The Total Synthesis of Natural Products *via* Cascade Reactions

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Contents

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Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any other university or 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.

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4-5-21

Laura J. Burchill Date

Abbreviations

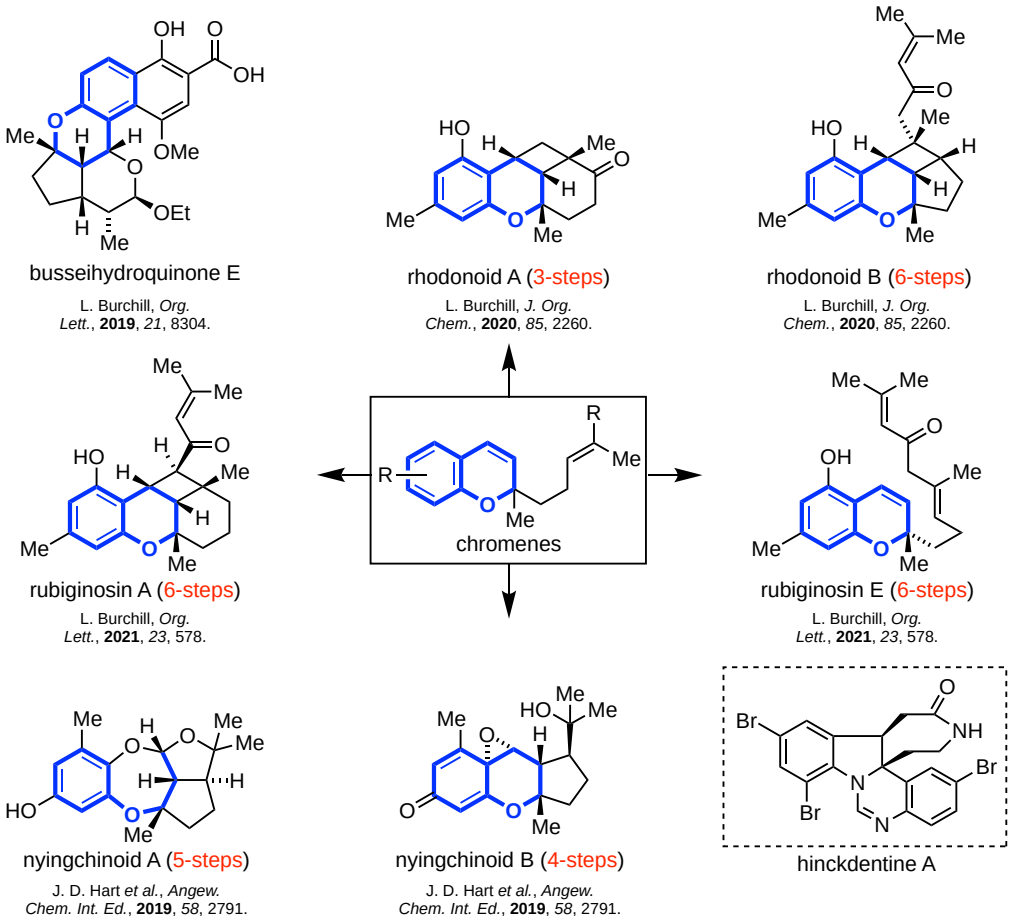
Ac	acetate
AIBN	azobisisobutyronitrile
Am	amyl
aq.	aqueous
atm	atmosphere
ATP	adenosine triphosphate
Bn	benzyl
br	broad
Calcd	calculated
CBL	cannabicyclol
CoA	coenzyme A
d	day(s)
DBU	1,8-diazabicycloundec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
decomp.	decomposition
DFT	density functional theory
DIC	*N,N'*-diisoprropylcarbodiimide
DMA	*N,N*-dimethylacetamide
DMAPP	dimethylallyl pyrophosphate
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DOXP	1-deoxy-xylulose 5-phosphate
DXP	1-deoxy-D-xylulose 5-phosphate
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDDA	ethylenediaminediacetate
ee	enantiomeric excess
equiv.	equivalents
F_d	ferredoxin
FMO	frontier molecular orbital
FPP	farnesyl pyrophosphate
FTIR	Fourier transform infrared spectroscopy

g	gram(s)
GGP	geranylgeranyl pyrophosphate
GPP	geranyl pyrophosphate
G3P	glyceraldehyde-3-phosphate
h	hour(s)
het.	heterocycle
HMB-PP	(*E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate
HOMO	highest occupied molecular orbital
IPP	isopentenyl pyrophosphate
ISC	intersystem crossing
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
LUMO	lowest occupied molecular orbital
MB	methylene blue
m-CPBA	*meta*-chloroperoxybenzoic acid
MEcPP	2-*C*-methyl-D-erythritol-2,4-cyclopyrophosphate
MEP	2-*C*-methylerythritol 4-phosphate
min	minute(s)
MLCT	metal to ligand charge transfer
mol	mole(s)
MP	melting point
MS	molecular sieves
MsCl	mesyl chloride
$NAD(P)^+$	nicotinamide adenine dinucleotide (phosphate)
NBS	*N*-bromosuccinamide
NCS	*N*-chlorosuccinimide
NHC	*N*-heterocyclic carbene
NMO	*N*-methylmorpholine *N*-oxide
NR	no reaction
o-QM	*ortho*-quinone methide
Ox.	oxidation
PDI	perylene diimide

PMB	*p*-methoxybenzyl
p-QM	*para*-quinone methide
Piv	pivaloyl
quant.	quantitative
RB	rose bengal
Red.	reduction
ref.	reference
R_f	retention factor
ROS	reactive oxygen species
RSM	recovered starting material
rt	room temperature
sat.	saturated
SET	single electron transfer
SiO_2	silica gel
taut.	tautomerization
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyltrimethylsilyl
TFA	trifluoracetic acid
TFE	2,2,2-trifluroethanol
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TPAP	tetrapropylammonium perruthenate
TPP	tetraphenyl porphyrin
TS	transition state
wt./ wt.	weight/ weight

Abstract

The discipline of natural product synthesis serves to provide a platform for reaction discovery, the development of unique methodology, elucidation of biochemical pathways and structure conformation. This thesis will explore some bio-inspired cascade reactions towards the synthesis of the busseihydroquinone (chapter two), rhodonoid (chapter three), rubiginosin (chapter four) and nyingchinoid (chapter five) families of natural products, through the synthesis and derivatization of chromenes (**Scheme 1**).[1] Efforts towards the total synthesis of the indole alkaloid (±)-hinckdentine A will also be explored (chapter Six).



Scheme 1 – Bio-inspired Approaches Towards the Total Synthesis of the Busseihydroquinone, Rhodonoid, Rubiginosin, and Nyingchinoid Families of Natural Products

It is hoped that these results will highlight the power of biomimetic cascade reactions in total synthesis and will offer insight into the challenges associated with these natural products.

[1] **For more work featuring the derivatization of chromenes see:** M. A. Coleman, L. Burchill, C. J. Sumby, J. H. George, *Org. Lett.*, 2019, 21, 8776.

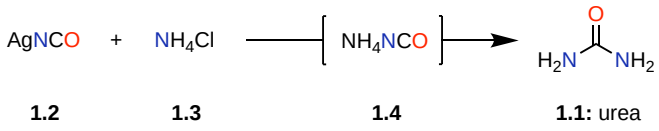
Chapter One – Introduction to Natural Product Synthesis

1.1 Natural Products

At the beginning of the eighteenth century the word 'organic' referred to a substance obtained directly or indirectly from a living entity.[1] It was not until the 1770s that French chemist Antione Lavoisier established the composition of these natural products. Showing through combustion that all vegetable derived substances were composed of carbon, hydrogen and oxygen; while animal derived substances also contained nitrogen, phosphorus and sulfur.[2]

At the time, the idea that all of life's complexities could be explained so succinctly by a composition of only six elements seemed inconceivable. Yet, the simple act of mixing these elements did not spontaneously produce life.[3] In an attempt to explain this, scientists began championing a new belief system "*vitalism*", the idea that all organic substances were produced under the influence of a 'vital force' and regulated by principles different from those of inorganic substances.[4] Consequently, it was thought impossible to prepare any organic substance artificially or synthetically in a laboratory.

This belief went unquestioned until 1828, when German chemist Friedrich Wöhler famously produced urea (**1.1**) from inorganic silver isocyanate **1.2** and inorganic ammonium chloride **1.3** through an ammonium isocyanate intermediate **1.4** (**Scheme 1.1**).[5] Wöhler's synthesis marked a pioneering advancement towards this new field of chemistry, organic chemistry.



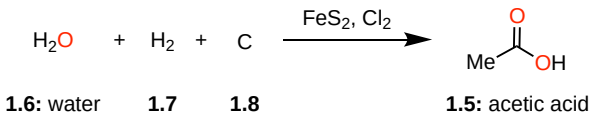
1.2 **1.3** **1.4** **1.1:** urea

Scheme 1.1 – Wöhler's Synthesis of Urea[5]

Despite the structural simplicity of urea (**1.1**) containing only one carbon atom and no carbon-carbon or carbon-hydrogen bonds, this reaction (later named the Wöhler reaction) is the first reported example of natural product synthesis, the art of constructing molecules of nature in the laboratory.[6] At the time, Wöhler's synthesis served to correct the notion of "*vitalism*" showing that the synthesis of organic molecules was not exclusive to nature, and that organic compounds could in fact be synthesized from inorganic substances.

It should be acknowledged that the dissolution of "*vitalism*", a theory that had been championed for many years by many luminaries was destined to be a slow process. Indeed, it would take over 50 years to refute these alchemic ideas within scientific circles.[7] Biologist Louis Pasteur was famous for his scepticism, creating debate in 1857 with rival chemist Justus Von Liebig, arguing that only living organisms were responsible for the process of fermentation.[8] In non-scientific circles today these belief systems are still common, particularly in alternative medicines.[7]

The next significant milestone for the early pioneers of organic chemistry was overcome some 20 years after the Wöhler synthesis in 1845 by another German chemist A. W. Hermann Kolbe, uniting two carbon atoms to synthesize acetic acid (**1.5**).[9] This was done through reaction of water (**1.6**), hydrogen **1.7** and elemental carbon **1.8** in the presence of chlorine and iron disulphide (**Scheme 1.2**). At the time this synthesis was unprecedented, involving the construction of an organic molecule from the simplest of units, the elements themselves.



Scheme 1.2 – Kolbe's Synthesis of Acetic Acid[9]

Naturally, the synthesis of both urea (**1.1**) and acetic acid (**1.5**) were not isolated discoveries but occurred in the midst of a chemical revolution of modern organic chemistry.[10] These days, natural product synthesis is considered the flagship of organic synthesis. In pursuit of synthesizing natural products chemists hope to develop efficient and elegant synthetic routes, pushing chemical boundaries towards targets with higher molecular complexity and showcasing the scope and limitations of chemical synthesis at any given time. However, whether successful or not, greater value often lies in the endeavour of natural product synthesis which provides a platform for reaction discovery and the testing of novel methodology.[11] Additionally, natural product synthesis provides structure confirmation (and often structural revision), develops reactions with controlled stereochemistry, and serves to synthesize compounds without the exhaustive mining of natural supplies.[12] This last point is of particular importance when quantities accessible in nature are infeasible from a pharmaceutical perspective. Moreover, the inherent biological activity of these compounds often makes them good lead targets towards more effective and potent drugs. This was best summarized by Nobel laureate Vladimir Prelog[13] who stated:

"Natural products are the result of three billion years of development of the living world, and they have survived the natural selection process over a long period of evolution. I am convinced they always carry a message, which is our job to decipher"

— Vladimir Prelog, 1975

In fact, studies show that more than one third of all US FDA approved drugs over the past 20 years are derived from or inspired by natural products, and that more than 65% of the developed small-molecule cancer drugs from 1981 – 2019 originated from natural products.[14]

1.2 The Biosynthesis of Natural Products

In the broad sense, natural products can be classified according to two distinct classes; primary metabolites and secondary metabolites.[15] Primary metabolites are chemicals necessary for physiological functions required for the normal growth, development and reproduction of cells. This includes nucleic acids, amino acids (i.e. **1.9, 1.10** and **1.11**), proteins, carbohydrates (i.e. **1.12**), and lipids, as well as urea (**1.1**) and acetic acid (**1.5**) (*vide supra*) (**Figure 1.1**).[16] As primary metabolites are crucial for all living organisms there is often very little structural diversity in these metabolites, even between different genus and kingdoms.

Conversely, secondary metabolites are chemicals not directly involved in these critical processes. Instead, they often possess cytotoxic properties which have been optimized through evolution as agents against competing organisms. As a result, secondary metabolites tend to be more structurally diverse, possessing unique and complex molecular architectures with interesting pharmacological properties.[17] It is for this reason that secondary metabolites such as alkaloids (i.e. **1.13**), terpenoids (i.e. **1.14**), flavonoids, glycosides and polyketides (i.e. **1.15**) remain at the forefront of natural product synthesis (**Figure 1.1**).

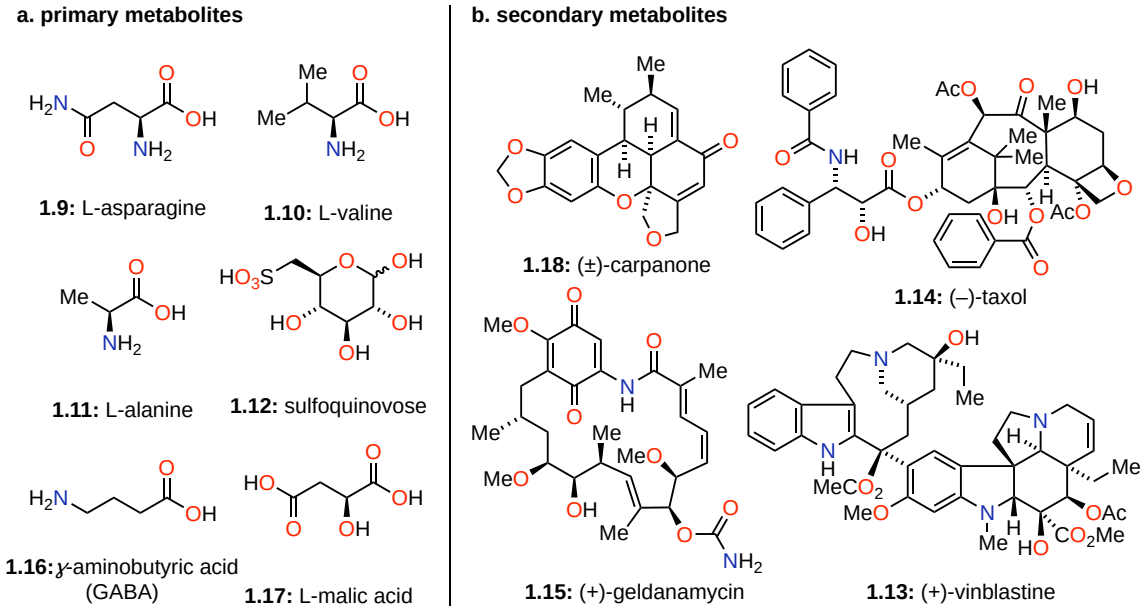
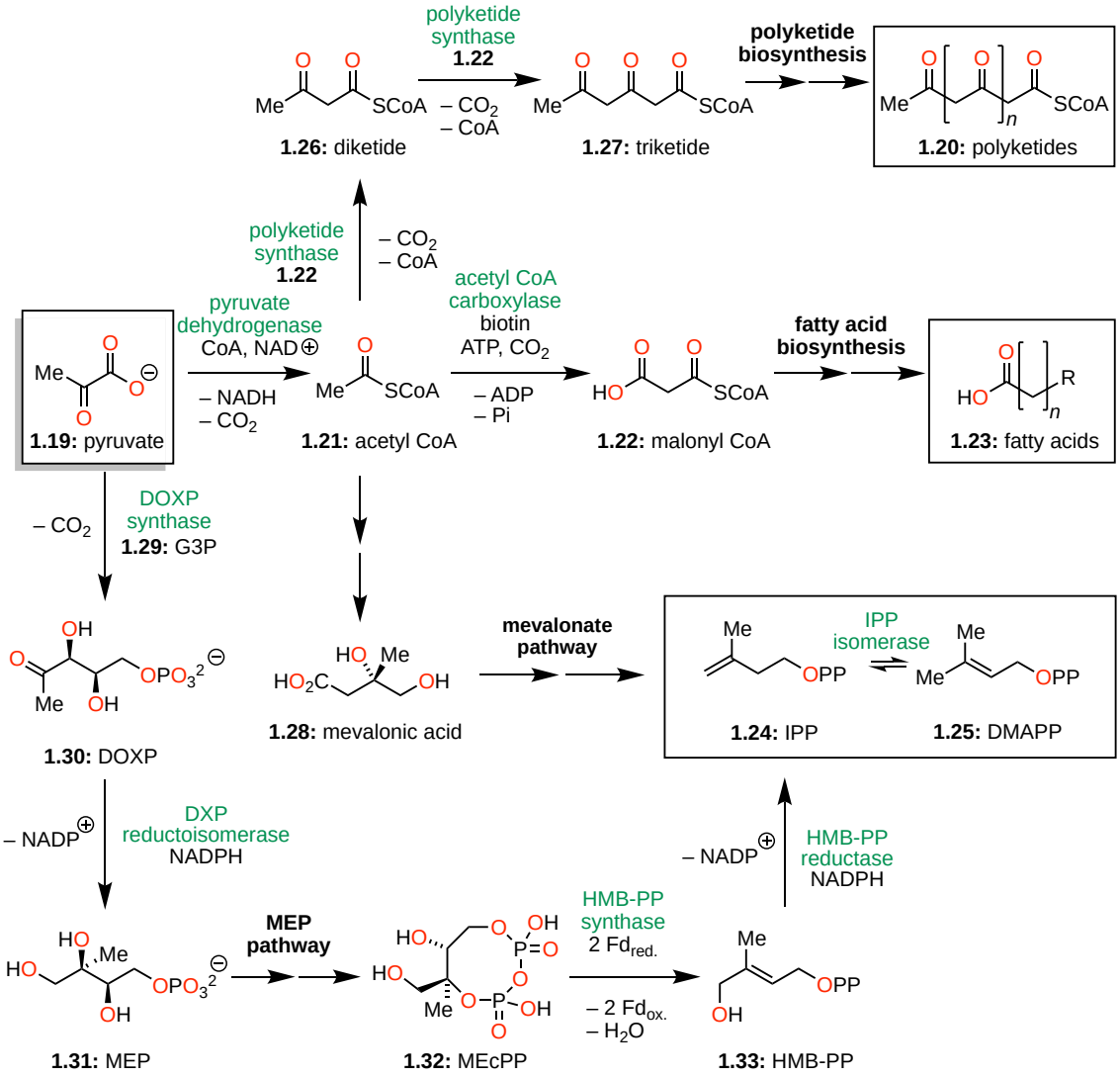


Figure 1.1 – Examples of Primary (a) and Secondary Metabolites (b)[15 - 17]

Evidently it follows that the same compounds responsible for primary metabolism, are also responsible for the production of secondary metabolites. One example of this includes pyruvate (**1.19**), which is not only a fundamental molecule in primary metabolism (within the citric acid cycle) but is also a direct precursor towards various secondary metabolites.[18, 19] This includes polyketides **1.20** formed from repeat condensation/ decarboxylation reactions of acetyl CoA (**1.21**) and malonyl CoA (**1.22**) in the presence of a polyketide synthase enzyme (**Scheme 1.3**). Fatty acids **1.23**, synthesized through an acyl CoA carboxylase enzyme, and terpenes derived from isopentenyl pyrophosphate (IPP) (**1.24**) and dimethylallyl pyrophosphate (DMAPP) units (**1.25**). Interestingly, terpene biosynthesis occurs *via* two distinct pathways: the mevalonate pathway and the MEP (2-*C*-methylerythritol 4-phosphate) pathway.[20, 21] The mevalonate pathway is generally used by most eukaryotes (including archaea and humans), while the MEP pathway is more common in eubacteria. Naturally there are clear exemptions to this rule, for example both pathways are found to occur in plants with the MEP pathway occurring in plastids and the mevalonate pathway occurring in the cytosol of the cell.



Scheme 1.3 – The Biosynthesis of Various Secondary Metabolites from Pyruvate[20, 21]

Polyketide units act as powerful compounds towards the divergent biosynthesis of a range of natural products through cyclization to give phenolic natural products (i.e. **1.34** – **1.37**), as well as through reduction and elimination reactions giving rise to a wide range of functional groups such as alcohols, ketones, cyclic ethers (i.e. **1.38**), alkenes and alkanes (**Figure 1.2**).[22]

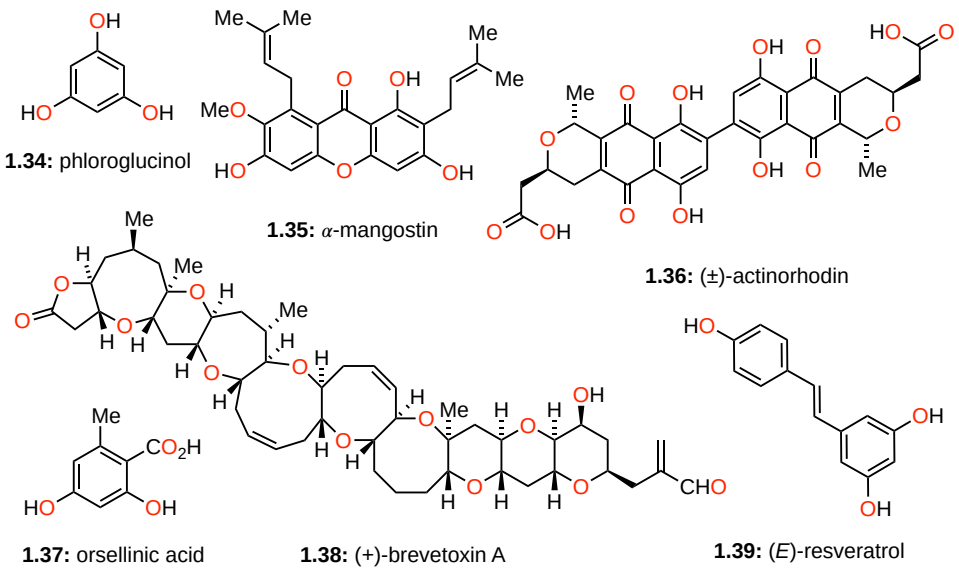
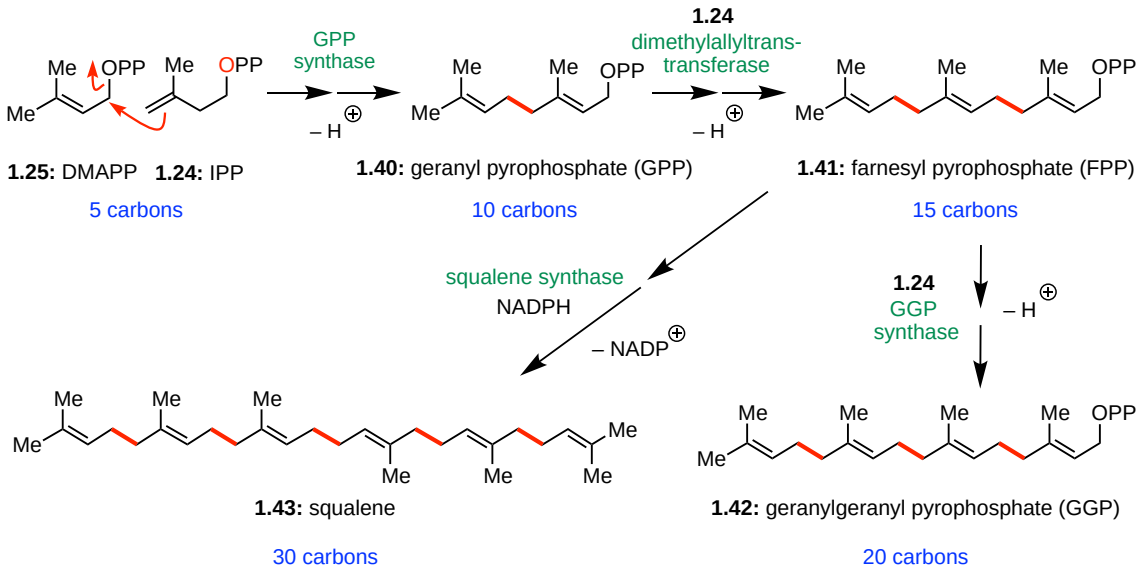


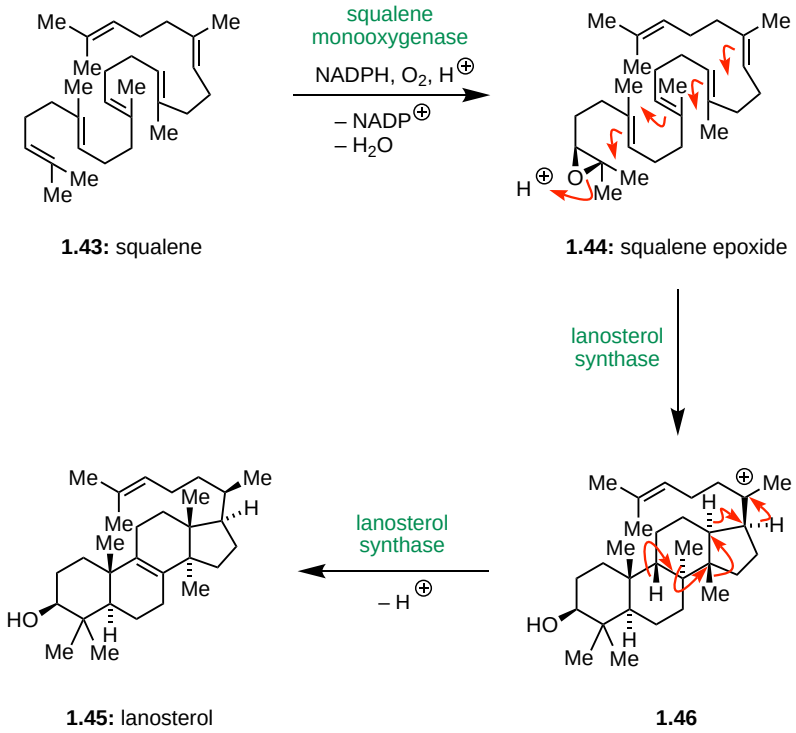
Figure 1.2 – Examples of Polyketide Derived Natural Products[22]

Additionally, terpenes derived from IPP (**1.24**) and DMAPP (**1.25**) are formed *via* nucleophilic attack of the IPP terminal alkene toward the allylic carbon of DMAPP.[23] Formation of an alkene from the resulting carbocation occurs to give geranyl pyrophosphate (GPP) (**1.40**) (**Scheme 1.4**). This compound can undergo hydrolysis to give geraniol or can undergo further electrophilic reactions to give farnesyl pyrophosphate (FPP) (**1.41**), geranylgeranyl pyrophosphate (GGP) (**1.42**), and squalene (**1.43**).[24] As the carbon skeleton is derived from both regularly and irregularly linked isoprene units, the resulting terpenes are only ever a factor of 5 carbon units. This is known as the biogenetic isoprene C_5 rule and was first described by Leopold Ružička in 1953.[25]



Scheme 1.4 – The Biosynthesis of Various Terpenes from IPP and DMAPP[24]

Terpenes are not only responsible for many of the fragrances abundant in plants, but they also play a crucial role in the biosynthesis of more complex natural products such as steroids.[26] This occurs *via* oxidation of squalene (**1.43**) to squalene epoxide (**1.44**), followed by a polyene cyclization and a series of Wagner-Meerwein 1,2-shifts to afford lanosterol (**1.45**) (**Scheme 1.5**).[27] Lanosterol itself is the direct biosynthetic precursor to all animal and fungal steroids.



1.43: squalene

1.44: squalene epoxide

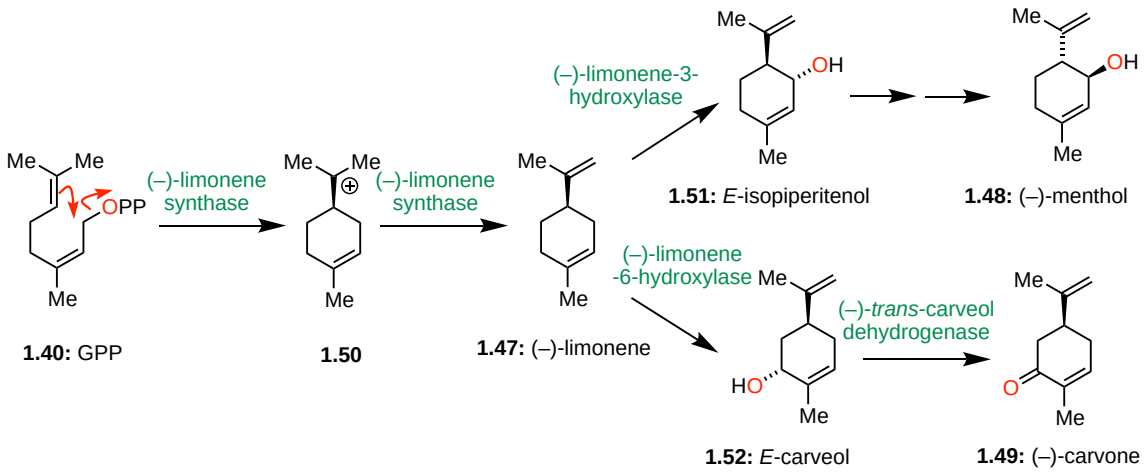
1.45: lanosterol

1.46

Scheme 1.5 – The Biosynthesis of Lanosterol from Squalene[27]

Steroids have crucial roles in cell metabolism as hormone signalling molecules within the endocrine system, and as important components of the plasma membrane responsible for the control of membrane fluidity.[28] Investigations into the biological activity of these compounds first began in the early 1930s when it was found that extracts of adrenocortical tissue could counteract acute adrenal failure.[29] Since then, steroids have been widely used in the pharmaceutical industry to treat a range of diseases such as anaemia,[30] asthma, [31] brain tumours, [32] breast cancer, [33] osteoporosis[34] and psoriasis to name a few.[35] Indeed, the history behind steroid biosynthesis is quite intriguing and will be revisited later in this chapter (*vide infra*).

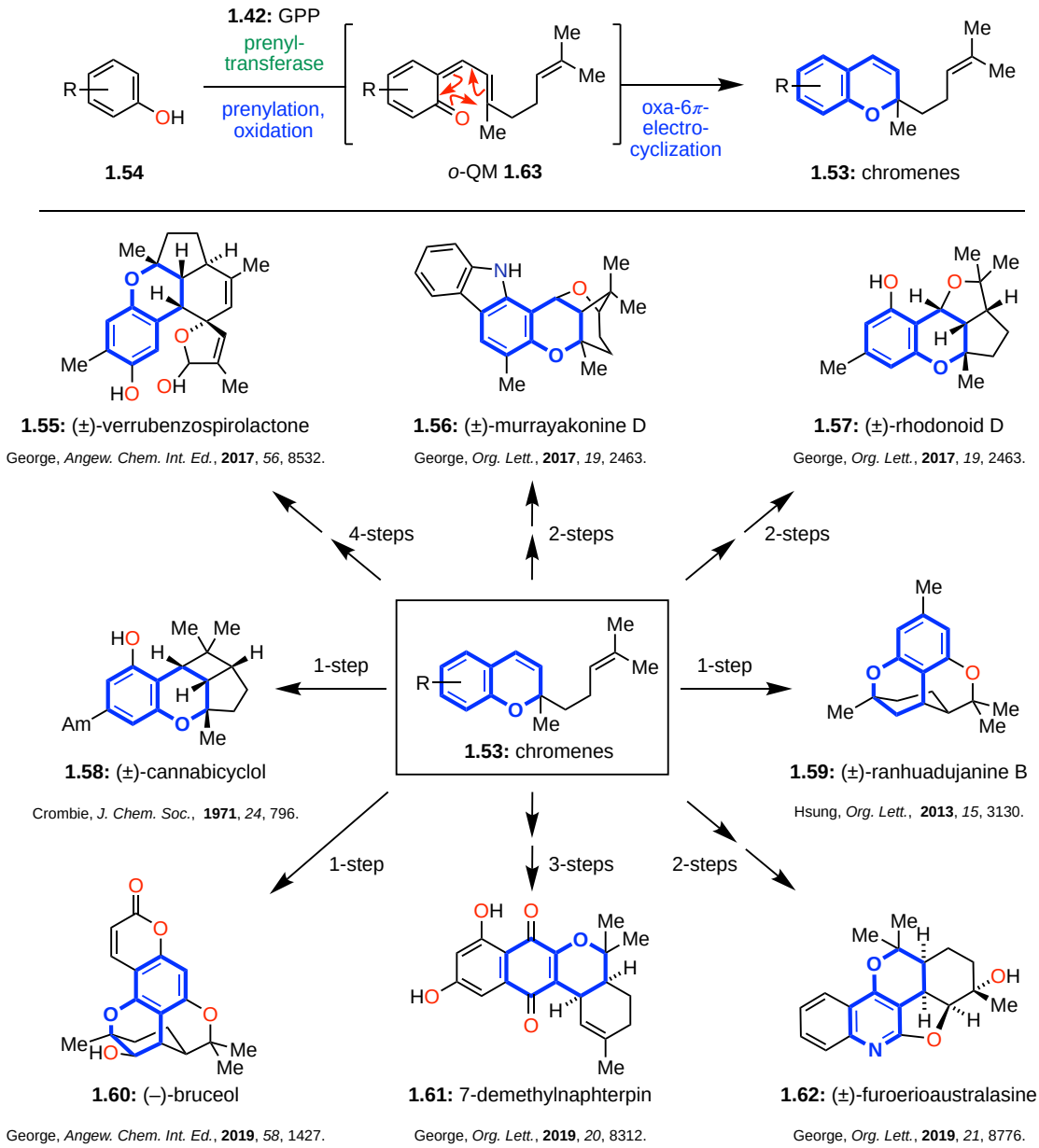
Linear terpenes can also undergo electrophilic cyclization reactions to give compounds such as (–)-limonene (**1.47**). These cyclic terpenes can then undergo oxidation in the presence of various cytochrome P450 enzymes to give terpenoid natural products such as (–)-menthol (**1.48**) and (–)-carvone (**1.49**) (**Scheme 1.6**).[36, 37] Terpenoids are derived from terpenes typically through addition of oxygen and often through cyclization reactions. Not only are they a major contributor to the chiral pool,[38] they are also a diverse class of natural products in their own right. In fact, it is estimated that around 60% of natural products are terpenoids.[39]



1.40: GPP **1.50** **1.47:** (–)-limonene **1.51:** *E*-isopiperitenol **1.48:** (–)-menthol **1.52:** *E*-carveol **1.49:** (–)-carvone

Scheme 1.6 – The Biosynthesis of (–)-Menthol and (–)-Carvone[36, 37]

Terpenoids can be further derivatized to give natural products with mixed biosynthetic origins known as meroterpenoids. One notable example includes the biosynthesis of chromenes **1.53** derived from prenylation, oxidation and electrocyclization reactions of polyketide derived phenols **1.54** (**Scheme 1.7**).[40] Chromenes can then undergo further reactions such as allylic oxidations, cycloadditions and epoxidations to give more complex natural products (i.e. **1.55** – **1.62**).[41 - 47] This field was pioneered by British chemist Leslie Crombie, whose work will be the basis of much of this thesis (*vide infra*).[48] Although transformations involving chromenes in nature occur through enzyme facilitated pathways, these reactions are often predisposed and can be mimicked synthetically in the laboratory through the use of the appropriate reaction conditions. This approach to total synthesis is known as biomimetic chemistry.[49, 50]

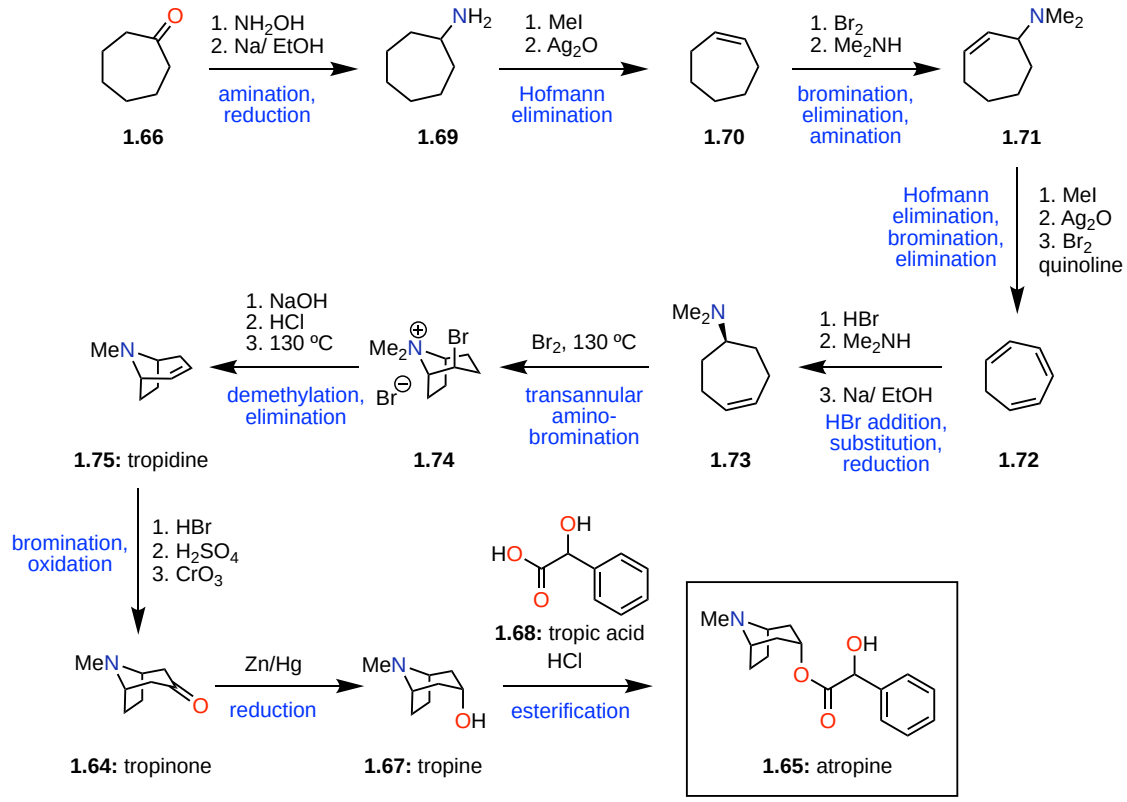


Scheme 1.7 – Natural Products Synthesized from Chromenes[41 - 47]

1.3 The History of Biomimetic Synthesis

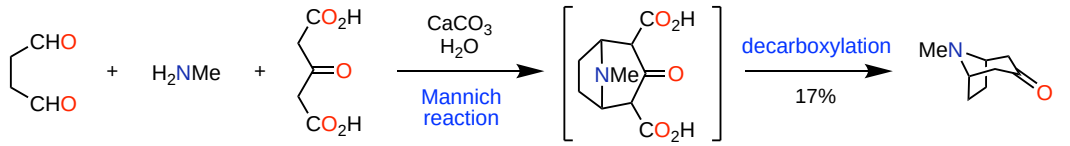
The concept of biomimetic synthesis was first proposed by British Nobel laureate Sir Robert Robinson in 1917 referring to the execution of a series of reactions designed to parallel or mimic a proposed biosynthesis.[51] However the term was not coined until some 56 years later in 1973 by Ronald Breslow.[49] Robinson is also credited with achieving the earliest reported biomimetic total synthesis involving the alkaloid tropinone (**1.64**), a synthetic precursor to the drug atropine (**1.65**) known commercially today as Atropen.[51]

Curiously, atropine itself is a compound with a rich history. It is one of the key bioactive compounds found in the *Solanaceae* family of plants including *Atropa belladonna* (deadly nightshade) and *Mandragora officinarum* (mandrake), plants famous for their medicinal and hallucinogenic effects.[52] It was first isolated in 1831 by pharmacist Heinrich F. G. Mein,[53] and later synthesized by chemist and Nobel laureate Richard Willstätter in 1903.[54] It is important to recognize that although Willstätter synthesis was pivotal in providing structure confirmation at the time, it was a convoluted synthesis requiring 19-steps for the conversion of cycloheptanone **1.66** to tropinone (**1.64**) and had an overall yield of 0.8% (**Scheme 1.8**). Reduction of tropinone with zinc amalgam to the alcohol tropine (**1.67**), followed by esterification with tropic acid (**1.68**) then afforded atropine (**1.65**).



Scheme 1.8 – Willstätter's Total Synthesis of Atropine[54]

In 1914 at the start of World War I there was a great need for large quantities of atropine due to its use as an antidote to counter the effects of G-Series nerve agent being used in Germany at the time.[7] It was then that Robinson developed a one-pot synthesis of tropinone synthesized through a double Mannich reaction of succinaldehyde (**1.76**), methylamine (**1.77**), and acetonedicarboxylic acid (**1.78**) (**Scheme 1.9**).[51] Although the initial yield of 17% was poor, subsequent improvements exceeded 90%.[55]

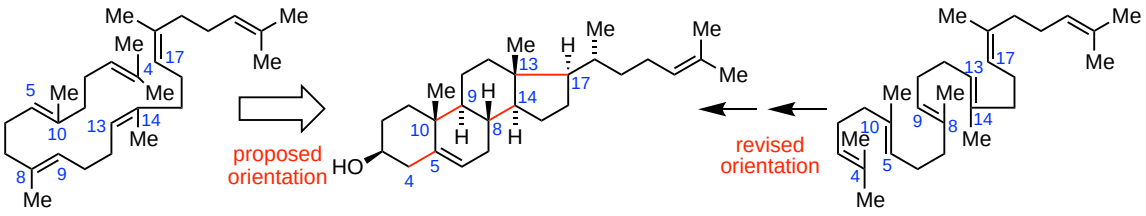


1.76 **1.77** **1.78** **1.79** **1.64:** tropinone

Scheme 1.9 – Robinson's Biomimetic Synthesis of Tropinone[51]

Robinson's total synthesis of tropinone represents a remarkable achievement in organic synthesis, being ahead of its time in terms of retrosynthetic logic and being many years before the biosynthesis was elucidated.[56] What is unique about this synthesis is that it not only serves as a reminder of the importance of biomimetic chemistry in the development of complex molecule synthesis, but it also highlights the direct application of total synthesis to serve the needs of the general public.

Later that year, Robinson went on to propose that squalene (**1.43**) *could* be a possible precursor to cholesterol (**1.80**), and in 1934 proposed a concept for this transformation (**Scheme 1.10**).[57, 58] Although Robinson's initial assignment was incorrect, work in this area was continued in 1945 by Robert B. Woodward and Konrad E. Bloch using isotopic labelling experiments to outline the pathway from squalene to cholesterol, this time featuring a revised orientation of squalene.[59]



1.43: squalene
Robinson, *Chem. Ind.*, **1934**, *53*, 1062.

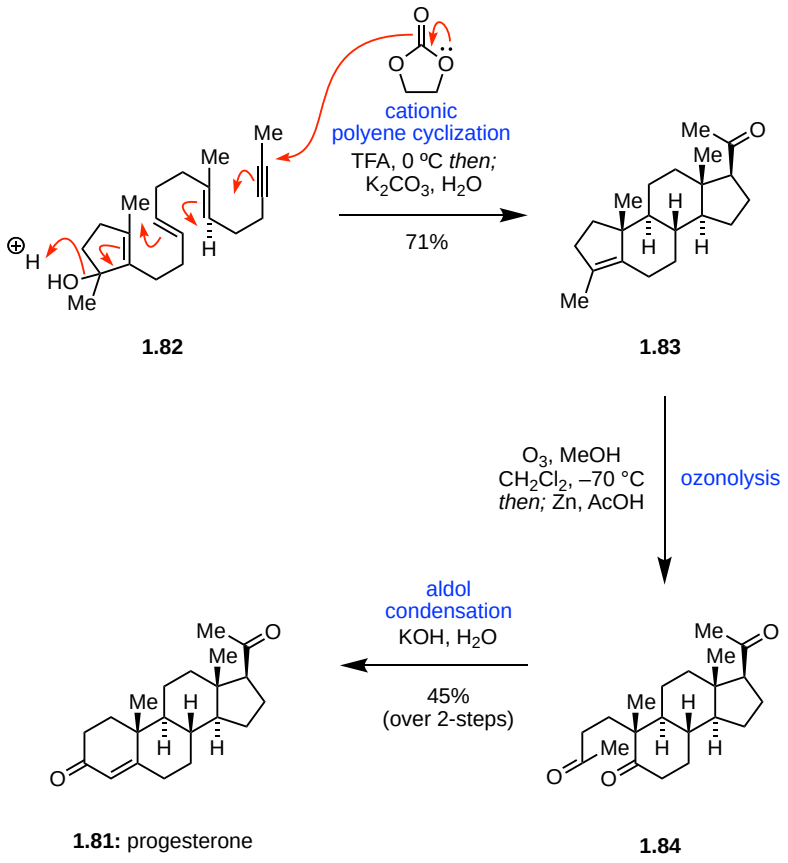
1.80: cholesterol

1.43: squalene
Woodward, *J. Biol. Chem.*, **1953**, *200*, 135.

Scheme 1.10 – Robinson and Woodward's Proposal for Cholesterol Biosynthesis[57 – 59]

Further work in the 1950s by pioneers Sir Derek H. R. Barton, Gilbert Stork and Albert Eschenmoser then led to a new field of chemistry, polyene cyclization and the development of the Stork-Eschenmoser hypothesis.[60] This hypothesis proposed that the biosynthesis of cholesterol was occurring through a cationic cyclization pathway from the linear polyene squalene to the tetracyclic product lanosterol (**1.45**).

It was not until 1962 that Eugene Tamelen was the first to identify squalene epoxide (**1.44**) as the precursor in the biosynthesis of cholesterol (*vide supra*).[27] Extensive studies by William S. Johnson later investigated the requirements and constraints of these polyene cyclizations. Specifically, how different chemical reagents such as Lewis acids and Brønsted acids could be used to aid the stabilization of these proposed cationic carbenium intermediates, that would ordinarily be stabilized under enzymatic control. One example includes the total synthesis of progesterone (**1.81**) synthesized through a bio-inspired cationic polyene cyclization of **1.82** (**Scheme 1.11**).[61] This polyene cyclization occurs through an acid promoted elimination of water and a tandem 1,5-diene and alkyne cyclization to give **1.83**. Ozonolysis then affords the triketone **1.84**, and aldol condensation gives progesterone (**1.81**) in 45% over 2-steps.



Scheme 1.11 – Johnson's Bio-inspired Synthesis of progesterone

Of course, biomimetic synthesis is somewhat limited favouring reactions in nature that are not under enzymatic control. This subject was explored by Clayton Heathcock: [62]

"The basic assumption of this approach is that nature is the quintessential process development chemist. We think that the molecular frameworks of most natural products arise by intrinsically

favourable chemical pathways – favourable enough that the skeleton could have arisen by a non-enzymatic reaction in the primitive organism. If a molecule produced in this purely chemical manner was beneficial to the organism, enzymes would have evolved to facilitate the production of this useful material"

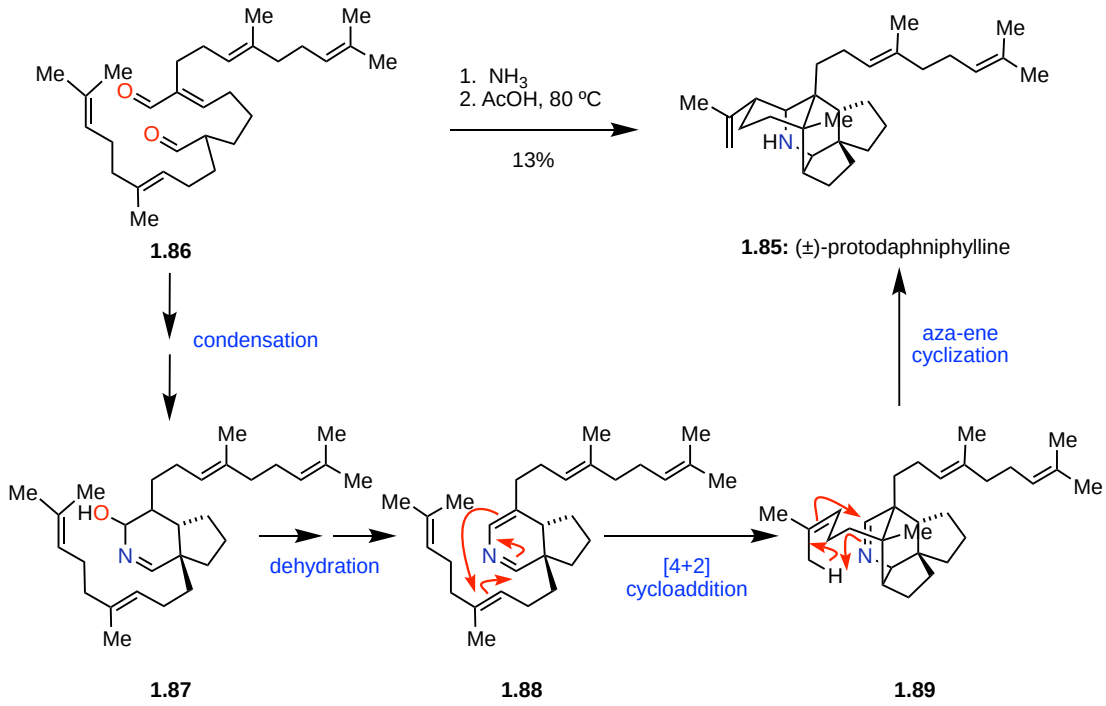
— Clayton Heathcock, 1996

Heathcock highlights the obvious bias for biomimetic chemistry to favour reactions under non-enzymatic control and suggests that the production of spontaneously arising compounds which confer a benefit to an organism may evolve to be synthesized under enzymatic control. Implying that most biological reaction pathways have a degree of predisposed reactivity. Provided that the suitable reagents and conditions are identified it is possible that reactions occurring in nature under enzymatic control can be mimicked synthetically in a laboratory without the need for enzymes.

1.4 Reaction Cascades in Biomimetic Synthesis

A cascade reaction, also known as a tandem or domino reaction, comprises of two or more consecutive reactions that occur spontaneously with each sequence being reliant on the previous step.[63] Not only does this allow for a large number of transformations to occur in a single step, increasing efficiency and decreasing the purifications required, but it also affords the ability to install molecular complexity in a selective manner.

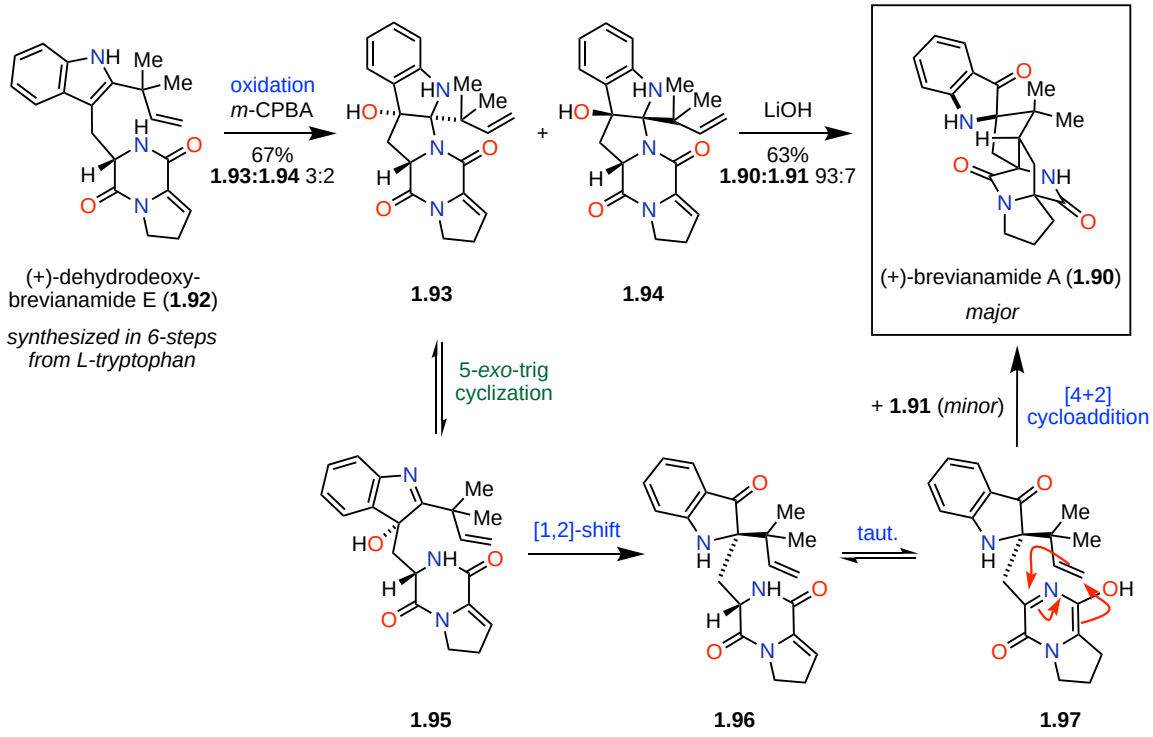
One example includes Heathcock's total synthesis of (±)-protodaphniphylline (**1.85**) from the squalene derived acyclic dialdehyde **1.86** (**Scheme 1.12**).[64] This cascade is proposed to occur through condensation of ammonia with **1.86** to afford the α-hydroxy imine **1.87**. Further dehydration then gives the corresponding 2,3-dihydropyridine **1.88** intermediate, which undergoes an acid catalyzed [4+2] cycloaddition to give imine **1.89**. Finally, a concomitant aza-ene cyclization then affords (±)-protodaphniphylline (**1.85**) in 13% as a single diastereomer.



Scheme 1.12 – Heathcock's Biomimetic Total Synthesis of (±)-Protodaphniphylline[64]

This impressive reaction cascade results in the formation of 7 new bonds and 5 new rings in a single step! Later work on this sequence, through substitution of ammonia with methyl amine gave an improved yield of 65% and efforts towards a "diversity orientated synthesis" have led to the synthesis of a wide range of *daphniphyllum* alkaloid natural products.[65]

Another more recent example of the use of cascade reactions in biomimetic synthesis includes the total synthesis of (+)-brevianamide A and B (**1.90** and **1.91**) through the biosynthetic precursor (+)-dehdydroxy-brevanamide E (**1.92**).[66] In this sequence (+)-dehdydroxy-brevanamide E is oxidized in the presence of *m*-CPBA to give intermediates **1.93** and **1.94** (**Scheme 1.13**). Further reaction in the presence of LiOH then mediates the key one-pot reaction cascade, involving a 5-*exo*-trig ring opening, [1,2]-shift and a [4+2] cycloaddition of to afford (+)-brevianamide A (*as the major product*) alongside (+)-brevianamide B (*minor product, not shown*) in a combined yield of 63%. This work by the Lawrence group, highlights how cascade reactions in biomimetic synthesis can be used to clarify biosynthetic pathways.



Scheme 1.13 – Biomimetic Synthesis of (+)-Brevianamide A and B[66]

1.5 Dearomatization Approaches to Biomimetic Chemistry

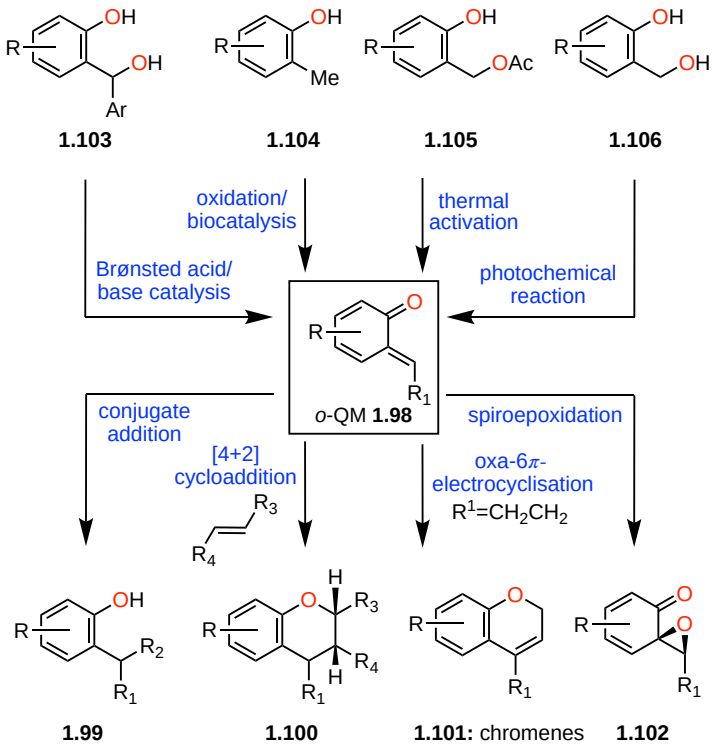
One approach towards initiating cascade reactions is through dearomatization. Dearomatization reactions are organic reactions involving the loss of aromaticity in arenes. Due to the high stability of aromatic structures and their prevalence in nature, once dearomatized the formation of reactive transient intermediates such *ortho*- and *para*- quinone methides (*o*-QMs and *p*-QMs) are then primed to undergo further reaction cascades.[67]

Furthermore, *o*- and *p*-QMs have been shown to play important roles in the biosynthesis of many complex natural products.[68] Recent work by Alison R. H. Narayan's group in this area has extended to the use of biocatalysts in the dearomatization of resorcinol type phenols.[69] In simple terms, this involves the use of enzymes to perform chemical transformations that are not native to the original substrate.

A variety of other methods to induce dearomatization also exist. This includes thermal dearomatization,[70] reduction (through formal addition of one or more molecules of H_2 *e.g. Birch reduction*),[71] oxidation (*via* organic oxidants such as hypervalent iodine, electrochemical oxidation or *via* transition metal oxidants),[72] photochemical dearomatization,[73] transition metal induced

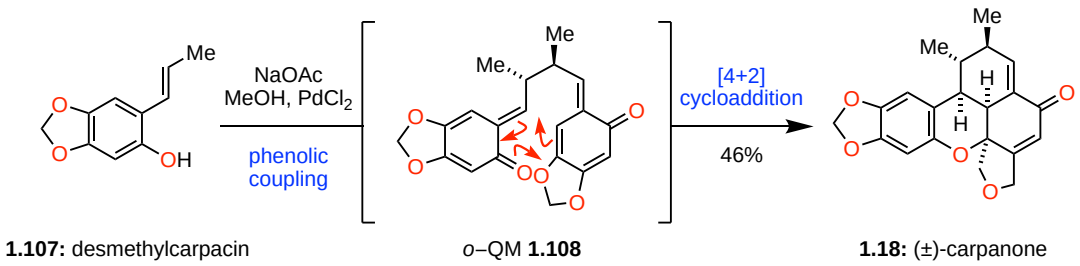
dearomatization (such as Büchner ring expansions),[74] Brønsted catalyzed dearomatization and alkylative dearomatization (**Scheme 1.14**).[75]

After dearomatization has occurred, the corresponding *o*- and *p*-QMs (i.e. **1.98**) are then able to provide direct access to a range of unique transformations. Most commonly this includes conjugate additions (i.e. **1.99**), [4+2] cycloadditions (i.e. **1.100**) and oxa-6π-electrocyclizations which result in the formation of (2H)-chromenes (i.e. **1.101**). More recently, spiroepoxidations (i.e. **1.102**) have become an increasingly popular strategy in biomimetic chemistry, and will be explored later in this thesis (chapter Five, *vide infra*).[76]



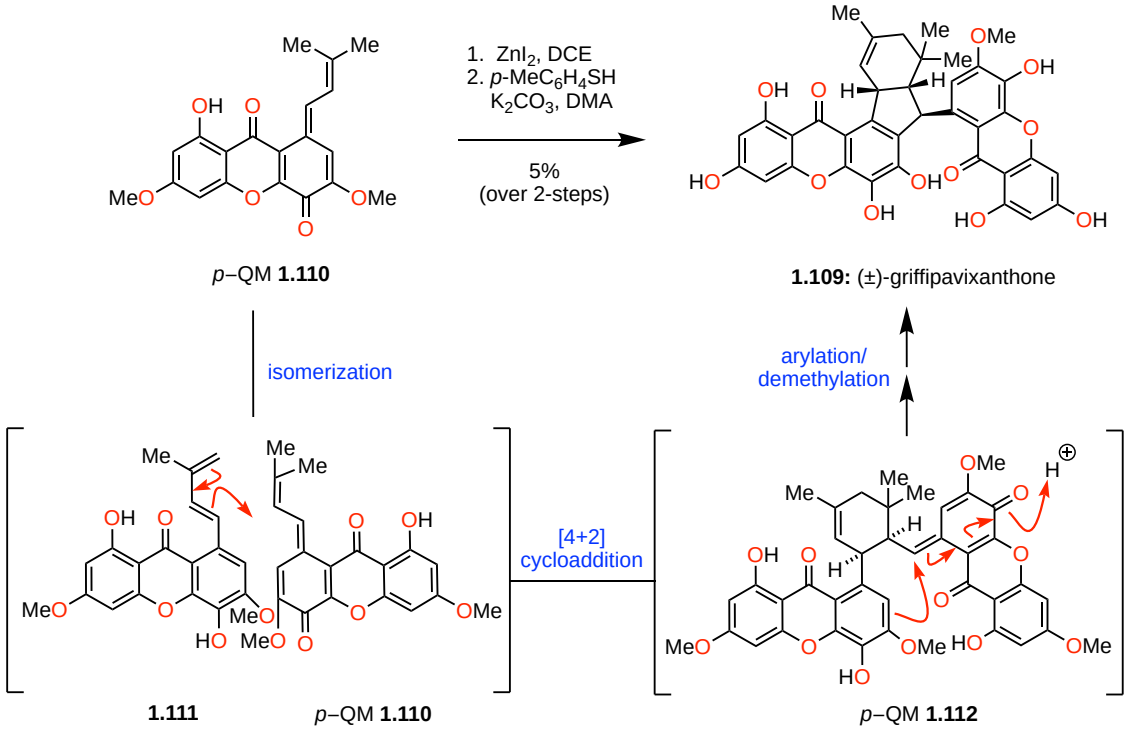
Scheme 1.14 – Methods for the Generation and Derivatization of *o*-QMs[76]

Arguably one of the most notable examples of biomimetic total synthesis through an *o*-QM includes Chapman's biomimetic synthesis of (±)-carpanone (**1.18**) (**Scheme 1.15**).[77] First published in 1971, this sequence involves phenolic coupling of sesamol derived desmethylcarpacin **1.107** to afford the corresponding *o*-QM **1.108**. A subsequent [4+2] cycloaddition then reveals (±)-carpanone (**1.18**) in 46%, forming 2 new rings and 5 new stereocentres in one step!



Scheme 1.15 – Chapman's Biomimetic Synthesis of (±)-Carpanone[77]

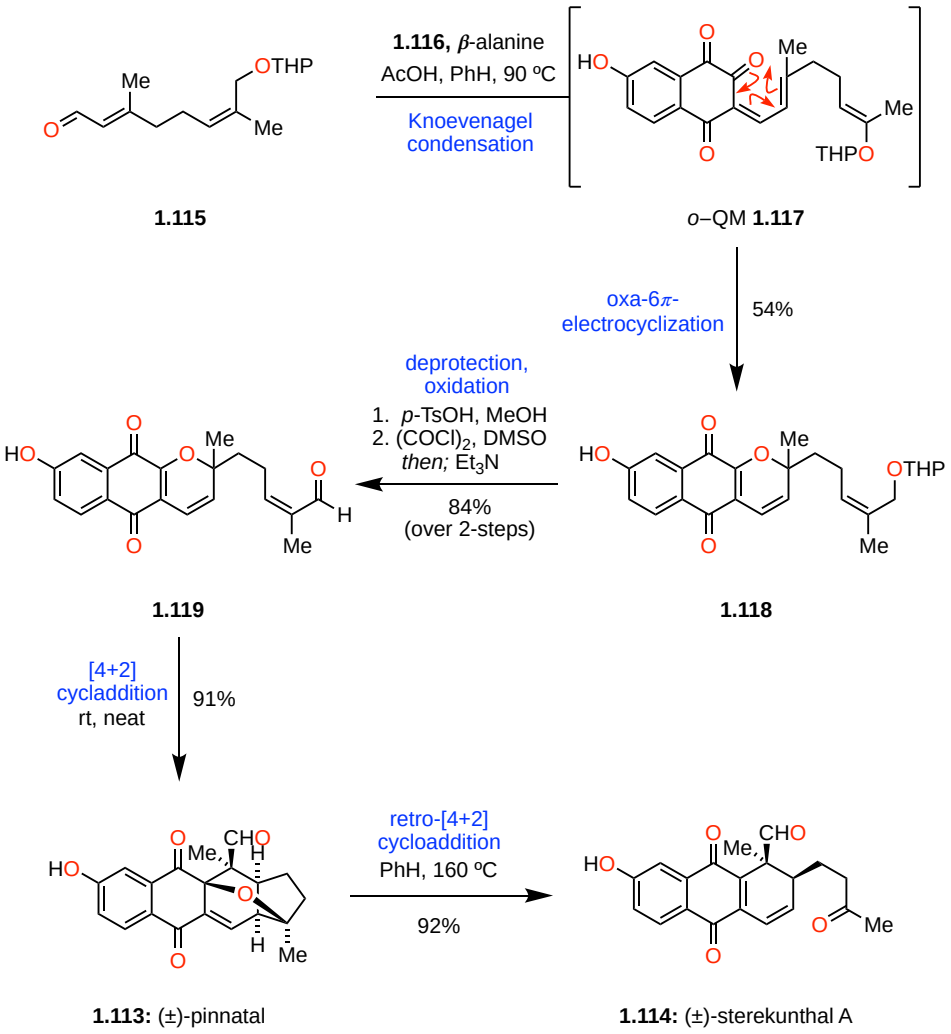
Additionally, *p*-QMs have also been used extensively in biomimetic dimerization reactions. This includes the first reported total synthesis of (±)-griffipavixanthone (**1.109**) by John Porco's group (**Scheme 1.16**).[78] In this example, a readily accessible vinyl *p*-QM xanthone based monomer **1.110** underwent a ZnI_2 mediated [4+2] cycloaddition between an *in situ* generated diene **1.111**. Further arylation of the resulting *p*-QM **1.112** and finally demethylation then gave (±)-griffipavixanthone.



Scheme 1.16 – Reichl's Biomimetic Synthesis of (±)-Griffipavixanthone[78]

Despite this reaction being initially poor yielding (only 5% over 2-steps), further modification towards an asymmetric synthesis using a chiral phosphoric acid led to an improved yield of 25%, with remarkable enantioselectivity of 99% ee.[79]

Of course, *o*- and *p*-QMs aren't only restricted to [4+2] cycloadditions but can undergo a variety of transformations. Perhaps one of the most common is the reaction of *o*-QMs to undergo oxa-6π-electrocyclizations resulting in the formation of chromenes **1.101** (*vide supra*). This approach was emphasised in Malerich and Trauner's total synthesis of (±)-pinnatal (**1.113**) and (±)-sterekunthal A (**1.114**) (**Scheme 1.17**).[80] In this sequence Knoevenagel condensation of aldehyde **1.115** with the hydroxynapthoquinone **1.116** afforded the 1,2-dicarbonyl **1.117**. The corresponding oxa-6π-electrocyclization reaction then provided the THP protected chromene **1.118**. Acidic cleavage and oxidation gave aldehyde **1.119**. Interestingly, but perhaps not unsurprisingly **1.119** reacted spontaneously at room temperature to afford (±)-pinnatal (**1.113**) in 91%. Heating **1.113** in benzene then gave the co-isolated natural product (±)-sterekunthal A (**1.114**) *via* a retro Diels-Alder. In this sequence it is the synthesis of the functionalized aldehyde **1.119** that allows quick access to **1.113** and **1.114**. This concept of using functionalized aldehydes in chromenylation reactions with be explored later in chapter four (*vide infra*).



Scheme 1.17 – Malerich and Trauner's Total Synthesis of (±)-pinnatal and (±)-sterekunthal A[80]

These syntheses not only showcase how the reactivity of dearomatized structures through *o*- and *p*-QMs can enable unique transformations, but also highlight the importance of biosynthetic speculation. Through the consideration of biosynthetic routes with the help of co-isolated natural products, it becomes easier to facilitate the divergent synthesis of whole families of natural products. Furthermore, biosynthetic speculation can also assist in the case of natural product misassignment.

1.6 Bio-Inspired Structural Revisions of Natural Products

By the end of the 19th century, structural determination of compounds was considered a laborious task often requiring years of work. Efforts to identify molecular structures were focused exclusively through chemical synthesis by means of degradation and derivatization studies, with specific focus on the identification of functional groups.[81]

Notable examples include some of the work of Richard Willstätter who determined the structure of a variety of tropane alkaloids including atropine (**1.65**), hyoscyamine, scopolamine, calystegine and cocaine (*vide supra*).[54] He also went on to research the chemical composition of chlorophyll, identifying two major types of chlorophyll (known today as chlorophyll A and chlorophyll B).[82] Willstätter determined their formulae correctly as $C_{55}H_{72}O_5N_4Mg$ and $C_{55}H_{70}O_6N_4Mg$ respectively and demonstrated that both molecules contained four pyrrole rings, plus a carboxyl group esterified with a long chain alcohol phytol. While the complete structures of chlorophyll still eluded him, Willstätter was awarded the Nobel Prize in 1915 for his work.[83] In fact, it was not until 40 years later that R. B. Woodward reported the first total synthesis of these chlorophylls.[84]

In the 1930s X-ray crystallography was developed, and quickly became considered the cutting-edge standard for structural elucidation.[81] Of course, X-ray crystallography is somewhat limited requiring the correct properties and sufficient material for crystallization. However, in the late 1950s NMR spectroscopy established itself as an indispensable tool for structural elucidation.[81] With all these advancements in analytical characterisation techniques, these days structural elucidation is considered standard. This was best sumized by Koji Nakanishi: [85]

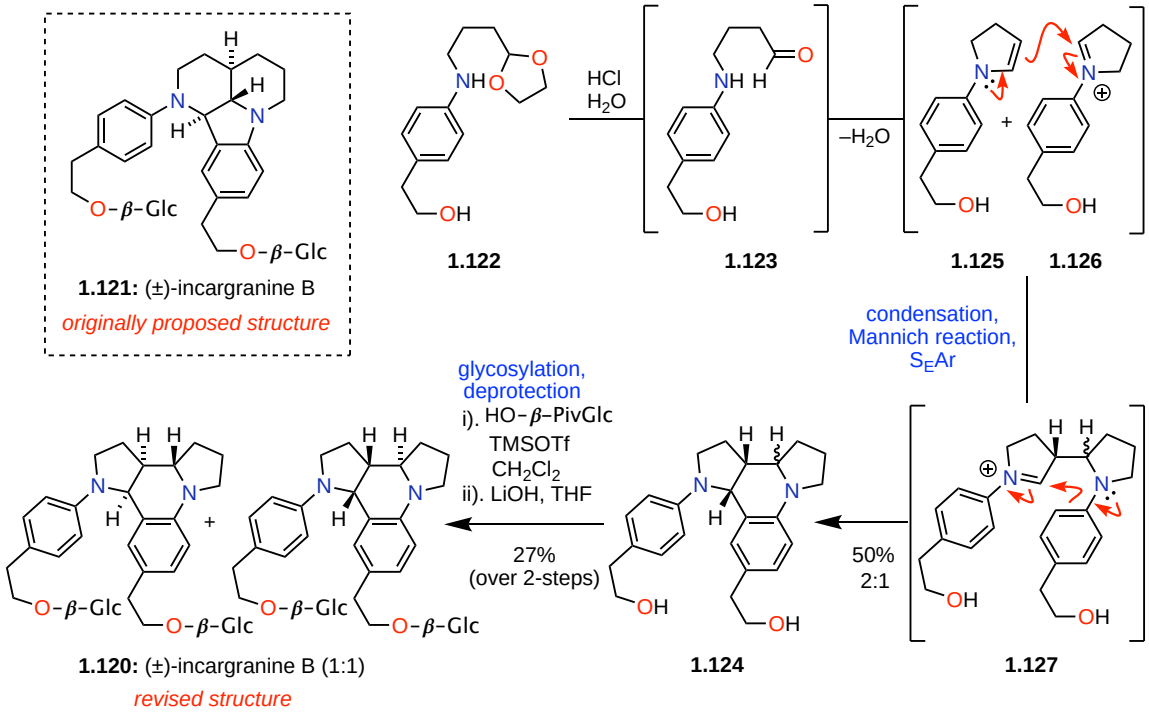
"Until the mid-1960s, structure determination was an art that could be likened to solving a detective case, but with the spectacular advancement in spectroscopy it has become less inspiring, and since the mid-1980s, in most cases, structure determination has become routine"

— Koji Nakanishi, 1991

It is important to realise that although structural determination benefits from the vast array of analytical techniques now available, there are still inherent challenges towards the elucidation of complex natural products. Indeed, even today a surprisingly large number of structural misassignments are still reported in the literature and the value of using biosynthetic rational for structural determination remains.[86]

One example includes the total synthesis of (±)-incargranine B (**1.120**) reported by the Lawrence group. Incargranine B was first isolated in 2010 by Shen and co-workers,[87] and was initially assigned to have the novel indolo[1,7]napthyridine alkaloid structure **1.121** (**Scheme 1.18**). Despite the structurally sound NMR assignment of compound **1.121**, biosynthetic speculation suggested that the proposed structure was incorrect. Specifically, this natural product was believed to be ornithine derived, in which case the breakage and formation of a strangely high number of bonds would have had to occur. Instead, it was proposed that a more biosynthetically plausible structure involving a dipyrroloquinoline would be more plausible.

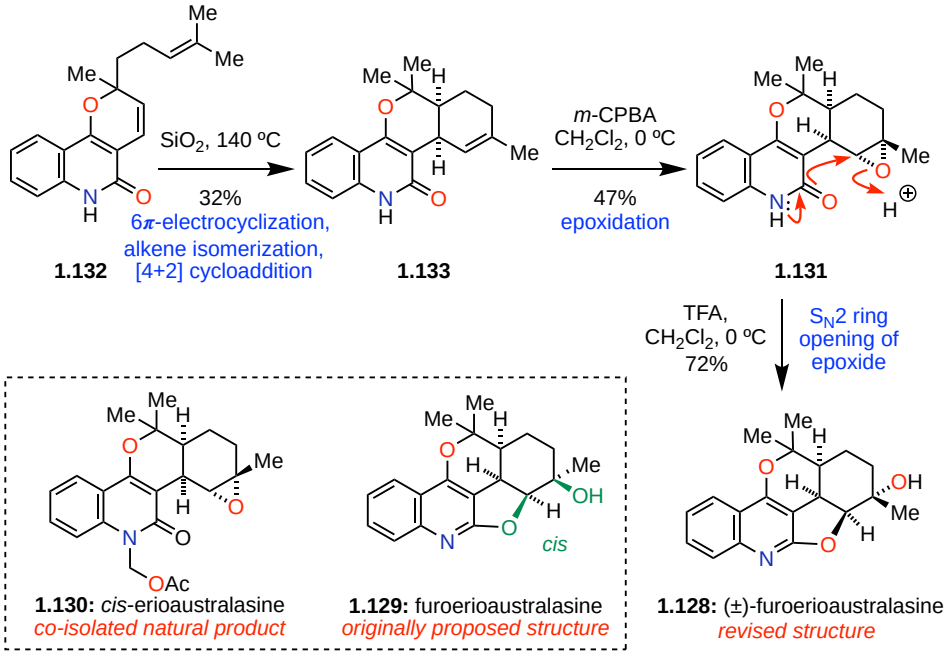
To test this proposal, a structural revision through total synthesis was reported.[88] This involved conversion of an acetal protected precursor **1.122** to aldehyde **1.123** in the presence of $HCl_{(aq)}$ followed by a condensation/ Mannich/ S_EAr cascade sequence to afford diol **1.124** in a 50% yield. Subsequent glycosylation and global deprotection then gave the desired target **1.120**, which gratifyingly matched the original analytical data of (±)-incargranine B.[87]



Scheme 1.18 – The Structural Revision of (±)-Incargranine B[88]

Another more recent example of structural revision is the total synthesis of (±)-furoerioaustralasine (**1.128**) reported in our group in 2019 (**Scheme 1.19**).[44] The structure of (±)-furoerioaustralasine was initially missassigned with a reported *cis* relationship between the oxy and hydroxyl substituents (**1.129**).[89] In this case it was the co-isolated natural product *cis*-erioaustralasine (**1.130**) that led to a proposed misassignment. It was envisaged that *cis*-erioaustralasine could in fact be a direct precursor to (±)-furoerioaustralasine. This could occur through an intramolecular S_N2 ring opening of the epoxide (**1.131**) to afford (±)-furoerioaustralasine with a *trans* relationship, rather than the reported *cis* configuration.

Thermal rearrangement of chromene **1.132** involving a retro-6π-electrocyclization, alkene isomerisation and an intramolecular hetero-Diels-Alder reaction then afforded the intermediate enone **1.133** in 32%. Next, epoxidation with *m*-CPBA gave the desired *exo* epoxide **1.131** in 47% and finally treatment with TFA afforded (±)-furoerioaustralasine (**1.128**) in 77%. Pleasingly, the obtained NMR data was shown to match that of the reported isolation data.[89]



Scheme 1.19 –Total Synthesis of (±)-furoerioaustralasine (1.128)[44]

These examples covered in this chapter, not only highlight the enduring value of biomimetic chemistry, but showcase the importance of biosynthetic speculation in the structural revision of natural products. Herein, this thesis will attempt to explore the biomimetic chemistry of a few select examples of natural products, through the use of cascade reactions and dearomatization strategies.

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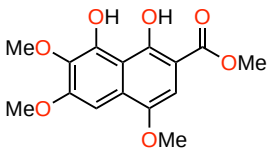
Chapter Two – Investigations Towards the Busseihydroquinone and Parvinaphthol Families of Natural Products

This work was completed with assistance from postdoctoral fellow Dr. Henry P. Pepper, who did preliminary work on this project, synthesizing the key orcinol model study enol ether and cyclobutane

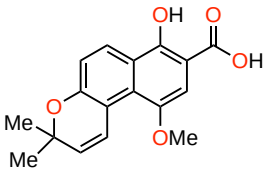
2.1 Introduction

2.1.1 Busseihydroquinone and Parvinaphthol Families of Natural Products

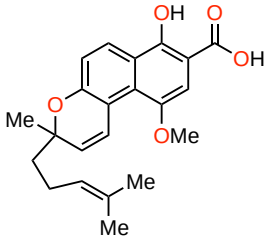
Rubiaceae is a diverse family of flowering plants native to tropical and sub-tropical regions. This family contains plants of the genus *Pentas* which have been used extensively in traditional medicines for the treatment of malaria, ascariasis, lymphadenitis, snake bites and a variety of other conditions.[1] These plants are an abundant source of polycyclic meroterpenoid natural products such as busseihydroquinones A – E (**2.1** – **2.5**), first isolated from *Pentas bussei* in 2012 and parvinaphthols A – C (**2.6** – **2.8**) isolated from *Pentas parvifola* in 2016. There is also an unnamed but structurally relevant natural product **2.9**, which was isolated from *Pentas bussei* by Bukuru and co-workers (**Figure 2.1**).[2, 3, 4]



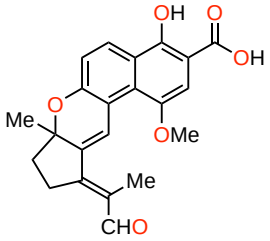
2.1: busseihydroquinone A



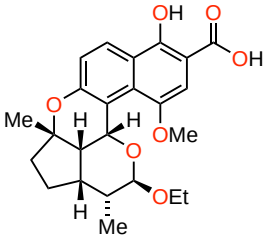
2.2: busseihydroquinone B



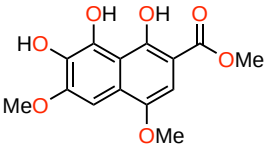
2.3: busseihydroquinone C



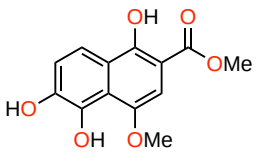
2.4: busseihydroquinone D



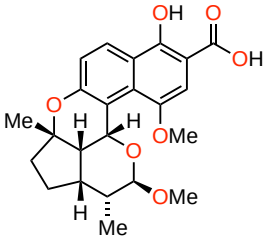
2.5: busseihydroquinone E



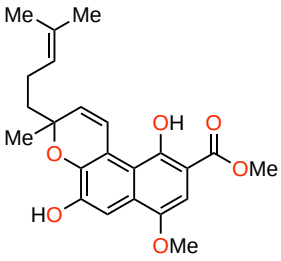
2.6: parvinaphthol A



2.7: parvinaphthol B



2.8: parvinaphthol C

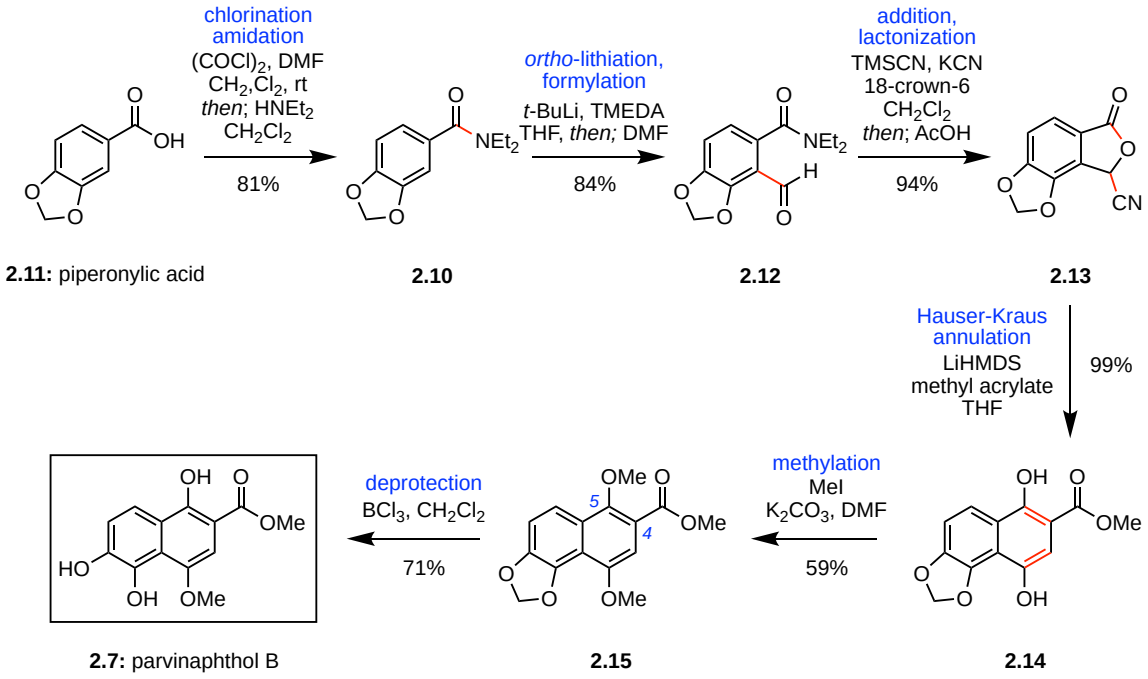


2.9

Figure 2.1 – Busseihydroquinones A – F, parvinaphthols A – C and 2.9[2, 3, 4]

2.1.2 Total Synthesis of Parvinaphthol B by Ahn and Han

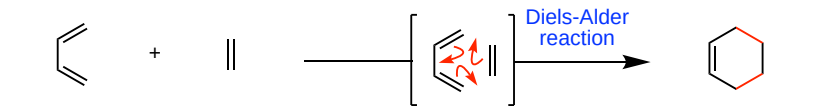
To date, the only reported total synthesis of members of the parvinaphthol and busseihydroquinone family is the synthesis of parvinaphthol B (**2.7**) reported by Ahn and Han in 2017.[5] This sequence commenced with the preparation of the known amide **2.10** *via* synthesis of an acid chloride and subsequent amidation of piperonylic acid (**2.11**) (**Scheme 2.1**).[6] Aldehyde **2.12** was obtained in excellent yield by *ortho*- lithiation of amide **2.10** using *t*-BuLi and formylation with DMF.[7] *Ortho*- formyl benzamide **2.12** was then cyclized according to a literature procedure to give cyano-isobenzofuranone **2.13**.[8] A Hauser-Kraus annulation of isobenzofuranone **2.13** with methyl acrylate using LiHMDS was then performed to afford dihydroxynapthoate **2.14** in quantitative yield. Unfortunately, direct *O*-methylation of 1,4-dihydroxynapthoate **2.14** did not proceed selectively. Alternatively, a 2-step dimethylation and deprotection was used to introduce the methyl group into the correct position in 42% over 2-steps. Presumably, the selective deprotection occurred due to the hydrogen bond stability between the **C4** and **C5** of **2.15**, affording a concise synthesis of **2.7** in 6 linear steps and an overall yield of 27%.



Scheme 2.1 – Han and Ahn's Total Synthesis of Parvinaphthol B[5]

2.1.3 The Diels-Alder Reaction

Arguably one of the most important reactions that has influenced total synthesis over the last century is the Diels-Alder reaction. This reaction involves a pericyclic [4+2] addition between a *Z*-conjugated diene (i.e. **2.16**) and at least one π bond (typically a substituted alkene i.e. **2.17**) resulting in the formation of a cyclohexene derivative (i.e. **2.18**) (**Scheme 2.2**).



2.16: butadine **2.17:** ethylene **2.18:** cyclohexene

Scheme 2.2 – The Diels-Alder Reaction

This reaction occurs *via* a single cyclic transition state and proceeds through thermally permitted suprafacial/ suprafacial interactions of the diene's 4π electron system with the 2π electron system of the dienophile,[9] and is best depicted through consideration of frontier molecular orbital (FMO) theory (**Figure 2.2**).

In "normal" electron demand Diels-Alder reactions, it is the highest occupied molecular orbital (HOMO) of the electron rich diene which interacts with the lowest unoccupied molecular orbital (LUMO) of the electron poor dienophile and leads to the formation of a second bonding molecular orbital which is of lower overall energy making the Diels-Alder reaction highly favourable.

Interestingly, this [4+2] cycloaddition can also occur between an electron poor diene and an electron rich dienophile when the HOMO-LUMO energy gap is close enough in energy. In this case, the diene is acting as the LUMO and the dienophile as the HOMO. This is known as an inverse electron demand Diels-Alder reaction and often requires the use of hetero-atoms for this polarity reversal to occur. Because of this, the inverse Diels-Alder reaction is often used in natural product synthesis where target molecules containing heterocycles are prevalent.

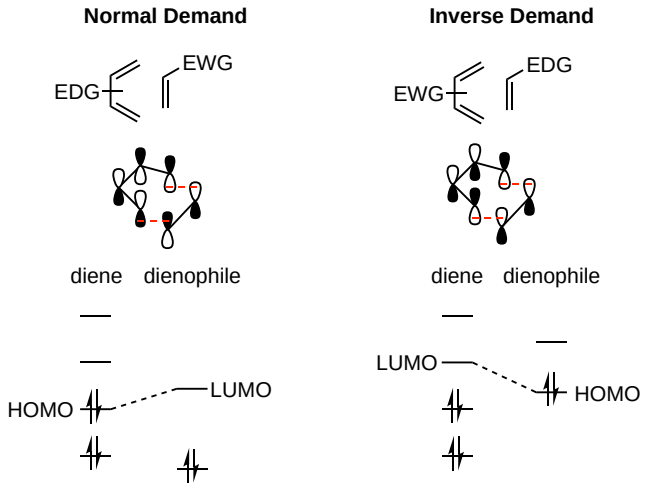
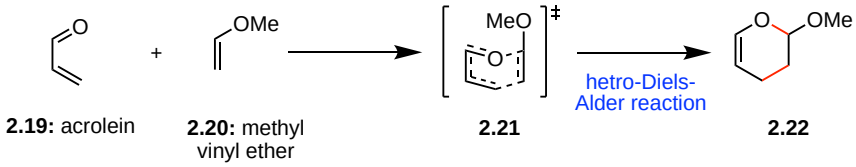


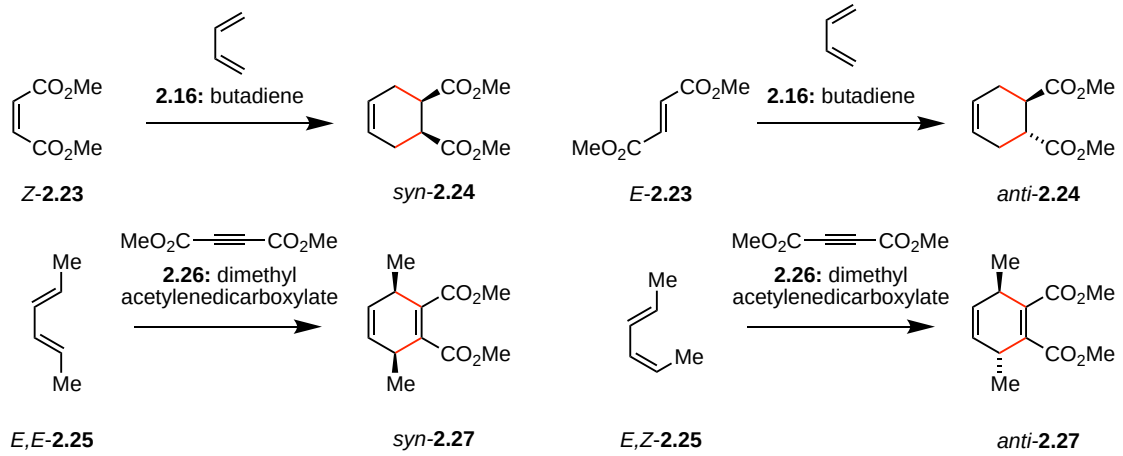
Figure 2.2 – FMO Diagram of Inverse and Normal Diels-Alder Reactions

Unlike the normal demand Diels-Alder reaction, the mechanism for the inverse demand reaction is not fully understood.[10] The accepted view is that most inverse Diels-Alder reactions occur *via* an asynchronous mechanism where not all bonds are formed and broken at the same time. What is certain, is that this mechanism occurs through a boat-like transition state.[11] For example, the oxa-Diels-Alder reaction between acrolein (**2.19**) and methyl vinyl ether (**2.20**) proceeds through **2.21** to afford the dihydropyran (**2.22**) (**Scheme 2.3**).



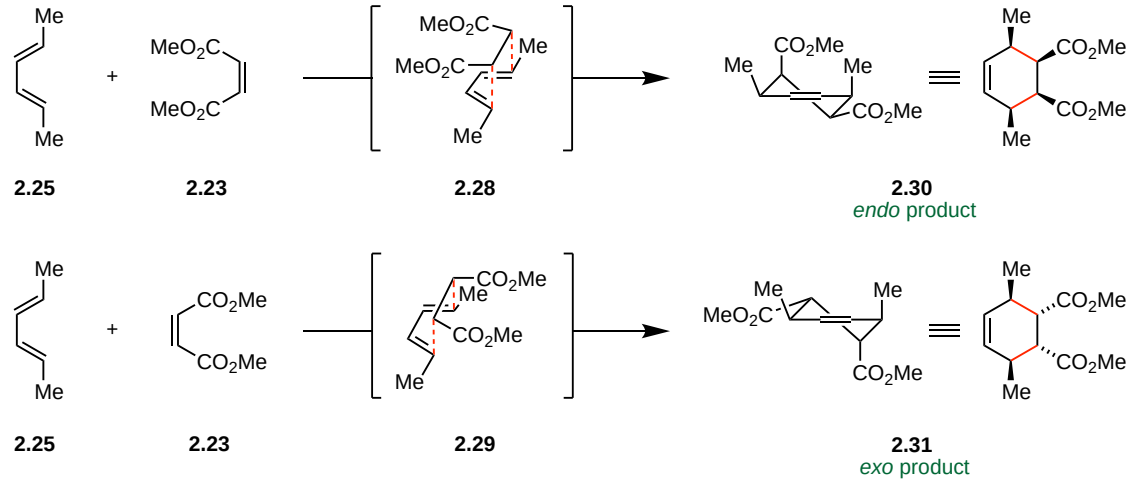
Scheme 2.3 – The Inverse Demand Diels-Alder Reaction

As normal demand Diels-Alder reactions are concerted these cycloadditions are stereospecific, resulting in *syn*-addition with respect to the diene and dienophile components (**Scheme 2.4**). This can be observed by looking at the *Z*-dienophile dimethyl maleate (*Z*-**2.23**), which gives rise to a *syn*-cyclohexene *syn*-**2.24** when reacted with butadiene (**2.16**). While *E*-dimethyl maleate (*E*-**2.23**) affords the *anti*-cyclohexene product *anti*-**2.24**. Additionally it follows that both the *Z,Z* and *E,E*-dienes (i.e. *E,E*-**2.25**) when reacted with dimethyl acetylenedicarboxylate (**2.26**) give *syn*-cyclohexene products (i.e. *syn*-**2.27**), while *Z,E*-distributed diene gives the *anti*-cyclohexene product (i.e. *anti*-**2.27**).



Scheme 2.4 – Stereospecific Diels-Alder Reactions

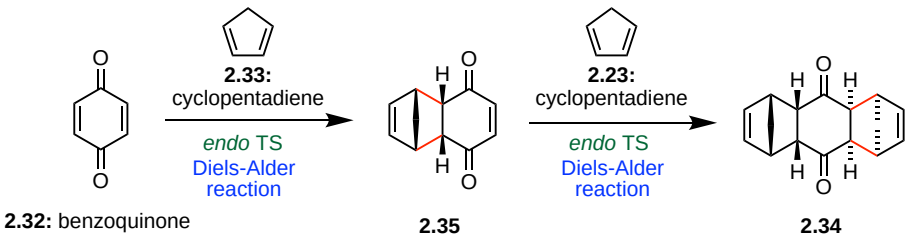
In contrast, Diels-Alder reactions in which neighbouring stereocentres are formed next to the new bond are under stereoselective control. There are two different possible stereochemical outcomes based on the orientation of the dienophile with respect to the diene; either *endo* (with the dienophile molecular orbitals underneath the diene i.e **2.28**) or *exo* (with the dienophile molecular orbitals away from the diene i.e. **2.29**) (**Scheme 2.5**). For normal demand Diels-Alder reactions the stereochemical outcomes can often be predicted. Despite being more stereochemically hindered, the *endo* transition state is typically preferred due to favourable interactions between the π systems of the diene and the dienophile. This is known as the secondary orbital effect and was first proposed by Woodward and Hoffmann.[12]



Scheme 2.5 – Stereoselective Diels-Alder Reactions

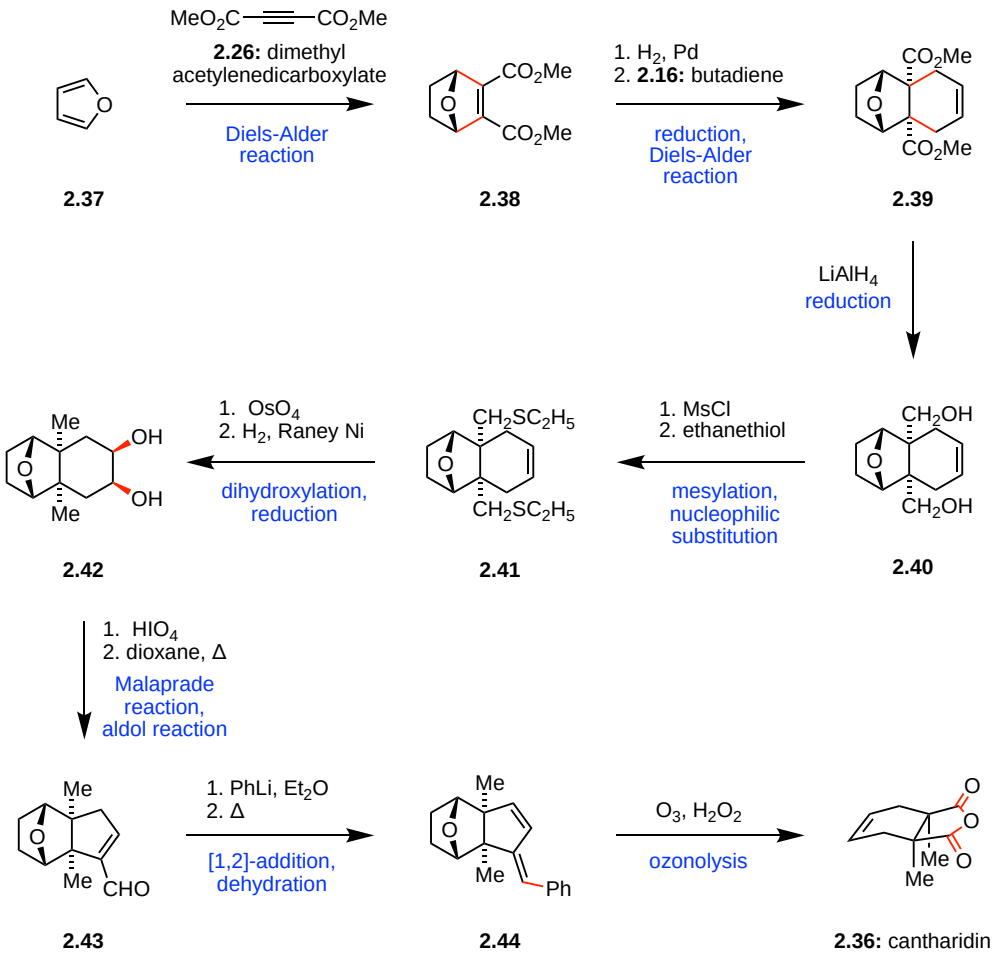
2.1.4 History of the Normal Demand Diels-Alder Reaction

In 1928 the Diels-Alder reaction was first disclosed by Otto Diels and Kurt Alder, who reacted benzoquinone (**2.32**) and cyclopentadiene (**2.33**) to afford **2.34** through the mono adduct **2.35** (**Scheme 2.6**).[13] Over the next 10 years Diels went on to further publish a total of 28 articles in this area, and in 1950 both Alder and Diels were awarded the Nobel prize in chemistry.[14]



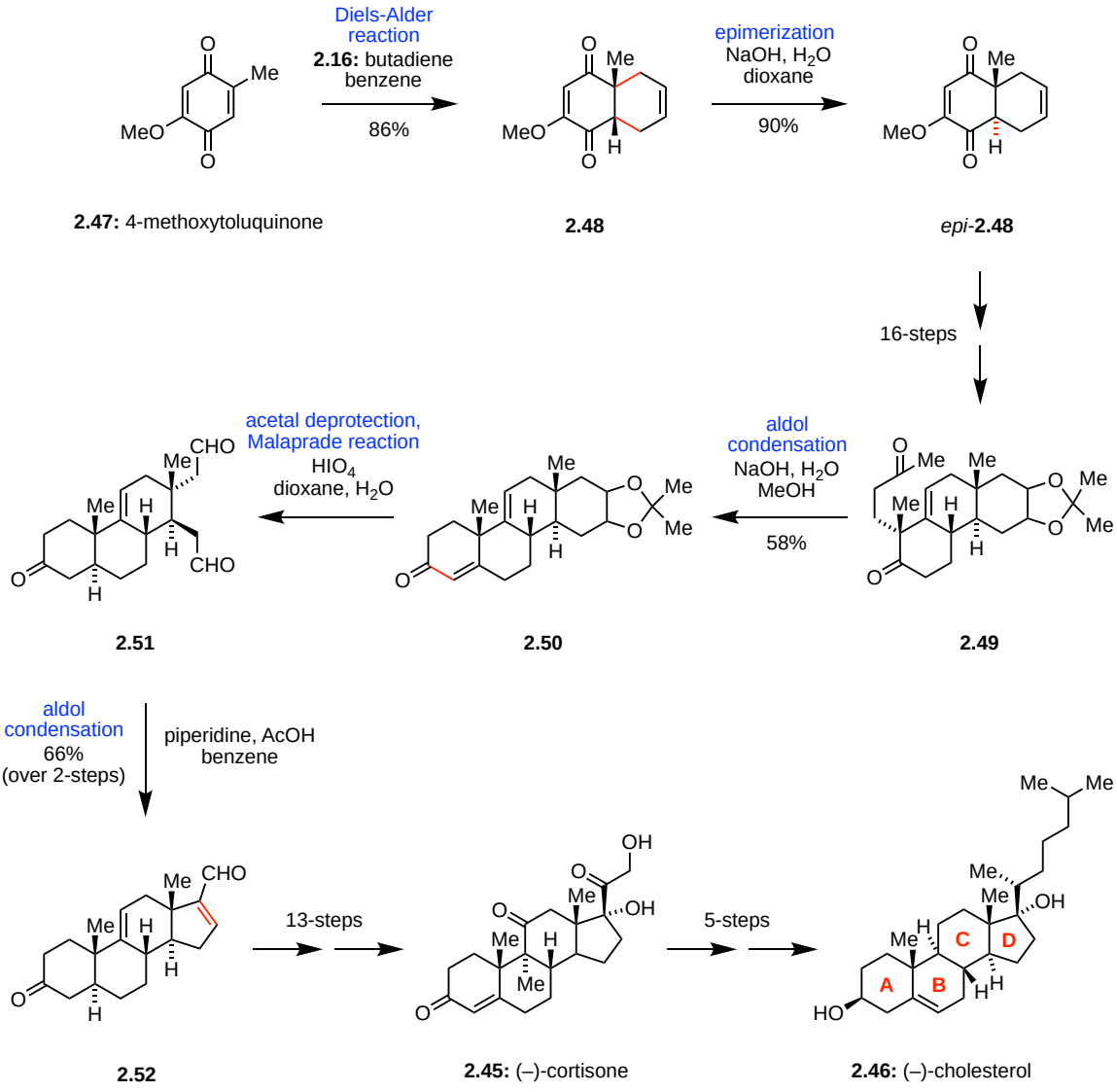
Scheme 2.6 – The First Reported Example of a Diels-Alder Reaction[13]

It seems for the most part the synthetic community were slow to apply the Diels-Alder reaction in the context of total synthesis. It wasn't until 1951 when Gilbert Stork and co-workers reported the total synthesis of cantharidin (**2.36**).[15] This was achieved in 15 linear steps, starting from a Diels-Alder reaction of furan (**2.37**) and dimethyl acetylenedicarboxylate (**2.26**) to afford **2.38**, followed by a hydrogenation and a second Diels-Alder reaction with butadiene (**2.16**) to afford **2.39** (**Scheme 2.7**). Next, reduction with $LiAlH_4$ gave the diol **2.40**, which was mesylated and formation of the thiolate **2.41** occurred through reaction with ethanethiol. Dihydroxylation of the ethylenic bond from reaction of **2.41** with OsO_4 and thioether reduction using H_2 and Raney Ni afforded **2.42**. A Malaprade reaction[16] with periodic acid then gave glycol cleavage of the vicinal diol to afford the corresponding dial which was primed to undergo an aldol reaction affording aldehyde **2.43**. Addition of PhLi and an anionotropic rearrangement then gave **2.44**. Finally, dehydration, ozonolysis and treatment with hydrogen peroxide then gave cantharidin (**2.36**).



Scheme 2.7 – Stork's Total Synthesis of cantharidin[15]

One year later in 1952, Woodward and co-workers reported the use of the Diels-Alder reaction in a 35 linear step synthesis of (−)-cortisone (**2.45**) and 40-step synthesis of (−)-cholesterol (**2.46**) (**Scheme 2.8**).[17] This was achieved through reaction of butadiene (**2.16**) with 4-methoxytoluquinone (**2.47**) to afford the Diels-Alder product **2.48** in 86% and furnishing the **C** ring system. Epimerization through reaction with NaOH then gave the desired *anti*-stereochemistry across the ring junction of *epi*-**2.48**, followed by a 16-step synthesis of the ketone **2.49**. Aldol condensation then afforded the enone **2.50** resulting in cyclization of the **A** ring system. Next a one-pot acetal deprotection and Malaprade reaction gave the dialdehyde **2.51**, followed by a second aldol reaction to give the **D** ring system of the α,β-unsaturated aldehyde **2.52** in 66% over 2-steps. Finally (−)-cortisone (**2.45**) was then synthesized in 13-steps which could be further derivatized to afford (−)-cholesterol (**2.46**).

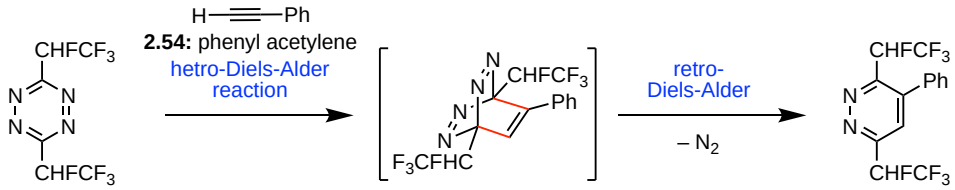


Scheme 2.8 – Woodward's Total Synthesis of (−)-cortisone and (−)-cholesterol[17]

These two examples highlight the importance of the Diels-Alder reaction in complex molecule synthesis. They also demonstrate the importance of approaching complex molecules through rational synthetic design, a strategy that first emerged in the 1950s and was further expanded by the development of the Woodward-Hoffman rules in 1965.[18] This allowed for the prediction of stereochemistry and rationalization of activation energies in pericyclic reactions (*including the Diels-Alder reaction*) and helped make the Diels-Alder reaction more accessible to modern synthetic chemistry problems.

2.1.5 History of the Inverse Demand Diels-Alder Reaction

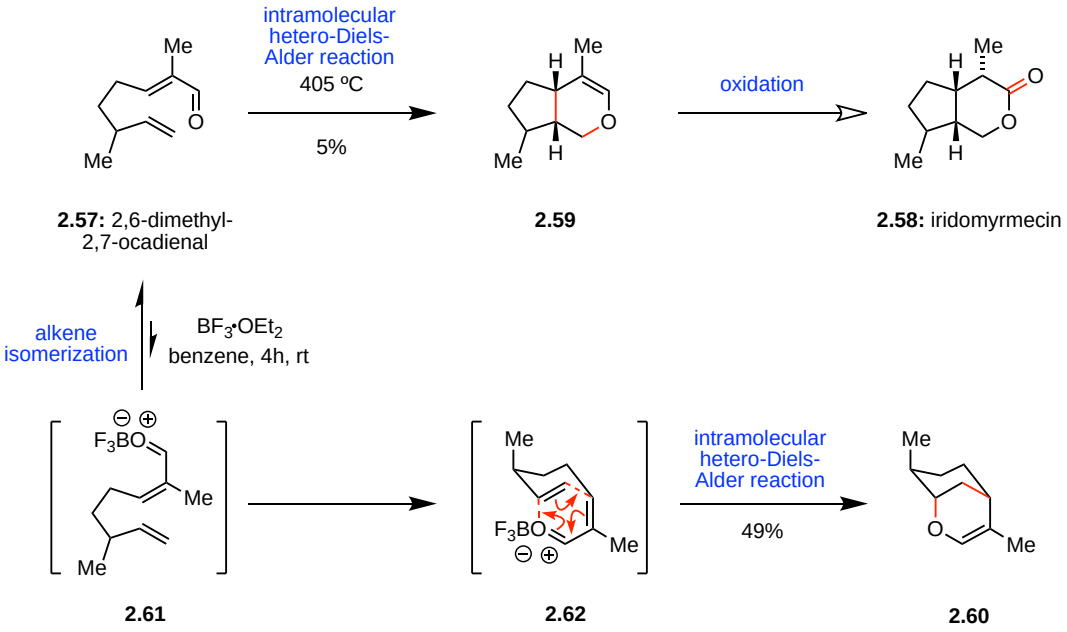
In contrast to the normal demand Diels-Alder reaction, less is known about the inception of the reverse demand Diels-Alder reaction. This is most likely due to challenges associated with the identification of normal and inverse electron demand reactions before the development of current computational methods and initial lack of understanding surrounding FMO theory.[19] In a general sense, one of the earliest examples of inverse Diels-Alder reactions is often attributed to work by Carboni and Lindsey (**Scheme 2.9**).[20] In 1959 they reported the first example of a Diels-Alder reaction between the electron deficient perfluroalkyl tetrazine **2.53** and phenyl acetylene (**2.54**). This reaction (which is often referred to as the Carboni-Lindsey reaction) resulted in the formation of the intermediate **2.55**, which underwent a retro-Diels-Alder reaction through loss of N_2 to afford the pyridazine **2.56**.



Scheme 2.9 – Carboni and Lindsey's 1959 Synthesis of pyridazine 2.56[20]

Another example includes work by Barry Snider and John Duncia in 1980 who reported the synthesis of various inverse Diels-Alder reactions of 2,6-dimethyl-2,7-octadienal (**2.57**) (**Scheme 2.10**).[21] In an attempted total synthesis of the insecticide iridomyrmecin (**2.58**), **2.57** was heated to 405 °C in a vapour phase pyrolysis flow system to afford the dihydropyran **2.59** in 5%. Unfortunately, even after attempting this reaction at a range of different temperatures this reaction was low yielding and afforded a complex mixture of ene adducts. Interestingly it was

found that treatment of **2.57** with the Lewis acid $BF_3{\cdot}OEt_2$ gave another inverse Diels-Alder product **2.60** in 49%. Presumably this was forming through isomerization of the α,β-unsaturated aldehyde to give **2.61**, which allowed for an intramolecular Diels-Alder reaction through **2.62**.

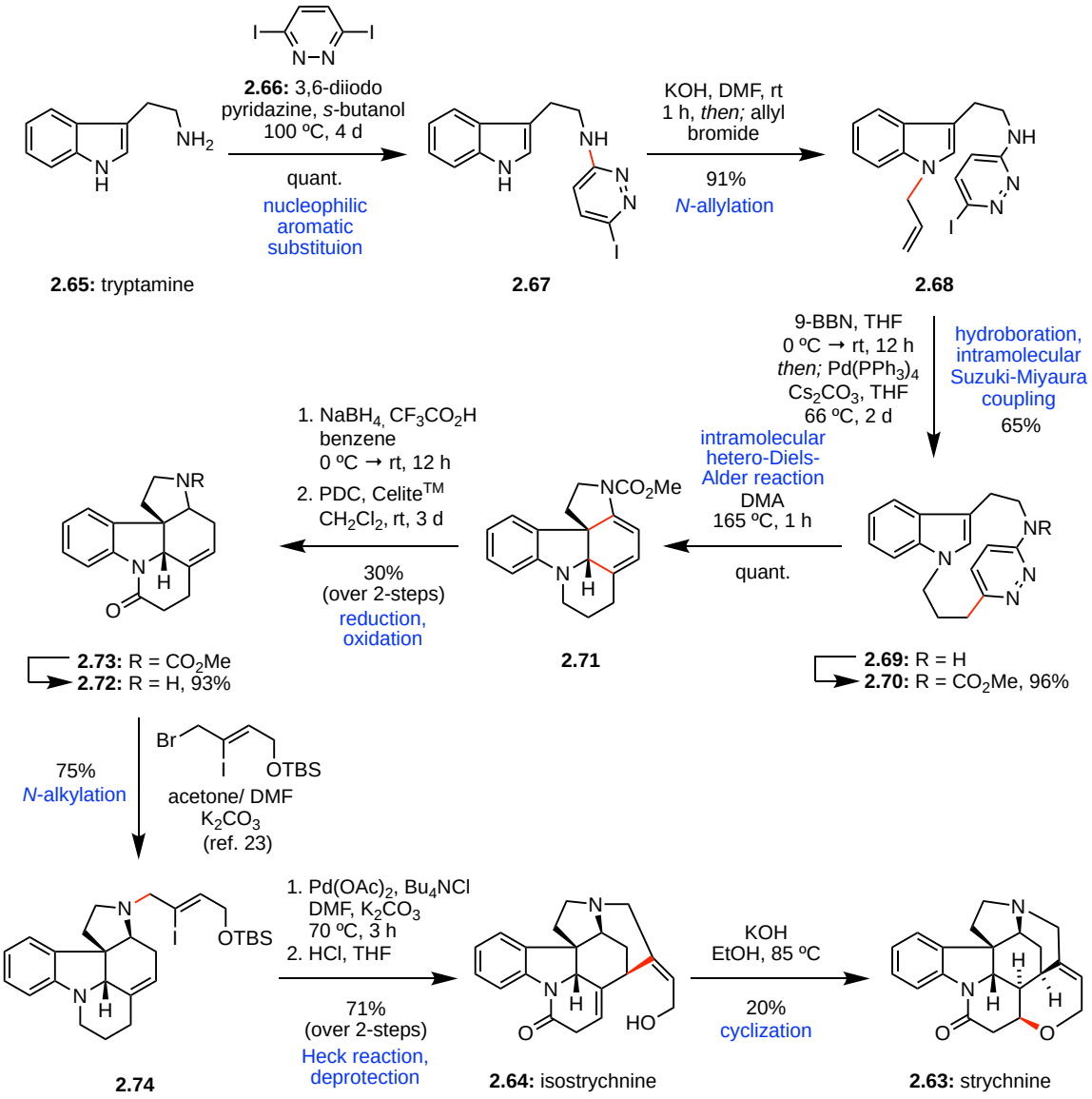


2.57: 2,6-dimethyl-2,7-ocadienal | **2.59** | **2.58:** iridomyrmecin

2.61 | **2.62** | **2.60**

Scheme 2.10 – Snider and Duncia's Inverse Diels-Alder Reactions[21]

One of the most well-known uses of an inverse Diels-Alder reaction includes the formal total synthesis of strychnine (**2.63**) and isostrychnine (**2.64**) reported by Bodwell in 2002 (**Scheme 2.11**).[22] This synthesis commenced through reaction of tryptamine (**2.65**) with 3,6-diisopyridazine (**2.66**) to afford **2.67**. *N*-allylation of the indole moiety then gave **2.68** in 91%, which was subjected to hydroboration and an intramolecular Suzuki-Miyaura coupling to afford the cyclophane **2.69** in 65%. Protection of the secondary amine as a methyl carbamate then gave **2.70**, which was heated at reflux in DMA to induce the inverse Diels-Alder reaction furnishing the key framework of **2.71**. Finally, a series of functional group interconversions including reduction, oxidation and deprotection gave **2.72** in 28% over 3-steps. This compound had been previously synthesized by Rawal and co-workers in 1994 and could be taken on to afford the formal total synthesis of isostrychnine (**2.64**) and strychnine (**2.63**).[23]



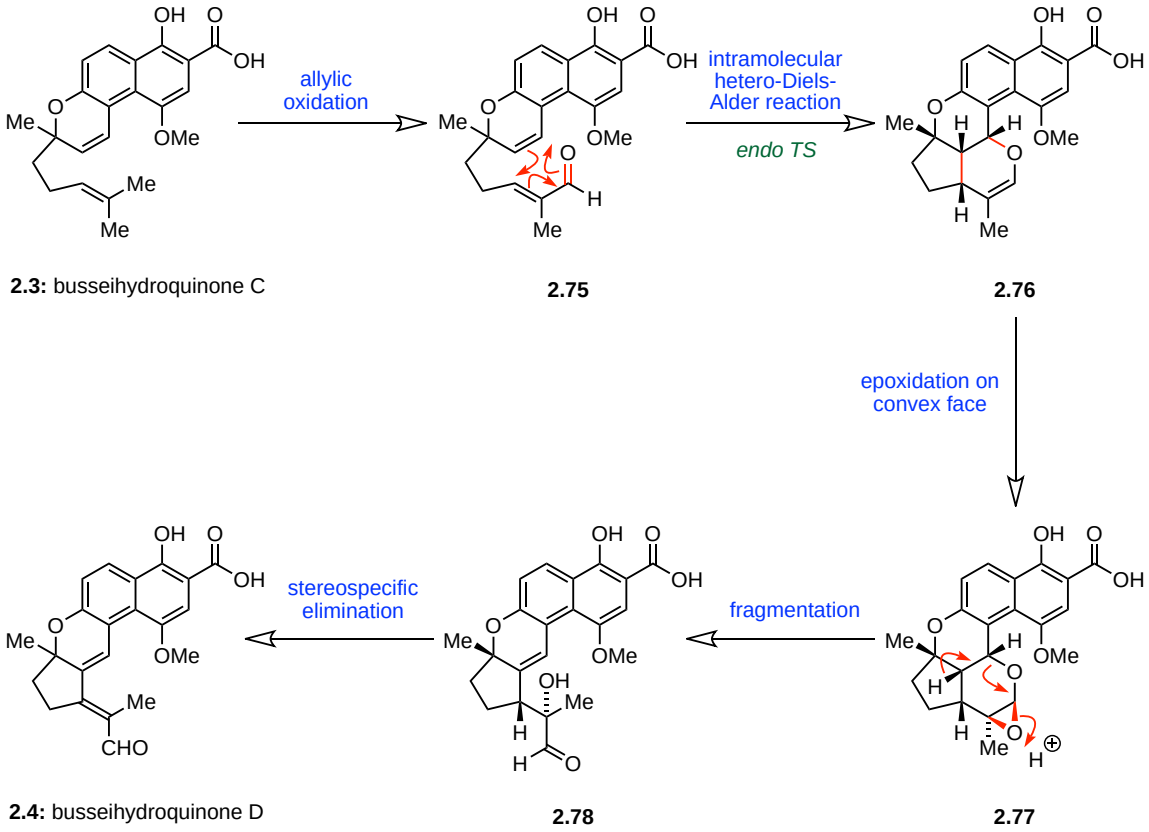
Scheme 2.11 – Li's Formal Synthesis of Strychnine and Isostrychnine[22]

Intrigued by the simplicity of these inverse demand Diels-Alder reactions, we considered that a similar approach may be applied to the total synthesis of busseihydroquinones C – E (**2.3** – **2.5**) and parvinaphthol C (**2.8**).

2.1.6 Proposed Biosynthesis of Busseihydroquinones C – E and Parvinaphthol C

In line with our groups current research into the biosynthesis of polyhydroxynaphthalene meroterpenoids[24] we became intrigued by the biosynthetic relationship between busseihydroquinones C – E (**2.3** – **2.5**) and parvinaphthol C (**2.8**). We were particularly facinated by the structures of **2.5** and **2.8**, which contain six contiguous stereocenters fused to a 6-5-6 ring system.

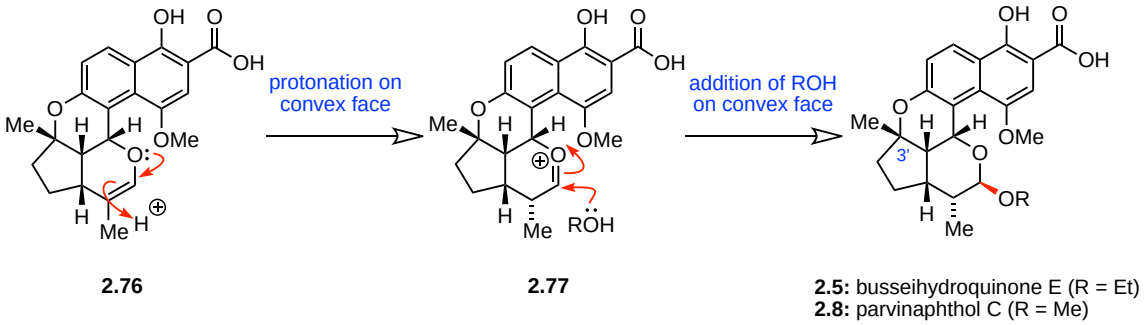
Our proposal linking the biosynthesis of busseihydroquinones C (**2.3**) and D (**2.4**) is outlined (**Scheme 2.12**). First, we envisaged that allylic oxidation of busseihydroquinone C (**2.3**) could afford the enal **2.75**, which would be primed to undergo an intramolecular inverse demand hetero-Diels–Alder reaction between the chromene alkene and the tethered α,β-unsaturated dienophile. This would give the cyclic enol ether **2.76** (most likely an undiscovered natural product) *via* an *endo* transition state. Next, epoxidation of the enol ether alkene **2.76** could occur to give **2.77**. Ring opening of the resultant epoxide would then afford α-hydroxyaldehyde **2.78** and subsequent elimination would afford busseihydroquinone D (**2.4**).



Scheme 2.12 – Proposed Biomimetic Synthesis of busseihydroquinone D

We anticipated that a biosynthetic pathway linking busseihydroquinone C (**2.3**) to busseihydroquinone E (**2.5**) and parvinaphthol C (**2.8**) could also be occurring from the same cyclic enol ether **2.76** (**Scheme 2.13**). Herein, we propose that **2.5** and **2.8** are likely isolation artifacts formed by the addition of MeOH or EtOH to the "undiscovered" natural product **2.76**. Both *Pentas bussei* and *Pentas parvifola* plants were extracted and purified with MeOH, EtOAc and oxalic-acid impregnated SiO_2, it is possible that in these conditions **2.76** could undergo protonation to afford

the oxonium ion **2.77** and that the nucleophilic addition of EtOH or MeOH would give **2.5** and **2.8**. Ethoxy groups are relatively rare in secondary metabolites, and it is not uncommon for natural product artifacts to arise from the interaction of MeOH or EtOH employed as solvents in the extraction process.[25]

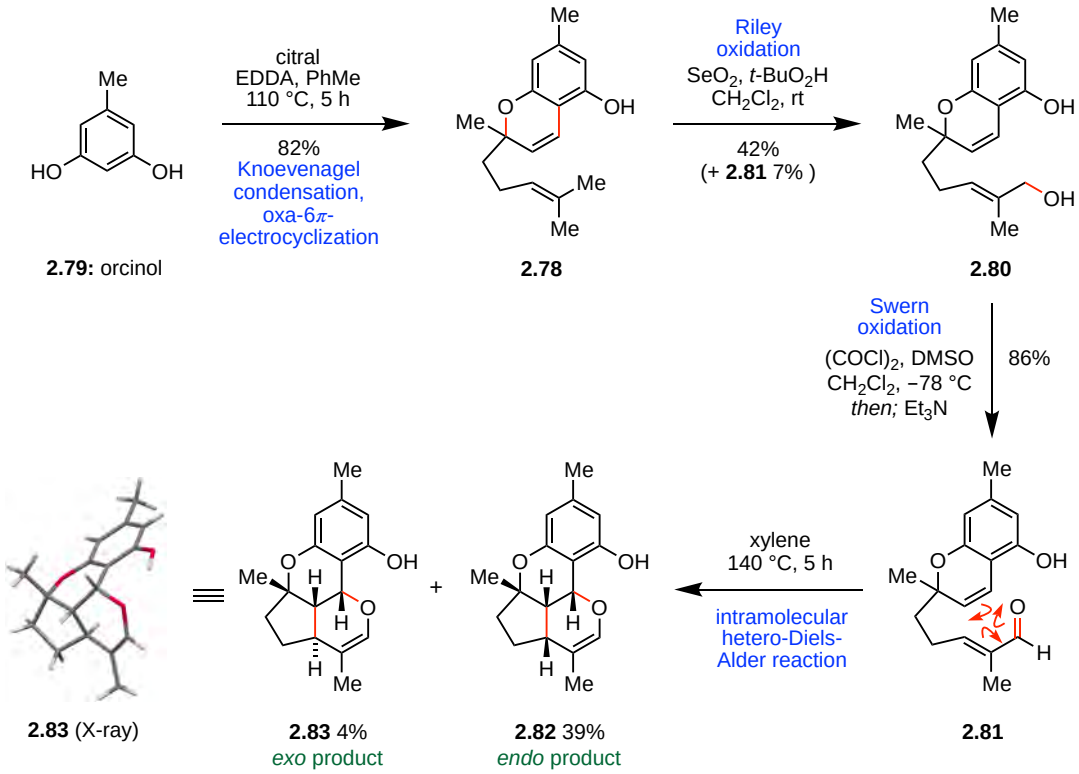


Scheme 2.13 – Proposed Biomimetic Synthesis of busseihydroquinone E and parvinaphthol C

2.2 Results and Discussion

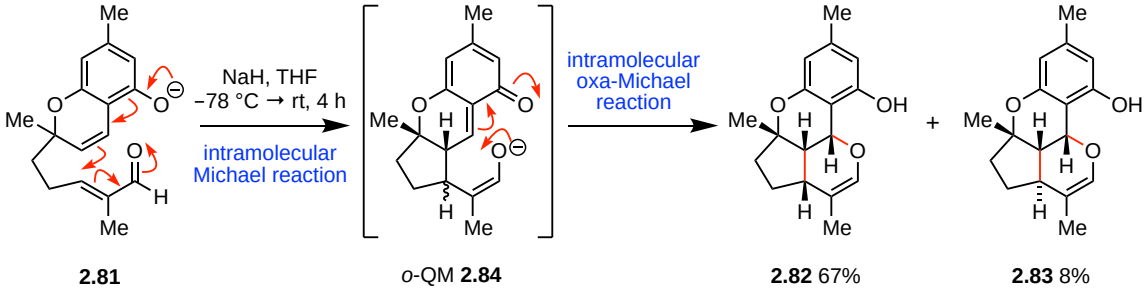
2.2.1 Orcinol Model Study Featuring *ortho*-Quinone Methide Cyclizations

Investigations into the biogenic relationship between the parvinaphthol and busseihydroquinone families began by targeting the synthesis of the known chromene **2.78** as a simplified model study of busseihydroquinone C (**2.3**) (**Scheme 2.14**). Condensation of orcinol (**2.79**) with citral according to a literature procedure by Lou *et al*. gave access to chromene **2.78** in 82%.[26] Riley oxidation of **2.78** using *t*-BuO_2H and catalytic SeO_2 afforded the allylic alcohol **2.80**, which was directly oxidized using Swern reaction conditions to give enal **2.81**. It was found that heating **2.81** at reflux in xylene afforded the Diels-Alder product **2.82** in 39% yield and the diastereoisomer **2.83** in 4% yield which was presumably forming *via* the less favorable *exo* transition state. The structure and relative configuration of **2.82** was supported using 2D NMR studies (see **2.4.4**), while the structure of **2.83** was proven unequivocally *via* single crystal X-ray diffraction.



Scheme 2.14 – Synthesis of the Key Enol Ether 2.82

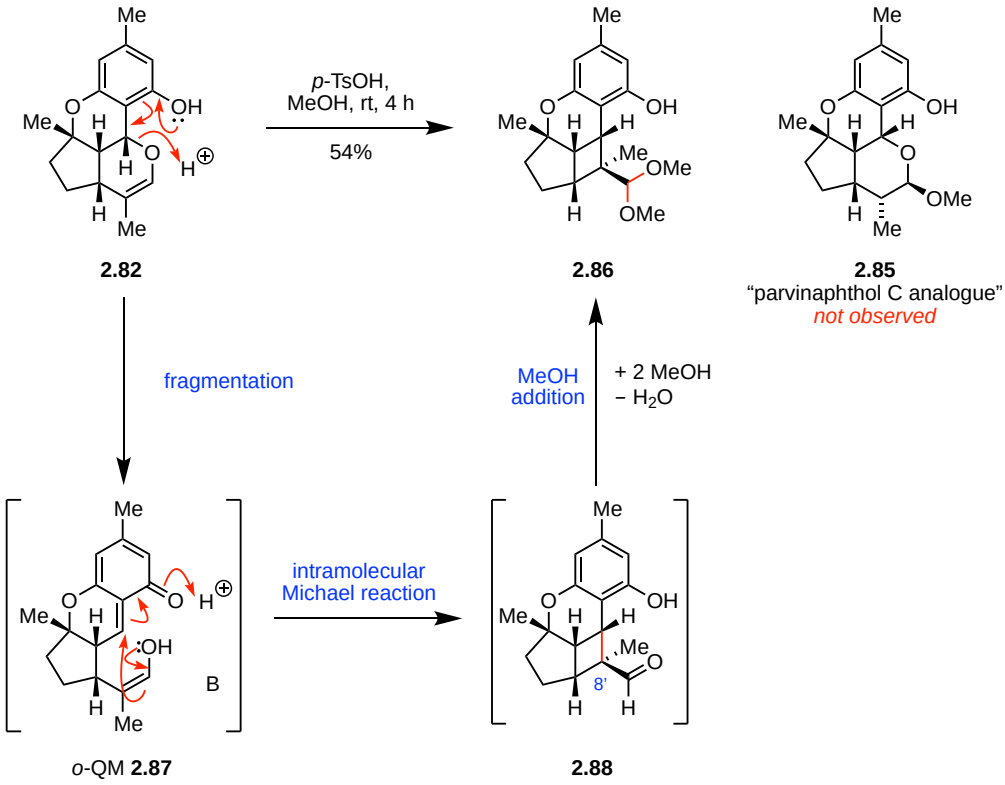
Alternatively, exposure of **2.81** to NaH in THF at −78 °C formed **2.82** and **2.83** in a slightly higher yield and improved selectivity (**Scheme 2.15**). Presumably this occurred in a stepwise manner, through an intramolecular Michael reaction to afford the *o*-QM **2.84**, followed by an intramolecular oxa-Michael reaction.



Scheme 2.15 – Stepwise Base Catalyzed [4+2] Cycloaddition of 2.81

With **2.82** in hand, we envisaged that exposure to acid and MeOH would result in protonation and a stereoselective addition of MeOH to the enol ether to afford the parvinaphthol C analogue **2.85**. Instead, **2.82** underwent a ring contraction to give the cyclobutane **2.86** in 54% (**Scheme 2.16**). Presumably this reaction was proceeding *via* an acid catalyzed ring-opening of **2.82** through a retro-oxa-Michael reaction to generate the *o*-QM enol **2.87** and a subsequent intramolecular

Michael reaction with attack of the enol at **C8'** to give aldehyde **2.88**. An acid catalyzed addition of MeOH to **2.88** then formed the dimethoxy acetal **2.86**. Interestingly this ring contraction of **2.82** represents a unique approach towards the synthesis of more functionalized cyclobutane meroterpenoids, which are more ordinarily synthesized by intramolecular [2+2] cycloadditions of chromenes (chapter Three, *vide infra*).[27]

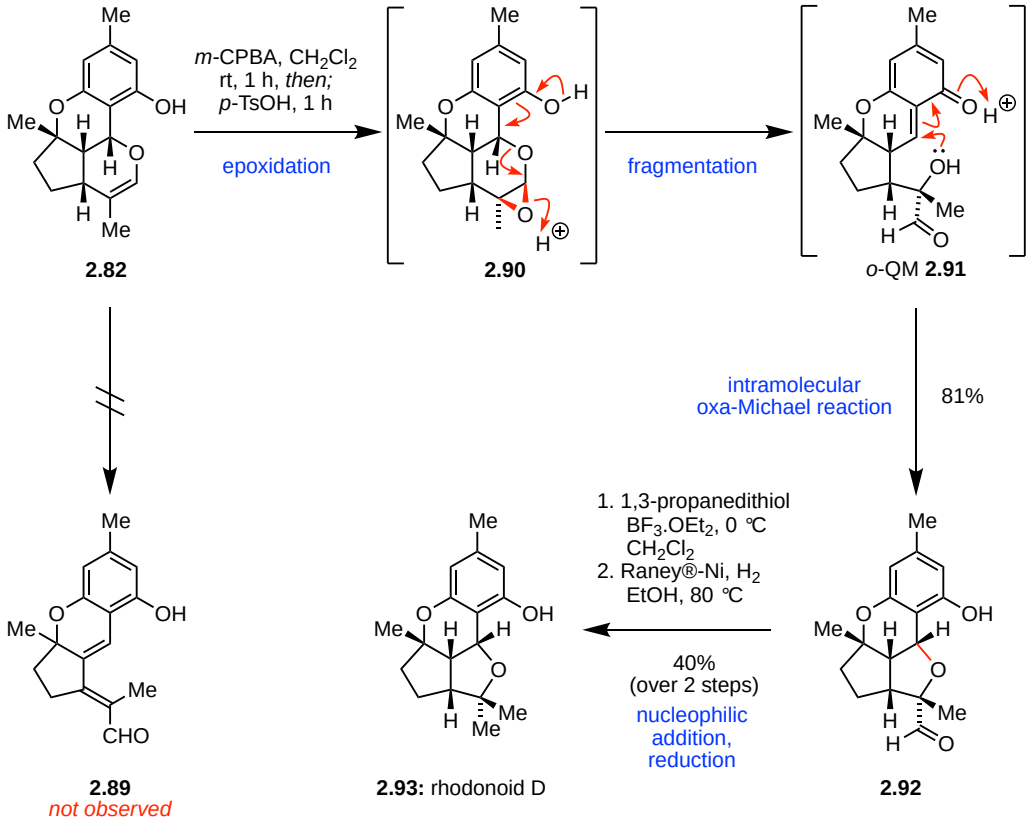


Scheme 2.16 – Ring Contraction of the Enol Ether 2.82

Unfortunately, any attempts to further functionalize the enol ether alkene of **2.82** through hydroboration (BH_3, THF *then;* H_2O_2, NaOH), oxymercuration ($Hg(OAc)_2$, THF *then;* $NaBH_4$), addition of oxalic acid (in MeOH), treatment with KOH (in MeOH/ H_2O) and refluxing in MeOH/ EtOH gave either no reaction or decomposition. Additionally, we also considered reduction of the enol ether alkene and a CH oxidation. However, exposure of **2.82** to hydrogenation conditions only gave undesired cleavage of the benzylic C-C bond.

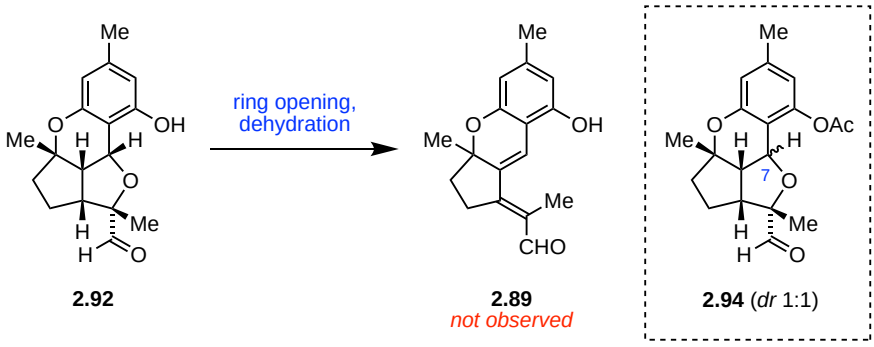
Next, we investigated conversion of the cyclic enol ether **2.82** to the busseihydroquinone D analogue **2.89** *via* an epoxidation, fragmentation and ring-opening cascade (**Scheme 2.17**). Epoxidation of **2.82** with *m*-CPBA occurred on the less hindered, convex face to give epoxide **2.90**, however this reaction gave decomposition upon work up. Instead, it was found that direct

treatment of a solution of **2.82** with *m*-CPBA, followed by the addition of *p*-TsOH after 1 h facilitated a ring-opening fragmentation to give the *o*-QM **2.91**. Disappointingly rather than the desired elimination reaction of **2.91**, we observed an intramolecular oxa-Michael reaction to give the tetracyclic aldehyde **2.92** in 81%. The relative configuration of **2.92** was determined by 2D NOESY studies. Serendipitously, aldehyde **2.92** contained the same ring system as the meroterpenoid rhodonoid D (**2.93**), and indeed **2.92** could be converted into **2.93** *via* reduction of an intermediate 1,3-dithiane.



Scheme 2.17 – Ring Contraction of the Enol Ether 2.82 and Synthesis of Rhodonoid D

Attempts to dehydrate **2.92** to give **2.89** were unsuccessful (**Table 2.1**). Treatment of **2.92** with 4Å molecular sieves gave no reaction (**entry 1**). Acidic conditions also gave no reaction (**entries 2** – **3**), while NaH gave decomposition (**entry 4**). In an attempt to trap the possible *o*-QM intermediate **2.91** and preclude the intramolecular oxa-Michael reaction, treatment of **2.92** with Ac_2O and pyridine at room temperature was undertaken (**entry 5**). However, this only afforded acetate protection and epimerization of the stereocenter at **C7** to give **2.94** in 1:1 mixture of diastereoisomers.

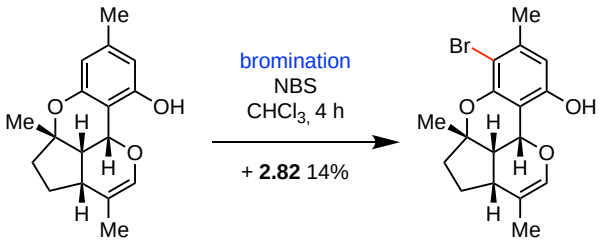


2.92 **2.89** *not observed* **2.94** (*dr* 1:1)

Table 2.1 – Attempted Ring Opening and Dehydration of 2.92 to 2.89

Entry	Reagent	Conditions	Result
1	--	THF, 4Å sieves, rt, 4 h	NR
2	H_2SO_4	MeOH, rt, 6 h	NR
3	H_3PO_4	THF, rt, 6 h	NR
4	NaH	PhMe, 4Å sieves, rt, 3 h	decomp.
5	Ac_2O	pyridine, rt, 3 h	**2.94** 33%

It was clear from our results that the key epoxidation and fragmentation were occurring, but that elimination proving challenging. This led us to consider that a similar fragmentation and elimination mediated reaction may be possible through a bromonium intermediate (analogous to the epoxide **2.91**), and that elimination may be favoured, due to the improved leaving group ability of the bromide. Unfortunately, reaction of the enol ether **2.82** with NBS (1.0 equiv.) in $CHCl_3$ at −10 °C gave only bromination to the aromatic ring, affording **2.95** in 68% (**Scheme 2.18**). While reaction with excess NBS only led to decomposition.

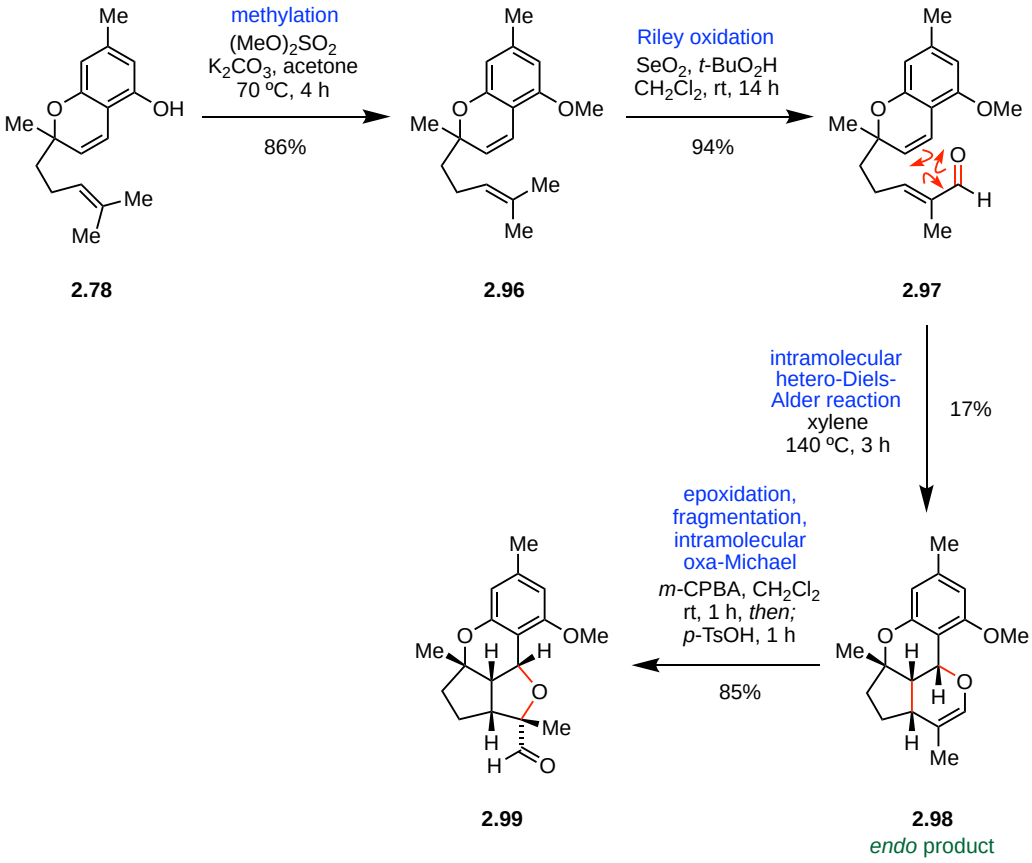


2.82 **2.95** 68%

Scheme 2.18 – Bromination of enol ether 2.82

Intrigued by the role of *o*-QMs in these cascade reactions, we wanted to investigate how protecting the free phenol would effect these transformations. To this end we synthesized the methoxy chromene **2.96** from the known chromene **2.78** in 86% through reaction with dimethyl

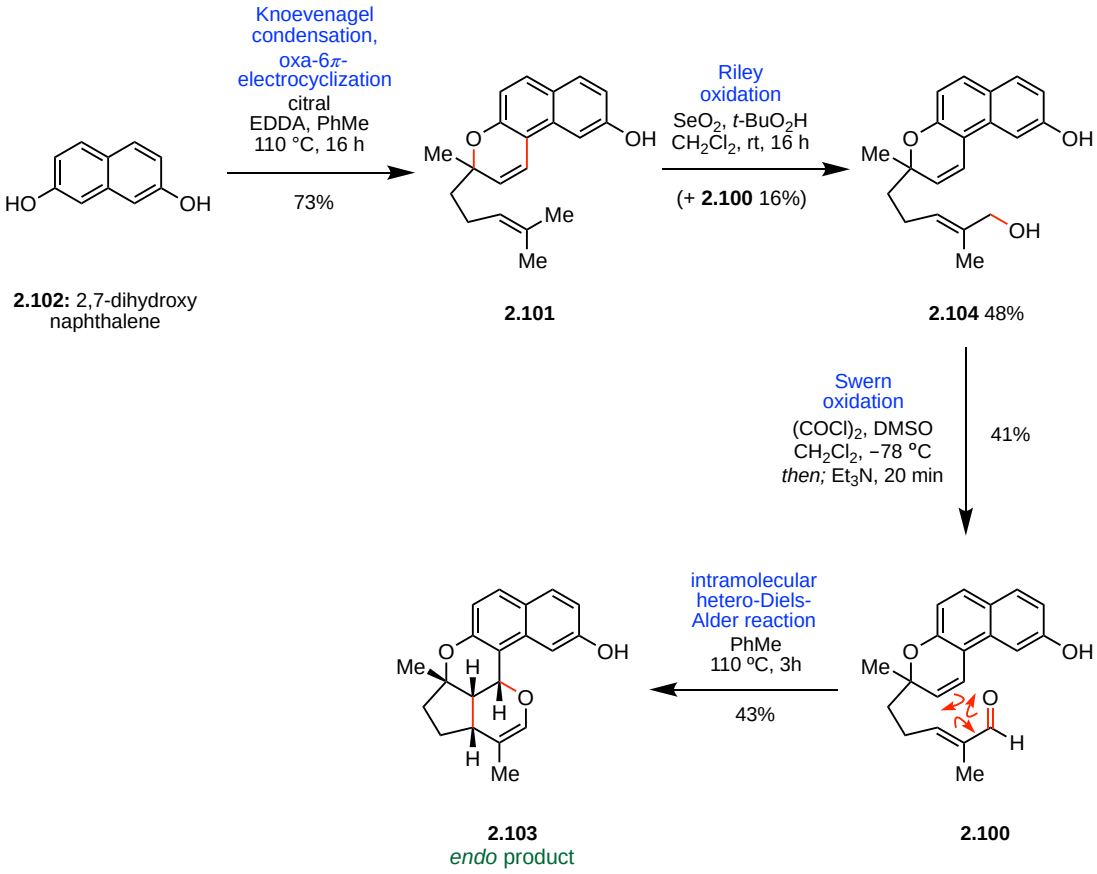
sulfate and K_2CO_3 (**Scheme 2.19**). Riley oxidation with *t*-BuO_2H and catalytic SeO_2 gave direct access to the methoxy protected enal **2.97** in 94% when the reaction was left for 14 h. Unsurprisingly, treatment of enal **2.97** with NaH, THF conditions at −78 °C gave no reaction, presumably as the key intramolecular Michael and oxa-Michael cascade was being suppressed. While thermal conditions through reflux in xylene gave the *endo* Diels–Alder product **2.98** exclusively in a poor yield of 17%. Further reaction of **2.98** when subjected to *m*-CPBA and *p*-TsOH gave the tetracycle **2.99** in 85%, analogous to results observed in the synthesis of **2.92**.



Scheme 2.19 – Investigation into *o*-QM Cascades of the Methoxy Protected Chromene 2.96

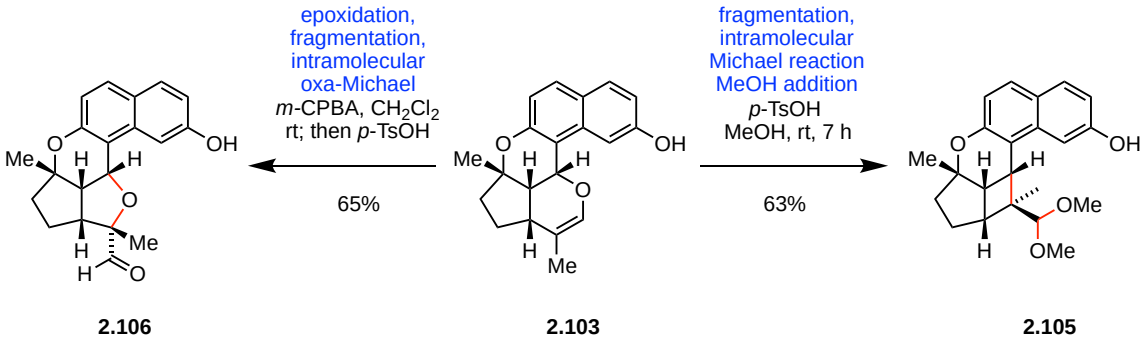
2.2.2 Naphthalene Model Study Featuring *ortho*-Quinone Methide Cyclizations

The undesired transformations of **2.82** into **2.86** (under acidic conditions) and **2.92** (under oxidative conditions) led us to attempt these reactions with a closer analogue of the proposed biosynthetic intermediate **2.100** (**Scheme 2.20**). The chromene **2.101** was synthesized from commercially available 2,7-dihydroxynaphthalene (**2.102**) through Knoevenagel condensation and oxa-6π-electrocyclization with citral and catalytic EDDA (10 mol%) in 73%. A 2-step allylic oxidation of chromene **2.101** then gave the α,β-unsaturated aldehyde **2.100**, which underwent a hetero-Diels-Alder reaction under thermal conditions at 110 °C to give **2.103** in 43%.



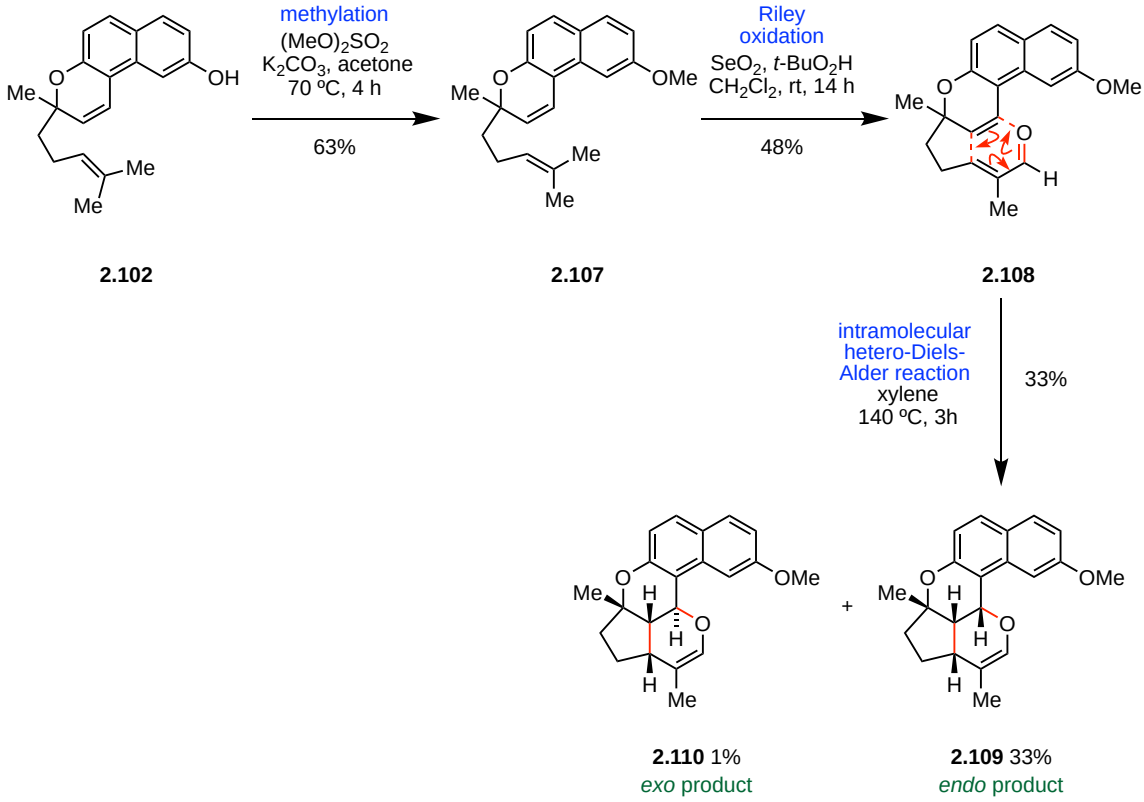
Scheme 2.20 – Synthesis of the Enol Ether 2.103

We hoped that **2.103** would undergo addition of MeOH or EtOH to give analogues of **2.5** and **2.9**, and an oxidative ring-opening to give an analogue of **2.4**. However, in a similar vein to our previous results treatment of **2.103** with acidic MeOH gave the cyclobutane **2.105**, while epoxidation and treatment with *p*-TsOH gave aldehyde **2.106** (**Scheme 2.21**).



Scheme 2.21 – Rearrangements of the Naphthalene Enol Ether 2.103

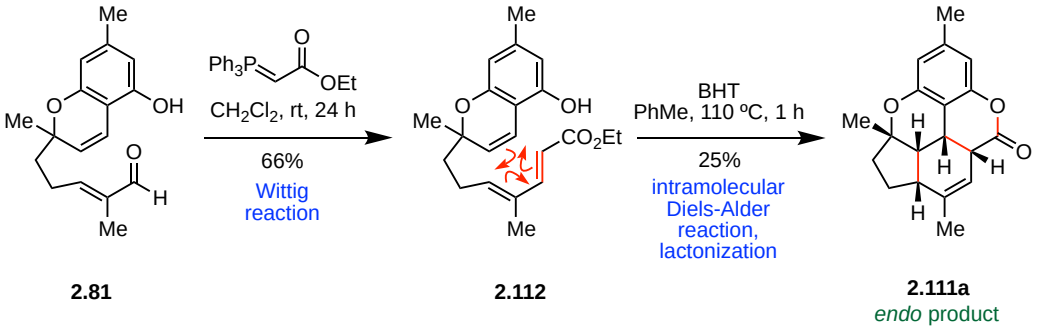
Similar to the orcinol model study, these rearrangements could be replicated with the methoxy protected naphthalene **2.107** (**Scheme 2.22**). Riley oxidation of **2.107** with *t*-BuO_2H and catalytic SeO_2 afforded enal **2.108** in 48%. Reflux of **2.108** for 3 h gave the intramolecular hetero-Diels-Alder *endo* product **2.109** in 33% and the minor diastereoisomer **2.110** synthesized through the *exo* transition state in 1%. Again, we observed a lower yield of **2.109** when compared to the free phenol, indicating the possibility that a naphthoquinone methide intermediate may be involved.



Scheme 2.22 – Investigation into *o*-QM Cascades of the Methoxy Protected Chromene 2.107

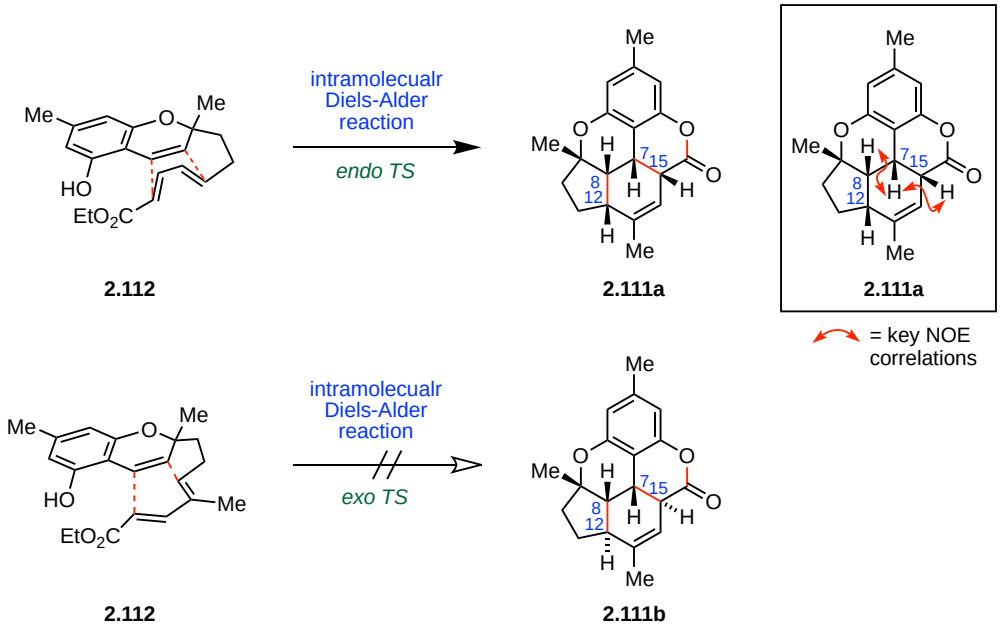
2.2.3 Normal Electron Demand Diels-Alder Reaction Cascades

Inspired by our success in the synthesis of model study enol ethers through inverse demand intramolecular hetero-Diels-Alder reactions, we considered the possibility of incorporating a Wittig reaction, normal demand intramolecular Diels-Alder reaction, and lactonization to afford **2.111a** (**Scheme 2.23**). This transformation intrigued us due to the formation of 5 stereocentres and 3 rings in a single step! Gratifyingly treatment of **2.81** with ethyl (triphenylphosphoranylidene) acetate at room temperature afforded the diene **2.112** in 66%. **2.112** was then heated to reflux in PhMe with the presence of catalytic BHT to afford **2.111a** in 25%.



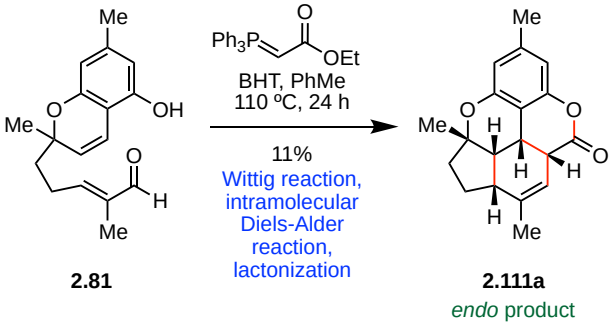
Scheme 2.23 – 2-Step Reaction of Enal 2.81 to Lactone 2.111a

Although the obtained ^{1}H NMR spectrum of **2.111a** had overlapping **H8** and **H12** signals, we were able to observe key NOE correlations between **H7** and **H15** and between **H7** and **H8** (see **2.4.4**), suggesting that the reaction was proceeding through the *endo* transition state rather than the *exo* transition state which would afford the epimers at **H15** and **H12** (**Scheme 2.24**).



Scheme 2.24 – Proposed *Endo* and *Exo* Transition States of 2.112

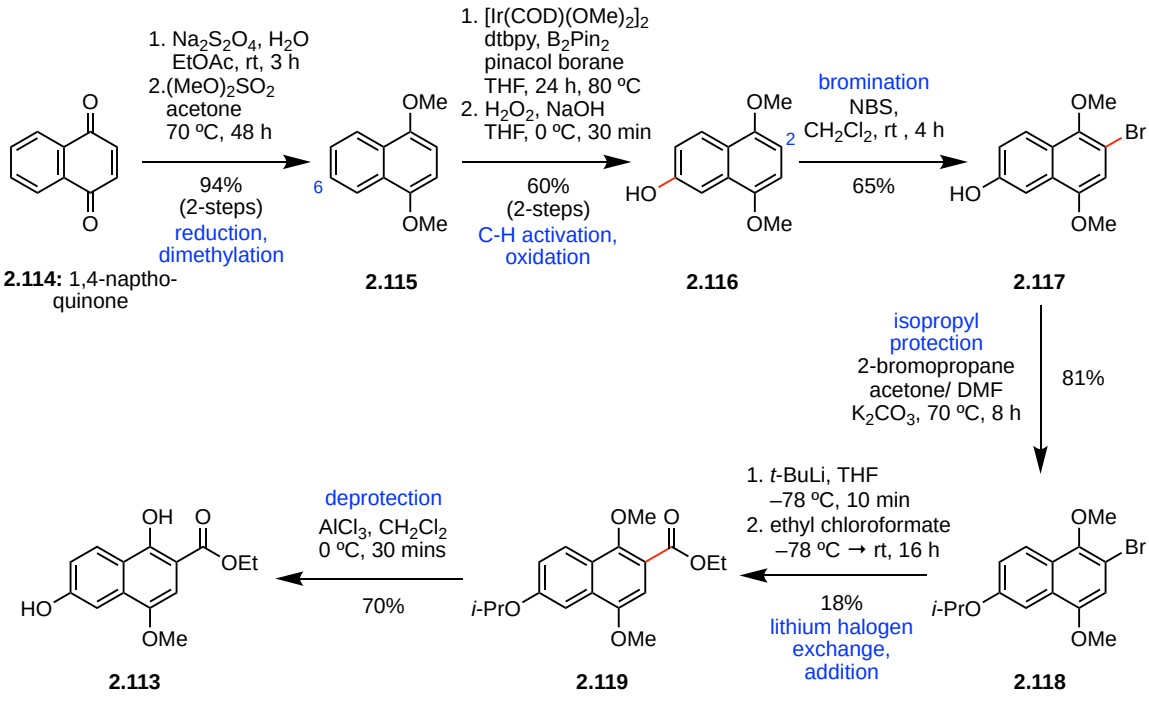
Due to the simplicity of the intramolecular Diels-Alder reaction to only require thermal conditions and due to the highly robust nature of most Wittig reactions, a one-pot reaction cascade from enal **2.81** to lactone **2.111a** was attempted (**Scheme 2.25**). It was found that refluxing **2.81**, ethyl (triphenylphosphoranylidene)acetate and BHT for 24 h gave the desired Wittig, intramolecular Diels-Alder reaction and lactonization cascade to afford **2.111a** in 11%.



Scheme 2.25 – One-Pot Reaction Cascade from Enal 2.81 to Lactone 2.111a

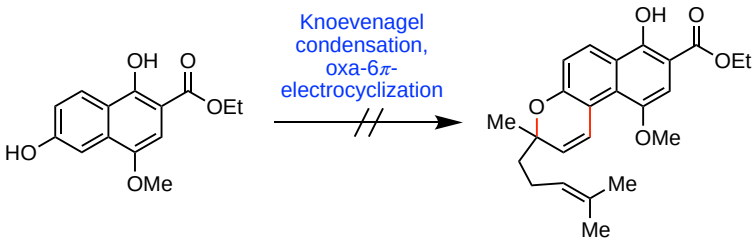
2.2.4 Initial Attempts Towards Busseihydroquinones C – E and Parvinaphthol C

With some interesting *ortho*-QM reaction cascades in hand and some promising results in the synthesis of the key enol ethers **2.82**, **2.98**, **2.103** and **2.109**, our efforts turned towards synthesis of the real parvinaphthol and busseihydroquinone system. We began our approach with an 8-step synthesis of **2.113** following literature conditions from Jeong and co-workers (**Scheme 2.26**).[28] This began with a reductive dimethylation of 1,4-napthoquinone (**2.114**) to give 1,4-dimethoxynapthelene (**2.115**) in 94%. An iridium catalyzed C-H activation at **C6** then afforded a borane ester which was oxidized directly to give phenol **2.116** in 60% (over 2-steps). Next, bromination at **C2** with NBS gave **2.117** in 65%, followed by isopropyl protection to afford **2.118**. A lithium halogen exchange of **2.118** through reaction with *t*-BuLi followed by addition of ethyl chloroformate then gave **2.119** in 18% which was treated with $AlCl_3$ to give **2.113**.



Scheme 2.26 – Literature Synthesis of 2.113 from Jeong *et al.*[28]

We investigated conditions for synthesis of chromene **2.120**, which upon hydrolysis of the ethyl ester would provide busseihydroquinone C (**2.3**). Unfortunately, all attempts of Knoevenagel condensation and oxa-6π-electrocyclization cascades failed (**Table 2.2**). Reaction conditions using EDDA at 3 mol% and 10 mol% gave no reaction, even when left for 48 h (**entries 1**—**2**). While reaction conditions developed by Chauder and co-workers ($PhB(OH)_2$ and AcOH) gave no reaction (**entry 3**).[29] Treatment of **2.113** with pyridine (**entries 4**—**5**) and piperidine (**entry 6**) gave decomposition. Finally, we attempted chromenylation with $Ti(Oi\text{-}Pr)_4$ at −78 °C → rt, however once more no reaction was observed (**entry 7**).



2.113 **2.120**

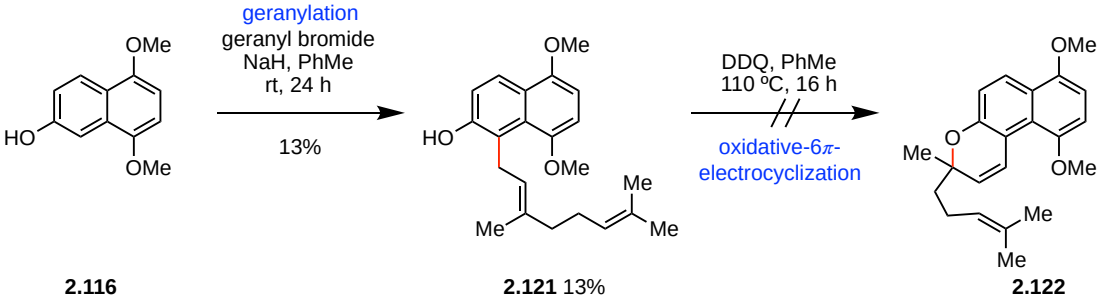
Table 2.2 – Conditions Screened for the Synthesis of Chromene 2.120

Entry	Conditions	Temperature	Time	Result
1	citral, EDDA (3 mol%) PhMe	120 °C	48 h	NR
2	citral, EDDA (10 mol%), PhMe	120 °C	8 h	NR
3	citral, $PhB(OH)_2$ AcOH, PhMe	120 °C	24 h	NR
4	citral, pyridine PhMe	120 °C	24 h	decomp.
5	citral, pyridine	120 °C	24 h	decomp.
6	citral, piperidene Ac_2O, EtOAc	0 °C → 90 °C	18 h	decomp.
7	citral, $Ti(Oi\text{-}Pr)_4$ PhMe	−78 °C → rt	16 h	NR

2.2.5 Further Efforts Towards the Busseihydroquinone and Parvinaphthol Families

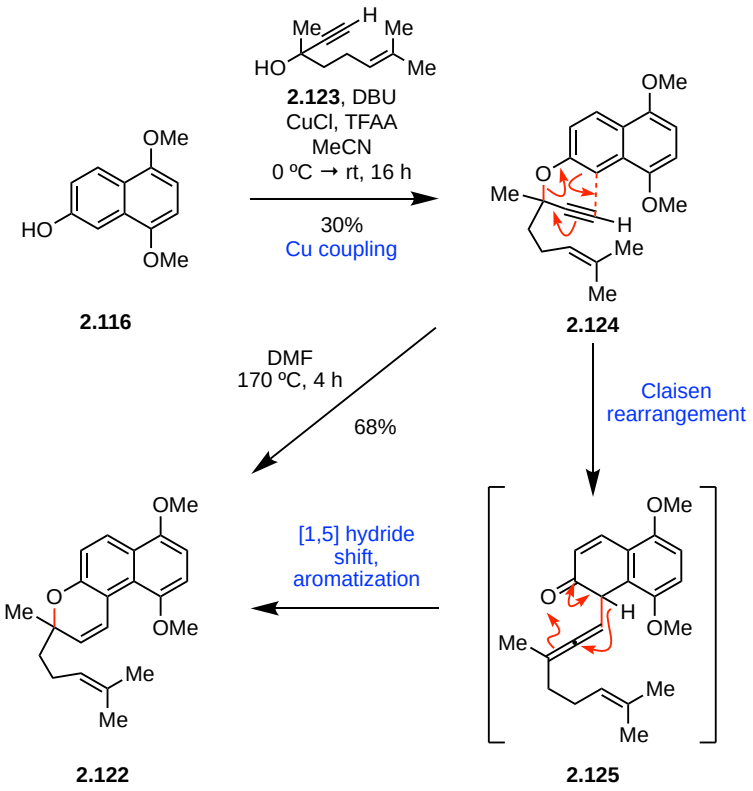
A revised approach featuring an earlier chromenylation was attempted, we hoped that the more electron rich naphthol **2.116** would give better yields as well as allowing us access to larger quantities of starting material. Unfortunately, treatment with citral using the standard chromenylation reaction conditions as previously described (i.e. **Table 2.2**) gave identical results. Instead, we attempted a 2-step chromenylation through geranylation and oxidation (**Scheme**

2.27). Treatment of **2.116** with geranyl bromide gave the desired product **2.121**, however reaction with DDQ gave decomposition.



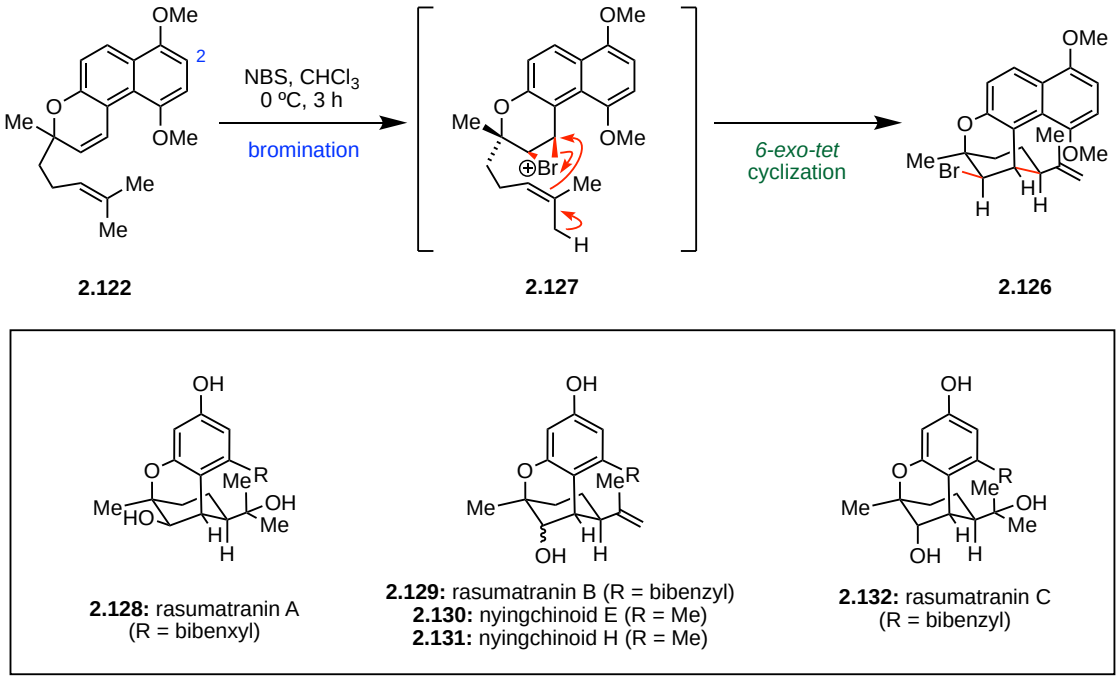
Scheme 2.27 – Attempted 2-Step Chromenylation of 2.116

Interestingly, literature from as early as 1962 by Iwai *et al*. report the similar challenges in the synthesis of naphthalene chromenes.[30] To overcome these issues the authors report a unique approach through intermediate propargyl ethers. Following a modified procedure from Godfrey and co-workers we performed a Cu mediated coupling between **2.116** and the literature compound **2.123** affording **2.124** in 30% (**Scheme 2.28**).[31] A thermally induced Claisen rearrangement, 1,5-hydrogen shift and aromatization then provided the desired chromene **2.122** in 68% through reflux in DMF.



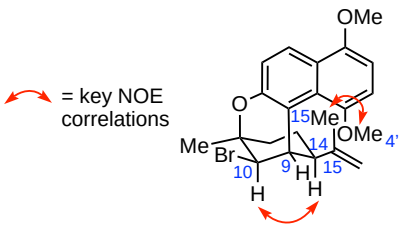
Scheme 2.28 – 2-Step Synthesis of Chromene 2.122 from 2.116

Our attention then turned towards activation of the **C2** position to install the carboxylic acid motif of busseihydroquinone C (**2.3**). Frustratingly, Vilsmeier-Haack formylation conditions only resulted in decomposition of **2.122**. Interestingly, an attempted bromination of **2.122** at **C2** through reaction with NBS in CH_2Cl_2 at 0 °C gave **2.126** in 38% (**Scheme 2.29**). This reaction is presumably proceeding through the bromonium intermediate **2.127** followed by a *6-endo-tet* cyclization. Serendipitously, the scaffold for **2.127** is analogous to another class of natural products rasumatranins A—C and nyingchinoids E and H (i.e. **2.128** – **2.132**). We propose that these compounds are formed *via* an analogous route, through a selective epoxidation rather than bromination of the chromene motif. Investigation into similar epoxidations and brominations of 2H-chromenes have been previously reported in our group,[32] however the total synthesis of **2.128** – **2.132** is yet to be realized.



Scheme 2.29 – Synthesis of 2.126 Through Bromination of 2.112

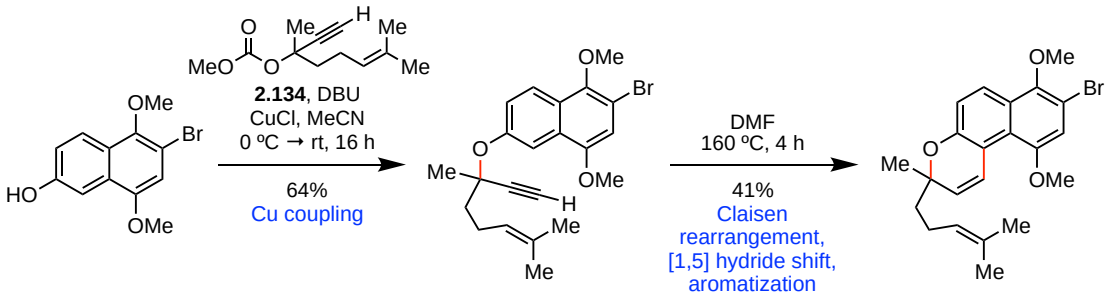
Bromination and *6-endo-tet* cyclization of **2.122** to afford **2.126** resulted in the formation of 4 new stereocentres, careful analysis of the ^{1}H NMR spectrum of **2.126** allowed us to assign the relative stereochemistry (**Figure 2.3**). We observed key NOE correlations between the methoxy at **H4'** and the methyl group at **H15** which would be only possible with the **H15** terminal alkene in the axial position. Additionally, there was a strong diagnostic 1,3-diaxial correlation between **H10** and **H14**.



2.126

Figure 2.3 – Relative Configuration of 2.126

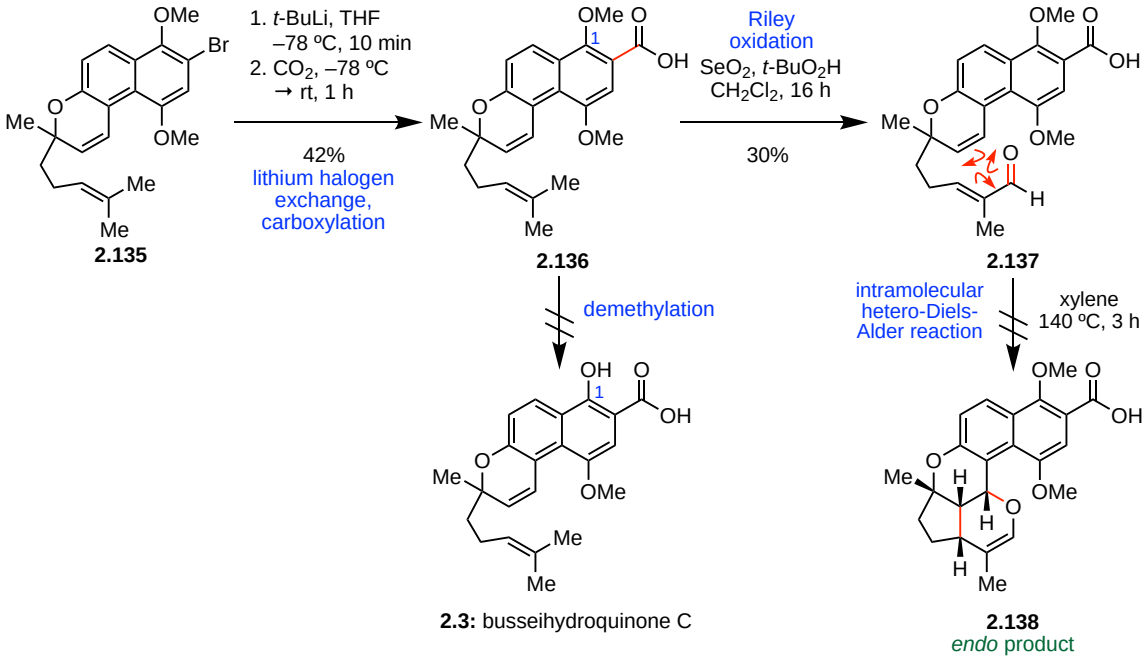
Having succeeded in the synthesis of the chromene **2.122** but unable to functionalize at the **C2** carbon, we attempted the 2-step chromenylation of **2.117** through an analogous propargyl ether **2.133** (**Scheme 2.30**). We observed higher yields of **2.133** when using the methoxy carbonate **2.134** rather than the *in-situ* acetate protected **2.123**, affording access to **2.133** in 64%. Analogous to the synthesis of **2.122**, treatment of **2.133** afforded **2.135** this time in 41% yield.



2.117 **2.133** **2.135**

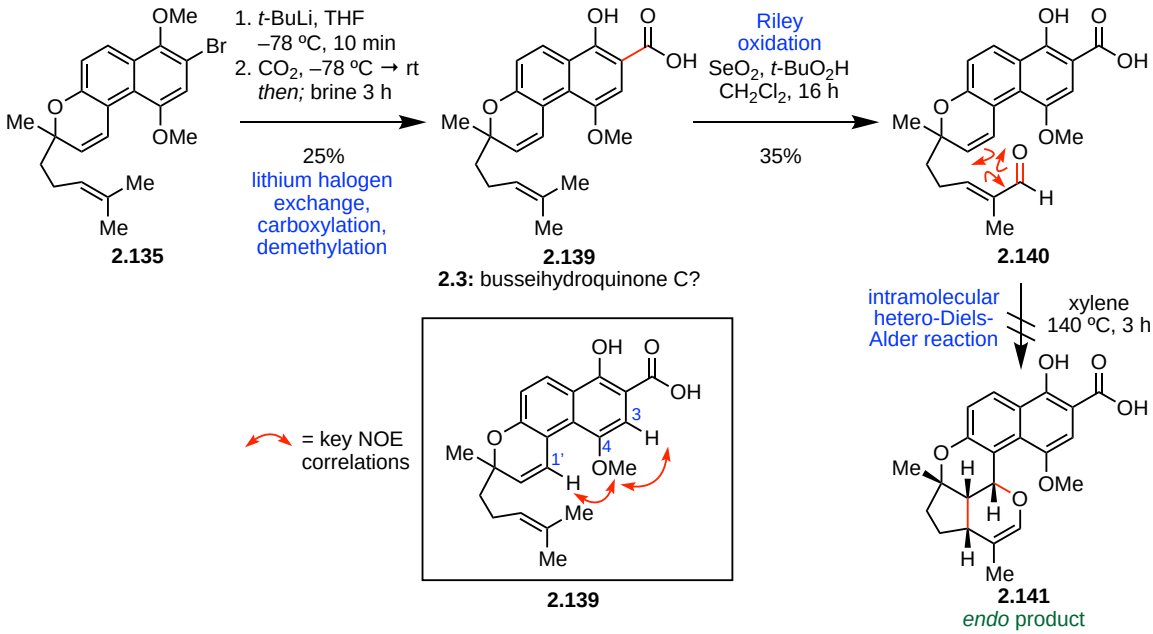
Scheme 2.30 – Synthesis of Chromene 2.135

With access to **2.135**, a direct carboxylation through lithium halogen exchange and reaction with anhydrous CO_2 gave **2.136** in 42% (**Scheme 2.31**). Unfortunately, all attempts to selectively remove the methoxy protecting group at **C1** failed. Reaction with BBr_3, HBr and $AlCl_3$ conditions all afforded decomposition of **2.136** rather than formation of busseihydroquinone C (**2.3**). Instead, we decided to continue this synthesis forward performing a Riley oxidation of **2.136** to give enal **2.137** in 30% yield through reaction with catalytic SeO_2 and *t*-BuO_2H. Disappointingly, heating **2.137** at reflux in xylene did not give the desired intramolecular hetero-Diels-Alder product **2.138** only decomposition of the starting material was observed.

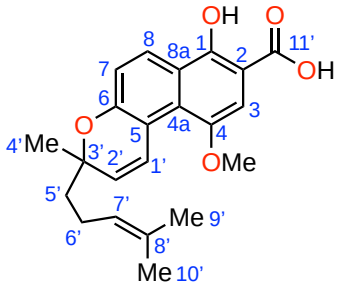


Scheme 2.31 – Attempted Intramolecular Hetero-Diels-Alder Reaction of enal 2.137

Surprisingly, it was found that when quenching the lithium halogen exchange/ carboxylation reaction with sat. brine$_{(aq)}$ and leaving the solution to stir for 2 h we obtained what we assigned to be **2.139** directly (**Scheme 2.32**). Frustratingly, we observed the ^{1}H NMR of **2.139** had all the expected key diagnostic NOE correlations (i.e. between **C3** and **C4**-OMe, and between **C4**-OMe and **C1'**), however the obtained spectra did not match that of the natural product **2.3** (**Table 2.3**). We continued with this synthesis affording enal **2.140** from reaction of **2.139**, however the attempted intramolecular hetero-Diels-Alder reaction failed giving only decomposition of **2.140**.



Scheme 2.32 – Attempted Intramolecular Hetero-Diels-Alder Reaction of Enal 2.140



2.139
2.3: busseihydroquinone C?

Table 2.3 – Comparison of the Reported and Obtained NMR Spectra of 2.3 and 2.139

Assignment	^{1}H NMR (d_6-DMSO)		^{13}C NMR	
	Sample 2.139 (600 MHz)	Natural Sample (800 MHz) Endale *et al.*[2]	Sample 2.139 (150 MHz) $CDCl_3$	Natural Sample (800 MHz) d_6-DMSO Endale *et al.*[2]
1	--	--	179.3	155.0
2	--	--	128.0	102.9
3	6.66 (s)	7.06 (s)	105.7	104.3
4	--	--	155.1	148.5
4a	--	--	124.5	125.9
5	--	--	114.9	114.3
6	--	--	151.7	154.4
7	7.09 (d, *J* = 9.5 Hz)	7.10 (d, *J* = 8.7 Hz)	117.4	118.2
8	8.27 (d, *J* = 9.6 Hz)	8.11 (d, *J* = 8.7 Hz)	129.6	124.8
8a	--	--	130.3	120.8
1’	7.64 (d, *J* = 10.3 Hz)	7.70 (d, *J* = 10.4 Hz)	124.2	122.5
2’	5.64 (d, *J* = 10.3 Hz)	5.68 (d, *J* = 10.4 Hz)	125.9	127.3
3’	--	--	77.1	77.4
4’	1.38 (s)	1.37 (s)	25.6	25.4
5’	1.72 – 1.69 (m)	1.67 (m)	40.5	39.9
6’	2.09 – 2.06 (m)	2.05 (m)	22.9	22.2
7’	5.10 (t, *J* = 7.4 Hz)	5.05 (t, *J* = 6.8 Hz)	124.4	123.9
8’	--	--	131.8	130.9
9’	1.52 (s)	1.49 (s)	25.8	17.4
10’	1.61(s)	1.59 (s)	17.7	25.3
11’	--	--	185.7	172.6
1’OH	13.05 (br s)	12.20 (br s)	--	--
4’OMe	3.89 (s)	3.85 (s)	55.7	55.7

2.3 Conclusion and Future Work

In summary, we have reported some short model studies featuring the synthesis of the polycyclic scaffold of busseihydroquinone E (**2.3**) and parvinaphthol C (**2.8**), achieved *via* diastereoselective intramolecular hetero-Diels-Alder reactions of chromene intermediates under basic or thermal conditions. From this key framework, some interesting *o*-QM cascade reactions involving the

synthesis of ring contracted cyclobutane and furan products was developed. This led to a new and high yielding approach towards the total synthesis of rhodonoid D (**2.93**).

We also believe efforts towards busseihydroquinone C (**2.3**) should be revisited and that a possible reassignment should be strongly considered. Finally, the synthesis of bromide **2.126** *via* a bromination and *6-endo-tet* cyclization cascade has inspired us to develop a biosynthetic proposal towards rasumatranins A—C and nyingchinoids E and H (i.e. **2.128** — **2.132**). We hope to explore this chemistry within our group in the future.

2.4 Experimental

2.4.1 General Methods

All chemicals used were purchased from commercial suppliers and used as received. All reactions were performed under an inert atmosphere of N_2 unless otherwise stated. Thin layer chromatography was performed using aluminium sheets coated with silica gel. Visualization was aided by viewing under a *UV* lamp and staining with the appropriate stain followed by heating. All R_f values were measured to the nearest 0.05. Flash chromatography was performed using 40-63 micron grade silica gel. Melting points were recorded on a digital melting point apparatus and are uncorrected. Infrared spectra were recorded using an FT-IR spectrometer as the neat compounds. High field NMR was recorded using a 600 MHz spectrometer (^{1}H at 600 MHz, ^{13}C at 150 MHz) or a 500 MHz spectrometer (^{1}H at 500 MHz, ^{13}C at 125 MHz). The solvent used for NMR spectra was $CDCl_3$ unless otherwise specified. ^{1}H chemical shifts are reported in ppm on the δ-scale relative to TMS (δ 0.0) and ^{13}C{^{1}H} NMR are reported in ppm relative to chloroform (δ 77.16). Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet and (m) multiplet. All J-values were rounded to the nearest 0.1 Hz. ESI high resolution mass spectra were recorded on a Q-TOF mass spectrometer. Photochemistry with *UVA* light was performed using a generic brand commercial LED *UV* light globe; wavelength: 365 nm. Photochemistry with *UVC* light was performed using a generic brand commercial LED *UV* light globe; wavelength: 254 nm. Photochemical reactions with visible light were performed with a conventional commercial LED desk lamp at 240 V with a 4 W 5000 K 32 mÅ globe. Reactions conducted under 470 nm blue LED lamp were performed using a 19-24VDC 40W Kessil A160WE.

2.4.2 Experimental Procedures

2.79: orcinol **2.78**

To a solution of orcinol (**2.79**) (10.0 g, 81.0 mmol, 1.0 equiv.) in PhMe (250 mL) at room temperature was added citral (12.3 mL, 81.0 mmol, 1.0 equiv.) and EDDA (500 mg, 2.43 mmol, 3 mol%). The reaction was stirred at 110 °C for 5 h. The mixture was cooled to room temperature, then concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (8:1 hexanes/ EtOAc) to give chromene **2.78** (17.2 g, 82%) as an orange oil. Data for **2.78** matched that previously reported in the literature.[26]

Data for 2.78:

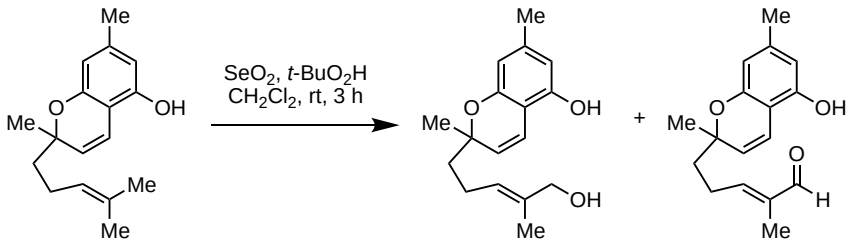
R_f: 0.40 (5:1 hexanes/ EtOAc).

FTIR (neat): 3387, 2970, 2924, 1625, 1578, 1509, 1450, 1377, 1330, 1250 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.61 (d, *J* = 10.0 Hz, 1H), 6.24 (s, 1H), 6.11 (s, 1H), 5.49 (d, *J* = 10.0 Hz, 1H), 5.10 (t, *J* = 7.2 Hz, 1H), 4.73 (br s, 1H), 2.20 (s, 3H), 2.13 – 2.07 (m, 2H), 1.75 – 1.70 (m, 1H), 1.66 (s, 3H), 1.65 – 1.61 (m, 1H), 1.58 (s, 3H), 1.37 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.3, 151.2, 139.7, 131.8, 127.4, 124.4, 116.9, 110.0, 108.5, 106.9, 78.4, 41.3, 26.4, 25.8, 22.9, 21.7, 17.8 ppm.

HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{17}H_{21}O_2$ 257.1547; found 257.1539.



2.78 **2.80** 42% **2.81** 7%

Chromene **2.78** (1.20 g, 4.83 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (70 mL) and SeO_2 (108 mg, 0.970 mmol, 20 mol%) was added, followed by *t*-BuO_2H (3.20 mL, 5.50 M, 17.4 mmol, 3.6 equiv.). The reaction was left to stir at room temperature for 3 h, quenched with sat. $Na_2SO_{3\,(aq)}$ (70 mL) and the product was extracted with CH_2Cl_2 (70 mL). The organic phase was further washed with sat. brine (70 mL), dried with $MgSO_4$, filtered, concentrated and the residue was purified *via* flash chromatography on SiO_2 (2:1 hexanes/ EtOAc) to give allylic alcohol **2.80** (560 mg, 42%) as an orange oil and aldehyde **2.81** (90 mg, 7%) as a red oil.

Data for 2.80:

R_f: 0.30 (3:1 hexanes/ EtOAc).

FTIR (neat): 3361, 2970, 2922, 1665, 1623, 1578, 1449, 1420, 1328, 1271, 1196, 1138, 1096, 1060, 991, 823 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.35 (s, 1H), 6.69 (d, *J* = 10.0 Hz, 1H), 6.51 (t, *J* = 7.5 Hz, 1H), 6.20 (s, 1H), 6.14 (s, 1H), 5.45 (d, *J* = 10.0 Hz, 1H), 5.36 (br s, 1H), 2.57 – 2.43 (m, 2H), 2.20 (s, 3H), 1.92 – 1.80 (m, 2H), 1.71 (s, 3H), 1.41 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 195.8, 155.4, 153.9, 151.6, 140.1, 139.4, 126.1, 117.9, 109.7, 108.8, 106.6, 78.1, 39.7, 26.7, 24.3, 21.7, 9.3 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{23}O_3$ 275.1640; found 275.1642.

Data for 2.81:

R_f: 0.10 (2:1 hexanes/ EtOAc).

FTIR (neat): 3310, 2971, 2921, 2861, 1623, 1578, 1509, 1449, 1328, 1285, 1197, 1140, 1078, 1060, 990, 907, 823, 774, 731 cm^{-1}.

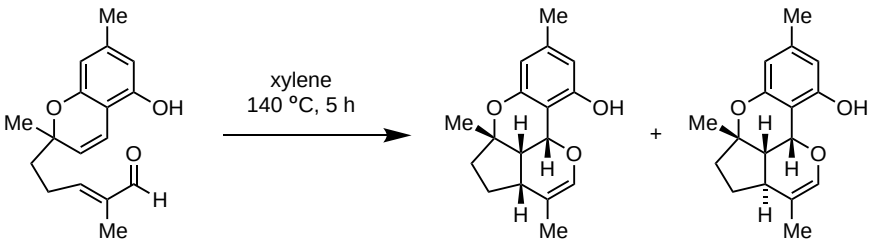
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.63 (d, *J* = 10.0 Hz, 1H), 6.21 (s, 1H), 6.10 (s, 1H), 5.53 (br s, 1H), 5.45 (d, *J* = 10.0 Hz), 5.40 (t, *J* = 7.1 Hz, 1H), 3.97 (s, 2H), 2.19 – 2.17 (m, 2H), 1.79 – 1.67 (m, 2H), 1.62 (s, 3H), 1.5 (br s, 1H), 1.38 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.1, 151.5, 139.7, 134.7, 126.8, 126.6, 117.2, 109.6, 108.5, 106.8, 78.3, 69.2, 40.9, 26.7, 22.6, 21.6, 13.7 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{21}O_3$ 273.1485; found 273.1488.

2.80 **2.81**

A solution of $(COCl)_2$ (0.20 mL, 2.34 mmol, 1.2 equiv.) in CH_2Cl_2 (20 mL) was cooled to –78 °C. DMSO (0.33 mL, 4.67 mmol, 2.4 equiv.) was added and the reaction mixture was stirred for 20 min. The reaction mixture was then added to a second solution of allylic alcohol **2.80** (534 mg, 1.95 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) at –78 °C. The reaction was stirred for 10 min, followed by addition of Et_3N (1.62 mL, 11.7 mmol, 6.0 equiv.) after which time the solution was left to warm to room temperature over 1 h. Distilled H_2O (20 mL) was added to quench the reaction, the product was extracted with CH_2Cl_2 (40 mL) and the organic solution was washed with sat. brine (40 mL), dried with $MgSO_4$, filtered and concentrated. Purification *via* flash chromatography on SiO_2 (4:1 hexanes/ EtOAc) afforded aldehyde **2.81** (530 mg, 86%). Data for **2.81** matched that previously obtained.



2.81 **2.82** 39% **2.83** 4%

Aldehyde **2.81** (2.12 g, 7.40 mmol, 1.0 equiv.) was dissolved in xylene (70 mL) and heated to 140 °C and stirred for 5 h. After this time the solution was concentrated and purified *via* flash chromatography on SiO_2 (6:1 hexanes/ EtOAc) to give enol ether **2.82** (825 mg, 39%) as an orange solid and **2.83** (83 mg, 4%) as a white solid.

Data for 2.82:

R_f: 0.40 (3:1 hexanes/ EtOAc).

MP: 129 – 133 °C.

FTIR (neat): 3409, 2955, 2870, 1651, 1634, 1576, 1499, 1446, 1380, 1358, 1334, 1200, 1178, 1142, 1121, 1081, 1063, 996, 1018, 996, 889, 823, 708, 676 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (br s, 1H), 6.27 (s, 1H), 6.20 (s, 1H), 6.16 (s, 1H), 5.32 (d, *J* = 8.3 Hz, 1H), 2.70 (m, 1H), 2.58 (t, *J* = 9.4 Hz, 1H), 2.21 (s, 3H), 2.04 (m, 1H), 1.93 – 1.87 (m, 1H), 1.73 – 1.58 (m, 1H), 1.54 (s, 3H), 1.53 – 1.48 (m, 1H), 1.43 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9, 155.8, 140.3, 134.7, 118.0, 109.6, 109.4, 105.1, 85.9, 66.4, 44.7, 40.1, 37.4, 29.5, 25.8, 21.5, 16.2 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{21}O_3$ 273.1485; found 273.1486.

Data for 2.83:

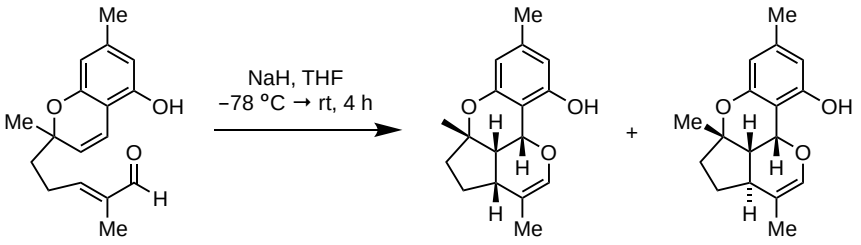
R_f: 0.60 (3:1 hexanes/ EtOAc).

FTIR (neat): 3392, 2960, 2881, 1675, 1628, 1595, 1510, 1415, 1357, 1302, 1182, 1122, 1059, 998, 920, 901, 827 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.50 (br s, 1H), 6.29 (s, 1H), 6.17 (s, 1H), 6.09 (s, 1H), 5.54 (d, *J* = 6.4 Hz, 1H), 2.48 – 2.41 (m, 1H), 2.26 – 2.22 (m, 1H), 2.21 (s, 3H), 2.03 – 1.95 (m, 2H), 1.87 – 1.83 (m, 1H), 1.57 (s, 3H), 1.47 – 1.41 (m, 1H), 1.39 (s, 3H) ppm.

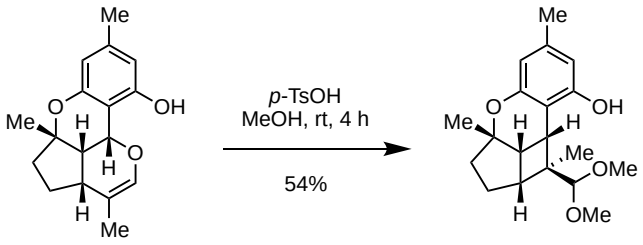
^{13}C NMR (150 MHz, $CDCl_3$): δ 157.5, 152.4, 140.7, 134.9, 113.2, 109.9, 109.3, 104.4, 84.3, 69.9, 46.9, 39.4, 35.9, 24.7, 23.8, 21.5, 15.0 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{21}O_3$ 273.1485; found 273.1484.



2.81 **2.82** 67% **2.83** 8%

Aldehyde **2.81** (305 mg, 1.12 mmol, 1.0 equiv.) was dissolved in THF (18 mL) and cooled to 0 °C. NaH (60% wt./ wt., 90 mg, 2.24 mmol, 2.0 equiv.) was then added in small portions and the reaction was stirred at room temperature for 4 h. The solution was then quenched with sat. $NH_4Cl_{(aq)}$ and extracted with Et_2O (3 x 10 mL). Combined organic extracts were dried with $MgSO_4$, concentrated and purified *via* flash chromatography on SiO_2 (6:1 hexanes/ EtOAc) to give enol ether **2.82** as the major diastereoisomer (205 mg, 67%) and **2.83** as the minor diastereoisomer (25 mg, 8%). Data for **2.82** and **2.83** matched that previously obtained.



2.82 **2.86**

To a solution of enol ether **2.82** (56 mg, 0.210 mmol, 1.0 equiv.) in MeOH (3 mL) was added *p*-toluenesulfonic acid (5 mg, 0.020 mmol, 10 mol%). The reaction was stirred at room temperature for 4 h, then distilled water was added (5 mL) and the product was extracted with Et_2O (3 x 5 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. Purification *via* flash chromatography on SiO_2 (6:1 hexanes/ EtOAc) then gave acetal **2.86** (35 mg, 54%) as an orange solid.

Data for 2.86:

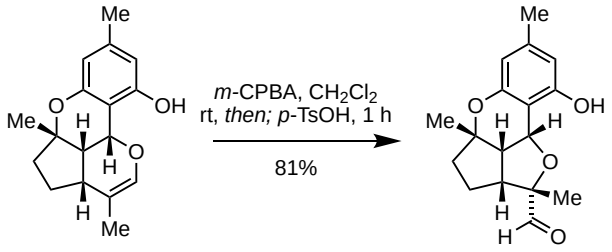
R_f: 0.40 (3:1 hexanes/ EtOAc).

FTIR (neat): 3344, 2950, 1630, 1575, 1497, 1450, 1354, 1316, 1293, 1206, 1176, 1129, 1100, 1077, 1057, 999, 982, 948, 908, 824, 736 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (br s, 1H), 6.26 (m, *J* = 6.4 Hz, 2H), 4.29 (s, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.28 (d, *J* = 9.9 Hz, 1H), 2.63 (t, *J* = 7.5 Hz, 1H), 2.56 (m, 1H), 2.22 (s, 3H), 1.94 (m, 1H), 1.71 – 1.62 (m, 3H), 1.39 (s, 3H), 0.84 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.6, 153.9, 138.4, 114.4, 110.2, 108.7, 105.2, 82.5, 59.6, 58.8, 47.2, 40.9, 39.2, 37.9, 29.8, 28.1, 25.4, 21.5, 10.6 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{27}O_4$ 319.1904; found 319.1894.



2.82 **2.92**

Enol ether **2.82** (191 mg, 0.667 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (20 mL) and *m*-CPBA (77%, 173 mg, 1.00 mmol, 1.5 equiv.) was added. The resulting solution was stirred at room temperature for 1 h, then *p*-toluenesulfonic acid (250 mg, 1.31 mmol, 2.0 equiv.) was added and the solution was stirred for a further for 1 h. The reaction was then quenched with sat. $NaSO_{3(aq.)}$ (20 mL), the organic layer was then further washed with sat. $NaHCO_{3(aq.)}$ (2 x 20 mL) and extracted with CH_2Cl_2 (2 x 20 mL), dried with $MgSO_4$ and filtered. Concentration afforded furan **2.92** (155 mg, 81%), which was used without further purification.

Data for 2.92:

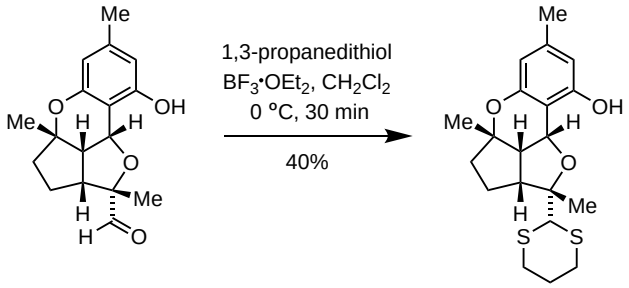
R_f: 0.40 (7:1 hexanes/ EtOAc).

FTIR (neat): 3443, 2971, 2935, 1734, 1630, 1585, 1458, 1378, 1272, 1195, 1134, 1069, 998 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.75 (s, 1H), 6.48 (br s, 1H), 6.39 (s, 1H), 6.34 (s, 1H), 5.18 (d, *J* = 8.3 Hz, 1H), 2.92 – 2.86 (m, 2H), 2.25 (s, 3H), 1.96 – 1.89 (m, 1H), 1.77 – 1.69 (m, 1H), 1.66 – 1.59 (m, 1H), 1.52 – 1.47 (m, 1H), 1.45 (s, 3H), 1.41 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.9, 155.9, 152.6, 140.8, 110.7, 109.8, 106.4, 89.3, 83.0, 70.3, 52.6, 51.2, 36.2, 27.1, 24.8, 21.7, 21.6 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{21}O_5$ 289.1434; found 289.1423.



2.92 **2.142**

To a solution of furan **2.92** (250 mg, 0.870 mmol, 1.0 equiv.) under N_2 in dry CH_2Cl_2 (20 mL) was added 1,3-propanedithiol (0.29 mL, 2.88 mmol, 3.0 equiv.) and $BF_3{\cdot}OEt_2$ (400 mg, 0.35 mL, 2.82 mmol, 3.0 equiv.) at 0 °C. The reaction mixture was stirred for 30 min at room temperature and quenched by the addition of sat. $NaHCO_{3(aq)}$ (20 mL). The organic layer was then separated and the aqueous phase was further extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 (9:1 hexanes/ EtOAc) then afforded dithiane **2.142** (93 mg, 40%) as a yellow solid.

Data for 2.142:

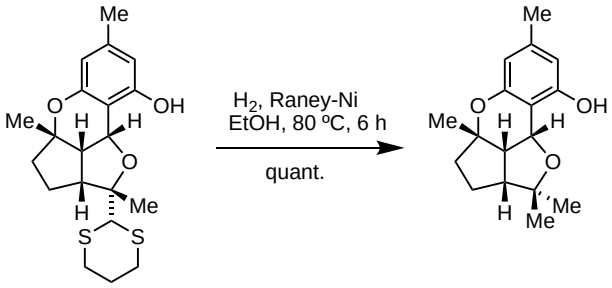
R_f: 0.30 (9:1 hexanes/ EtOAc).

FTIR (neat): 3435, 2972, 1635, 1583, 1459, 1378, 1359, 1459, 1378, 1359, 1275, 1194, 1146, 1104, 1129, 1065, 997, 908, 831, 774, 730 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.96 (br s, 1H), 6.36 (s, 1H), 6.29 (s, 1H), 4.96 (d, *J* = 9.1 Hz, 1H), 4.28 (s, 1H), 2.95 – 2.73 (m, 6H), 2.23 (s, 3H), 1.90 – 1.76 (m, 4H), 1.50 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.1, 151.8, 140.2, 110.2, 109.9, 107.3, 86.6, 82.7, 69.6, 56.1,51.6, 51.6, 35.4, 31.1, 30.8, 27.9, 26.1, 24.3, 22.8, 21.6 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{27}O_3S_2$ 379.1369; found 379.1392.



2.142 **2.93:** rhodonoid D

To a solution of dithiane **2.142** (52 mg, 0.136 mmol, 1.0 equiv.) in dry EtOH (10 mL) was added Raney® Nickel (0.6 mL, 2400 slurry in H_2O). H_2 was sparged through the solution for 10 min, then the reaction was heated at reflux under H_2 for 6 h and filtered through Celite (washed with EtOAc). The solution was then concentrated to give rhodonoid D (**2.93**) (37 mg, 0.130 mmol, *quant.*) as a white solid. Data for rhodonoid D (**2.93**) matched that previously reported in literature.[33]

Data for rhodonoid D (2.93):

R_f: 0.55 (2:1 hexanes/ EtOAc).

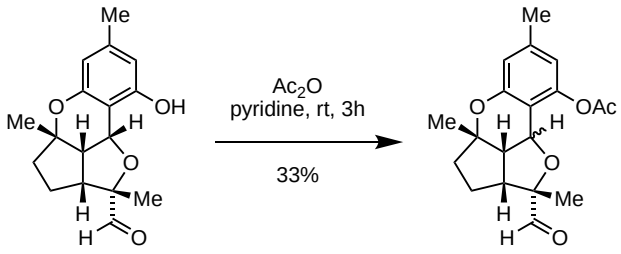
MP: 162 – 165 °C.

FTIR (neat): 3435, 2970, 2921, 2853, 1636, 1586, 1460, 1370, 1326, 1299, 1190 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92 (s, 1H), 6.35 (s, 1H), 6.29 (s, 1H), 4.92 (d, *J* = 9.1 Hz, 1H), 2.82 (t, *J* = 8.5 Hz, 1H), 2.56 (ddd, *J* = 9.9, 8.0, 3.8 Hz, 1H), 2.23 (s, 3H), 1.85 – 1.78 (m, 1H), 1.75 – 1.72 (m, 1H), 1.67 – 1.61 (m, 1H), 1.48 (s, 3H), 1.44 – 1.40 (m, 1H), 1.33 (s, 3H), 1.29 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.1, 151.7, 139.9, 110.0, 109.2, 107.3, 83.2, 82.9, 68.8, 51.6, 51.5, 34.9, 28.0, 27.5, 24.13, 24.07, 21.5 ppm.

HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{17}H_{21}O_3$ 273.1492; found 273.1489.



2.92 **2.94**

To aldehyde **2.92** (30 mg, 0.10 mmol, 1.0 equiv.) in pyridine (2 mL) was added dropwise at room temperature Ac_2O (0.02 mL, 0.22 mmol, 2.2 equiv.). After 3 h the reaction was quenched upon addition of sat. brine (5 mL) and product was extracted EtOAc (3 x 5 mL), dried with $MgSO_4$, filtered and concentrated. Purification by column chromatography on SiO_2 (20:1 hexanes/ EtOAc) then gave **2.94** (11 mg, 33%) as a 1:1 mixture of epimers.

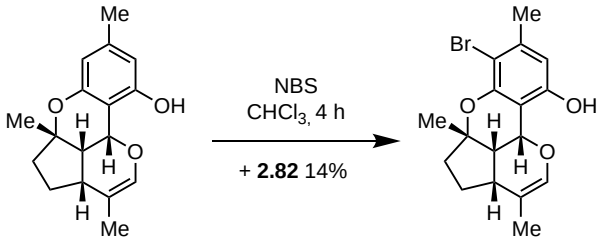
Partial Data for 2.94:

R_f: 0.40 (20:1 hexanes/ EtOAc).

FTIR (neat): 2931, 1771, 1735, 1200, 1134 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.71 (s, 2H), 6.64 (s, 1H), 6.60 (s, 1H), 6.58 (s, 1H), 6.51 (s, 1H), 5.06 (d, *J* = 8.6 Hz, 1H), 4.89 (d, *J* = 8.6 Hz, 1H), 2.88 (q, *J* = 8.6 Hz, 1H), 2.78 (t, *J* = 8.6 Hz, 1H), 2.74 – 2.69 (m, 1H), 2.65 – 2.61 (m, 1H) 2.30 (s, 6H), 2.28 (s, 6H), 2.09 – 2.05 (m, 1H), 1.82 – 1.70 (m, 4H), 1.62 – 1.55 (m, 4H), 1.37 (s, 3H), 1.32 (s, 3H), 1.32 (s, 3H), 1.26 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 205.4, 169.6, 154.9, 149.9, 140.7, 117.1, 116.4, 112.2, 87.8, 86.1, 67.8, 55.4, 51.9, 40.4, 26.1, 25.6, 21.6, 21.0, 21.0 ppm.



2.82 **2.95** 68%

To a solution of **2.82** (100 mg, 0.476 mmol, 1.0 equiv.) in $CHCl_3$ (20 mL) at −10 °C was added NBS (37 mg, 0.428 mmol, 0.9 equiv.). The solution was left to warm to room temperature over 4 h, then quenched with $NH_4Cl_{(aq)}$ (20 mL) and product extracted $CHCl_3$ (3 x 20 mL), dried with $MgSO_4$, filtered and concentrated. Purification by flash chromatography on SiO_2 (9:1 hexanes/ EtOAc) then afforded bromide **2.95** (87 mg, 68%) and the recovered starting material **2.82** (14 mg, 14%). Data for **2.82** matched that previously obtained.

Data for 2.95:

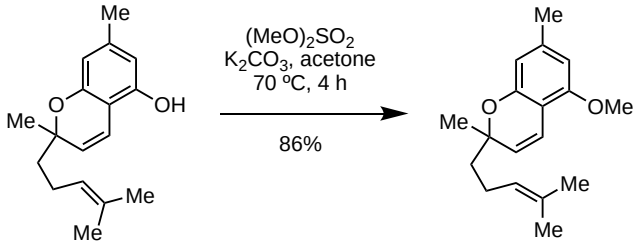
R_f: 0.10 (4:1 hexanes/ EtOAc).

FTIR (neat): 3384, 2961, 1675, 1618, 1572, 1451, 1360, 1304, 1170, 995, 836 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.84 (br s, 1H), 6.40 (s, 1H), 6.27 (s, 1H), 5.19 (d, *J* = 6.6 Hz, 1H), 2.81 – 2.61 (m, 1H), 2.48 (dd, *J* = 10.1, 6.6 Hz, 1H), 2.32 (s, 3H), 2.07 – 2.01 (m, 1H), 1.87 – 1.78 (m, 1H), 1.77 – 1.72 (m, 1H), 1.66 – 1.60 (m, 2H), 1.34 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.0, 151.2, 139.4, 137.7, 115.7, 112.1, 108.7, 104.5, 86.2, 65.7, 46.5, 39.3, 37.9, 28.6, 27.0, 23.3, 16.3 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{20}O_3Br$ 351.0590; found 351.0585.



2.78 **2.96**

To a solution of **2.78** (5.11 g, 9.00 mmol, 1.0 equiv.) in acetone (150 mL) was added K_2CO_3 (6.45 g, 46.8 mmol, 5.2 equiv.) and dimethyl sulfate (1.70 mL, 17.9 mmol, 2.0 equiv.). The solution was heated to reflux for 2 h, then cooled and distilled water (150 mL) added. The product was extracted with EtOAc (3 x 150 mL), dried $MgSO_4$, filtered and concentrated. Purification by flash chromatography on SiO_2 (9:1 hexanes/ EtOAc) then afforded chromene **2.96** (4.64 g, 86%) as a clear oil.

Data for 2.96:

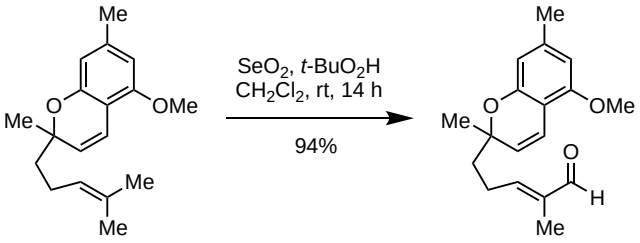
R_f: 0.50 (9:1 hexanes/ EtOAc).

FTIR (neat): 2967, 1613, 1572, 1453, 1387, 1229, 1144, 1024, 814 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.66 (d, *J* = 10.0, 1H), 6.28 (s, 1H), 6.22 (s, 1H), 5.46 (d, *J* = 10.0 Hz, 1H), 5.10 (t, *J* = 1.3 Hz, 1H), 3.80 (s, 3H), 2.27 (s, 3H), 2.16 – 2.05 (m, 2H), 1.76 – 1.61 (m, 2H), 1.73 (s, 3H), 1.37 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.2, 154.0, 139.5, 131.7, 126.9, 124.5, 117.4, 110.1, 108.0, 104.0, 78.2, 55.7, 41.3, 26.4, 25.8, 22.9, 22.1, 17.8 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{25}O_2$ 273.1849; found 273.1847.



2.96 **2.97**

Chromene **2.96** (4.02 g, 14.7 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (150 mL), SeO_2 (420 mg, 2.94 mmol, 20 mol%) and *t*-BuO_2H (9.4 mL, 51.5 mmol, 3.5 equiv.) was added. The reaction was left to stir for 14 h at room temperature then quenched with sat. $NH_4Cl_{(aq)}$ (150 mL) and product extracted CH_2Cl_2 (3 x 150 mL) and concentrated. The crude was then purified *via* flash column chromatography on SiO_2 (9:1 hexanes/ EtOAc) to afford **2.97** (4.00 g, 94%) as an orange oil.

Data for 2.97:

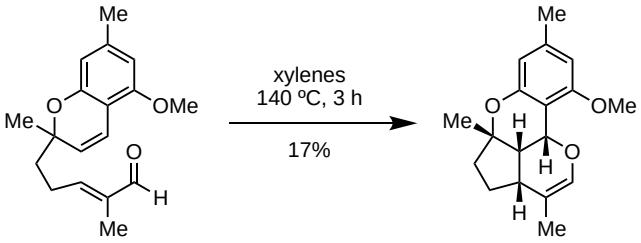
R_f: 0.40 (9:1 hexanes/ EtOAc).

FTIR (neat): 2966, 1683, 1612, 1572, 1462, 1388, 1226, 1017 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.35 (s, 1H), 6.70 (d, *J* = 10.0 Hz, 1H), 6.49 (t, *J* = 1.5 Hz, 1H), 6.25 (s, 1H), 6.22 (s, 1H), 5.42 (d, *J* = 10.0 Hz, 1H), 3.80 (s, 3H), 2.57 – 2.43 (m, 2H), 2.26 (s, 3H), 1.92 – 1.76 (m, 2H), 1.69 (s, 3H), 1.40 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 195.4, 155.3, 154.8, 153.6, 139.9, 139.4, 125.8, 118.2, 109.9, 104.2, 77.9, 55.7, 39.7, 26.7, 25.9, 24.3, 22.1, 9.2 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{23}O_3$ 287.1638; found 287.1642.



2.97 **2.98**

A solution of **2.97** (232 mg, 0.810 mmol, 1.0 equiv.) in xylene (20 mL) was heated at reflux. After 3 h the reaction was concentrated *in vacuo*. The crude was then purified *via* flash column chromatography on SiO_2 (20:1 hexanes/ EtOAc) to afford **2.98** (40 mg, 17%) as an orange solid.

Data for 2.98:

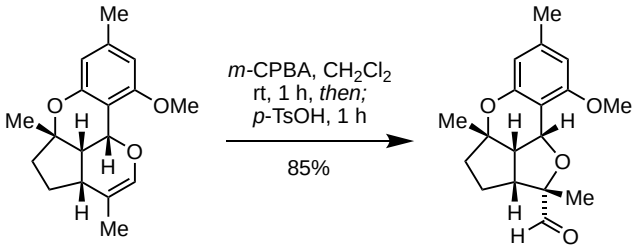
R_f: 0.60 (20:1 hexanes/ EtOAc).

FTIR (neat): 2925, 1674, 1617, 1590, 1463, 1227, 1124, 823 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.42 (s, 2H), 6.35 (s, 1H), 5.02 (d, *J* = 4.7 Hz, 1H), 3.81 (s, 3H), 2.70 (t, *J* = 8.2 Hz, 1H), 2.30 (s, 3H), 2.23 (ds, *J* = 9.2, 4.7 Hz, 1H), 2.08 – 2.01 (m, 1H), 1.83 (dd, *J* = 12.3, 4.9 Hz, 1H), 1.78 – 1.67 (m, 2H), 1.61 (s, 3H), 1.27 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.2, 156.3, 141.2, 141.2, 140.5, 116, 112.4, 112.4, 112.4, 111.7, 105.3, 105.2, 105.2, 85.7, 64.1, 64.0, 55.8, 55.8, 49.1, 38.6, 28.5, 27.8, 22.1, 16.7 ppm.

HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{18}H_{21}O_3$ 285.1491; found 285.1486.



2.97 **2.98**

Enol ether **2.98**(149 mg, 0.460 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (40 mL) and *m*-CPBA (77% wt./ wt., 159 mg, 0.920 mmol, 2.0 equiv.) was added. The resulting solution was stirred at room temperature for 1 h, then *p*-toluenesulfonic acid (132 mg, 0.700 mmol, 1.5 equiv.) was added and the solution was stirred for a further for 1 h. The reaction was then quenched with sat. $NaSO_{3(aq.)}$ (20 mL), the organic layer was then further washed with sat. $NaHCO_{3(aq.)}$ (2 x 20 mL) and extracted with CH_2Cl_2 (2 x 40 mL), dried with $MgSO_4$ and filtered. Concentration afforded furan **2.98** (134 mg, 85%) as a clear oil, which was used without further purification.

Data for 2.98:

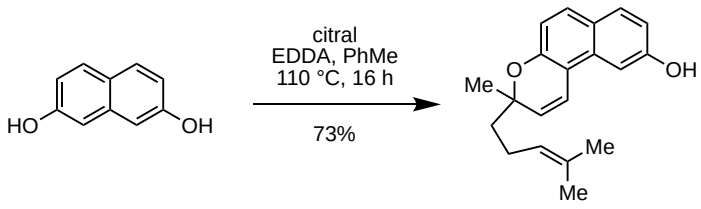
R_f: 0.20 (9:1 hexanes/ EtOAc).

FTIR (neat): 2966, 1734, 1618, 1591, 1464, 1373, 1231, 1137, 1110, 982 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.76 (s, 1H), 6.38 (s, 1H), 6.37 (s, 1H), 5.43 (d, *J* = 8.6 Hz, 1H), 3.85 (s, 3H), 2.88 (q, *J* = 7.7 Hz, 1H), 2.80 (t, *J* = 8.9 Hz, 1H), 2.30 (s, 3H), 2.11 (ddd, *J* = 12.9, 6.0, 2.5 Hz, 1H), 1.89 – 1.79 (m, 1H), 1.76 – 1.68 (m, 1H), 1.64 – 1.58 (m, 1H), 1.37 (s, 3H), 1.25 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 206.0, 158.2, 155.9, 140.8, 112.5, 108.3, 105.2, 87.5, 87.3, 66.9, 56.9, 56.0, 52.8, 42.3, 26.7, 24.9, 22.1, 21.1 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{23}O_4$ 303.1591; found 303.1592.



2.102: 2,7-dihydroxynaphthalene

2.101

To a solution of 2,7-dihydroxynaphthalene (**2.102**) (5.00 g, 31.2 mmol, 1.0 equiv.) in PhMe (150 mL) was added citral (5.32 mL, 31.2 mmol, 1.0 equiv.) and EDDA (170 mg, 0.030 mmol, 10 mol%). The reaction mixture was heated to reflux at 110 °C for 16 h, then cooled to room temperature and concentrated *in vacuo*. The residue was purified *via* flash chromatography on SiO_2 (8:1 hexanes/ EtOAc) to give chromene **2.101** (6.71 g, 73%) as a brown oil. Data for **2.101** matched that previously reported in the literature.[34]

Data for 2.101:

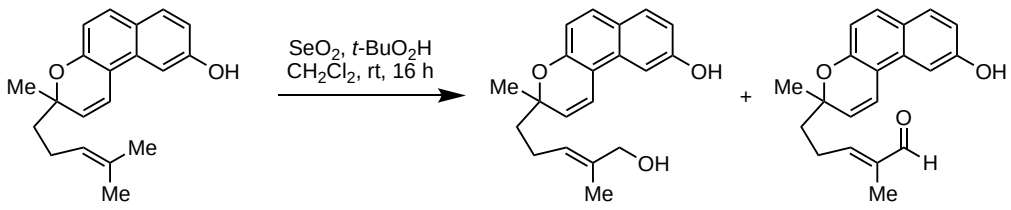
R_f: 0.20 (8:1 hexanes/ EtOAc).

FTIR (neat): 3370, 2969, 2023, 1700, 1621, 1517, 1449, 1376, 1283, 1212, 1181, 1088, 915 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.8 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.23 (d, *J* = 2.5 Hz, 1H), 6.97 – 6.85 (m, 3H), 5.63 (d, *J* = 10.0 Hz, 1H), 5.15 (bs, 1H), 5.11 (t, *J* = 7.2 Hz, 1H), 2.19 – 2.11 (m, 2H), 1.79 (m, 2H), 1.66 (s, 3H), 1.58 (s, 3H), 1.44 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.3, 152.0, 131.9, 131.5, 130.6, 129.3, 128.1, 124.7, 124.3, 118.8, 116.2, 114.9, 112.5, 104.0, 78.5, 41.0, 26.2, 25.8, 22.9, 17.8 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{23}O_2$ 295.1693; found 295.1694.



2.101 **2.104** 48% **2.100** 16%

To a solution of chromene **2.101** (4.84 g, 16.0 mmol, 1.0 equiv.) in CH_2Cl_2 (50 mL) at room temperature was added SeO_2 (180 mg, 1.60 mmol, 10 mol%) and *t*-BuO_2H (11.9 mL, 5.50 M in decane, 4.0 equiv.). The reaction was stirred at room temperature for 16 h, then quenched by addition of sat. $Na_2SO_{4(aq)}$ (50 mL). The organic layer was separated, washed with brine (2 x 50 mL) and the aqueous phase was further extracted with CH_2Cl_2 (2 x 50 mL). The organic layers were combined, then dried with $MgSO_4$, filtered, concentrated and purified *via* flash chromatography on SiO_2 (2:1 hexanes/ EtOAc) to give alcohol **2.104** (2.44 g, 48%) as an orange oil and aldehyde **2.100** (830 mg, 16%) as a red oil.

Data for 2.104:

R_f: 0.05 (9:1 hexanes/ EtOAc).

FTIR (neat): 3294, 2975, 2867, 1621, 1517, 1449, 1379, 1285, 1219, 1182, 1100, 1013, 915 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.7 Hz, 1H), 7.52 (d, *J* = 8.7 Hz, 1H), 7.21 (d, *J* = 2.4 Hz, 1H), 6.92 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 6.83 (d, *J* = 10.0 Hz, 1H), 5.53 (d, *J* = 10.0, 1H), 5.45 (t, *J* = 7.1 Hz, 1H), 3.98 (s, 2H), 2.21 – 2.16 (m, 2H), 1.78 – 1.66 (m, 2H), 1.61 (s, 3H), 1.40 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.9, 151.7, 134.6, 131.5, 130.5, 129.4, 127.7, 127.7, 126.4, 124.5, 119.0, 115.8, 112.3, 103.9, 78.4, 69.0, 40.5, 26.2, 22.6, 13.7 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{23}O_3$ 311.1642; found 311.1636.

Data for 2.100:

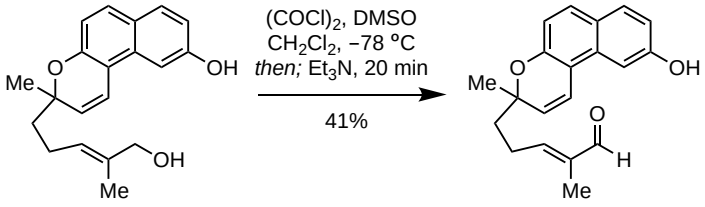
R_f: 0.10 (2:1 hexanes/ EtOAc).

FTIR (neat): 3350, 2924, 2971, 1665, 1634, 1620, 1516, 1451, 1377, 1284, 1238, 1216, 1183, 1133, 1082, 916, 820, 781, 729 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.36 (s, 1H), 7.62 (d, *J* = 8.8 Hz), 7.56 (d, *J* = 8.8 Hz, 1H), 7.24 (d, *J* = 2.3 Hz, 1H), 6.95 – 6.94 (m, 2H), 6.86 (d, *J* = 8.8 Hz), 6.51 (tt, *J* = 7.5, 1.4 Hz, 1H), 5.64 (bs, 1H), 5.60 (d, *J* = 10.0 Hz, 1H), 2.62 – 2.46 (m, 2H), 1.97 – 1.85 (m, 2H), 1.70 (s, 3H), 1.47 (s, 3H) ppm.

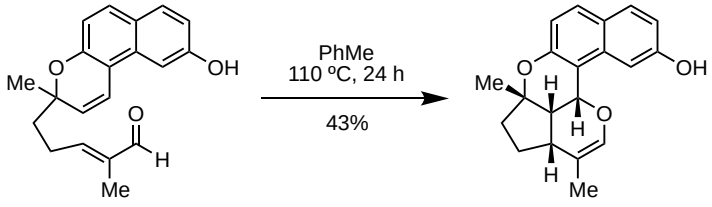
^{13}C NMR (150 MHz, $CDCl_3$): δ 195.7, 155.1, 154.7, 151.7, 139.4, 131.5, 130.6, 129.7, 127.0, 124.7, 119.6, 115.8, 115.3, 112.1, 103.9, 78.2, 39.4, 26.4, 24.3, 9.3 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{21}O_3$ 309.1489; found 309.1480.



2.104 **2.100**

To a solution of DMSO (0.34 mL, 4.82 mmol, 3.0 equiv.) in CH_2Cl_2 (45 mL) at –78 °C was added dropwise $(COCl)_2$ (0.16 mL, 1.93 mmol, 1.2 equiv.). The reaction mixture was stirred for 10 min at –78 °C, then alcohol **2.104** (500 mg, 1.58 mmol, 1.0 equiv.) was added as a solution in CH_2Cl_2 (5 mL) and the solution was stirred for a further 10 min. Et_3N (2.20 mL, 15.8 mmol, 10.0 equiv.) was then added dropwise and the reaction was stirred for a further 20 min. The reaction mixture was quenched upon addition of distilled water (100 mL), extracted with CH_2Cl_2 (2 x 50 mL), washed with sat. brine (4 x 50 mL) and dried with $MgSO_4$. The resultant mixture was filtered, concentrated *in vacuo* and purified *via* flash chromatography on SiO_2 (2:1 hexanes/ EtOAc) to give aldehyde **2.100** (203 mg, 41%). Data for **2.100** matched that previously obtained.



2.100 **2.103**

A solution of aldehyde **2.100** (67 mg, 0.215 mmol, 1.0 equiv.) in PhMe (10 mL) was heated to reflux at 110 °C. After 24 h the reaction was cooled to room temperature, concentrated in vacuo, and purified *via* flash chromatography (9:1 hexanes/ EtOAc) to afford enol ether **2.103** (29 mg, 43%) as a yellow solid.

Data for 2.103:

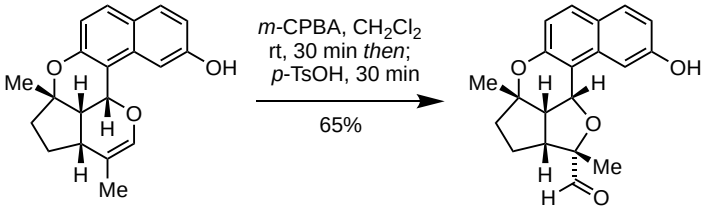
R_f: 0.70 (2:1 hexanes/ EtOAc).

FTIR (neat): 3296, 2974, 2249, 1675, 1624, 1518, 1452, 1376, 1238, 1218, 1186, 1134, 907 cm^{-1}.

^{1}H NMR (600 MHz, d_6-acetone): δ 8.51 (bs, 1H), 7.75 – 7.55 (m, 2H), 7.36 (s, 1H), 6.97 (dd, *J* = 8.8, 1.4 Hz), 6.83 (d, *J* = 8.7, 1H), 6.30 (s, 1H), 5.21 (d, *J* = 5.7 Hz), 2.80 – 2.69 (m, 1H), 2.47 (dd, *J* = 9.7, 5.7 Hz, 1H), 2.02 – 1.95 (m, 1H), 1.86 – 1.72 (m, 2H), 1.71 – 1.64 (m, 1H), 1.59 (s, 3H), 1.26 (s, 3H) ppm.

^{13}C NMR (150 MHz, d_6-acetone): δ 157.1, 154.8, 140.9, 135.0, 130.9, 130.7, 125.4, 117.3, 116.3, 116.0, 115.7, 105.1, 85.9, 66.6, 48.8, 39.3, 38.8, 28.7, 27.9, 16.6 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{21}O_3$ 309.1489; found 309.1486.



2.103 **2.106**

Enol ether **2.103** (332 mg, 1.07 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (50 mL) and *m*-CPBA (77%, 360 mg, 1.30 mmol, 2.0 equiv.) was added. The resultant solution was stirred at room temperature for 30 min, then *p*-toluenesulfonic acid (300 mg, 1.58 mmol, 1.5 equiv.) was added and the reaction mixture was stirred for a further 30 min. The reaction mixture was then quenched by addition of distilled water (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL), dried with $MgSO_4$, filtered and concentrated. Crystallisation from acetone then afforded furan **2.106** (227 mg, 65%) as a white solid.

Data for 2.106:

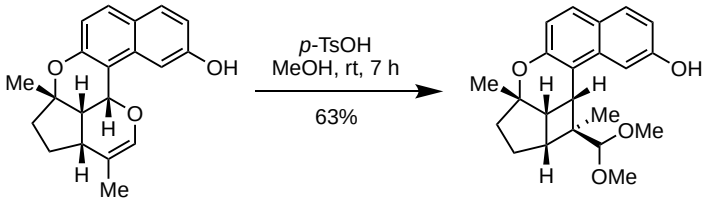
R_f: 0.60 (2:1 hexanes/ EtOAc).

FTIR (neat): 3372, 2971, 1733, 1691, 1625, 1517, 1449, 1375, 1286, 1241, 1217, 1199, 1134, 967, 836, 711 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.65 (s, 1H), 8.60 (s, 1H), 7.65 (dd, *J* = 8.8, 5.6 Hz, 2H), 7.49 (d, *J* = 2.4 Hz, 1H), 6.97 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.83 (d, *J* = 8.8 Hz, 1H), 5.46 (d, *J* = 8.3 Hz, 1H), 2.97 – 2.90 (m, 2H), 2.01 – 1.97 (m, 1H), 1.72 – 1.64 (m, 2H), 1.55 (dd, *J* = 12.3, 6.2 Hz, 1H), 1.42 (s, 3H), 1.37 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 205.0, 157.1, 152.3, 136.1, 130.8, 130.7, 125.1, 117.1, 116.3, 112.6, 106.5, 88.5, 84.7, 70.0, 54.4, 50.7, 38.7, 26.6, 25.7, 20.9 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{21}O_4$ 325.1434; found 325.1436.



2.103 **2.105**

Enol ether **2.103** (69 mg, 0.207 mmol, 1.0 equiv.) was dissolved in MeOH (5.0 mL) and *p*-TsOH (4 mg, 0.020 mmol, 10 mol%) added. The solution was stirred at room temperature for 7 h, then reaction quenched upon addition of sat. $NaHCO_{3(aq)}$ (10 ml). Product was extracted with CH_2Cl_2 (3 x 5 mL) and combined organic extracts were washed with distilled water (10 mL), dried with $MgSO_4$, filtered and concentrated. Purification *via* flash chromatography (2:1 hexanes/ EtOAc) gave acetal **2.105** (47 mg, 63%) as a white solid.

Data for 2.105:

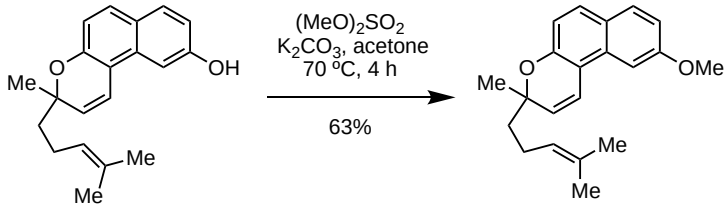
R_f: 0.50 (1:1 hexanes/ EtOAc).

FTIR (neat): 2971, 2929, 1682, 1619, 1514, 1464, 1429, 1381, 1224, 1181, 1102, 1031, 916 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.36 (s, 1H), 7.63 (d, *J* = 8.9 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.21 (d, *J* = 2.4 Hz, 1H), 7.08 – 6.95 (m, 2H), 6.88 (dd, *J* = 8.8, 0.7 Hz, 1H), 6.49 (t, *J* = 7.4, 1H), 5.64 (d, *J* = 10.0 Hz, 1H), 3.93 (s, 3H), 2.61 – 2.47 (m, 2H), 1.97 – 1.88 (m, 2H), 1.70 (s, 3H), 1.49 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 195.3, 158.7, 154.5, 151.7, 139.5, 131.3, 130.2, 129.5, 127.1, 124.7,119.6, 115.7, 112.5, 100.5, 78.1, 55.4, 39.4, 26.3, 24.2, 9.23 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{27}O_4$ 355.1909; found 355.1908.



2.101 **2.107**

Chromene **2.101** (3.34 g, 11.3 mmol, 1.0 equiv.) was dissolved in acetone (60 mL), K_2CO_2 (8.15 g, 58.9 mmol, 5.2 equiv.) and dimethyl sulfate (6.61 mL, 69.8 mmol, 6.2 equiv.) was added. The reaction was then headed to reflux for 4 h. The product was then cooled to room temperature quenched by addition of sat. brine (60 mL) and product extracted with EtOAc (3 x 60 mL), dried with $MgSO_4$, filtered and concentrated. Purification *via* flash chromatography on SiO_2 (20:1 hexanes/ EtOAc) gave **2.107** (2.22 g, 63%) as a yellow oil.

Data for 2.107:

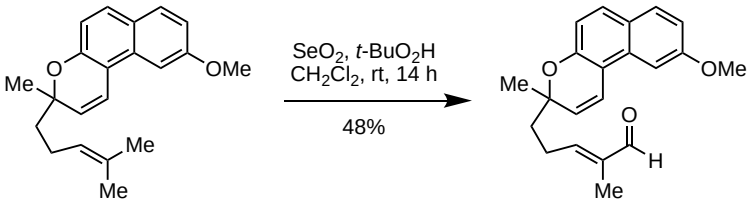
R_f: 0.60 (9:1 hexanes/ EtOAc).

FTIR (neat): 2924, 1620, 1514, 1429, 1225, 1033, 913, 726 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.9 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.21 (d, *J* = 2.4 Hz, 1H), 7.04 – 6.96 (m, 2H), 6.90 (dd, *J* = 8.7, 0.8 Hz, 1H), 5.66 (d, *J* = 10.0 Hz, 1H), 5.15 – 5.06 (m, 1H), 3.93 (s, 3H), 2.23 – 2.08 (m, 2H), 1.84 – 1.69 (m, 2H), 1.66 (s, 3H), 1.58 (s, 3H), 1.44 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.6, 152.0, 131.8, 131.3, 130.2, 129.2, 128.1, 124.7, 124.3, 118.9, 116.1, 115.5, 112.9, 100.5, 78.4, 55.4, 41.0, 26.2, 25.8, 22.9, 17.8 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{25}O_2$ 309.1849; found 309.1843.



2.107 **2.108**

To a solution of chromene **2.107** (5.01 g, 16.2 mmol) in CH_2Cl_2 (100 mL) was added *t*-BuO_2H (10.6 mL, 3.24 mmol, 5.5 M in decane, 20 mol%) and SeO_2 (0.36 g, 58.3 mmol, 3.6 equiv.) the reaction was left to stir at room temperature. After 16 h the solution was quenched sat. $Na_2SO_{4(aq)}$ (100 mL), product extracted CH_2Cl_2 (3 x 100 mL), dried with $MgSO_4$, filtered and concentrated. Purification *via* flash column chromatography on SiO_2 (9:1 hexanes/ EtOAc) then afforded **2.108** (2.58 g, 48%) as an orange oil.

Data for 2.108:

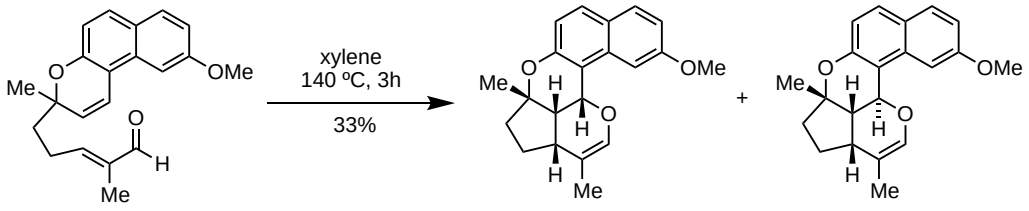
R_f: 0.20 (9:1 hexanes/ EtOAc).

FTIR (neat): 2972, 1683, 1620, 1381, 1224, 1031, 915, 729 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.36 (s, 1H), 7.63 (d, *J* = 8.9 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.21 (d, *J* = 2.5 Hz, 1H), 7.04 (d, *J* = 10.0 Hz, 1H), 7.00 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 1H), 6.49 (t, *J* = 7.4 Hz, 1H), 5.64 (d, *J* = 10.0 Hz, 1H), 3.93 (s, 3H), 2.61 – 2.49 (m, 2H), 1.99 – 1.86 (m, 2H), 1.70 (d, *J* = 1.1 Hz, 3H), 1.49 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 195.3, 158.7, 154.4, 151.6, 139.5, 131.3, 130.2, 129.5, 127.1, 124.7, 119.6, 115.7, 115.7, 112.5, 100.5, 78.1, 55.4, 39.4, 26.3, 24.2, 9.2 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{23}O_3$ 323.1642; found 323.1644.



2.108 **2.109** 33% **2.110** 1%

A solution of aldehyde **2.108** (80 mg, 0.215 mmol, 1.0 equiv.) in xylene (5 mL) was heated to reflux at 140 °C. After 3 h the reaction was cooled to room temperature, concentrated *in vacuo*, and purified *via* flash chromatography on SiO_2 (9:1 hexanes/ EtOAc) to afford enol ether **2.109** (27 mg, 33%) as an orange solid and **2.110** (1 mg, 1%) as the minor product.

Data for 2.109:

R_f: 0.50 (9:1 hexanes/ EtOAc).

FTIR (neat): 2961, 1610, 1516, 1464, 1224, 1032, 922, 833, 667 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (dd, *J* = 8.8, 6.0 Hz, 2H), 7.34 (d, *J* = 2.5 Hz, 1H), 7.05 – 7.01 (m, 1H), 6.99 (d, *J* = 8.7 Hz, 1H), 6.42 (s, 1H), 5.33 (d, *J* = 5.5 Hz, 1H), 3.94 (s, 3H), 2.82 (t, *J* = 8.2 Hz, 1H), 2.48 (dd, *J* = 9.5, 5.5 Hz, 1H), 2.15 (td, *J* = 13.7, 12.6, 7.7 Hz, 1H), 1.93 – 1.75 (m, 4H), 1.66 (s, 3H), 1.34 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.8, 154.2, 140.6, 133.5, 130.3, 130.2, 125.2, 117.6, 116.0, 115.9, 114.8, 101.0, 85.6, 66.2, 55.5, 48.8, 38.7, 38.4, 28.3, 27.9, 16.7 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{23}O_3$ 323.1642; found 323.1634.

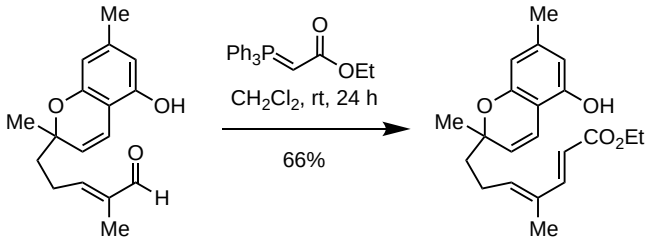
Partial Data for 2.110:

R_f: 0.60 (9:1 hexanes/ EtOAc).

FTIR (neat): 2950, 1725, 1622, 1515, 1461, 1237, 1132 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 2.5 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 6.99 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 6.16 (s, 1H), 5.75 (d, *J* = 7.3 Hz, 1H), 3.95 (s, 3H), 2.65 – 2.58 (m, 1H), 2.35 – 2.26 (m, 1H), 2.11 – 1.97 (m, 4H), 1.58 (s, 3H), 1.39 (s, 3H) ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{23}O_3$ 323.1642; found 323.1642.



2.108 **2.112**

To a solution of **2.108** (108 mg, 0.394 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) at room temperature was added ethyl (triphenylphosphoranylidene)acetate (274 mg, 0.788 mmol, 2.0 equiv.). After 16 h the reaction was quenched with sat. brine (10 mL) and product extracted with CH_2Cl_2 (3 x 10 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography on SiO_2 (9:1 hexanes/ EtOAc) then gave **2.112** (88 mg, 66%) as an oil.

Data for 2.112:

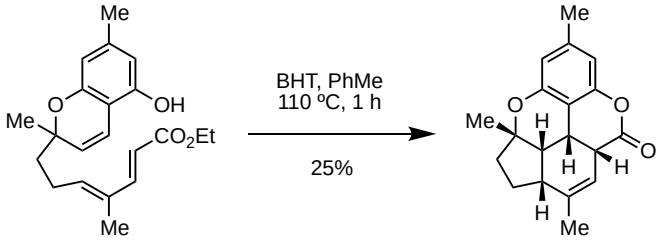
R_f: 0.30 (20:1 hexanes/ EtOAc).

FTIR (neat): 3383, 2923, 1684, 1610, 1578, 1447, 1381, 1268, 1185, 1060, 824 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (d, *J* = 15.6 Hz, 1H), 6.67 (d, *J* = 9.8, 1H), 6.21 (s, 1H), 6.14 (s, 1H), 5.88 (t, *J* = 7.5 Hz, 1H), 5.80 (br s, 1H), 5.77 (d, *J* = 15.7 Hz, 1H), 5.44 (d, *J* = 10.0 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.38 – 2.29 (m, 2H), 2.18 (s, 3H), 1.82 – 1.70 (m, 2H), 1.73 (s, 3H), 1.38 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 167.9, 154.0, 151.4, 149.8, 141.9, 139.9, 133.1, 126.6, 117.5, 115.6, 109.8, 108.6, 106.7, 78.1, 60.4, 40.3, 26.6, 23.9, 21.7, 14.5, 12.2 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{27}O_4$ 343.1904; found 343.1906.



2.112 **2.111a**

To a solution of **2.112** (55 mg, 0.158 mmol, 1.0 equiv.) in PhMe (5 mL) was added BHT (13 mg, 0.032 mmol, 20 mol%) and the reaction was heated to reflux. After 1 h the reaction was concentrated and the crude residue purified by flash column chromatography on SiO_2 (20:1 hexanes/ EtOAc) to give **2.111a** (12 mg, 25%) as an orange oil.

Data for 2.111a:

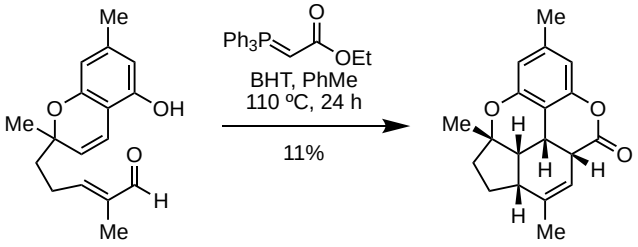
R_f: 0.30 (20:1 hexanes/ EtOAc).

FTIR (neat): 2963, 1760, 1633, 1591, 1444, 1332, 1216, 1083, 879 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.36 (s, 1H), 6.34 (s, 1H), 5.08 (m, 1H), 3.53 – 3.48 (m, 1H), 3.38 (t, *J* = 5.9 Hz, 1H), 2.50 (d, *J* = 6.6 Hz, 2H), 2.23 (s, 3H), 2.11 (dd, *J* = 12.7, 5.4 Hz, 1H), 1.94 – 1.89 (m, 1H), 1.72 – 1.65 (m, 1H), 1.58 (s, 3H), 1.51 (s, 3H), 1.36 – 1.30 (m, 1H) ppm.

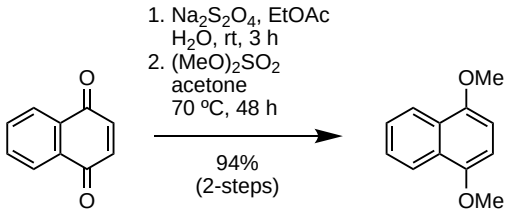
^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 155.0, 150.5, 141.0, 138.9, 114.0, 112.0, 108.0, 102.4, 85.4, 41.8, 41.2, 40.6, 40.4, 29.7, 25.8, 23.5, 21.5, 21.3 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{21}O_3$ 297.1485; found 297.1495.



2.108 **2.111**

To a solution of aldehyde **2.108** (255 mg, 769 mmol, 1.0 equiv.) in PhMe (30 mL) was added BHT (41 mg, 0.153 mmol, 20 mol%) and ethyl (triphenylphosphoranylidene)acetate (820 mg, 1.92 mmol, 2.5 equiv.), the solution was heated to reflux. After 24 h sat. brine (60 mL) was added and the product was extracted with EtOAc (3 x 60 mL), dried with $MgSO_4$, filtered and concentrated. Purification *via* flash chromatography on SiO_2 (20:1 hexanes/ EtOAc) then gave **2.111a** (32 mg, 11% over 2-steps). Data for **2.111a** matched that previously obtained.



2.114: 1,4-napthoquinone **2.115**

To a solution of $Na_2S_2O_4$ (190 g, 1.09 mol, 8.7 equiv.) in H_2O (500 mL), was added EtOAc (500 mL) and 1,4-napthoquinone (**2.114**) (20 g, 0.126 mmol, 1.0 equiv.). The reaction was left to stir at room temperature for 3 h, then organic layer was separated and aqueous layer further extracted with EtOAc (2 x 500 mL). The combined organic layers were then concentrated *in vacuo* and the crude residue dissolved in acetone (250 mL). K_2CO_3 (92 g, 0.665 mmol, 5.3 equiv.) was then added, followed by dimethylsulfate (60 mL, 0.665 mmol, 5.3 equiv.) and the solution was left to reflux. After 48 h, sat. brine (500 mL) was added and product extracted with EtOAc (3 x 250 mL), dried with $MgSO_4$, filtered and concentrated. Purification by flash column chromatography on SiO_2 (9:1 hexanes/ EtOAc) then gave **2.115** (22.3 g, 94%) as a white solid. Data for **2.115** matched that previously reported in the literature.[28]

Data for 2.115:

R_f: 0.80 ($CHCl_3$).

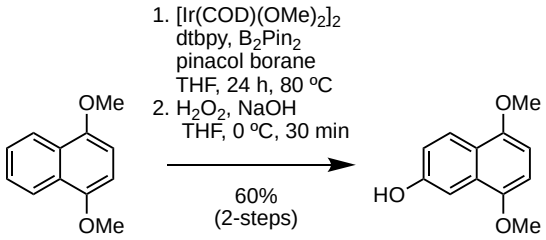
MP: 86 – 88 °C (lit. 84 – 86 °C).[28]

FTIR (neat): 2955, 1630, 1593, 1463, 1446, 1383, 1269, 1237, 1023 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 – 8.13 (m, 2H), 7.54 (ddd, *J* = 6.5, 3.3, 2.2 Hz, 2H), 6.72 (s, 2H), 3.98 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 149.7, 126.5, 126.5, 126.0, 121.9, 121.9, 121.9, 103.3, 103.3, 55.8 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{12}H_{13}O_2$ 189.0910; found 189.0909.



2.115 **2.116**

To a solution of **2.115** (10.0 g, 53.1 mmol, 1.0 equiv.) in dry THF (250 mL) was added B_2Pin_2 (13.5 g, 53.1 mmol, 1.0 equiv.), dtbpy (0.04 g, 1.06 mmol, 2 mol%), $Ir(COD)OMe_2$ (40 mg, 0.531 mmol, 1 mol%) and pinacol borane (0.8 mL, 5.31 mmol, 10 mol%). The solution was left to stir at reflux for 24 h, then cooled to room temperature and filtered through a pad of Celite® (THF) and concentrated *in vacuo*. The crude pinacol ester was dissolved in THF (250 mL), cooled to 0 °C and H_2O_2 (100 mL, 30% wt./ wt. in H_2O) added followed by 1M $NaOH_{(aq)}$ (100 mL). After 30 mins, EtOAc (250 mL) was added and the organic layer extracted, dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* flash column chromatography on SiO_2 (2:1 hexanes/ EtOAc) then gave **2.116** (6.53 g, 60%) as a brown oil. Data for **2.116** matched that previously reported in the literature.[28]

Data for 2.116:

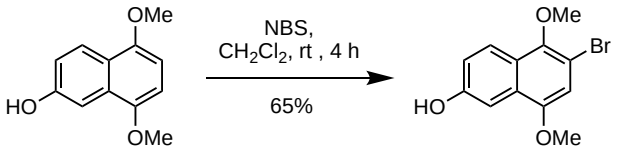
R_f: 0.70 (CH_2Cl_2).

FTIR (neat): 3352, 2999, 2937, 2836, 1631, 1602, 1519, 1461, 1379, 1262, 1216, 1194, 1155, 1095, 1000, 972, 917, 863, 798, 711, 665 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (d, *J* = 9.0 Hz, 1H), 7.52 (d, *J* = 2.6 Hz, 1H), 7.12 (dd, *J* = 9.1, 2.6 Hz, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 6.55 (d, *J* = 8.3 Hz, 1H), 5.78 (br s, 1H), 3.93 (d, *J* = 7.5 Hz, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.1, 148.6, 127.9, 124.2, 121.7, 117.3, 117.2, 104.5, 104.4, 101.1, 56.0, 55.9 ppm.

HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{12}H_{11}O_3$ 203.0714; found 203.0700.



2.116 **2.117**

To a solution of **2.116** (1.14 g, 5.58 mmol, 1.0 equiv.) in $CHCl_3$ (50 mL) was added NBS (1.09 g, 6.14 mmol, 1.1 equiv.) at room temperature. The reaction was left to stir for 4 h then quenched upon addition of sat. $Na_2SO_{4(aq)}$ (50 mL) and product extracted $CHCl_3$ (3 x 50 mL), dried $MgSO_4$, filtered and concentrated. Purification *via* flash chromatography (4:1 hexanes/ EtOAc) then gave **2.117** (1.29 g, 65%) as an orange solid. Data for **2.117** matched that previously reported in the literature.[28]

Data for 2.117:

R_f: 0.20 (9:1 hexanes/ EtOAc).

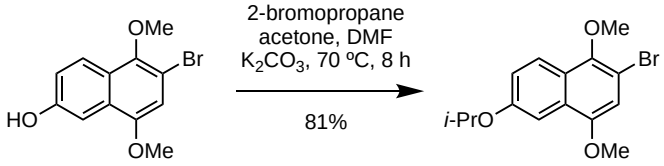
MP: 108 – 109 °C.

FTIR (neat): 3425, 3350, 2933, 1627, 1608, 1588, 1566, 1458, 1439, 1383, 1321, 1281, 1241, 1191, 1076, 1004, 970, 823, 777, 744 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.97 (d, *J* = 9.0 Hz, 1H), 7.49 (d, *J* = 2.6 Hz, 1H), 7.16 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.84 (s, 1H), 5.33 (br s, 1H), 3.94 (s, 6H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 153.9, 151.3, 147.1, 127.3, 124.4, 124.3, 118.9, 109.1, 108.7, 105.3, 61.7, 56.0 ppm.

HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{12}H_{10}O_3Br$ 280.9819; found 280.9806.



2.117 **2.118**

To a stirred solution of **2.117** (1.62 g, 5.75 mmol, 1.0 equiv.) in acetone/ DMF (12:1, 30 mL) was added K_2CO_3 (3.16 g, 22.9 mmol, 4.0 equiv.), TBAI (211 mg, 0.572 mmol, 10 mol%) and 2-bromopropane (0.54 mL, 5.75 mmol, 1.0 equiv.). The reaction was heated to reflux for 16 h then cooled to room temperature, quenched with 1M $HCl_{(aq)}$ (30 mL) and product extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was filtered through a short pad of SiO_2 and Celite® (CH_2Cl_2) to afford **2.118** (1.90 g, 81%) as an orange oil. Data for **2.118** matched that previously reported in the literature.[28]

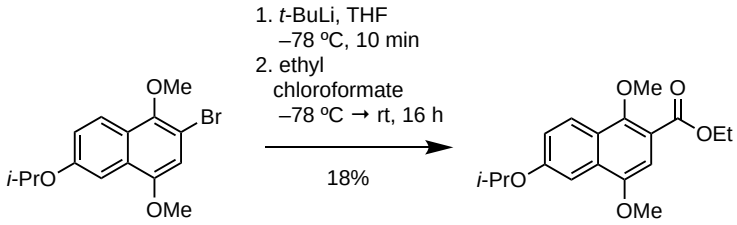
Data for 2.118:

R_f: 0.50 (20:1 hexanes/ EtOAc).

FTIR (neat): 2976, 1620, 1579, 1463, 1347, 1238, 1112, 997 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, *J* = 9.1 Hz, 1H), 7.52 (d, *J* = 2.4 Hz, 1H), 7.19 (dd, *J* = 9.1, 2.5 Hz, 1H), 6.86 (s, 1H), 4.81 – 4.69 (m, 1H), 3.95 (d, *J* = 2.7 Hz, 6H), 1.42 (d, *J* = 6.1 Hz, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.2, 151.4, 147.1, 127.2, 124.2, 123.8, 120.9, 108.8, 108.5, 103.6, 70.0, 61.5, 55.9, 22.1 ppm.



2.118 **2.119**

To a solution of **2.118** (2.00 g, 6.15 mmol, 1.0 equiv.) in THF (40 mL) under N_2 was added dropwise at –78 °C *t*-BuLi (7.3 mL, 12.3 mmol, 1.7M in hexane, 2.0 equiv.). The reaction was left to stir for 10 min, followed by a dropwise addition of ethyl chloroformate (3.3 mL, 12.3 mmol, 1.7 M in hexane, 2.0 equiv.). After 5 min the reaction was warmed to room temperature and left to stir 16 h. The reaction was then quenched sat. $NH_4Cl_{(aq)}$ (40 mL), product extracted with EtOAc (3 x 40 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* flash chromatography (19:1 → 9:1 hexanes/ EtOAc, gradient elution) then gave **2.119** (342 mg, 18%) as a yellow solid. Data for **2.119** matched that previously reported in the literature.[28]

Data for 2.119:

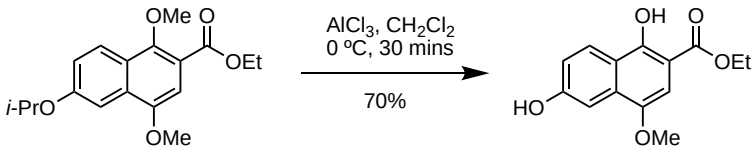
R_f: 0.50 (10:1 hexanes/ EtOAc).

FTIR (neat): 2978, 1719, 1621, 1463, 1372, 1272, 983, 792 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (d, *J* = 9.1 Hz, 1H), 7.52 (d, *J* = 2.6 Hz, 1H), 7.20 – 7.16 (m, 2H), 4.78 (p, *J* = 6.1 Hz, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H), 1.41 (d, *J* = 6.0 Hz, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.6, 157.9, 152.6, 150.4, 130.6, 125.6, 124.2, 120.5, 116.5, 104.5, 103.0, 70.0, 63.4, 61.1, 55.8, 22.1, 14.5 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{23}O_5$ 319.1540; found 319.1539.



2.119 **2.113**

To a stirred solution of **2.119** (72 mg, 0.226 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) at 0 °C was added $AlCl_3$ (300 mg, 2.26 mmol, 10.0 equiv.) portion wise over 5 min. The reaction was left to stir for 30 min, then diluted with CH_2Cl_2 (5 mL) and quenched with sat. $NH_4Cl_{(aq)}$ (10 mL). The organic layer was separated, then aqueous layer was further extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* flash chromatography (9:1 → 1:1 hexanes/ EtOAc, gradient elution) then gave **2.113** (15 mg, 70%) as an orange solid. Data for **2.113** matched that previously reported in the literature.[28]

Data for 2.113:

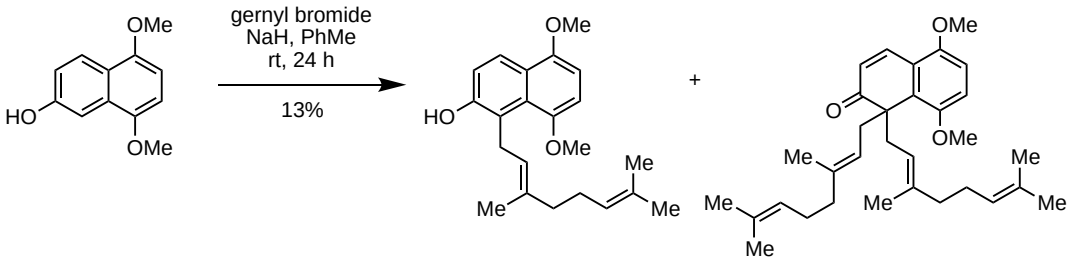
R_f: 0.60 (1:1 hexanes/ EtOAc).

FTIR (neat): 3420, 1627, 1600, 1526, 1469, 1396, 1375, 1336, 1249, 1240, 1199, 1158, 1088, 1022, 994, 945, 853, 944, 788, 779, 713 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.73 (s, 1H), 8.30 (d, *J* = 9.0 Hz, 1H), 7.48 (d, *J* = 2.6 Hz, 1H), 7.13 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.01 (s, 1H), 5.38 (s, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 3.95 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (125 MHz, d_6-acetone): δ 172.1, 159.7, 156.9, 147.7, 133.1, 126.7, 120.5, 118.9, 105.6, 103.0, 101.9, 62.2, 56.1, 14.7 ppm.

HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{14}H_{13}O_5$ 261.0768; found 261.0765.



2.116 **2.121** 13% **2.143** 10%

To solution of phenol **2.116** (854 mg, 4.18 mmol) in PhMe (10 mL) was added portion wise NaH (170 mg, 4.18 mmol, 60 wt./ wt., 1.0 equiv.) at room temperature and reaction was left to stir for 1 h. The solution was then cooled to 0 °C and geranyl bromide (0.74 mL, 0.9 equiv.) added dropwise, the reaction was left to warm to room temperature. After 24 h the reaction was quenched upon addition of distilled H_2O (10 mL) and products extracted with EtOAc (3 x 10 mL). The combined organic layers were then dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* flash chromatography (9:1 hexanes/ EtOAc) then gave **2.121** (182 mg, 13%) as a yellow oil and **2.143** (205 mg, 10%) as yellow oil.

Data for 2.121:

R_f: 0.20 (20:1 hexanes/ EtOAc).

FTIR (neat): 3382, 2932, 2838, 1664, 1606, 1590, 1481, 1440, 1412, 1378, 1274, 1166, 1194, 1106, 1081, 1050, 1000, 946, 800, 732, 717 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (d, *J* = 9.0 Hz, 1H), 7.11 (d, *J* = 9.0 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 5.43 (br s, 1H), 5.38 (m, 1H), 5.09 – 5.04 (m, 1H), 4.16 (d, *J* = 6.5 Hz, 2H), 3.94 (s, 3H), 3.88 (s, 3H), 2.17 – 2.05 (m, 4H), 1.89 (d, *J* = 1.5 Hz, 3H), 1.68 (d, *J* = 1.5 Hz, 3H), 1.61 (d, *J* = 1.4 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.6, 151.3, 150.3, 136.0, 131.8, 126.5, 124.2, 124.1, 123.3, 122.0, 119.7, 117.6, 106.5, 101.2, 56.2, 55.9, 39.8, 27.1, 26.7, 25.8, 17.8, 16.4 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{29}O_3$ 341.2111; found 341.2110.

Data for 2.143:

R_f: 0.45 (20:1 hexanes/ EtOAc).

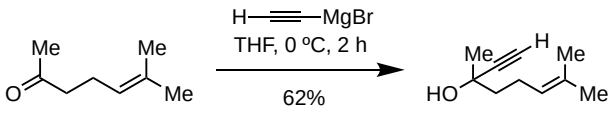
FTIR (neat): 2914, 2853, 1651, 1591, 1475, 1437, 1390, 1295, 1240, 1229, 1198, 1096, 947, 886, 834, 799, 719 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, *J* = 10.1 Hz, 1H), 6.87 (d, *J* = 9.0 Hz, 1H), 6.76 (d, *J* = 9.0 Hz, 1H), 6.11 (d, *J* = 10.1 Hz, 1H), 4.86 (m, 2H), 4.58 (m, 2H), 3.82 (d, *J* = 2.8 Hz, 6H), 3.27 (dd, *J* = 13.7, 7.6 Hz, 2H), 2.72 (dd, *J* = 13.7, 7.4 Hz, 2H), 1.79 – 1.67 (m, 8H), 1.60 (s, 6H), 1.48 (s, 6H), 1.41 (s,

6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 205.3, 151.9, 151.0, 138.9, 136.8, 133.5, 131.1, 129.0, 125.3, 124.5, 122.4, 119.8, 113.2, 109.3, 56.0, 55.5, 39.8, 37.7, 26.8, 25.7, 17.7, 16.1 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{32}H_{45}O_3$ 477.3363; found 477.3379.



2.144 **2.123**

To a solution of 6-methylhept-5-en-2-one (**2.144**) (1.05 mL, 7.11 mmol, 1.0 equiv.) in THF (20 mL) at 0 °C was added ethynyl magnesium bromide (21.4 mL, 10.7 mmol, 1.5 equiv.) and solution was stirred for 2 h. The reaction was then quenched sat. $NH_4Cl_{(aq)}$ (20 mL) and product extracted with Et_2O (3 x 40 mL), dried with $MgSO_2$, filtered and concentrated. Purification *via* flash chromatography (9:1 hexanes/ EtOAc) then gave **2.123** (672 mg, 62%) as a yellow oil. Data for **2.123** matched that previously reported in literature.[31]

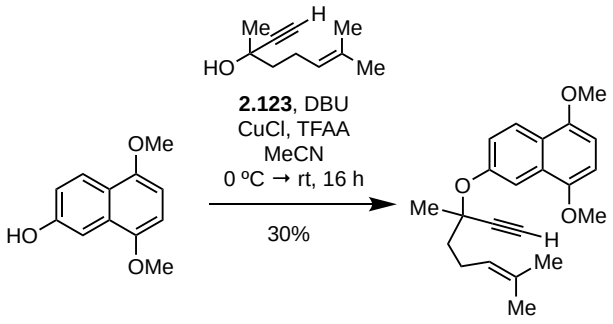
Data for 2.123:

FTIR (neat): 3403, 2930, 1726, 1450, 1375, 1119, 907 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.19 – 5.06 (m, 1H), 2.47 – 2.33 (m, 1H), 2.42 (s, 1H), 2.29 – 2.21 (m, 1H), 2.18 – 2.11 (m, 1H), 1.70 – 1.64 (m, 2H), 1.66 (s, 3H), 1.61 (s, 3H), 1.46 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 132.5, 123.8, 87.8, 71.5, 68.3, 43.3, 29.8, 25.7, 23.6, 17.8 ppm.

HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{10}H_{15}O$ 151.1119; found 151.1128.



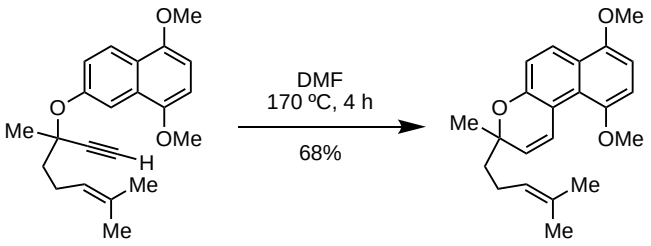
2.116 **2.124**

A solution of the propargyl **2.123** (600 mg, 1.7 mmol, 1.0 equiv.) in MeCN (10 mL) was cooled to −10 °C and DBU (0.34 mL, 2.2 mmol, 1.3 equiv.) added. Trifluoracetic acid (TFAA) (0.25 mL, 1.7 mmol, 1.0 equiv.) was then added dropwise over 25 min at 0 °C. The resulting solution was left to stir for 30 min, then added dropwise to a solution of **2.116** (500 mg, 1.7 mmol, 1.0 equiv.) in MeCN (10 mL) at −10 °C to room temperature. After 16 h the reaction was quenched upon addition of sat. $NH_4Cl_{(aq)}$ (20 mL), and the product extracted with EtOAc (3 x 20 mL), dried with $MgSO_4$, filtered and concentrated. Purification *via* flash chromatography (9:1 hexanes/ EtOAc) then gave **2.124** (174 mg, 30%) as a yellow oil.

Partial Data for 2.124:

R_f: 0.80 (9:1 hexanes/ EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (d, *J* = 9.1 Hz, 1H), 7.99 (d, *J* = 2.4 Hz, 1H), 7.39 (dd, *J* = 9.1, 2.5 Hz, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 6.60 (d, *J* = 8.2 Hz, 1H), 5.23 – 5.16 (m, 1H), 3.95 (s, 6H), 2.63 (s, 1H), 2.40 – 2.29 (m, 2H), 2.03 – 1.90 (m, 2H), 1.71 (s, 3H), 1.66 (s, 6H) ppm.



2.124 **2.122**

A solution of **2.124** (56 mg, 0.165 mmol, 1.0 equiv.) in DMF (5 mL) was heated to reflux. After 5 h the solution was cooled to room temperature and EtOAc (20 mL) added. The solution was then washed with sat. brine (5 x 20 mL) and the organic layer dried with $MgSO_4$, filtered and concentrated. Purification by flash column chromatography on SiO_2 (20:1 hexanes/ EtOAc) then afforded **2.122** (38 mg, 68%) as a yellow oil.

Data for 2.122:

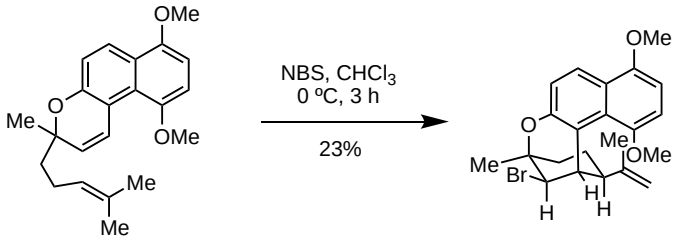
R_f: 0.60 (20:1 hexanes/ EtOAc).

FTIR (neat): 2934, 1616, 1457, 1411, 1336, 1240, 1229, 1059, 1010, 800 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, *J* = 9.0 Hz, 1H), 7.80 (dd, *J* = 10.3, 0.8 Hz, 1H), 7.04 (dd, *J* = 9.0, 0.8 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 5.55 (d, *J* = 10.3 Hz, 1H), 5.14 – 5.05 (m, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 2.20 – 2.10 (m, 2H), 1.79 – 1.72 (m, 2H), 1.65 (s, 3H), 1.58 (s, 3H), 1.43 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 152.6, 151.2, 150.3, 131.7, 126.5, 124.4, 123.7, 123.6, 123.2, 122.8, 118.3, 114.5, 107.2, 101.4, 77.1, 56.3, 55.9, 40.5, 25.8, 25.6, 22.9, 17.8 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{27}O_3$ 339.1955; found 339.1924.



2.122 **2.126**

To a solution of dimethoxy chromene **2.122** (75 mg, 0.222 mmol. 1.0 equiv.) in $CHCl_3$ (10 mL) was added NBS (40 mg, 0.222 mmol, 1.0 equiv.) at 0 °C. The solution was left to stir and slowly warmed to room temperature over 3 h and quenched upon addition of sat. brine (10 mL). The organic layer was separated and the aqueous layer further extracted with $CHCl_3$ (2 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification *via* flash column chromatography on SiO_2 (9:1 hexanes/ EtOAc) then gave **2.126** (21 mg, 23%) as an orange solid.

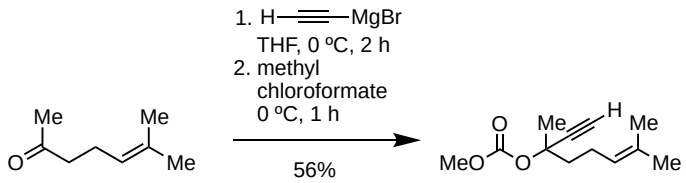
Data for 2.126:

R_f: 0.50 (20:1 hexanes/ EtOAc).

FTIR (neat): 2930, 2851, 1726, 1604, 1456, 1441, 1413, 1376, 1340, 1323, 1260, 1244, 1217, 1147, 1094, 1042, 1001, 958, 930, 885, 822, 795, 727, 703 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (d, *J* = 9.2 Hz, 1H), 7.07 (d, *J* = 9.2 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.52 (d, *J* = 8.4 Hz, 1H), 5.46 (t, *J* = 3.3 Hz, 1H), 4.58 (d, *J* = 3.4 Hz, 1H), 4.38 – 4.35 (m, 1H), 3.96 – 3.95 (m, 1H), 3.91 (s, 3H), 3.77 (s, 3H), 2.52 (dt, *J* = 13.1, 3.3 Hz, 1H), 2.27 (ddd, *J* = 13.9, 4.4, 2.1 Hz, 1H), 1.73 (dd, *J* = 13.7, 4.9 Hz, 1H), 1.62 – 1.55 (m, 1H), 1.54 (s, 3H), 1.49 (s, 3H), 1.38 – 1.33 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ154.7, 151.6, 150.0, 146.6, 127.5, 122.7, 122.4, 117.2, 112.1, 111.0, 105.9, 101.0, 74.8, 57.9, 55.8, 55.5, 52.8, 43.5, 41.3, 28.2, 23.6, 22.9 ppm.



2.144 **2.134**

To a solution 6-methylhept-5-en-one (**2.144**) (2.94 mL, 20.0 mmol, 1.0 equiv.) in THF (20 mL) at −78 °C was added a solution of ethynyl magnesium bromide (51 mL, 25.5 mmol, 0.5M in THF, 1.3 equiv.) in THF (50 mL). The mixture was slowly warmed to room temperature and stirred for 2.5 h, then cooled back to −78 °C. Methyl chloroformate (3.06, 32.0 mmol, 1.6 equiv.) was then added dropwise over a period of 5 min. The solution was then warmed to room temperate and left for a further 2 h. Finally the reaction was quenched upon addition of sat. $NaHCO_{3(aq)}$ (50 mL), and product extracted with Et_2O (3 x 50 mL), dried with $MgSO_4$, filtered and concentrated. Purification *via* flash chromatography (100:1 → 20:1 hexanes/ Et_2O, gradient elution) then gave **2.134** (2.75 g, 56%) as a yellow oil. Data for **2.134** matched that previously reported in the literature.[35]

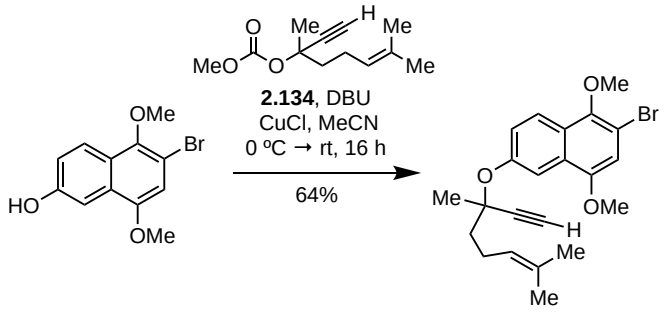
Partial Data for 2.134:

R_f: 0.45 (9:1 hexanes/ EtOAc).

FTIR (neat): 3289, 1754, 1440, 1230, 1167, 1074, 912, 994, 732 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.11 (ddt, *J* = 8.6, 5.7, 1.5 Hz, 1H), 3.76 (s, 3H), 2.59 (s, 1H), 2.27 – 2.13 (m, 2H), 2.04 – 1.94 (m, 1H), 1.87 (s, 1H), 1.72 (s, 3H), 1.68 (s, 3H), 1.62 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.8, 132.8, 123.2, 83.4, 77.2, 74.1, 54.6, 41.5, 26.5, 25.9, 23.1, 17.0 ppm.



2.126 **2.133**

To a solution of bromide **2.126** (500 mg, 1.7 mmol, 1.0 equiv.) in MeCN (100 mL) was added dropwise at 0 °C DBU (0.52 mg, 3.4 mmol, 2.0 equiv.) and CuCl (16 mg, 0.085 mmol, 5 mol%). A dropwise addition of **2.134** (550 mg, 2.6 mmol, 1.5 equiv.) in MeCN (100 mL) and reaction left to warm slowly to room temperature and stirred for 16 h. Reaction was then quenched with sat. $NH_4Cl_{(aq)}$ (200 mL) and extracted with EtOAc (3 x 200 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* flash chromatography on SiO_2 (20:5 hexanes/ EtOAc) then gave **2.133** (1.18 mg, 64%) as a yellow oil.

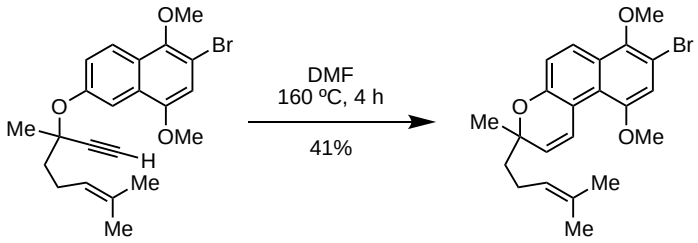
Partial Data for 2.133:

R_f: 0.45 (20:1 hexanes/ EtOAc).

FTIR (neat): 3291, 2967, 1737, 1580, 1462, 1347, 1233, 1196, 1168, 1096, 975, 823 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 – 7.94 (m, 2H), 7.42 (dd, *J* = 9.1, 2.4 Hz, 1H), 6.85 (s, 1H), 5.24 – 5.10 (m, 1H), 3.95 (s, 6H), 2.64 (s, 1H), 2.38 – 2.26 (m, 2H), 2.03 – 1.95 (m, 1H), 1.95 – 1.88 (m, 1H), 1.70 (s, 3H), 1.66 (s, 3H), 1.65 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.9, 151.9, 147.0, 132.4, 126.8, 125.5, 123.8, 123.6, 123.2, 112.0, 110.0, 108.5, 85.0, 75.8, 75.6, 61.6, 56.1, 42.7, 27.1, 25.8, 23.3, 17.8 ppm.



2.134 **2.135**

A solution of **2.134** (459 mg, 1.10 mmol, 1.0 equiv.) in DMF (5 mL) was heated to reflux. After 5 h the solution was cooled to room temperature and EtOAc (20 mL) added. The solution was then washed with sat. brine (5 x 20 mL) and the organic layer dried with $MgSO_4$, filtered and concentrated. Purification by flash column chromatography on SiO_2 (20:1 hexanes/ EtOAc) then afforded **2.135** (190 mg, 41%) as a yellow oil.

Data for 2.135:

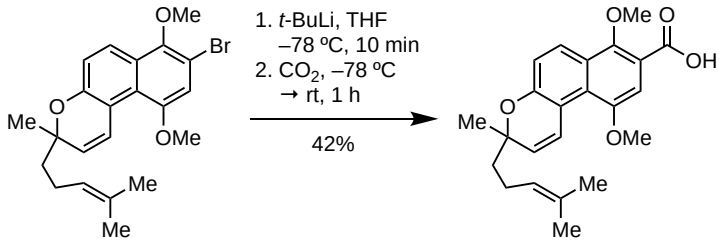
R_f: 0.45 (9:1 hexanes/ EtOAc).

FTIR (neat): 2030, 1589, 1564, 1455, 1326, 1198, 1982, 1045, 991, 822 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, *J* = 9.0 Hz, 1H), 7.62 (d, *J* = 10.3 Hz, 1H), 7.00 (d, *J* = 9.0 Hz, 1H), 6.78 (s, 1H), 5.47 (d, *J* = 10.3 Hz, 1H), 5.01 (t, *J* = 7.2 Hz, 1H), 3.82 (s, 6H), 2.09 – 2.01 (m, 2H), 1.72 – 1.62 (m, 2H), 1.56 (s, 3H), 1.48 (s, 3H), 1.34 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.9, 152.5, 147.5, 131.8, 127.1, 125.8, 124.3, 123.6, 123.3, 122.6, 119.9, 115.3, 110.6, 108.6, 77.3, 61.5, 56.0, 40.6, 25.8, 25.7, 22.9, 17.7 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{26}O_3Br$ 417.1060; found 417.1057.



2.125 **2.136**

To a solution of **2.125** (200 mg, 0.479 mmol, 1.0 equiv.) in THF (10 mL) was added at −78 °C *t*-BuLi (0.98 mL, 1.68 mmol, 1.7 M, 3.5 equiv.) and the reaction was left to stir 10 min. CO_2 (bubbled through phosphorus pentoxide) was then passed through the solution at 1 atm for 30 min. The reaction was then slowly warmed to room temperature and quenched upon addition of sat. $NH_4Cl_{(aq)}$ (10 mL) and product extracted with EtOAc (3 x 10 mL), dried with $MgSO_4$, filtered and concentrated. Purification *via* flash chromatography (20:1 CH_2Cl_2/ MeOH) then gave **2.136** (83 mg, 16%) as an orange solid and **2.122** (77 mg, 42%).

Data for 2.136:

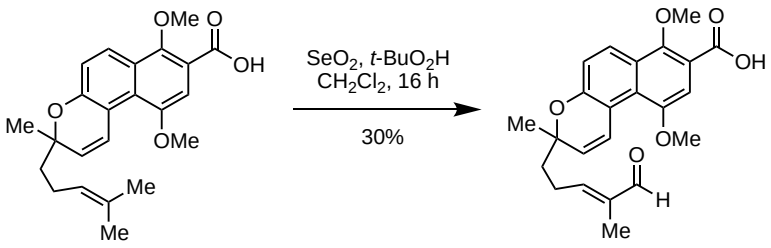
R_f: 0.60 (20:1 hexanes/ EtOAc).

FTIR (neat): 2926, 1685, 1607, 1454, 1344, 1262, 1221, 1049, 995, 830 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.32 (br s, 1H), 7.92 (d, *J* = 9.0 Hz, 1H), 7.76 (d, *J* = 10.4 Hz, 1H), 7.36 (s, 1H), 7.16 (d, *J* = 9.0 Hz, 1H), 5.60 (d, *J* = 10.3 Hz, 1H), 5.10 (tt, *J* = 7.1, 1.4 Hz, 1H), 4.05 (s, 3H), 3.99 (s, 3H), 2.19 – 2.11 (m, 2H), 1.77 (ddd, *J* = 16.9, 10.3, 6.2 Hz, 2H), 1.66 (s, 3H), 1.58 (s, 3H), 1.45 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.0, 154.8, 154.2, 151.7, 132.0, 127.4, 126.7, 124.3, 124.1, 123.7, 123.1, 120.3, 115.7, 114.7, 105.8, 78.0, 64.49, 56.0, 40.8, 26.0, 25.8, 22.9 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{27}O_5$ 383.1853; found 383.1863.



2.136 **2.137**

To a solution of **2.136** (28 mg, 0.073 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) was added SeO_2 (2 mg, 0.015 mmol, 0.2 equiv.) and *t*-BuO_2H (0.05 mL, 0.263 mmol, 3.6 equiv.) at room temperature. The reaction was left to stir for 16 h then quenched upon addition of sat. $Na_2SO_{4(aq)}$ (10 mL) and product extracted CH_2Cl_2 (3 x 10 mL), dried $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* flash chromatography (20:1 CH_2Cl_2/ MeOH) then gave **2.137** (9 mg, 30%) as an orange oil.

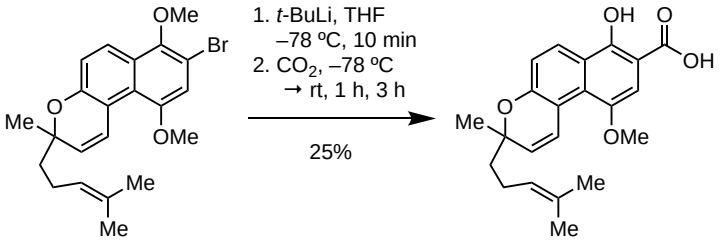
Partial Data for 2.137:

R_f: 0.90 (20:1 CH_2Cl_2/ MeOH).

FTIR (neat): 2924, 2851, 1720, 1608, 1456, 1378, 1258, 1207, 1128 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.36 (s, 1H), 8.31 (d, *J* = 9.6 Hz, 1H), 7.76 (d, *J* = 10.3 Hz, 1H), 7.03 (d, *J* = 9.5 Hz, 1H), 6.73 (s, 1H), 6.50 (t, *J* = 7.4 Hz, 1H), 5.51 (d, *J* = 10.2 Hz, 1H), 3.94 (s, 6H), 2.58 – 2.51 (m, 2H), 1.96 – 1.91 (m, 2H), 1.48 (s, 4H), 1.27 (s, 3H) ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{25}O_6$ 397.1646; found 397.1647.



2.135 **2.139**

To a solution of **2.135** (38 mg, 0.091 mmol, 1.0 equiv.) in THF (3 mL) was added at −78 °C *t*-BuLi (0.25 mL, 0.319 mmol, 1.7 M, 3.5 equiv.) and the reaction was left to stir 10 min. CO_2 (bubbled through phosphorus pentoxide) was then passed through the solution at 1 atm for 30 min. The reaction was then slowly warmed to room temperature and quenched upon addition of sat. brine (10 mL) and product extracted with EtOAc (3 x 10 mL), dried with $MgSO_4$, filtered and concentrated. Purification *via* flash chromatography (20:1 CH_2Cl_2/ MeOH) then gave **2.139** (9 mg, 25%) as an orange solid and **2.122** (6 mg, 17%).

Data for 2.139:

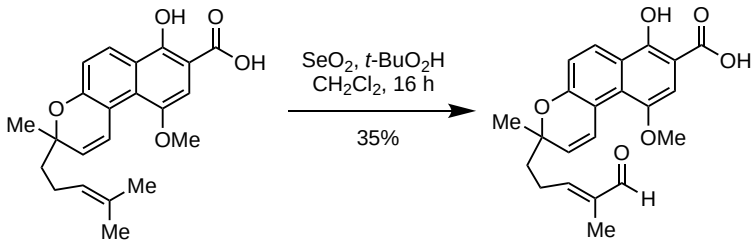
R_f: 0.45 (9:1 CH_2Cl_2/ MeOH).

FTIR (neat): 2925, 1694, 1454, 1368, 1267, 1209, 1139, 1089, 1030, 825 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (d, *J* = 9.6 Hz, 1H), 7.69 (d, *J* = 10.3 Hz, 1H), 7.02 (d, *J* = 9.5 Hz, 1H), 6.70 (s, 1H), 5.51 (d, *J* = 10.3 Hz, 1H), 5.10 (td, *J* = 7.1, 3.6 Hz, 1H), 3.91 (s, 3H), 2.18 – 2.10 (m, *J* = 5.6 Hz, 2H), 1.78 – 1.72 (m, *J* = 7.1 Hz, 2H), 1.65 (s, 3H), 1.57 (s, 3H), 1.42 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 185.7, 179.3, 155.1, 151.7, 137.0, 131.8, 130.3, 129.6, 128.0, 125.9, 124.5, 124.2, 117.4, 114.9, 105.7, 77.1, 55.6, 40.5, 33.2, 25.8, 25.6, 22.9 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{24}O_5Na$ 391.1516; found 391.1537.



2.139 **2.140**

To a solution of **2.139** (20 mg, 0.053 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) was added SeO_2 (1 mg, 0.009 mmol, 20 mol%) and *t*-BuO_2H (0.03 mL, 0.191 mmol, 3.6 equiv.) at room temperature. The reaction was left to stir for 16 h then quenched upon addition of sat. $Na_2SO_{4(aq)}$ (10 mL) and product extracted CH_2Cl_2 (3 x 10 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* flash chromatography (20:1 CH_2Cl_2/ MeOH) then gave **2.140** (7 mg, 35%) as an orange oil.

Data for 2.140:

R_f: 0.15 (20:1 CH_2Cl_2/ MeOH).

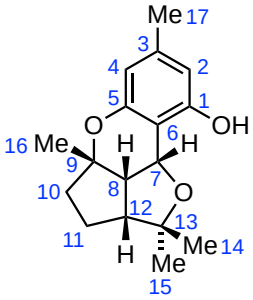
FTIR (neat): 2965, 2927, 1687, 1607, 1458, 1365, 1263, 1137, 1087, 1016 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.36 (s, 1H), 8.31 (d, *J* = 9.5 Hz, 1H), 7.76 (d, *J* = 10.3 Hz, 1H), 7.03 (d, *J* = 9.5 Hz, 1H), 6.74 (s, 1H), 6.50 (td, *J* = 7.4, 1.5 Hz, 1H), 5.51 (d, *J* = 10.3 Hz, 1H), 3.93 (s, 3H), 2.57 – 2.52 (m, 2H), 1.96 – 1.91 (m, 2H), 1.48 (s, 3H), 1.26 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 195.4, 177.4, 155.1, 154.7, 151.4, 139.5, 137.0, 130.4, 129.9, 128.2, 125.0, 124.9, 124.5, 117.2, 114.6, 105.9, 76.8, 55.7, 39.0, 29.8, 24.3, 9.3 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{23}O_6$ 383.1489; found 383.1492.

