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Development of Sustainable Catalytic Methods for Organic Synthesis

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DECLARATION

I declare that:

a) this thesis has been composed by the candidate, and
b) that the work contained in this thesis is the candidate's own, unless otherwise referenced
c) that the work contained in this thesis has not been submitted for any other degree or professional qualification

Peter DaBell, 7th of August 2019

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Finally, thanks to my family and friends for all of their support, especially Ruth for putting up with everything over the years, I couldn't have done it without you.

Abbreviations

δ	chemical shift
ν	absorption maxima
Ac	acetyl
aq.	aqueous
atm	atmosphere
ATP	Adenosine triphosphate
B-H-9-BBN	9-Boracyclo(3.3.1)nonane
BINAP	(2,2′ -bis(diphenylphosphino)-1,1′-binapthyl
BINOL	1,1′-Bi-2-napthol
Bn	benzyl
br	broad
Bpin	pinacolborane
Bu	butyl
CAN	ceric ammonium nitrate
COSY	Correlation Spectroscopy
d.r.	diastereomeric ratio
d	doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMP	Dess-Martin Periodinane
ESI	Electrospray Ionisation
e.e.	enantiomeric excess
e.r.	enantiomeric ratio
Et	ethyl

eq.	equivalent
Fe(PDP)	(2*S*,2′*S*-(−)-[*N*,*N*′-Bis(2-pyridylmethyl)]-2,2′-bipyrrolidine bis(acetonitrile)iron(II) hexafluoroantimonate
$FMNH_2$	Flavin mononucleotide
g	gram(s)
h	hour
HMBC	Heteronuclear Multiple-Bond Correlation
HPLC	High-performance liquid chromatography
HSQC	Heteronuclear Single Quantum Correlation
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
IBX	2-iodoxybenzoic acid
Ipc	isopinocampheyl
IR	infrared
J	coupling constant
L	litre
m	multiplet
M^+	molecular ion
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
min	minutes
mol	mole(s)
MW	microwave
m/z	mass to charge ratio
NAD^+/NADH	nicotinamide adenine dinucleotide
$NADP^+$/NADPH	nicotinamide adenine dinucleotide phosphate

NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
OAC	oxygenated aromatic compound
ppm	parts per million
Ph	phenyl
Pr	propyl
p-TSOH	*para*-tolenesulfonic acid
t	*tert* (tertiary)
t	triplet
TACN	1,4,7-triazacyclononane
TADDOL	α,α,α',α'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
TPA	tris(2-pyridylmethyl)amine
UV	ultraviolet

Lay Summary

A major issue within chemistry is the use of expensive, non-renewable and toxic reagents or catalysts to carry out organic reactions. A lot of work has been carried out on the replacement of these with processes employing compounds that are inexpensive and abundant. This thesis presents two separate projects, but both of which aimed to develop sustainable procedures for use in organic transformations.

The first project concerned the planned use of iron or copper catalysts for an oxidation reaction to convert simple and widely available aromatic compounds, such as phenol, into more complex molecules, with a wide range of applications. The aim was then to use this reaction in a total synthesis of the complex natural product fatouapilosin. Inspiration was taken from how we understand reactions to take place, and compounds to be made, within nature, ie. in a biomimetic manner. Although we did not achieve the initial aims of this project, the results obtained enabled us to further our understanding of the behaviour and reactivity of these types of compounds in nature and in the laboratory.

The second project concerned the use of boron-containing catalysts to carry out a reduction reaction of ketone compounds in a selective manner. Some compounds exist as a pair of molecules, or enantiomers, that are mirror images of each other. Different enantiomers can have vastly different properties, but it can often be very difficult to separate them. This project developed a reaction using an enantioselective boron catalyst to reduce ketones, and give the alcohol product with a high ratio of one enantiomer over the other.

Abstract

This thesis covers two separate projects, but both of which can be linked by the overall aim to develop sustainable catalytic methodology for use in organic synthesis. A concerted effort has been made to move away from procedures within organic chemistry that use non-renewable expensive and toxic materials as reagents and catalysts, particularly those containing second and third row transition metals, and instead to develop processes that utilise sustainable, abundant and inexpensive reagents, such as base-metals and main group elements.

The first project was the attempted development of an oxidative ring contraction of aromatic compounds, with the goal of applying it in the biomimetic total synthesis of fatouapilosin. The second project concerned the development of the borane-catalysed enantioselective hydroboration and reduction of propargylic ketones.

Chapter 1 is an introduction to the first project, giving details regarding the isolation and proposed biosynthetic route to fatouapilosin, as well as giving an overview of the area of biomimetic total synthesis. The oxidative ring contraction reaction, the use of iron and copper for oxidation of organic compounds, and the potential of phenols as a renewable source of carbon are also discussed.

Chapter 2 describes the first total synthesis of the coumarin natural product brosiparin, an important precursor in the proposed synthesis of fatouapilosin, which was the planned substrate on which to develop a method of oxidative ring contraction. Brosiparin was successfully prepared in a three-step procedure from pyrogallol, with an initial double demethylation followed by an *O*-prenylation, then a tandem Wittig olefination/*para*-Claisen rearrangement/lactonisation sequence.

Chapter 3 focuses on the oxidation chemistry of brosiparin, and the efforts to develop a reliable method of oxidative ring contraction. Unfortunately trials with a wide variety of oxidising agents, including iron and copper catalysts, did not result in the desired transformation. The use of phenyliododiacetate (PIDA) enabled us to access a masked *ortho*-quinone compound, from which further reactions were attempted, including an

interesting aryl-aryl coupling reaction, but the unprotected *ortho*-quinone proved very unstable and difficult to work with.

Chapter 4 covers the second project, and starts with a broad introduction to the area of hydroboration, followed by a more focused look at enantioselective hydroboration and reduction of ketones. The successful development of an enantioselective reduction of propargylic ketones using substoichiometric myrtanyl borane with stoichiometric HBpin is then described. The reaction was shown by ^{1}H and ^{11}B NMR studies to proceed via a transborylation mechanism, and was applied to other propargylic ketone substrates.

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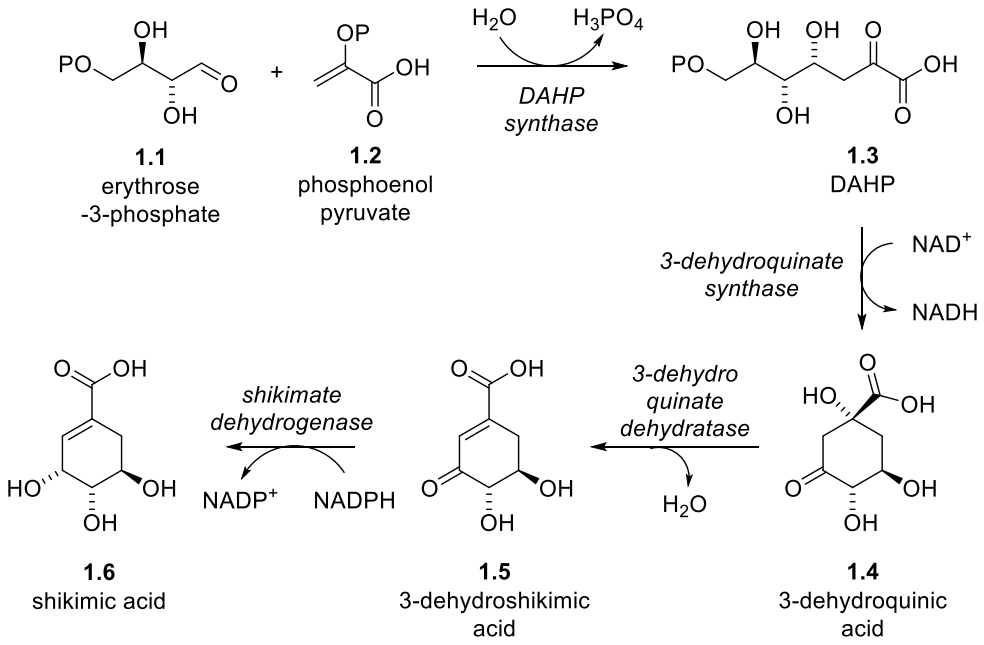
Chapter 1 – Introduction

1.1 - Fatouapilosin

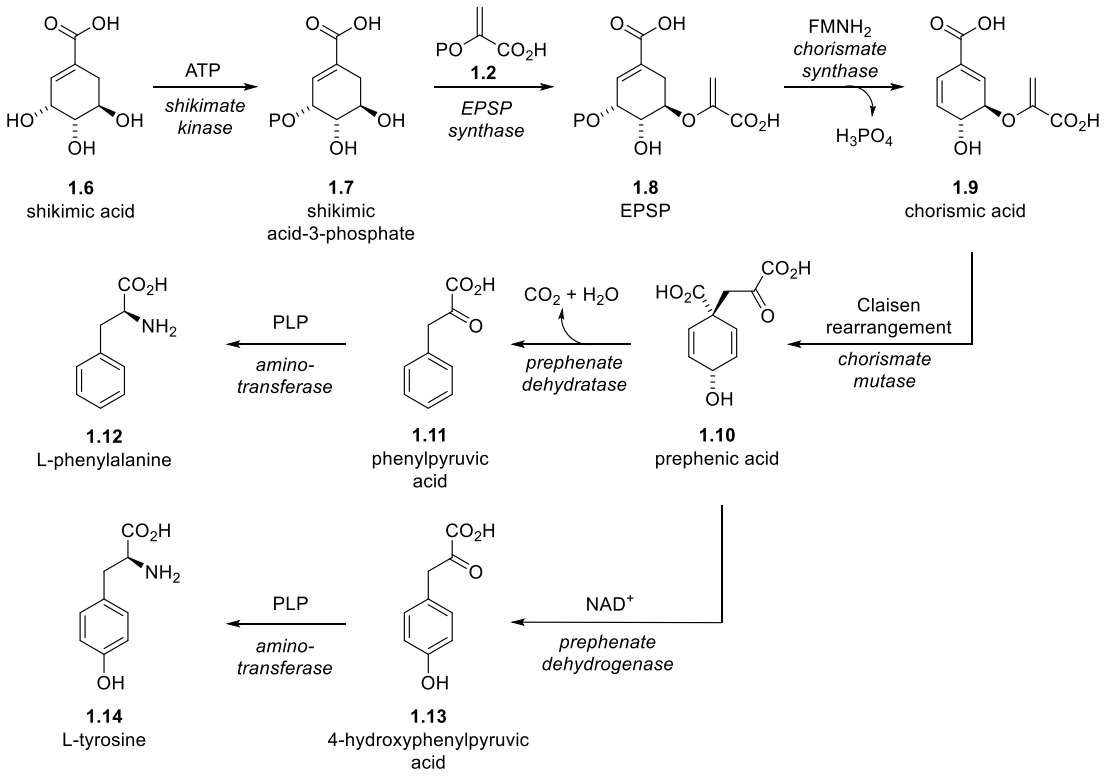
1.1.1 – Coumarin Natural Products: Biosynthesis and Examples

Coumarin natural products, of which hundreds of examples exist, are part of the phenylpropanoid family of naturally occurring organic compounds. These derive in nature from the amino acids phenylalanine and tyrosine, which in turn are formed through the shikimic acid pathway.[3-4] The shikimic acid pathway is a metabolic pathway used by plants and microorganisms (but not by animals), to produce aromatic amino acids, namely phenylalanine, tyrosine and tryptophan. The pathway begins with the aldol reaction between erythrose-4-phosphate (**1.1**) and phosphoenol pyruvate (**1.2**), to give 3-deoxy-D-arabino-heptulosonate-7-phosphate (DAHP, **1.3**), a reaction mediated by the DAHP synthase enzyme (Scheme **1.1**). The DHQ synthase enzyme then catalyses the conversion of DAHP (**1.3**) to 3-dehydroquinate (DHQ, **1.4**) in a 5-step sequence.[4] DHQ (**1.4**) is then dehydrated by the enzyme 3-dehydroquinate dehydratase to give 3-dehydroshikimic acid (**1.5**), which subsequently undergoes reduction by shikimate dehydrogenase and NADPH to give the key intermediate shikimic acid (**1.6**), for which the pathway is named (Scheme **1.1**).



Scheme 1.1 – Biosynthesis of shikimic acid

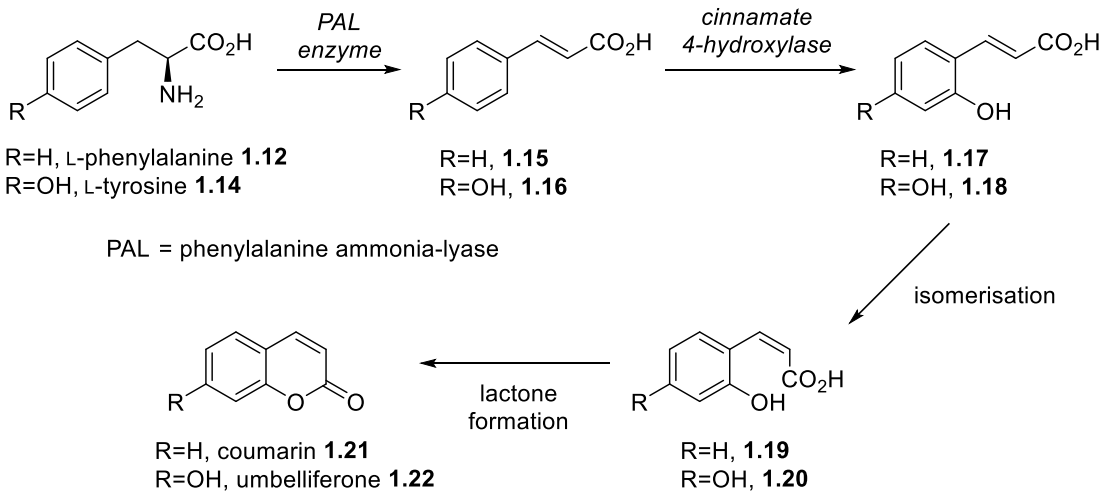
Phosphorylation of shikimic acid (**1.6**) by shikimate kinase and ATP gives shikimic acid-3-phosphate (**1.7**), which then couples with phosphoenol pyruvate (**1.2**), to give 5-enolpyruvylshikimate-3-phosphate (EPSP, **1.8**), using the enzyme EPSP synthase. A chorismate synthase-mediated elimination of the phosphate group results in the formation of chorismic acid (**1.9**), a key intermediate from which the pathway branches out to either form tryptophan, or phenylalanine and tyrosine. The route to the latter two amino acids proceeds by conversion of chorismic acid (**1.9**) to prephenic acid (**1.10**), by a chorismate mutase-mediated Claisen rearrangement. From prephenic acid (**1.10**) the pathway branches once more; conversion to phenylpyruvic acid (**1.11**) with prephenate dehydratase, via loss of CO_2 and H_2O, can be followed by transamination to give L-phenylalanine (**1.12**). Prephenic acid (**1.10**) can also be converted to 4-hydroxyphenylpyruvic acid (**1.13**) by decarboxylation with prephenate dehydrogenase. Subsequent enzyme-mediated transamination results in the formation of L-tyrosine (**1.14**) (Scheme **1.2**).[3-4]



Scheme 1.2 – Formation of amino acids via shikimic acid pathway

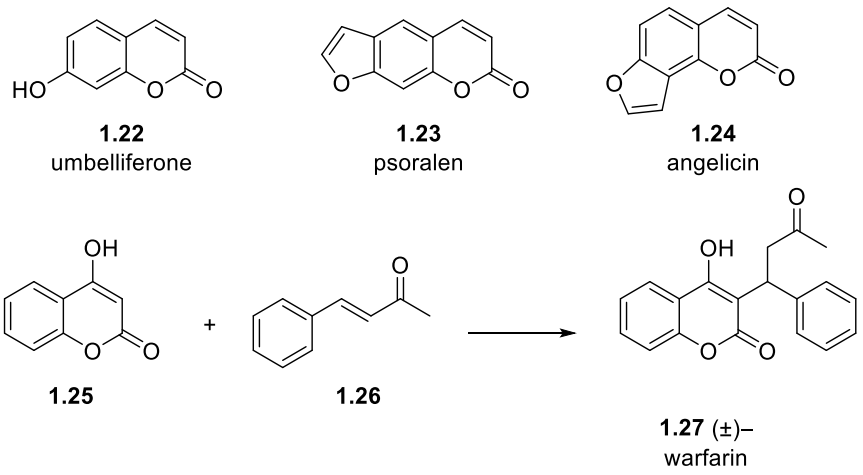
Phenylalanine and tyrosine, as phenylpropanoid (C_6C_3) building blocks are precursors for a large variety of different types of natural products, including coumarins. The

frequent first step from the aromatic amino acids is the elimination of ammonia from the side chain, to give the appropriate *trans*-cinnamic acid; cinnamic acid (**1.15**) from phenylalanine, and 4-coumaric acid (**1.16**) from tyrosine. The coumarin framework is accessed from these cinnamic acids by o*rtho*-hydroxylation, and subsequent *trans-cis* isomerisation and lactone formation, resulting in the formation of coumarin (**1.21**) or umbelliferone (**1.22**) (Scheme **1.3**).[3-4]



Scheme 1.3 – Formation of coumarins from aromatic amino acids

Many examples of coumarin natural products have previously been studied, and they have a wide variety of applications. Particularly prevalent examples include umbelliferone (**1.22**), which absorbs ultraviolet light and is used in sunscreens, and the furanocoumarin compounds psoralen (**1.23**) and angelicin (**1.24**), both of which have been used in the treatment of skin conditions, and skin cancer (Scheme **1.4**).[5] A number of drug molecules have also been derived from naturally occurring coumarins, including the anticoagulant warfarin (**1.27**), which is derived from the condensation reaction of 4-hydroxycoumarin (**1.25**) with benzalacetone (**1.26**) (Scheme **1.4**),[6] and is widely used to prevent blood clotting by inhibiting vitamin K production.[7]



Scheme 1.4 – Examples of coumarin natural products, and synthesis of coumarin-derived drug molecule warfarin

A number of dimeric coumarin natural products are known, including chimsalicifoliusins A and B (**1.28** and **1.29**), diseselin B (**1.30**) and jayantinin (**1.31**).[8-10] The monomeric units are either connected via a direct C–C aryl-aryl bond (**1.29** and **1.31**), through a linking oxygen (**1.28**), or in the case of diseselin B (**1.40**), through a cycloaddition of the coumarin C=C bonds of each sub-unit, forming a cyclobutane group (Figure **1.1**).

