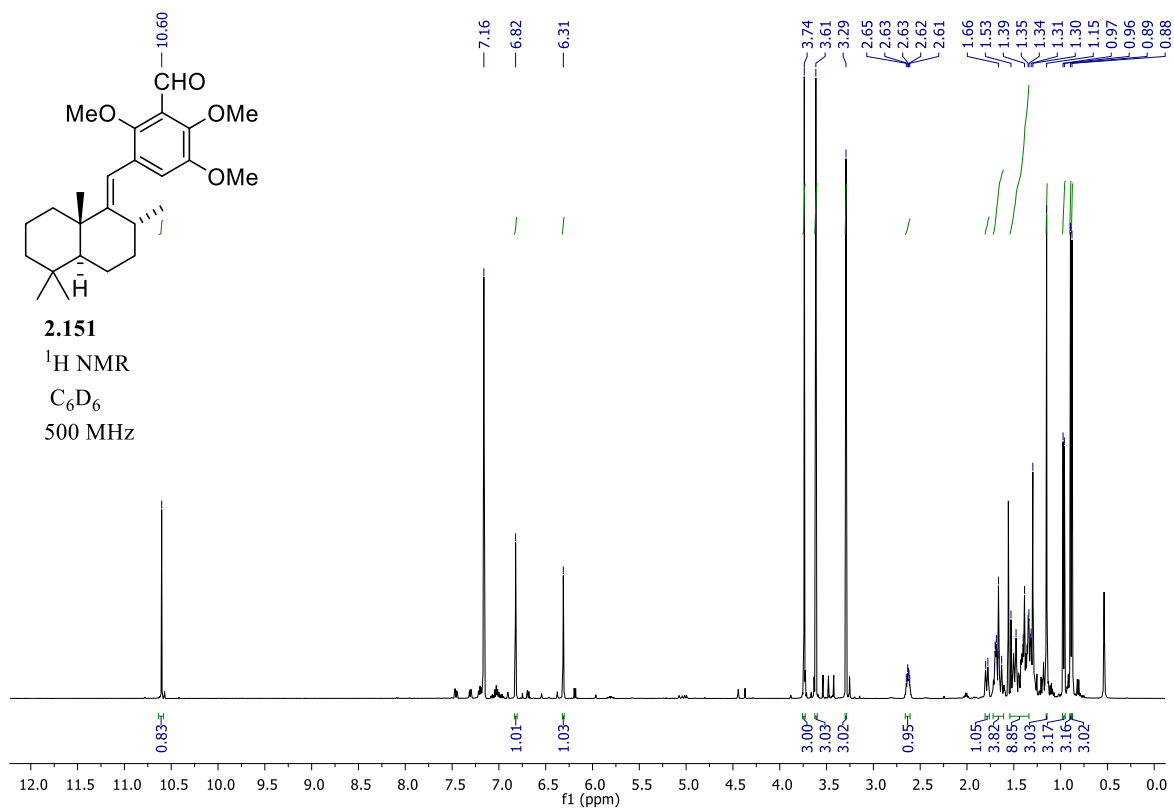
HSQC

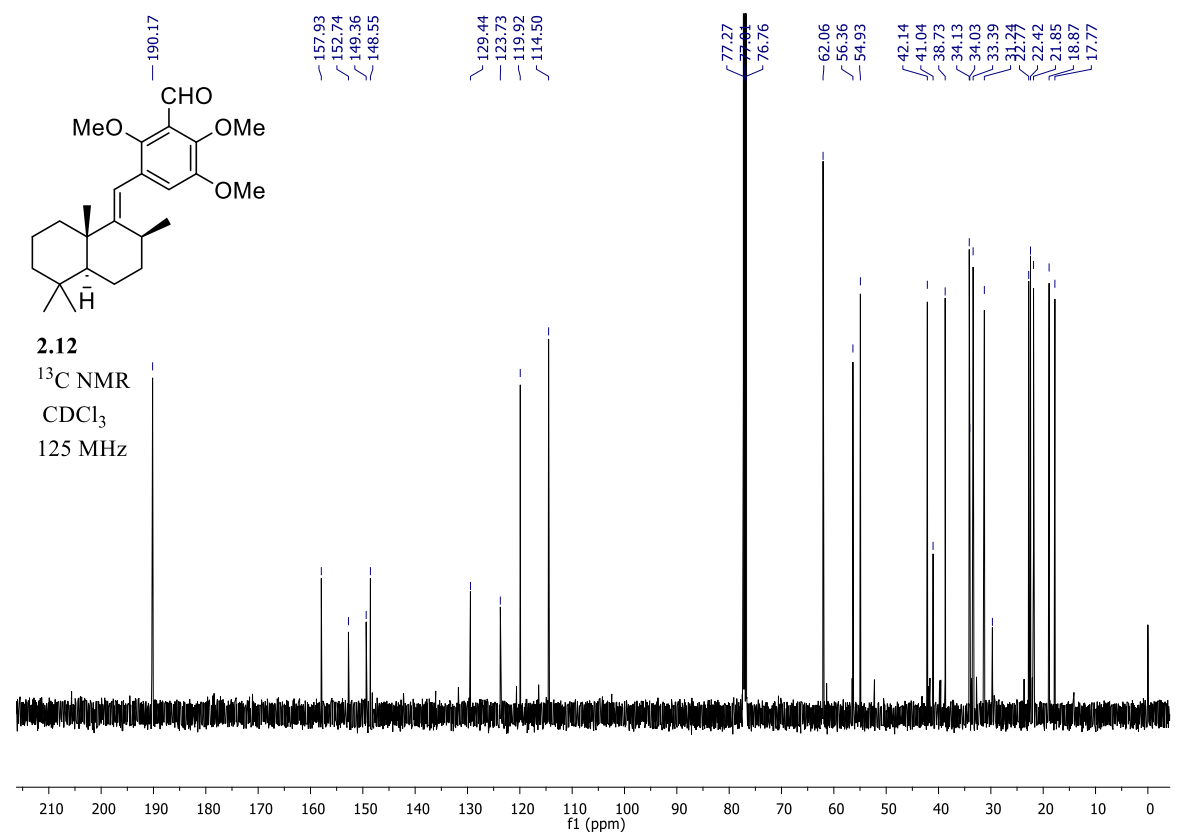
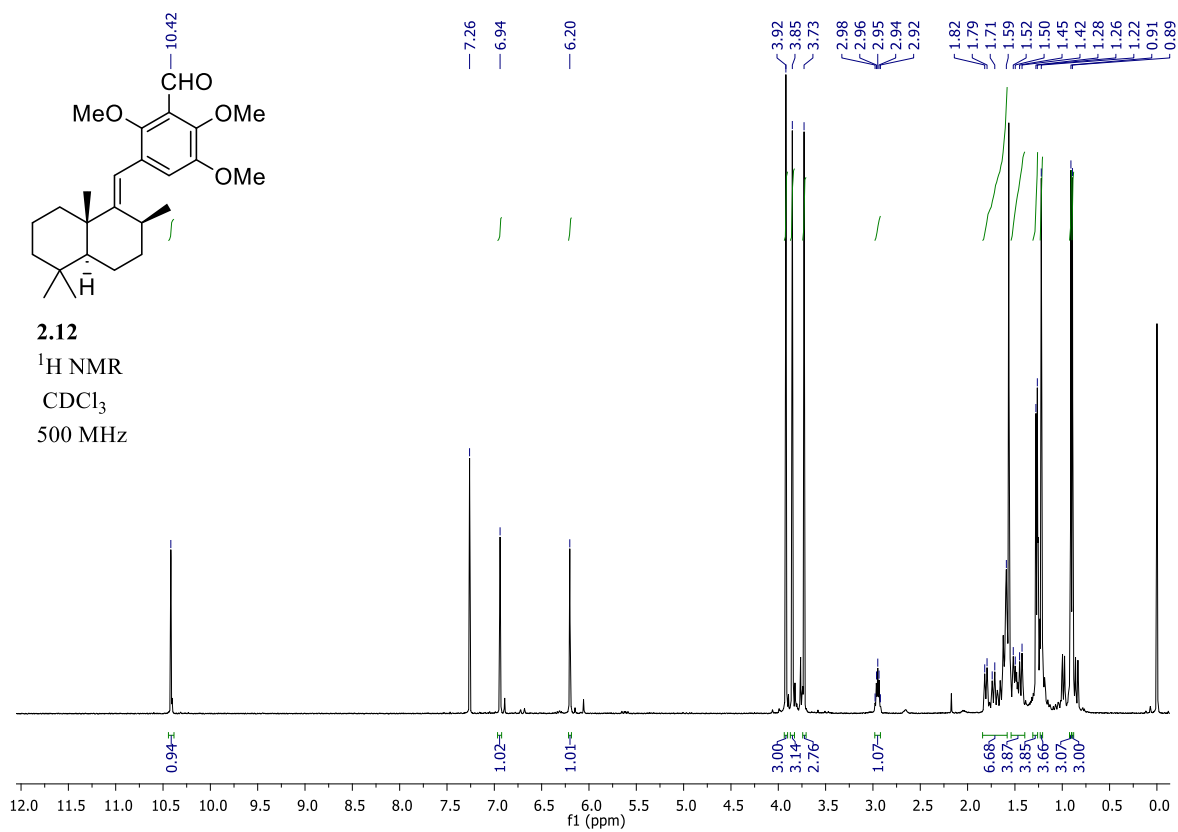
CD₃OD

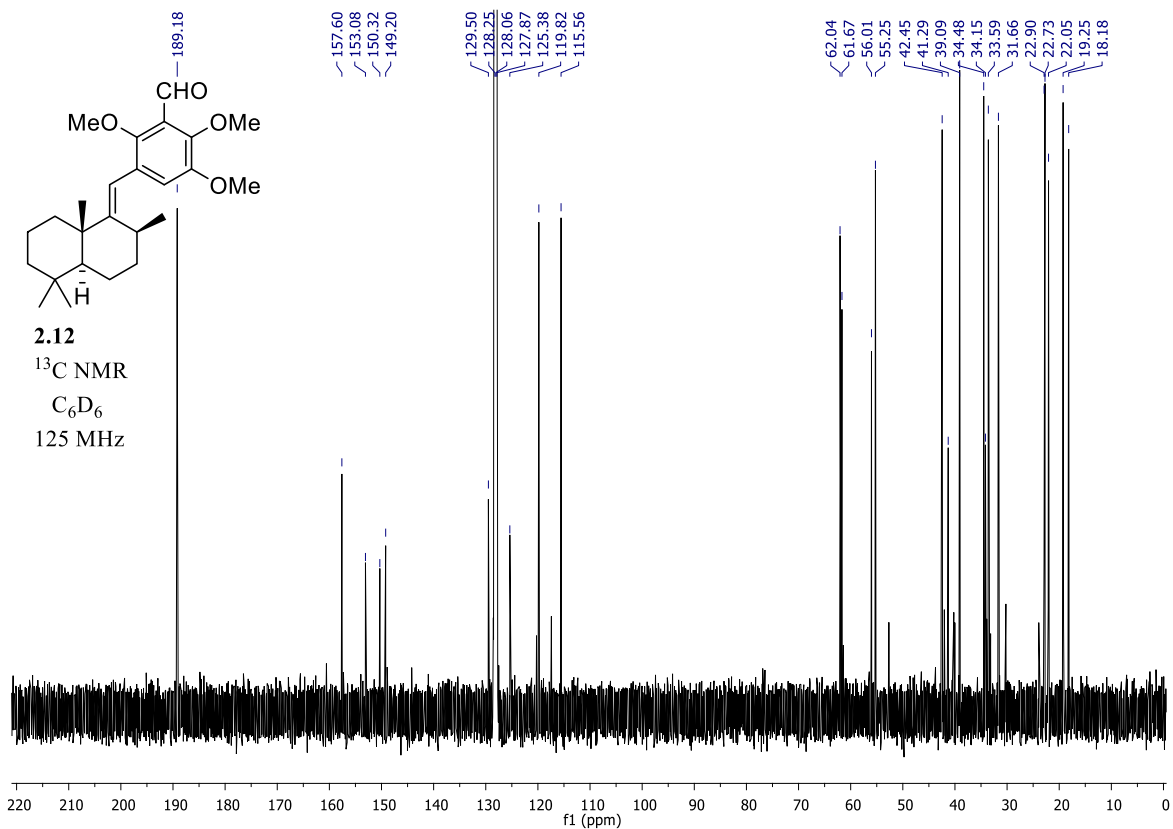
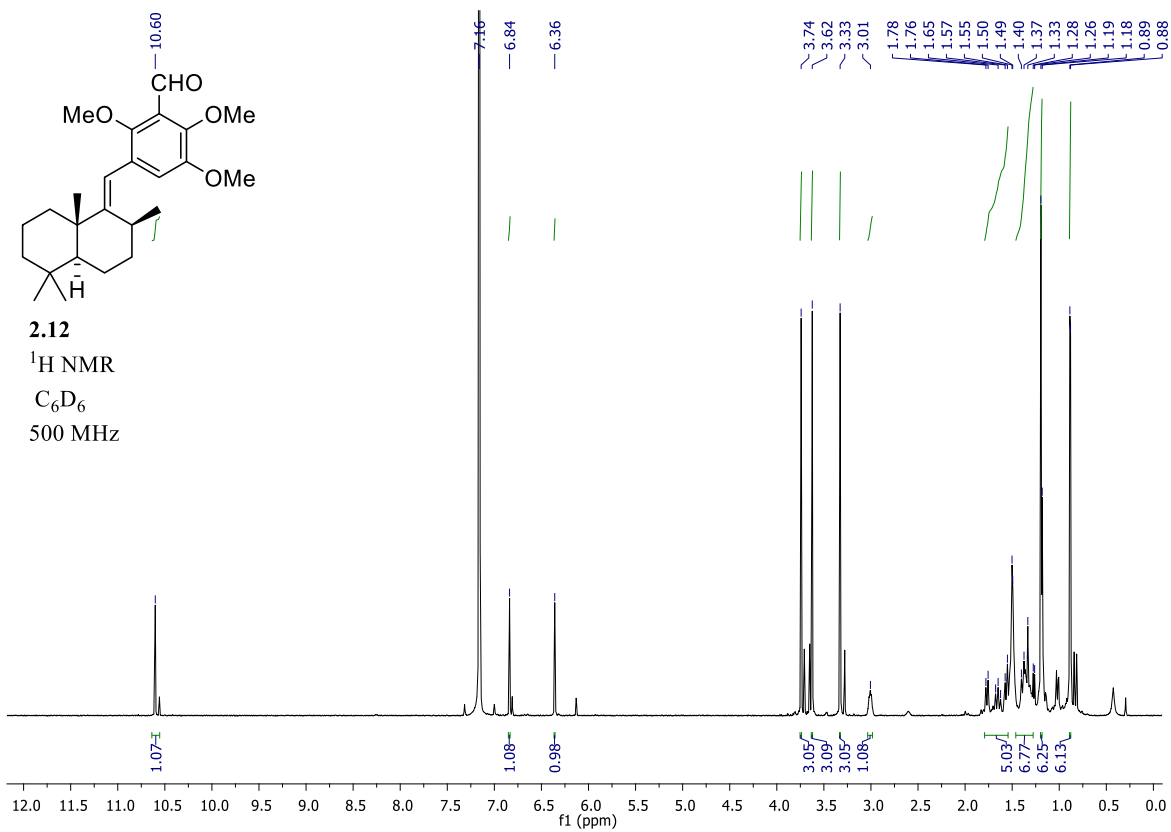
500 MHz

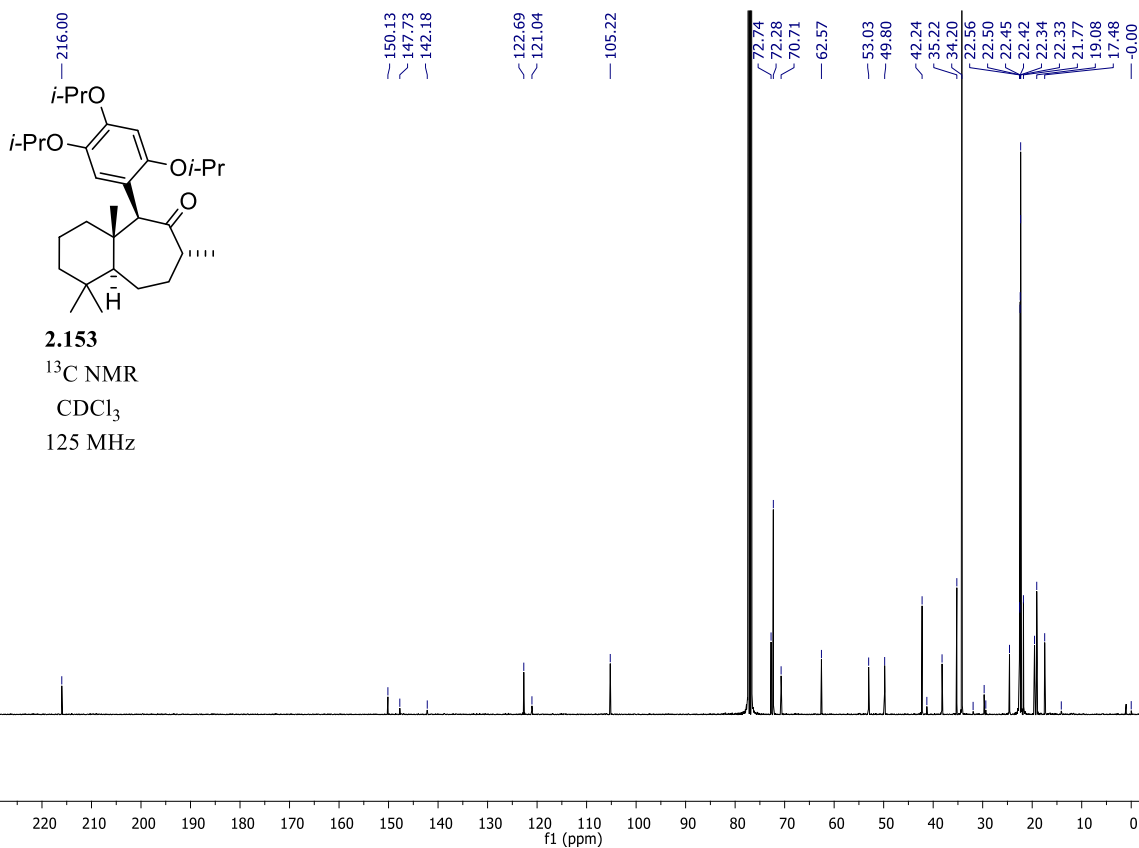
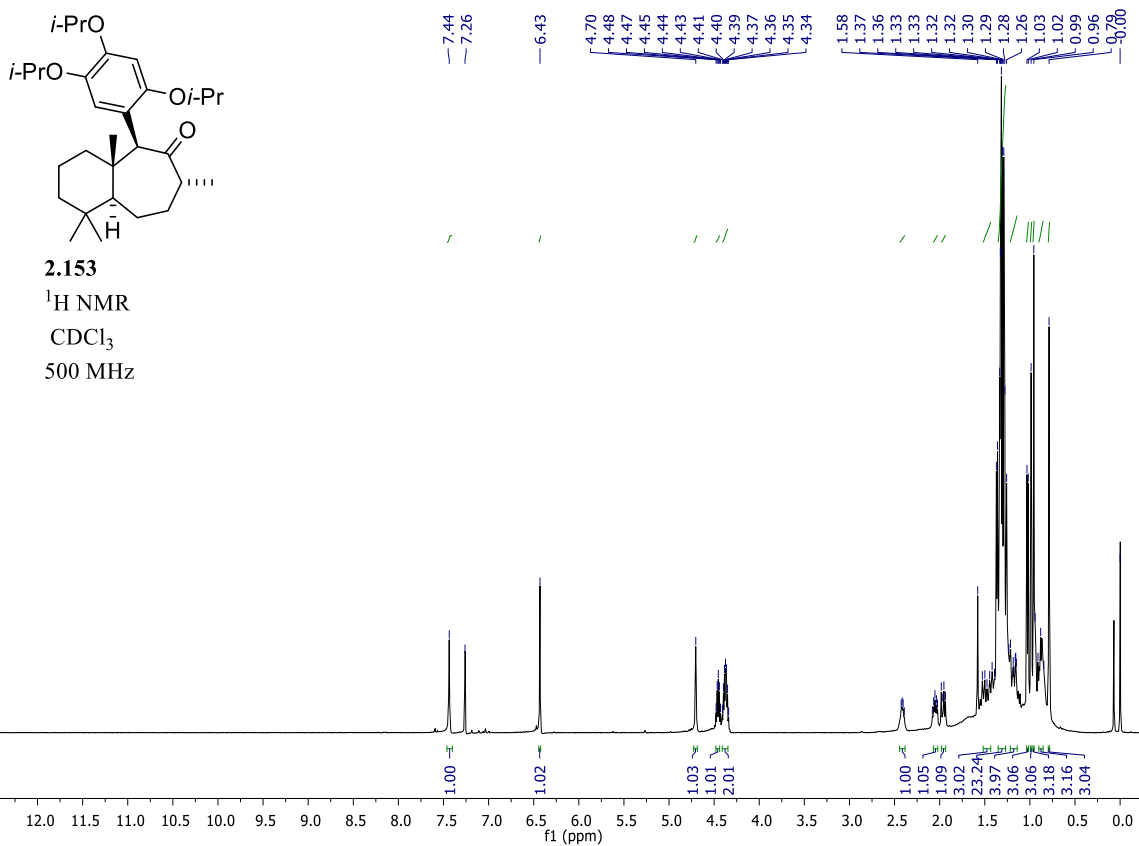


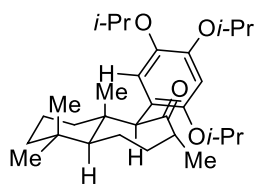




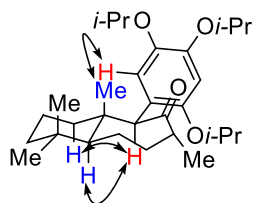
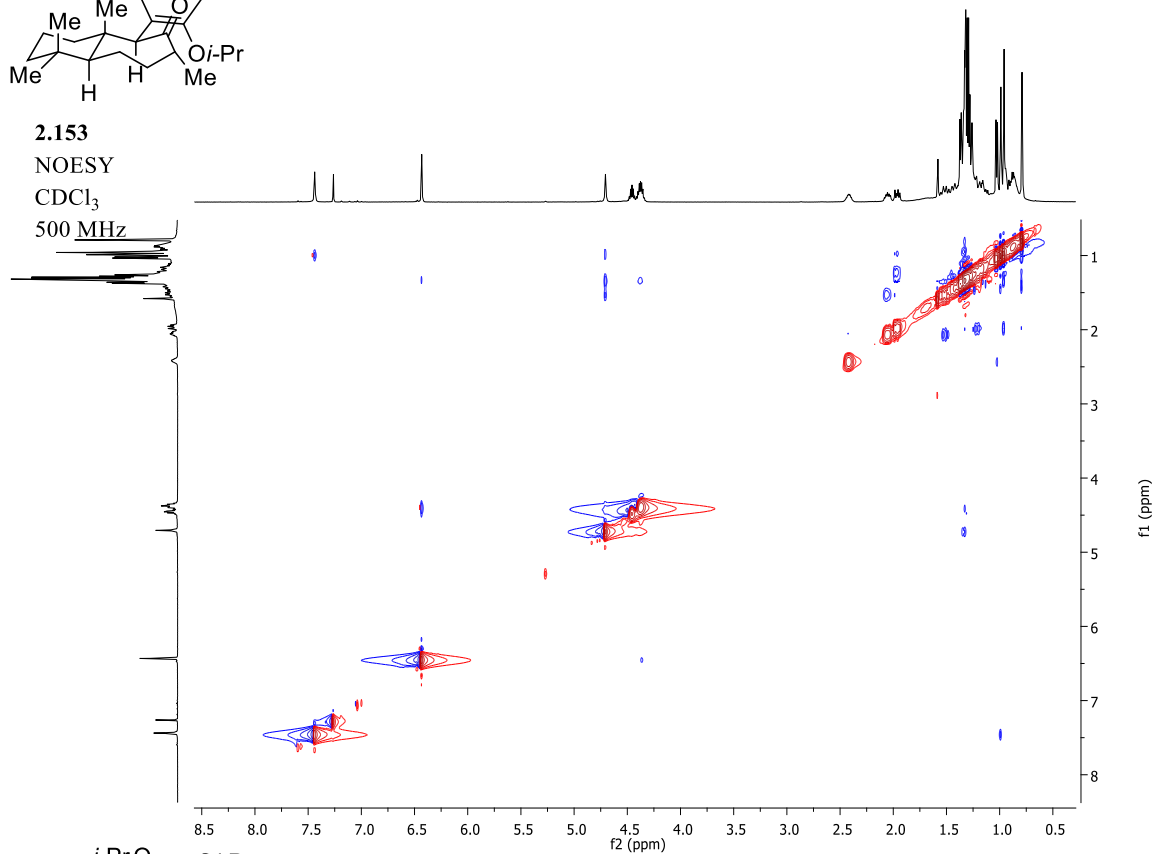




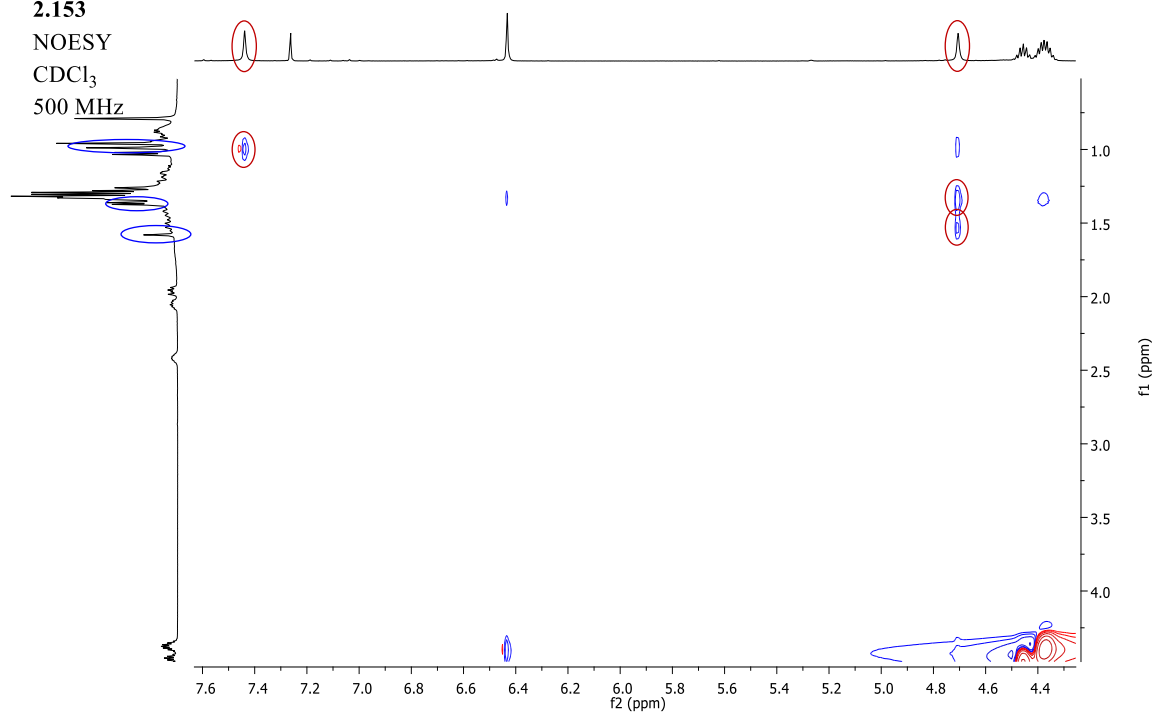


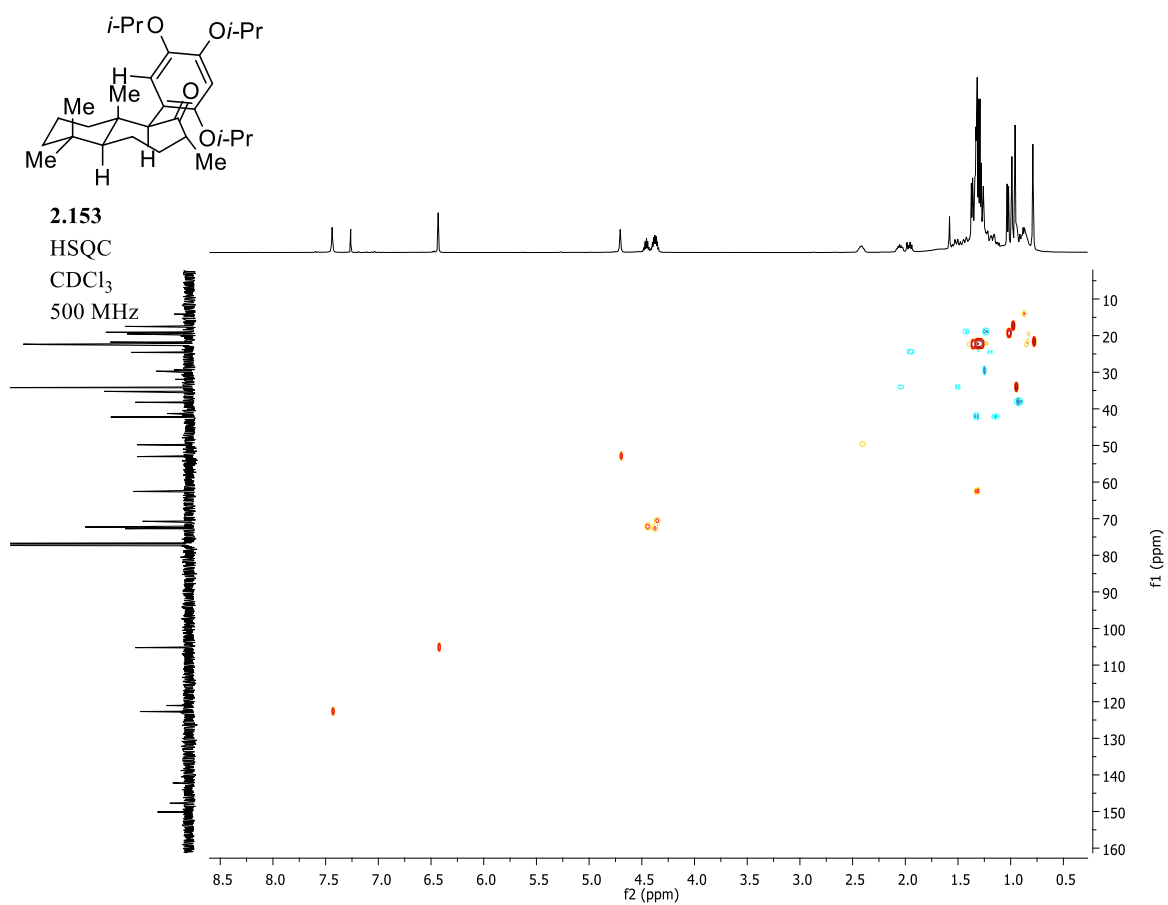
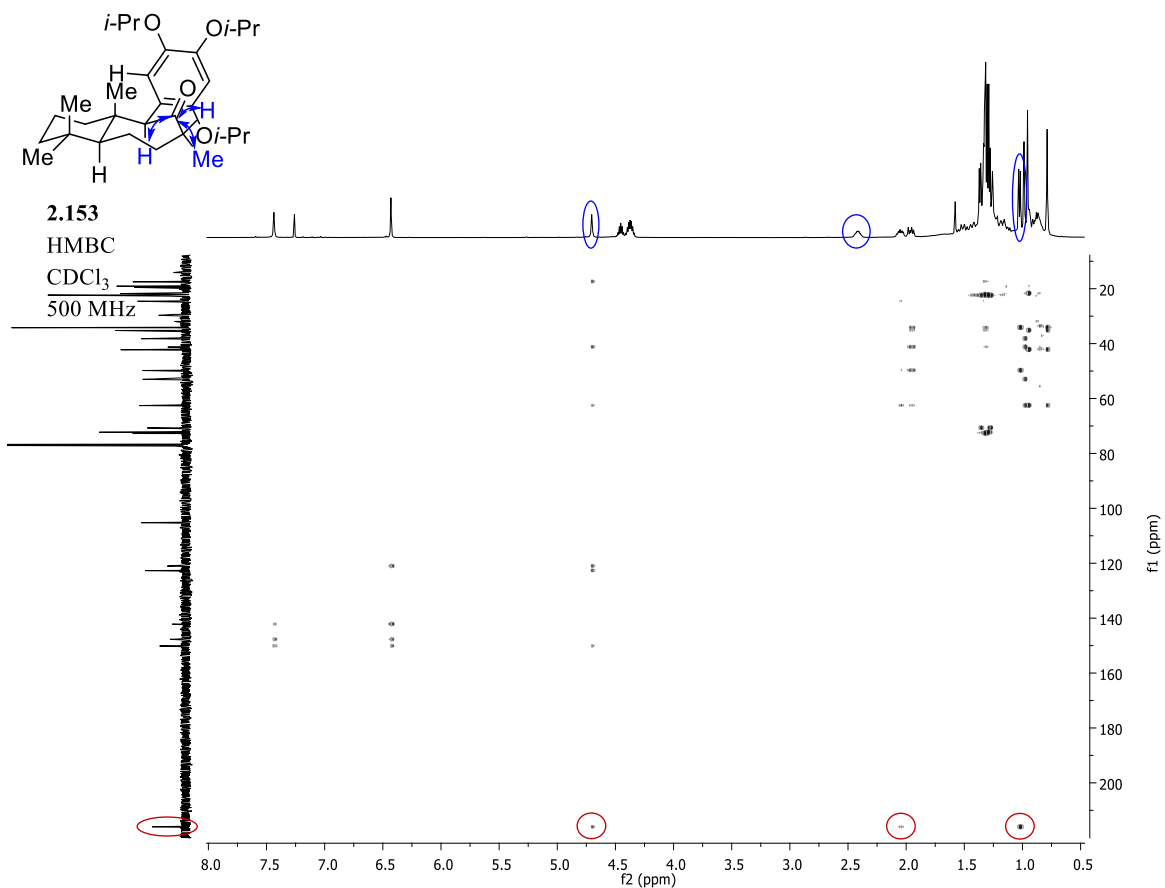


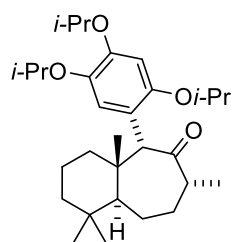
2.153
NOESY
CDCl₃
500 MHz



2.153
NOESY
CDCl₃
500 MHz





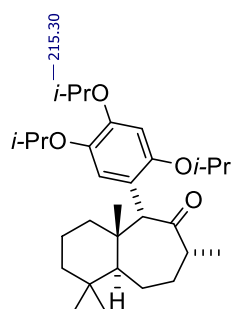
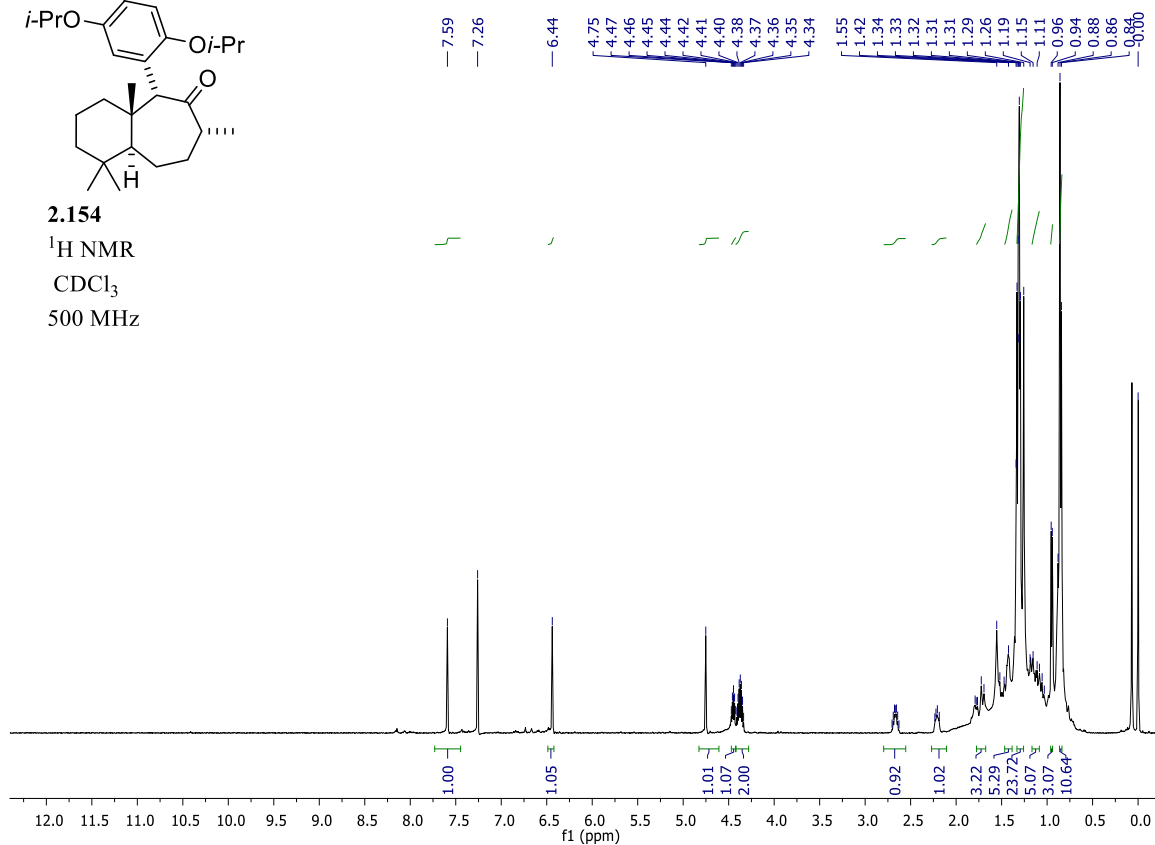


2.154

¹H NMR

CDCl₃

500 MHz

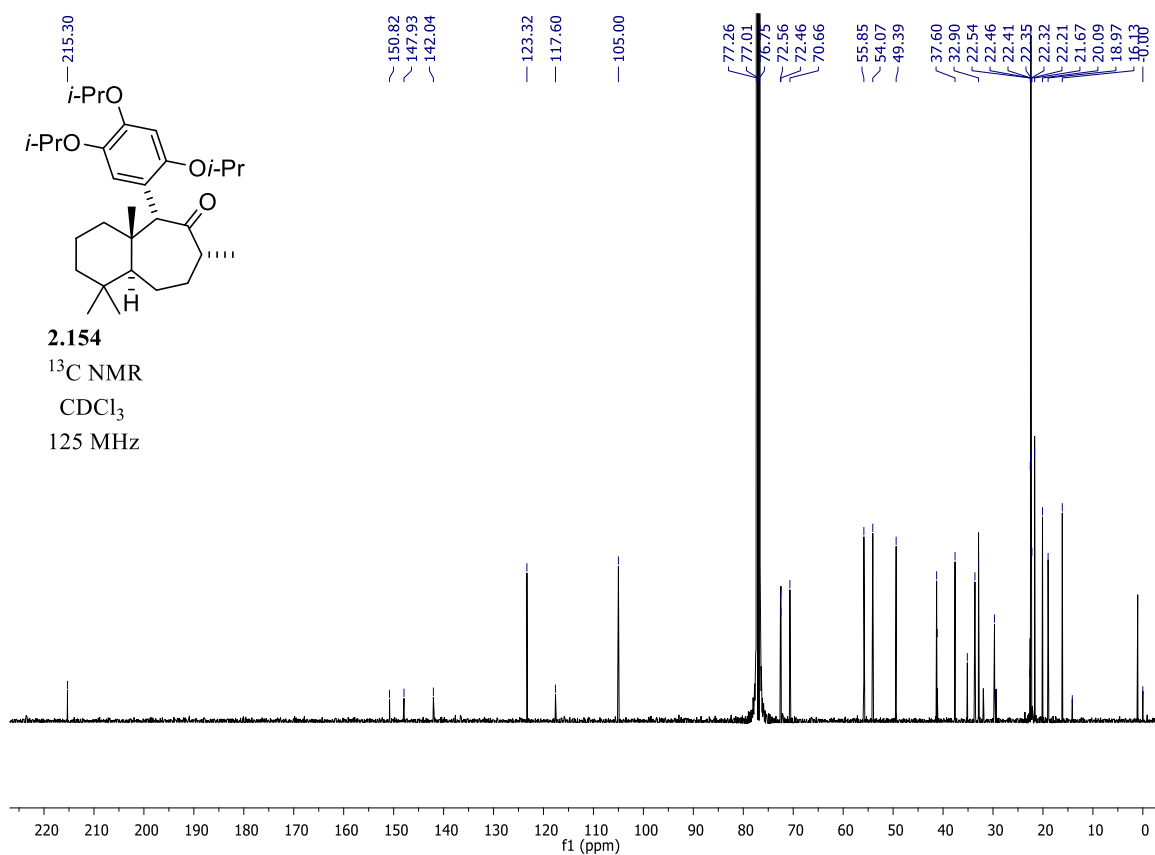


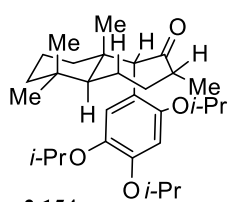
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¹³C NMR

CDCl₃

125 MHz



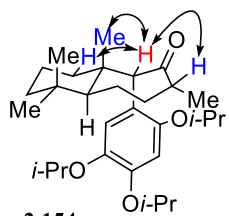
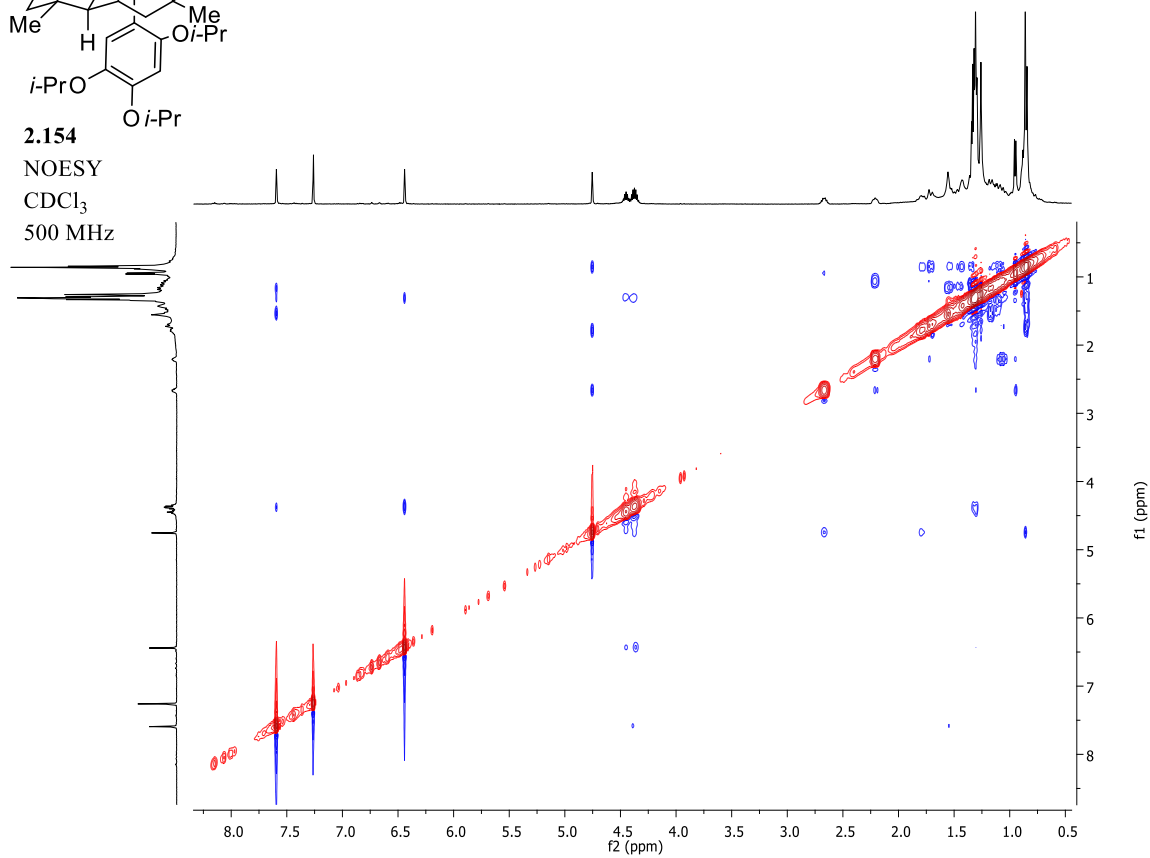


2.154

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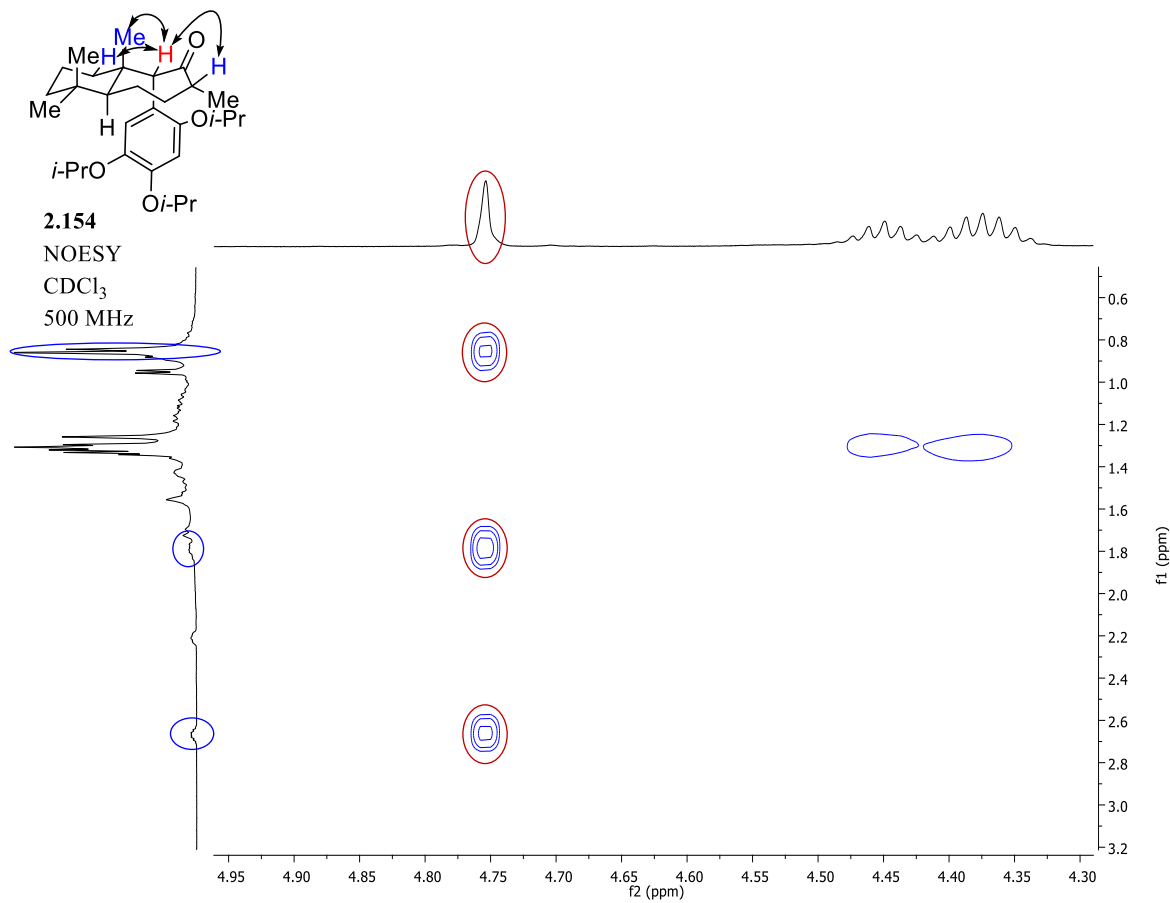


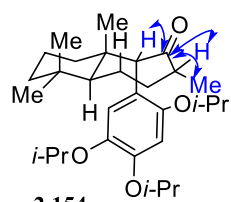
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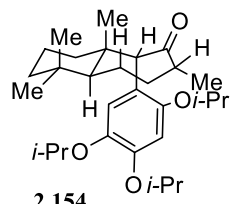
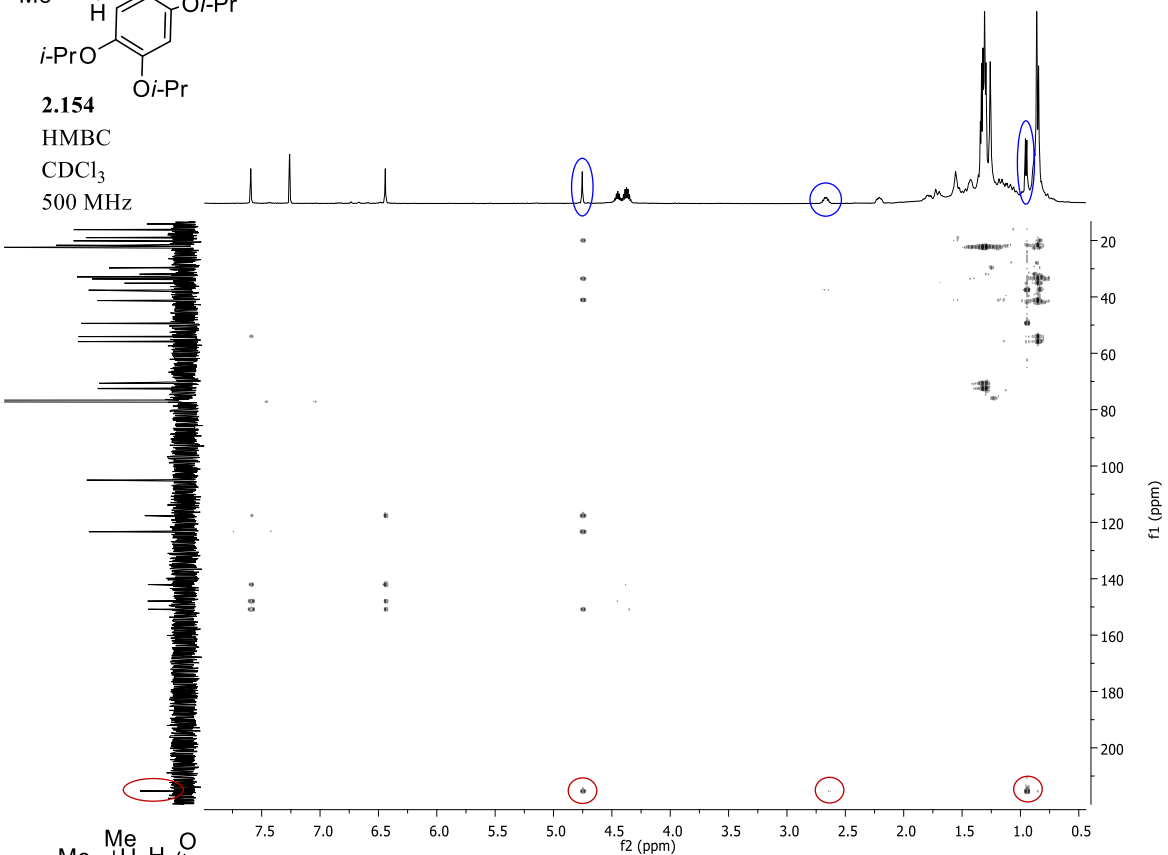
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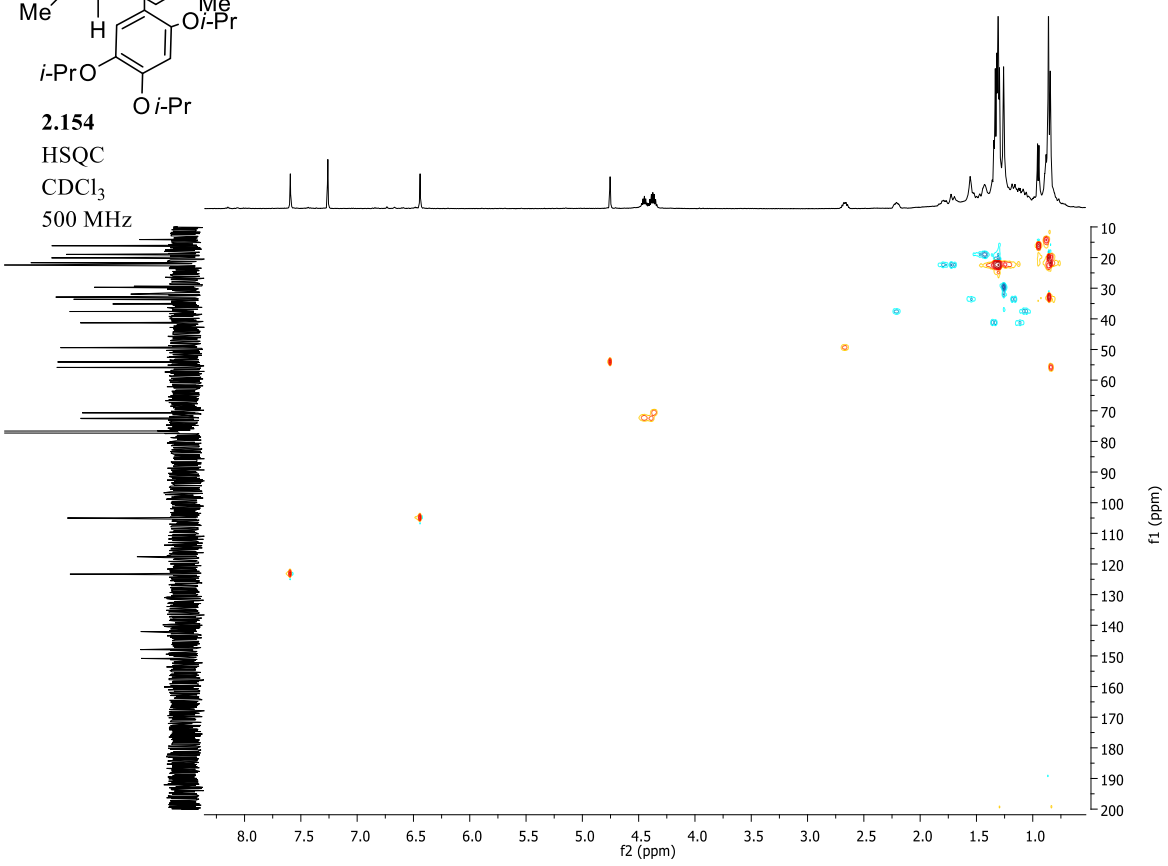


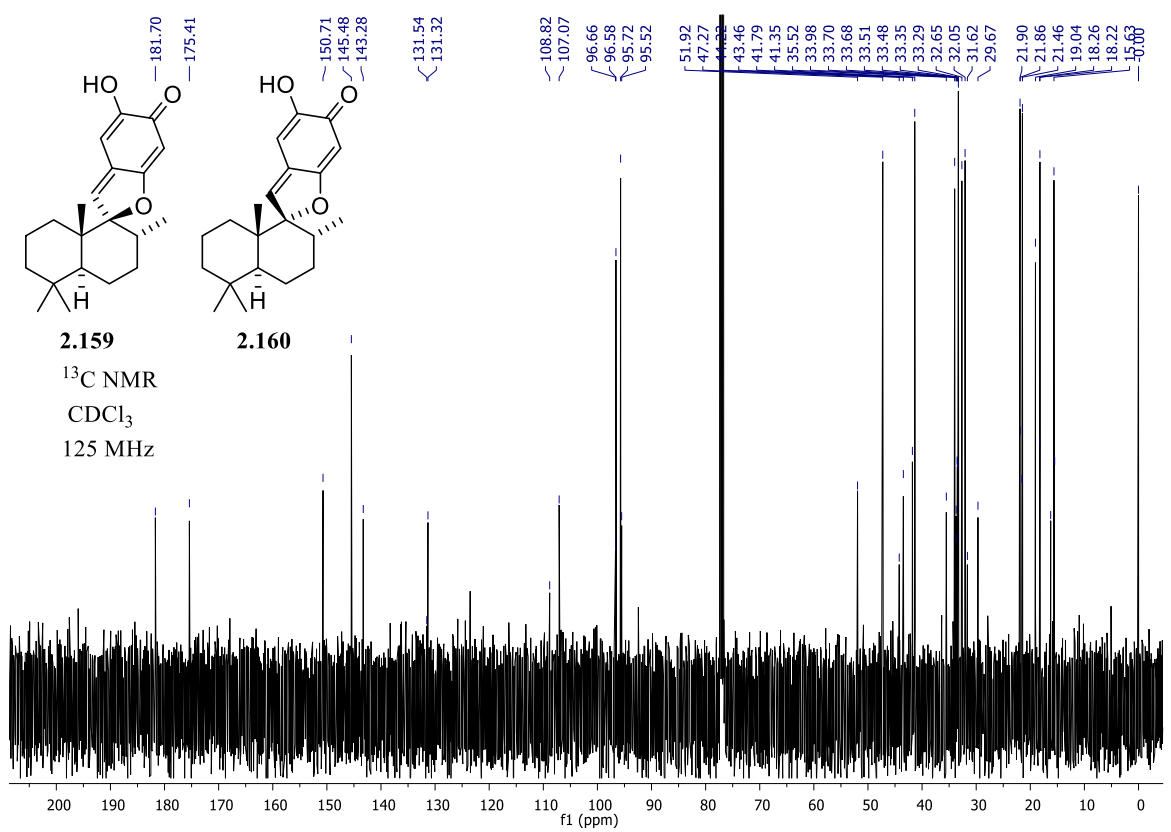
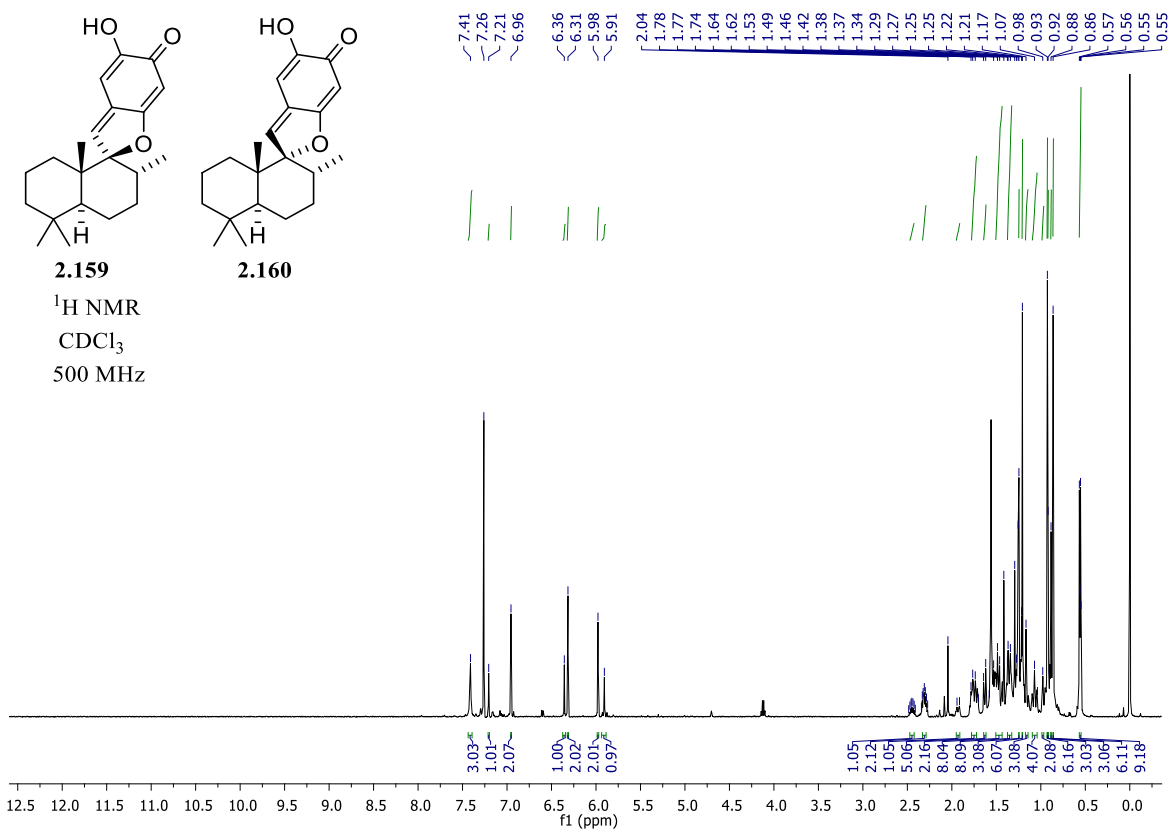