2.4.3 NMR Comparison Data



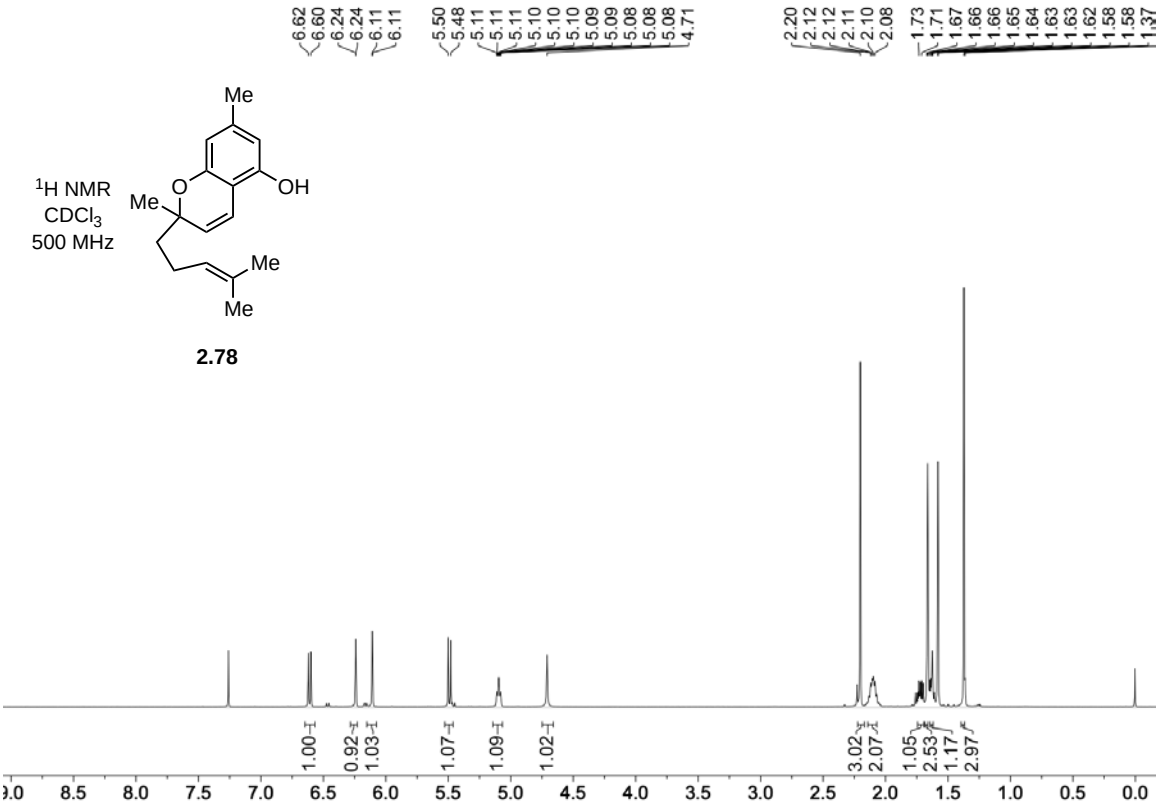
2.93: rhodonoid D

Table 2.4 – ^{1}H and ^{13}C NMR Comparison of Natural and Synthetic Rhodonoid D

Assignment	Natural Sample ^{1}H NMR (400 MHz, $CDCl_3$) Hou *et al.*[33]	Synthetic Sample ^{1}H NMR (600 MHz, $CDCl_3$)	Natural Sample ^{1}H NMR (150 MHz, $CDCl_3$) Hou *et al.*[33]	Synthetic Sample ^{13}C NMR (125 MHz, $CDCl_3$)
1	--	--	155.7	155.6
2	6.30 (br s)	6.30 (br s)	108.6	108.5
3	--	--	140.4	140.2
4	6.26 (br s)	6.26 (s)	110.0	109.8
5	--	--	152.8	152.6
6	--	--	108.0	107.8
7	5.04 (d, *J* = 4.3 Hz)	5.05 (d, *J* = 4.2 Hz)	69.1	68.9
8	1.83 (d, *J* = 4.3 Hz)	1.87 – 1.81 (m)	51.3	51.1
9	--	--	77.7	77.5
10	1.82 (dd, *J* = 13.7, 6.0 Hz) 1.49 (dd, *J* = 13.7, 6.0 Hz)	1.87 – 1.81 (m) 1.49 (dd, *J* = 14.6, 5.7 Hz)	27.7	27.6
11	1.71 (m)	1.73 – 1.69 (m)	27.1	27.0
12	3.85 (br s)	3.85 (s)	82.2	82.0
13			42.8	42.6
14	1.29 (s)	1.29 (s)	28.1	27.9
15	1.26 (s)	1.26 (s)	23.1	23.0
16	1.63 (s)	1.64 (s)	30.3	30.1
17	2.23 (s)	2.23 (s)	21.6	21.5
1-OH	--	5.64 (br s)	--	--

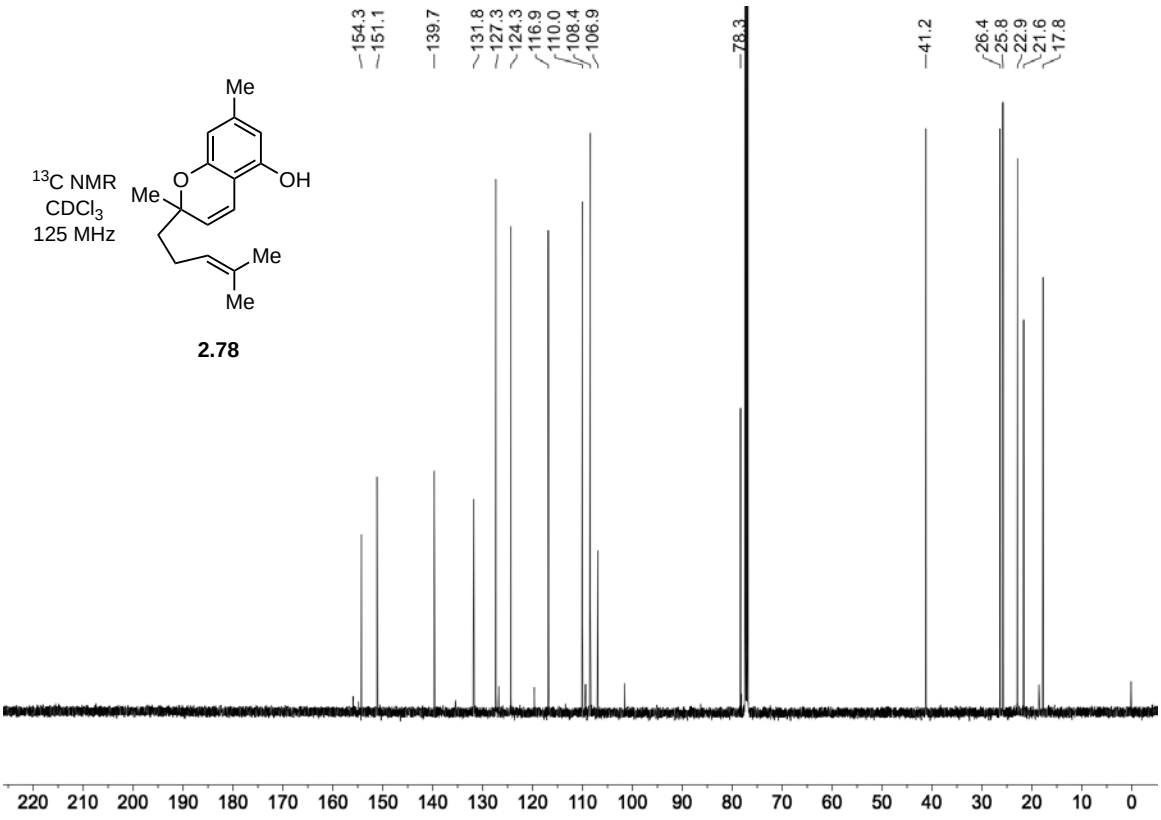
2.4.4 NMR Spectra

Data for 2.78



^{1}H NMR
$CDCl_3$
500 MHz

2.78

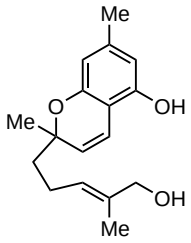


^{13}C NMR
$CDCl_3$
125 MHz

2.78

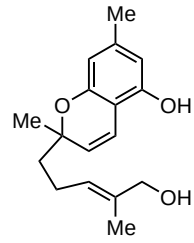
Data for 2.80

^{1}H NMR
$CDCl_3$
500 MHz



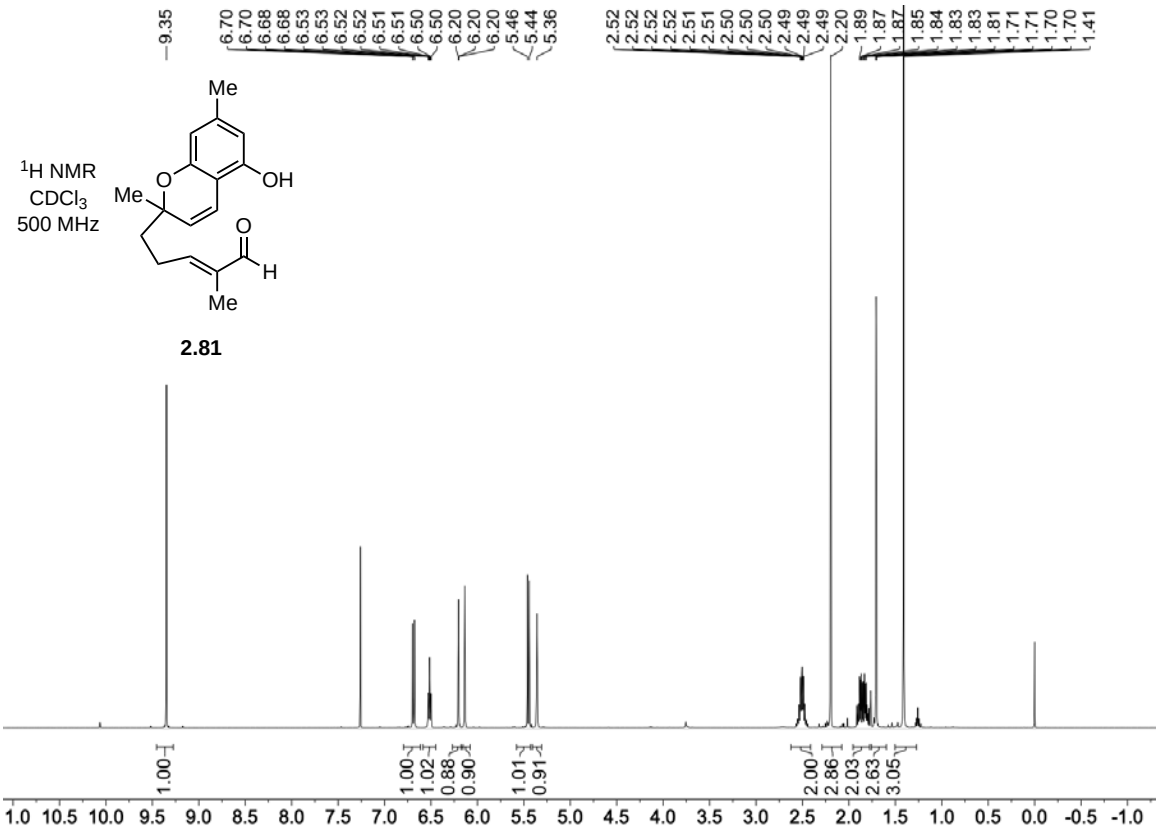
2.80

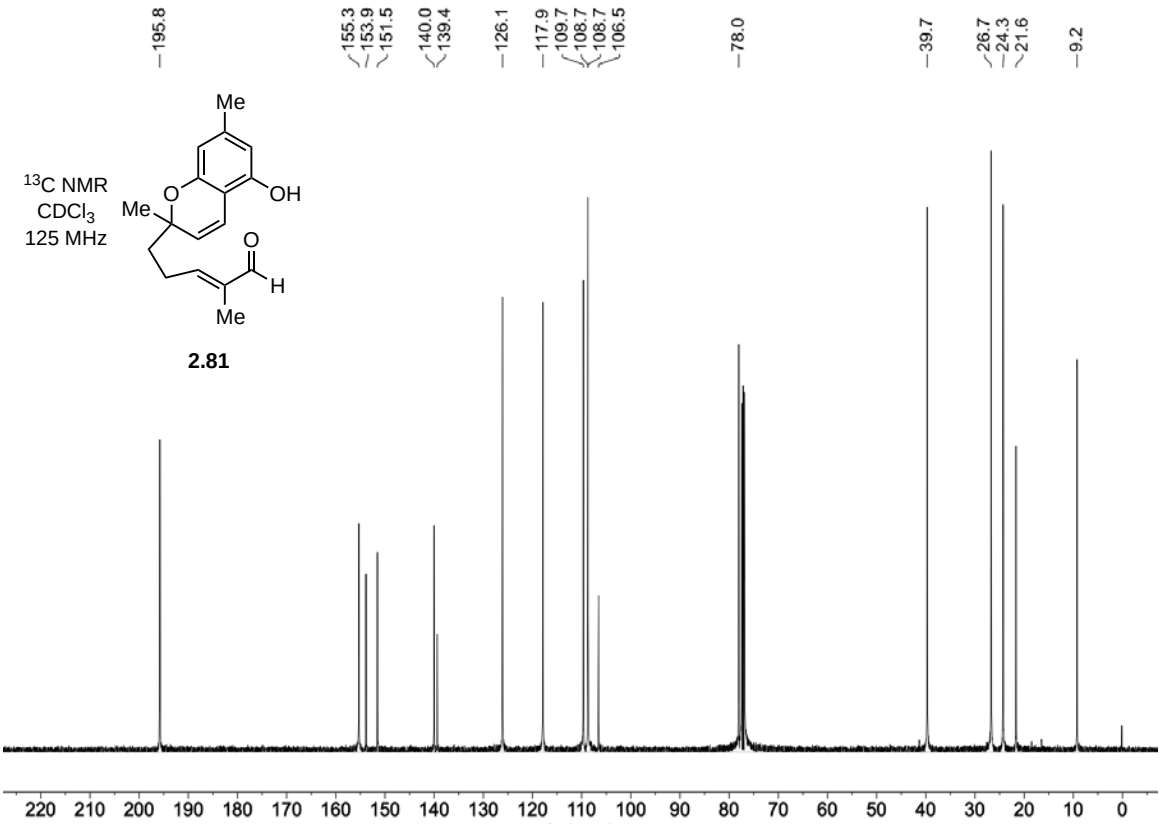
^{13}C NMR
$CDCl_3$
125 MHz



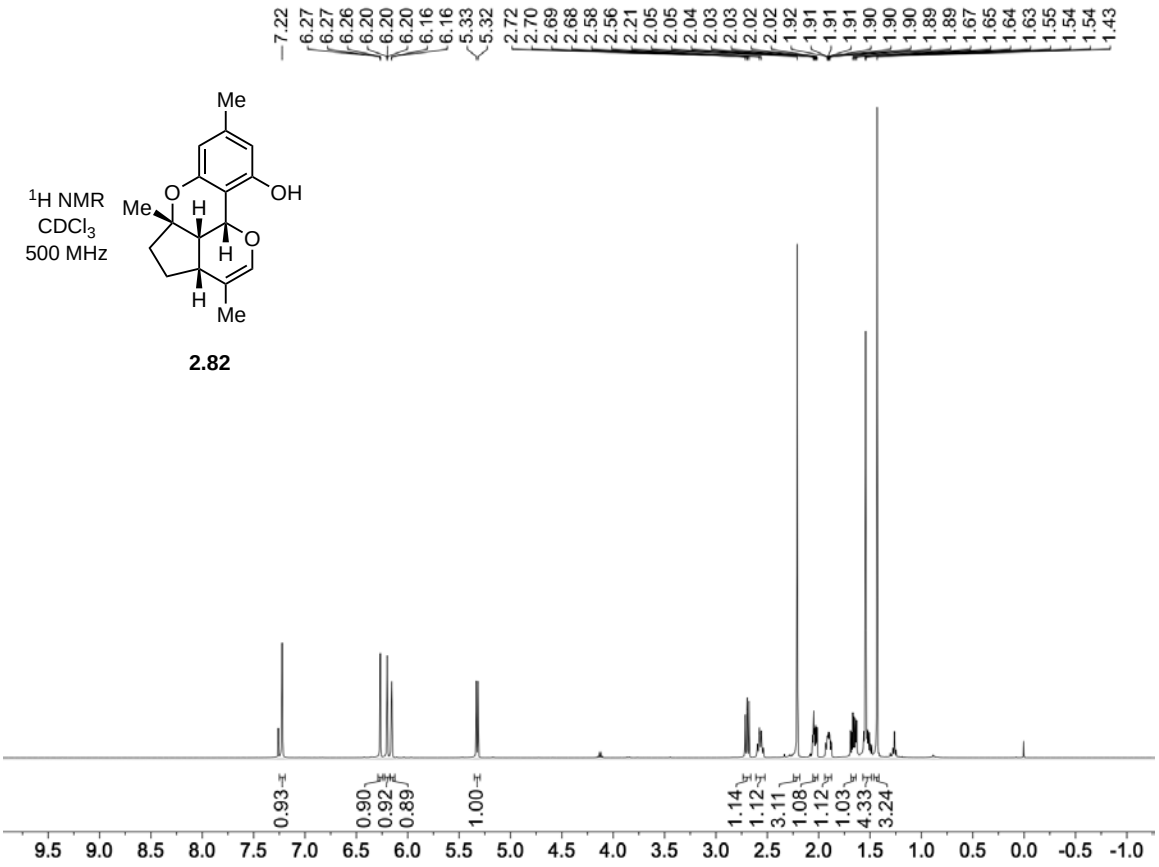
2.80

Data for 2.81


^{1}H NMR
$CDCl_3$
500 MHz
Me
O
OH
Me
O
H
Me
2.81

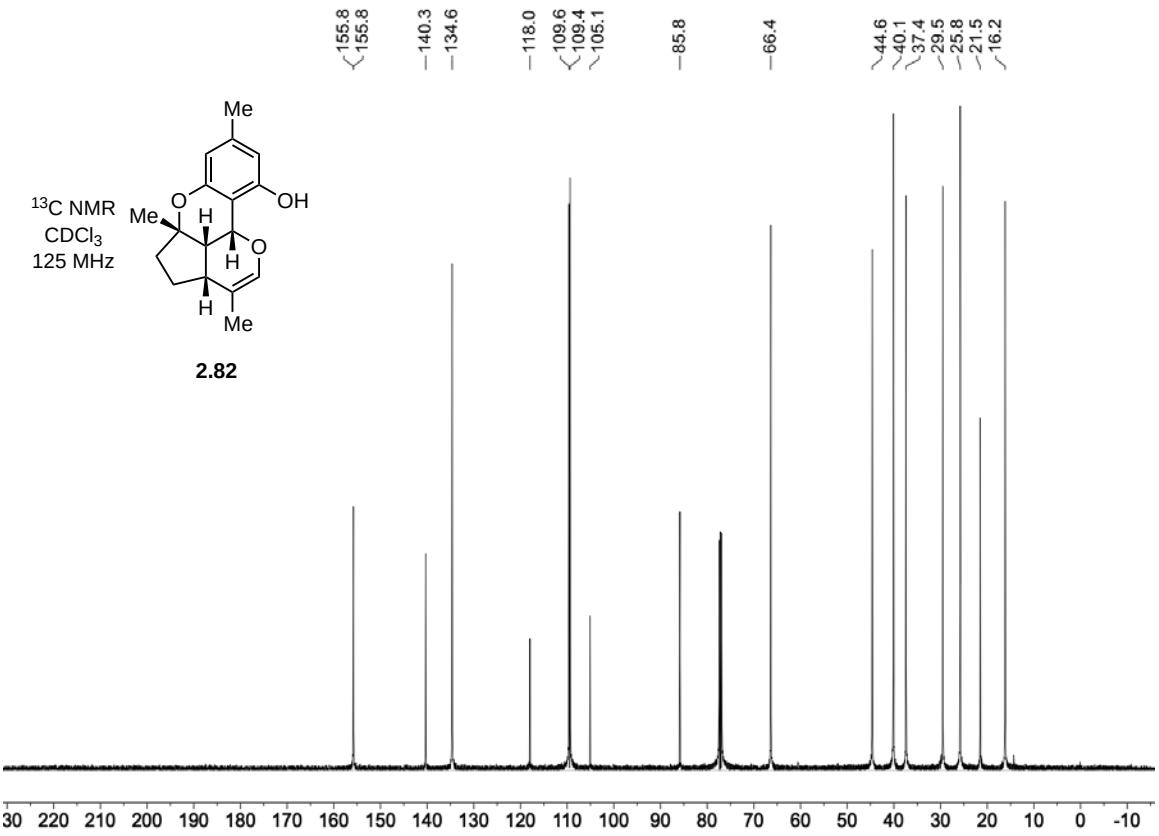

^{13}C NMR
$CDCl_3$
125 MHz
Me
O
OH
Me
O
H
Me
2.81

Data for 2.82



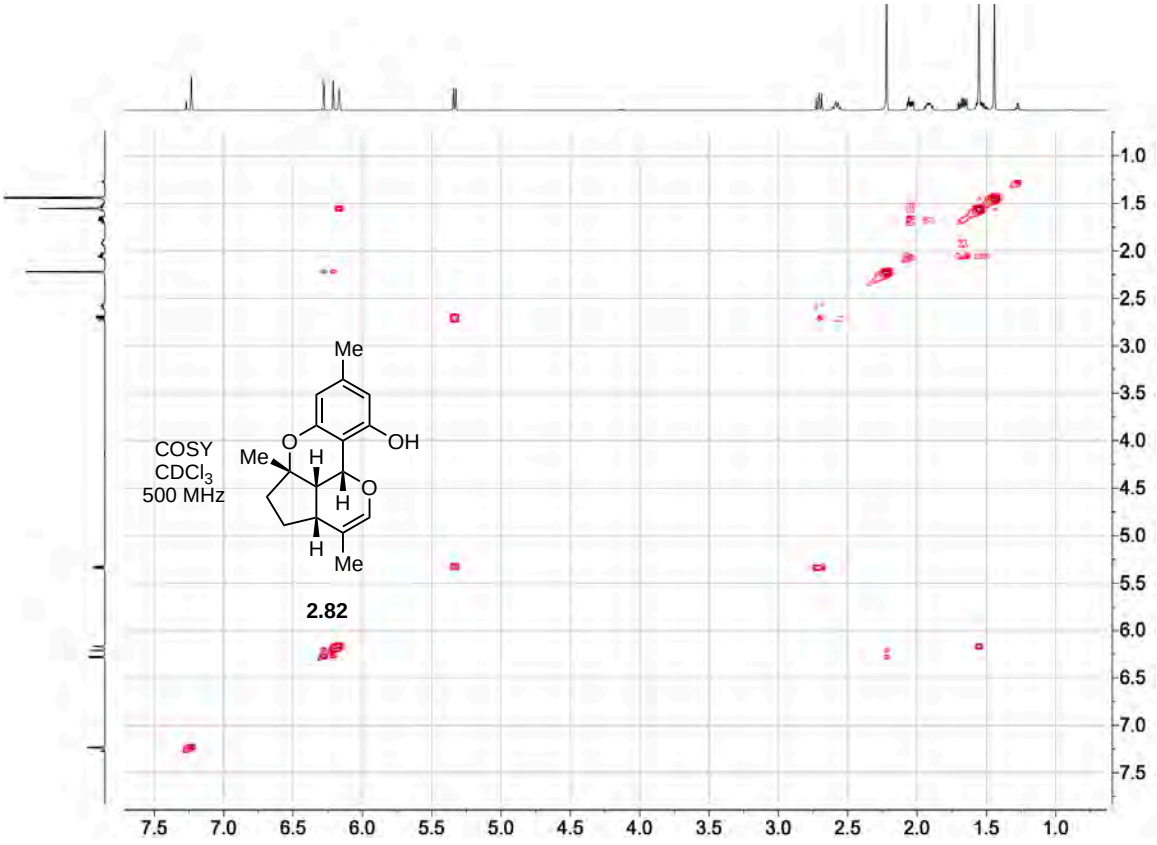
^{1}H NMR
$CDCl_3$
500 MHz

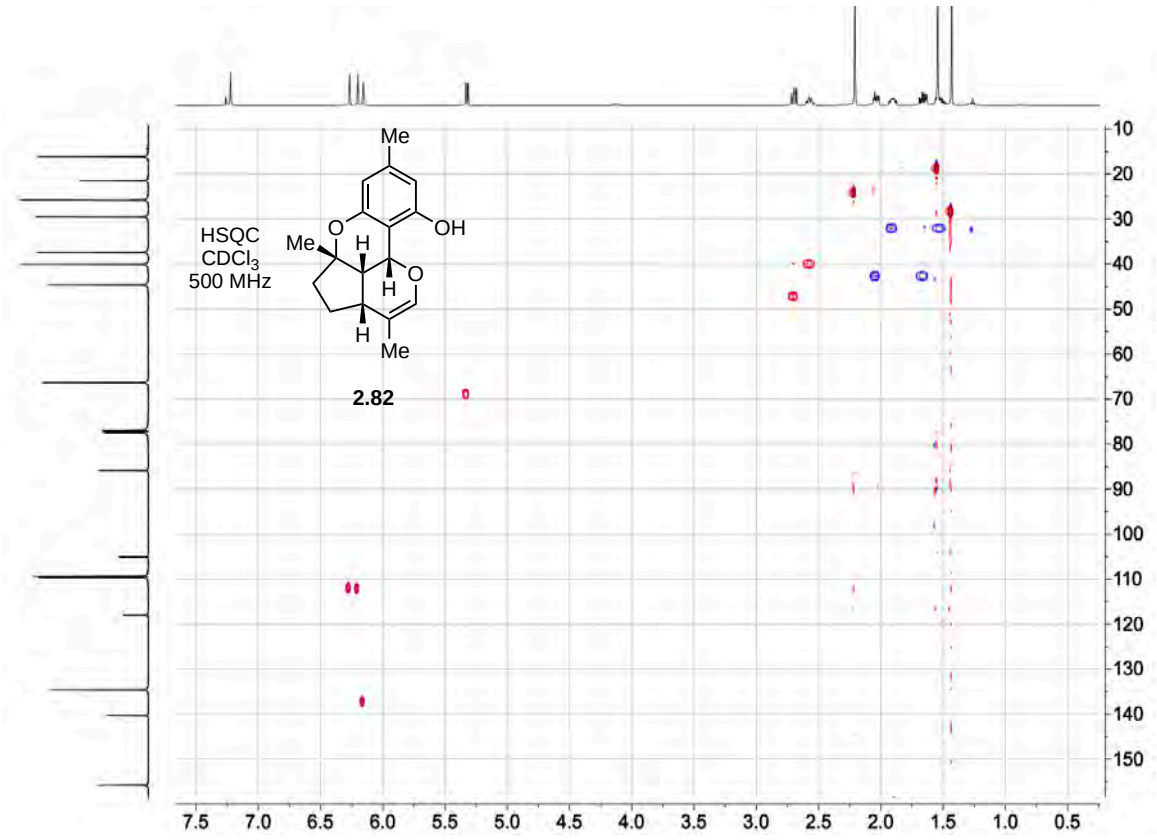
2.82

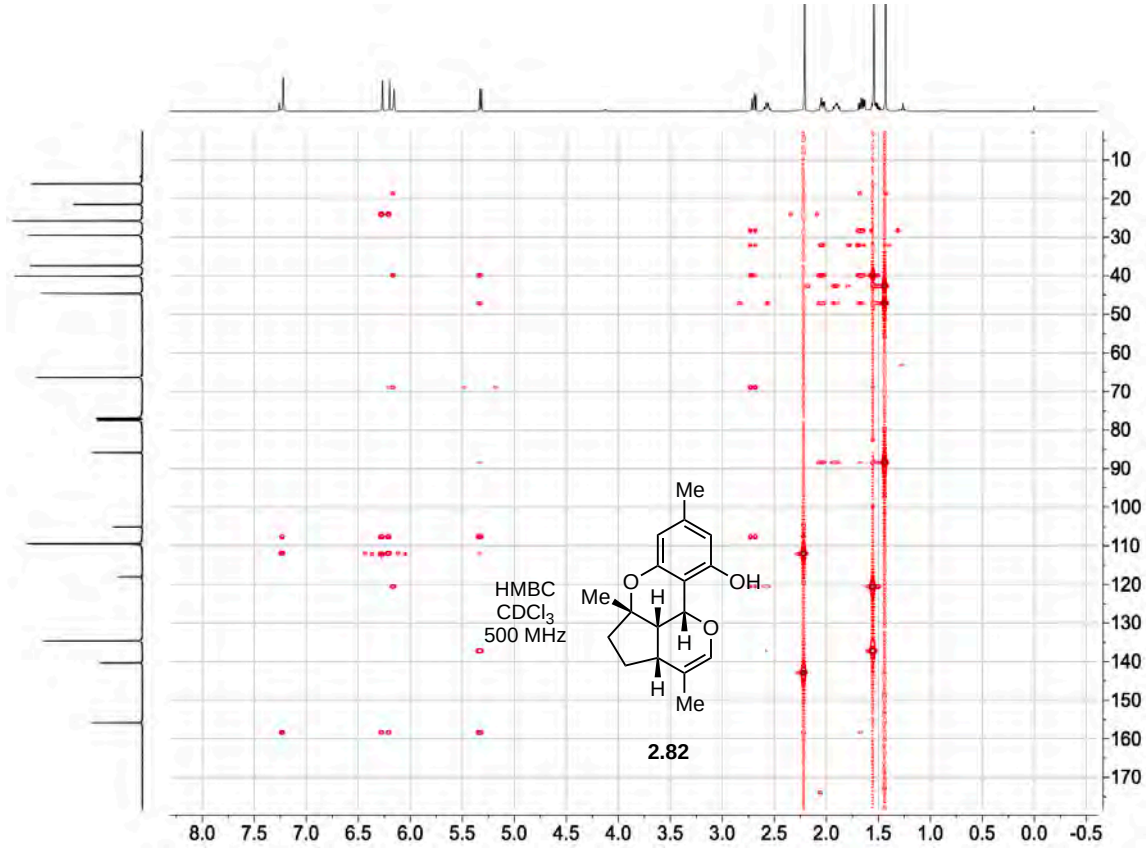


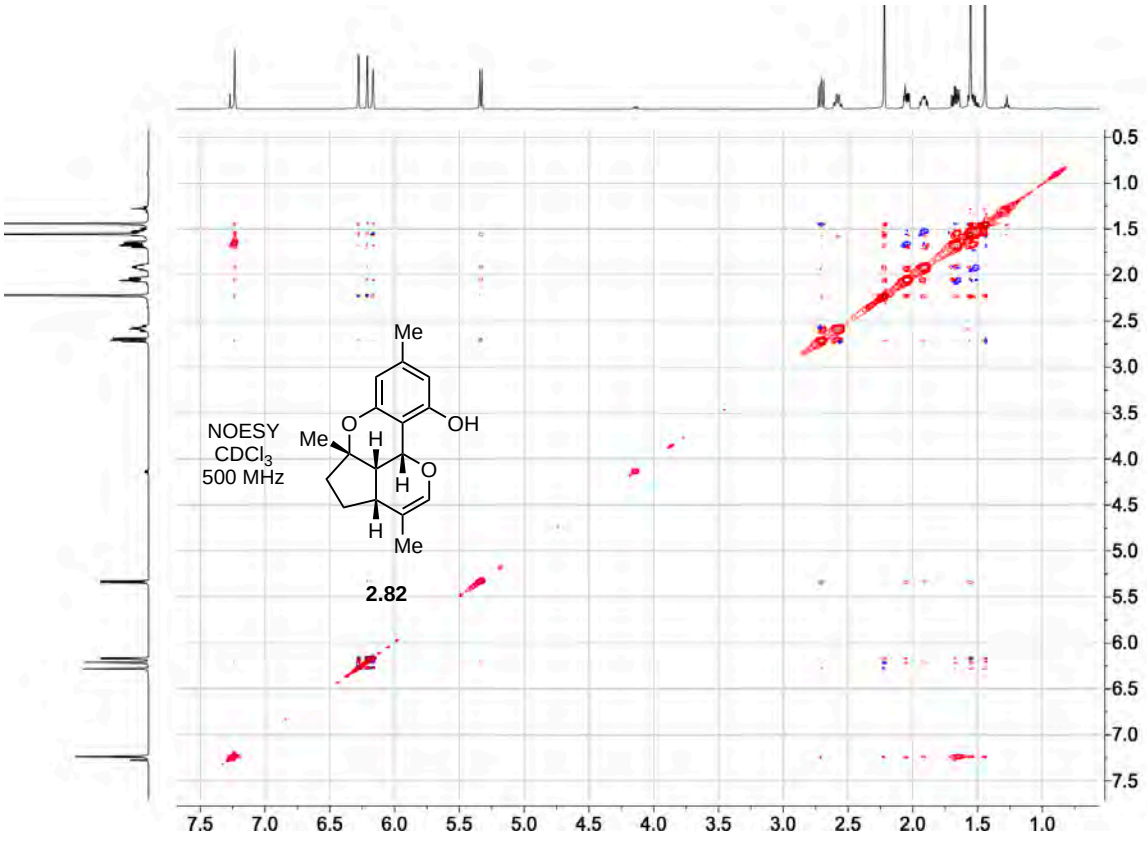
^{13}C NMR
$CDCl_3$
125 MHz

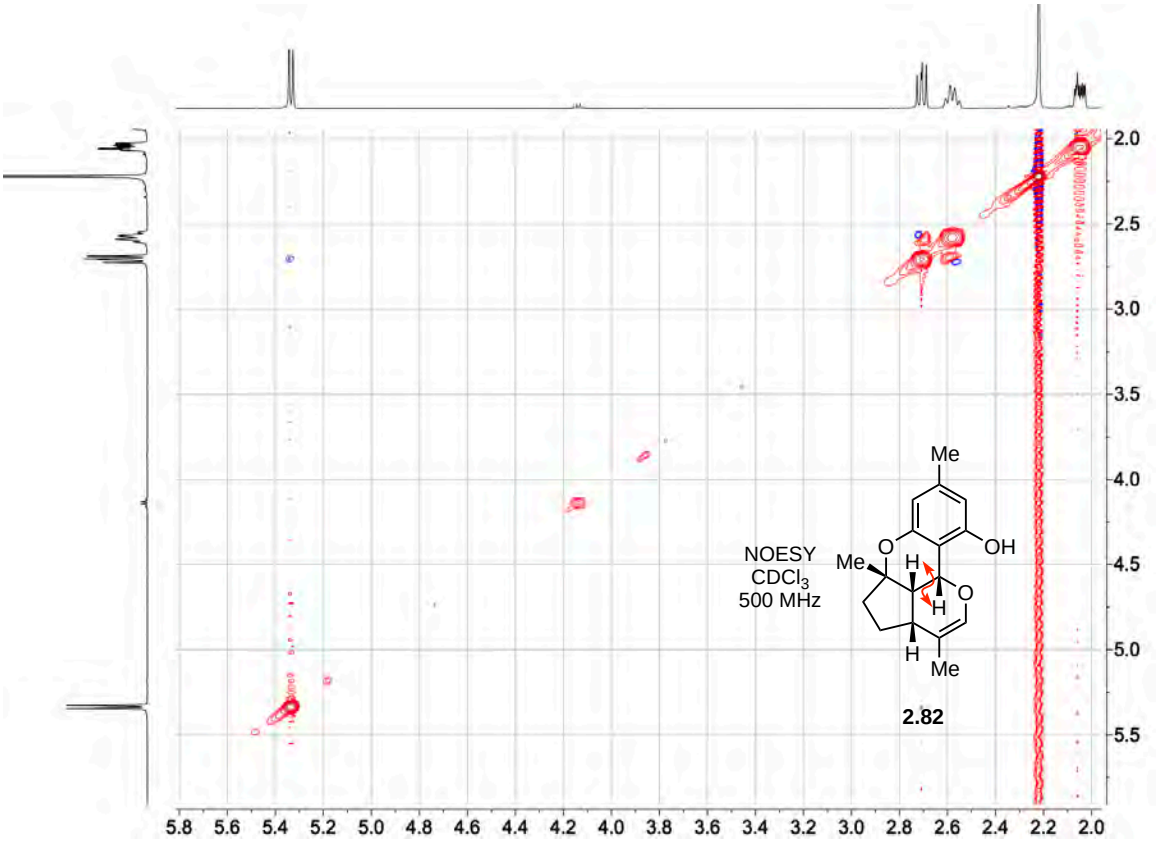
2.82

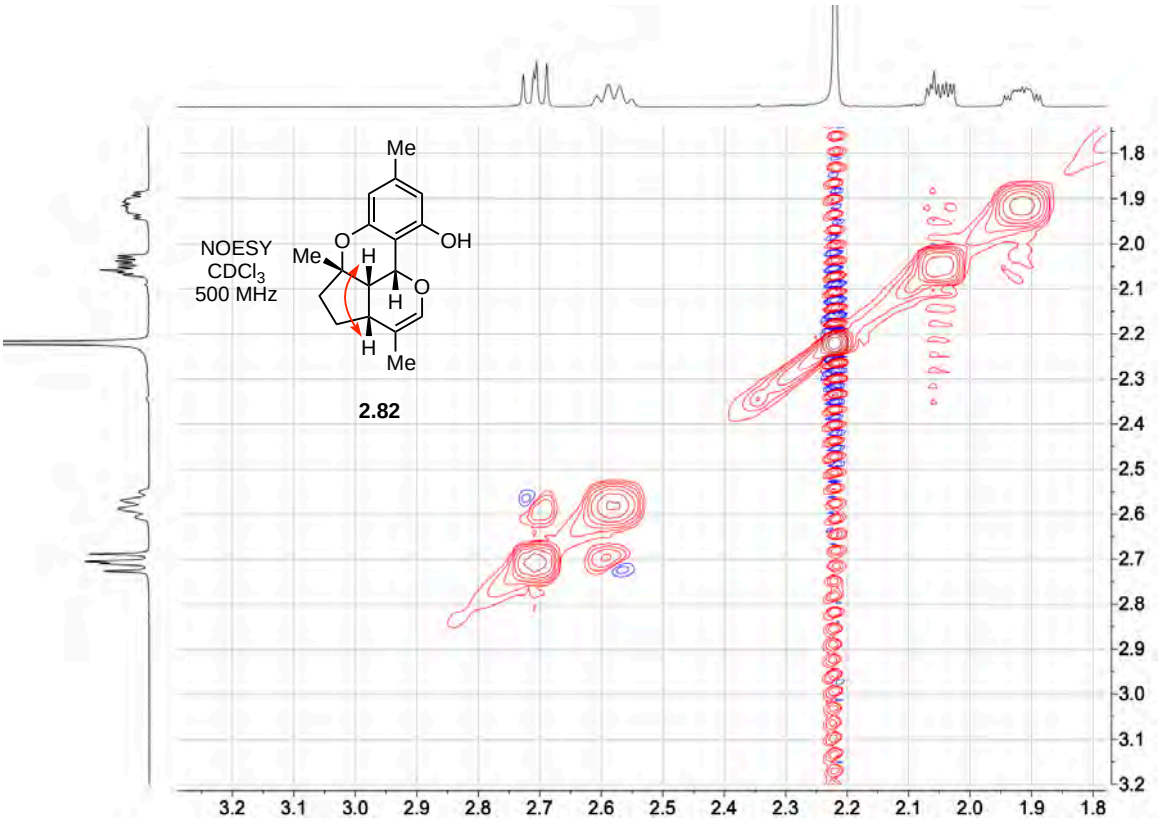

COSY
CDCl3
500 MHz
Me
OH
Me
O
H
O
H
H
Me
2.82


HSQC
CDCl3
500 MHz
Me
OH
Me
O
H
O
H
H
Me
2.82


HMBC
CDCl3
500 MHz
Me
OH
Me
O
H
O
H
H
Me
2.82

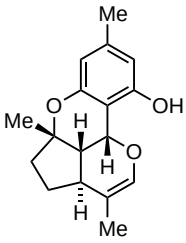

NOESY
CDCl3
500 MHz
Me
OH
Me
O
H
O
H
H
Me
2.82


NOESY
CDCl3
500 MHz
Me
OH
O
H
Me
2.82


NOESY
CDCl3
500 MHz
Me
OH
O
H
Me
2.82

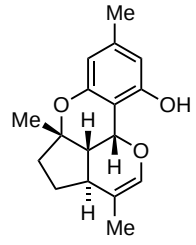
Data for 2.83

^{1}H NMR
$CDCl_3$
600 MHz

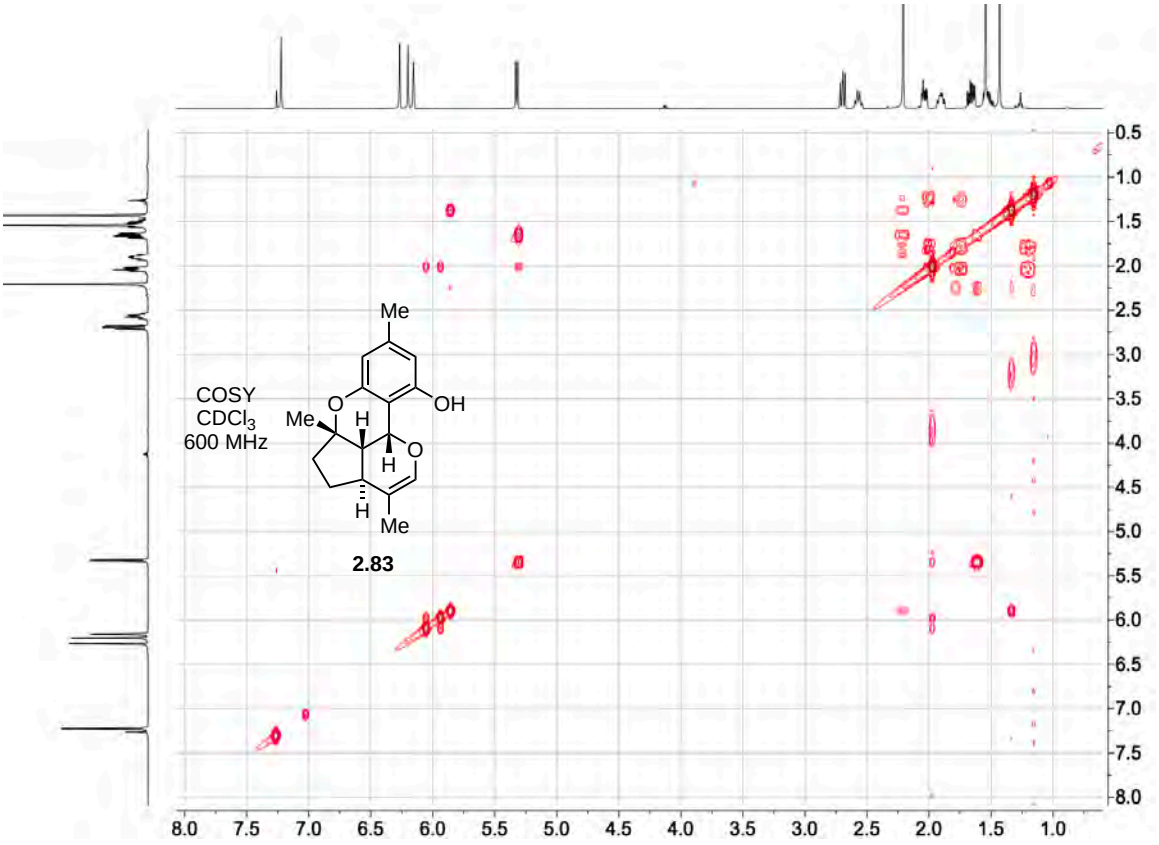


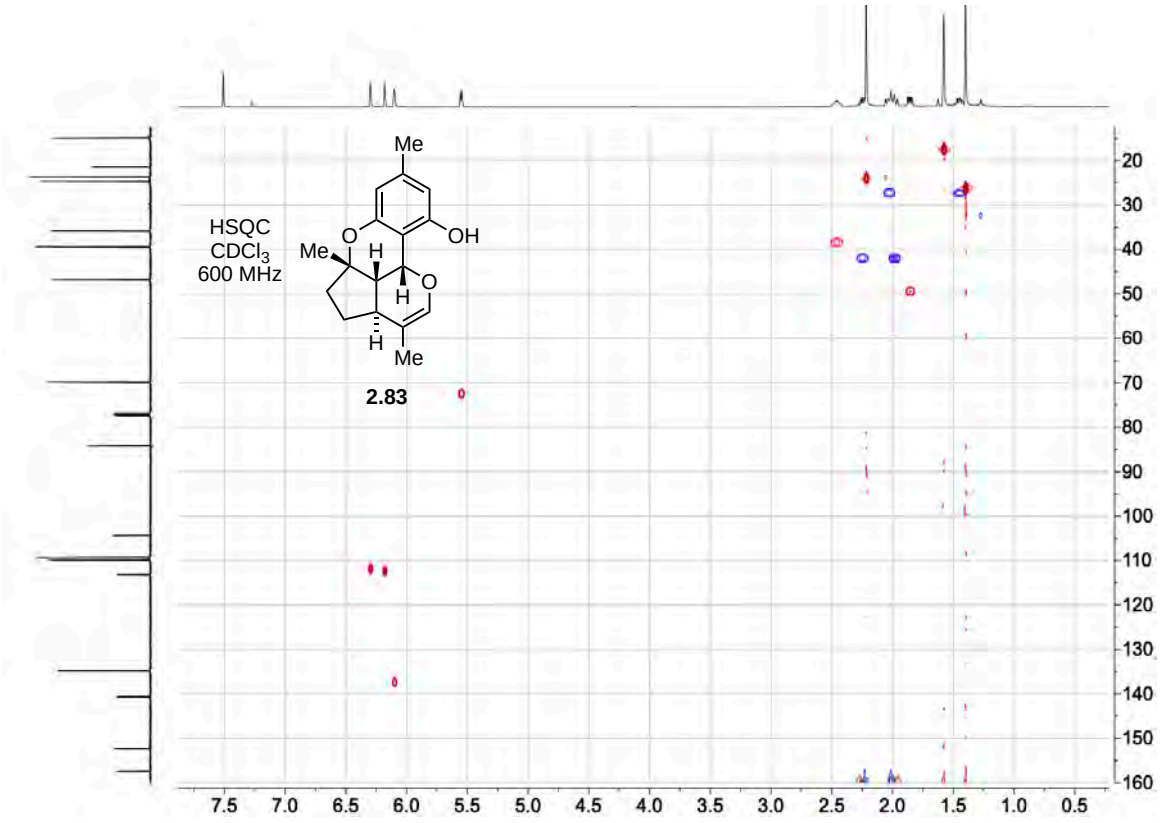
2.83

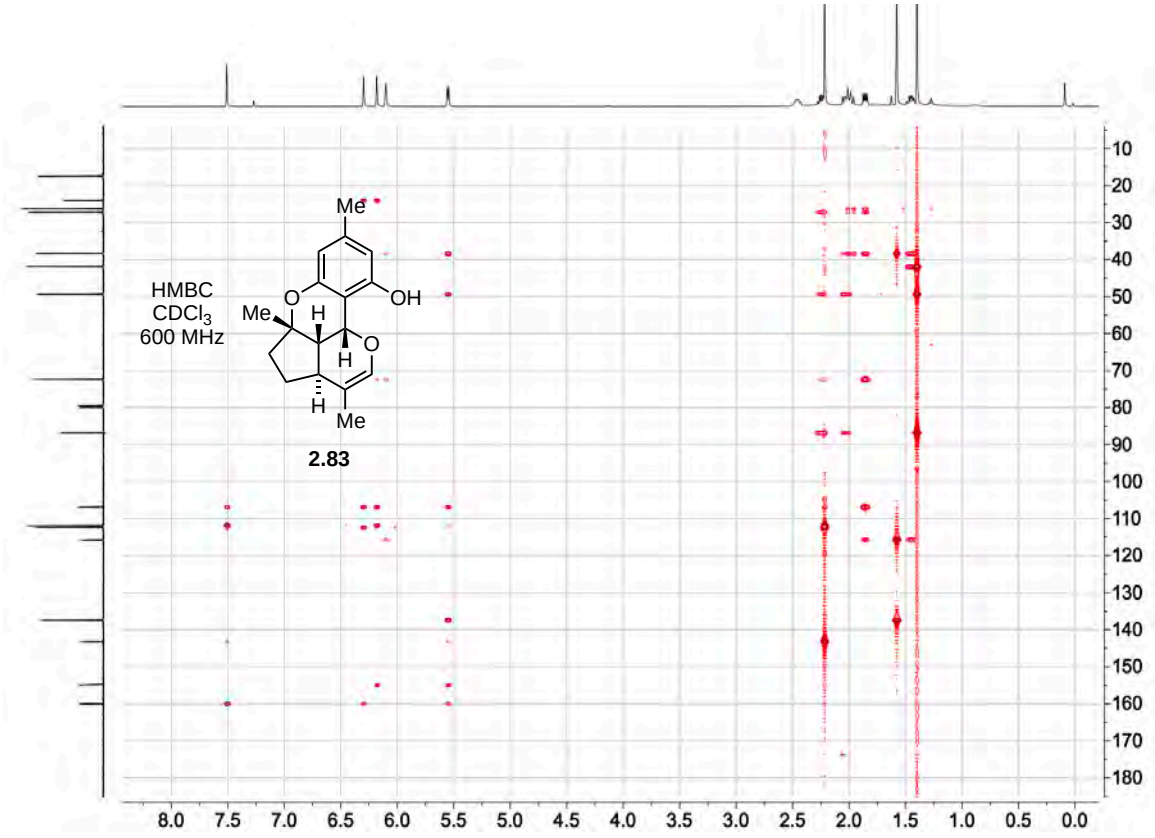
^{13}C NMR
$CDCl_3$
150 MHz

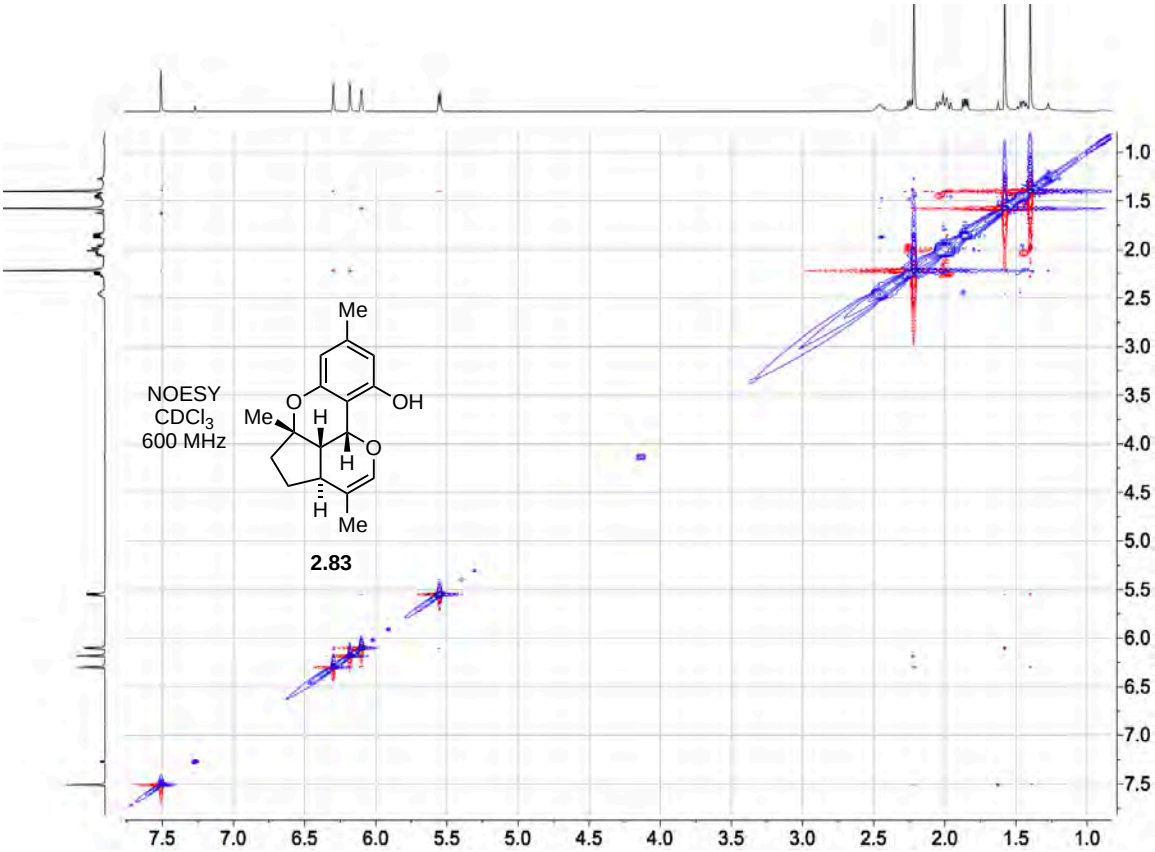


2.83

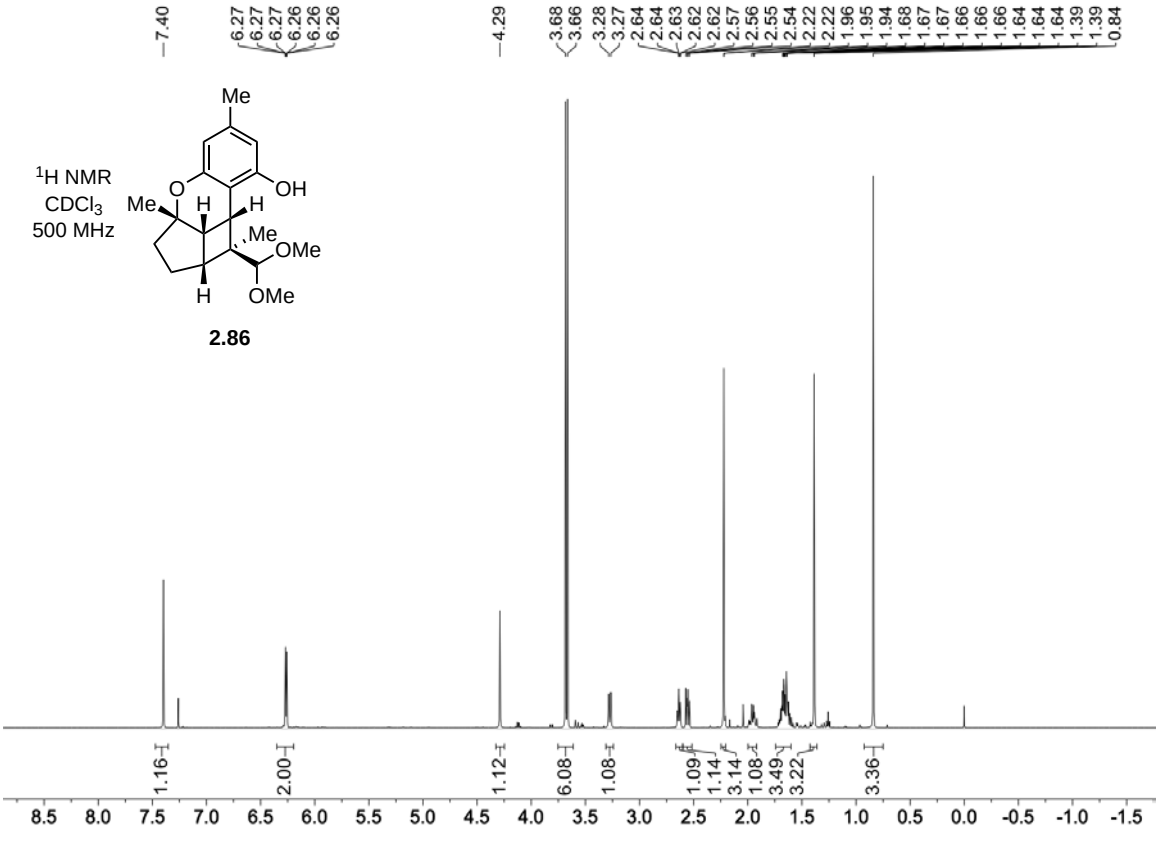

COSY
CDCl3
600 MHz
Me
O
H
OH
Me
H
O
H
H
Me
2.83

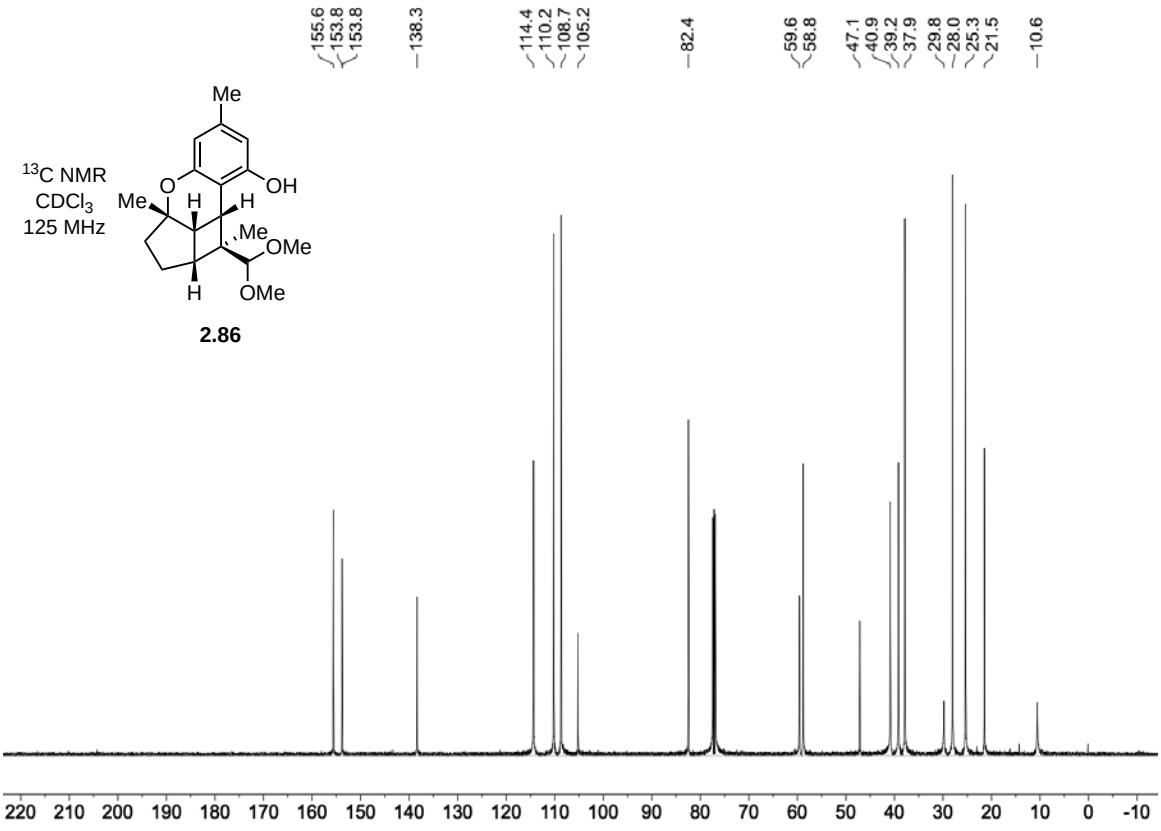

HSQC
CDCl3
600 MHz
Me
O
H
OH
Me
H
O
H
H
Me
2.83

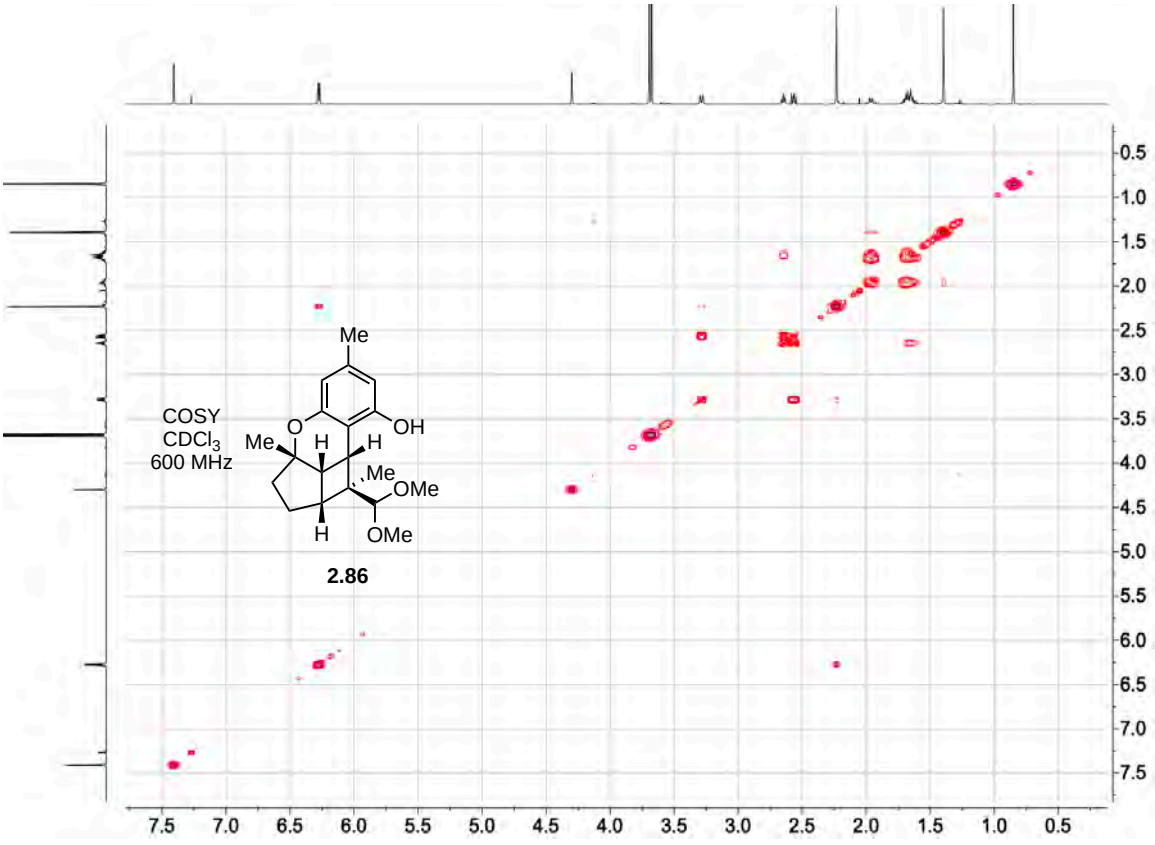

HMBC
CDCl3
600 MHz
Me
O
OH
Me
H
H
O
H
Me
2.83

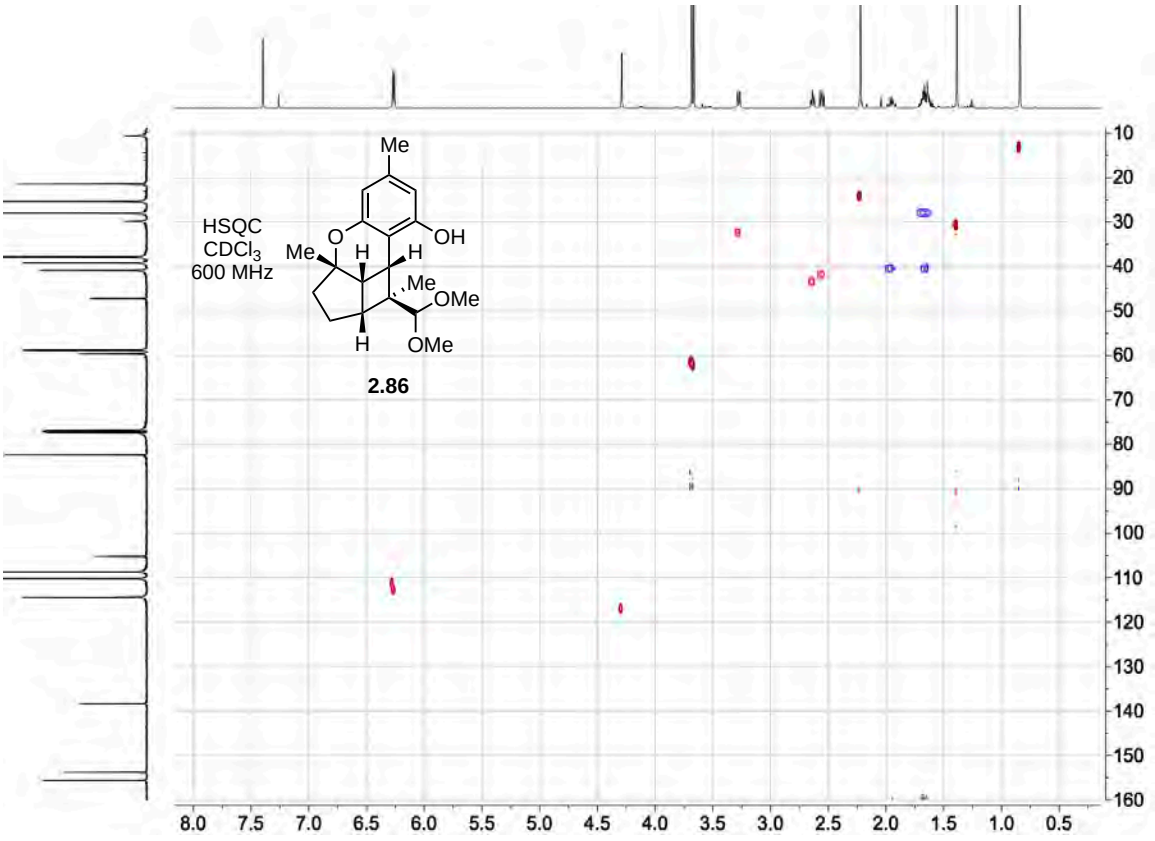

NOESY
CDCl3
600 MHz
Me
O
OH
Me
H
H
O
H
Me
2.83

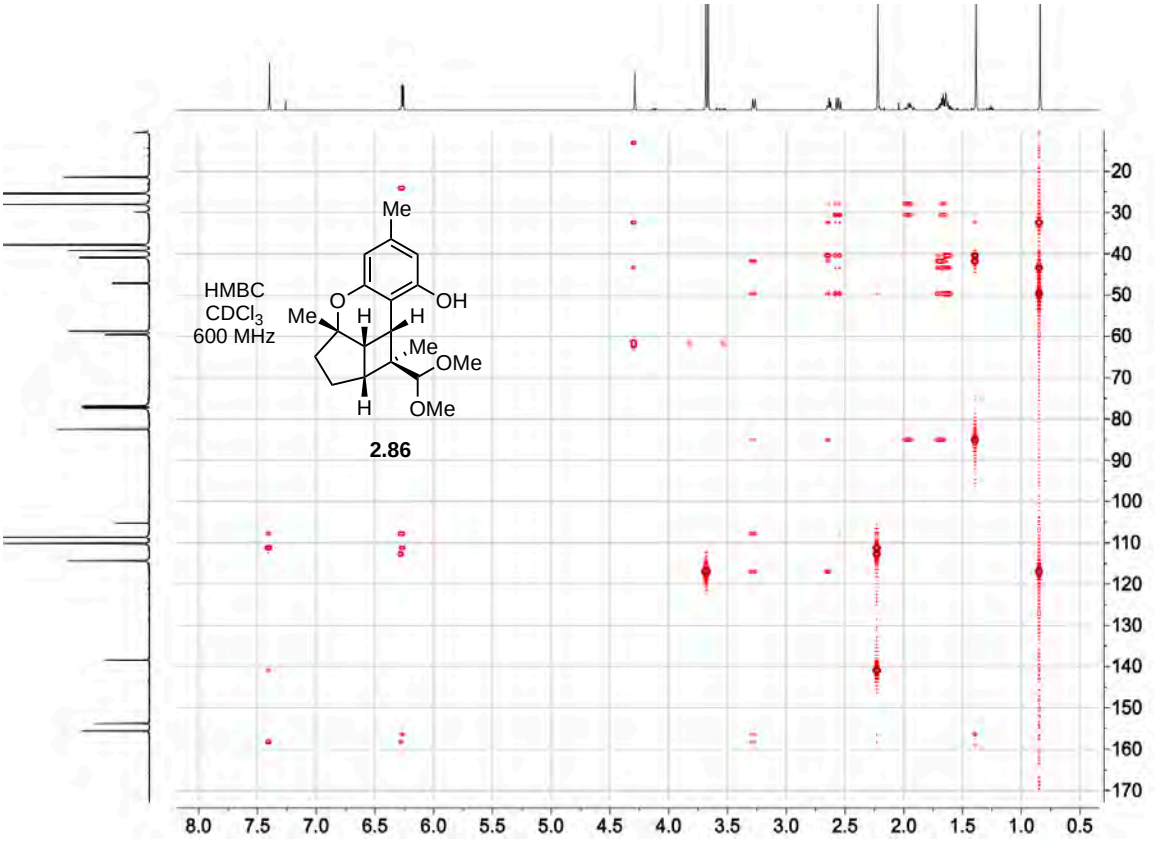
Data for 2.86

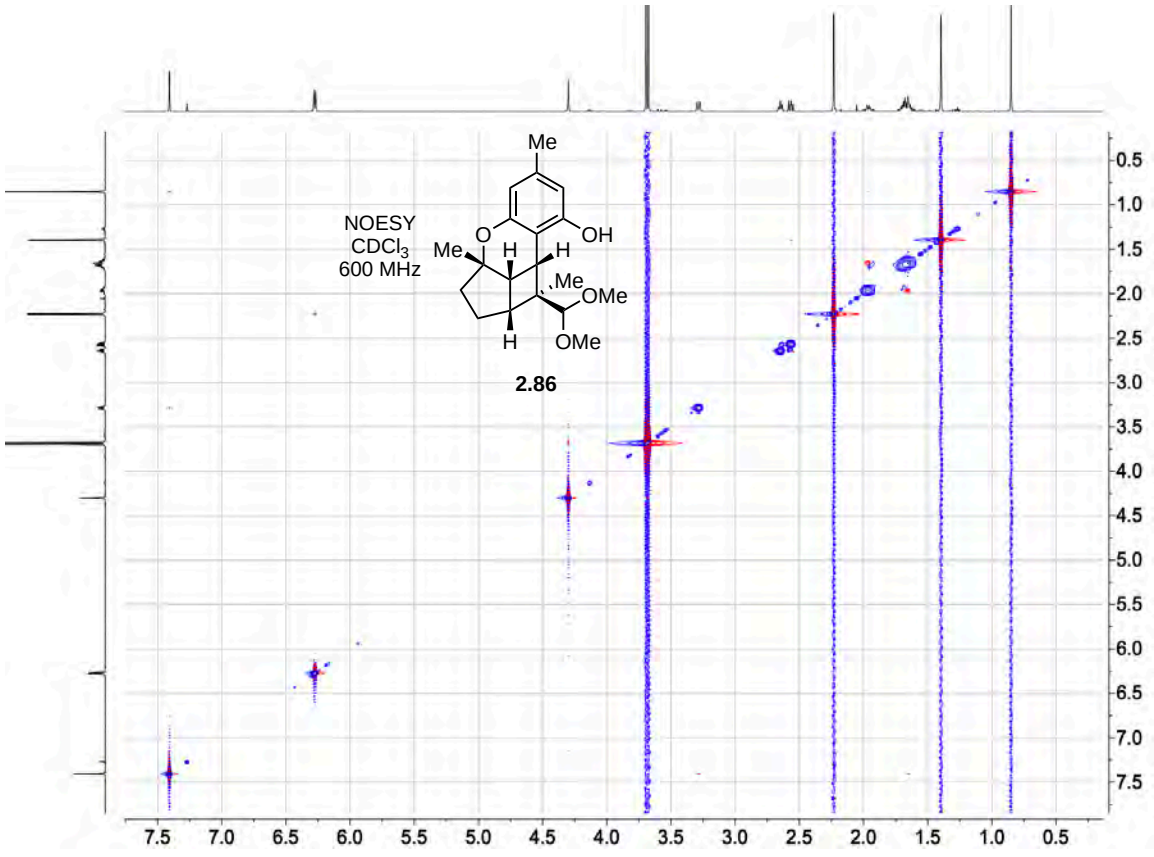

7.40
6.27
6.27
6.27
6.26
6.26
6.26
4.29
3.68
3.66
3.28
3.27
2.64
2.64
2.63
2.62
2.62
2.57
2.56
2.55
2.54
2.22
2.22
1.96
1.95
1.94
1.68
1.67
1.67
1.66
1.66
1.66
1.64
1.64
1.64
1.39
1.39
0.84
1H NMR
CDCl3
500 MHz
Me
O
OH
Me
H
H
Me
OMe
H
OMe
2.86
1.16
2.00
1.12
6.08
1.08
1.09
1.14
3.14
1.08
3.49
3.22
3.36
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5


155.6
153.8
153.8
138.3
114.4
110.2
108.7
105.2
82.4
59.6
58.8
47.1
40.9
39.2
37.9
29.8
28.0
25.3
21.5
10.6
13C NMR
CDCl3
125 MHz
Me
O
OH
Me
H
H
Me
OMe
H
OMe
2.86
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

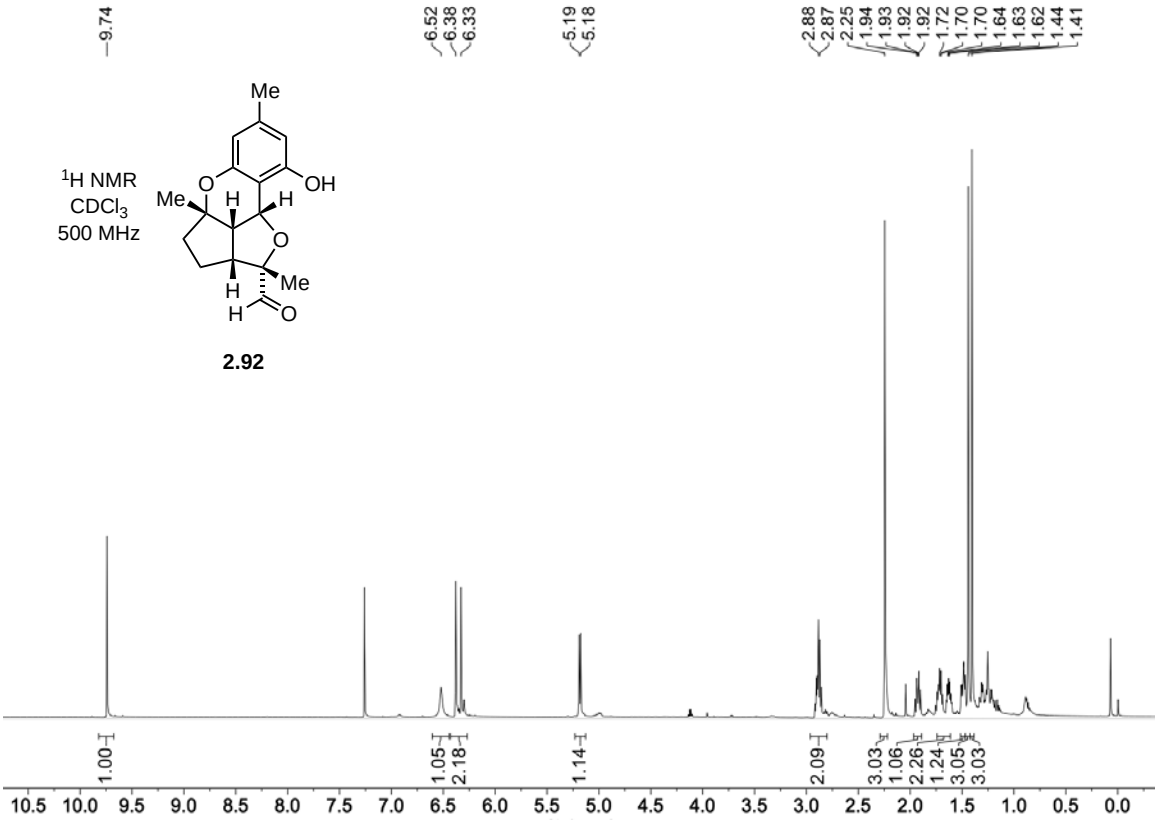

COSY
CDCl3
600 MHz
Me
O
OH
Me
H
H
Me
OMe
H
OMe
2.86


HSQC
CDCl3
600 MHz
Me
O
OH
Me
H
H
Me
OMe
H
OMe
2.86

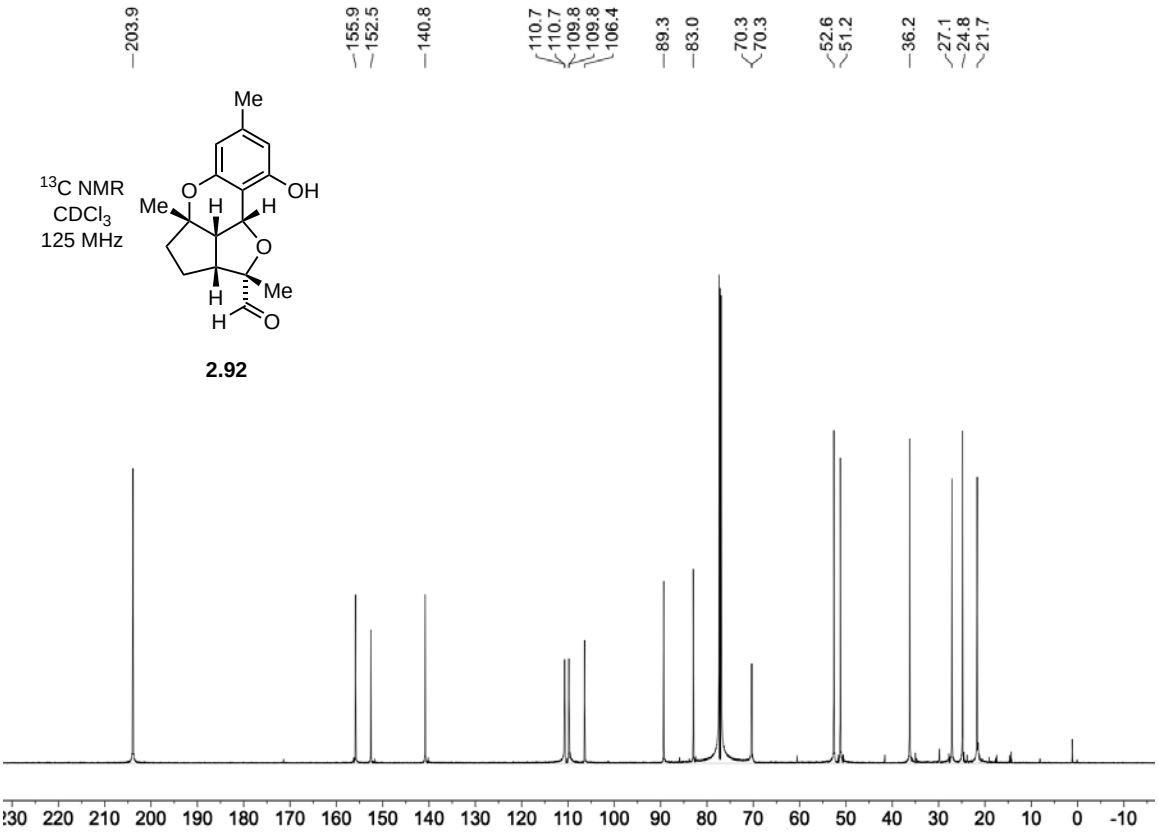

HMBC
CDCl3
600 MHz
Me
O
H
H
OH
Me
Me
OMe
H
OMe
2.86


NOESY
CDCl3
600 MHz
Me
O
H
H
OH
Me
Me
OMe
H
OMe
2.86

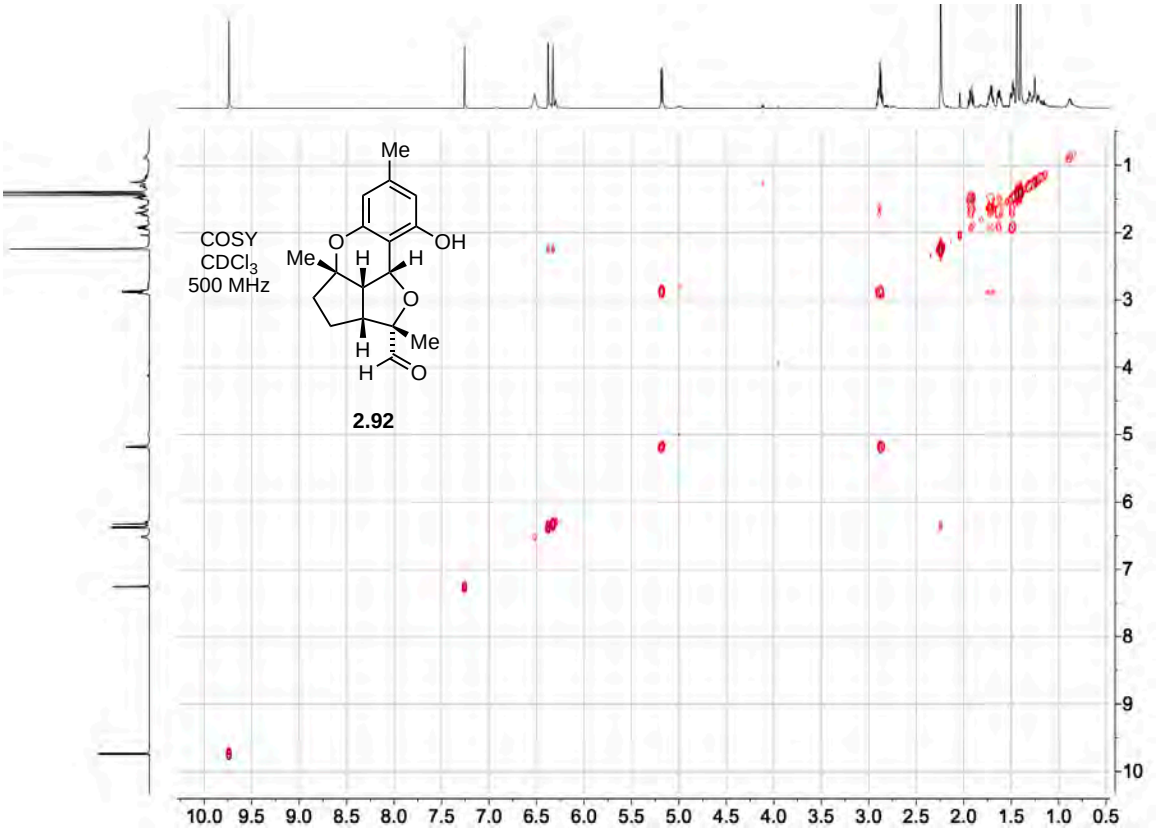
Data for 2.92

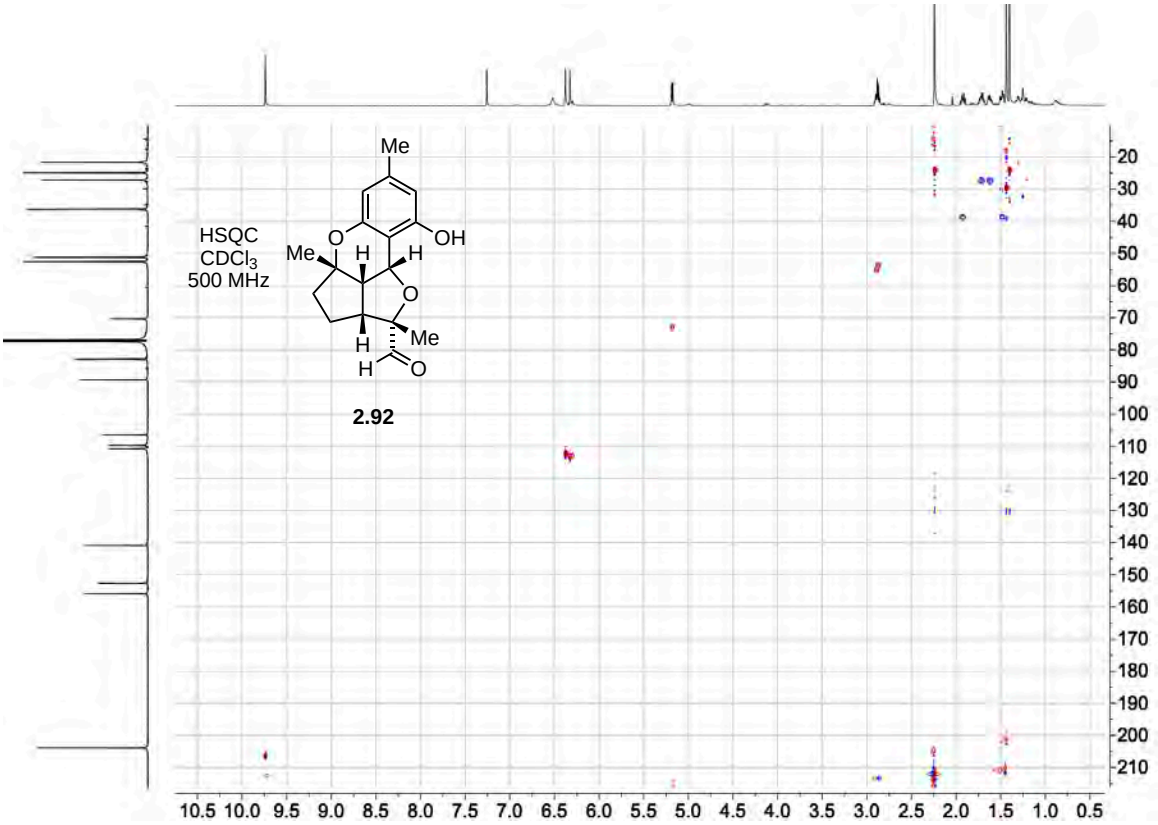


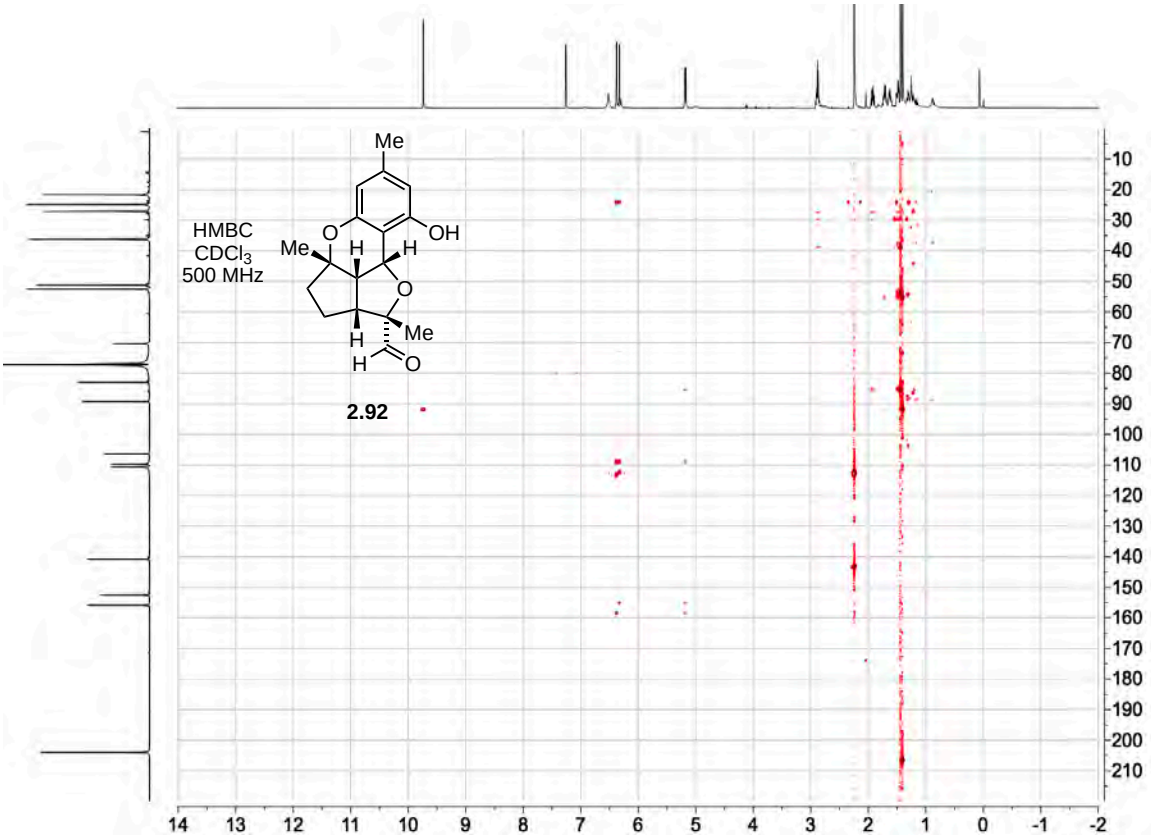
2.92

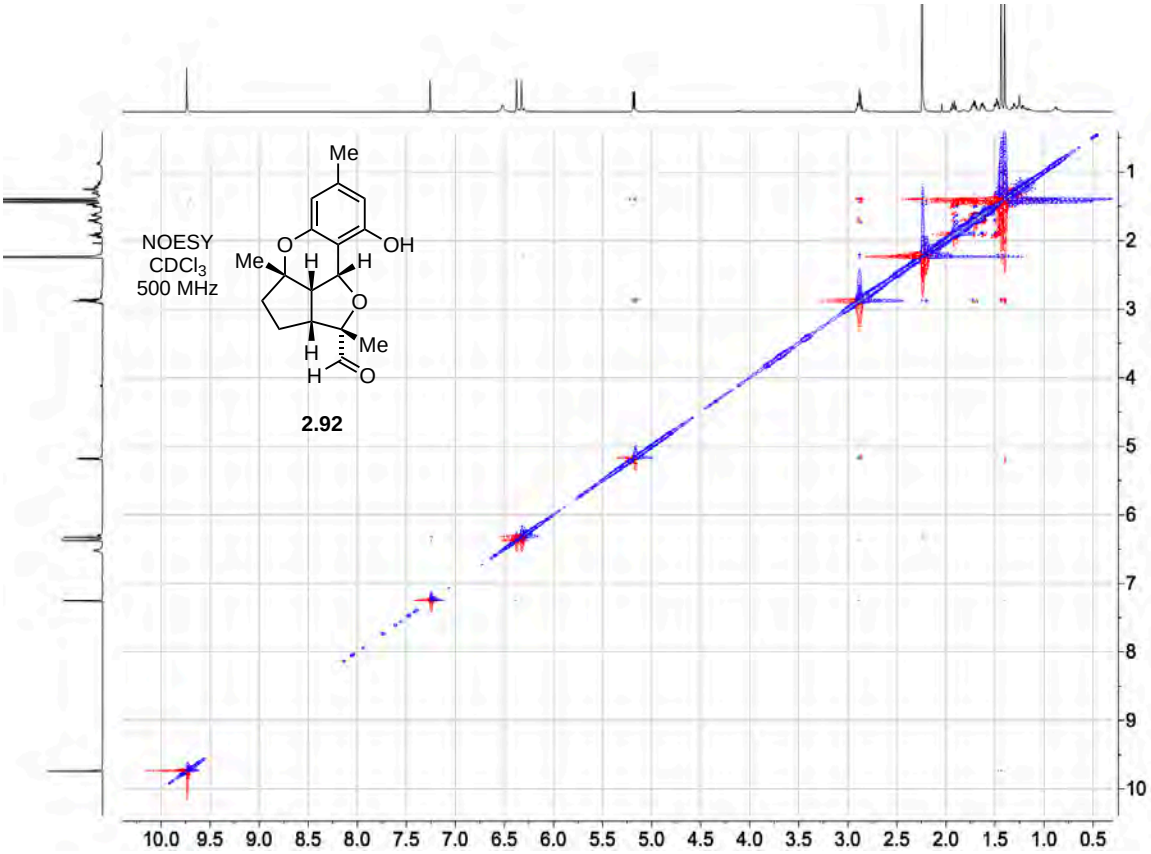


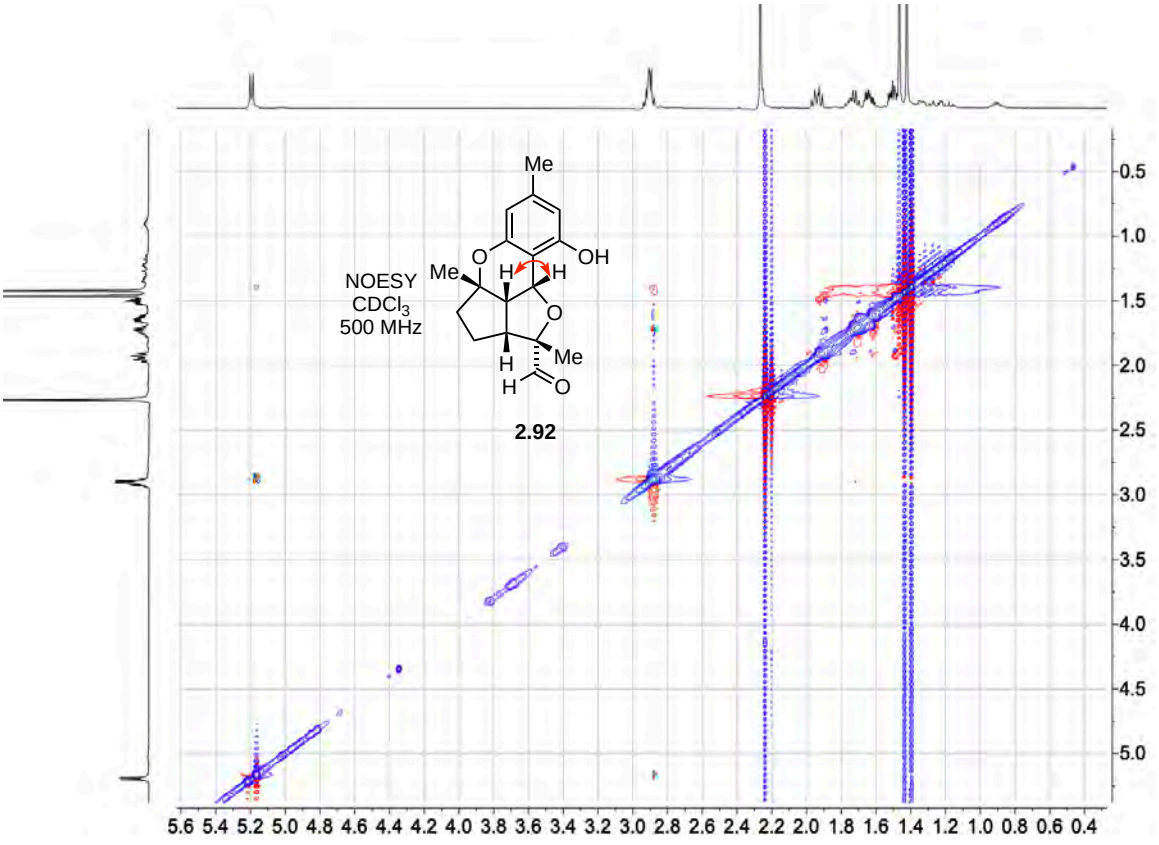
2.92

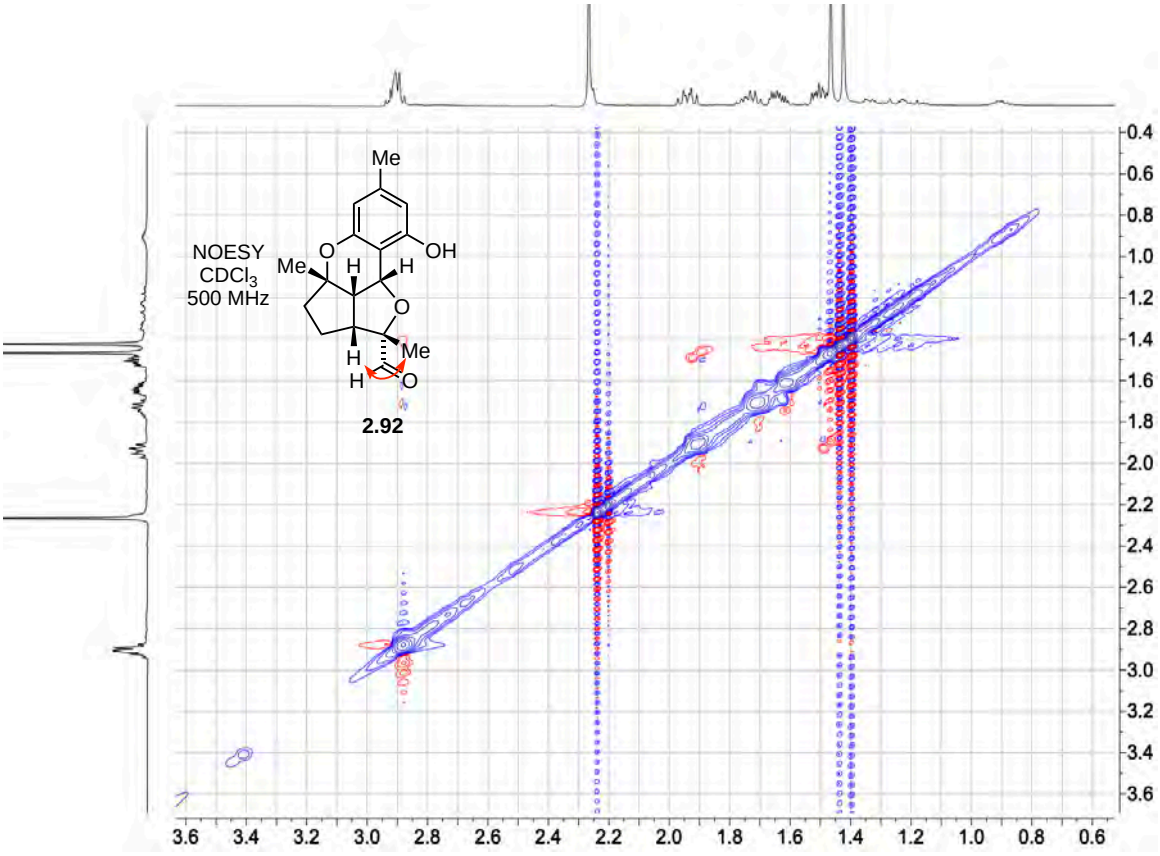

COSY
CDCl3
500 MHz
Me
OH
Me
O
H
H
O
H
Me
H
O
2.92
1
2
3
4
5
6
7
8
9
10
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5


HSQC
CDCl3
500 MHz
Me
OH
Me
O
H
H
O
H
Me
H
O
2.92
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5


HMBC
CDCl3
500 MHz
Me
O
H
OH
Me
H
O
H
Me
H
O
2.92

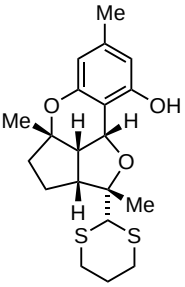

NOESY
CDCl3
500 MHz
Me
O
H
OH
Me
H
O
H
Me
H
O
2.92


NOESY
CDCl3
500 MHz
Me
OH
Me
O
H
H
O
H
Me
H
O
2.92
5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0


NOESY
CDCl3
500 MHz
Me
OH
Me
O
H
H
O
H
Me
H
O
2.92
3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0 2.2 2.4 2.6 2.8 3.0 3.2 3.4 3.6

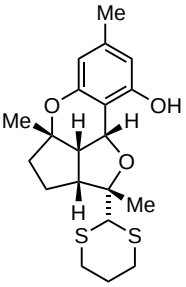
Data for 2.142

^{1}H NMR
$CDCl_3$
500 MHz



2.142

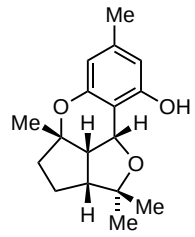
^{13}C NMR
$CDCl_3$
125 MHz



2.142

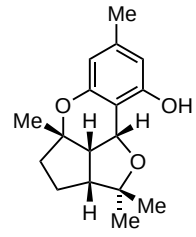
Data for rhodonoid D (2.93)

^{1}H NMR
$CDCl_3$
500 MHz

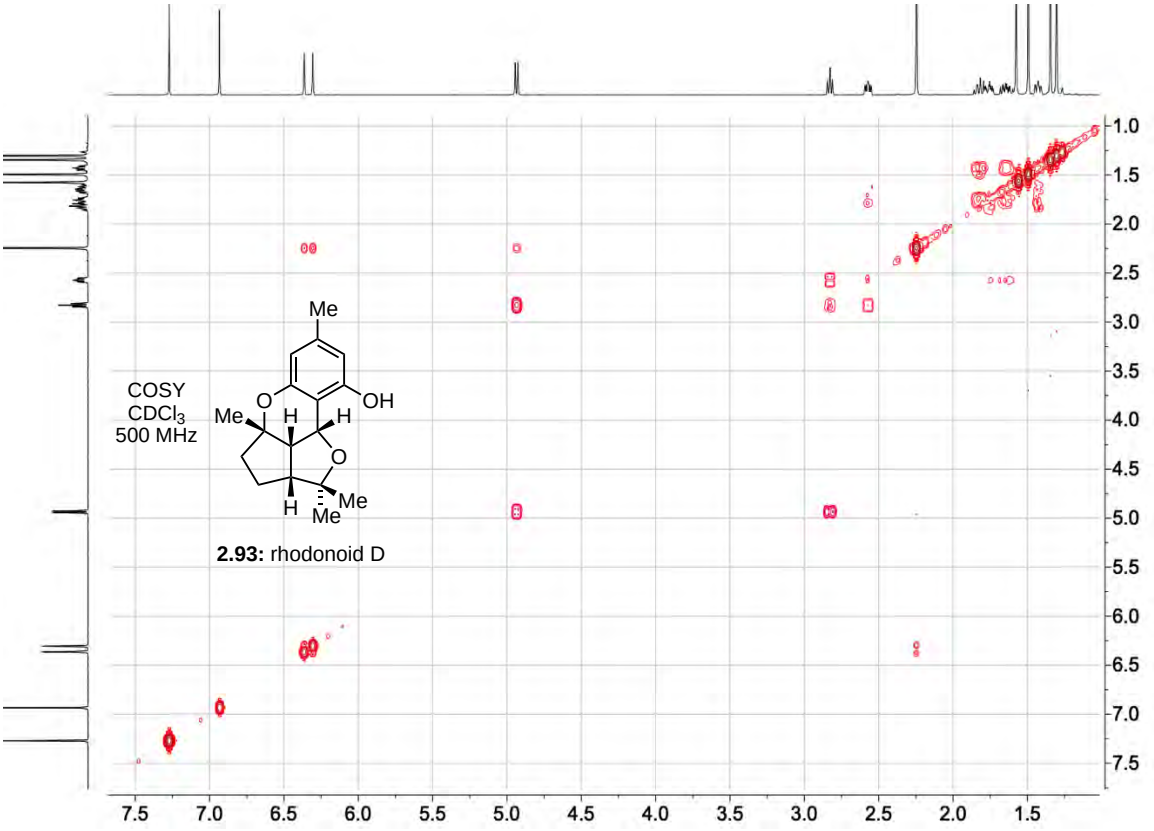


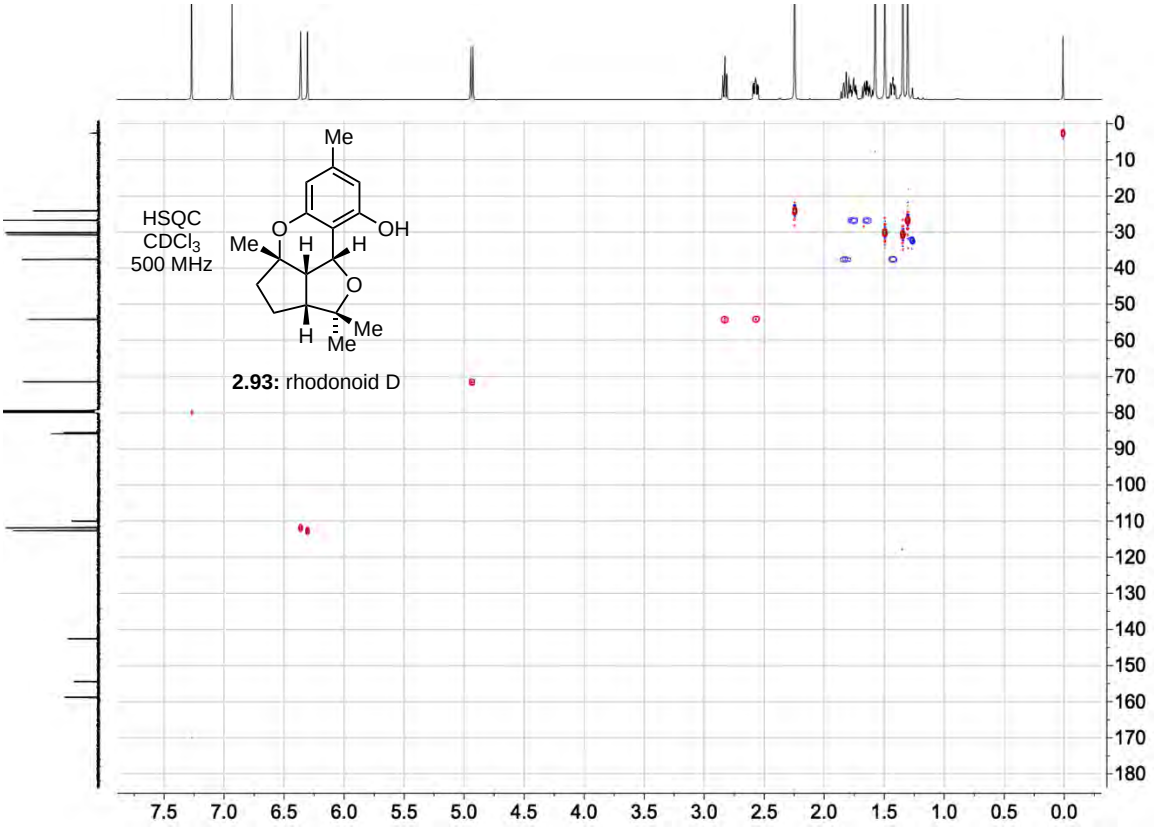
2.93: rhodonoid D

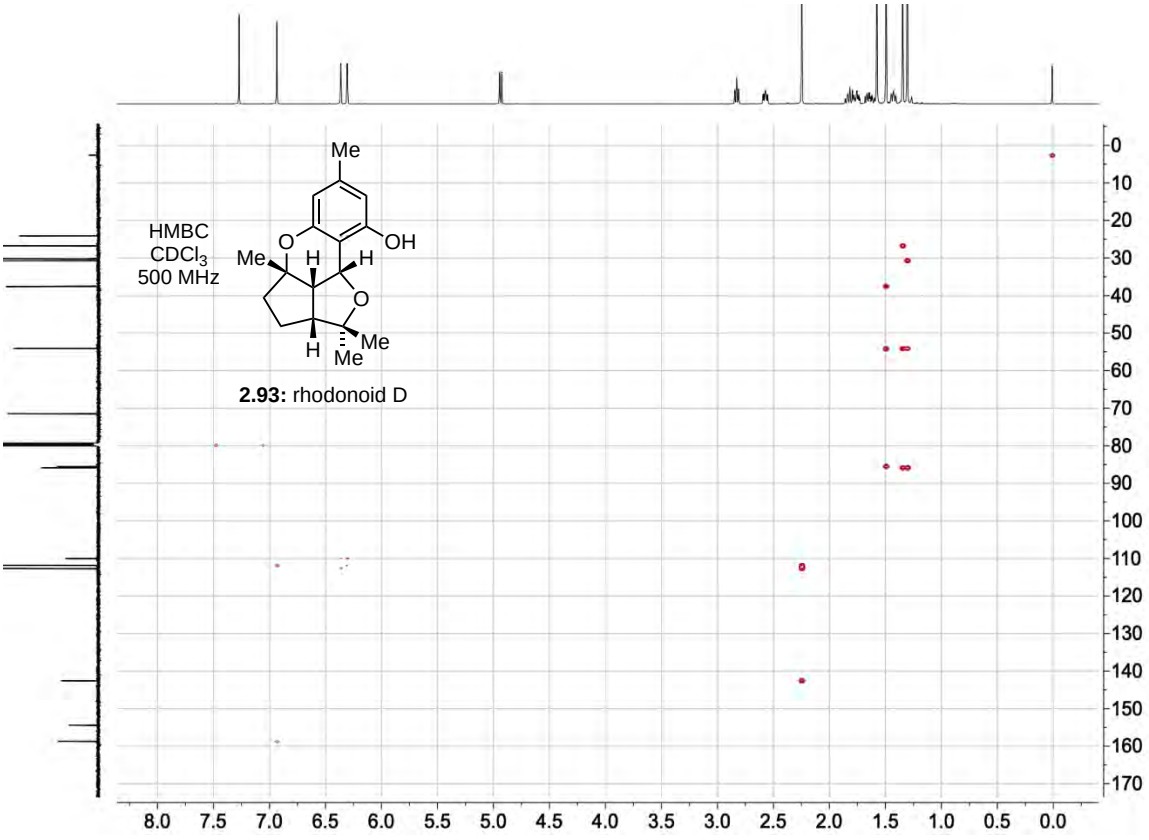
^{13}C NMR
$CDCl_3$
125 MHz

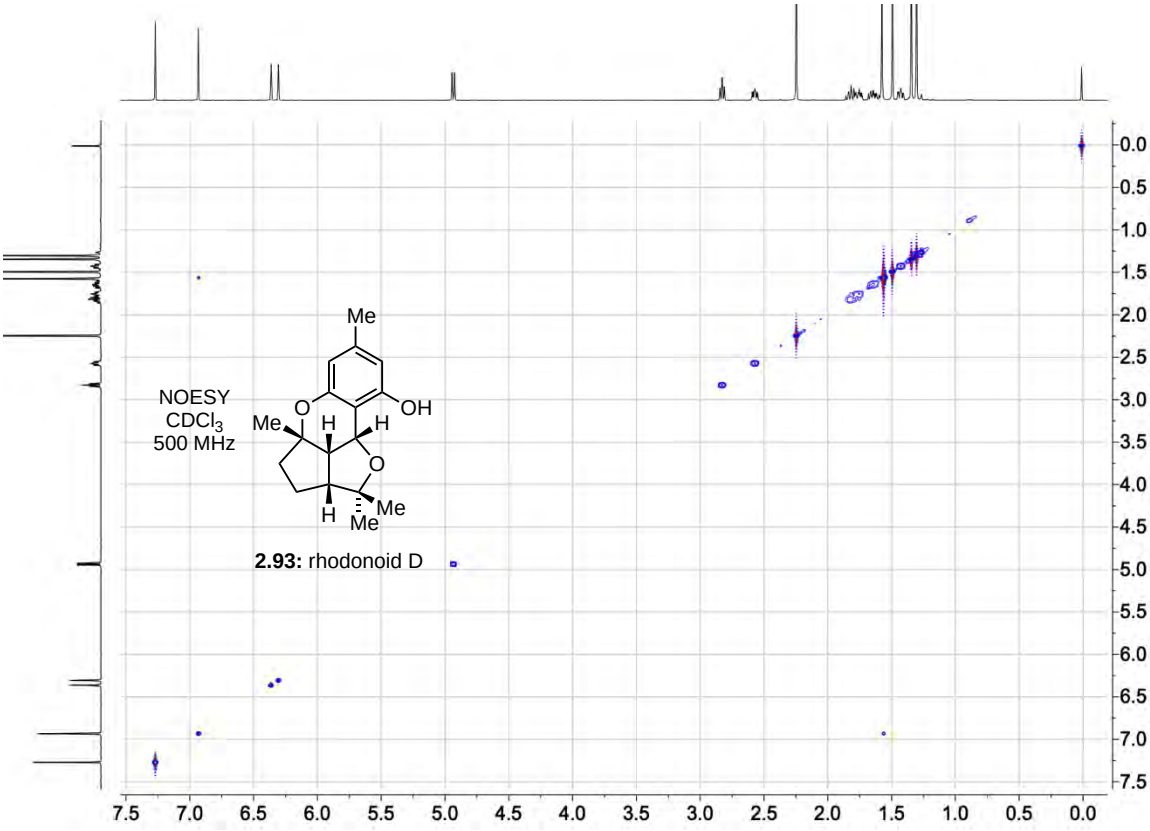


2.93: rhodonoid D

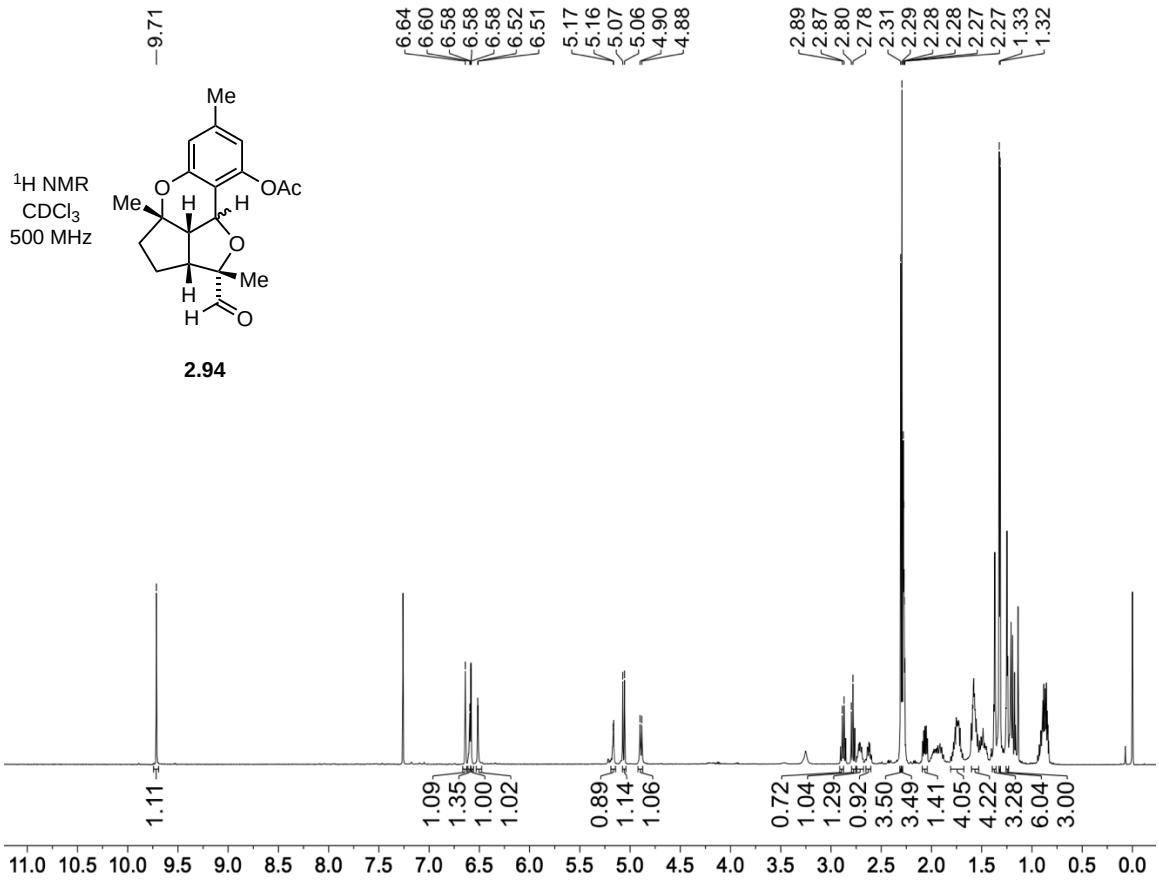

COSY
CDCl3
500 MHz
Me
OH
Me
O
H
H
O
H
Me
Me
2.93: rhodonoid D

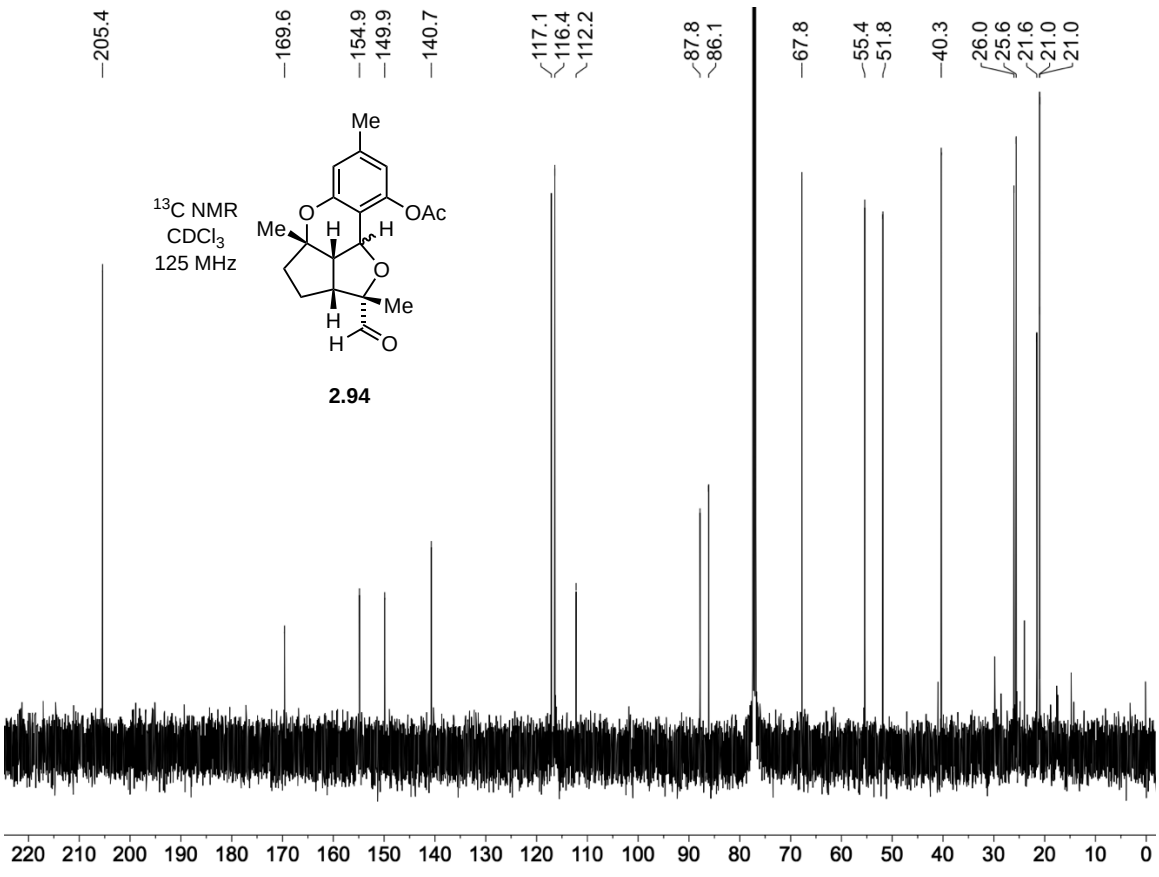

HSQC
CDCl3
500 MHz
Me
OH
Me
O
H
H
O
H
Me
Me
2.93: rhodonoid D


HMBC
CDCl3
500 MHz
Me
O
OH
Me
H
H
O
H
Me
Me
2.93: rhodonoid D
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

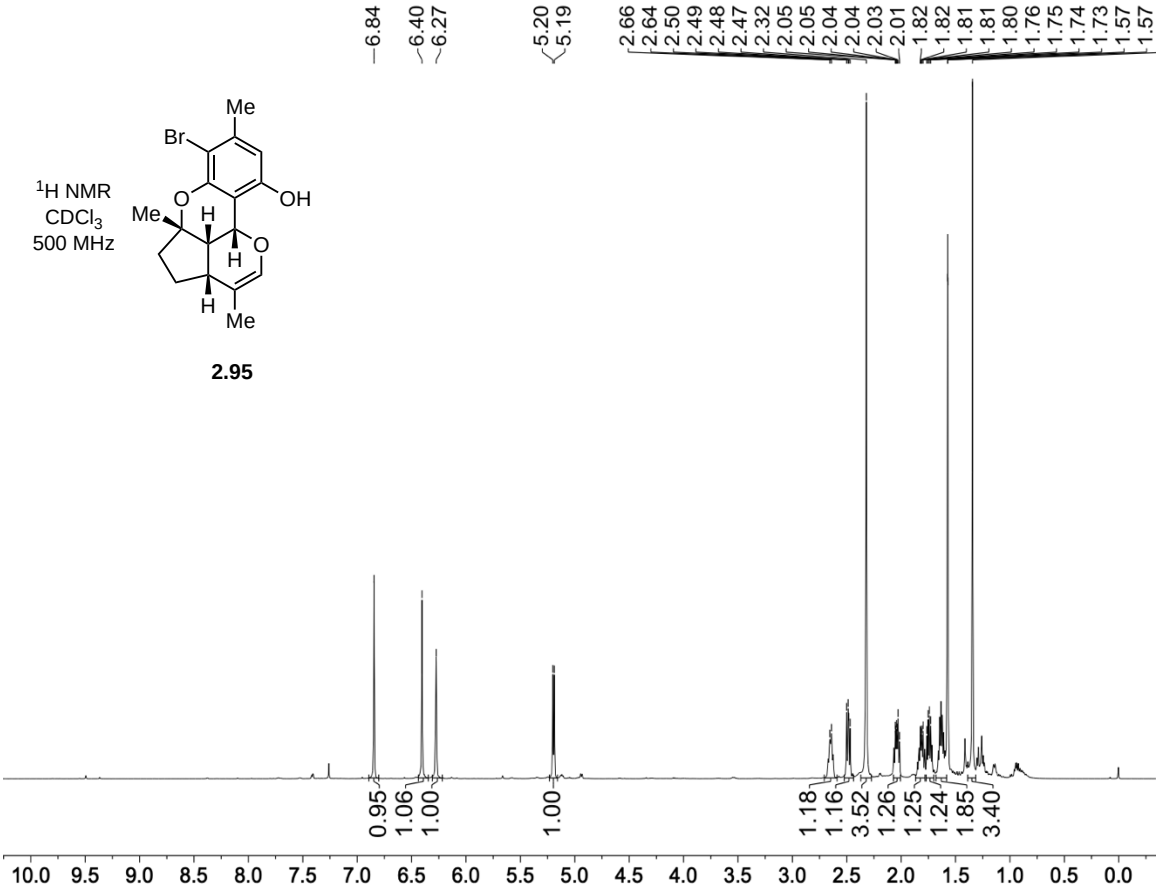

NOESY
CDCl3
500 MHz
Me
O
OH
Me
H
H
O
H
Me
Me
2.93: rhodonoid D
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

Data for 2.94


9.71
6.64
6.60
6.58
6.58
6.58
6.52
6.51
5.17
5.16
5.07
5.06
4.90
4.88
2.89
2.87
2.80
2.78
2.31
2.29
2.28
2.28
2.27
2.27
1.33
1.32
1H NMR
CDCl3
500 MHz
Me
OAc
Me
O
H
H
O
Me
H
H
O
2.94
1.11
1.09
1.35
1.00
1.02
0.89
1.14
1.06
0.72
1.04
1.29
0.92
3.50
3.49
1.41
4.05
4.22
3.28
6.04
3.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

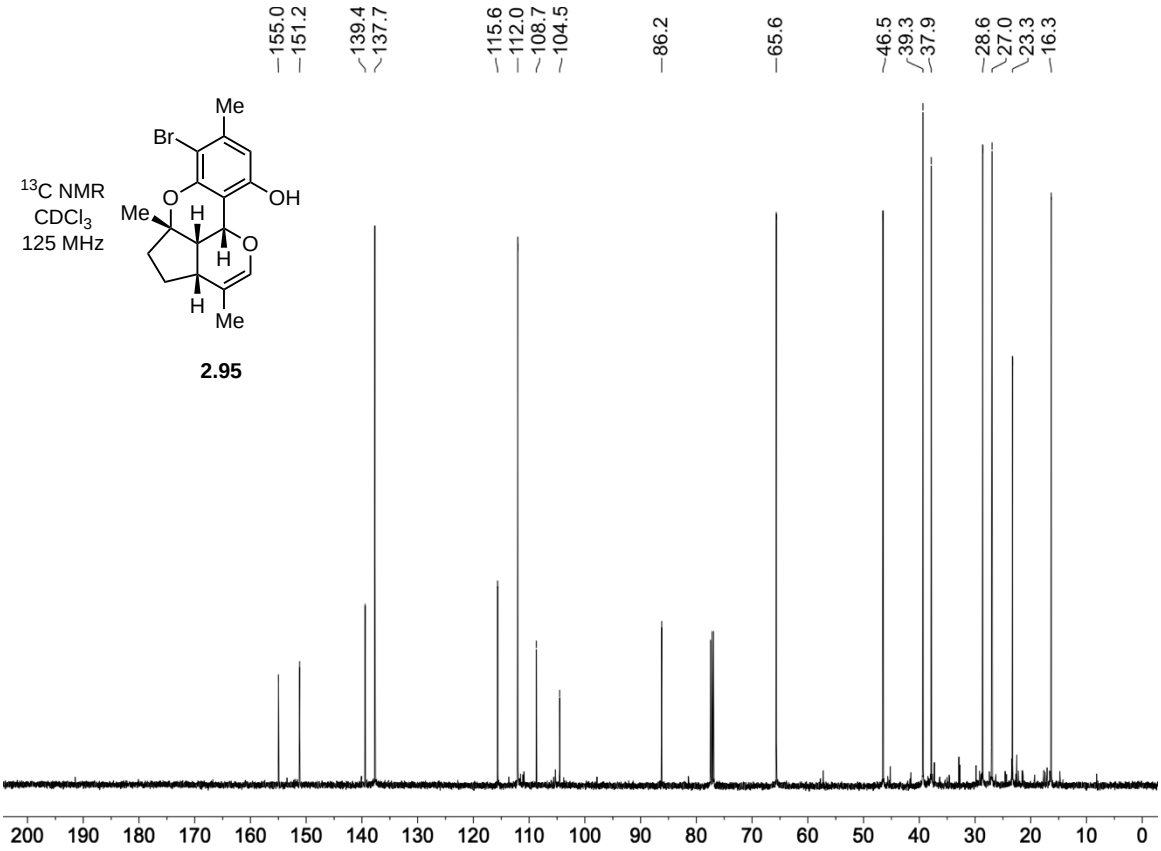

205.4
169.6
154.9
149.9
140.7
117.1
116.4
112.2
87.8
86.1
67.8
55.4
51.8
40.3
26.0
25.6
21.6
21.0
21.0
13C NMR
CDCl3
125 MHz
Me
OAc
Me
O
H
H
O
Me
H
H
O
2.94
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Data for 2.95:



^{1}H NMR
$CDCl_3$
500 MHz

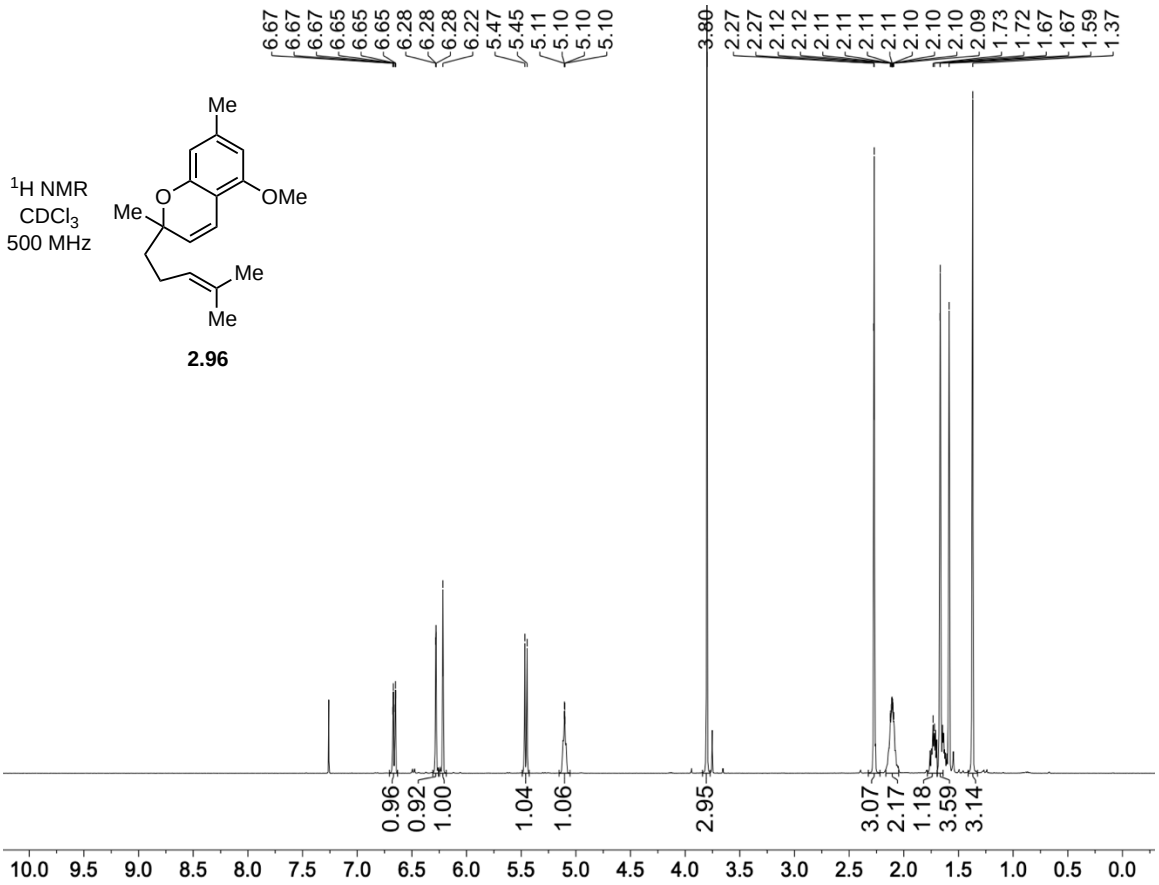
2.95



^{13}C NMR
$CDCl_3$
125 MHz

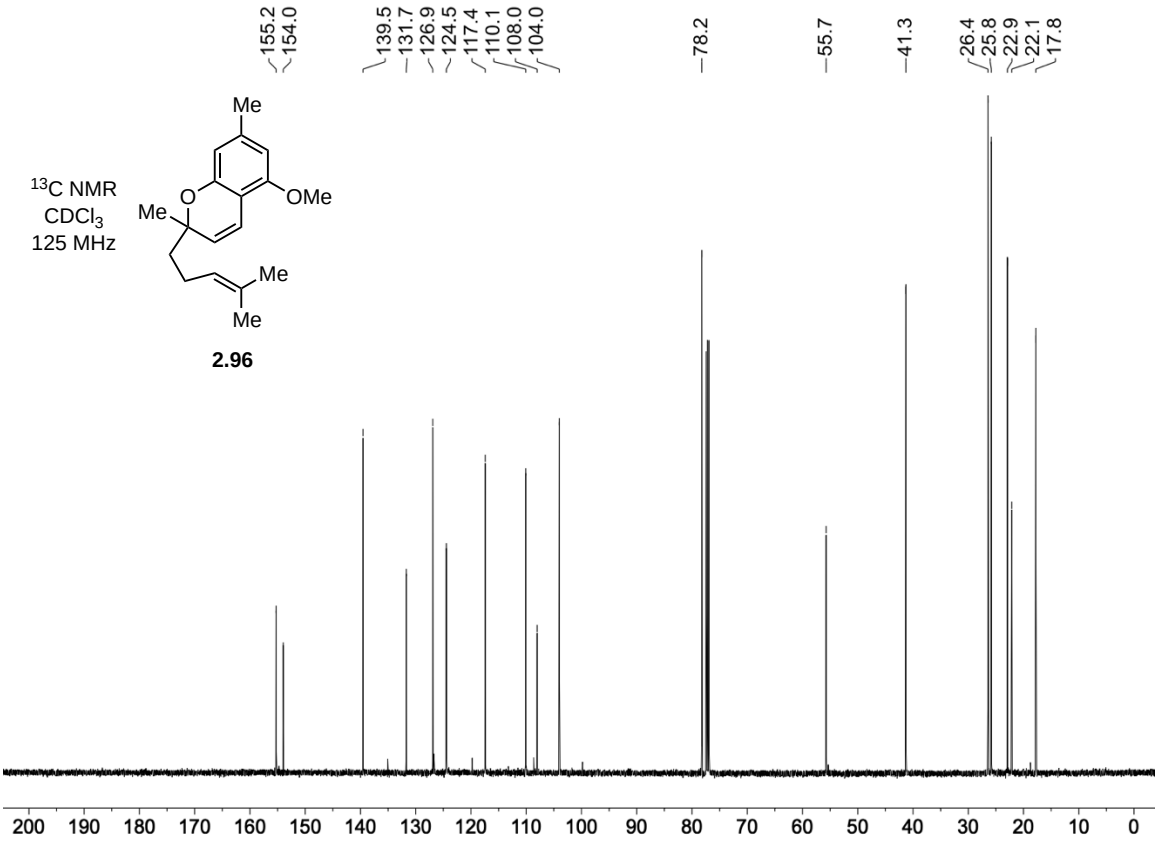
2.95

Data for 2.96



^{1}H NMR
$CDCl_3$
500 MHz

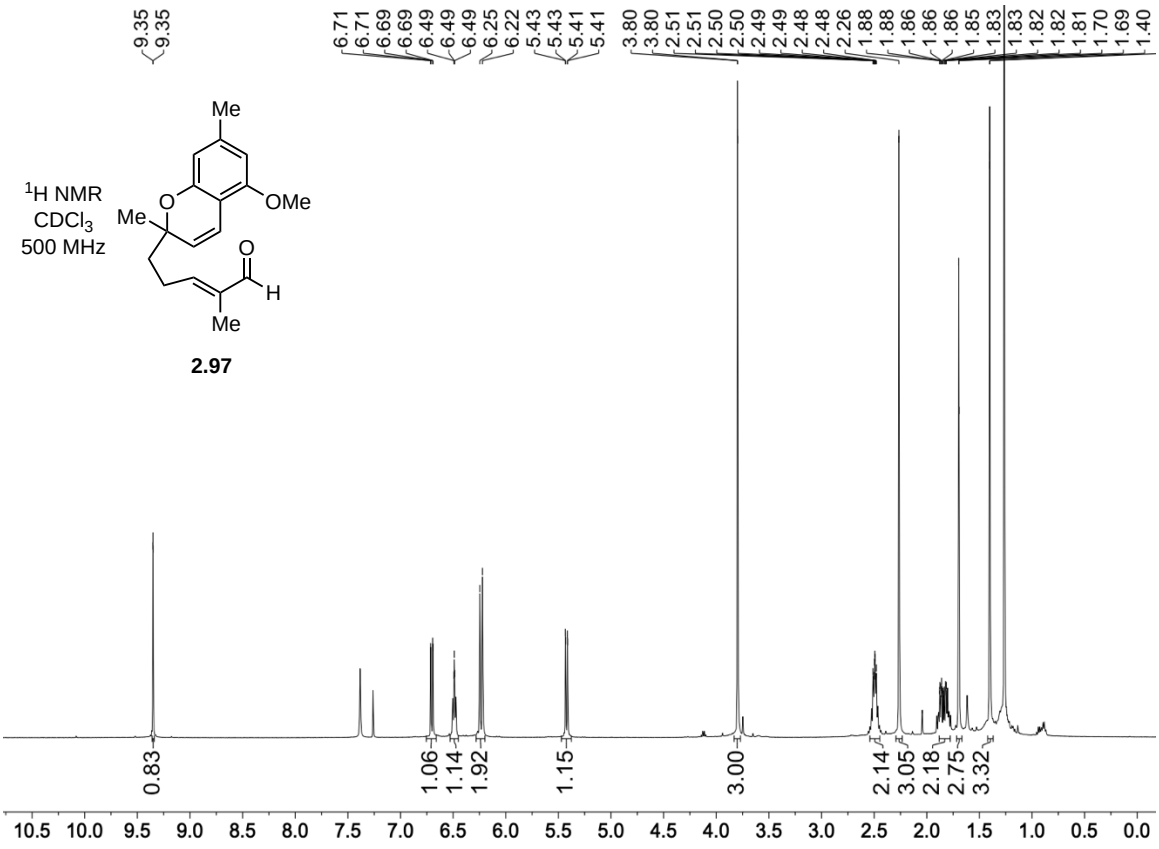
2.96

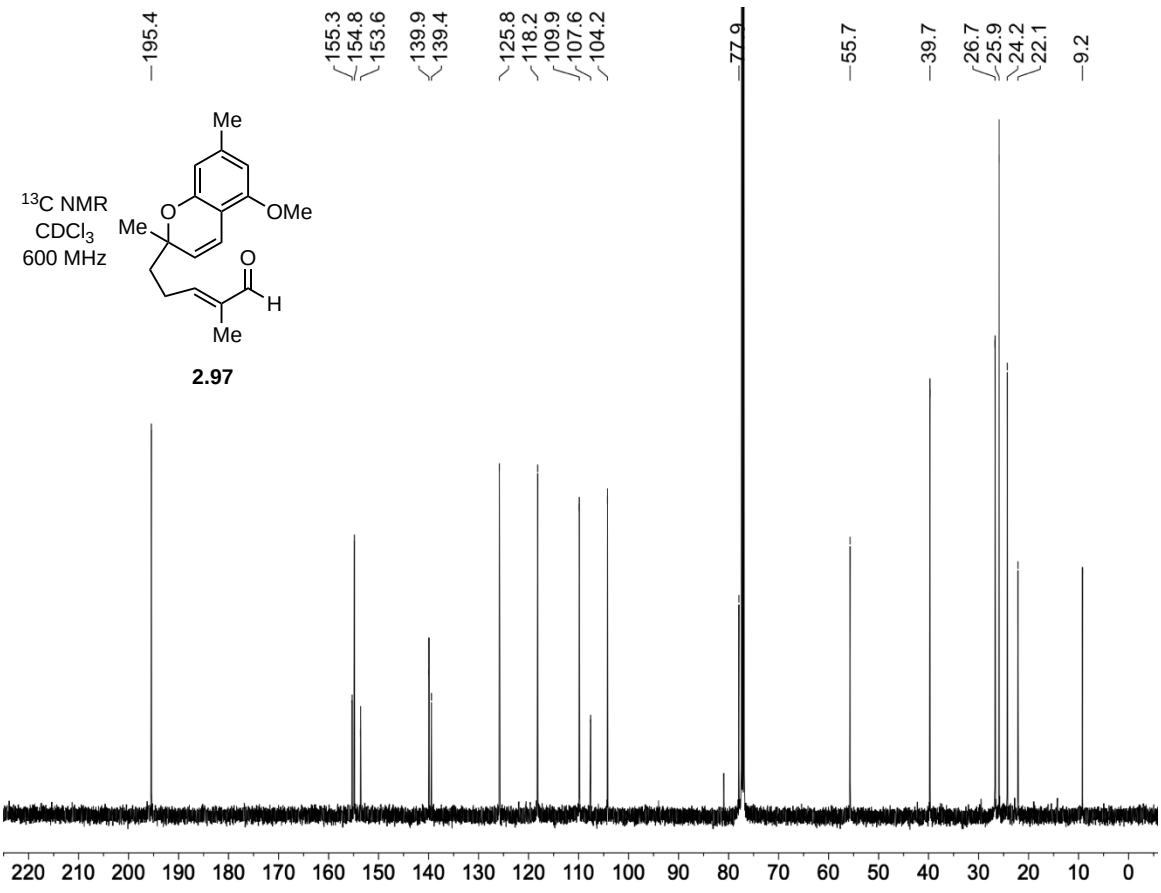


^{13}C NMR
$CDCl_3$
125 MHz

2.96

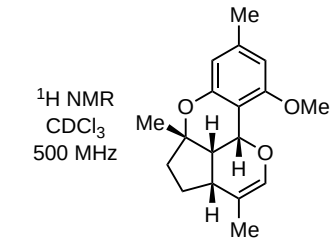
Data for 2.97


9.35
9.35
6.71
6.71
6.69
6.69
6.49
6.49
6.49
6.49
6.25
6.22
5.43
5.43
5.41
5.41
3.80
3.80
2.51
2.51
2.50
2.50
2.49
2.49
2.48
2.48
2.26
1.88
1.88
1.86
1.86
1.86
1.85
1.83
1.83
1.82
1.82
1.81
1.70
1.69
1.40
Me
OMe
Me
O
O
H
Me
^{1}H NMR
$CDCl_3$
500 MHz
2.97
0.83
1.06
1.14
1.92
1.15
3.00
2.14
3.05
2.18
2.75
3.32
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


195.4
155.3
154.8
153.6
139.9
139.4
125.8
118.2
109.9
107.6
104.2
77.9
55.7
39.7
26.7
25.9
24.2
22.1
9.2
Me
OMe
Me
O
O
H
Me
^{13}C NMR
$CDCl_3$
600 MHz
2.97
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

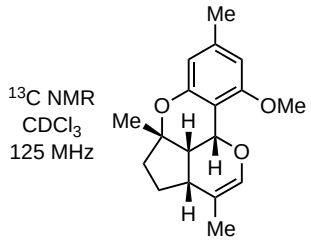
Data for 2.98

^{1}H NMR
$CDCl_3$
500 MHz

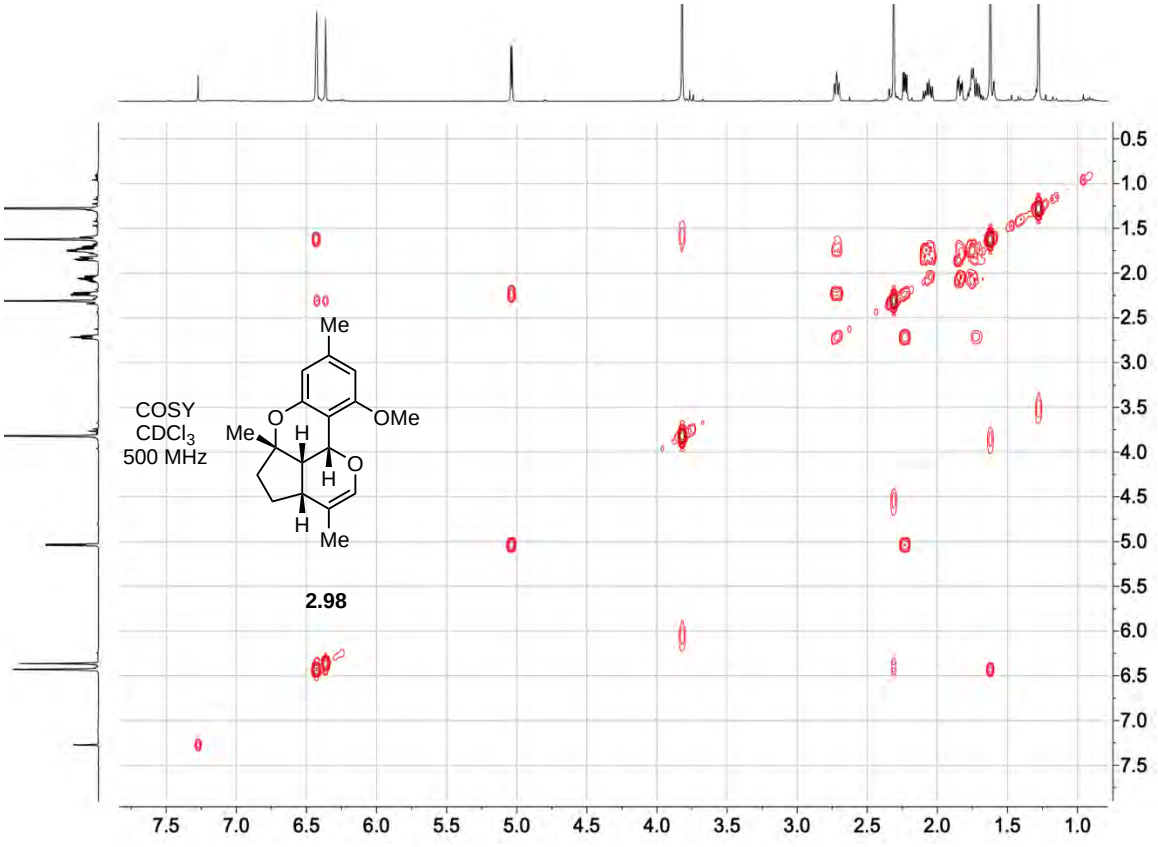


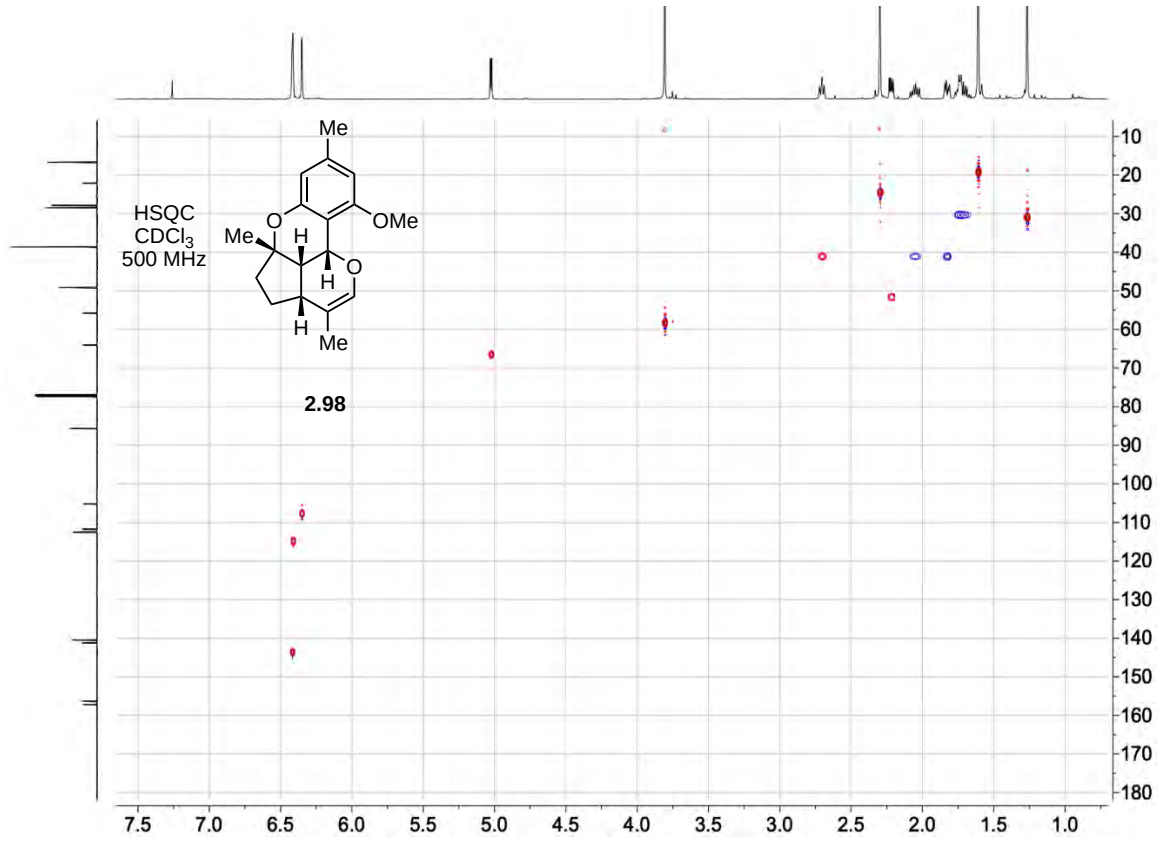
2.98

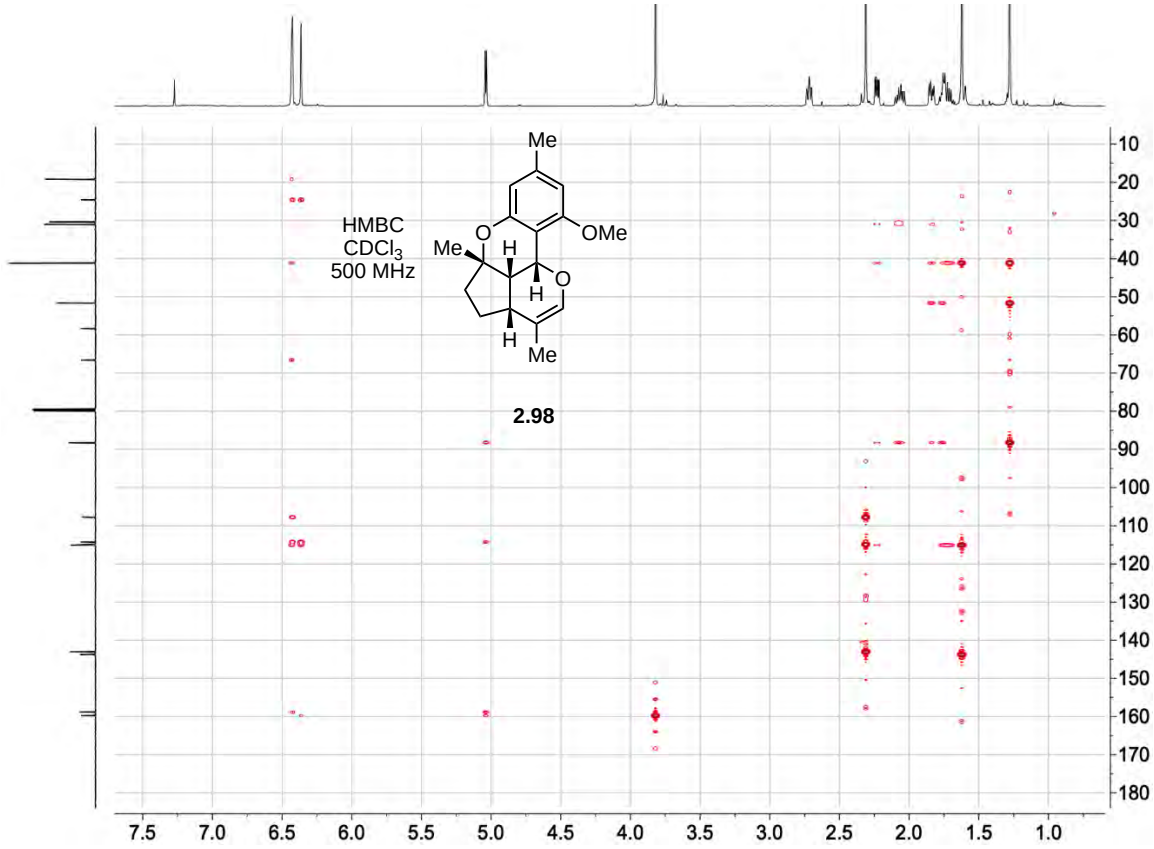
^{13}C NMR
$CDCl_3$
125 MHz



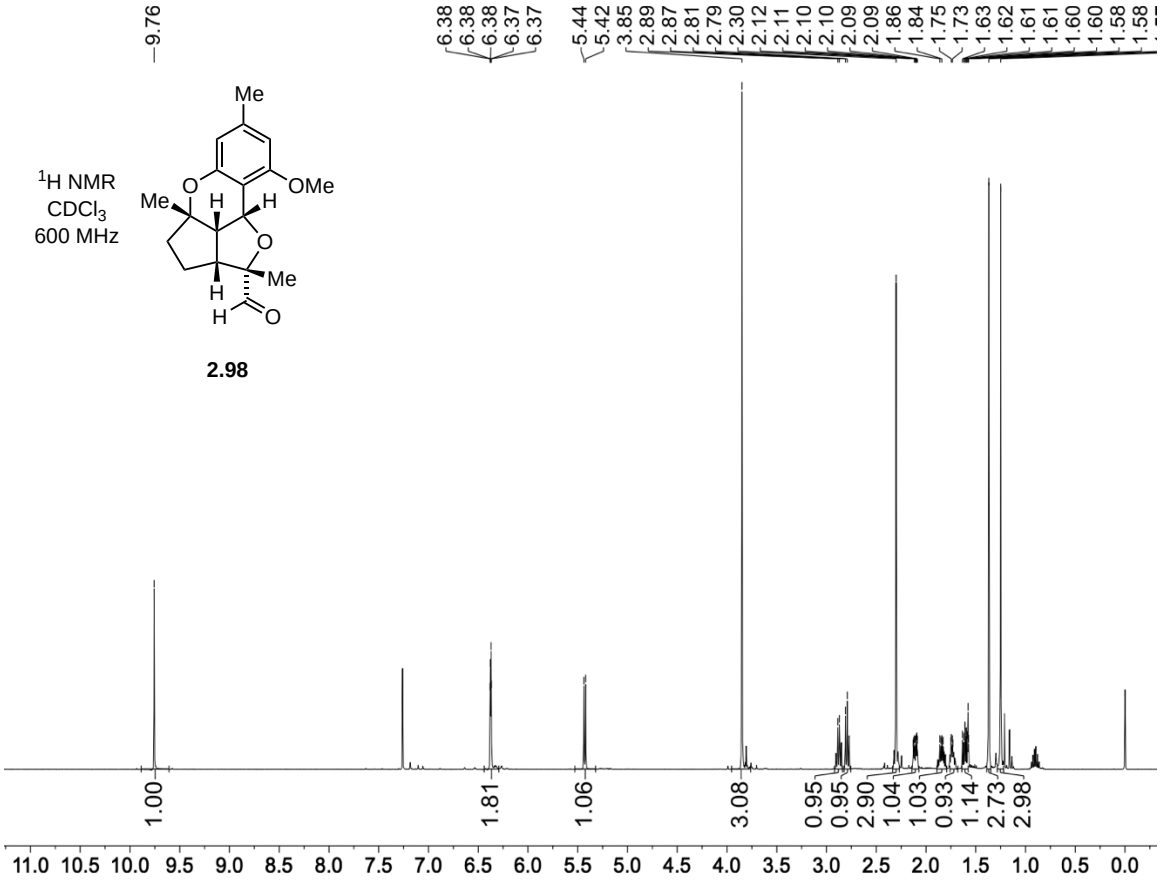
2.98


COSY
CDCl3
500 MHz
Me
O
Me
H
OMe
O
H
H
Me
2.98

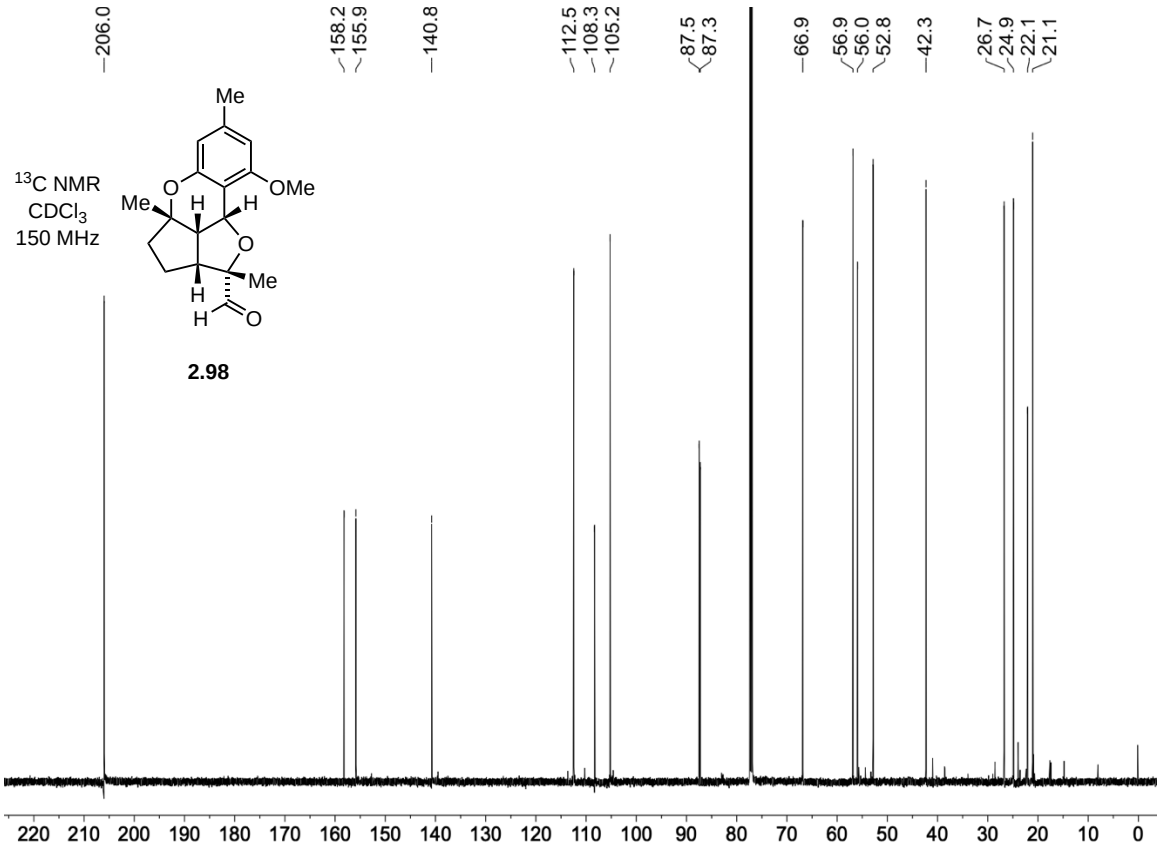

HSQC
CDCl3
500 MHz
Me
O
Me
H
OMe
O
H
H
Me
2.98


HMBC
CDCl3
500 MHz
Me
O
OMe
Me
H
H
O
H
Me
2.98
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

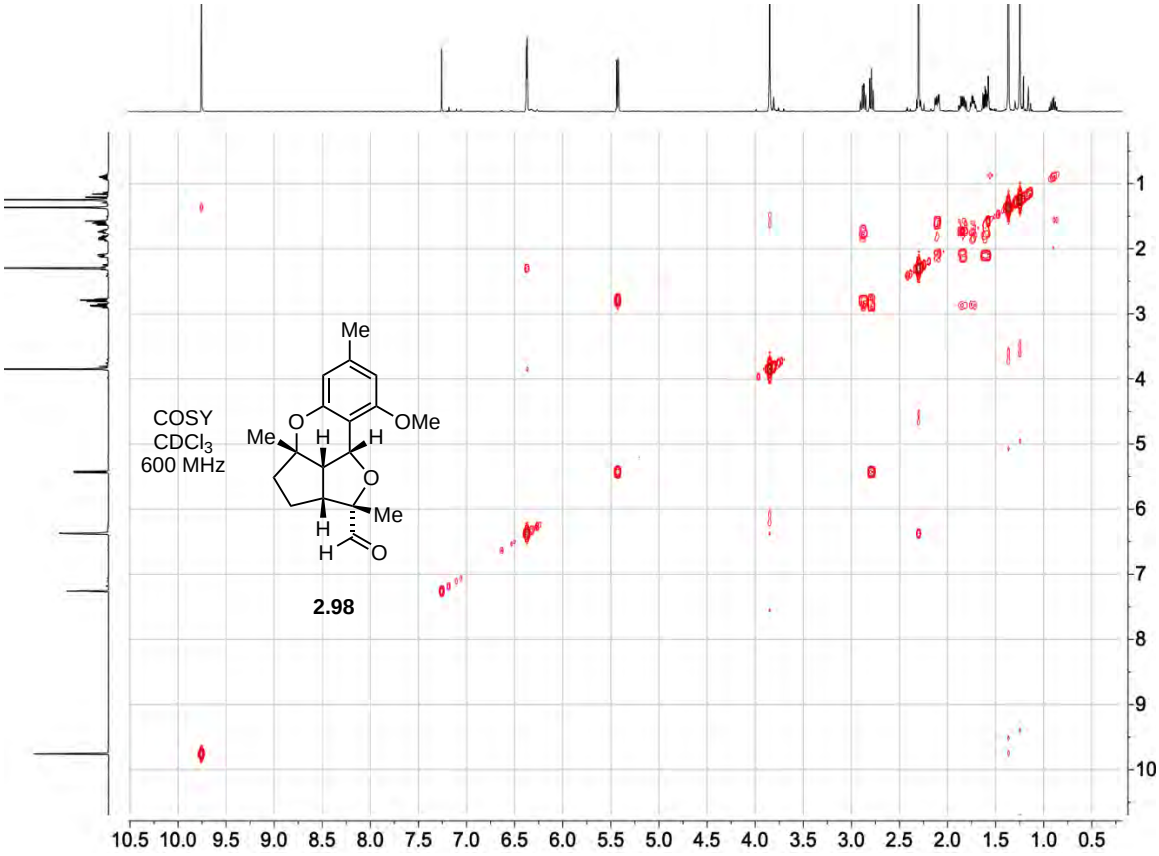
Data for 2.98

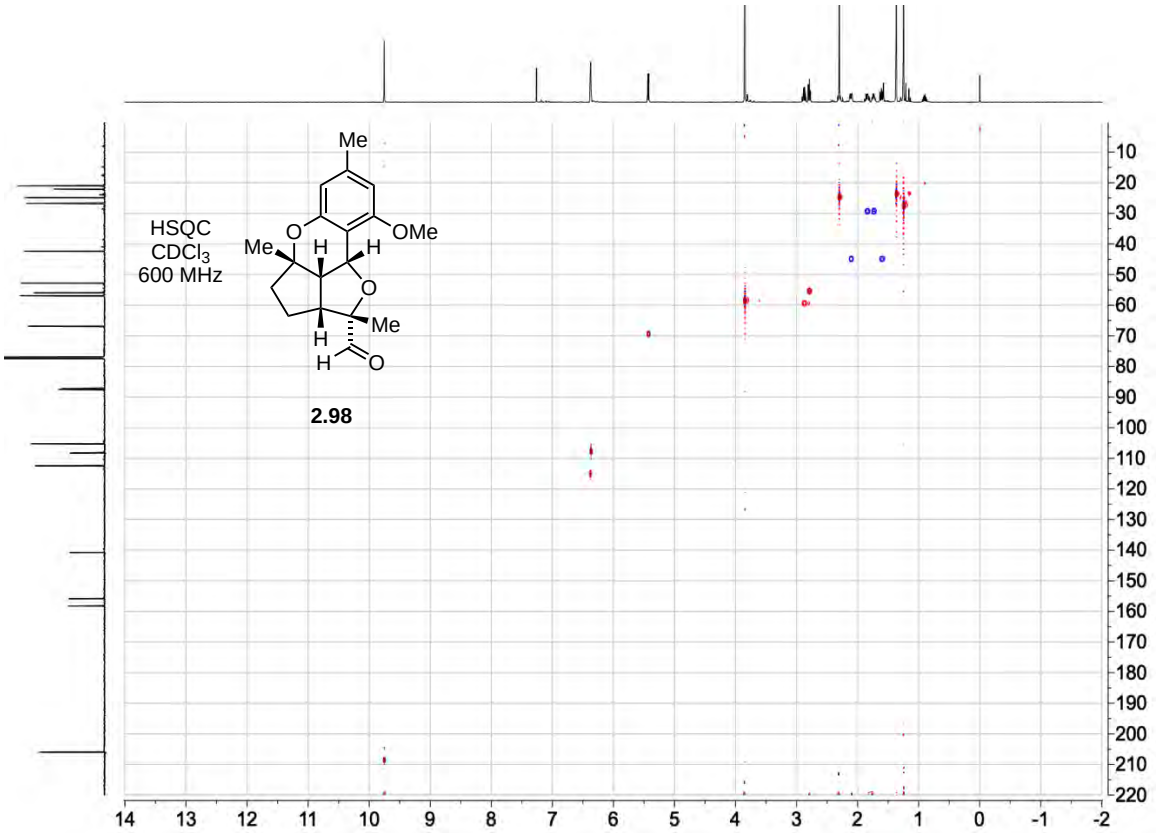


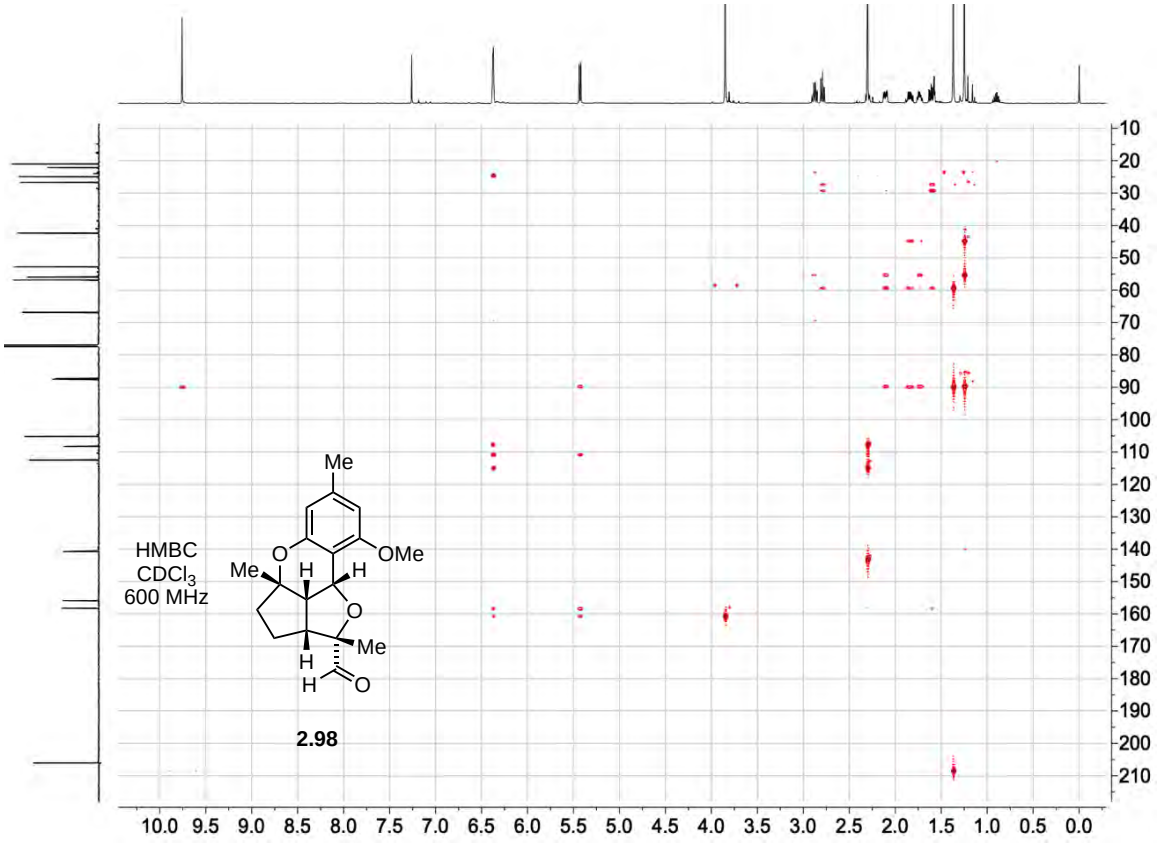
2.98

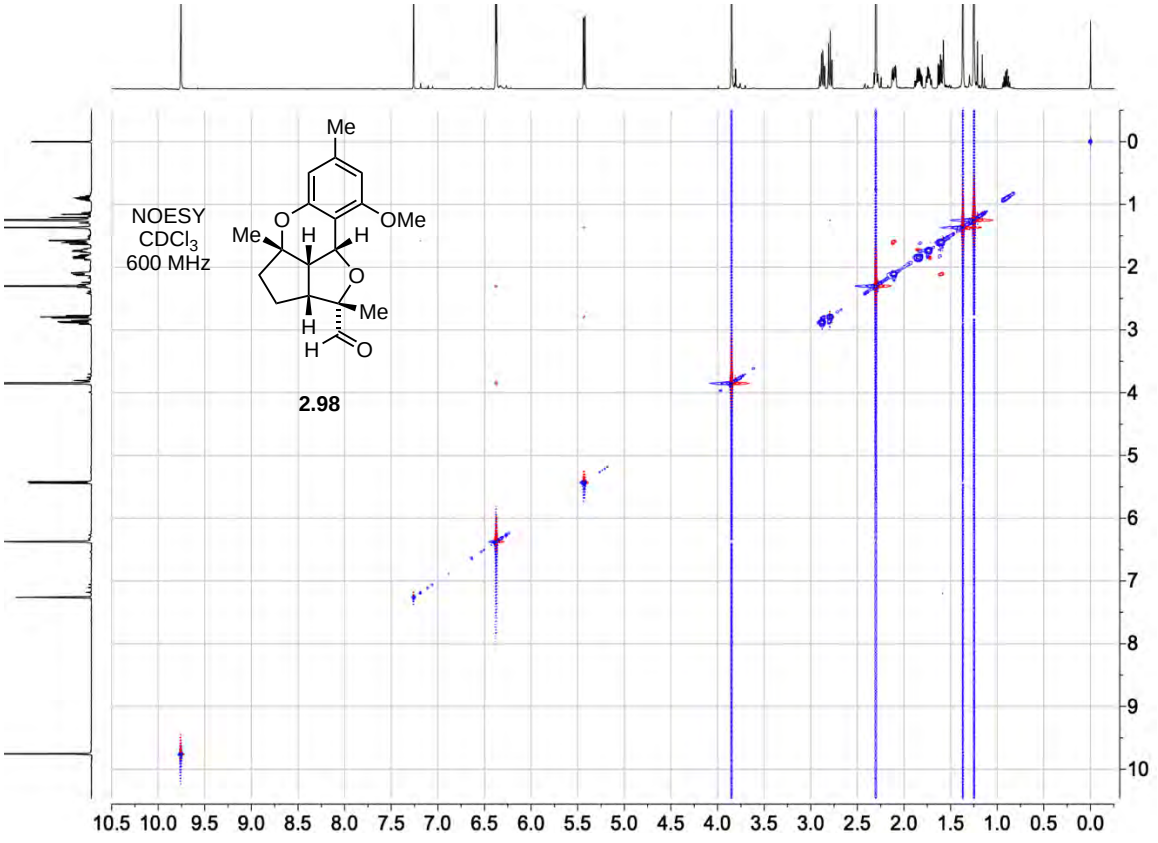


2.98

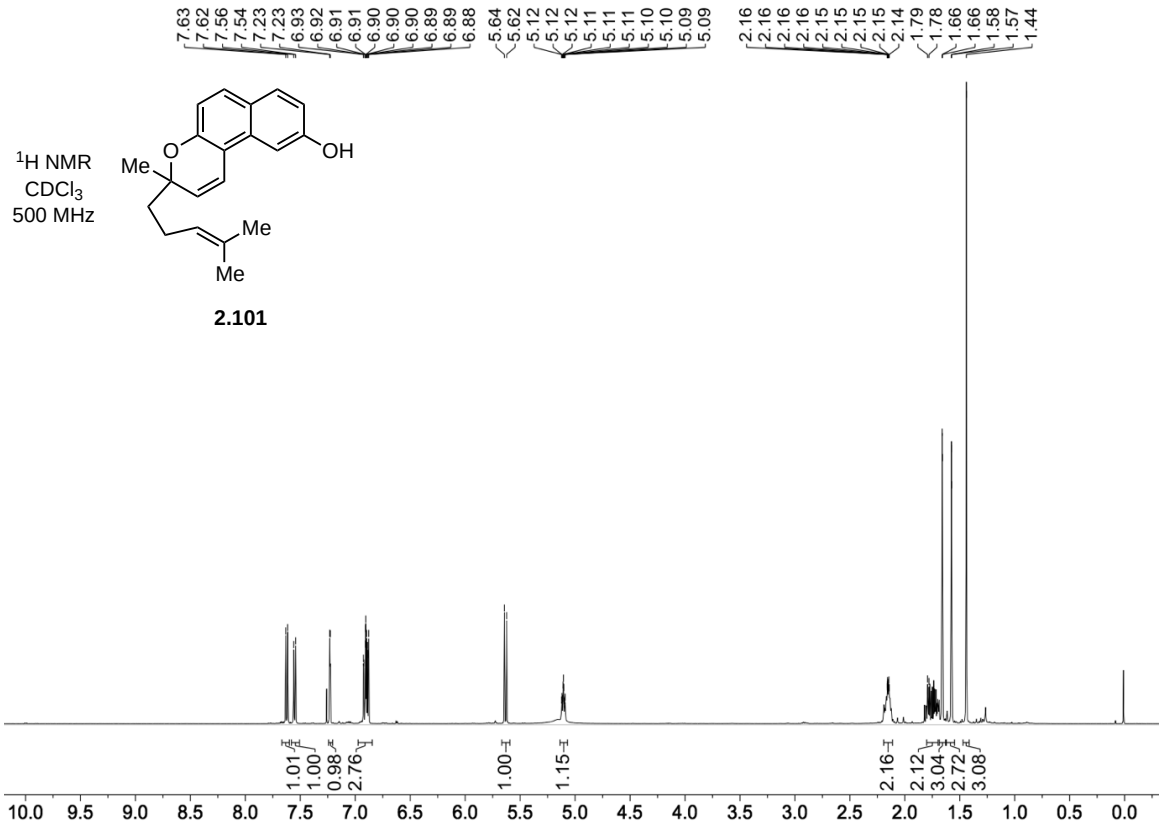

COSY
CDCl3
600 MHz
Me
O
H
H
OMe
Me
O
Me
H
H
O
2.98


HSQC
CDCl3
600 MHz
Me
O
H
H
OMe
Me
O
Me
H
H
O
2.98


HMBC
CDCl3
600 MHz
Me
O
OMe
Me
H
H
O
Me
H
H
O
2.98

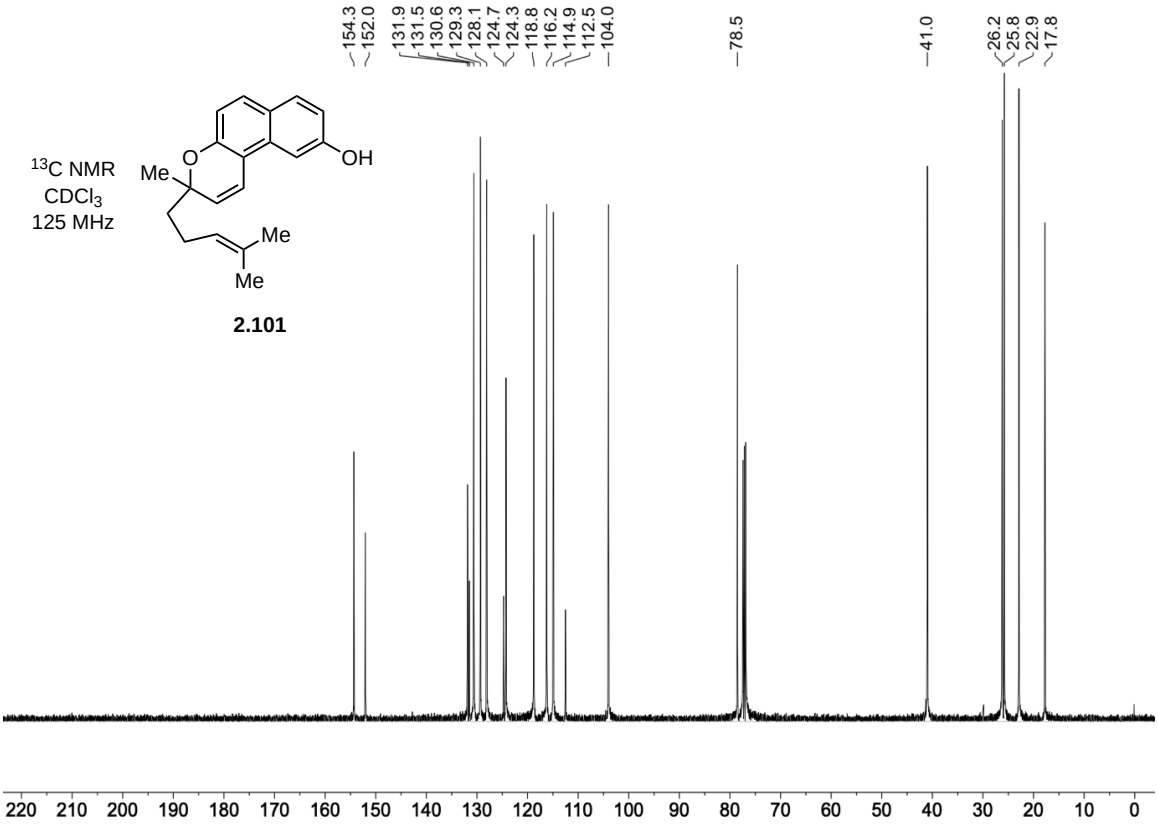

NOESY
CDCl3
600 MHz
Me
O
OMe
Me
H
H
O
Me
H
H
O
2.98

Data for 2.101



^{1}H NMR
$CDCl_3$
500 MHz

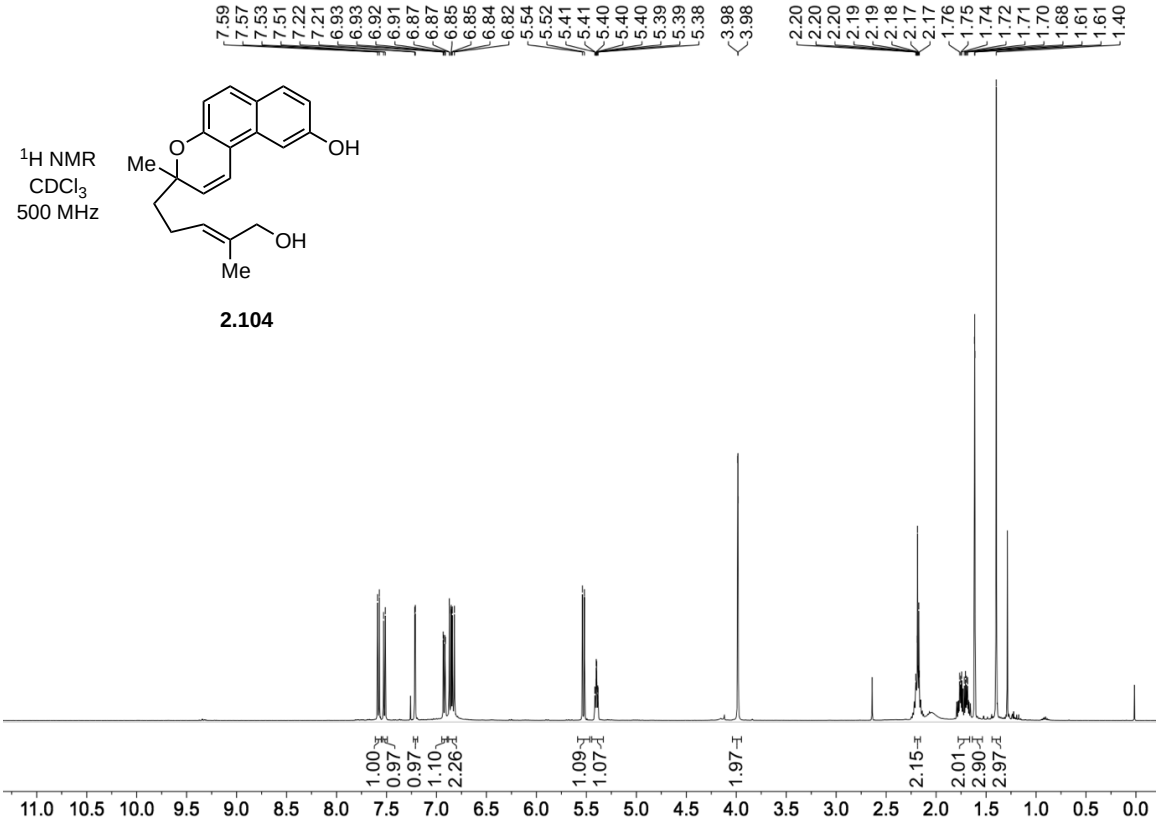
2.101

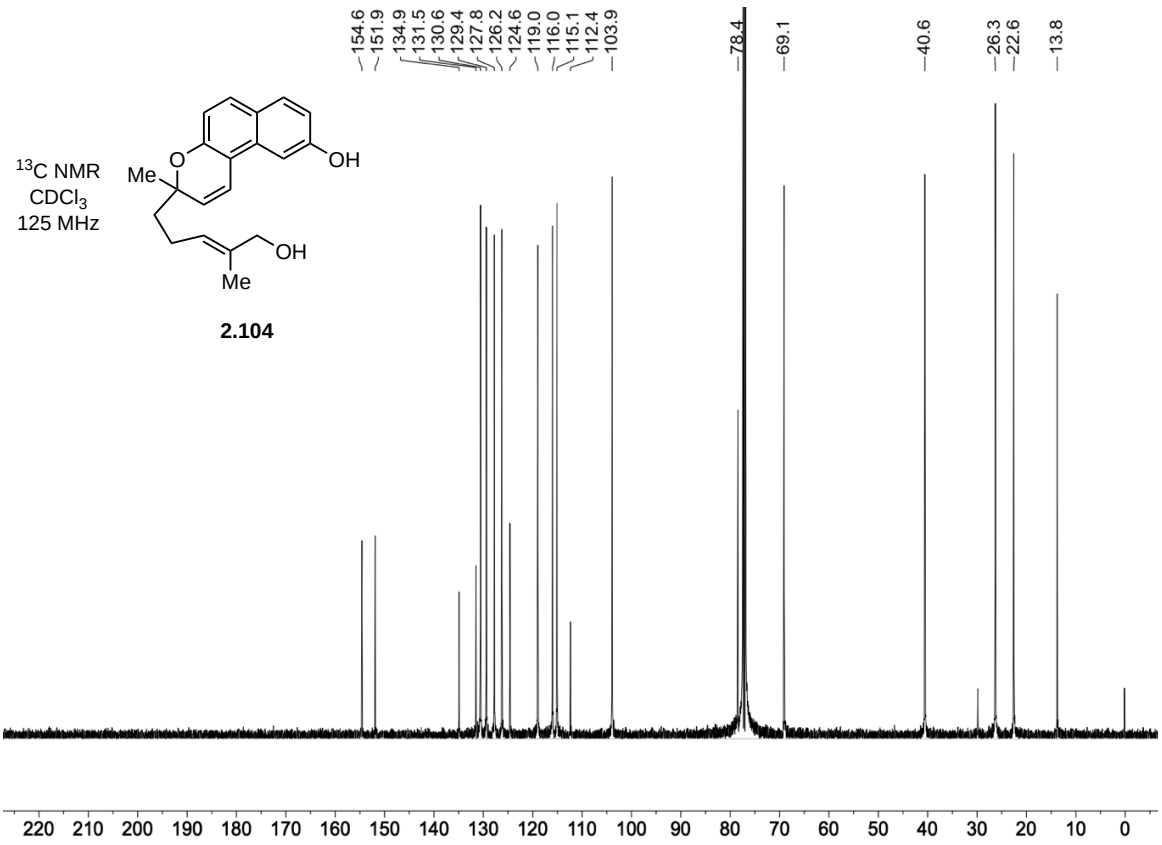


^{13}C NMR
$CDCl_3$
125 MHz

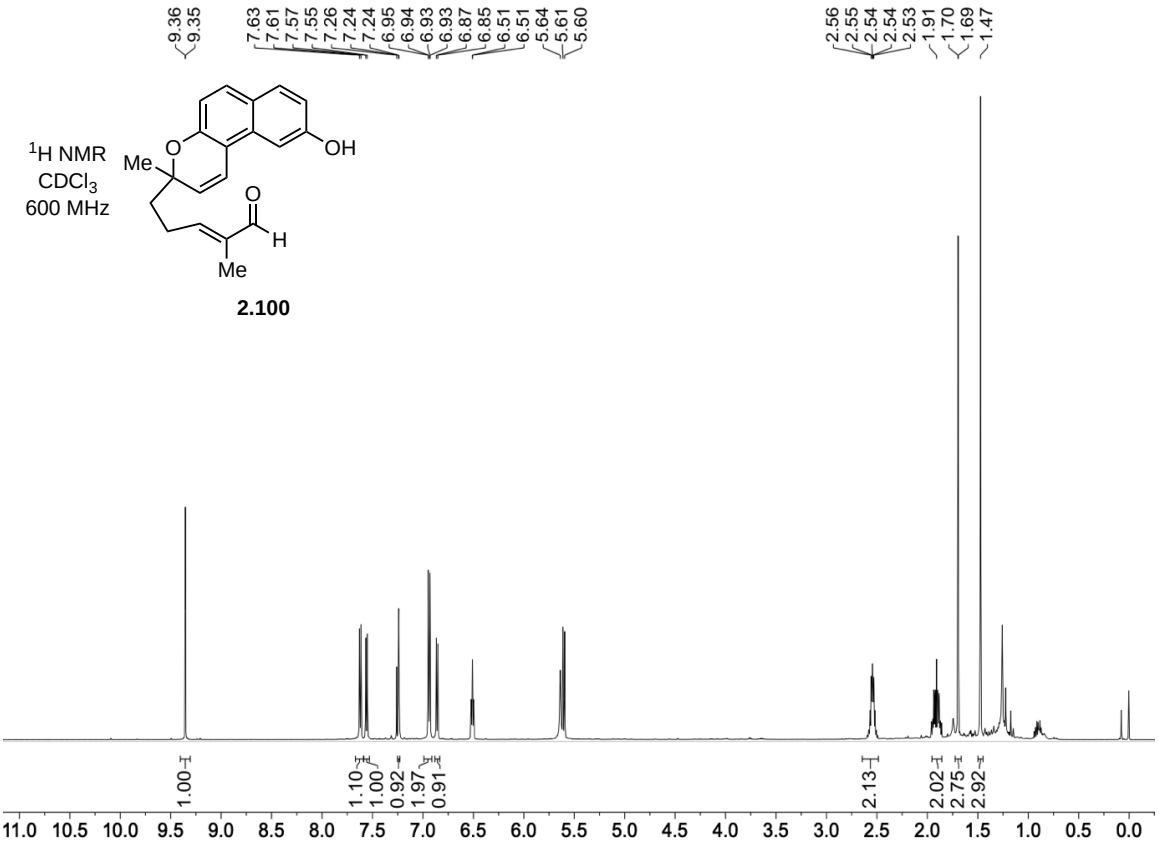
2.101

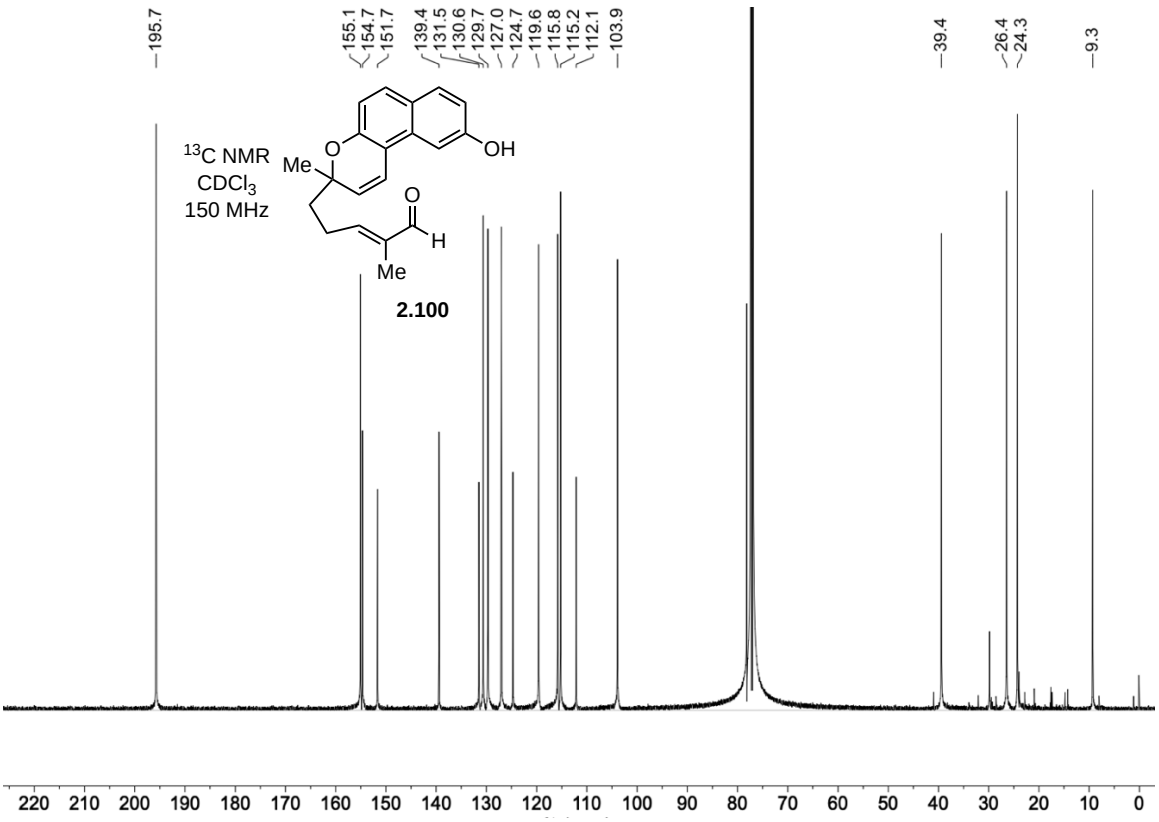
Data for 2.104



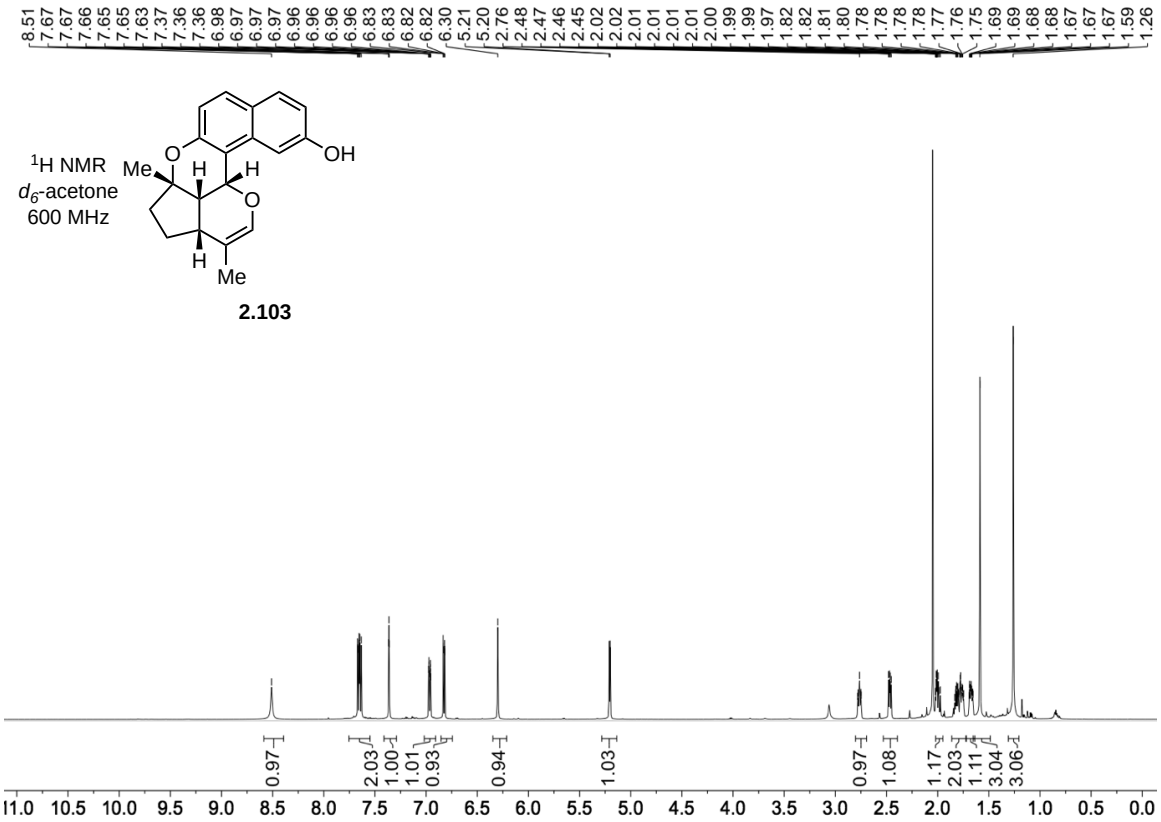


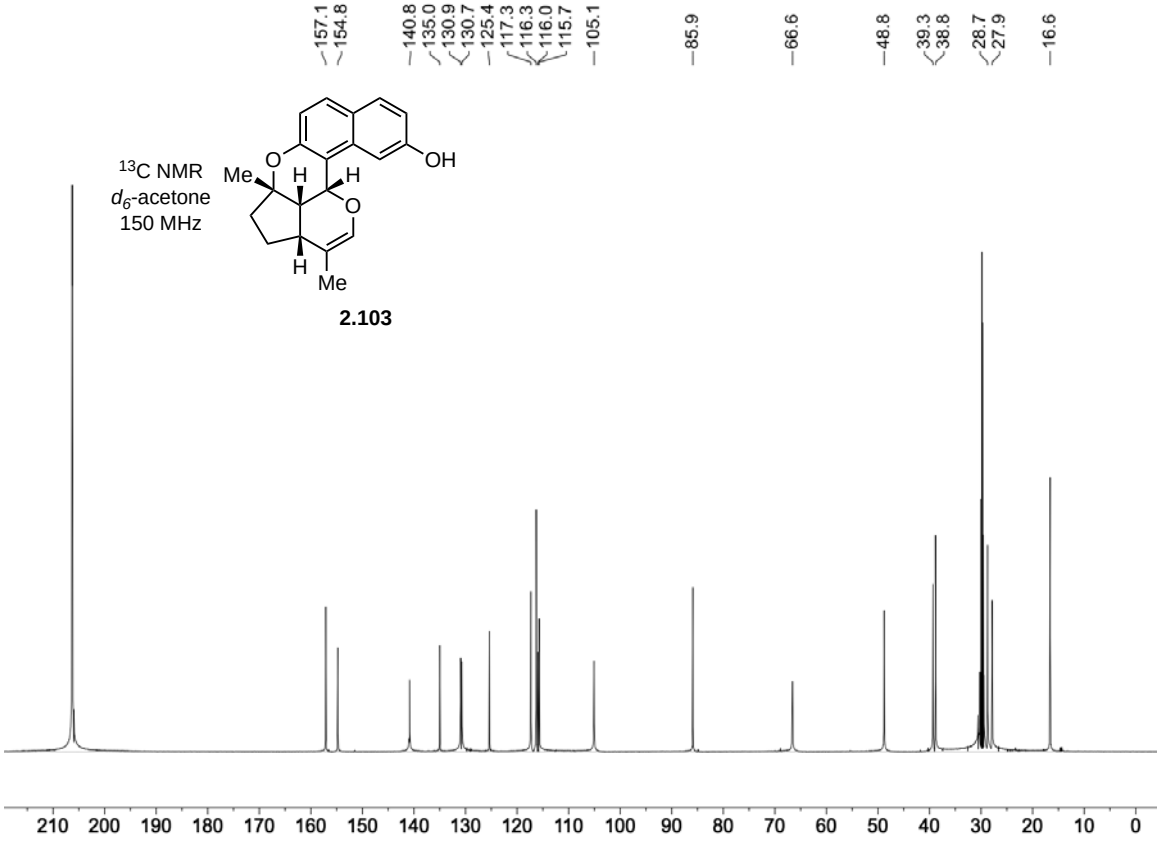
Data for 2.100

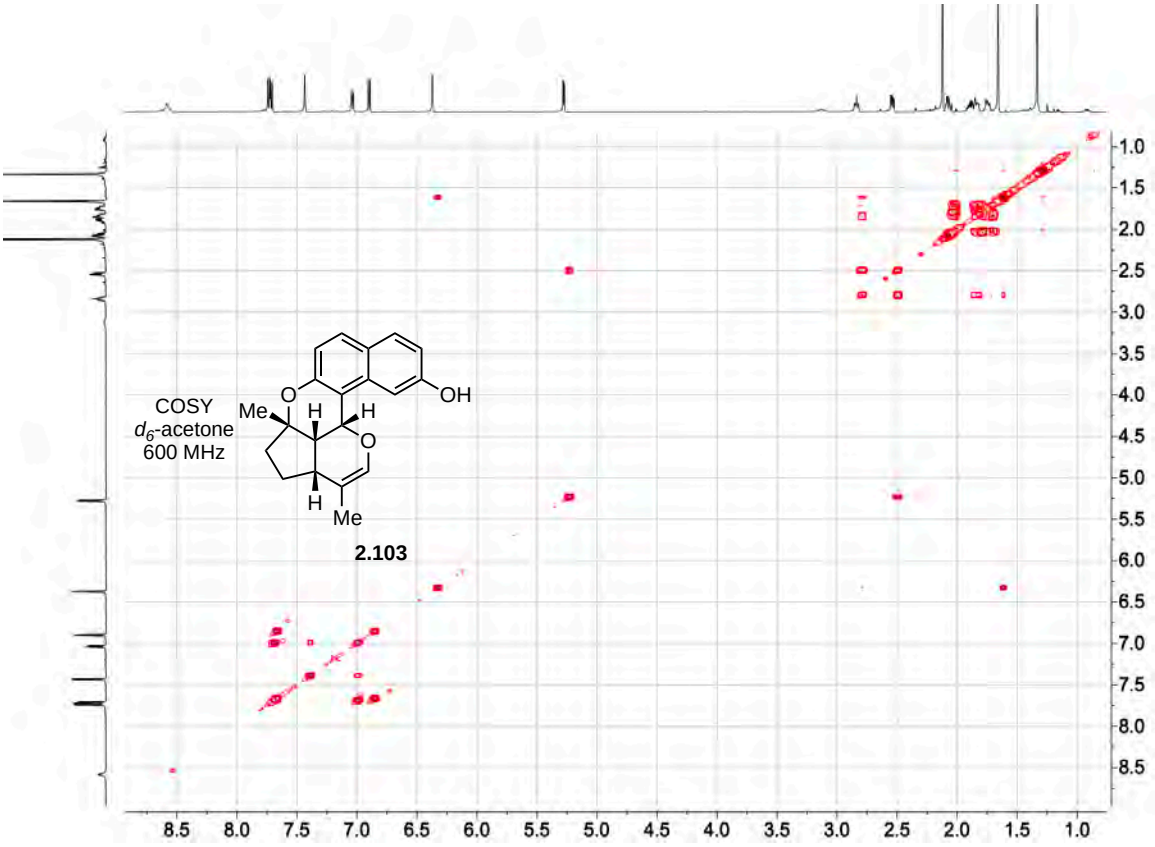


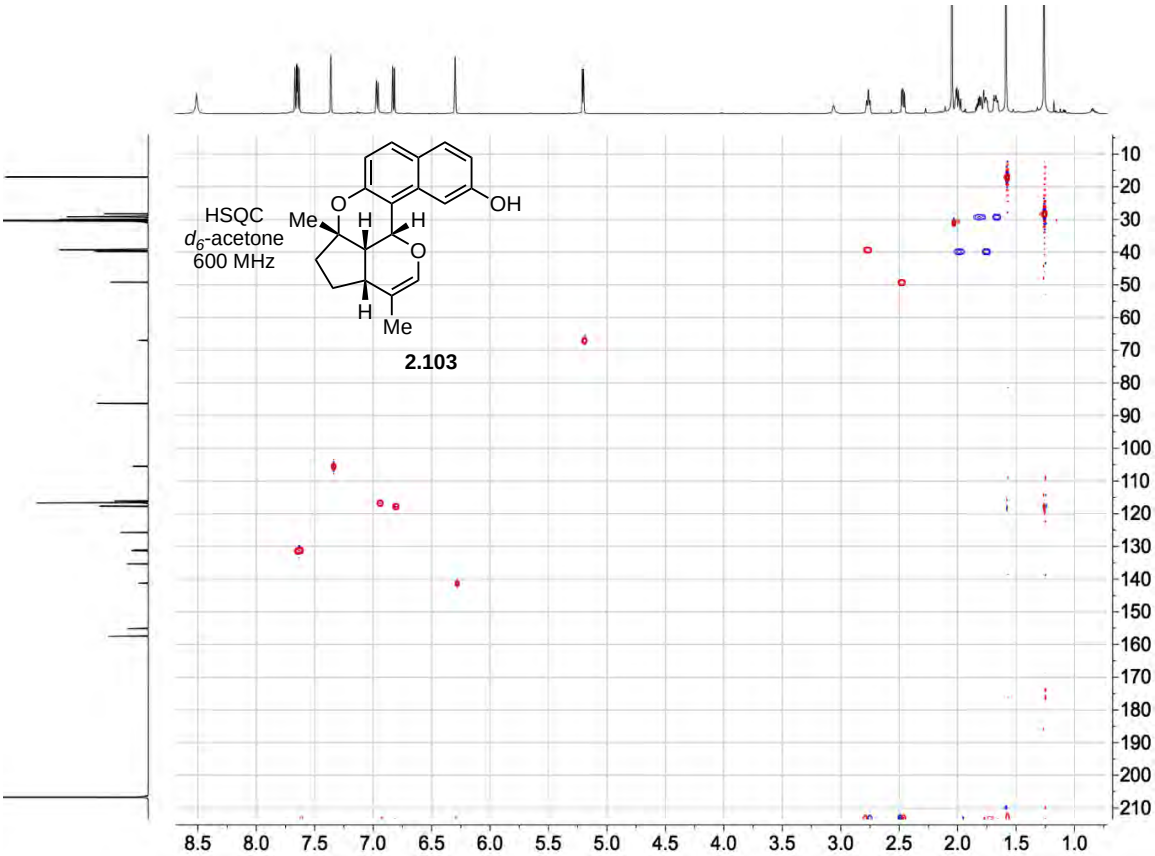


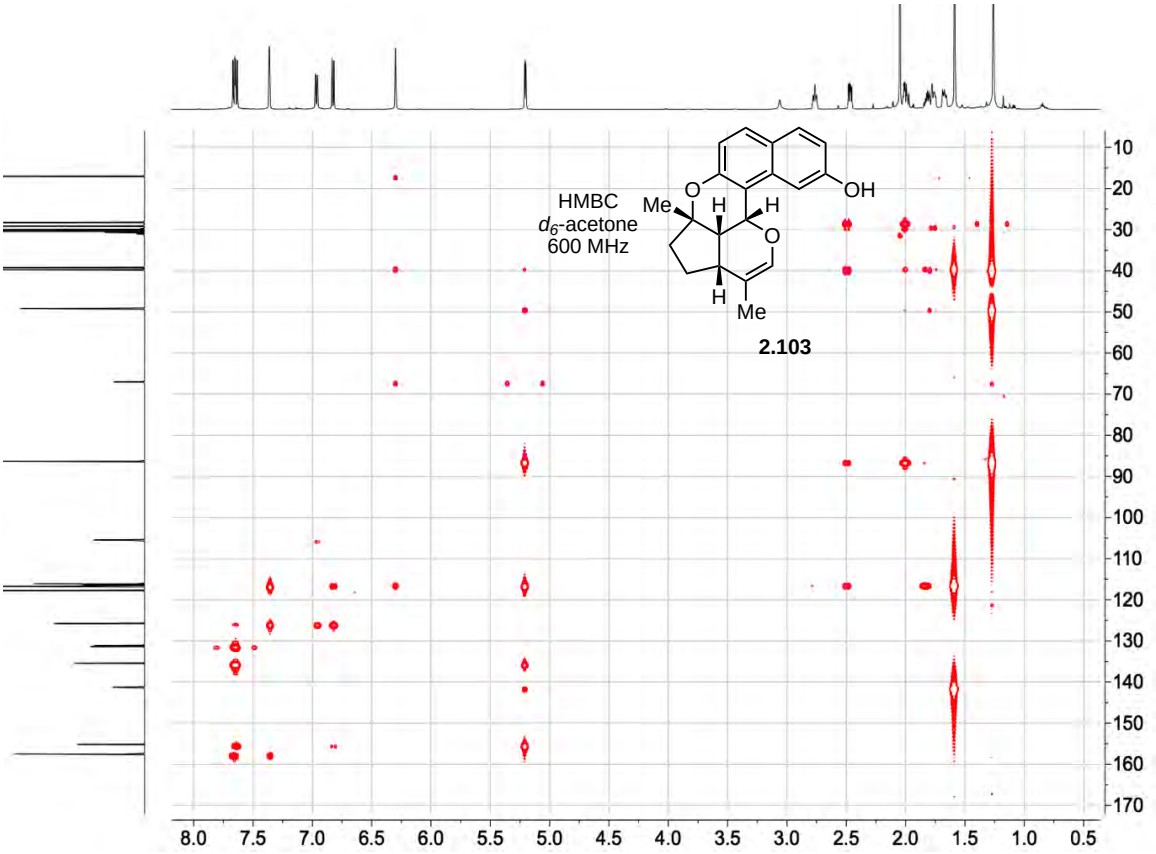
Data for 2.103

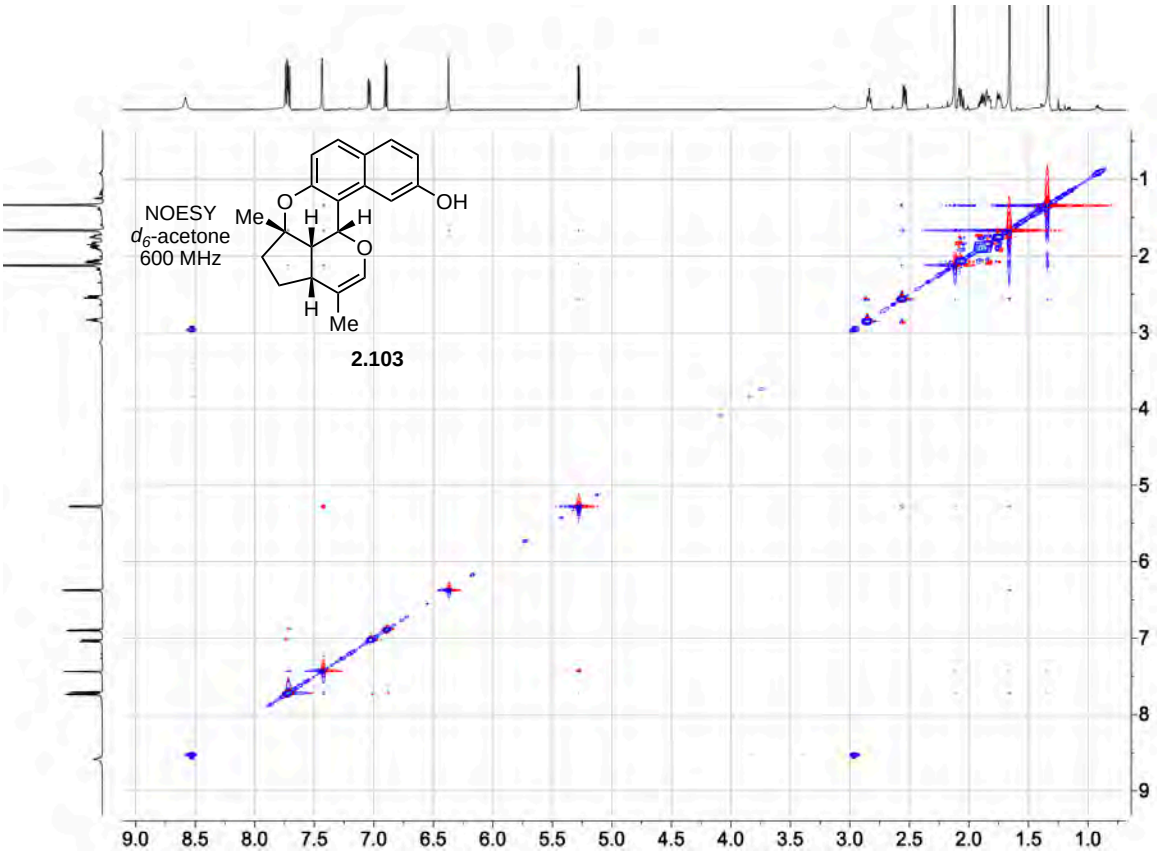


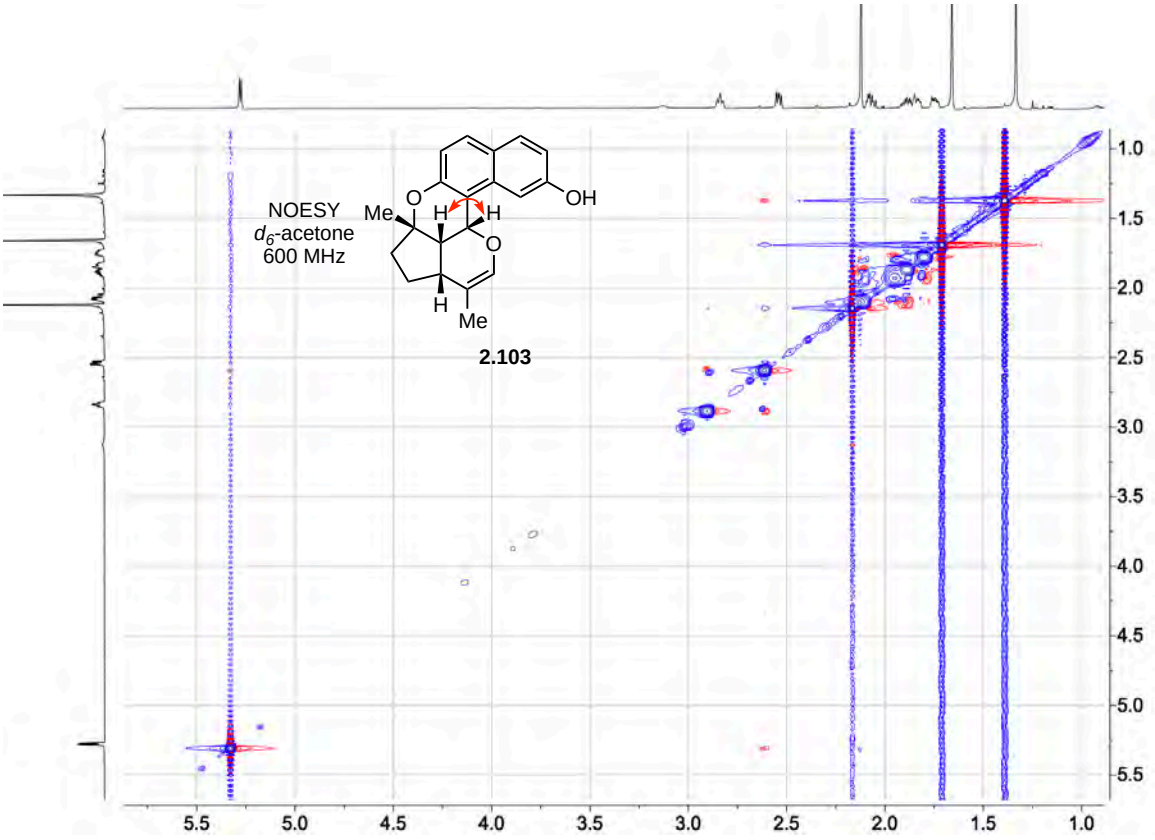



COSY
d_6-acetone
600 MHz
Me
O
H
H
OH
O
H
Me
2.103


HSQC
d_6-acetone
600 MHz
Me
O
H
H
OH
O
H
Me
2.103


HMBC
d_6-acetone
600 MHz
Me
O
H
H
OH
O
H
Me
2.103
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


NOESY
d_6-acetone
600 MHz
Me
O
H
H
OH
O
H
Me
2.103
1
2
3
4
5
6
7
8
9
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0


NOESY
d_6-acetone
600 MHz
Me
O
H
H
OH
O
H
Me
2.103
5.5
5.0
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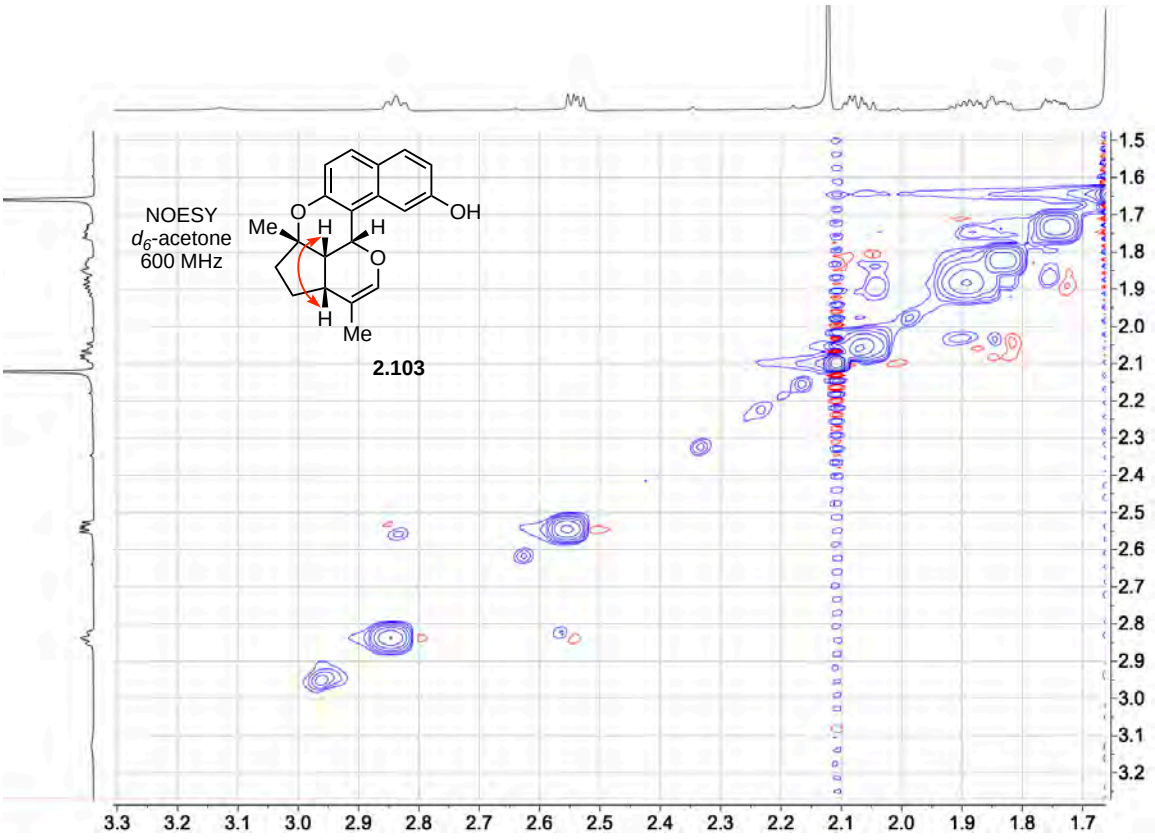
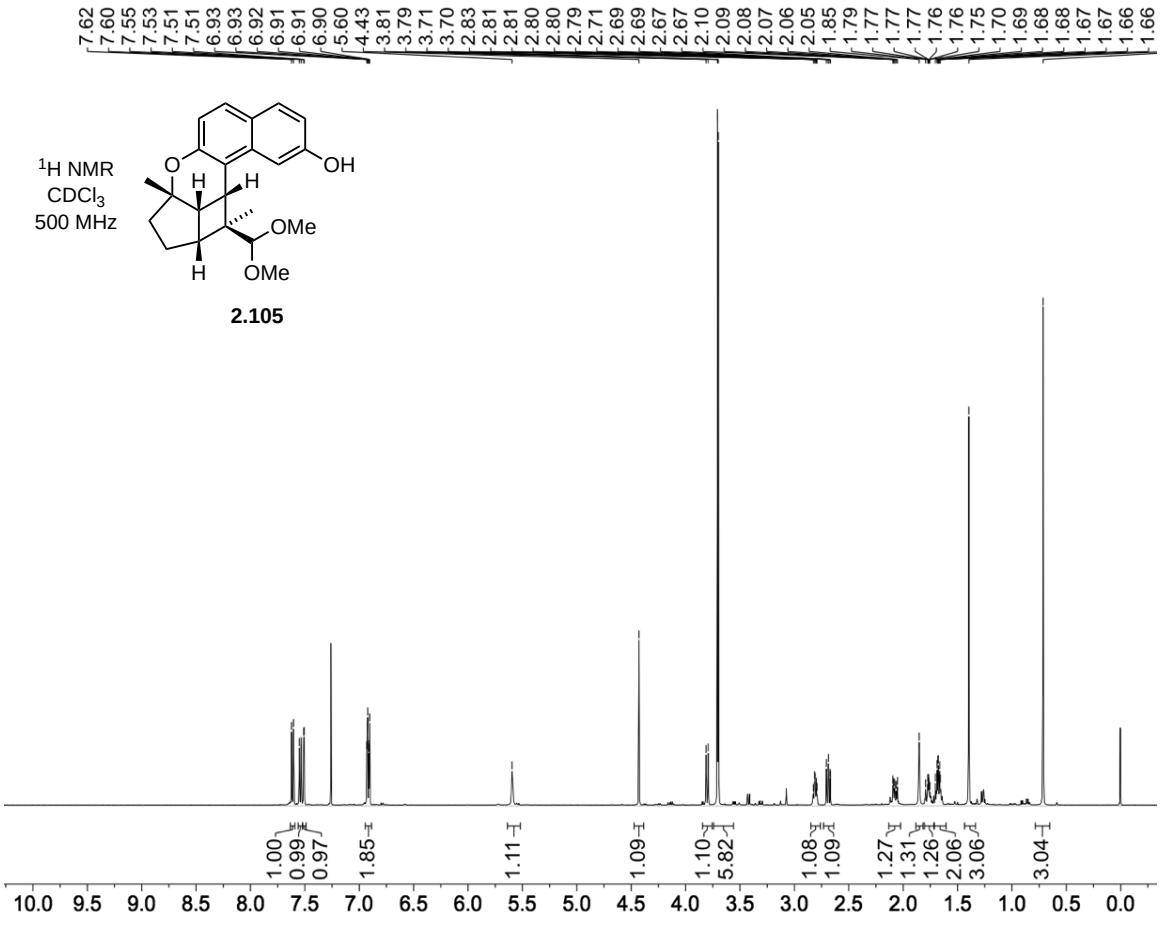
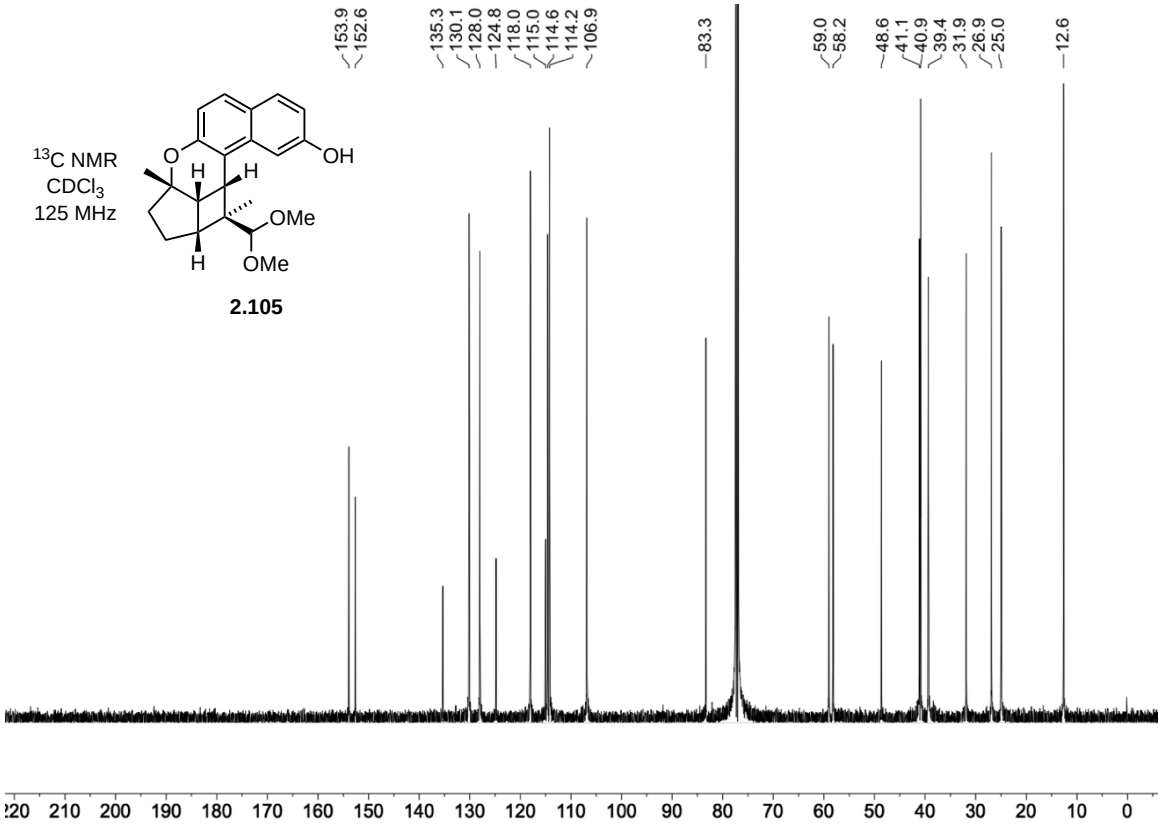
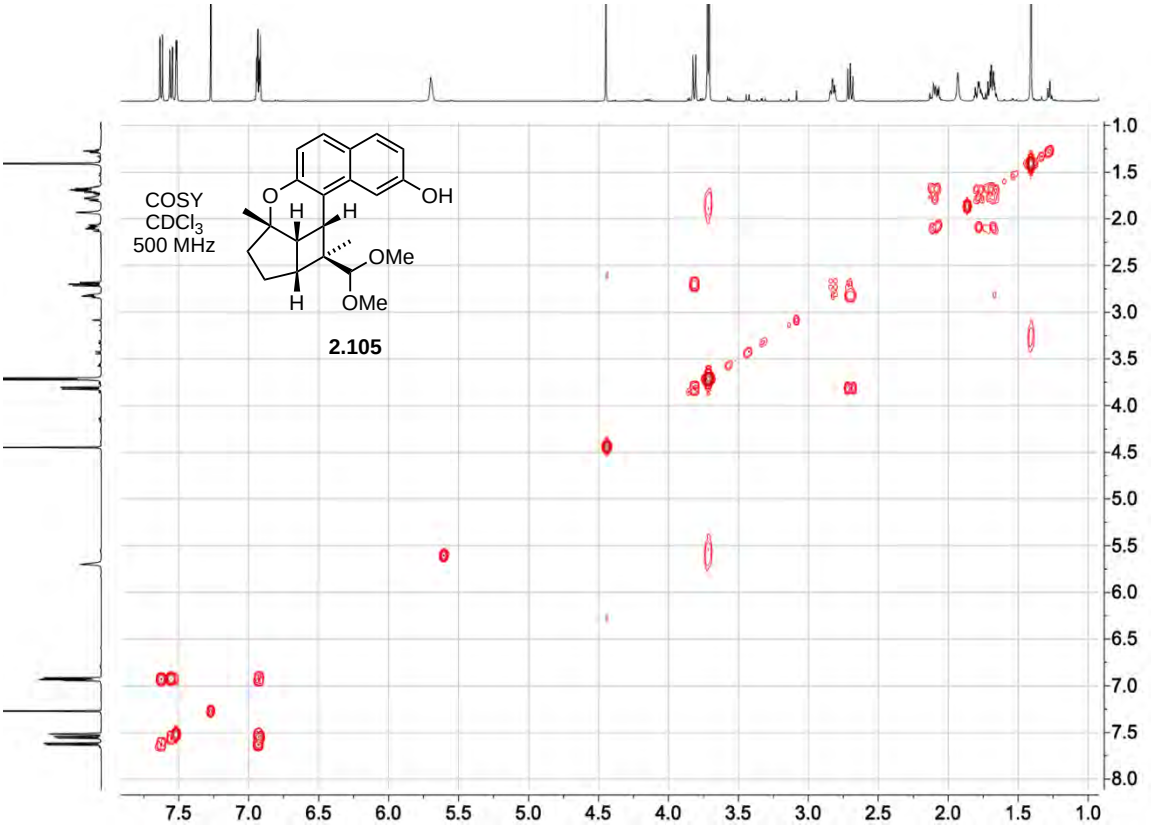
3.5
3.0
2.5
2.0
1.5
1.0

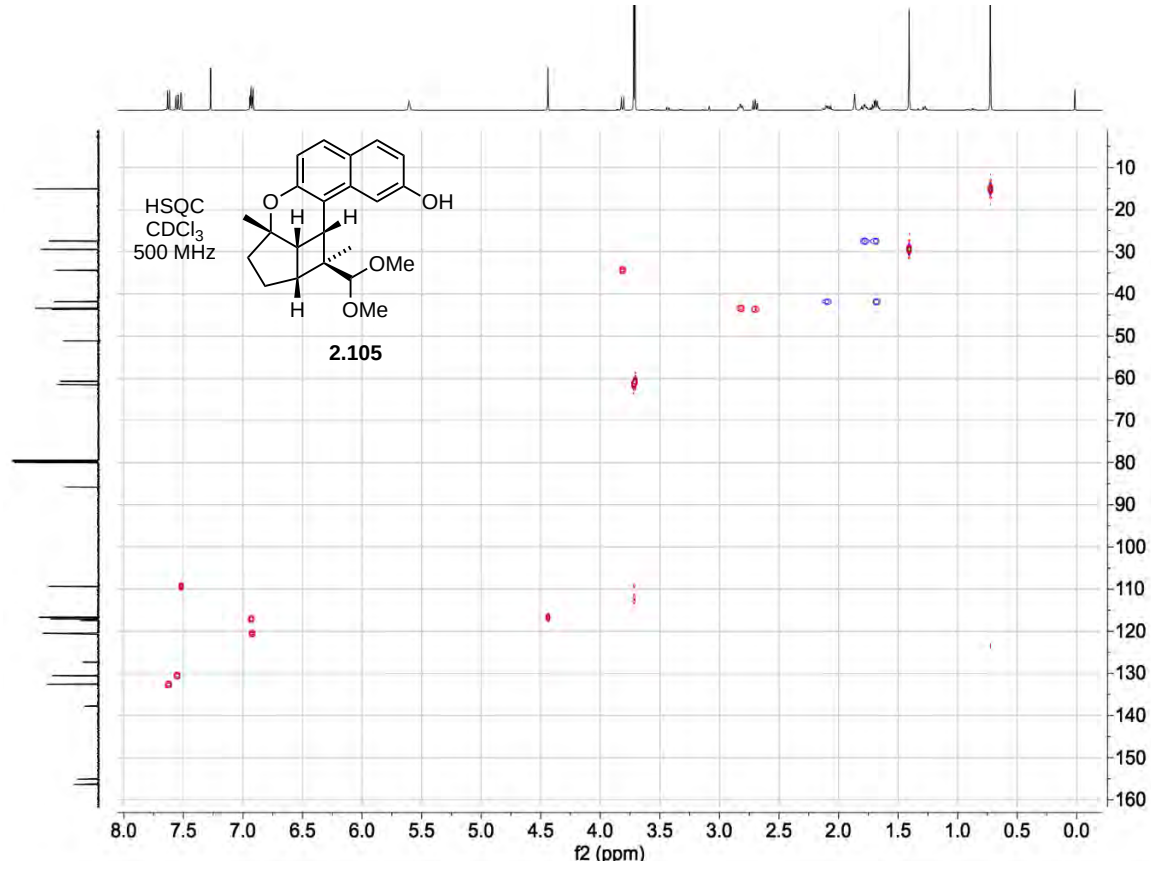

NOESY
d_6-acetone
600 MHz
Me
O
H
H
OH
O
H
Me
2.103
3.3
3.2
3.1
3.0
2.9
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7

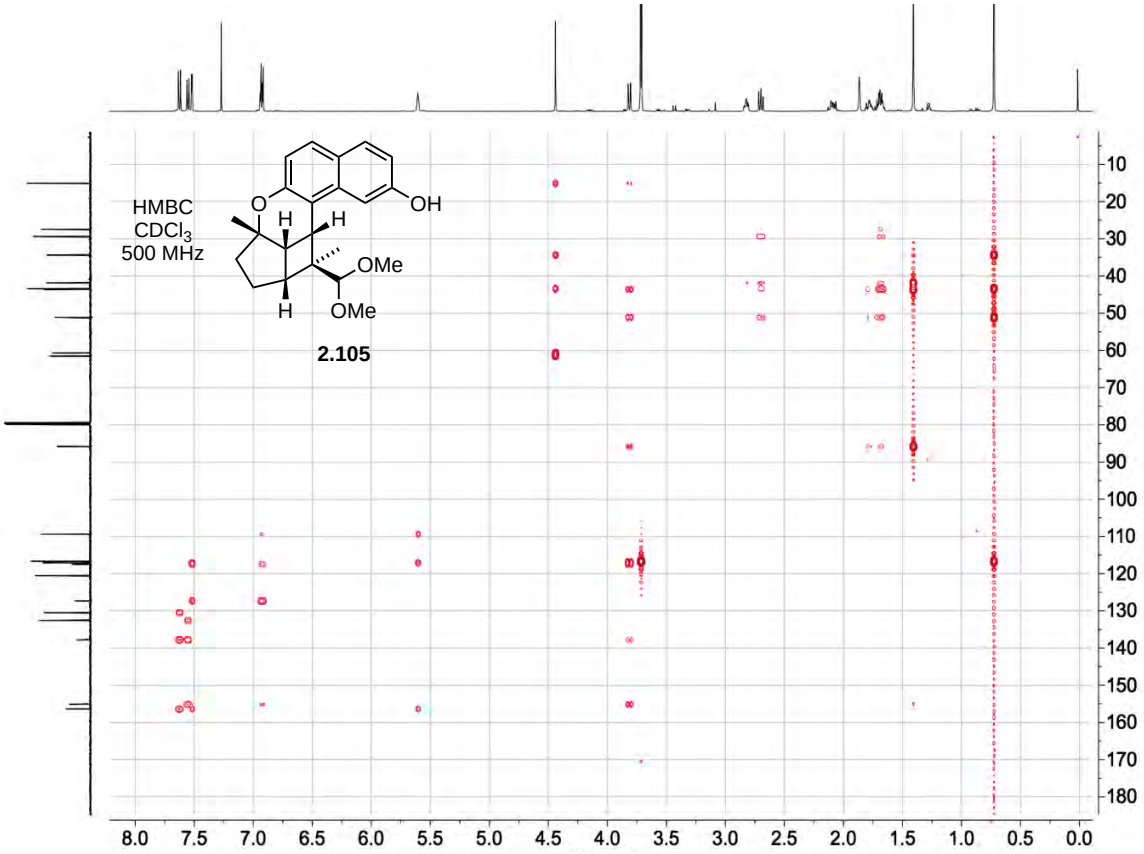
Data for 2.105

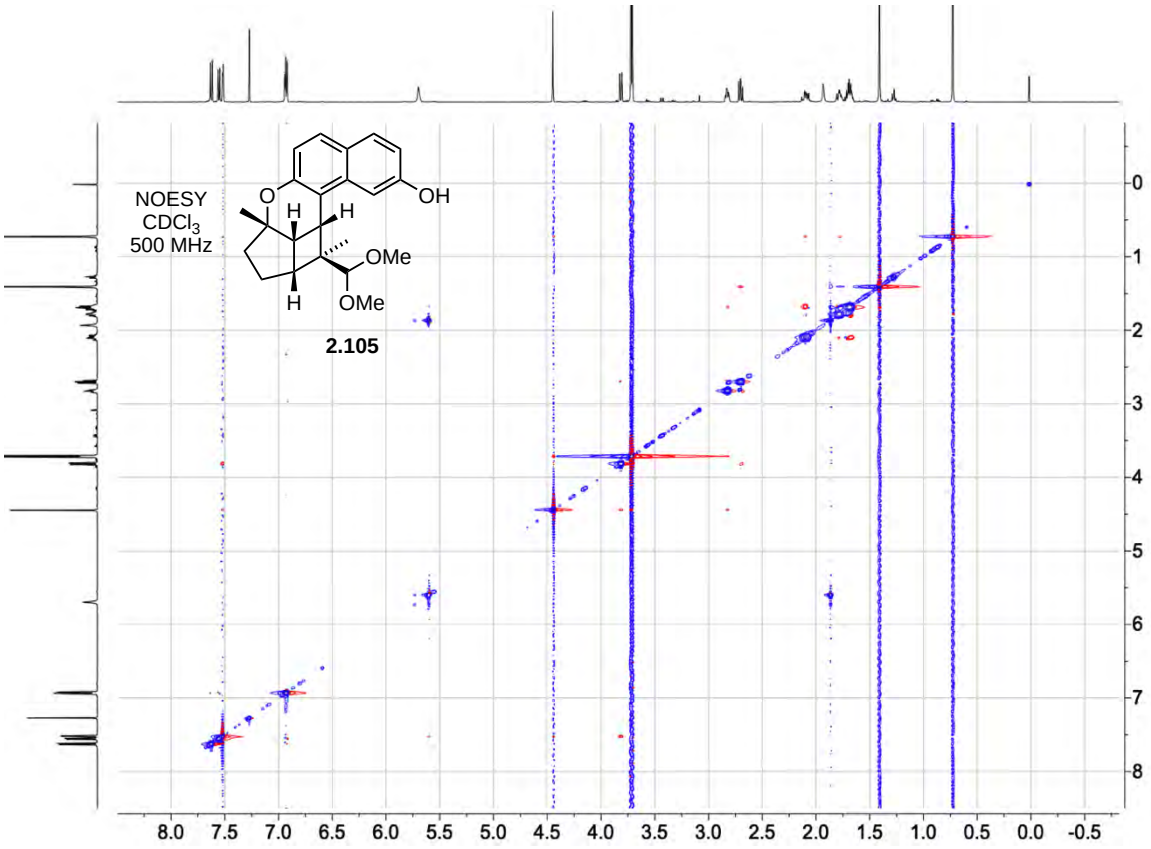




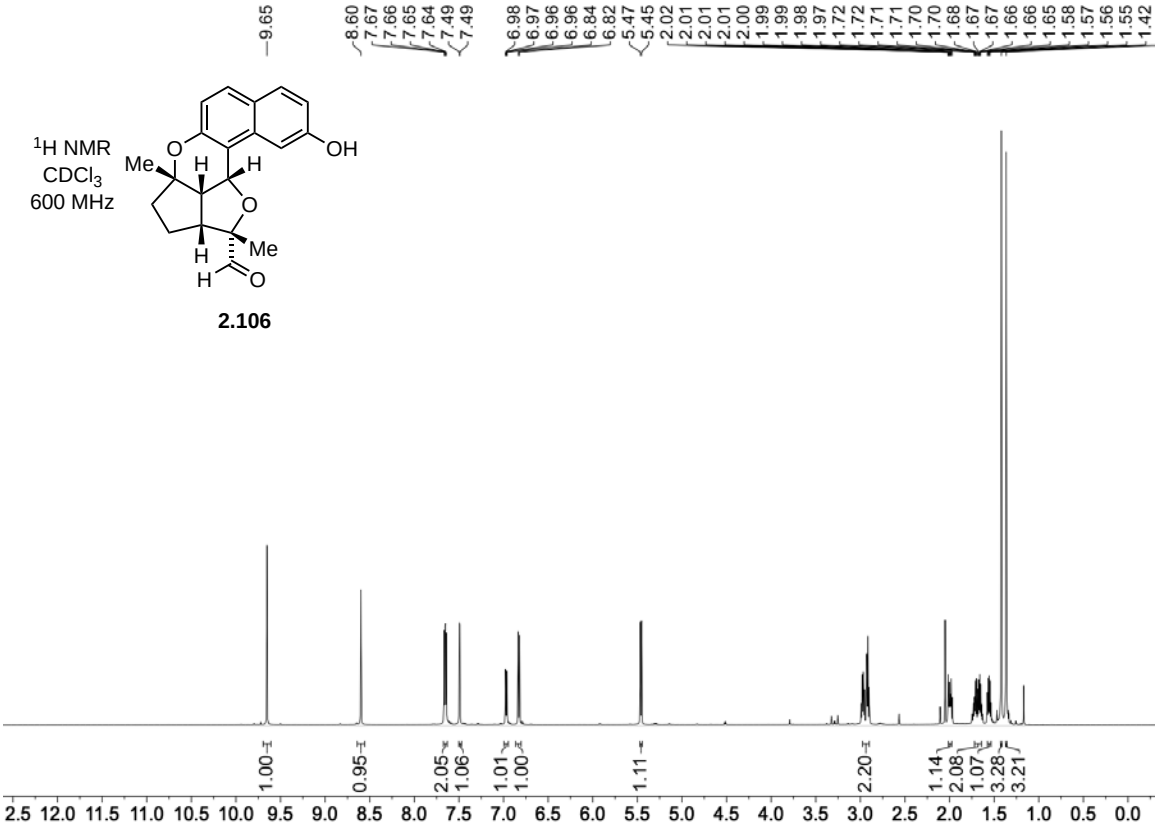

COSY
CDCl3
500 MHz
O
H
H
OH
OMe
H
OMe
2.105


HSQC
CDCl3
500 MHz
O
H
H
OH
OMe
H
OMe
2.105
f2 (ppm)

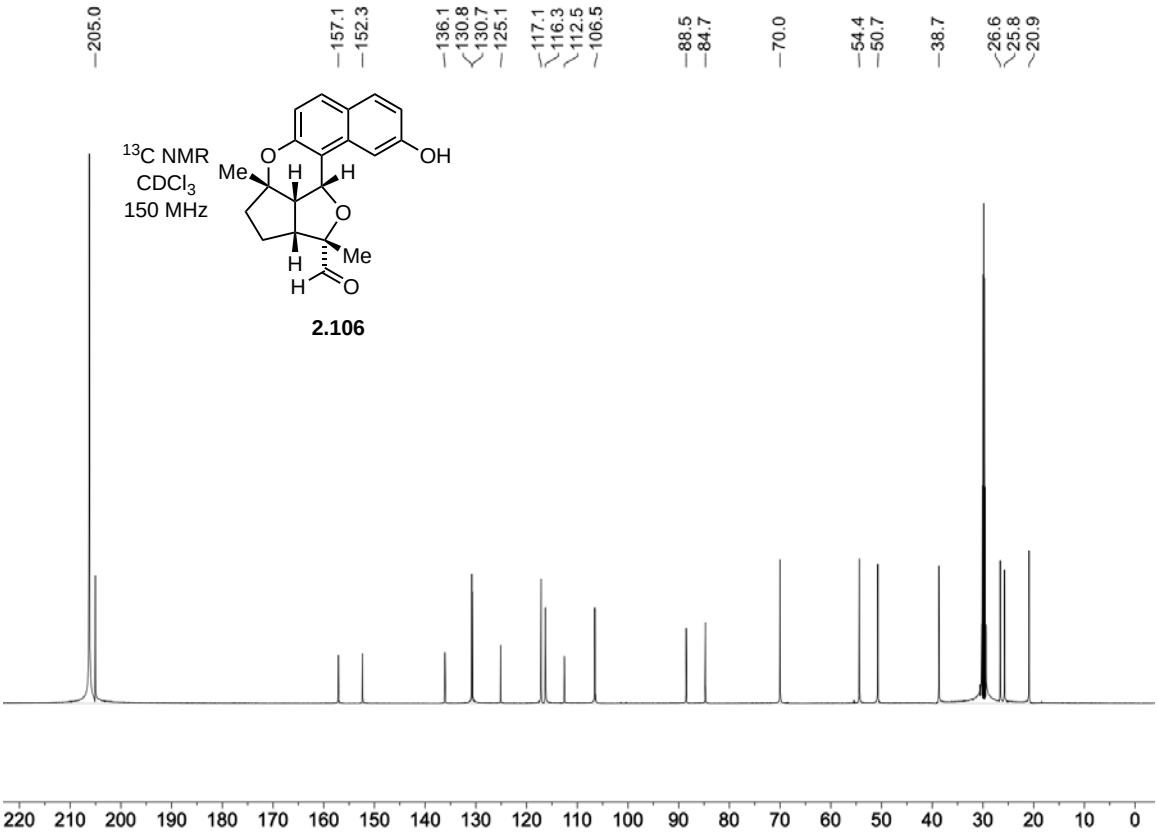

HMBC
CDCl3
500 MHz
O
H
H
OH
OMe
H
OMe
2.105


NOESY
CDCl3
500 MHz
O
H
H
OH
OMe
H
OMe
2.105

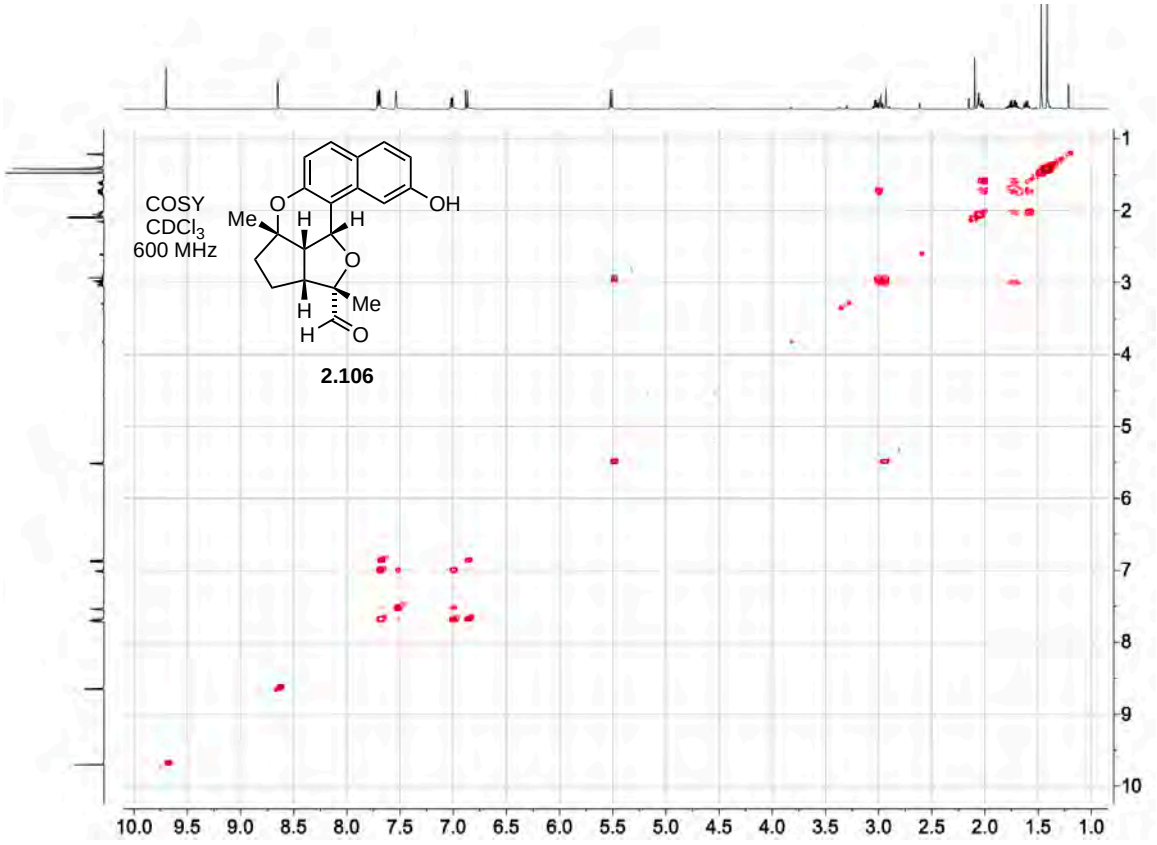
Data for 2.106

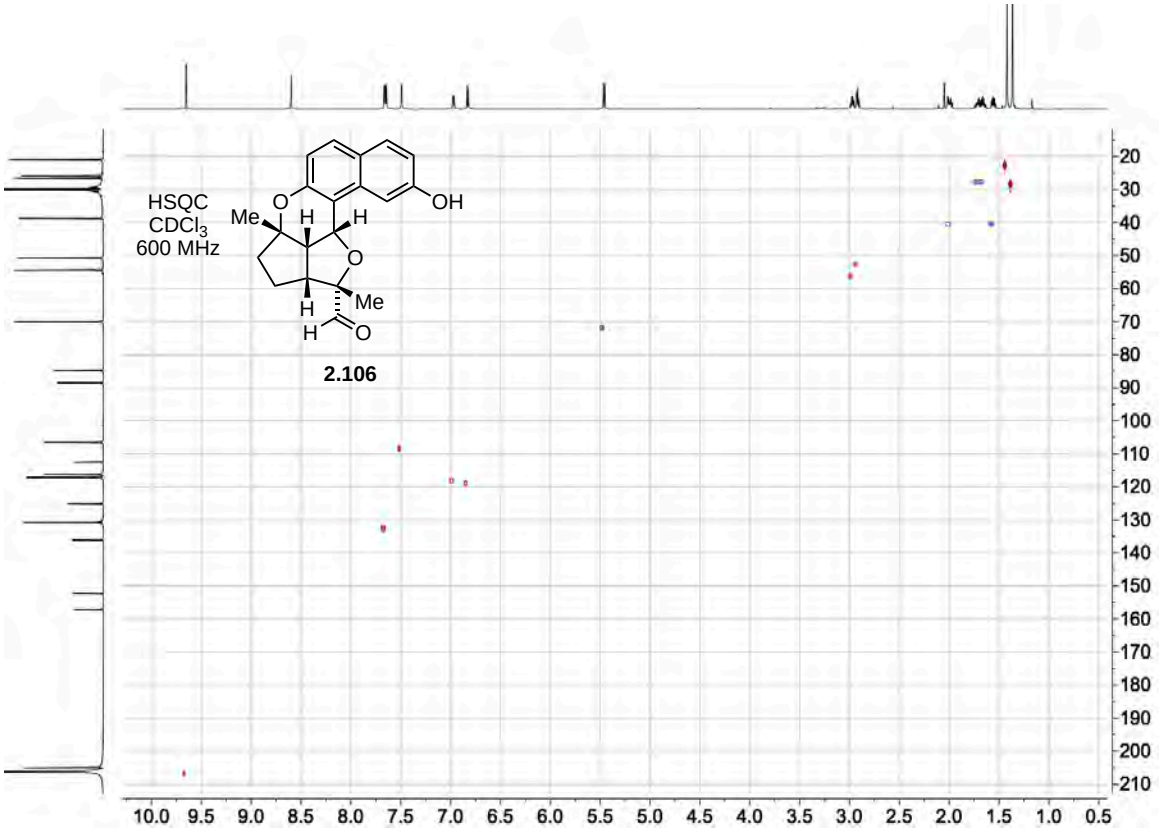


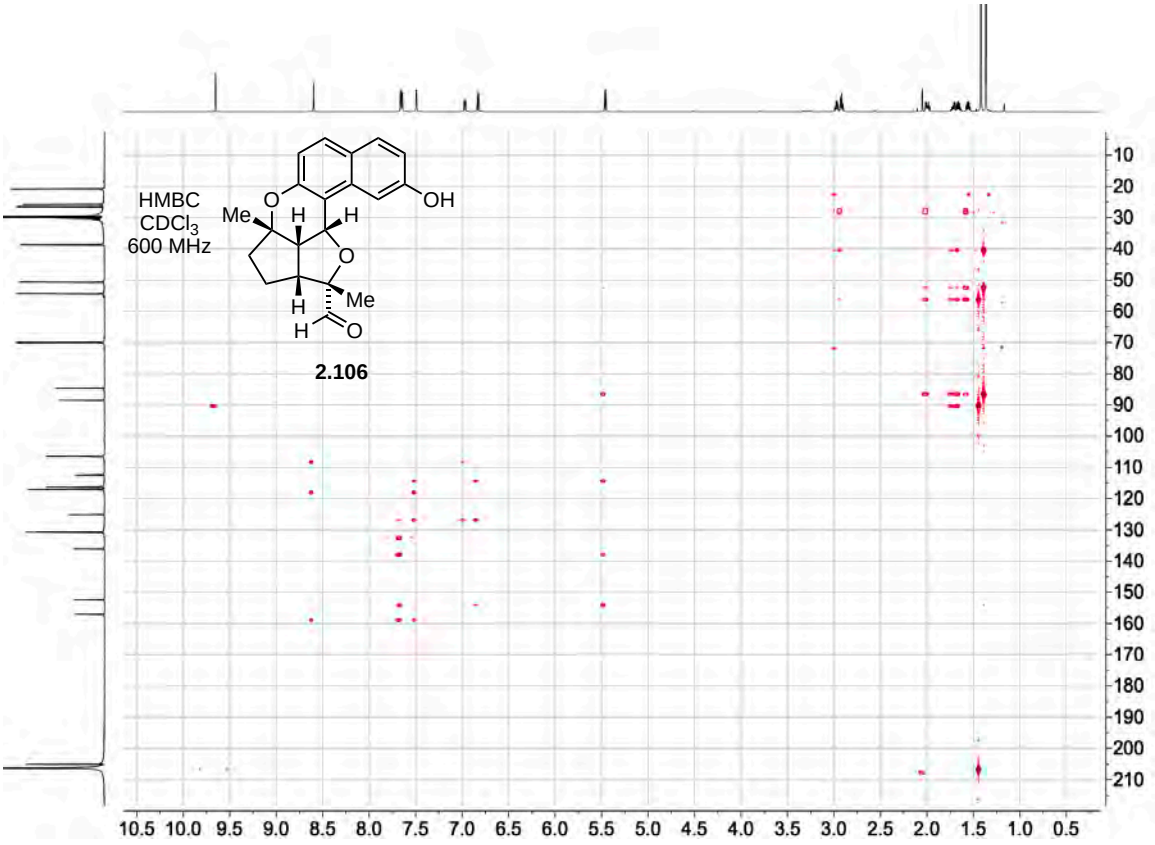
2.106

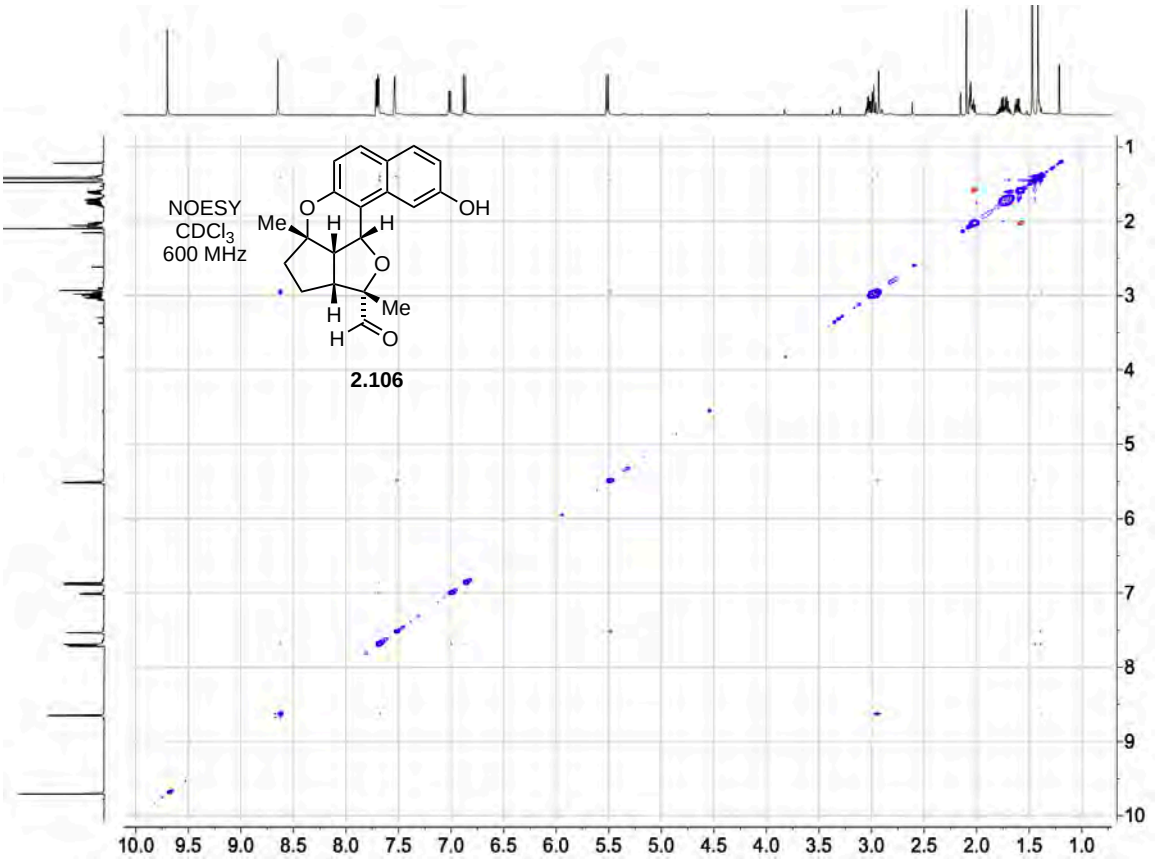


2.106


COSY
CDCl3
600 MHz
Me
O
H
H
OH
O
H
Me
H
O
2.106


HSQC
CDCl3
600 MHz
Me
O
H
H
OH
O
H
Me
H
O
2.106


HMBC
CDCl3
600 MHz
Me
O
H
H
OH
O
Me
H
H
O
2.106


NOESY
CDCl3
600 MHz
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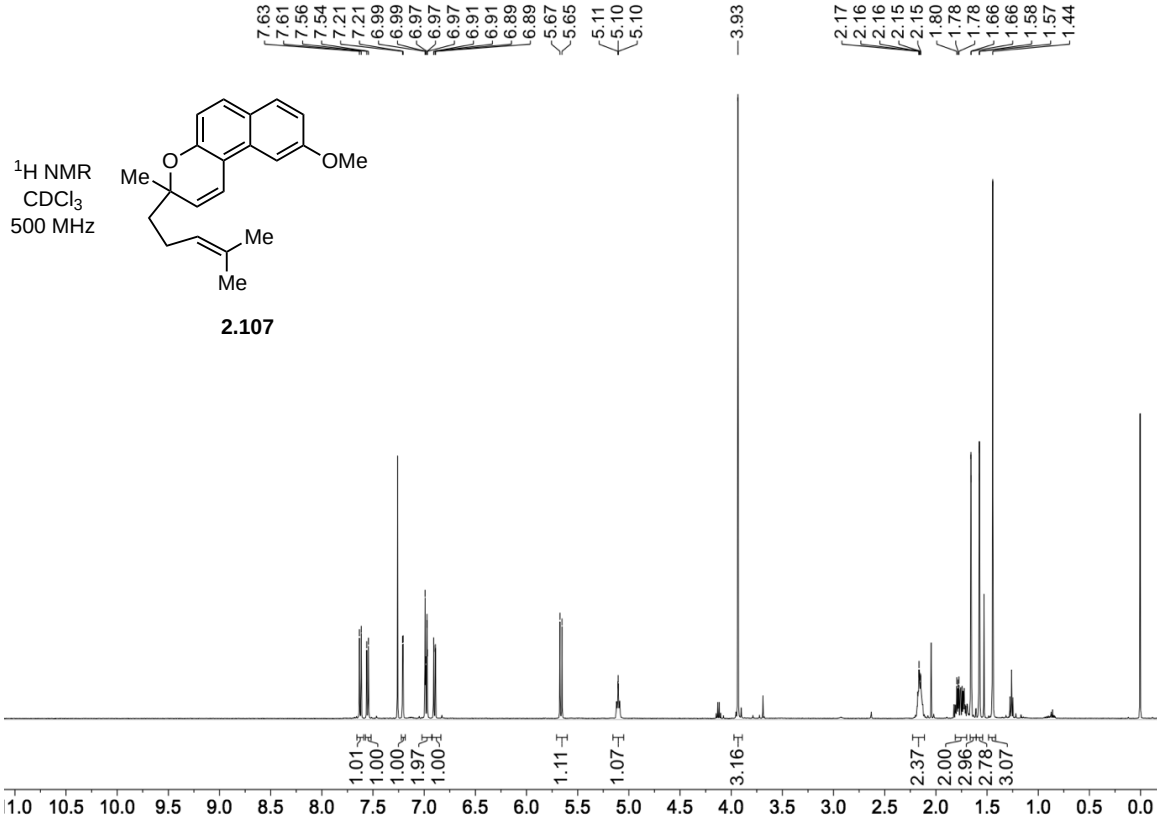
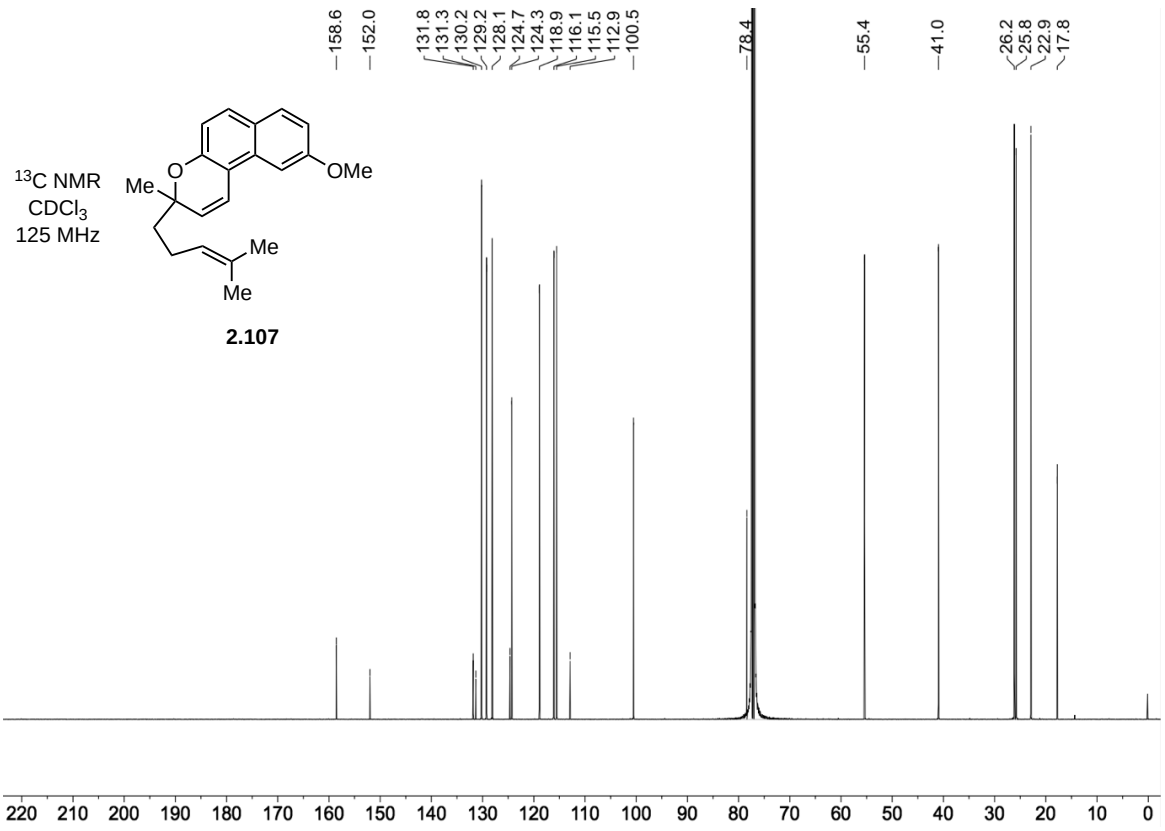
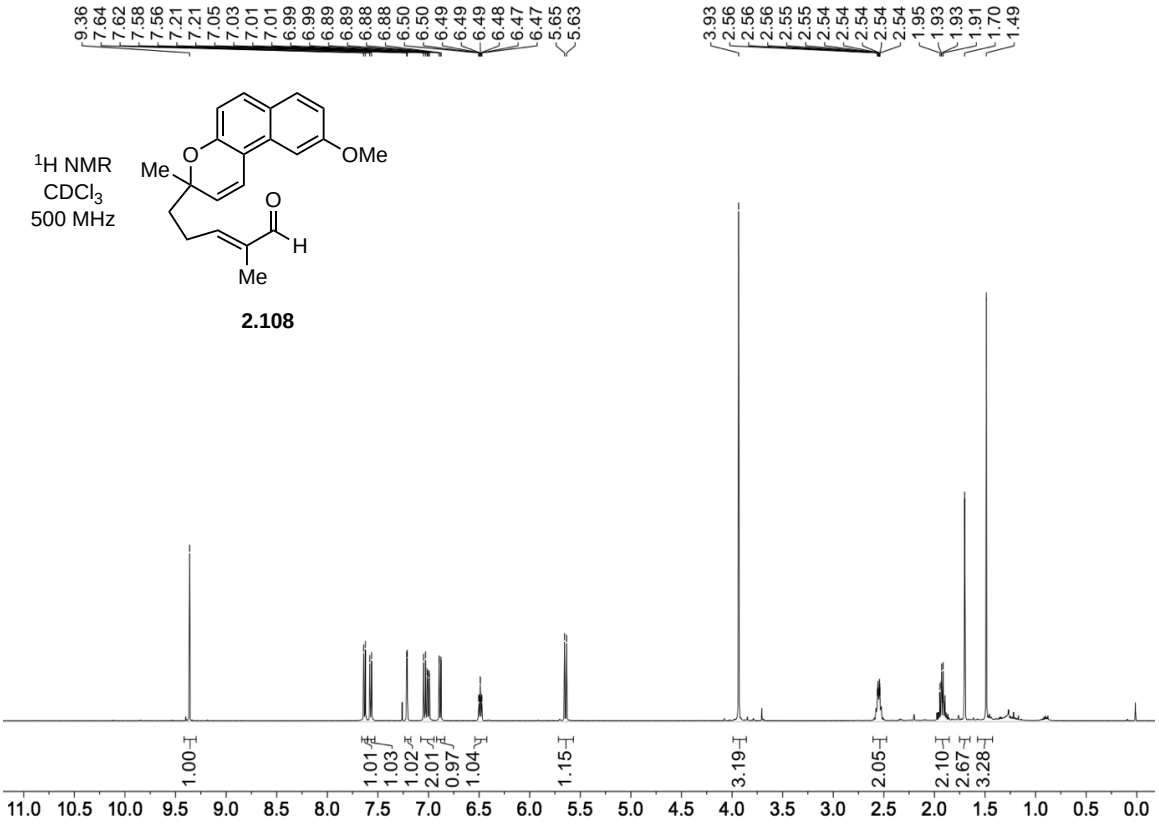
O
H
H
OH
O
Me
H
H
O
2.106

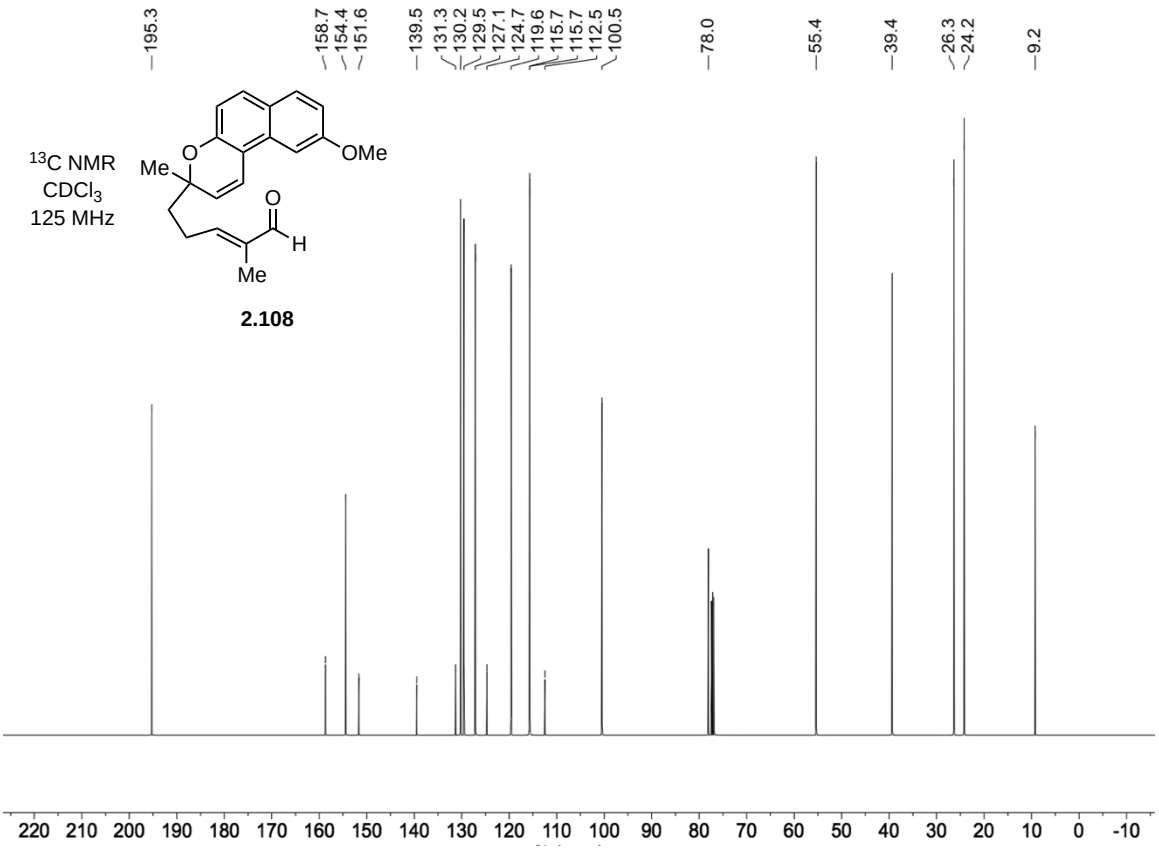
Data for 2.107



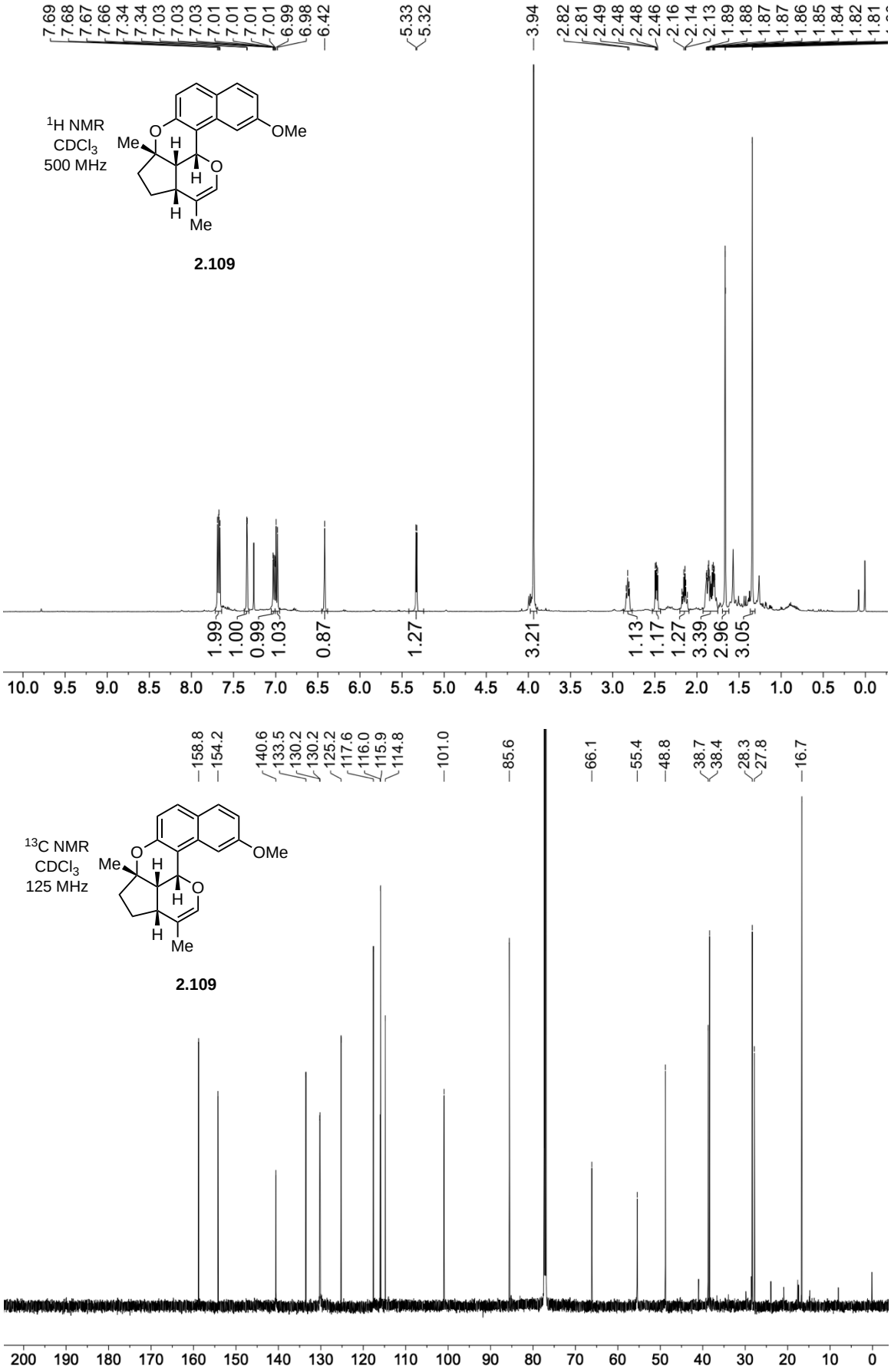


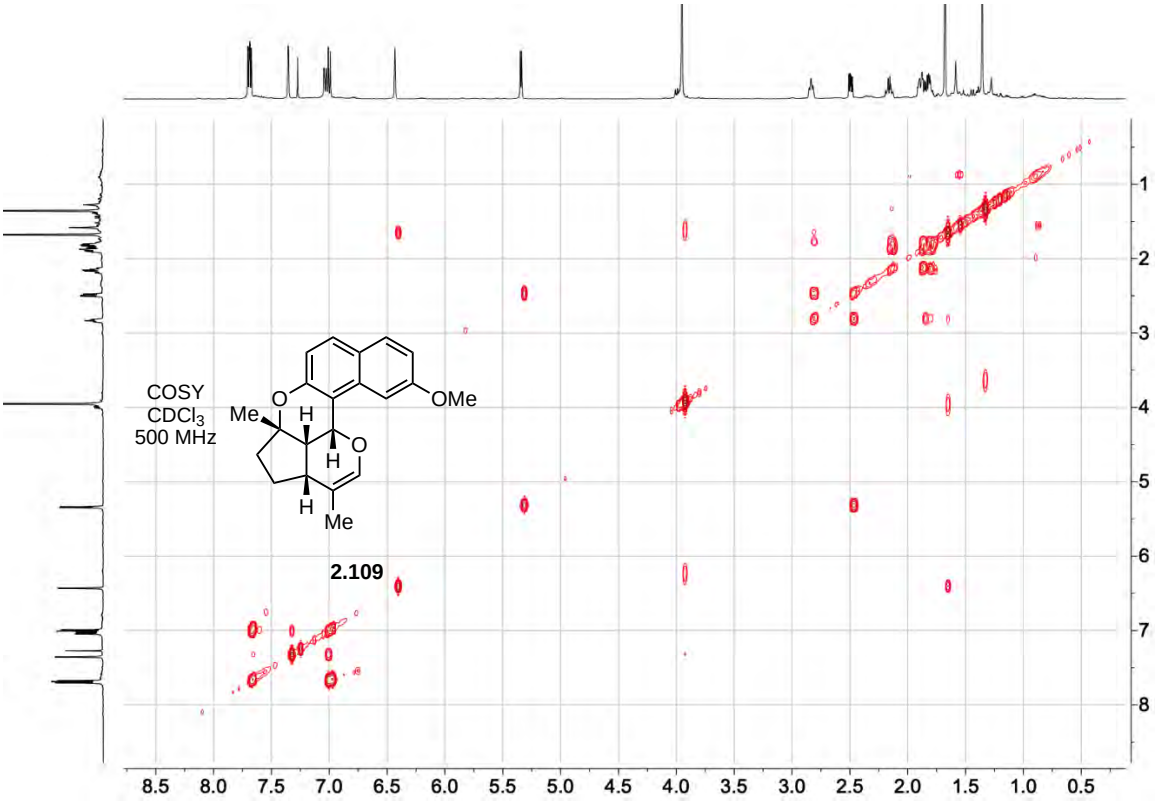
Data for 2.108

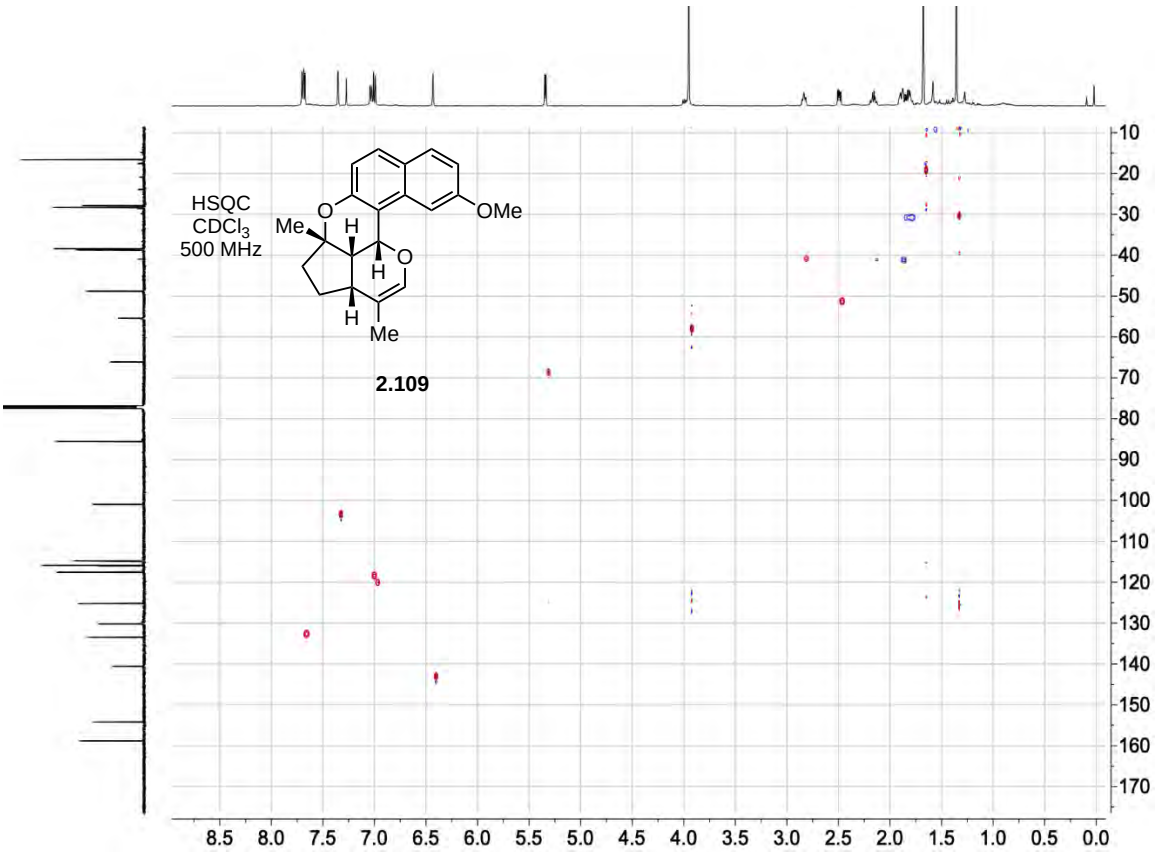


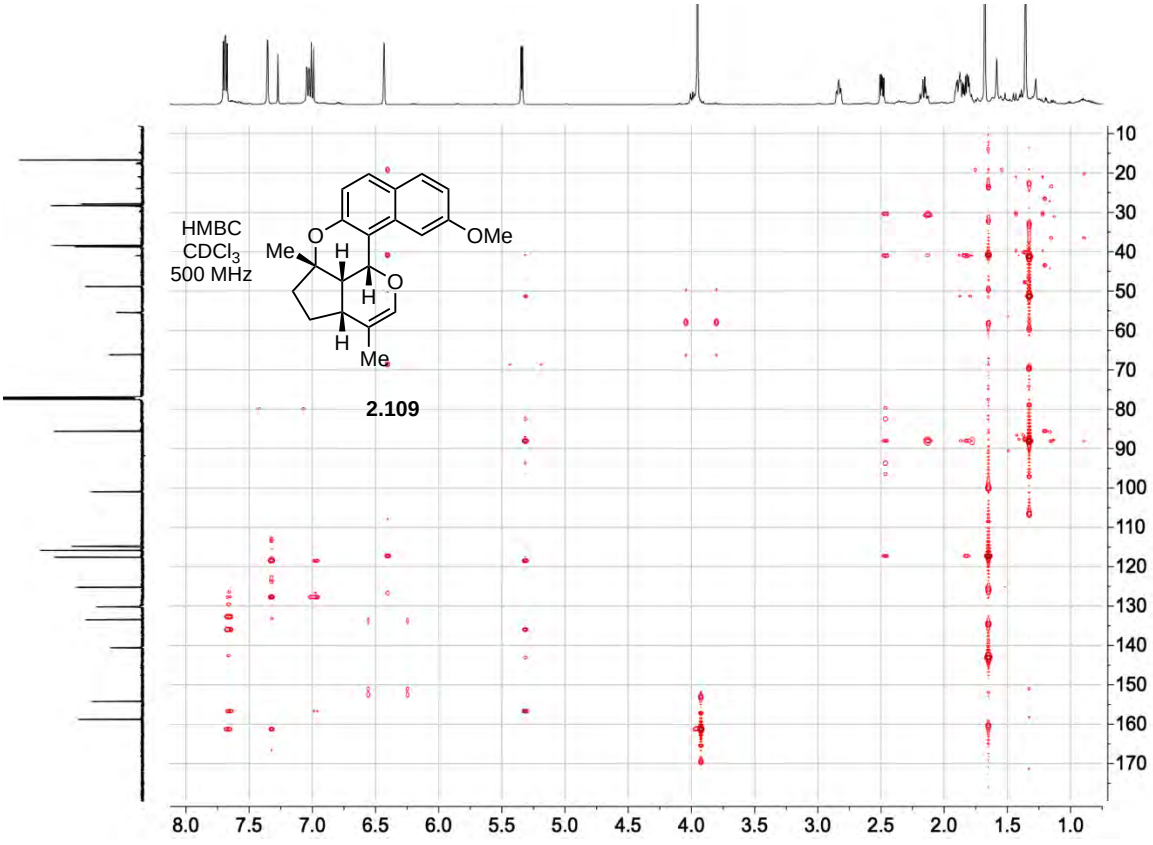


Data for 2.109

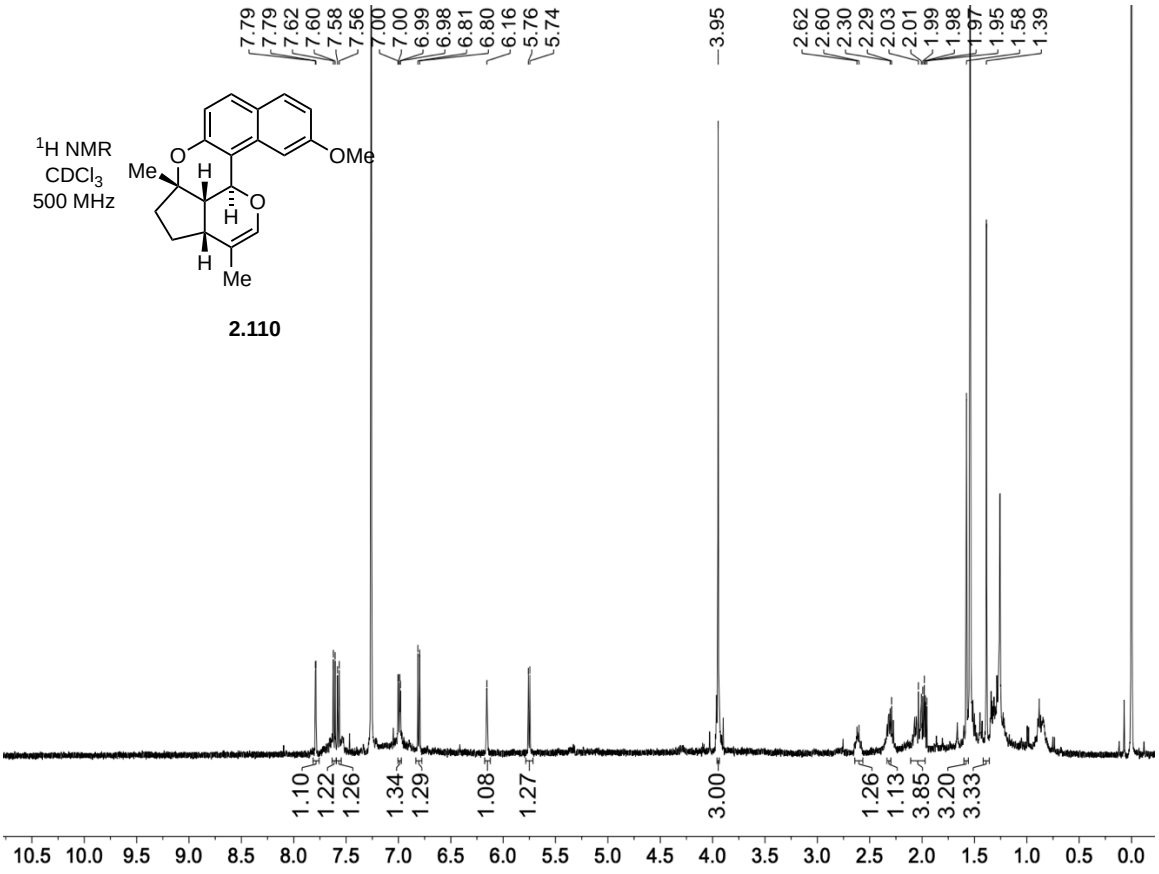



COSY
CDCl3
500 MHz
Me
O
H
OMe
O
H
H
Me
2.109
1
2
3
4
5
6
7
8
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5


HSQC
CDCl3
500 MHz
Me
O
H
OMe
O
H
H
Me
2.109
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


HMBC
CDCl3
500 MHz
Me
O
H
OMe
H
O
H
Me
2.109
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

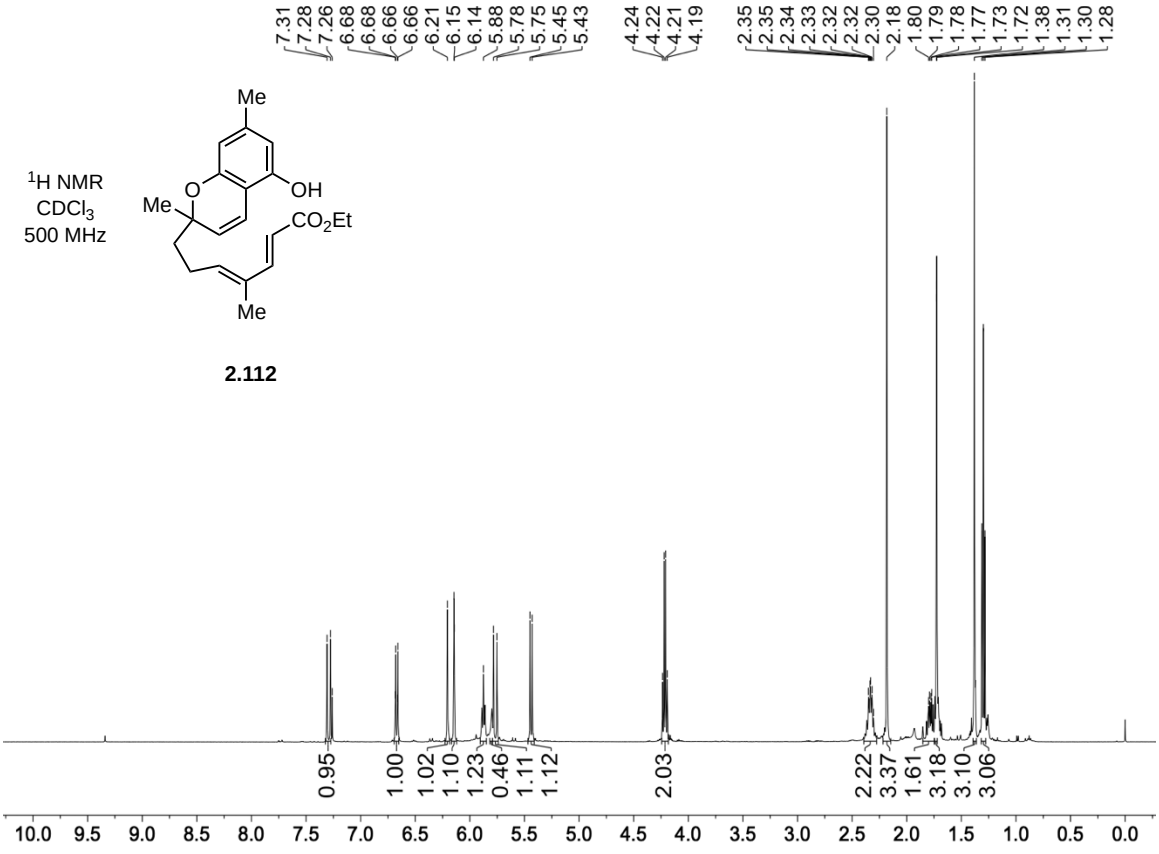
Data for 2.110



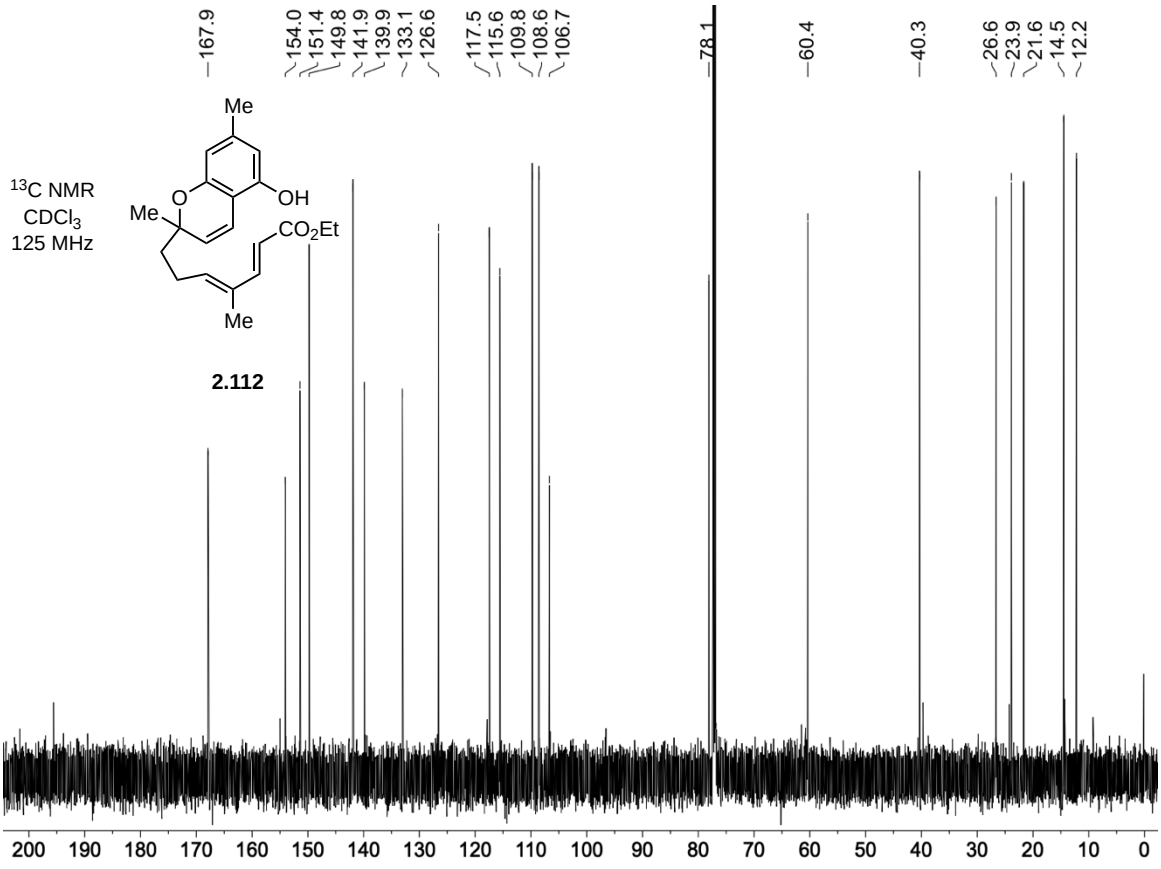
^{1}H NMR
$CDCl_3$
500 MHz

2.110

Data for 2.112



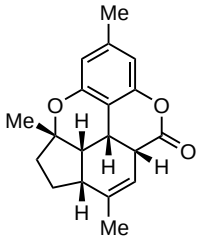
2.112



2.112

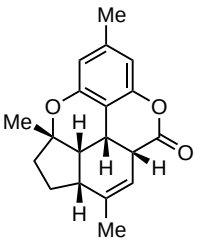
Data for 2.111a

^{1}H NMR
$CDCl_3$
500 MHz

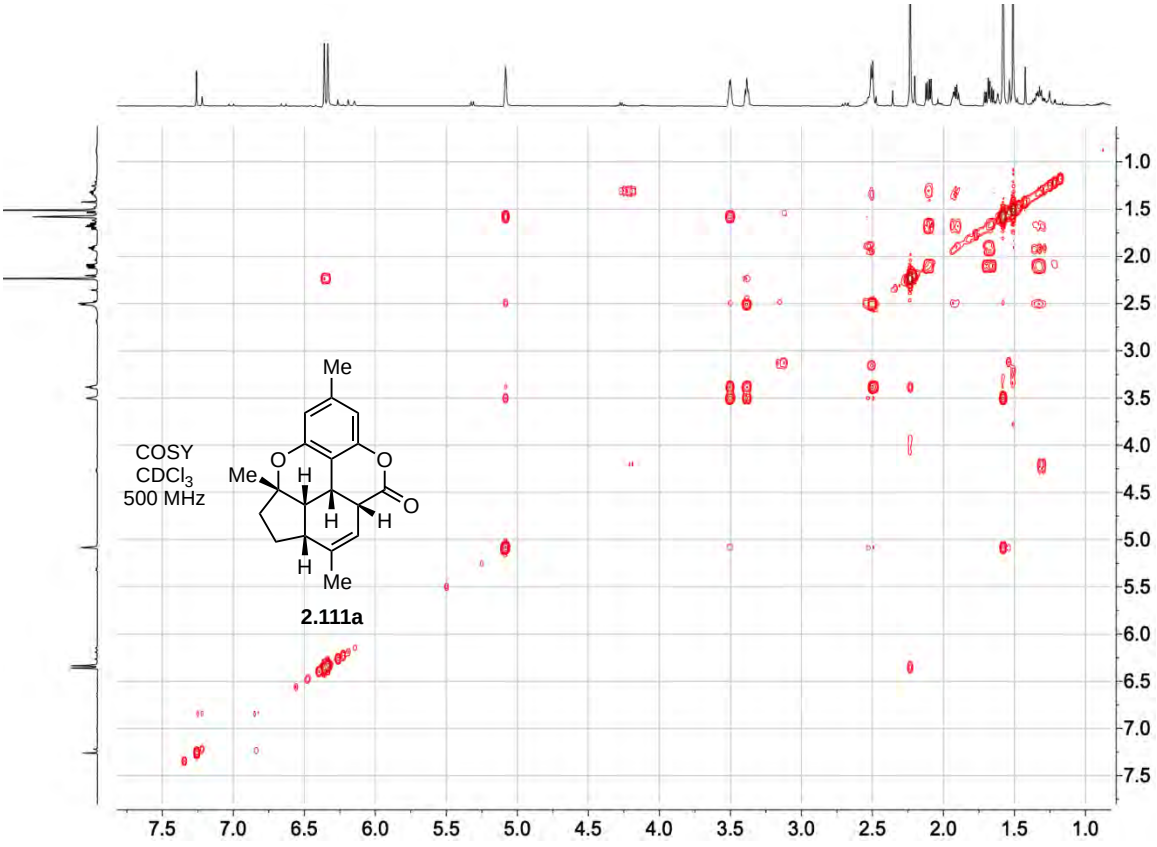


2.111a

^{13}C NMR
$CDCl_3$
125 MHz



2.111a


COSY
CDCl3
500 MHz
Me
Me
O
H
O
O
H
H
H
H
Me
2.111a
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
7.5
7.0
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5.0
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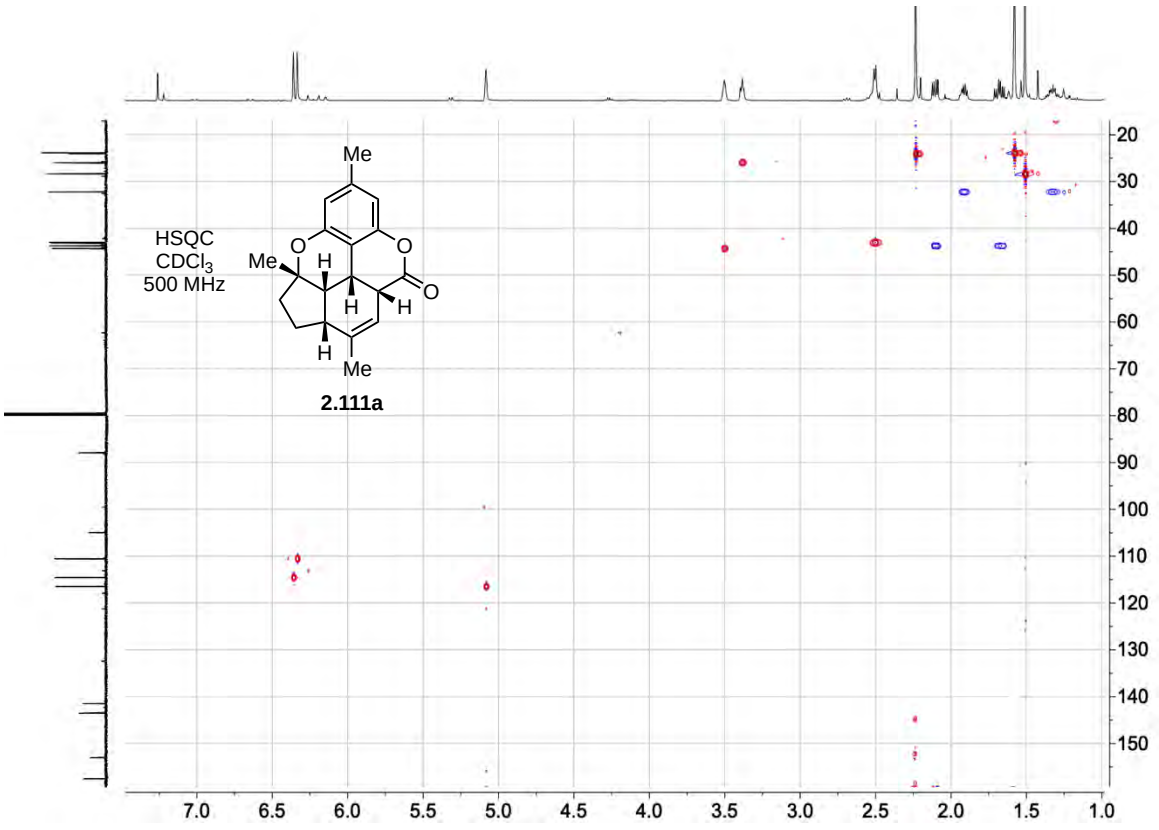
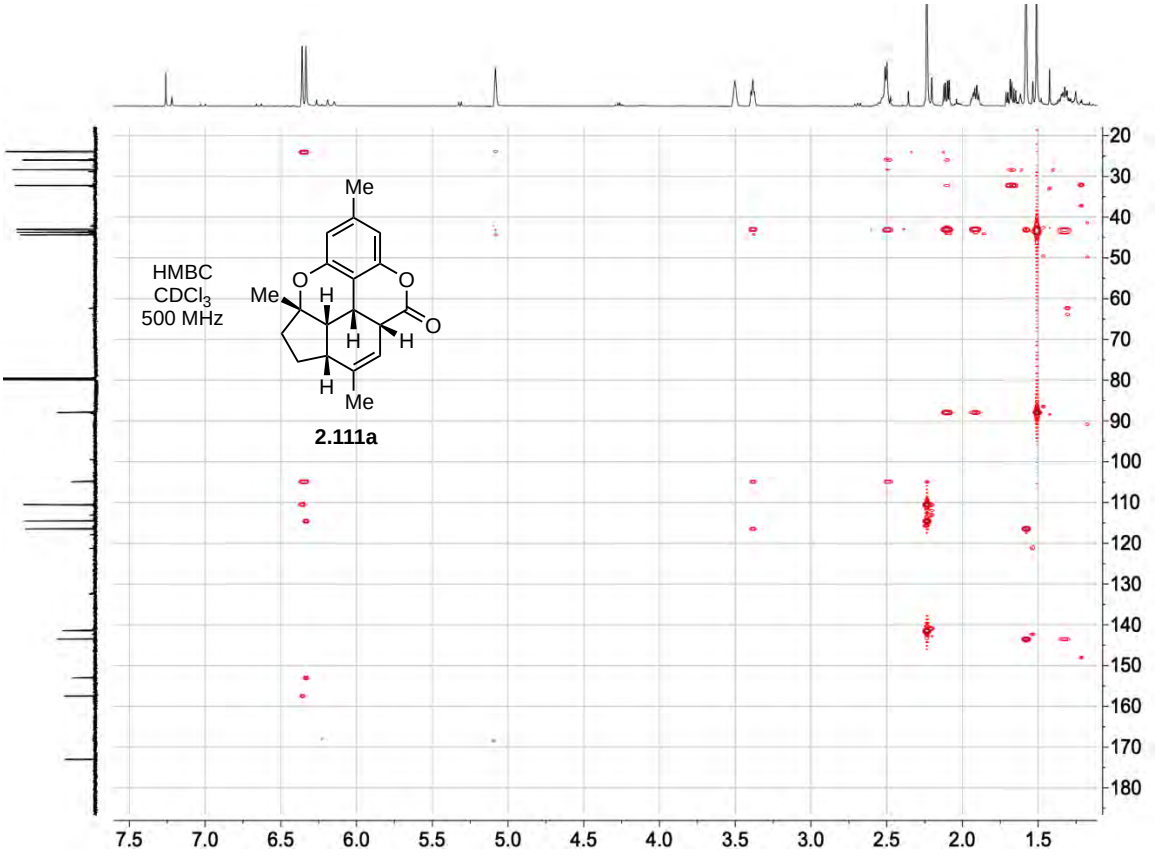
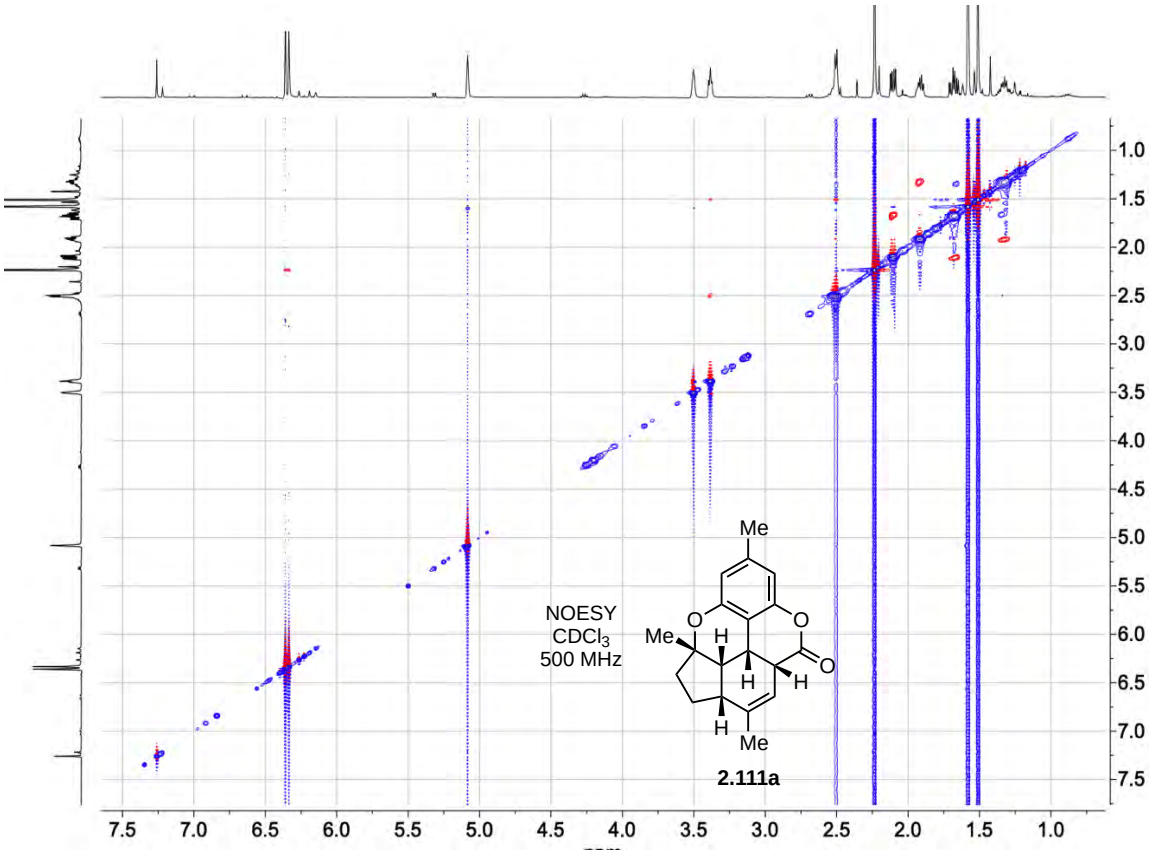
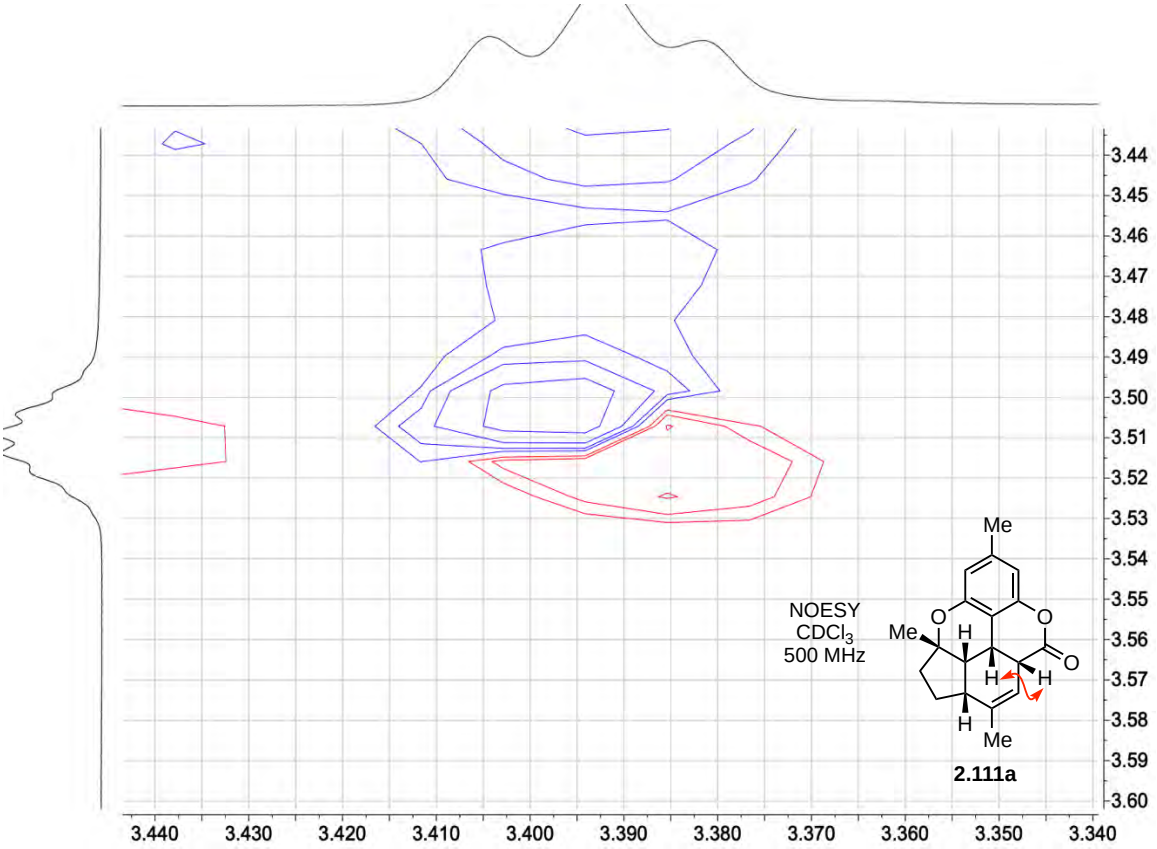
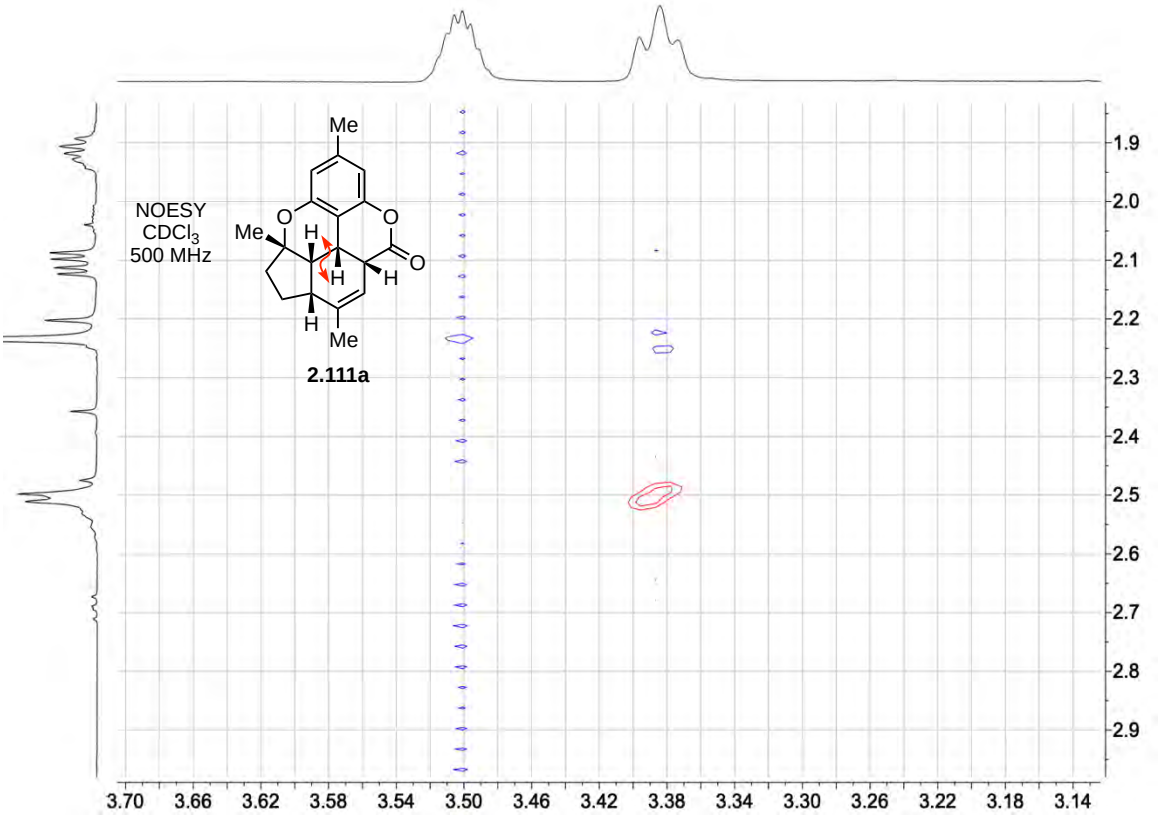
3.5
3.0
2.5
2.0
1.5
1.0


HSQC
CDCl3
500 MHz
Me
Me
O
H
O
O
H
H
H
H
Me
2.111a
20
30
40
50
60
70
80
90
100
110
120
130
140
150
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

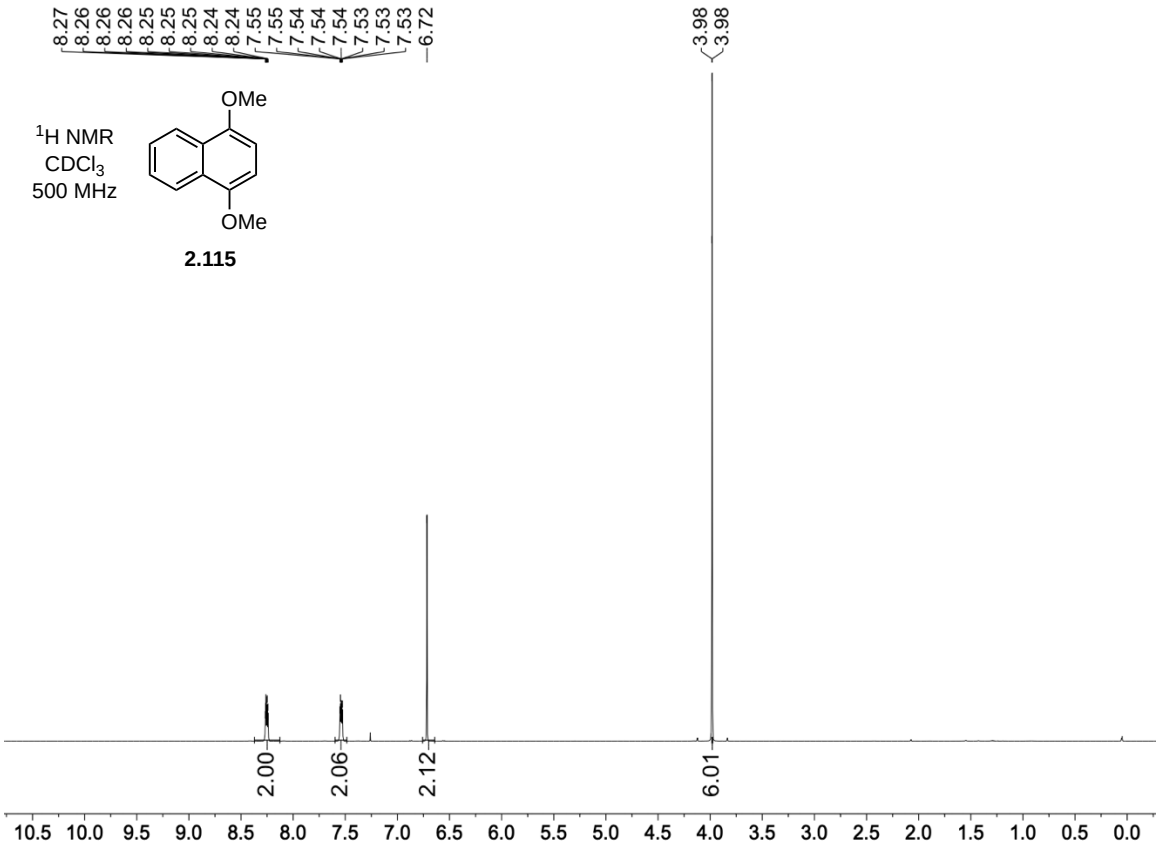

HMBC
CDCl3
500 MHz
Me
O
H
Me
O
O
H
H
H
Me
2.111a

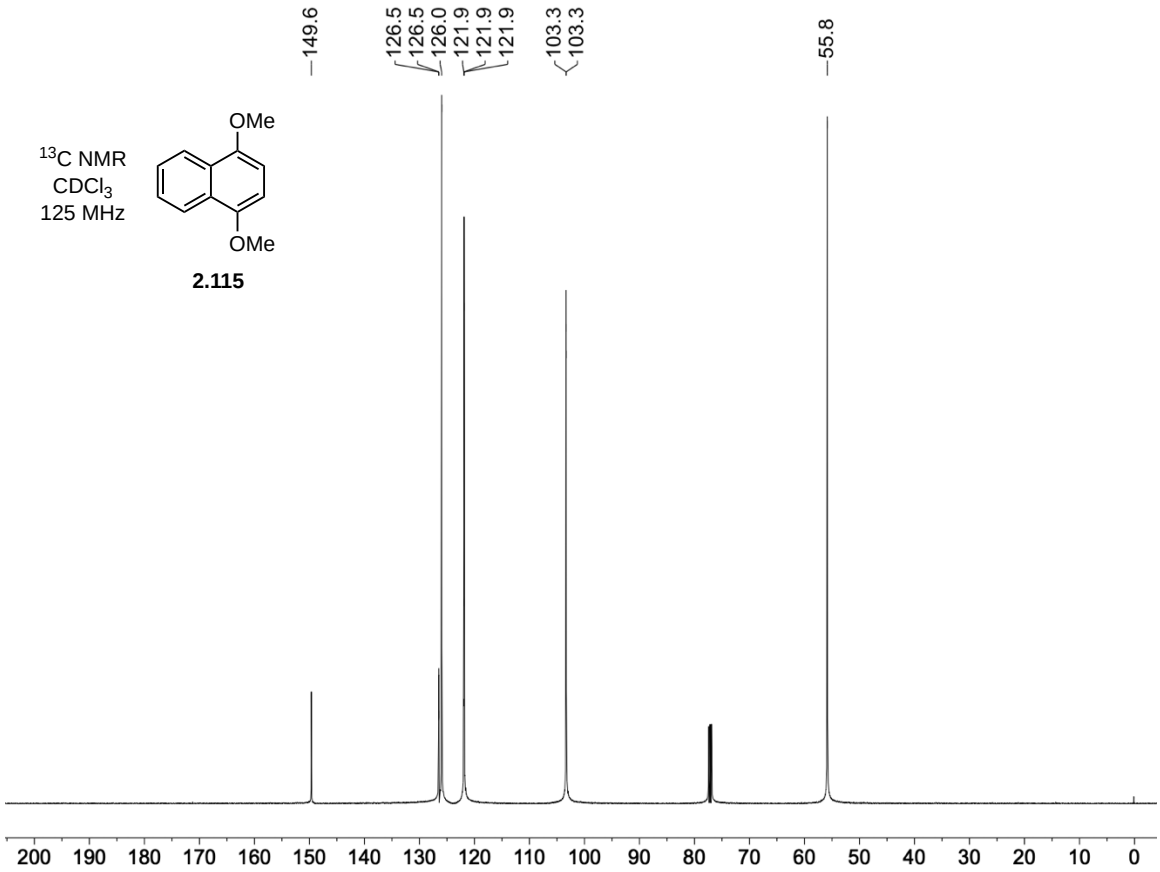

NOESY
CDCl3
500 MHz
Me
O
H
Me
O
O
H
H
H
Me
2.111a


NOESY
CDCl3
500 MHz
Me
O
O
Me
H
O
H
H
H
Me
2.111a
3.44
3.45
3.46
3.47
3.48
3.49
3.50
3.51
3.52
3.53
3.54
3.55
3.56
3.57
3.58
3.59
3.60
3.440
3.430
3.420
3.410
3.400
3.390
3.380
3.370
3.360
3.350
3.340

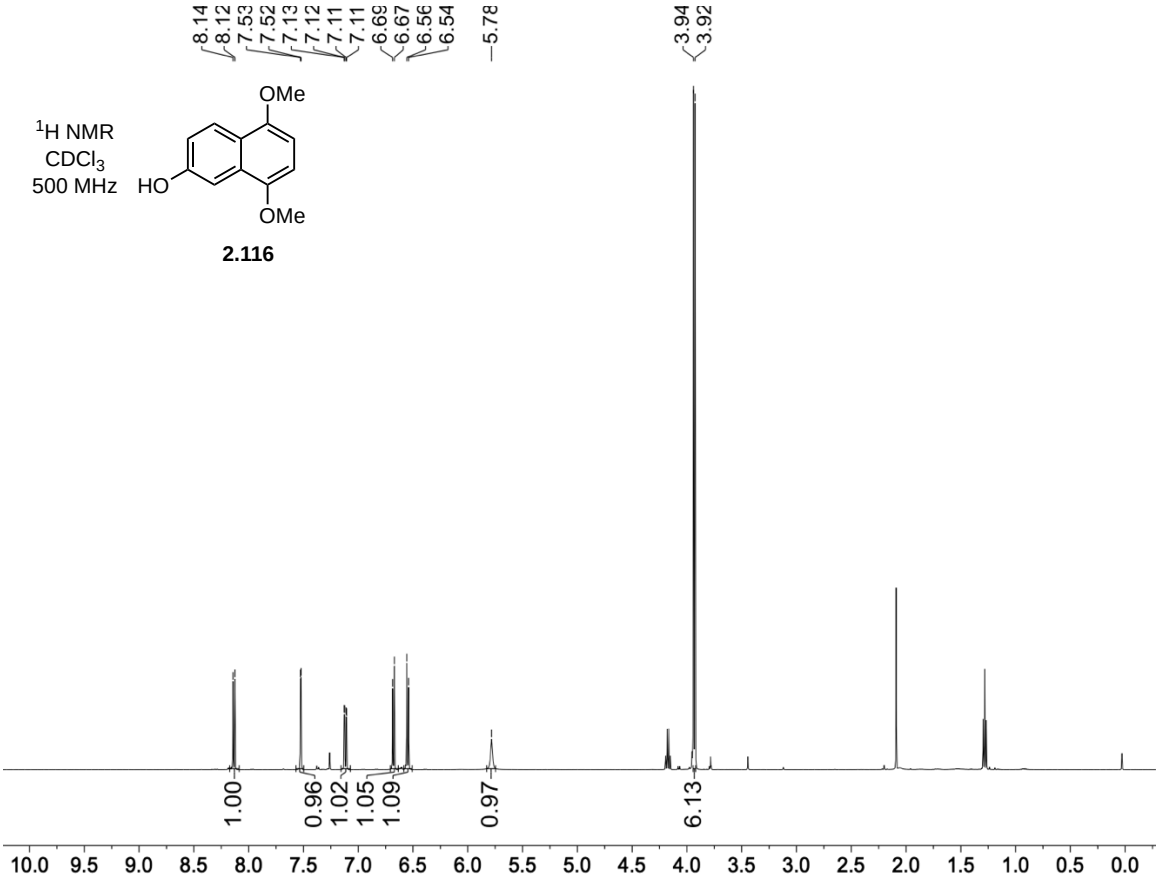

NOESY
CDCl3
500 MHz
Me
O
O
Me
H
O
H
H
H
Me
2.111a
1.9
2.0
2.1
2.2
2.3
2.4
2.5
2.6
2.7
2.8
2.9
3.70
3.66
3.62
3.58
3.54
3.50
3.46
3.42
3.38
3.34
3.30
3.26
3.22
3.18
3.14

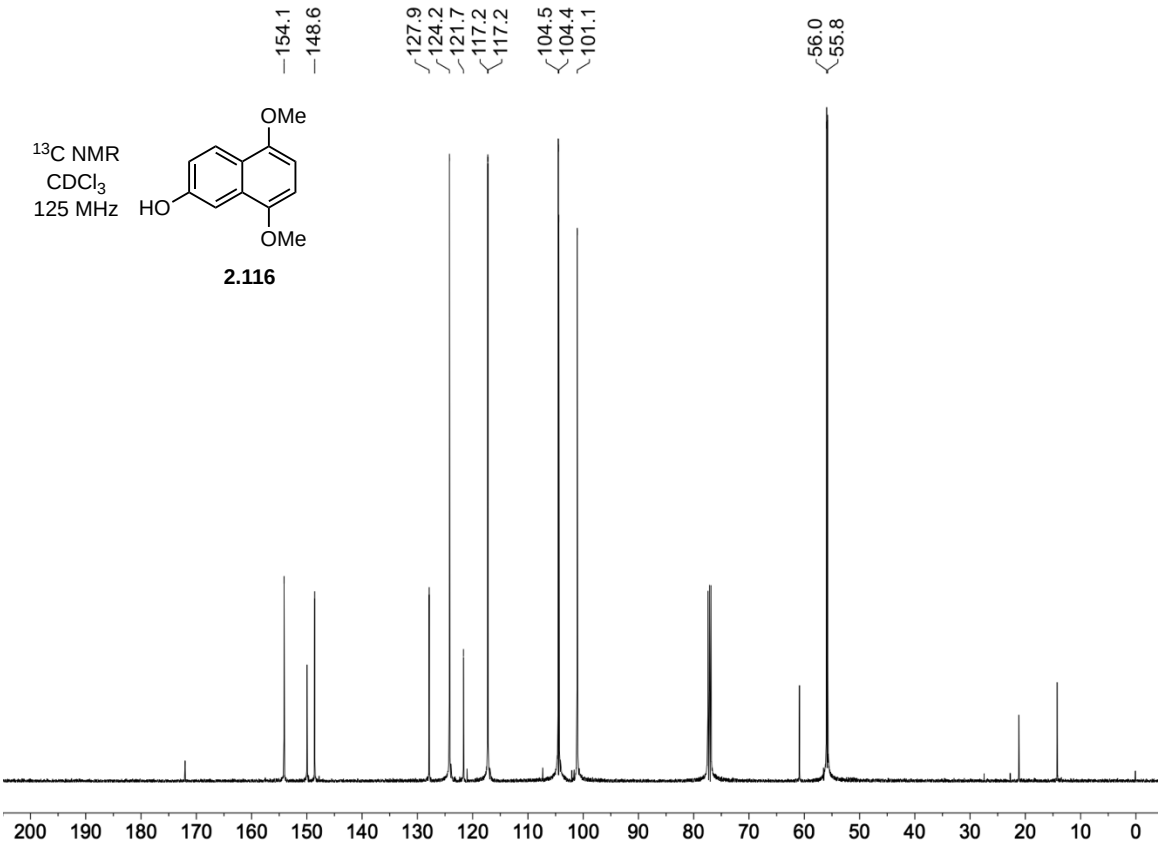
Data for 2.115



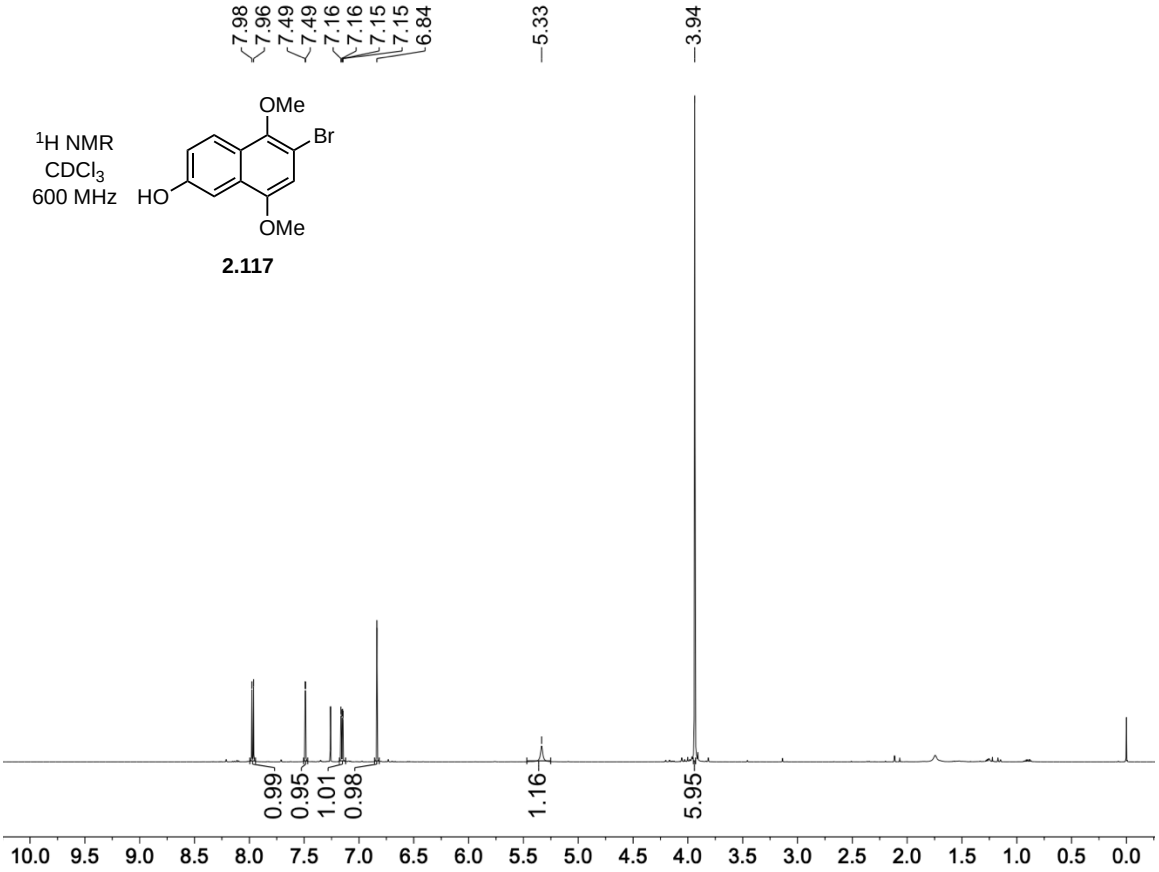


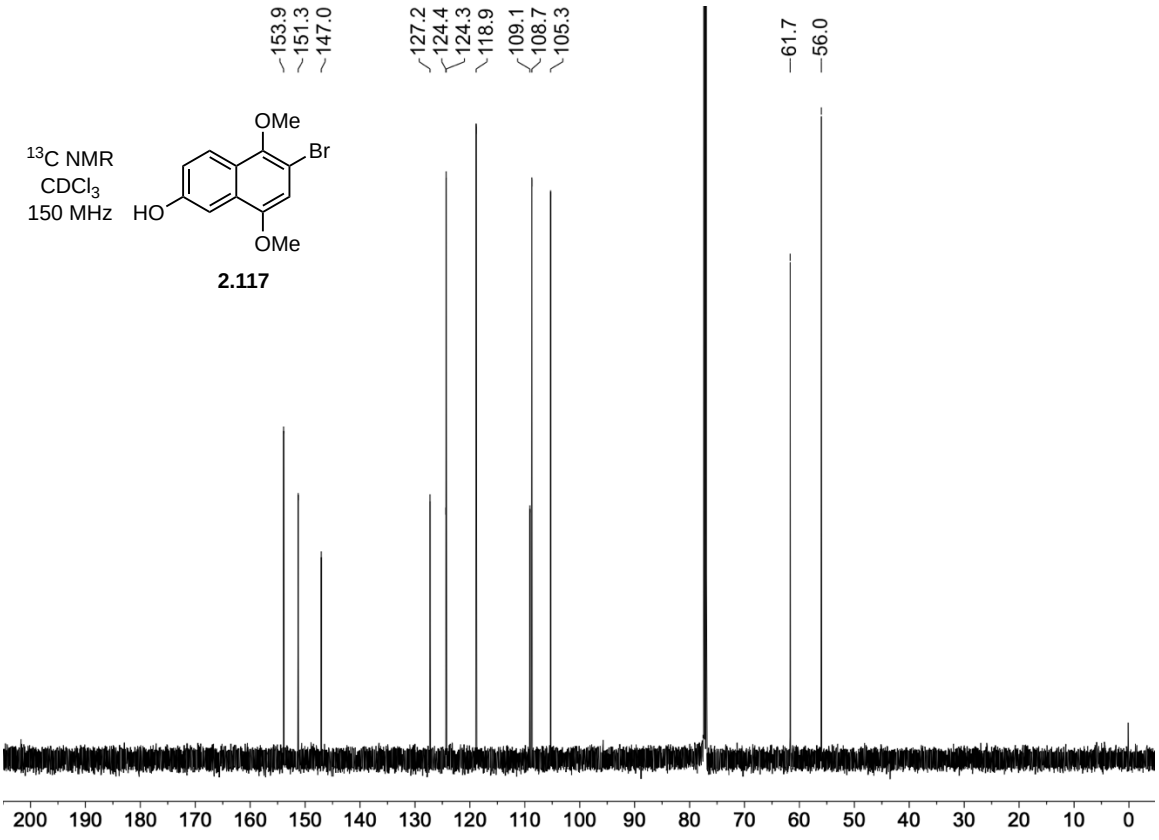
Data for 2.116



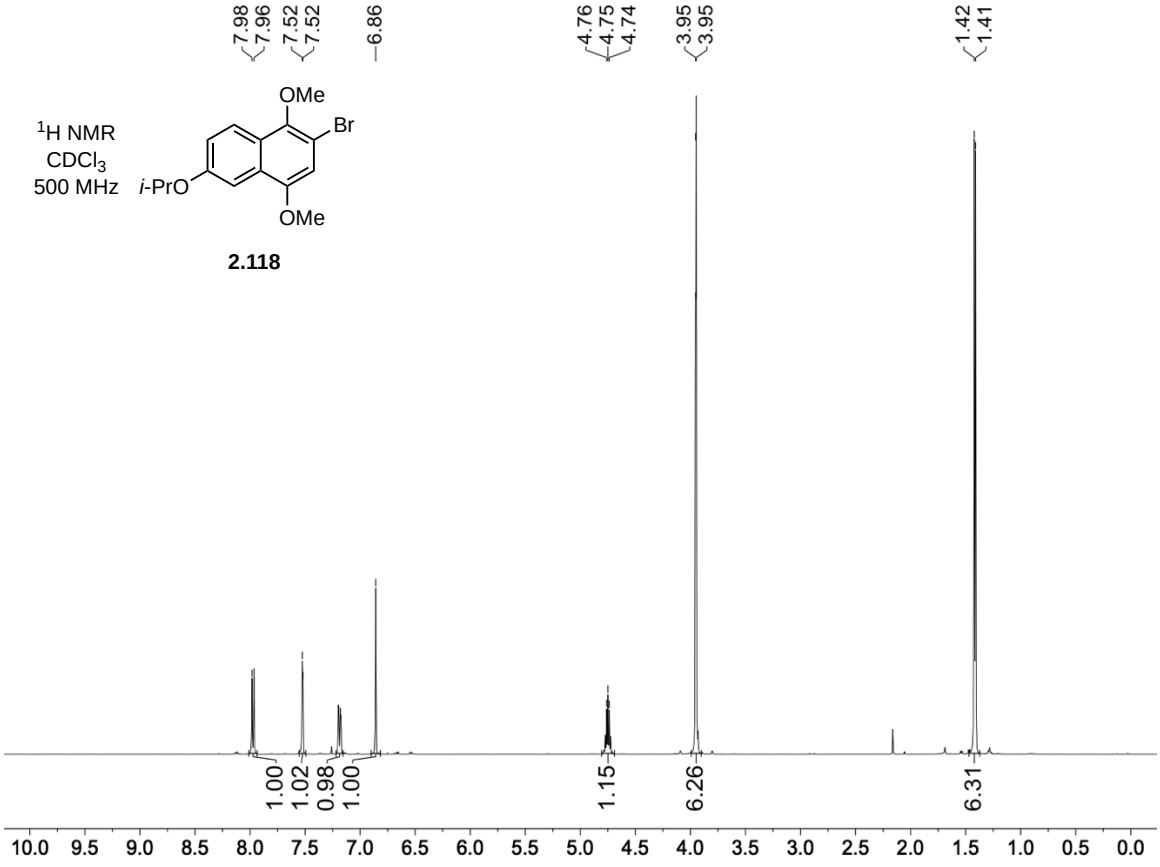


Data for 2.117

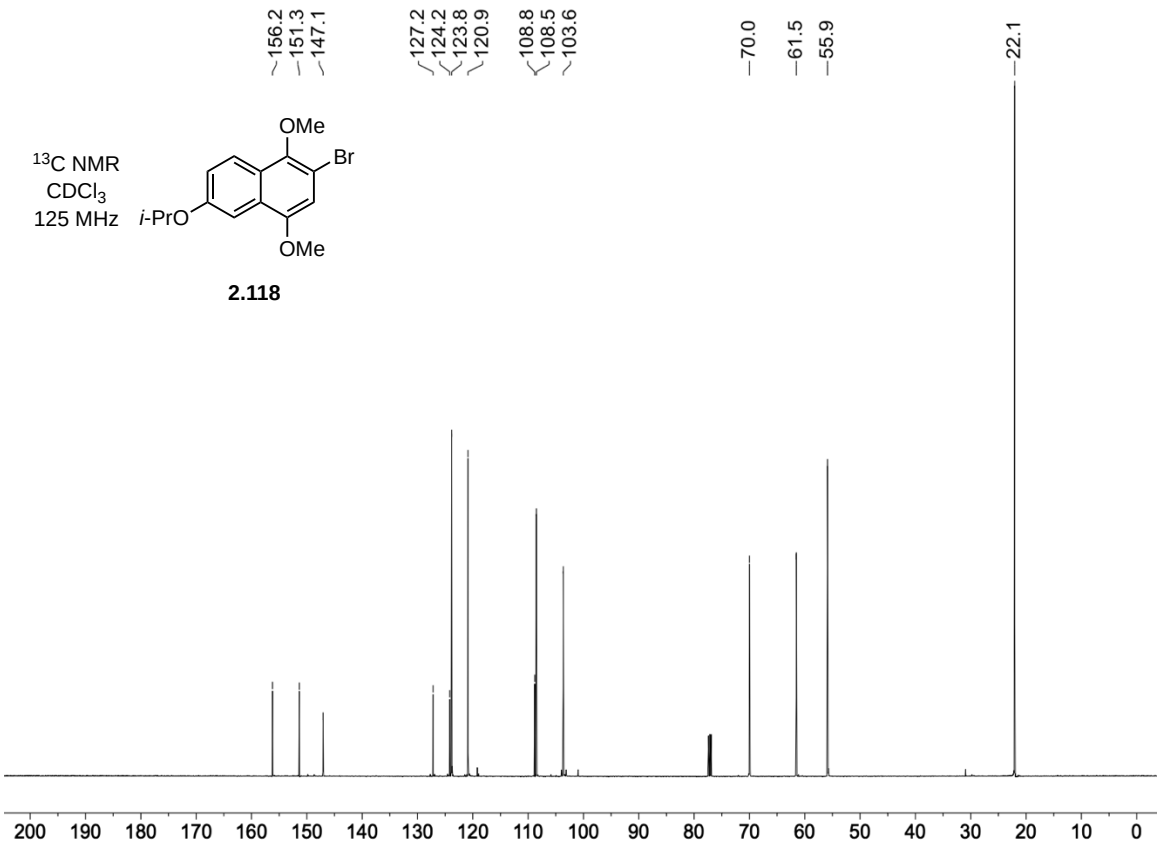




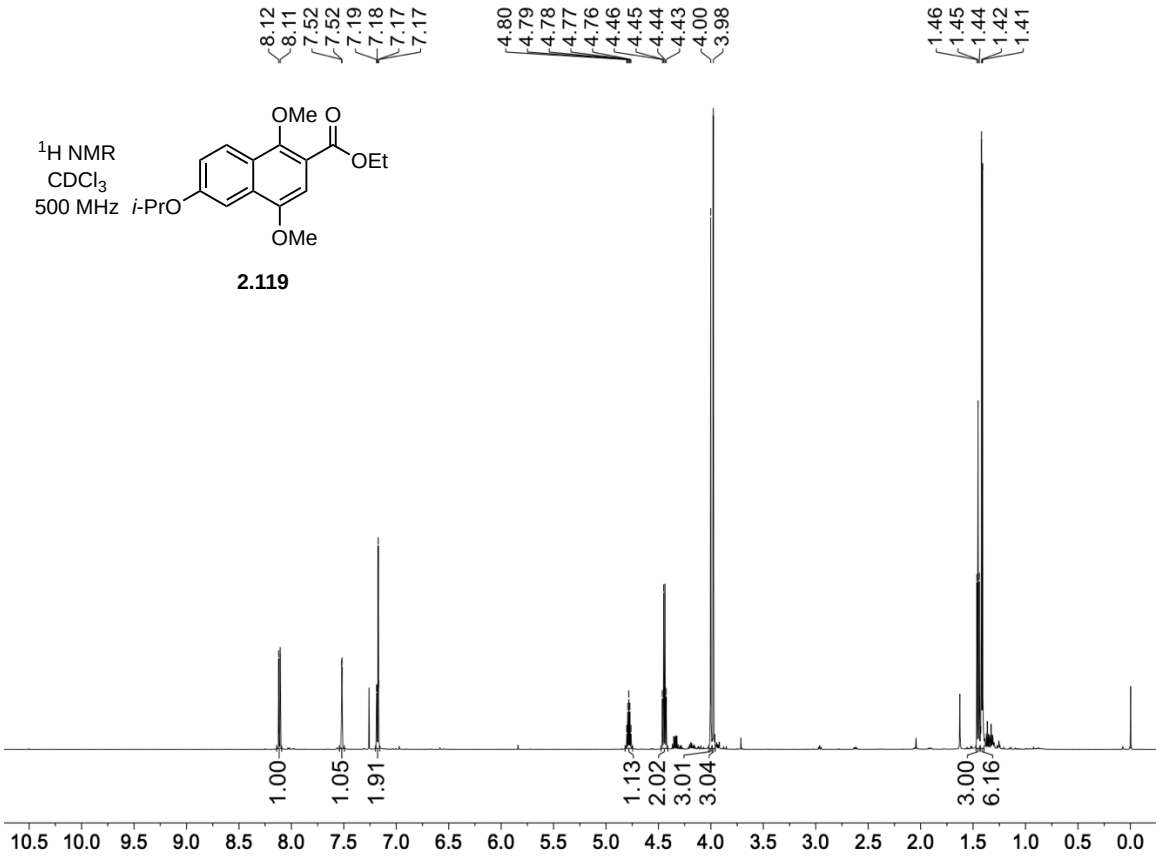
Data for 2.118

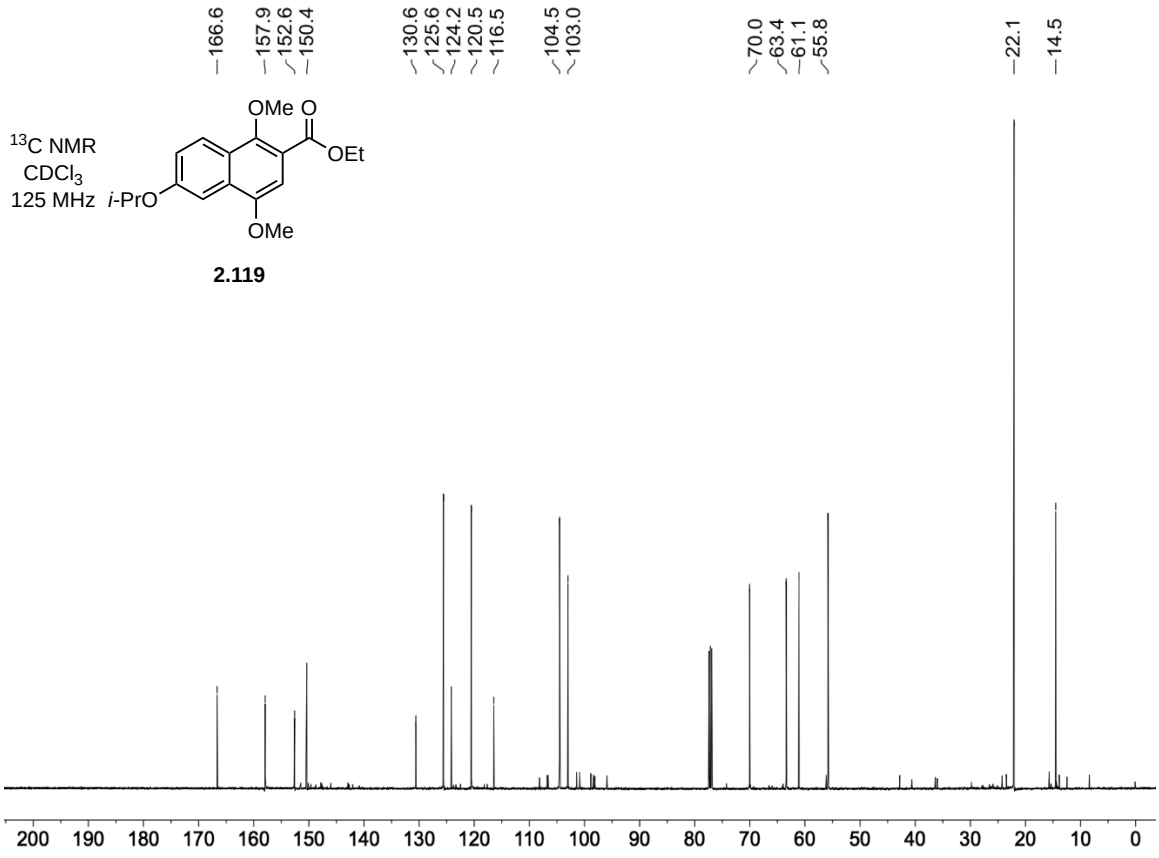


2.118

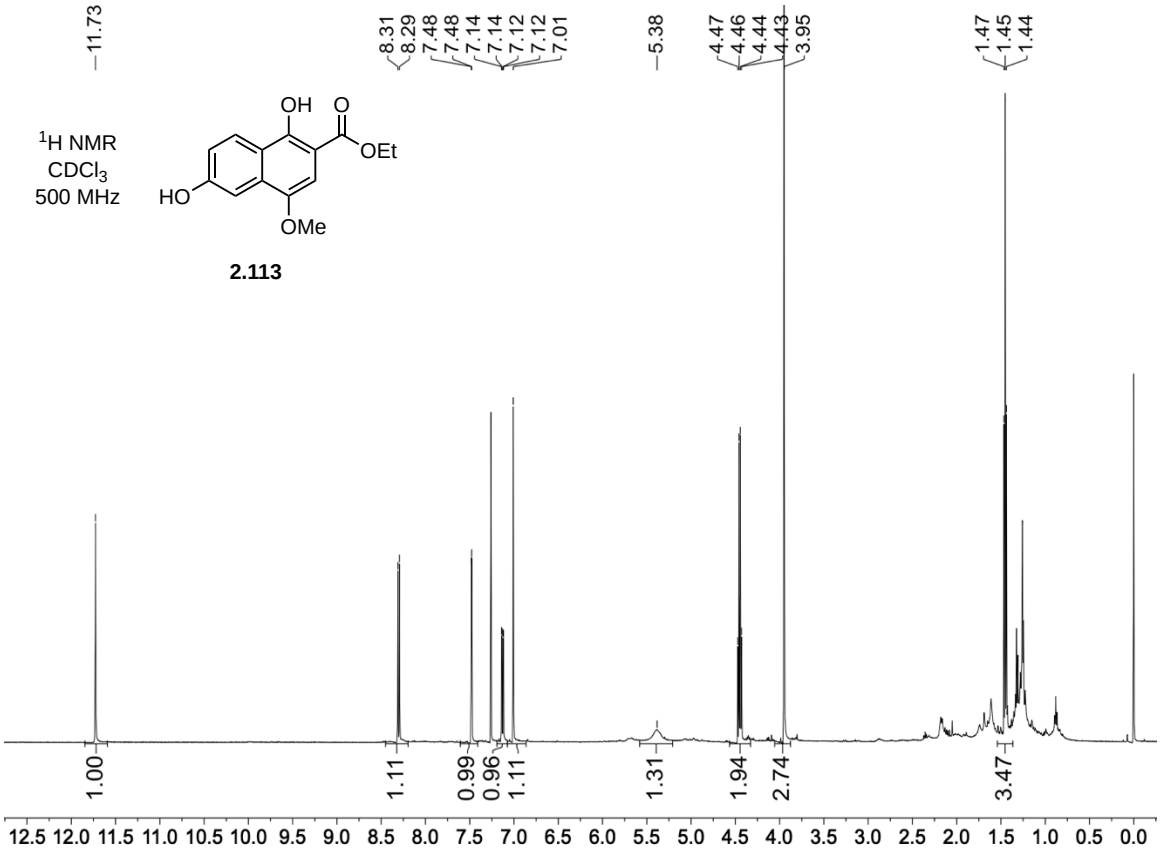


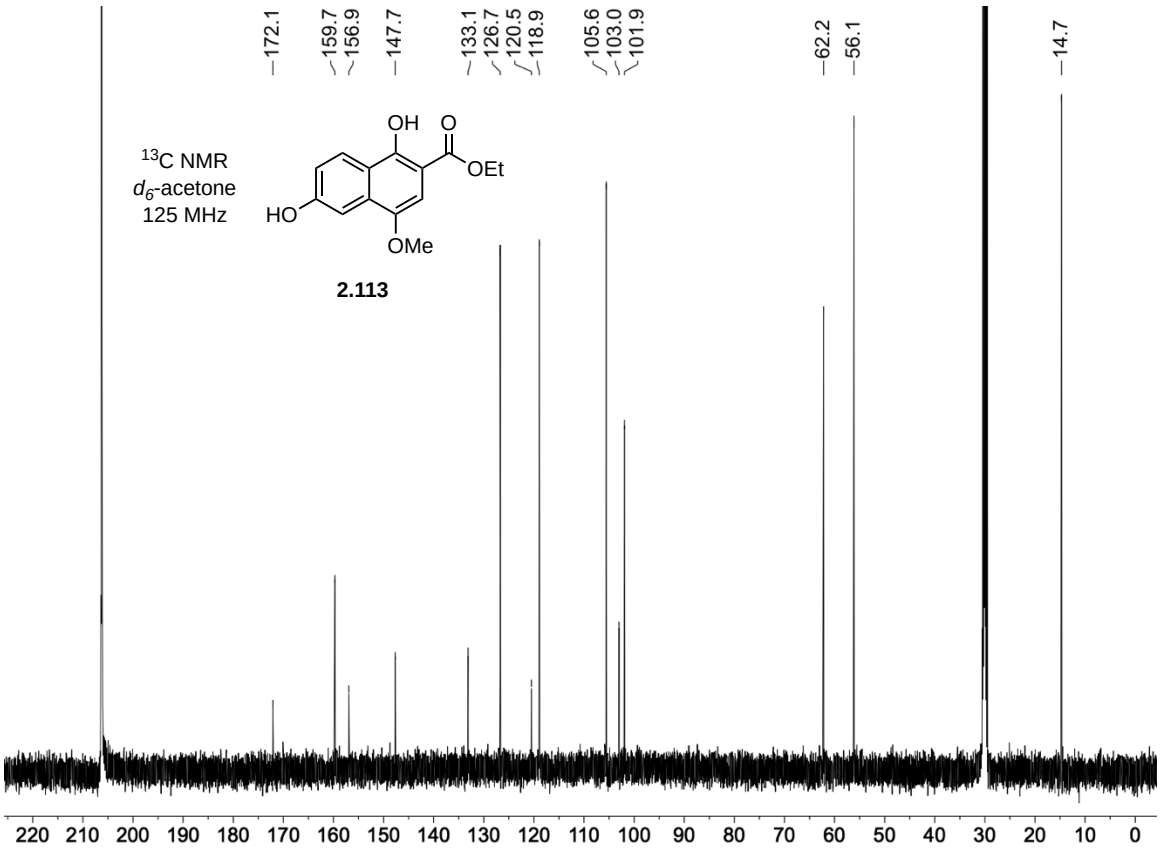
Data for 2.119





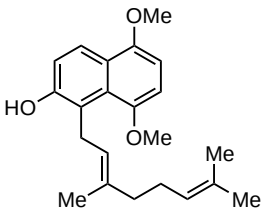
Data for 2.113





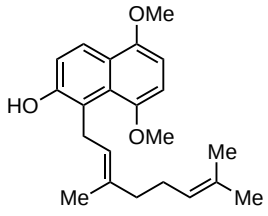
Data for 2.121

^{1}H NMR
$CDCl_3$
500 MHz



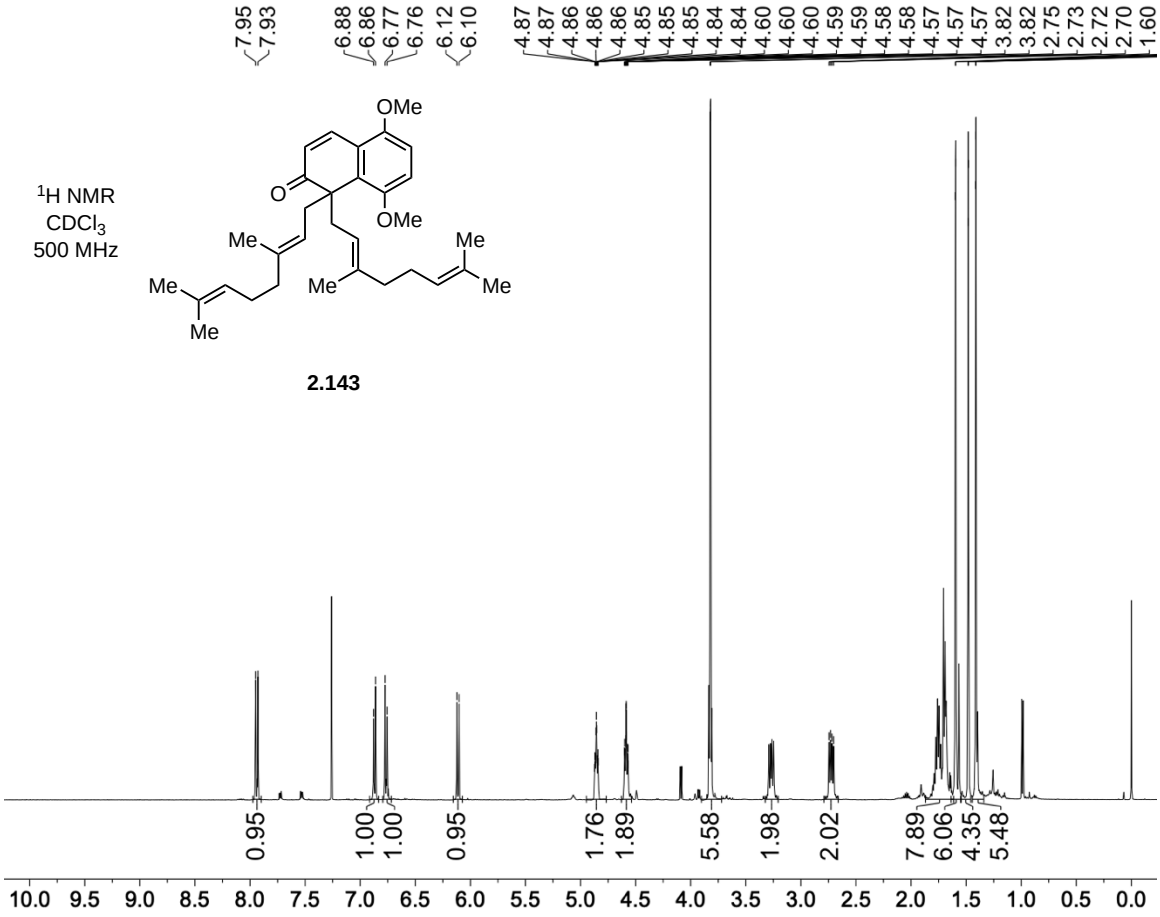
2.121

^{13}C NMR
$CDCl_3$
125 MHz

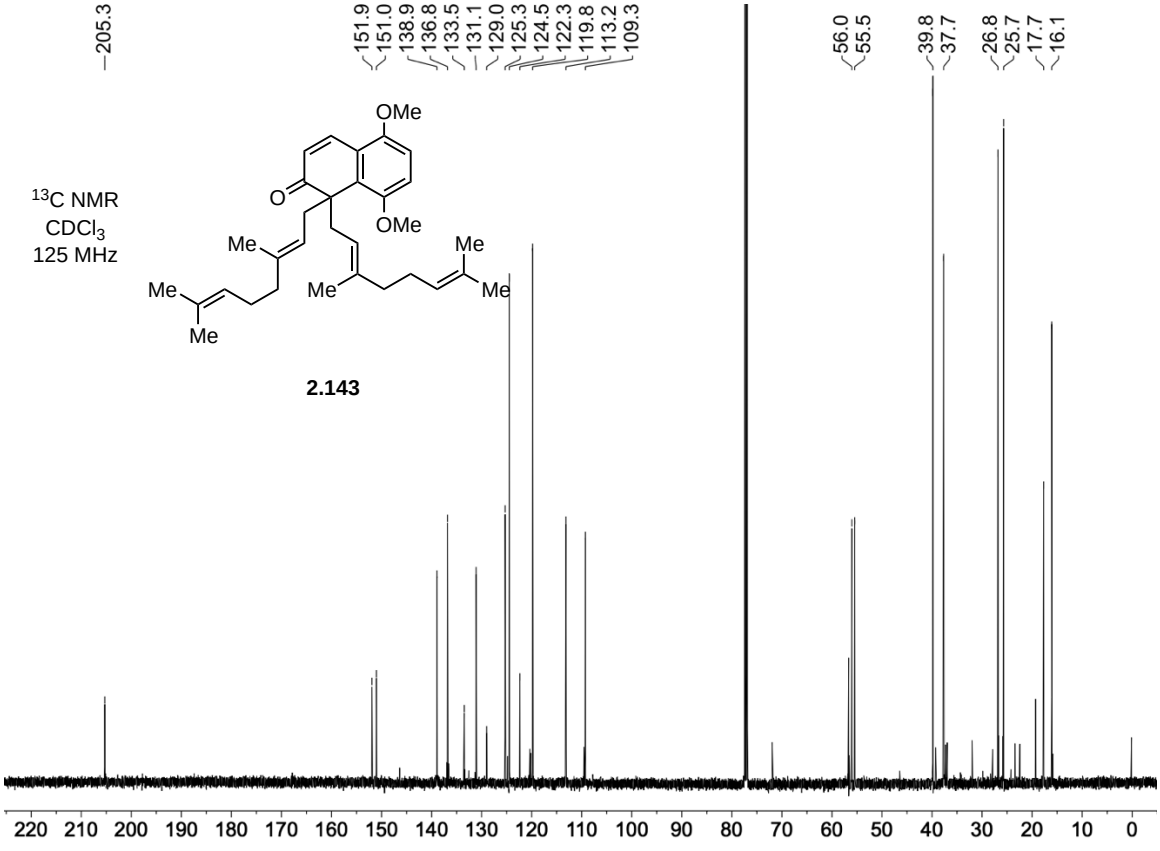


2.121

Data for 2.143



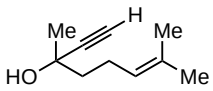
2.143



2.143

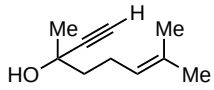
Data for 2.123

^{1}H NMR
$CDCl_3$
500 MHz



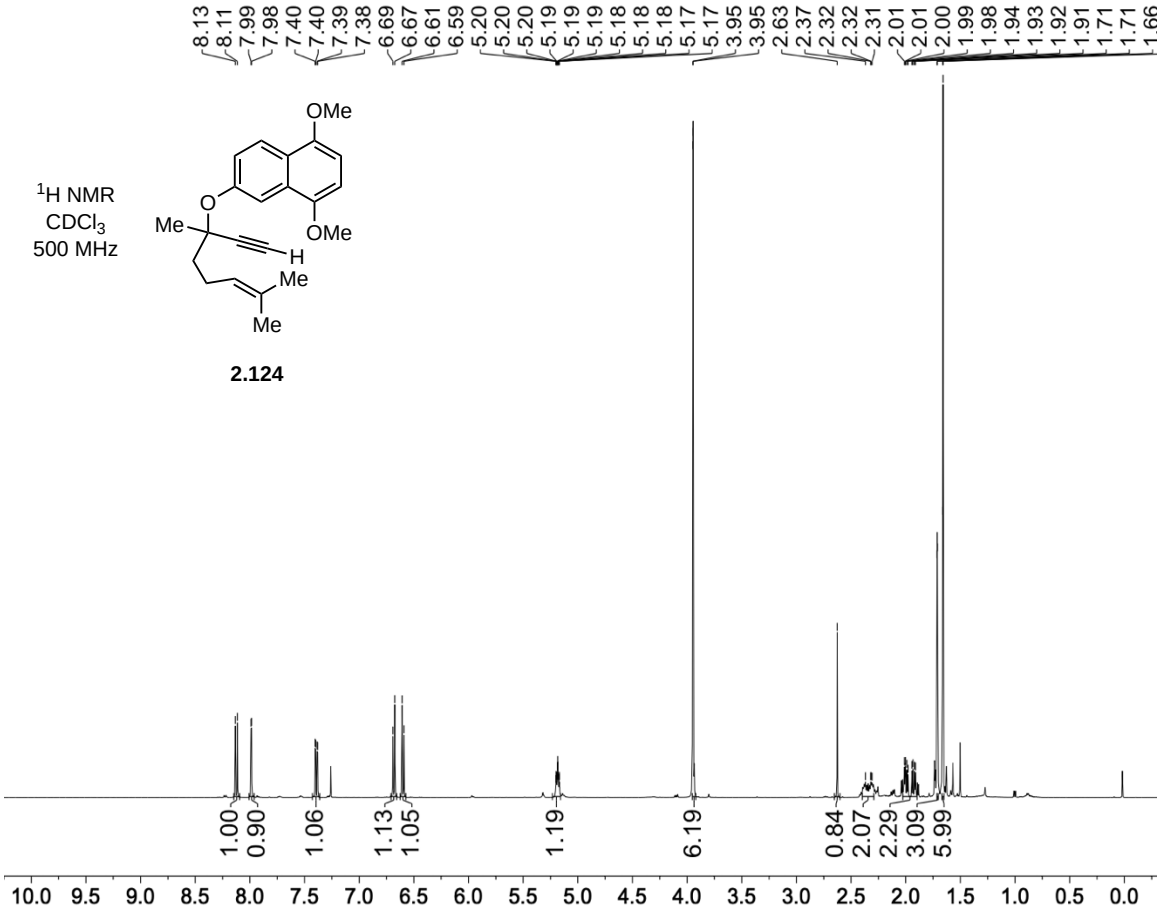
2.123

^{13}C NMR
$CDCl_3$
125 MHz

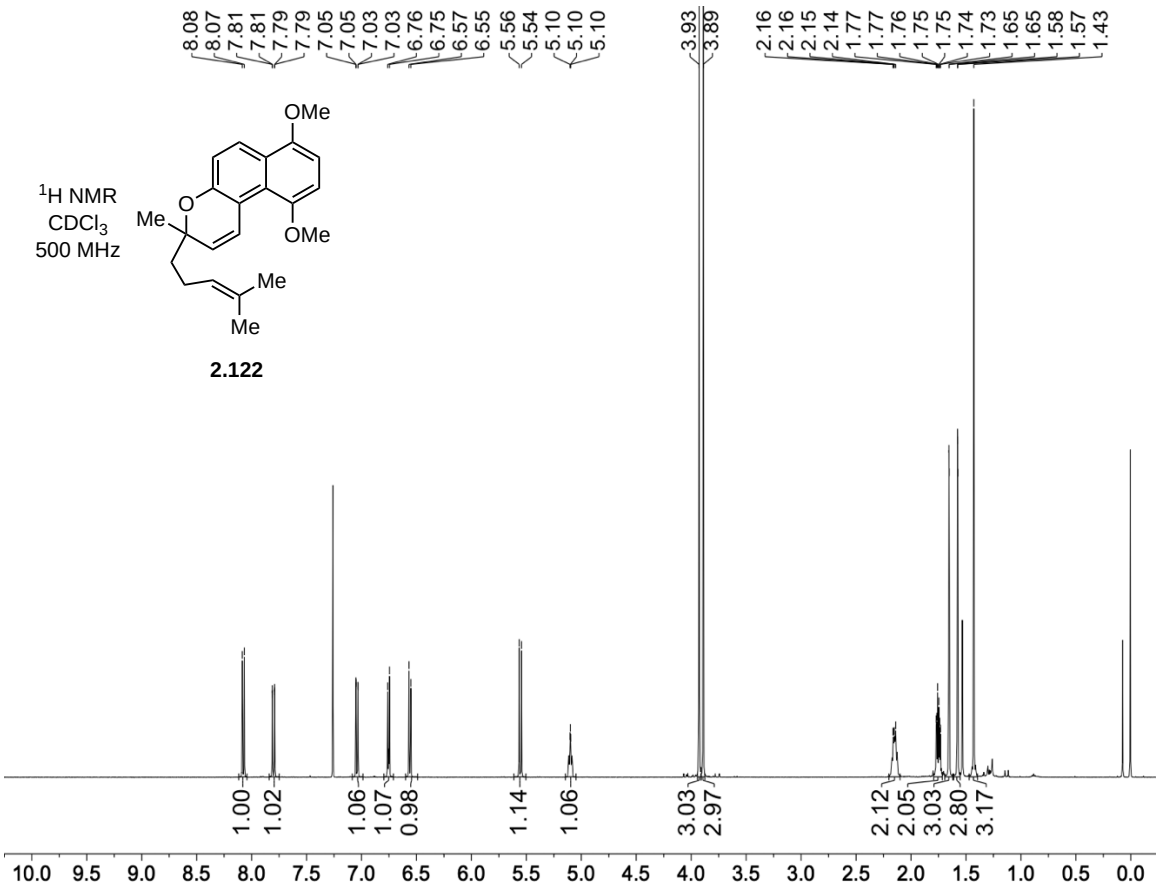


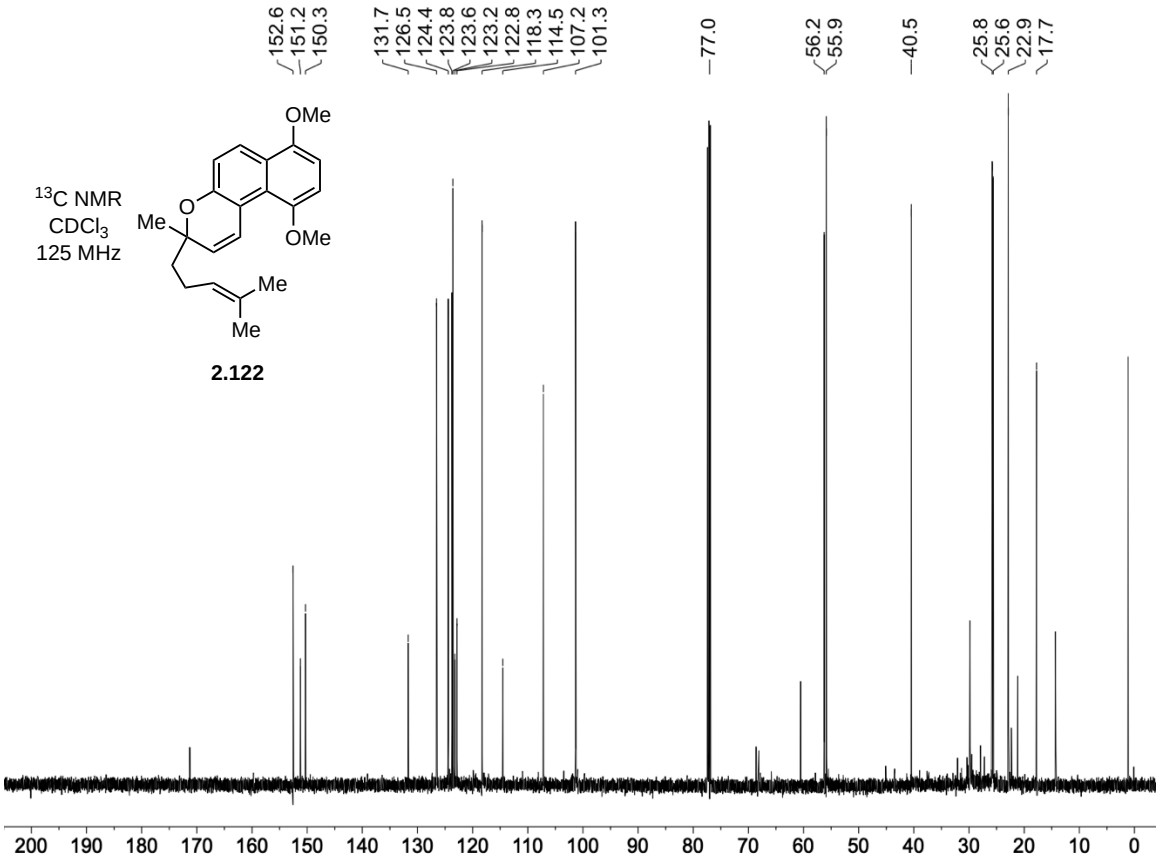
2.123

Data for 2.124

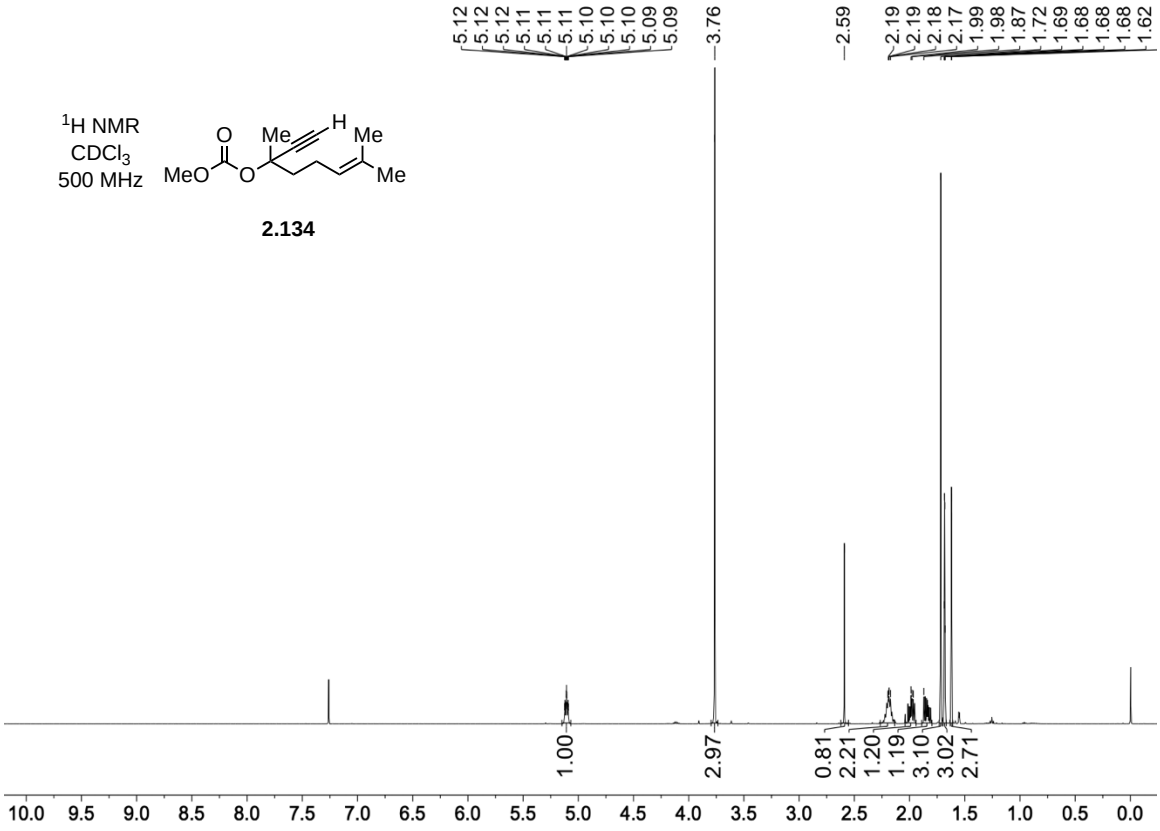


Data for 2.122



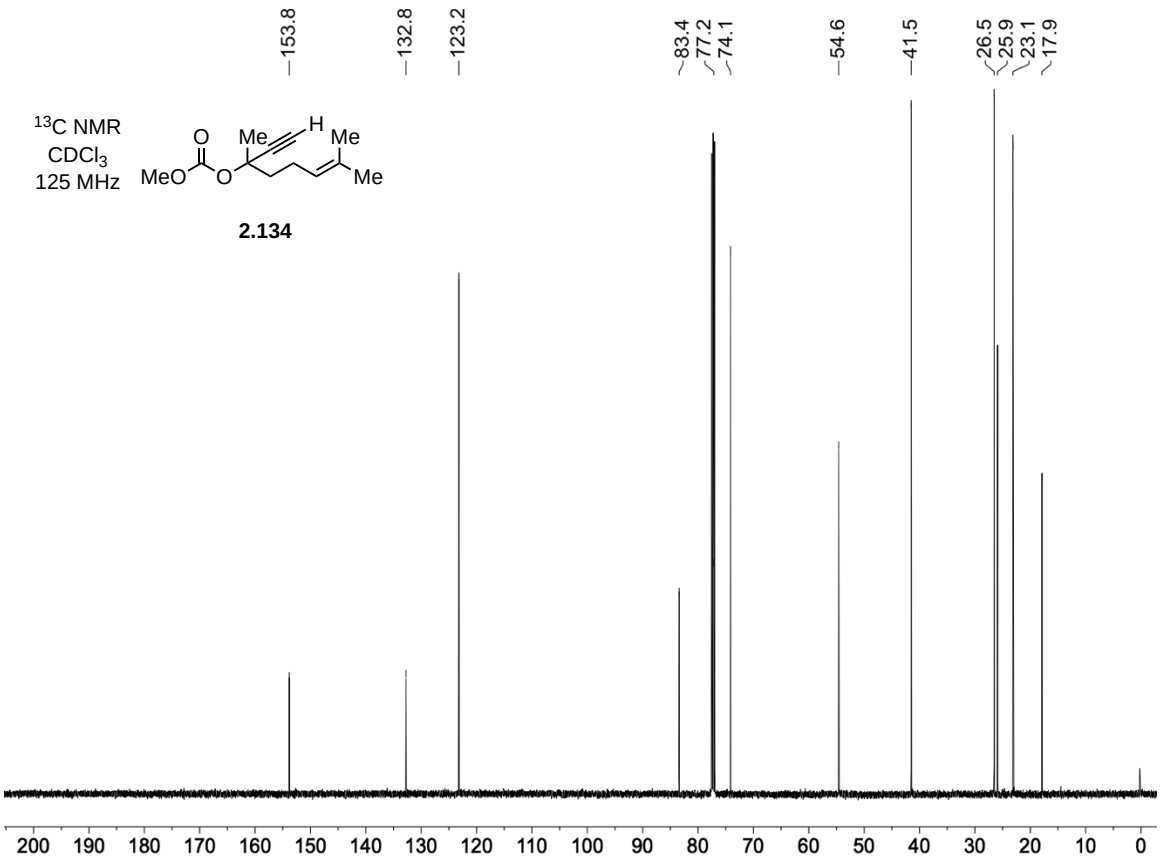


Data for 2.134



^{1}H NMR
$CDCl_3$
500 MHz

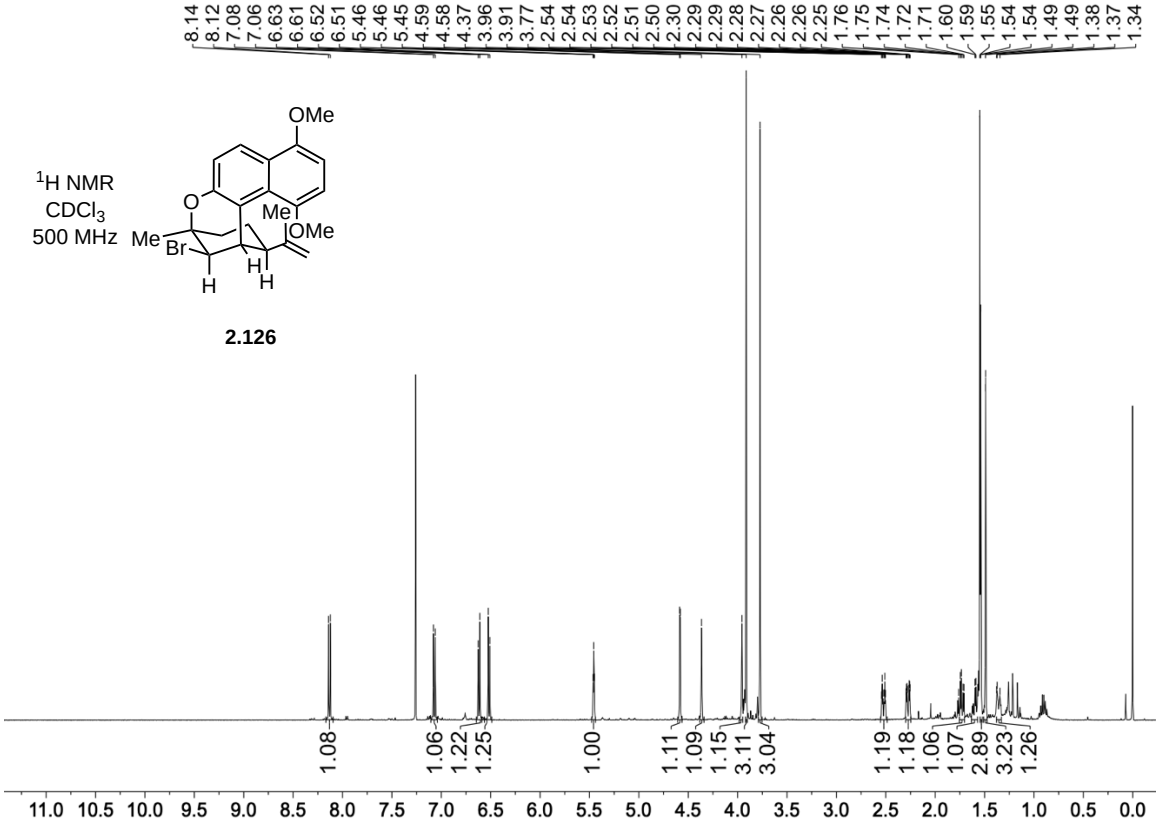
2.134



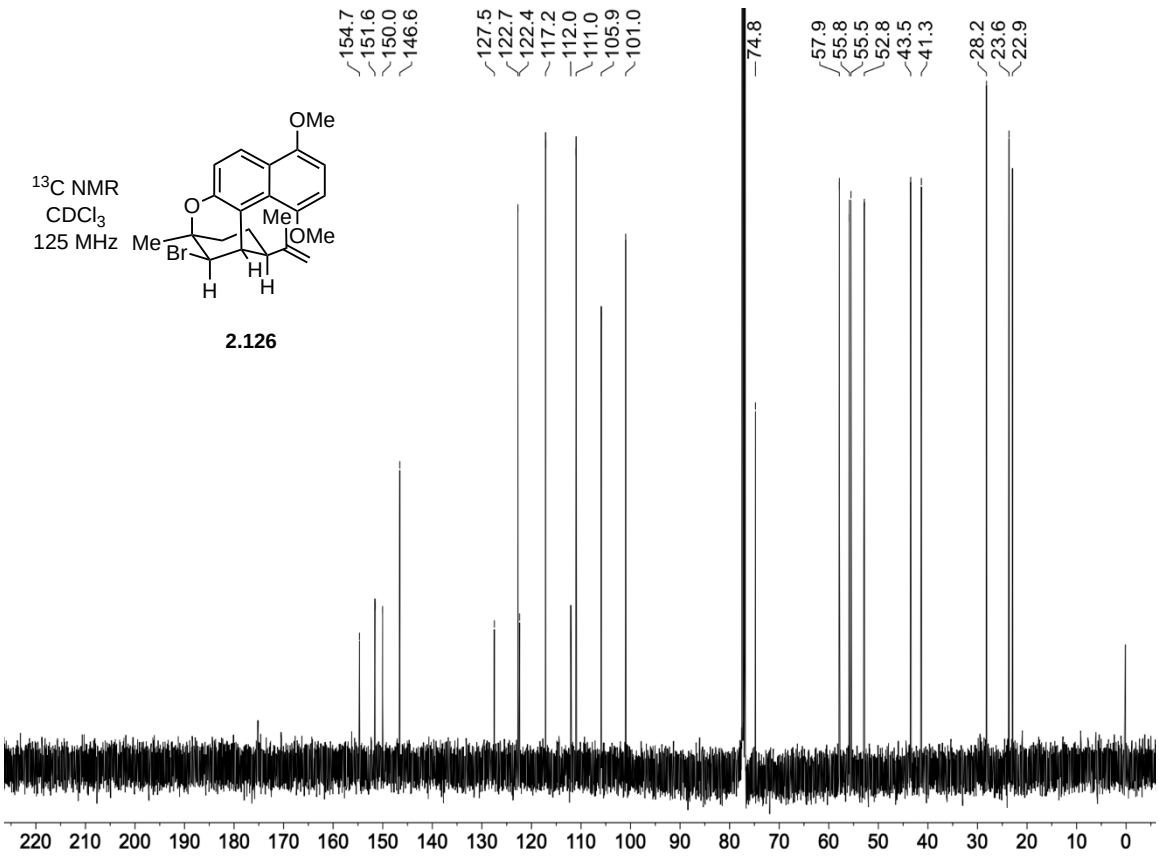
^{13}C NMR
$CDCl_3$
125 MHz

2.134

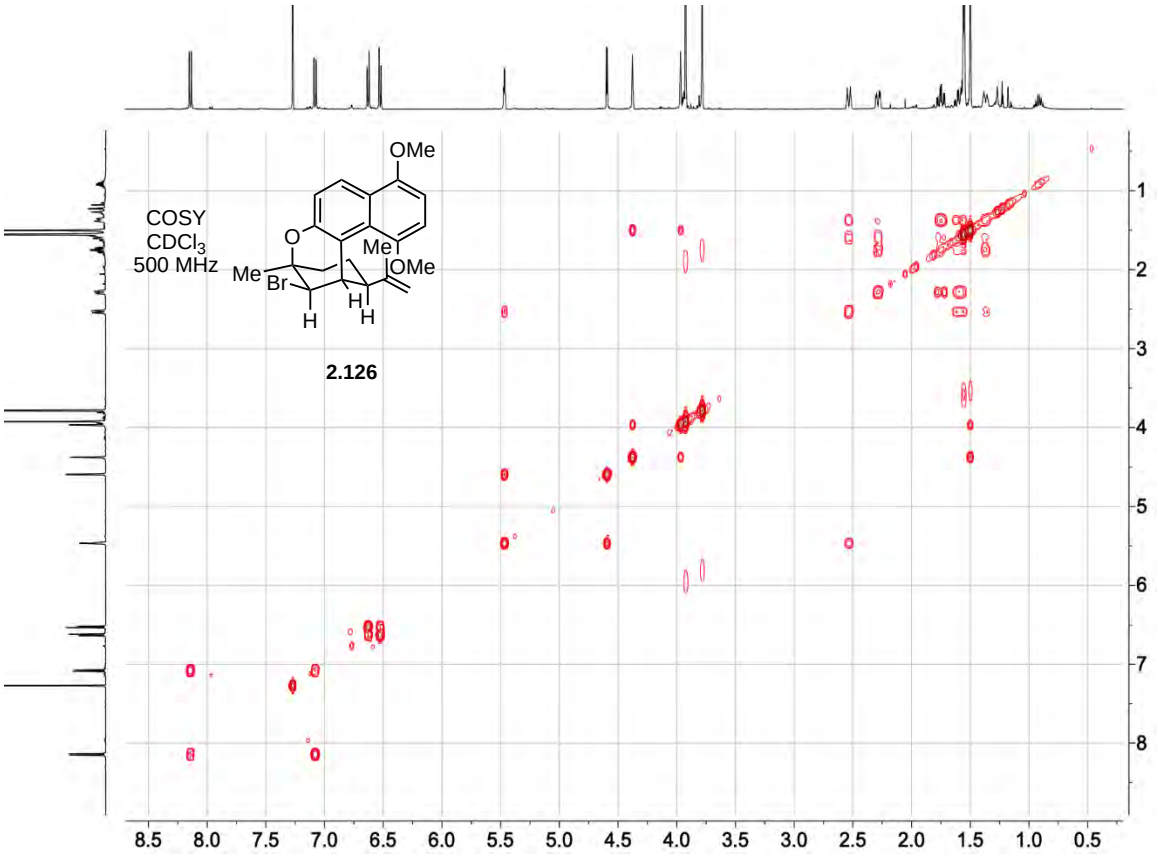
Data for 2.126



2.126



2.126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500 MHz
OMe
Me
O
Me
Br
OMe
H
H
H
2.126
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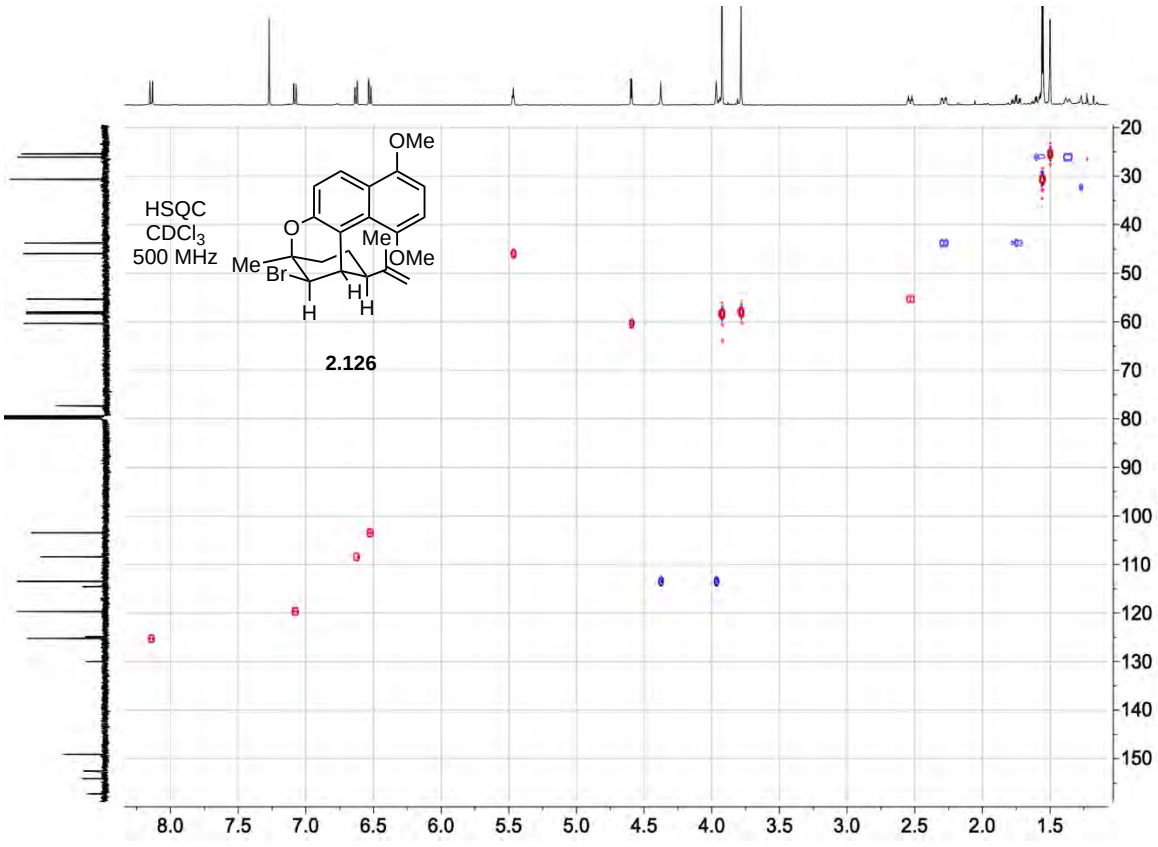
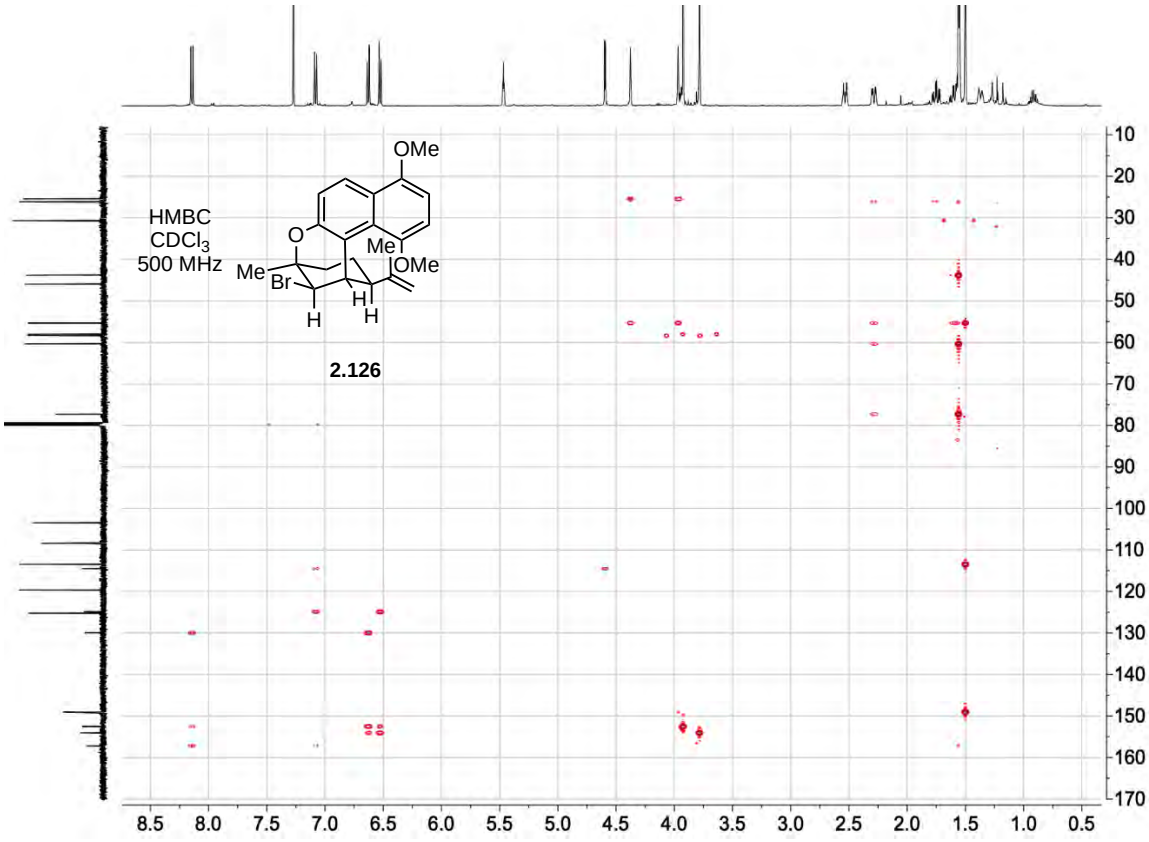
1 2 3 4 5 6 7 8