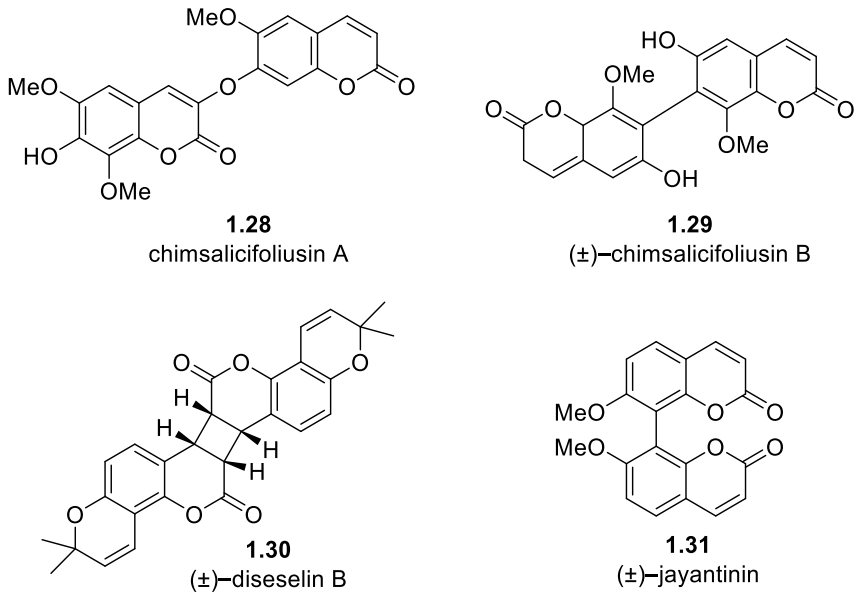
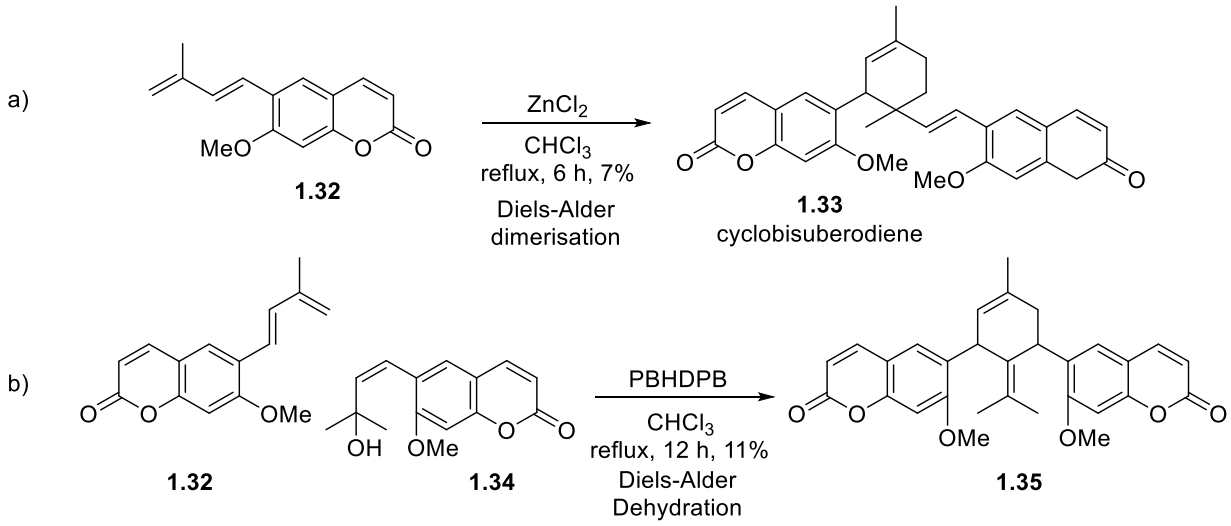


Figure 1.1 – Examples of dimeric coumarin natural products

A further example comes from the work of Reisch and co-workers,[11] who carried out the synthesis of the naturally occurring dimeric coumarin compound cyclobisuberodiene (**1.33**), by a Diels–Alder type reaction between the diene side chains of each (*E*)-

suberodiene (**1.32**) monomer, after reflux with $ZnCl_2$ (Scheme **1.5a**). The same authors also carried out the synthesis of another dimeric coumarin compound **1.35**, by a Diels–Alder reaction of (*Z*)-suberenol (**1.34**) and (*E*)-suberodiene (**1.32**), followed by dehydration (Scheme **1.5b)**.[12]



Scheme 1.5 – a) Dimeric coumarin formation of cyclobisuberodiene; b) Synthesis of 6',6-[1,4(8)-*p*-Menthadiene-3,5-diyl]bis(7-methoxycoumarin), via Diels–Alder type reactions

1.1.2 – Isolation

Fatouapilosin (**1.36**) is a novel dimeric coumarin-derived natural product that was first isolated by Chiang and co-workers in 2010, from the *Fatoua pilosa* plant, a small herb that grows mainly in Taiwan.[1] It was isolated alongside 18 other known compounds, which included simple coumarin compounds umbelliferone (**1.22**), scopoletin (**1.37**), and phellodenol-A (**1.38**), as well as pyranocoumarin compound xanthyletin (**1.39**)**,** and six furanocoumarins (**1.40**-**1.45**) (Figure **1.2**). Other isolates included, steroids, chalcone, quinone and triterpenoid derived compounds, all of which were analysed by ^{1}H and ^{13}C NMR spectroscopy, and characterised by comparison to authentic samples and literature values.

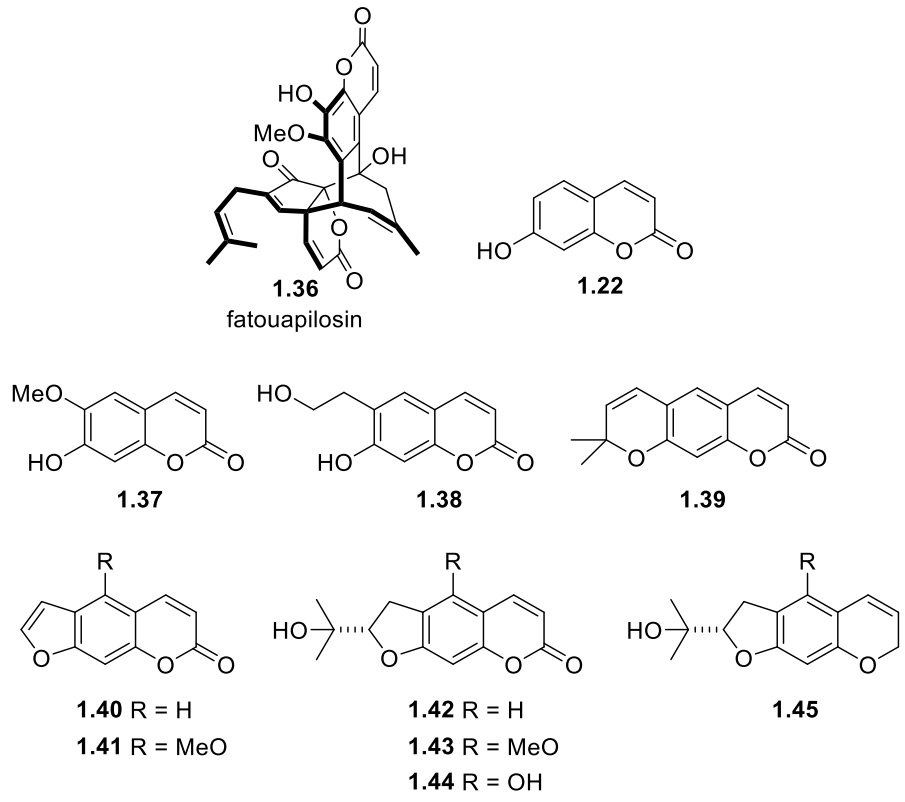
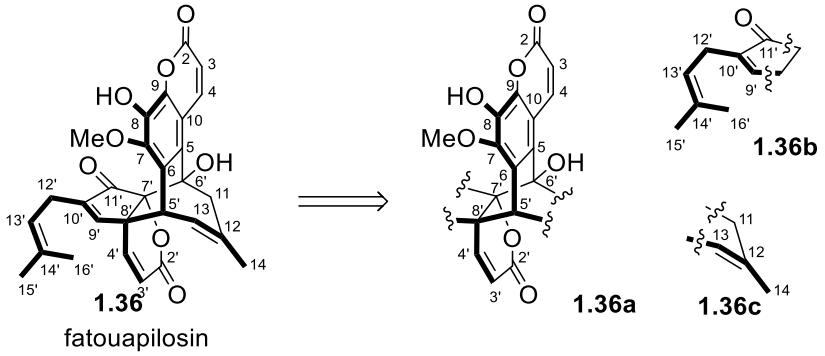


Figure 1.2 – Compounds isolated by Chiang and co-workers from *fatoua pilosa*

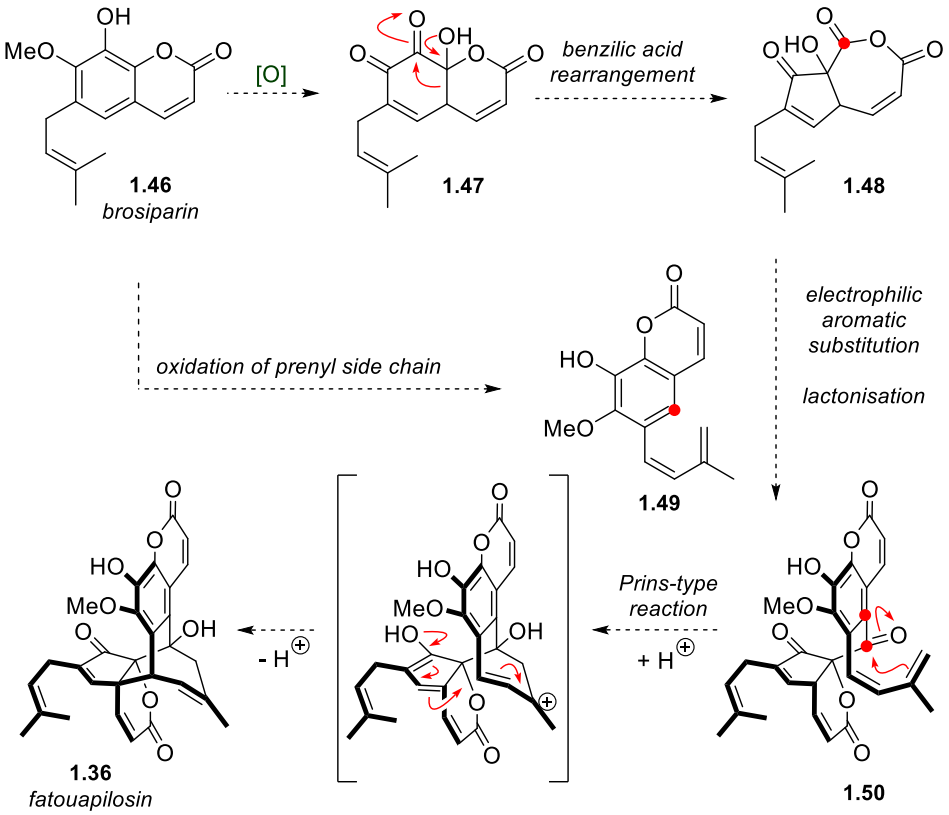
Chiang and co-workers were able to elucidate the structure of fatouapilosin (**1.36**) using a range of different analytical methods. The molecular mass and formula were determined from HRMS, and UV absorption maxima matched known literature values corresponding to a phenolic 7,8-dioxygenated coumarin system.[2] Signals from the IR spectrum indicated the presence of O–H and C=O lactone groups, while 1D ^{1}H NMR spectroscopic data showed two sets of vicinal proton couplings, characteristic of a coumarin structure, along with peaks indicating the presence of a prenyl group. After extensive analysis of 2D NMR spectroscopic data, particularly the COSY, NOESY, HSQC and HMBC spectra, Chiang and co-workers proposed a unique dimeric coumarin-derived skeleton.[1] Partial substructures **1.36a**, **1.36b** and **1.36c** were initially suggested, based on the COSY spectrum, with HMBC data subsequently used to link them together (Scheme **1.6**). Key cross-peaks between H-9′ and C-4′, C-7′ and C-8′, showed that fragments **1.36a** and **1.36b** were linked together at C-7′ and C-8′, whereas cross-peaks between H-11 and C-6′, as well as H-13 proton and C-5′ showed that fragments **1.36a** and **1.36c** were linked at C-5′ and C-6′.[1] NOESY experiments were used to determine the relative configuration of fatouapilosin, with no cross-peak observed between H-9′ and H-13**,** which suggested that fragments **1.36b** and **1.36c** were *anti* to each other.



Scheme 1.6 – Elucidation of the structure of fatouapilosin (1.36)

1.1.3 – Proposed Biosynthesis of Fatouapilosin

When examining the structure of fatouapilosin (**1.36**), it is clear that there is a latent symmetry, with two prenyl-coumarin-derived subunits present. This indicated that the natural product may form in nature via a dimerisation reaction. A biosynthetic route to fatouapilosin (**1.36**) was proposed (Scheme **1.7**), which centres around the pseudo-dimerisation of two coumarin subunits (**1.48** and **1.49**), both derived from the naturally occurring 6-prenylcoumarin compound brosiparin (**1.46**). Diene **1.49** would form by the oxidation of the prenyl group of brosiparin (**1.46**). A proposed oxidation and ring contraction of brosiparin (**1.46**) could then afford the 5,7-bicycle **1.48**. The cyclic anhydride of compound **1.48** would then undergo electrophilic aromatic substitution with the other monomeric unit **1.49**, before rapid lactonisation of the resultant hydroxy acid, giving compound **1.50**. Following this, an intra-molecular Prins reaction between the terminal alkene and newly formed ketone of compound **1.50** would form the central 7-membered ring, with a subsequent domino-Prins sequence forming two new C–C bonds to give the final compound fatouapilosin (**1.36**).



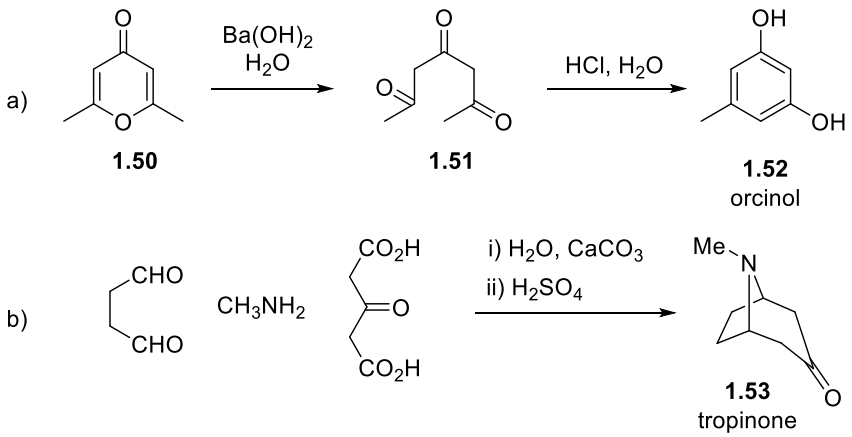
Scheme 1.7 – Proposed biosynthetic route to fatouapilosin

1.1.4 – Biomimetic Synthesis

The total synthesis of a natural product in which reactions are carried out that are closely related to those in a proposed biosynthetic route, or that mimic known enzymatic transformations, is known as a *biomimetic* synthesis. The overall concept of biomimetics, or biomimicry, is defined as the imitation of nature to solve complex human problems, and has been utilised for hundreds of years, from Leonardo Da Vinci's 15th century attempts to invent a flying machine inspired by the flight and anatomy of birds,[13] to the modern-day design of bioinspired nanomaterials for tissue engineering and bone regeneration.[14] Despite centuries of biomimetic research, the term itself was only coined in the 1950s by Otto Schmitt, who studied the nerves in squid, and attempted to engineer devices based on nerve propagation.[13]

In the field of organic synthesis, the earliest reports of biomimetic synthesis included those of Collie, who synthesised orcinol (**1.52**) from dimethylpyrone (**1.50**) through a polyketide intermediate (**1.51**) (Scheme **1.8a**),[15] and Robinson, who prepared tropinone (**1.53**) by a three component condensation of succindialdehyde, methylamine and acetone

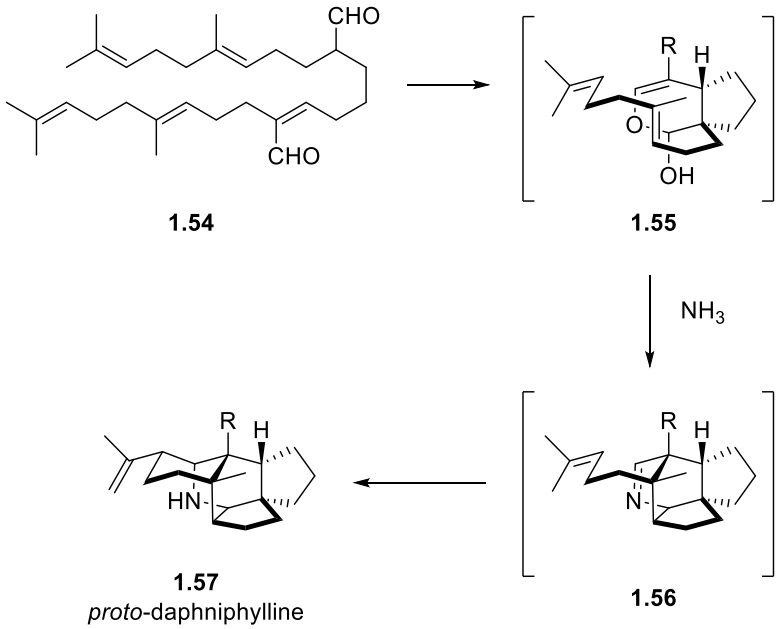
dicarboxylic acid (Scheme **1.8b**).[16] Neither of these landmark examples, however, are likely to have been initially planned out as biomimetic syntheses, but both helped to lay the foundations for future biomimetic study in total synthesis, and the eventual establishment of biomimetic synthesis as a distinct field in its own right.



Scheme 1.8 – a) Collie's synthesis of orcinol (1.52); b) Robinson's synthesis of tropinone (1.53)

In 1961, van Tamelen became the first to attempt to define this area of work, describing a synthesis that was "designed to follow, in at least its major aspects, biosynthetic pathways proved or presumed to be used in the natural construction of the end product" as a 'biogenetic-type' synthesis.[17] Breslow in 1972 went a step further, and defined the whole area of biomimetic chemistry as "the branch of organic chemistry which attempts to imitate natural reactions and enzymatic processes as a way to improve the power of organic chemistry."[18] By carrying out a synthesis in a biomimetic manner, it is possible to learn more about the inherent reactivity and behaviour of naturally occurring compounds and to develop bio-inspired reactions and multi-reaction sequences that rapidly generate molecular complexity.[18] Mimicking a biosynthetic pathway can often lead to a much shorter total synthesis in terms of step count, with the use of protecting groups and functional group-interconversions minimised. A particular example that showcases the power of biomimetic strategy is Heathcock and Piettre's synthesis of *proto*-daphniphylline (**1.57**), in which a biomimetic Michael, Diels–Alder, *aza*-Prins cascade is used to form two C–N bonds, four C–C bonds, and generate five rings in one sequence (Scheme **1.9**).[19] This biomimetic approach was applied in the short synthesis

of the related compound methyl homodaphniphyllate, which had taken 19 steps to synthesise when using a standard retrosynthetic strategy.[19]



Scheme 1.9 – Biomimetic total synthesis of *proto*-daphniphylline

One of the main areas of interest within the Lawrence group is the biomimetic total synthesis of natural products by taking inspiration from biosynthetic pathways. The syntheses have typically involved a key biomimetic dimerisation step, and include the natural products incarviditone (**1.58**), incarvilleatone (**1.59**), (−)-angiopterlactone B (**1.60**) and thymarnicol (**1.61**) (Figure **1.3**), all of which were synthesised in remarkably few steps.[20-22]

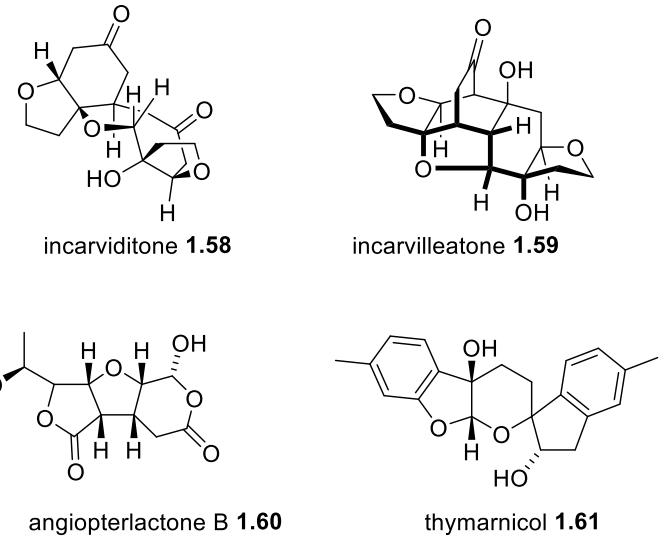


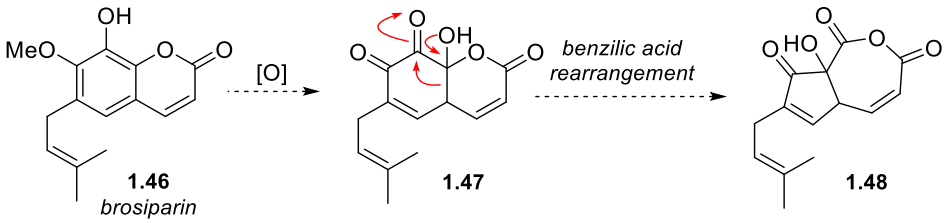
Figure 1.3 – Previous dimeric natural products synthesised in the Lawrence group

We envisaged that by designing a synthetic route to fatouapilosin (**1.36**), based closely on the proposed biosynthesis (Scheme **1.7**), it would be possible to carry out a short biomimetic total synthesis of this complex dimeric natural product. Oxidative ring contraction, one of the key steps highlighted in the proposed biosynthetic route, is an underdeveloped area in organic synthesis, so the potential to develop new, and applicable methodology for this transformation would be a significant area of interest within this project.

1.2 - Oxidative Ring Contraction

1.2.1 – A key step in the proposed biosynthesis of fatouapilosin (**1.36**)

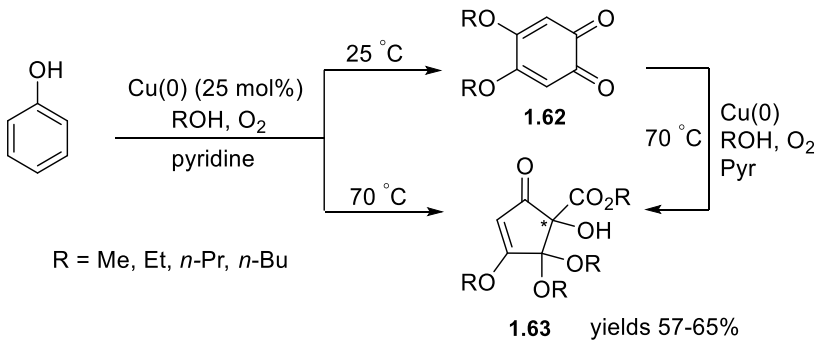
It was suggested in the proposed biosynthesis that the oxidative ring contraction of brosiparin (**1.46**) would occur by initial oxidation of brosiparin (**1.46**) to the quinone compound **1.47**, that could then undergo a ring contraction via a 1,2-shift forming a 5,7-bicyclic compound (**1.48**). One of our main tasks therefore, would be to find the right conditions to carry out this oxidative ring contractive transformation of brosiparin. By following this biosynthetic hypothesis we hoped to achieve the generation of complexity and stereogenicity in one step, from a relatively simple starting material.