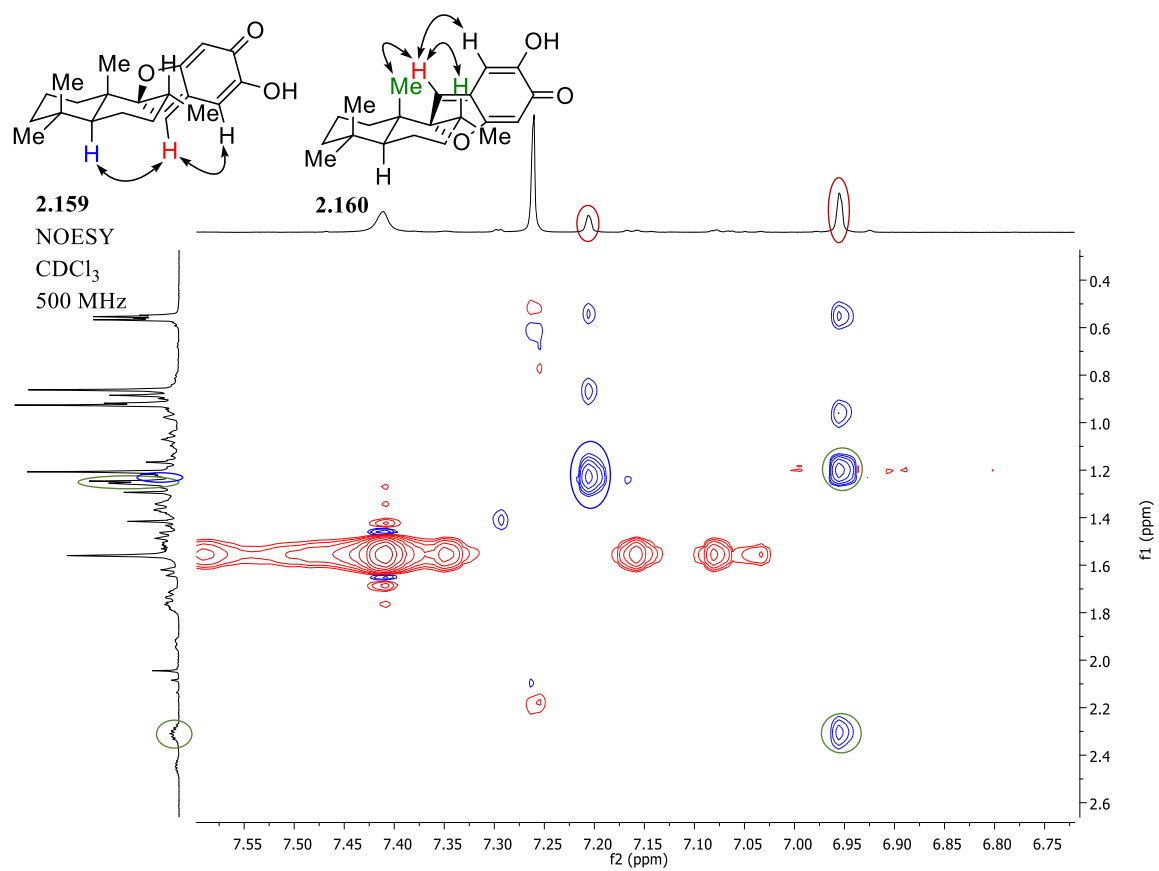
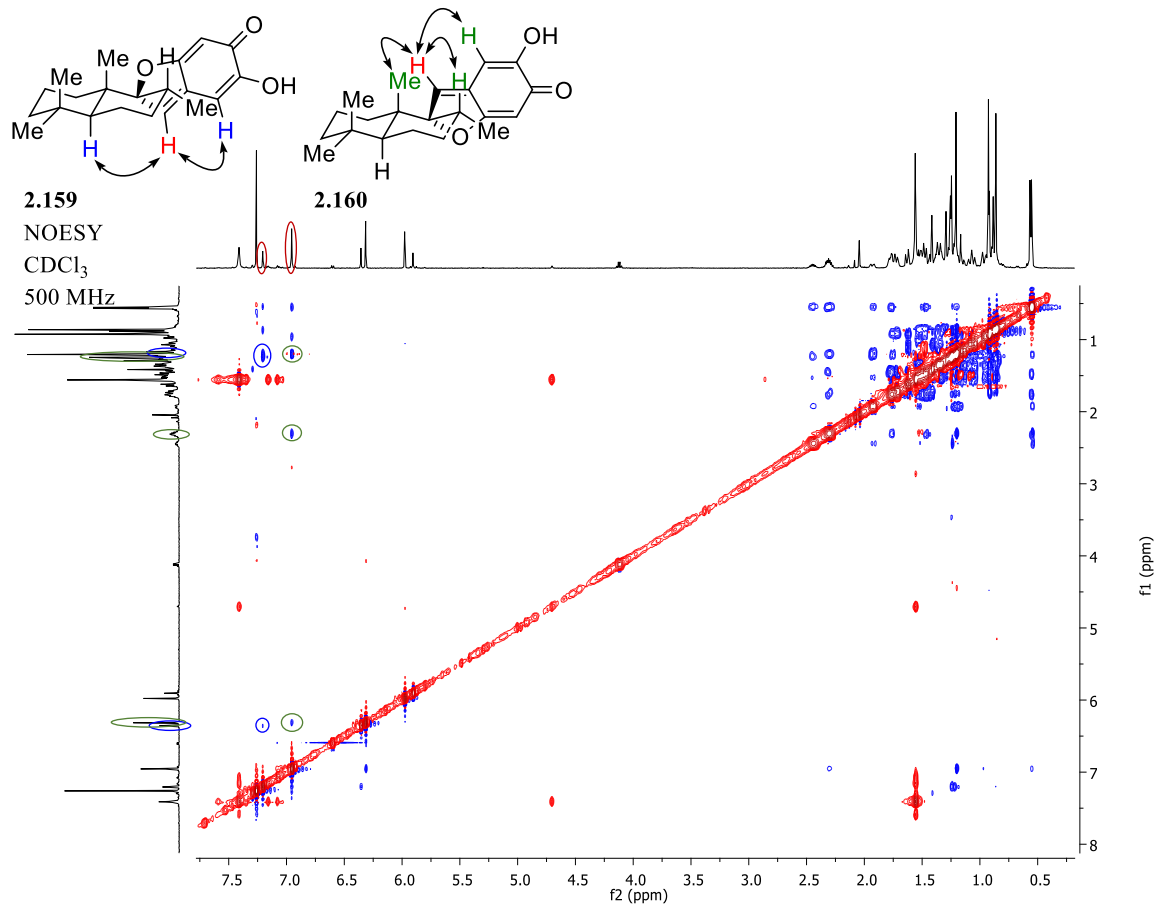
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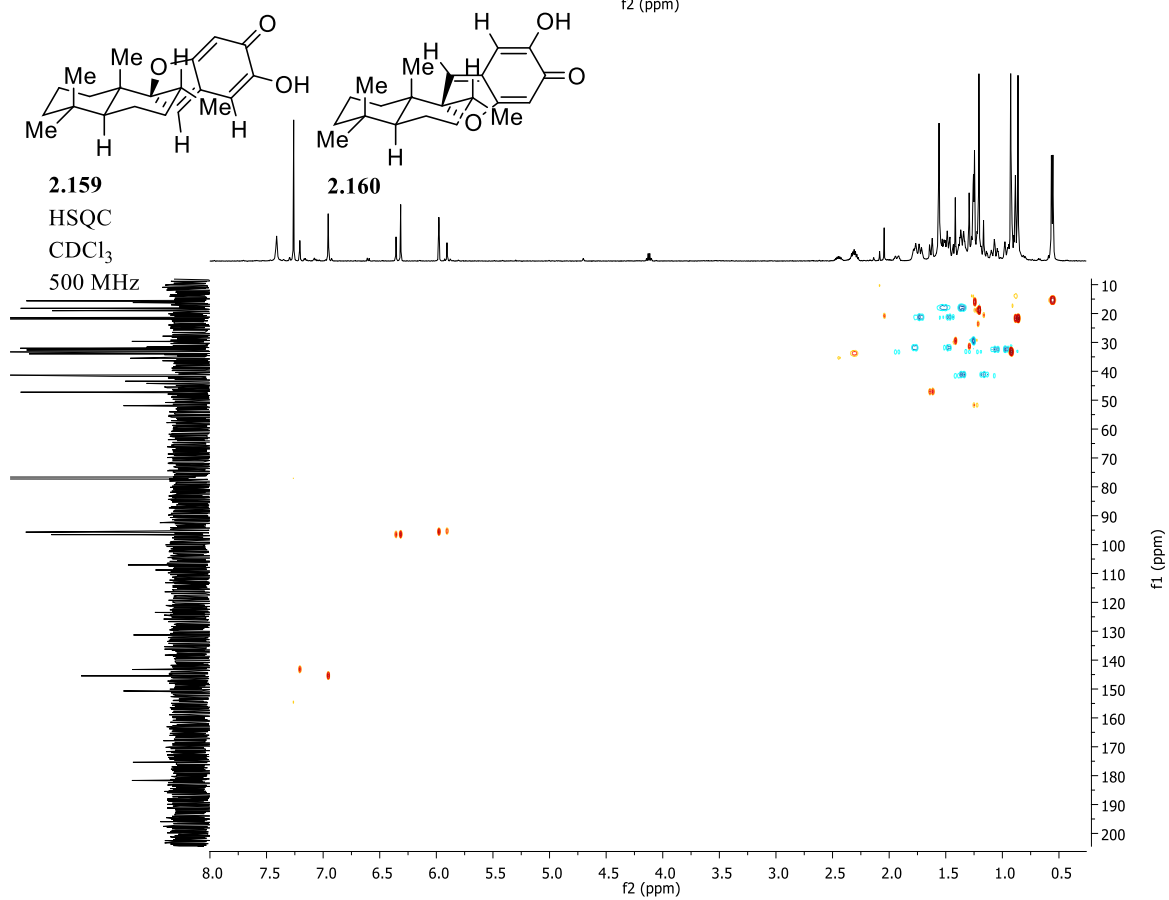
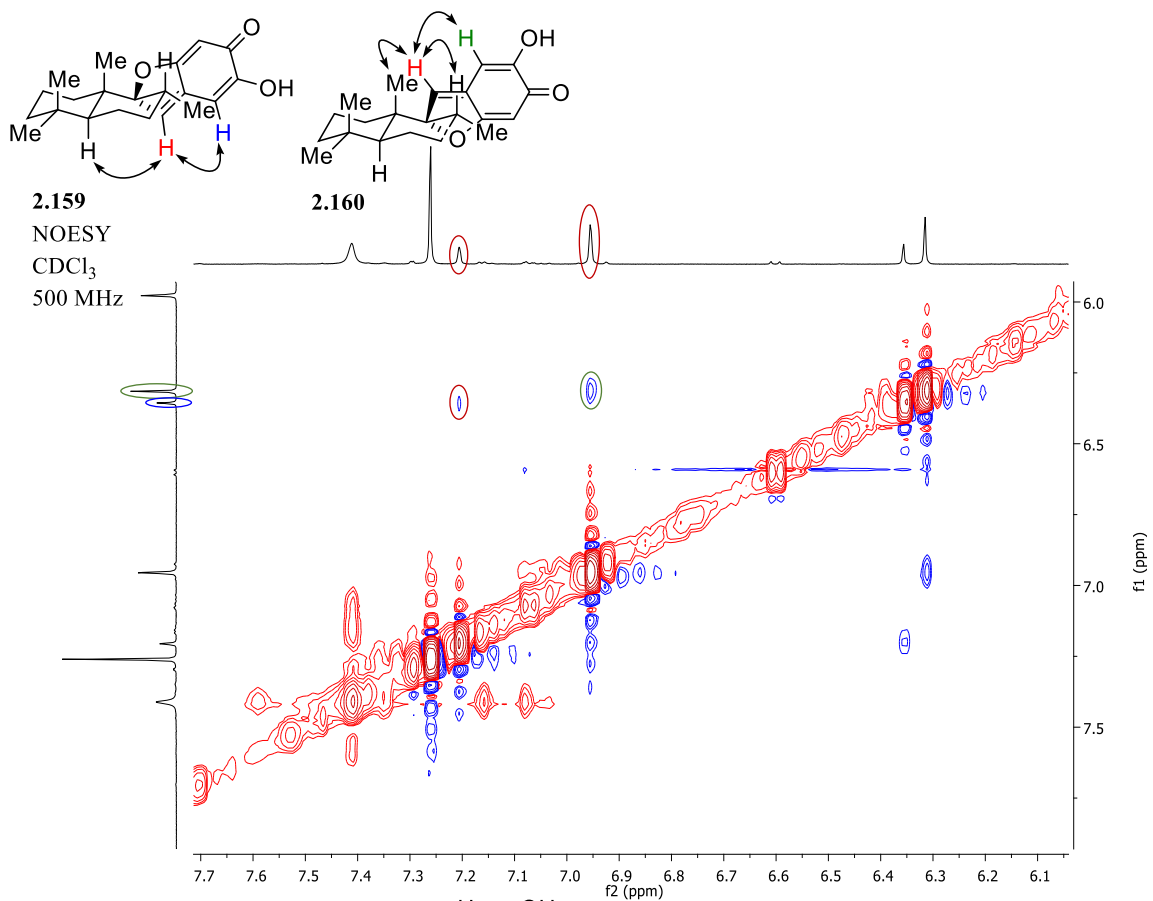


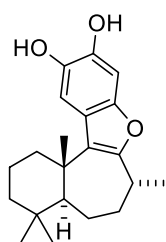
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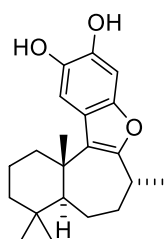
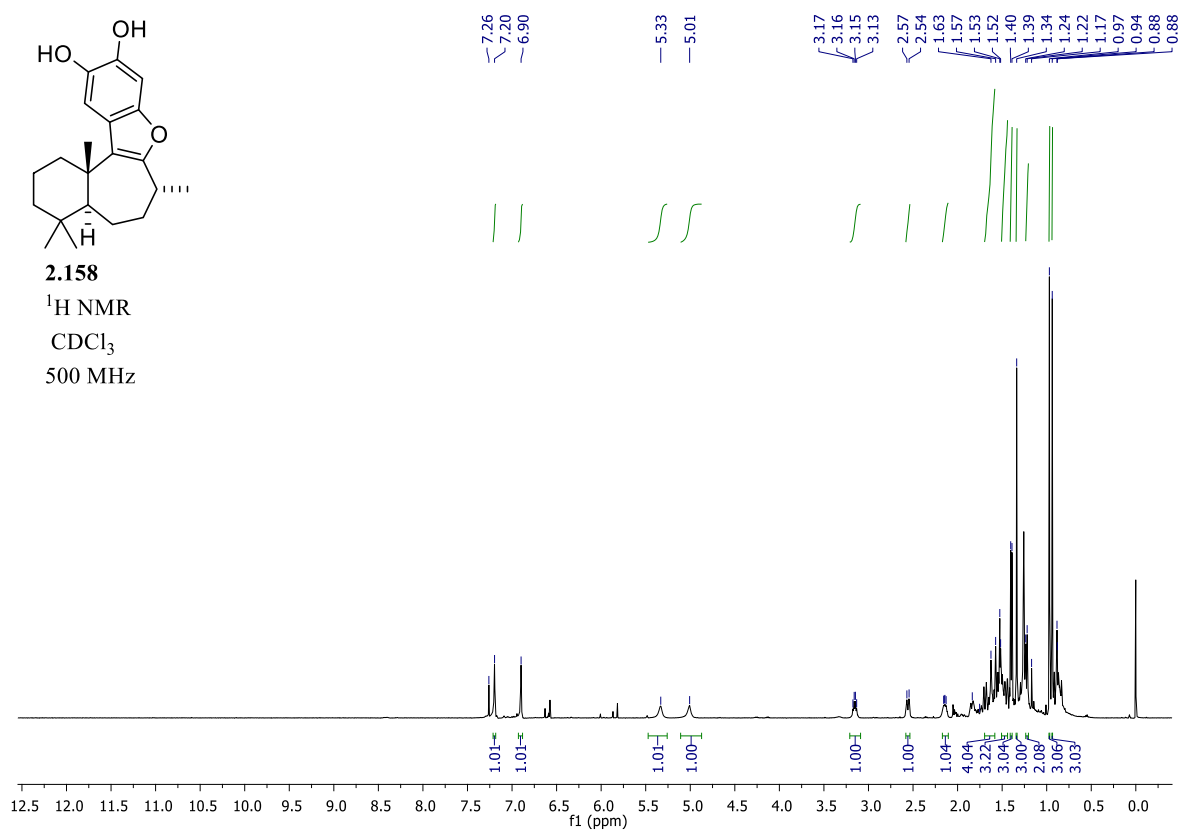


2.158

¹H NMR

CDCl₃

500 MHz

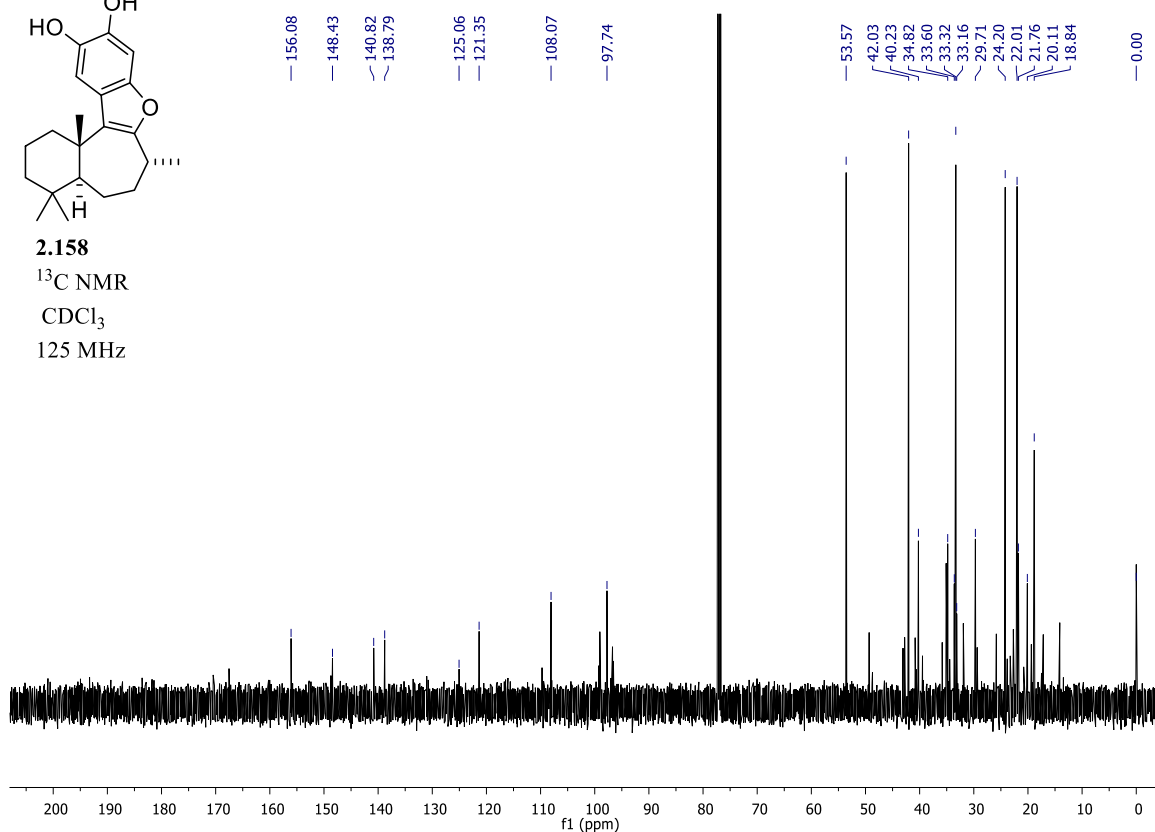


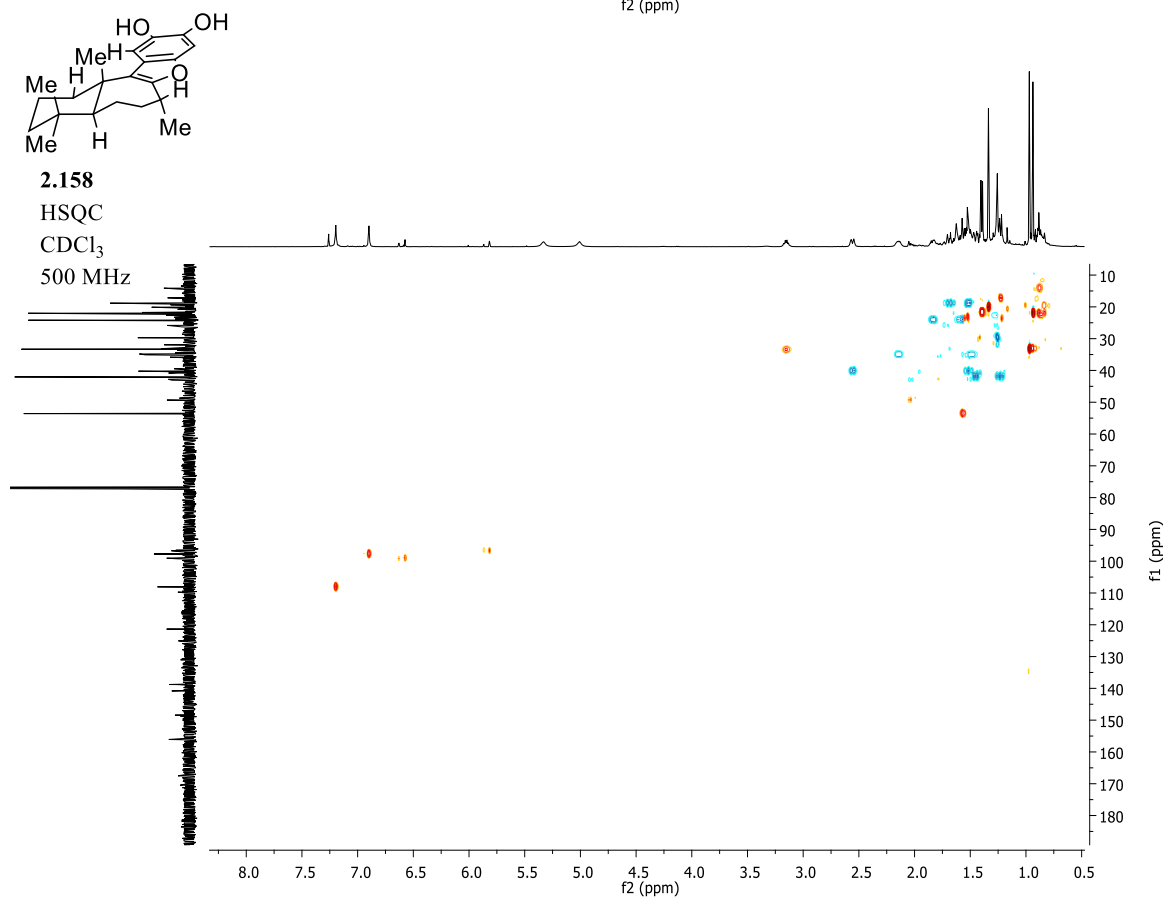
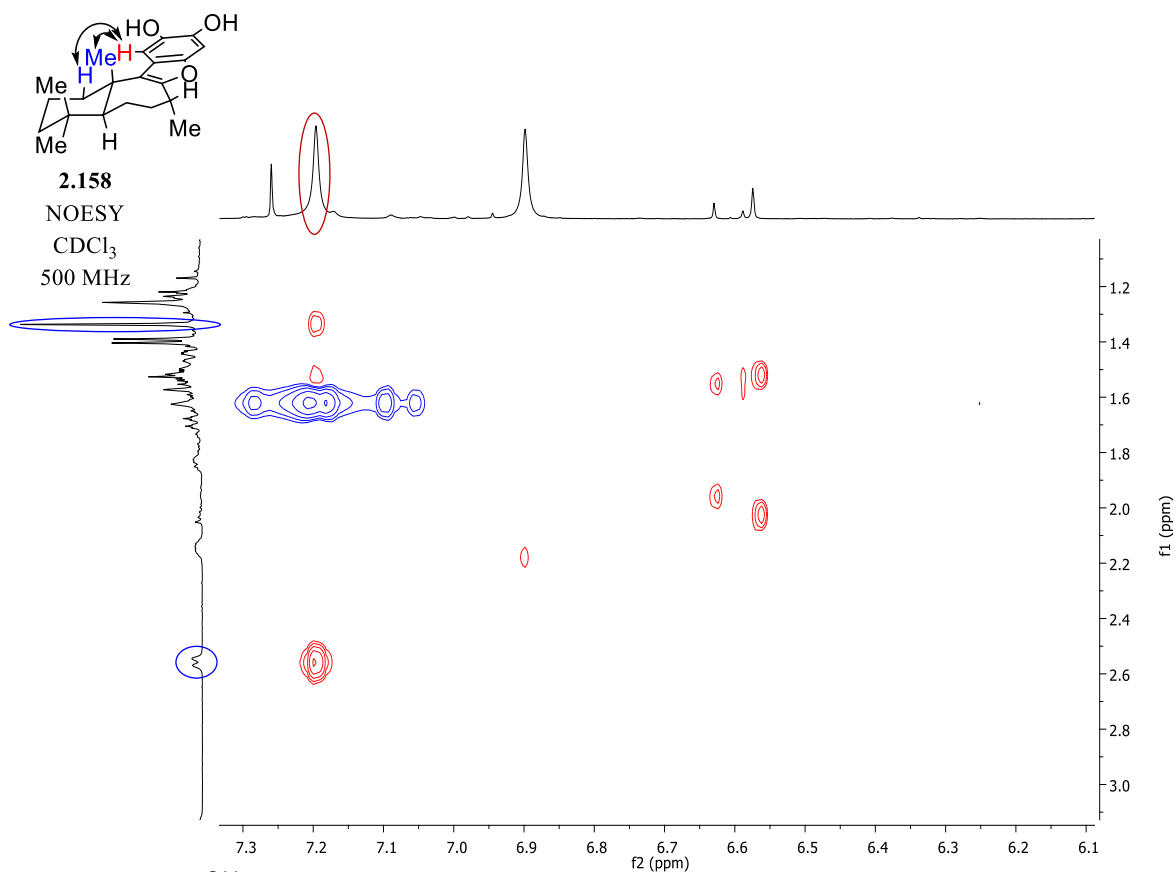
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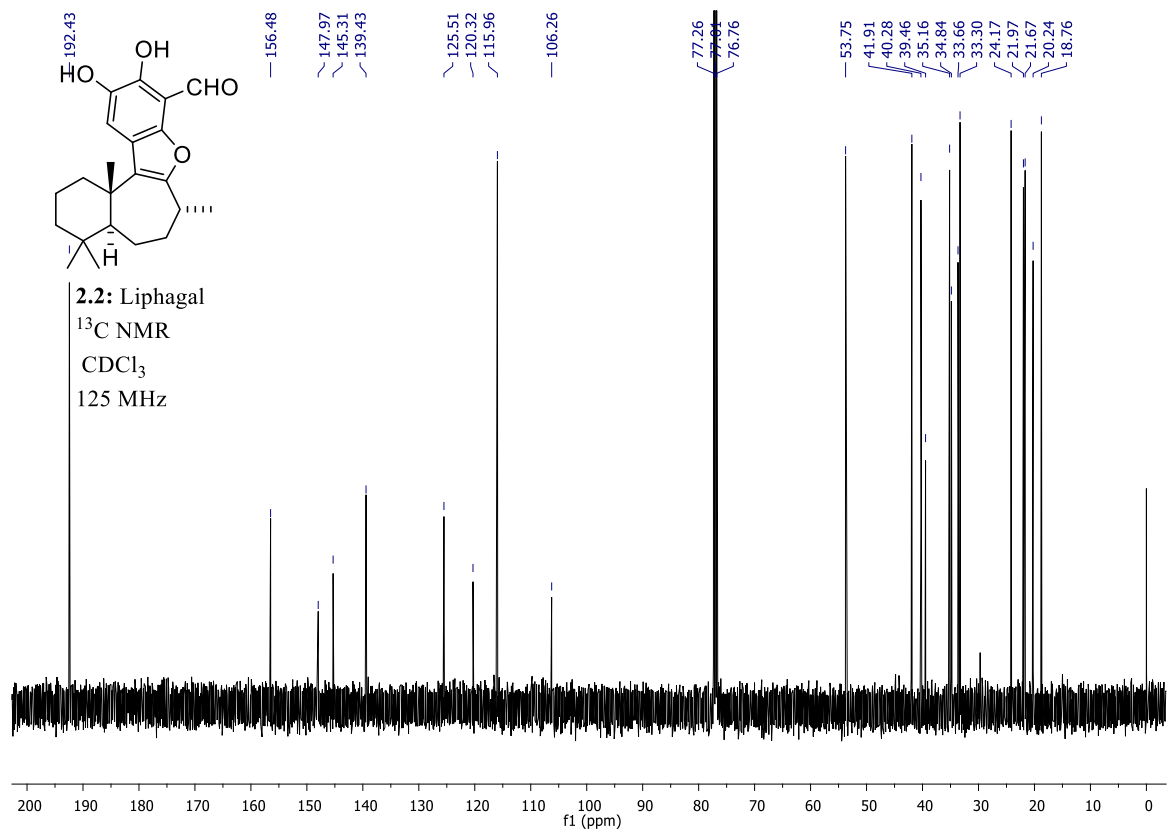
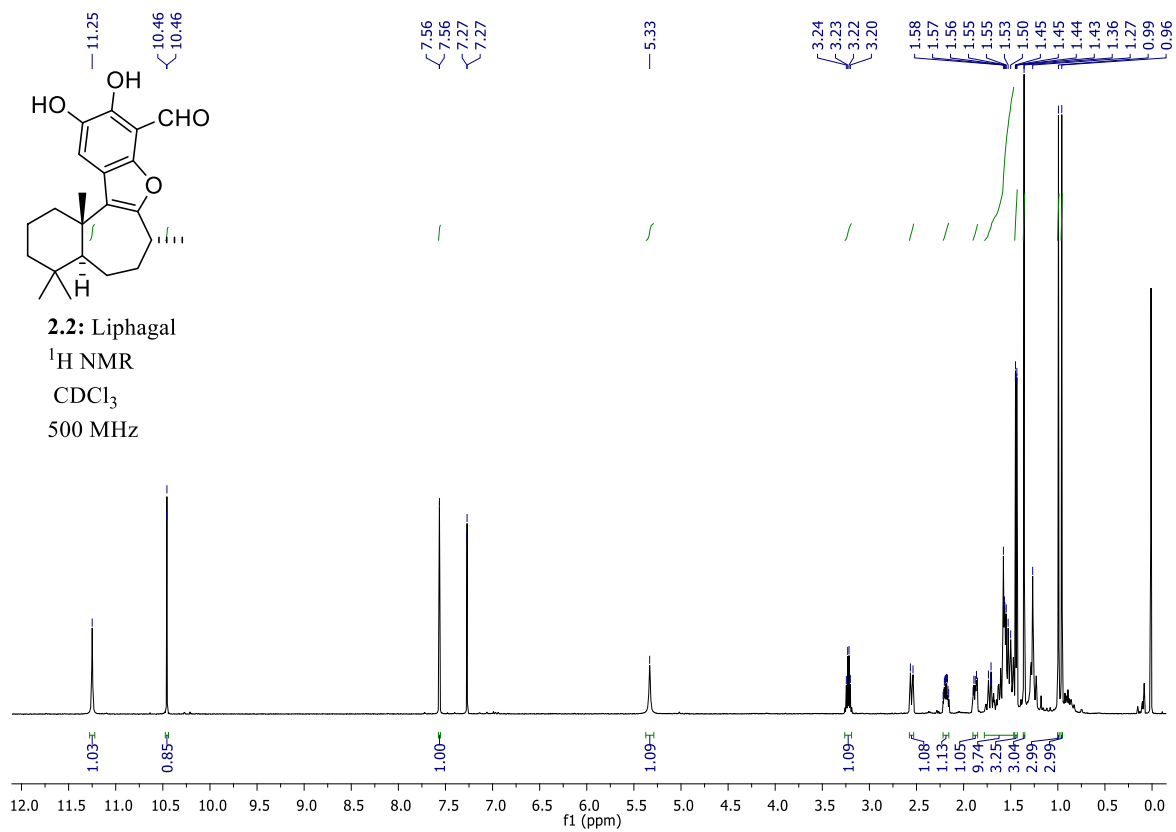
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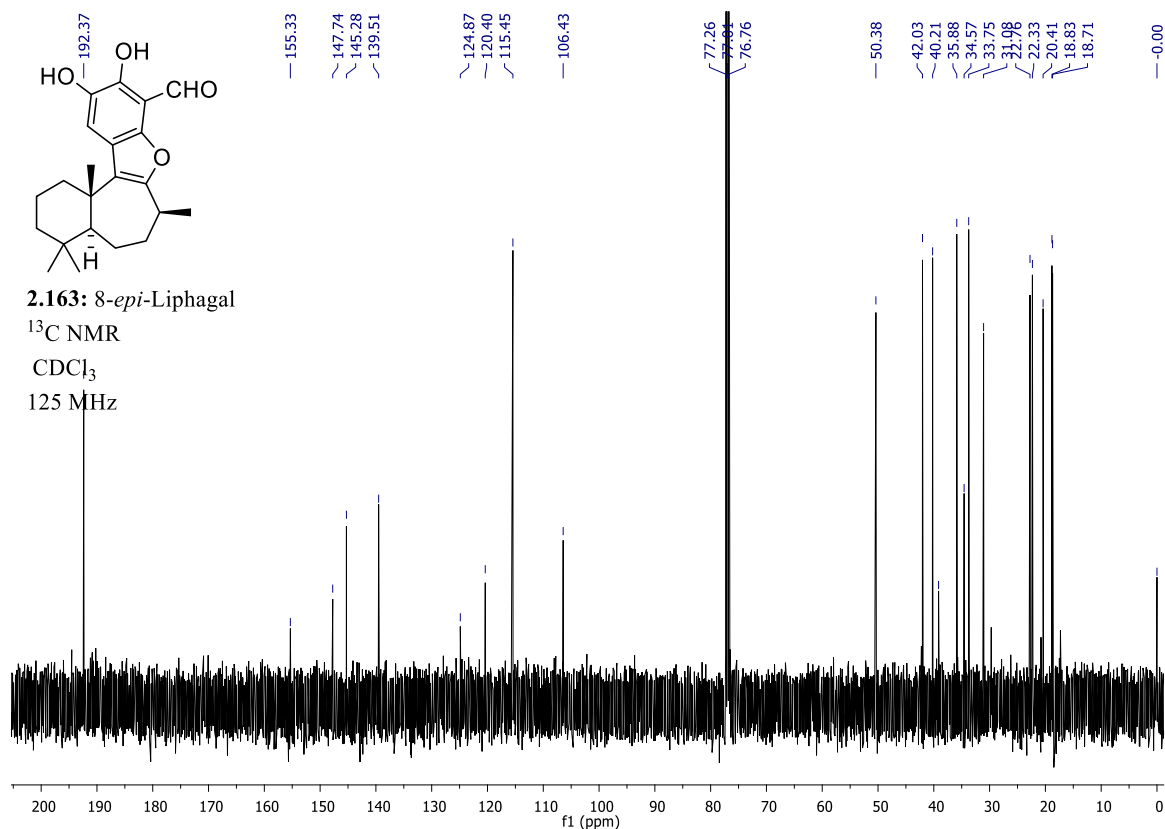
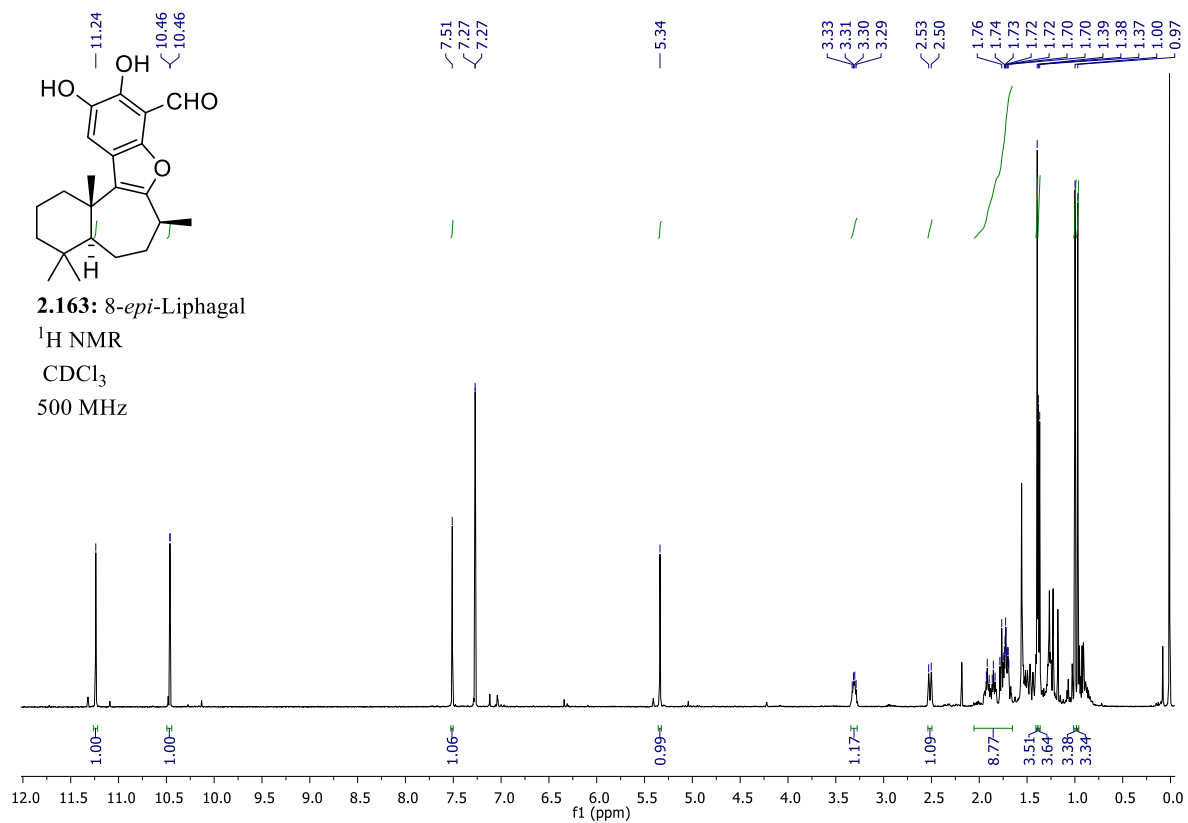
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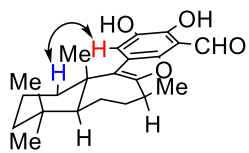
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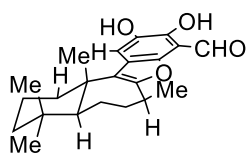
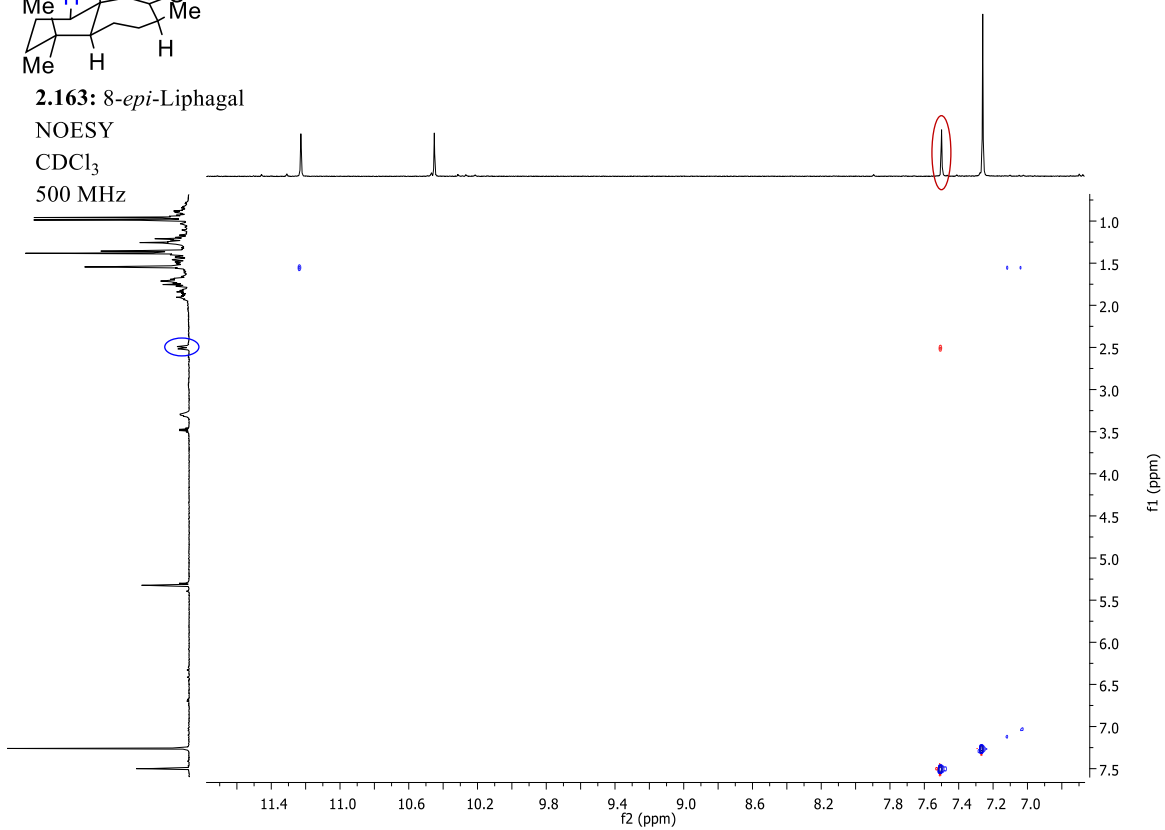


2.163: 8-*epi*-Liphagal

NOESY

CDCl₃

500 MHz

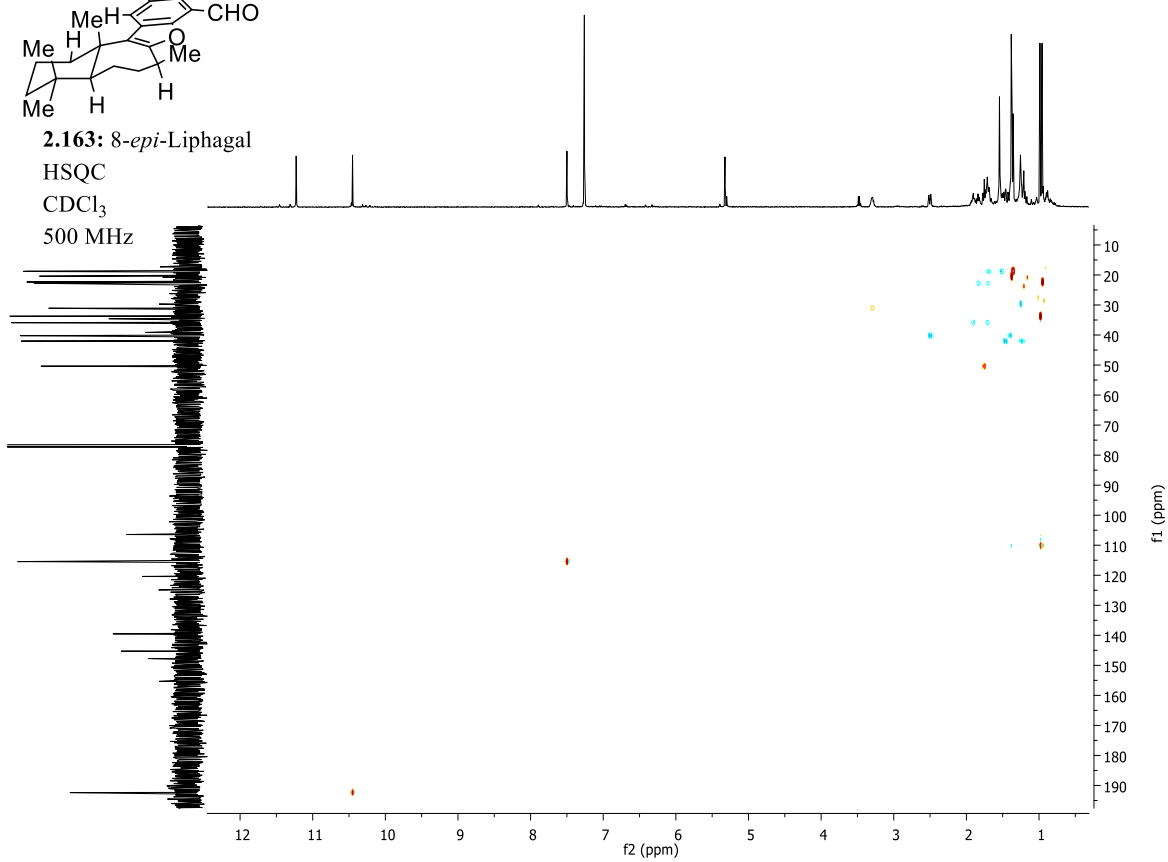


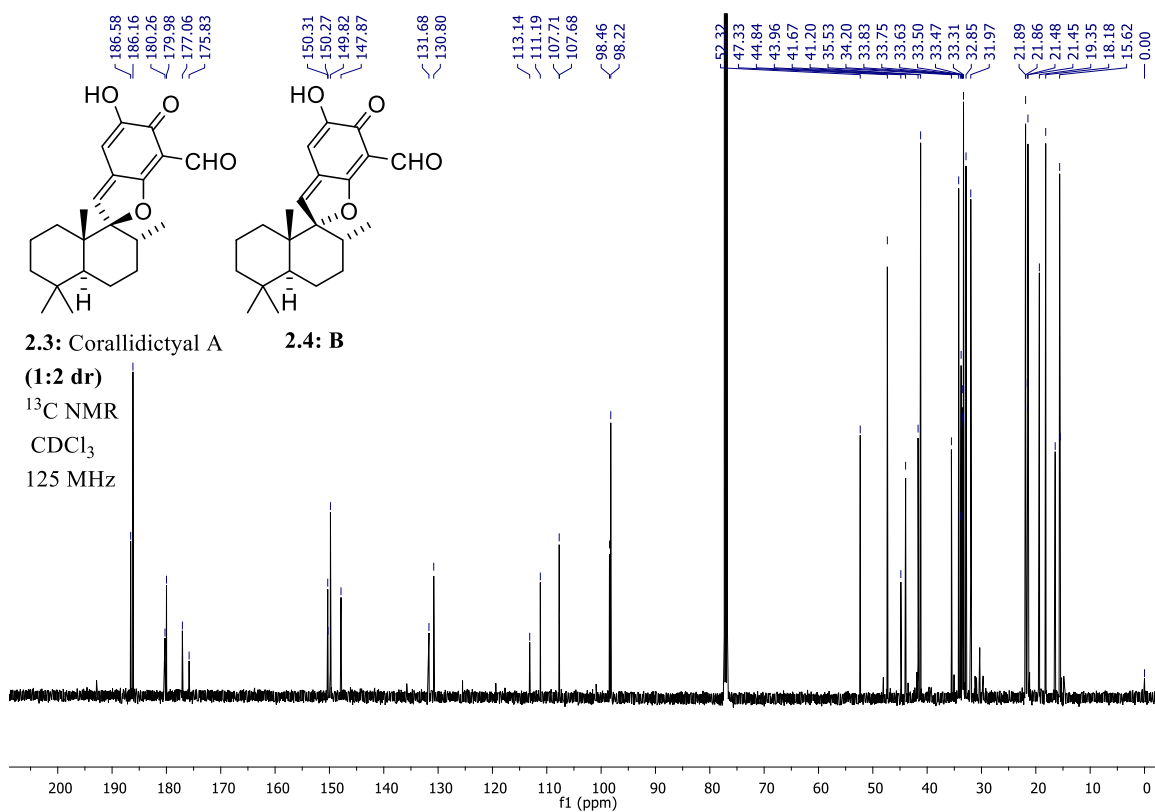
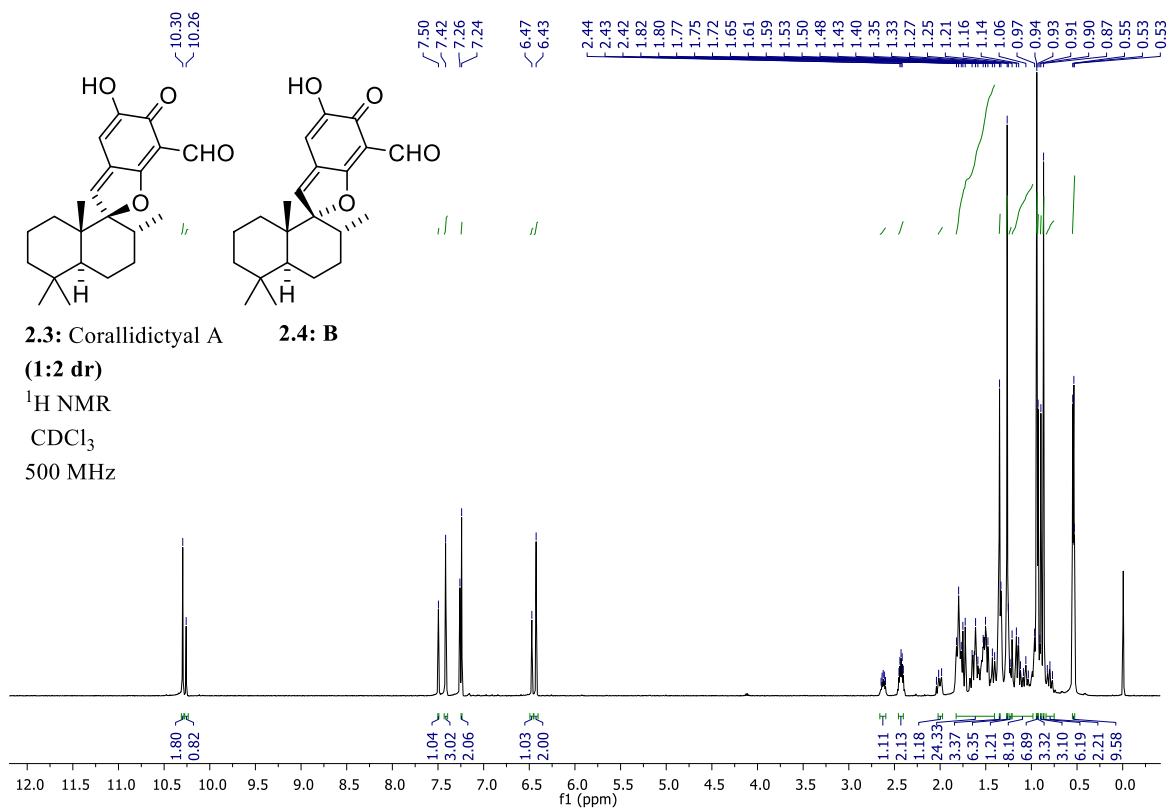
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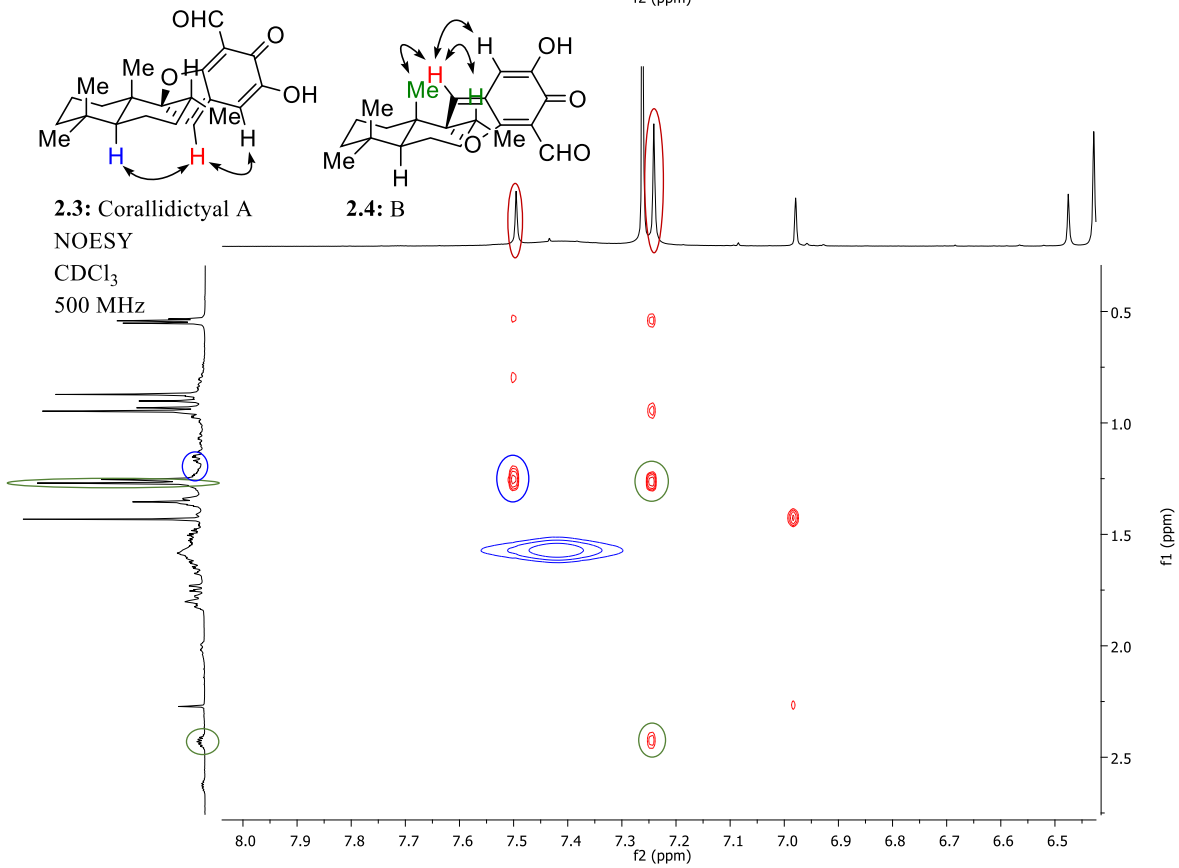
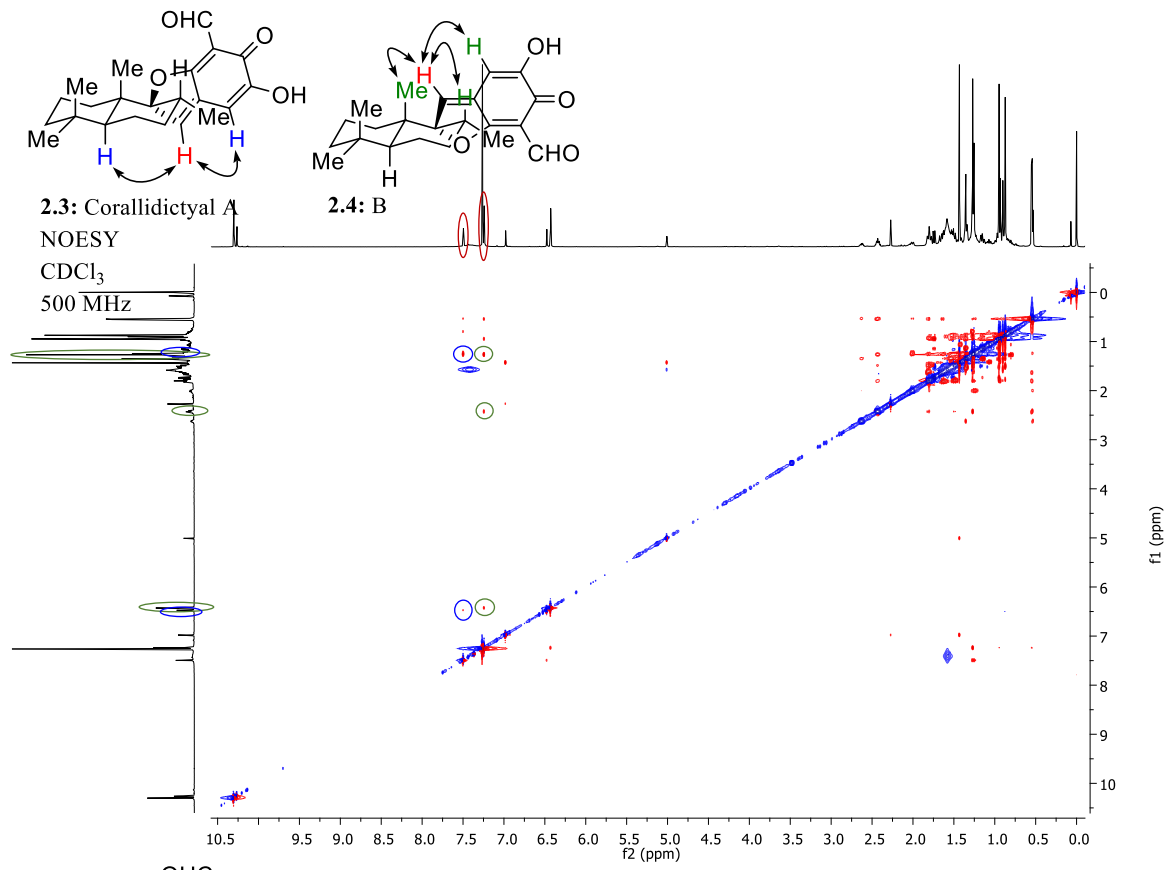
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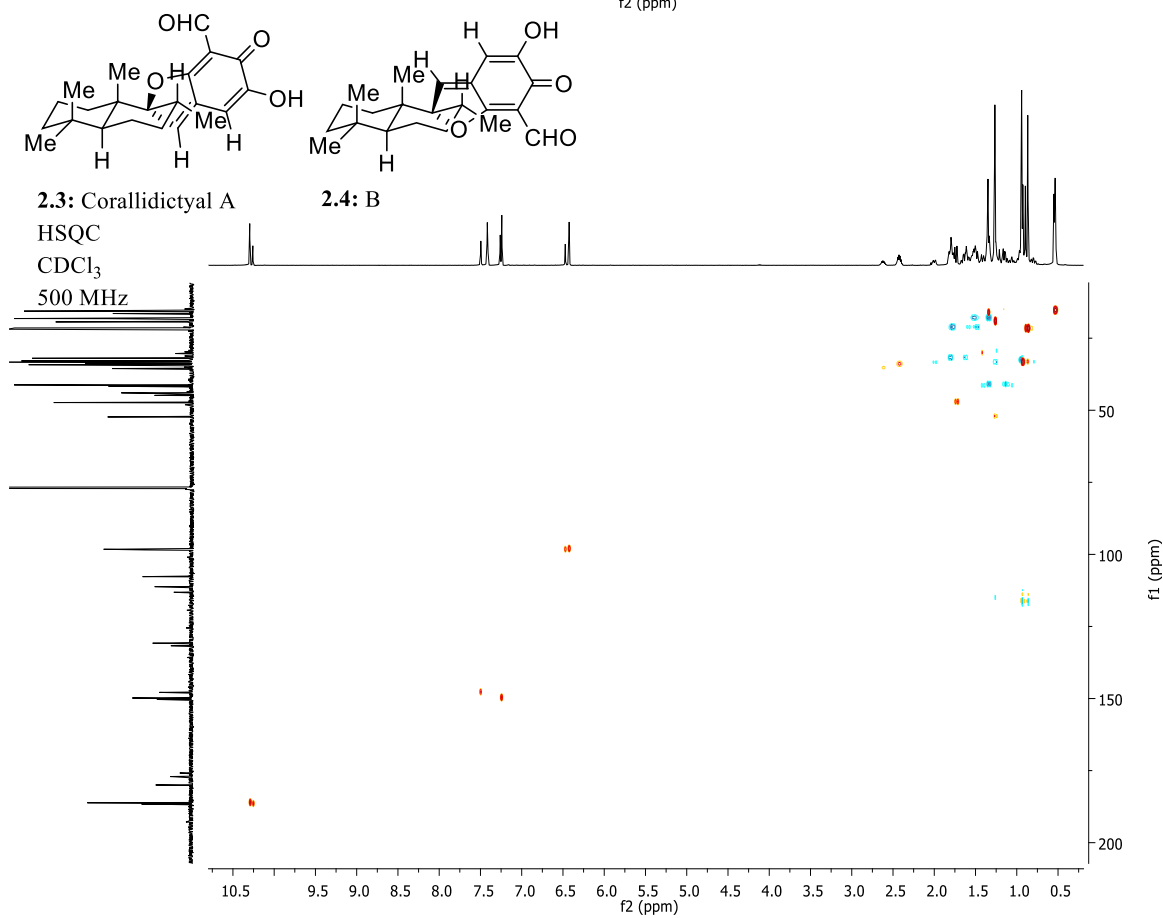
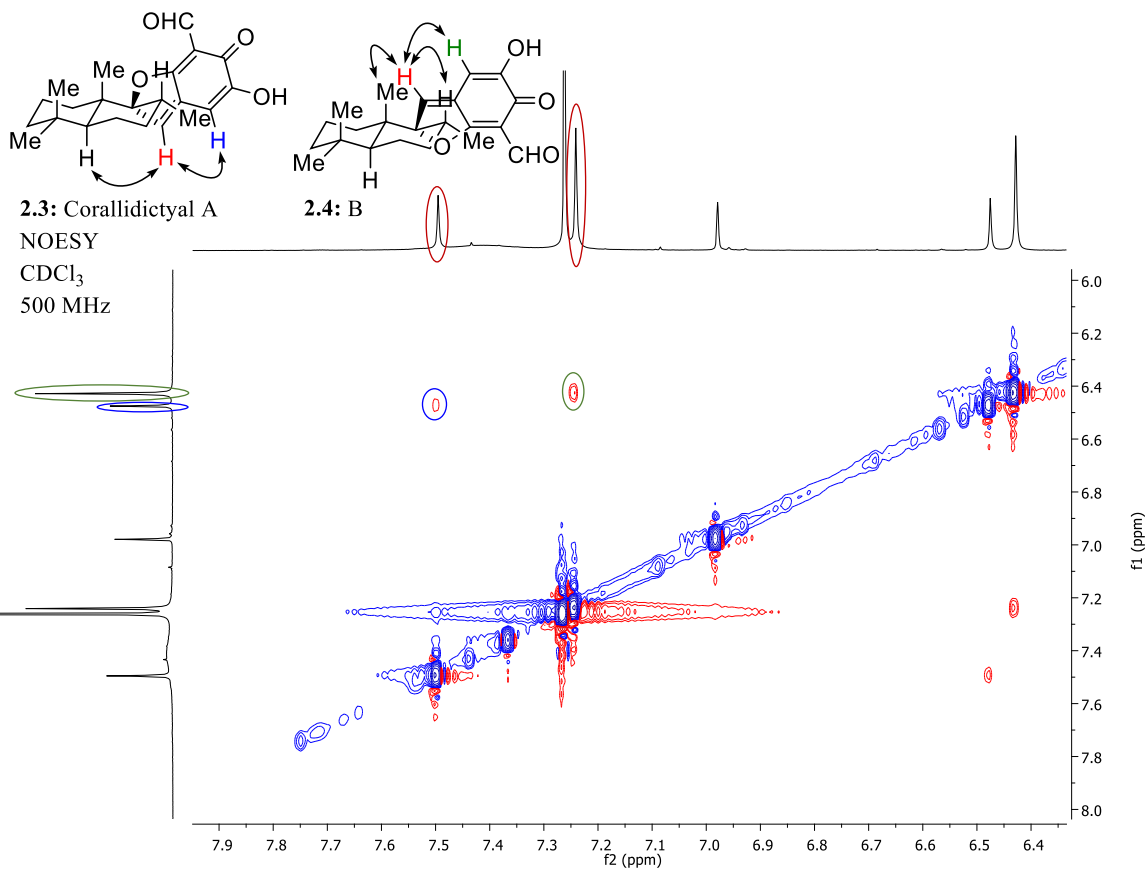
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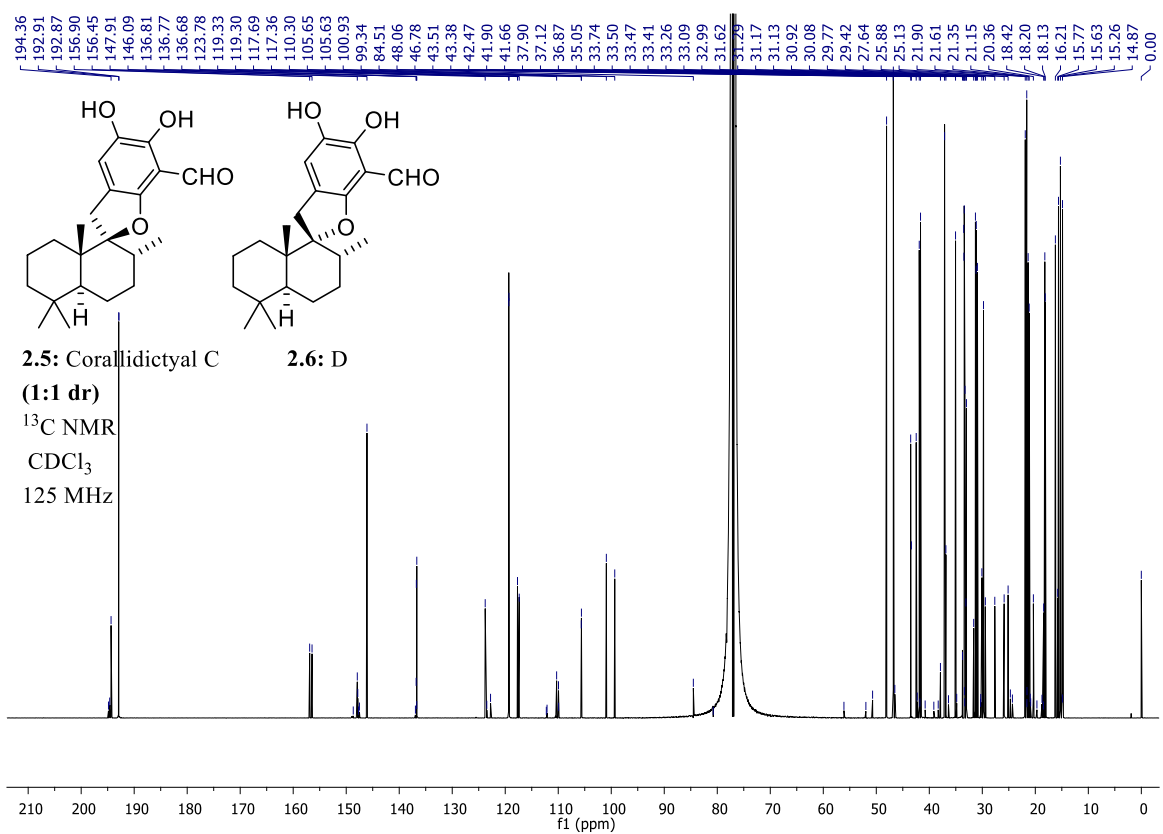
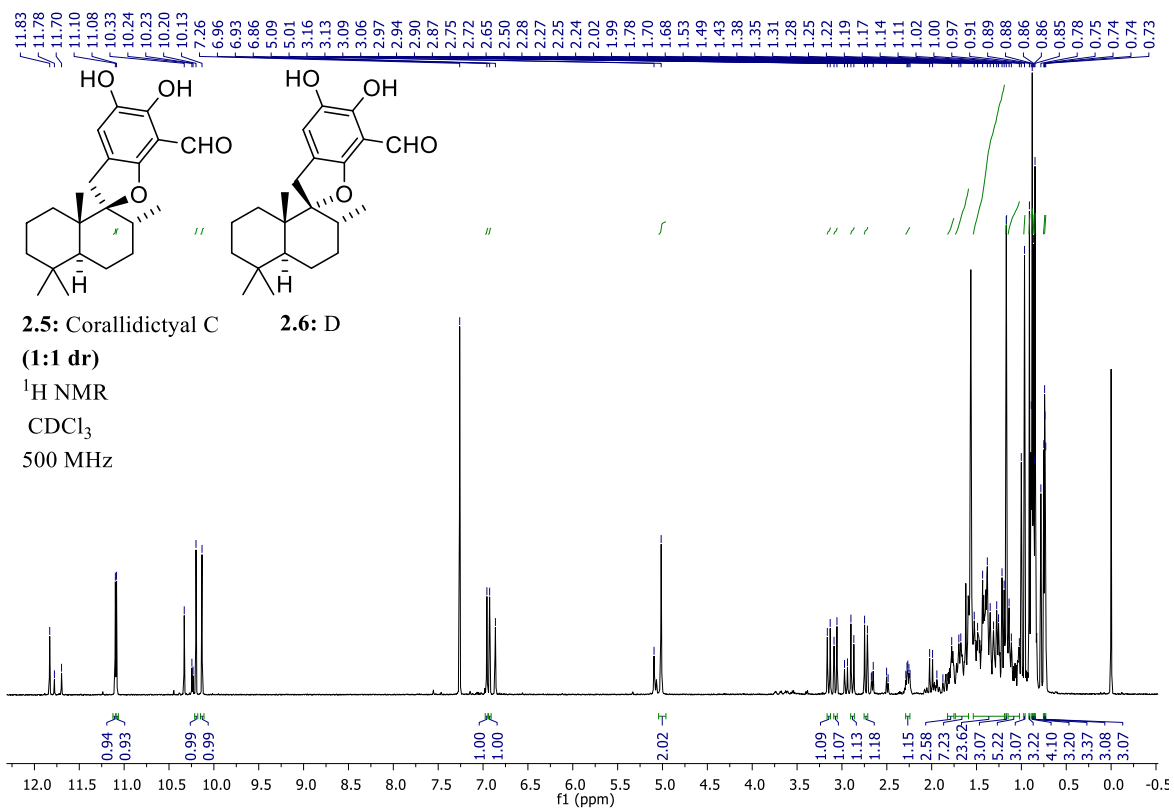
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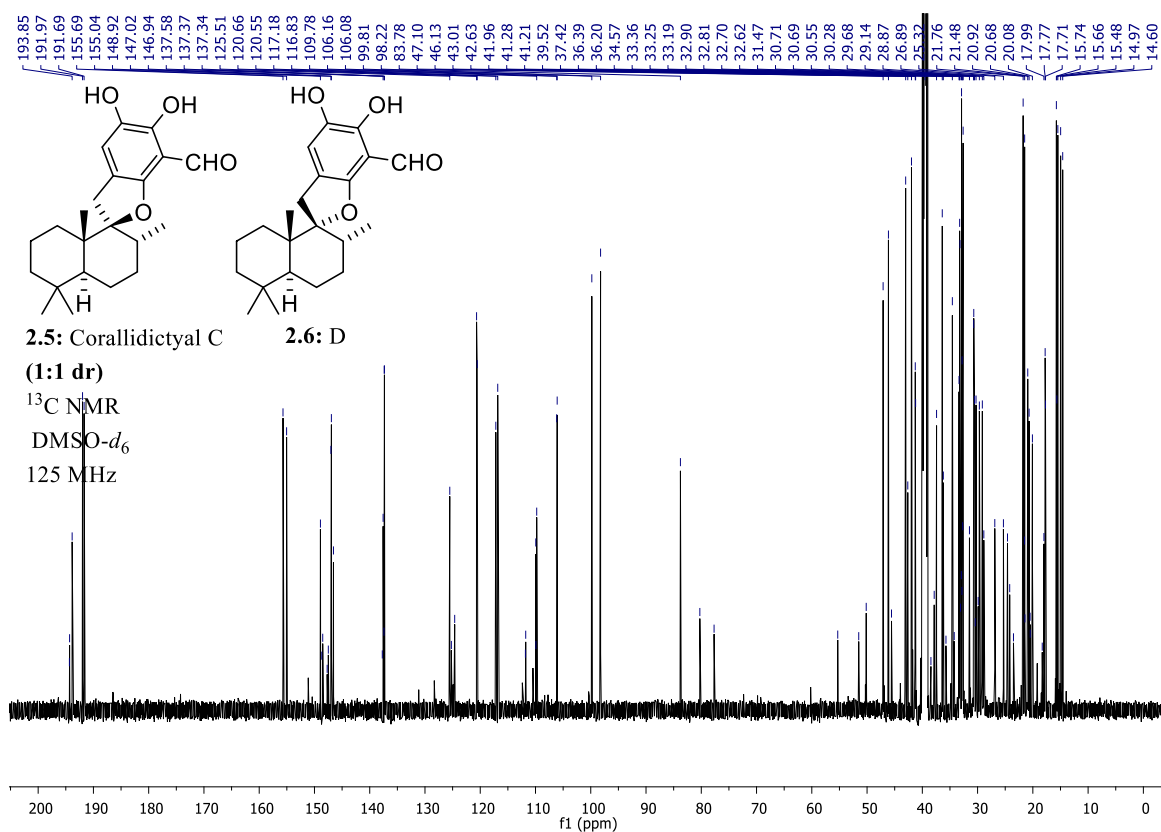
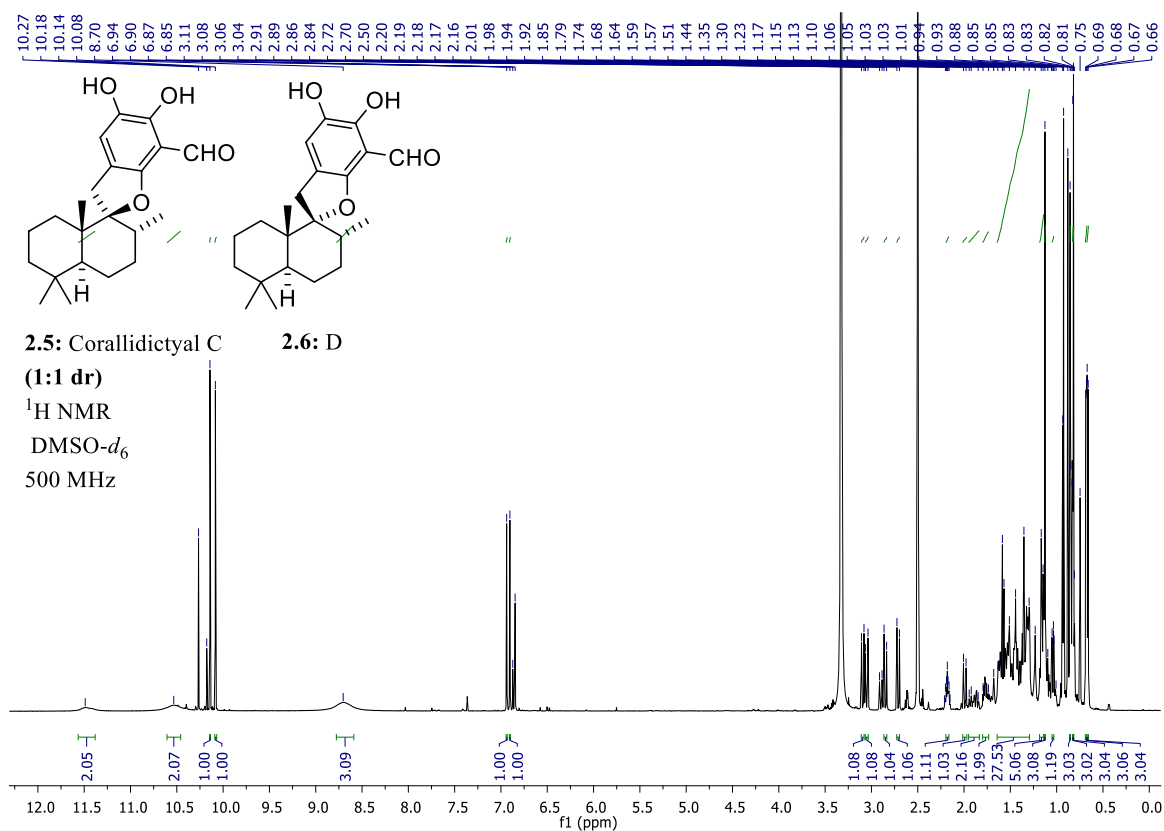