HSQC
CDCl3
500 MHz
OMe
Me
O
Me
Br
OMe
H
H
H
2.126
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
20 30 40 50 60 70 80 90 100 110 120 130 140 150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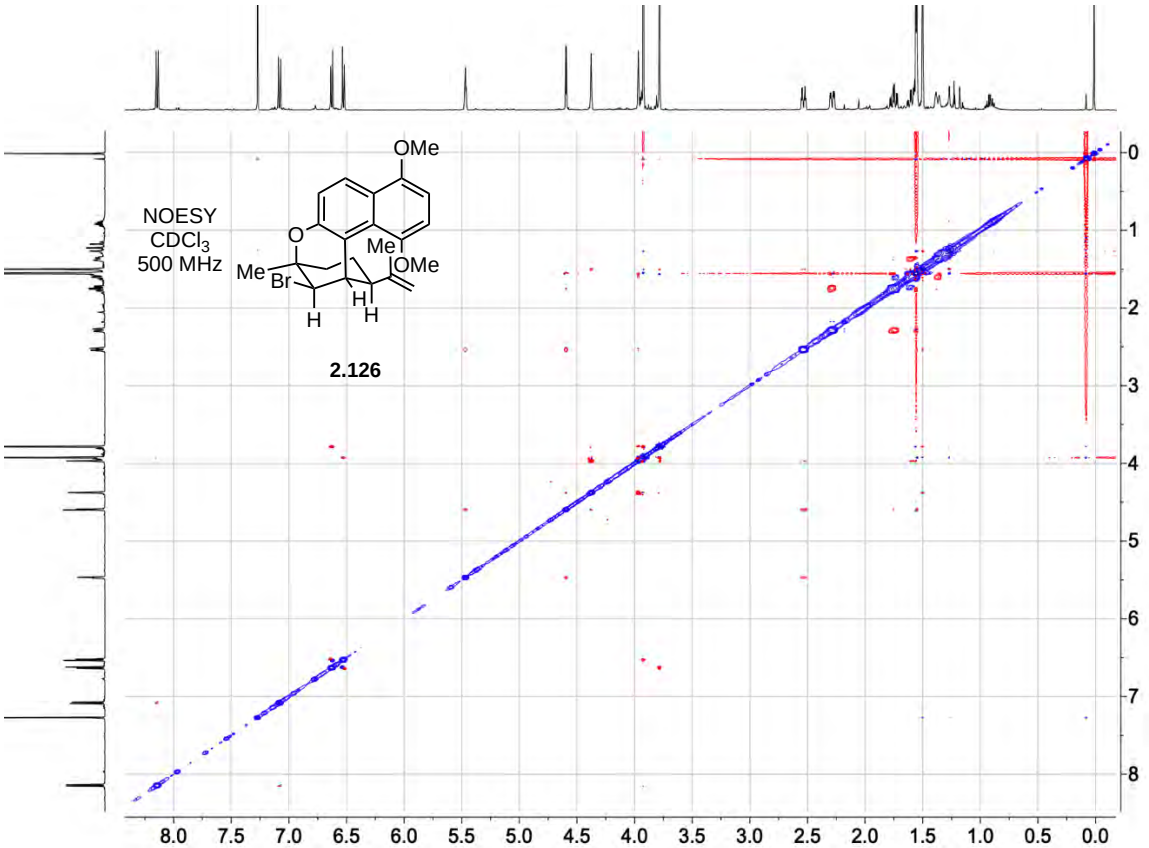
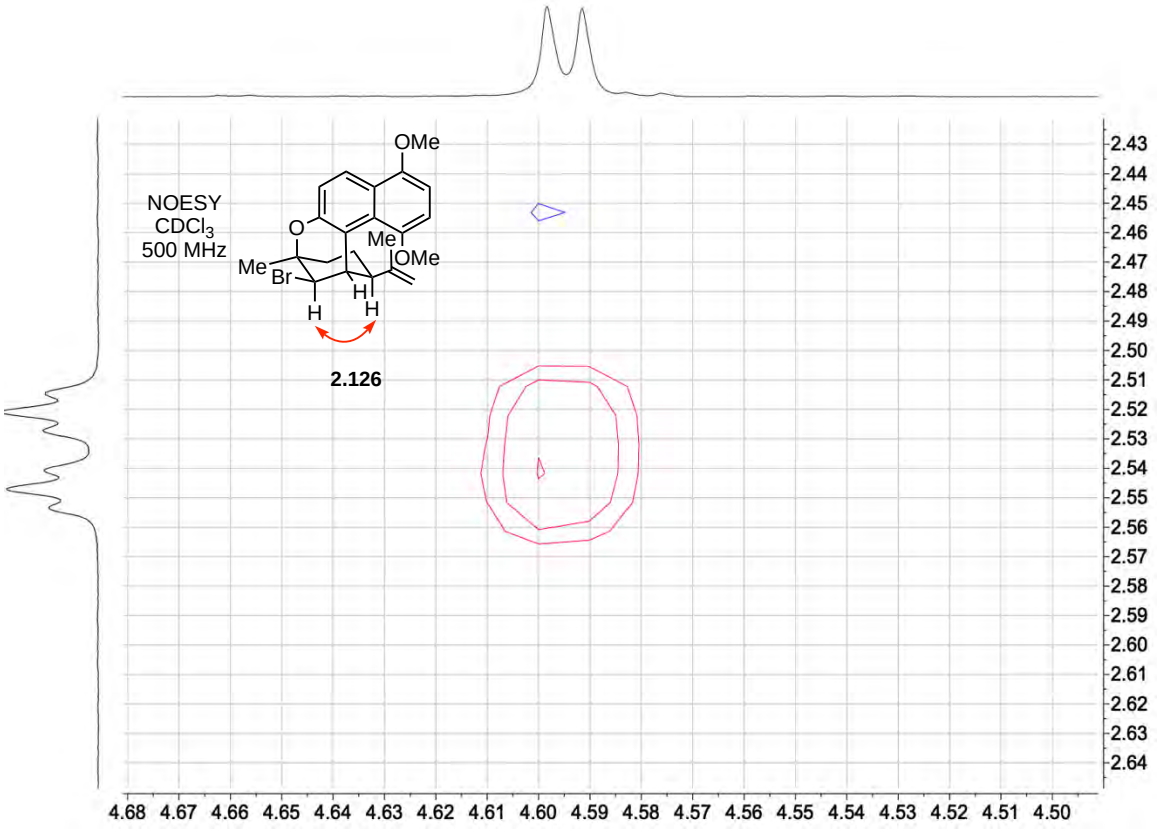
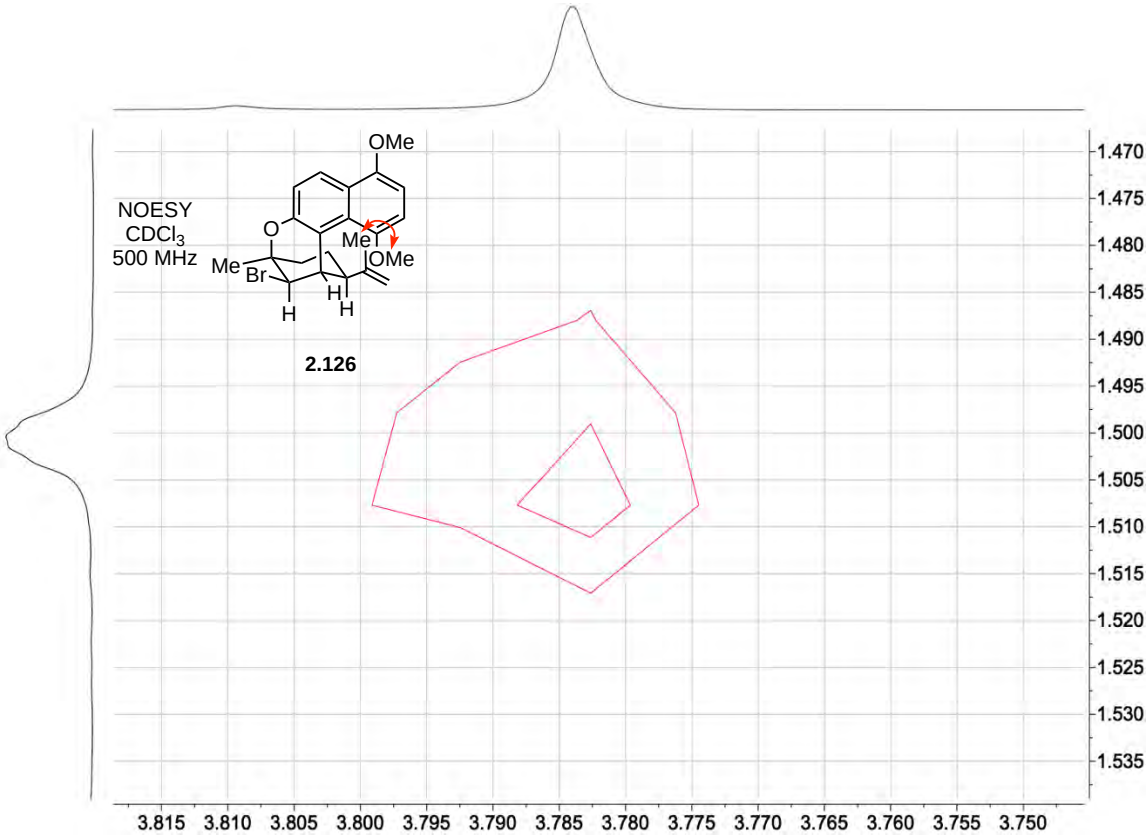
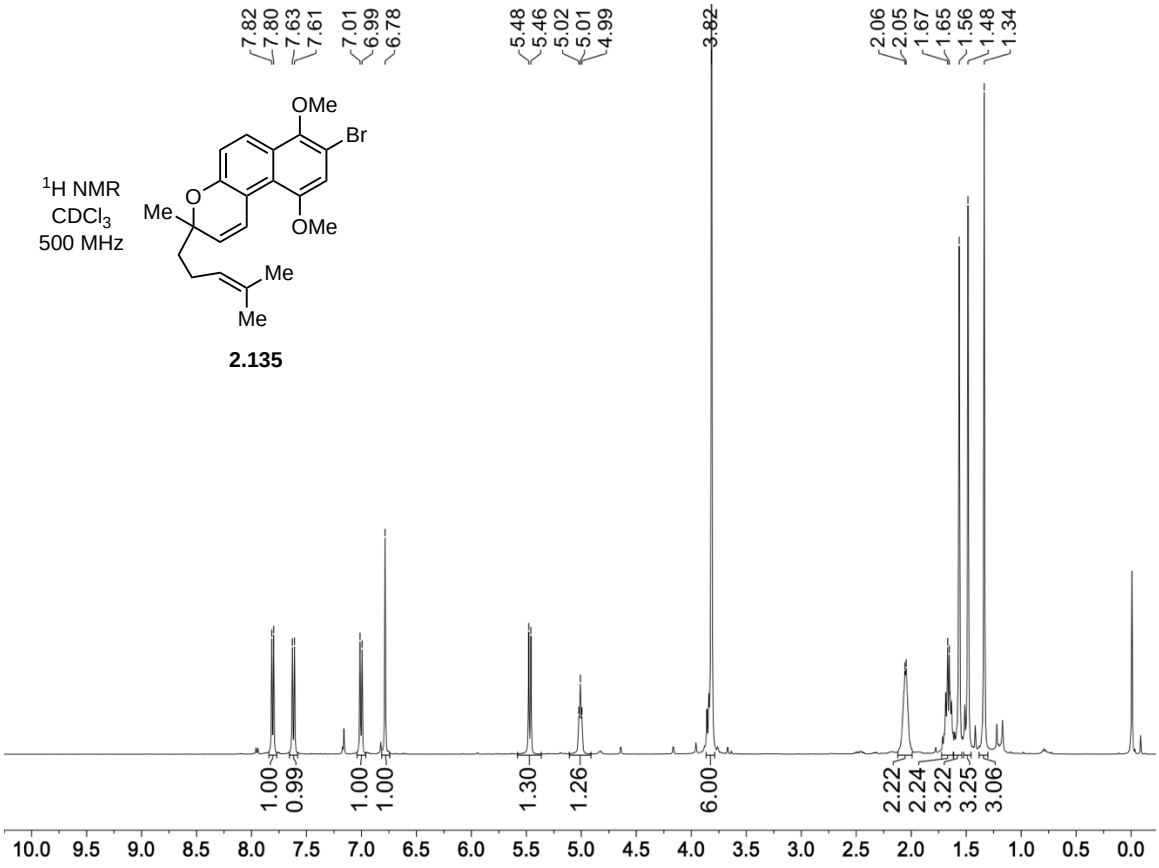
CDCl3
500 MHz
OMe
O
Me
Me
Br
OMe
H
H
H
2.126

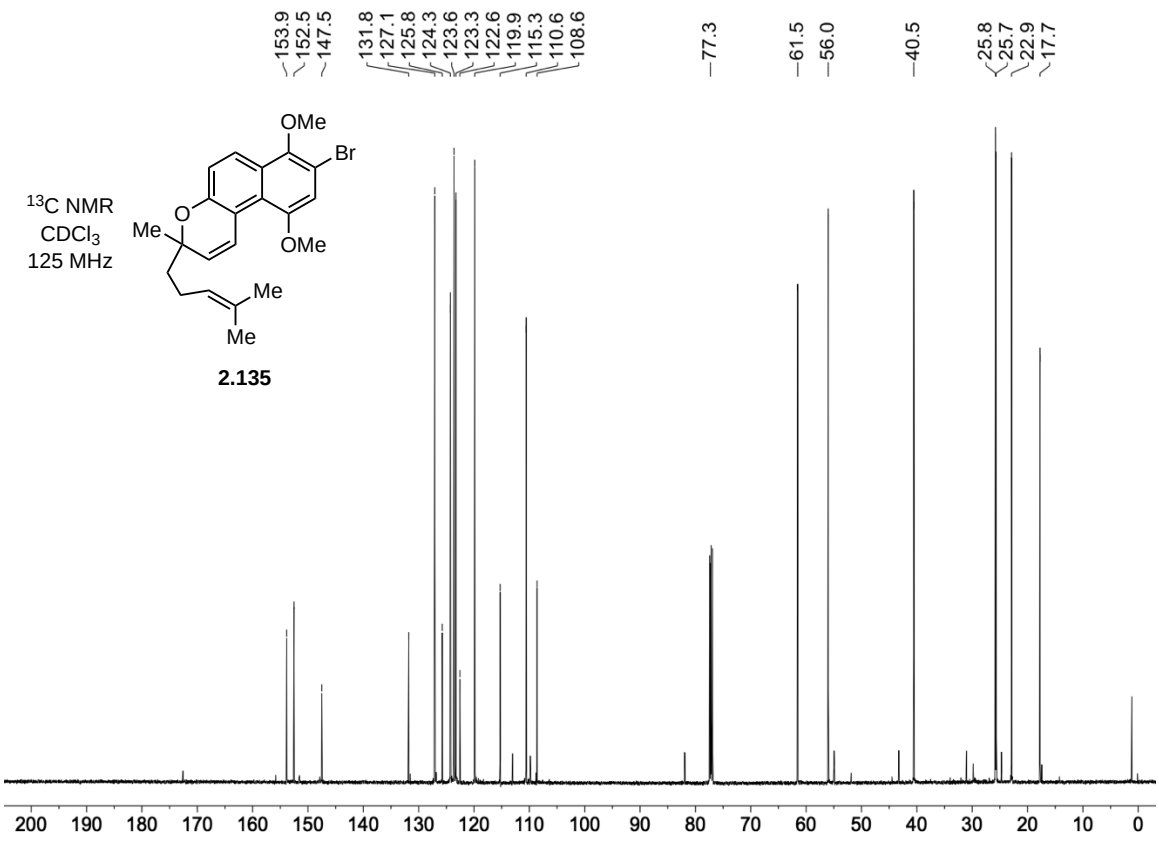

NOESY
CDCl3
500 MHz
OMe
O
Me
Me
Br
OMe
H
H
H
2.126


NOESY
CDCl3
500 MHz
OMe
O
Me
Me
Br
OMe
H
H
H
2.126
2.43
2.44
2.45
2.46
2.47
2.48
2.49
2.50
2.51
2.52
2.53
2.54
2.55
2.56
2.57
2.58
2.59
2.60
2.61
2.62
2.63
2.64
4.68 4.67 4.66 4.65 4.64 4.63 4.62 4.61 4.60 4.59 4.58 4.57 4.56 4.55 4.54 4.53 4.52 4.51 4.50

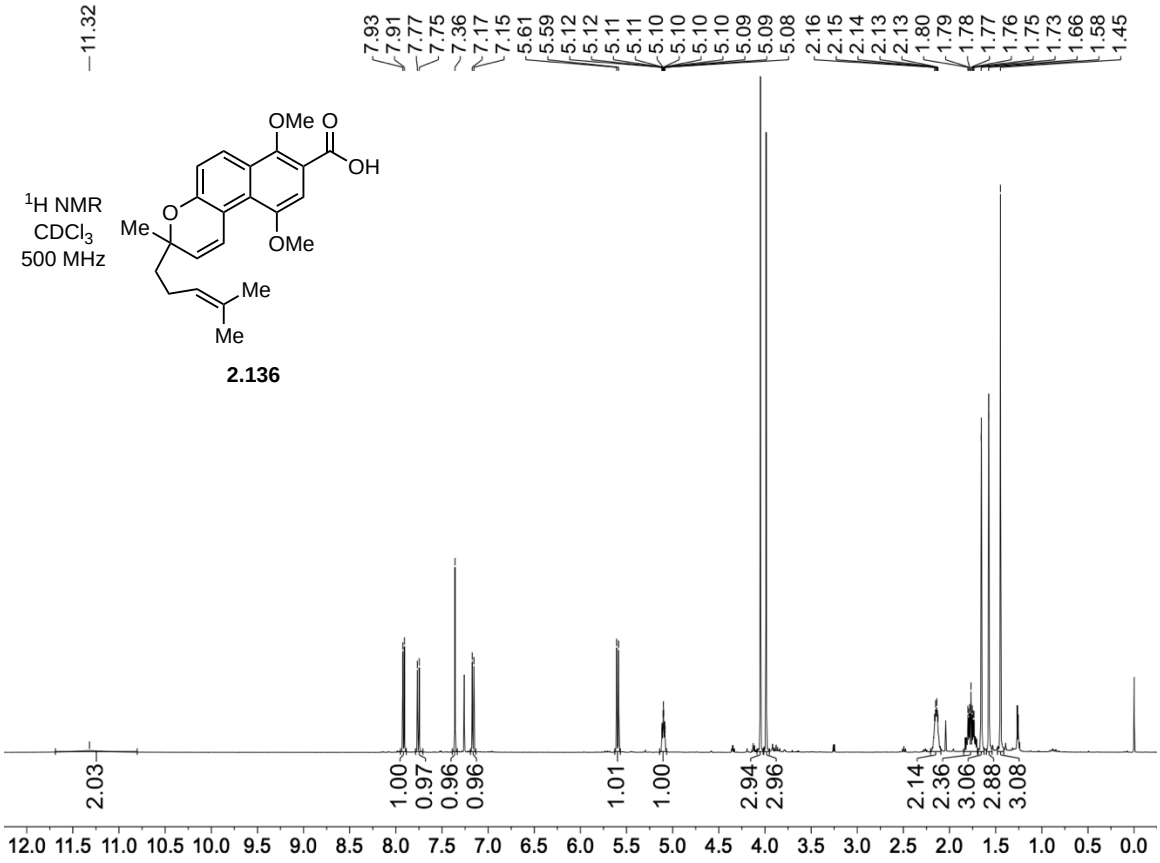

NOESY
CDCl3
500 MHz
OMe
O
Me
Me
Br
OMe
H
H
H
2.126
1.470
1.475
1.480
1.485
1.490
1.495
1.500
1.505
1.510
1.515
1.520
1.525
1.530
1.535
3.815 3.810 3.805 3.800 3.795 3.790 3.785 3.780 3.775 3.770 3.765 3.760 3.755 3.750

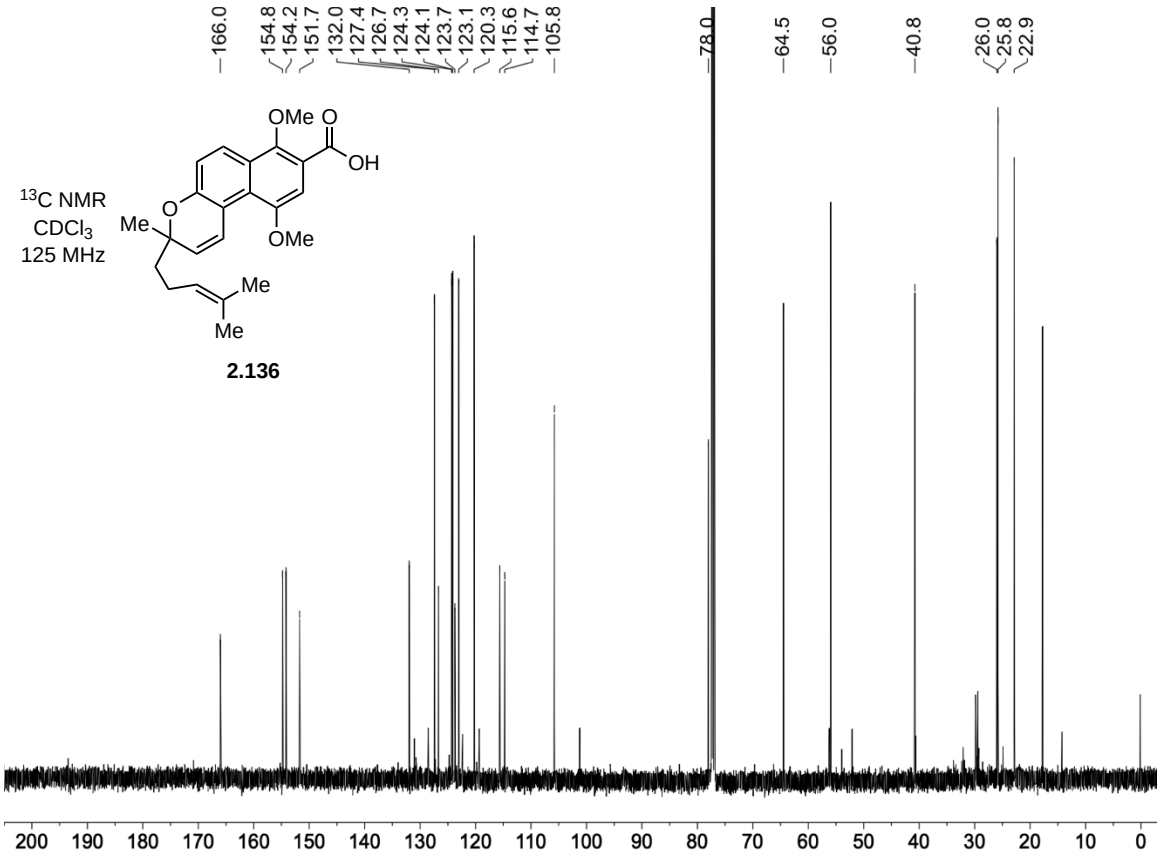
Data for 2.135



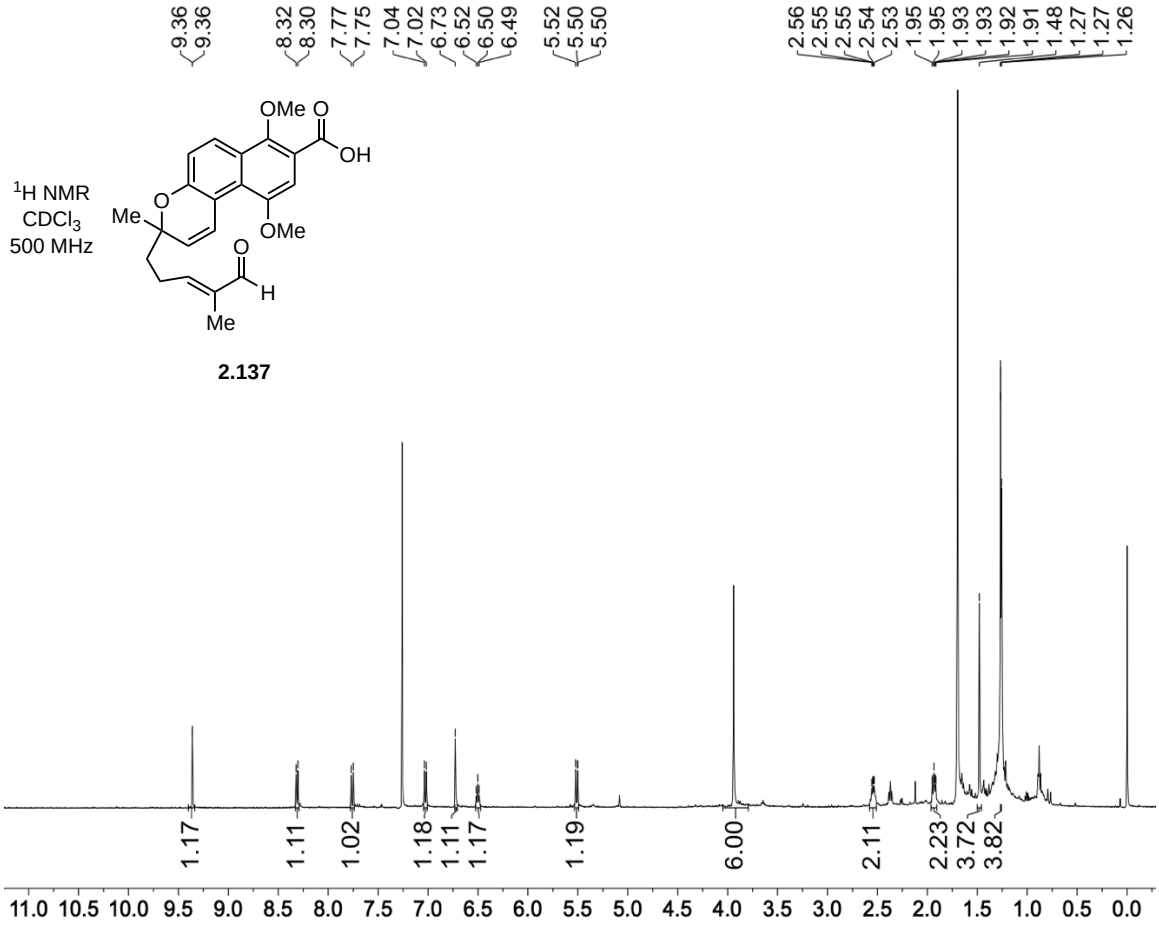


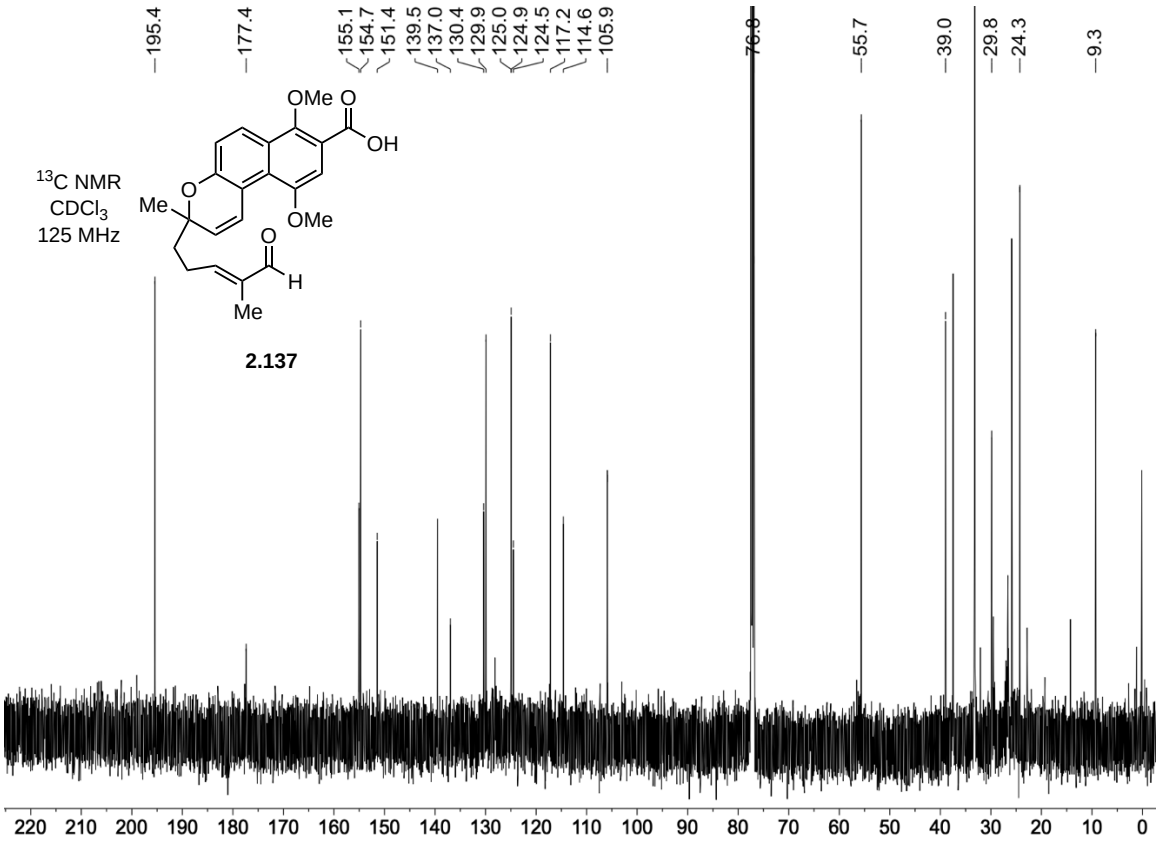
Data for 2.136

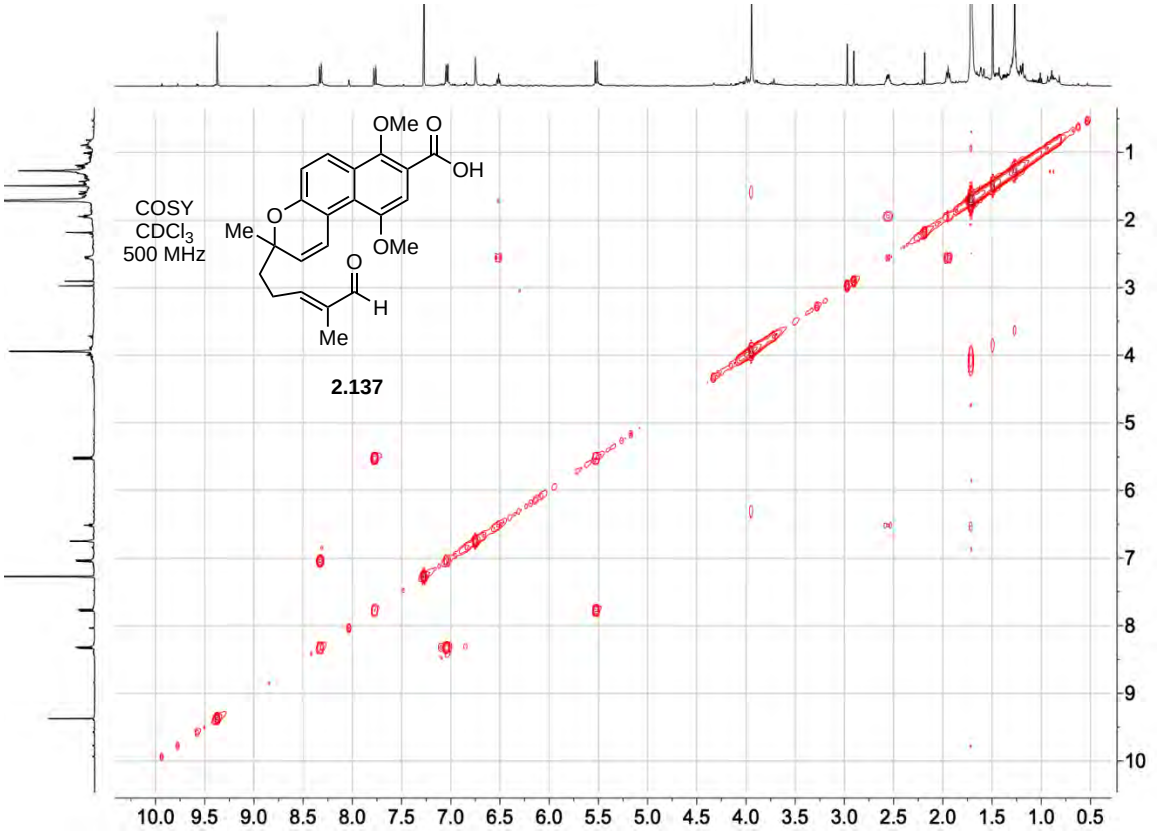


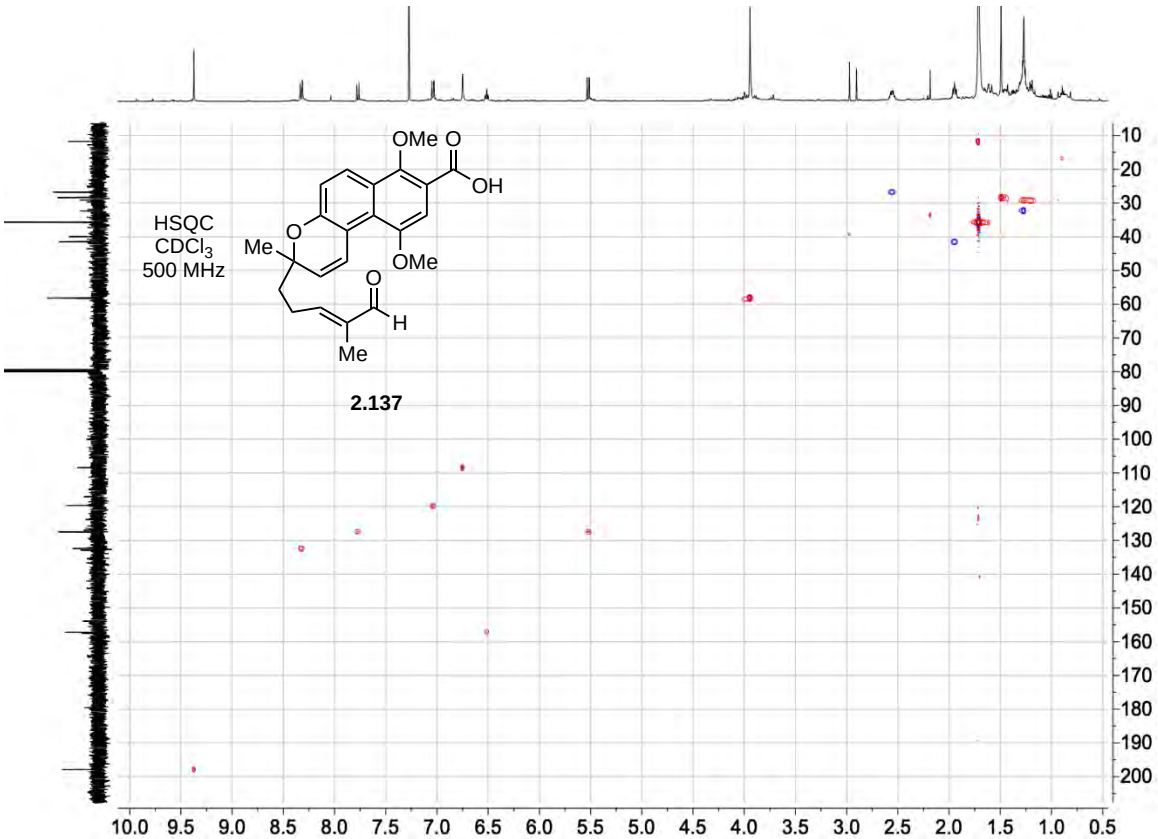


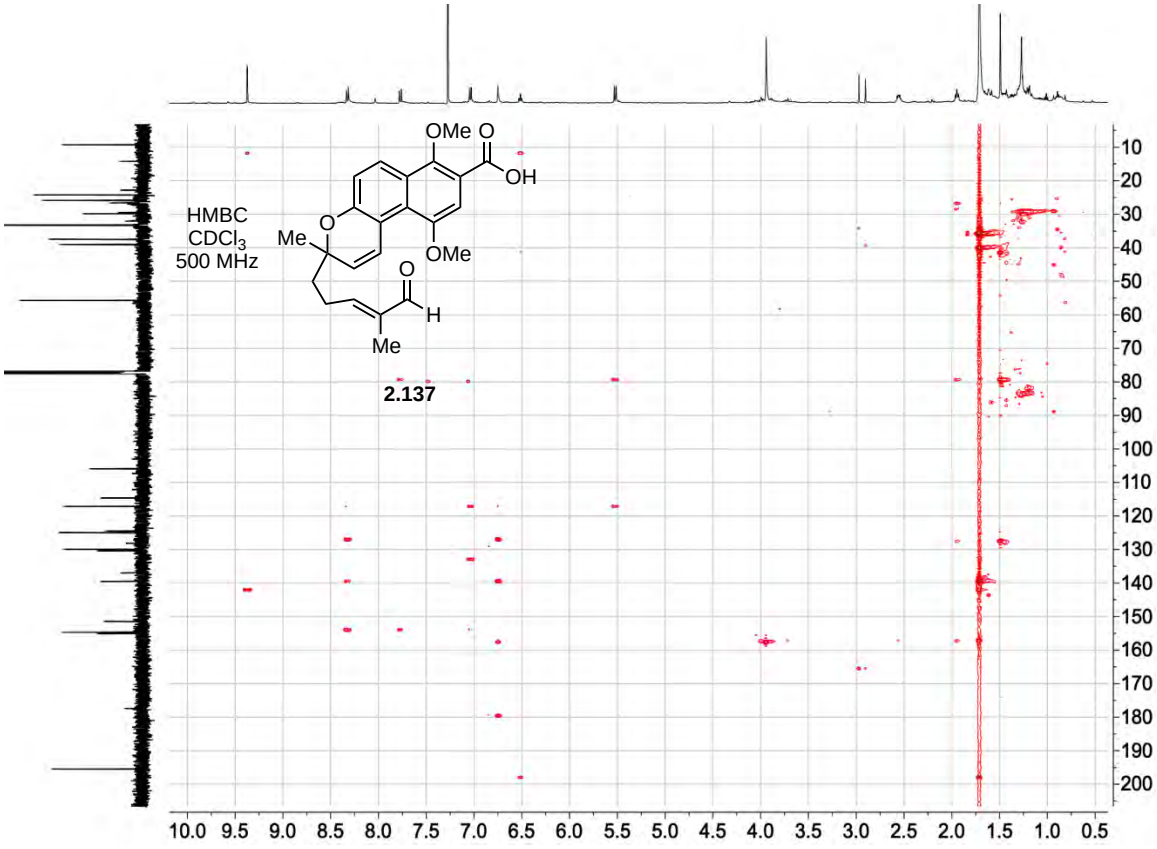
Data for 2.137



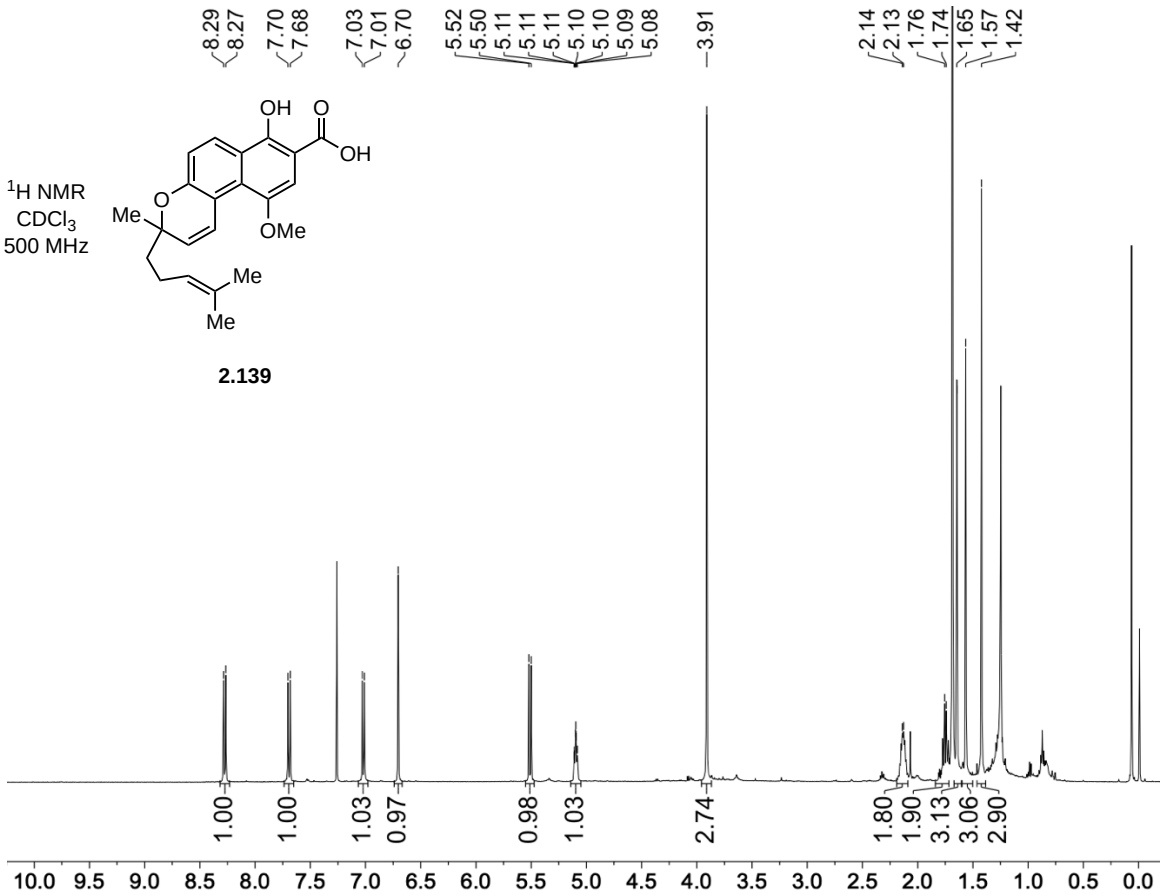


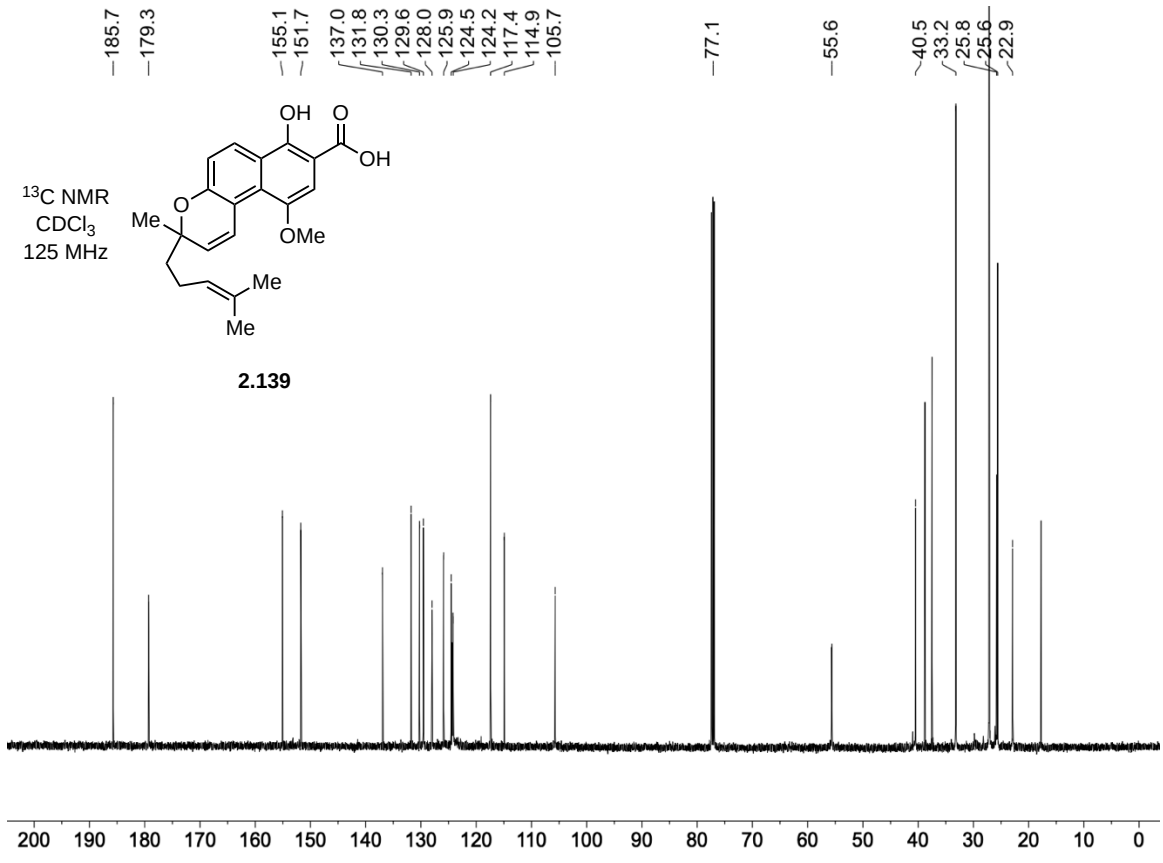

COSY
CDCl3
500 MHz
OMe O
OH
O
Me
OMe
O
H
Me
2.137

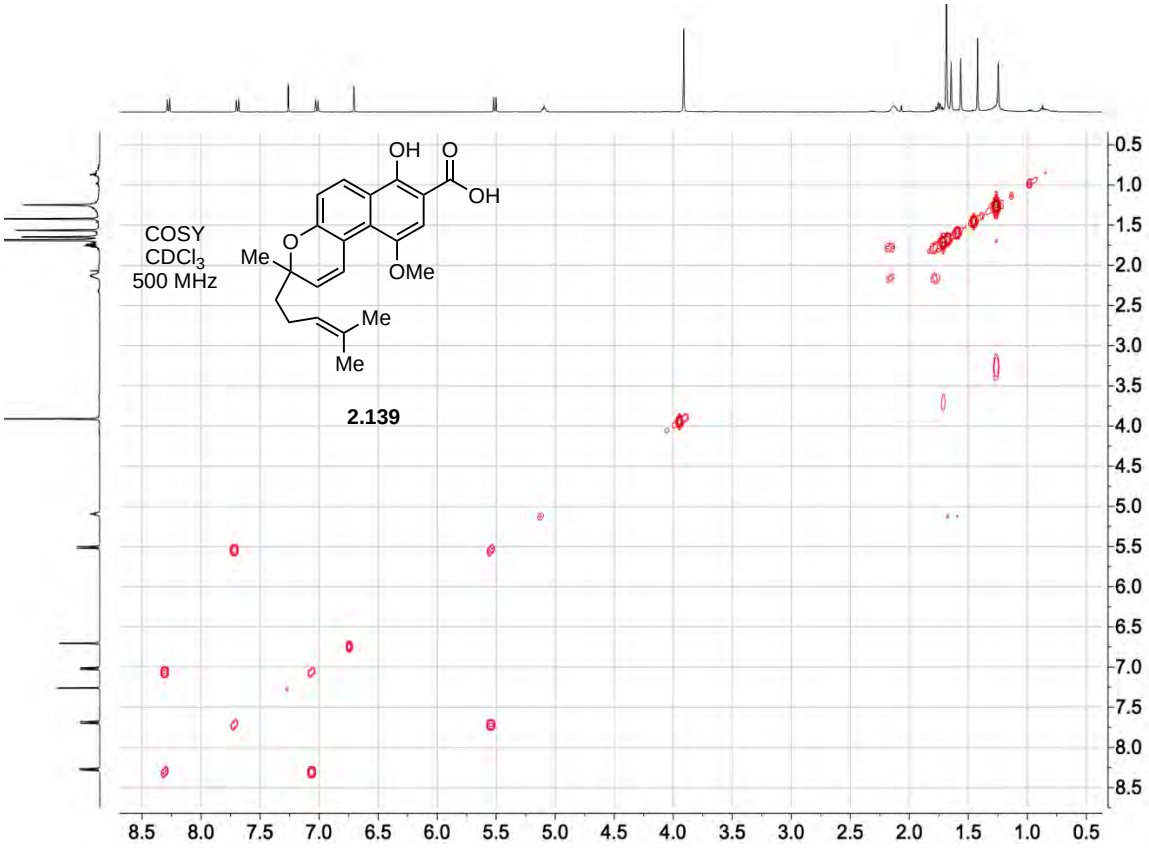

HSQC
CDCl3
500 MHz
OMe O
OH
O
Me
OMe
O
H
Me
2.137


HMBC
CDCl3
500 MHz
OMe
O
OH
Me
O
OMe
O
H
Me
2.137
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200

Data for 2.139



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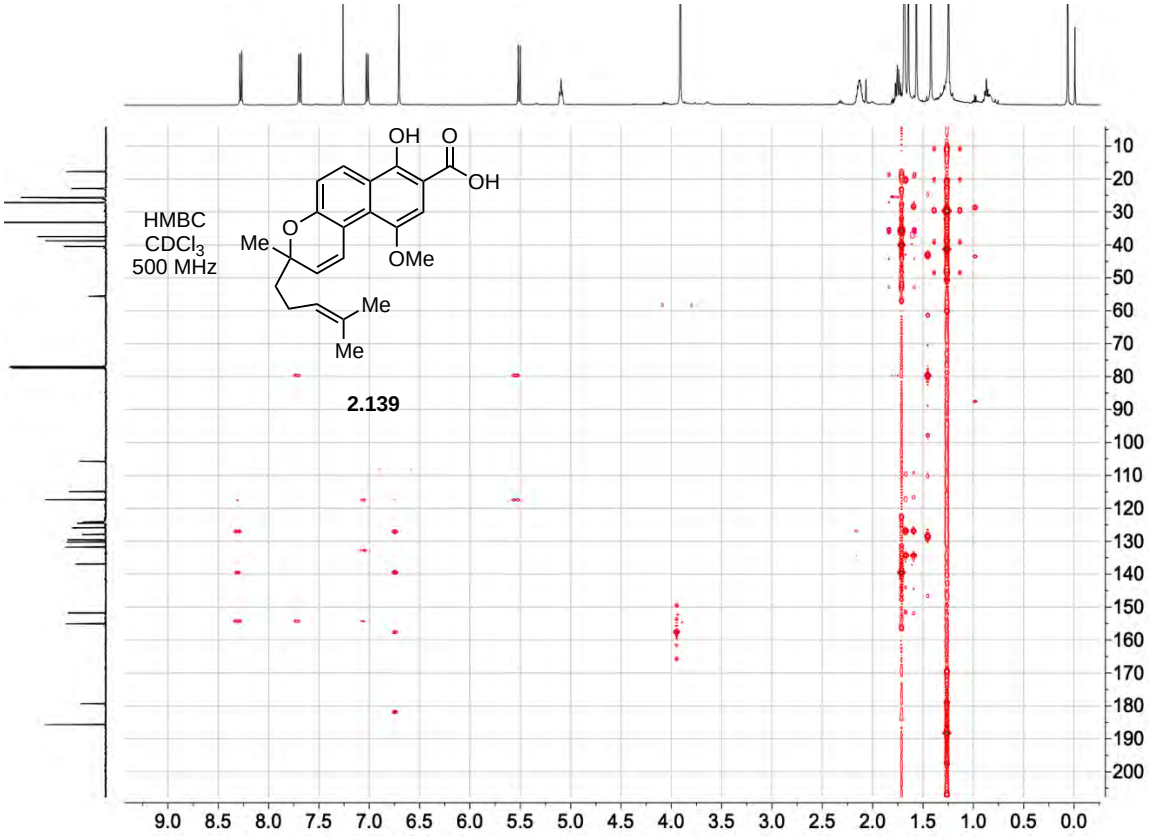
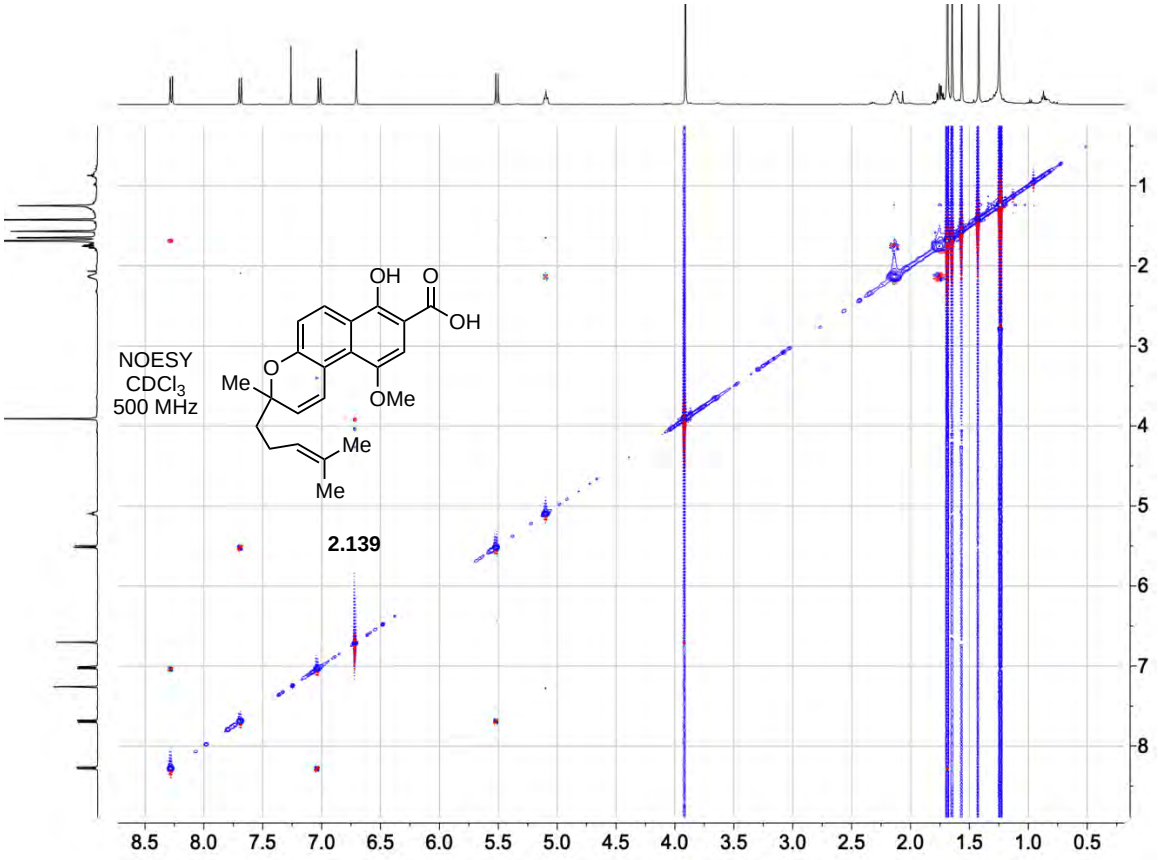
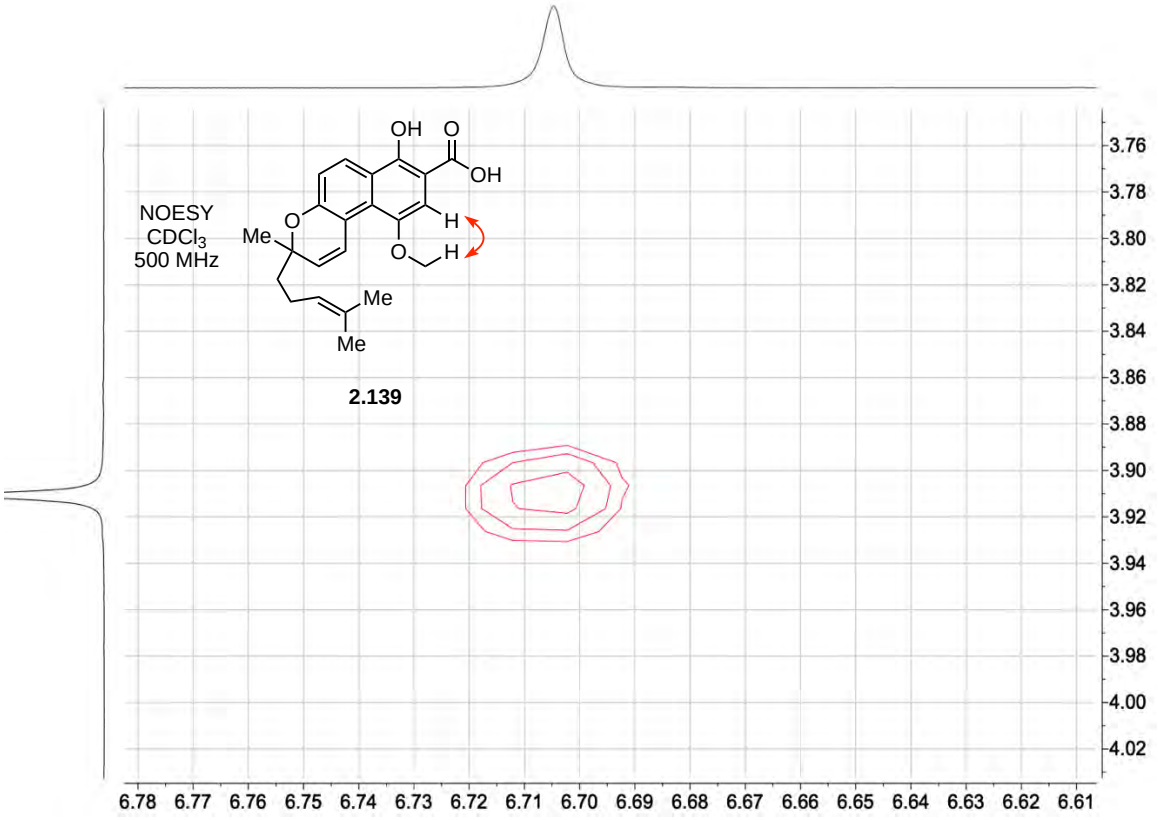
CDCl3
500 MHz
OH
O
OH
Me
O
OMe
Me
Me
2.139


HMBC
CDCl3
500 MHz
OH
O
OH
Me
O
OMe
Me
Me
2.139


NOESY
CDCl3
500 MHz
OH
O
OH
Me
O
OMe
Me
Me
2.139
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
1 2 3 4 5 6 7 8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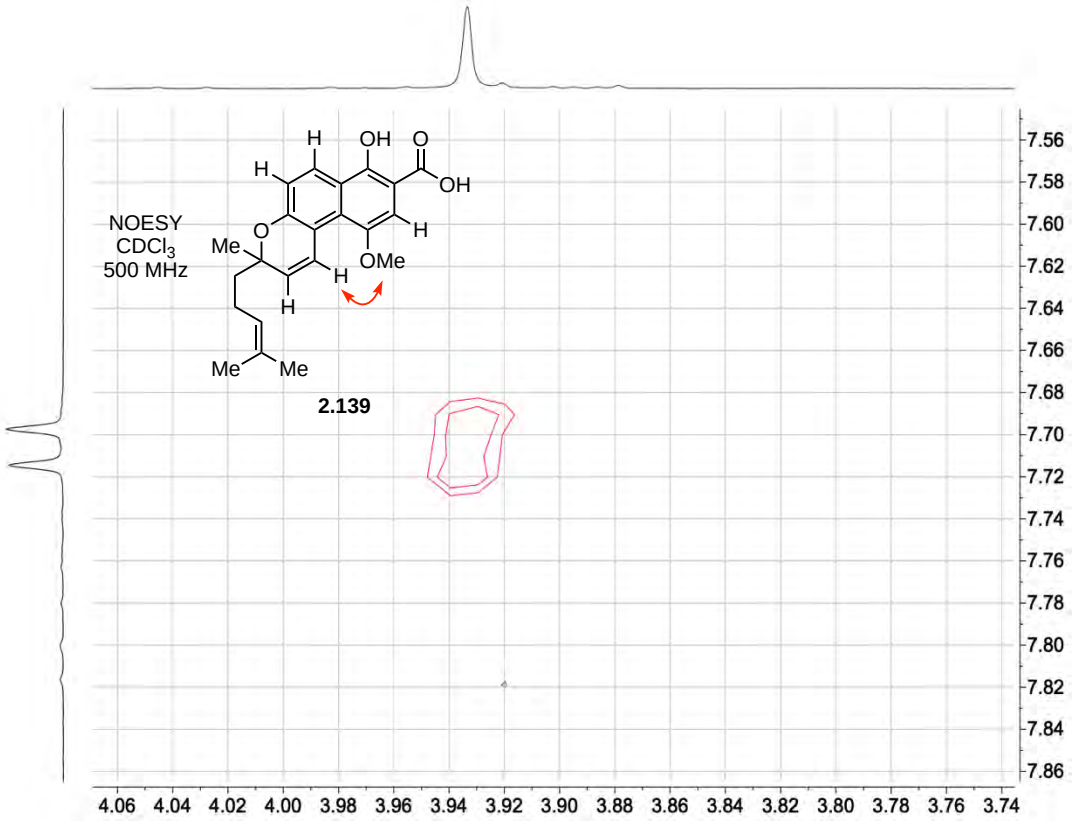
CDCl3
500 MHz
OH
O
OH
Me
O
H
O
H
Me
Me
2.139
6.78 6.77 6.76 6.75 6.74 6.73 6.72 6.71 6.70 6.69 6.68 6.67 6.66 6.65 6.64 6.63 6.62 6.61
3.76 3.78 3.80 3.82 3.84 3.86 3.88 3.90 3.92 3.94 3.96 3.98 4.00 4.02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CDCl3
500 MHz
2.139
7.56
7.58
7.60
7.62
7.64
7.66
7.68
7.70
7.72
7.74
7.76
7.78
7.80
7.82
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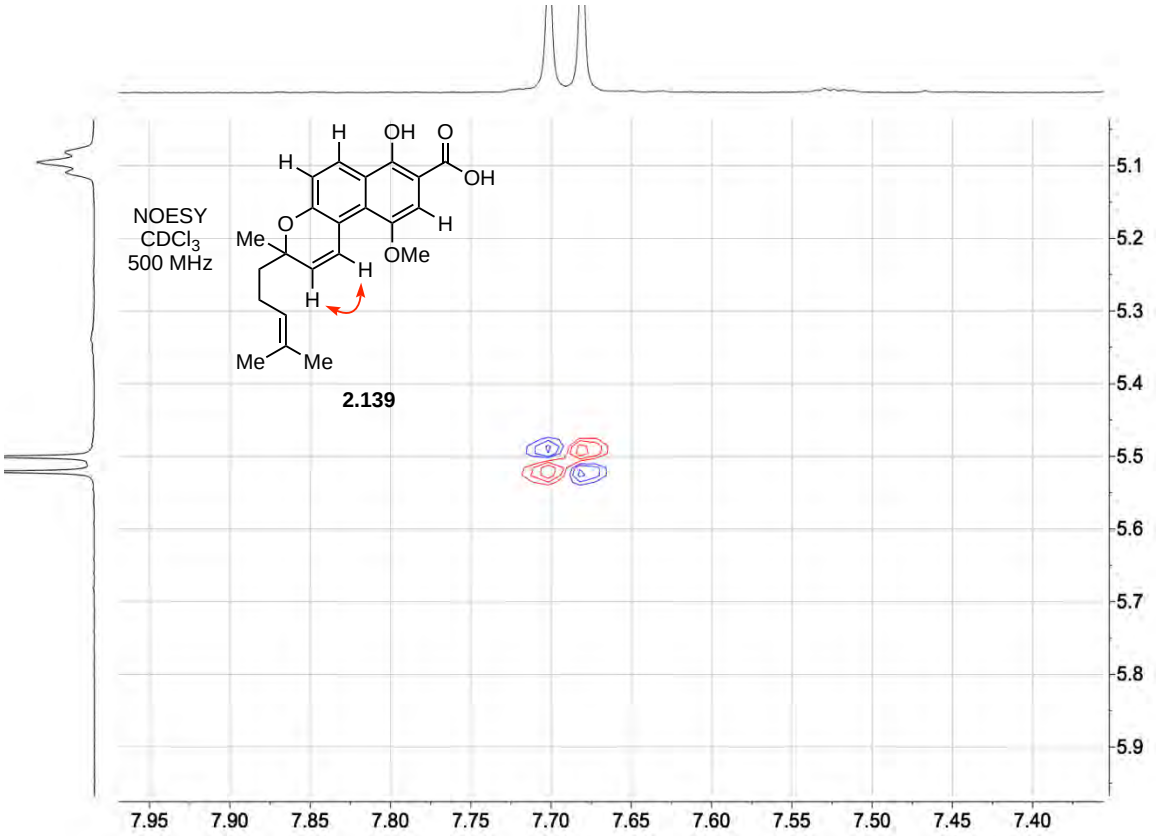
NOESY
CDCl3
500 MHz
2.139
5.1
5.2
5.3
5.4
5.5
5.6
5.7
5.8
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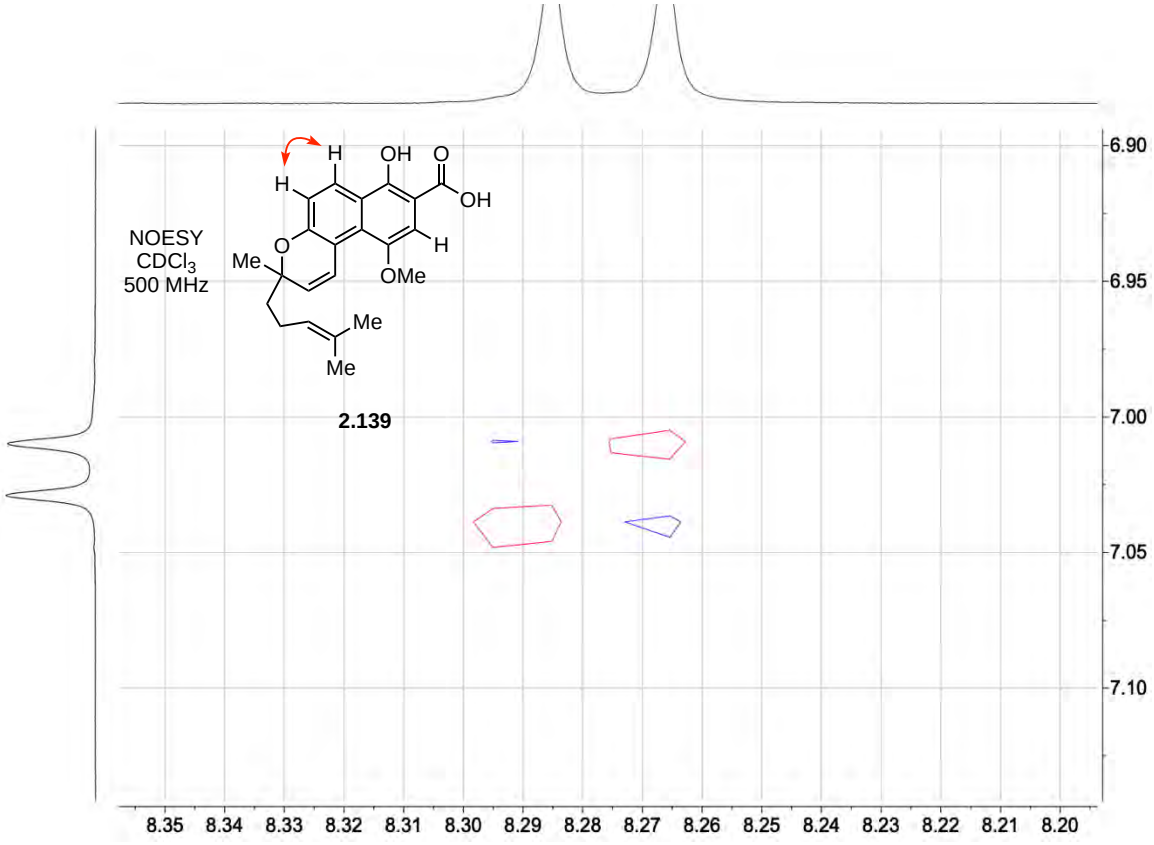
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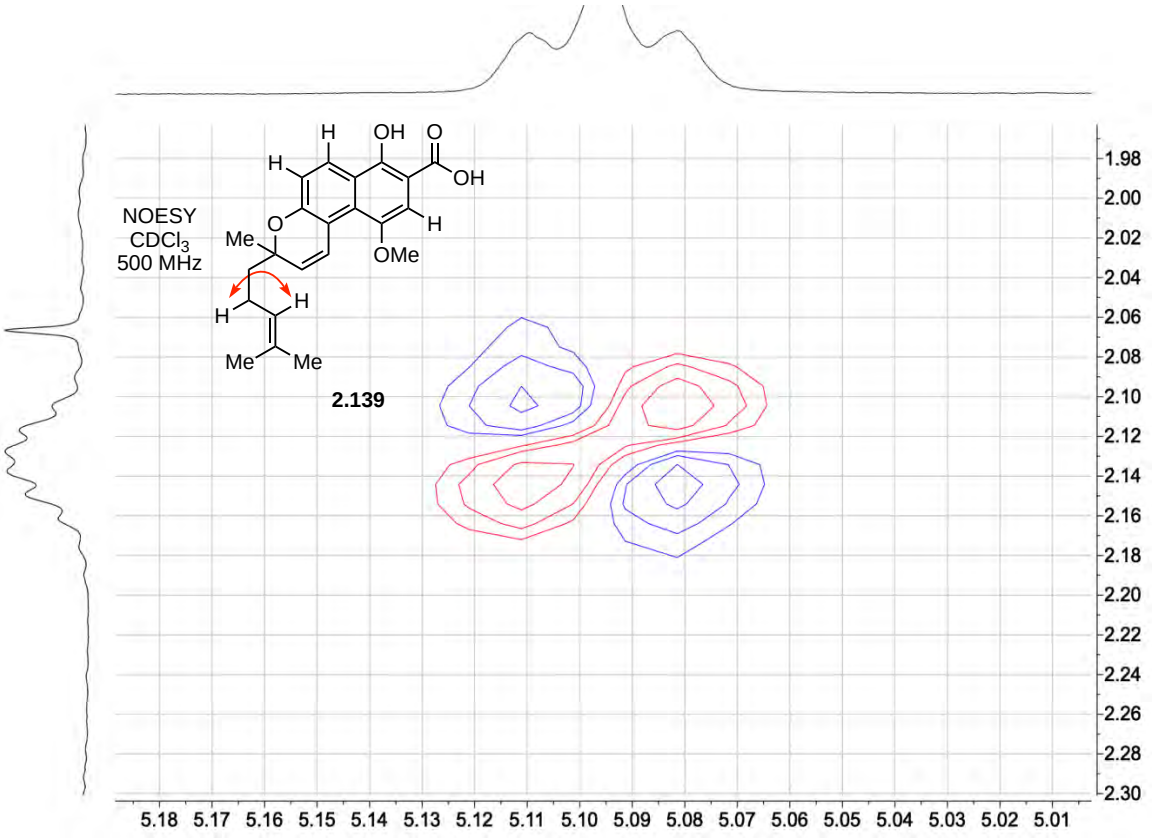
CDCl3
500 MHz
H
OH
O
OH
H
H
O
Me
OMe
Me
Me
2.139
6.90
6.95
7.00
7.05
7.10
8.35 8.34 8.33 8.32 8.31 8.30 8.29 8.28 8.27 8.26 8.25 8.24 8.23 8.22 8.21 8.20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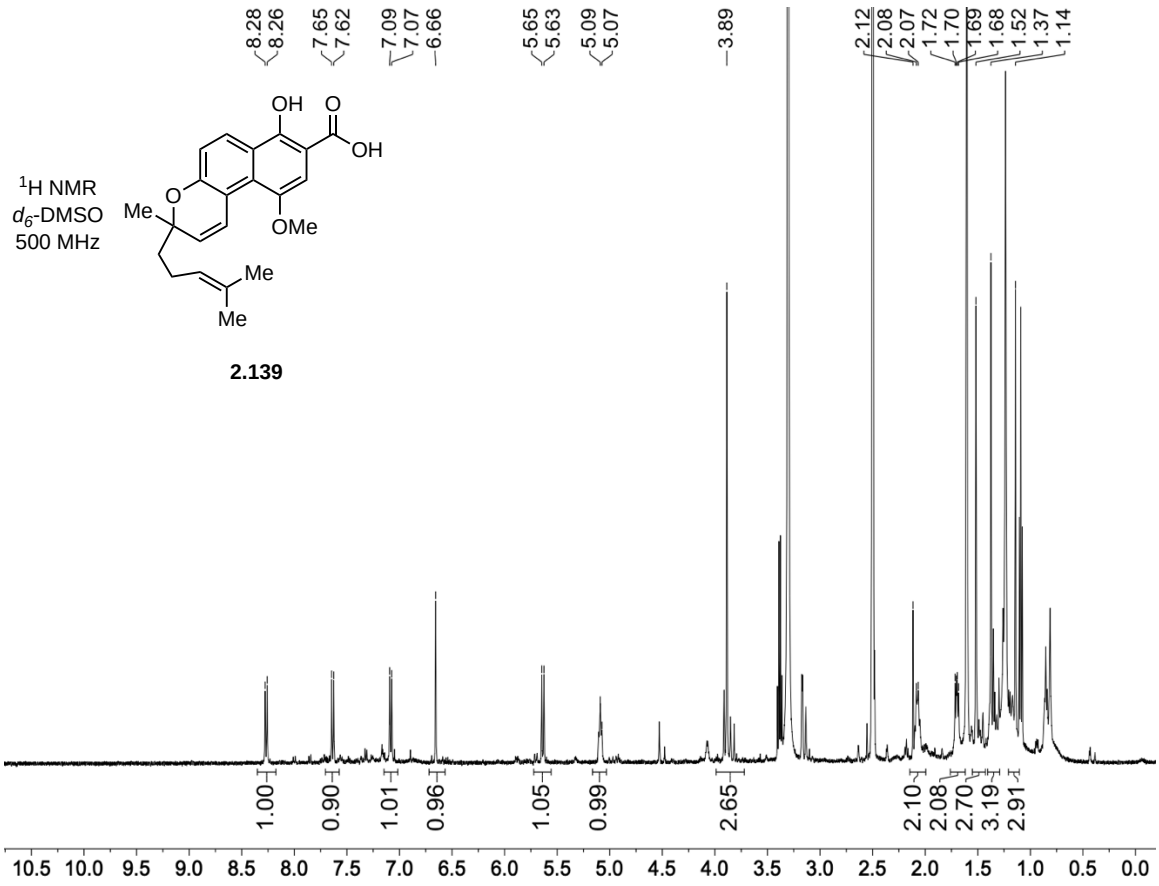
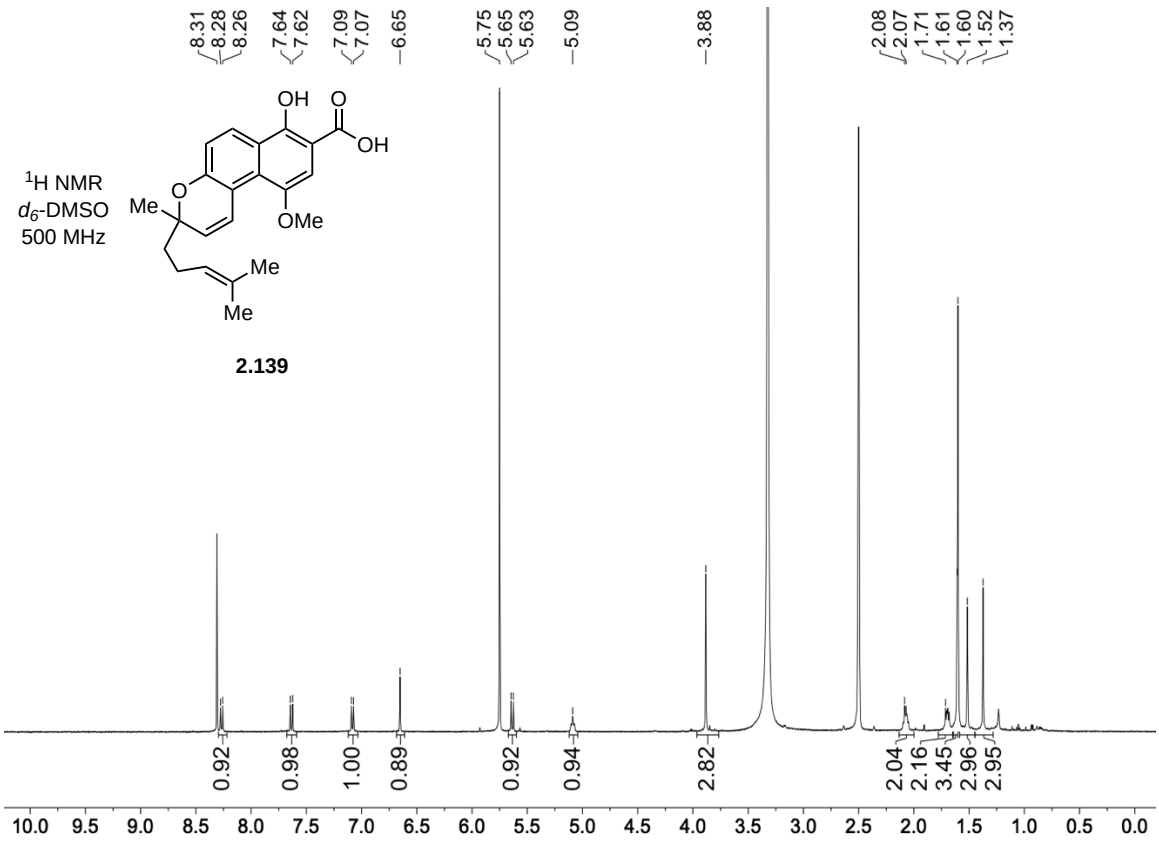
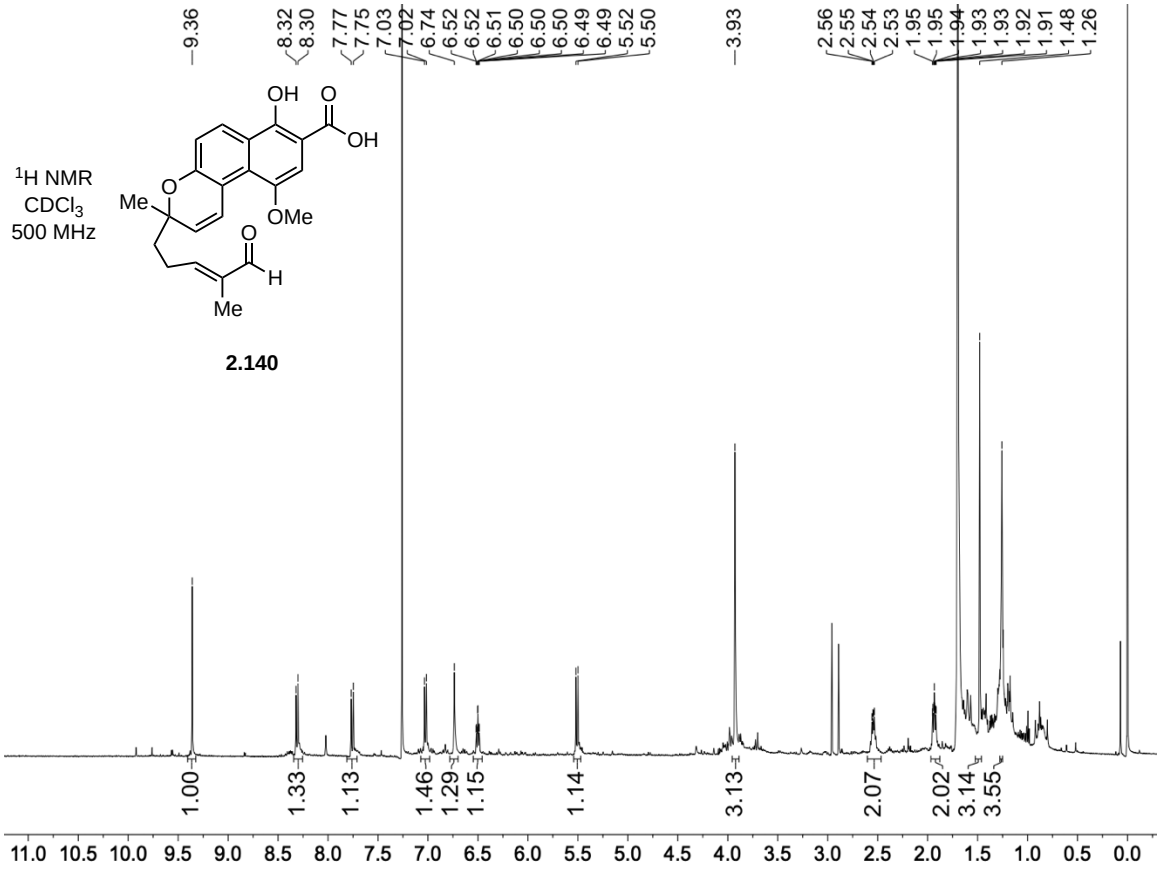
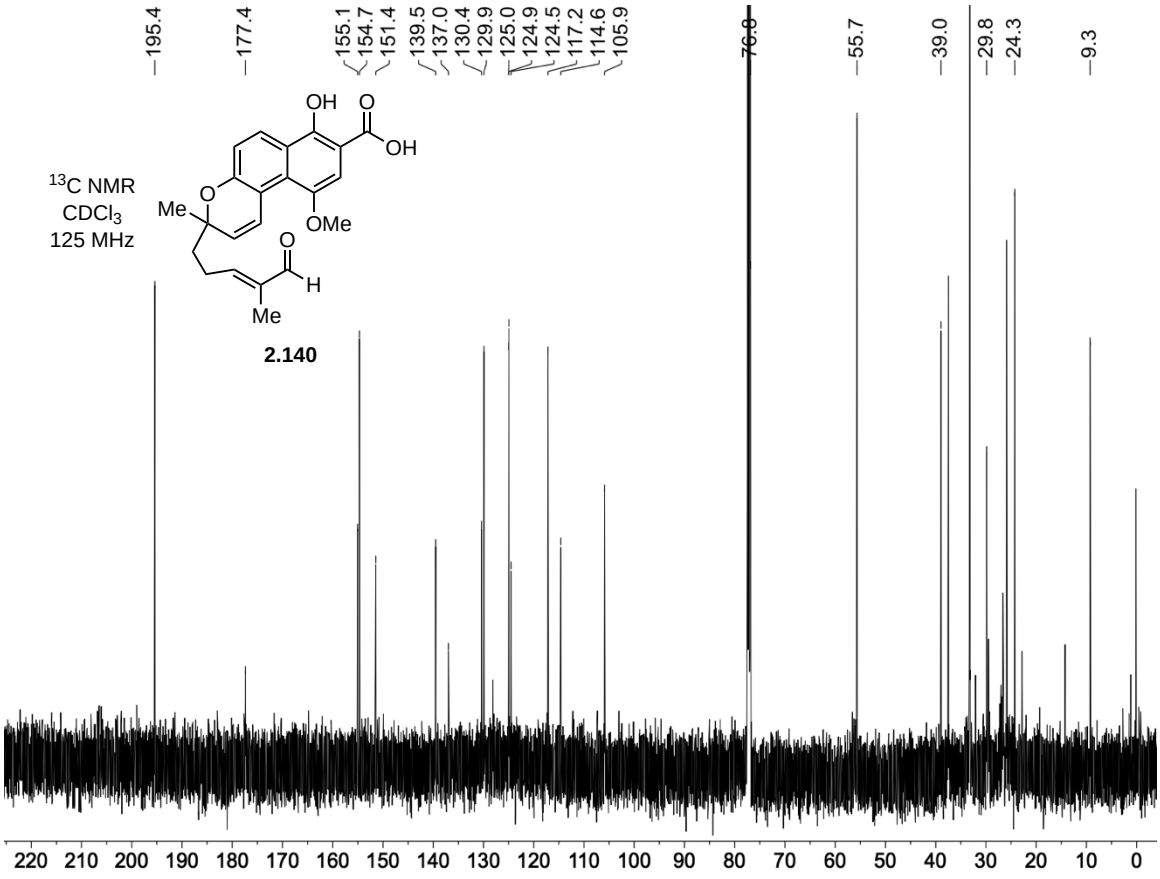
CDCl3
500 MHz
H
OH
O
OH
H
H
O
Me
OMe
H
H
Me
Me
2.139
1.98
2.00
2.02
2.04
2.06
2.08
2.10
2.12
2.14
2.16
2.18
2.20
2.22
2.24
2.26
2.28
2.30
5.18 5.17 5.16 5.15 5.14 5.13 5.12 5.11 5.10 5.09 5.08 5.07 5.06 5.05 5.04 5.03 5.02 5.01

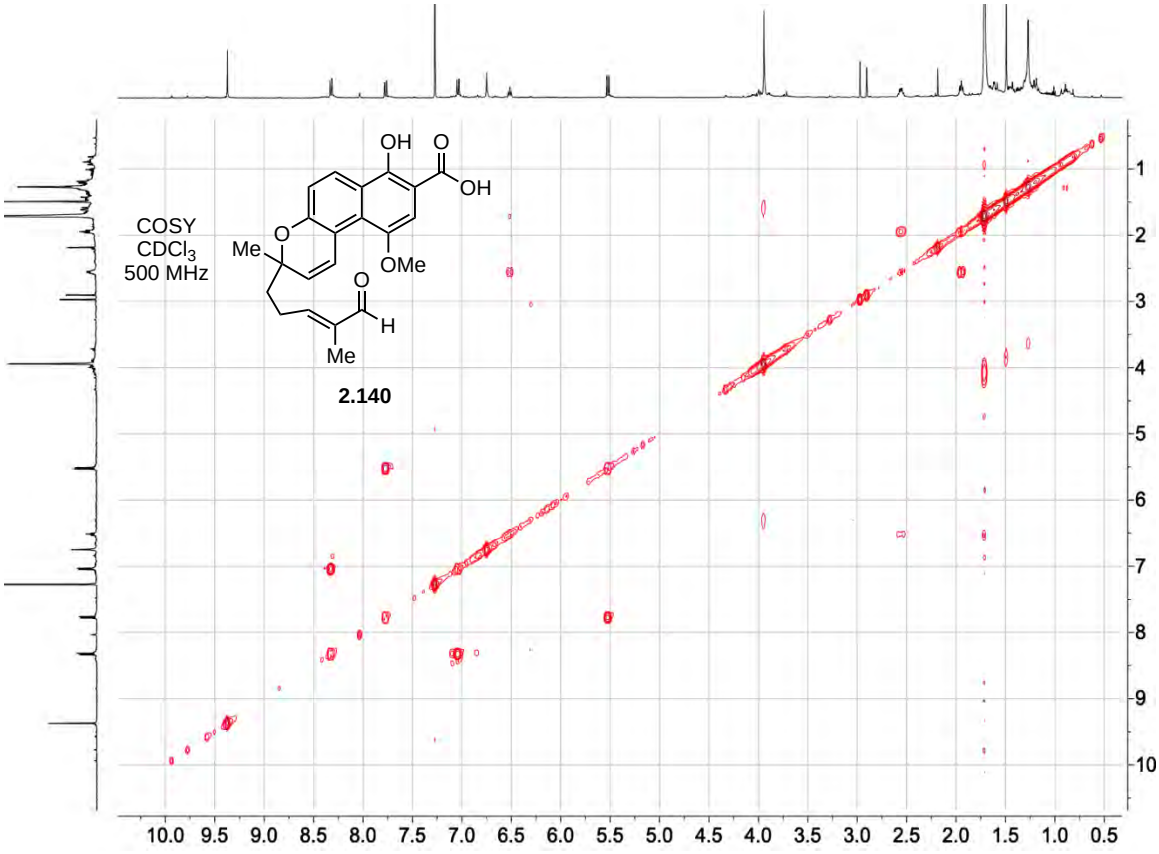

8.28
8.26
7.65
7.62
7.09
7.07
6.66
5.65
5.63
5.09
5.07
3.89
2.12
2.08
2.07
1.72
1.70
1.69
1.68
1.52
1.37
1.14
OH
O
OH
O
Me
OMe
Me
Me
1H NMR
d6-DMSO
500 MHz
2.139
1.00
0.90
1.01
0.96
1.05
0.99
2.65
2.10
2.08
2.70
3.19
2.91
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


8.31
8.28
8.26
7.64
7.62
7.09
7.07
6.65
5.75
5.65
5.63
5.09
3.88
2.08
2.07
1.71
1.61
1.60
1.52
1.37
OH
O
OH
O
Me
OMe
Me
Me
1H NMR
d6-DMSO
500 MHz
2.139
0.92
0.98
1.00
0.89
0.92
0.94
2.82
2.04
2.16
3.45
2.96
2.95
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

Data for 2.140



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CDCl3
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O
OH
Me
O
OMe
O
H
Me
2.140
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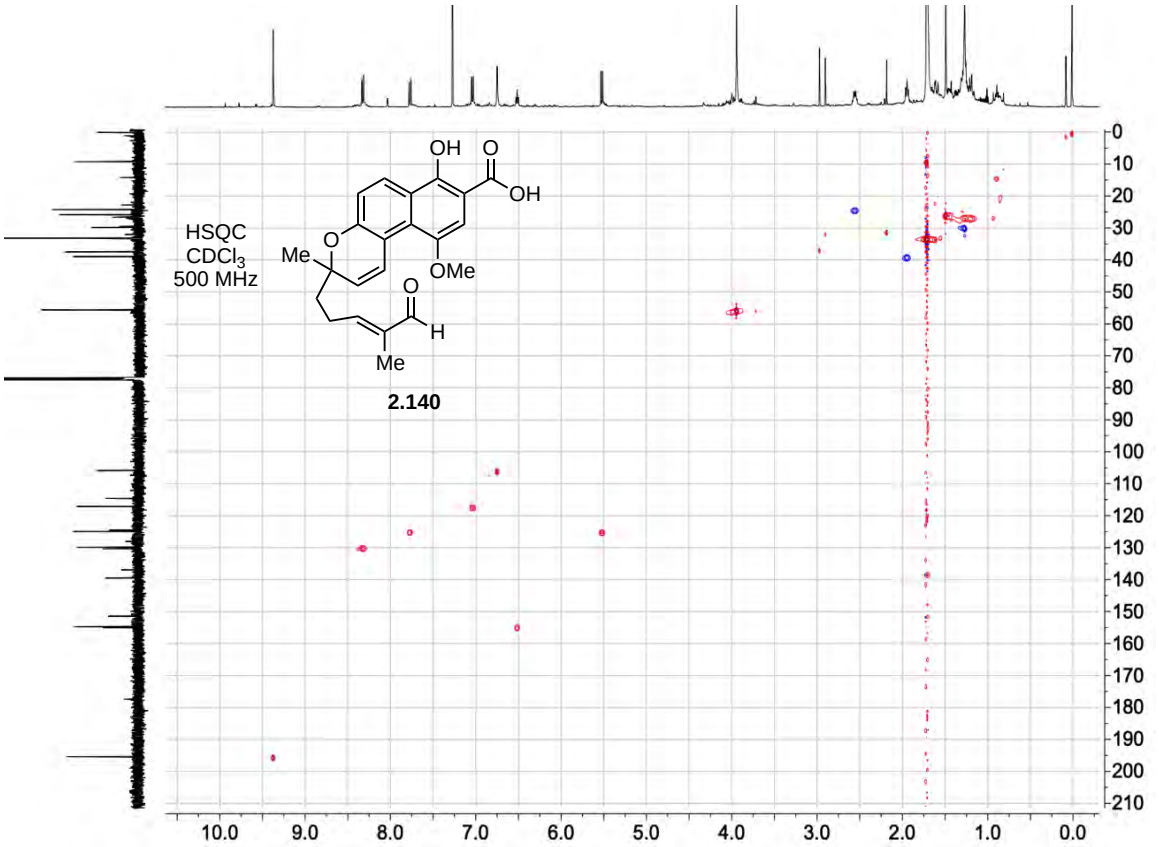
1 2 3 4 5 6 7 8 9 10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500 MHz
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O
OH
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O
OMe
O
H
Me
2.140
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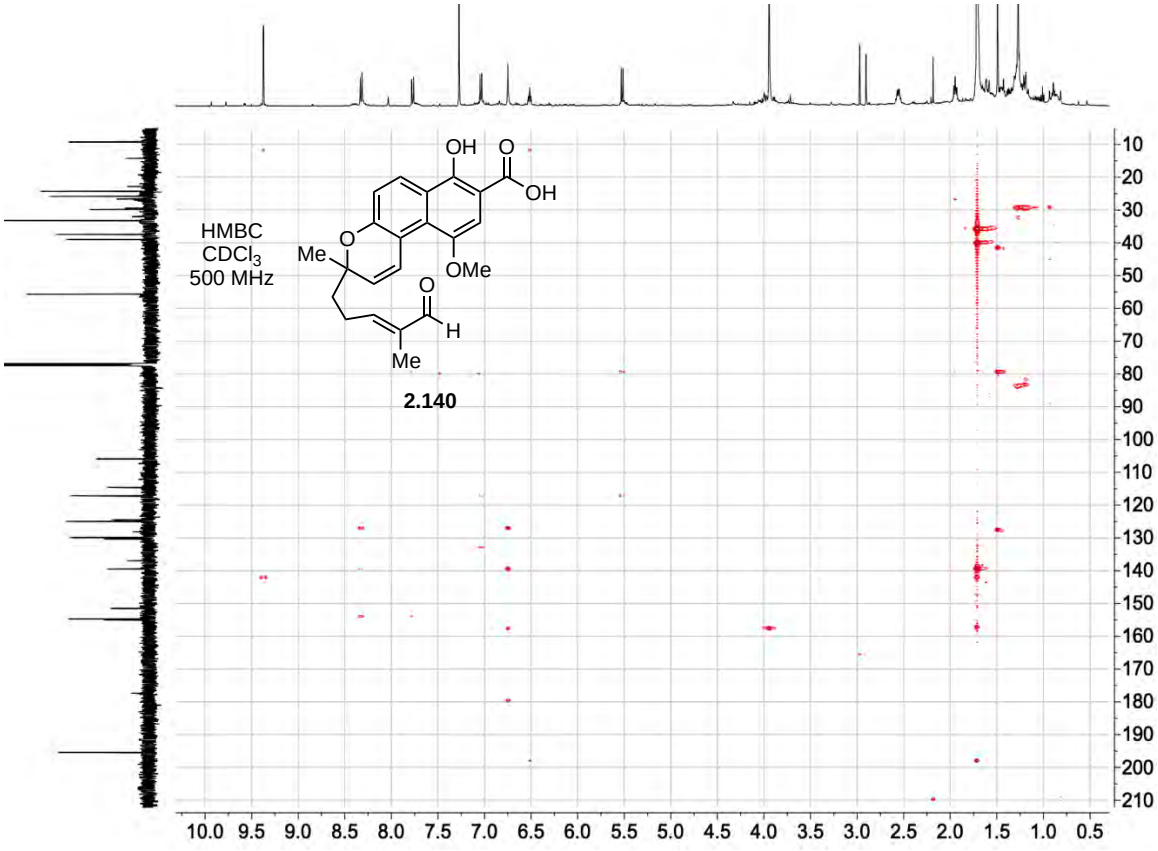
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210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H
Me
2.140
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210

2.4.5 Single Crystal X-Ray Data

A single crystal of **2.83** was mounted in paratone-N oil on a plastic loop and X-ray diffraction data were collected at 150(2) K on an Oxford X-calibur single crystal diffractometer using Mo Kα radiation. The data set was corrected for absorption using a multi-scan method, and the structures solved by direct methods using SHELXS-2008 and refined by full-matrix least squares on F2 by SHELXL-2015,[36] interfaced through the programs X-Seed[37] and Olex[2] (**Table 2.5 – 2.11**).[38] Unless otherwise stated, non-hydrogen atoms were refined anisotropically and hydrogen atoms were included as invariants at geometrically estimated positions. Full data for the structure determination have been deposited with the Cambridge Crystallographic Data Centre as CCDC 1944007. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Street, Cambridge CB2 1EZ, U.K. (fax, +44-1223-336-033; e-mail, deposit@ccdc.cam.ac.uk). Compound **2.83** is a racemic mixture and so the isomer that matches best to that of the natural product is shown. The tables below provide the crystal data and structure refinement details for compound **2.83**.

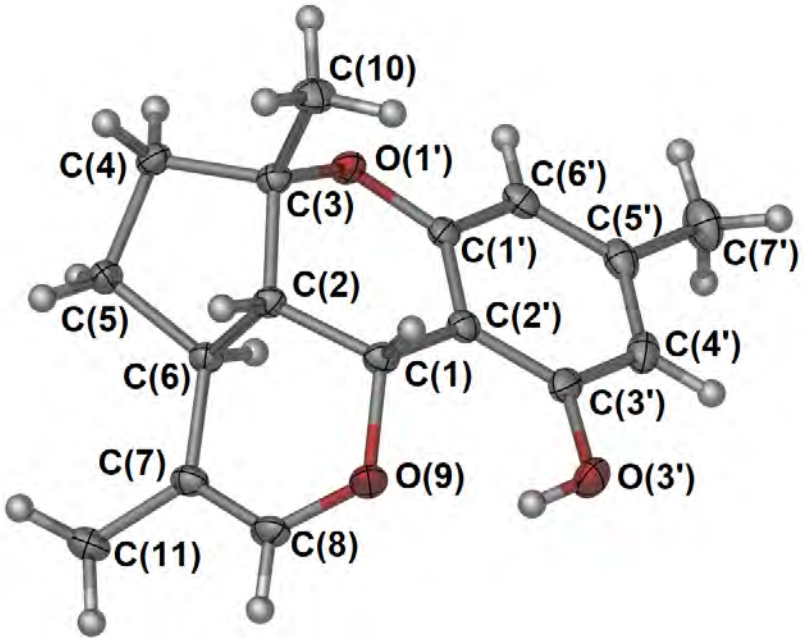

Figure 2.4 – A perspective view of 2.83 with thermal ellipsoids shown at the 50% probability level and crystallographic numbering for the non-hydrogen atoms.

Table 2.5 – Crystal data and structure refinement for 2.83.

Identification code	15-HP-80
CCDC number	1944007
Empirical formula	$C_{17}H_{20}O_3$
Formula weight	272.33
Temperature/K	150(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	9.7012(5)
b/Å	8.9372(4)
c/Å	16.3979(10)
α/°	90
β/°	107.029(6)
γ/°	90
Volume/Å^3	1359.39(13)
Z	4
ρ_{calc}g/cm^3	1.331
μ/mm^{-1}	0.090
F(000)	584.0
Crystal size/mm^3	0.57 × 0.47 × 0.06
Radiation	MoKα (λ = 0.71073)
2θ range for data collection/°	7.316 to 58.424
Index ranges	-13 ≤ h ≤ 12, -12 ≤ k ≤ 12, -21 ≤ l ≤ 20
Reflections collected	13296
Independent reflections	3260 [R_{int} = 0.0304, R_{sigma} = 0.0252]
Data/restraints/parameters	3260/0/185
Goodness-of-fit on F^2	1.039
Final R indexes [I>=2σ (I)]	R_1 = 0.0431, wR_2 = 0.1077
Final R indexes [all data]	R_1 = 0.0527, wR_2 = 0.1140
Largest diff. peak/hole / e Å^{-3}	0.34/-0.19

Table 2.6 — Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for 15. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O1'	5412.3(9)	2733.4(10)	9100.5(5)	19.4(2)
C1	3125.9(12)	3878.1(14)	7634.4(8)	18.4(3)
C1'	3986.2(13)	2469.9(13)	9028.5(8)	16.7(2)
C2	4684.8(12)	3751.9(14)	7660.0(7)	16.5(2)
C2'	2845.2(13)	2949.2(14)	8335.1(8)	17.1(2)
O3'	267.1(9)	3030.6(12)	7688.5(6)	27.5(2)
C3	5771.9(12)	3841.8(14)	8541.4(8)	17.3(3)
C3'	1441.8(13)	2587.1(14)	8343.8(8)	20.1(3)
C4	7154.4(12)	3261.9(15)	8367.4(8)	19.2(3)
C4'	1185.7(14)	1791.3(15)	9008.8(9)	23.3(3)
C5	6672.7(13)	2307.8(16)	7542.1(8)	23.1(3)
C5'	2336.1(14)	1310.6(14)	9687.8(8)	22.5(3)
C6	5022.4(12)	2233.3(14)	7335.5(8)	17.3(3)
C6'	3733.2(14)	1647.2(14)	9692.6(8)	19.8(3)
C7	4065.3(13)	2021.6(15)	6439.7(8)	19.6(3)
C7'	2075.8(17)	412.9(17)	10406.6(10)	32.3(3)
C8	2751.5(13)	2616.3(15)	6248.7(8)	22.0(3)
O9	2179.3(9)	3429.3(12)	6794.6(6)	25.4(2)
C10	5901.9(14)	5349.8(15)	8978.0(9)	24.9(3)
C11	4555.3(15)	1125.5(16)	5801.3(8)	25.3(3)

Table 2.7 —Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for 15. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1'	16.2(4)	24.5(5)	15.7(4)	4.1(3)	1.9(3)	-0.3(3)
C1	16.9(5)	19.4(6)	16.8(6)	1.2(5)	1.6(5)	2.1(5)
C1'	17.8(5)	15.4(6)	17.1(6)	-3.7(4)	5.4(5)	-0.2(4)
C2	15.8(5)	17.7(6)	14.8(6)	2.8(4)	2.6(4)	-0.1(4)
C2'	18.8(5)	15.9(6)	17.0(6)	-2.4(4)	5.6(5)	0.3(4)
O3'	15.9(4)	38.5(6)	27.1(5)	1.8(4)	4.8(4)	2.0(4)
C3	16.8(5)	17.4(6)	16.3(6)	1.5(4)	2.6(4)	-1.5(4)
C3'	17.9(6)	20.0(6)	22.6(6)	-4.4(5)	6.2(5)	1.3(5)
C4	15.2(5)	22.2(6)	18.8(6)	0.7(5)	2.6(5)	-0.7(5)
C4'	22.5(6)	21.4(6)	29.8(7)	-4.2(5)	13.6(5)	-3.2(5)
C5	16.4(6)	33.5(7)	18.6(6)	-2.6(5)	4.0(5)	1.7(5)
C5'	31.1(7)	16.9(6)	23.7(7)	-2.9(5)	14.4(5)	-1.3(5)
C6	16.7(5)	20.2(6)	13.9(6)	1.3(4)	2.7(4)	0.9(4)
C6'	26.3(6)	17.0(6)	16.5(6)	-1.4(5)	7.0(5)	1.7(5)
C7	21.6(6)	21.8(6)	14.0(6)	1.0(5)	3.0(5)	-3.3(5)
C7'	42.1(8)	28.8(8)	32.7(8)	5.4(6)	21.1(7)	-0.2(6)
C8	21.4(6)	29.1(7)	13.2(6)	3.0(5)	1.2(5)	-2.7(5)
O9	16.6(4)	40.7(6)	16.0(5)	1.9(4)	0.0(3)	3.9(4)
C10	25.3(6)	21.0(6)	25.7(7)	-4.7(5)	3.3(5)	-1.1(5)
C11	28.6(7)	27.8(7)	17.8(6)	-3.1(5)	4.0(5)	-1.3(6)

Table 2.8 – Bond Lengths for 2.83.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1'	C1'	1.3740(14)	C3	C10	1.5139(18)
O1'	C3	1.4597(14)	C3'	C4'	1.3840(19)
C1	C2	1.5048(16)	C4	C5	1.5514(18)
C1	C2'	1.5056(17)	C4'	C5'	1.3935(19)
C1	O9	1.4697(15)	C5	C6	1.5378(16)
C1'	C2'	1.4016(17)	C5'	C6'	1.3861(18)
C1'	C6'	1.3940(17)	C5'	C7'	1.5070(19)
C2	C3	1.5214(16)	C6	C7	1.5023(16)
C2	C6	1.5279(17)	C7	C8	1.3309(18)
C2'	C3'	1.4035(17)	C7	C11	1.5016(18)
O3'	C3'	1.3760(15)	C8	O9	1.3887(16)
C3	C4	1.5404(17)			

Table 2.9 – Bond Angles for 2.83.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C1'	O1'	C3	118.83(9)	O3'	C3'	C2'	120.64(12)
C2	C1	C2'	110.02(10)	O3'	C3'	C4'	117.68(11)
O9	C1	C2	110.66(10)	C4'	C3'	C2'	121.67(12)
O9	C1	C2'	111.19(10)	C3	C4	C5	106.87(9)
O1'	C1'	C2'	123.61(11)	C3'	C4'	C5'	120.09(12)
O1'	C1'	C6'	115.25(11)	C6	C5	C4	104.13(10)
C6'	C1'	C2'	121.13(11)	C4'	C5'	C7'	120.70(12)
C1	C2	C3	115.72(10)	C6'	C5'	C4'	119.38(12)
C1	C2	C6	111.90(10)	C6'	C5'	C7'	119.92(12)
C3	C2	C6	102.60(9)	C2	C6	C5	101.56(10)
C1'	C2'	C1	120.74(11)	C7	C6	C2	108.56(10)
C1'	C2'	C3'	117.34(11)	C7	C6	C5	121.76(10)
C3'	C2'	C1	121.85(11)	C5'	C6'	C1'	120.38(12)
O1'	C3	C2	109.52(9)	C8	C7	C6	117.05(11)
O1'	C3	C4	105.61(9)	C8	C7	C11	121.73(12)
O1'	C3	C10	108.01(10)	C11	C7	C6	121.18(11)
C2	C3	C4	101.85(10)	C7	C8	O9	126.39(11)
C10	C3	C2	115.77(10)	C8	O9	C1	119.26(9)
C10	C3	C4	115.51(10)				

Table 2.10 – Torsion Angles for 2.83.

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
O1'	C1'	C2'	C1	-3.44(18)	O3'	C3'	C4'	C5'	179.81(11)
O1'	C1'	C2'	C3'	179.42(11)	C3	O1'	C1'	C2'	14.45(17)
O1'	C1'	C6'	C5'	-179.89(11)	C3	O1'	C1'	C6'	-166.98(10)
O1'	C3	C4	C5	91.89(11)	C3	C2	C6	C5	-47.78(11)
C1	C2	C3	O1'	53.96(14)	C3	C2	C6	C7	-177.22(9)
C1	C2	C3	C4	165.43(10)	C3	C4	C5	C6	-6.34(13)
C1	C2	C3	C10	-68.42(14)	C3'	C4'	C5'	C6'	0.49(19)
C1	C2	C6	C5	-172.46(10)	C3'	C4'	C5'	C7'	-178.60(12)
C1	C2	C6	C7	58.10(13)	C4	C5	C6	C2	32.59(12)
C1	C2'	C3'	O3'	2.35(18)	C4	C5	C6	C7	153.17(12)
C1	C2'	C3'	C4'	-176.99(12)	C4'	C5'	C6'	C1'	0.55(19)
C1'	O1'	C3	C2	-37.83(14)	C5	C6	C7	C8	-150.44(13)
C1'	O1'	C3	C4	-146.81(10)	C5	C6	C7	C11	31.91(18)
C1'	O1'	C3	C10	89.07(12)	C6	C2	C3	O1'	-68.18(11)
C1'	C2'	C3'	O3'	179.45(11)	C6	C2	C3	C4	43.30(11)
C1'	C2'	C3'	C4'	0.12(18)	C6	C2	C3	C10	169.44(11)
C2	C1	C2'	C1'	17.77(16)	C6	C7	C8	O9	0.7(2)
C2	C1	C2'	C3'	-165.23(11)	C6'	C1'	C2'	C1	178.07(11)
C2	C1	O9	C8	16.71(15)	C6'	C1'	C2'	C3'	0.94(18)
C2	C3	C4	C5	-22.51(13)	C7	C8	O9	C1	8.8(2)
C2	C6	C7	C8	-33.29(15)	C7'	C5'	C6'	C1'	179.65(12)
C2	C6	C7	C11	149.06(12)	O9	C1	C2	C3	-166.73(10)
C2'	C1	C2	C3	-43.47(14)	O9	C1	C2	C6	-49.70(13)
C2'	C1	C2	C6	73.57(13)	O9	C1	C2'	C1'	140.72(11)
C2'	C1	O9	C8	-105.87(12)	O9	C1	C2'	C3'	-42.28(15)
C2'	C1'	C6'	C5'	-1.29(18)	C10	C3	C4	C5	-148.83(11)
C2'	C3'	C4'	C5'	-0.83(19)	C11	C7	C8	O9	178.33(12)

Table 2.11 — Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 2.83.

Atom	*x*	*y*	*z*	U(eq)
H1	2920	4948	7734	22
H2	4908	4555	7293	20
H3'	529	3223	7255	33
H4A	7720	2645	8851	23
H4B	7760	4110	8290	23
H4'	224	1572	9002	28
H5A	6957	2791	7073	28
H5B	7102	1294	7639	28
H6	4781	1439	7701	21
H6'	4523	1315	10151	24
H7'A	2980	315	10867	48
H7'B	1718	-583	10198	48
H7'C	1359	924	10622	48
H8	2146	2470	5683	26
H10A	6663	5307	9523	37
H10B	4984	5604	9080	37
H10C	6143	6114	8613	37
H11A	3799	1128	5253	38
H11B	4751	94	6005	38
H11C	5436	1570	5729	38

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Chapter Three – Synthesis of Rhodonoids A, B, E and F Enabled by Singlet Oxygen

3.1 Introduction

3.1.1 Isolation of the Rhodonoid Family of Natural Products

Rhododendron is a genus of woody plants belonging to the Ericaceae family and is famous for possessing a diverse range of phytochemicals. One species, *Rhododendron capitatum* is a flowering plant containing the polycyclic meroterpenoids rhodonoids A – G (**3.1** – **3.7**) isolated from the aerial part of the plant (**Figure 3.1**).[1, 2] Despite the stereochemically rich nature of these structures, the rhodonoids were all isolated as partial racemates. This implies that the key steps in their biosynthesis is not under enzymatic control, making the rhodonoids attractive targets for biomimetic synthesis.

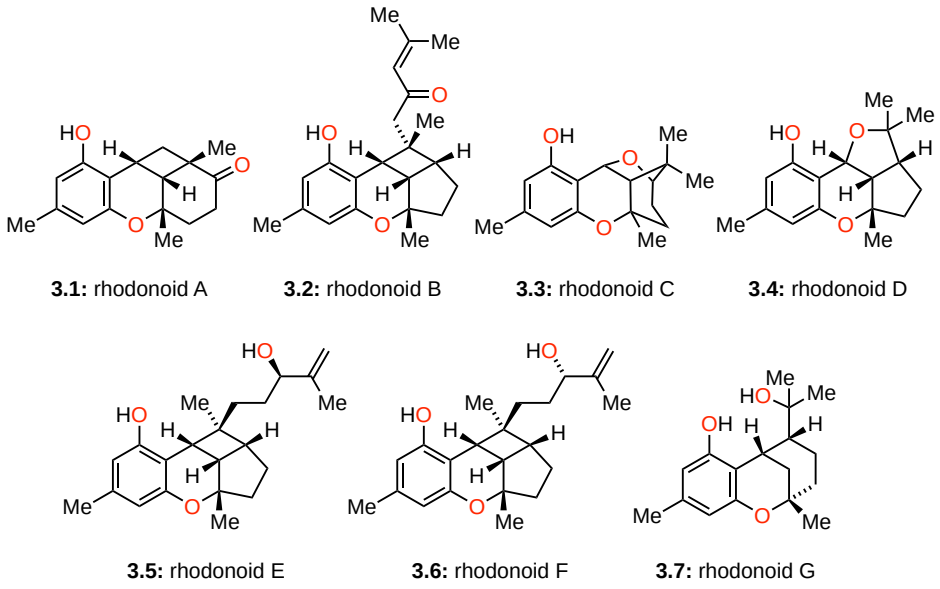
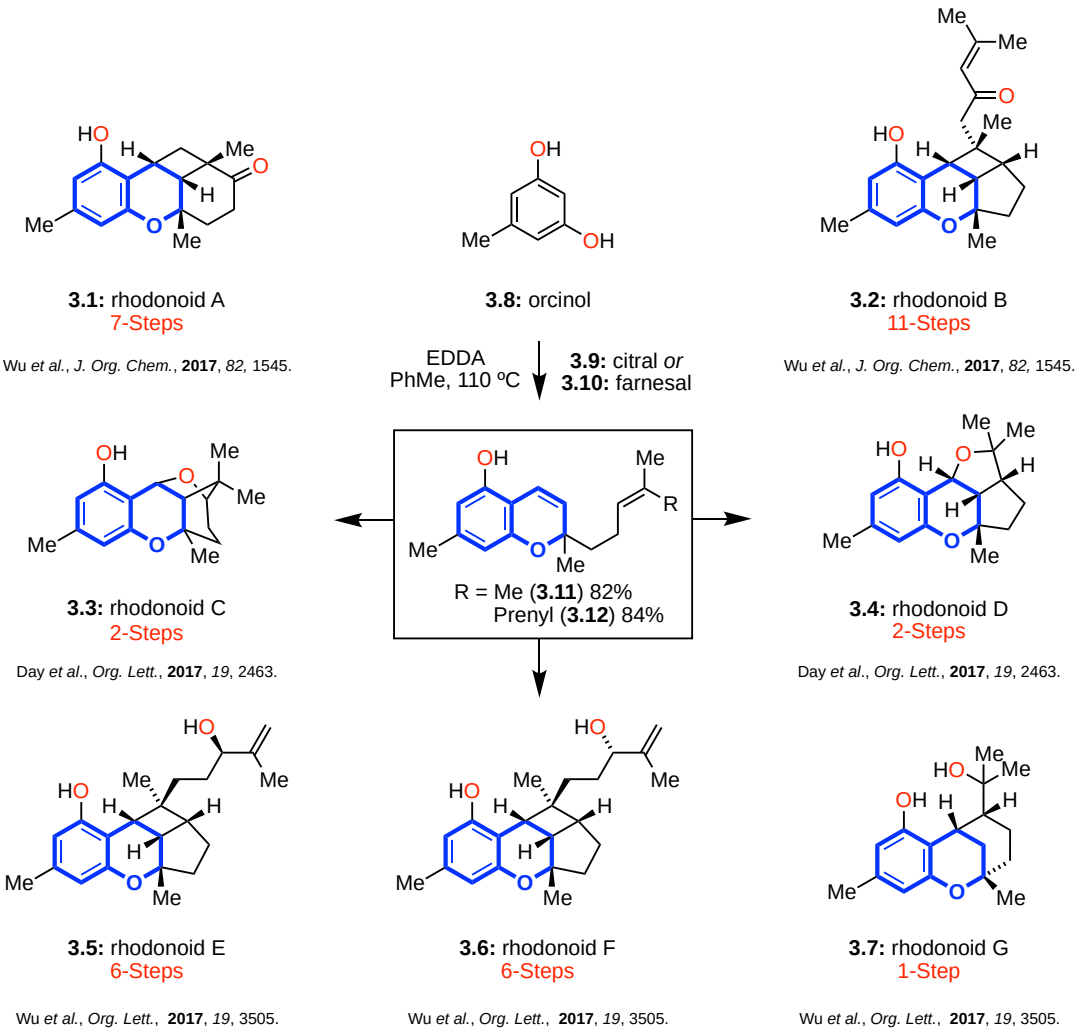


Figure 3.1 – Rhodonoids A – G Isolated from *Rhododendron Capitatum*[1, 2]

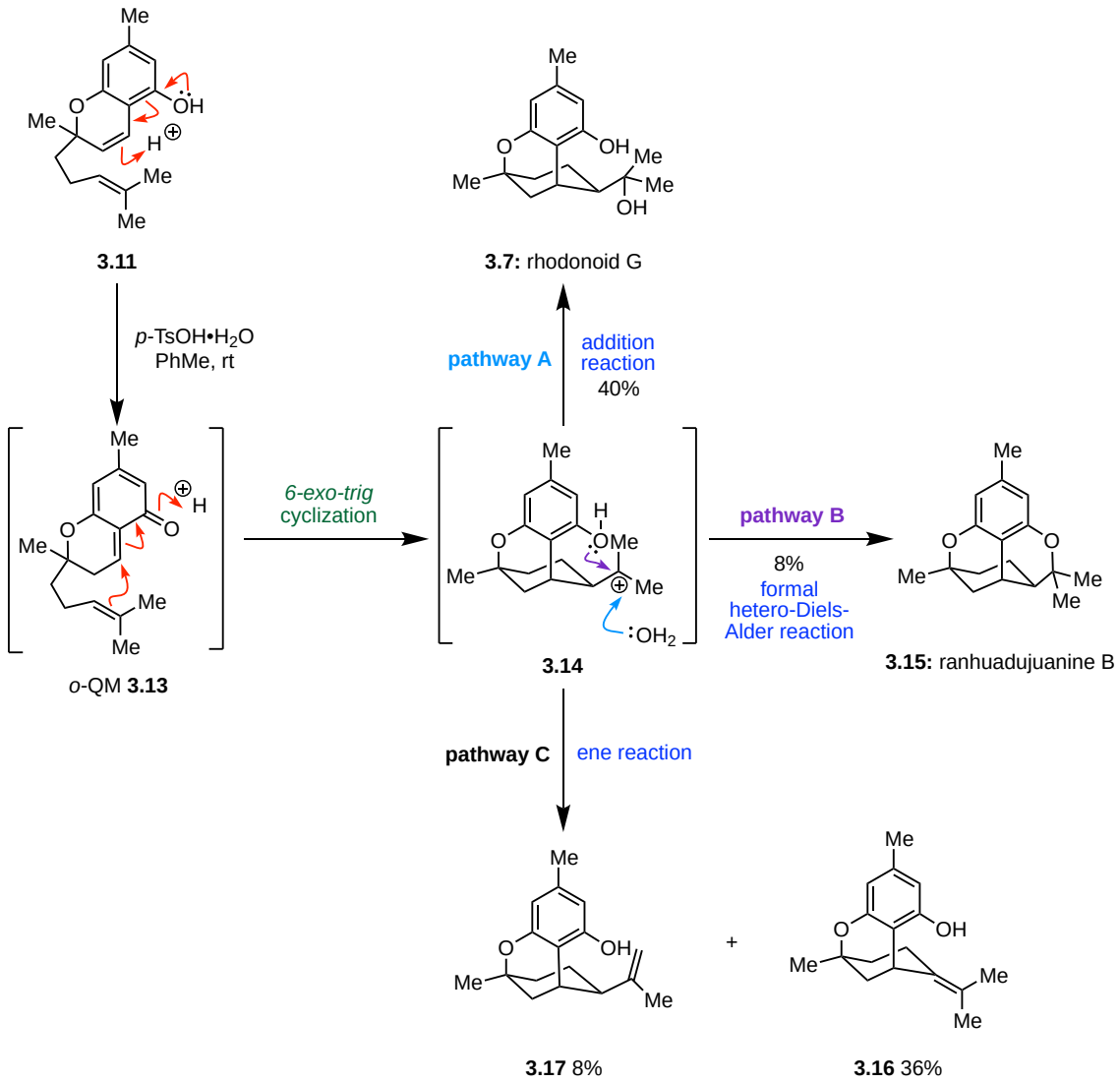
Biomimetic approaches towards the total synthesis of rhodonoids A – G (**3.1** – **3.7**) have all been previously achieved from commercially available orcinol (**3.8**) (**Scheme 3.1**).[3 - 5] Knoevenagel condensation and oxa-6π-electrocyclization with either citral (**3.9**) or farnesal (**3.10**) affords the corresponding chromenes **3.11** and **3.12** respectively. Perhaps unsurprisingly, both chromenes are natural products themselves with **3.11** being an unnamed natural product isolated from a plant of the same genus *Rhododendron anthopogonides*.[6] While confluentin (**3.12**) was first isolated as a novel metabolite from the fungi *Albatrellus ovinus.*[7] Further functionalization of the prenyl moiety *via* either epoxidation or electrophilic addition reactions then affords rhodonoids A – G (**3.1** – **3.7**), the work of which will be described in full detail herein in this introduction.



Scheme 3.1 – Total Synthesis of Rhodonoids (A – G) *via* Chromenes 3.11 and 3.12[3 - 5]

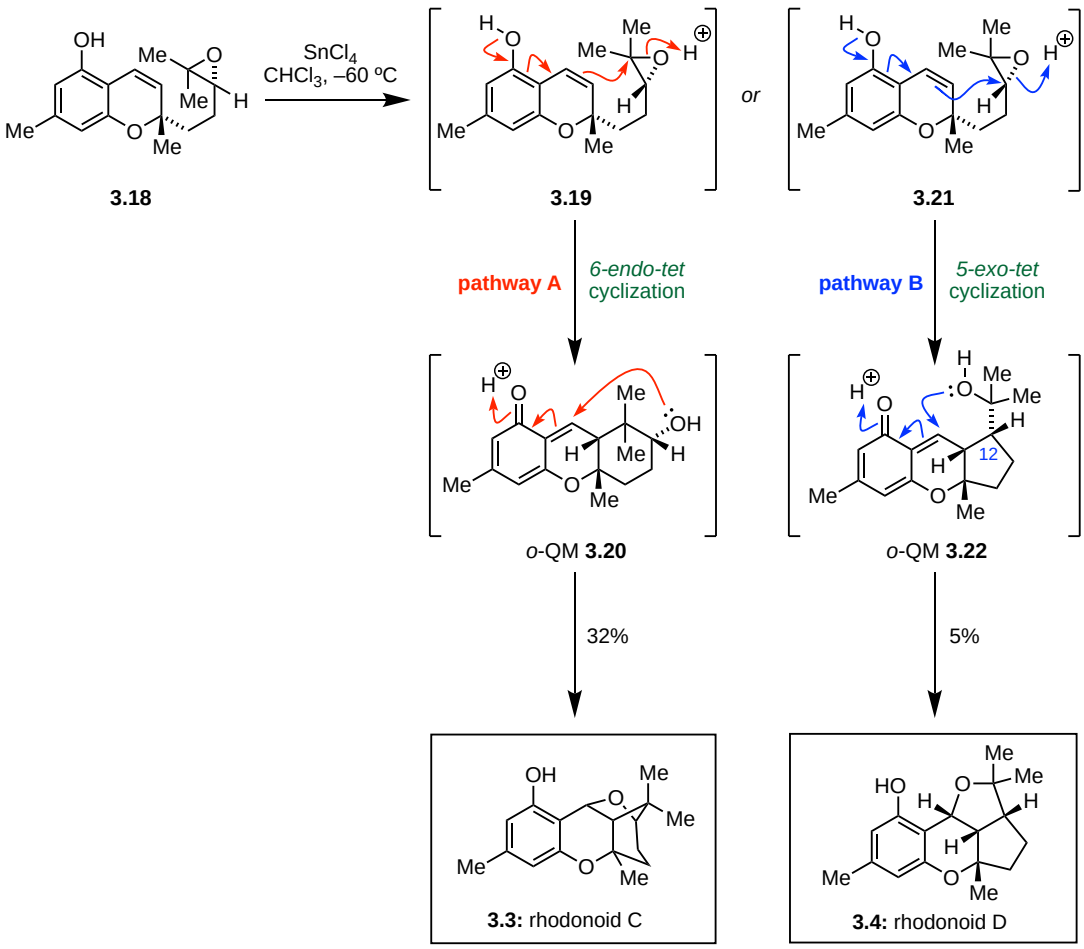
3.1.2 The Total Synthesis of the Rhodonoids C, D and G

In 2017, Wu *et al.* reported the first total synthesis of rhodonoid G (**3.7**) (**Scheme 3.2**).[3] This was achieved through treatment of chromene **3.11** with *p*-TsOH to afford the *o*-QM **3.13**. Formation of the corresponding carbocation **3.14** *via* a *6-exo-trig* cyclization followed by the addition of water then gave rhodonoid G (**3.7**) in 40% (**pathway A**). Interestingly, formation of the citran natural product ranhuadujuanine B (**3.15**) also occurred presumably *via* a stepwise hetro-Diels-Alder reaction (**pathway B**), whilst an ene reaction afforded the elimination products **3.16** and **3.17** in 36% and 8% respectively (**pathway C**).



Scheme 3.2 – Wu and Co-Workers Total Synthesis of rhodonoid G[3]

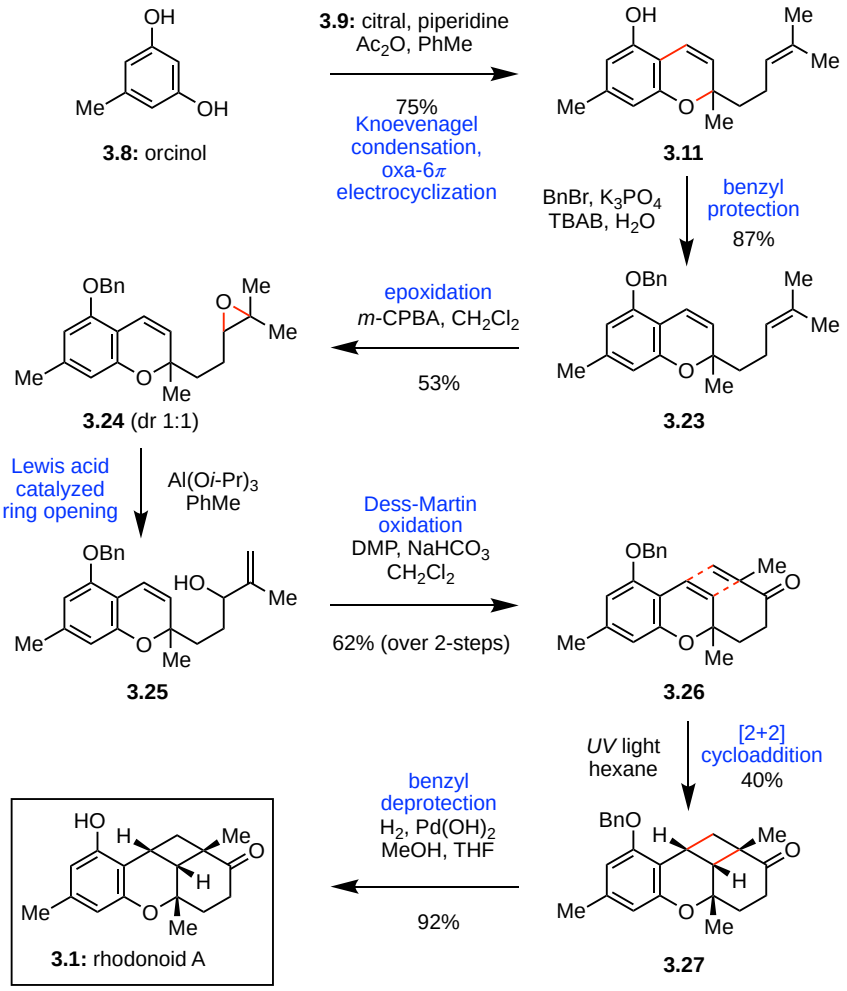
Our group has reported the divergent synthesis of rhodonoids C and D (**3.3** and **3.4**) again *via* biomimetic cascade reactions (**Scheme 3.3**).[4] This involved the regioselective epoxidation of chromene **3.11** to afford **3.18** (dr 1:1). Treatment with $SnCl_4$ resulted in an acid catalyzed 6-*endo-tet* ring opening, most likely *via* the S_N1 mechanism **3.19**. Cyclization of the corresponding *o*-QM **3.20** then afforded rhodonoid C (**3.3**) in 32% (**pathway A**). Simultaneously a 5-*exo-tet* ring opening of **3.21** (leading to inversion at **C12**) also occurred, this time *via* the S_N2 mechanism to afford *o*-QM **3.22**. Nucleophilic attack of the tertiary alcohol to the *o*-QM **3.22** then resulted in rearomatization to give rhodonoid D (**3.4**) in 5% (**pathway B**).



Scheme 3.3 – Total Synthesis of Rhodonoids C and D by Day *et al.*[4]

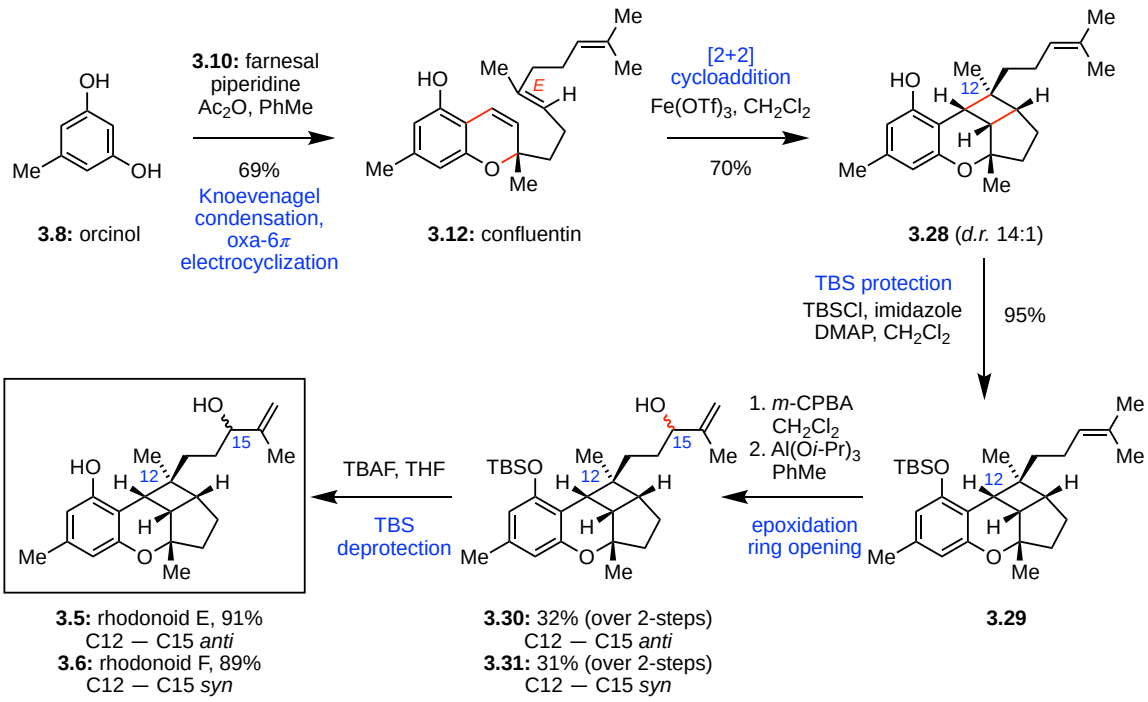
3.1.3 The Total Syntheses of the Rhodonoids A, B, E and F

Wu and co-workers also reported the total synthesis of rhodonoid A (**3.1**) in 2017. This began with Knoevenagel condensation and oxa-6π-electrocyclization of orcinol (**3.8**) and citral (**3.9**) to give chromene **3.11** (**Scheme 3.4**).[5] Benzyl protection of the free phenol then afforded **3.23**, followed by epoxidation with *m*-CPBA to give **3.24** in 53% (dr 1:1). Ring opening of epoxide **3.24** with the Lewis acid Al(O*i*-Pr)$_3$ provided access to the allylic alcohol **3.25**, which was oxidized using Dess-Martin periodinane conditions to give the α,β-unsaturated ketone **3.26** in 62% over 2-steps. A [2+2] cycloaddition of the enone **3.26** under *UV* light, and subsequent benzyl deprotection then afforded rhodonoid A (**3.1**). Overall, this sequence had a low total yield of 8% and required 7-linear steps for the synthesis of **3.1** from orcinol (**3.8**).



Scheme 3.4 – The Total Synthesis of Rhodonoid A by Wu and Co-Workers[5]

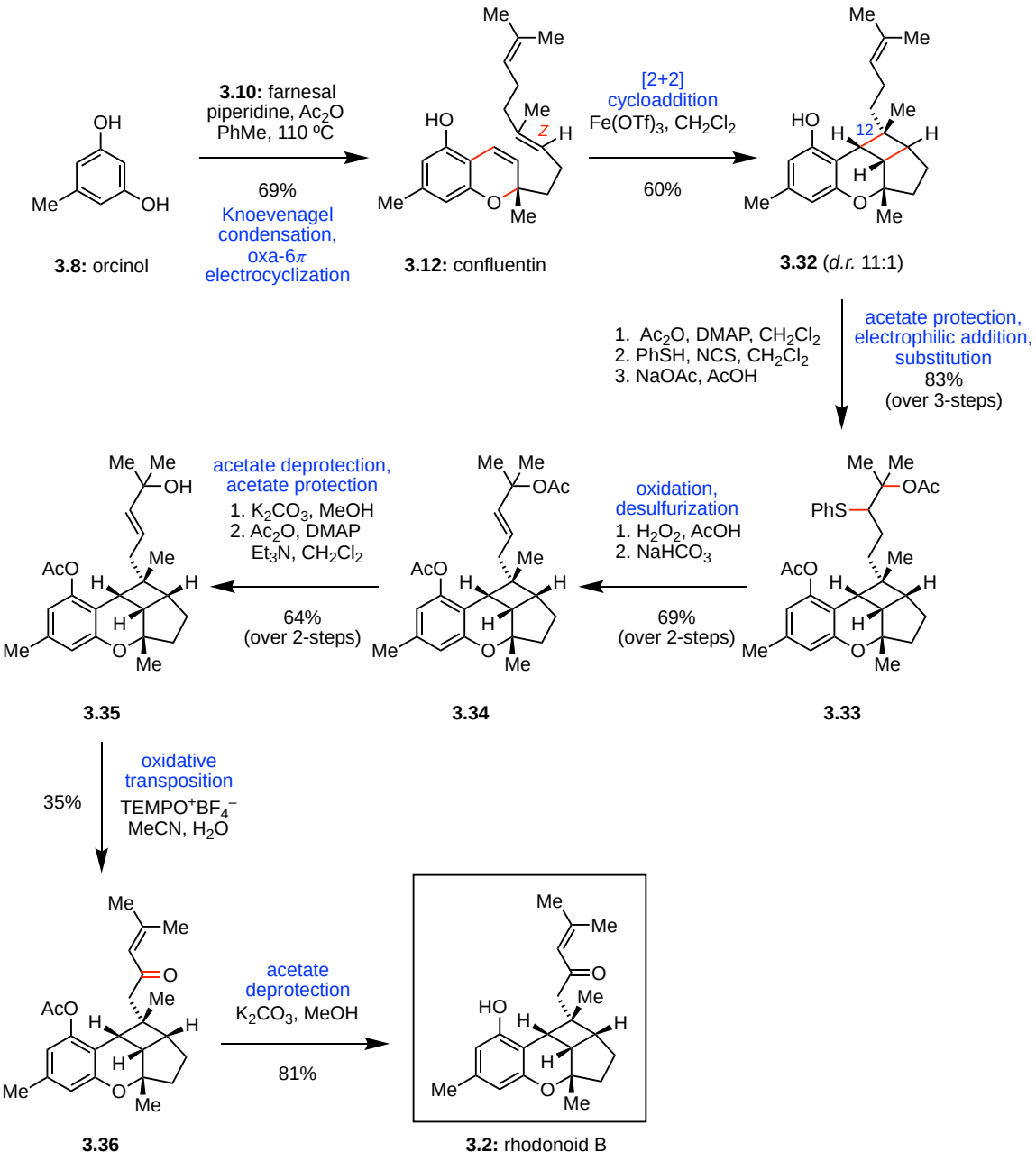
Similarly, to rhodonoids A, C, D, and G, rhodonoids E and F (**3.5** and **3.6**) were also synthesized from a chromene precursor. However this time Wu and co-workers employed the C_{15} merosesquiterpenoid *E*-confluentin (**3.12**) (**Scheme 3.5**).[3] A cationic [2+2] cycloaddition with $Fe(OTf)_3$ afforded the tetracycle **3.28** in a 70% yield. TBS protection of the free phenol **3.28** then gave **3.29**, followed by epoxidation with *m*-CPBA and a Lewis acid catalyzed ring opening to afford the **C12** epimers **3.30** and **3.31**. Finally, TBAF deprotection then gave the desired natural products rhodonoid E (**3.5**) and rhodonoid F (**3.6**) in 91% and 89% respectively.



Scheme 3.5 – Wu and Co-Workers Total Synthesis of Rhodonoids E and F[3]

The total synthesis of rhodonoid B (**3.2**) also began from confluentin (**3.12**), however this time from the *Z* isomer (*derived from 6Z-farnesal*) (**Scheme 3.6**).[5] A cationic [2+2] cycloaddition of this isomer with $Fe(OTf)_3$ afforded tetracycle **3.32** as the major diastereoisomer in 60% (*epimer of **3.28***). Acetate protection followed by electrophilic addition of benzenesulphenyl chloride and substitution with sodium acetate provided tertiary acetoxy sulphide **3.33** in 83%. A 2-step oxidation with H_2O_2 followed by desulfurization then gave **3.34** in 69%. **3.34** was converted to the monoacetate protected phenol **3.35**, then a $TEMPO^+BF_4^-$ oxidative allylic transposition and subsequent deacylation afforded rhodonoid B (**3.2**) in a 28% yield over 2-steps. In total, the synthesis of rhodonoid B (**3.2**) was achieved in a lengthy 11-step route, with an overall yield of 4%.

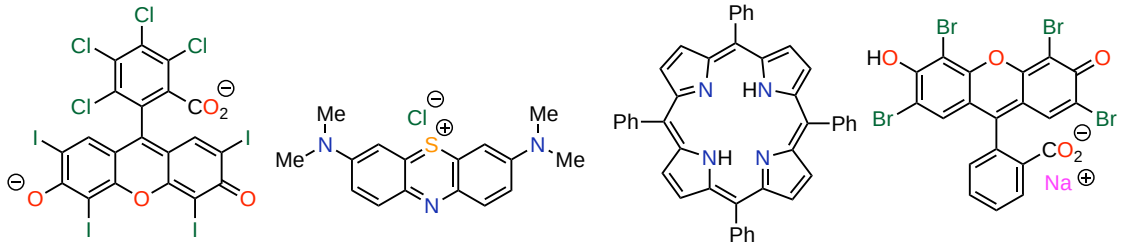
The high step count required for the synthesis of rhodonoids A, B, E and F (as described) in combination with the low yielding nature of these reactions prompted us to consider our own biomimetic route. We envisaged that one solution to achieve this would be through various unique photooxygenation cascade reactions, which we hoped could be employed to gain access to these natural products through a more efficient and higher yielding biomimetic route.



Scheme 3.6 – 11-Step Total Synthesis of Rhodonoid B from Wu *et al.*[5]

3.1.4 Photooxygenation Reactions

Photooxygenation reactions refer to any reaction that occurs with oxidation, light, and the incorporation of molecular oxygen. These reactions are initiated through a photosensitiser, usually a dye or pigment that often contains aromatic functionality (i.e. rose bengal (**3.37**), methylene blue (**3.38**), tetraphenylporphyrin (TPP) (**3.39**), and eosin (**3.40**)) (**Figure 3.2**).



3.37: rose bengal (RB) **3.38:** methylene blue (MB) **3.39:** tetraphenylporphyrin (TPP) **3.40:** eosin

Figure 3.2 – Common Photosensitisers for Photooxygenation Reactions

These photosensitisers (**sens**) enter an excited singlet state (^{1}**Sens***) when exposed to a specific wavelength of light. Intersystem crossing (**ISC**) then occurs converting this singlet state to a more stable triplet state (^{3}**Sens***). The resultant sensitizer is then able to convert its energy *via* a series of reaction cascades to either molecular oxygen (^{3}**O$_2$**) or to the substrate of the photooxygenation process (**Figure 3.3**).[8, 9]

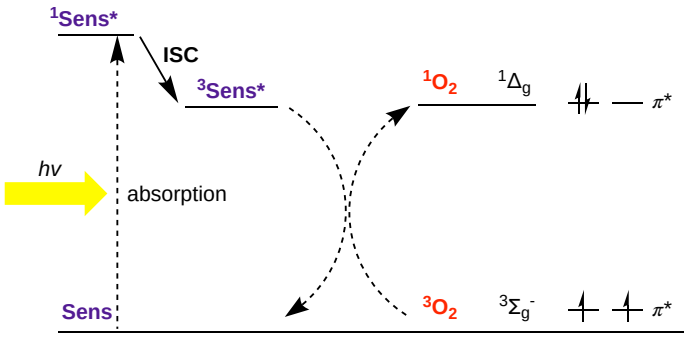
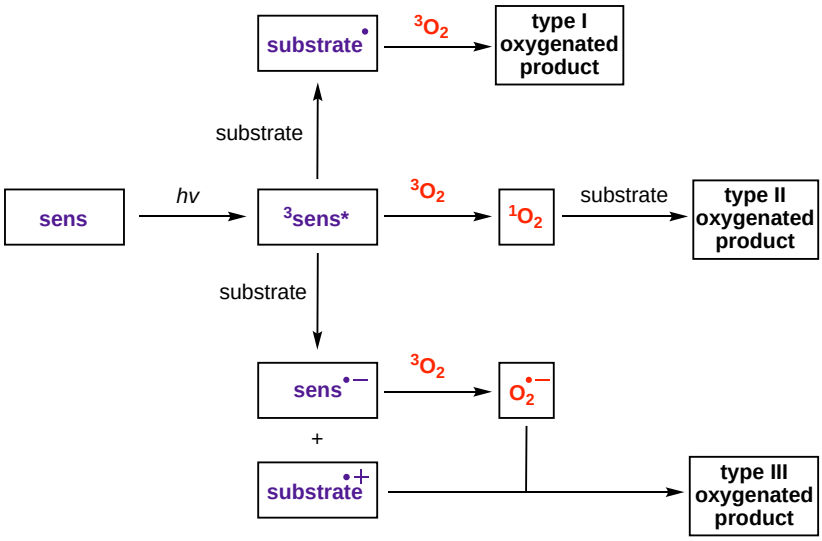


Figure 3.3 – Photooxygenation Reactions with Photosensitisers

There are three types of photooxygenation reactions (Type I, II, and III) based according to the order of transient intermediates formed. In type I reactions the photoactivated sensitiser (^{3}**sens***) interacts to afford a radical substrate, typically through homolytic bond cleavage. This substrate then reacts with ground state molecular oxygen (^{3}**O$_2$**) to yield the photooxygenation product (**Scheme 3.7**).[10]

In type II reactions, the triplet state photosensitiser (^{3}**sens***) acts directly with molecular oxygen (^{3}**O$_2$**) to generate the reactive oxygen species (ROS), singlet oxygen (^{1}**O$_2$**). Singlet oxygen can then add to the substrate in a variety of ways, including Schenck-ene reactions to give hydroperoxides and cycloadditions to afford endoperoxides (**Scheme 3.7**).

During type III reactions an electron transfer between (^{3}sens*) and the substrate results in formation of both a radical anionic photosensitiser and cationic substrate. The resulting anionic photosensitiser then transfers an electron to molecular oxygen ($^3O_2$) affording a superoxide anion ($O_2^{\bullet -}$). Further reaction of the superoxide anion and cationic substrate then gives the oxygenated product (**Scheme 3.7**).



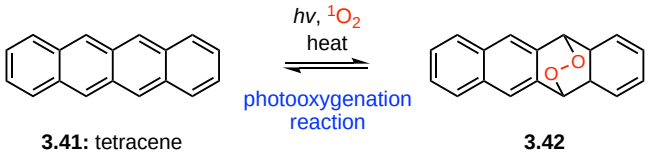
Scheme 3.7 – Type I, II, and III Photooxygenation Reactions

All three types of photooxygenation reactions have been applied in the context of total synthesis.[11 - 14] However notably, type II photooxygenation reactions have been the most extensively used (presumably due to the low energy thresholds required to generate singlet oxygen).

Of course, in nature the most abundant photosensitisers are chlorophylls, present in all plants (and some cyanobacteria) that undergo photosynthesis.[15] Photooxygenation reactions are ubiquitous to nature, occurring in the presence of sunlight and atmospheric oxygen. These reactions are ideal for use in biomimetic synthesis, as they can be mimicked synthetically in a laboratory with use of the appropriate reaction conditions.

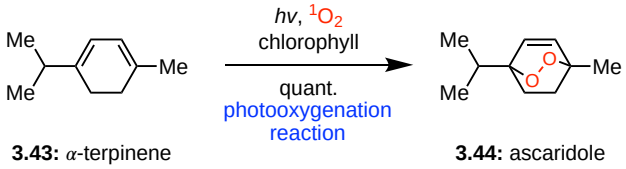
The first reported example of a photooxygenation reaction was in 1867 by Carl J. Fritzsche, who observed the reversible formation of a precipitate in a solution of tetracene (**3.41**) that was exposed to air and ambient light (**Scheme 3.8**).[16] At the time, the structure of the reagent and product was unknown, and it was not until some 60 years later with the help of chemists Charles Moureu,[17] Adolf Windaus[18] and Hans Kautsky[19] that evidence for a metastable reactive state of

molecular oxygen was reported. Only in 1968 was the structure of singlet oxygen unequivocally established by Christopher S. Foote.[20]



Scheme 3.8 – The First Example of Photooxygenation by Fritzsche in 1867[16]

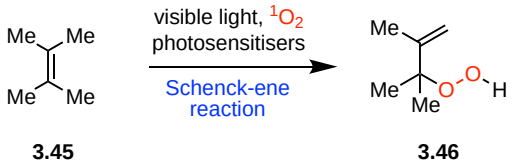
In 1944, Schenck and Ziegler reported the first example into the use of singlet oxygen ($^1O_2$) in total synthesis.[21] Irradiation of α-terpinene (**3.43**) in the presence of the photosensitiser eosin (**3.40**), afforded ascaridole (**3.44**). In the following years this synthesis was improved by the choice of a more suitable chlorophyll photosensitiser to give ascaridole (**3.44**) in quantitative yield (**Scheme 3.9**).[22]



Scheme 3.9 – Schenck and Ziegler's Total Synthesis of ascaridole[22]

3.1.5 Schenck-Ene (Singlet Oxygen-Ene) Reactions

In 1948, Schenck also reported the first dye sensitized singlet oxygen-ene reaction of terpenes (known today as the Schenck-ene reaction).[23] Later work then focused on the photooxygenation of tetramethylethylene with a variety of photosensitisers (i.e. rose bengal (**3.37**), methylene blue (**3.38**), and chlorophyll) (**Scheme 3.10**).[24]

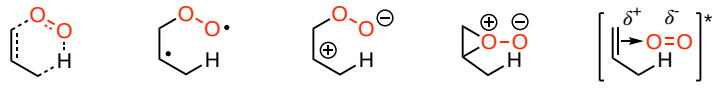


Scheme 3.10 – Schenck's 1958 Singlet Oxygen-Ene Reaction[24]

Efforts towards the elucidation of the Schenk-ene reaction mechanism have been extensively studied. This ranges from the identification of the reactive intermediates *via* spectral,[25,] photochemical,[20, 26] and more classical chemical experiments.[20] Additionally, various kinetic

isotope effects[20, 27] and solvent dependence studies have been performed.[28] Theoretical models have also been used to analyse these reactions ranging from frontier molecular orbital theory[29] to more sophisticated *ab initio* methods.[30] Of course, predicting the reaction coordinate of electronically excited molecules such as singlet oxygen using current theoretical methods is somewhat limited (*even with the best models*). Instead, this reaction mechanism is better elucidated through experimental data.

On account of the reactive nature of the Schenck-ene reaction, a diverse range of mechanisms have been suggested. Arguments in favour of a concerted pathway *via* the transition state **3.47**,[31] or a stepwise mechanism *via* the biradical intermediate **3.48** have both been proposed.[30] Furthermore, zwitterionic intermediates (i.e. **3.49**)[32] and perepoxide like intermediates (i.e. **3.50**),[33] through the formation of a reversible exciplex **3.51** have also been implicated in this mechanism (**Figure 3.4**).[34]



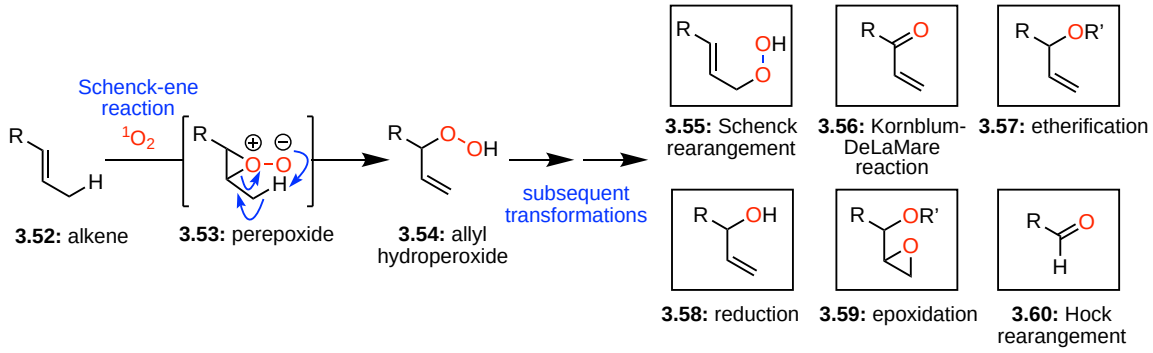
3.47 **3.48** **3.49** **3.50** **3.51**

Figure 3.4 – Proposed Transition States Intermediates for the Schenck-ene Reaction[31 - 34]

Kinetic data clearly favours a stepwise mechanism[32] while the suprafacial selectivity and lack of Markovnikov orientation rules out the intermediary of any longer lived diradical (i.e. **3.48**) and zwitterionic intermediates (i.e. **3.49**).[32, 35]

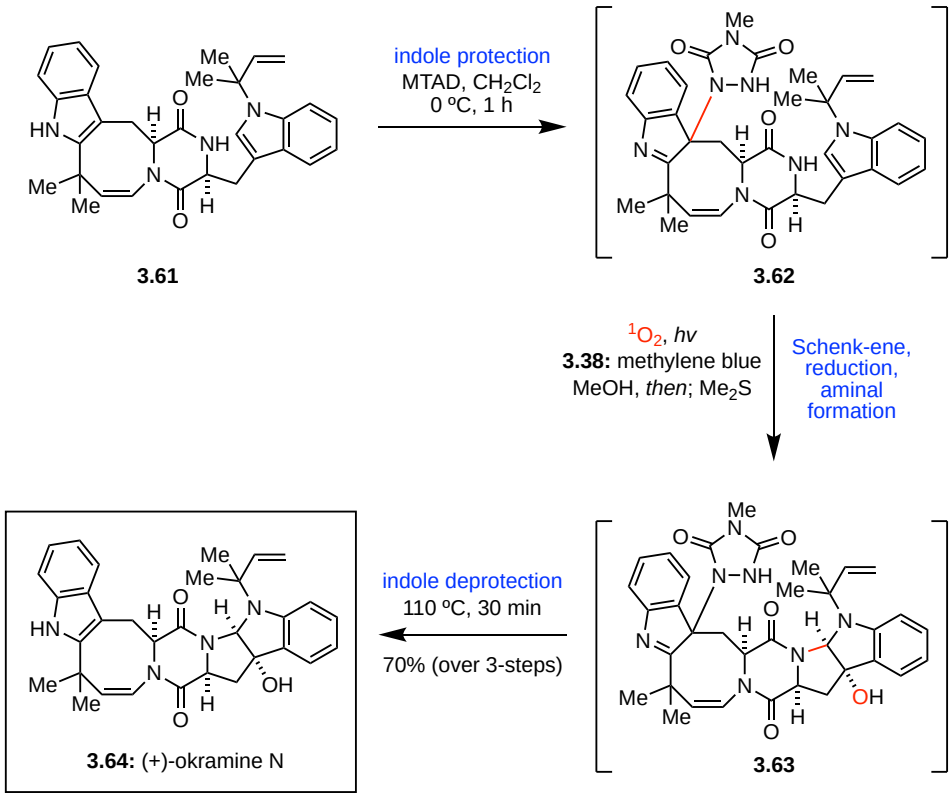
To date, the majority of experimental data accumulated suggest that the first identifiable step in the sequence is the reversible formation of an exciplex **3.51**, formed from an excited state charge transfer complex of singlet oxygen ($^1O_2$) and the alkene **3.52**.[32, 34] Conversion of this complex **3.51** into the perepoxide **3.50** then occurs as the rate limiting step, which is dependent on the electron density of the alkene. This perepoxide intermediate **3.50** was first proposed by D. B. Sharp in 1960.[36] Provided the presence of an allylic γ-hydrogen atom (ideally perpendicular to the alkene) a 1,3-allylic transposition and ring opening of the perepoxide (ene reaction) then occurs to afford hydroperoxide **3.54**. The products of the Schenk-ene reaction can then undergo subsequent transformations to afford a wide range of chemical structures and building blocks (**3.55** – **3.60**) (**Scheme 3.11**).[9, 37, 38] In this chapter we hope to further explore some of these transformations, particularly we are interested in the Schenck rearrangement (i.e. **3.55**), Kornblum-DeLaMare

rearrangement (i.e. **3.56**) and reduction reactions. The mechanisms of these reactions will be discussed later in this chapter (*vide infra*).



Scheme 3.11 – The Schenck-ene Reaction and Subsequent Transformations[32 – 38]

Another example in the use of the Schenck-ene reaction in total synthesis includes the synthesis of (+)-okramine N (**3.64**) reported by Baran *et al.* in 2003 (**Scheme 3.12**).[39] In this sequence diketopiperazine **3.64** is synthesized in 3-steps from commercially available (*S*)-tryptophan methyl ester. A one-pot indole protection with *N*-methyltriazolinedione (MTAD), followed by a Schenck-ene reaction, reduction and aminal formation then afforded intermediate **3.63**. Finally, indole deprotection gave (+)-okramine N (**3.61**) in a total yield of 20% over 4-steps.



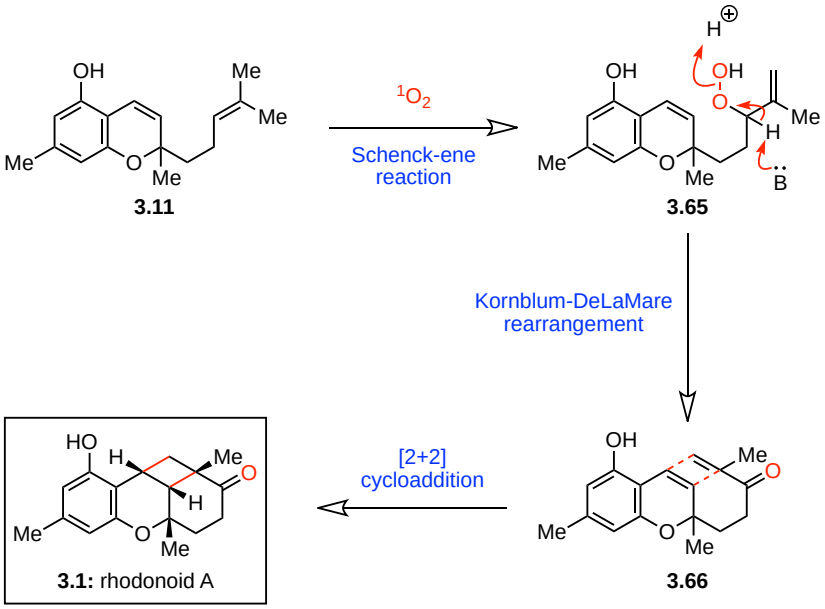
Scheme 3.12 – Baran's and Co-Workers Total Synthesis of (+)-okramine N[39]

Not only does the Schenck-ene reaction exhibit high sustainability, with 100% atom economy, but it also employs relatively cheap and abundant reagents such as O_2, metal-free catalysts, alkenes and visible light. Additionally, these reactions also occur with good regio-, and stereochemical control, allowing for the synthesis of complex molecules with stereochemical complexity.[38]

Today, Schenck-ene reactions have become a powerful avenue enabling direct access to a diverse set of allylic alcohol and oxidized derivatives. Photooxygenation represents one of the most important hydrocarbon functionalization reactions available to the synthetic organic chemist. It is hoped that a Schenck-ene reaction could be employed in the biomimetic total synthesis of rhodonoids A, B, E, and F.

3.1.6 Proposed Biogenic Relationship Between Rhodonoids A, B, E and F

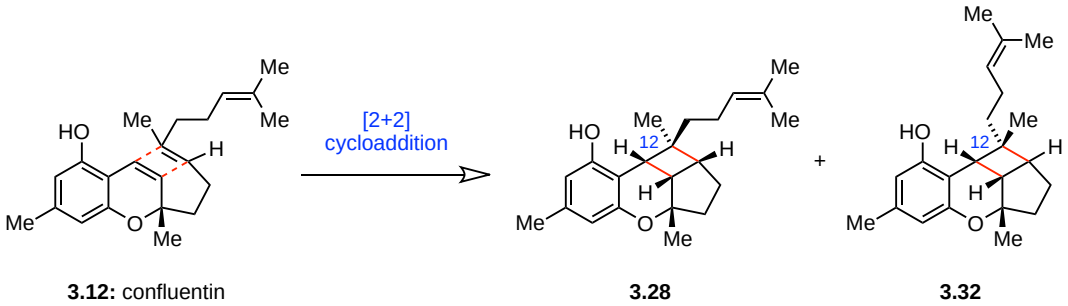
Given that chromene **3.11** has previously been shown *via* biomimetic synthesis to be the probable precursor of the monoterpenoids rhodonoids C, D, G and ranhuadujuanine B (being synthesized in 1-step from **3.11**) we thought it likely that it would could also be the precursor of rhodonoid A (**3.1**).[3, 4] A singlet oxygen-ene reaction of the prenyl chromene **3.11** could give hydroperoxide **3.65** (**Scheme 3.13**). We then envisaged a Kornblum-DeLaMare rearangement would give **3.66**, *via* a base catalyzed α-proton abstraction and O-O cleavage to form a ketone. A subsequent intramolecular [2+2] photocycloaddition could then afford rhodonoid A (**3.1**).



Scheme 3.13 – The Proposed Biosynthesis of Rhodonoid A

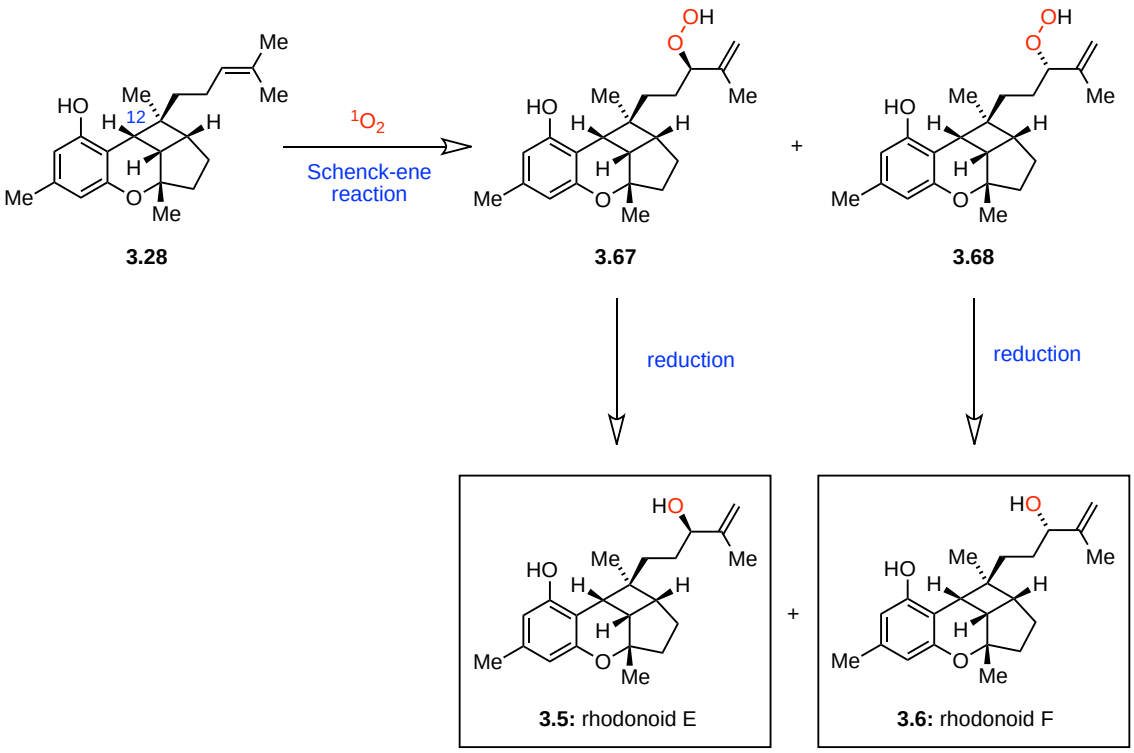
Singlet oxygen-ene reactions could also be implicated in the biosynthesis of rhodonoids B, E and F (**3.2, 3.5** and **3.6**). First, orcinol derived confluentin (**3.12**) (as a *E* and *Z* mixture) could undergo

a [2+2] photocycloaddition to afford the cyclobutane diasteromers **3.28** and **3.32** (epimers at **C12**) (**Scheme 3.14**).



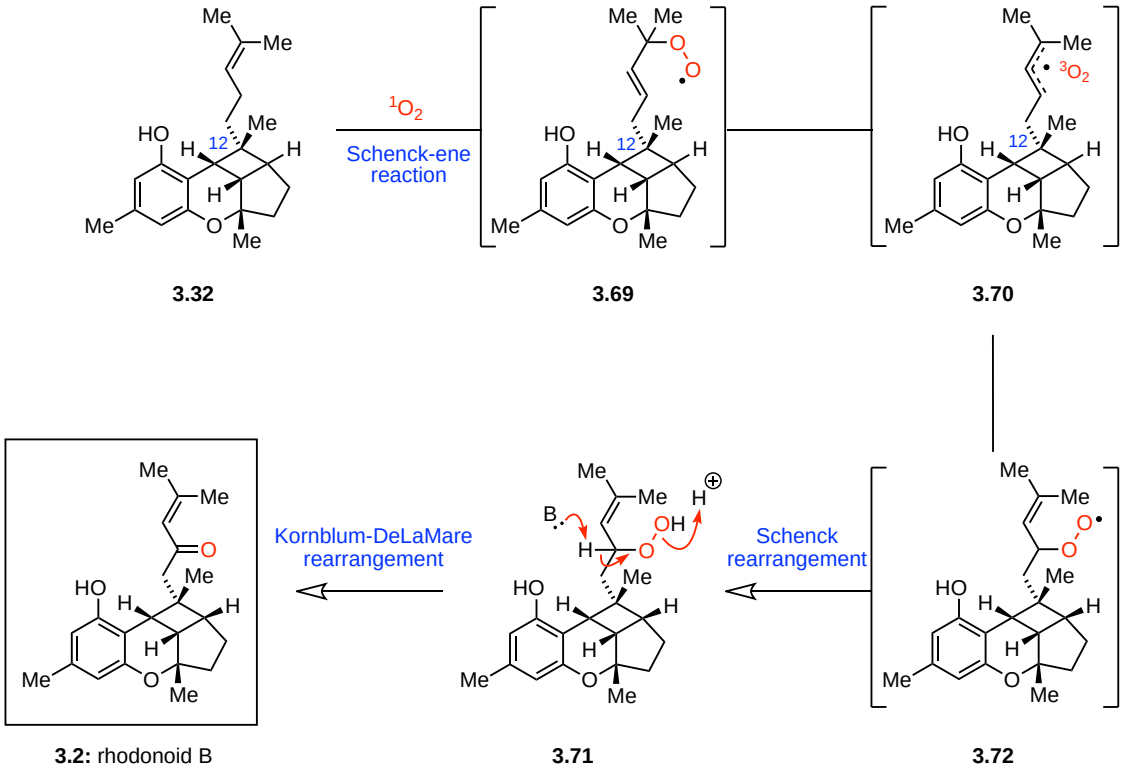
Scheme 3.14 – [2+2] cycloaddition of confluentin to afford 3.28 and 3.32

A Schenck-ene reaction of the cyclobutane **3.28** could form the diasteromeric hydroperoxides **3.67** and **3.68**, which after reduction would afford rhodonoid E (**3.5**) and rhodonoid F (**3.6**) respectively (**Scheme 3.15**).



Scheme 3.15 – Proposed Biosynthesis of Rhodonoids E and F

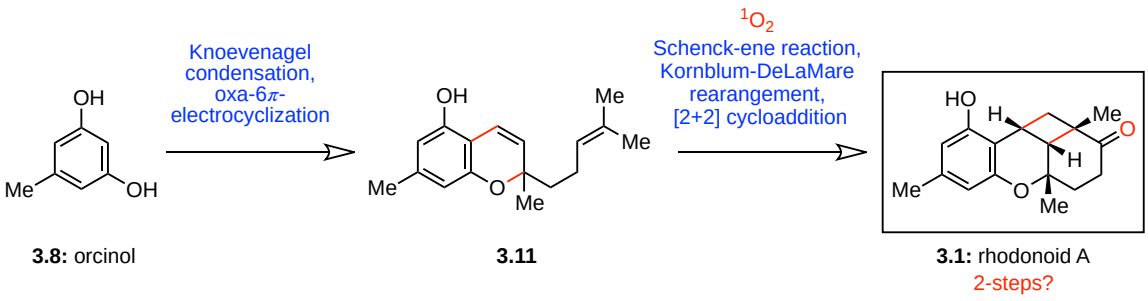
We also proposed that Rhodonoid B (**3.2**) could be synthesized from a singlet oxygen-ene reaction of cyclobutane **3.32** to afford the peroxy radical **3.69** (**Scheme 3.16**). A Schenck rearangement of this reactive radical intermediate *via* the disassociative η^3 radical **3.70**, would give a 1,3-transposition, followed by a H atom abstraction to give the hydroperoxide **3.71**. A base catalyzed Kornblum-DeLaMare rearrangement would then afford rhodonoid B (**3.2**).



Scheme 3.16 – The Proposed Biosynthesis of Rhodonoid B

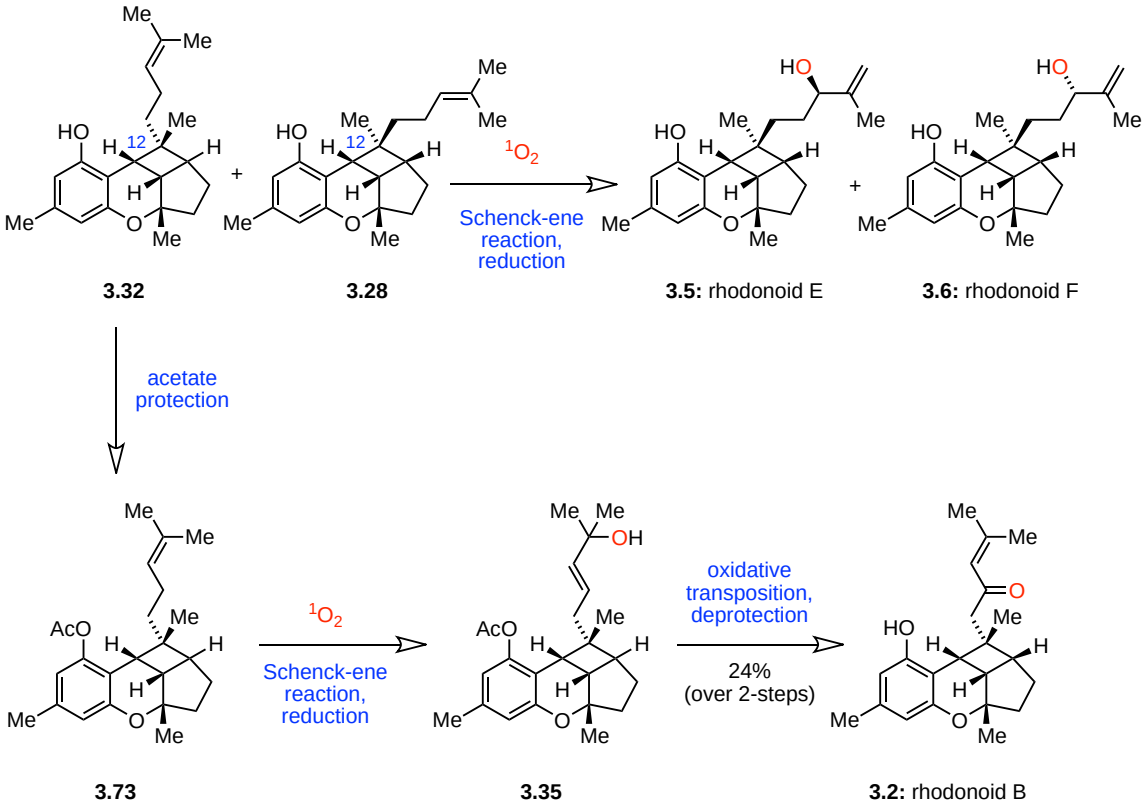
3.1.7 Project Aims

We aimed to test the proposal of this biosynthesis through a total synthesis of rhodonoids A, B, E and F from the polyketide derived and comercially available orcinol (**3.8**). The ideal outcome would be to synthesize rhodonoid A (**3.1**) in 1-step from chromene (**3.11**) through a one-pot Schenk-ene, Kornblum-DeLaMare, and [2+2] cycloaddition cascade. As irradiation with light is required for both the synthesis of singlet oxygen (necessary for the Schenck-ene reaction) and the [2+2] cycloaddition this was thought to be a plausible (**Scheme 3.17**). If this direct approach was found to be infeasibile, a more cautious stepwise approach could be investigated.



Scheme 3.17 – Proposed 2-Step Biomimetic Syntheis of Rhodonoid A

It was also hoped that a one-pot cascade *via* a Schenk-ene and reduction of tetracycle **3.68** could afford rhodonoids E and F (**3.5** and **3.6**). Whilst rhodonoid B (**3.2**) could be acessed through a formal total synthesis of the intermediate hydroperoxide **3.35** which following literature procedures can undergo a 2-step oxidative transposition to give rhodonoid B (**3.2**) (**Scheme 3.18**).

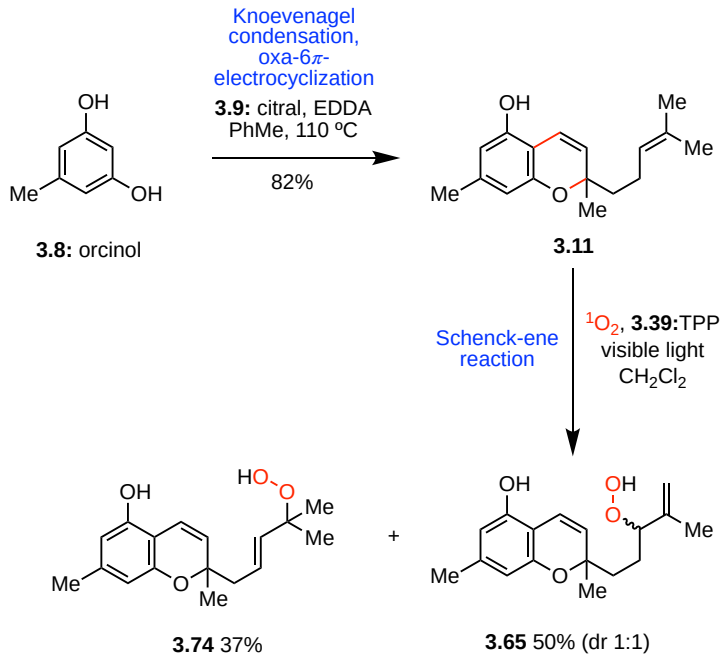


Scheme 3.18 – Proposed Biomimetic Syntheis of Rhodonoids B, E and F

3.2 Results and Discussion

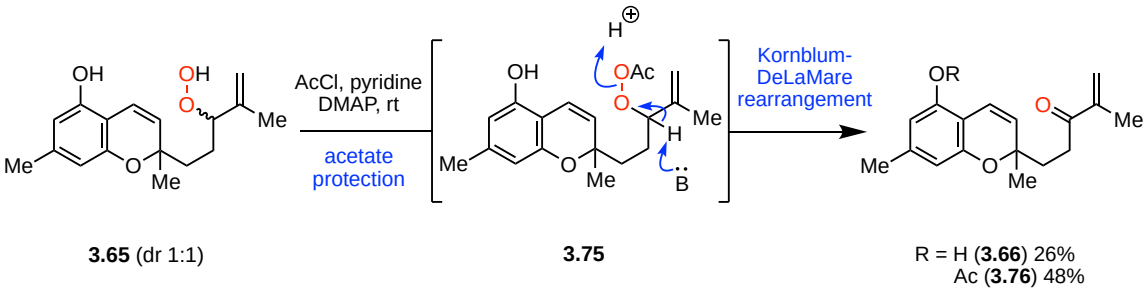
3.2.1 The Biomimetic Total Synthesis of Rhodonoid A

The synthesis of rhodonoid A (**3.1**) began with chromene **3.11**, which was prepared from orcinol (**3.8**) using catalytic EDDA and citral (**3.9**) according to known procedure.[4] A Schenck-ene reaction of **3.11** in the presence of O_2, visible light and TPP (**3.39**) then afforded the hydroperoxide **3.74** in 37% and the desired regioisomer **3.65** in 50% as a 1:1 mixture of diastereoisomers (**Scheme 3.19**).



Scheme 3.19 – Synthesis of Chromene 3.11 and hydroperoxides 3.65 and 3.74

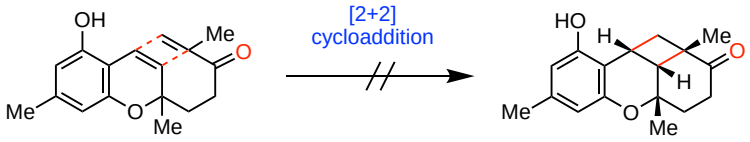
Treatment of hydroperoxide **3.65** with Et_3N in CH_2Cl_2 at room temperature then gave the Kornblum-DeLaMare product **3.66** in a low yield of 8%. Dissappointingly, reaction with either pyridine or piperidine only afforded trace amounts of the desired product. The best results were obtained upon reaction of **3.65** with acetyl chloride, pyridine and DMAP. Presumably this reaction occured through the peroxy intermediate **3.75**, with DMAP acting as a nucleophillic catalyst to activate the Kornblum-DeLaMare rearrangement.[38] Unsuprisingly, the formation of the acetate protected α,β-unsaturated ketone **3.76** was also observed (**Scheme 3.20**).



Scheme 3.20 – Kornblum-DeLaMare Rearrangement of hydroperoxide 3.65

With **3.66** in hand, attempts towards a photocatalyzed [2+2] cycloaddition were investigated (**Table 3.1**). An initial attempt using identical conditions to that previously reported by Hsung and Tang in their [2+2] cycloadition of a Bn protected varient **3.20** was attempted (**entry 1**).[5] Unfortunately, the free phenol **3.65** was not soluble in hexane, and upon treatment with *UV* light

no reaction was observed. Of course, these types of [2+2] cycloaddition reactions do not have to occur exclusively through direct excitation with *UV* light, but can also be induced through an energy transfer from a photoexcited sensitizer.[40] Due to the ability of acetone to act as a triplet sensetizer, we attempted this reaction with acetone and *UV* light at room temperature (**entries 2 and 3**). Again, no reaction was observed after 8 h and only decomposition after 24 h. Further attempts with the thioxanthone photosensitizers **3.77** and the pyrylium photosensitizer **3.78** also gave no reaction (**entries 4 – 6**). A more biomimetic attempt through the use of sunlight rather than *UV* light was also attempted, this time using the methylene blue photosensitizer **3.38**, unfortunately no reaction was observed (**entry 7**).

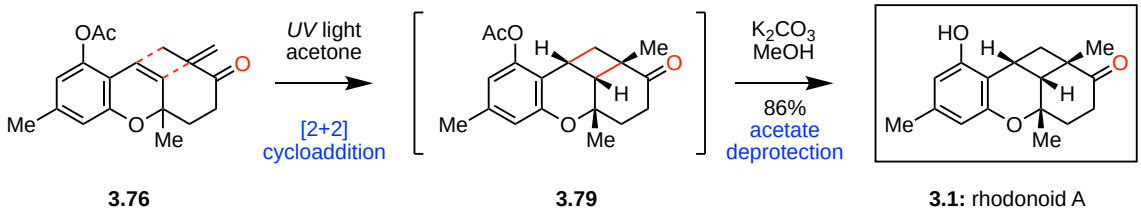


3.66 **3.1:** rhodonoid A

Table 3.1 – Conditions Screened for the Photochemical [2+2] Cycloaddition of 3.66

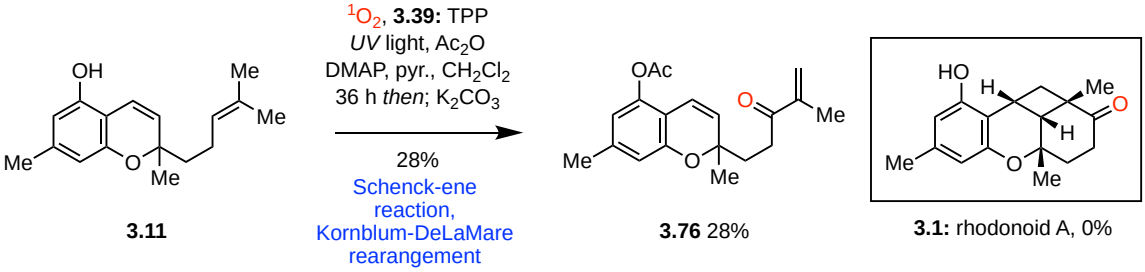
Entry	Photosensitizer (2 mol%)	Light Source	Conditions	Result
1	--	*UVA*	hexane, rt, 12 *h*	NR
2	--	*UVA*	acetone, rt, 8 h	NR
3	--	*UVA*	acetone, rt, 24 h	decomp.
4	**3.77:** thioxanthone	*UVA*	THF, rt, 16 h	NR
5	**3.77:** thioxanthone	*UVA*	acetone, rt, 48 h	decomp.
6	**3.78:** 4-MeO-TPT	**Blue LED**	DCE, 0 °C, 5 h	decomp.
7	**3.38:** methylene blue	sunlight	$CDCl_3$, rt, 4 h	NR

Having already serendipitously gained access to the acetate protected α,β-unsaturated ketone **3.76** the attempted [2+2] photocyclization was attempted again. Gratifyingly, exposure of **3.76** to *UV* light in hexane afforded intermediate **3.79**, direct treatment with K_2CO_3 and MeOH then afforded rhodonoid A (**3.1**) in 51% over 2-steps. Alternatively, use of acetone instead of hexane gave an imporoved yield of 86% (**Scheme 3.21**).



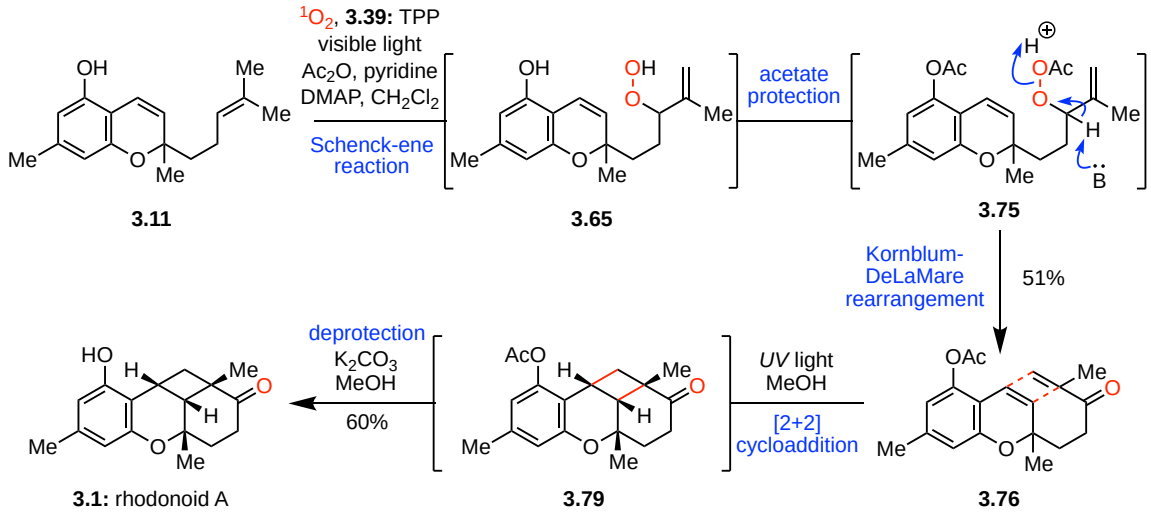
Scheme 3.21 – Photochemical [2+2] Cycloaddition of 3.80 to Rhodonoid A

Having achieved the synthesis of rhodonoid A (**3.1**), our efforts turned towards the development of a one-pot, photochemical method for the direct conversion of **3.11** into **3.1**. Reaction of chromene **3.11** with TPP (**3.39**), O_2, Ac_2O, DMAP and pyridine in the presence of *UVA* light was undertaken. These reaction conditions were first disclosed by Laroche and Nay in their investigations of the photooxygenation of resinic diterpenes.[38] Addition of K_2CO_3 was then added in the hope of an acetate deprotection to afford rhodonoid A (**3.1**) (**Scheme 3.22**). Regrettably, we only observed formation of the α,β-unsaturated ketone **3.76** in 28%. This suggeted that the desired Schenck-ene and Kornblum-DeLaMare cascade were infact occuring, but that the reaction was not undergoing the desired [2+2] cycloaddition or deprotection.



Scheme 3.22 – Attempts Towards a One-Pot Synthesis of Rhodonoid A

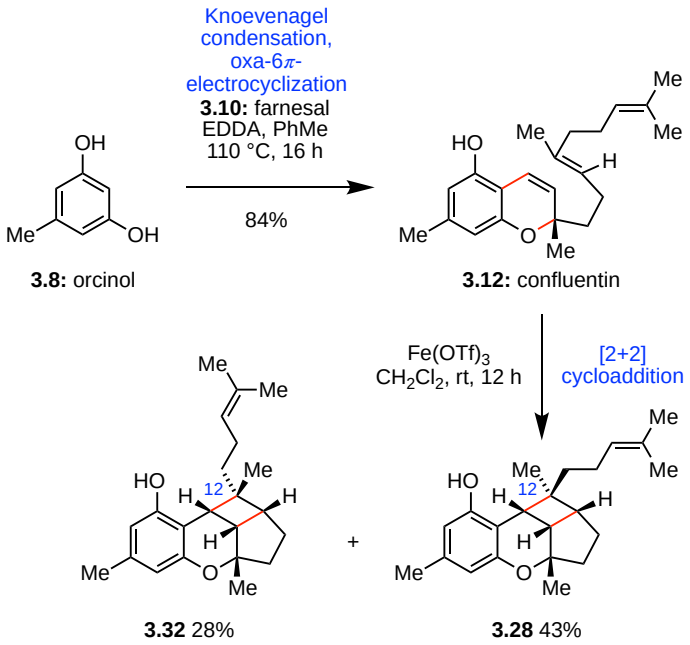
Although our initial attempt at a one-pot transformation proved elusive, efforts towards a more efficient two-step sequence were investigated. Gratifyingly it was found that a one-pot Schenck-ene/ Kornblum-DeLaMare rearrangement of chromene **3.11** was successful this time with visible light to afford the α,β-unsaturated ketone **3.76** in 51% after flash chromatography. Enone **3.76** was then disolved in MeOH and left under *UV* light at room temperature to form **3.79**, which was subsequently deprotected by direct addition of K_2CO_3 to afford rhodonoid A (**3.1**) in 60% yield (**Scheme 3.23**). This 2-step (31% overall yield) sequence compares favourably to the previous synthesis of rhodonoid A (**3.1**) by to Wu and co-workers, who reported a 6-step (11% overall yield) synthesis to convert **3.11** into **3.1**.[5]



Scheme 3.23 – 2-Step Sequence from Chromene 3.11 to Rhodonoid A

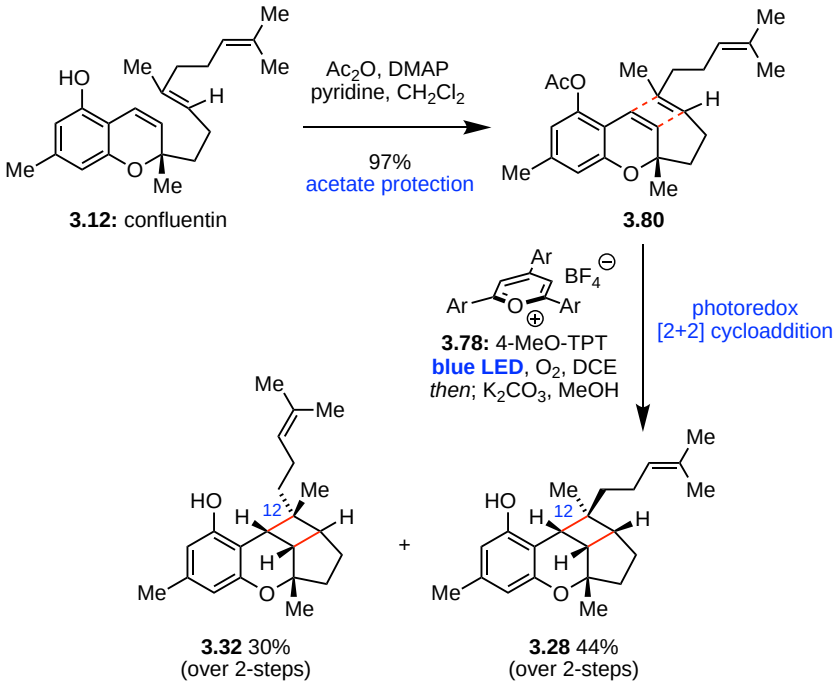
3.2.2 The Biomimetic Total Synthesis of Rhodonoids B, E and F

The Schenck-ene reaction was also invoked in the biomimetic synthesis of rhodonoids B, E and F. Confluentin (**3.12**) was synthesized as a 1.4:1 mixture of *E* and *Z* alkene isomers, through reaction of orcinol (**3.8**) with farnesal (**3.10**, as mixture of isomers) and catalytic EDDA.[3] Wu *et al*. previously reported the diastereoselective synthesis of confluentin (**3.12**) through preparation of farnesal as single *Z* and *E* alkenes. Instead we decided to carry out a divergent intramolecular Lewis acid catalyzed [2+2] cycloaddition with $Fe(OTf)_3$ on the mixture to give **3.28** and **3.32** in 43% and 28% respectively (**Scheme 3.24**). Cyclobutanes **3.28** and **3.32** were separable by careful flash chromatography on SiO_2. Frustratingly, all attempts towards a photochemical [2+2] cycloadditions of Confluentin (**3.12**) using *UVA* light gave only decomposition.



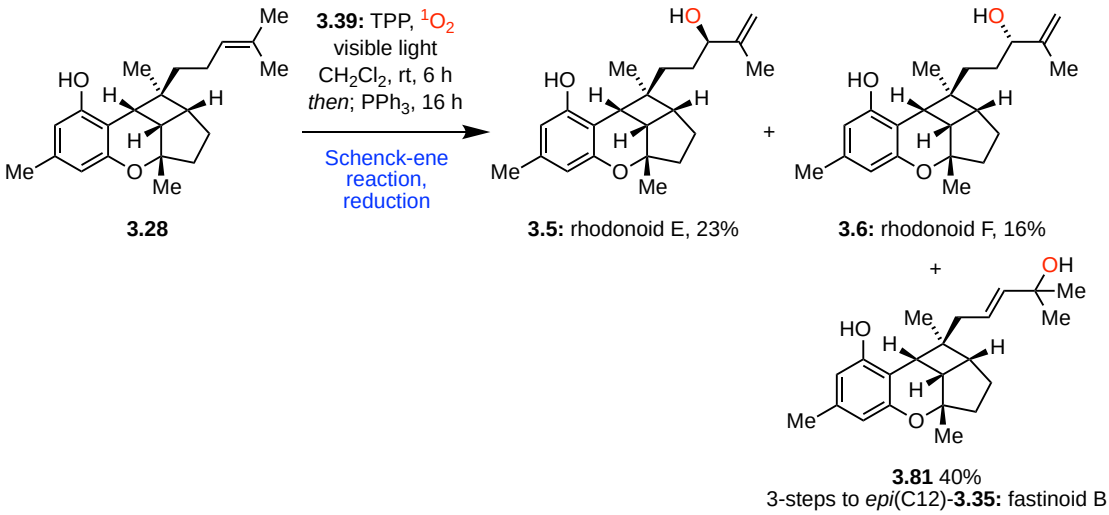
Scheme 3.24 – Lewis Acid Catalyzed [2+2] Cycloaddition of Confluentin

Alternatively, the desired [2+2] cycloaddition could also be achieved through acetate protection to afford chromene **3.80**, as 1:1.4 mixture of *Z* and *E* alkene isomers. Subsequent [2+2] cycloaddition in the presence of the triarylpyrylium organic photocatalyst 4-MeO-TPT (**3.78**). Subsequent deprotection then afforded tetracycles **3.28** and **3.32** in 44% and 30% respectively (**Scheme 3.25**).



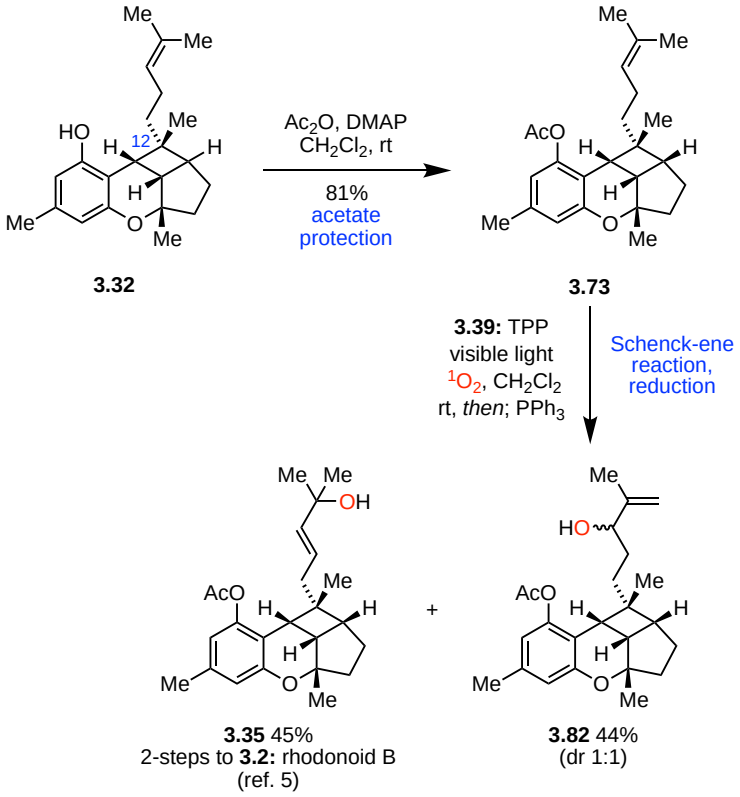
Scheme 3.25 – Photoredox [2+2] Cycloaddition of Confluentin

A Schenck-ene reaction of cyclobutane **3.28** using TPP (**3.78**) as a photosensitizer followed by direct reduction of the hydroperoxide intermediates with PPh_3 afforded rhodonoid E (**3.5**) and rhodonoid F (**3.6**) in 23% and 16% yield respectively (**Scheme 3.26**). The tertiary alcohol and proposed natural product **3.81** was also obtained in 40%. Interestingly, **3.81** completes a formal total synthesis of a related natural product fastinoid B (*epi*-**3.35**), which is an epimer of rhodonoid B (**3.35**). These compounds were separable by careful flash chromatography using SiO_2 impregnated with 1% silver nitrate.[41] In comparison Wu and co-workers converted **3.28** into rhodonoid E (**3.5**) and rhodonoid F (**3.6**) in 4-steps and with an overall yield of 28% and 26% respectively.[3]



Scheme 3.26 – The Total Synthesis of Rhodonoids E and F

Next, we employed singlet oxygen chemistry in the formal synthesis of rhodonoid B (**3.2**), which was achieved by formation of a tertiary alcohol **3.35**. This intermediate has been converted to **3.2** by Wu *et al.* in 2 further steps.[5] First, cyclobutane **3.32** was acylated to afford **3.73**, followed by Schenck-ene reaction and reduction of the hydroperoxide using PPh_3 to give **3.35** in 45%, alongside the secondary allylic alcohol diastereomers **3.82** which were isolated as an inseparable mixture (**Scheme 3.27**). Wu's previous synthesis of rhodonoid B (**3.2**) used 7-steps (37% yield) to convert **3.32** into **3.2**, compared to our 2-step synthesis (36% yield).[5]

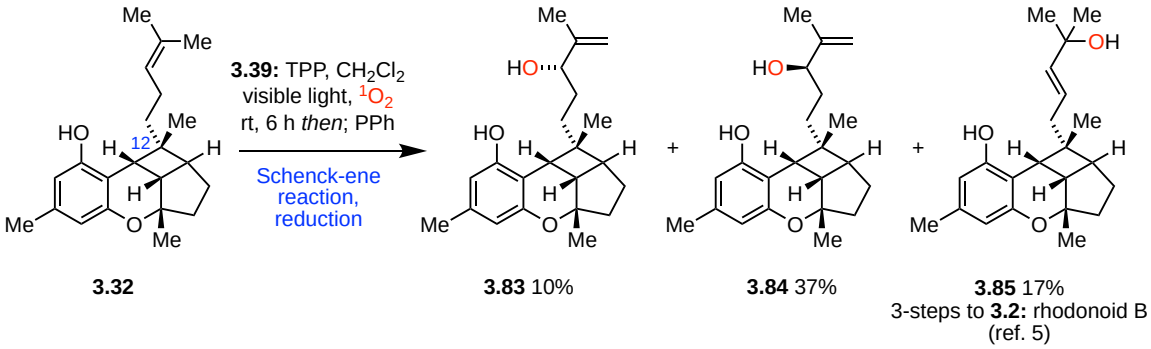


Scheme 3.27 – Formal Total Synthesis of Rhodonoid B

3.2.3 Synthesis of Rhodonoid E and F Analogues

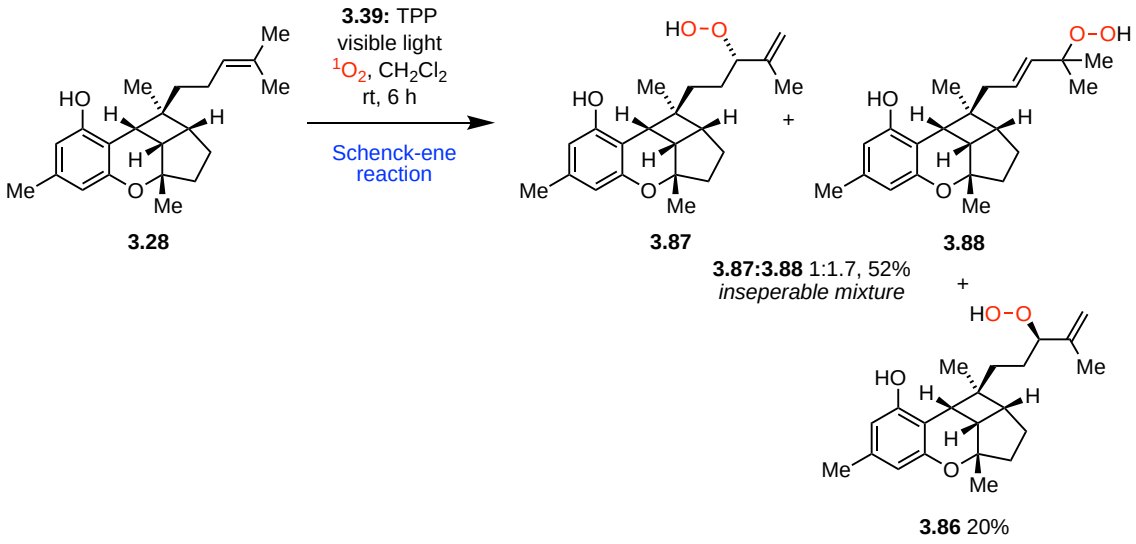
In addition to the synthesis of rhodonoids E and F, we through it might also be useful to synthesize both analogues of these natural products with epimerization at **C12**. It is hoped that in doing this these structures not only showcase our methodology (allowing us divergent access to a wide range of substrates in a small number of steps) but might also prove useful for future isolation work, as we suspect these compounds may be undiscovered natural products.

A Schenck-ene reaction of cyclobutane **3.32** using TPP (**3.39**) as a photosensitizer followed by reduction of the hydroperoxide intermediates with PPh_3 gave access to analogues **3.83**, **3.84** and tertiary alcohol **3.85** in 10%, 37% and 17% respectively (**Scheme 3.28**).



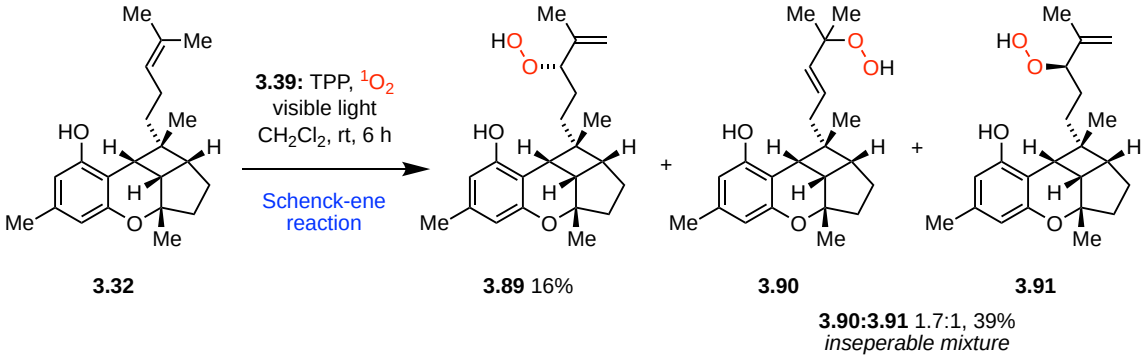
Scheme 3.28 – Synthesis of Rhodonoid E and F analogues

Efforts towards the synthesis of the hydroperoxide natural product precursors were also undertaken on both cyclobutane **3.28** (precursors to rhodonoid E (**3.5**), rhodonoid F (**3.6**) and **3.81**) and **3.32** (precursors to **3.83**, **3.84** and **3.85**). Reaction of **3.28** with TPP (**3.39**) using Schenck-ene conditions afforded hydroperoxide **3.86** in 20%. Unfortunately, **3.87** and **3.88** proved inseparable and formed in a combined yield 52% as a 1:1.7 mixture (**Scheme 3.29**).



Scheme 3.29 – Synthesis of Rhodonoid E and F hydroperoxide precursors

Alternatively, the same reaction conditions were employed using cyclobutane **3.32** to afford the hydroperoxide **3.89** in 16% and **3.90** and **3.91** in 30% as an inseparable mix (1.7:1) (**Scheme 3.30**).



Scheme 3.30 – Synthesis of hydroperoxides 3.89, 3.90 and 3.91

3.3 Conclusion

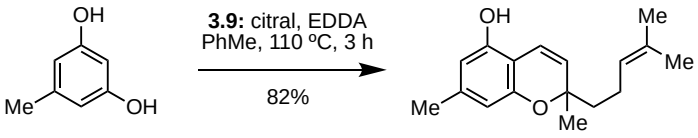
By employing bio-inspired singlet oxygen-ene chemistry as a selective and mild oxidant we have reduced the step count of previous total syntheses of rhodonoids A, B, E and F. The 3-step total synthesis of rhodonoid A (**3.1**) features a one-pot Schenck-ene reaction and Kornblum-DeLaMare rearrangement, followed by an intramolecular [2+2] photocycloaddition. While the total synthesis of rhodonoids B, E and F feature one-pot Schenck-ene/ reduction reactions.

3.4 Experimental

3.4.1 General Methods

All chemicals used were purchased from commercial suppliers and used as received. All reactions were performed under an inert atmosphere of N_2 unless otherwise stated. Thin layer chromatography was performed using aluminium sheets coated with silica gel. Visualization was aided by viewing under a *UV* lamp and staining with the appropriate stain followed by heating. All R_f values were measured to the nearest 0.05. Flash chromatography was performed using 40-63 micron grade silica gel. Melting points were recorded on a digital melting point apparatus and are uncorrected. Infrared spectra were recorded using an FT-IR spectrometer as the neat compounds. High field NMR was recorded using a 600 MHz spectrometer (^{1}H at 600 MHz, ^{13}C at 150 MHz) or a 500 MHz spectrometer (^{1}H at 500 MHz, ^{13}C at 125 MHz). The solvent used for NMR spectra was $CDCl_3$ unless otherwise specified. ^{1}H chemical shifts are reported in ppm on the δ-scale relative to TMS (δ 0.0) and ^{13}C{^{1}H} NMR are reported in ppm relative to chloroform (δ 77.16). Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet and (m) multiplet. All J-values were rounded to the nearest 0.1 Hz. ESI high resolution mass spectra were recorded on a Q-TOF mass spectrometer. Photochemistry with *UVA* light was performed using a generic brand commercial LED *UV* light globe; wavelength: 365 nm. Photochemistry with *UVC* light was performed using a generic brand commercial LED *UV* light globe; wavelength: 254 nm. Photochemical reactions with visible light were performed with a conventional commercial LED desk lamp at 240 V with a 4 W 5000 K 32 mÅ globe. Reactions conducted under 470 nm blue LED lamp were performed using a 19-24VDC 40W Kessil A160WE.

3.4.2 Experimental Procedures



3.8: orcinol **3.11**

To a solution of orcinol (**3.8**) (10.0 g, 80.6 mmol, 1.0 equiv.) in PhMe (250 mL) at room temperature was added citral (**3.9**) (12.3 mL, 80.6 mmol, 1.0 equiv.) and EDDA (430 mg, 2.42 mmol, 3 mol%). The reaction was stirred at reflux for 3 h. The mixture was cooled to room temperature, then concentrated *in vacuo* and purified *via* flash column chromatography on SiO_2 (8:1 hexanes/ EtOAc) to afford chromene **3.11** (17.2 g, 66.6 mmol, 82%) as an orange oil. Data for **3.11** matched that previously reported in the literature.[4]

Data for 3.11:

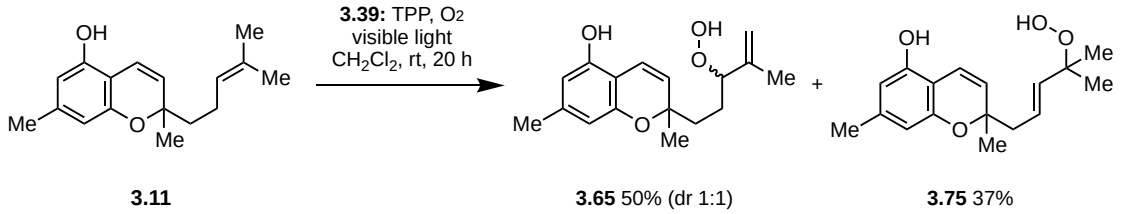
R_f: 0.40 (5:1 hexanes/ EtOAc).

FTIR (neat): 3387, 2923, 1625, 1449, 1376, 1329, 1250, 1196, 1142, 1084, 1060, 907 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.61 (d, *J* = 10.0 Hz, 1H), 6.24 (s, 1H), 6.11 (s, 1H), 5.49 (d, *J* = 10.0 Hz, 1H), 5.10 (t, *J* = 7.1 Hz, 1H), 4.71 (br s, 1H), 2.20 (s, 3H), 2.13 – 2.07 (m, 2H), 1.72 (dd, *J* = 10.7, 5.9 Hz, 1H), 1.66 (s, 3H), 1.66 – 1.63 (m, 1H), 1.58 (s, 3H), 1.37 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.1, 151.0, 139.5, 131.6, 127.2, 124.2, 117.0, 109.9, 108.3, 106.7, 78.2, 41.1, 26.2, 25.7, 22.7, 21.5, 17.6 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{17}H_{24}O_2$ 259.1693, found 259.1692.



3.11 **3.65** 50% (dr 1:1) **3.75** 37%

Chromene **3.11** (230 mg, 0.890 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (10 mL), followed by addition of tetraphenylporphyrin (TPP) (**3.39**) (10 mg, 0.016 mmol, 2 mol%). The reaction was stirred at room temperature in a borosilicate glass test tube while exposed to visible light and with O_2 bubbled through the solution for 20 h. The reaction was then concentrated and purified *via* flash chromatography on SiO_2 (9:1 CH_2Cl_2/ EtOAc) to give the desired hydroperoxide **3.65** (130 mg, 50%) as a 1:1 mixture of diastereoisomers and the tertiary hydroperoxide **3.74** (95 mg, 37%).

Data for 3.65:

R_f: 0.25 (20:1 EtOAc/ CH_2Cl_2).

FTIR (neat): 3393, 2924, 1625, 1578, 1450, 1376, 1330, 1199, 1139, 1067, 992, 905 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (m, 1H), 6.62 (d, *J* = 10.0 Hz, 1H), 6.22 (s, 1H), 6.11 (s, 1H), 5.44 (dd, *J* = 10.0 Hz, 1H), 5.01 – 4.99 (m, 2H), 4.83 (br s, 1H), 4.31 (t, *J* = 6.6 Hz, 1H), 2.20 (s, 3H), 1.71 (m, 7H), 1.36 (s, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 154.0, 154.0, 151.2, 151.2, 143.6, 143.5, 139.8, 126.8, 126.7, 117.4, 117.3, 114.7, 114.5, 109.9, 108.6, 108.6, 108.6, 106.7, 89.8, 89.7, 78.2, 78.0, 37.3, 37.0, 26.6, 26.4, 25.6, 25.3, 21.6, 17.4, 17.4 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{17}H_{23}O_4$ 291.1591, found 291.1591.

Data for 3.74:

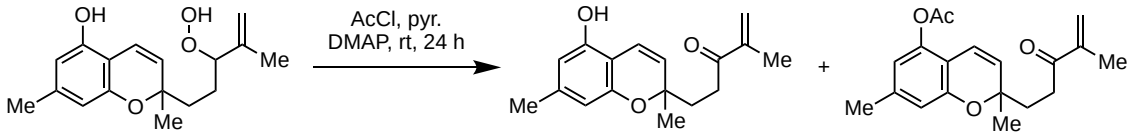
R_f: 0.15 (20:1 EtOAc/ CH_2Cl_2).

FTIR (neat): 3384, 2927, 1624, 1579, 1452, 1377, 1262, 1201 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 (br s, 1H), 6.64 (d, *J* = 10.0, 1H), 6.21 (s, 1H), 6.11 (s, 1H), 5.80 – 5.70 (m, 1H), 5.60 – 5.50 (m, 1H), 5.47 – 5.42 (m, 1H), 5.17 (br s, 1H), 2.45 – 2.35 (m, 2H), 2.18 (s, 3H), 1.40 (s, 3H), 1.26 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.2, 151.34, 140.0, 137.0, 126.6, 126.4, 117.5, 109.5, 108.7, 107.0, 82.4, 78.0, 44.4, 26.8, 24.3, 24.3, 21.6 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{17}H_{23}O_4$ 291.1591, found 291.1591.



3.65 **3.66** 26% **3.76** 48%

Hydroperoxide **3.65** (275 mg, 0.947 mmol, 1.0 equiv.) was dissolved in pyridine (20 mL) and 4-dimethylaminopyridine (DMAP) (12 mg, 0.095 mmol, 10 mol%) added, followed by a dropwise addition of AcCl (0.081 mL, 1.13 mmol, 1.2 equiv.). The reaction was left to stir at room temperature for 24 h, then quenched upon addition of H_2O (30 mL), and product extracted with EtOAc (2 x 20 mL). The combined organic layers were then washed with 0.5 M $CuSO_{4(aq)}$ (3 x 60 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* flash chromatography on SiO_2 (9:1 hexanes/ EtOAc) then afforded acetate protected enone **3.76** (143 mg, 48%) as a white solid and enone **3.66** (53 mg, 26%) as a yellow oil.

Data for 3.66:

R_f: 0.55 (8:2 hexanes/ EtOAc).

FTIR (neat): 3395, 2926, 1665, 1625, 1579, 1451, 1375, 1329, 1139, 992 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.64 (d, *J* = 9.9 Hz, 1H), 6.22 (s, 1H), 6.13 (s, 1H), 5.93 (s, 1H), 5.72 (s, 1H), 5.44 (d, *J* = 9.9 Hz, 1H), 4.85 (br s, 1H), 2.85 (dddd, *J* = 61.9, 16.9, 9.7, 5.9 Hz), 2.20 (s, 3H), 2.01 (dd, *J* = 5.9, 1.7 Hz, 2H), 1.85 (s, 3H), 1.38 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 202.1, 154.0, 151.3, 144.5, 139.9, 126.6, 124.9, 117.7, 109.9, 108.6, 106.6, 78.0, 35.8, 32.7, 26.7, 21.6, 17.8 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{17}H_{21}O_3$ 273.1485, found 273.1488.

Data for 3.76:

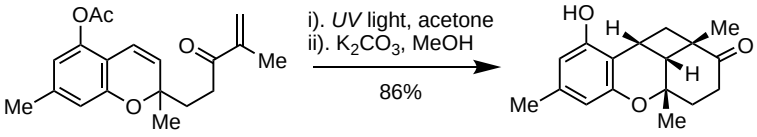
R_f: 0.30 (9:1 hexanes/ EtOAc).

FTIR (neat): 2925, 1769, 1676, 1451, 1190 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.48 (s, 1H), 6.41 (s, 1H), 6.33 (d, *J* = 10.0 Hz, 1H), 5.92 (s, 1H), 5.71 (d, *J* = 1.6 Hz, 1H), 5.49 (d, *J* = 10.0 Hz, 1H), 2.83 (dddd, *J* = 69.0, 17.1, 10.1, 5.4 Hz, 2H), 2.29 (s, 3H), 2.25 (s, 3H), 2.08 – 1.93 (m, 2H), 1.90 – 1.79 (m, 3H), 1.38 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 201.6, 169.3, 153.8, 146.3, 144.3, 139.7, 128.6, 124.9, 117.4, 115.0, 114.7, 111.3, 78.3, 35.8, 32.5, 26.9, 21.6, 20.9, 17.7 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{19}H_{23}O_4$ 315.1591, found 315.1591.



3.76 **3.1:** rhodonoid A

A solution of enone **3.76** (68 mg, 0.216 mmol, 1.0 equiv.) in acetone (3 mL) was left in a borosilicate sealed vial placed within a water condenser and irradiated from beneath with *UV* light at a distance of 5 cm for 24 h at room temperature. The resultant solution was then concentrated, and the crude mixture dissolved in MeOH (3 mL) and K_2CO_3 (49 mg, 0.354 mmol, 1.6 equiv.) was then added in one portion. The reaction was then stirred for 1 h at room temperature. Distilled H_2O (5 mL) was then added, and the product was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then dried with $MgSO_4$, filtered and concentrated. Purification *via* flash chromatography (9:1 hexanes/ EtOAc) afforded rhodonoid A (**3.1**) as a white solid (45 mg, 86%). Data for rhodonoid A (**3.1**) matched that previously reported in the literature.[2]

Data for rhodonoid A (3.1):

R_f: 0.20 (8:2 hexanes/ EtOAc).

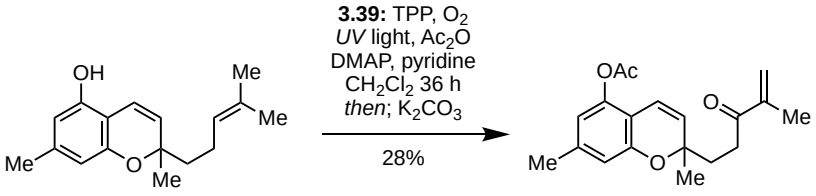
MP: 179.6 – 180.2 °C (recryst. MeOH) (lit. 180.0 – 181.0 °C).[1]

FTIR (neat): 2965, 1687, 1625, 1514, 1420, 1187, 1069 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.34 (s, 1H), 6.21 (s, 1H), 4.59 (s, 1H), 3.80 - 3.73 (m, 1H), 2.78 (ddd, *J* = 18.1, 10.9, 7.1 Hz, 1H), 2.59 (d, *J* = 9.5 Hz, 1H), 2.42 (ddd, *J* = 18.3, 6.8, 3.4 Hz, 1H), 2.39 – 2.33 (m, 1H), 2.33 – 2.30 (m, 1H), 2.22 (s, 3H), 2.16 (dd, *J* = 12.2, 7.1 Hz, 1H), 2.03 (ddd, *J* = 14.0, 10.9, 6.8 Hz, 1H), 1.44 (s, 3H), 1.16 (s, 3H) ppm.

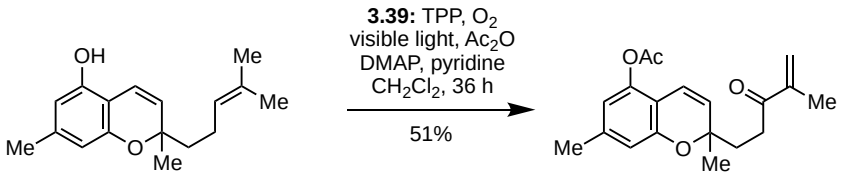
^{13}C NMR (150 MHz, $CDCl_3$): δ 216.5, 154.1, 152.8, 137.5, 112.6, 112.0, 109.3, 73.5, 51.1, 43.9, 39.0, 34.1, 33.7, 25.4, 24.9, 21.9, 21.3 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{17}H_{21}O_3$ 273.1485, found 273.1485.



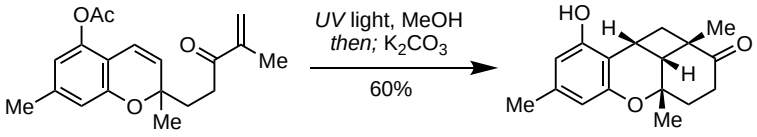
3.11 **3.76**

Using modified conditions reported by Laroche and Nay *et al*.,[38] chromene **3.11** (69 mg, 0.275 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (4 mL), followed by addition of tetraphenylporphyrin (TPP) (**3.39**) (3 mg, 0.005 mmol, 2 mol%), pyridine (0.13 mL, 16.5 mmol, 60.0 equiv.), Ac_2O (2.61 mL, 27.5 mmol, 100 equiv.) and DMAP (1 mg, 0.006 mmol, 2 mol%). The reaction was stirred at room temperature in a borosilicate glass test tube while exposed to *UV* light at a distance of 10 cm from the irradiation vessel and with O_2 bubbled through the solution for 36 h. K_2CO_3 (114 mg, 0.825 mmol, 3.0 equiv.) was then added to the solution and reaction left to stir further for 5 h. The reaction was then quenched by addition of distilled H_2O (10 mL). The organic phase was then separated, and the aqueous phase further extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were then washed with 0.5 M $CuSO_{4(aq)}$ (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified *via* flash chromatography on SiO_2 (CH_2Cl_2) to give enone **3.76** (24 mg, 28%) as a white solid. Data for **3.76** matched that previously obtained.



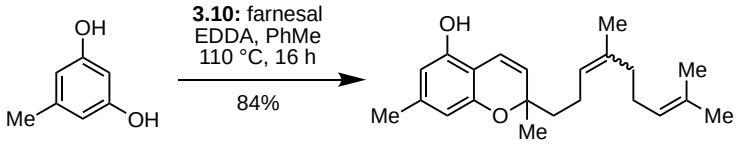
3.11 **3.76**

Using modified conditions reported by Laroche and Nay *et al*.,[38] chromene **3.11** (450 mg, 1.80 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (30 mL), followed by addition of tetraphenylporphyrin (TPP) (**3.39**) (22 mg, 0.036 mmol, 2 mol%), pyridine (8.70 mL, 108 mmol, 60 equiv.), Ac_2O (17.0 mL, 180 mmol, 100 equiv.) and DMAP (4 mg, 0.036 mmol, 2 mol%). The reaction was stirred at room temperature in a borosilicate glass test tube while exposed to visible light at a distance of 10 cm from the irradiation vessel and with O_2 bubbled through the solution for 36 h. The reaction was then quenched by addition of distilled H_2O (40 mL). The organic phase was then separated, and the aqueous phase further extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were then washed with 0.5 M $CuSO_{4(aq)}$ (3 x 60 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified *via* flash chromatography on SiO_2 (CH_2Cl_2) to give the desired enone **3.76** (283 mg, 51%) as a white solid. Data for **3.76** matched that previously obtained.



3.76 **3.1:** rhodonoid A

A solution of enone **3.76** (57 mg, 0.181 mmol, 1.0 equiv.) in MeOH (3 mL) was left in a borosilicate sealed vial placed within a water condenser and irradiated from beneath with *UV* light at a distance of 5 cm for 24 h at room temperature. K_2CO_3 (62 mg, 0.450 mmol, 2.5 equiv.) was then added in one portion and the reaction was stirred for 1 h. H_2O (5 mL) was added, and the product extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then dried with $MgSO_4$, filtered and concentrated. Purification *via* flash chromatography on SiO_2 (9:1 hexanes/ EtOAc) afforded rhodonoid A (**3.1**) as a white solid (30 mg, 60%). Data for rhodonoid A (**3.1**) matched that previously obtained.



3.8: orcinol **3.12:** confluentin

To a solution of orcinol (**3.8**) (12.9 g, 103.9 mmol, 1.0 equiv.) in PhMe (300 mL) at room temperature was added farnesal (**3.10**) (*mixture of isomers*, 22.9 g, 103.9 mmol, 1.0 equiv.) and EDDA (190 mg, 10.4 mmol, 10 mol%). The reaction was stirred at reflux for 16 h. The mixture was cooled to room temperature, then concentrated *in vacuo*. Purification *via* flash column chromatography on SiO_2 (10:1 hexanes/ EtOAc) then afforded confluentin (**3.12**) as a 1:1.4 mixture of *Z:E* isomers (28.6 g, 84%). Data for confluentin (**3.12**) matched that previously reported in the literature.[3]

Data for confluentin (3.12):

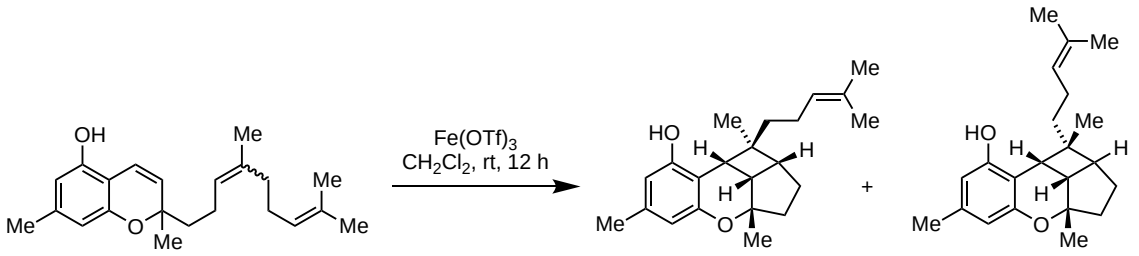
R_f: 0.50 (8:2 hexanes/ EtOAc).

FTIR (neat): 2967, 1626, 1578, 1448, 1249, 1197, 1091 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.60 (d, *J* = 9.9 Hz, 1H), 6.24 (d, *J* = 4.0 Hz, 1H), 6.11 (s, 1H), 5.49 (dd, *J* = 10.0, 8.4 Hz, 1H), 5.17 – 5.04 (m, 2H), 4.70 (s, 1H), 2.20 (s, 3H), 2.15 – 1.94 (m, 6H), 1.76 – 1.70 (m, 2H), 1.67 (s, 3H), 1.62 – 1.57 (m, 6H), 1.38 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 154.3, 151.2, 139.7, 139.7, 135.5, 135.4, 131.5, 127.4, 127.3, 125.0, 124.5, 124.2, 116.9, 116.8, 110.0, 110.0, 108.4, 106.9, 78.4, 78.3, 41.5, 41.2, 39.8, 32.0, 26.8, 26.7, 26.4, 26.4, 25.9, 25.8, 23.5, 22.8, 22.6, 21.6, 17.8, 17.8, 16.1 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{22}H_{31}O_2$ 327.2319, found 327.2319.



3.12: confluentin **3.28** 43% **3.32** 28%

Using a modified procedure from Tang *et al*.,[3] $Fe(OTf)_3$ (50 mg, 0.099 mmol, 0.3 equiv.) was added in one portion to a solution of a 1:1.4 *Z:E* mixture of **3.12** (100 mg, 0.306 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) under N_2 at –78 °C. The reaction was warmed to room temperature and left to stir for 12 h, then quenched with sat. $NaHCO_{3(aq)}$ (30 mL). The product was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic extracts were washed with brine (60 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Careful flash chromatography on SiO_2 (50:1 hexanes/ EtOAc) then afforded **3.28** as a white solid (42 mg, 43%) followed by **3.32** as an off white solid (28 mg, 28%). Data for **3.28** and **3.32** matched that previously reported in literature.[3]

Data for 3.32:
R_f: 0.20 (20:1 hexanes/ EtOAc).

FTIR (neat): 2950, 1626, 1452, 1375, 1054 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.32 (s, 1H), 6.18 (s, 1H), 4.94 (t, *J* = 4.9 Hz, 1H), 4.46 (br s, 1H), 3.12 (d, *J* = 9.7 Hz, 1H), 2.57 (dd, *J* = 9.8, 8.2 Hz, 1H), 2.42 (td, *J* = 8.3, 3.6 Hz, 1H), 2.22 (s, 3H), 2.05 (dt, *J* = 12.9, 7.5 Hz, 1H), 1.86 – 1.61 (m, 5H), 1.60 (s, 3H), 1.49 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H), 1.28 – 1.11 (m, 2H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 154.7, 153.9, 137.5, 130.7, 125.4, 111.6, 108.7, 108.3, 83.7, 46.2, 42.4, 40.2, 38.6, 36.1, 31.2, 30.5, 26.4, 26.1, 25.8, 23.5, 21.4, 17.7 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{22}H_{31}O_2$ 327.2319, found 327.2319.

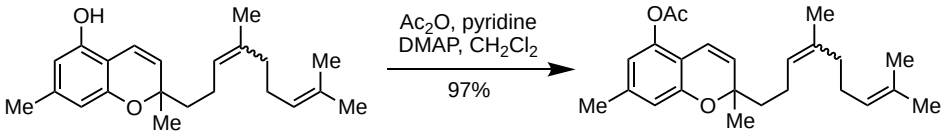
Data for 3.28:
R_f: 0.20 (20:1 hexanes/ EtOAc).

FTIR (neat): 2927, 1625, 1584, 1453, 1251, 1052 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.32 (s, 1H), 6.17 (s, 1H), 5.17 (t, J = 7.0 Hz, 1H), 4.48 (s, 1H), 3.06 (d, *J* = 9.6 Hz, 1H), 2.56 (dd, *J* = 9.6, 7.7 Hz, 1H), 2.47 (t, *J* = 7.5 Hz, 1H), 2.22 (s, 3H), 2.18 – 2.04 (m, 1H), 2.03 – 1.91 (m, 2H), 1.76 (ddd, J = 13.3, 11.6, 5.1 Hz, 1H), 1.71 (s, 3H), 1.70 – 1.59 (m, 4H), 1.63 (s, 3H), 1.36 (s, 3H), 0.76 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 154.6, 154.1, 137.6, 131.4, 125.1, 111.5, 108.5, 108.2, 83.5, 46.8, 44.4, 42.4, 39.1, 38.6, 35.6, 27.4, 25.9, 25.7, 22.9, 21.3, 17.8, 15.1 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{22}H_{31}O_2$ 327.2319, found 327.2318.



3.12: confluentin

3.80

To a solution of confluentin **3.12** (500 mg, 1.53 mmol, 1.0 equiv.) in CH_2Cl_2 (100 mL) at room temperature, was added pyridine (0.015 mL, 0.982 mmol, 0.5 equiv.), Ac_2O (0.23 g, 2.30 mmol, 1.5 equiv.) and then DMAP (18 mg, 0.153 mmol, 0.10 equiv.). The solution was left to stir for 30 min, and reaction quenched upon addition of 0.5 M $CuSO_{4\,(aq)}$ (100 mL). The organic layer was separated then further washed with 0.5 M $CuSO_{4\,(aq)}$ (2 x 100 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* flash chromatography on SiO_2 (20:1 hexanes/ EtOAc) then afforded chromene **3.80** (542 mg, 97%) as an orange oil.

Data for 3.80:

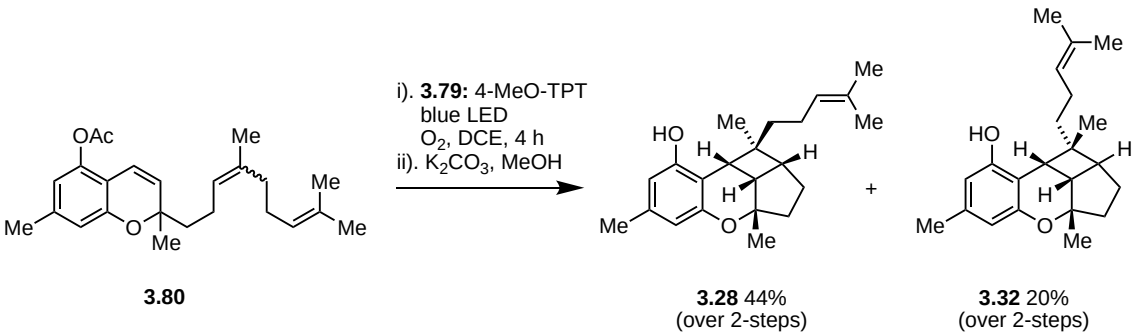
R_f: 0.60 (9:1 hexanes/ EtOAc).

FTIR (neat): 2967, 1701, 1625, 1566, 1448, 1368, 1198, 1057, 775 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.51 – 6.49 (m, 1H), 6.41 (s, 1H), 6.32 (d, J = 10.0 Hz, 1H), 5.56 – 5.52 (m, 1H), 5.14 – 5.07 (m, 2H), 2.30 (s, 3H), 2.26 (s, 3H), 2.16 – 1.91 (m, 7H), 1.78 – 1.56 (m, 10H), 1.37 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 169.4, 169.4, 154.0, 146.3, 139.5, 139.5, 135.6, 135.5, 131.7, 131.5, 129.4, 129.4, 124.9, 124.5, 124.0, 116.8, 116.7, 114.8, 114.8, 114.8, 114.8, 111.6, 111.6, 78.7, 78.6, 41.5, 41.3, 39.8, 32.0, 26.8, 26.7, 26.5, 26.4, 25.9, 25.8, 23.5, 22.7, 22.6, 21.6, 21.0, 17.8, 17.8, 16.1 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{24}H_{33}O_3$ 369.2421, found 369.2424.

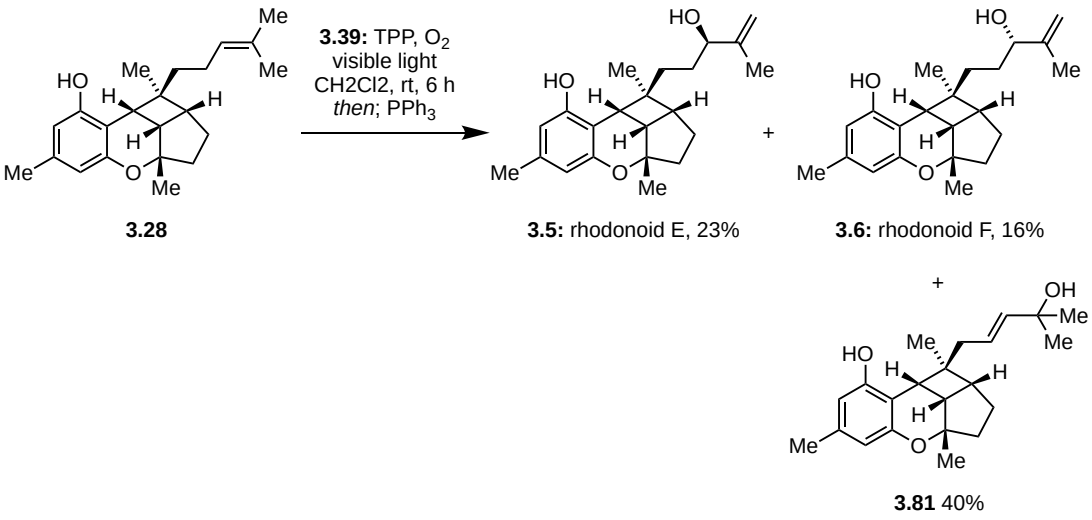


3.80

3.28 44%
(over 2-steps)

3.32 20%
(over 2-steps)

Chromene **3.80** (52 mg, 0.159 mmol, 1.0 equiv.) was dissolved in DCE (16 mL, 0.01 M) and 4-MeO-TPT (**3.79**) (2 mg, 0.003 mmol, 2 mol%) was added. The reaction was then cooled to 0 °C, O_2 was then bubbled through the solution and the reaction was left to stir while exposed to a 470 nm blue LED lamp for 4 h. After this time the reaction was concentrated *in vacuo*, and the crude residue dissolved in MeOH (10 mL). K_2CO_3 (46 mg, 0.334 mmol, 2.1 equiv.) was added in one portion and the solution left to stir for 1 h. H_2O (20 mL) and CH_2Cl_2 (20 mL) was then added, and organic layer separated, dried with $MgSO_4$ and filtered. The solution was concentrated *in vacuo* and purified *via* careful flash chromatography on SiO_2 (50:1 hexanes/ EtOAc) to afford **3.28** as a white solid (23 mg, 44%) followed by **3.32** as an off white solid (15 mg, 30%). Data for **3.28** and **3.32** matched that previously obtained and previously reported in the literature.[3]



To a borosilicate glass test tube containing **3.28** (188 mg, 0.661 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) was added TPP (**3.39**) (8 mg, 0.013 mmol, 2 mol%). O_2 was bubbled through the solution while it was stirred at room temperature and exposed to visible light at a distance of 10 cm from the irradiation vessel for 6 h. PPh_3 (350 mg, 1.32 mmol, 2.0 equiv.) was then added and the reaction was stirred for a further 16 h under N_2. The solution was then concentrated in vacuo and purified *via* flash chromatography on SiO_2 (9:1 CH_2Cl_2/ EtOAc) to give rhodonoid E (**3.5**) as a white solid (49 mg, 23%) and a mixture of rhodonoid F (**3.6**) and allylic alcohol **3.81** (133 mg, 63%). The mixture was then further purified *via* flash chromatography using 1% wt./ wt. $AgNO_3$ impregnated SiO_2 (7:3 hexanes/ EtOAc) with early fractions containing the allylic alcohol **3.81** (86 mg, 40%) as a red oil and later fractions containing rhodonoid F (**3.6**) as a white solid (35 mg, 16%). Data for rhodonoid E (**3.5**) and rhodonoid F (**3.6**) matched that previously reported in literature.[3]

Data for rhodonoid E (**3.5**)**:**

R_f: 0.40 (9:1 CH_2Cl_2/ EtOAc).

MP: 123.7 – 125.0 °C (recryst. $CHCl_3$) (lit. 86 – 87 °C).

FTIR (neat): 2925, 1621, 1415, 1259, 1118, 1055 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.32 (s, 1H), 6.16 (s, 1H), 4.99 (s, 1H), 4.87 (s, 1H), 4.61 (br s, 1H), 4.10 (t, *J* = 5.0 Hz, 1H), 3.09 (d, *J* = 9.6 Hz, 1H), 2.56 (dd, *J* = 9.6, 7.8 Hz, 1H), 2.43 (td, *J* = 7.8, 4.1 Hz, 1H), 2.22 (s, 3H), 2.07 – 1.94 (m, 1H), 1.76 (s, 3H), 1.73 – 1.59 (m, 6H), 1.54 – 1.49 (m, 1H), 1.35 (s, 3H), 0.73 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 154.6, 154.1, 147.7, 137.6, 111.5, 111.3, 108.6, 108.2, 83.6, 76.6, 44.5, 42.3, 42.0, 39.2, 38.8, 35.3, 29.4, 27.3, 25.7, 21.4, 17.8, 15.3 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{22}H_{31}O_3$ 343.2268, found 343.2280.

Data for rhodonoid F (3.6):

R_f: 0.20 (8:2 hexanes/ EtOAc).

MP: 149.2 – 150.6 °C (lit. 152 – 153 °C).[1]

FTIR (neat): 2944, 1624, 1419, 1260, 1137 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.31 (s, 1H), 6.17 (s, 1H), 4.98 (s, 1H), 4.87 (s, 1H), 4.79 (br s, 1H), 4.10 (t, *J* = 6.2 Hz, 1H), 3.11 (d, *J* = 9.6 Hz, 1H), 2.55 (dd, *J* = 9.6, 7.9 Hz, 1H), 2.41 (td, *J* = 7.4, 3.5, Hz, 1H), 2.21 (s, 3H), 2.02 – 1.95 (m, 1H), 1.87 – 1.80 (m, 1H), 1.76 (s, 3H), 1.70 – 1.50 (m, 6H), 1.34 (s, 3H), 0.73 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 154.6, 154.2, 147.6, 137.5, 111.5, 111.4, 108.7, 108.3, 83.6, 76.7, 44.7, 42.4, 42.2, 39.2, 38.8, 35.2, 29.5, 27.2, 25.6, 21.4, 17.7, 15.2 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{31}O_3$ 343.2268, found 343.2272.

Data for 3.81:

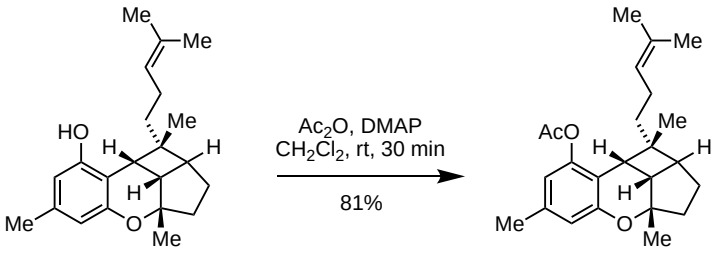
R_f: 0.20 (8:2 hexanes/ EtOAc).

FTIR (neat): 2968, 1624, 1585, 1455, 1328, 1137 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.30 (s, 1H), 6.21 (s, 1H), 5.89 – 5.87 (m, 2H), 5.01 (br s, 1H), 3.05 (d, *J* = 9.7 Hz, 1H), 2.59 (dd, *J* = 9.7, 7.7 Hz, 1H), 2.44 – 2.37 (m, 2H), 2.32 (dd, *J* = 12.5, 3.2 Hz, 1H), 2.21 (s, 3H), 2.0 – 1.96 (m, 1H), 1.75 – 1.56 (m, 3H), 1.36 (s, 9H), 0.79 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 154.4, 154.3, 143.3, 138.0, 123.3, 111.2, 108.4, 107.6, 83.1, 71.0, 48.9, 45.7, 42.4, 38.7, 38.2, 33.2, 29.9, 29.7, 27.4, 25.5, 21.4, 15.3 ppm.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{30}O_3Na$ 365.2087, found 365.2085.



3.32 **3.73**

Following a modified procedure from Wu *et al*.,[3] Ac_2O (0.04 mL, 0.367 mmol, 2.0 equiv.) was added dropwise to a solution of **3.32** (60 mg, 0.184 mmol, 1.0 equiv.) and DMAP (33 mg, 0.275 mmol, 1.5 equiv.) in CH_2Cl_2 (10 mL). The resulting mixture was stirred at room temperature for 30 min, then quenched by addition of sat. $NaHCO_{3(aq)}$ (20 mL). The resultant mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification *via* flash chromatography on SiO_2 (19:1 hexanes/ EtOAc) afforded acetate **3.73** (55 mg, 81%) as a colourless oil.

Data for 3.73:

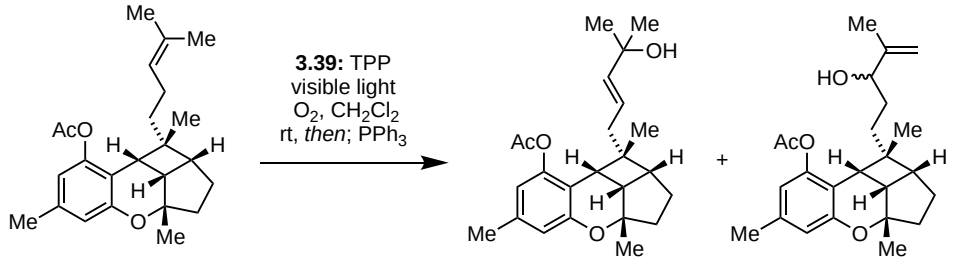
R_f: 0.30 (19:1 hexanes/ EtOAc).

FTIR (neat): 2949, 1768, 1626, 1451, 1371, 1052 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.60 (s, 1H), 6.48 (s, 1H), 4.94 (t, *J* = 7.8 Hz, 1H), 2.99 (d, *J* = 9.8 Hz, 1H), 2.55 (t, *J* = 9.1 Hz, 1H), 2.42 (td, *J* = 8.5, 5.8 Hz, 1H), 2.29 (s, 3H), 2.27 (s, 3H), 2.04 (dt, *J* = 13.1, 6.6 Hz, 1H), 1.84 – 1.67 (m, 4H), 1.66 – 1.58 (m, 1H), 1.61 (s, 3H), 1.50 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H), 1.21 – 1.12 (m, 1H), 1.01 (ddd, J = 14.0, 12.1, 5.8 Hz, 1H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 169.2, 154.8, 149.1, 137.4, 130.7, 125.2, 116.8, 115.2, 114.7, 84.1, 46.1, 42.7, 40.7, 38.9, 36.5, 31.3, 30.6, 26.1, 25.8, 25.7, 23.3, 21.4, 21.3, 17.6 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{24}H_{33}O_3$ 369.2424, found 369.2428.



3.73 **3.35** 45% **3.82** 44%

To a solution of **3.73** (101 mg, 0.311 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) in a 25 mL borosilicate glass test tube was added TPP (**3.39**) (4 mg, 0.007 mmol, 2 mol%) and O_2 was sparged through the solution for 10 min. Visible light was applied to the solution at a distance of 10 cm from the irradiation vessel which was stirred for 6 h at room temperature. PPh_3 (163 mg, 0.621 mmol, 2.0 equiv.) was then added to the solution in one portion and the reaction was stirred at room temperature under N_2 for 8 h. The reaction was concentrated *in vacuo* and purified *via* flash chromatography on SiO_2 (9:1 CH_2Cl_2/ EtOAc) to afford **3.35** (53 mg, 45%) as a yellow oil and **3.82** (42 mg, 44%) as a yellow solid and as a 1:1 mixture of diastereomers. Data for **3.35** matched that previously reported.[3]

Data for 3.35:

R_f: 0.35 (9:1 CH_2Cl_2/ EtOAc).

FTIR (neat): 948, 1768, 1750, 1626, 1576, 1371, 1198 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.61 (s, 1H), 6.47 (s, 1H), 5.43 (d, J = 16.0 Hz, 1H), 5.38 – 5.31 (m, 1H), 3.05 (d, J = 9.5 Hz, 1H), 2.54 (t, J = 9.2 Hz, 1H), 2.45 (dt, J = 8.9, 4.2 Hz, 1H), 2.28 (s, 6H), 2.08 – 1.97 (m, 2H), 1.94 – 1.84 (m, 1H), 1.76 – 1.70 (m, 2H), 1.64 – 1.59 (m, 1H), 1.28 (s, 6H), 1.22 (s, 6H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 169.3, 154.9, 149.0, 140.2, 137.6, 123.7, 117.0, 115.3, 114.8, 84.3, 70.7, 46.4, 42.2, 40.8, 39.4, 36.1, 34.8, 31.1, 30.0, 29.9, 26.0, 25.6, 21.4, 21.3 ppm.

HRMS (**ESI**) **m/z:** $[M+NH_4]^+$ Calcd for $C_{24}H_{36}O_4N$ 402.2639, found 402.2639.

Data for 3.82:

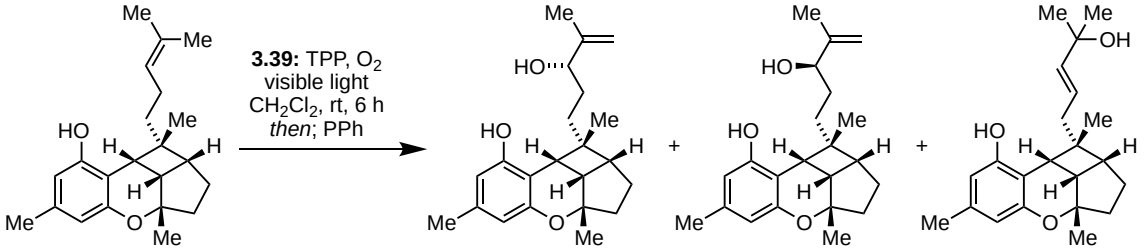
R_f: 0.50 (9:1 CH_2Cl_2/ EtOAc).

FTIR (neat): 2970, 1771, 1466, 1306, 1160, 1107 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.61 (s, 1H), 6.47 (s overlapped, *J* = 6.8 Hz, 1H), 4.80 (d, *J* = 4.7 Hz, 1H), 4.73 (d, *J* = 4.7 Hz, 1H), 3.78 – 3.73 (m, 1H), 3.01 (t, *J* = 9.3 Hz, 1H), 2.54 (t, *J* = 9.3 Hz, 1H), 2.44 – 2.39 (m, 1H), 2.27 (s, 6H), 2.08 – 2.01 (m, 1H), 1.90 – 1.82 (m, 1H), 1.74 – 1.67 (m, 2H), 1.63 (s, 3H), 1.59 (s, 3H), 1.59 – 1.55 (m, 1H), 1.30 (s, 3H), 1.28 (s, 3H), 1.10 – 1.09 (m, 1H), 1.00 – 0.92 (m, 1H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 169.3, 169.2, 154.9, 154.9, 149.0, 149.0, 147.8, 147.7, 137.5, 137.5, 116.9, 116.8, 115.3, 115.2, 114.9, 114.8, 110.8, 110.7, 84.3, 84.2, 76.6, 76.5, 46.3, 46.2, 42.5, 42.4 41.0, 40.8, 39.3, 39.2, 36.4, 36.3, 30.7, 30.4, 30.2, 27.7, 27.7, 25.9, 25.7, 25.6, 25.5, 21.4, 21.4, 21.3, 17.8, 17.6 ppm.

HRMS (**ESI**) **m/z:** $[M+Na]^+$ Calcd for $C_{24}H_{32}O_4Na$ 407.2193, found 407.2199.



3.32 **3.83** 10% **3.84** 37% **3.85** 17%

To a solution of **3.32** (61 mg, 0.214 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) in a 25 mL borosilicate glass test tube was added TPP (**3.39**) (3 mg, 0.004 mmol, 2 mol%) and O_2 was sparged through the solution for 10 min. Visible light was applied to the solution at a distance of 10 cm from the irradiation vessel which was stirred for 6 h at room temperature. PPh_3 (112 mg, 0.428 mmol, 2.0 equiv.) was then added to the solution in one portion and the reaction was stirred at room temperature under N_2 for 8 h. The reaction was concentrated *in vacuo* and purified *via* flash chromatography on SiO_2 (9:1 CH_2Cl_2/ EtOAc) to afford **3.83** (7 mg, 10%) and an inseparable mixture of **3.84** and **3.85**. The mixture was then further purified by flash chromatography (7:3 hexanes/ EtOAc) to afford **3.84** (26 mg, 37%) as a yellow oil and **3.85** (12 mg, 17%) as a yellow oil.

Data for 3.83:

R_f: 0.40 (9:1 CH_2Cl_2/ EtOAc).

FTIR (neat): 3357, 2949, 1624, 1587, 1451, 1374, 1129, 1057, 996, 902, 732 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.33 (s, 1H), 6.16 (s, 1H), 4.81 – 4.72 (m, 1H), 4.73 – 4.71 (m, 1H), 4.61 (br s, 1H), 3.72 (dd, *J* = 7.7, 4.0 Hz, 1H), 3.16 (d, *J* = 9.7 Hz, 1H), 2.56 (t, *J* = 9.1 Hz, 1H), 2.44 (td, *J* = 8.43, 3.77 Hz, 1H), 2.21 (s, 3H), 2.06 (dd, *J* = 13.0, 6.8 Hz, 1H), 1.84 (dd, *J* = 6.7, 3.9 Hz, 1H), 1.72 – 1.59 (m, 2H), 1.35 (s, 3H), 1.30 (s, 3H) ppm.

^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$): δ 154.9, 153.7, 147.9, 137.5, 111.7, 110.6, 109.2, 108.4, 83.9, 76.7, 46.5, 42.2, 40.5, 39.1, 35.7, 30.6, 30.3, 27.7, 26.0, 25.6, 21.4, 17.7 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{22}H_{31}O_3$ 343.2268, found 343.2269.

Data for 3.84:

R_f: 0.20 (4:1 hexanes/ EtOAc).

FTIR (neat): 3359, 1623, 1586, 1512, 1449, 1373, 1329, 1056, 996, 906, 825, 733 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.32 (s, 1H), 6.15 (s, 1H), 5.02 (br s, 1H), 4.97 – 4.80 (m, 1H), 4.72 – 4.70 (m, 1H), 3.72 (dd, *J* = 7.8, 3.9 Hz, 1H), 3.16 (d, *J* = 9.7 Hz, 1H), 2.55 (t, *J* = 9.1 Hz, 1H), 2.43 (d, *J* = 3.9 Hz, 1H), 2.20 (s, 3H), 2.10 – 2.02 (m, 1H), 1.87 – 1.80 (m, 1H), 1.70 – 1.58 (m, 3H), 1.56 (s, 3H), 1.34 (s, 3H), 1.29 (s, 6H), 0.90 (dd, *J* = 17.1, 10.2 Hz, 1H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 154.9, 153.8, 147.7, 137.4, 111.6, 111.6, 110.7, 109.3, 108.5, 83.9, 46.5, 42.1, 40.5, 39.1, 35.7, 30.5, 30.2, 27.6, 26.0, 25.6, 21.3, 17.6 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{22}H_{31}O_3$ 343.2268, found 343.22577.

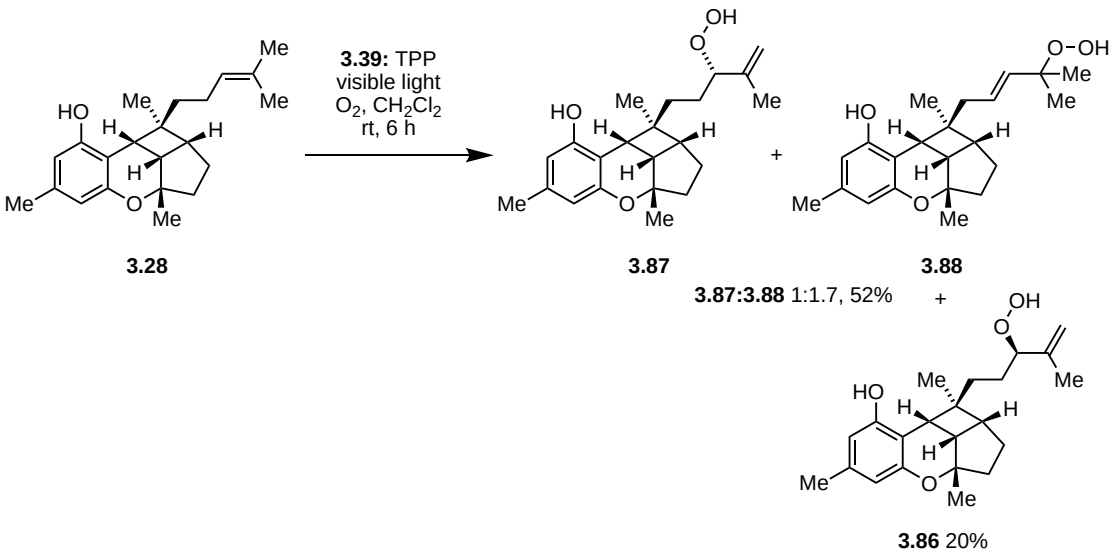
Data for 3.85:

R_f: 0.25 (7:3 hexanes/ EtOAc).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.33 (s, 1H), 6.18 (s, 1H), 5.42 – 5.38 (m, 2H), 4.84 (br s, 1H), 3.18 (d, *J* = 9.7 Hz, 1H), 2.57 (dd, *J* = 9.7, 8.3 Hz, 1H), 2.46 (m, 1H), 2.22 (s, 3H), 2.09 – 1.98 (m, 2H), 1.70 – 1.52 (s, 3H), 1.35 (s, 3H), 1.37 – 1.36 (m, 1H), 1.32 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 154.8, 153.9, 139.8, 137.7, 124.4, 111.7, 109.0, 108.5, 83.7, 71.0, 46.6, 42.0, 40.2, 38.9, 35.7, 34.8, 31.0, 30.0, 29.8, 26.3, 25.9, 21.4 ppm.

HRMS (**ESI**) **m/z:** $[M-H]^-$ Calcd for $C_{22}H_{29}O_3$ 341.2116, found 341.2122.



To a solution of tetracycle **3.28** (226 mg, 0.687 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL), in a 25 mL borosilicate glass test tube was added TPP (**3.39**) (10 mg, 0.014 mmol, 2 mol%) and O_2 was sparged through the solution for 10 min. Visible light was applied to the solution at a distance of 10 cm from the irradiation vessel which was stirred for 6 h at room temperature. The reaction was concentrated *in vacuo* and purified *via* flash chromatography on SiO_2 (9:1 EtOAc/ hexanes) to afford **3.86** (51 mg, 20%) as a yellow oil and **3.87** and **3.88** (135 mg, 52%) as a yellow oil and a 1:1.7 mixture of isomers.

Data for 3.86:

R_f: 0.50 (9:1 hexanes/ EtOAc).

FTIR (neat): 3390, 2951, 1625, 1585, 1453, 1327, 1253, 1137, 1053, 1137, 1053, 996 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.77 (s, 1H), 6.32 (s, 1H), 6.14 (s, 1H), 5.06 (m, 2H), 4.44 (m, *J* = 1.2 Hz, 1H), 4.33 (t, *J* = 6.7 Hz, 1H), 3.05 (d, *J* = 9.6 Hz, 1H), 2.56 (dd, *J* = 9.7, 7.7 Hz, 1H), 2.43 – 2.40 (m, 1H), 2.21 (s, 3H), 2.02 – 1.93 (m, 1H), 1.76 (s, 3H), 1.75 – 1.59 (m, 5H), 1.56 (s, 2H), 1.35 (s, 3H), 0.72 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 154.7, 154.0, 143.8, 137.6, 114.6, 111.6, 108.5, 108.1, 90.5, 83.5, 44.5, 42.2, 42.2, 39.1, 38.6, 35.4, 27.3, 25.6, 25.6, 21.3, 17.4, 15.0 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{22}H_{31}O_4$ 359.2248, found 359.2218.

Data for 3.87 and 3.88:

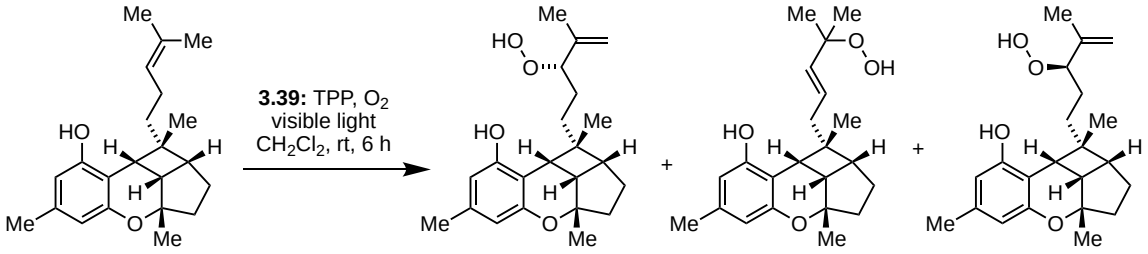
R_f: 0.40 (9:1 hexanes/ EtOAc).

FTIR (neat): 3392, 2948, 1625, 1584, 1376, 1137, 1053, 995, 729 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): (*mix of isomers*) δ 8.44 (s, 1H), 8.17 (s, 1.7H), 6.32 (s, 1.7H), 6.30 (s, 1H), 6.21 (s, 1.7H), 6.15 (s, 1H), 5.96 – 5.89 (m, 1.7H), 5.76 – 5.71 (m, 1.7H), 5.39 (br s, 1.7H), 5.32 – 5.29 (m, 1H), 5.05 (m, 2.0), 4.33 (t, *J* = 6.7 Hz, 1.7H), 3.11 – 3.04 (m, 2.7H), 2.58 – 2.50 (m, 2H), 2.47 – 2.29 (m, 5H), 2.19 (s, 5H), 2.0 – 1.97 (m, 3H), 1.76 (s, 3H), 1.73 – 1.51 (11H), 1.38 (s, 5H), 1.37 (s, 5H), 1.34 (s, 6H), 0.79 (s, 5H), 0.71 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): (*mix of isomers*) δ 154.4, 154.3, 154.2, 154.1, 143.8, 143.7, 137.7, 137.4, 137.3, 128.3, 114.8, 114.5, 111.4, 111.2, 108.7, 108.4, 108.3, 90.5, 83.6, 83.4, 49.2, 45.3, 44.5, 42.3, 42.2, 42.0, 39.1, 38.9, 38.5, 38.3, 35.3, 35.2, 33.6, 27.2, 25.5, 25.4, 24.7, 24.4, 21.3, 17.1, 15.5, 15.0 ppm.

HRMS (**ESI**) **m/z:** $[M+K]^+$ Calcd for $C_{22}H_{30}O_4K$ 423.1932, found 423.1979.



3.32 **3.89** 16% **3.90** **3.91**

3.90:3.91 1.7:1, 39%

To a solution of tetracycle **3.32** (126 mg, 0.443 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL), in a 25 mL borosilicate glass test tube was added TPP (**3.39**) (5 mg, 0.009 mmol, 2 mol%) and O_2 was sparged through the solution for 10 min. Visible light was applied to the solution at a distance of 10 cm from the irradiation vessel which was stirred for 6 h at room temperature. The reaction was concentrated *in vacuo* and purified *via* flash chromatography on SiO_2 (9:1 CH_2Cl_2/ EtOAc) to afford **3.89** (26 mg, 16%) as a yellow oil and **3.90** and **3.91** (61 mg, 39%) as a yellow oil and a 1.7:1 mixture of isomers.

Data for 3.89:

R_f: 0.60 (9:1 CH_2Cl_2/ EtOAc).

FTIR (neat): 3392, 2951, 1625, 1586, 1452, 1375, 1330, 1133, 1056, 996 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.68 (br s, 1H), 6.33 (s, 1H), 6.16 (s, 1H), 4.93 – 4.89 (m, 1H), 4.85 – 4.84 (m, 1H), 4.55 (br s, 1H), 4.02 (dd, *J* = 7.1, 5.5 Hz, 1H), 3.15 (d, *J* = 9.7 Hz, 1H), 2.55 (t, *J* = 9.1 Hz, 1H), 2.42 (td, *J* = 8.4, 3.7 Hz, 1H), 2.22 (s, 3H), 2.09 – 2.01 (m, 1H), 1.83 – 1.75 (m, 1H), 1.69 – 1.60 (m, 2H), 1.58 (s, 3H), 1.35 – 1.18 (m, 4H), 1.32 (s, 3H), 1.30 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 154.9, 153.7, 144.2, 137.6, 113.6, 111.8, 109.0, 108.4, 90.5, 83.90, 46.4, 42.1, 40.4, 39.0, 35.7, 30.3, 27.7, 26.5, 26.1, 25.6, 21.3, 17.3 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{22}H_{31}O_4$ 359.2217, found 359.2218.

Data for 3.90 and 3.91:

R_f: 0.50 (9:1 CH_2Cl_2/ EtOAc).

FTIR (neat): 3391, 2949, 1625, 1585, 1419, 1375, 1329, 1138, 1054, 995 cm^{-1}.

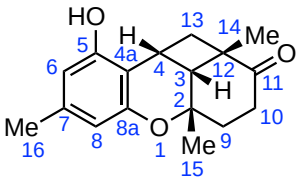
^{1}H NMR (500 MHz, $CDCl_3$): (*mix of isomers*) δ 7.86 (br s, 1H), 7.66 (br s, 1.7H), 6.35 (s, 1.7 H), 6.32 (s, 1H), 6.21 (s, 1.7H), 6.17 (s, 1H), 5.51 – 5.45 (m, 1.7H), 5.20 (br s, 1.7H), 5.17 (d, *J* = 15.3 Hz, 1.7H), 5.05 – 5.03 (br s, 1H), 4.92 – 4.90 (m, 1H), 4.87 – 4.87 (m, 1H), 4.00 – 3.97 (m, 1H), 3.23 (d, *J* = 9.65 Hz, 1.7H), 3.17 (d, *J* = 9.78 Hz, 1H), 2.58 – 2.53 (m, 3H), 2.50 – 2.46 (2H), 2.21 (s, 8H), 2.07

– 1.58 (m, 7H), 1.88 – 1.33 (m, 2H), 1.73 – 1.53 (m, 8H), 1.37 – 1.36 (m, 5H), 1.35 (s, 5H), 1.33 (s, 3H), 1.30 (s, 10H), 1.27 (s, 5H), 1.21 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): (*mix of isomers*) δ 154.9, 154.8, 153.9, 153.7, 144.2, 137.7, 137.5, 134.8, 129.6, 113.8, 111.9, 111.5, 109.4, 109.0, 108.7, 108.5, 90.4, 83.9, 83.8, 82.4, 46.8, 46.2, 42.0, 40.5, 40.4, 39.3, 38.9, 35.8, 35.5, 35.2, 30.9, 30.3, 27.6, 26.2, 26.0, 25.9, 25.8, 25.7, 24.8, 24.1, 21.4, 17.5 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{22}H_{31}O_4$ 359.2235, found 359.2217.