Scheme 1.10 – Proposed oxidative ring contraction of brosiparin (1.46)

1.2.2 – Copper-mediated ring-contraction of phenol

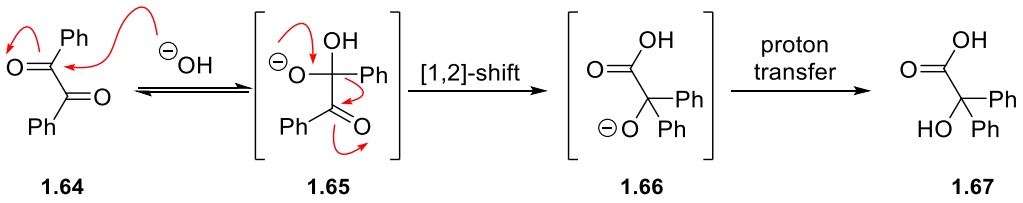
A highly significant result was reported by Rossi and co-workers, who carried out the oxidation of phenol in the presence of copper (25 mol%), pyridine, methanol and molecular oxygen.[23] At room temperature, substituted benzoquinone **1.62** was formed, a result in line with previous reported oxidations of phenols.[24] However, when the reaction was carried out at 70 °C an unexpected ring contraction of phenol was observed, giving a substituted cyclopentenone compound **1.63** (Scheme **1.11**). Unlike the vast majority of phenolic oxidation reactions, this ring contraction introduced stereochemistry into the product, as well as functional group diversity, and Rossi proposed that this could potentially be an effective and facile method of producing cyclopentenone derivatives from an inexpensive and abundant starting material.[23] The reaction was also carried out in ethanol, propan-1-ol and butan-1-ol, leading to subsequent variation in the R groups of the products.



Scheme 1.11 – Ring contractive benzilic acid rearrangement of simple phenols

1.2.3 – Benzilic-acid rearrangement mechanism

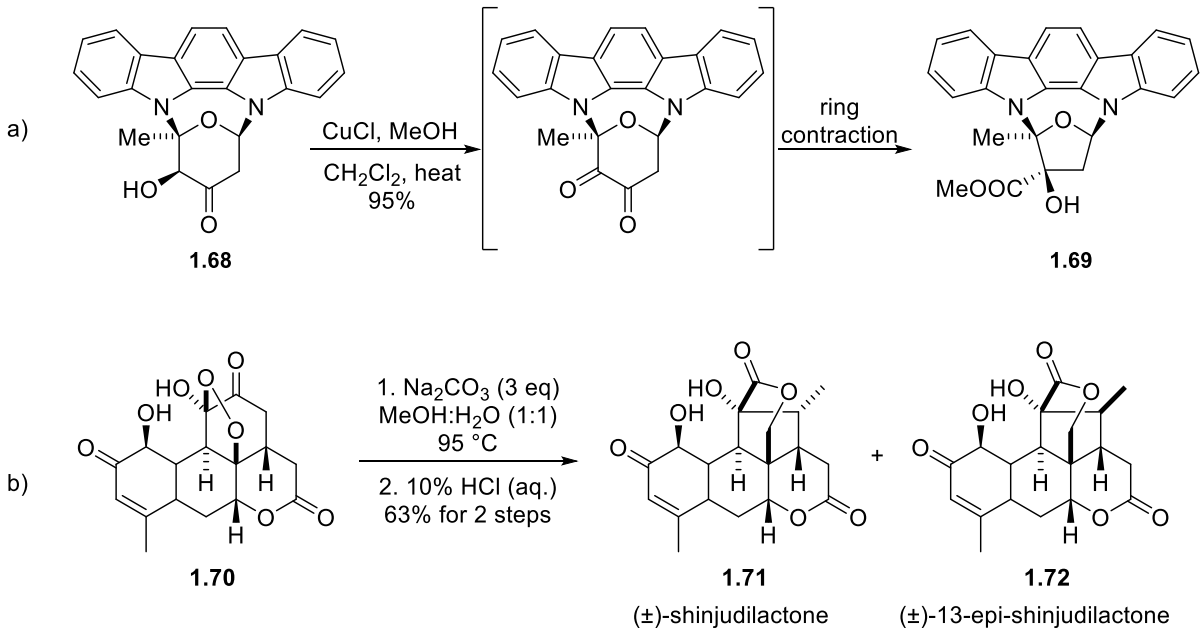
A further interesting observation from the work of Rossi and co-workers, was that when substituted benzoquinone **1.62** was resubmitted to the oxidation conditions, it cleanly underwent ring contraction to give the cyclopentenone derivative **1.63** (Scheme **1.11**). As a result, it was speculated that benzoquinone **1.62** was an intermediate formed during the oxidative ring contraction of phenol. The reaction was therefore proposed to proceed by a benzilic acid rearrangement-type mechanism. The benzilic acid rearrangement is the base-mediated rearrangement of 1,2-diketones into α-hydroxy-carboxylic acids, and is so named for the reaction of benzil (**1.64**) with potassium hydroxide to form benzilic acid (**1.67**), which was first performed by Liebig in 1838.[25-26] Initial addition of hydroxide into one of the benzil ketone groups to form alkoxide (**1.65**) is followed by a 1,2-aryl shift, giving, on acidic workup, the α-hydroxy-carboxylic acid **1.67** (Scheme **1.12**).



Scheme 1.12 – Mechanism of benzilic acid rearrangement

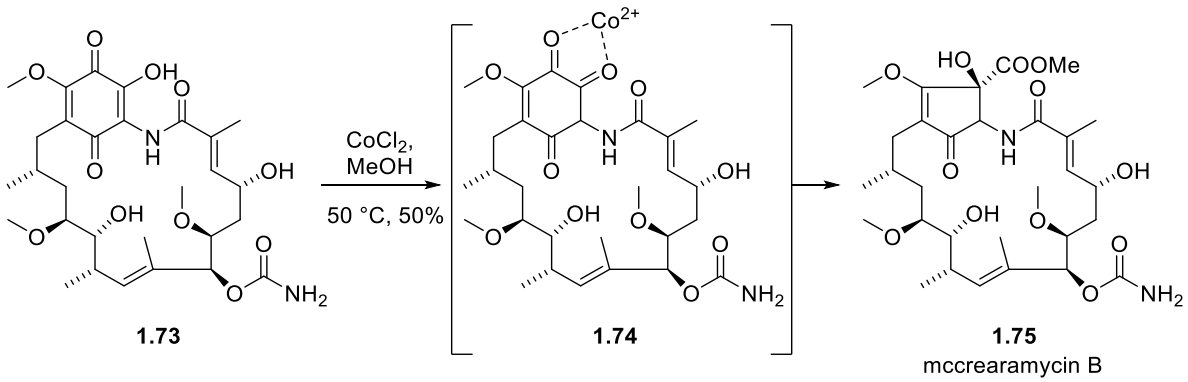
1.2.4 – Examples of oxidative ring contractions in total synthesis

Several notable examples of ring-contractions by benzilic acid rearrangement have been reported, including in the work of Wood and co-workers, who carried out the reaction on a pyranosylated indolocarbazole (**1.68**) (Scheme **1.13a**).[27] Grieco and co-workers also utilised ring contractive benzilic acid rearrangement as a key step in the total synthesis of (±)-shinjudilactone (**1.71**) and (±)-13-*epi*-shinjudilactone (**1.72**), which were formed as a 1:1 ratio from the benzilic acid rearrangement of a common precursor (**1.70**) (Scheme **1.13b**).[28]



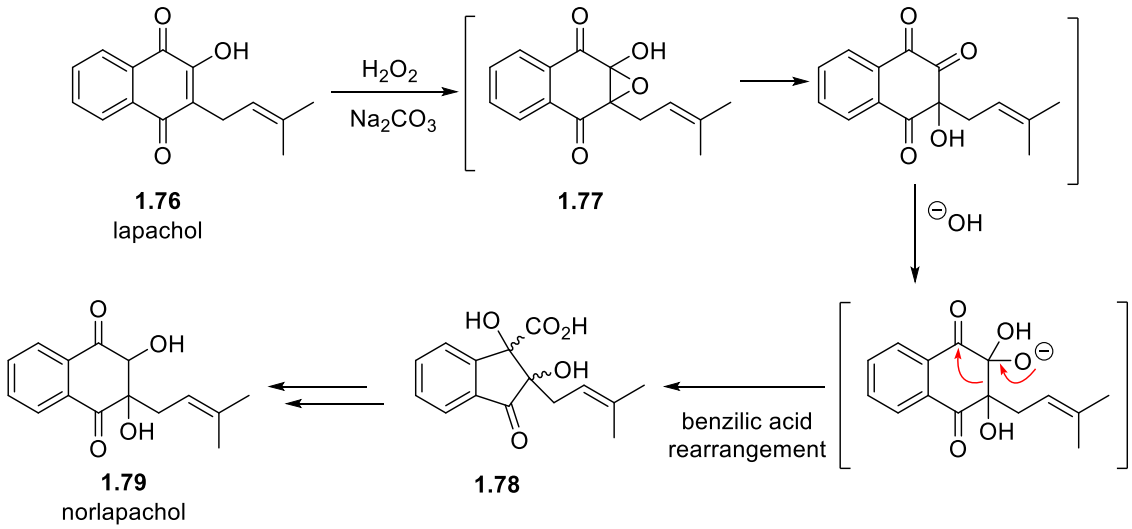
Scheme 1.13 – Applications of ring contractive benzilic acid rearrangement in the synthesis of a) pyranosylated indolocarbazole 1.70 and b) (±)-shinjudilactones 1.71 & 1.72

Further examples of the ring contractive benzilic acid rearrangement include Thorson and co-workers' total synthesis of mccrearamycins A-D, in which a key step involves the formation of a 5-membered cyclopentenone compound from a hydroxyquinone.[29] This transformation was metal-mediated and required 2 equivalents of cobalt chloride, with proposed oxidation of compound **1.73** to the corresponding ortho-quinone **1.74** followed by coordination of Co^{II} to *ortho*-quinone **1.74** and benzilic acid rearrangement to form the cyclopentenone in mccrearamycin B (**1.75)** (Scheme **1.14**).



Scheme 1.14 – Cobalt(II)-mediated benzilic acid rearrangement in the total synthesis of mccrearamycins

The synthesis of norlapachol (**1.79**) by Eyong and co-workers also utilises a benzilic acid rearrangement step as part of an overall Hooker oxidation sequence.[30] Epoxidation of napthoquinone compound lapachol (**1.76**) gave intermediate **1.77**, which underwent benzilic acid rearrangement in basic conditions to give indane carboxylic acid derivative **1.78** (Scheme **1.15**). Subsequent oxidative diol cleavage and intramolecular aldol reformed the napthoquinone ring system, and decarboxylation gave norlapachol (**1.79**) in an overall one-pot Hooker oxidation reaction.



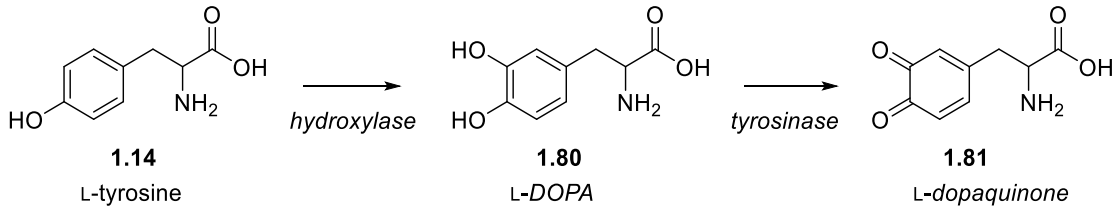
Scheme 1.15 – Benzilic acid rearrangement in the total synthesis of norlapachol

Although these examples of ring contraction of quinones by benzilic acid rearrangement exist in the literature, they have only been applied to specialised systems, and require the use of superstoichiometric reagents. Rossi's copper-catalysed ring contraction of phenol seemingly represents the only substoichiometric ring contraction of an inexpensive and abundant aromatic starting material. If we could build on his work, and develop a catalytic methodology that could be both used in the total synthesis of fatouapilosin (**1.36**), and applied generally to a range of oxygenated aromatic compounds, it could represent an excellent method of generating complex stereogenic molecules containing a range of functional groups from readily available and renewable carbon sources.

1.3 – Base metal-catalysed oxidation reactions

1.3.1 – Introduction

This project, aiming to combine biomimetic total synthesis with the development of base-metal catalysed methodology was designed as a collaboration between the Lawrence and Thomas groups. The Thomas group's expertise lies in the development of new catalytic methodologies for organic synthesis, using renewable, inexpensive and non-toxic reagents and catalysts. Iron, cobalt, manganese and aluminium-catalysed hydrofunctionalisation reactions have all been reported by the group in recent years.[31-34] It was hoped that catalytic methodology could be developed and applied to the oxidation and subsequent ring contraction of oxygenated aromatic compounds. In nature, there are a number of enzymes that carry out oxidative transformations, and many of them contain iron or copper at their core.[35-36] A particularly relevant example for this project is in the formation of L-dopaquinone (**1.81**), which is formed in nature by the oxidation of phenolic amino-acid L-tyrosine (**1.14**) to the catechol-containing L-DOPA (**1.80**), by an iron-centred hydroxylase enzyme. A copper-centred tyrosinase enzyme then catalyses the oxidation of L-DOPA (**1.80**) to L-dopaquinone (**1.81**) (Scheme **1.16**).[37]



Scheme 1.16 – Biosynthesis of L-dopaquinone (1.81)

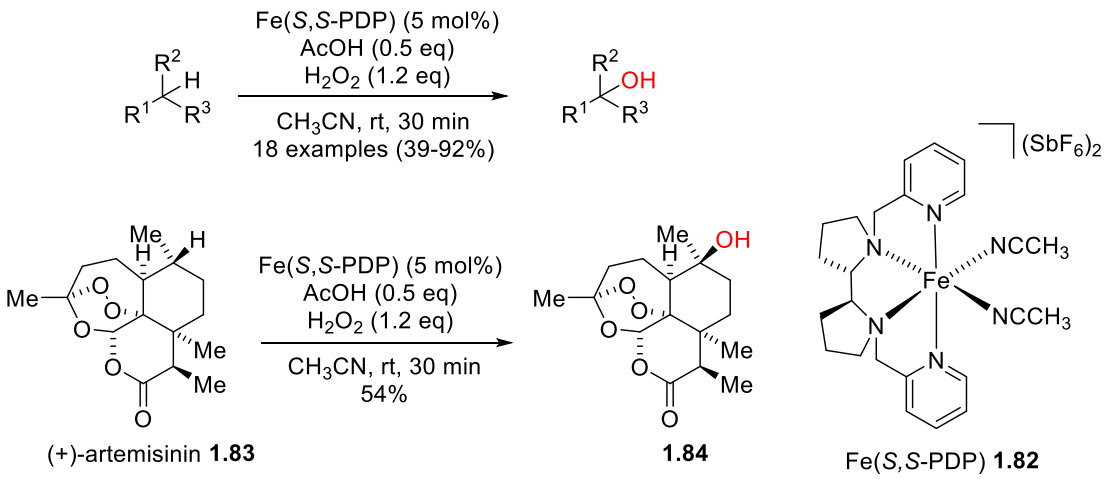
Given the Thomas group's experience in developing iron-catalysed reactions, as well as the precedent set by Rossi's use of copper (Section 1.2.2), use of catalysts containing these two metals seemed like an ideal starting point for investigations.

1.3.2 – Iron-catalysed oxidation

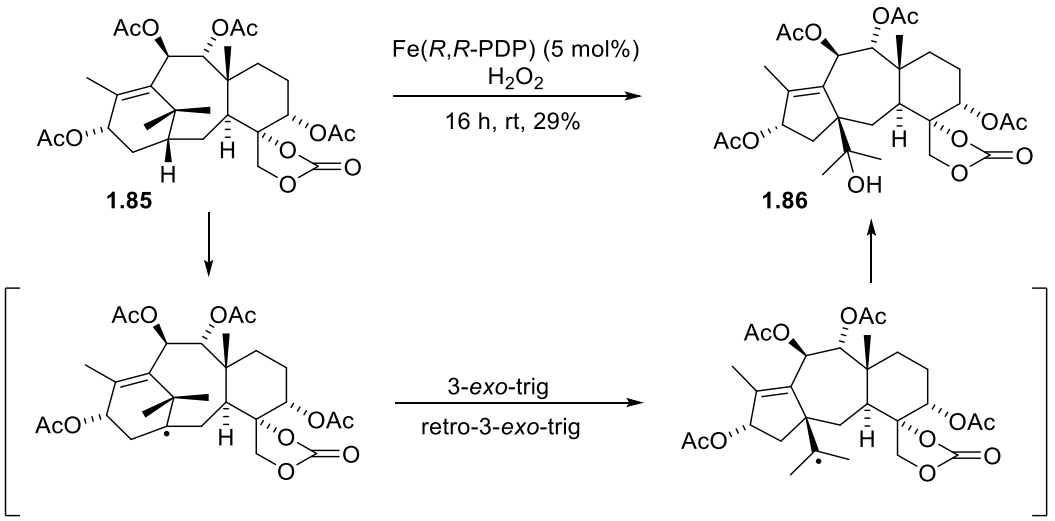
Iron-catalysed oxidation reactions are very common in nature.[38] A large number of biological transformations are achieved by selective enzymatic oxidation of both activated and unactivated C–H bonds, by cytochrome P450 enzymes.[39] Heme-containing oxygenases and both mononuclear and diiron non-heme enzymes have also been used

for this function.[40-41] In recent years, investigation into iron-catalysed oxidation reactions in organic synthesis has significantly increased, often taking inspiration from processes that occur in nature.[42] A number of catalysts have attempted to replicate the activity of cytochrome P450 by mimicking the heme structure, and incorporating multidentate porphyrin-type ligands around a metal centre.[43] Recent insight into the nature of non-heme iron oxygenase enzymes, however, has led to an increase in the use of non-heme ligands.[40, 44] Iron complexes have been studied which use tetradentate nitrogen donor ligands, and have two coordination sites available for peroxide binding and activation, compared with only one in heme complexes.[43]

White has developed a tetradentate amine Fe(PDP) catalyst (**1.82**) which, in combination with hydrogen peroxide, selectively oxidises aliphatic C–H bonds across a broad range of substrates (Scheme **1.17**).[45] Selectivity was achieved on the basis of the electronic and steric properties of the C–H bond, with carboxylate directing-groups used for the formation of 5-membered lactone products. Predictable oxidation of complex natural products and their derivatives, such as (+)-artemisinin (**1.83**) have been carried out, exemplifying the potential of this reaction for complex natural product and pharmaceutical synthesis (Scheme **1.17**).[45] White has also carried out iron-catalysed oxidations using the Fe(PDP) catalyst to form nortaxane structures (eg. **1.86**) from taxanes (eg. **1.85**), by a domino 3-*exo*-trig, retro-3-*exo*-trig reaction (Scheme **1.18**).[46] This method offers great potential for the diversification of complex natural product derivatives.