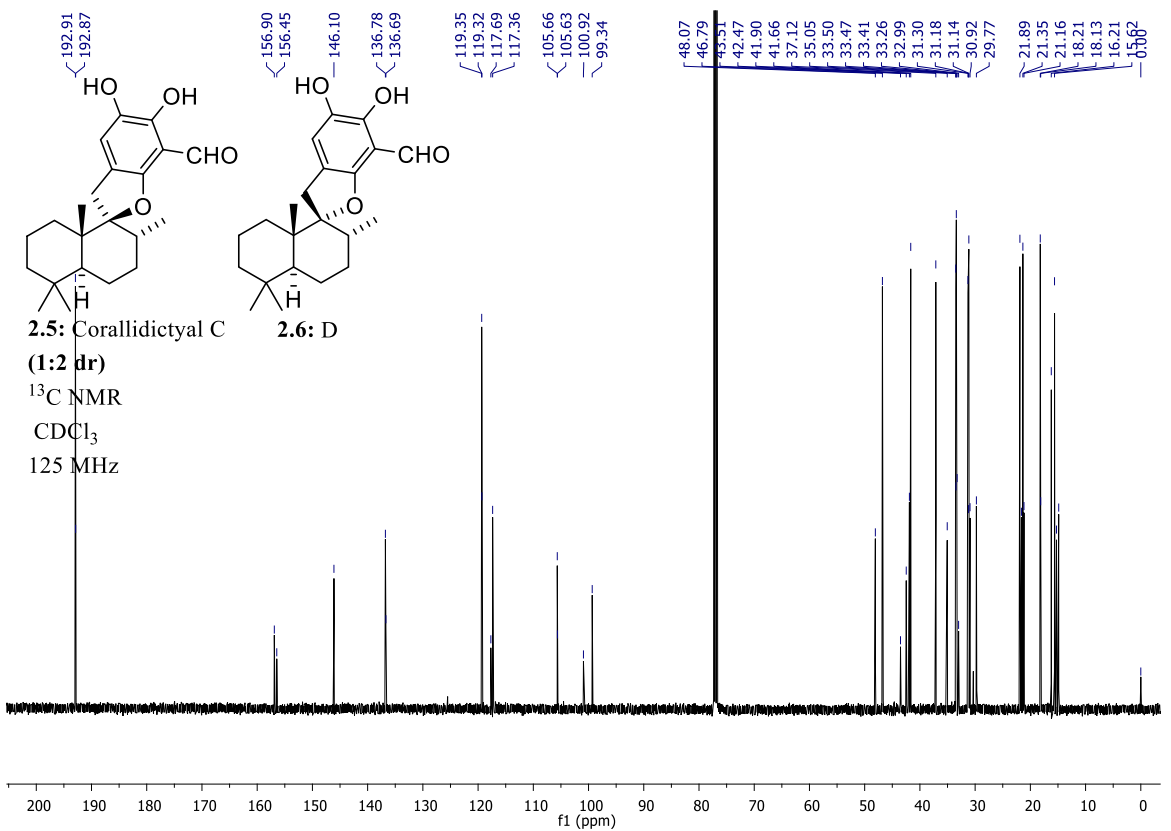
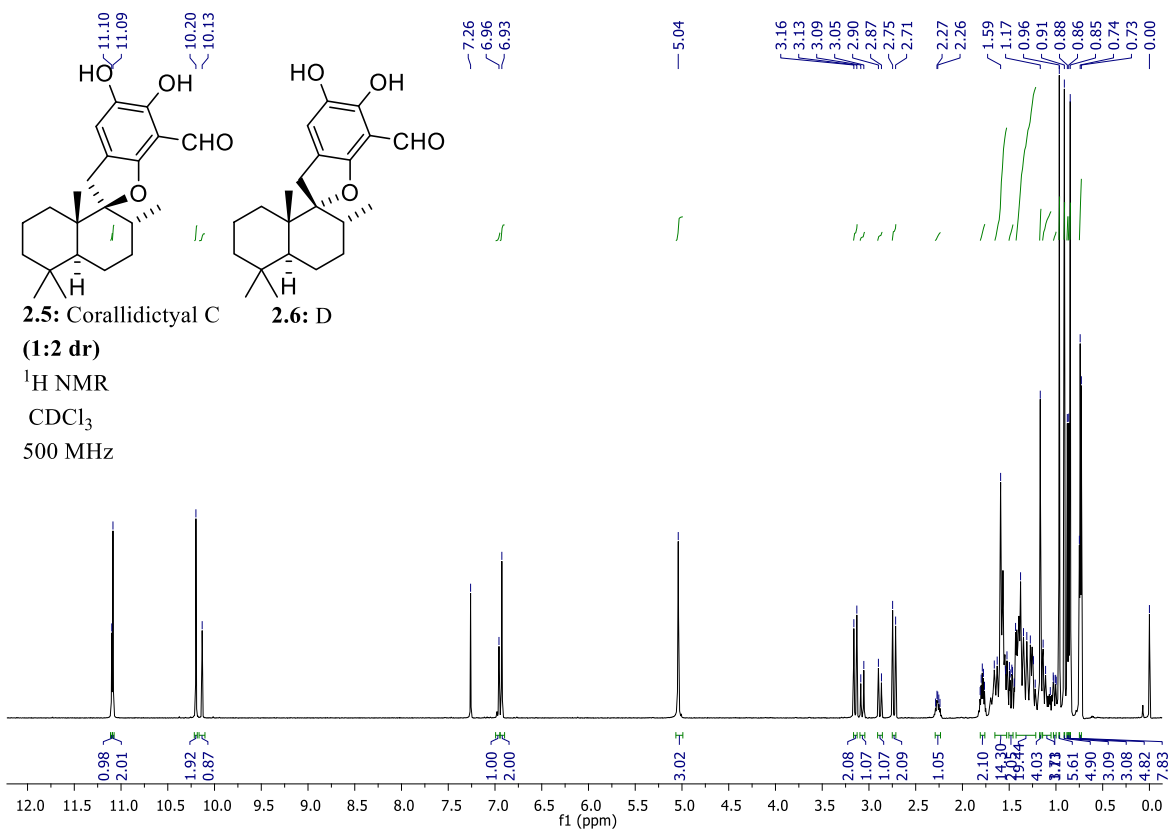


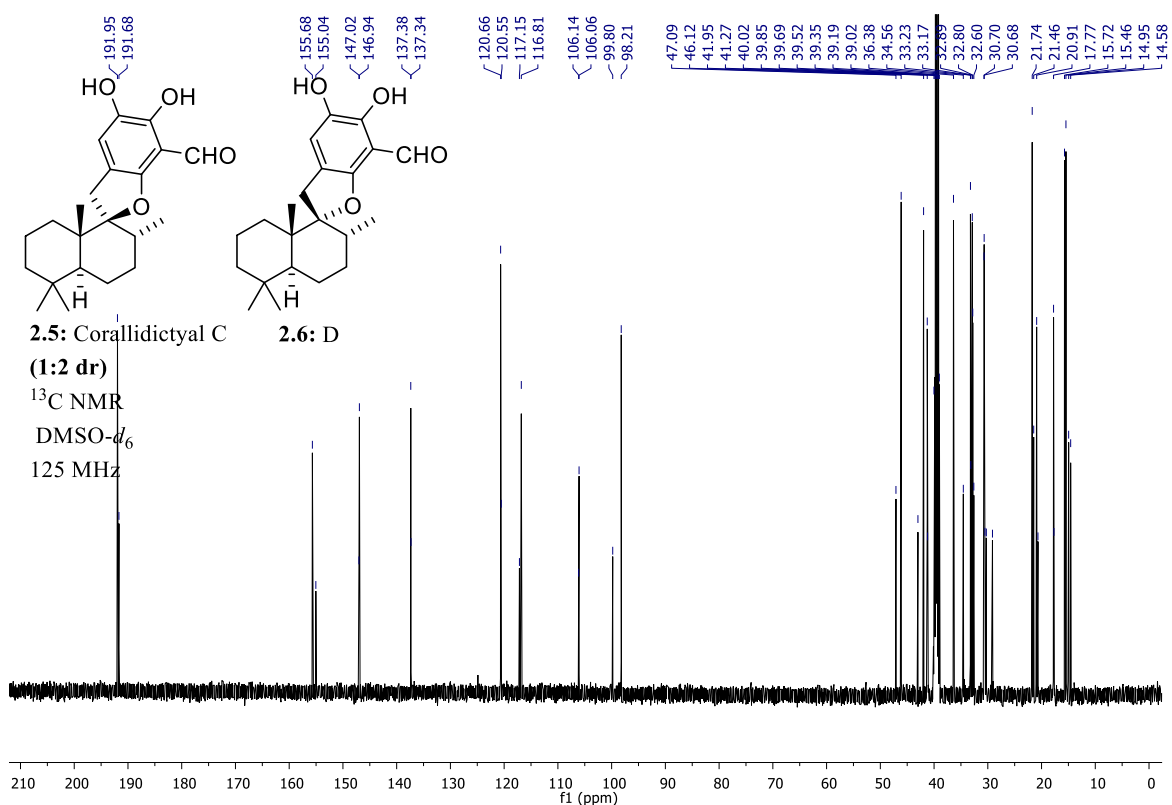
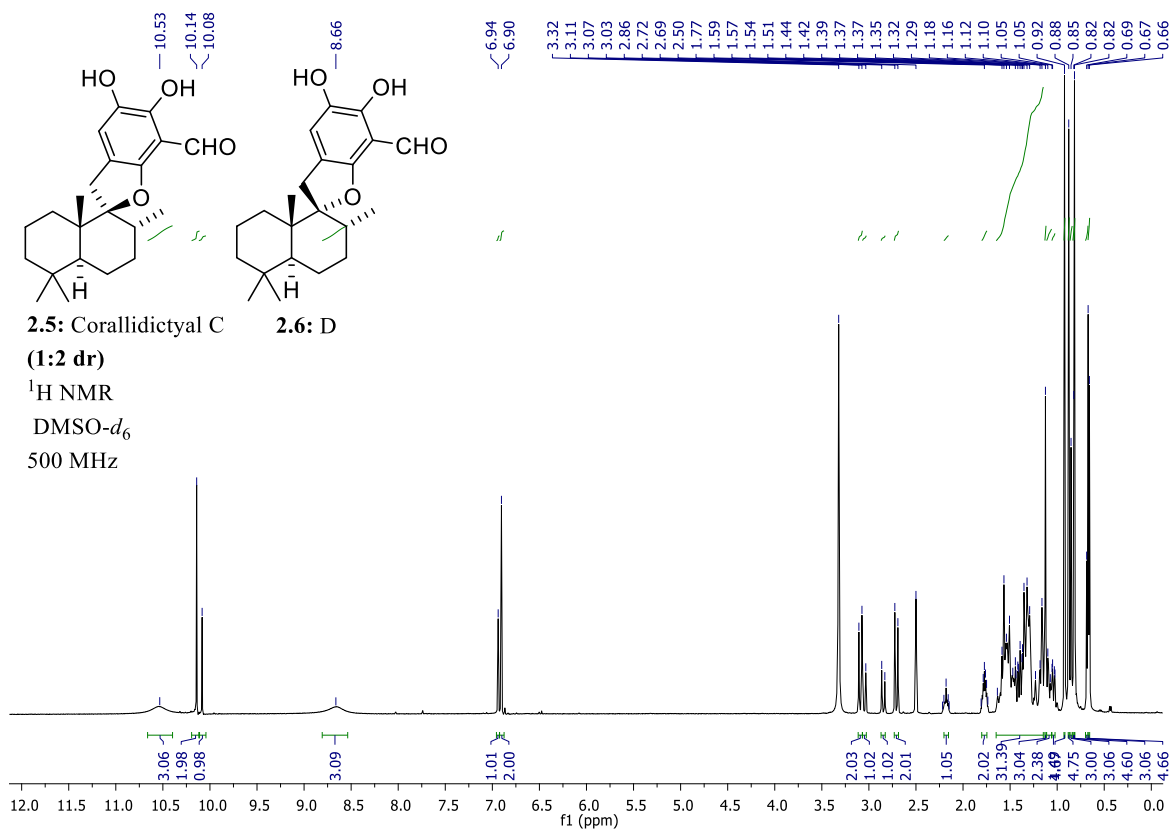


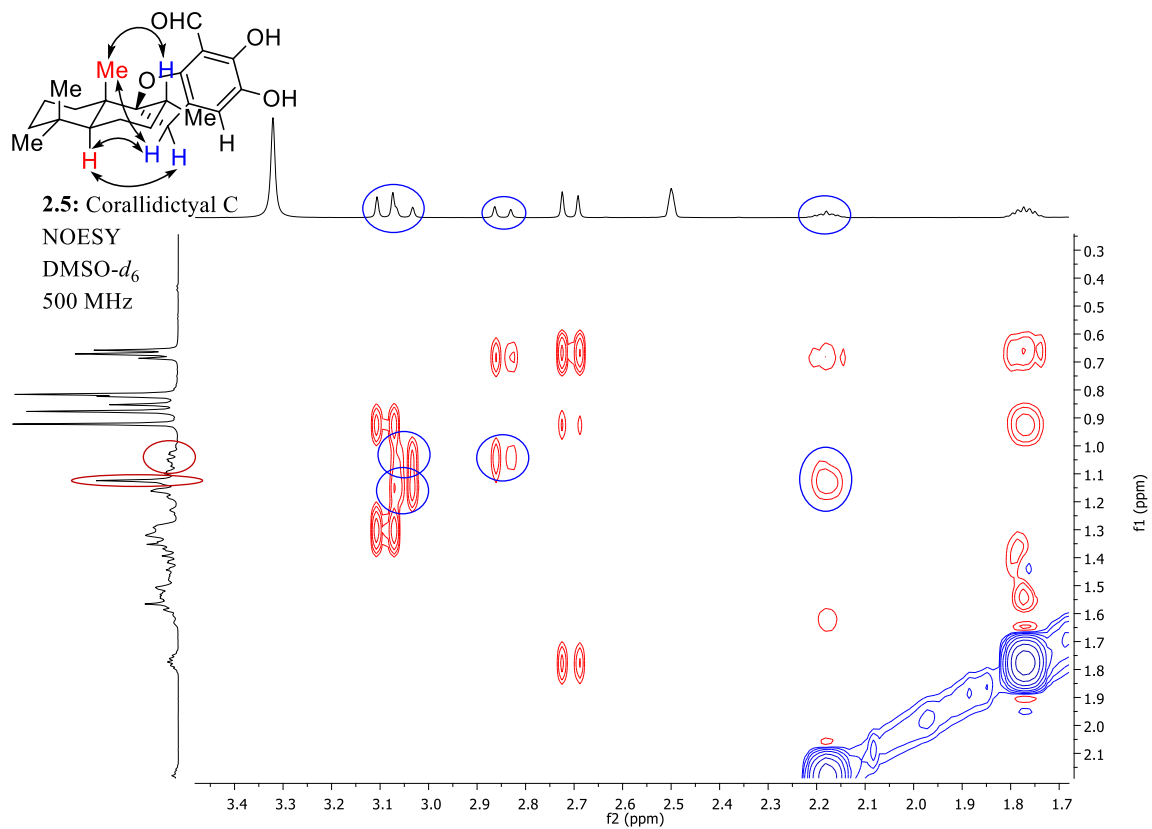
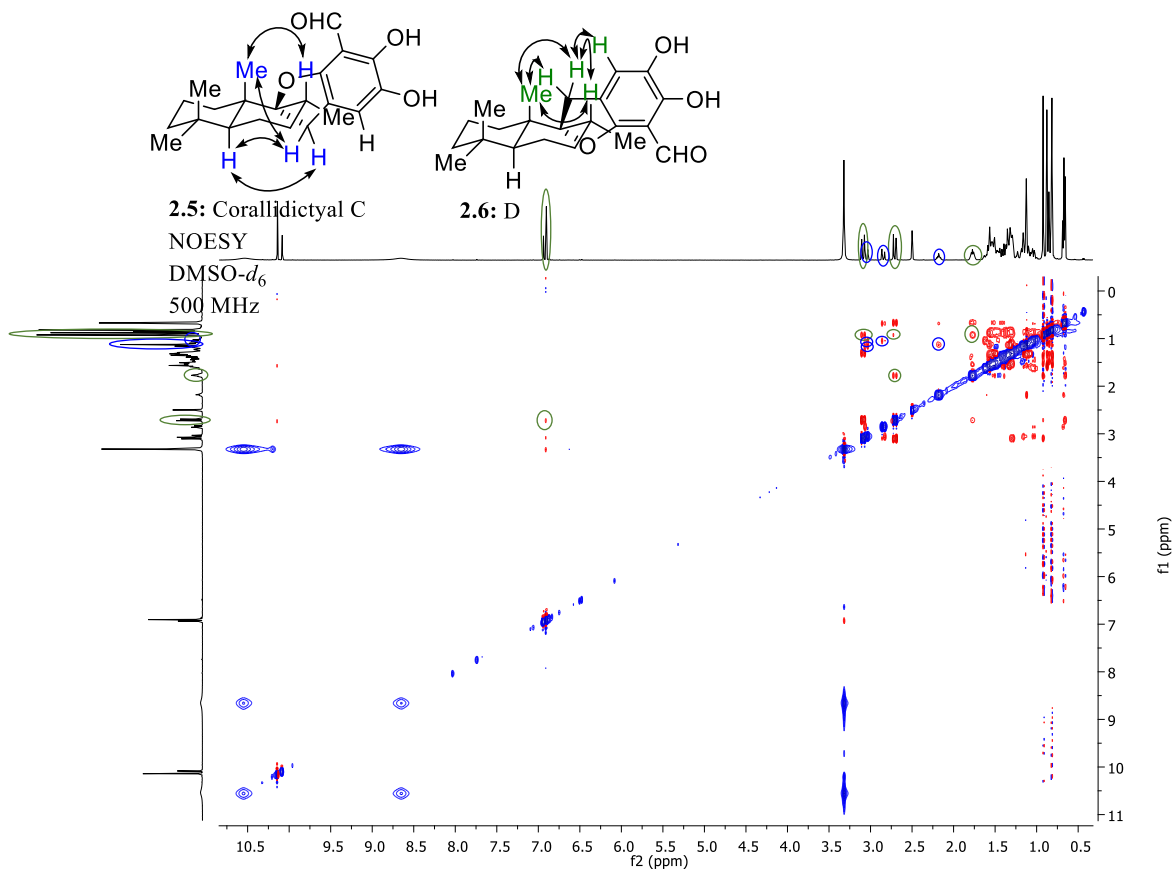


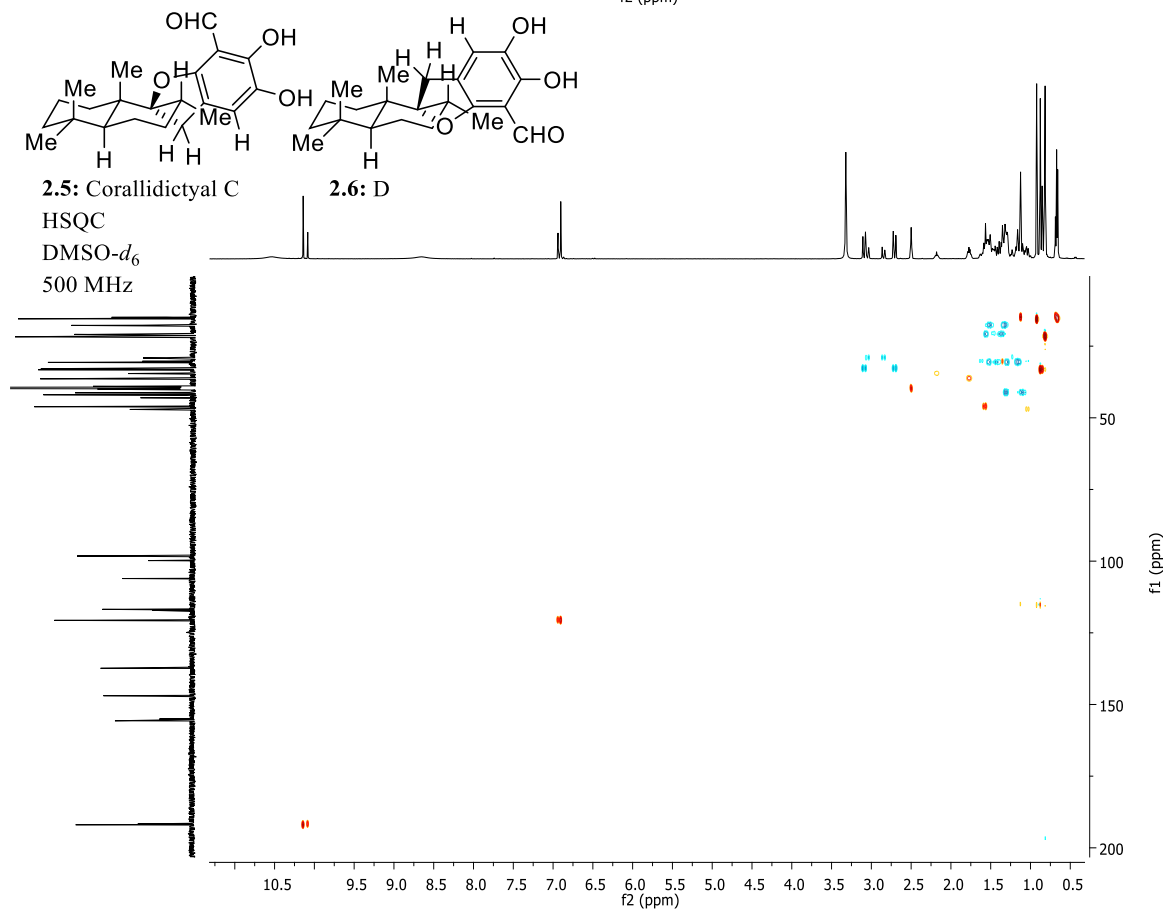
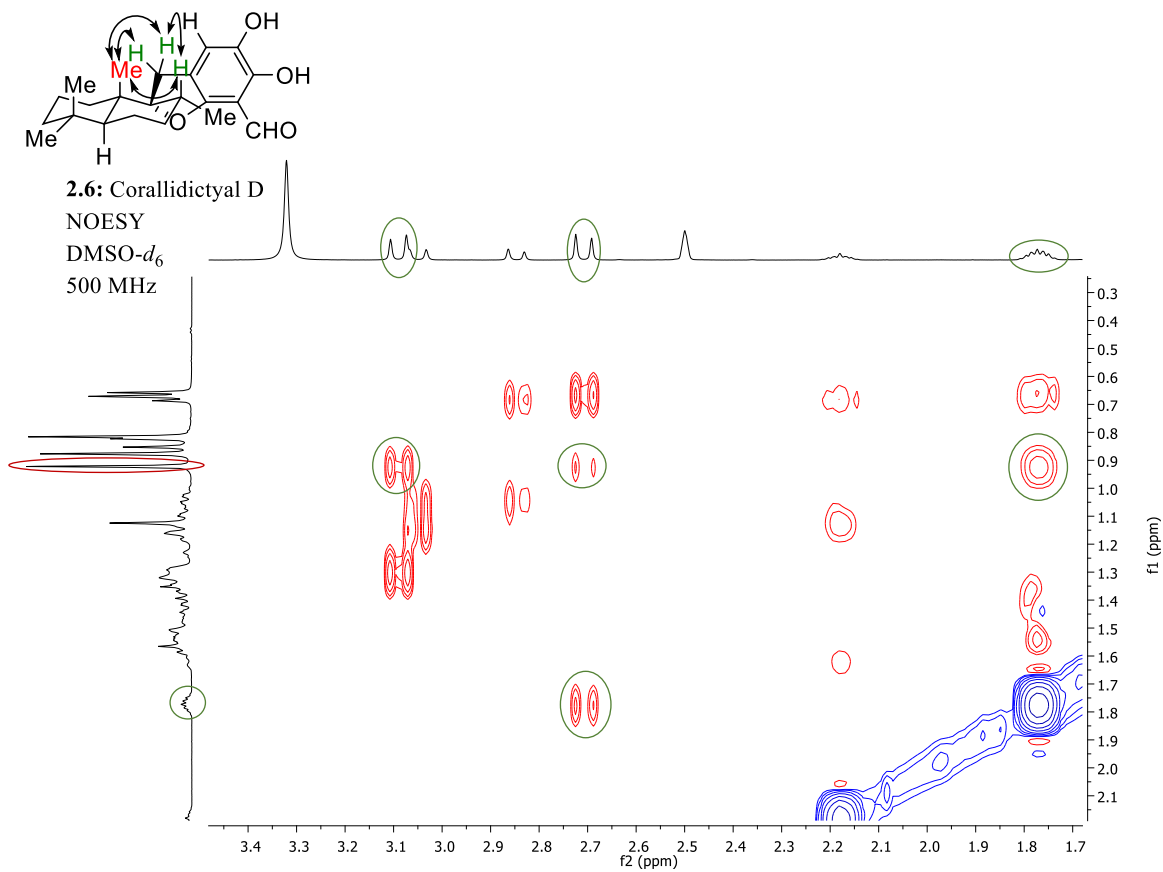












CHAPTER 3

Investigations into the Biomimetic Synthesis of the Spiroketal Natural Products, Virgatolides

A – C

3.1 Spiroketal Natural Products, Virgatolides A – C

3.1.1 Isolation of the Virgatolides A – C

The virgatolides A – C (**3.1** – **3.3**) are a family of benzannulated spiroketal natural products that were first isolated by Che from the invasive endophytic fungus, *Pestalotiopsis virgatula*.^[145] EtOAc extracts of the fungi cultures were found to be cytotoxic against HeLa cells (cervical epithelium), and upon fractionation of the extracts the virgatolides A – C (**3.1** – **3.3**) were afforded,^[145] along with the previously isolated pestaphthalides A (**3.4**) & B (**3.5**) (Figure 3.1).^[146] The structural configuration of virgatolides A – C (**3.1** – **3.3**) were determined via 2D NMR studies and the relative configurations were based upon X-ray crystallographic analysis of virgatolide A (**3.1**) (Figure 3.1).^[145] Virgatolides A & B (**3.1** & **3.2**) were found to possess the same isobenzofuranone framework as pestaphthalide A (**3.4**), and virgatolide C (**3.3**) with that of pestaphthalide B (**3.5**) (Figure 3.1). The absolute configurations of virgatolides A (**3.1**) & B (**3.2**) were determined by CD spectral comparison with pestaphthalide A (**3.4**). The absolute configuration of virgatolide C (**3.3**) was determined based on its shared chirality with pestaphthalide B (**3.5**) via CD spectral analysis (Figure 3.1).

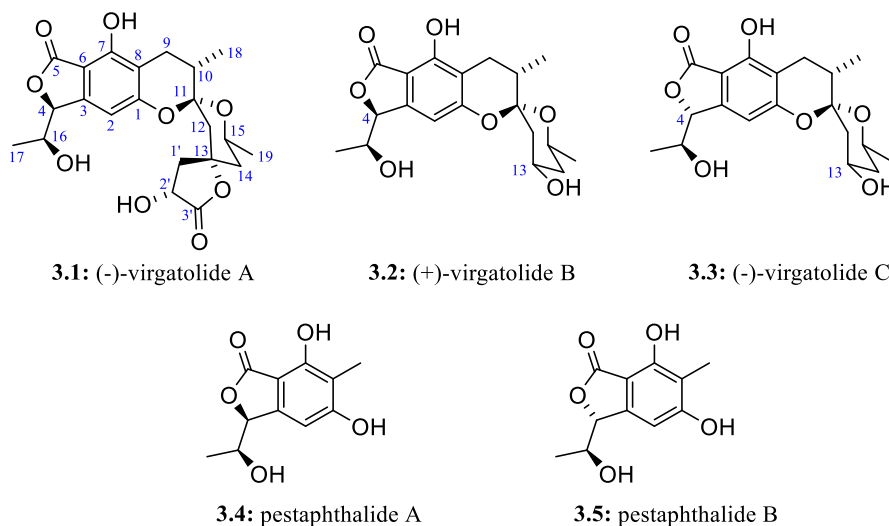
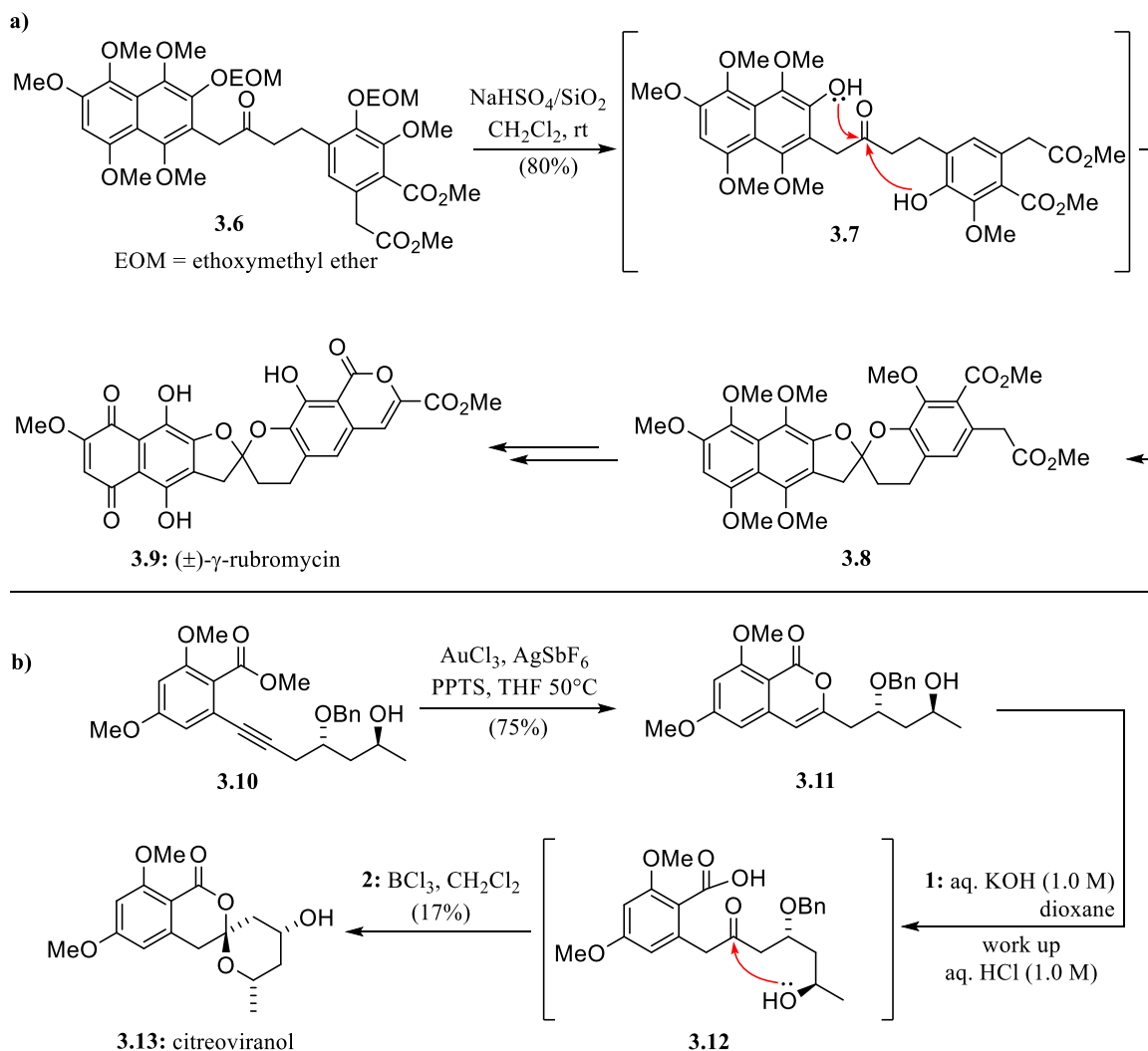


Figure 3.1: Isolated natural products, virgatolides A – C (**3.1** – **3.3**),^[145] and pestaphthalides A (**3.4**) & B (**3.5**) from the fungus *Pestalotiopsis virgatula*.^[146]

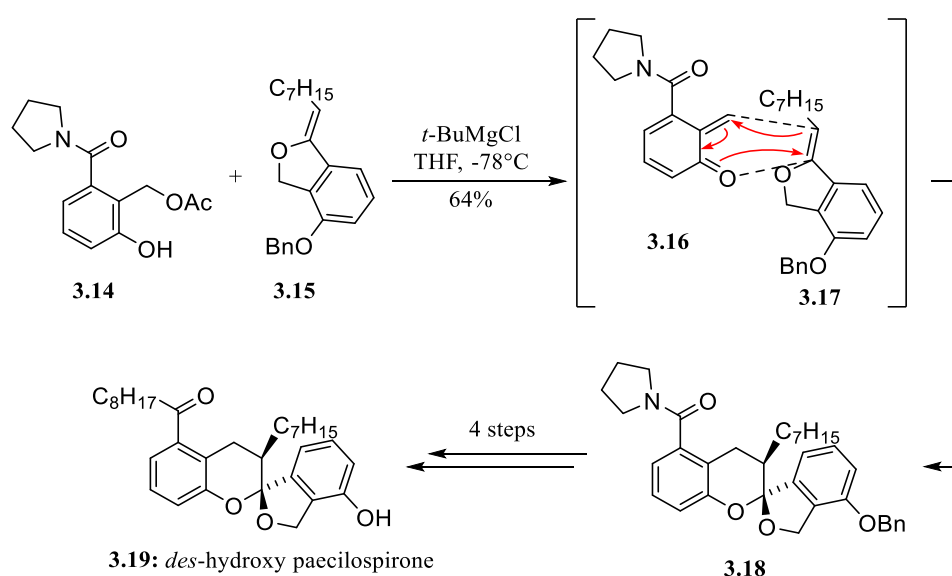
3.1.2 Introduction to Spiroketal Natural Products



Scheme 3.1: Examples of cyclisation reactions of spiroketal natural products, **a)** formal racemic synthesis of (±)-γ-rubromycin (**3.9**) by Brimble *et al.*^[147] **b)** Two-step gold/acid mediated spirocyclisation in the total synthesis of citreoviranol (**3.13**) by Brimble *et al.*^[148]

Benzannulated spiroketal natural products, characterised by spiroketal substituents fused with aryl moieties, are relatively rare throughout the literature.^[149] 5,6 spirocyclic benzannulated ketals appear to be the most prevalent natural products discovered in this family, followed by 5,5 spiroketal systems. However, fewer examples of 6,6 benzannulated spiroketal natural products have been discovered, making them particularly novel amongst an already unique and expanding field of secondary metabolites. Various methods of synthesising these unique spiroketal natural products have been investigated from the more pragmatic acid catalysed spirocyclisation approach (**3.6** – **3.8**),^[147] to unconventional two-step spirocyclisation methods involving gold catalysts to afford the desired spiro lactone moiety (**3.10** – **3.13**) (scheme 3.1).^[148]

The use of *ortho*-quinone methides (*o*-QM) in the synthesis of benzannulated spiroketals, acting as dienes that can participate in cycloadditions, has become an increasingly investigated viable strategy. However, few successful examples of these spirocyclisation transformations, employing *o*-QMs in the total synthesis of benzannulated spiroketal natural products, have been reported. Pettus *et al* reported a protocol for the synthesis of *des*-hydroxy paecilospirone (**3.19**) via a cycloaddition of an *in situ* generated *o*-QM (**3.16**) from phenol **3.14** to afford the key spiroketal moiety **3.18** (scheme 3.2).^[150] The *o*-QM protocol developed by Pettus was employed in the synthesis of multiple spiroketal natural products, highlighting the versatility of these highly reactive species, and hence, their legitimacy as a biosynthetic precursor in nature.

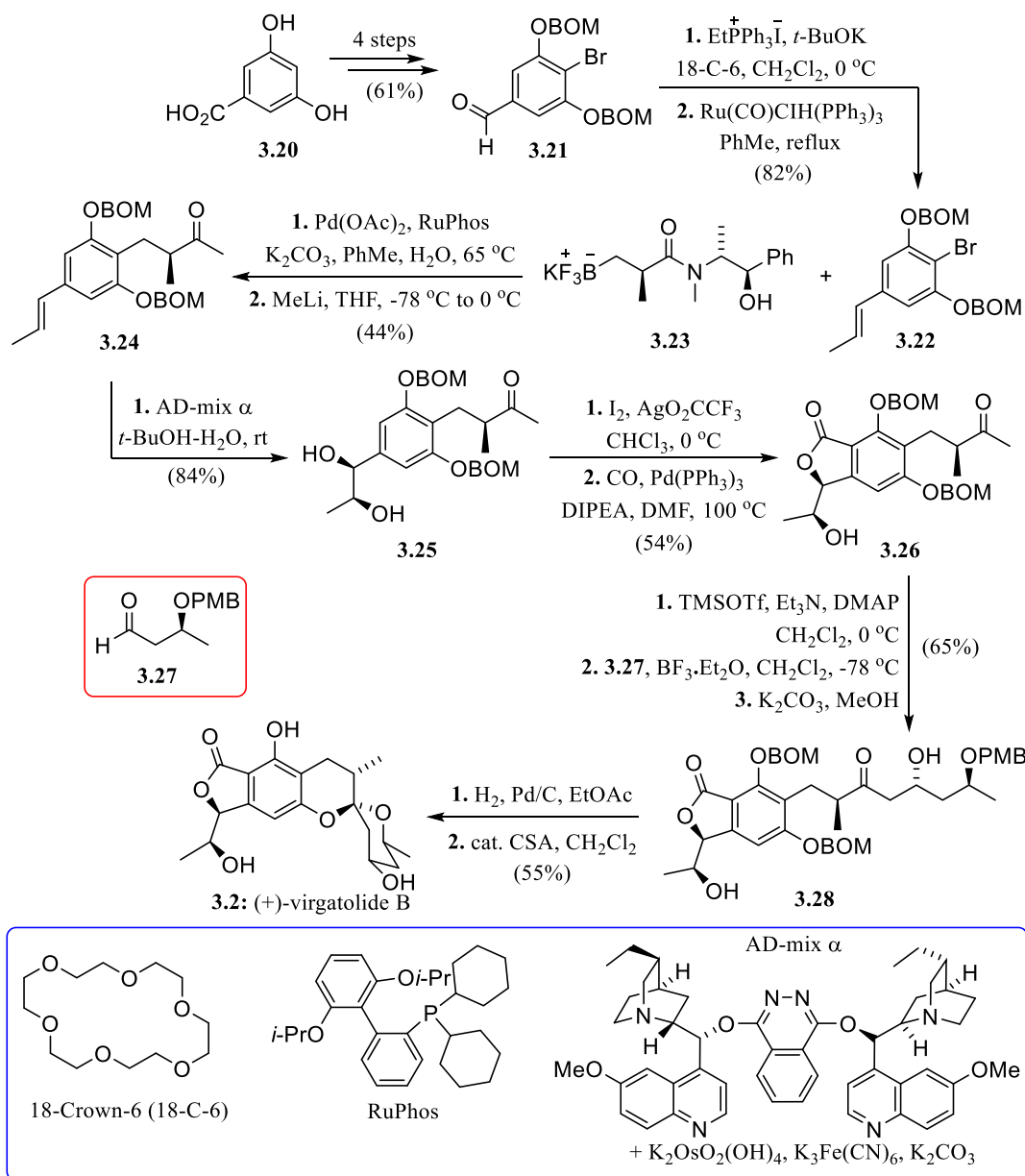


Scheme 3.2: Pettus and co-worker's formal synthesis of *des*-hydroxy paecilospirone (**3.19**) via a [4 + 2] cycloaddition, detailing their optimised *o*-QM protocol.^[150]

3.1.3 Previous work on Virgatolide B

In 2013, Brimble and co-workers published the first total synthesis of virgatolide B (**3.2**),^{[151],[152]} which entailed a convergent linear synthetic method (scheme 3.3). The authors sought to gradually build up molecular complexity to enable greater synthetic control, which led to the synthesis of virgatolide B (**3.2**) in an overall yield of 3.5% from dihydroxybenzoic acid (**3.20**) via 15 steps. The synthesis of virgatolide B (**3.2**) was predicated upon the acquirement of **3.22** and **3.23**, that would serve as Suzuki coupling partners to afford the desired carbon scaffold **3.24**, which could be gradually, yet selectively built upon. Brimble foresaw that the installation of the *E*-alkene (**3.22**) was required prior to the Suzuki alkylation of **3.22** and **3.23**, in preparation of the anticipated Sharpless asymmetric dihydroxylation. However, following the Grignard alkylation of aldehyde **3.10**, the subsequent elimination

was found to afford an inseparable mixture of *E/Z* isomers, which was resolved to exclusively afford the desired *E*-isomer **3.22** upon the addition of Ru(CO)ClH(PPh₃)₃.



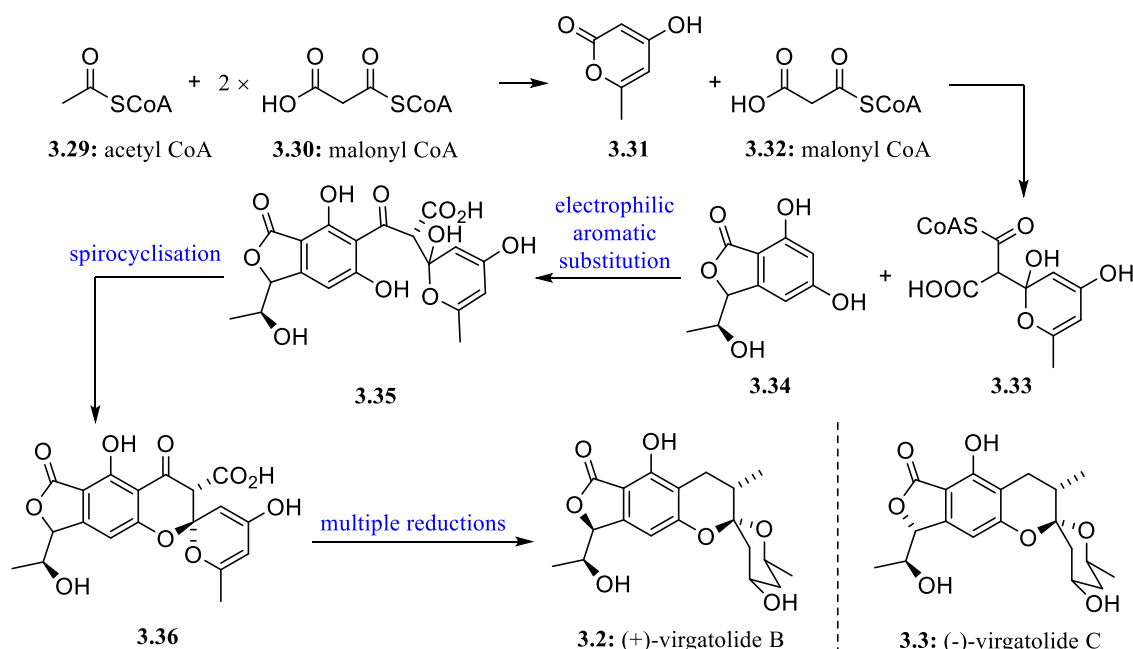
Scheme 3.3: Total synthesis of virgatolide B **3.2** by Brimble *et al.*^[152]

In the presence of RuPhos, trifluoroboratoamide **3.23** was coupled to the sterically hindered bromide **3.22** under Suzuki conditions, and the afforded amide was cleaved with MeLi (scheme 3.3). Dihydroxylation of the resultant *E*-alkenyl ketone **3.24** with AD-mix- α gave **3.25**, and the isobenzofuranone moiety was installed via a two-step protocol. Diol **3.14** underwent a regioselective mono-iodination and a subsequent palladium catalysed carbonylation to yield phthalide **3.26**. In order to install the spiroketal moiety, following installation of the isobenzofuranone scaffold, phthalide **3.26** was subjected to a solution of TMSOTf in the presence of DMAP. The resultant TMS enol-ether was immediately subjected to a Mukaiyama aldol reaction with aldehyde **3.27**, and TMS cleavage was

achieved upon the addition of K_2CO_3 . **3.28** was hydrogenated to remove the BOM protecting groups, and the key spirocyclisation event was achieved via catalytic camphorsulfonic acid, which concluded Brimble's total synthesis of (+)-virgatalide B (**3.2**).

3.1.4 Che's Biosynthetic Proposal for the Virgatalides

Che and co-workers detailed a proposal for the biosynthesis of virgatalide B (**3.2**) within the original isolation paper (scheme 3.4). The proposal detailed two successive condensation reactions of malonyl CoA (**3.30**) with acetyl CoA (**3.29**) to afford pyranol **3.33**, which was theorised to undergo an electrophilic aromatic substitution with a demethyl pestaphthalide **3.34**. The coupled pyran **3.35** was proposed to undergo a spirocyclisation, and Che argued the resulting spiroketal **3.36** would undergo several stereospecific reductions to obtain virgatalide B (**3.2**) in nature.^[145]



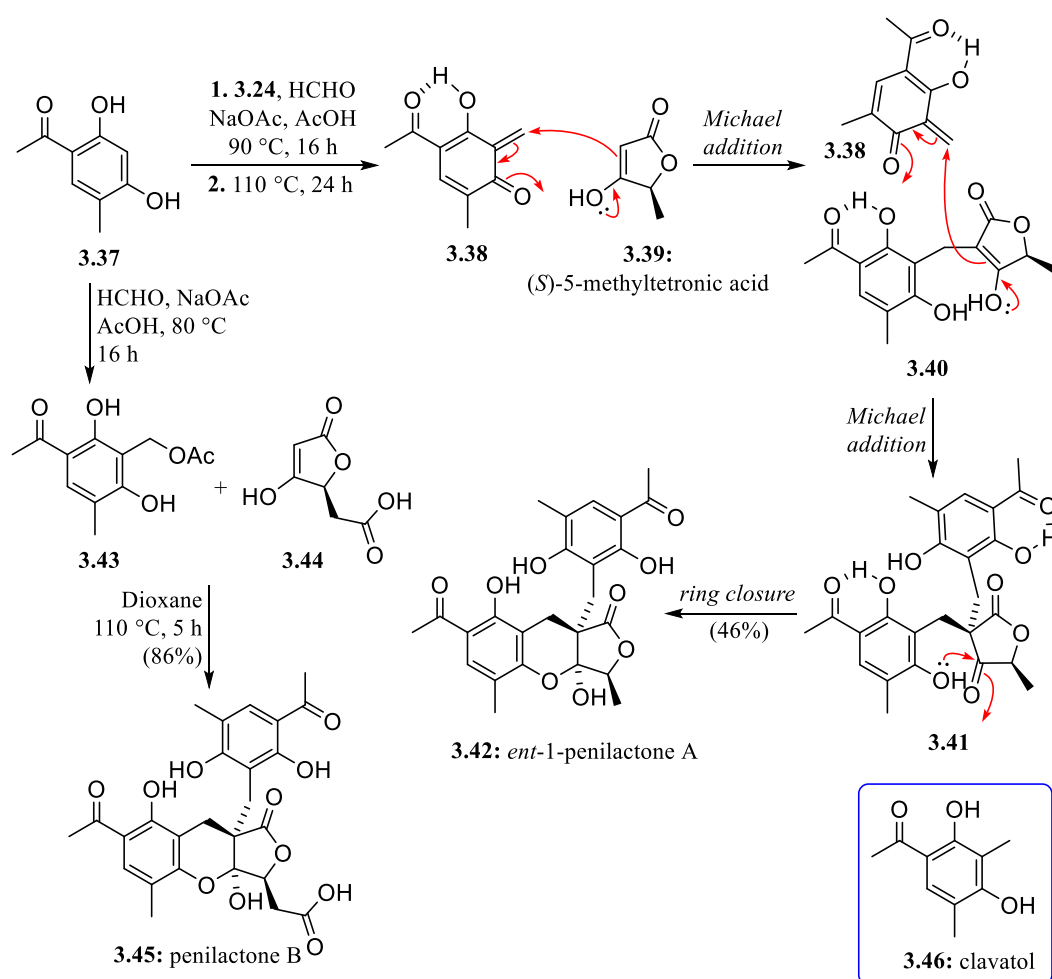
Scheme 3.4: Proposed biosynthesis of virgatalides B (**3.2**) and C (**3.3**) by Che *et al.*^[145]

Although the above proposed biosynthetic pathway appears plausible, significant issues regarding stereochemical control are evident. Given that the virgatalides A – C (**3.1** – **3.3**) were discovered as enantiopure products,^[145] stringent biosynthetic mechanistic controls, such as substrate-specific enzymes, would need to be introduced for Che's proposal to be plausible. Specialised substrate-specific enzymes could direct the various proposed events detailed, such as the spirocyclisation of benzofuranone **3.34** with the enzymatically bound pyranol **3.33** and the several preceding stereoselective reductions of **3.36** to obtain enantiopure virgatalide B (**3.2**). As such, the proposed pathway appears to be unnecessarily

convoluted and for these stated reasons, we would argue that Che's biosynthetic pathway is unlikely to occur in nature.

3.2 Our Proposed Biosynthetic Pathway of Virgatolides A – C and Previous Related Work

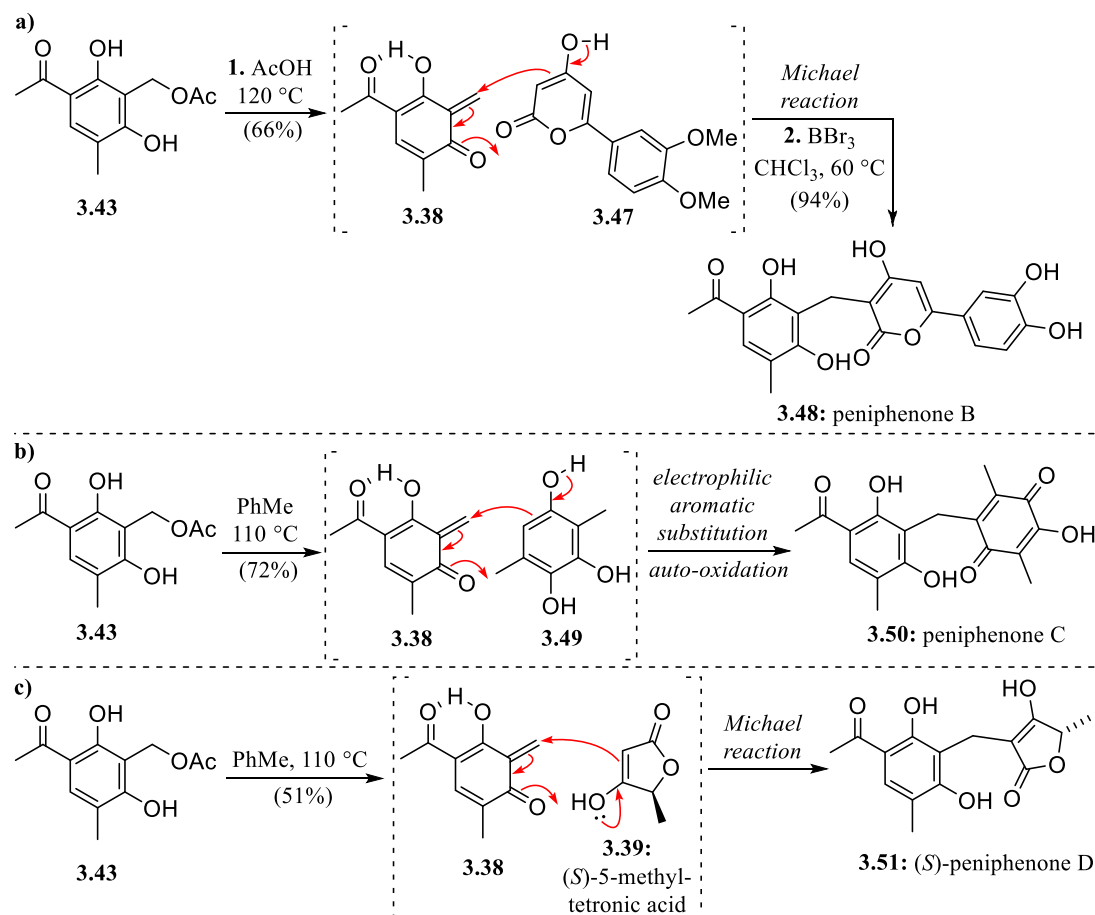
3.2.1 Biomimetic Synthesis of Penilactones and Peniphenones via Employment of a Universal *o*-QM Intermediate



Scheme 3.5: One-pot, biogenically inspired synthesis of the unnatural *ent*-penilactone A epimer (**3.42**) and penilactone B (**3.45**), by Spence and George.^[153]

Previously, our group had worked on a series of related natural products that shared similar biosynthetic intermediates, namely the penilactones and the peniphenones.^[153,154] The link between these secondary metabolites was their shared biogenic precursor clavatul **3.46**. Spence and George published two biogenically inspired syntheses for the total synthesis of penilactone B (**3.45**) alongside the unnatural isomer *ent*-penilactone A (**3.42**) in 2013

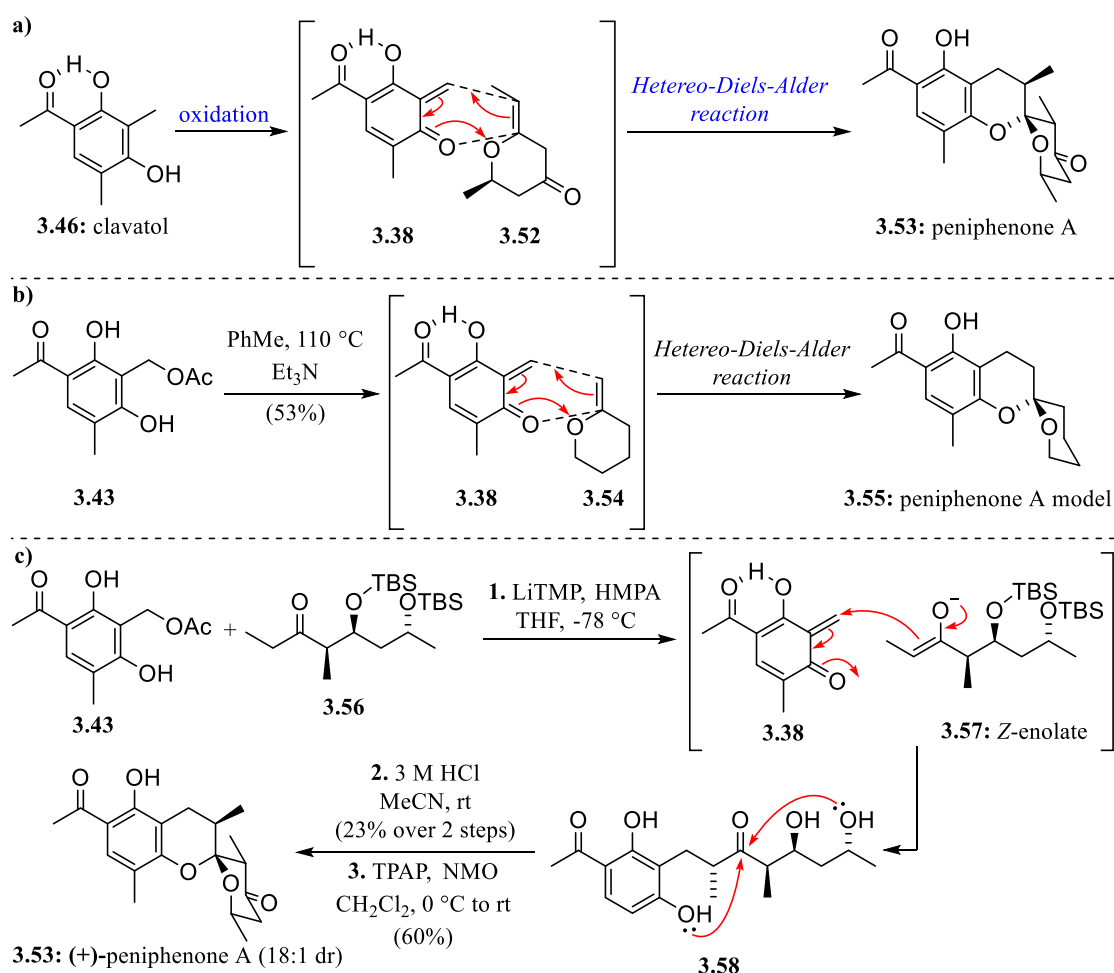
(scheme 3.5),^[153] and the peniphenones A – D (**3.53**, **3.48**, **3.50**, **3.51**) in 2015 (scheme 3.6 and 3.7).^[154] The biogenically inspired synthesis of both the penilactones and peniphenones detailed an *o*-QM intermediate (**3.38**) that was generated from the clavatul acetate derivative **3.43**. The acetate moiety was shown to serve as a labile leaving group that could eliminate under acidic, basic or thermal conditions to generate a highly reactive *o*-QM intermediate (**3.38**).



Scheme 3.6: Divergent, biogenically inspired synthesis of the peniphenones B – D (**3.48**, **3.50**, **3.51**) via *o*-QM precursor **3.43**, by Spence and George.^[154]

In Spence and George's biogenically inspired synthesis of *ent*-penilactone A (**3.42**), *o*-QM **3.38** was formed *in situ* from demethyl clavatul **3.37**, which spontaneously underwent β -elimination to generate the active *o*-QM **3.23** (scheme 3.5).^[153] (*S*)-5-methyltetronic acid (**3.39**) was found to undergo two consecutive Michael additions (**3.39** and **3.40**) with the *in situ* generated *o*-QM **3.38**, and upon ring closure (**3.41**), *ent*-penilactone A (**3.42**) was afforded in 46% yield. In the synthesis of penilactone B (**3.45**), the one-pot, biogenically inspired cascade sequence was restricted to the addition of the clavatul acetate derivative **3.43**, as it could not be generated *in situ* due to the presence of the carboxylic acid moiety of tetronic acid **3.44**.^[153] Under thermal conditions, addition of tetronic acid **3.44** with *o*-QM

precursor **3.43** led to a reaction cascade to give penilactone B (**3.45**), analogous to the sequence of cascade events (**3.39** to **3.41**) found with *ent*-penilactone A (**3.42**). The total syntheses of both *ent*-penilactone A (**3.42**) and penilactone B (**3.45**) serve as intriguing biomimetic transformations of *o*-QMs, adding validity to the ever-expanding proposed presence of these highly reactive species as biosynthetic intermediates in nature. Further investigation into biogenically viable *o*-QM intermediates came with our group's synthesis of the peniphenones A – D (**3.53**, **3.48**, **3.50**, **3.51**), where the previously explored *o*-QM precursor **3.43** was employed in a series of biogenically inspired coupling reactions, lending itself as a divergent biosynthetic intermediate (scheme 3.6).^[154]



Scheme 3.7: Spence and George's biosynthetic proposal of peniphenone A (**3.53**), and their [4 + 2] model synthesis of peniphenone A (**3.55**) via the *o*-QM precursor **3.43**.^[154]

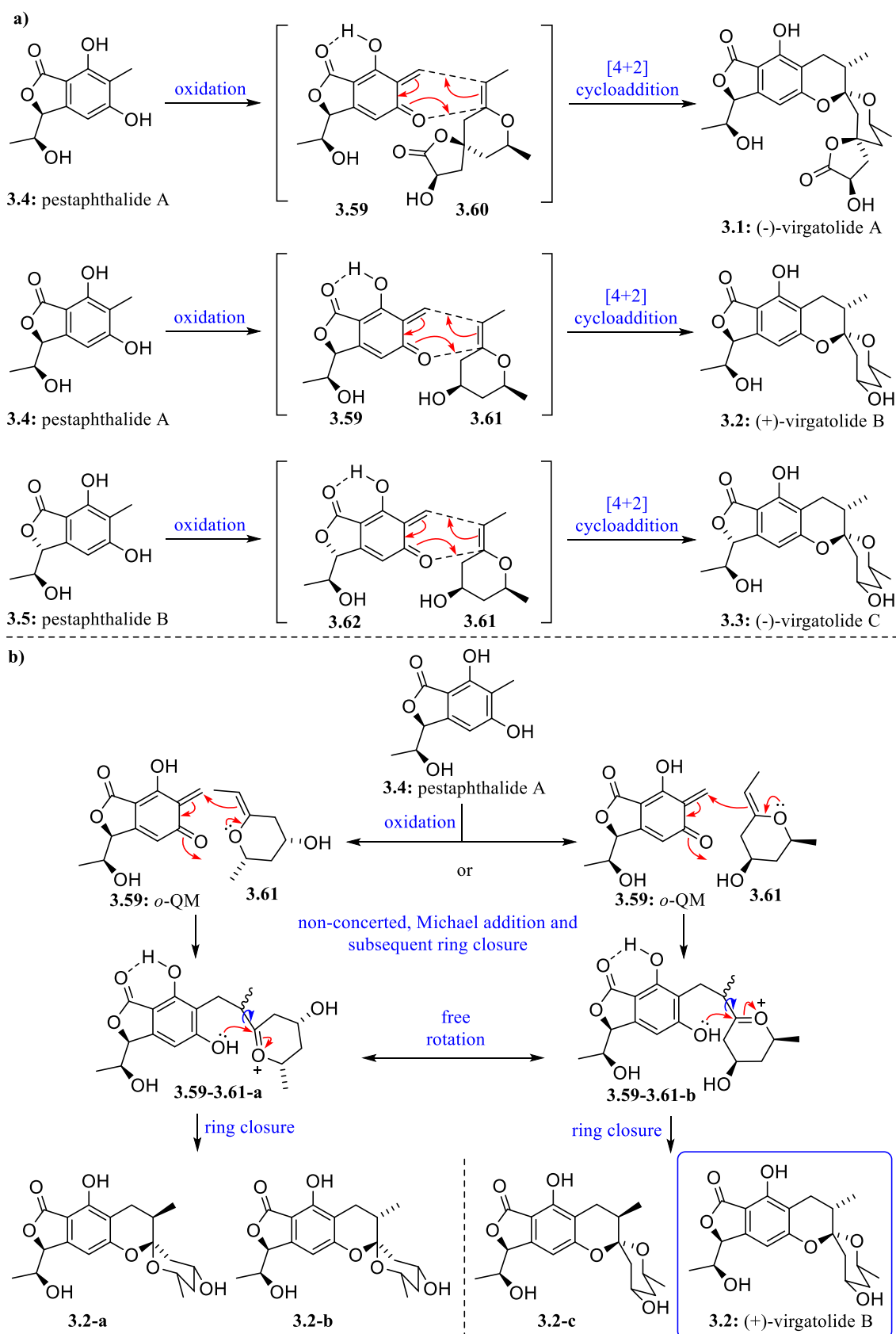
In Addition to accommodating a clavatul moiety, shared between both the peniphenones (**3.53**, **3.48**, **3.50**, **3.51**) and penilactones (**3.42** & **3.45**),^[153] peniphenone D (**3.51**) was also found to possess an abridged 5-methyltetronic acid (**3.39**) substituent,^[154] highlighting the two families seemingly related biogenic origins (scheme 3.6). Spence was able to control the formation of (*S*)-peniphenone D (**3.51**) by addition of both clavatul acetate **3.43** and (*S*)-5-

methyltetronic acid (**3.39**) in an equal molar ratio, which ensured a second Michael reaction of did not occur.^[154] Peniphenones B (**3.48**) and C (**3.50**) were afforded from arylated lactone **3.47** and triphenol **3.49** respectively, by employing *o*-QM precursor **3.43** as a universal substrate.