3.4.3 NMR Comparison Data



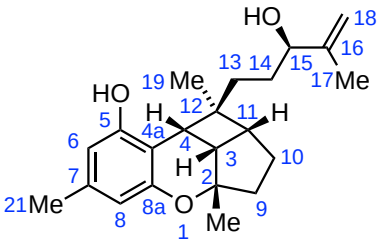
3.1: rhodonoid A

Table 3.2 – ^{1}H NMR Comparison Data for Rhodonoid A

NMR Assignment	Synthetic sample ($CDCl_3$) Yu Tang *et al.* (2017)[5] (500 MHz)	Natural Sample ($CDCl_3$) Ai-Jun Hou *et al.* (2017)[2] (500 MHz)	Synthetic sample ($CDCl_3$) George *et al.* (2019) (600 MHz)
3	2.58 (d, *J* = 9.5 Hz)	2.59 (d, *J* = 9.5 Hz)	2.59 (d, *J* = 9.5 Hz)
4	3.71 – 3.80 (m)	3.75 (td, *J* = 9.5, 7.0 Hz)	3.75 (m)
6	6.32 (s)	6.33 (br s)	6.34 (s)
8	6.21 (s)	6.21 (br s)	6.21 (s)
9	1.98 – 2.07 (m) 2.29 – 2.38 (m)	2.03 (ddd, *J* = 14.0, 11.0, 7.0 Hz) 2.33 (ddd, *J* = 14.0, 7.0, 3.5 Hz)	2.03 (ddd, *J* = 14.0, 10.9, 6.8 Hz) 2.32 (m)
10	2.74 – 2.84 (m) 2.39 – 2.44 (m)	2.78 (ddd, *J* = 18.0, 11.0, 7.0 Hz) 2.42 (ddd, *J* = 18.0, 7.0, 3.5 Hz)	2.78 (ddd, *J* = 18.1, 10.9, 7.1 Hz) 2.42 (ddd, *J* = 18.3, 6.8, 3.4 Hz)
13	2.14 - 2.18 (m) 2.39 – 2.44 (m)	2.18 (dd, *J* = 12.0, 7.0 Hz) 2.36 (br dd, *J* = 12.0, 9.5 Hz)	2.16 (dd, *J* = 12.2, 7.1 Hz) 2.36 (m)
14	1.43 (s)	1.44 (s)	1.44 (s)
15	1.15 (s)	1.15 (s)	1.16 (s)
16	2.20 (s)	2.21 (s)	2.22 (s)
OH	5.29 (br s)	4.78 (br s)	4.59 (s)

Table 3.3 – ^{13}C NMR ($CDCl_3$) Comparison Data for Rhodonoid A

NMR Assignment	Synthetic sample ($CDCl_3$) Yu Tang *et al.* (2017)[5] (125 MHz)	Natural Sample ($CDCl_3$) Ai-Jun Hou *et al.* (2017)[2] (125 MHz)	Synthetic sample ($CDCl_3$) George *et al.* (2019) (600 MHz)
2	73.5	73.6	73.5
3	51.1	51.2	51.1
4	21.8	21.9	21.9
4a	112.5	112.6	112.6
5	154.1	154.3	154.1
6	112.5	112.3	112.0
7	137.4	137.6	137.5
8	109.3	109.3	109.3
8a	152.7	152.6	152.8
9	34.1	34.2	34.1
10	33.6	33.7	33.7
11	216.2	215.7	216.5
12	43.8	43.9	43.9
13	38.9	39.0	39.0
14	24.9	25.0	24.9
15	25.4	25.6	25.4
16	21.2	21.4	21.3



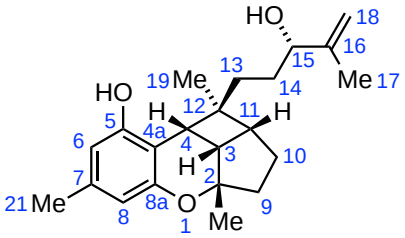
3.5: rhodonoid E

Table 3.4 – ^{1}H NMR Comparison Data for Rhodonoid E

NMR Assignment	Synthetic sample ($CDCl_3$) Yu Tang *et al.* (2017)[3] (500 MHz)	Natural Sample ($CDCl_3$) Ai-Jun Hou *et al.* (2015)[1] (500 MHz)	Synthetic sample ($CDCl_3$) George *et al.* (2019) (600 MHz)
3	2.52 – 2.58 (m)	2.56 (dd, *J* = 9.6, 7.8 Hz)	2.56 (dd, *J* = 9.6, 7.8 Hz)
4	3.09 (d, *J* = 9.5 Hz)	3.09 (d, *J* = 9.6 Hz)	3.09 (d, *J* = 9.6 Hz)
6	6.16 (s)	6.16 (br s)	6.16 (s)
8	6.31 (s)	6.31 (br s)	6.32 (s)
9	1.94 – 2.00 (m) 1.60 – 1.74 (m)	1.98 (m) 1.60 (m)	1.98 (m) 1.60 (m)
10	1.60 – 1.74 (m)	1.64 (m)	1.64 (m)
11	2.43 (td, *J* = 8.0, 3.5 Hz)	2.43 (td, *J* = 7.8, 3.0 Hz)	2.43 (td, *J* = 7.8, 4.1 Hz)
13	1.60 – 1.74 (m)	1.65 (m) 1.72 (m)	1.65 (m) 1.72 (m)
14	1.48 – 1.53 (m) 1.60 – 1.74 (m)	1.51 (m) 1.72 (m)	1.51 (m) 1.72 (m)
15	4.10 (t, *J* = 5.5 Hz)	4.10 (br t, *J* = 5.7 Hz)	4.10 (t, *J* = 5.0 Hz)
17	4.87 (s) 4.99 (s)	4.87 (br s) 4.99 (br s)	4.87 (s) 4.99 (s)
18	1.76 (s)	1.76 (br s)	1.76 (s)
19	0.73 (s)	0.73 (s)	0.73 (s)
20	1.35 (s)	1.35 (s)	1.35 (s)
21	2.22 (s)	2.22 (s)	2.22 (s)
5-OH	4.67 (s)	4.69 (br s)	4.61 (br s)

Table 3.5 – ^{13}C NMR ($CDCl_3$) Comparison Data for Rhodonoid E

NMR Assignment	Synthetic sample ($CDCl_3$) Yu Tang *et al.* (2017)[3] (125 MHz)	Natural Sample ($CDCl_3$) Ai-Jun Hou *et al.* (2015)[1] (125 MHz)	Synthetic sample ($CDCl_3$) George *et al.* (2019) (150 MHz)
2	83.4	83.5	83.6
3	39.0	39.1	39.2
4	35.1	35.3	35.3
4a	108.4	108.6	108.6
5	153.9	154.1	154.1
6	108.1	108.2	108.2
7	137.4	137.6	137.6
8	111.3	111.5	111.5
8a	154.5	154.6	154.6
9	38.6	38.7	38.8
10	25.5	25.6	25.7
11	44.4	44.5	44.5
12	42.1	42.3	42.3
13	41.8	41.9	42.0
14	29.3	29.4	29.4
15	76.5	76.6	76.6
16	147.5	147.7	147.7
17	111.3	111.3	111.3
18	17.7	17.8	17.8
19	15.1	15.3	15.3
20	27.1	27.3	27.3
21	21.2	21.4	21.4



3.6: rhodonoid F

Table 3.6 – ^{1}H NMR Comparison Data for Rhodonoid F

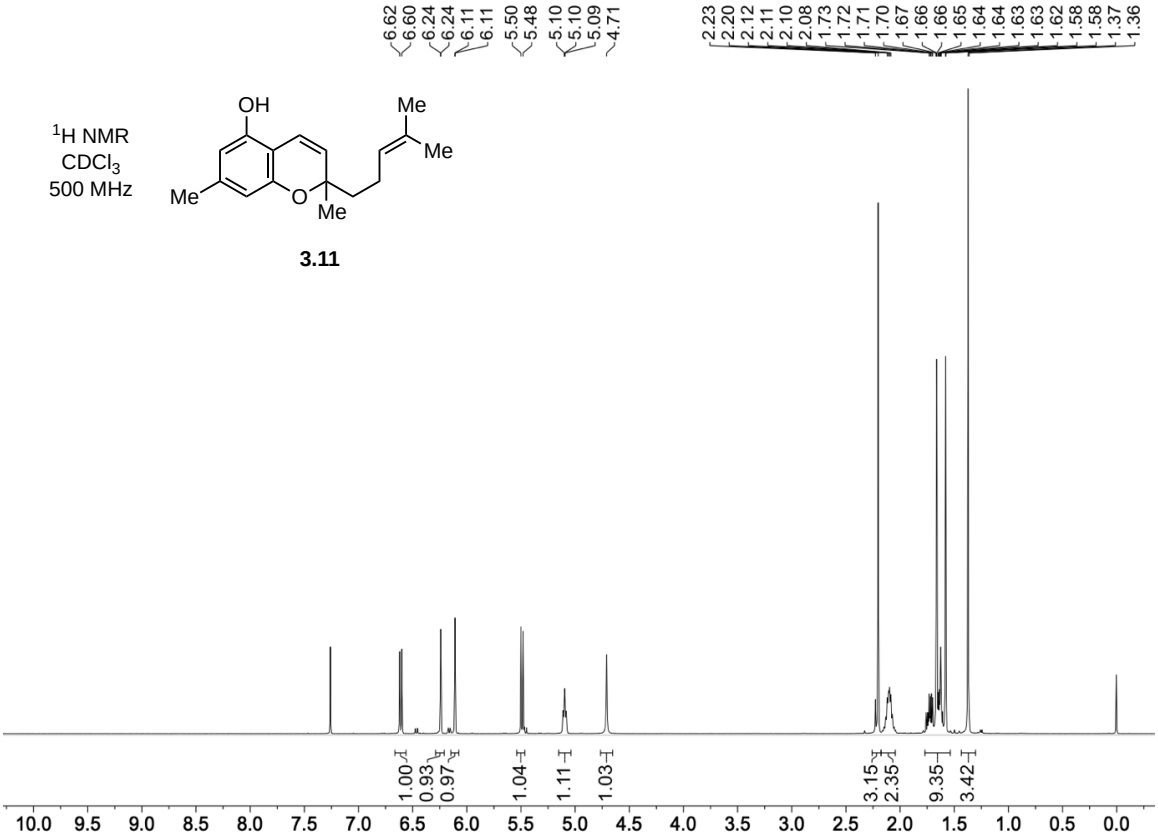
NMR Assignment	Synthetic sample ($CDCl_3$) Yu Tang *et al.* (2017)[3] (500 MHz)	Natural Sample ($CDCl_3$) Ai-Jun Hou *et al.* (2015)[1] (500 MHz)	Synthetic sample ($CDCl_3$) George *et al.* (2019) (600 MHz)
3	2.52 – 2.57 (m)	2.55 (dd, *J* = 9.6, 7.8 Hz)	2.55 (dd, *J* = 9.6, 7.9 Hz)
4	3.11 (d, *J* = 9.5 Hz)	3.10 (d, *J* = 9.6 Hz)	3.11 (d, *J* = 9.6 Hz)
6	6.16 (s)	6.17 (br s)	6.17 (s)
8	6.31 (s)	6.31 (br s)	6.31 (s)
9	1.95 – 2.00 (m) 1.50 – 1.70 (m)	1.98 (m) 1.61 (m)	1.98 (m) 1.61 (m)
10	1.50 – 1.70 (m)	1.65 (m)	1.65 (m)
11	2.43 (td, *J* = 3.5, 8 Hz)	2.41 (td, *J* = 7.8, 3.0 Hz)	2.41 (td, *J* = 7.4, 3.5 Hz)
13	1.50 – 1.70 (m) 1.80 – 1.87 (m)	1.58 (m) 1.83 (m)	1.58 (m) 1.83 (m)
14	1.50 – 1.70 (m)	1.56 (m) 1.67 (m)	1.56 (m) 1.67 (m)
15	4.10 (t, *J* = 6.5 Hz)	4.10 (br t, 6.0)	4.10 (t, *J* = 6.2 Hz)
17	4.87 (s) 4.98 (s)	4.88 (br s) 4.98 (br s)	4.87 (s) 4.98 (s)
18	1.76 (s)	1.76 (br s)	1.76 (s)
19	0.72 (s)	0.73 (s)	0.73 (s)
20	1.34 (s)	1.34 (s)	1.34 (s)
21	2.21 (s)	2.22 (s)	2.21 (s)
5-OH	5.08 (s)	4.81 (br s)	4.79 (br s)

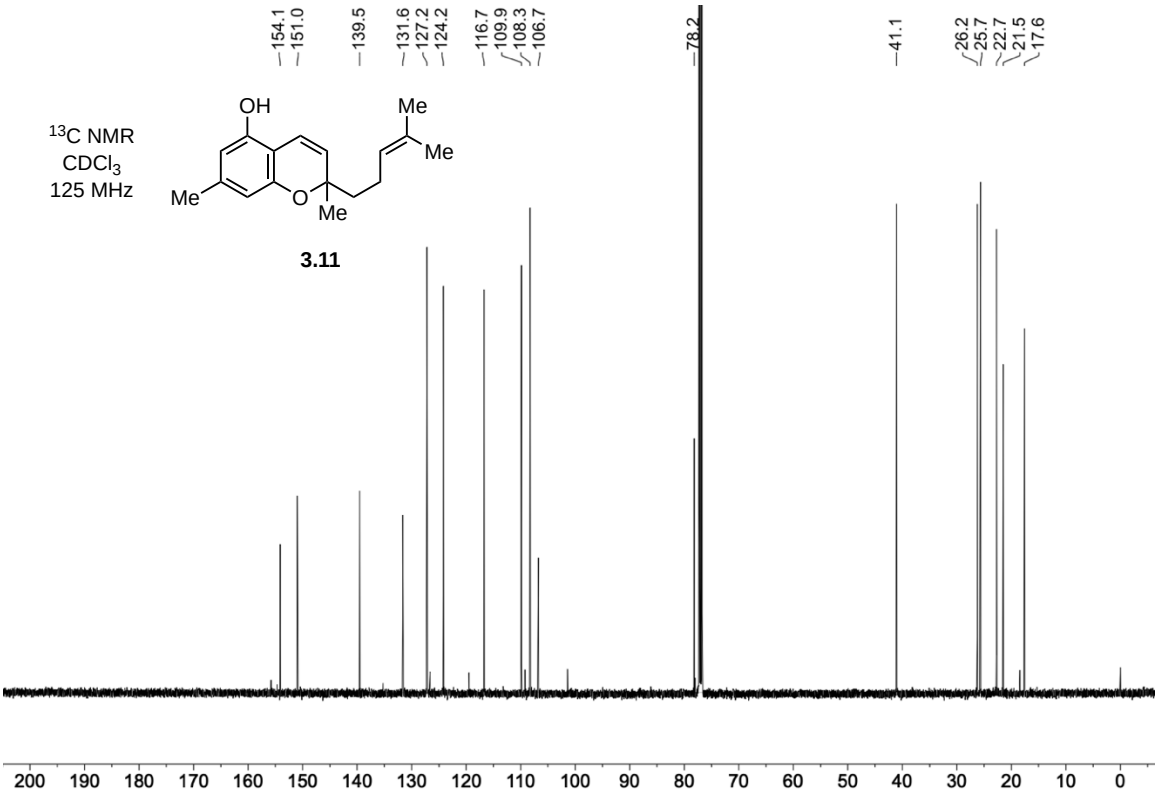
Table 3.7 – ^{13}C NMR ($CDCl_3$) Comparison Data for Rhodonoid F

NMR Assignment	Synthetic sample ($CDCl_3$) Yu Tang *et al.* (2017)[3] (125 MHz)	Natural Sample ^{13}C ($CDCl_3$) Ai-Jun Hou *et al.* (2015)[1] (125 MHz)	Synthetic sample ($CDCl_3$) George *et al.* (2019) (150 MHz)
2	83.4	83.6	83.6
3	39.1	39.2	39.2
4	35.1	35.2	35.2
4a	108.6	108.7	108.7
5	154.1	154.1	154.2
6	108.2	108.3	108.3
7	137.4	137.6	137.5
8	111.2	111.4	111.5
8a	154.5	154.6	154.6
9	38.7	38.8	38.8
10	25.5	25.6	25.6
11	44.6	44.7	44.7
12	42.2	42.4	42.4
13	42.1	42.2	42.2
14	29.3	29.5	29.5
15	76.9	76.7	76.7
16	147.4	147.6	147.6
17	111.4	111.5	111.4
18	17.5	17.7	17.7
19	15.1	15.3	15.2
20	27.0	27.2	27.2
21	21.2	21.4	21.4

3.4.4 NMR Spectra

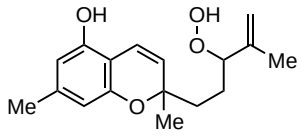
Data for 3.11





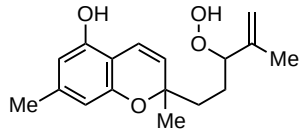
Data for 3.65

^{1}H NMR
$CDCl_3$
500 MHz



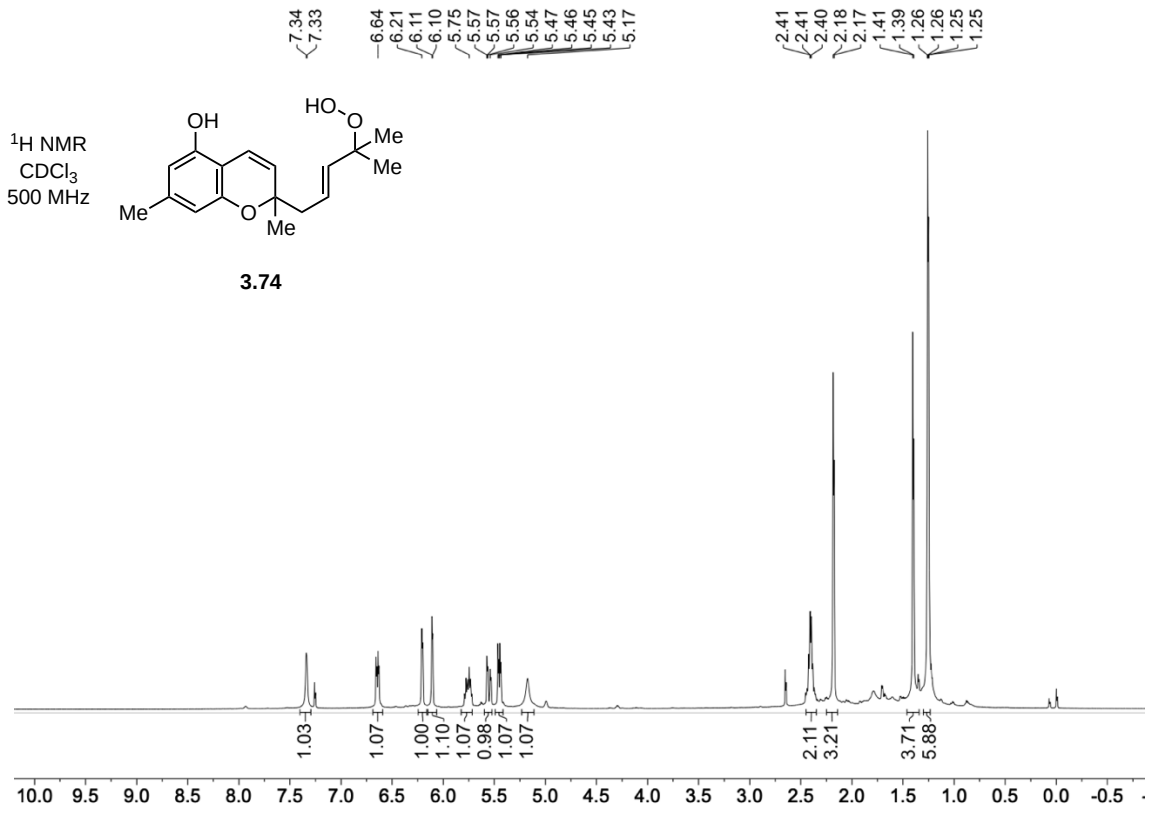
3.65

^{13}C NMR
$CDCl_3$
125 MHz



3.65

Data for 3.74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5.47
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5.45
5.43
5.17
2.41
2.41
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1.25
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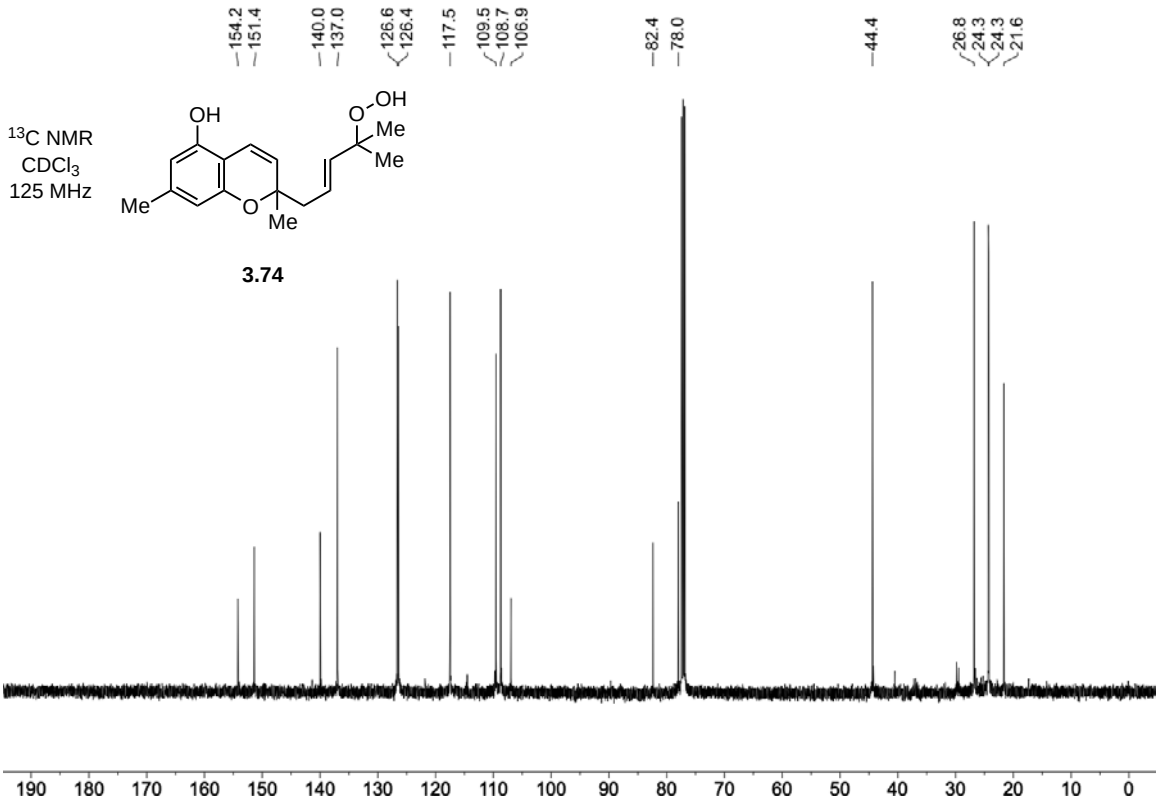
500 MHz
OH
HO
O
Me
Me
Me
O
Me
3.74
1.03
1.07
1.00
1.10
1.07
0.98
1.07
1.07
2.11
3.21
3.71
5.88
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5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26.8
24.3
24.3
21.6
13C NMR
CDCl3
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Me
O
Me
3.74
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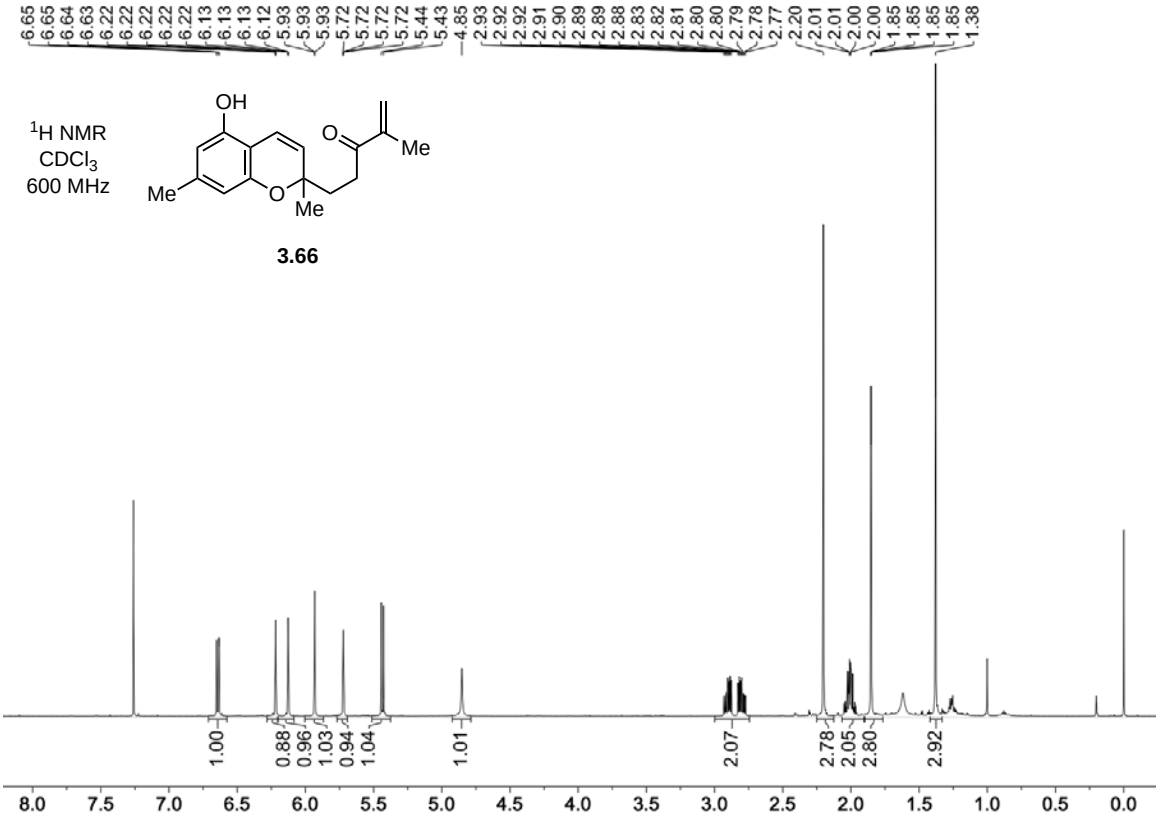
Data for 3.66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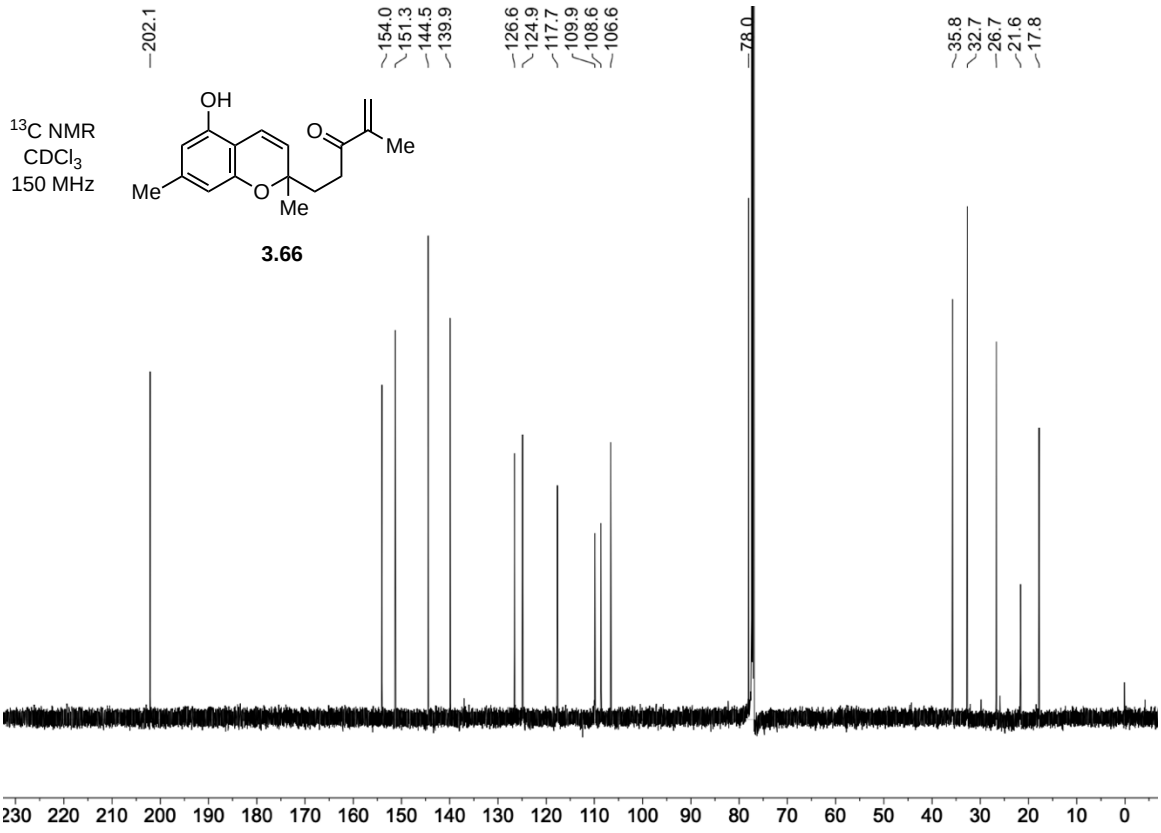
1H NMR
CDCl3
600 MHz
OH
O
Me
Me
O
Me
3.66
1.00 0.88 0.96 1.03 0.94 1.04 1.01 2.07 2.78 2.05 2.80 2.92
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


202.1
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78.0
35.8 32.7 26.7 21.6 17.8
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CDCl3
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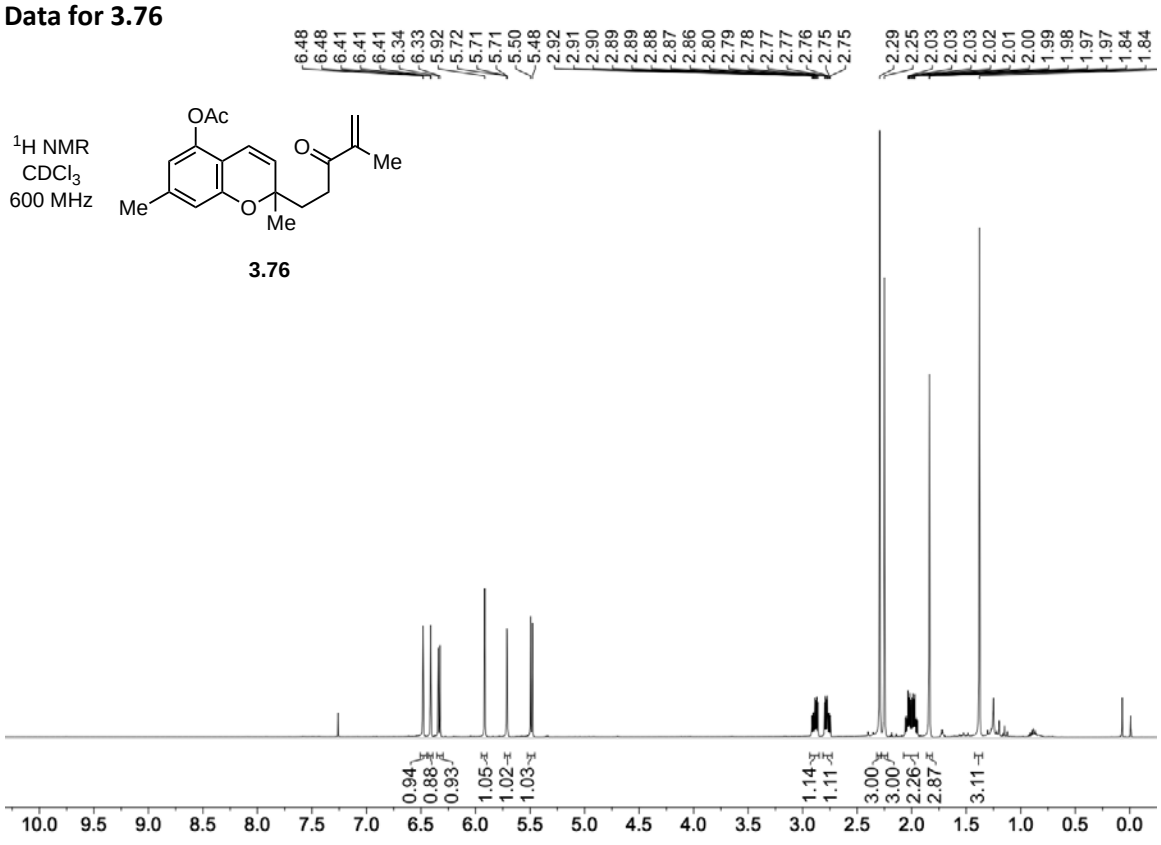
Data for 3.76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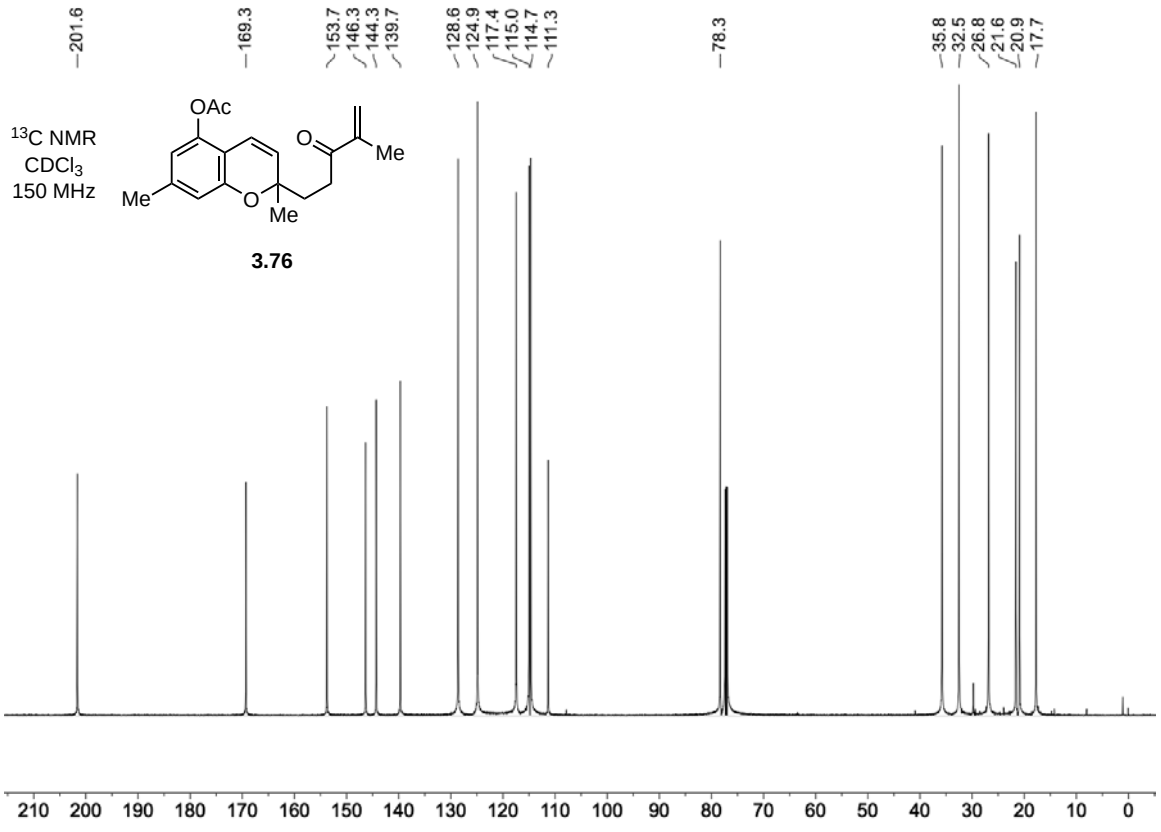
1H NMR
CDCl3
600 MHz
OAc
O
Me
Me
O
Me
3.76
0.94 0.88 0.93 1.05 1.02 1.03 1.14 1.11 3.00 3.00 2.26 2.87 3.11
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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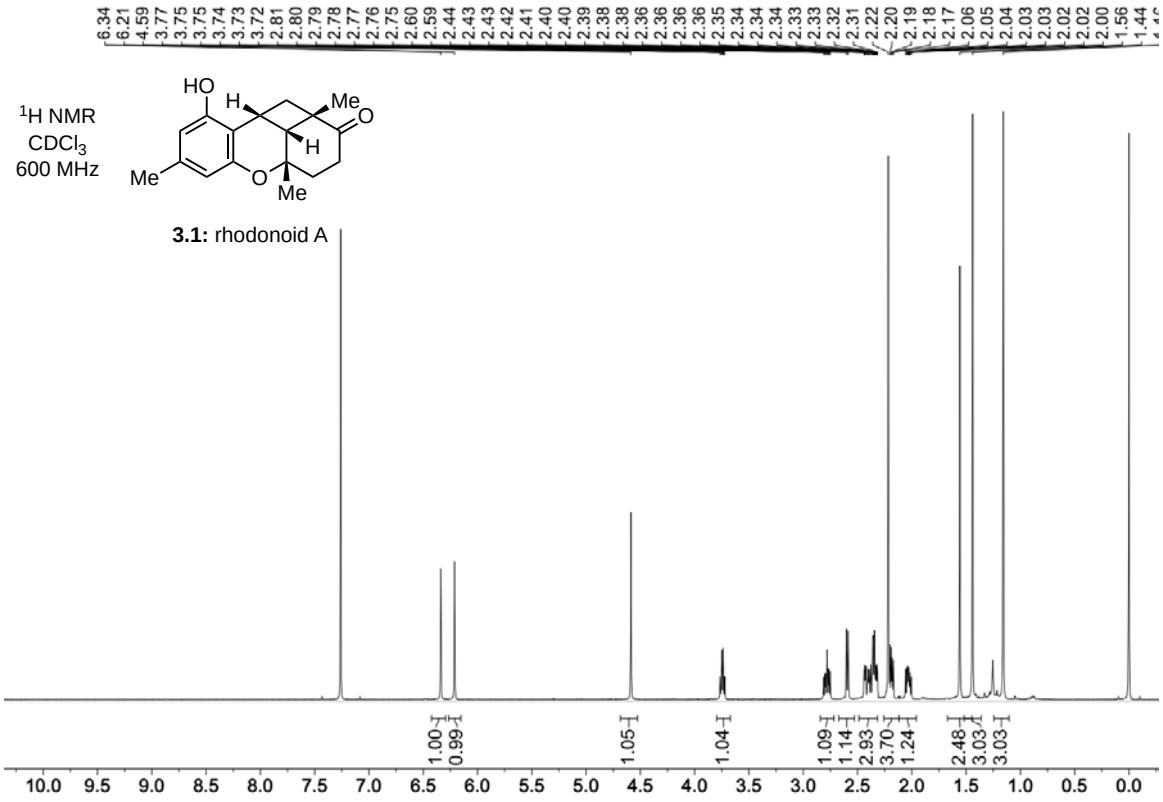
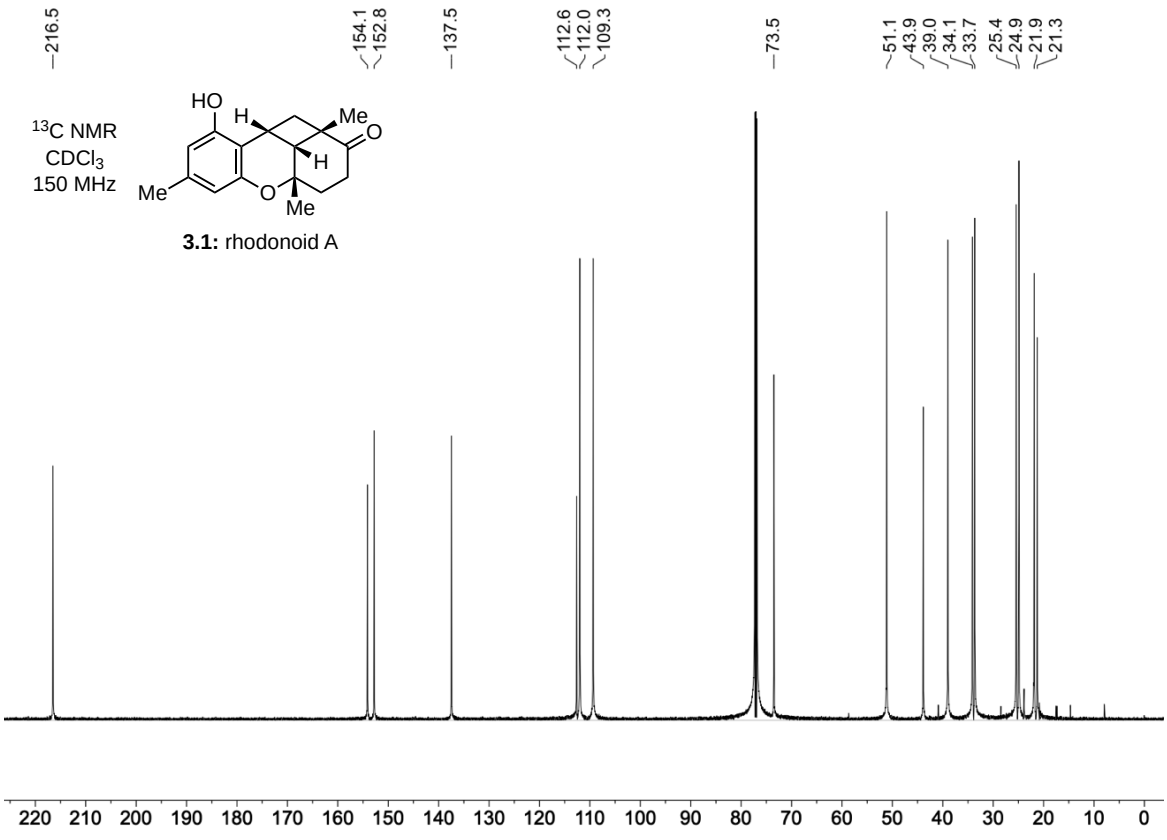
13C NMR
CDCl3
150 MHz
OAc
O
Me
Me
O
Me
3.76
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

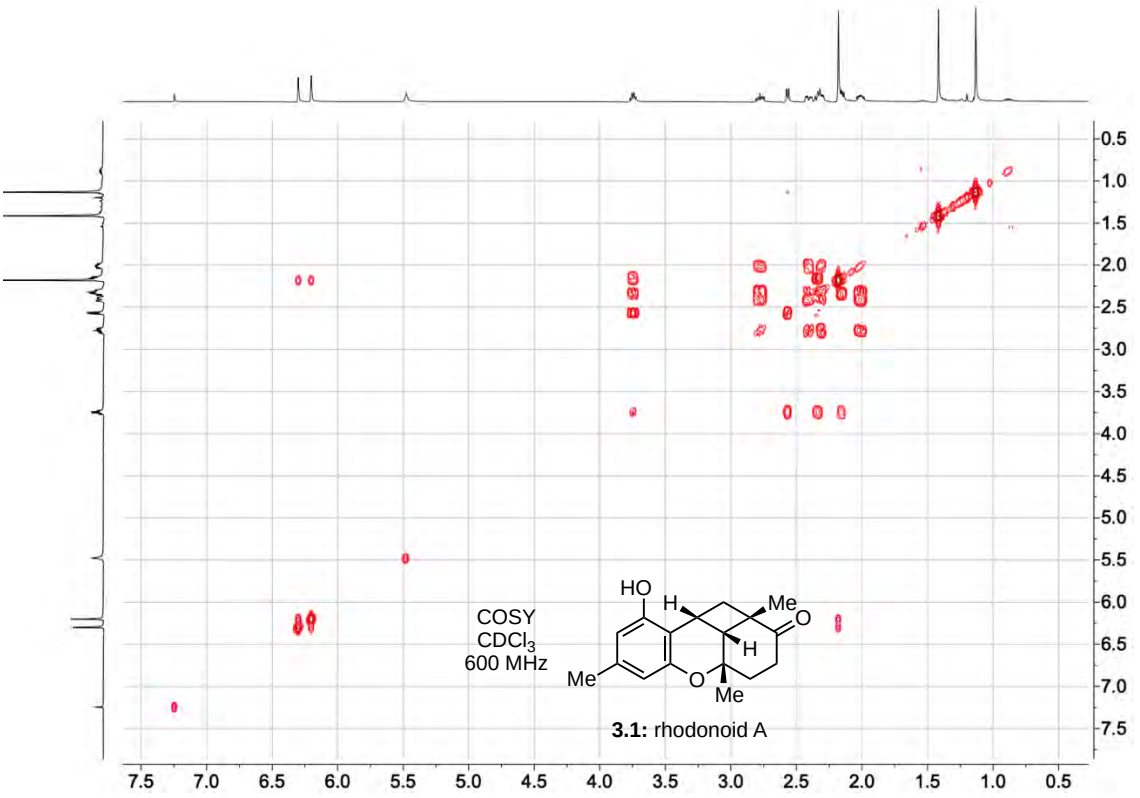
Data for Rhodonoid A (3.1)



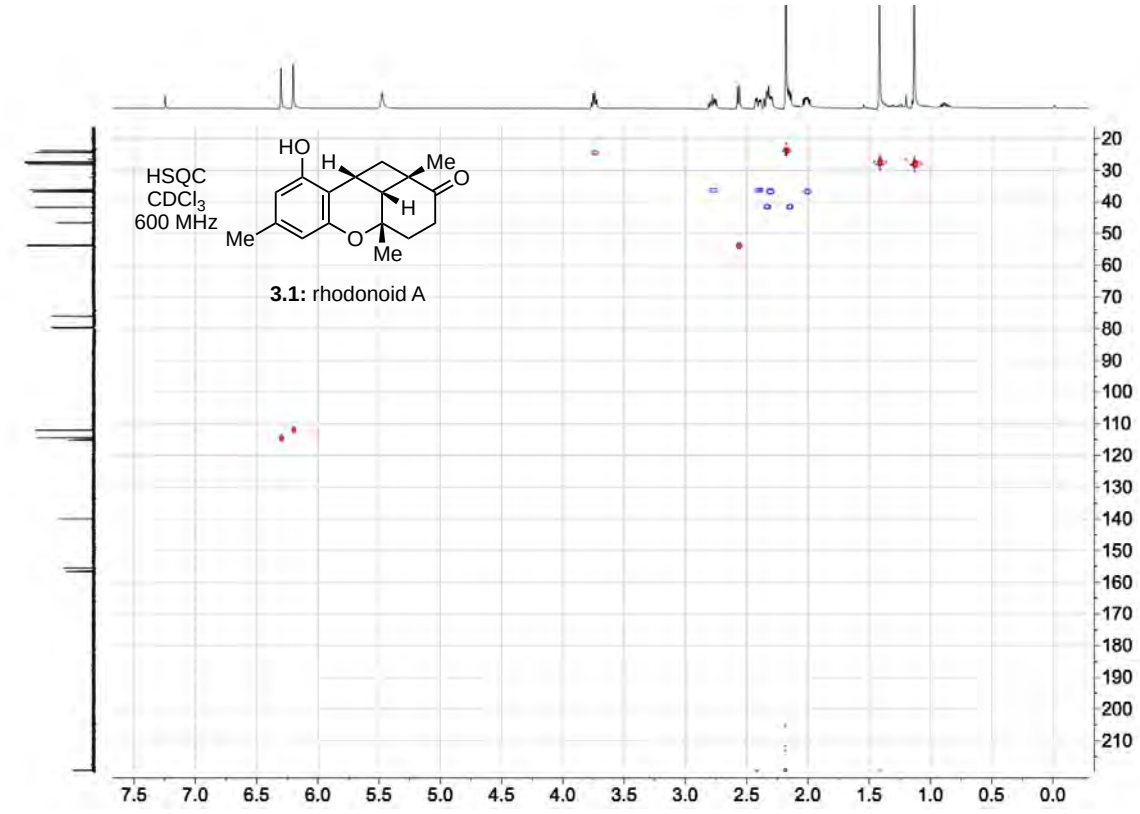
3.1: rhodonoid A



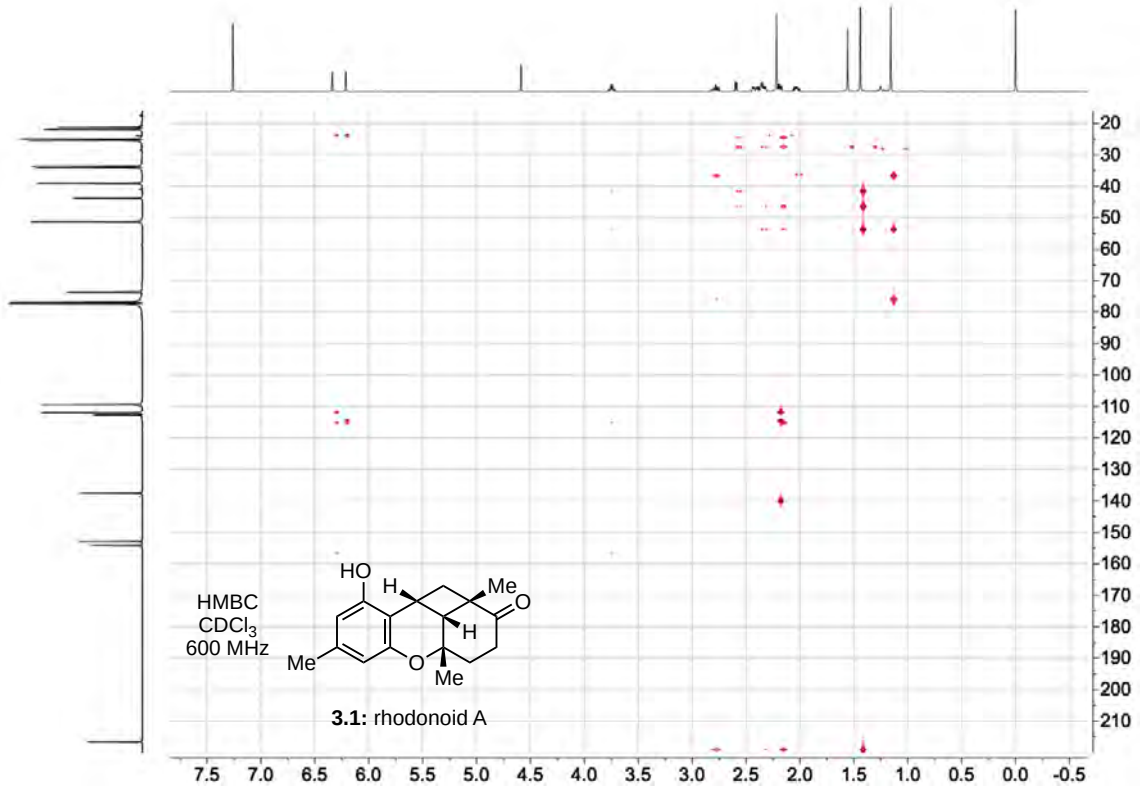
3.1: rhodonoid A



3.1: rhodonoid A

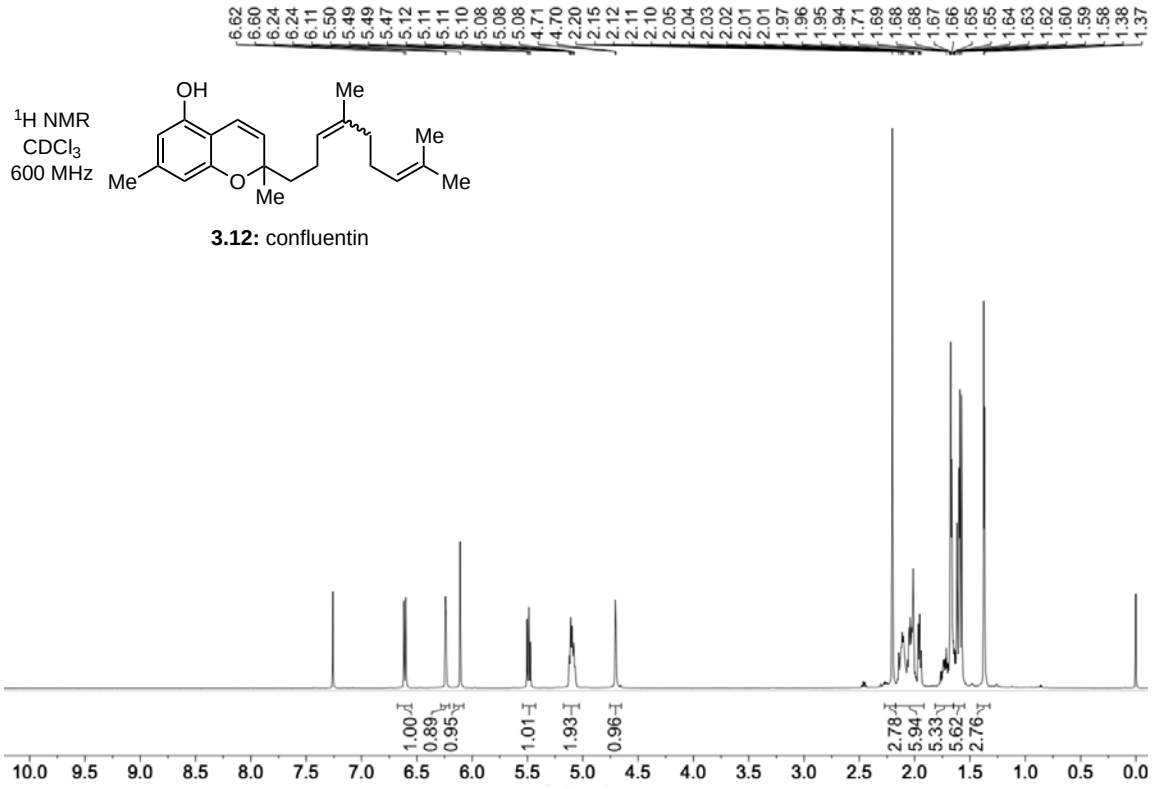


3.1: rhodonoid A

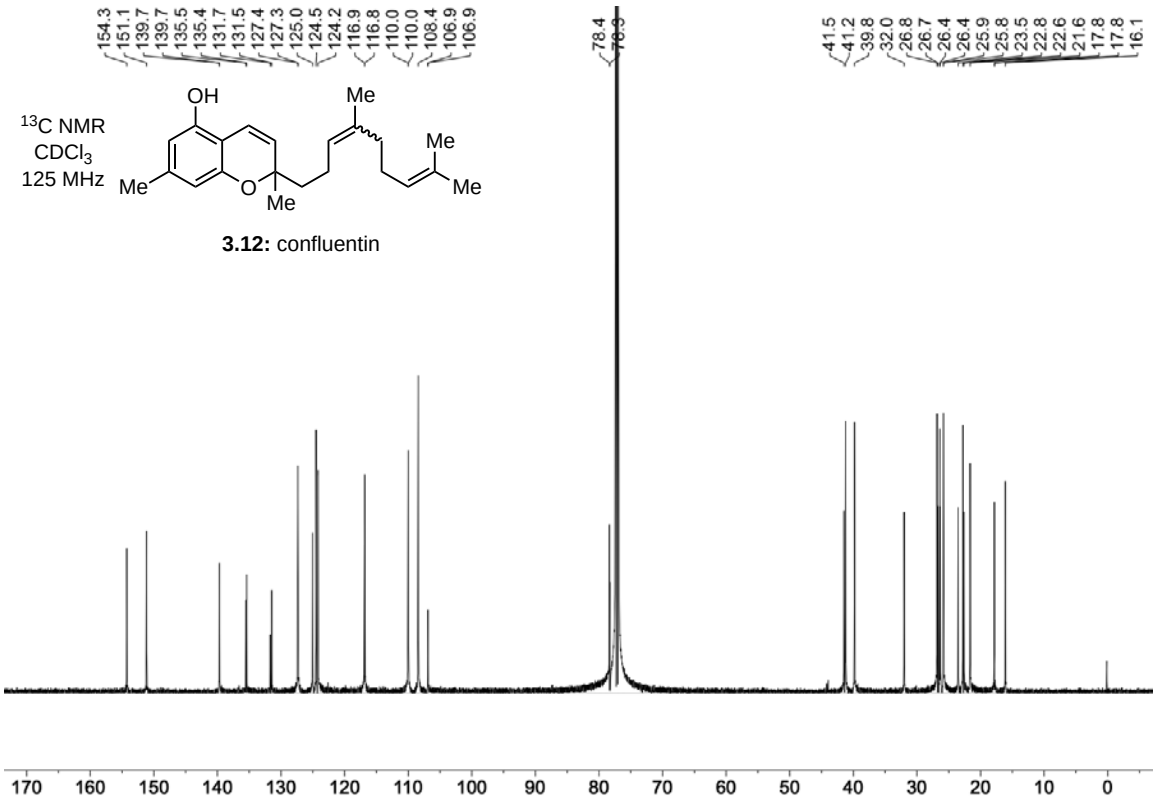


3.1: rhodonoid A

Data for confluentin (3.12)

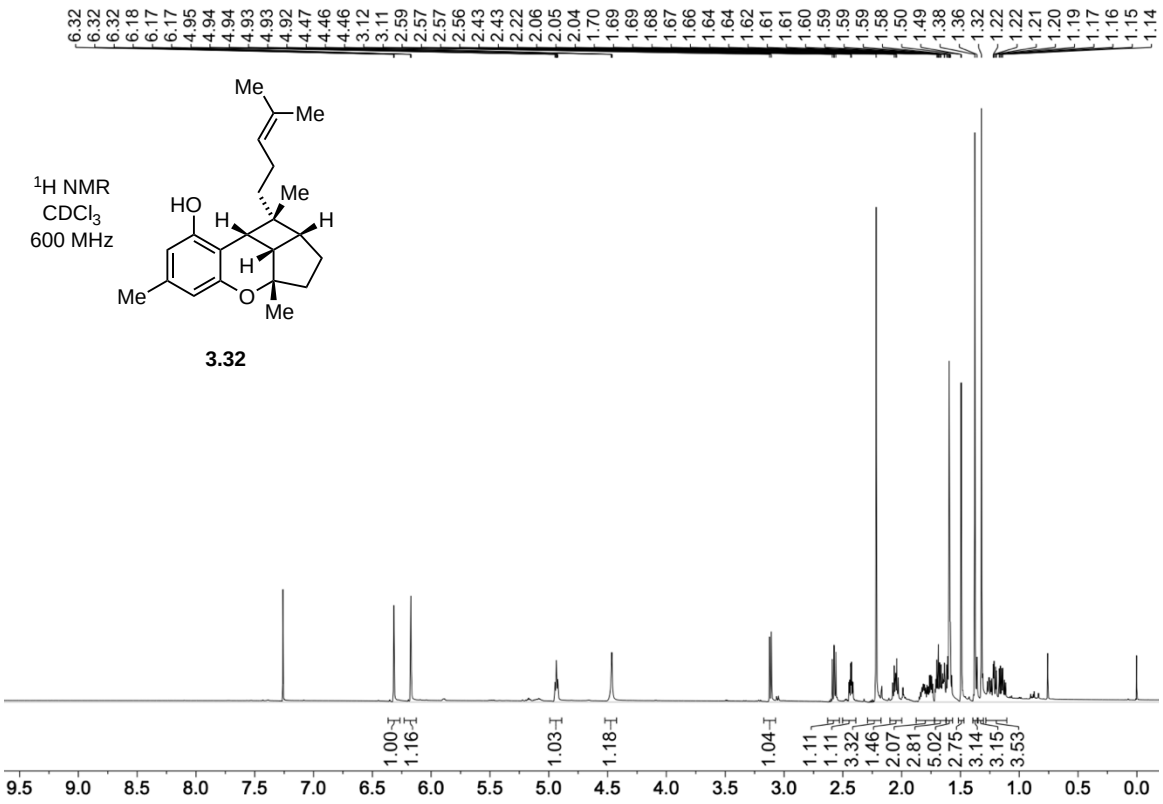


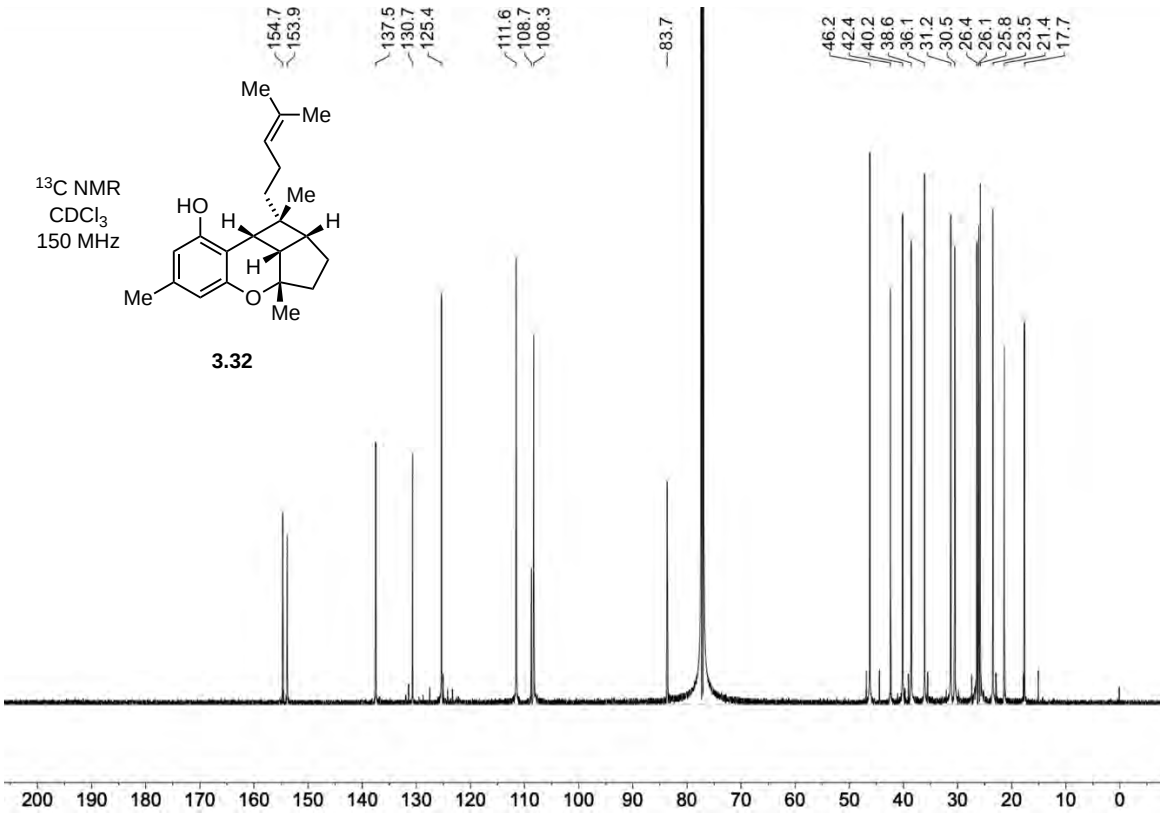
3.12: confluentin

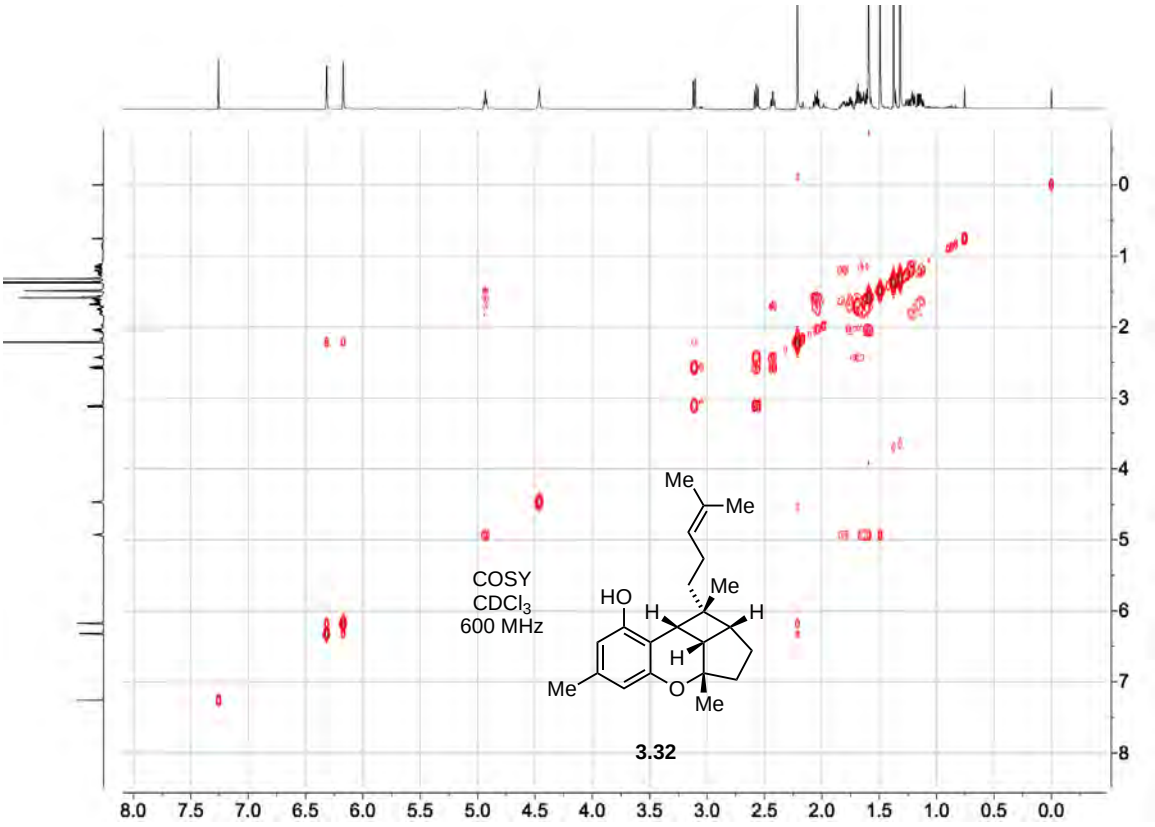


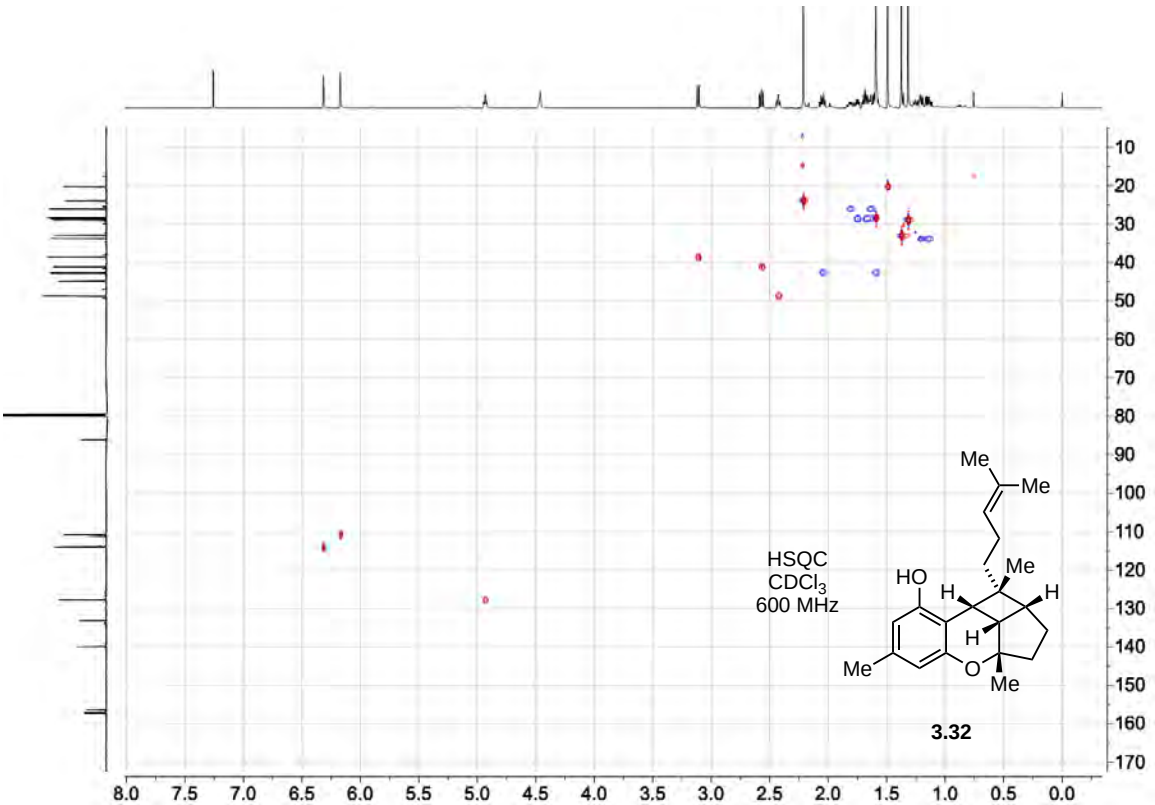
3.12: confluentin

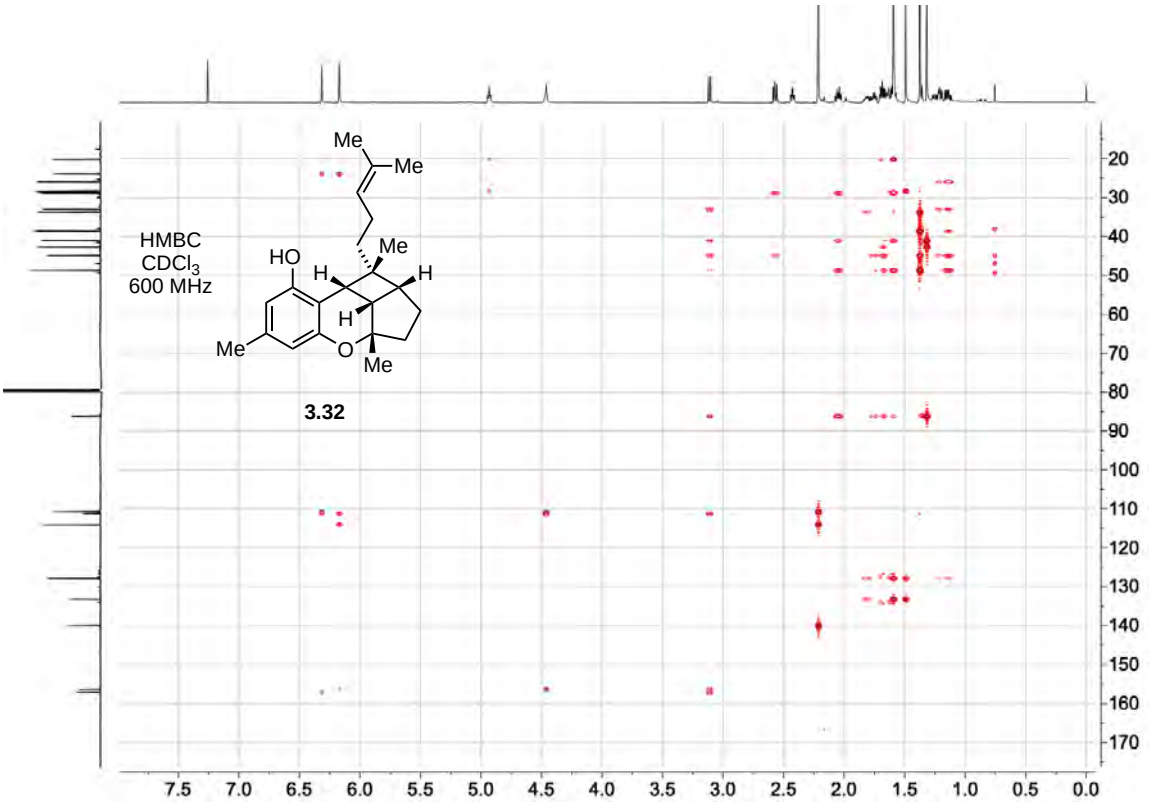
Data for 3.32

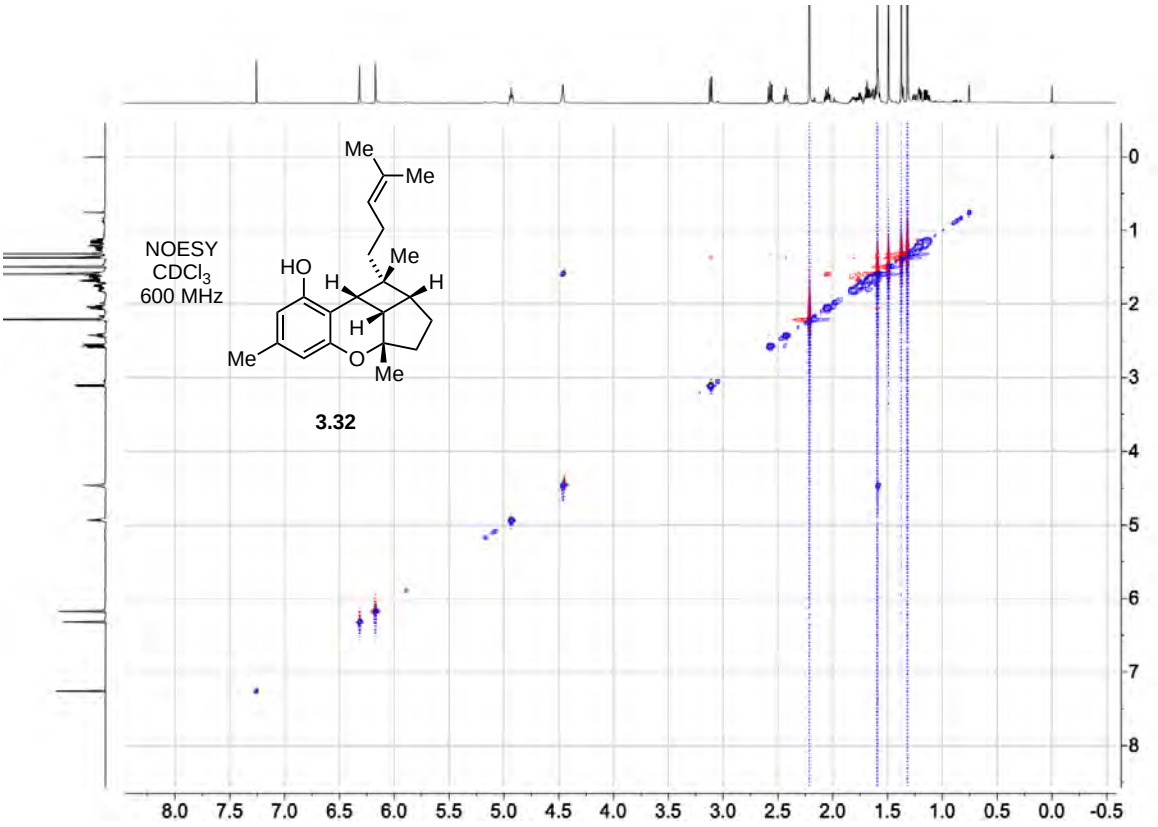

6.32 6.32 6.32 6.18 6.17 6.17 4.95 4.94 4.94 4.93 4.93 4.92 4.47 4.46 4.46 3.12 3.11 2.59 2.57 2.57 2.56 2.43 2.43 2.22 2.06 2.05 2.04 1.70 1.69 1.69 1.68 1.67 1.66 1.64 1.64 1.62 1.61 1.61 1.60 1.59 1.59 1.59 1.58 1.50 1.49 1.38 1.36 1.32 1.22 1.22 1.21 1.20 1.19 1.17 1.16 1.15 1.14
1H NMR
CDCl3
600 MHz
Me
Me
HO
H
Me
H
H
Me
O
Me
3.32
1.00 1.16 1.03 1.18 1.04 1.11 1.11 3.32 1.46 2.07 2.81 5.02 2.75 3.14 3.15 3.53
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


154.7 153.9 137.5 130.7 125.4 111.6 108.7 108.3 83.7 46.2 42.4 40.2 38.6 36.1 31.2 30.5 26.4 26.1 25.8 23.5 21.4 17.7
13C NMR
CDCl3
150 MHz
Me
Me
HO
H
Me
H
H
Me
O
Me
3.32
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

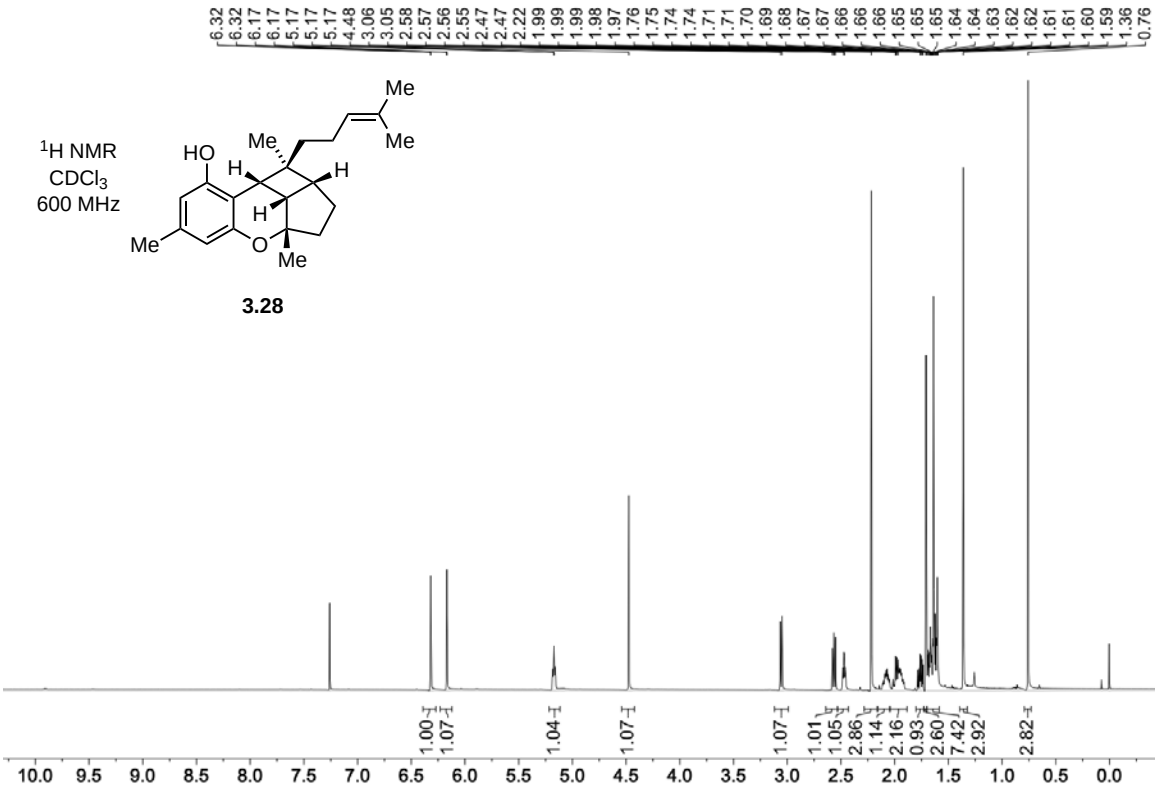

COSY
CDCl3
600 MHz
HO
H
H
H
Me
Me
Me
Me
O
Me
3.32

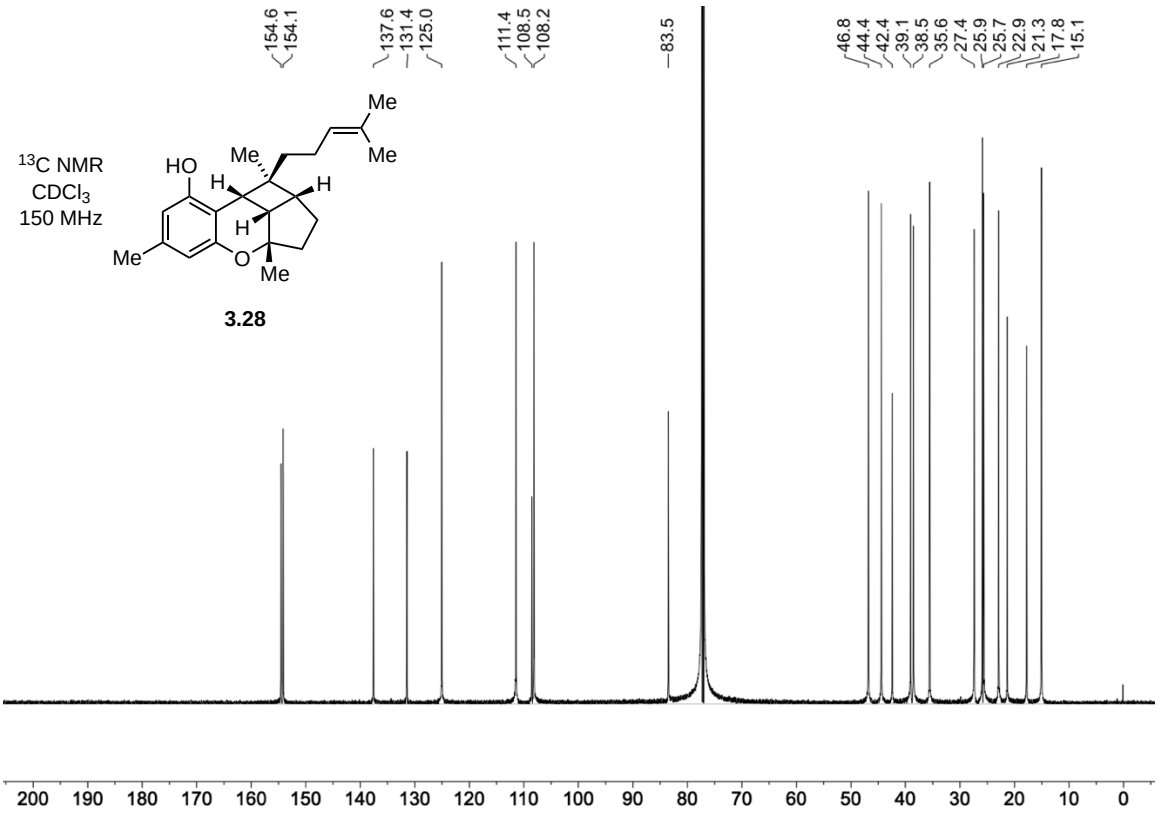

HSQC
CDCl3
600 MHz
HO
H
H
H
Me
Me
Me
Me
O
Me
3.32

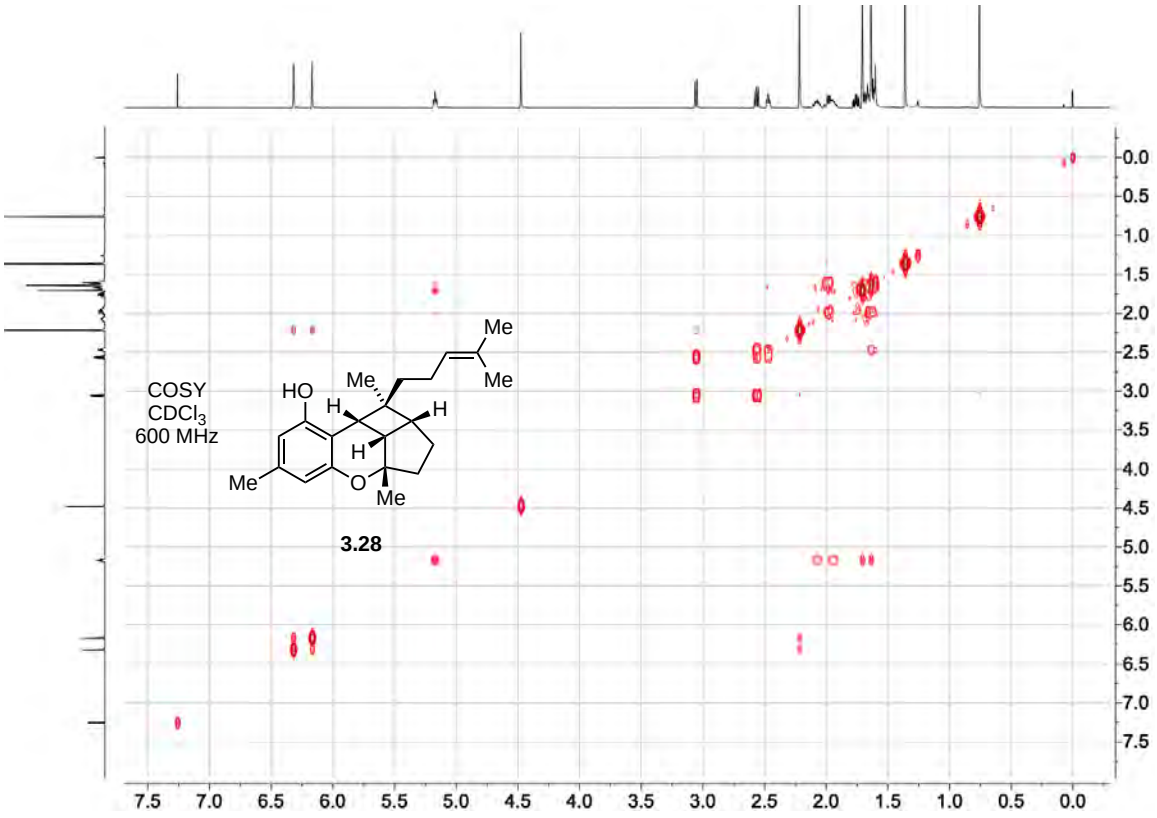

HMBC
CDCl3
600 MHz
Me
Me
HO
H
Me
H
H
Me
O
Me
3.32

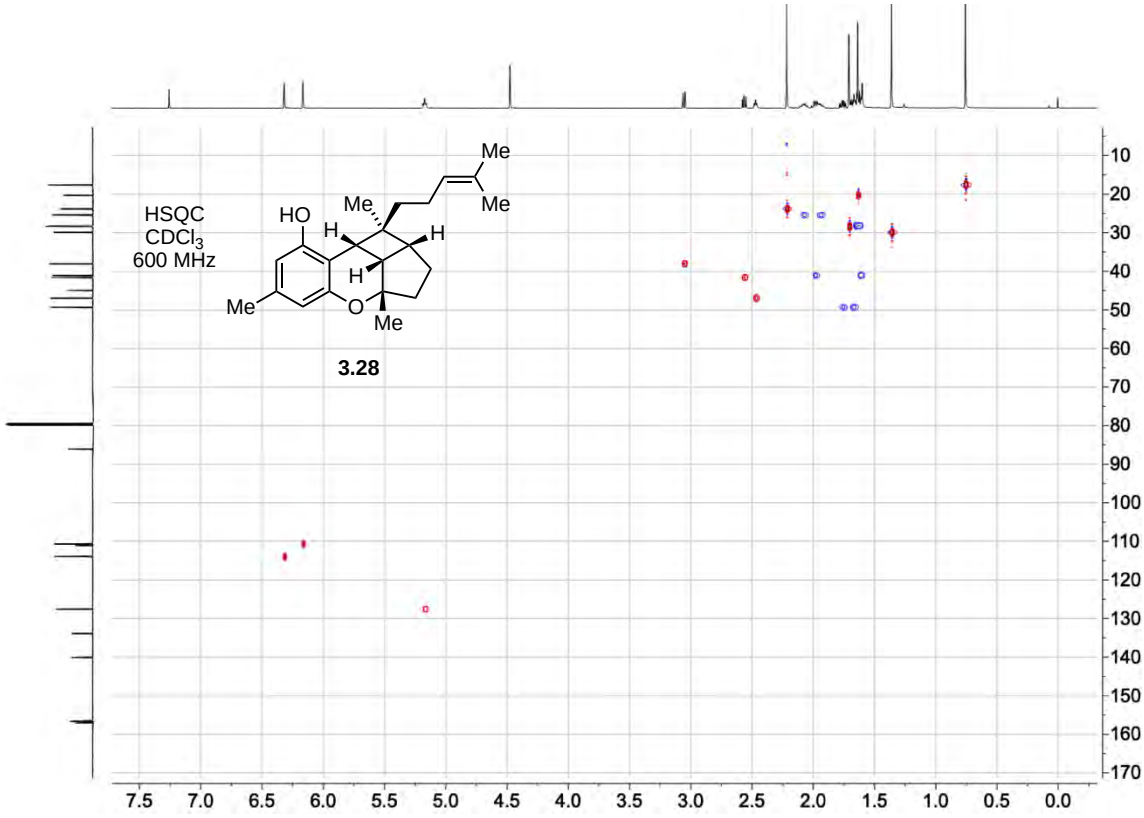

NOESY
CDCl3
600 MHz
Me
Me
HO
H
Me
H
H
Me
O
Me
3.32

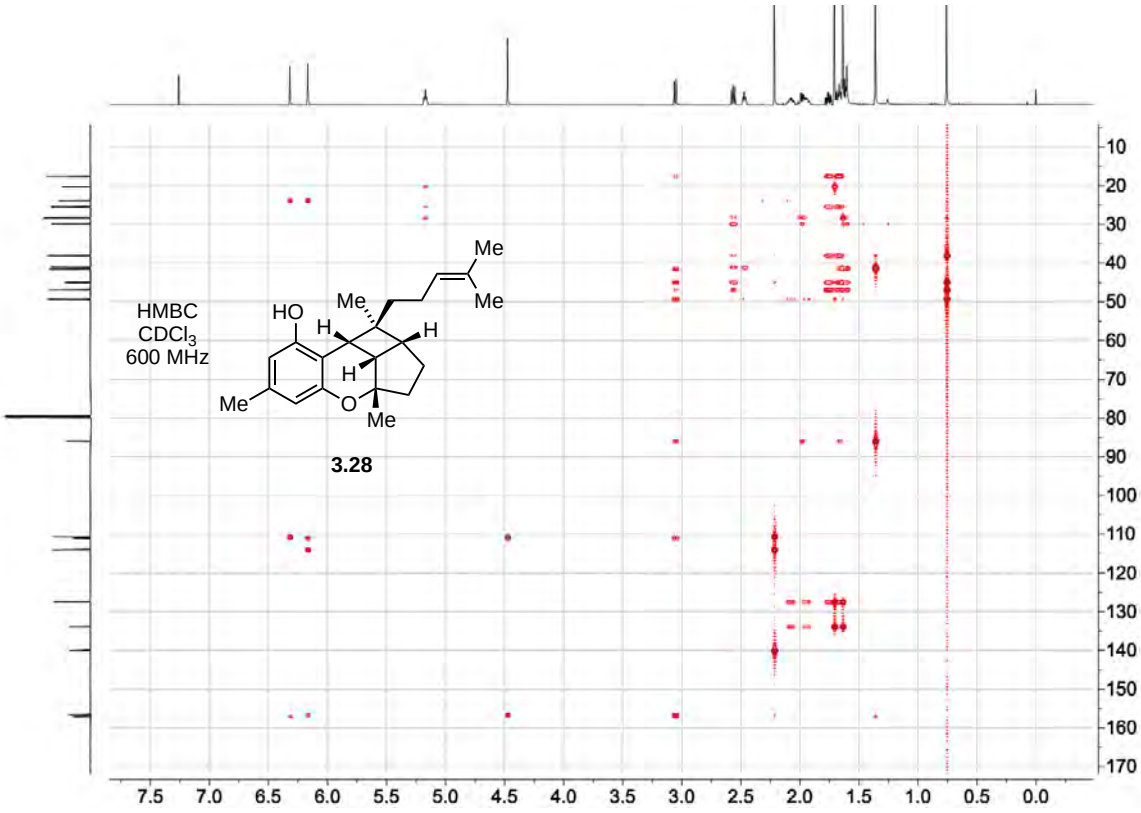
Data for 3.28

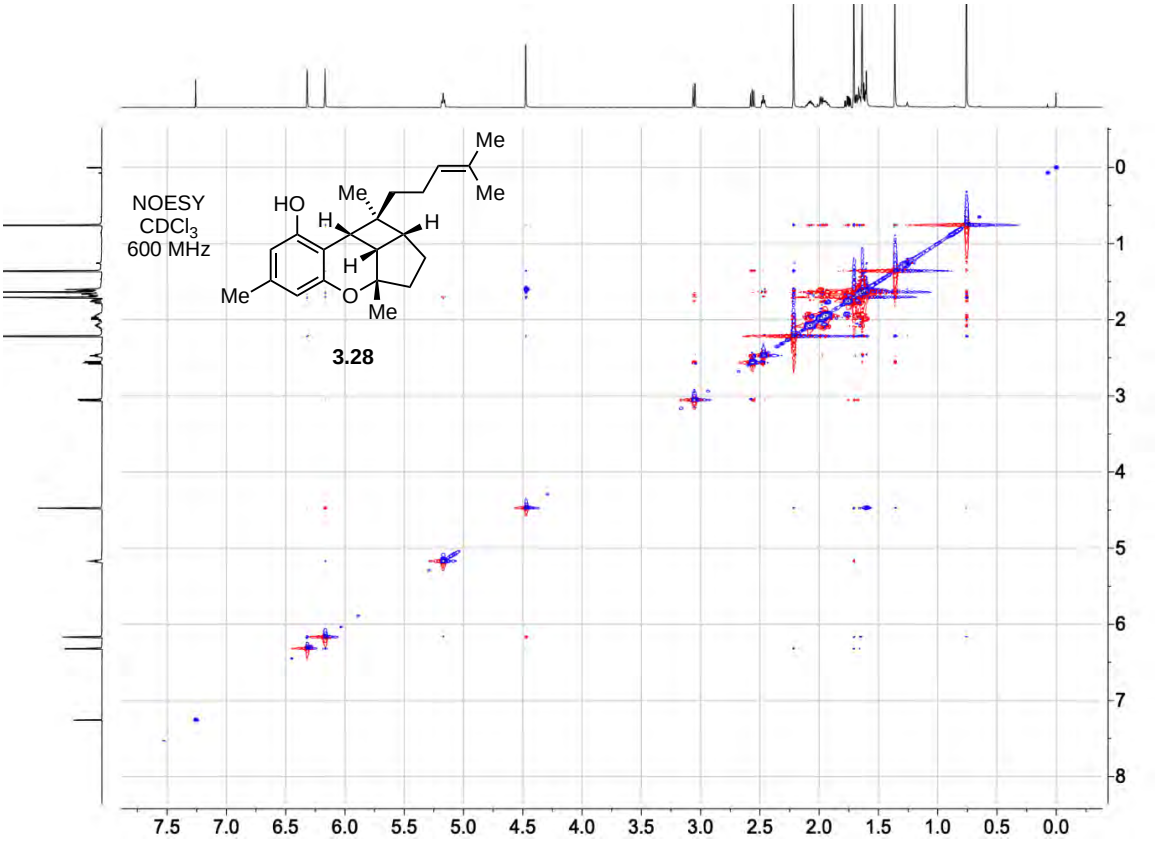

^{1}H NMR
$CDCl_3$
600 MHz
HO
Me
H
H
H
Me
Me
Me
O
Me
Me
3.28


^{13}C NMR
$CDCl_3$
150 MHz
HO
Me
H
H
H
Me
Me
Me
O
Me
Me
3.28

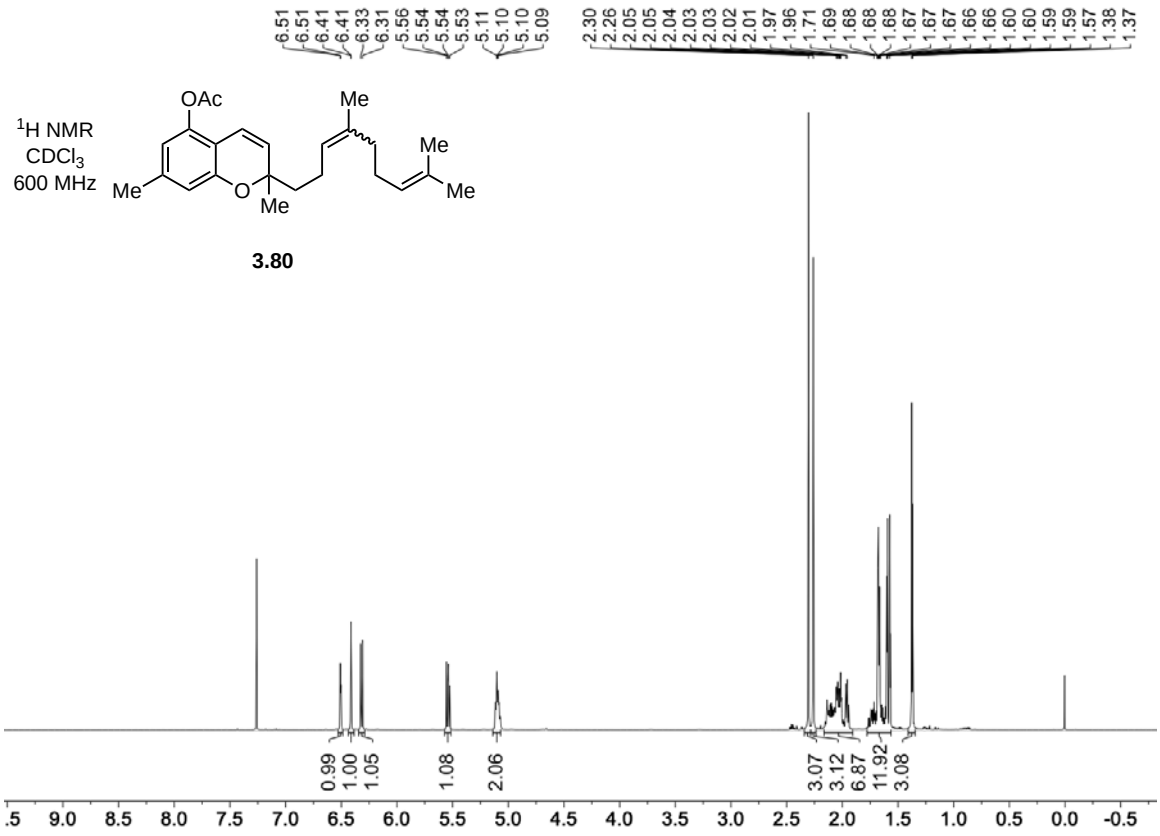

COSY
CDCl3
600 MHz
HO
Me
H
H
H
Me
O
Me
Me
Me
3.28

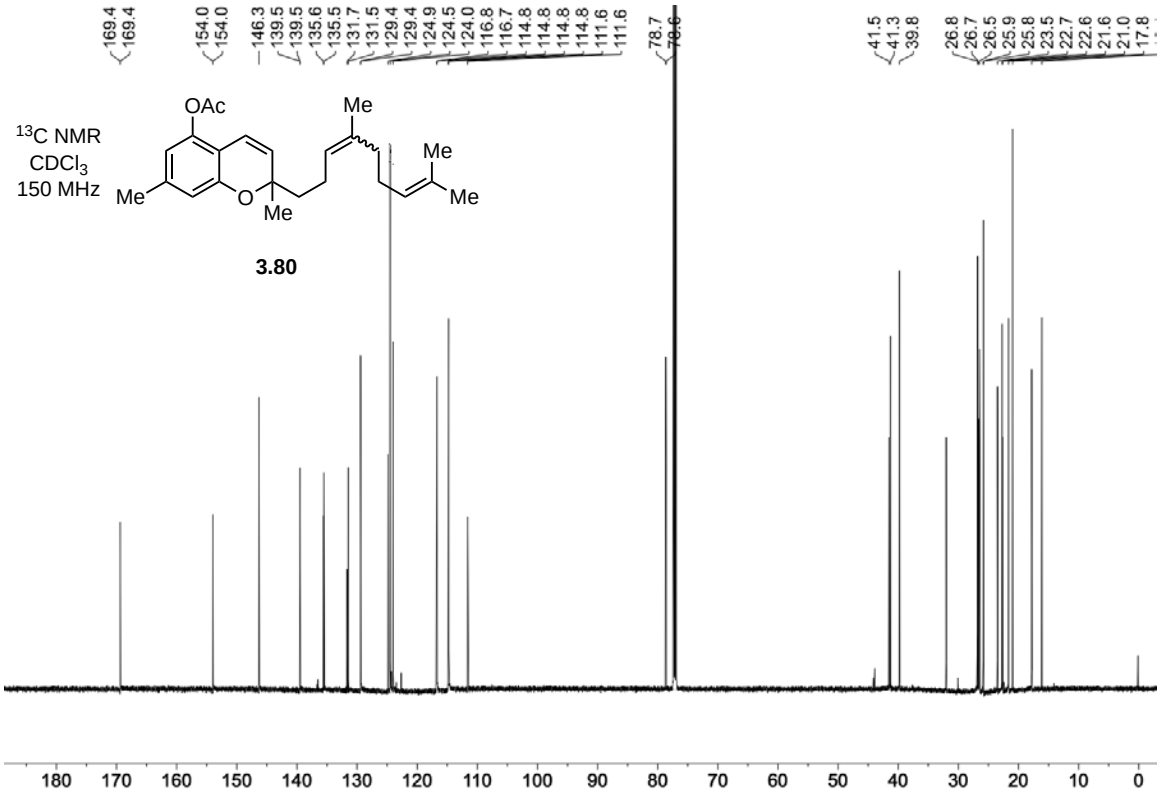

HSQC
CDCl3
600 MHz
HO
Me
H
H
H
Me
O
Me
Me
Me
3.28


HMBC
CDCl3
600 MHz
HO
Me
H
Me
H
H
Me
O
Me
Me
Me
3.28


NOESY
CDCl3
600 MHz
HO
Me
H
Me
H
H
Me
O
Me
Me
Me
3.28

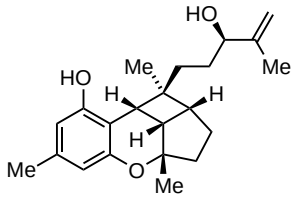
Data for 3.80


6.51
6.51
6.41
6.41
6.33
6.31
5.56
5.54
5.54
5.53
5.11
5.10
5.10
5.09
2.30
2.26
2.05
2.05
2.04
2.03
2.03
2.02
2.01
1.97
1.96
1.71
1.69
1.68
1.68
1.68
1.67
1.67
1.67
1.66
1.66
1.60
1.60
1.59
1.59
1.57
1.38
1.37
1H NMR
CDCl3
600 MHz
OAc
Me
Me
Me
Me
O
Me
3.80
0.99
1.00
1.05
1.08
2.06
3.07
3.12
6.87
11.92
3.08
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


169.4
169.4
154.0
154.0
146.3
139.5
139.5
135.6
135.5
131.7
131.5
129.4
129.4
124.9
124.5
124.0
116.8
116.7
114.8
114.8
114.8
114.8
111.6
111.6
78.7
78.6
41.5
41.3
39.8
26.8
26.7
26.5
25.9
25.8
23.5
22.7
22.6
21.6
21.0
17.8
13C NMR
CDCl3
150 MHz
OAc
Me
Me
Me
Me
O
Me
3.80
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

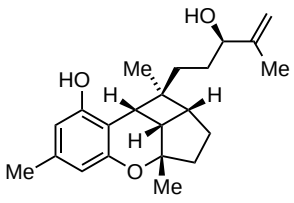
Data for Rhodonoid E (3.5)

^{1}H NMR
$CDCl_3$
600 MHz

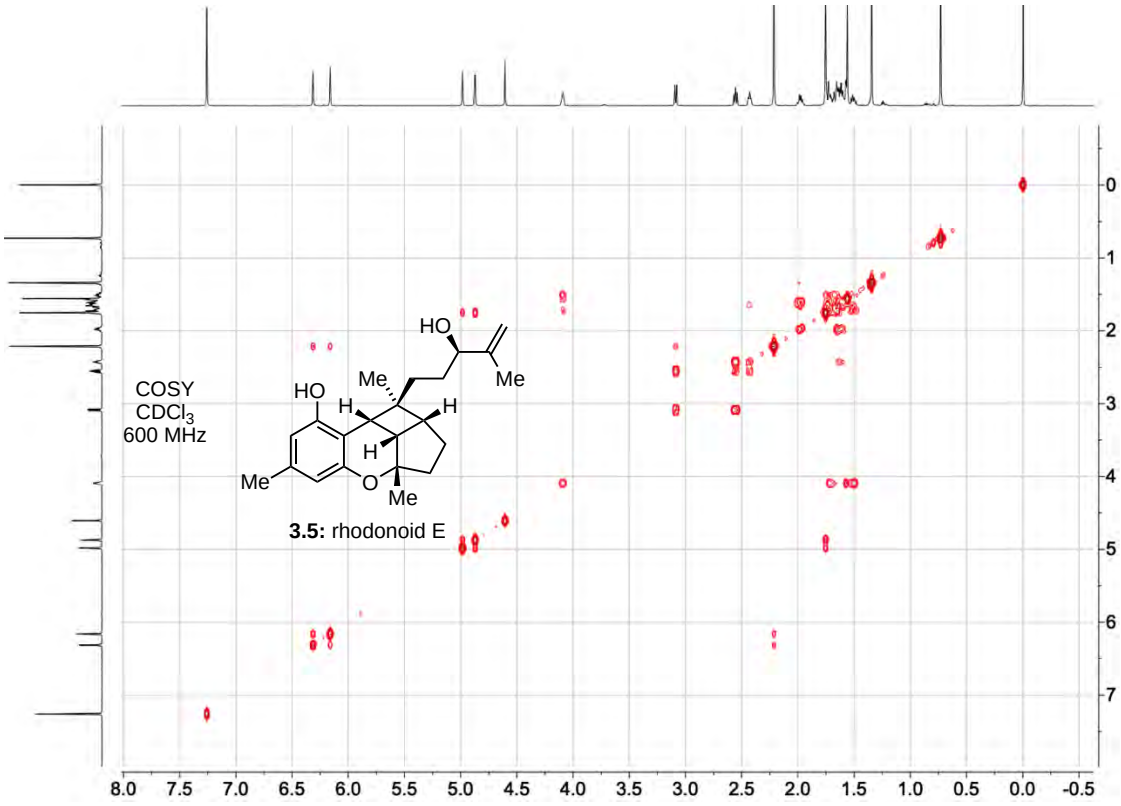


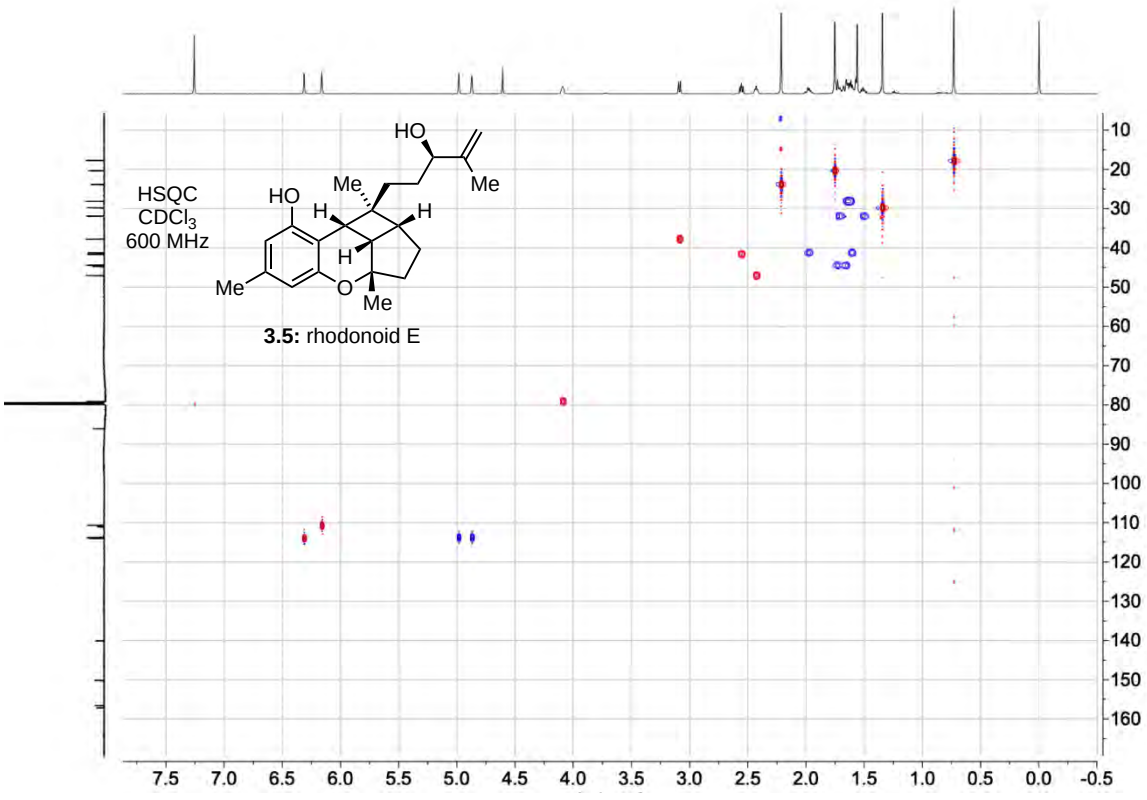
3.5: rhodonoid E

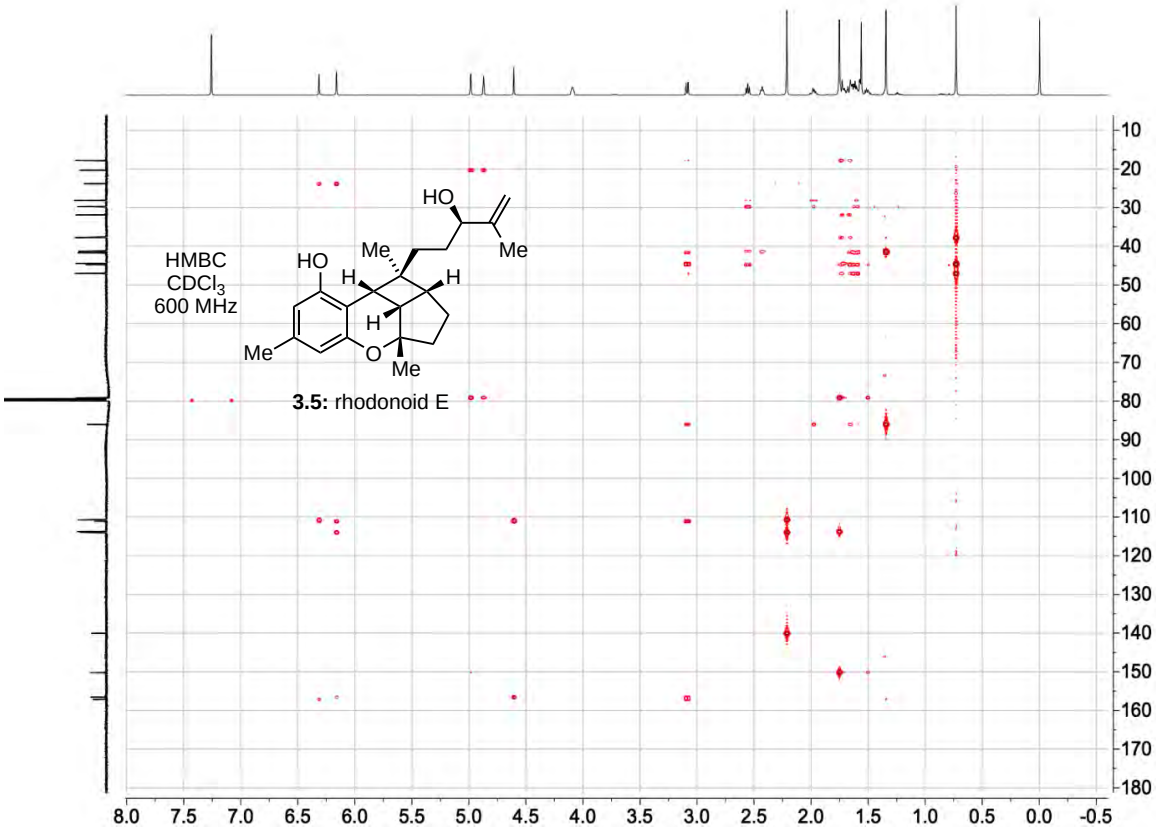
^{13}C NMR
$CDCl_3$
150 MHz

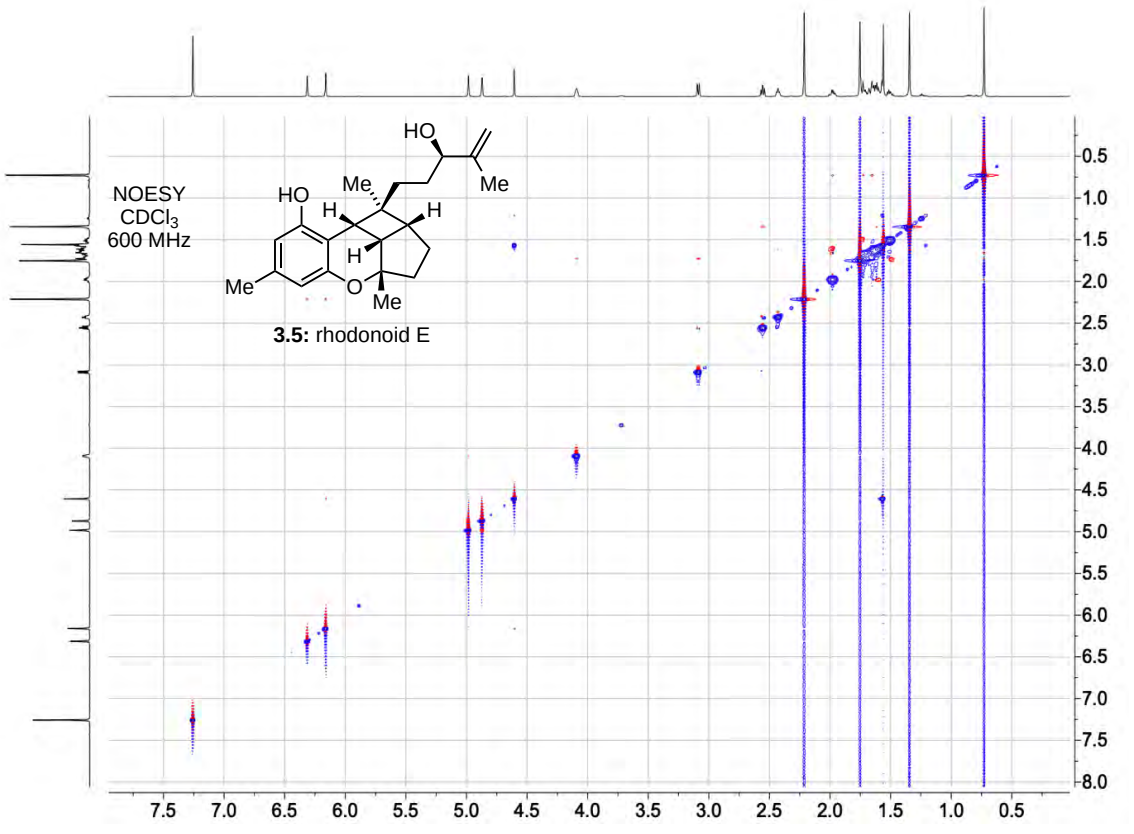


3.5: rhodonoid E

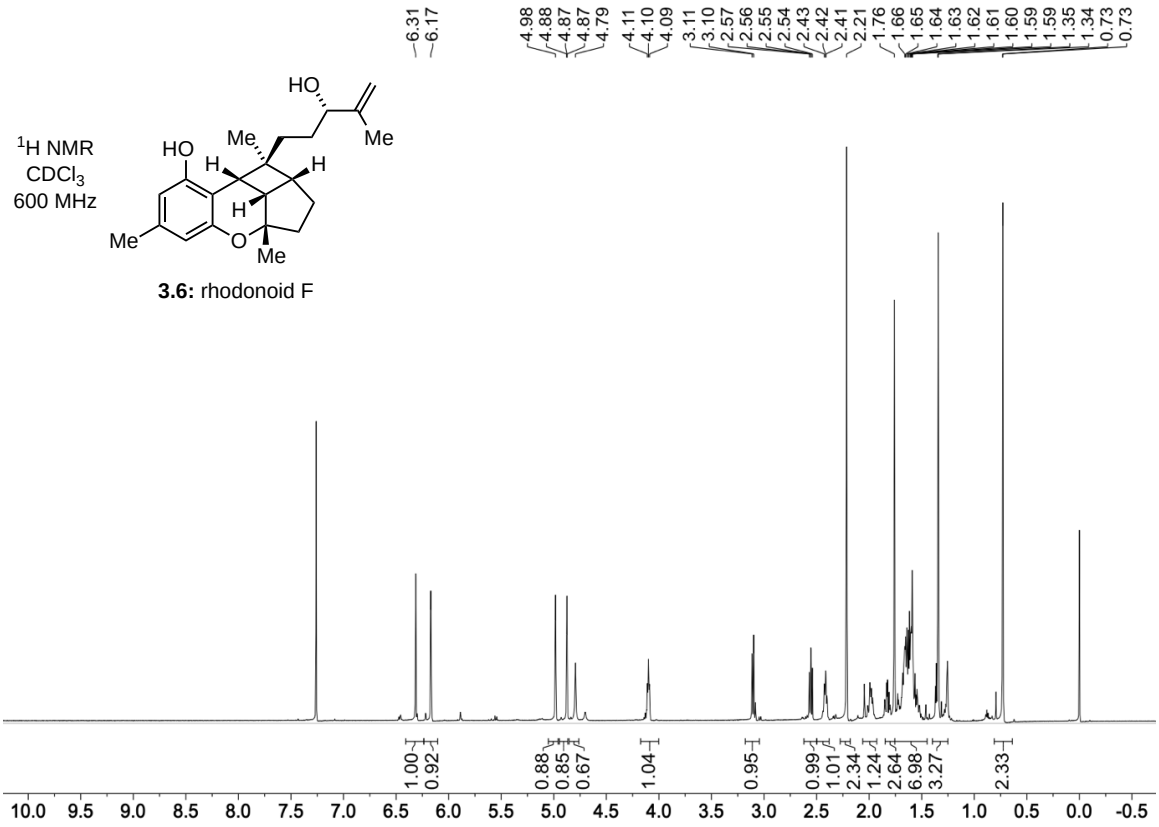

COSY
CDCl3
600 MHz
HO
Me
HO
H
H
H
Me
O
Me
Me
3.5: rhodonoid E


HSQC
CDCl3
600 MHz
HO
Me
HO
H
H
H
Me
O
Me
Me
3.5: rhodonoid E

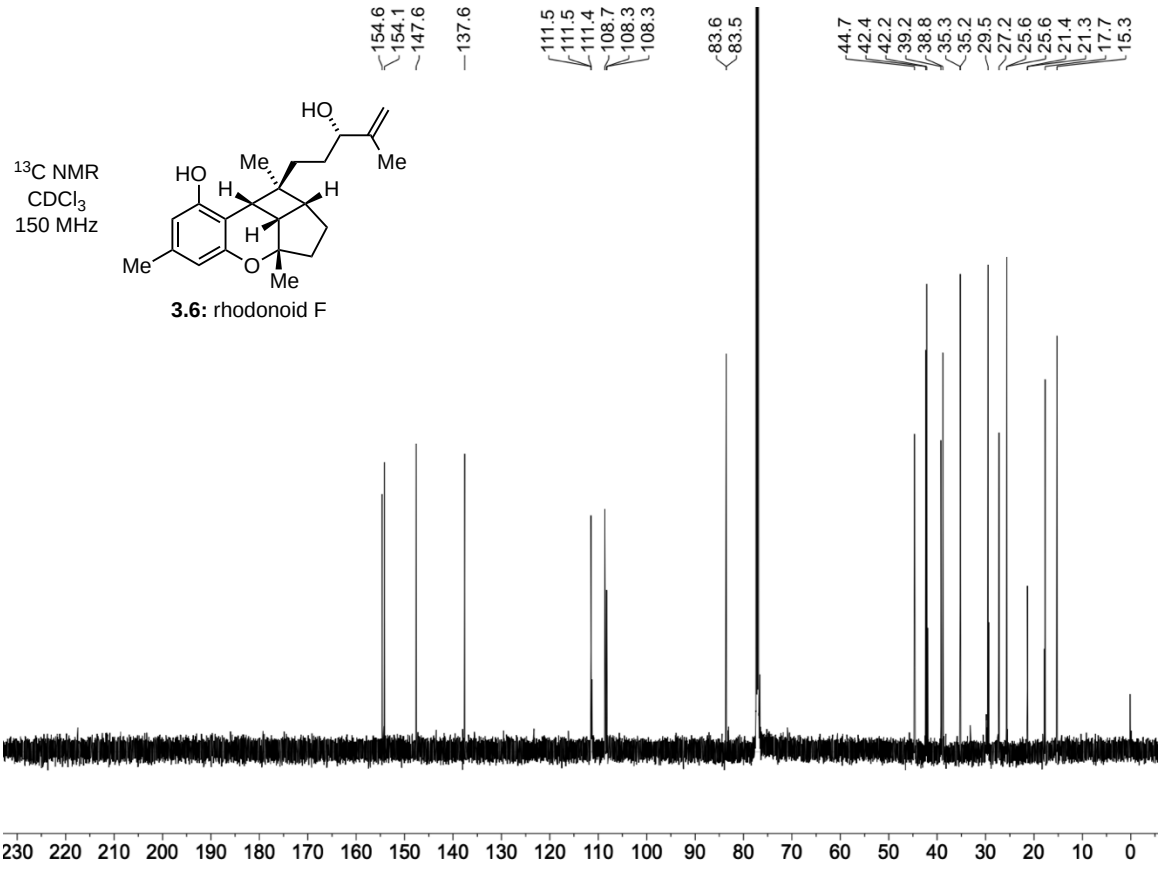

HMBC
CDCl3
600 MHz
HO
Me
H
H
H
Me
O
Me
HO
Me
3.5: rhodonoid E


NOESY
CDCl3
600 MHz
HO
Me
H
H
H
Me
O
Me
HO
Me
3.5: rhodonoid E

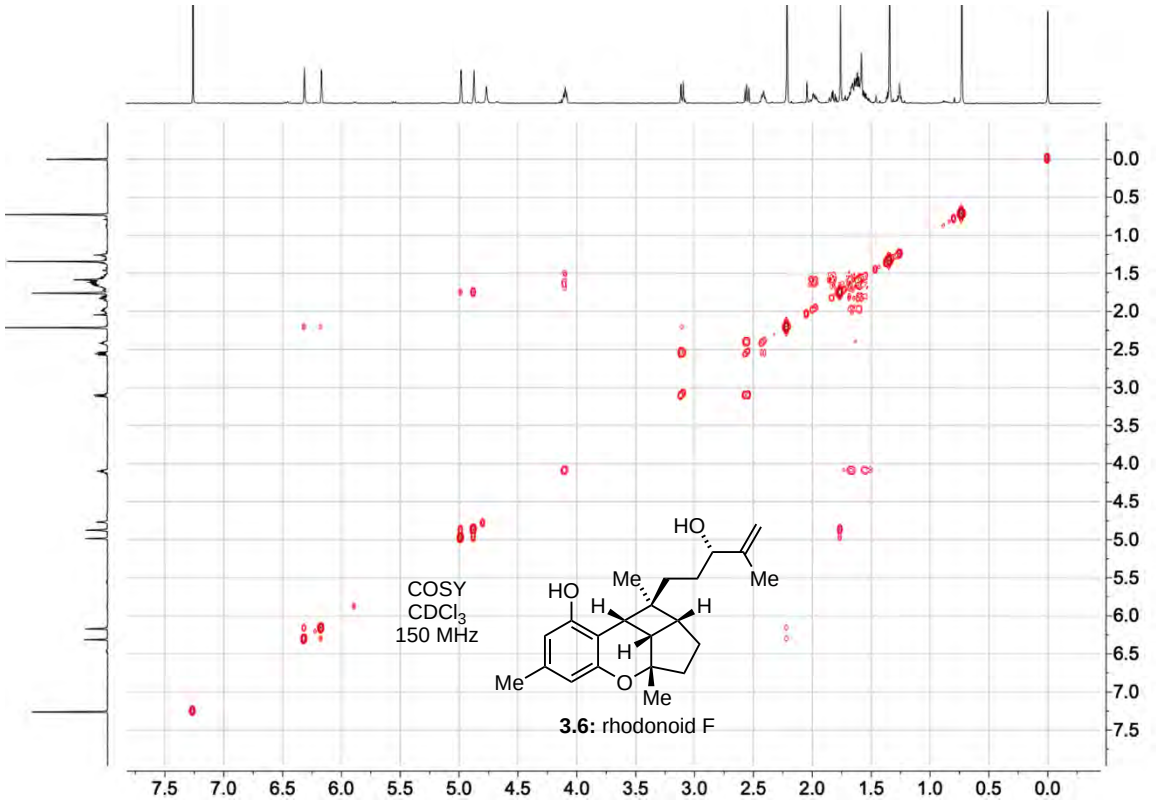
Data for Rhodonoid F (3.6)

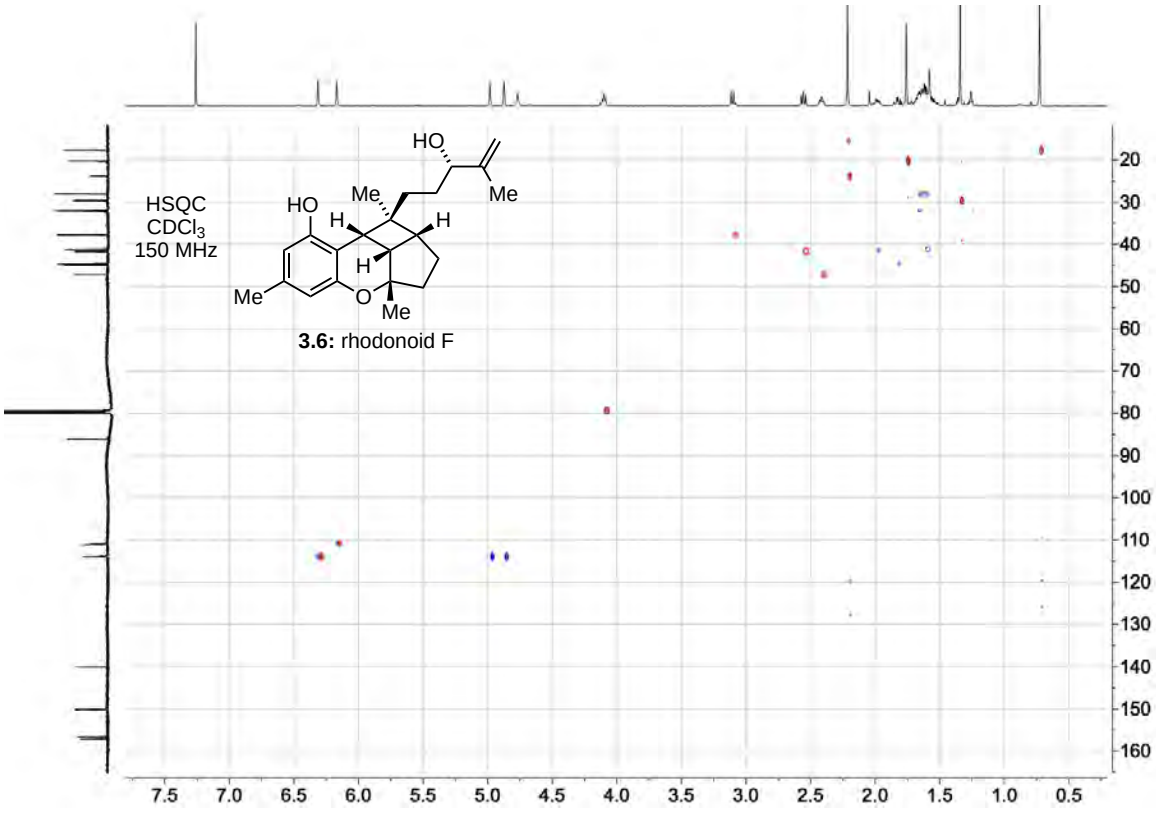


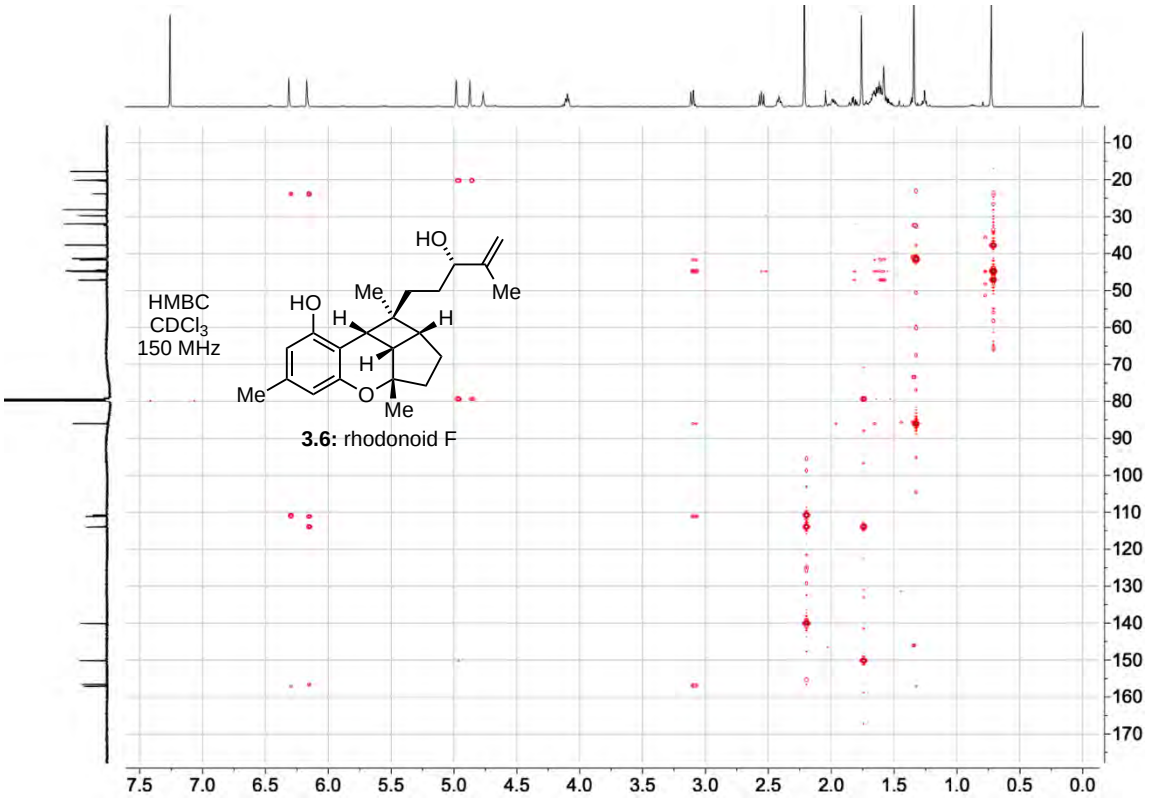
3.6: rhodonoid F

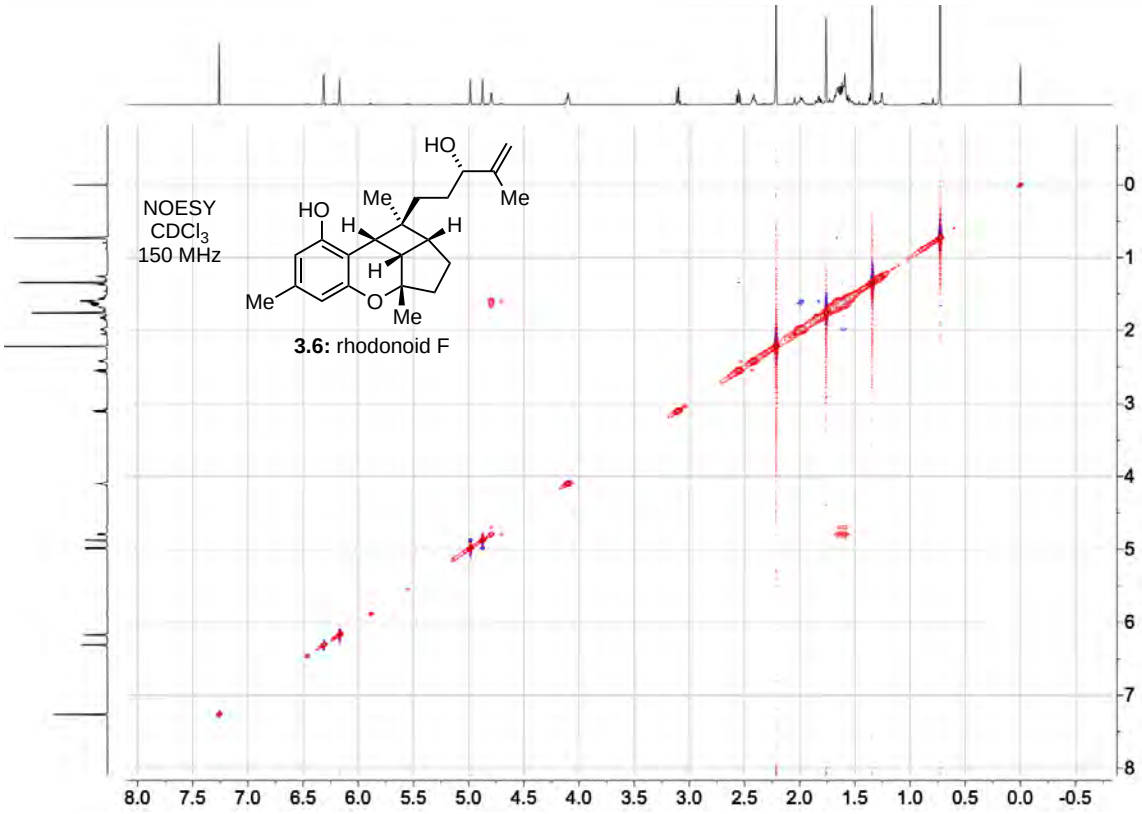


3.6: rhodonoid F


COSY
CDCl3
150 MHz
HO
Me
Me
HO
H
H
H
Me
O
Me
3.6: rhodonoid F

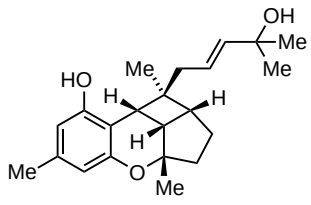

HSQC
CDCl3
150 MHz
HO
Me
Me
HO
H
H
H
Me
O
Me
3.6: rhodonoid F


HMBC
CDCl3
150 MHz
HO
Me
Me
HO
H
H
H
Me
O
Me
3.6: rhodonoid F


NOESY
CDCl3
150 MHz
HO
Me
Me
HO
H
H
H
Me
O
Me
3.6: rhodonoid F

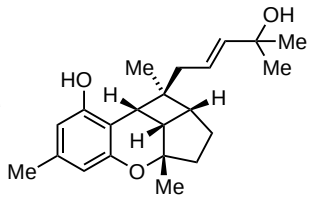
Data for 3.81

^{1}H NMR
$CDCl_3$
600 MHz

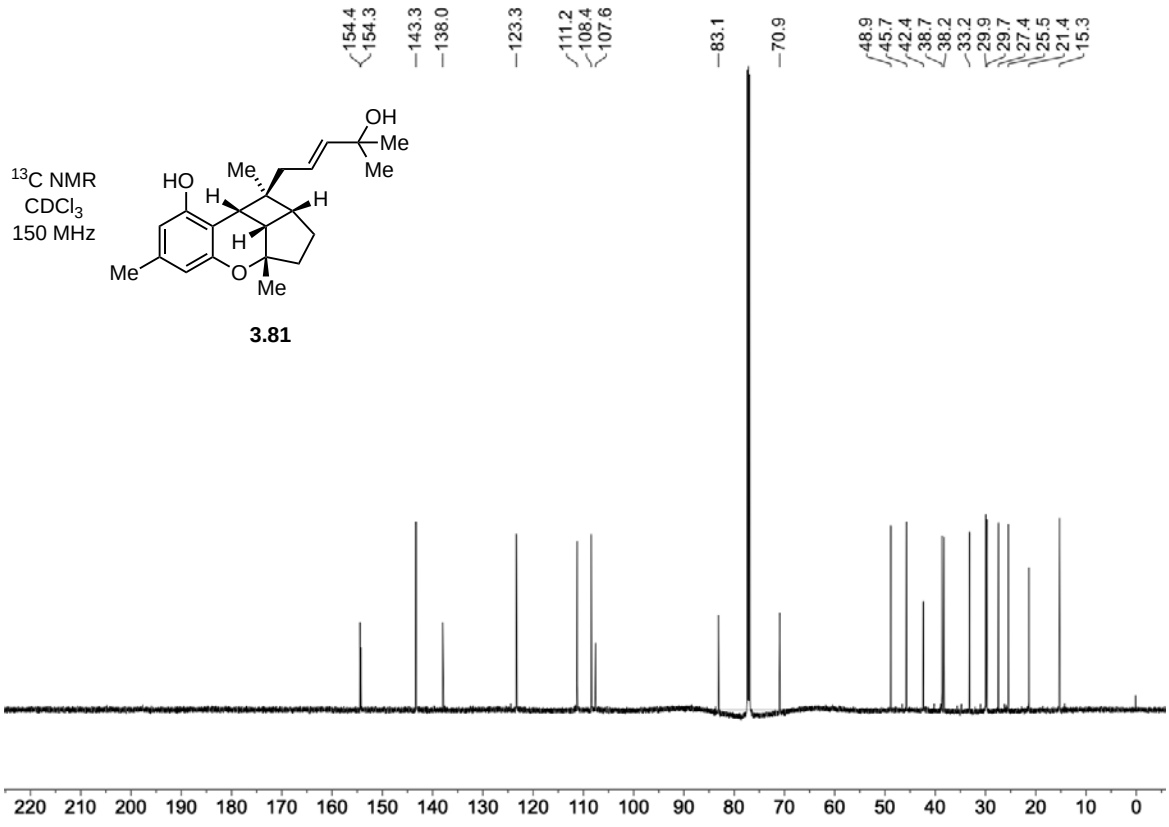


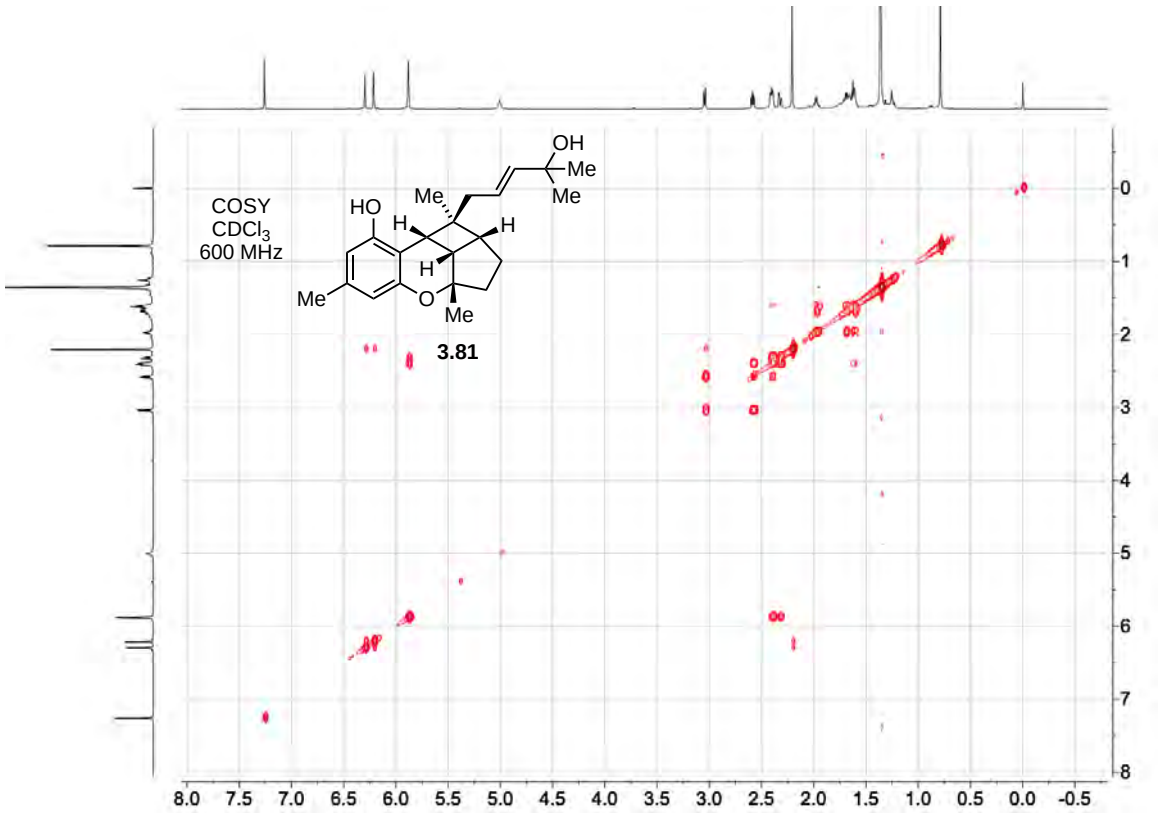
3.81

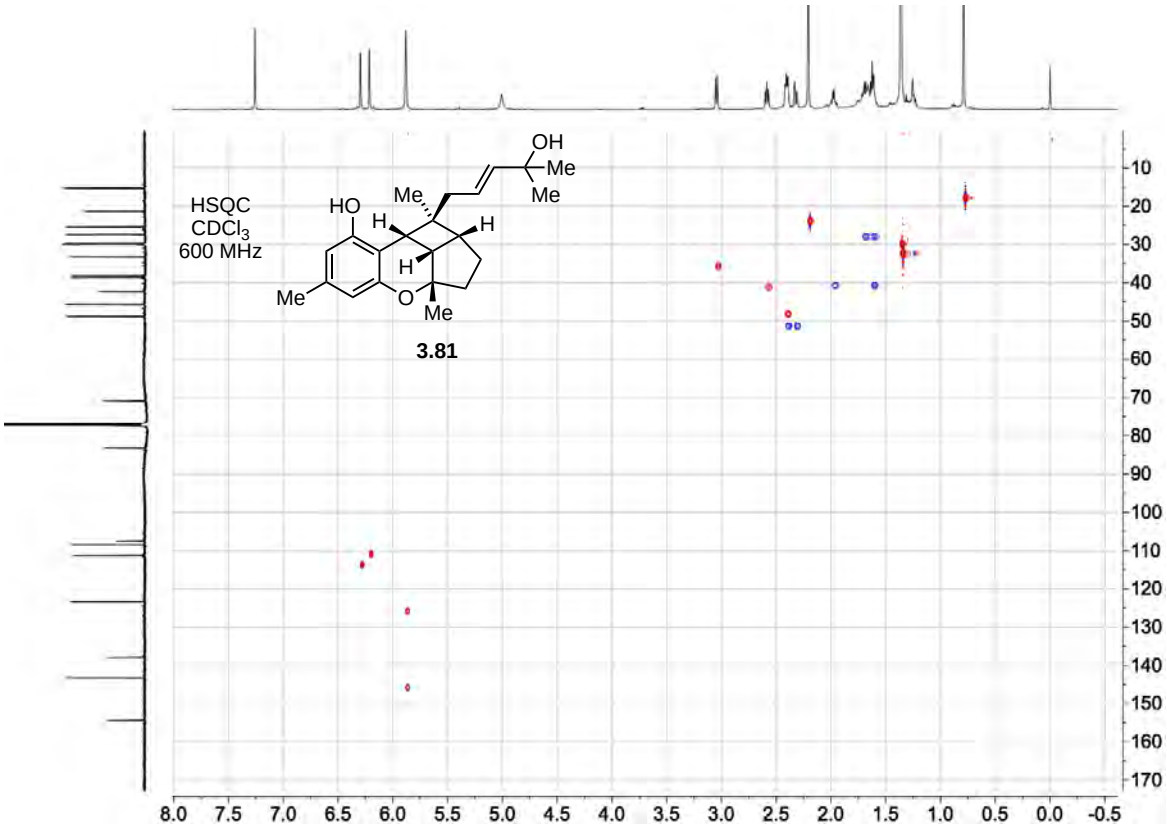
^{1}H NMR
d_6-acetone
600 MHz

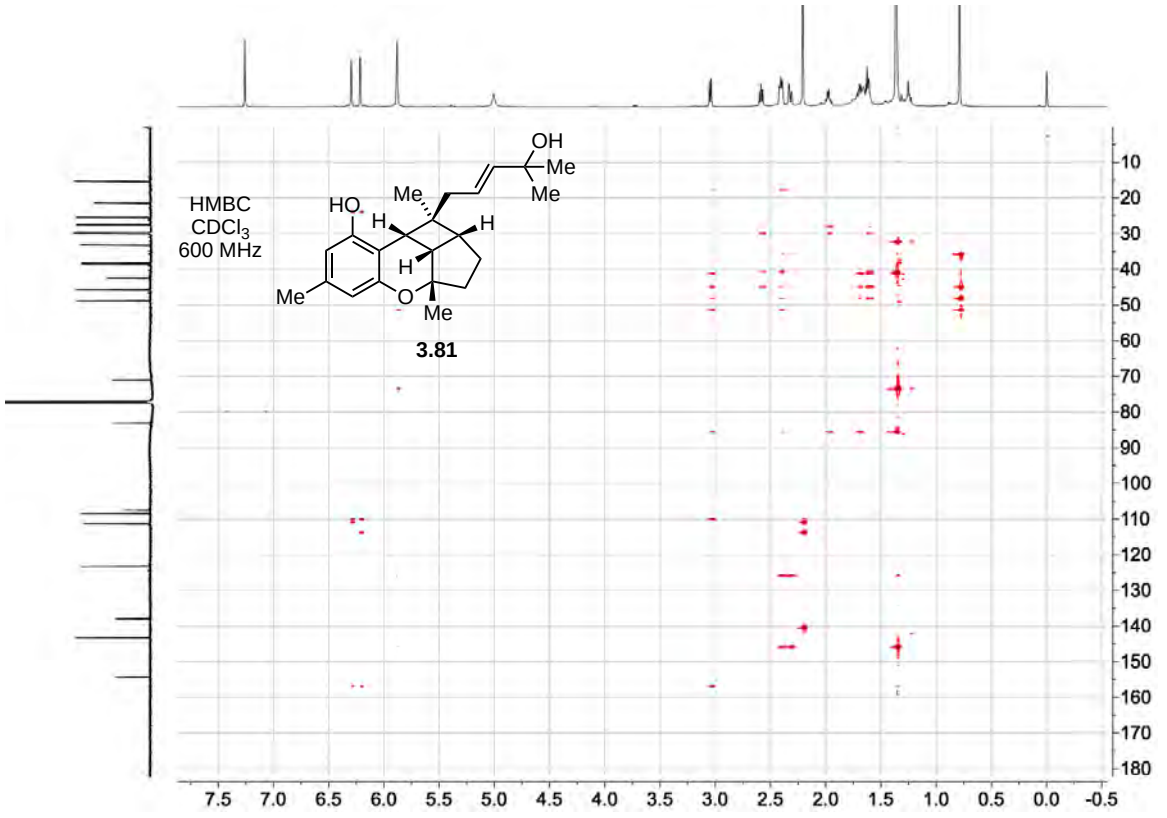


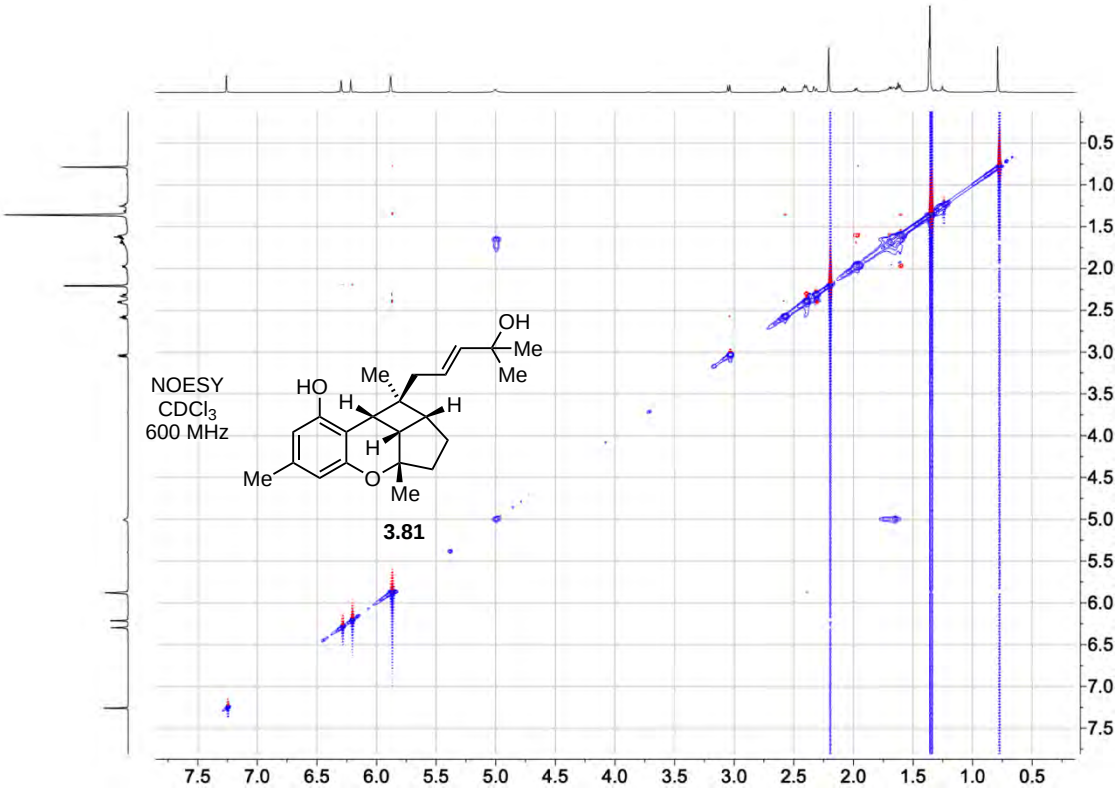
3.81


154.4
154.3
143.3
138.0
123.3
111.2
108.4
107.6
83.1
70.9
48.9
45.7
42.4
38.7
38.2
33.2
29.9
29.7
27.4
25.5
21.4
15.3
13C NMR
CDCl3
150 MHz
OH
Me
Me
Me
HO
H
H
H
Me
O
Me
3.81
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

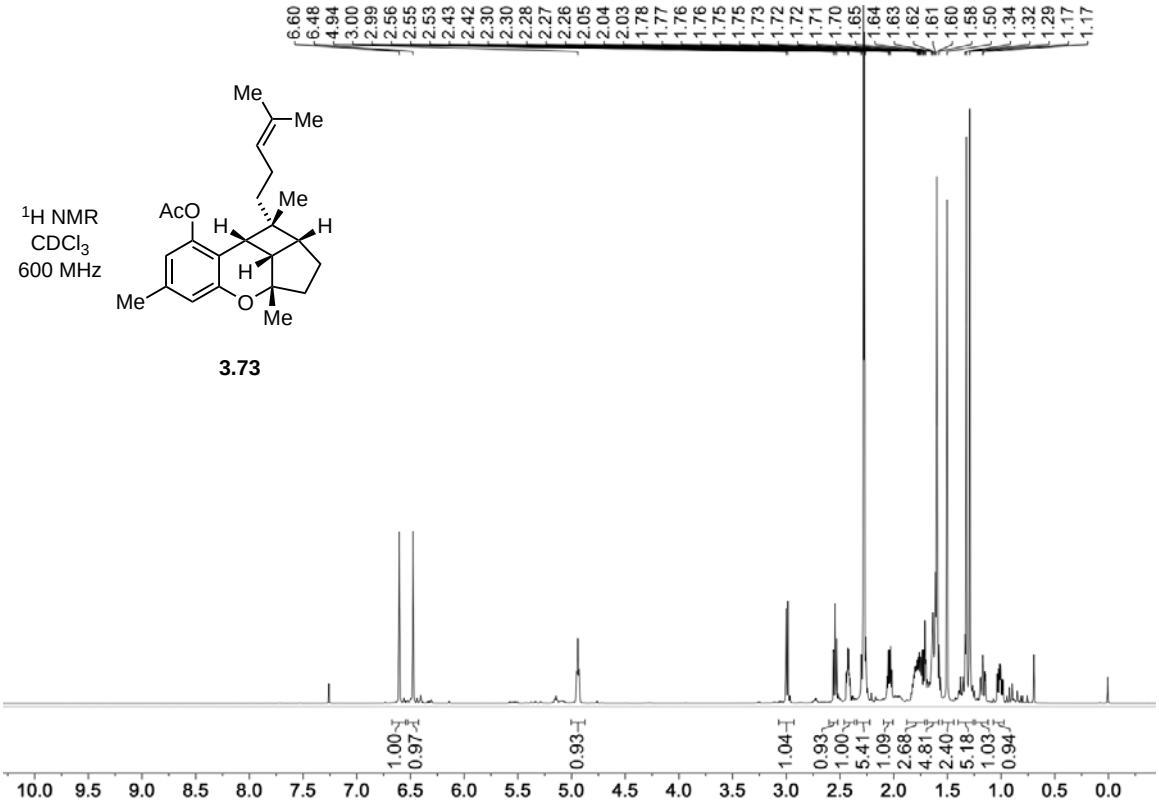

COSY
CDCl3
600 MHz
OH
Me
Me
Me
HO
H
H
H
Me
O
Me
3.81
0
1
2
3
4
5
6
7
8
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5


HSQC
CDCl3
600 MHz
HO
Me
H
H
H
Me
O
Me
OH
Me
Me
3.81
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170


HMBC
CDCl3
600 MHz
HO
Me
H
H
H
Me
O
Me
OH
Me
Me
3.81
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180

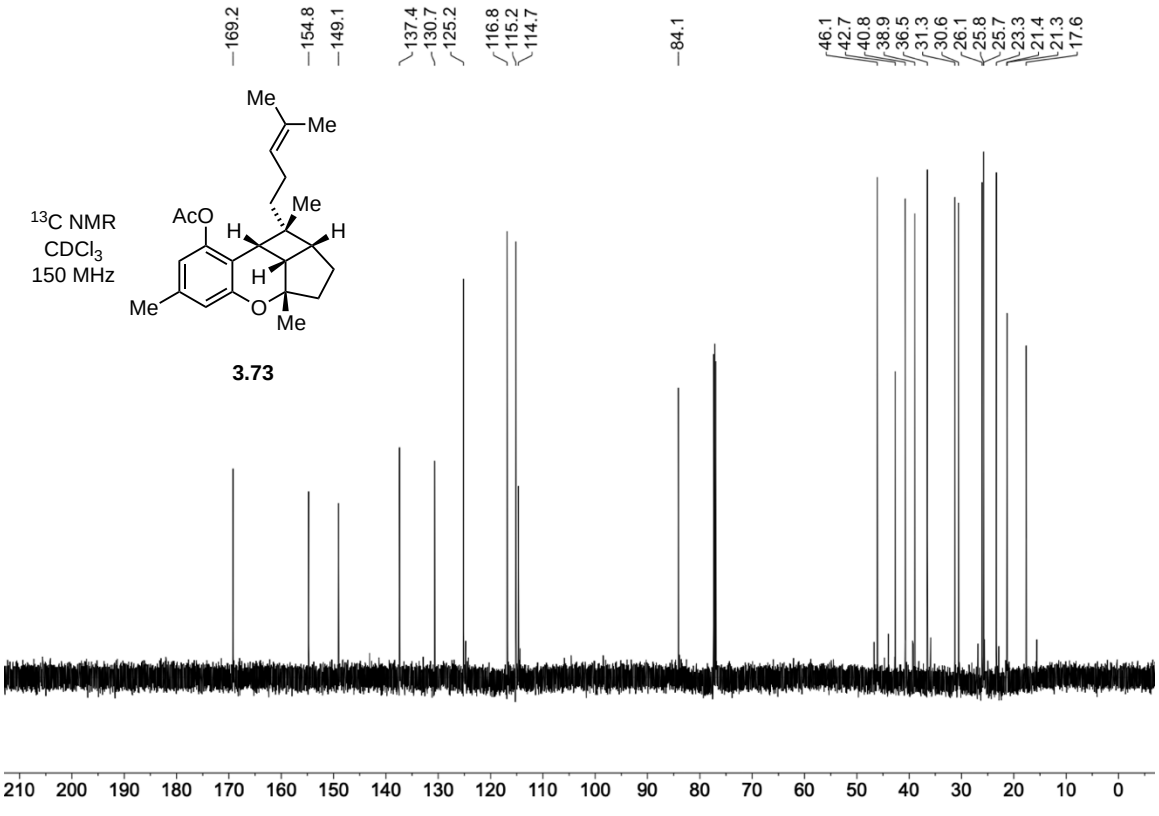

NOESY
CDCl3
600 MHz
HO
Me
H
H
H
Me
O
Me
OH
Me
Me
3.81
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

Data for 3.83



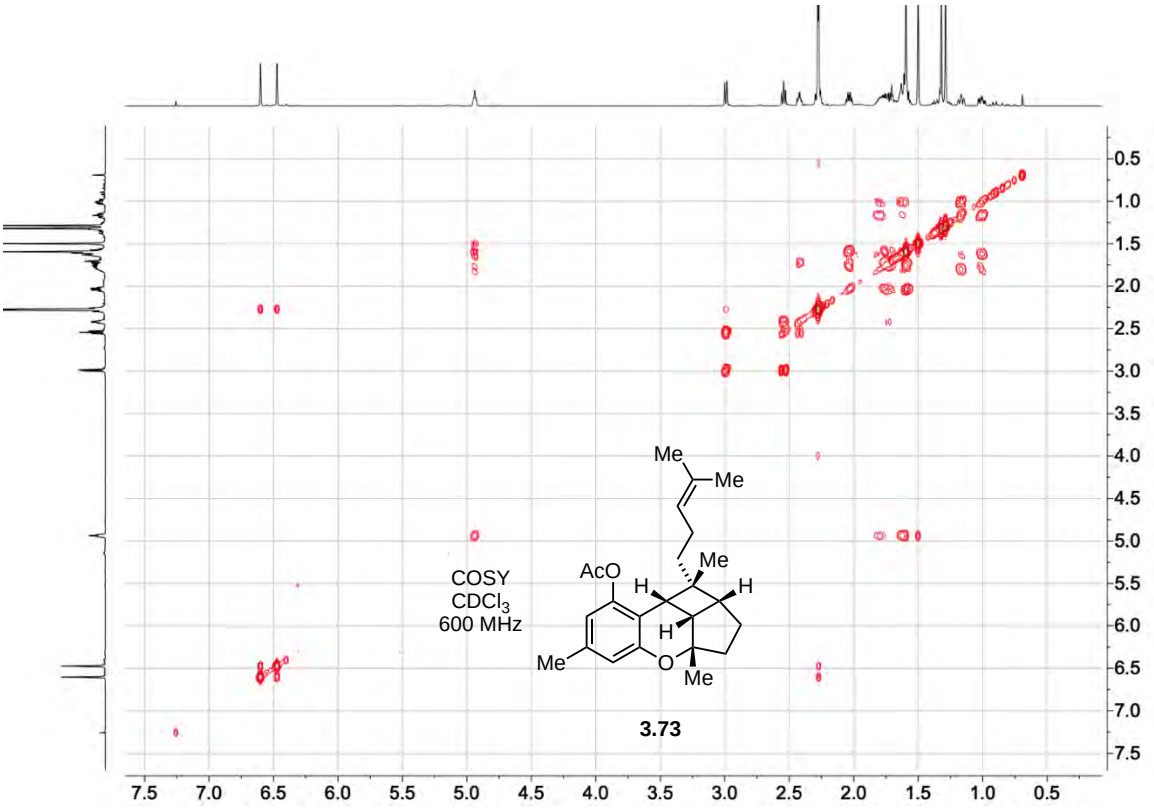
^{1}H NMR
$CDCl_3$
600 MHz

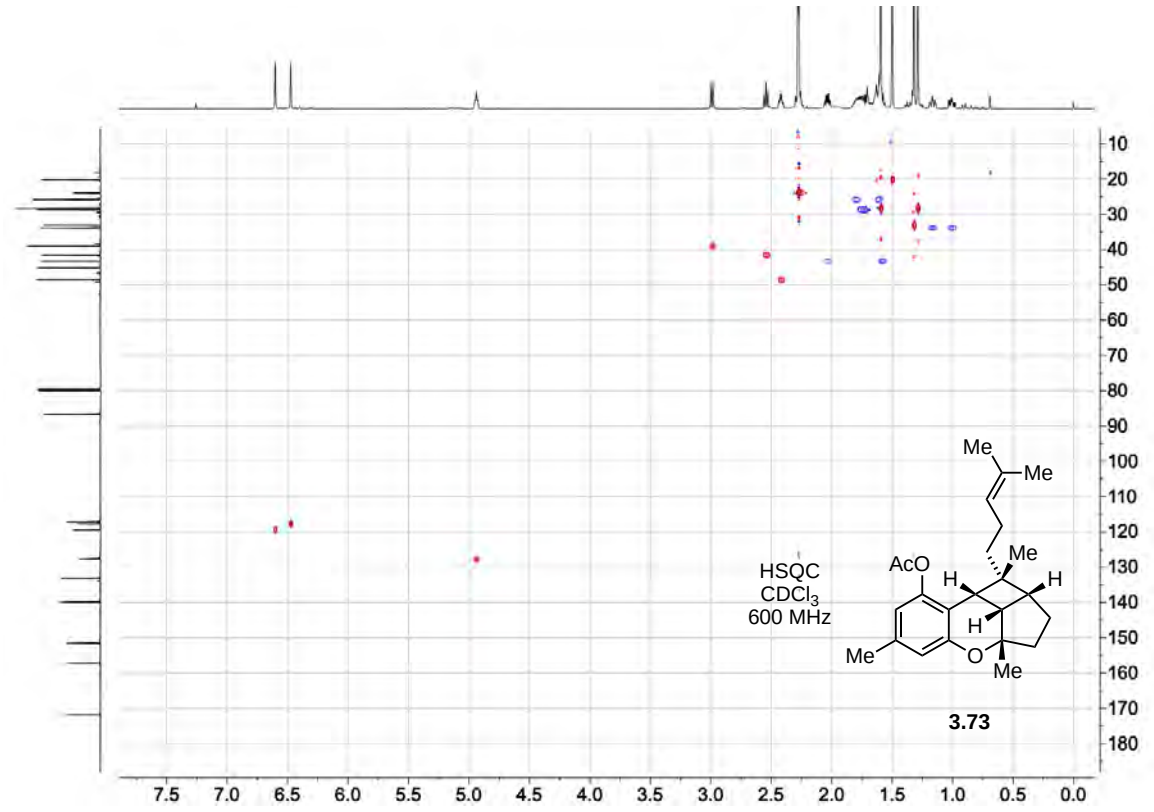
3.73

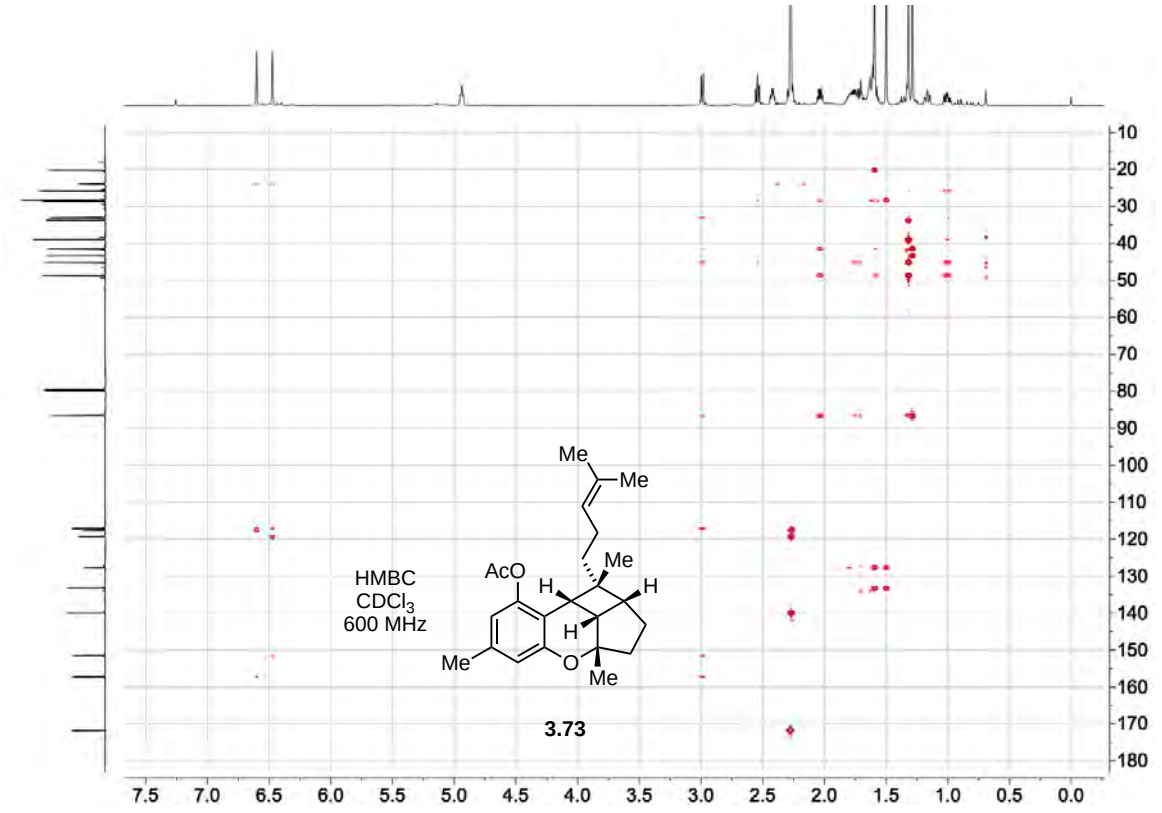


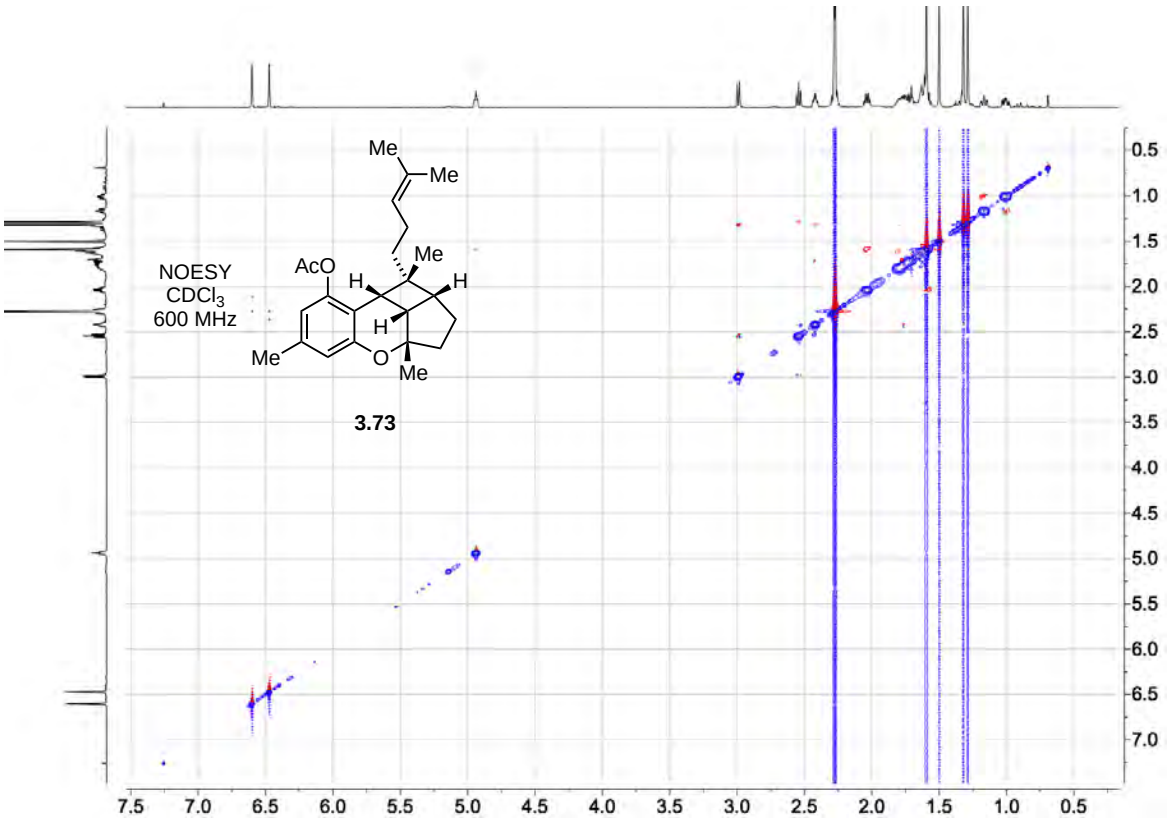
^{13}C NMR
$CDCl_3$
150 MHz

3.73

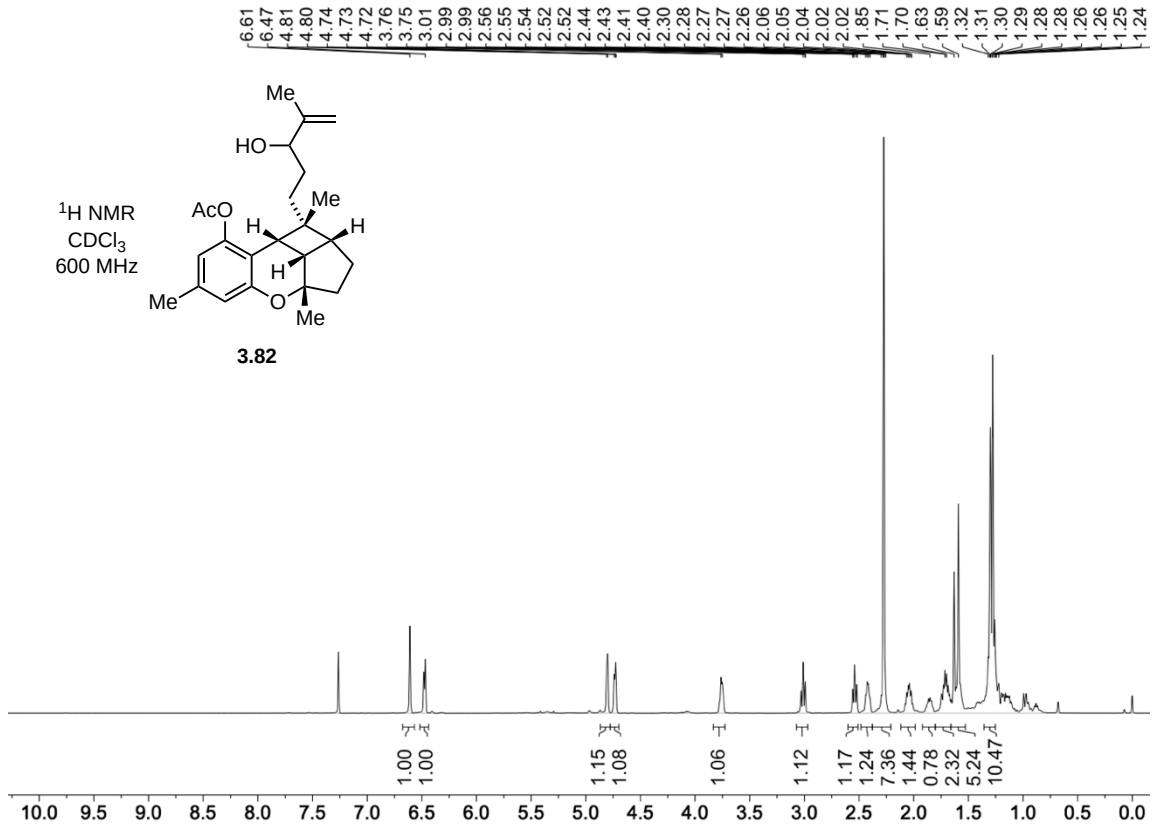

COSY
CDCl3
600 MHz
AcO
Me
Me
Me
H
H
H
Me
O
Me
3.73


HSQC
CDCl3
600 MHz
AcO
Me
Me
Me
H
H
H
Me
O
Me
3.73


HMBC
CDCl3
600 MHz
Me
Me
Me
AcO
H
H
H
Me
O
Me
3.73

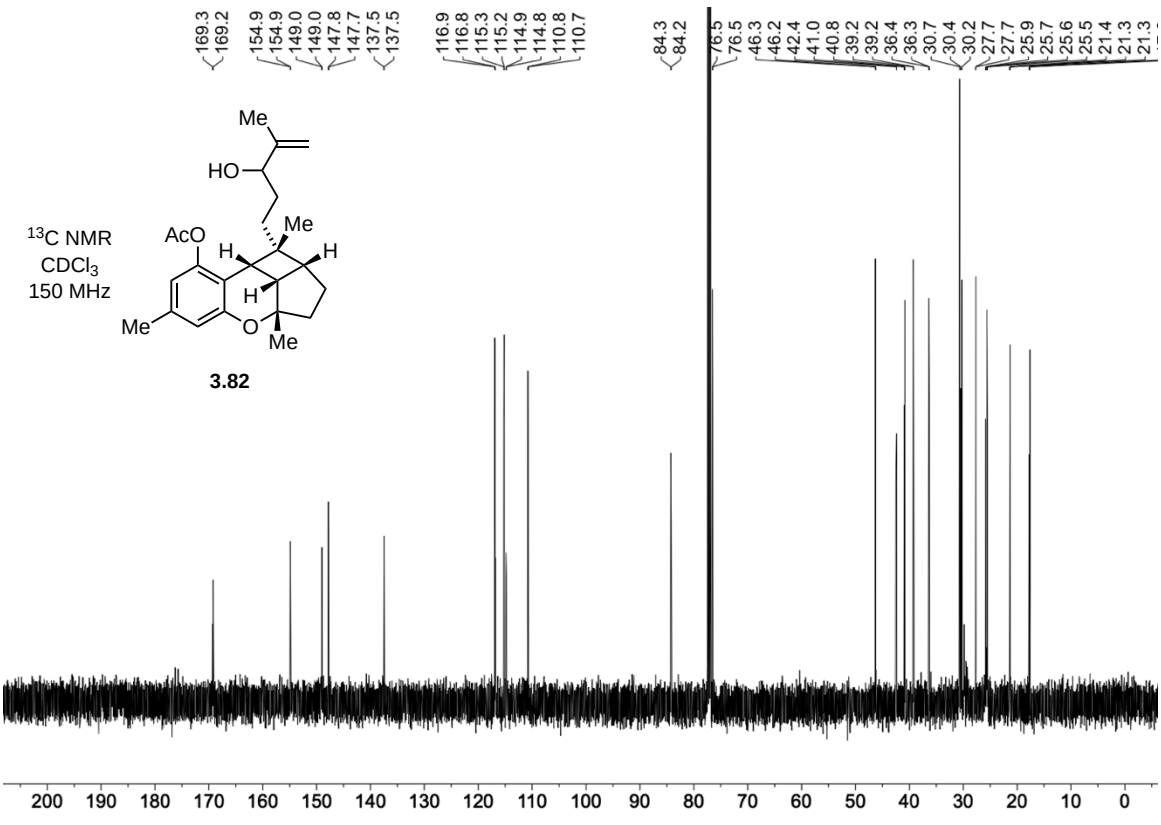

NOESY
CDCl3
600 MHz
Me
Me
Me
AcO
H
H
H
Me
O
Me
3.73

Data for 3.82



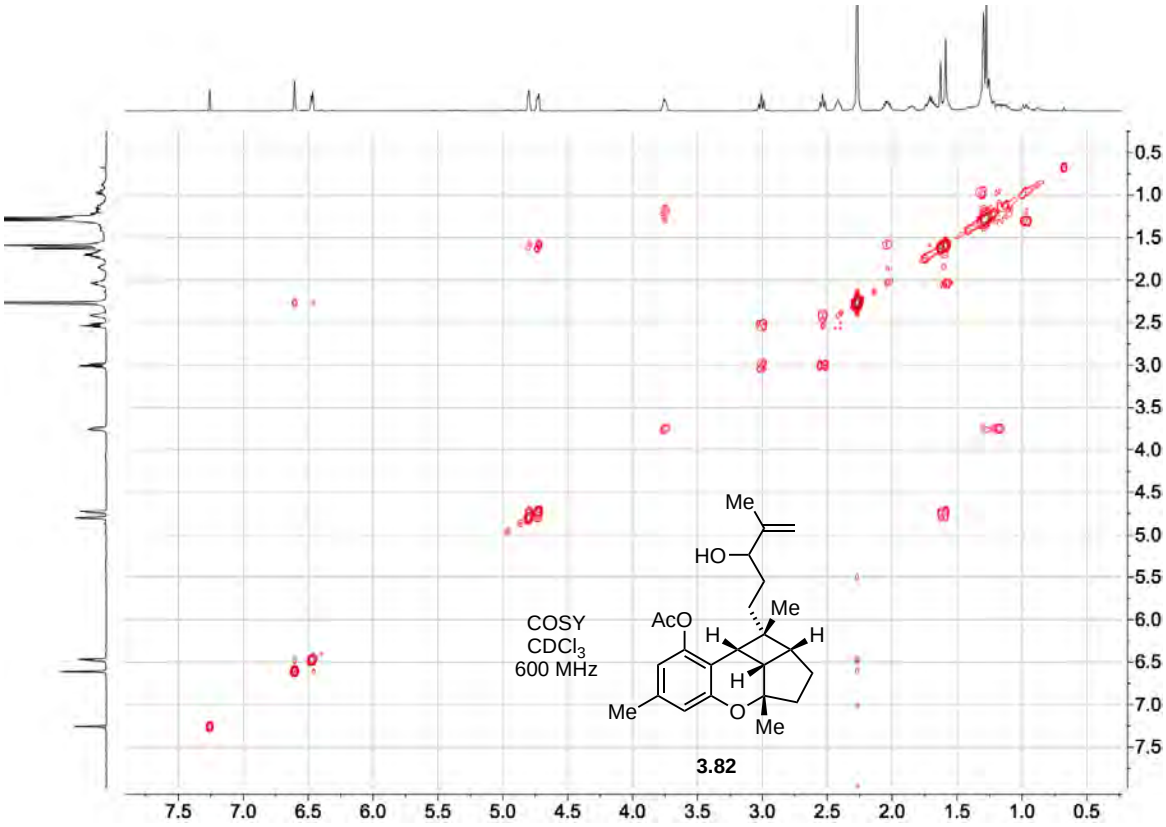
^{1}H NMR
$CDCl_3$
600 MHz

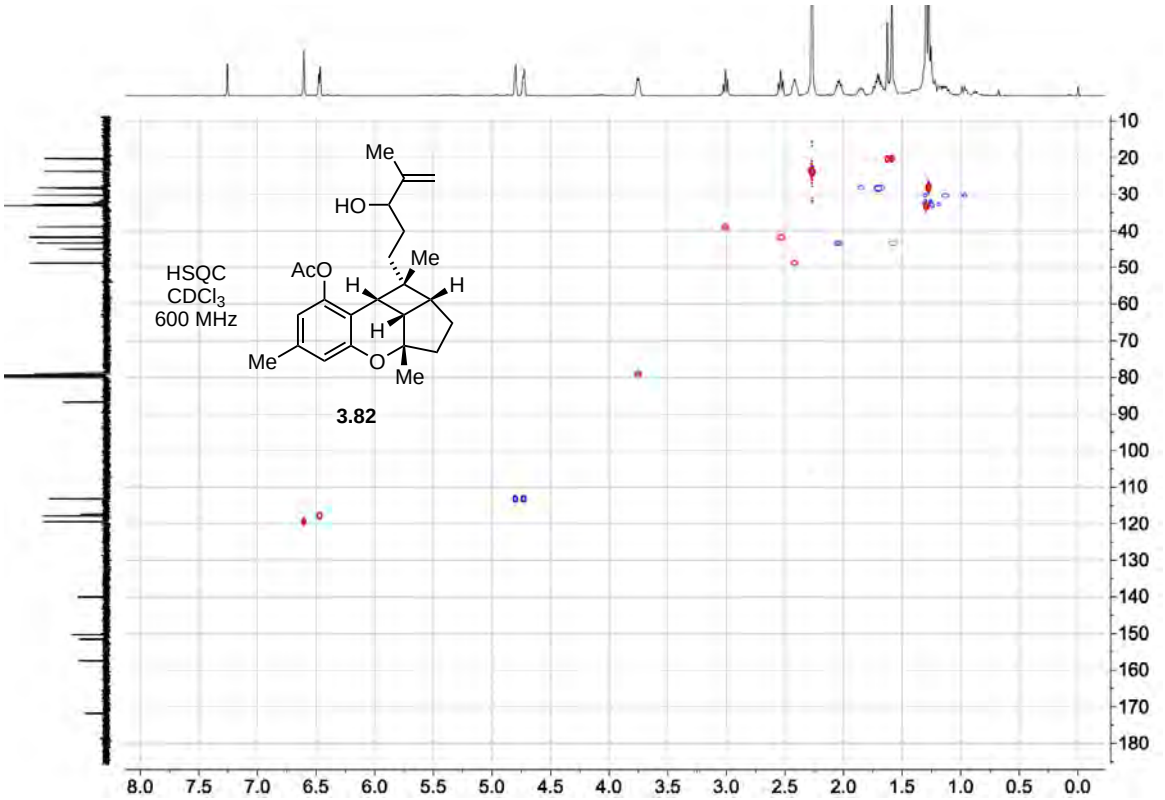
3.82

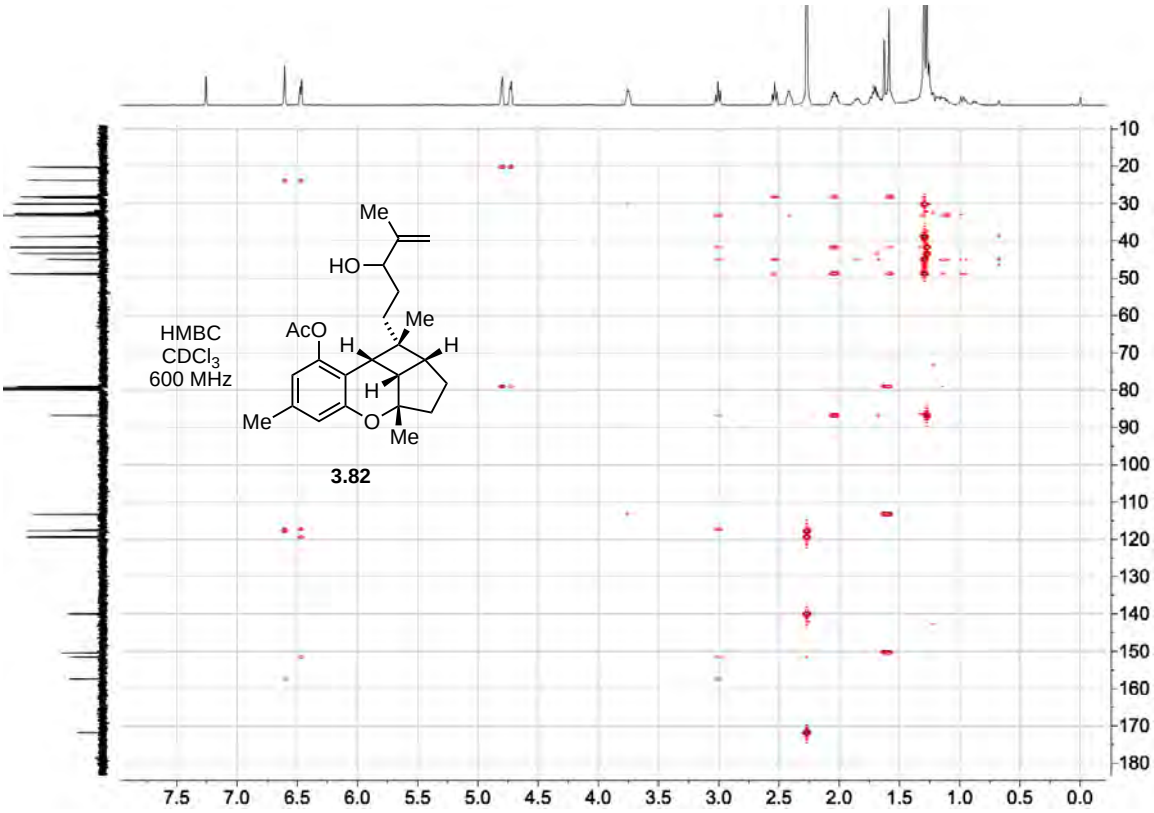


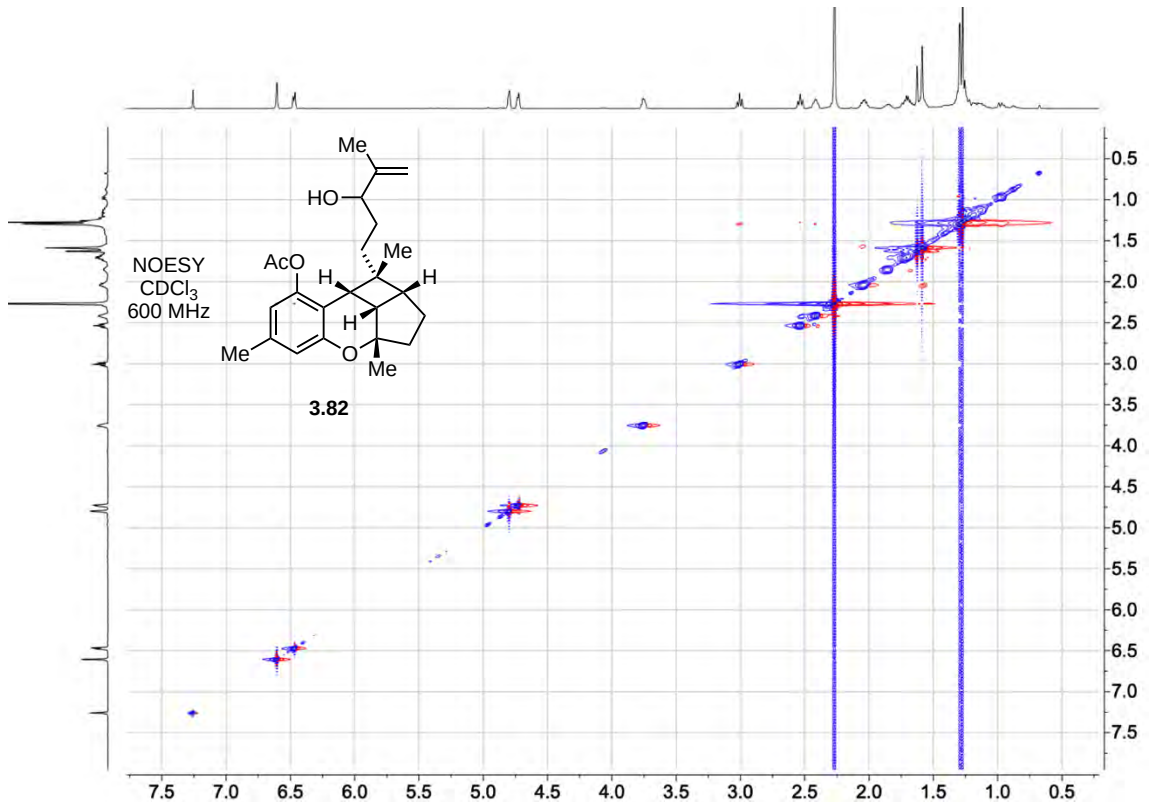
^{13}C NMR
$CDCl_3$
150 MHz

3.82


COSY
CDCl3
600 MHz
Me
HO
Me
AcO
H
H
H
Me
O
Me
3.82

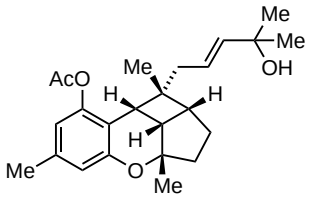

HSQC
CDCl3
600 MHz
Me
HO
Me
AcO
H
H
H
Me
O
Me
3.82


HMBC
CDCl3
600 MHz
Me
HO
Me
AcO
H
H
H
Me
O
Me
3.82


NOESY
CDCl3
600 MHz
Me
HO
Me
AcO
H
H
H
Me
O
Me
3.82

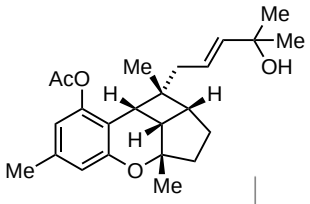
Data for 3.35

^{1}H NMR
$CDCl_3$
600 MHz

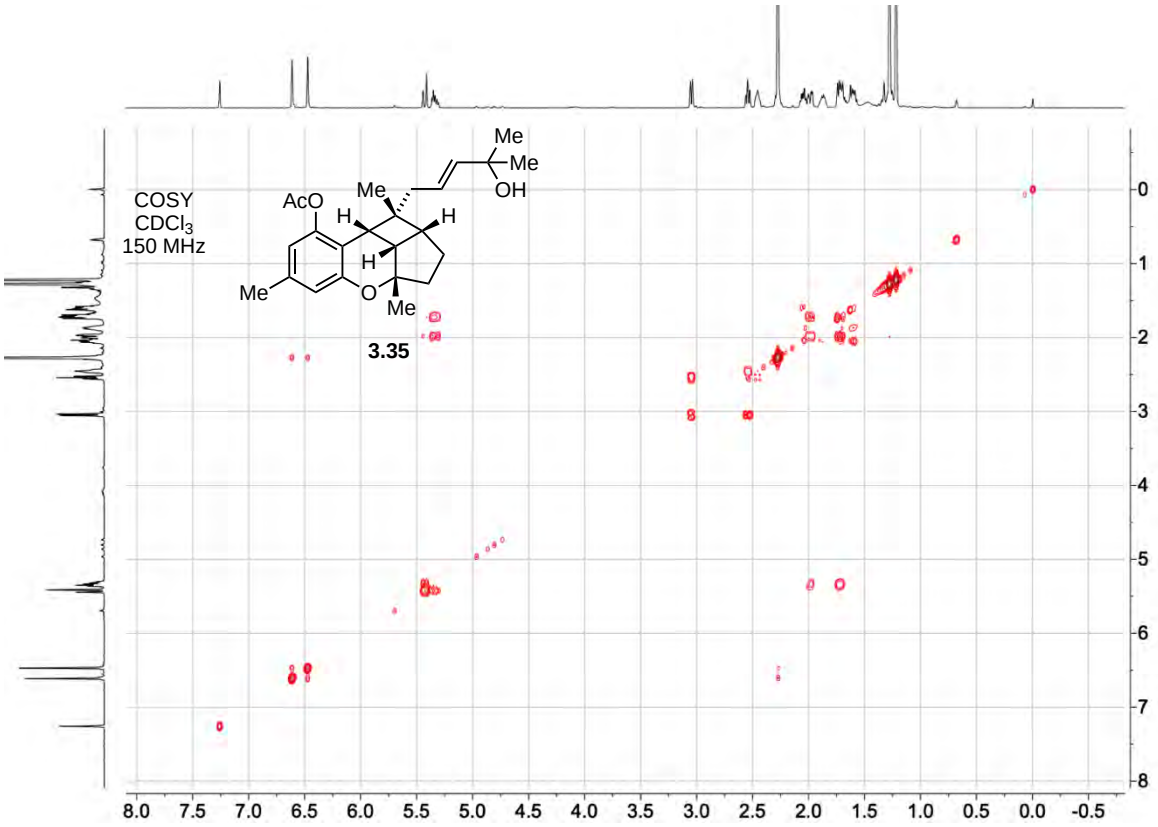


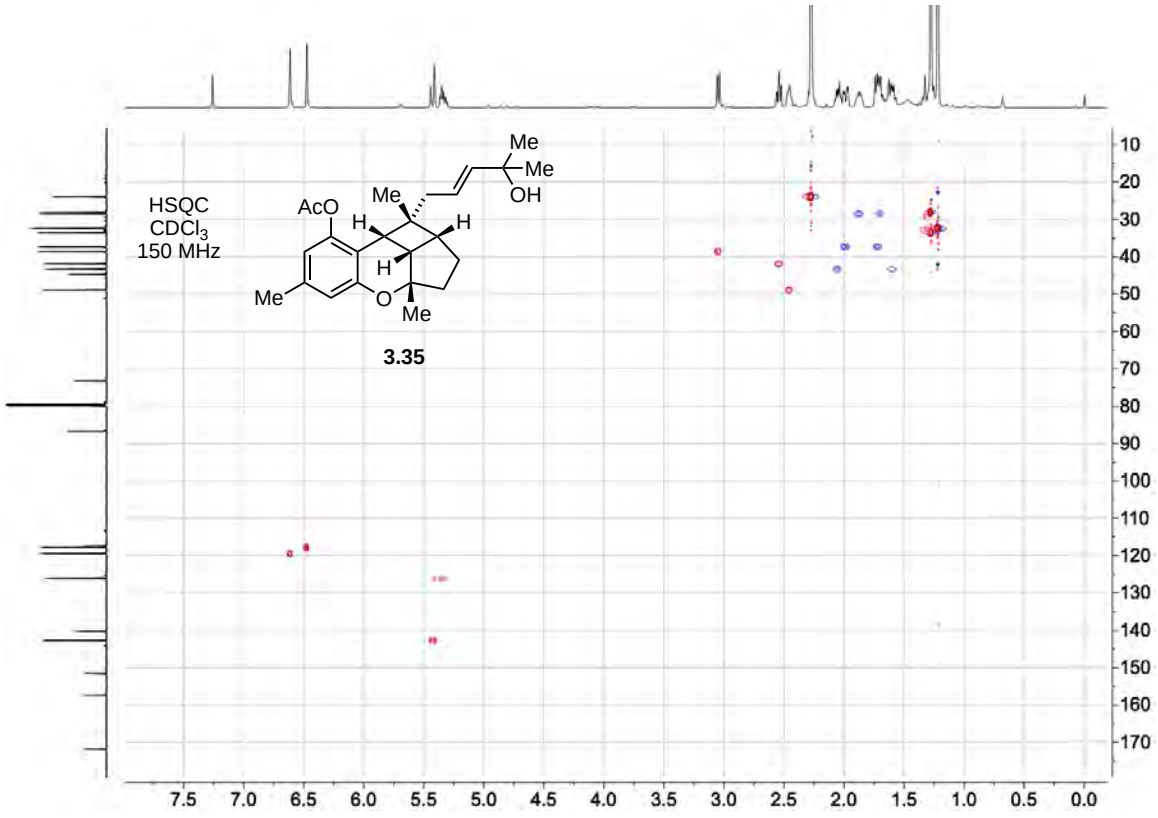
3.35

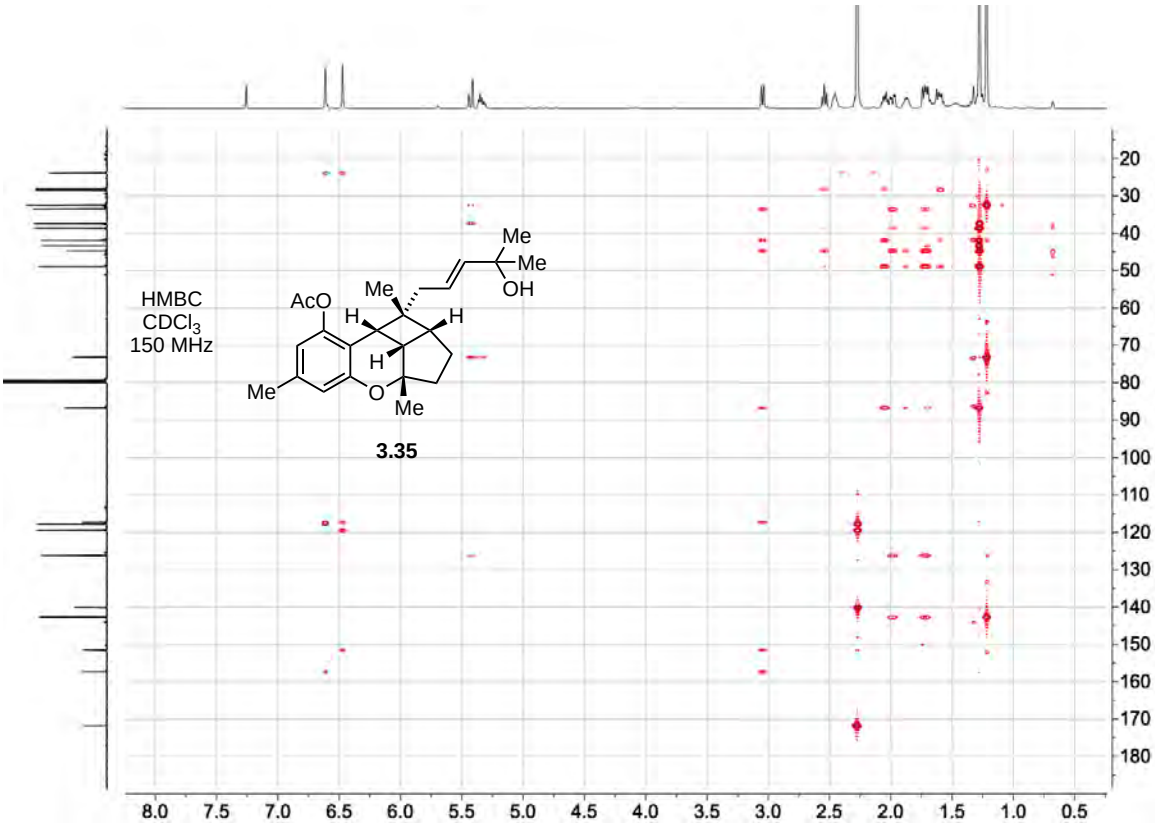
^{13}C NMR
$CDCl_3$
150 MHz

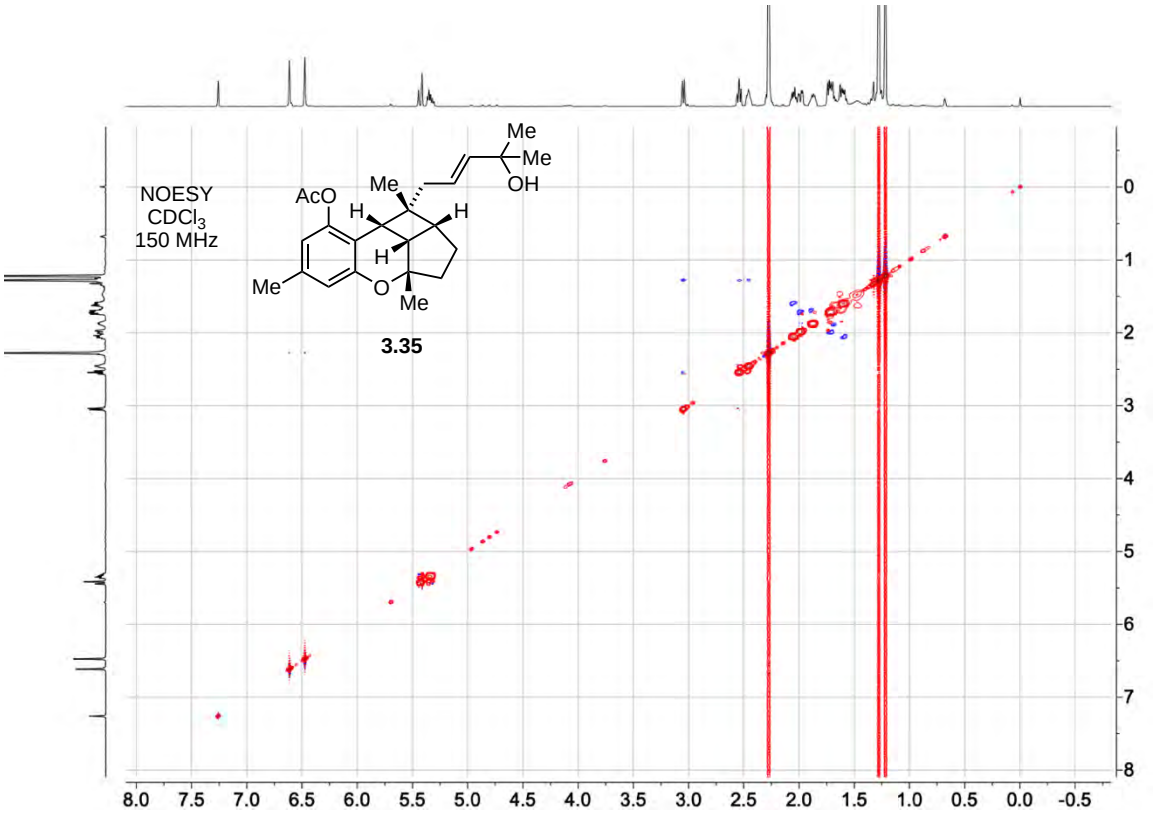


3.35

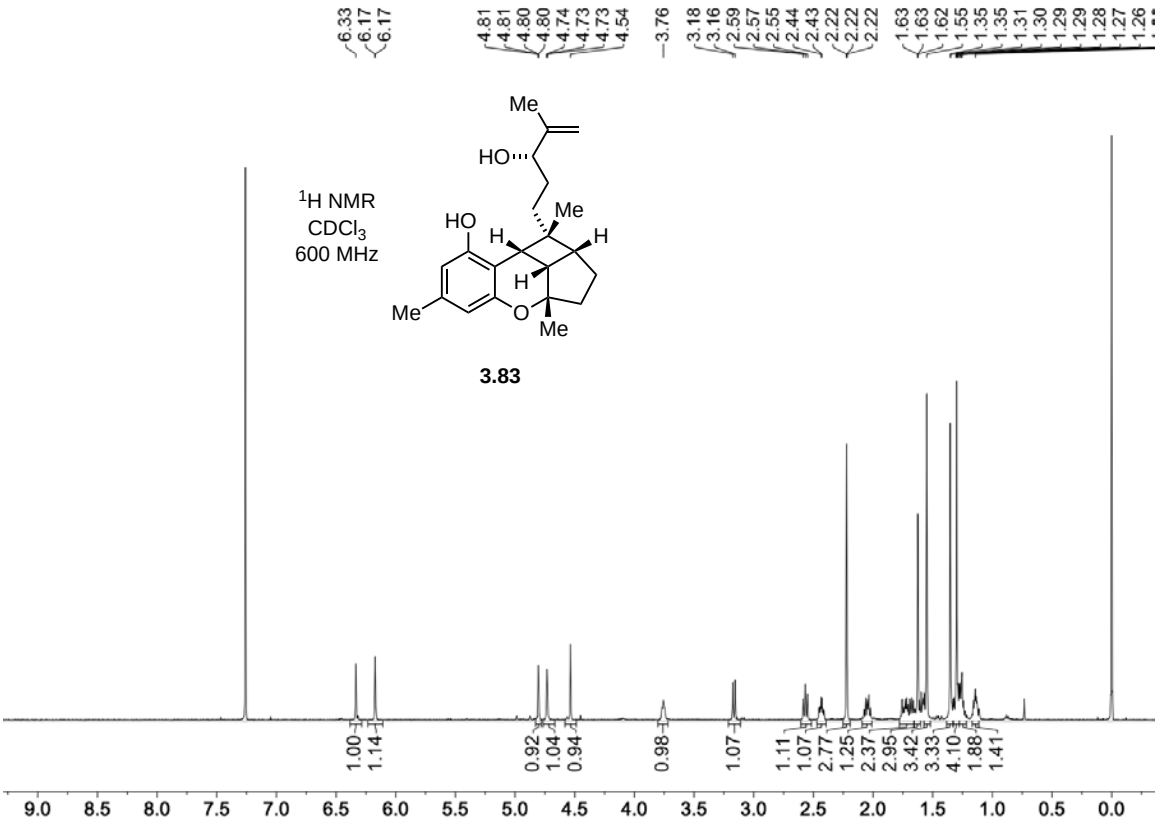

COSY
CDCl3
150 MHz
AcO
Me
H
H
H
Me
O
Me
Me
Me
OH
3.35
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
0 1 2 3 4 5 6 7 8

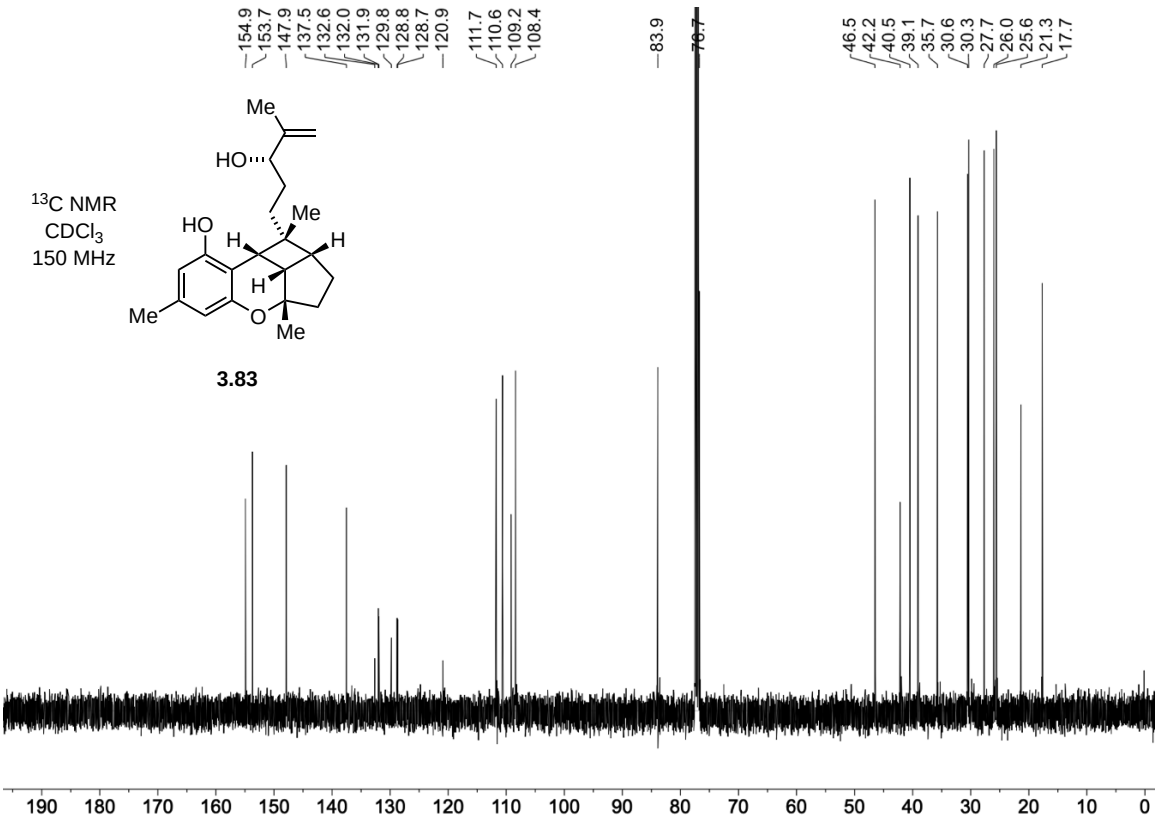

HSQC
CDCl3
150 MHz
AcO
Me
H
H
H
Me
O
Me
Me
Me
OH
3.35
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170


HMBC
CDCl3
150 MHz
AcO
Me
H
H
H
Me
Me
Me
OH
O
Me
3.35


NOESY
CDCl3
150 MHz
AcO
Me
H
H
H
Me
Me
Me
OH
O
Me
3.35

Data for 3.83


6.33
6.17
6.17
4.81
4.81
4.80
4.80
4.74
4.73
4.73
4.54
3.76
3.18
3.16
2.59
2.57
2.55
2.44
2.43
2.22
2.22
2.22
1.63
1.63
1.62
1.55
1.35
1.35
1.31
1.30
1.29
1.29
1.28
1.27
1.26
Me
HO
Me
HO
H
H
H
Me
O
Me
1H NMR
CDCl3
600 MHz
3.83
1.00
1.14
0.92
1.04
0.94
0.98
1.07
1.11
1.07
2.77
1.25
2.37
2.95
3.42
3.33
4.10
1.88
1.41
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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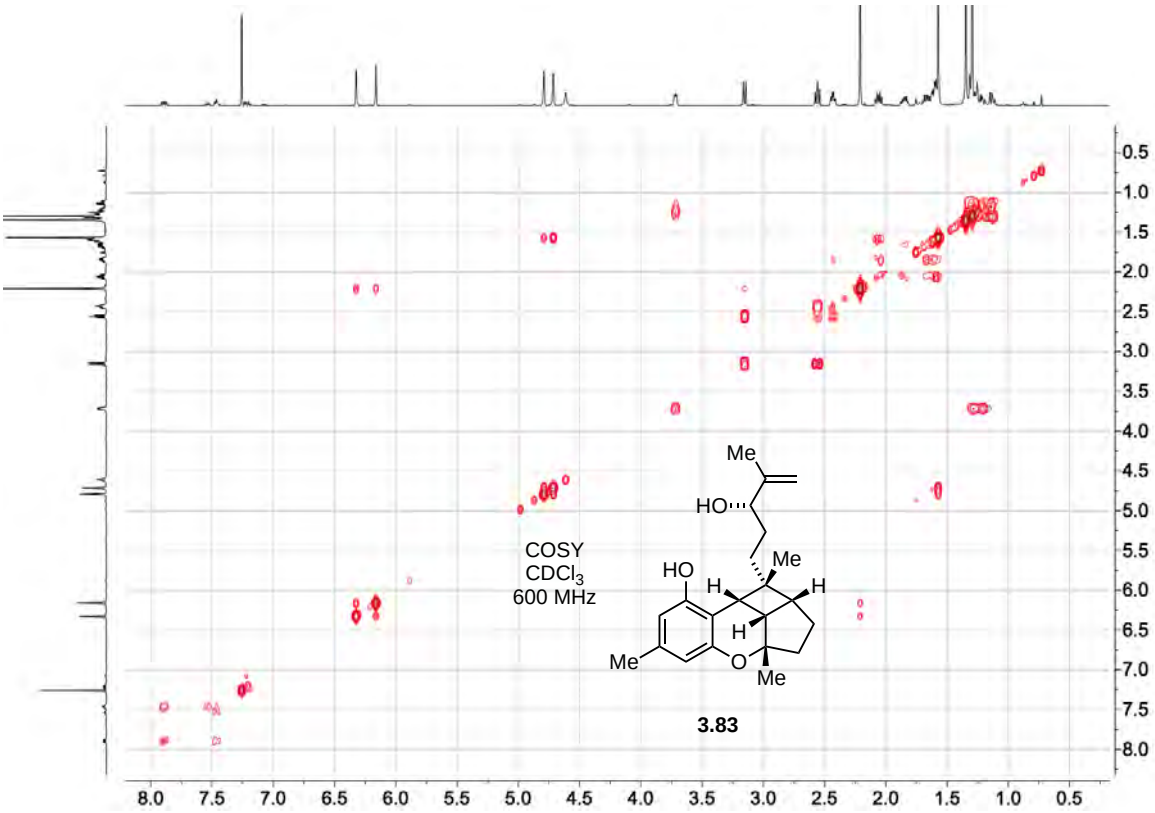
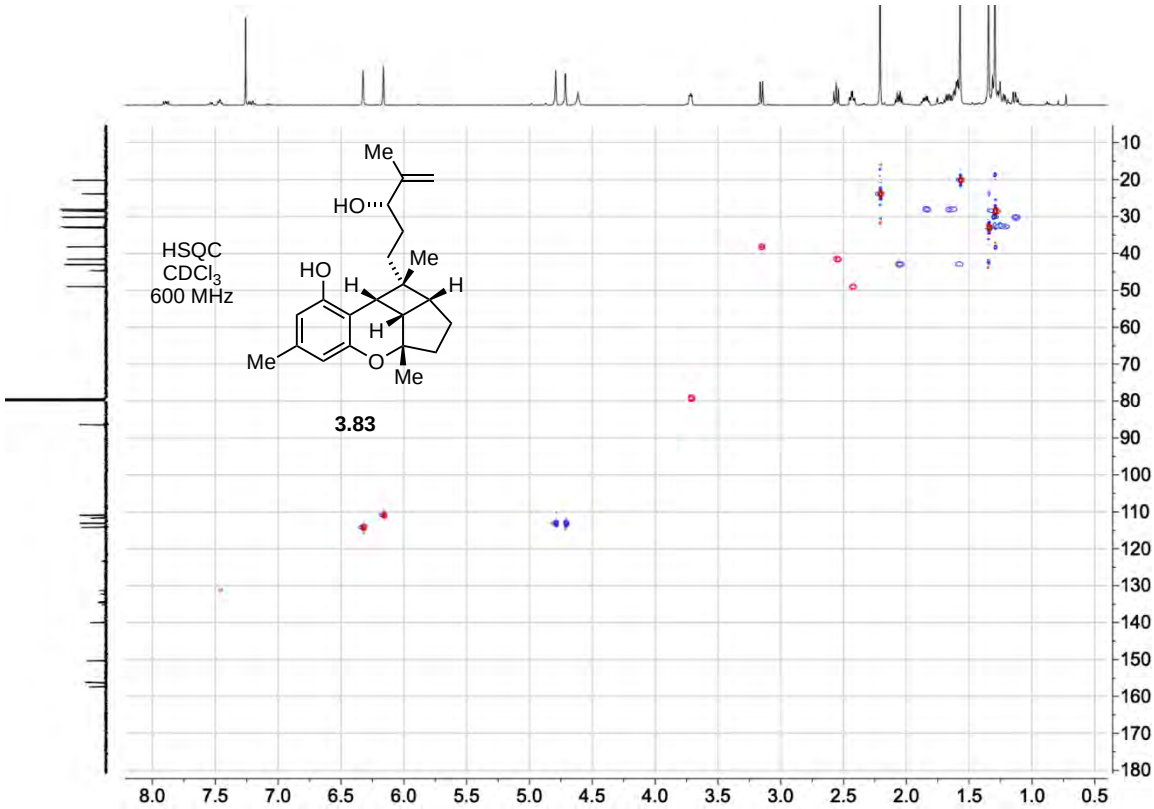
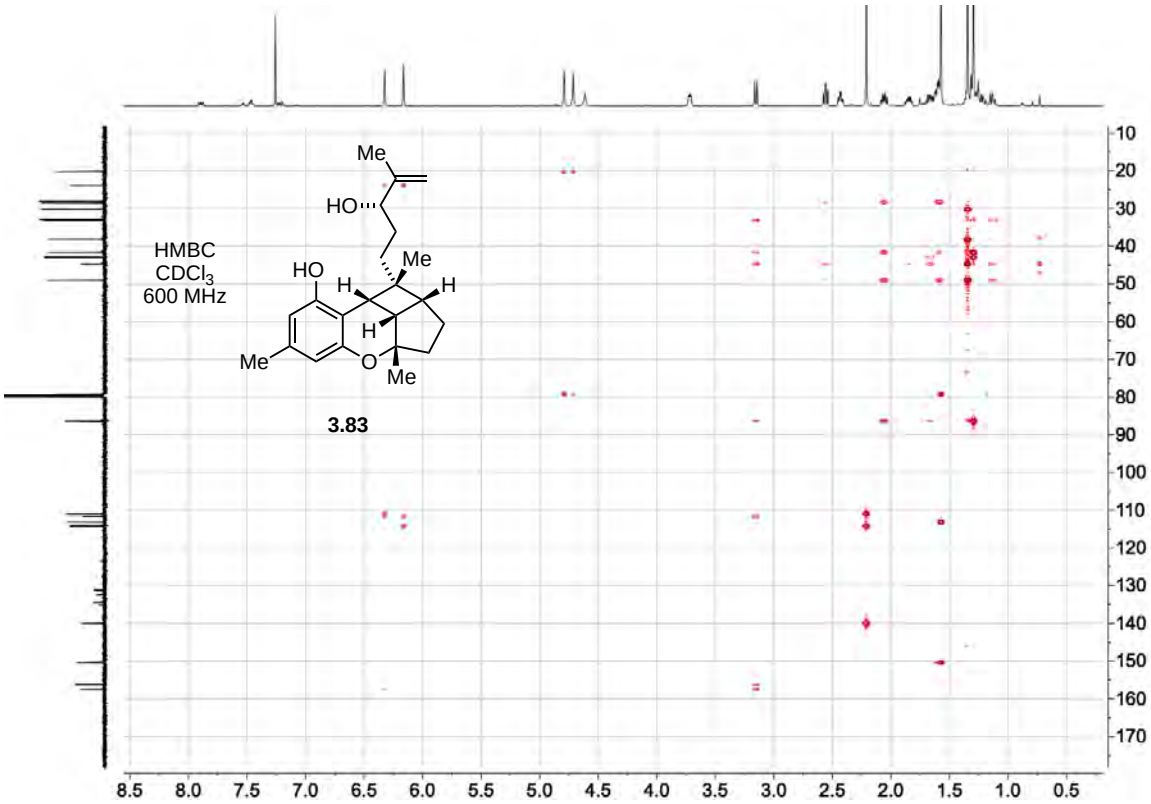
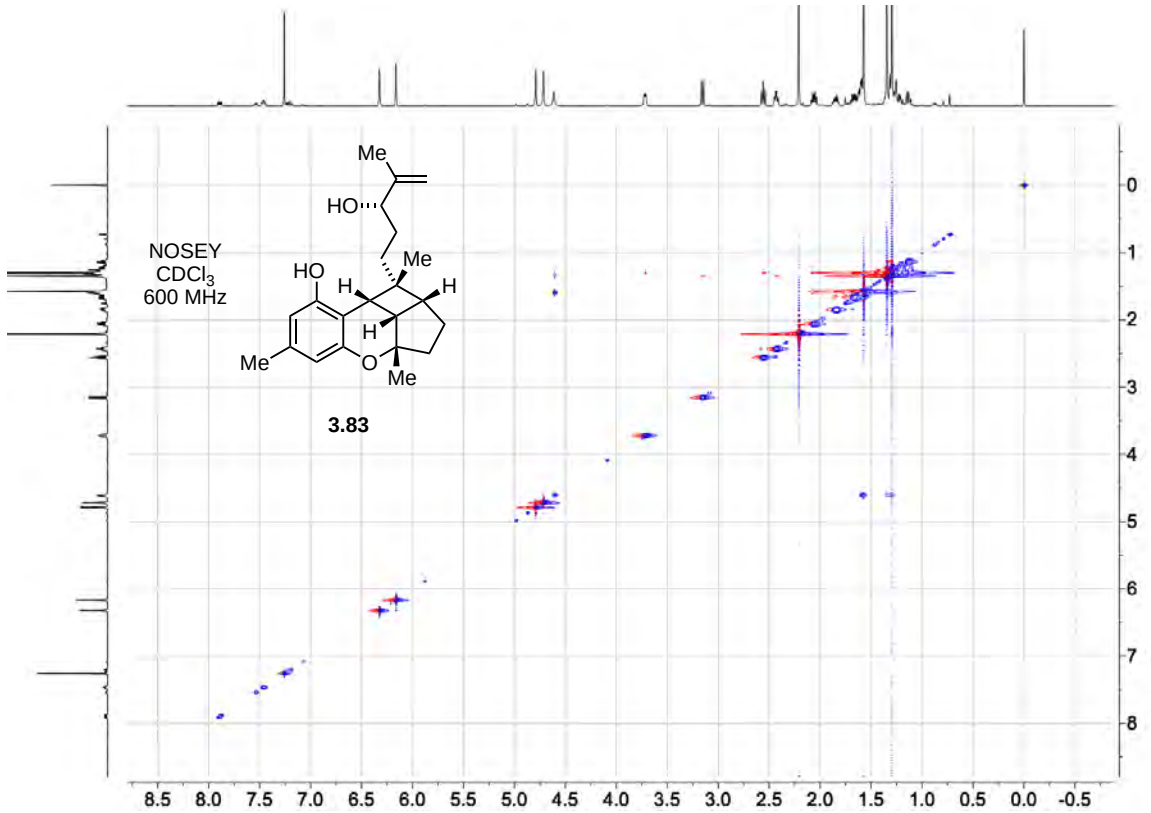
153.7
147.9
137.5
132.6
132.0
131.9
129.8
128.8
128.7
120.9
111.7
110.6
109.2
108.4
83.9
76.7
46.5
42.2
40.5
39.1
35.7
30.6
30.3
27.7
26.0
25.6
21.3
17.7
Me
HO
Me
HO
H
H
H
Me
O
Me
13C NMR
CDCl3
150 MHz
3.83
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

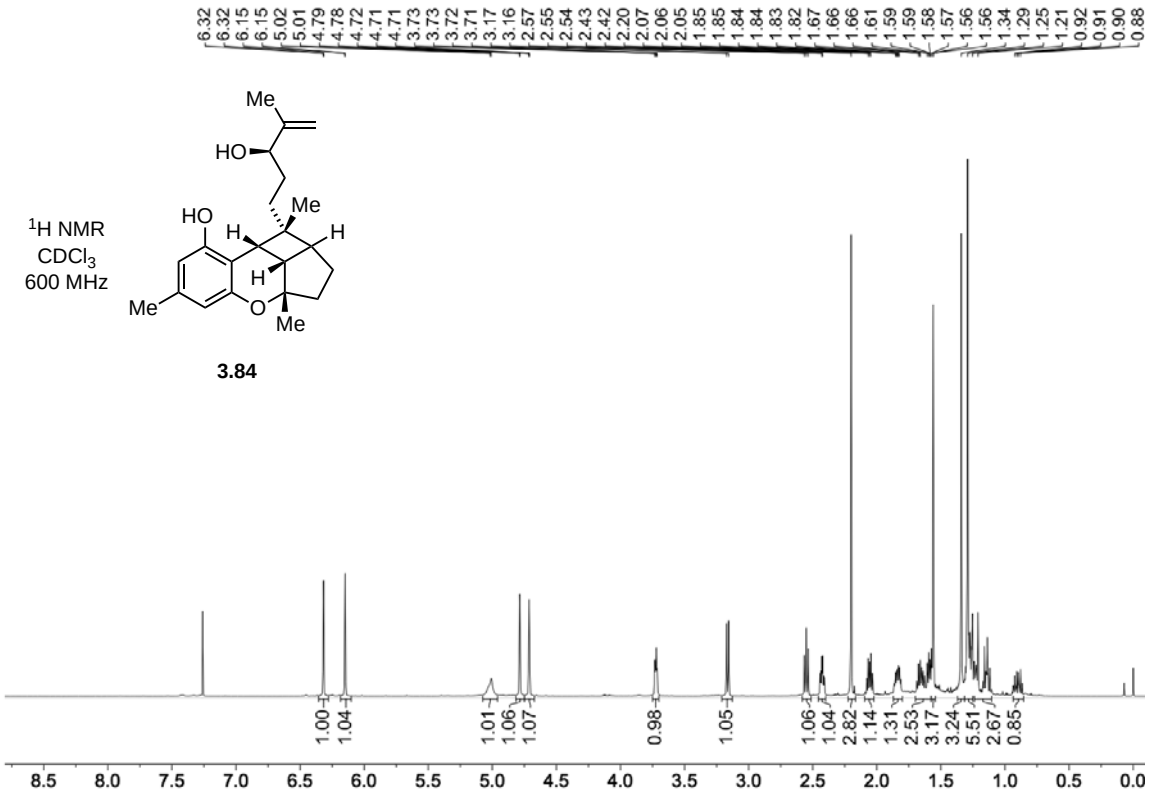

COSY
CDCl3
600 MHz
Me
HO
Me
HO
H
H
H
Me
O
Me
3.83


HSQC
CDCl3
600 MHz
Me
HO
Me
HO
H
H
H
Me
O
Me
3.83


HMBC
CDCl3
600 MHz
Me
HO
Me
HO
H
H
H
Me
O
Me
3.83


NOSEY
CDCl3
600 MHz
Me
HO
Me
HO
H
H
H
Me
O
Me
3.83

Data for 3.84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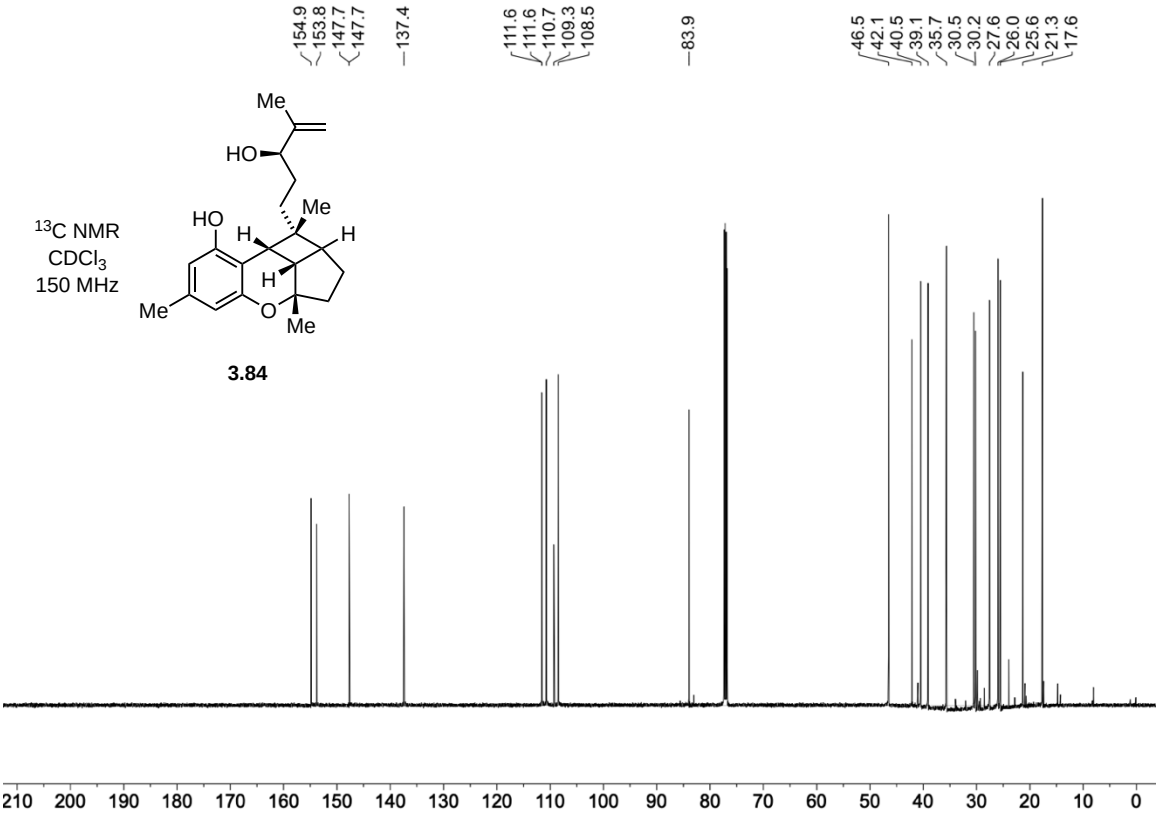
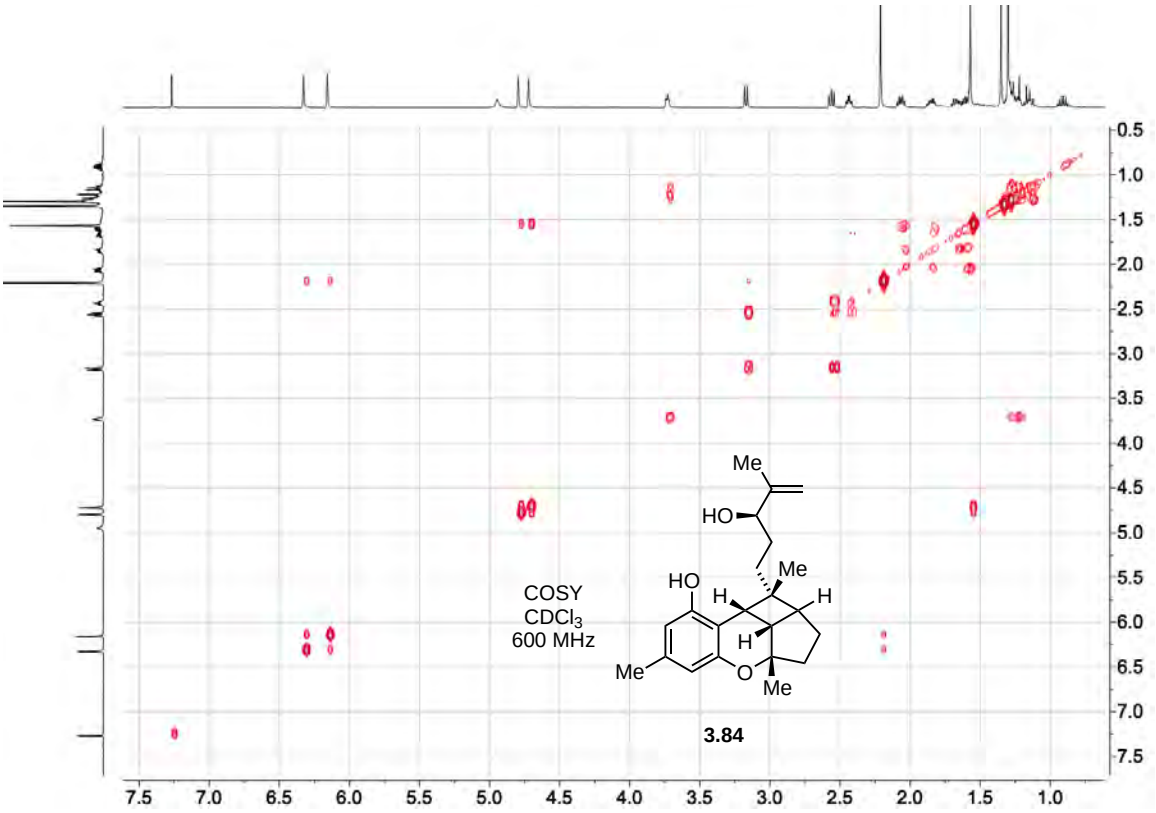
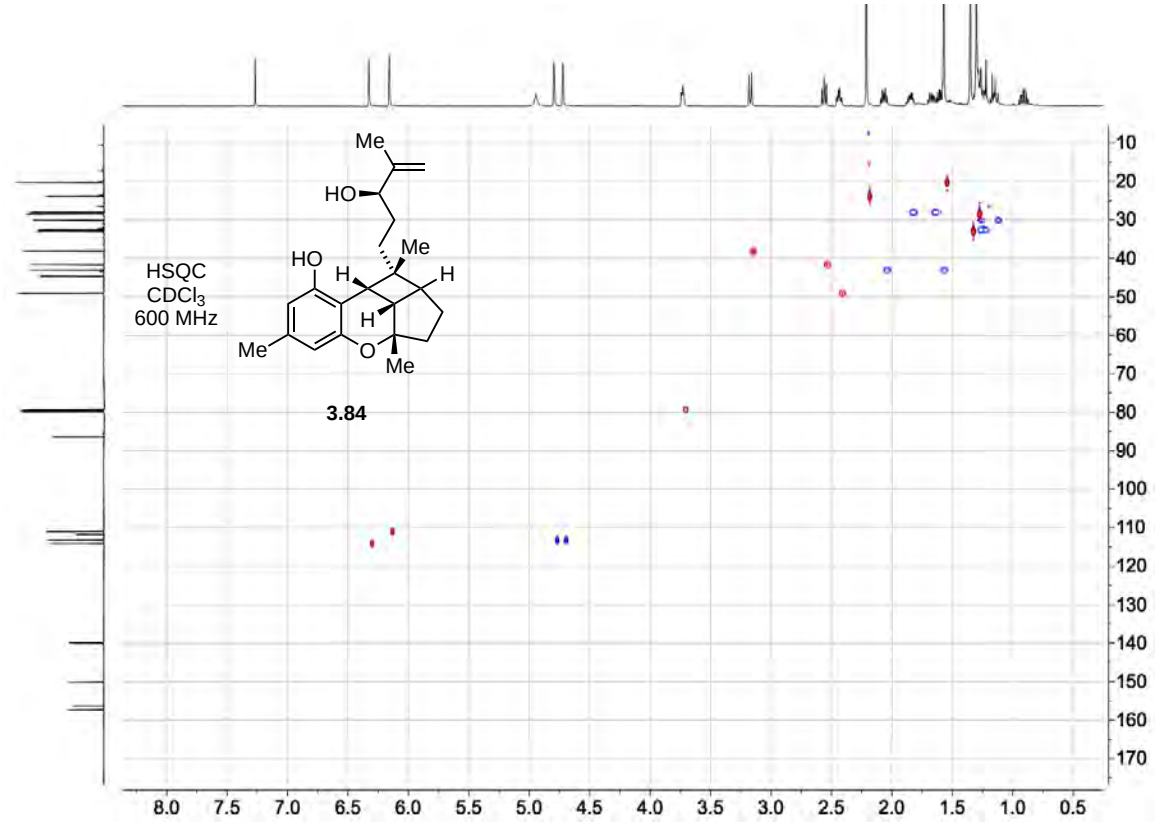
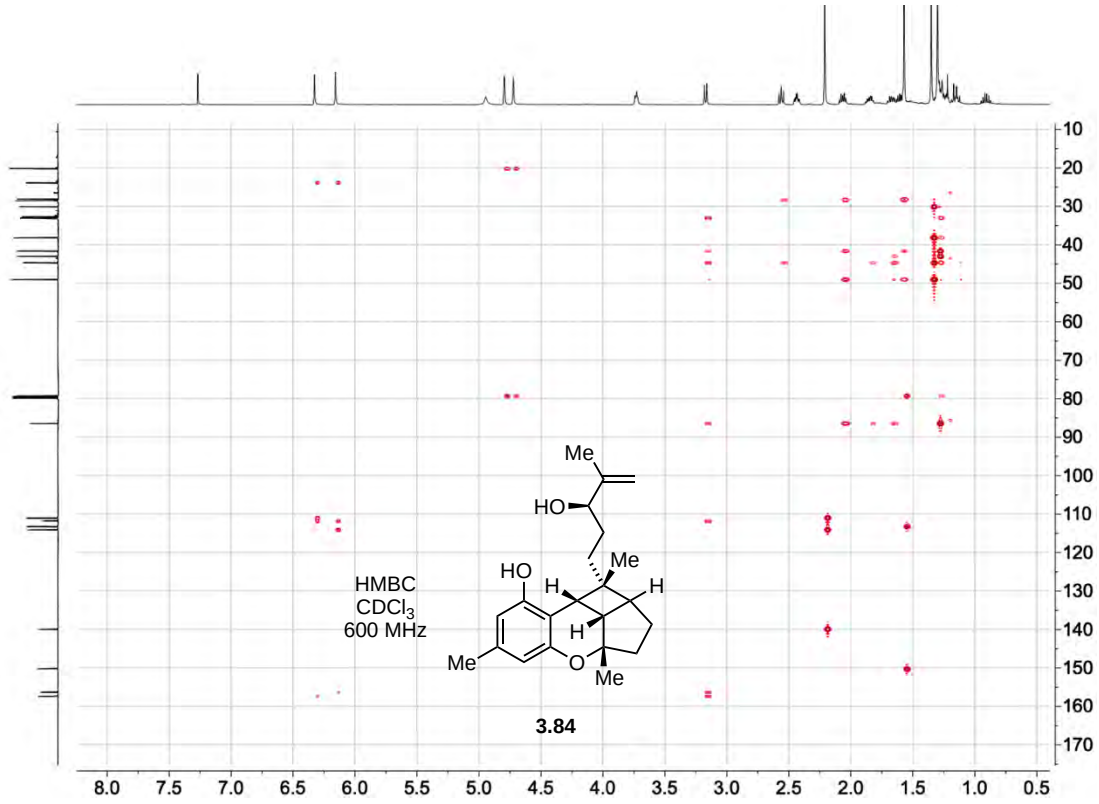
6.32
6.15
6.15
5.02
5.01
4.79
4.78
4.72
4.71
4.71
3.73
3.73
3.72
3.71
3.17
3.16
2.57
2.55
2.54
2.43
2.42
2.20
2.07
2.06
2.05
1.85
1.85
1.84
1.84
1.83
1.82
1.67
1.66
1.66
1.61
1.59
1.59
1.58
1.57
1.56
1.56
1.34
1.29
1.25
1.21
0.92
0.91
0.90
0.88
Me
HO
Me
HO
H
H
H
Me
O
Me
1H NMR
CDCl3
600 MHz
3.84
1.00
1.04
1.01
1.06
1.07
0.98
1.05
1.06
1.04
2.82
1.14
1.31
2.53
3.17
3.24
5.51
2.67
0.85
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


154.9
153.8
147.7
147.7
137.4
111.6
111.6
110.7
109.3
108.5
83.9
46.5
42.1
40.5
39.1
35.7
30.5
30.2
27.6
26.0
25.6
21.3
17.6
Me
HO
Me
HO
H
H
H
Me
O
Me
13C NMR
CDCl3
150 MHz
3.84
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


COSY
CDCl3
600 MHz
Me
HO
Me
HO
H
H
H
Me
O
Me
3.84


HSQC
CDCl3
600 MHz
Me
HO
Me
HO
H
H
H
Me
O
Me
3.84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Me
HO
Me
HO
H
H
H
Me
O
Me
3.84

Data for 3.85

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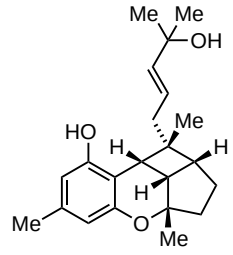
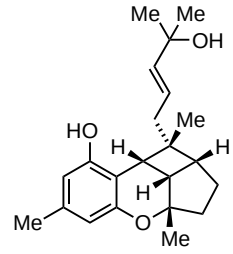
600 MHz



3.85

^{13}C NMR
$CDCl_3$
150 MHz



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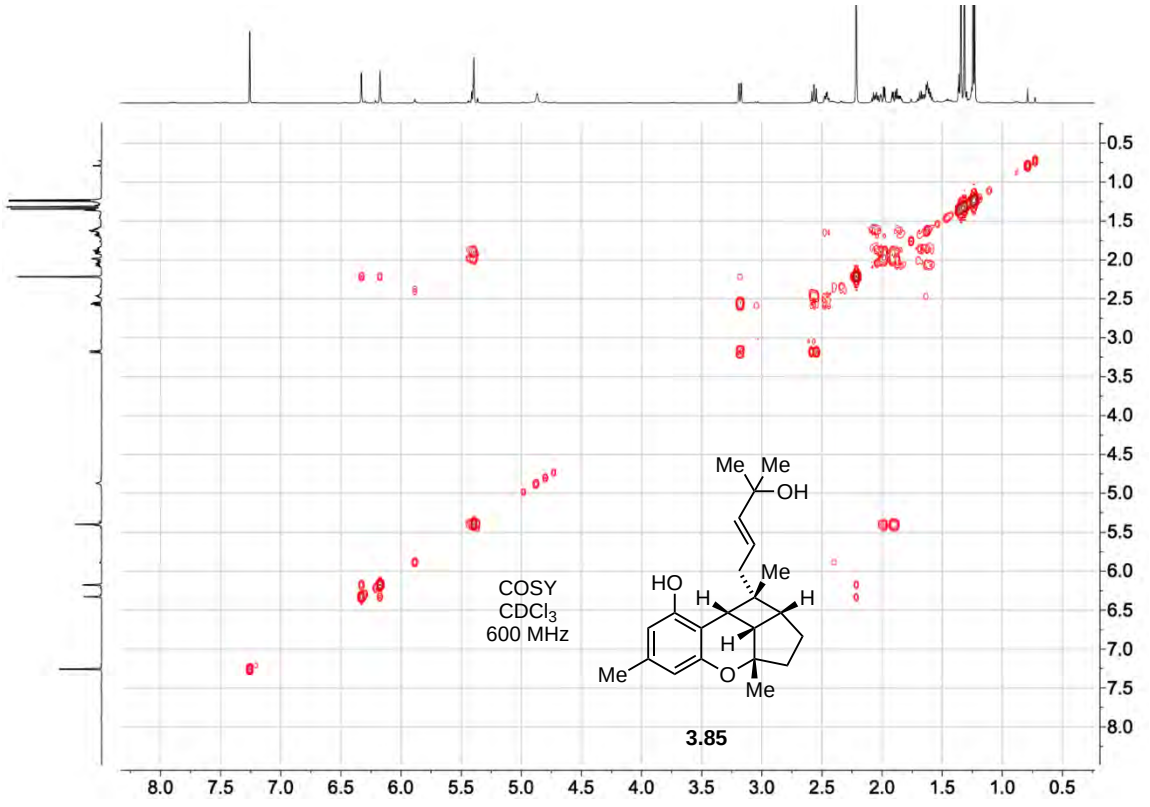
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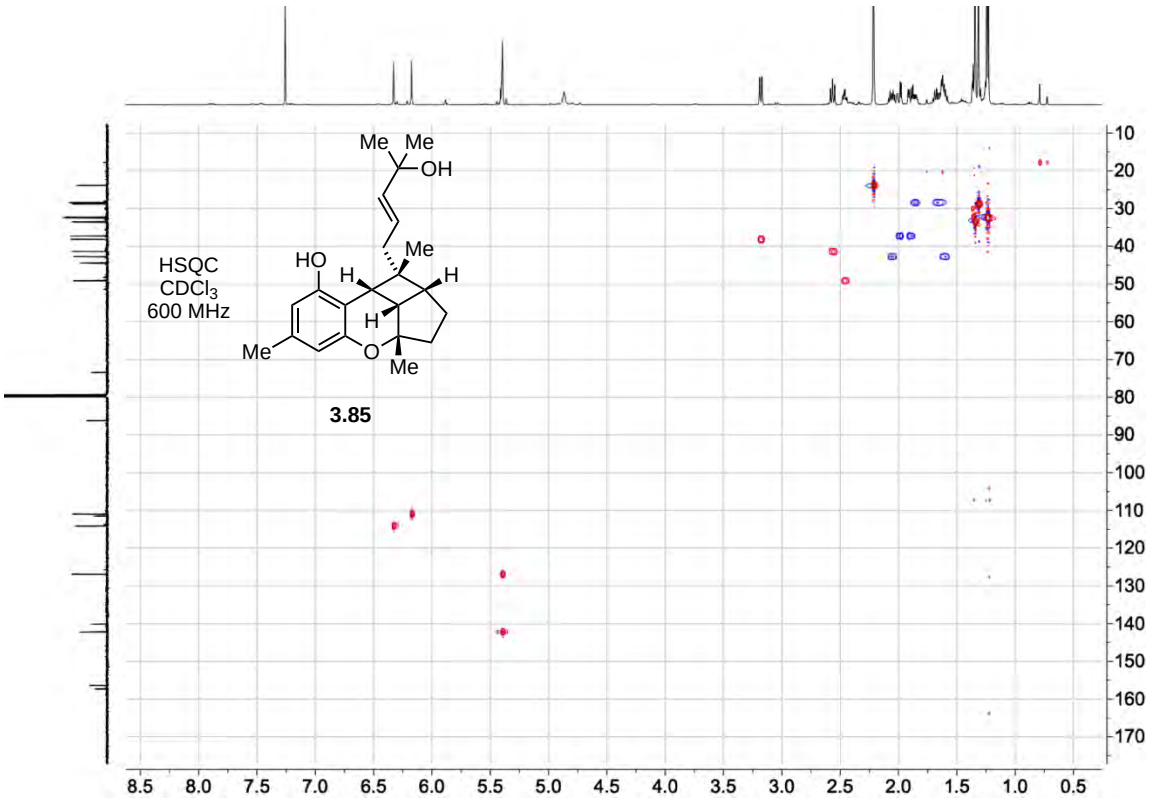
Me
HO
H
H
H
Me
O
Me
3.85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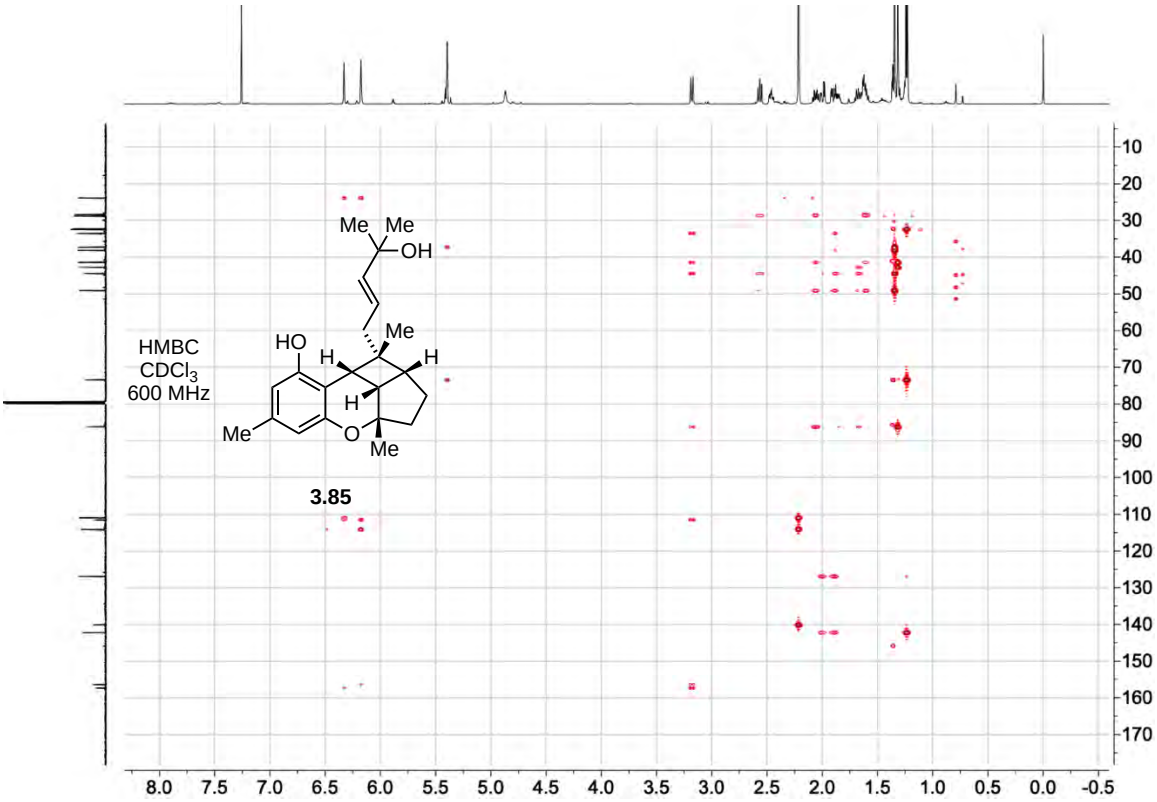
H
Me
O
Me
3.85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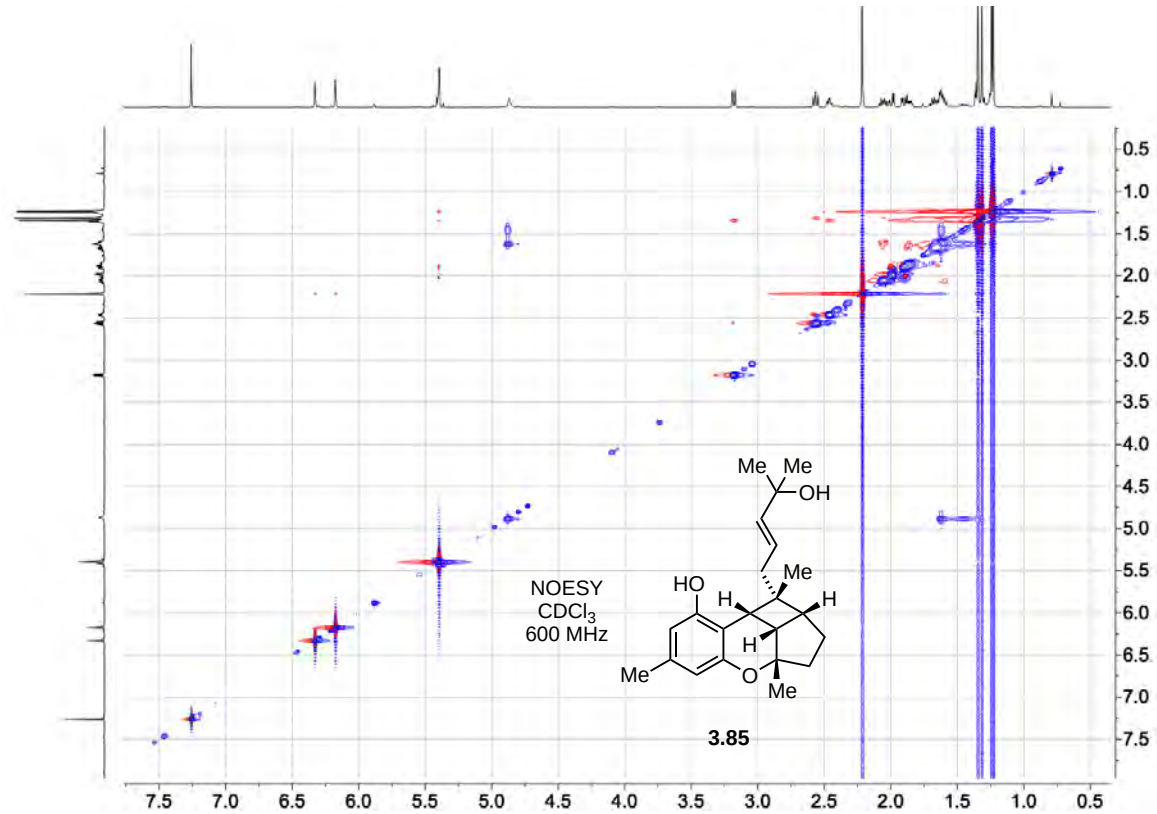
Me
3.85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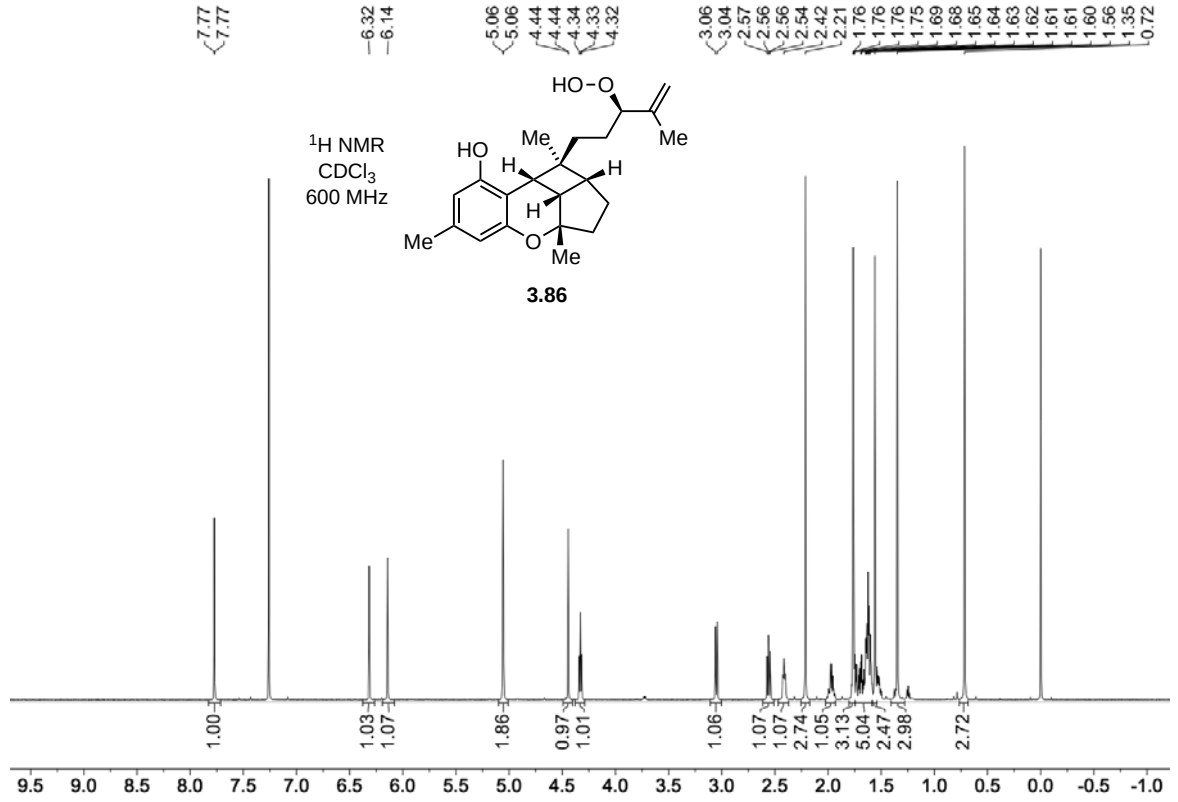
O
Me
3.85

Data for 3.86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7.77
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4.32
3.06
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2.56
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2.54
2.42
2.21
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1.75
1.69
1.68
1.65
1.64
1.63
1.62
1.61
1.61
1.60
1.56
1.35
0.72
1H NMR
CDCl3
600 MHz
HO
HO–O
Me
Me
H
H
H
Me
O
Me
3.86
1.00
1.03
1.07
1.86
0.97
1.01
1.06
1.07
1.07
2.74
1.05
3.13
5.04
2.47
2.98
2.72
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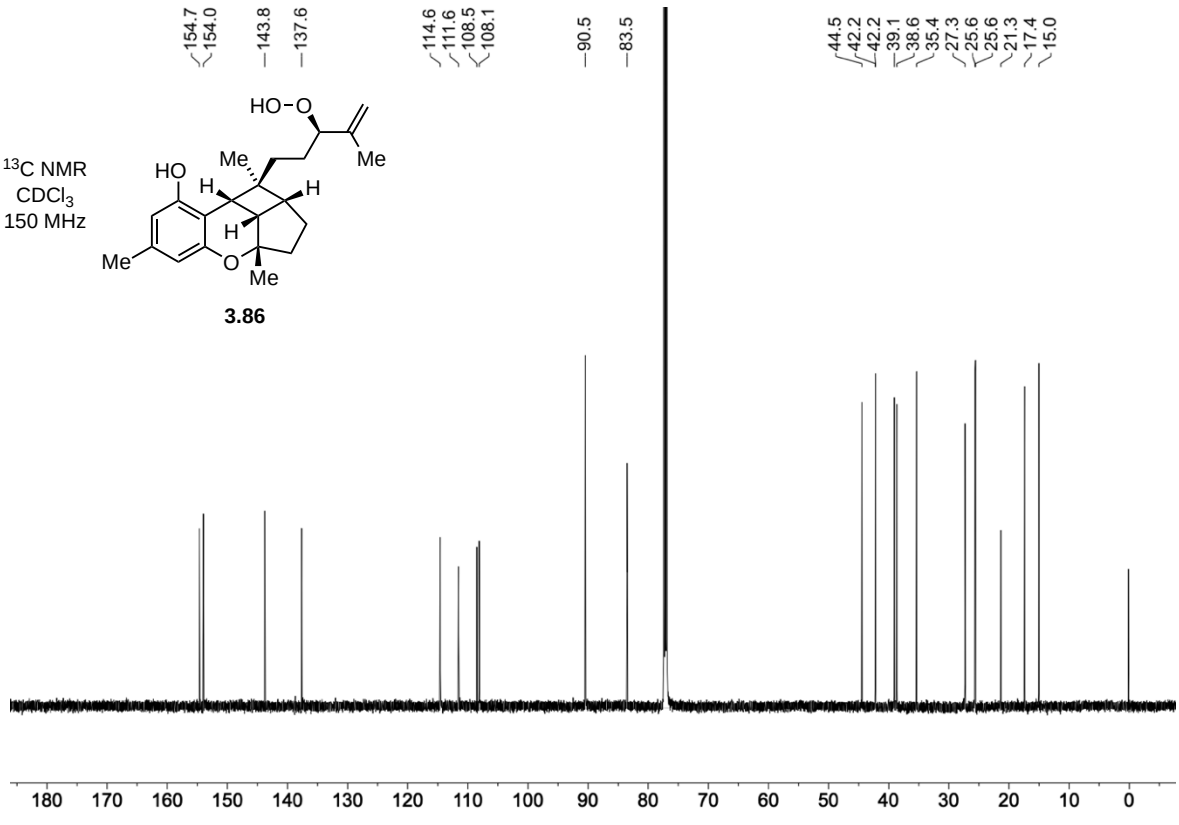
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42.2
39.1
38.6
35.4
27.3
25.6
25.6
21.3
17.4
15.0
13C NMR
CDCl3
150 MHz
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HO–O
Me
Me
H
H
H
Me
O
Me
3.86
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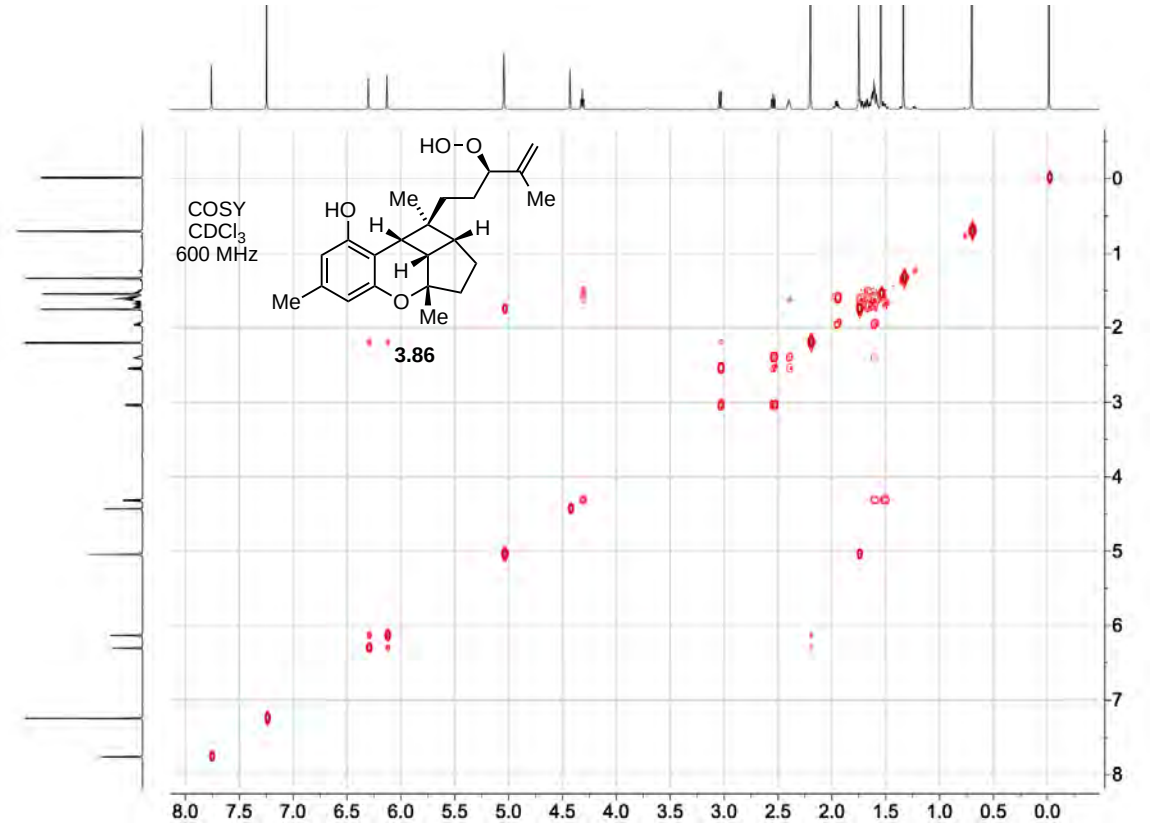
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600 MHz
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Me
HO
Me
H
H
H
Me
O
Me
3.86
0
1
2
3
4
5
6
7
8
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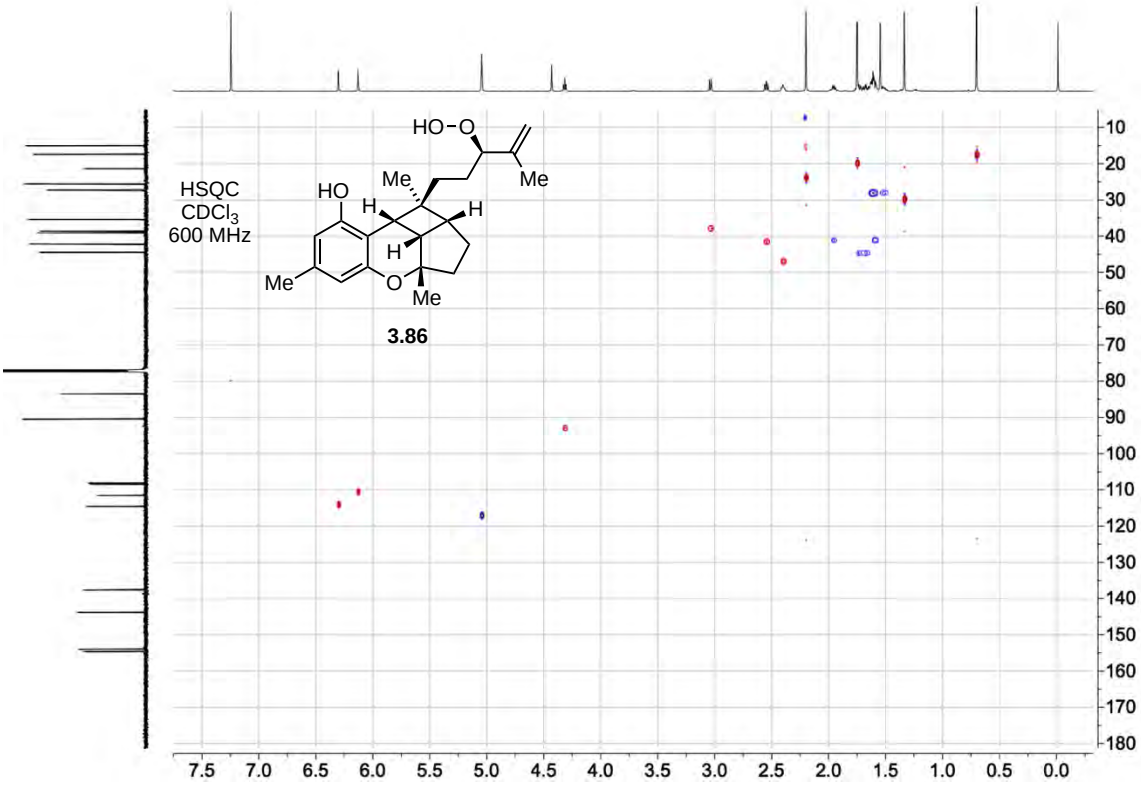
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600 MHz
HO-O
Me
HO
Me
H
H
H
Me
O
Me
3.86
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
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170
180
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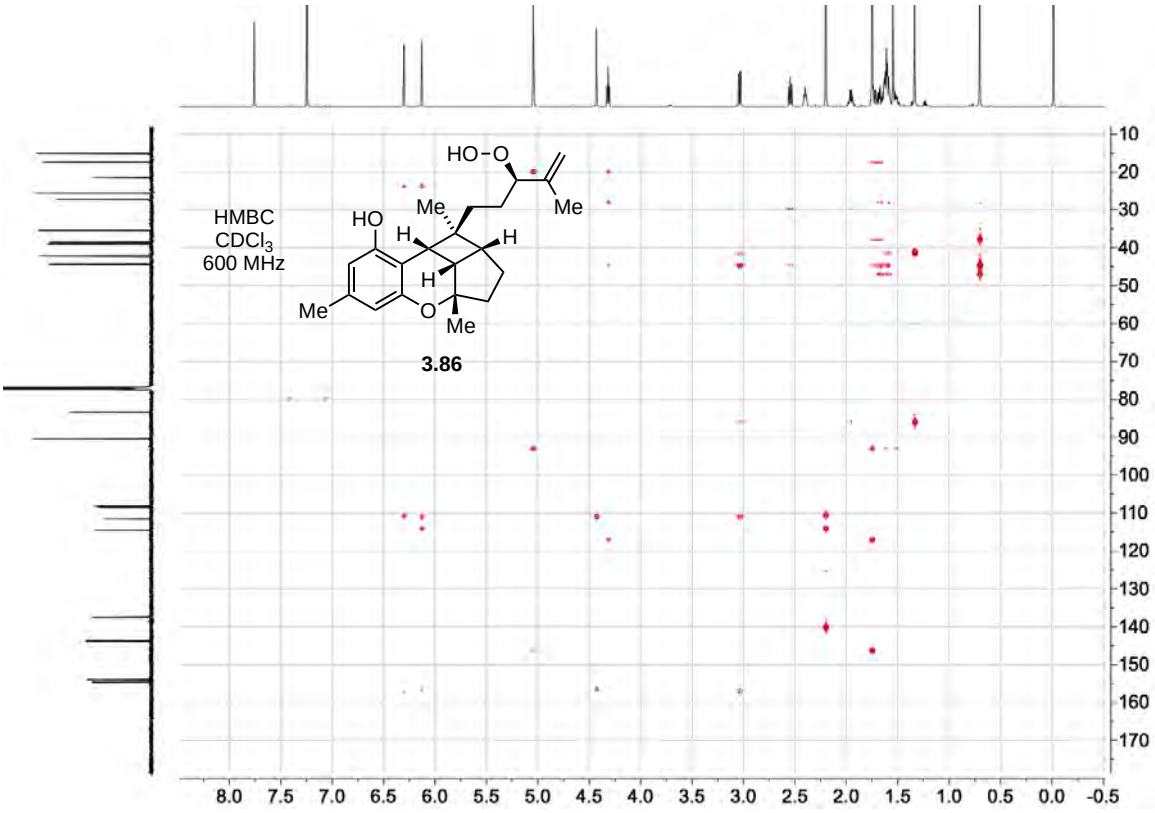
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600 MHz
HO-O
Me
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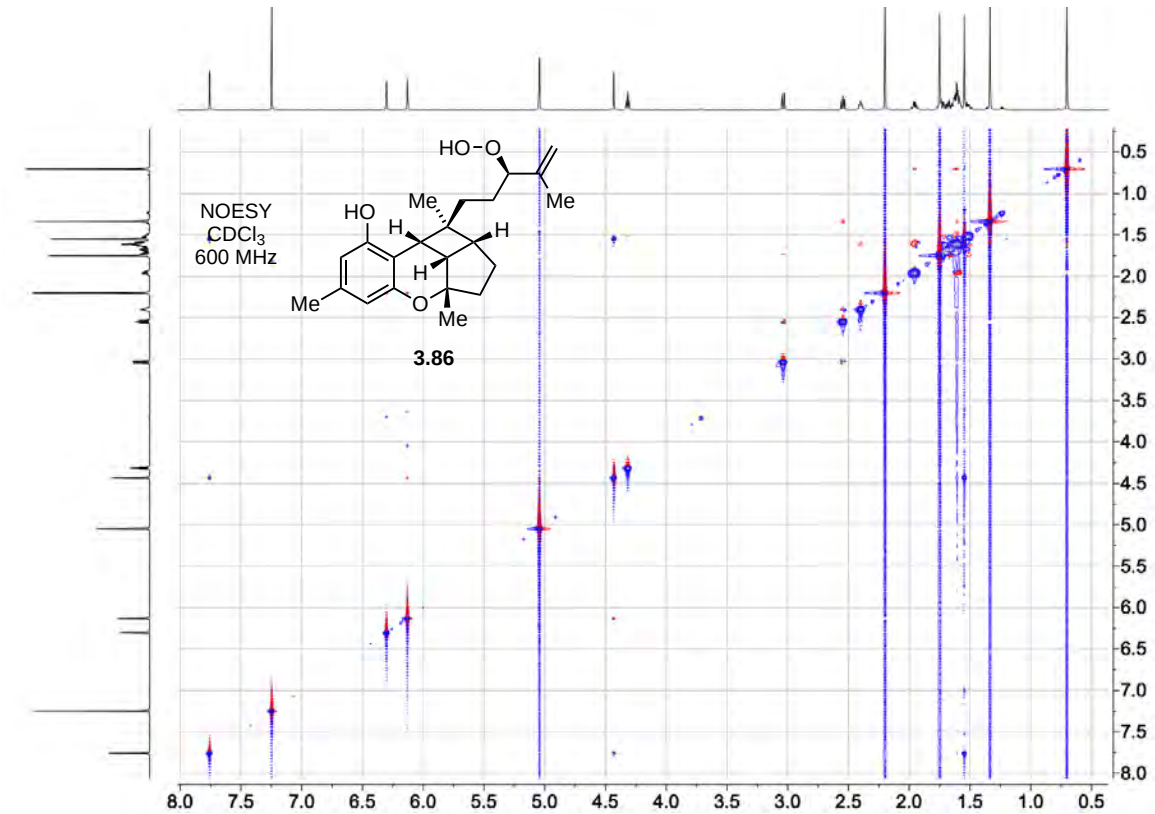
H
H
H
Me
O
Me
Me
3.86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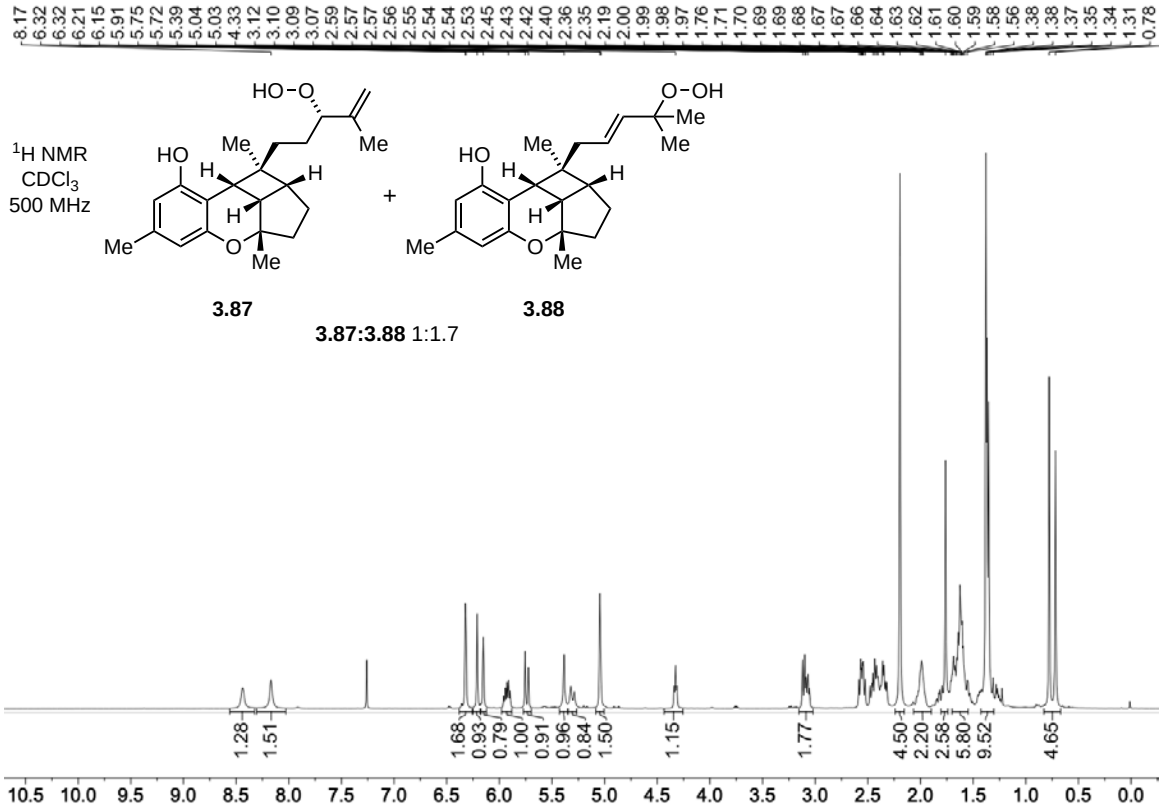
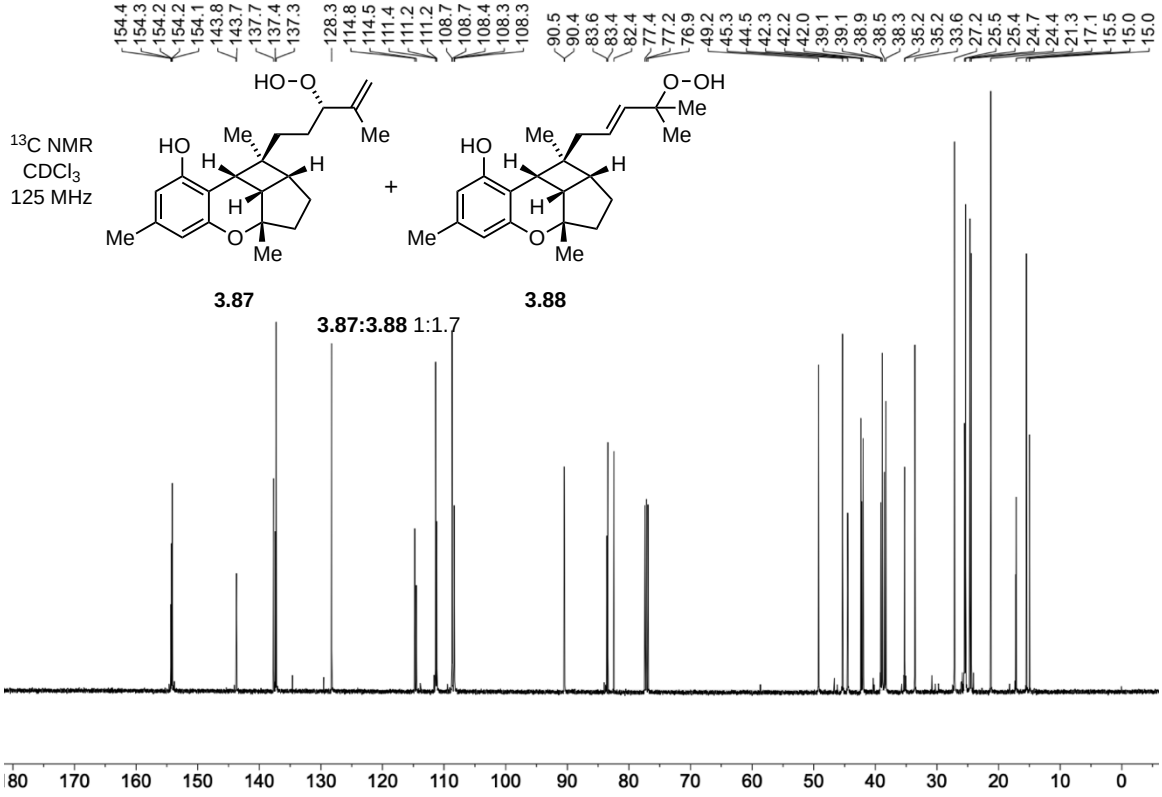
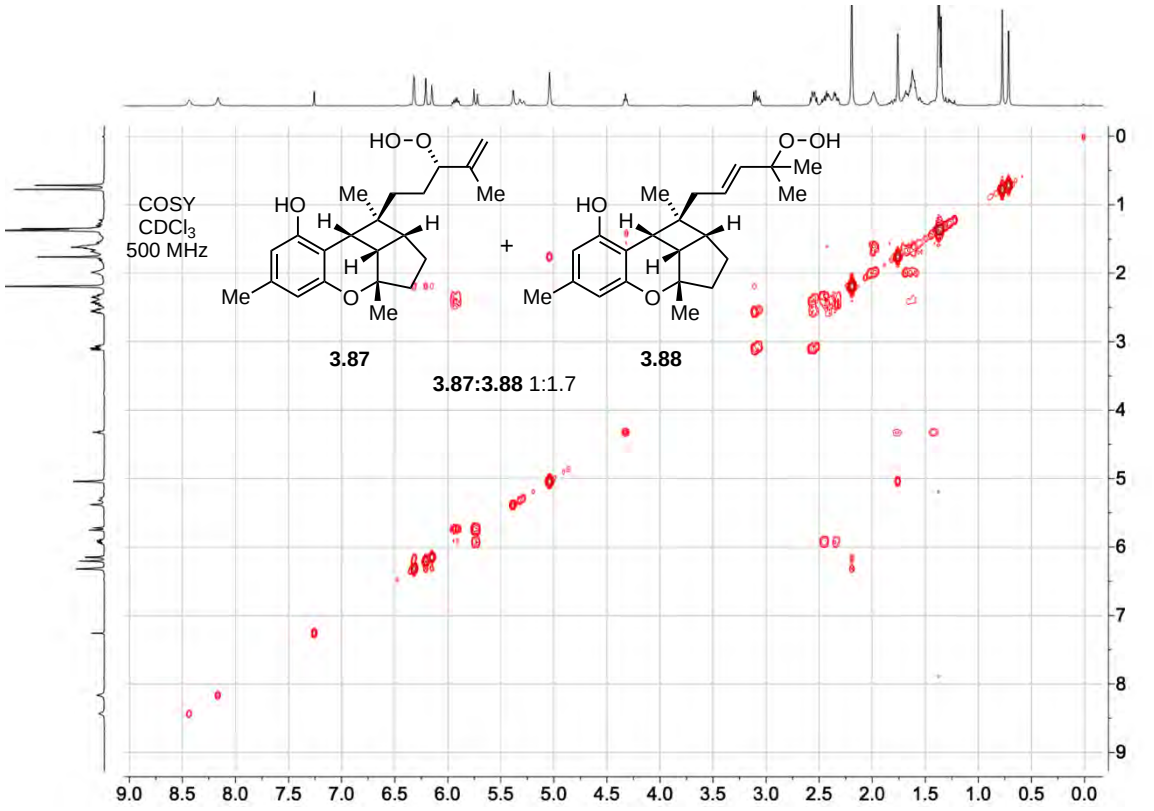
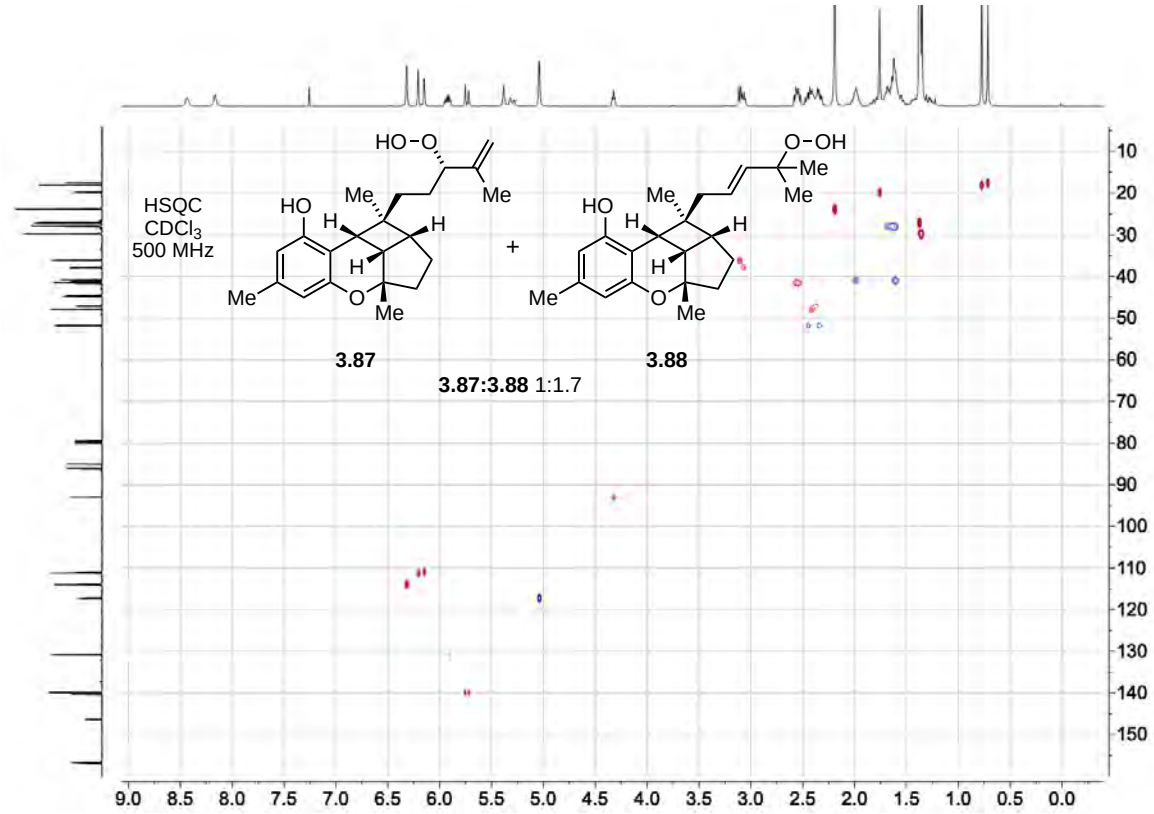
CDCl3
600 MHz
HO-O
Me
HO
H
H
H
Me
O
Me
Me
3.86

Data for 3.87 and 3.88






COSY
CDCl3
500 MHz
HO
HO-O
Me
Me
H
H
H
Me
O
Me
+
O-OH
Me
Me
3.87
3.88
3.87:3.88 1:1.7
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
0 1 2 3 4 5 6 7 8 9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HO
HO-O
Me
Me
H
H
H
Me
O
Me
+
O-OH
Me
Me
3.87
3.88
3.87:3.88 1:1.7
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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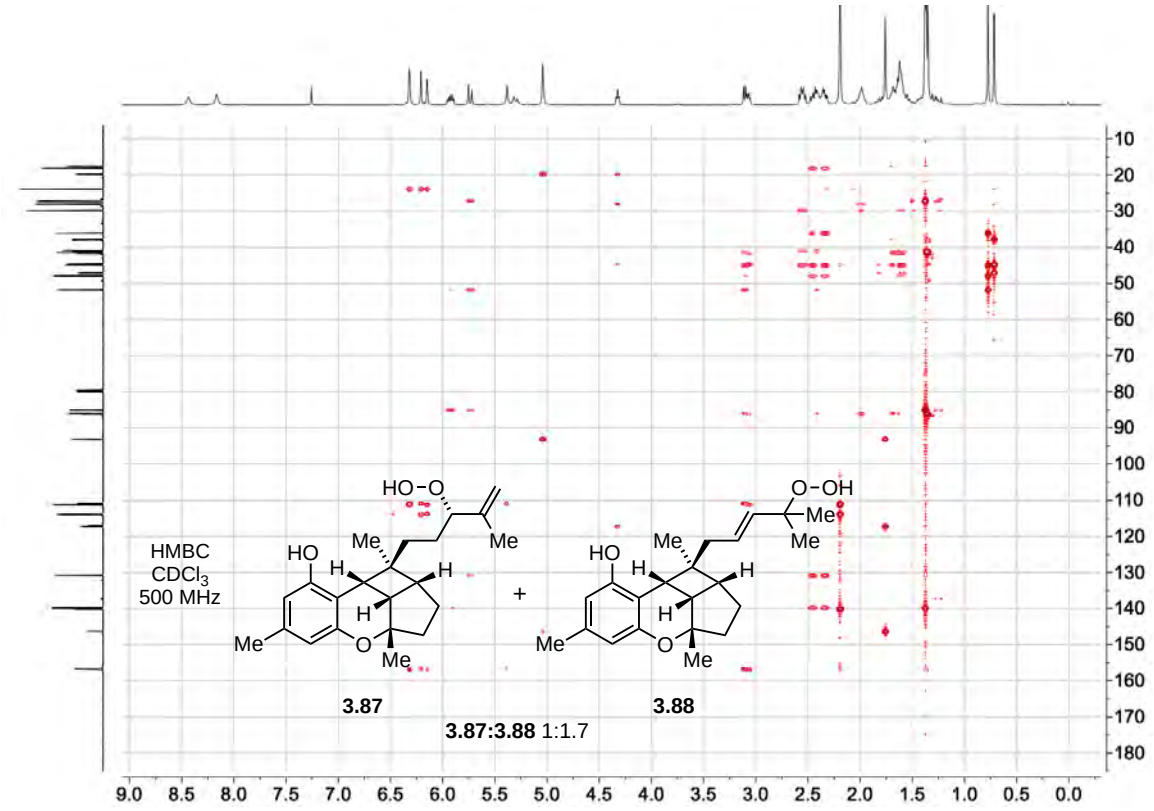
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CDCl3
500 MHz
HO-O
Me
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Me
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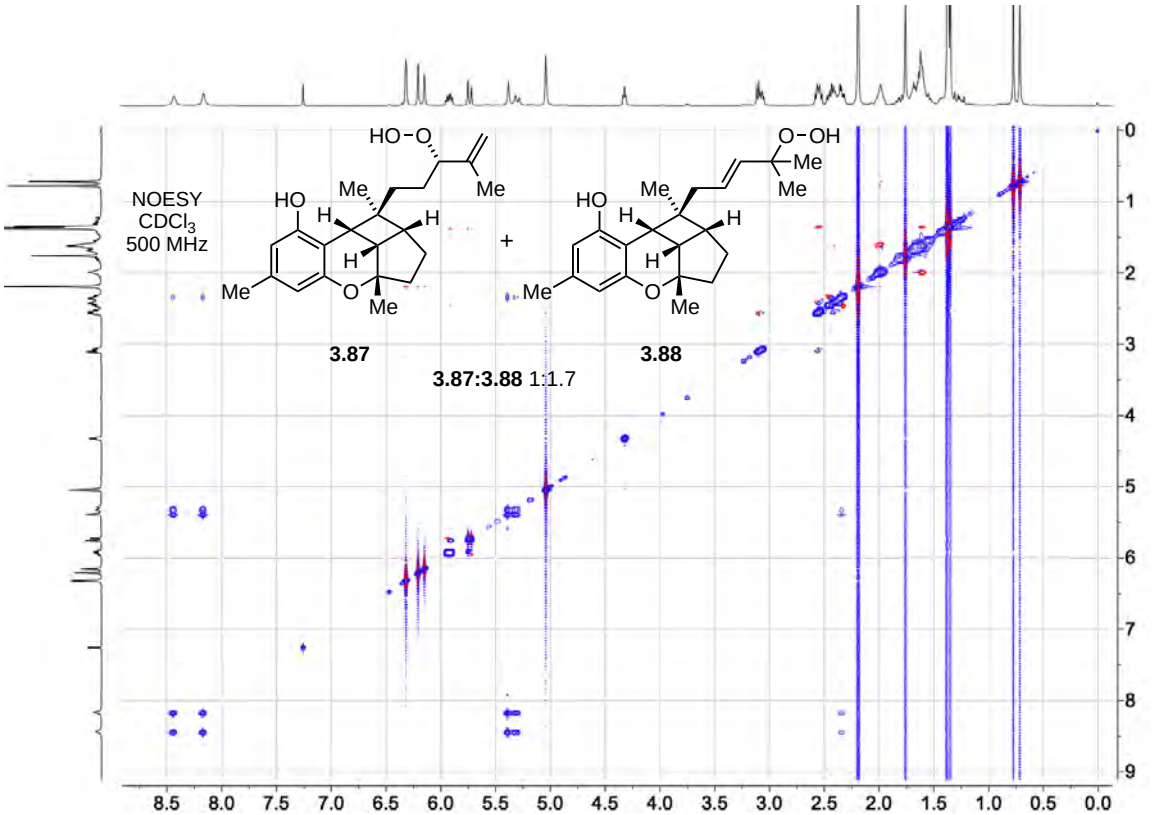
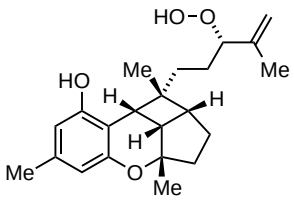
Me
+
O-OH
Me
Me
3.87
3.88
3.87:3.88 1:1.7


NOESY
CDCl3
500 MHz
HO-O
Me
Me
HO
H
H
H
Me
O
Me
+
O-OH
Me
Me
3.87
3.88
3.87:3.88 1:1.7

Data for 3.89

^{1}H NMR
$CDCl_3$
600 MHz



3.89

^{13}C NMR
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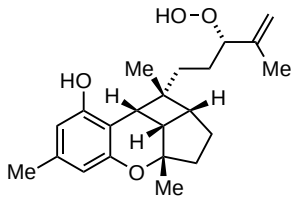
150 MHz



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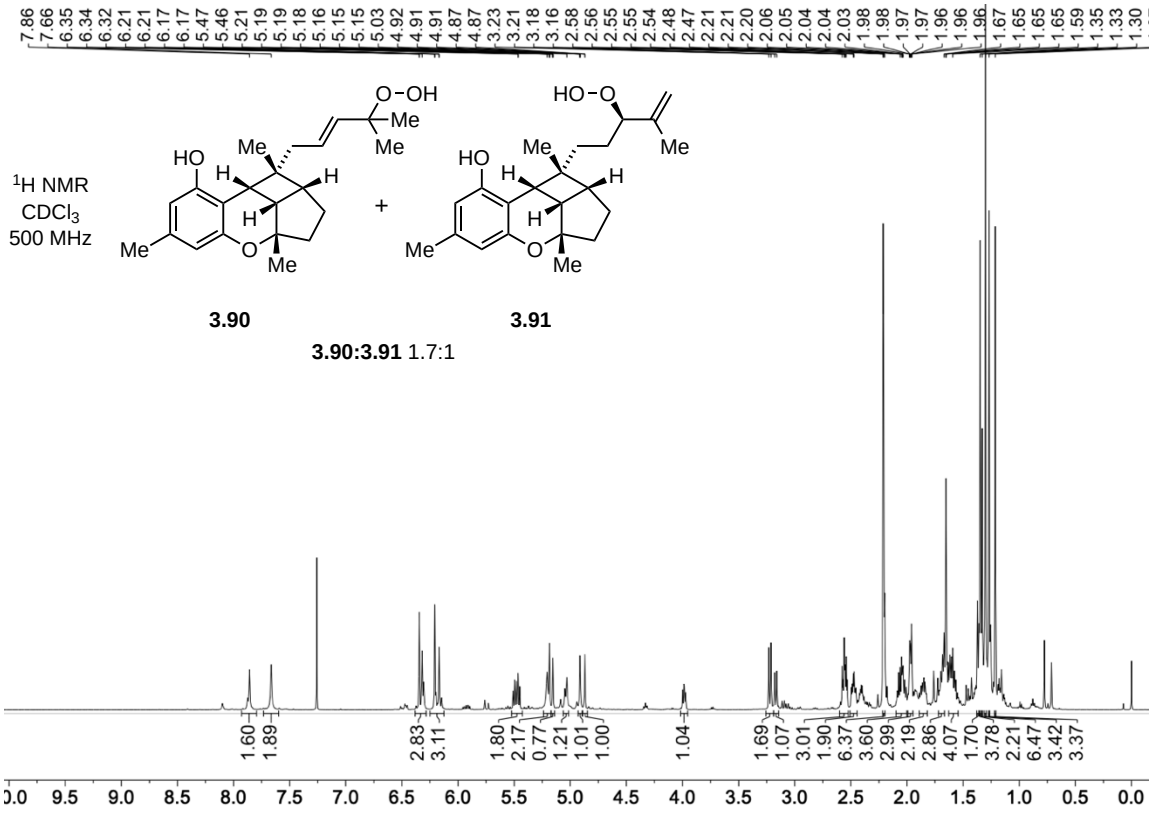
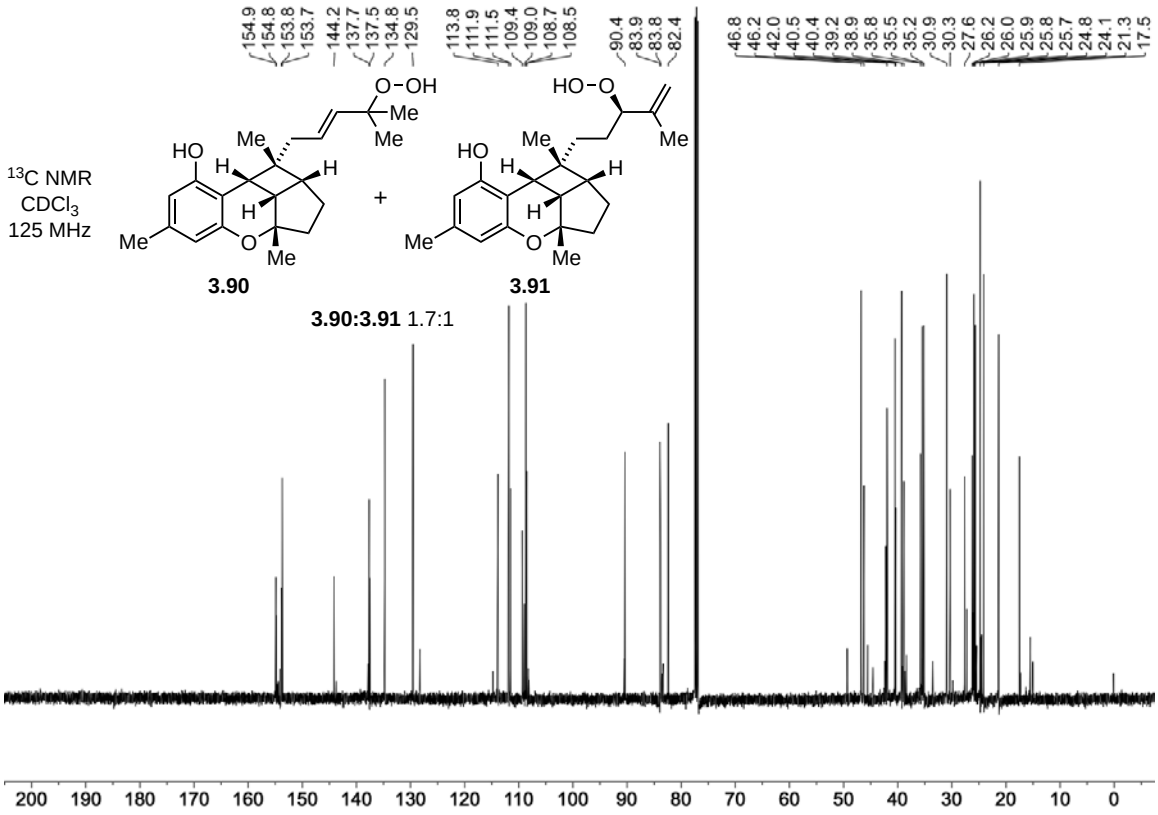
Data for 3.90 and 3.91





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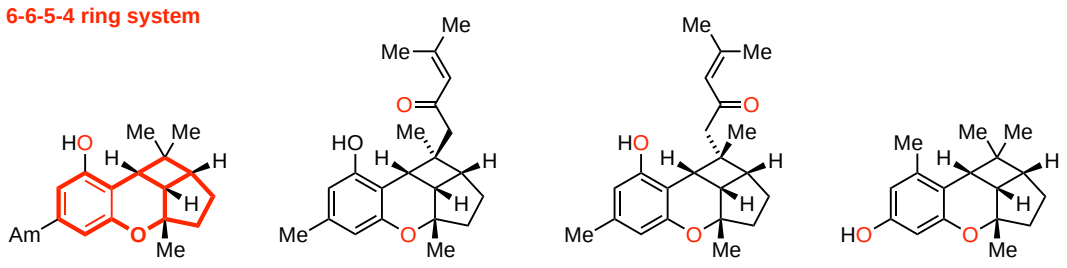
Chapter Four – Biomimetic Total Synthesis of the Rubiginosins

This work was completed with assistance from Mr. Aaron Day who helped with key chromenylation reactions and Postdoctoral researcher Dr. Oussama Yahiaoui who brought through material for us

4.1 Introduction

4.1.1 Isolation of the Rubiginosin and Anthopogochromane Natural Products

Rhododendron plants are a diverse source of stereochemically complex, polycyclic meroterpenoids. Amongst the various possible scaffolds, the **6-6-5-4** ring system is relatively abundant in plant natural products (**Figure 4.1**). Perhaps one of the most well-known example is cannabicyclol (CBL) (**4.1**),[1] synthesized *via* intramolecular [2+2] cycloadditions using photochemical,[2] thermal,[3] or acidic conditions.[4] *Rhododendron* natural products with this scaffold have been explored extensively in this thesis, including the synthesis of fastinoid B (**4.2**), rhodonoid B (**4.3**) (*vide supra, chapter three*), and nyingchinoid D (**4.4**) (*vide infra, chapter five*).



4.1: cannabicyclol (CBL) **4.2:** fastinoid B **4.3:** rhodonoid B **4.4:** nyingchinoid D

Figure 4.1 – *Rhododendron* Tetracyclic Chromanes with the 6-6-5-4 Ring System

Another scaffold found belonging to the *Rhododendron* family includes the **6-6-6-4** ring system (**Figure 4.2**). Interestingly however, this ring system is comparatively rare in natural products. The simplest natural product with this structure is the monoterpenoid rhodonoid A (**4.5**), isolated from *Rhododendron capitatum*.[5] Additionally there are also five merosesquiterpenoids with this ring system. The first, rubiginosin G (**4.6**) was reported in 2009 and isolated from *Rhododendron adamsii*, however at the time its relative configuration was not assigned and it was not named.[6] It was later re-isolated in 2018, this time from *Rhododendron rubiginosum* alongside rubiginosin A and B (**4.7** and **4.8**).[7] Other natural products with this scaffold include anthopogochromane (**4.9**) isolated from *Rhododendron anthopogonoides*,[8] and fastinoid C (**4.10**) isolated from *Rhododendron fastigiatum*.[9]

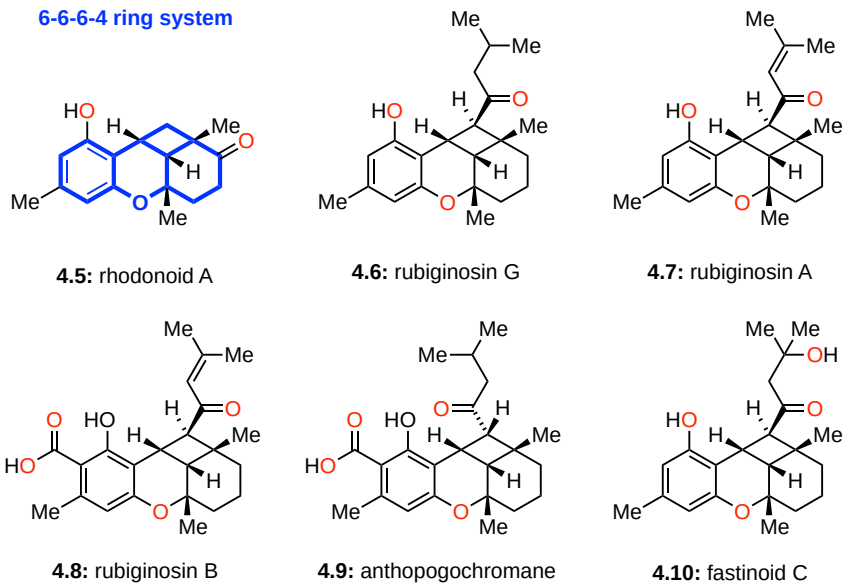


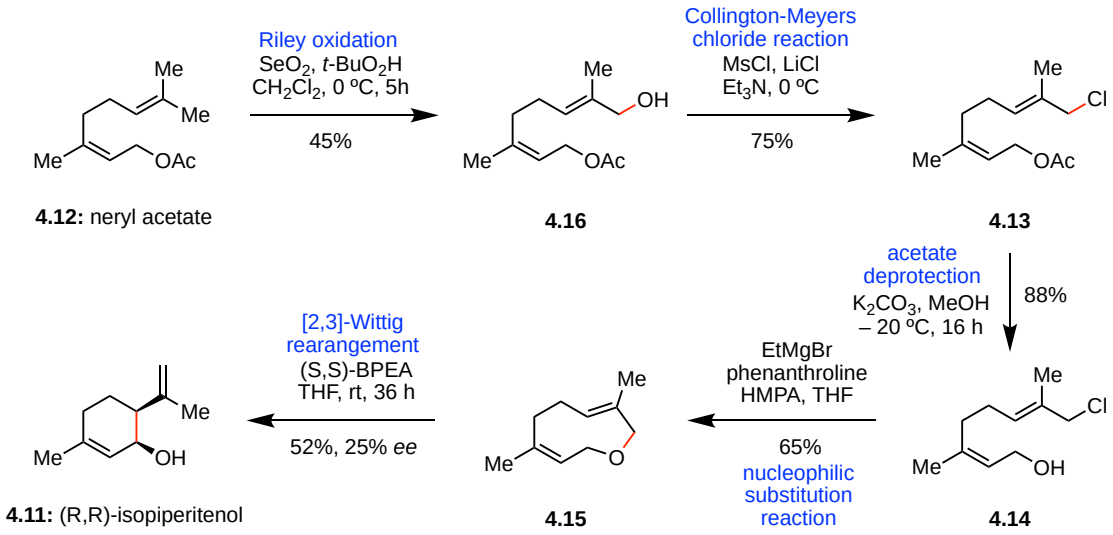
Figure 4.2 – *Rhododendron* Tetracyclic Chromanes with the 6-6-6-4 Ring System

Despite the stereochemically rich nature of the **6-6-6-4** and **6-6-5-4** ring systems, these structures were all isolated as partial racemates, suggesting that their biosynthesis is not under enzymatic control, making them ideal targets towards a biomimetic synthesis.

4.1.2 Total Synthesis of Natural Products Through Functionalized Hydrocarbons

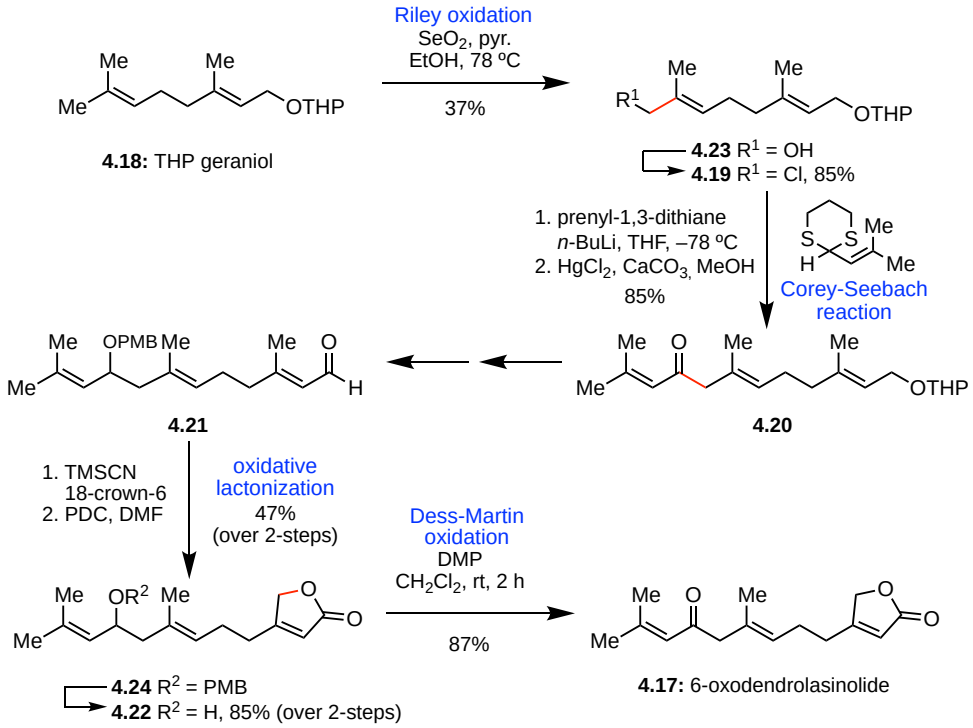
One strategy towards the synthesis of natural products is through functionalized hydrocarbons derived from C_{10} monoterpenoids. There are many advantages to this approach, including the direct access to cheap and abundant starting materials allowing for the synthesis of large quantities of natural products. Additionally, the synthesis of decorated hydrocarbons is often synthetically straightforward, and the electronics of these compounds can be carefully tuned, priming these substrates to undergo unusual cascade reactions and allowing the late-stage diversification of whole families of natural products.

Notable examples include Marshall and Lebreton's synthesis of (R,R)-isopiperitenol (**4.11**) (**Scheme 4.1**).[10] Riley oxidation of neryl acetate (**4.12**) followed by a Collington-Meyers chloride reaction,[10] gave the corresponding chloride **4.13**. Deprotection and cyclization of the resultant alcohol **4.14** through treatment with EtMgBr and HMPA then afforded the diallylic cyclized ether **4.15** in 65%. Finally, a base-induced [2,3]-Wittig rearrangement with (S,S)-BPEA gave (R,R)-isopiperitenol (**4.11**) in 52% and 25% *ee*.



Scheme 4.1 – Marshall and Lebreton's Total Synthesis of (R,R)-isopiperitenol[10]

Another example includes the total synthesis of the sesquiterpene lactone 6-oxodendrolasinolide (**4.17**) reported by Li *et al.* in 2007 (**Scheme 4.2**).[11] This begins with Riley oxidation of the THP protected geraniol **4.18**. An Appel reaction then affords the allylic chloride **4.19**, which undergoes a 2-step Corey-Seebach reaction to give **4.20** in 85%. Functional group manipulation involving reduction, PMB protection, THP deprotection, and oxidation then gives the key functionalized aldehyde **4.21** (in 4-steps). Oxidative lactonization and deprotection then affords **4.22** and finally Dess-Martin periodate oxidation gives 6-oxodendrolasinolide (**4.17**) in 87%.



Scheme 4.2 – Li and Co-Workers Total Synthesis of 6-oxodendrolasinolide[11]

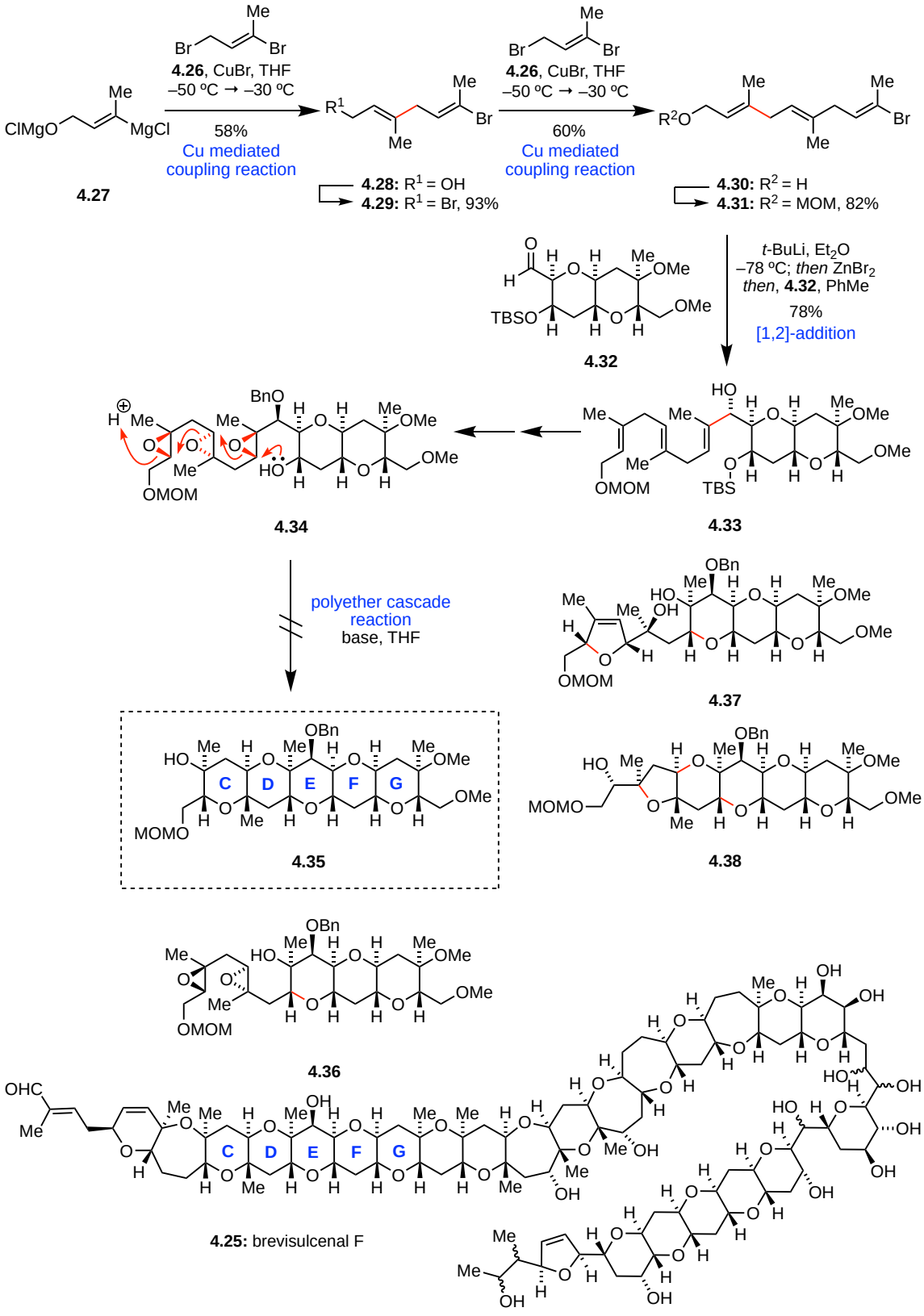
4.1.3 Bio-Inspired Cascade Reactions of Functionalized Hydrocarbons

Functionalized hydrocarbons have also emerged as a powerful strategy in bio-inspired cascade reactions. This can be seen in Jamison and Katcher's efforts towards the **C**, **D**, **E**, **F** and **G** ring of brevisulcenal F (**4.25**) through epoxide ring opening cascades (**Scheme 4.3**).[12]

Coupling of the allylic bromide **4.26** to the Grignard reagent **4.27** afforded diene **4.28** as a single isomer in 58%. An Appel reaction of the allylic alcohol then then gave the bromide **4.29**, followed by another Cu mediated allylation with **4.26** to afford the triene **4.30**. The alcohol was then protected as the MOM ether **4.31** and a 1,2-addition with aldehyde **4.32** afforded **4.33** followed by a 2-step epimerization. Next, a series of Sharpless and Shi epoxidation followed by a Bn protection afforded the key triepoxide **4.34**.

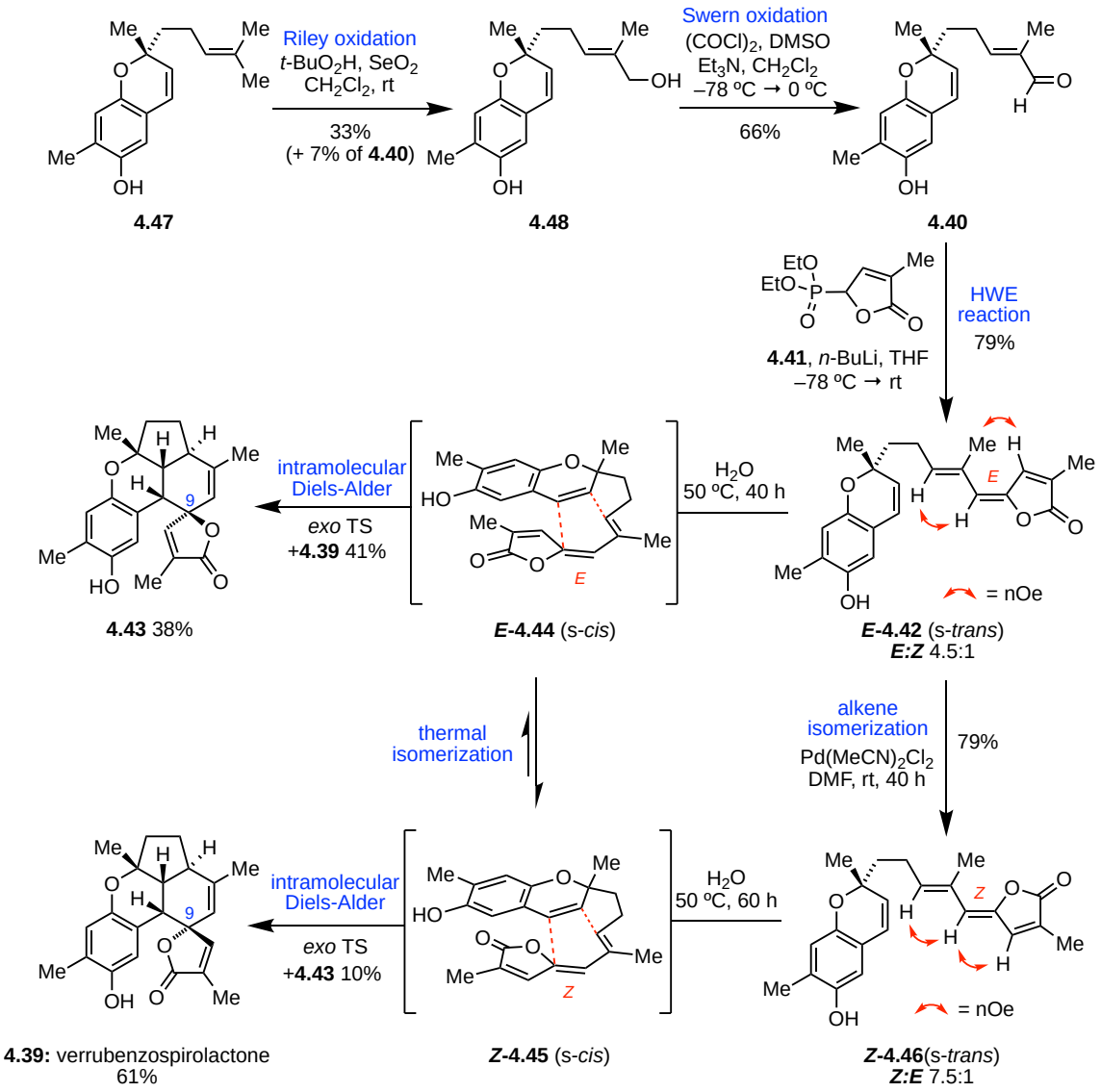
Unfortunately, all attempts towards the target **C**, **D**, and **E** rings of **4.38** were unsuccessful. The key reaction cascade was attempted with KHMDS, however this was only partially successful affording the diepoxide **4.36**. Presumably due to the sterically hindered tertiary alkoxide impeding attack of this nucleophile onto the second epoxide. Formation of the diol **4.37** was also observed, *via* the elimination and subsequent ring opening of **4.36**. Reaction with NaHMDS as a base gave similar results affording **4.36** and **4.37** in a 2:1 ratio. While reaction with LiHMDS afforded the pentad **4.38**, indicating that the **C** ring had cyclized in a 5-*exo* manner rather than the desired 6-*endo* cyclization.

Although the desired product **4.35** was not observed, this impressive attempt towards brevisulcenal (**4.25**) highlights the role of functionalized hydrocarbons in bio-inspired cascade reactions. It is expected that these efforts will provide future insight for the optimization of marine ladder polyether cascade reactions.



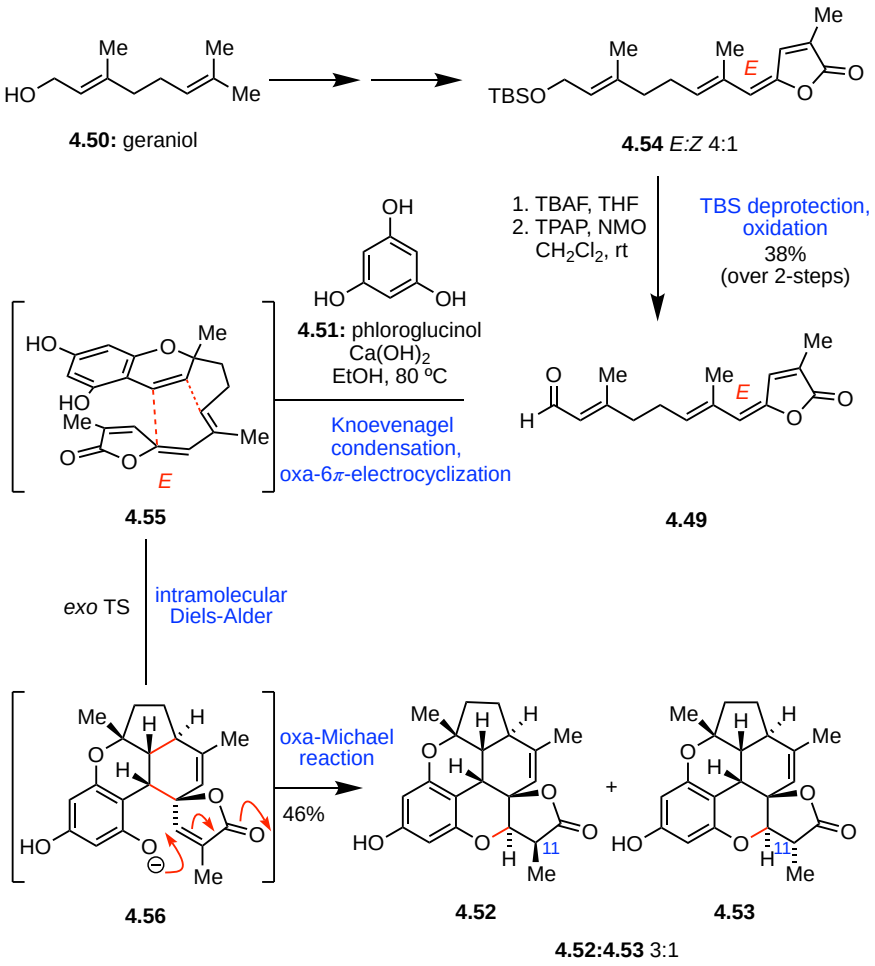
Scheme 4.3 – Jamison and Katcher's Convergent Studies Towards Brevisulcenal F[12]

Work within our group, has also featured bio-inspired cascade reactions of functionalized hydrocarbons. In 2017, Lam and co-workers reported the total synthesis of (±)-verrubenzospirolactone (**4.39**) (**Scheme 4.4**).[13] This 5-step total synthesis features a 2-step Riley oxidation to aldehyde **4.40**, followed by a Horner-Wadsworth-Emmons reaction with phosphonate **4.41** to give the triene *E*-**4.42** in 79%. Heating of ***E*-4.42** at 50 °C gave the intramolecular Diels-Alder product verrubenzospirolactone (**4.39**) in 41% alongside the **C9** epimer **4.43** in 38%. Clearly, some isomerization of ***E*-4.44** into the more stable ***Z*-4.46** occurred, leading to a greater yield of **4.43** than expected. Alkene isomerization using catalytic $(MeCN)_2PdCl_2$ in DMF gave a 7.5:1 mixture in favour of the desired ***Z*-4.43**. Heating of ***Z*-4.46** at 50 °C gave verrubenzospirolactone (**4.39**) in an improved yield of 61%, alongside **4.43** in 10%.



Scheme 4.4 – Lam and Co-Workers Total Synthesis of (±)-Verrubenzospirolactone[13]

Next, the structure of **4.39** was used as motivation for a multibond-forming, quadruple cascade reaction (**Scheme 4.5**). Incorporation of the triene unit into a functionalized aldehyde inspired the synthesis of **4.49** in 6-steps from geraniol **4.50**. Next, the key reaction cascade with phloroglucinol **4.51** involving a Knoevenagel condensation, oxa-6π-electrocyclization, intramolecular Diels-Alder and oxa-Michael sequence. Treatment of **4.49** and **4.51** with $Ca(OH)_2$ generated a 3:1 mixture of **4.52** and **4.53** (**C11** epimers) in 46%. This impressive cascade results in the formation of 7 stereocentres, 4 rings, 3 C—C bonds and 2 C—O bonds in one step!



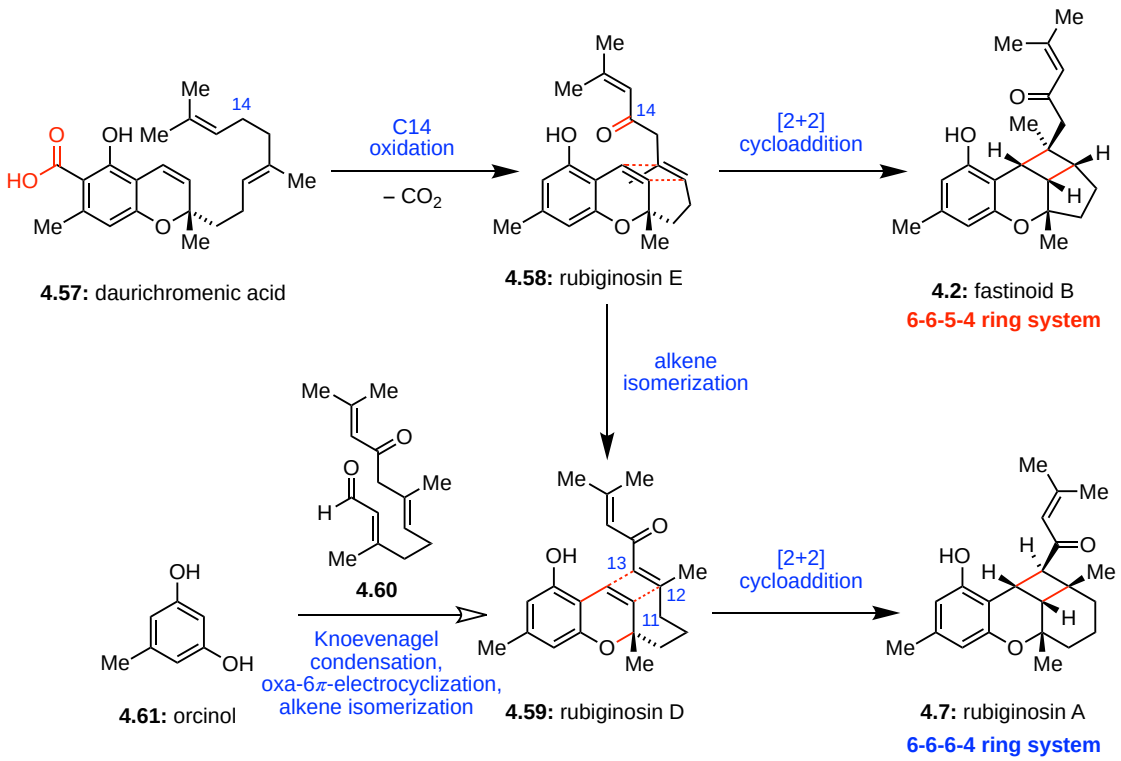
Scheme 4.5 – Cascade Reaction Inspired by Verrubenzospirolactone[13]

4.1.4 Proposed Biosynthesis of the Rubiginosins

Given the co-isolation of the **6-6-5-4** ring system meroterpenoids with the related **6-6-6-4** meroterpenoids and simpler chromene natural products (i.e. daurichromenic acid (**4.57**)),[6] a unified biosynthesis to access both scaffolds was envisaged involving alkene isomerization as the key point of divergence (**Scheme 4.6**).

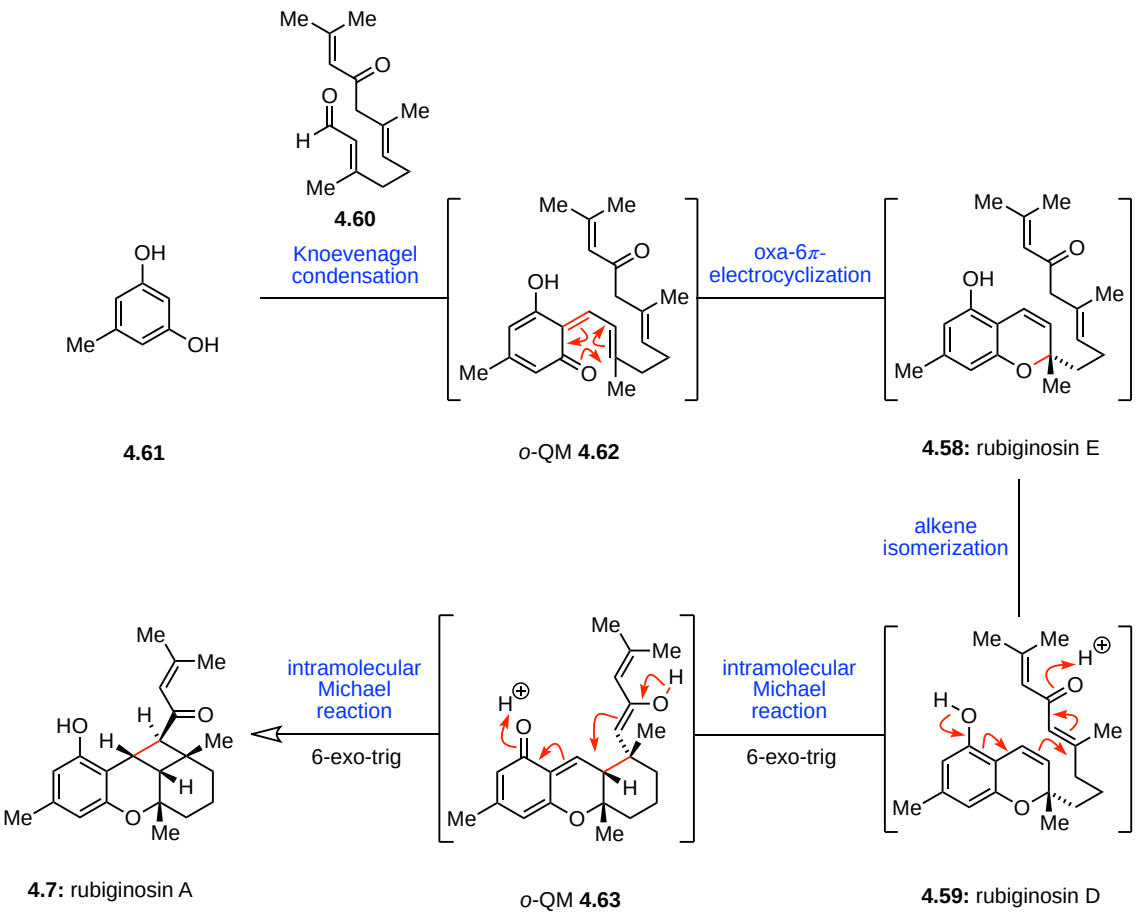
We propose that in nature a **C14** oxidation and decarboxylation of daurichromenic acid (**4.57**) could afford the chromene natural product rubiginosin E (**4.58**). A subsequent [2+2] cycloaddition of **4.58** would then give access to the **6-6-5-4** scaffold. Provided the alkene stereochemistry of **4.58** is retained, this cycloaddition would afford fastinoid B (**4.2**), while rhodonoid B (**4.3**) would presumably be biosynthesized through the *Z*-alkene. Additionally, alkene isomerization of **4.58** (possibly occurring in nature *via* a photochemical [1,3]-H shift) from Δ^{11} to Δ^{12} would give the 2H-chromene rubiginosin D (**4.59**). Due to the conjugation of the α,β-unsaturated enone **4.59**, we thought a stepwise [2+2] cycloaddition to provide access to **6-6-6-4** ring systems (i.e. rubiginosin A (**4.7**)) could be possible.

It was envisaged that most direct route towards a divergent biomimetic synthesis of both chromene natural products, and the **6-6-5-4** and **6-6-6-4** ring systems, would be through the synthesis of a functionalized aldehyde. In this case, the synthesis of a *pre*-oxidised terpene (i.e. **4.60**), which could undergo a Knoevenagel condensation with orcinol **4.61**, and subsequent oxa-6π-electrocyclization to afford the chromene natural products rubiginosin D (**4.59**) and rubiginosin E (**4.58**). It was hoped that subsequent [2+2] cycloadditions could provide direct access to the whole family of *Rhododendron* natural products.



Scheme 4.6 – Proposed Biosynthesis of the Rubiginosins A, D and E, and Fastinoid B

This approach would ideally be accompanied by a second challenge, a one-step cascade combining Knoevenagel condensation, oxa-6π-electrocyclization, alkene isomerization and a formal [2+2] cycloaddition of orcinol **4.61** and aldehyde **4.60** (**Scheme 4.7**). It is hoped that this bio-inspired cascade reaction will allow a short total synthesis of racemic rubiginosin A (**4.7**) forming 5 stereocentres, 3 C-C bonds, 1 C-O bond and 3 rings in a single step!

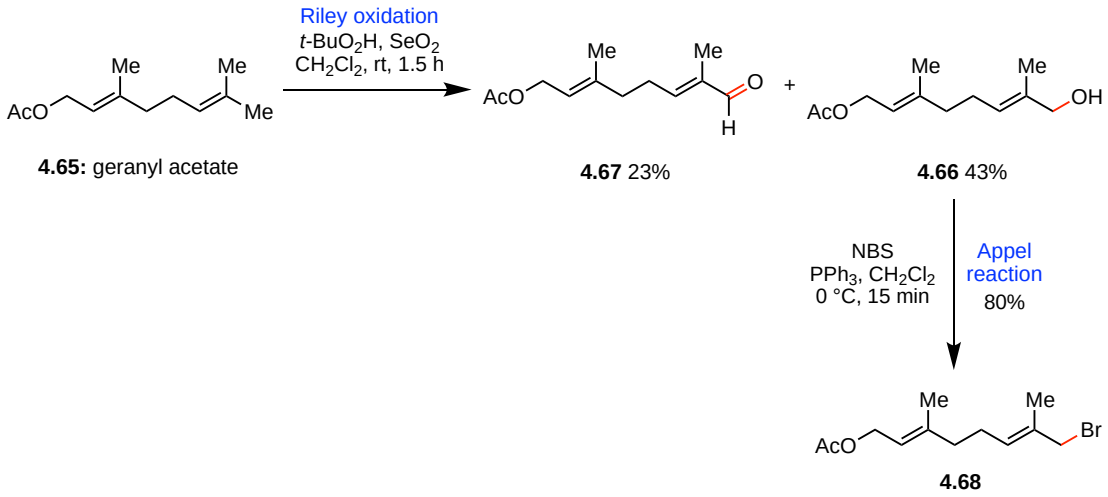


Scheme 4.7 – Bio-inspired Cascade Synthesis of Rubiginosin A

4.2 Results and Discussion

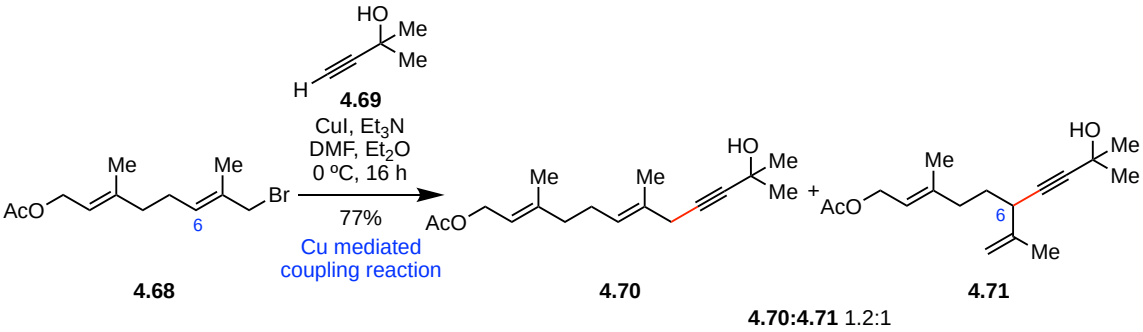
4.2.1 Synthesis of Key Functionalized Aldehydes

Synthesis of two key α,β-unsaturated aldehydes (**4.60** and **4.64**) commenced from geranyl acetate (**4.65**) (**Scheme 4.8**). Following a known procedure from Yeom *et al.* a SeO_2 mediated Riley oxidation afforded 8-hydroxygeraniol **4.66** in 43% yield, alongside the aldehyde **4.67** in 23%.[14] Next, an Appel reaction using stoichiometric NBS and PPh_3 at 0 °C afforded the bromogeranyl acetate **4.68** in 80%.



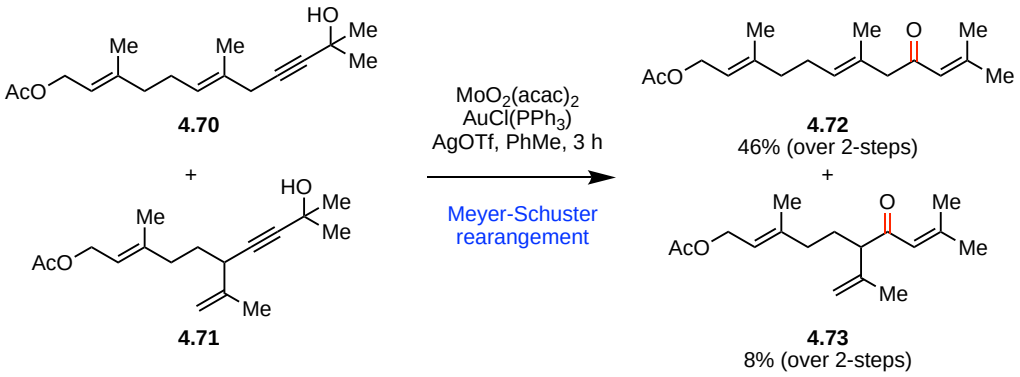
Scheme 4.8 – Synthesis of the allylic bromide 4.68

Substitution of **4.68** with the alkynyl copper derived from the acetylene **4.69** was achieved following a modified procedure by Oehlschlager and co-workers (**Scheme 4.9**).[15] This involved addition of **4.69** to stoichiometric CuI and Et_3N, followed by addition of the bromide **4.68** at 0° C to afford alkynol **4.70**. Unfortunately, a competing S_N2' substitution at **C6** was observed resulting in formation of the by-product **4.71**. All attempt to supress the formation of **4.71** by screening different thermal conditions and addition rates of the bromide **4.68** were unsuccessful. Instead, the inseparable mixture of **4.70** and **4.71** (as a 1.2:1 mixture) was taken on in the next step without further purification.



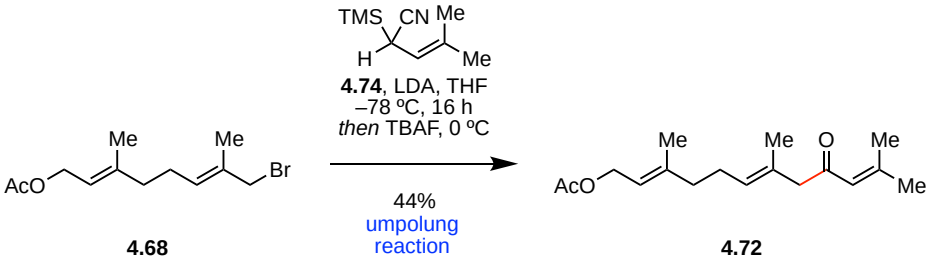
Scheme 4.9 – CuI Mediated Coupling of bromide 4.68 and alkyne 4.69[15]

A Meyer-Schuster rearrangement of alkynol **4.70** and **4.71** then afforded the enone **4.72** in 46%, and **4.73** in 8% (over 2-steps) (**Scheme 4.10**). This was achieved using conditions developed by Hodgson and co-workers, which employed catalytic $AuCl(PPh_3)$, $MoO_2(acac)_2$, and AgOTf.[16]



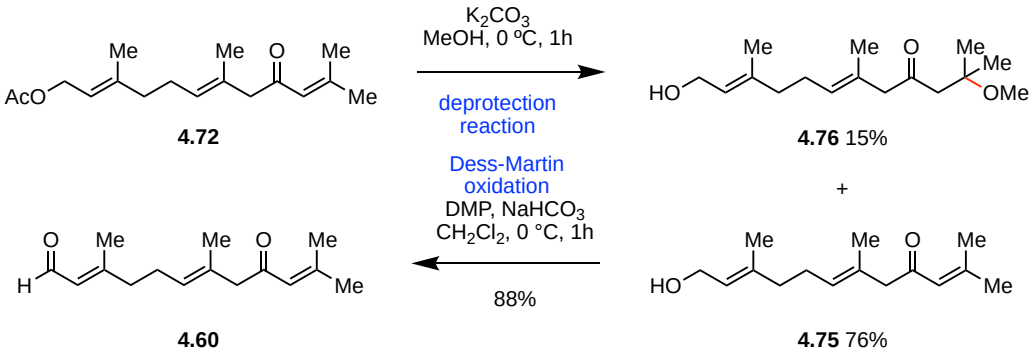
Scheme 4.10 – Meyer-Schuster Rearrangement of alkynol 4.70 and 4.71

Alternatively, following a modified procedure from Li *et al.* a one-pot umpolung coupling with bromide **4.68** and the prenal derived TMS **4.74** in the presence of LDA at –78 °C gave direct access to enone **4.72** in 44% (**Scheme 4.11**).[17] Unfortunately, this result was not reproducible, and reaction gave poor yields upon scale up past ≈ 1 – 2 g.



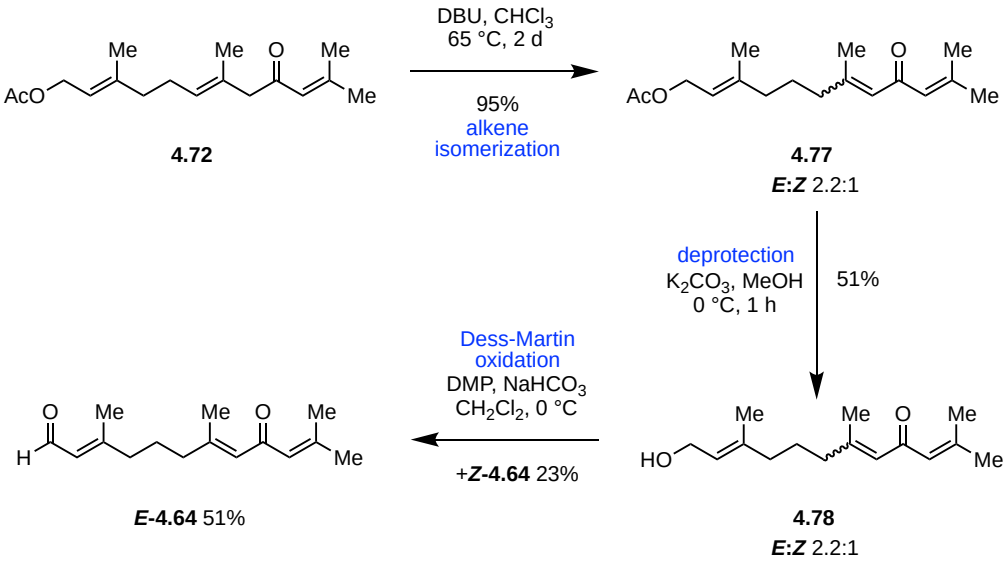
Scheme 4.11 – Umpolung coupling of bromide 4.68 and 4.74

Acetate hydrolysis of **4.72**, afforded **4.75** in 76% alongside the conjugate addition by-product **4.76** in 15% (**Scheme 4.12**). Subsequent Dess-Martin oxidation of the allylic alcohol **4.75** then afforded the key aldehyde **4.60** in 88%.



Scheme 4.12 – Synthesis of Key Aldehyde 4.60

The isomeric aldehyde ***E*-4.64** was also be synthesized this time by employing a DBU catalyzed alkene isomerisation of **4.72**, which afforded the dienone **4.77** in 95% yield as a 2.2:1 mixture of *E*- and *Z*-isomers (**Scheme 4.13**). Deacylation and oxidation of **4.77** then gave the desired aldehyde ***E*-4.64** as a single stereoisomer in 26% over 2-steps (after careful purification by flash column chromatography), alongside a 23% yield of ***Z*-4.64**. High purity aldehyde ***Z*-4.64** could also be obtained by recrystallization in hexanes.



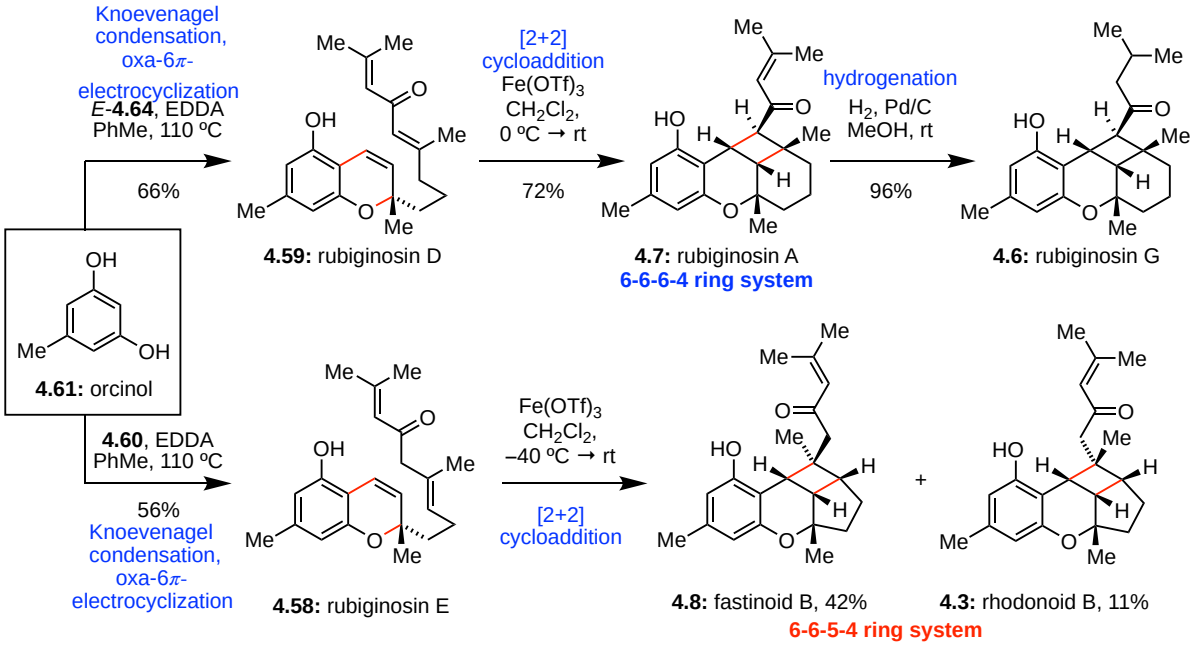
Scheme 4.13 – DBU Alkene Isomerisation of 4.72 to Afford the Key Aldehyde *E*-4.64

With the α,β-unsaturated aldehydes **4.60** and **4.64** in hand, our attention turned toward the synthesis of rubiginosins A, D, E, and G, fastinoid B, C, and Rhodonoid B.

4.2.2 Synthesis of Rubiginosins A, D, E, and G, Fastinoid B, and Rhodonoid B

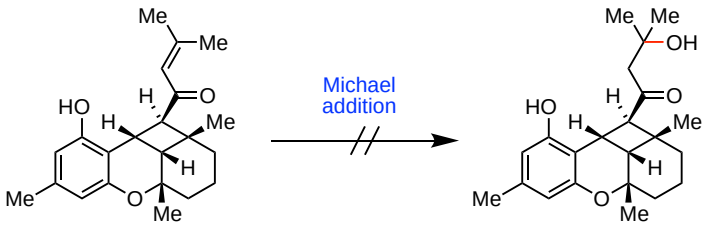
We began our investigation focusing on a less ambitious, stepwise approach that would enable the divergent synthesis of several natural products (**Scheme 4.14**). Chromenylation of **4.61** with aldehyde ***E*-4.64** was achieved using 10 mol% EDDA in PhMe following conditions developed by Lee and co-workers,[18] giving rubiginosin D (**4.59**) as a single regioisomer in 66% yield. Intrestingly, we observed a *trace* of rubiginosin A (**4.7**) in the crude NMR spectra. Next, following a modified procedure from Wu *et al.*, a cationic $Fe(OTf)_3$ [2+2] cycloaddition of **4.59** then afforded rubiginosin A (**4.7**) in 72% yield as a single diastereoisomer.[19] Hydrogenation of the α,β-unsaturated alkene **4.7** then afforded rubiginosin G (**4.6**) in 96% yield.

Additionally, a chromenylation of **4.61** with aldehyde **4.60** in the presence of catalytic EDDA afforded rubiginosin E (**4.58**) in 56% yield. Rubiginosin E was then treated to the analogous $Fe(OTf)_3$ cationic [2+2] cycloaddition conditions, which proceeded non-stereoselective manner forming both fastinoid B (**4.8**, 42% yield) and rhodonoid B (**4.3**, 11% yield), while photochemical and basic conditions were unsuccessful. All attempted conversion of rubiginosin E (**4.58**) to rubiginosin A (**4.7**) *via* UV, photochemical, and acidic conditions only afforded decomposition or no reaction.



Scheme 4.14 – Total Synthesis of Rubiginosins A, D, E, and G, Fastinoid B, and Rhodonoid B

Various conditions towards the synthesis of fastinoid C (**4.10**) through a Michael addition from rubiginosin A (**4.7**) were screened (**Table 4.1**). Unfortunately, reaction of **4.7** with base conditions gave no reaction, while reactions with acid in aqueous conditions only resulted in decomposition (**entries 1 – 4**). Refluxing in water gave no reaction (**entry 5**) and oxy-mercuriation conditions afforded decomposition (**entry 6**).



4.7: rubiginosin A

4.10: fastinoid C

Table 4.1 – Efforts Towards the Total Synthesis of Fastinoid C

Entry	Conditions	Solvent	Temperature	Time	Result
1	K_2CO_3	THF/ H_2O	rt	3 d	**RSM** 37%
2	*p*-TsOH	PhMe/ H_2O	100 °C	6 h	decomp.
3	H_2SO_4	THF/ H_2O	66 °C	5 h	decomp.
4	oxalic acid	DMSO/ H_2O	100 °C	3 h	decomp.
5	--	H_2O	100 °C	3 h	NR
6	$Hg(OAc)_2$ *then* $NaBH_4$, NaOH	THF/ H_2O	66 °C	2 h	decomp.

4.2.3 Bio-Inspired Cascade Reactions of Rubiginosin A

A variety of conditions for the key bio-inspired cascade reaction of rubiginosin A (**4.7**) were investigated (**Table 4.2**). Reaction of the key aldehyde **4.60** with orcinol (**4.61**) was attempted using $Ca(OH)_2$, pyridine, piperidine and Ac_2O conditions (**entries 1 - 3**). Unfortunately, these conditions only gave either decomposition or no reaction. Reaction with Ti(O*i*-Pr)$_4$ only afforded the bis-chromene **4.79** in 39% (**entry 4**). Reaction with 10 mol% EDDA afforded rubiginosin E (**4.58**) in 56%, however was not successful in pushing the key cascade to completion even when left for a longer period of time (**entry 5**). Gratifyingly, employing modified chromenylation conditions from Chauder *et al.* using AcOH and $PhB(OH)_2$ gave rubiginosin A (**4.7**) in 10% with the regio-isomer "iso-rubiginosin A"(**4.80**) in 31%.[20] Interestingly a 2% yield of Ar-turmerone (**4.81**) was observed. (**entry 6**). It was found that increasing the amount of acetic acid led to a diminished yield of rubiginosin A and an increase in Ar-turmerone (**4.81**) 22% yield (**entry 7**).

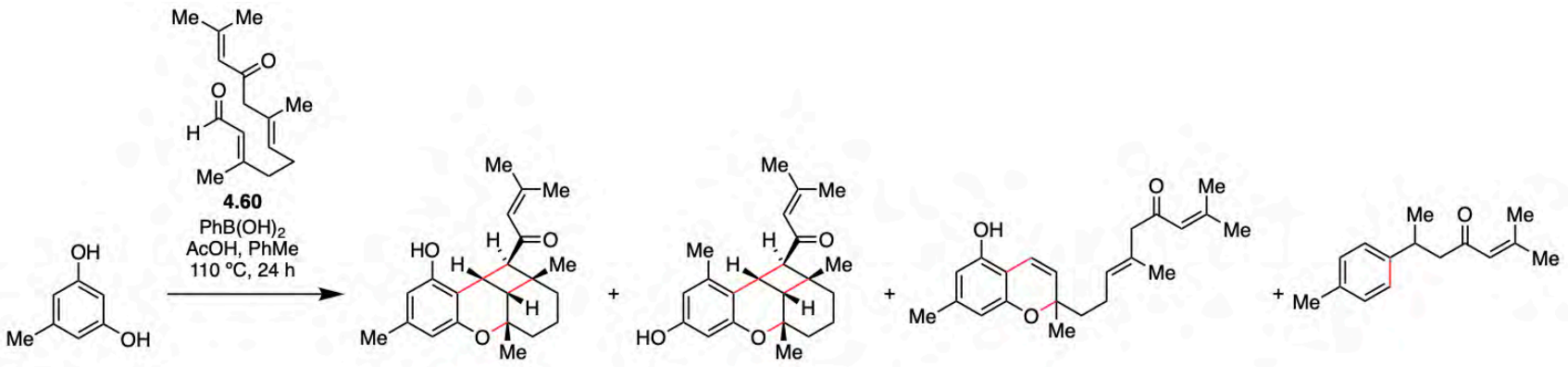
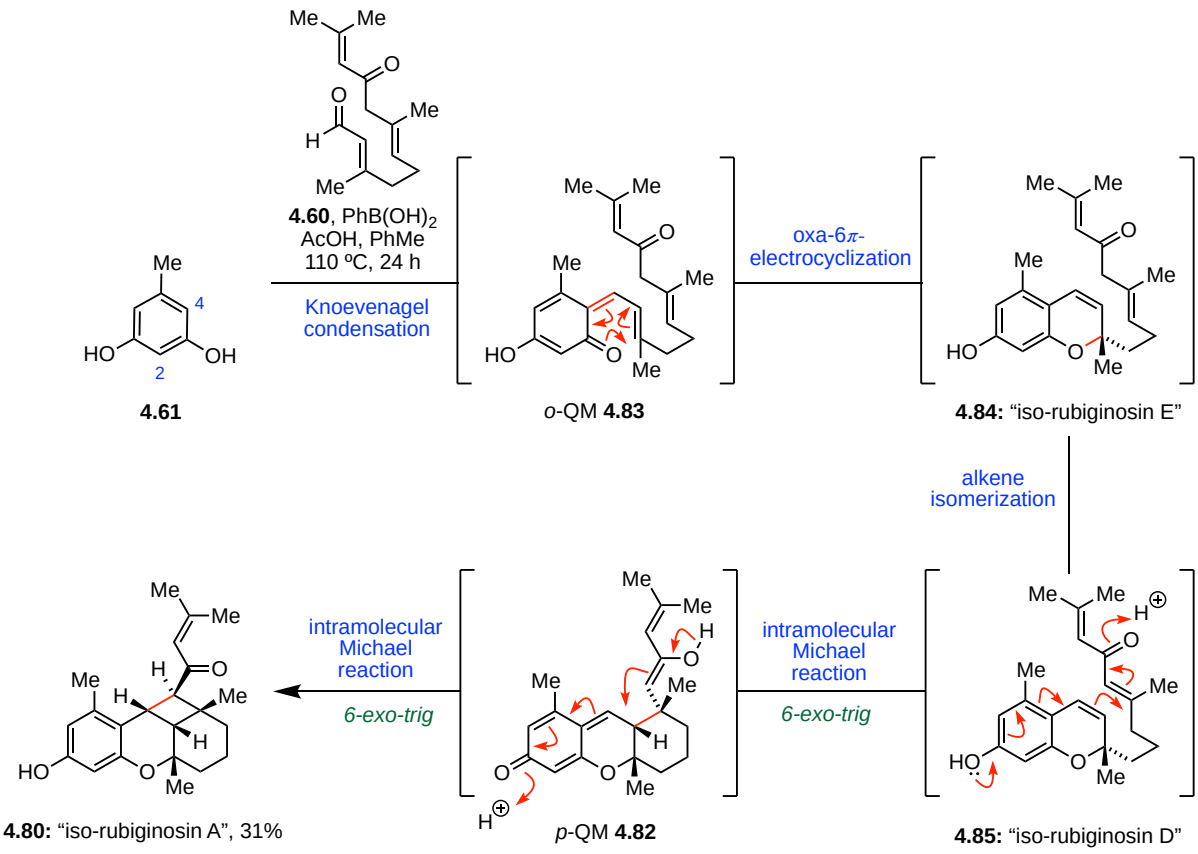


Table 4.2 – Key Bio-Inspired Cascade Reactions of Rubiginosin A (4.7)

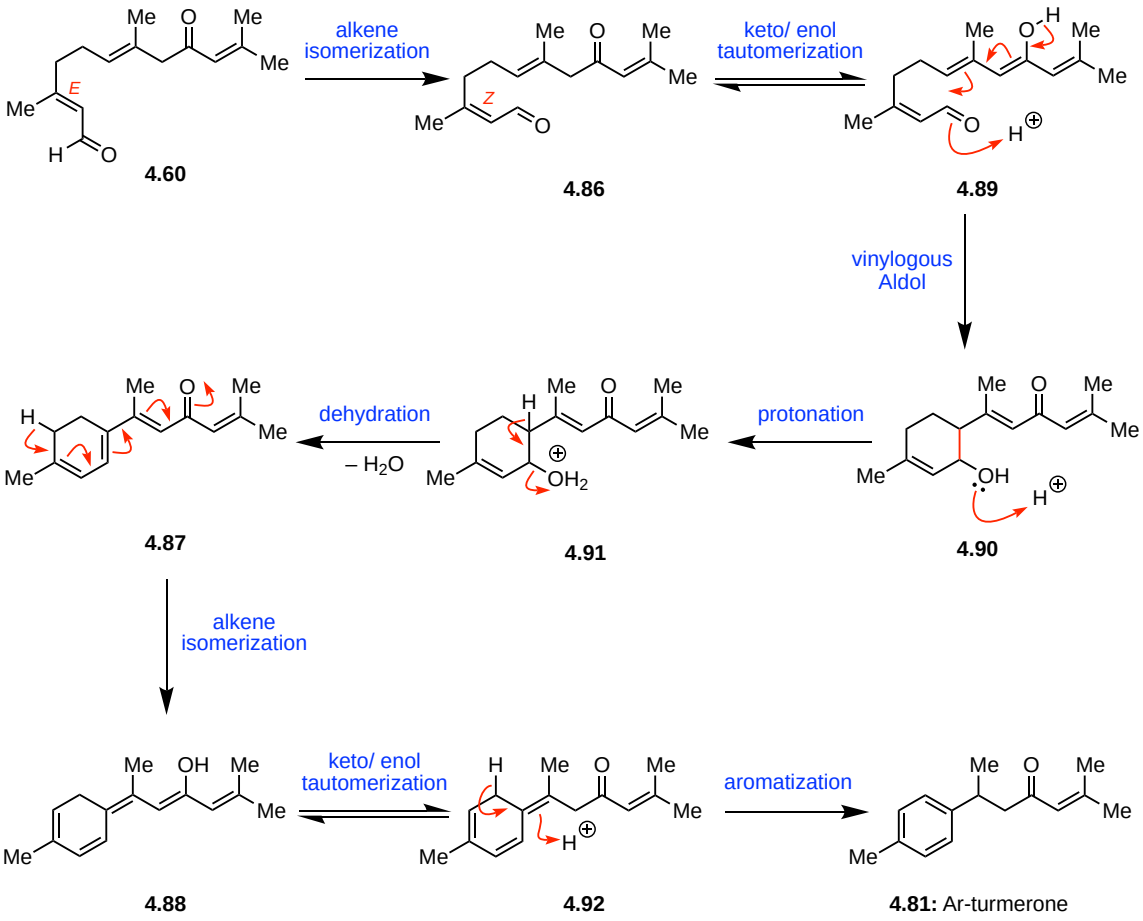
Entry	Conditions	Solvent	Temperature	Time	Result					
					4.7	4.80	4.58	4.81	4.79	Comment
1	$Ca(OH)_2$ (50 mol%)	*i*-PrOH	83 °C	48 h	--	--	--	--	--	NR
2	pyridine	--	115 °C	6 h	--	--	--	--	--	decomp.
3	piperidine (2.2 Equiv.), Ac_2O (2.2 Equiv.)	PhMe	110 °C	1 h	--	--	--	--	--	decomp.
4	$Ti(O\textit{i}\text{-}Pr)_4$ (4.0 Equiv.)	PhMe	–78 °C → rt	16 h	--	--	--	--	39%	--
5	EDDA (10 mol%)	PhMe	110 °C	2 h	--	--	56%	--	--	--
6	$PhB(OH)_2$ (1.5 Equiv.) AcOH (1.0 Equiv.)	PhMe	110 °C	24 h	10%	31%	--	2%	--	--
7	$PhB(OH)_2$ (1.5 Equiv.) AcOH (2.0 Equiv.)	PhMe	110 °C	24 h	3%	--	--	22%	--	--

Presumably, synthesis of "iso-rubiginosin A" (**4.80**) occurs through an analogous route to rubiginosin A (**4.7**) (*vide supra*, **Scheme 4.8**) (i.e. Knoevenagel condensation, oxa-6π-electrocyclization, alkene isomerisation and a stepwise [2+2] cycloaddition), however this time with Knoevenagel condensation occurring at the **C4** position and proceeding through the *p*-QM **4.82** rather than an *o*-QM (**Scheme 4.15**).



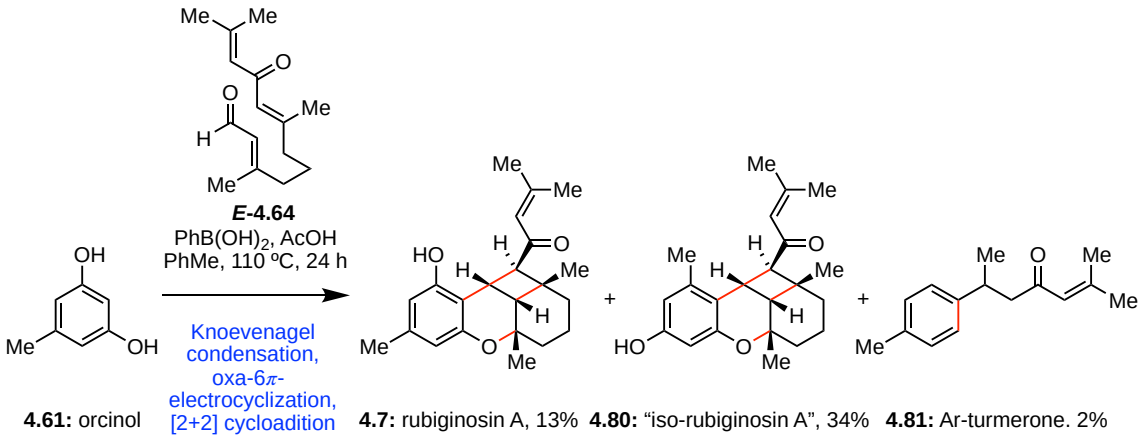
Scheme 4.15 – One-Pot Reaction Cascade of "Iso-Rubiginosin A"

The synthesis of the Ar-turmerone (**4.81**) most likely occurs through an acid catalyzed alkene isomerization of **4.60** to form **4.86**, followed by a vinylogous Aldol condensation to give **4.87**. Finally, alkene isomerization to **4.88** and aromatization to afford Ar-turmerone (**4.81**) in 22%, from reaction with $PhB(OH)_2$, AcOH and reflux in PhMe (**Scheme 4.16**).



Scheme 4.16 – Proposed Mechanism for Ar-turmerone

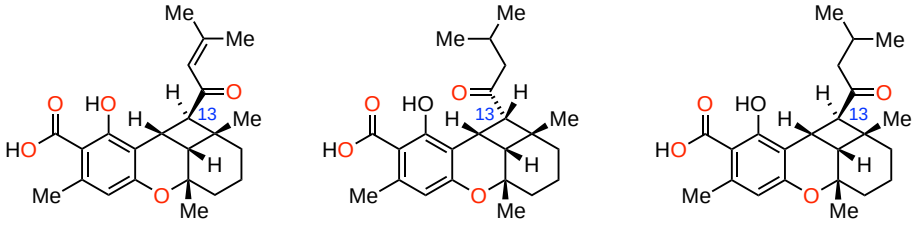
To determine if the alkene isomerization step was responsible for the low overall yield of rubiginosin A (**4.7**), orcinol (**4.61**) was condensed with the pre-isomerized aldehyde ***E*-4.64** (**Scheme 4.17**). Unfortunately, these conditions gave only a slightly improved yield of 13% for rubiginosin A (**4.7**).



Scheme 4.17 – Bio-inspired Cascade Reaction Using Pre-Isomerized Aldehyde *E*-4.64

4.2.4 Structural Revision of Anthopogochromane

To date all *Rhododendron* natural products with the **6-6-6-4** ring system, possess the same relative configuration around the cyclobutane core, except for anthopogochromane (**4.9**) which has the opposite configuration at **C13**. Prompting us to pursue the synthesis of a revised structure of anthopogochromane (**4.93**) (**Figure 4.3**).



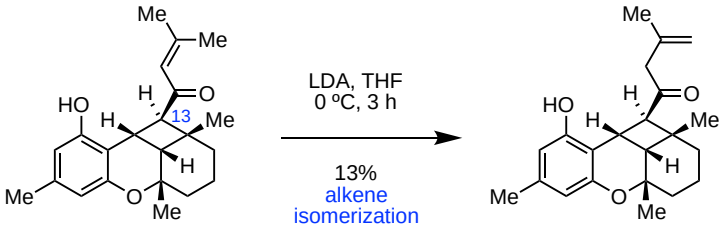
4.8: rubiginosin B

4.9: anthopogochromane *originally proposed structure*

4.93: anthopogochromane *revised structure*

Figure 4.3 – Proposed Structural Revision of anthopogochromane

First, an attempt to epimerize the key **C13** carbon was undertaken using LDA at –78 °C. Unfortunately, however this only resulted in the isomerization of the α,β-unsaturated alkene **4.94** in 13% (**Scheme 4.18**).

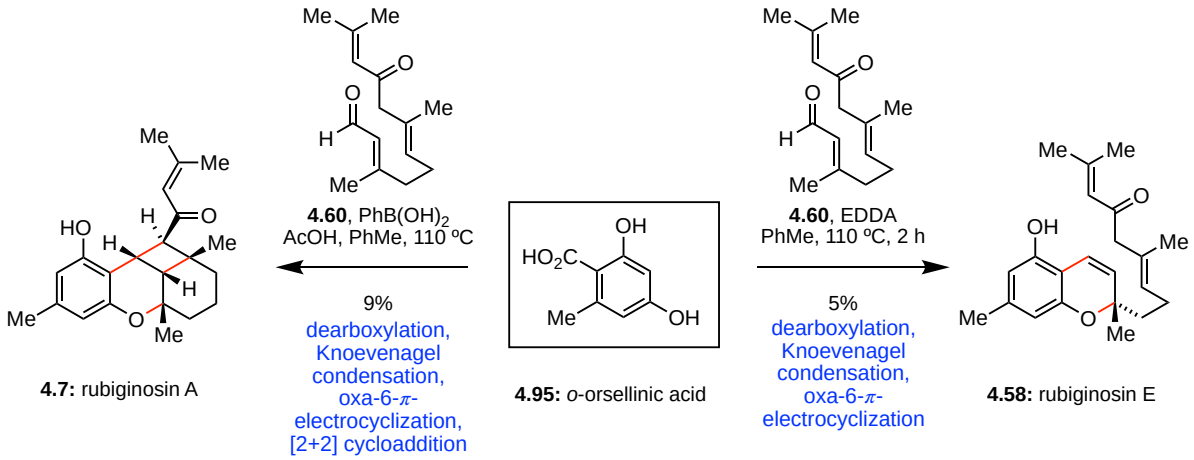


4.7: rubiginosin A

4.94

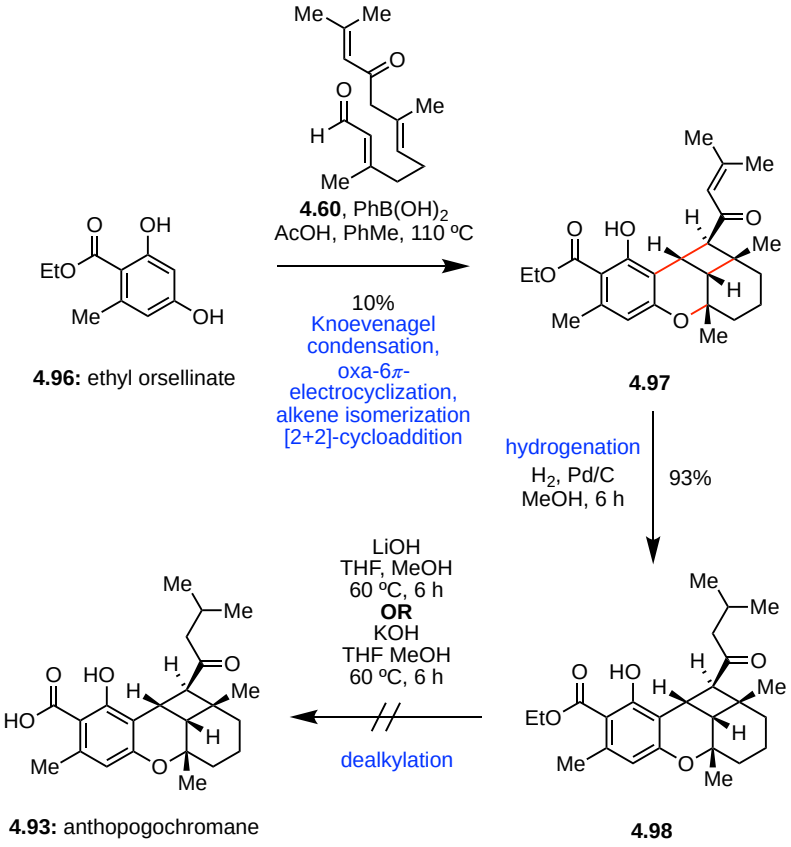
Scheme 4.18 – Attempted Epimerization of Rubiginosin A

Reaction of the key aldehyde **4.60** and with *o*-orsellinic acid **4.95** unfortunately gave the decarboxylated rubiginosin E (**4.58**) presumably due to harsh thermal conditions. While the one-pot reaction cascade conditions (stoichiometric $PhB(OH)_2$ in AcOH/ PhMe) only afforded rubiginosin A (**4.7**) (**Scheme 4.19**).[20] Based on this observation, these same conditions with the lower boiling point solvent benzene were attempted. However, disappointingly no reaction was observed.



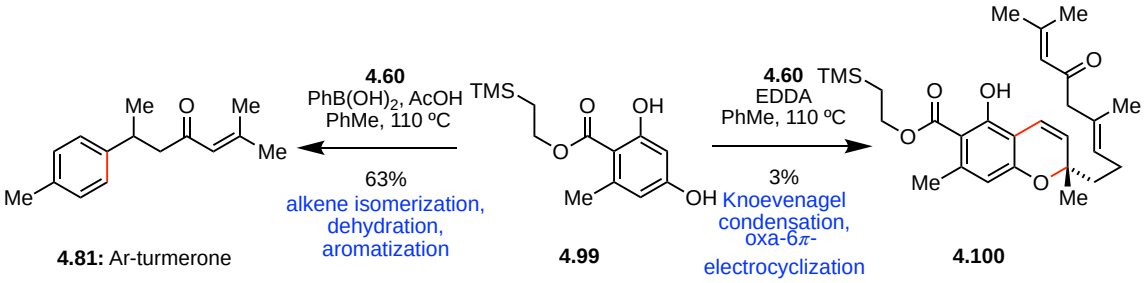
Scheme 4.19 – Reaction of *o*-orsellinic acid with Aldehyde 4.60

In an attempt to avoid the observed decarboxylation, an alternative route using commercially available ethyl orsellinate (**4.96**) was investigated (**Scheme 4.20**). The key Knoevenagel/ oxa-6π-electrocyclization/ alkene isomerisation and formal [2+2] cycloaddition proceeded smoothly to afford **4.97** in 10%. Reduction of the resulting enone using Pd/C hydrogenation conditions then afforded the corresponding ethyl ester **4.98** in 93%. Surprisingly, hydrolysis of the ethyl ester proved difficult. Addition of LiOH at 60 °C THF/ MeOH for 6 h gave only recovered starting material, while KOH led to decomposition.



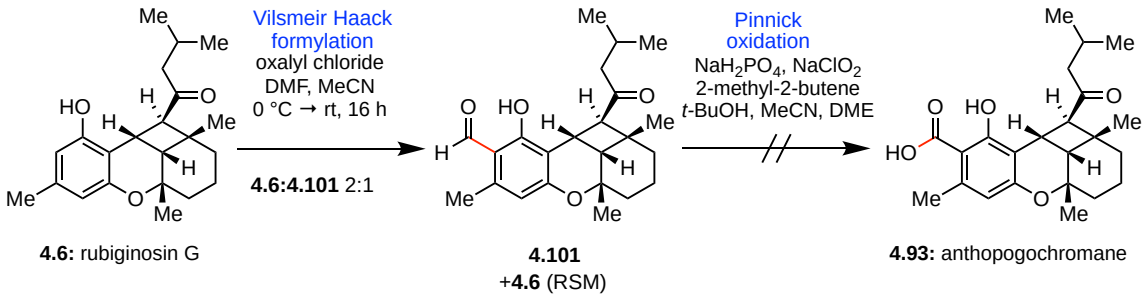
Scheme 4.20 – Reaction of Ethyl Orsellinate with 4.60

With limited access to **4.98**, partially due to the low yielding nature in the synthesis of **4.97** we abandoned this approach and consulted that literature. Similar results by Kang *et al.* also observed the difficult in removing the ethyl ester protected acids, leading us to attempt the key step with a more labile TMS protected ester **4.99**.[21] Unfortunately, reaction conditions with $PhB(OH)_2$ and AcOH only afforded Ar-turmerone (**4.81**). While reaction with $Ca(OH)_2$ gave decomposition of the starting materials. Reflux of the TMS protected acid **4.99** and aldehyde **4.60** with catalytic EDDA gave a 3% yield of the corresponding chromene **4.100**, making it challenging to explore further derivatization to anthopogochromane (**4.93**) (**Scheme 4.21**).



Scheme 4.21 – Reactions of Aldehyde 4.60 with TMS Protected Ester 4.99

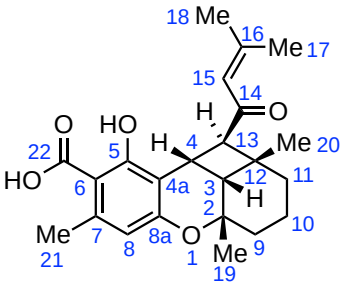
Finally, a two-step formylation/ oxidation of rubiginosin G (**4.6**) was attempted following a modified procedure by Luo and co-workers.[22] Gratifyingly, Vilsmeier-Haack conditions afforded the desired aldehyde **4.101** albeit as a 2:1 mixture of **4.61:4.101**. All attempts to force this reaction to completion through addition of excess oxalyl chloride and use of high temperature conditions was not successful. Unfortunately, attempted oxidation of this mixture to anthopogochromane (**4.93**) only resulted in decomposition (**Scheme 4.22**).



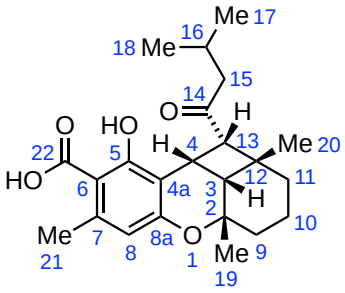
Scheme 4.22 – Attempted Oxidation of Rubiginosin G to Anthopogochromane

Despite our best efforts, attempts towards the synthesis of **4.93** remained elusive. Instead, we compared the reported ^{1}H NMR spectra of anthopogochromane to rubiginosin B (**4.8**), whose structure was unequivocally proven by single crystal X-ray diffraction (**Table 4.3**). We found that these

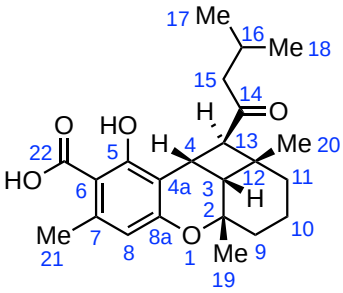
NMR spectra to be almost identical, including diagnostic chemical shifts and coupling constants for **H3**, **H4** and **H13** around the cyclobutane ring.