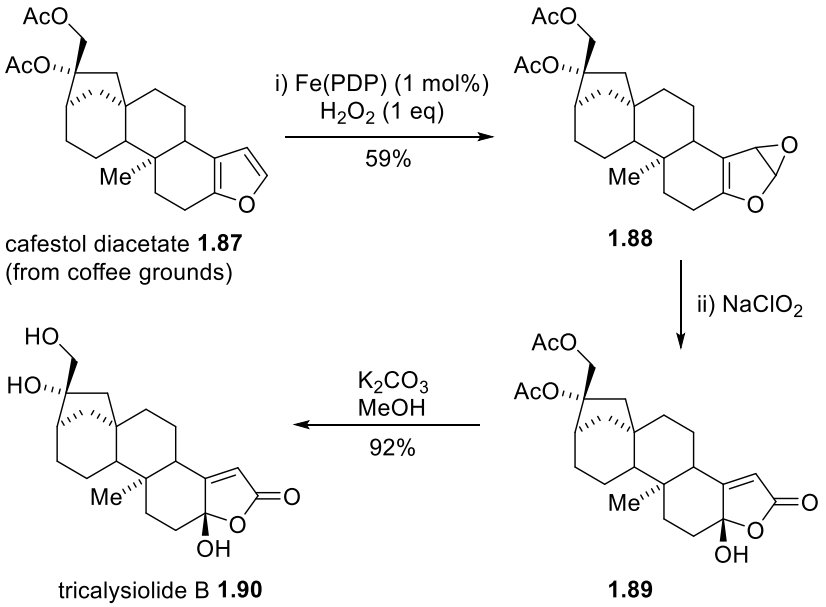


Scheme 1.17 – Iron-catalysed C–H oxidation scope and oxidation of (+)-artemisinin



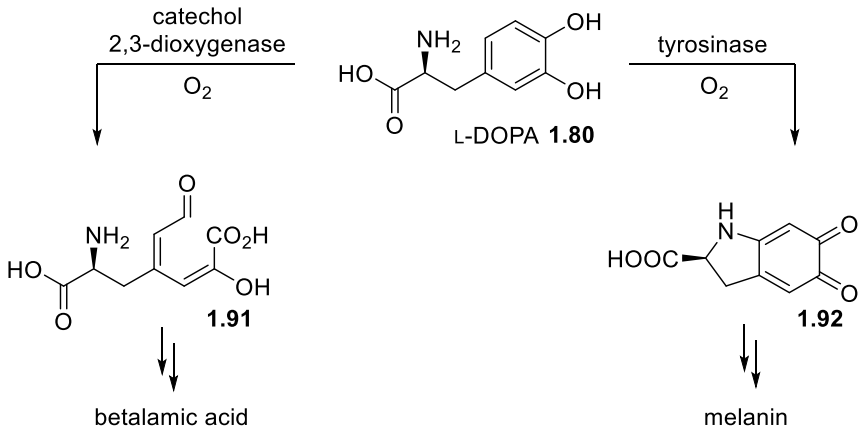
Scheme 1.18 – Iron-catalysed synthesis of nortaxanes from taxanes, through a carbon-centred radical

Further work from White has seen the use of Fe(PDP) catalyst **1.82** to oxidise cafestol, (a terpene found in coffee) to the diterpene natural product tricalysolide B (**1.90**) (Scheme **1.19**).[47] The Fe(PDP) complex (**1.82**) acts as an enzyme mimic, and supports the hypothesis that this class of natural products are derived from cafestol through a cytochrome P-450-mediated furan oxidation. Cafestol diacetate (**1.87**) underwent iron-catalysed epoxidation, to form compound **1.88**, followed by further oxidation using $NaClO_2$ to give the hydroxy-lactone product **1.89** as a single diastereomer. Acetate cleavage then resulted in the formation of tricalysolide B (**1.90**)



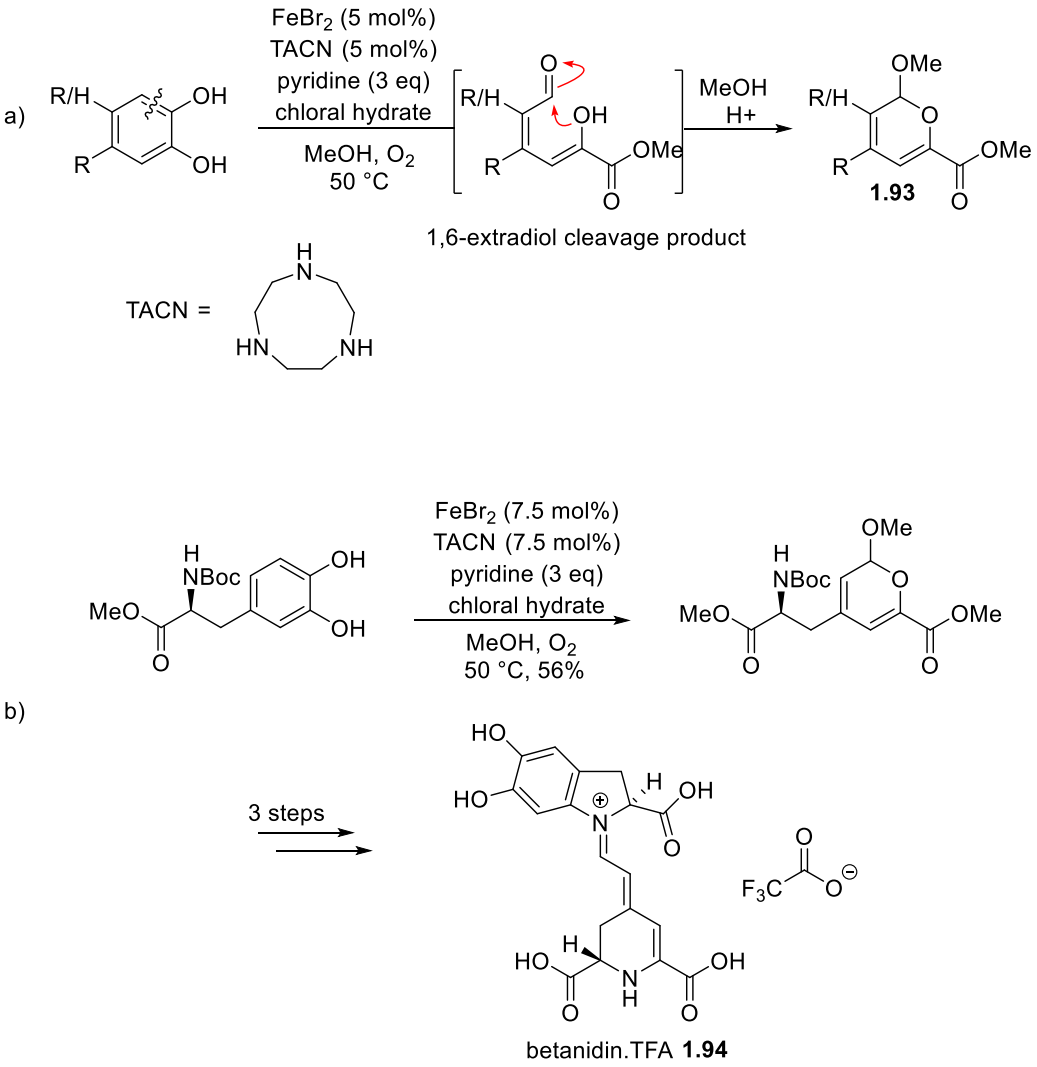
Scheme 1.19 – Synthesis of tricalysiolide B using iron-catalysed epoxidation

The enzymatic oxidation of L-DOPA (**1.80**) has been proposed in the biosynthesis of melanin, with the catechol group of L-DOPA (**1.80**) undergoing oxidation to the corresponding *ortho*-quinone (**1.92**).[48] However, an alternative pathway, often found in certain plants and fungi, involves the extra-diol cleavage of the catechol group by catechol-2,3-dioxygenase enzymes, to give compound **1.91**, an intermediate in the biosynthesis of betalamic acid (Scheme **1.20**).[49]



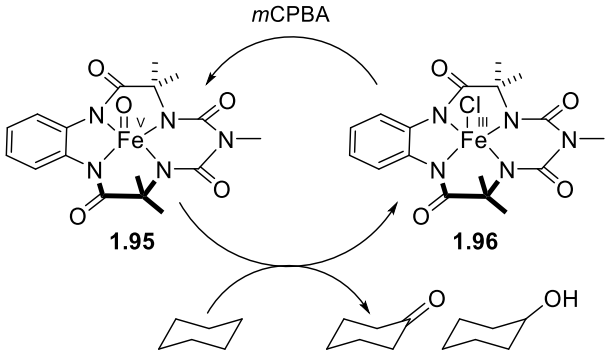
Scheme 1.20 – Enzyme-catalysed oxidative transformations of L-DOPA

Trauner carried out a biomimetic extra-diol cleavage of catechols using an $FeBr_2$ and 1,4,7-triazacyclononane (TACN) catalytic system, to give 2-methoxy-2-*H*-pyrans (eg. **1.93**) The reaction was used in the 5-step synthesis of betanidin (**1.94**), which is formed using two separate derivatives of L-DOPA (Scheme **1.21**).[37]



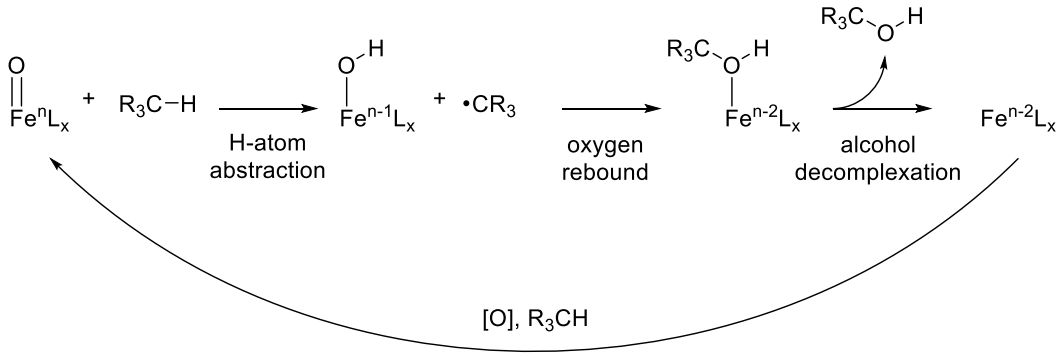
Scheme 1.21 – a) Iron-catalysed extra-diol catechol cleavage to form pyrans, and b) in the synthesis of betanidin (1.94)

A number of examples of high oxidation state iron-species have been reported for the oxidation of C–H and C–O bonds.[50-51] These include the work of Sen Gupta and co-workers, who have developed a peroxidase-mimicking iron(V)-oxo complex (**1.95**) with a tetra-amido macrocyclic ligand (TAML), for use in the oxidation of a range of alkanes and alcohols (Scheme **1.22**).[52-53] The active iron (V)-oxo species was proposed to form *in situ* from the reaction of iron(III) chloride complex **1.96** with *m*CPBA.[52]



Scheme 1.22 – High-valent iron-oxo oxidation catalysis

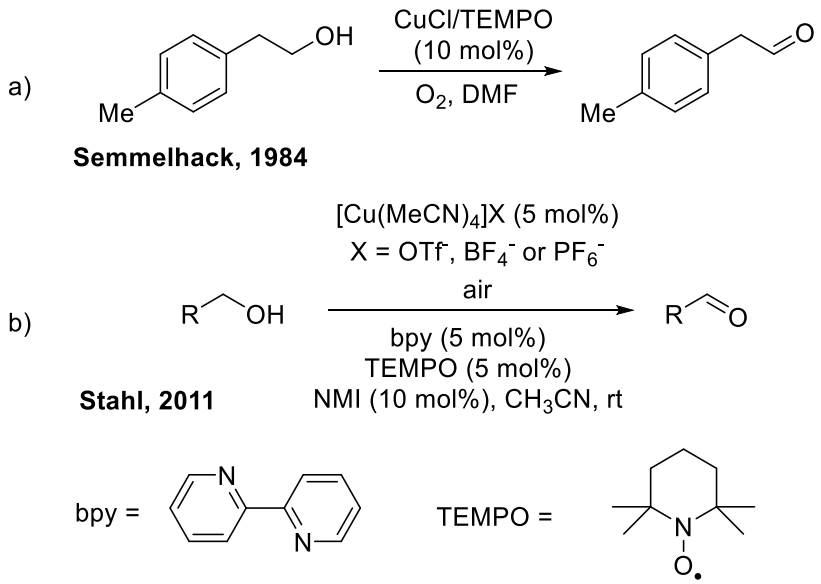
The generally accepted mechanism for enzymatic iron-catalysed hydroxylation, as well as by biomimetic iron-centred catalysts, is the oxygen rebound mechanism.[39, 54] The first step is hydrogen atom abstraction from a C–H bond in the substrate by the high-valent iron-oxo species (Fe^{n}=O, n usually = IV or V), resulting in the substrate radical R· and a reduced iron hydroxide species (Fe^{n-1} –OH) (Scheme **1.23**). The rebound step then proceeds by the addition of the organic radical (R·) to the oxygen bound to the iron centre, forming an alcohol, which then dissociates from iron, generating the R–OH product and an iron(n-2) complex, which is subsequently oxidised and re-enters the catalytic cycle.



Scheme 1.23 – Oxygen rebound mechanism for iron-catalysed C–H hydroxylation

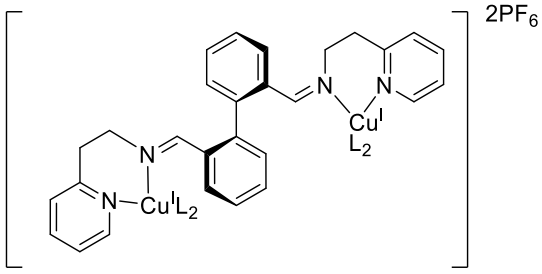
1.3.3 – Copper-catalysed oxidation

Copper catalysts have been used in a range of aerobic oxidations, often taking inspiration from the many copper-based oxidation enzymes. The ability of copper to easily access oxidation states from Cu^0 to Cu^{III} allows it to act through one-electron or two-electron processes, and to associate with a wide variety of functional groups. A number of reviews on copper oxidation chemistry have recently been published, covering the copper-catalysed oxidation of a number of different reaction types, including, but not limited to the oxidation of hydrocarbons, alcohols, carbonyls, phenols, imines, amines and thiols.[55-57] Of particular interest for this project was the use of copper for the oxidation of alcohols and phenols. A number of reports on the copper-catalysed aerobic oxidation of alcohols have been developed, with several examples employing the use of the *N*-oxide compound TEMPO. Semmelheck and co-workers reported one of the earliest examples of this system, combining CuCl and TEMPO (10 mol% of each), with O_2 as the oxidant, for the oxidation of a series of primary benzylic and allylic alcohols (Scheme **1.24**).[58] This system and others, including those reported by Sheldon, Knochel and Marko had limited applicability in traditional synthetic chemistry applications, either due to reduced activity with aliphatic alcohols, or because of the use of pure O_2 or fluorinated solvents.[59-61] Stahl and Hoover, however, developed a highly practical catalyst system using a Cu^I salt with a 2,2′-bipyridine (bpy) ligand and TEMPO. They were able to oxidise a wide range of primary (and unprotected secondary) alcohol substrates to the corresponding aldehydes or ketones, using ambient air as oxidant (Scheme **1.24**).[62]

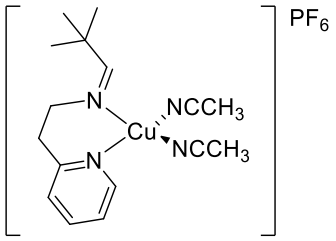


Scheme 1.24 – Examples of copper-catalysed alcohol oxidation reported by a) Semmelhack and b) Stahl

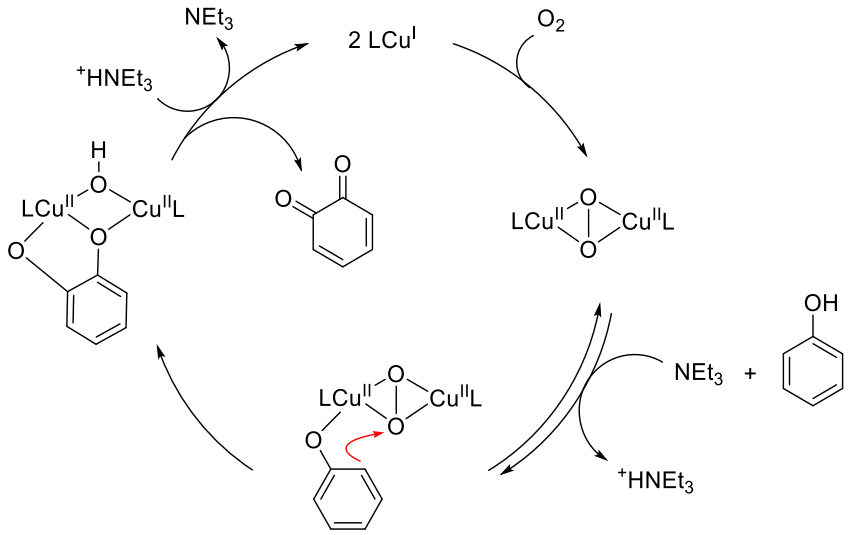
As previously referred to (section 1.3.1), copper is present in tyrosinase enzymes that can carry out the oxidation of phenols to catechols and subsequently quinones.[63] Catechol oxidase is another example of a copper-containing enzyme, that can oxidise catechols to quinones. The active sites of both of these enzymes contain a binuclear copper centre coordinated by six histidine residues. The enzymes have been shown to bind dioxygen in a bridging structure, where the Cu^{I} centres in the deoxy state are converted into Cu^{II} in the oxy state.[63] A significant amount of work has been reported concerning the development of copper catalysts for the oxidation of phenols to *ortho*-quinones with O_2 as a stoichiometric oxidant, by mimicking the reactivity of these enzymes. Initially this was mainly limited to the use of stoichiometric copper reagents,[64] with only a few reports of catalytic oxidation.[65] Early examples of the use of substoichiometric copper catalysts for phenol oxidation included the work of Reglier and co-workers, who developed a dinuclear copper catalyst with a polydentate imine ligand (**1.97**), with Tuzcek and co-workers later reporting a similar mononuclear copper(I) complex (**1.98**) (Scheme **1.25**).[66] In both of these processes the catalytic reaction proceeded via an oxo-bridged active species, following the reaction of the complex with molecular oxygen, as shown in the general mechanism for phenol to quinone oxidation, as proposed by Stack, Herres-Pawlis and co-workers (Scheme **1.25**).[67] However, these examples were limited to small scale and incomplete conversion and used superstoichiometric triethylamine, so did not find practical application.



1.97 **Reglier, 1990**

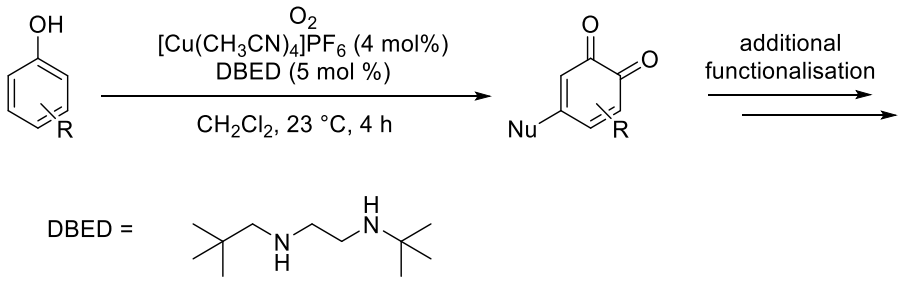


1.98 **Tuscek, 2010**



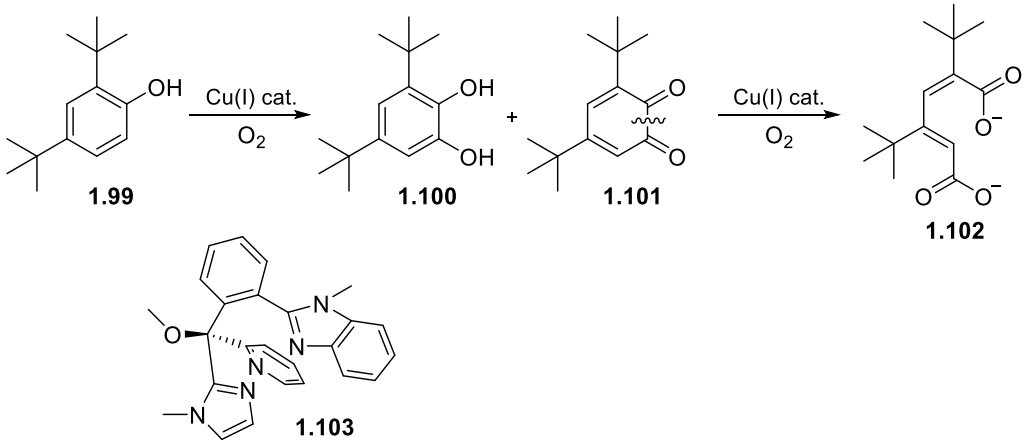
Scheme 1.25 – Early examples of tyrosinase-mimicking copper oxidation catalysts, and general phenol to quinone oxidation mechanism

Recently, a significant amount of work in this area has been carried out by Lumb and co-workers, who developed a practical catalytic aerobic oxygenation of phenols to *ortho*-quinones, using a Cu^{I} complex, $[Cu(CH_3CN)_4]PF_6$ along with di-*tert*-butylethylenediamine , with very low catalyst loadings (Scheme **1.26**).[68] The resultant *ortho*-quinones have been shown to be very versatile intermediates, and Lumb was able to use this method to synthesise a range of polyfunctional heterocyclic compounds.[69] This work has also been applied to a range of primary and benzylic alcohols, to enable a catalytic oxidation that does not require use of an external *N*-oxide co-oxidant such as TEMPO.[70]



Scheme 1.26 – Lumb's copper-catalysed oxygenation of phenols to *ortho*-quinones

Limberg and co-workers reported a more unusual example, where they developed Cu^{I} complexes containing tripodal ligands with three pyridiyl/imidazoyl *N*-donor units (such as **1.103**), that mimicked both monooxygenase and catechol dioxygenase enzyme activity.[71] Dioxygenase enzymes are responsible for C–C bond cleavage of catechols, which is an important part of several metabolic pathways. Limberg's complexes catalysed the oxidation of phenol **1.99** to the corresponding catechol (**1.100**) and quinone (**1.101**), which was then followed by an oxidative cleavage step to give dicarboxylate compound **1.102**, which could lead to a number of different oxidation products (Scheme **1.27**).