Spence and George proposed that peniphenone A (**3.53**) could form in nature via a [4 + 2] cycloaddition of *o*-QM **3.38** and *Z*-exocyclic enol ether (**3.52**) (scheme 3.7).^[154] However, the desired *Z*-exocyclic enol ether **3.52** proved difficult to synthesise, and as such, peniphenone A (**3.53**) was synthesised in a non-biomimetic linear manner in good enantioselectivity (**3.56** – **3.58**) (scheme 3.7). Nonetheless, Spence and George investigated a model system, which led to the acquisition of **3.55** via a successful hetero-Diels-Alder cyclisation between *in situ* generated *o*-QM **3.38** and exocyclic enol ether **3.54**. Our group's work on the peniphenones and penilactones demonstrate that in addition to sharing the common clavatul subunit, the two families may also share the biogenic *o*-QM intermediate **3.38**, highlighting their seemingly analogous biosynthetic pathways in nature.

3.2.2 Our Proposal for the Biosynthetic Origins of Virgatolides A – C

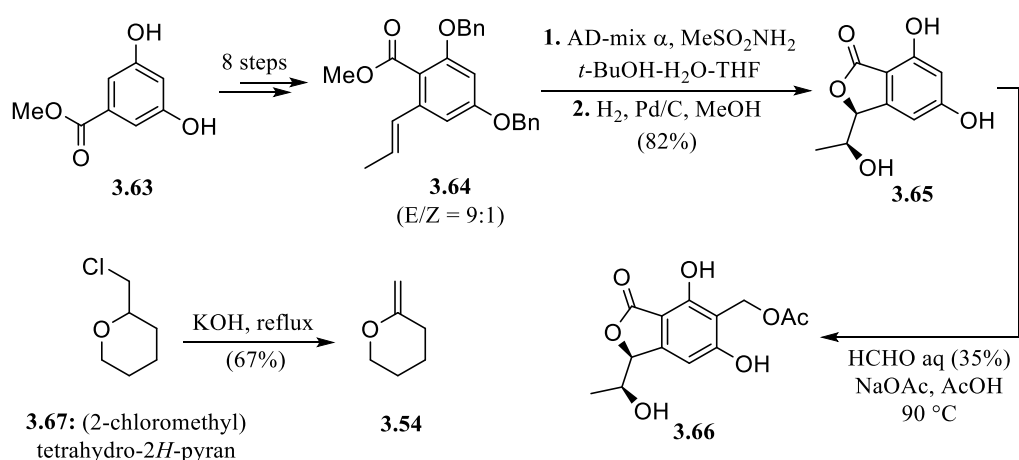
Here, we propose an alternative biosynthetic pathway for the virgatolides A – C (**3.1** – **3.3**), that runs counter to Che's seemingly convoluted proposal (scheme 3.8 – a). Our proposal details the involvement of the co-isolated natural products pestaphthalides A (**3.4**) & B (**3.5**), which would serve as biogenic precursors to the proposed *o*-QMs **3.59** and **3.62** respectively. *o*-QM **3.59**, derived from the oxidation of pestaphthalide A (**3.4**), would serve as a reactive diene to undergo a [4 + 2] hetero-Diels-Alder cycloaddition with the proposed *Z*-exocyclic enol ethers, **3.60** and **3.61**, to afford both virgatolides A (**3.1**) and B (**3.2**) respectively. Additionally, as virgatolides B (**3.2**) & C (**3.3**) differ only by their isobenzofuranone moiety, our proposal details that *o*-QM **3.62**, derived from pestaphthalide B (**3.5**), could undergo an analogous [4 + 2] cycloaddition with *Z*-exocyclic enol ether **3.61** to afford virgatolide C (**3.3**) in nature. We hypothesise that our biosynthetic proposal, with a hetero-Diels-Alder reaction as the pivotal biogenic step, would lead to the emergence of virgatolides A – C (**3.1** – **3.3**) possessing the correct stereoconfiguration without the need to introduce specific, resource demanding enzymes, as detailed in Che's proposal (scheme 3.4). The stereoconfiguration of the proposed *o*-QMs, **3.59** or **3.62**, and the *Z*-exocyclic enol ethers, **3.60** or **3.61**, would in theory dictate the stereochemical outcome of the spirocyclisation event (Scheme 3.8 – a).^[154]



Scheme 3.8, a): Our proposed biosynthesis of virgatolides A – C (**3.1** – **3.3**) via [4 + 2] cycloaddition of *o*-QM **3.59** or **3.62** with *Z*-exocyclic enol ether **3.60** or **3.61**. **b):** Alternative proposed biosynthesis of virgatolide B (**3.2**) via a non-concerted stepwise, Michael addition and subsequent ring closure of *o*-QM **3.61** with *Z*-exocyclic enol ether **3.61**.

Alternatively, the biosynthesis of the virgatolides (**3.1** – **3.3**) can be envisioned to proceed via a non-concerted, stepwise mechanism in nature (scheme 3.8 – b). Upon the formation of **3.59** from pestaphthalide A (**3.4**), *o*-QM **3.59** may undergo nucleophilic attack from *Z*-exocyclic enol ether **3.61** to generate either intermediate **3.59-3.61-a** or **-b**. Both theoretical Michael/Mannich manifold intermediates **3.59-3.61-a** and **-b** would be expected to freely interchange via rotation of the newly formed carbon-carbon bond, and hence, could potentially afford four products (**3.2** to **3.2-c**), including the desired natural virgatolide stereoisomer (**3.2**: (+)-virgatolide B)

3.2.3 Spence's Unpublished Virgatolide B Model Studies



Scheme 3.9: Unpublished synthesis of the *o*-QM precursor **3.66**, and simplified exocyclic enol ether **3.54**, by Spence and George.^[13,154–159]

Our group has previously investigated a model system of virgatolide B (**3.2**) in accordance with our stated biosynthetic proposal.^[154] The model system investigated conditions for the proposed [4 + 2] hetero-Diels-Alder cycloaddition between *o*-QM precursor **3.66** and exocyclic enol ether **3.54** to obtain virgatolide B analogue **3.68** (Table 3.1). The *o*-QM precursor **3.66** was synthesised over 11 steps from commercially available methyl 3,5-dihydroxybenzoate **3.63**,^[156–159] and the simplified exocyclic enol ether **3.54** was acquired from commercially available (2-chloromethyl)tetrahydro-2*H*-pyran (**3.67**) (scheme 3.9). Due to issues regarding stability, **3.54** was used immediately upon preparation for investigations into the model hetero-Diels-Alder spiro-ketalisation reaction.^[154,155]

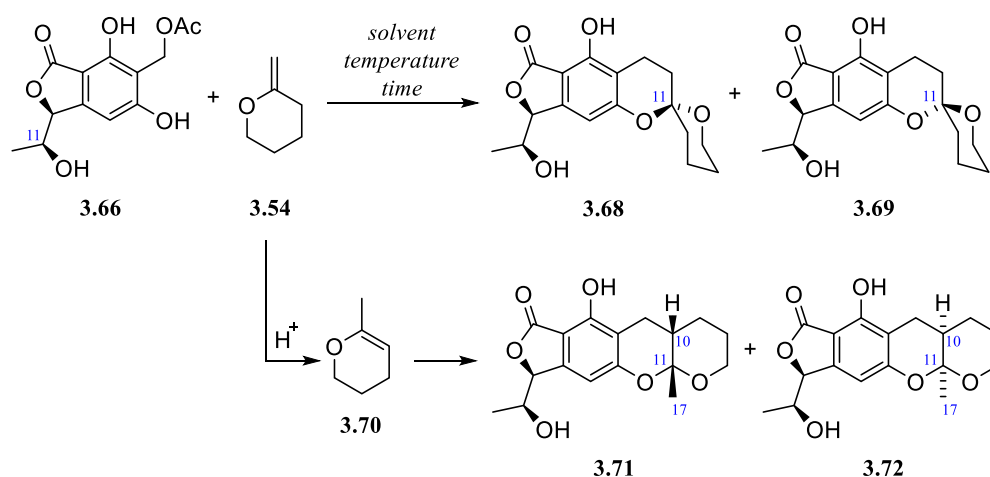


Table 3.1: Screening of conditions for the [4 + 2] cycloaddition of *o*-QM precursor **3.66** and simplified exocyclic enol ether **3.54**, by Spence and George.

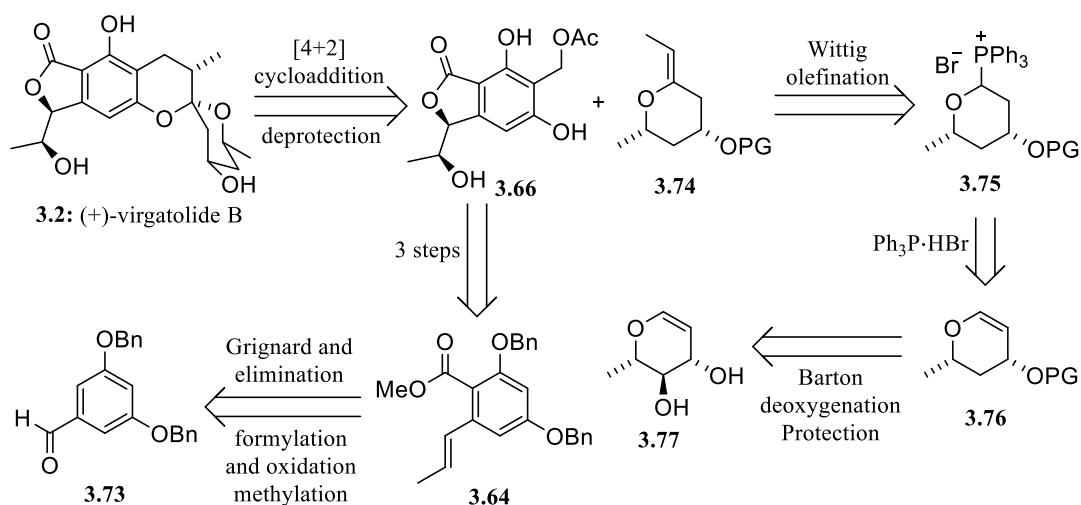
Entry	Reagents (eq)	Conditions	Yield/Ratio of	
			3.68:3.69	3.71:3.72
1	3.66 & 3.54 (1:1)	PhMe, 110 °C, 16 h	trace	19% (1:1)
2	3.66 & 3.54 (1:10)	PhMe, 110 °C, 16 h	8% (4:1)	2% (N.D.)
3	3.66 & 3.54 (1:3)	Dioxane, 110 °C, 16 h	12% (1:1.2)	trace
4	3.66 & 3.54	Et ₃ N, PhMe, 100 °C, 16 h	0%	0%

Investigation into model [4 + 2] cycloaddition reactions commenced with the screening of thermal conditions, following the successful synthesis of the *o*-QM precursor **3.66** and model exocyclic enol ether **3.54** (scheme 3.9). Spence found that heating the reactants **3.66** & **3.54** in toluene (table 3.1, entry 1) led to isolation of only trace quantities of the desired spiroketal as a set of epimers **3.68** & **3.69**, and primarily afforded the undesired 6,6 fused ring isomers **3.71** & **3.72**. The emergence of the fused ring by-products was attributed to isomerisation of **3.54** to endocyclic enol ether **3.70**, catalysed by liberated acetic acid following generation of *o*-QM **3.59**. However, employment of a 1:10 ratio of reactants, **3.66** to **3.54**, led to the acquisition of target epimers, **3.68** & **3.69** in a 4:1 ratio respectively (table 3.1, entry 3). Spence argued that reducing the equivalents of *o*-QM precursor **3.66**, relative to **3.54**, limited the number of available protons that could isomerise exocyclic enol ether **3.54**, which therefore, would reduce the formation frequency of the undesired by-products **3.71** & **3.72**. Upon changing solvent to dioxane, and further fine tuning the reactant ratio (table 3.1, entry 2), Spence almost entirely eliminated the formation of the 6,6 fused isomers **3.71** & **3.72**, while also maximising the formation of the desired virgatolide B epimers **3.68** & **3.69**, isolated in a 1:1.2 ratio respectively. Finally, attempts at buffering the *in situ* generated acetic acid with Et₃N failed to produce any products (**3.68**, **3.69**, **3.71**, **3.72**) and the reaction

mixture was reported to undergo decomposition upon heating. Spence proposed that the secondary alcohol at C11 on the *o*-QM precursor **3.66**, was unstable under basic conditions and may interfere with formation of the *o*-QM **3.59**.

3.2.4 Retrosynthetic Analysis of Virgatolide B

Based upon Spence's model studies, we propose a retrosynthetic pathway for virgatolide B (**3.2**) that would lead to the necessary acquisition of a protected *Z*-exocyclic enol ether **3.74** and Spence's *o*-QM precursor **3.66** (scheme 3.10). As synthesis of the *o*-QM precursor **3.66** has been previously explored, we did not seek to further optimised Spence's developed route.



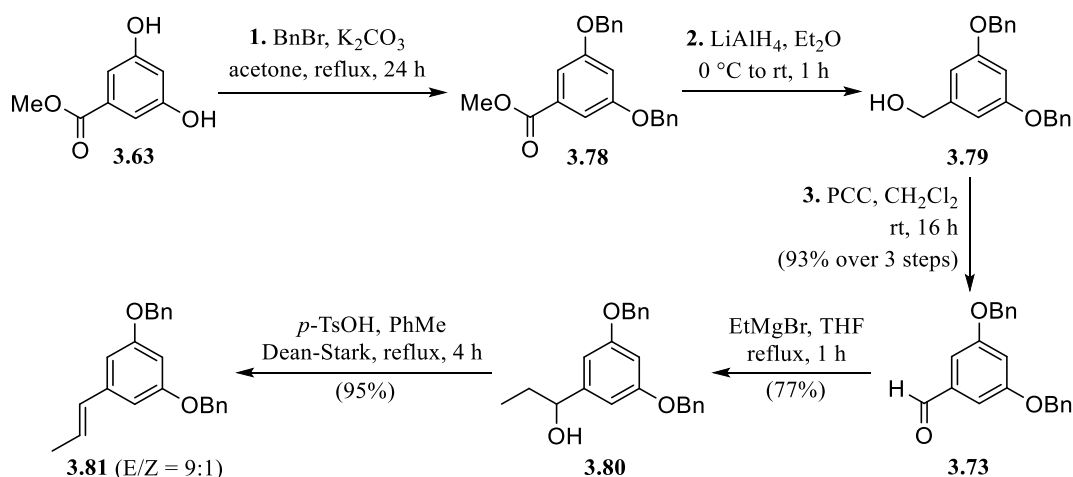
Scheme 3.10: Retrosynthetic analysis of virgatolide B (**3.2**).

Access to *Z*-exocyclic enol ether **3.74** was envisioned by a Wittig olefination of acetaldehyde with Wittig salt **3.75**, which in turn could be accessed from a protected endocyclic enol ether (**3.76**) (scheme 3.10). However, there are few examples of compounds akin to that of **3.76** which have been reported throughout the literature that can be accessed from readily available materials.^[160] Endocyclic enol ether **3.76** could potentially be accessed from diol **3.77** via a synthetic route akin to a protocol reported by Paquette.^[160] However, issues regarding both regioselective installation of a given protecting group, and its stability towards acid and base conditions become apparent, upon consideration of the anticipated synthesis and activation of the desired Wittig salt (**3.75**). For the reasons stated above, due to their inert nature and selective method of removal, a benzyl ether protecting group strategy was selected as our first choice. However, we did foresee issues regarding the removal of a benzyl ether protecting group following the anticipated success of the [4 + 2] spirocyclisation event, as any spiroketal moiety was suspected to be unstable under both reductive and oxidative conditions.

3.3 Pursuit of Virgatolide B

We set out to synthesise virgatolide B (**3.2**) in accordance with our biosynthetic proposal, where a hetero-Diels-Alder cycloaddition between *o*-QM **3.59** and a protected *Z*-exocyclic enol-ether **3.74** could afford the spiroketal moiety. We sought to mirror Spence's previously developed and modified synthetic protocol for the desired *o*-QM precursor **3.66** (scheme 3.9) and to develop a synthetic protocol to access *Z*-exocyclic enol-ether **3.74** (*vide supra*).

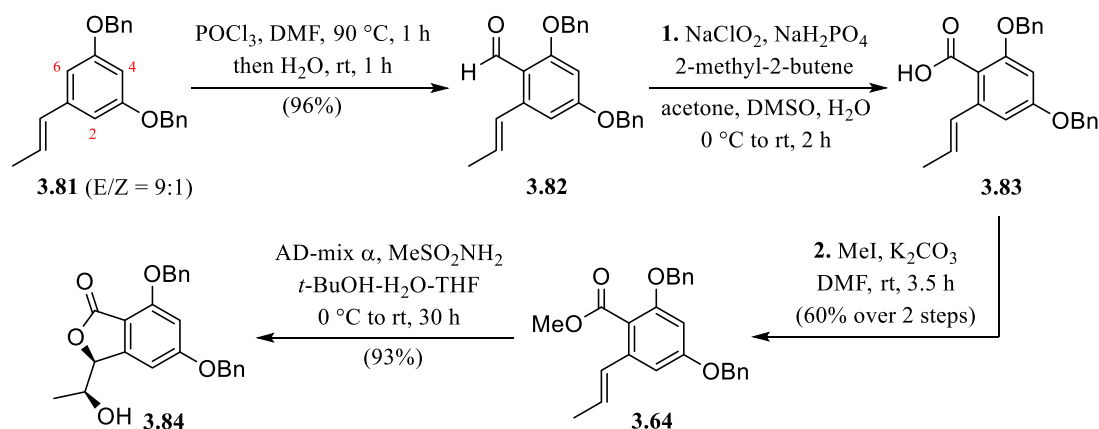
3.3.1 Synthesis of Benzofuranone *o*-QM Precursor **3.66**



Scheme 3.11: Synthesis of *E*-alkene **3.81** from commercially available methyl 3,5-dihydroxybenzoate **3.63**.^[159]

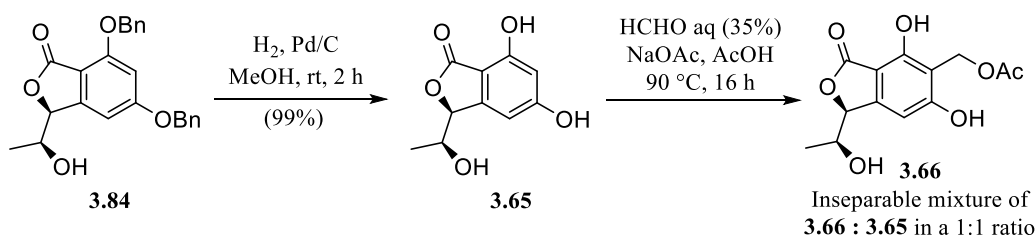
As detailed in Spence's protocol, methyl 3,5-dihydroxybenzoate **3.63** was employed as a suitable starting material in our pursuit of *o*-QM precursor **3.66**. Following a three step protocol to benzaldehyde **3.73** by Bojja, methyl 3,5-dihydroxybenzoate **3.63** was benzylated upon addition of BnBr in acetone with K₂CO₃ under reflux (scheme 3.11).^[159] The resultant crude benzyl protected ester **3.78** was reduced with excess LiAlH₄, and the afforded impure alcohol **3.79** was subsequently oxidised via addition of two molar equivalents of PCC in CH₂Cl₂. Freshly acquired aldehyde **3.73** was synthesised in an impressive yield of 93% over three steps. Next, we set out to install the required *E*-alkenyl substituent in anticipation of the Sharpless asymmetric dihydroxylation, which would afford the isobenzofuranone moiety, characteristic of both virgatolide B (**3.2**) and pestaphthalide A (**3.4**). Benzaldehyde **3.73** was alkylated under standard Grignard conditions with freshly prepared EtMgBr in Et₂O to give alcohol **3.80**. However, more consistent yields were achieved upon changing the solvent system to THF, as employment of Et₂O in large scale reactions did not afford **3.80** in reliable yields. We suspect the inability to heat the reaction while employing Et₂O led to incomplete *in situ* generation of EtMgBr from EtBr and Mg, thereby reducing the

potential yield of alcohol **3.80**. Following Spence's optimised conditions, **3.80** was eliminated with *p*-TsOH under reflux using a Dean-Stark apparatus. Interestingly, the isolated ratio of *E/Z* alkene isomers **3.81** was seemingly dependent on the initial purity of the alkyl alcohol **3.80**, as indicated by the poor 3:1 *E/Z* selectivity observed when using slightly impure starting material. However, provided that **3.80** was completely void of contaminating aldehyde **3.73**, reproducible 9:1, *E/Z* ratios of alkene **3.81** were achieved (scheme 3.11).



Scheme 3.12: Installation of the desired lactone moiety to afford **3.84**, via a Sharpless asymmetric dihydroxylation.^[13,156,157,161]

Introduction of the methyl ester, adjacent to the newly installed *E*-alkene moiety, was required for the desired *in situ* lactonization to proceed during the Sharpless dihydroxylation event, as report by Spence (scheme 3.12). The methyl ester moiety could be introduced via three steps, first by regioselective formylation **3.82**, followed by a Pinnick oxidation to carboxylic acid **3.83** and finally methylation to afford ester **3.64**.^[156,157,161] We predicted that the C4 position of alkene **3.81**, during a Vilsmeier-Haack formylation, was sterically inaccessible, leaving the C2/C6 positions available to undergo formylation, which proceeded to afford benzaldehyde **3.82** exclusively as the desired regioisomer under standard conditions. Aldehyde **3.82** was oxidised under Pinnick conditions, and the afforded carboxylic acid **3.83** was subsequently methylated with MeI, which gave the desired methyl ester **3.64** in a yield of 60% over 2 steps.^[156,157,161] NMR analysis of the afforded methyl ester **3.64** revealed that the alkene had not undergone isomerisation, maintaining its favourable 9:1 *E/Z* ratio. Under a modified Sharpless asymmetric dihydroxylation protocol, methyl ester **3.64** was stereoselectively dihydroxylated upon addition of AD-mix- α in the presence of the co-catalyst MeSO_2NH_2 (scheme 3.12).^[13] NMR analysis of purified **3.84** confirmed the presence of the desired lactone moiety, thereby verifying Spence's observation of an *in situ* lactonization during the dihydroxylation of methyl ester **3.64**.



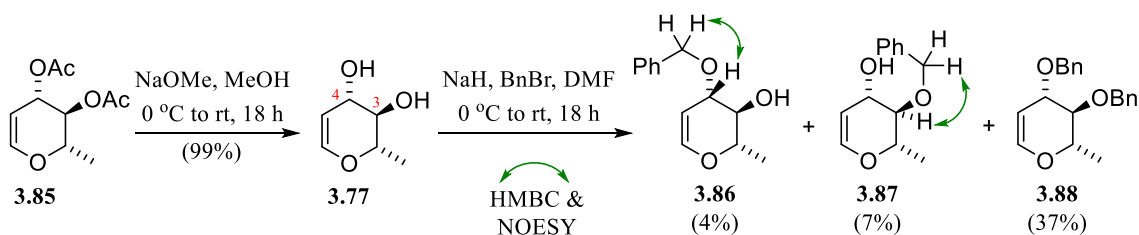
Scheme 3.13: Synthesis of *o*-QM precursor **3.66**.^[153,154,162]

In preparation of installing the methylene acetate moiety, which would serve to initiate the formation of *o*-QM **3.59**, the benzyl ether protecting groups of the acquired lactone **3.84** were removed via a palladium catalysed hydrogenation to afford isobenzofuranone **3.65** in quantitative yield (scheme 3.13). Finally, *o*-QM precursor **3.66** was prepared upon addition of isobenzofuranone **3.84** to a mixture of aqueous 35% formaldehyde solution with NaOAc in AcOH, and the resultant mixture was heated overnight.^[153,154,162] Formation of the desired *o*-QM precursor **3.66** is postulated to have formed first by formylation of isobenzofuranone **3.84**, which was theorised to undergo spontaneous elimination to generate *o*-QM **3.59** and upon nucleophilic attack from acetate, **3.66** was afforded. ¹H and ¹³C NMR analysis revealed that the crude product existed as a mixture of starting material isobenzofuranone **3.65** and **3.66** in a 1:1 ratio.^[153,154] The crude precursor **3.66** could not be recrystallised, and attempts to purify the mixture via column chromatography were unsuccessful, most likely due to the sensitive nature of the methylene acetate moiety, and therefore, **3.66** was used immediately upon isolation.

3.3.2 Synthesis of *Z*-Exocyclic Enol Ether via a Wittig Olefination

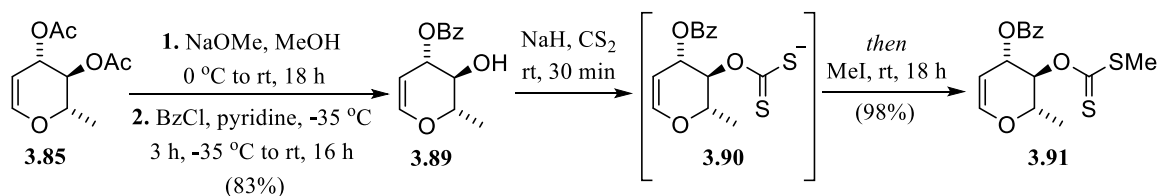
As described in our retrosynthetic analysis (scheme 3.10), an inert yet selectively labile protecting group was required in order to synthesise the desired protected *Z*-exocyclic enol ether **3.74**. Based on these requirements, benzyl ether was chosen due to its favourable stability under acidic and basic conditions. The enantiopure, commercially available 3,4-Di-O-acetyl-6-deoxy-L-glucal (**3.85**) served as the starting point of our route to the desired *Z*-exocyclic enol ether **3.74**. As there was no way to regioselectively remove the acetate ester at the C4 position, both esters would need to be hydrolysed, and the C4 alcohol of the resulting diol **3.77** would need to be regioselectively protected. Unfortunately, alternative commercially available starting materials that could afford our desired *Z*-exocyclic enol ether **3.74** did not appear feasible. However, Paquette *et al* reported a protocol that detailed hydrolysis of the commercially available diester **3.85**, and the resultant diol **3.77** was regioselectively protected with benzoyl chloride.^[160] With this in mind, we anticipated that

diol **3.77** may undergo a regioselective protection with benzyl bromide, analogous to Paquette's benzoyl protection method.



Scheme 3.14: Ester hydrolysis, and attempted mono-benzyl protection of diol **3.77**.^[160]

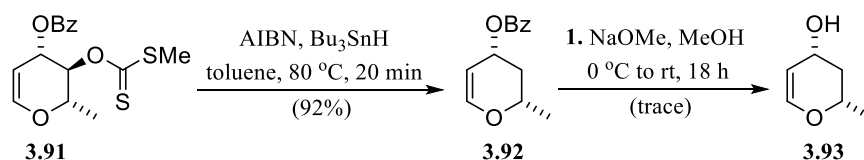
In preparation of our attempted regioselective benzylation, 3,4-Di-O-acetyl-6-deoxy-L-glucal (**3.85**) was subjected to catalytic NaOMe in MeOH, as described by Paquette (scheme 3.14).^[160] Regioselective benzylation was attempted via the drop-wise addition of BnBr to a mixture of diol **3.77** and NaH in DMF. However, despite attempts to minimise the formation of undesired protection products **3.87** & **3.88** by the gradual addition of BnBr over 3 hours, the desired benzylated regioisomer **3.86** was isolated as the minor product in very poor yield. Investigation into alternative aprotic solvents, temperature protocols, bases, and addition of TBAI failed to resolve the non-selective issues that appeared inherent with the benzylation of diol **3.77**.



Scheme 3.15: Ester hydrolysis, regioselective benzoyl protection **3.89**, and synthesis of xanthate **3.91** in preparation of Barton deoxygenation.^[160]

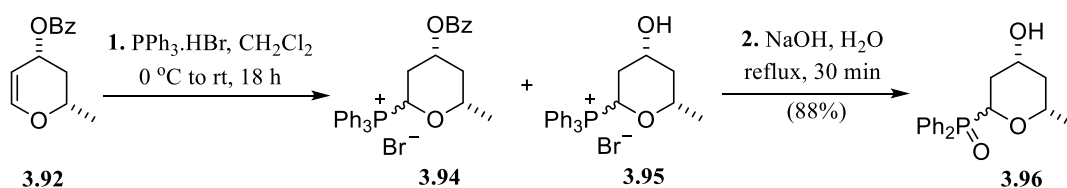
We sought to mirror Paquette's benzoyl protection protocol to regioselectively protect the C4 alcohol of diol **3.77**.^[160] Following Paquette's one-pot protocol, 3,4-Di-O-acetyl-6-deoxy-L-glucal (**3.85**) was subjected to catalytic NaOMe in MeOH, and the solvent was removed. The resultant crude diol **3.77** was taken up in pyridine, cooled and regioselectively protected by gradual addition of benzoyl chloride over 3 hours to afford enol ether **3.89** (scheme 3.15).^[160] Continuing in our synthesis from the successful regioselective mono-benzylation, installation of a methyl xanthate substituent was required for the anticipated Barton deoxygenation at the C3 alcohol, to obtain the characteristic carbon framework of our proposed biogenically inspired precursor, *Z*-exocyclic enol-ether **3.74**.^[160] The C3-methyl xanthate was installed via a one-pot, alkylation of the C3 hydroxy (**3.89**) with CS₂, to give xanthate **3.90** *in situ*, which upon addition of MeI, underwent methylation to afford

3.91 in near quantitative yield (scheme 3.15). Following Paquette's protocol, methyl xanthate **3.91** was subjected to thermal Barton deoxygenation conditions with Bu_3SnH in toluene and the radical initiator AIBN.^[160] After 20 minutes, the solvent was removed and the resulting residue was rapidly flushed through a column of Et_3N neutralised silica due to the alleged instability of **3.92**, as reported by Paquette. Due to concerns regarding the incompatibility of the benzoyl ester in the foreseen Wittig olefination reaction, we attempted to change to a more robust protecting group. However, upon subjecting **3.92** to Paquette's previously explored ester hydrolysis conditions employing catalytic NaOMe in MeOH,^[160] only trace quantities of the alcohol **3.93** could be isolated following column chromatography (scheme 3.16). **3.93** was found to be a mixture with the methyl benzoate, which could not be removed under reduced pressure due to the apparent volatility of alcohol **3.93**.



Scheme 3.16: Barton deoxygenation, and attempted deprotection to obtain alcohol **3.93**.^[160]

Due to issues regarding the removal of the benzoyl ester, a more suitable, inert protecting group could not be installed, and we therefore proceeded in our pursuit of Wittig salt **3.94** from benzoyl protected enol ether **3.92** (scheme 3.17). Ley *et al* reported a procedure in 1985, that detailed the synthesis of a series useful Wittig salts that could be generated by treatment of cyclic enol ethers with gaseous HCl in benzene.^[163] Upon addition of PPh_3 , the resulting cyclic chlorinated enol ethers were shown to undergo nucleophilic attack to afford the desired Wittig salt.^[163] However, we suspected that addition of any gaseous hydrogen halide would hydrolyse the benzoyl ester of **3.92**, thereby introducing significant issues upon base activation of the Wittig salt to the corresponding desired ylide. For this reason, the triphenylphosphine conjugate base of hydrogen bromide, $\text{PPh}_3 \cdot \text{HBr}$, was employed in our attempts to the synthesis **3.94**. As $\text{PPh}_3 \cdot \text{HBr}$ was a conjugate base of HBr, we anticipated that upon the attempted synthesis of Wittig salt **3.94**, the conjugate acid may be more tolerant to the benzoyl protecting group of enol ether **3.92**.



Scheme 3.17: Attempted synthesis of Wittig salt **3.94** and diphenylphosphine oxide **3.96**.^[163]

Treatment of benzoyl enol ether **3.92** with $\text{PPh}_3 \cdot \text{HBr}$ led to the isolation of benzoyl protected Wittig salt **3.94** as a mixture with the deprotected salt **3.95**, as revealed by ^1H and ^{13}C NMR analysis of the crude, inseparable salts (scheme 3.17). Decomposition ensued upon efforts to activate the Wittig salts (**3.94** and **3.95**) with strong bases, such as *n*-BuLi, *t*-BuLi or LDA, and no observable product had formed following the addition of acetaldehyde to the reaction mixture.^[163] As the Wittig salts could not be separated or successfully activated, we turned our attention to obtaining the deprotected diphenylphosphine oxide ether **3.96**, which could be obtained by heating **3.94** & **3.95** under refluxing aqueous NaOH solution, as reported by Ley.^[163] The mixture of Wittig salts **3.94** & **3.95** was heated under basic hydrolysing conditions to afford the deprotected diphenylphosphine oxide **3.96**, which could not be adequately purified due to issues regarding its stability. Despite their initial discovery in 1958 by Horner *et al.*,^[164–168] few examples of Horner-Wittig olefinations have been reported throughout the literature. Regardless of their lack of usage within the literature, Warren and Ley noted that phosphine oxide carbanion species that possess electron donating β -oxygen substituents have been observed to suffer thermal instability compared to their ylide counterparts.^[163,169] Thus, diphenylphosphine oxides that possess β -electron donating substituents were claimed to afford more stable carbanion species *in situ* than ylides.

With the diphenylphosphine oxide ether **3.96** in hand, we set out to screen olefination conditions utilising non-nucleophilic bases that might be more tolerant of the free hydroxy group at C4 (table 3.2). Attempts to deprotonate **3.96** to the carbanion with LiHMDS (entry 1, table 3.2), LDA (entry 2, table 3.2), *t*-BuOK (entry 3, table 3.2) or NaH (entry 4, table 3.2) led to the same observed formation of a deep red solution, characteristic of the active diphenyl oxyphosphonium carbanion species, as described by Ley.^[163] However, despite the apparent appearance of this anionic species, addition of acetaldehyde did not yield any observable product. Upon investigation of *n*-BuLi (entry 5, table 3.2), the anticipated characteristic red colourisation of the reaction mixture was not observed and decomposition of **3.96** ensued. We suspected that the free hydroxy group was deprotonated in preference to the electronically withdrawn proton at C2, which may have prevented formation of the active carbanionic species (table 3.2).

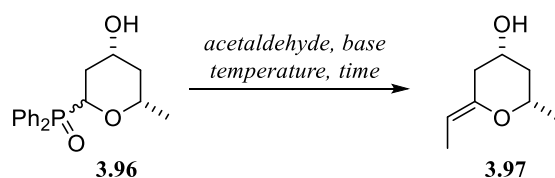
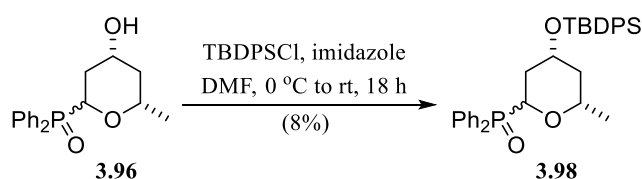


Table 3.2: Screening of conditions for the Horner-Wittig olefination of **3.96** with acetaldehyde.

Entry	Base (eq)/Solvent	Conditions	Outcome
1	LiHMDS (2) / THF	-78 °C to rt, 1 h	complex mixture
2	LDA (2) / THF	-78 °C to 0 °C, 1 h	decomposition
3	<i>t</i> -BuOK (2) / THF	0 °C to 40 °C, 5 h	complex mixture
4	NaH (2) / THF	0 °C to rt, 8 h	complex mixture
5	<i>n</i> -BuLi (1.5) / THF	-78 °C to 0 °C, 1 h	decomposition

As diphenylphosphine oxide ether **3.96** could not be selectively deprotonated with any conventional base, protecting the free C4 alcohol appeared necessary to continue with our olefination route. However, suitable protecting groups were limited, as upon attempting to install a chosen protecting group, we would suspect that any reasonably strong base may deprotonate the C2 proton of **3.96** to potentially afford the oxyphosphonium carbanion (table 3.2). Silyl ethers were investigated as a viable protecting group strategy, as few options appeared available to us due to the relatively harsh installation conditions required for most alternative strategies. Simpler silyl chlorides, such TMSCl and TBSCl, for the protection of diphenylphosphine oxide ether **3.96**, failed to afford any of the respective anticipated silyl ethers. However, changing to a larger silyl chloride, *t*-butyldiphenylsilyl ether **3.98** was afforded upon subjecting **3.96** to a solution of TBDPSCl with imidazole in DMF, albeit in a very low yield (scheme 3.18).^[170]

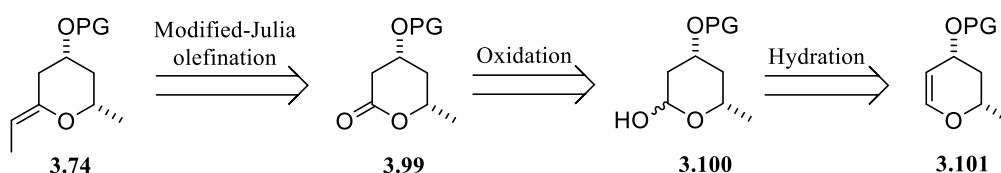


Scheme 3.18: Attempted *t*-butyldiphenylsilyl protection of **3.96**.^[170]

3.3.3 Pursuit of *Z*-Exocyclic Enol Ether via a Modified-Julia Olefination

With so many complications inherent to the Wittig and Horner-Wittig olefination route, we sought to revise our approach to *Z*-exocyclic enol ether **3.74**. Revision of the literature led us to a series of methodology articles reported by Gueyrard that detailed the olefination of lactones via a modified-Julia protocol.^[171–173] Gueyrard had published multiple articles

focused around developing protocols for the olefination of lactones to afford cyclic enol ethers akin to our desired *Z*-exocyclic enol ether **3.74**.^[173] Therefore, based on Gueyrard's protocol, we set out to synthesise the desired *Z*-exocyclic enol ether **3.74** from lactone **3.99** (scheme 3.19). However, acquiring a protected lactone **3.99** from diol **3.77** would prove difficult, as the lactone moiety was expected to be incompatible with Paquette's explored route and an alternative starting material did not appear feasible.^[174] Therefore, our new focus shifted towards developing a protocol for the conversion of endocyclic enol ether **3.92** to lactone **3.99**. We foresaw that the simplest approach to acquiring **3.99** was through hydration of endocyclic enol ether **3.92** to a lactol, which could be theoretically oxidised to afford the desired lactone (scheme 3.19).



Scheme 3.19: Revised retrosynthesis of **3.74**.

With the new goal of accessing lactone **3.99**, we set out to synthesise lactol **3.102-a** via hydration of benzoyl protected ether **3.92**. With few examples for the synthesis of lactols from enol ethers akin to our own (**3.102-a**), we initially set out to investigate relatively mild acidic conditions for the hydration of **3.92**. Pyridinium *p*-toluenesulfonate in a mixture of THF/H₂O (entry 1, table 3.3) led to the slow decomposition of enol ether **3.92**, while addition of AcOH (entry 2, table 3.3) failed to afford any products, as it was suspected to be inadequately acidic. As predicted, all strong acids investigated, such as TFA (entry 3, table 3.3), *p*-TsOH·H₂O (entry 4, table 3.3), and aq. HCl (entry 5, table 3.3) failed to afford any desired lactol **3.102-a** and appeared to induce decomposition of the starting endocyclic enol ether **3.92**. A protocol by Gilmore detailed an alternative hydration method, where exocyclic enol-ethers could be treated with Ph₃P·HBr in THF to afford their corresponding lactols.^[175] As reported by Gilmore, in the form of its triphenylphosphine conjugate base, HBr could induce addition across the alkenyl carbons, and the corresponding newly formed C-Br bond could subsequently undergo nucleophilic attack by water *in situ* to afford the desired lactol **3.102-a** (entry 6, table 3.3). However, upon subjecting benzoyl protected enol ether **3.92** to Ph₃P·HBr, formation of the desired lactol **3.102-a** was not observed, and only decomposition by-products, unreacted enol ether **3.92**, and a mixture of unresolvable by-products were isolated. Given that no identifiable products were isolated upon attempting to hydrate benzoyl protected enol ether **3.92** (table 3.3), we suspect **3.92** may have undergone an elimination sequence, akin to that of **3.102-b** to **3.102-d**, to generate substituted pyran **3.102-**

d (table 3.1, table 3.3, b). Upon formation of the plausible pyran intermediate **3.102-d**, an acid catalysed polymerisation could ensue, leading to the degraded unresolvable mixture observed for all conditions investigated (table 3.1).

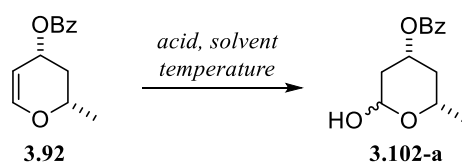
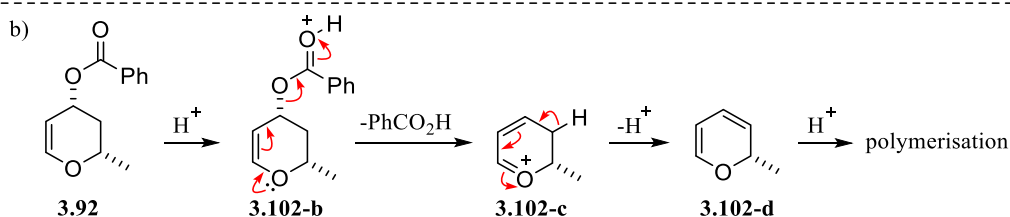


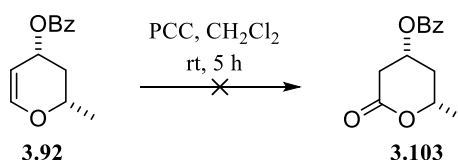
Table 3.3: Attempted hydration of benzoyl protected enol-ether **3.92** to lactol **3.102-a**.^[175,176]

Entry	Acid (eq)/Solvent	Conditions	Outcome
1	Pyridinium <i>p</i> -toluenesulfonate (2) / THF:H ₂ O	rt, 8 h	decomposition
2	AcOH (2) / THF:H ₂ O	rt, 16 h	no product
3	TFA (1.1) / THF:H ₂ O	0 °C to rt, 3 h	decomposition
4	<i>p</i> -TsOH (1.1) / THF:H ₂ O	0 °C to rt, 1 h	decomposition
5	aq. HCl (1.1) / THF:H ₂ O	0 °C, 1 h	decomposition
6	Ph ₃ P·HBr (1.2) / THF then H ₂ O	rt, 3 h	decomposition



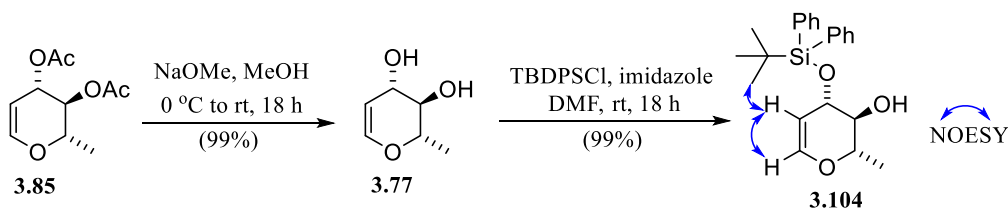
b): suspected acid catalysed side reaction, potentially leading to polymerisation via pyran **3.102-b**.

As all the investigated hydration conditions either led to decomposition, or were suspected to eliminate the benzoyl moiety, we set out to investigate a new protocol to access the desired lactone **3.103** (scheme 3.20). In 1977, Piancatelli reported an unconventional method for acquiring lactones and esters from enol ethers directly via oxidation with pyridinium chlorochromate (PCC).^[177] Following Piancatelli's general procedure, benzoyl protected endocyclic enol ether **3.92** was subjected to a suspension of 1.5 equivalents of PCC in CH₂Cl₂, and the mixture was stirred for 5 hours (scheme 3.20). However, upon the attempted purification of the reaction mixture, no desired benzoyl protected lactone **3.103** was observed, and only a seemingly degraded, complex mixture of unidentifiable by-products was obtained. Similarly, we suspect that PCC may have been too acidic of a reagent, and **3.92** could have undergone a similar sequence as previously proposed (table 3.3, b) to afford pyran **3.102-b**, which may have undergone polymerisation to afford the observed unresolvable mixture of seemingly degraded by-products.



Scheme 3.20: Attempted oxidation of benzoyl protected enol-ether **3.92** to lactone **3.103**.^[177]

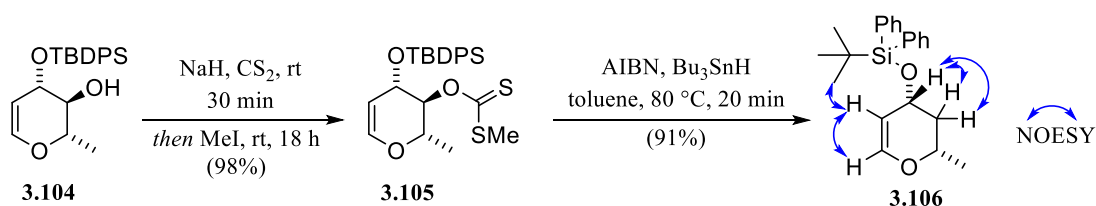
As investigated hydration conditions and Piancatelli's protocol with PCC failed to afford any desired product, the benzoyl ester was appeared to be highly susceptible to hydrolysis under acidic conditions. Therefore, we set out to investigate a new protecting group strategy, which would prove more resilient to acidic conditions. Choosing an alternative suitable protecting group appeared difficult, as regioselectivity issues had previously proved problematic, as was observed in the attempted regioselective benzylation of diol **3.77** (scheme 3.14). Based on our previous investigations for the protection of diol **3.77**, we postulated that a reagent that was both sterically hindered and possessed a labile leaving group was required in order to achieve regioselective protection of the C4 hydroxyl substituent. A given reagent that met these requirements would be expected to react rapidly at reduced temperatures in a regioselective manner. Therefore, based on this set of criteria, few protecting groups appeared suitable outside of a selection of common silyl ethers. TBDPS was the first silyl protecting group investigated in our strategy due to its significantly sterically hindered substituents, while also displaying the most inert reactivity towards acidic conditions of the other commonly available silyl chlorides. TBDPS protected enol ether **3.104** was prepared in near quantitative yield by stirring a mixture of diol **3.77**, TBDPSCl and imidazole in DMF overnight at room temperature (scheme 3.21). The desired C4 silyl protected regioisomer **3.104** was confirmed as the exclusive product as indicated by key NOE correlations and comparison of the obtained ¹H & ¹³C NMR spectra peaks with that of the literature.^[178]



Scheme 3.21: Ester hydrolysis, followed by mono-silyl protection of **3.104**.^[160,178,179]

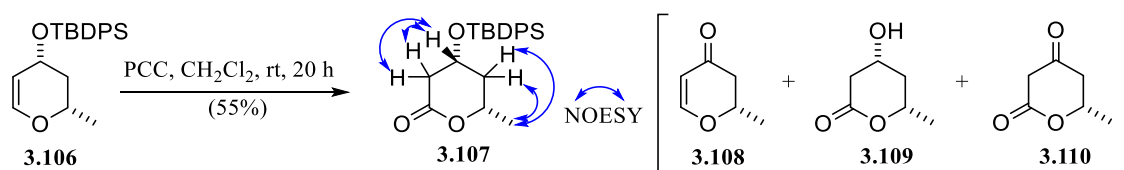
Following the successful regioselective silyl protection of diol **3.77**, we set out to deoxygenate **3.104** under the same Barton conditions that were previously investigated for our benzoyl ester route.^[160] Following the previously explored two-step, one-pot method for the synthesis of benzoyl methyl xanthate **3.91** (scheme 3.15), silyl protected alcohol **3.104**

was subjected to a suspension of NaH in CS₂, followed by addition of MeI to afford methylated xanthate **3.105** (scheme 3.21). Upon isolation, methyl xanthate **3.105** was heated in toluene with Bu₃SnH and AIBN to afford the desired deoxygenated enol ether **3.106**.



Scheme 3.21: Synthesis of silyl protected enol ether **3.106** via Barton deoxygenation.^[160]

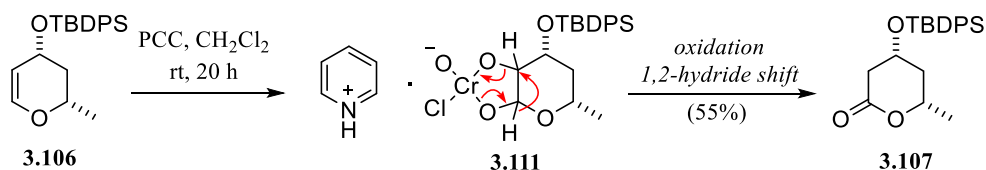
Employing Piancatelli's procedure as a template,^[177] endocyclic enol ether **3.106** was subjected to a suspension of 1.5 equivalents of PCC in CH₂Cl₂ and the mixture was stirred overnight to afford the desired lactone **3.107** in a reasonable yield of 55% (scheme 3.22). While monitoring the oxidation of the enol ether **3.106** by TLC analysis, a series of polar by-products were observed to form, which were isolated as an inseparable mixture. ¹³C NMR analysis of the mixture revealed multiple sp² deshielded carbon shifts that were in the range of typical carbonyl species. Piancatelli reported the appropriate afforded esters and lactones in yields typical of 75 - 95%, which were notably higher yields than achieved for our oxidation of **3.106** to **3.107**. We suspect the disparity in yields observed with our endocyclic enol ether system (**3.106**) may lie with the apparent lability of the TBDPS ether, where cleavage facilitated by chromic acid upon addition of PCC could lead to the formation of a mixture of hydrolysed and oxidised undesired by-products (**3.108** – **3.110**) (scheme 3.22). All attempts to further optimise the oxidation protocol, by varying the relative molar equivalents of PCC added, along with physical conditions, such as temperature and reaction times, failed to afford yields in excess of 55%.



Scheme 3.22: Synthesis of lactone **3.107** via PCC mediated oxidation of endocyclic enol ether **3.106**, and proposed constituents (**3.08** – **3.110**) of the inseparable mixture of undesired by-products.^[177]

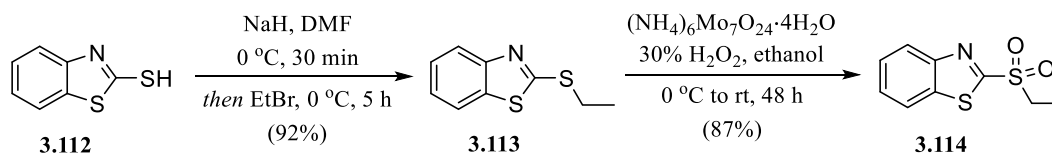
In his original paper, Piancatelli proposed a mechanism for the direct oxidation of various enol ethers with PCC.^[177] Piancatelli postulated that the oxidation event could be initiated by an electrophilic attack of PCC with a given enol ether (**3.106**), to generate an unstable cyclic intermediate, such as **3.111** (scheme 3.23). Piancatelli theorised the unstable 5-membered species (**3.111**) would undergo a spontaneous pericyclic heterolytic cleavage at

the Cr-O and C-O bonds, alongside a concerted hydride shift to afford the desired lactone (**3.107**).



Scheme 3.23: Proposed mechanism for oxidation of enol ether **3.106** to lactone **3.107**.^[177]

With access to lactone **3.107**, we set out to acquire a suitable alkylating reagent for the anticipated modified-Julia olefination, and thereby sought to synthesise ethylsulfonyl benzothiazole **3.114** in two steps via a literature procedure (scheme 3.24).^[173] First, *S*-alkylation was achieved via a one-pot protocol, by deprotonation of commercially available mercaptobenzothiazole **3.112**, and addition of ethyl bromide gave ethylthio-benzothiazole **3.113** in good yield.^[180] Next, the resultant alkylated thio-benzothiazole **3.113** was subjected to a mixture of catalytic ammonium heptamolybdate and hydrogen peroxide to afford the desired *S*-oxidised ethylsulfonyl benzothiazole **3.114**.^[172] Synthesis of ethylsulfonyl benzothiazole **3.114** proved to be efficient, simple, and could be prepared in large quantities if needed.



Scheme 3.24: Preparation of ethylsulfonyl benzothiazole **3.114**.^[172]

With both the lactone **3.107** and ethyl-sulfonylbenzothiazole **3.114** in hand, we set out to investigate the synthesis of *Z*-exocyclic enol ether **3.115** via both standard modified-Julia olefination methods and a protocol published by Gueyrard (table 3.4).^[171–173] Standard modified-Julia olefination protocols have been largely limited to ketone & aldehyde substrates, and generally require a strong base, such as LDA or *n*-BuLi, to deprotonate the α -proton of a substituted sulfonylbenzothiazole (**3.114**).^[181,182] However, over the last decade, Gueyrard had published a series of articles detailing the optimisation of a modified-Julia method that could extend the scope of the olefination protocol to lactones and anhydrides, by employing $\text{BF}_3 \cdot \text{OEt}_2$ as an activating agent.^[171–173,183,184]

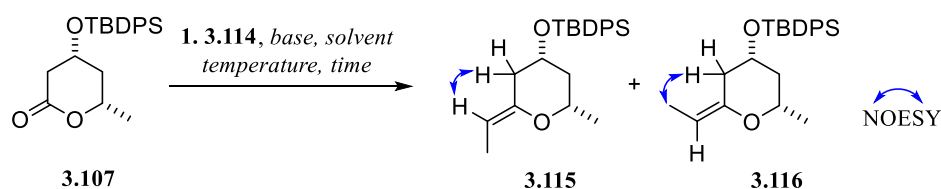


Table 3.4: Modified-Julia olefination of lactone **3.107**, with ethylsulfonyl benzothiazole **3.114**.

Entry	Base (eq)/Additive (eq)	Conditions	Outcome Ratio of Z:E (3.115:3.116)
1	LiHMDS (1.5)	THF, -78 °C to rt, 2 h	no product, SM
2	KHMDS (1.5)	THF, -78 °C to rt, 2 h	no product, SM
3	LDA (1.2)	THF, -78 °C to 0 °C, 2 h	decomposition
4	<i>t</i> -BuLi (1.2)	THF, -78 °C to 0 °C, 1 h	decomposition
5	<i>t</i> -BuOK (2)	THF, 0 °C to rt, 16 h	no reaction, SM
6	NaH (1.2)	THF, 0 °C to rt, 5 h	complex mixture, no product
7	LiHMDS (1.3)/BF ₃ ·OEt ₂ (1.3)	THF, -78 °C to rt, 1 h	24% (1.4:1)
8	KHMDS (1.3)/BF ₃ ·OEt ₂ (1.3)	THF, -78 °C to rt, 1 h	19% (1.4:1)

We initially sought to trial standard modified-Julia protocols with various bases, to observe if our lactone system (**3.107**) could undergo olefination in the absence of a Lewis acid additive.^[171,172,182] In the attempted olefination of lactone **3.107** with ethyl sulfonylbenzothiazole **3.114**, both LiHMDS (entry 1, table 3.4) and KHMDS (entry 2, table 3.4) failed to afford any observable product and only small quantities of lactone **3.107** were recovered upon purification of the reaction mixture. Stronger, yet sterically smaller bases, such as LDA (entry 3, table 3.4) and *n*-BuLi (entry 4, table 3.4), also failed to afford any isolatable product and only gradual degradation of the reaction mixture ensued. Additionally, both *t*-BuOK (entry 5, table 3.4) and NaH (entry 6, table 3.4) did not yield any desired *Z*-exocyclic enol ether **3.115**. Under Gueyrard's protocol, the employment of BF₃·OEt₂ as an activating agent, with either LiHMDS (entry 7, table 3.4) or KHMDS (entry 8, table 3.4), led to the formation of an inseparable mixture of adducts. According to Gueyrard, this mixture of hemiketal-sulfonylbenzothiazole adducts could not undergo spontaneous decomposition *in situ* to the corresponding exocyclic enol ethers, unlike their ketone and aldehyde counterparts. Instead, the hemiketal adducts could only be hydrolysed upon stirring the crude mixture in a concentrated solution of DBU in THF, following quenching of the reaction.^[173,183] Thus, following alkylation of **3.107**, in the presence of BF₃·OEt₂ with either LiHMDS (entry 7, table 3.4) or KHMDS (entry 8, table 3.4), the crude hemiketal adducts were subjected to DBU in THF to afford an inseparable mixture of *Z/E*-exocyclic enol ethers

3.115:3.116 in a 1.4:1 ratio respectively. Gueyrard had also reported an alternative method for the olefination of anhydrides, where decomposition of the hemiketal adducts to the desired olefins could be achieved upon concentration of the quenched reaction mixture over SiO₂.^[184,185] However, quenching the alkylation reaction with AcOH and concentrating the resultant adducts over SiO₂ failed to yield any *Z/E*-exocyclic enol ethers **3.115:3.116**, and instead only afforded the crude mixture of hemiketal adducts.

Gueyrard and co-workers had not formerly proposed a mechanism that could rationalise, and consequently predict the stereochemical outcome for their BF₃·OEt₂ mediated olefination protocol, and only noted that both lactones & anhydrides did not undergo spontaneous decomposition to their corresponding enol-ethers *in situ*. According to Gueyrard, the improved yields of the desired enol-ethers obtained were attributed to the strong electrophilic properties of BF₃·OEt₂, which were suspected to increase the nucleophilic nature of the carbonyl moiety of a given lactone substrate, thereby promoting favourable reaction kinetics for the olefination event (entries 7 & 8 table 3.4).^[173,183] Furthermore, BF₃·OEt₂ most likely partakes in the condensation transition state of lactone **3.107** with benzothiazole **3.114**. As such, BF₃·OEt₂ would be expected to replace the base counter ion (LiHMDS or KHMDS) within the transition state. Hence, if a chosen base differed solely in the size of its counter ion (Li⁺ or K⁺), then we would expect that the counter ion, regardless of its size, would not influence the ratio of products isolated under Gueyrard's method.^[173,183] As such, the employment of BF₃·OEt₂ may explain the consistent *Z/E* ratio of enol ethers (**3.115:3.116**) isolated, irrespective of the silylamide base, LiHMDS (entry 7, table 3.4) or KHMDS (entry 8, table 3.4), employed. Despite attempts to further optimise Gueyrard's protocol in the pursuit of *Z*-exocyclic enol ether **3.115**, issues regarding stereoselectivity and yields could not be resolved. Thus, we did not persist in efforts to further optimise the synthesis of *Z*-exocyclic enol ether **3.115** and sought to explore our proposed key biomimetic hetero-Diels-Alder spirocyclisation reaction to obtain virgatolide B (**3.2**).

3.3.4 Attempted Hetero-Diels-Alder Reaction, Virgatolide B

Despite the inability to further optimise the modified-Julia reaction in the pursuit of *Z*-exocyclic enol ether **3.115**, we continued with our biogenically inspired synthesis of virgatolide B (**3.2**) via a hetero-Diels-Alder reaction. As *Z*-exocyclic enol ether **3.115** could neither be synthesised in good yield or acquired exclusively as the desired isomer, we pressed onward to virgatolide B (**3.2**), initially investigating Spence's thermal model conditions with our more complex *Z*-exocyclic enol ether **3.115** system. However, under

thermal conditions, neither spirocycle **3.117**, virgatolide B (**3.2**) or other identifiable by-products were observed to form under various relative molar ratios of **3.66** to **3.115:3.116** (entries 1, 2, 3, table 3.5). In contrast to Spence's successful model system, changing solvents from toluene to dioxane also failed to yield any identifiable products (entry 4, table 3.5). All thermal conditions explored failed to afford any desired products (**3.2** or **3.117**), and only unidentifiable complex mixtures were isolated (entries 1 – 4, table 3.5). Under the thermal conditions investigated thus far, none of the isolated complex mixtures contained any ^1H or ^{13}C NMR signals that resembled virgatolide B (**3.2**) or the desired protected precursor **3.117**. Next, exploration of alkaline conditions with Et_3N led to the gradual degradation of the reactants in either toluene or dioxane (entries 6 & 8, table 3.5), and rapid decomposition ensued upon heating the reactants (entries 5 & 7, table 3.5). Finally, substituting Et_3N for NaHCO_3 also failed to afford any distinguishable products, and only complex mixtures were obtained following purification of the reaction mixture (entries 9 & 10, table 3.5).

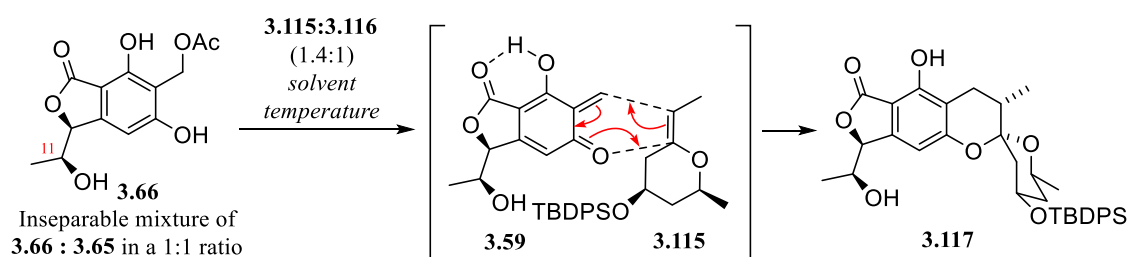
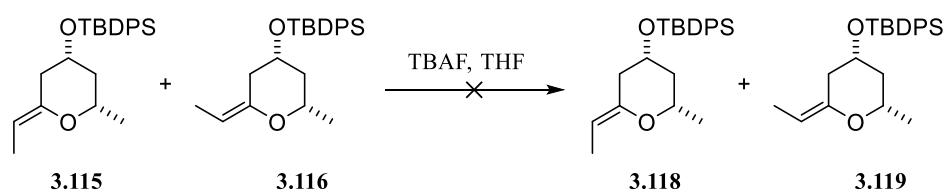


Table 3.5: Attempted synthesis of virgatolide B precursor **3.117** via a 4 + 2 cycloaddition of *o*-QM precursor **3.66** with *Z/E*-exocyclic enol ethers **3.115:3.116** (1.4:1 ratio respectively).

Entry	Reagents (eq)	Solvent/Conditions	Outcome
1	3.66 and 3.115:3.116 (1:1)	PhMe, 110 °C, 16 h	complex mixture
2	3.66 and 3.115:3.116 (1:5)	PhMe, 110 °C, 16 h	complex mixture
3	3.66 and 3.115:3.116 (1:10)	PhMe, 110 °C, 16 h	complex mixture
4	3.66 and 3.115:3.116 (1:5)	dioxane, 110 °C, 16 h	complex mixture
5	3.66 and 3.115:3.116 (1:5)	Et_3N , PhMe, 100 °C, 6 h	decomposition
6	3.66 and 3.115:3.116 (1:5)	Et_3N , PhMe, rt, 6 h	decomposition
7	3.66 and 3.115:3.116 (1:5)	Et_3N , dioxane, 100 °C, 5 h	decomposition
8	3.66 and 3.115:3.116 (1:5)	Et_3N , dioxane, rt, 16 h	decomposition
9	3.66 and 3.115:3.116 (1:5)	NaHCO_3 , dioxane, 100 °C, 5 h	decomposition
10	3.66 and 3.115:3.116 (1:5)	NaHCO_3 , dioxane, rt, 16 h	decomposition

Consistent with our findings, Spence argued that the secondary alcohol at C11 of **3.66** was sensitive under alkaline conditions, and that upon the addition of a base, decomposition would ensue. Under basic conditions, the C11 alcohol may have proven to be sufficiently nucleophilic, which may have resulted in **3.66** preferentially self-condensing with the *in situ* generated *o*-QM **3.59** via nucleophilic attack. We suspect that under solvent only conditions (entries 1 – 4, table 3.5), *Z*-exocyclic enol ether **3.115** isomerises to the undesired endo isomer *in situ*, catalysed via acetic acid following β -elimination of **3.66** to *o*-QM **3.59**, as observed under Spence's model system (table 3.1). Isomerisation of the already unfavourable mixture of *Z/E*-exocyclic enol ethers **3.115:3.116**, alongside apparent decomposition, may have led to the formation of what appeared to be a series of unpurifiable, unidentifiable complex mixtures. An alternative explanation may reside with the bulky OTBDPS protecting group, which could have prevented the hetero-Diels-Alder transition state from proceeding. Therefore, to exclude the possibility of the TBDPS protecting group impeding the formation of the hetero-Diels-Alder transition state, we set out to cleave the silyl ether of *Z/E*-exocyclic enol ethers **3.115:3.116** (1.4:1 ratio). However, all attempts to cleave the TBDPS ether of **3.115:3.116** failed to afford any observable product, and no isolatable products (**3.118** & **3.119**), including starting material, were recovered following the addition of TBAF (scheme 3.25). Thus, virgatolide B (**3.2**) and the protected precursor **3.117** could not be synthesised in accordance with our biogenically inspired proposal.