4.8: rubiginosin B



4.9: anthopogochromane
originally proposed structure



4.93: anthopogochromane
revised structure

Table 4.3 – NMR comparison of Rubiginosin B and Anthopogochromane

NMR Assignment	Rubiginosin B ($CDCl_3$) Yang *et al.* (2018)[7]		Anthopogochromane ($CDCl_3$) Kitanaka *et al.* (2010)[8]	
	^{1}H NMR (600 MHz)	^{13}C NMR (150 MHz)	^{1}H NMR (500 MHz)	^{13}C NMR (125 MHz)
2	--	77.4	--	77.2
3	1.89 (d, *J* = 9.8 Hz)	46.5	1.88 (d, *J* = 9.1 Hz)	46.3
4	4.27 (dd, *J* = 9.8, 8.9 Hz)	24.0	4.24 (dd, *J* = 9.1, 8.5 Hz)	23.8
4a	--	114.0	--	113.3
5	--	161.1	--	160.3
6	--	105.2	--	104.7
7	--	142.5	--	142.3
8	6.35 s	114.8	6.33 (s)	114.6
8a	--	160.7	--	160.9
9	1.35 (m) 2.08 (m)	36.3	2.15 (m)	36.2
10	1.64 (m) 1.98 (m)	17.2	1.38 (m)	17.2
11	1.25 (m) 1.84 (m)	34.1	1.61 (m)	34.0
12	--	39.0	--	38.8
13	3.01 (d, *J* = 8.9 Hz)	57.5	3.00 (d, *J* = 8.5 Hz)	56.4
14	--	200.2	--	210.2
15	5.97 (s)	123.5	2.25 (m)	51.9
16	--	155.9	2.13 (m)	24.1
17	2.14 (s)	21.1	0.84 (d, *J* = 6.2 Hz)	22.8
18	1.85 (s)	28.0	0.84 (d, *J* = 6.2 Hz)	22.8
19	1.06 (s)	29.0	1.05 (s)	29.0
20	1.12 (s)	25.5	1.13 (s)	25.4
21	2.54 (s)	24.3	2.52 (s)	24.4
22 (COOH)	--	175.1	11.75 (s)	174.8

The primary argument for the originally proposed anthopogochromane **4.9** was based on an observed NOE interaction between **H13** and **H4** (**Figure 4.4**). However, in our obtained NMR spectra we also noticed a weak NOE interaction between the **H13** and **H4** protons of synthetic rubiginosin A (**4.7**) and rubiginosin G (**4.6**). However, we observed a stronger, more diagnostic interaction between **H13** and **H10** which confirms the relative configuration. We therefore propose a structural revision of anthopogochromane to **4.93**. This reassignment is also supported by our biosynthetic proposal of anthopogochromane through a stereoselective stepwise [2+2] cycloaddition of anthopogochromene (**4.93**).

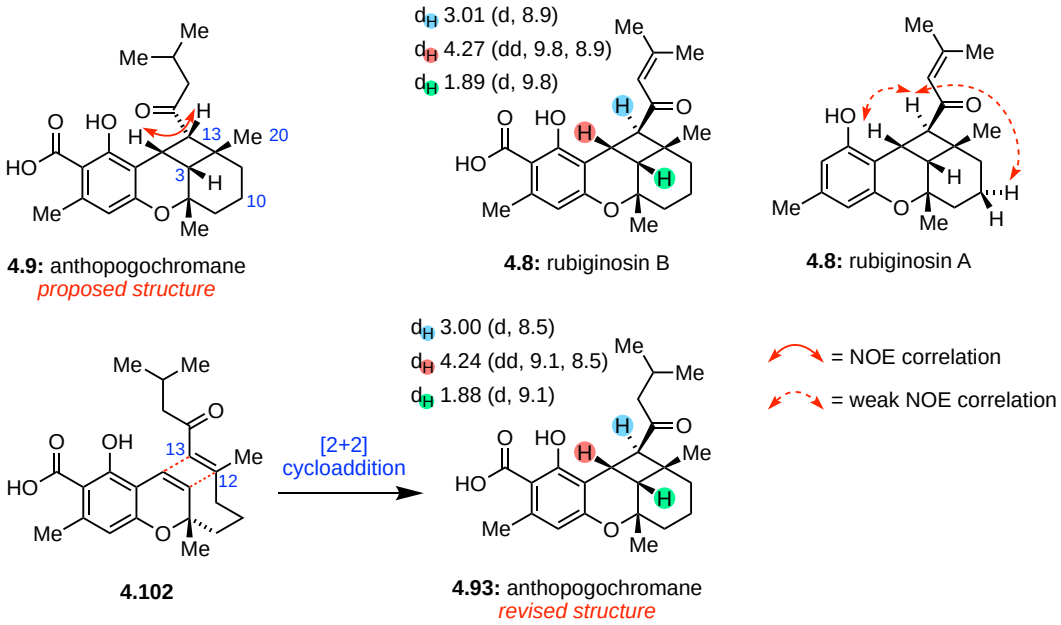


Figure 4.4 – Structural Revision of Anthopogochromane

4.3 Conclusion

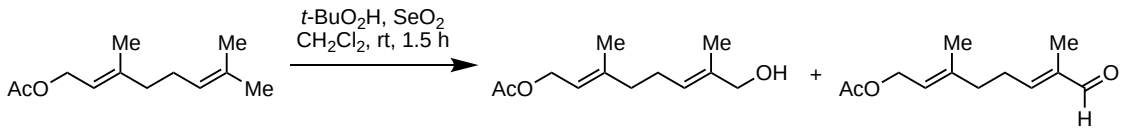
In summary, we report the synthesis of 6 members of the rubiginosin family of *Rhododendron* merosesquiterpenoids using a bio-inspired strategy. Synthesis of functionalized aldehydes **4.60** and **4.64** allowed us direct access to both **6-6-6-6** and **6-6-5-4** ring systems in both stepwise and cascade sequences. Unfortunately, efforts towards synthesizing a revised structure of anthopogochromane **4.93** proved elusive. However, re-evaluation of the NMR data for anthopogochromane indicates that a structural revision is required.[23]

4.4 Experimental

4.4.1 General Methods

All chemicals used were purchased from commercial suppliers and used as received. All reactions were performed under an inert atmosphere of N_2 unless otherwise stated. Thin layer chromatography was performed using aluminium sheets coated with silica gel. Visualization was aided by viewing under a *UV* lamp and staining with the appropriate stain followed by heating. All R_f values were measured to the nearest 0.05. Flash chromatography was performed using 40-63 micron grade silica gel. Melting points were recorded on a digital melting point apparatus and are uncorrected. Infrared spectra were recorded using an FT-IR spectrometer as the neat compounds. High field NMR was recorded using a 600 MHz spectrometer (^{1}H at 600 MHz, ^{13}C at 150 MHz) or a 500 MHz spectrometer (^{1}H at 500 MHz, ^{13}C at 125 MHz). The solvent used for NMR spectra was $CDCl_3$ unless otherwise specified. ^{1}H chemical shifts are reported in ppm on the δ-scale relative to TMS (δ 0.0) and ^{13}C{^{1}H} NMR are reported in ppm relative to chloroform (δ 77.16). Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet and (m) multiplet. All J-values were rounded to the nearest 0.1 Hz. ESI high resolution mass spectra were recorded on a Q-TOF mass spectrometer. Photochemistry with *UVA* light was performed using a generic brand commercial LED *UV* light globe; wavelength: 365 nm. Photochemistry with *UVC* light was performed using a generic brand commercial LED *UV* light globe; wavelength: 254 nm. Photochemical reactions with visible light were performed with a conventional commercial LED desk lamp at 240 V with a 4 W 5000 K 32 mÅ globe. Reactions conducted under 470 nm blue LED lamp were performed using a 19-24VDC 40W Kessil A160WE.

4.4.2 Experimental Procedures



4.65: geranyl acetate **4.66** 43% **4.67** 23%

To a solution of geranyl acetate (**4.65**) (20.0 g, 102 mmol, 1.0 equiv.) in CH_2Cl_2 (500 mL) at room temperature was added SeO_2 (4.53 g, 40.8 mmol, 40 mol%), and *t*-BuO_2H (55.6 mL, 306 mmol, 5.50 M in decane, 30 mol%). The reaction was stirred at room temperature for 1.5 h, then quenched with sat. $Na_2S_2O_{3(aq)}$ (500 mL). The organic layer was separated, and further extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were filtered, then washed with brine (400 mL) and the organic layer dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (5:1 → 1:1 hexanes/ Et_2O, gradient elution) to afford aldehyde **4.67** (4.94 g, 23%) and the desired allylic alcohol **4.66** (9.05 g, 43%) as yellow oils. Data for **4.66** and **4.67** matched that previously reported in the literature.[14]

Data for 4.66:

R_f: 0.40 (2:1 hexanes/ EtOAc).

FTIR (neat): 3428, 2921, 1738, 1444, 1366, 1233, 1022, 954 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.36 – 5.33 (m, 2H), 4.58 (d, *J* = 7.1 Hz, 2H), 3.99 (s, 2H), 2.18 – 2.16 (m, 2H), 2.10 – 2.08 (m, 2H), 2.05 (s 3H), 1.70 (s, 3H), 1.66 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 141.8, 135.4, 125.5, 118.9, 69.1, 61.6, 39.2, 25.8, 21.2, 16.5, 13.8 ppm.

HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{12}H_{19}O_3$ 211.1340; found 211.1344.

Data for 4.67:

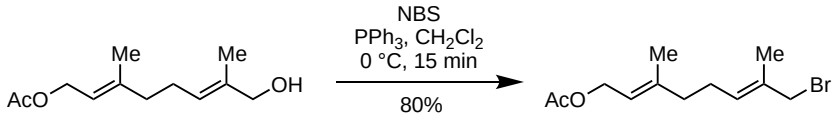
R_f: 0.75 (2:1 hexanes/ EtOAc).

FTIR (neat): 2417, 2977, 1736, 1075, 1445, 1381, 1364, 1231, 1024, 845 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.34 (s, 1H), 6.40 (t, *J* = 6.9 Hz, 1H), 5.34 (t, *J* = 7.5 Hz, 1H), 4.54 (d, *J* = 7.0 Hz, 2H), 2.45 (q, *J* = 7.5 Hz, 2H), 2.19 (t, *J* = 7.6 Hz, 2H), 2.00 (s, 3H), 1.70 (s, 3H), 1.70 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 195.1, 171.0, 153.4, 140.4, 139.7, 119.7, 61.1, 37.8, 27.0, 21.0, 16.4, 9.2 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{12}H_{19}O_3$ 211.1329; found 211.1331.



4.66 **4.68**

To a solution of allylic alcohol **4.66** (24.0 g, 113 mmol, 1.0 equiv.) in CH_2Cl_2 (400 mL) was added PPh_3 (38.5 g, 147 mmol, 1.3 equiv.). The mixture was cooled to 0 °C, then NBS (26.2 g, 147 mmol, 1.3 equiv.) was added portion-wise. The reaction was stirred at 0 °C for 5 min, then warmed to room temperature and stirred for a further 10 min. The reaction was quenched by addition of sat. $Na_2S_2O_{3(aq)}$ (300 mL), and the organic layer separated and concentrated *in vacuo*. The residue was dissolved in dichloromethane (30 mL), then Et_2O (200 mL) and hexanes (400 mL) were added. The resultant suspension was filtered through celite, removing excess triphenylphosphine oxide, and succinamide. The filtrate was then concentrated, and residue purified by flash column chromatography on SiO_2 (10:1 → 6:1 hexanes/ Et_2O, gradient elution) to afford the allylic bromide **4.68** (25.0 g, 80%) as a clear oil. Data for **4.68** matched that previously reported in literature.[24]

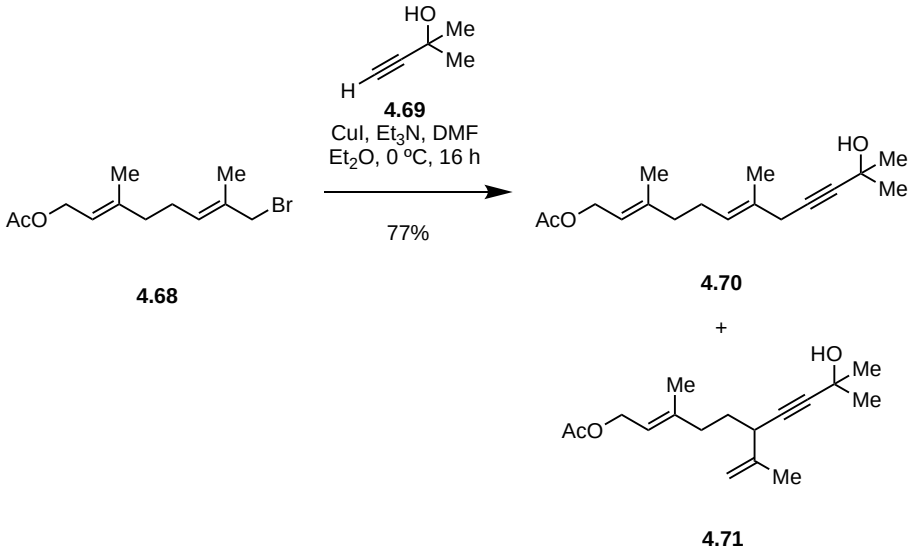
Data for 4.68:

R_f: 0.40 (4:1 hexanes/ EtOAc).

FTIR (neat): 3424, 2964, 1738, 1444, 1366, 1220, 1024, 756 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.56 (t, *J* = 7.0 Hz, 1H), 5.35 – 5.33 (m, 1H), 4.58 (dd, *J* = 7.1, 2.1 Hz, 2H), 3.96 (s, 2H), 2.19 – 2.15 (m, 2H), 2.10 – 2.09 (m, 2H), 2.06 (s, 3H), 1.76 (s, 3H), 1.70 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 141.5, 132.6, 130.6, 119.0, 61.4, 41.7, 38.7, 26.6, 21.2, 16.6, 14.8 ppm.



Using modified conditions from Oehlschlager *et al.*,[15] CuI (13.0 g, 68.2 mmol, 1.2 equiv.) was added to a solution of 2-methylbut-3-yn-2-ol (**4.69**) (6.60 mL, 68.2 mmol, 1.2 equiv.) and Et_3N (9.50 mL, 68.2 mmol, 1.2 equiv.) in DMF (80 mL) and Et_2O (80 mL) and the reaction mixture was stirred for 1 h at room temperature. A solution of allylic bromide **4.68** (14.8 g, 56.7 mmol, 1.0 equiv.) in Et_2O (80 mL) was added to the reaction mixture and stirred for a further 16 h at room temperature. The reaction mixture was quenched with sat. $NH_4Cl_{(aq)}$ (80 mL). The aqueous layer was extracted with Et_2O (3 × 80 mL) and the combined organic extracts were dried with $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography on SiO_2 (4:1 hexanes/ EtOAc) to give a yellow oil of the propargylic alcohols **4.70** and **4.71** (9.97 g, 77%) as a 1.2:1 mixture. These products were then taken on as a crude mixture and used without further purification.

Data for 4.70:

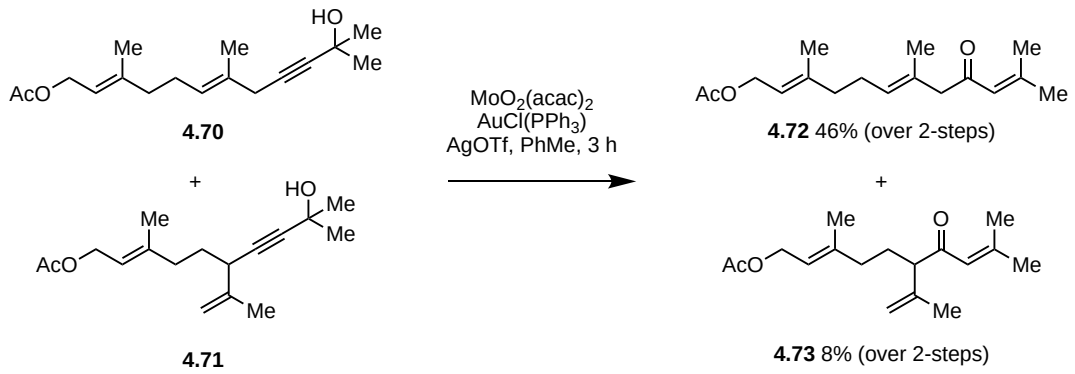
R_f: 0.20 (20:1 hexanes/ EtOAc).

FTIR (neat): 3428, 2981, 1736, 1443, 1365, 1232, 1167, 1023, 949, 754, 667 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.35 – 5.34 (m, 2H), 4.59 (d, *J* = 7.0 Hz, 2H), 2.87 (s, 1H), 2.14 (t, *J* = 7.2 Hz, 2H), 2.07 – 2.05 (m, 2H), 2.05 (s, 3H), 1.71 (s 3H), 1.65 (s, 3H), 1.51 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 141.7, 130.5, 125.1, 118.7, 112.2, 87.6, 80.0, 65.4, 61.5, 39.3, 31.9, 28.7, 26.2, 21.1, 19.8, 16.2 ppm.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{26}O_3Na$ 301.1774; found 301.1777.



Using modified conditions from Hodgson *et al.*,[16] $MoO_2(acac)_2$ (712 mg, 1.66 mmol, 5 mol%), $AuCl(PPh_3)$ (1.07 mg, 2.18 mmol, 5 mol%) and AgOTf (560 mg, 2.18 mmol, 5 mol%) were added successively to a 1.2:1 mixture of alkyne **4.70** and **4.71** (9.97 g, 43.7 mmol, 1.0 equiv.) in dry toluene (350 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h, filtered through a pad of Celite and washed with Et_2O (500 mL). The filtrate was concentrated and purified by flash column chromatography on SiO_2 (9:1 hexanes/ EtOAc) to afford **4.73** (904 mg, 8% over 2-steps) and **4.72** (5.94 g, 46% over 2-steps) as a yellow oil.

Data for 4.72:

R_f: 0.20 (9:1 hexanes/ EtOAc).

FTIR (neat): 2975, 1738, 1685, 1618, 1446, 1380, 1333, 1233, 1024, 915, 732 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.11 – 6.10 (m, 1H), 5.36 – 5.33 (m, 1H), 5.26 – 5.22 (m, 1H), 4.58 (d, *J* = 6.9 Hz, 2H), 3.04 (s, 2H), 2.21 – 2.15 (m, 2H), 2.14 (d, *J* = 1.3 Hz, 2H), 2.10 – 2.07 (m, 2H), 2.05 (s, 3H), 1.88 (d, *J* = 1.3 Hz, 3H), 1.71 (s, 3H), 1.62 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 199.4, 171.3, 155.8, 142.1, 130.3, 128.6, 123.0, 118.7, 61.5, 55.5, 39.3, 27.8, 26.5, 21.2, 20.8, 16.6, 16.6 ppm.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{26}O_3Na$ 301.1774; found 301.1777.

Data for 4.73:

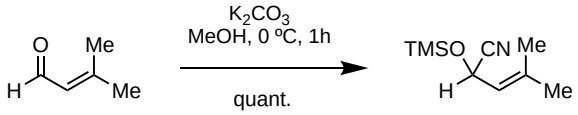
R_f: 0.30 (9:1 hexanes/ EtOAc).

FTIR (neat): 2936, 1737, 1685, 1621, 1440, 1367, 1230, 1022, 967, 912 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.11 – 6.10 (m, 1H), 5.30 (t, *J* = 7.3 Hz, 1H), 4.90 (t, *J* = 1.6 Hz, 1H), 4.86 – 4.87 (m, 1H), 4.54 (d, *J* = 7.0 Hz, 2H), 3.03 – 3.00 (m, 1H), 2.10 (s, 3H), 2.01 (s, 3H), 1.92 – 1.90 (m, 3H), 1.84 (s, 3H), 1.65 (s, 3H), 1.60 (s, 3H), 1.61 – 1.55 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.1, 171.1, 155.9, 143.2, 141.9, 122.9, 118.8, 114.7, 61.4, 60.9, 37.2, 27.8, 26.5, 21.1, 20.8, 19.9, 16.4 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{27}O_3$ 279.1955; found 279.1956.



4.103: prenal

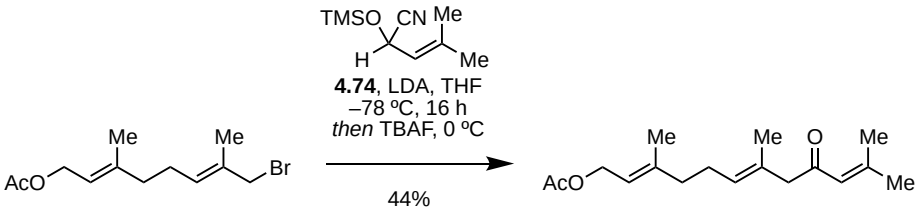
4.74

Using modified conditions from Li and co-workers,[17] TMSCN (1.61 g, 13.9 mmol, 1.2 equiv.) was added to prenal **4.103** (1.27 mL, 11.6 mmol, 1.0 equiv.) and K_2CO_3 (240 mg, 1.74 mmol, 15 mol%) at room temperature. The reaction was left to stir for 16 h, then concentrated in *vacuo* and purified *via* flash column chromatography on SiO_2 (5:1 hexanes/ EtOAc) to afford **4.74** (2.21 g, quant.) as a yellow oil. Data for **4.74** matched that previously reported.[17]

Data for 4.74

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.37 – 5.33 (m, 1H), 5.08 (d, *J* = 8.6 Hz, 1H), 1.78 (s, 3H), 1.73 (s, 3H), 0.20 (s, 9H) ppm.

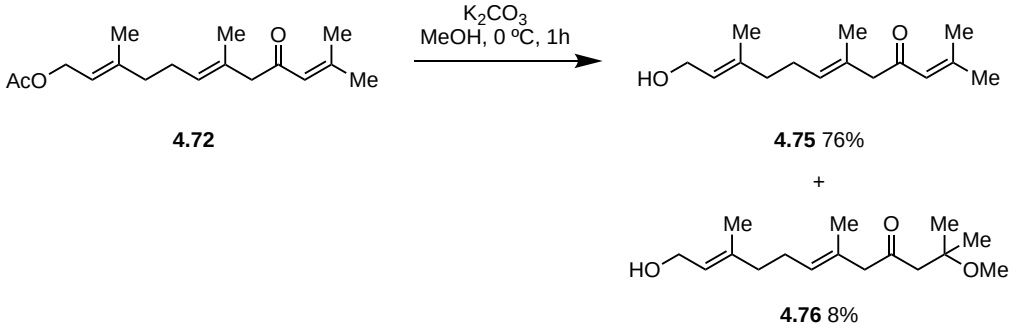
^{13}C NMR (125 MHz, $CDCl_3$): δ 120.5, 60.1, 45.1, 24.3, 22.7, 22.1, –0.2 ppm.



4.68 **4.72**

To a solution of diisopropyl amine (0.81 mL, 5.75 mmol, 1.5 equiv.) in dry THF (10 mL) at –78 °C was added *n*-BuLi (2.3 mL, 2.5M in hexane, 1.5 equiv.). The solution was warmed to 0 °C and left to stir for 5 min, then cooled back to –78 °C and the TMSCN reagent **4.74** (760 mg, 5.75 mmol, 1.5 equiv.) added. Next, the allylic bromide **4.68** (1.0 g, 3.83 mmol, 1.0 equiv.) in THF (7 mL) was added dropwise to the solution and the reaction was left to stir at –78 °C for 3 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (10 mL) and the organic layer extracted (3 x 10 mL), dried with $MgSO_4$, filtered and concentrated.

The crude residue was dissolved in THF (5 mL) and TBAF (3.83 mL, 1.0 M in THF, 1.0 equiv.) was added dropwise at room temperature. After 5 min the reaction was quenched with sat. brine (5 mL) and the product extracted CH_2Cl_2 (3 x 5 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* flash column chromatography on SiO_2 (9:1 hexanes/ EtOAc) then afforded **4.72** (473 mg, 44%) as a yellow oil. Data for **4.72** matched that previously obtained.



4.72 **4.75** 76% **4.76** 8%

To a solution of ketone **4.72** (1.01 g, 3.63 mmol, 1.0 equiv.) in MeOH (20 mL) at 0 °C was added K_2CO_3 (501 mg, 3.63 mmol, 1.0 equiv.) portion-wise. The reaction was stirred at 0 °C for 1 h, brine (50 mL) was added and the mixture was extracted with Et_2O (30 mL × 3). The combined organic extracts were washed with brine (30 mL × 3), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (4:1 → 2:1 hexanes/ EtOAc) to afford **4.75** as a clear colourless oil (654 mg, 76%) and the Michael addition product **4.76** (77 mg, 8%) as a yellow oil.

Data for 4.75:

R_f: 0.20 (4:1 hexanes/ EtOAc).

FTIR (neat): 3500, 2915, 1685, 1618, 1445, 1007 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.08 – 6.07 (m, 1H), 5.40 – 5.37 (m, 1H), 5.20 – 5.17 (m, 1H), 4.12 (d, *J* = 6.9 Hz, 2H), 3.02 (s, 2H), 2.18 – 2.14 (m, 2H), 2.11 (s, 3H), 2.05 (t, *J* = 7.6 Hz, 2H), 1.86 (s, 3H), 1.65 (s, 3H), 1.59 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 199.5, 155.9, 138.9, 130.0, 128.8, 124.1, 123.1, 59.4, 55.3, 39.2, 27.8, 26.4, 20.8, 16.6, 16.3 ppm.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{24}O_2Na$ 259.1669; found 259.1670.

Data for 4.76:

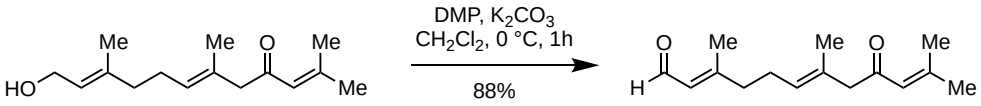
R_f: 0.10 (7:3 hexanes/ EtOAc).

FTIR (neat): 3358, 2973, 1708, 1380, 1367, 1226, 1184, 1068, 1002 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.39 (t, *J* = 1.3 Hz, 1H), 5.19 (t, *J* = 7.0 Hz, 1H), 4.13 (d, *J* = 6.9 Hz, 2H), 3.20 (s, 3H), 3.09 (s, 2H), 2.58 (s, 2H), 2.23 – 2.13 (m, 2H), 2.09 – 2.05 (m, 2H), 1.66 (s, 3H), 1.59 (s, 3H), 1.24 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 208.6, 138.8, 129.5, 129.4, 124.4, 74.6, 59.4, 55.9, 51.5, 49.2, 39.2, 26.2, 24.8, 24.0, 16.6, 16.2 ppm.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{28}O_3Na$ 291.1931; found 291.1934.



4.75 **4.60**

To a solution of **4.75** (654 mg, 2.77 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) at 0 °C was added $NaHCO_3$ (465 mg, 5.53 mmol, 2.0 equiv.), followed by DMP (1.76 g, 4.15 mmol, 1.5 equiv.). The reaction was stirred at 0 °C for 1 h, then hexanes (80 mL) was added. The resultant suspension was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (4:1 hexanes/ EtOAc) to afford aldehyde **4.60** as a pale, light yellow oil (573 mg, 88%).

Data for 4.60:

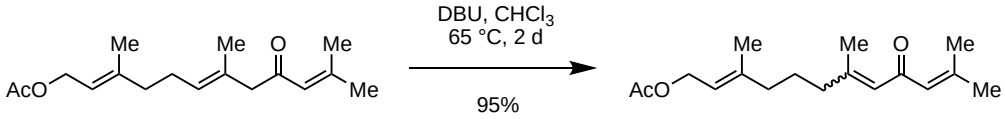
R_f: 0.40 (7:3 hexanes/ EtOAc).

FTIR (neat): 2915, 1673, 1619, 1445, 1383, 1194, 1121 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.99 (d, *J* = 8.0 Hz, 1H), 6.08 (s, 1H), 5.88 (d, *J* = 8.0 Hz, 1H), 5.22 – 5.20 (m, 1H), 3.04 (s, 2H), 2.29 – 2.26 (m, 4H), 2.17 (s, 3H), 2.14 (s, 3H), 1.88 (s, 3H), 1.63 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 199.1, 191.4, 163.5, 156.2, 131.4, 127.7, 127.3, 123.0, 55.2, 40.4, 27.9, 25.9, 20.9, 17.7, 16.7 ppm.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{22}O_2Na$ 257.1512; found 257.1515.



4.71 **4.77**
E*:*Z 2.2:1

To a solution of **4.72** (1.21 g, 4.35 mmol, 1.0 equiv.) in $CHCl_3$ (20 mL) was added DBU (0.80 mL, 5.21 mmol, 1.2 equiv.) and the reaction was left to stir at reflux for 2 d. The resulting solution was then concentrated and purified by flash column chromatography on SiO_2 (4:1 hexanes/ Et_2O) to afford a yellow oil of ***E*-4.77** and ***Z*-4.77** as a 2.2:1 mixture of diastereomers (1.15 g, 95%). Although these products were then taken on as a crude mixture and used without further purification, it was found that a small sample of pure material could be isolated for analytical characterisation purposes.

Data for *E*-4.77:

R_f: 0.25 (4:1 hexanes/ EtOAc).

FTIR (neat): 2936, 1737, 1672, 1443, 1380, 1229, 1108, 1022, 955, 877, 756 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.05 (m, 1H), 6.01 (m, 1H), 5.36 – 5.30 (m, 1H), 4.57 (dd, *J* = 7.2, 2.4 Hz, 2H), 2.15 (s, 3H), 2.14 (s, 3H), 2.10 – 2.06 (m, 2H), 2.04 (s, 3H), 2.04 – 2.00 (m, 2H), 1.88 (s, 3H), 1.63 – 1.58 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 191.7, 171.2, 157.5, 154.5, 141.8, 126.4, 125.9, 119.0, 61.4, 40.8, 39.1, 27.9, 25.5, 21.1, 20.7, 19.2, 16.4 ppm.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{26}O_3Na$ 301.1774; found 301.1773.

Data for *Z*-4.77:

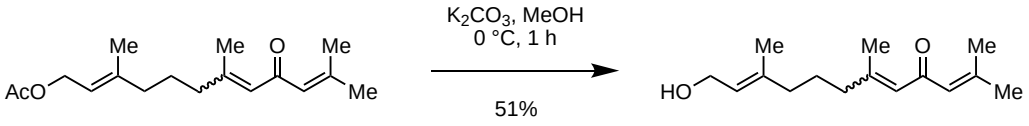
R_f: 0.30 (4:1 hexanes/ EtOAc).

FTIR (neat): 2936, 1736, 1672, 1623, 1444, 1378, 1228, 1112, 1023, 1023, 955, 870 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.02 (m, 2H), 5.36 – 5.30 (m, 1H), 4.56 (d, *J* = 6.8 Hz, 2H), 2.61 – 2.54 (m, 2H), 2.14 (s, 3H), 2.11 – 2.05 (m, 2H), 2.03 (s, 3H), 1.86 (dd, *J* = 5.6, 1.3 Hz, 6H), 1.69 (s, 3H), 1.59 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 191.7, 171.2, 157.5, 154.5, 142.0, 126.6, 126.4, 118.7, 61.5, 39.3, 34.4, 27.8, 26.5, 25.5, 21.1, 20.7, 16.5 ppm.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{26}O_3Na$ 301.1774; found 301.1774.



4.77
E*:*Z 2.2:1

4.78
E*:*Z 2.2:1

To a solution of ***E*-4.77** and ***Z*-4.77** as a 2.2:1 mixture of diastereomers (1.15 g, 4.13 mmol, 1.0 equiv.) in MeOH (20 mL) was added portion-wise K_2CO_3 (0.57 g, 4.13 mmol, 1.0 equiv.) at 0 °C. The reaction was left to stir for 1 h, then quenched upon addition of distilled water (30 mL). Extraction with $CHCl_3$ (3 x 30 mL) was performed, and the solution was dried with $MgSO_4$, concentrated and purified by flash column chromatography on SiO_2 (3:1 hexanes/ EtOAc) to afford a yellow oil of ***E*-4.78** and ***Z*-4.78** as a 2.2:1 mixture of diastereoisomers (502 mg, 51%). Although these products were then taken on as a crude mixture and used without further purification, it was found that a small sample of pure material could be isolated for analytical characterisation purposes.

Data for *E*-4.78:

R_f: 0.20 (3:1 hexane/ EtOAc).

FTIR (neat): 3410, 2935, 1671, 1443, 1381, 1218, 1112, 1005, 875 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.04 – 6.04 (m, 2H), 5.41 – 5.38 (m, 1H), 4.14 (d, *J* = 6.7 Hz, 1H), 2.175 (s, 6H), 2.11 (t, *J* = 7.7 Hz, 2H), 2.02 (t, *J* = 7.6 Hz, 2H), 1.89 (s, 3H), 1.67 (s, 3H), 1.63 – 1.58 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 191.8, 157.7, 154.5, 139.1, 126.4, 125.9, 124.1, 59.4, 40.9, 39.1, 27.9, 26., 25.6, 19.2, 16.3 ppm.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{24}O_2Na$ 259.1669; found 259.1668.

Data for *Z*-4.78:

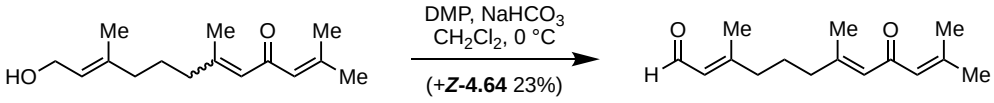
R_f: 0.20 (3:1 hexanes/ EtOAc).

FTIR (neat): 3411, 2933, 1670, 1620, 1443, 1379, 1221, 1112, 1000, 870, 772 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.99 – 5.97 (m, 2H), 5.40 (t, *J* = 5.5 Hz, 1H), 4.14 (d, *J* = 7.0 Hz, 2H), 2.61 – 2.57 (m, 2H), 2.21 – 2.14 (br s, 1H), 2.10 (s, 3H), 2.02 (t, *J* = 7.5 Hz, 2H), 1.84 – 1.81 (m, 6H), 1.63 (s, 3H), 1.58 – 1.51 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 191.8, 157.7, 154.5, 139.1, 126.4, 123.9, 59.4, 59.4, 39.2, 32.8, 27.8, 26.2, 25.5, 20.7, 16.3 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{24}O_2$ 235.1693; found 235.1697.



4.78
E:Z 2.2:1

***E*-4.64** 51%

To a solution of ***E*-4.78** and ***Z*-4.78** as a 2.2:1 mixture of diastereomers (502 mg, 2.12 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) at 0 °C was added $NaHCO_3$ (360 mg, 4.25 mmol, 2.0 equiv.) and Dess-Martin periodinane (1.35 g, 3.18 mmol, 1.5 equiv.). The solution was left to stir for 1.5 h then quenched upon addition of sat. $NaHCO_{3(aq)}$ (30 mL). The organic layer was extracted with CH_2Cl_2 (3 x 30 mL), dried with $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography on SiO_2 (4:1 hexanes/ Et_2O) then afforded ***Z*-4.64** (113 mg, 12% over 2-steps) and ***E*-4.64** (252 mg, 26% over 2-steps) as yellow oils. If needed further recrystallisation of the *trans* isomer ***E*-4.64** with hexanes at 0 °C could also be performed.

Data for *E*-4.64:

R_f: 0.15 (4:1 hexanes/ Et_2O).

FTIR (neat): 2941, 1671, 1625, 1443, 1382, 1217, 1195, 1109, 1044, 873 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.00 (d, *J* = 7.9 Hz, 1H), 6.07 – 6.06 (m, 1H), 6.03 – 6.02 (m, 1H), 5.89 (dq, *J* = 7.9, 1.2 Hz, 1H), 2.23 – 2.19 (m, 2H), 2.19 – 2.13 (m, 8H), 1.90 (s, 3H), 1.73 – 1.70 (m, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 191.6, 191.3, 163.2, 156.4, 155.0, 127.7, 126.3, 126.3, 40.7, 40.0, 27.9, 25.0, 20.7, 19.1, 17.7 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{23}O_2$ 235.1693; found 235.1696.

Data for *Z*-4.64:

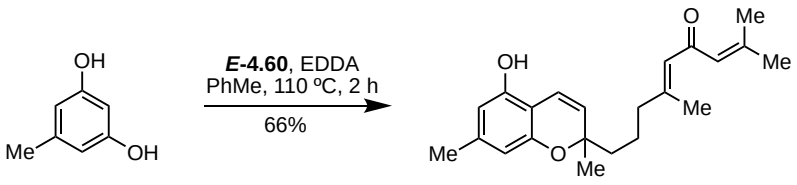
R_f: 0.20 (4:1 hexanes/ Et_2O).

FTIR (neat): 2935, 1670, 1444, 1380, 1194, 1113, 1045, 872, 773 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.99 (d, *J* = 8.0 Hz, 1H), 6.06 – 6.04 (m, 2H), 5.89 (d, *J* = 8.1 Hz, 1H), 2.62 (t, *J* = 7.8, 2H), 2.28 (t, *J* = 7.8 Hz, 2H), 2.19 (s, 3H), 2.15 (s, 3H), 1.88 (s, 6H), 1.69 (pent, *J* = 7.8 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 191.5, 191.1, 164.2, 157.2, 154.8, 127.5, 126.9, 126.3, 40.7, 33.2, 27.9, 25.8, 25.5, 20.7, 17.7 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{23}O_2$ 235.1693; found 235.1697.



4.61: orcinol

4.59: rubiginosin D

To a solution of aldehyde ***E*-4.61** (50 mg, 0.213 mmol, 1.0 equiv.) in PhMe (8 mL) was added orcinol monohydrate **4.61** (40 mg, 0.320 mmol, 1.5 equiv.), and EDDA (4 mg, 0.021 mmol, 10 mol%). The mixture was heated to reflux for 2 h, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on a Biotage® Isolera™ 1.2.1 (4:1 → 2:1 hexanes/ Et_2O, gradient elution) to afford rubiginosin D (**4.59**) as a light brown oil (48 mg, 66%). Data for rubiginosin D (**4.59**) matched that previously reported in literature.[7]

Data for rubiginosin D (4.59):

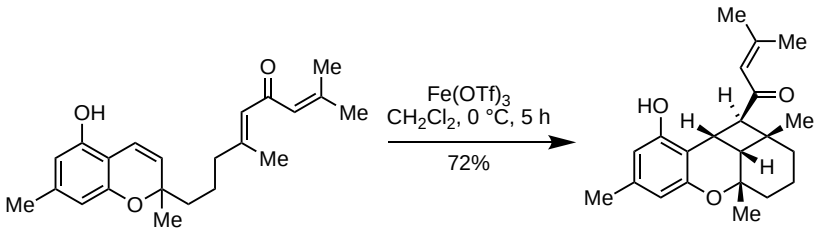
R_f: 0.20 (2:1 hexanes/ Et_2O).

FTIR (neat): 3360, 2923, 1620, 1444, 1330, 1218, 1097, 992, 824, 775 cm^{-1}.

^{1}H NMR (600 MHz, CD_3OD): δ 6.64 (dd, *J* = 10.0, 0.7 Hz, 1H), 6.14 (s, 1H), 6.10 – 6.09 (m, 1H), 6.07 (s, 1H), 6.06 – 6.05 (m, 1H), 5.45 (d, *J* = 10.0 Hz, 1H), 2.16 (s, 3H), 2.16 – 2.13 (m, 2H), 2.12 (s, 3H), 2.08 (s, 3H), 1.90 (s, 3H), 1.63 – 1.62 (m, 4H), 1.32 (s, 3H) ppm.

^{13}C NMR (150 MHz, CD_3OD): δ 193.8, 159.5, 156.2, 155.2, 154.2, 140.4, 127.3, 127.1, 126.8, 118.9, 109.3, 109.2, 108.1, 78.9, 42.2, 41.4, 27.8, 26.6, 22.9, 21.7, 20.8, 19.3 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{29}O_3$ 341.2111; found 341.2116.



4.59: rubiginosin D

4.7: rubiginosin A

To a solution of rubiginosin D (**4.59**) (46 mg, 0.135 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) at 0 °C was added $Fe(OTf)_3$ (20 mg, 0.040 mmol, 0.3 equiv.) and the reaction was left to slowly warm to room temperature over 5 h. Then quenched upon addition of brine (10 mL) and the products extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography on SiO_2 (19:1 hexanes/ EtOAc) then afforded rubiginosin A (**4.7**) (33 mg, 72%) as a white solid. Data for rubiginosin A (**4.7**) matched that previously reported in literature.[7]

Data for rubiginosin A (4.7):

MP: 137.5 – 138.9 °C (lit. 142 – 144 °C).[7]

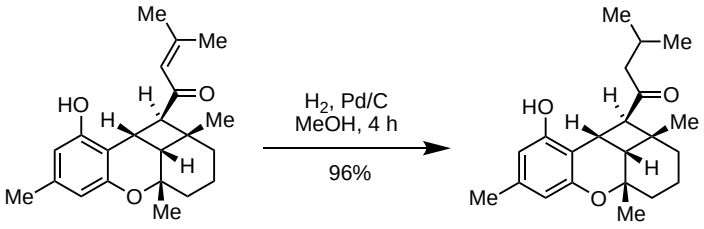
R_f: 0.40 (9:1 hexanes/ EtOAc).

FTIR (neat): 2248, 2929, 1728, 1660, 1608, 1584, 1447, 1368, 1323, 1187, 1132, 1062 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.48 (br s, 1H), 6.40 (s, 1H), 6.30 (s, 1H), 5.87 (m, 1H), 3.82 (t, *J* = 9.3 Hz, 1H), 2.96 (d, *J* = 9.3 Hz, 1H), 2.23 (s, 3H), 2.16 (s, 3H), 2.01 – 1.93 (m, 1H), 2.09 (dt, *J* = 13.9, 3.7 Hz) 1.90 (s, 3H), 1.89 – 1.84 (m, 1H), 1.82 (d, *J* = 9.8 Hz, 1H), 1.70 – 1.62 (m, 1H), 1.37 – 1.24 (m, 2H), 1.15 (s, 3H), 1.14 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 203.2, 158.1, 154.4, 153.4, 138.0, 122.4, 112.1, 111.5, 110.6, 75.3, 58.0, 45.1, 39.5, 36.4, 34.4, 29.7, 28.2, 25.9, 24.0, 21.6, 21.5, 17.4 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{29}O_3$ 341.2111; found 341.2113.



4.7: rubiginosin A **4.6:** rubiginosin G

To a solution of rubiginosin A (**4.7**) (30 mg, 0.059 mmol, 1.0 equiv.) in dry MeOH (15 mL) was added portion-wise Pd/C (55 mg, 0.005 mmol, 10% w/w, 10 mol%). The solution was then put under vacuum/ flushed with H_2 three times and the reaction was left to stir at room temperature for 4 h. The reaction was then filtered through celite with EtOAc and concentrated to afford rubiginosin G (**4.6**) (29 mg, 96%) as a clear oil. Data for rubiginosin G (**4.6**) matched that previously reported in literature.[7]

Data for rubiginosin G (4.6):

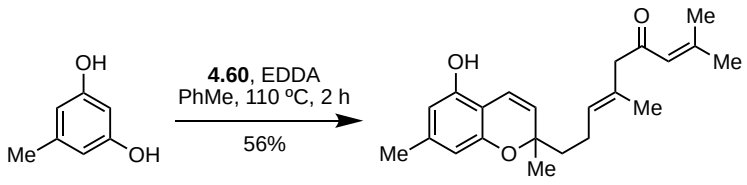
R_f: 0.20 (19:1 hexanes/ EtOAc).

FTIR (neat): 3395, 2956, 2929, 1682, 1631, 1585, 1456, 1370, 1323, 1260, 1127, 1059, 908 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.83 (s, 1H), 6.40 (s, 1H), 6.31 (s, 1H), 3.81 (t, *J* = 9.4 Hz, 1H), 2.91 (d, *J* = 9.4 Hz, 1H), 2.23 (s, 3H), 2.18 (dd, *J* = 13.5, 6.6 Hz, 1H), 2.15 – 2.10 (m, 1H), 2.09 – 2.05 (m, 1H), 2.00 – 1.91 (m, 1H), 1.87 – 1.81 (m, 1H), 1.80 (d, *J* = 9.3 Hz, 1H), 1.70 - 1.63 (m), 1.37 – 1.33 (m, 1H), 1.33 – 1.28 (m, 1H), 1.17 (s, 3H), 1.11 (s, 3H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 213.9, 154.5, 153.1, 138.1, 111.8, 111.7, 110.6, 75.3, 57.4, 50.9, 45.2, 39.4, 36.6, 34.5, 29.6, 25.8, 24.2, 23.9, 23.0, 22.8, 21.6, 17.3 ppm.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{30}O_3Na$ 365.2087; found 365.2082.



4.61: orcinol

4.58: rubiginosin E

To a solution of aldehyde **4.60** (287 mg, 1.22 mmol, 1.0 equiv.) in PhMe (10 mL) was added orcinol monohydrate **4.61** (228 mg, 1.84 mmol, 1.5 equiv.), and EDDA (22 mg, 0.122 mmol, 10 mol%). The mixture was heated to reflux for 2 h, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (4:1 → 2:1 hexanes/ Et_2O, gradient elution) to afford rubiginosin E (**4.58**) as a light brown oil (234 mg, 56%). Data for rubiginosin E (**4.58**) matched that previously reported in literature.[7]

Data for rubiginosin E (4.58):

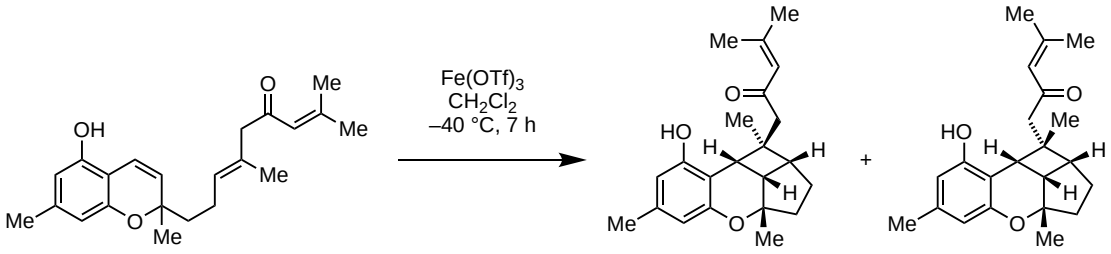
R_f: 0.20 (2:1 hexanes/ Et_2O).

FTIR (neat): 3365, 2972, 2920, 1676, 1621, 1579, 1445, 1328, 1280, 1204, 1140, 1097, 1073 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.63 (d, *J* = 10.0 Hz, 1H), 6.18 (br s, 1H), 6.14 (s, 1H), 6.08 (s, 1H), 5.46 (d, *J* = 10.0 Hz, 1H), 5.29 (t, *J* = 7.2 Hz, 1H), 3.02 (s, 2H), 2.19 – 2.14 (m, 2H), 2.16 (s, 3H), 2.11 (s, 3H), 1.88 (s, 3H), 1.73 – 1.64 (m, 2H), 1.56 (s, 3H), 1.33 (s, 3H) ppm.

^{13}C NMR (150 MHz, CD_3OD): δ 201.9, 157.8, 155.2, 154.2, 140.4, 130.7, 130.6, 127.1, 123.9, 118.8, 109.3, 109.2, 108.1, 78.9, 56.0, 41.7, 27.7, 26.6, 23.9, 21.7, 20.8, 16.3 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{29}O_3$ 341.2111; found 341.2110.



4.58: rubiginosin E

4.8: fastinoid B, 42%

4.3: rhodonoid B, 11%

To a solution of rubiginosin E (**4.58**) (53 mg, 0.156 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) at –40 °C was added $Fe(OTf)_3$ (23 mg, 0.047 mmol, 0.3 equiv.) and reaction was left to stir 7 h. Brine (10 mL) was added and the solution extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were dried with $MgSO_4$, filtered and concentrated. Purification by flash chromatography on SiO_2 (20:1 hexanes/ EtOAc) afforded fastinoid B (**4.8**) (22 mg, 42%) and rhodonoid B (**4.3**) (6 mg, 11%). Data for fastinoid B (**4.8**) and rhodonoid B (**4.3**) matched that previously reported in literature. [5,9]

Data for fastinoid B (4.8):

R_f: 0.25 (20:1 hexanes/ EtOAc).

FTIR (neat): 3250, 2947, 1678, 1613, 1574, 1490, 1444, 1376, 1177, 1057, 910, 827 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.25 (s, 1H), 6.39 (s, 1H), 6.27 (s, 1H), 6.11 (s, 1H), 3.38 (d, *J* = 9.6 Hz, 1H), 2.97 (d, *J* = 17.7 Hz, 1H), 2.79 (d, *J* = 17.7 Hz, 1H), 2.68 (t, *J* = 8.8 Hz, 1H), 2.31 (td, *J* = 8.4, 2.9 Hz, 1H), 2.23 (s, 3H), 2.20 (s, 3H), 2.08 – 2.02 (m, 1H), 1.92 (s, 3H), 1.80 – 1.73 (m, 1H), 1.66 – 1.59 (m, 1H), 1.56 – 1.51 (m, 1H), 1.31 (s, 3H), 0.84 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 203.1, 159.6, 156.2, 154.6, 138.2, 124.1, 110.8, 110.4, 108.0, 83.0, 58.7, 46.9, 41.7, 40.6, 38.5, 34.2, 28.2, 26.3, 24.8, 21.5, 21.3, 15.5 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{29}O_3$ 341.2111; found 341.2115.

Data for rhodonoid B (4.3):

R_f: 0.20 (20:1 hexanes/ EtOAc).

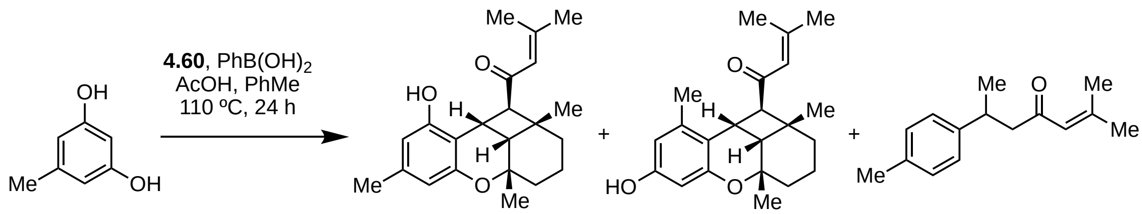
MP: 145.3 – 149.8 °C (lit. 148 – 149 °C).[5]

FTIR (neat): 3395, 2949, 1677, 1619, 1585, 1444, 1418, 1328, 1139, 1054, 907, 825 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.33 (s, 1H), 6.25 (s, 1H), 5.89 – 5.88 (m, 1H), 5.35 (s, 1H), 3.18 (d, *J* = 9.3 Hz, 1H), 2.62 (td, *J* = 8.0, 2.6 Hz), 2.60 (dd, *J* = 9.0, 8.0 Hz, 1H), 2.47 (d, *J* = 18.3 Hz, 1H), 2.42 (d, *J* = 18.3 Hz, 1H), 2.22 (s, 3H), 2.04 (s, 3H), 1.98 – 1.90 (m, 1H), 1.78 (s, 3H), 1.75 – 1.68 (m, 1H), 1.66 – 1.61 (m, 1H), 1.60 – 1.56 (m, 1H), 1.54 (s, 3H), 1.32 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 201.6, 154.5, 154.4, 154.2, 137.8, 125.0, 111.9, 109.6, 109.6, 83.9, 47.0, 45.6, 41.7, 39.5, 39.1, 36.5, 30.5, 27.7, 26.9, 26.4, 21.4, 20.7 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{29}O_3$ 341.2111; found 341.2114.



4.61: orcinol **4.7:** rubiginosin A, 10% **4.80:** "iso-rubiginosin A", 31% **4.81:** Ar-turmerone, 2%

To a solution of aldehyde **4.60** (146 mg, 0.623 mmol, 1.0 equiv.) in PhMe (10 mL) was added orcinol monohydrate **4.61** (130 mg, 0.935 mmol, 1.5 equiv.), phenylboronic acid (110 mg, 0.935 mmol, 1.5 equiv.) and acetic acid (0.04 mL, 0.623 mmol, 1.0 equiv.). The solution was heated to reflux and left to stir for 24 hours, then concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (20:1 → 9:1 hexanes/ EtOAc, gradient elution) to afford Ar-turmerone (**4.81**) (3 mg, 2%) as a yellow solid, rubiginosin A (**4.7**) (22 mg, 10%) and "iso-rubiginosin A" (**4.80**) (39 mg, 31%) as a white solid. Data for rubiginosin A (**4.7**) and Ar-turmerone (**4.80**) matched that previously obtained and previously reported in the literature.[7, 25]

Data for 4.80:

R_f: 0.30 (3:1 hexanes/ EtOAc).

FTIR (neat): 3407, 2930, 1667, 1615, 1445, 1379, 1328, 1130, 985 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.27 (d, *J* = 2.4 Hz, 1H), 6.24 (d, *J* = 2.4 Hz, 1H), 5.82 – 5.80 (m, 1H), 4.65 (br s, 1H), 4.02 (t, *J* = 8.9 Hz, 1H), 3.19 (d, *J* = 9.1 Hz, 1H), 2.38 (s, 3H), 2.11 (s, 3H), 2.09 – 2.02 (m, 2H), 1.84 (s, 3H), 1.84 – 1.81 (m, 1H), 1.78 (d, *J* = 8.9 Hz, 1H), 1.67 – 1.61 (m, 1H), 1.37 – 1.31 (m, 1H), 1.25 – 1.17 (m, 1H), 1.08 (s, 3H), 0.99 (s, 3H) ppm.

^{13}C NMR (120 MHz, $CDCl_3$): δ 200.0, 156.1, 154.5, 154.4, 137.2, 124.2, 120.4, 110.4, 104.0, 75.8, 57.7, 47.7, 38.9, 37.1, 34.4, 28.8, 27.8, 26.6, 25.6, 20.9, 19.3, 17.3 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{29}O_3$ 341.2111, found 341.2114.

Data for Ar-turmerone (4.81):

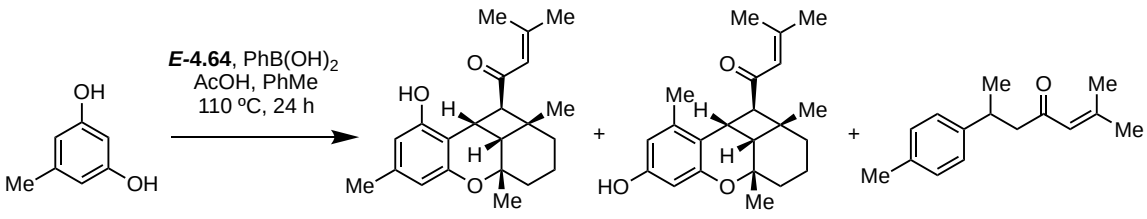
R_f: 0.45 (9:1 hexanes/ EtOAc).

FTIR (neat): 2962, 2925, 1686, 1619, 1515, 1446, 1378, 1112, 1011, 819 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 – 7.08 (m, 4H), 6.07 – 6.00 (m, 1H), 3.33 – 3.25 (m, 1H), 2.71 (dd, *J* = 15.7, 6.1 Hz, 1H), 2.61 (dd, *J* = 15.7, 8.3 Hz, 1H), 2.31 (s, 3H), 2.11 (s, 3H), 1.86 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H) ppm.

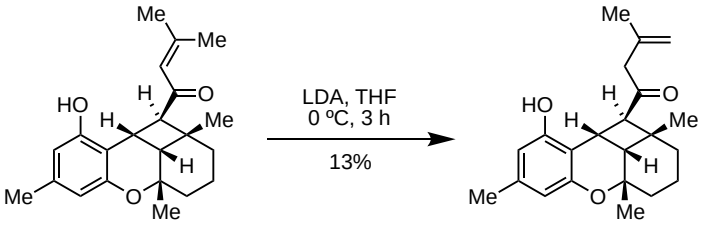
^{13}C NMR (120 MHz, $CDCl_3$): δ 200.0, 155.2, 143.8, 135.7, 129.2, 126.8, 124.2, 52.8, 35.4, 27.8, 22.1, 21.1, 20.9 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{20}O$ 217.1587, found 217.1587.



4.61: orcinol **4.7:** rubiginosin A, 13% **4.80:** "iso-rubiginosin A", 34% **4.81:** Ar-turmerone, 2%

To a solution of aldehyde ***E*-4.64** (146 mg, 0.623 mmol, 1.0 equiv.) in PhMe (10 mL) was added orcinol monohydrate **4.61** (130 mg, 0.935 mmol, 1.5 equiv.), phenylboronic acid (110 mg, 0.935 mmol, 1.5 equiv.) and acetic acid (0.04 mL, 0.623 mmol, 1.0 equiv.). The solution was heated to reflux and left to stir for 24 hours, then concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (20:1 → 9:1 hexanes/ EtOAc, gradient elution) to afford Ar-turmerone (**4.81**) (3 mg, 2%), rubiginosin A (**4.7**) (22 mg, 10%) and "iso-rubiginosin A" (**4.80**) (39 mg, 31%) as a white solid. Data for rubiginosin A (**4.7**), "iso-rubiginosin A" (**4.80**) and Ar-turmerone (**4.81**) matched that previously obtained and previously reported in the literature.[7, 25]



4.7: rubiginosin A

4.94

To a solution of diisopropyl amine (0.02 mL, 0.113 mmol, 2.5 equiv.) in THF (2.5 mL) at 0 °C was added dropwise *n*-BuLi (0.02 mL, 0.113 mmol, 11.0 M, 2.5 equiv.) and stirred for 5 min at room temperature. The solution was then cooled to 0 °C and rubiginosin A (**4.7**) (15 mg, 0.045 mmol, 1.0 equiv.) dissolved in THF (2.5 mL) was added dropwise and left to stir for 3 h. The reaction was then quenched sat. $NH_4Cl_{(aq)}$ and product extracted with Et_2O (3 x 5 mL), dried with $MgSO_4$, filtered and concentrated. Purification *via* flash chromatography on SiO_2 (20:1 → 9:1 hexanes/ EtOAc, gradient elution) afforded **4.94** (2 mg, 13%) as a clear oil.

Data for 4.94:

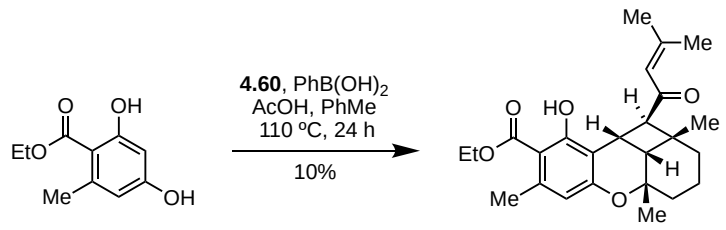
R_f: 0.20 (19:1 hexanes/ EtOAc).

FTIR (neat): 3501, 2927, 1690, 1653, 1636, 1584, 1457, 1325, 1183, 1130 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.61 (br s, 1H), 6.40 (s, 1H), 6.31 (s, 1H), 4.91 – 4.90 (m, 1H), 4.73 – 4.71 (m, 1H), 3.83 (t, *J* = 9.3 Hz, 1H), 3.05 (d, J = 9.3 Hz, 1H), 3.03 – 3.02 (m, 2H), 2.23 (s, 3H), 2.10 – 2.05 (m, 1H), 2.00 – 1.92 (m, 1H), 1.89 – 1.85 (m, 1H), 1.81 (d, *J* = 9.2 Hz, 1H), 1.70 (s, 3H), 1.69 – 1.63 (m, 1H), 1.38 – 1.31 (m, 2H), 1.20 (s, 3H), 1.11 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 211.8, 154.6, 153.1, 138.3, 138.2, 115.6, 111.8, 111.7, 110.6, 75.3, 56.7, 50.8, 45.3, 39.6, 36.6, 34.4, 29.5, 25.8, 24.0, 22.9, 21.6, 17.3 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{29}O_3$ 341.2124, found 341.2124.



4.96: ethyl orsellinate

4.97

To a solution of ethyl orsellinate (**4.96**) (128 mg, 0.653 mmol, 2.0 equiv.) in PhMe (3 mL) was added aldehyde (**4.60**) (77 mg, 0.327 mmol, 1.0 equiv.), $PhB(OH)_2$ (60 mg, 0.491 mmol, 1.5 equiv.) and AcOH (0.02 mL, 0.327 mmol, 1.0 equiv.). The reaction was left to heat at reflux for 24 h. Then concentrated *in vacuo*. Purification by flash chromatography on SiO_2 (9:1 hexanes/ EtOAc) afforded **4.97** (25 mg, 10%) as a clear oil.

Data for 4.97:

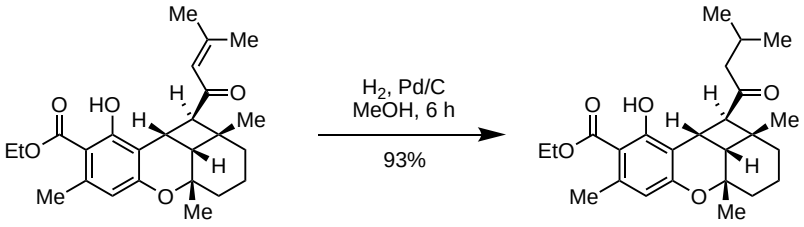
R_f: 0.40 (19:1 hexanes/ EtOAc).

FTIR (neat): 2972, 2934, 1652, 1619, 1315, 1297, 1284, 1248, 1176, 1133, cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.89 (br s, 1H), 6.29 (s, 1H), 6.00 (s, 1H), 4.38 (d, *J* = 7.1 Hz, 2H), 4.30 (s, 1H), 3.03 (d, *J* = 9.0 Hz, 1H), 2.47 (s, 3H), 2.13 (s, 3H), 2.08 – 1.96 (m, 3H), 1.87 – 1.80 (m, 2H), 1.84 (s, 3H) 1.62 (t, *J* = 7.3 Hz, 3H), 1.34 – 1.29 (m, 2H), 1.12 (s, 3H), 1.02 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.0, 172.0, 160.7, 159.9, 155.1, 140.7, 123.7, 114.3, 114.2, 106.4, 71.9, 61.3, 57.2, 46.9, 36.6, 34.2, 29.9, 28.9, 27.9, 25.5, 24.4, 24.3, 21.0, 17.3, 14.4 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{25}H_{33}O_5$ 413.2323, found 413.2320.



4.97 **4.98**

Chromene **4.97** (10 mg, 0.024 mmol, 1.0 equiv.) was dissolved in dry MeOH (5 mL) and Pd/C (3 mg, 0.002 mmol, 10% wt./ wt., 10 mol%) added. The reaction was placed under an atmosphere of vacuum/ H_2 three times, then left to stir under an atmosphere of H_2 at room temperature for 3 h. The solution was then filtered through celite with $CHCl_3$ to afford **4.98** (9 mg, 93%) as a clear oil.

Data for 4.98:

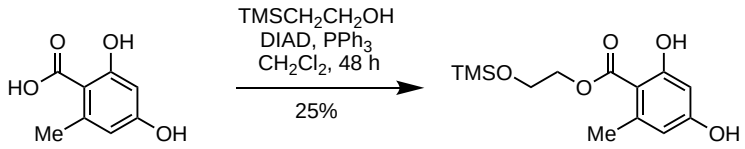
R_f: 0.55 ($CHCl_3$).

FTIR (neat): 3501, 2927, 1690, 1653, 1636, 1584, 1457, 1325, 1183, 1130 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.90 (s, 1H), 6.30 (s, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 4.26 (t, *J* = 9.0 Hz), 2.97 (d, *J* = 8.9 Hz, 1H), 2.48 (s, 3H), 2.23 (dd, *J* = 16.4, 5.8 Hz, 1H), 2.16 – 2.01 (m, 4H), 2.00 – 1.89 (m, 2H), 1.87 (d, *J* = 9.1 Hz, 1H), 1.83 – 1.76 (m, 1H), 1.61 – 1.58 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.14 (s, 3H), 1.03 (s, 3H), 0.84 (t, *J* = 5.9 Hz, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 209.6, 172.1, 160.9, 159.8, 140.8, 114.3, 113.8, 106.3, 72.0, 61.3, 56.4, 51.9, 46.6, 36.2, 34.0, 28.9, 25.5, 24.5, 24.4, 24.0, 22.9, 22.8, 17.2, 14.4 ppm.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{34}O_5$ 437.2297, found 437.2297.



4.95: *o*-orsellinic acid

4.99

To a solution of *o*-orsellinic acid (**4.95**) (2.71 g, 16.1 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) at room temperature was added PPh_3 (6.30 g, 24.2 mmol, 1.5 equiv.), 2-(trimethylsilyl)ethanol (2.8 mL, 10.3 mmol, 1.2 equiv.) and a dropwise addition of DIAD (4.75 mL, 24.2 mmol, 1.5 equiv.). The reaction mixture was left to stir for 48 h, then filtered and quenched sat. brine (30 mL). The product was extracted CH_2Cl_2 (3 x 30 mL), dried $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* flash chromatography on SiO_2 (9:1 hexanes/ EtOAc) afforded **4.99** (1.07 g, 25%). Data for **4.99** matched that previously reported in literature.[21]

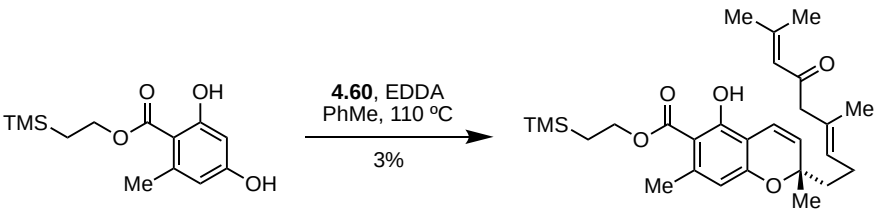
Data for 4.99:

R_f: 0.15 (9:1, hexanes/ EtOAc).

FTIR (neat): 3500, 2955, 1617, 1588, 1314, 1300, 1197, 1170, 1107, 1060, 995 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.89 (s, 1H), 6.28 (d, *J* = 2.5 Hz, 1H), 6.24 – 6.20 (m, 1H), 5.54 (s, 1H), 4.53 – 4.30 (m, 2H), 2.61 – 2.41 (m, 3H), 1.27 – 1.07 (m, 2H), 0.88 (s, 9H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 165.3, 160.5, 144.2, 111.6, 105.9, 101.4, 63.9, 24.5, 17.8 ppm.



To a solution of **4.99** (407 mg, 1.52 mmol, 1.0 equiv.) in PhMe (4 mL) was added aldehyde **4.60** (356 mg, 1.52 mmol, 1.0 equiv.) and EDDA (27 mg, 0.152 mmol, 10 mol%). The solution was left to stir at reflux for 3 h, after which time it was concentrated and purified *via* flash chromatography on SiO_2 (9:1 hexanes/ EtOAc) to afford **4.100** (22 mg, 3%) as a brown oil.

Data for 4.100:

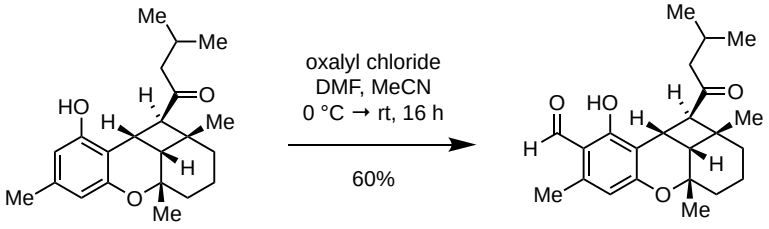
R_f: 0.50 (9:1 hexanes/ EtOAc).

FTIR (neat): 3025, 1646, 1566, 1454, 1420, 1383, 1314, 1250, 1117, 1057, 1009, 858 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 12.09 (s, 1H), 6.73 (d, *J* = 10.3 Hz, 1H), 6.16 (s, 1H), 6.06 – 5.96 (m, 1H), 5.45 (d, *J* = 10.3 Hz, 1H), 5.23 (t, *J* = 7.2 Hz, 1H), 4.49 – 4.32 (m, 2H), 3.00 (s, 2H), 2.47 (s, 3H), 2.20 – 2.14 (m, 2H), 2.13 (s, 3H), 1.86 (s, 3H), 1.76 – 1.65 (m, 2H), 1.58 (s, 3H), 1.39 (s, 3H), 1.19 – 1.12 (m, 2H), 0.08 (s, 9H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 199.4, 172.2, 159.9, 157.7, 155.8, 143.0, 130.2, 128.9, 126.1, 123.0, 117.1, 107.1, 105.4, 79.7, 63.7, 55.4, 41.4, 27.8, 27.2, 24.7, 23.0, 22.6, 21.9, 20.8, 20.7, 17.8, 16.5, −1.4 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{28}H_{41}O_5Si$ 485.2718, found 487.2716.



4.6: rubiginosin G

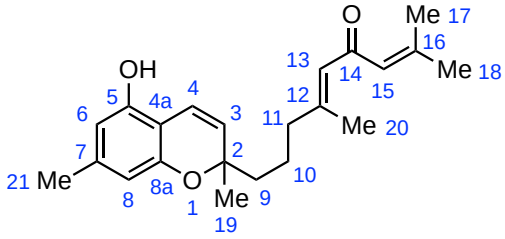
4.101

Following a modified literature procedure from Luo and co-workers,[22] dry DMF (1 mL) was cooled to 0 °C and oxalyl chloride (0.175 mL, 2.04 mmol, 17 equiv.) was added dropwise. The solution was left to stir for 30 min then rubiginosin G (39 mg, 0.120 mmol, 1.0 equiv.) in MeCN (4 mL) was added dropwise. The reaction was then left to stir for a further 6 h at room temperature, then concentrated *in vacuo* and purified *via* flash chromatography on SiO_2 (9:1 hexanes/ EtOAc) to afford the recovered starting material **4.6** and **4.101** (25.3 mg, 60%) as a (2.0:1) mixture.

Partial Data for 4.101:

^{1}H NMR (500 MHz, $CDCl_3$): δ 12.57 (s, 1H), 10.10 (brs, 1H), 6.98 (s, 1H), 4.36 (t, *J* = 8.8 Hz, 1H), 2.95 (d, J = 8.8 Hz, 1H), 2.52 – 2.49 (m, 2H), 2.28 (s, 3H), 2.01 (m, 2H), 1.89 (d, *J* = 9.6 Hz, 2H), 1.68 – 1.62 (m, 4H), 1.43 (s, 3H), 1.15 – 1.13 (m, 3H), 1.06 – 1.05 (m, 3H), 1.01 (s, 3H), 0.89 – 0.85 (m, 1H) ppm.

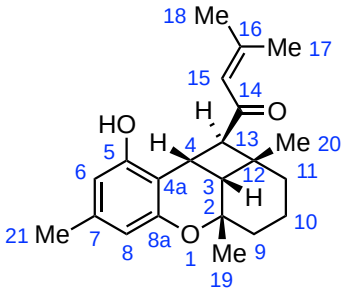
4.4.3 NMR Comparison Data



4.59: rubiginosin D

Table 4.4 – ^{1}H NMR and ^{13}C NMR Comparison for Rubiginosin D

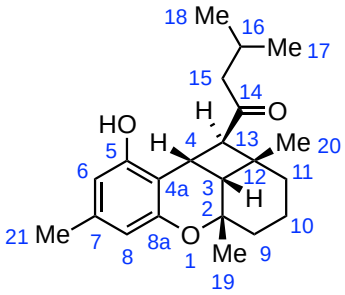
NMR Assignment	Synthetic Sample (CD_3OD) George *et al.* (2021)		Natural Sample (CD_3OD) Yang *et al.* (2018)[7]	
	^{1}H NMR (600 MHz)	^{13}C NMR (150 MHz)	^{1}H NMR (500 MHz)	^{13}C NMR (125 MHz)
2	--	78.9	--	78.9
3	5.45 (d, *J* = 10.0 Hz)	127.1	5.45 (d, *J* = 9.8 Hz)	127.1
4	6.64 (dd, *J* = 10.0, 0.7 Hz)	118.9	6.64 (d, *J* = 9.8 Hz)	118.8
4a	--	108.1	--	108.1
5	--	155.2	--	158.2
6	6.07 (s)	109.2	6.14 (s)	109.3
7	--	140.4	--	140.4
8	6.14 (s)	109.3	6.08 (s)	109.3
8a	--	154.2	--	154.2
9	1.63 – 1.62 (m)	41.4	1.63 (m)	41.4
10	1.63 – 1.62 (m)	22.9	1.63 (m)	22.9
11	2.16 – 2.13 (m)	42.2	2.16 (m)	42.2
12	--	159.5	--	159.5
13	6.06 – 6.05 (m)	126.8	6.09 (m)	126.8
14	--	193.8	--	193.9
15	6.10 – 6.09 (m)	127.3	6.10 (m)	127.3
16	--	156.2	--	155.2
17	2.12 (s)	20.8	2.12 (s)	20.7
18	1.90 (s)	27.8	1.90 (s)	27.7
19	1.32 (s)	26.6	1.33 (s)	26.6
20	2.08 (s)	19.3	2.08 (s)	19.3
21	2.16 (s)	21.7	2.16 (s)	21.7



4.7: rubiginosin A

Table 4.5 – ^{1}H NMR and ^{13}C NMR Comparison for Rubiginosin A

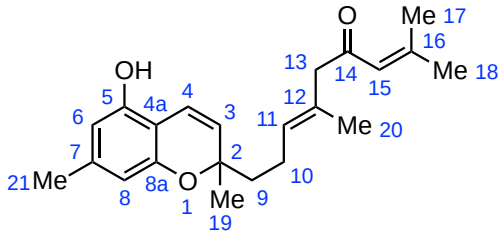
NMR Assignment	Synthetic Sample ($CDCl_3$) George *et al*. (2021)		Natural Sample ($CDCl_3$) Yang *et al.* (2018)[7]	
	^{1}H NMR (600 MHz)	^{13}C NMR (150 MHz)	^{1}H NMR (500 MHz)	^{13}C NMR (125 MHz)
2	--	75.3	--	75.3
3	1.82 (d, *J* = 9.8 Hz)	45.1	1.82 (d, *J* = 9.8 Hz)	45.1
4	3.82 (t, *J* = 9.3 Hz)	24.0	3.83 (t, *J* = 9.3 Hz)	24.0
4a	--	112.1	--	112.0
5	--	153.4	--	154.4
5-OH	7.48 (s)	--	--	--
6	6.40 (s)	110.6	6.31 (s)	111.5
7	--	138.0	--	137.9
8	6.30 (s)	111.5	6.41 (s)	110.6
8a	--	154.4	--	153.4
9	1.37 – 1.24 (m) 2.09 (dt, *J* = 13.9, 3.7 Hz)	36.4	1.37 (m) 2.07 (m)	36.4
10	1.70 – 1.62 (m) 2.01 – 1.93 (m)	17.4	1.66 (m) 1.97 (m)	17.4
11	1.37 – 1.24 (m) 1.89 – 1.84 (m)	34.4	1.30 (m) 1.88 (m)	34.4
12	--	39.5	--	39.4
13	2.96 (d, *J* = 9.3 Hz)	58.0	2.97 (d, *J* = 9.3 Hz)	58.0
14	--	203.2	--	203.2
15	5.87 (m)	122.4	5.88 (m)	122.4
16	--	158.1	--	158.0
17	2.16 (s)	21.5	2.17 (s)	21.5
18	1.90 (s)	28.2	1.91 (s)	28.2
19	1.14 (s)	29.7	1.14 (s)	29.6
20	1.15 (s)	25.9	1.16 (s)	25.8
21	2.23 (s)	21.6	2.23 (s)	21.5



4.6: rubiginosin G

Table 4.6 – ^{1}H NMR and ^{13}C NMR Comparison for Rubiginosin G

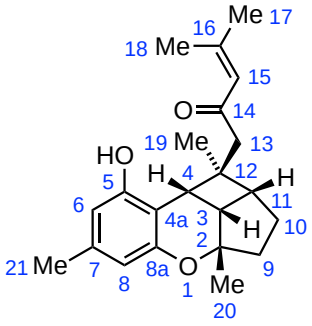
NMR Assignment	Synthetic Sample ($CDCl_3$) George *et al*. (2021)		Natural Sample ($CDCl_3$) Yang *et al.* (2018)[7]	
	^{1}H NMR (600 MHz)	^{13}C NMR (150 MHz)	^{1}H NMR (500 MHz)	^{13}C NMR (125 MHz)
2	--	75.3	--	75.3
3	1.80 (d, *J* = 9.3 Hz)	45.2	1.79 (d, *J* = 9.5 Hz)	45.2
4	3.81 (t, *J* = 9.4 Hz)	23.9	3.81 (t, *J* = 9.5 Hz)	23.9
4a	--	111.8	--	111.9
5	--	153.1	--	154.6
5-OH	6.83 (s)	--	--	--
6	6.40 (s)	110.6	6.30 (s)	111.8
7	--	138.1	--	138.2
8	6.31 (s)	111.7	6.40 (s)	110.6
8a	--	154.5	--	153.2
9	1.37 – 1.33 (m) 2.09 – 2.05 (m)	36.6	1.34 (m) 2.08 (m)	36.6
10	1.70 – 1.63 (m) 2.00 – 1.91 (m)	17.3	1.65 (m) 1.95 (m)	17.3
11	1.33 – 1.28 (m) 1.87 – 1.81 (m)	34.5	1.30 (m) 1.84 (m)	34.5
12	--	39.4	--	39.5
13	2.91 (d, *J* = 9.4 Hz)	57.4	2.91 (d, *J* = 9.8 Hz)	57.4
14	--	213.9	--	213.9
15	2.18 (dd, *J* = 13.5, 6.6 Hz)	50.9	2.17 (m)	50.9
16	2.15 – 2.10 (m)	24.2	2.11 (m)	24.3
17	0.89 (d, *J* = 6.4 Hz)	23.0	0.89 (d, *J* = 6.7 Hz)	23.0
18	0.86 (d, *J* = 6.4 Hz)	22.8	0.86 (d, *J* = 6.7 Hz)	22.8
19	1.11 (s)	29.6	1.11 (s)	29.6
20	1.17 (s)	25.8	1.17 (s)	25.9
21	2.23 (s)	21.6	2.23 (s)	21.6



4.58: rubiginosin E

Table 4.7 – ^{1}H NMR and ^{13}C NMR Comparison for Rubiginosin E

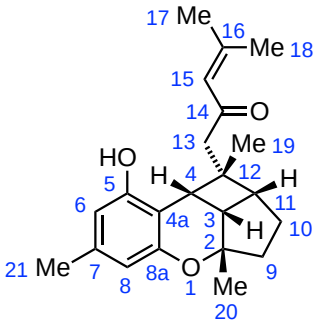
NMR Assignment	Synthetic Sample (CD_3OD) George *et al*. (2021)		Natural Sample (CD_3OD) Yang *et al.* (2018)[7]	
	^{1}H NMR (600 MHz)	^{13}C NMR (150 MHz)	^{1}H NMR (500 MHz)	^{13}C NMR (125 MHz)
2	--	78.9	--	78.9
3	5.46 (d, *J* = 10.0 Hz)	127.1	5.46 (d, *J* = 9.9 Hz)	127.1
4	6.63 (d, *J* = 10.0 Hz)	118.8	6.63 (d, *J* = 9.9 Hz)	118.8
4a	--	108.1	--	109.2
5	--	155.2	--	155.2
6	6.08 (s)	109.3	6.14 (s)	109.4
7	--	140.4	--	140.4
8	6.14 (s)	109.2	6.08 (s)	109.2
8a	--	154.2	--	154.1
9	1.73 – 1.64 (m)	41.7	1.68 (m)	41.7
10	2.19 – 2.14 (m)	23.9	2.16 (m)	23.9
11	5.29 (t, *J* = 7.2 Hz)	130.6	5.29 (m)	130.6
12	--	130.7	--	130.7
13	3.02 (s)	56.0	3.02 (s)	56.0
14	--	201.9	--	201.9
15	6.18 (br s)	123.9	6.18 (m)	123.9
16	--	157.8	--	157.8
17	2.11 (s)	20.8	2.11 (s)	20.8
18	1.88 (s)	27.7	1.88 (s)	27.7
19	1.33 (s)	26.6	1.33 (s)	26.6
20	1.56 (s)	16.3	1.56 (s)	16.5
21	2.16 (s)	21.7	2.16 (s)	21.7



4.8: fastinoid B

Table 4.8 – ^{1}H NMR and ^{13}C NMR Comparison for Fastinoid B

NMR Assignment	Synthetic Sample ($CDCl_3$) George *et al.* (2021)		Natural Sample ($CDCl_3$) Hou *et al.* (2019)[9]	
	^{1}H NMR (600 MHz)	^{13}C NMR (150 MHz)	^{1}H NMR (500 MHz)	^{13}C NMR (125 MHz)
2	--	83.0	--	83.0
3	2.68 (t, *J* = 8.8 Hz)	40.6	2.68 (t, *J* = 8.8 Hz)	40.6
4	3.38 (d, *J* = 9.6 Hz)	34.2	3.38 (d, *J* = 10.0 Hz)	34.3
4a	--	108.0	--	108.0
5	--	156.2	--	156.2
5-OH	9.25 (s)	--	--	--
6	6.39 (s)	110.4	6.39 (br s)	110.4
7	--	138.2	--	138.2
8	6.27 (s)	110.8	6.27 (br s)	110.8
8a	--	154.6	--	154.6
9	2.08 – 2.02 (m) 1.56 – 1.51 (m)	38.5	2.04 (m) 1.54 (m)	38.6
10	1.80 – 1.73 (m) 1.66 – 1.59 (m)	24.8	1.76 (m) 1.63 (m)	24.8
11	2.31 (td, *J* = 8.4, 2.9 Hz)	46.9	2.31 (td, *J* = 8.4, 2.4 Hz)	47.0
12	--	41.7	--	41.8
13	2.97 (d, *J* = 17.7 Hz) 2.79 (d, *J* = 17.7 Hz)	58.7	2.97 (d, *J* = 17.6 Hz) 2.79 (d, *J* = 17.6 Hz)	58.7
14	--	203.1	--	203.1
15	6.11 (s)	124.2	6.11 (br s)	124.2
16	--	159.6	--	159.6
17	1.92 (s)	28.2	1.93 (br s)	28.2
18	2.20 (s)	21.5	2.21 (br s)	21.5
19	0.84 (s)	15.5	0.84 (s)	15.5
20	1.31 (s)	26.3	1.32 (s)	26.3
21	2.23 (s)	21.3	2.23 (s)	21.3



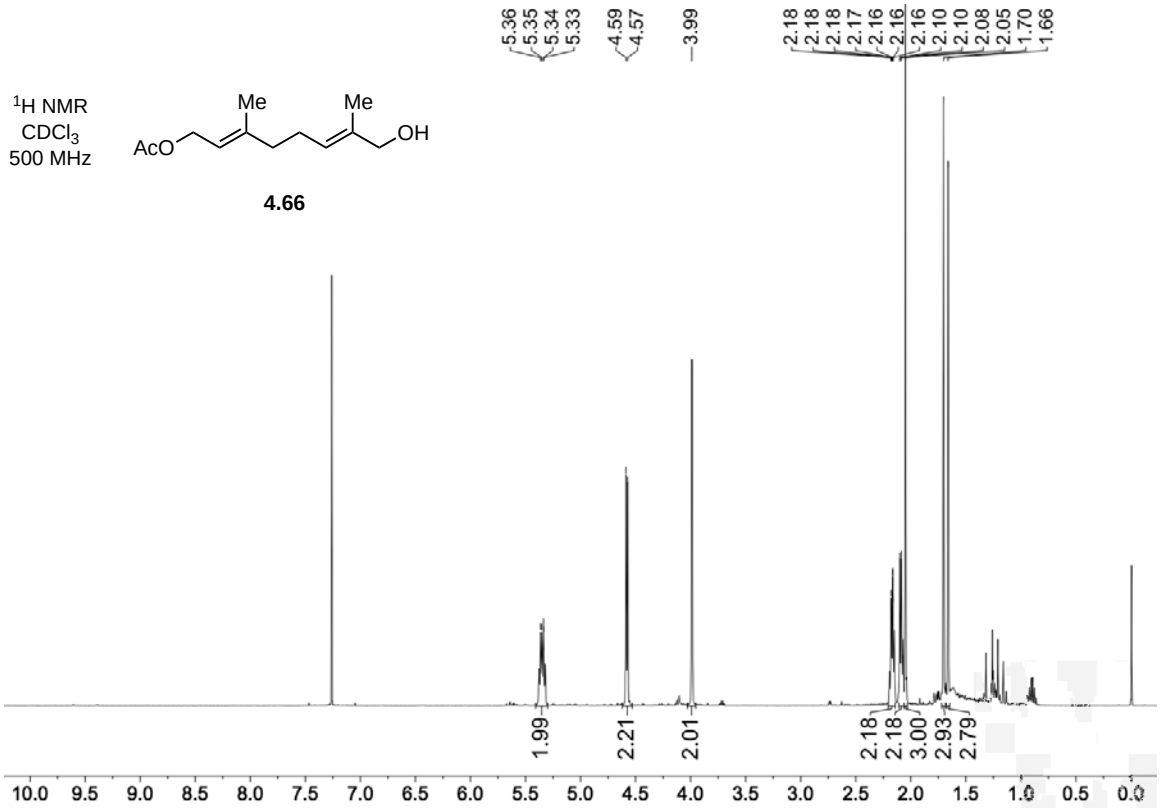
4.3: rhodonoid B

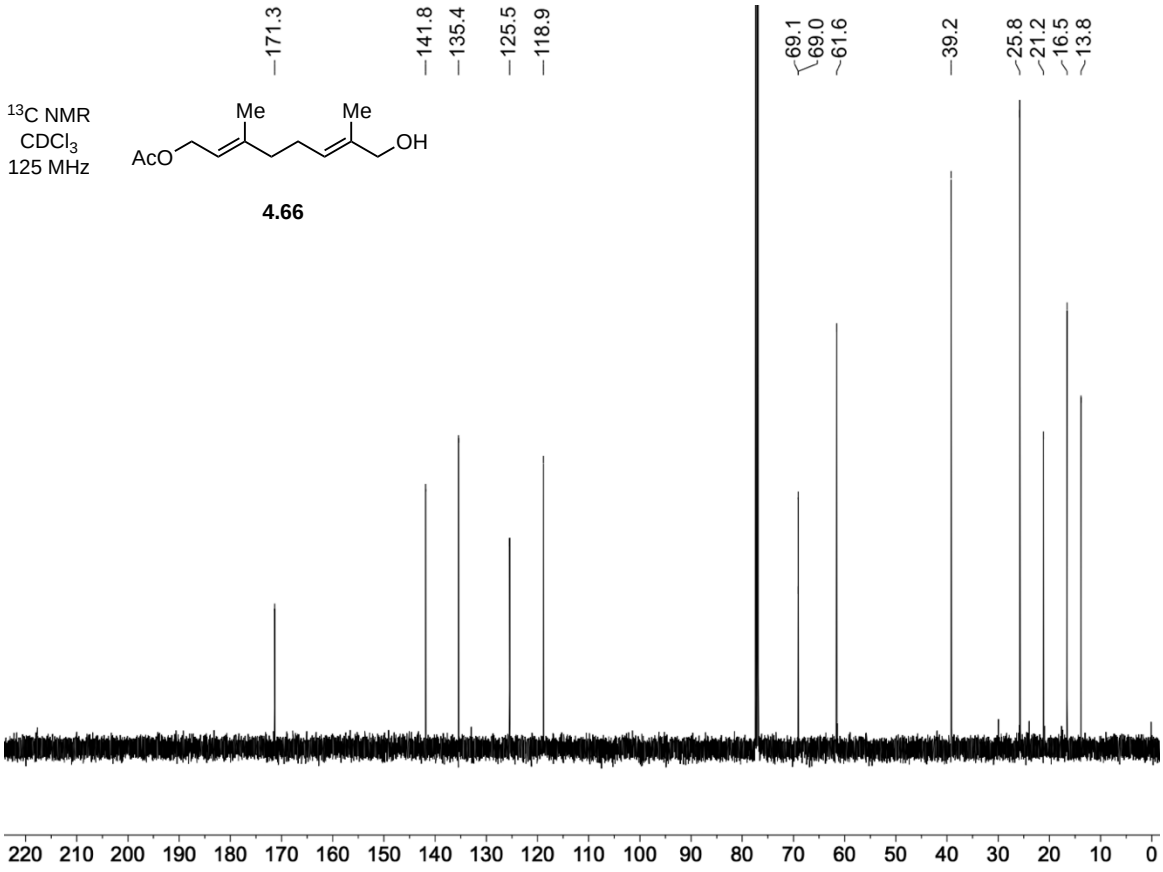
Table 4.9 – ^{1}H NMR and ^{13}C NMR Comparison for Rhodonoid B

NMR Assignment	Synthetic Sample ($CDCl_3$) George *et al.* (2021)		Natural Sample ($CDCl_3$) Hou *et al.* (2015)[5]	
	^{1}H NMR (600 MHz)	^{13}C NMR (150 MHz)	^{1}H NMR (600 MHz)	^{13}C NMR (150 MHz)
2	--	83.9	--	83.9
3	2.60 (dd, *J* = 9.0, 8.0 Hz)	39.1	2.59 (dd, *J* = 9.0, 8.0 Hz)	39.1
4	3.18 (d, *J* = 9.3 Hz)	36.5	3.17 (d, *J* = 9.0 Hz)	36.6
4a	--	109.6	--	109.6
5	--	154.2	--	154.2
5-OH	5.35 (br s)	--	5.42 (br s)	--
6	6.25 (s)	109.6	6.25 (br s)	109.6
7	--	137.8	--	137.8
8	6.33 (s)	111.9	6.33 (br s)	111.9
8a	--	154.5	--	154.6
9	1.60 – 1.56 (m) 1.98 – 1.90 (m)	39.5	1.94 (m) 1.58 (m)	39.5
10	1.66 – 1.61 (m) 1.75 – 1.68 (m, 1H)	26.9	1.72 (m) 1.63 (m)	26.9
11	2.62 (td, *J* = 8.0, 2.6 Hz)	47.0	2.62 (m)	47.0
12	--	41.7	--	41.7
13	2.42 (d, *J* = 18.3 Hz) 2.47 (d, *J* = 18.3 Hz)	45.6	2.41 (d, *J* = 18.6 Hz) 2.49 (d, *J* = 18.6 Hz)	45.6
14	--	201.6	--	201.6
15	5.89 – 5.88 (m)	125.0	5.89 (br s)	125.0
16	--	154.4	--	154.4
17	1.78 (s)	27.7	1.78 (br s)	27.7
18	2.04 (s)	20.7	2.04 (br s)	20.7
19	1.54 (s)	30.5	1.53 (s)	30.5
20	1.32 (s)	26.4	1.32 (s)	26.4
21	2.22 (s)	21.4	2.22 (s)	21.4

4.4.4 NMR Spectra

Data for 4.66





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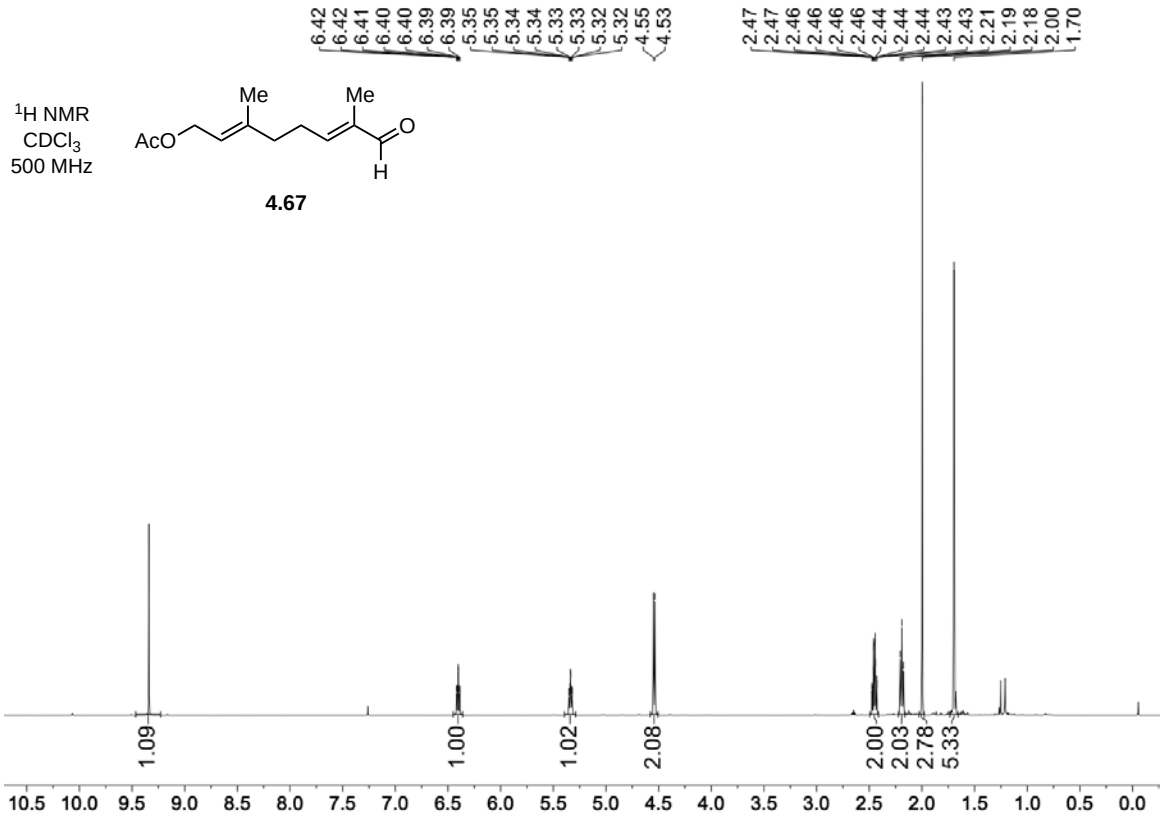
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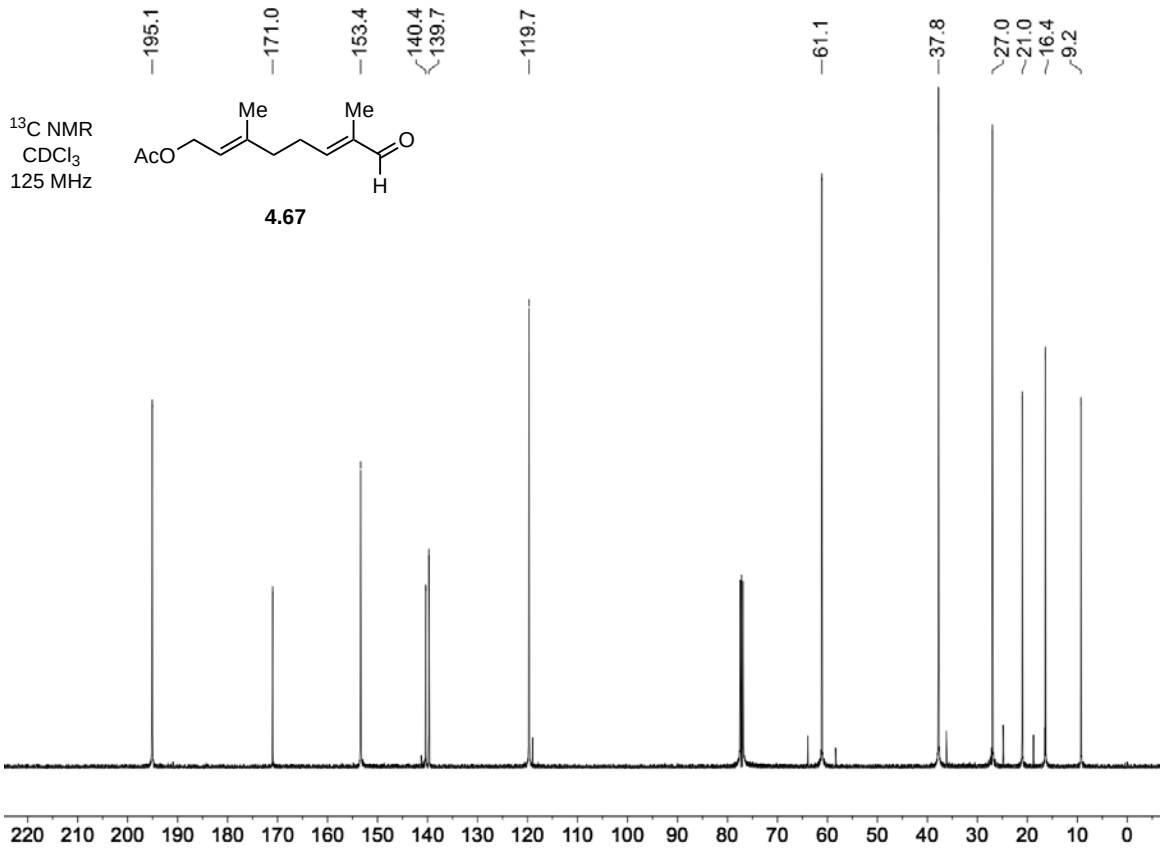
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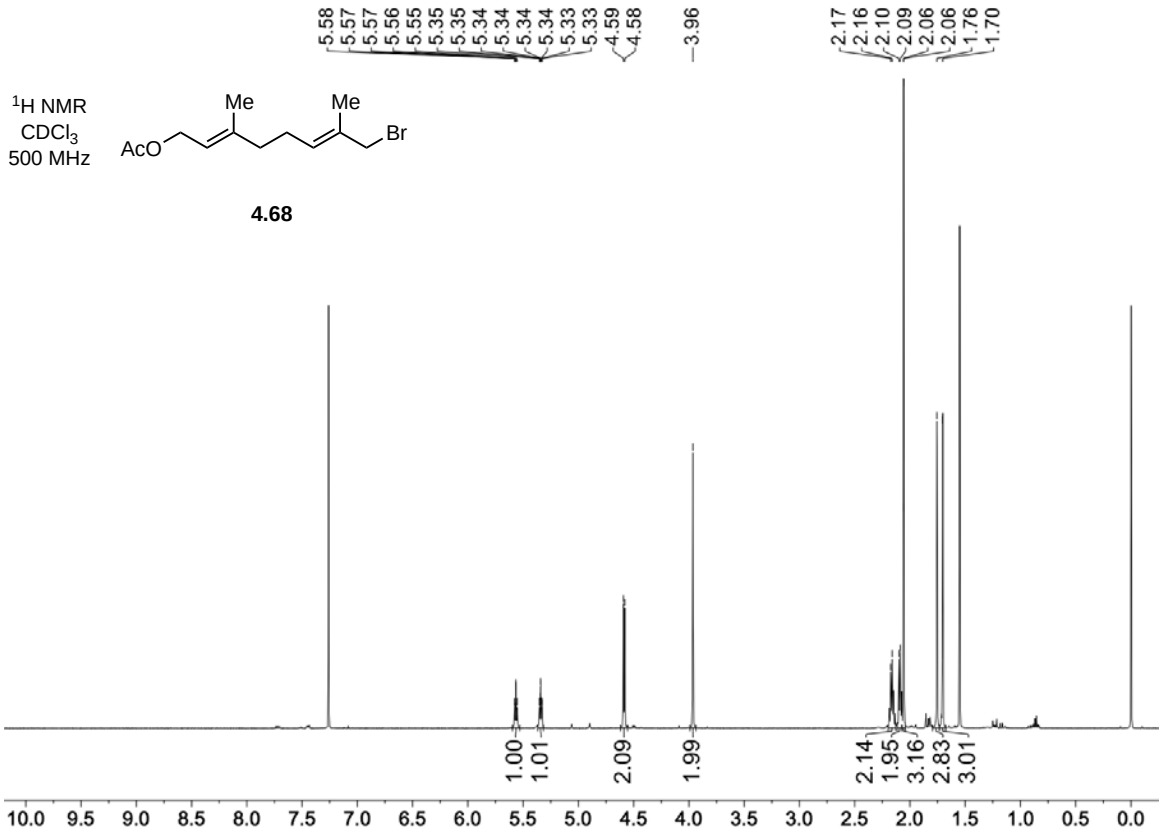
Data for 4.68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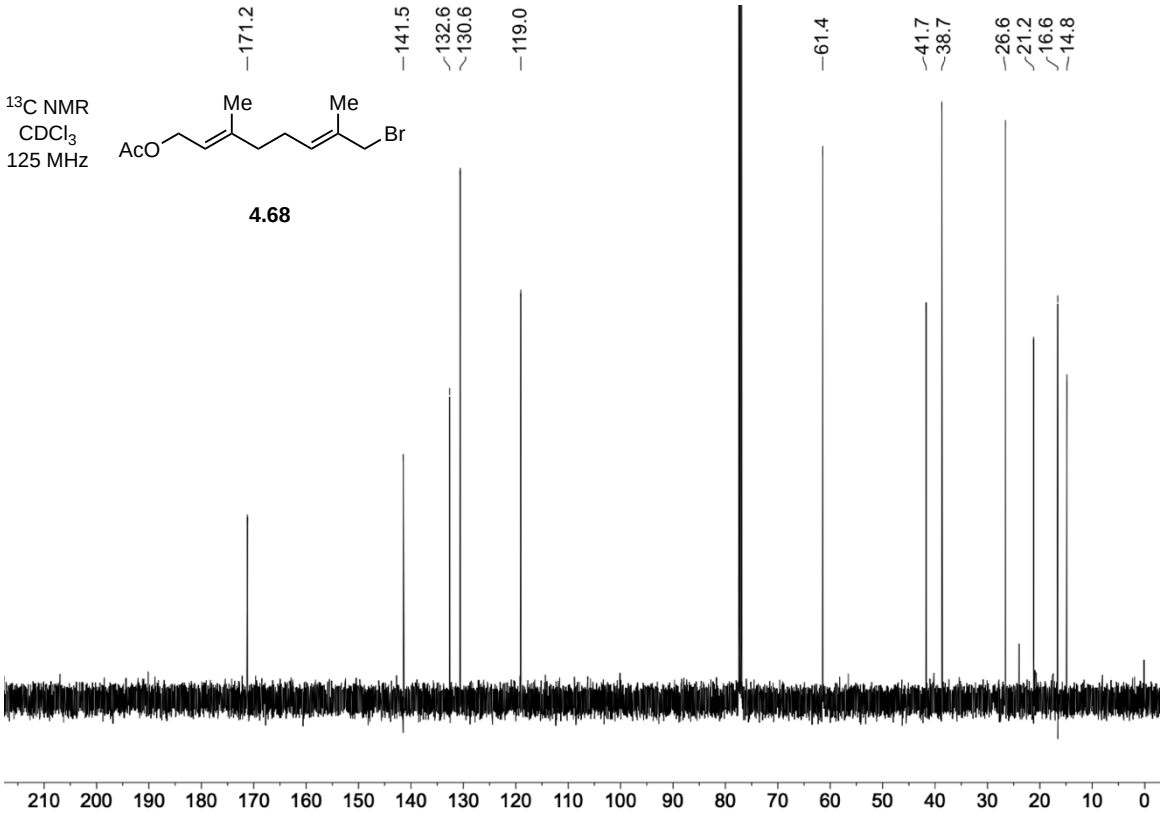
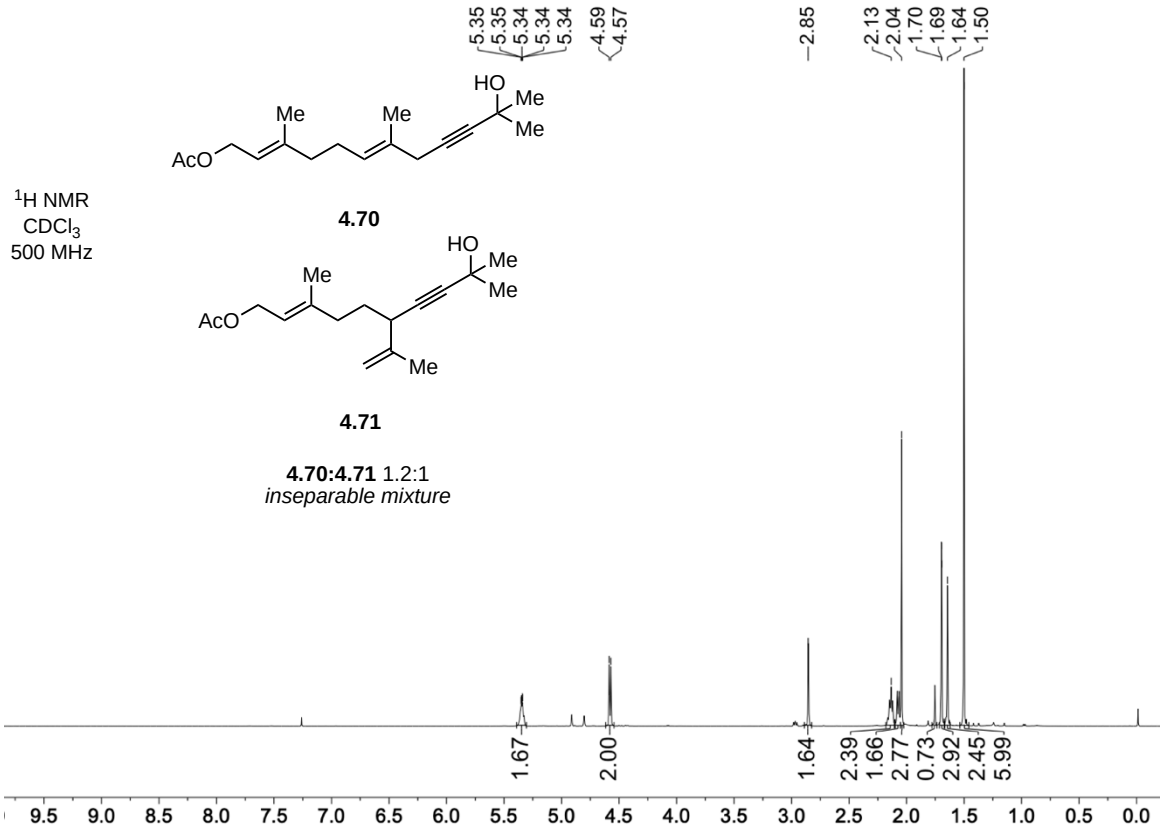
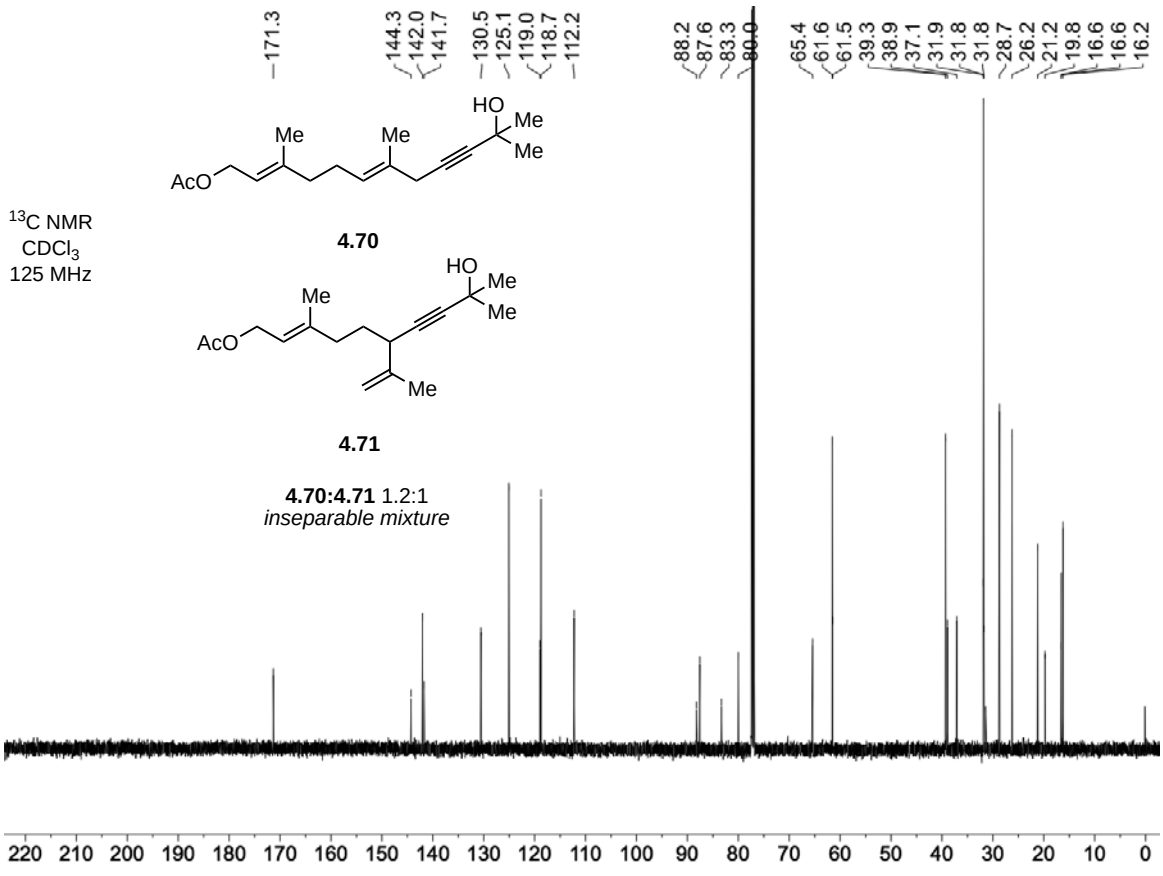
4.68
1.00
1.01
2.09
1.99
2.14
1.95
3.16
2.83
3.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

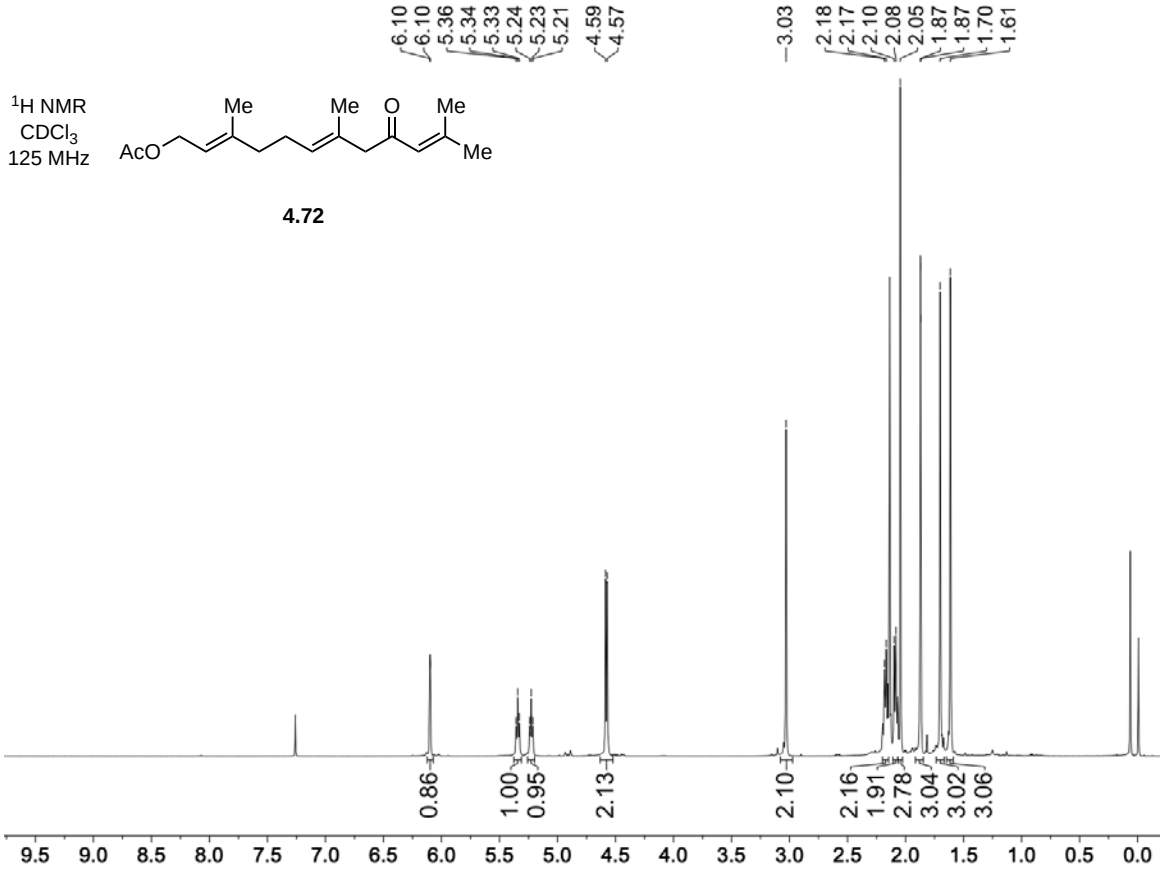

171.2
141.5
132.6
130.6
119.0
61.4
41.7
38.7
26.6
21.2
16.6
14.8
13C NMR
CDCl3
125 MHz
Me
Me
AcO
Br
4.68
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Data for 4.70 and 4.71

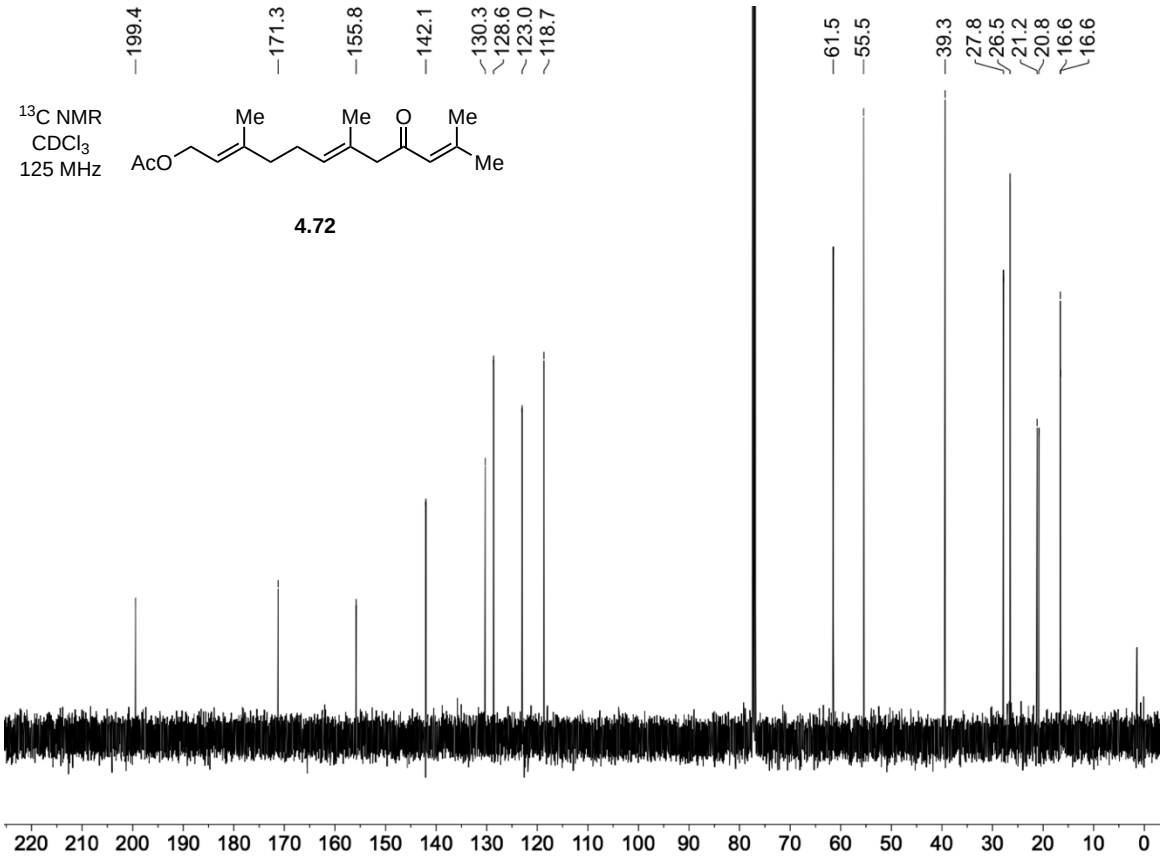




Data for 4.72

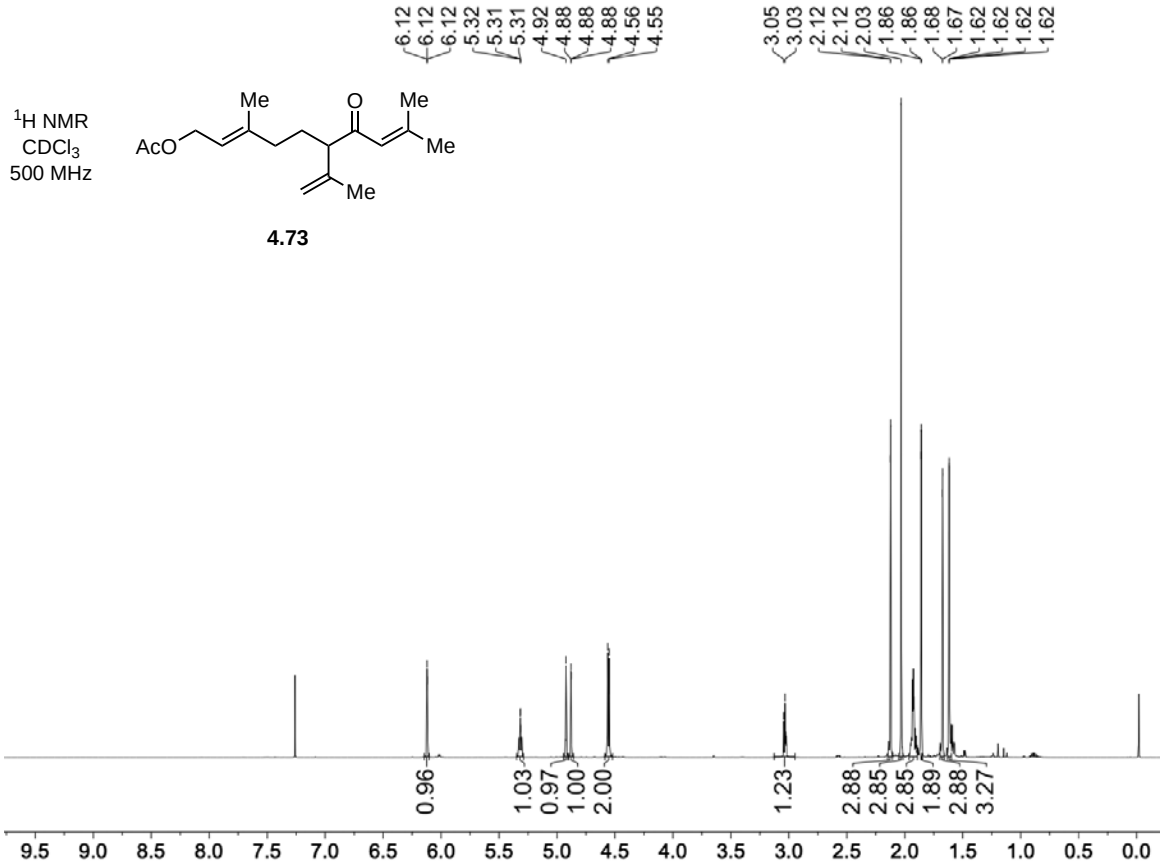


4.72

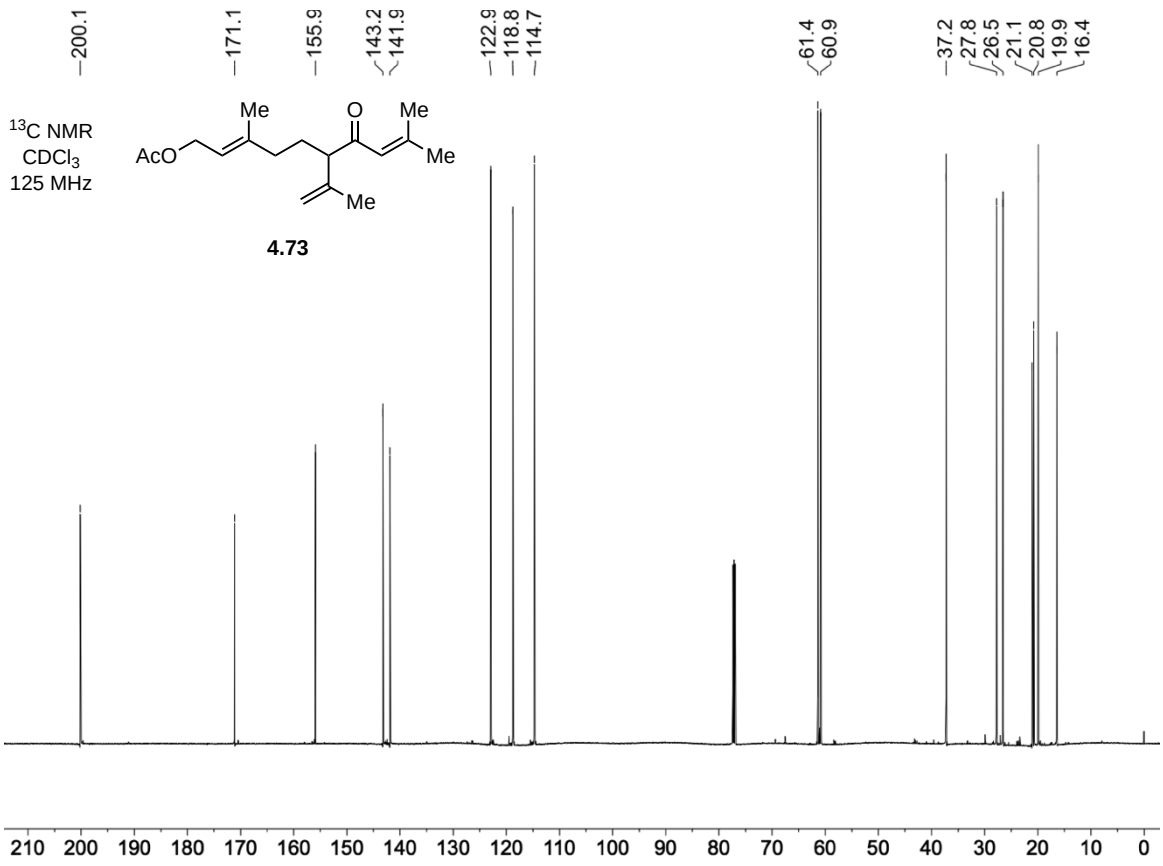


4.72

Data for 4.73



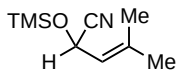
4.73



4.73

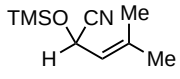
Data for 4.74

^{1}H NMR
$CDCl_3$
500 MHz



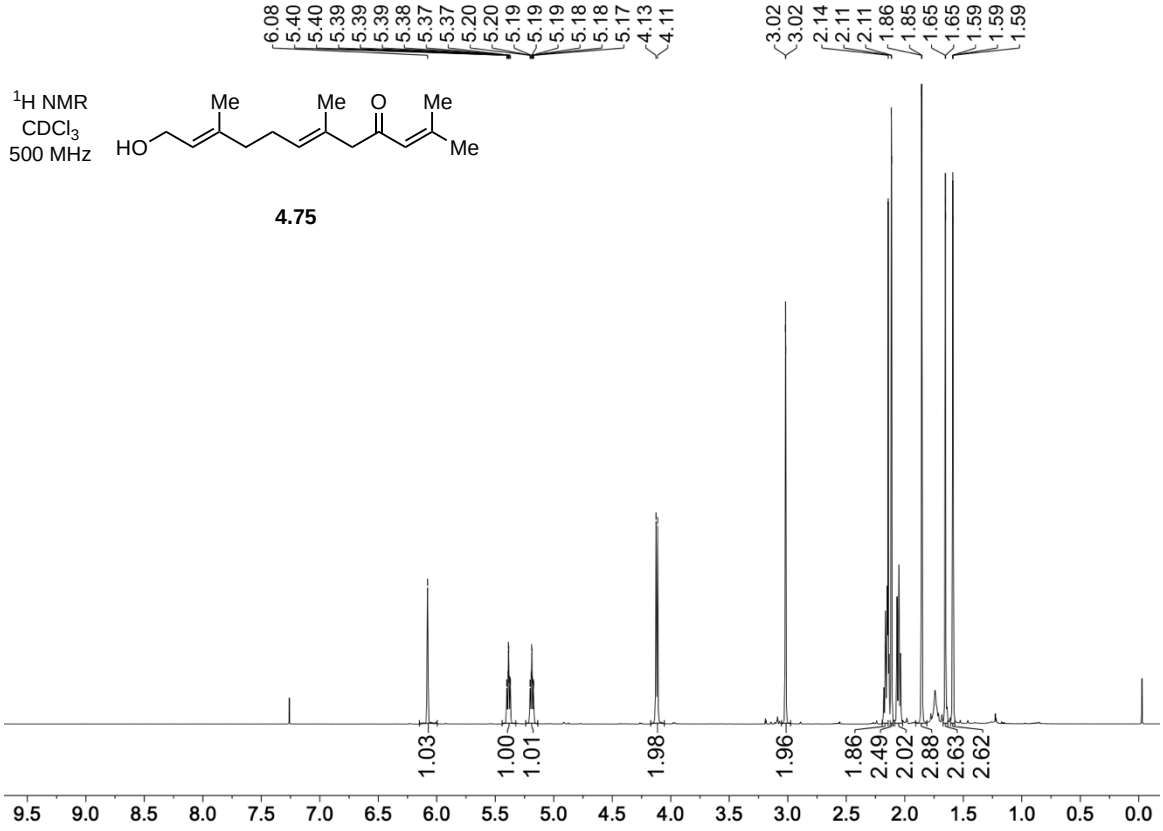
4.74

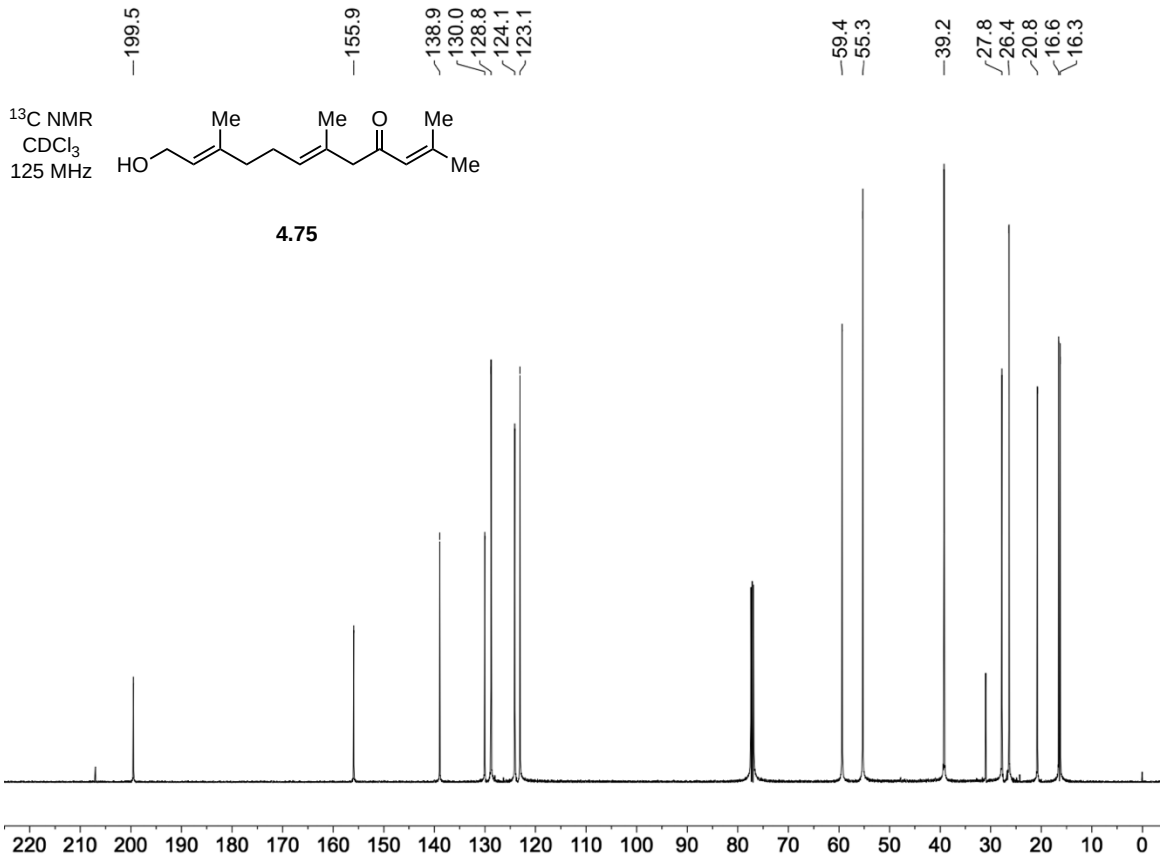
^{13}C NMR
$CDCl_3$
125 MHz



4.74

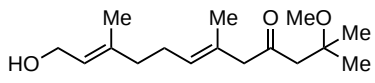
Data for 4.75


6.08
5.40
5.40
5.39
5.39
5.39
5.38
5.37
5.37
5.20
5.20
5.19
5.19
5.19
5.18
5.18
5.17
4.13
4.11
3.02
3.02
2.14
2.11
2.11
1.86
1.85
1.65
1.65
1.59
1.59
1.59
1H NMR
CDCl3
500 MHz
Me
Me
O
Me
HO
Me
4.75
1.03
1.00
1.01
1.98
1.96
1.86
2.49
2.02
2.88
2.63
2.62
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


199.5
155.9
138.9
130.0
128.8
124.1
123.1
59.4
55.3
39.2
27.8
26.4
20.8
16.6
16.3
13C NMR
CDCl3
125 MHz
Me
Me
O
Me
HO
Me
4.75
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

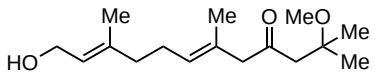
Data for 4.76

^{1}H NMR
$CDCl_3$
500 MHz



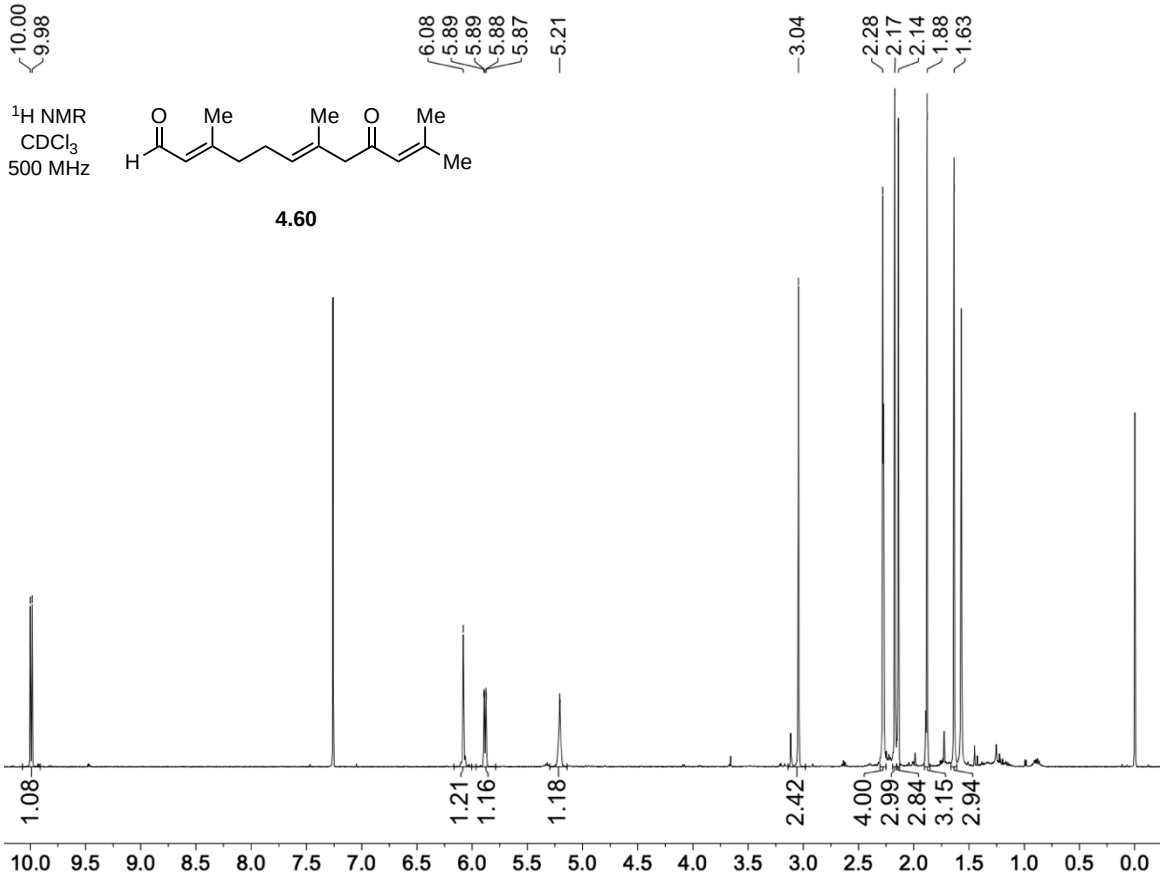
4.76

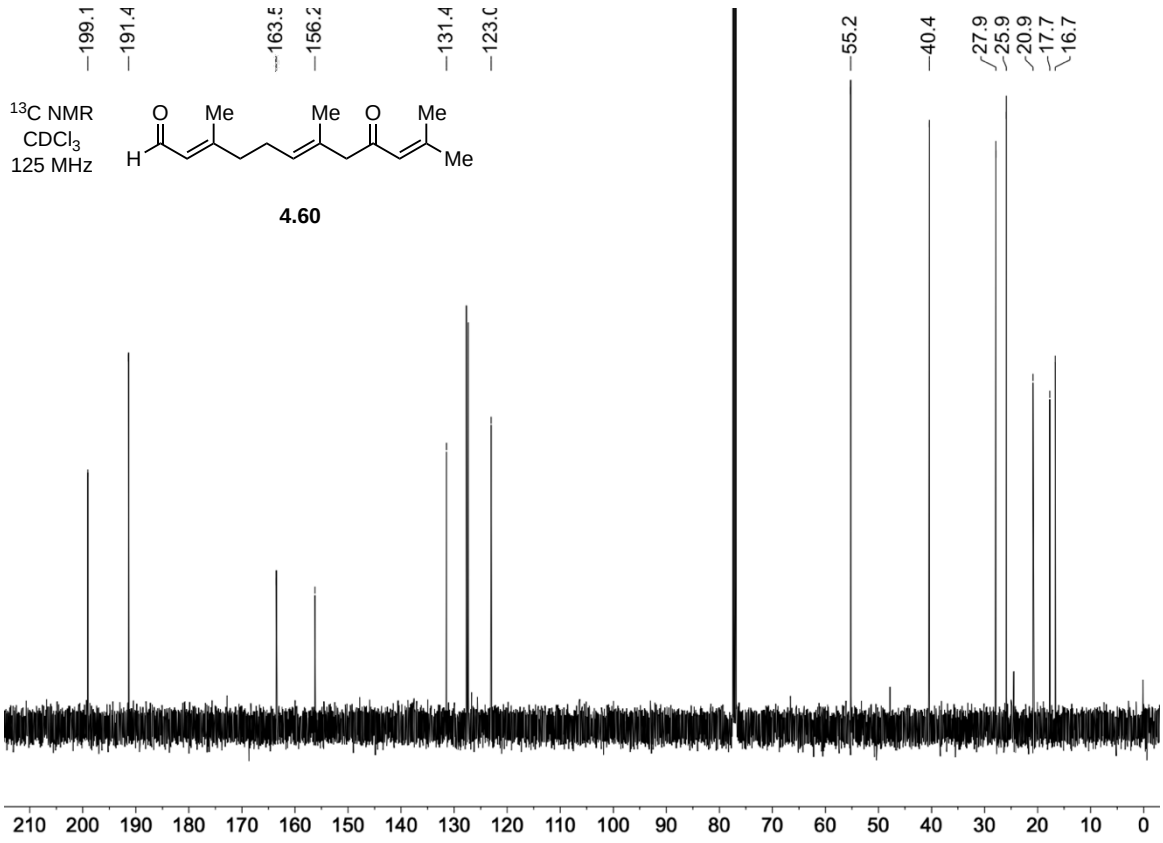
^{13}C NMR
$CDCl_3$
125 MHz



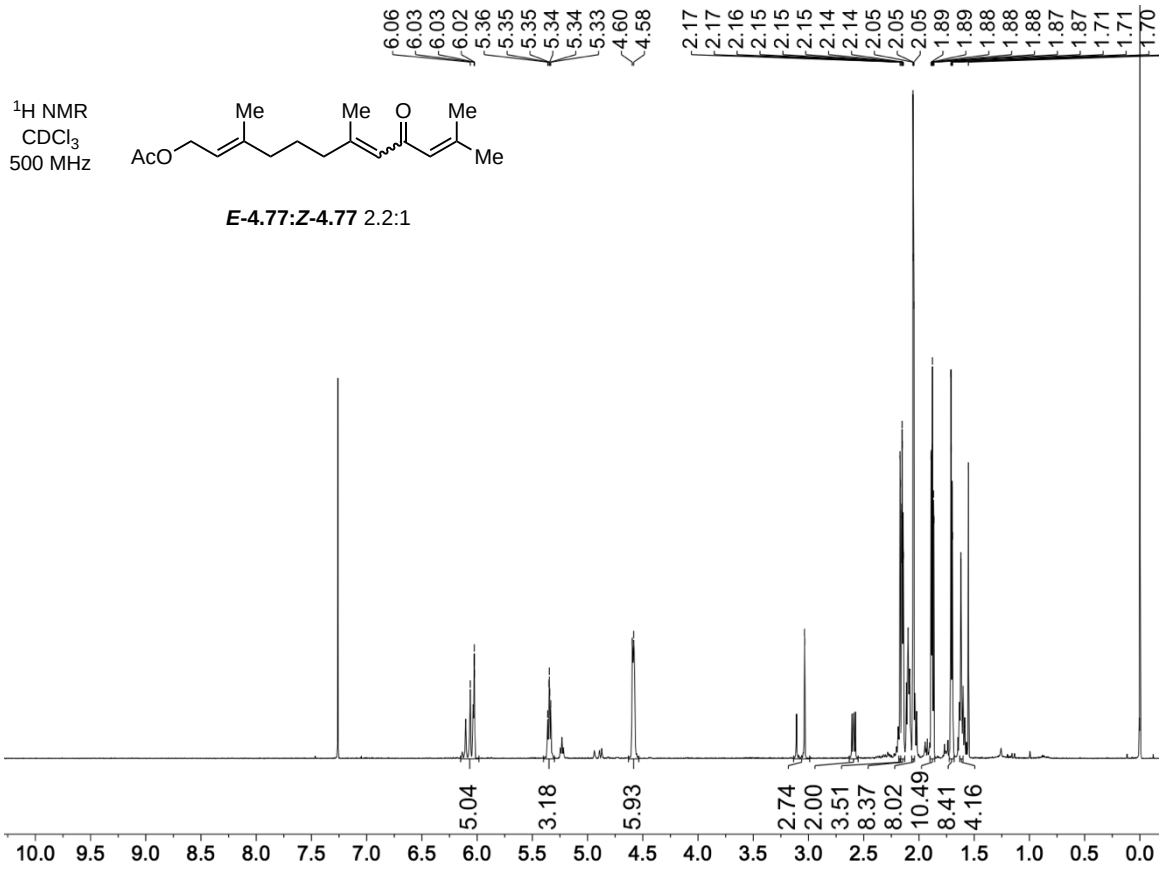
4.76

Data for 4.60

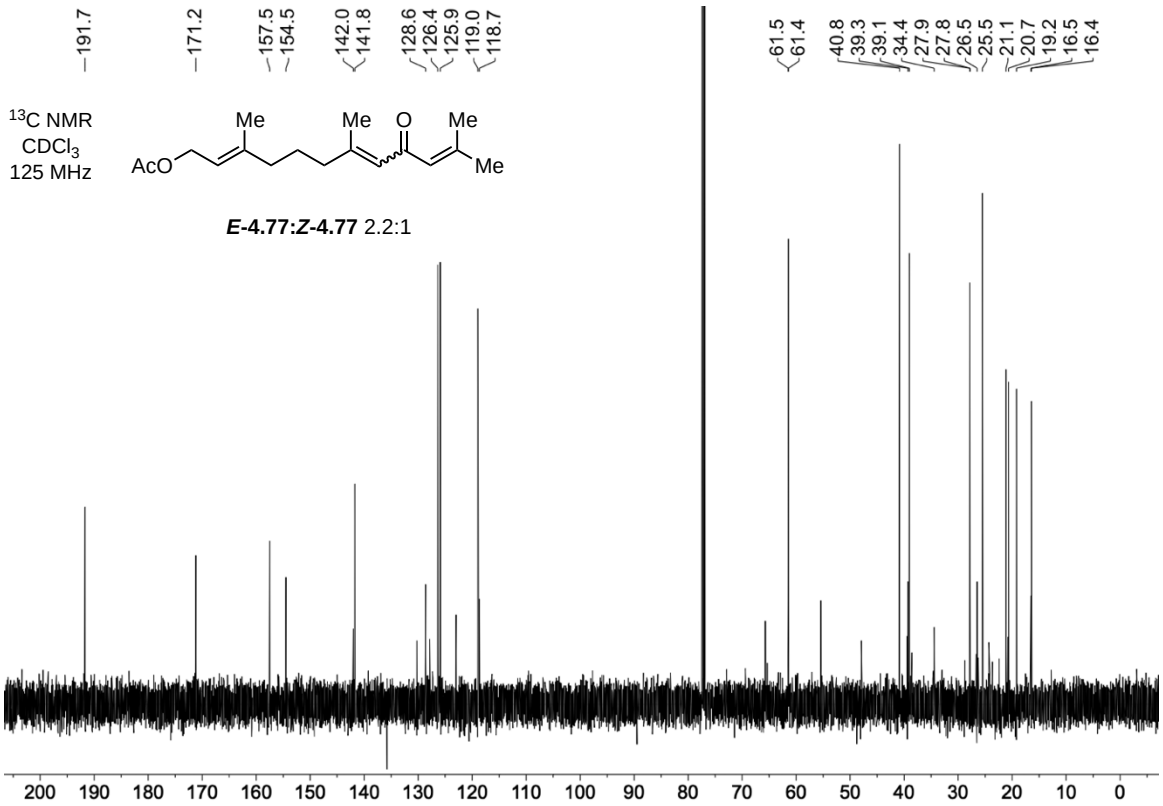

10.00
9.98
6.08
5.89
5.89
5.88
5.87
5.21
3.04
2.28
2.17
2.14
1.88
1.63
^{1}H NMR
$CDCl_3$
500 MHz
O
Me
Me
O
Me
H
Me
4.60
1.08
1.21
1.16
1.18
2.42
4.00
2.99
2.84
3.15
2.94
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


199.1
191.4
163.5
156.2
131.4
123.0
55.2
40.4
27.9
25.9
20.9
17.7
16.7
^{13}C NMR
$CDCl_3$
125 MHz
O
Me
Me
O
Me
H
Me
4.60
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Data for 4.77

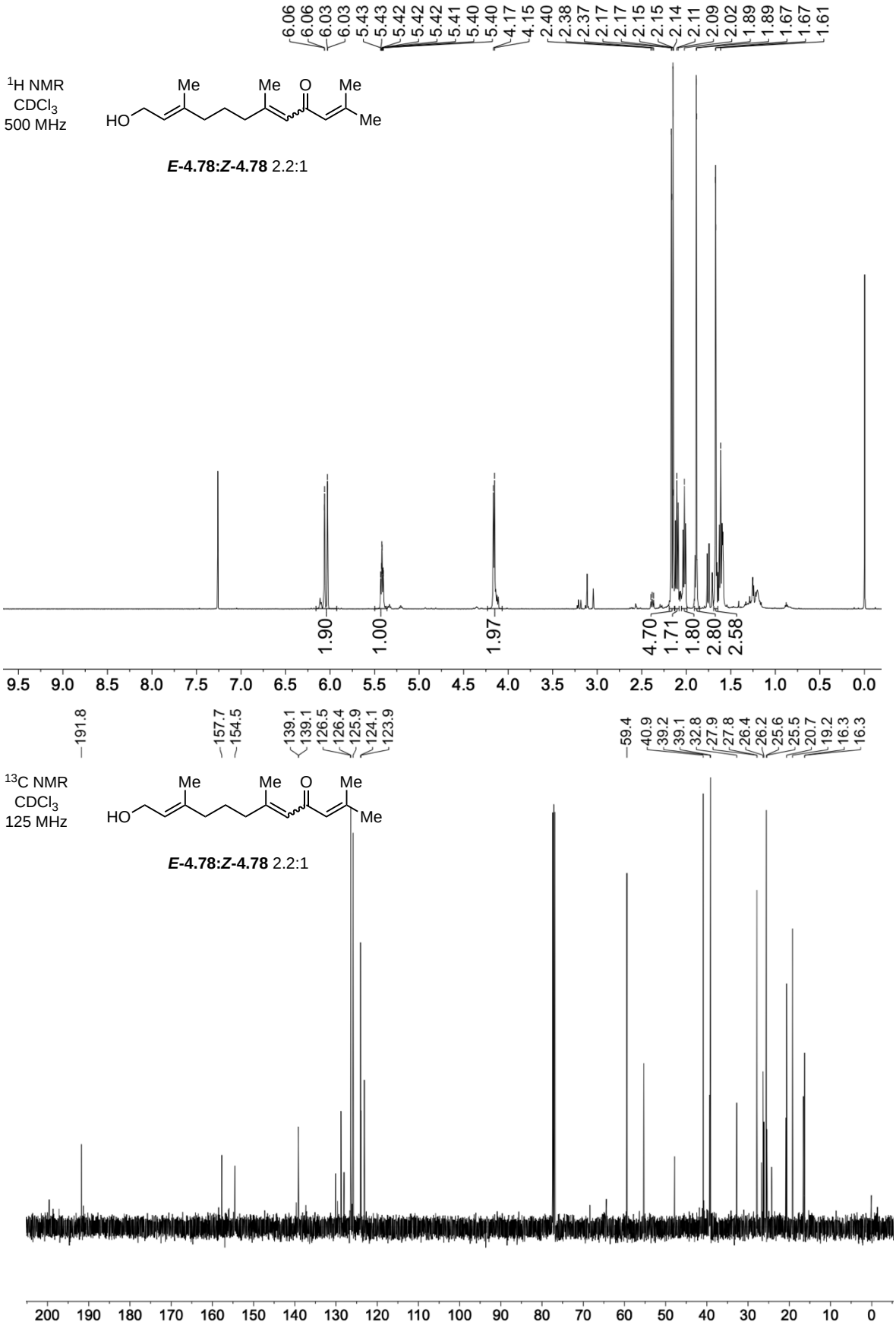


***E*-4.77:*Z*-4.77** 2.2:1

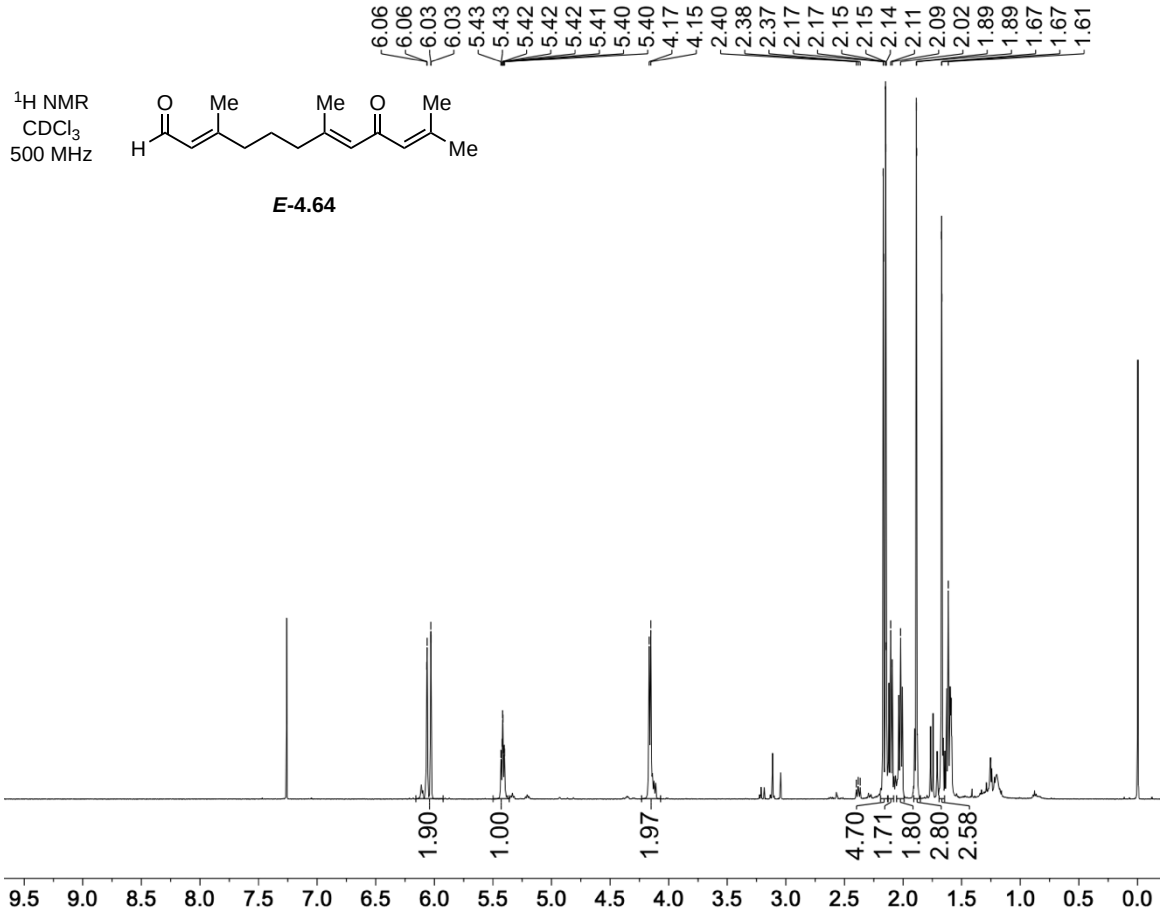


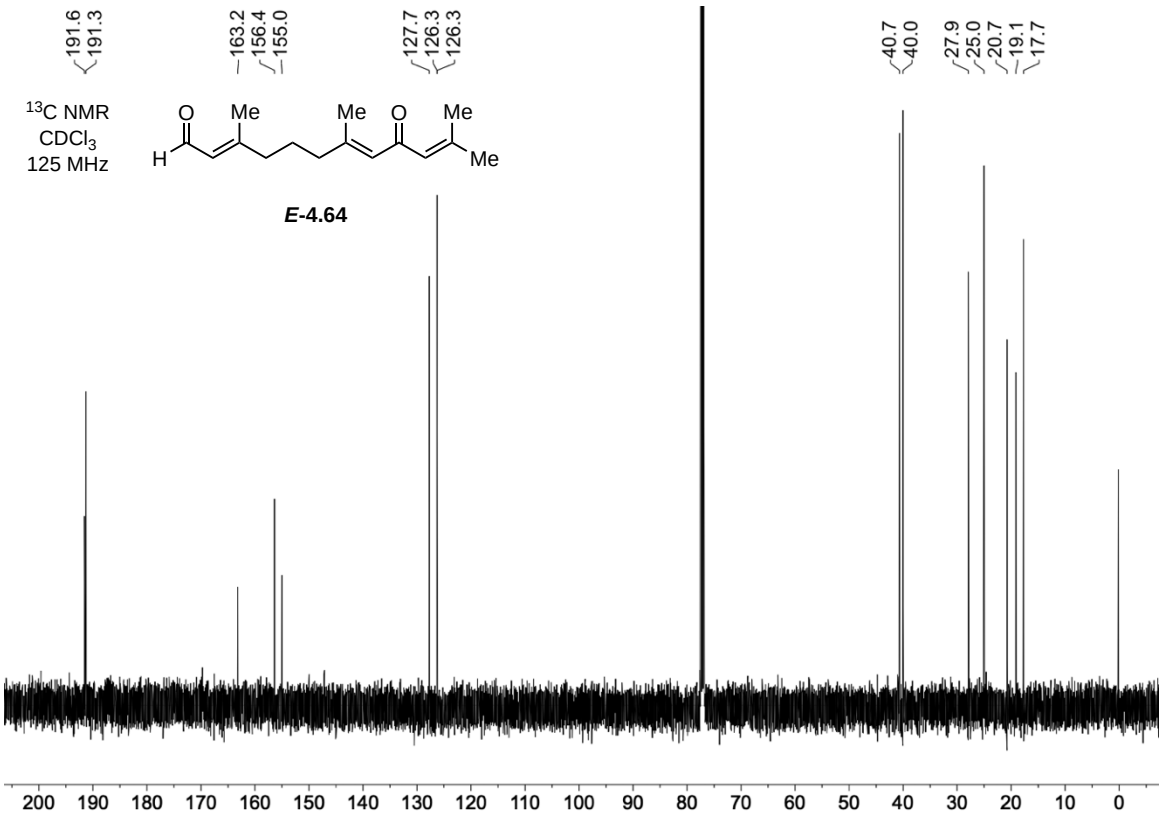
***E*-4.77:*Z*-4.77** 2.2:1

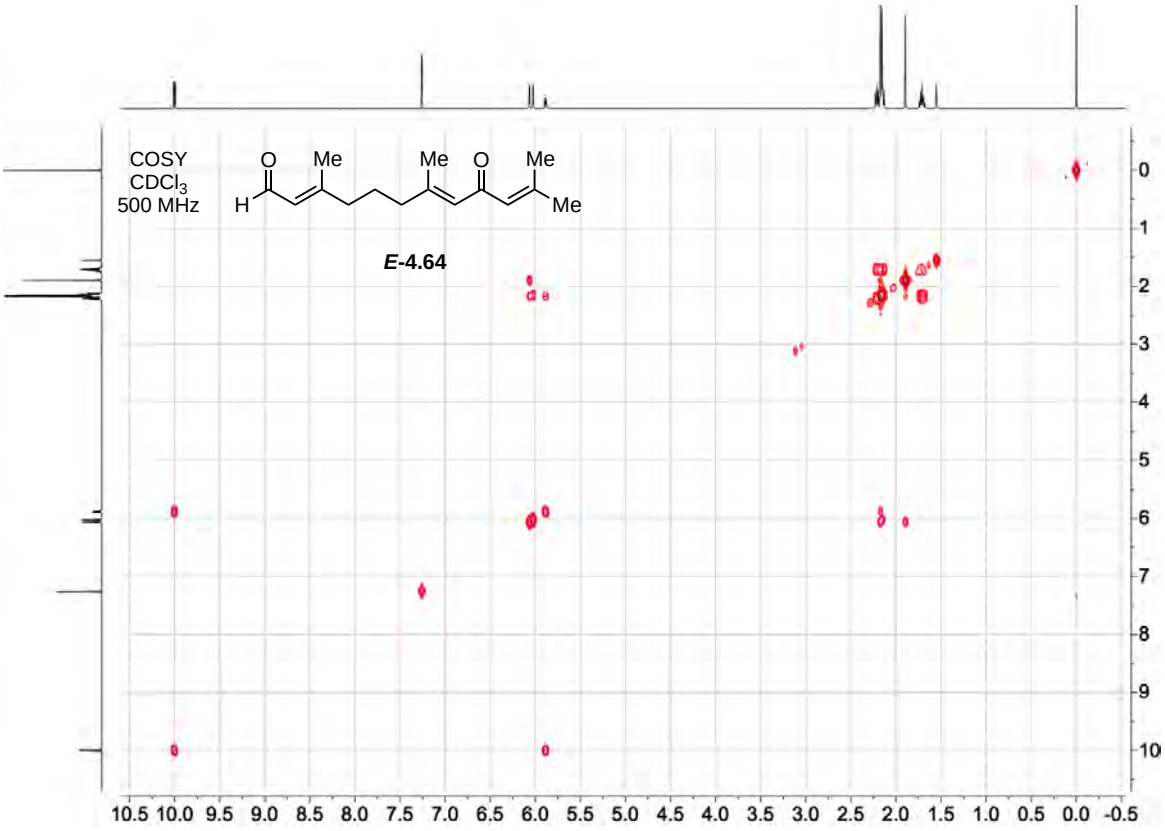
Data for 4.78

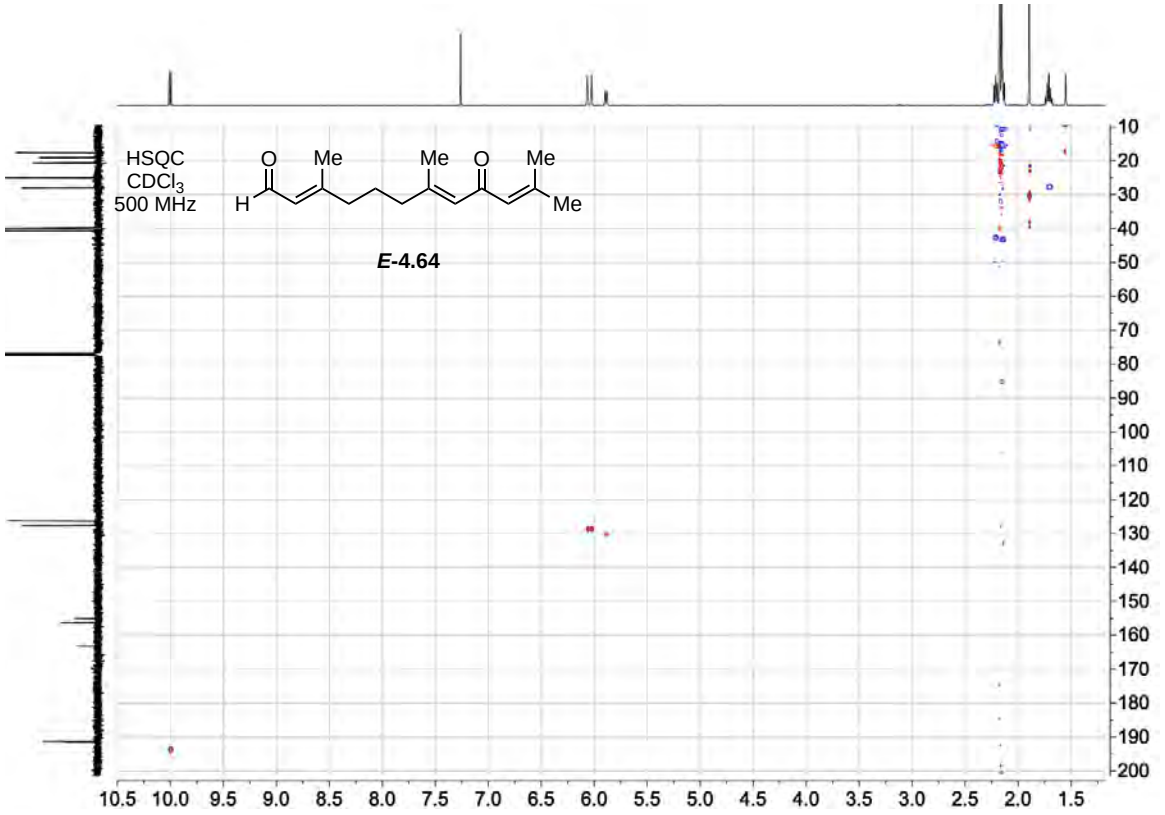

6.06
6.06
6.03
6.03
5.43
5.43
5.42
5.42
5.42
5.41
5.40
5.40
4.17
4.15
2.40
2.38
2.37
2.17
2.17
2.15
2.15
2.14
2.11
2.09
2.02
1.89
1.89
1.67
1.67
1.61
1H NMR
CDCl3
500 MHz
Me
Me
O
Me
HO
Me
E-4.78:Z-4.78 2.2:1
1.90
1.00
1.97
4.70
1.71
1.80
2.80
2.58
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
191.8
157.7
154.5
139.1
139.1
126.5
126.4
125.9
124.1
123.9
59.4
40.9
39.2
39.1
32.8
27.9
27.8
26.4
26.2
25.6
25.5
20.7
19.2
16.3
16.3
13C NMR
CDCl3
125 MHz
Me
Me
O
Me
HO
Me
E-4.78:Z-4.78 2.2:1
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

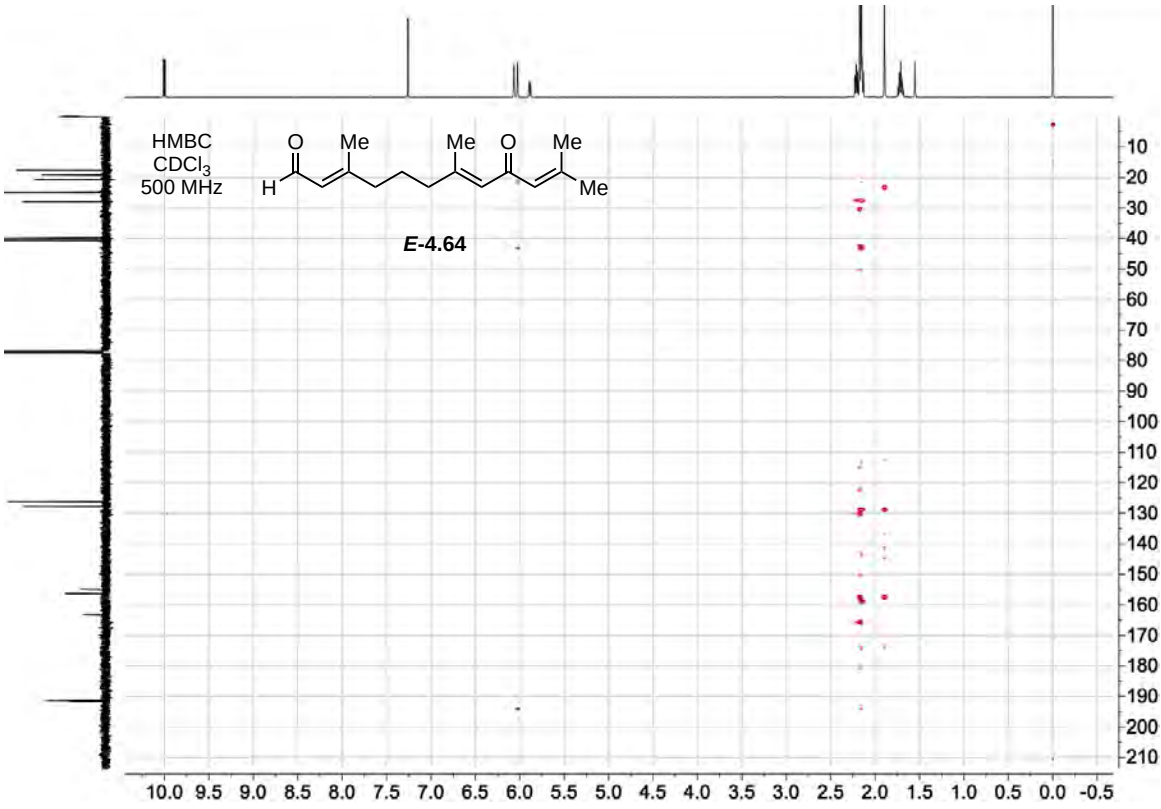
Data for *E*-4.64

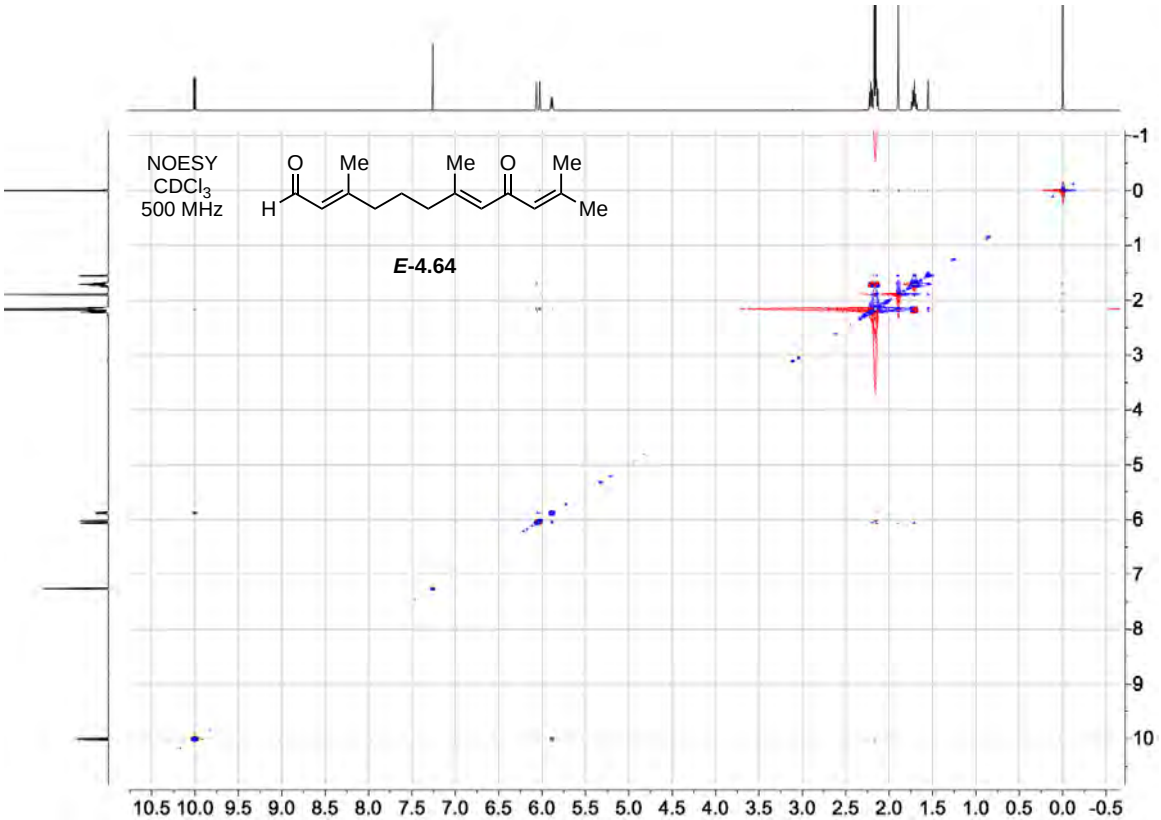


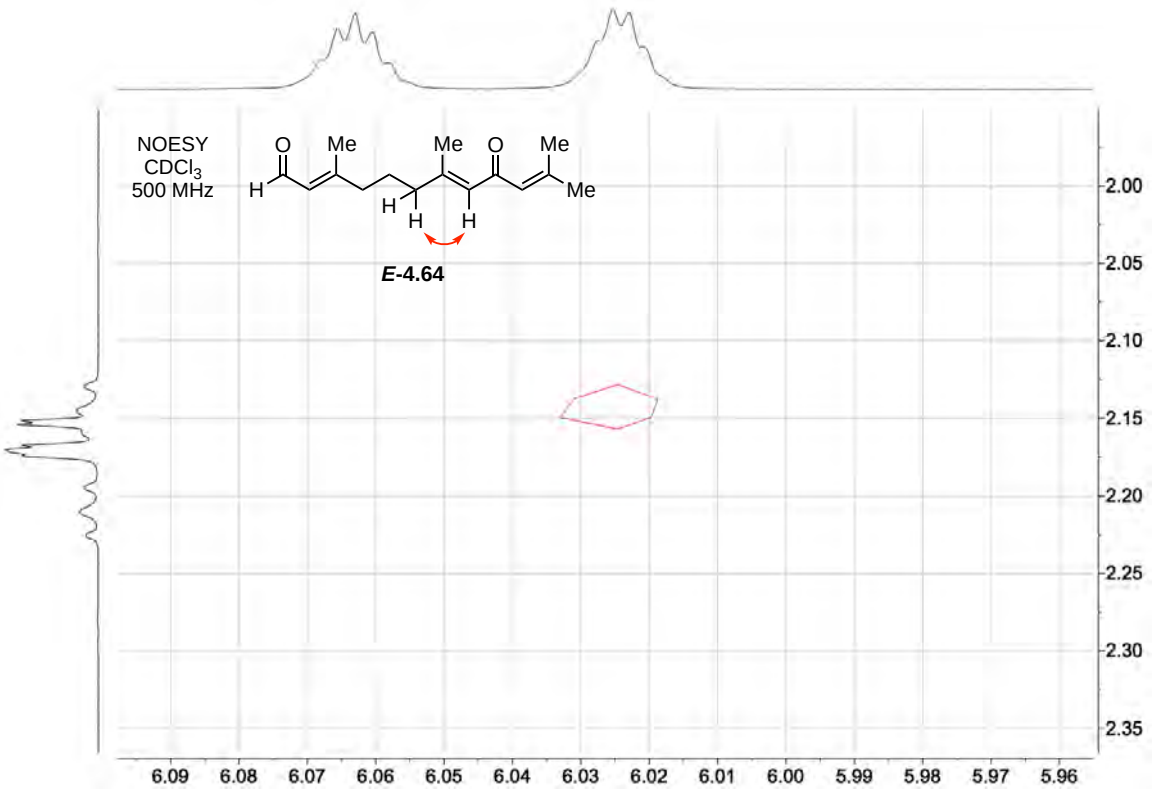



COSY
CDCl3
500 MHz
O
Me
Me
O
Me
H
Me
E-4.64
0
1
2
3
4
5
6
7
8
9
10
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

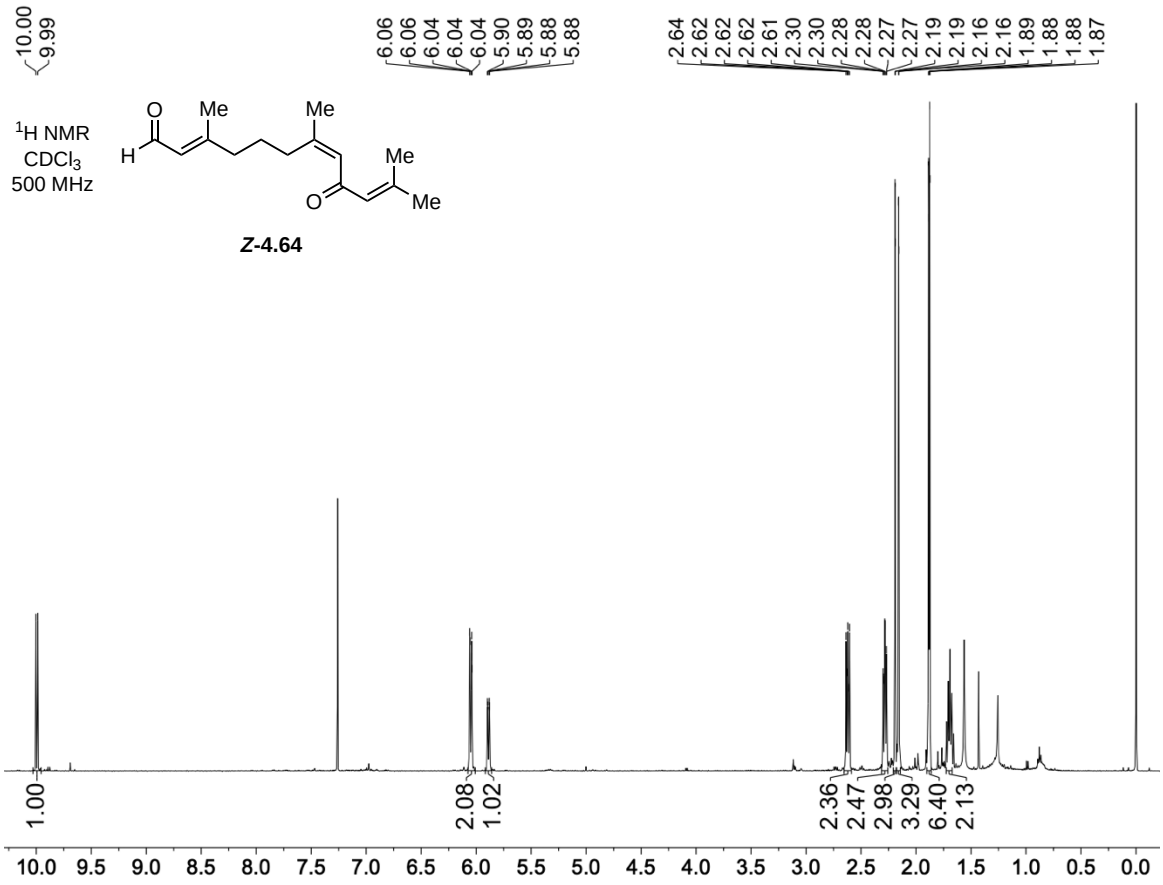

HSQC
CDCl3
500 MHz
O
Me
Me
O
Me
H
Me
E-4.64
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5

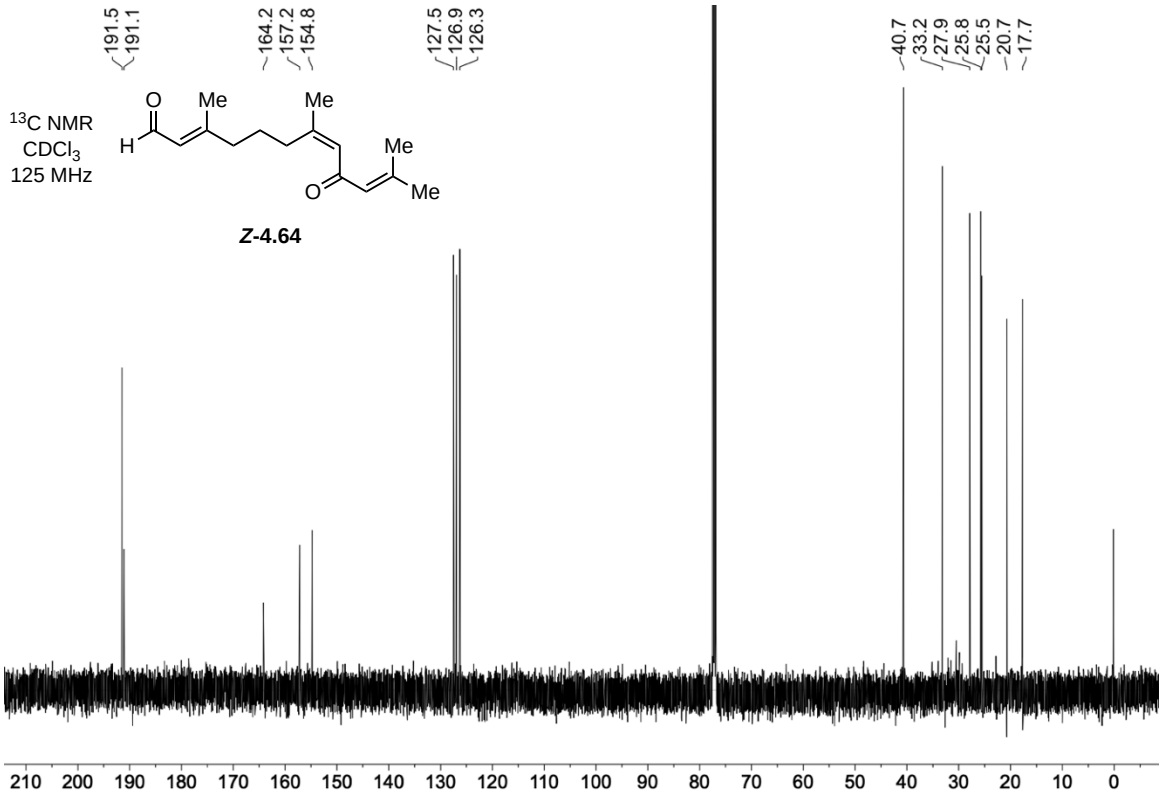

HMBC
CDCl3
500 MHz
O
Me
Me
O
Me
H
Me
E-4.64

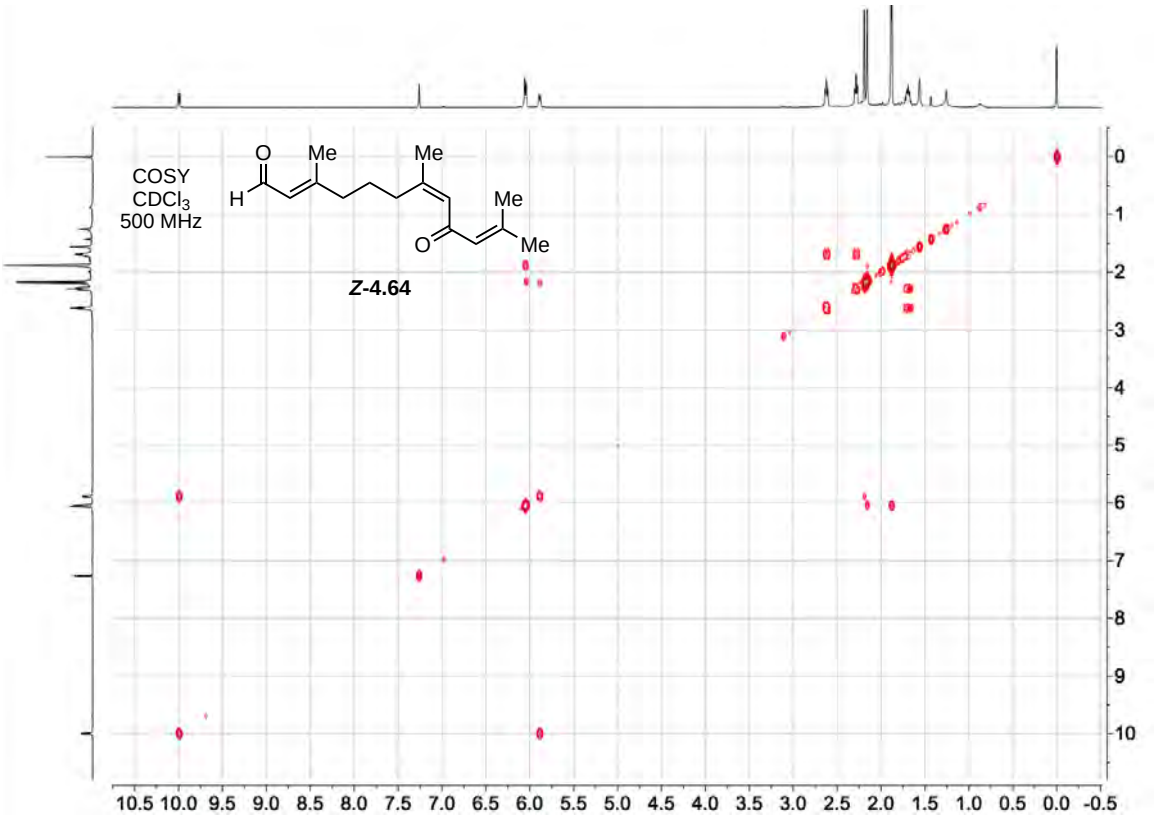

NOESY
CDCl3
500 MHz
O
Me
Me
O
Me
H
Me
E-4.64

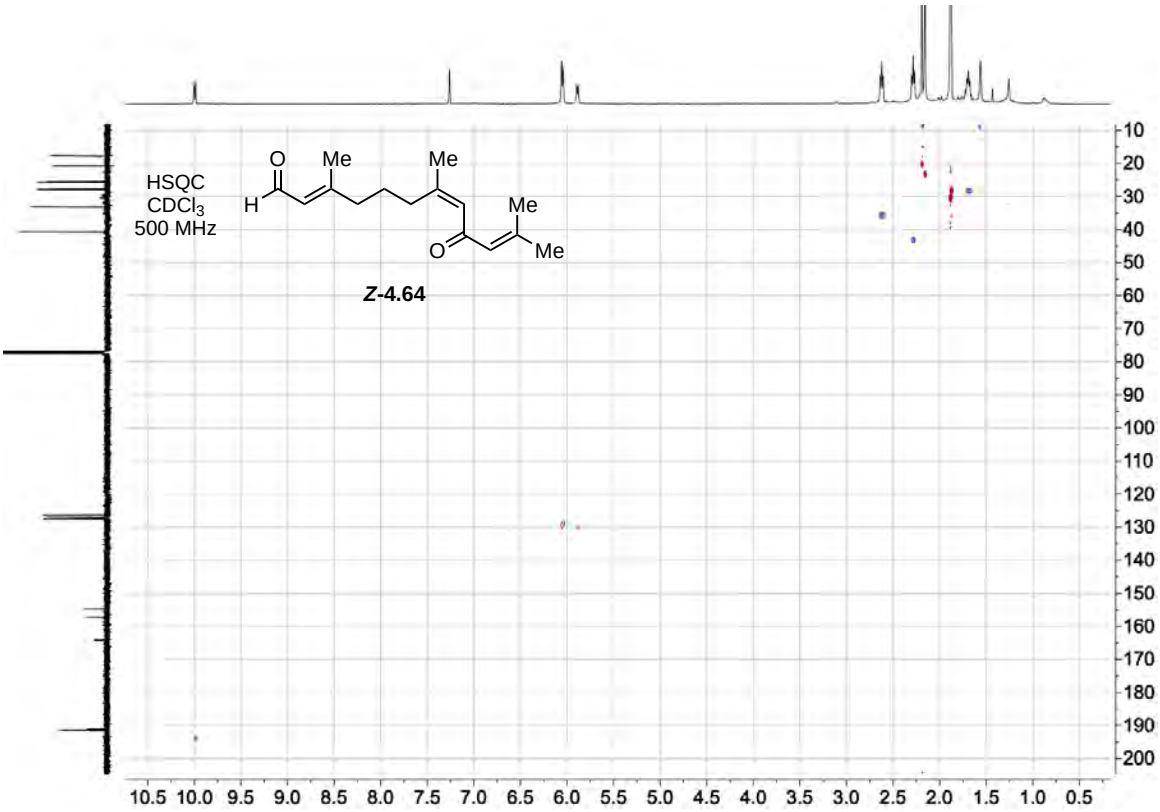

NOESY
CDCl3
500 MHz
O
Me
Me
O
Me
H
H
H
H
Me
E-4.64
2.00
2.05
2.10
2.15
2.20
2.25
2.30
2.35
6.09
6.08
6.07
6.06
6.05
6.04
6.03
6.02
6.01
6.00
5.99
5.98
5.97
5.96

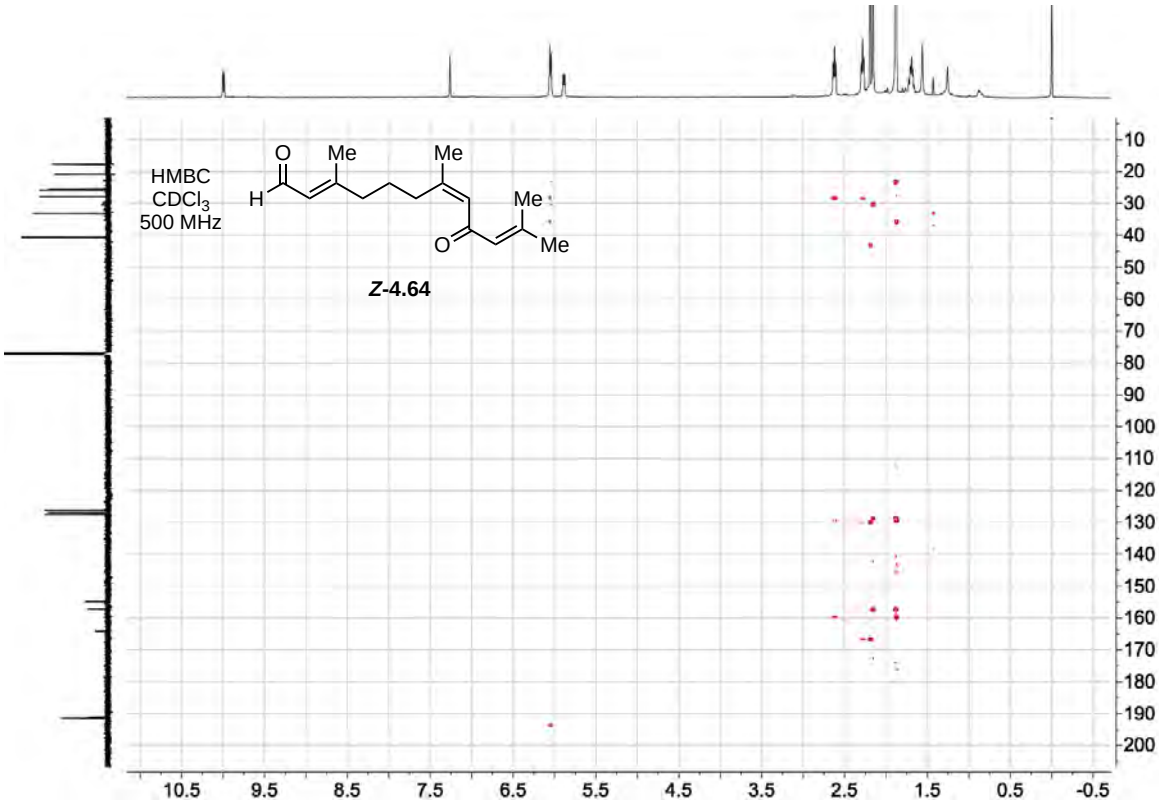
Data for *Z*-4.64

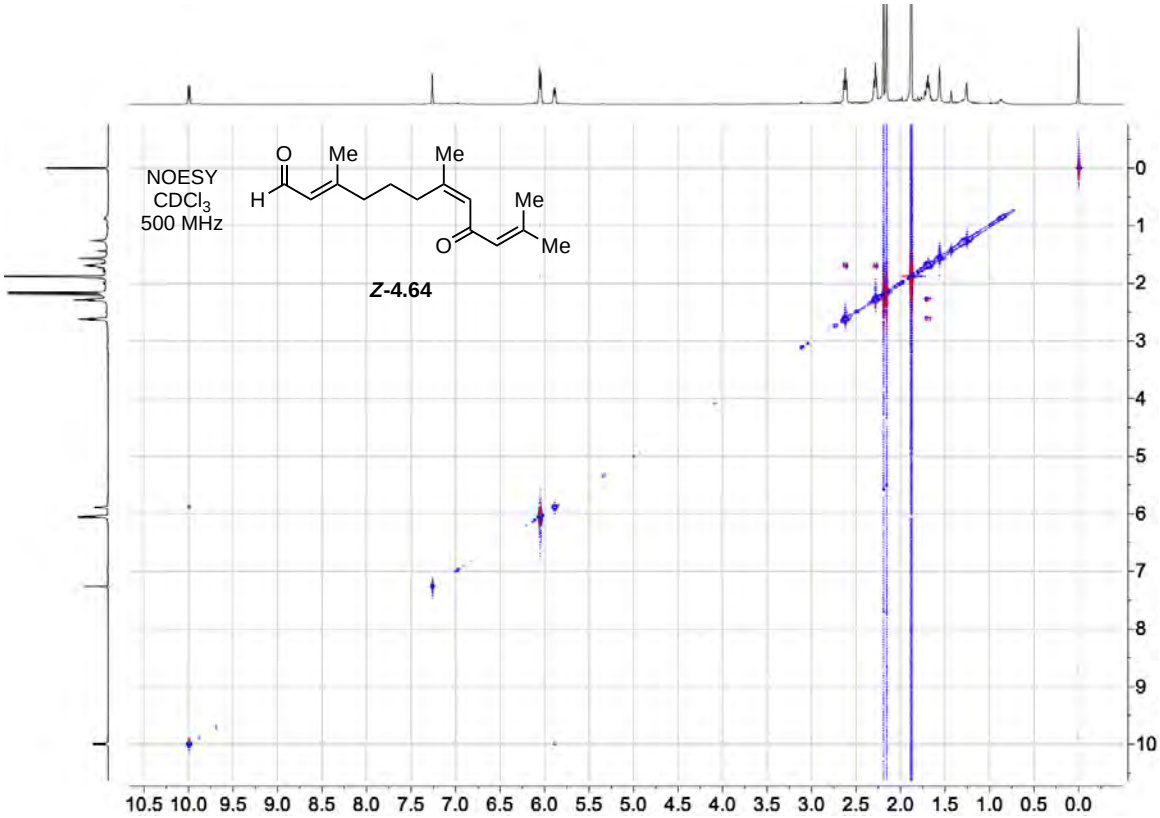




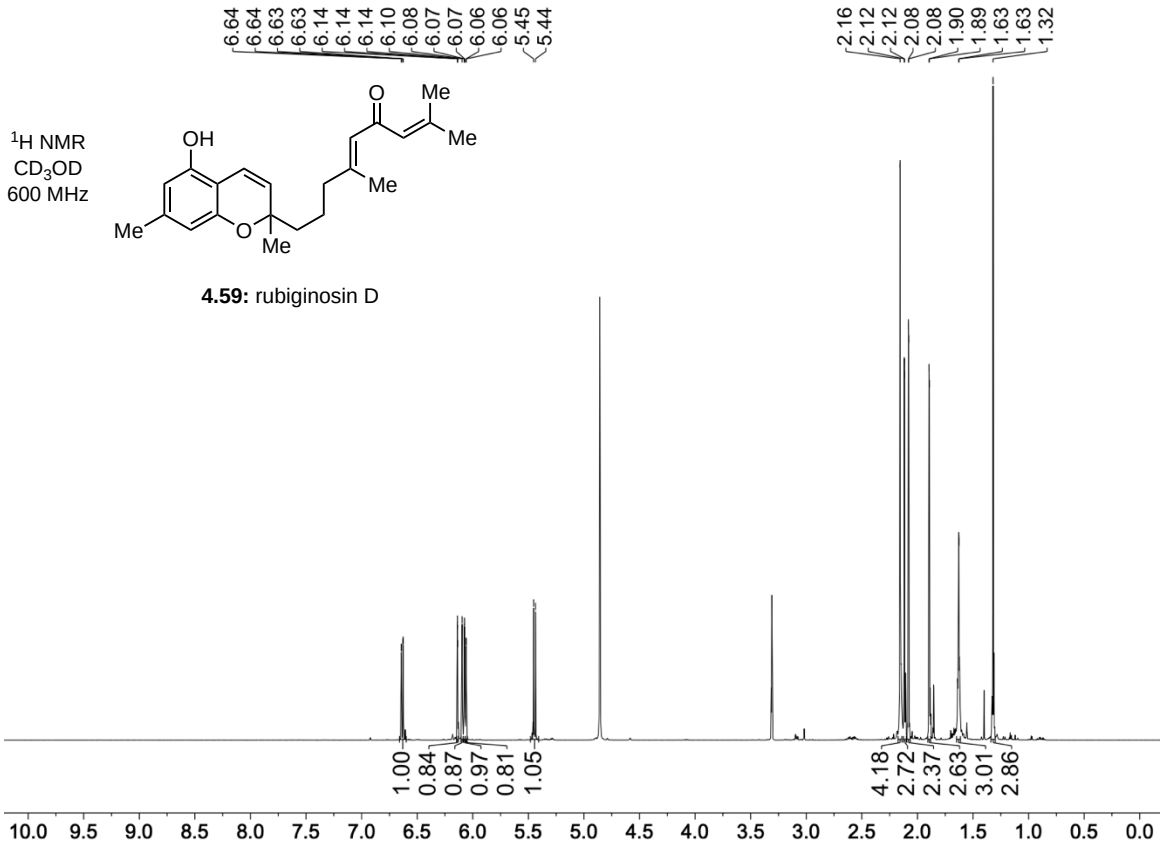

COSY
CDCl3
500 MHz
O
H
Me
Me
Me
O
Me
Z-4.64


HSQC
CDCl3
500 MHz
O
H
Me
Me
Me
O
Me
Z-4.64

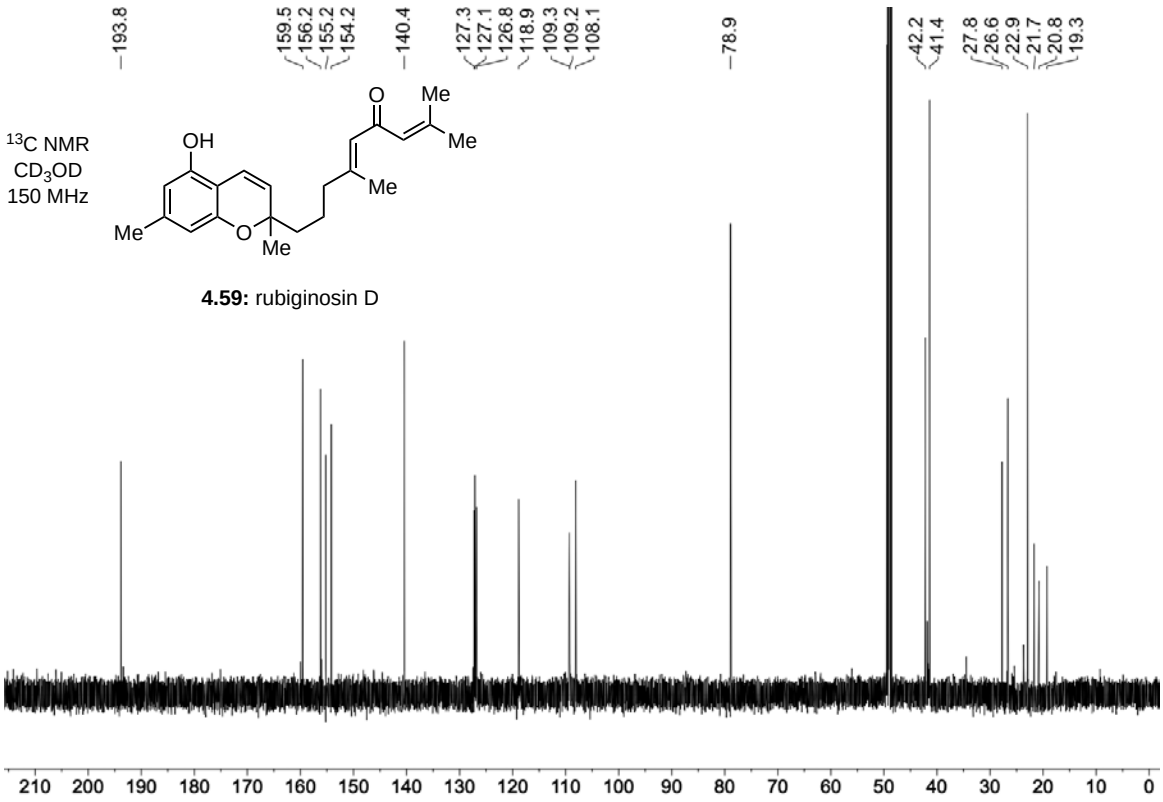

HMBC
CDCl3
500 MHz
O
Me
Me
H
Me
O
Me
Z-4.64
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5


NOESY
CDCl3
500 MHz
O
Me
Me
H
Me
O
Me
Z-4.64
0
1
2
3
4
5
6
7
8
9
10
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

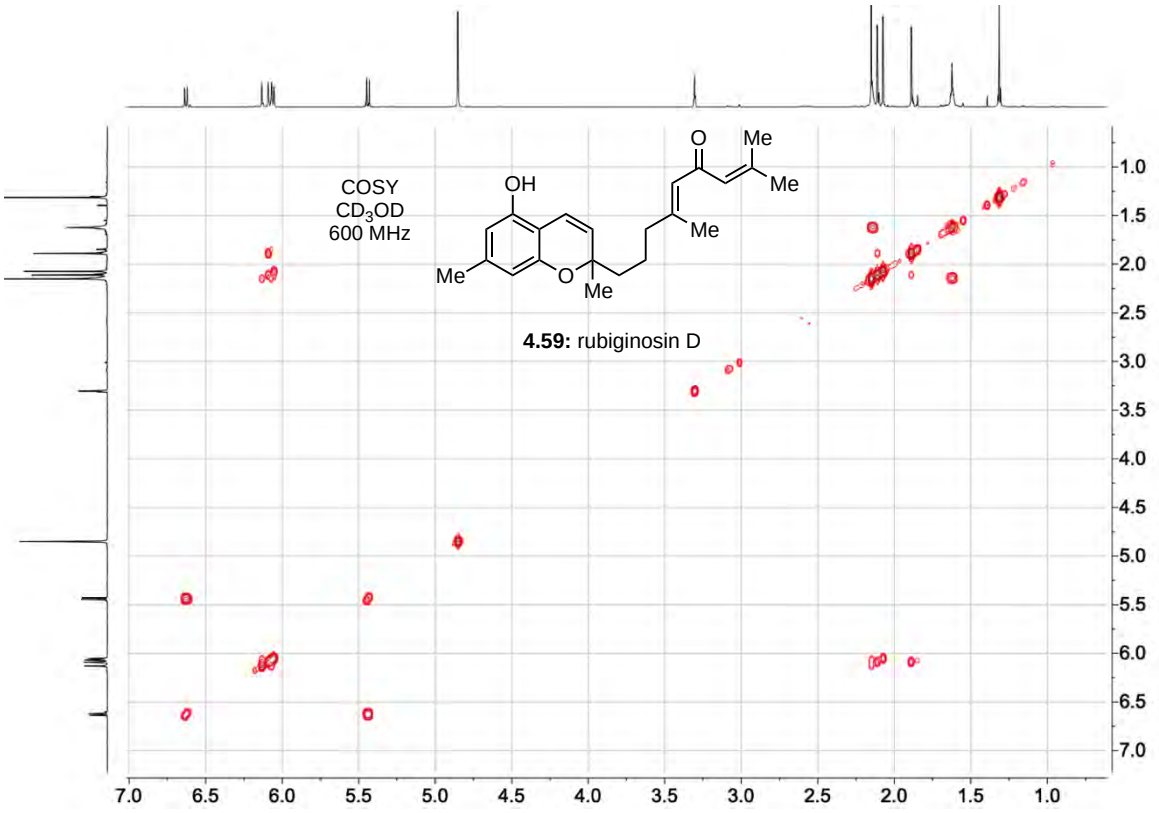
Data for rubiginosin D (4.59)

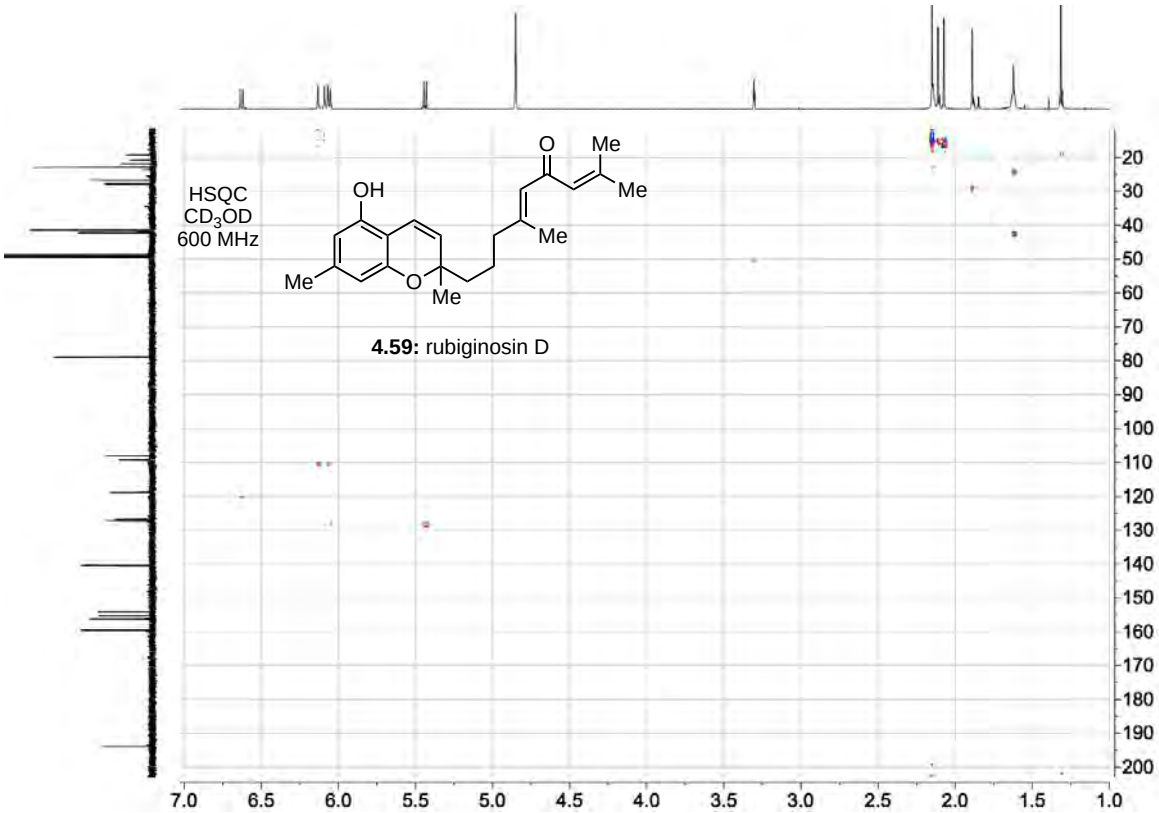


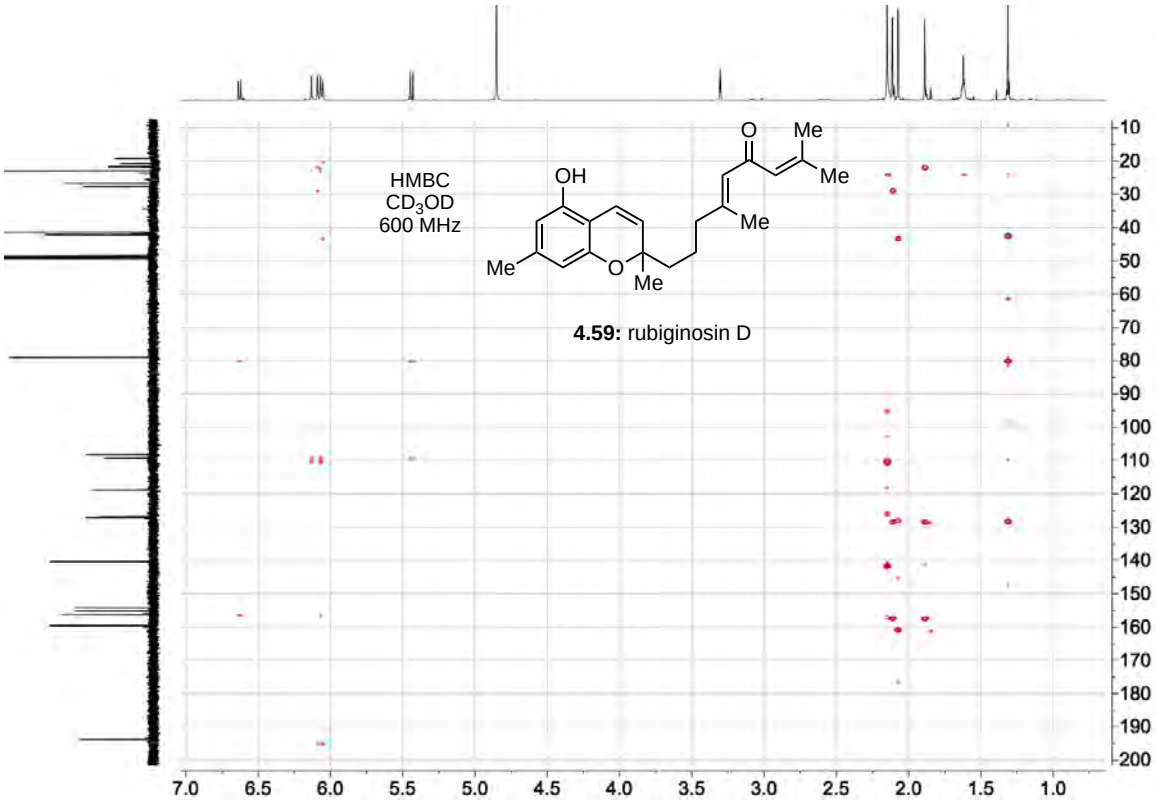
4.59: rubiginosin D



4.59: rubiginosin D

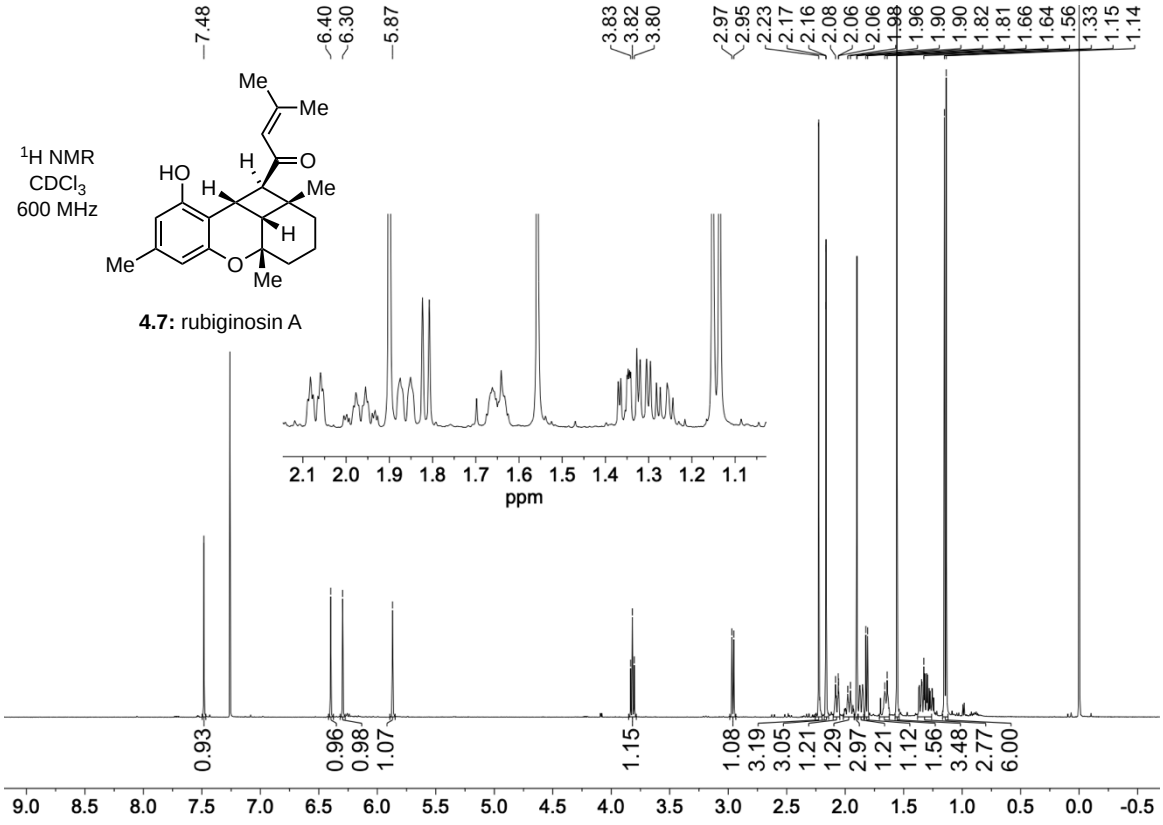

COSY
CD3OD
600 MHz
OH
O
Me
Me
Me
Me
O
Me
4.59: rubiginosin D
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

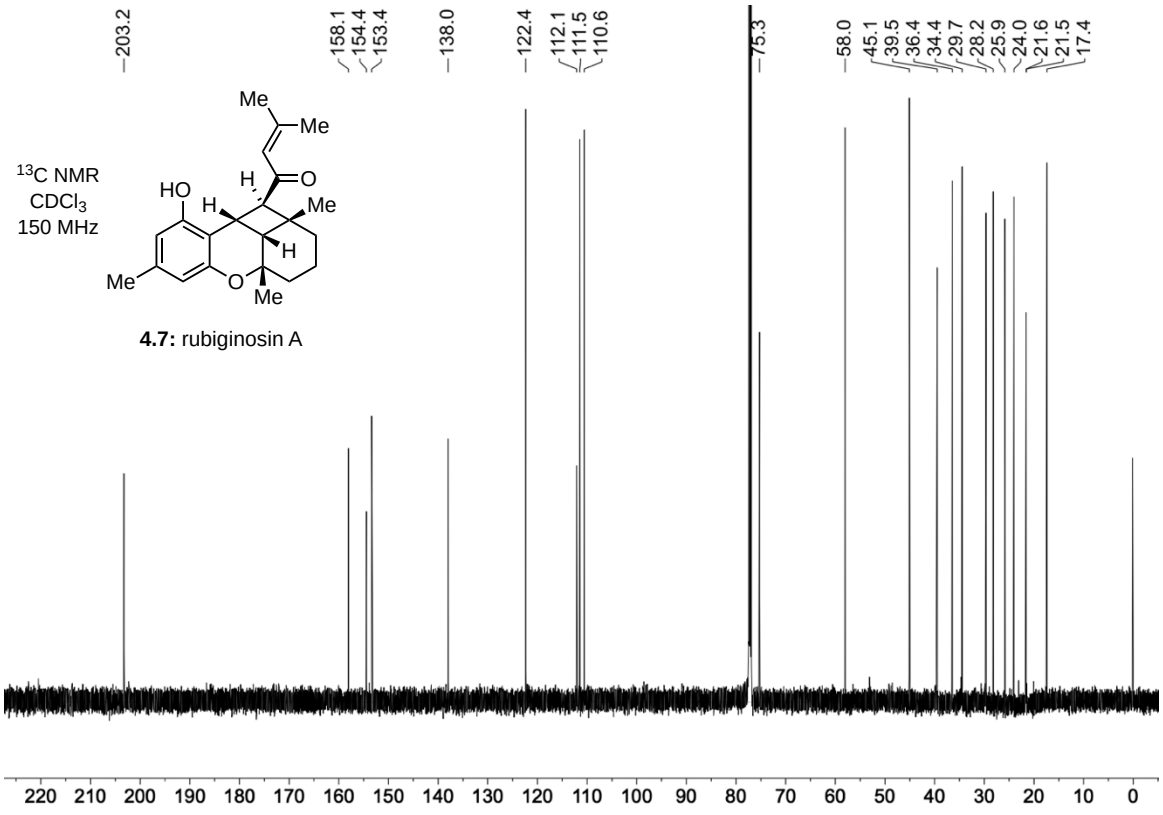

HSQC
CD3OD
600 MHz
OH
O
Me
Me
Me
Me
O
Me
4.59: rubiginosin D
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

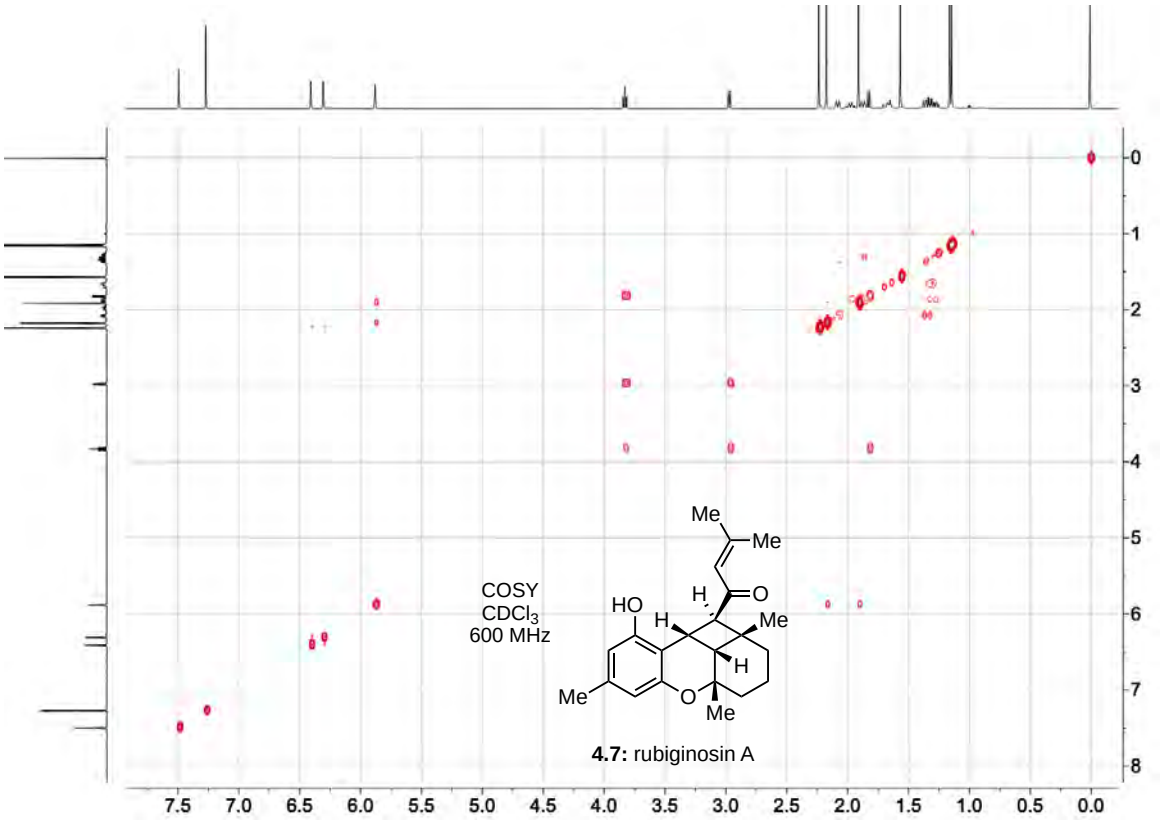


4.59: rubiginosin D

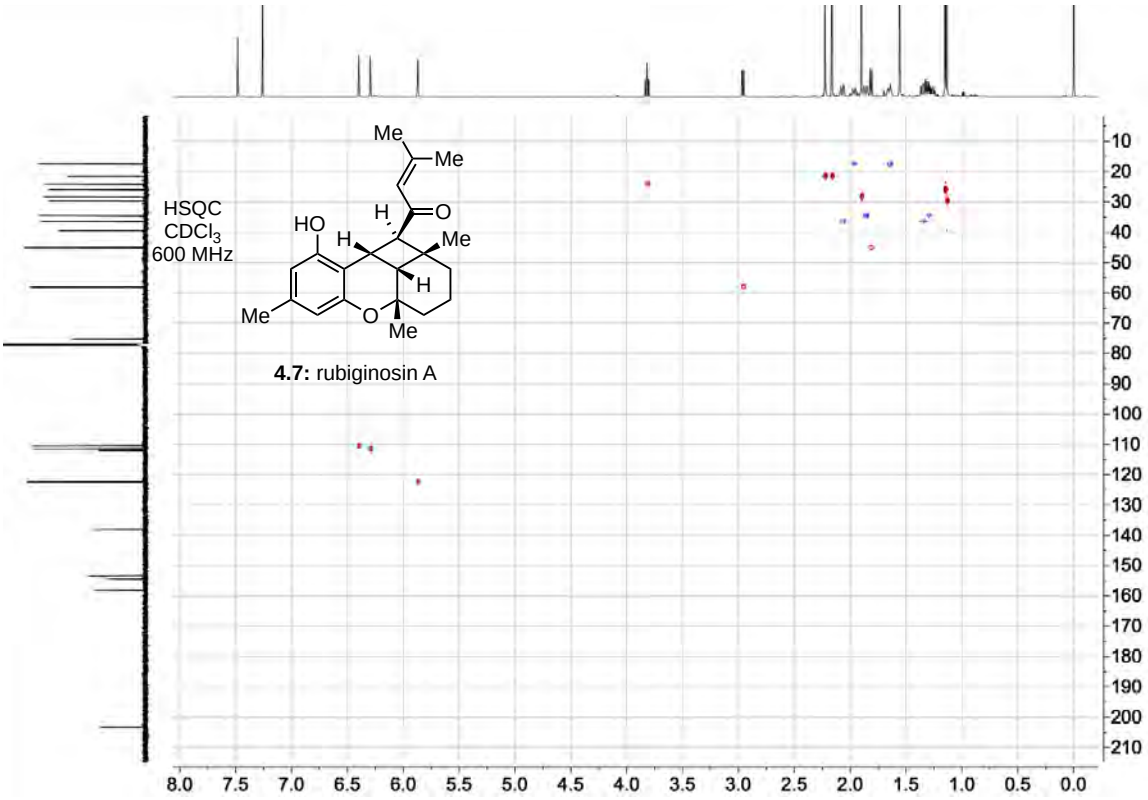
Data for rubiginosin A (4.7)



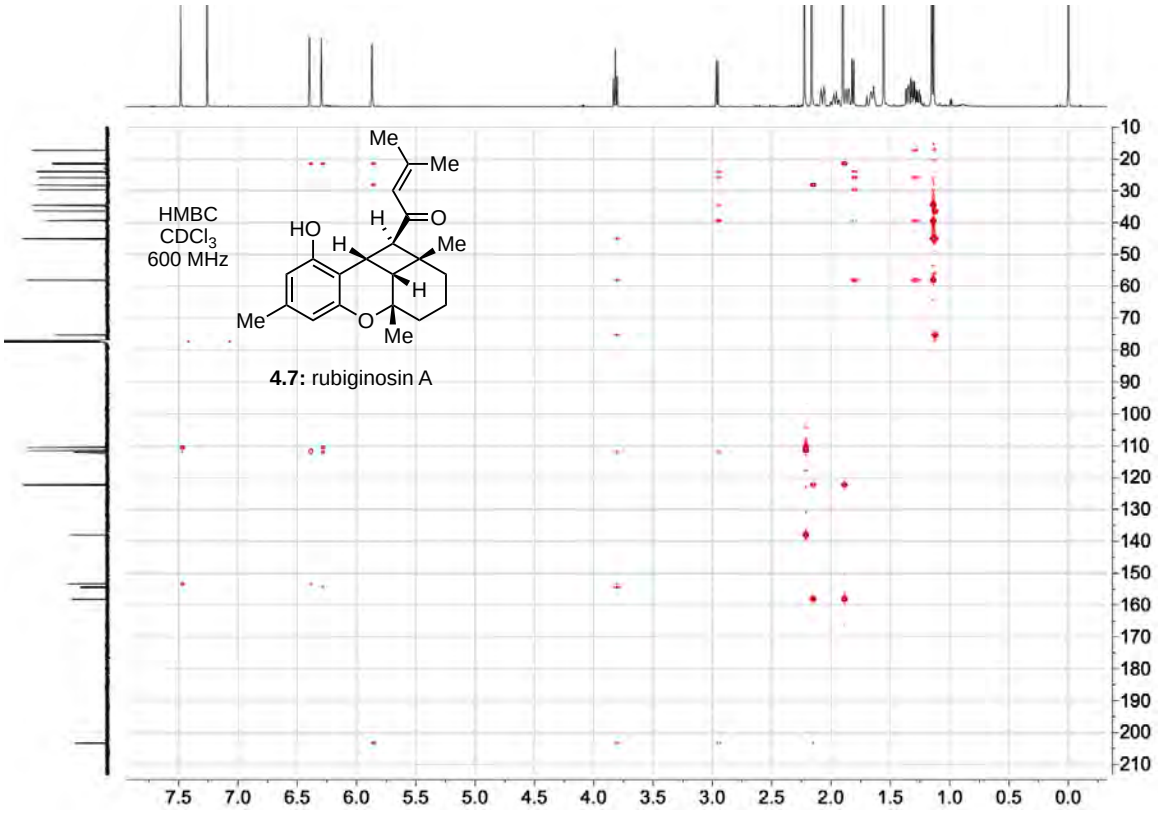




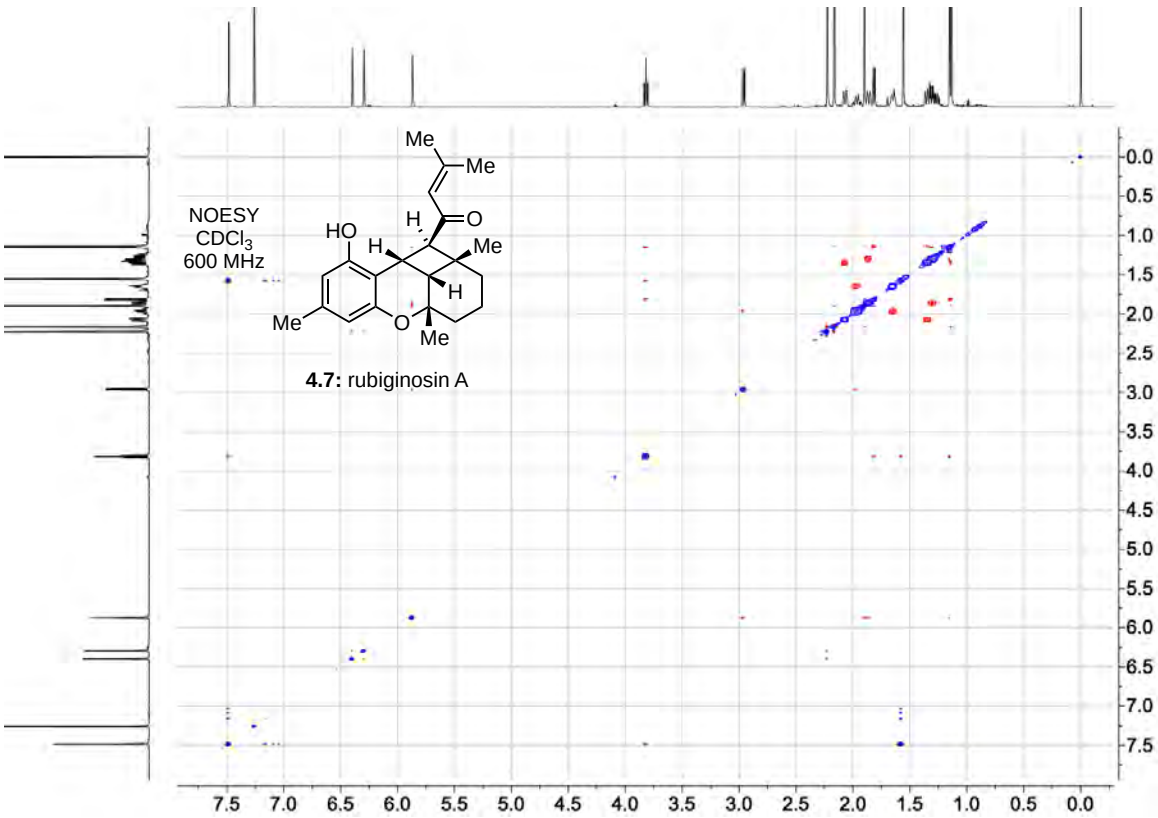
4.7: rubiginosin A



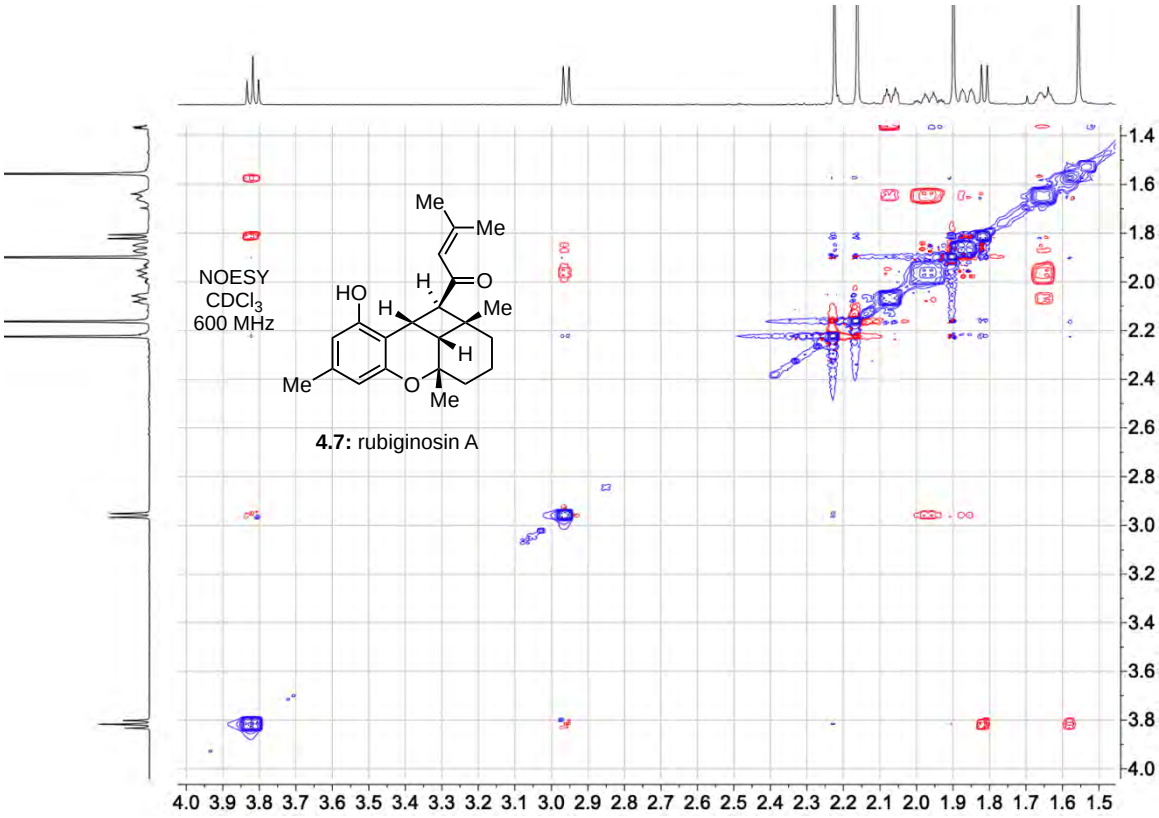
4.7: rubiginosin A



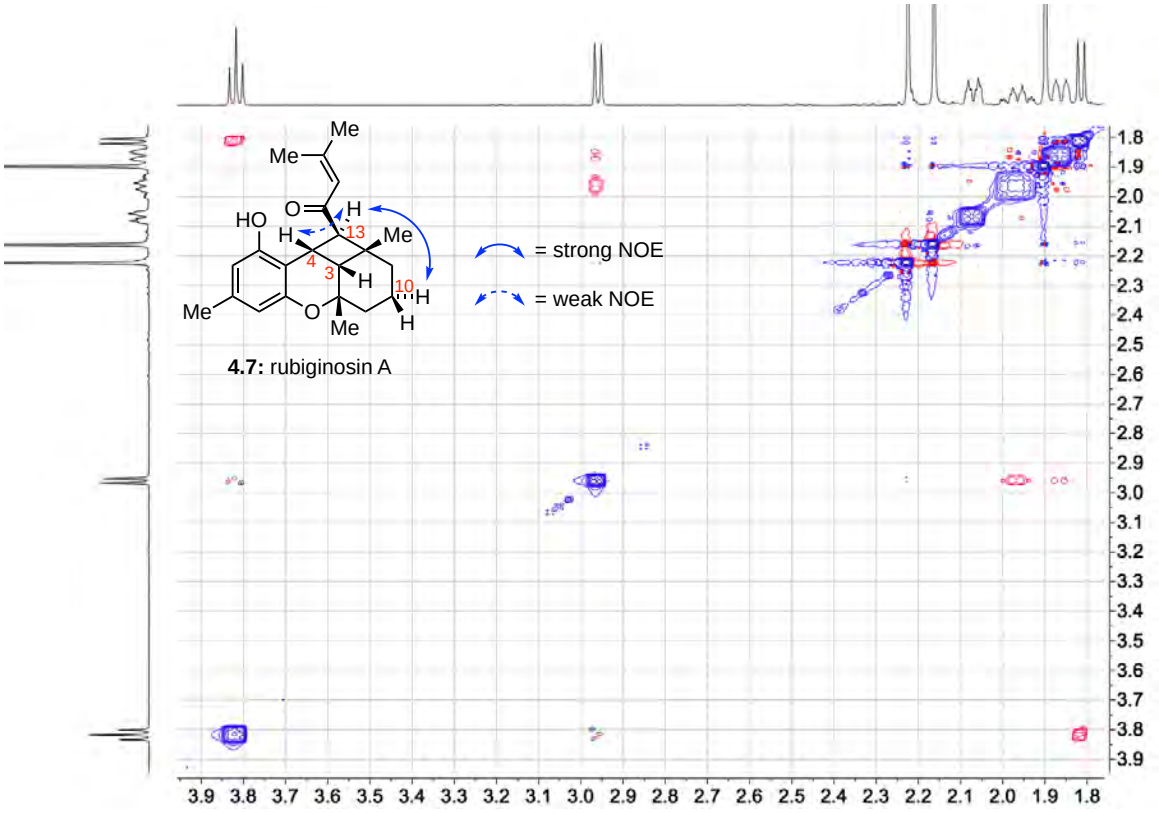
4.7: rubiginosin A



4.7: rubiginosin A



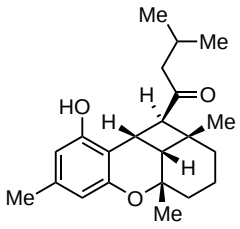
4.7: rubiginosin A



4.7: rubiginosin A

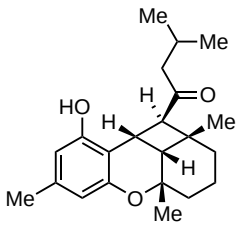
Data for rubiginosin G (4.6)

^{1}H NMR
$CDCl_3$
600 MHz

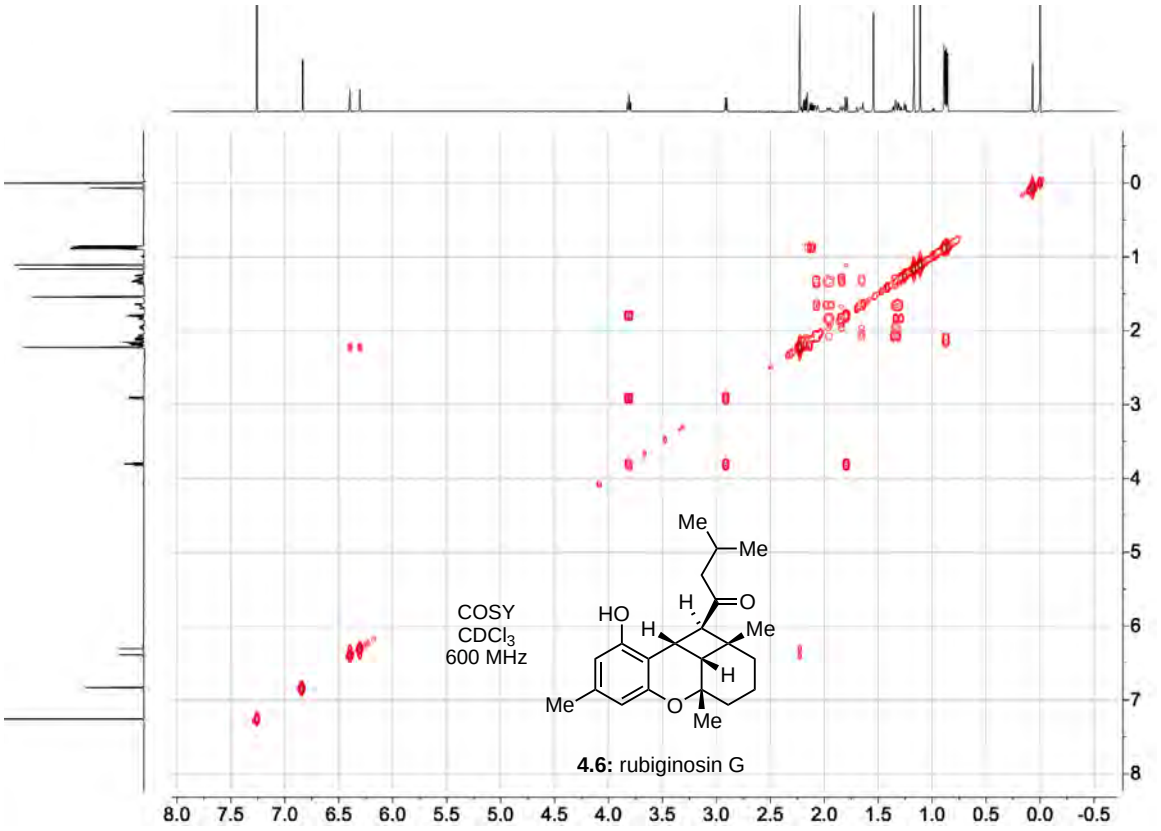


4.6: rubiginosin G

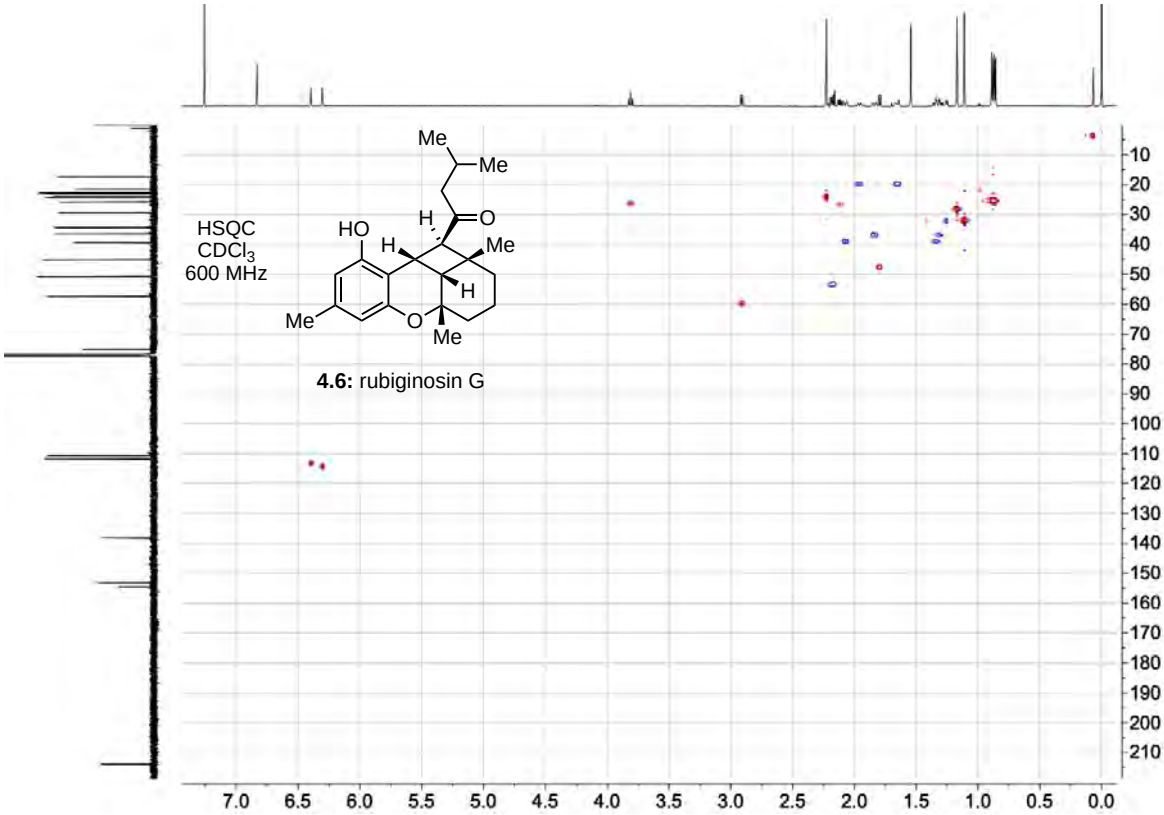
^{13}C NMR
$CDCl_3$
150 MHz



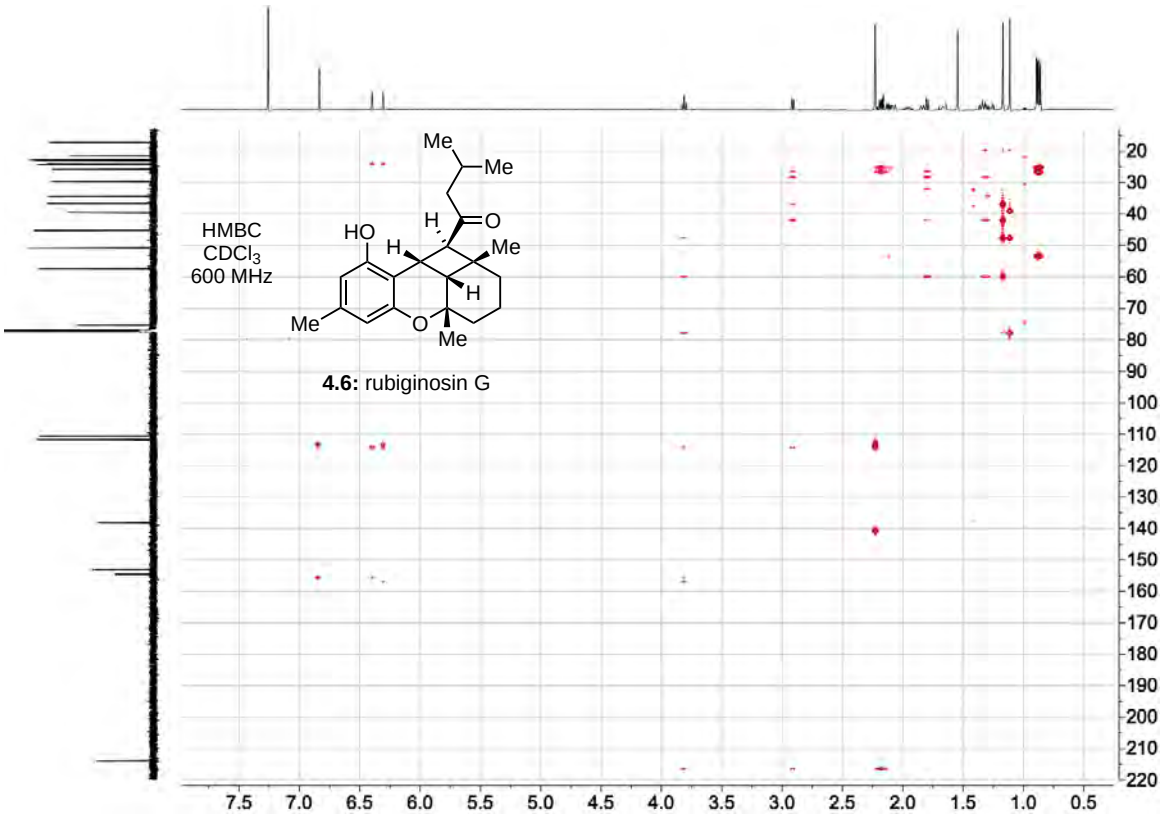
4.6: rubiginosin G



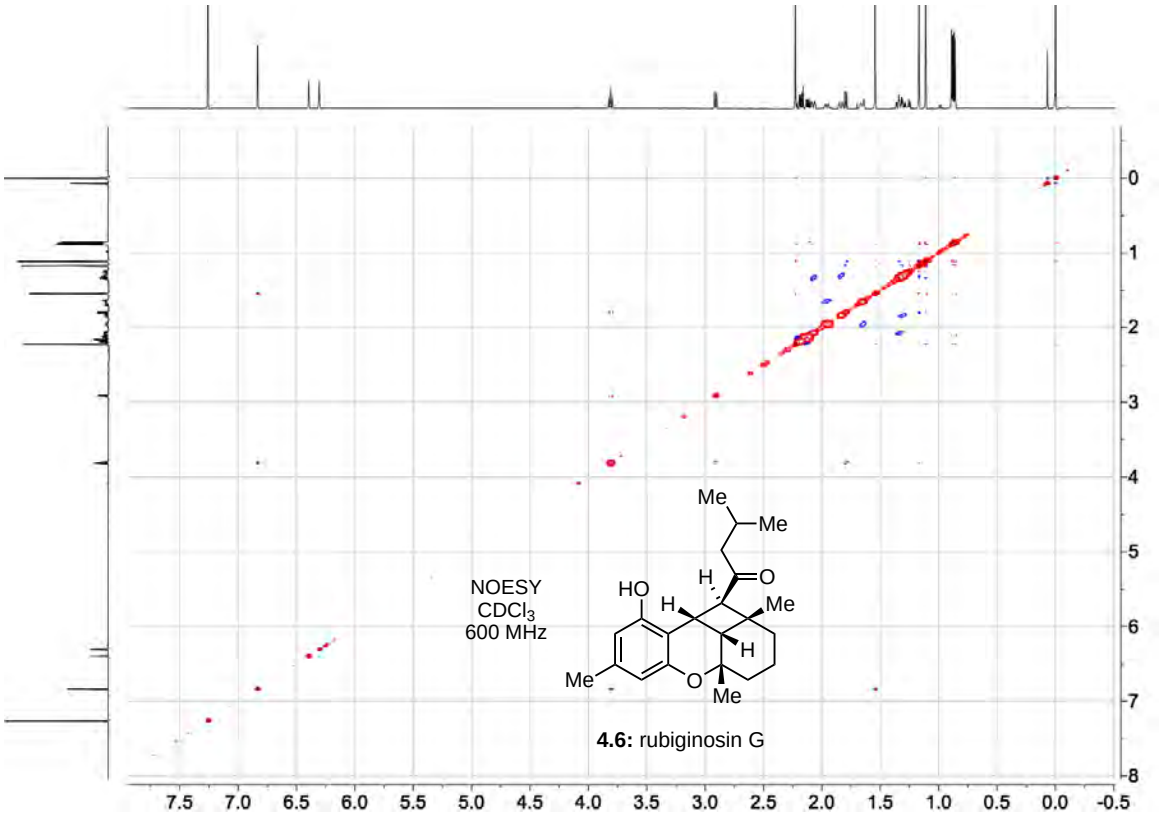
4.6: rubiginosin G



4.6: rubiginosin G

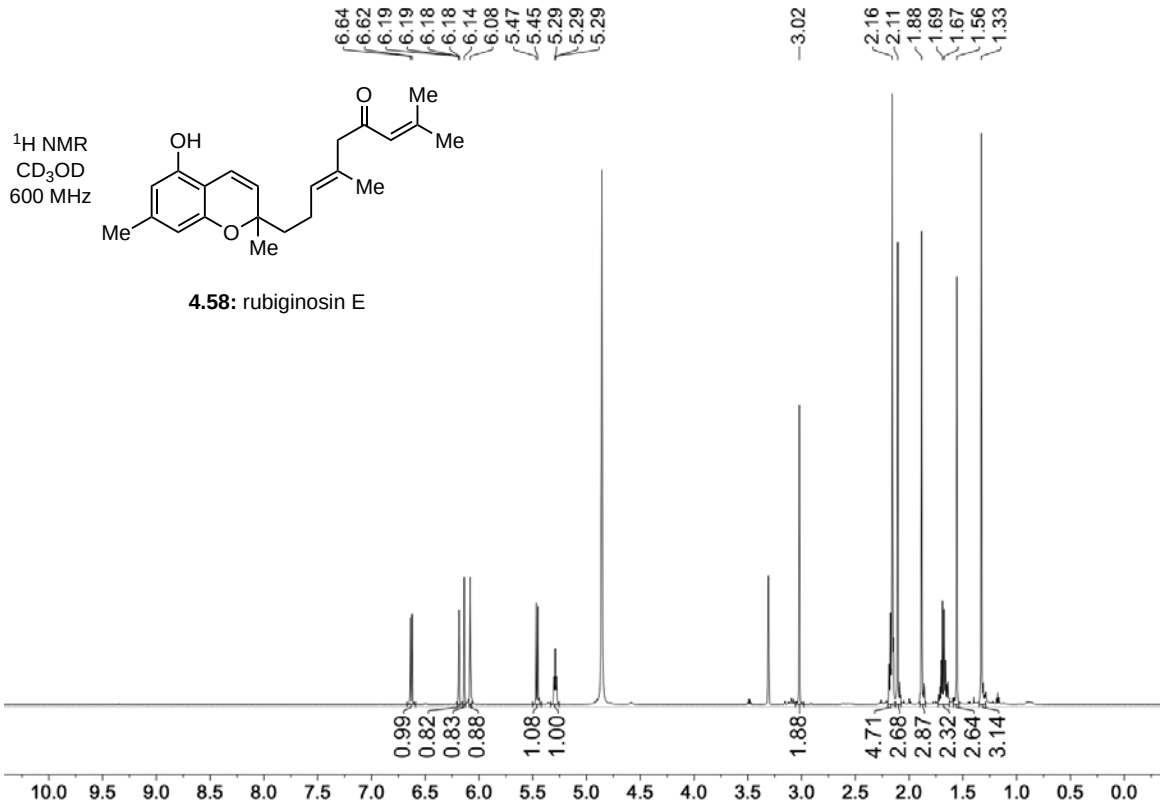


4.6: rubiginosin G

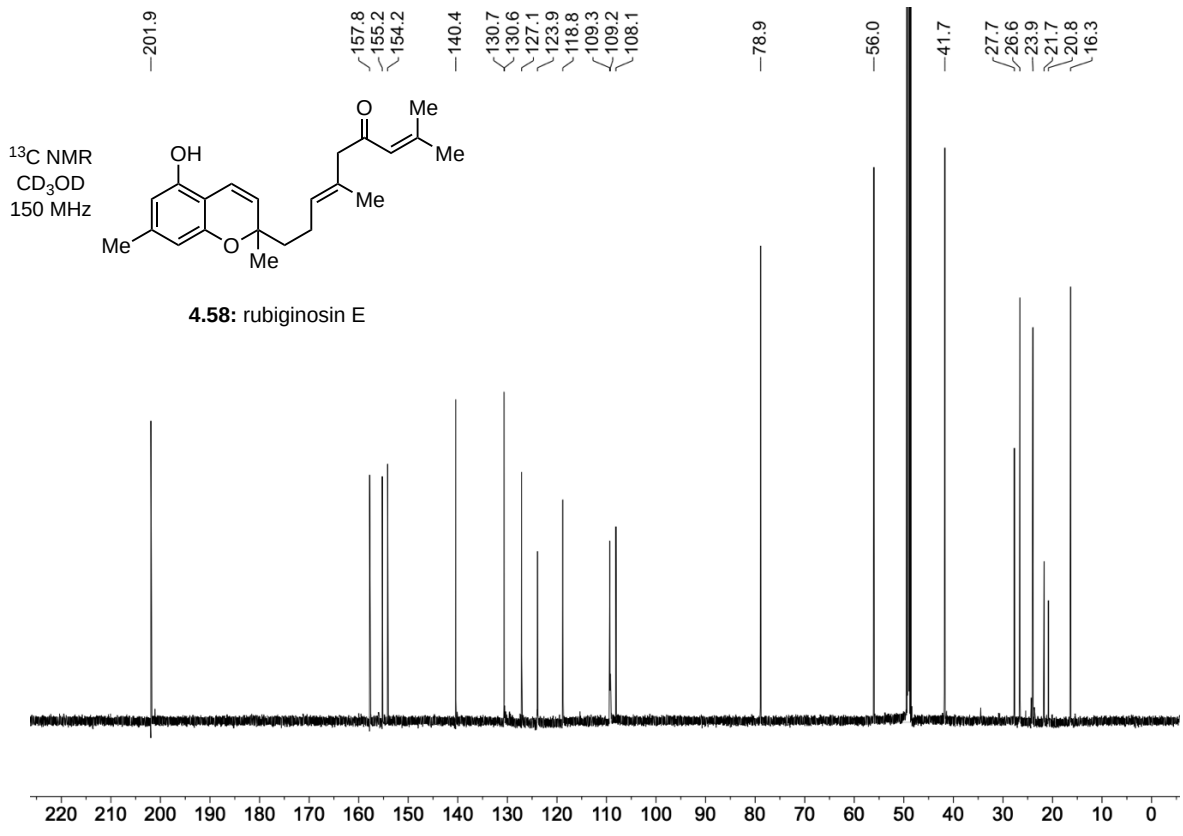


4.6: rubiginosin G

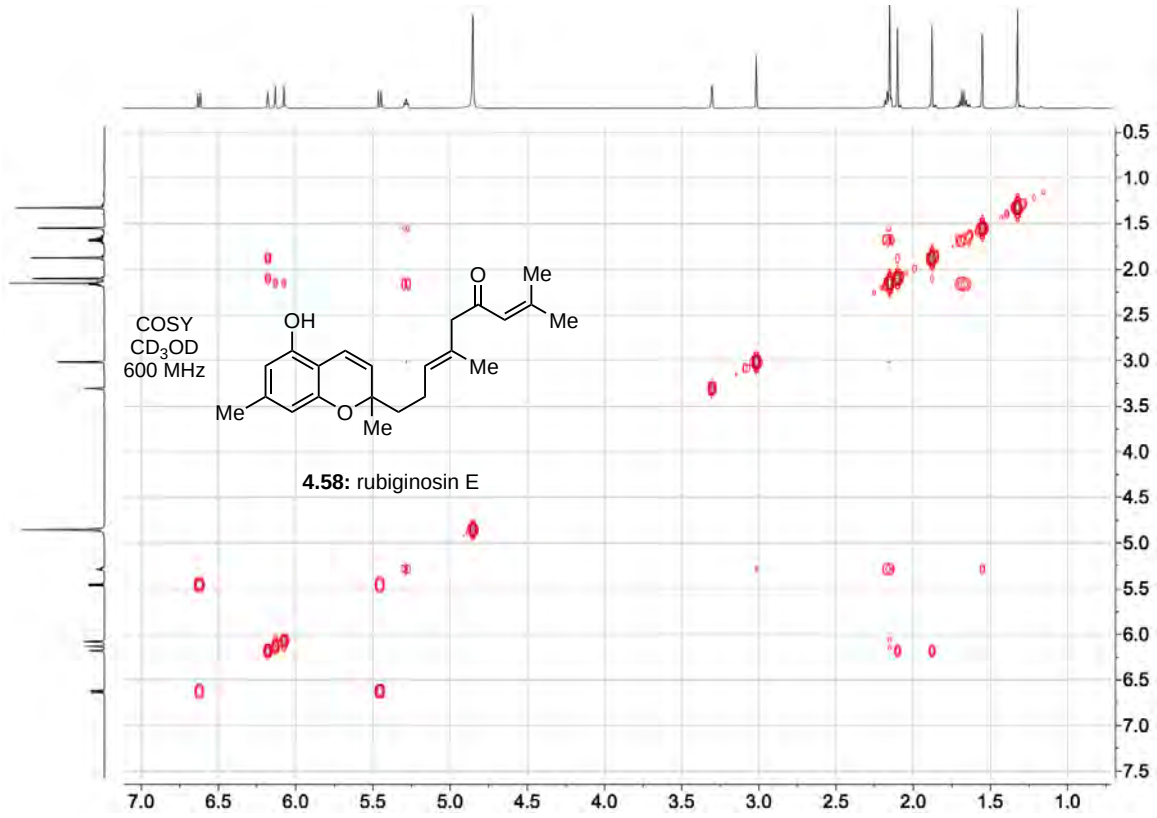
Data for rubiginosin E (4.58)

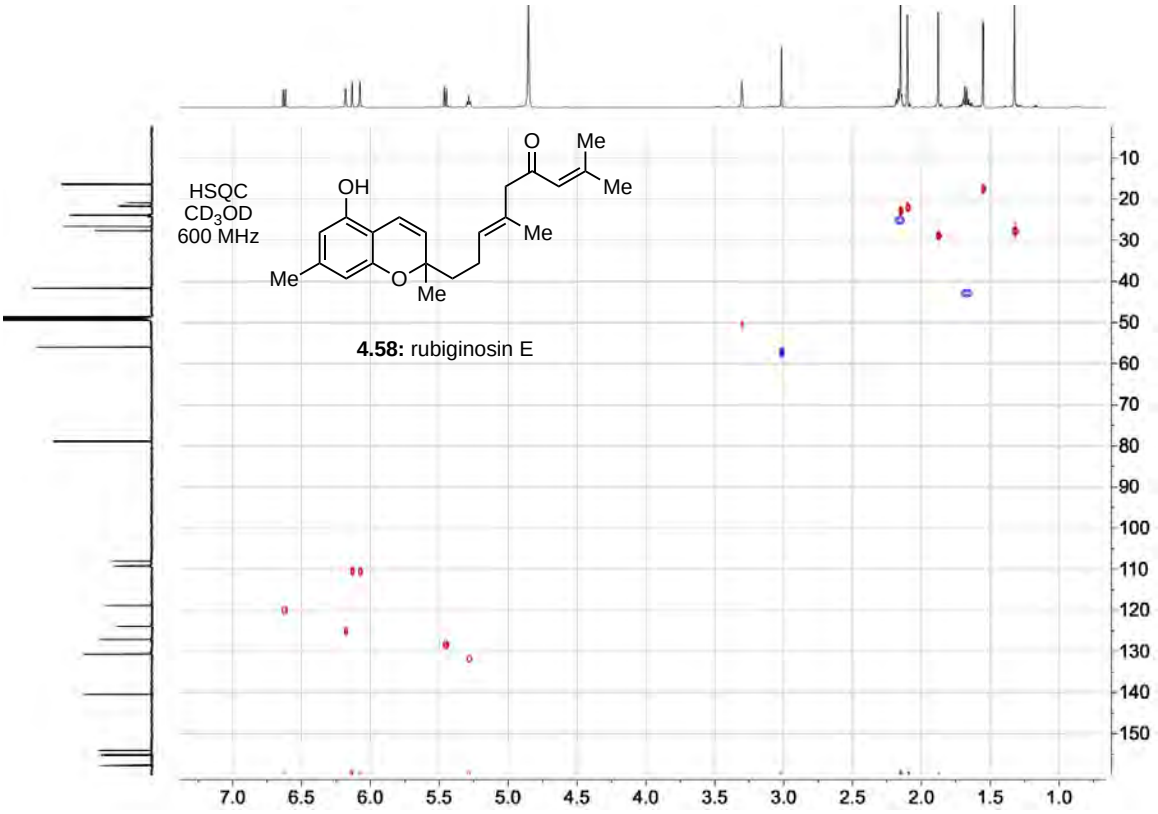


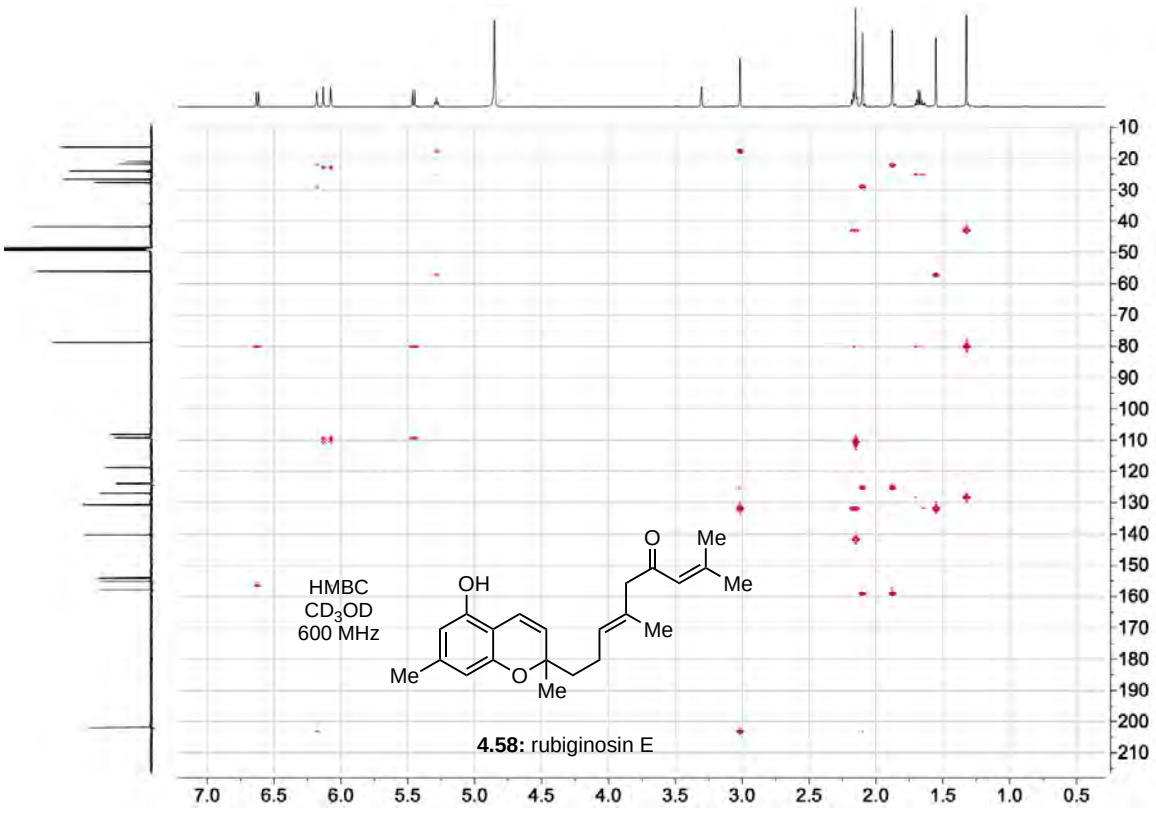
4.58: rubiginosin E



4.58: rubiginosin E


COSY
CD3OD
600 MHz
OH
O
Me
Me
Me
Me
O
Me
4.58: rubiginosin E

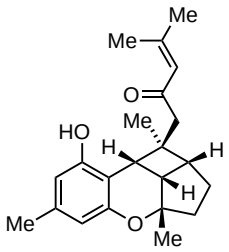

HSQC
CD3OD
600 MHz
OH
O
Me
Me
Me
Me
O
Me
4.58: rubiginosin E



4.58: rubiginosin E

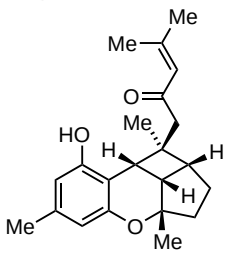
Data for fastinoid B (4.8)

^{1}H NMR
$CDCl_3$
600 MHz

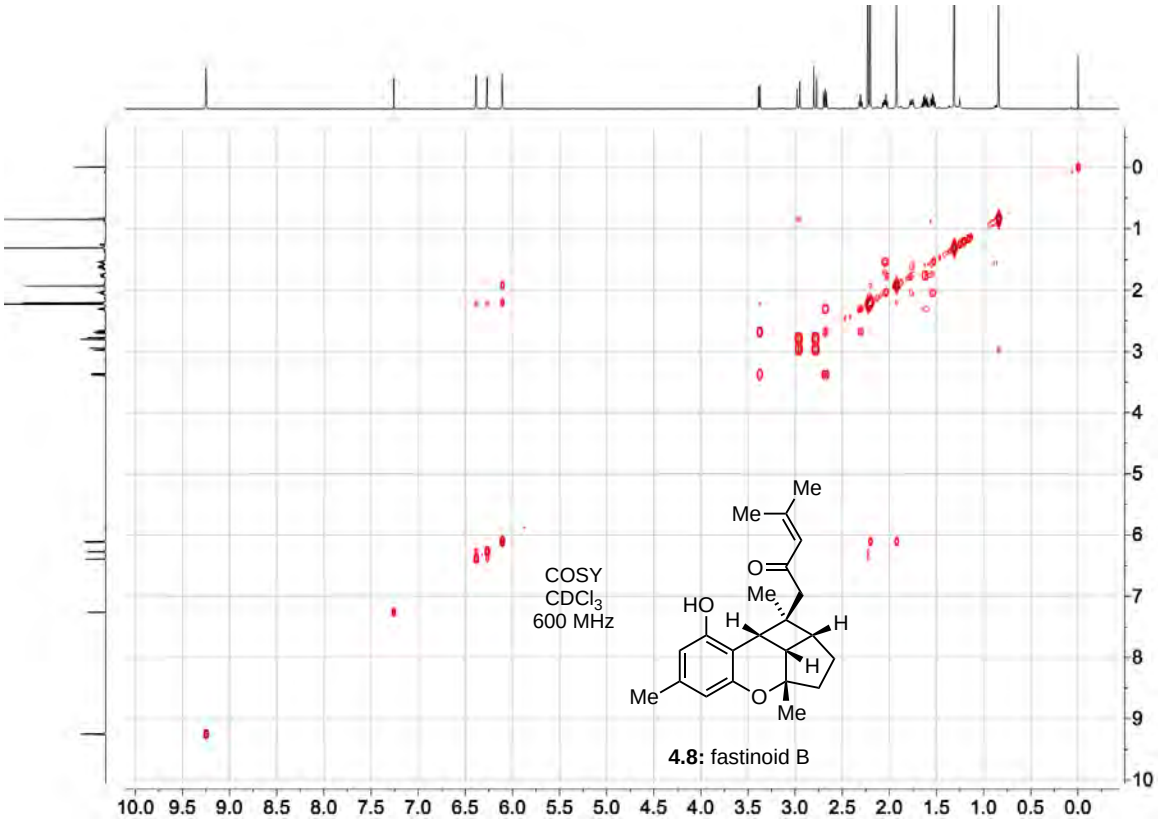


4.8: fastinoid B

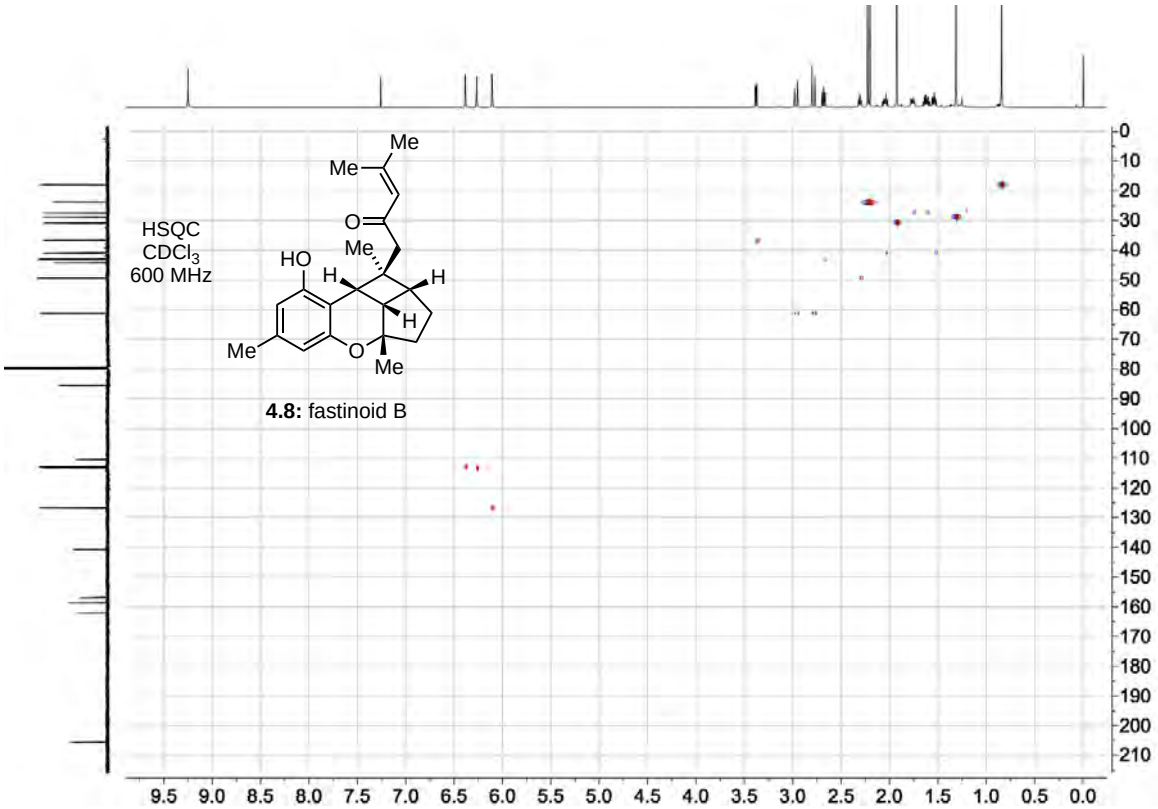
^{13}C NMR
$CDCl_3$
150 MHz



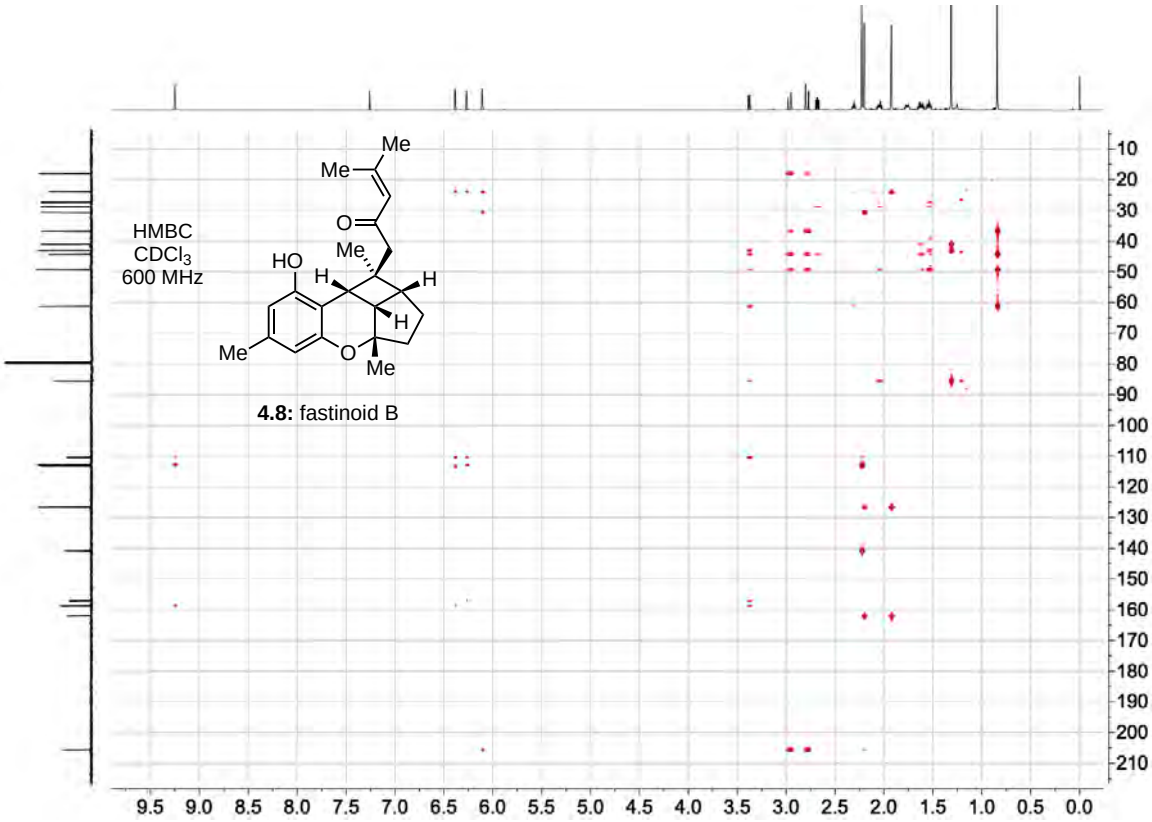
4.8: fastinoid B



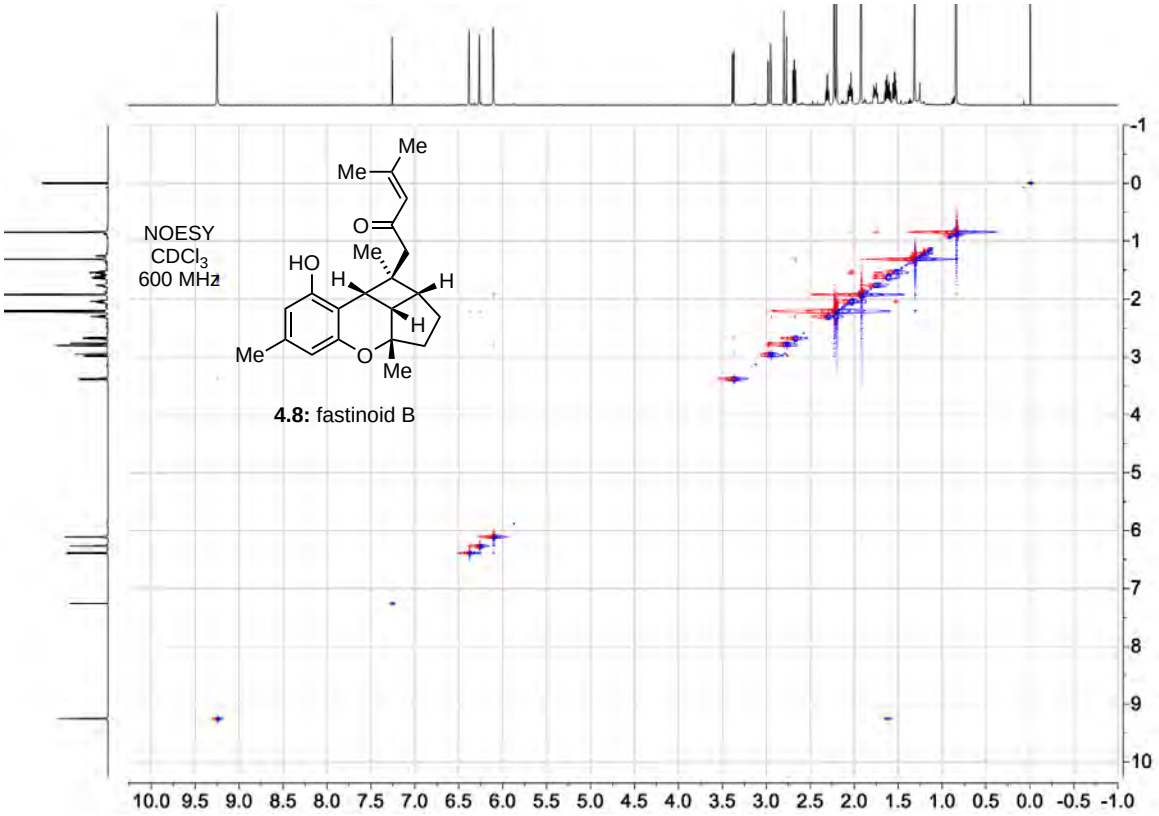
4.8: fastinoid B



4.8: fastinoid B



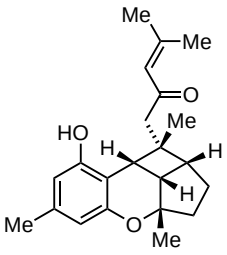
4.8: fastinoid B



4.8: fastinoid B

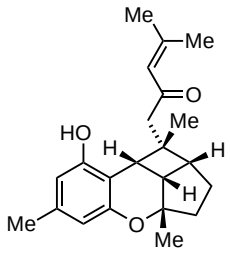
Data for rhodonoid B (4.3)

^{1}H NMR
$CDCl_3$
600 MHz

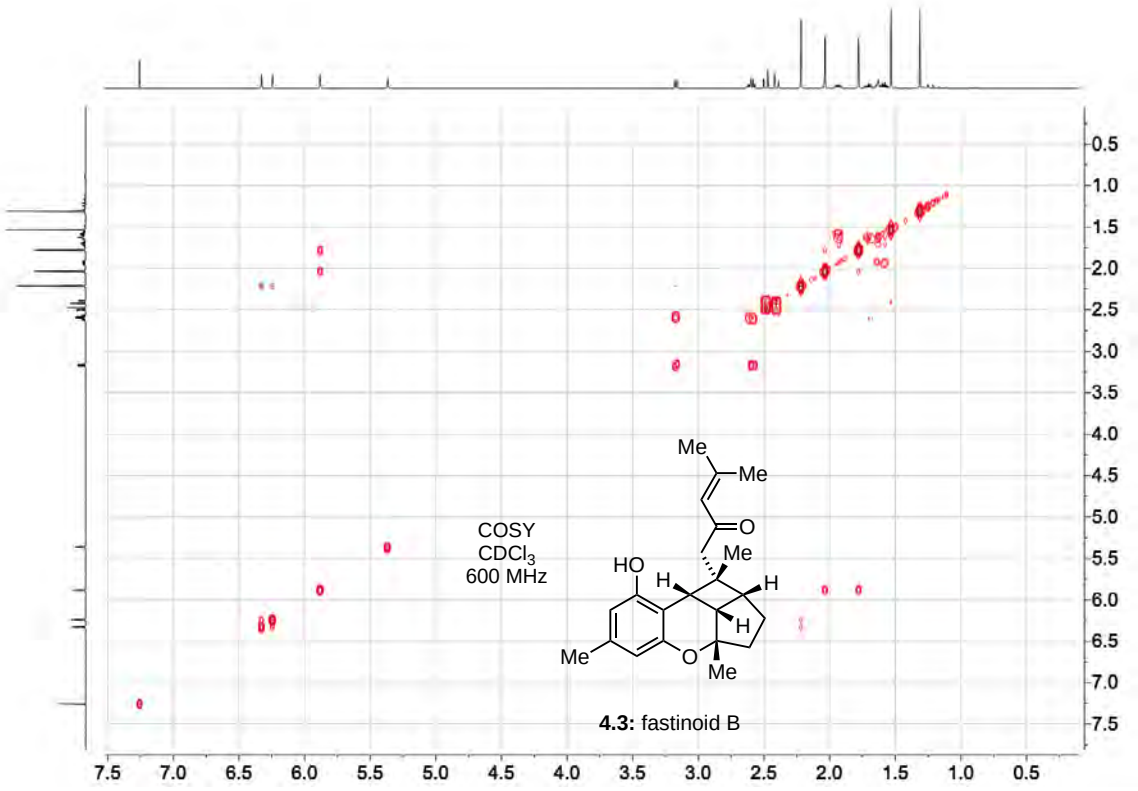


4.3: fastinoid B

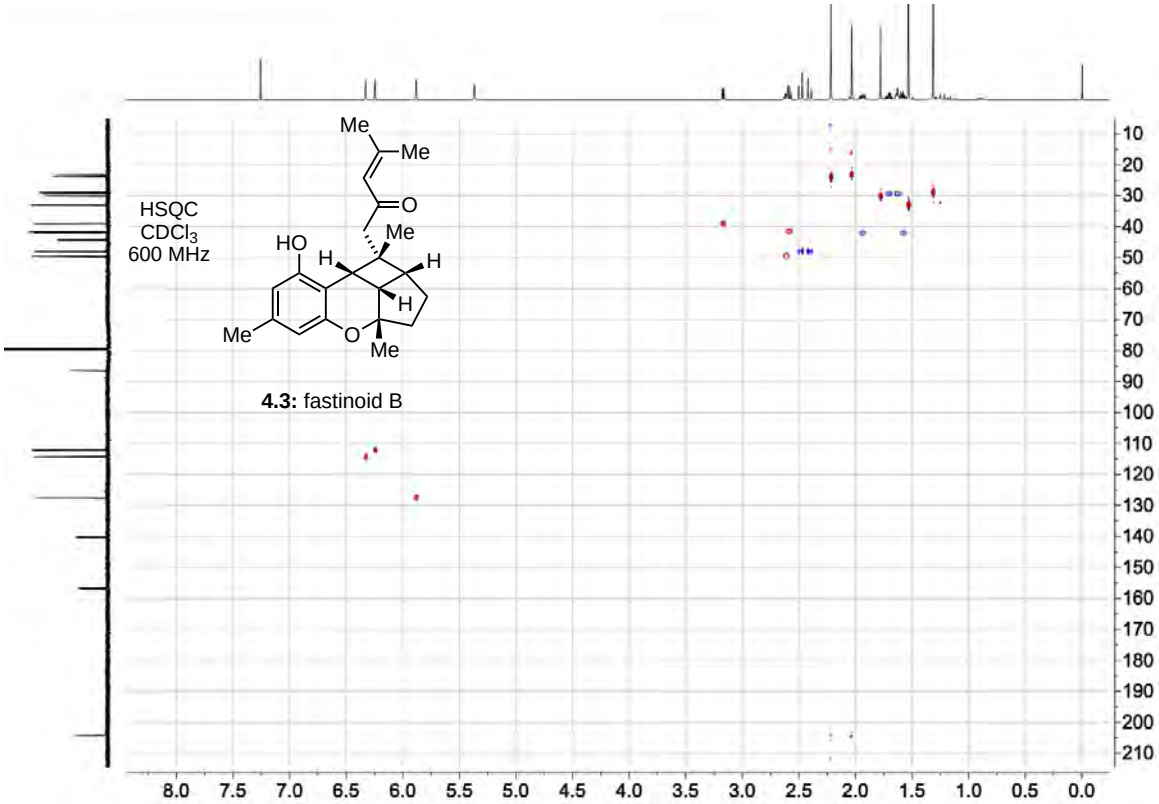
^{13}C NMR
$CDCl_3$
150 MHz



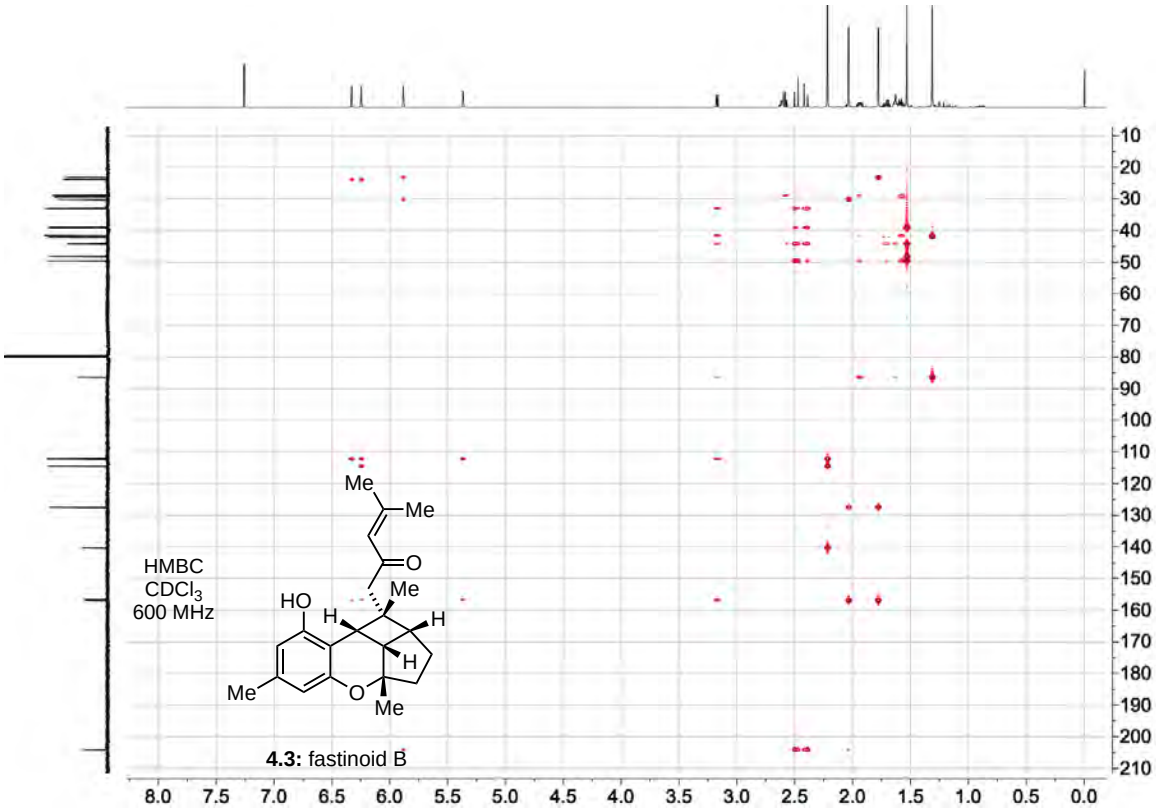
4.3: fastinoid B

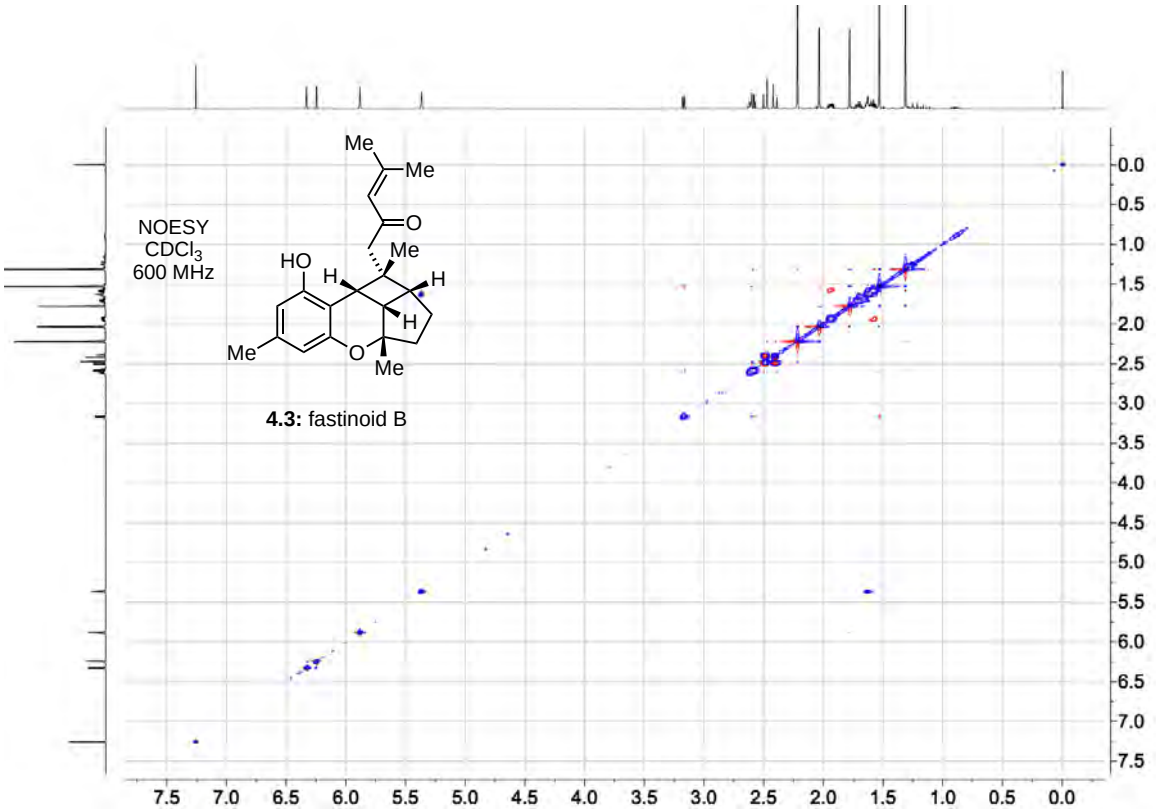


4.3: fastinoid B



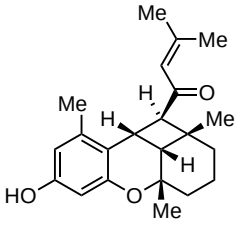
4.3: fastinoid B


HMBC
CDCl3
600 MHz
Me
Me
O
Me
HO
H
H
H
Me
O
Me
4.3: fastinoid B


NOESY
CDCl3
600 MHz
Me
Me
O
Me
HO
H
H
H
Me
O
Me
4.3: fastinoid B

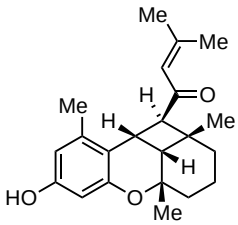
Data for "iso-rubiginosin A" (4.89)

^{1}H NMR
$CDCl_3$
500 MHz

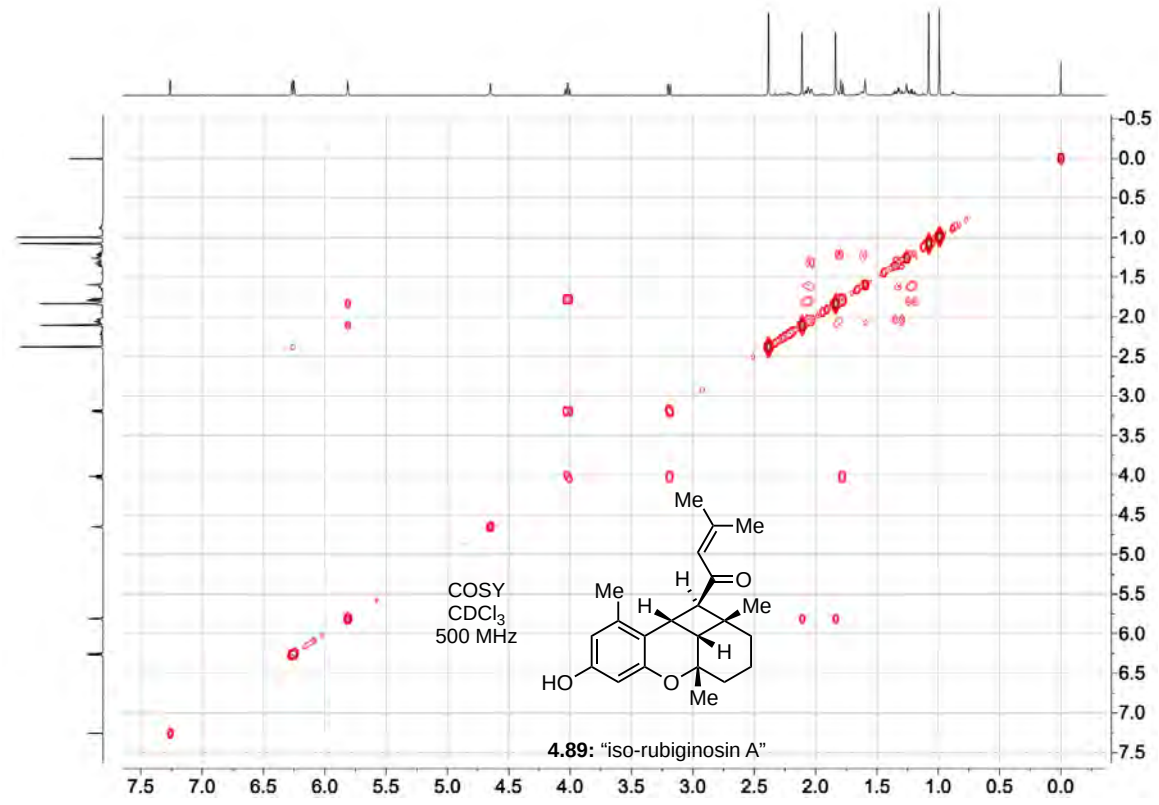


4.89: "iso-rubiginosin A"

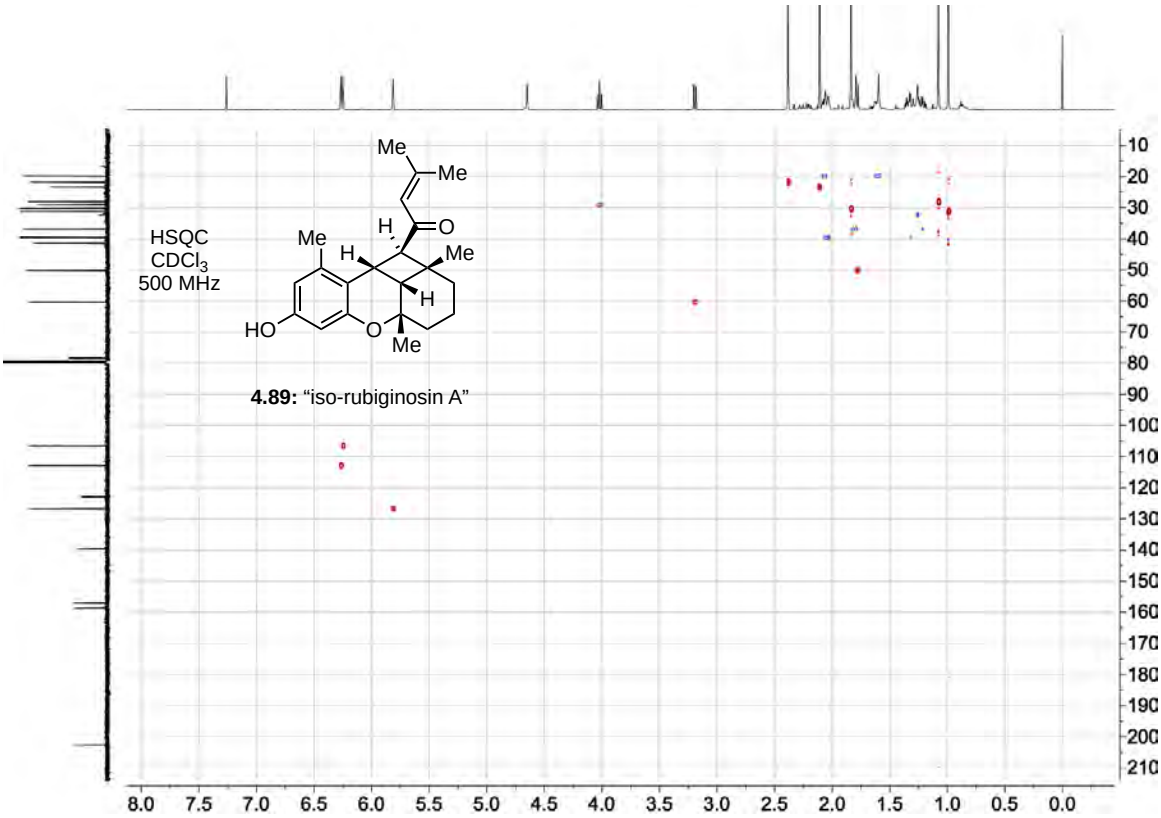
^{13}C NMR
$CDCl_3$
125 MHz



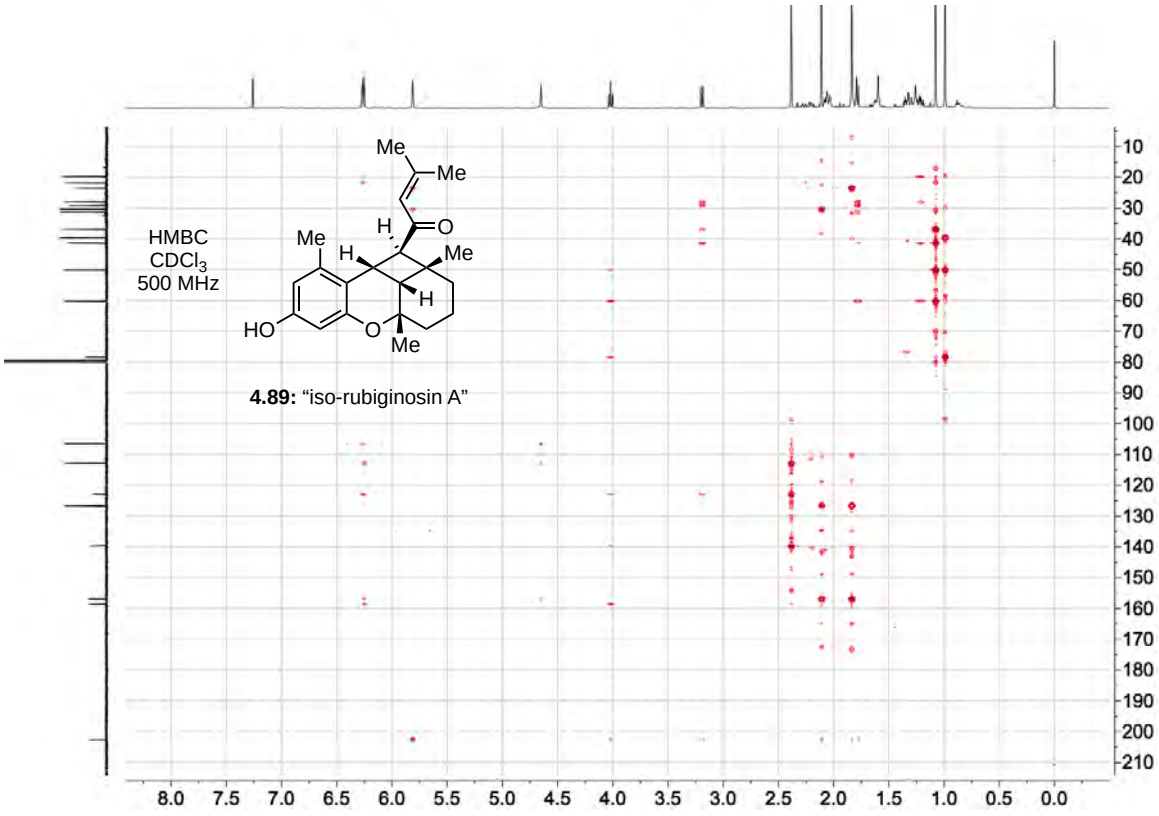
4.89: "iso-rubiginosin A"

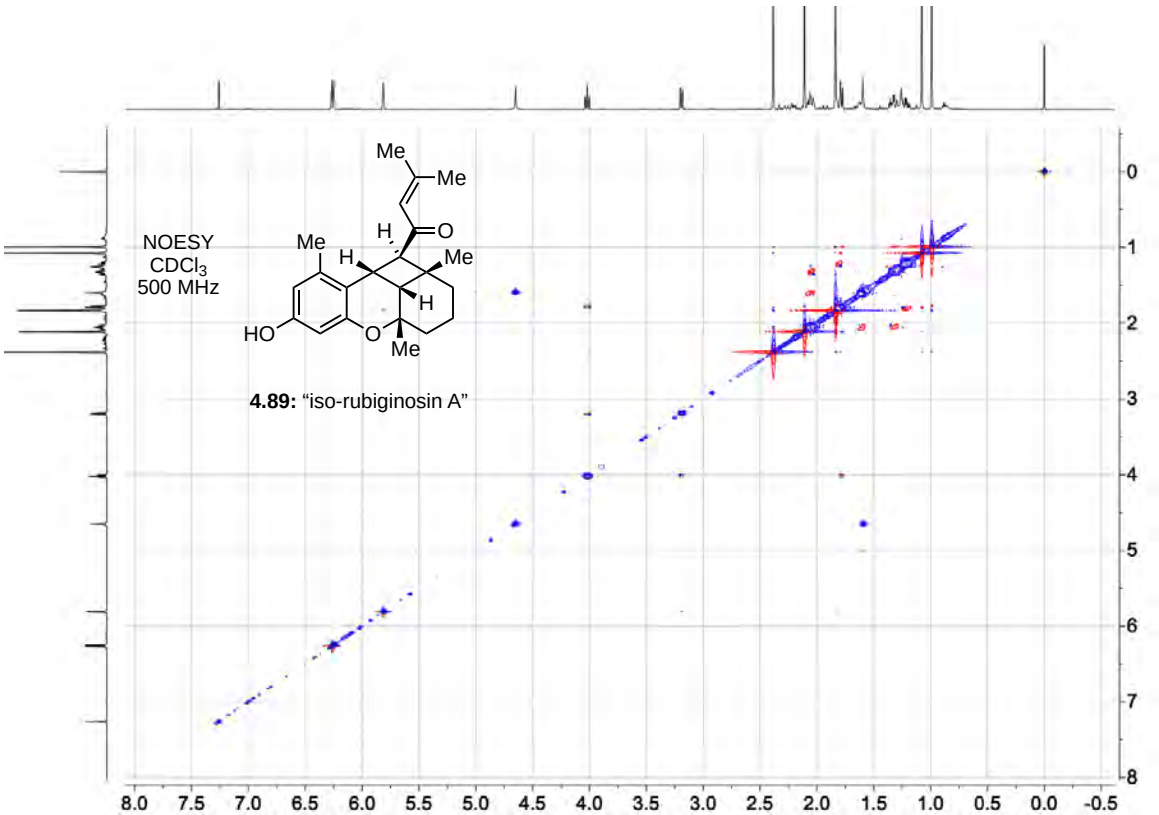


4.89: "iso-rubiginosin A"

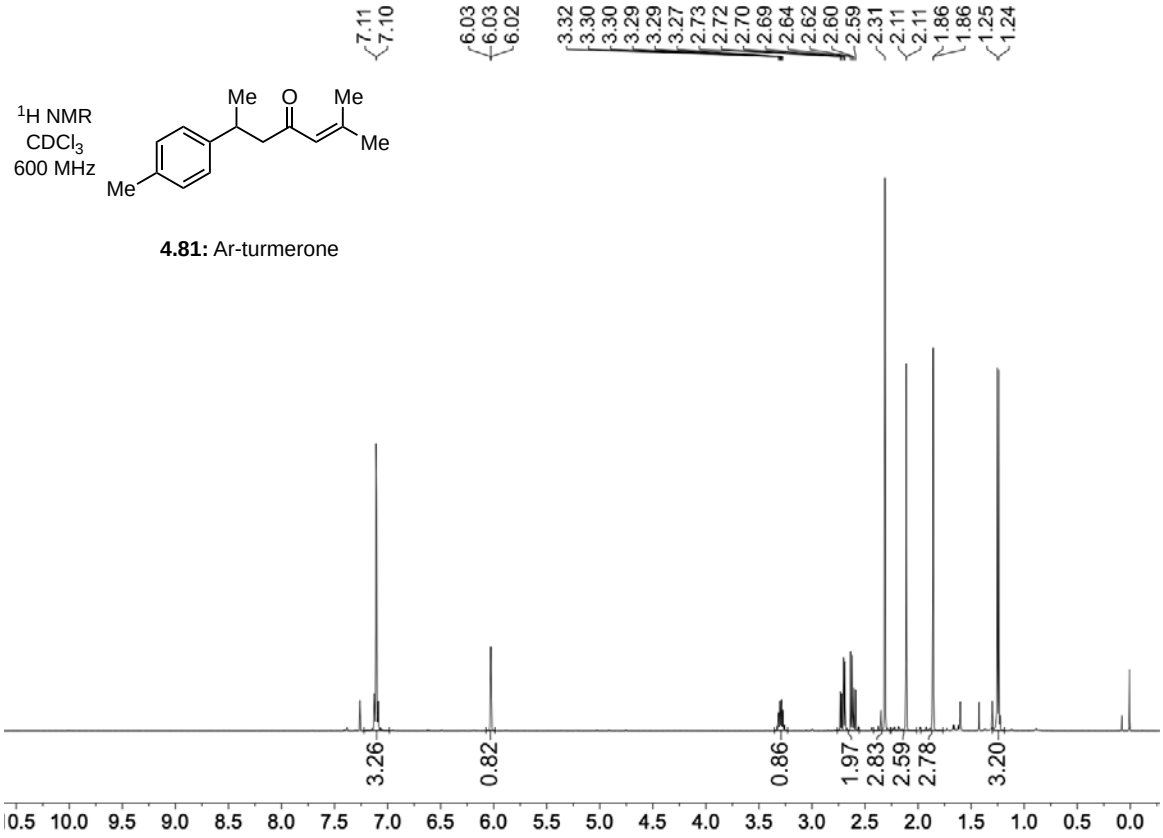


4.89: "iso-rubiginosin A"

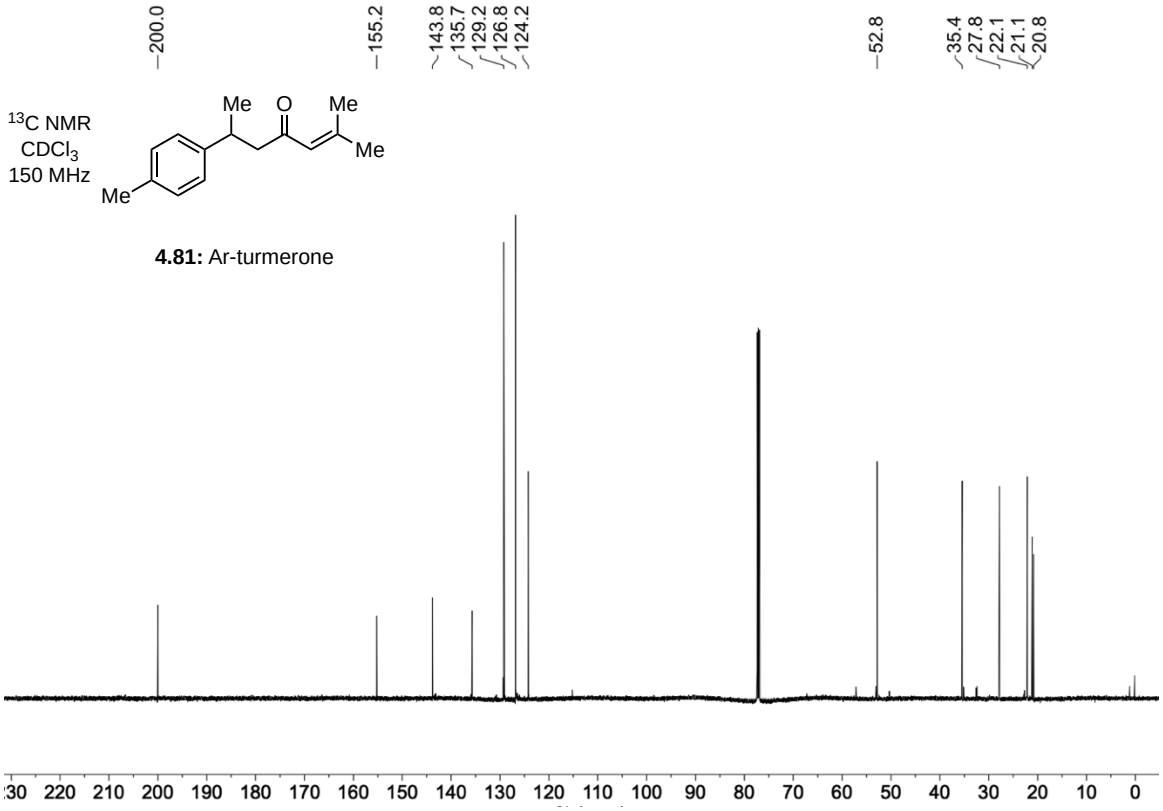

HMBC
CDCl3
500 MHz
Me
Me
H
O
Me
H
Me
H
HO
O
Me
4.89: "iso-rubiginosin A"
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


NOESY
CDCl3
500 MHz
Me
Me
H
O
Me
H
Me
H
HO
O
Me
4.89: "iso-rubiginosin A"
0
1
2
3
4
5
6
7
8
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

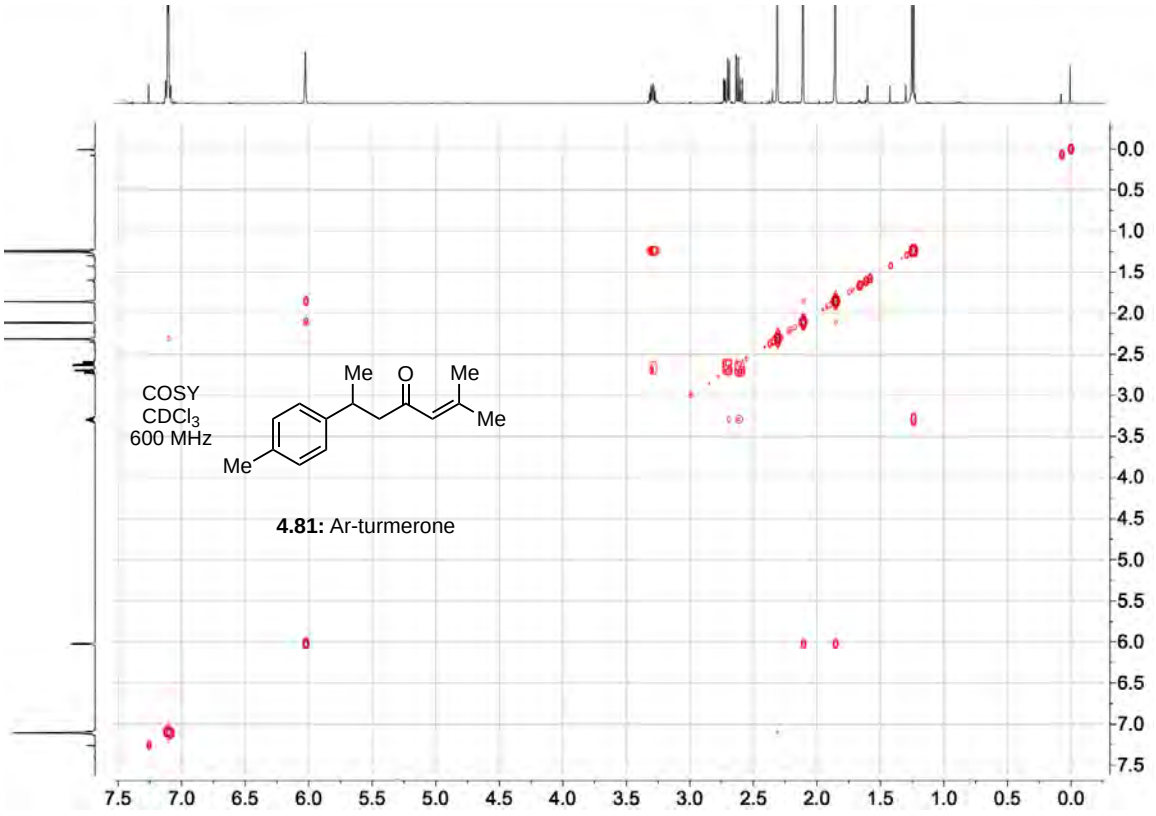
Data for Ar-turmerone (4.81)



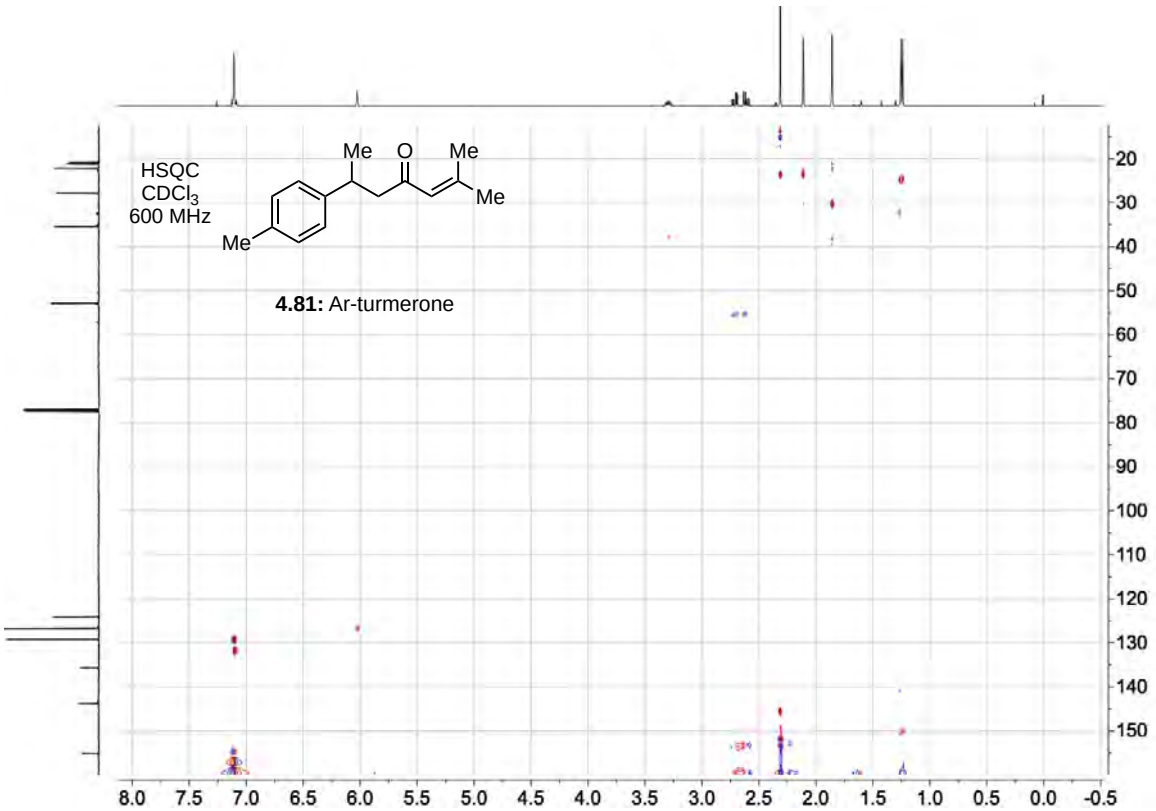
4.81: Ar-turmerone



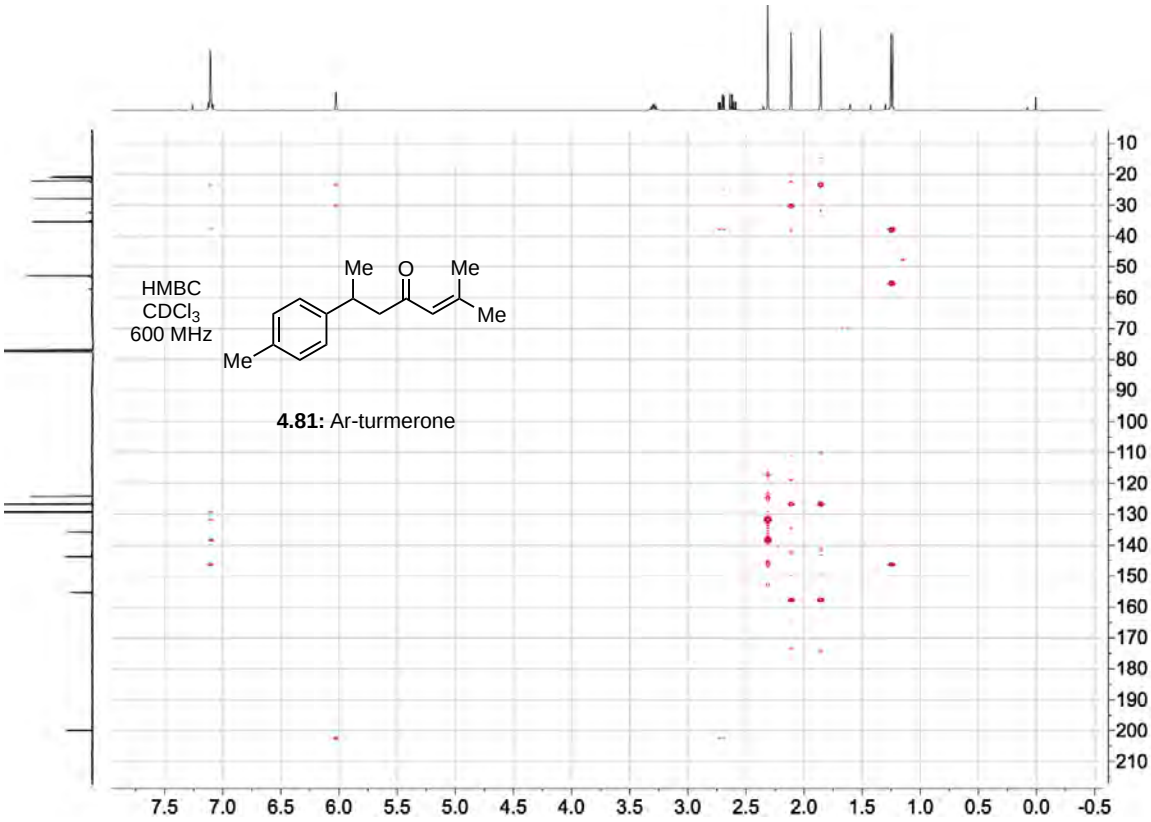
4.81: Ar-turmerone



4.81: Ar-turmerone



4.81: Ar-turmerone



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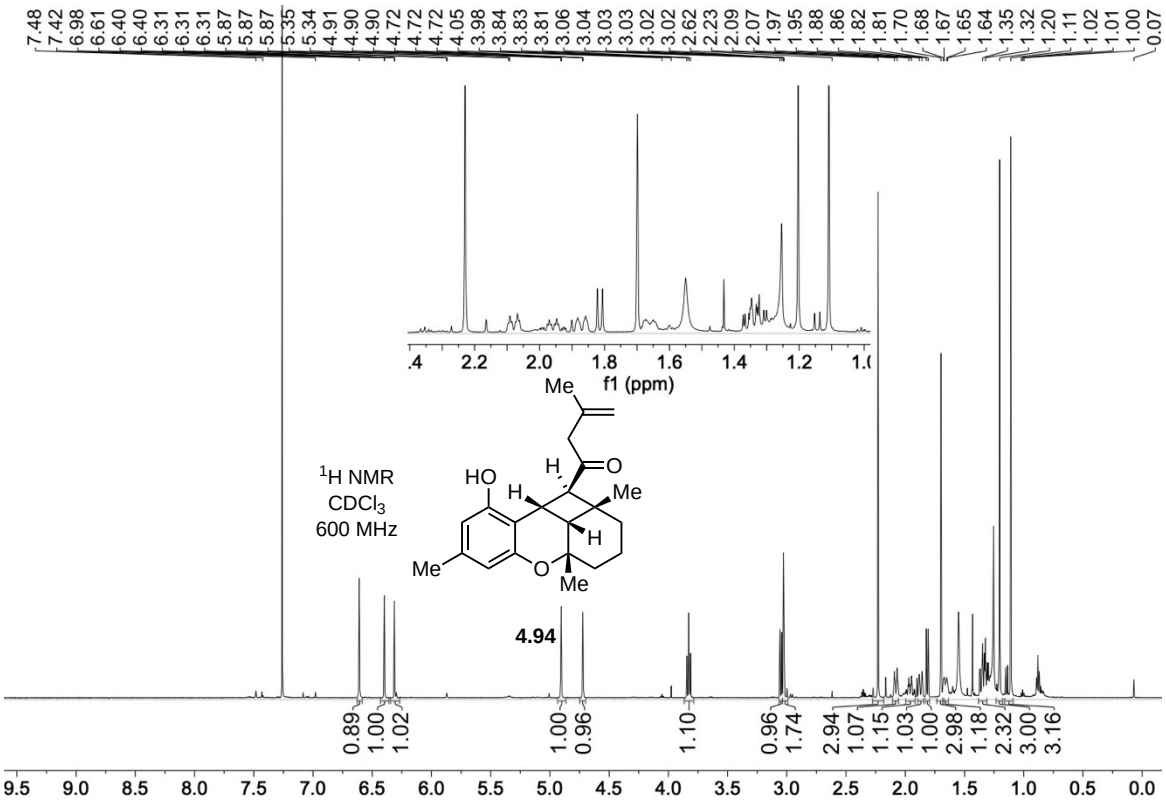

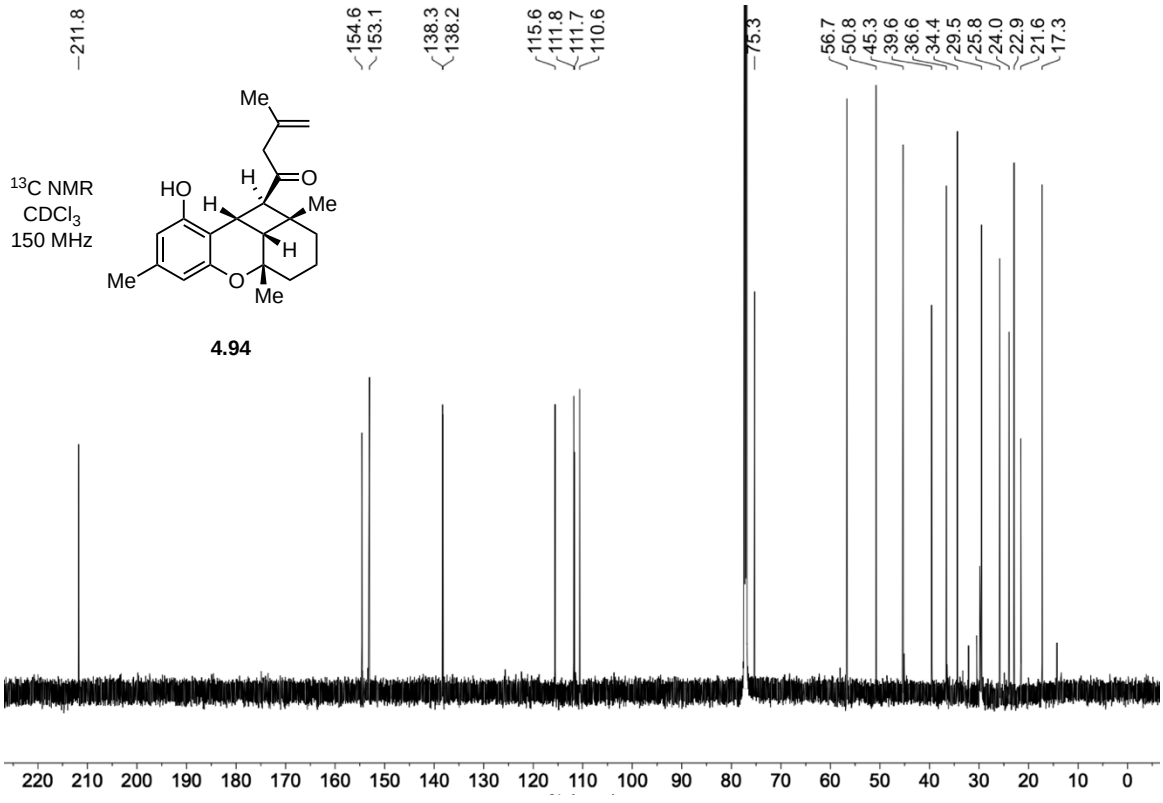

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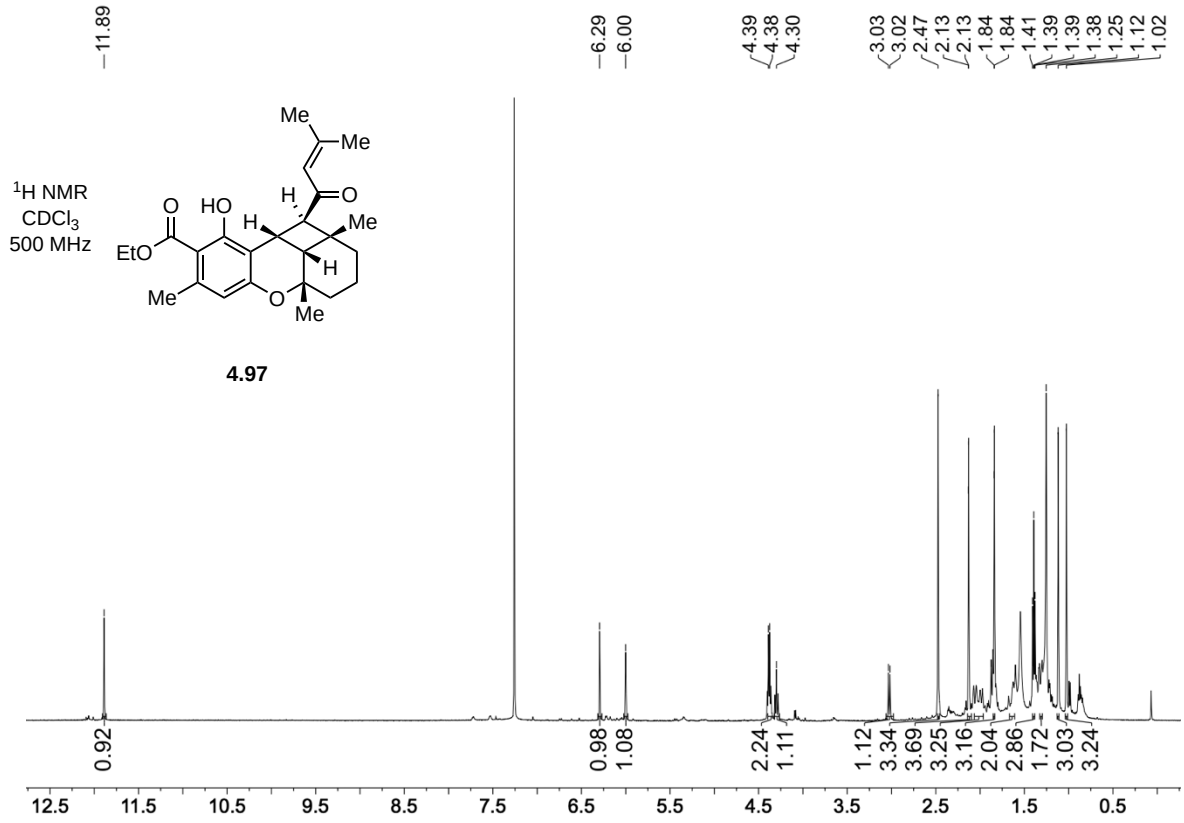
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1.38
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EtO
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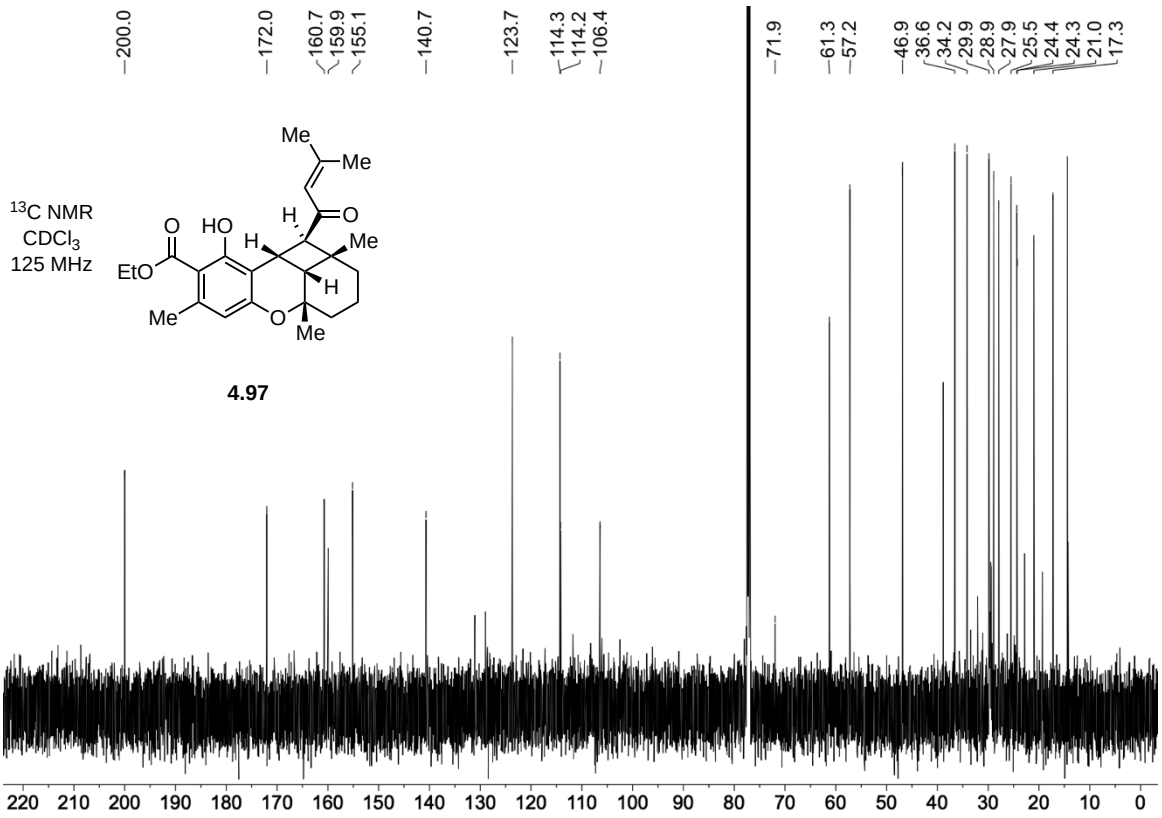
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24.3
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EtO
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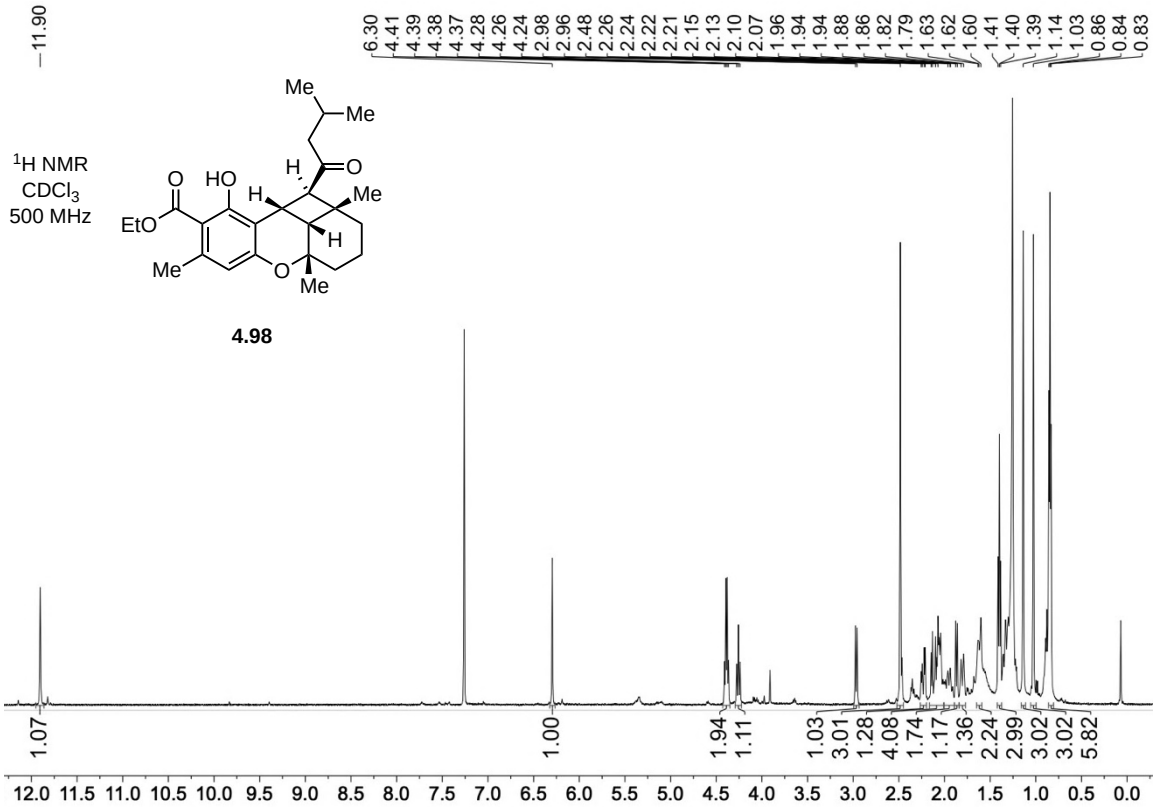
Data for 4.98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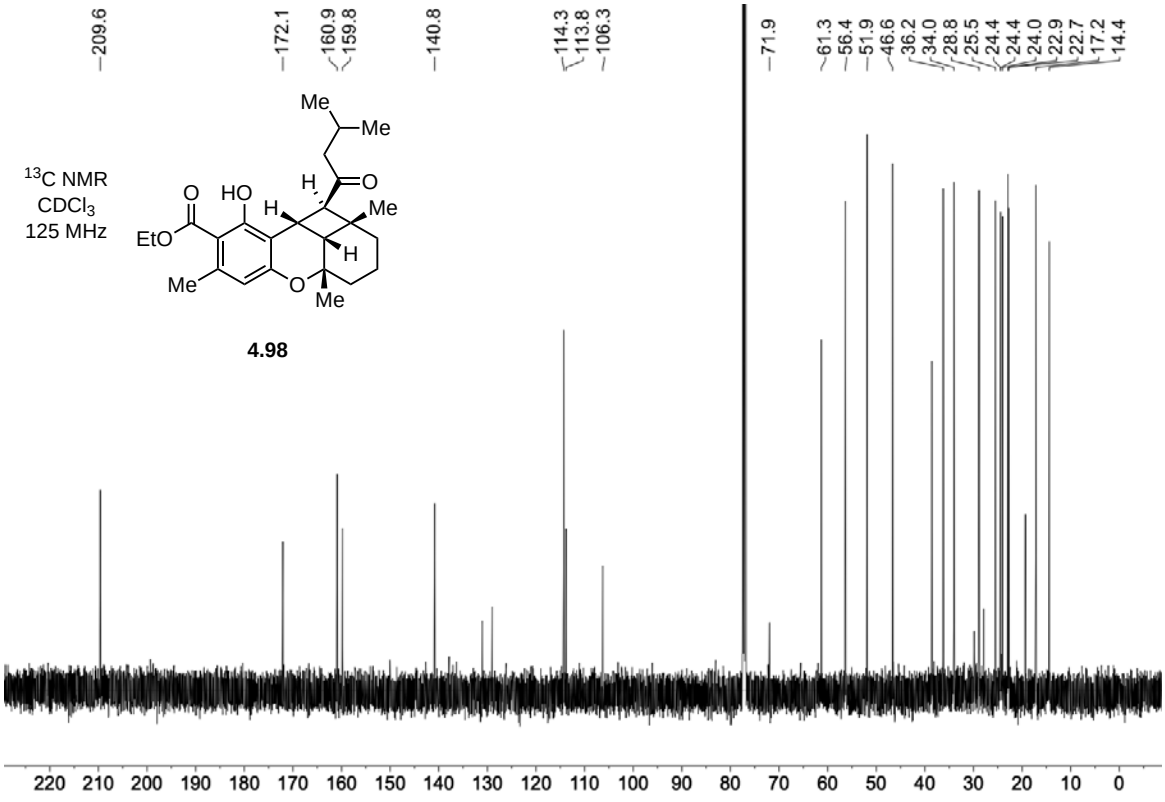
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24.0
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22.7
17.2
14.4
13C NMR
CDCl3
125 MHz
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Me
H
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4.98
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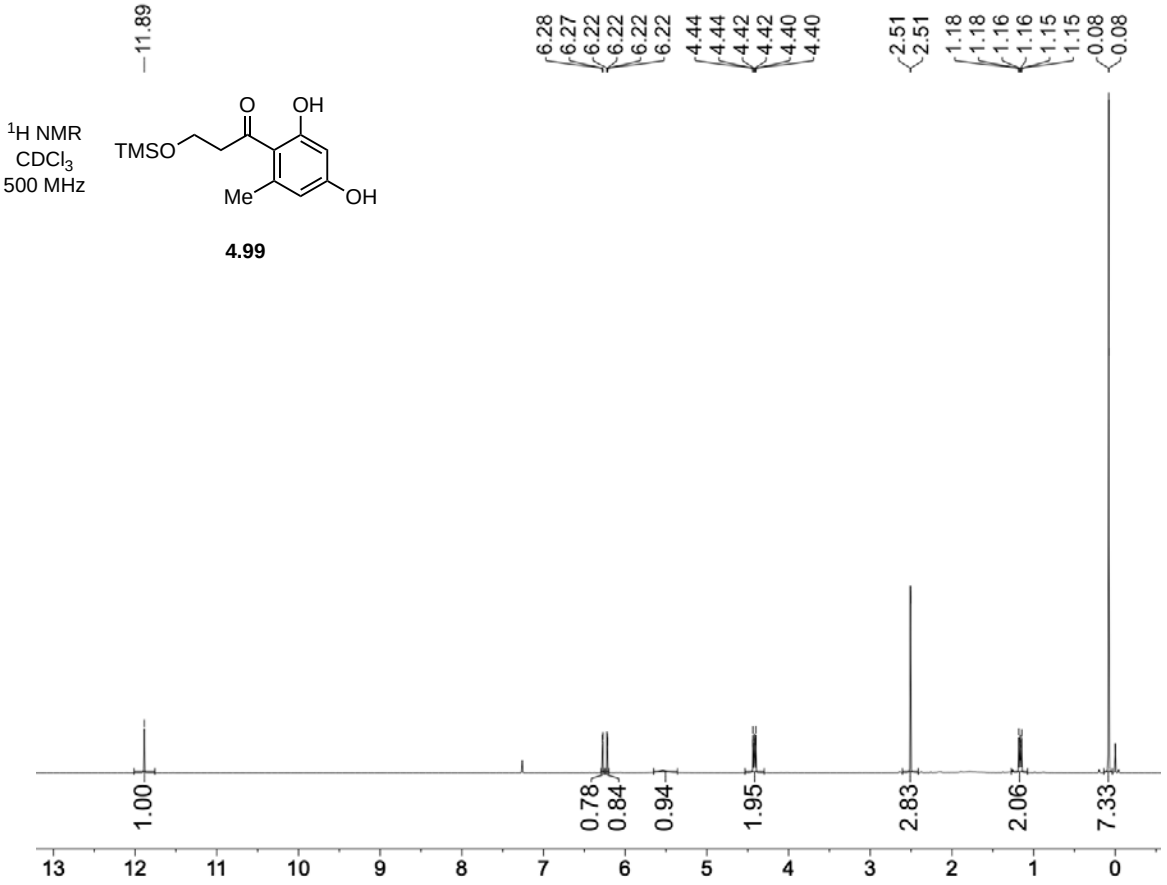
Data for 4.99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1.18
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1.16
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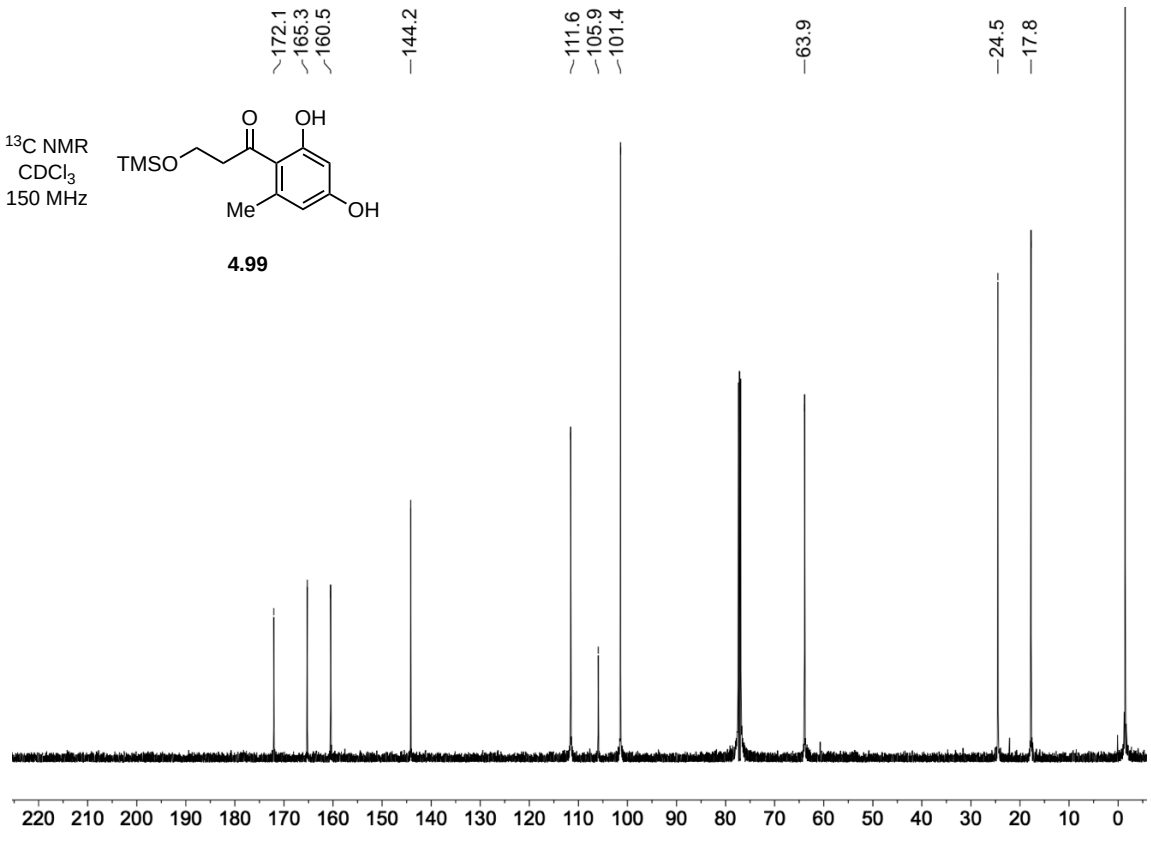
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63.9
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17.8
13C NMR
CDCl3
150 MHz
TMSO
O
OH
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OH
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Data for 4.100

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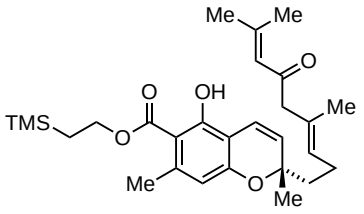
$CDCl_3$
500 MHz



4.100

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$CDCl_3$
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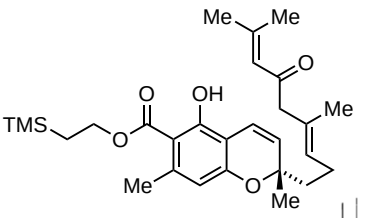

4.100

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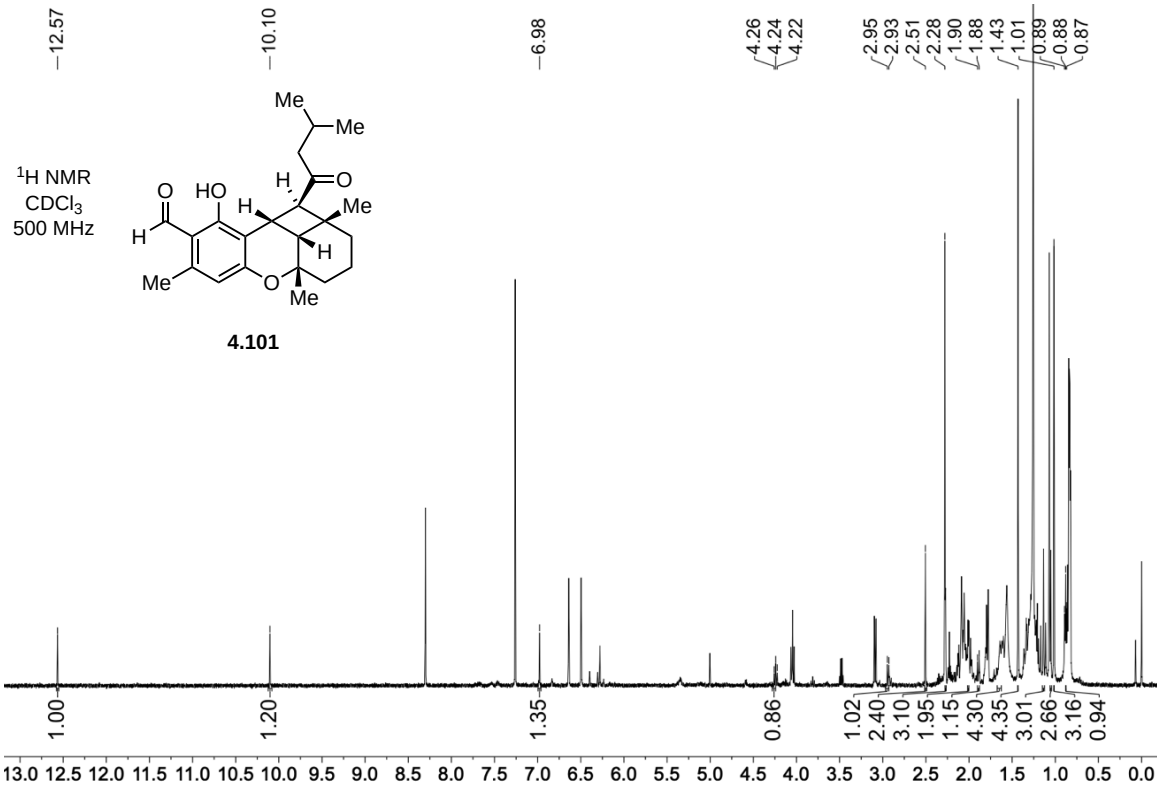

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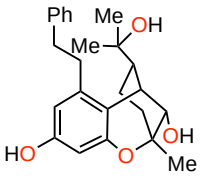
Chapter Five – Biomimetic Synthesis of Nyingchinoids A, B, D and Rasumatranin D

This work was completed with help from Mr Jacob Hart (who assisted the synthesis of Nyingchinoids A, B and D) and Mr. Aaron Day (for stereochemistry discussions). Biological testing was done by Ornella Romeo and Dr. Danny Wilson from the School of Biological Sciences, University of Adelaide

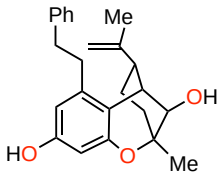
5.1 Introduction

5.1.1 Isolation of Nyingchinoids A, B, D and Rasumatranin D

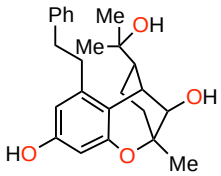
In 2017, Wang *et al.* reported the bibenzyl-based meroterpenoids rasumatranins A – D (**5.1 – 5.4**) isolated from the Chinese liverwort *Radula sumatrana* (**Figure 5.1**).[1] A year later the structurally similar Nyingchinoids A – H (**5.5** – **5.8**) isolated from the flowering plant *Rhododendron nyingchiense* were disclosed by Huang and co-workers.[2] These natural products were each identified as scalemic mixtures by chiral HPLC.