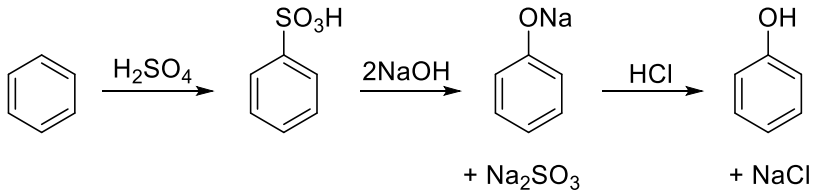


Scheme 1.27 – Oxidation and oxidative cleavage of phenolic compounds

1.4 - Oxygenated aromatic compounds

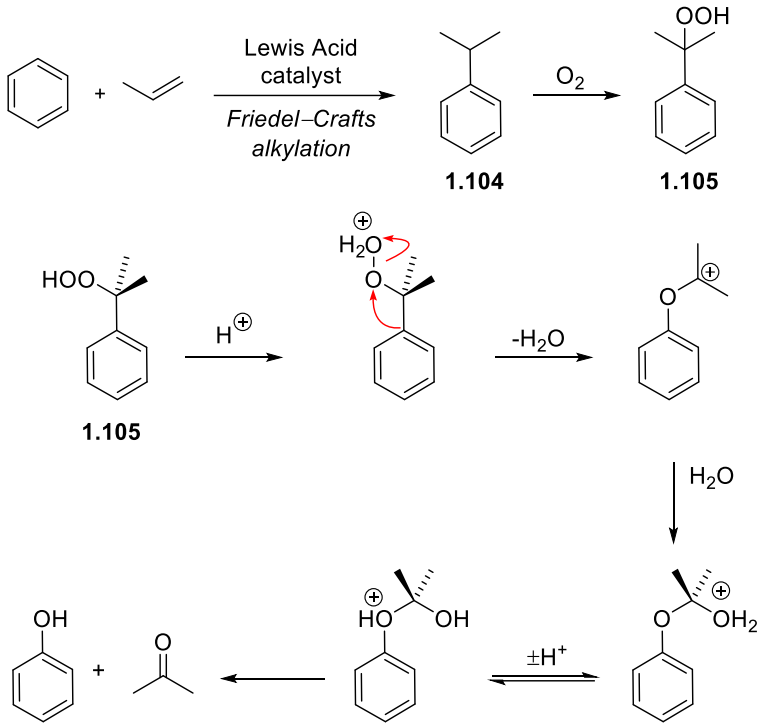
Among the many reasons for the interest in the oxidation of phenols is their vast abundance and potential for functionalization to useful materials, dyes, biologically active compounds and natural products.[72] Phenols and other oxygenated aromatic

compounds (OACs) are often readily available feedstock chemicals, the bulk of which are synthesised from petroleum-derived hydrocarbons.[73] Phenol was first discovered by Runge in 1834, who isolated it from coal tar,[74] with subsequent work by Laurent and Kekule enabling the determination of its molecular structure by 1858.[72] Until the end of the 19th century all phenol was extracted from coal, and mainly used as a disinfectant, but in the 1900s demand for phenol-based polymers and bisphenol compounds grew.[72] Subsequently, the benzenesulfonate process was developed to produce phenol on an industrial scale. This involved the reaction of benzene with sulphuric acid to give benzene sulfonic acid, with subsequent reaction with sodium hydroxide leading to sodium phenoxide, which was then converted to phenol using hydrochloric acid (Scheme **1.28**).[75]



Scheme 1.28 – Benzenesulfonate process to produce phenol

Nowadays, approximately ten million tonnes of phenol are produced each year, the majority from the cumene process (also known as the Hock process), which has replaced the benzenesulfonate process, largely due to the fact that it produces less waste products. A key feature of the cumene process is that both phenol and fellow commodity chemical acetone are produced from inexpensive, petroleum-derived hydrocarbon starting materials benzene and propylene (Scheme **1.29**).[76] Initial Friedel-Crafts alkylation of benzene by propylene, using an acid catalyst (generally phosphoric acid) leads to formation of cumene (**1.104**). Cumene hydroperoxide (**1.105**) is formed by oxidation of cumene (**1.104**) in air, which proceeds by initial benzylic proton abstraction from cumene, then reaction of the resulting cumene radical with molecular oxygen. The following step is the acidic hydrolysis of cumene hydroperoxide (**1.105**), which results in formation of phenol and acetone, via a Hock rearrangement mechanism (Scheme **1.29**).[76]



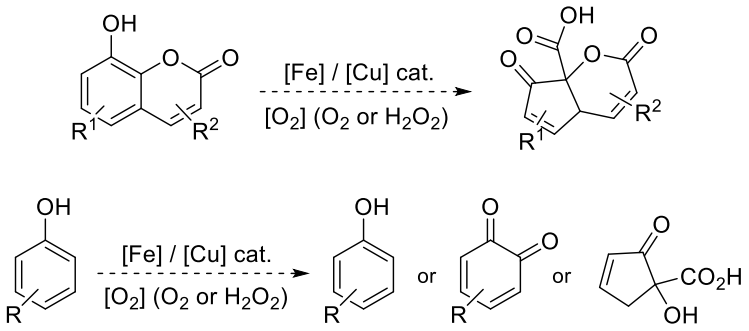
Scheme 1.29 – Cumene process to form phenol and acetone

The co-production aspect of the cumene process can be a major advantage, but only if both products are in similar demand. Overproduction can decrease the economic viability of the process, and as a result co-product free routes to phenol have been explored, including direct oxidation of benzene to phenol, but none of these processes have thus far been commercialised on a large-scale.[72]

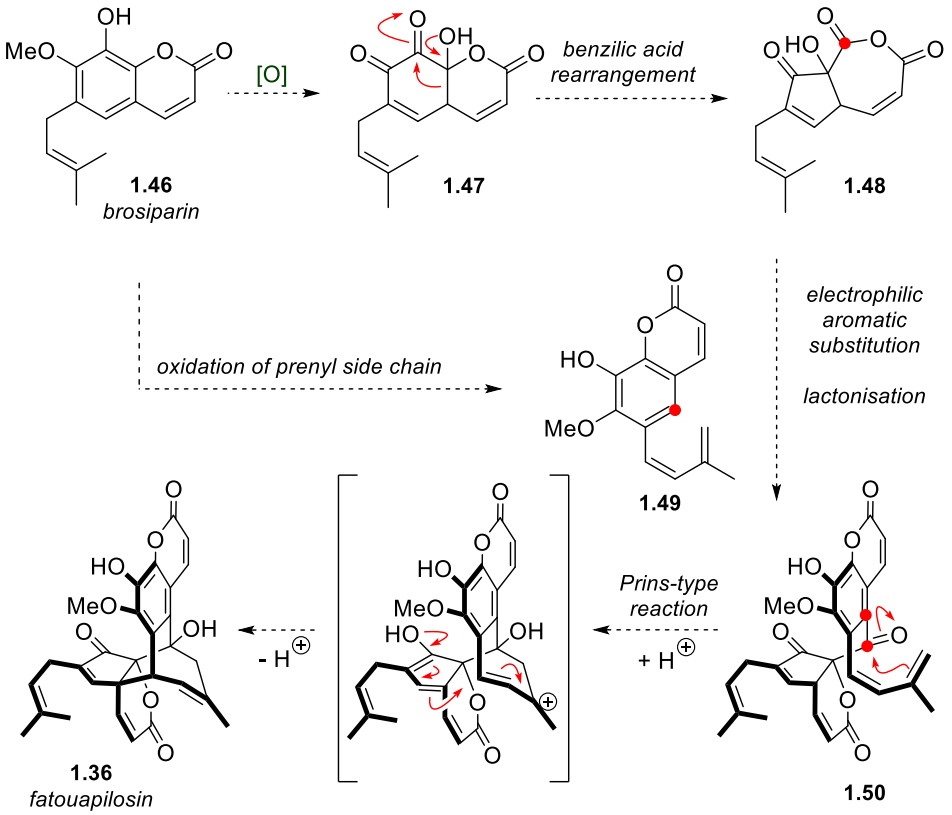
In recent years the recovery of OACs from renewable sources such as plant biomass (particularly from lignin) has received increased attention.[73, 77] However, these aromatic compounds generally have flat structures that lack functional diversity and stereochemical complexity. The development of oxidative chemistry to functionalise phenols and OACs would introduce a renewable starting point for the synthesis of more complex molecules for use in the synthesis and production of fine chemicals.[77]

1.5 - Project Aims

The main aim of this project was to develop a sustainable and biomimetic method of oxidative ring contraction of phenolic compounds, enabling the generation of complex molecules from simple and abundant aromatic starting materials (Scheme **1.30**). We aimed to use earth-abundant and sustainable transition metals as catalysts, and to test the reactions with a large variety of oxygenated aromatic compounds, with the objective of developing a general procedure for the oxidative ring contraction of phenols and oxygenated aromatic compounds. The typical development paradigm for catalysis is to develop the system using simple substrates, then increase complexity to increase the robustness and scope of the catalysts. However, this project will take an alternative route, by starting with brosiparin, a complex substrate, which we strongly suspect to undergo the targeted oxidative ring contraction in nature. It was hoped that this reactivity could be exploited, and the catalysts tailored for this type of reaction, and demonstrate high robustness and functional group tolerance from the start. In this way, a number of potential issues can be overcome early on, and a method of catalysis that is applicable to a vast range of complex substrates and tolerant to a number of functional groups can be established. We would then hopefully also be able to achieve a short, biomimetic total synthesis of fatouapilosin (**1.36**) (Scheme **1.31**).



Scheme 1.30 – Envisaged biomimetic oxidation of OACs



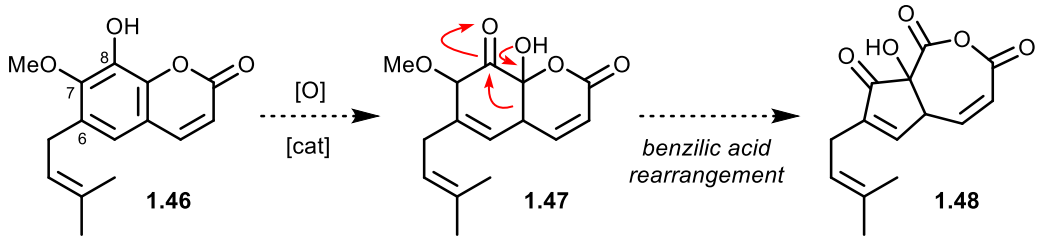
Scheme 1.31 – Proposed biosynthesis of fatouapilosin via oxidative ring-contractive benzilic acid rearrangement

Chapter 2 – Synthesis of Brosiparin

2.1 – Brosiparin

2.1.1 - Introduction

As described previously, an important intermediate in the proposed biosynthesis of fatouapilosin (**1.36**) (Scheme **2.1**) is the monomeric coumarin, brosiparin (**1.46**). Brosiparin (**1.46**), itself a natural product that has never previously been synthesised, contains a coumarin backbone, with a prenyl group at the 6-position, a methoxy group at the 7-position and a hydroxyl group at the 8-position (Scheme **2.1**). The key step in the proposed route to fatouapilosin (**1.36**) involves the oxidation and benzilic acid rearrangement of brosiparin (**1.46**) to compound **1.47**, with a 6- to 5-membered ring contraction similar to that previously described in Scheme **1.11**, Chapter **1**.



Scheme 2.1 – Brosiparin oxidation and subsequent benzilic acid rearrangement

It was decided that the start point of the project would be the synthesis of brosiparin (**1.46**), as it is both an important precursor in the total synthesis of fatouapilosin (**1.36**) and an ideal initial substrate to develop a catalytic method of oxidative ring contraction by benzilic acid rearrangement. Starting with simple phenols and building up complexity could lead to problems down the line, but the use of a more complex substrate, such as brosiparin (**1.46**), which contains multiple functionalities, could avoid any potential issues. Another major factor in this decision is the fact that if the biosynthetic proposal is correct, we can aim to mimic the ring contraction that occurs in nature, as brosiparin (**1.46**) should be predisposed to this kind of reactivity.

2.1.2 – Isolation

Brosiparin (**1.46**) was first isolated in Brazil in 1971 by Braz Filho and co-workers. It was extracted from the bark of the *Brosimum rubescens* plant, along with a number of other similar coumarin derived compounds (Figure **2.1**).[78] *Brosimum rubescens* is a member of the Moraceae family and its heartwood, which is often used in carpentry, contains a large proportion of the known coumarin xanthyletin **1.39**, along with minor amounts of other known coumarins, 7-demethylsuberosin **2.1** and luvangetin **2.2**. Two novel coumarins were also isolated, namely brosiparin **1.46** and brosiprenin **2.3**. Both contain prenyl side chains at C-6 hydroxy- and methoxy- groups at the C-7 and C-8, with brosiprenin **2.3** displaying an addition prenyl group at C-5.

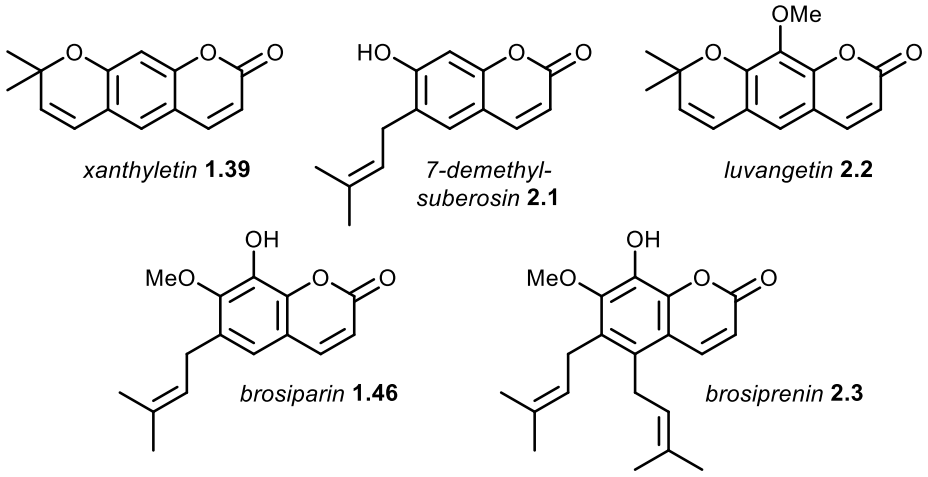
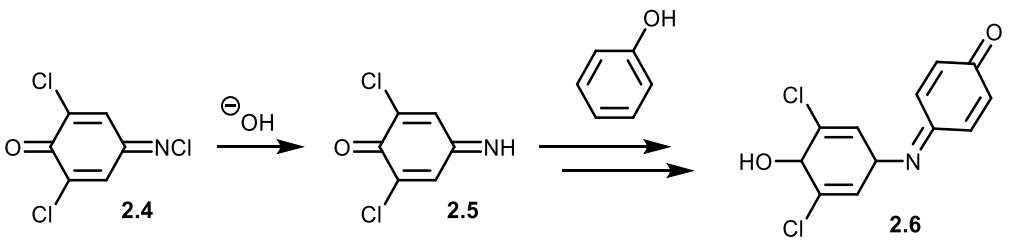


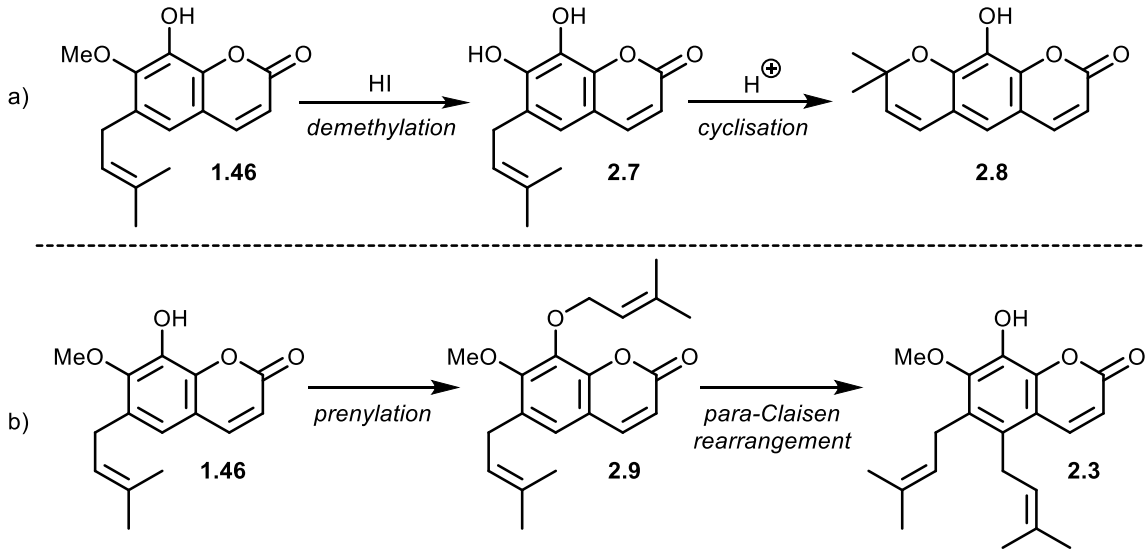
Figure 2.1 – Coumarins derived from *Brosimum rubescens*

Tests were carried out on the novel compounds brosiparin (**1.46**) and brosiprenin (**2.3**) in order to elucidate their structures and confirm the positions of each functional group. Both compounds were acetylated and the resulting UV spectra showed peaks typical of 7-alkoxycoumarins. A Gibbs test was carried out on brosiparin (**1.46**) with a positive result, leading the isolation chemists to suggest that the hydroxyl group was *para* to the unsubstituted aromatic position. The Gibbs test is used to determine the presence of phenols, by the reaction of Gibbs reagent (**2.4**) with a phenol unsubstituted at the *para*-position. The Gibbs reagent adds to the *para*-position of the molecule to form an indophenol (eg. **2.6**), which results in a dramatic colour change with pH (Scheme **2.2**).[79] Although the Gibbs test was widely used for this purpose at the time, subsequent literature has suggested that many para-substituted phenols do indeed react with Gibbs reagent, and form indophenol products.



Scheme 2.2 – Gibbs test, used to confirm the presence of phenols

A strong suggestion that the methoxy group was adjacent to the prenyl group was given by the acid-catalysed cyclisation of the prenyl group only occurring after cleavage of the methoxy group (Scheme **2.3a**). The structure of brosiprenin (**2.3**) was confirmed by comparison of the isolated sample with a synthetic sample prepared by prenylation of brosiparin **(1.46)**, then *para*-Claisen rearrangement of the resultant *O*-prenylated compound **2.9** to give brosiprenin **(2.3**) (Scheme **2.3b**).