Scheme 3.25: Attempted deprotection of *Z/E*-exocyclic enol ethers **3.115:3.116** (1.4:1 ratio).

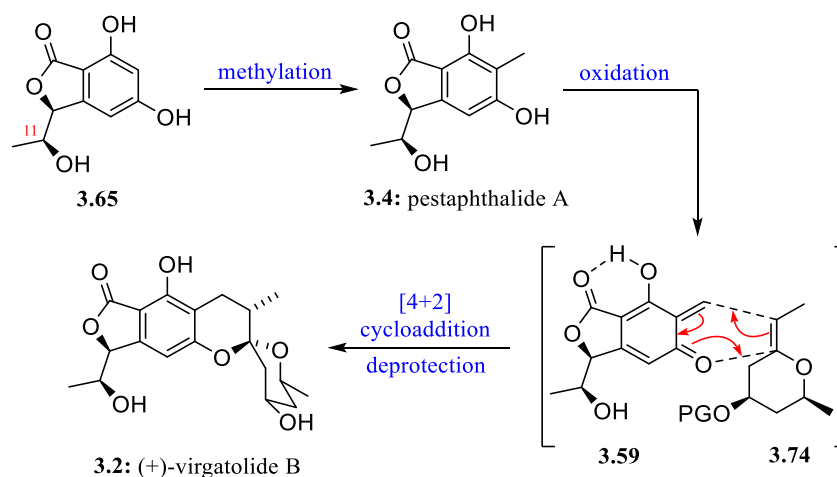
3.4 Summary and Future Directions

Despite our proposed, biogenically inspired hetero-Diels-Alder pathway failing to afford virgatolide B (**3.2**), we were able to synthesise both cycloaddition substrates, *o*-QM **3.66** and *Z*-exocyclic enol ether **3.115**. With minor modifications to Spence's protocol, benzofuranone **3.65** was synthesised in 10 synthetic steps, in an overall yield of 36%, slightly improving upon Spence's overall yield of 32% for **3.65**. Benzofuranone **3.65** was successfully converted to the pivotal *o*-QM precursor **3.66**, albeit as a crude mixture with **3.65**, and could not be purified due to issues regarding the inherent instability of the methenyl acetate moiety. The failed attempted synthesis of *Z*-exocyclic enol ether **3.74**, via a

Wittig/Horner-Wittig olefination, was attributed to the labile nature of the benzoyl protecting group. Due to the restricted viable synthetic route available from 3,4-Di-O-acetyl-6-deoxy-L-glucal (**3.85**), alternative protecting group strategies were highly limited. However, upon changing to a TBDPS protecting group strategy early in the synthetic route, and shifting our focus to a suitable lactone in the pursuit of *Z*-exocyclic enol ether **3.115**, lactone **3.107** was acquired from 3,4-Di-O-acetyl-6-deoxy-L-glucal (**3.85**) over 5 steps, in an overall yield of 49%. Under Gueyrard's modified-Julia protocol, lactone **3.107** was demonstrated to undergo olefination in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ to afford the desired *Z/E*-exocyclic enol ethers **3.115:3.116**, in a 1.4:1 ratio respectively.

Finally, investigation into our proposed biogenically inspired hetero-Diels-Alder spirocyclisation reaction between *Z*-exocyclic enol ether **3.115** (as a mixture of *Z/E*-isomers **3.115:3.116**, in a 1.4:1 ratio) and the *in situ* generated *o*-QM **3.59**, failed to afford either virgatolide B (**3.2**) or the anticipated TBDPS protected precursor **1.117** (table 3.5). Based upon NMR analysis of the isolated fractions, the absence of observable characteristic peaks for the expected desired products (**3.2** or **1.117**) indicated the possibility of multiple unfavourable side reactions occurring within the vessel. The failure of the investigated conditions was suspected to be primarily attributed to the *in situ* isomerisation of the *Z/E*-exocyclic enol ethers **3.115:3.116** to the endo isomer, akin to Spence's model system. Suspected isomerisation of *Z*-exocyclic enol ether **3.115** to the endo isomer, analogous to Spence's model system (table 3.1), may have led to consumption of the dienophile **3.115**. Additionally, the large TBDPS ether protecting group of *Z*-exocyclic enol ether **3.115** may have impeded the hetero-Diels-Alder transition state from forming. However, given that the protecting group is relatively distal from the exocyclic alkene, this prediction would appear unlikely. Thus, degradation of the reactants (**3.115**, **3.66**, and **3.59**) and isomerisation of *Z*-exocyclic enol ether **3.115** appears to be the most likely explanation for the failed attempted synthesis of spiroketal TBDPS ether **3.117**.

3.4.1 Future directions



Scheme 3.26: Potential future biosynthetically inspired total synthesis of virgatolide B (3.2)

Future investigations into the synthesis of virgatolide B (3.2), in accordance with our biosynthetic proposal, would need to address two key issues. First, to investigate an alternative pathway to obtain protected *Z*-exocyclic enol-ether 3.74, either by changing to a smaller protecting group for the modified-Julia olefination pathway explored, or to develop an entirely new synthetic route. Second, to synthesise an *o*-QM precursor that could be activated to the corresponding *o*-QM 3.59 under mild conditions. As stated in our proposal, pestaphthalide A (3.4) may serve as a direct biogenic source of *o*-QM 3.59 in the biosynthesis of virgatolides A (3.1) and B (3.2). Thus, a selective methylation of benzofuranone 3.65, followed by an oxidative dearomatisation of pestaphthalide A (3.4), could generate *o*-QM 3.59 *in situ*. Additionally, any oxidant employed, such as PIDA (phenyliodine(III) diacetate) or lead acetate, must prove tolerant of both the C11 alcohol of pestaphthalide A (3.4) and the *Z*-exocyclic enol-ether 3.74 dienophile.

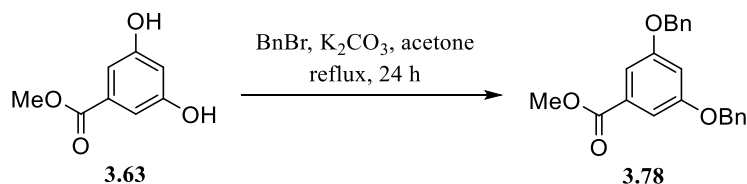
3.5 Supporting Information

3.5.1 General Experimental

All commercially obtained chemicals were used without further purification. Solvents stated as dry, were either collected from a solvent purification system (THF or DMF) or distilled under an atmosphere of nitrogen and stored over 3Å molecular sieves. Thin-layer chromatography (TLC) was conducted on Merck silica gel 60 F₂₅₄ aluminium sheets and visualised under a UV lamp or with ceric ammonium molybdate (CAM), vanillin or potassium permanganate staining followed by heated. All R_f values were rounded to the nearest 0.01. Unless stated otherwise, Davisil 43-60 micron chromatographic silica media was used for flash chromatography. ¹H and ¹³C NMR spectra were either recorded on an Agilent 500 spectrometer (¹H at 500 MHz, ¹³C at 125 MHz) or on an Agilent spectrometer with a 600 MHz Oxford magnet, with a cryoprobe (¹H at 600 MHz, ¹³C at 150 MHz) in CDCl₃ as the solvent, unless specified. ¹H and ¹³C chemical shifts are reported in ppm relative to TMS (δ 0.0). All *J* values were quoted to the nearest 0.1 Hz. Multiplicities are reported as (br) Broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (qnt) quintet, (sext) sextet and (m) multiplet. IR spectra were recorded on a Perkin-Elmer Fourier-Transform Infrared (FT-IR) spectrometer on a nickel-selenide crystal as neat compounds. High resolution mass spectra were obtained on an Agilent ESI high resolution mass spectrometer. Melting points were recorded on a Reichert electrothermal melting point apparatus and are uncorrected. Optical rotations were obtained on an Anton Paar MCP 100 Polarimeter in CHCl₃.

3.5.2 Experimental Procedures

Methyl 3,5-dibenzyloxybenzoate **3.78**



To a solution of methyl 3,5-dihydroxybenzoate **3.63** (20.0 g, 119 mmol) and K_2CO_3 (34.5 g, 250 mmol) in acetone (200 mL), was added BnBr (29.7 mL, 250 mmol) and the mixture was heated under reflux for 24 h. K_2CO_3 was filtered off, and the filtrate was concentrated *in vacuo*. The resultant residue was taken up in EtOAc (250 mL) and H_2O (200 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (2×200 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (petrol/ethyl acetate, 4:1) to give methyl 3,5-dibenzyloxybenzoate **3.78** as an off-white precipitate (41.1 g, quantitative). The spectroscopic data was consistent with that reported in the literature.^[159]

Rf = 0.5 (petroleum ether/EtOAc, 2:1)

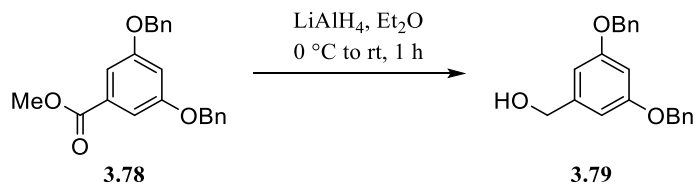
MP: 68-71 °C

IR (neat): 2950, 1720, 1594, 1443, 1347, 1324, 1299, 1234, 1156, 1055 cm^{-1}

1H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, $J = 7.1$ Hz, 4H), 7.38 (t, $J = 7.4$ Hz, 4H), 7.34 (d, $J = 7.1$ Hz, 2H), 7.30 (d, $J = 2.3$ Hz, 2H), 6.80 (t, $J = 2.3$ Hz, 1H), 5.06 (s, 4H), 3.90 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 159.8, 136.5, 132.1, 128.6, 128.1, 127.6, 108.4, 107.3, 70.3, 52.3.

3,5-Dibenzyloxybenzyl alcohol **3.79**



To a suspension of LiAlH₄ (3.27 g, 86.2 mmol) in Et₂O (200 mL) at 0 °C, was added methyl 3,5-dibenzyloxybenzoate **3.78** (15.0 g, 43.1 mmol) in Et₂O (100 mL) dropwise. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched by the dropwise addition of H₂O (4 mL) and was stirred for 5 min. 15% NaOH solution (4 mL) was added to the quenched mixture, followed by addition of H₂O (8 mL) and was further stirred for 15 minutes. The formed aluminium precipitate was filtered, and the filtrate was concentrated *in vacuo* to give 3,5-dibenzyloxybenzyl alcohol **3.79** (13.33 g) as a white solid, which was used in the next step without purification. The spectroscopic data was consistent with that reported in the literature.^[159]

Rf = 0.25 (petroleum ether/EtOAc, 2:1)

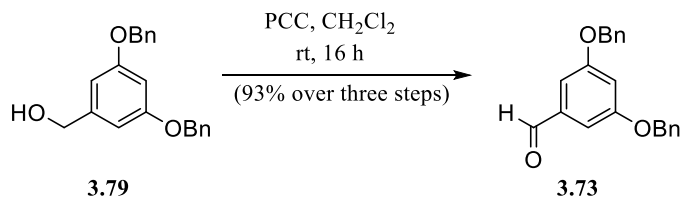
MP: 78-80 °C

IR (neat): 3314, 2904, 1592, 1443, 1369, 1351, 1285, 1152, 1023, 988 cm⁻¹

¹H NMR (600 MHz, CDCl₃) δ 7.40 (d, *J* = 7.2 Hz, 4H), 7.37 (t, *J* = 7.6 Hz, 4H), 7.31 (t, *J* = 7.2 Hz, 2H), 6.60 (s, 2H), 6.54 (s, 1H), 5.01 (s, 4H), 4.59 (d, *J* = 5.7 Hz, 2H), 1.80 (t, *J* = 5.7 Hz, 1H).

¹³C NMR (150 MHz, CDCl₃) δ 160.2, 143.4, 136.8, 128.6, 128.0, 127.5, 105.7, 101.3, 70.1, 65.3.

3,5-Dibenzyloxybenzaldehyde **3.73**



To a solution of 3,5-dibenzyloxybenzyl alcohol **3.79** (13.3 g, 41.5 mmol) in CH₂Cl₂ (250 mL), was added pyridinium chlorochromate (11.1 g, 51.5 mmol) and then the reaction mixture was stirred at room temperature for 16 h. The resulting mixture was filtered through a pad of CeliteTM, and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography on SiO₂ (petrol/ethyl acetate, 4:1) to give 3,5-dibenzyloxybenzaldehyde **3.73** (12.8 g, 93% over two steps) as a white solid. The spectroscopic data was consistent with that reported in the literature.^[159]

Rf = 0.60 (petroleum ether/EtOAc, 2:1)

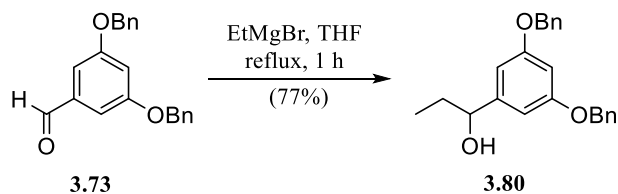
MP: 79-80 °C

IR (neat): 3032, 1687, 1608, 1593, 1448, 1383, 1351, 1297, 1172, 1049 cm⁻¹

¹H NMR (600 MHz, CDCl₃) δ 9.89 (d, *J* = 0.5 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 4H), 7.39 (t, *J* = 7.5 Hz, 4H), 7.34 (t, *J* = 7.1 Hz, 2H), 7.10 (d, *J* = 1.6 Hz, 2H), 6.86 (s, 1H), 5.08 (s, 4H).

¹³C NMR (150 MHz, CDCl₃) δ 191.8, 160.4, 138.4, 136.2, 128.7, 128.2, 127.6, 108.7, 108.3, 70.4.

1-(3,5-Dibenzyloxyphenyl)propan-1-ol **3.80**



A solution of bromoethane (7.2 mL, 97 mmol) in dry THF (240 mL) was slowly added to magnesium turnings (3.2 g, 132 mmol) and stirred at 50 °C until the majority of the magnesium turnings had been consumed. 3,5-dibenzyloxybenzaldehyde **3.73** (20.4 g, 64.1 mmol) in THF (240 mL) was then added dropwise, and the reaction mixture was then stirred while heating under reflux for 1 h. The reaction was quenched with sat. aqueous NH₄Cl (200 mL) and the resulting mixture was extracted with Et₂O (2 × 300 mL). The combined organics were dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by recrystallisation from diethyl ether:petrol to give 1-(3,5-dibenzyloxyphenyl)propan-1-ol **3.80** (17.29 g, 77%) as a white crystalline solid.

Rf = 0.45 (petroleum ether/EtOAc, 2:1)

MP: 72-73 °C

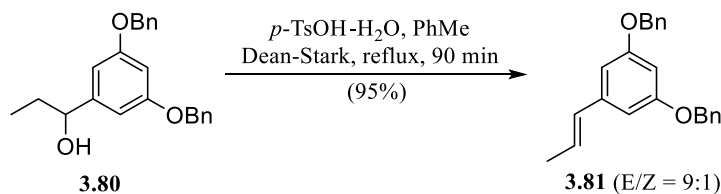
IR (neat): 3257, 2967, 1739, 1609, 1593, 1446, 1357, 1291, 1159, 1039, 833 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ 7.42 (d, *J* = 7.4 Hz, 4H), 7.38 (t, *J* = 7.5 Hz, 4H), 7.32 (t, *J* = 7.1 Hz, 2H), 6.61 (d, *J* = 2.2 Hz, 2H), 6.54 (t, *J* = 2.0 Hz, 1H), 5.03 (s, 4H), 4.53 (td, *J* = 6.6, 3.5 Hz, 1H), 1.79 (d, *J* = 3.7 Hz, 1H), 1.84 – 1.67 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 160.0, 147.2, 136.9, 128.58, 128.56, 128.0, 127.58, 127.56, 105.1, 101.1, 76.0, 70.1, 31.8, 10.1.

HRMS (ESI): calculated for C₂₃H₂₄O₃, 349.1798 [M+H]⁺, found 349.1810.

(E)-(3,5-Dibenzyloxyphenyl)prop-2-ene 3.81



To a solution of 1-(3,5-dibenzyloxyphenyl)propan-1-ol **3.80** (1.00 g, 2.87 mmol) in toluene (110 mL), was added *p*-TsOH·H₂O (55 mg, 0.29 mmol) and the mixture was heated under reflux with a Dean-Stark apparatus for 90 min. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography on SiO₂ (petrol/ethyl acetate, 15:1) to give (E)-(3,5-dibenzyloxyphenyl)prop-2-ene **3.81** (900 mg, 95%) as a pale yellow oil.

R_f = 0.60 (petroleum ether/EtOAc, 2:1)

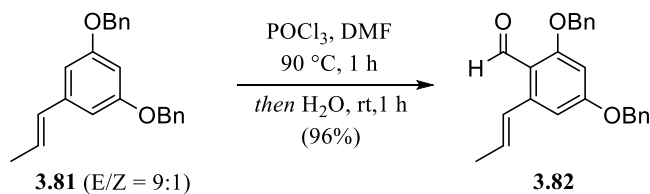
IR (neat): 3030, 1584, 1453, 1437, 1374, 1282, 1155, 1048, 960 cm⁻¹

¹H NMR (600 MHz, CDCl₃) δ 7.42 (d, *J* = 7.4 Hz, 4H), 7.38 (t, *J* = 7.5 Hz, 4H), 7.36 – 7.29 (m, 2H), 6.59 (d, *J* = 2.1 Hz, 2H), 6.48 (t, *J* = 2.1 Hz, 1H), 6.32 (d, *J* = 15.8 Hz, 1H), 6.20 (dq, *J* = 15.6, 6.5 Hz, 1H), 5.03 (s, 4H), 1.86 (d, *J* = 6.5 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 160.1, 140.1, 137.0, 130.9, 128.6, 128.0, 127.6, 127.5, 126.4, 105.2, 100.7, 70.1, 18.4.

HRMS (ESI): calculated for C₂₃H₂₂O₂, 331.1693 [M+H]⁺, found 331.1692.

(E)-2,4-Dibenzyloxy-6-(prop-1-en-1-yl)benzaldehyde 3.82



To a solution of (*E*)-(3,5-dibenzyloxyphenyl)prop-2-ene **3.81** (2.21 g, 6.7 mmol) in DMF (35 mL) at $0\text{ }^\circ\text{C}$, was added POCl_3 (0.95 mL, 10.2 mmol) and the mixture was stirred for 30 min. The reaction was then heated at $90\text{ }^\circ\text{C}$ and stirred for 1 h. H_2O (30 mL) was added and the resulting mixture was stirred at room temperature for 1 h. The mixture was diluted with EtOAc (150 mL), the organic phases was separated, and the aqueous phase was extracted with EtOAc ($2 \times 100\text{ mL}$). The combined organic extracts were washed with brine ($3 \times 100\text{ mL}$), dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (petrol/ethyl acetate, 4:1) to give *E*-2,4-dibenzyloxy-6-(prop-1-en-1-yl)benzaldehyde **3.82** (2.3 g, 96%) as a white solid.

R_f = 0.50 (petroleum ether/EtOAc, 4:1)

MP: 82-83 $^\circ\text{C}$

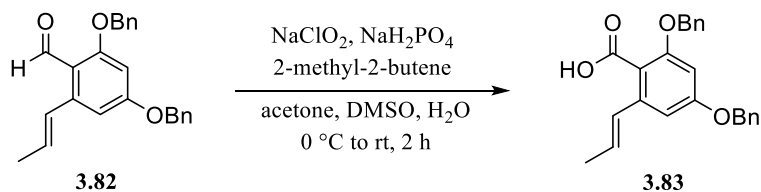
IR (neat): 2897, 1683, 1593, 1567, 1417, 1371, 1336, 1277, 1149, 1039, 964 cm^{-1}

^1H NMR (600 MHz, CDCl_3) δ 10.56 (s, 1H), 7.45 – 7.30 (m, 11H), 6.68 (d, $J = 1.9\text{ Hz}$, 1H), 6.49 (d, $J = 2.1\text{ Hz}$, 2H), 6.14 (dq, $J = 13.3, 6.6\text{ Hz}$, 1H), 5.10 (s, 2H), 5.09 (s, 2H), 1.91 (dd, $J = 6.7, 1.4\text{ Hz}$, 3H).

^{13}C NMR (150 MHz, CDCl_3) δ 190.6, 163.9, 163.5, 143.6, 136.01, 135.99, 130.05, 129.98, 128.73, 128.69, 128.3, 128.2, 127.6, 127.3, 116.3, 105.3, 98.6, 70.7, 70.2, 18.7.

HRMS (ESI): calculated for $\text{C}_{24}\text{H}_{22}\text{O}_3$, 359.1642 $[\text{M}+\text{H}]^+$, found 359.1653.

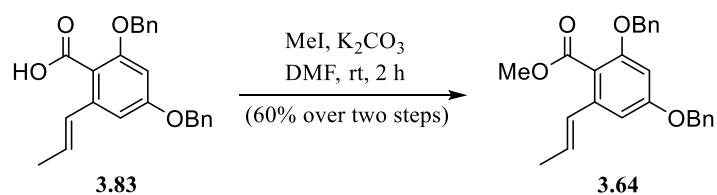
(E)-2,4-Bis(benzyloxy)-6-(prop-1-en-1-yl)benzoic acid 3.83



To a solution of aldehyde **3.82** (9.91 g, 27.65 mmol) in DMSO (200 mL) and Acetone (200 mL) at 0 °C, was added 2-methyl-2-butene (17.9 mL, 169.0 mmol). A solution of NaH₂PO₄ (19.9 g, 165.9 mmol) and NaClO₂·3H₂O (15.0 g, 103.8 mmol) in H₂O (200 mL), was added and the resulting reaction mixture was stirred at 0 °C for 30 min. The cooled mixture was warmed to room temperature and stirred for a further 2 h. The reaction mixture was diluted with H₂O (400 mL) and extracted with EtOAc (450 mL). The organic phase was separated, and the aqueous phase was re-extracted with EtOAc (2 × 200 mL). The combined organic extracts were washed with brine (3 × 350 mL), dried over MgSO₄ and concentrated *in vacuo* to give crude carboxylic acid **3.83** (8.35 g), which was carried through to the next step without further purification.

Rf = 0.1 (petroleum ether/EtOAc, 4:1)

(E)-Methyl 2,4-bis(benzyloxy)-6-(prop-1-ene)benzoate 3.64



To a solution of carboxylic acid **3.83** (8.35 g, 22.3 mmol) in DMF (165 mL), was added K₂CO₃ (6.1 g, 44.1 mmol) at room temperature and the mixture was stirred for 1 h. Iodomethane (2.7 mL, 43.4 mmol) was added and the resultant reaction mixture was further stirred at room temperature for 2 h. The reaction was quenched with sat. NH₄Cl (100 mL) and diluted with EtOAc (450 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (2 × 200 mL). The combined organic extracts were washed with brine (3 × 350 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on SiO₂ (petrol/ethyl acetate, 4:1) to give methyl ester **3.64** (6.45 g, 60% over 2 steps) as a yellow solid.

R_f = 0.45 (petroleum ether/EtOAc, 4:1)

MP: 90-92 °C

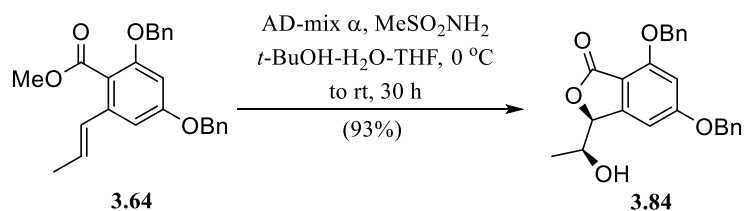
IR (neat): 2947, 1725, 1597, 1580, 1433, 1377, 1263, 1167, 1092, 1040 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ 7.41 – 7.28 (m, 10H), 6.69 (s, 1H), 6.46 (s, 1H), 6.39 (d, *J* = 15.6 Hz, 1H), 6.22 – 6.15 (m, 1H), 5.04 (d, *J* = 4.3 Hz, 4H), 3.88 (s, 3H), 1.86 (d, *J* = 6.7 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 168.6, 160.4, 157.1, 138.1, 136.6, 136.5, 129.3, 128.7, 128.5, 128.1, 127.8, 127.7, 127.5, 126.9, 116.1, 103.1, 99.6, 70.5, 70.2, 52.2, 18.7.

HRMS (ESI): calculated for C₂₅H₂₄O₄, 389.1747 [M+H]⁺, found 389.1745.

Dibenzoyloxy-isobenzofuranone **3.84**



To a solution of ester **3.64** (3 g, 7.7 mmol) and methanesulfonamide (0.87 g, 9.15 mmol) in $t\text{-BuOH}$ (89 mL), H_2O (89 mL) and THF (45 mL) at $0\text{ }^\circ\text{C}$, was added AD-mix α (21.7 g). The reaction mixture was allowed to warm to room temperature and stirred for 30 h. Na_2SO_3 (22 g) was added to the reaction mixture and was stirred for 15 min at room temperature. The resultant mixture was diluted with H_2O (250 mL) and EtOAc (350 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc ($2 \times 200\text{ mL}$). The combined organic extracts were washed with brine (200 mL), dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (petrol/ethyl acetate, 2:1) to give lactone **3.84** (2.81 g, 93%) as a white solid.

Rf = 0.20 (petroleum ether/EtOAc, 1:1)

$[\alpha]_D^{25} = -32.1$ (c 1.0, CHCl_3)

MP: $110\text{-}112\text{ }^\circ\text{C}$

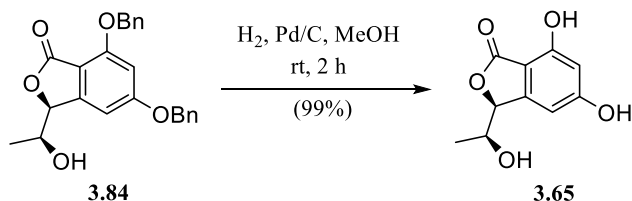
IR (neat): 3415, 2927, 1738, 1603, 1451, 1334, 1210, 1161, 1064, 1021 cm^{-1}

$^1\text{H NMR}$ (500 MHz, CD_3OD) δ 6.44 (s, 1H), 6.28 (d, $J = 1.5\text{ Hz}$, 1H), 5.23 (d, $J = 3.2\text{ Hz}$, 1H), 4.13 (qd, $J = 6.5, 3.4\text{ Hz}$, 1H), 1.23 (d, $J = 6.5\text{ Hz}$, 3H).

$^{13}\text{C NMR}$ (125 MHz, CD_3OD) δ 172.2, 167.2, 159.6, 153.0, 105.4, 103.8, 102.5, 84.7, 68.8, 18.6.

HRMS (ESI): calculated for $\text{C}_{24}\text{H}_{22}\text{O}_5$, 413.1359 $[\text{M}+\text{Na}]^+$, found 413.1365.

Dihydroxy-isobenzofuranone **3.65**



Lactone **3.84** (1.00 g, 2.56 mmol) was dissolved in MeOH (100 mL) and the flask was purged with N₂. Pd/C (100 mg) was added and the flask was purged with H₂ (1 balloon). The reaction was stirred at room temperature for 2 h. The reaction mixture was then filtered through a pad of CeliteTM and washed with MeOH. The filtrate was concentrated *in vacuo* to give deprotected isobenzofuran **3.65** (533 mg, 99%) as a colourless crystalline solid, which was used without purification.

Rf = 0.1 (petroleum ether/EtOAc, 1:1)

$[\alpha]_D^{25} = +44.9$ (c 1.0, MeOH)

MP: 195-197 °C

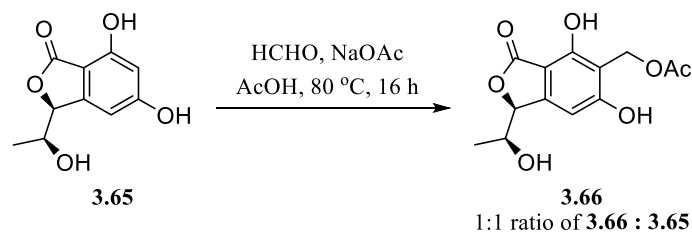
IR (neat): 3146, 1720, 1686, 1606, 1478, 1352, 1216, 1162, 1062, 980 cm⁻¹

¹H NMR (500 MHz, CD₃OD) δ 6.46 (s, 1H), 6.31 (s, 1H), 5.24 (d, *J* = 3.2 Hz, 1H), 4.58 (br s, 2H), 4.16 – 4.12 (m, 1H), 1.23 (d, *J* = 6.5 Hz, 3H).

¹³C NMR (125 MHz, CD₃OD) δ 172.1, 166.8, 159.6, 153.0, 105.6, 103.7, 102.5, 84.8, 68.8, 18.6.

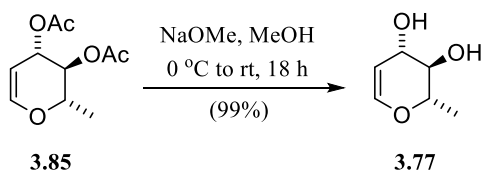
HRMS (ESI): calculated for C₁₀H₁₀O₅, 211.0601 [M+H]⁺, found 211.0600.

Benzofuranone *o*-QM precursor **3.66**



To a solution of isobenzofuran **3.65** (1.128 g, 5.37 mmol) and NaOAc·3H₂O (79 mg, 5.37 mmol) in AcOH (5 mL), was added formaldehyde solution (37% in H₂O, 0.34 mL, 10.76 mmol) and the resulting reaction mixture was heated at 80 °C for 16 h. The mixture was poured onto sat. NaHCO₃ (250 mL) and diluted with EtOAc (250 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (2 × 150 mL). The combined organic extracts were washed with sat. aqueous NaHCO₃ (250 mL), brine (250 mL), dried over MgSO₄ and concentrated *in vacuo* to give *o*-QM precursor **3.66** (1.02 g) as a yellow brown solid as an inseparable mixture with starting material **3.65**. The crude product was used without purification.

Diol 3.77



To a solution of 3,4-Di-O-acetyl-6-deoxy-L-glucal **3.85** (10 g, 46.7 mmol) in MeOH (250 mL) at 0 °C, was added NaOMe (100 mg, 1.85 mmol, 4 % mol eq) and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by flash column chromatography on SiO₂ (petrol/ethyl acetate, 1:1) to give diol **3.77** as a white powder (6.03 g, 99%).

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

[α]_D²⁵ = +16.65 (c 0.78, CHCl₃)

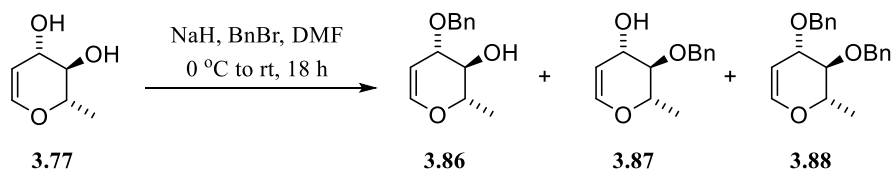
¹H NMR (500 MHz, CDCl₃): δ 6.32 (d, *J* = 5.95 Hz, 1H), δ 4.72 (dd, *J* = 5.95 Hz, *J* = 1.95 Hz, 1H), 4.24 – 4.19 (m, 1H), 3.90 – 3.84 (m, 1H), 3.45 – 3.41 (m, 1H), 2.35 (d, *J* = 3.45 Hz, 1H), 1.82 (d, *J* = 5.9 Hz, 1H), 1.39 (d, *J* = 6.35 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 144.8, 102.7, 75.6, 74.4, 70.4, 17.1

IR (neat): 3263, 1644, 1413, 1226, 1043 cm⁻¹.

HRMS (ESI): calculated for C₆H₁₀O₃, 153.0522 [M+Na]⁺, found 153.0523.

Benzyl protected enol ether **3.86**



To a solution of diol **3.77** (4.52 g, 34.7 mmol) in DMF (250 mL) at 0 °C, was added NaH (60% dispersion, 1.53g, 38.3 mmol) and the resulting mixture was stirred at 0 °C for 1 h. BnBr (4.13 ml, 34.8 mmol) was added to the reaction mixture, followed by warming the mixture to room temperature and the resultant mixture was further stirred for 18 h. The mixture was quenched with sat. NH₄Cl aqueous solution (150 mL) while cooling on an ice bath. The mixture was then extracted with diethyl ether (400 mL) and the organic extracts were washed with water (2 × 100 mL), brine (3 × 100 mL), and the organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography on SiO₂ (petrol/ethyl acetate, 5:1) to give benzyl protected enol ethers **3.86** (0.283 g, 4%), **3.87** (0.562 g, 7%), **3.88** (4.02 g, 37%), and recovered starting material diol **3.77** (1.03 g, 23%) as white powders.

3.86 R_f = 0.40 (petrol/EtOAc, 2:1)

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

3.88 R_f = 0.67 (petrol/EtOAc, 2:1)

3.86 $[\alpha]_D^{25} = +80.8$ (c 1.87, CHCl₃)

3.87 $[\alpha]_D^{25} = +63.9$ (c 1.2, CHCl₃)

3.88 $[\alpha]_D^{25} = -12.7$ (c 0.83, CHCl₃)

NMR data for **3.86**;

¹H NMR (500 MHz, CDCl₃): δ 7.38 – 7.28 (m, 3H), 7.36 (d, J = 4.4 Hz, 2H), 6.35 (dd, J = 6.2 Hz, J = 1.2 Hz, 1H), 4.85 (dd, J = 6.2 Hz, J = 2.2 Hz, 1H), 4.71 (d, J = 11.8 Hz, 1H), 4.55 (d, J = 11.8 Hz, 1H), 4.06 – 4.04 (m, 1H), 3.92 – 3.87 (m, 1H), 3.64 – 3.60 (m, 1H), 2.17 (d, J = 3.7 Hz, 1H), 1.38 (d, J = 6.4 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃): δ 144.97, 144.64, 138.31, 128.54, 127.84, 127.81, 99.69, 82.44, 76.84, 74.43, 72.75, 70.51, 17.14.

NMR data 3.87;

¹H NMR (500 MHz, CDCl₃): δ 7.38 – 7.29 (m, 5H), 6.32 (d, *J* = 6.0 Hz, 1H), 4.82 (q, *J* = 11.6 Hz, 2H), 4.69 (dd, *J* = 6.1 Hz, *J* = 2.3 Hz, 1H), 4.35 (br s, 1H), 3.28 (dd, *J* = 9.4 Hz, *J* = 7 Hz, 1H), 1.70 (br s, 1H), 1.41 (d, *J* = 6.4 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃): δ 144.63, 138.25, 128.57, 127.95, 103.12, 82.44, 74.23, 74.09, 69.99, 17.63.

NMR data 3.88;

¹H NMR (500 MHz, CDCl₃): δ 7.36 – 7.27 (m, 10H), 6.36 (d, *J* = 6.2 Hz, 1H), 4.88 (d, *J* = 11.4 Hz, 1H), 4.86 (dd, *J* = 6.5 Hz, *J* = 2.4 Hz, 1H), 4.71 (d, *J* = 11.4 Hz, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.57 (d, *J* = 11.7 Hz, 1H), 4.22 – 4.21 (m, 1H), 3.98 – 3.92 (m, 1H), 3.49 (dd, *J* = 8.8 Hz, *J* = 6.5 Hz, 1H), 1.70 (br s, 1H), 1.18 (d, *J* = 6.4 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃): δ 144.76, 138.40, 138.26, 128.37, 128.36, 127.92, 127.71, 127.59, 100.11, 79.51, 76.42, 74.02, 73.94, 70.50, 17.47.

3.86 IR (neat): 3064, 2877, 1646, 1454, 1237, 1100, cm⁻¹.

3.87 IR (neat): 3432, 2862, 1645, 1454, 1232, 1056 cm⁻¹.

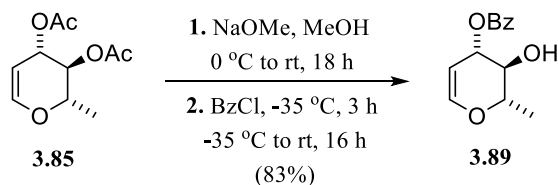
3.88 IR (neat): 3273, 2914, 1645, 1454, 1227, 1114 cm⁻¹.

3.86 (mono – benzylated) HRMS (ESI): calculated for C₁₃H₁₆O₃, 243.0995 [M+Na]⁺, found 243.0994.

3.87 (mono – benzylated) HRMS (ESI): calculated for C₁₃H₁₆O₃, 243.0995 [M+Na]⁺, found 243.0998.

3.88 (di – benzylated) HRMS (ESI): calculated for C₂₀H₂₂O₃, 333.1461 [M+Na]⁺, found 333.1465.

Benzoyl hydroxy enol ether **3.89**



To a solution of 3,4-Di-O-acetyl-6-deoxy-L-glucal **3.85** (5 g, 23.3 mmol) in MeOH (125 mL) at 0 °C, was added NaOMe (50 mg, 0.93 mmol, 4 % mol eq) and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo*, and the residue was taken up in toluene (40 mL) and the solvent was removed under reduced pressure. The crude alcohol was taken up in pyridine (70 mL), and while cooling at -35 °C, benzoyl chloride (2.6 mL, 22.4 mmol) was added dropwise over 2 h. The reaction mixture was stirred for a further 2 h at -35 °C, before being warmed to room temperature and stirred overnight. MeOH (20 mL) was added to the reaction mixture and was further stirred for 2 h. The solvent was removed under reduced pressure, and the crude residue was purified by flash column chromatography on SiO₂ (petrol/ethyl acetate, 5:1) to give benzoyl hydroxy enol ether **3.89** as a white powder (4.36 g, 83%). The spectroscopic data was consistent with that reported in the literature.^[160]

R_f = 0.54 (petrol/EtOAc, 2:1)

[α]_D²⁵ = +87.6 (c 0.65, CHCl₃)

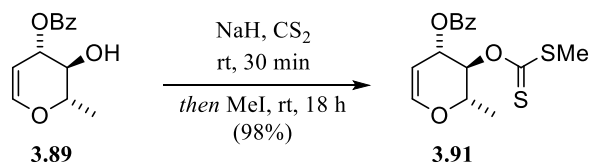
¹H NMR (500 MHz, CDCl₃): δ 8.05 (d, *J* = 8.1 Hz, 2H), δ 7.58 (t, *J* = 7.5 Hz, 1H), δ 7.45 (d, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 6.49 (d, *J* = 6.1 Hz, 1H), 5.48 – 5.46 (m, 1H), 4.83 (dd, *J* = 6.1 Hz, *J* = 2.6 Hz, 1H), 4.04 – 3.98 (m, 1H), 3.78 (dd, *J* = 8.9 Hz, *J* = 6.5 Hz, 1H), 1.45 (d, *J* = 6.35 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 168.1, 146.8, 133.6, 133.4, 130.2, 129.8, 129.6, 128.5, 98.8, 74.8, 74.3, 72.7, 17.1.

IR (neat): 3449, 3069, 2936, 1716, 1697, 1451, 1271, cm⁻¹.

HRMS (ESI): calculated for C₁₃H₁₄O₄, 257.0790 [M+Na]⁺, found 257.0788.

Benzoyl protected *S*-methyl xanthate **3.91**



To a solution of benzoyl protected enol ether **3.89** (4.36 g, 18.6 mmol) in CS₂ (130 mL) at room temperature, was added NaH (60 % dispersion, 0.80 g, 20.0 mmol) and the resulting dispersion was stirred for 30 min. MeI (1.16 mL, 18.6 mmol) was added to the yellow dispersion and was stirred at room temperature for 18 h. The mixture was quenched with sat. NH₄Cl aqueous solution (200 mL) while cooling on an ice bath. The diluted mixture was extracted with diethyl ether (400 mL) and the organic extracts were sequentially washed with water (200 mL) and brine (3 × 200 mL). The organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography on SiO₂ (petrol/ethyl acetate, 4:1) to give benzoyl protected *S*-methyl xanthate **3.91** as a bright yellow oil (5.9 g, 98%). The spectroscopic data was consistent with that reported in the literature.^[160]

R_f = 0.58 (petrol/EtOAc, 2:1)

[α]_D²⁵ = -8.21 (c 3.0, CHCl₃)

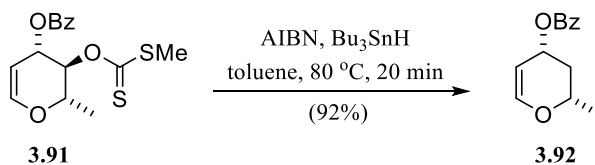
¹H NMR (500 MHz, CDCl₃): δ 8.00 (d, *J* = 7.2 Hz, 2H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 2H), 6.51 (d, *J* = 6.2 Hz, 1H), 6.17 (dd, *J* = 7 Hz, *J* = 7 Hz, 1H), 5.67 – 5.65 (m, 1H), 5.00 (dd, *J* = 6.2 Hz, *J* = 6.2 Hz, 1H), 4.41 (qnt, *J* = 6.7 Hz, 1H), 2.56 (s, 3H), 1.46 (d, *J* = 6.27 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 215.6, 165.8, 146.1, 133.2, 129.9, 129.8, 128.4, 98.4, 79.3, 72.2, 68.0, 19.3, 16.4.

IR (neat): 3456, 3063, 2924, 1720, 1646, 1268, cm⁻¹.

HRMS (ESI): calculated for C₁₅H₁₆O₄S₂, 325.0563 [M+H]⁺, found 325.0549, 326.0595 (isotope), 328.0578 (isotope). 347.0388 [M+Na]⁺, found 347.0453.

Benzoyl enol ether **3.92**



To a solution of benzoyl protected methyl xanthate **3.91** (1.0 g, 3.08 mmol) in toluene (80 mL) at 80 °C, was added AIBN (0.2 M, 1.6 mL, 0.32 mmol), Bu₃SnH (2 mL, 7.42 mmol) and the reaction mixture was stirred at 80 °C for 20 min, before being cooled to room temperature. The resultant mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on neutralised SiO₂ (loaded with 2% Et₃N in petrol, ran with petrol/ethyl acetate, 10:1) to give benzoyl enol ether **3.92** as a colourless oil (0.62 g, 92%).

R_f = 0.69 (petrol/EtOAc, 2:1)

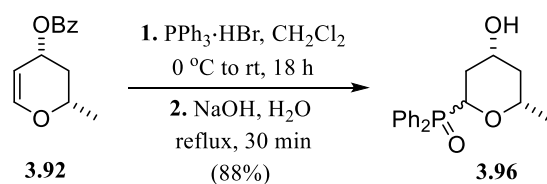
[α]_D²⁵ = +188.5 (c 0.95, CHCl₃)

¹H NMR (500 MHz, CDCl₃): δ 8.05 (d, *J* = 7.3 Hz, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 6.51 (d, *J* = 6.2 Hz, 1H), 5.67 – 5.64 (m, 1H), 4.90 – 4.88 (m, 1H), 4.27 – 4.21 (m, 1H), 2.38 (dd, *J* = 13 Hz, *J* = 6.5 Hz, 1H), 1.90 – 1.84 (m, 1H), 1.39 (d, *J* = 6.5 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃): δ 166.8, 146.8, 132.9, 130.4, 129.6, 128.3, 100.7, 70.8, 66.1, 35.1, 20.6.

IR (neat): 3067, 2932, 1713, 1644, 1451, 1273, 1235, 1092 cm⁻¹.

Diphenylphosphine oxide ether **3.96**



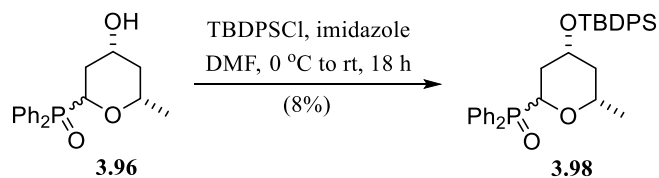
To a solution of benzoyl enol ether **3.92** (0.62 g, 2.84 mmol) in CH_2Cl_2 (50 mL) at $0\text{ }^\circ\text{C}$, was added $\text{PPh}_3 \cdot \text{HBr}$ (0.975 g, 2.84 mmol) and the reaction mixture was warmed to room temperature and stirred for 18 h. The solvent was concentrated *in vacuo* to give crude triphenyl phosphine bromide salt as an off-white solid which was taken up an aqueous solution of NaOH (0.86 g, 21.5 mmol) in water (50 mL). The resulting reaction mixture was heated under reflux for 30 min before being cooled to room temperature. The aqueous mixture was extracted with CHCl_3 ($3 \times 100\text{ ml}$) and the extracts were sequentially washed with water (150 mL) and brine (100 mL). The extracts were dried over MgSO_4 and concentrated *in vacuo* to give diphenylphosphine oxide ether **3.96** as an impure off-white waxy oil (0.79 g, 88%), which was used without purification.

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

IR (neat): 3384, 3055, 1715, 1590, 1436, 1181, 1118 cm^{-1} .

HRMS (ESI): calculated for $\text{C}_{18}\text{H}_{21}\text{O}_3\text{P}$, 339.1121 $[\text{M}+\text{Na}]^+$, found 339.1121.

TBDPS diphenylphosphine oxide ether **3.98**



To a solution of diphenylphosphine oxide ether **3.96** (79 mg, 0.25 mmol) and imidazole (26 mg, 0.38 mmol) in DMF (2 mL) at 0 °C, was added TBDPSCl (0.08 mL, 0.29 mmol). The resulting reaction mixture was warmed to room temperature and stirred for 18 h. The mixture was taken up in water (15 mL) and was extracted with CHCl₃ (2 × 10 mL). The extracts were sequentially washed with water (15 mL), brine (3 × 10 mL), then dried over MgSO₄ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on SiO₂ (petrol/ethyl acetate, 2:1) to give TBDPS diphenylphosphine oxide ether **3.98** (11.5 mg, 8 %) as off-white waxy oil, and starting material **3.96**, was re-isolated as an impure, partially degraded mixture of unknown products (8.0 mg, 10%).

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

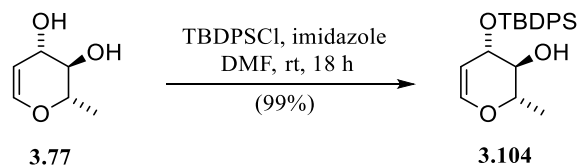
¹H NMR (500 MHz, CDCl₃): δ 7.85 – 7.81 (m, 2H), 7.65 – 7.31 (m, 18H), 4.76 (t, *J* = 5.3 Hz, 1H), 4.66 – 4.61 (m, 1H), 4.20 – 4.16 (m, 1H), 1.92 – 1.71 (m, 3H), 1.42 – 1.36 (m, 1H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.05 (s, 9H).

¹³C NMR (125 MHz, CDCl₃): δ 135.7, 134.2, 134.1, 131.8, 131.68, 131.65, 131.60, 131.58, 131.12, 131.05, 130.9, 129.58, 129.56, 128.6, 128.5, 128.4, 128.3, 127.58, 127.57, 70.5, 69.9, 69.71, 69.67, 65.4, 65.3, 40.5, 32.7, 32.6, 27.0, 21.1, 19.2.

IR (neat): 3342, 3071, 2931, 1721, 1437, 1199, 1104, 1061 cm⁻¹.

HRMS (ESI): calculated for C₃₄H₃₉O₃PSi, 577.2298 [M+Na]⁺, found 577.2293.

TBDPS hydroxy enol ether **3.104**



To a solution of diol **3.77** (6.08 g, 46.7 mmol) and imidazole (4.08 g, 60 mmol) in DMF (50 mL) at 0 °C, was added TBDPSCl (14.6 mL, 56 mmol) and the resulting mixture was stirred at room temperature for 18 h. The mixture was diluted with water (500 mL) and extracted with diethyl ether (600 mL). The organic extracts were sequentially washed with 1 M HCl aqueous solution (100 mL), brine (2 × 200 mL). The organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/ethyl acetate, 10:1) to give TBDPS hydroxy enol ether **3.104** as a colourless oil (16.99 g, 99%). The spectroscopic data was consistent with that reported in the literature.^[178]

R_f = 0.47 (petrol/EtOAc, 2:1)

[α]_D²⁵ = +24.4 (c 0.36, CHCl₃)

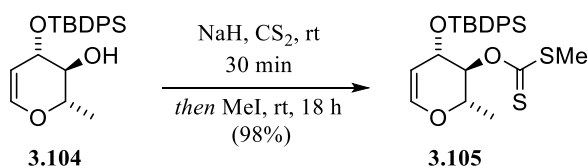
¹H NMR (500 MHz, CDCl₃): δ 7.72 – 7.69 (m, 4H), 7.46 – 7.38 (m, 6H), 6.19 (d, *J* = 6.4 Hz, 1H), 4.55 (dd, *J* = 6.4 Hz, *J* = 2.1 Hz, 1H), 4.27 – 4.23 (m, 1H), 3.83 – 3.77 (m, 1H), 3.62 – 3.58 (m, 1H), 1.83 (d, *J* = 4.2 Hz, 1H), 1.35 (d, *J* = 6.4 Hz, 3H), 1.08 (s, 9H).

¹³C NMR (125 MHz, CDCl₃): δ 143.7, 135.9, 135.7, 134.8, 133.8, 133.7, 130.0, 129.9, 129.7, 127.9, 127.7, 103.0, 75.0, 74.2, 71.3, 27.0, 26.6, 19.3, 17.1.

IR (neat): 3464, 2932, 2858, 1644, 1427, 1106, 737 cm⁻¹.

HRMS (ESI): calculated for C₂₂H₂₈O₃Si, 336.1880 [M+H]⁺, found 369.1886.

TBDPS *S*-methyl xanthate **3.105**



To a solution of TBDPS hydroxy enol ether **3.104** (2.55 g, 6.92 mmol) in CS₂ (60 mL) at room temperature, was added NaH (60 % dispersion, 0.42 g, 10.5 mmol) and the resulting dispersion was stirred for 30 min. MeI (0.47 mL, 7.55 mmol), was added to the yellow dispersion and was stirred at room temperature for 18 h. The mixture was quenched with sat. aqueous NH₄Cl aqueous solution (40 mL) while cooled on an ice bath. The diluted mixture was extracted with diethyl ether (150 mL) and the organic extracts were sequentially washed with water (100 mL) and brine (3 × 100 mL). The organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO₂ (petrol/ethyl acetate, 10:1) to give TBDPS *S*-methyl xanthate **3.105** as a bright yellow oil (3.1 g, 98%).

$R_f = 0.60$ (petrol/EtOAc, 2:1)

$[\alpha]_D^{25} = -16.88$ (c 2.79, CHCl₃)

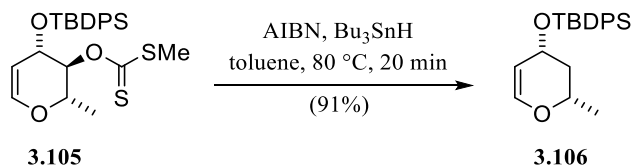
¹H NMR (500 MHz, CDCl₃): 7.70 (t, $J = 7.7$ Hz, 2H), δ 7.67 (t, $J = 7.7$ Hz, 2H), 7.44 – 7.35 (m, 6H), 6.23 (t, $J = 6.2$ Hz, 1H), 6.01 (t, $J = 5.7$ Hz, 1H), 4.49 (dd, $J = 5.7$ Hz, $J = 3.1$ Hz, 1H), 4.37 (m, 1H), 4.18 (q, $J = 6.6$ Hz, 1H), 2.51 (s, 3H), 1.42 (d, $J = 6.6$ Hz, 3H), 1.03 (s, 9H).

¹³C NMR (125 MHz, CDCl₃): δ 215.3, 143.4, 136.0, 129.8, 129.7, 127.7, 127.6, 102.2, 82.6, 72.2, 66.5, 36.1, 26.8, 19.2, 19.1, 16.6, 11.4.

IR (neat): 3070, 2930, 2857, 1645, 1427, 1213, 1060 cm⁻¹.

HRMS (ESI): calculated for C₂₄H₃₀O₃S₂Si, 481.1301 [M+Na]⁺, found 481.1298.

TBDPS enol ether **3.106**



To a solution of TBDPS *S*-methyl xanthate **3.105** (6.52 g, 14.2 mmol) in toluene (390 mL) at 80°C, was added AIBN (0.2 M, 14.2 mL, 2.84 mmol), Bu₃SnH (7.7 mL, 28.6 mmol) and the reaction mixture was stirred at 80 °C for 20 min, before being cooled to room temperature. The mixture was concentrated *in vacuo* and the resultant residue was purified by flash column chromatography on neutralised SiO₂ (loaded with 2% Et₃N in petrol, run with petrol/ethyl acetate, 10:1) to give TBDPS enol ether **3.106** as a colourless oil (4.58 g, 91%).

R_f = 0.74 (petrol/EtOAc, 2:1)

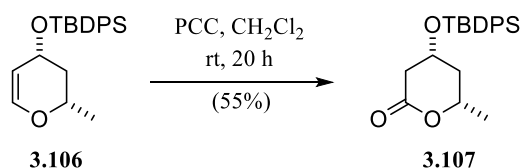
$[\alpha]_D^{25} = +9.81$ (c 2.1, CHCl₃)

¹H NMR (500 MHz, CDCl₃): δ 7.69 – 7.66 (m, 4H), 7.44 – 7.36 (m, 6H), 6.26 (d, *J* = 6.2 Hz, 1H), 4.64 – 4.63 (m, 1H), 4.46 – 4.43 (m, 1H), 3.92 – 3.86 (m, 1H), 1.89 – 1.85 (m, 1H), 1.78 – 1.71 (m, 1H), 1.23 (d, *J* = 6.4 Hz, 3H), 1.06 (s, 9H).

¹³C NMR (125 MHz, CDCl₃): δ 144.3, 135.8, 135.7, 134.24, 134.15, 129.6, 127.6, 105.7, 71.0, 64.3, 39.3, 26.9, 20.9, 19.1.

IR (neat): 3070, 2932, 2858, 1642, 1427, 1236, 1099, 1057 cm⁻¹.

TBDPS lactone **3.107**



To a solution of TBDPS enol ether **3.106** (4.58 g, 13.0 mmol) in CH₂Cl₂ (500 mL) at room temperature, was added PCC (4.21 g, 19.5 mmol) and the reaction mixture was stirred at room temperature for 20 h. The mixture was filtered through a pad of CeliteTM, concentrated *in vacuo* and the residue was purified by flash column chromatography on SiO₂ (petrol/diethyl ether, 3:1) to give TBDPS lactone **3.107** as a colourless oil (2.61 g, 55%).

R_f = 0.5 (petrol/EtOAc, 2:1)

$[\alpha]_D^{25} = +6.56$ (c 0.61, CHCl₃)

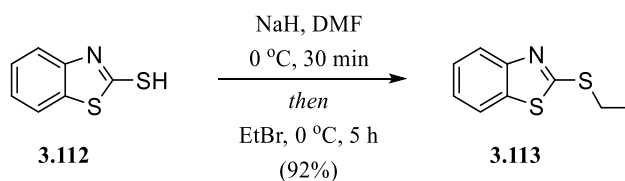
¹H NMR (500 MHz, CDCl₃): δ 7.65 – 7.63 (m, 4H), 7.47 – 7.38 (m, 6H), 4.14 – 4.07 (m, 2H), 2.67 (dd, *J* = 17.2 Hz, *J* = 5.95 Hz, 1H), 2.48 (dd, *J* = 17.2 Hz, *J* = 7.9 Hz, 1H), 2.05 – 2.00 (m, 1H), 1.68 – 1.57 (m, 1H), 1.33 (d, *J* = 6.3 Hz, 3H), 1.06 (s, 9H).

¹³C NMR (125 MHz, CDCl₃): δ 170.1, 135.71, 135.65, 135.64, 133.4, 133.2, 130.1, 130.0, 127.9, 127.8, 73.3, 65.3, 40.0, 39.6, 26.8, 21.4, 19.0.

IR (neat): 3071, 2932, 2858, 1736, 1427, 1235, 1104 cm⁻¹.

HRMS (ESI): calculated for C₂₂H₂₈O₄, 391.1706 [M+Na]⁺, found 391.1702.

2-(Ethylthio)benzo[*d*]thiazole **3.113**



To a solution of mercaptothiazole **3.112** (11.94 g, 71.4 mmol) in DMF (250 mL) at 0 °C, was added NaH (60 % dispersion, 3.7 g, 92.5 mmol) and the reaction mixture was stirred at 0 °C for 30 min. Bromoethane (5.35 mL, 72.2 mmol) was added dropwise to the cooled reaction mixture and was stirred for a further 5 h at 0 °C. The reaction was quenched with sat. aqueous NH₄Cl solution (40 mL) and water (50 mL). The aqueous mixture was extracted with 1:1 diethyl ether:CH₂Cl₂ (2 × 250 mL), and the organic extracts were washed with brine (3 × 200 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on SiO₂ (petrol/diethyl ether, 9:1) to give 2-(ethylthio)benzo[*d*]thiazole **3.113** as a white crystalline solid (12.79 g, 92%). The spectroscopic data was consistent with that reported in the literature.^[172]

R_f = 0.73 (petrol/EtOAc, 1:1)

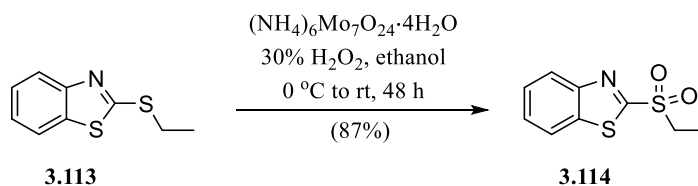
¹H NMR (500 MHz, CDCl₃): δ 7.87 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.41 (dd, *J* = 8.1 Hz, *J* = 7.35 Hz, 1H), 7.29 (dd, *J* = 8.0 Hz, *J* = 7.35 Hz, 1H), 3.36 (q, *J* = 7.4 Hz, 2H), 1.49 (d, *J* = 7.4 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 167.0, 153.4, 135.2, 126.0, 124.1, 121.5, 120.9, 28.0, 14.6.

IR (neat): 3062, 2969, 2927, 1456, 1426, 992, 773 cm⁻¹.

HRMS (ESI): calculated for C₉H₉NS₂, 196.0256 [M+H]⁺, found 196.0251

2-(Ethylsulfonyl)benzo[*d*]thiazole **3.114**



To a solution of $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$ (16.07 g, 13.0 mmol) in 30% H_2O_2 (221 mL, 2.2 mol) at 0 °C, was added a solution of 2-(ethylthio)benzo[*d*]thiazole **3.113** (12.7 g, 65.0 mmol) in ethanol (75 mL). The resulting reaction mixture was warmed to room temperature and stirred for 48 h, before being quenched with aqueous H_2SO_4 (10%, 10 mL). The organic solvent was removed under reduced pressure and the aqueous mixture was extracted with 1:1 diethyl ether: CH_2Cl_2 (2×250 mL) and the organic extracts were washed with brine (200 mL), dried over MgSO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on SiO_2 (CH_2Cl_2 /petrol, 4:1) to give 2-(ethylsulfonyl)benzo[*d*]thiazole **3.114** as a white crystalline solid (12.79 g, 87%). The spectroscopic data was consistent with that reported in the literature.^[172]

$R_f = 0.1$ (CH_2Cl_2 /petrol, 1:1)

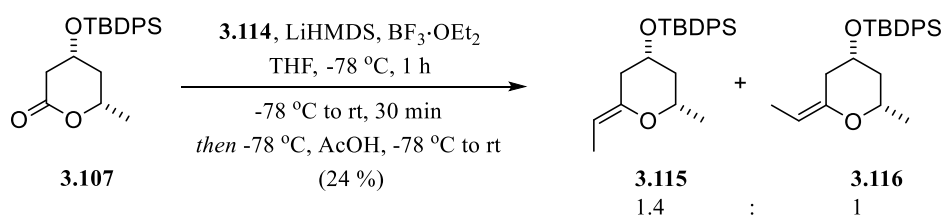
$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 8.23 (d, $J = 8.1$ Hz, 1H), 8.02 (d, $J = 8.1$ Hz, 1H), 7.66 – 7.59 (m, 2H), 3.55 (q, $J = 7.45$ Hz, 2H), 1.45 (t, $J = 7.45$ Hz, 3H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 165.4, 152.8, 136.8, 128.0, 127.7, 125.5, 122.3, 49.3, 7.2

IR (neat): 3065, 2923, 1799, 1554, 1471, 1310, 1140 cm^{-1} .

HRMS (ESI): calculated for $\text{C}_9\text{H}_9\text{NO}_2\text{S}_2$, 249.9965 $[\text{M}+\text{Na}]^+$, found 249.9966.

Z/E-Exocyclic enol ethers 3.115:3.116



To a solution of TBDPS lactone **3.107** (140 mg, 0.380 mmol) and 2-(ethylsulfonyl)benzo[*d*]thiazole **3.114** (74 mg, 0.326 mmol) in THF (5 mL) at -78 °C, was added BF₃·OEt₂ (0.06 ml, 0.5 mmol) followed by LiHMDS (1 M, 0.5 ml, 0.5 mmol) and the reaction mixture was stirred at -78 °C for 1 h. The reaction mixture warmed to room temperature and stirred for a further 30 min. The reaction mixture was again cooled to -78 °C and quenched with AcOH (0.1 ml), followed by warming to room temperature. The mixture was concentrated *in vacuo* and the resultant residue was taken up in THF (5 ml), and DBU (0.2 ml, 1.34 mmol) was added to the reaction mixture in one portion, followed by stirring at room temperature overnight. The solvent was removed under reduced pressure and the resulting residue was purified by flash column chromatography on SiO₂ (petrol/EtOAc, 10:1) to give *Z*-exocyclic enol ether **3.115** as a colourless oil (34.5 mg, 24%), which was found to be a mixture of *Z*/*E* isomers **3.115**:**3.116** in a 1.4:1 ratio respectively.

R_f = 0.8 (petrol/EtOAc, 2:1)

¹H NMR data for *Z*-exocyclic enol ether **3.115**

¹H NMR (500 MHz, CDCl₃): δ 7.71 – 7.66 (m, 4H), 7.44 – 7.37 (m, 6H), 4.38 (qd, *J* = 6.7 Hz, *J* = 1.5 Hz, 1H), 3.78 – 3.70 (m, 1H), 3.37 – 3.31 (m, 1H), 2.25 (ddd, *J* = 12.8 Hz, *J* = 5 Hz, *J* = 1.9 Hz, 1H), 2.13 – 2.08 (m, 1H), 1.89 – 1.80 (m, 1H), 1.53 – 1.46 (m, 1H), 1.49 (dd, *J* = 6.7 Hz, *J* = 2.1 Hz, 3H), 1.24 (d, *J* = 6.2 Hz, 3H), 1.06 (s, 9H).

¹H NMR data for *E*-exocyclic enol ether **3.116**

¹H NMR (500 MHz, CDCl₃): δ 7.71 – 7.66 (m, 4H), 7.44 – 7.37 (m, 6H), 4.41 – 4.37 (qd, *J* = 7.0 Hz, *J* = 1.6 Hz, 1H), 3.78 – 3.70 (m, 1H), 3.37 – 3.31 (m, 1H), 2.53 (ddd, *J* = 13.3 Hz, *J* = 4.8 Hz, *J* = 1.8 Hz, 1H), 1.89 – 1.80 (m, 2H), 1.53 – 1.46 (m, 1H), 1.29 (dd, *J* = 7.1 Hz, *J* = 1.1 Hz, 3H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.08 (s, 9H).

¹³C NMR for *Z*/*E*-exocyclic enol ethers **3.115**:**3.116**

¹³C NMR (125 MHz, CDCl₃): δ 150.6, 150.2, 135.76, 135.72, 135.70, 134.32, 134.28, 134.2, 129.71, 129.65, 129.64, 129.62, 127.63, 127.59, 127.574, 127.566, 127.53, 127.50,

103.95, 103.90, 73.1, 72.6, 69.1, 68.7, 43.1, 42.9, 39.9, 34.0, 26.97, 26.93, 26.91, 21.7, 21.6, 19.1, 10.9, 9.7.

IR (neat): 3071, 2932, 2858, 1685, 1590, 1428, 1104 cm^{-1} .