5.1: rasumatranin A



5.2: rasumatranin B



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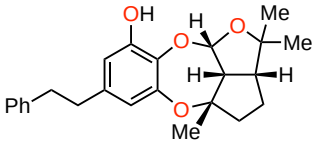

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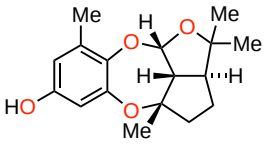
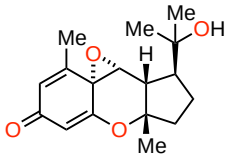


5.5: nyingchinoids A



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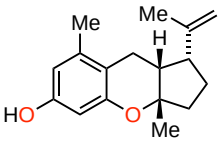

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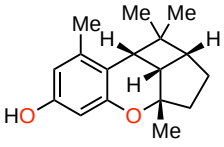
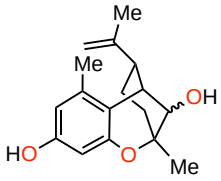
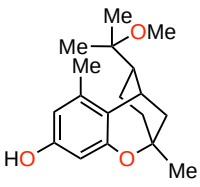


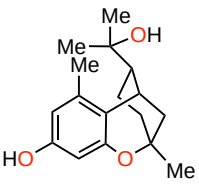
5.8: nyingchinoid D



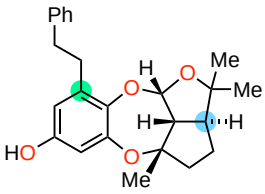
5.9: nyingchinoid E **3S**
5.10: nyingchinoid H **3R**



5.11: nyingchinoid F



5.12: nyingchinoid G



5.13: rasumatranin D
revised structure

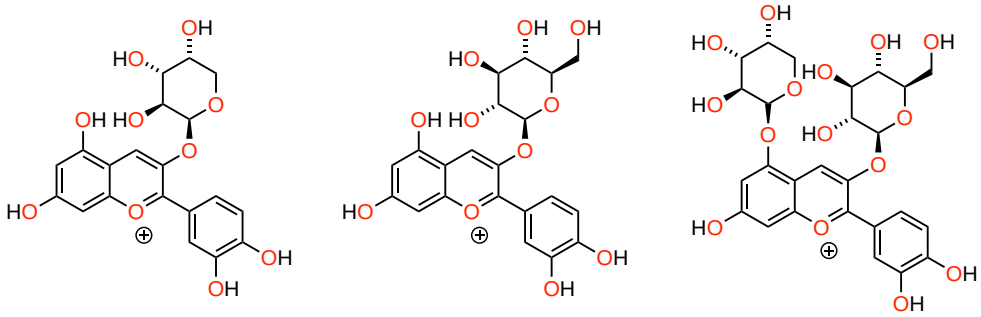
Figure 5.1 – Rasumatranins A – D and Nyingchinoids A – H[1, 2]

5.1.2 Identification of Anthocyanidins in the *Rhododendron Nyingchiense* Species

Continuing our investigations into compounds isolated from the *Rhododendron* genus, we began investigating other common co-isolated natural products. Specifically, we became interested in the pigment responsible for the red-purple flower colour in *Rhododendron nyingchiense*; one of the major ornamental characteristics of all *Rhododendron* plants) (**Figure 5.2**).[3]

Figure 5.2 – Different Flowering *Rhododendron* Species (Image from Du *et al.*)[3]

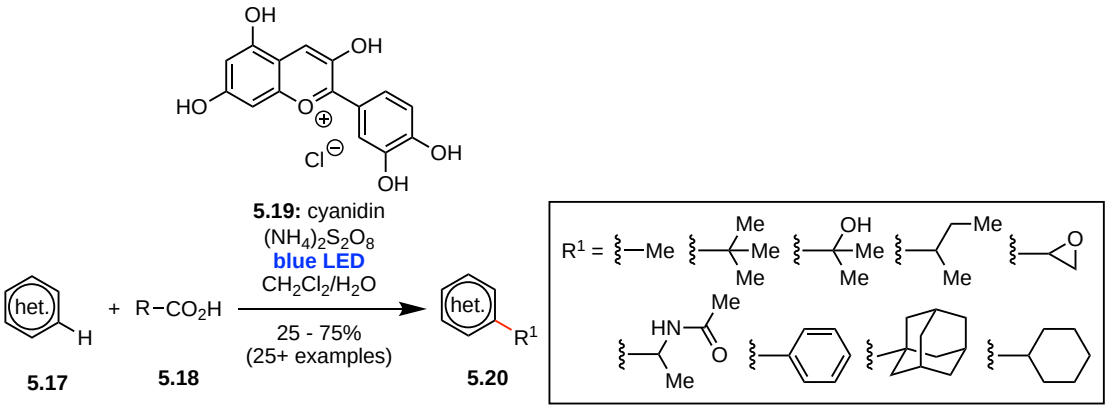
These pigments are largely derived from flavonol and anthocyanin compounds, isolated from the petals of a range of different *Rhododendron* species including *Rhododendron agastum, fortunei, chihsinianum, strigosum* and *rubiginosum* to name a few. In 2016, Liu and co-workers reported the co-isolation of 7 flavonols and 3 different anthocyanins from *Rhododendron nyingchiense*; cyanidin-3-*O*-arabinoside (**5.14**), cyanidin-3-*O*-glucoside (**5.15**) and cyanidin-3-*O*-glucoside-5-*O*-arabinoside (**5.16**) (**Figure 5.3**).[4]



5.14: cyanidin-3-*O*-arabinoside **5.15:** cyanidin-3-*O*-glucoside **5.16:** cyanidin-3-*O*-glucoside-5-*O*-arabinoside

Figure 5.3 – Cyanidins from *Rhododendron nyingchiense*[4]

Recently, Guo *et al.* reported the first visible light induced decarboxylation alkylation of heterocycles **5.17** and aliphatic carboxylic acids **5.18** using the simplest anthocyanidin analogue cyanidin (**5.19**) to synthesize a variety of substituted hectocycles (**5.20**) (**Scheme 5.1**).[5]



Scheme 5.1 – First Reported Example of a Photocatalyzed Anthocyanin Reaction[5]

This use of cyanidin (**5.19**) as a photoredox catalyst prompted us to question the role of analogous anthocyanidins (**5.14** – **5.16**) (co-isolated with the *nyingchinoid* family of natural products) both in broader plant metabolism and in providing insight into the possible biosynthesis of nyingchinoids A, B, and D and rasumatranin D *via* photoredox catalysis.

5.1.3 Photoredox Catalysis

Photoredox catalysis is the conversion of visible light into chemical energy through excitation of a sensitiser and a single electron transfer (**SET**) reaction.[6] This leads to the formation of radical substrates which can access unique modes of reactivity that would not otherwise occur. Once this redox process has occurred, the catalyst relaxes back its ground state and can be regenerated to turn over the catalytic cycle.

The simplified concept of photoredox catalysis is described below (**Figure 5.4**). Here visible light absorption, and a spin-allowed metal to ligand charge transfer (**MLCT**) allows the catalyst $[Ru(bpy)_3]^{2+}$ to enter an excited state. Intersystem crossing (**ISC**) then occurs to afford a highly reactive triplet excited state (with two unpaired electrons) which undergoes SET reduction or/ and SET oxidation.

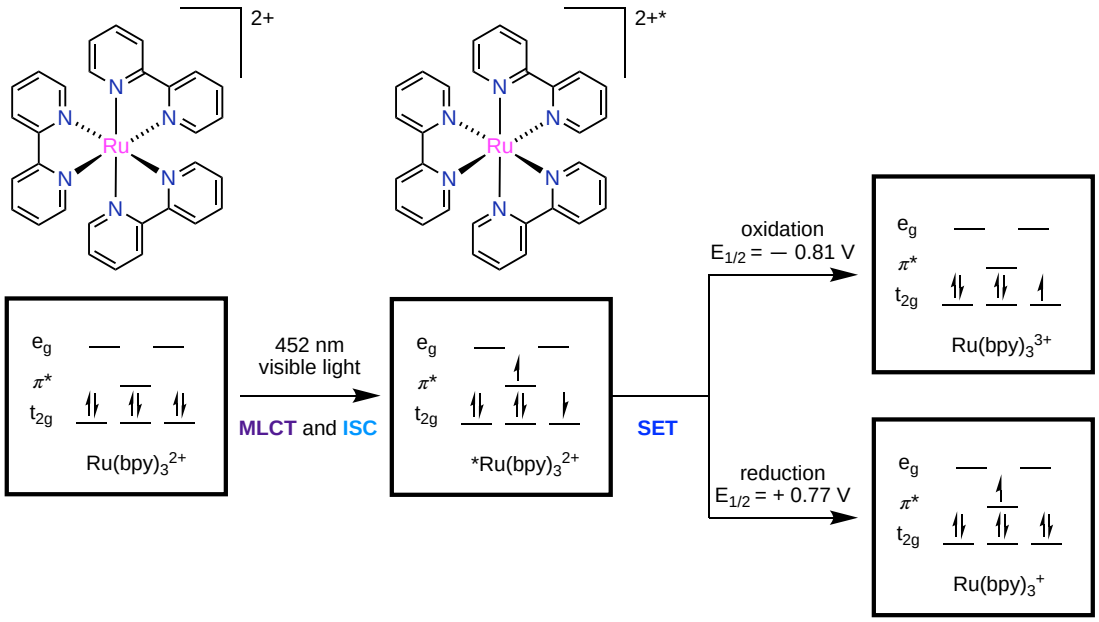


Figure 5.4 – Reactivity of the Photoredox Catalyst $[Ru(bpy)_3]^{2+}$

These photoredox catalysts can be classified into three major classes: transition metal complexes, organic dyes, and semiconductors.[6] They can act as both strong oxidants and reductants providing unique reaction environments and facilitating the ability to access new chemical reactivities.

In the case of transition metal photocatalysts, the oxidative or reductive power can be fine-tuned through careful choice of the metal (i.e. Ru, Ir, Ti, Cu) and ligands used (often polypyridyl) (**Figure 5.5**). As a general rule the oxidative and reductive power is largely influenced by the ligands.[7] Indeed, the synthesis of these catalysts is typically synthetically straightforward, and a wide range of substitution is tolerated on the polypyridyl ligand framework.[8]

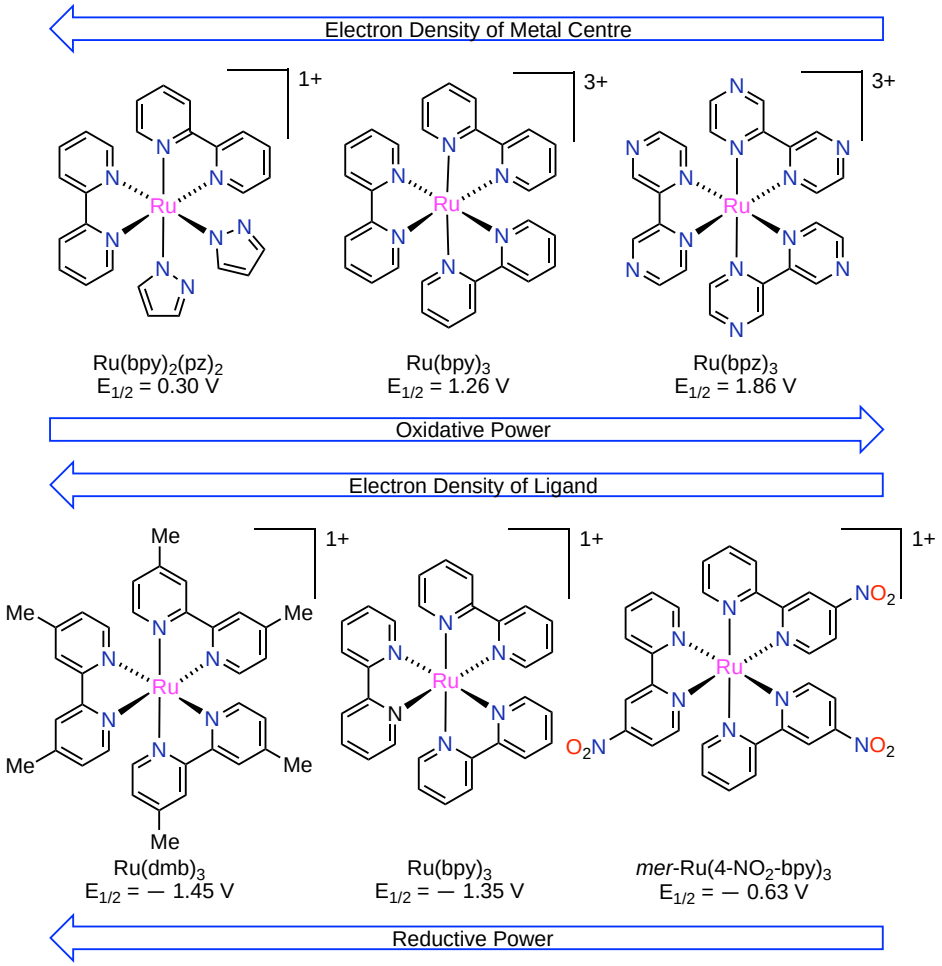


Figure 5.5 – Oxidative and Reductive Power of Ruthenium Based Photoredox Catalysts

Organic photoredox catalysts have also been extensively reported in the literature, providing some advantage over transition metal photoredox catalysts; primarily due to their low toxicity, higher tolerance towards moisture, and not needing the presence of rare and precious metals.[9, 10] Common examples include those photosensitisers previously described in chapter three; rose bengal (RB) (**5.21**), methylene blue (MB) (**5.22**), tetraphenyl porphyrin (TPP) (**5.23**), and fluorescein (**5.24**) (**Figure 5.6**). Alongside more heavily developed photocatalysts such as the acridiniums (i.e. **5.25**),[11] perylene diimide (PDI) (i.e. **5.26**),[12] and various pyrylium salts (i.e. **5.27**) later developed by Nicewicz and co-workers.[13]

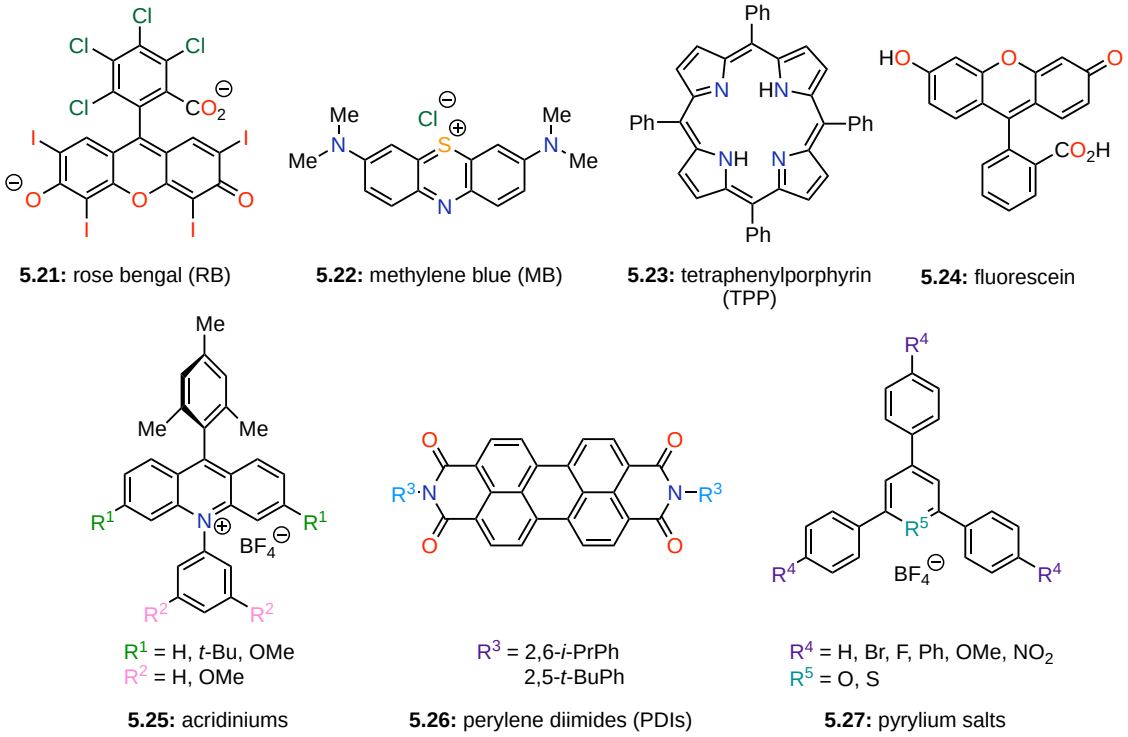
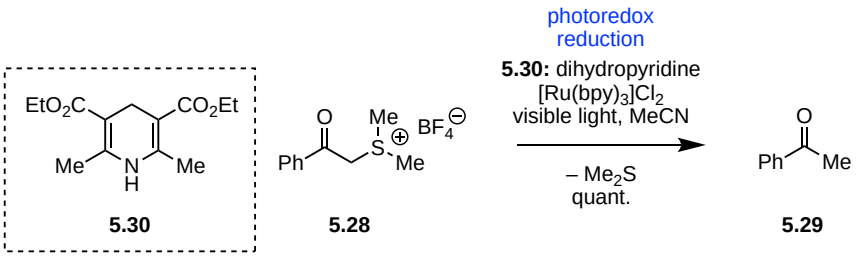


Figure 5.6 – Common Examples of Organic Photoredox Catalysts

5.1.4 A Brief History of Photoredox Catalysis

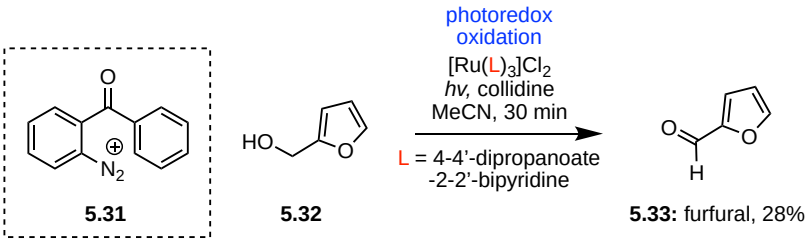
Stories of scientific discovery often begin with a lightbulb moment. Ironically for photoredox catalysis this story begins with an actual lightbulb. In 1978 Hedstrand and co-workers reported a $[Ru(bpy)_3]Cl_2$ visible light catalyzed reduction of sulfonium ions (**5.28**) into alkanes (**5.29**) using *N*-substituted 1,4-dihydropyridines (**5.30**) (**Scheme 5.2**).[14]



Scheme 5.2 – First Reported Example of Photoredox Catalysis[14]

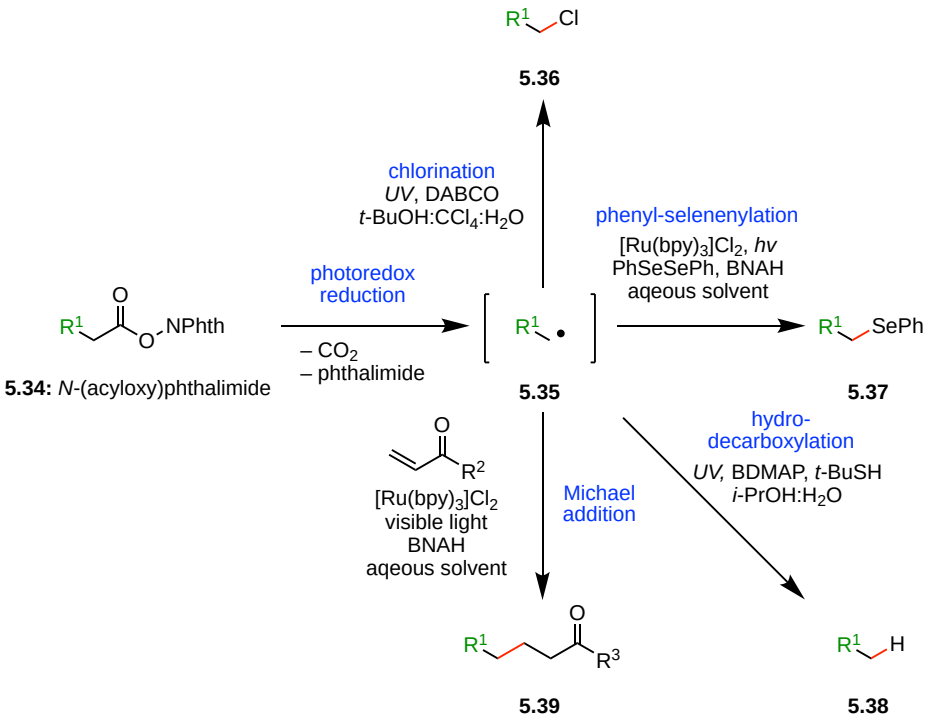
Shortly after, between the years 1981 and 1990 Fukuzumi, Hironaka, Ishitani and Pac reported similar $[Ru(bpy)_3]Cl_2$ photocatalyzed catalyzed reductions.[15-17] While the first oxidative photoredox catalyzed reaction was discovered in 1984 by Deronzier and Cano-Yelo using an aryl diazonium salt **5.31** for the conversion of alcohols **5.32** into their corresponding aldehydes **5.33** (**Scheme 5.3**).[18] Deronzier also

went on to disclose the first photoredox redox neutral transformation through a $[Ru(bpy)_3Cl_2]$ mediated Pschorr reaction.[19]



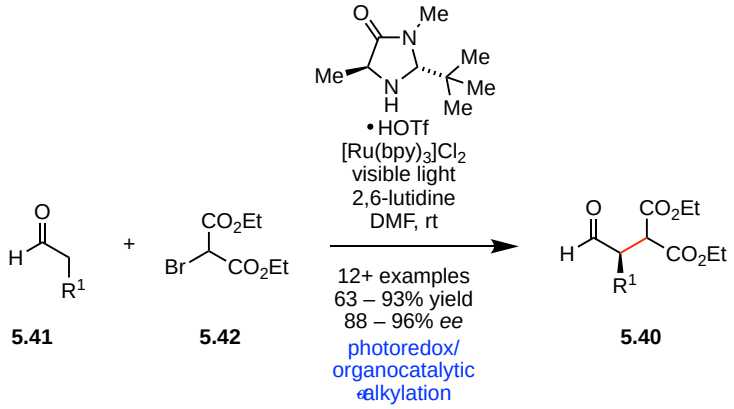
Scheme 5.3 – First Reported Oxidative Photoredox Catalyzed Reaction[18]

Further work by Okada, then described the preparation of *N*-(acyloxy)phthalimides **5.34** from carboxylic acids and their use as alkyl radical intermediates which can be intercepted for a diverse range of chemical transformations (**Scheme 5.4**).[20 - 23] In these reactions a single electron reduction with a photoexcited catalyst affords phthalimide, CO_2 and the carbon radical **5.35**, which can undergo a variety of reactions including chlorination (i.e **5.36**), phenyl-selenenylation (i.e. **5.37**), hydro-decarboxylation (*via* a hydrogen atom extraction from *t*-butyl thiol) (i.e. **5.38**) and conjugate additions (i.e. **5.39**).



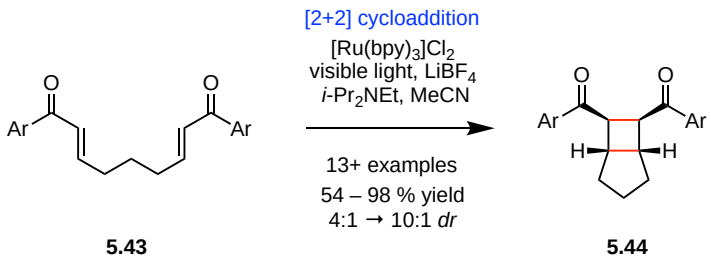
Scheme 5.4 – Okada's Investigations into the Photoredox Transformations of Phthalimides[20 - 23]

Remarkably, despite early demonstrations into the direct application of photoredox catalysis in organic synthesis this area remained relatively unexplored for the next 15 years, with ruthenium polypyridyl catalysts only being used in the area of solar cell research.[24] It was not until 2008 when both MacMillan and Yoon independently published separate papers using visible light photoredox catalysis that its significance was fully realized. Work by MacMillan and his postdoctoral researcher David Nicewicz (whose catalysts will be explored later in this chapter, *vide infra*) focused on the formation of an enantioselective α-alkylation of aldehydes **5.40** (**Scheme 5.5**).[25] This was achieved through a dual organocatalytic and photoredox catalytic cycle, combining two approaches in one sequence. Use of the ruthenium photoredox catalyst $[Ru(bpy)_3]Cl_2$ and an organic catalyst allowed the reaction to proceed with a simple household compact fluorescent lightbulb under mild reaction conditions.



Scheme 5.5 – MacMillan and Nicewicz's Enantioselective α-Alkylation of Aldehydes[25]

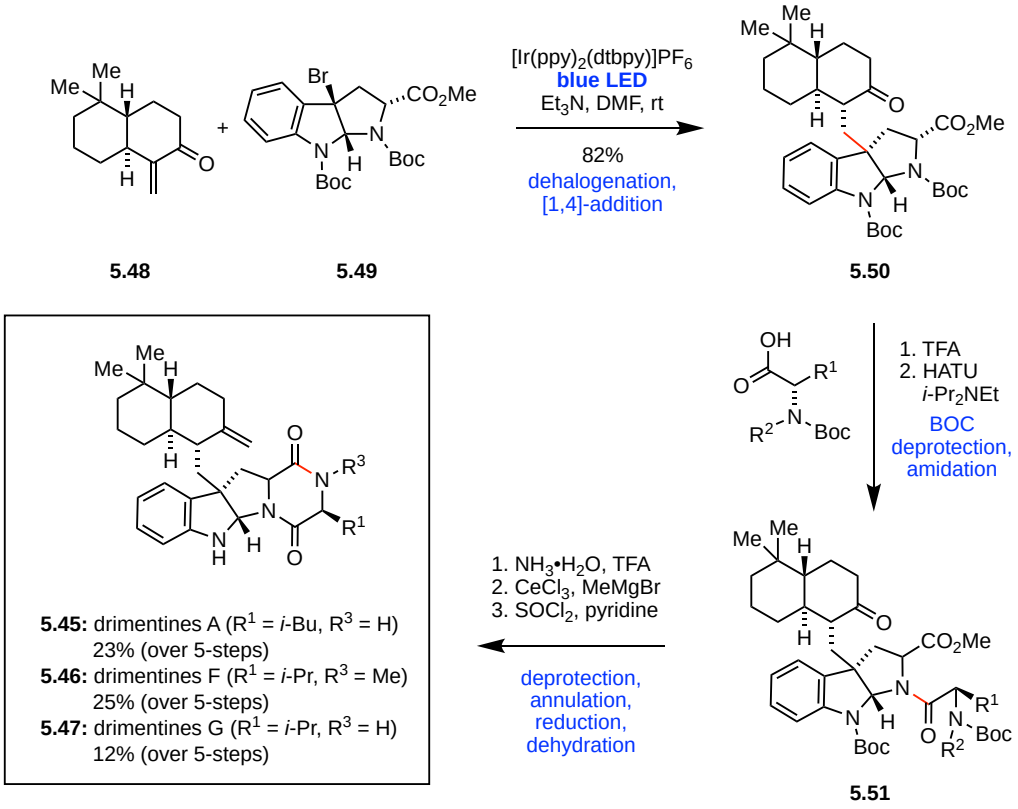
In 2008, in a completely unrelated area of chemistry Yoon's group reported a reversible photoredox catalyzed intramolecular [2+2] cycloaddition of the bis-styrenes **5.43** employing $[Ru(bpy)_3]Cl_2$ and the Lewis acids $LiBF_4$ through reaction with visible light (**Scheme 5.6**).[26]



Scheme 5.6 – Intramolecular [2+2] Bis-enone Cycloaddition Reaction[26]

Shortly after, Narayanam *et al.* disclosed a dehalogenation reaction of α-acyl and benzylic halides.[27] Photoredox catalysis can also be applied to the total synthesis of natural products. Recently, Li and

co-workers reported the reductive dehalogenation of **C3** bromopyrrolindolines in the divergent synthesis of the drimentine alkaloids A, F, and G (**5.45** – **5.47**) (**Scheme 5.7**).[28] This synthesis featured a uniquely effective intermolecular radical 1,4-addition of **5.48** with the conjugate acceptor **5.49** to afford **5.50**. The divergent synthesis of drimentines A, F and G was then realized through deprotection and amidation to give **5.51**, followed by deprotection/ annulation, reduction and dehydration.

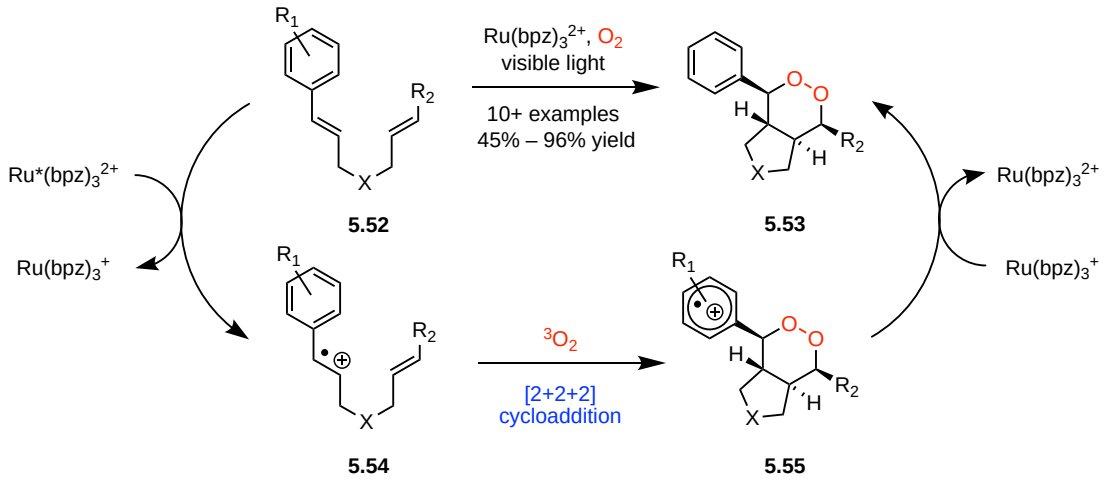


Scheme 5.7 – Total Synthesis of Drimentines A, F and G Through Photoredox Catalysis[28]

Today photoredox catalysis is currently one of the most popular areas in organic chemistry, with the number of publications increasing by a factor of 10 in less than 5 years. Photoredox catalysis has become a powerful strategy for the activation of small molecules and generation of reactive radical intermediates, leading to the development of new chemical transformations and umpolung reactivity.

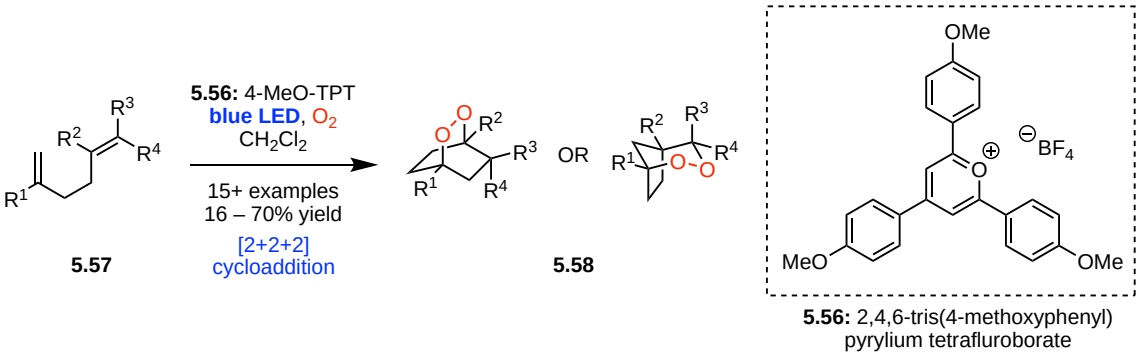
5.1.5 Photoredox Catalyzed [2+2+2] Cycloadditions

Both the Nicewicz and Yoon groups have employed photoredox catalyzed [2+2+2] cycloadditions of triplet oxygen with distonic cation radical intermediates in the synthesis of endoperoxides.[29, 30] In the Yoon group this was achieved using polypyridyl ruthenium (II) catalysts to synthesise endoperoxides **5.53** from bis(enone) substrates **5.52** in good to excellent yields (**Scheme 5.8**).



Scheme 5.8 – Yoon's $Ru(bpz)_3^{2+}$ catalyzed [2+2+2] Cycloadditions of Bis(enone) substrates[29]

Almost simultaneously, Nicewicz and Gesmundo disclosed similar [2+2+2] cycloadditions. They found that using the triarylpyrylium salt **5.56** catalyst, they were able to increase the substrate scope to non-styrene compounds (**Scheme 5.9**). The authors also observed that electron rich arenes **5.57** were required for the oxidation of the olefin and crucial for the stability of the distonic cation radical (**Scheme 5.9**).[30]

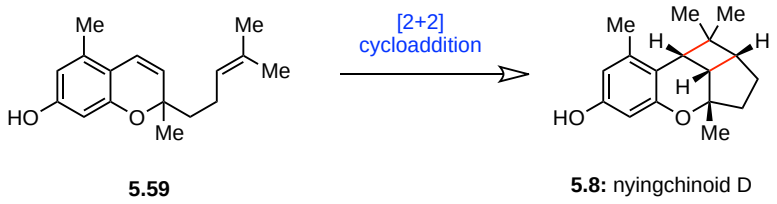


Scheme 5.9 – [2+2+2] Cycloadditions Using the Triarylpyrylium 5.62[30]

Intrigued by these [2+2+2] cycloadditions obtained from readily oxidizable olefins, alongside the presence of the co-isolated and cyanidins (**5.14 – 5.16**) as potential photoredox catalysts we considered the possibility that a similar photoredox catalyzed reaction may be occurring in nature for the biosynthesis of nyingchinoids A, B and rasumatranin D.

5.1.6 Biogenic Relationships Between Nyingchinoid A, B, D and Rasumatranin D

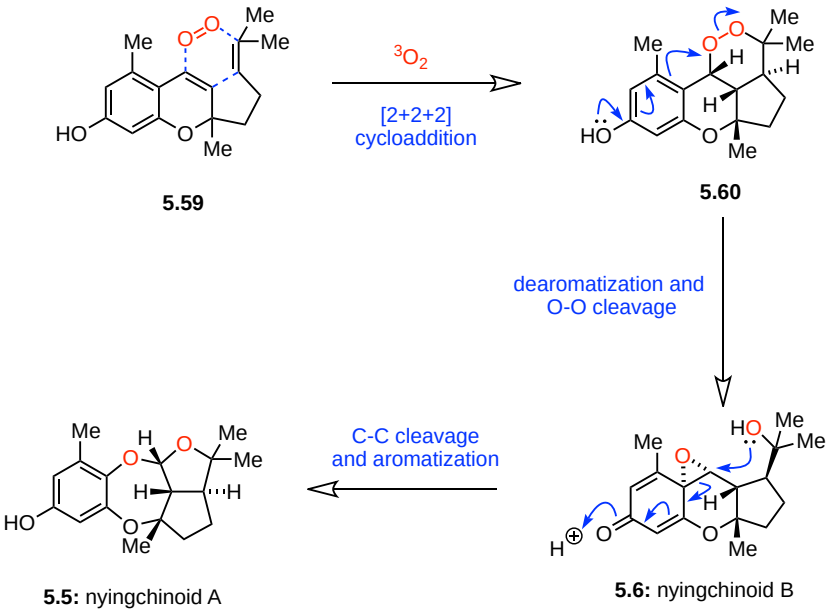
We were particularly interested in the biosynthetic relationships between nyingchinoids A, B and D and the possible biosynthetic precursor, chromene **5.59**. In chapter four the **6-6-5-4** ring system, was extensively discussed being arguably the most common scaffold in *Rhododendron* natural products. It is most likely that nyingchinoid D (**5.8**) is formed through a visible light catalyzed intramolecular [2+2] cycloaddition (**Scheme 5.10**).



5.59 **5.8:** nyingchinoid D

Scheme 5.10 – Proposed Biosynthesis of Nyingchinoid D Through a [2+2] Cycloaddition

What is less clear is the biosynthetic link between nyingchinoids A, B and chromene **5.59**. One possibility is the formation of a 1,2-dioxane **5.60** arising from a photoredox catalyzed [2+2+2] cycloaddition between triplet oxygen the chromene and prenyl alkene of **5.61** (**Scheme 5.11**). Dearomatization of endoperoxide **5.60** through O-O cleavage would then afford nyingchinoid B (**5.6**). While a nucleophilic attack to the spiroepoxide would afford the ring expansion product nyingchinoid A (**5.5**) through C-C bond scission. In nature, these types of reactions would most likely occur in chlorophyll photosystems which possess unique oxidative environments to facilitate cascades not accessible *via* thermal conditions.

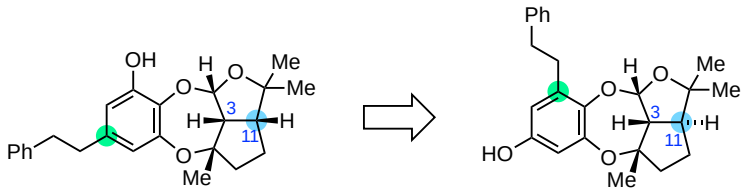


5.59 **5.60**

5.5: nyingchinoid A **5.6:** nyingchinoid B

Scheme 5.11 – Proposed Biosynthesis of Nyingchinoids A and B

We also suspect that the structurally similar rasumatranin D (**5.4**), might in fact be misassigned (**Figure 5.7**). We were suspicious of the reported *syn* stereochemistry across the **C3** and **C11** ring junction in the NMR spectra, which was different to that of nyingchinoid A (**5.5**). Additionally, the bibenzyl substitution pattern around the aromatic ring seemed dubious due to its differing regiochemistry when compared to the other rasumatranin co-isolated natural products (**5.1** – **5.3**).



5.4: rasumatranin D
originally proposed structure

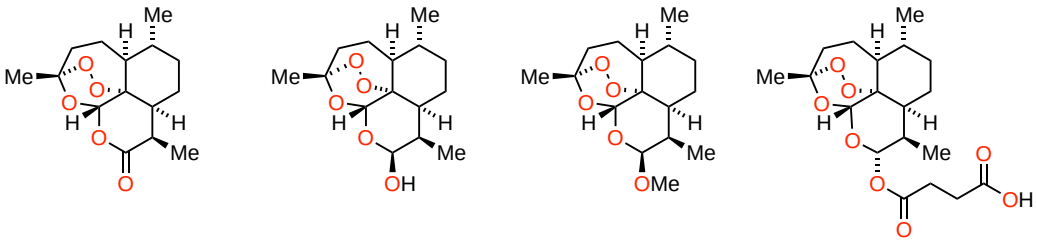
5.13: rasumatranin D
revised structure

Figure 5.7 – Proposed Structural Revision of Rasumatranin D

Applying photocatalysts we hope to mimic our proposed biosynthesis and describe investigations into the biomimetic synthesis of nyingchinoids A, B, D and synthesis and structural revision of rasumatranin D. We also hoped that this synthesis could allow us to develop a bio-inspired approach towards some novel endoperoxides, which could possess some interesting antimalarial properties.

5.1.7 A Bio-Inspired Approach Towards Antimalarial Endoperoxides

Annually, there are approximately 228 million cases and 405,000 deaths due to malaria disease.[31] Current *anti*-malarial medications, including those treating the highly resistant *Plasmodium falciparum*, are heavily reliant on the natural product artemisinin (**5.61**) and artemisinin-based combination therapies (ACTs) (**Figure 5.8**).[32] Recently, several Southeast Asian countries have reported parasites with decreased sensitivity to ACTs.[33] Thus, the discover of new bio-inspired endoperoxides remains a significant interest.



5.61: artemisinin (ART)

5.62: dihydroartemisinin (DHA)

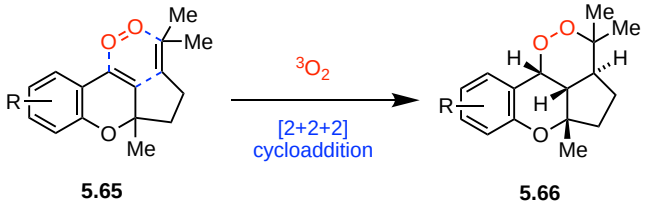
5.63: artemether (ATM)

5.64: artesunate (AS)

Figure 5.8 – Artemisinin Based Combination Therapies (ACTs)

It is the unusual peroxide bridge in ACTs which acts as a pharmacophore, undergoing homolytic cleavage when exposed to haemoglobin.[34] This results in the formation of reactive oxygen species (ROS) (i.e. hydroxyl radicals and superoxide anions) which exclusively damage malaria specific proteins and result in parasitic death.

As we hope to generate chromene derived endoperoxides in the synthesizing nyingchinoids A, B, D and rasumatranin D, we envisaged that this project could be expanded through the synthesis of a diverse library of endoperoxide analogues (**Scheme 5.12**). Not only will this allow for the rapid generation of substrates, but it will also allow for the easy functionalization of these analogues based on resultant structure activity relationships (SAR). If successful we hope that these molecules could be used to improve drug treatment approaches for malaria.



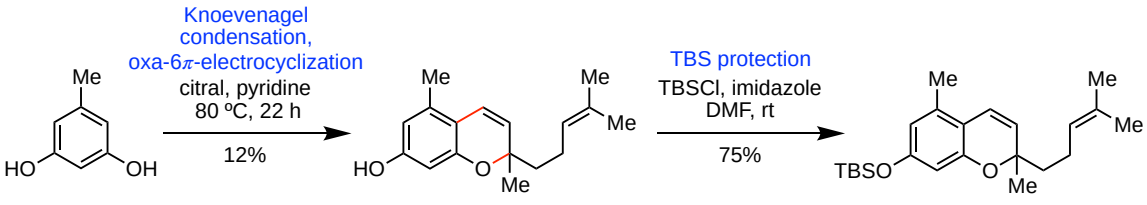
5.65 **5.66**

Scheme 5.12 – A Divergent Approach Towards the Synthesis of Endoperoxides

5.2 Results and Discussion

5.2.1 Total Synthesis of Nyingchinoids A, B and D

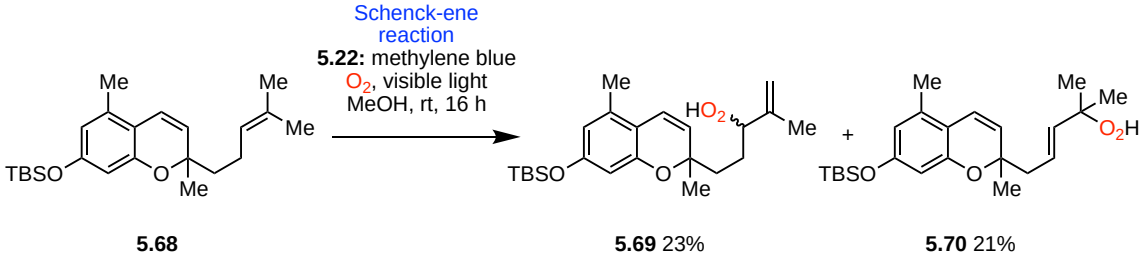
The biomimetic synthesis of nyingchinoids A (**5.5**), B (**5.6**), and D (**5.8**) began with the synthesis of the racemic chromene **5.59** through a 1-step condensation of orcinol (**5.67**) with citral according to a literature procedure (**Scheme 5.13**).[35] Conversion of chromene **5.59** into the endoperoxide **5.60** using a variety of oxidation conditions was attempted, however direct attempts to oxidise **5.59** to a phenoxy radical using standard photoredox conditions (in the presence of O_2) only afforded decomposition. Instead, **5.59** was protected as the TBS-ether **5.68** in 75% through reaction with TBSCl and imidazole in DMF.



5.67: orcinol **5.59** **5.68**

Scheme 5.13 – Synthesis of the TBS Protected Chromene 5.68

Exposure of **5.68** to conditions known to generate singlet oxygen (e.g. methylene blue, O_2, MeOH, visible light) gave products (**5.69** and **5.70**) formed exclusively by oxygenation of the prenyl motif, rather than reaction at the chromene (**Scheme 5.14**). This was perhaps unsurprising as similar results were previously observed in chapter three (*vide supra*).[36]



Scheme 5.14 – Reaction of Chromene 5.68 With Singlet Oxygen

Instead, treatment of **5.68** using conditions developed by Nicewicz (4-MeO-TPT (**5.56**) photocatalyst, 1 atm O_2, **blue LED**, DCE) gave, cyclobutane **5.71** after 20 minutes as the exclusive product observed in the crude ^{1}H NMR spectrum (**Figure 5.9**). After purification, **5.71** was isolated in 87% yield. Treatment of **5.71** with TBAF the afforded nyingchinoid D (**5.8**) in 86% yield. Additionally, a one-pot, 2-step procedure was successful for the direct conversion of **5.68** into **5.8**, which was achieved in a 51% yield. To our delight, on repeating this [2+2] cycloaddition we observed gradual formation of the key endoperoxide **5.72** (as a single diastereoisomer) when the reaction was run for 7 hours, allowing us access to **5.72** in 60% yield (**Scheme 5.15**).

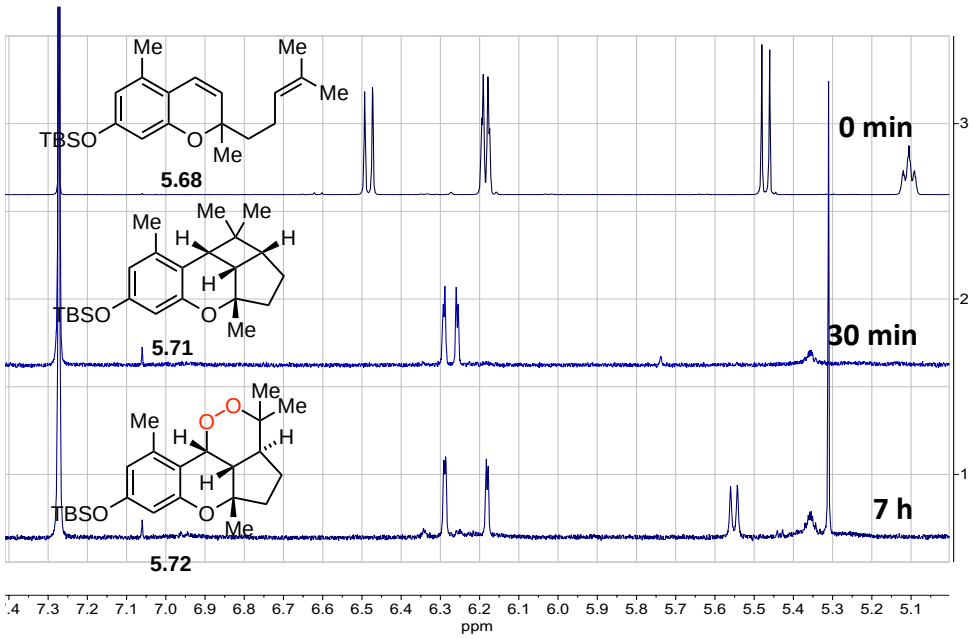
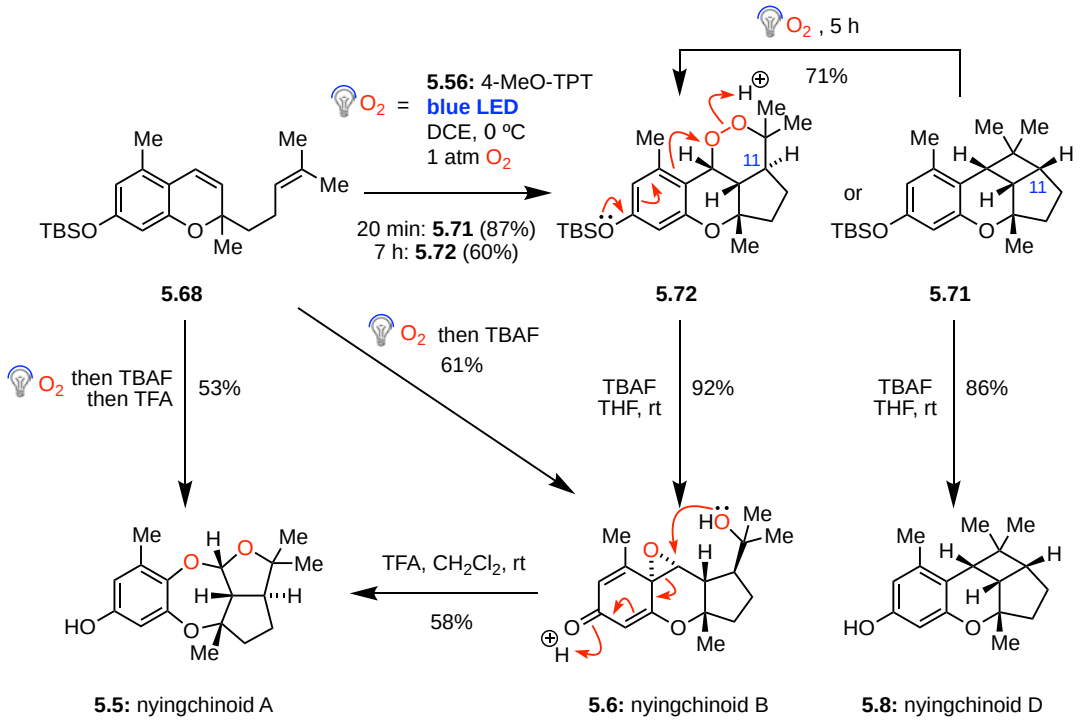


Figure 5.9 – Crude ^{1}H NMR Showing a 0 min, 30 min, and 7 h Time Elapse

Pleasingly, treatment of endoperoxide **5.72** with TBAF formed nyingchinoid B (**5.6**) in 92% yield *via* deprotection through formation of an intermediate phenoxide anion, which dearomatized and underwent O-O cleavage to afford the spiroepoxide nyingchinoid B (**5.6**) (**Scheme 5.15**). An acid catalyzed C-C cleavage and aromatization using TFA in CH_2Cl_2 then gave nyingchinoid A (**5.5**) in 58% yield.

Next our efforts turned towards the transformation of chromene **5.68** to form **5.6** and **5.5** in a one-pot procedure. Gratifyingly, photoredox catalyzed aerobic [2+2+2] cycloaddition of **5.68** followed by the direct addition of TBAF afforded **5.6** in 61% yield, while addition of TBAF followed by TFA gave **5.5** in 53%. The last sequence of **5.68** into **5.5** involves the construction of 2 rings, 3 stereocentres, 4 C-O bonds and 1 C-C bond, alongside the scission of 1 O-O bond and 1 C-C bond!



Scheme 5.15 – Biomimetic Synthesis of Nyingchinoids A, B and D

Pleasingly, our obtained NMR spectra of **5.5**, **5.6** and **5.8** matched that previously reported by Hou and co-workers.[2] Additionally, we obtained crystal structures of nyingchinoids A and B to unequivocally prove their structure and relative configuration (**Figure 5.10**).

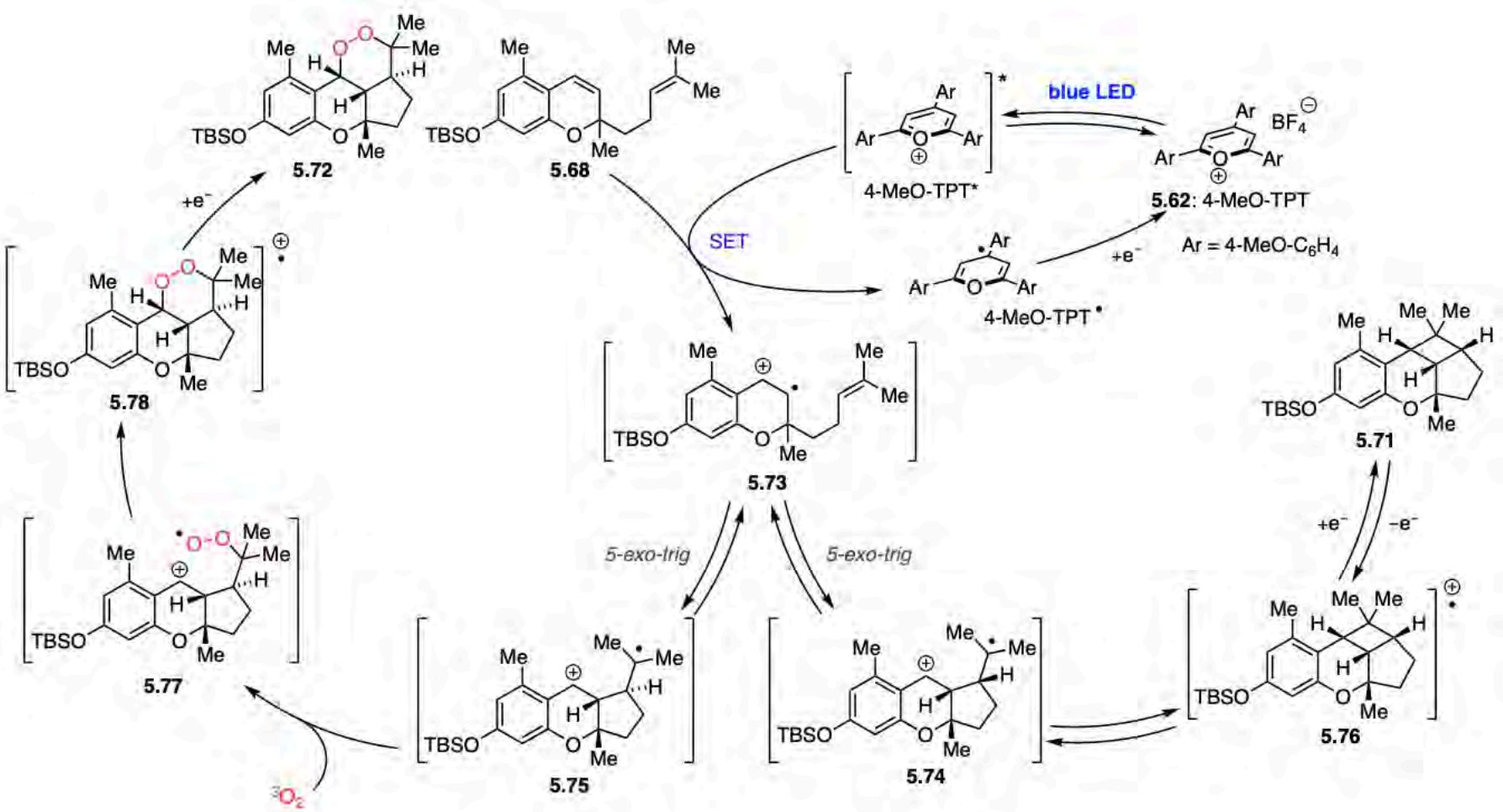
5.5: nyingchinoid A **5.6:** nyingchinoid B

Figure 5.10 – X-Ray Structure of Nyingchinoids A and B

These results clearly indicated the photoredox catalyzed intramolecular [2+2] cycloaddition of **5.68** to be reversible. Indeed, we found that re-treating cyclobutane **5.71** to 4-MeO-TPT (**5.56**) under aerobic conditions formed enone **5.72** in 71% yield, with epimerization at **C11** indicating that cycloreversion had occured before the [2+2+2] cycloaddition. In previous studies of photocatalytic, intermolecular [2+2] cycloadditions of electron-rich styrenes, Yoon has also observed the reversibility of similar cyclobutane reactions when using the highly oxidizing photocatalyst $Ru(bpz)_3^{2+}$ (*vide supra*) (**Scheme 5.8**).[26]

With this in mind, a mechanistic cycle for the aerobic [2+2+2] cycloaddition of **5.68** that incorporates a reversible [2+2] cycloaddition is described herein (**Scheme 5.16**). First, we propose the photocatalyst **5.59** is activated by **blue LED** light to afford the photoexcited 4-MeO-TPT*, containing a high oxidation potential (+1.74 V) capable of oxidizing the electron-rich chromene **5.68** through a single electron transfer (SET) to give radical cation **5.73**. *5-exo-trig* cyclization of **5.73** would then generate the diastereomeric, distonic radical cations **5.74** and **5.75**. Diastereomer **5.74** has *syn*-stereochemistry across the **C3** and **C11** carbons and is primed to undergo further cyclization to give **5.76**, followed by reduction to give **5.71** as the kinetic product. Based on experimental results, we believe these transformations to be reversible through *re*-oxidation of **5.71** by 4-MeO-TPT* and reversion to **5.73** through a retro-[2+2] of **5.74**. Alternatively, due to the *anti*-stereochemistry across the **C3** and **C11** carbons **5.75** is unable to undergo reductive cyclization, instead **5.75** it is trapped by triplet oxygen to give **5** the peroxy radical cation **5.77**. Single electron reduction of **5.78** then affords the thermodynamic product **5.72**.

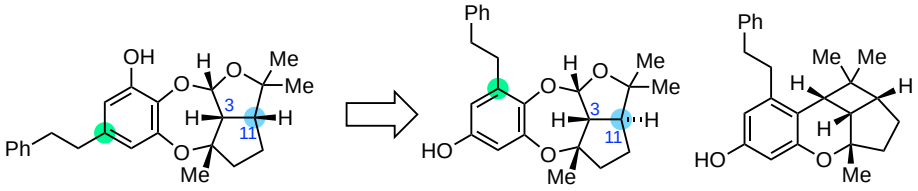
With the assistance of Assoc. Prof. David M. Huang computational modeling using density functional theory (DFT) showed that this stepwise mechanistic pathway was supported, indicating both *5-exo-trig* cyclizations of radical cation **5.73** to be reversible, hence confirming **5.72** as the thermodynamic product.



Scheme 5.16 – Mechanistic Proposal for the Photocatalyzed Cyclization of Chromene (5.68)

5.2.2 Total Synthesis and Structural Revision of Rasumatranin D

Next, our efforts turned towards the total synthesis of rasumatranin D (**5.4**). Although there was no accompanying X-ray structure of **5.4**, close inspection of the reported NMR spectra of nyingchinoid A (**5.5**) suggested two major areas of structural reassignments were required (**Figure 5.11**).



5.5: rasumatranin D
originally proposed structure

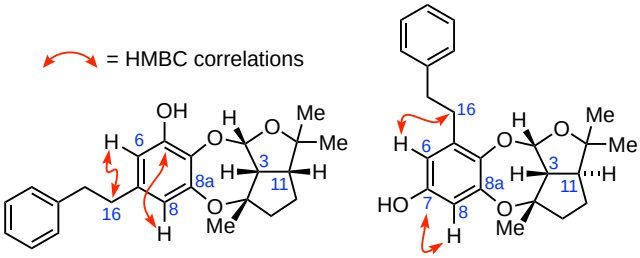
5.13: rasumatranin D
revised structure

5.79: *o*-bibenzyl-cannabicyclol

Figure 5.11 – Proposed Structural Revision of Rasumatranin D

Firstly, comparison of the NMR spectra of nyingchinoid A (**5.5**), whose structure has been unambiguously proven by X-ray crystallography, with that of the previously reported and co-isolated natural product *o*-bibenzyl-cannabicyclol (**5.79**), suggested that the substitution pattern around the aromatic ring was incorrect.[37] In fact, rasumatranin D (**5.4**) is the only member of the rasumatranin family with differing regiochemistry regarding the chromene and the bibenzyl side chain. Careful examination of the HMBC spectra of the originally proposed rasumatranin D (**5.4**) shows discrepancies with the key correlations (**Figure 5.12**).

Specifically, we were intrigued by the report of **H6** to **C16** coupling and suspicious lack of coupling between **H8** and **C16**. As these two HMBC correlation should be equidistant it is unlikely looking at the originally proposed structure for **5.5** that the **H8** and **C16** correlation is absent. However, if the bibenzyl fragment was aligned with that the previous reported rasumatranin natural products the only interaction observed would indeed be the **H6** to **C16** correlation. Additionally, they also observed an unlikely long range ^{4}J coupling between **H8** and **C5**. Instead in our revised structure **5.13** this would be a more plausible ^{2}J coupling between **H8** and **H7**. These correlations provide evidence for a revised regiochemistry of rasumatranin D (**5.13**).



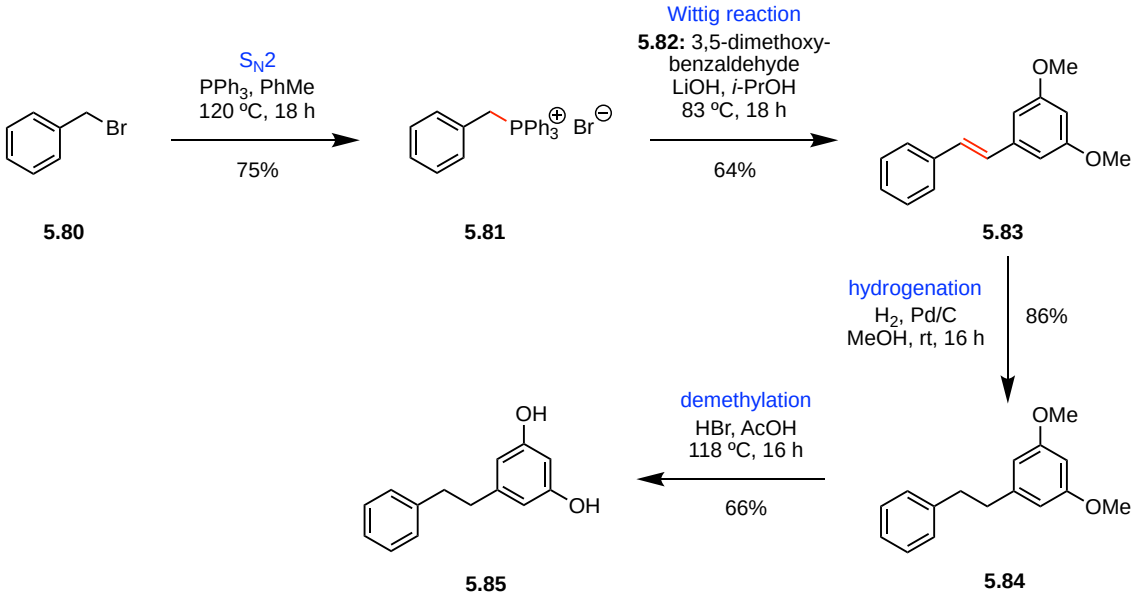
5.4: rasumatranin D
originally proposed structure

5.13: rasumatranin D
revised structure

Figure 5.12 – Revised Regiochemistry and Stereochemistry of Rasumatranin D

Secondly, our mechanistic proposal for the [2+2] and [2+2+2] cycloadditions of the chromene **5.68**, and the requirement of the *anti*-stereochemistry across the **C3** and **C11** carbons to impede reductive cyclization suggested that the relative configuration at **C11** should be reassigned to as in **5.13** (analogous to nyingchinoid A). Specifically, it was the coupling constant of 14 Hz between **H3** and **H11** and the absence of a NOE interaction, which strongly indicated a *trans* relationship at this ring junction. We therefore proposed a structural reassignment of **5.4** to **5.13,** which additionally provide more clarity into the proposed biosynthesis.

Following known literature procedures by Svenson and co-workers, synthesis of the revised structure of rasumatranin D (**5.13**) commenced from reaction of benzyl bromide (**5.80**) with triphenyl phosphine to afford the phosphonium salt **5.81** in 75%.[38] Wittig olefination between **5.81** and 3,5-dimethoxybenzaldehyde (**5.82**) then gave *E*-3,5-dimethoxy stilbene (**5.83**) in 64%. Hydrogenation of **5.83** using H_2 and Pd/C afforded **5.84** in 91%, and deprotection with HBr afforded the bibenzyl resorcinol **5.85** in 66% (**Scheme 5.17**).

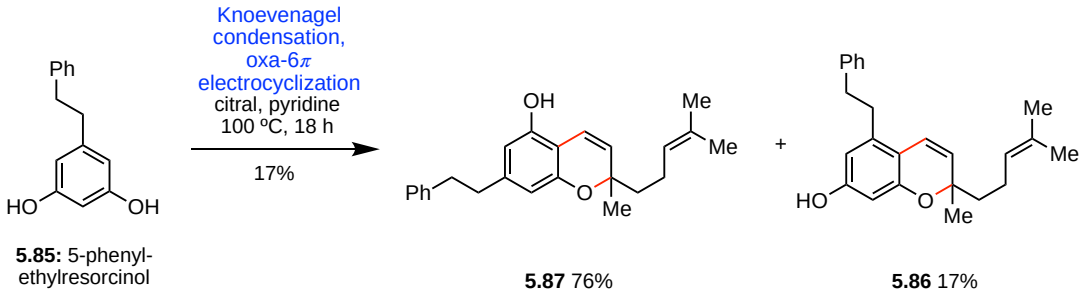


5.80 **5.81** **5.83** **5.84** **5.85**

Scheme 5.17 – Synthesis of the Bibenzyl Resorcinol 5.85[38]

Next, conditions towards the chromenylation of **5.85** to give the *ortho*-bibenzyl chromene (**5.86**) were screened. Unfortunately reflux of **5.85** with citral, $Ca(OH)_2$ in EtOH only gave decomposition, while reflux in PhMe with citral and 10 mol% EDDA afforded only the *para*-bibenzyl chromene (**5.87**) and the *bis*-chromene (**5.88**). Instead following a modified literature procedure from Crombie *et al.*

reaction of **5.85** with pyridine and citral at reflux afforded both **5.87** and a small amount of **5.86** in 17% (**Scheme 5.18**).[37]



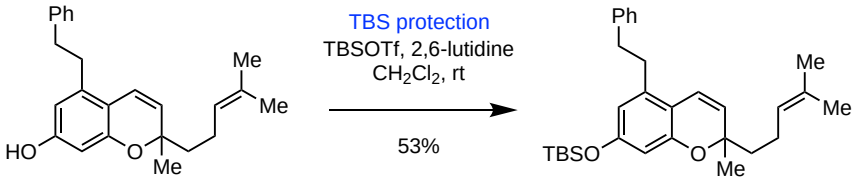
5.85: 5-phenyl-ethylresorcinol

5.87 76%

5.86 17%

Scheme 5.18 – Synthesis of the *ortho*-bibenzyl chromene 5.86[37]

Next, **5.89** was synthesised by TBS-protection of chromene **5.86** through reaction with TBSOTf and catalytic 2,6-lutidine in 53% (**Scheme 5.19**).

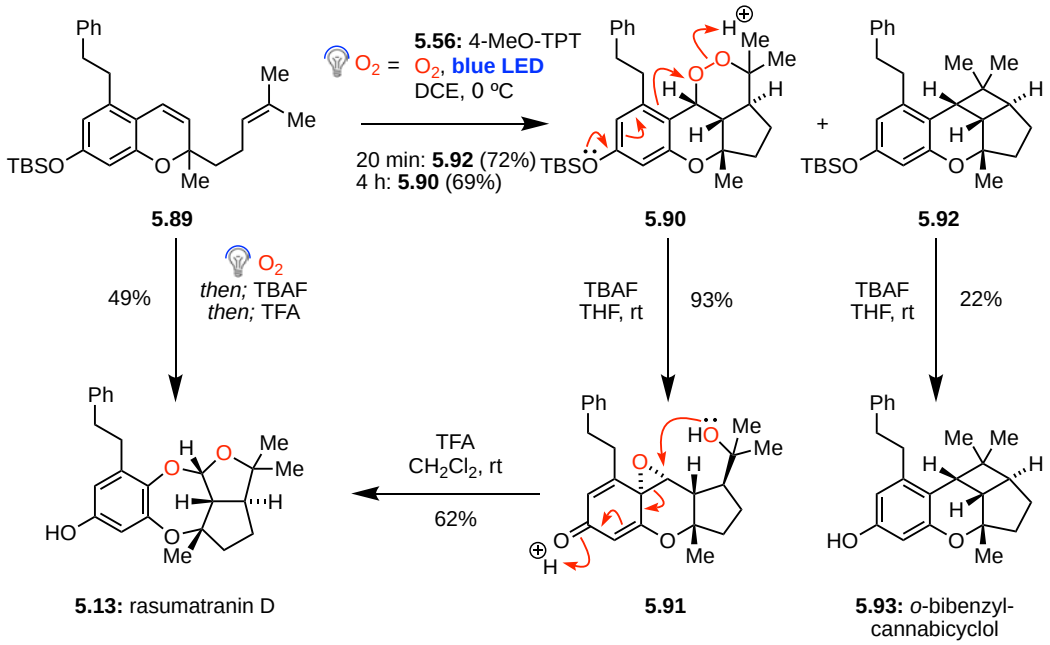


5.86 **5.89**

Scheme 5.19 – TBS protection of 5.86 to 5.89

The key photoredox catalyzed aerobic [2+2+2] cycloaddition of **5.89**, using the same conditions previously described, then afforded the endoperoxide **5.90** (**Scheme 5.20**). Treatment of **5.90** with TBAF formed the nyingchinoid B analogue **5.91** (presumably an undiscovered natural product), which gave rasumatranin D (**5.13**) on exposure to TFA. Gratifyingly the obtained NMR data for **5.13** showed excellent agreement with the published data for natural rasumatranin D, confirming our proposed structural revision.[1] An efficent one-pot conversion of **5.89** into **5.13** was also achieved in 49% yield.

In a similar vein to the nyingchinoid system, we found the photoredox catalyzed [2+2] cycloaddition of **5.89** using the 4-MeO-TPT (**5.56**) photocatalyst to be reversible. If the reaction was quenched and purified after 20 mins, we obtained **5.92** in 72%. Deprotection of **5.92** with TBAF at room temperature then gave the co-isolated natural product *o*-bibenzyl cannabicyclol **5.93** in 22%. However, we found that a direct one pot 2-step procedure from **5.89** was more effective affording **5.93** in 54%.

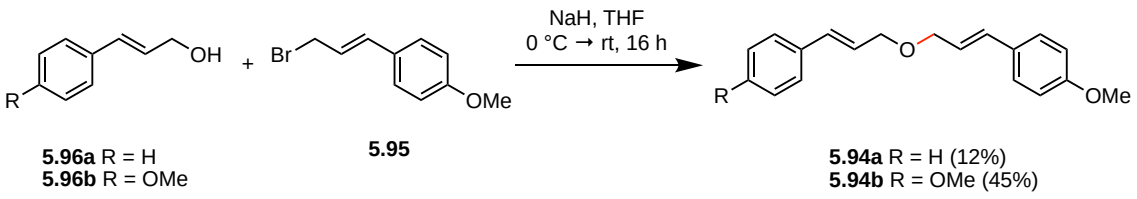


Scheme 5.20 – Synthesis of the Revised Structure of Rasumatranin D

5.2.3 Investigation into the Reversibility of Photoredox [2+2] Cycloadditions

After having successfully synthesized nyingchinoids A, B, D and rasumatranin D, our interest turned towards the reversibility of photoredox catalyzed [2+2] and aerobic [2+2+2] cycloadditions. We were especially interested in revisiting work by Yoon and Nicewicz to determine if these reactions were occurring as competing or reversible reactions.[30, 31] This was in part driven by our findings into the reversible nature of [2+2] cycloadditions in both the nyingchinoid and rasumatranin systems.

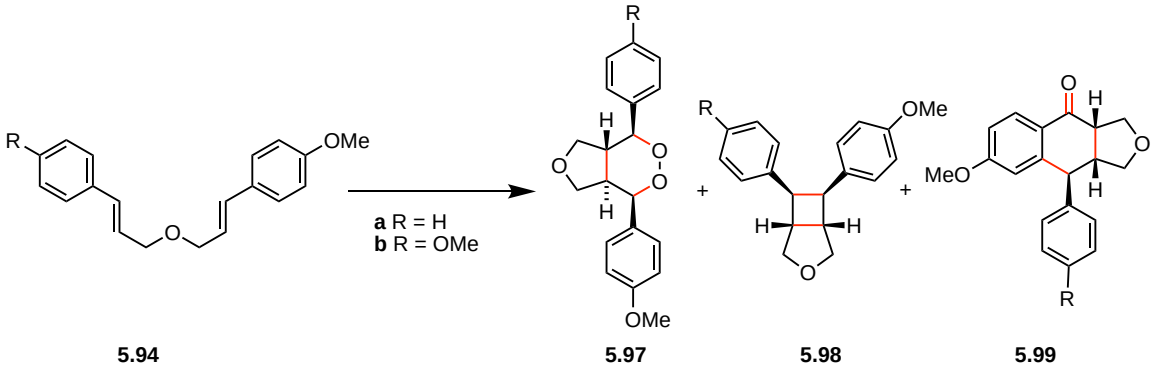
As a short mechanistic study, we gained access to the two bis(styrene) substrates (**5.94**), through coupling of an allylic bromide (**5.95**) with either the phenyl (**a**) or *p*-methoxy cinnamyl (**b**) alcohols (**5.96**) following a known literature procedure (**Scheme 5.21**).[30]



Scheme 5.21 – Synthesis of bis(styrene) substrates 5.94

With **5.94** in hand both bis(styrenes) were screened for reversibility (**Table 5.1**). The phenyl substrate **5.94a** was reacted following modified procedures from Yoon *et al.* employing the $[Ru(bpz)_3][PF_6]_2$ photocatalyst which was reacted with **O_2**, at 0 °C and irradiated with visible light. It was found that

despite leaving this reaction for extended periods none of the expected reversibility was observed. Instead, these reactions gave slow decomposition rather than an increased yield of the endoperoxide **5.97a** (**entries 1 – 4**). Treatment of **5.94a** following conditions developed by Nicewicz also showed comparable results, giving only a minor improvement in the yield of **5.97a** when left for 4 h (**entries 5 – 7**). The *p*-OMe bis(styrene) **5.94b** showed similar results to **5.94A**, albeit with slightly lower yields (**entries 8 – 10**).

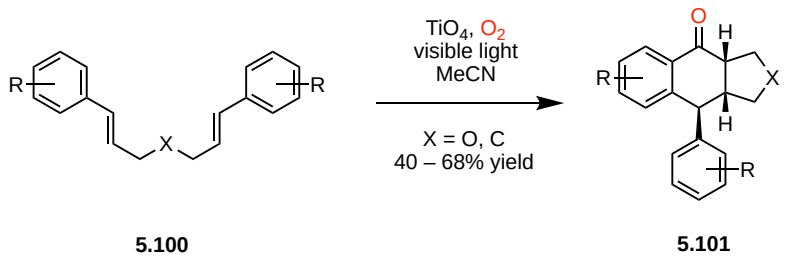


5.94 **5.97** **5.98** **5.99**

Table 5.1 – Key Investigations into the Reversibility of [2+2] Photoredox Cycloadditions

Entry	R	Conditions	Solvent	Catalyst	5.97	5.98	5.99	RSM
1	H	O_2, 1 h, 0 °C visible light	$MeNO_2$	$[Ru(bpz)_3][PF_6]_2$	--	--	*trace*	91%
2	H	O_2, 2 h, 0 °C visible light	$MeNO_2$	$[Ru(bpz)_3][PF_6]_2$	44%	20%	*trace*	17%
3	H	O_2, 4 h, 0 °C visible light	$MeNO_2$	$[Ru(bpz)_3][PF_6]_2$	10%	10%	*trace*	40%
4	H	O_2, 5 h, 0 °C visible light	$MeNO_2$	$[Ru(bpz)_3][PF_6]_2$	13%	9%	*trace*	11%
5	H	O_2, 1 h – 41 °C **blue LED**	CH_2Cl_2	**5.56:** 4-MeO-TPT (2 mol%)	24%	*trace*	--	26%
6	H	O_2, 2 h – 41 °C **blue LED**	CH_2Cl_2	**5.56:** 4-MeO-TPT (2 mol%)	21%	*trace*	--	25%
7	H	O_2, 4 h – 41 °C **blue LED**	CH_2Cl_2	**5.56:** 4-MeO-TPT (2 mol%)	37%	*trace*	--	0%
8	OMe	O_2, 1 h, 0 °C visible light	$MeNO_2$	$[Ru(bpz)_3][PF_6]_2$	4%	7%	*trace*	53%
9	OMe	O_2, 2 h, 0 °C visible light	$MeNO_2$	$[Ru(bpz)_3][PF_6]_2$	19%	20%	*trace*	20%
10	OMe	O_2, 5 h, 0 °C visible light	$MeNO_2$	$[Ru(bpz)_3][PF_6]_2$	21%	21%	*trace*	9%

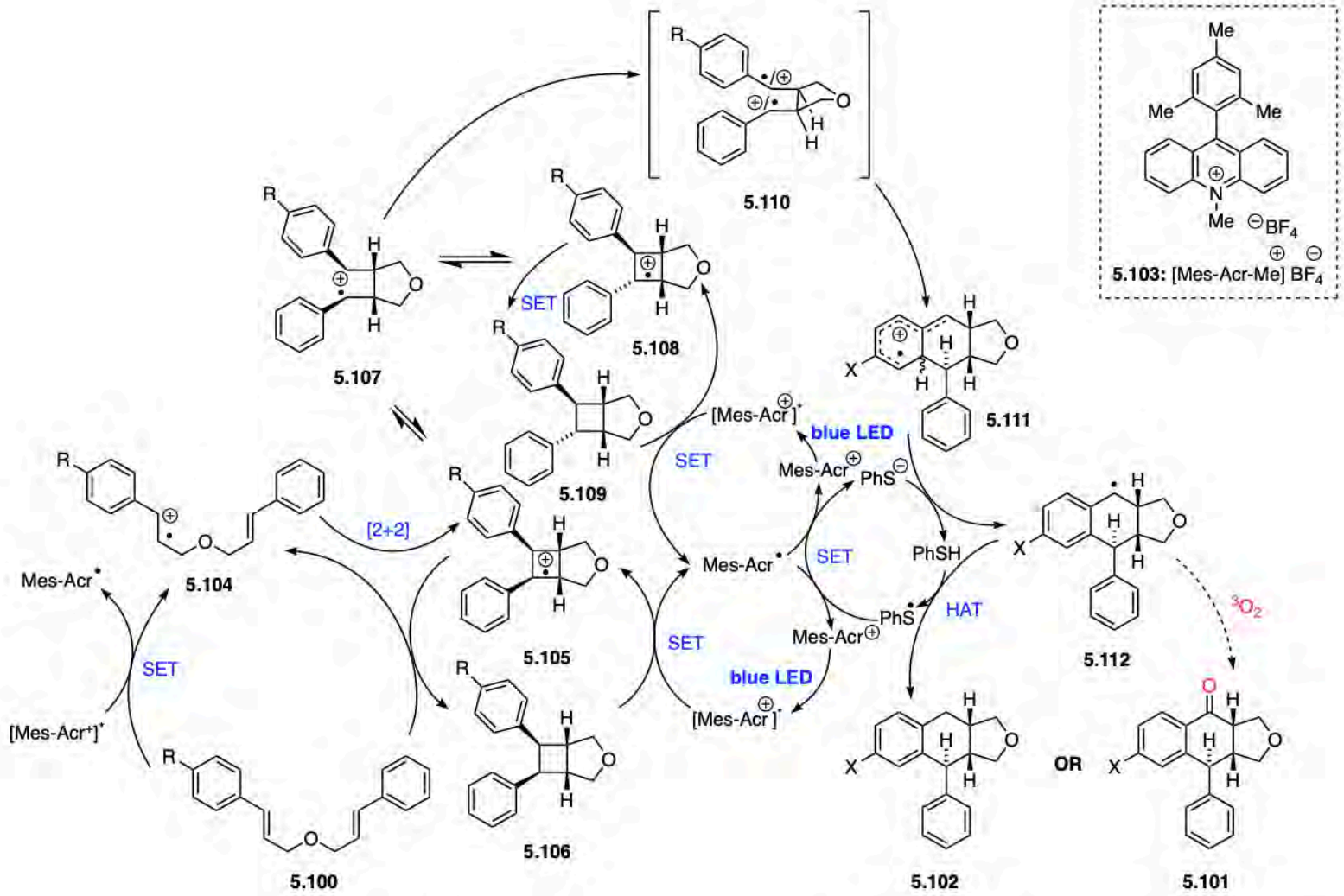
Interestingly it was observed that the crude ^{1}H NMR using Yoon's $[Ru(bpz)_3][PF_6]_2$ photoredox catalyzed conditions showed *trace* of the aryl tetralones **5.99**. Looking through the literature we found a previous report by Liu and co-workers who used a TiO_4 photoredox cyclization of bis(styrenes) **5.100** through reaction with **O_2** and visible light (**Scheme 5.22**).[39]



5.100 **5.101**

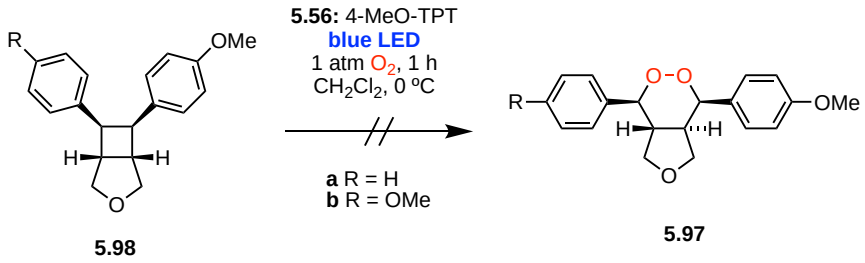
Scheme 5.22 – Liu's TiO_4 Mediated Cyclization of bis(styrenes) 5.100[39]

Not long after our findings further work by Xiang *et al.* was disclosed showing more detailed insights into a similar photoredox catalyzed mechanism behind the synthesis of a related compound **5.102** (**Scheme 5.23**).[40] This reaction is proposed to occur through oxidation of **5.100** by the excited acridinium salt $[(Mes\text{-}AcrMe)BF_4^-]$* **5.103*** to afford the radical cation **5.104**. An intramolecular [2+2] cycloaddition would then give **5.105** which would go on to give the *Z* cyclobutane **5.106**. A reversible *re*-oxidation with **5.103*** could regenerate **5.105** which upon cleavage of the benzylic C-C bond would afford **5.107**. Next cycloreversion would give **5.108** followed by a SET ring closure which would give the more thermodynamically stable reversible formation of *E* cyclobutane **5.109**. Additionally, **5.107** could also undergo an electrophilic or radical cyclization *via* the transition state **5.110** to provide the radical cation **5.111**. Deprotonation of **5.111** through reaction with thiophenolate would then afford the radical **5.112**. Finally, an intermolecular hydrogen atom abstraction would provide the *endo*-Diels-Alder adduct **5.102** or in the case of our findings and work by Liu this species could be intercepted with triplet oxygen, resulting in the formation of the ketone **1.101**.



Scheme 5.23 – Proposed Mechanism for the Formation of 5.10[38]

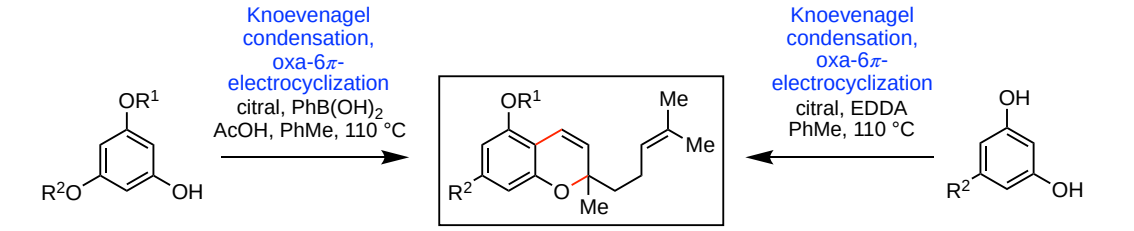
Finally, the obtained cyclobutanes **5.98** were attempted to react under photoredox conditions in hope of forming the endoperoxides **5.97**. Unfortunately, these reactions only gave decomposition proving unequivocally that these reactions were indeed not reversible (**Scheme 5.24**).



Scheme 5.24 – Attempted Synthesis of Endoperoxides 5.97 from Cyclobutanes 5.98

5.2.4 Synthesis and Evaluation of Antimalarial Endoperoxides

Having achieved the total synthesis of nyingchinoids A, B, D and rasumatranin D, and having investigated the reversibility of these reactions, our investigations turned towards the synthesis of a library of endoperoxide analogues. Four different chromenes (**5.113** – **5.116**) were synthesized in good to excellent yields by employing standard chromenylation conditions through condensation of various phenols (**5.117** – **5.119**) with citral in the presence of either catalytic EDDA, or $PhB(OH)_2$ and AcOH (**Scheme 5.25**).[41 – 47]



5.117: (R^1 = Bn, R^2 = Bn)
5.118: (R^1 = Me, R^2 = Me)

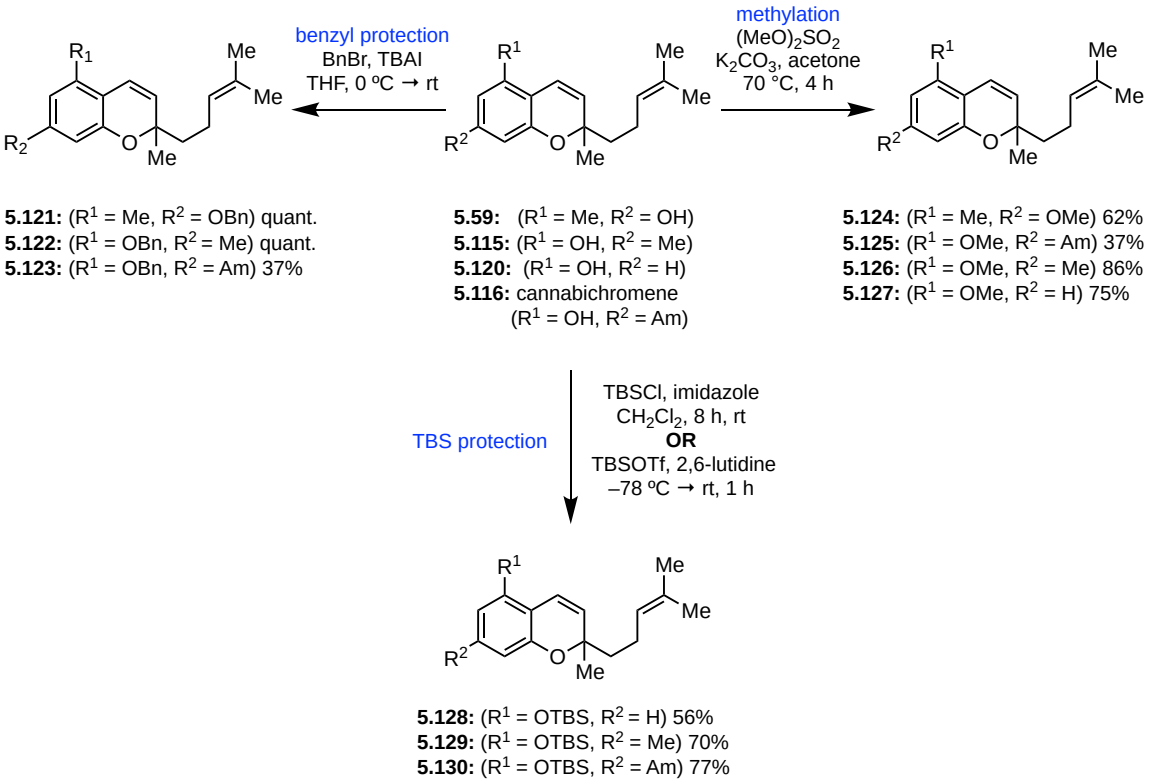
5.113: (R^1 = Bn, R^2 = OBn) 60%
5.114: (R^1 = Me, R^2 = OMe) 89%
5.115: (R^1 = H, R^2 = Me) 82%
5.116: cannabichromene
(R^1 = H, R^2 = Am) 82%

5.119: olivetol (R^2 = Am)
5.67: orcinol (R^2 = Me)

Scheme 5.25 – Synthesis of Various Chromenes 5.113 – 5.115

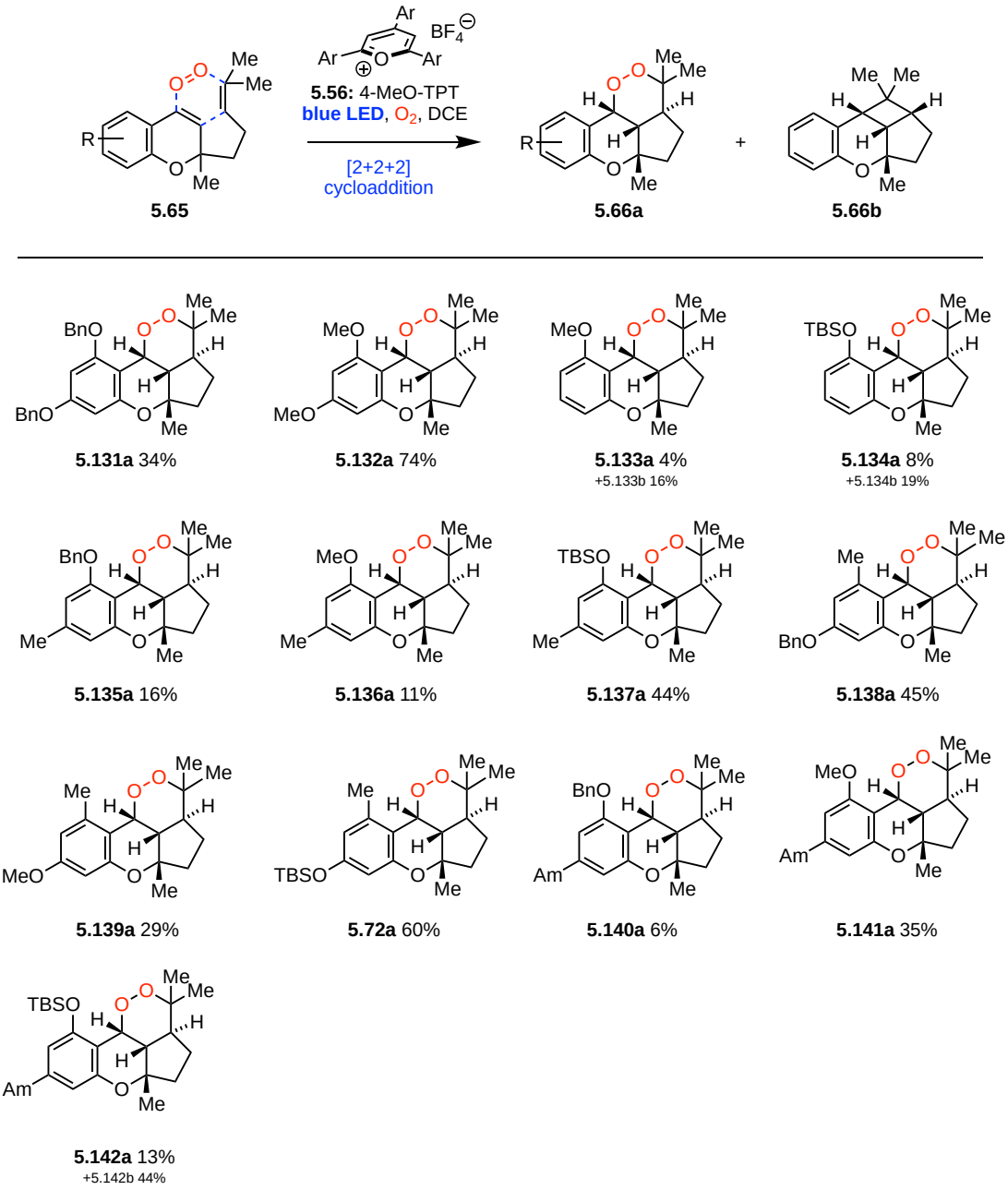
Next, the phenol chromenes (**5.116** and **5.116**), alongside the previously synthesised nyingchinoid chromene **5.59** and the resorcinol chromene **5.120*** were protected using standard conditions either through benzylation, methylation or/ and TBS protection. This allowed us divergent access to a library of chromenes **5.121** – **5.130** (**Scheme 5.26**).

***5.120** was synthesized according to a literature procedure from Katakawa and co-workers and a small sample was gifted to this project by PhD Student Lauren Murray.[43]



Scheme 5.26 – Synthesis of Various Protected Chromenes 5.121 – 5.130

Subsequent treatment of these protected chromenes with the 4-MeO-TPT (**5.56**) photocatalyst in DCE and 1 atm O_2 while irradiated with **blue LED** light afforded the endoperoxides **5.131a** – **5.142a** (**Scheme 5.27**). Intrestingly, we found no major trend between the electronics of these chromenes and the yields. We did however observe that three of the photoredox reactions afforded the cyclobutane products **5.133b**, **5.134b** and **5.142b**, even when these reactions were left for extended time periods (over 6 h). This suggested that the initial *5-exo-trig* reactions were occurring in a non-reversible manner. It also became clear to us that the more sterically hindered benzyl and Amyl functional groups were not well tolerated.



Scheme 5.27 – Synthesis of Key Endoperoxides 5.131a – 5.142a and 5.72a

Finally, a small sample of the endoperoxides **5.131a** – **5.142a**, alongside the cyclobutane products and a selection of the previously described natural products (*from chapters two, three and four*) were tested for antimalarial activity. This was performed in three separate rounds, done in collaboration with Ornella Romeo and Dr. Danny Wilson from the School of Biological Sciences, University of Adelaide. Initial testing (**Figure 5.13**) showed promising results, it was observed that the three endoperoxides **5.136a** (**LB15**), **5.138a** (**LB17**), **5.140a** (**LB16**) had good ability at reducing parasitic growth, with **5.138a** and **5.140a** having a IC_{50} of approximately 1 μM.

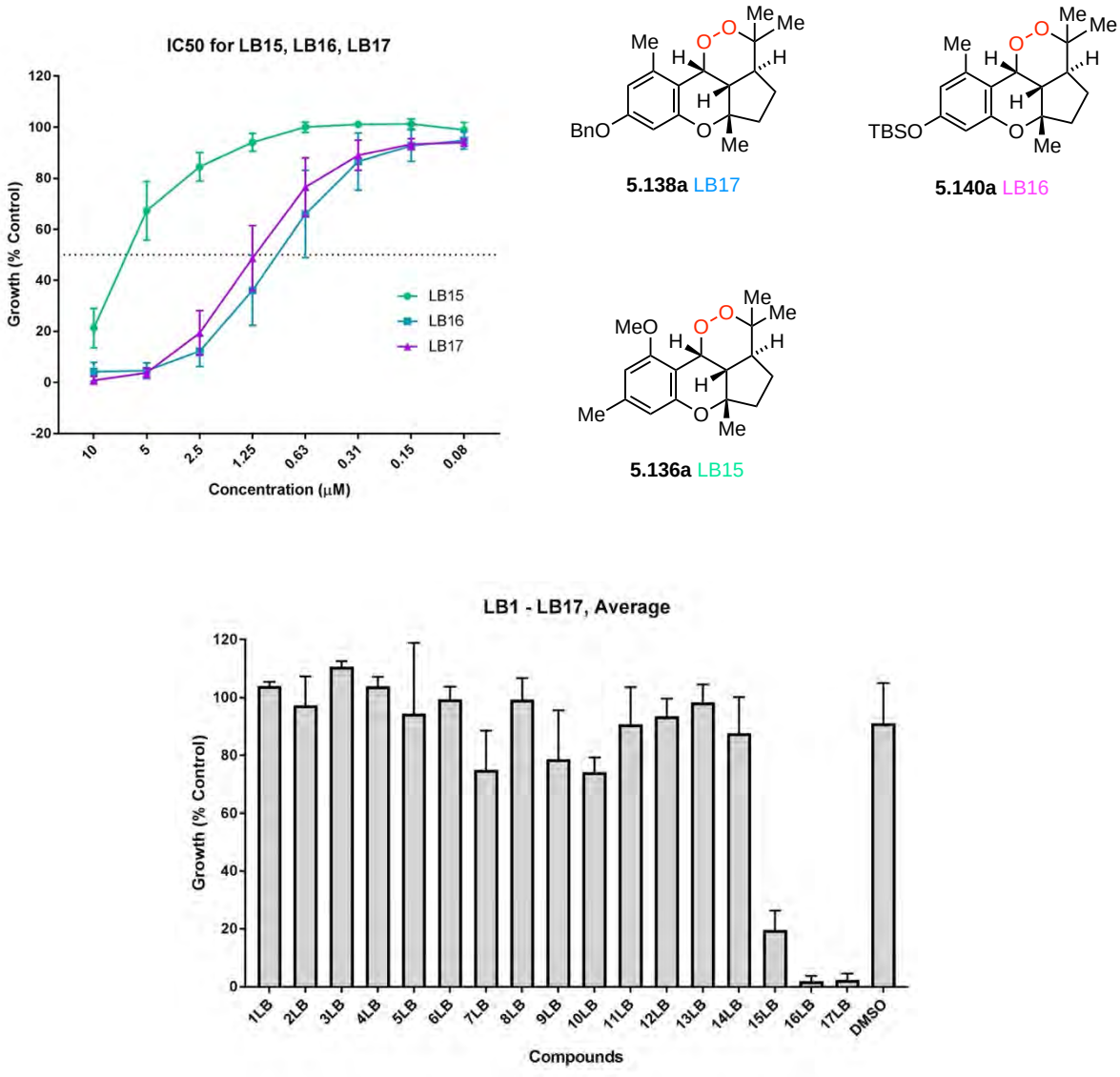


Figure 5.13 – Testing of Key Endoperoxides for Antimalarial Activity

In the second round of testing (**Figure 5.13**) we observed improved results, identifying 4 compounds (**5.133a** (**LB35**), **5.134a** (**LB39**), **5.135a** (**LB33**) and **5.139a** (**LB34**)) which reduced parasitic growth >75% (**Figure 5.14**)! The IC_{50} values for these compounds were then compared to that of the commercially available drugs used for the treatment of malaria; dihydroartemisinin (DHA) (**5.62**) and chloroquine (**5.143**). To our delight, the endoperoxide **5.133a** (**LB35**) had an $IC_{50} \approx 0.5\ \mu M$. Although this result is not as impressive as the commercial drugs, it represented a significant step forward in comparison with our previous results.

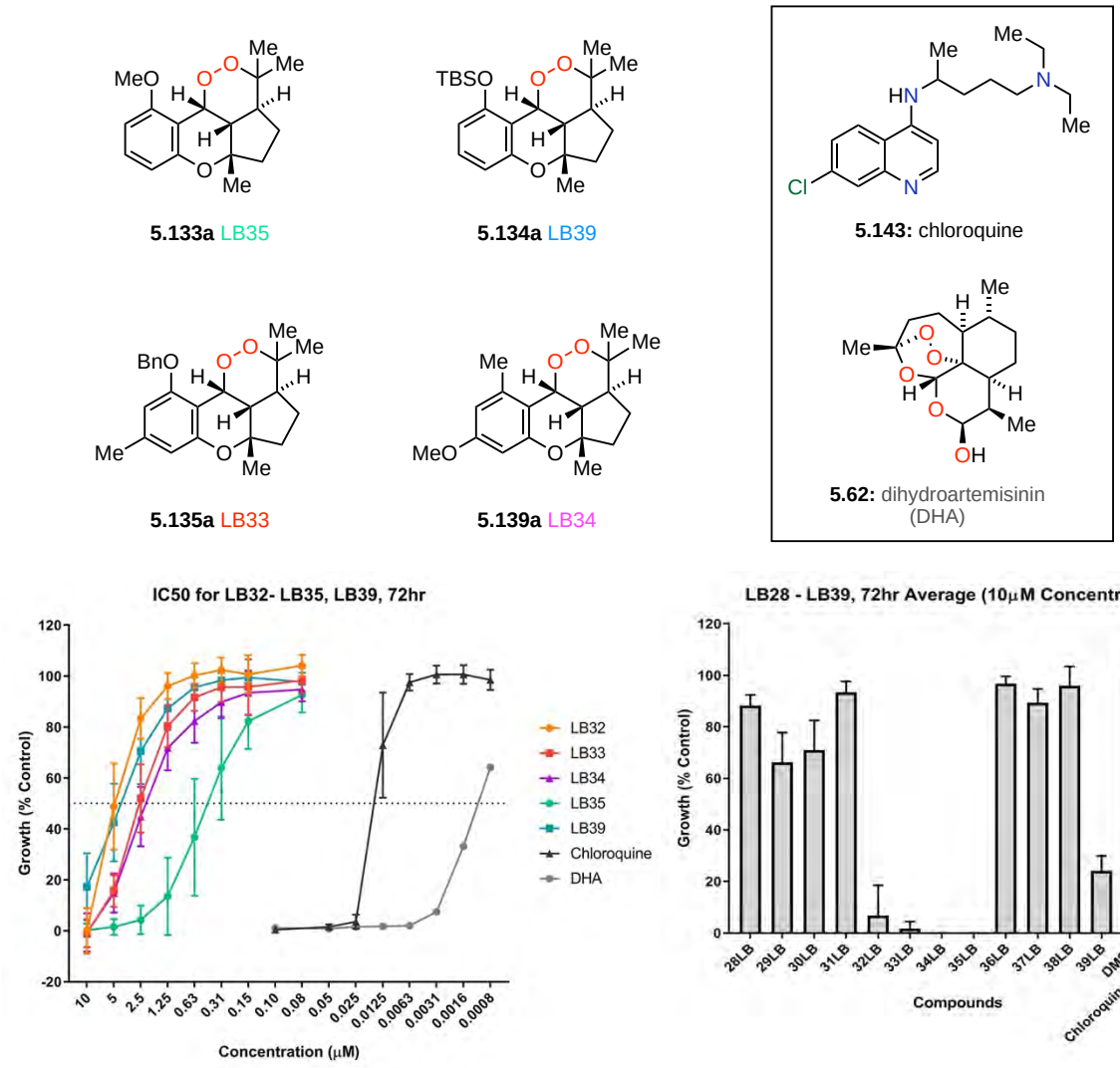


Figure 5.14 – Testing of Key Endoperoxides for Antimalarial Activity

In our final testing round, we became interested in the cannabinoid endoperoxides, derived from the natural product cannabichromene (**5.116**) (**Figure 5.15**). Disappointingly, these endoperoxides did not afford as promising results as we had hoped. Only two endoperoxide candidates showing good antimalarial activities were observed (**5.141a** (**LB51**), and **5.142a** (**LB52**)). These compounds had higher IC_{50} values of approximately 0.7 – 1 μM when compared to the lead compound **5.133a** (**LB35**).

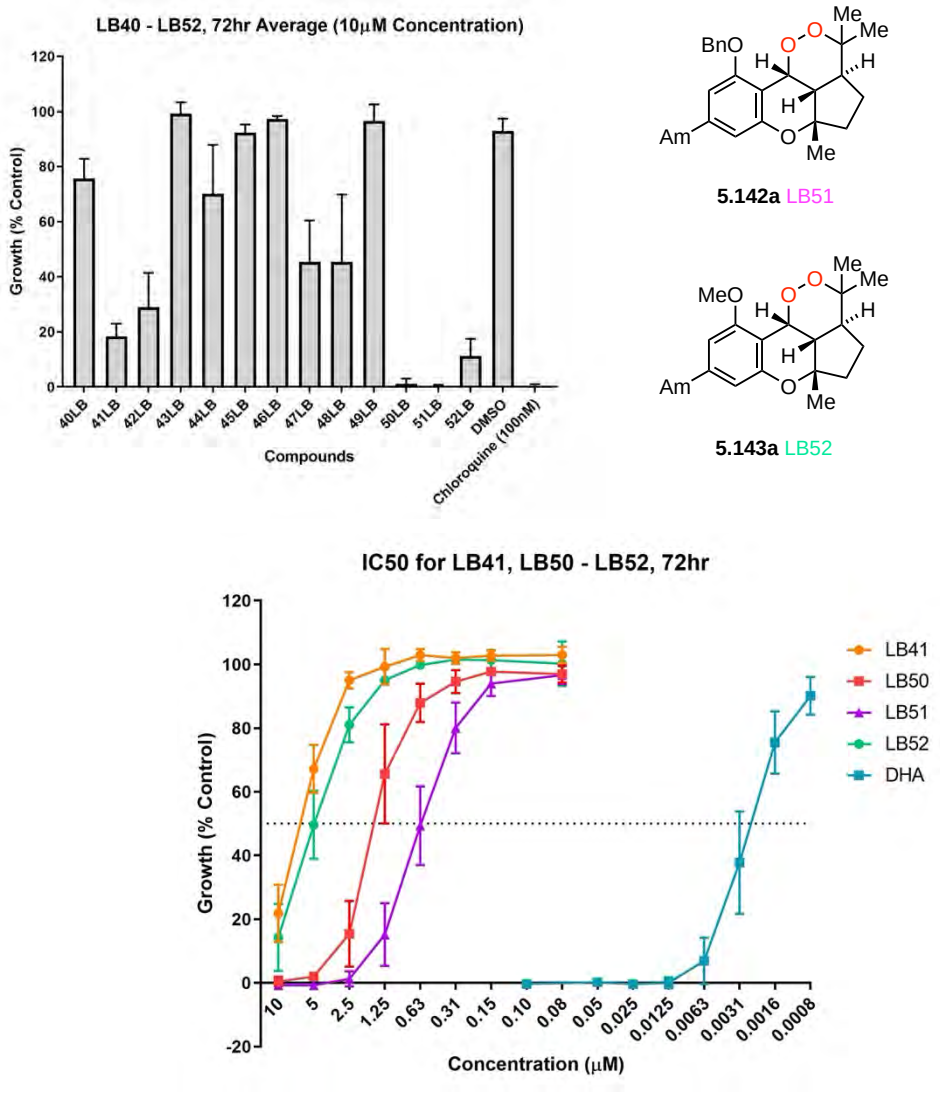


Figure 5.15 – Testing of Key Endoperoxides for Antimalarial Activity

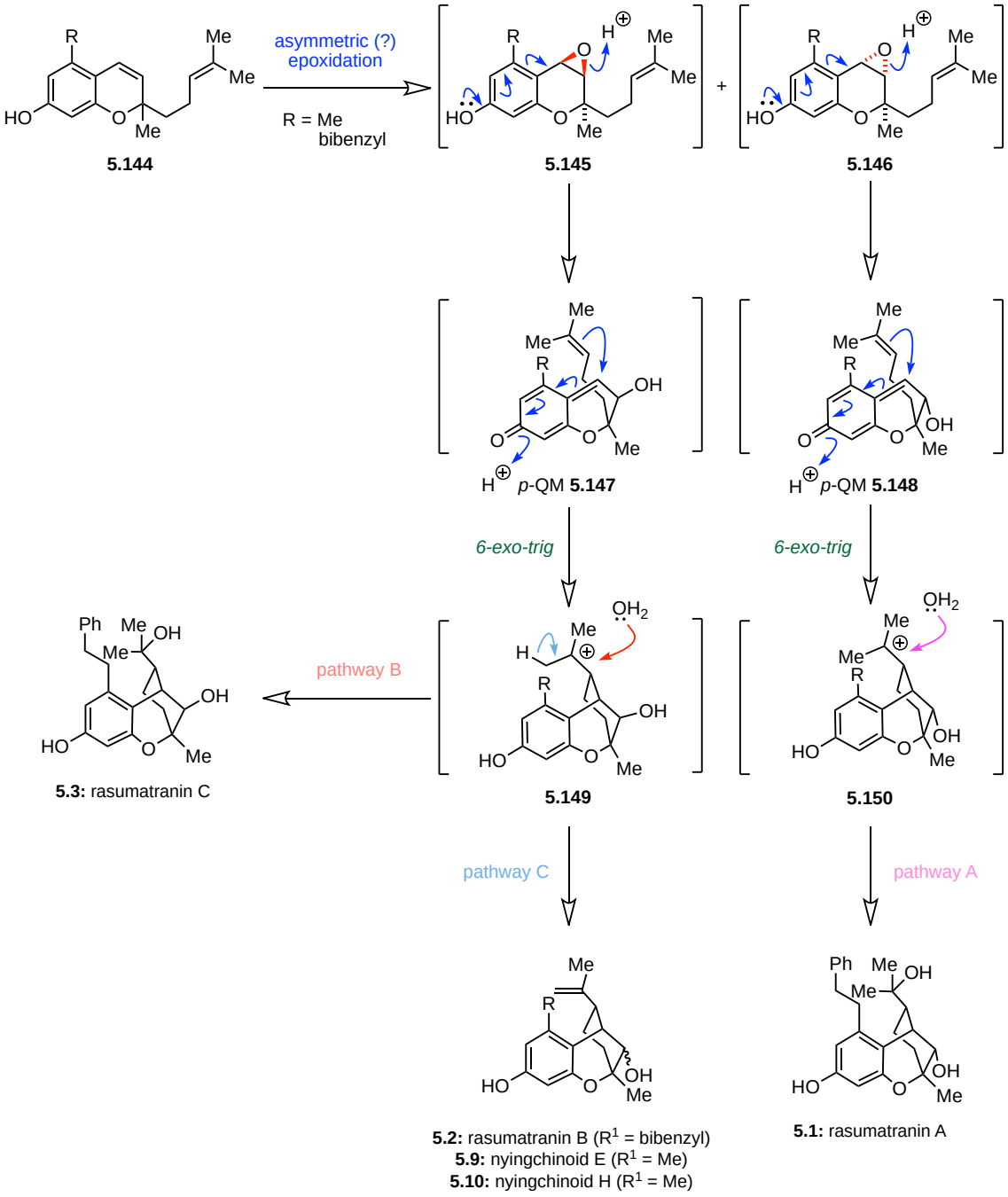
5.3 Conclusion

5.3.1 Future Directions

One future aim for this project is to expand our total synthesis to include rasumatranins A – C (**5.1** – **5.3**) and nyingchinoids E – H (**5.9** – **5.12**). We serendipitously reported the synthesis of a similar scaffold containing this 6–6–6 ring system while working on the total synthesis of the parvinaphthols (chapter two, *vide supra*), and we propose that a similar approach through a selective oxidation could allow access to these class of natural products.

This approach would begin from the epoxidation of the chromene ring **5.144** to afford diastereomers **5.145** and **5.146** (**Scheme 5.28**). Next, ring opening and formation of the *p*-QM **5.147** and **5.148**, followed by a *6-exo-trig* cyclization would afford the carbocations **5.149** and **5.150**. We propose that

carbocations **5.149** and **5.150** are direct precursors to rasumatranins A – C and nyingchinoids E – H. Addition of water to the carbocations would give access to rasumatranin A (**5.1**) and rasumatranin C (**5.3**) (pathway A, pathway B). While an ene reaction of **5.149** would afford rasumatranin B (**5.2**), nyingchinoid E (**5.9**) and nyingchinoid H (**5.10**) (pathway C). Ideally this total synthesis would be accompanied by a second challenge, whether or not this could be achieved asymmetrically. Recent work within out group has shown the asymmetric epoxidation and ring opening of related systems.[48]



Scheme 5.28 – Proposed Biosynthesis of Rasumatranins A – C and Nyingchinoids E – H

5.3.2 Summary

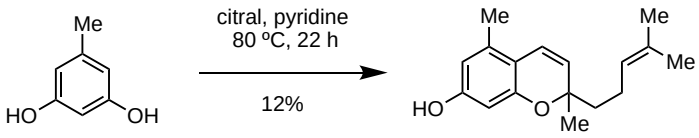
In conclusion, we report the biomimetic synthesis of nyingchinoids A (**5.5**), B (**5.6**) and D (**5.8**), and confirm the structural revision of rasumatranin D (**5.13**). This was achieved through visible light photoredox catalyzed [2+2] and [2+2+2] cycloadditions of electron-rich chromenes and further multi-step dearomatization and ring expansion cascades. Synthesis of nyingchinoids A (**5.5**) and B (**5.6**) from the common chromene intermediate (**5.68**) gives good insight into the biosynthesis of these natural products through predisposed and highly diastereoselective reactions. Although, investigations into the reversibility of related [2+2+2] cycloadditions with bis(styrene) substrates suggests these reactions are irreversible, we observed reversibility when performing more similar cycloadditions on chromene analogues. This has allowed us to synthesize a family of related endoperoxides, which were found to have excellent antimalarial properties.

5.4 Experimental

5.4.1 General Methods

All chemicals used were purchased from commercial suppliers and used as received. All reactions were performed under an inert atmosphere of N_2 unless otherwise stated. Thin layer chromatography was performed using aluminium sheets coated with silica gel. Visualization was aided by viewing under a *UV* lamp and staining with the appropriate stain followed by heating. All R_f values were measured to the nearest 0.05. Flash chromatography was performed using 40-63 micron grade silica gel. Melting points were recorded on a digital melting point apparatus and are uncorrected. Infrared spectra were recorded using an FT-IR spectrometer as the neat compounds. High field NMR was recorded using a 600 MHz spectrometer (^{1}H at 600 MHz, ^{13}C at 150 MHz) or a 500 MHz spectrometer (^{1}H at 500 MHz, ^{13}C at 125 MHz). The solvent used for NMR spectra was $CDCl_3$ unless otherwise specified. ^{1}H chemical shifts are reported in ppm on the δ-scale relative to TMS (δ 0.0) and ^{13}C{^{1}H} NMR are reported in ppm relative to chloroform (δ 77.16). Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet and (m) multiplet. All J-values were rounded to the nearest 0.1 Hz. ESI high resolution mass spectra were recorded on a Q-TOF mass spectrometer. Photochemistry with *UVA* light was performed using a generic brand commercial LED *UV* light globe; wavelength: 365 nm. Photochemistry with *UVC* light was performed using a generic brand commercial LED *UV* light globe; wavelength: 254 nm. Photochemical reactions with visible light were performed with a conventional commercial LED desk lamp at 240 V with a 4 W 5000 K 32 mÅ globe. Reactions conducted under 470 nm blue LED lamp were performed using a 19-24VDC 40W Kessil A160WE.

5.4.2 Experimental Procedures



5.67: orcinol **5.59**

To a solution of orcinol (**5.67**) (10.1 g, 81.4 mmol, 1.0 equiv.) in pyridine (6.70 mL, 6.58 g, 83.2 mmol, 1.0 equiv.) was added citral (14.8 g, 97.2 mmol, 1.2 equiv.). The reaction was stirred at 80 °C for 22 h, then cooled to room temperature, concentrated *in vacuo*, and purified by flash chromatography on SiO_2 (4:1 $CHCl_3$/ cyclohexane) to give chromene **5.59** as a clear oil (2.61 g, 12%). Data for **5.59** matched that previously reported in the literature.[32]

Data for 5.59:

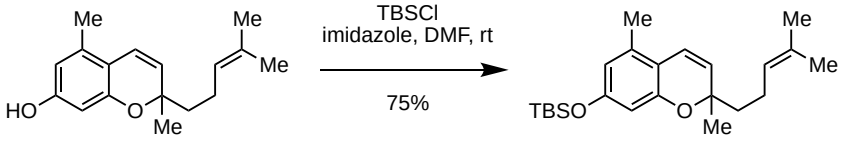
R_f: 0.40 (4:1 $CHCl_3$/ cyclohexane).

FTIR (**neat**)**:** 3384, 2968, 1586, 1609, 1461, 1325, 1137, 838 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.47 (d, *J* = 10.1 Hz, 1H), 6.17 (s, 1H), 6.16 (s, 1H), 5.46 (d, *J* = 10.1 Hz, 1H), 5.10 (t, *J* = 7.1 Hz, 1H), 4.72 (br s, 1H), 2.23 (s, 3H), 2.10 (dt, *J* = 16.8, 6.7 Hz, 2H), 1.76 – 1.67 (m, 2H), 1.66 (s, 3H), 1.58 (s, 3H), 1.36 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.8, 154.7, 135.2, 131.6, 126.6, 124.2, 119.5, 113.2, 109.2, 101.4, 78.0, 41.0, 26.2, 25.7, 22.7, 18.4, 17.6 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{17}H_{23}O_2$ 259.1698, found 259.1691.



5.65 **5.68**

To a solution of chromene **5.65** (1.27 g, 4.92 mmol, 1.0 equiv.) in DMF (50 mL) was added TBSCl (1.76 g, 11.6 mmol, 2.4 equiv.) and imidazole (800 mg, 11.6 mmol, 2.4 equiv.). Reaction was left to stir at room temperature for 4 h. EtOAc (50 mL) then added, and solution washed with 5% $LiCl_{(aq)}$ (2 × 30 mL), sat. $NH_4Cl_{(aq)}$ solution (2 × 30 mL) and sat. brine (2 × 30 mL). The solution was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (30:1 hexanes/ Et_2O) to give the corresponding TBS chromene **5.68** as a colourless oil (1.38 g, 75%).

Data for 5.68:

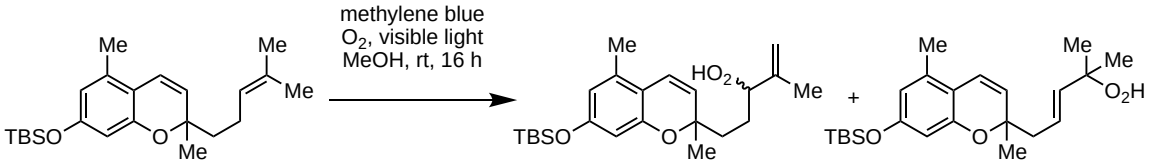
R_f: 0.70 (4:1 hexanes/ EtOAc).

FTIR (**neat**)**:** 2957, 2929, 2858, 1604, 1482, 1330, 1252, 1151, 838, 779 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.47 (d, *J* = 10.0 Hz, 1H), 6.18 (d, *J* = 2.2 Hz, 1H), 6.16 (d, *J* = 2.2 Hz, 1H), 5.46 (d, *J* = 10.0 Hz, 1H), 5.12 – 5.07 (m, 1H), 2.21 (s, 3H), 2.14 – 2.06 (m, 2H), 1.73 – 1.67 (m, 2H), 1.66 (s, 3H), 1.58 (s, 3H), 1.36 (s, 3H), 0.97 (s, 9H), 0.19 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9, 154.3, 134.7, 131.6, 126.8, 126.8, 124.2, 119.7, 114.2, 113.8, 106.0, 77.8, 41.0, 26.2, 25.7, 22.7, 18.4, 18.2, 17.6, – 4.4 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{37}O_2Si$ 373.2557, found 373.2553.



5.68 **5.69** 23% **5.70** 21%

5.68 (82 mg, 0.220 mmol, 1.0 equiv.) dissolved in MeOH (10 mL) and O_2 was bubbled through the solution for 10 min. Methylene blue (1 mg, 0.004 mmol, 2 mol%) was then added and the solution was left to stir under 1 atm of O_2 and irradiated with a 200 W incandescent bulb and left to stir for 16 h. The solution was then concentrated *in vacuo* and purified by flash chromatography on SiO_2 (3:2 PhMe/ CH_2Cl_2) to give the **5.69** (20 mg, 23%) as a 1:1 mixture of diastereoisomers and **5.70** (18 mg, 21%).

Data for 5.69:

R_f: 0.30 (3:2 PhMe/ CH_2Cl_2).

FTIR (**neat**)**:** 2929, 1605, 1567, 1483, 1330, 1253, 1152, 1004, 839 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, *J* = 6.6 Hz, 1H), 6.48 (d, *J* = 10.0 Hz, 1H), 6.18 (s, 1H), 6.14 (s, 1H), 5.41 (dd, *J* = 10.0, 4.9 Hz, 1H), 5.02 – 5.00 (m, 2H), 4.29 (m, 1H), 2.21 (s, 3H), 1.79 – 1.63 (m, 4H), 1.71 (s, 3H), 1.34 (s, 3H), 0.96 (s, 9H), 0.19 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.0, 154.1, 154.1, 143.5, 143.4, 134.8, 134.8, 126.4, 126.2, 126.2, 120.1, 114.5, 114.3, 113.6, 113.5, 106.0, 89.6, 89.6, 77.6, 77.4, 37.1, 36.7, 26.4, 26.1, 25.6, 25.5, 25.1, 18.4, 18.4, 18.2, 17.3, 17.2, -4.4 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{37}O_4Si$, found 405.2452.

Data for 5.70:

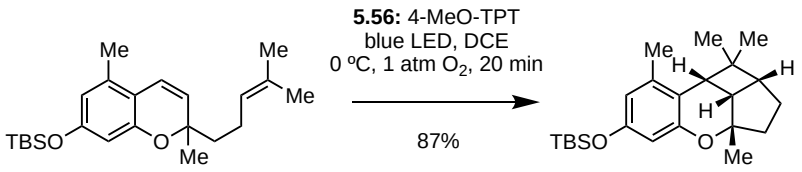
R_f: 0.20 (3:2 PhMe/ CH_2Cl_2).

FTIR (**neat**)**:** 2930, 1605, 1567, 1483, 1331, 1254, 1151, 1005, 770 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (br s, 1H), 6.50 (d, *J* = 10.0 Hz, 1H), 6.20 (d, *J* = 2.3 Hz, 1H), 6.16 (d, *J* = 2.4 Hz, 1H), 5.82 – 5.72 (m, 1H), 5.61 – 5.53 (m, 1H), 5.45 (d, *J* = 10.0 Hz, 1H), 2.42 (ddd, *J* = 7.4, 3.6, 1.2 Hz, 2H), 2.22 (s, 3H), 1.41 (s, 3H), 1.28 (s, 6H), 0.98 (s, 9H), 0.20 (s, 5H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.1, 154.3, 136.8, 134.9, 126.4, 126.1, 120.1, 114.5, 113.6, 105.9, 82.1, 44.0, 26.5, 25.6, 24.3, 24.1, 18.4, 18.2, -4.4 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{37}O_4Si$, found 405.2455.



5.68 **5.71**

O_2 gas was bubbled through a solution of **5.68** (109 mg, 2.93 mmol, 1.0 equiv.) in DCE (25 mL) for 10 minutes. 4-MeO-TPT (**5.56**) (3 mg, 0.006 mmol, 2 mol%) was then added and the reaction mixture was stirred under 1 atm of O_2 while exposed to a 470 nm blue LED lamp at 0 °C for 20 min. The reaction mixture was then concentrated *in vacuo* and purified by flash chromatography on SiO_2 (30:1 hexanes/ Et_2O) to give cyclobutane **5.71** as a colourless oil (95 mg, 87%).

Data for 5.71:

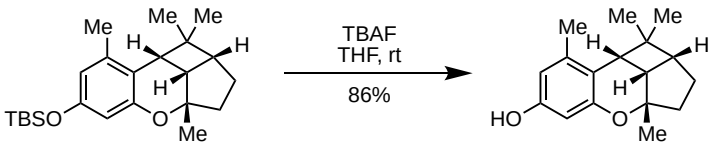
R_f: 0.70 (4:1 hexanes/ EtOAc).

FTIR (**neat**)**:** 2949, 2929, 2858, 1610, 1577, 1473, 1329, 1252, 1146, 837, 778 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.28 (d, *J* = 2.4 Hz, 1H), 6.25 (d, *J* = 2.4 Hz, 1H), 3.09 (d, *J* = 9.7 Hz, 1H), 2.55 (t, *J* = 8.2 Hz, 1H), 2.40 (td, *J* = 7.9, 2.5 Hz, 1H), 2.10 (s, 3H), 2.00 – 1.95 (m, 1H), 1.76 – 1.70 (m, 1H), 1.66 – 1.57 (m, 2H), 1.38 (s, 3H), 1.32 (s, 3H), 0.97 (s, 9H), 0.65 (s, 3H), 0.19 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.3, 154.2, 137.9, 116.6, 114.7, 107.4, 83.0, 46.5, 39.6, 39.3, 39.2, 38.0, 34.0, 26.7, 25.7, 25.4, 20.1, 18.4, 18.1, – 4.4 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{23}H_{37}O_2Si$ 373.2563, found 373.2560.



5.71 **5.8:** nyingchinoid D

To a solution of **5.71** (95 mg, 2.55 mmol, 1.0 equiv.) in THF (4 mL) was added TBAF (1.0 M in THF, 0.25 mL, 2.55 mmol, 1.0 equiv.) and the reaction was stirred at room temperature for 5 min. The mixture was then diluted with EtOAc (20 mL), washed with sat. brine (2 × 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (8:1 → 4:1 hexanes/ EtOAc, gradient elution) to give nyingchinoid D (**5.8**) as a colourless oil (27 mg, 86%). Data for nyingchinoid D (**5.8**) matched that previously reported in literature. [2]

Data for nyingchinoid D (5.8):

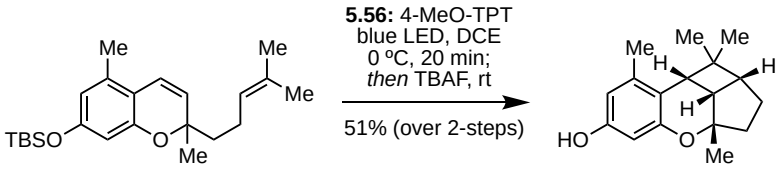
R_f: 0.40 (4:1 hexanes/ EtOAc).

FTIR (**neat**)**:** 3388, 2947, 1614, 1594, 1458, 1139, 840 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.28 (d, *J* = 2.6 Hz, 1H), 6.24 (d, *J* = 2.6 Hz, 1H), 4.70 (br s, 1H), 3.08 (d, *J* = 9.7 Hz, 1H), 2.55 (dd, *J* = 9.7, 8.9, 1H), 2.41 (td, *J* = 8.1, 2.7 Hz, 1H), 2.11 (s, 3H), 2.01 – 1.95 (m, 1H), 1.72 – 1.71 (m, 1H), 1.67 – 1.57 (m, 2H), 1.38 (s, 3H), 1.32 (s, 3H), 0.66 (s, 3H) ppm.

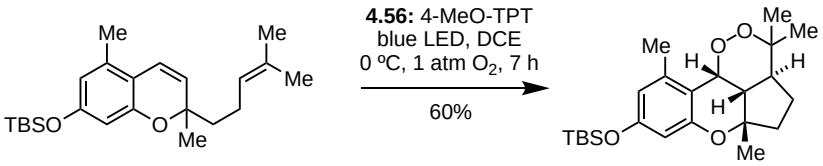
^{13}C NMR (125 MHz, $CDCl_3$): δ 154.6, 154.2, 138.4, 116.0, 109.9, 102.8, 83.3, 46.5, 39.6, 39.4, 39.2, 37.9, 34.0, 26.6, 25.4, 20.1, 18.5 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{17}H_{23}O_2$ 259.1698, found 259.1693.



5.68 **5.8:** nyingchinoid D

To a solution of **5.68** (115 mg, 0.300 mmol, 1.0 equiv.) in DCE (15 mL) was added 4-MeO-TPT (**5.56**) (2 mg, 0.006 mmol, 2 mol%) and the reaction mixture was stirred under N_2 while exposed to a 470 nm blue LED lamp at 0 °C for 20 min. TBAF (1.0 M solution in THF, 0.30 ml, 0.300 mmol, 1.0 equiv.) was then added to the mixture at room temperature and the reaction mixture was stirred for 5 min. The reaction mixture was then diluted with CH_2Cl_2 (10 mL), washed with sat. brine (2 × 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (8:1 hexanes/ EtOAc) to give nyingchinoid D (**5.6**) (40 mg, 51% over 2-steps). Data for nyingchinoid D (**5.6**) matched that previously obtained and previously reported in the literature.[2]



5.68 **5.72**

O_2 was bubbled through a solution of **5.68** (174 mg, 0.467 mmol, 1.0 equiv.) in DCE (45 mL). After 10 minutes reaction was cooled to 0 °C, 4-MeO-TPT (**5.56**) (5 mg, 0.009 mmol, 2 mol%) was then added and the reaction mixture was stirred under 1 atm of O_2 while exposed to a 470 nm blue LED lamp for 7 h. The reaction mixture was then concentrated *in vacuo* and purified by flash chromatography on SiO_2 (30:1 hexanes/ Et_2O) to give the endoperoxide **5.72** (115 mg, 60%) as a colourless oil.

Data for 5.72:

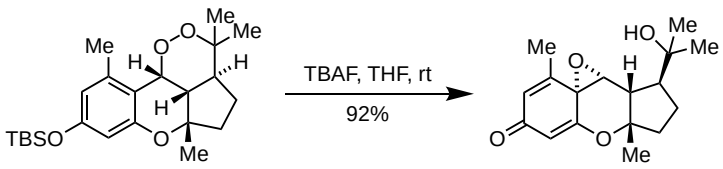
R_f: 0.30 (40:1 hexanes/ EtOAc).

FTIR (**neat**)**:** 2958, 2930, 2858, 1607, 1578, 1473, 1331, 1254, 1150, 844, 781 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.28 (d, *J* = 2.4 Hz, 1H), 6.17 (d, *J* = 2.4 Hz, 1H), 5.54 (d, *J* = 8.7 Hz, 1H), 2.53 (td, *J* = 12.5, 7.7 Hz, 1H), 2.33 (s, 3H), 2.27 – 2.23 (m, 1H), 2.07 (dd, *J* = 13.4, 8.7 Hz, 1H), 1.99 (ddd, *J* = 13.4, 11.5, 3.2 Hz, 1H), 1.84 – 1.81 (m, 1H), 1.50 – 1.42 (m, 1H), 1.32 (s, 3H), 1.27 (s, 3H), 1.12 (s, 3H), 0.96 (s, 9H), 0.19 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.8, 155.6, 141.1, 115.6, 109.8, 107.3, 84.0, 82.7, 74.1, 46.1, 45.5, 39.6, 26.9, 25.6, 22.8, 22.5, 19.3, 19.0, 18.1, – 4.4 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{37}O_4Si$ $[M+H]^+$ 405.2456, found 405.2454.



5.72 **5.6:** nyingchinoid B

To a solution of endoperoxide **5.72** (41 mg, 0.102 mmol, 1.0 equiv.) in THF (1 mL) at room temperature was added TBAF (1.0 M solution in THF, 0.10 mL, 0.10 mmol, 1.0 equiv.) and the reaction mixture was stirred for 1 h. Further TBAF (1.0 M solution in THF, 0.10 mL, 0.10 mmol) was added, then the mixture was diluted with EtOAc (20 mL), washed with sat. brine (2 × 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (7:1 EtOAc/ hexanes) to give nyingchinoid B (**5.6**) (27 mg, 92%) as a colourless oil. Data for nyingchinoid B (**5.6**) matched that previously reported in literature.[2]

Data for nyingchinoid B (5.6):

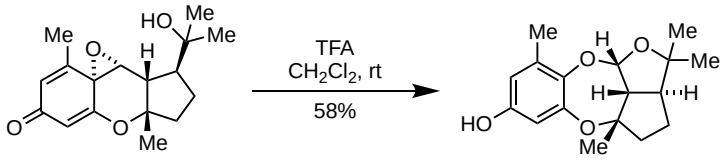
R_f: 0.35 (7:1 EtOAc/ hexanes).

FTIR (**neat**)**:** 3413, 2969, 1658, 1600, 1421, 1219, 1128, 884 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.26 (t, *J* = 1.7 Hz, 1H), 5.97 (d, *J* = 2.0 Hz, 1H), 4.03 (d, *J* = 3.8 Hz, 1H), 2.55 (dd, *J* = 17.0, 8.0 Hz, 1H), 2.20 (dd, *J* = 8.0, 3.8 Hz, 1H), 2.10 – 2.03 (m, 1H), 1.93 – 1.88 (m, 1H), 1.88 – 1.85 (m, 1H), 1.84 (d, *J* = 1.5 Hz, 3H), 1.46 – 1.41 (m, 1H), 1.34 (s, 3H), 1.29 (s, 3H), 1.23 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 187.5, 167.1, 148.9, 131.7, 114.9, 90.7, 72.1, 63.6, 54.5, 53.7, 43.5, 40.3, 30.2, 27.2, 25.9, 25.3, 15.8 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{17}H_{23}O_4$ 291.1591, found 291.1594.



5.6: nyingchinoid B **5.5:** nyingchinoid A

To a solution of nyingchinoid B (**5.6**) (35 mg, 0.121 mmol, 1.0 equiv.) in CH_2Cl_2 (3 mL) was added TFA (0.01 mL, 0.120 mmol, 1.0 equiv.) and the solution was stirred at room temperature for 20 min. The reaction mixture was quenched with sat. $NaHCO_{3(aq)}$ solution (10 mL) and the organic layer was separated and washed with sat. brine (2 × 10 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (4:1 → 1:1 hexanes/ EtOAc, gradient elution) to give nyingchinoid A (**5.5**) as an orange oil (20 mg, 58%). Data for nyingchinoid A (**5.5**) matched that previously reported in literature. [2]

Data for nyingchinoid A (5.5):

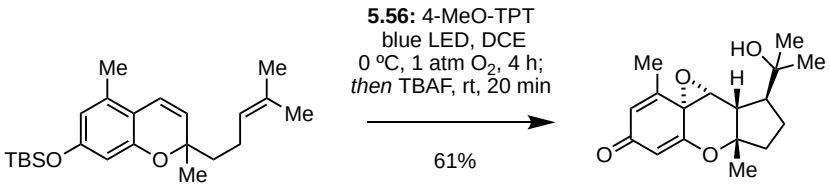
R_f: 0.75 (4:1 EtOAc/ hexanes).

FTIR (**neat**)**:** 3364, 2970, 1596, 1464, 1137, 1025, 904, 728 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.40 (d, *J* = 3.0 Hz, 1H), 6.32 (d, *J* = 3.0 Hz, 1H), 4.94 (br s, 1H), 4.92 (d, *J* = 3.0 Hz, 1H), 3.42 (ddd, *J* = 14.4, 12.6, 6.0 Hz, 1H), 2.57 (dt, *J* = 14.7, 8.8 Hz, 1H), 2.37 (ddd, *J* = 14.7, 9.9, 1.6 Hz, 1H), 2.22 (s, 3H), 2.13 (dd, *J* = 14.1, 3.1 Hz, 1H), 1.79 – 1.77 (m, 1H), 1.52 (s, 3H), 1.39 – 1.31 (m, 1H), 1.28 (s, 3H), 1.17 (s, 3H) ppm.

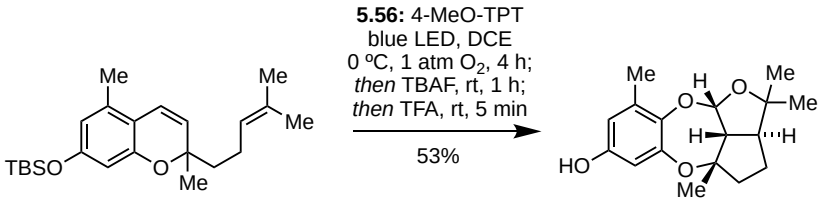
^{13}C NMR (125 MHz, $CDCl_3$): δ 151.7, 151.3 138.6, 133.8, 112.9, 109.5, 96.1, 81.2, 80.1, 64.1, 51.9, 47.3, 29.7, 24.8, 22.7, 21.3, 16.4 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{17}H_{23}O_4$ $[M+H]^+$ 291.1591, found 291.1591.



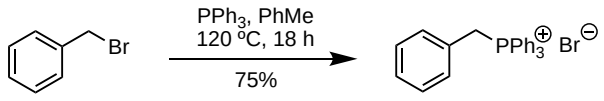
5.68 **5.6:** nyingchinoid B

O_2 was bubbled through a solution of **5.68** (124 mg, 0.333 mmol, 1.0 equiv.) in DCE (35 ml). After 10 min the reaction was cooled to 0 °C and 4-MeO-TPT (**5.56**) (3.2 mg, 0.007 mmol, 2 mol%) was added. The reaction mixture was stirred under 1 atm of O_2 while exposed to 470 nm blue LED lamp for 4 h. TBAF (1.0 M in THF, 0.33 ml, 0.333 mmol, 1.0 equiv.) was then added and the reaction mixture was stirred for 20 min at room temperature. The reaction mixture was quenched with sat. $NH_4Cl_{(aq)}$ solution (35 mL) and the organic layer was separated and washed with sat. $NaHCO_{3(aq)}$ (35 mL) and sat. brine (35 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (4:1 → 1:1 hexanes/ EtOAc, gradient elution) to give nyingchinoid B (**5.6**) as a colourless oil (58 mg, 61%). Data for nyingchinoid B (**5.6**) matched that previously obtained and previously reported in the literature. [2]



5.68 **5.5:** nyingchinoid A

O_2 was bubbled through a solution of **5.68** (108 mg, 0.290 mmol, 1.0 equiv.) in DCE (30 mL). After 10 minutes the reaction mixture was cooled to 0 °C, and 4-MeO-TPT (**5.56**) (3 mg, 0.006 mmol, 2 mol%) was added. The reaction mixture was then stirred under 1 atm of O_2 while exposed to a 470 nm blue LED lamp for 4 h. TBAF (1.0 M in THF, 0.29 ml, 0.290 mmol, 1.0 equiv.) was added and the reaction mixture was stirred for 1 h, followed by TFA (0.04 ml, 0.58 mmol, 2.0 equiv.) and stirring was continued for 10 minutes. The reaction mixture was quenched with sat. $NaHCO_{3(aq)}$ solution (20 mL) and the organic layer was separated and washed with sat. $NaHCO_{3(aq)}$ solution (20 mL) and brine (20 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (4:1 → 1:1 hexanes/ EtOAc, gradient elution) to give nyingchinoid A (**5.5**) as a pale yellow solid (45 mg, 53%). Data for nyingchinoid A (**5.5**) matched that previously obtained and previously reported in the literature. [2]



5.80 **5.81**

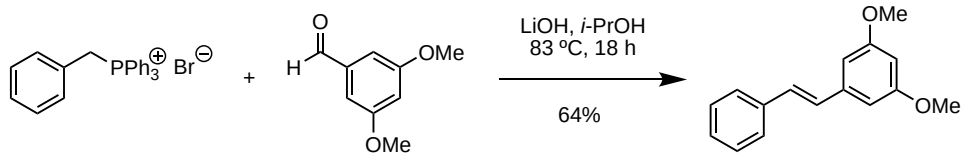
To a solution of benzyl bromide (**5.80**) (9.56 mL, 80.4 mmol, 1.0 equiv.) in PhMe (420 mL) was added PPh_3 (21.1 g, 80.4 mmol, 1.0 equiv.) at room temperature, and the solution was heated to 120 °C for 18 h. The resulting white precipitate was then filtered and further washed with PhMe (200 mL) and dried *in vacuo* to afford benzyltriphenylphosphonium bromide (**5.81**) (52.4 g, 75%) as a white solid. Data for **5.81** matched that previously reported in literature.[35]

Data for 5.81:

FTIR (**neat**)**:** 3053, 1587, 1484, 1436, 1189, 1112, 995, 719 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 – 7.72 (m, 8H), 7.70 – 7.66 (m, 2H), 7.66 – 7.62 (m, 5H), 7.56 – 7.52 (m, 1H), 7.49 – 7.43 (m, 3H), 7.22 – 7.20 (m, 1H), 5.44 (d, J = 14.4 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 134.9, 134.9, 134.5, 134.4, 132.1, 132.1, 131.9, 131.9, 131.6, 131.5, 130.2, 130.1, 128.8, 128.8, 128.5, 128.4, 128.4, 128.4, 118.3, 117.6, 31.1, 30.8 ppm.



5.81 **5.82** **5.83**

Lithium hydroxide (410 mg, 17.1 mmol, 1.5 equiv.) was added to a stirred solution of benzyltriphenylphosphonium bromide (**5.81**) (5.00 g, 11.4 mmol, 1.0 equiv.) in *i*-PrOH (100 mL) and the reaction was left to stir for 15 min at room temperature. 3,5-dimethoxybenzaldehyde (**5.82**) (1.90 g, 11.4 mmol, 1.0 equiv.) was then added and reaction heated to reflux for 16 h. The reaction was then cooled and quenched upon addition of brine (100 mL) and product was extracted with EtOAc (3 x 100 mL) and purified *via* flash chromatography on SiO_2 (4:1 hexanes/ EtOAc) to give the Wittig product (**5.83**) (1.76 g, 64%) as a white solid. Data for **5.83** matched that previously reported in the literature.[35]

Data for 5.83:

R_f: 0.45 (9:1 hexanes/ EtOAc).

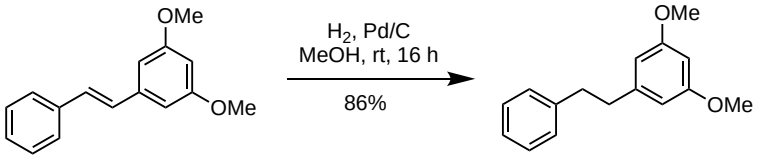
MP: 53 – 54 °C (lit. 53 – 55 °C).[35]

FTIR (**neat**)**:** 2837, 1712, 1590, 1457, 1424, 1350, 1295, 1203, 1060, 959, 826 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.1 Hz, 2H), 7.33 (t, *J* = Hz, 2H), 7.25 – 7.20 (m, 1H), 7.09 – 6.97 (m, 2H), 6.65 (s, 2H), 6.38 (d, *J* = 2.2 Hz), 3.79 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.0, 139.3, 137.1, 129.2, 128.7, 128.6, 127.7, 126.5, 104.6, 100.0, 55.3 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{16}H_{17}O_2$ 241.1223, found 241.1227.



5.83 **5.84**

To a solution of **5.83** (1.56 g, 6.50 mmol, 1.0 equiv.) in MeOH (150 mL) was added portion-wise Pd/C (10% wt./ wt., 700 mg, 0.65 mmol, 10 mol%). The reaction was purged with H_2/ vacuum three times and reaction left to stir at room temperature for 16 h. The solution was then filtered through celite the concentrated *in vacuo* to afford a **5.84** (1.35 g, 86%). Data for **5.84** matched that previously reported in the literature.[35]

Data for 5.84:

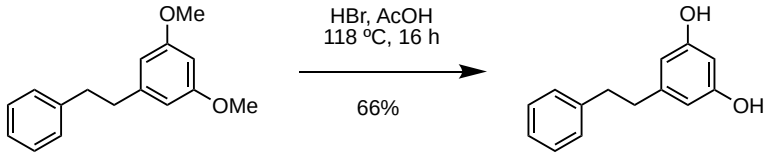
R_f: 0.40 (9:1 hexanes/ EtOAc).

FTIR (**neat**)**:** 2935, 1736, 1594, 1455, 1428, 1349, 1295, 1203, 1060, 909, 731 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.28 (m, 2H), 7.25 – 7.19 (m, 3H), 6.38 (t, *J* = 2.0 Hz, 2H), 6.35 (q, *J* = 2.0 Hz, 1H), 3.79 (s, 6H), 2.92 (dd, J = 11.3, 1.6 Hz, 4H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ160.7, 144.1, 141.7, 128.4, 128.3, 125.9, 106.5, 98.0, 38.2, 37.6 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{16}H_{19}O_2$ 243.1380, found 243.1380.



5.84 **5.85**

To a solution of **5.84** (1.24 g, 5.1 mmol, 1.0 equiv.) in AcOH (10 mL) was added HBr (6.0 mL,1.0 mol, 33% wt./ wt. in AcOH, 20 equiv.) and the reaction was left to reflux. After 16 h the solution was quenched with sat. brine (10 mL) and product extracted with EtOAc (3 x 10 mL), dried with $MgSO_4$, filtered and concentrated. Purification *via* flash chromatography on SiO_2 (4:1 hexanes/ EtOAc) gave the diol **5.85** (715 mg, 66%) as pale yellow oil. Data for **5.85** matched that previously reported in the literature.[35]

Data for 5.85:

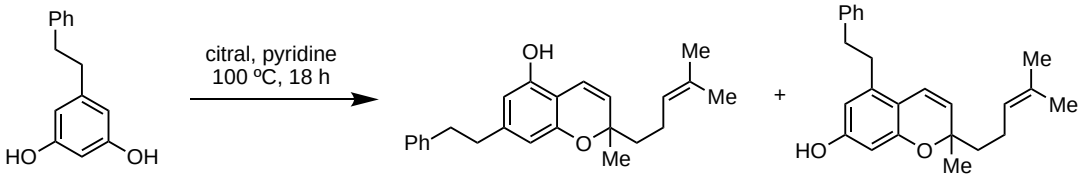
R_f: 0.35 (3:2 hexanes/ EtOAc).

FTIR (**neat**)**:** 3342, 1698, 1599, 1495, 1453, 1143, 999, 974, 837, 748 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (dd, *J* = 8.1, 6.8 Hz, 2H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.14 – 7.09 (m, 2H), 6.23 (d, *J* = 2.3 Hz, 2H), 6.16 (t, J = 2.2 Hz, 1H), 5.48 (br s, 2H), 2.85 – 2.71 (m, 4H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.3, 145.0, 141.5, 128.4, 128.3, 128.3, 125.9, 108.3, 100.6, 37.5, 37.2 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{14}H_{15}O_2$ 215.1067, found 215.1063.



5.85: 5-phenyl-ethylresorcinol

5.87 76%

5.86 17%

To a solution of 5-phenylethylresorcinol (**5.85**) (1.15 g, 5.37 mmol, 1.0 equiv.) in pyridine (0.46 mL, 5.37 mmol, 1.0 equiv.) was added citral (1.19 mL, 7.00 mmol, 1.3 equiv.) and the resultant mixture was stirred at 100 °C for 18 h. EtOAc (50 mL) was added, and the solution was washed with 1 M $HCl_{(aq)}$ (30 mL) and 1 M $CuSO_{4(aq)}$ (2 × 50 mL). The organic solution was then dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (4:1 $CHCl_3$/ cyclohexane) then (9:1 → 4:1, hexanes/ EtOAc, gradient elution) to give chromene **5.87** (1.44 g, 76%) as a yellow oil alongside chromene **5.86** (313 mg, 17%) as a red oil. Data for **5.86** and **5.87** matched that previously reported in literature.[37]

Data for 5.87:

R_f: 0.20 (20:1 hexanes/ EtOAc).

FTIR (**neat**)**:** 3387, 2970, 2924, 1622, 1496, 1431, 1376, 1141, 1083, 1055, 821, 774 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (dd, *J* = 7.1, 1.1 Hz, 2H), 7.24 – 7.14 (m, 3H), 6.64 (d, *J* = 10.0 Hz, 1H), 6.31 (s, 1H), 6.11 (s, 1H), 5.52 (d, *J* = 10.0 Hz, 1H), 5.17 – 5.08 (m, 1H), 4.98 (br s, 1H), 2.93 – 2.83 (m, 2H), 2.81 – 2.71 (m, 2H), 2.18 – 2.08 (m, 2H), 1.76 – 1.66, 2H), 1.69 (s, 3H), 1.60 (s, 3H), 1.40 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.1, 151.1, 143.5, 143.5, 141.7, 131.6, 128.4, 128.4, 128.3, 128.3, 128.3, 127.4, 125.9, 124.2, 116.8, 109.1, 107.7, 107.3, 78.3, 41.1, 37.9, 37.4, 26.2, 25.6, 22.7, 17.6 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{24}H_{29}O_2$ 349.2162, found 349.2120.

Data for 5.86:

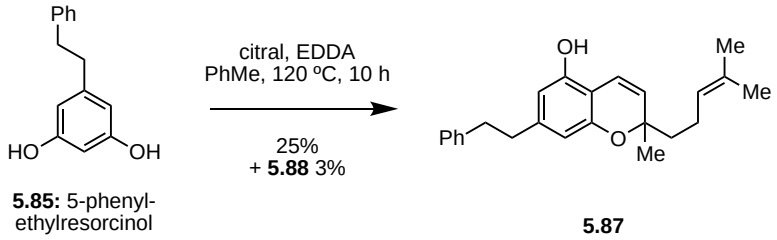
R_f: 0.30 (4:1 hexanes/ EtOAc).

FTIR (**neat**)**:** 3387, 2928, 1610, 1452, 1139 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 – 7.16 (m, 5H), 6.47 (d, *J* = 10.1 Hz, 1H), 6.18 (d, *J* = 2.3 Hz, 1H), 6.16 (d, *J* = 2.5 Hz, 1H), 5.46 (d, *J* = 10.1 Hz, 1H), 5.10 (t, *J* = 7.8 Hz, 1H), 4.64 (br s, 1H), 2.85 – 2.83 (m, 4H), 2.11 – 2.08 (m, 2H), 1.67 (s, 3H), 1.59 (s, 3H), 1.36 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9, 154.9, 141.5, 139.0, 131.7, 128.4, 128.4, 126.9, 126.0, 124.2, 119.1, 112.8, 108.4, 101.8, 77.9, 40.9, 37.4, 34.4, 26.2, 25.7, 22.7, 17.6 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{24}H_{29}O_2$ 349.2162, found 349.2160.



5.85: 5-phenyl-ethylresorcinol

5.87

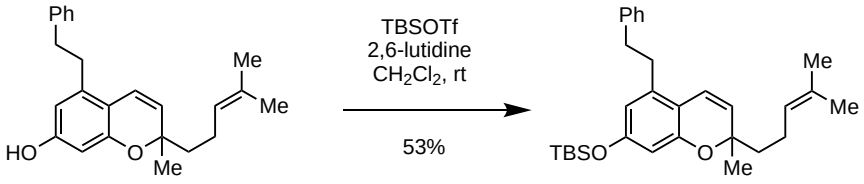
To a solution of 5-phenylethylresorcinol (**5.85**) (1.06 g, 5.00 mmol, 1.0 equiv.) in PhMe (50 mL) and EDDA (180 mg, 0.980 mmol, 0.05 equiv.) was added citral (0.84 mL, 5.00 mmol, 1.0 equiv.) and the resultant mixture was stirred at 120 °C for 40 h. The solution was then cooled, concentrated *in vacuo* and residue was purified by flash chromatography on SiO_2 (15:1 → 10:1 hexanes/ EtOAc, gradient elution) to give the bis-chromene **5.88** (43 mg, 3%) and chromene **5.87** (382 mg, 22%) as a red oil. Data for **5.87** matched that previously obtained and previously reported in the literature.[37]

Data for 5.88:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.26 (m, 2H), 7.22 – 7.17 (m, 3H), 6.70 (d, J = 10.0 Hz, 1H), 6.48 (d, J = 10.0 Hz, 1H), 6.21 (s, 1H), 5.51 – 5.46 (m, 2H), 5.12 (t, *J* = 5.7 Hz, 2H), 2.83 (s, 6H), 2.16 – 2.11 (m, 4H), 1.75 – 1.61 (m, 4H), 1.68 (s, 6H), 1.40 -1.39 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.5, 149.0, 141.8, 138.2, 131.6, 131.6, 131.5, 128.4, 127.1, 127.1, 126.6, 125.9, 124.3, 119.5, 117.2, 112.3, 109.0, 108.3, 78.3, 77.8, 41.2, 40.8, 37.4, 34.6, 26.4, 25.9, 25.7, 25.7, 22.7, 22.7, 17.6, 17.6 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{34}H_{43}O_3$ 499.3207, found 499.3209.



5.86 **5.89**

To a solution of chromene **5.86** (384 mg, 1.10 mmol, 1.0 equiv.) in dry CH_2Cl_2 (20 mL) was added 2,6-lutidine (0.260 mL, 2.20 mmol, 2.0 equiv.), and TBSOTf (0.320 mL, 1.65 mmol, 1.5 equiv.). The reaction mixture was stirred at room temperature for 20 min. Then the reaction was quenched upon addition of a sat. $NH_4Cl_{(aq)}$ (20 mL). The organic layer was separated and further extraction of the aqueous layer with CH_2Cl_2 (3 x 20 mL) performed. Combined organic extracts were dried with $MgSO_4$, filtered, and concentrated *in vacuo.* The residue was purified by flash chromatography on SiO_2 (30:1 hexanes/ Et_2O) to give **5.89** as a colourless oil (270 mg, 53%).

Data for 5.89:

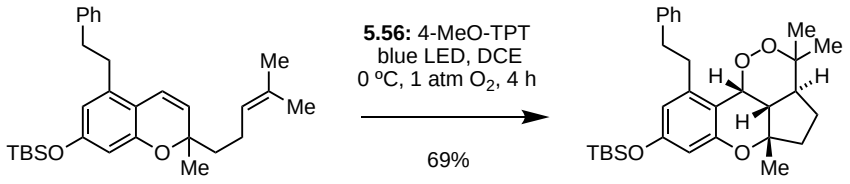
R_f: 0.75 (4:1 hexanes/ EtOAc).

FTIR (**neat**)**:** 2929, 2858, 1604, 1473, 1253, 1154, 842, 781 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.26 (m, 2H), 7.21 – 7.16 (m, 3H), 6.49 (d, *J* = 10.0 Hz, 1H), 6.48 (d, *J* = 10.0 Hz, 1H), 6.18 (d, *J* = 2.2 Hz, 1H), 6.15 (d, *J* = 2.2 Hz, 1H), 5.47 (d, *J* = 10.0 Hz, 1H), 5.09 (t, *J* = 7.3 Hz, 1.0 Hz), 2.84 (m, 4H), 2.13 – 2.06 (m, 2H), 1.72 – 1.57 (m, 2H), 1.68 (s, 3H), 1.59 (s, 3H), 1.37 (s, 3H), 0.97 (s, 9H), 0.17 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.0, 154.5, 141.6, 138.4, 131.6, 128.4, 128.4, 127.2, 125.9, 124.2, 119.3, 113.5, 113.3, 106.5, 77.7, 40.9, 37.4, 34.3, 26.1, 25.7, 25.7, 22.7, 18.2, 17.6, – 4.4 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{30}H_{43}O_2Si$ 463.3027, found 463.3024.



5.89 **5.90**

O_2 gas was bubbled through a solution of **5.89** (60 mg, 0.130 mmol, 1.0 equiv.) in DCE (13 mL) for 10 min. 4-MeO-TPT (**5.56**) (1 mg, 0.003 mmol, 2 mol%) was then added and the reaction mixture was stirred under 1 atm of O_2 while exposed to a 470 nm blue LED lamp at 0 °C for 4 h. The reaction mixture was then concentrated *in vacuo* and purified by flash chromatography on SiO_2 (30:1 hexanes/ Et_2O) to give the endoperoxide **5.90** (45 mg, 69%) as a colourless oil.

Data for 5.90:

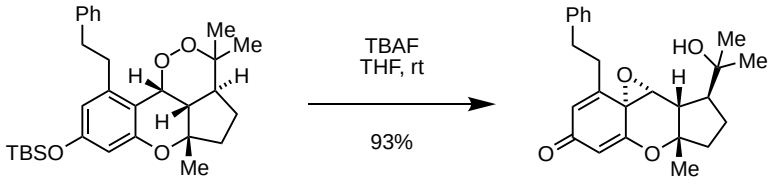
R_f: 0.40 (9:1 hexanes/ EtOAc).

FTIR (**neat**)**:** 2929, 1605, 1575, 1147, 837 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (dd, *J* = 9.3, 3.6 Hz, 2H), 7.19 – 7.15 (m, 3H), 6.33 (d, *J* = 2.4 Hz, 1H), 6.19 (d, *J* = 2.4 Hz, 1H), 5.35 (d, *J* = 8.7 Hz, 1H), 3.07 – 2.97 (m, 2H), 2.93 – 2.88 (m, 1H), 2.83 – 2.77 (m, 1H), 2.51 (td, *J* = 12.5, 7.7 Hz, 1H), 2.25 – 2.19 (m, 1H), 1.98 (dd, *J* = 13.2, 8.6 Hz, 2H), 1.82 – 1.76 (m, 1H), 1.45 – 1.39 (m, 1H), 1.31 (s, 3H), 1.19 (s, 3H), 1.09 (s, 3H), 0.97 (s, 9H), 0.18 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.9, 155.7, 144.8, 141.9, 128.6, 128.2, 125.7, 114.7, 109.7, 107.6, 83.8, 82.6, 73.7, 46.1, 45.5, 39.5, 37.8, 34.1, 26.9, 25.7, 22.7, 22.4, 19.0, 18.1, – 4.4 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{30}H_{43}O_4Si$ 495.2925, found 495.2914.



5.90 **5.91**

To a solution of endoperoxide **5.90** (42 mg, 0.085 mmol, 1.0 equiv.) in THF (2 mL) at room temperature was added TBAF (1.0 M solution in THF, 0.085 ml, 0.085 mmol, 1.0 equiv.) and the reaction mixture was stirred for 5 min. The mixture was diluted with EtOAc (10 mL), washed with sat. brine (2 × 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (7:1 EtOAc/ hexanes) to give epoxide **5.91** as a colourless oil (30 mg, 93%).

Data for 5.91:

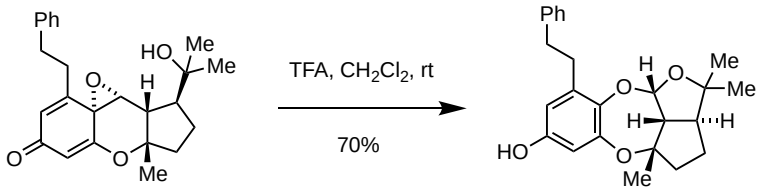
R_f: 0.45 (4:1 EtOAc/ hexanes).

FTIR (**neat**)**:** 3407, 2968, 1654, 1598, 1420, 1219, 888 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (m, 2H), 7.18 (dd, *J* = 17.7, 7.3 Hz, 3H), 6.33 (d, *J* = 1.9 Hz, 1H), 6.00 (d, *J* = 1.9 Hz, 1H), 3.90 (d, *J* = 3.9 Hz, 1H), 2.84 – 2.80 (m, 2H), 2.53 – 2.49 (m, 1H), 2.44 (ddd, *J* = 8.6, 6.2, 2.9 Hz, 1H), 2.32 – 2.23 (m, 1H), 2.12 – 2.03 (m, 2H), 1.91 – 1.83 (m, 2H), 1.43 – 1.39 (m, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 1.21 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 187.5, 167.2, 151.9, 140.5, 130.8, 128.6, 128.4, 126.4, 115.0, 90.7, 72.1, 63.5, 54.3, 53.6, 43.5, 40.3, 34.3, 30.1, 29.8, 27.1, 25.9, 25.3 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{24}H_{29}O_4$ 381.2060, found 381.2057.



5.91 **5.4:** rasumatranin D

To a solution of **5.91** (39 mg, 0.103 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) was added TFA (0.005 ml, 0.07 mmol, 70 mol%) and the reaction mixture was stirred at room temperature for 5 min and then quenched with saturated sat. $NaHCO_{3(aq)}$ solution (10 mL). The organic layer was separated and washed with sat. $NaHCO_{3(aq)}$ solution (10 mL) and sat. brine (2 × 10 mL), dried over $MgSO_4$, concentrated *in vacuo* and then purified by flash chromatography on SiO_2 (4:1 → 1:1 hexanes/ EtOAc) to give rasumatranin D (**5.4**) as a white solid (28 mg, 70%).

Data for rasumatranin D (5.4):

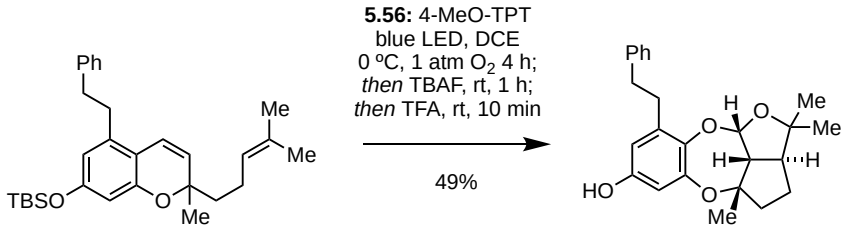
R_f: 0.65 (4:1 EtOAc/ hexanes).

FTIR (**neat**)**:** 3348, 2970, 1602, 1554, 1136, 1027, 729 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 – 7.21 (m, 2H), 7.17 – 7.13 (m, 3H), 6.37 (d, *J* = 3.0 Hz, 1H), 6.35 (d, *J* = 3.0 Hz, 1H), 4.92 (br s, 1H), 4.65 (d, *J* = 3.0 Hz, 1H), 3.42 (ddd, *J* = 14.0, 12.6, 6.0 Hz, 1H), 2.97 – 2.92 (m, 1H), 2.92 – 2.90 (m, 1H), 2.89 – 2.82 (m, 1H), 2.79 (ddd, *J* = 10.4, 7.4, 5.1 Hz, 1H), 2.57 (dt, *J* = 14.6, 8.8 Hz, 1H), 2.36 (ddd, *J* = 14.6, 9.9, 1.6 Hz, 1H), 2.08 (dd, *J* = 14.6, 3.1 Hz, 1H), 1.76 (dddd, *J* = 11.2, 7.9, 6.1, 1.5 Hz, 1H), 1.51 (s, 3H), 1.38 – 1.29 (m, 1H), 1.27 (s, 3H), 1.16 (s, 3H) ppm.

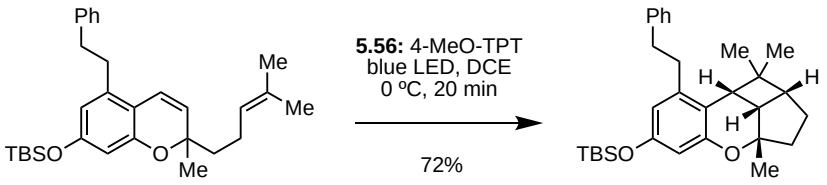
^{13}C NMR (125 MHz, $CDCl_3$): δ 151.8, 151.3, 141.8, 138.5, 137.4, 128.7, 128.2, 125.8, 112.0, 109.9, 96.5, 81.1, 79.9, 64.2, 51.9, 47.2, 36.7, 32.0, 29.7, 24.7, 22.7, 21.2 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{24}H_{29}O_4$ 381.2060, found 381.2057.



5.89 **5.4:** rasumatranin D

O_2 was bubbled through a solution of **5.89** (84 mg, 0.182 mmol, 1.0 equiv.) in DCE (20 mL, 0.01 M). After 10 minutes the reaction mixture was cooled to 0 °C, and 4-MeO-TPT (**5.56**) (2 mg, 0.004 mmol, 2 mol%) was added. The reaction mixture was then stirred under 1 atm of O_2 while exposed to a 470 nm blue LED lamp for 4 h. TBAF (1.0 M in THF, 0.18 ml, 0.182 mmol, 1.0 equiv.) was added and the reaction mixture was stirred for 1 h, followed by TFA (0.030 ml, 0.26 mmol, 1.5 equiv.) and stirring was continued for 10 minutes. The reaction mixture was quenched with sat. $NaHCO_{3(aq)}$ (15 mL) and the organic layer was separated and washed with brine (15 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (4:1 → 1:1, hexanes/ EtOAc, gradient elution) to give rasumatranin D (**5.4**) as a white solid (34 mg, 49%). Data for **5.4** matched that previously obtained and reported in the literature.[1]



5.89 **5.92**

To a solution of **5.89** (130 mg, 0.280 mmol, 1.0 equiv.) in DCE (28 mL) was added 4-MeO-TPT (**5.56**) (2 mg, 0.006 mmol, 2 mol%) and the reaction mixture was exposed to a 470 nm blue LED lamp at 0 °C for 20 min. The reaction mixture was then concentrated *in vacuo* and purified by flash chromatography on SiO_2 (30:1 hexanes/ Et_2O) to give the cyclol **5.92** as a colourless oil (94 mg, 72%).

Data for 5.92:

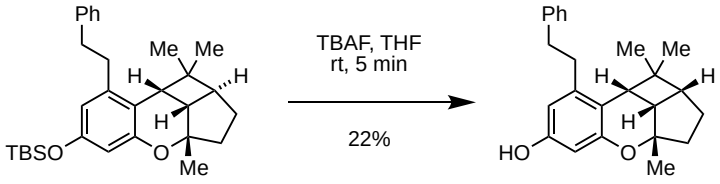
R_f: 0.80 (8:1 hexanes/ EtOAc).

FTIR (**neat**)**:** 2929, 2858, 1696, 1607, 1575, 1472, 1425, 1252, 1146, 1019, 812, 780 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.26 (m, 2H), 7.21 – 7.15 (m, 3H), 6.34 (d, *J* = 2.5 Hz, 1H), 6.29 (d, *J* = 2.5 Hz, 1H), 3.09 (d, *J* = 9.0 Hz, 1H), 2.80 (d, *J* = 7.3 Hz, 2H), 2.72 (t, *J* = 8.0 Hz, 2H), 2.50 (t, *J* = 9.0 Hz, 1H), 2.01 – 1.94 (m, 1H), 1.75 – 1.66 (m, 2H), 1.65 – 1.59 (m, 2H), 1.36 (s, 3H), 1.29 (s, 3H), 0.98 (s, 9H), 0.62 (s, 3H), 018 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.6, 154.4, 141.9, 141.4, 128.5, 128.4, 128.4, 125.9, 113.7, 108.1, 83.3, 46.5, 41.0, 39.9, 39.8, 37.4, 37.2, 34.8, 34.2, 26.1, 25.7, 25.7, 25.3, 18.8, −4.4 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{30}H_{43}O_2Si$ 463.3027, found 463.3023.



5.92 **5.93:** *o*-bibenzyl-cannabicyclol

To a solution of **5.92** (94 mg, 0.203 mmol, 1.0 equiv.) in THF (4 mL) at room temperature was added TBAF (1.0 M solution in THF, 0.20 ml, 0.203 mmol, 1.0 equiv.) and the reaction mixture was stirred for 5 min. The mixture was diluted with EtOAc (10 mL), washed with sat. brine (2 × 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (4:1 EtOAc/ hexanes) to give *o*-bibenzyl cannabicyclol (**5.93**) (22 mg, 22%). Data for *o*-bibenzyl cannabicyclol (**5.93**) matched that previously reported in the literature.[34]

Data for *o*-bibenzyl cannabicyclol (5.93):

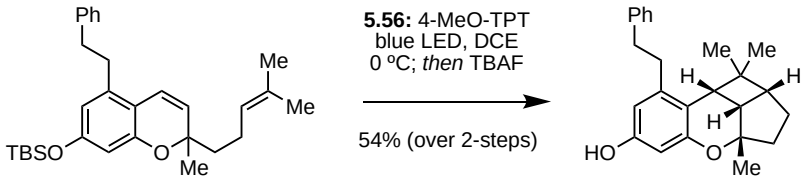
R_f: 0.90 (3:2 hexanes/ EtOAc).

FTIR (**neat**)**:** 3382, 2947, 1615, 1593, 1453, 1331, 1115, 1032, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (t, *J* = 7.4 Hz, 2H), 7.22 – 7.18 (m, 3H), 6.36 (d, *J* = 2.6 Hz, 1H), 6.28 (d, *J* = 2.6 Hz, 1H), 4.80 (br s, 1H), 3.10 (d, *J* = 9.6 Hz, 1H), 2.84 – 2.70 (m, 2H), 2.76 – 2.69 (m, 2H), 2.52 (t, *J* = 9.0 Hz, 1H), 2.42 (dt, *J* = 8.0, 3.2 Hz), 1.74 – 1.58 (m, 4H), 1.37 (s, 3H), 1.30 (s, 3H), 0.63 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.9, 154.4, 142.0, 141.9, 128.4, 128.4, 125.9, 116.1, 108.8, 103.5, 83.5, 46.5, 39.9, 39.9, 39.8, 37.3, 37.1, 34.9, 34.1, 26.0, 25.3, 18.8 ppm.

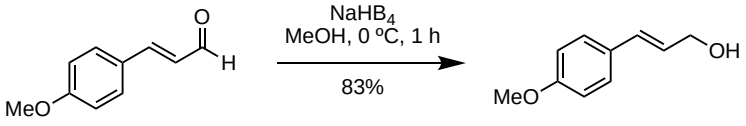
HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{24}H_{29}O_2$ 349.2168, found 349.2147.



5.89

5.93: *o*-bibenzyl-cannabicyclol

To a solution of **5.89** (67 mg, 0.145 mmol, 1.0 equiv.) in DCE (25 mL, 0.01 M) was added 4-MeO-TPT (**5.56**) (2 mg, 0.006 mmol, 2 mol%) and the reaction mixture was stirred under N_2 while exposed to a 470 nm blue LED lamp at 0 °C for 15 min. TBAF (1.0 M solution in THF, 0.14 ml, 0.145 mmol, 1.0 equiv.) was then added to the mixture at room temperature and the reaction mixture was stirred for 5 min. The reaction mixture was then diluted with CH_2Cl_2 (10 mL), washed with sat. brine (2 × 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (4:1 EtOAc/ hexanes) to give *o*-bibenzyl cannabicyclol (**5.93**) (28 mg, 54% over 2-steps). Data for *o*-bibenzyl cannabicyclol (**5.93**) matched that previously obtained and previously reported in the literature.[34]



5.151 **5.96b**

$NaBH_4$ (2.68 g, 70.9 mmol, 1.15 equiv.) was added to a solution of *E-para*-methoxycinnamaldehyde **5.151** (10.0 g, 61.7 mmol, 1.0 equiv.) in MeOH (250 mL) at 0 °C. After 1 h the reaction was quenched upon addition of sat. brine (250 mL) and diluted with CH_2Cl_2 (250 mL), the organic layer was separated and further extracted with CH_2Cl_2 (2 x 250 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated to give 4-methyl cinnamyl alcohol **5.96b** (8.45 g, 83%) as an orange oil. Data for **5.96B** matched that previously reported in literature.[26, 30]

Data for 5.96b:

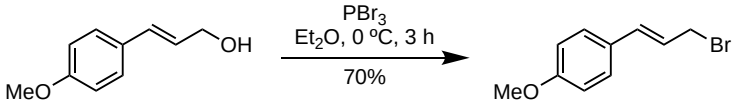
R_f: 0.30 (6:4 hexanes/ EtOAc).

FTIR (**neat**)**:** 3356, 2839, 1654, 1605, 1510, 1458, 1305, 1269, 1250, 1174, 1127, 1085, 1006 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.56 (dt, *J* = 15.9, 1.6 Hz), 6.24 (dt, *J* = 15.8, 5.9 Hz, 1H), 4.30 (d, *J* = 5.9 Hz, 2H), 3.81 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 131.0, 129.4, 127.7, 126.3, 114.0, 63.9, 55.3 ppm.

HRMS (**ESI**) **m/z:** $[M+Na]^+$ Calcd for $C_{10}H_{12}O_2Na$ 187.0730, found 187.0735.



5.96b **5.95**

To a stirring solution of the allylic alcohol **5.96b** (6.0 g, 36.5 mmol, 1.0 equiv.) in Et_2O (110 mL) at 0 °C was added PBr_3 (1.37 mL, 14.6 mmol, 40 mol%) in the absence of light. The reaction was further stirred for 3 h, then poured over sat. $NaHCO_{3(aq)}$ (110 mL) and the organic layer separated. The aqueous layer was further extracted with Et_2O (2 x 110 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford **5.95** (5.76 g, 70%) directly as a white solid. Data for **5.95** matched that previously reported in the literature.[26, 30]

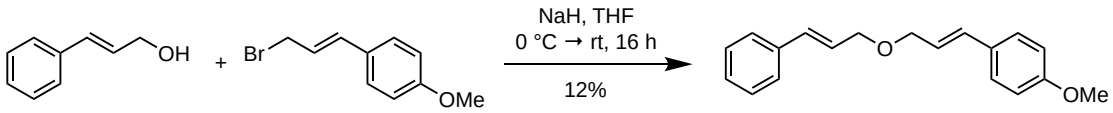
Data for 5.95:

FTIR (**neat**)**:** 2959, 1643, 1603, 1509, 1469, 1437, 1415, 1309, 1286, 1248, 1176, 1141, 1064, 1029, 969, 826, 810, 829 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 15.5 Hz, 1H), 6.26 (dt, *J* = 15.7, 7.9 Hz, 1H), 4.17 (dd, *J* = 7.9, 1.0 Hz, 2H), 3.82 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 159.8, 134.2, 128.0, 123.0, 114.1, 55.3, 34.2 ppm.

HRMS (**ESI**) **m/z:** $[M+Na]^+$ Calcd for $C_{11}H_{14}O_2Na$ 201.0886, found 201.0881.



5.96a **5.95** **5.94a**

Alcohol **5.96a** (1.47 g, 10.9 mmol, 1.0 equiv.) in THF (10 mL) was added dropwise to a solution of NaH (0.73 g, 17.5 mmol, 50% wt./ wt. 1.6 equiv.) in THF (15 mL). The solution was stirred at 0 °C for 30 min, then the bromide **5.95** (3.13 g, 13.1 mmol, 1.2 equiv.) in THF (10 mL) was added dropwise and reaction was warmed to room temperature and left to stir for 16 h. Solution was quenched upon addition of sat. $NH_4Cl_{(aq)}$ (35 mL) and the organic layer was extracted with Et_2O (3 x 35 mL), dried with $MgSO_4$, filtered and concentrated. Purification by flash chromatography on SiO_2 (9:1 hexanes/ EtOAc) gave **5.94a** (395 mg, 12%). Data for **5.94a** matched that previously reported in the literature.[26, 30]

Data for 5.94a:

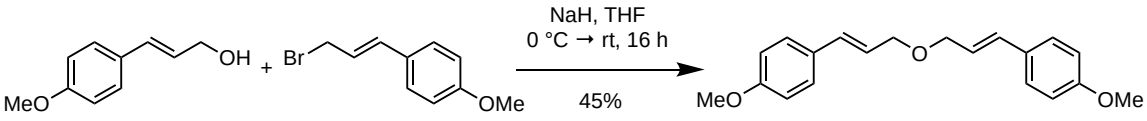
R_f: 0.55 (9:1 hexanes/ EtOAc).

FTIR (**neat**)**:** 3002, 2837, 1607, 1495, 1248, 1175, 1104, 1034, 967, 840 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, *J* = 7.4 Hz, 2H), 7.36 – 7.28 (m, 4H), 7.25 (d, J = 8.7 Hz, 1H), 6.90 – 6.80 (m, 2H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.58 (d, *J* = 15.9 Hz, 1H), 6.33 (d, *J* = 15.9 Hz, 1H), 6.19 (d, *J* = 15.9 Hz, 1H), 4.19 (ddd, J = 7.5, 6.1, 1.4 Hz), 3.81 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 136.8, 132.5, 132.4, 129.5, 128.5, 127.7, 127.7, 126.5, 126.1, 123.7, 114.0, 71.0, 70.6, 55.3 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{19}H_{21}O_2$ 281.1536, found 281.1458.



5.96b **5.95** **5.94b**

Alcohol **5.96b** (1.47 g, 8.95 mmol, 1.0 equiv.) in THF (10 mL) was added dropwise to a solution of NaH (50% wt./ wt., 0.68 g, 14.3 mmol, 1.6 equiv.) in THF (15 mL). The solution was stirred at 0 °C for 30 min, then the bromide **5.95** (2.46 g, 10.8 mmol, 1.2 equiv.) in THF (10 mL) was added dropwise and reaction was warmed to room temperature and left to stir for 16 h. The solution was quenched upon addition of sat. $NH_4Cl_{(aq)}$ (35 mL) and the organic layer was extracted with Et_2O (3 x 35 mL), dried with $MgSO_4$, filtered and concentrated to give a yellow solid **5.94b** (1.25 g, 45%). Data for **5.94b** matched that previously reported in the literature.[26, 30]

Data for 5.94b:

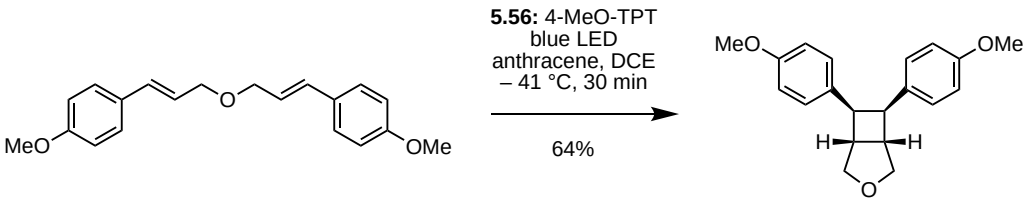
R_f: 0.80 (1:1 EtOAc/ hexanes).

FTIR (**neat**)**:** 2962, 1603, 1510, 1464, 1440, 1418, 1356, 1309, 1209, 1275, 1175, 1127, 1100, 1028, 1053, 968, 840, 812 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.7 Hz, 4H), 6.87 (d, *J* = 8.7 Hz, 4H), 6.59 (d, *J* = 15.8 Hz, 2H), 6.21 (dt, *J* = 15.8, 6.2 Hz, 2H), 4.19 (dd, *J* = 6.2, 1.4 Hz, 4H), 3.82 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 132.3, 129.5, 127.7, 123.8, 114.0, 70.8, 55.3, 55.3 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{20}H_{23}O_3$ 311.1642, found 311.1646.



5.94b **5.98b**

Following a modified procedure from Nicewicz *et al.,* **5.94b** (108 mg, 0.348 mmol, 1.0 equiv.) in DCE (22 mL) was cooled to 0 °C. 4-MeO-TPT (**5.56**) (5 mg, 0.018 mmol, 5 mol%) and anthracene (34 mg, 0.105 mmol, 30 mol%) was added and solution irradiated with a 470 nm blue LED lamp.[25] The solution was left to stir for 1 h, then concentrated and product was purified by flash chromatography on SiO_2 (8:1 hexanes/ EtOAc) to afford **5.98b** (72 mg, 64%) as a white solid. Data for **5.98b** matched that previously reported in the literature.[25]

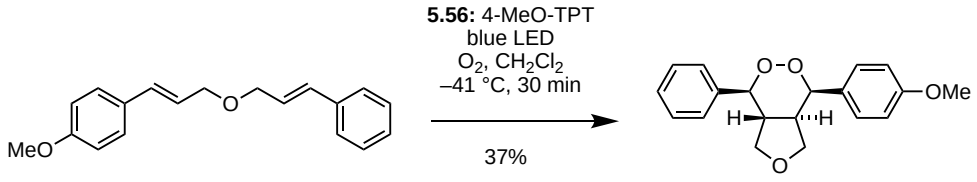
Data for 5.98b:

R_f: 0.75 (1:1 hexanes/ EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.85 (d, *J* = 8.4 Hz, 4H), 6.64 (d, *J* = 8.4 Hz, 4H), 4.08 (d, *J* = 9.3 Hz, 2H), 3.70 (s, 6H), 3.65 (d, *J* = 3.9 Hz, 2H), 3.23 (br s, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.5, 133.1, 129.0, 113.2, 74.0, 55.1, 46.5, 42.5 ppm.

HRMS (**ESI**) **m/z:** $[M+H]^+$ Calcd for $C_{20}H_{23}O_3$ 311.1642, found 311.1646.



5.94a **5.98a**

O_2 was bubbled through the solution of **5.94a** (110 mg, 0.39 mmol, 1.0 equiv.) in CH_2Cl_2 (17 mL) at −41 °C for 10 min. 4-MeO-TPT (**5.56**) (3 mg, 0.008 mmol, 2 mol%) was then added and the reaction was left to stir under 1 atm of O_2 for 4h while exposed to a 470 nm blue LED lamp. The solution was then concentrated and purified by flash chromatography on SiO_2 (4:1 hexanes/ EtOAc) to afford the endoperoxide **5.98a** (46 mg, 37%) as a yellow solid. Data for **5.98a** matched that previously reported in literature.[25]

Data for 5.98a:

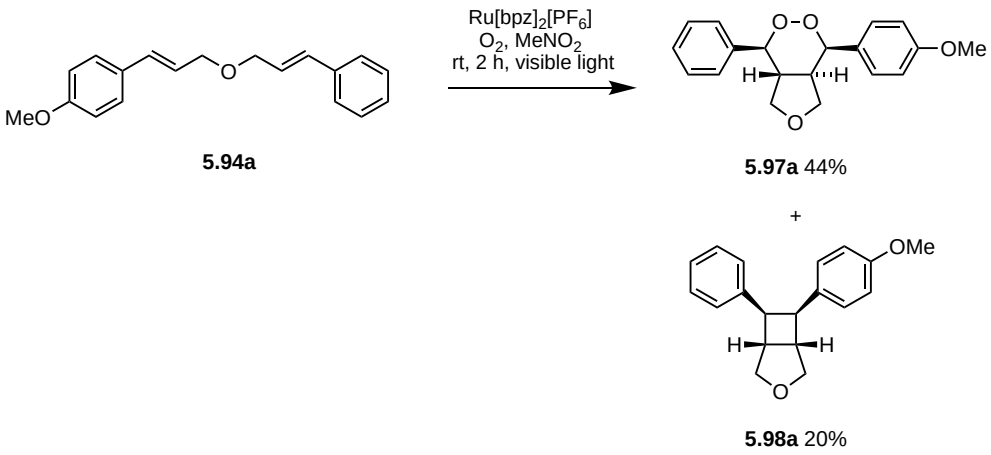
R_f: 0.30 (9:1 hexanes/ EtOAc).

FTIR (**neat**)**:** 2928, 1609, 1514, 1251, 1177, 1030, 967 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.7 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.36 – 7.29 (m, 3H), 6.92 (d, *J* = 8.7 Hz, 2H), 5.57 (d, *J* = 5.8 Hz, 1H), 5.06 (d, *J* = 9.9 Hz, 1H), 4.18 (t, *J* = 7.3 Hz, 1H), 3.80 (s, 3H), 3.78 (d, *J* = 9.6 Hz, 1H), 3.45 (dd, *J* = 10.8, 7.9 Hz, 1H), 3.26 (dd, *J* = 11.3, 7.6 Hz, 1H), 2.90 – 2.80 (m, 1H), 2.68 – 2.57 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.3, 137.0, 129.0, 128.2, 128.2, 127.6, 127.0, 114.2, 87.4, 83.1, 83.1, 68.9, 68.0, 55.3, 46.5, 41.2 ppm.

HRMS (**ESI**) **m/z:** $[M+Na]^+$ Calcd for $C_{19}H_{20}O_4Na$ 335.1254, found 335.1257.



5.94a

5.97a 44%

+

5.98a 20%

To a solution of the **5.94a** (103 mg, 0.37 mmol, 1.0 equiv.) was added $Ru[bpz]_2[PF_6]$ (2 mg, 0.007 mmol, 2 mol%) and O_2 was bubbled through the solution at room temperature for 10 min. The solution was then irradiated with a 200 W incandescent bulb and left to stir under 1 atm O_2 for 2 h. The solution was then concentrated and purified by flash chromatography on SiO_2 (4:1 hexanes/ EtOAc) to afford the cyclobutane **5.98a** (20 mg, 20%) as a white solid, the endoperoxide **5.97A** (51 mg, 44%) as a yellow solid. Data for **5.98a** and **5.97a** matched that previously obtained and previously reported in literature.[25, 26]

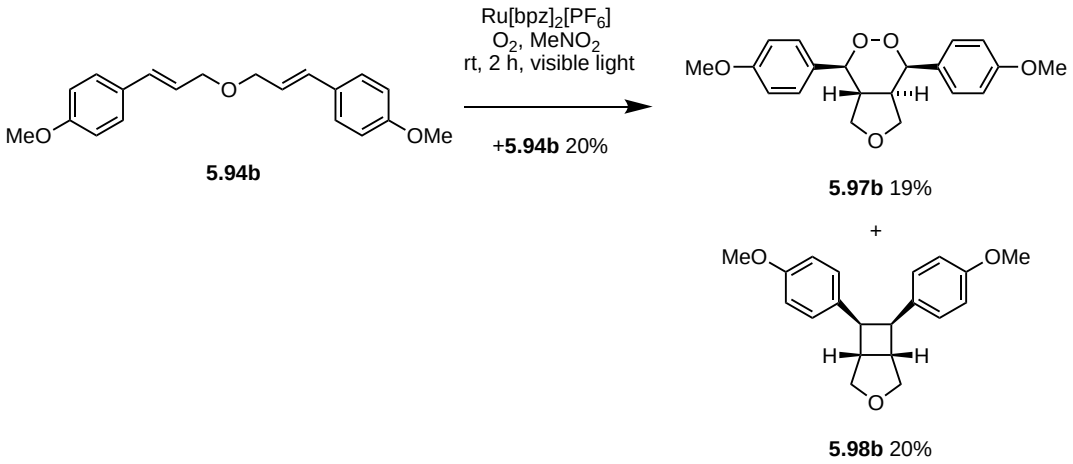
Data for 5.98a:

R_f: 0.70 (4:1 hexanes/ EtOAc).

FTIR (**neat**)**:** 2956, 2828, 1610, 1512, 1248, 1178, 1036, 830 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.09 (t, *J* = 7.6 Hz, 2H), 7.03 – 6.99 (m, 1H), 6.96 – 6.91 (m, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.62 (d, *J* = 8.7 Hz, 2H), 4.09 (d, *J* = 9.4 Hz, 2H), 3.69 (d, *J* = 9.5 Hz, 7H), 3.29 (d, *J* = 4.7 Hz, 1H), 3.24 (s, 1H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 157.5, 140.9, 133.0, 129.0, 128.1, 127.7, 125.6, 113.1, 74.0, 74.0, 55.1, 47.2, 46.5, 42.6, 42.0.



To a solution of the **5.94b** (100 mg, 0.320 mmol, 1.0 equiv.) was added $Ru[bpz]_2[PF_6]$ (2 mg, 0.007 mmol, 2 mol%) and O_2 was bubbled through the solution at room temperature for 10 min. The solution was then irradiated with a 200 W incandescent bulb and left to stir under 1 atm O_2 for 2 h. The solution was then concentrated and purified by flash chromatography on SiO_2 (4:1 hexanes/ EtOAc) to afford the cyclobutane **5.98b** (20 mg, 20%) as a white solid, the endoperoxide **5.97b** (21 mg, 19%) as a yellow solid and recovered starting material **5.94b** (20 mg, 20%). Data for **5.98b** and **5.97b** matched that previously obtained and previously reported in literature.[25, 26]

Data for 5.97b:

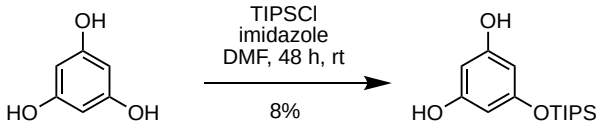
R_f: 0.50 (91:1 hexanes/ EtOAc).

FTIR (**neat**)**:** 2971, 1159, 1028, 732, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 6.94 – 6.88 (m, 4H), 5.52 (d, *J* = 5.7 Hz, 1H), 5.03 (d, *J* = 9.8 Hz, 1H), 4.14 (t, *J* =7.3 Hz, 1H), 3.82 – 3.79 (m, 7H), 3.44 (dd, *J* = 10.8, 7.9 Hz, 1H), 3.23 (dd, *J* = 11.3, 7.6 Hz, 1H), 2.88 – 2.76 (m, 1H), 2.71 – 2.60 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.3, 159.0, 129.1, 129.0, 128.9, 128.4, 114.2, 113.6, 87.3, 82.9, 68.9, 68.1, 55.3, 55.2, 46.7, 41.2 ppm.

HRMS (**ESI**) **m/z:** $[M-H]^-$ Calcd for $C_{20}H_{22}O_5$ 343.1540, found 343.1473.



5.152: phloroglucinol **5.153**

To a solution of phloroglucinol (**5.152**) (5.0 g, 39.7 mmol, 1.0 equiv.) in DMF (80 mL) was added imidazole (801 mg, 11.9 mmol, 30 mol%) and TIPSCl (2.54 mL, 11.9 mmol, 30 mol%) at room temperature. After 48 h the reaction was diluted with Et_2O (80 mL) and the organic layer was washed with distilled water (80 mL) and further washed with sat. brine (3 x 80 mL). The organic layer was then dried with $MgSO_4$, filtered, concentrated *in vacuo* and purified *via* flash column chromatography on SiO_2 (9:1 hexanes/ EtOAc) to afford **5.153** (92 mg, 8%) as a clear oil. Data for **5.154** matched that previously reported in literature.[41]

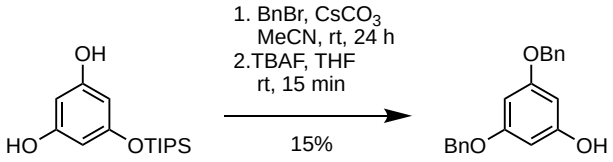
Partial Data for 5.153:

R_f: 0.30 (3:1 hexanes/ EtOAc).

FTIR (neat): 3303, 2945, 2867, 1600, 1464, 1147, 1025, 998 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.98 (d, *J* = 2.1 Hz, 2H), 5.96 – 5.95 (m, 1H), 1.28 – 1.21 (m, 3H), 1.09 (d, *J* = 7.0 Hz, 18H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.3, 157.4, 100.4, 96.3, 18.0, 12.8 ppm.



5.153 **5.117**

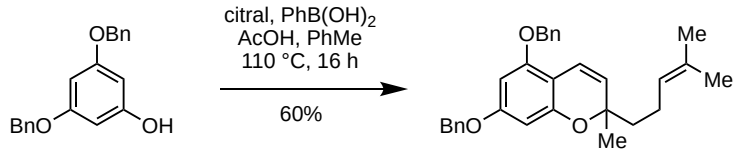
To a solution of **5.153** (500 mg, 1.77 mmol, 1.0 equiv.) in MeCN (20 mL) was added Cs_2CO_3 (576 mg, 1.77 mmol, 1.0 equiv.) and BnBr (0.45 mL, 3.71 mmol, 2.1 equiv.) at room temperature. After 24 h the reaction was diluted with Et_2O (20 mL), washed with distilled water (20 mL) and sat. brine (20 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was redissolved in THF (20 mL) and TBAF (1.76 mL, 1.77 mmol, 1.0 M THF, 1.0 equiv.) was added at room temperature. After 15 min, the reaction was then diluted with Et_2O (20 mL) and washed with sat. brine (40 mL). The organic layer was then dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* flash column chromatography on SiO_2 (5:1 hexanes/ EtOAc) then afforded **5.117** (83 mg, 15%) as a clear oil. Data for **5.117** matched that previously reported in the literature.[41]

Partial Data for 5.117:

Rf: 0.30 (3:1 hexanes/ EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 – 7.36 (m, 8H), 7.34 (t, *J* = 6.9 Hz, 2H), 6.25 (t, *J* = 2.1 Hz, 1H), 6.12 (d, *J* = 2.1 Hz, 2H), 5.28 (br s, 1H), 4.99 (s, 4H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.9, 157.5, 136.9, 128.7, 128.1, 127.7, 95.6, 95.0, 70.2 ppm.



5.117: 3,5-dimethoxy -phenol

5.113

To a solution of 3,5-dibenzylphenol (**5.117**) (83 mg, 0.270 mmol, 1.0 equiv.) in PhMe (15 mL) was added citral (0.05 mL, 0.270 mmol, 1.0 equiv.), $PhB(OH)_2$ (10 mg, 0.014 mmol, 5 mol%) and AcOH (0.05 mL, 0.054 mmol, 20 mol%). The reaction was stirred at 110 °C for 16 h. The mixture was cooled to room temperature, then concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (9:1 hexanes/ EtOAc) to give chromene **5.113** (66 mg, 60%) as a yellow oil.

Data for 5.113:

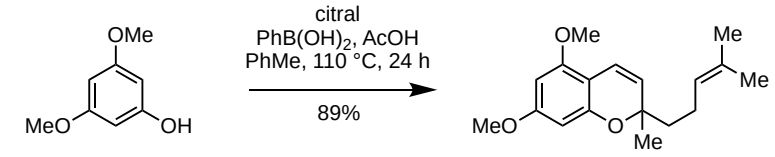
R_f: 0.65 (9:1 hexanes/ EtOAc).

FTIR (neat): 2966, 2922, 1610, 1575, 1434, 1373, 1100, 813 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 – 7.35 (m, 8H), 7.36 – 7.32 (m, 2H), 6.72 (d, *J* = 10.0 Hz, 1H), 6.18 (d, *J* = 2.3 Hz, 1H), 6.16 (d, *J* = 2.3 Hz, 1H), 5.40 (d, *J* = 10.0 Hz, 1H), 5.18 – 5.10 (m, 1H), 5.03 (s, 2H), 5.01 (s, 2H), 2.18 – 2.11 (m, 2H), 1.78 – 1.64 (m, 2H), 1.70 (s, 3H), 1.61 (s, 3H), 1.41 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.2, 155.4, 155.1, 137.1, 137.0, 131.7, 128.7, 128.6, 128.1, 128.0, 127.7, 127.5, 125.1, 124.4, 117.5, 104.8, 95.4, 93.5, 78.8, 70.4, 70.2, 41.3, 26.5, 25.8, 22.9, 17.8 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{30}H_{33}O_3$ 441.2924; found 441.2419.



5.118: 3,5-dimethoxy -phenol

5.114

To a solution of 3,5-dimethoxyphenol (**5.116**) (1.00 g, 6.49 mmol) in PhMe (30 mL) was added citral (1.11 mL, 6.49 mmol, 1.5 equiv.), $PhB(OH)_2$ (40 mg, 0.342 mmol, 5 mol%) and AcOH (0.08 mL, 1.29 mmol, 20 mol%). The reaction was stirred at 110 °C for 24 h. The mixture was cooled to room temperature, then concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (9:1 hexanes/ EtOAc) to give chromene **5.114** (1.66 g, 89%) as an orange oil. Data for **5.114** matched that previously reported in the literature.[42]

Data for 5.114:

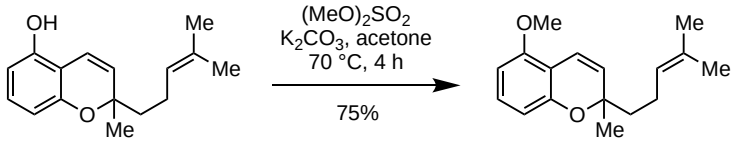
R_f: 0.80 (9:1 hexanes/ EtOAc).

FTIR (neat): 2966, 2925, 2840, 1611, 1578, 1495, 1202, 1146, 1113, 1050 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.61 (d, *J* = 10.0 Hz, 1H), 6.02 (d, *J* = 2.3 Hz, 1H), 5.99 (d, *J* = 2.3 Hz, 1H), 5.37 (d, *J* = 10.0 Hz, 1H), 5.12-5.08 (m, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 2.14-2.07 (m, 2H), 1.76-1.70 (m, 1H), 1.66 (s, 3H), 1.65-1.61 (m, 1H), 1.58 (s, 3H), 1.37 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.1, 156.2, 155.1, 131.7, 125.0, 124.4, 117.3, 104.2, 94.0, 91.5, 78.7, 55.7, 55.5, 41.3, 26.4, 25.8, 22.9, 17.8 ppm.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{24}O_3Na$ 311.1618; found 311.1618.



5.120 **5.127**

To a solution of **5.120** (1.50 g, 5.73 mmol, 1.0 equiv.)* in acetone (30 mL) was added K_2CO_3 (4.41 g, 20.1 mmol, 5.2 equiv.) and dimethyl sulfate (1.16 mL, 11.5 mmol, 2.0 equiv.). The solution was heated to reflux for 4 h, then cooled and distilled water (30 mL) added. The product was extracted with EtOAc (3 x 30 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography on SiO_2 (19:1 hexanes/ EtOAc) then afforded chromene **5.127** (1.19 mg, 75%) as a clear oil.

Data for 5.127:

R_f: 0.60 (9:1 hexanes/ Et_2O).

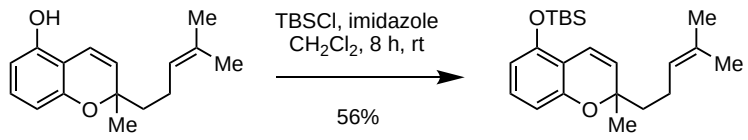
FTIR (neat): 2950, 1601, 1466, 1252, 1098, 751 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.03 (t, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 10.0 Hz, 1H), 6.45 – 6.40 (d, *J* = 8.2 Hz, 1H), 6.39 (d, *J* = 8.2 Hz, 1H), 5.52 (d, *J* = 10.0 Hz, 1H), 5.13 – 5.06 (m, 1H), 3.81 (s, 3H), 2.15 – 2.08 (m, 2H), 1.78 – 1.62 (m, 2H), 1.66 (s, 3H), 1.57 (s, 3H), 1.38 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 155.4, 154.1, 131.8, 129.0, 128.0, 124.3, 117.4, 110.6, 109.5, 102.9, 78.2, 55.8, 41.2, 26.4, 25.8, 22.9, 17.8 ppm.

HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{17}H_{21}O_2$ 257.1542; found 257.1546.

***5.120** was synthesized according to a literature procedure from Katakawa and co-workers, and a small sample was gifted to this project by PhD Student Lauren Murray.[43]



5.120 **5.128**

To a solution of **5.120** (1.00 g, 4.10 mmol, 1.0 equiv.)* in CH_2Cl_2 (40 mL) was added imidazole (330 mg, 4.92 mmol, 1.2 equiv.) and TBSCl (740 mg, 4.92 mmol, 1.2 equiv.) at room temperature. After 8 h the reaction was quenched upon addition of distilled H_2O (40 mL) and the product was extracted with CH_2Cl_2 (2 x 40 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 (19:1 hexanes/ EtOAc) then afforded chromene **5.128** (812 mg, 56%) as a clear oil.

Data for 5.128:

R_f: 0.60 (19:1 hexanes/ EtOAc).

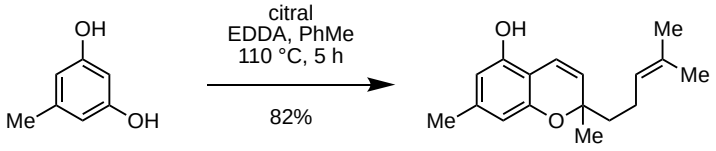
FTIR (neat): 2958, 2929, 1634, 1600, 1472, 1459, 1387,1287, 1217, 1153, 1084, 1056, 922 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92 (t, *J* = 8.1 Hz, 1H), 6.64 (d, *J* = 10.0 Hz, 1H), 6.41 (d, *J* = 8.2 Hz, 1H), 6.32 (d, *J* = 8.2 Hz, 1H), 5.51 (d, *J* = 10.0 Hz, 1H), 5.14 – 5.06 (m, 1H), 2.13 – 2.08 (m, 2H), 1.77 – 1.59 (m, 2H), 1.66 (s, 3H), 1.57 (s, 3H), 1.37 (s, 3H), 1.01 (s, 9H), 0.21 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.5, 151.59, 131.8, 128.7, 128.2, 124.4, 118.2, 113.5, 111.6, 109.7, 78.1, 41.3, 26.4, 26.0, 25.8, 22.9, 18.5, 17.8, -4.1 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{35}O_2Si$ 359.2401; found 359.2400.

***5.121** was synthesized according to a literature procedure from Katakawa and co-workers, and a small sample was gifted to this project by PhD Student Lauren Murray.[43]



5.67: orcinol **5.115**

To a solution of orcinol (**5.67**) (10.0 g, 81.0 mmol, 1.0 equiv.) in PhMe (250 mL) at room temperature was added citral (12.3 mL, 81.0 mmol, 1.0 equiv.) and EDDA (500 mg, 2.43 mmol, 3 mol%). The reaction was stirred at 110 °C for 5 h. The mixture was cooled to room temperature, then concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (8:1 hexanes/ EtOAc) to give chromene **5.115** (17.2 g, 82%) as an orange oil. Data for **5.115** matched that previously reported in the literature.[44]

Data for 5.115:

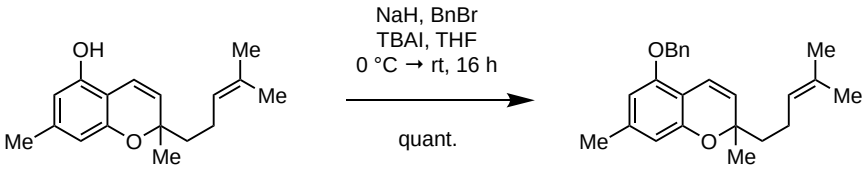
R_f: 0.40 (5:1 hexanes/ EtOAc).

FTIR (neat): 3387, 2970, 2924, 1625, 1578, 1509, 1450, 1377, 1330, 1250 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.61 (d, *J* = 10.0 Hz, 1H), 6.24 (s, 1H), 6.11 (s, 1H), 5.49 (d, *J* = 10.0 Hz, 1H), 5.10 (t, *J* = 7.2 Hz, 1H), 4.73 (br s, 1H), 2.20 (s, 3H), 2.13 – 2.07 (m, 2H), 1.75 – 1.70 (m, 1H), 1.66 (s, 3H), 1.65 – 1.61 (m, 1H), 1.58 (s, 3H), 1.37 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.3, 151.2, 139.7, 131.8, 127.4, 124.4, 116.9, 110.0, 108.5, 106.9, 78.4, 41.3, 26.4, 25.8, 22.9, 21.7, 17.8 ppm.

HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{17}H_{21}O_2$ 257.1547; found 257.1539.



5.115 **5.121**

To a solution of **5.115** (1.00 mg, 3.86 mmol, 1.0 equiv.) in THF (120 mL) was added NaH (240 mg, 4.63 mmol, 50% wt./ wt. 1.2 equiv.), TBAI (1.84 g, 4.63 mmol, 1.2 equiv.) and benzyl bromide (0.60 mL, 4.63 mmol, 1.2 equiv.) at 0 °C. The solution was then warmed to room temperature and left to stir. After 16 h, the reaction was quenched upon addition of distilled H_2O (60 mL) and the product was extracted with CH_2Cl_2 (60 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* flash column chromatography on SiO_2 (9:1 hexanes/ EtOAc) then afforded **5.121** (1.35 g, quant.) as a yellow oil.

Data for 5.121:

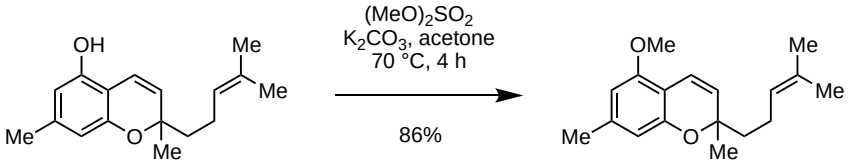
R_f: 0.70 (19:1 hexanes/ EtOAc).

FTIR (neat): 2968, 2920, 1613, 1571, 1452, 1375, 1329, 1231, 1102 900 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44 (d, *J* = 7.1 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.1 Hz, 1H), 6.73 (d, *J* = 10.0 Hz, 1H), 6.30 (s, 2H), 5.45 (d, *J* = 10.0 Hz, 1H), 5.13 – 5.07 (m, 1H), 5.04 (s, 2H), 2.26 (s, 3H), 2.15 – 2.05 (m, 2H), 1.73 – 1.61 (m, 2H), 1.66 (s, 3H), 1.58 (s, 3H), 1.37 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 154.4, 154.0, 139.5, 137.4, 131.7, 128.6, 128.0, 127.5, 126.9, 124.4, 117.6, 110.3, 108.4, 105.3, 78.3, 70.4, 41.3, 26.5, 25.8, 22.9, 22.2, 17.8 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{24}H_{29}O_2$ 349.2162; found 349.2158.



5.115 **5.126**

To a solution of **5.115** (5.11 g, 9.00 mmol, 1.0 equiv.) in acetone (150 mL) was added K_2CO_3 (6.45 g, 46.8 mmol, 5.2 equiv.) and dimethyl sulfate (1.70 mL, 17.9 mmol, 2.0 equiv.). The solution was heated to reflux for 4 h, then cooled and distilled water (150 mL) added. The product was extracted with EtOAc (3 x 150 mL), dried with $MgSO_4$, filtered and concentrated. Purification by flash column chromatography on SiO_2 (9:1 hexanes/ EtOAc) then afforded chromene **5.126** (4.64 g, 86%) as a clear oil. Data for **5.126** matched that previously reported in the literature.[45]

Data for 5.126:

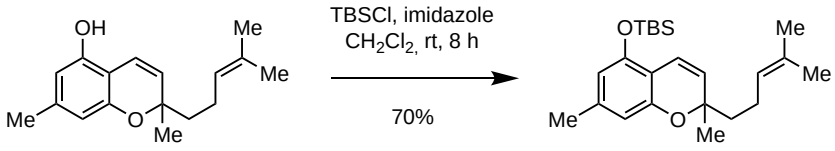
R_f: 0.50 (9:1 hexanes/ EtOAc).

FTIR (neat): 2967, 1613, 1572, 1453, 1387, 1229, 1144, 1024, 814 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.66 (d, *J* = 10.0, 1H), 6.28 (s, 1H), 6.22 (s, 1H), 5.46 (d, *J* = 10.0 Hz, 1H), 5.10 (t, *J* = 1.3 Hz, 1H), 3.80 (s, 3H), 2.27 (s, 3H), 2.16 – 2.05 (m, 2H), 1.76 – 1.61 (m, 2H), 1.73 (s, 3H), 1.37 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.2, 154.0, 139.5, 131.7, 126.9, 124.5, 117.4, 110.1, 108.0, 104.0, 78.2, 55.7, 41.3, 26.4, 25.8, 22.9, 22.1, 17.8 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{25}O_2$ 273.1849; found 273.1847.



5.115 **5.129**

To a solution of **5.115** (1.00 g, 3.87 mmol, 1.0 equiv.) in CH_2Cl_2 (40 mL) was added imidazole (310 mg, 4.64 mmol, 1.2 equiv.) and TBSCl (700 mg, 4.64 mmol, 1.2 equiv.) at room temperature. After 8 h the reaction was quenched upon addition of distilled water (40 mL) and the product was extracted with CH_2Cl_2 (2 x 40 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography on SiO_2 (19:1 hexanes/ EtOAc) then afforded chromene **5.129** (1.00 g, 70%) as a clear oil.

Data for 5.129:

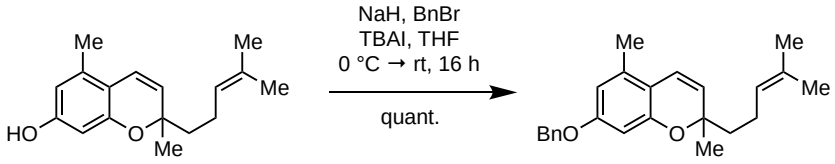
R_f: 0.15 (hexanes).

FTIR (neat): 2929, 1614, 1566, 1461, 1387, 1252, 1096, 839, 779 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.60 (d, *J* = 10.0 Hz, 1H), 6.26 (s, 1H), 6.14 (s, 1H), 5.44 (d, *J* = 10.0 Hz, 1H), 5.09 (ddt, *J* = 7.2, 5.7, 1.5 Hz, 1H), 2.20 (s, 3H), 2.15 – 2.04 (m, 2H), 1.75 – 1.61 (m, 2H), 1.66 (s, 3H), 1.57 (s, 3H), 1.36 (s, 3H), 1.00 (s, 9H), 0.20 (s, 6H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 154.2, 151.4, 139.2, 131.7, 127.0, 124.4, 118.2, 112.5, 110.8, 110.4, 78.1, 41.3, 26.4, 26.0, 25.8, 22.9, 21.8, 18.5, 17.8, -4.1 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{37}O_2Si$ 373.2557; found 373.2556.



5.59 **5.121**

To a solution of **5.59** (540 mg, 2.10 mmol, 1.0 equiv.) in THF (60 mL) was added NaH (120 mg, 2.52 mmol, 50% wt./ wt., 1.2 equiv.), TBAI (920 mg, 2.52 mmol, 1.2 equiv.) and benzyl bromide (0.30 mL, 2.52 mmol, 1.2 equiv.) at 0 °C. The solution was then warmed to room temperature. After 16 h, the reaction was quenched upon addition of distilled water (60 mL) and the product was extracted with CH_2Cl_2 (2 x 60 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* flash column chromatography on SiO_2 (19:1 hexanes/ EtOAc) then afforded **5.121** (718 mg, quant.) as a yellow oil.

Data for 5.121:

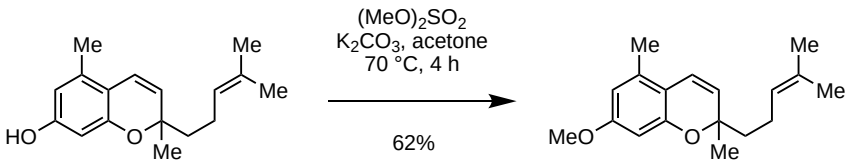
R_f: 0.60 (19:1 hexanes/ EtOAc).

FTIR (neat): 2968, 1607, 1328, 1146, 1028, 988 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44 – 7.40 (m, 2H), 7.38 (t, *J* = 8.5, 2H), 7.32 (t, *J* = 7.2 Hz, 1H), 6.48 (d, *J* = 10.0 Hz, 1H), 6.34 (d, *J* = 2.5 Hz, 1H), 6.32 (d, *J* = 2.5 Hz, 1H), 5.47 (d, *J* = 10.1 Hz, 1H), 5.10 (t, *J* = 1.5 Hz, 1H), 5.00 (s, 2H), 2.25 (s, 3H), 2.16 – 2.04 (m, 2H), 1.74 – 1.62 (m, 1H), 1.66 (s, 3H), 1.58 (s, 3H), 1.37 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 159.3, 154.7, 137.2, 135.1, 131.8, 128.7, 128.0, 127.6, 126.8, 124.4, 119.7, 113.5, 109.4, 1007, 78.1, 70.0, 41.2, 26.4, 25.8, 22.9, 18.8, 17.8 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{24}H_{29}O_2$ 349.2166; found 349.2162.



5.59 **5.124**

To a solution of **5.59** (1.0 g, 3.87 mmol, 1.0 equiv.) in acetone (30 mL) was added K_2CO_3 (6.45 g, 20.1 mmol, 5.2 equiv.) and dimethyl sulfate (1.70 mL, 20.1 mmol, 2.0 equiv.). The solution was heated to reflux for 4 h, then cooled and distilled water (30 mL) added. The product was extracted with EtOAc (3 x 30 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 (9:1 hexanes/ EtOAc) afforded chromene **5.124** (646 mg, 62%) as a clear oil.

Data for 5.124:

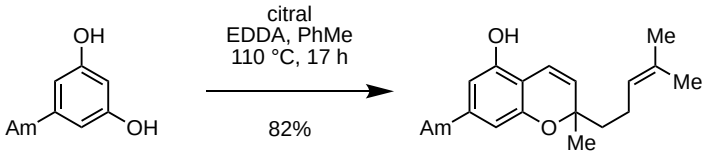
R_f: 0.65 (9:1 hexanes/ EtOAc).

FTIR (neat): 2923, 1608, 1491, 1330, 1147, 1052, 838 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.66 (d, *J* = 10.0 Hz, 1H), 6.28 (s, 1H), 6.22 (s, 1H), 5.46 (d, *J* = 10.0 Hz, 1H), 5.10 (t, *J* = 5.7 Hz, 1H), 3.80 (s, 3H), 2.27 (s, 3H), 2.17 – 2.09 (m, 2H), 1.78 – 1.63 (m, 2H), 1.66 (s, 3H), 1.58 (s, 3H), 1.37 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 160.1, 154.7, 135.1, 131.8, 126.7, 124.4, 119.7, 113.2, 108.6, 99.7, 78.1, 55.3, 41.2, 26.4, 25.8, 22.9, 18.8, 17.8 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{25}O_2$ 273.1849; found 273.1845.



5.119: olivetol **5.116:** cannabichromene

To a solution of olivetol (**5.119**)(4.00 g, 22.2 mmol, 1.0 equiv.) in PhMe (150 mL) was added citral (4.60 mL, 26.6 mmol, 1.2 equiv.) and EDDA (400 mg, 2.2 mmol, 10 mol%). The reaction mixture was stirred at 110 °C for 17 hr, cooled to room temperature, concentrated *in vacuo,* and purified by flash column chromatography on SiO_2 (10:1 hexanes/ EtOAc) to afford cannabichromene (**5.116**) (5.73 g, 82%) as an orange oil. Data for **5.116** matched that previously reported in literature.[46]

Data for 5.116:

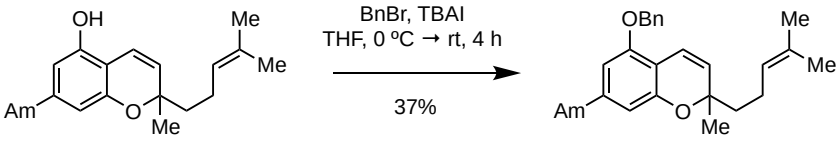
R_f: 0.20 (10:1 hexanes/ EtOAc).

FTIR (neat): 3392, 2926, 1621, 1579, 1426, 1051, 754 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.61 (d, *J* = 10.0 Hz, 1H), 6.25 (s, 1H), 6.12 (s, 1H), 5.49 (d, *J* = 10.0 Hz, 1H), 5.12-5.07 (m, 1H), 4.64 (br s, 1H), 2.45 (t, *J* = 7.7 Hz, 2H), 2.14-2.06 (m, 2H), 1.76-1.64 (m. 2H), 1.66 (s, 3H), 1.58 (s, 3H), 1.58-1.54 (m, 2H), 1.38 (s, 3H), 1.36-1.31 (m, 2H), 1.31-1.25 (m, 2H), 0.88 (t, *J* = 6.9, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.2, 151.0, 144.9, 131.7, 127.4, 124.3, 116.9, 109.3, 107.7, 107.1, 78.3, 41.2, 36.1, 31.6, 30.8, 26.4, 25.8, 22.9, 22.7, 17.8, 14.2 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{31}O_2$ 315.2319; found 315.2319.



5.116: cannabichromene

5.123

To a solution of cannabichromene (**5.116**) (300 mg, 0.96 mmol, 1.0 equiv.) in THF (30 mL) was added NaH (50 mg, 1.11 mmol, 50% wt./ wt., 1.2 equiv.) at 0 °C, followed by TBAI (420 mg, 1.25 mmol) and BnBr (140 mg, 1.15 mmol). The reaction mixture stirred and warmed to room temperature over 4 hr. The reaction was quenched with distilled water (30 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried with $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash column chromatography on SiO_2 (19:1 hexanes/ EtOAc) to afford **5.123** (157 mg, 37%) as a crystalline orange solid.

Data for 5.123:

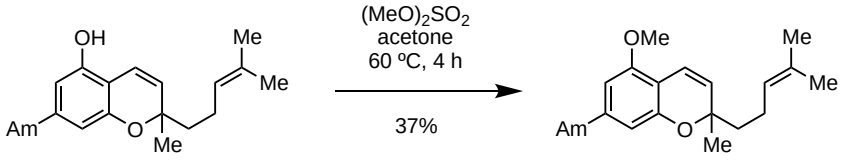
R_f: 0.40 (19:1 hexanes/ EtOAc).

FTIR (neat): 2960, 2927, 2857, 1612, 1589, 1428, 1110, 732, 695 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.35-7.30 (m, 1H), 6.74 (d, *J* = 10.0 Hz, 1H), 6.23 (s, 1H), 6.31 (s, 1H), 5.46 (d, *J* = 10.0 Hz, 1H), 5.11 (t, 7.0 Hz, 1H), 5.06 (s, 2H), 2.50 (t, *J* = 7.7 Hz, 2H), 2.16-2.08 (m, 2H), 1.77- 1.62 (m, 2H), 1.67 (s, 3H), 1.60 (s, 3H), 1.39 (s, 3H), 1.58-1.54 (m, 2H), 1.36-1.33 (m, 2H), 1.33-1.27 (m, 2H), 0.90 (t, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.4, 154.0, 144.7, 137.5, 131.7, 128.6, 127.9, 127.5, 127.0, 124.4, 117.7, 109.6, 108.6, 104.8, 78.2, 70.4, 41.3, 36.5, 31.6, 31.0, 26.5, 25.8, 22.9, 22.7, 17.8, 14.2 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{28}H_{37}O_2$ 405.2788; found 405.2784.



5.116: cannabichromene **5.125**

To a solution of cannabichromene (**5.116**) (300 mg, 0.95 mmol, 1.0 equiv.) in acetone (30 mL) was added K_3CO_3 (670 mg, 4.96 mmol, 5.0 equiv.) and dimethyl sulfate (180 mg, 1.91 mmol, 2.0 equiv.). The reaction mixture was stirred at 60 °C for 4 hr. The reaction was quenched with distilled water (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried with $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash column chromatography on SiO_2 (19:1 hexanes/ EtOAc) to afford methoxy olivetol chromene (**5.125**) (250 mg, 81%) as a yellow oil. Data for **5.116** matched that previously reported in the literature.[47]

Data for 5.125:

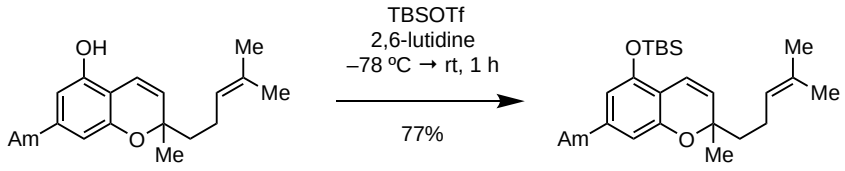
R_f: 0.60 (9:1 hexanes/ EtOAc).

FTIR (neat): 2928, 2871, 2857, 1612, 1569, 1451, 1423, 1217, 1100, 908, 822, 774, 733 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.66 (d, *J* = 9.9 Hz, 1H), 6.29 (s, 1H), 6.21 (s, 1H), 5.45 (d, *J* = 10.0 Hz, 1H), 5.12-5.07 (m, 1H), 3.80 (s, 3H), 2.50 (t, *J* = 7.6 Hz, 2H), 2.14-2.06 (m, 2H), 1.76-1.63 (m, 2H), 1.66 (s, 3H), 1.61-1.58 (m, 2H), 1.60 (s, 3H), 1.37 (s, 3H), 1.36-1.32 (m, 2H), 1.32-1.29 (m, 2H), 0.89 (t, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.2, 153.9, 144.7, 131.7, 126.9, 124.4, 117.4, 109.3, 108.2, 103.3, 78.2, 55.7, 41.2, 36.6, 31.7, 31.0, 26.4, 25.8, 22.9, 22.7, 17.8, 14.2 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{33}O_2$ 329.2475; found 329.2477.



5.115: cannabichromene **5.130**

To a solution of cannabichromene (**5.115**) (300 mg, 0.95 mmol, 1.0 equiv.) in dry CH_2Cl_2 (20 mL) was added 2,6-lutidine (0.22 g, 1.9 mmol, 2.0 equiv.) and TBSOTf (0.33 g, 1.4 mmol, 1.5 equiv.). The reaction mixture was stirred at –78 °C and slowly warmed to room temperature over 1 hr. The reaction was quenched upon addition of sat. $NH_4Cl_{(aq)}$ (3 x 20 mL) and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash column chromatography on SiO_2 (30:1 hexanes/ EtOAc) then afforded **5.130** (312 mg, 77%) as a yellow oil.

Data for 5.130:

R_f: 0.50 (19:1 hexanes/ EtOAc).

FTIR (neat): 2929, 1612, 1563, 1462, 1426, 1387, 1253, 1214, 1103, 1005, 836, 778, 759 cm^{-1}.

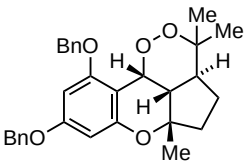
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.61 (d, *J* = 10.0 Hz, 1H), 6.28 (s, 1H), 6.16 (s, 1H), 5.45 (d, *J* = 10.0 Hz, 1H), 5.13-5.08 (m, 1H), 2.45 (t, *J* = 7.7 Hz, 2H), 2.14-2.07 (m, 2H), 1.75-1.60 (m, 2H), 1.67 (s, 3H), 1.60 (s, 3H), 1.57-1.53 (m, 2H), 1.37 (s, 3H), 1.35-1.32 (m, 2H), 1.32-1.28 (m, 2H), 1.01 (s, 9H), 0.89 (t, *J* = 6.7 Hz, 3H), 0.21 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 151.1, 151.3, 144.3, 131.7, 127.1, 124.4, 118.3, 111.9, 111.0, 109.8, 78.1, 41.3, 36.1, 31.6, 30.8, 26.4, 26.1, 26.0, 25.8, 22.9, 22.7, 18.5, 17.8, 14.2 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{45}O_2Si$ 429.3183; found 429.3183.

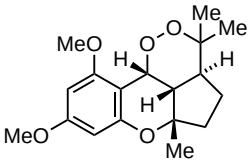
5.4.3 General Method for the Synthesis of Endoperoxides (5.131a – 5.142a)

To a solution of chromene (1.0 equiv.) in DCE (0.01 M) was added 4-MeO-TPT (**5.56**) (2 mol %) and the reaction mixture was stirred at 0 °C under 1 atm of O_2 while exposed to a 470 nm blue LED lamp. The reaction mixture was then concentrated *in vacuo* and purified by flash column chromatography on SiO_2 (eluent as specified) to afford the corresponding endoperoxides and cyclobutane product (**5.131 – 5.42**).



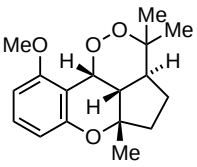
5.131a 34%

5.131: Reaction left for 2 h. Purification by flash column chromatography on SiO_2 (9:1 hexanes/ EtOAc) afforded (**5.131a**) (26 mg, 34%) as a clear oil. **Data for 5.131a: R_f:** 0.50 (9:1 hexanes/ EtOAc). **FTIR (neat):** 2969, 1612, 1587, 1498, 1453, 1434, 1096, 734 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.45 (d, *J* = 7.0 Hz, 2H), 7.42 – 7.25 (m, 8H), 6.20 (d, *J* = 2.3 Hz, 1H), 6.12 (d, *J* = 2.3 Hz, 1H), 5.76 (d, *J* = 8.8 Hz, 1H), 5.12 (d, *J* = 12.2 Hz, 1H), 5.01 (d, *J* = 12.1 Hz, 1H), 4.97 (d, *J* = 5.9 Hz, 2H), 2.60 – 2.52 (m, 1H), 2.30 – 2.23 (m, 1H), 2.09 (dd, *J* = 13.4, 8.8 Hz, 1H), 2.04 – 1.97 (m, 1H), 1.85 – 1.77 (m, 1H), 1.47 (dt, *J* = 12.0, 6.0 Hz, 1H), 1.35 (s, 3H), 1.29 (s, 3H), 1.12 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 161.2, 159.9, 156.7, 137.2, 136.8, 128.7, 128.6, 128.2, 127.8, 127.7, 127.1, 100.8, 96.4, 94.7, 84.9, 82.6, 72.0, 70.3, 70.3, 70.2, 70.2, 70.2, 46.1, 45.7, 39.7, 27.1, 22.9, 22.5, 19.3 ppm. **HRMS:** calculated for $C_{30}H_{33}O_5$ $[M+H]^+$ 473.2323, found 473.2325.



5.132a 74%

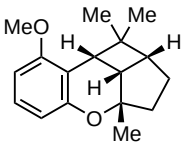
5.132: Reaction left for 1 h. Purification by flash column chromatography on SiO_2 (19:1 hexanes/ EtOAc) afforded (**5.132a**) (82 mg, 74%) as a white solid. **Data for 5.132a: MP:** 138 – 142 °C. **R_f:** 0.20 (9:1 hexanes/ EtOAc). **FTIR (neat):** 3109, 1702, 1605, 1451, 1398, 1234, 1180, 1101, 870, 786 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 6.04 (d, *J* = 2.3 Hz, 1H), 6.00 (d, *J* = 2.3 Hz, 1H), 5.64 (d, *J* = 8.8 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 2.54-2.47 (m, 1H), 2.23 (ddd, *J* = 14.6, 9.3, 7.1 Hz, 1H), 2.05 (dd, *J* = 13.4, 8.8 Hz, 1H), 1.99 (ddd, *J* = 14.6, 11.4, 3.3 Hz, 1H), 1.82-1.74 (m, 1H), 1.49-1.41 (m, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 1.08 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 162.0, 160.9, 156.5, 99.9, 94.9, 92.5, 84.8, 82.5, 72.0, 55.8, 55.3, 45.9, 45.7, 39.7, 27.0, 22.9, 22.5, 19.1 ppm. **HRMS:** calculated for $C_{18}H_{25}O_5$ $[M+H]^+$ 321.1697, found 321.1699.



5.133a 4%

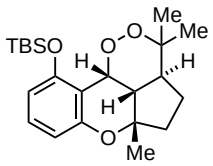
5.133: Reaction left for 5 h. Purification by flash column chromatography on SiO_2 (9:1 hexanes/ EtOAc) afforded (**5.133a**) (10 mg, 4%) as a clear oil and (**5.134b**) (42 mg, 16%) as a clear oil. **Data for 5.133a: R_f:** 0.30 (9:1 hexanes/ EtOAc). **FTIR (neat):** 2968, 1605, 1588, 1468, 1249, 1249, 1089 cm^{-1}. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.16 (t, *J* = 8.2 Hz, 1H), 6.46 (d, *J* = 8.2 Hz, 1H), 6.45 (d, *J* = 8.2 Hz, 1H), 5.71 (d, *J* = 8.7 Hz, 1H), 3.82 (s, 3H),

2.56 – 2.50 (m, 1H), 2.30 – 2.23 (m, 1H), 2.09 (dd, *J* = 13.3, 8.7 Hz, 1H), 2.03 – 1.97 (m, 1H), 1.83 – 1.78 (m, 1H), 1.51 – 1.38 (m, 2H), 1.31 (s, 3H), 1.28 (s, 3H), 1.11 (s, 3H) ppm. **^{13}C NMR (150 MHz, $CDCl_3$):** δ 160.1, 155.7, 130.6, 111.2, 107.2, 103.5, 84.6, 82.8, 72.2, 56.0, 55.4, 45.8, 39.7, 27.0, 22.9, 22.5, 19.1 ppm. **HRMS:** calculated for $C_{17}H_{22}O_4$ $[M-H]^-$ 289.1445, found 289.1420.



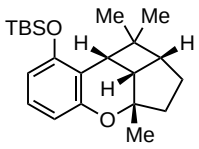
5.133b 16%

Partial Data for 5.133b: R_f: 0.80 (9:1 hexanes/ EtOAc). **FTIR (neat):** 2958, 1674, 1581, 1462, 1137, 1087, 912 cm^{-1}. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.05 (t, *J* = 8.2 Hz, 1H), 6.50 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.41 (dd, *J* = 8.1, 1.0 Hz, 1H), 3.77 (s, 3H), 3.12 (d, *J* = 9.6 Hz, 1H), 2.56 (dd, *J* = 9.7, 7.3 Hz, 1H), 2.38 (t, *J* = 7.3 Hz, 1H), 1.69 – 1.59 (m, 2H), 1.62 – 1.57 (m, 2H), 1.38 (s, 3H), 1.35 (s, 3H), 0.70 (s, 3H) ppm. **^{13}C NMR (150 MHz, $CDCl_3$):** δ 158.4, 154.1, 127.1, 113.2, 111.0, 102.1, 83.3, 55.1, 46.5, 39.3, 38.0, 37.9, 36.6, 33.9, 27.9, 25.9, 17.9 ppm.



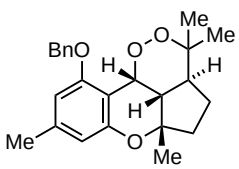
5.134a 8%

5.134: Reaction left for 48 h. Purification by flash column chromatography on SiO_2 (19:1 hexanes/ EtOAc) afforded (**5.134a**) (16 mg, 8%) and (**5.134b**) (38 mg, 19%). **Data for 5.134a: R_f:** 0.50 (9:1 hexanes/ EtOAc). **FTIR (neat):** 2995, 1603, 1583, 1470, 1375, 1361, 1243, 1171, 1046, 1059 cm^{-1}. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.05 (t, *J* = 8.2 Hz, 1H), 6.45 (d, *J* = 8.1 Hz, 1H), 6.41 (d, *J* = 8.1 Hz, 1H), 5.63 (d, *J* = 8.8 Hz, 1H), 2.59 – 2.49 (m, 1H), 2.29 – 2.22 (m, 1H), 2.07 (dd, *J* = 13.4, 8.8 Hz, 1H), 2.58 – 2.50 (m, 1H), 2.28 – 2.23 (m, 1H), 1.49 – 1.45 (m, 1H), 1.31 (s, 3H), 1.27 (s, 3H), 1.08 (s, 3H), 1.03 (s, 9H), 0.27 (s, 3H), 0.21 (s, 3H) ppm. **^{13}C NMR (150 MHz, $CDCl_3$):** δ 156.5, 156.0, 130.3, 111.9, 111.4, 110.3, 84.4, 82.4, 72.0, 46.3, 45.7, 39.8, 27.1, 26.0, 22.9, 22.4, 19.4, 18.5, -4.1 ppm. **HRMS:** calculated for $C_{22}H_{35}O_4Si$ $[M+H]^+$ 391.2299, found 391.2297.



5.134b 19%

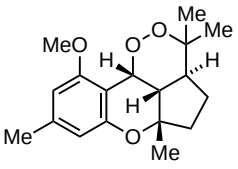
Data for 5.134b: R_f: 0.60 (9:1 hexanes/ EtOAc). **FTIR (neat):** 2951, 1582, 1459, 1245, 1053, 838 cm^{-1}. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.94 (t, *J* = 8.1 Hz, 1H), 6.50 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.40 (dd, *J* = 8.1, 1.1 Hz, 1H), 3.20 (d, *J* = 9.6 Hz, 1H), 2.55 (dd, *J* = 9.6, 7.9 Hz, 1H), 2.43 – 2.35 (m, 1H), 2.05 – 1.94 (m, 1H), 1.75 – 1.66 (m, 1H), 1.65 – 1.59 (m, 2H), 1.38 (s, 3H), 1.34 (s, 3H), 1.00 (s, 9H), 0.70 (s, 3H), 0.28 (s, 3H), 0.23 (s, 3H) ppm. **^{13}C NMR (150 MHz, $CDCl_3$):** δ 154.7, 126.6, 116.4, 111.4, 110.9, 83.5, 46.7, 39.9, 39.1, 39.0, 36.4, 34.3, 27.0, 26.3, 25.6, 18.8, 18.4, -2.8, -3.6 ppm. **HRMS:** calculated for $C_{22}H_{35}O_2Si$ $[M+H]^+$ 359.2401, found 359.32400.



5.135a 16%

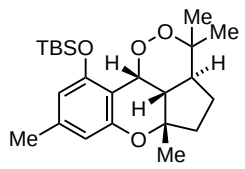
5.135: Reaction left for 5 h. Purification by flash column chromatography on SiO_2 (19:1 hexanes/ EtOAc) afforded (**5.135a**) (35 mg, 16%). **Data for 5.135a: R_f:** 0.40 (9:1 hexanes/ EtOAc). **FTIR (neat):** 2969, 1617, 1582, 1453, 1361, 1166, 1097 cm^{-1}. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.47 (d, *J* = 7.0 Hz, 2H), 7.37 (t, *J* = 7.6

Hz, 2H), 7.29 (d, *J* = 7.4 Hz, 1H), 6.34 (s, 1H), 6.31 (s, 1H), 5.77 (d, *J* = 8.6 Hz, 1H), 5.15 (d, *J* = 12.1 Hz, 1H), 5.04 (d, *J* = 12.2 Hz, 1H), 2.58 – 2.51 (m, 1H), 2.25 (s, 3H), 2.09 (dd, *J* = 13.4, 8.7 Hz, 1H), 2.02 – 1.96 (m, 1H), 1.82 – 1.77 (m, 1H), 1.50 – 1.41 (m, 2H), 1.33 (s, 3H), 1.27 (s, 3H), 1.11 (s, 3H) ppm. **^{13}C NMR (150 MHz, $CDCl_3$):** δ 159.0, 155.6, 141.1, 137.5, 128.7, 128.6, 127.7, 127.1, 111.9, 108.5, 106.3, 84.5, 82.6, 72.1, 70.4, 45.7, 39.7, 27.1, 22.9, 22.5, 22.0, 19.3 ppm. **HRMS:** calculated for $C_{24}H_{29}O_4$ $[M+H]^+$ 381.2060, found 381.2060.



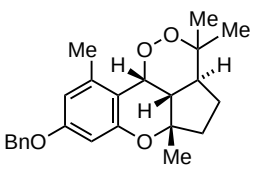
5.136a 11%

5.136: Reaction left for 4 h. Purification by flash column chromatography on SiO_2 (19:1 hexanes/ EtOAc) afforded (**5.136**) (42 mg, 11%) as a yellow oil. **Data for 5.136: MP:** 138 – 142 °C. **R_f:** 0.25 (19:1 hexanes/ EtOAc). **R_f:** 0.45 (9:1 hexanes/ EtOAc). **FTIR (neat):** 2968, 1617, 1582, 1461, 1417, 1361, 1229, 1147, 1055, 817 cm^{-1}. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.29 (s, 1H), 6.27 (s, 1H), 5.67 (d, *J* = 8.7 Hz, 1H), 3.80 (s, 3H), 2.51 (td, *J* = 12.6, 7.6 Hz, 1H), 2.27 (s, 3H), 2.26 – 2.22 (m, 1H), 2.07 (dd, *J* = 13.4, 8.8 Hz, 1H), 1.98 (ddd, *J* = 14.7, 11.4, 3.3 Hz, 1H), 1.82 – 1.76 (m, 1H), 1.49 – 1.41 (m, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 1.09 (s, 3H) ppm. **^{13}C NMR (150 MHz, $CDCl_3$):** δ 159.9, 155.4, 141.1, 111.5, 104.7, 104.2, 84.4, 82.6, 72.1, 55.9, 46.0, 45.7, 39.7, 27.0, 22.9, 22.5, 22.0, 19.1 ppm. **HRMS:** calculated for $C_{18}H_{25}O_4$ $[M+H]^+$ 305.1747, found 305.1745.



5.137a 44%

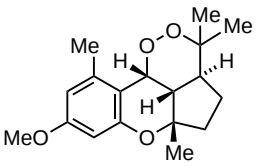
5.137: Reaction left for 6 h. Purification by flash column chromatography on SiO_2 (9:1 hexanes/ EtOAc) afforded (**5.137a**) (1.16 g, 44%) as a clear oil. **R_f:** 0.40 (19:1 hexanes/ EtOAc). **FTIR (neat):** 2961, 1616, 1577, 1461, 1361, 1251, 1166, 1085, 1003, 838, 780 cm^{-1}. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.29 (d, *J* = 1.6 Hz, 1H), 6.24 (d, *J* = 1.6 Hz, 1H), 5.60 (d, *J* = 8.8 Hz, 1H), 2.53 (ddd, *J* = 13.4, 11.9, 7.6 Hz, 1H), 2.28 – 2.23 (m, 1H), 2.22 (s, 3H), 2.05 (dd, *J* = 13.4, 8.8 Hz, 1H), 1.99 (ddd, *J* = 14.7, 11.5, 3.3 Hz, 1H), 1.82 – 1.75 (m, 1H), 1.50 – 1.42 (m, 1H), 1.32 (s, 3H), 1.27 (s, 3H), 1.08 (s, 3H), 1.04 (s, 9H), 0.27 (s, 3H), 0.22 (s, 3H) ppm. **^{13}C NMR (150 MHz, $CDCl_3$):** δ 156.2, 155.7, 140.7, 112.9, 112.0, 107.3, 84.2, 82.3, 71.9, 46.2, 45.7, 39.8, 27.0, 22.9, 22.4, 21.7, 19.4, 18.5, -4.1, -4.1 ppm. **HRMS:** calculated for $C_{23}H_{37}O_4Si$ $[M+H]^+$ 405.2456, found 405.2457.



5.138a 45%

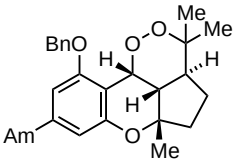
5.138: Reaction left for 6 h. Purification by flash column chromatography on SiO_2 (19:1 hexanes/ EtOAc) afforded (**5.138a**) (60 mg, 45%) as a clear oil. **Data for 5.138a: R_f:** 0.40 (9:1 hexanes/ EtOAc). **FTIR (neat):** 2969, 1609, 1582, 1453, 1143, 840 732 cm^{-1}. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.43 – 7.37 (m, 4H), 7.35 – 7.32 (m, 1H), 6.47 (d, *J* = 2.6 Hz, 1H), 6.33 (d, *J* = 2.6 Hz, 1H), 5.57 (d, *J* = 8.6 Hz, 1H), 5.00 (d, *J* = 4.6 Hz,

2H), 2.58 – 2.46 (m, 1H), 2.38 (s, 3H), 2.29 – 2.24 (m, 1H), 2.10 (dd, *J* = 13.4, 8.6 Hz, 1H), 2.01 (ddd, *J* = 14.8, 11.4, 3.2 Hz, 1H), 1.85 – 1.80 (m, 1H), 1.51 – 1.41 (m, 1H), 1.33 (s, 3H), 1.30 (s, 3H), 1.14 (s, 3H) ppm. **^{13}C NMR (150 MHz, $CDCl_3$):** δ 160.1, 155.9, 141.4, 137.0, 128.7, 128.0, 127.6, 111.0, 109.4, 101.6, 84.2, 82.8, 74.1, 69.9, 45.6, 39., 26.9, 24.0, 23.0, 22.6, 19.6, 19.1 ppm. **HRMS:** calculated for $C_{24}H_{29}O_4$ $[M+H]^+$ 381.2060, found 381.2060.



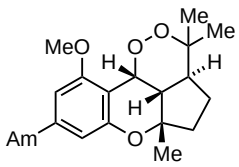
5.139a 29%

5.139a: Reaction left for 5 h. Purification by flash column chromatography on SiO_2 (19:1 hexanes/ EtOAc) afforded (**5.139a**) (65 mg, 29%) as a clear oil. **Data for 5.139a: R_f:** 0.25 (19:1 hexanes/ EtOAc). **FTIR (neat):** 2927, 1611, 1582, 1143, 1048, 951, 839 cm^{-1}. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.36 (d, *J* = 2.6 Hz, 1H), 6.23 (d, *J* = 2.6 Hz, 1H), 5.55 (d, *J* = 8.6 Hz, 1H), 3.74 (s, 3H), 2.54 – 2.47 (m, 1H), 2.36 (s, 3H), 2.29 – 2.21 (m, 1H), 2.09 (dd, *J* = 13.4, 8.6 Hz, 1H), 2.00 (ddd, *J* = 14.6, 11.4, 3.2 Hz, 1H), 1.86 – 1.77 (m, 1H), 1.51 – 1.43 (m, 1H), 1.31 (s, 3H), 1.29 (s, 3H), 1.12 (s, 3H) ppm. **^{13}C NMR (150 MHz, $CDCl_3$):** δ 160.8, 155.9, 141.4, 110.3, 109.1, 100.7, 84.2, 82.8, 74.1, 55.2, 46.1, 45.7, 39.6, 26.9, 22.9, 22.6, 19.6, 19.1 ppm. **HRMS:** calculated for $C_{18}H_{25}O_4$ $[M+H]^+$ 305.1747, found 305.1740.



5.140a 6%

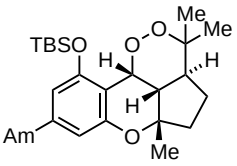
5.140: Reaction left for 5 h. Purification by flash column chromatography on SiO_2 (19:1 hexanes/ EtOAc) afforded (**5.140a**) (11 mg, 6%) as a clear oil. **Data for 5.140a: R_f:** 0.40 (19:1 hexanes/ EtOAc). **FTIR (neat):** 2931, 1165, 1150, 952, 825 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.48 (d, *J* = 7.7 Hz, 2H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.7 Hz, 1H), 6.35 (s, 1H), 6.32 (s, 1H), 5.77 (d, *J* = 8.7 Hz, 1H), 5.16 (d, *J* = 12.0 Hz, 1H), 5.04 (d, *J* = 12.1 Hz, 1H), 2.60-2.53 (m, 1H), 2.51-5.47 (m, 2H), 2.26 (ddd, *J* = 14.5, 9.3, 7.1 Hz, 1H), 2.09 (dd, *J* = 13.4, 8.7 Hz, 1H), 2.00 (ddd, *J* = 14.7, 11.5, 3.3 Hz, 1H), 1.84-1.78 (m, 1H), 1.59-1.55 (m, 2H), 1.51-1.42 (m, 2H), 1.34 (s, 3H), 1.32-1.28 (m, 3H), 1.28 (s, 3H) 1.12 (s, 3H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 158.9, 155.5, 146.2, 137.5, 128.6, 127.6, 127.2, 111.2, 105.8, 105.1, 84.5, 82.6, 72.2, 70.4, 46.1, 45.7, 39.7, 36.4, 31.6, 30.7, 27.1, 22.9, 22.7, 22.5, 19.3, 14.2 ppm. **HRMS:** calculated for $C_{28}H_{36}O_4$ $[M+H]^+$ 437.2685, found 437.2686.



5.141a 35%

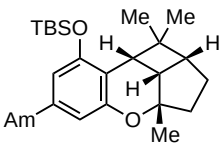
5.141a: Reaction left for 6 h. Purification by flash column chromatography on SiO_2 (19:1 hexanes/ EtOAc) afforded (**5.141a**) (88 mg, 35%) as a clear oil. **Data for 5.141a: R_f:** 0.20 (9:1 hexanes/ EtOAc). **FTIR (neat):** 2961, 2931, 2873, 2859, 1166, 1147, 1090, 1025, 974, 931, 907, 826 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 6.30 (s, 1H), 6.28 (s, 1H), 5.68 (d, *J* = 8.7 Hz, 1H), 3.81 (s, 3H), 2.57-2.53 (m, 1H), 2.53-2.49 (m, 2H), 2.25 (ddd, *J* = 14.5, 9.4, 7.1 Hz, 1H), 2.07 (dd, *J* = 13.4, 8.7 Hz, 1H), 1.99 (dd, *J* = 14.7, 11.4, 3.3 Hz, 1H), 1.80 (dddd, *J* = 12.5, 9.2, 7.6, 3.2 Hz, 1H), 1.62-1.56 (m, 2H), 1.50-1.42 (m, 1H), 1.35-1.30 (m, 4H), 1.31 (s,

3H), 1.27 (s, 3H), 1.10 (s, 3H), 0.89 (t, *J* = 6.8 Hz, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 159.9, 155.4, 146.2, 110.8, 104.5, 104.1, 84.5, 82.7, 72.3, 55.9, 46.0, 45.7, 39.8, 36.4, 31.7, 30.8, 27.0, 23.0, 22.7, 22.5, 19.2, 14.2 ppm. **HRMS:** calculated for $C_{22}H_{33}O_4$ $[M+H]^+$ 361.2373, found 361.2373.



5.142a 13%

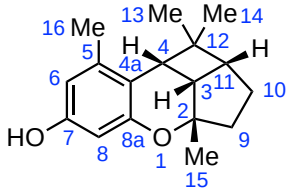
5.142: Reaction left for 6 h. Purification by flash column chromatography on SiO_2 (19:1 hexanes/ EtOAc) afforded (**5.142a**) (25 mg, 13%) as a clear oil and (**5.142b**) (82 mg, 44%) as a white solid **Data for 5.142a: R_f:** 0.40 (19:1 hexanes/ EtOAc). **FTIR (neat):** 2956, 2929, 2858, 1615, 1575, 1463, 1429, 1362, 1252, 1166, 1075, 839, 781cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 6.29 (d, *J* = 1.5 Hz, 1H), 6.24 (d, *J* = 1.5 Hz, 1H), 5.60 (d, *J* = 8.9 Hz, 1H), 2.57-2.50 (m, 1H), 2.47 (td, *J* = 7.5, 2.4 Hz, 1H), 2.24 (ddd, *J* = 14.5, 9.4, 7.0 Hz, 1H), 2.05 (dd, *J* = 13.5, 8.9 Hz, 1H), 1.98 (ddd, *J* = 14.7, 11.4, 3.3 Hz, 1H), 1.82-1.74 (m, 1H), 1.59-1.53 (m, 2H), 1.50-1.42 (m, 2H), 1.35-1.31 (m, 2H), 1.31 (s, 3H), 1.30-1.28 (m, 2H), 1.26 (s, 3H), 1.08 (s, 3H), 1.03 (s, 9H), 0.88 (t, *J* = 6.9 Hz, 3H), 0.26 (s, 3H), 0.21 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 156.2, 155.6, 145.8, 112.4, 111.3, 107.5, 84.3, 82.3, 72.0, 46.3, 45.7, 39.8, 36.0, 31.6, 30.7, 27.1, 26.1, 22.9, 22.7, 22.4, 19.4, 18.5, 14.2, -4.0 ppm. **HRMS:** calculated for $C_{27}H_{45}O_4Si$ $[M+H]^+$ 461.3082, found 461.3084.



5.142b 44%

Data for 5.142b: MP: 138 – 142 °C. **R_f:** 0.70 (19:1 hexanes/ EtOAc). **FTIR (neat):** 2955, 2930, 2859, 1615, 1572, 1462, 1424, 1254, 1136, 1082, 1064, 907, 836, 781 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 6.34 (s, 1H), 6.22 (s, 1H), 3.41 (d, *J* = 9.6 Hz, 1H), 2.53 (dd, *J* = 9.6, 7.8 Hz, 1H), 2.46 (t, 7.6 Hz, 2H), 2.36 (td, *J* = 7.8, 2.7 Hz, 1H), 2.02-1.94 (m, 1H), 1.73-1.66 (m, 1H), 1.62-1.58 (m, 2H), 1.58-1.53 (m, 2H), 1.36 (s, 3H), 1.34 (s, 3H), 1.32-1.29 (m, 2H), 1.29-1.26 (m, 2H), 0.99 (s, 12H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.27 (s, 3H), 0.22 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 154.4, 141.8, 113.2, 111.4, 111.2, 83.3, 46.7, 39.8, 38.9, 38.8, 36.4, 35.8, 34.3, 31.6, 30.9, 27.3, 26.4, 25.7, 22.7, 18.8, 18.3, 14.2, -2.7, -3.6 ppm. **HRMS:** calculated for $C_{27}H_{45}O_2Si$ $[M+H]^+$ 429.3183, found 429.3185.

5.4.4 NMR Comparison Data

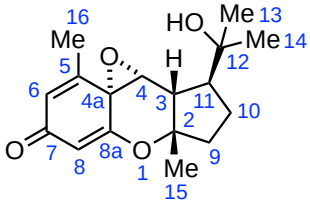


5.8: nyingchinoid D

Table 5.2 - ^{1}H NMR and ^{13}C NMR Comparison for Nyingchinoid B (5.8)

NMR Assignment	Synthetic Sample ($CDCl_3$) George *et al.* (2019)		Natural sample ($CDCl_3$) Yang *et al.* (2018)[2]	
	^{1}H NMR (500 MHz)	^{13}C NMR (125 MHz)	^{1}H NMR (600 MHz)	^{13}C NMR (150 MHz)
2		83.3	--	83.4
3	2.55 (dd, *J* = 9.7, 8.0 Hz)	39.2	2.56 (dd, *J* = 9.6, 8.0 Hz)	39.3
4	3.08 (d, *J* = 9.7 Hz)	37.9	3.08 (d, *J* = 9.6 Hz)	38.0
4a	--	116.0	--	116.2
5	--	138.4	--	138.6
6	6.28 (d, *J* = 2.6 Hz)	109.9	6.28 (d, *J* = 2.4 Hz)	111.0*
7	--	154.2	--	154.4
8	6.24 (d, *J* = 2.6 Hz)	102.8	6.24 (d, *J* = 2.4 Hz)	102.9
8a	--	154.6	--	154.7
9	1.98 (m) 1.60 (m)	39.4	1.98 (m) 1.60 (m)	39.5
10	1.72 (m) 1.63 (m)	25.4	1.72 (m) 1.63 (m)	25.5
11	2.41 (td, *J* = 8.1, 2.7 Hz)	46.5	2.41 (td, *J* = 8.0, 3.0 Hz)	46.6
12	--	39.6	--	39.7
13	1.38 (s)	34.0	1.38 (s)	34.1
14	0.66 (s)	18.5	0.66 (s)	18.7
15	1.32 (s)	26.6	1.32 (s)	26.8
16	2.11 (s)	20.1	2.11 (s)	20.2
7-OH	4.70 (br s)	--	--	--

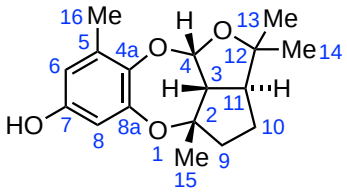
* Typographical error in manuscript – should be 110.0 ppm.



5.6: nyingchinoid B

Table 5.3 - ^{1}H NMR and ^{13}C NMR Comparison for Nyingchinoid B (5.6)

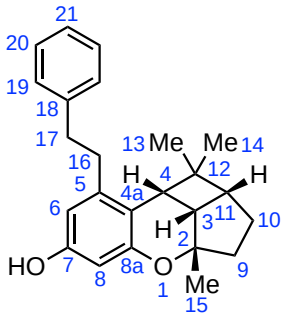
NMR Assignment	Synthetic Sample ($CDCl_3$) George *et al.* (2019)		Natural sample ($CDCl_3$) Yang *et al.* (2018)[2]	
	^{1}H NMR (500 MHz)	^{13}C NMR (125 MHz)	^{1}H NMR (400 MHz)	^{13}C NMR (150 MHz)
2	--	90.7		90.9
3	2.20 (dd, *J* = 8.0, 3.8 Hz)	43.5	2.20 (dd, *J* = 8.0, 4.0 Hz)	43.7
4	4.03 (d, *J* = 3.8 Hz)	63.6	4.03 (d, *J* = 4.0 Hz)	63.7
4a	--	54.5	--	54.7
5	--	148.9	--	149.0
6	6.26 (t, *J* = 1.7 Hz)	131.7	6.28 (br s)	131.9
7	--	187.5	--	187.7
8	5.97 (d, *J* = 2.0 Hz)	114.9	6.00 (d, *J* = 1.6 Hz)	115.3
8a	--	167.1	--	167.2
9	2.07 (m) 1.86 (m)	40.3	2.08 (m) 1.88 (m)	40.5
10	1.89 (m) 1.43 (m)	25.3	1.91 (m) 1.43 (m)	25.5
11	2.55 (m)	53.7	2.55 (q, *J* = 8.0 Hz)	53.8
12	--	72.1	--	72.4
13	1.23 (s)	25.9	1.24 (s)	26.0
14	1.34 (s)	30.2	1.35 (s)	30.4
15	1.29 (s)	27.2	1.30 (s)	27.3
16	1.84 (d, *J* = 1.5 Hz)	15.8	1.86 (br s)	16.0



5.5: nyingchinoid A

Table 5.4 - ^{1}H NMR and ^{13}C NMR Comparison for Nyingchinoid A (5.5)

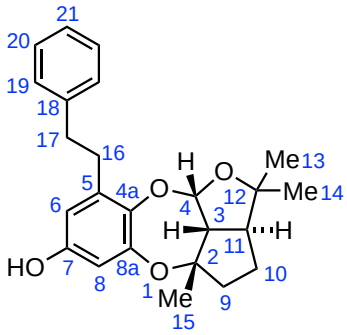
NMR Assignment	Synthetic Sample ($CDCl_3$) George *et al.* (2019)		Natural sample ($CDCl_3$) Yang *et al.* (2018)[2]	
	^{1}H NMR (500 MHz)	^{13}C NMR (125 MHz)	^{1}H NMR (600 MHz)	^{13}C NMR (150 MHz)
2		81.2		81.3
3	2.13 (dd, J = 14.1, 3.1 Hz)	64.1	2.13 (dd, J = 14.4, 3.0 Hz)	64.3
4	4.92 (d, J = 3.0 Hz)	96.1	4.91 (d, J = 3.0 Hz)	96.3
4a	--	138.6	--	138.7
5	--	133.8	--	134.0
6	6.40 (d, J = 3.0 Hz)	112.9	6.40 (d, J = 3.0 Hz)	113.0
7	--	151.7	--	151.9
8	6.32, (d, J = 3.0 Hz)	109.5	6.32 (d, J = 3.0 Hz)	109.7
8a	--	151.3	--	151.5
9	2.57 (dt, J = 14.7, 8.8 Hz) 2.37 (ddd, J = 14.7, 9.9, 1.6 Hz)	47.3	2.57 (dt, J = 15.0, 9.0 Hz) 2.37 (ddd, J = 15.0, 10.0, 1.2 Hz)	47.4
10	1.77 (m) 1.34 (m)	21.3	1.77 (m) 1.34 (m)	21.4
11	3.42 (ddd, J = 14.4, 12.6, 6.0 Hz)	51.9	3.42 (ddd, J = 14.4, 12.6, 6.0 Hz)	52.1
12	--	80.1	--	80.2
13	1.52 (s)	29.7	1.52 (s)	29.8
14	1.17 (s)	22.7	1.17 (s)	22.9
15	1.28 (s)	24.8	1.28 (s)	24.9
16	2.22, s	16.4	2.23, s	16.6
7-OH	4.94 (br s)	--	--	--



5.93: bibenzyl-cannabicyclol

Table 5.5 - ^{1}H NMR and ^{13}C NMR Comparison for *o*-bibenzyl cannabicyclol (5.93)

NMR Assignment	Synthetic Sample ($CDCl_3$)		Natural sample ($CDCl_3$) Crombie *et al.* (1988)[1]	
	^{1}H NMR (500 MHz)	^{13}C NMR (125 MHz)	^{1}H NMR	^{13}C NMR
2	--	83.5	--	83.5
3	2.52 (t, *J* = 9.0 Hz)	46.5	2.51 (t, *J* = 8.8 Hz)	46.6
4	2.42 (dt, *J* = 8.0, 3.4 9 Hz)	37.3	2.42 (dt, *J* = 8.0, 3.4 Hz)	37.3
4a	--	116.1	--	126.6
5	--	141.9	--	141.9
6	6.36 (d, *J* = 2.6 Hz)	108.1	6.35 (d, *J* = 2.3 Hz)	108.1
7	--	154.9	--	155.0
8	6.28 (d, *J* = 2.6 Hz)	103.5	6.27 (d, *J* = 2.3 Hz)	103.4
8a	--	154.4	--	154.5
9	1.74 – 1.58 (m)	39.9	1.68 (m)	40.0
10	1.74 – 1.58 (m)	26.0	1.68 (m)	26.0
11	3.10 (d, *J* = 9.6 Hz)	39.9	3.09 (d, *J* = 9.5 Hz)	40.0
12	--	39.8	--	40.0
13	1.37 (s)	25.3	1.25 (s)	25.3
14	0.63 (s)	18.8	0.62 (s)	18.9
15	1.30 (s)	34.1	1.36 (s)	34.1
16	2.84 – 2.69 (m)	34.9	2.76 (s)	34.9
17	2.84 – 2.69 (m)	37.1	2.76 (s)	37.2
18	--	142.0	--	142.1
19	7.22 – 7.18 (m)	128.4	7.33 – 7.13 (m)	128.4
20	7.29 (t, *J* = 7.4 Hz)	128.4	7.33 – 7.13 (m)	128.4
21	7.22 – 7.18 (m)	125.9	7.33 – 7.13 (m)	126.0
7-OH	4.80 (br s)	--	4.75 (br s)	--



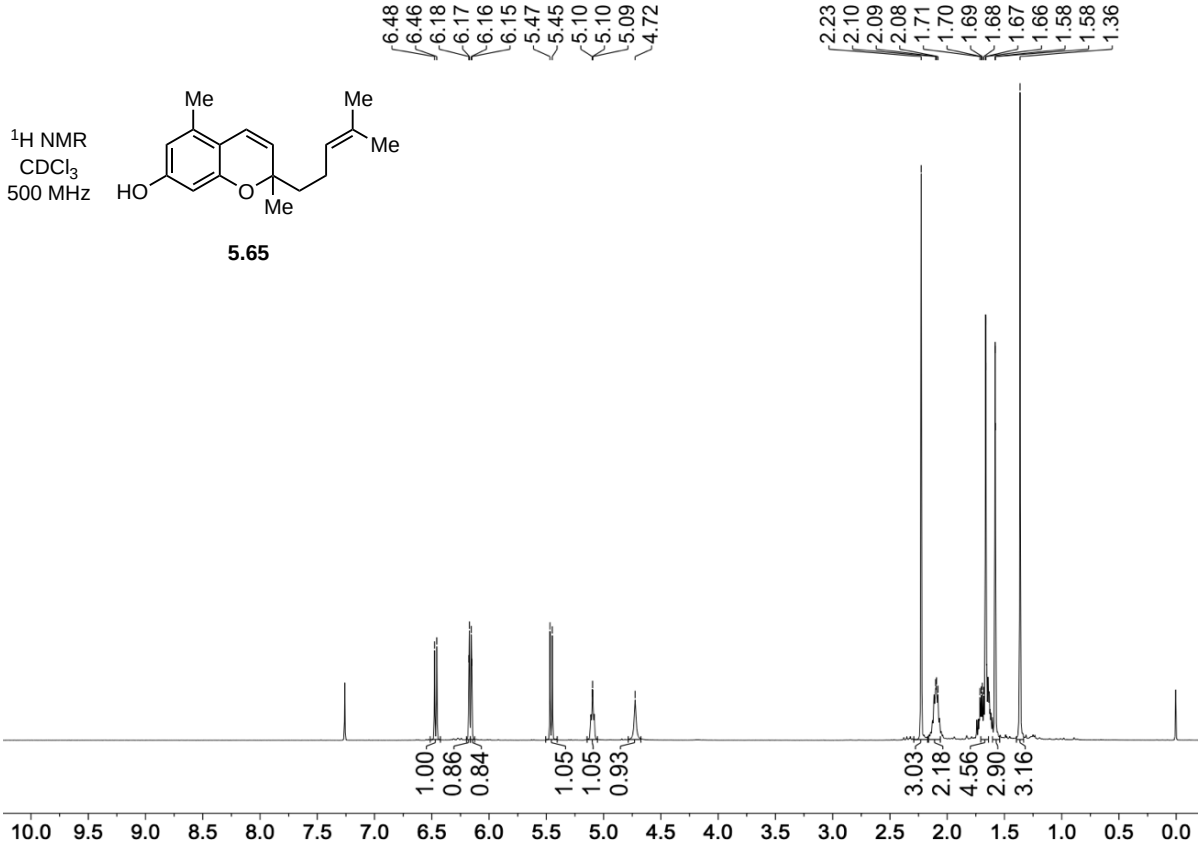
5.4: rasumatranin D

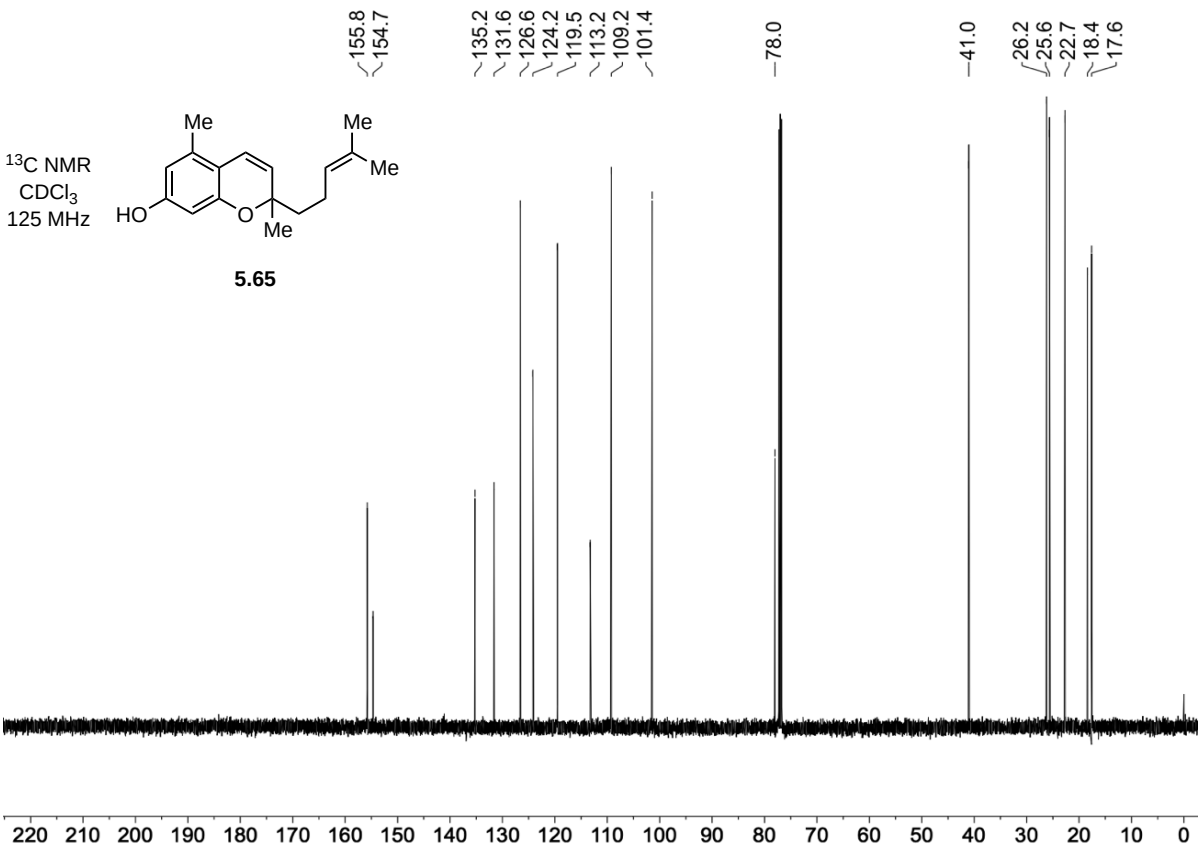
Table 5.6 - ^{1}H NMR and ^{13}C NMR Comparison for Rasumatranin D (5.4)

NMR Assignment	Synthetic Sample (d_6-acetone) George *et al.* (2019)		Natural sample (d_6-acetone) Lou *et al.* (2017)[1]	
	^{1}H NMR (500 MHz)	^{13}C NMR (125 MHz)	^{1}H NMR (600 MHz)	^{13}C NMR (150 MHz)
2	--	81.6	--	81.6
3	2.25 (dd, *J* = 14.1, 3.0 Hz)	64.7	2.26 (dd, *J* = 14.0, 3.0 Hz)	64.7
4	4.72 (d, *J* = 3.0 Hz)	97.4	4.71 (d, *J* = 3.0 Hz)	97.5
4a	--	138.7	--	138.7
5	--	137.7	--	137.8
6	6.47 (d, *J* = 3.0 Hz)	112.6	6.47 (d, *J* = 2.9 Hz)	112.6
7	--	152.4	--	154.4
8	6.33 (d, *J* = 3.0 Hz)	110.6	6.32 (d, *J* = 2.9 Hz)	110.6
8a	--	154.4	--	154.7
9	2.48 (dt, *J* = 14.4, 8.7 Hz) 2.39 (ddd, *J* = 14.4, 9.9, 1.7 Hz)	48.0	2.48 (dt, *J* = 14.4, 8.7 Hz) 2.39 (ddd, *J* = 14.4, 9.9, 1.5 Hz)	48.0
10	1.73 (m)	21.8	1.73 (m)	21.8
11	3.36 (ddd, *J* = 14.1, 12.6, 6.0 Hz)	53.0	3.36 (ddd, *J* = 14.0, 12.8, 6.0 Hz)	53.0
12	--	79.7	--	79.7
13	1.14 (s)	23.0	1.13 (s)	23.0
14	1.43 (s)	30.2	1.43 (s)	30.4
15	1.29 (s)	24.7	1.28 (s)	24.8
16	2.91 (m)	33.1	2.91 (m)	33.2
17	2.80 (m)	37.7	2.80 (m)	37.7
18	--	143.0	--	143.0
19	7.27 (m)	129.0	7.27 (m)	129.1
20	7.22 (m)	129.3	7.22 (m)	129.3
21	7.17 (m)	126.6	7.17 (tt, *J* = 7.2, 1.3 Hz)	126.6
7-OH	8.02 (s)	--	8.07 (s)	--

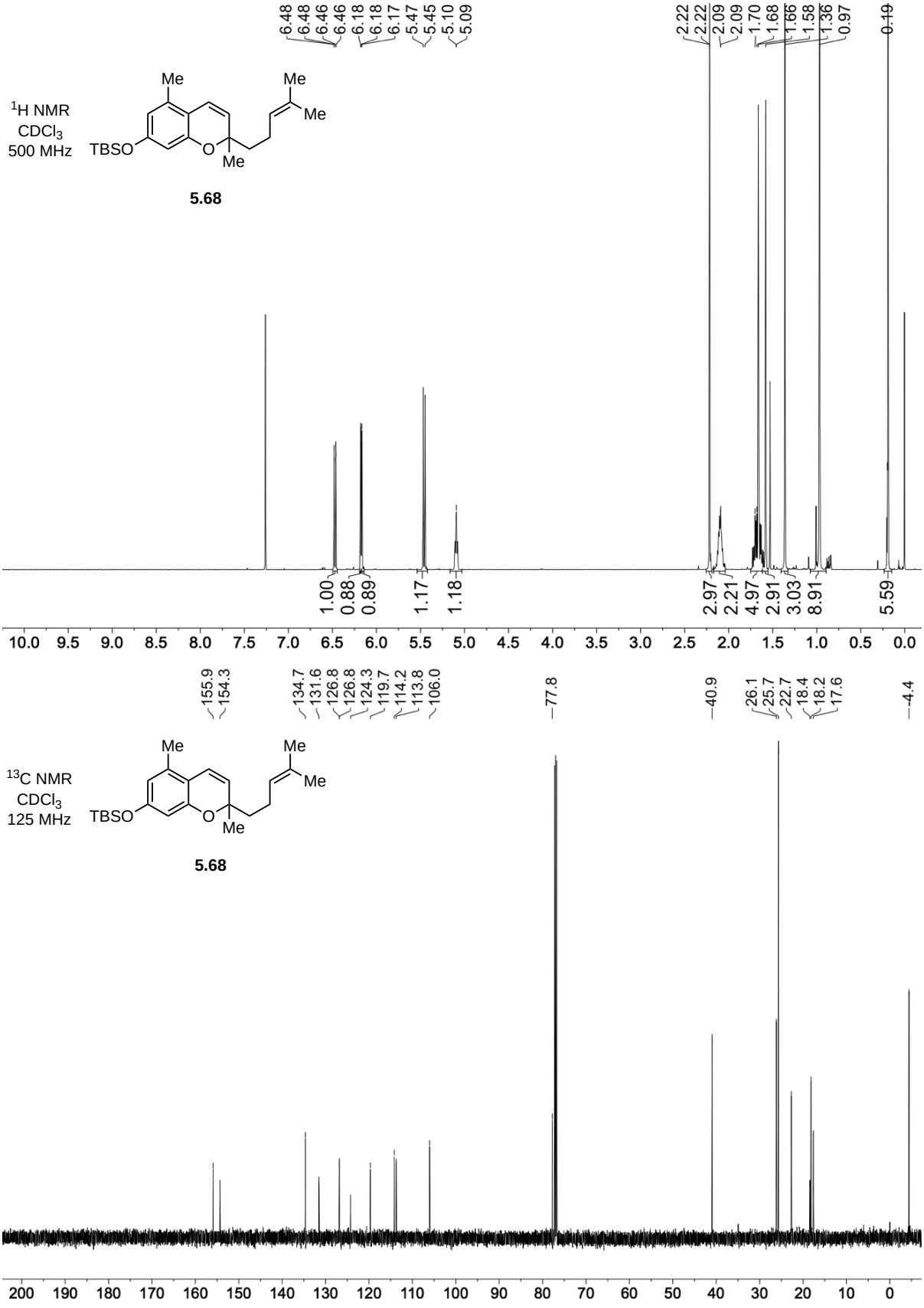
5.4.5 NMR Spectra

Data for 5.65

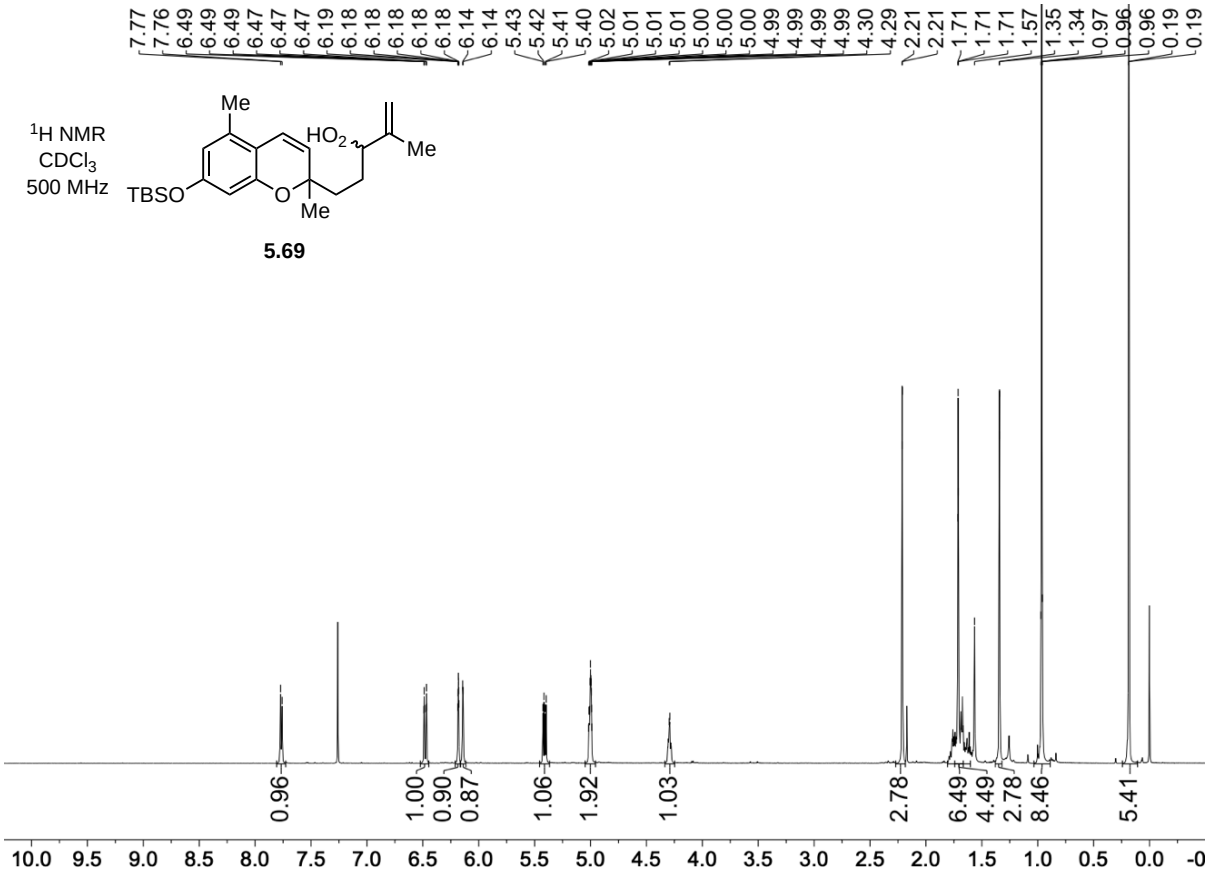




Data for 5.68

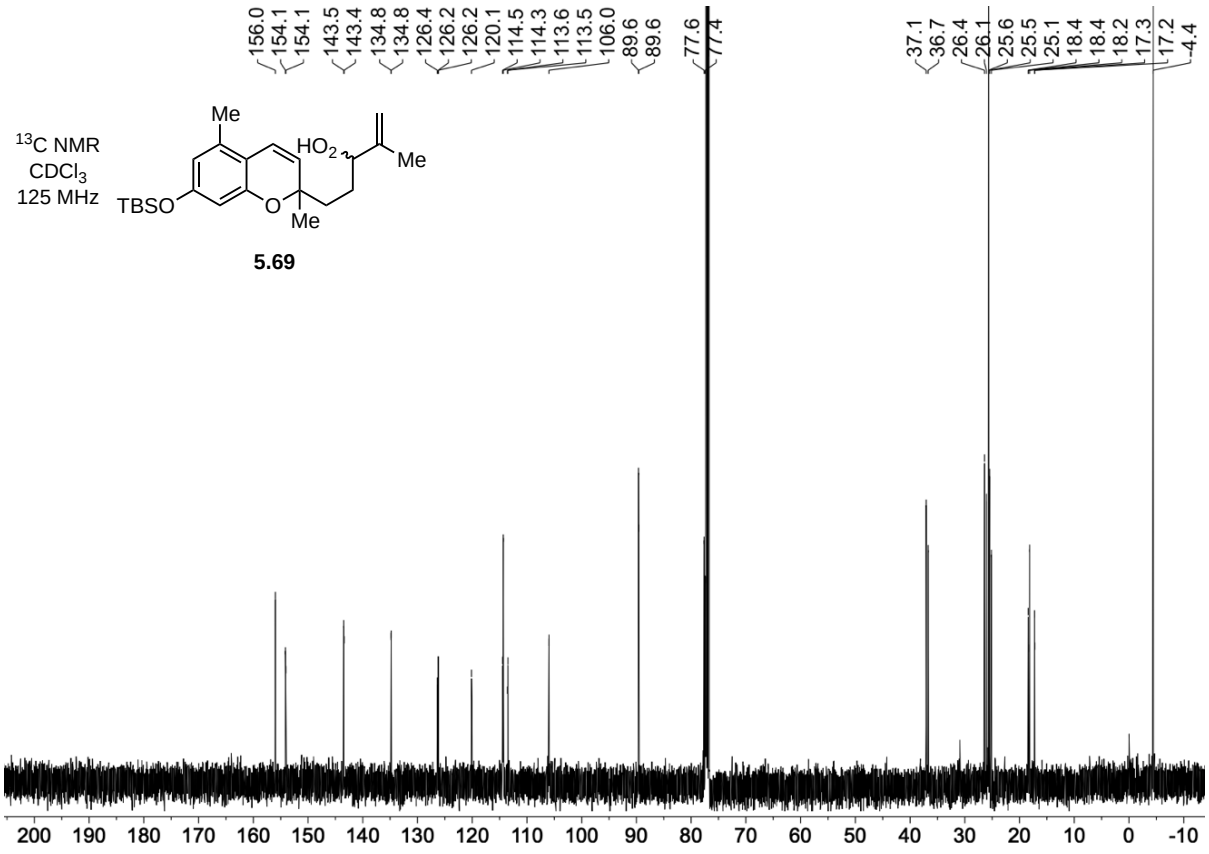

6.48
6.48
6.46
6.46
6.18
6.18
6.17
5.47
5.45
5.10
5.09
2.22
2.22
2.09
2.09
1.70
1.68
1.66
1.58
1.36
0.97
0.19
1H NMR
CDCl3
500 MHz
Me
Me
Me
TBSO
O
Me
5.68
1.00
0.88
0.89
1.17
1.18
2.97
2.21
4.97
2.91
3.03
8.91
5.59
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
155.9
154.3
134.7
131.6
126.8
126.8
124.3
119.7
114.2
113.8
106.0
77.8
40.9
26.1
25.7
22.7
18.4
18.2
17.6
-4.4
13C NMR
CDCl3
125 MHz
Me
Me
Me
TBSO
O
Me
5.68
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Data for 5.69



^{1}H NMR
$CDCl_3$
500 MHz

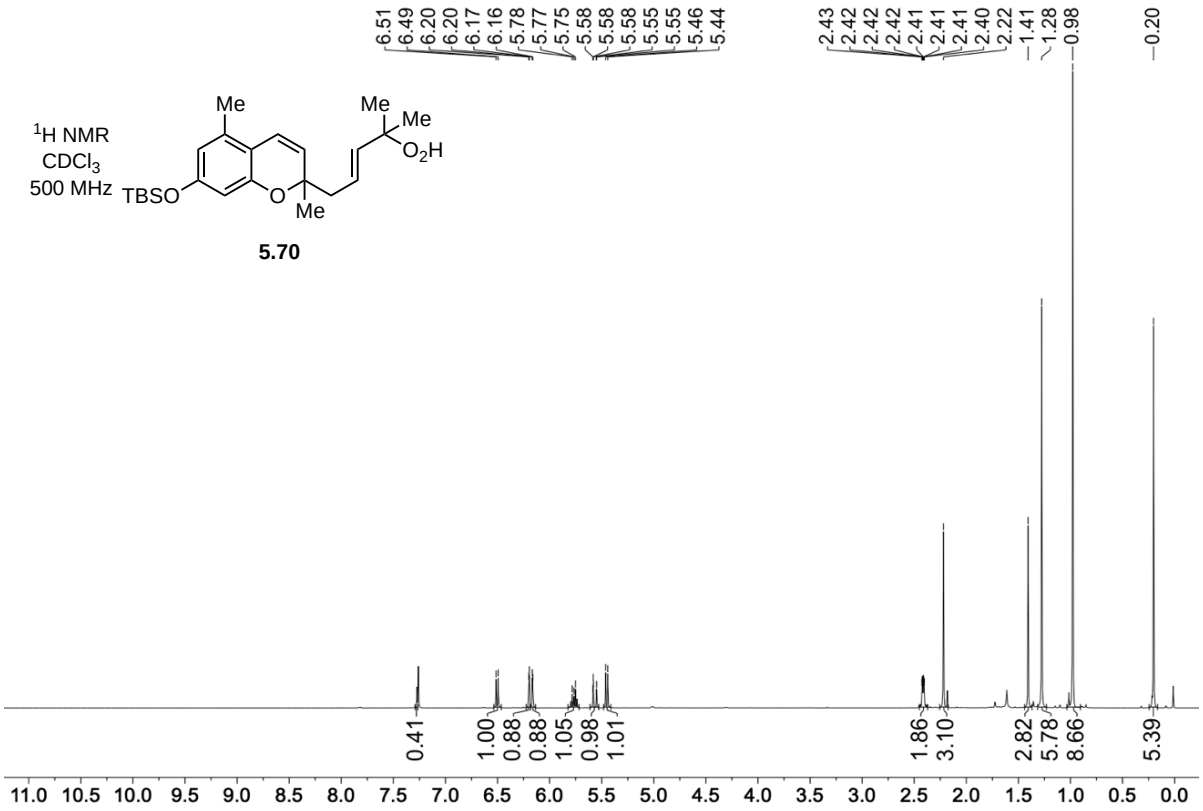
5.69

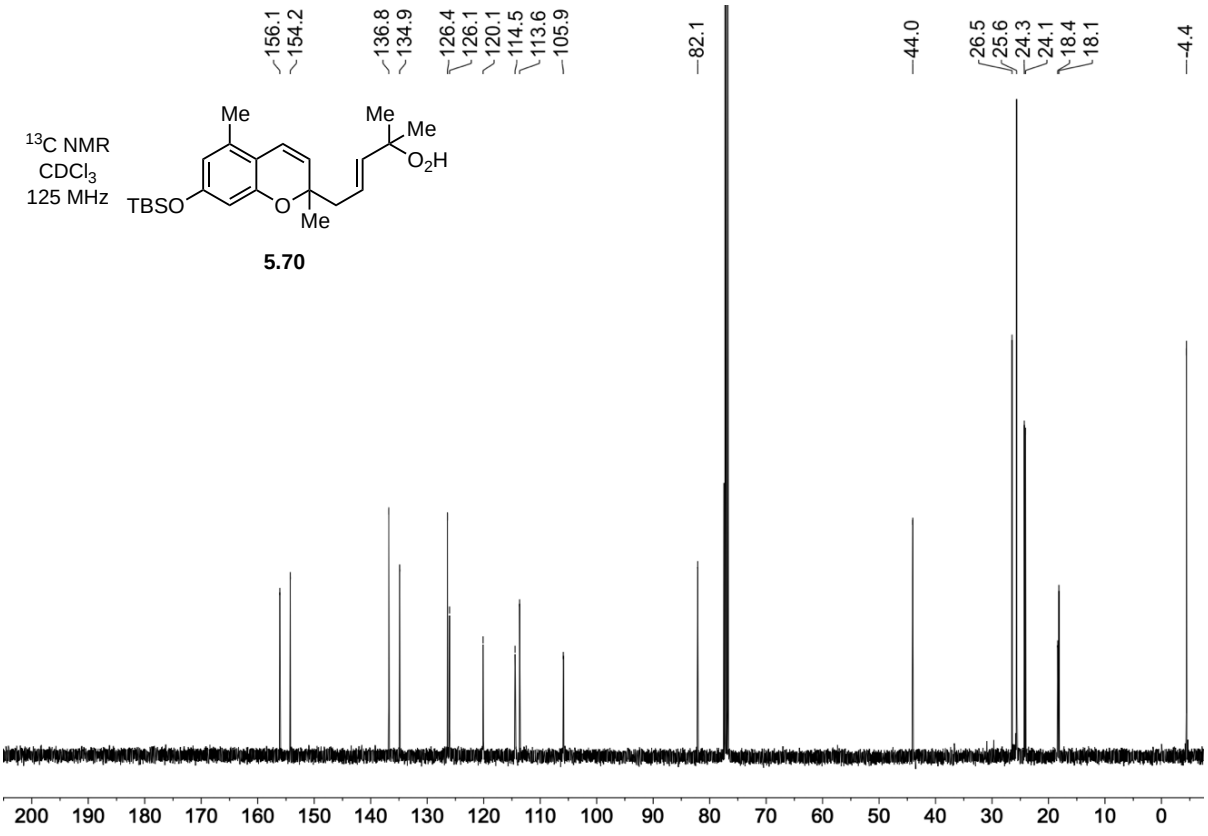


^{13}C NMR
$CDCl_3$
125 MHz

5.69

Data for 5.70


6.51
6.49
6.20
6.20
6.17
6.16
5.78
5.77
5.75
5.58
5.58
5.58
5.55
5.55
5.46
5.44
2.43
2.42
2.42
2.42
2.41
2.41
2.41
2.40
2.22
1.41
1.28
0.98
0.20
^{1}H NMR
$CDCl_3$
500 MHz
Me
Me
Me
O_2H
TBSO
O
Me
5.70
0.41
1.00
0.88
0.88
1.05
0.98
1.01
1.86
3.10
2.82
5.78
8.66
5.39
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


156.1
154.2
136.8
134.9
126.4
126.1
120.1
114.5
113.6
105.9
82.1
44.0
26.5
25.6
24.3
24.1
18.4
18.1
-4.4
^{13}C NMR
$CDCl_3$
125 MHz
Me
Me
Me
O_2H
TBSO
O
Me
5.70
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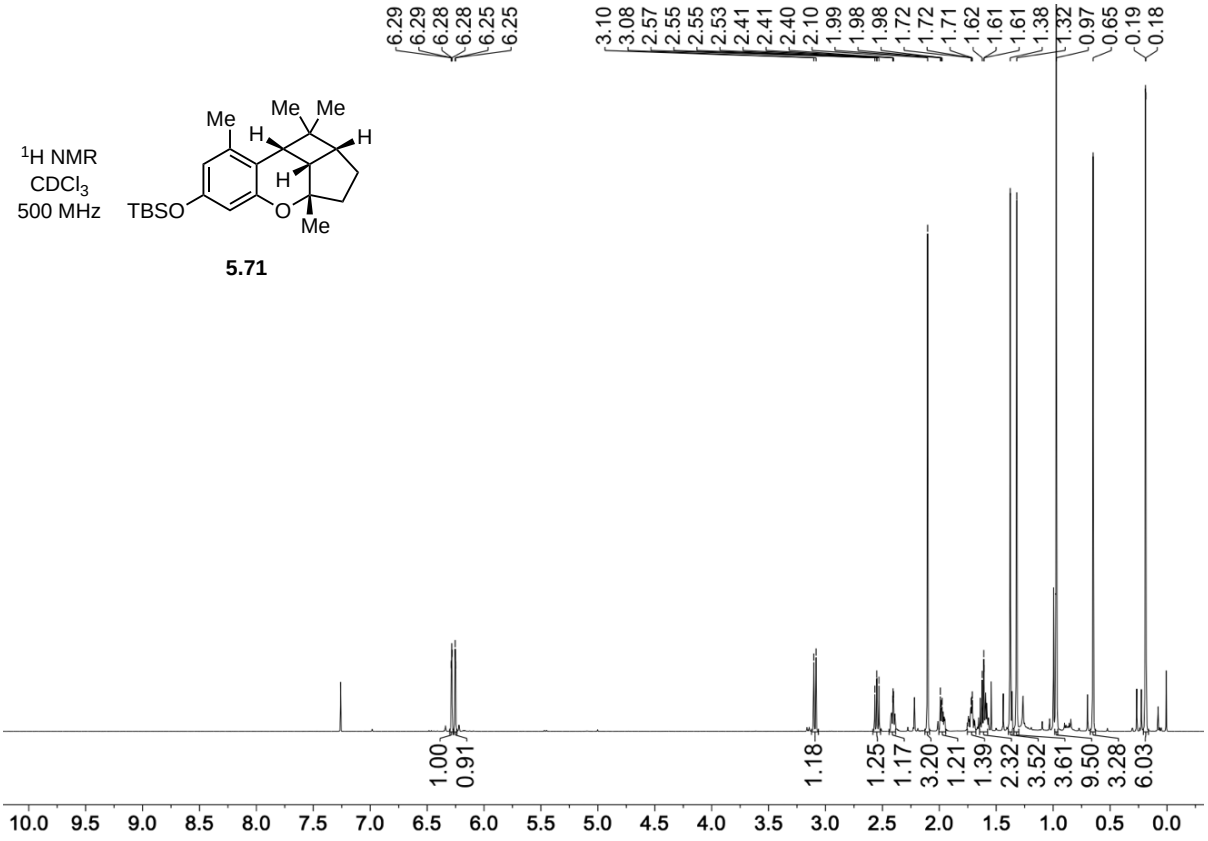
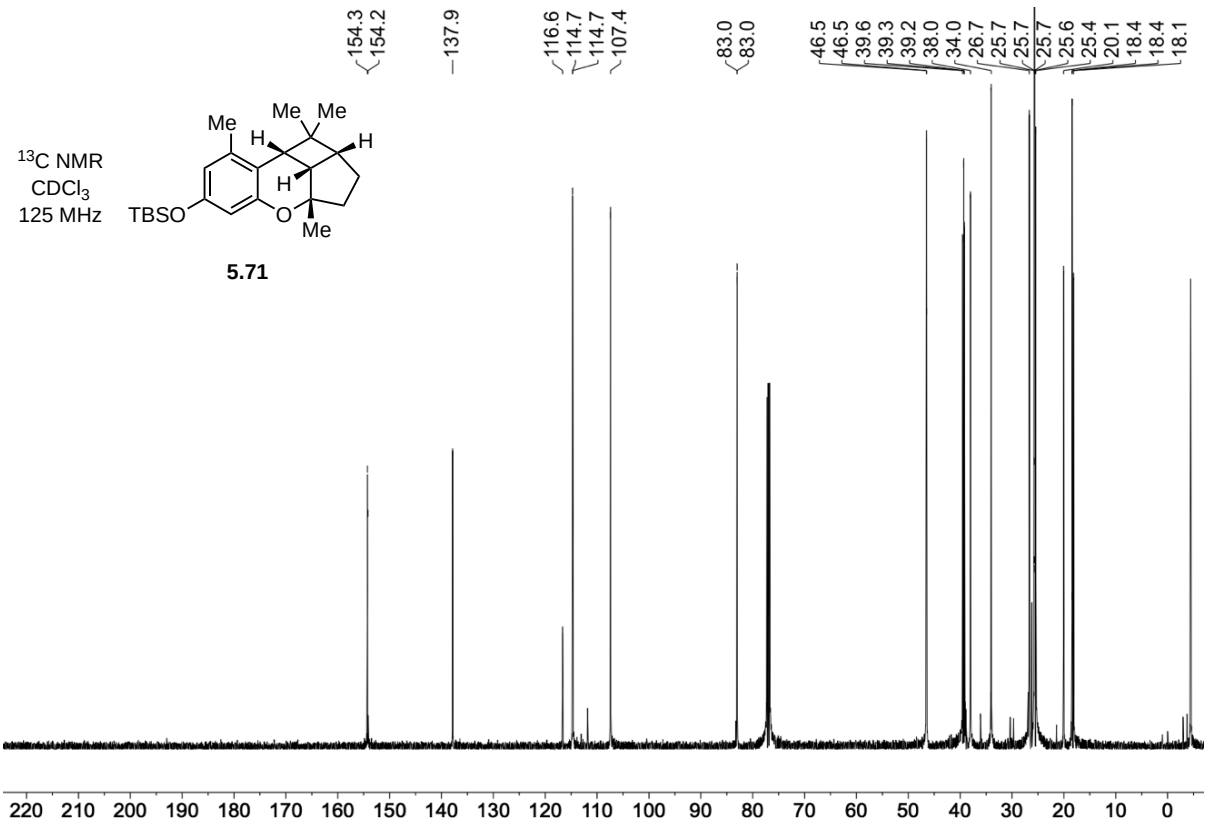
Data for 5.71



^{1}H NMR
$CDCl_3$
500 MHz

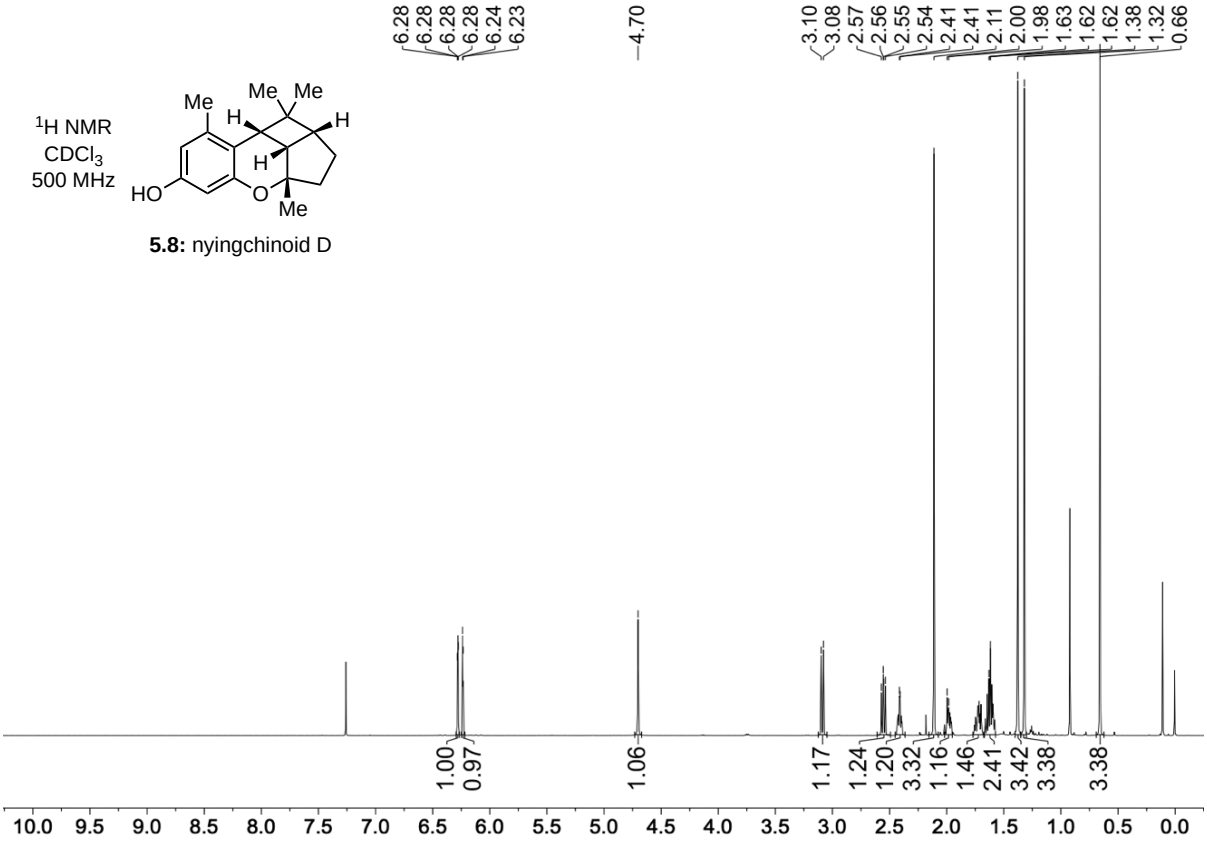
5.71



^{13}C NMR
$CDCl_3$
125 MHz

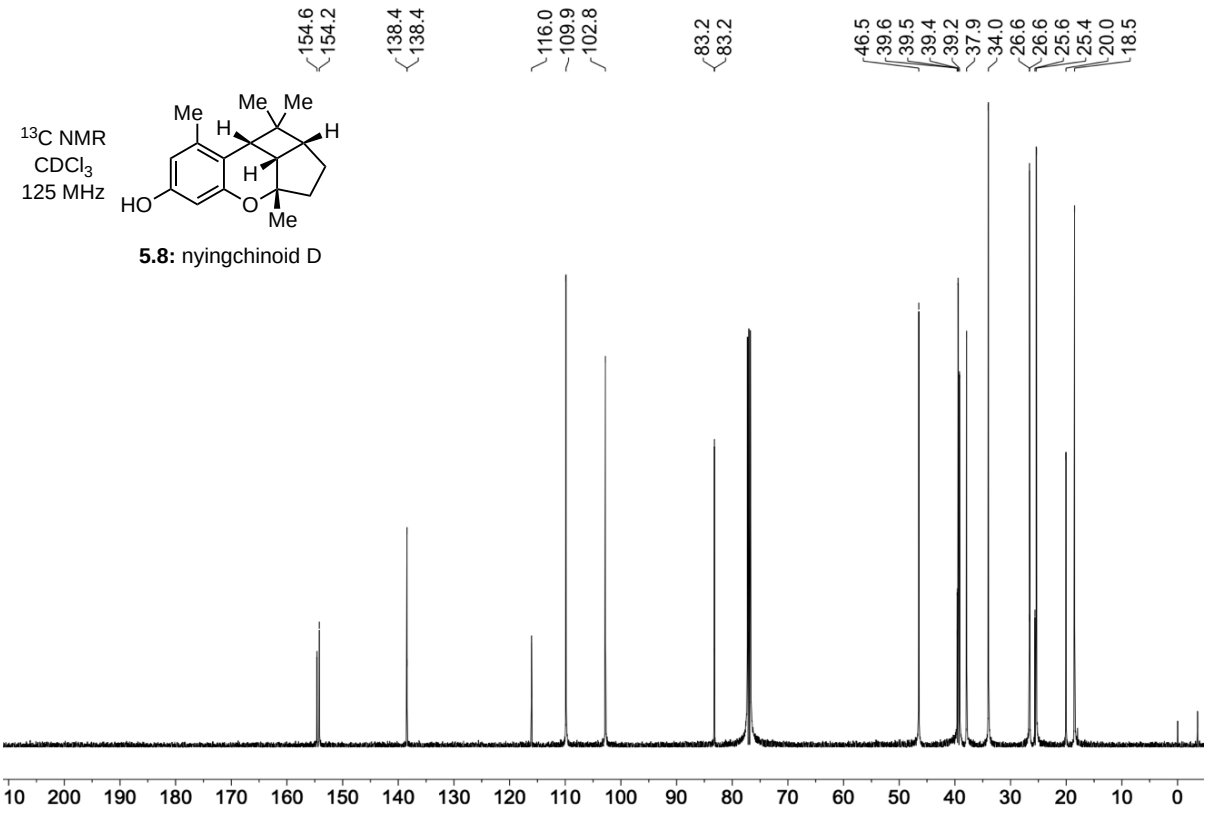
5.71

Data for nyingchinoid D (5.8)



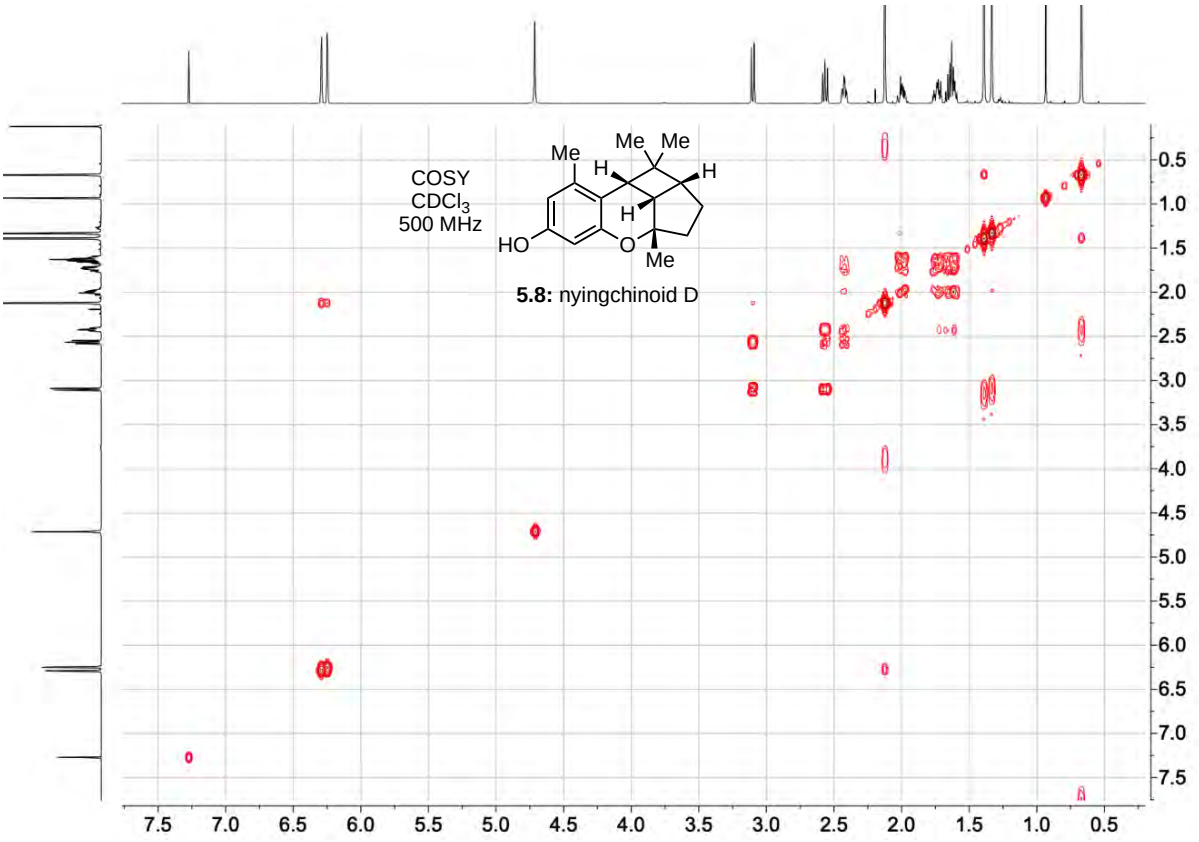
^{1}H NMR
$CDCl_3$
500 MHz

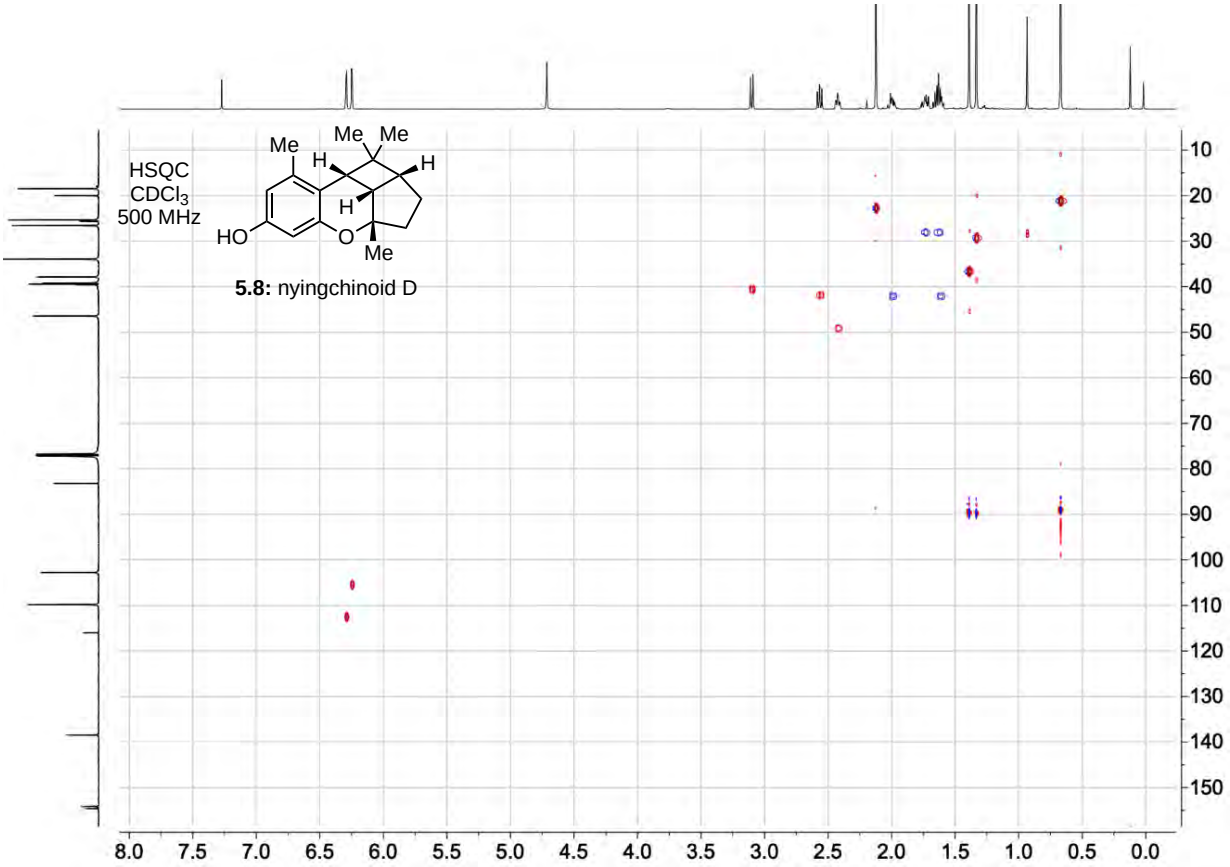
5.8: nyingchinoid D



^{13}C NMR
$CDCl_3$
125 MHz

5.8: nyingchinoid D


COSY
CDCl3
500 MHz
Me
Me
Me
H
H
H
HO
O
Me
5.8: nyingchinoid D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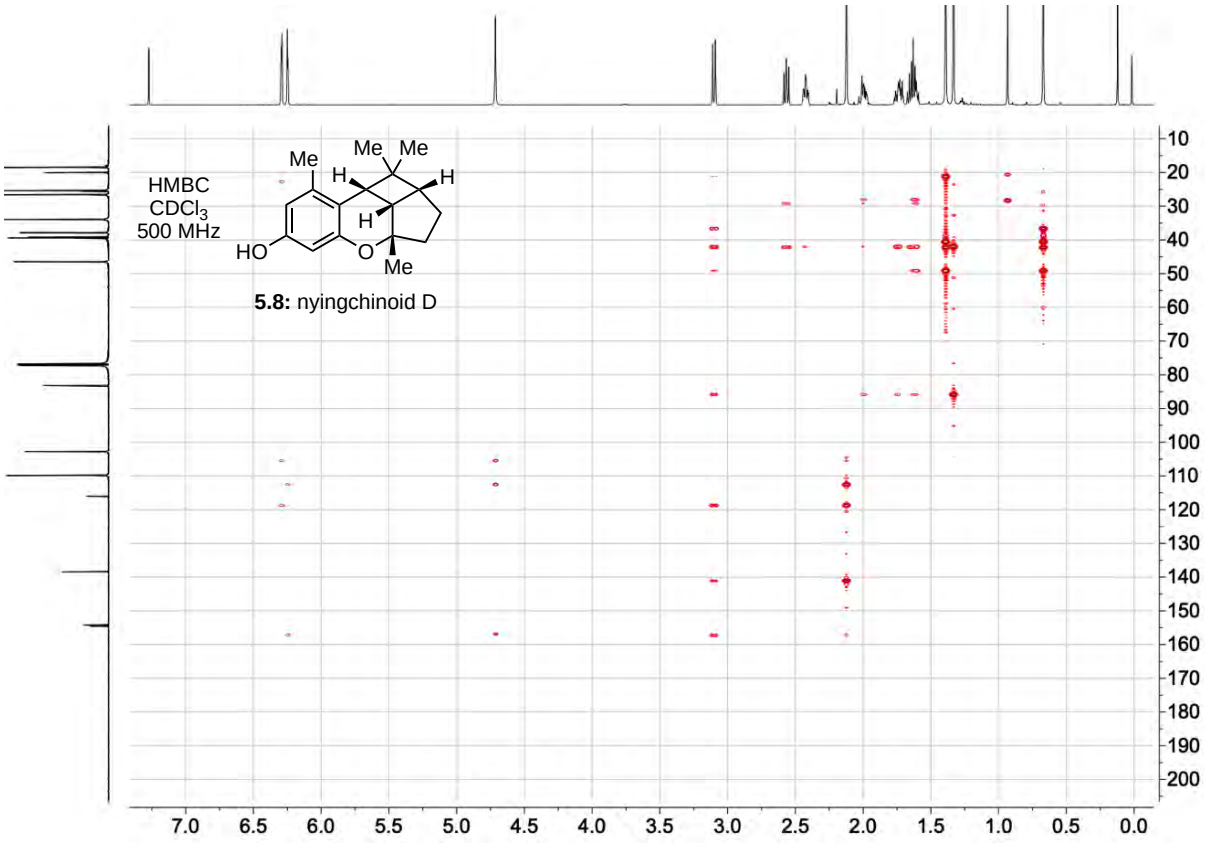
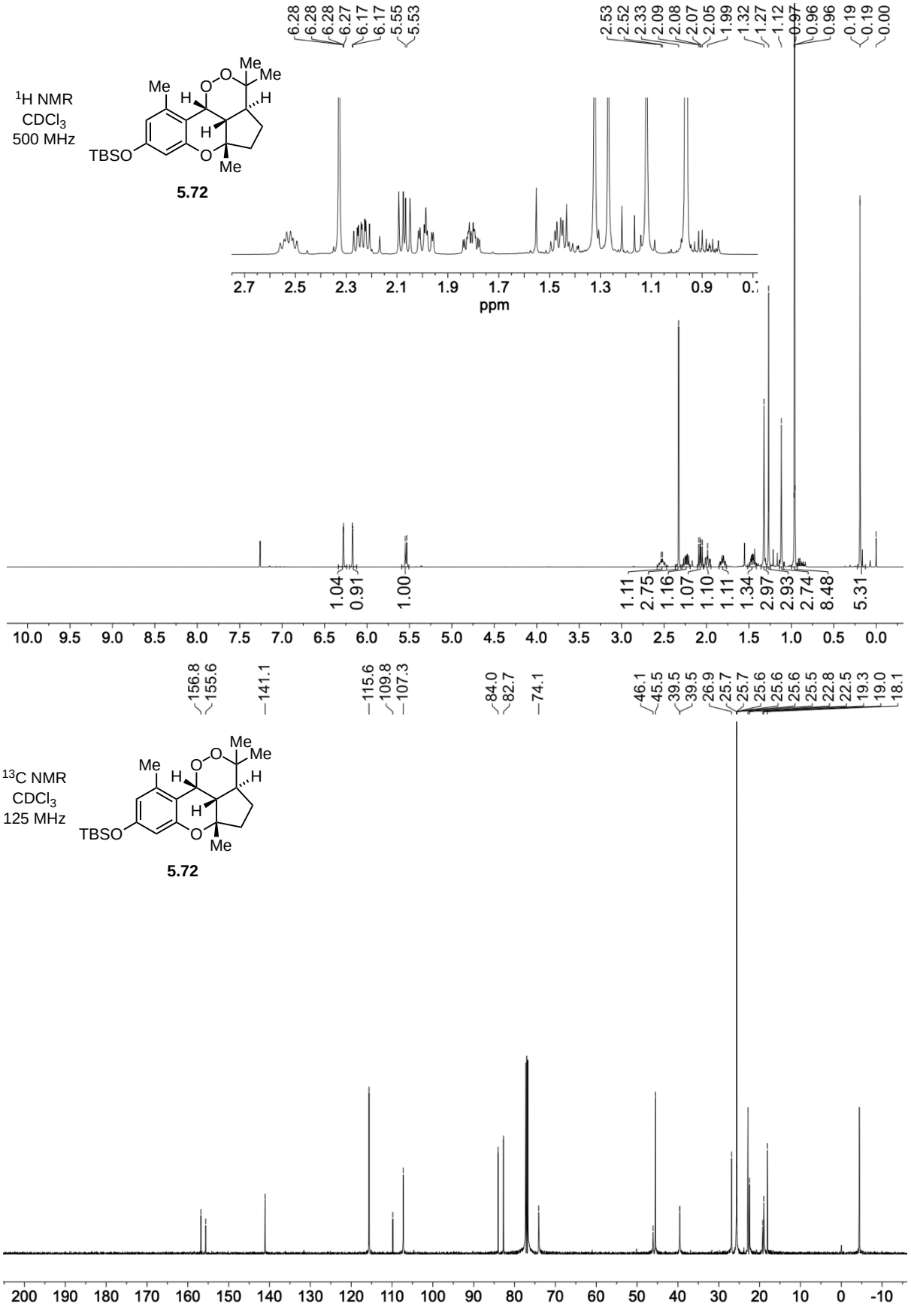
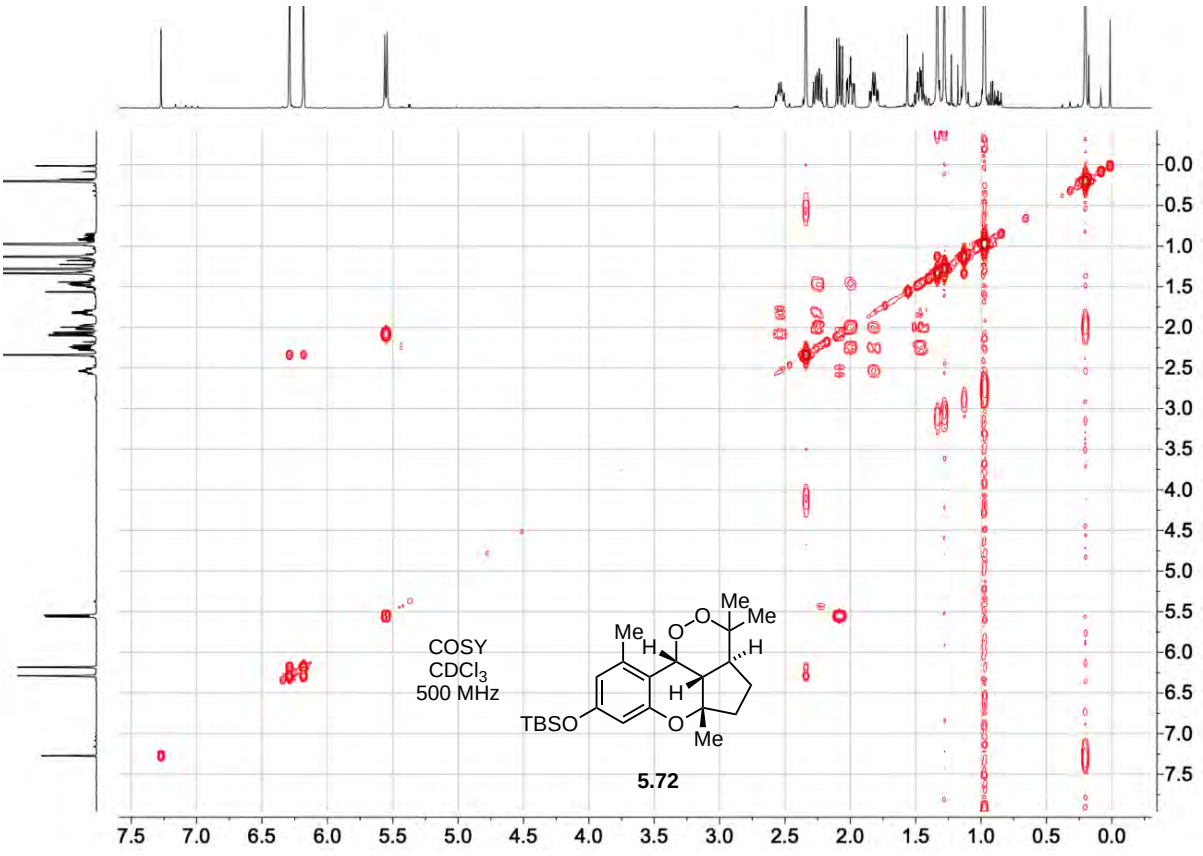
CDCl3
500 MHz
Me
Me
Me
H
H
H
HO
O
Me
5.8: nyingchinoid D