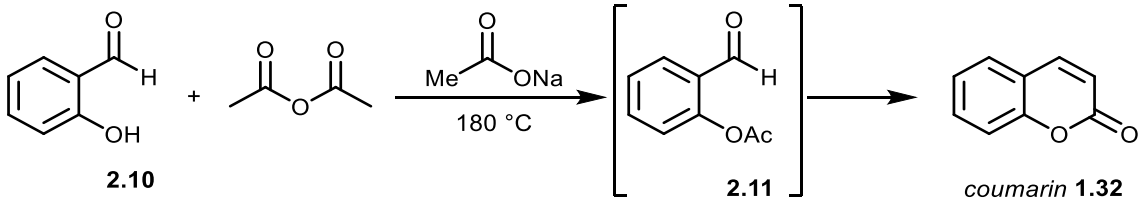


Scheme 2.3 – a) Studies carried out to determine the structure of brosiparin (1.46); b) to determine to structure of brosiprenin (2.3)

2.2 – Design of synthesis

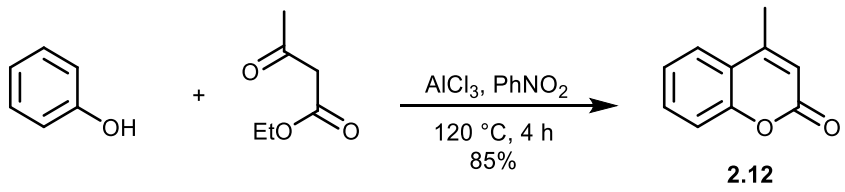
2.2.1 – Coumarin formation methods

The key step in the synthesis of brosiparin (**1.46)** would be the formation of the coumarin framework. A number of different methods have been reported for the synthesis of coumarin and coumarin-derived compounds.[80] A well-established and particularly prevalent method is the Perkin reaction, which was first reported in 1868.[81] Salicylaldehyde (**2.10**) was heated with acetic anhydride and sodium acetate, with an intermediate *O*-acetyl salicylaldehyde (**2.11**) formed, which underwent an intramolecular aldol-type condensation to form coumarin (**1.32**) (Scheme **2.4**). The Perkin reaction has been used to form a number of substituted coumarins, but a major drawback is the difficult formation of 2-hydroxybenzaldehyde starting materials from substituted phenols.[80]



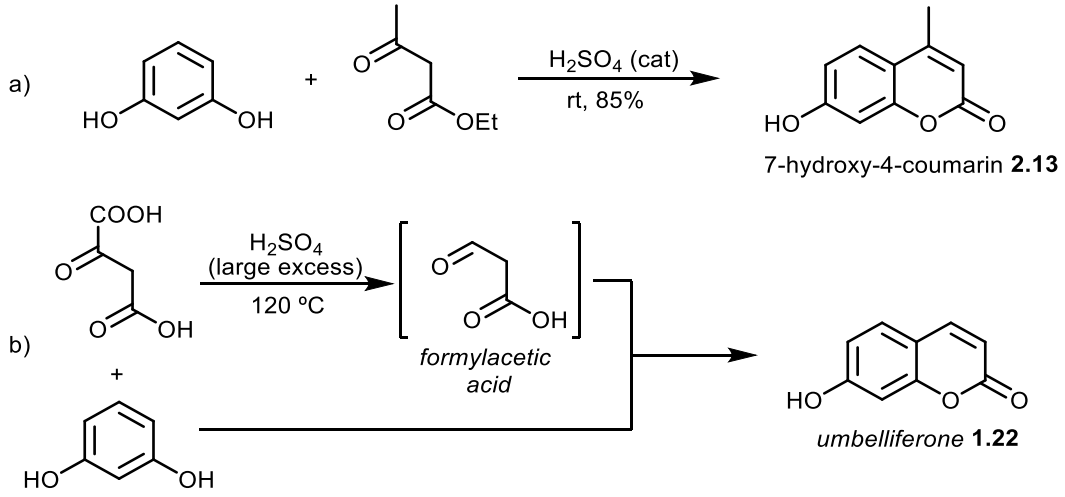
Scheme 2.4 – Perkin reaction to form coumarin

Other reported coumarin formation methods include the use of Claisen, Wittig and Knoevenagel chemistry.[80, 82-84] However, we initially considered that the most promising method for the synthesis of brosiparin (**1.46**) would be the Pechmann condensation, first reported in 1884.[85] The Pechmann condensation involves the reaction of phenols with β-keto esters using Lewis acids, such as $AlCl_3$, to catalyse the transesterification, followed by a Friedel-Crafts type cyclisation to form the new ring system.



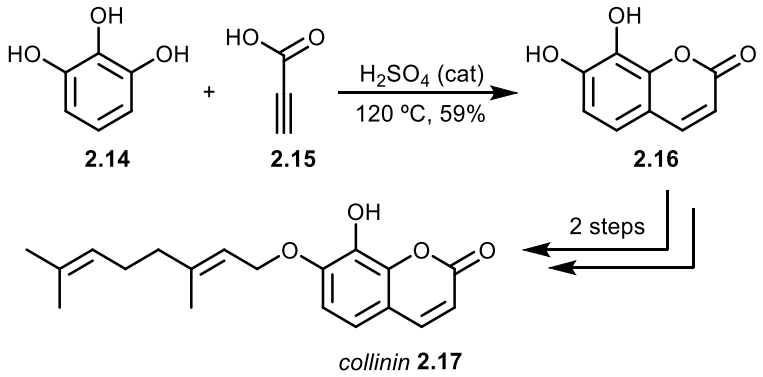
Scheme 2.5 – Formation of 4-methylcoumarin (2.12) by Lewis acid-catalysed Pechmann reaction

A drawback of this reaction is the fairly harsh conditions required, typically at temperatures between 100-130 °C, though it has been shown that Pechmann reactions of highly-activated phenols can occur at room temperature using ethyl acetoacetate and catalytic sulfuric acid (Scheme **2.6a**).[86] To form coumarins unsubstituted at the 4-position (such as brosiparin (**1.46**)), however, requires the use of formylacetic acid or esters. These compounds are unstable, so must be prepared *in situ* from malic acid and super-stoichiometric sulfuric acid at temperatures above 100 °C, such as in the formation of the natural product umbelliferone **1.22** (Scheme **2.6b**).[87]



Scheme 2.6 – Pechmann reactions using sulfuric acid to form a) 7-hydroxy-4-methylcoumarin and b) umbelliferone

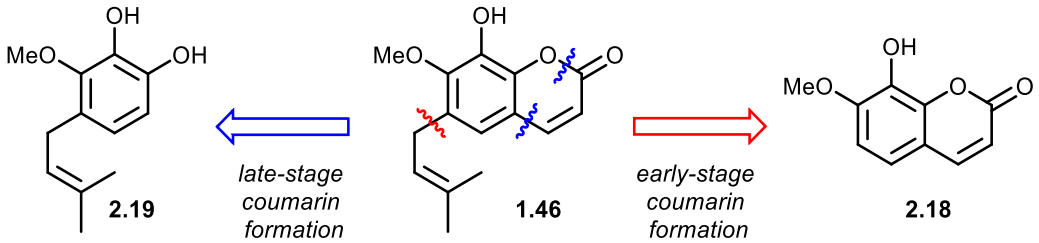
More recently, a synthesis of 7,8-dihydroxycoumarin (**2.16**) was reported by Curini as part of the total synthesis of the coumarin derived natural product collinin (**2.17**) (Scheme **2.7**).[88] The reaction of pyrogallol (**2.14**) and propiolic acid (**2.15**) in solvent-free conditions with a catalytic amount of concentrated sulphuric acid gave coumarin compound (**2.16**) in a reasonable yield of 59%. This straightforward formation of a 7,8-disubstituted coumarin was ideally suited for the synthesis of brosiparin (**1.46**).



Scheme 2.7 – Curini's synthesis of 7,8-dihydroxycoumarin (2.16) in the total synthesis of collinin (2.17)

2.2.2 – Retrosynthesis and planned routes

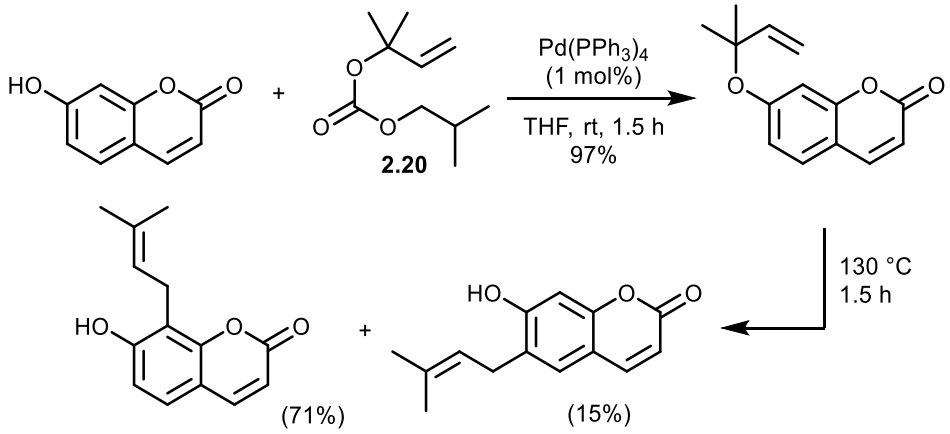
When examining the molecule retrosynthetically, it became clear that there were two obvious points of disconnection, leading to two main synthetic strategies. The first would involve the synthesis of the main coumarin backbone, to give compound **2.18** followed by selective prenylation at the 6-position on the ring whereas the alternative is to form the coumarin as the final step, with earlier prenylation of an aromatic ring to give a compound such as **2.19** (Scheme **2.8**).



Scheme 2.8 - Retrosynthetic strategies for the formation of brosiparin (1.46)

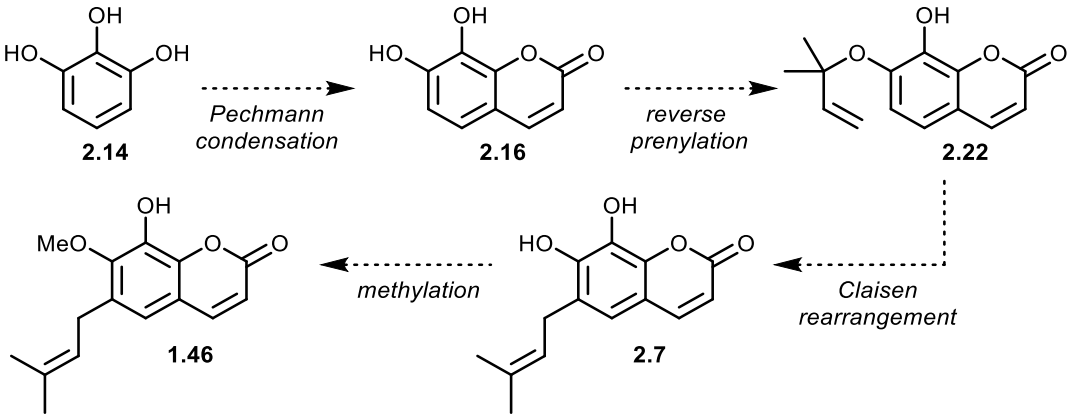
The initial plan was to focus on the early-stage coumarin formation route to brosiparin (**1.46**). The first step would be formation of 7,8-dihydroxycoumarin (**2.16**) from pyrogallol (**2.14**) by Curini's protocol, using a Pechmann condensation.[88] The second step would involve reverse prenylation of the hydroxyl group at the C-7 position, using a Tsuji–Trost allylation reaction. Subsequent Claisen rearrangement would then give compound **2.7**, with the prenyl group now at the C-6 position. In the total synthesis of angelmarin, Hamada has used this two-step sequence to install a prenyl group on a similar coumarin system.[89] Using carbonate reagent **2.20** and catalytic $Pd(PPh_3)_4$, the reverse

prenyl group was installed, then the product heated to 130 °C to give a mixture of 6- and 8-prenylated compounds (Scheme **2.9**).



Scheme 2.9 – Two-step prenylation in Hamada's synthesis of angelmarin

After prenylation, a selective methylation of the C7-hydroxyl group would need to be achieved to give brosiparin (**1.46**) in a planned four-step synthesis (Scheme **2.10**).



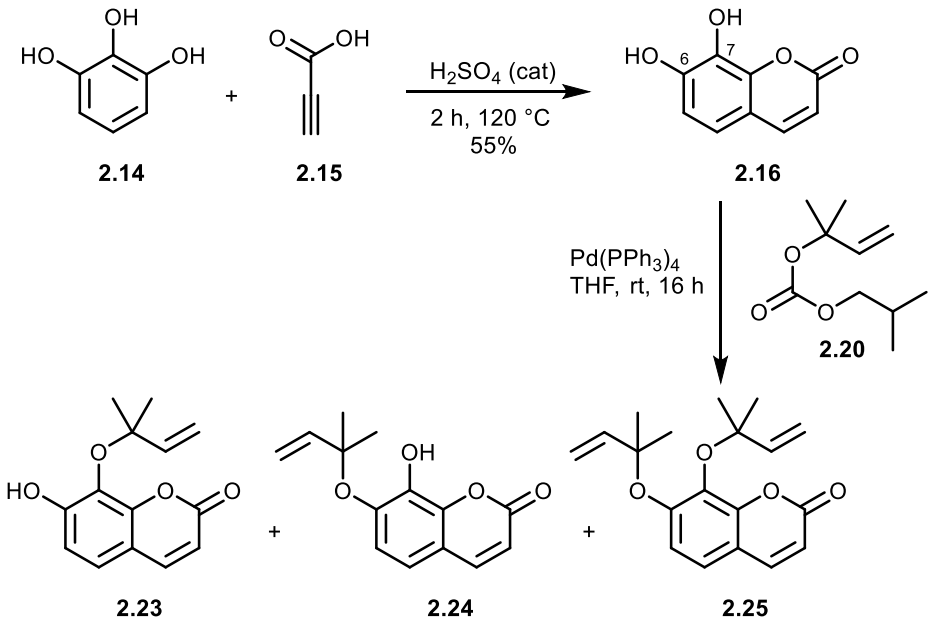
Scheme 2.10 – **Planned four-step route to brosiparin**

2.3 – Early-stage Coumarin Formation Route

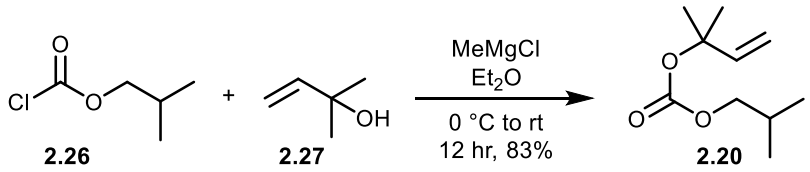
2.3.1 – Coumarin Formation then Reverse Prenylation

The synthesis started with the formation of 7,8-dihydroxycoumarin (**2.16**) from the reaction of pyrogallol (**2.14**) and propiolic acid (**2.15**), catalysed by one drop of concentrated sulphuric acid, with the reaction proceeding fairly smoothly at 120 °C. After

unsuccessful attempts to purify the product by recrystallisation and column chromatography, we eventually found that trituration with Et_2O afforded the pure product (**2.16**), albeit in moderate yield. Back-extraction from the aqueous phase with Et_2O increased the yield to 50%, which compared favourably to the 59% yield reported in literature.[88] Subsequently, compound **2.16** was subjected to the reverse prenylation reaction using carbonate **2.20** and $Pd(PPh_3)_4$. Carbonate **2.20**, the same reagent used for reverse prenylation in Hamada's synthesis of angelmarin, was formed by the reaction of isobutyl chloroformate (**2.26**) and 2-methyl-3-buten-2-ol (**2.27**), a procedure reported in literature (Scheme **2.12**).[90] It was hoped that the selective alkylation of the hydroxyl at C-7 would occur, however, the reaction gave an inseparable mixture of compounds exhibiting reverse prenylation at both the C-7 and C-8 hydroxyl groups (**2.23** & **2.24)** (Scheme **2.11**), as well as bis-prenylated compound **2.25**. Unfortunately, altering the reaction time, order of addition and catalyst loading had no effect on this result. $NaHCO_3$ was added in to the reaction in an attempt to selectively form a sodium phenoxide from the C-6 hydroxyl group and therefore direct the alkylation to that position, but disappointingly the same mixture of compounds was observed.



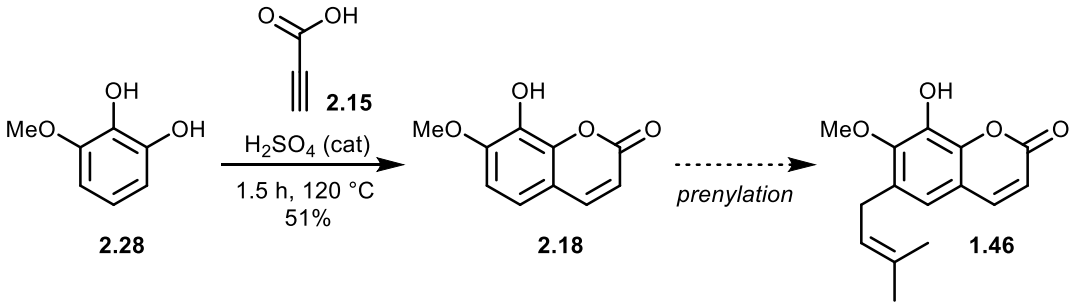
Scheme 2.11 – Coumarin formation followed by attempted reverse prenylation



Scheme 2.12 – Synthesis of carbonate reagent 2.20

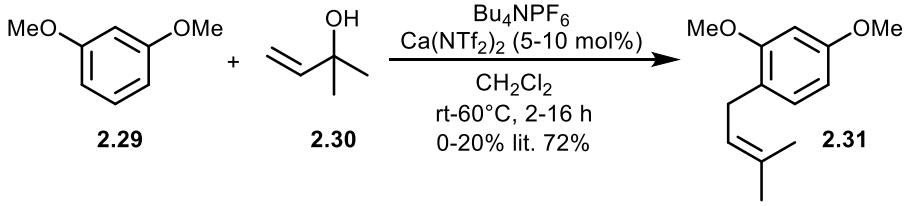
2.3.2 – Coumarin formation then direct prenylation

Given that selective reverse prenylation at the C-7 hydroxyl group seemed unlikely, an alternative approach was envisaged utilising a direct prenylation, by formation of a new C–C bond on the coumarin ring system, rather than the initial selective reverse prenylation of the C-7 hydroxyl and subsequent Claisen rearrangement. Rather than carrying out this reaction using 7,8-dihydroxycoumarin (**2.16**), coumarin **2.18** was prepared using the same Pechmann reaction conditions described previously, but starting from 3-methoxycatechol (**2.28**) rather than pyrogallol (**2.14**) (Scheme **2.13**). This would avoid the selective methylation required later on in the originally envisioned synthesis (Scheme **2.10**).



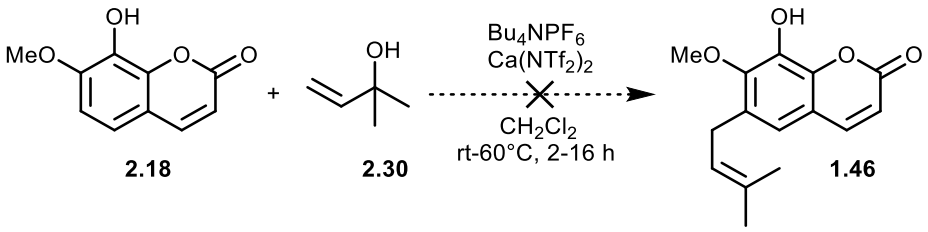
Scheme 2.13 – Proposed direct prenylation route to brosiparin (1.46)

A promising method to achieve this was reported by Niggemann and Meel, who developed a calcium-catalysed Friedel–Crafts alkylation of arenes with secondary or tertiary benzylic, allylic and propargylic alcohols.[91] These reactions were carried out under mild conditions; at room temperature with no addition of strong acids or bases required. A particularly relevant result was the addition of allylic alcohol **2.30** to 1,3-dimethoxybenzene (**2.29**) to give prenylated compound **2.31** (Scheme **2.14**).



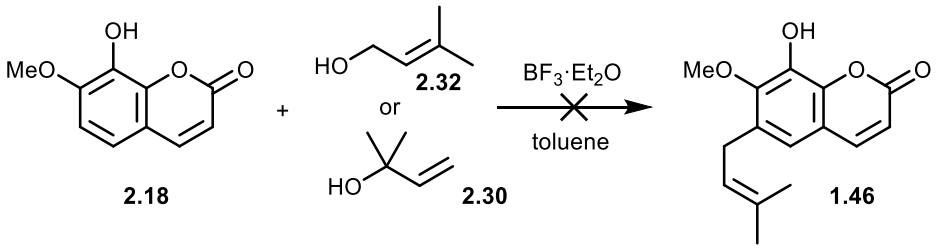
Scheme 2.14 – Calcium-catalysed Friedel–Crafts addition of alcohols to arenes

It was envisaged that subjecting coumarin **2.18** to these conditions would lead to the formation of brosiparin (**1.46**), however, no reaction was observed. Increased temperature, reaction times and catalyst loading did not change the outcome, with only unreacted starting material observed on each occasion (Scheme **2.15**). As Niggemann had reported a wide range of arenes that reacted successfully and in high yield, it was quite surprising that no reaction at all occurred with coumarin (**2.18**). Attempts to repeat the literature reaction of dimethoxybenzene (**2.29**) and allylic alcohol were carried out, but disappointingly only gave the product (**2.31**) in low yields, between 10-20%, compared to the 72% reported in the paper. Again, increased temperature, catalyst loading and reaction time did not significantly improve this.



Scheme 2.15 – Attempt to carry out Friedel-Crafts addition to coumarin 2.18

Boron trifluoride diethyl etherate has also been reported to mediate the prenylation of a variety of aromatic compounds, including a coumarin, with either allylic alcohol **2.30** or prenyl alcohol **2.32**.[92] These approaches were both trialled, using coumarin **2.18** and 1.5 equivalents of $BF_3{\cdot}Et_2O$. However, no reaction took place, with only unreacted starting material observed even when the temperature, reaction time, and equivalents of alcohol and $BF_3{\cdot}Et_2O$ were increased (Scheme **2.16**).