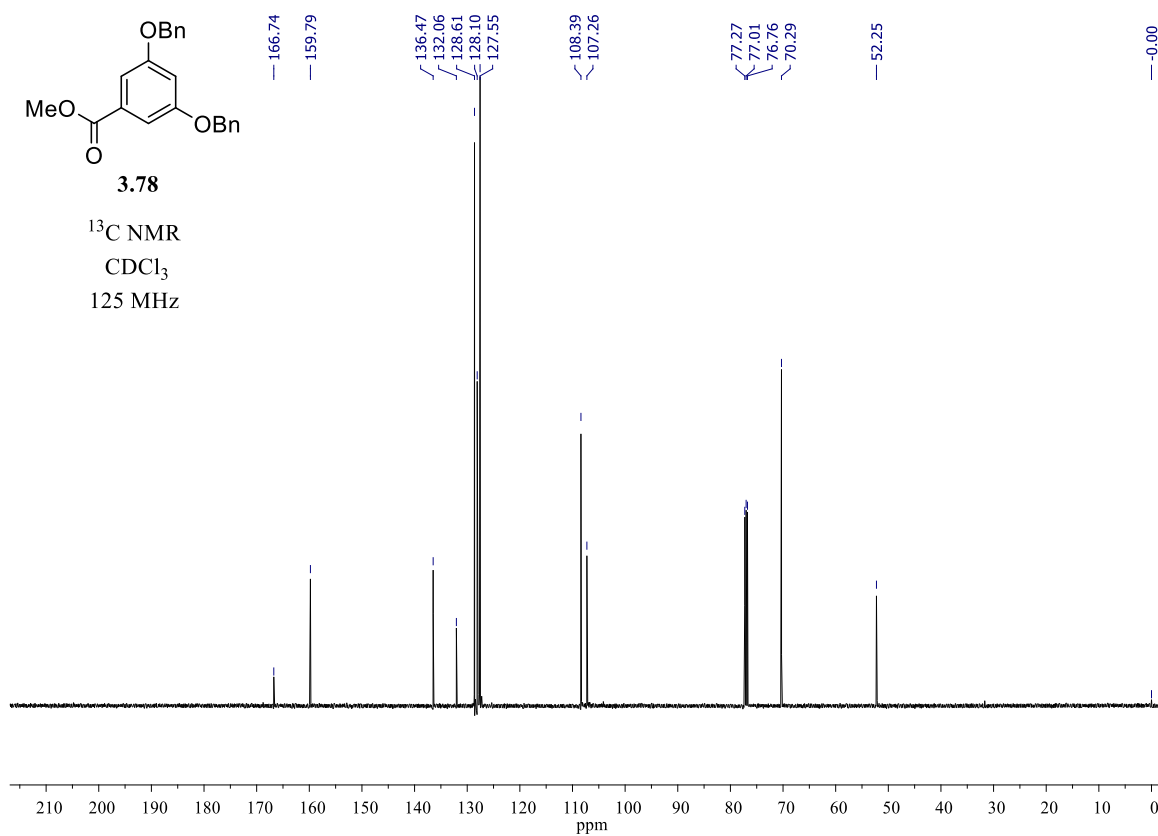
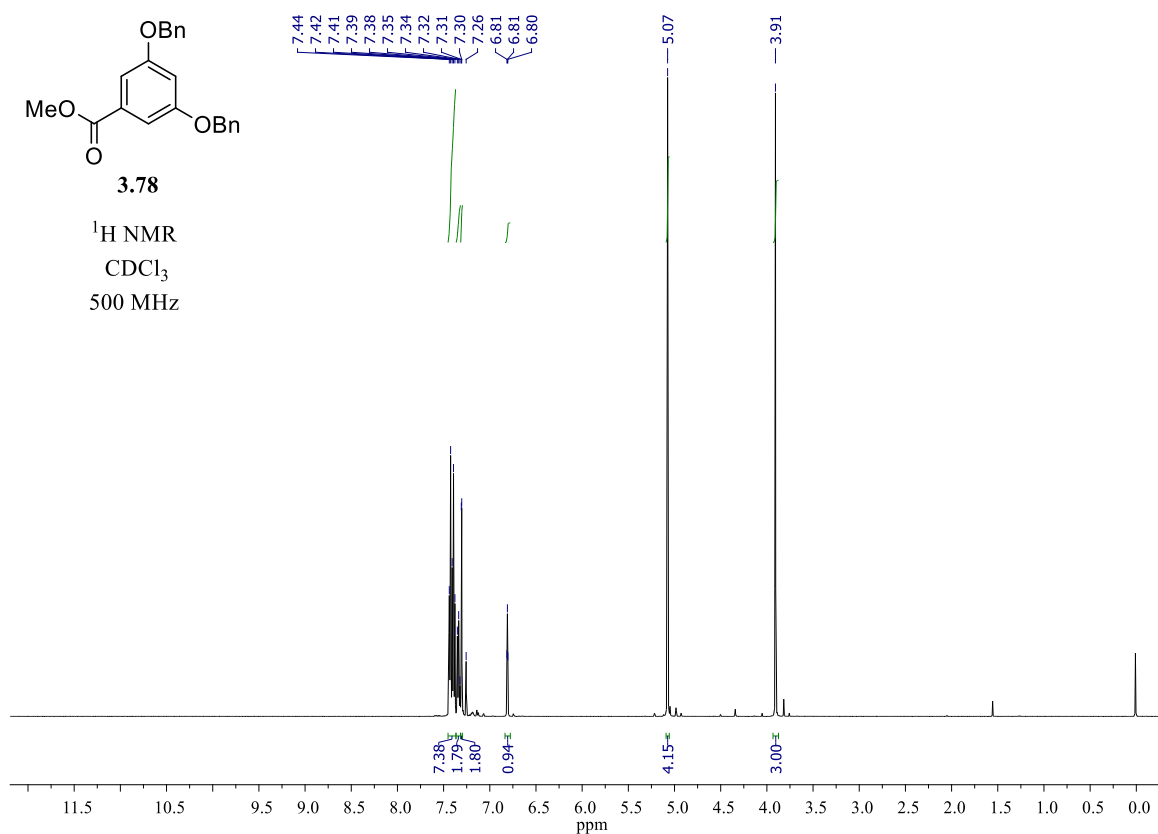
HRMS (ESI): calculated for $\text{C}_{24}\text{H}_{32}\text{O}_2\text{Si}$, 381.2244 $[\text{M}+\text{H}]^+$, found 381.2248.

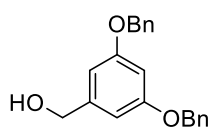
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3.7 NMR Spectra



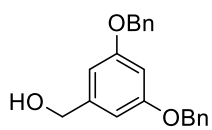
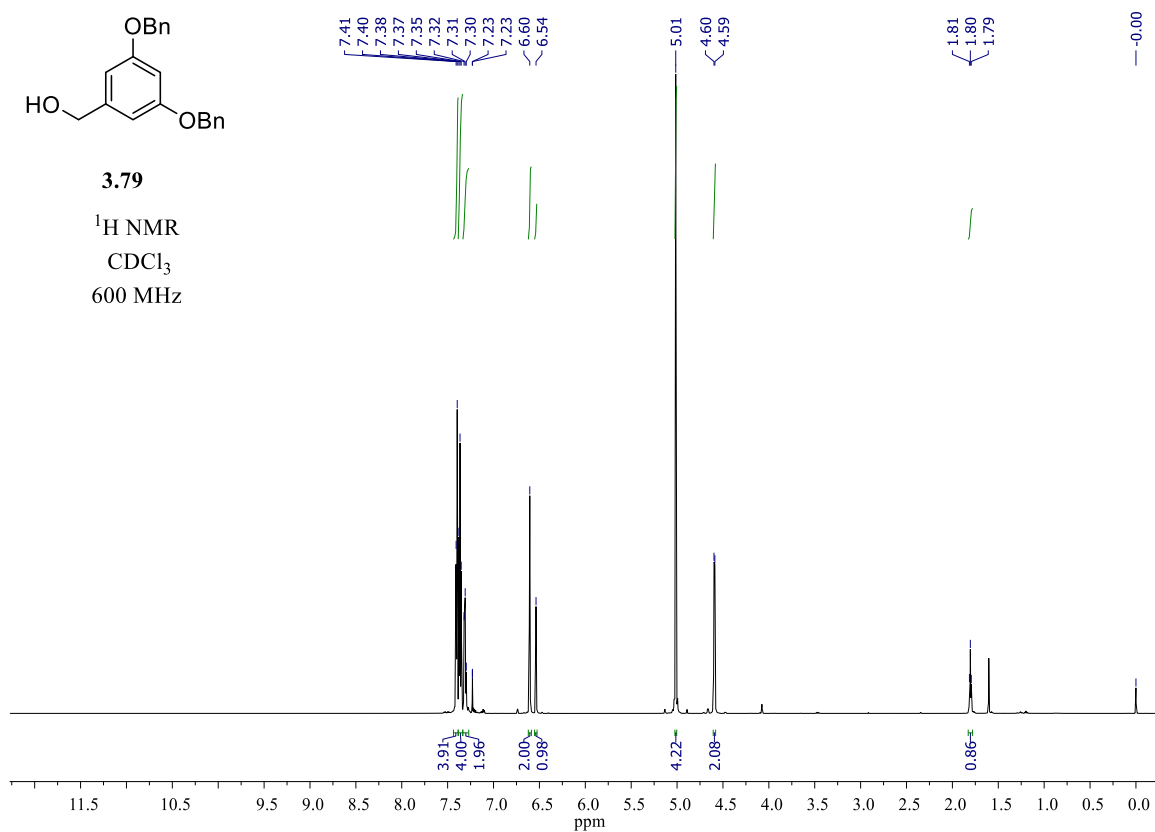


3.79

¹H NMR

CDCl₃

600 MHz

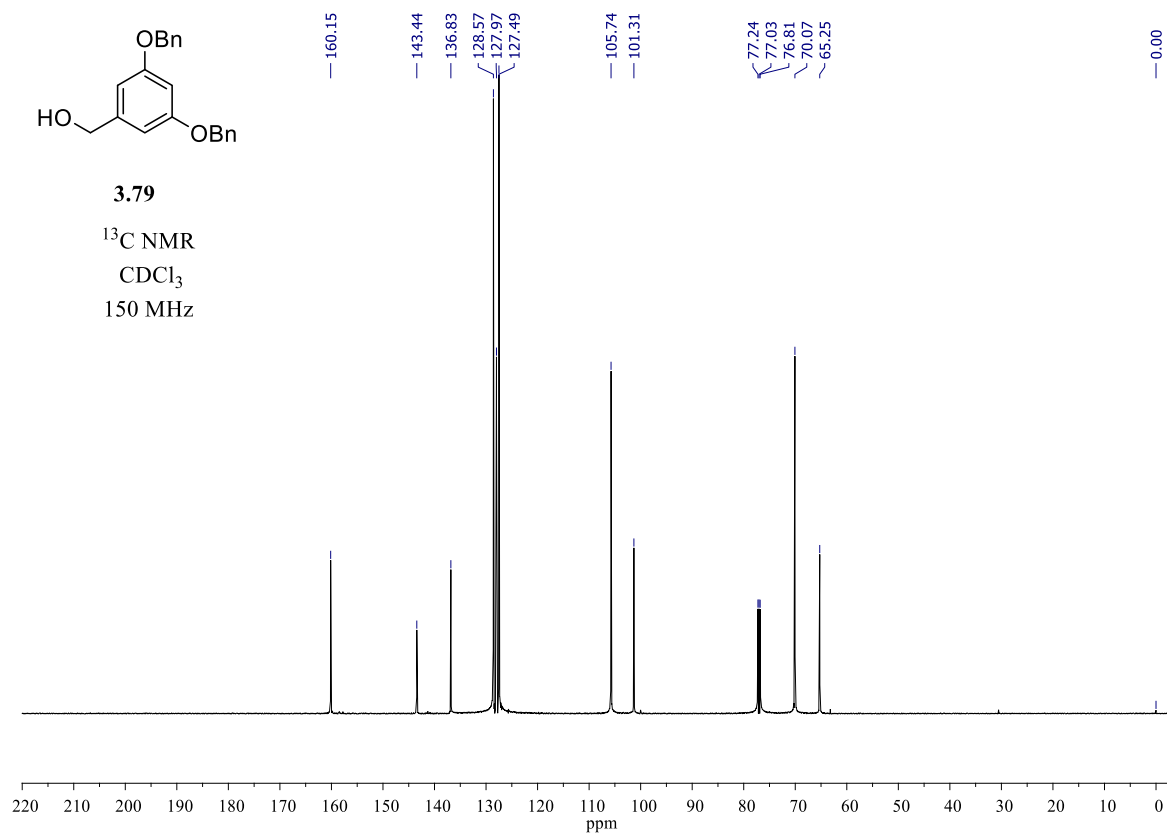


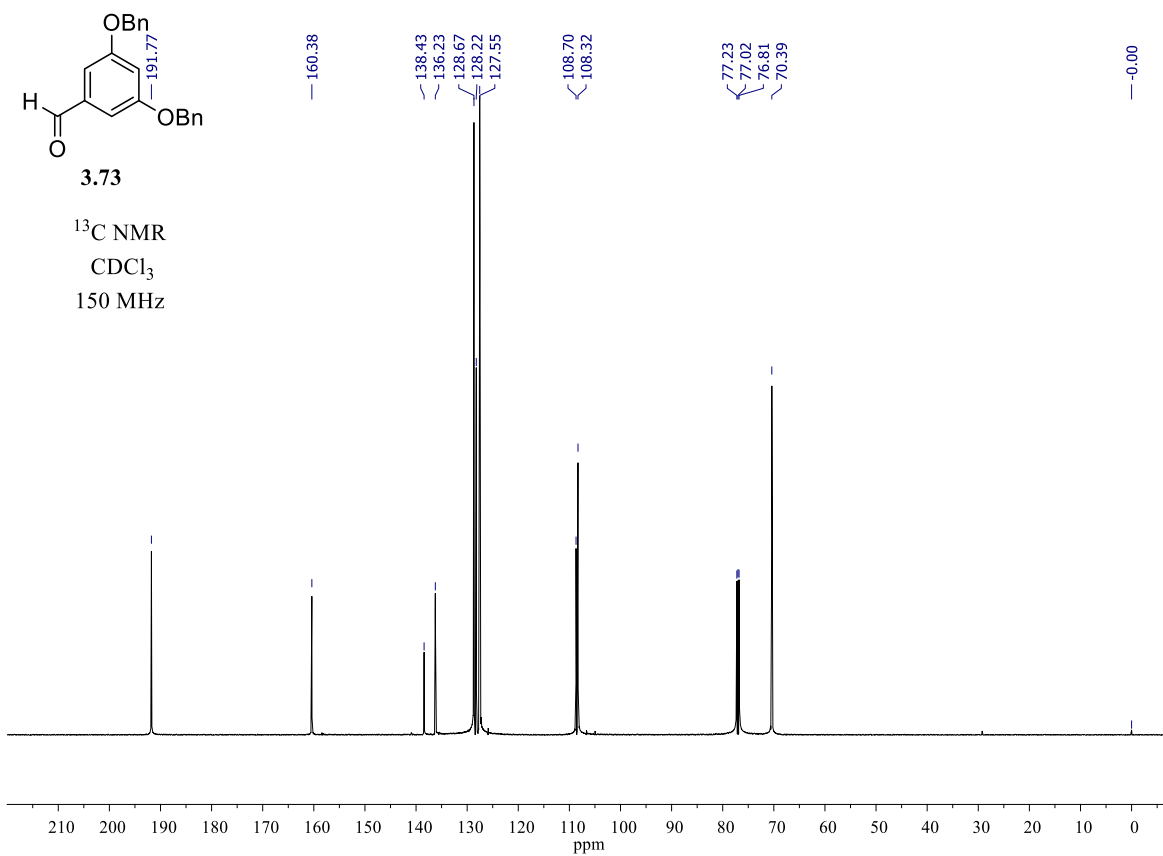
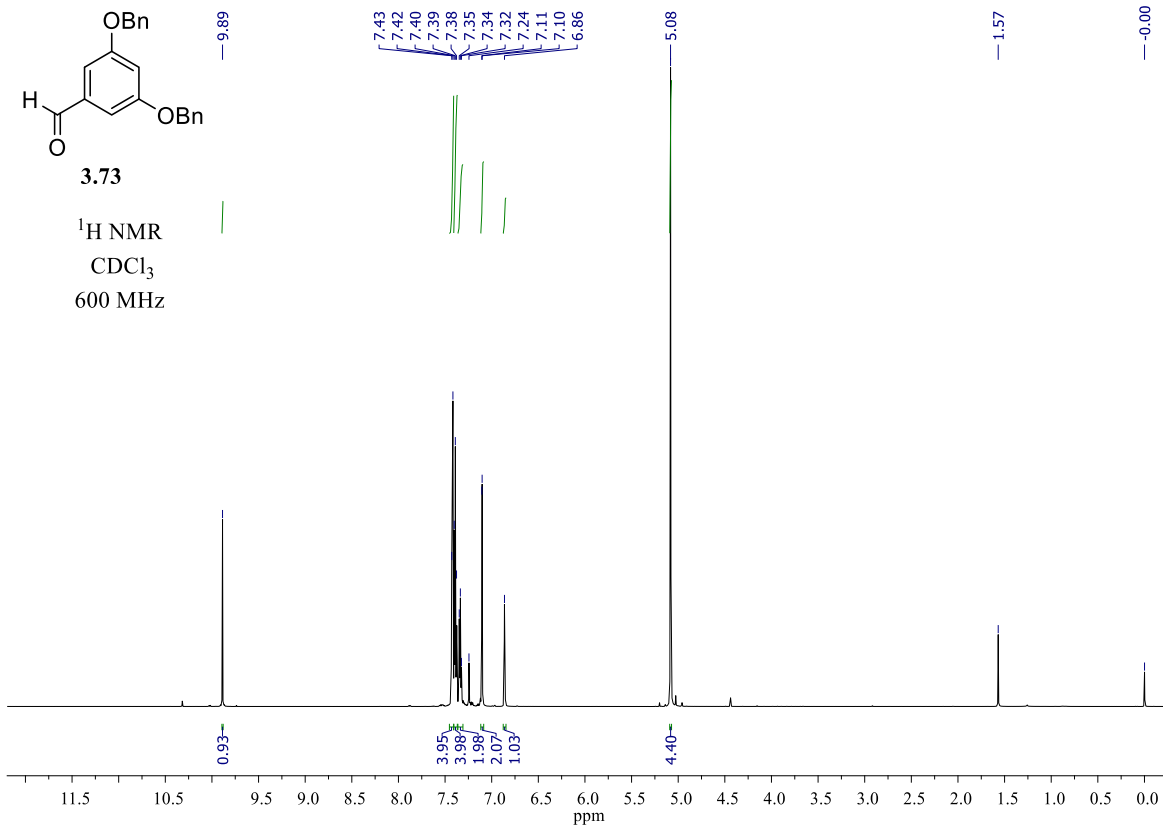
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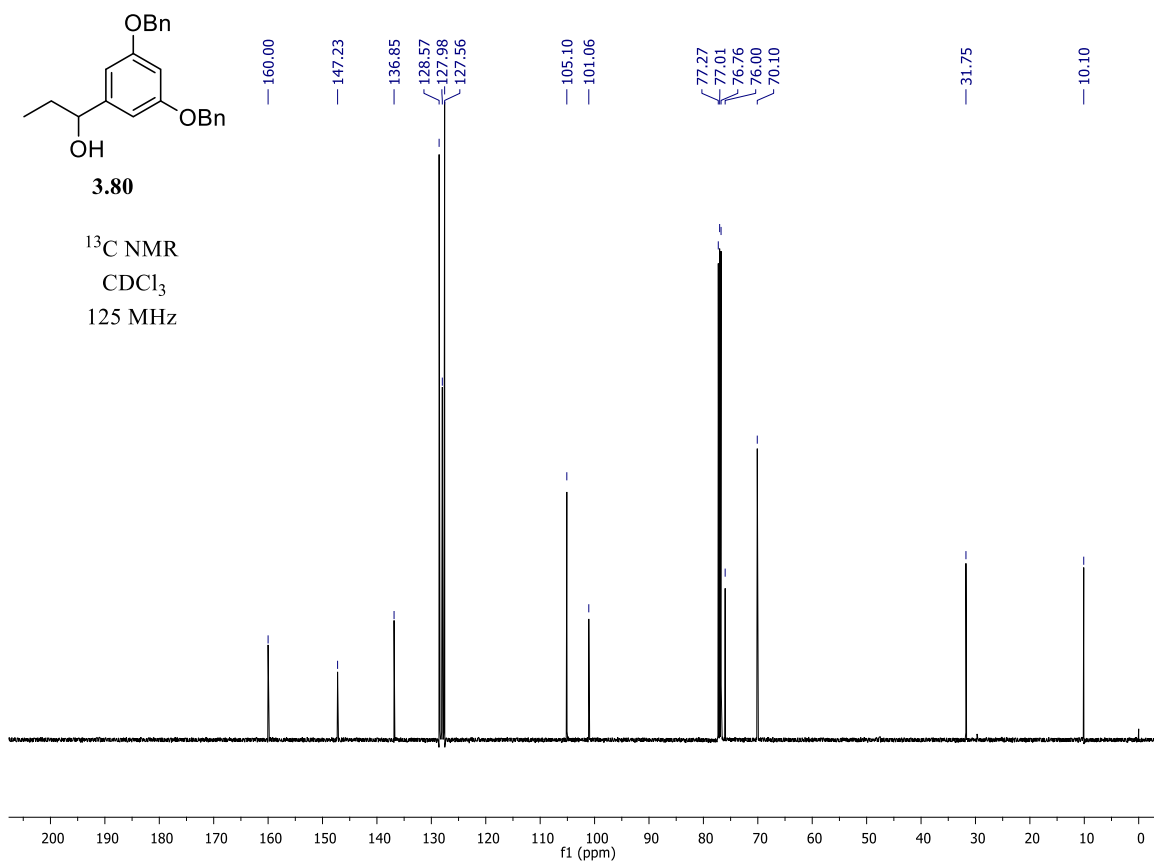
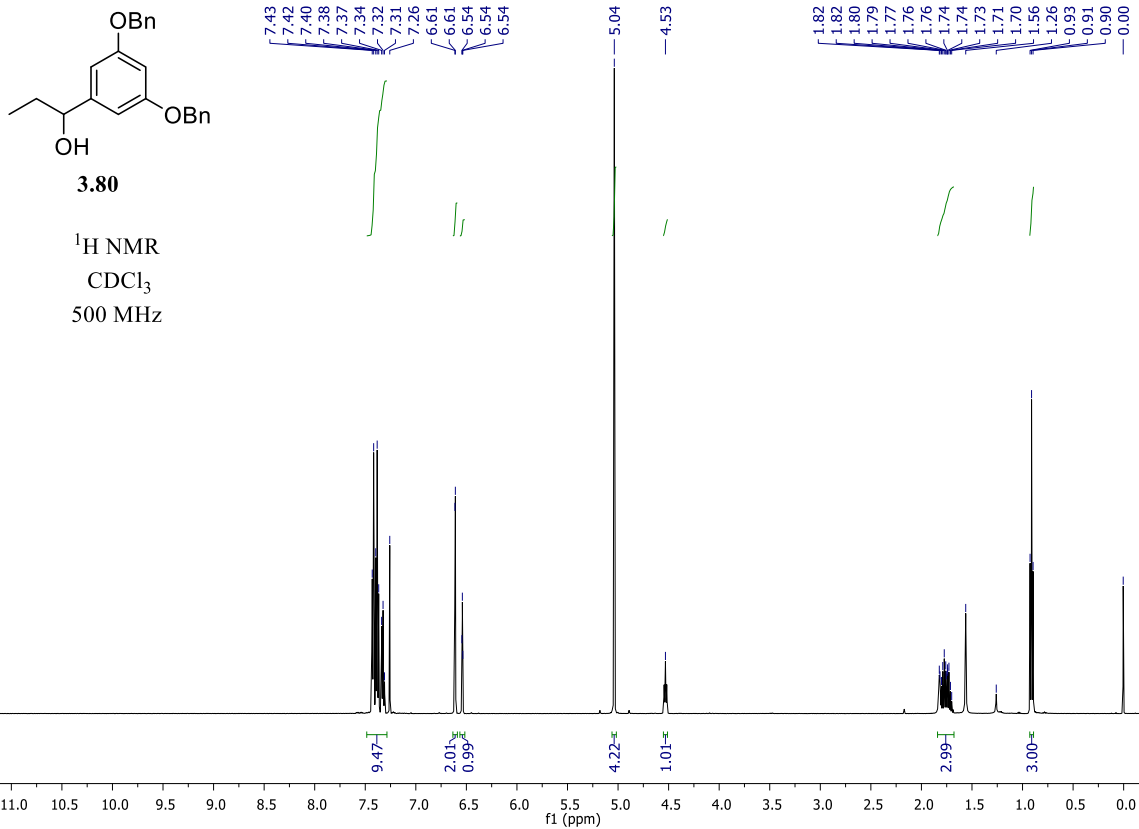
¹³C NMR

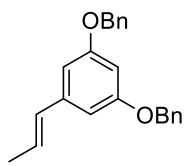
CDCl₃

150 MHz



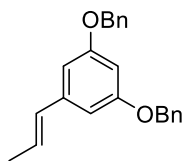
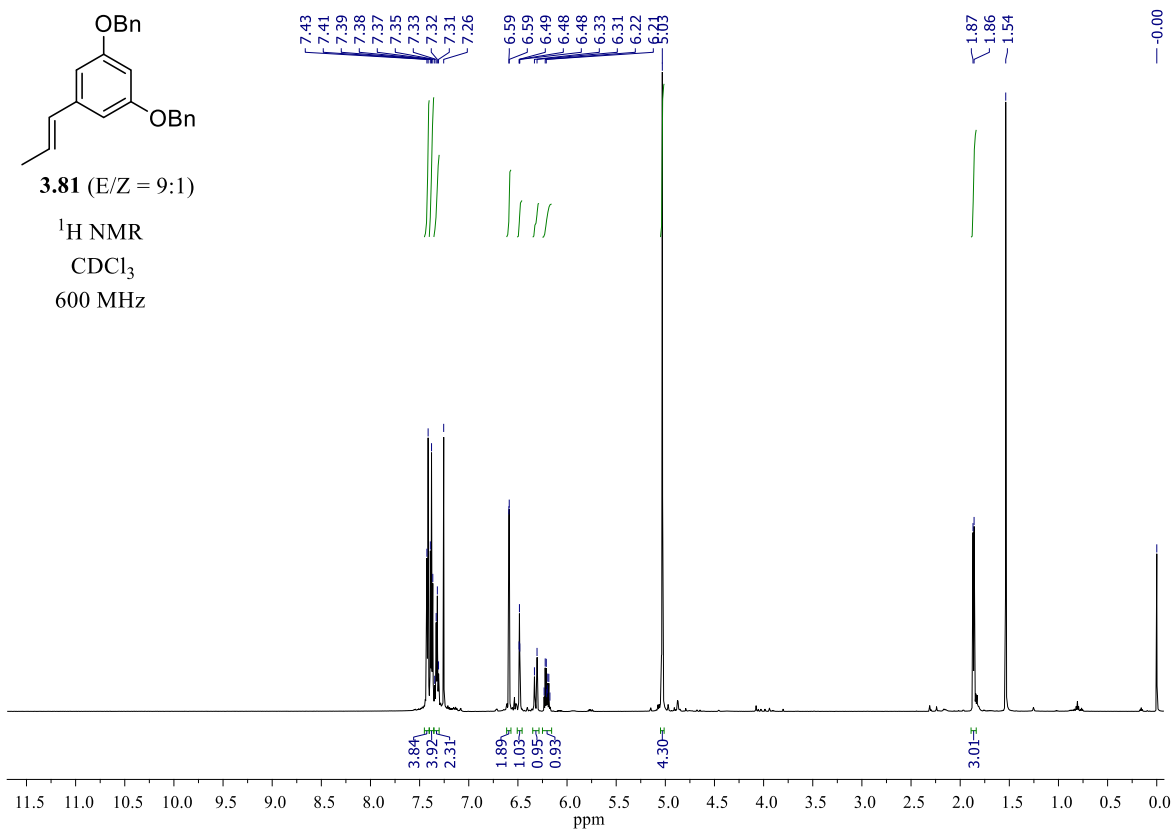






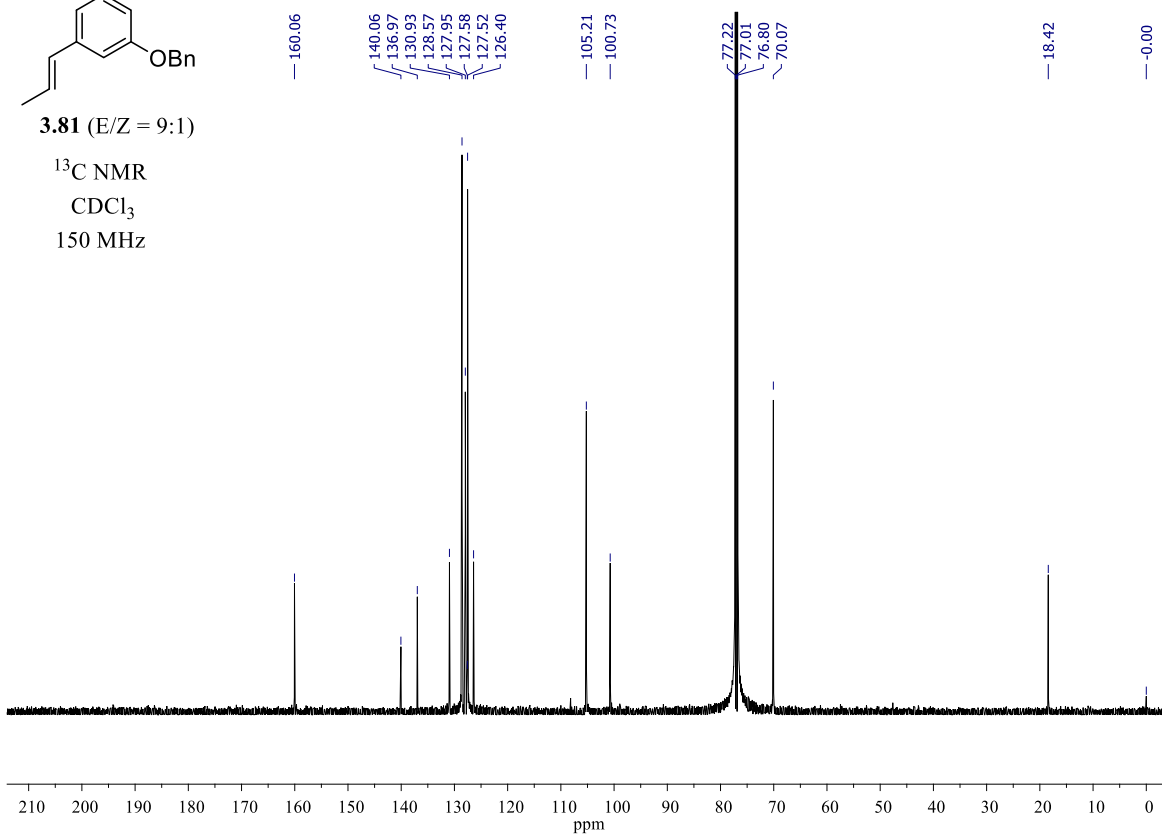
3.81 (E/Z = 9:1)

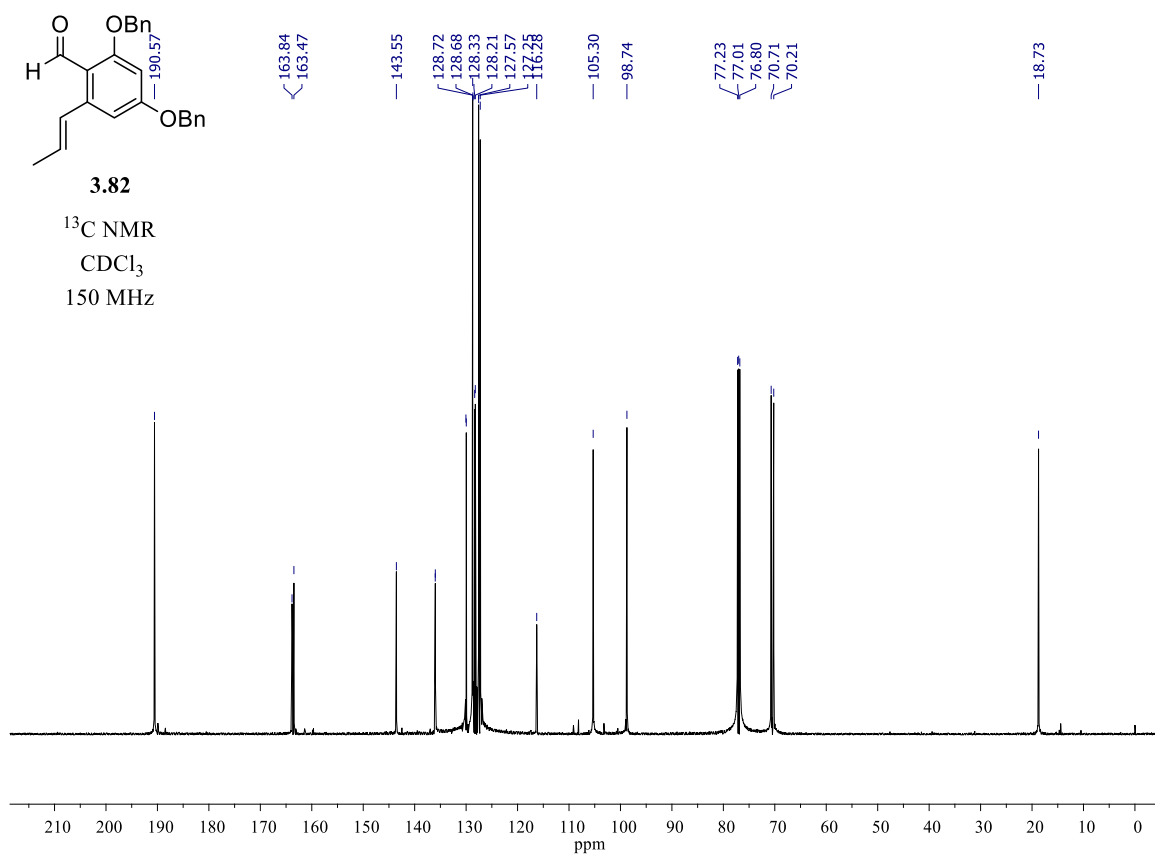
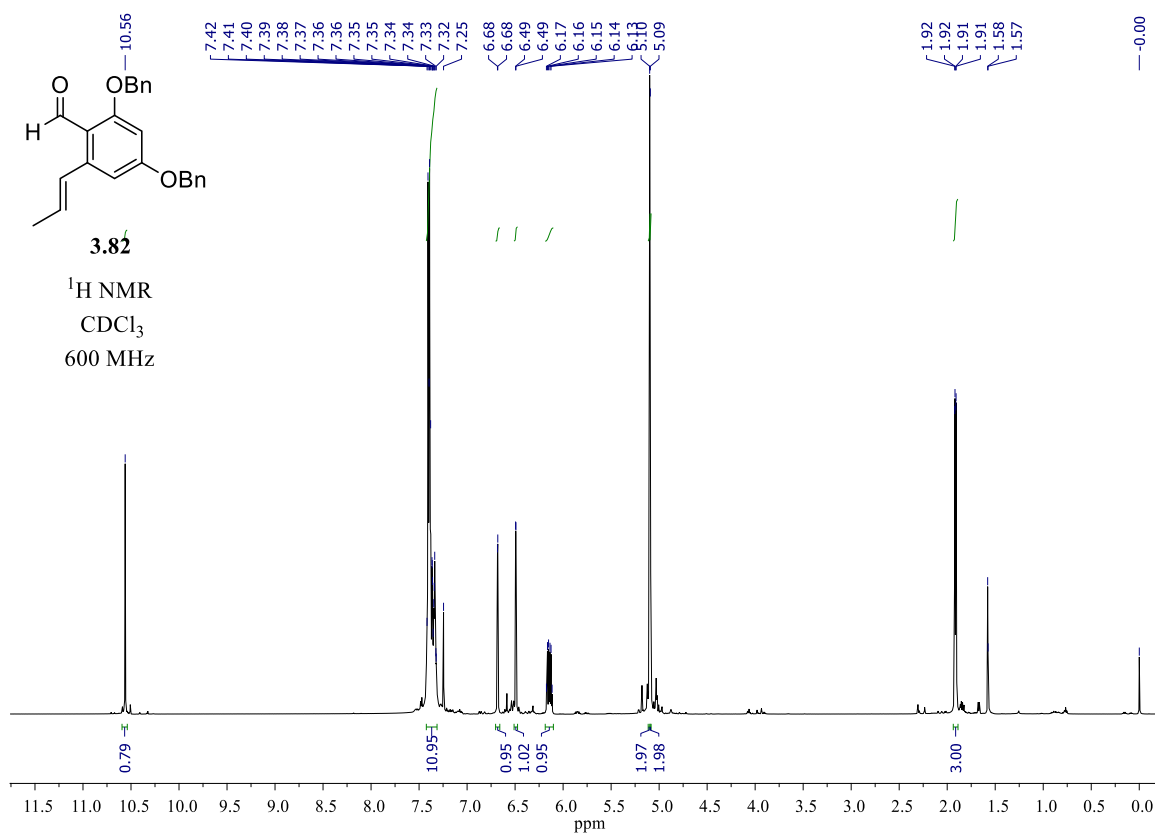
$^1\text{H NMR}$
 CDCl_3
 600 MHz

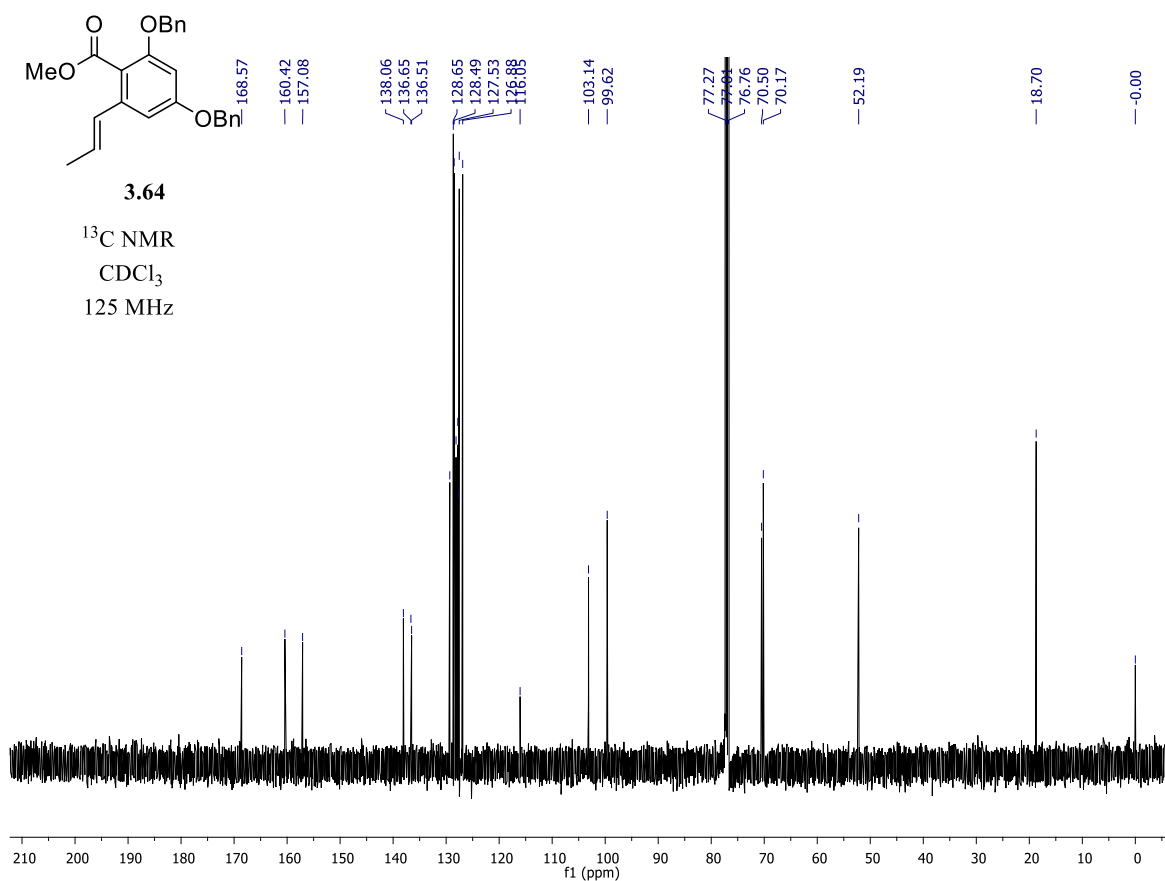
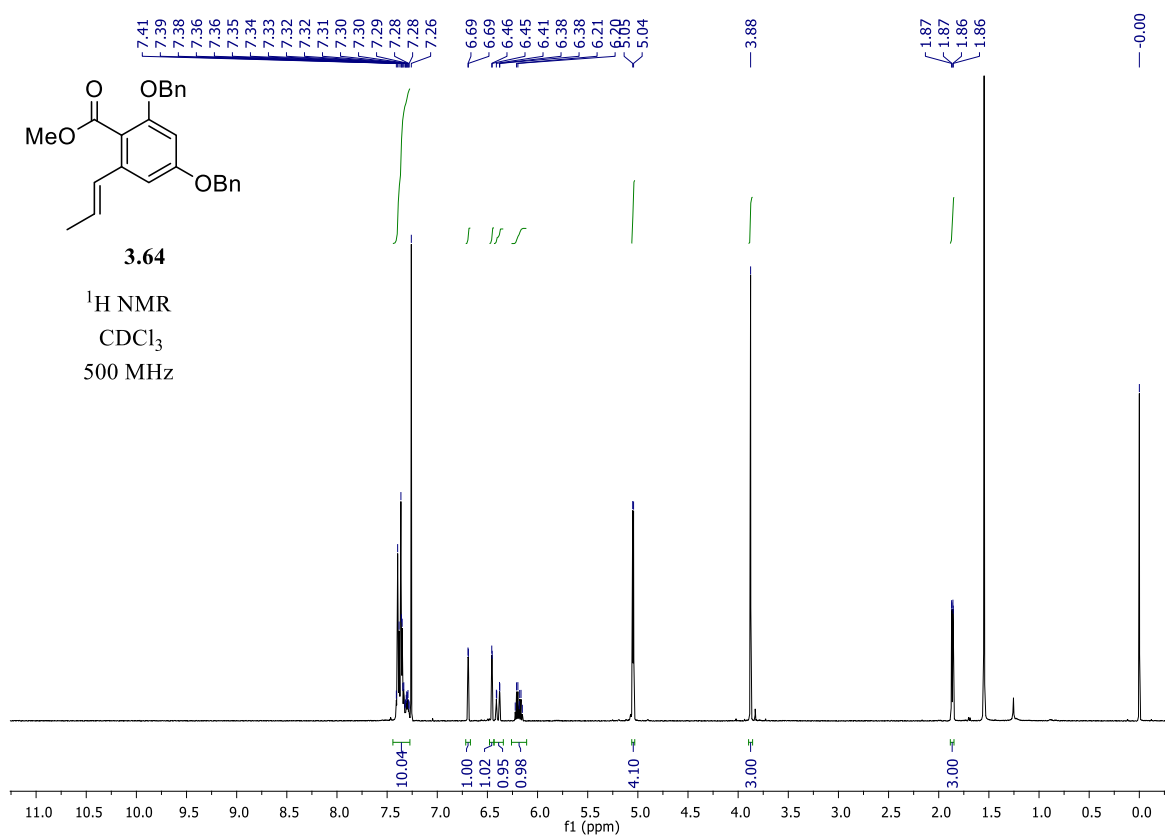


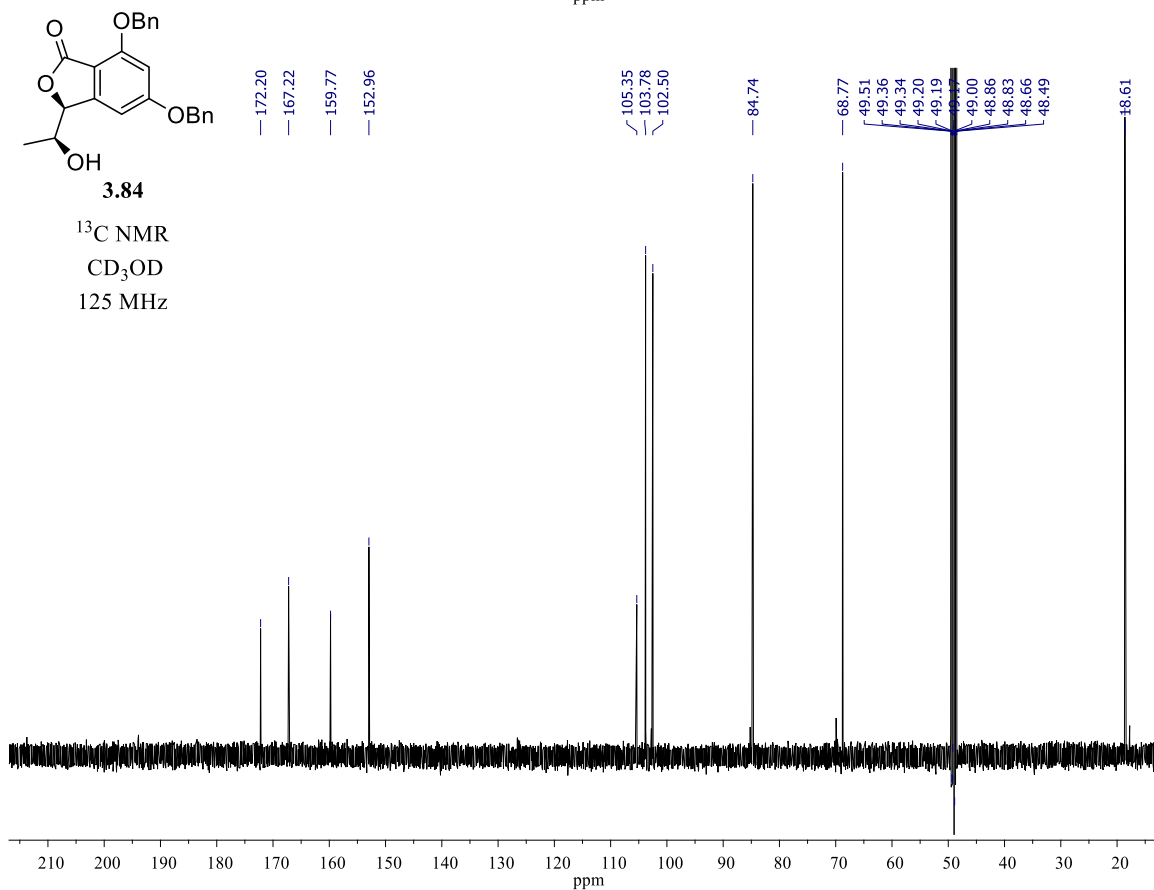
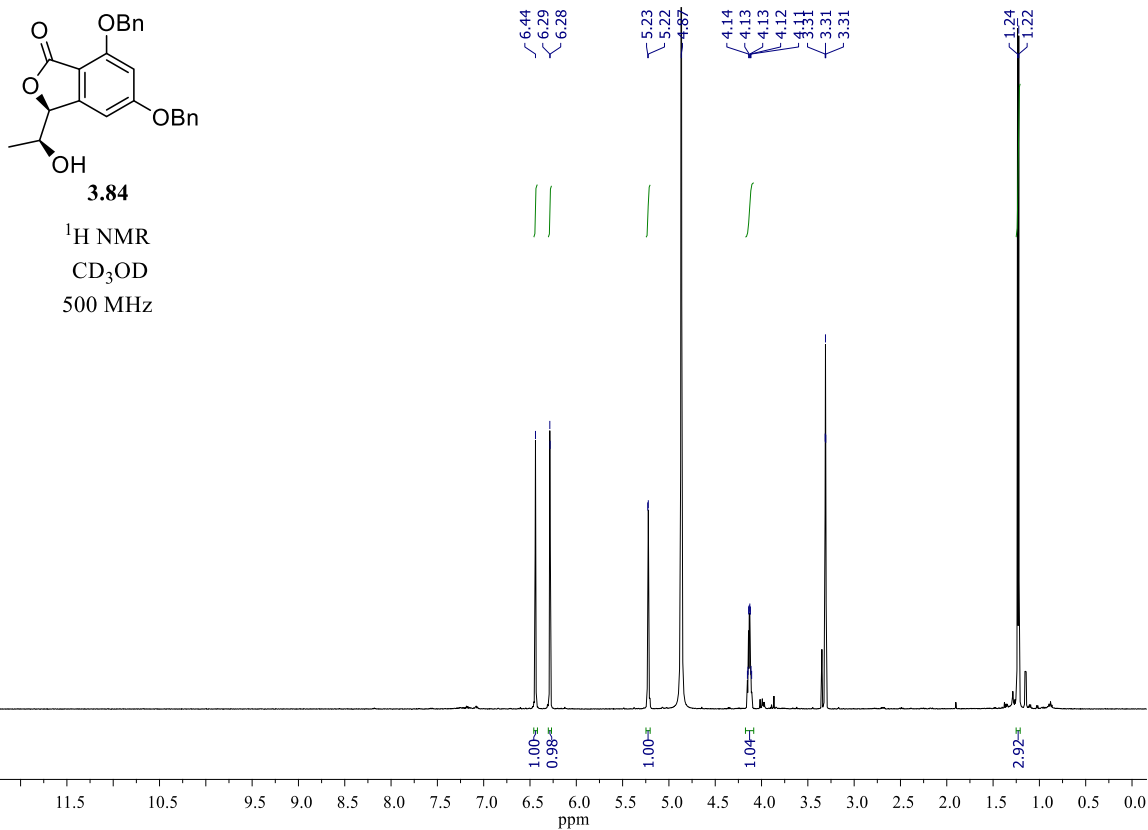
3.81 (E/Z = 9:1)

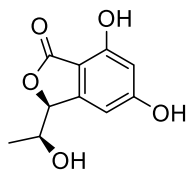
$^{13}\text{C NMR}$
 CDCl_3
 150 MHz





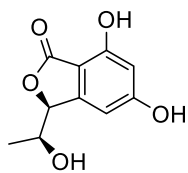
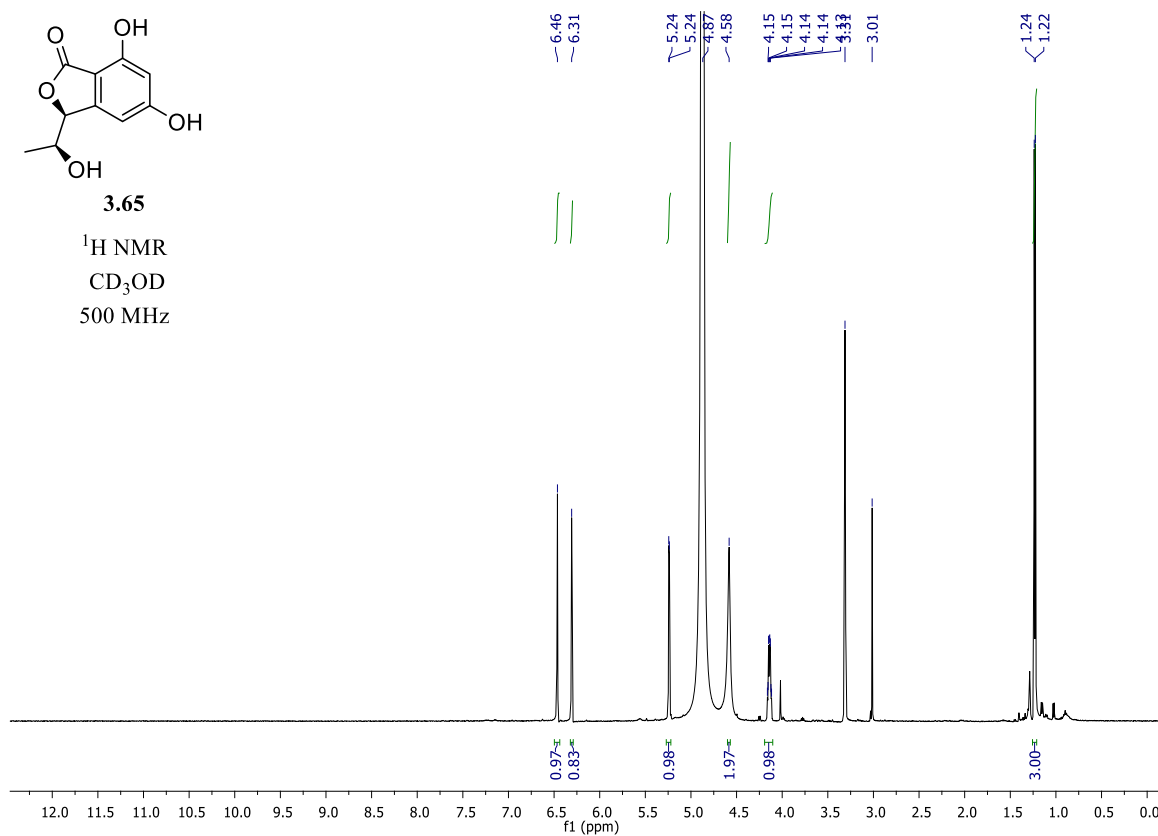






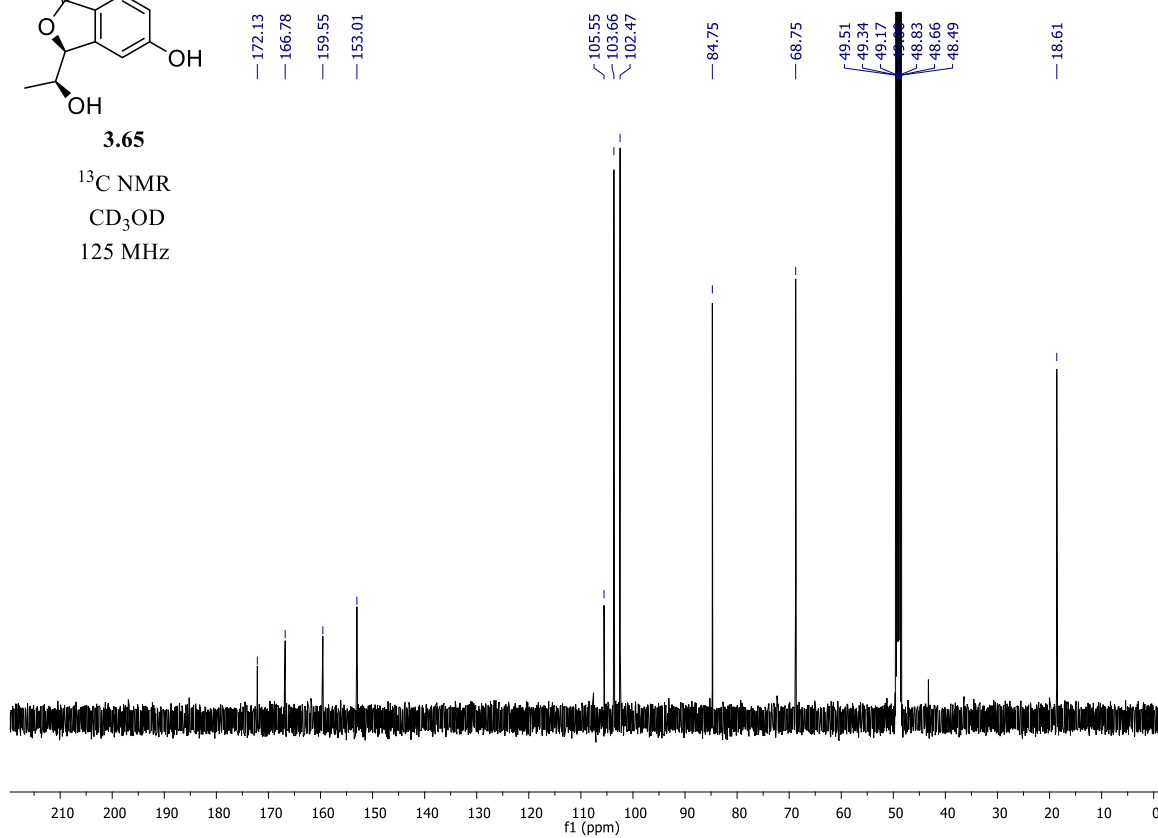
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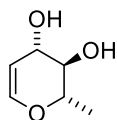
¹H NMR
CD₃OD
500 MHz



3.65

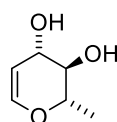
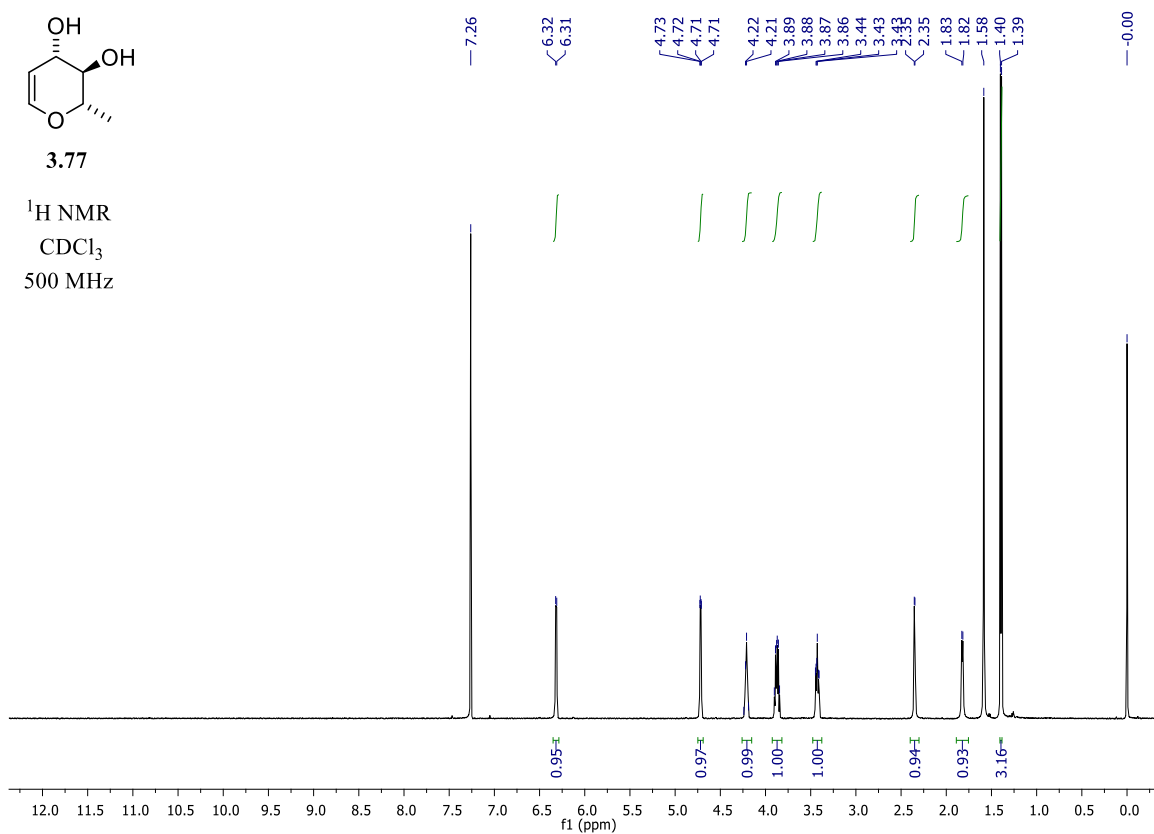
¹³C NMR
CD₃OD
125 MHz





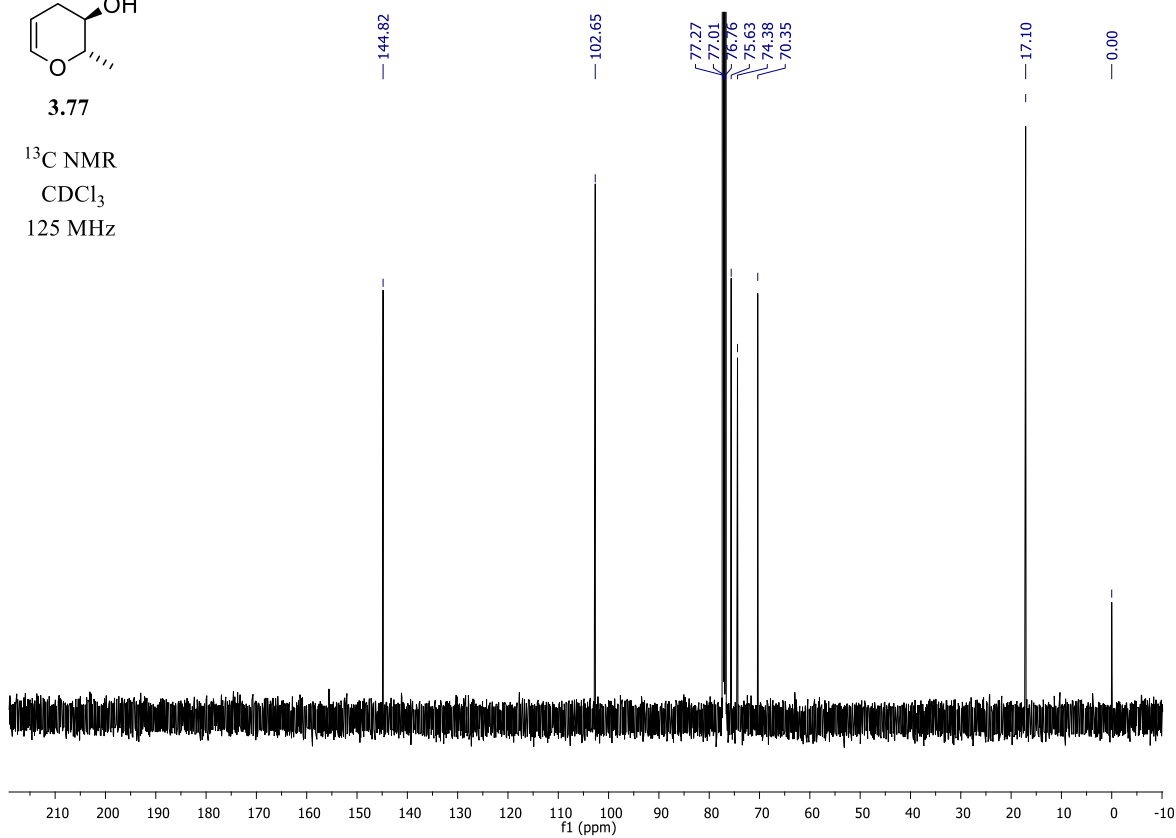
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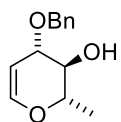
¹H NMR
CDCl₃
500 MHz



3.77

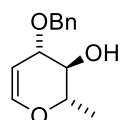
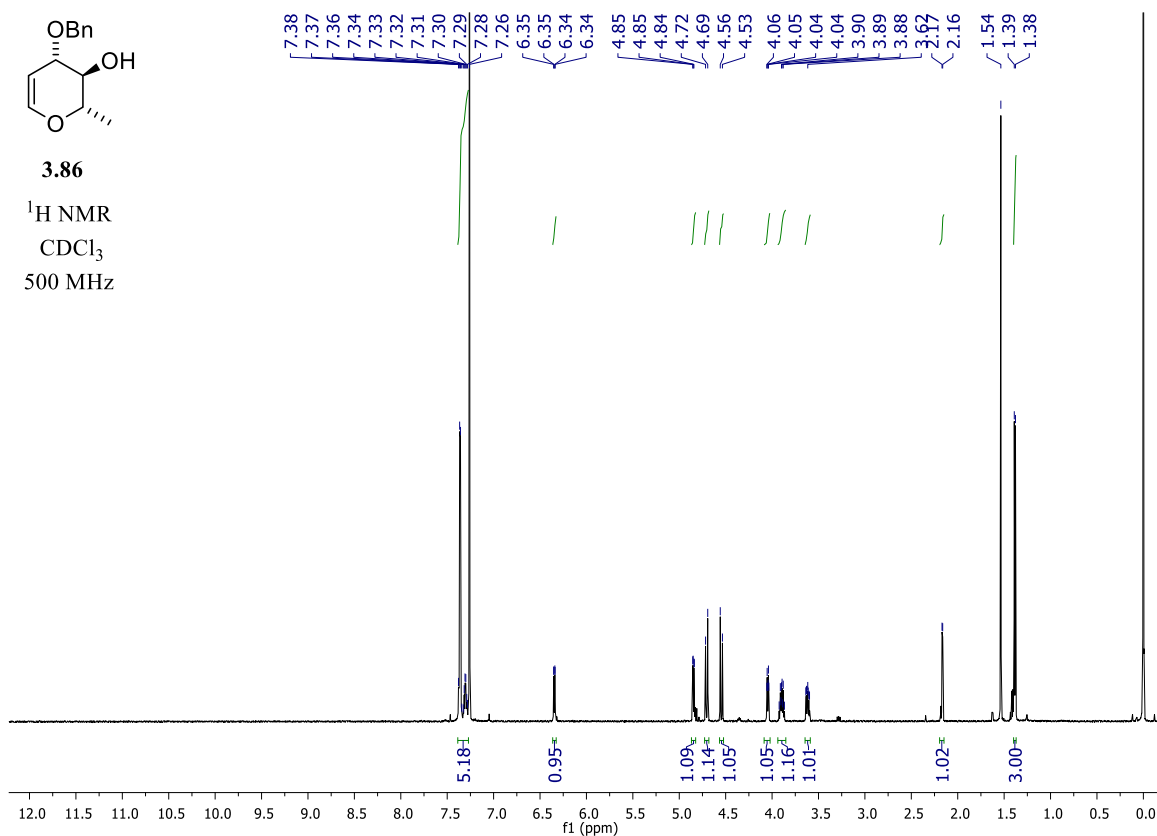
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CDCl₃
125 MHz





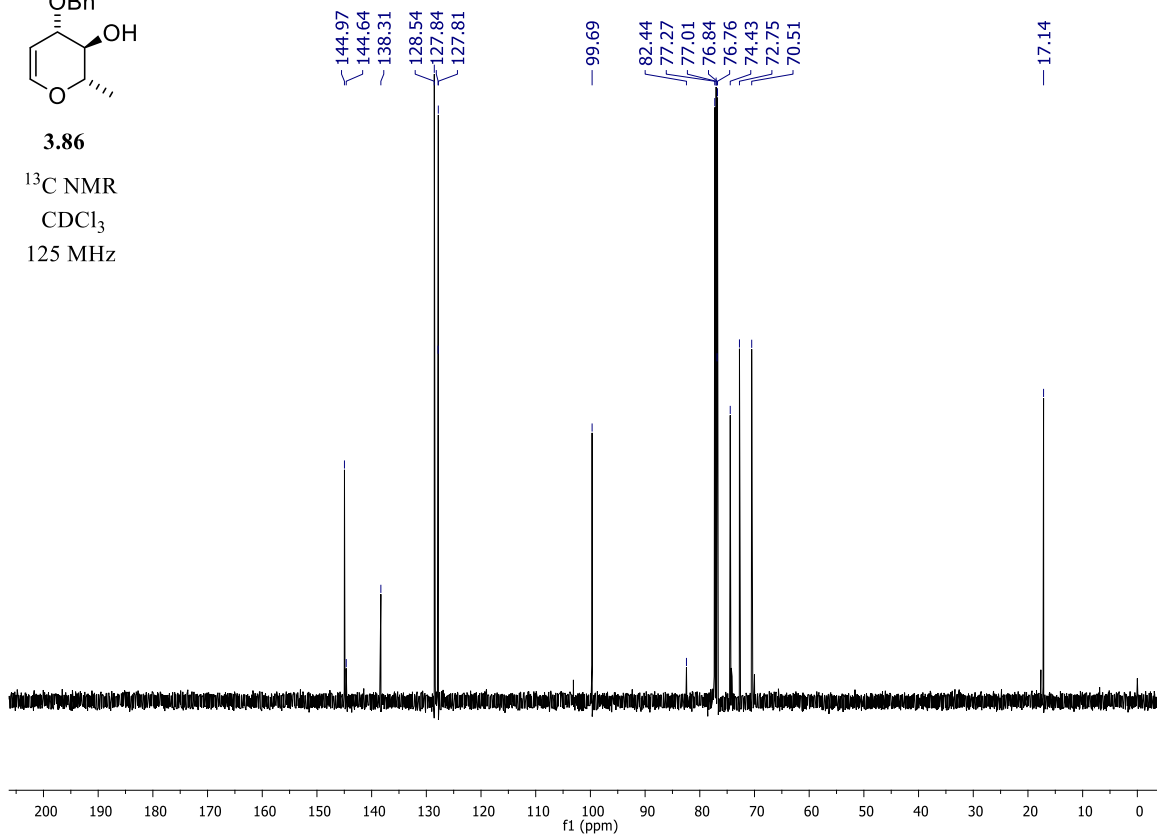
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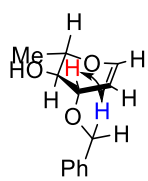
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CDCl₃
500 MHz