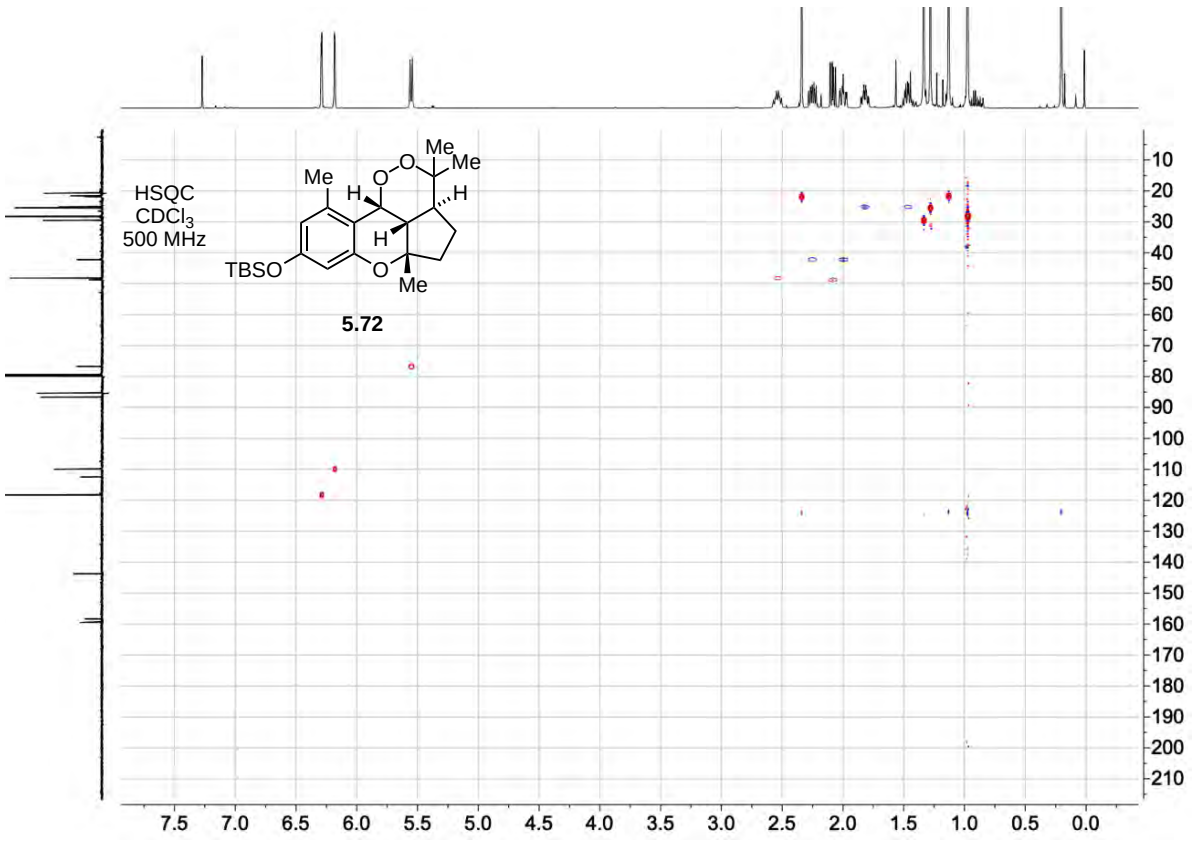


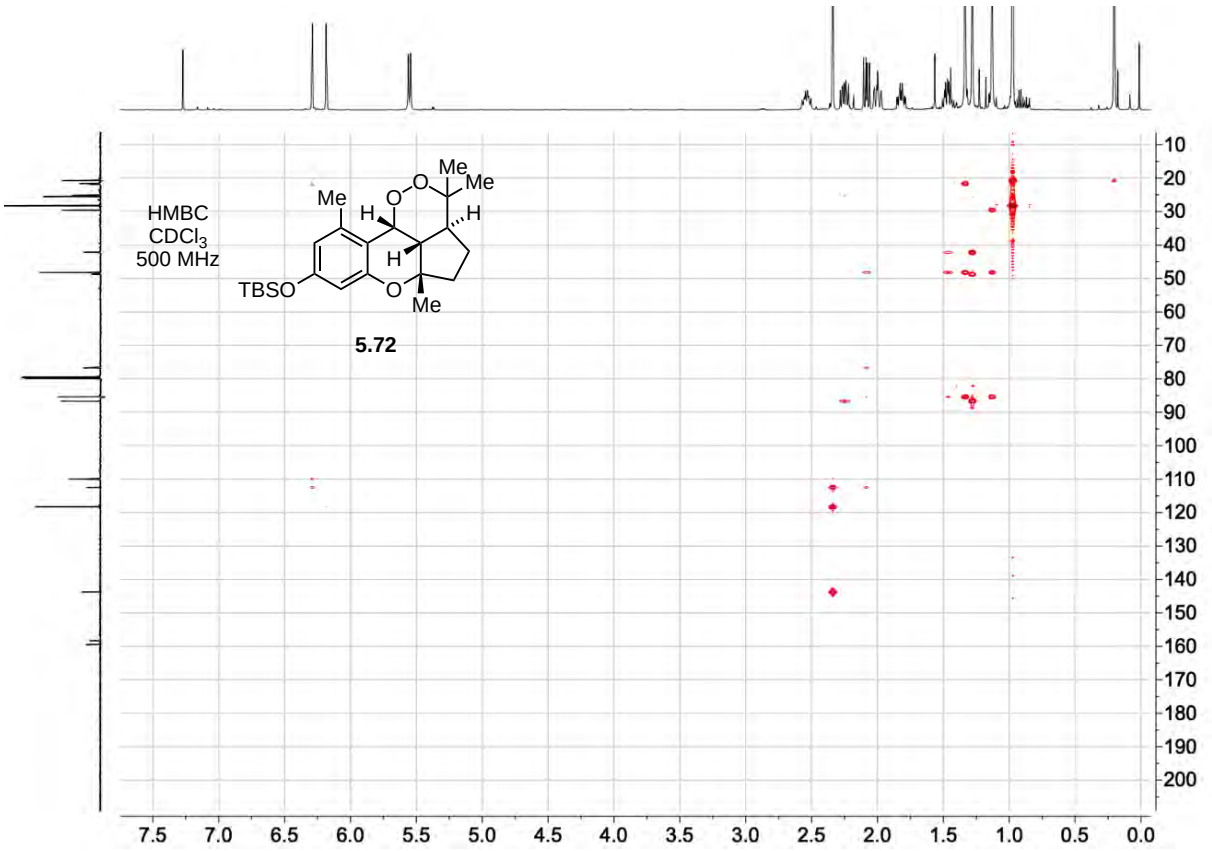
5.8: nyingchinoid D

Data for 5.72



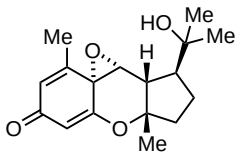

COSY
CDCl3
500 MHz
Me
Me
Me
H
O
O
H
H
TBSO
O
Me
5.72


HSQC
CDCl3
500 MHz
Me
Me
Me
H
O
O
H
H
TBSO
O
Me
5.72


HMBC
CDCl3
500 MHz
Me
H
O
O
Me
Me
H
H
TBSO
O
Me
5.72
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

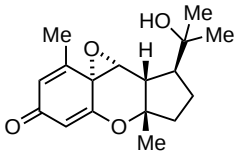
Data for nyingchinoid B (5.6)

^{1}H NMR
$CDCl_3$
500 MHz

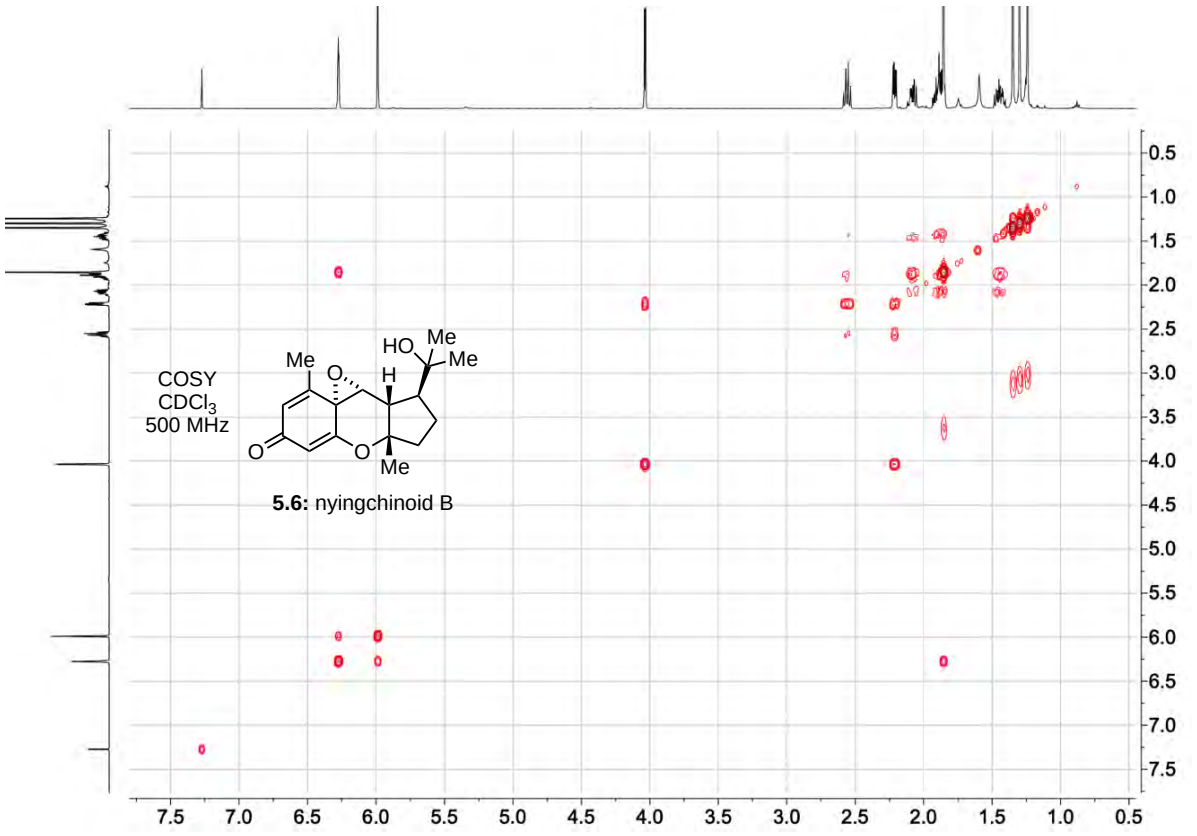


5.6: nyingchinoid B

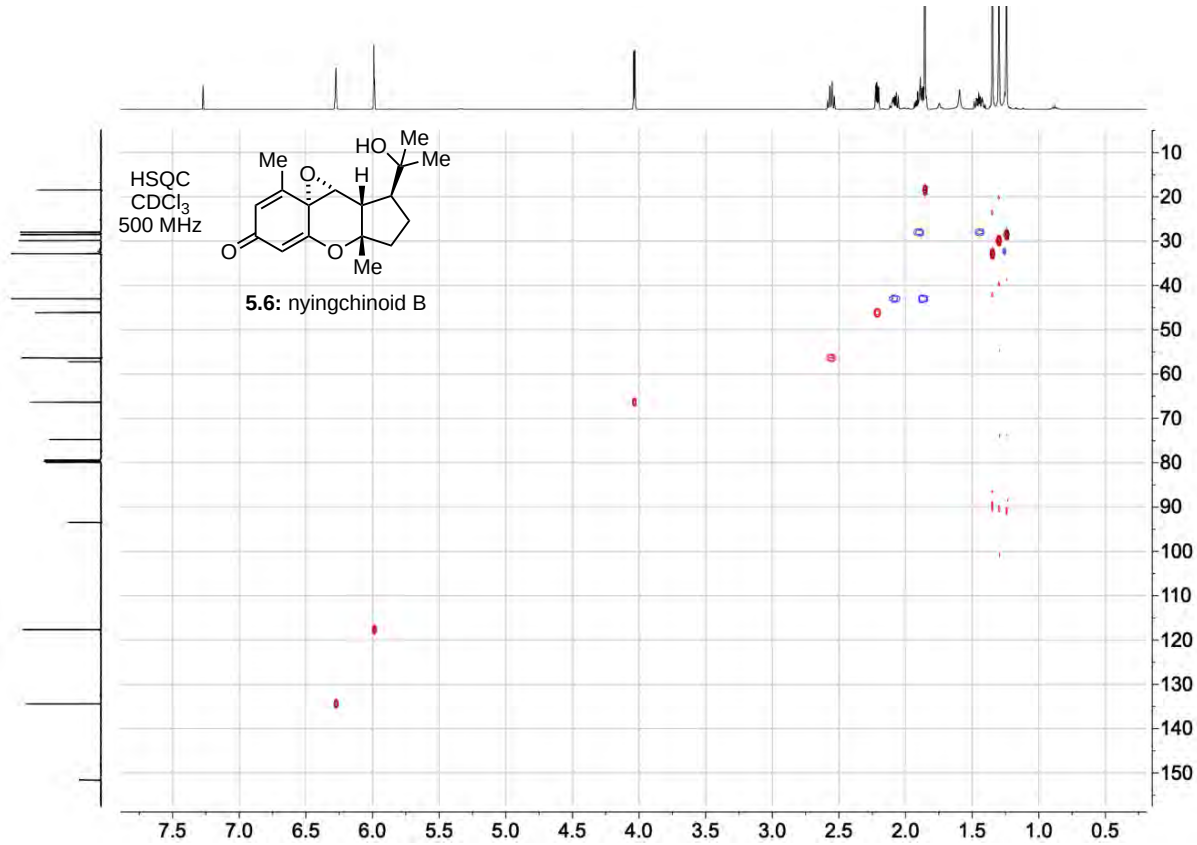
^{13}C NMR
$CDCl_3$
125 MHz



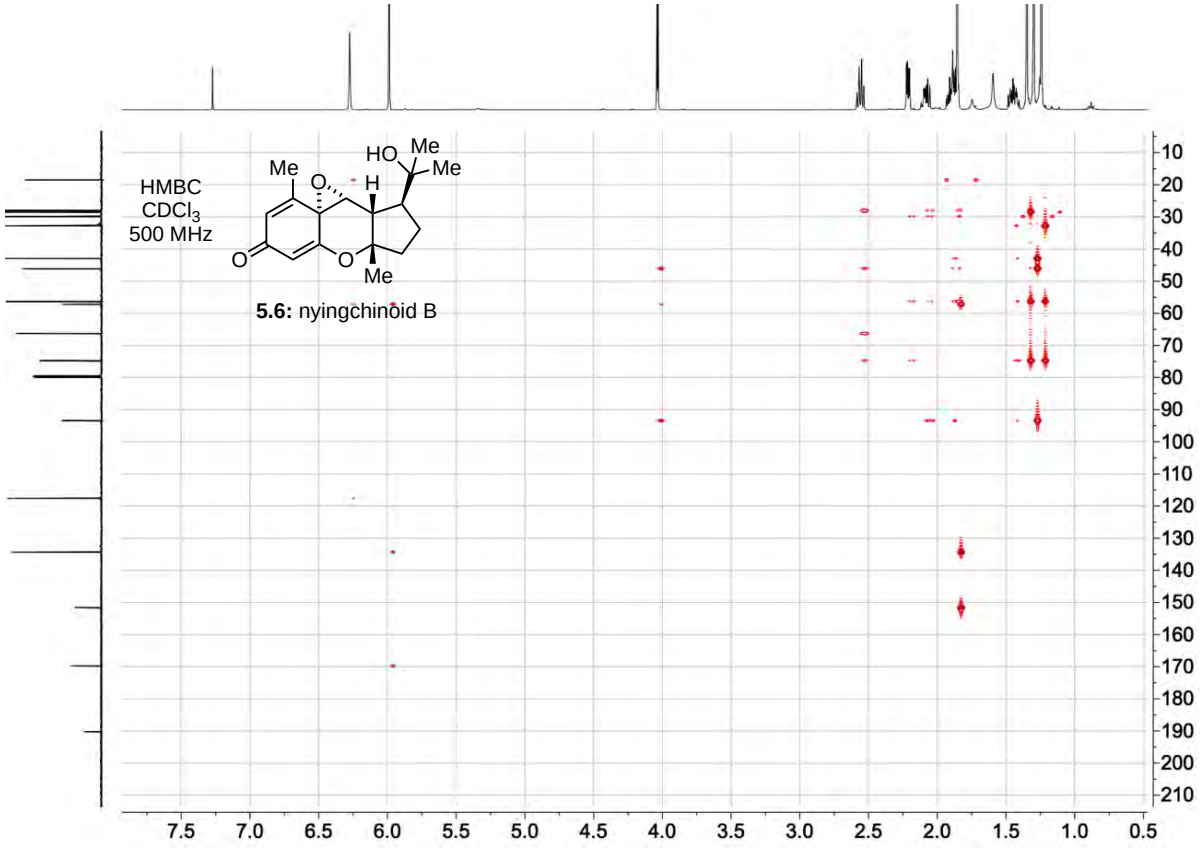
5.6: nyingchinoid B



5.6: nyingchinoid B



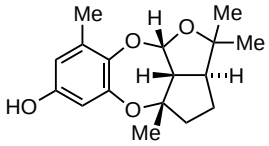
5.6: nyingchinoid B



5.6: nyingchinoid B

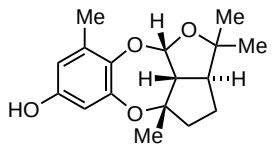
Data for nyingchinoid A (5.5)

^{1}H NMR
$CDCl_3$
500 MHz

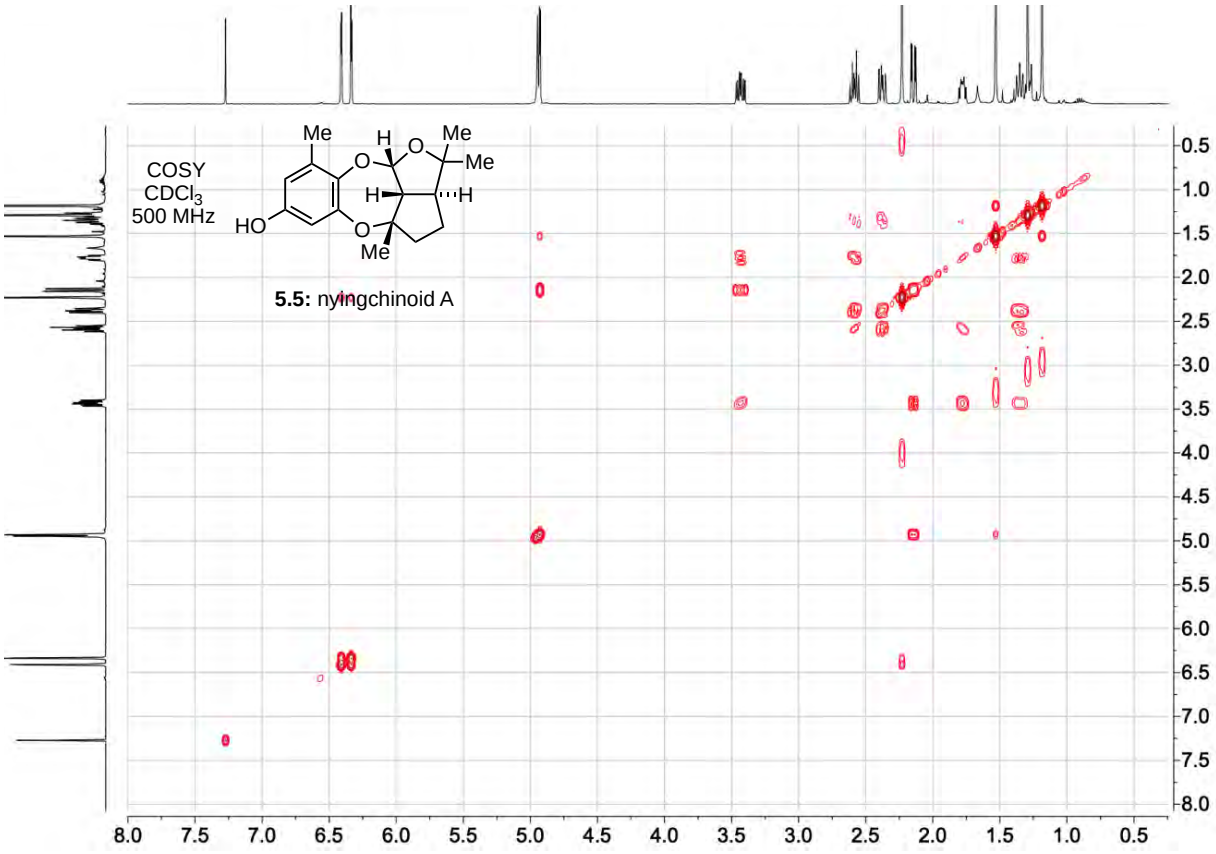


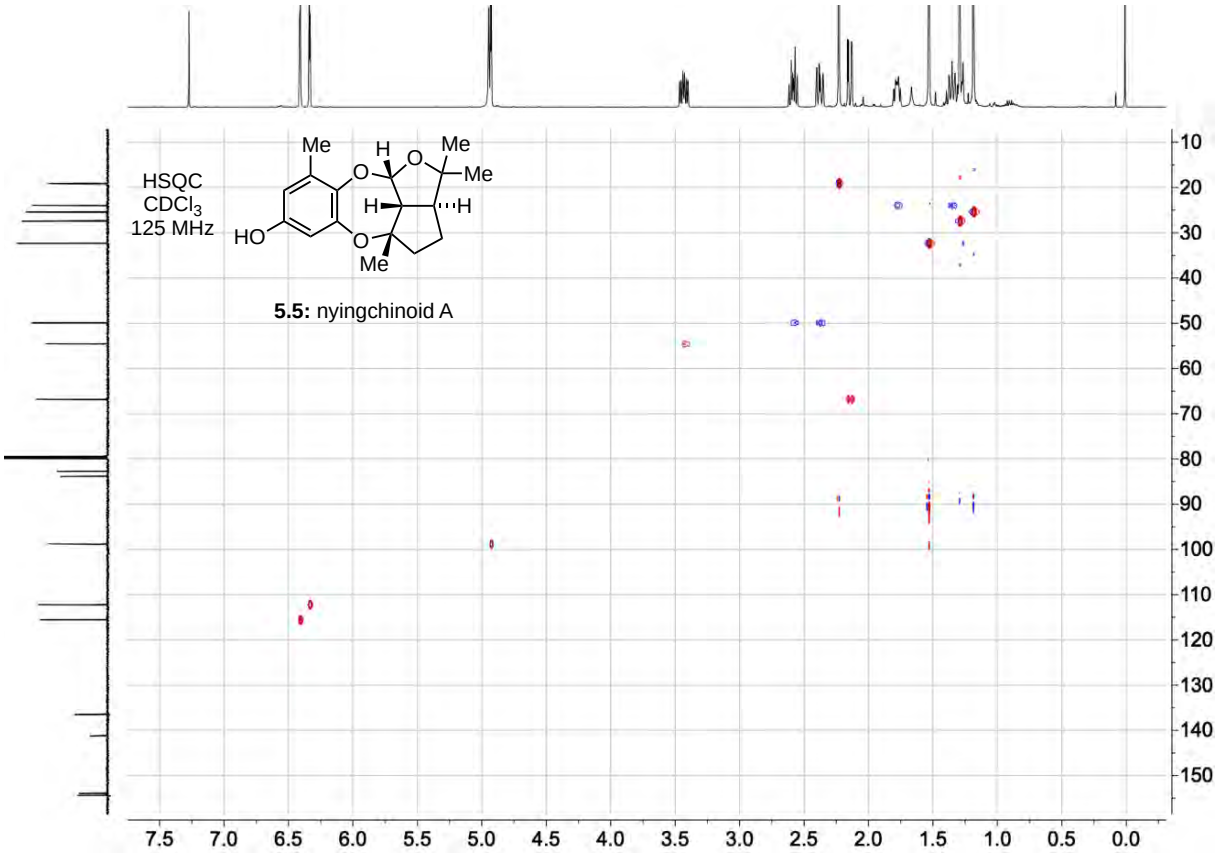
5.5: nyingchinoid A

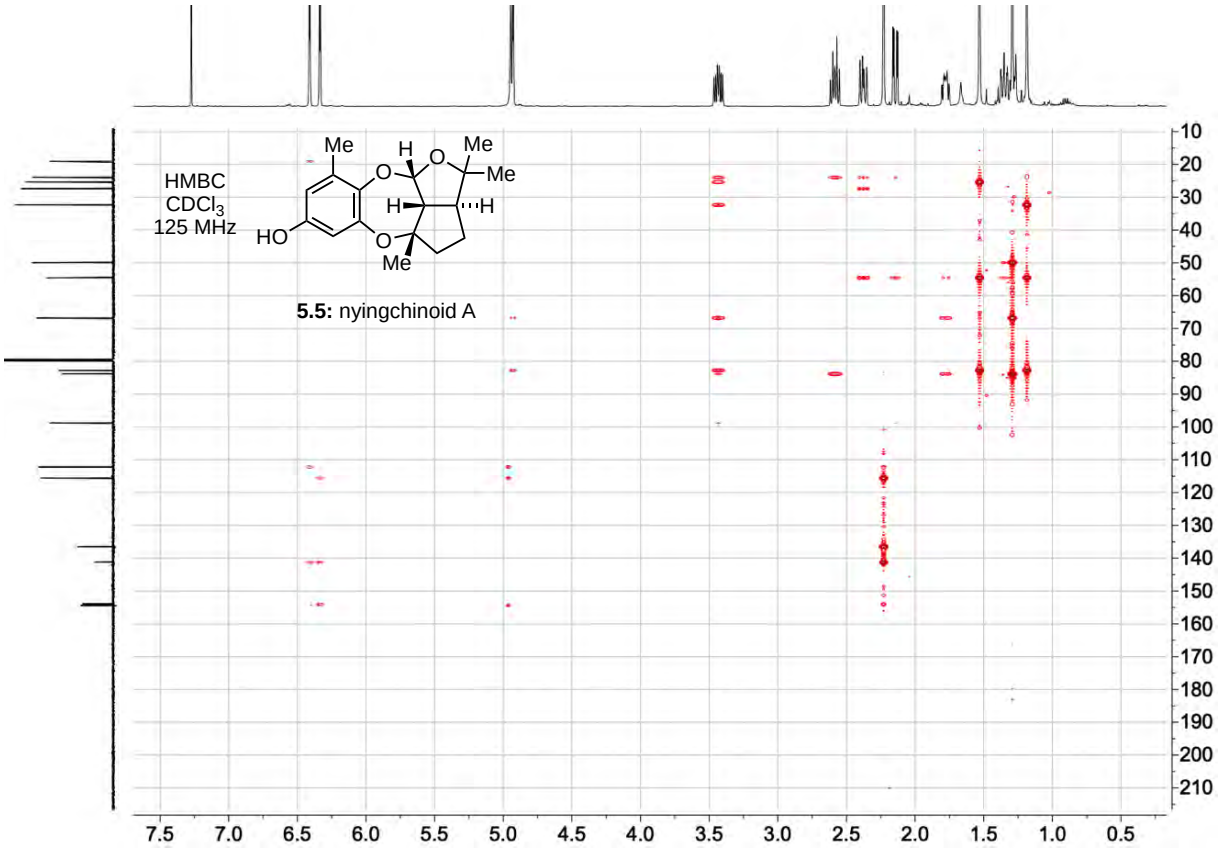
^{13}C NMR
$CDCl_3$
125 MHz



5.5: nyingchinoid A

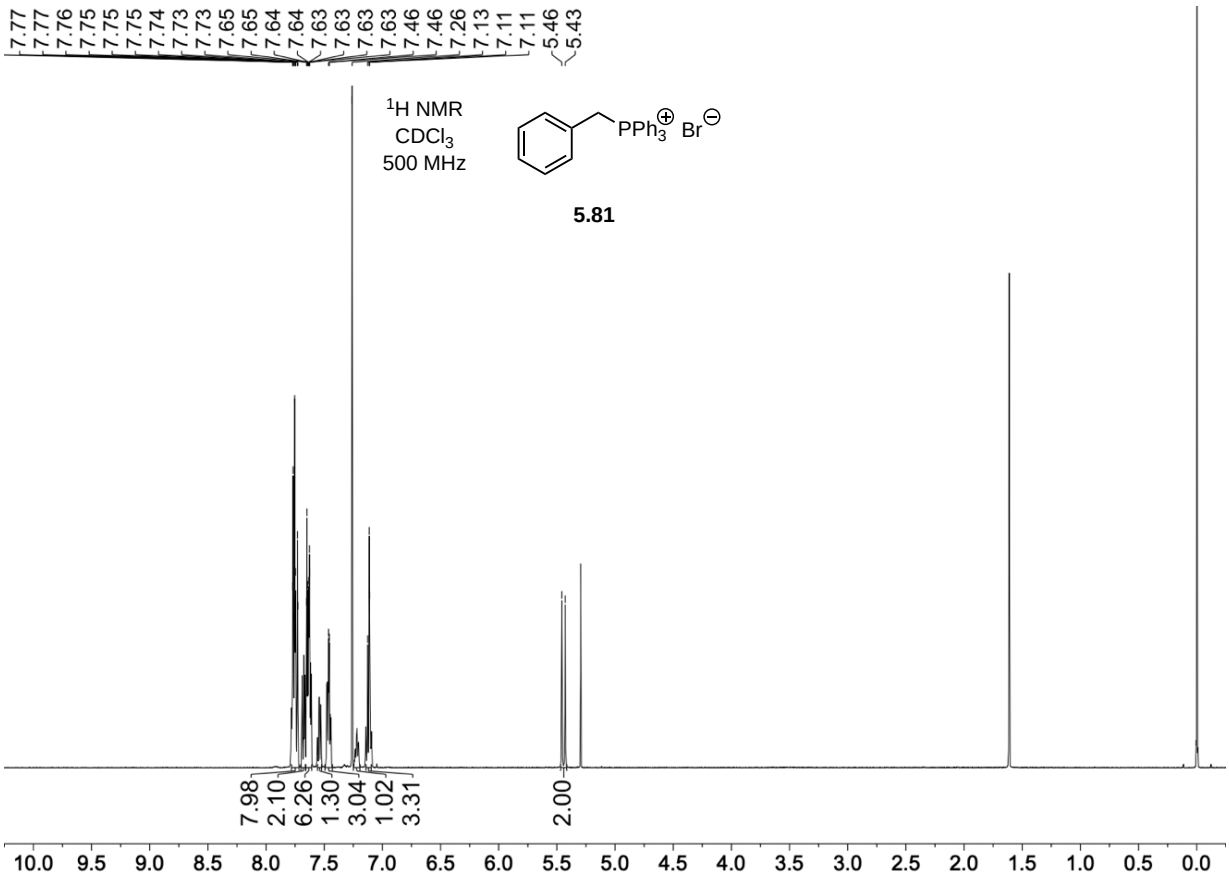

COSY
CDCl3
500 MHz
Me
H
O
Me
Me
H
H
HO
O
Me
5.5: nyingchinoid A

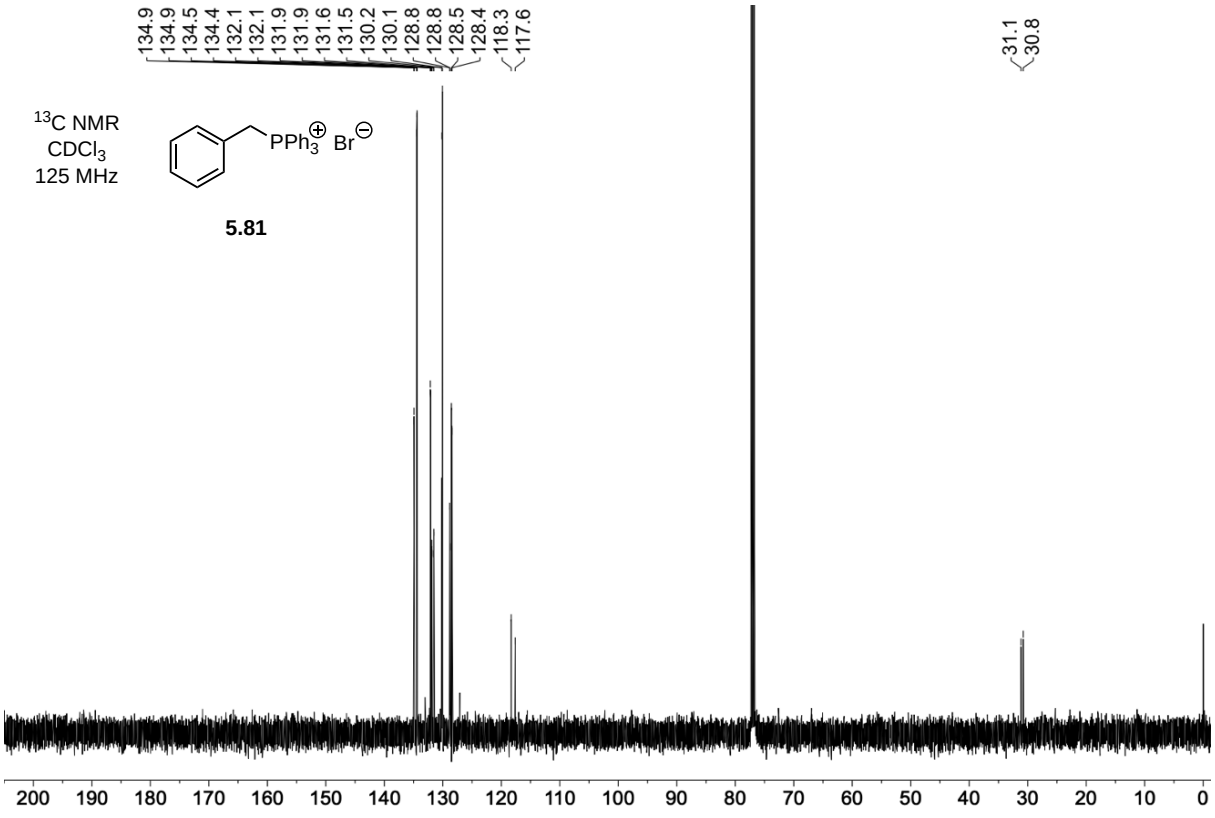

HSQC
CDCl3
125 MHz
Me
H
O
Me
Me
H
H
HO
O
Me
5.5: nyingchinoid A



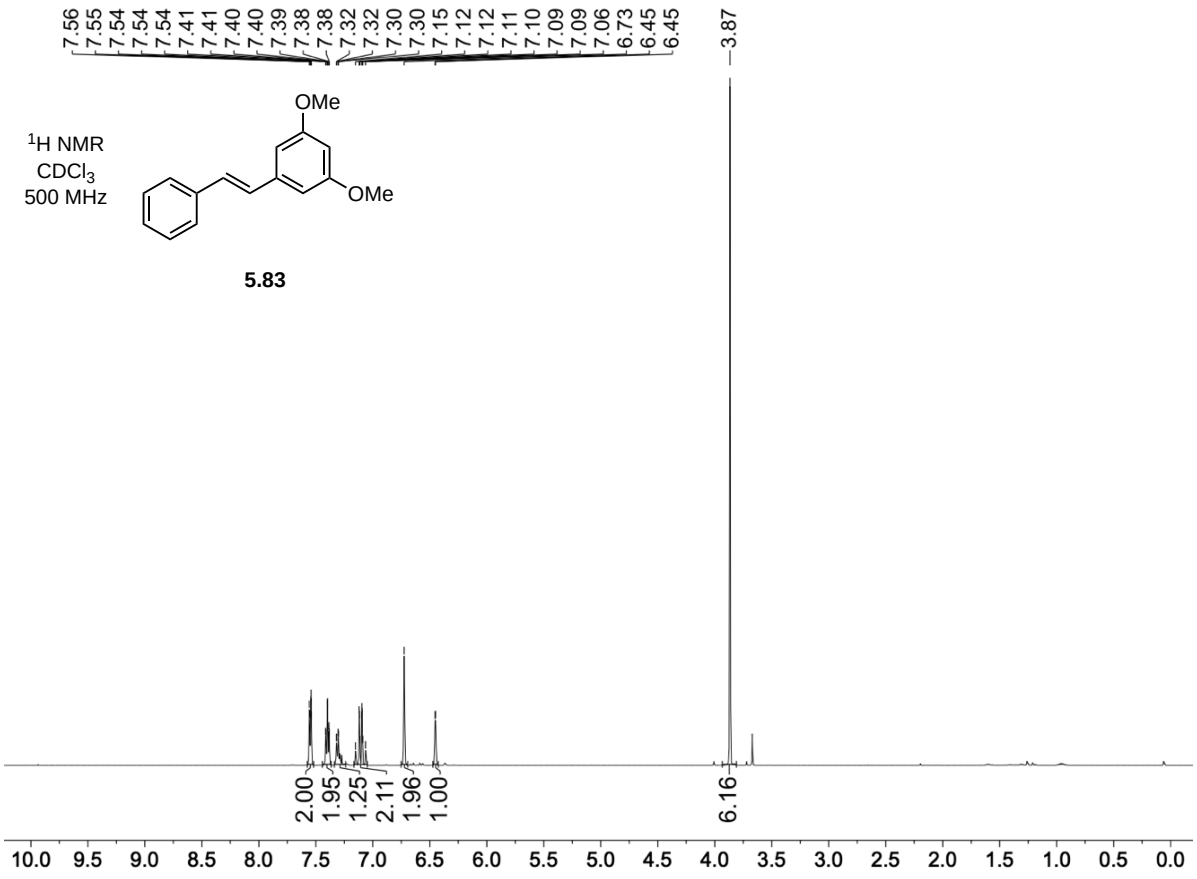
5.5: nyingchinoid A

Data for 5.81

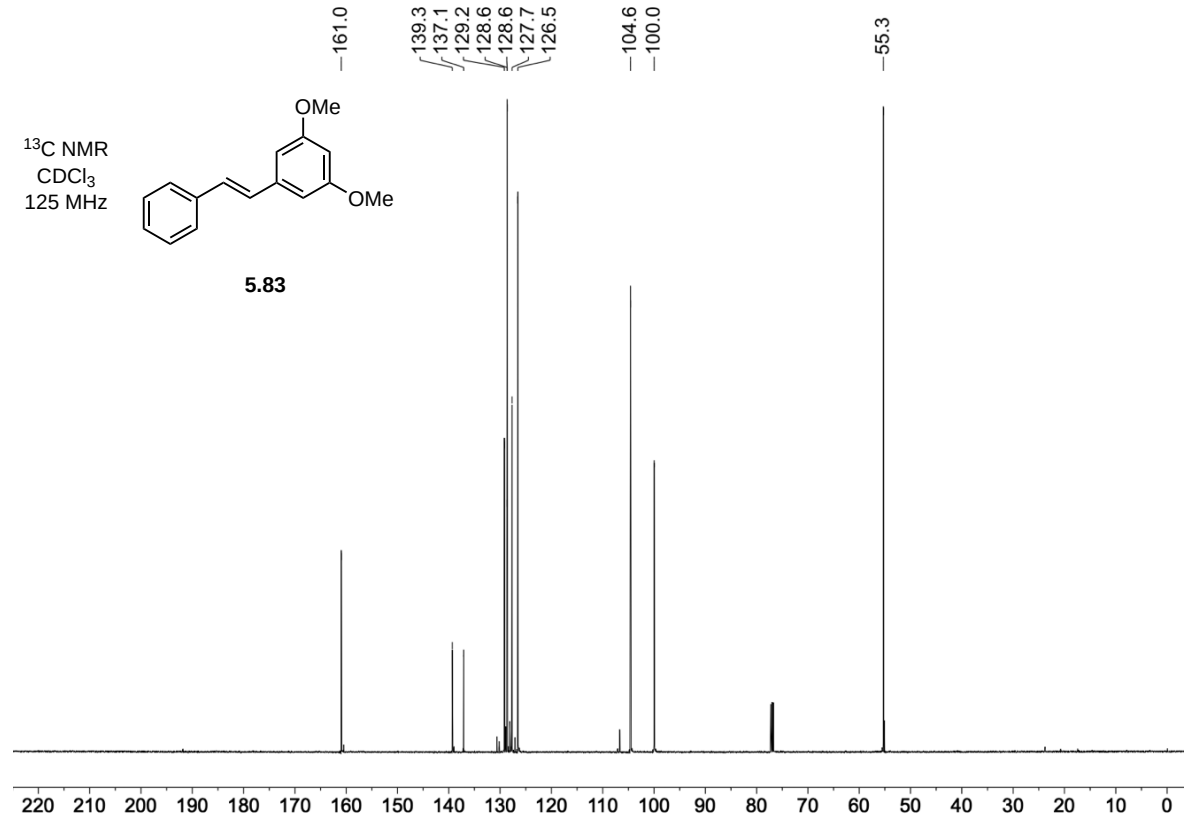

7.77
7.77
7.76
7.75
7.75
7.75
7.74
7.73
7.73
7.65
7.65
7.64
7.64
7.63
7.63
7.63
7.63
7.46
7.46
7.26
7.13
7.11
7.11
5.46
5.43
1H NMR
CDCl3
500 MHz
PPh3 Br
5.81
7.98
2.10
6.26
1.30
3.04
1.02
3.31
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


134.9
134.9
134.5
134.4
132.1
132.1
131.9
131.9
131.6
131.5
130.2
130.1
128.8
128.8
128.5
128.4
118.3
117.6
31.1
30.8
13C NMR
CDCl3
125 MHz
PPh3 Br
5.81
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Data for 5.83

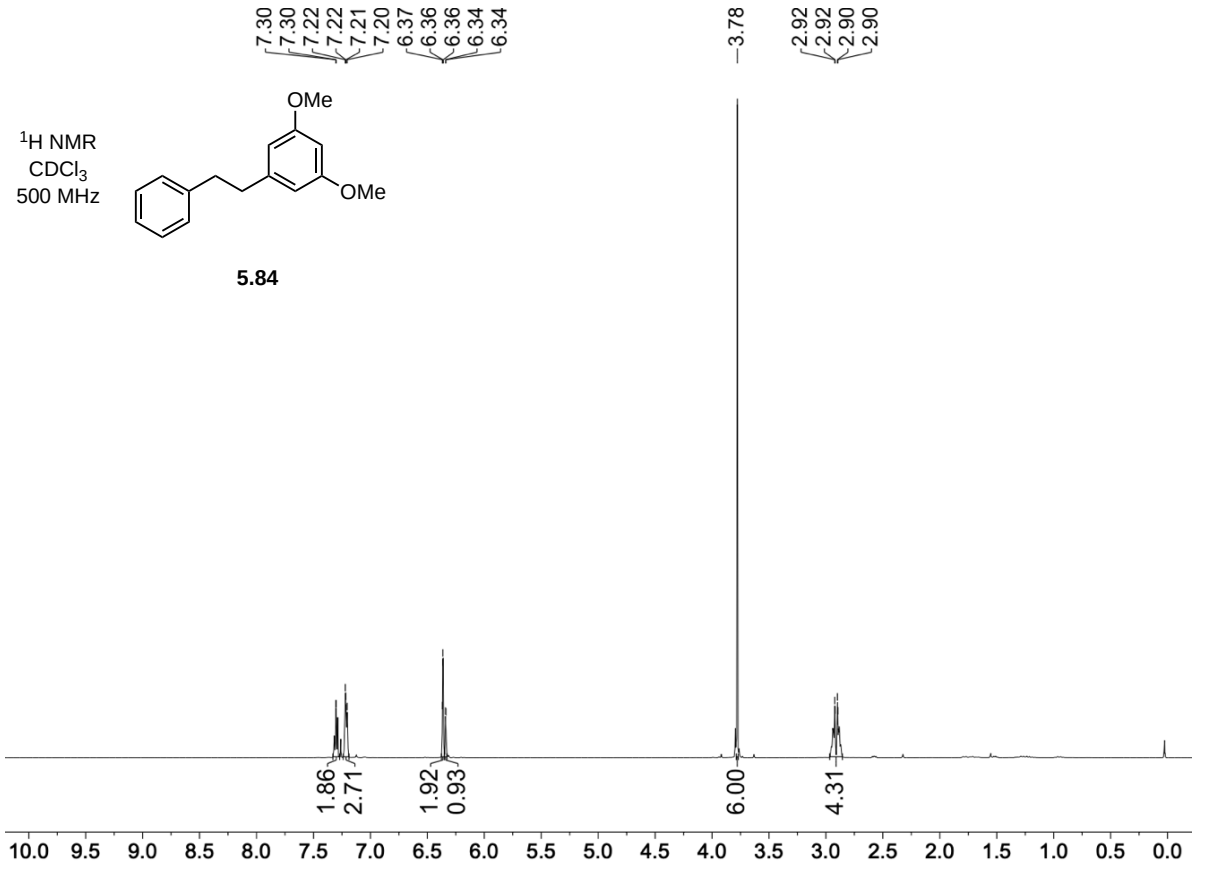


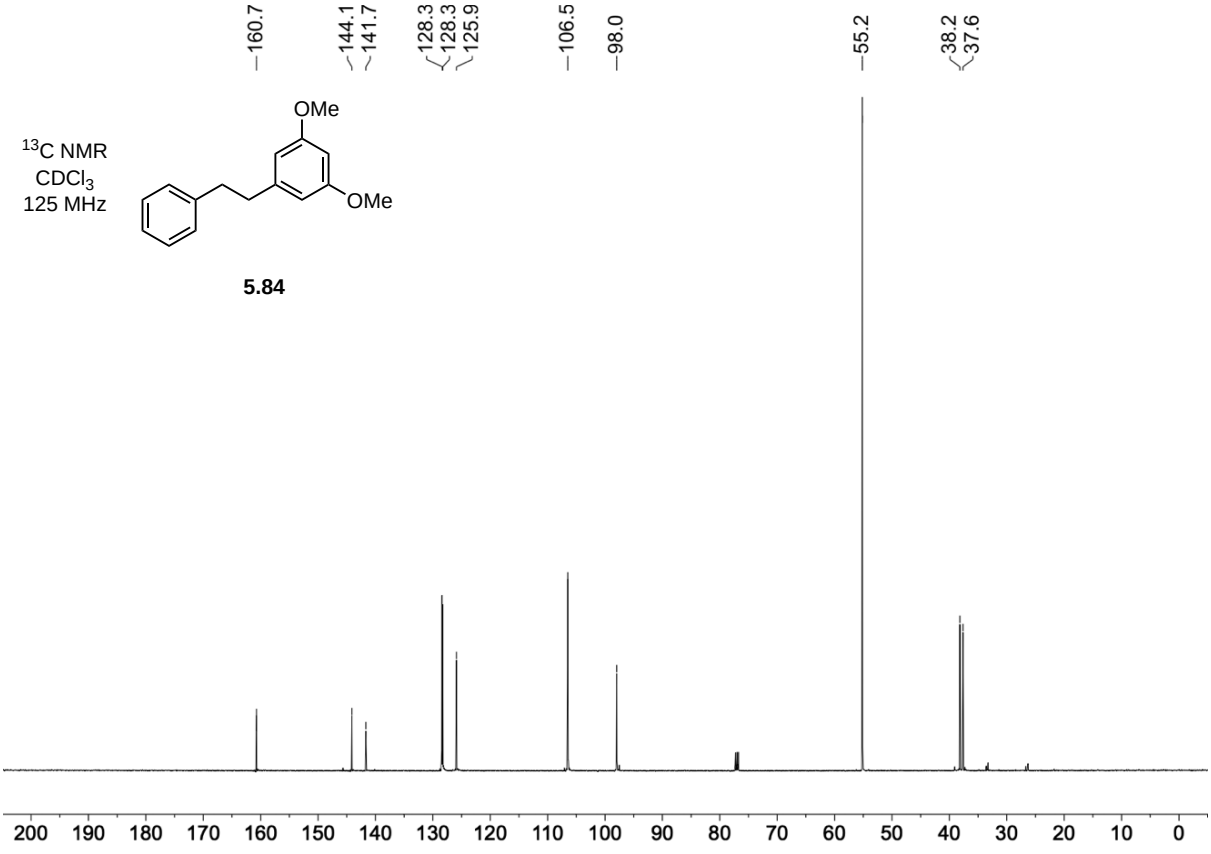
5.83



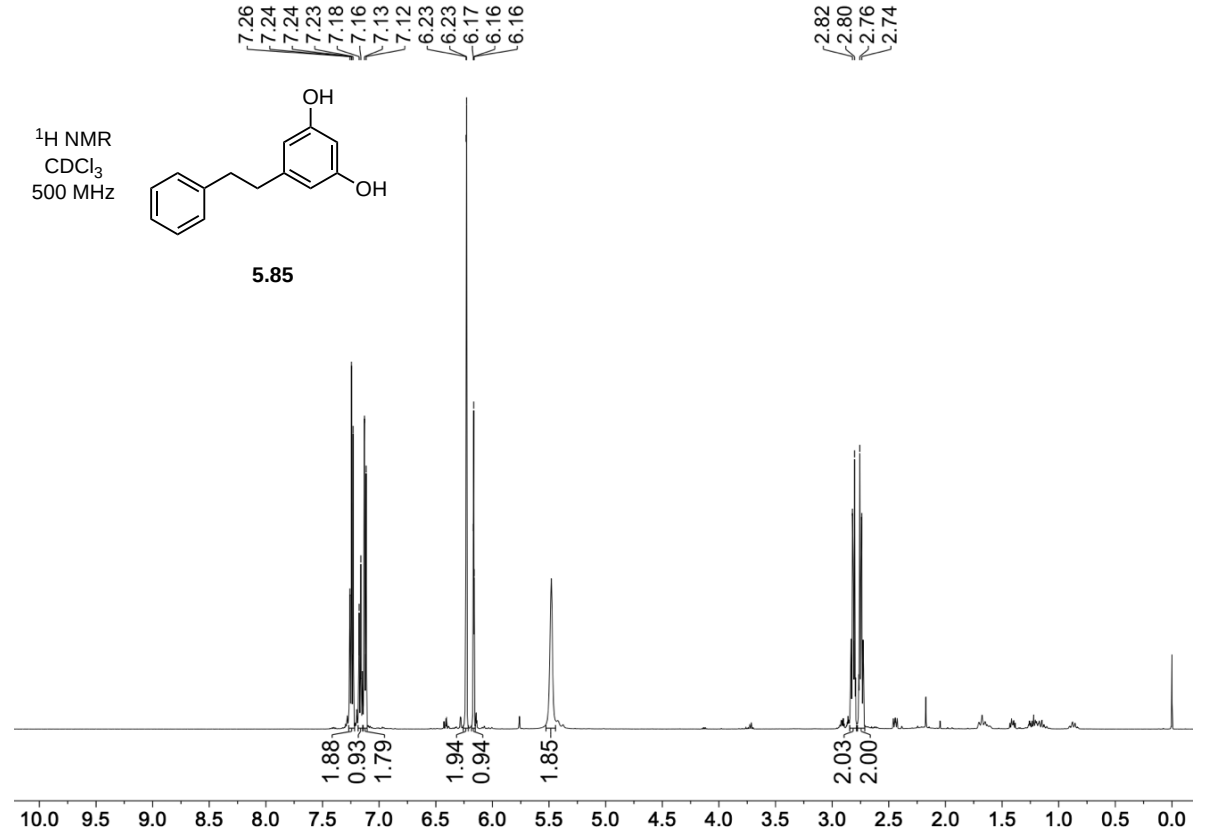
5.83

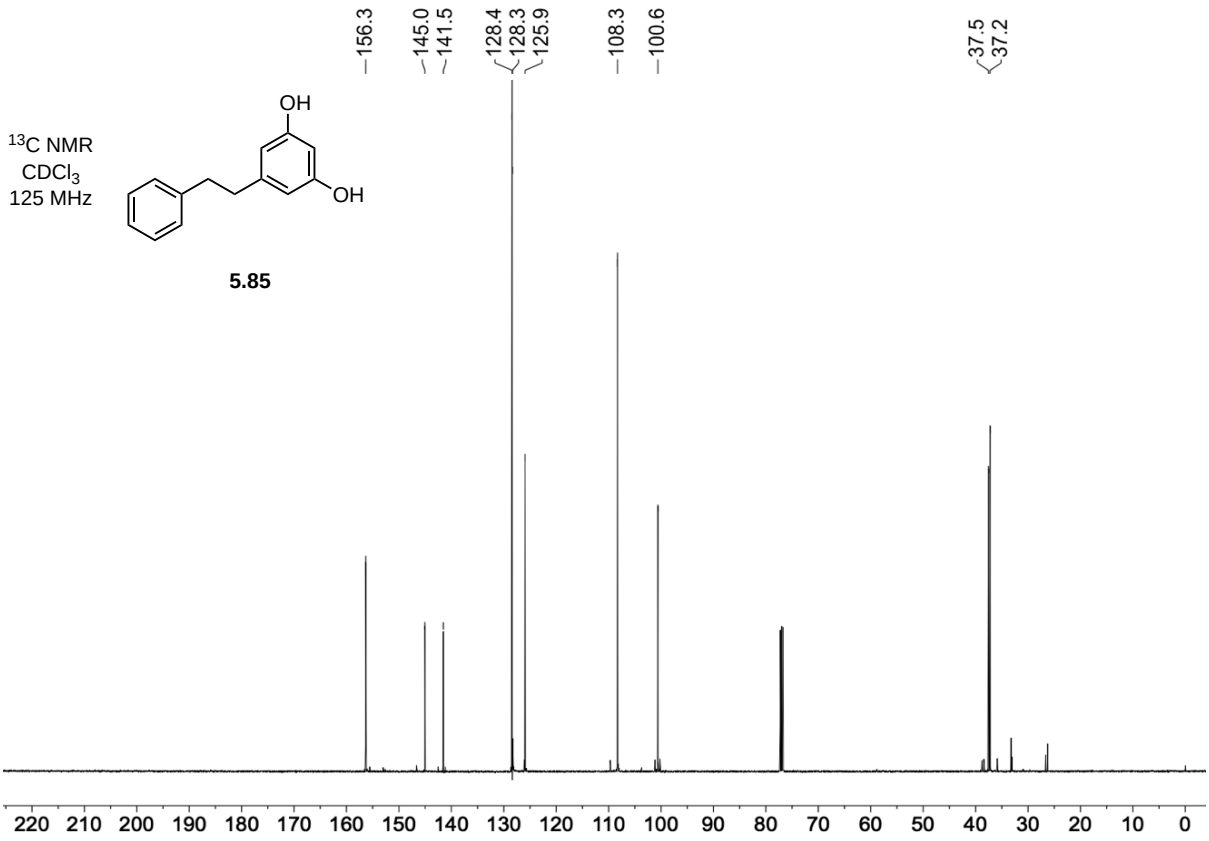
Data for 5.84


7.30
7.30
7.22
7.22
7.21
7.20
6.37
6.36
6.36
6.34
6.34
3.78
2.92
2.92
2.90
2.90
2.90
1H NMR
CDCl3
500 MHz
OMe
OMe
5.84
1.86
2.71
1.92
0.93
6.00
4.31
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

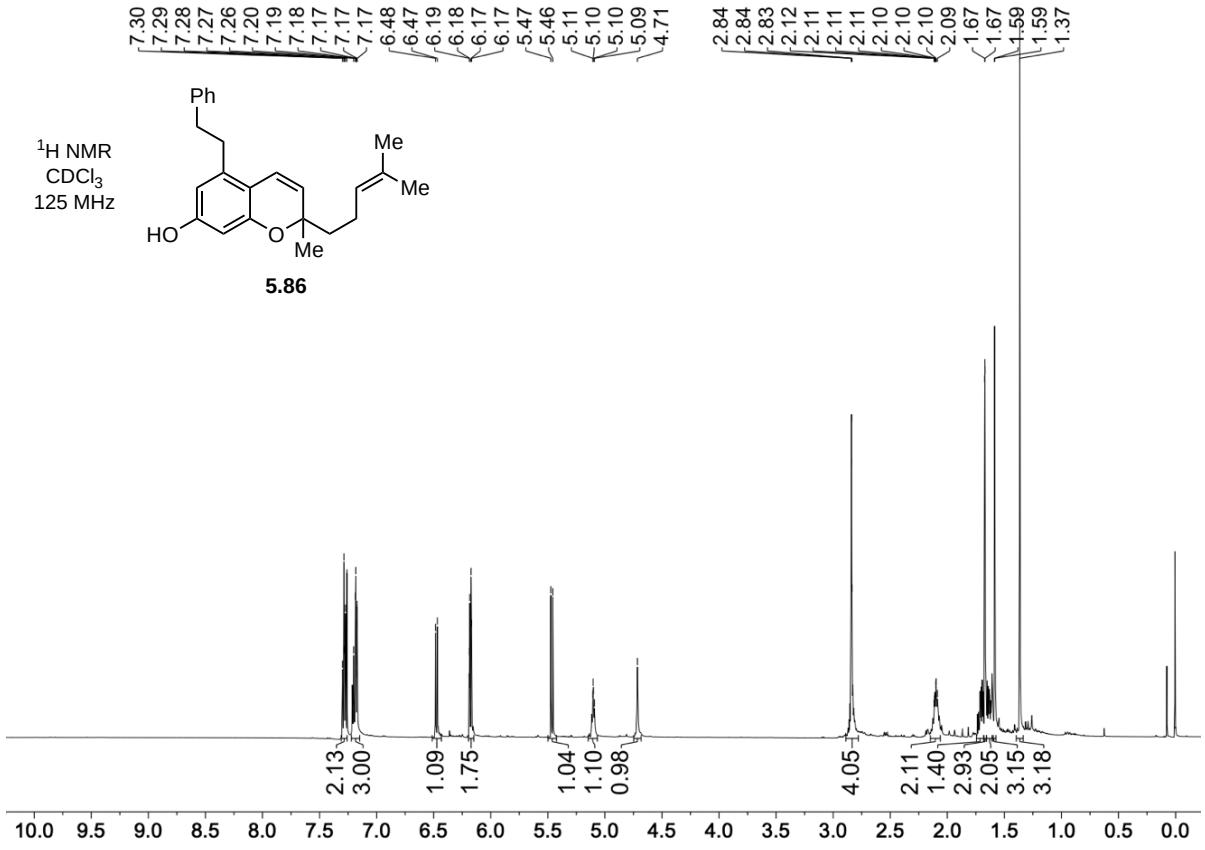

160.7
144.1
141.7
128.3
128.3
125.9
106.5
98.0
55.2
38.2
37.6
13C NMR
CDCl3
125 MHz
OMe
OMe
5.84
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

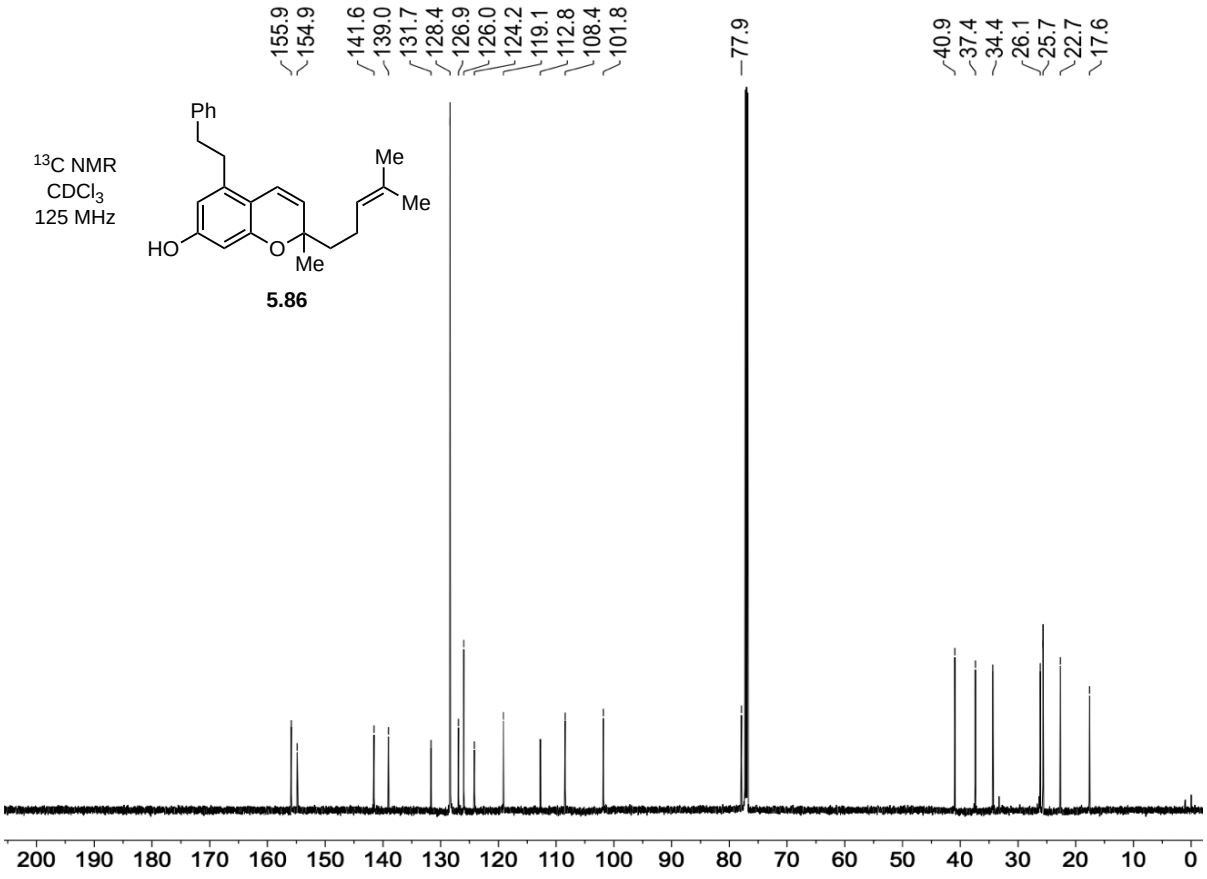
Data for 5.85


7.26
7.24
7.24
7.23
7.18
7.16
7.13
7.12
6.23
6.23
6.17
6.16
6.16
2.82
2.80
2.76
2.74
^{1}H NMR
$CDCl_3$
500 MHz
OH
OH
5.85
1.88
0.93
1.79
1.94
0.94
1.85
2.03
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

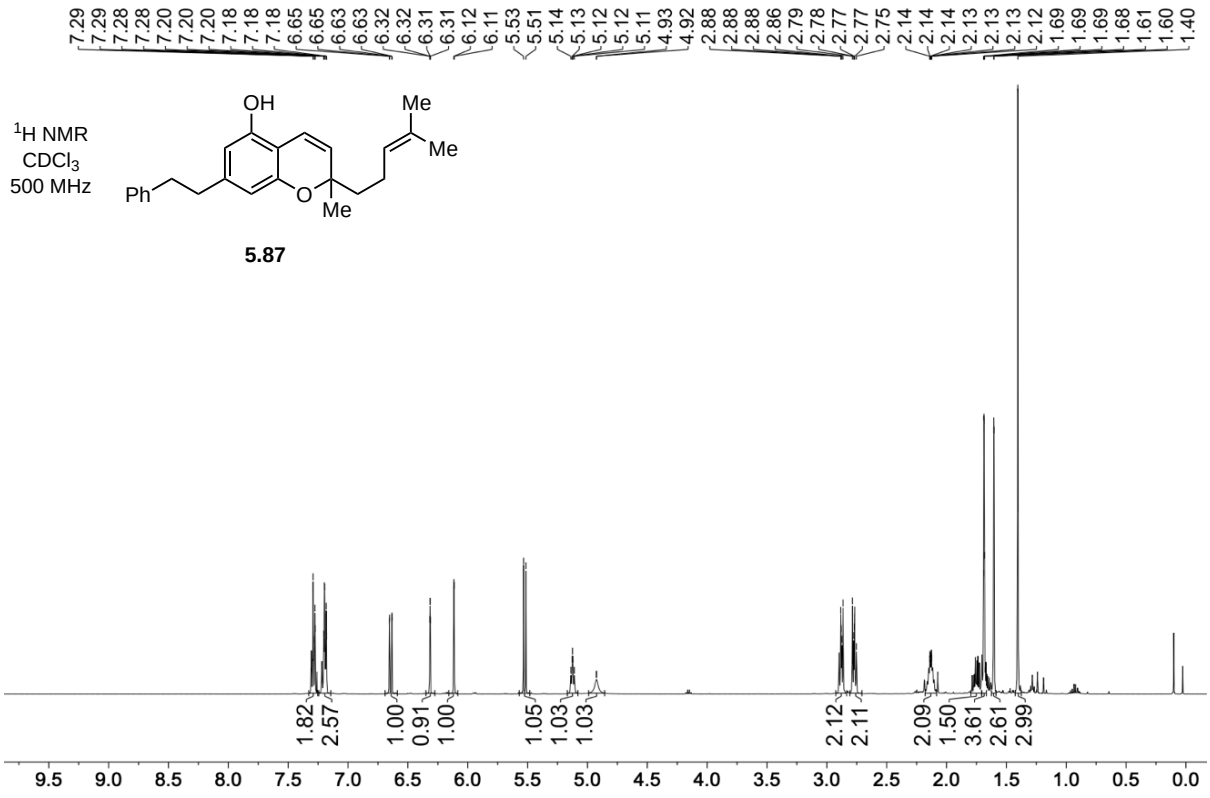

156.3
145.0
141.5
128.4
128.3
125.9
108.3
100.6
37.5
37.2
^{13}C NMR
$CDCl_3$
125 MHz
OH
OH
5.85
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

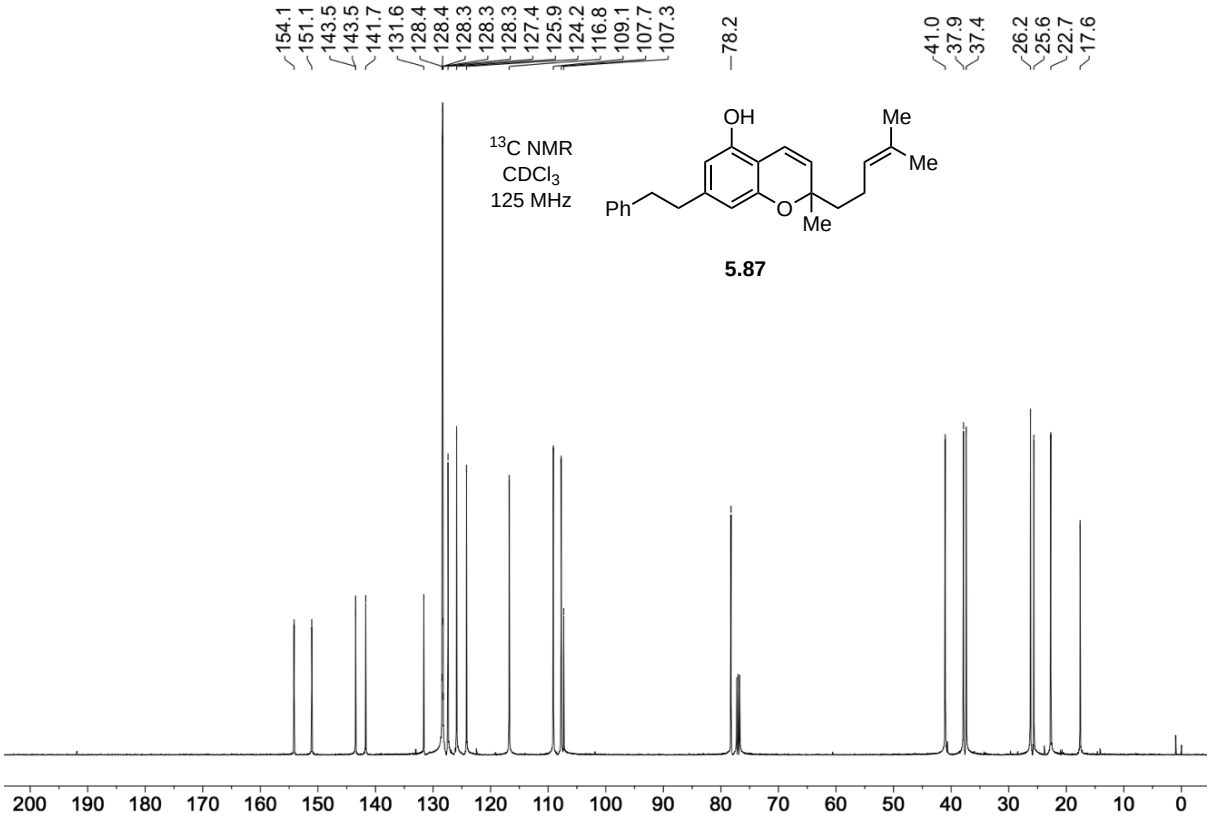
Data for 5.86


7.30 7.29 7.28 7.27 7.26 7.20 7.19 7.18 7.17 7.17 7.17 6.48 6.47 6.19 6.18 6.17 6.17 5.47 5.46 5.11 5.10 5.10 5.09 4.71
2.84 2.84 2.83 2.12 2.11 2.11 2.11 2.10 2.10 2.10 2.09 1.67 1.59 1.59 1.37
^{1}H NMR
$CDCl_3$
125 MHz
Ph
Me
Me
HO
O
Me
5.86
2.13 3.00 1.09 1.75 1.04 1.10 0.98 4.05 2.11 1.40 2.93 2.05 3.15 3.18
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

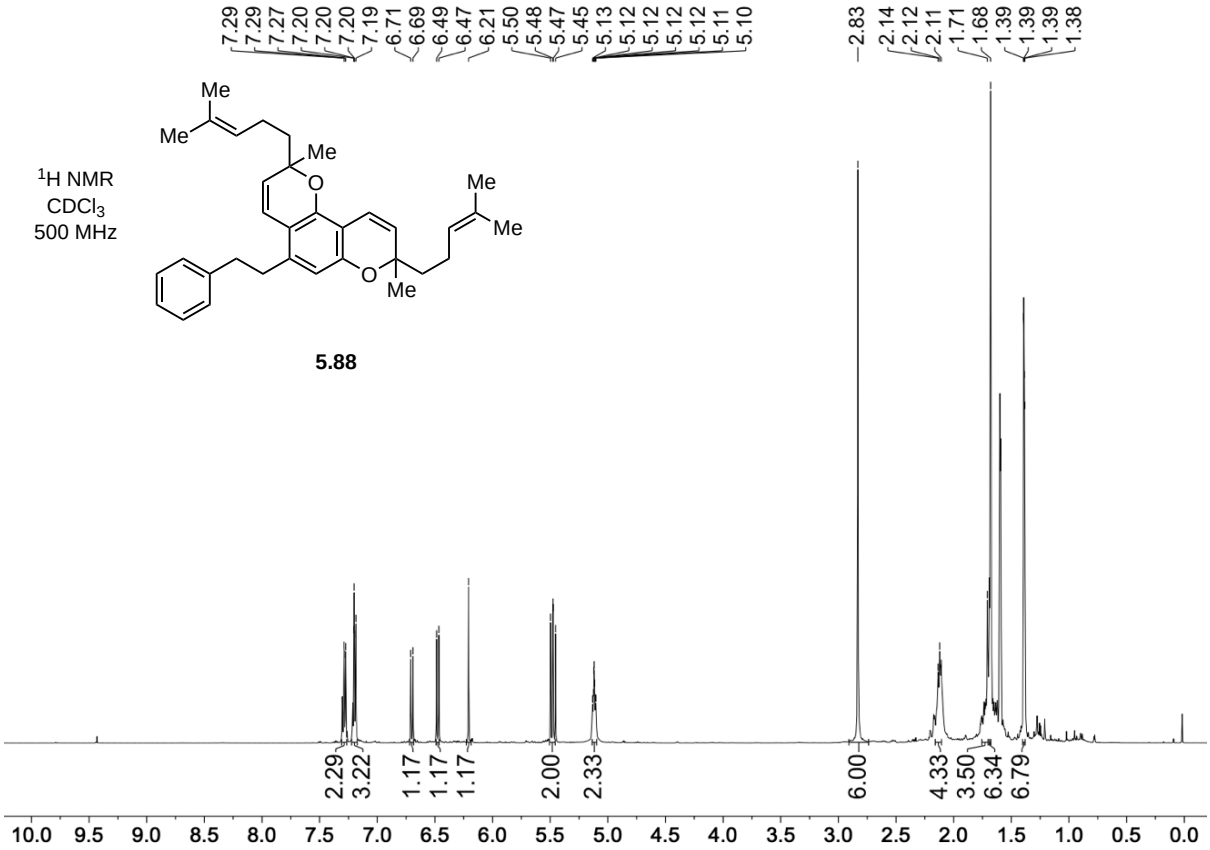

155.9 154.9 141.6 139.0 131.7 128.4 126.9 126.0 124.2 119.1 112.8 108.4 101.8
77.9
40.9 37.4 34.4 26.1 25.7 22.7 17.6
^{13}C NMR
$CDCl_3$
125 MHz
Ph
Me
Me
HO
O
Me
5.86
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Data for 5.87

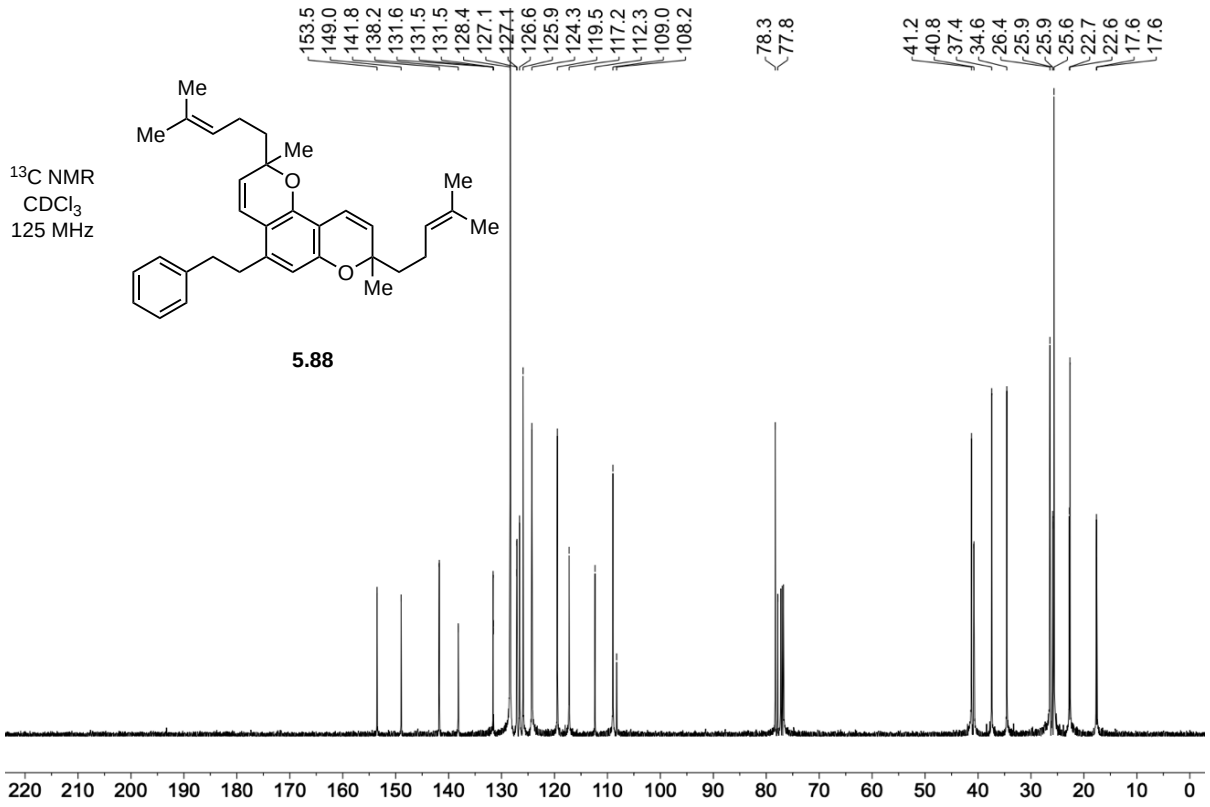

7.29 7.29 7.28 7.28 7.20 7.20 7.20 7.18 7.18 7.18 6.65 6.65 6.63 6.63 6.32 6.32 6.31 6.31 6.12 6.11 5.53 5.51 5.14 5.13 5.12 5.12 5.11 4.93 4.92 2.88 2.88 2.88 2.86 2.79 2.78 2.77 2.77 2.75 2.14 2.14 2.14 2.13 2.13 2.13 2.12 1.69 1.69 1.69 1.68 1.61 1.60 1.40
1H NMR
CDCl3
500 MHz
OH
Me
Me
Ph
O
Me
5.87
1.82 2.57 1.00 0.91 1.00 1.05 1.03 1.03 2.12 2.11 2.09 1.50 3.61 2.61 2.99
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


154.1 151.1 143.5 143.5 141.7 131.6 128.4 128.4 128.3 128.3 128.3 127.4 125.9 124.2 116.8 109.1 107.7 107.3
78.2
41.0 37.9 37.4
26.2 25.6 22.7 17.6
13C NMR
CDCl3
125 MHz
OH
Me
Me
Ph
O
Me
5.87
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Data for 5.88

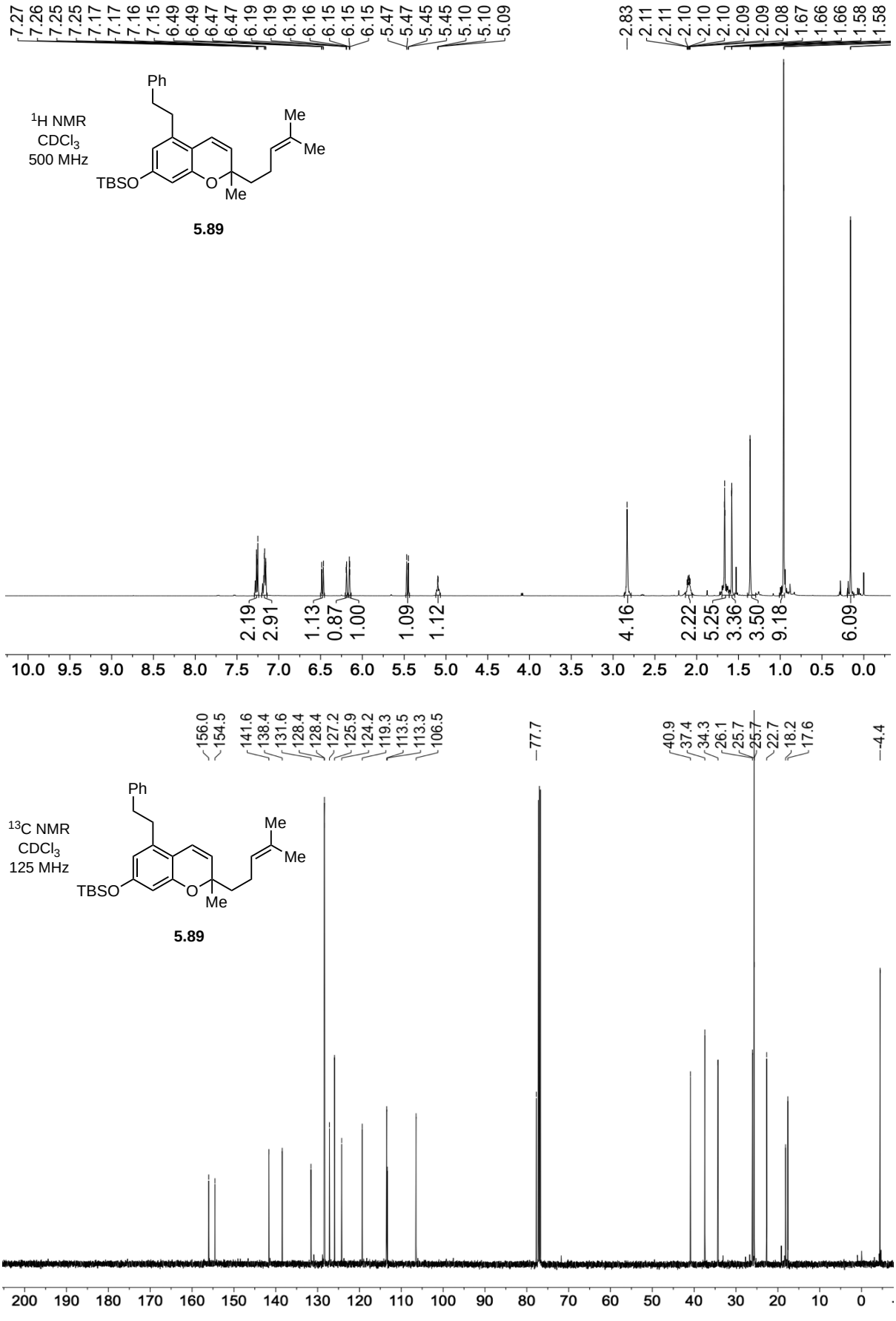


5.88

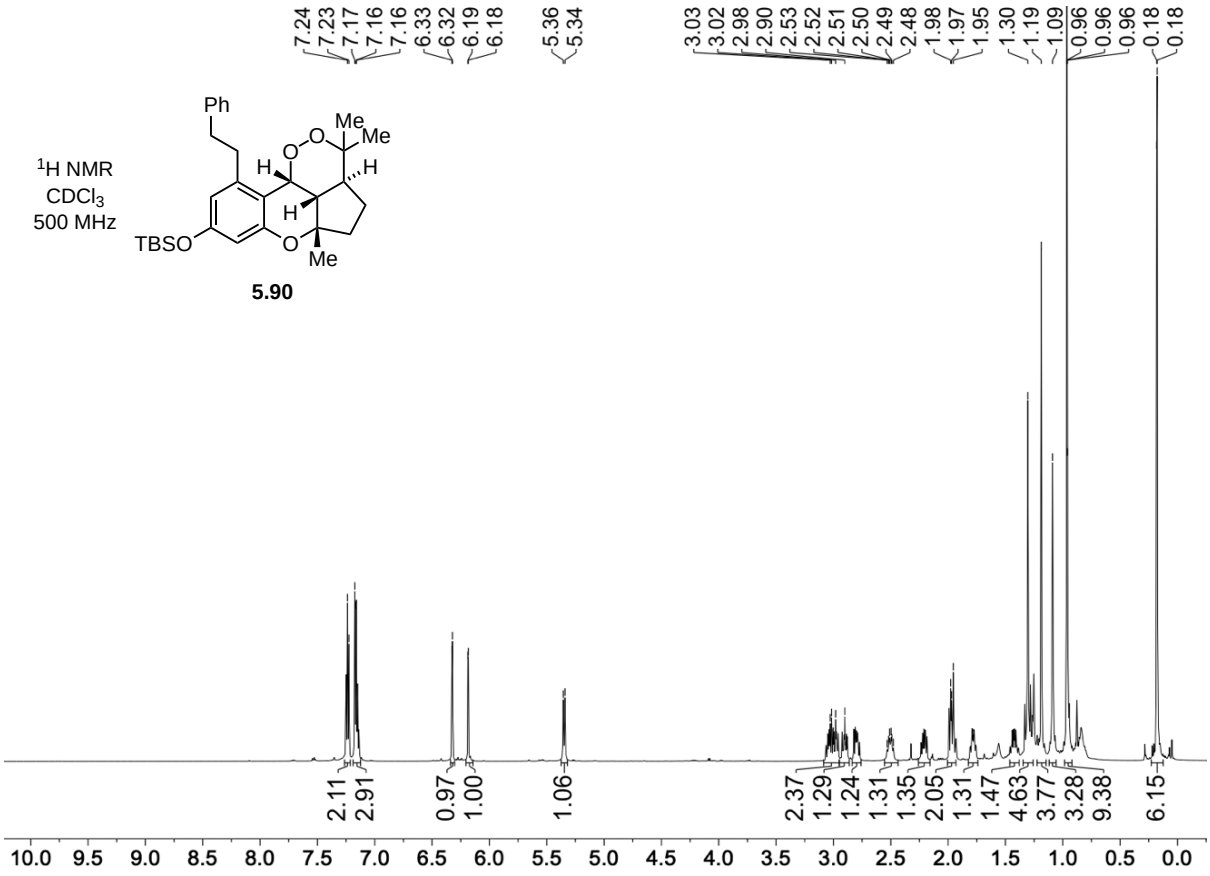


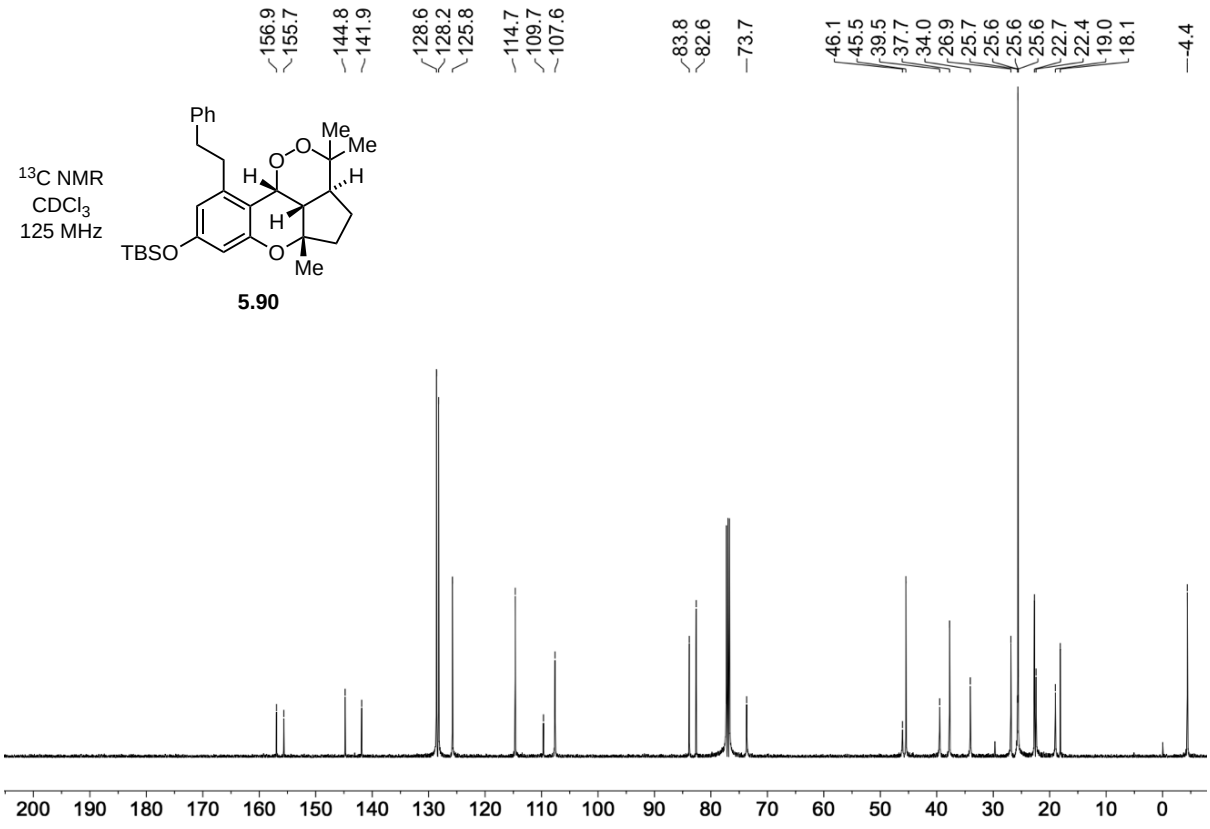
5.88

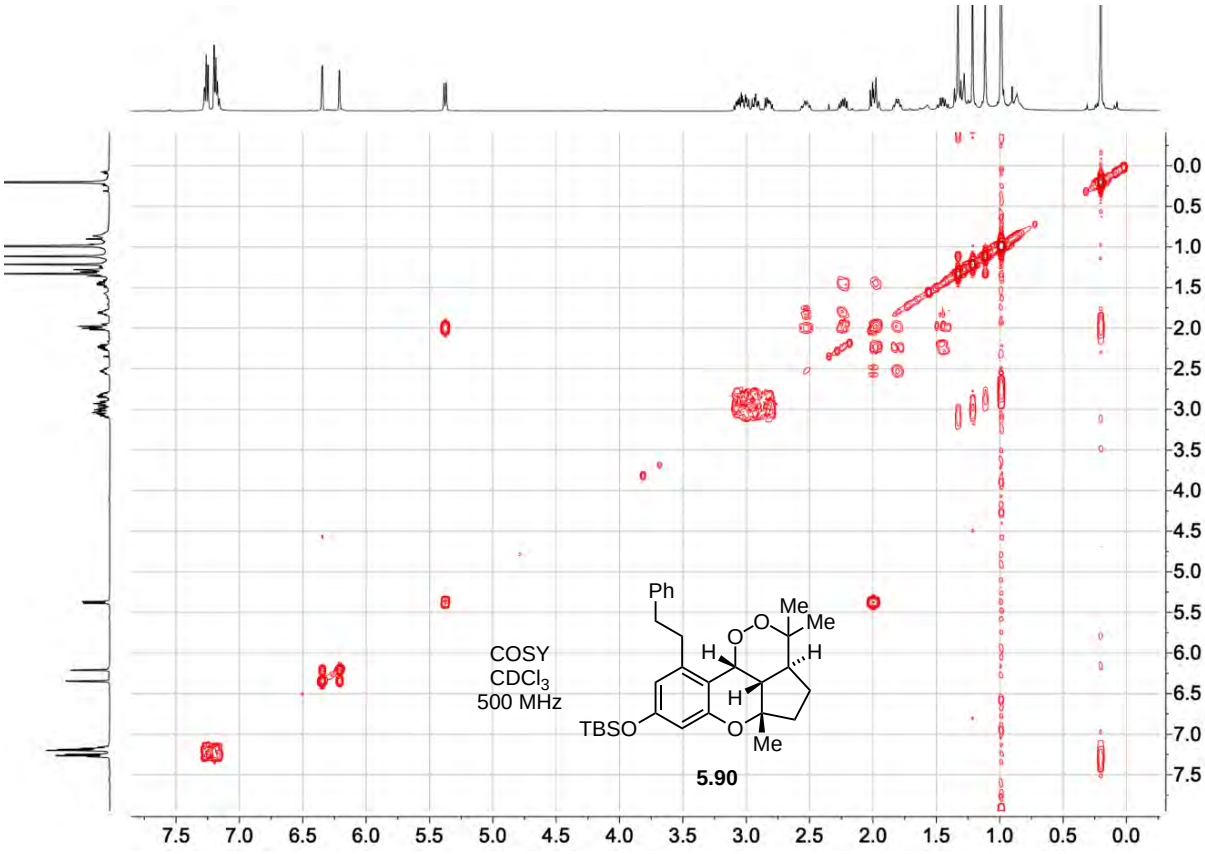
Data for 5.89

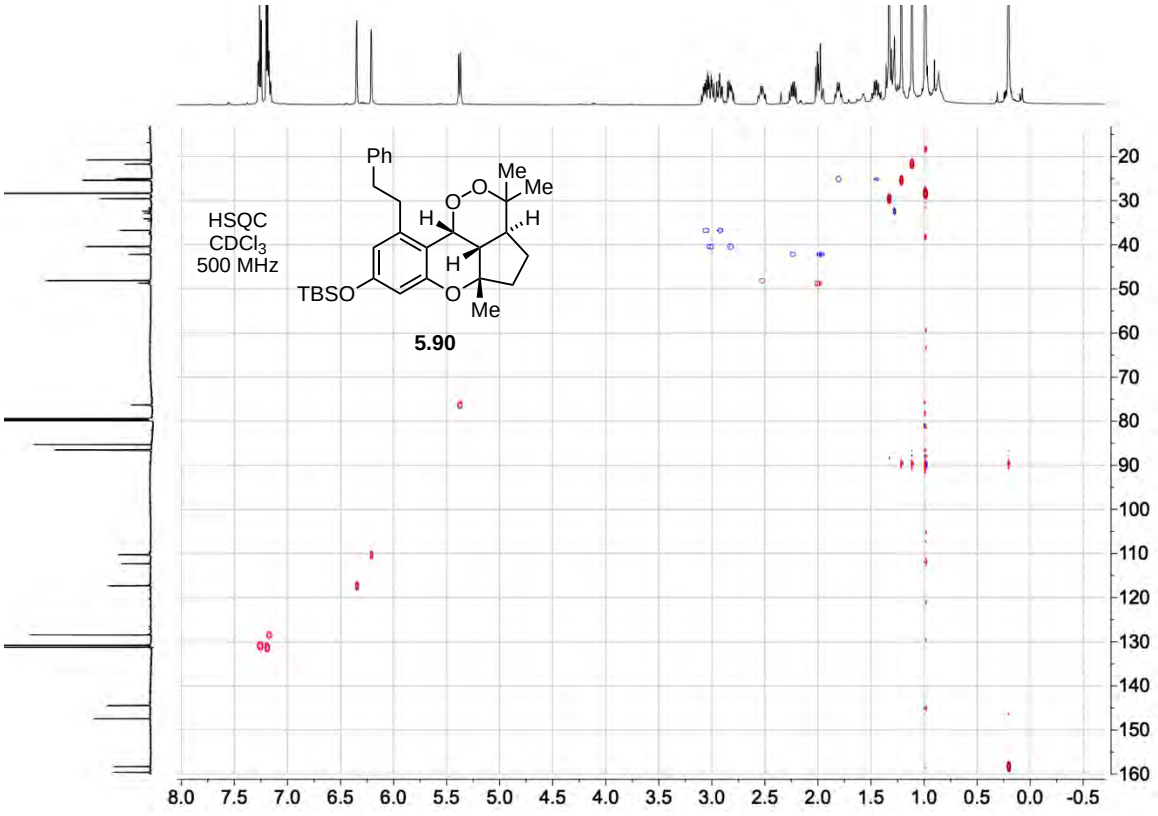

7.27 7.26 7.25 7.25 7.17 7.17 7.16 7.15 6.49 6.49 6.47 6.47 6.19 6.19 6.19 6.16 6.15 6.15 6.15 5.47 5.47 5.45 5.45 5.10 5.10 5.09
2.83 2.11 2.11 2.10 2.10 2.10 2.09 2.09 2.08 1.67 1.66 1.58 1.58
1H NMR
CDCl3
500 MHz
Ph
Me
Me
TBSO
O
Me
5.89
2.19 2.91 1.13 0.87 1.00 1.09 1.12 4.16 2.22 5.25 3.36 3.50 9.18 6.09
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
156.0 154.5 141.6 138.4 131.6 128.4 128.4 127.2 125.9 124.2 119.3 113.5 113.3 106.5
77.7
40.9 37.4 34.3 26.1 25.7 25.7 22.7 18.2 17.6
-4.4
13C NMR
CDCl3
125 MHz
Ph
Me
Me
TBSO
O
Me
5.89
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

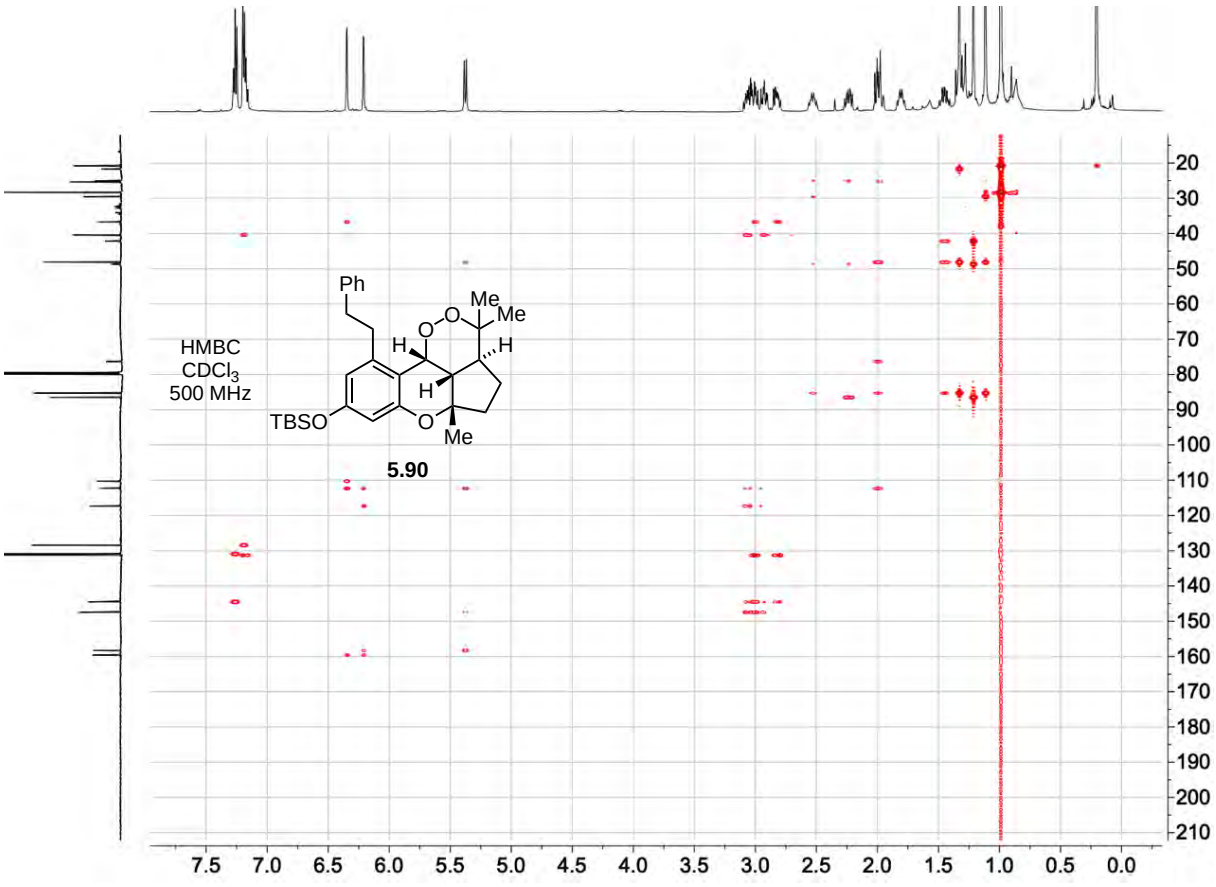
Data for 5.90

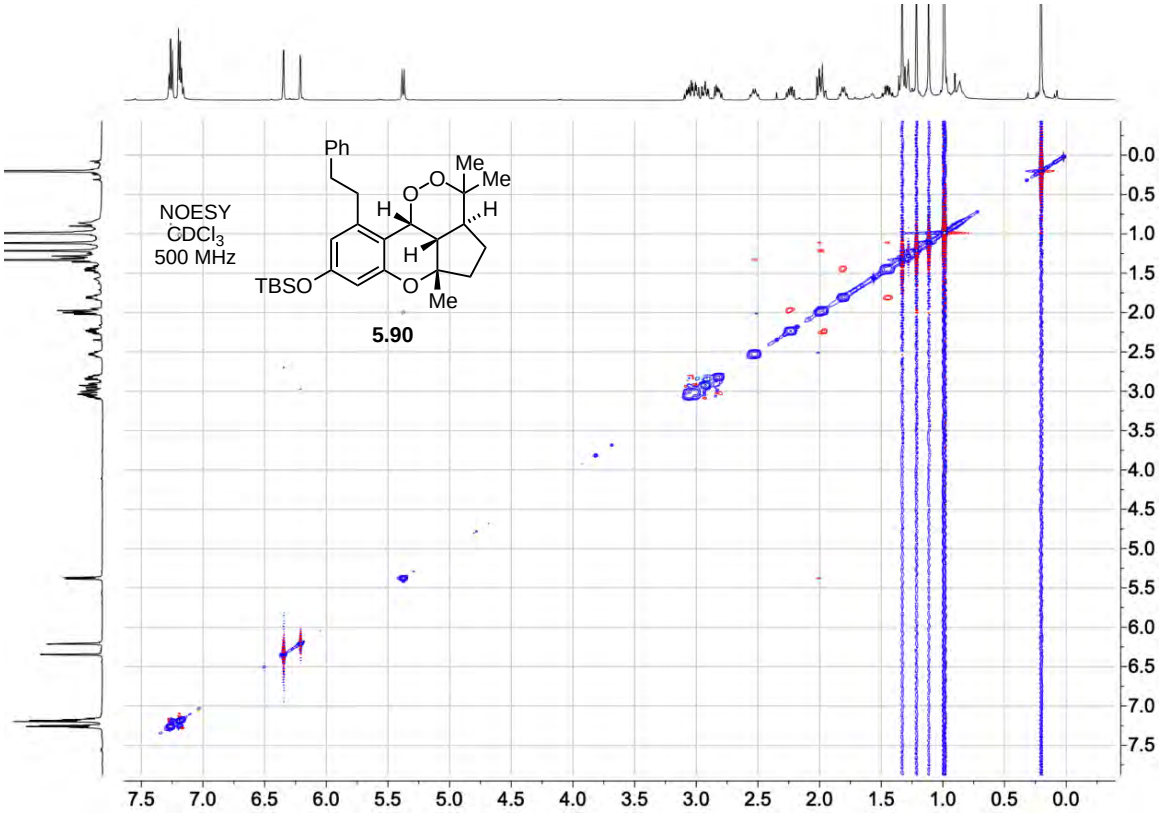

7.24
7.23
7.17
7.16
7.16
6.33
6.32
6.19
6.18
5.36
5.34
3.03
3.02
2.98
2.90
2.53
2.52
2.51
2.50
2.49
2.48
1.98
1.97
1.95
1.30
1.19
1.09
0.96
0.96
0.96
0.18
0.18
Ph
Me
Me
O
O
H
H
H
TBSO
O
Me
1H NMR
CDCl3
500 MHz
5.90
2.11
2.91
0.97
1.00
1.06
2.37
1.29
1.24
1.31
1.35
2.05
1.31
1.47
4.63
3.77
3.28
9.38
6.15
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


156.9
155.7
144.8
141.9
128.6
128.2
125.8
114.7
109.7
107.6
83.8
82.6
73.7
46.1
45.5
39.5
37.7
34.0
26.9
25.7
25.6
25.6
25.6
22.7
22.4
19.0
18.1
-4.4
Ph
Me
Me
O
O
H
H
H
TBSO
O
Me
13C NMR
CDCl3
125 MHz
5.90
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

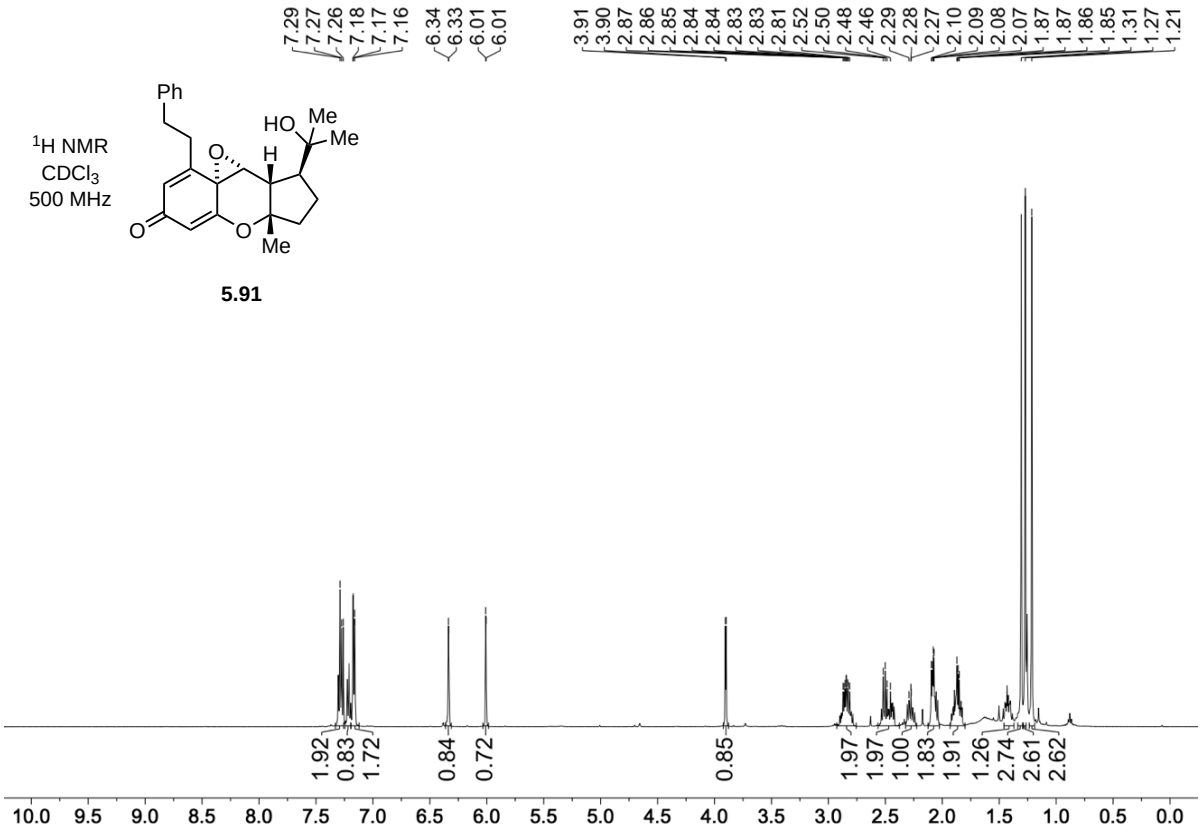

COSY
CDCl3
500 MHz
Ph
Me
Me
O
O
H
H
H
TBSO
O
Me
5.90

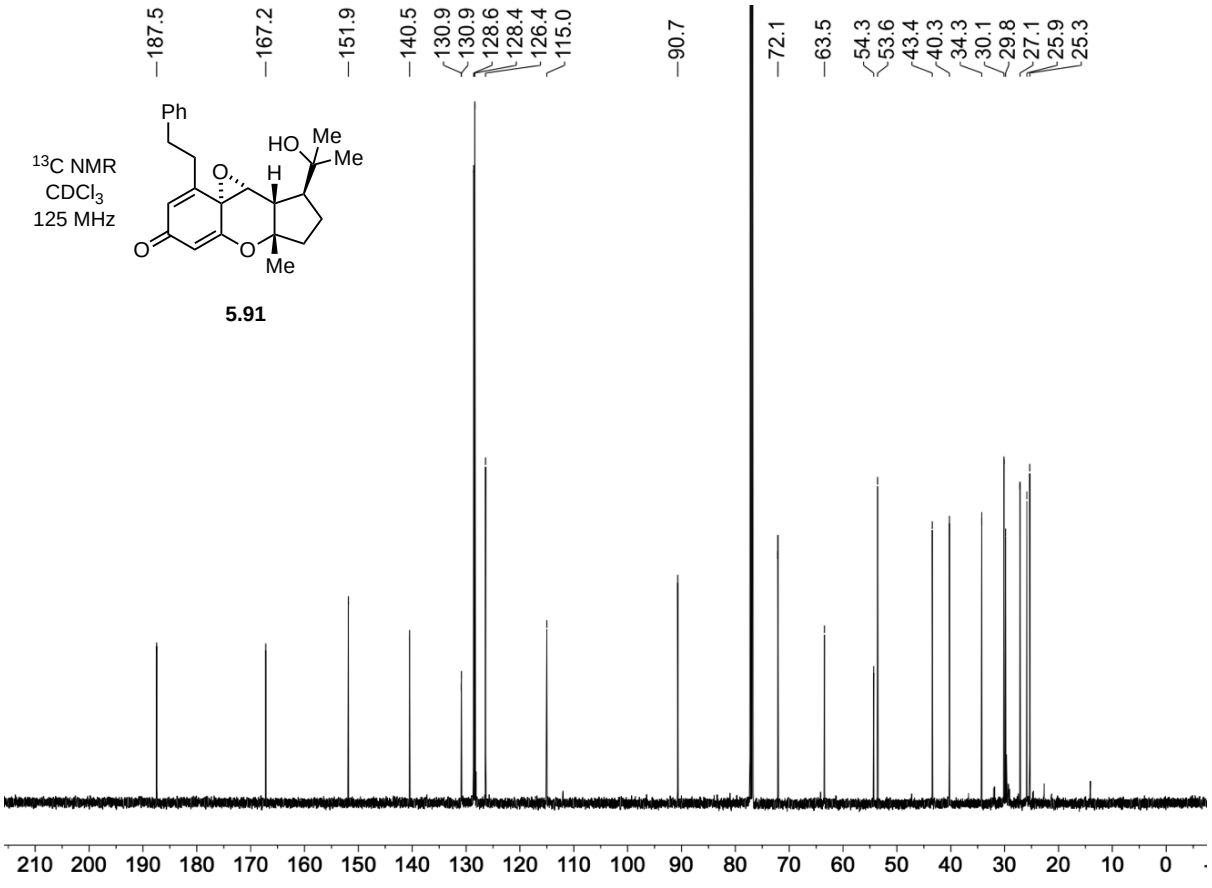

HSQC
CDCl3
500 MHz
Ph
Me
Me
O
O
H
H
H
TBSO
O
Me
5.90

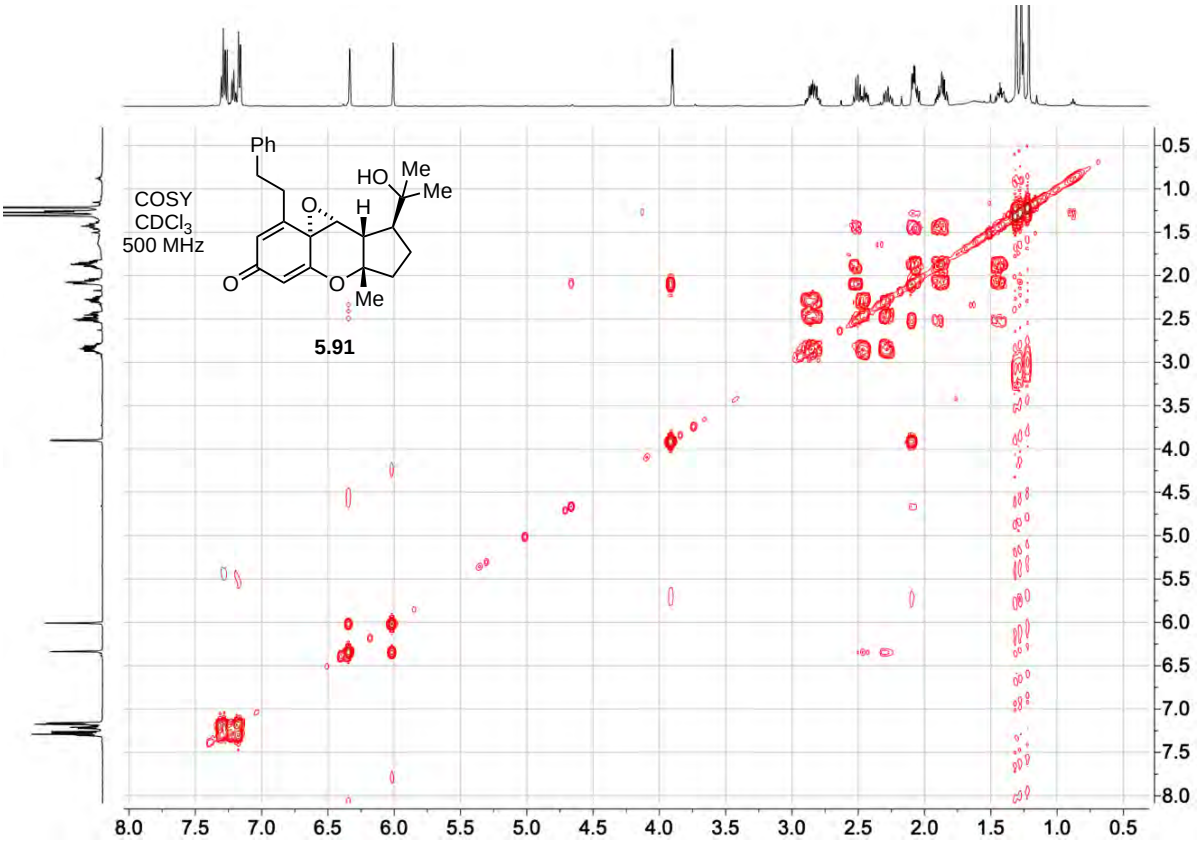

HMBC
CDCl3
500 MHz
Ph
Me
Me
O
O
H
H
H
TBSO
O
Me
5.90

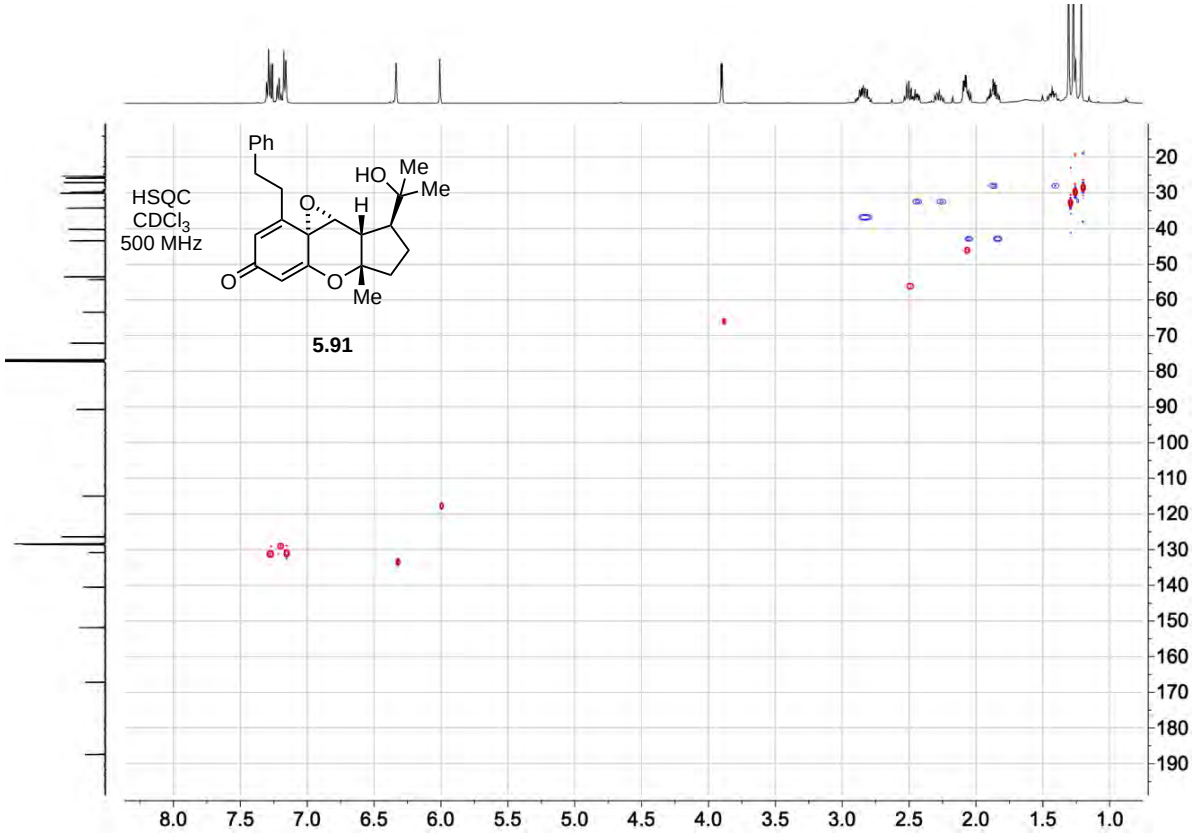

NOESY
CDCl3
500 MHz
Ph
Me
Me
O
O
H
H
H
TBSO
O
Me
5.90

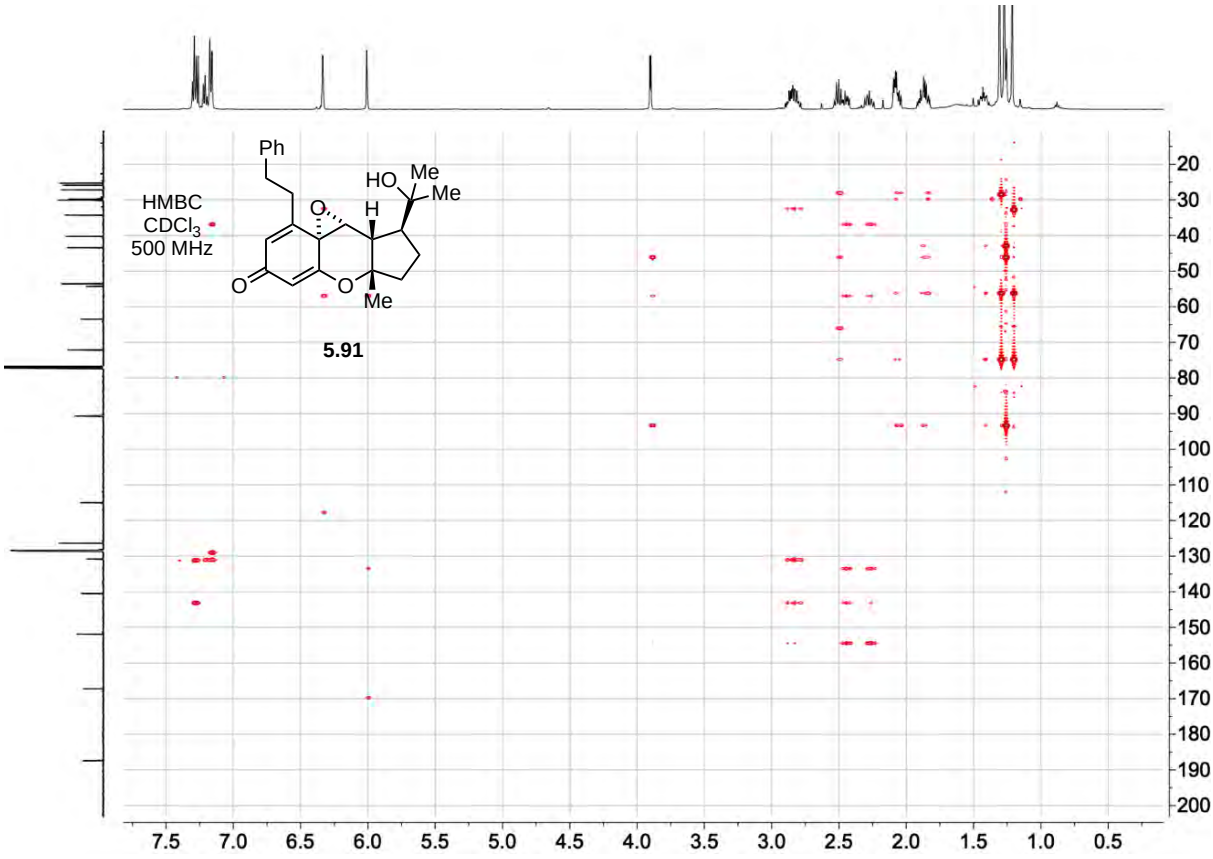
Data for 5.91


7.29
7.27
7.26
7.18
7.17
7.16
6.34
6.33
6.01
6.01
3.91
3.90
2.87
2.86
2.85
2.84
2.84
2.83
2.83
2.81
2.52
2.50
2.48
2.46
2.29
2.28
2.27
2.10
2.09
2.08
2.07
1.87
1.87
1.86
1.85
1.31
1.27
1.21
Ph
HO
Me
Me
O
H
O
O
Me
1H NMR
CDCl3
500 MHz
5.91
1.92
0.83
1.72
0.84
0.72
0.85
1.97
1.97
1.00
1.83
1.91
1.26
2.74
2.61
2.62
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

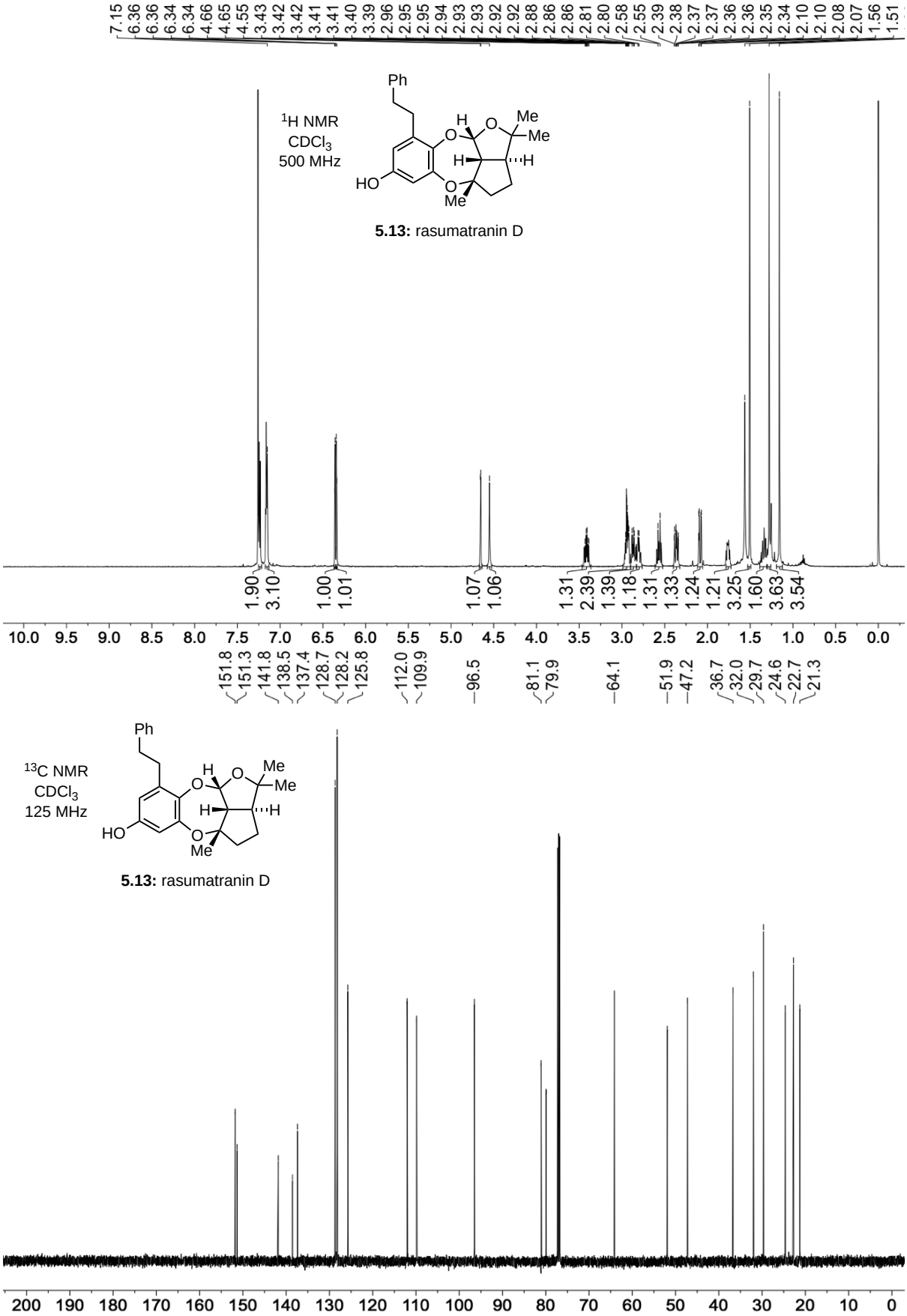

187.5
167.2
151.9
140.5
130.9
130.9
128.6
128.4
126.4
115.0
90.7
72.1
63.5
54.3
53.6
43.4
40.3
34.3
30.1
29.8
27.1
25.9
25.3
Ph
HO
Me
Me
O
H
O
O
Me
13C NMR
CDCl3
125 MHz
5.91
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


COSY
CDCl3
500 MHz
Ph
HO
Me
Me
O
H
O
O
Me
5.91


HSQC
CDCl3
500 MHz
Ph
HO
Me
Me
O
H
O
O
Me
5.91

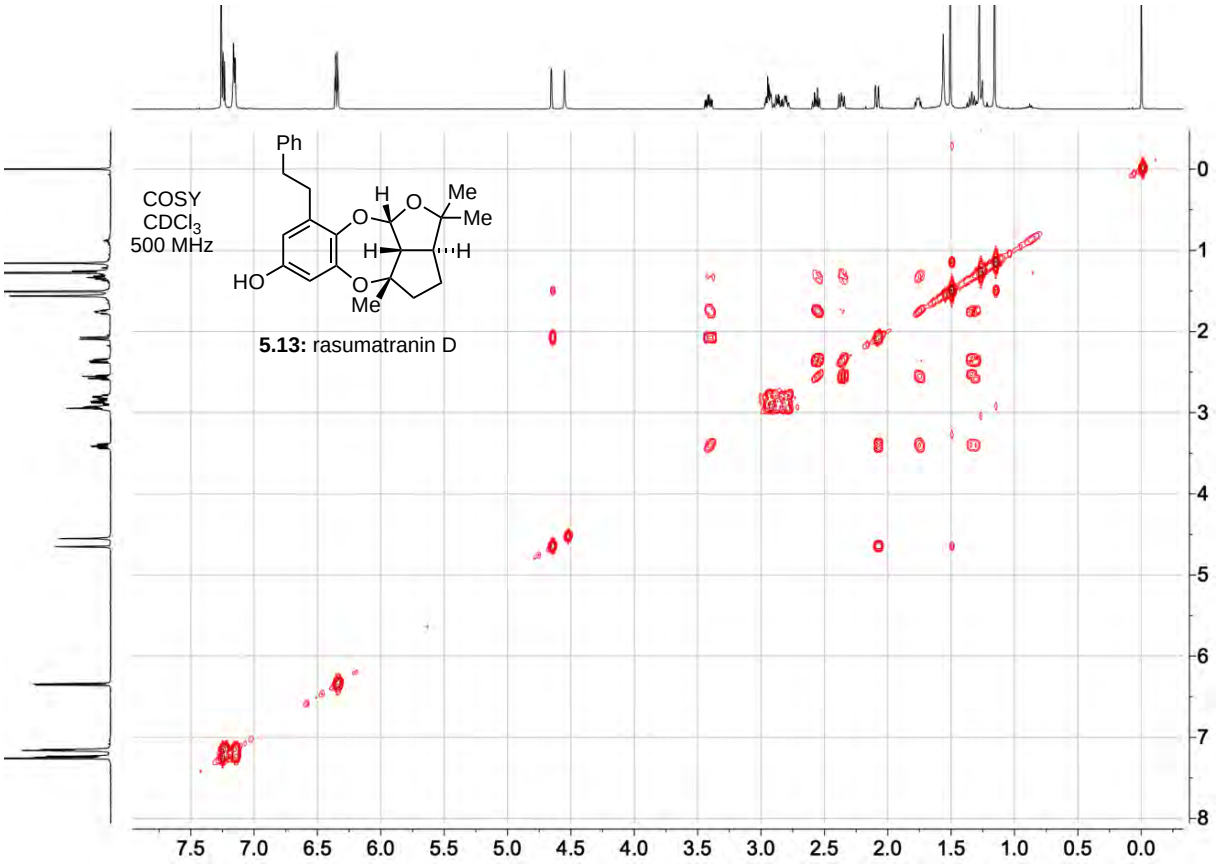

HMBC
CDCl3
500 MHz
Ph
HO
Me
Me
O
H
O
O
Me
5.91
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

Data for Rasumatranin (5.13)

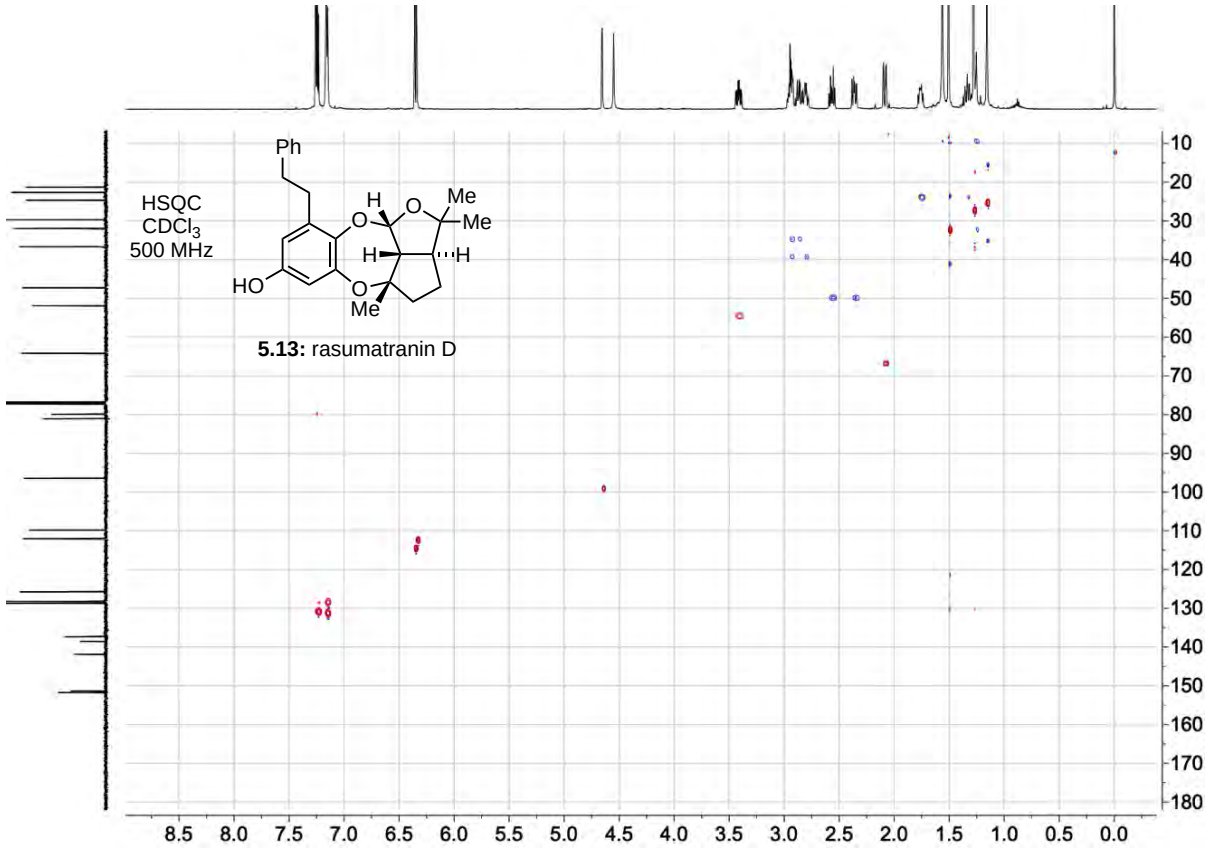


5.13: rasumatranin D

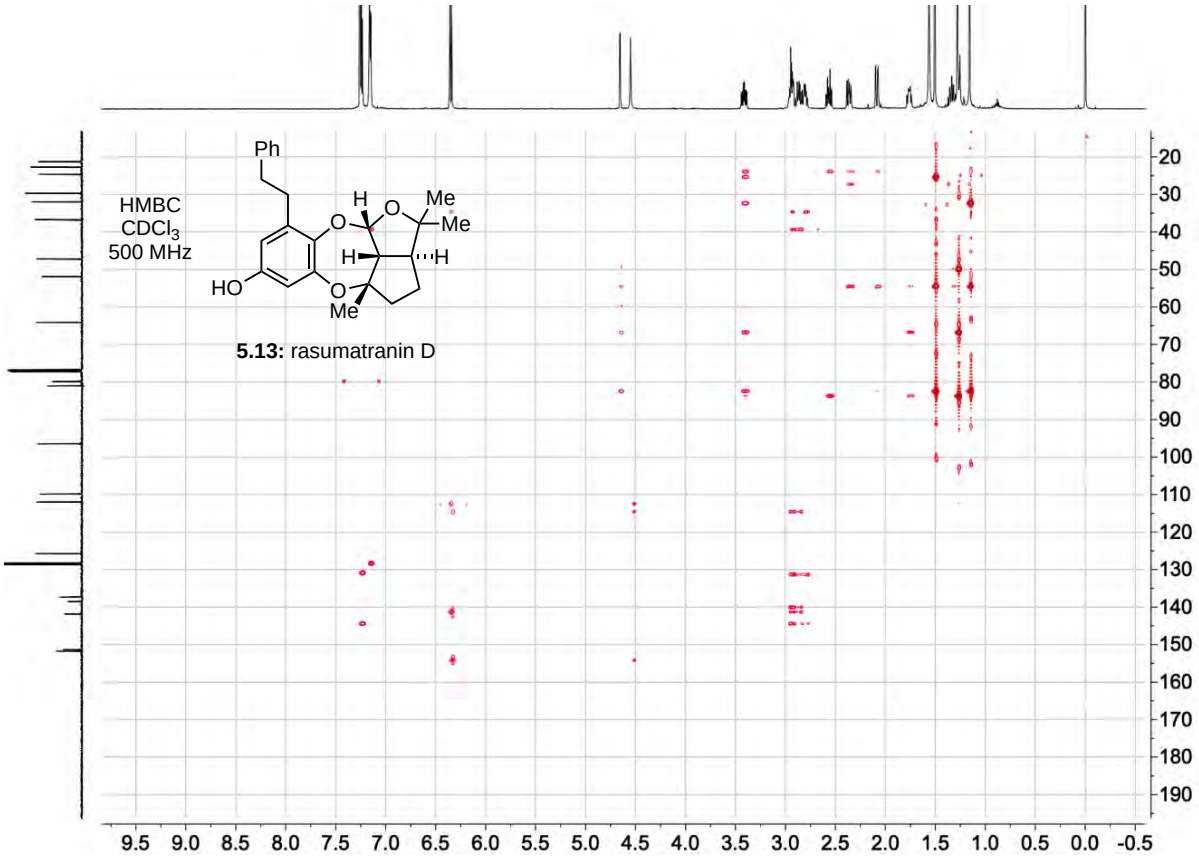
5.13: rasumatranin D

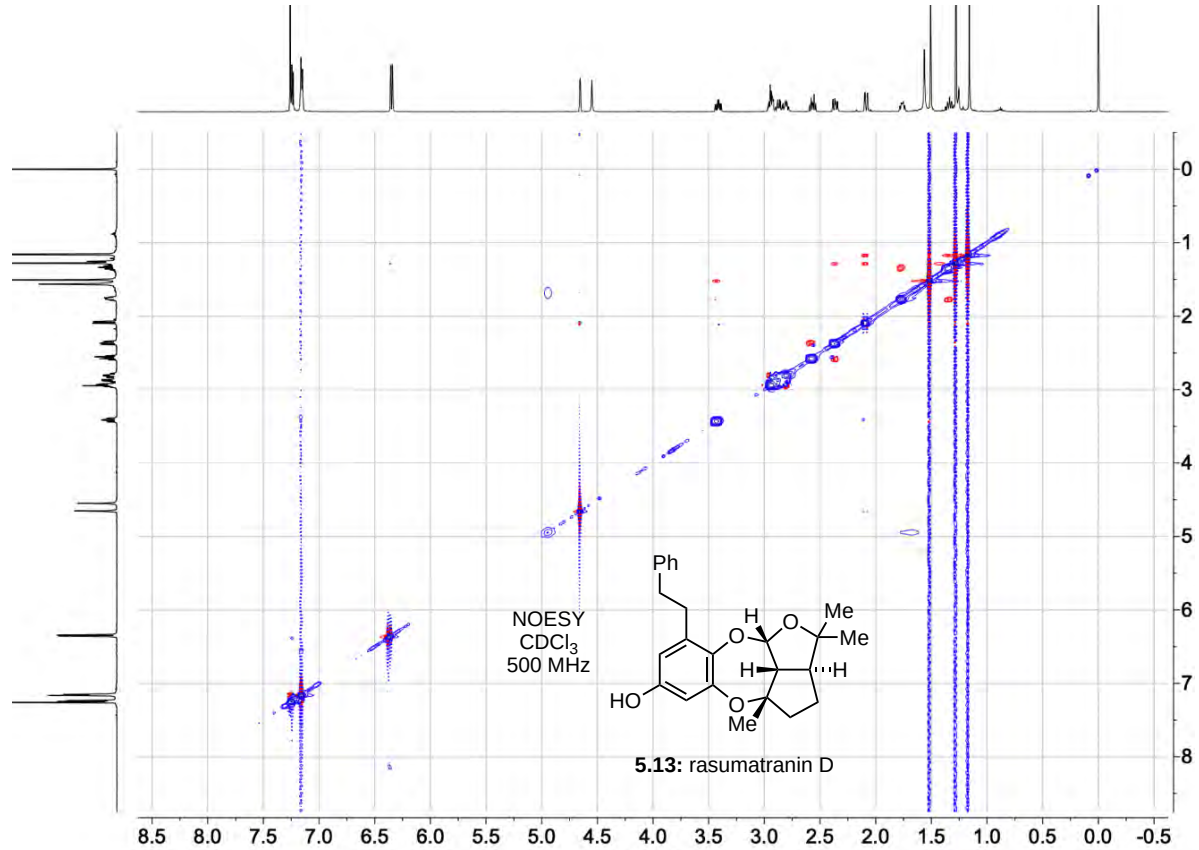


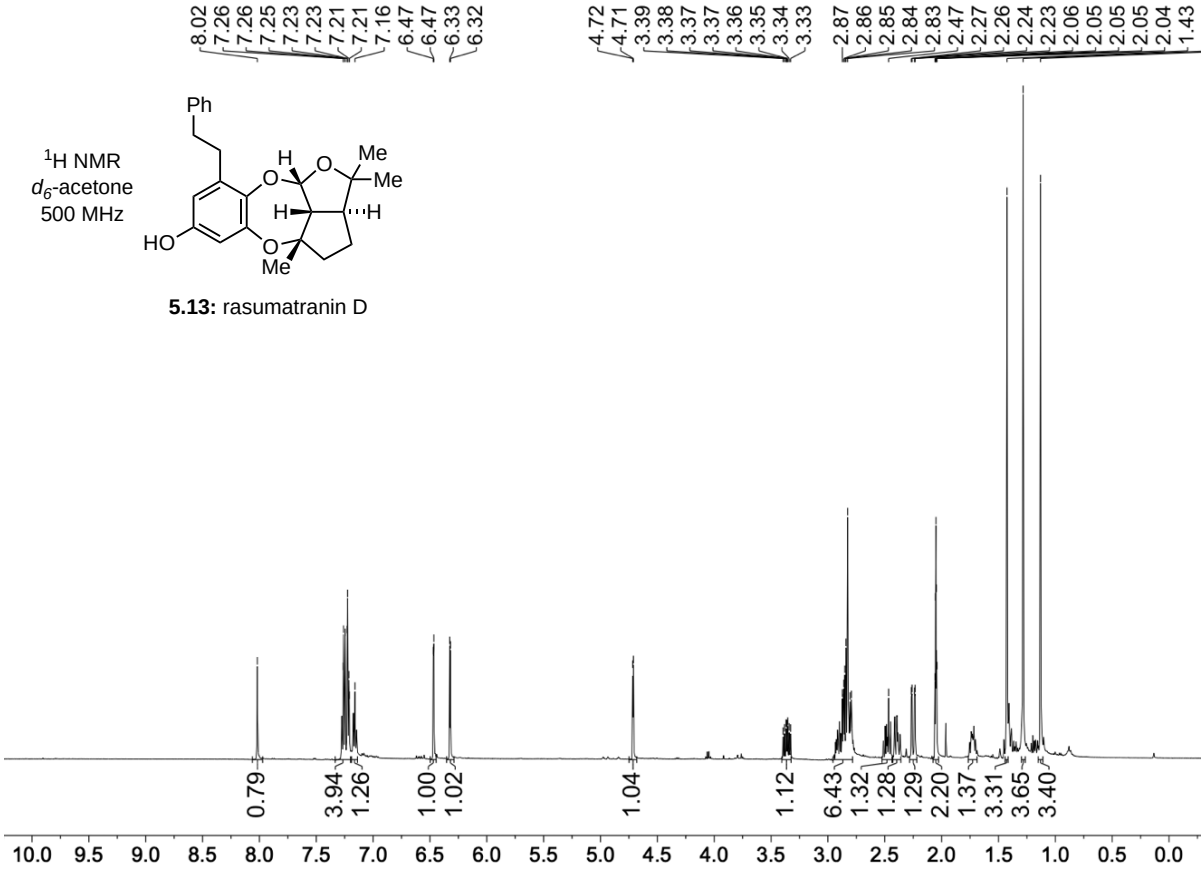
5.13: rasumatranin D



5.13: rasumatranin D

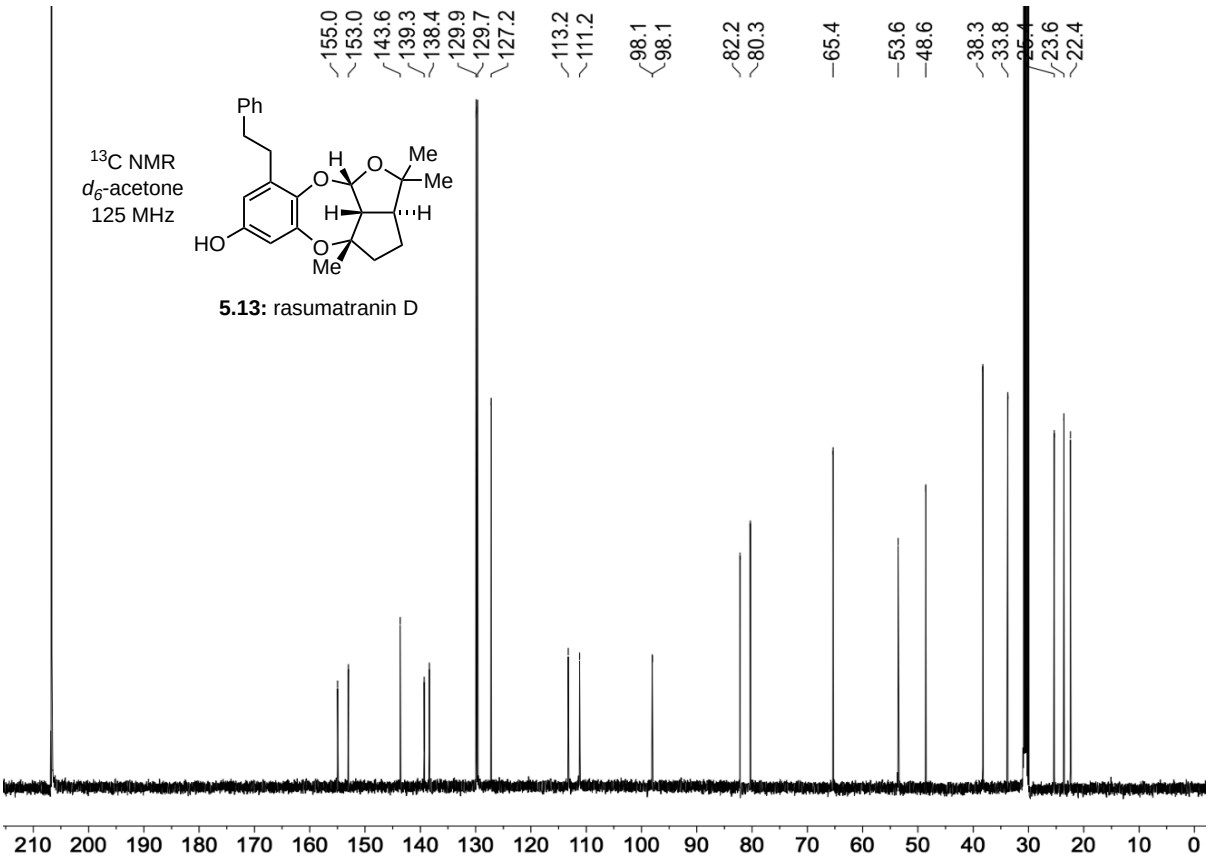

HMBC
CDCl3
500 MHz
Ph
H
O
Me
Me
O
H
H
HO
O
Me
5.13: rasumatranin D


NOESY
CDCl3
500 MHz
Ph
H
O
Me
Me
O
H
H
HO
O
Me
5.13: rasumatranin D



^{1}H NMR
d_6-acetone
500 MHz

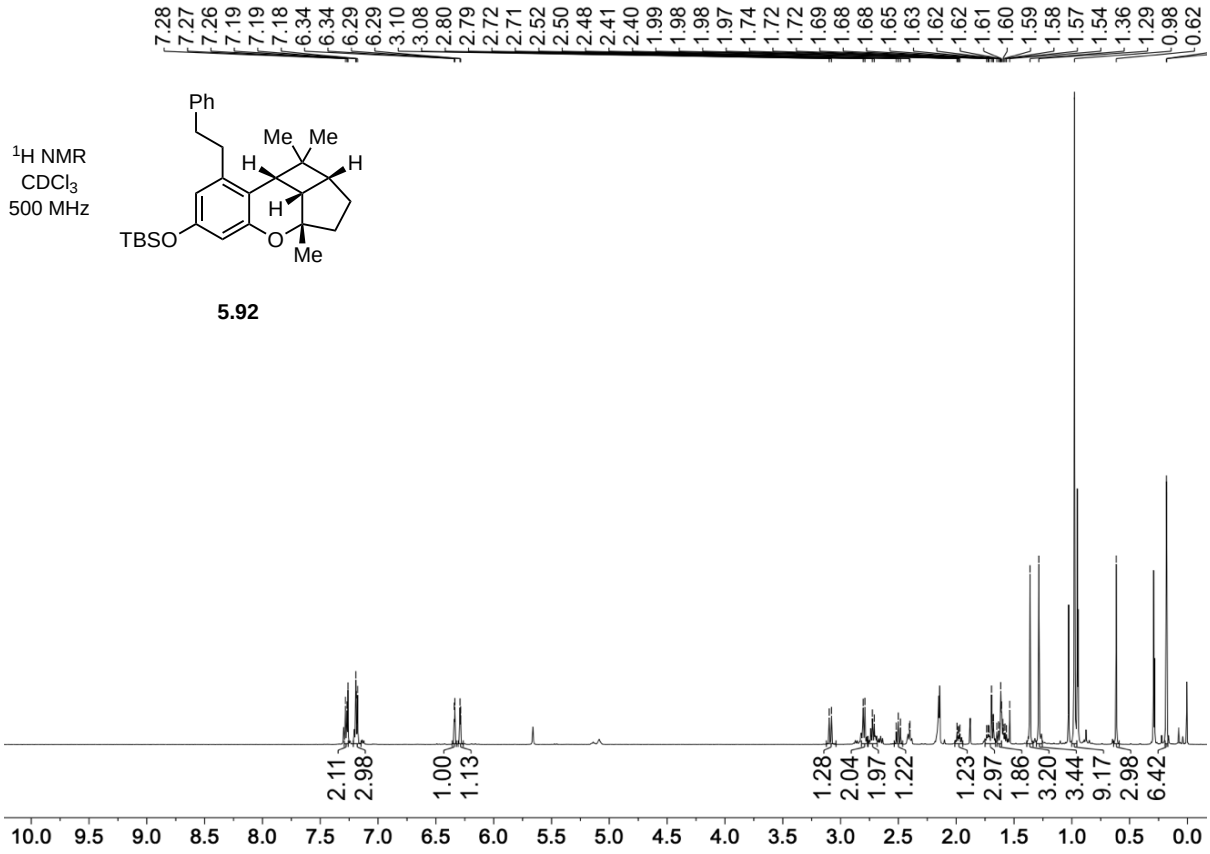
5.13: rasumatranin D



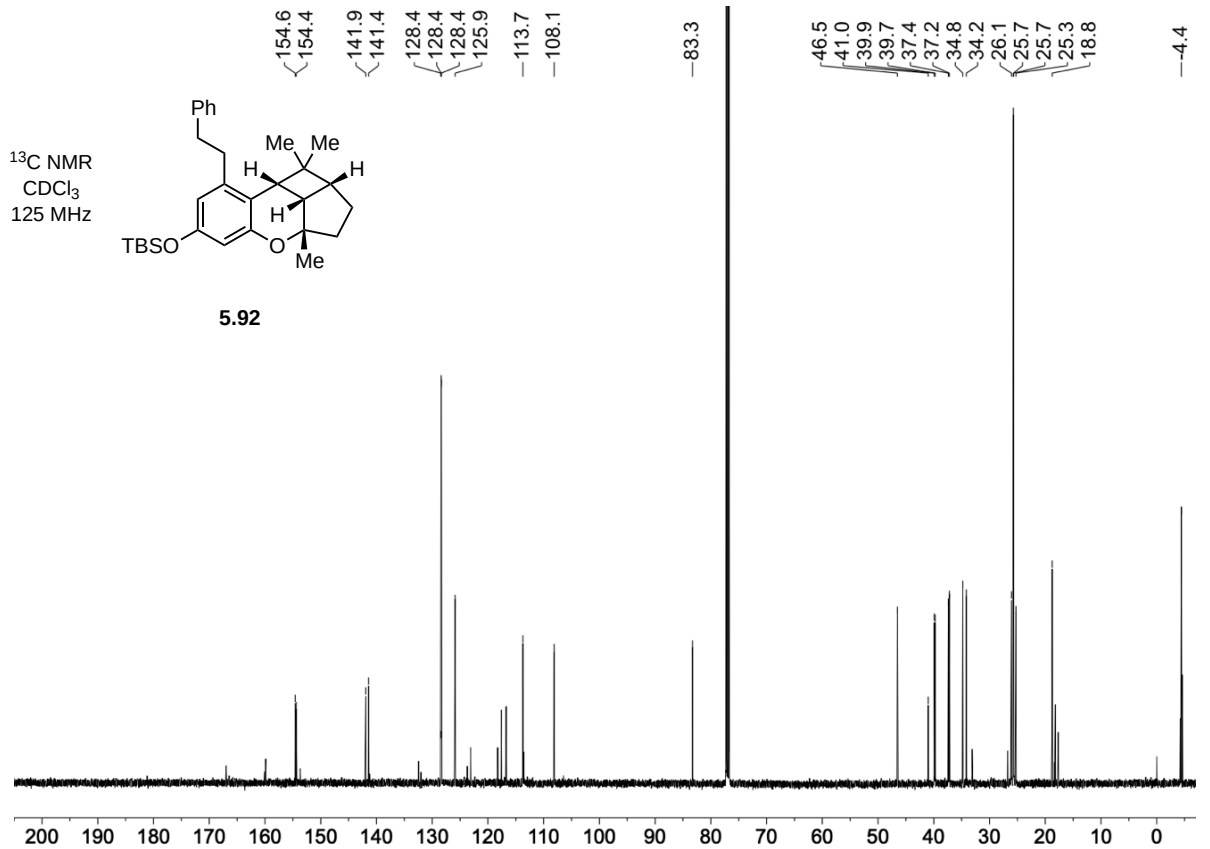
^{13}C NMR
d_6-acetone
125 MHz

5.13: rasumatranin D

Data for 5.92

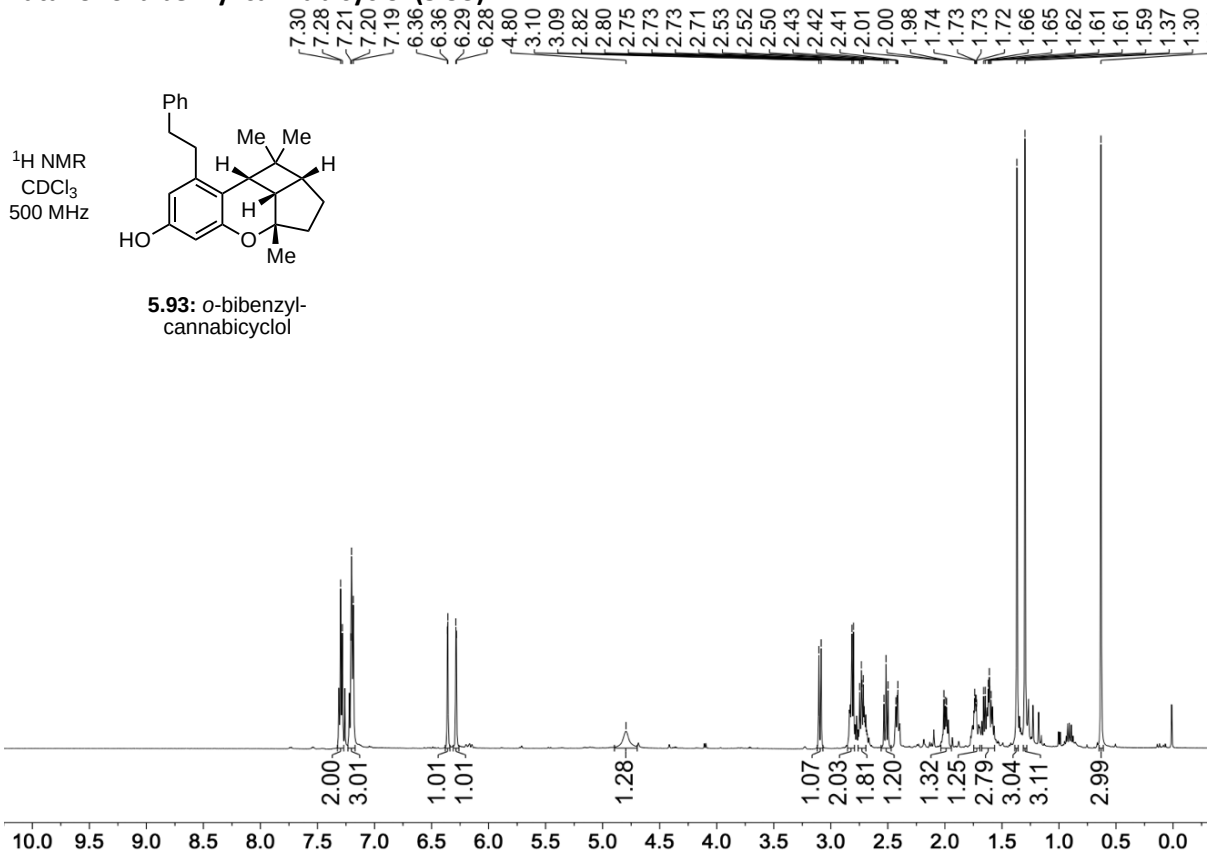


5.92



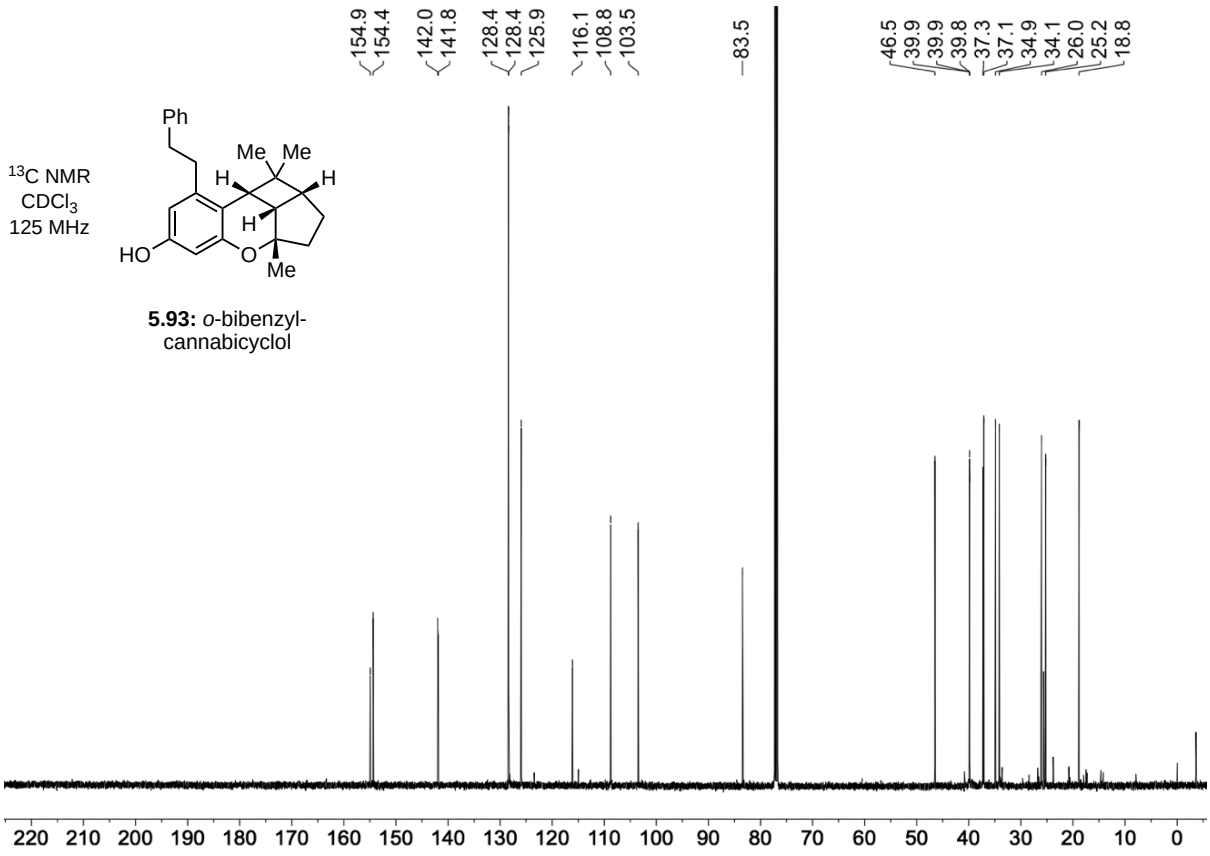
5.92

Data for *o*-bibenzyl cannabicyclol (5.93)



^{1}H NMR
$CDCl_3$
500 MHz

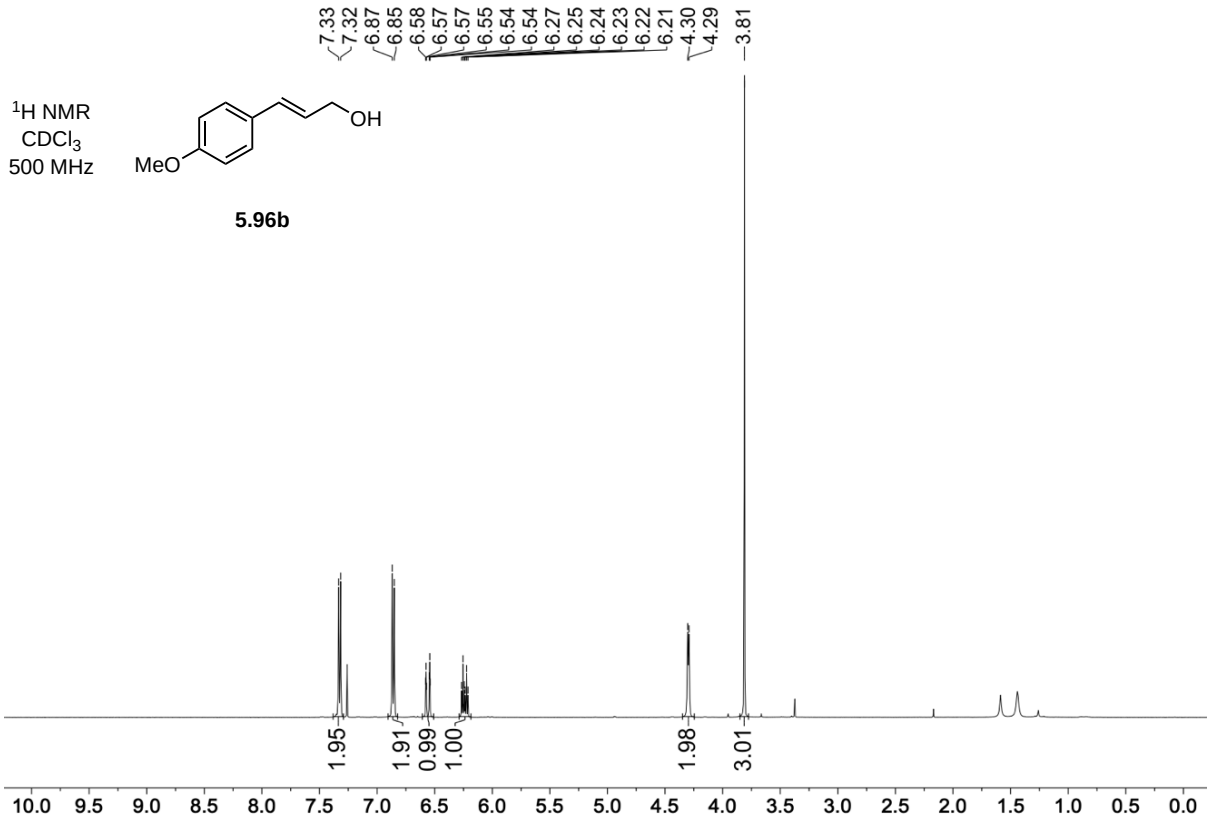
5.93: *o*-bibenzyl-cannabicyclol

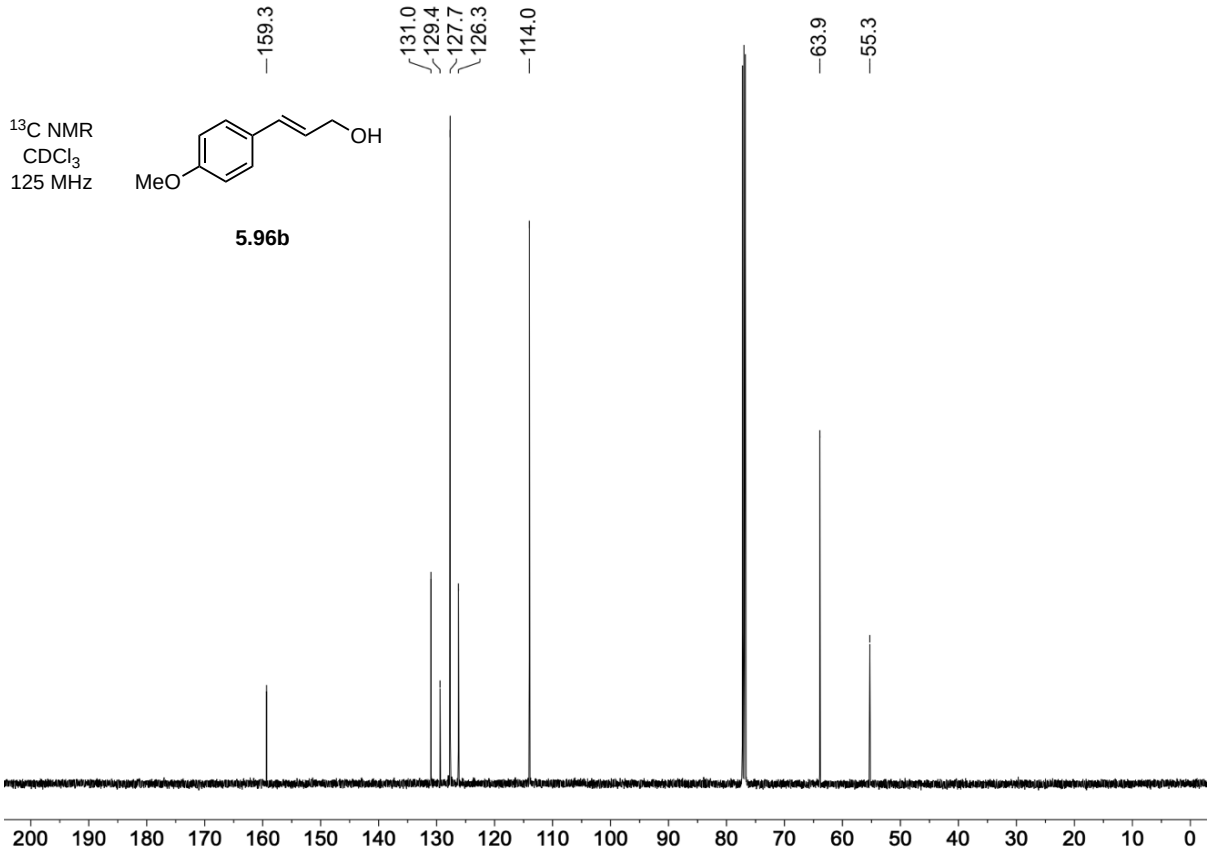


^{13}C NMR
$CDCl_3$
125 MHz

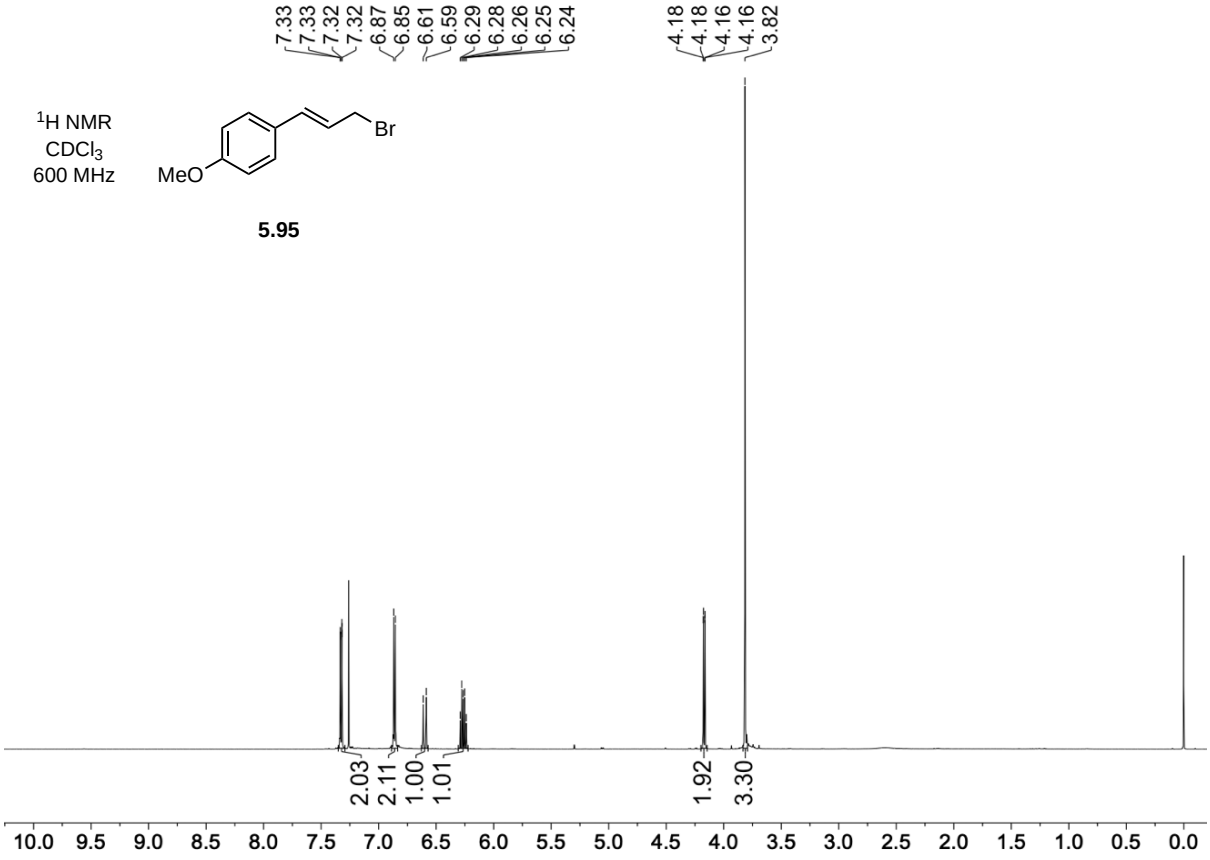
5.93: *o*-bibenzyl-cannabicyclol

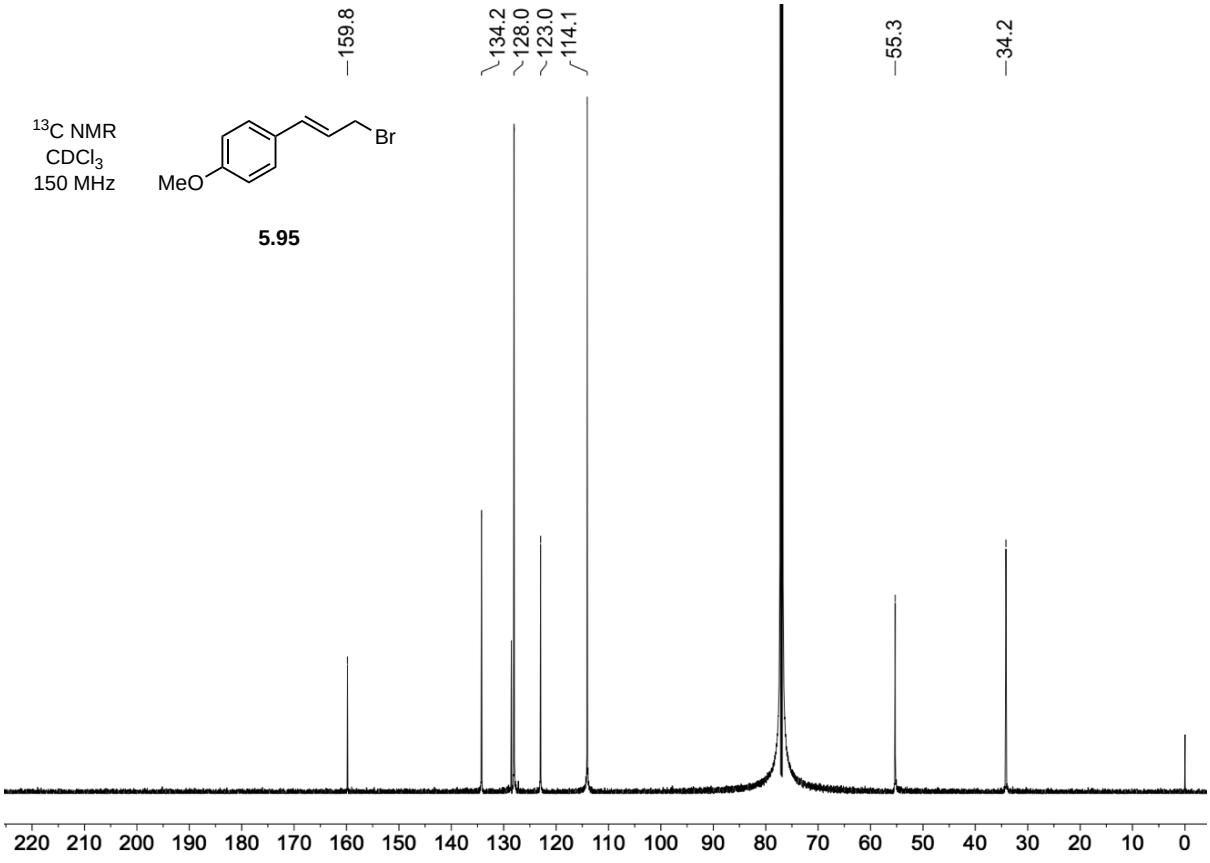
Data for 5.96b



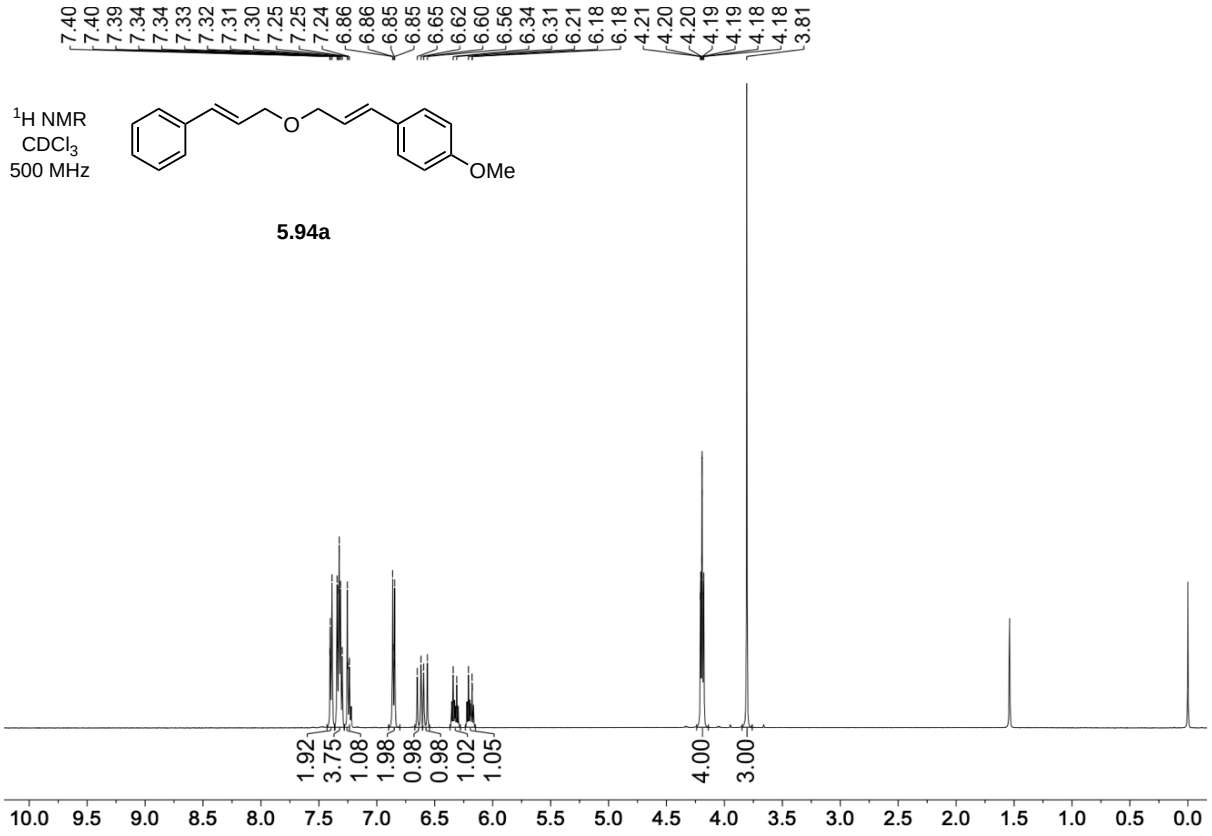


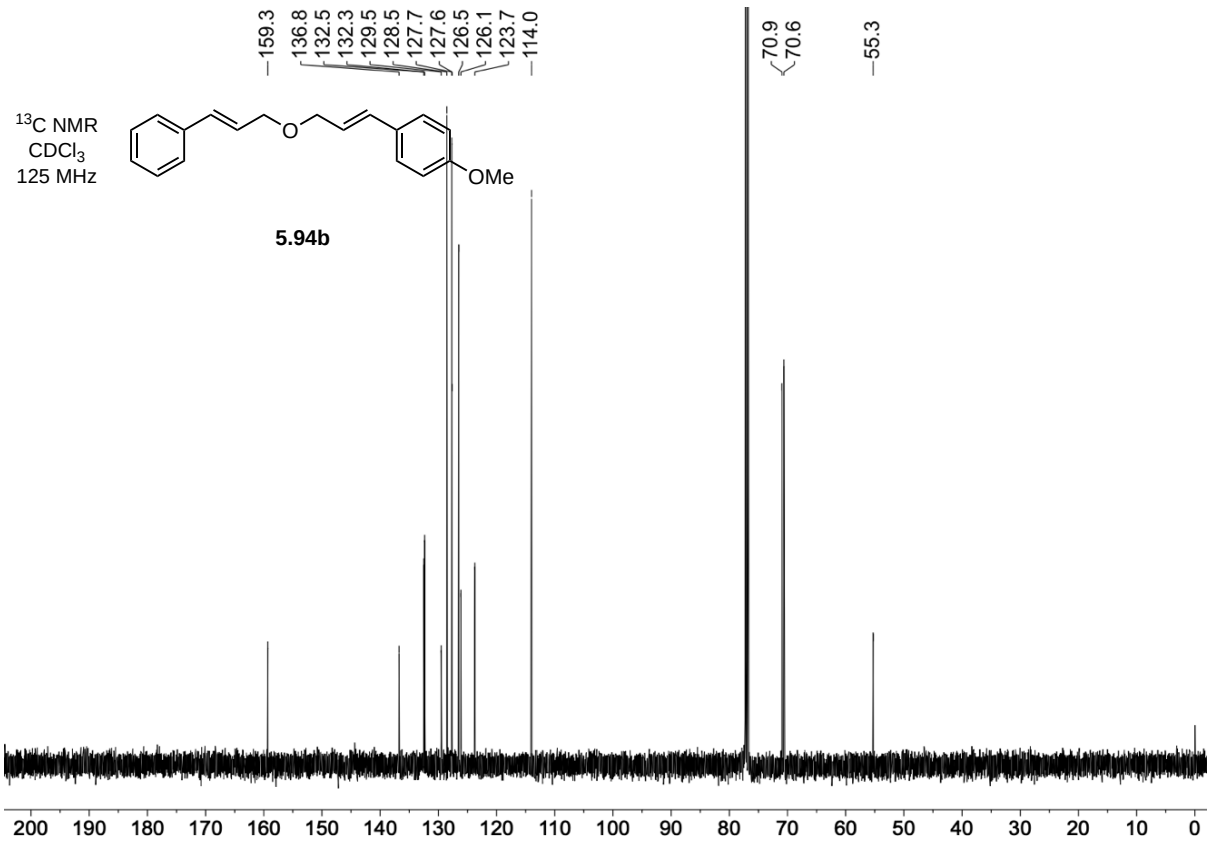
Data for 5.95


7.33
7.33
7.32
7.32
6.87
6.85
6.61
6.59
6.29
6.28
6.26
6.25
6.24
4.18
4.18
4.16
4.16
3.82
1H NMR
CDCl3
600 MHz
Br
MeO
5.95
2.03
2.11
1.00
1.01
1.92
3.30
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

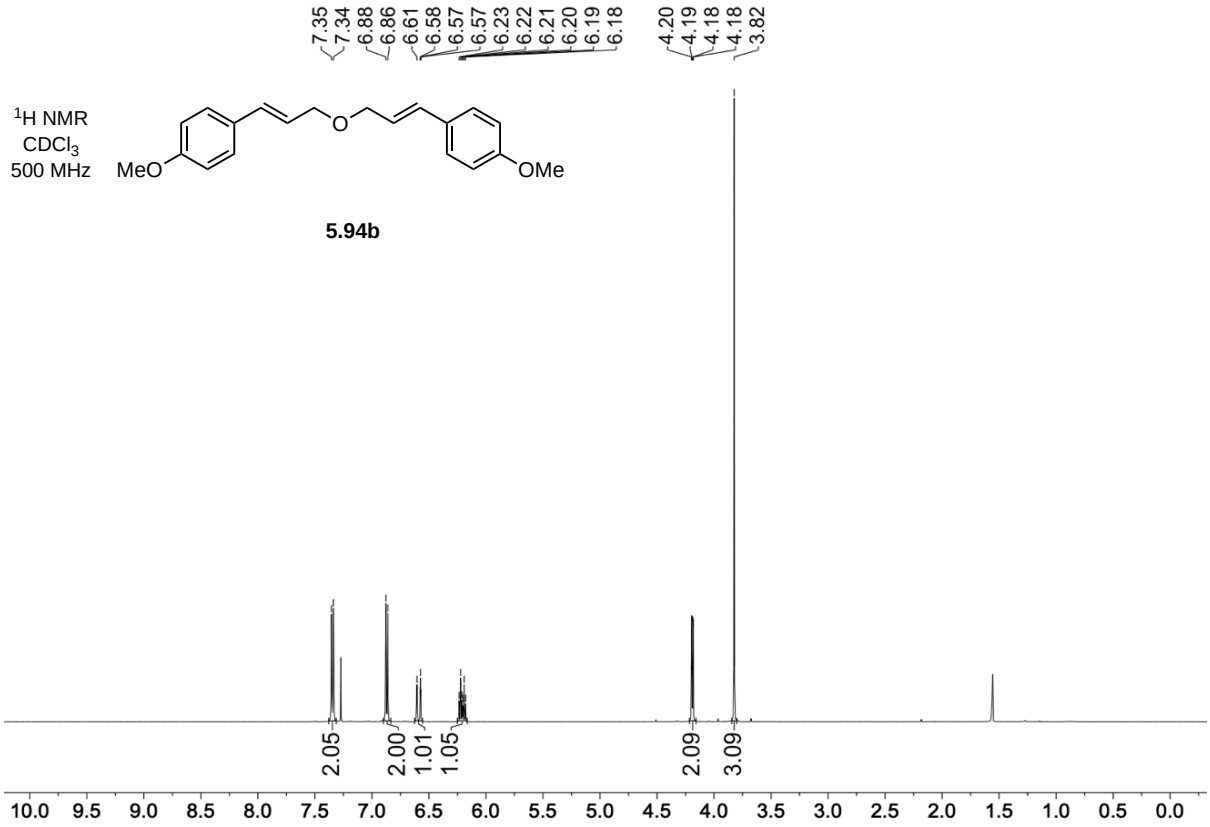

159.8
134.2
128.0
123.0
114.1
55.3
34.2
13C NMR
CDCl3
150 MHz
Br
MeO
5.95
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