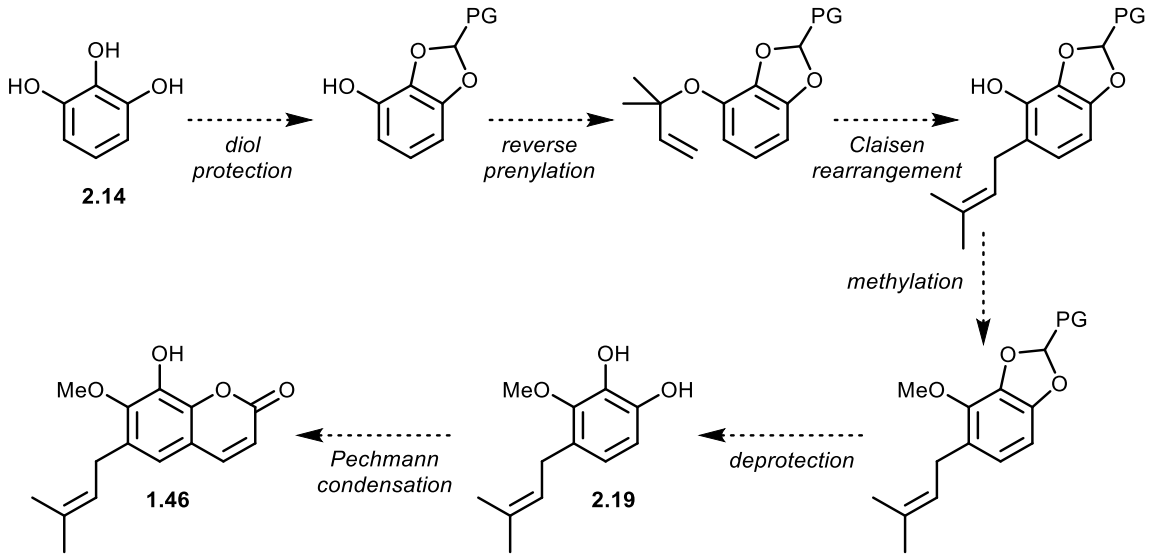


Scheme 2.16 – Attempted $BF_3{\cdot}Et_2O$-mediated prenylation of coumarin 2.18

2.4 - Late Stage Coumarin Formation Route

2.4.1 – Design of Synthetic Route

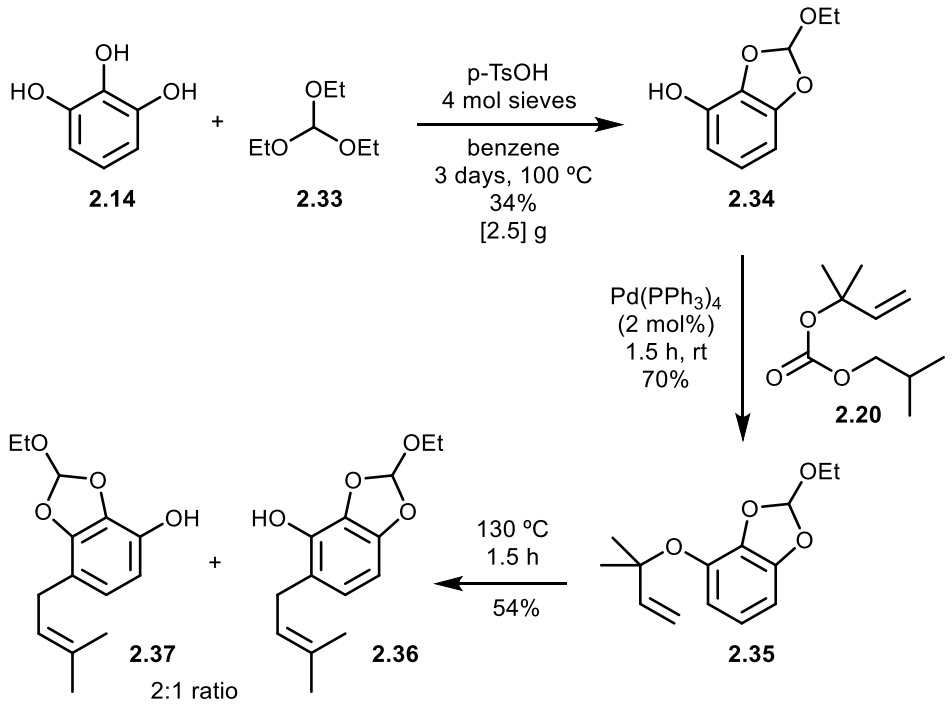
At this juncture it was decided to attempt the early stage prenylation route instead. This route would begin with protection of two of the hydroxyl groups on pyrogallol (**2.14**), ideally as an acetal. This would leave one hydroxyl group free, thus avoiding any selectivity issues in the next step – reverse prenylation. Claisen rearrangement would then install a standard prenyl group at the position adjacent to the once-again free hydroxyl group, which would subsequently be methylated. Deprotection of the diol would give compound **2.19**, which would be primed to undergo a Pechmann condensation to form the coumarin ring system of brosiparin (**1.46**) (Scheme **2.17**).



Scheme 2.17 – Proposed route to brosiparin via diol protection

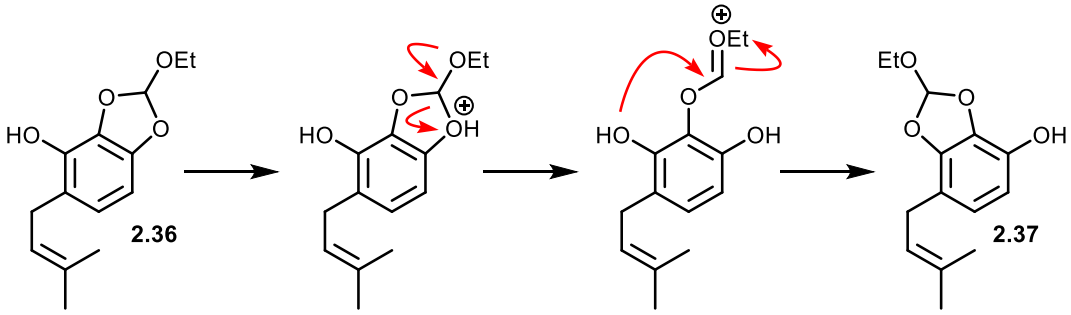
2.4.2 – Orthoester Protection Strategy

The first step of the synthesis would be protection of two of the hydroxyl groups using a known procedure to react pyrogallol **2.14** with triethyl orthoformate (**2.33**), thus protecting the diol as an orthoester (Scheme **2.18**).[93] Compound **2.34** was formed in a moderate yield – but on a large enough scale (2.5 g prepared from 5 g of starting material) to justify moving forward to the next step. This time the reverse prenylation of the remaining free hydroxyl group proceeded smoothly, giving compound **2.35** in high yield.



Scheme 2.18 – Orthoester protection followed by reverse prenylation and Claisen rearrangement

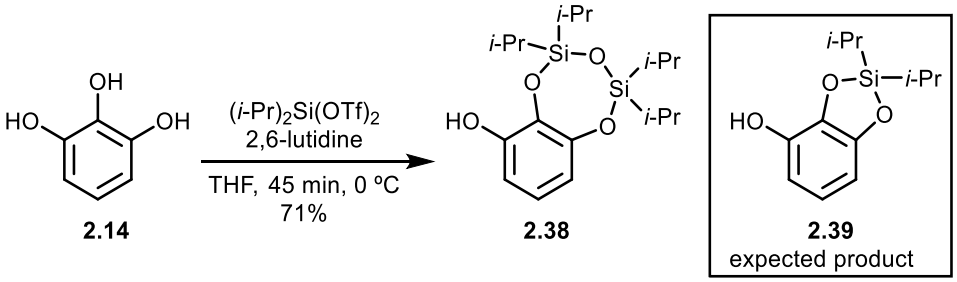
When the subsequent Claisen rearrangement was attempted, however, a mixture of products **2.36** and **2.37** was formed, seemingly due to unwanted migration of the orthoester. (Scheme **2.19**). Attempts to prevent the transorthoesterification and resultant formation of **2.37**, by either adding base (K_2CO_3) or lowering the reaction temperature to 90 °C, had no effect, and compound **2.37** was still observed as the major product, rather than target compound **2.36**. Although the two products could be separated fairly easily, and methylation of the free hydroxyl group of compound **2.36** was successfully carried out on a small scale, the low yield compared to the migration product **2.37** meant that a different approach would have to be taken.



Scheme 2.19 – Proposed mechanism of protecting group migration

2.4.3 – Attempted Silane Protection

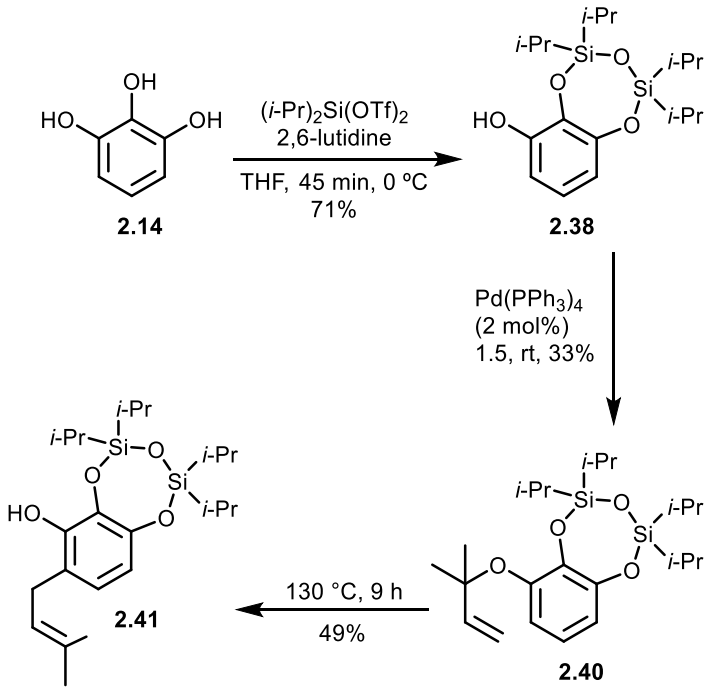
Different protecting groups were trialled with the aim of preventing any migration in the subsequent Claisen rearrangement. Initial attempts focused on diisopropylsilane, the use of which as a protecting group had been reported by Corey in the total synthesis of isoproterenol.[94] However, after extensive analysis of ^{1}H and ^{13}C NMR, and particularly mass spectrometry, it was concluded that rather than the expected silane protected compound **2.39**, compound **2.38**, containing a 7-membered siloxane ring, had been formed instead in fairly high yield (Scheme **2.20**). This may have been the result of the reaction not being kept completely anhydrous.



Scheme 2.20 – Attempted silane protection of pyrogallol (2.14)

Although the expected protecting group had not formed, siloxane-protected compound **2.38** was still taken forward to the reverse prenylation step, which formed compound **2.40** in moderate yield. The subsequent Claisen rearrangement, despite proceeding without migration of the protecting group, was particularly sluggish, with only 49% conversion to compound **2.41** after 9 hours. (Scheme **2.21**). However, the siloxane protecting group proved capricious, and when subjected to higher temperatures or column chromatography would unpredictably be cleaved. These issues made it

impossible to reliably scale up the reactions, so once again, a different protecting group method would need to be used.

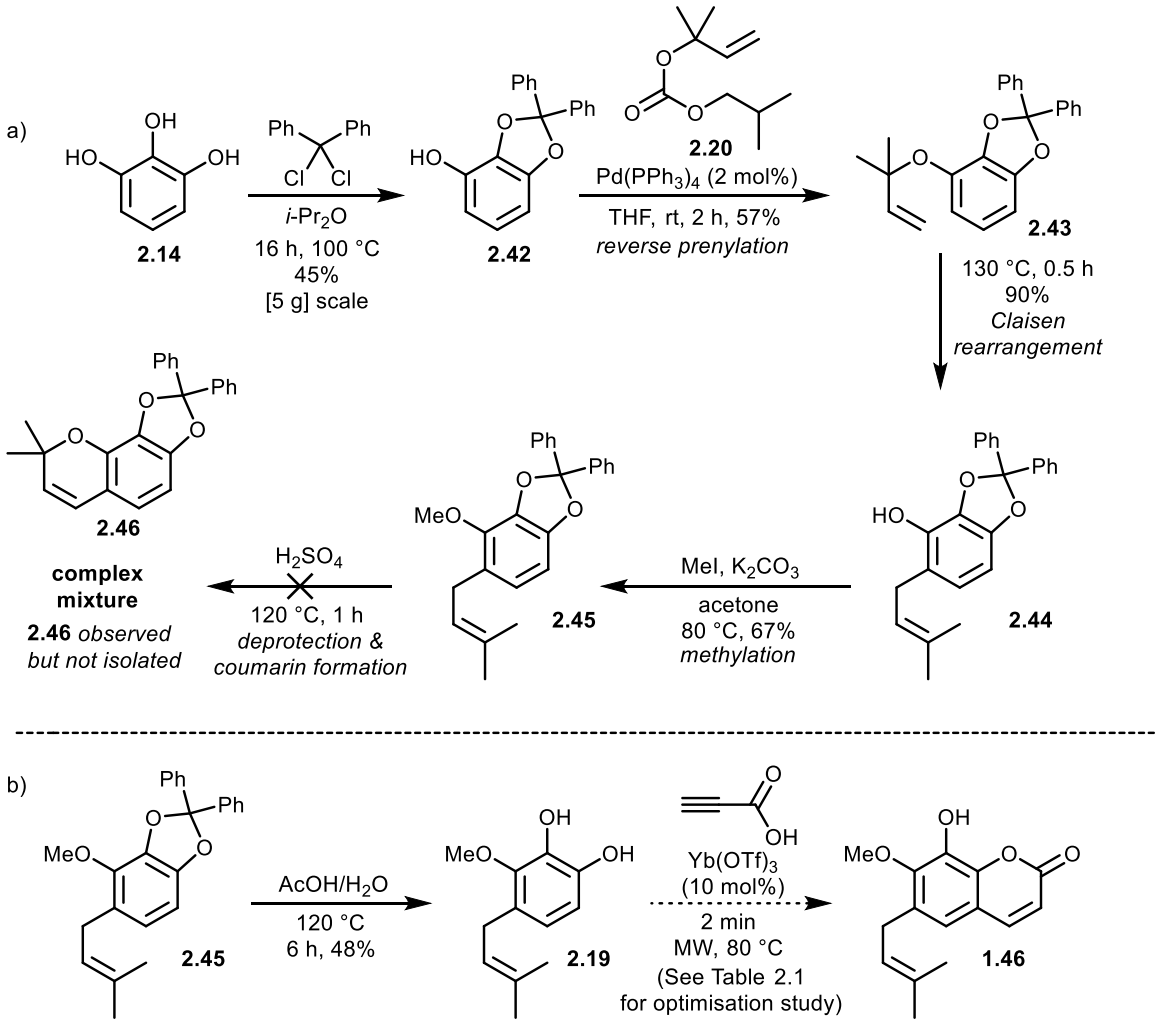


Scheme 2.21 – Reverse prenylation and Claisen rearrangement of siloxane protected compound

2.4.4 – Diphenyl Acetal Protection

Examples of a diphenyl acetal diol protection exist in the literature, so this option was pursued, due to reagent availability and the relative simplicity of the procedure.[95] The initial protection was carried out with dichlorodiphenylmethane using diphenyl ether as solvent (Scheme **2.22a**). Although the target compound was formed in a reasonable yield, it proved very difficult and laborious to remove the high-boiling solvent, and therefore decreased the amount of product isolated. As a result, the much lower-boiling diisopropyl ether was used, with the reaction giving the protected compound **2.42** in higher yield, though with a longer reaction time required. Although the yield was fairly moderate, the reaction was easily scalable, so large amounts (~5 g) of product could be prepared in a single batch. The reverse prenylation of compound **2.42** with carbonate **2.20** proceeded efficiently, giving compound **2.43** in high yield, before the Claisen rearrangement was attempted once more. With this protecting group, only very small amounts of migration were observed, with the target compound **2.44** isolated in a 90% yield. The methoxy group was installed successfully using methyl iodide and potassium carbonate, with

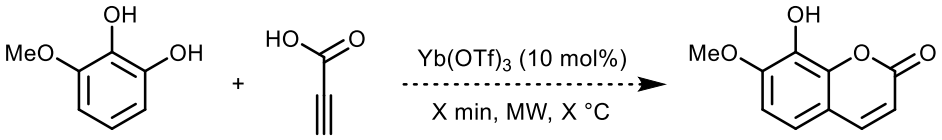
compound **2.45** formed in 67% yield. At this point a one-pot deprotection-coumarin formation was attempted. Ideally the concentrated sulfuric acid would both deprotect the diphenyl acetal and catalyse the coumarin formation, via a Pechmann condensation (Scheme **2.22a**). However, analysis by NMR spectroscopy showed a complex mixture of unwanted compounds, including those resulting from demethylation and cyclisation of the alkenyl side chain. Consequently, these two steps were tackled separately, with deprotection occurring via the use of acetic acid, to afford the diol product **2.19** in a moderate yield (Scheme **2.22b**).[96] Unfortunately, when compound **2.19** was subjected to the standard coumarin formation conditions used previously, cyclisation of the prenyl side chain was always observed. To avoid this, a Pechmann condensation procedure using milder conditions was needed, but the vast majority of coumarins unsubstituted at the 4-position had only been synthesised this way using strong acids as catalysts. However, a recent publication reported a range of substituted coumarins formed by a ytterbium triflate-catalysed Pechmann condensation with propiolic acid under microwave conditions.[97]



Scheme 2.22 – a) Diphenyl acetal protection route to brosiparin (1.46) b) - Deprotection, then envisaged coumarin formation with $Yb(OTf)_3$

Due to the differences between the microwave used in the literature and the one at our disposal, reaction conditions were optimised using 3-methoxycatechol **2.28**, to make 7-methoxy-8-dihydroxycoumarin **2.18** (Table **2.1**). It was found that the size of MW vial, the reaction temperature, time and the amount of propiolic acid all had significant effects on the reaction. The best conditions were found to use a 2-5 mL (recommended volume) vial, with a large excess (5 equivalents) of propiolic acid at a higher temperature than quoted in literature, 120 °C rather than 80 °C. Increasing the reaction time (20 mins, entry 4 vs 5) did not seem to affect the conversion, and using an even larger excess of propiolic acid (20 equivalents, entry 10 vs 11) also did not make any difference. With these conditions, complete conversion was achieved with a 92% isolated yield of compound **2.18** (Entry 12, Table **2.1**).

Table 2.1 – Optimisation of MW coumarin formation using $Yb(OTf)_3$



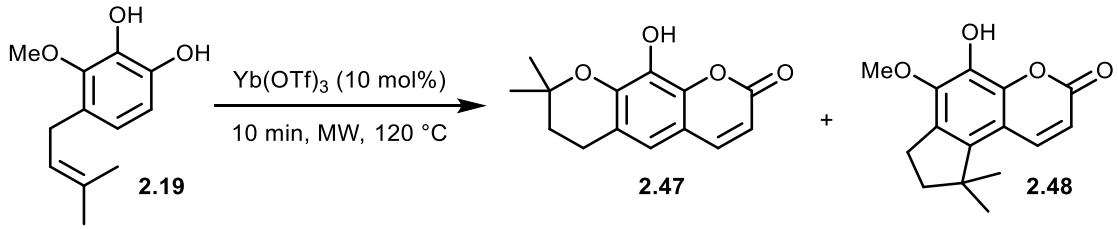
2.28 **2.15** **2.18**

Entry	*Scale (mg)*	*$Yb(OTf)_3$ (mol %)*	*Vial (mL)*	*Temp (°C)*	*Time (min)*	*Propiolic Acid (eq.)*	*Conv*
a	200	10	2-5	80	2	1.1	15%
b	200	10	2-5	80	10	1.1	22%
c	200	10	2-5	80	20	1.1	43%
d	200	10	2-5	80	10	5	80% (75%)
e	200	10	2-5	80	20	5	80%
f	10	10	0.5-2	80	10	5	11%
g	50	10	2-5	80	10	5	30%
h	200	10	2-5	120	10	1.1	37%
i	200	10	2-5	180	10	1.1	63%
j	50	10	0.5-2	80	10	5	70% (67%)
k	50	10	2-5	80	10	20	62%
l	200	10	2-5	120	10	5	100% (92%)

*isolated yield in brackets

The reaction was then attempted using compound **2.19**, in order to form brosiparin (**1.46**). However, despite successful formation of the coumarin ring system, unwanted cyclisation of the prenyl side chain was consistently observed, with NMR spectra indicated a mixture of unwanted compounds **2.47** and **2.48**, which were not isolated. These resulted either from demethylation and subsequent 6-membered ring formation onto the now free C-7 hydroxyl group, or from formation of a 5-membered ring by cyclisation onto the C-5 ring carbon. When the reaction was trialled at lower temperatures and with shorter reaction times, the cyclisation was still always observed. With no Lewis

acid catalyst present, no reaction took place. Literature searches have shown that Pechmann condensation reactions to form coumarins from substituted phenols invariably require acid catalysis, so once again, a new strategy was needed.