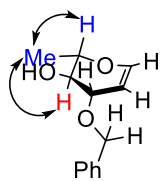
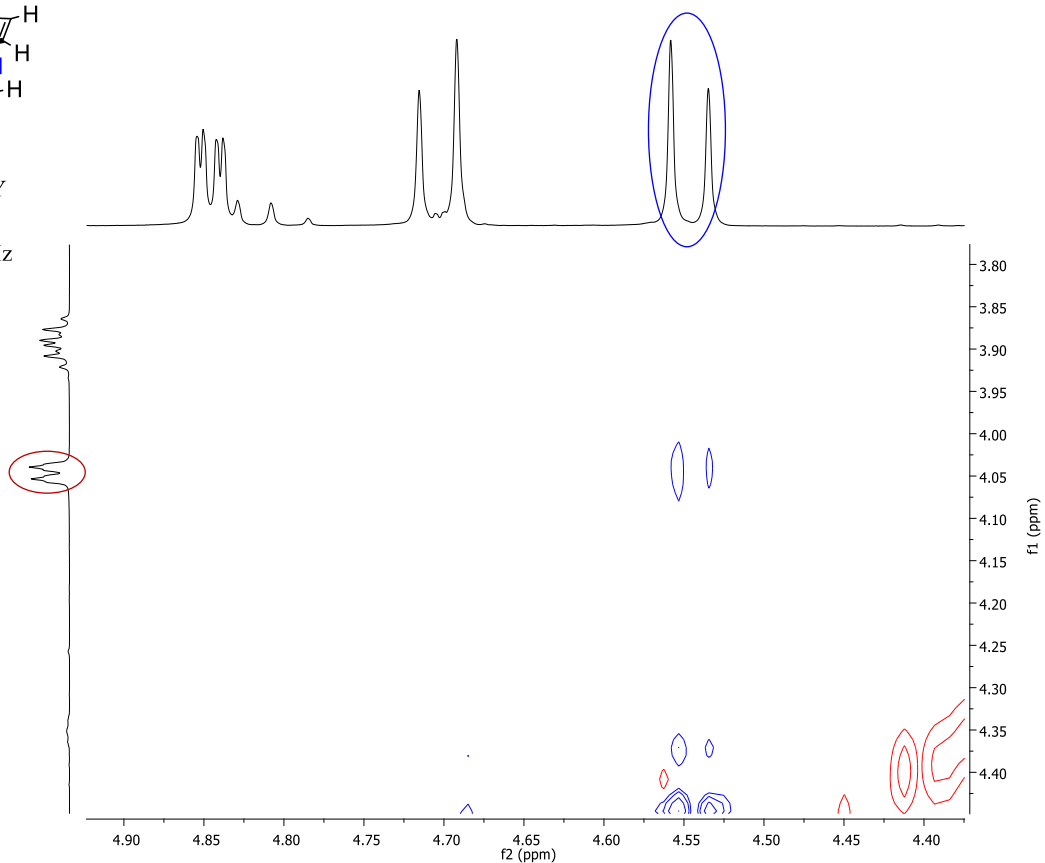
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¹³C NMR
CDCl₃
125 MHz

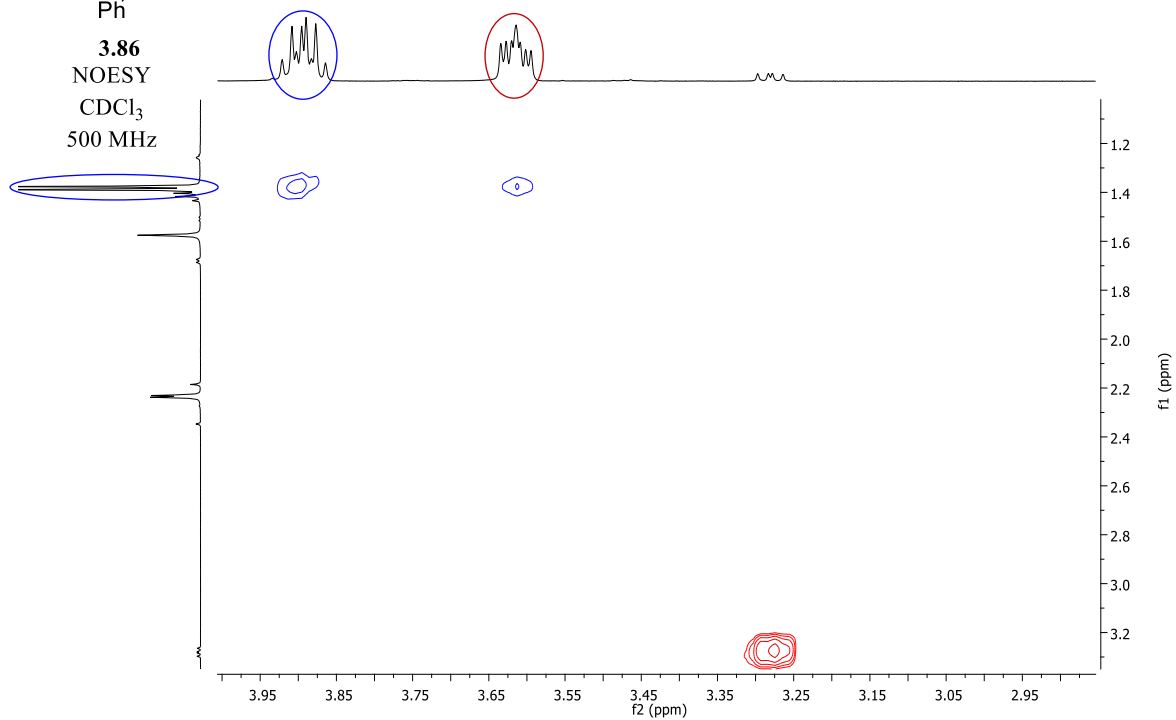


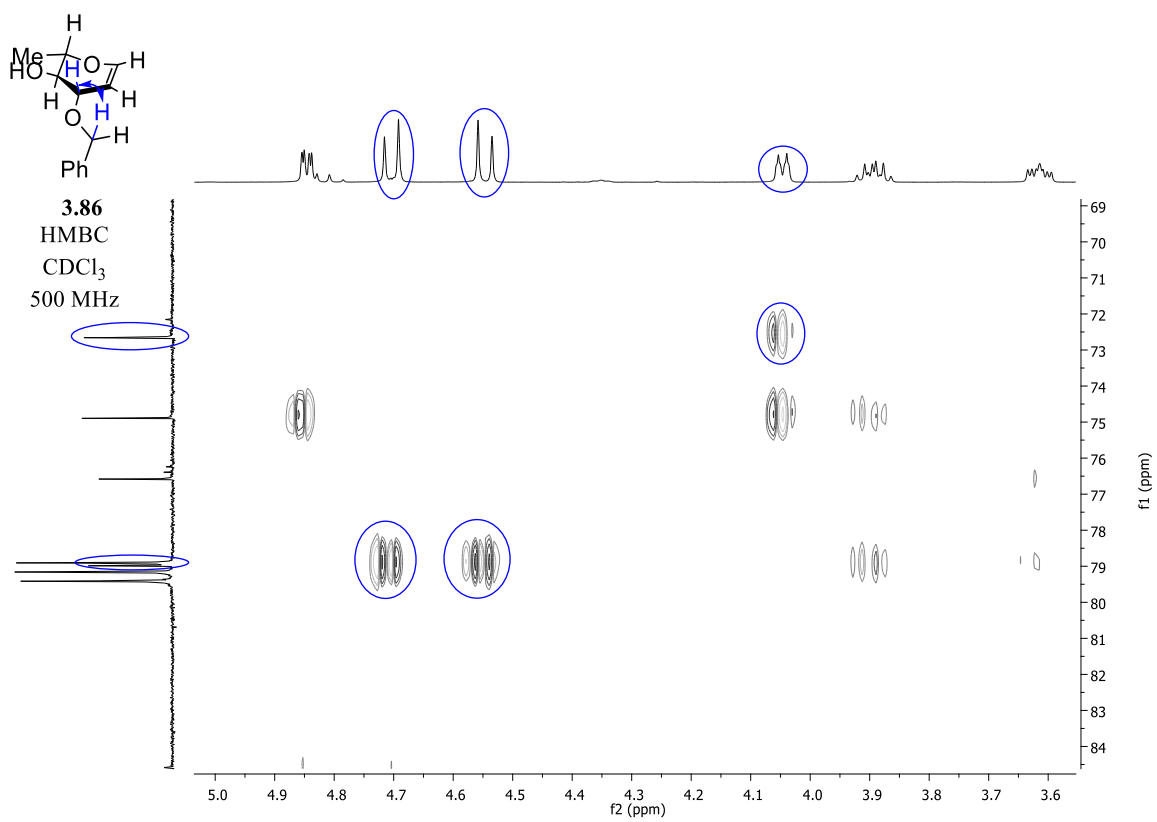
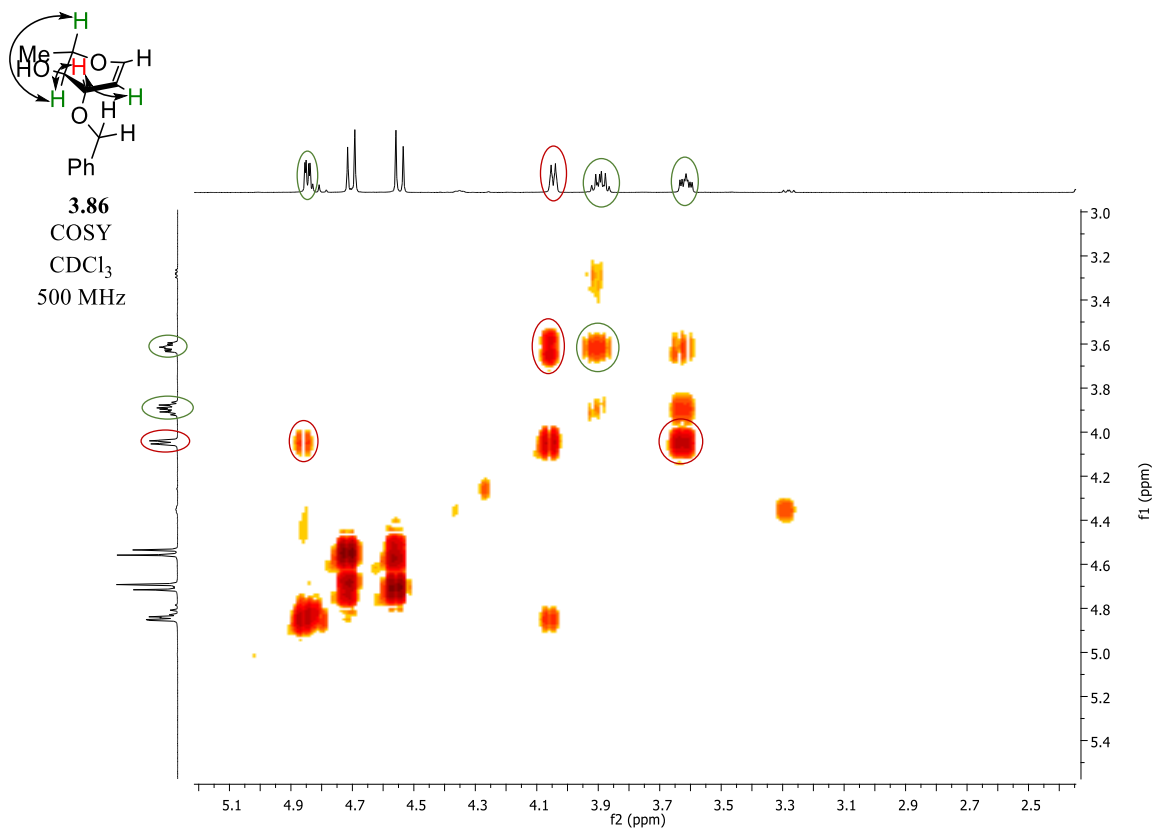


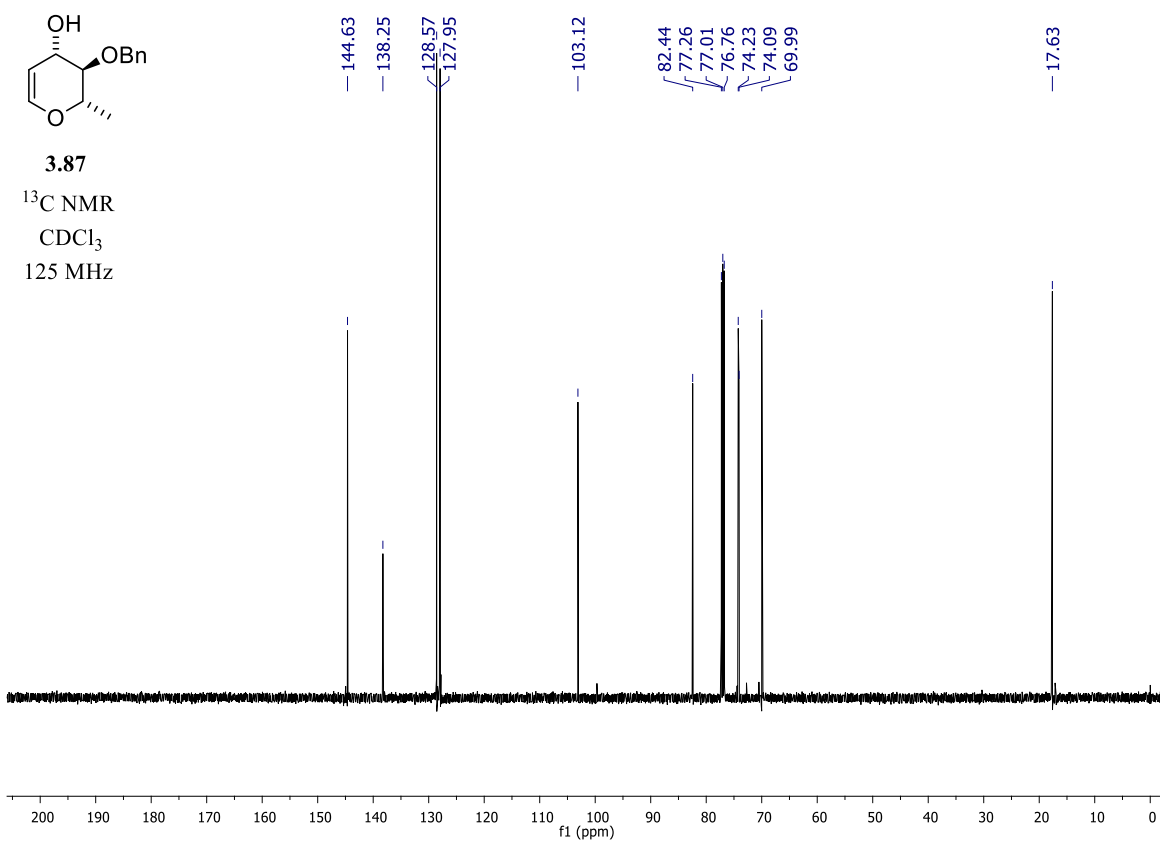
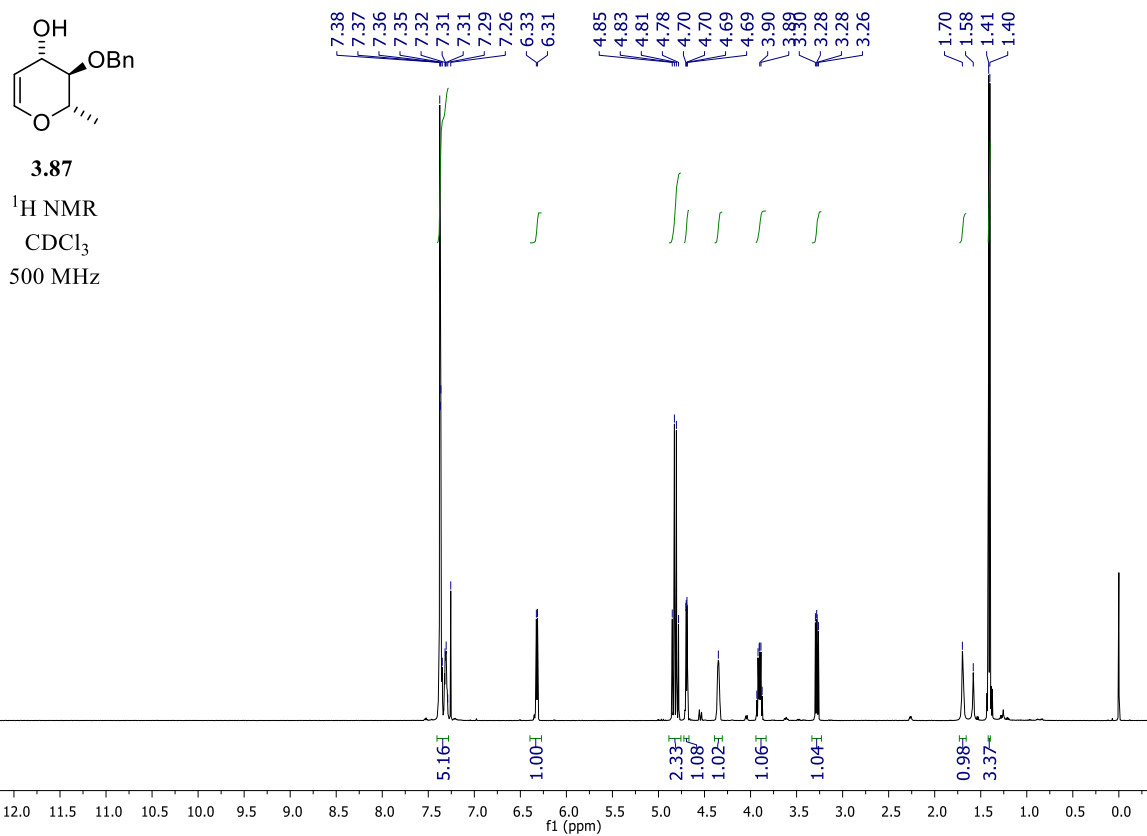
3.86
NOESY
CDCl₃
500 MHz

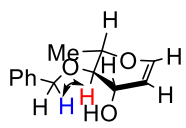


3.86
NOESY
CDCl₃
500 MHz

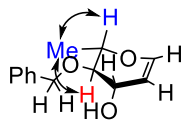
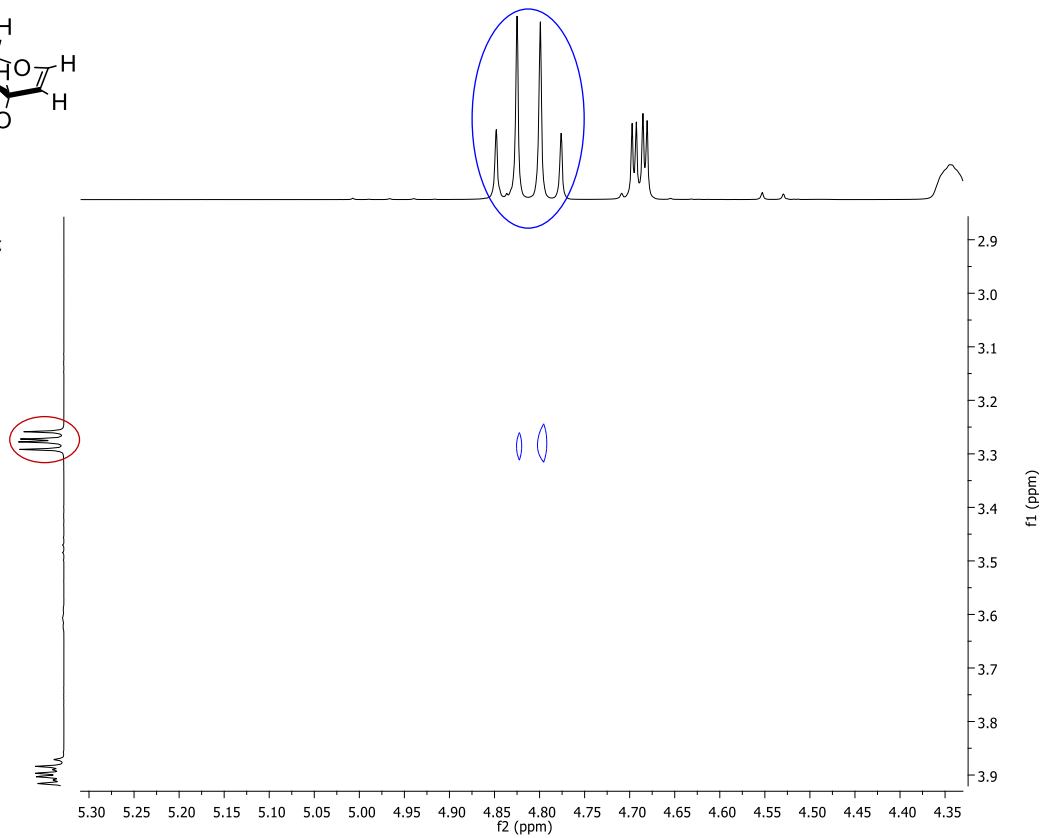




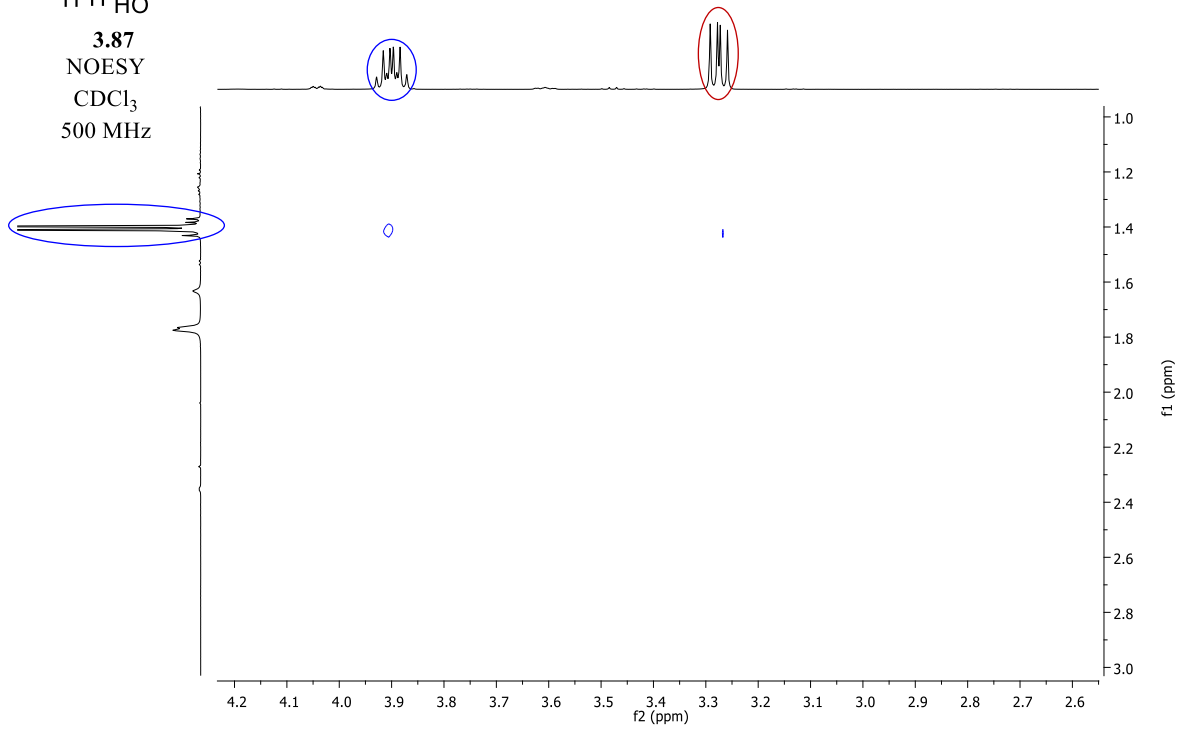


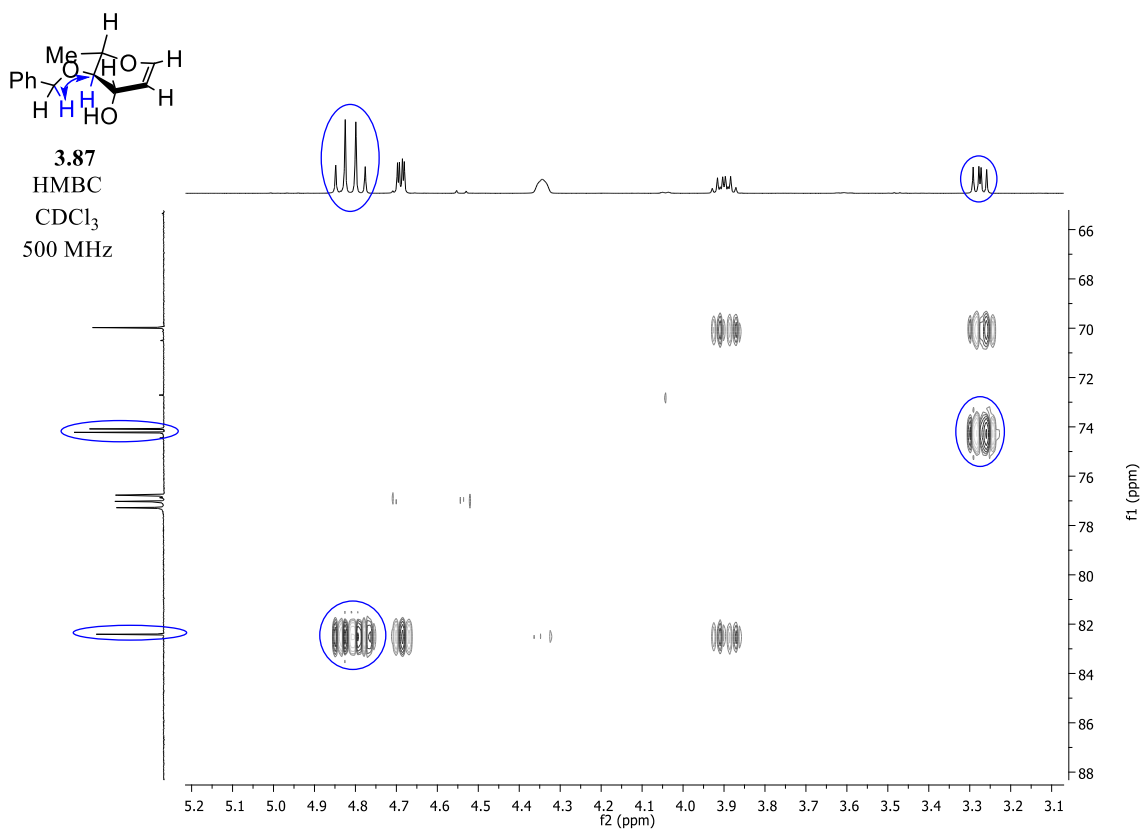
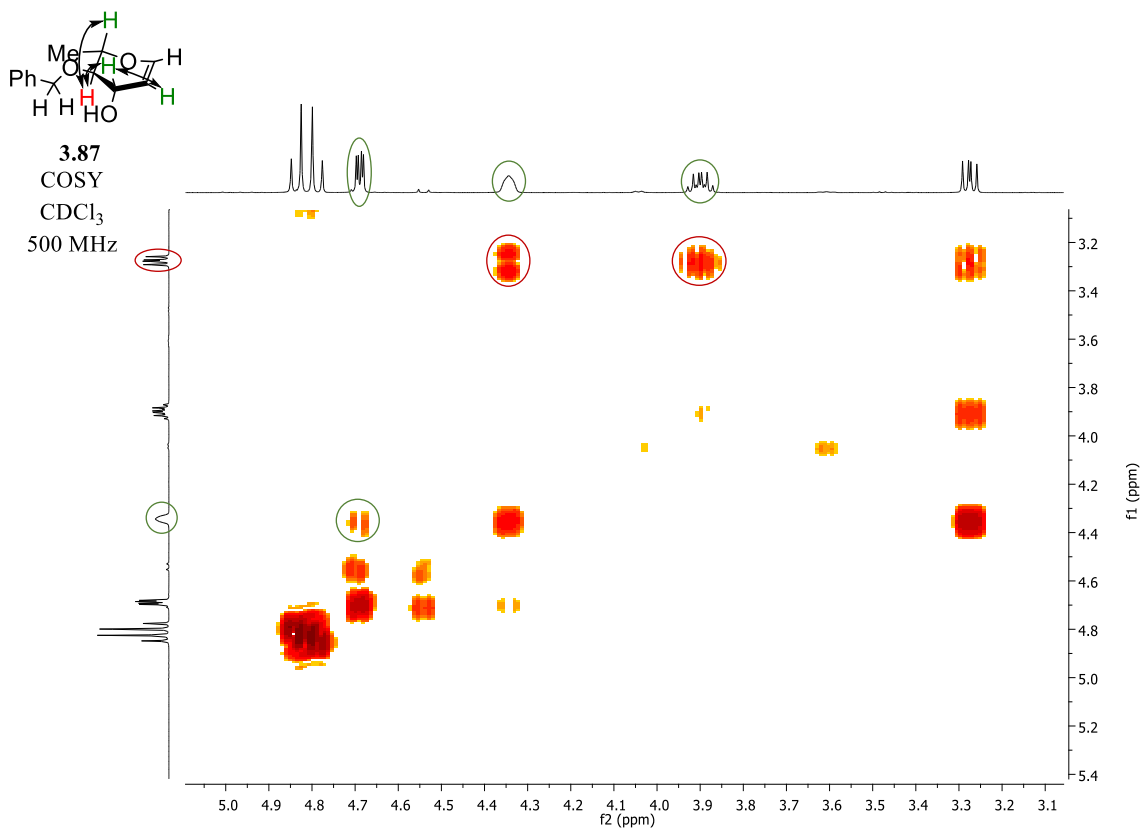


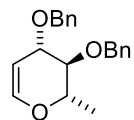
3.87
NOESY
CDCl₃
500 MHz



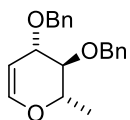
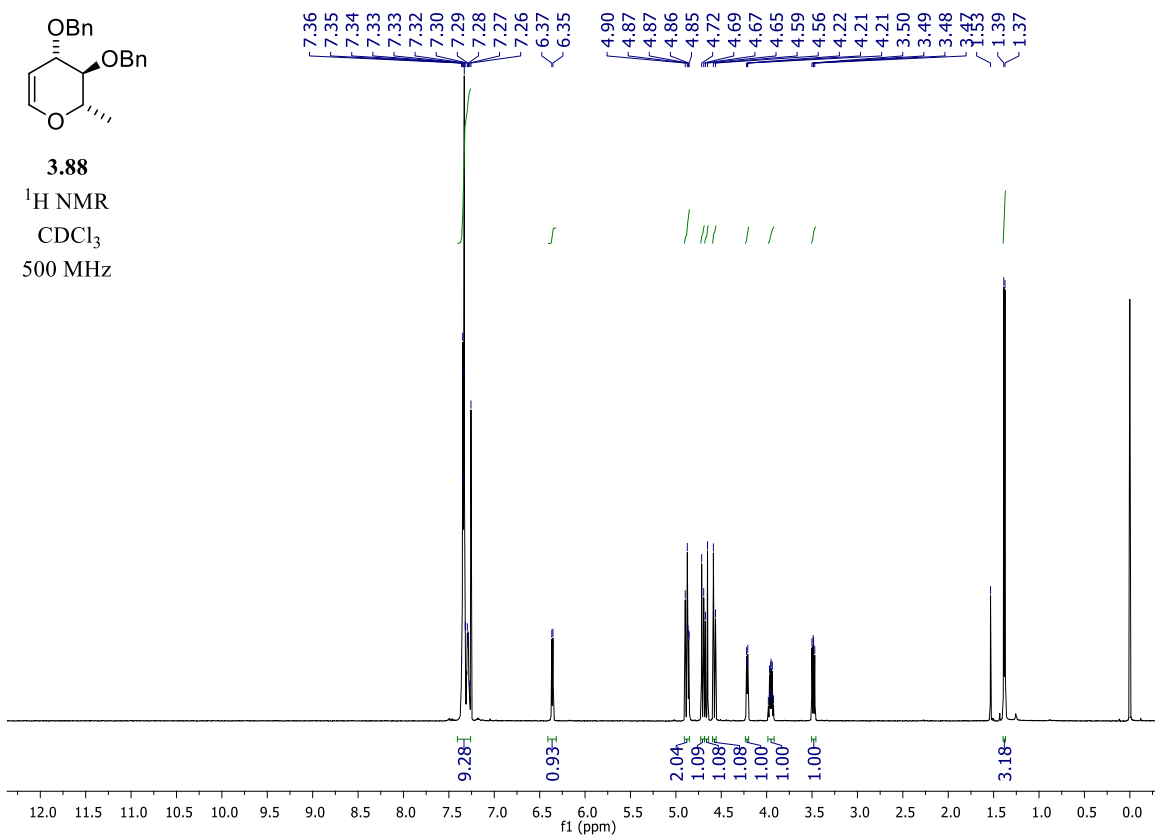
3.87
NOESY
CDCl₃
500 MHz



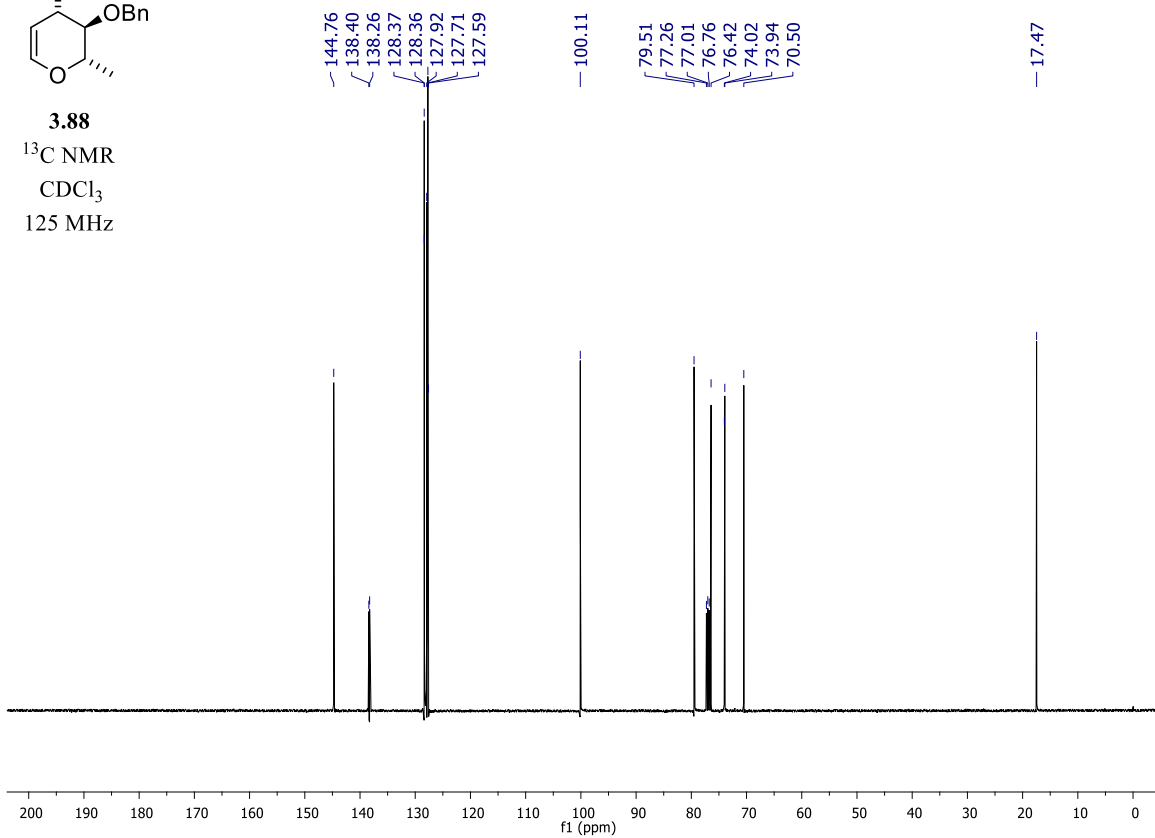


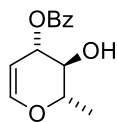


3.88
¹H NMR
 CDCl₃
 500 MHz



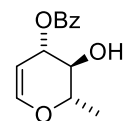
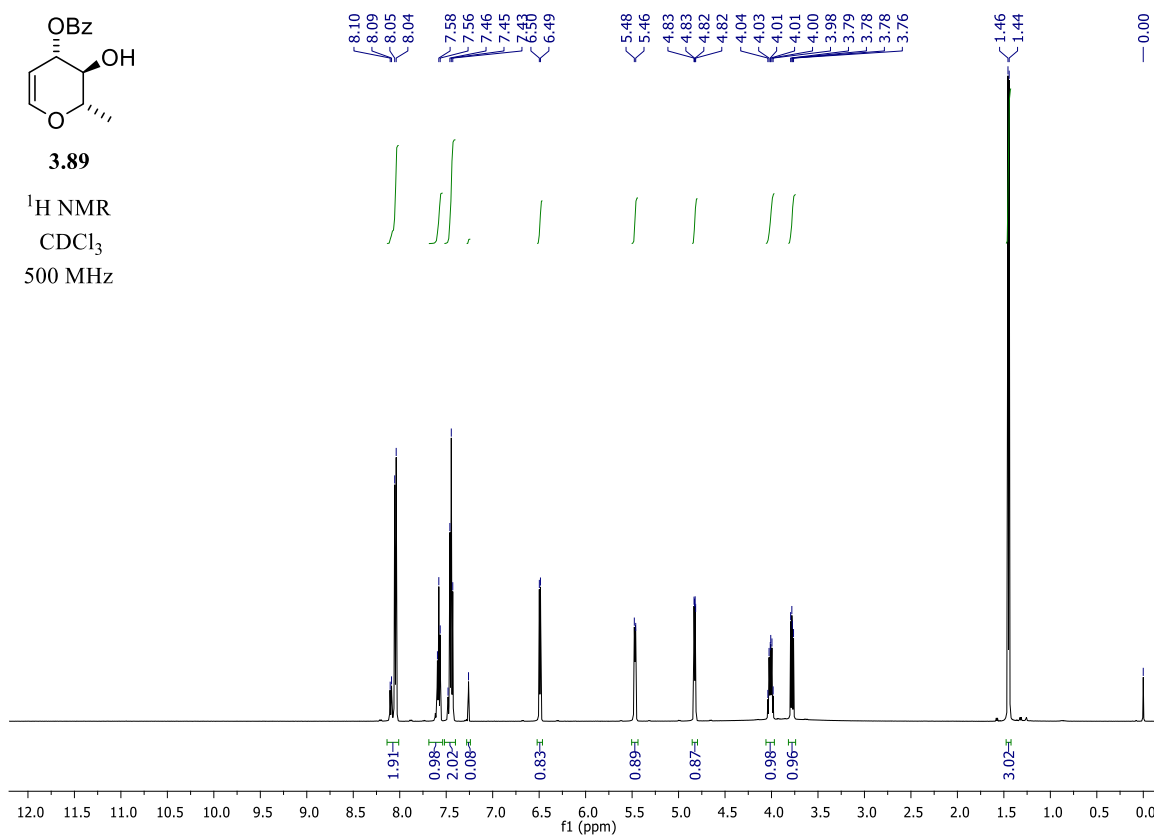
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¹³C NMR
 CDCl₃
 125 MHz





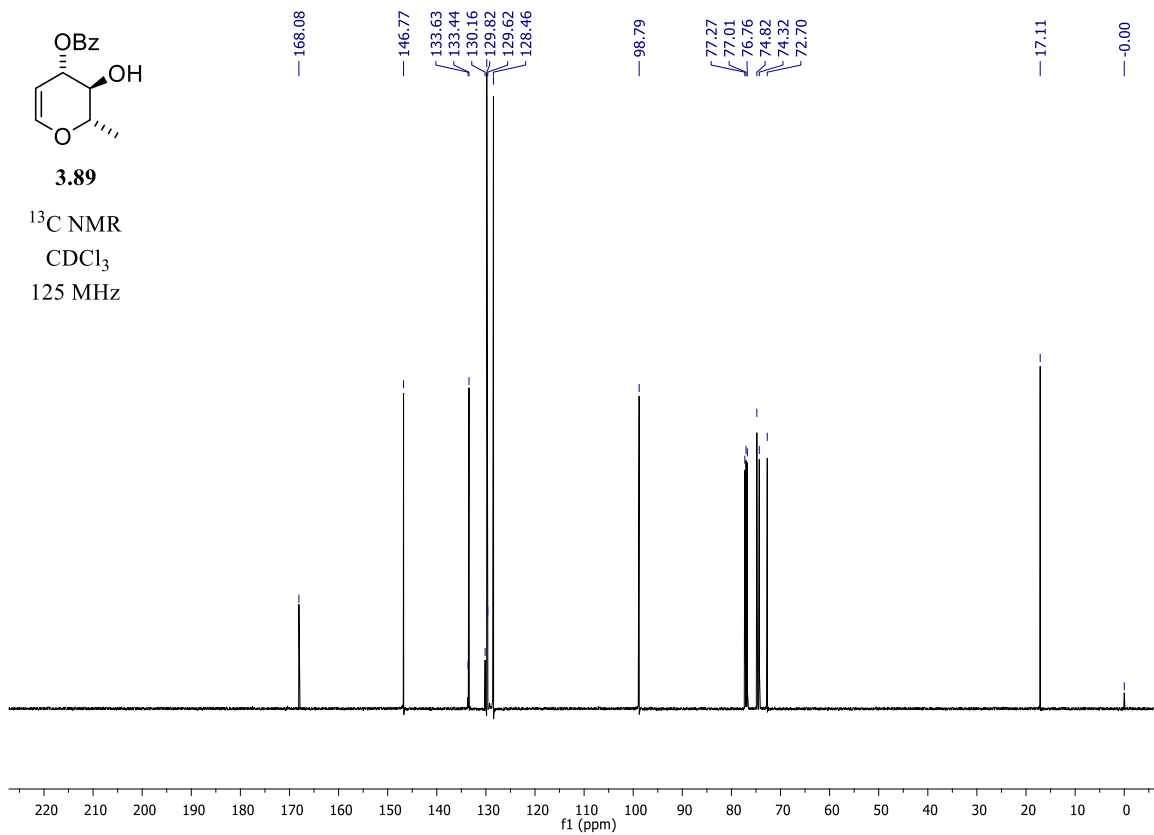
3.89

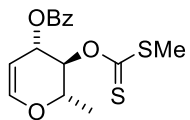
¹H NMR
CDCl₃
500 MHz



3.89

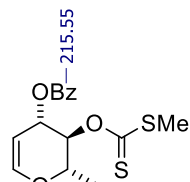
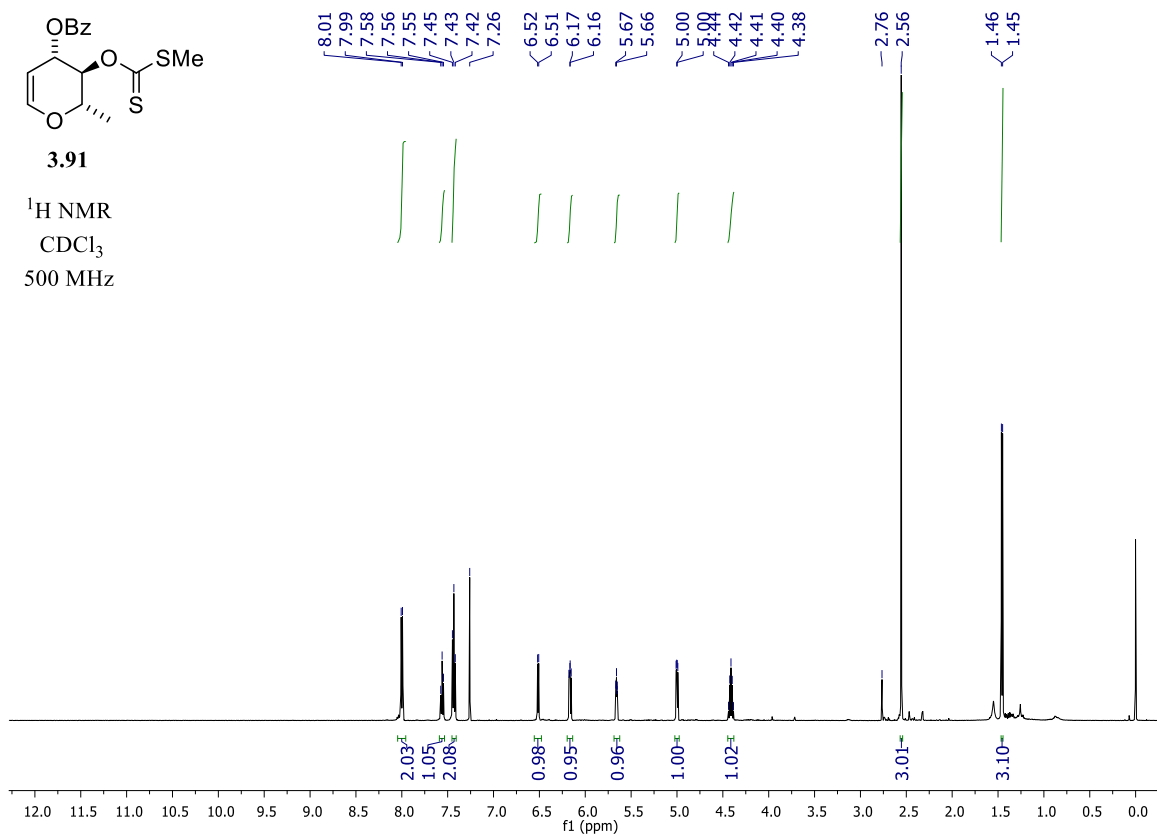
¹³C NMR
CDCl₃
125 MHz





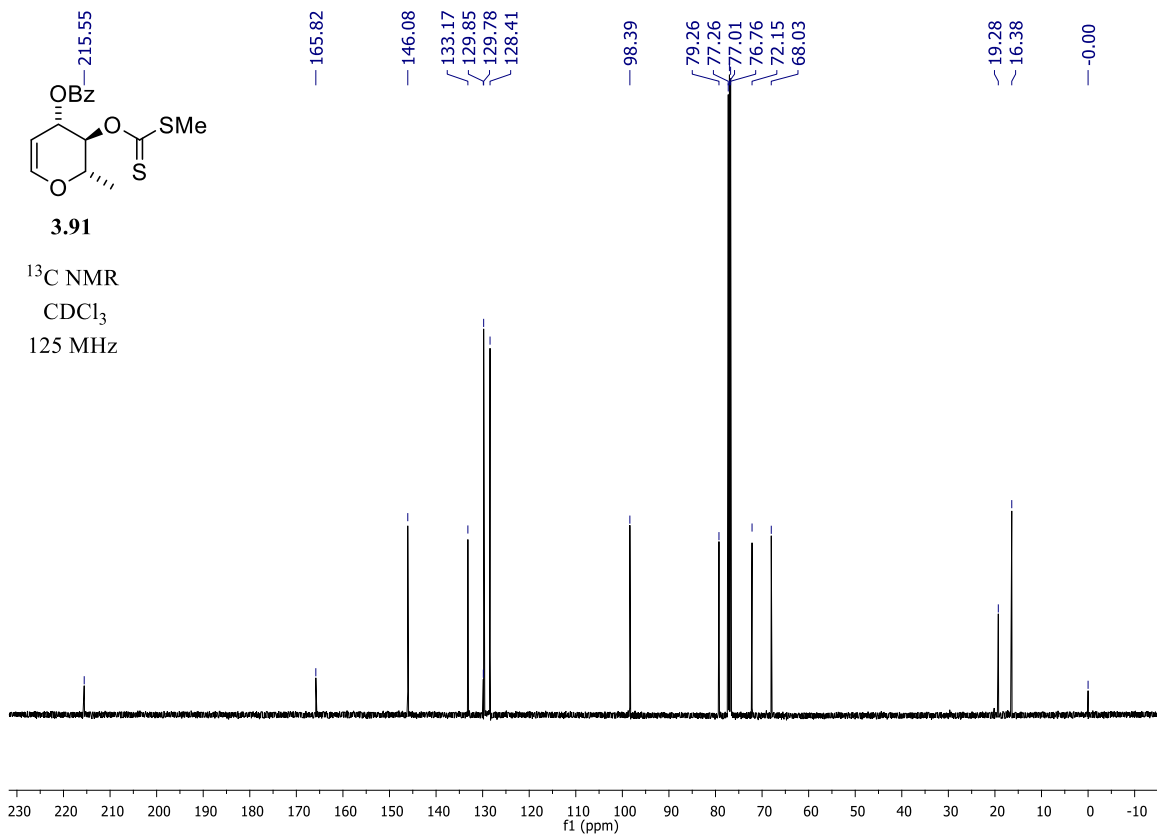
3.91

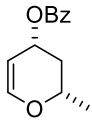
¹H NMR
CDCl₃
500 MHz



3.91

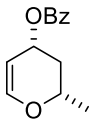
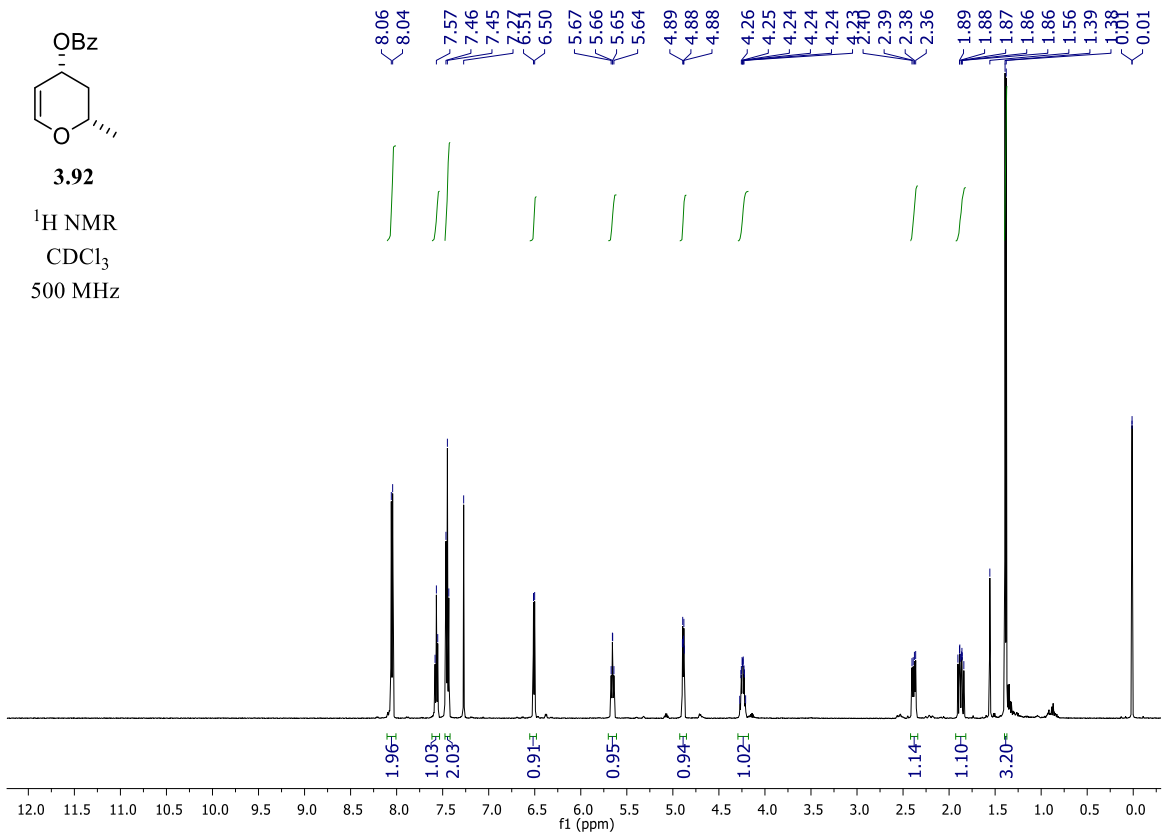
¹³C NMR
CDCl₃
125 MHz





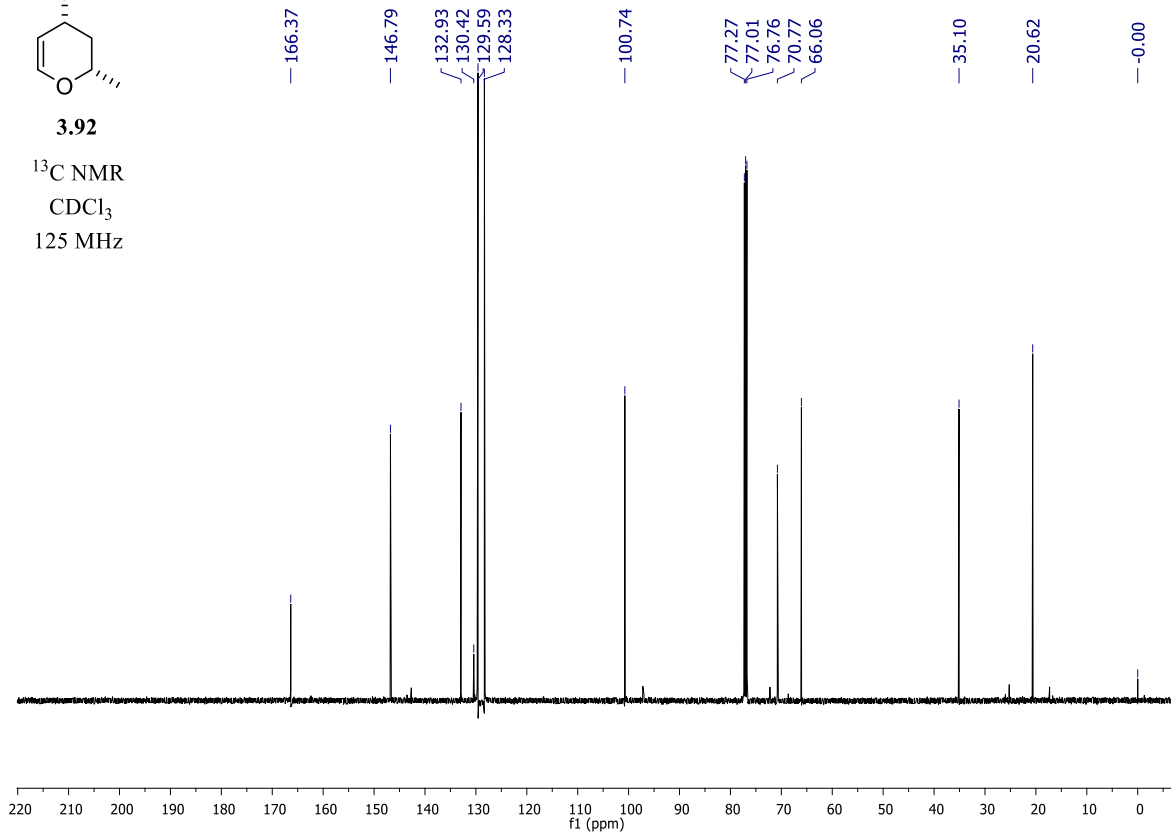
3.92

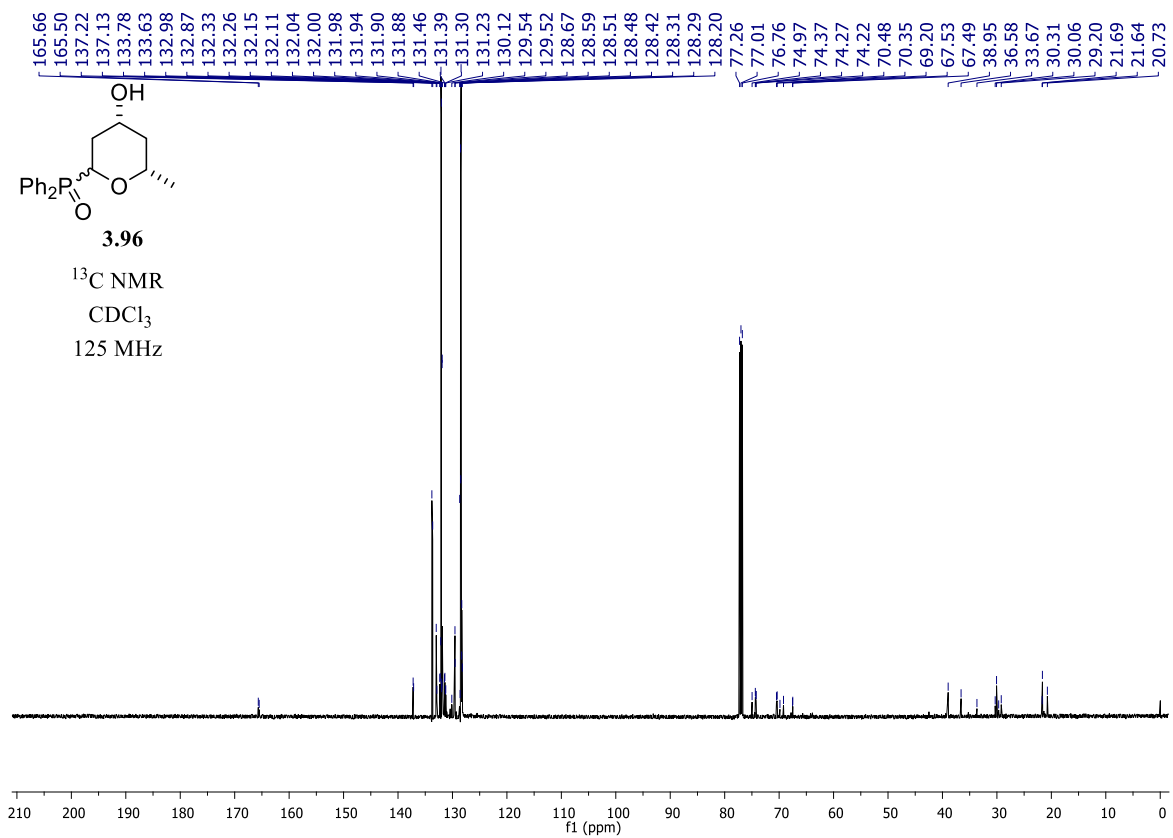
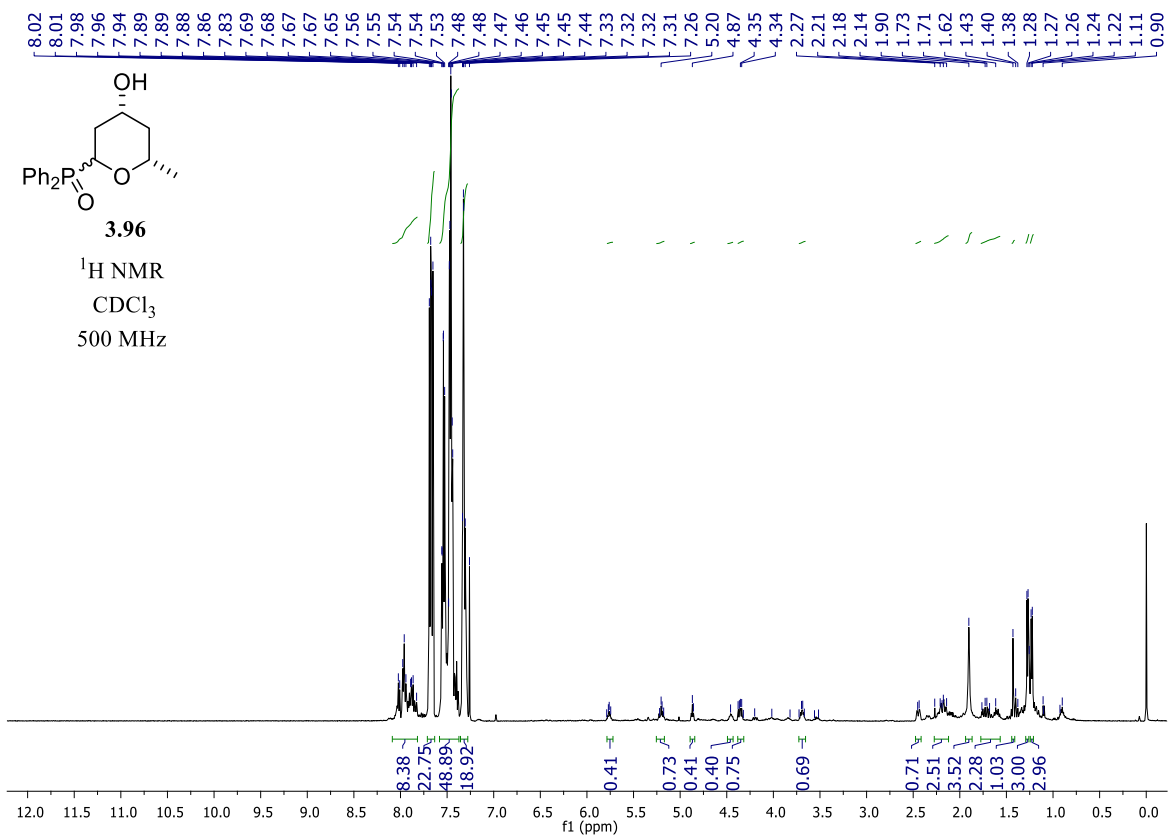
¹H NMR
CDCl₃
500 MHz

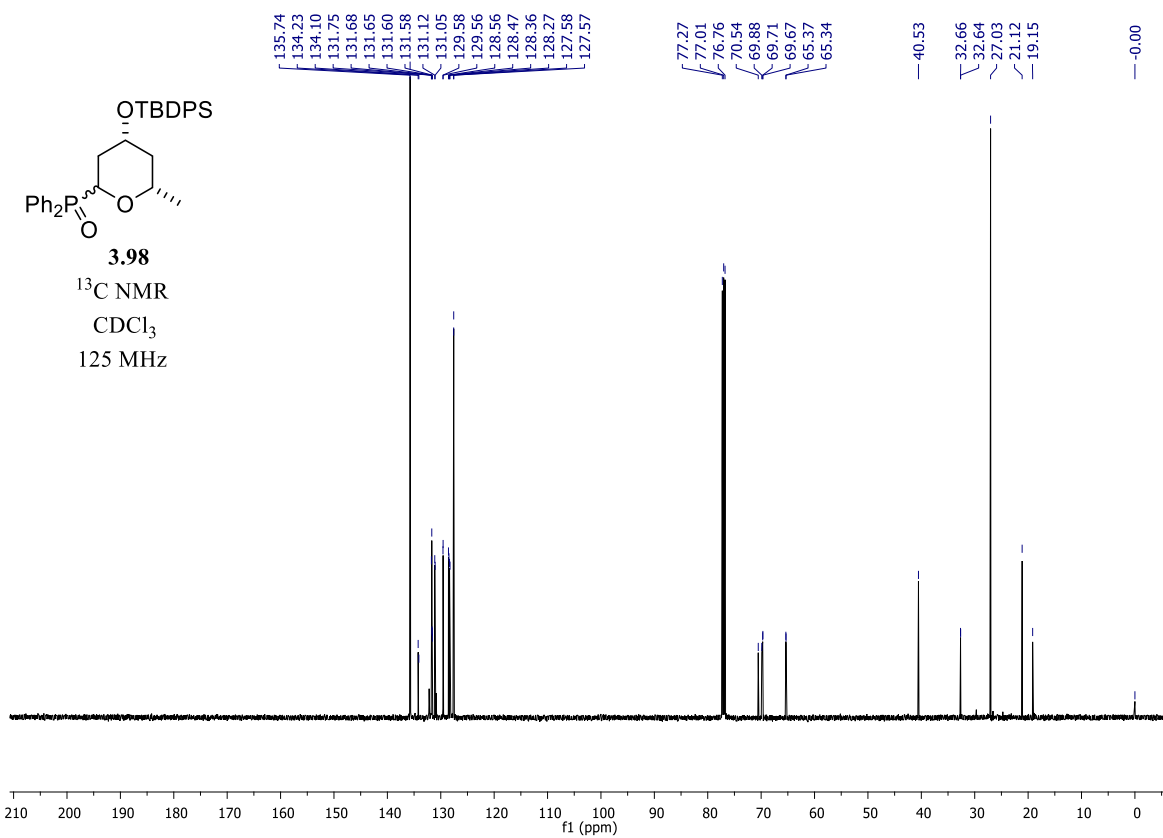
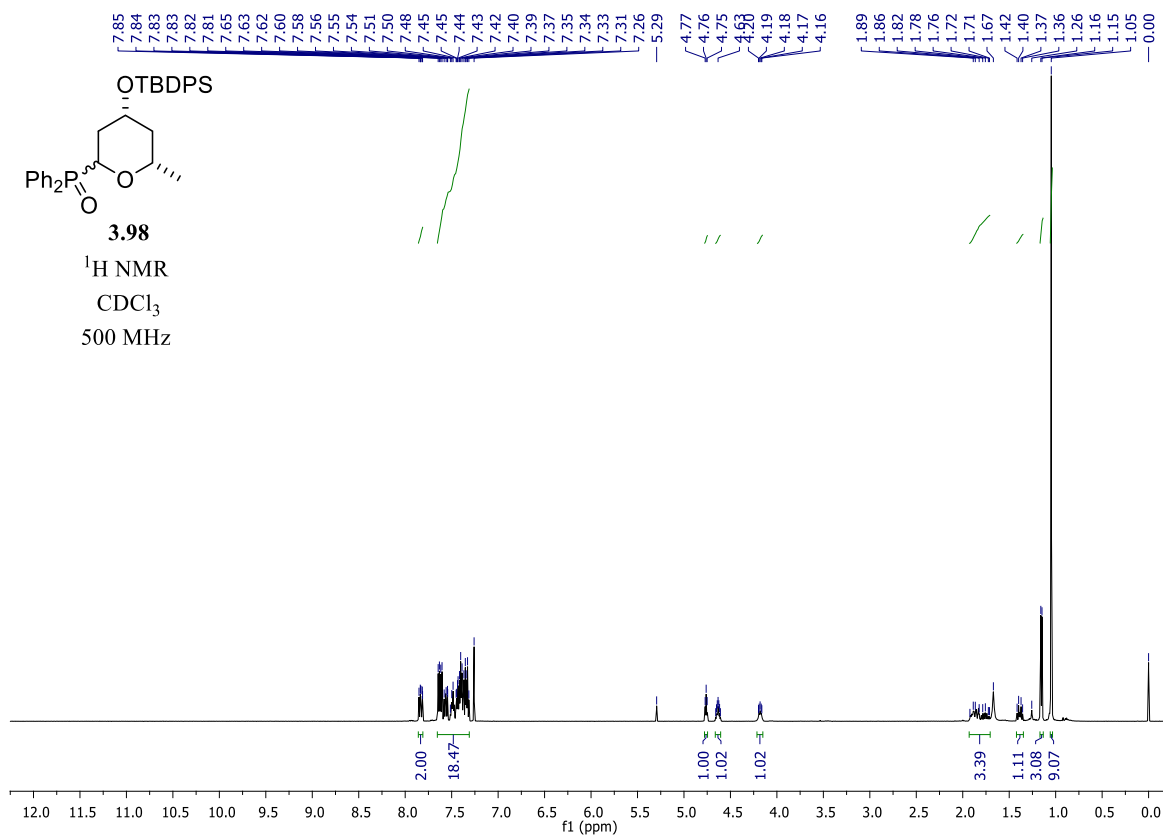