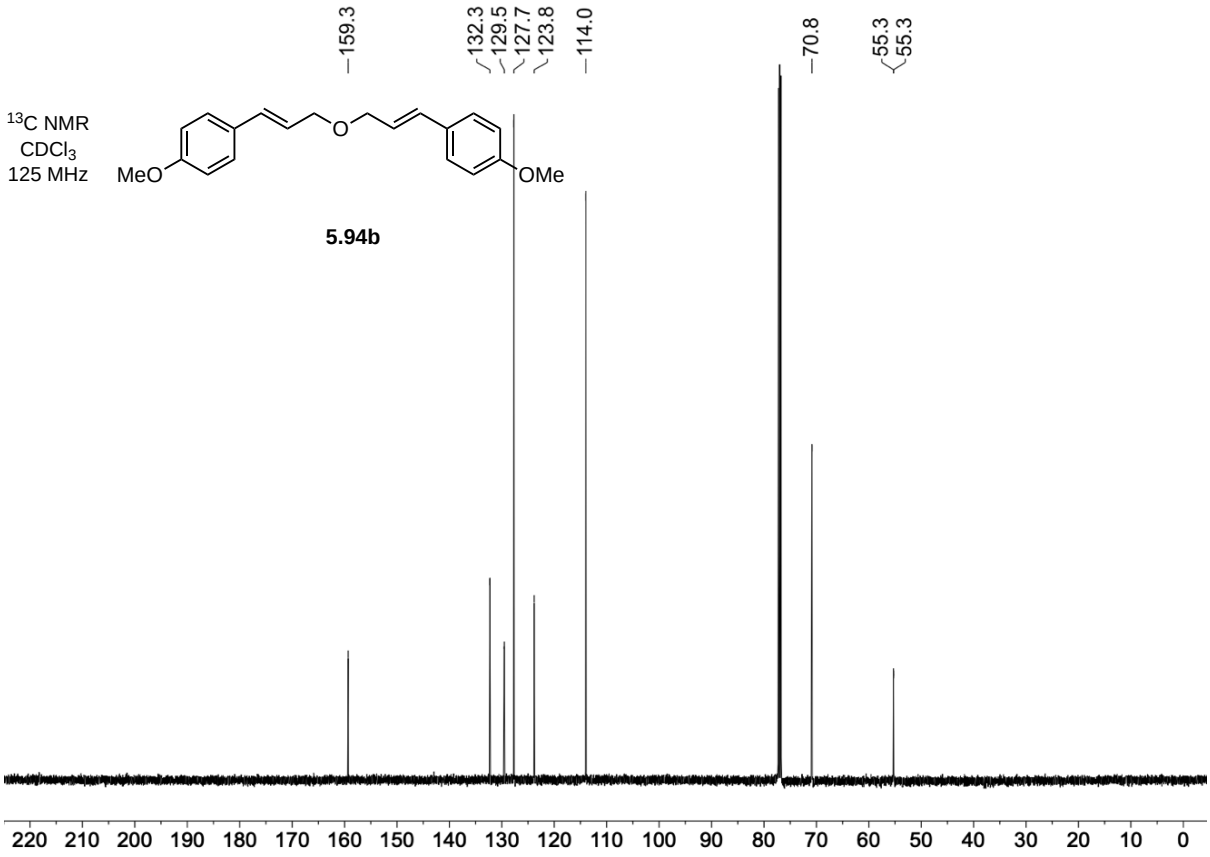
Data for 5.94a



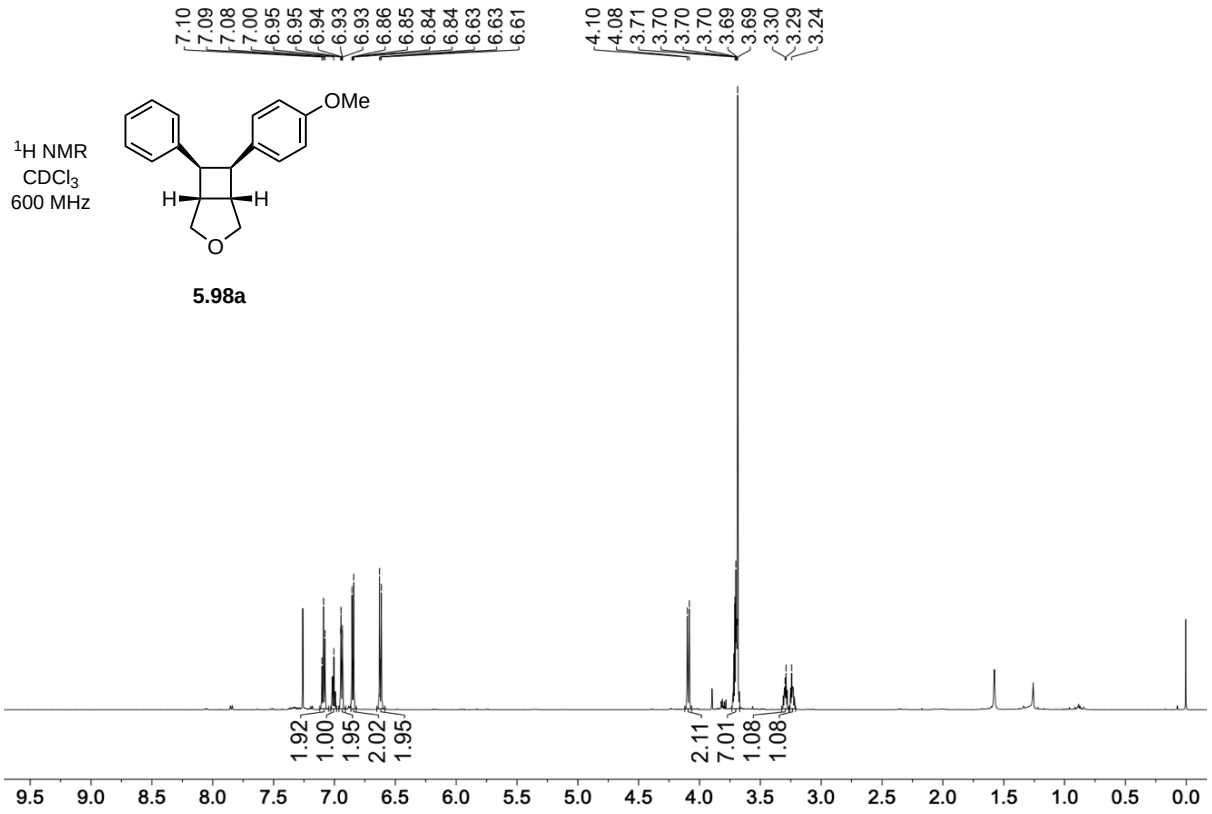


Data for 5.94b



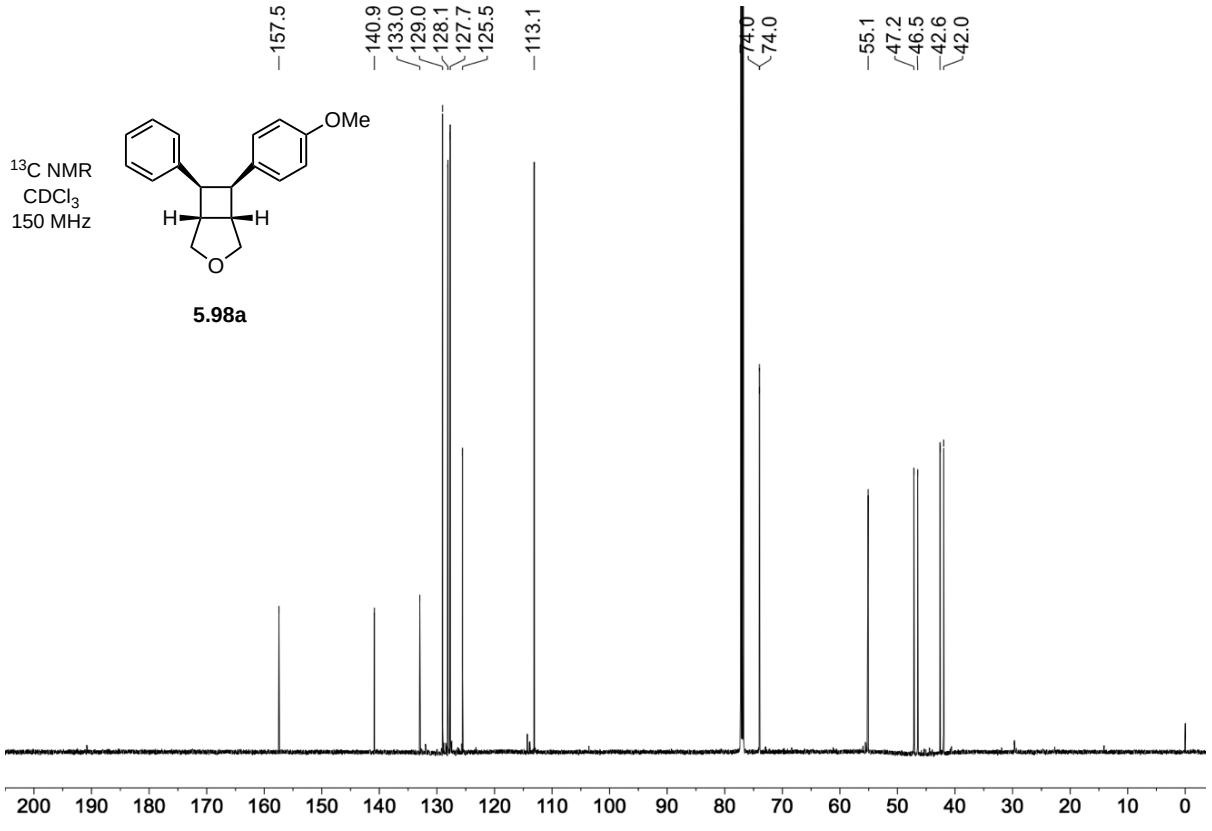


Data for 5.98a



^{1}H NMR
$CDCl_3$
600 MHz

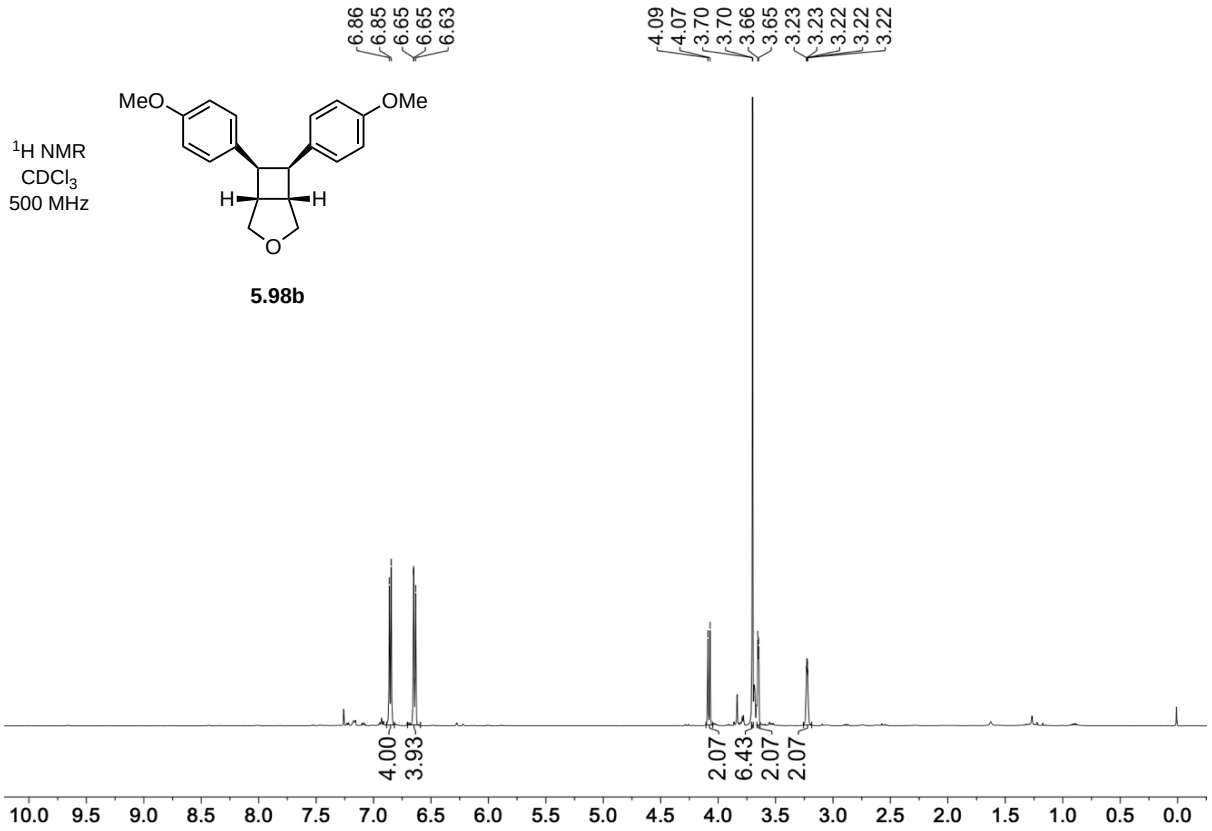
5.98a



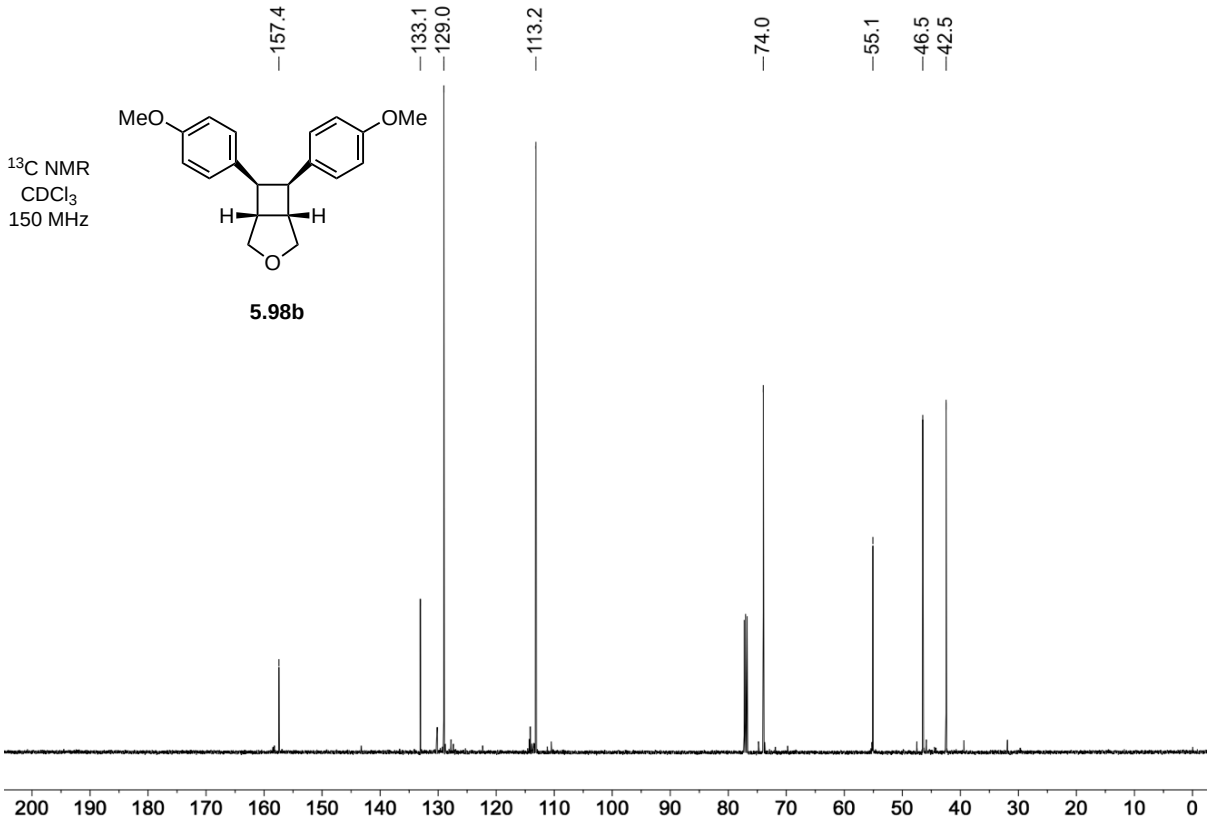
^{13}C NMR
$CDCl_3$
150 MHz

5.98a

Data for 5.98b

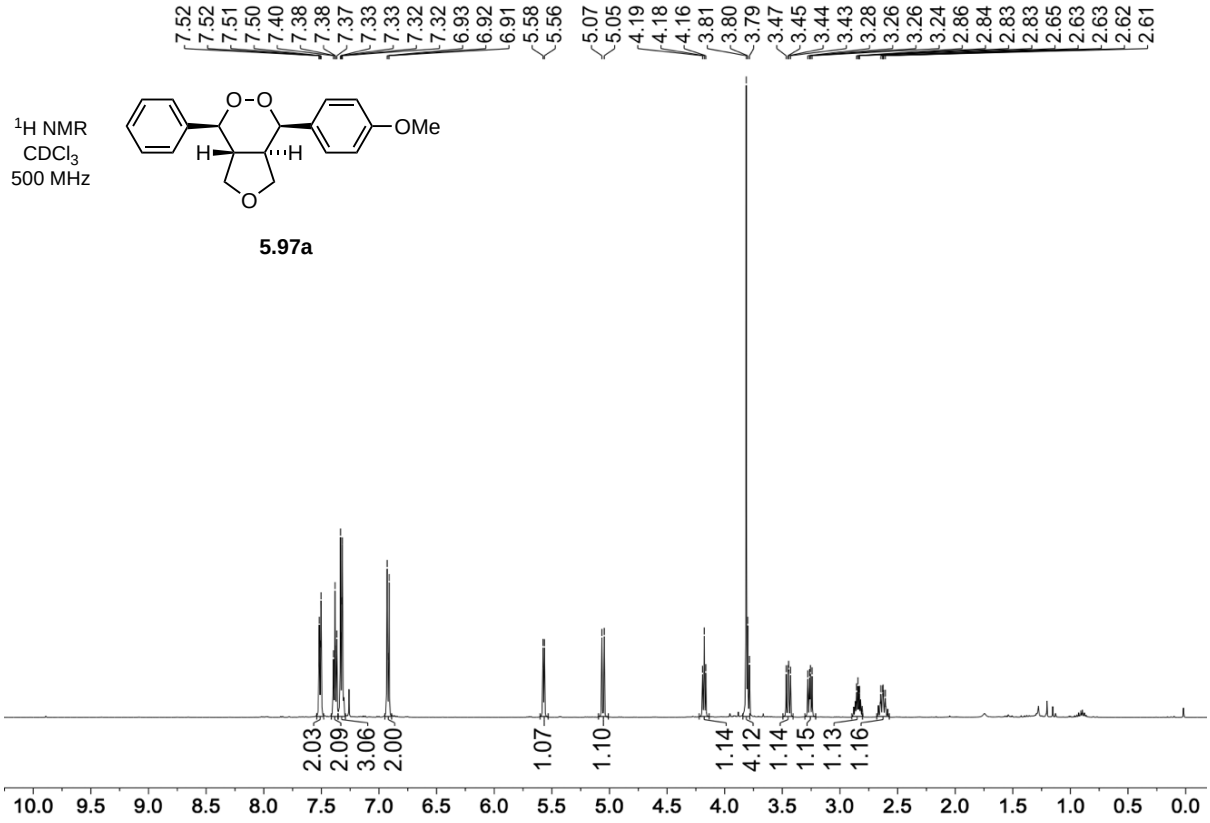


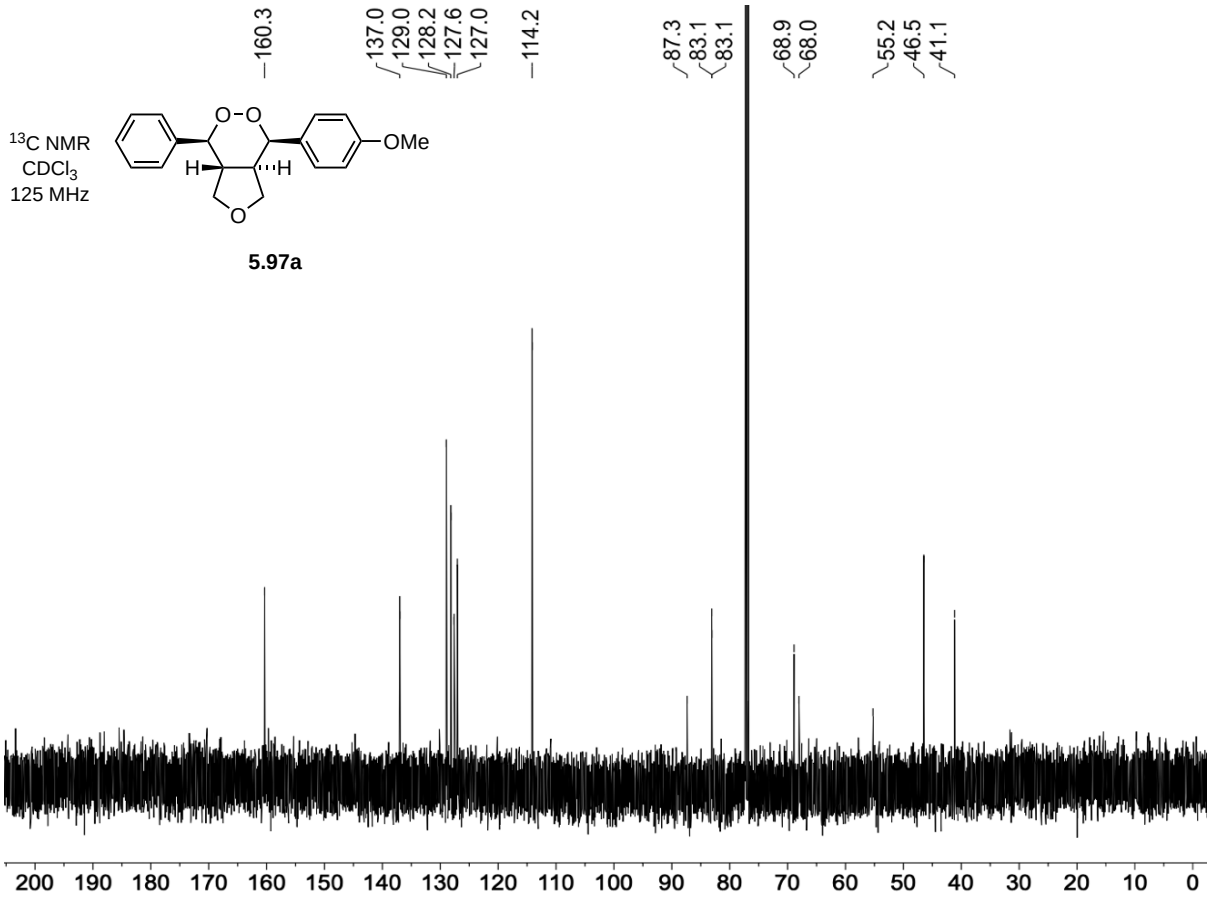
5.98b



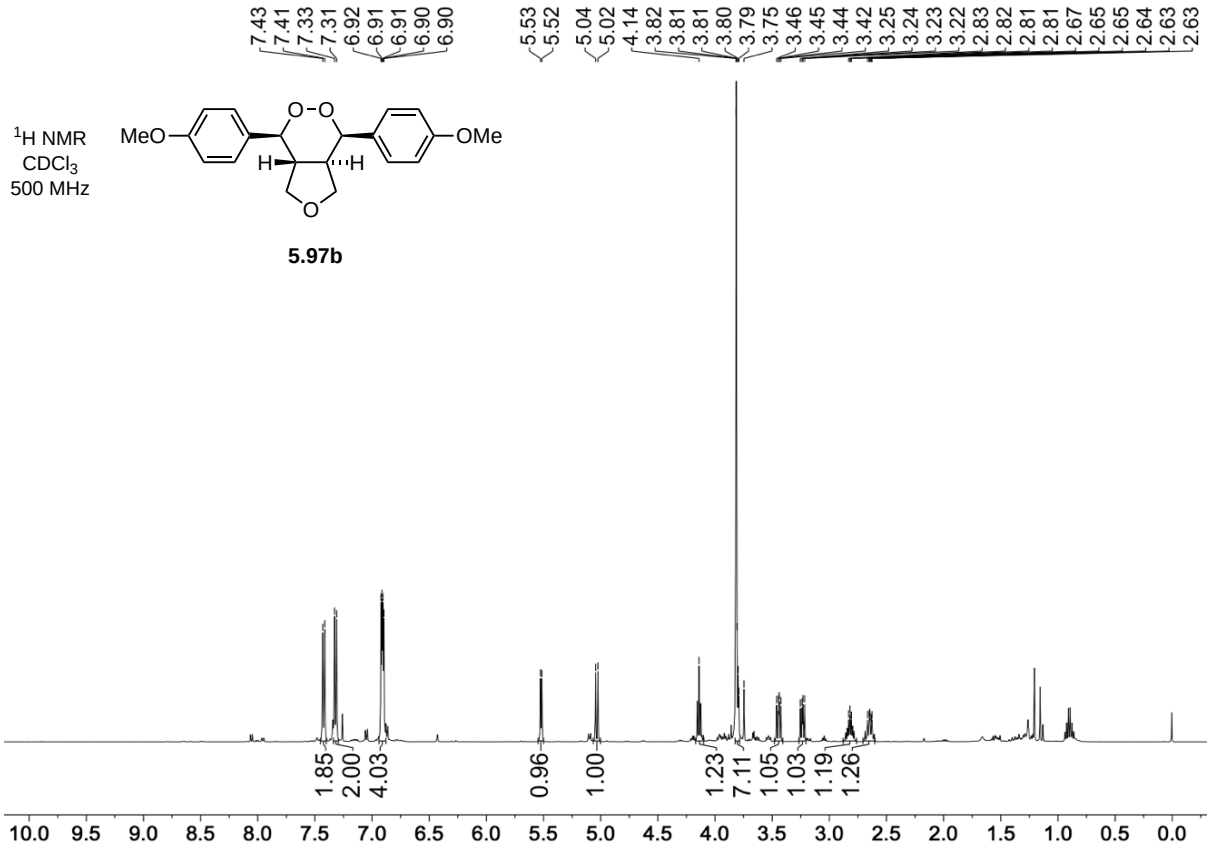
5.98b

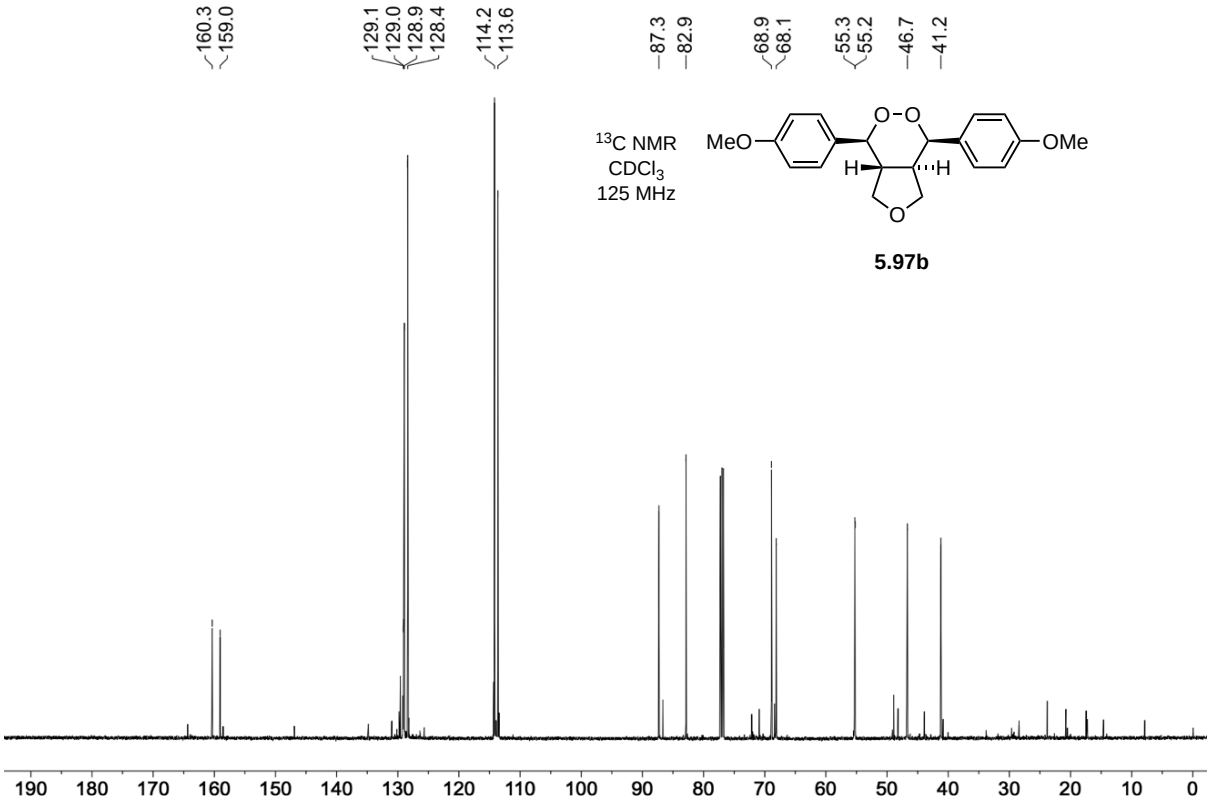
Data for 5.97a



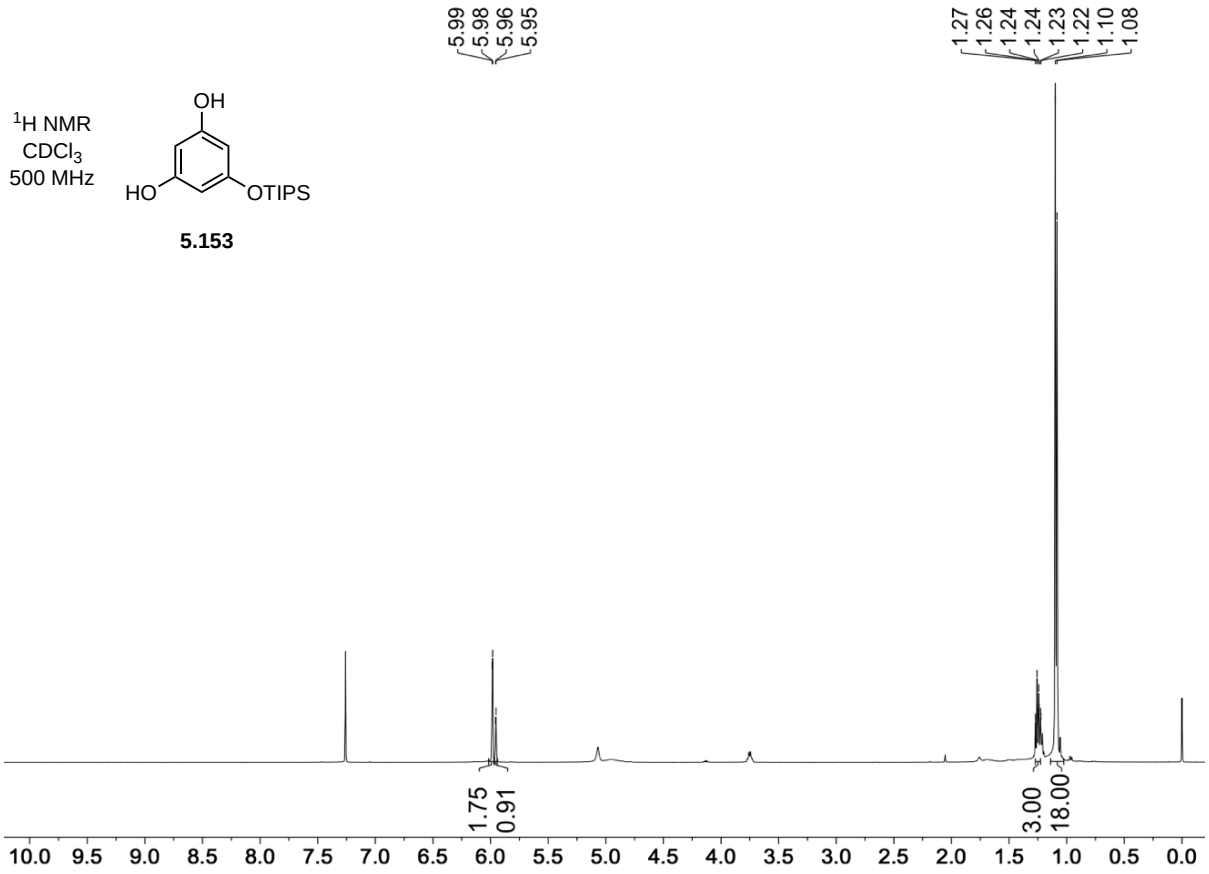


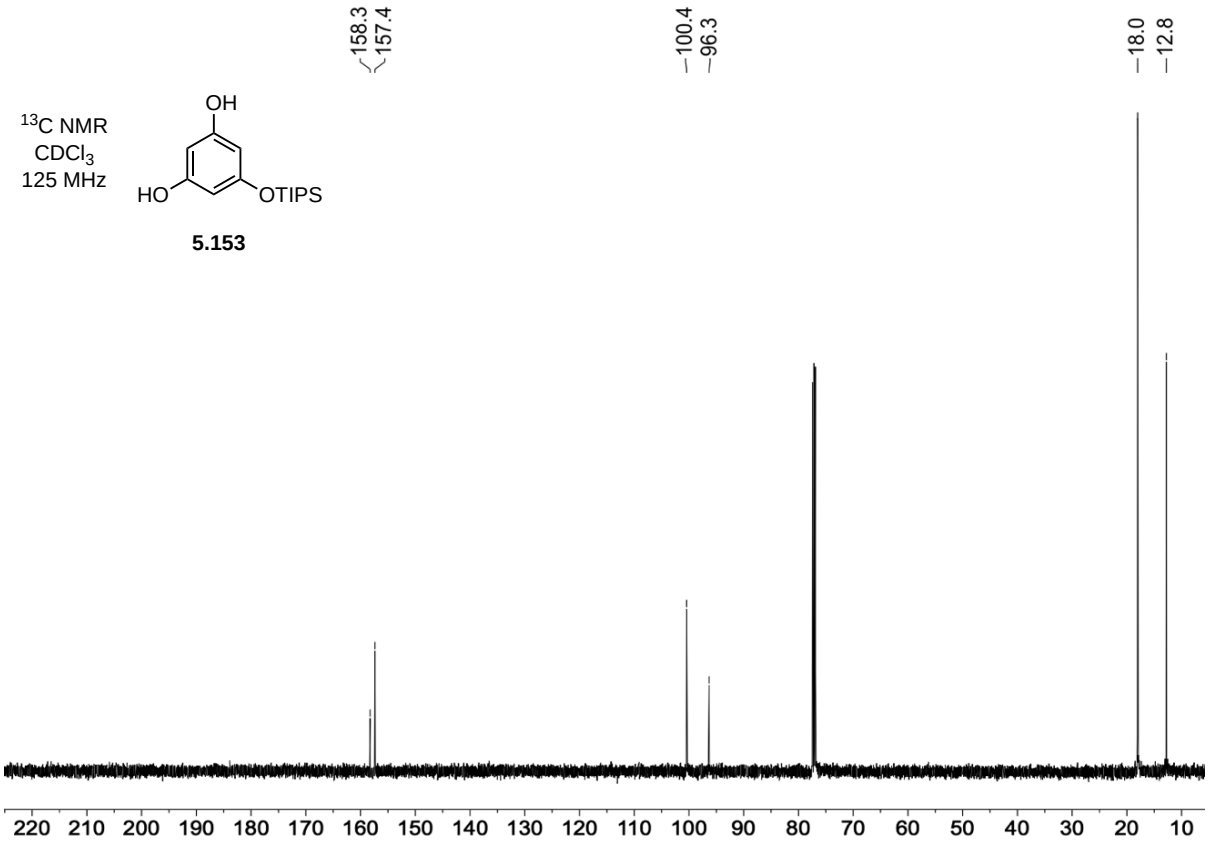
Data for 5.97b



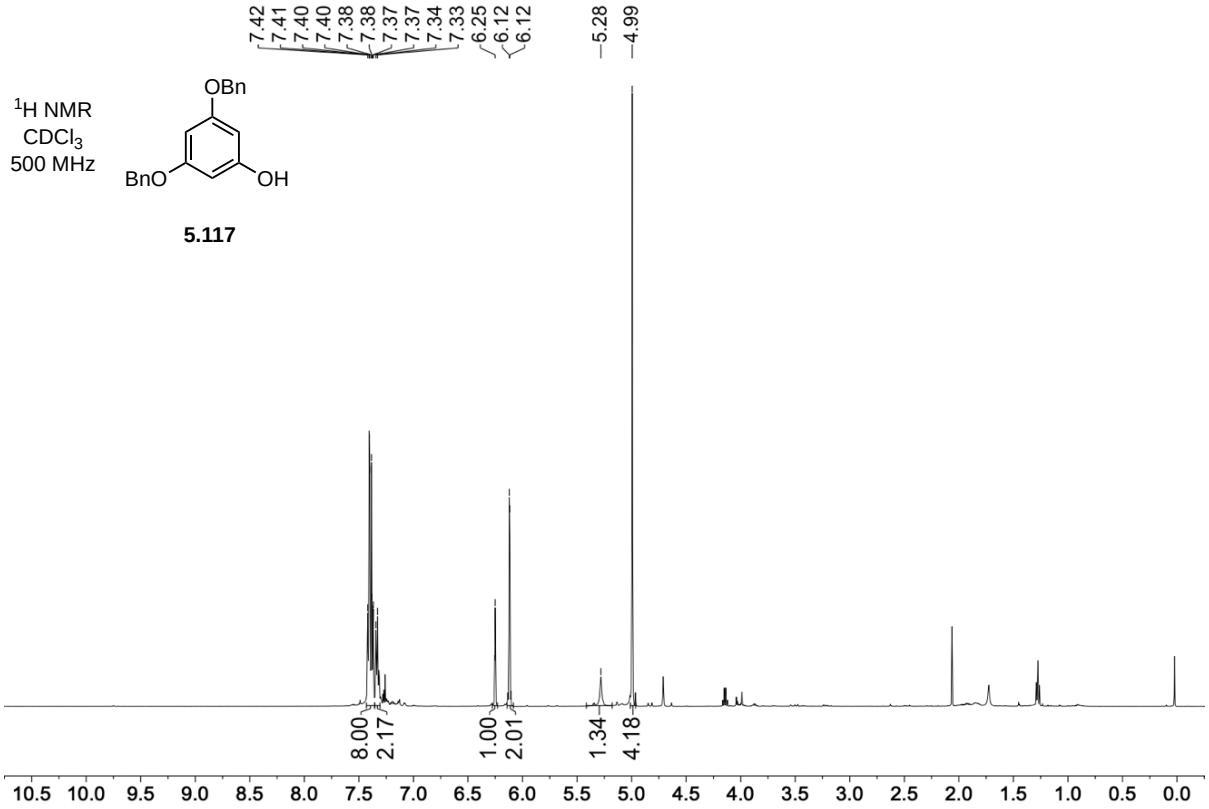


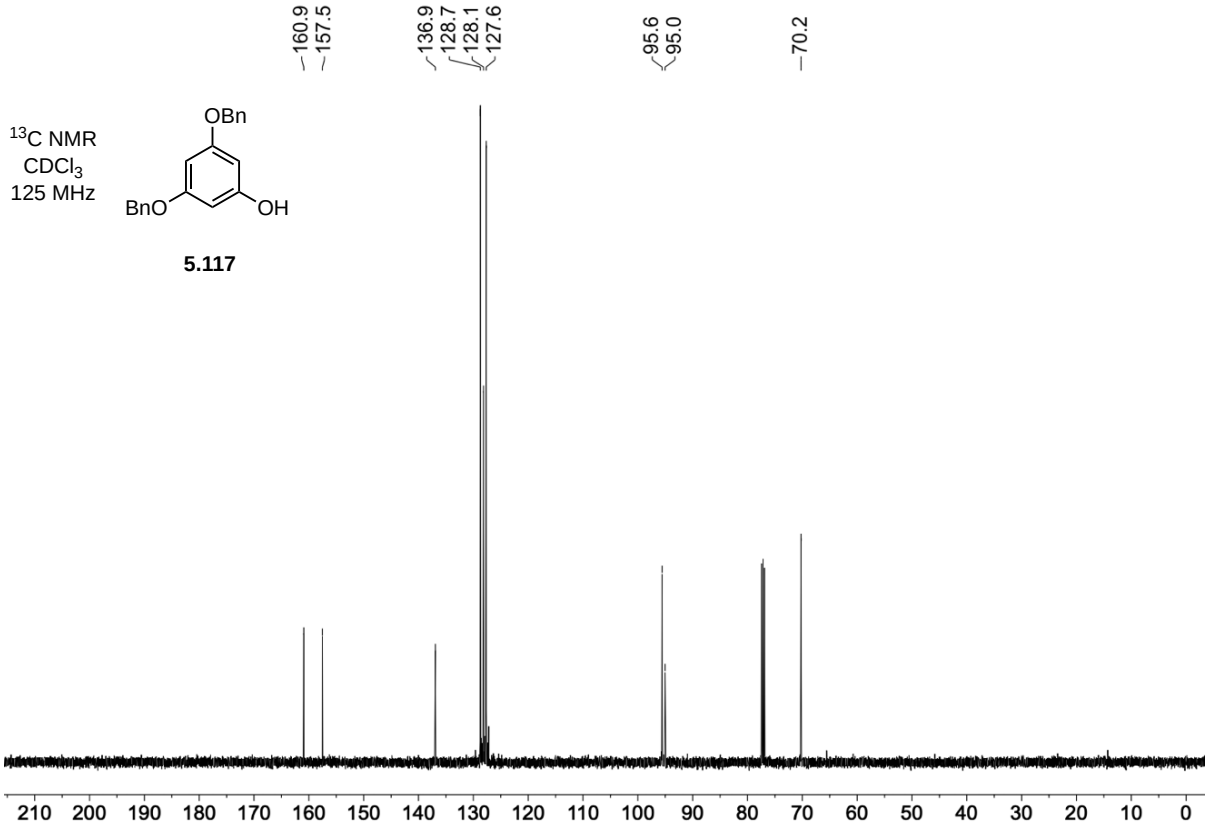
Data for 5.153



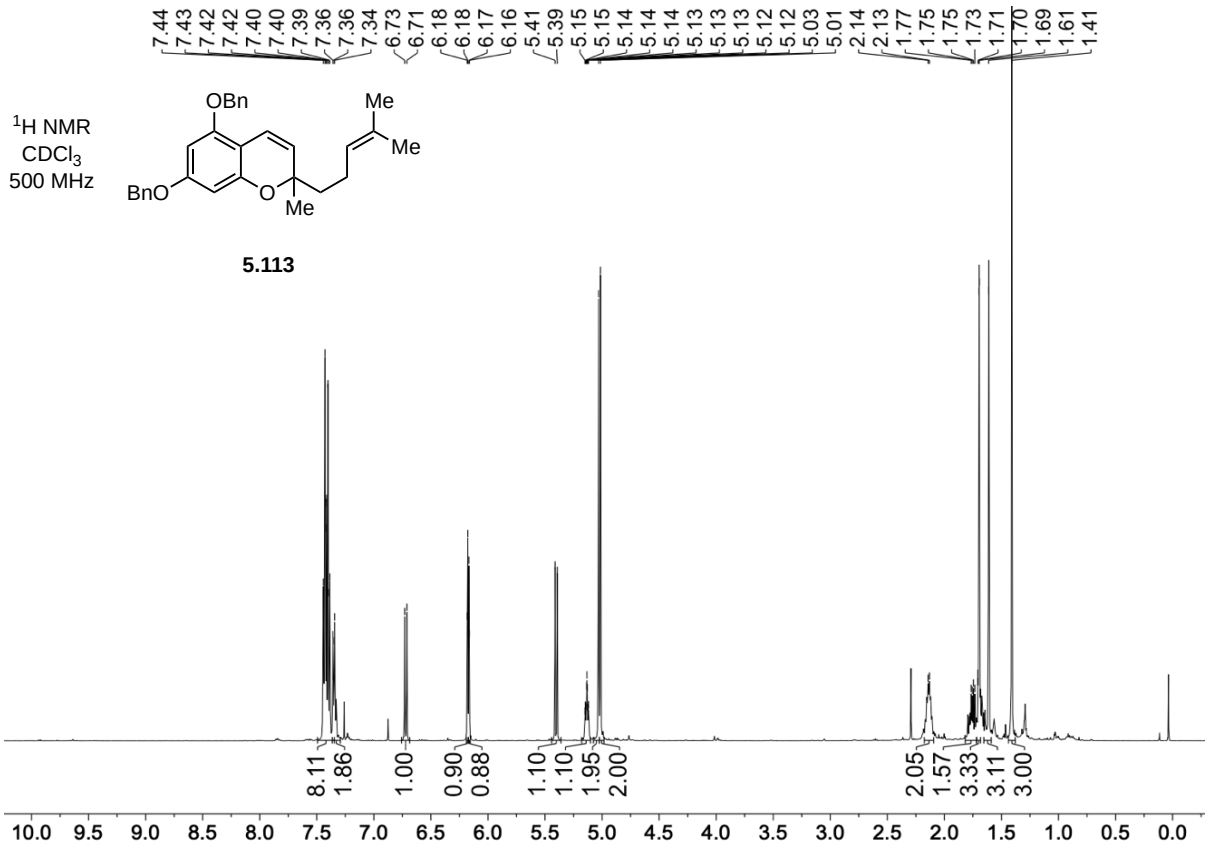


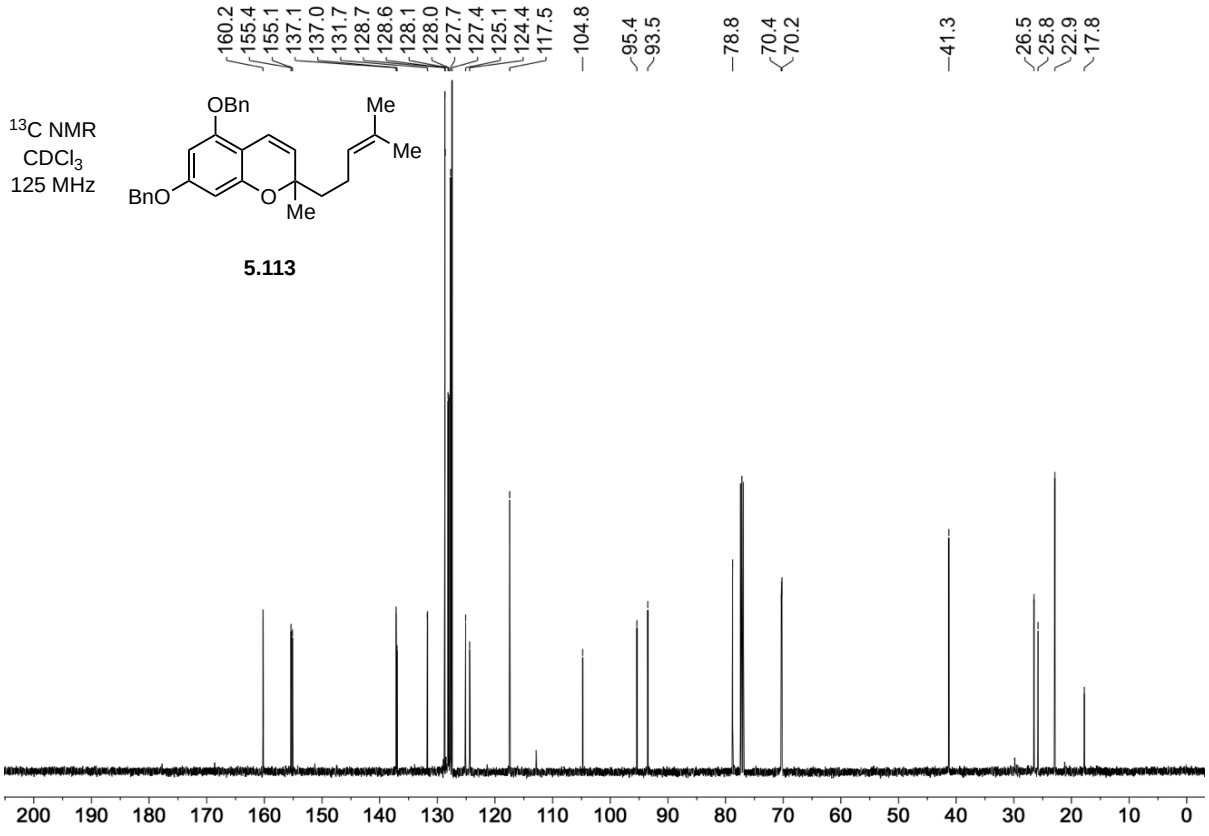
Data for 5.117



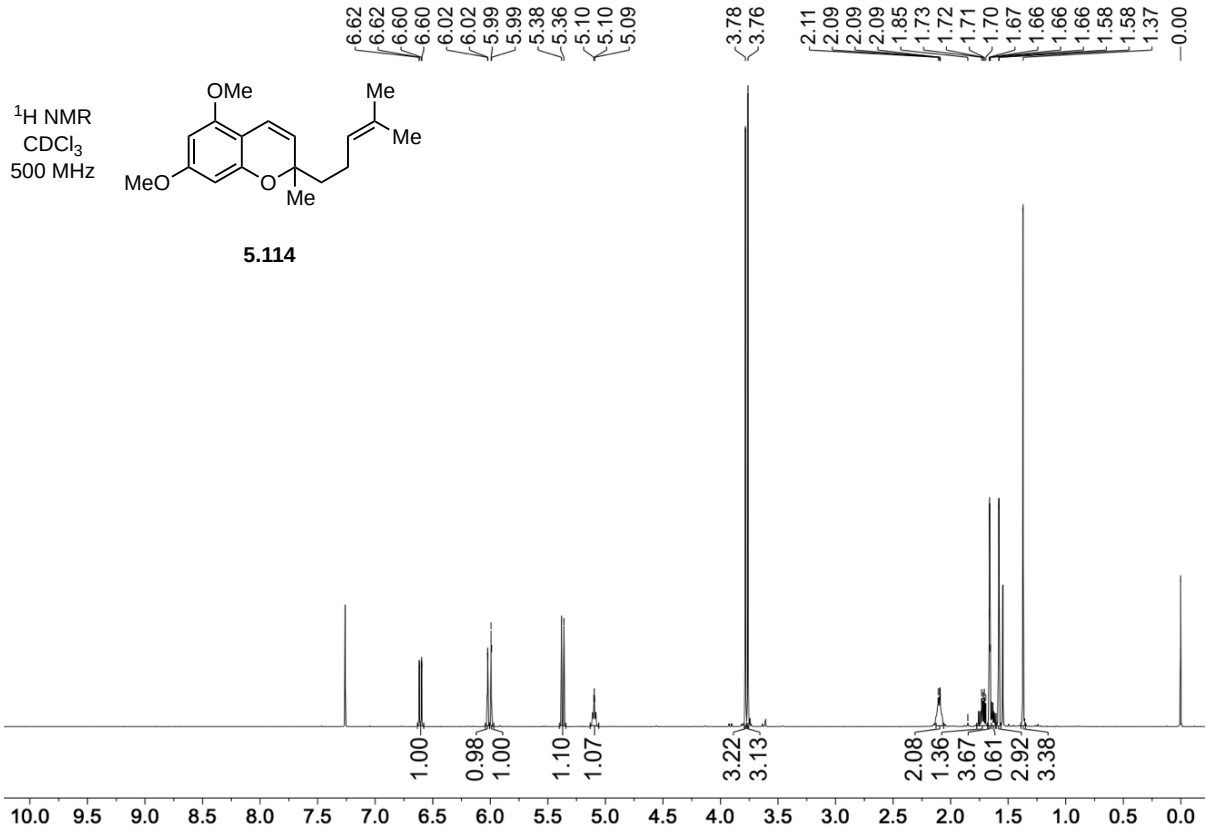


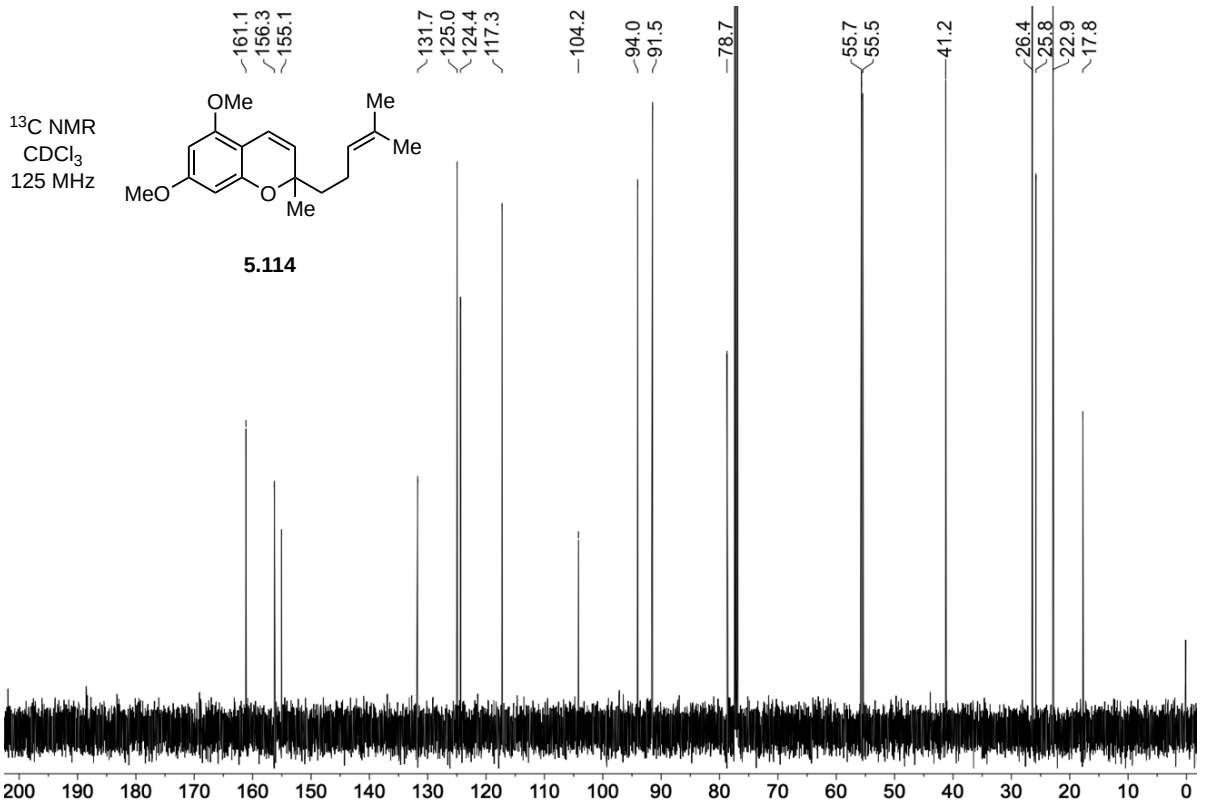
Data for 5.113



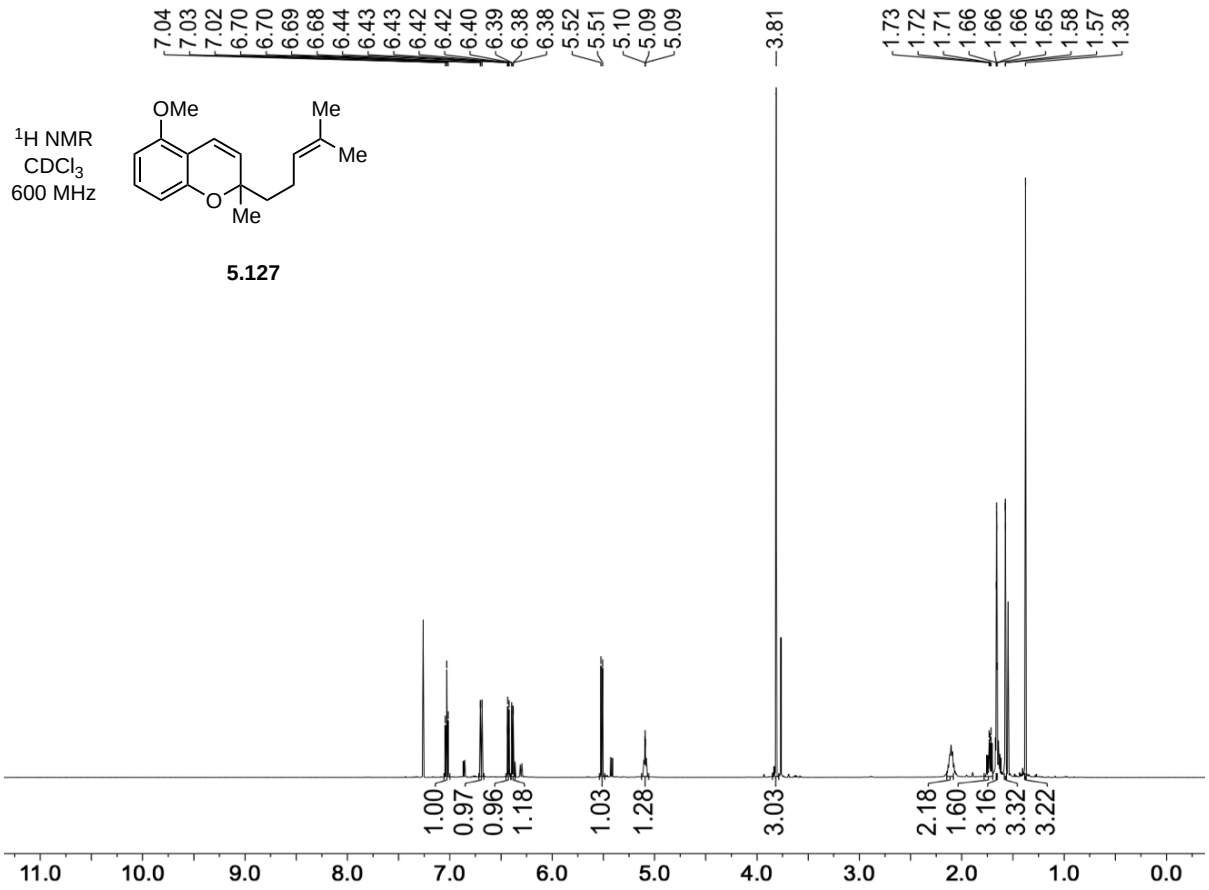


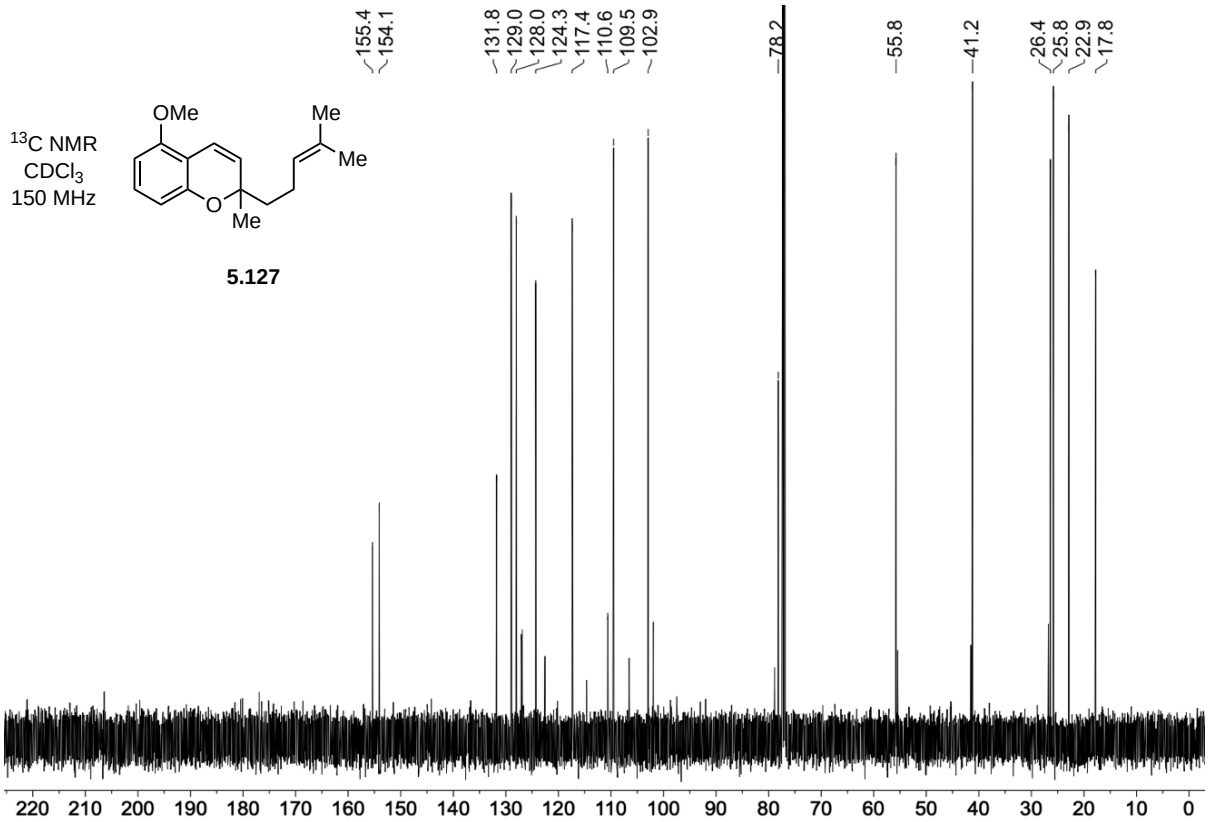
Data for 5.114



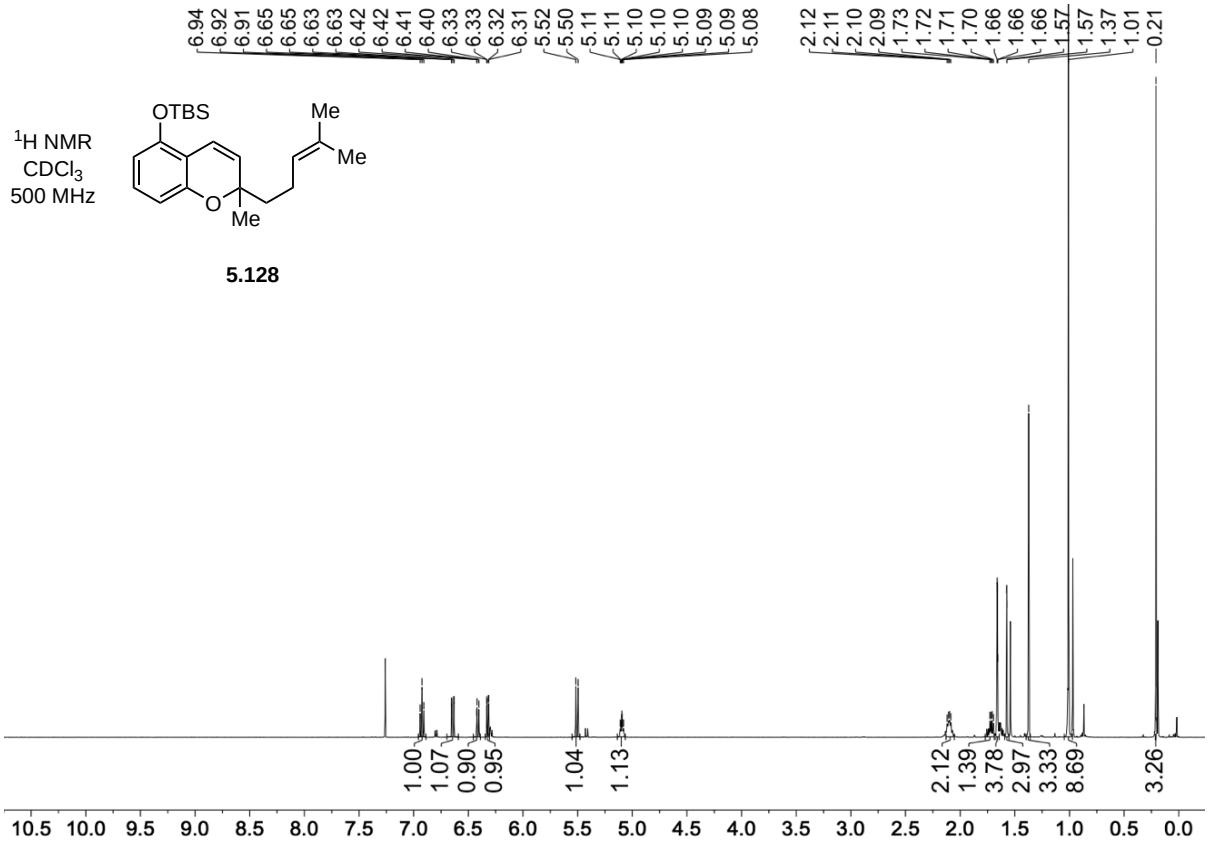


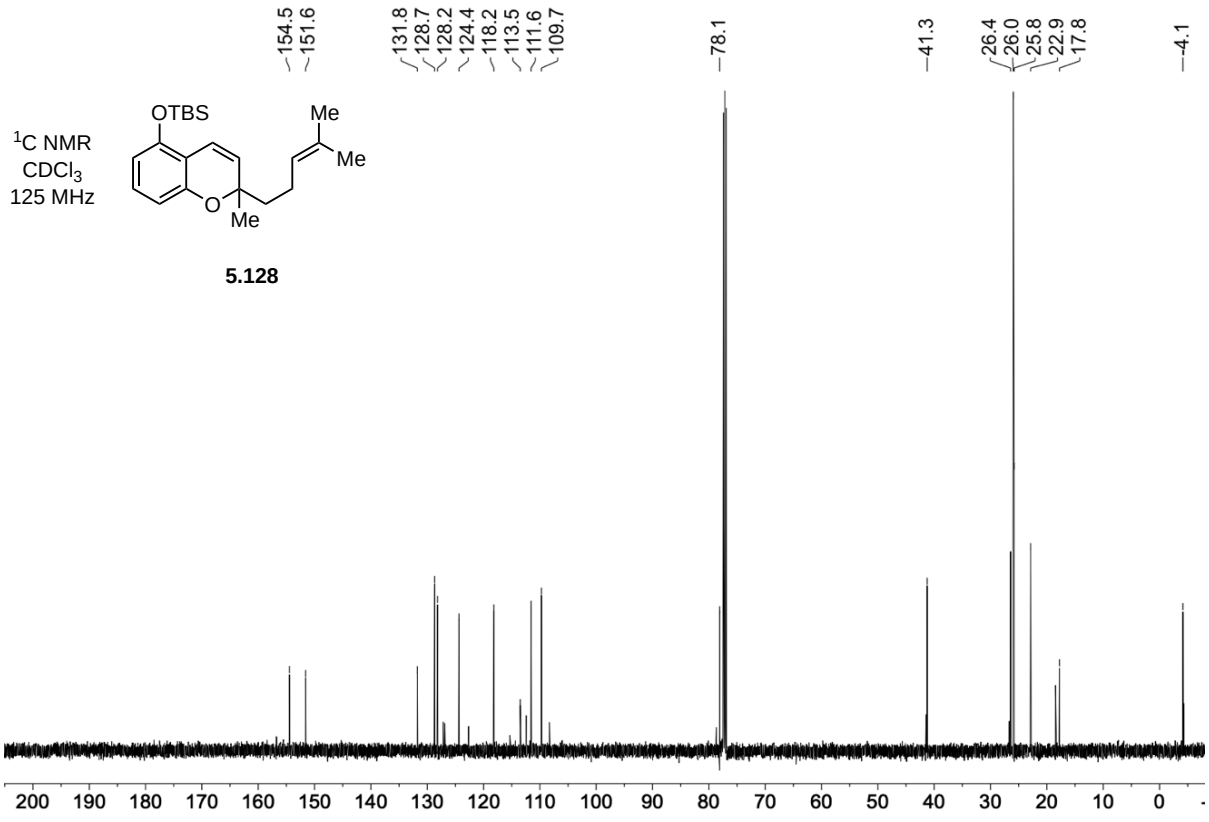
Data for 5.137



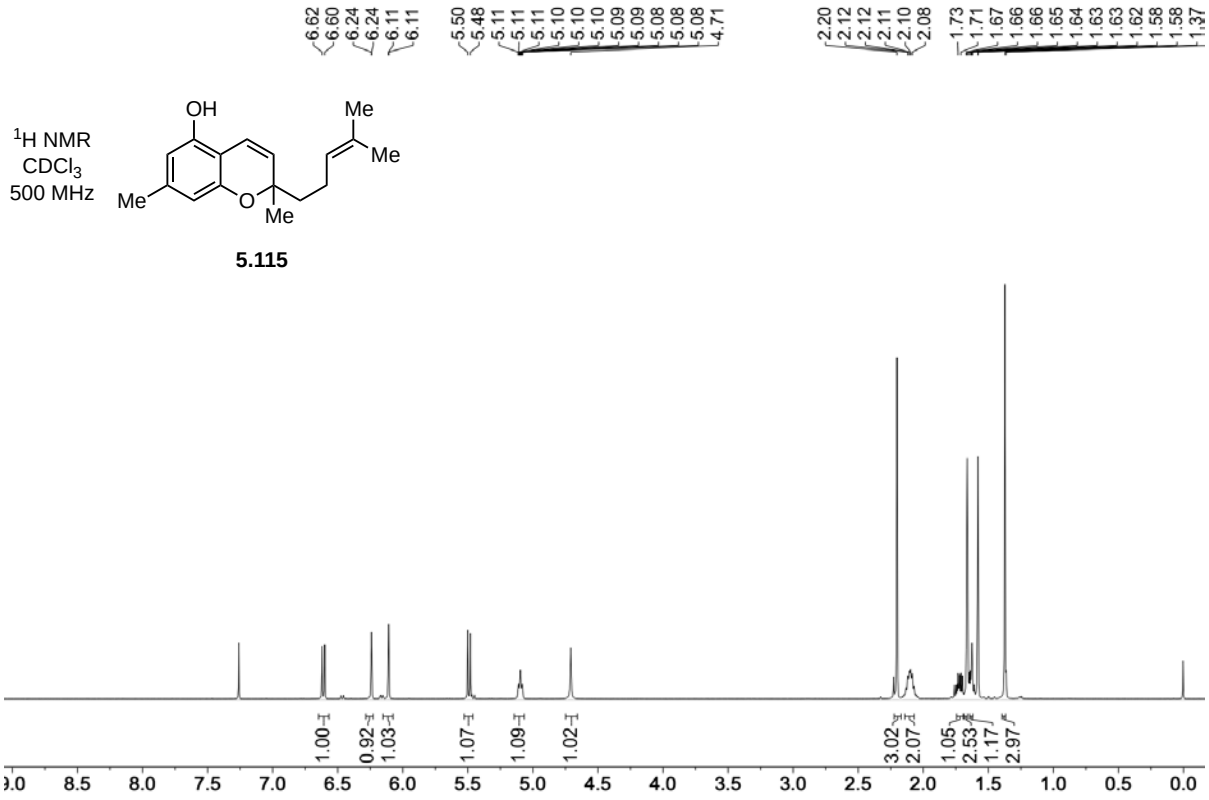


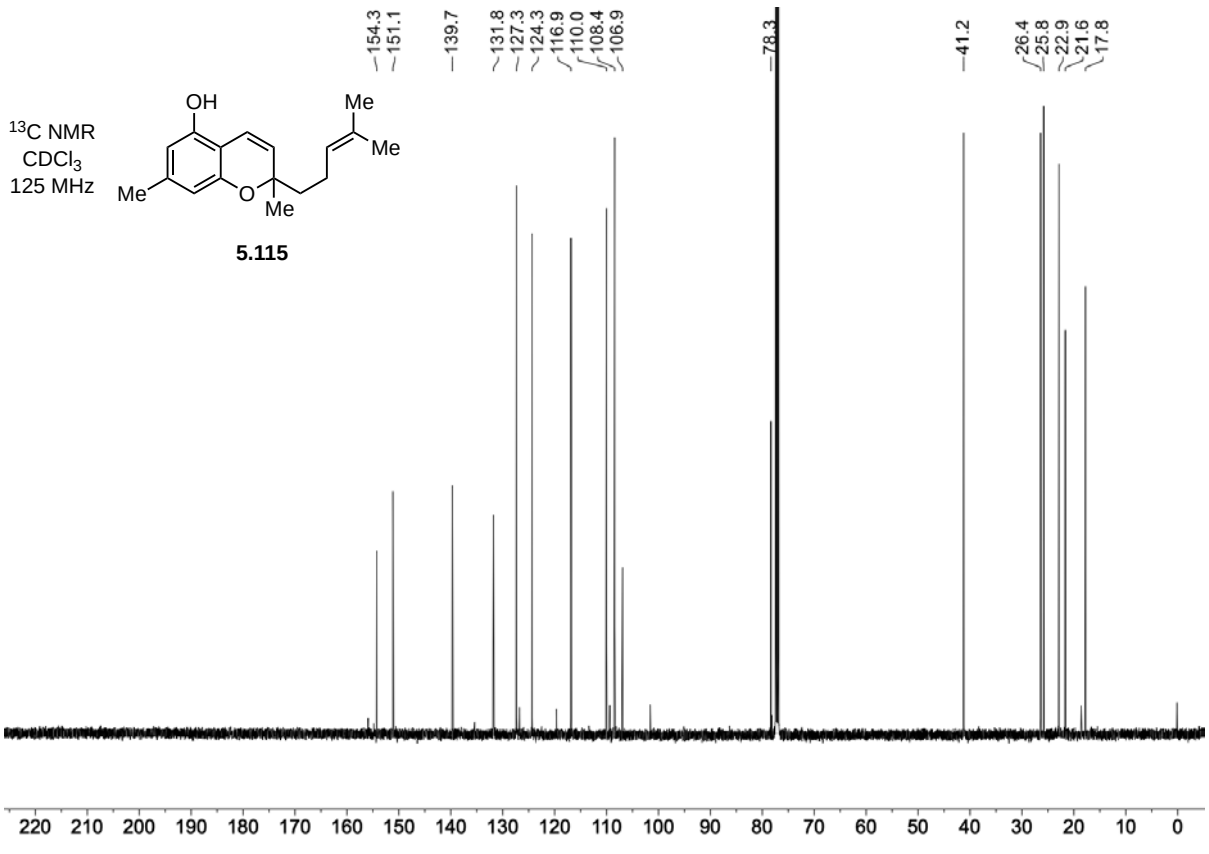
Data for 5.128



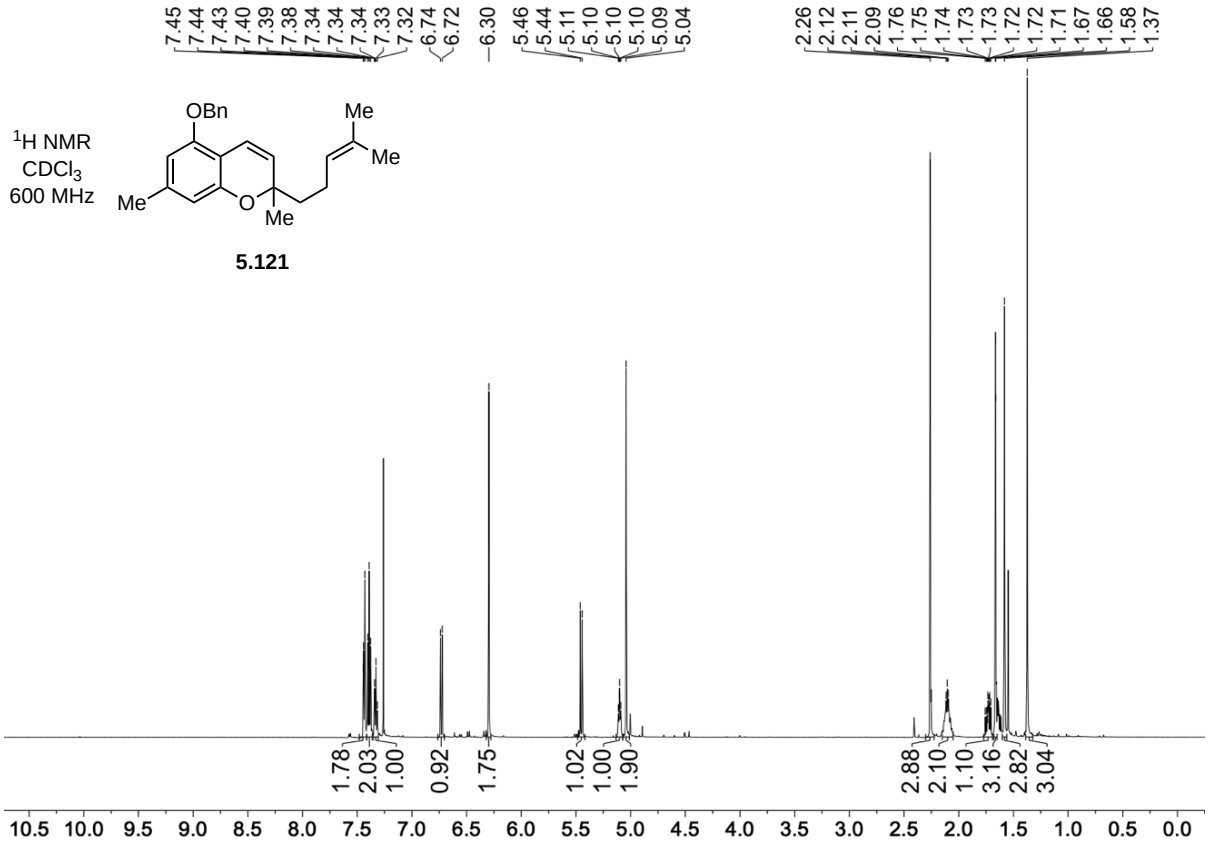


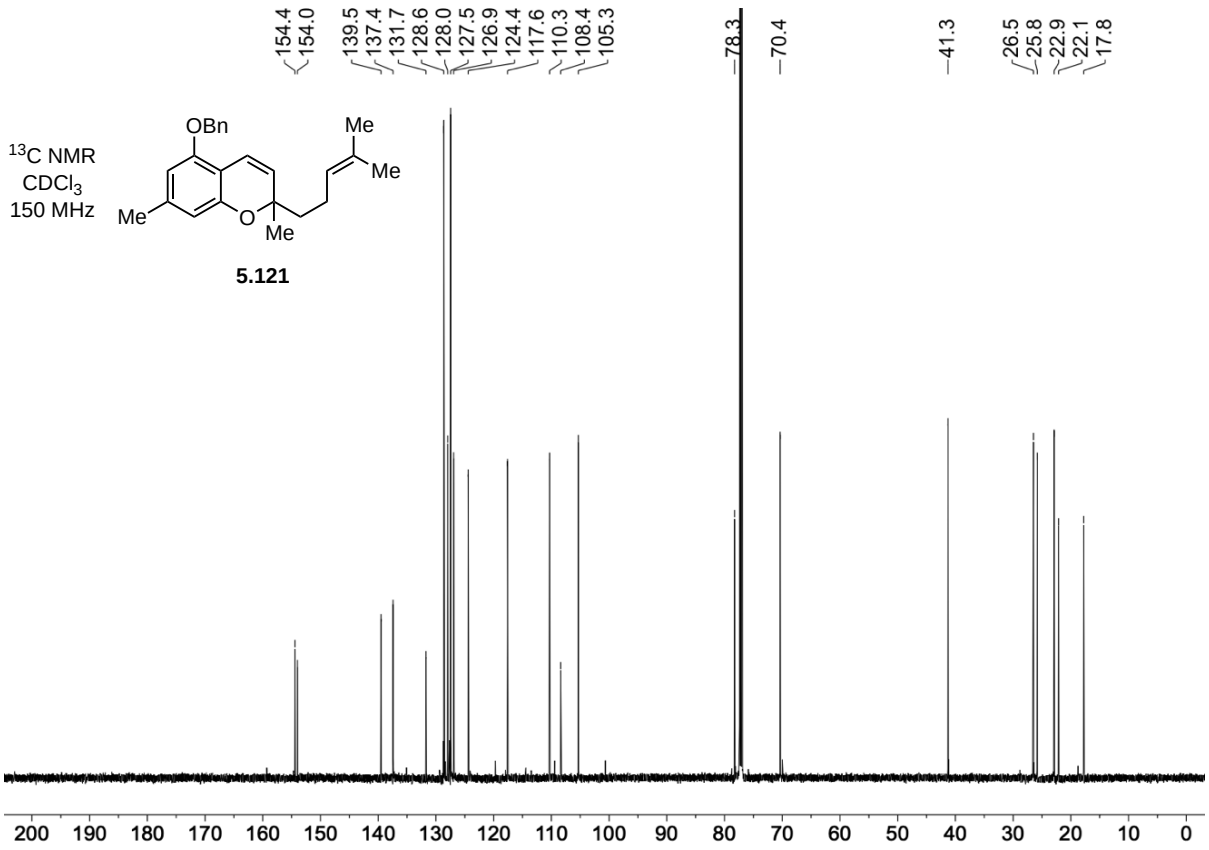
Data for 5.115



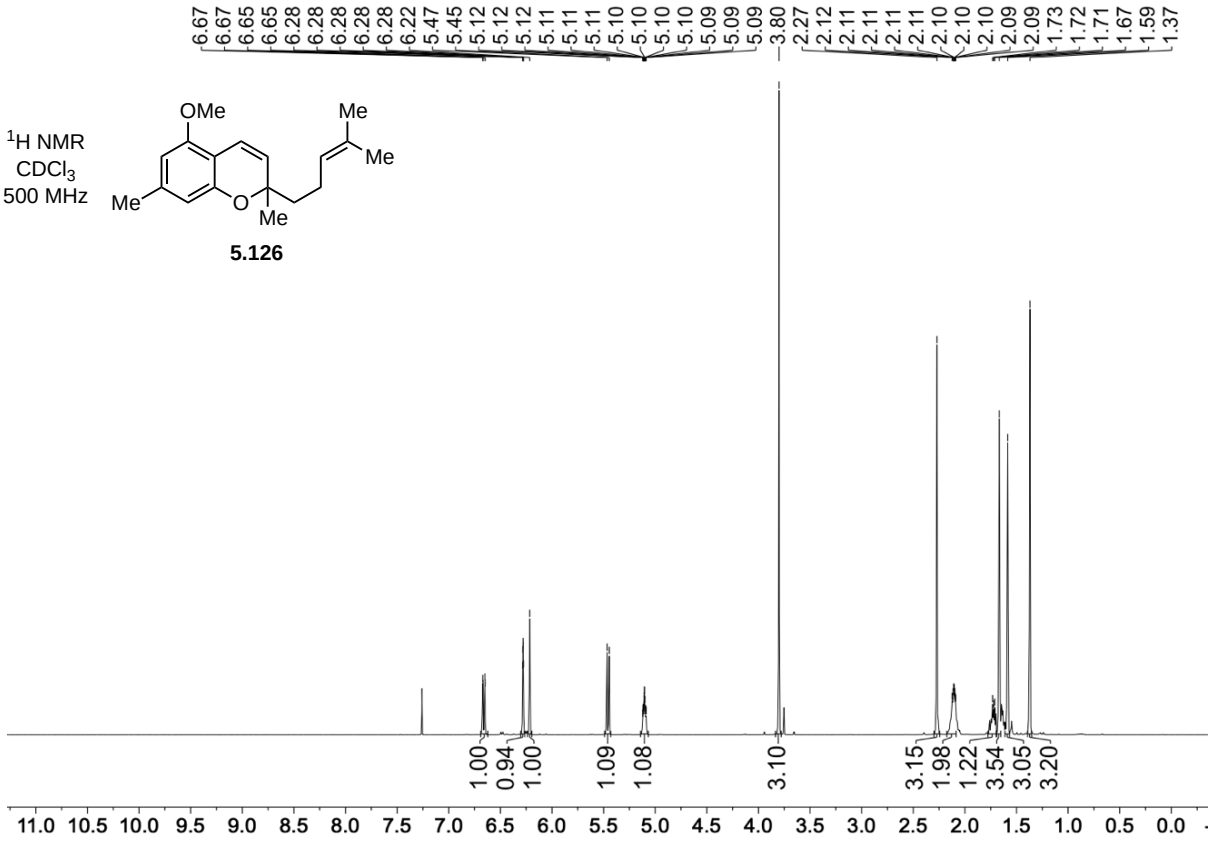


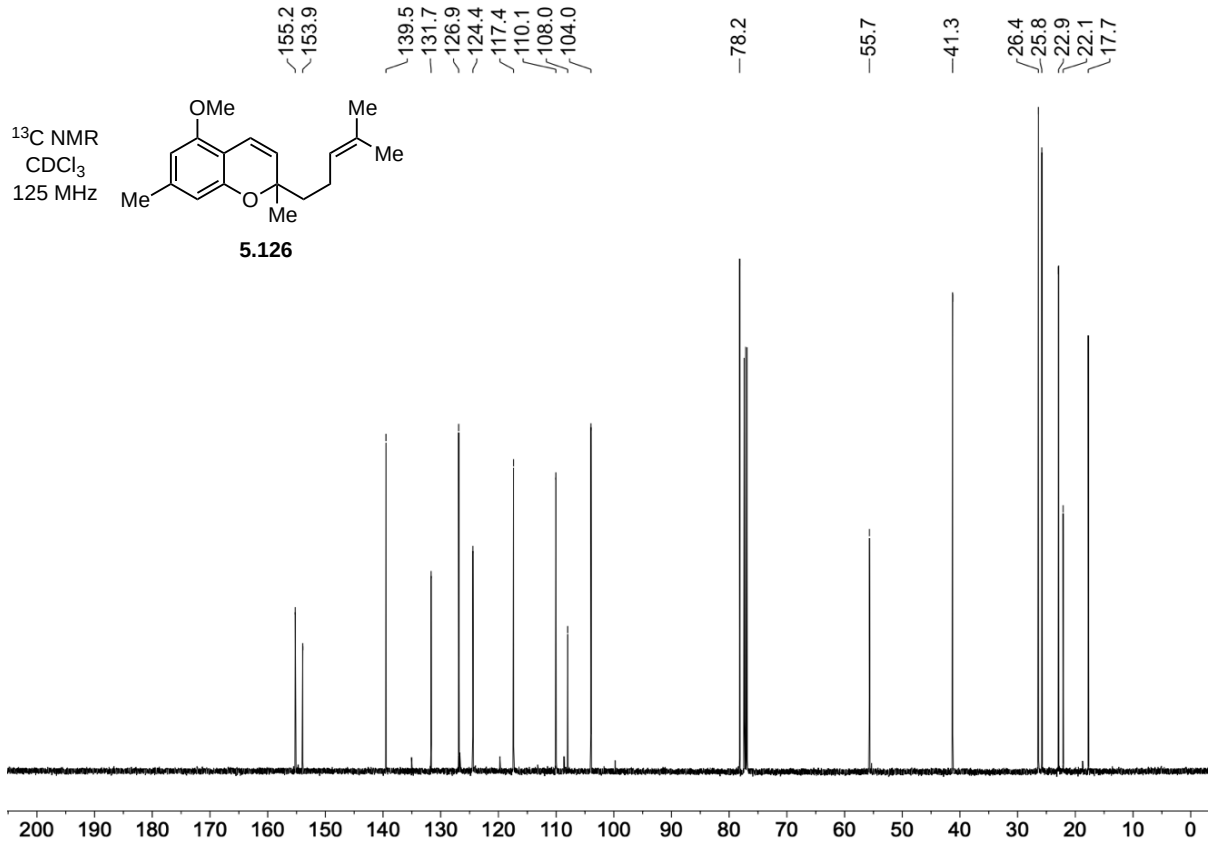
Data for 5.121



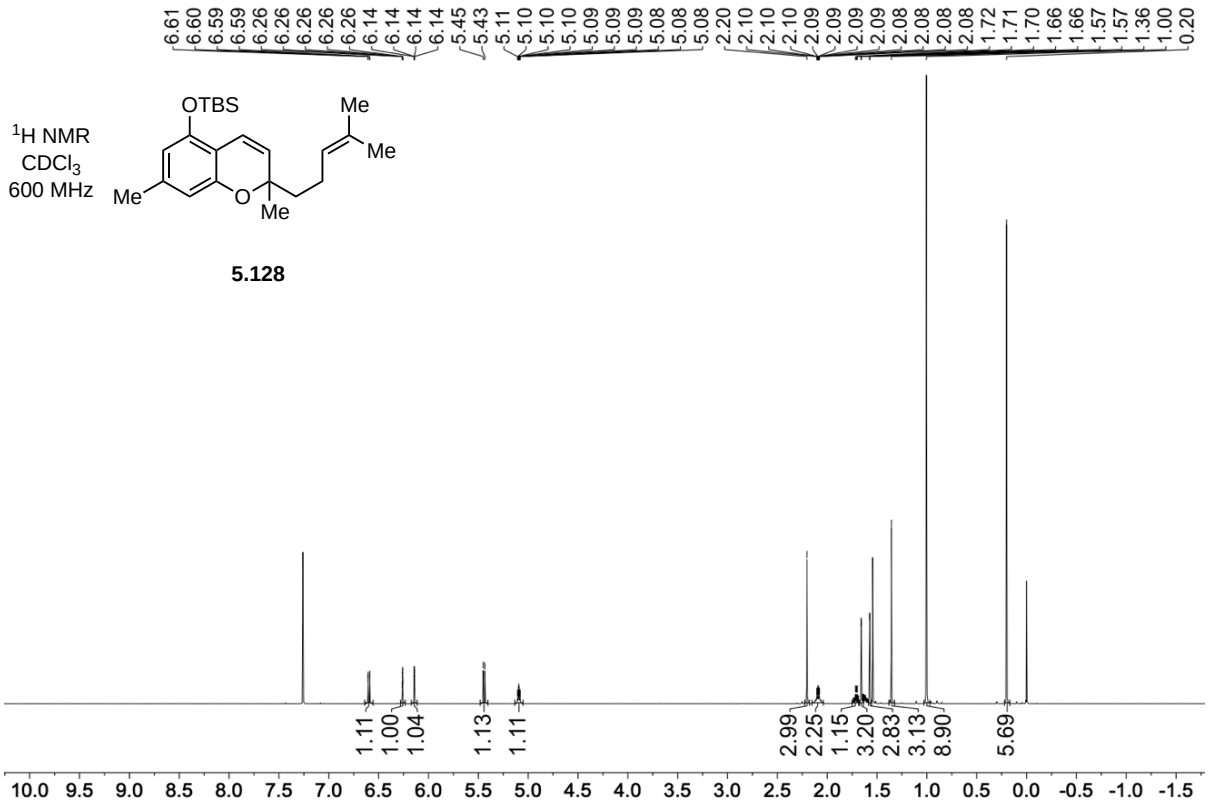


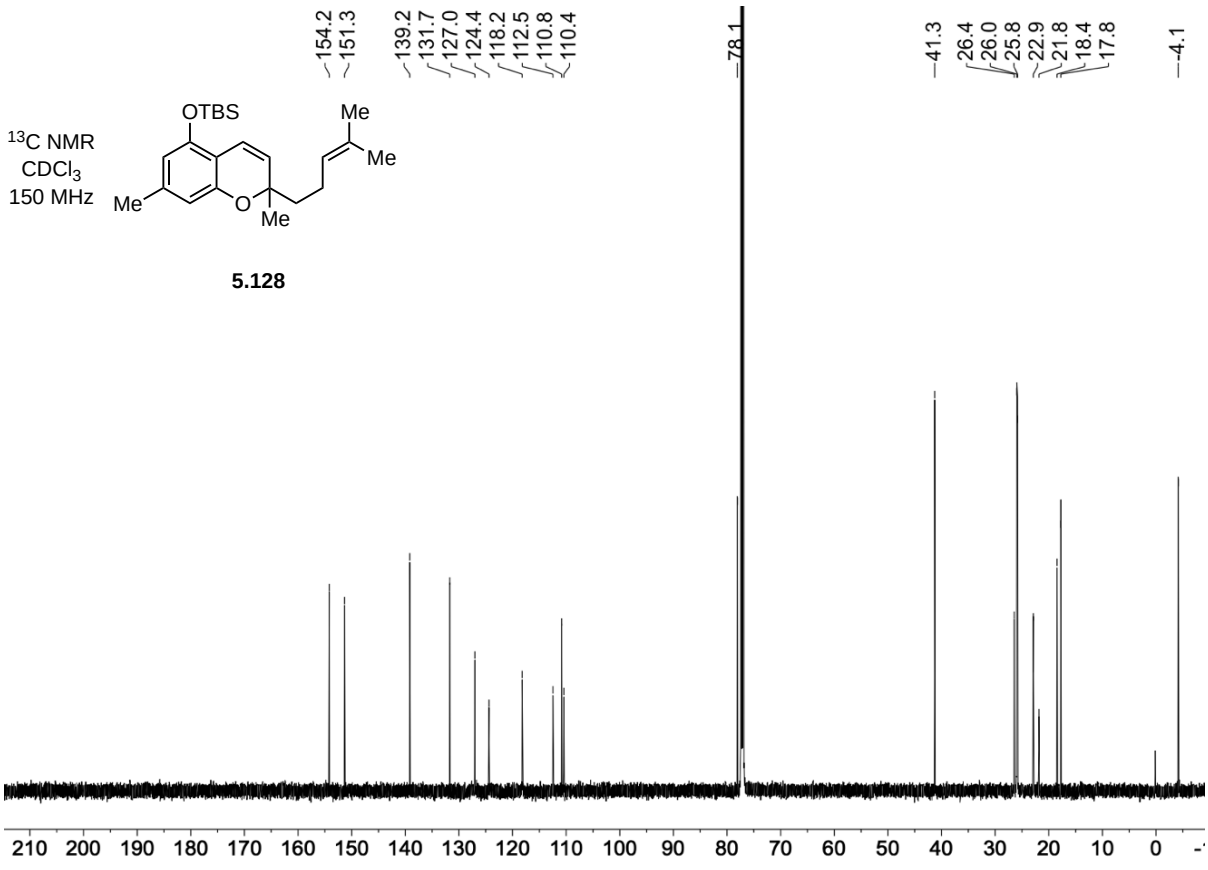
Data for 5.126



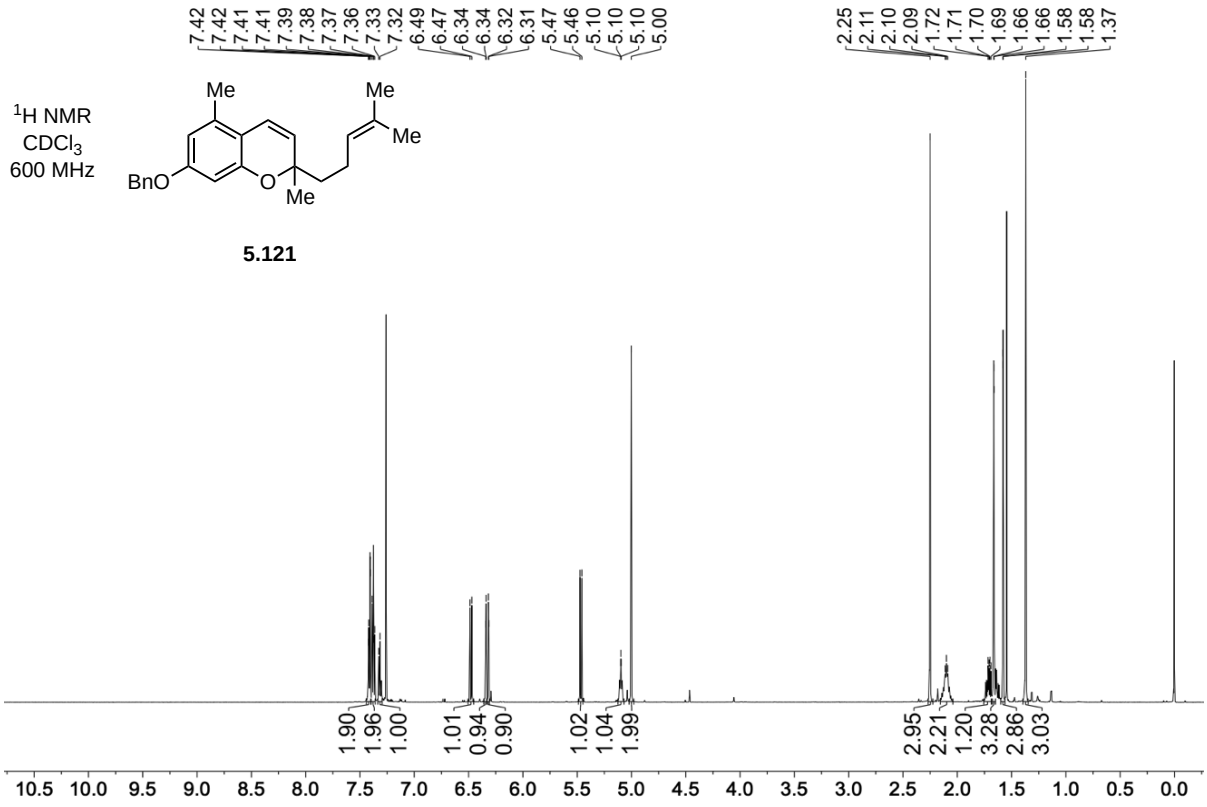


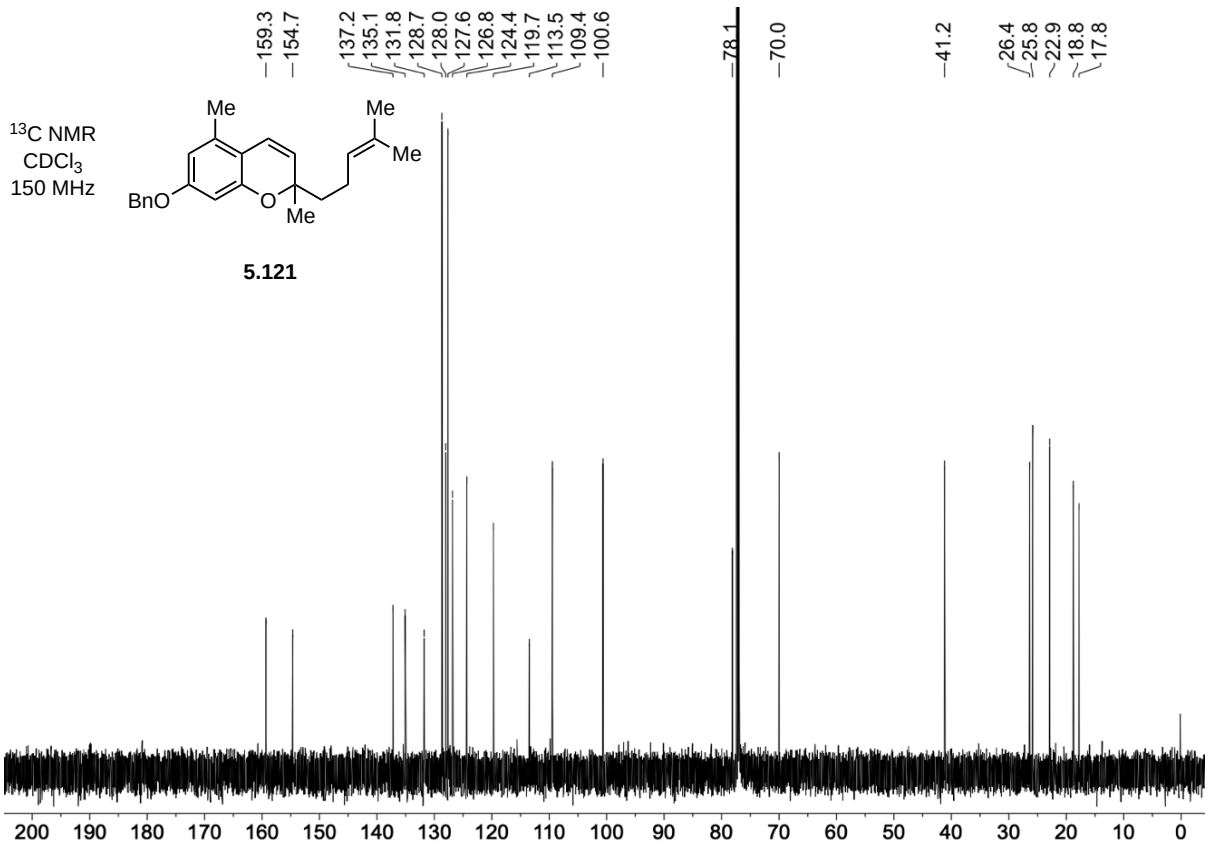
Data for 5.128



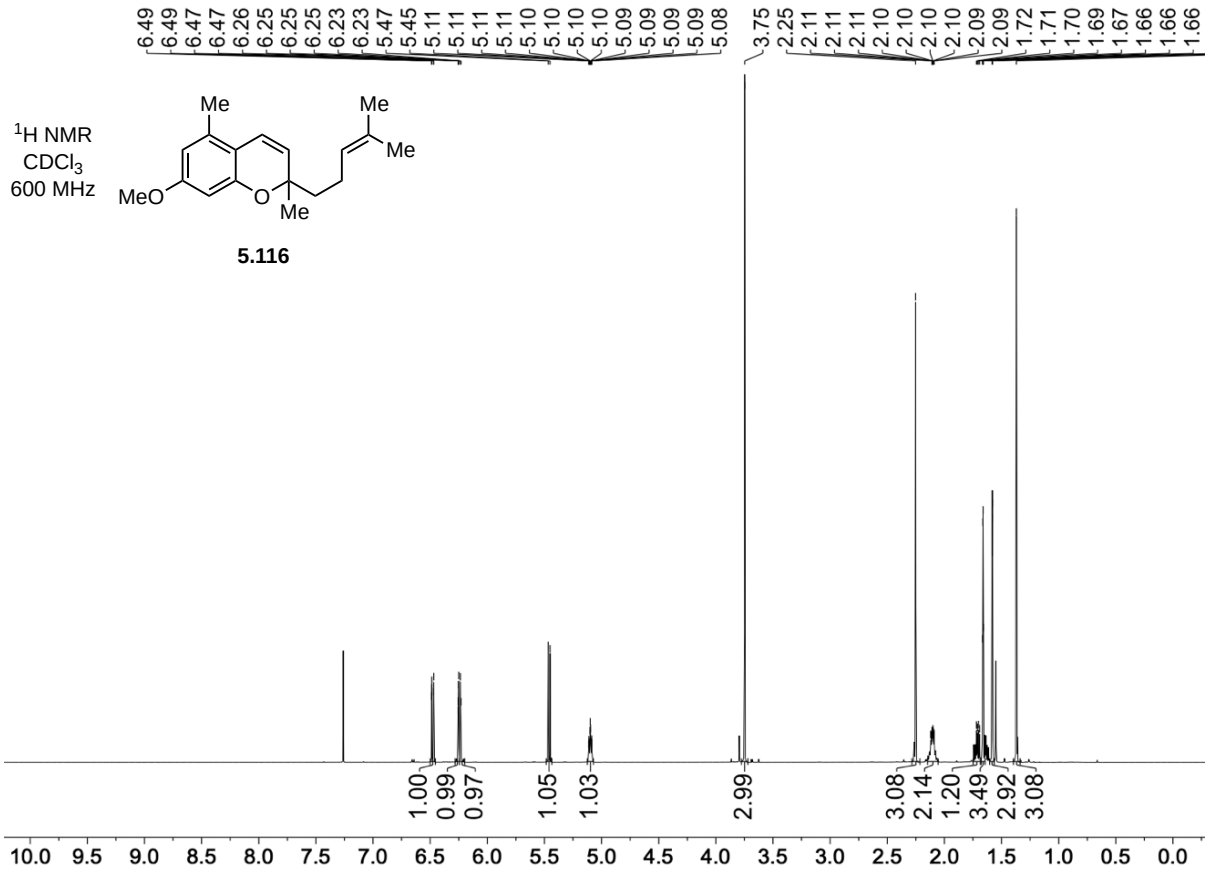


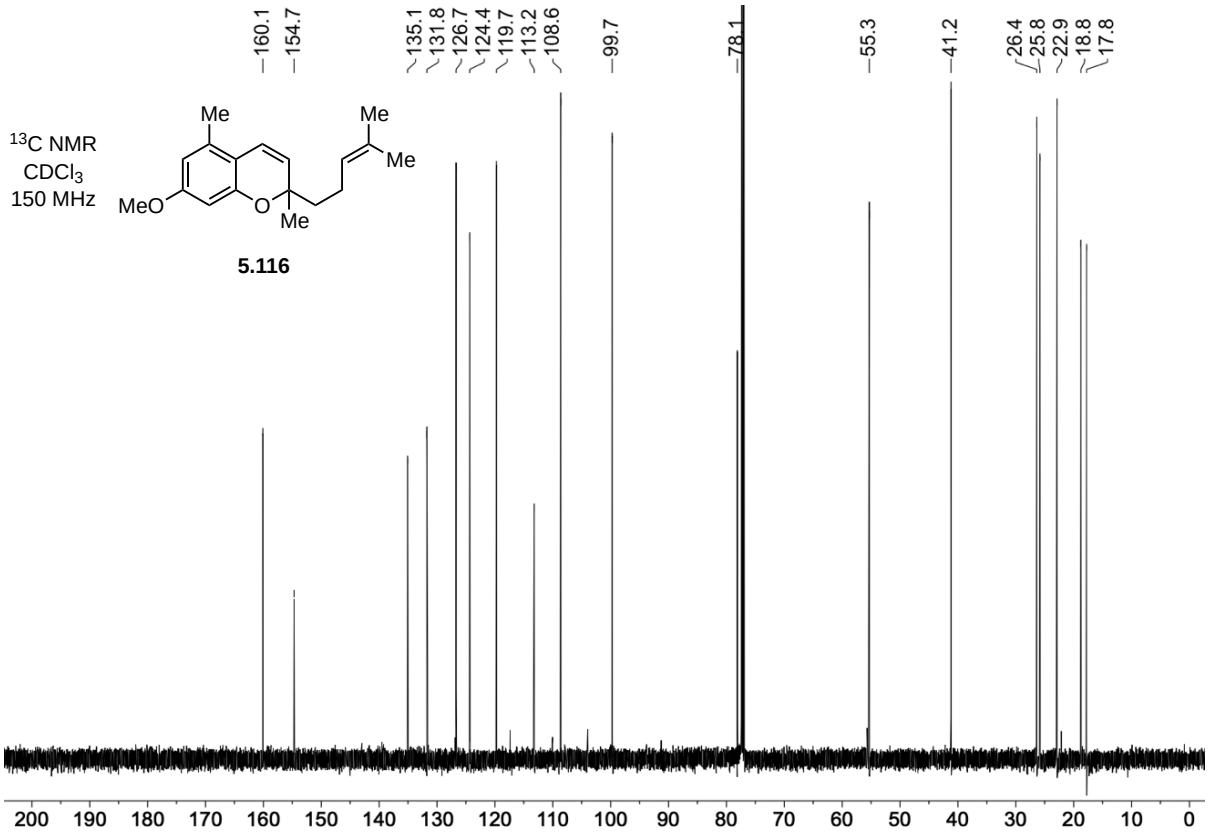
Data for 5.121



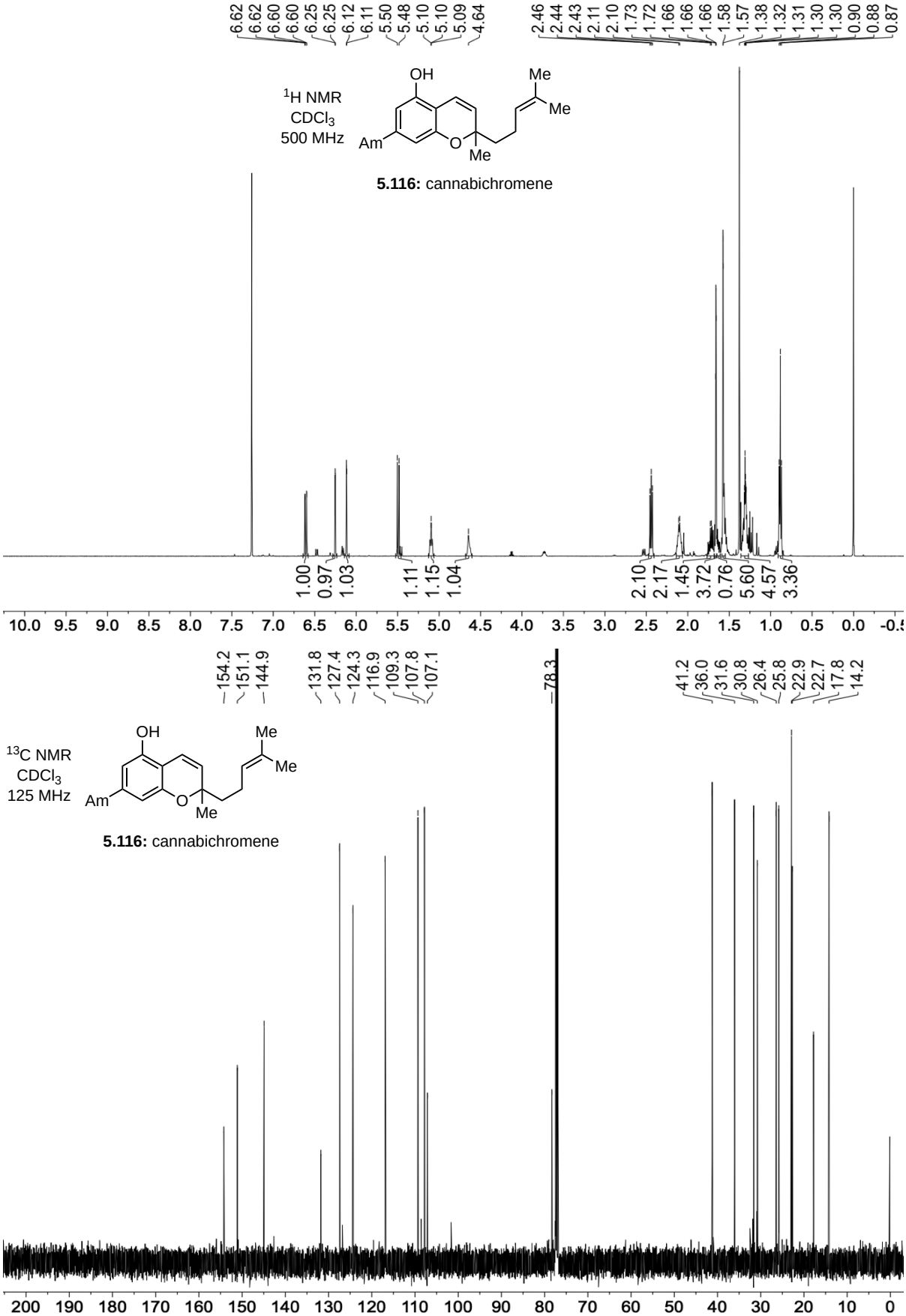


Data for 5.116

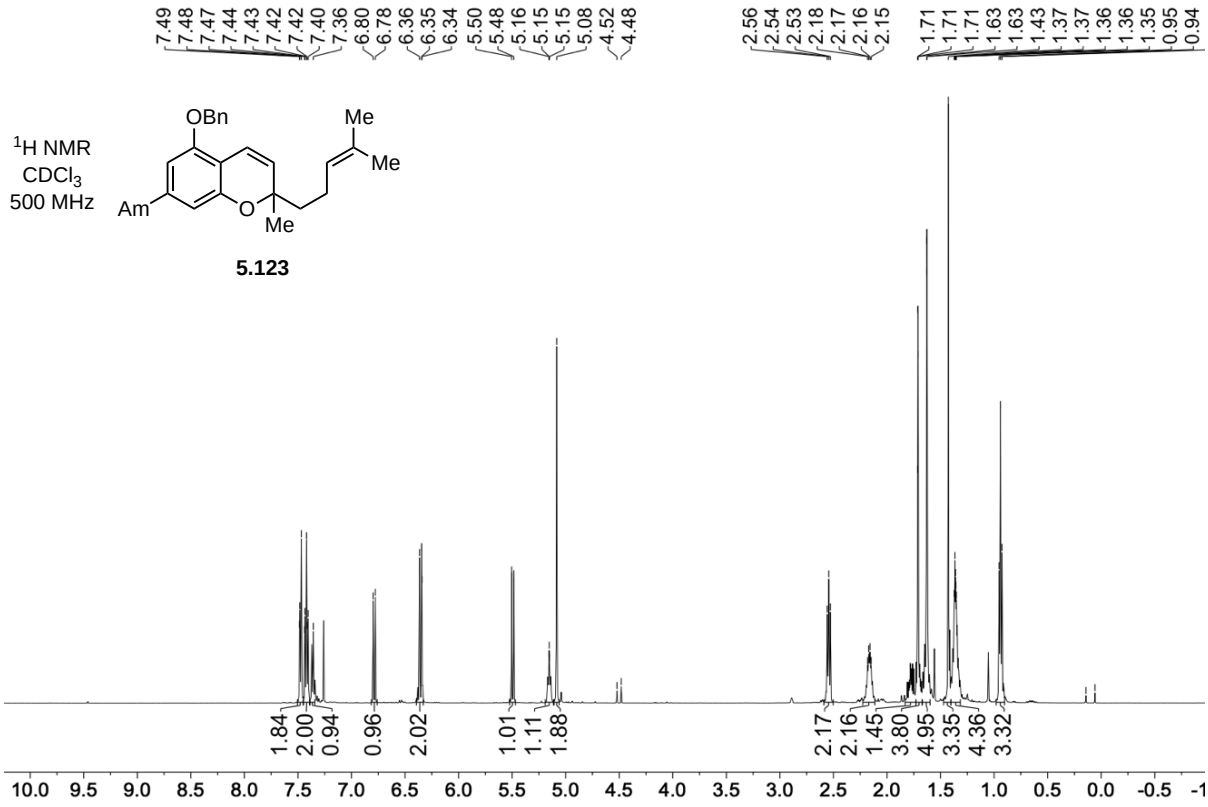


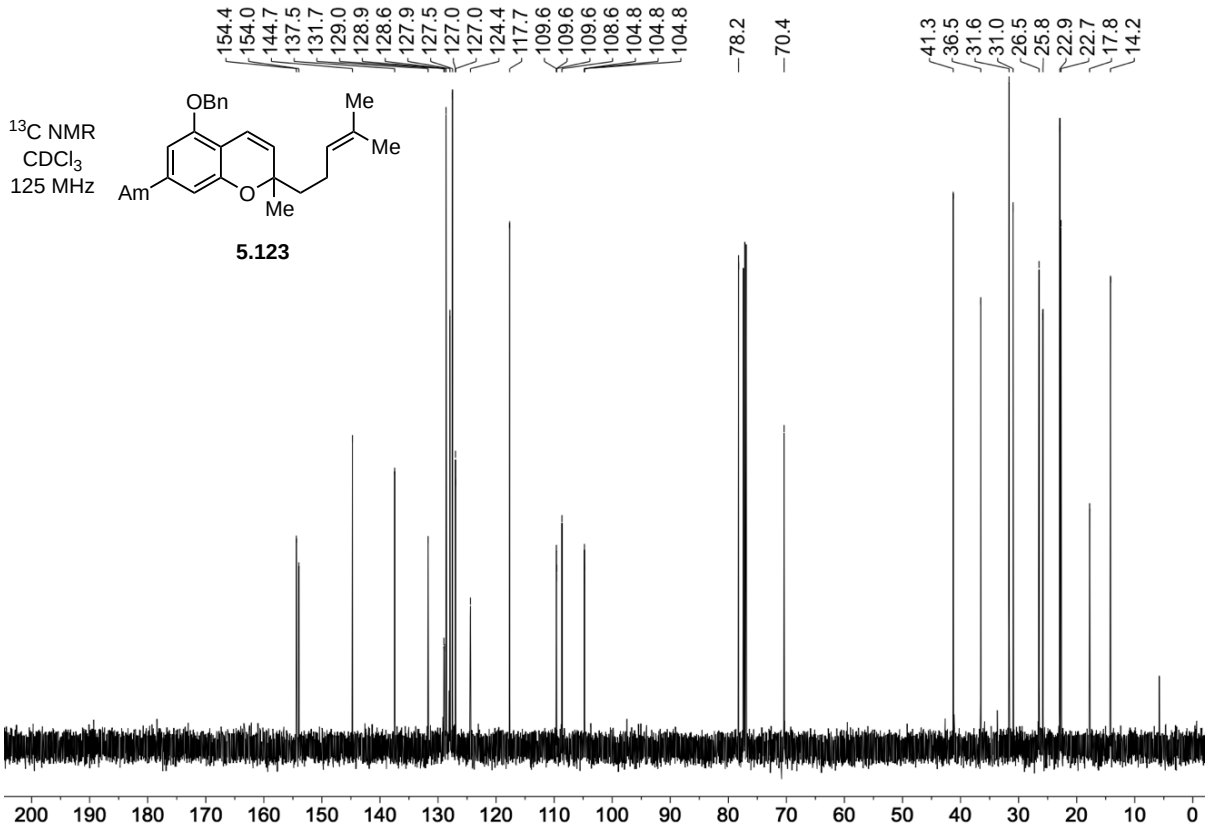


Data for 5.116

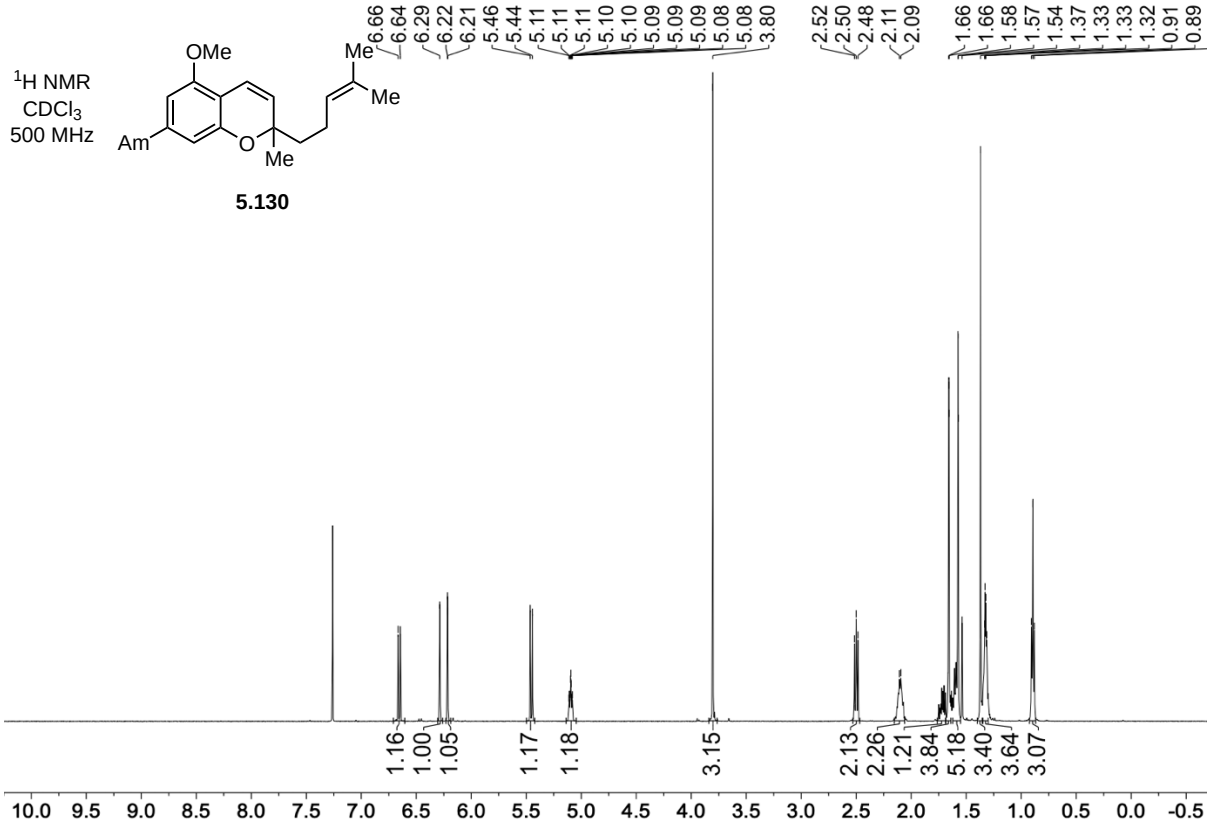


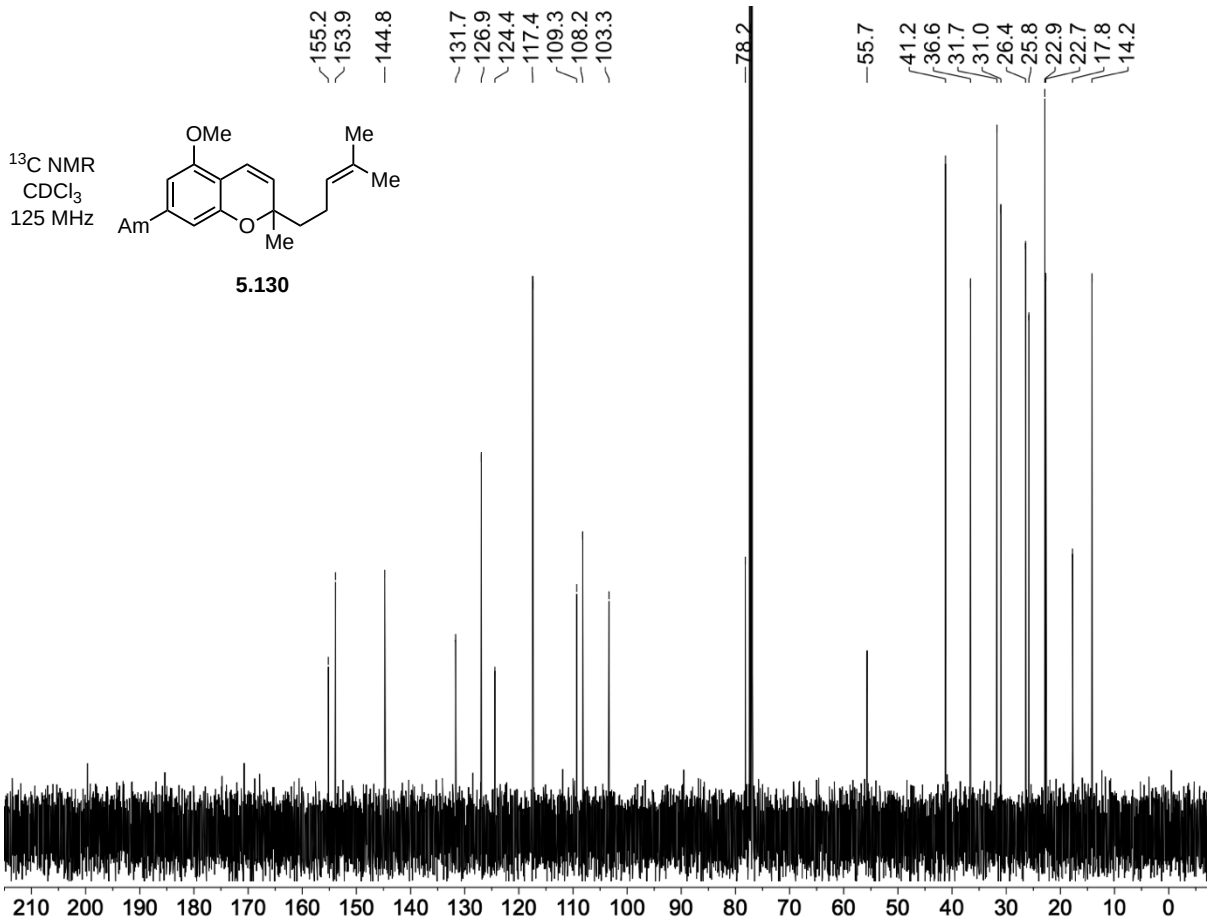
Data for 5.123



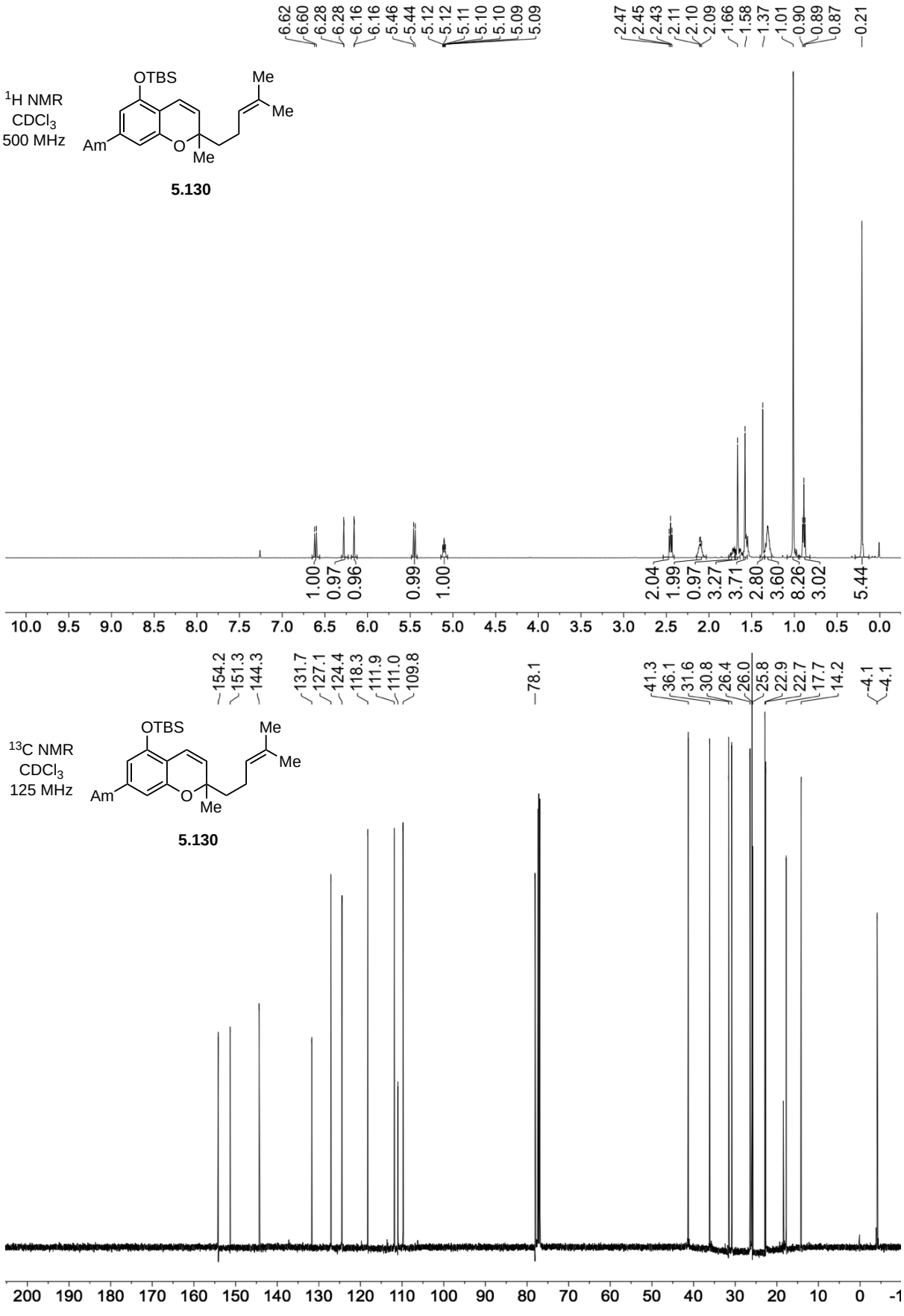


Data for 5.125

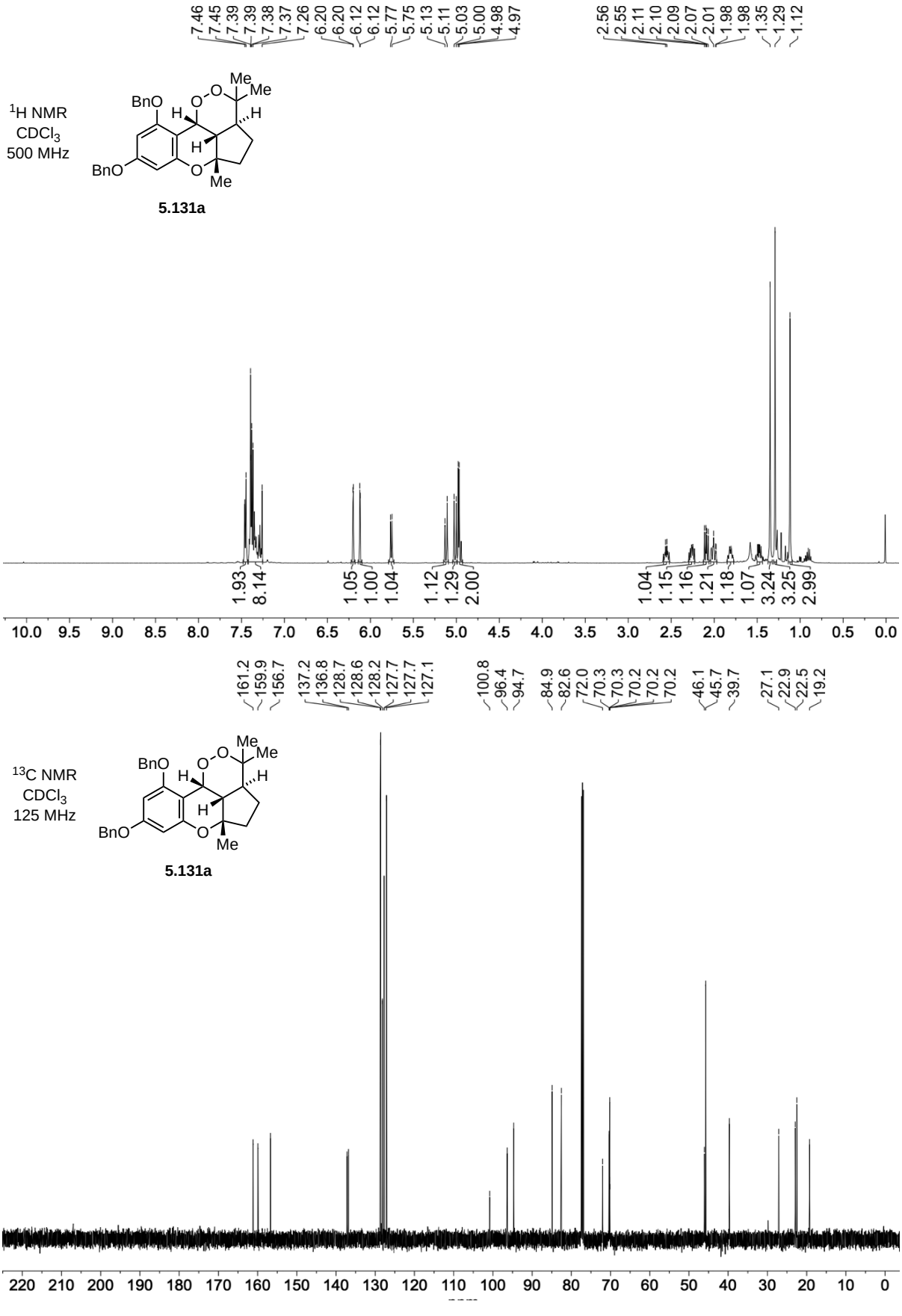




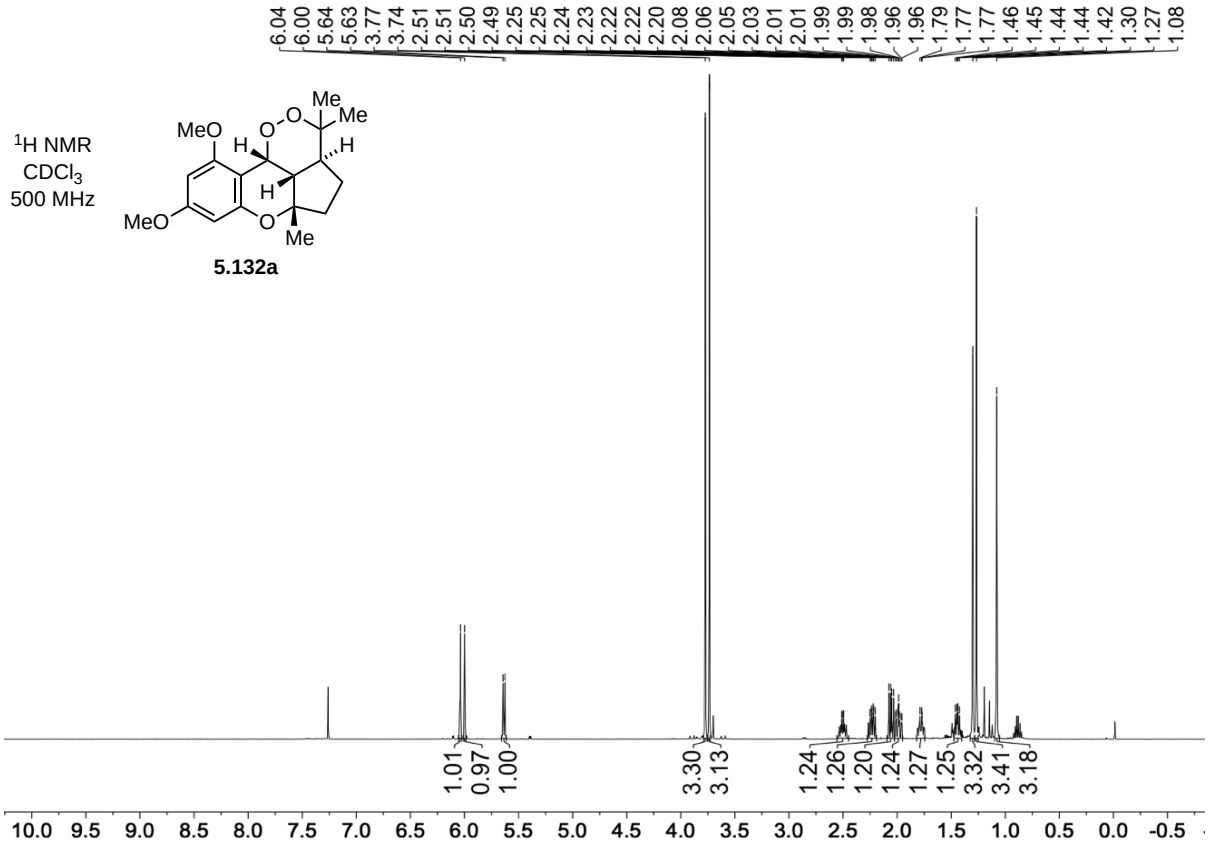
Data for 5.130



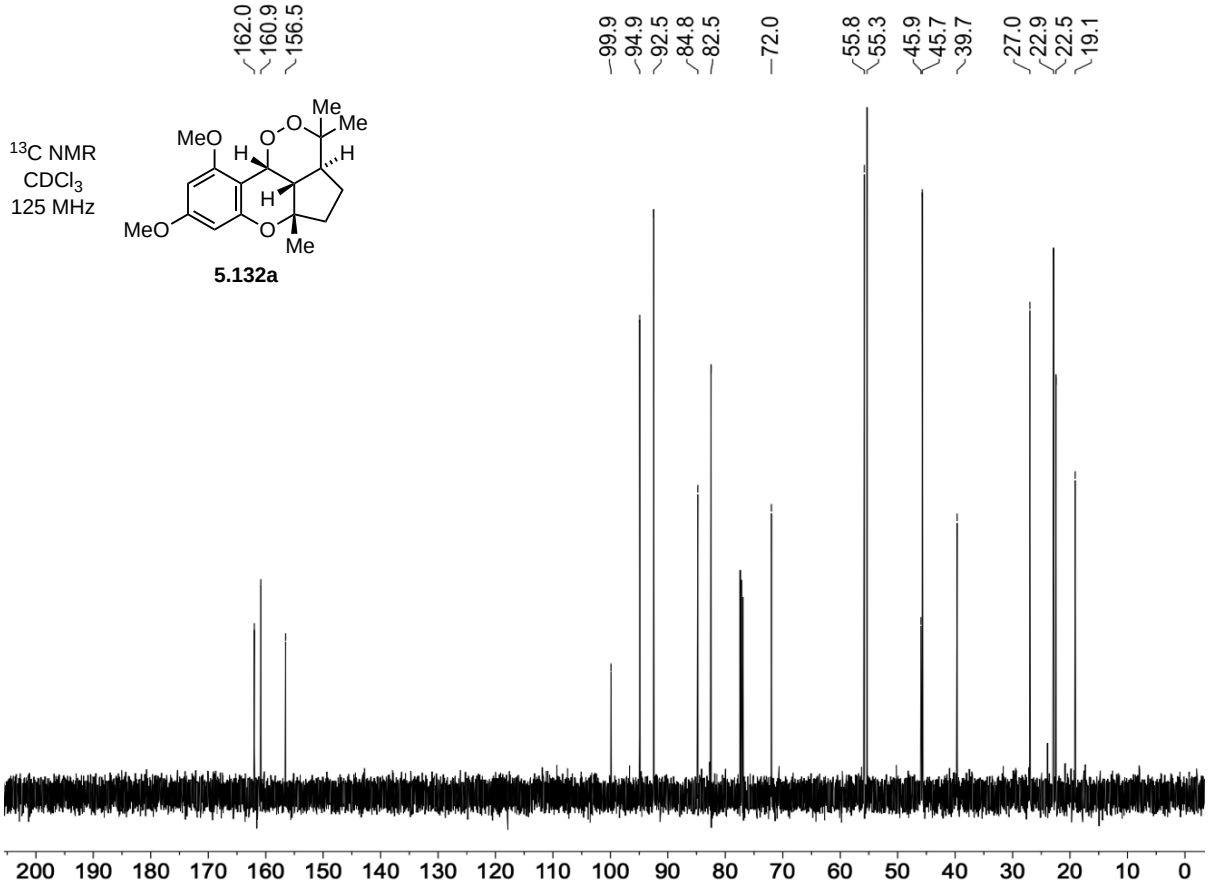
Data for 5.131a



Data for 5.132a

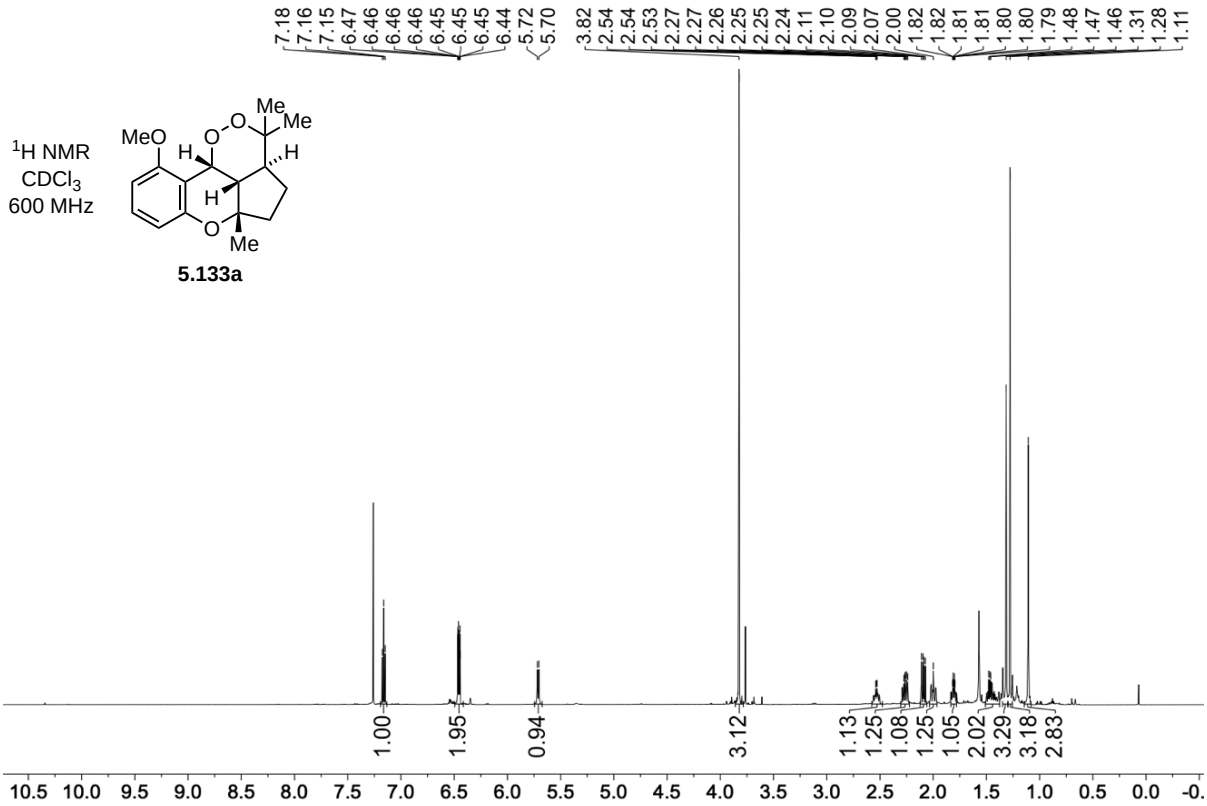


5.132a

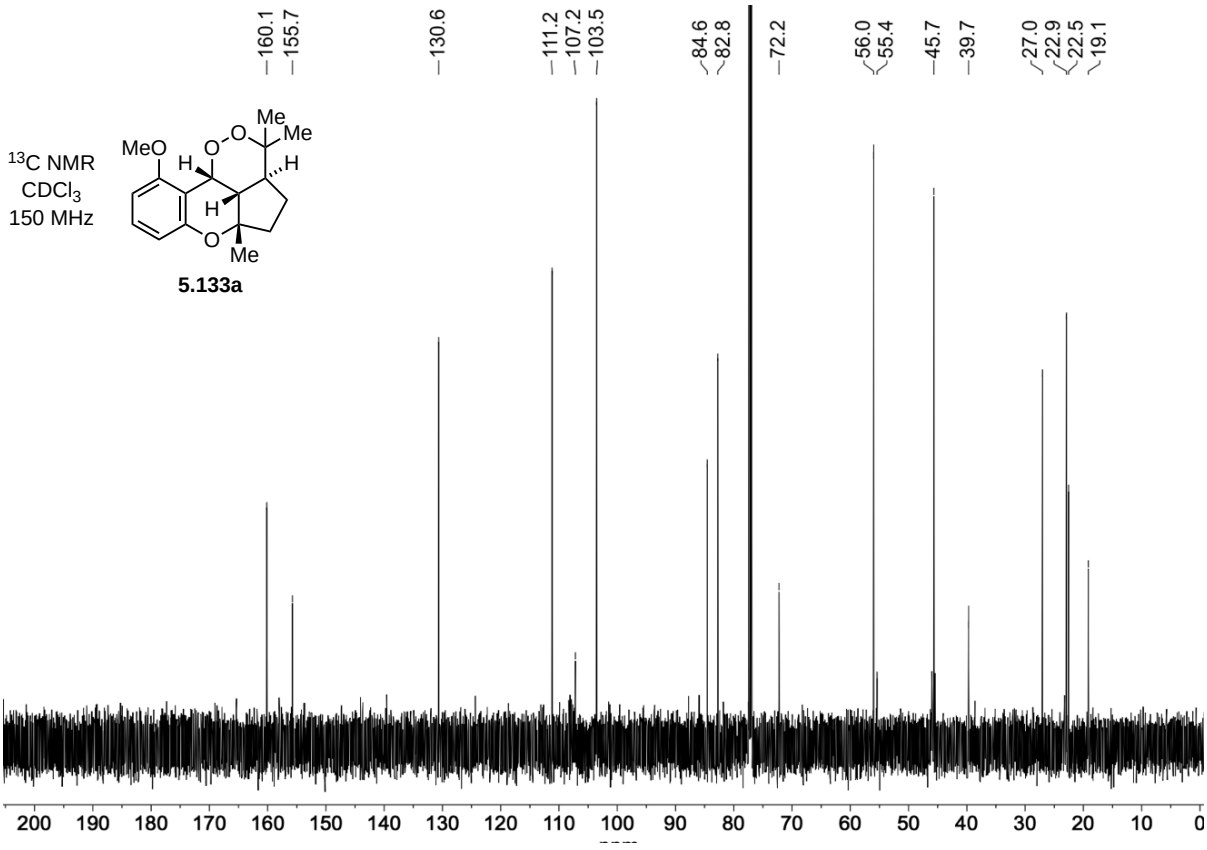


5.132a

Data for 5.133a

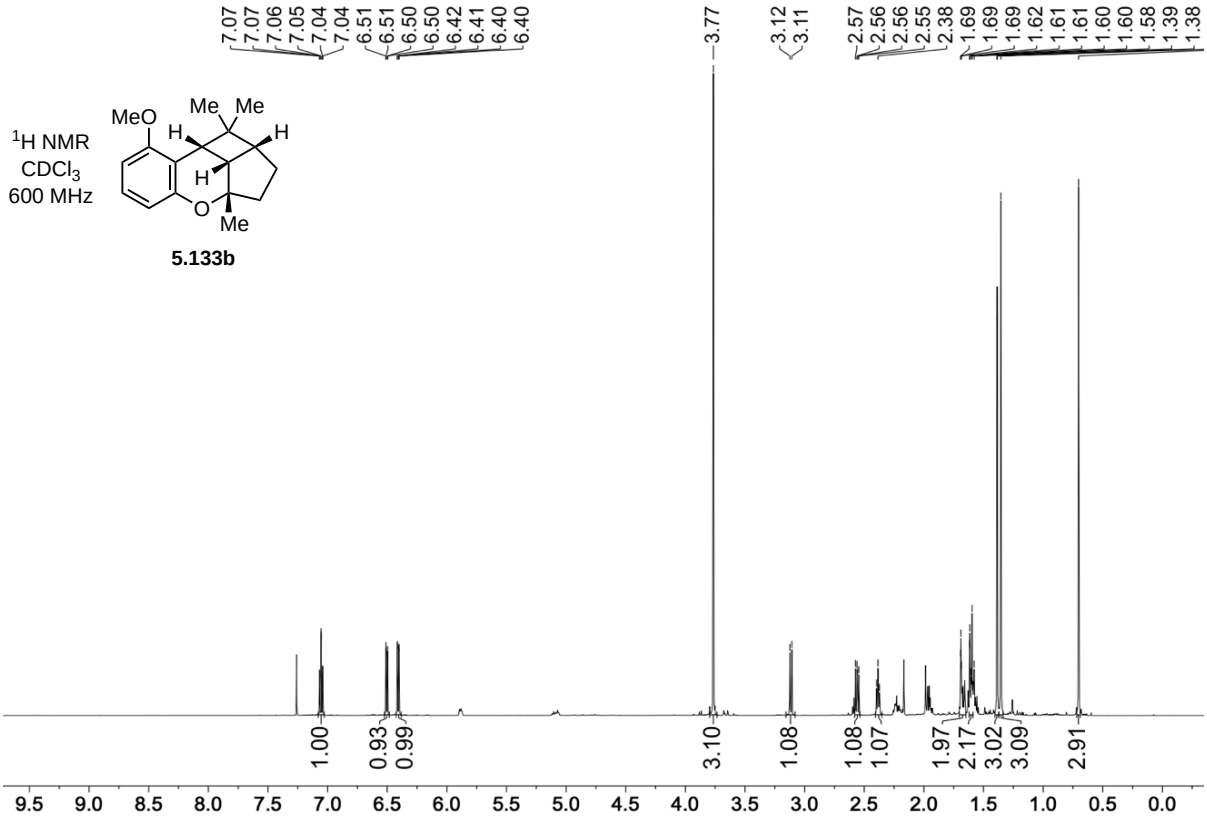


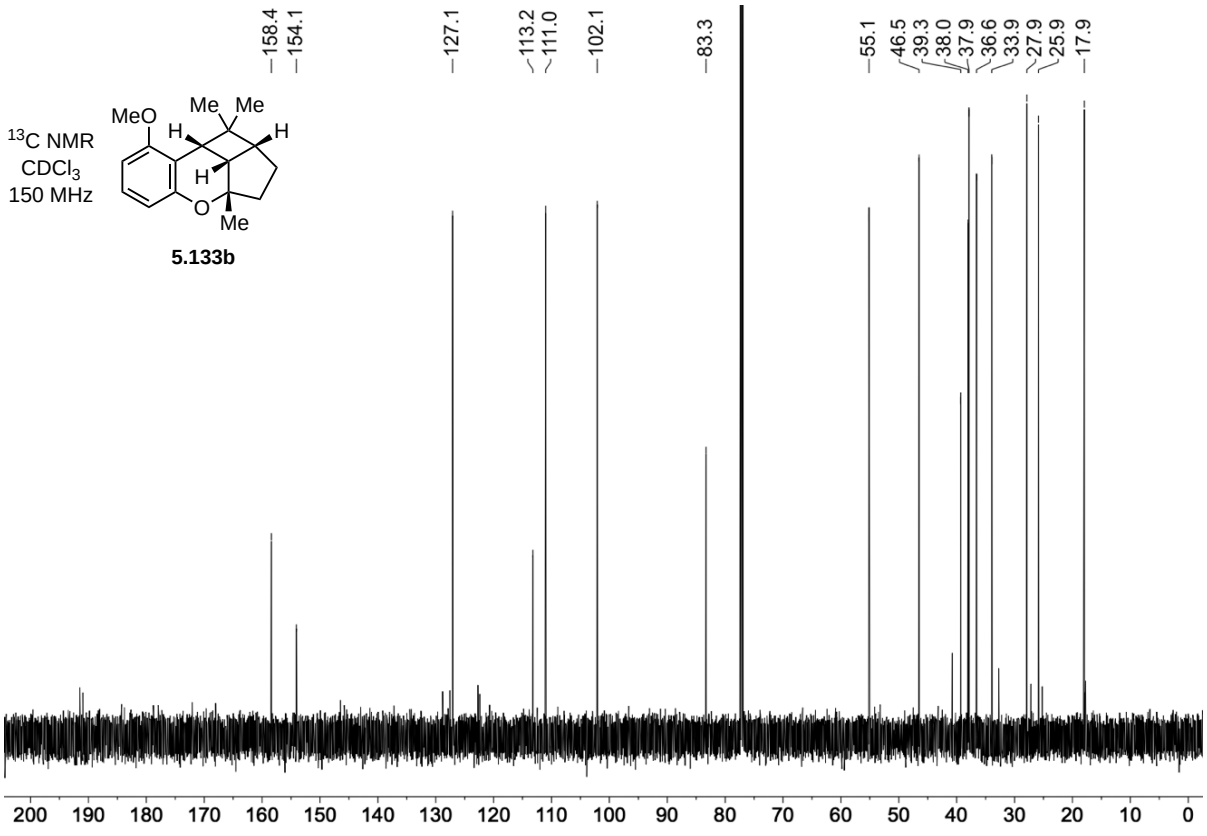
5.133a



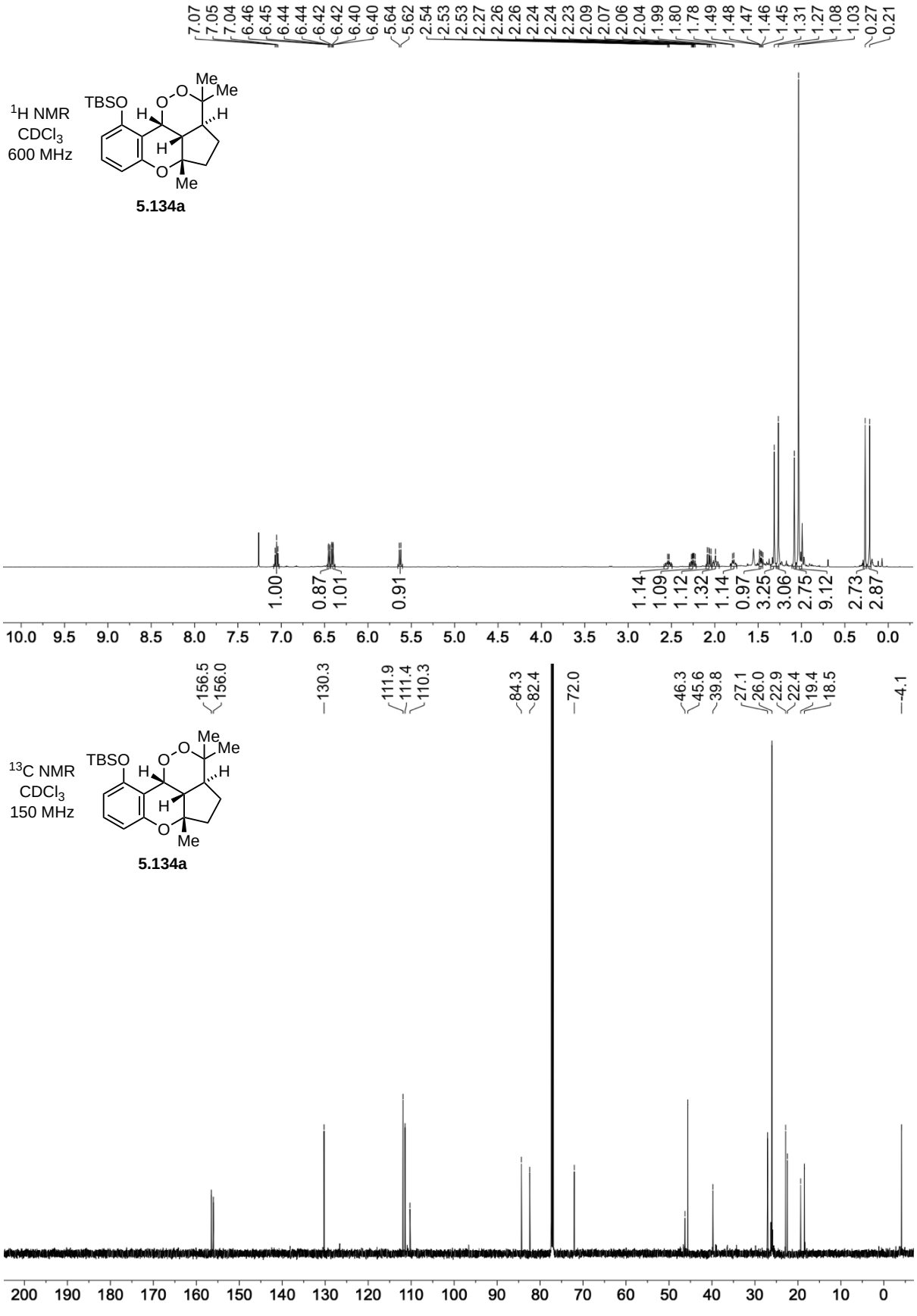
5.133a

Data for 5.133a

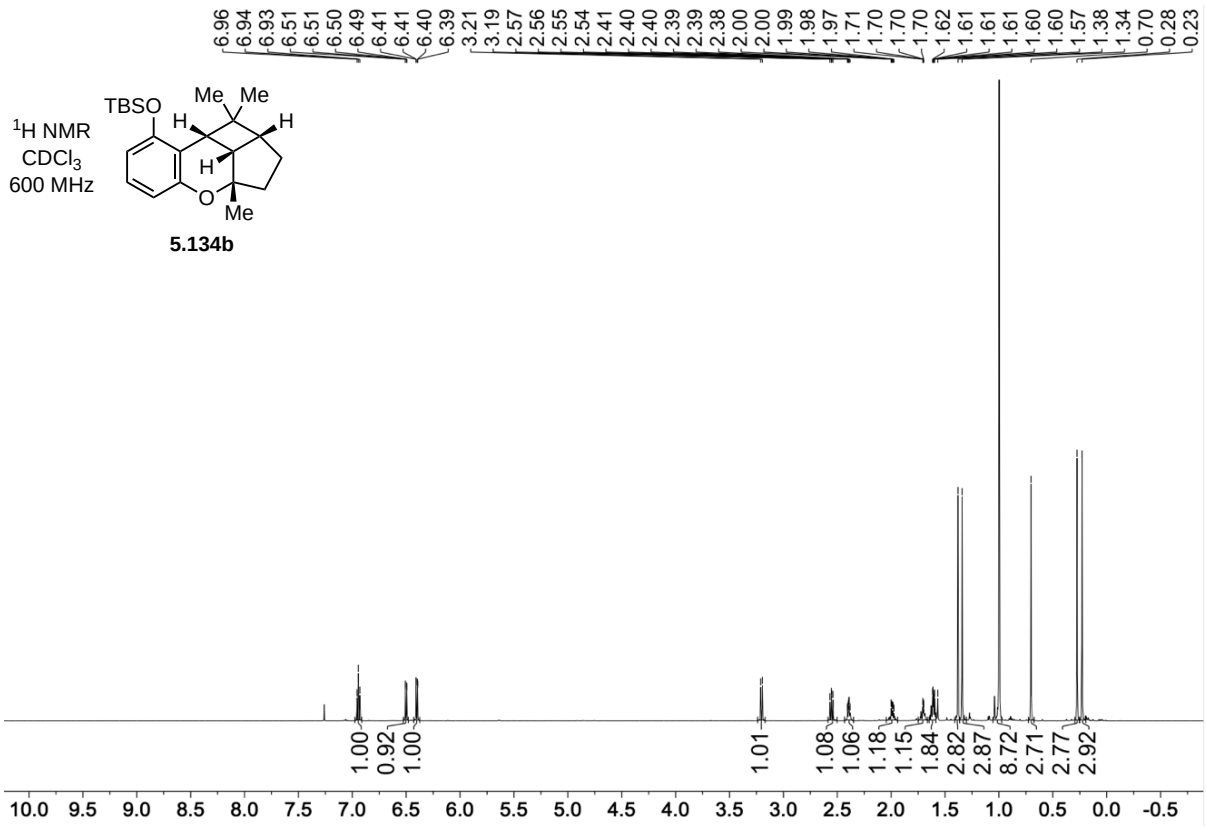


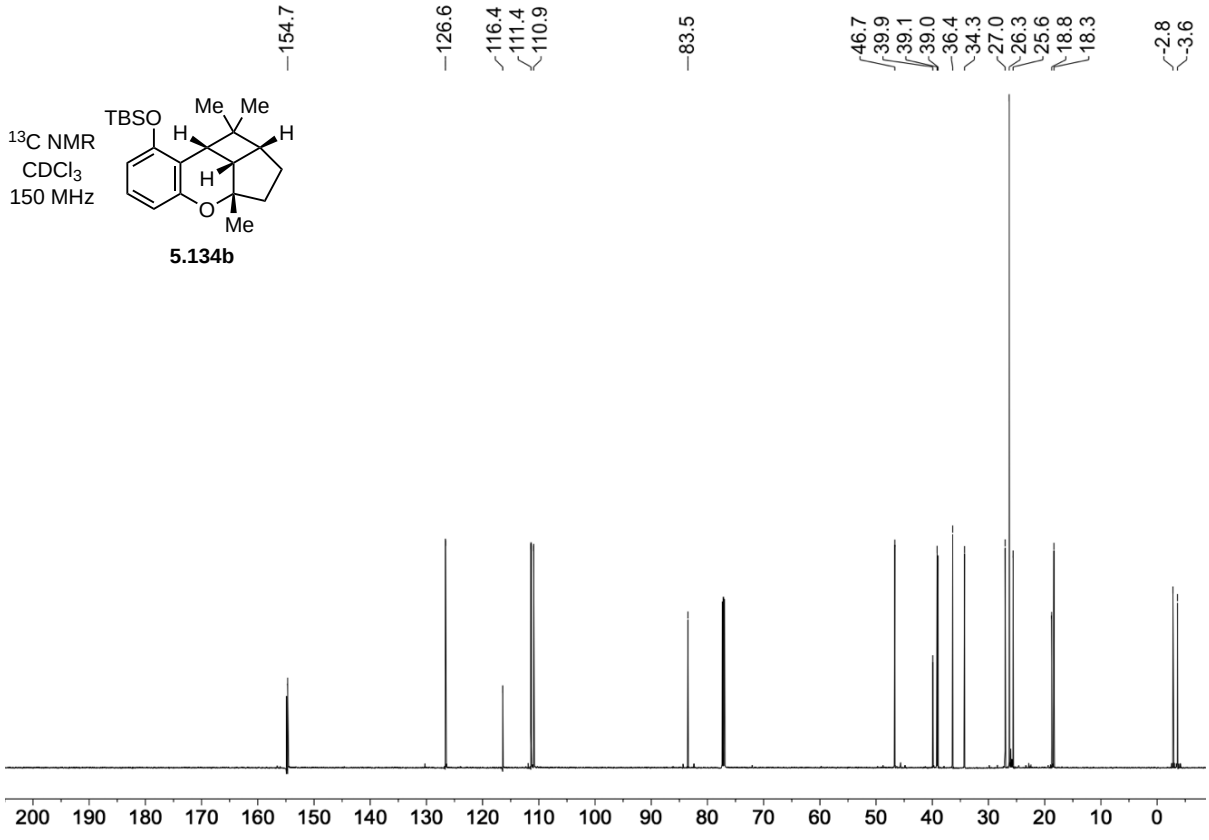


Data for 5.134a



Data for 5.134b

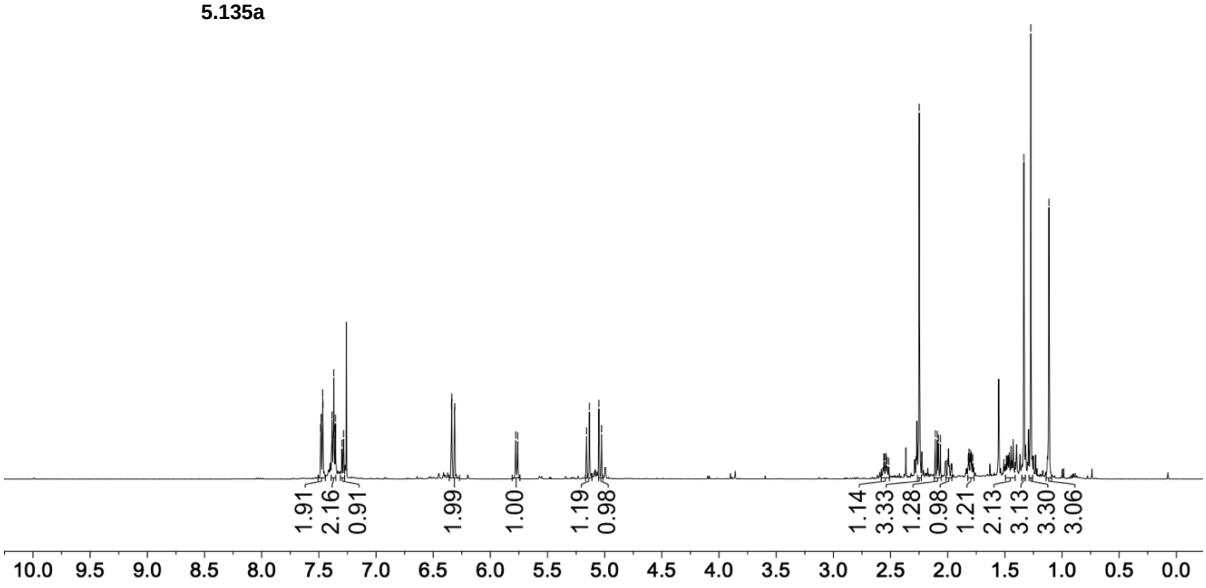


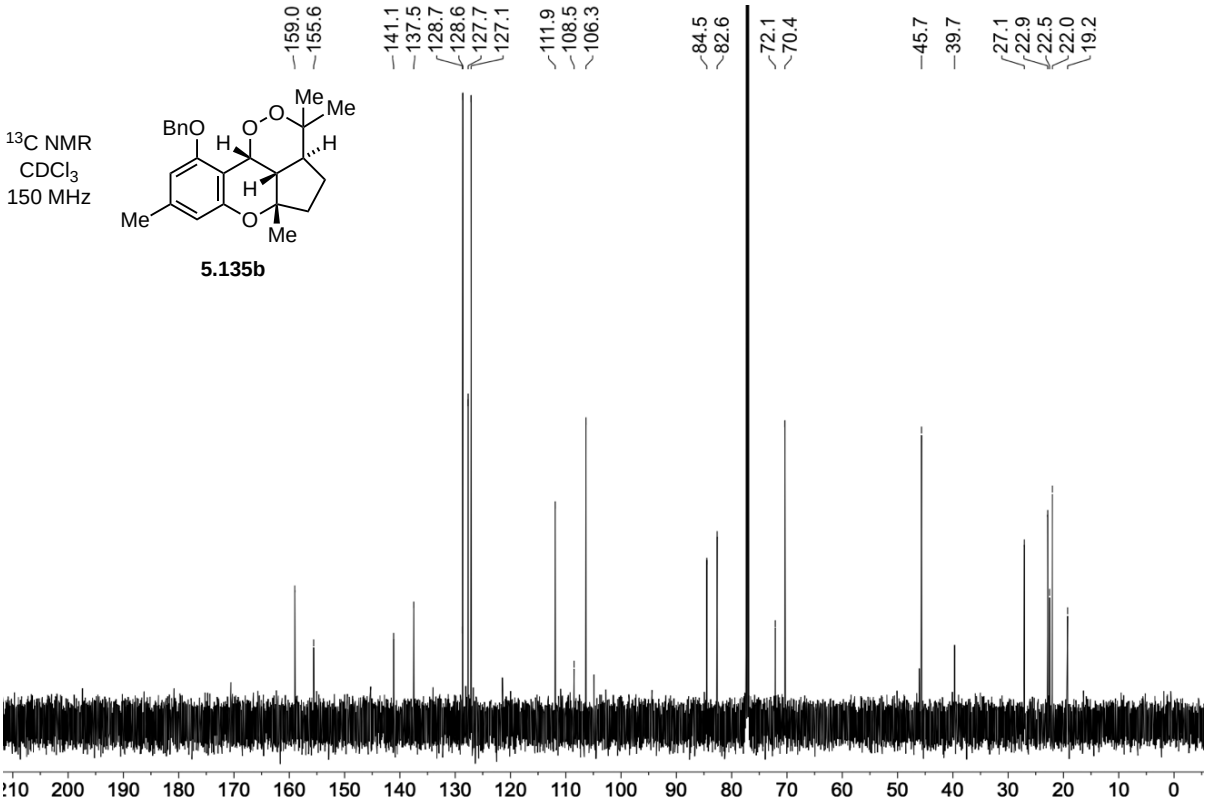


Data for 5.135a

^{1}H NMR
$CDCl_3$
600 MHz

5.135a

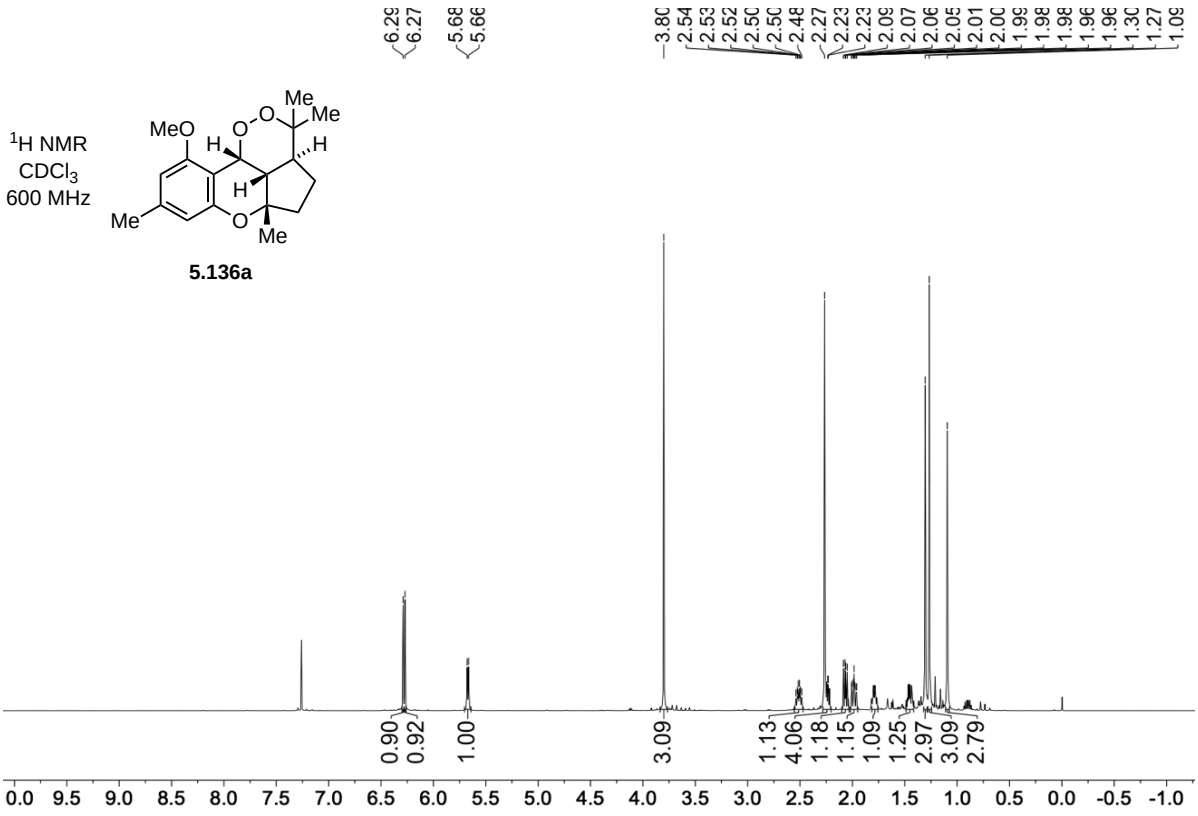


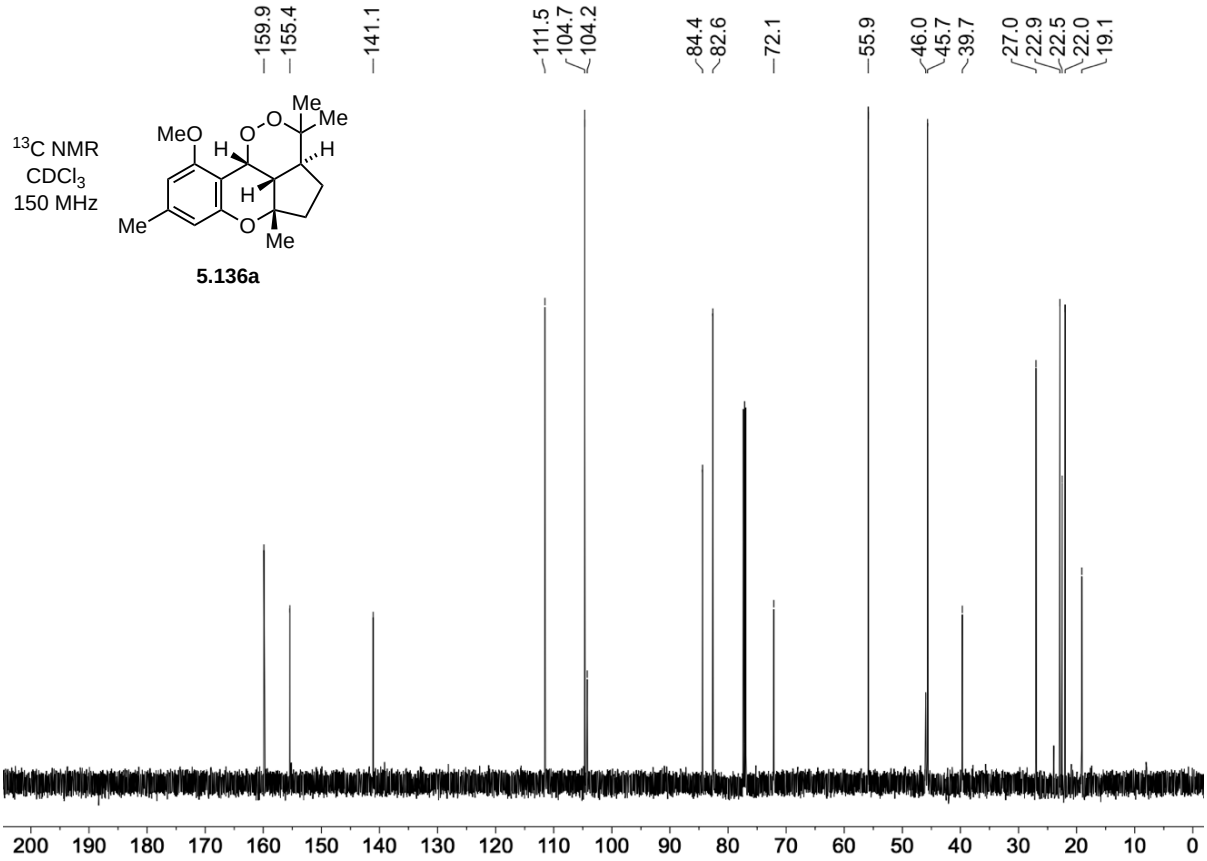


^{13}C NMR
$CDCl_3$
150 MHz

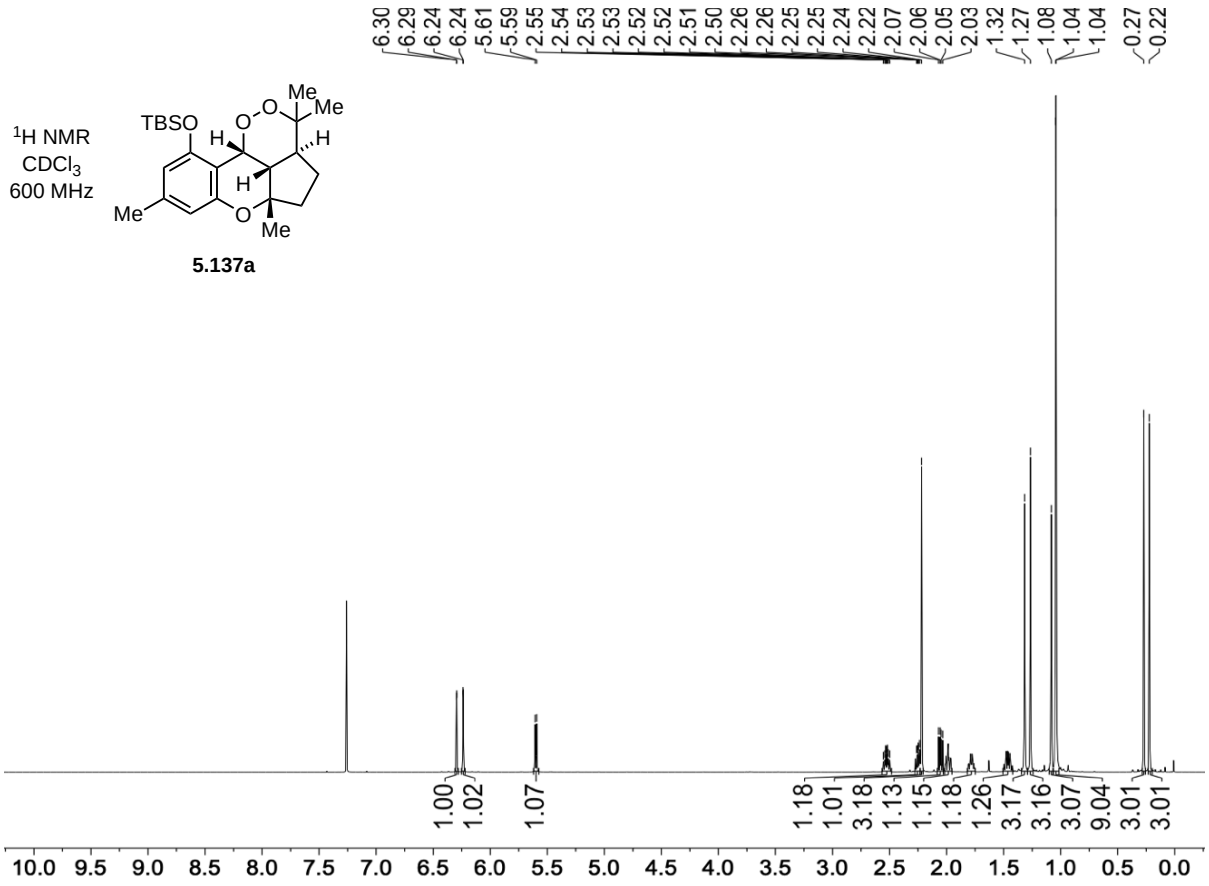
5.135b

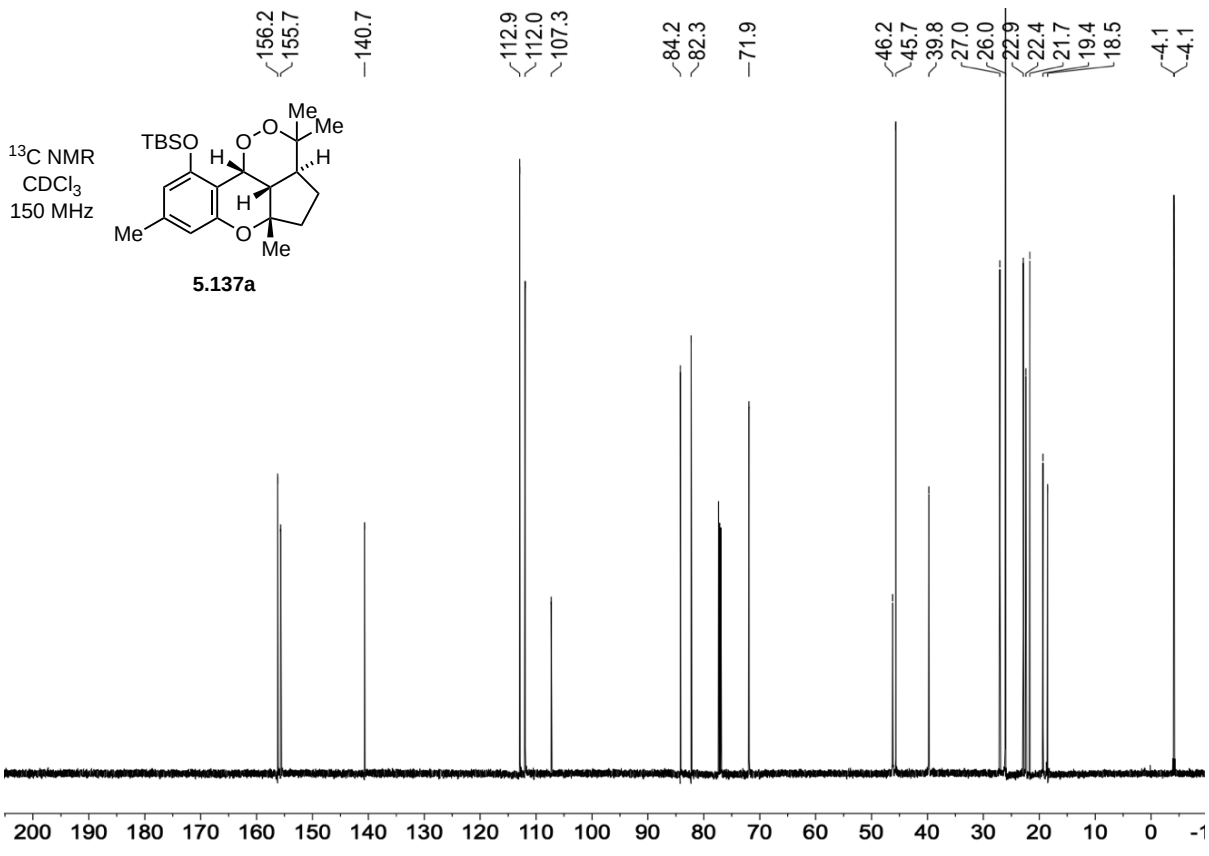
Data for 5.136a



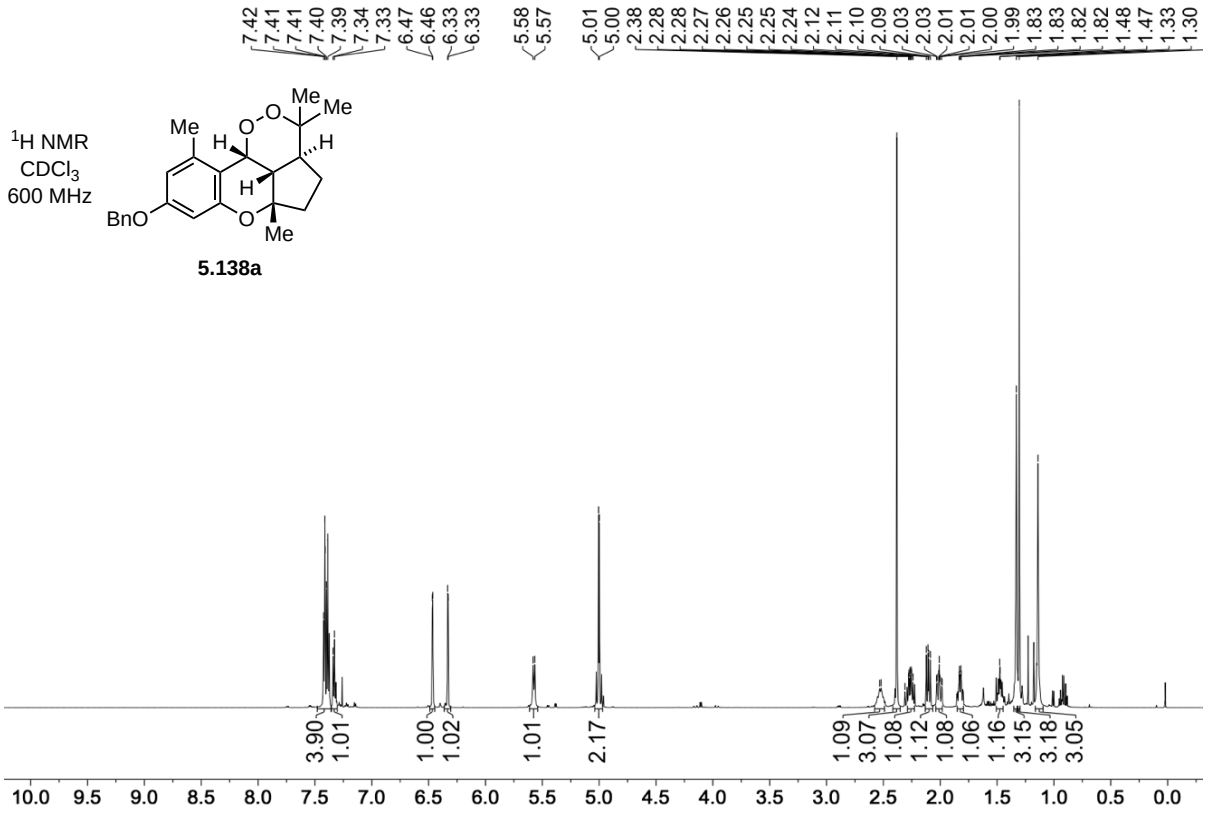


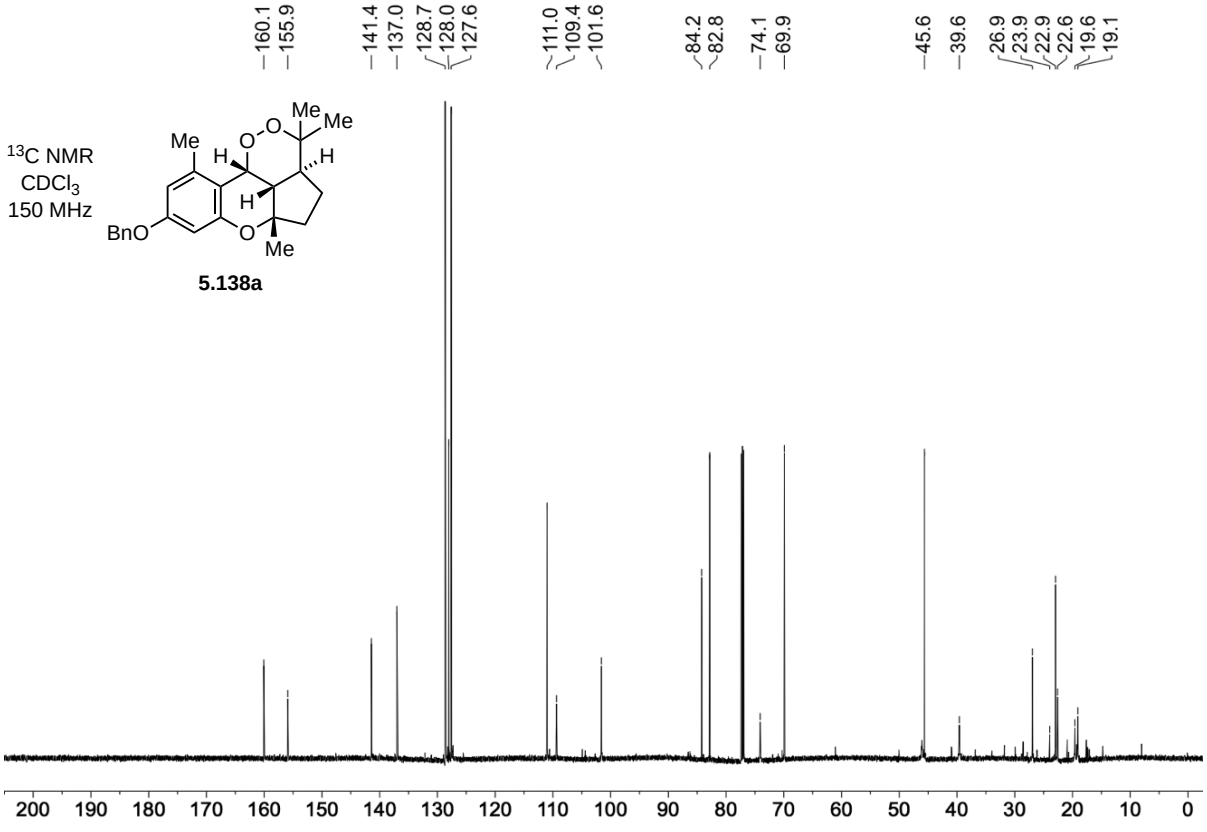
Data for 5.137a





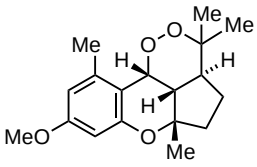
Data for 5.138a





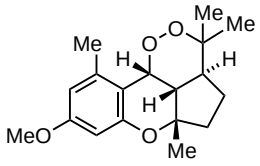
Data for 5.139a

^{1}H NMR
$CDCl_3$
600 MHz



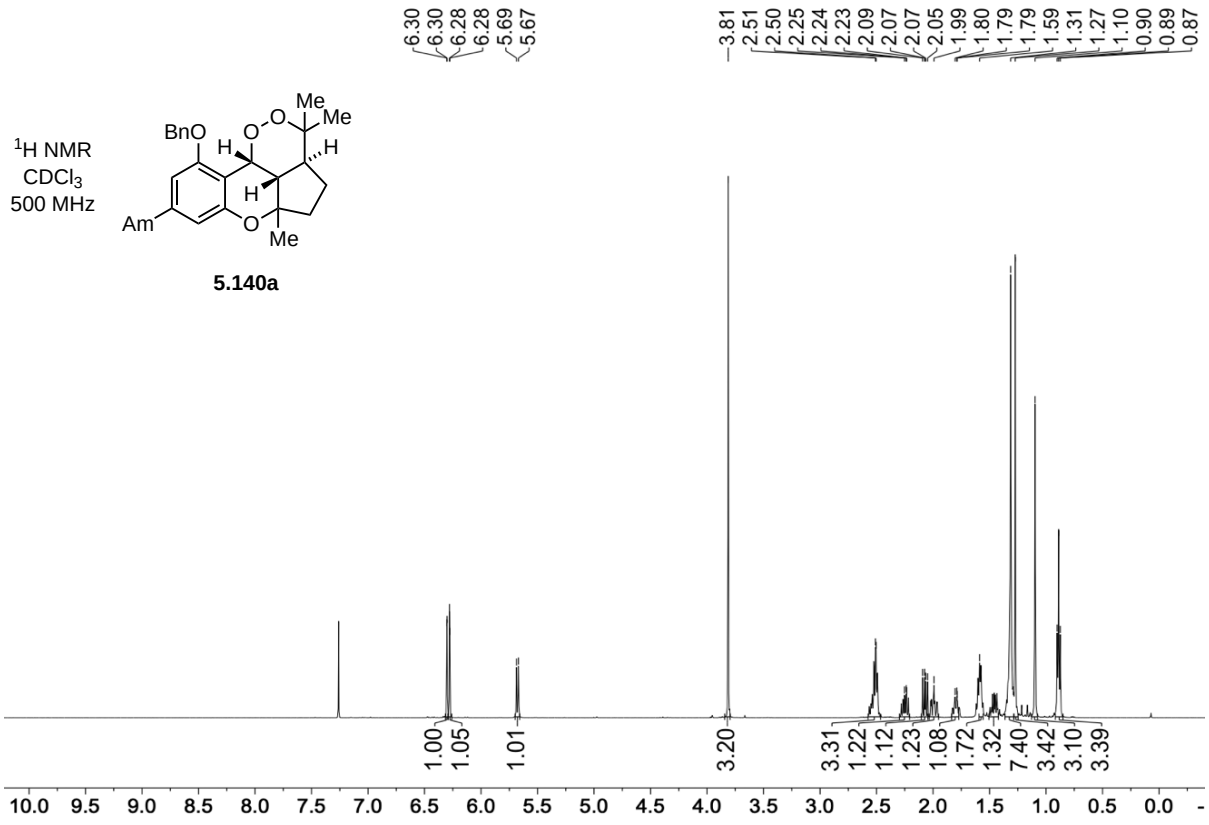
5.139a

^{13}C NMR
$CDCl_3$
150 MHz

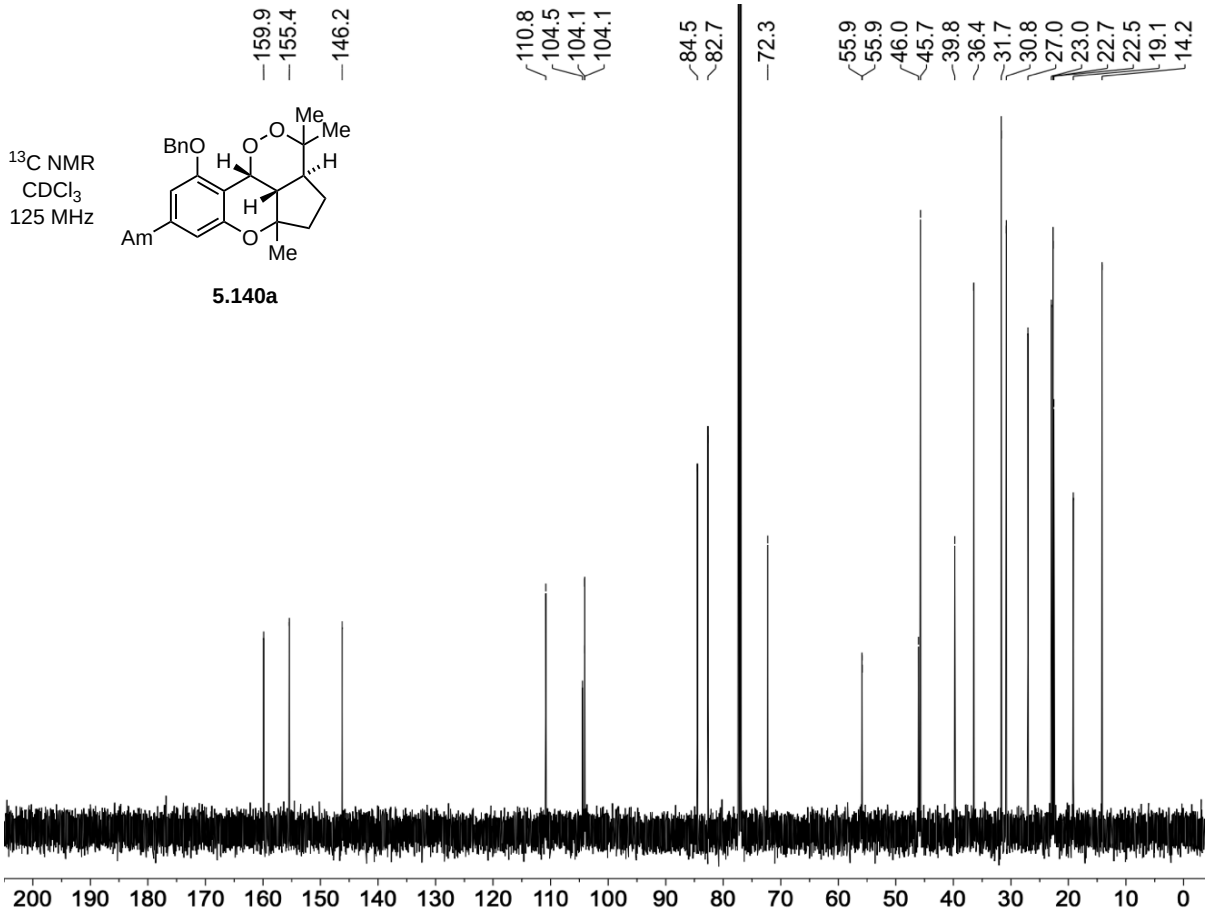


5.139a

Data for 5.140a

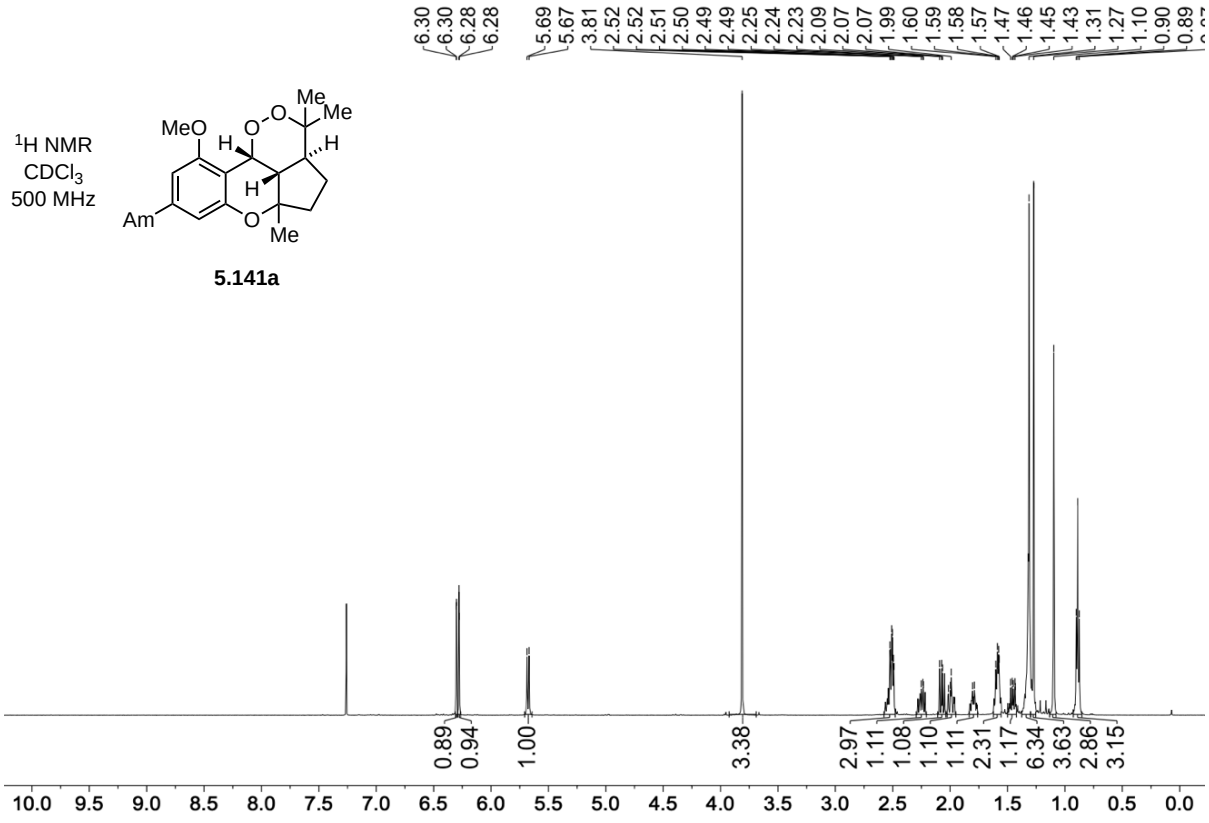


5.140a



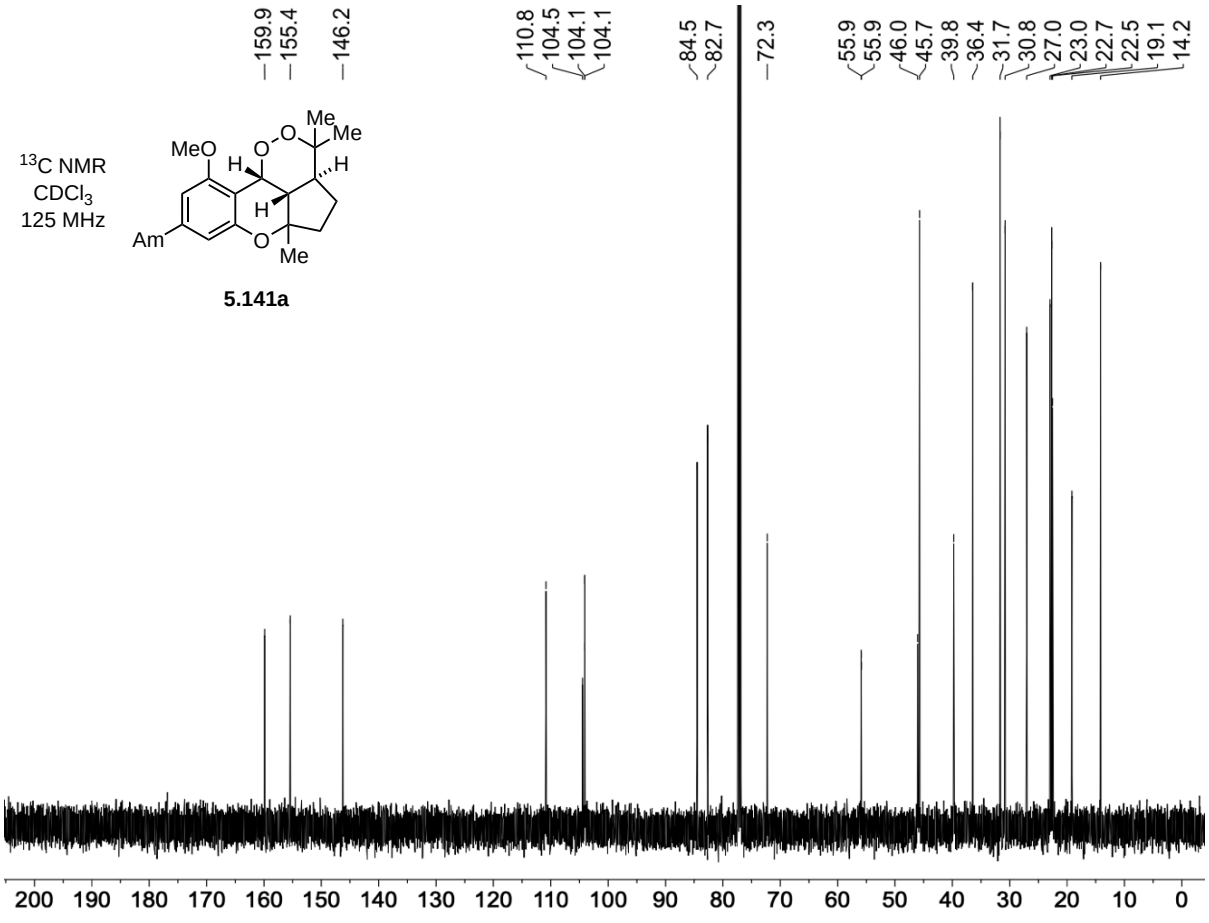
5.140a

Data for 5.141a



^{1}H NMR
$CDCl_3$
500 MHz

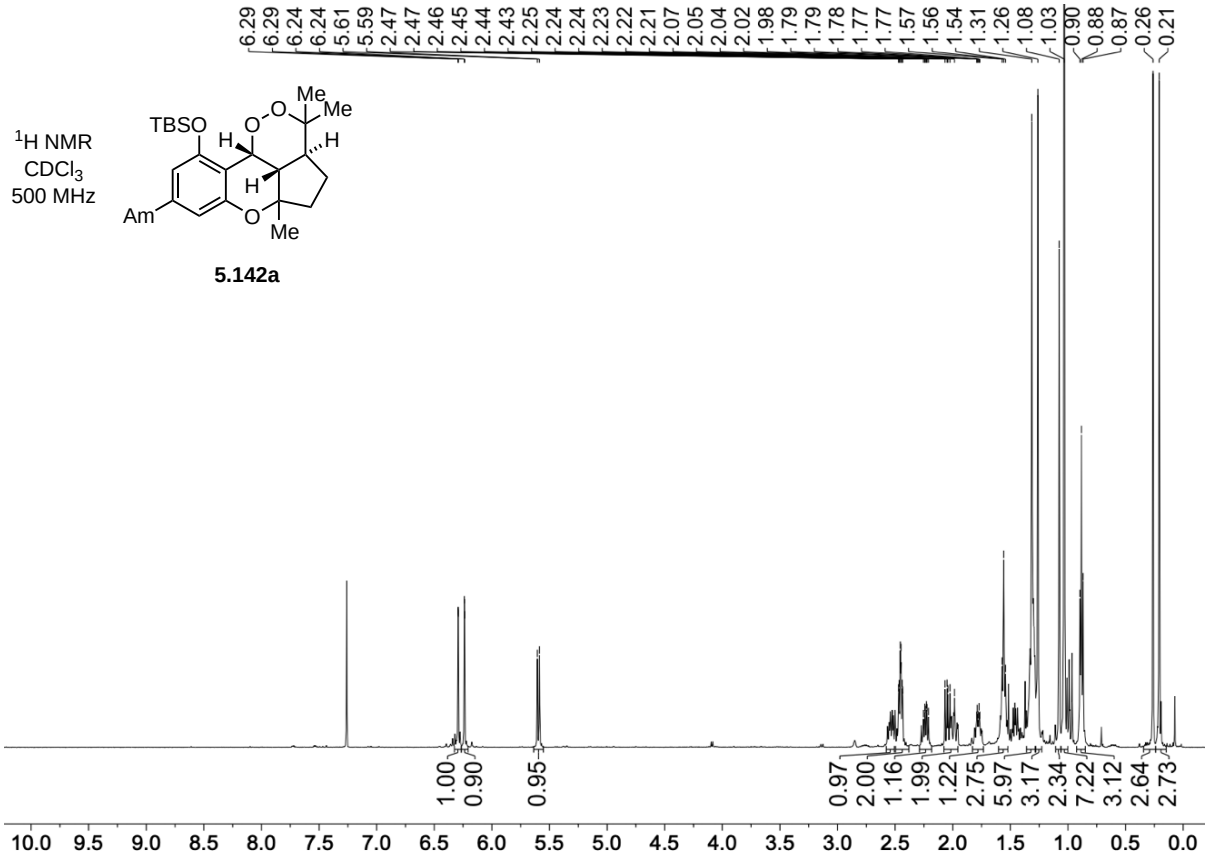
5.141a



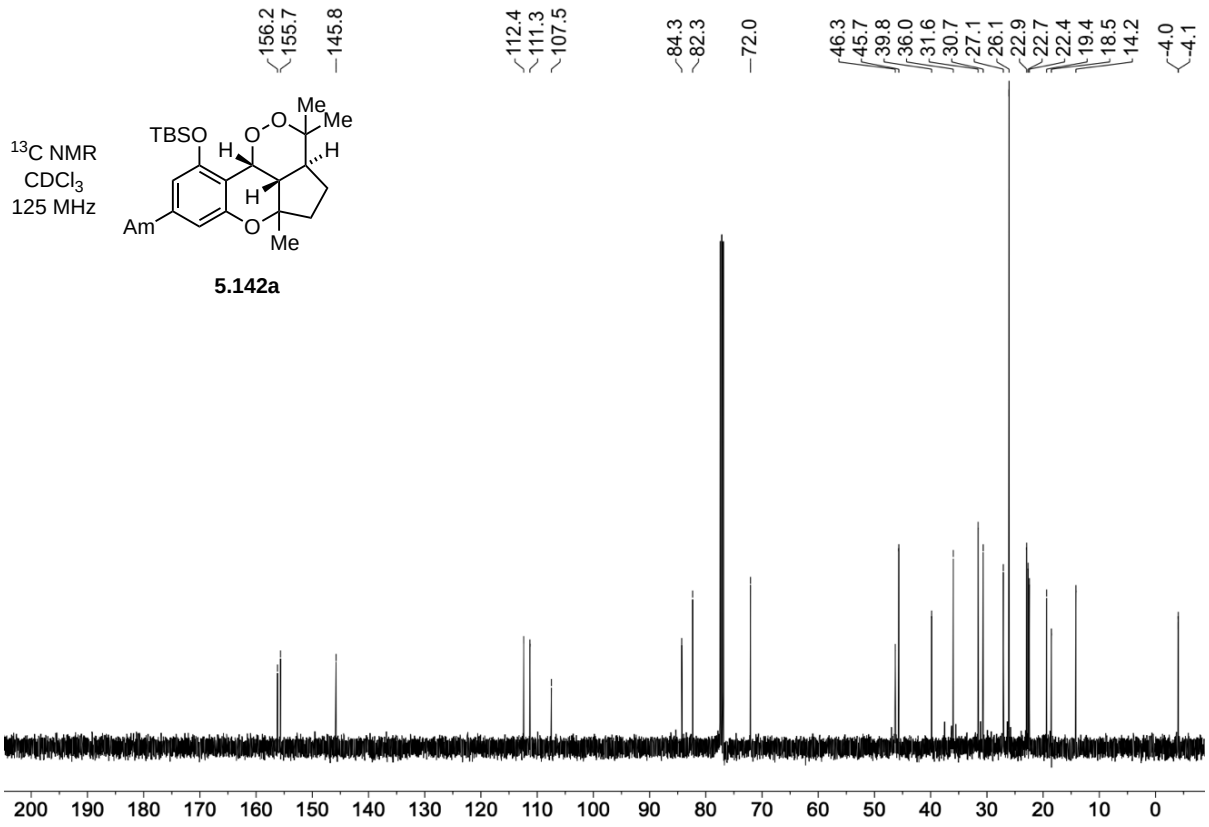
^{13}C NMR
$CDCl_3$
125 MHz

5.141a

Data for 5.142a

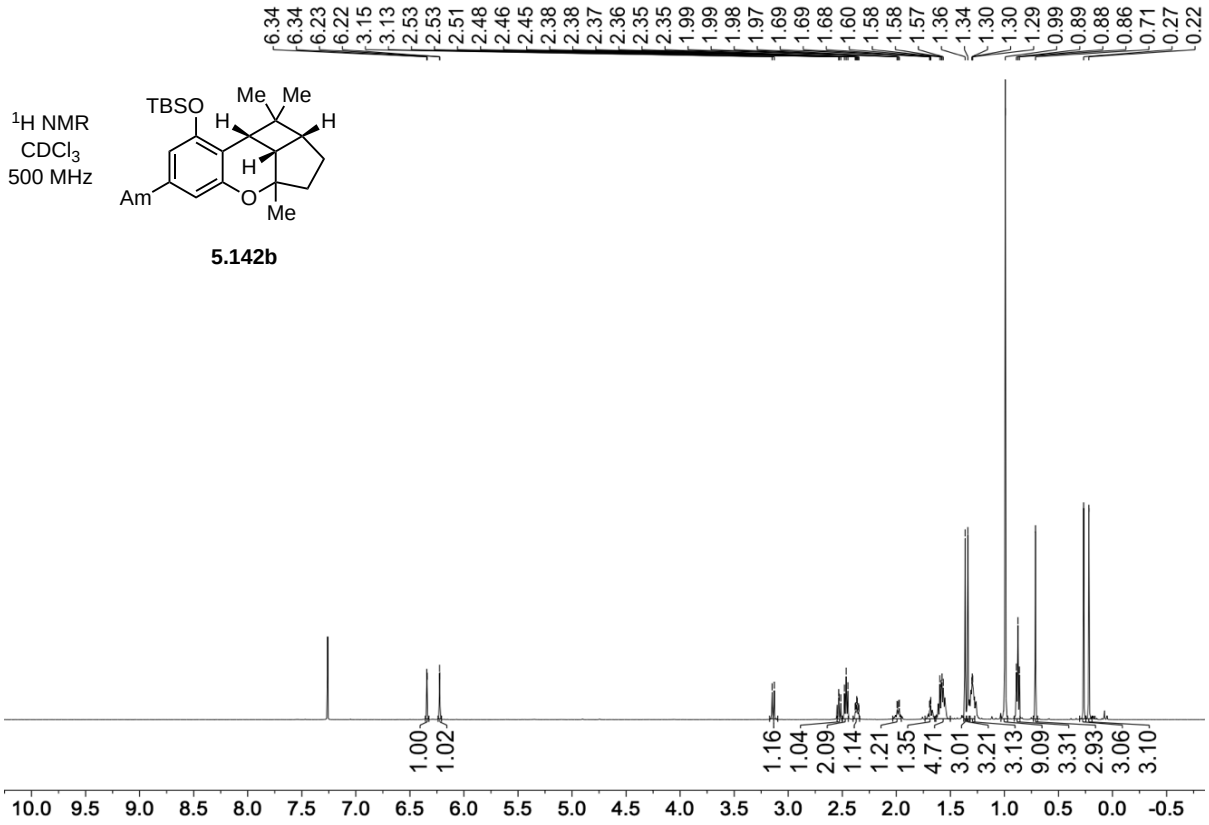


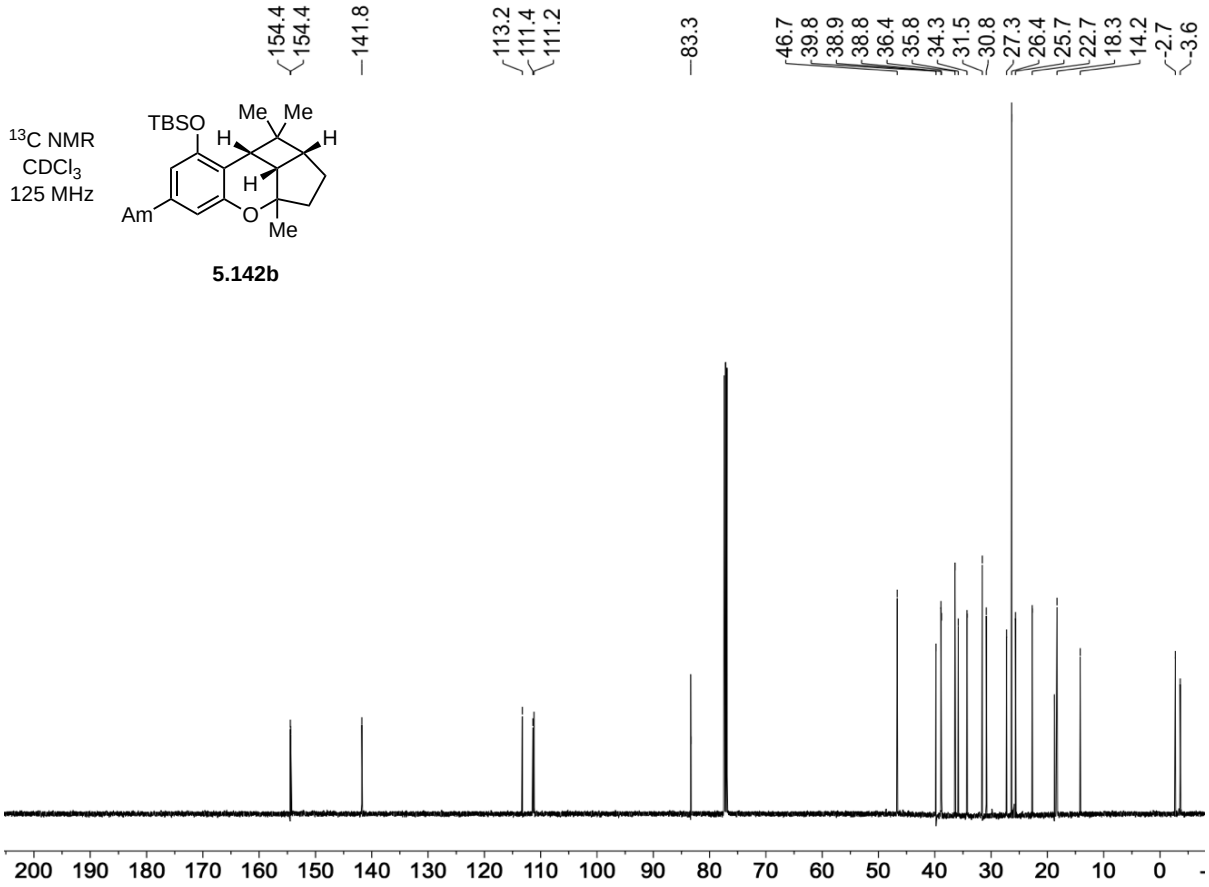
5.142a



5.142a

Data for 5.142b



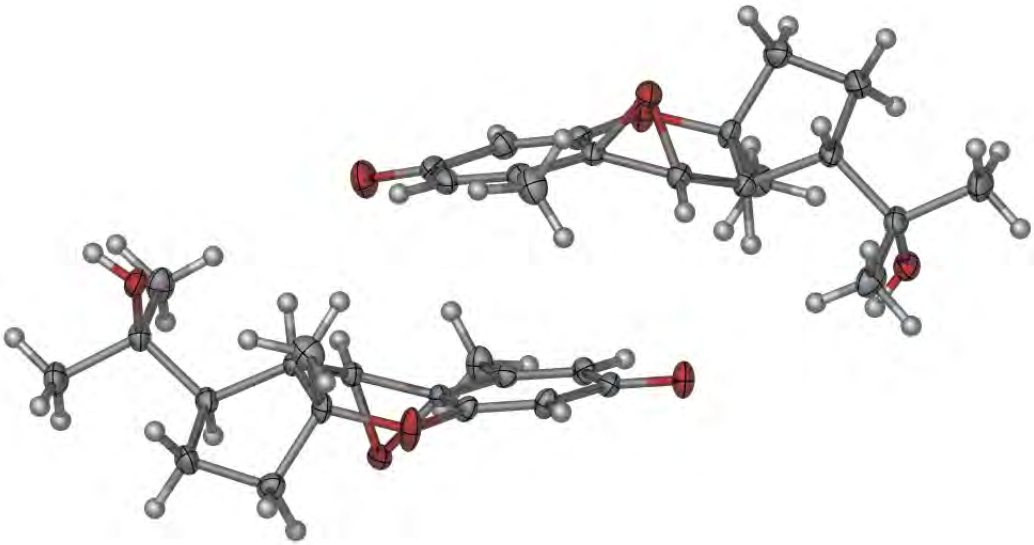


5.4.6 Single Crystal X-Ray Data

A crystal of nyingchinoid B (**5.6**) was mounted under paratone-N oil on a nylon loop, and X-ray diffraction data were collected at 150(2) K with Mo Kα radiation (λ = 0.7107 Å) on an Oxford Diffraction X-calibur small molecule diffractometer.[49] The data set was corrected for absorption and the structure solved by direct methods using SHELXS-2014 and refined by full matrix least-squares on F^2 by SHELXL-2014, interfaced through the program X-Seed.[50] In general, all non-hydrogen atoms were refined anisotropically, and hydrogen atoms were included as invariants at geometrically estimated positions. Details of data collection and structure refinement are given below. CCDC number 1882907 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal data for nyingchinoid B (5.6). $C_{17}H_{22}O_4$, F.w. 290.34, monoclinic, $P2_1/n$, a 11.7425(5), b 14.6257(5), c 17.7664(6) Å, β 95.029(3)°, V 3039.5(2) Å^3, Z = 8, D_{calc} = 1.269 Mg/m^3, μ 0.089 mm^{-1}, F(000) 1248, crystal size 0.30 × 0.30 × 0.30 mm^3, θ range for data collection 3.43 to 28.22°, Ind. reflns 6484, Obs. reflns 4598, R_{int} 0.0424, GoF 1.024, R_1 [I>2σ(I)] 0.0468, wR_2 (all data) 0.1117, largest diff. peak and hole 0.261 and -0.210 e.Å^{-3}. In the structure of nyingchinoid B two molecules are present in the asymmetric unit. These two molecules are enantiomers but are not related by symmetry due to the differing hydrogen bonding interactions of the hydroxyl group in each molecule (**C12** and **C32** respectively).

A.



B.

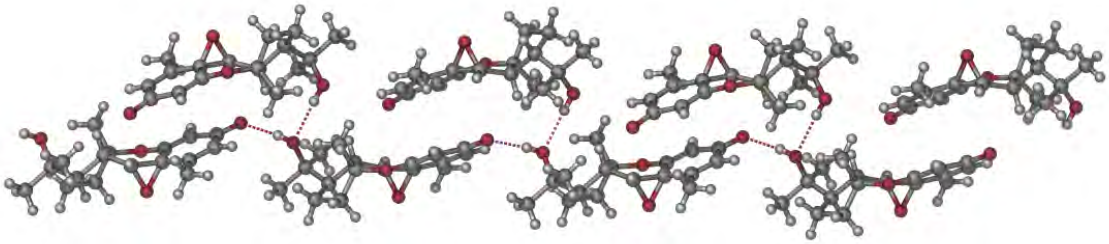


Figure 5.12 — A. A representation of the structure of nyingchinoid B with ellipsoids presented with 50% probability level. Carbon - grey; hydrogen - white; and oxygen - red. B. A view of the hydrogen bonded chains shown the crystallographically distinct environments for the two molecules in the asymmetric unit.

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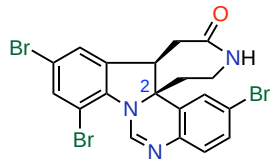
Chapter Six – Efforts Towards the Total Synthesis of Hinckdentine A

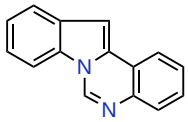
6.1 Introduction

6.1.1 Hinckdentine A Isolation

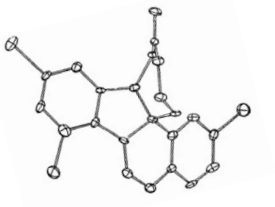
(+)-Hinckdentine A (**6.1**) is a tribrominated indole alkaloid, first isolated in 1987 by Blackman and co-workers (**Figure 6.1**).[1] It was collected from shallow waters off the eastern coast of Tasmania and extracted from the marine bryozoan *Hincksinoflustra denticulate*. (+)-Hinckdentine A (**6.1**) features a unique brominated indolo[1,2-*c*]quinazoline (**6.2**) core fused to a 7-membered lactam. It also possesses a synthetically challenging C2 quaternary centre, and its absolute stereochemistry has been unambiguously determined by single crystal X-ray diffraction. Due to its low abundance in nature (isolation yield of 0.0005% wt./ wt.) the biological activity of **6.1** has not been reported, however certain derivatives containing the quinazoline core (**6.2**) have been shown to exhibit potent cataleptogenic, antibacterial and antifungal activities.[2]



6.1: (+)-hinckdentine A



6.2: indolo[1,2-*c*]quinazoline]

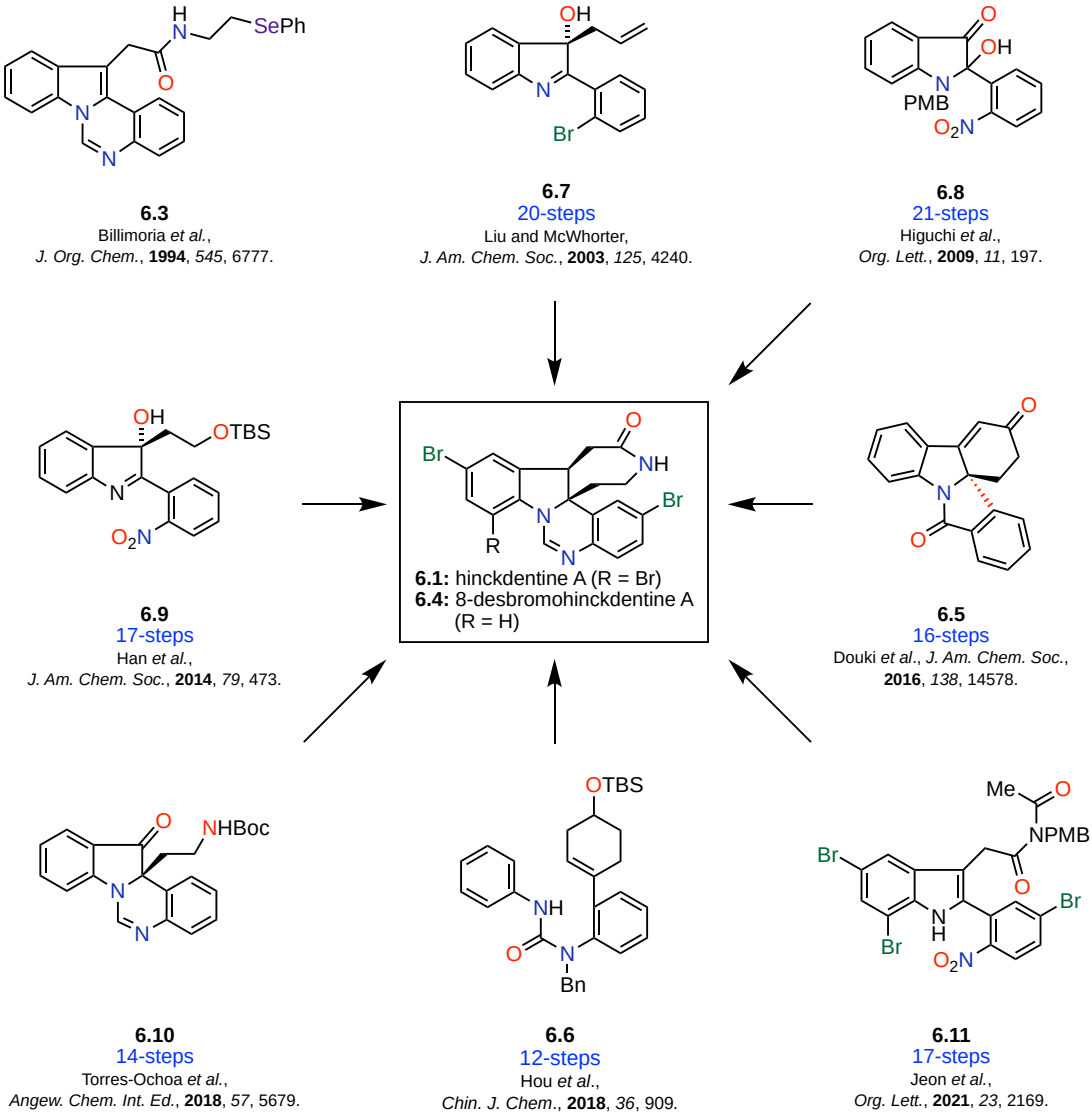


6.1: (+)-hinckdentine A
X-ray stucture

Figure 6.1 – (+)-Hinckdentine A

(+)-Hinckdentine A (**6.1**) presents itself as an intriguing target for synthetic chemists and although biosynthetic proposals have been put forward (see work by Ruan and co-workers),[3] the exact biosynthetic pathway remains elusive. Despite this, the synthesis of **6.1** has been extensively reported in the literature (**Scheme 6.1**).[4] In 1994, Billimoria and co-workers reported the first total synthesis of (±)-hinckdentine A (**6.1**) through a selenium initiated radical cyclization of **6.3** to form the lactam motif of **6.1** (**Scheme 6.1**).[5] Unfortunately these attempts were unsuccessful, and it wasn't until 2003 that the synthesis of the racemic 8-desbromohinckdentine A analogue (**6.4**) was achieved by Liu and McWhoter.[6] Six years later Higuchi *et al.* disclosed the first reported synthesis of (±)-hinckdentine A (**6.1**) in 21-steps,[7] while a formal 17-step total synthesis of the unnatural enantiomer (−)-hinckdentine A (**6.1**) was reported by Han and co-workers in 2014.[8] In 2016, the first asymmetric synthesis of the natural (+)-hinckdentine A (**6.1**) was reported by the Fukuyama group.[9] This featured an asymmetric dearomatization cyclization of a functionalized *N*-acyl tetrahydrocarbazole to give the enone **6.5**. In 2018, Torres-Ochoa *et al.* reported a 14-step total synthesis of (+)-hinckdentine A (**6.1**)[10] and later that year the Xu group went on to publish a 12-step synthesis featuring a unique electrochemical dehydrogenative [3+2]-annulation of **6.6**.[11] Finally, the most recent reported total synthesis of **6.1** was

described in 2021 by Jeon *et al.* featuring an imino-Stetter reaction.[12] Herein, this introduction will attempt to summarize all 7 successful total syntheses of hinckdentine A (**6.1**).

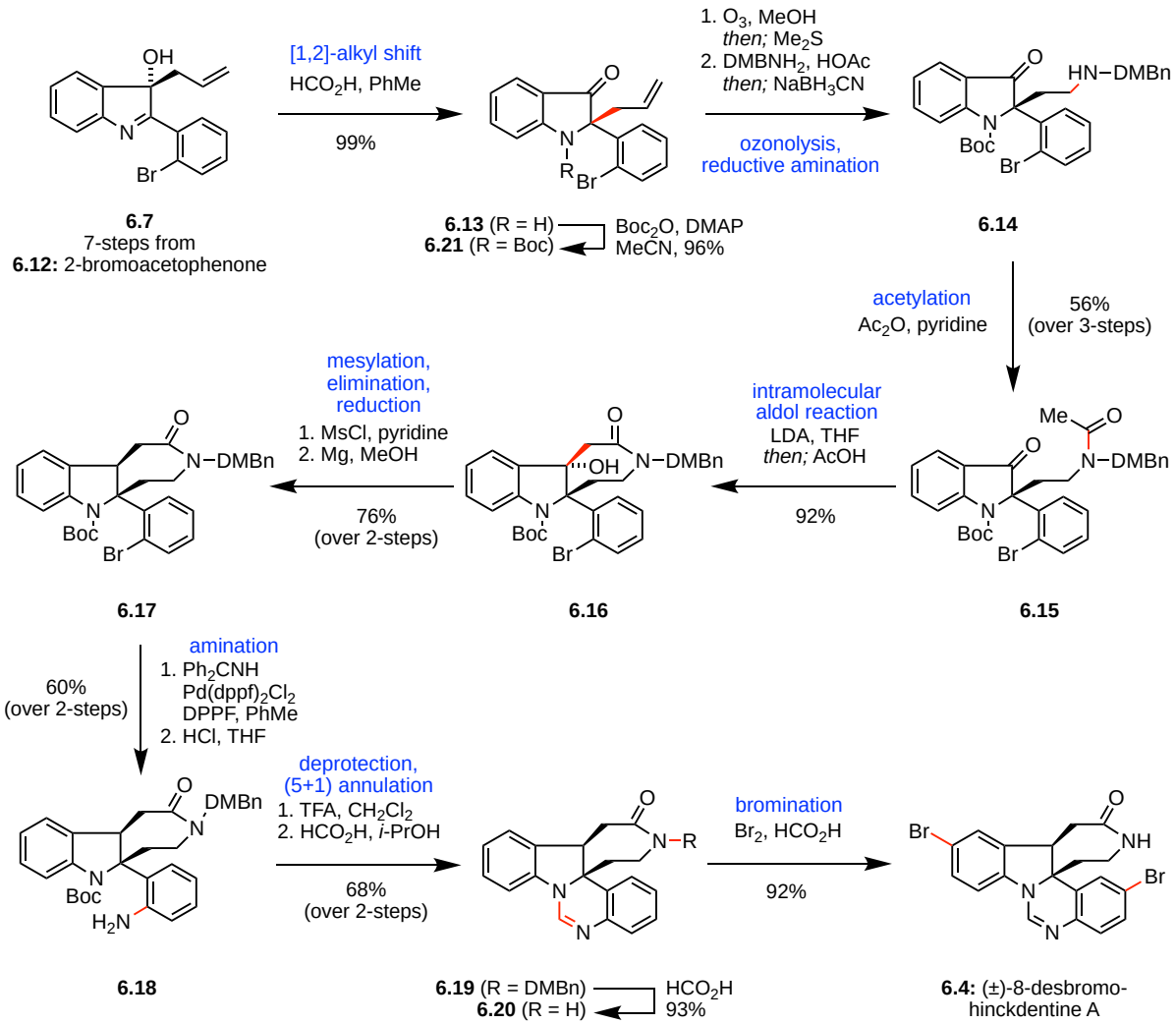


Scheme 6.1 – Previous Syntheses of Hinckdentine A and 8-desbromohinckdentine A[5-12]

6.1.2 Total Synthesis of 8-Desbromohinckdentine A by Liu and McWhorter

In 2003, Liu and McWhorter published a synthetic approach to (±)-hinckdentine A (**6.1**) which hinged on a late stage tribromination of the quinazoline (**6.2**) core (**Scheme 6.2**).[6] This synthesis began following a 7-step synthesis of **6.7** from 2-bromoacetophenone (**6.12**), which underwent a [1,2]-alkyl shift under acidic conditions to afford 3-oxindole **6.13** in quantitative yield. Boc protection, ozonolysis and reductive amination with 2,4-dimethoxybenzylamine then afforded **6.14**. Subsequent acetylation afforded **6.15** in 56% over 3-steps, followed by an intramolecular aldol reaction to give the azepinoindolone **6.16** in 92%. Next mesylation, elimination and reduction afforded **6.17** in 76% over 2-steps. This was followed by amination to give **6.18**, which underwent Boc deprotection and annulation with formic acid to afford **6.19**. An independent formic acid mediated deprotection then

gave **6.20**. Finally, treatment with bromine afforded (±)-desbromohinckdentine A (**6.4**) in 92%. Unfortunately, all attempts to synthesize the tribrominated (±)-hinckdentine A (**6.1**) only gave inseparable mixtures of bromine regioisomers. Overall, the synthesis of **6.4** was achieved in 20-steps.

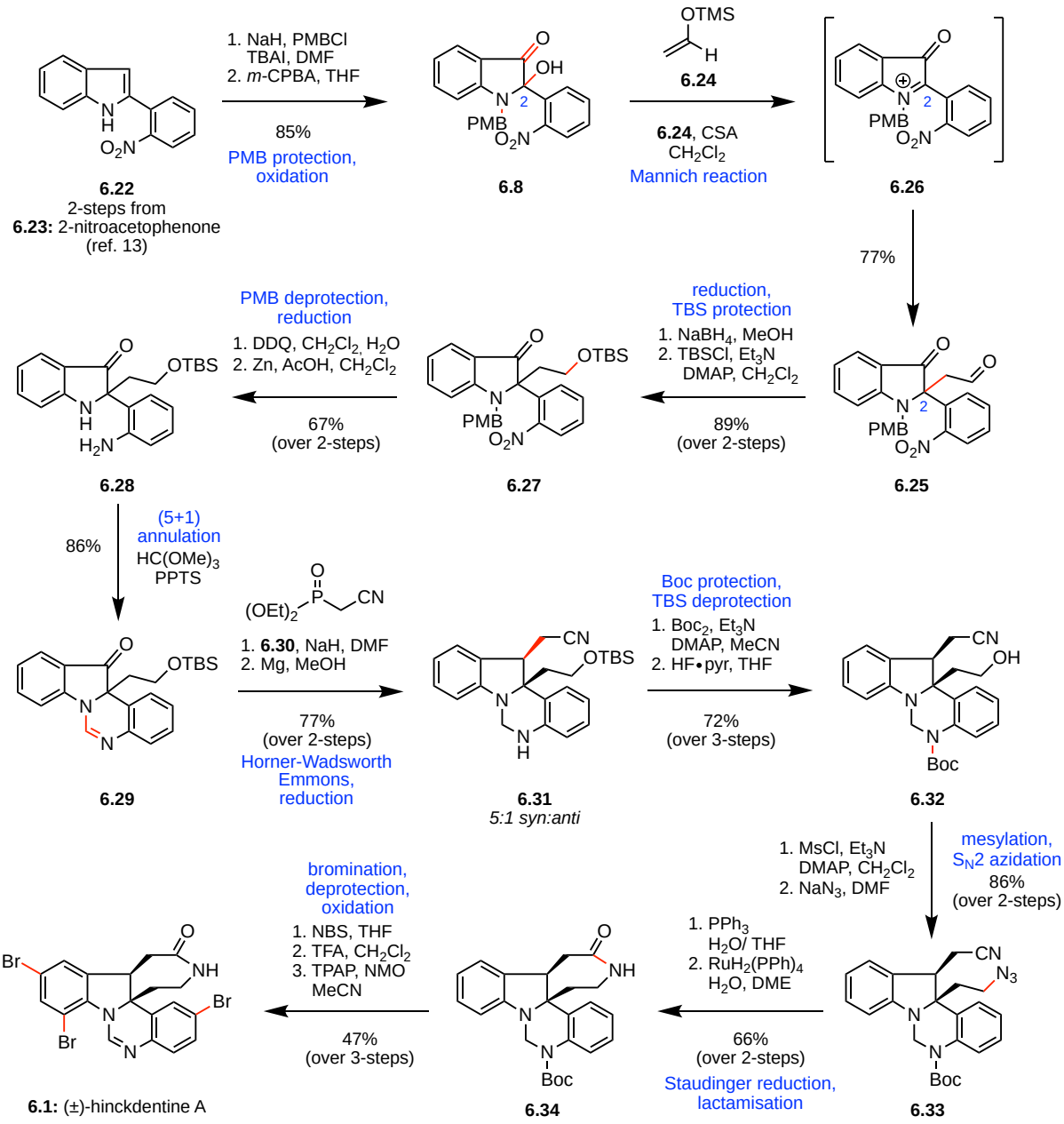


Scheme 6.2 – Liu and McWhorter's Synthesis of 8-Desbromohinckdentine A[6]

6.1.3 Total Synthesis of (±)-Hinckdentine A by Higuchi and Co-workers

In 2009, the first total synthesis of (±)-hinckdentine A (**6.1**) was reported by Higuchi and co-workers.[7] This began with a 2-step synthesis of **6.22** from 2-nitroacetephenone (**6.23**) following a literature procedure from MacPhillamy *et al.*.[13] PMB protection of **6.22** followed by oxidation then afforded **6.8**. Reaction of **6.8** with the silyl enol ether **6.24** in the presence of CSA gave the Mannich addition product **6.25** in 77%. Presumably, this reaction proceeded through the α-ketoiminium ion **6.26** allowing for the formation of the C2 quaternary centre. The aldehyde **6.25** was then reduced and TBS protected to give **6.27** in 89% over 2-steps. PMB deprotection and reduction of the nitro group afforded **6.28**. Treatment of **6.28** with trimethyl orthoformate gave the quinazoline ring of **6.29** and a Horner-Wadsworth-Emmons reaction with the cyanophosphonate ester **6.30** followed by reduction gave

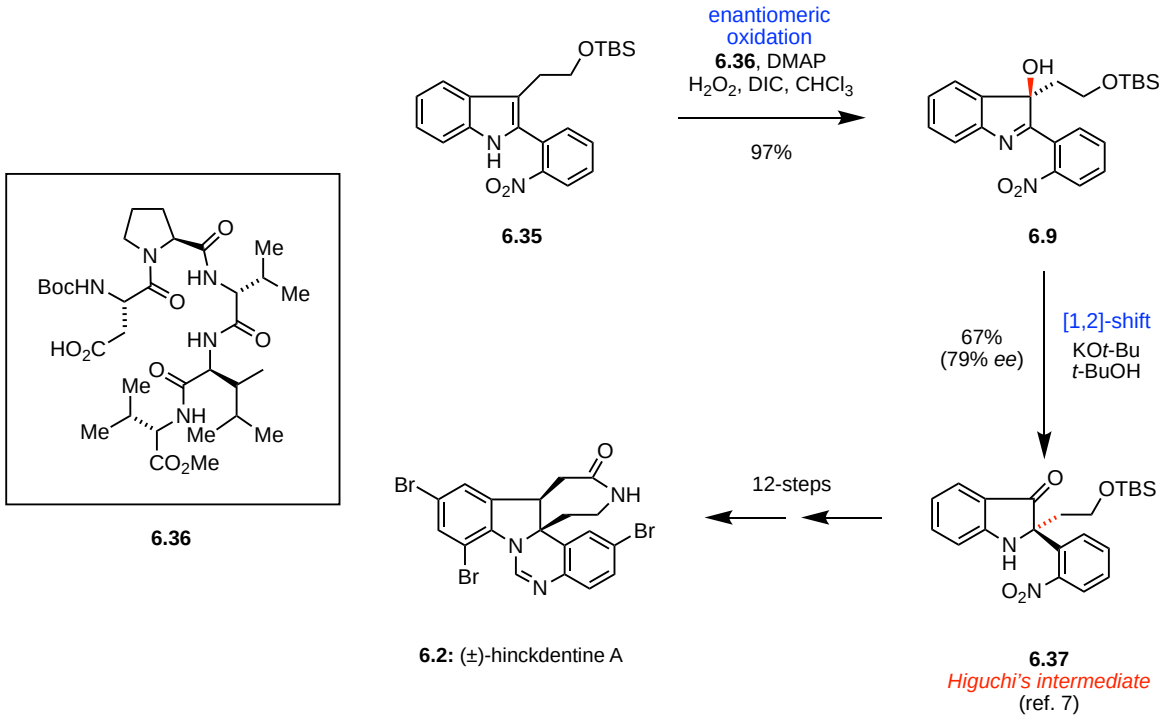
6.31. Boc and TBS deprotection then afforded alcohol **6.32**, which was activated with mesyl chloride and substituted with NaN_3 to afford **6.33**. A Staudinger reduction and a ruthenium mediated lactamisation then gave **6.34** affording the key pentacyclic framework. Interestingly, the authors found that a late-stage bromination with NBS afforded the desired tribrominated product. This success was attributed to steric hinderance of the Boc group on the quinazoline ring, presumably precluding over bromination (unlike Liu and McWhorter's observations).[6] Deprotection and subsequent oxidation then gave (±)-hinckdentine A (**6.1**) in 47% over 3-steps. In total, this synthesis was achieved in 21-linear steps, featuring a unique Mannich reaction to form the key C2 quaternary centre and a ruthenium catalyzed lactamisation.



Scheme 6.3 – Total Synthesis of Hinckdentine A by Higuchi *et al.*[7]

6.1.4 Formal Synthesis of (–)-Hinckdentine A by Han *et al.*

Han and co-workers completed an asymmetric formal synthesis of the unnatural enantiomer of (–)-hinckdentine A (**6.1**) in 2014 (**Scheme 6.4**).[8] Although the author's original intention involved the total synthesis of a family of trigonoliimines, the synthetic methodology developed facilitated an enantiomeric oxidation of **6.35** mediated by the aspartyl peptide catalyst **6.36**. This afforded **6.9** in 97% yield and 79% *ee*. A *t*-BuOK facilitated [1,2]-alkyl shift of **6.9** then afforded **6.37**, which serves as an intermediate in Higuchi's total synthesis of (±)-hinckdentine A (**6.1**).[7] This approach shortened the previous total synthesis of **6.1** from 20-steps (Liu and McWhorter) and 21-steps (Higuchi *et al.*) down to 17-steps.[6,7]

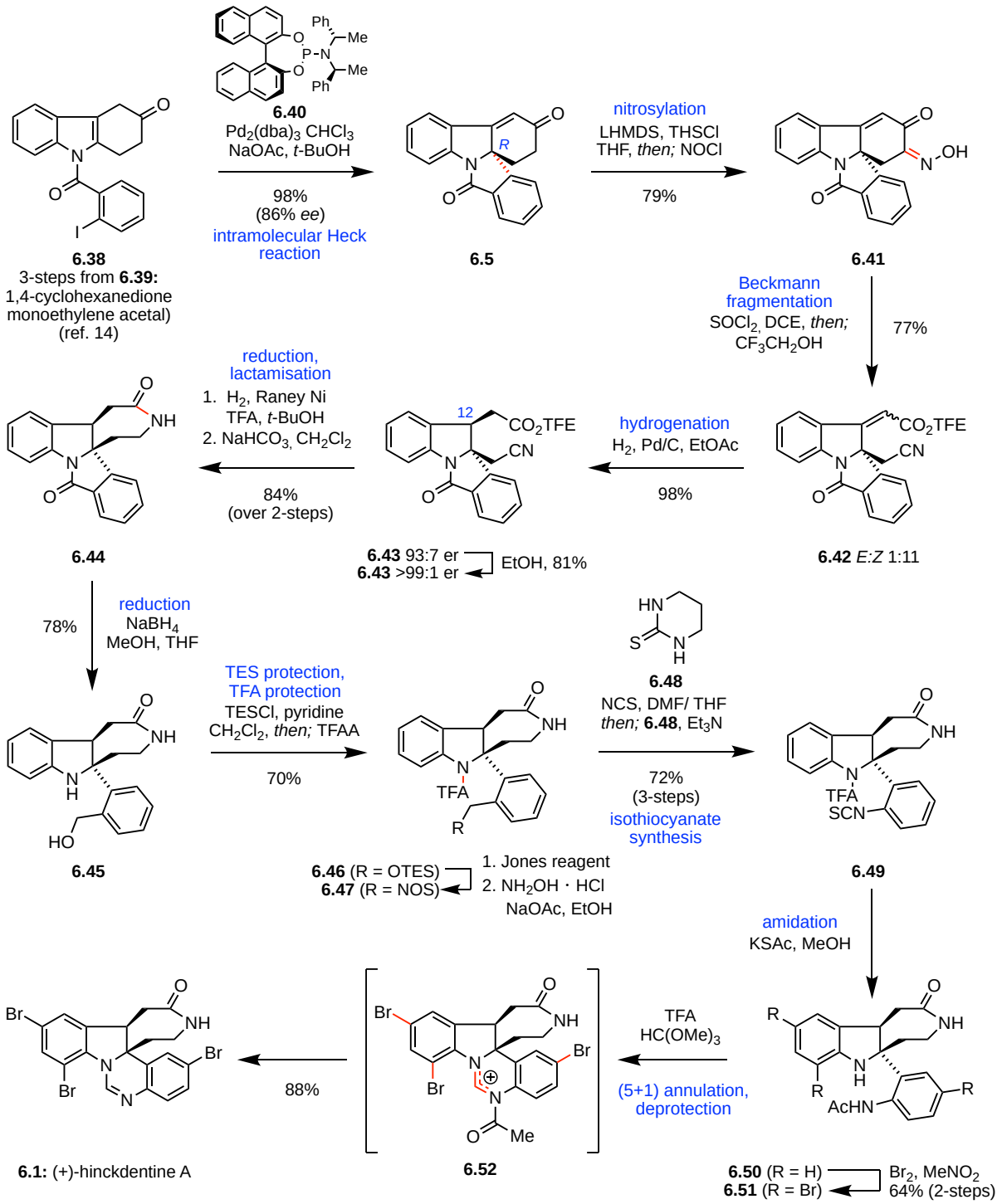


Scheme 6.4 – Formal Synthesis of (–)-Hinckdentine A by Han *et al.*[8]

6.1.5 Total Synthesis of (+)-Hinckdentine A by Douki and Co-workers

Two years later in 2016, the Fukuyama group reported the first asymmetric total synthesis of natural (+)-hinckdentine A (**6.1**) (**Scheme 6.5**).[9] This was achieved using a 3-step literature synthesis of the *N*-benzoyl tetrahydrocarbozole (**6.38**) from **6.39**, following work by Liu and co-workers.[14] A palladium catalyzed intramolecular Heck dearomatization cyclization then afforded **6.5** in 98% (and 86% *ee*) employing the phosphoramidite ligand **6.40** developed by Teichert and co-workers.[15] The chiral intermediate **6.5** then underwent reaction with nitrosyl chloride to afford the ketoxime **6.41** in 79%. All attempts to effect a direct Beckmann rearrangement failed, instead a Beckmann fragmentation through reaction of **6.41** with $SOCl_2$ then trifluoroethanol (TFE) gave **6.42** in 77% and as a 1:11 mixture

of *E:Z* isomers. Hydrogenation with catalytic Pd/C then afforded **6.43** in 98%. It was found that rinsing the crystals of **6.43** in EtOH at 0 °C gave the enantiomerically pure **6.43**. A second hydrogenation, this time with Raney Ni, followed by treatment with $NaHCO_3$ afforded the desired lactam **6.44** in 84% over 2-steps. Reduction and amide cleavage then gave **6.45**, which was subsequently TES and TFA protected. Oxidation with Jones reagent and conversion to the aldoxime **6.47** was achieved, followed by a modified procedure from Kim *et al.* involving direct conversion of **6.47** into the isothiocyanate **6.49** after reaction with the pyrimidinethione **6.48**.[16] Potassium thioacetate then afforded the anilide **6.50** which was primed for bromination to give **6.51** in 64% over 2-steps. Finally, treatment of **6.51** with trimethyl orthoformate under acidic conditions afforded (+)-hinckdentine A (**6.1**), presumably through the amidinium intermediate **6.52**. This synthesis by Douki and co-workers features a palladium catalyzed intramolecular Heck dearomatization cyclization using a phosphoramidite ligand as the key step, alongside a $NaHCO_3$ mediated lactamisation and a late stage tribromination. Overall, this impressive synthesis of **6.1** is achieved in 16-steps and is the first reported asymmetric total synthesis of the natural (+)-hinckdentine A (**6.1**).

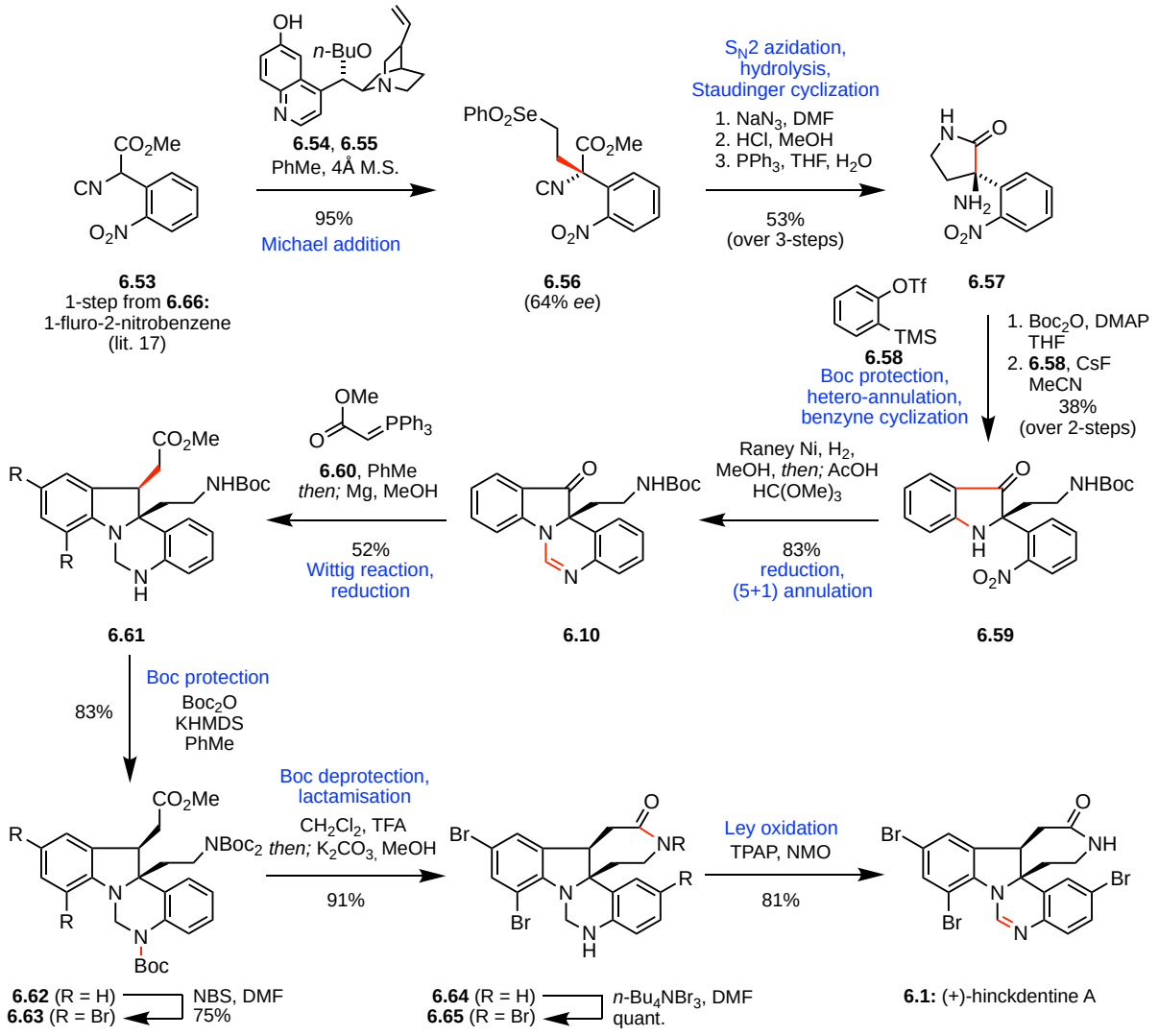


Scheme 6.5 – Total Synthesis of (+)-Hinckdentine A by Douki *et al.* [9]

6.1.6 Total Synthesis of (+)-Hinckdentine A by Torres-Ochoa *et al.*

In 2018, the Zhu group reported a 14-step asymmetric total synthesis of (+)-hinckdentine A (**6.1**) achieved through a catalytic asymmetric Michael addition (**Scheme 6.6**).[10] This involved treatment of the isocyanoacetate **6.55** with vinyl selenone (**6.54**) and the quinidine derived catalyst **6.53** to afford **6.56** in an excellent yield of 95% and a modest *ee* of 64%. Next, a series of reactions involving azide

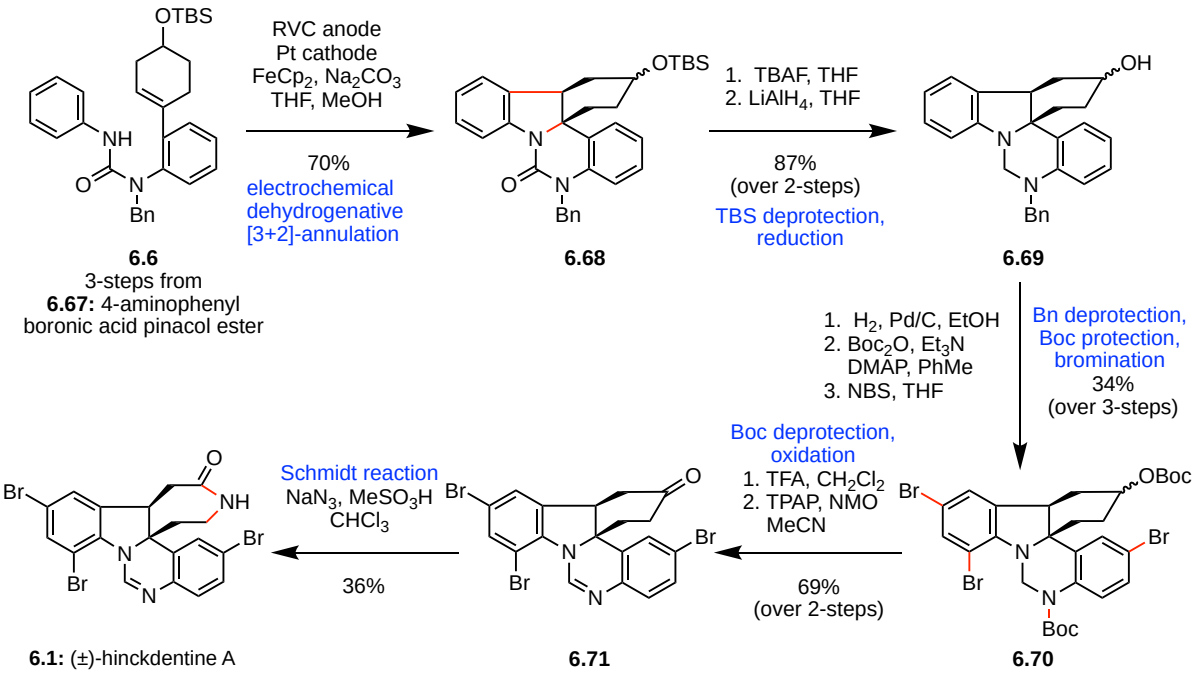
displacement, isocyanide hydrolysis and a Staudinger cyclization gave **6.57** in 53% over 3-steps. Boc protection, subsequent hetro-annulation and an intramolecular cyclization with an *in situ* generated benzyne (from **6.58**) then formed the indole **6.59** in 38%. Reduction of the nitro motif of **6.59** afforded the corresponding aniline, which was subsequently treated with trimethyl orthoformate to give the quinazoline core of **6.10** in 83%. Wittig reaction between **6.59** and methyl (triphenylphosphoranylidene)acetate (**6.60**) followed by a 1,4-reduction gave **6.61** in 52%. Next, Boc protection with Boc_2O and KHMDS afforded **6.62**, which underwent a regioselective debromination through reaction with NBS to afford **6.63** in 75%. Unfortunately, all efforts towards the tribrominated product failed at this step. Instead, removal of the Boc protecting group and concomitant lactamisation gave the desired pentacycle **6.64**. It was found that tetrabutylammonium tribromide was unique at effecting the desired bromination to give **6.65** in quantitative yield. Finally, TPAP oxidation afforded (+)-hinckdentine A (**6.1**) in 81%.



Scheme 6.6 – Total Synthesis of (+)-Hinckdentine A by Torres-Ochoa and co-workers[10]

6.1.7 Total Synthesis of (±)-Hinckdentine A by Hou and Co-workers

To date the shortest and arguably the most elegant synthesis of (±)-hinckdentine A (**6.1**) was published in 2018 by Hou and co-workers (**Scheme 6.7**).[11] This synthesis begins with a 3-step synthesis of the urea **6.6** which undergoes a key electrochemical dehydrogenative [3+2] annulation to give **6.68** in 70%. This impressive transformation forms the core quinazoline (**6.2**) scaffold in a single step highlighting the power of electrochemistry in the construction of complex polycyclic frameworks. TBS deprotection and reduction then affords **6.69** in 87% over 2-steps. Subsequent Bn deprotection, Boc protection and bromination through treatment with NBS then afforded **6.70**. Boc deprotection and oxidation then sets up the synthesis of **6.71** which undergoes a Schmidt reaction to give the ring expanded product (±)-hinckdentine A (**6.1**) in 36%.

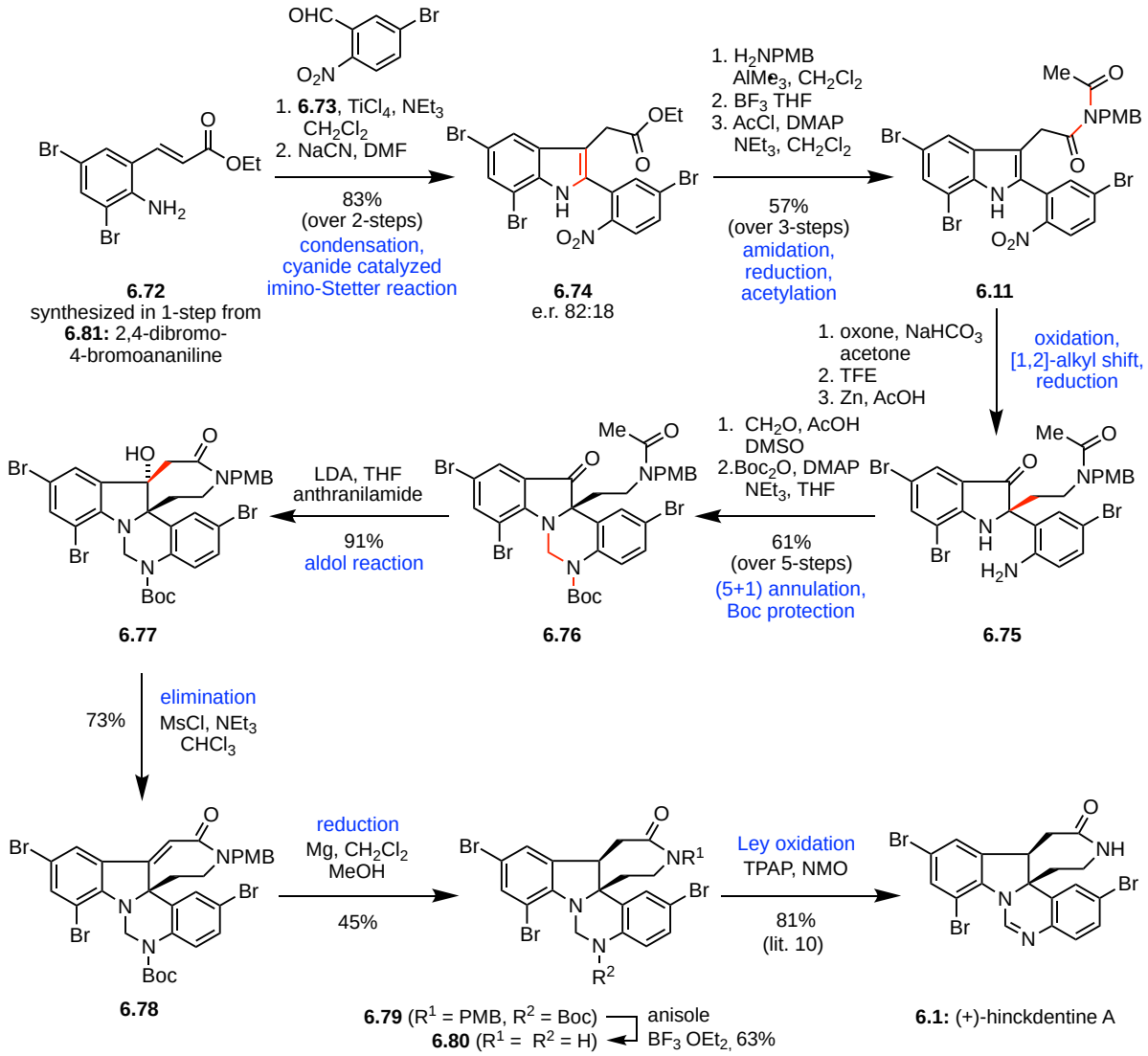


Scheme 6.7 – Total Synthesis of (±)-Hinckdentine A by Hou and co-workers[11]

6.1.8 Total Synthesis of (±)-Hinckdentine A by Jeon and Co-workers

The most recent total synthesis of (±)-hinckdentine A (**6.1**) was reported by Jeon *et al.* in 2021 (**Scheme 6.8**).[12] This began through a $TiCl_4$ mediated condensation of amino-3,5-cinnamate (**6.72**) with 5-bromo-2-nitrobenzaldehyde (**6.73**), followed by a cyanide catalyzed imino-Stetter reaction to afford **6.74** in 83% over 2-steps. Amidation of the ester with *p*-methoxybenzyl (PMB) amine, followed by reduction with BH_3 afforded a secondary amine, which was reacted with AcCl to give the tertiary amide **6.11**. Next, oxidation of **6.11** with Oxone gave the 3-hydroxy indolenine. Thermal rearrangement then afforded a [1,2]-alkyl shift installing the quaternary centre at C2, and subsequent reduction of the nitro group gave the aniline **6.75**. The tetrahydroquinazoline ring was then constructed through

reaction with formaldehyde and Boc protection to afford **6.76**. An aldol reaction with LDA at –78 °C then afforded **6.77** in 91%. Dehydration of the C3 hydroxyl group through mesylation and elimination then provided the α,β-unsaturated lactam **6.78** in 73%. Selective reduction of **6.78** with magnesium then gave **6.79** in 45%, followed by treatment with BF_3 in anisole, enabled the global deprotection of **6.79** to **6.80** in 63%. Finally, Ley oxidation of **6.80** with TPAP according to the literature procedure by Torres-Ochoa *et al.* then afforded a total synthesis of (±)-hinckdentine A (**6.1**) in 81%.[10]



Scheme 6.8 – Total Synthesis of (±)-Hinckdentine A by Jeon and co-workers[12]

6.1.9 Proposal for the Total Synthesis of (±)-Hinckdentine A

Interestingly, when we looked carefully through these previous syntheses, we observed the common intermediate **6.82** (**Figure 6.2**). This indol-3-one intermediate was found in all approaches to **6.1** with the exception of work by Douki *et al.* and work by Hou and co-workers.[9, 11] Clearly, efforts towards the total synthesis of (±)-hinckdentine A (**6.1**) have been suffering from a lack of original chemistry. We

felt that the prospects of an efficient synthesis could be rapidly improved through a more biomimetic approach featuring the formamide **6.83**.

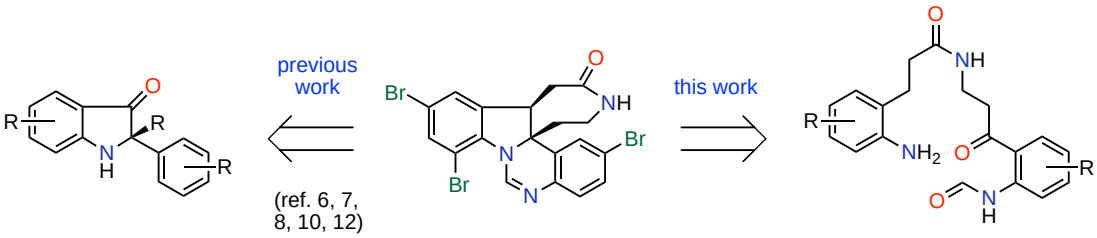
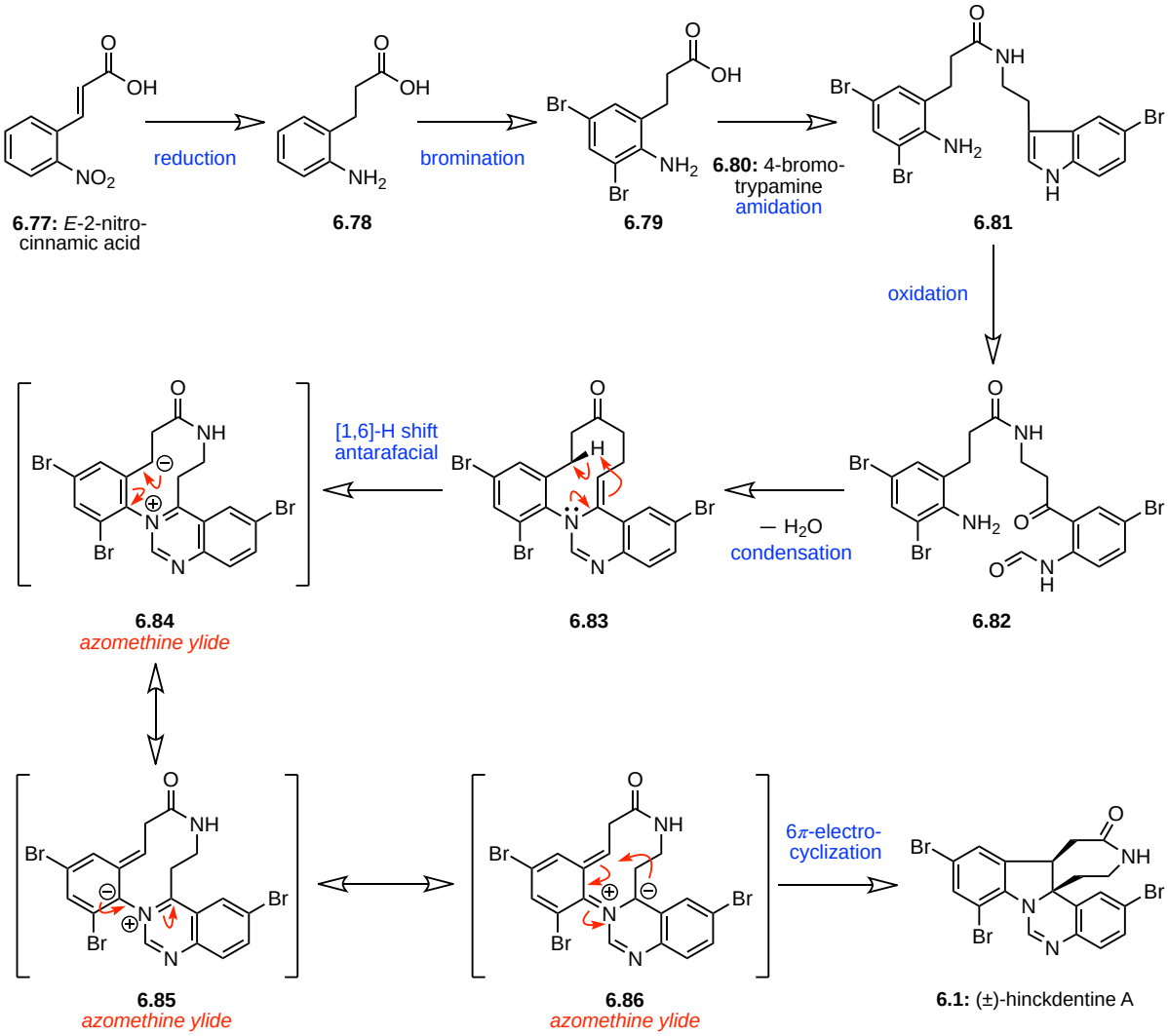


Figure 6.2 – Our Approach to the Total Synthesis of (±)-Hinckdentine A

Our proposal for the total synthesis of (±)-hinckdentine A (**6.1**) begins from reduction of commercially available *E*-2-nitro-cinnamic acid (**6.77**) to afford **6.78** (**Scheme 6.9**). Dibromination of the resultant electron rich aniline would then afford **6.79**, followed by amidation with 5-bromo tryptamine (**6.80**) to give **6.81**. We then propose that a biomimetic oxidative ring opening of the electron rich indole carbon-carbon double bond would give **6.82**, unveiling the formamide and ketone functional groups which we hope to be the key precursor to (±)-hinckdentine A (**6.1**). An intramolecular condensation reaction between the aniline, the ketone and the formamide would then produce a pyrimidine moiety affording the cyclic enamine **6.83**. Similar condensation reactions have been reported by Hao *et al.* in the total synthesis of trigonoliimine A.[18] Next, we envisage that heating of **6.83** could result in an antarafacial [1,6]-H shift to afford the stabilized, and highly conjugated azomethine ylides which would exist in resonance (i.e. **6.84**, **6.85** and **6.86**). We predict that **6.86** could then ring close *via* a 6π-electrocyclization reaction to give (±)-hinckdentine A (**6.1**) in a 5-step total synthesis featuring a spectacular cascade of pericyclic reactions. Related pericyclic cascade reactions involving conjugated azomethine ylides have been previously observed.[19]

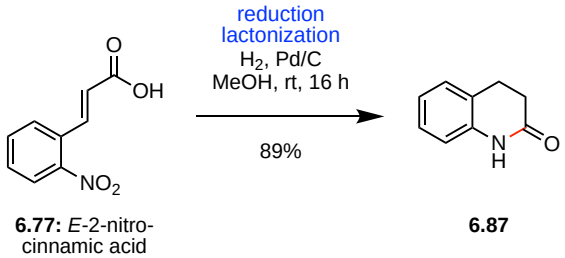


Scheme 6.9 – Proposed Total Synthesis of (±)-Hinckdentine A

6.2 Results and Discussion

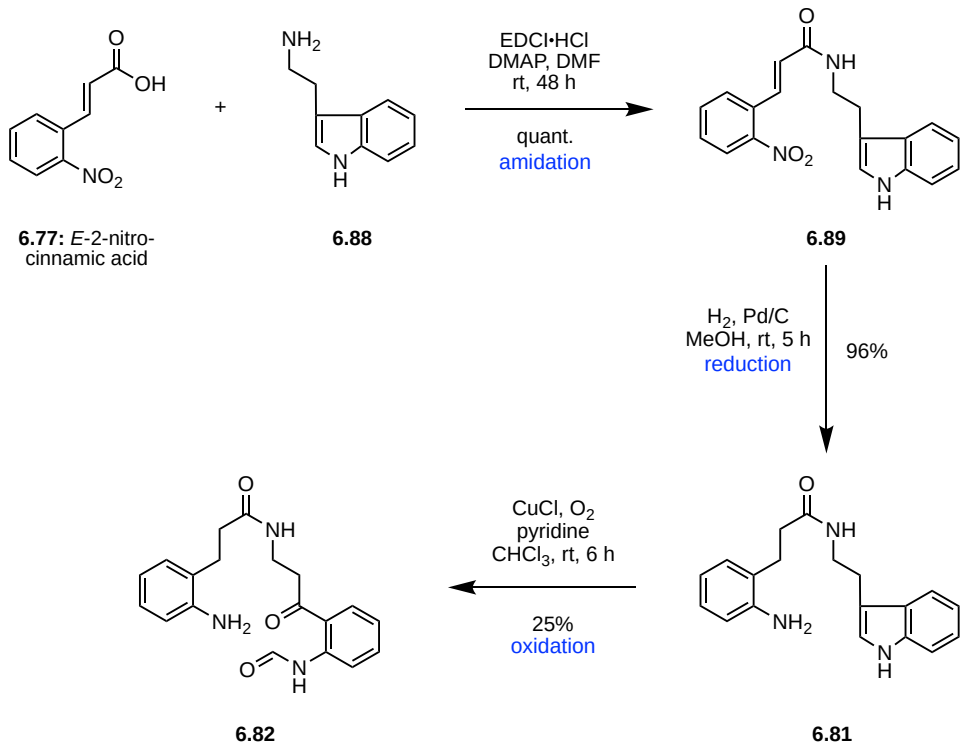
6.2.1 Initial Efforts Towards the Total Synthesis of (±)-Hinckdentine A

Synthesis of (±)-hinckdentine A (**6.1**) began with reduction of *E*-2-nitro-cinnamic acid (**6.77**), in an attempt to form aniline **6.78**. Unfortunately, reaction of **6.77** with catalytic Pd/C and H_2 gave the lactonized product **6.87** in 89%, presumably due to its high thermodynamic stability (**Scheme 6.10**). All attempts to suppress this cyclization through shorter reaction times failed.



Scheme 6.10 – Attempted Reduction of 6.77

To overcome this issue, we decided to change the order of our reactions. Instead, reaction of **6.77** with tryptamine (**6.88**), DCC and DMAP afforded the amide **6.89** in 20% (**Scheme 6.11**). Gratifyingly, we found that using the amide coupling reagent EDCI in the place of DCC gave a quantitative yield of **6.89** when the reaction was left for 48 h. Next, reduction of **6.89** afforded the aniline **6.81** in 96% and subsequent oxidation of the indole motif of **6.81** was attempted. Unfortunately, treatment of **6.81** with methylene blue and O_2 in CH_2Cl_2 gave only decomposition. However, we found that Tsuji's conditions (i.e. CuCl, O_2 and pyridine) afforded the key formamide **6.82** in a modest 25% yield.[20]



6.77: *E*-2-nitro-cinnamic acid

6.88

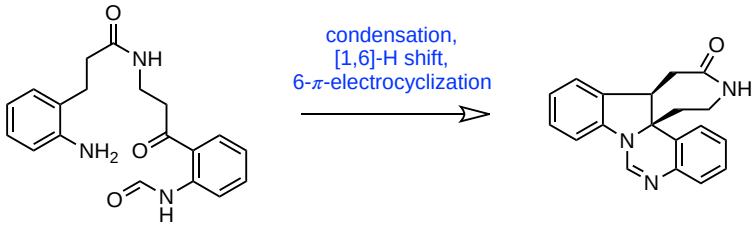
6.89

6.82

6.81

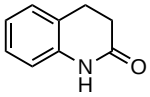
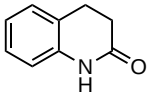
Scheme 6.11 – Synthesis of the Key Formamide 6.82

With **6.82** in hand, our efforts then turned towards screening conditions for the key condensation, [1,6]-H shift, and 6π-electrocyclization cascade to afford the hinckdentine A scaffold **6.90** (**Table 6.1**). It was found that leaving **6.82** in 4Å sieves at room temperature in CH_2Cl_2 gave starting material (**entry 1**), whilst heating **6.82** to reflux in PhMe resulted in formation of the undesired lactam **6.87** (**entry 2**). It became clear to us at this point that the formation of **6.87** was going to be problematic and that attempts to suppress this would be challenging. Next, a series of Lewis acids were screened (TMSCN, TMSOTf, *t*-BuMe$_2$OTf, $BF_3{\cdot}OEt_2$ and $SnCl_4$) (**entries 3 – 8**), however these reactions only resulted in decomposition or formation of the lactam **6.87**. Attempts to selectively activate the formamide functional group through reaction with $POCl_3$ and pyridine only gave decomposition (**entry 9**), while treatment with the Brønsted acid CSA gave no reaction (**entry 10**).



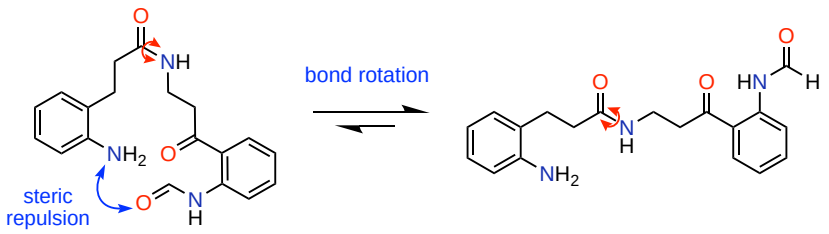
6.82 **6.90**
hinckdentine A scaffold

Table 6.1 – Conditions Screened for the Key Reaction Cascade of 6.82

Entry	Reagents	Solvent	Time	Temperature	Result
1	4Å sieves	$CHCl_3$	48 h	rt	NR
2	4Å sieves	PhMe	4 h	110 °C	 **6.87** 80%
3	TMSCN (1.0 equiv.)	CH_2Cl_2	8 h	rt	decomp.
4	TMSOTf (40 mol%) TMSCN (4.0 equiv.)	CH_2Cl_2	4 h	rt	 **6.87** 54%
5	TMSCN (1.0 equiv.) Et_3N (1.0 equiv.)	CH_2Cl_2	4 h	–78 °C → rt	decomp.
6	*t*-BuMe_2OTf (1.1 equiv.)	CH_2Cl_2	4 h	–78 °C → rt	decomp.
7	$BF_3{\cdot}OEt_2$ (1.0 equiv.)	CH_2Cl_2		–78 °C → rt	decomp.
8	$SnCl_4$ (10 mol%)	EtOH		rt	decomp.
9	$POCl_3$ (1.0 equiv.) pyridine (1.0 equiv.)	CH_2Cl_2	1 h	–78 °C → rt	decomp.
10	CSA (5 mol%)	CH_2Cl_2	8 h	rt	NR

6.2.2 Efforts Towards the Total Synthesis of (±)-Hinckdentine A Through a Bn Formamide

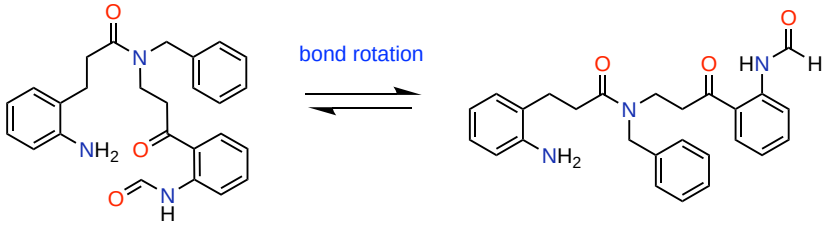
Aside from the obvious problematic formation of **6.87**, another explanation behind our lack of promising results could be due to the spatial conformation of **6.82**, which could be adopting a linear conformation in solution (due to steric repulsion) rather than undergoing condensation with aniline (**Figure 6.3**).



6.82 6.82

Figure 6.3 – Possible Conformations of the Formamide 6.82

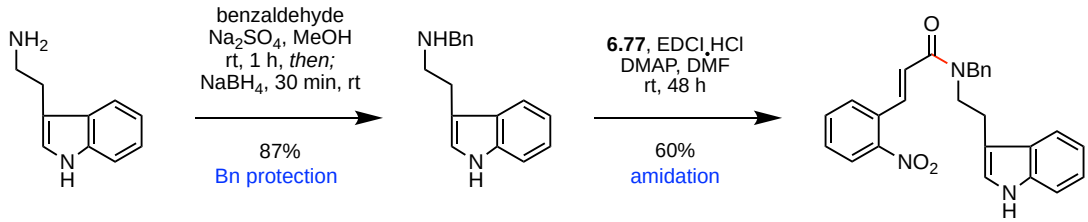
To overcome this issue, it was envisaged that protection of the amide **6.82** with a more sterically hindered benzyl group (i.e. **6.91**) could result in a more stable formation of the non-linear conformer and we hoped that this would help facilitate condensation and assist in the formation of the hinckdentine scaffold (**Figure 6.4**).



6.91 6.91

Figure 6.4 – Possible Conformations of the Formamide 6.91

The benzyl protected formamide **6.91** was synthesized analogous to our previous synthesis of **6.83**, except this time through the synthesis of the benzyl protected tryptamine **6.92** (**Scheme 6.12**). This was achieved following a literature procedure from Martin and Vanderwal through reductive amidation of **6.88** with benzaldehyde and treatment with $NaBH_4$, which afforded **6.92** in 87% yield.[21] Amidation of **6.92** with *E*-2-nitro-cinnamic acid (**6.77**), EDCI and DMAP then gave **6.93** in 60%. The yield for this amidation was lower than that observed when compared to the synthesis of the unprotected amide **6.89**, most likely due to a combination of steric and electronic effects.



6.88 6.92 6.93

Scheme 6.12 – Synthesis of Benzyl Protected Amide 6.93

Gratifyingly the obtained ^{1}H NMR spectra of **6.93** showed the presence of rotamers suggesting that the benzyl group was indeed serving its desired purpose (**Figure 6.5**). This can be very clearly seen by inspection of the alkyl peaks at **C8** and **C9**.

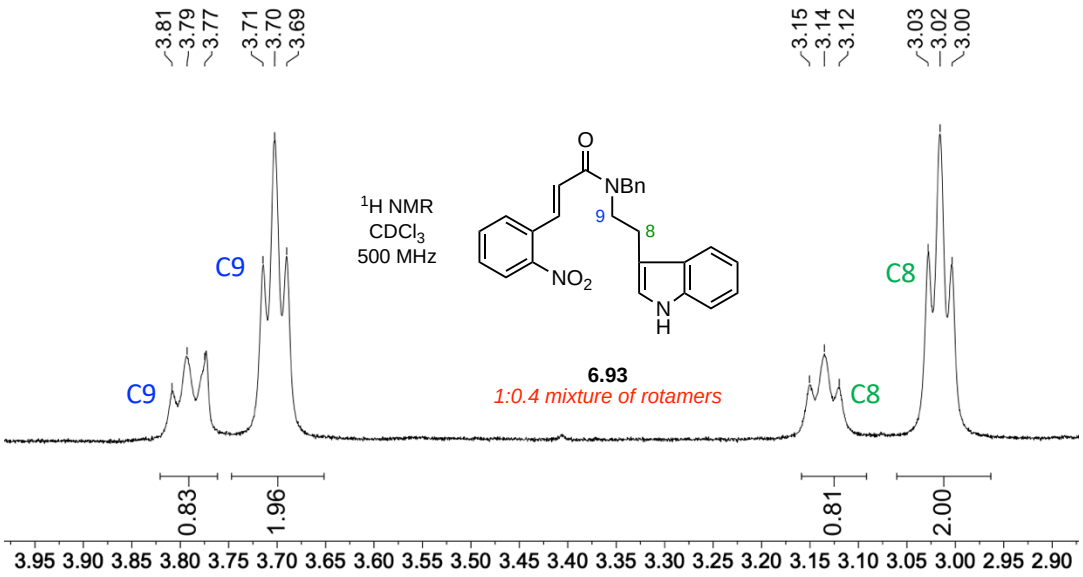
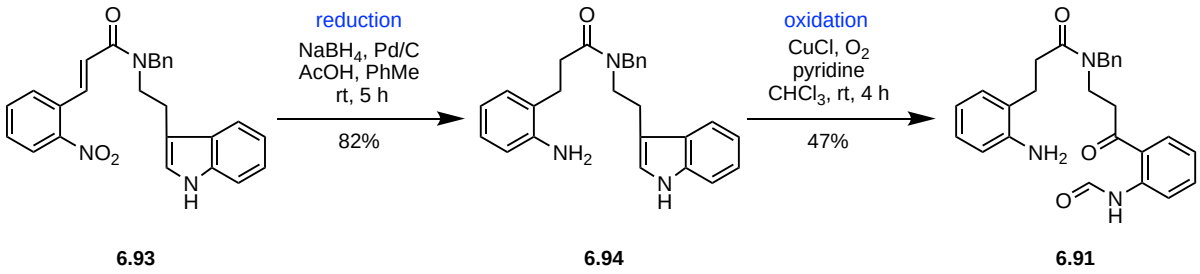


Figure 6.5 – ^{1}H NMR (500 MHz) of the Benzyl Protected Amide 6.93

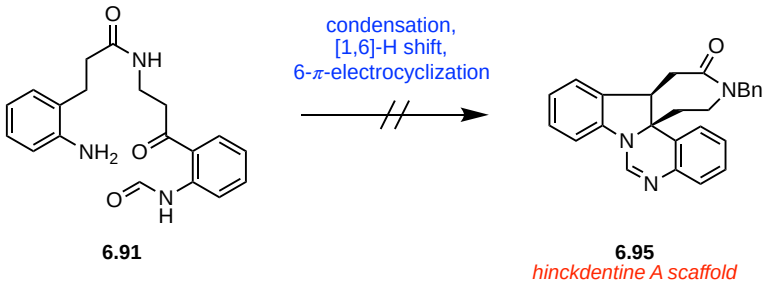
Chemoselective reduction of **6.93** following a modified procedure from Soom *et al.* using $NaBH_4$ and catalytic Pd/C then gave the reduced aniline **6.94** in 82%.[22] Oxidation again using conditions developed by Tsuji and co-workers afforded the desired formamide **6.91** (**Scheme 6.13**).[20]



Scheme 6.13 – Synthesis of the Benzyl Protected Formamide 6.91

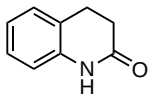
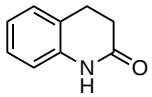
With access to the key formamide **6.91** our efforts then turned towards screening conditions for the key condensation, [1,6]-H shift, and 6π-electrocyclization cascade to afford the hinckdentine A scaffold **6.95** (**Table 6.2**). Unfortunately, similar to our previous observations we found that treatment of **6.91** with 4Å sieves and thermal heating only gave the lactam **6.87** in 27% (**entry 1**), while reactions with Lewis acids (i.e. TMSCN, TMSOTf, $BF_3{\cdot}OEt_2$ and $SnCl_4$) (**entries 2 – 6**) only resulted in decomposition or formation of **6.87**. Frustratingly, these reactions were much messier compared to

those seen previously in the key step reaction of the unprotected **6.82**. Reaction with $POCl_3$ and either pyridine or Et_3N only gave decomposition (**entries 7 – 8**), and finally we attempted treatment of **6.91** with the Brønsted acids CSA and TsOH (**entries 9 – 10**). Disappointingly, only decomposition was observed.



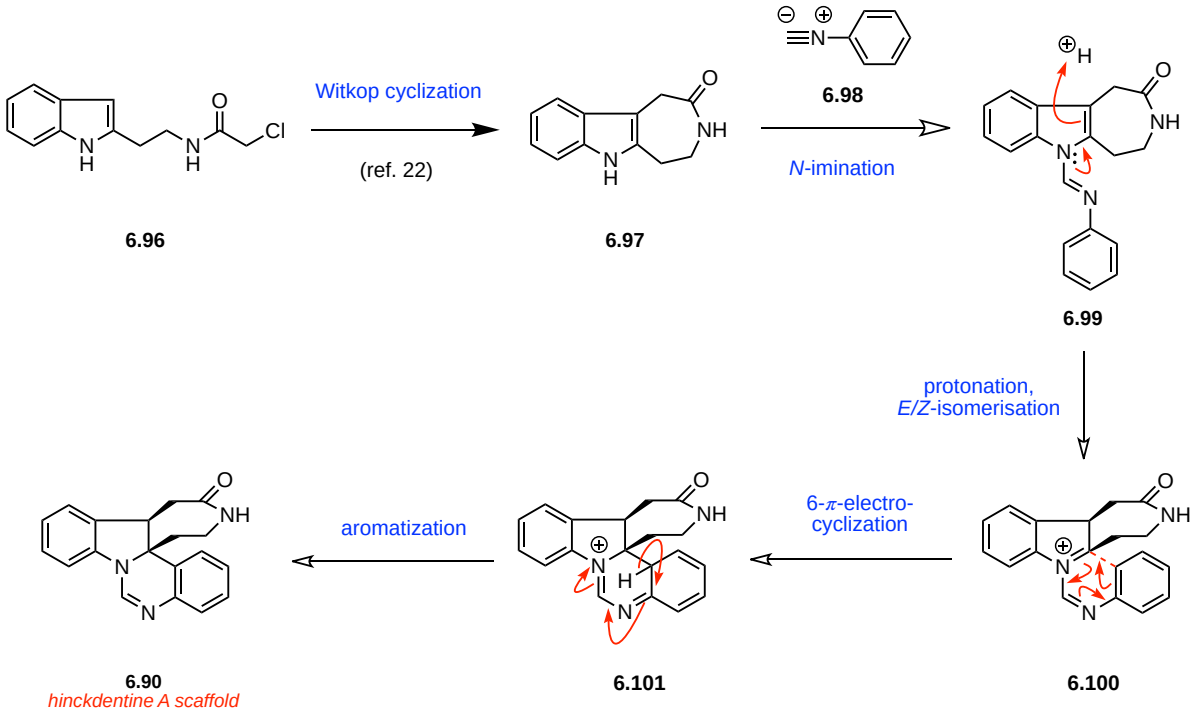
6.91 **6.95**
hinckdentine A scaffold

Table 6.2 – Conditions Screened for the Key Reaction Cascade of 6.91

Entry	Reagents	Solvent	Time	Temperature	Result
1	4Å sieves	PhMe	24 h	140 °C	 **6.87** 27%
2	TMSCN (3.0 equiv.)	THF	4 h	rt	decomp.
3	TMSOTf (40 mol%) TMSCN (4.0 equiv.)	CH_2Cl_2,	8 h	rt	 **6.87** 13%
4	$BF_3{\cdot}OEt_2$ (1.0 equiv.)	CH_2Cl_2		–78 °C → rt	decomp.
5	$BF_3{\cdot}OEt_2$ (2.0 equiv.) TMSCN (1.0 equiv.)	CH_2Cl_2	14 h	–78 °C → rt	decomp.
6	$SnCl_4$ (1.0 equiv.)	CH_2Cl_2	30 min	–78 °C → rt	decomp.
7	$POCl_3$ (1.0 equiv.) pyridine (1.0 equiv.)	CH_2Cl_2	1 h	–78 °C → rt	decomp.
8	$POCl_3$ (1.0 equiv.) Et_3N (1.0 equiv.)	THF	4 h	–78 °C → rt	decomp.
9	TsOH (20 mol%) 4Å sieves	CH_2Cl_2	6 h	rt	decomp.
10	CSA (5 mol%)	CH_2Cl_2	12 h	rt	decomp.

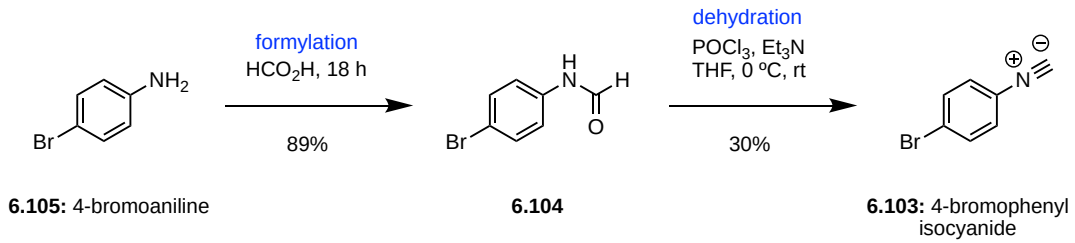
6.2.3 A Revised Model Study Towards the Total Synthesis of (±)-Hinckdentine A

Having made minimal progress towards the total synthesis of (±)-hinckdentine A (**6.1**) through our proposed biomimetic route, efforts turned towards a new yet equally ambitious non-biomimetic approach (**Scheme 6.16**). We envisaged this could be achieved through synthesis of the α-chloride **6.96**, which could undergo a Witkop cyclization reaction according to a literature procedure by Bhandari and co-workers to afford the lactam **6.97**.[23] We then hoped that treatment of the lactam **6.97** with a phenyl isocyanide (i.e. **6.98**) could afford the *N*-imination product **6.99**. Recent work by Kim and Hong highlighted the use of *N*-heterocyclic carbenes to catalyse similar transformations in good to excellent yields.[24] We then propose that **6.99** could undergo a protonation event and *E/Z*-isomerisation to afford the imine **6.100**, which would be primed to undergo a 6-π-electrocyclization to afford **6.101** and concomitant aromatization to afford the hinckdentine A scaffold **6.90**.



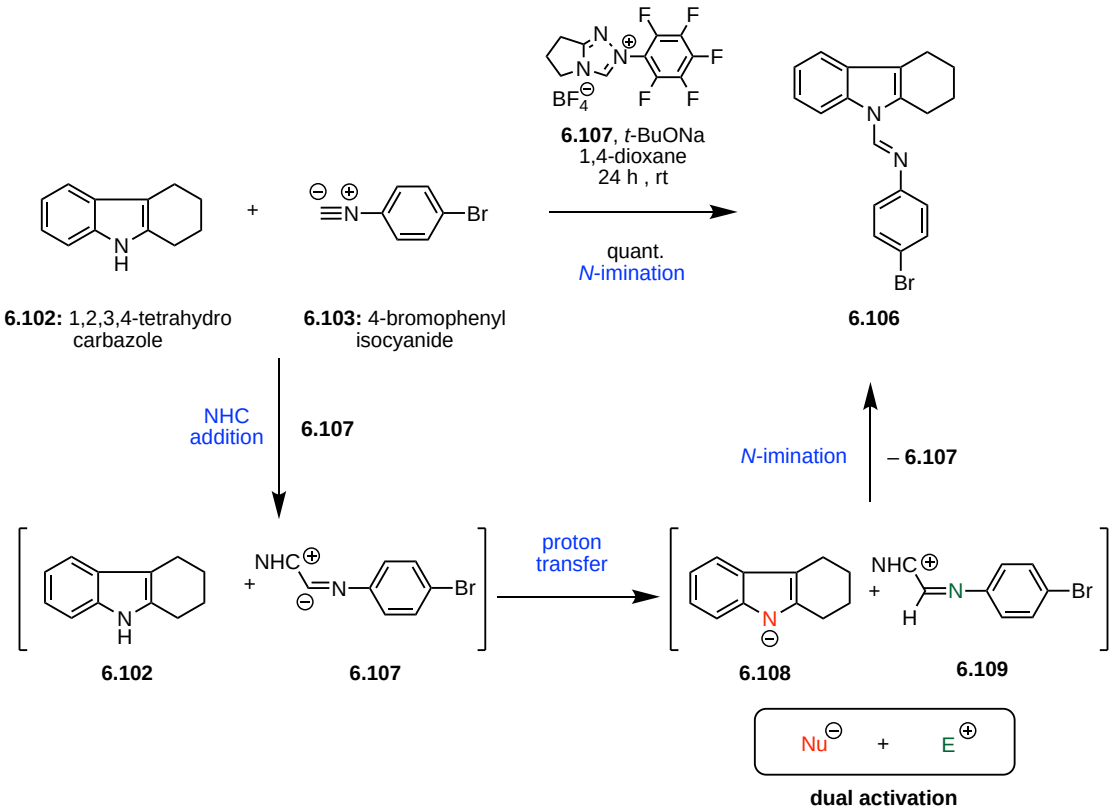
Scheme 6.14 – Revised Synthetic Proposal for the Hinckdentine A Scaffold 6.90

To begin our investigations into a revised synthesis of (±)-hinckdentine A (**6.1**) we targeted a short model study starting from commercially available 1,2,3,4-tetrahydrocarbazole (**6.102**). Synthesis of 4-bromophenyl isocyanide (**6.103**) was achieved following a two-step modified procedure from Hosseini-Sarvari and Sharghi (**Scheme 6.15**).[25] This occurred through synthesis of the formamide **6.104** from 4-bromoaniline (**6.105**) in 89%. Subsequent dehydration then afforded **6.103** in 30%.



Scheme 6.15 – Synthesis of 4-Bromophenyl isocyanide[25]

With **6.103** in hand, we then attempted the *N*-imination to form **6.106** following a literature procedure from Kim and Hong (**Scheme 6.16**).[24] Pleasingly we found that reaction of **6.102** with **6.103** in the presence of the NHC catalyst **6.107** gave the desired formamidine **6.106** in quantitative yield after stirring at room temperature for 24 h. It is proposed that this reaction occurs through a duel NHC organocatalytic activation of both the indole and the isocyanide. This involves addition of the NHC catalyst (**6.107**) to **6.103** which gives the imidoyl intermediate **6.107**. Next, a proton transfer then activates the carbazole (*via* deprotonation) to afford **6.108** and the imidoyl (*via* protonation) to afford **6.109**. This results in a dual activation of a nucleophile and an electrophile which couple to give the formamidine **6.106**.



Scheme 6.16 – *N*-Imination of indole 6.102

Having succeeded in the synthesis of **6.106**, conditions for the key protonation, *E/Z*-isomerisation, 6-π-electrocyclization and aromatization reaction cascade to form **6.110** was investigated (**Table 6.3**). Frustratingly, treatment of **6.110** under thermal conditions (**entries 1 – 3**) gave decomposition, while treatment in a microwave reactor gave no reaction (**entry 4**). Next, reaction of with various Brønsted acids (i.e *p*-TsOH·H_2O and CSA) were explored. However, these reactions only afforded the hydrolysis products **6.105** and **6.111** (**entries 5 – 6**). The Lewis acids BF_3·OEt_2, $MgBr_2$ and SiO_2 gave no reaction (**entries 7 – 9**), as did photoredox conditions (**entries 10 – 11**), meanwhile radical initiation using AIBN only led to decomposition of **6.106** (**entry 12**).

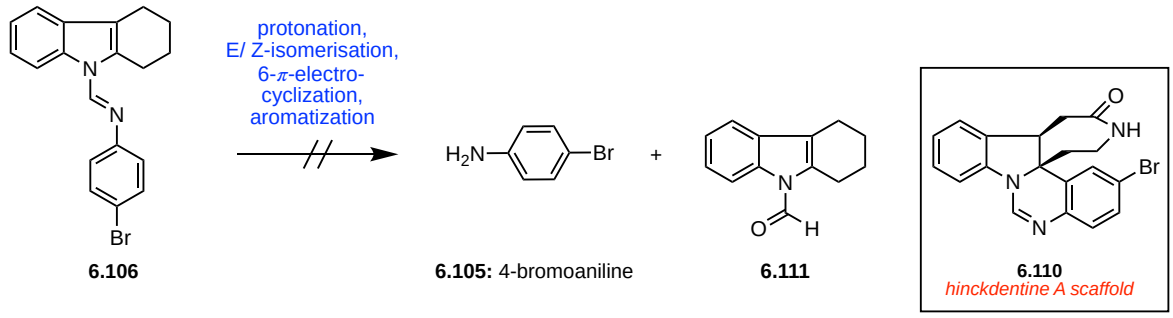


Table 6.3 – Attempts Towards the Key Reaction Cascade of 6.106

Entry	Reagents	Solvent/ Conditions	Time	Temperature	Result		
					6.105	6.111	Comment
1	--	DMF	5 h	153 °C	--	--	decomp.
2	--	*i*-PrOH	5 h	85 °C	--	--	decomp.
3	--	THF/ H_2O	24 h	66 °C	--	--	decomp.
4	--	benzene microwave	1 h	150 °C	--	--	NR
5	*p*-TsOH·H_2O (1.0 equiv.)	PhMe	3 h	rt	18%	50%	--
6	CSA (1.0 equiv.)	EtOH	3 h	rt	40%	40%	--
7	BF_3·OEt_2	THF	30 min	–78 °C	--	--	NR
8	$MgBr_2$	MeCN	16 h	80 °C	--	--	NR
9	SiO_2	--	7 h	140 °C	--	--	NR
10	$[Ru(bpz)_3](PF_6)_2$ (2 mol%)	$MeNO_2$ visible light	4 h	rt	--	--	NR
11	4-MeO-TPT	DCE **blue LED**	4 h	rt	--	--	NR
12	AIBN	benzene	5 h	60 °C	--	--	decomp.

Finally, we considered the possibility that this reaction might be better mediated through a light induced electrocyclization (**Table 6.4**). We found that the best way to screen a high throughput for these conditions was through monitoring the reaction of **6.106** with light in a variety of deuterated solvents over a period of 6 h. We began irradiating **6.106** to visible light in 6 different solvents (d_6-acetone, d_6-benzene, $CDCl_3$, d_6-DMSO, d_4-MeOH, d_5-pyridine), however in all cases no reaction was observed. Next, we screened *UVA* light which again gave no reaction, while *UVC* light either gave no reaction, decomposition or afforded the hydrolysis products **6.105** and **6.111**. Reaction with sunlight also gave no reaction.

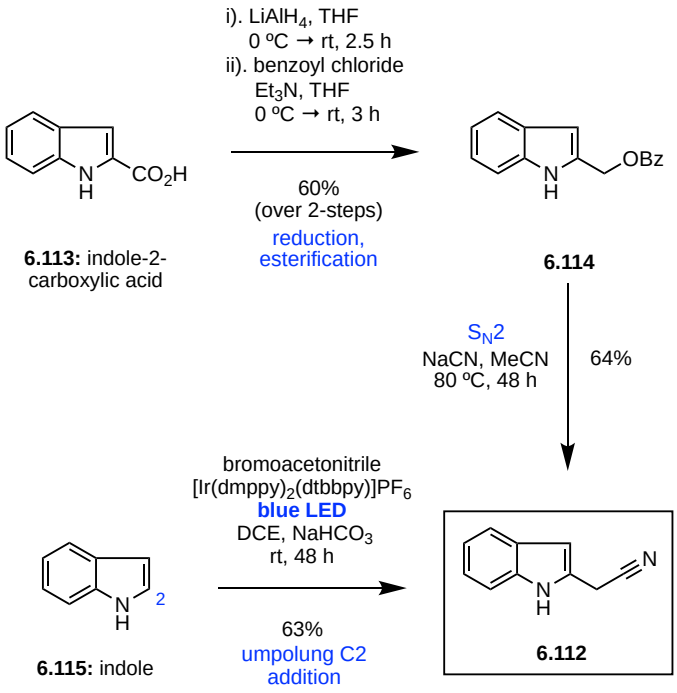
Table 6.4 – Attempts Towards the Key Reaction Cascade of 6.106

Entry	Reagents	*d*-Solvents	Time	Result
1	visible light	d_6-acetone	6 h	NR
		d_6-benzene		NR
		$CDCl_3$		NR
		d_6-DMSO		NR
		d_4-MeOH		NR
		d_5-pyridine		NR
2	*UVA*	d_6-acetone	6 h	NR
		d_6-benzene		NR
		$CDCl_3$		NR
		d_6-DMSO		NR
		d_4-MeOH		NR
		d_5-pyridine		NR
3	*UVC*	d_6-acetone	6 h	NR
		d_6-benzene		NR
		$CDCl_3$		decomp.
		d_6-DMSO		**6.105** + **6.111**
		d_4-MeOH		**6.105** + **6.111**
		d_5-pyridine		NR
4	sunlight	d_6-acetone	6 h	NR
		d_6-benzene		NR
		$CDCl_3$		NR
		d_6-DMSO		NR
		d_4-MeOH		NR
		d_5-pyridine		NR

6.2.4 Revised Efforts Towards the Total Synthesis of (±)-Hinckdentine A

Despite not being able to successfully achieve the key protonation, *E/ Z*-isomerisation, 6-π-electrocyclization and aromatization reaction cascade, we were still determined to attempt this cascade on the real system. To this end, we began by targeting synthesis of the nitrile **6.112**. Pleasingly

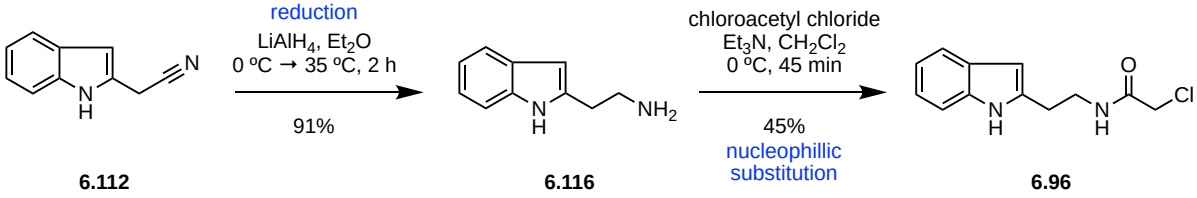
this could be achieved following a 3-step literature procedure from Nowacki and co-workers (**Scheme 6.17**).[26] This involved reduction of indole-2-carboxylic acid (**6.113**) with $LiAlH_4$, followed by benzoyl protection of the alcohol to give **6.114** in 60% (over 2-steps). Subsequent reaction with NaCN through reflux in MeCN for 48 h then afforded **6.112** in 64%. Alternatively, direct access to **6.112** could be achieved in 1-step from indole (**6.115**) through an $[Ir(dmppy)_2(dtbbpy)]PF_6$ mediated photoredox umpolung addition with bromoacetonitrile. This procedure was first reported in 2018 by O'Brien and co-workers.[27] Although this afforded **6.112** in 63%, we found that this reaction gave inconsistent and poor yields upon scale up, presumably this was due to difficulty of the **blue LED** to irradiate the solution well and uniformly on a large scale.



Scheme 6.17 – Synthesis of nitrile 6.112

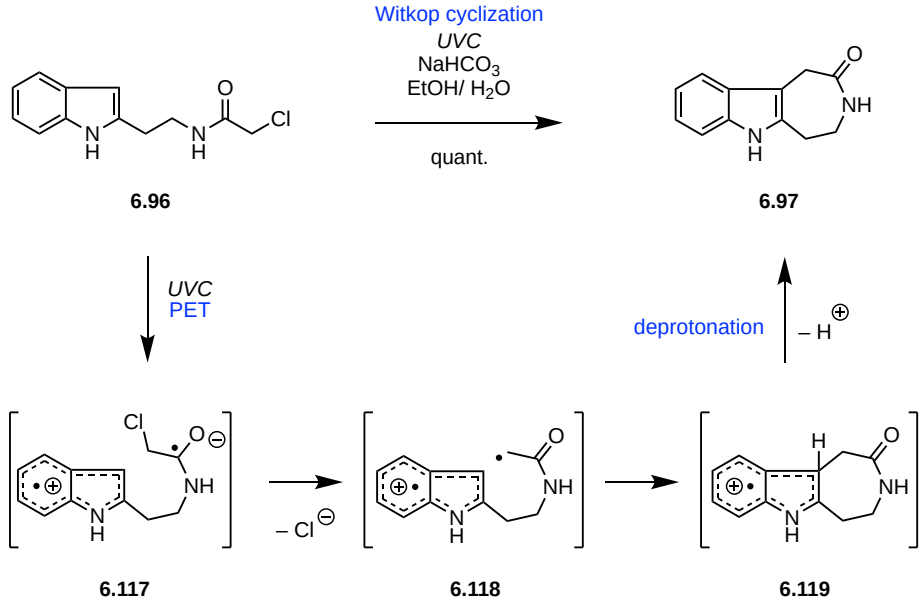
Reduction of the nitrile **6.112** was then attempted, in the hope of synthesizing isotryptamine **6.116**. Surprisingly this reaction was particularly challenging, all attempted reductions with $LiAlH_4$ in THF at a variety of temperatures failed, resulting only in decomposition. Additionally, we found that reductions with $LiAlH_4$ in Et_2O at room temperature failed. It was only upon heating this solution to reflux that formation of **6.116** was observed (**Scheme 6.18**). Frustratingly, this amine was not stable enough for purification by flash column chromatography on SiO_2 even with the addition of Et_3N or phosphate buffered (pH = 7) SiO_2. It was found that the best approach to purify this compound was simply through a telescopic work up. The crude **6.116** was then treated with chloroacetyl chloride in the presence of Et_3N at 0 °C. Pleasingly this gave the desired α-chloride (**6.96**) in 45%, however once more,

this compound was not stable to flash column chromatography on SiO_2 and the product was observed to be cleaner without any attempted purification.



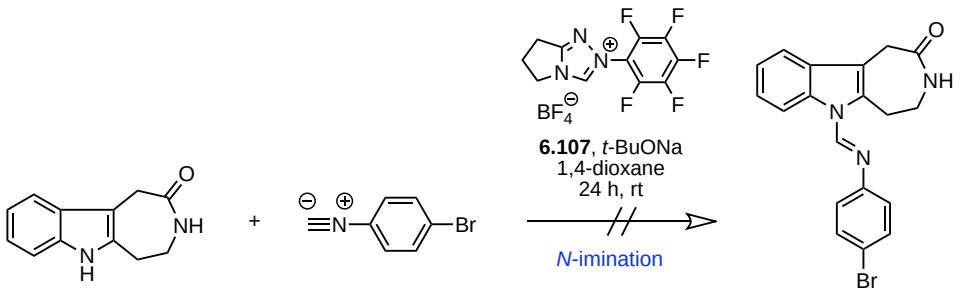
Scheme 6.18 – Synthesis of the α-Chloramide 6.96

Following a literature procedure from Bhandari *et al.* **6.96** was then reacted through a $NaHCO_3$ mediated Witkop cyclization affording **6.97** in quantitative yield (**Scheme 6.19**).[22] This reaction proceeds through a photon induced electron transfer (PET) to afford **6.117**. Subsequent dechlorination to **6.118**, followed by radical cyclization then gives **6.119** which undergoes a deprotonation to afford **6.97**.



Scheme 6.19 – Witkop Cyclization of 6.96 to 6.97

Treatment of the witkop product **6.97** with Kim and Hong's NHC organocatalytic *N*-imination was then attempted (**Scheme 6.20**). Unfortunately, all reactions of **6.97** with 4-bromo isocyanide (**6.103**) and the catalyst **6.107** only afforded decomposition. It is most likely that this was due to poor functional group tolerance of this reaction, which may not have been forgiving of the amide moiety.



Scheme 6.20 – Attempted *N*-Imination of 6.97

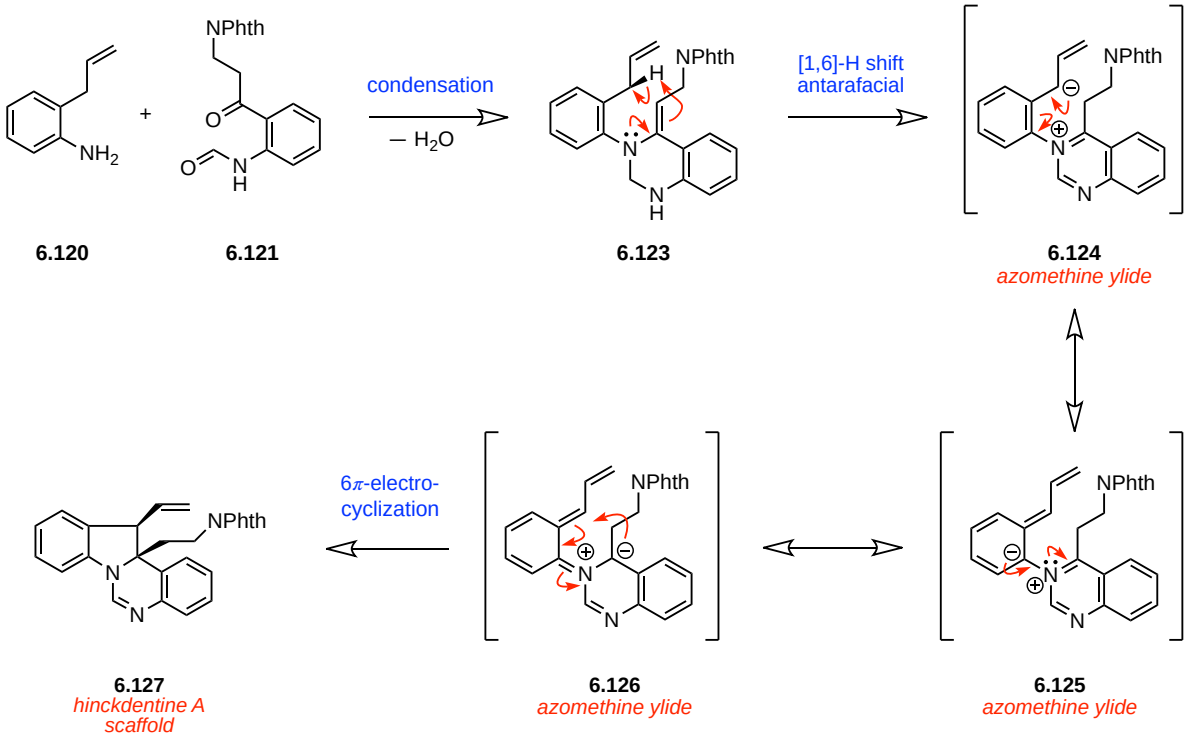
6.3 Conclusion and Future Work

6.3.1 Conclusion

In this chapter we have investigated some unique cascade reaction towards the total synthesis of (±)-hinckdentine A (**6.1**). Our initial attempt featured a biomimetic approach through the synthesis of a formamide (and later the synthesis of a benzyl protected formamide) where we investigated a condensation, [1,6]-H shift, and 6π-electrocyclization cascade. A non-biomimetic approach employing a Witkop cyclization, *N*-imination and a unique protonation, *E/Z*-isomerisation, 6-π-electrocyclization and aromatization reaction cascade was also explored. Unfortunately, although the synthesis of **6.1** was eluded in both approaches, we hope that these results offer some insight into the challenges associated in the synthesis of (±)-hinckdentine A (**6.1**).

6.3.2 Future Work

For future work we would like to revisit our first biomimetic approach. On reflection, it is possible that the difficulty we observed in this cascade may be due to the unfavoured formation of a 10 membered ring in the condensation reaction. Instead, it is possible that access to (±)-hinckdentine A (**6.1**) may be achieved through a more conservative intermolecular cascade reaction (**Scheme 6.21**). This would involve the reaction between two known compounds **6.120** and **6.121** which could undergo an analogous condensation, [1,6]-H shift, and 6π-electrocyclization cascade.



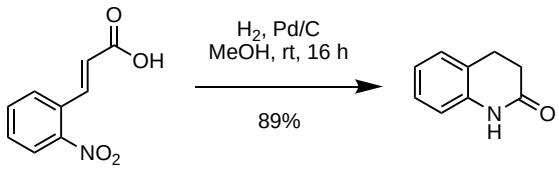
Scheme 6.21 – Future Work Towards the Total Synthesis of (±)-Hinckdentine A

6.4 Experimental

6.4.1 General Methods

All chemicals used were purchased from commercial suppliers and used as received. All reactions were performed under an inert atmosphere of N_2 unless otherwise stated. Thin layer chromatography was performed using aluminium sheets coated with silica gel. Visualization was aided by viewing under a *UV* lamp and staining with the appropriate stain followed by heating. All R_f values were measured to the nearest 0.05. Flash chromatography was performed using 40-63 micron grade silica gel. Melting points were recorded on a digital melting point apparatus and are uncorrected. Infrared spectra were recorded using an FT-IR spectrometer as the neat compounds. High field NMR was recorded using a 600 MHz spectrometer (^{1}H at 600 MHz, ^{13}C at 150 MHz) or a 500 MHz spectrometer (^{1}H at 500 MHz, ^{13}C at 125 MHz). The solvent used for NMR spectra was $CDCl_3$ unless otherwise specified. ^{1}H chemical shifts are reported in ppm on the δ-scale relative to TMS (δ 0.0) and ^{13}C{^{1}H} NMR are reported in ppm relative to chloroform (δ 77.16). Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet and (m) multiplet. All J-values were rounded to the nearest 0.1 Hz. ESI high resolution mass spectra were recorded on a Q-TOF mass spectrometer. Photochemistry with *UVA* light was performed using a generic brand commercial LED *UV* light globe; wavelength: 365 nm. Photochemistry with *UVC* light was performed using a generic brand commercial LED *UV* light globe; wavelength: 254 nm. Photochemical reactions with visible light were performed with a conventional commercial LED desk lamp at 240 V with a 4 W 5000 K 32 mÅ globe. Reactions conducted under 470 nm blue LED lamp were performed using a 19-24VDC 40W Kessil A160WE.

6.4.2 Experimental Procedures



6.77: *E*-2-nitro-cinnamic acid

6.87

To a solution of *E*-2-nitrocinnamic acid (**6.77**) (4.00 g, 20.0 mmol, 1.0 equiv.) in MeOH (20 mL) at room temperature was added portion wise Pd/C (1.37 g, 2.00 mmol, 10 mol %) and the solution was placed under an environment of vacuum/ H_2 three times, then left to stir under 1 atm of H_2. After 16 h the solution was filtered through a pad of celite^{TM} with EtOAc (300 mL) and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (9:1 hexanes/ EtOAc) to give lactam **6.87** (2.70 g, 89%) as white crystals. Data for **6.87** matched that previously reported in the literature.[28]

Data for 6.87:

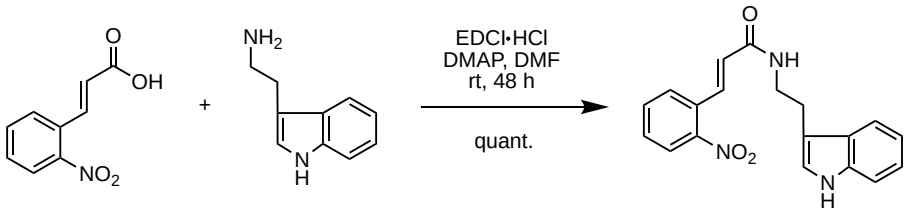
R_f: 0.20 (8:1 hexanes/ EtOAc).

FTIR (neat): 3185, 3089, 1686, 1593, 12491, 1436, 1390, 1340, 1281, 1246, 1198, 1033, 813 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.60 (s, 1H), 7.18 – 7.13 (m, 2H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 2.96 (t, *J* = 7.6 Hz, 2H), 2.65 (t, *J* = 7.6 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6, 137.5, 127.9, 127.6, 123.7, 123.1, 115.8, 30.8, 25.4 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_9H_{10}ON$ 148.0757; found 148.0763.



6.77: *E*-2-nitro-cinnamic acid **6.88** **6.89**

To a solution of *E*-2-nitrocinnamic acid (**6.77**) (2.50 g, 13.0 mmol, 1.0 equiv.) in DMF (30 mL) at room temperature was added tryptamine (**6.88**) (2.06 g, 13.0 mmol, 1.0 equiv.), DMAP (1.73 g, 14.2 mmol, 1.1 equiv.) and EDCI·HCl (2.47 g, 13.0 mmol, 1.0 equiv.). After 48 h, the reaction was quenched with sat. brine (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on SiO_2 (1:1 hexanes/ EtOAc) to give **6.89** (4.33 g, quant.) as a yellow solid.

Data for 6.89:

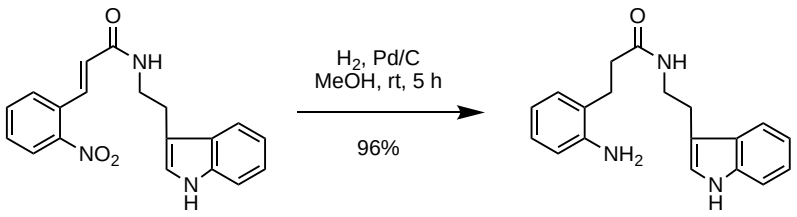
R_f: 0.20 (1:1 hexanes/ EtOAc).

FTIR (neat): 3322, 2980, 1647, 1603, 1534, 1432, 1340, 1223, 968 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (br s, 1H), 8.00 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.91 (d, *J* = 15.6 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.61 – 7.58 (m, 1H), 7.56 – 7.53 (m, 1H), 7.49 (td, *J* = 7.7, 1.6 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.22 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.17 – 7.12 (m, 1H), 7.10 (d, *J* = 2.3 Hz, 1H), 6.23 (d, *J* = 15.6 Hz, 1H), 5.77 (s, 1H), 3.75 (q, *J* = 6.4 Hz, 2H), 3.07 (t, *J* = 6.6 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.0, 136.6, 135.9, 133.5, 131.3, 129.9, 129.2, 127.5, 126.6, 125.0, 122.5, 122.4, 119.8, 118.9, 113.0, 111.5, 40.1, 25.4 ppm.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{17}O_3N_3Na$ 358.1162; found 358.1168.



6.89 **6.81**

To a solution of **6.89** (877 mg, 2.60 mmol, 1.0 equiv.) in MeOH (10 mL) at room temperature was added portion wise Pd/C (300 g, 0.260 mmol, 5% wt./ wt., 10 mol%) and the solution was placed under an environment of vacuum/ H_2 three times, then left to stir under 1 atm of H_2. After 5 h the solution was filtered through a pad of celite™ with EtOAc (200 mL) and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (neat EtOAc) to give **6.81** (769 mg, 96%) as an orange solid.

Data for 6.81:

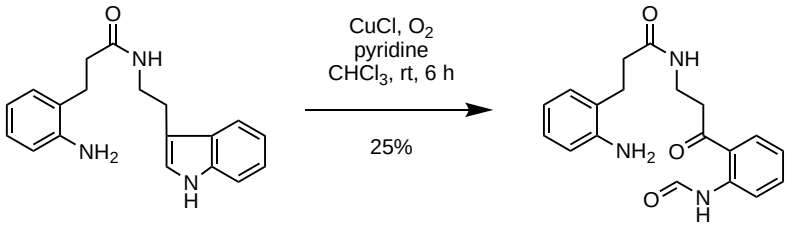
R_f: 0.10 (1:1 hexanes/ EtOAc).

FTIR (neat): 3291, 1649, 1581, 1515, 1451, 1198, 909, 751 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (br s, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.97 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.77 (s, 1H), 6.71 (t, *J* = 7.4 Hz, 1H), 6.63 (d, *J* = 7.9, 1H), 5.66 (br s, 1H), 3.86 (br s, 2H), 3.52 (q, *J* = 6.4 Hz, 2H), 2.87 (t, *J* = 6.7 Hz, 2H), 2.81 (t, *J* = 7.2 Hz, 2H), 2.37 (t, *J* = 7.2 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.9, 144.7, 136.5, 129.9, 127.5, 127.4, 125.6, 122.4, 122.2, 119.5, 118.8, 118.7, 116.1, 112.72, 111.4, 39.9, 36.5, 26.8, 25.2 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{22}ON_3$ 308.1757; found 308.1765.



6.81 **6.82**

To a solution of **6.81** (4.21 g, 13.7 mmol, 1.0 equiv.) in $CHCl_3$ (20 mL) at room temperature was added pyridine (3.0 mL, 37.2 mmol, 2.7 equiv.) and CuCl (1.08 g, 10.4 mmol, 80 mol%). The solution was placed under an environment of vacuum/ O_2 three times, then left to stir under 1 atm of O_2. After 6 h the solution was quenched upon addition of a 10% wt./ wt. citric $acid_{(aq)}$ solution (20 mL) and the reaction was left to stir for a further 15 mins. The organic layer was then separated and extracted with $CHCl_3$ (2 x 20 mL), dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on SiO_2 (EtOAc) to give **6.82** (1.17 g, 25%) as an orange oil.

Data for 6.82:

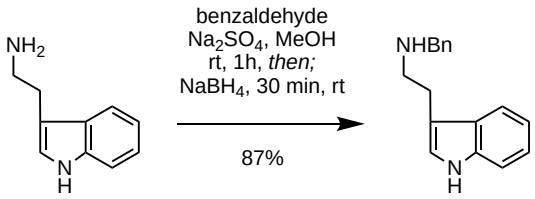
R_f: 0.20 (EtOAc).

FTIR (neat): 3344, 2924, 1614, 1547, 1450, 1208, 1160, 1065 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.47 (br s, 1H), 8.75 (d, *J* = 8.5 Hz, 1H), 8.48 (br s, 1H), 7.86 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 6.96 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 1H), 6.58 (td, *J* = 7.4, 1.2 Hz, 1H), 6.49 (d, *J* = 7.9 Hz, 1H), 6.10 – 6.02 (m, 1H), 3.84 (br s, 1H), 3.58 (q, *J* = 5.9 Hz, 2H), 3.17 (t, *J* = 5.7 Hz, 2H), 2.84 (t, *J* = 7.1 Hz, 2H), 2.48 (t, *J* = 7.1 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.5, 201.3, 172.9, 171.3, 159.9, 144.4, 135.6, 131.0, 129.9, 127.6, 125.2, 123.3, 121.8, 118.8, 116.0, 39.5, 36.4, 34.4, 27.0 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{22}O_3N_3$ 340.1656; found 340.1661.



6.88 **6.92**

Following a modified procedure from Martin and Vanderwal *et al.*,[21] a solution of tryptamine (**6.88**) (2.88 g, 18.0 mmol, 1.0 equiv.) was dissolved MeOH (20 mL) at room temperature and benzaldehyde (1.83 mL, 18.0 mmol, 1.0 equiv.) and Na_2SO_4 (1.37 g, 36.0 mmol, 2.0 equiv.) were added. The solution was left to stir under N_2 for 1 h, then cooled to 0 °C and $NaBH_4$ (680 mg, 18.0 mmol, 1.0 equiv.) added portion-wise. After 30 min distilled H_2O (20 mL) was added to quench the reaction, and the product was extracted with $CHCl_3$ (3 x 20 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo* to give **6.92** (3.92 g, 87%) as an orange oil. Data for **6.92** matched that previously reported in the literature.[21]

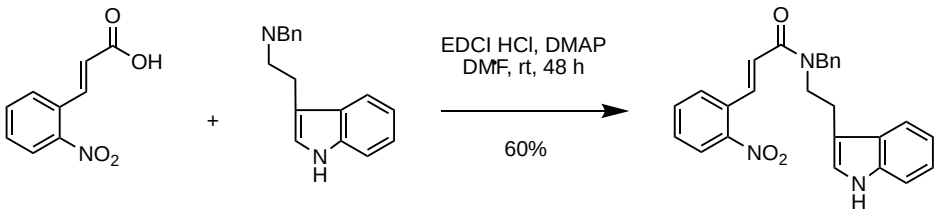
Data for 6.92:

FTIR (neat): 3413, 2842, 1730, 1454, 1247, 1094, 1044, 697 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (br s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.40 – 7.36 (m, 1H), 7.33 – 7.28 (m, 4H), 7.26 – 7.18 (m, 2H), 7.14 – 7.11 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 2.2 Hz, 1H), 3.84 (s, 2H), 3.05 – 2.99 (m, 4H), 1.54 (br s, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 140.0, 136.4, 128.4, 128.2, 127.4, 127.0, 122.2, 121.8, 119.1, 118.8, 113.4, 111.3, 53.8, 49.3, 25.6 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{19}N_2$ 251.1543; found 251.1547.



6.77: *E*-2-nitro-cinnamic acid **6.92** **6.93**

To a solution of **6.77** (6.06 g, 31.0 mmol, 1.0 equiv.) and **6.92** (7.84 g, 31.0 mol, 1.0 equiv.) in DMF (500 mL) was added DMAP (4.2 g, 34.0 mmol, 1.1 equiv.) and EDCI·HCl (6.6 g, 34.0 mmol, 1.1 equiv.) and the reaction was left to stir at room temperature. After 48 h the reaction was quenched with sat. brine (500 mL) and extracted with EtOAc (3 x 500 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on SiO_2 (7:3 hexanes/ EtOAc) to give **6.93** (17.7 g, 60%) as a yellow solid.

Data for 6.93:

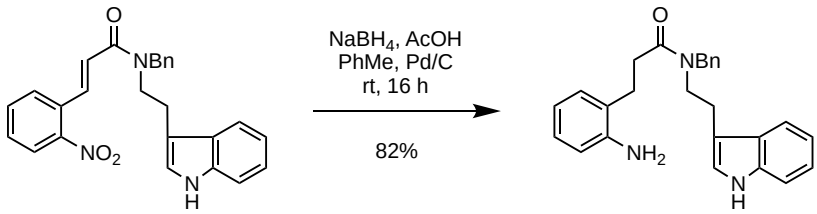
R_f: 0.70 (1:1 hexanes/ EtOAc).

FTIR (neat): 3280, 1619, 1495, 1452, 1230, 1018 cm^{-1}.

^{1}H NMR (500 MHz, d_6-DMSO, 1:0.4 *mixture of rotamers*): δ 10.78 (br s, 1H), 10.75 (br s, 0.4H), 7.98 (d, *J* = 8.1 Hz, 0.4H), 7.93 – 7.89 (m, 1H), 7.86 – 7.82 (m, 0.8H), 7.80 (s, 0.4H), 7.68 (t, *J* = 7.8 Hz, 0.4H), 7.57 (t, *J* = 7.8 Hz, 0.4H), 7.54 – 7.58 (m, 3H), 7.34 – 7.26 (m, 4.6H), 7.25 – 7.15 (m, 3.4H), 7.09 (s, 0.4H), 7.05 – 7.00 (m, 2.3H), 6.97 – 6.91 (t, 1.4H), 6.81 – 6.77 (m, 1H), 6.52 (d, 1H), 4.79 (s, 0.8H) 4.65(s, 2H), 3.66 (t, *J* = 6.8 Hz, 2H), 3.56 (t, *J* = 6.8 Hz, 2H), 2.85 – 2.86 (m, 2.8H) ppm.

^{13}C NMR (125 MHz, d_6-DMSO, 1:0.4 *mixture of rotamers*): δ 165.0, 165.0, 148.2, 138.2, 136.3, 136.3, 136.2, 135.0, 133.6, 133.5, 130.4, 130.0, 129.8, 129.2, 128.7, 128.6, 128.5, 128.0, 127.4, 127.2, 127.0, 126.9, 124.5, 124.4, 123.9, 123.4, 123.1, 122.7, 121.1, 121.0, 118.6, 118.4, 118.3, 118.0, 111.6, 111.4, 110.5, 50.8, 48.1, 47.4, 47.2, 24.2, 23.3 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{26}H_{24}O_3N_3$ 426.1812; found 426.1816.



6.93 **6.94**

To a solution of amide **6.93** (7.74 g, 18.0 mmol, 1.0 equiv.) in PhMe (500 mL) was added AcOH (3 mL), Pd/C (1.24 g, 0.90 mmol, 5% wt./ wt., 5 mol%) and $NaBH_4$ (2.40 g, 60.0 mmol, 3.5 equiv.). The solution was then stirred at room temperature for 16 h, then filtered through celite^{TM} (CH_2Cl_2) and product extracted with CH_2Cl_2 (3 x 500 mL). The combined organic extracts were then dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (7:3 hexanes/ EtOAc) to give **6.94** (5.96 g, 82%) as a yellow solid.

Data for 6.94:

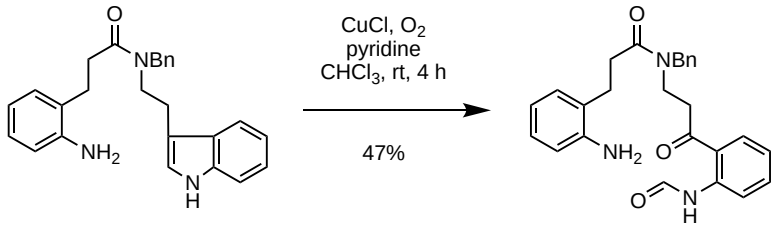
R_f: 0.60 (1:1 hexanes/ EtOAc).

FTIR (neat): 3245, 1687, 1630, 1580, 1450, 1296, 1196, 977 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, *1:1 mixture of rotamers*): δ 8.32 (s, 1H), 8.24 (s, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.42 – 7.22 (m, 9H), 7.26 – 7.03 (m, 10H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.91 – 6.86 (m, 2H), 6.83 (s, 1H), 6.78 – 6.63 (m, 4H), 4.66 (s, 2H), 4.35 (s, 2H), 3.96 – 3.59 (br s, 4H), 3.70 (t, *J* = 7.6 Hz, 2H), 3.49 (t, *J* = 7.2 Hz, 2H), 3.03 (t, *J* = 7.5 Hz, 2H), 2.94 (dt, *J* = 13.9, 7.2 Hz, 4H), 2.84 (t, *J* = 7.2 Hz, 2H), 2.70 (t, *J* = 7.2 Hz, 2H), 2.57 (t, *J* = 7.2 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, *1: 1 mixture of rotamers*): δ 173.4, 144.9, 144.8, 137.7, 137.0, 136.3, 136.3, 130.0, 129.9, 128.9, 128.7, 128.0, 127.6, 127.5, 127.4, 127.4, 127.3, 127.1, 126.4, 125.9, 125.9, 122.5, 122.3, 122.2, 122.0, 119.6, 119.4, 118.8, 118.7, 118.4, 116.0, 116.0, 113.1, 112.0, 111.6, 111.3, 51.9, 48.7, 47.9, 47.7, 33.2, 32.7, 26.8, 26.7, 24.5, 23.6 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{26}H_{28}N_3O$ 398.2227; found 398.2227.



6.94 **6.91**

To a solution of **6.94** (86 mg, 0.20 mmol, 1.0 equiv.) in $CHCl_3$ (5 mL) at room temperature was added pyridine (0.20 mL, 2.48 mmol, 12.4 equiv.) and CuCl (20 mg, 0.170 mmol, 80 mol%). The solution was placed under an environment of vacuum/ O_2 three times, then left to stir under 1 atm of O_2. After 4 h the solution was quenched upon addition of a 10% wt./ wt. citric $acid_{(aq)}$ solution (20 mL) and reaction was left to stir further for 15 mins. The organic layer was then separated and extracted with $CHCl_3$ (2 x 10 mL), dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on SiO_2 (neat EtOAc) to give **6.91** (42.0 mg, 47%) as an orange oil.

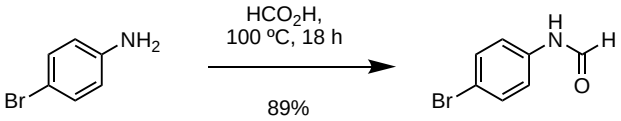
Partial Data for 6.91:

R_f: 0.40 (1:1 hexanes/ EtOAc).

FTIR (neat): 3245, 2913, 1687, 1631, 1580, 1512, 1496, 1450, 1296, 1196, 977 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.41 (br s, 1H), 11.28 (br s, 0.5H), 8.70 – 8.64 (m, 1H), 8.41 (s, 1H), 7.87 (d, *J* = 7.5 Hz, 1H), 7.52 – 7.46 (m, 2H), 7.26 – 6.95 (m, 10 H), 6.90 (d, *J* = 7.5 Hz, 1H), 6.67 – 6.55 (m, 3H), 4.57 (s, 1H), 4.50 (s, 2H), 3.98 (br s, 2H), 3.66 (t, *J* = 6.8 Hz, 2H), 3.60 (t, *J* = 7.3 Hz, 1H), 3.26 (t, *J* = 6.8 Hz, 2H), 2.97 – 2.89 (m, 2H), 2.83 (t, *J* = 7.2 Hz, 2H), 2.75 (t, *J* = 6.8 Hz, 1H), 2.63 (t, *J* = 7.2 Hz) ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{26}H_{28}O_3N_3$ 452.1950; found 452.1986.



6.105: 4-bromoaniline **6.104**

Following a modified literature procedure from Hosseini-Sarvari and Sharghi *et al*.,[25] 4-bromoaniline (**6.105**) (10.0 g, 58.1 mmol) was refluxed in formic acid (30 mL). After 18 h, EtOAc (100 mL) was added followed by sat. $NaHCO_{3(aq)}$ (100 mL) and the organic layer separated. The aqueous layers were further extracted with EtOAc (2 x 100 mL) then the combined organic layers were washed with sat. brine (2 x 100 mL), dried with $MgSO_4$, filtered and concentrated to give **6.104** (10.3 g, 89%) as a brown solid which was used directly without further purification. Data for **6.104** matched that previously reported in the literature.[25]

Data for 6.104:

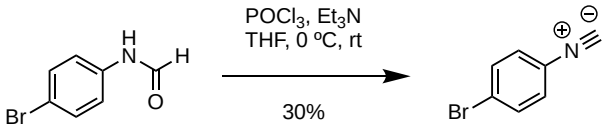
R_f: 0.10 (CH_2Cl_2).

FTIR (neat): 3262, 1685, 1489, 1395, 1306, 821 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$, *1.5:1 mixture of cis/ trans*): δ 8.46 (d, *J* = 11.3 Hz, 1H), 8.20 (s, 1.5H), 7.43 (br s, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.26 – 7.24 (m, 5H), 7.07 – 7.06 (m, 5H), 6.95 (br s, 1.5H), 6.77 (d, *J* = 8.8 Hz, 2H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$, *1.5:1 mixture of cis/ trans*): δ 162.0, 158.8, 135.98, 135.8, 133.0, 132.3, 121.6, 120.6, 118.5, 117.7 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for C_7H_7OBrN 199.9706; found 199.9713.



6.104 **6.103**

Following a modified literature procedure from Hosseini-Sarvari and Sharghi *et al*.,[25] Et_3N (24 mL, 0.170 mol, 3.3 equiv.) and $POCl_3$ (5.3 mL, 57.2 mmol, 1.1 equiv.) were added dropwise to a stirred solution of **6.104** (10.3 g, 52.0 mmol, 1.0 equiv.) in dry THF (30 mL) at 0 °C. After 2, h the reaction was quenched with distilled water (30 mL) and product extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with sat. brine (30 mL), dried with $MgSO_4$, filtered and concentrated. Trituration (9:1 hexanes/ EtOAc) then gave **6.103** (2.83 g, 30%) as a yellow solid. Data for **6.103** matched that previously reported in the literature.[25]

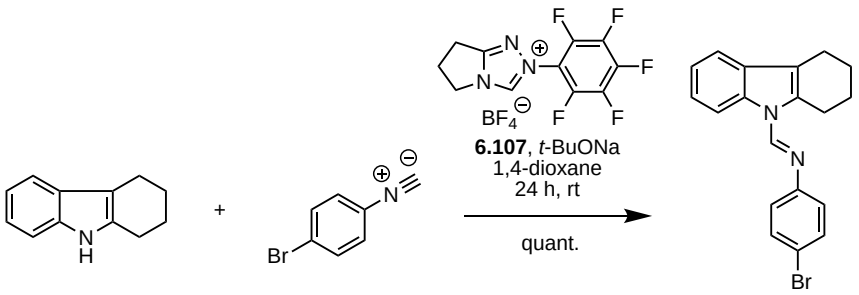
Partial Data for 6.103:

R_f: 0.40 (9:1 hexanes/ EtOAc).

FTIR (neat): 3087, 2125, 1670, 1481, 1402, 1070, 822 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.57 – 7.51 (d, *J* = 8.5 Hz, 2H), 7.27 – 7.24 (d, *J* = 8.5 Hz, 2H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 135.4, 134.8, 130.5, 126.1, 124.1 ppm.



6.102 **6.103** **6.106**

Following a modified literature procedure from Kim and Hong,[24] 1,2,3,4-tetrahydrocarbazole (**6.102**) (450 mg, 2.62 mmol, 1.0 equiv.), *t*-BuONa (48 mg, 0.79 mmol, 0.3 equiv.), and the triazolium NHC salt **6.107** (126 mg, 0.52 mmol, 0.20 equiv.) were dissolved in 1,4-dioxane (5 mL) at room temperature. **6.103** (642 mg, 5.24 mmol, 2.0 equiv.) was then added after 5 min, and after 24 h the solution was concentrated and residue purified by flash column chromatography on SiO_2 (9:1 hexanes/ EtOAc +1% Et_3N) to afford **6.106** (92 mg, quant.) as a yellow solid. Data for **6.106** matched that previously reported in the literature.[24]

Data for 6.106:

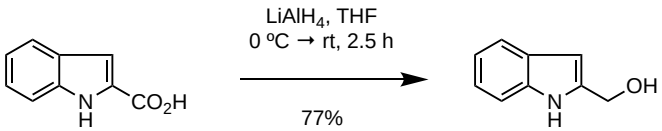
R_f: 0.50 (9:1 hexanes/ Et_2O).

FTIR (neat): 2843, 2122, 1641, 1456, 1208, 1068, 824 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (d, *J* = 8.1 Hz, 1H), 8.48 (s, 1H), 7.51 – 7.41 (m, 3H), 7.32 – 7.24 (m, 2H), 7.04 (d, *J* = 8.1 Hz, 1H), 2.88 (t, *J* = 6.1 Hz, 2H), 2.71 (t, *J* = 6.1, 2H), 2.04 – 1.94 (m, 2H), 1.94 – 1.84 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 149.7, 143.9, 135.4, 134.4, 132.3, 130.2, 123.6, 123.0, 122.9, 117.9, 117.8, 116.5, 115.3, 23.1, 22.8, 22.6, 21.0 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{18}BrN_2$ 353.0649; found 353.0669.



6.113: indole-2-carboxylic acid **6.129**

Following a modified procedure from Nowacki and co-workers,[26] a solution of indole-2-carboxylic acid (**6.113**) (4.73 g, 29.3 mmol, 1.0 equiv) was dissolved in dry THF (40 mL) and $LiAlH_4$ (19.0 mL, 38.1 mmol, 2.0 M in THF, 1.3 equiv.) added at 0 °C. The reaction was left to stir for 2.5 h, then quenched with a dropwise addition of distilled water (1.2 mL), 15% $NaOH_{(aq)}$ (1.2 mL) and distilled water (1.2 mL). The reaction was left to stir further for 30 min then filtered, and filtrate washed with Et_2O (4 x 25 mL). The filtrate was then dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* flash column chromatography on SiO_2 (4:1 → 2:1 hexanes/ EtOAc, gradient elution) then gave **6.129** (3.33g, 77%) as a white solid. Data for **6.129** matched that previously reported in the literature.[26]

Data for 6.129:

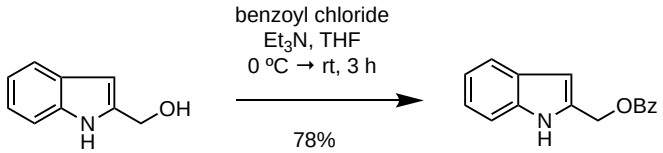
R_f: 0.10 (4:1 hexanes/ EtOAc).

FTIR (neat): 3375, 1618, 1488, 1453, 1416, 1339, 1289, 1230, 1137, 1058, 928 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (br s, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.15 (td, *J* = 7.9 1.3 Hz, 1H), 7.09 (td, *J* = 7.9, 1.3 Hz, 1H), 6.32 (s, 1H), 4.62 (s, 2H), 2.60 (s, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 137.6, 136.5, 128.1, 122.3, 120.7, 120.1, 111.2, 100.7, 58.6 ppm.

HRMS (ESI) m/z: $[M-H]^-$ Calcd for C_9H_8NO 146.0602; found 146.0611.



6.129 **6.114**

Following a modified procedure from Nowacki *et al*.,[26] **6.129** (3.29 g, 22.4 mmol, 1.0 equiv.) was dissolved in THF (80 mL), Et_3N (3.73 mL, 26.8 mmol, 1.2 equiv.) and benzoyl chloride (3.11 mL, 26.8 mmol, 1.2 equiv.) added at 0 °C. The solution was then left to warm to room temperature and the reaction was stirred for 3 h. A sat. $NaHCO_{3(aq)}$ (80 mL) solution was then used to quench the reaction and product extracted with EtOAc (5 x 50 mL). The combined organic layers were then washed with sat. brine (200 mL) and the organic layer dried with $MgSO_4$, filtered and concentrated *in vacuo* to give **6.114** (4.37 g, 78%) as a white solid which was used without further purification. Data for **6.114** matched that previously reported in the literature.[26]

Data for 6.114:

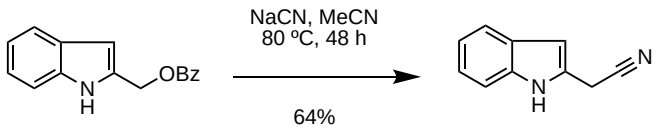
R_f: 0.45 (4:1 hexanes/ EtOAc).

FTIR (neat): 3350, 1704, 1453, 1273, 1097, 1097, 924 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.72 (br s, 1H), 8.07 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.64 – 7.53 (m, 2H), 7.46 – 7.42 (m, 2H), 7.37 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.20 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.13 – 7.07 (m, 1H), 6.62 (s, 1H), 5.49 (s, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.0, 136.8, 133.5, 133.2, 130.0, 129.8, 128.6, 127.7, 123.0, 121.1, 120.2, 111.3, 104.3, 60.4 ppm.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{13}O_2NNa$ 274.0838; found 274.0842.



6.114 **6.112**

Following a modified procedure from Nowacki *et al*.,[26] **6.114** (2.04 g, 8.11 mmol, 1.0 equiv.) was dissolved in MeCN (100 mL) and NaCN (790 mg, 16.2 mmol, 2.0 equiv.) was added at room temperature.[26] The suspension was then heated to 80 °C, left to stir for 48 h, cooled to room temperature, then quenched with sat. $NaHCO_{3(aq)}$ (100 mL). The product was extracted with EtOAc (3 x 100 mL), dried with $MgSO_4$, filtered and concentrated. Purification *via* flash column chromatography on SiO_2 (4:1 hexanes/ EtOAc) then gave **6.112** (812 mg, 64%) as a white solid. Data for **6.112** matched that previously reported in the literature.[26]

Data for 6.112:

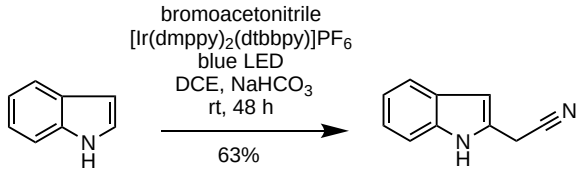
R_f: 0.20 (4:1 hexanes/ EtOAc).

FTIR (neat): 3392, 3052, 2255, 1453, 1299, 1007, 910 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (br s, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 7.1 Hz, 1H), 7.15 (t, *J* = 7.1 Hz, 1H), 6.48 (s, 1H), 3.88 (s, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 136.6, 128.1, 126.0, 122.8, 120.6, 120.5, 116.7, 111.1, 102.7, 17.5 ppm.

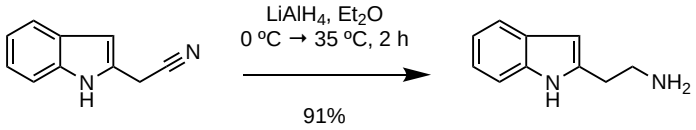
HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{10}H_9N_2$ 157.0760; found 157.0761.



6.115: indole

6.112

Following a modified procedure from O'Brien *et al*.,[27] indole (**6.115**) (1.95 g, 16.6 mmol, 2.0 equiv.), $NaHCO_3$ (1.40 g, 16.6 mmol, 2.0 equiv.), and $[Ir(dmppy)_2(dtbbpy)]PF_6$ (160 mg, 0.332 mmol, 0.02 mol%) was dissolved in DCE (4.2 mL). Bromoacetonitrile (0.58 mL, 8.3 mmol, 1.0 equiv.) was added at room temperature. N_2 was then bubbled through the solution for 5 min and the reaction was placed at a 5 cm distance while exposed to a 470 nm blue LED lamp at 0 °C. After 48 h, the reaction was concentrated and purified by flash column chromatography on SiO_2 (4:1 hexanes/ EtOAc) to afford **6.112** (821 mg, 63%) as a white solid. Data for **6.112** matched that previously obtained and previously reported in the literature.[27]



6.112 **6.116**

To a solution of **6.112** (106 mg, 0.68 mmol, 1.0 equiv.) in dry Et_2O (5 mL) was added dropwise $LiAlH_4$ (3.2 mL, 1.0 M in Et_2O, 3.2 mmol, 4.7 equiv.) at 0 °C. The solution was left to stir for 30 min, then warmed to room temperature and heated at reflux. After 2 h, the reaction was cooled to 0 °C and quenched upon a dropwise addition of distilled water (10 mL). The organic layer was extracted with Et_2O (3 x 10 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford **6.116** (100 mg, 91%) which was used directly without further purification. Data for **6.116** matched that previously reported in the literature.[29]

Data for 6.116:

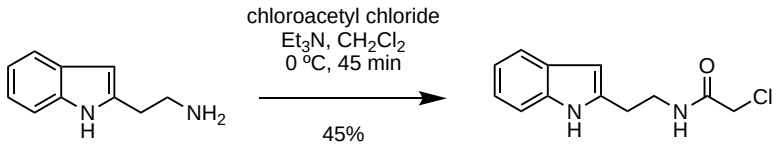
R_f: 0.05 (20:1 CH_2Cl_2/ MeOH).

FTIR (neat): 3394, 2868, 1583, 1456, 1288, 908, 744 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.05 (br s, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 7.1 Hz, 1H), 7.08 (t, *J* = 7.1 Hz, 1H),6.23 (s, 1H), 3.03 (t, *J* = 6.2 Hz, 2H), 2.84 (t, *J* = 6.2 Hz, 2H), 2.24 (br s, 2H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 138.2, 136.1, 128.7, 121.1, 119.9, 119.6, 110.7, 99.9, 41.6, 31.1 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{10}H_{13}N_2$ 161.1073; found 161.1073.



6.116 **6.96**

At 0 °C chloroacetyl chloride (0.38 mL, 4.60 mmol, 1.0 equiv.) was added dropwise to a stirring solution of **6.116** (735 mg, 4.80 mmol, 1.1 equiv.) and Et_3N (0.67 mL, 4.80 mmol, 1.1 equiv.) in CH_2Cl_2 (10 mL). The reaction was left to slowly warm to room temperature over 45 min, then quenched upon addition of distilled water (10 mL) and product extracted with CH_2Cl_2 (3 x 10 mL), dried with $MgSO_4$, filtered and concentrated to afford **6.96** (490 mg, 45%) as an orange oil which was used directly without further purification.

Data for 6.96:

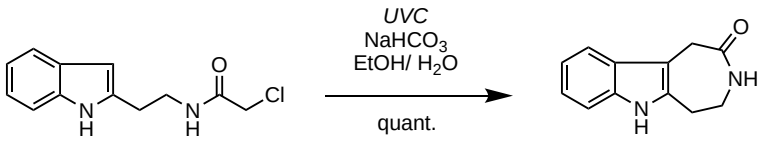
R_f: 0.20 (1:1 cyclohexane/ EtOAc).

FTIR (neat): 3393, 3299, 1655, 1533, 1412, 1288, 907 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (br s, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.79 (br s, 1H), 6.32 (s, 1H), 4.04 (s, 2H), 3.68 (q, *J* = 6.6 Hz, 2H), 3.03 (t, *J* = 6.8 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.6, 136.3, 135.8, 128.6, 121.5, 120.0, 119.8, 110.8, 100.5, 42.7, 39.4, 28.3 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{12}H_{14}OClN_2$ 237.0789; found 237.0367.



6.96 **6.97**

Following a modified procedure from Bhandari *et al*.,[22] **6.96** (42 mg, 0.177 mmol, 1.0 equiv.) was dissolved in EtOH (10 mL) and added to a solution of $NaHCO_3$ (24 mg, 0.230 mmol, 1.3 equiv.) in distilled water (10 mL). N_2 was then bubbled through the solution and the reaction was irradiated with a 254 nm *UV* LED lamp in a quartz vessel. After 16 h, the rection was concentrated and the crude residue purified *via* flash column chromatography on SiO_2 (20:1 MeOH/ $CHCl_3$) to afford **6.97** (35 mg, quant.) as a yellow solid. Data for **6.97** matched that previously reported in the literature.[22]

Data for 6.96:

R_f: 0.10 (10:1 hexanes/ EtOAc).

FTIR (neat): 3364, 1648, 1461, 1355, 749 cm^{-1}.

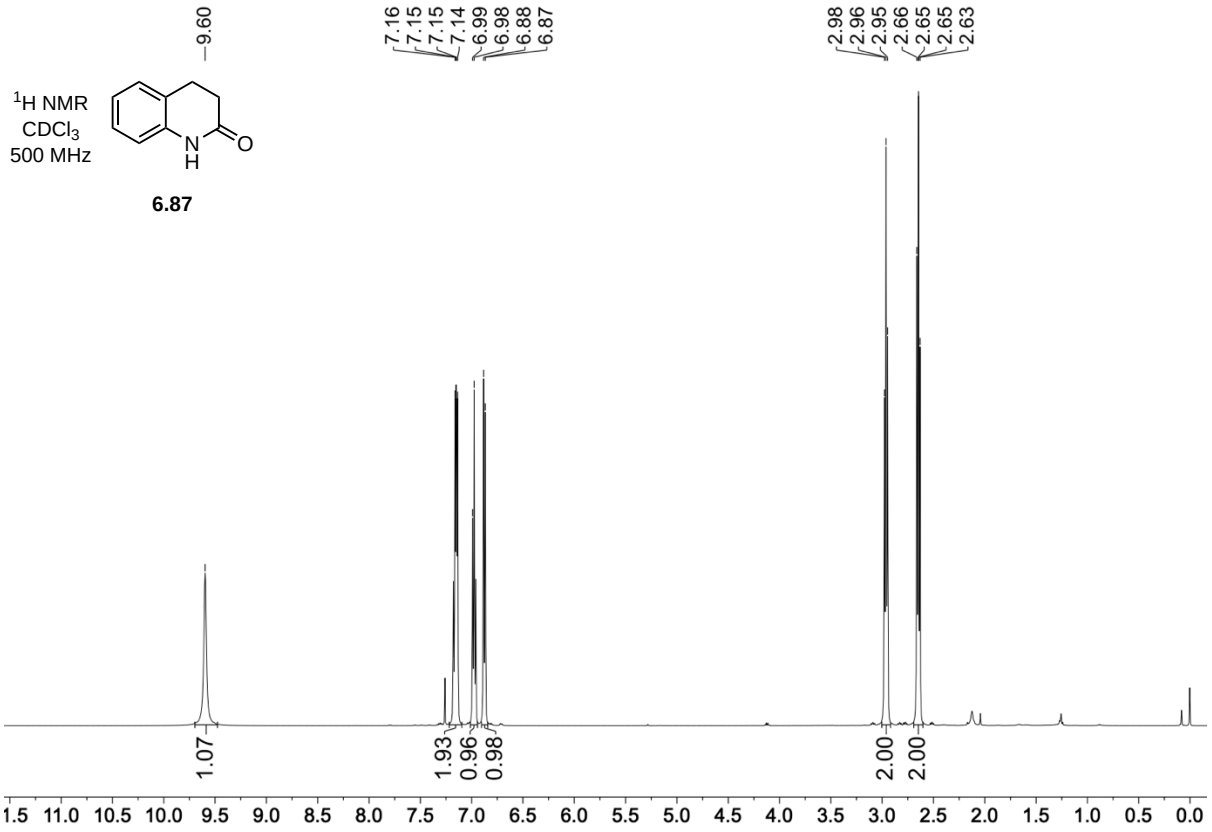
^{1}H NMR (600 MHz, d_4-MeOH): δ 7.43 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.04 (t, *J* = 8.0Hz, 1H), 7.00 (t, *J* = 8.0Hz, 1H), 3.71 – 3.65 (m, 2H), 3.32 – 3.30 (m, 2H), 2.98 – 2.96 (m, 2H) ppm.

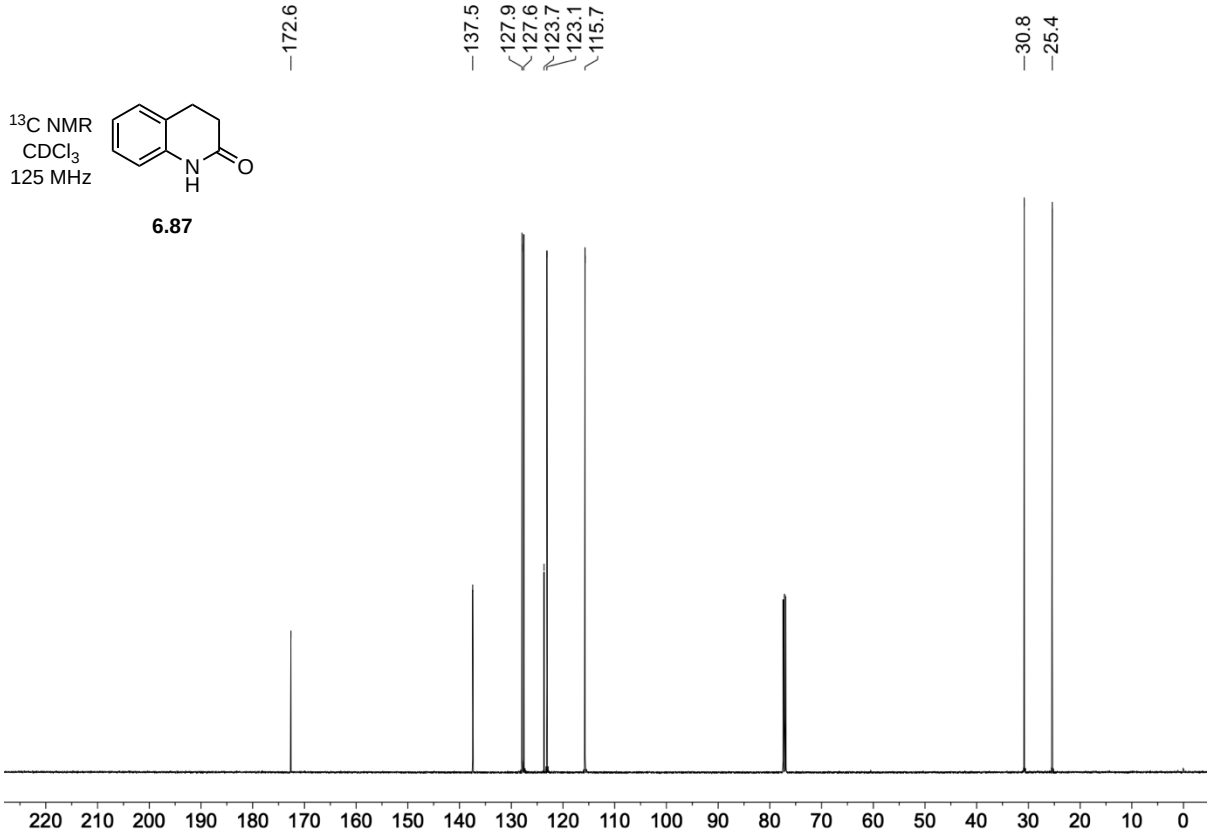
^{13}C NMR (150 MHz, d_4-MeOH): δ 179.2, 137.1, 134.3, 129.1, 122.1, 119.8, 116.0, 111.4, 102.9, 40.2, 31.8, 28.9 ppm.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{12}H_{12}ON_2$ 201.1028; found 201.1031.

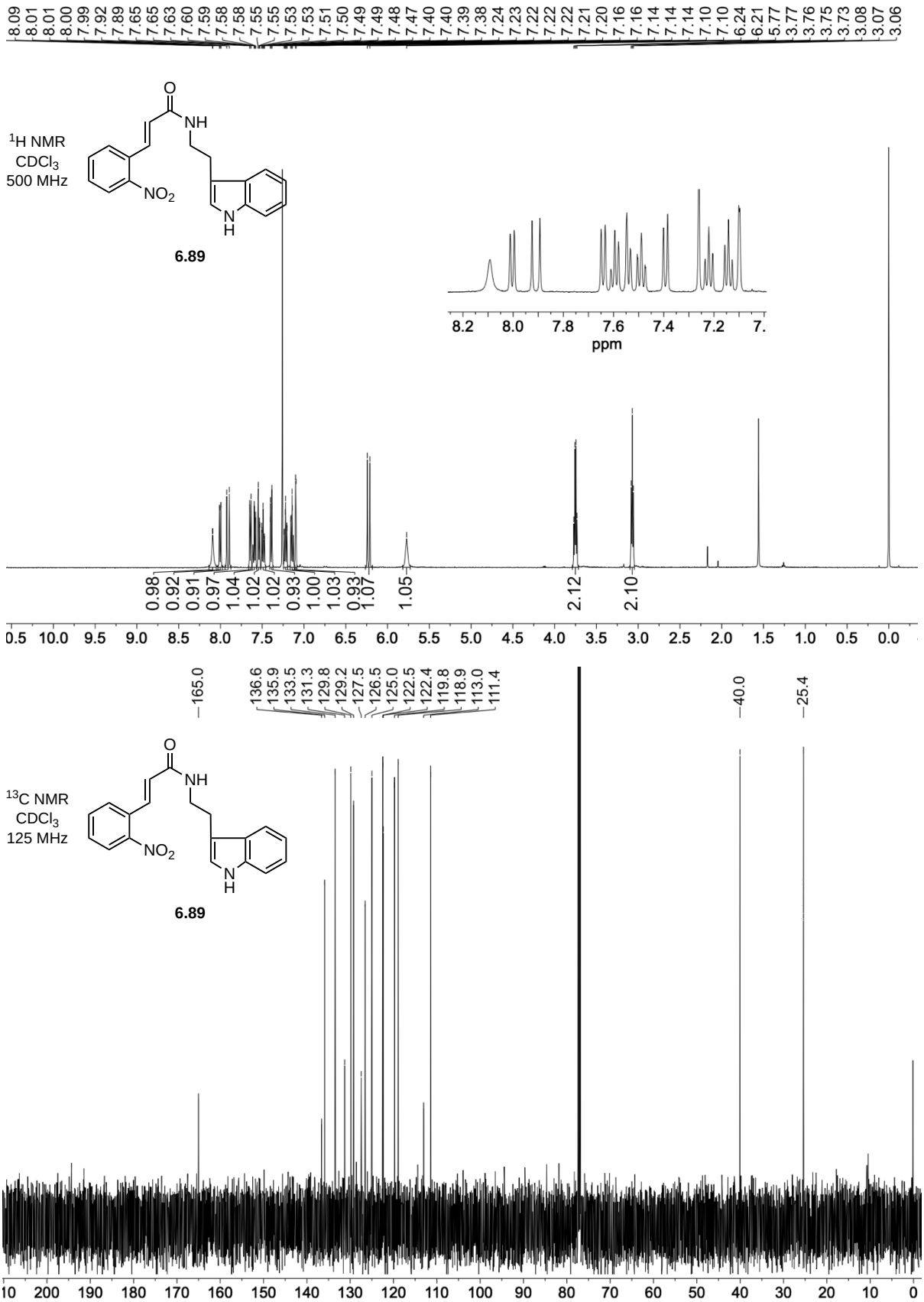
6.4.3 NMR Spectra

Data for 6.87

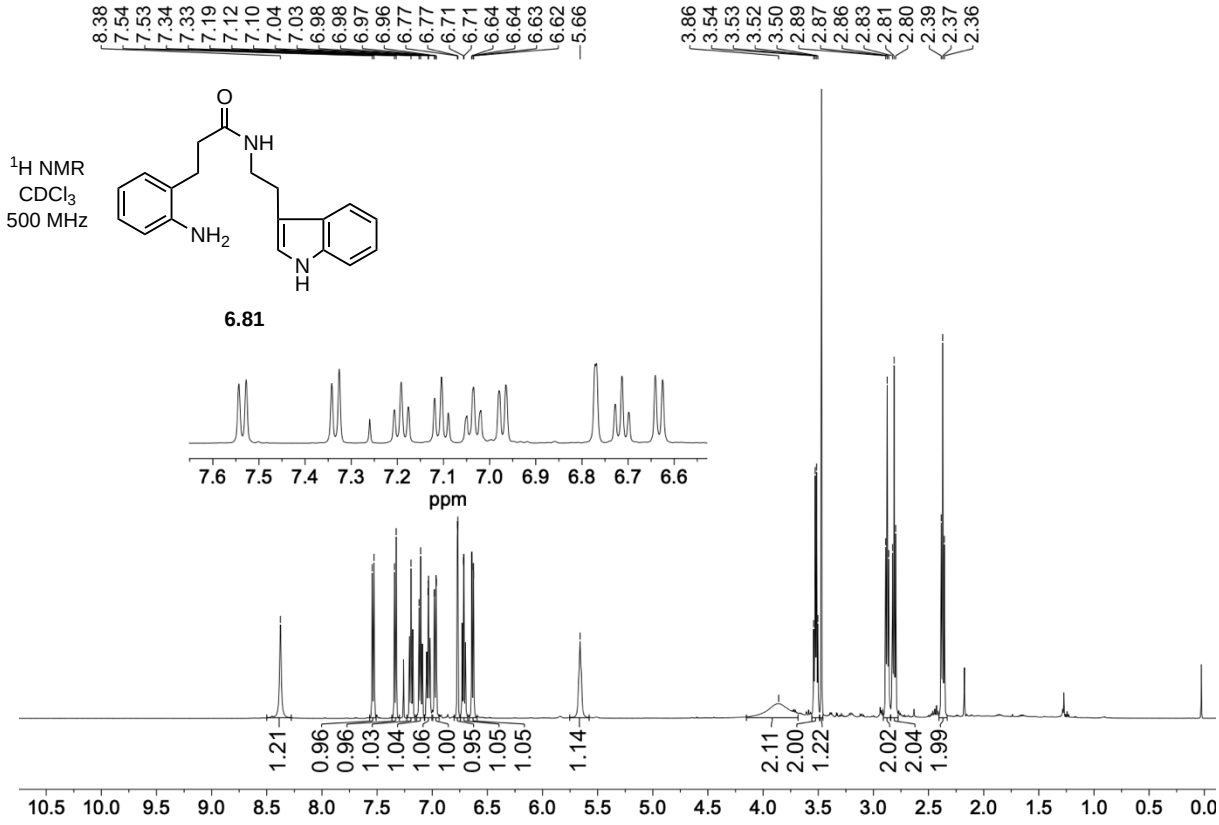


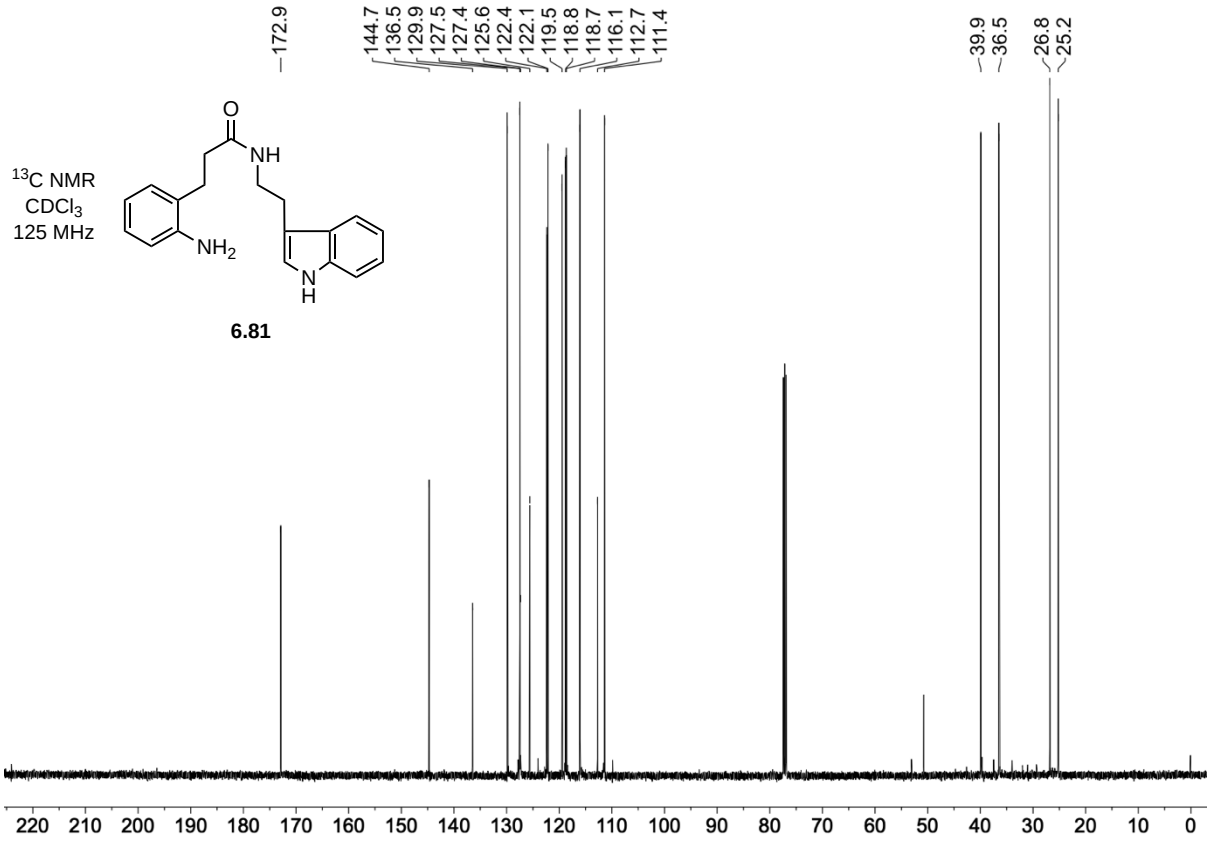


Data for 6.89

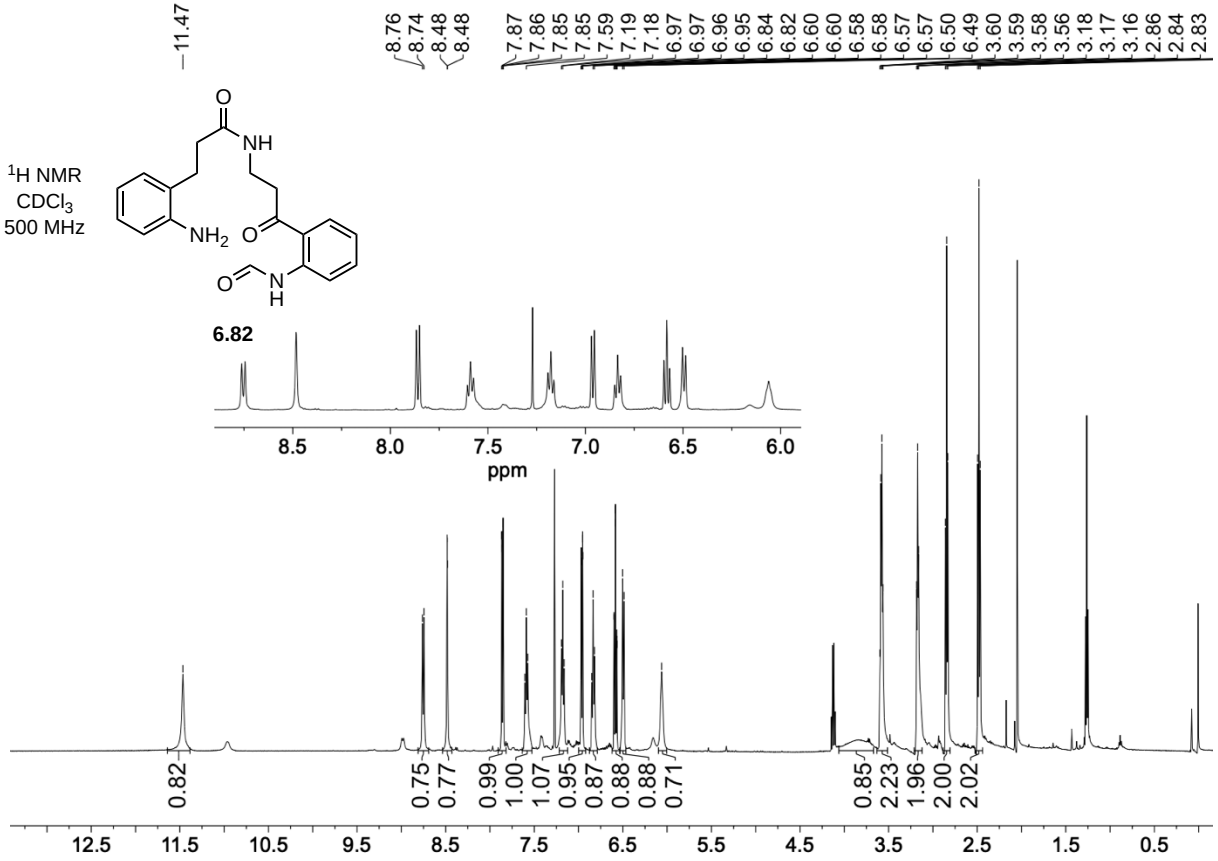

8.09 8.01 8.01 8.00 7.99 7.92 7.89 7.65 7.65 7.63 7.60 7.59 7.58 7.58 7.55 7.55 7.53 7.53 7.51 7.50 7.49 7.49 7.48 7.47 7.40 7.40 7.39 7.38 7.24 7.23 7.22 7.22 7.22 7.21 7.20 7.16 7.16 7.14 7.14 7.14 7.10 7.10 6.24 6.21 5.77 3.77 3.76 3.75 3.73 3.08 3.07 3.06
^{1}H NMR
$CDCl_3$
500 MHz
O
NH
NO_2
N
H
6.89
8.2 8.0 7.8 7.6 7.4 7.2 7.
ppm
0.98 0.92 0.91 0.97 1.04 1.02 1.02 0.93 1.00 1.03 0.93 1.07 1.05 2.12 2.10
0.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
165.0 136.6 135.9 133.5 131.3 129.8 129.2 127.5 126.5 125.0 122.5 122.4 119.8 118.9 113.0 111.4 40.0 25.4
^{13}C NMR
$CDCl_3$
125 MHz
O
NH
NO_2
N
H
6.89
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

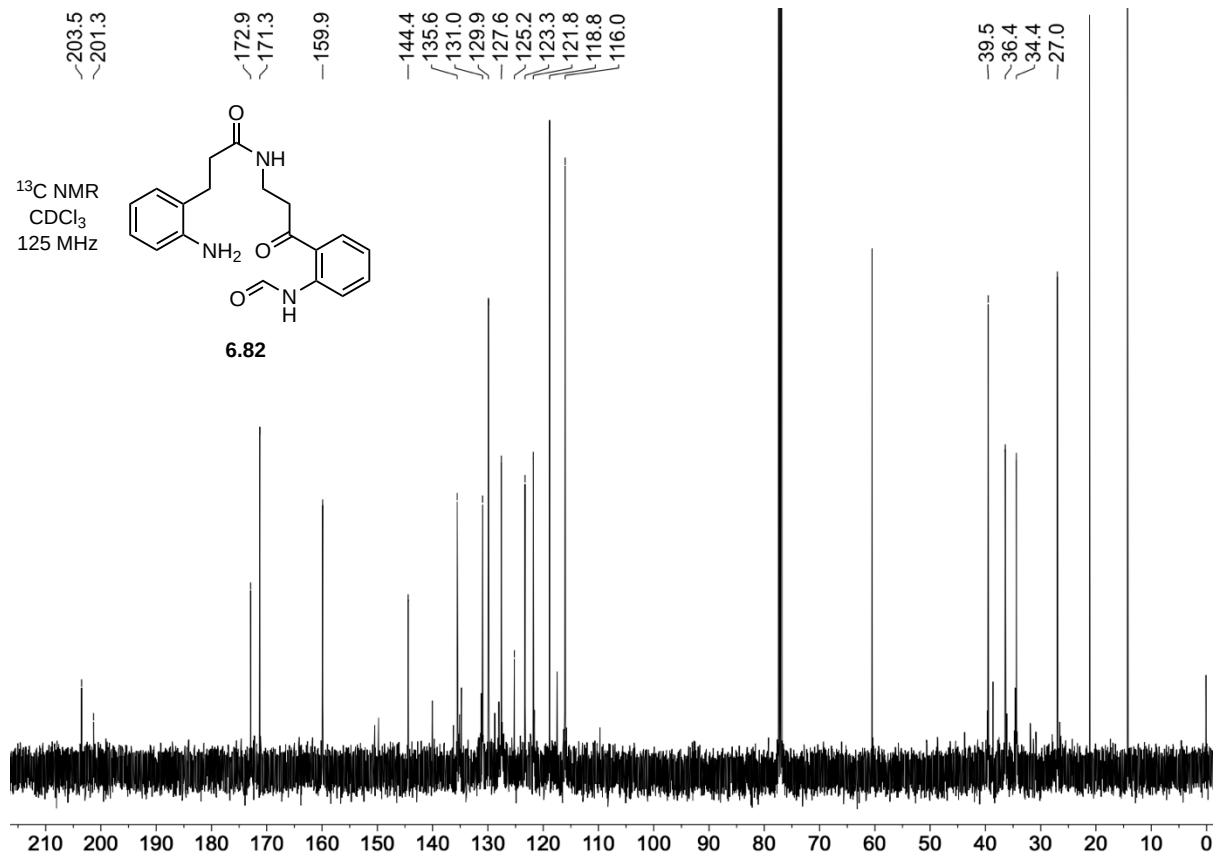
Data for 6.81


8.38
7.54
7.53
7.34
7.33
7.19
7.12
7.10
7.04
7.03
6.98
6.98
6.97
6.96
6.77
6.77
6.71
6.71
6.64
6.64
6.63
6.62
5.66
3.86
3.54
3.53
3.52
3.50
2.89
2.87
2.86
2.83
2.81
2.80
2.39
2.37
2.36
1H NMR
CDCl3
500 MHz
O
NH
NH2
N
H
6.81
7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6
ppm
1.21
0.96
0.96
1.03
1.04
1.06
1.00
0.95
1.05
1.05
1.14
2.11
2.00
1.22
2.02
2.04
1.99
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

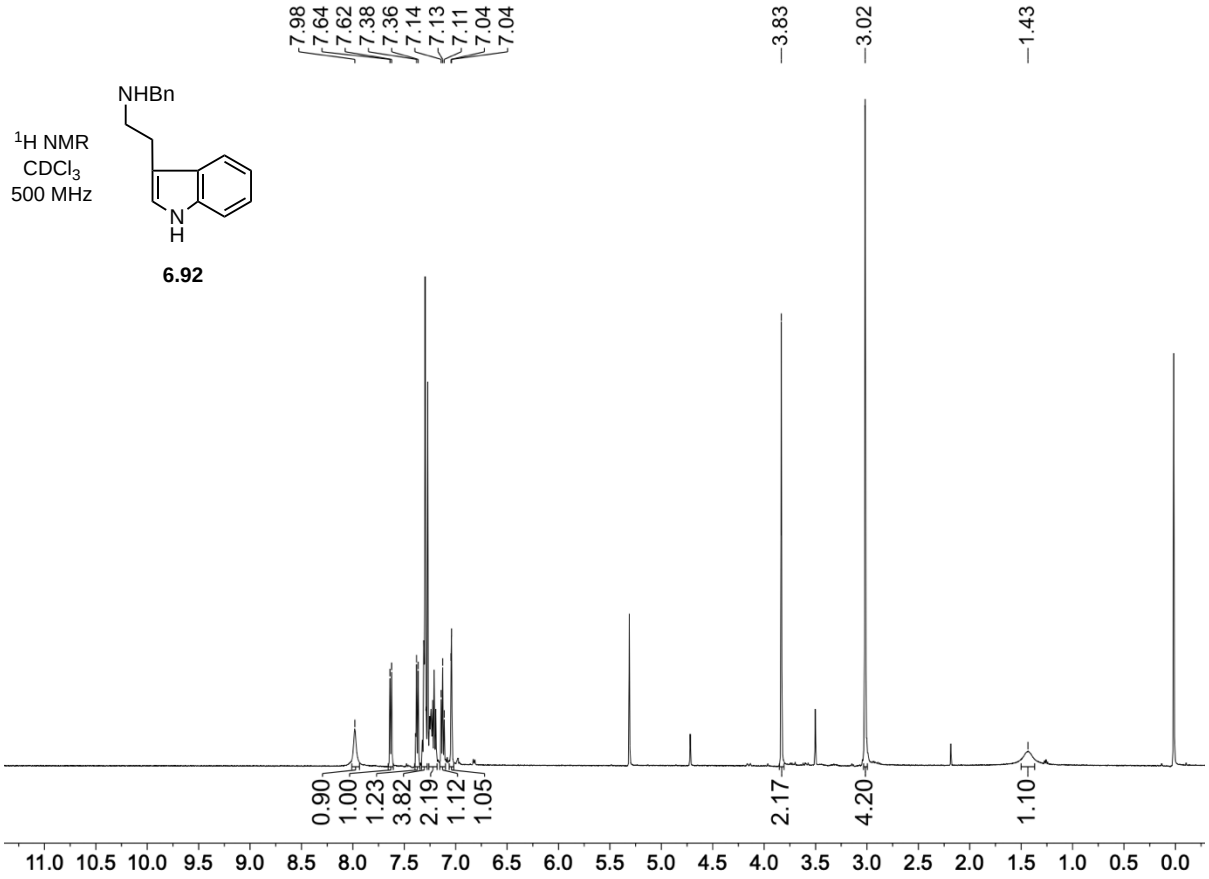

172.9
144.7
136.5
129.9
127.5
127.4
125.6
122.4
122.1
119.5
118.8
118.7
116.1
112.7
111.4
39.9
36.5
26.8
25.2
13C NMR
CDCl3
125 MHz
O
NH
NH2
N
H
6.81
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

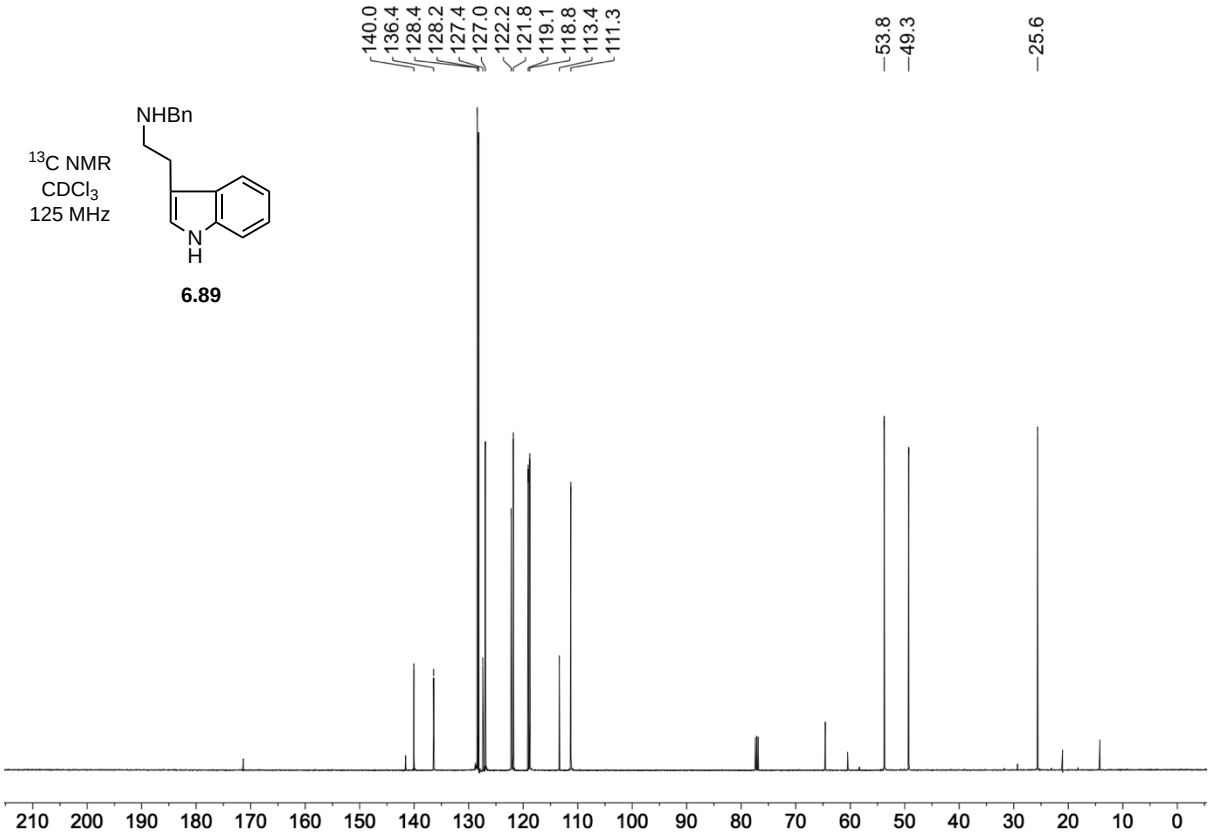
Data for 6.82


11.47
8.76
8.74
8.48
8.48
7.87
7.86
7.85
7.85
7.59
7.19
7.18
6.97
6.97
6.96
6.95
6.84
6.82
6.60
6.60
6.58
6.58
6.57
6.57
6.50
6.49
3.60
3.59
3.58
3.56
3.18
3.17
3.16
2.86
2.84
2.83
1H NMR
CDCl3
500 MHz
NH
NH2
O
N
H
6.82
8.5
8.0
7.5
7.0
6.5
6.0
ppm
0.82
0.75
0.77
0.99
1.00
1.07
0.95
0.87
0.88
0.88
0.71
0.85
2.23
1.96
2.00
2.02
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5

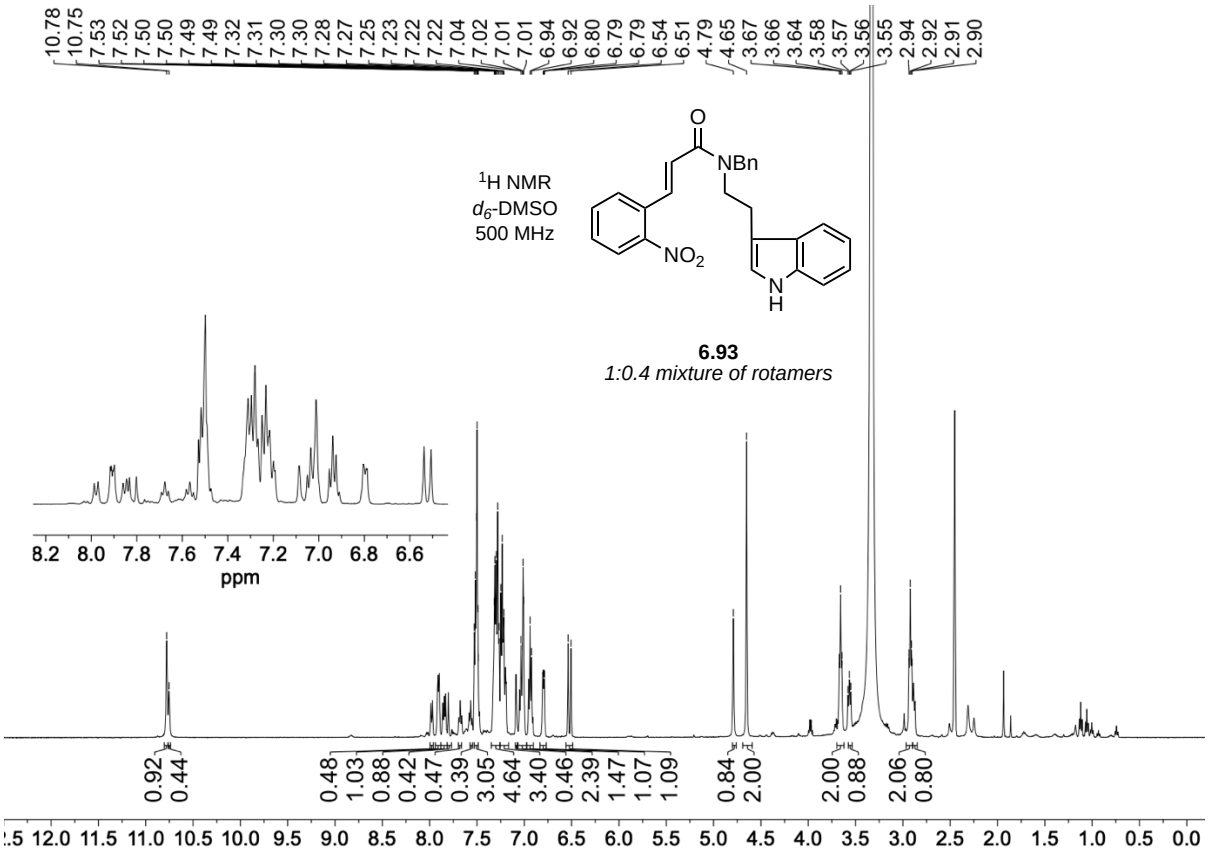

203.5
201.3
172.9
171.3
159.9
144.4
135.6
131.0
129.9
127.6
125.2
123.3
121.8
118.8
116.0
39.5
36.4
34.4
27.0
13C NMR
CDCl3
125 MHz
NH
NH2
O
N
H
6.82
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

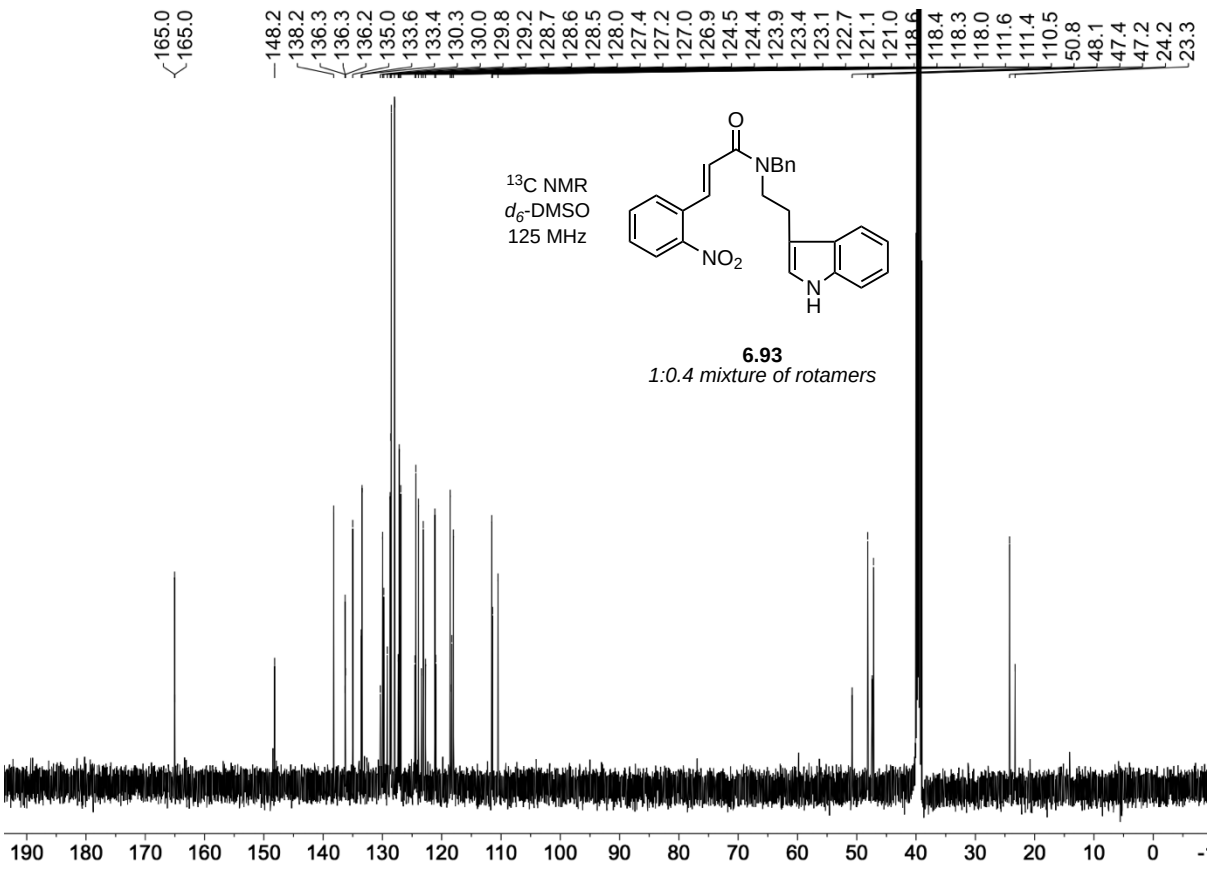
Data for 6.92

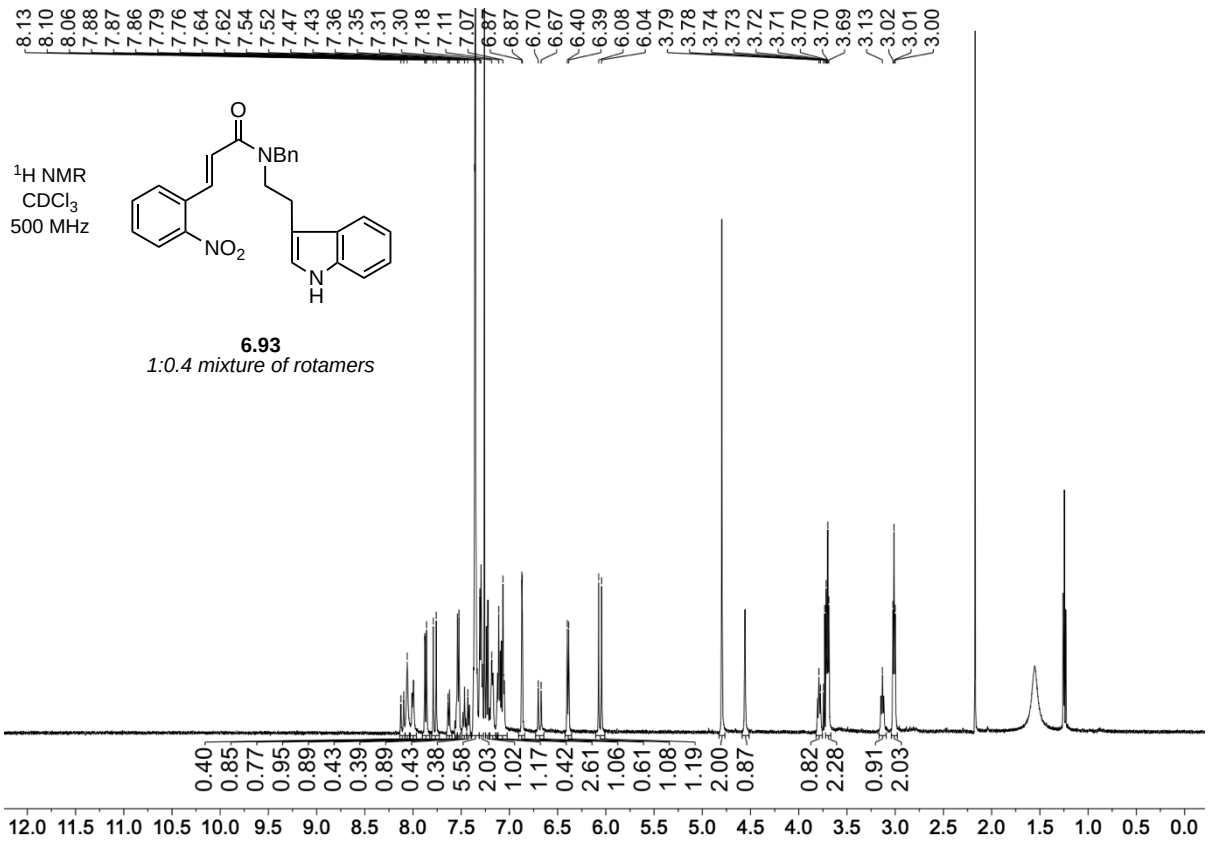

7.98
7.64
7.62
7.38
7.36
7.14
7.13
7.11
7.04
7.04
3.83
3.02
1.43
NHBn
1H NMR
CDCl3
500 MHz
N
H
6.92
0.90
1.00
1.23
3.82
2.19
1.12
1.05
2.17
4.20
1.10
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


140.0
136.4
128.4
128.2
127.4
127.0
122.2
121.8
119.1
118.8
113.4
111.3
53.8
49.3
25.6
NHBn
13C NMR
CDCl3
125 MHz
N
H
6.89
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Data for 6.93

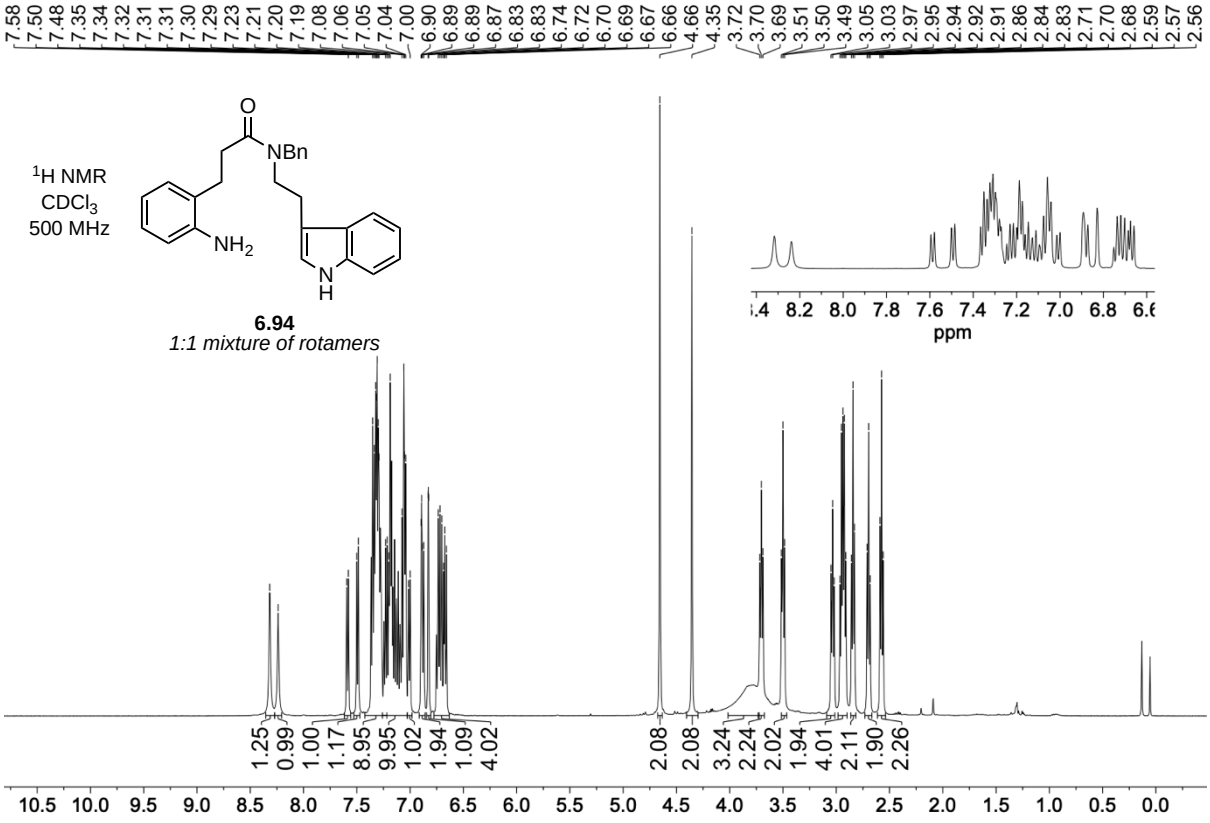

10.78 10.75 7.53 7.52 7.50 7.50 7.49 7.49 7.32 7.31 7.30 7.30 7.28 7.27 7.25 7.23 7.22 7.22 7.04 7.02 7.01 7.01 6.94 6.92 6.80 6.79 6.79 6.54 6.51 4.79 4.65 3.67 3.66 3.64 3.58 3.57 3.56 3.55 2.94 2.92 2.91 2.90
^{1}H NMR
d_6-DMSO
500 MHz
O
NBn
NO2
N
H
6.93
1:0.4 mixture of rotamers
8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6
ppm
0.92 0.44 0.48 1.03 0.88 0.42 0.47 0.39 3.05 4.64 3.40 0.46 2.39 1.47 1.07 1.09 0.84 2.00 2.00 0.88 2.06 0.80
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

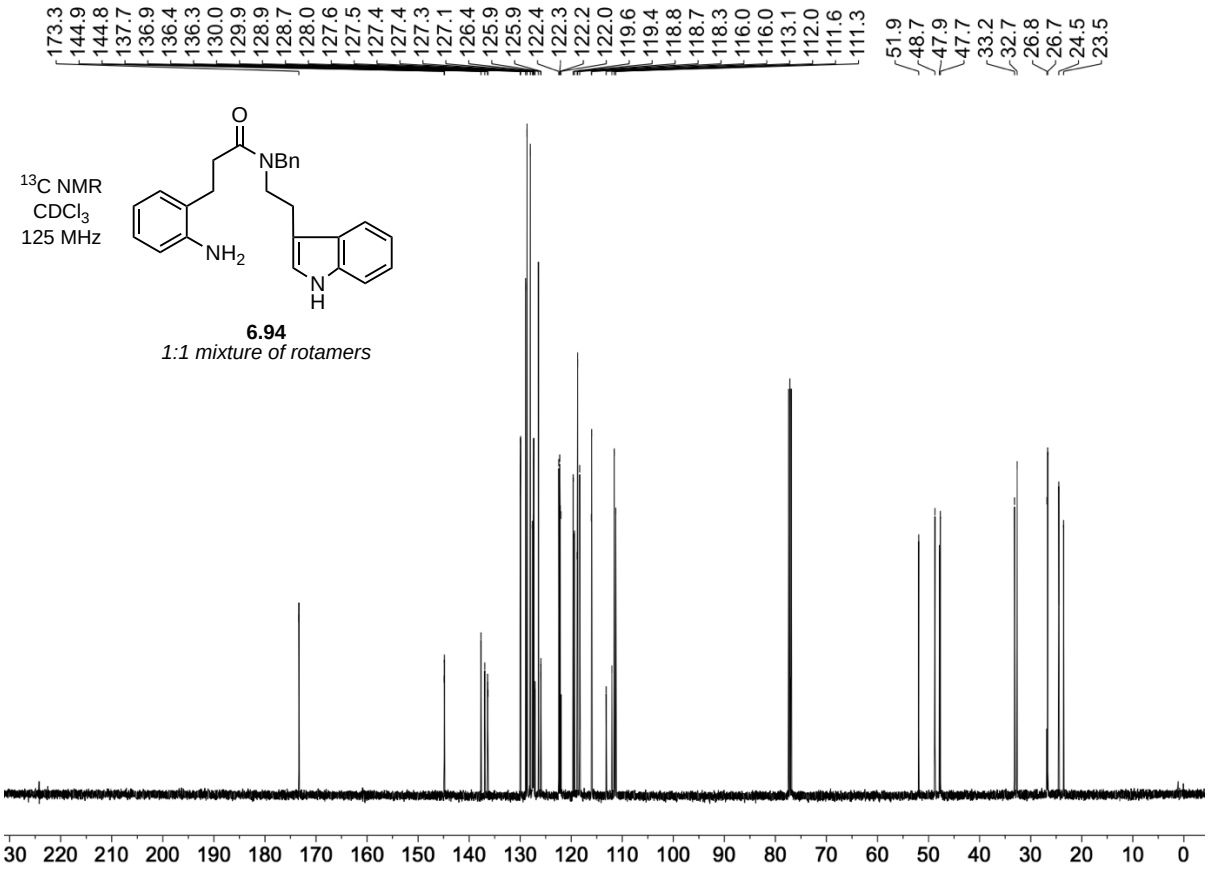

165.0 165.0 148.2 138.2 136.3 136.3 136.2 135.0 133.6 133.4 130.3 130.0 129.8 129.2 128.7 128.6 128.5 128.0 127.4 127.2 127.0 126.9 124.5 124.4 123.9 123.4 123.1 122.7 121.1 121.0 118.6 118.4 118.3 118.0 111.6 111.4 110.5 50.8 48.1 47.4 47.2 24.2 23.3
^{13}C NMR
d_6-DMSO
125 MHz
O
NBn
NO2
N
H
6.93
1:0.4 mixture of rotamers
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0



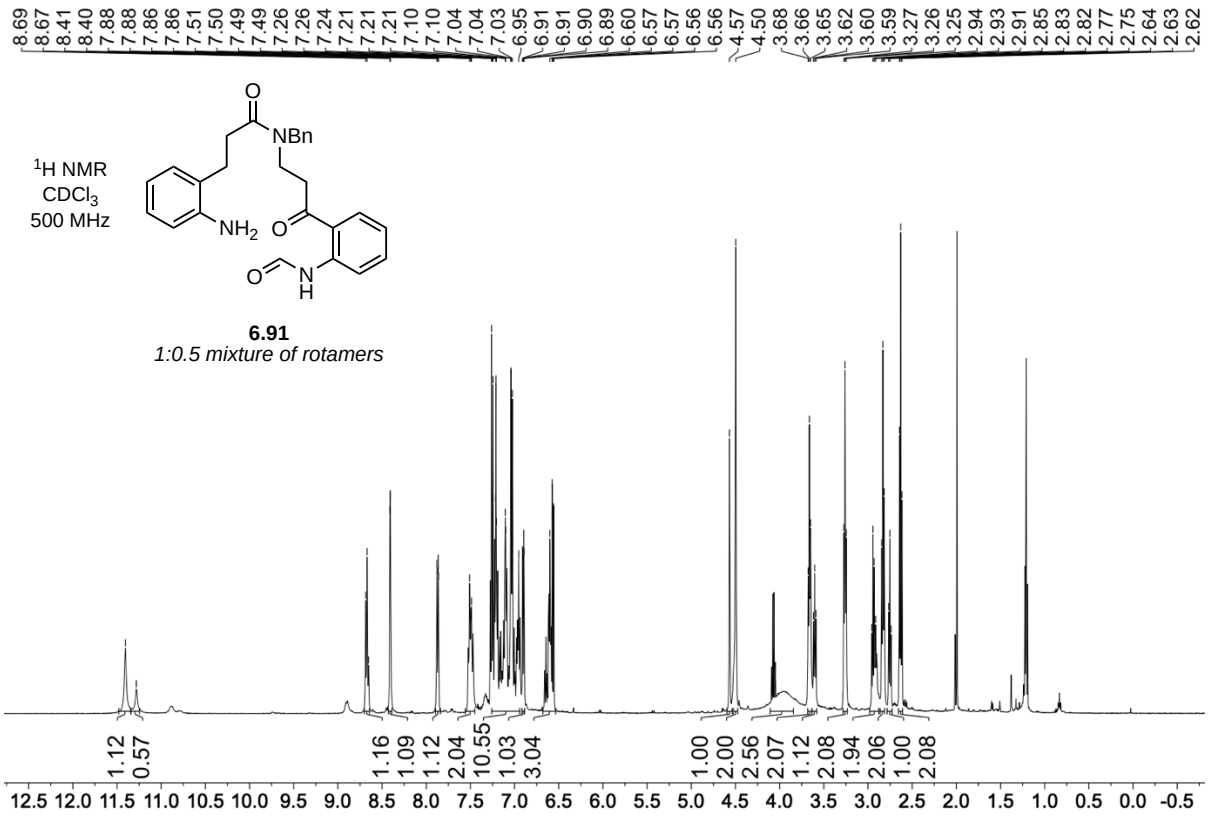
6.93
1:0.4 mixture of rotamers

Data for 6.94

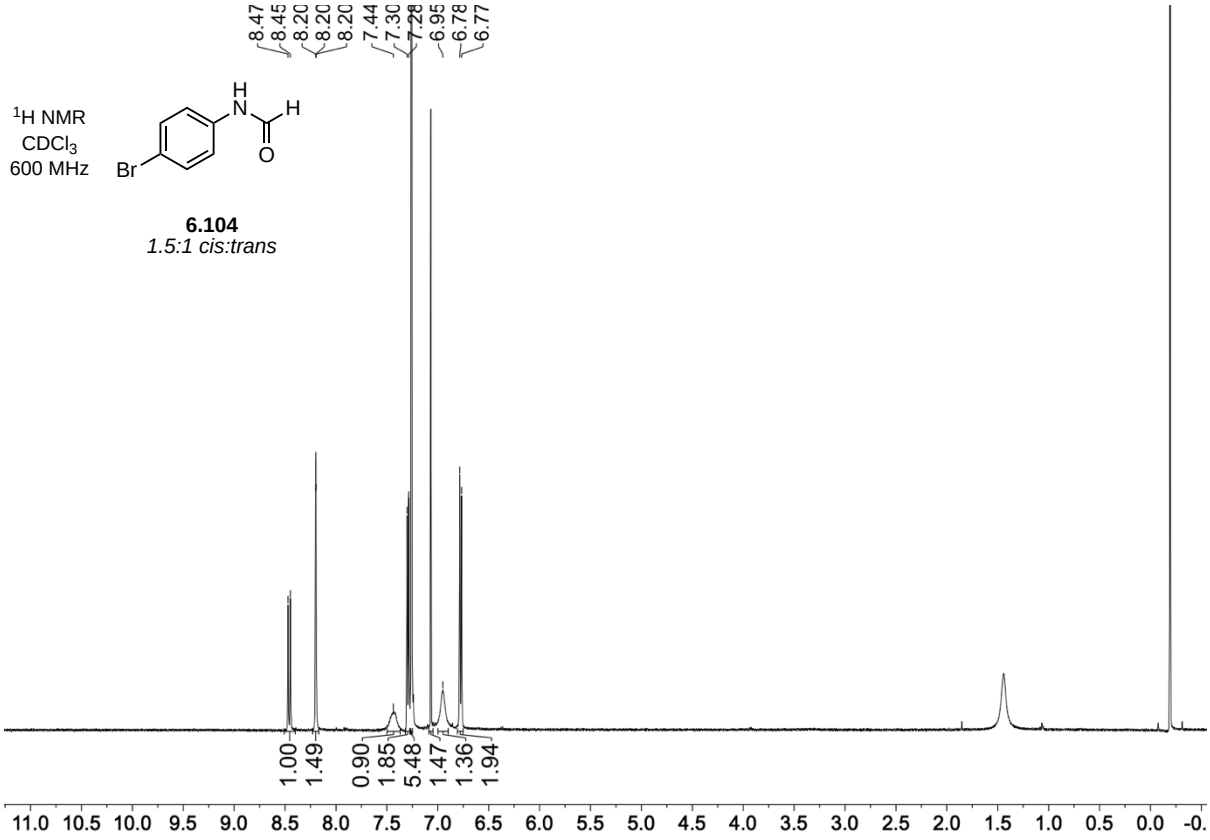

7.58 7.50 7.48 7.35 7.34 7.32 7.31 7.31 7.30 7.29 7.23 7.21 7.20 7.19 7.08 7.06 7.05 7.04 7.00 6.90 6.89 6.89 6.87 6.83 6.83 6.74 6.72 6.70 6.69 6.67 6.66 4.66 4.35 3.72 3.70 3.69 3.51 3.50 3.49 3.05 3.03 2.97 2.95 2.94 2.92 2.91 2.86 2.84 2.83 2.71 2.70 2.68 2.59 2.57 2.56
^{1}H NMR
$CDCl_3$
500 MHz
O
NBn
NH_2
N
H
6.94
1:1 mixture of rotamers
ppm
1.25 0.99 1.00 1.17 8.95 9.95 1.02 1.94 1.09 4.02 2.08 2.08 3.24 2.24 2.02 1.94 4.01 2.11 1.90 2.26


173.3 144.9 144.8 137.7 136.9 136.4 136.3 130.0 129.9 128.9 128.7 128.0 127.6 127.5 127.4 127.4 127.3 127.1 126.4 125.9 125.9 122.4 122.3 122.2 122.0 119.6 119.4 118.8 118.7 118.3 116.0 116.0 113.1 112.0 111.6 111.3 51.9 48.7 47.9 47.7 33.2 32.7 26.8 26.7 24.5 23.5
^{13}C NMR
$CDCl_3$
125 MHz
O
NBn
NH_2
N
H
6.94
1:1 mixture of rotamers

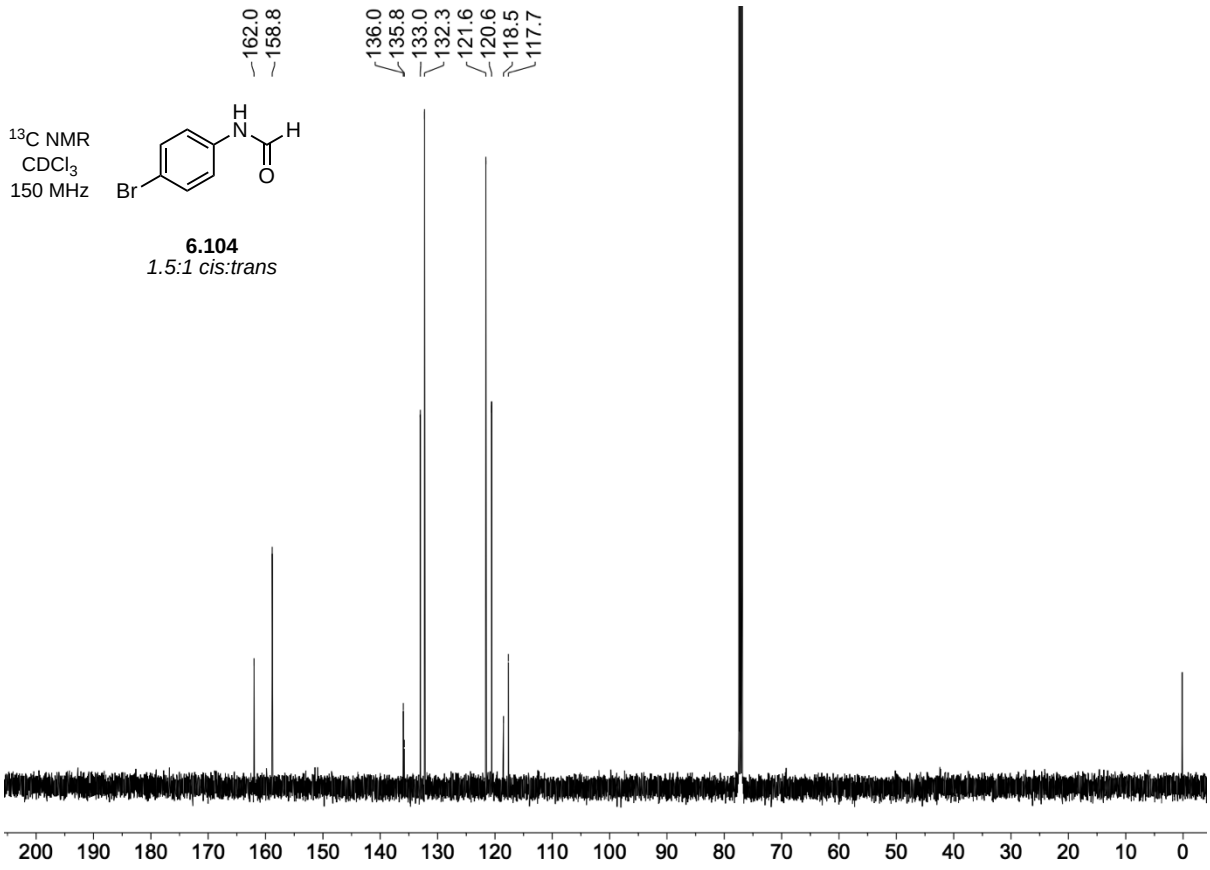
Partial Data for 6.91



Data for 6.104

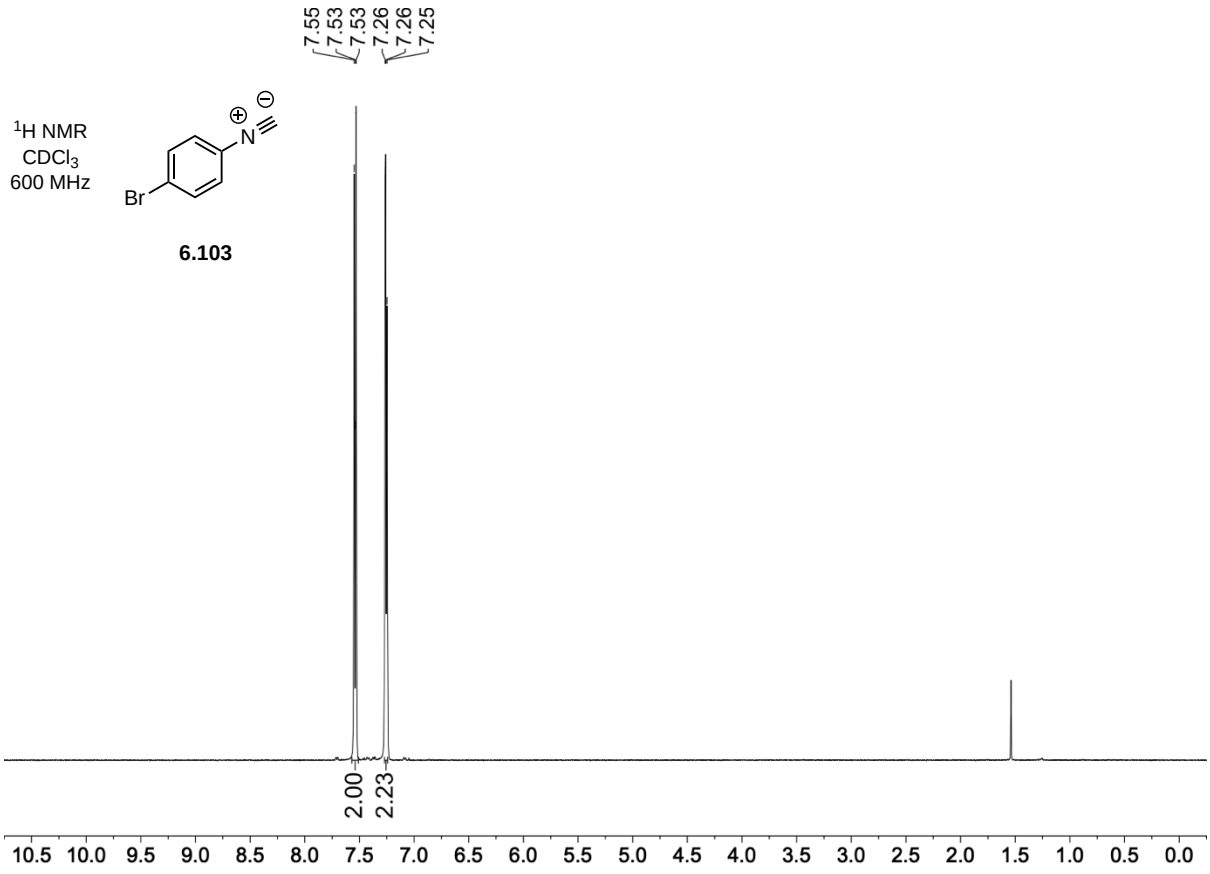


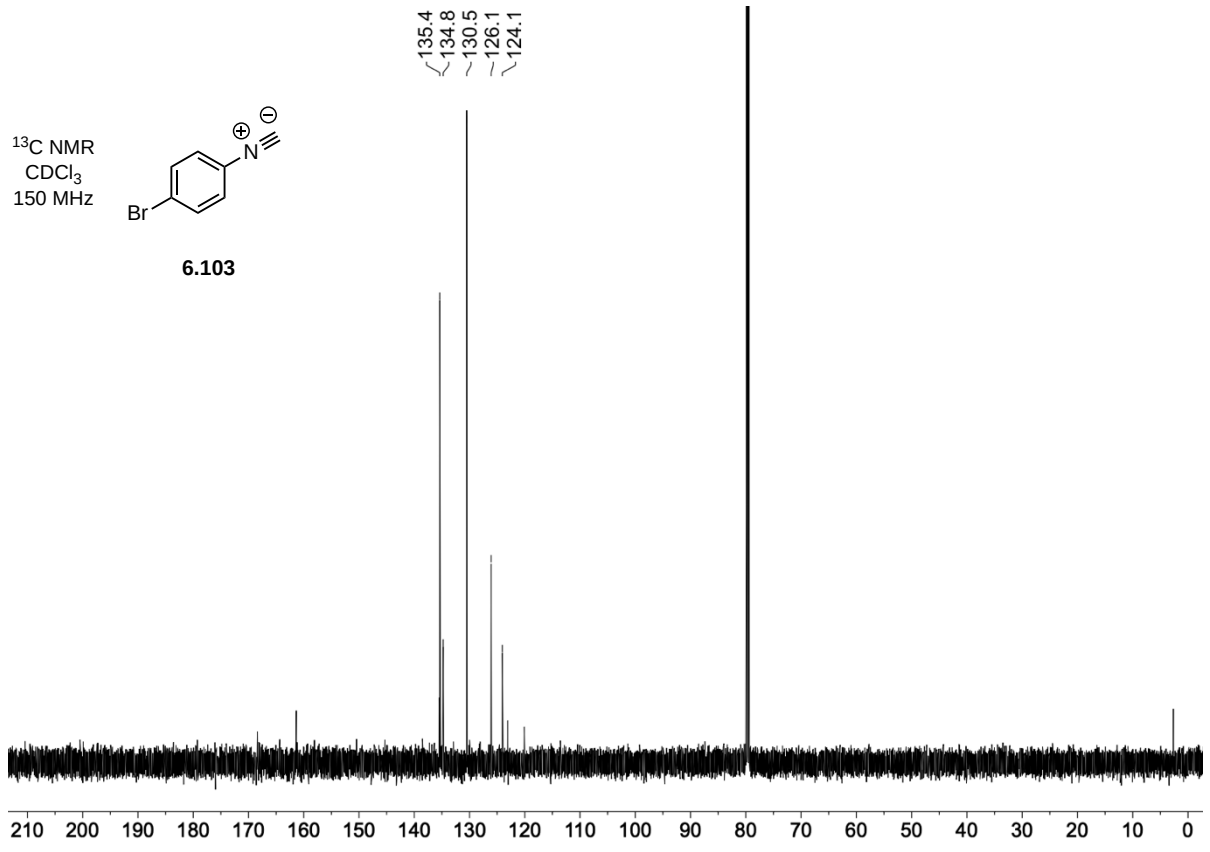
6.104
1.5:1 cis:trans



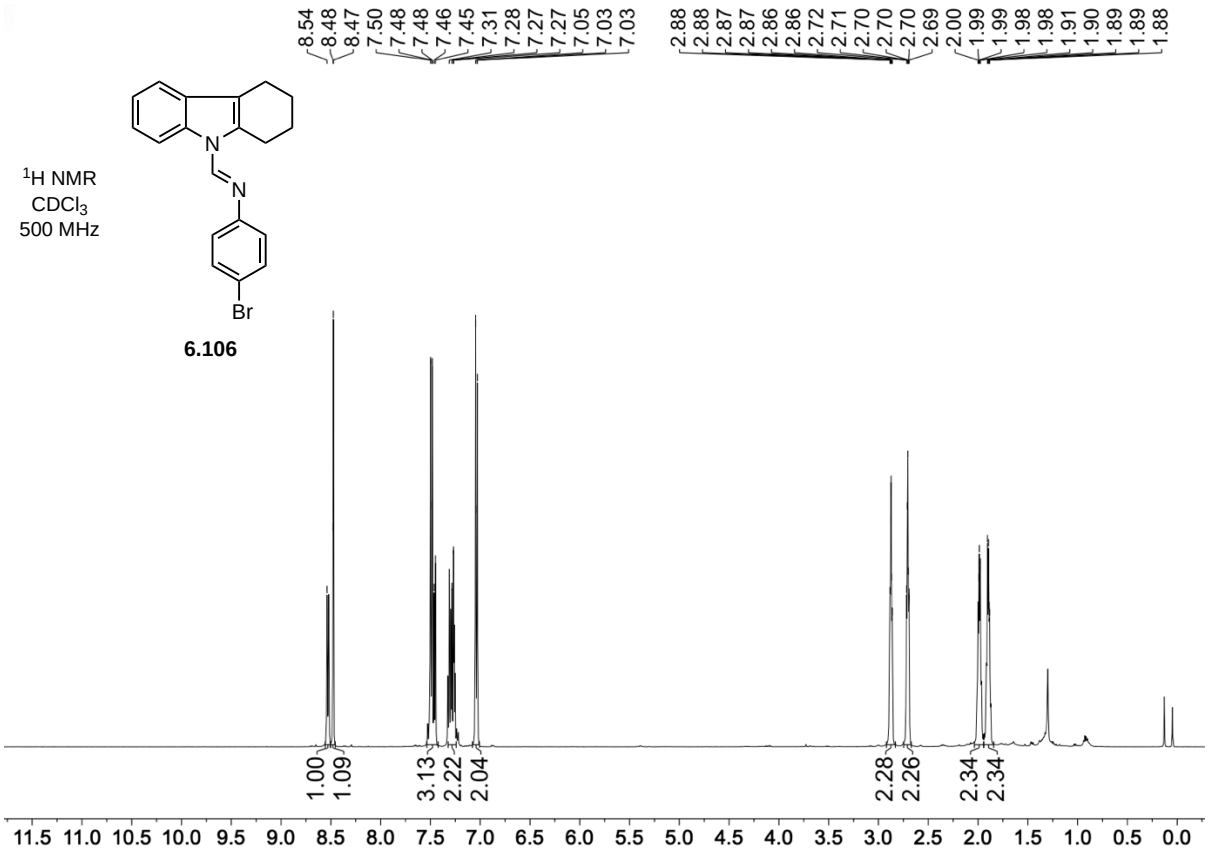
6.104
1.5:1 cis:trans

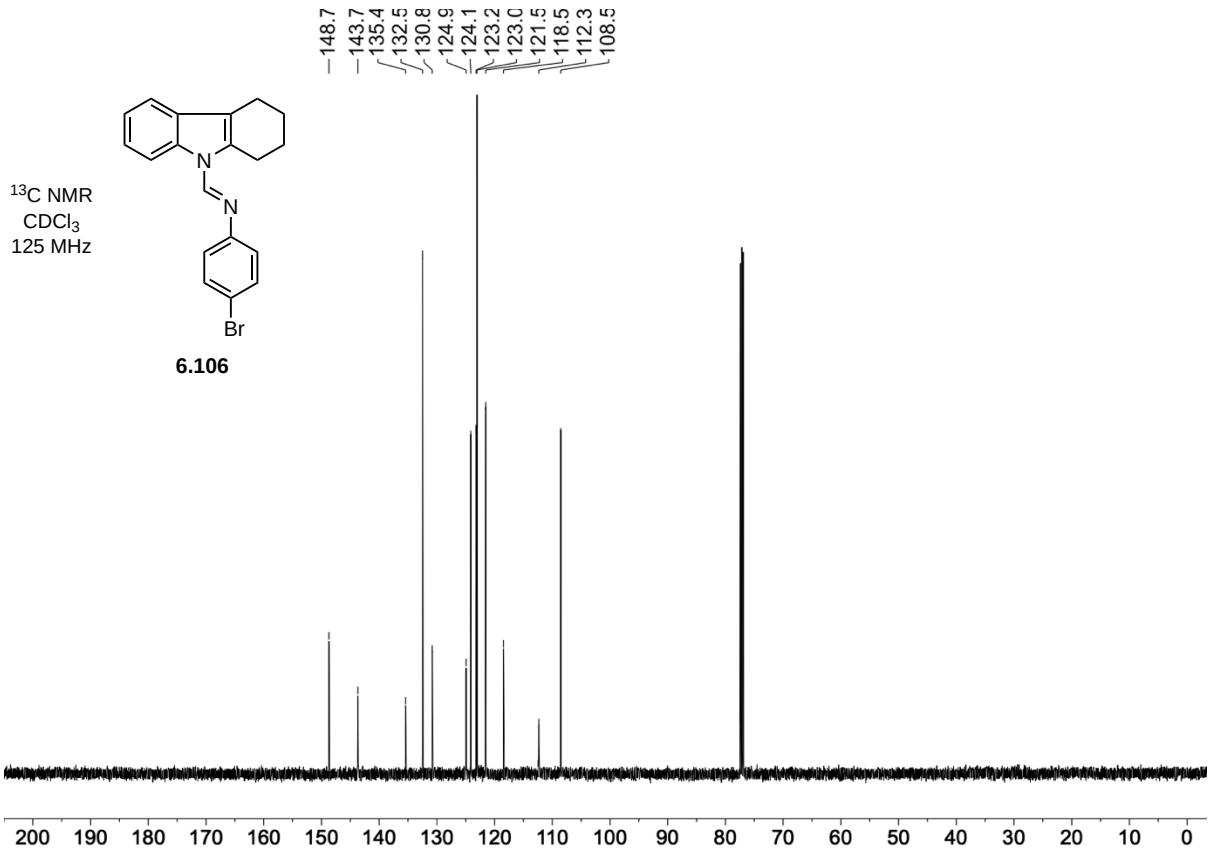
Data for 6.103



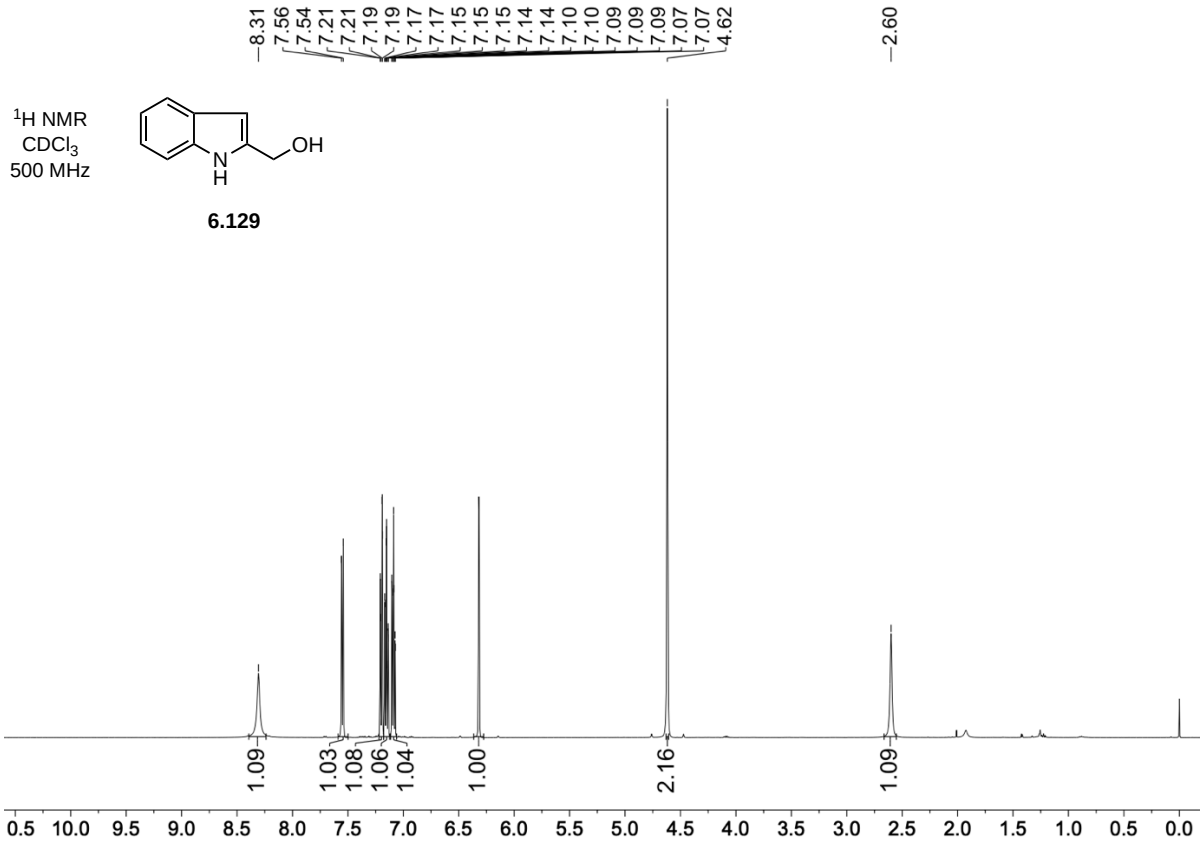


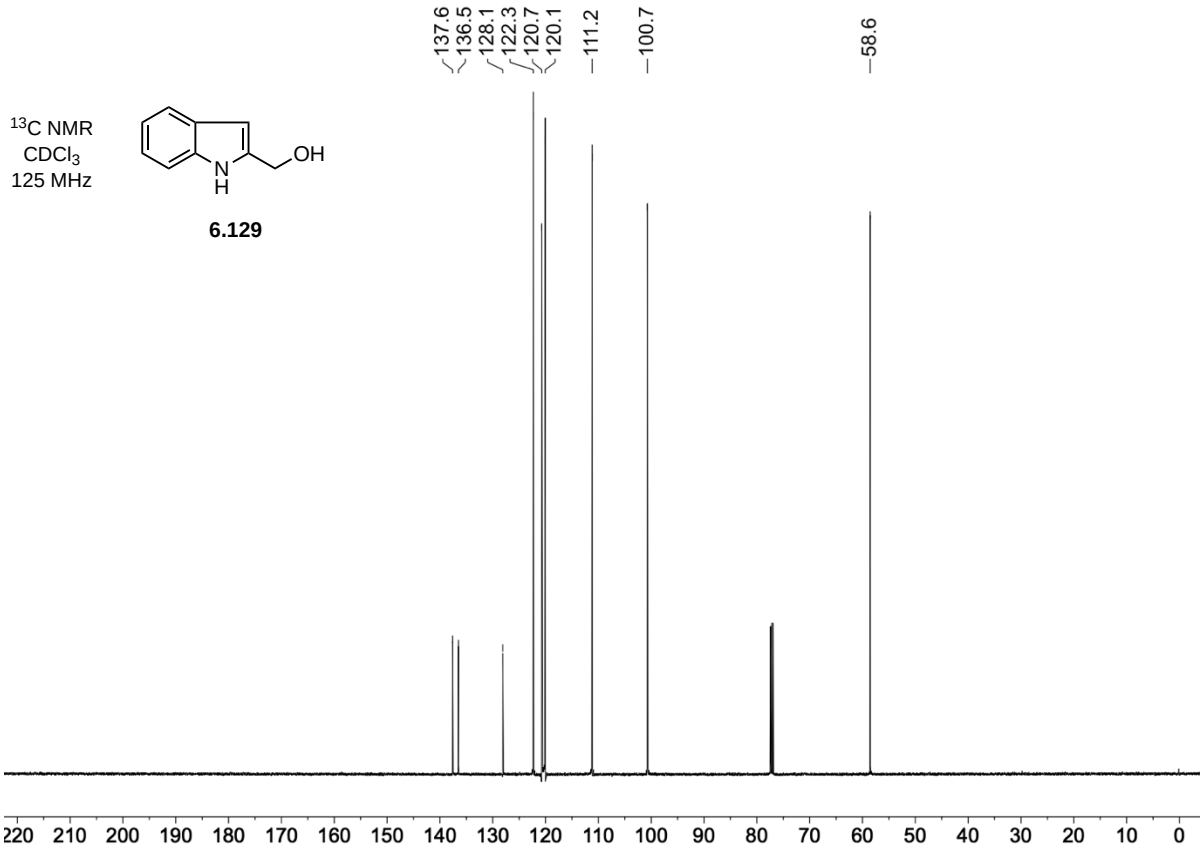
Data for 6.106



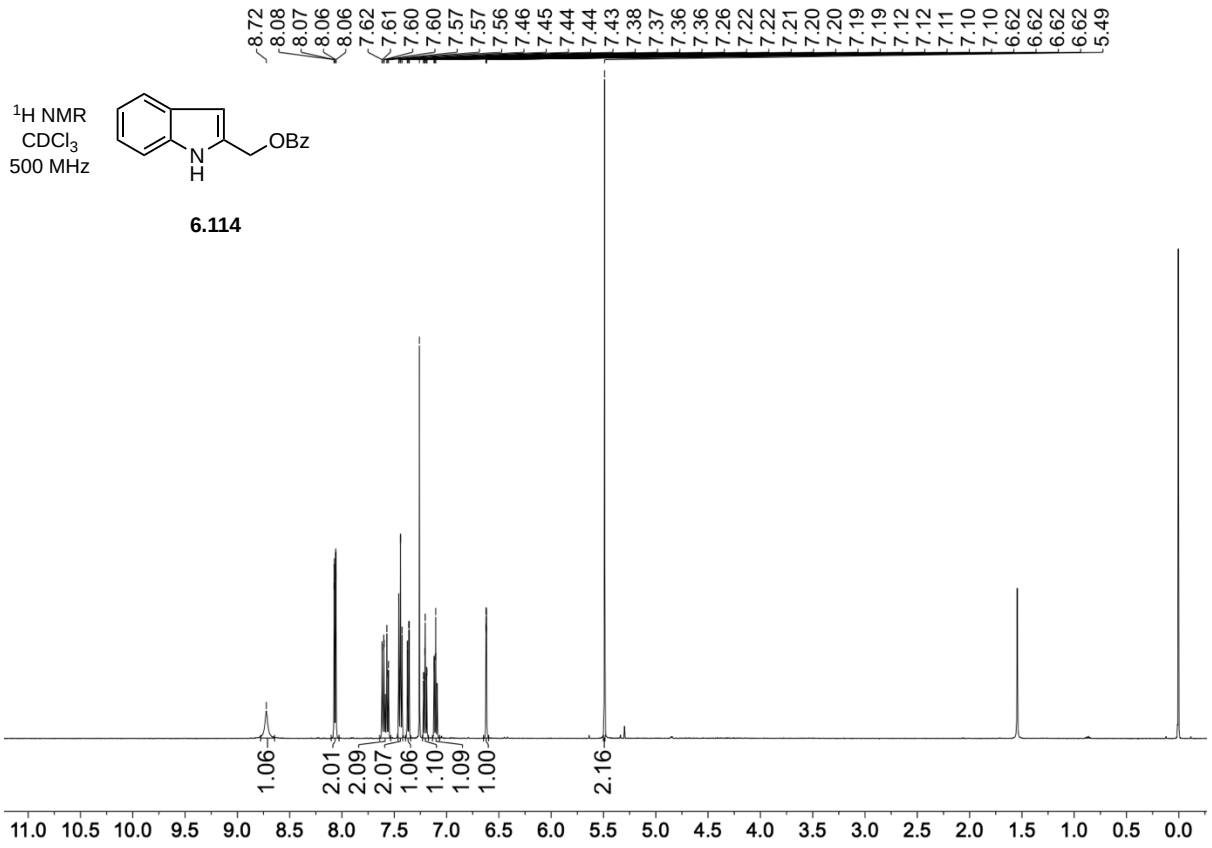


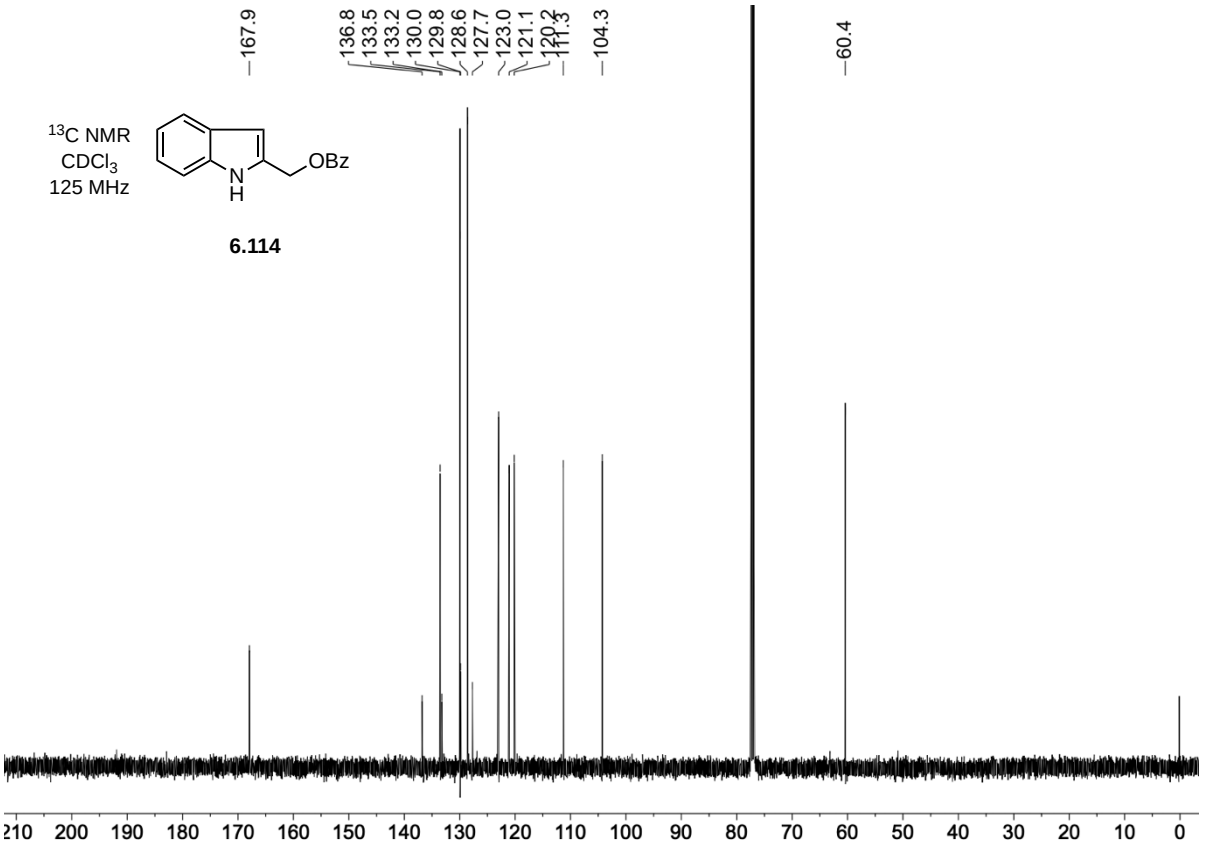
Data for 6.129



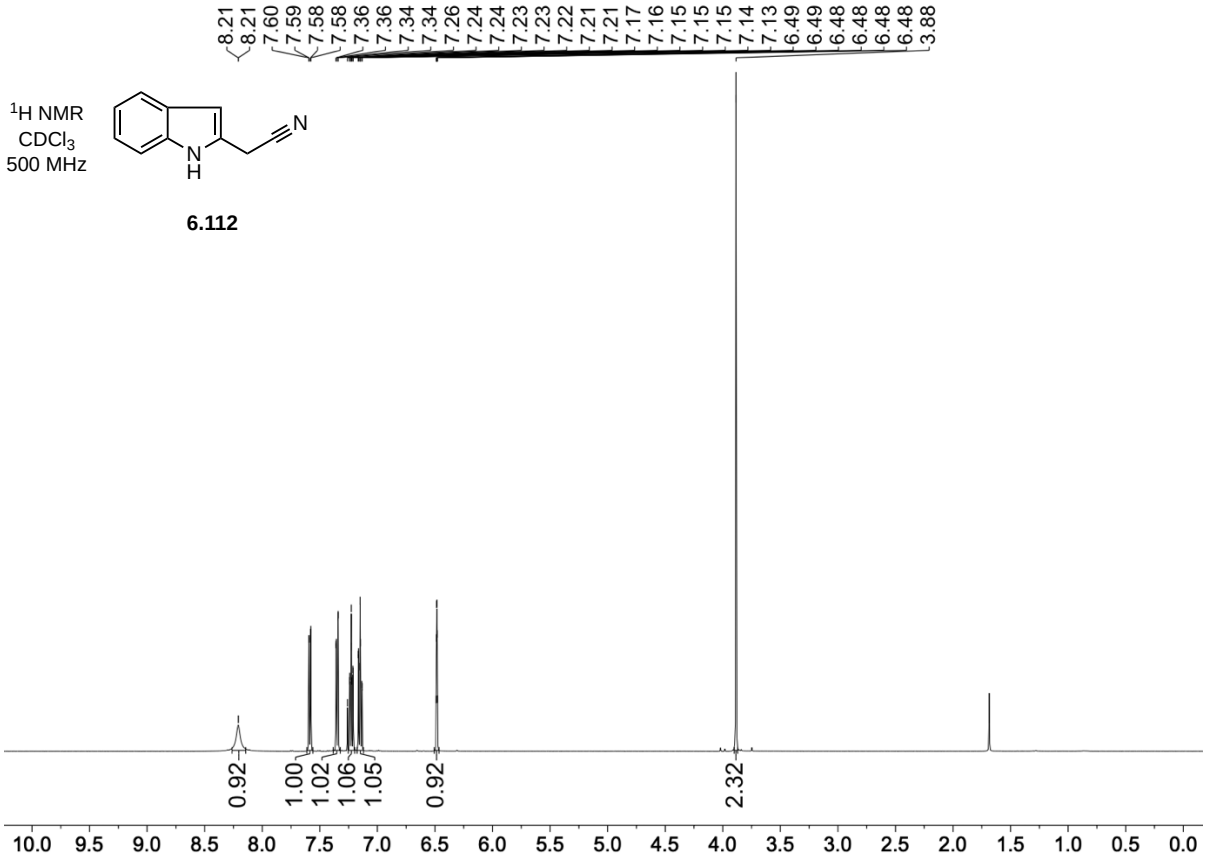


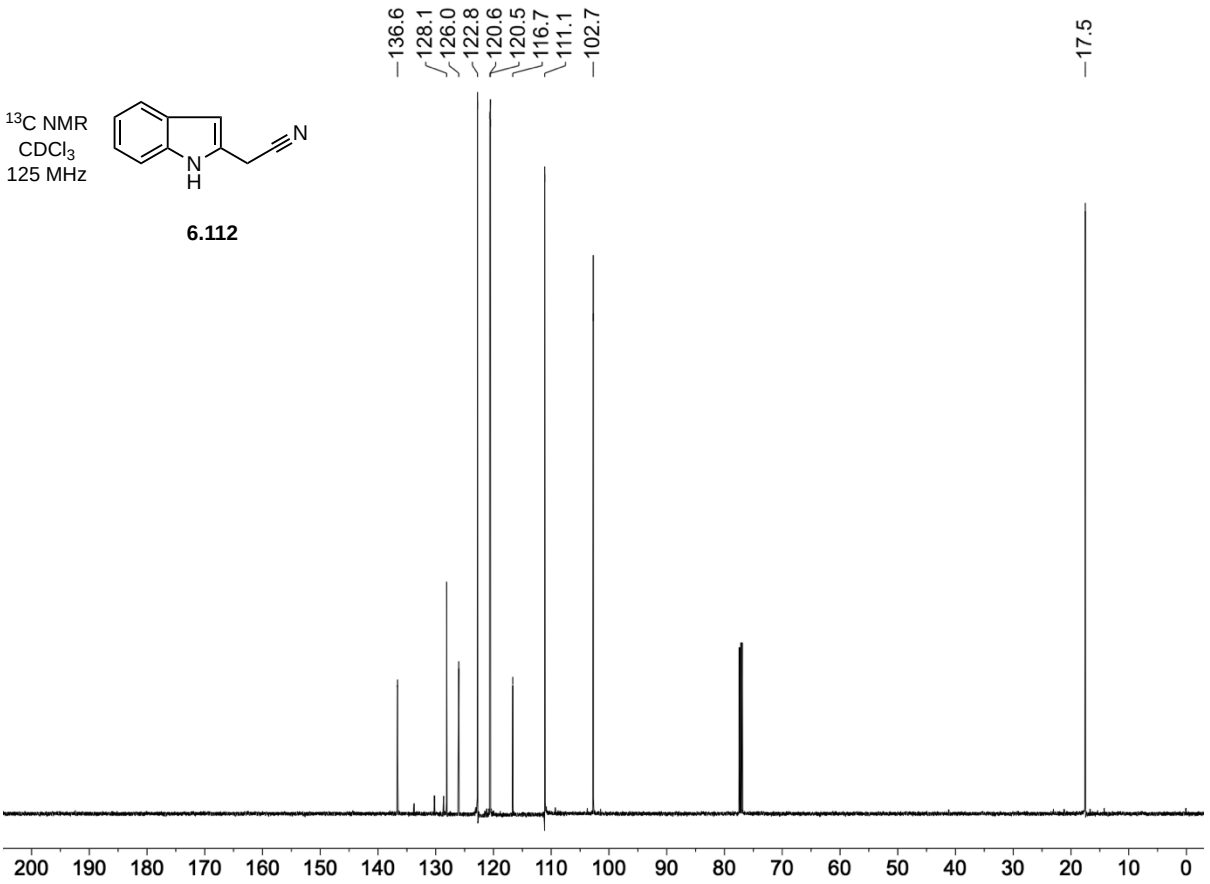
Data for 6.114



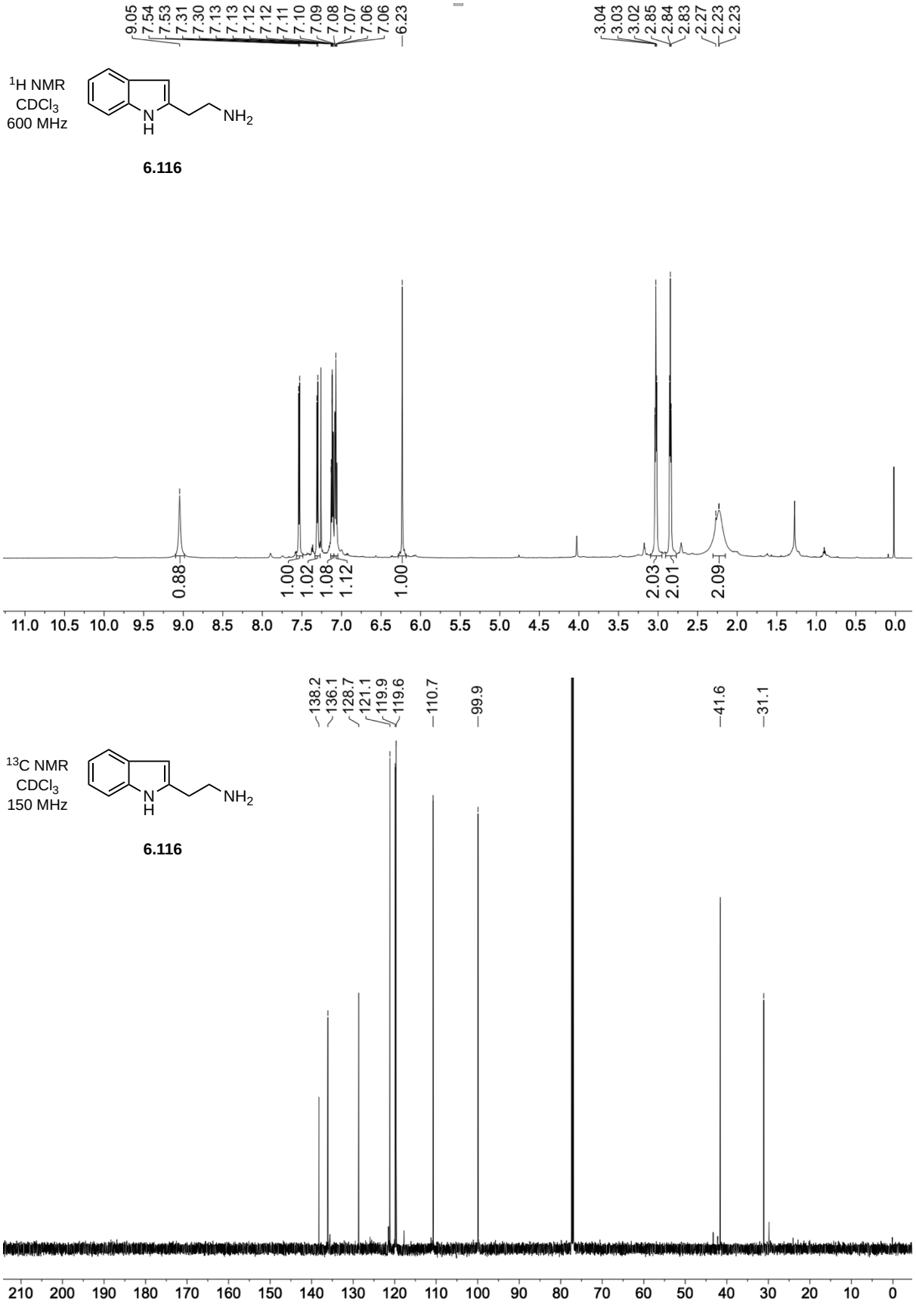


Data for 6.112

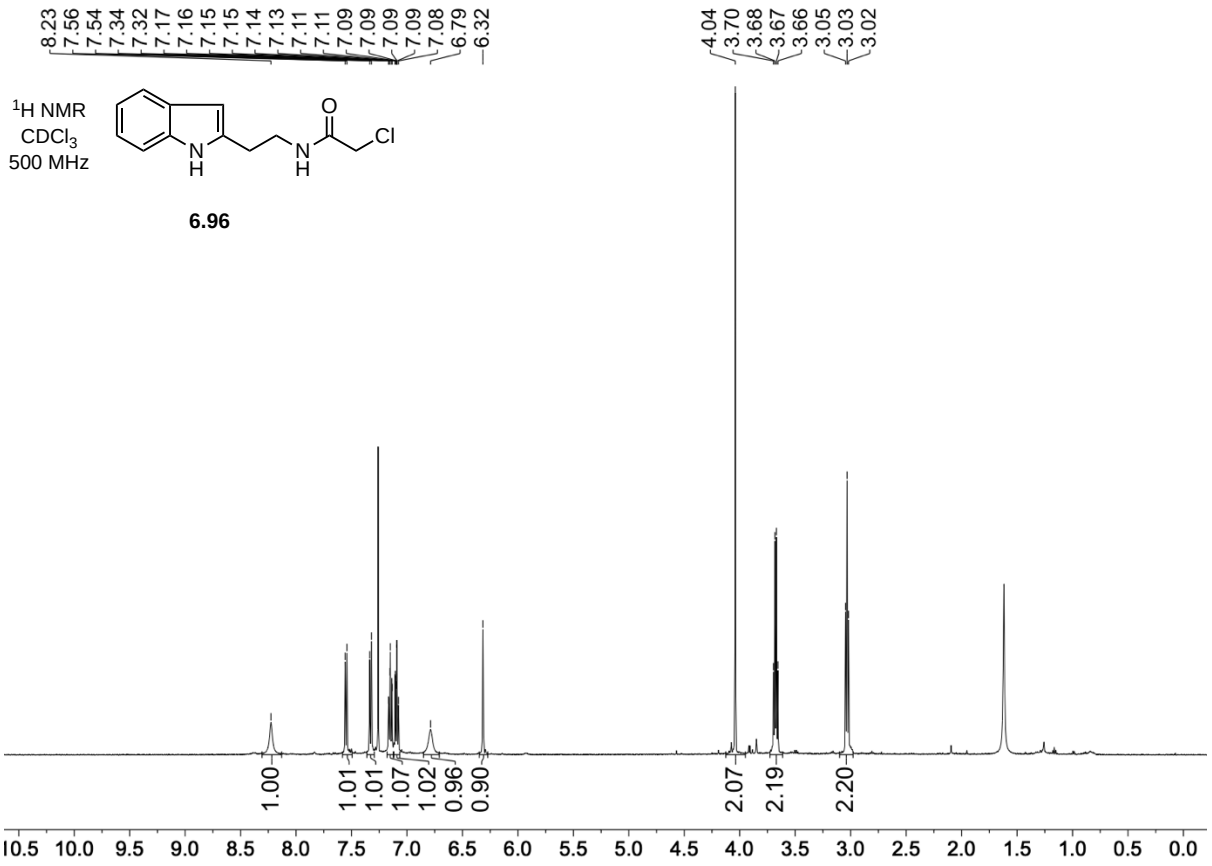


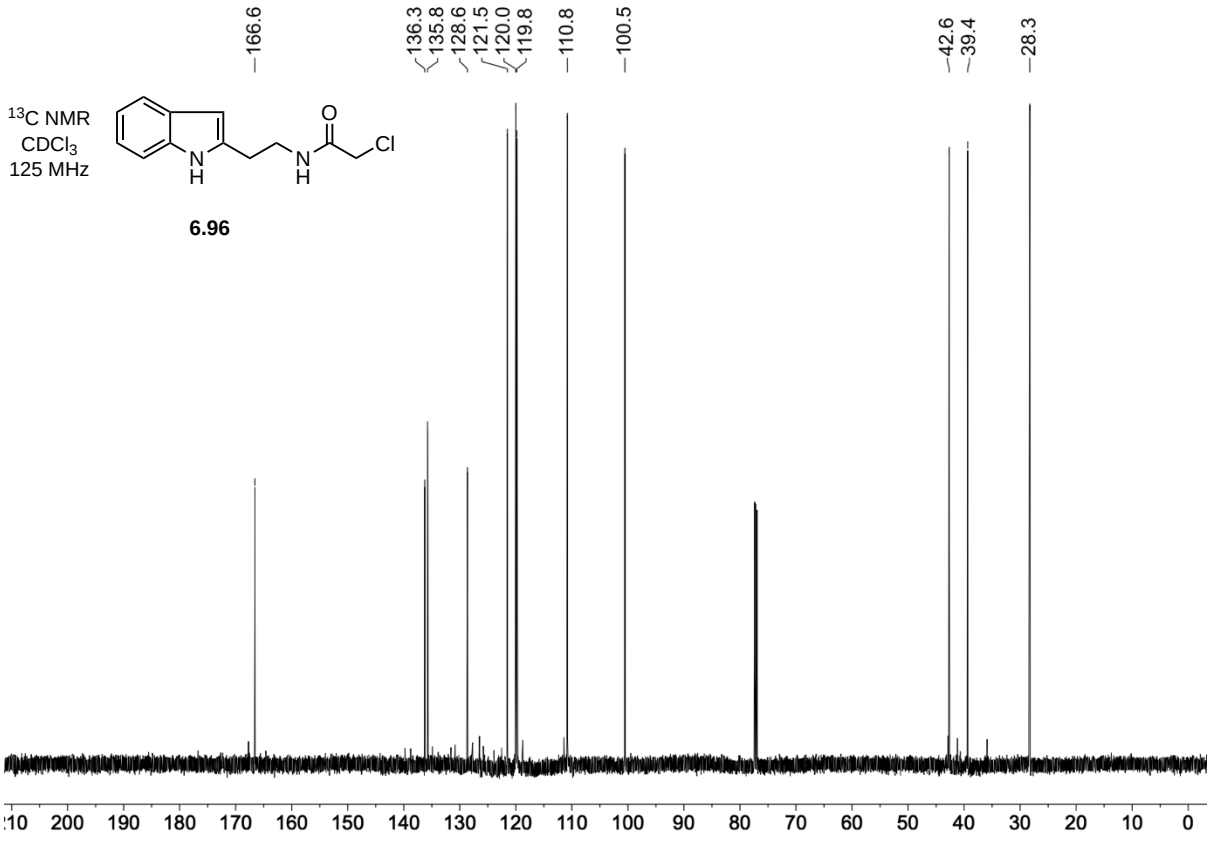


Data for 6.116

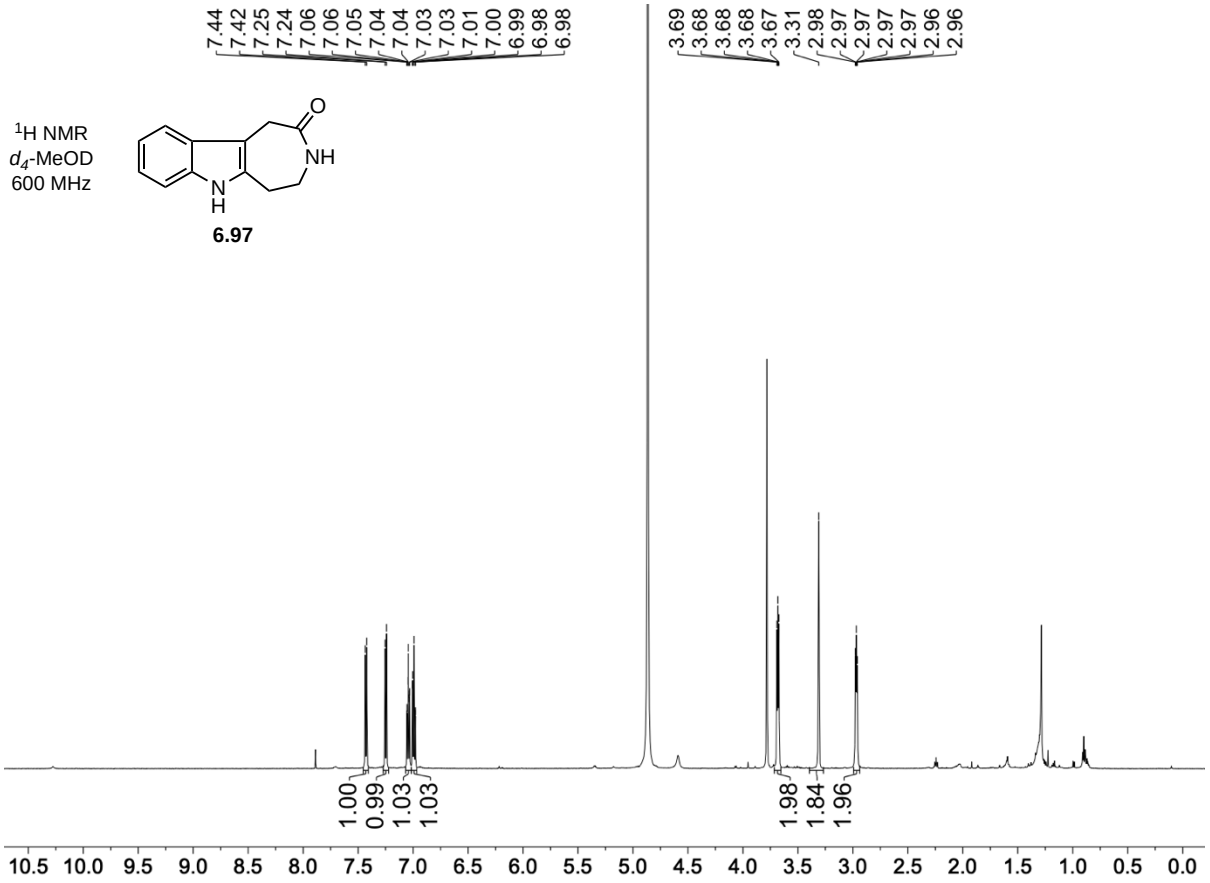


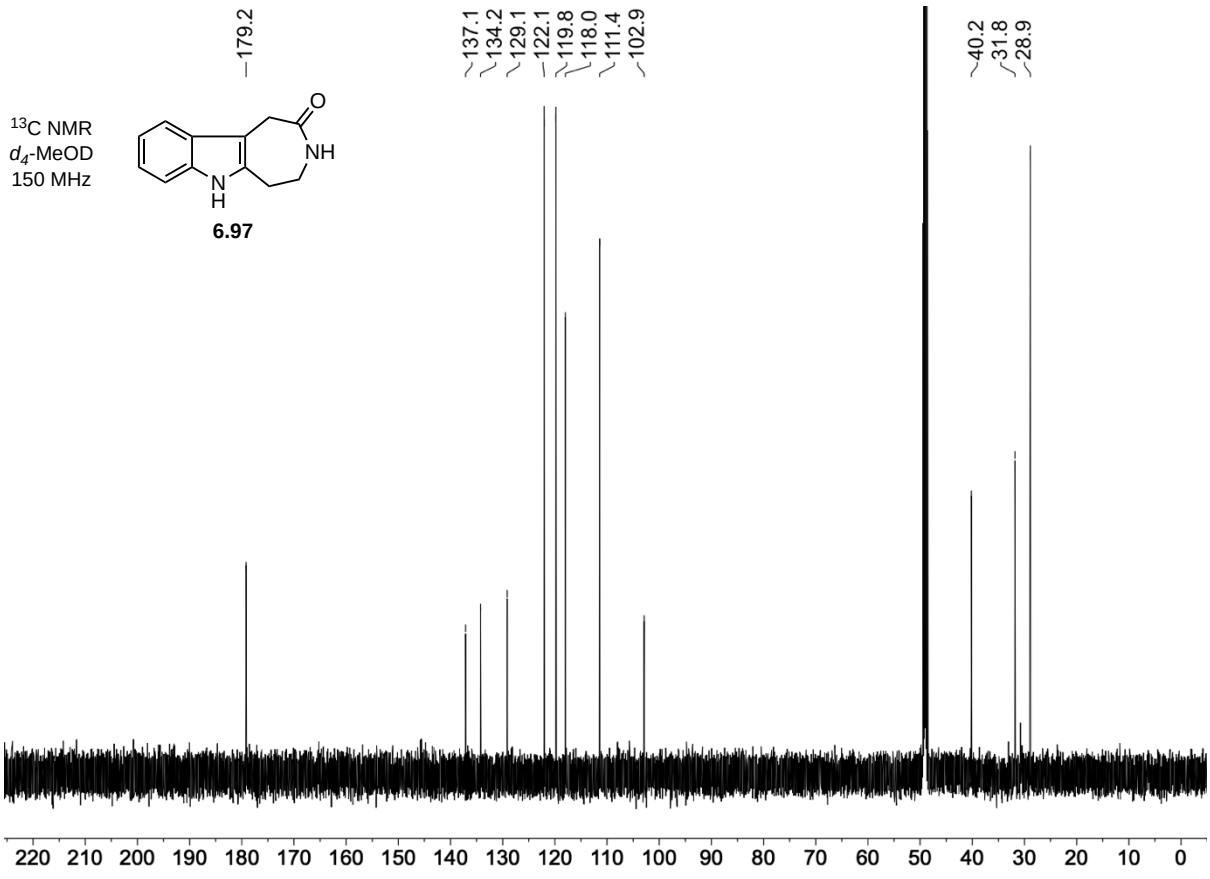
Data for 6.96

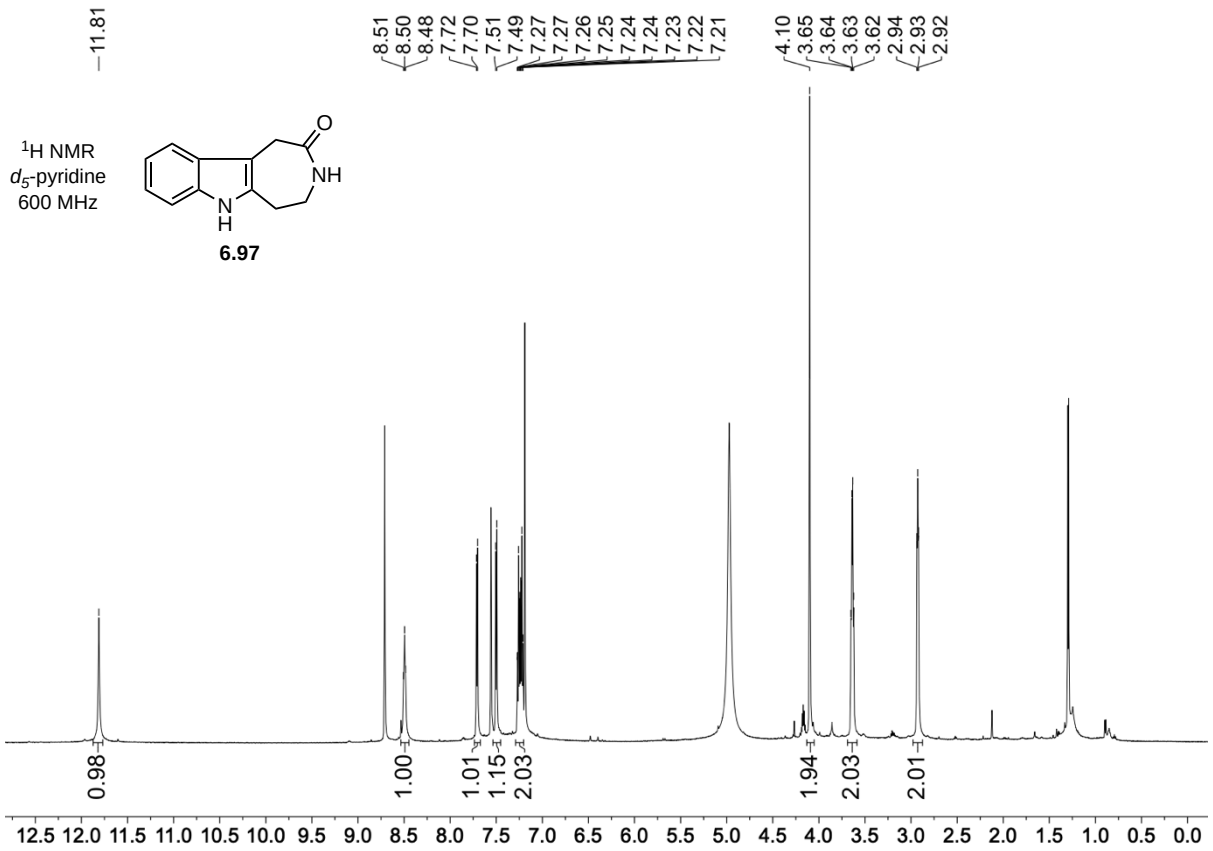

8.23
7.56
7.54
7.34
7.32
7.17
7.16
7.15
7.15
7.14
7.13
7.11
7.11
7.09
7.09
7.09
7.09
7.08
6.79
6.32
4.04
3.70
3.68
3.67
3.66
3.05
3.03
3.02
1H NMR
CDCl3
500 MHz
O
Cl
N
H
N
H
6.96
1.00
1.01
1.01
1.07
1.02
0.96
0.90
2.07
2.19
2.20
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


166.6
136.3
135.8
128.6
121.5
120.0
119.8
110.8
100.5
42.6
39.4
28.3
13C NMR
CDCl3
125 MHz
O
Cl
N
H
N
H
6.96
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Data for 6.97


7.44
7.42
7.25
7.24
7.06
7.06
7.05
7.04
7.04
7.03
7.03
7.01
7.00
6.99
6.98
6.98
3.69
3.68
3.68
3.68
3.67
3.31
2.98
2.97
2.97
2.97
2.97
2.96
2.96
1H NMR
d4-MeOD
600 MHz
O
NH
N
H
6.97
1.00
0.99
1.03
1.03
1.98
1.84
1.96
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


179.2
137.1
134.2
129.1
122.1
119.8
118.0
111.4
102.9
40.2
31.8
28.9
13C NMR
d4-MeOD
150 MHz
O
NH
N
H
6.97
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


11.81
8.51
8.50
8.48
7.72
7.70
7.51
7.49
7.27
7.27
7.26
7.25
7.24
7.24
7.23
7.22
7.21
4.10
3.65
3.64
3.63
3.62
2.94
2.93
2.92
1H NMR
d5-pyridine
600 MHz
O
NH
N
H
6.97
0.98
1.00
1.01
1.15
2.03
1.94
2.03
2.01
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

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