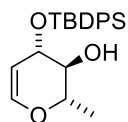
3.92

¹³C NMR
CDCl₃
125 MHz



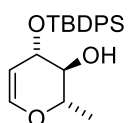
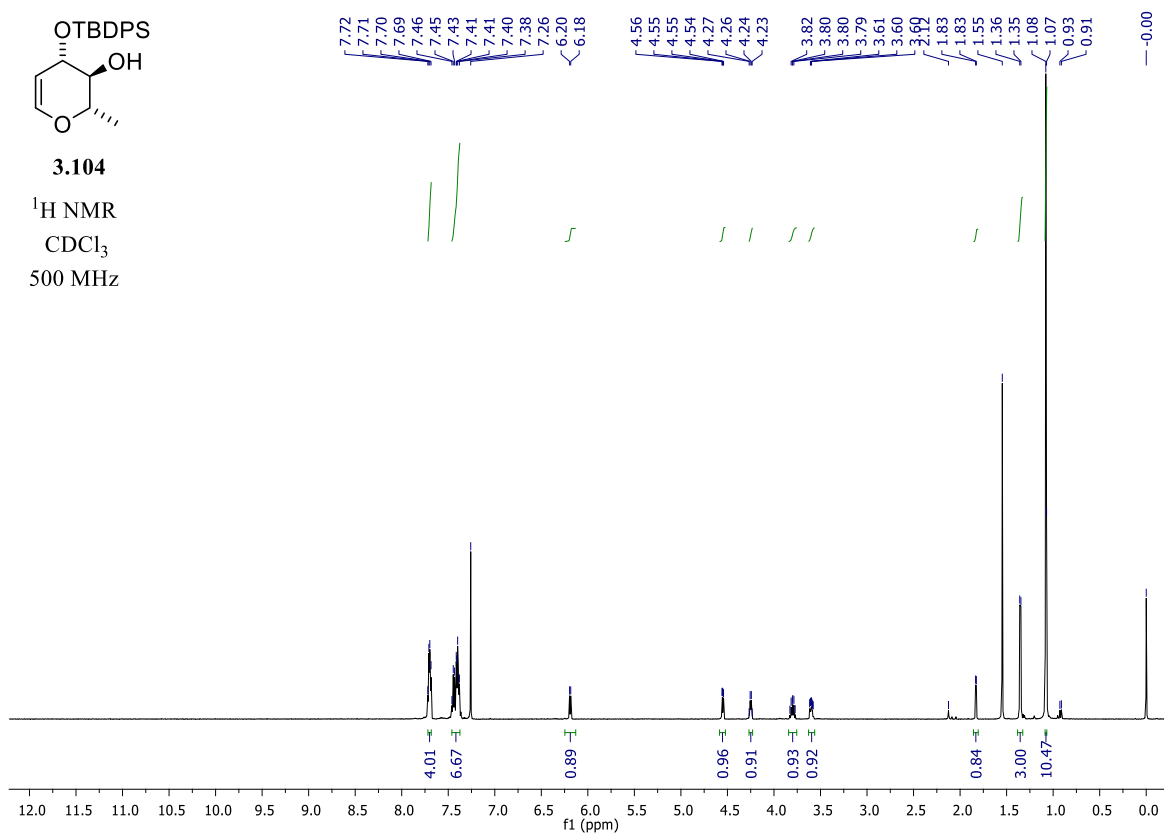






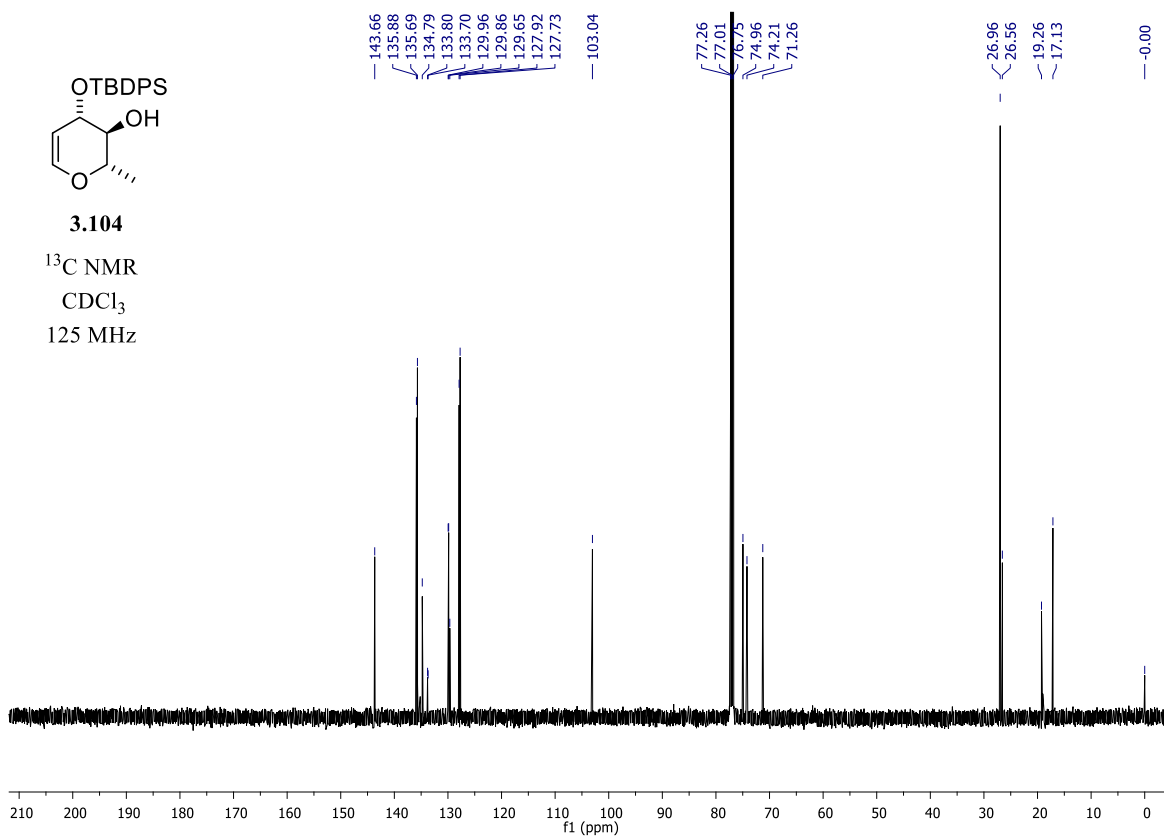
3.104

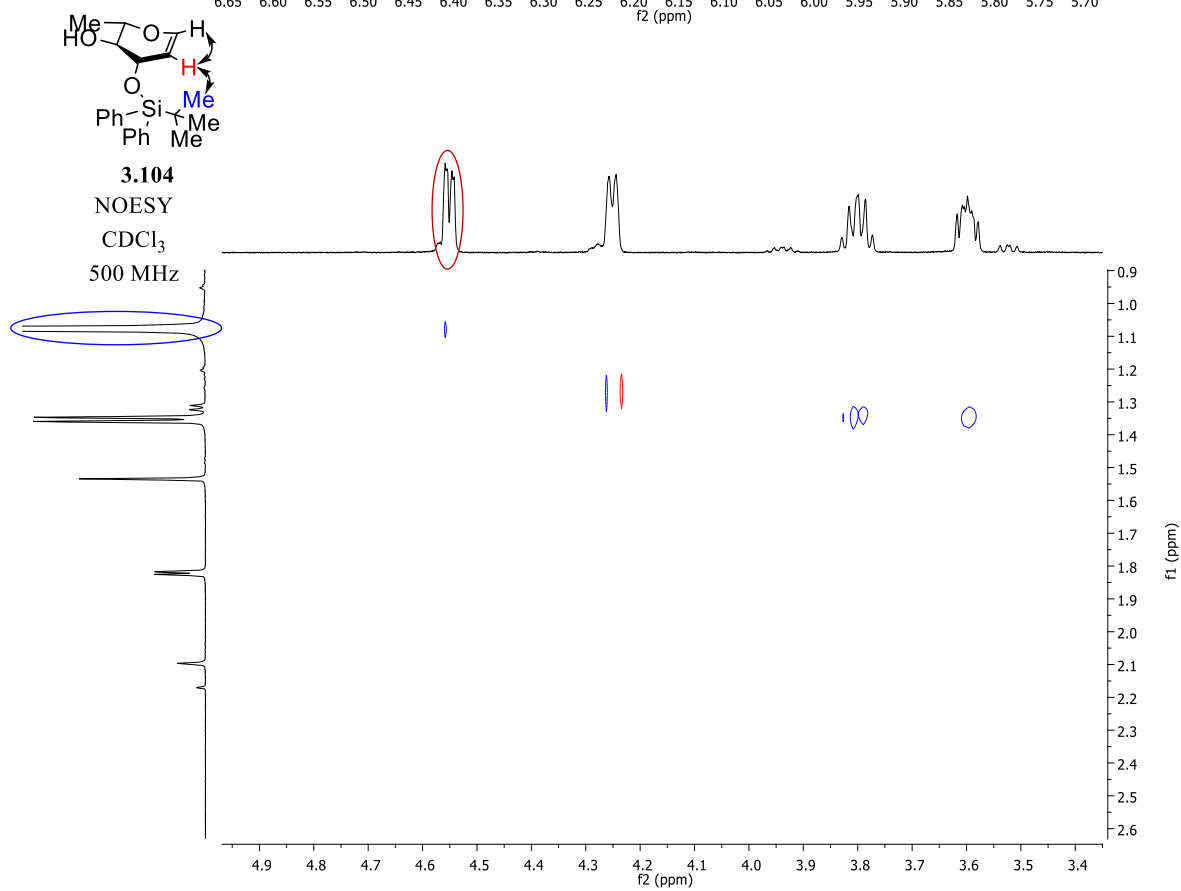
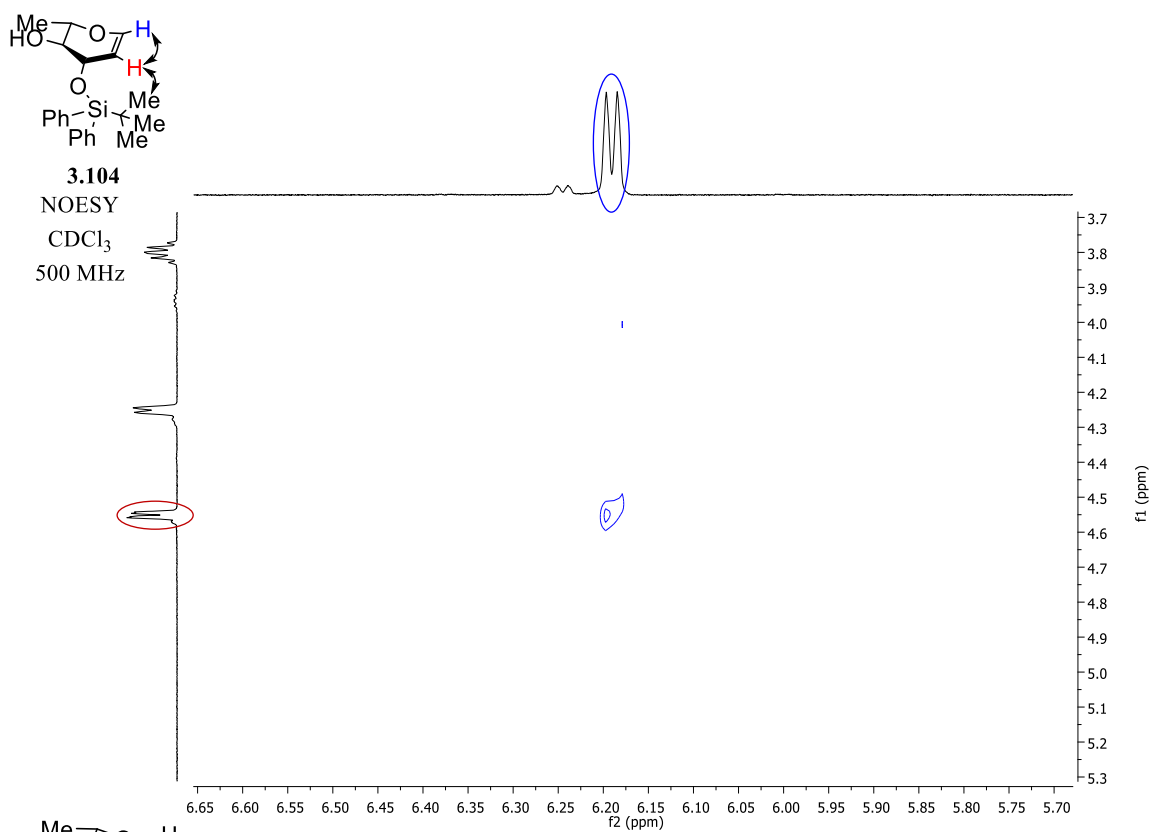
¹H NMR
 CDCl₃
 500 MHz

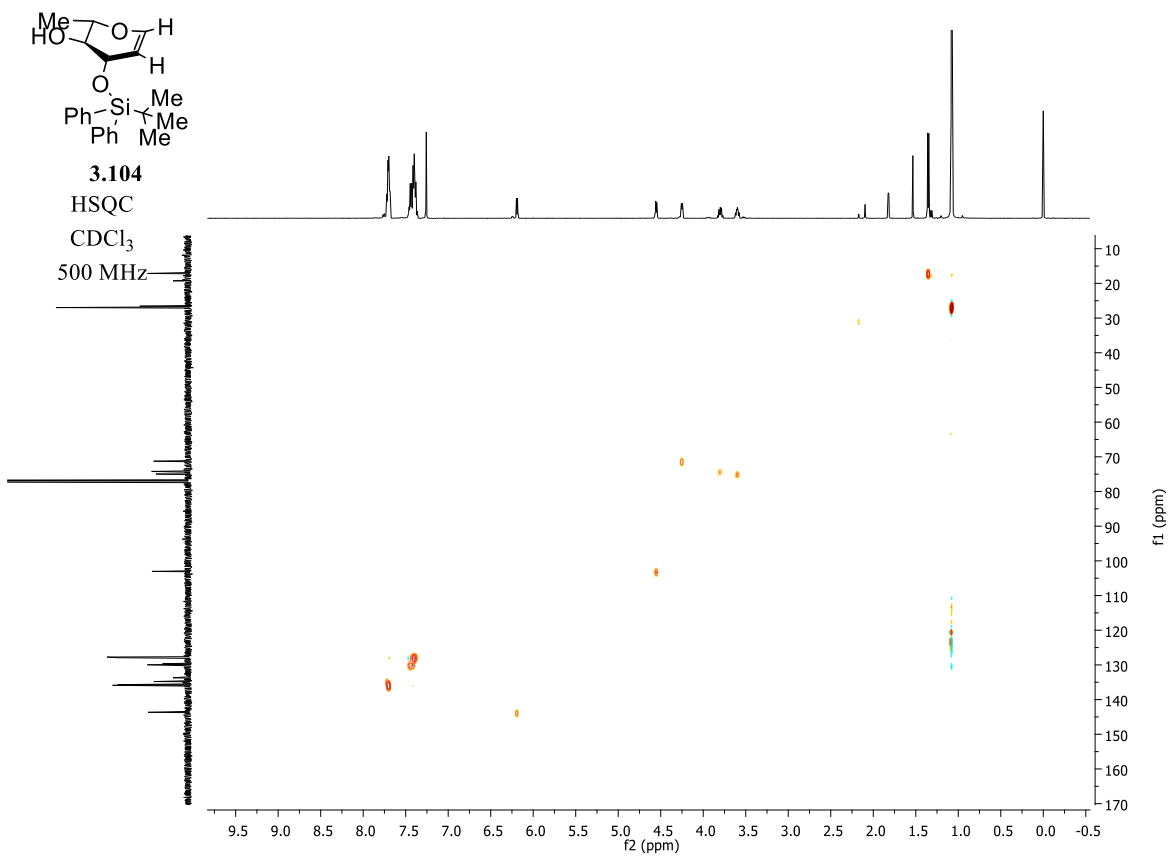
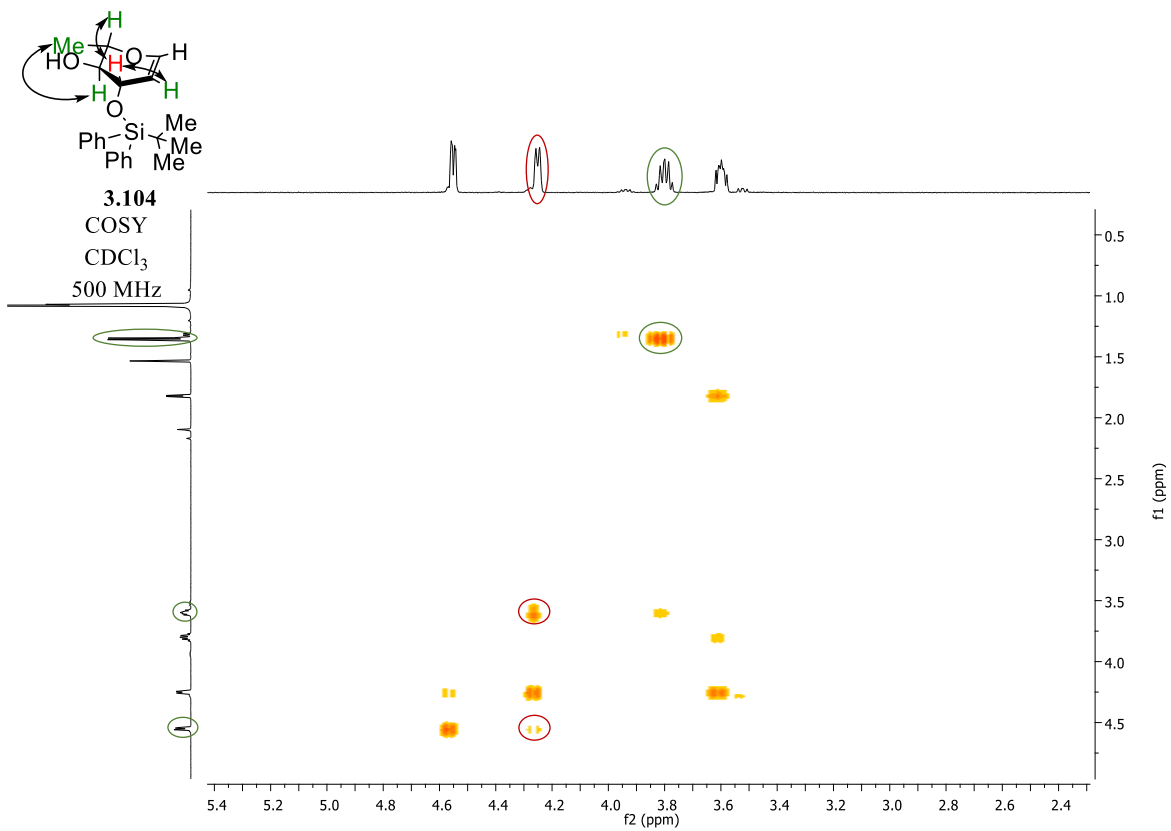


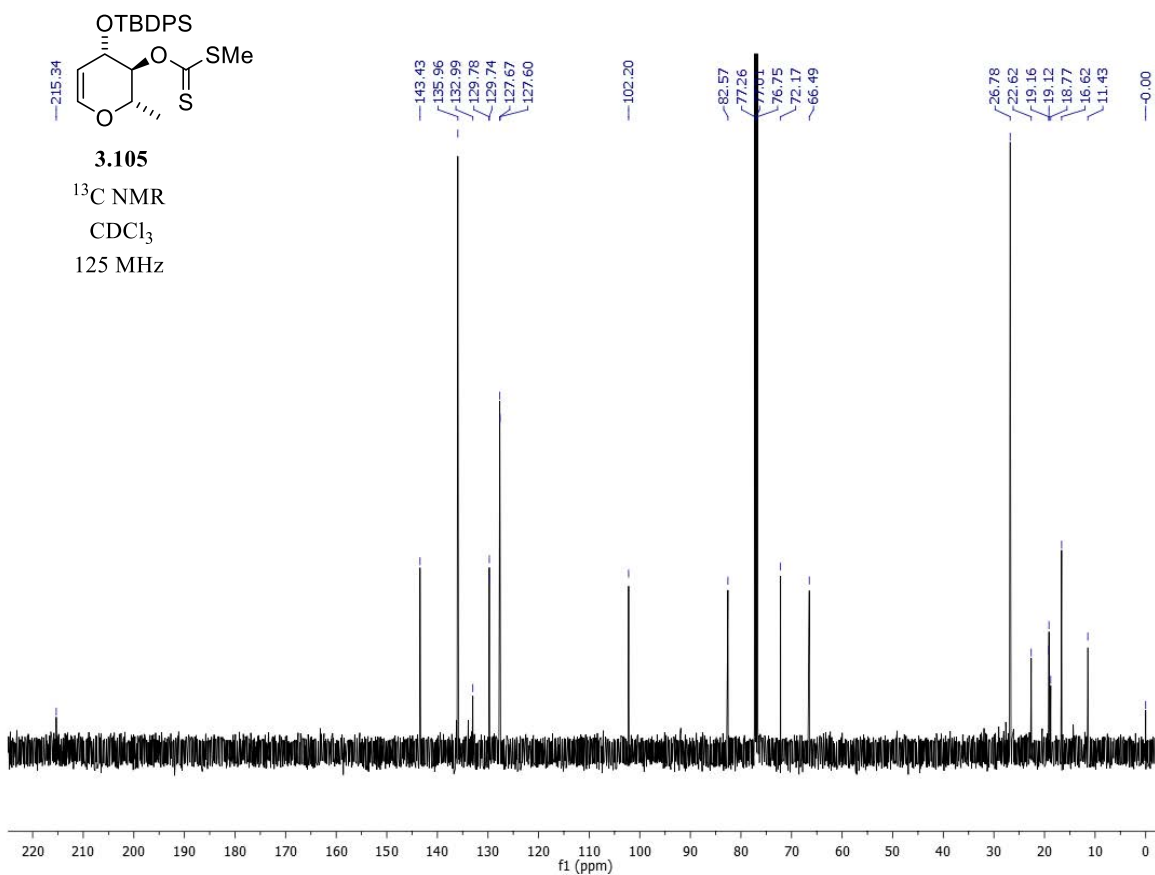
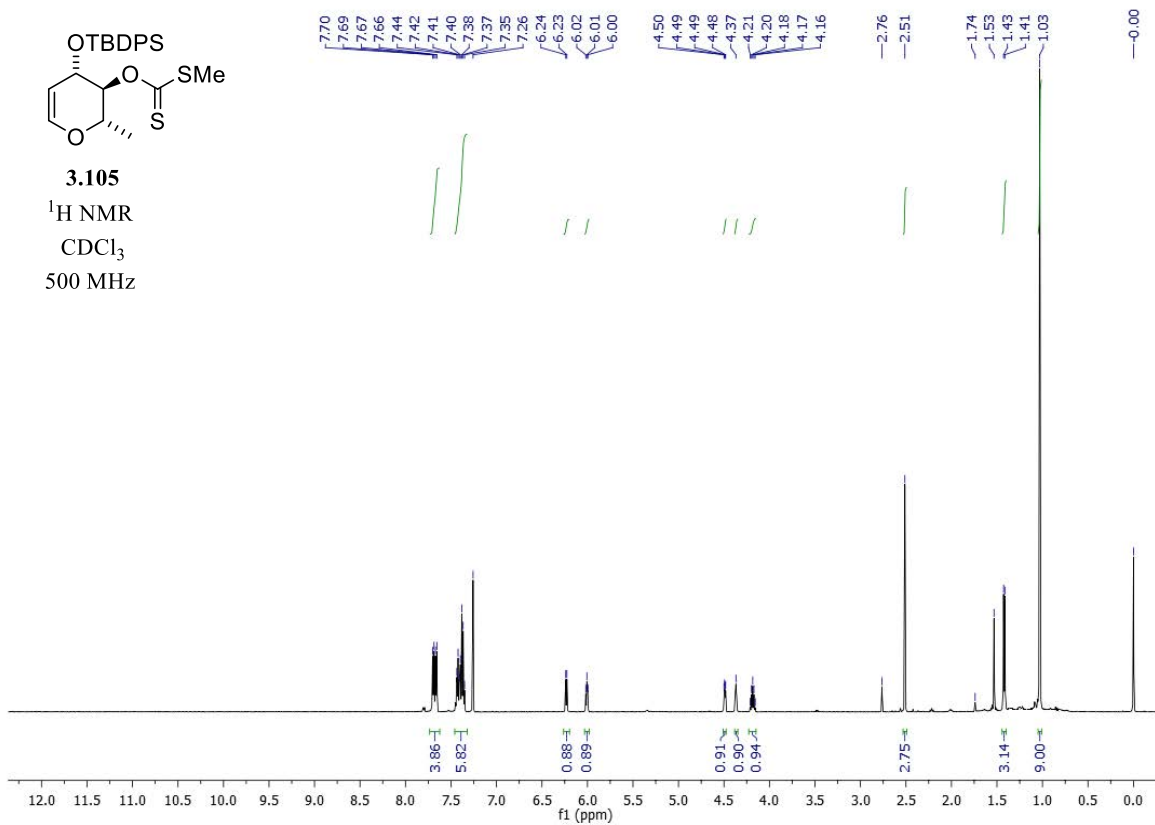
3.104

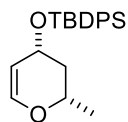
¹³C NMR
 CDCl₃
 125 MHz





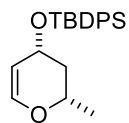
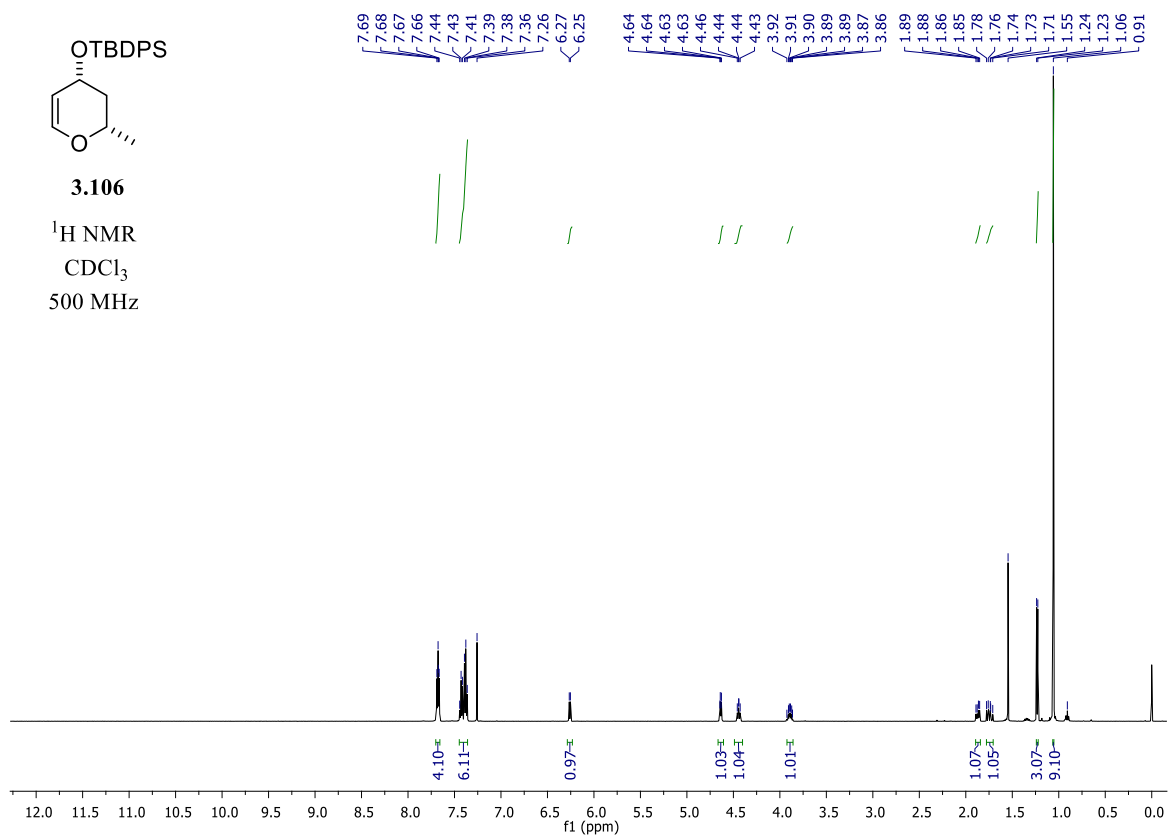






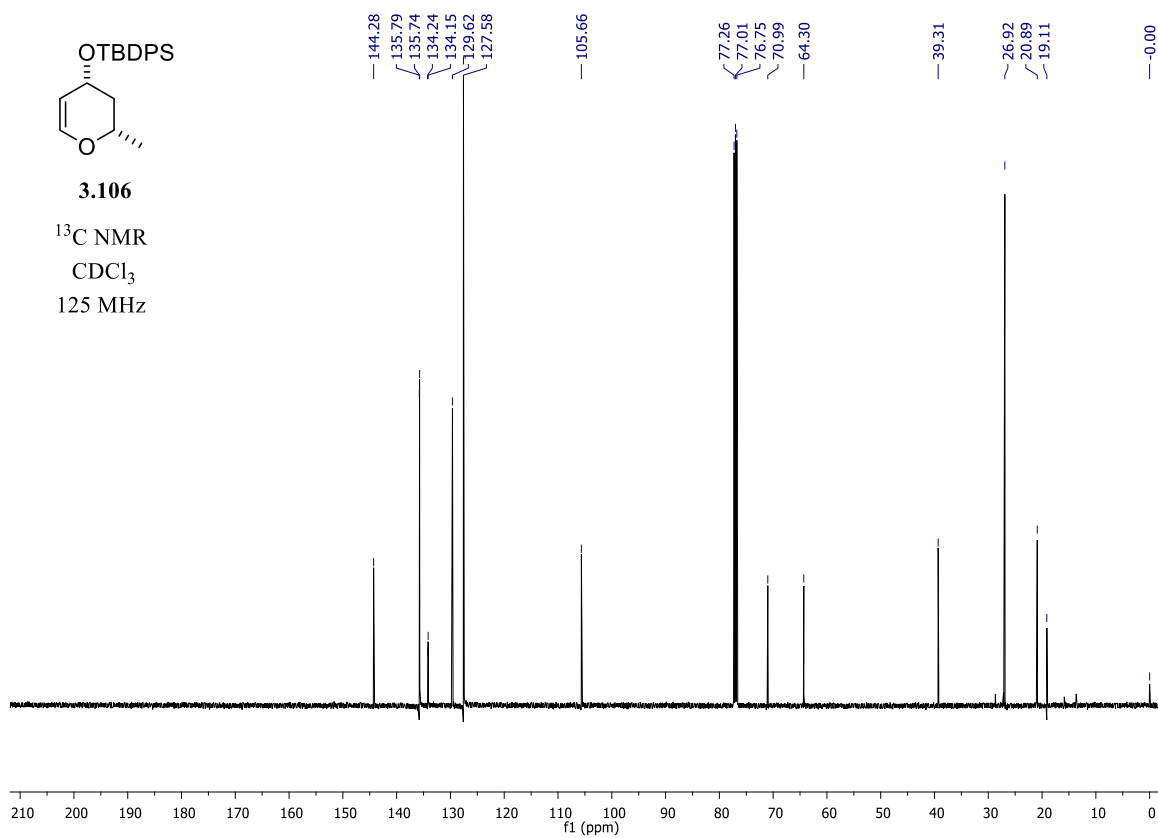
3.106

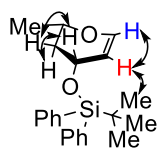
¹H NMR
CDCl₃
500 MHz



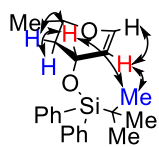
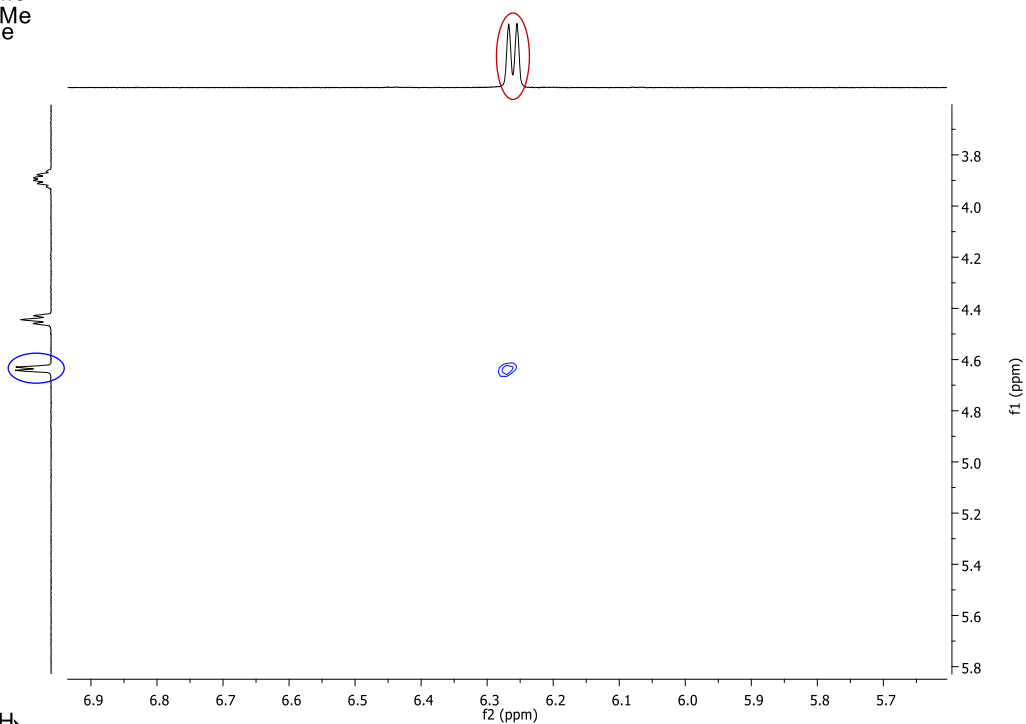
3.106

¹³C NMR
CDCl₃
125 MHz

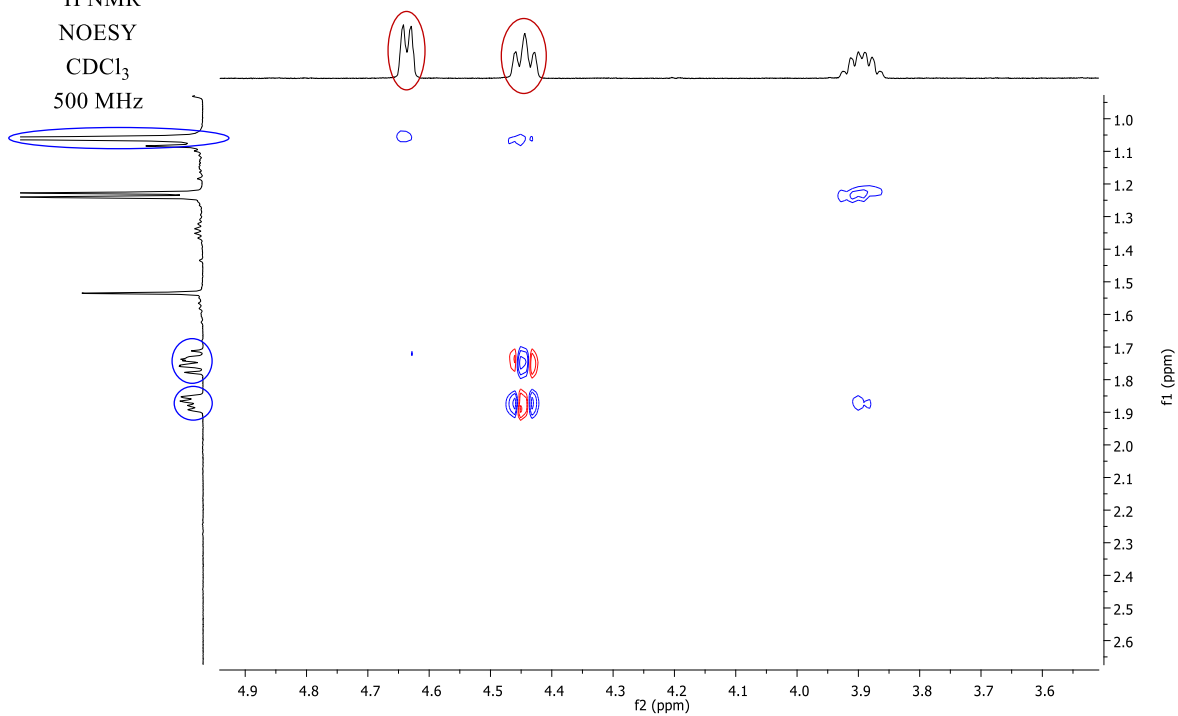


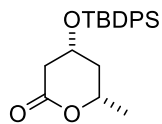


3.106
¹H NMR
 NOESY
 CDCl₃
 500 MHz



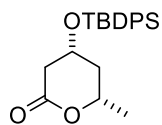
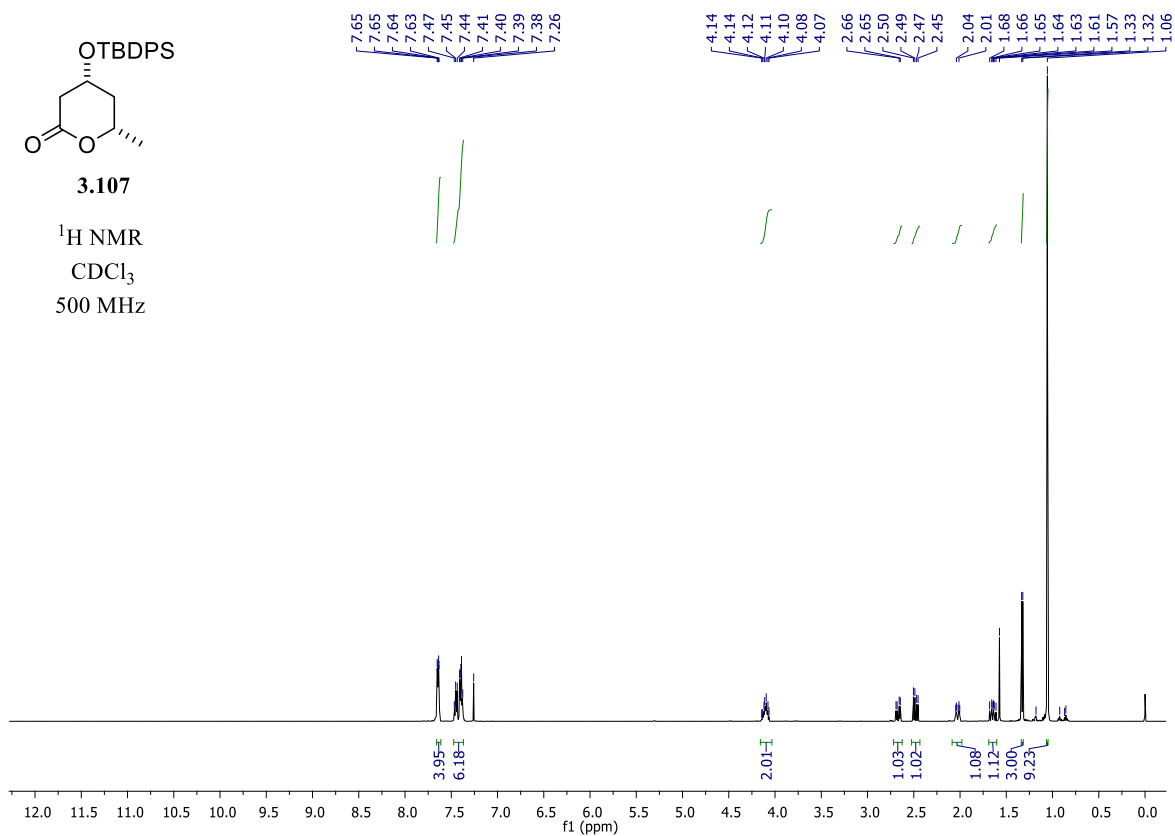
3.106
¹H NMR
 NOESY
 CDCl₃
 500 MHz





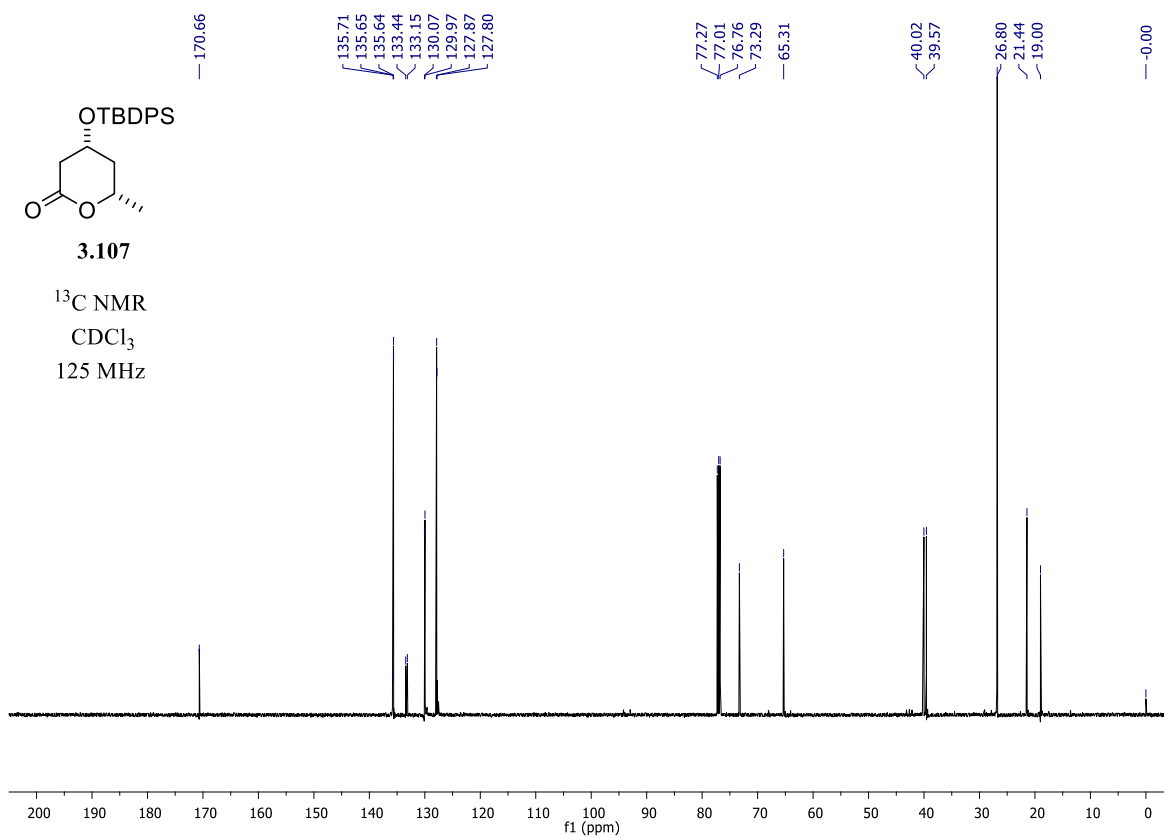
3.107

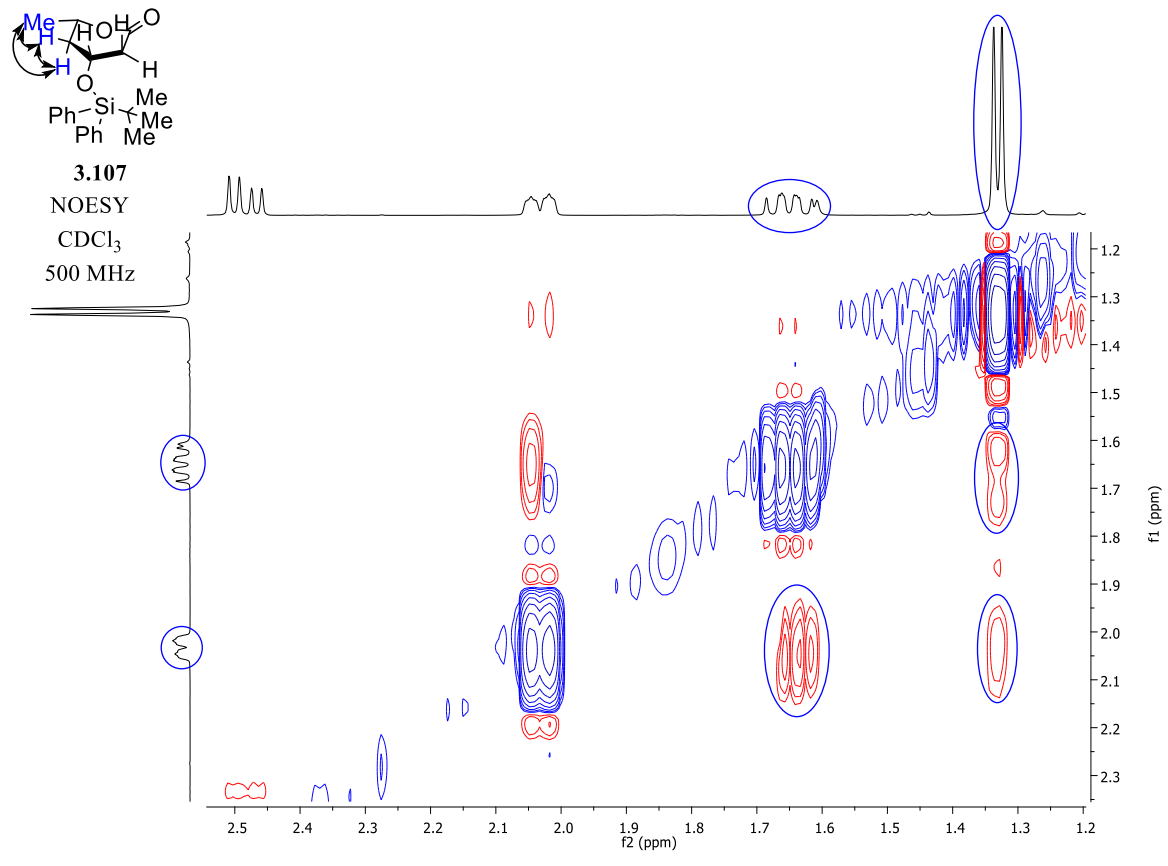
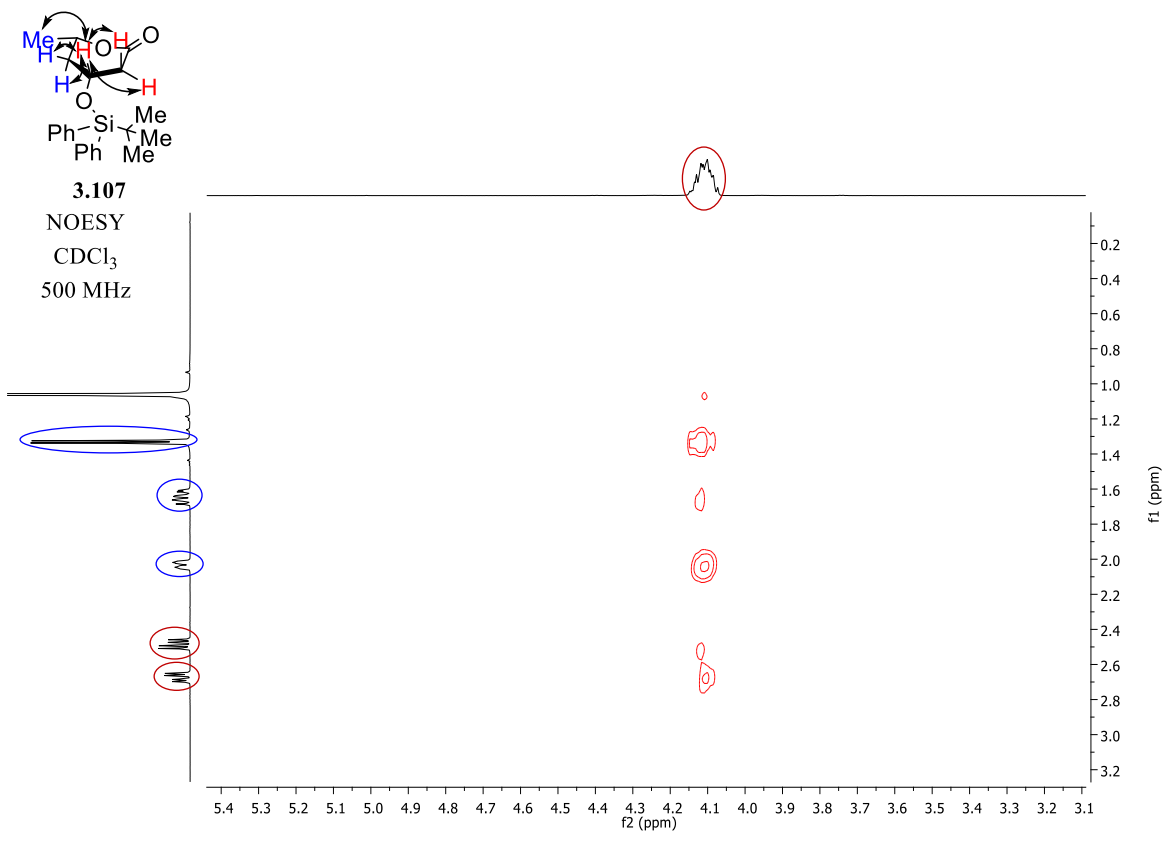
¹H NMR
CDCl₃
500 MHz

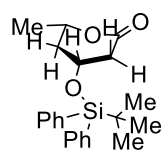


3.107

¹³C NMR
CDCl₃
125 MHz





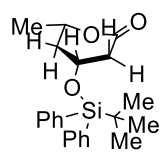
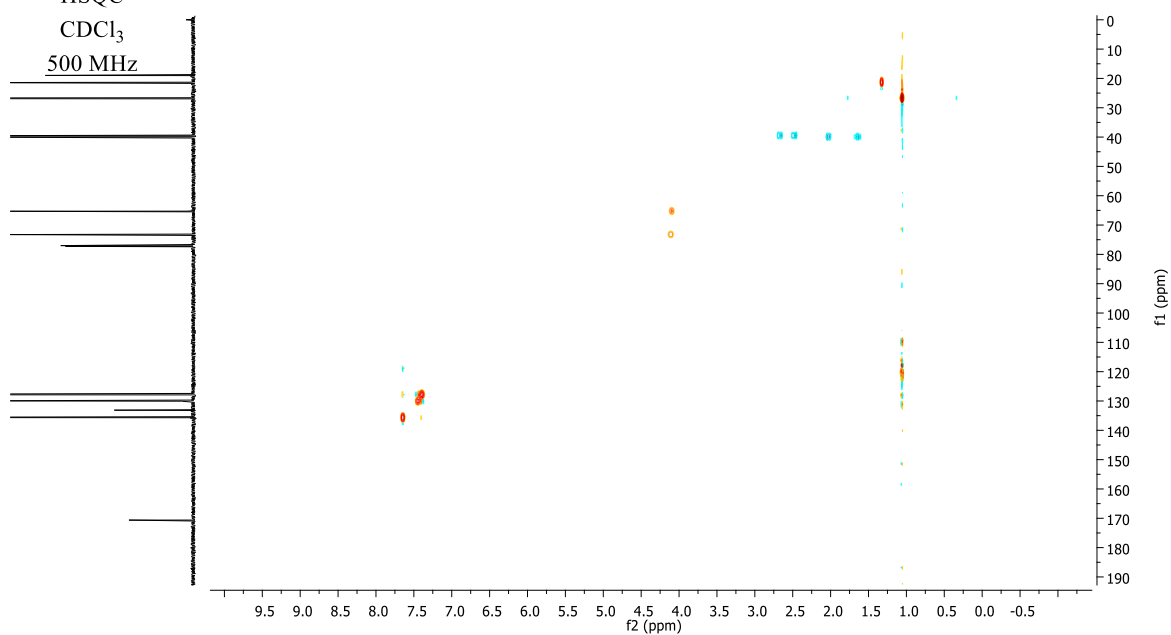


3.107

HSQC

CDCl₃

500 MHz

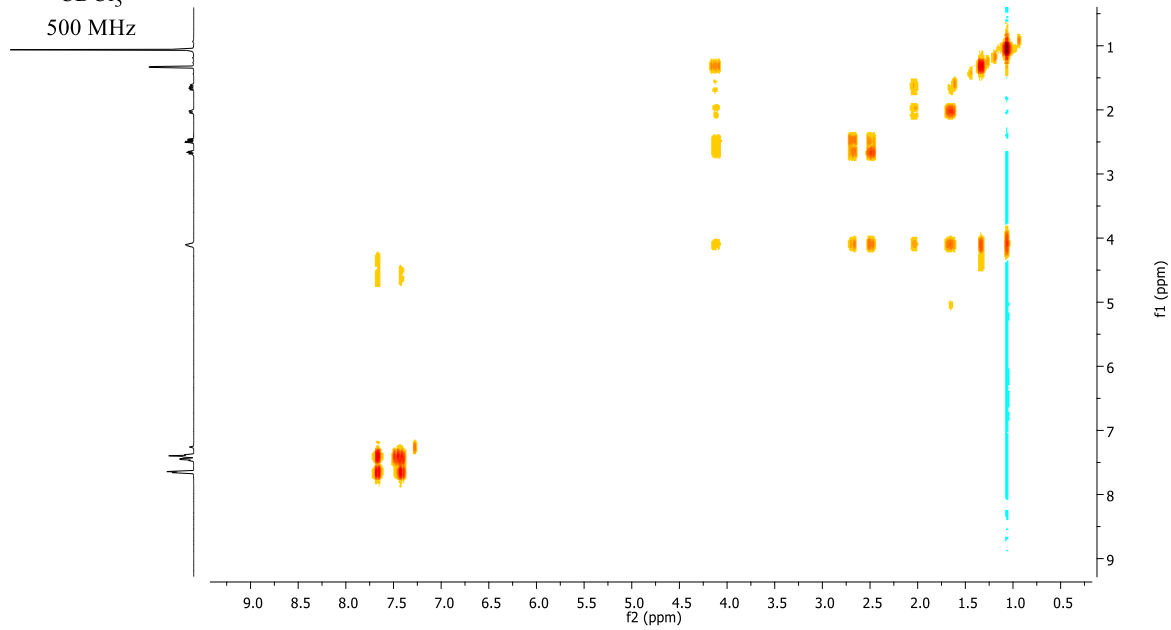


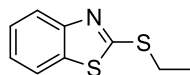
3.107

COSY

CDCl₃

500 MHz



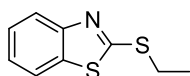
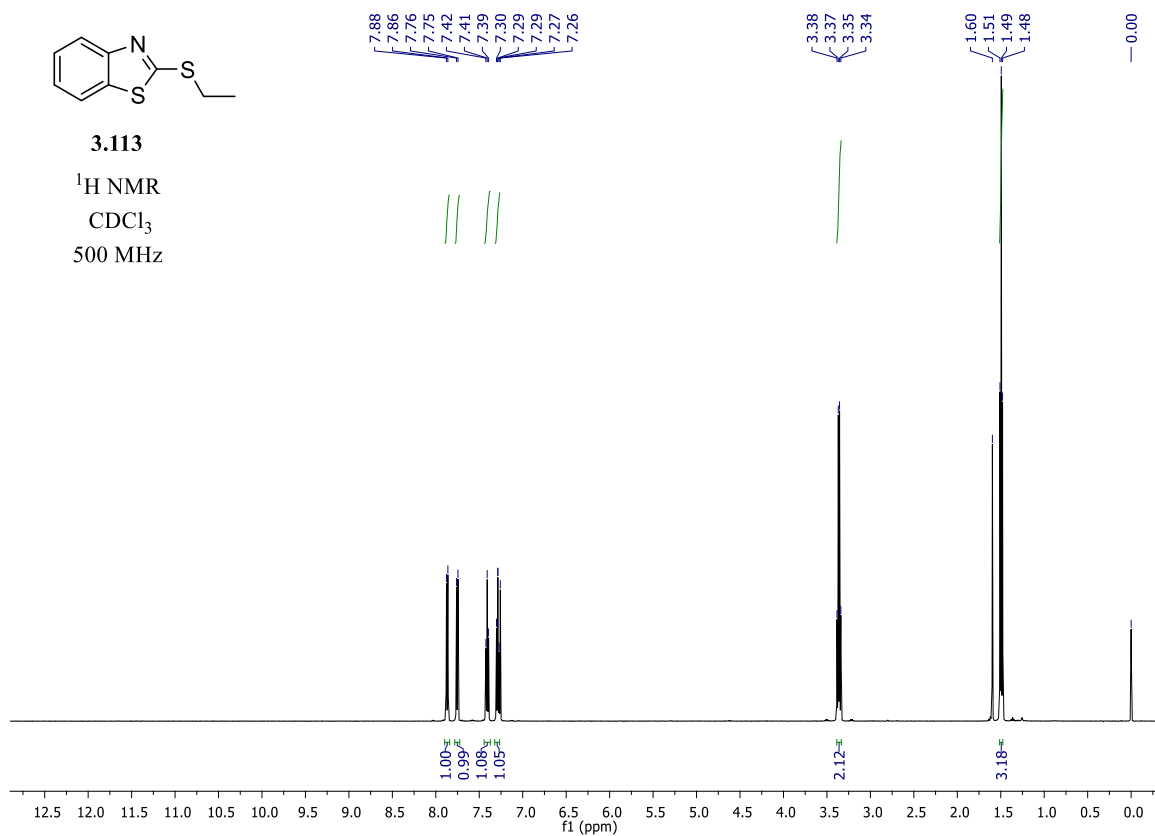


3.113

¹H NMR

CDCl₃

500 MHz

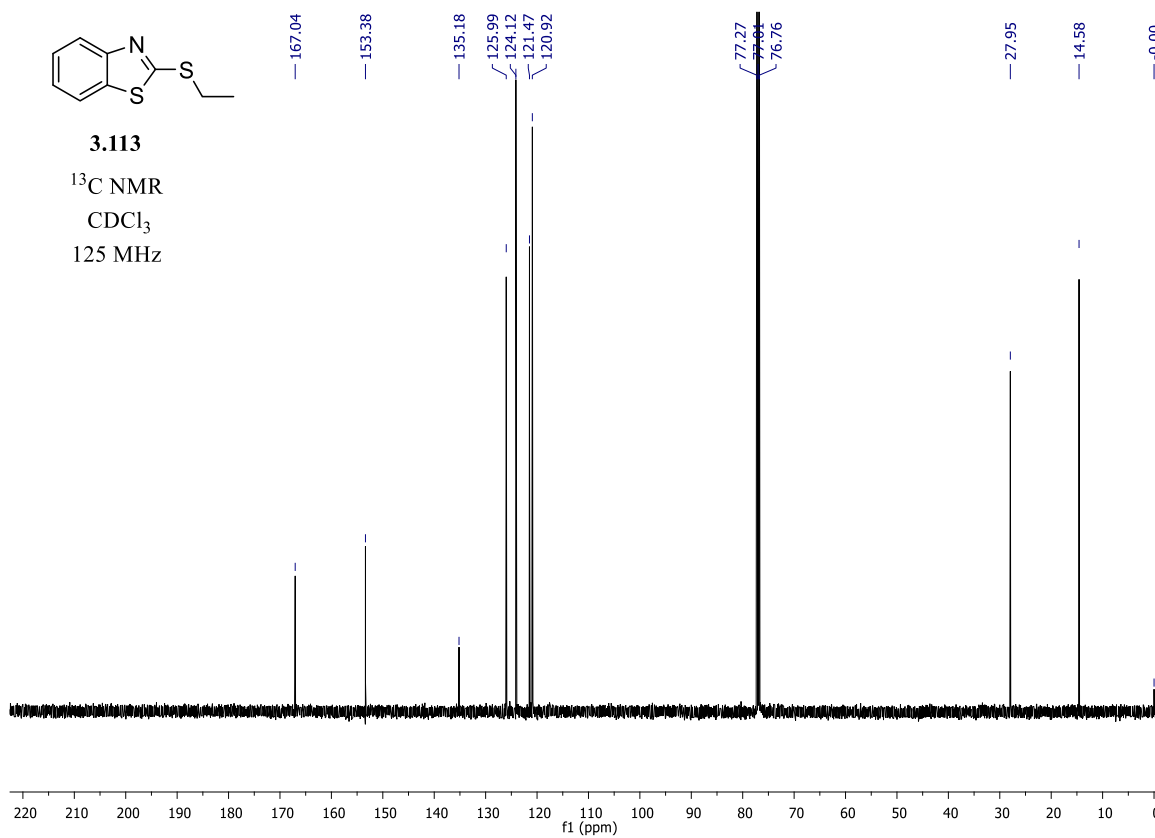


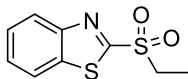
3.113

¹³C NMR

CDCl₃

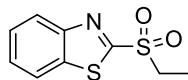
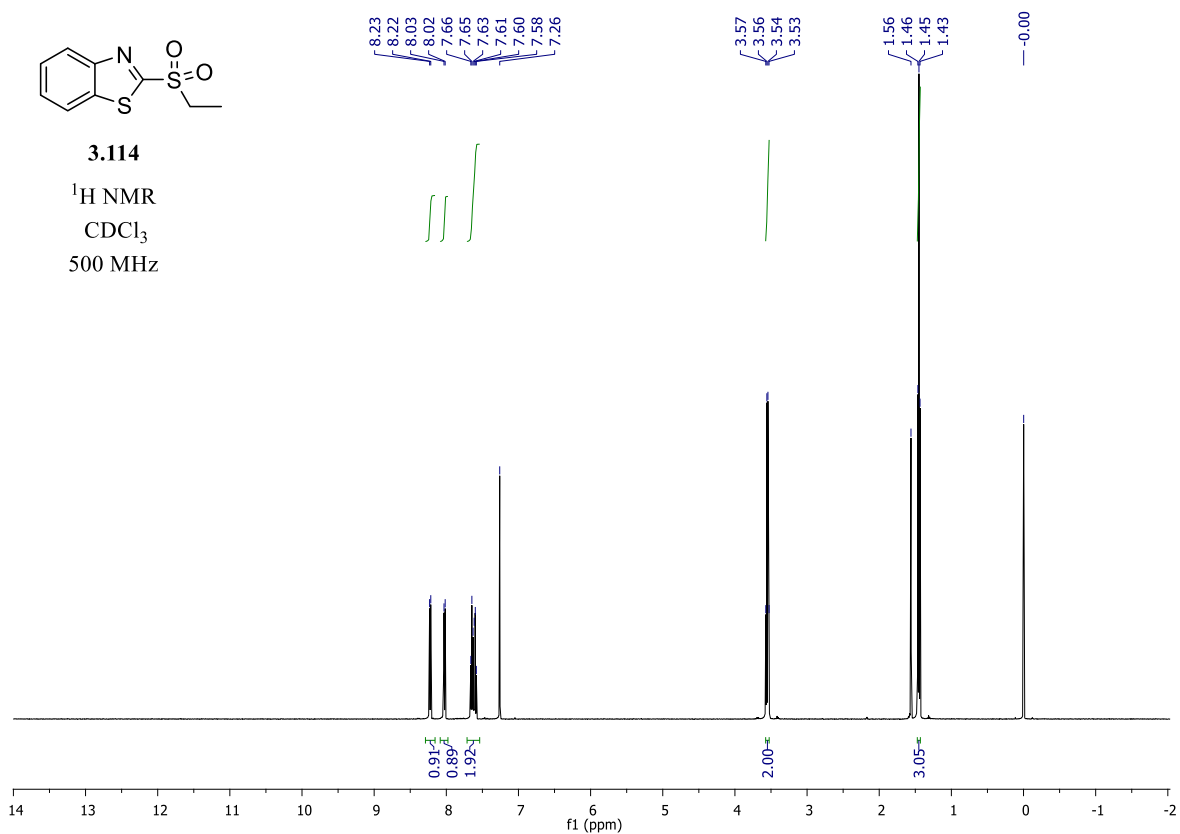
125 MHz





3.114

¹H NMR
CDCl₃
500 MHz



3.114

¹³C NMR
CDCl₃
125 MHz