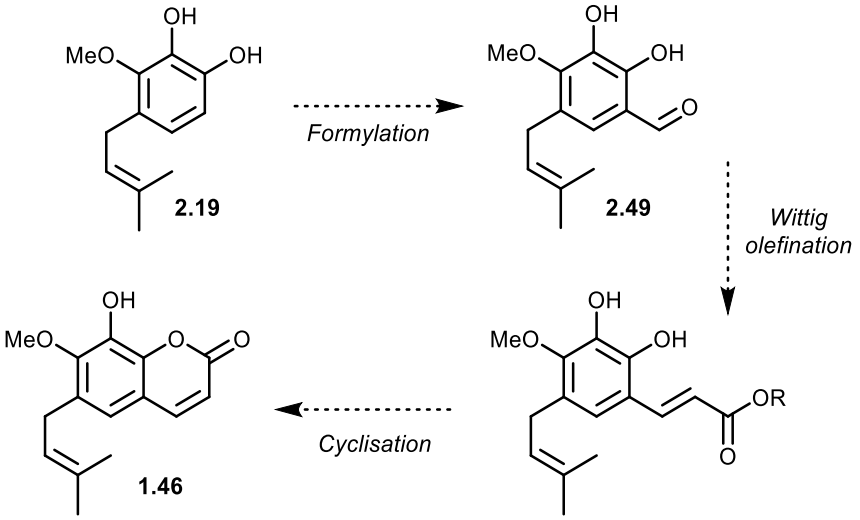


Scheme 2.23 – Attempted Pechmann condensation of 2.19 using $Yb(OTf)_3$

2.5 – Construction of Coumarin from Benzaldehyde Derivatives

2.5.1 – Planned route to Brosiparin

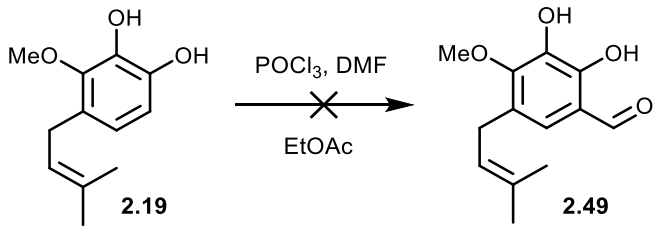
After the difficulties encountered with both the early and late stage coumarin formation routes, a third approach was designed. This would involve building the coumarin ring system on to a substituted benzaldehyde, such as compound **2.49** (Scheme **2.24**). This would ideally take place by carrying out a Wittig reaction to install an α,β-unsaturated carbonyl, then a cyclisation to form the right hand side of the coumarin. (Scheme **2.24**).



Scheme 2.24 – Planned route to brosiparin (1.46) from a benzaldehyde derivative

2.5.2 – Attempted Vilsmeier–Haack formylation

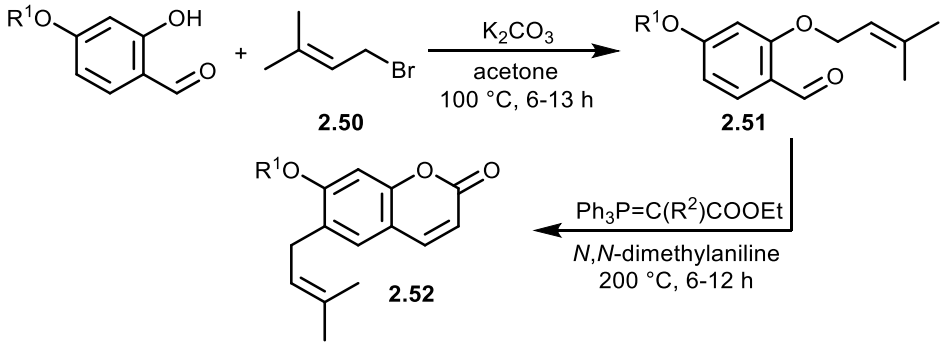
The first step of this planned synthesis was attempted by carrying out a Vilsmeier–Haack formylation on compound **2.19** (Scheme **2.25**).[98] However, the reaction proved unsuccessful, and despite varying the temperature and stoichiometry of the reaction, only unreacted starting material was returned in every case.



Scheme 2.25 – Attempted Vilsmeier-Haack reaction of compound 2.19

2.5.3 – Route from trimethoxybenzaldehyde

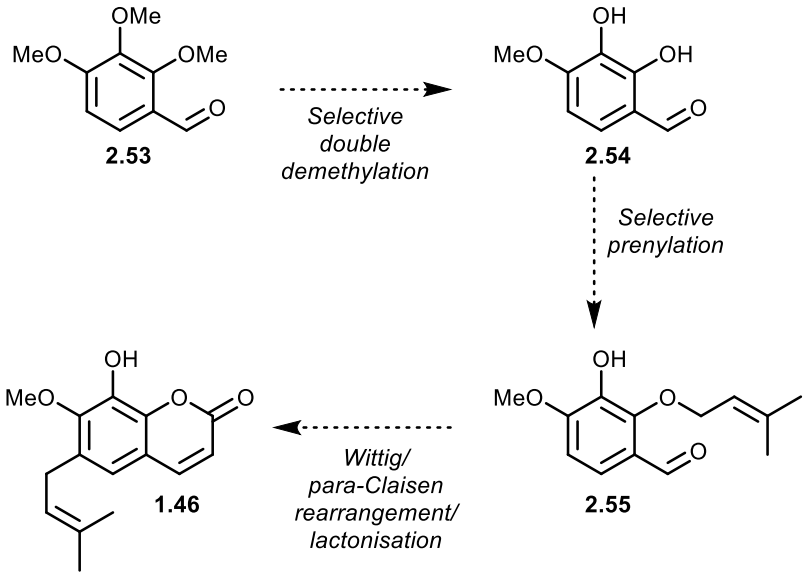
It was at this point that we came across a report by Mali et al. that showed that the synthesis of similar 6-prenylcoumarins could be achieved in two steps from the corresponding hydroxybenzaldehyde. Prenylation of the hydroxybenzaldehyde using prenyl bromide (**2.50**) to give compounds such as **2.51**, was followed by a very interesting one-pot tandem Wittig olefination, *para*-Claisen rearrangement and lactonisation to give the prenylated coumarin product **2.52** (Scheme **2.26**).[99]



Scheme 2.26 – Mali's general route to 6-prenylcoumarins

A route to brosiparin based on Mali's synthesis was proposed. As the dihydroxy benzaldehyde **2.54** is not commercially available, it would be necessary to prepare it from the inexpensive starting material trimethoxybenzaldehyde (**2.53**). The prenylation step would need to be selective at the C-2 hydroxyl group to give compound **2.55**, which

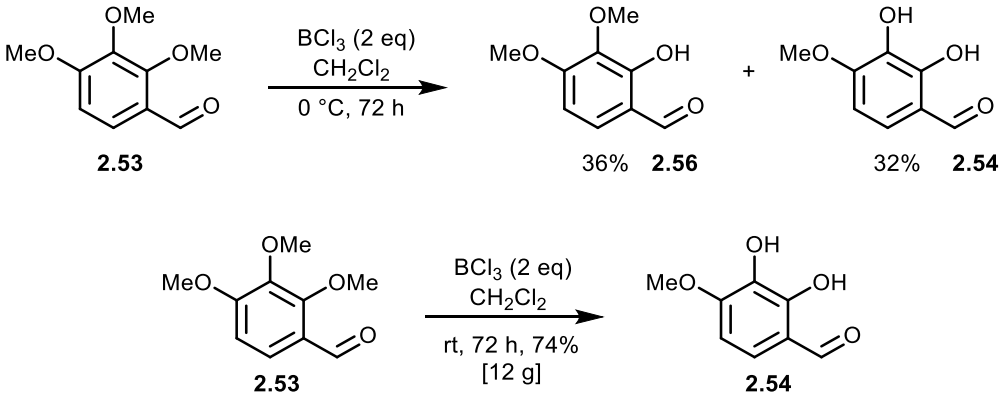
would then undergo the tandem Wittig/*para*-Claisen rearrangement/lactonisation to give brosiparin **1.46** (Scheme **2.27**).



Scheme 2.27 – Proposed route to brosiparin (1.46) from trimethoxybenzaldehyde (2.53)

2.5.4 – Double demethylation of trimethoxybenzaldehyde

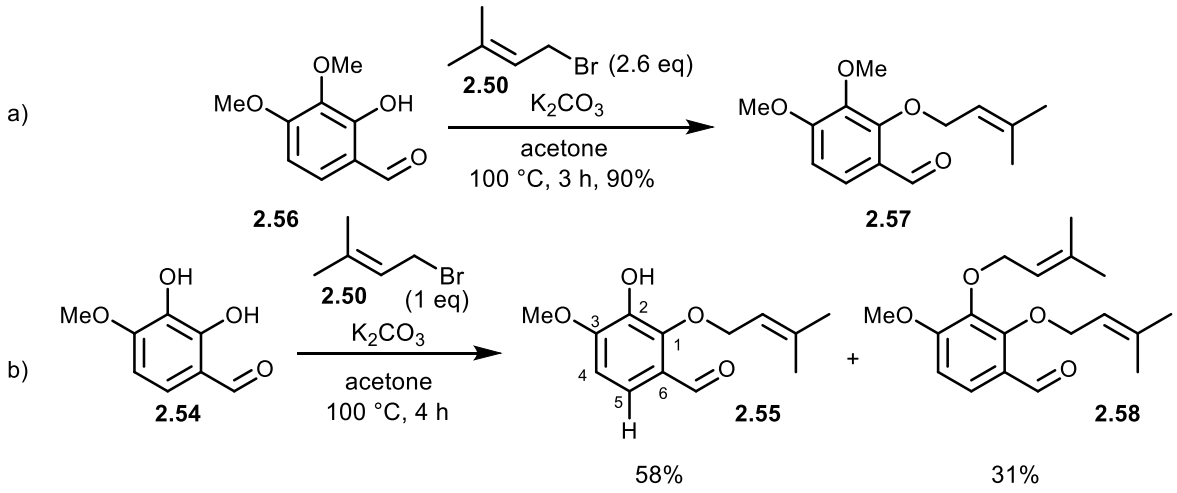
The first step of the synthesis was the selective double demethylation of the inexpensive starting material trimethoxybenzaldehyde (**2.53**), which was carried out according to a literature procedure using two equivalents of boron trichloride.[100] Initially the reaction was carried out at 0 °C for 48 hours, but an approximately 50:50 mixture of single and double-demethylation products was observed. However, when attempting the reaction at room temperature and extending the reaction time to 72 hours, the conversion to the desired compound **2.54** was increased and it was subsequently isolated by column chromatography in a 74% yield. It is proposed that the reaction is selective in this manner due to initial coordination of the BCl_3 to the aldehyde, followed by demethylation at the C-2 methoxy group. The boron would then coordinate to the resultant free oxygen, before demethylation takes place at the C-3 methoxy group.[101] When the reaction was carried out using a larger excess of BCl_3 (6 equivalents) the ^1H NMR spectrum showed some formation of trihydroxybenzaldehyde, as a result of triple demethylation was observed.



Scheme 2.28 – Impact of temperature, reaction time and stoichiometry on selective double demethylation of trimethoxybenzaldehyde 2.53

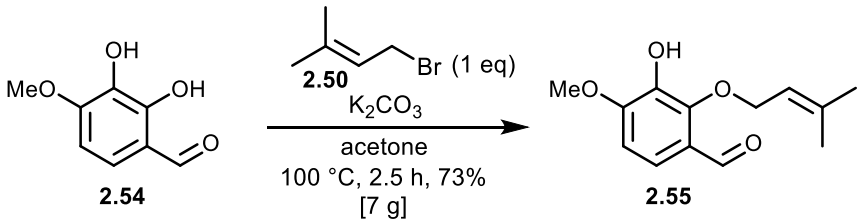
2.5.5 – Selective alkenylation using prenyl bromide

Following this step, the selective prenylation of the C-2 hydroxyl group was investigated. The general procedure described in the literature used one equivalent of prenyl bromide (**2.50**) along with potassium carbonate and was heated to reflux for 4 hours in acetone. The reaction was initially carried out using compound **2.56**, which resulted from a single demethylation, in order to test the protocol. As there were no issues of hydroxyl group selectivity using this compound, a larger excess of prenyl bromide was used (2.6 equivalents), and the reaction proceeded smoothly with complete conversion and very high isolated yield (Scheme **2.29a**). When the double demethylated compound **2.54** was used, with one equivalent of prenyl bromide (**2.50**), a mixture of products from both prenylation of solely the C-2 hydroxyl group, and also both hydroxyl groups, was observed (Scheme **2.29b**). Thankfully the ratio of products was approximately 2:1 in favour of the single prenylation product, and purification was possible by column chromatography using a 4:1 mixture of petroleum ether and ethyl acetate, to give the compound in a 58% yield. Analysis using 2D NMR techniques, particularly HSQC and HMBC, helped to confirm that prenylation had taken place at the C-2 rather than the C-3 hydroxyl group. The cross-peak between the ring proton adjacent to the formyl group (at C-5), and the carbon at C-1, as well as that between C-1 and the prenyl CH_2, were particularly important in elucidating the structure (see section **5.5** for annotated spectra).



Scheme 2.29 – Initial prenylation of a) compound 2.56 and b) 2.54 using prenyl bromide

However, the ratio of products was improved by decreasing the reaction time to 2.5 h, and carrying out dropwise addition of prenyl bromide, and the isolated yield of compound **2.55** increased to 73%. The reaction proved easily scalable, with approximately 7 g of product formed in one batch. (Scheme **2.30**).

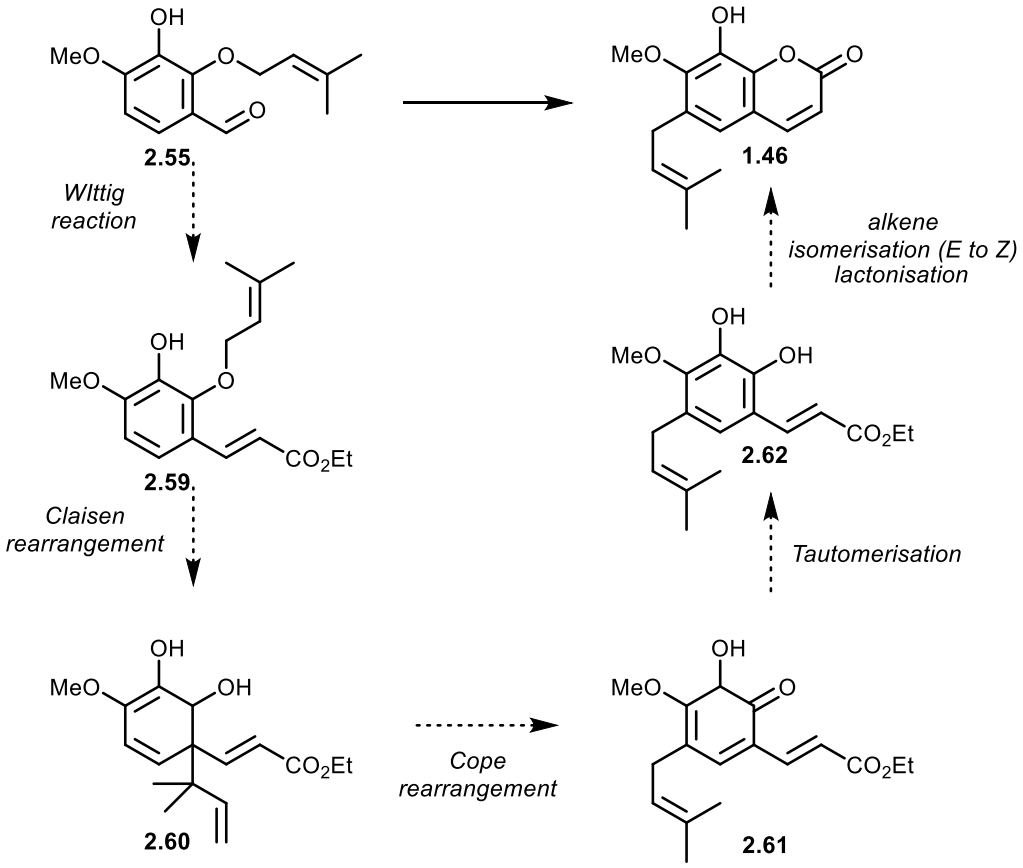


Scheme 2.30 – Optimised selective prenylation of compound 2.54

2.5.6 – One pot Wittig/*para*-Claisen/lactonisation

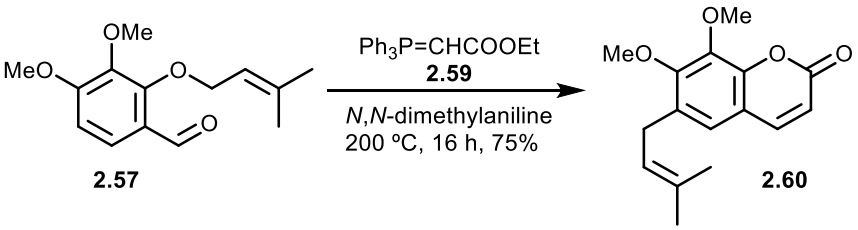
The final step in the synthesis would be the one-pot Wittig reaction/*para*-Claisen/cyclisation rearrangement to simultaneously form the coumarin ring system, while moving the prenyl group to the 6-position. It was proposed that the Wittig olefination to install the α,β-unsaturated carbonyl group would occur first to form compound **2.59**, followed by Claisen rearrangement of the prenyl group from the hydroxyl group, to form a reverse prenyl group on the same carbon as the olefin (Scheme **2.31**, compound **2.60**). The prenyl group will then undergo a second [3,3]-sigmatropic rearrangement, this time a Cope rearrangement, to give compound **2.61**. The tandem

Claisen and Cope rearrangement steps are collectively known as a *para*-Claisen rearrangement, as the prenyl group ends up in the *para*-position to the hydroxyl group.[102] After tautomerisation, compound **2.62** is then proposed to undergo an *E* to *Z* alkene isomerisation and lactonisation to form the coumarin ring system of brosiparin (**1.46**) (Scheme **2.31**).



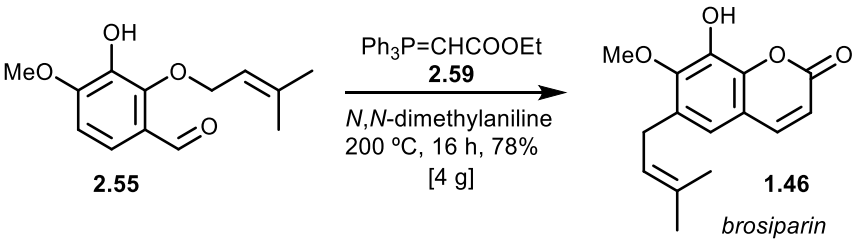
Scheme 2.31 – Proposed mechanism of one-pot Wittig/*para*-Claisen rearrangement/lactonisation

The tandem Wittig olefination/*para*-Claisen/lactonisation step was initially trialled on the dimethoxy compound **2.57**, using the conditions described by Mali. Compound **2.57** and phosphorane **2.59** were heated at 210 °C for 16 hours in *N*,*N*-dimethylaniline. Much to our delight, the reaction proceeded very smoothly, with the successful formation of the 6-prenylcoumarin compound **2.60** (*O*-methylbrosiparin) observed (Scheme **2.32**). Purification by column chromatography gave the product in a 75% yield. Analytical data for this compound matched previously reported data.[103]



Scheme 2.32 – Formation of coumarin 2.60

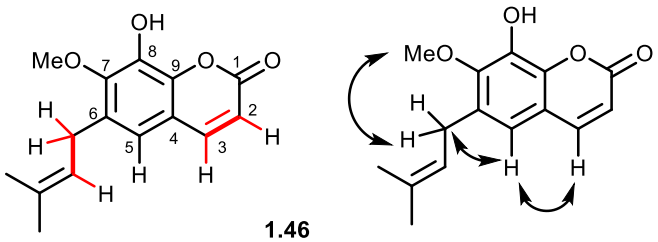
Buoyed by this success, the reaction was carried out on compound **2.55** in an attempt to form brosiparin (**1.46**) (Scheme **2.33**). Analysis of the ^{1}H NMR spectrum of an aliquot taken after 16 hours strongly suggested formation of brosiparin (**1.46**), with complete conversion from starting material. However, issues started to arise during purification. Despite the literature procedure stating that the solvent was simply removed under vacuum, in practice this proved to be very difficult, due to the high boiling point of the solvent (194 °C). It was possible to remove very small amounts of solvent (<1 mL) from aliquots on a rotary evaporator, but removing larger amounts proved incredibly difficult, even using a higher temperature water bath (~80 °C). Washing the crude reaction mixture with 1M aqueous HCl was effective in terms of solvent removal, but had the unwanted side effect of washing some of the product into the aqueous layer, thereby reducing the isolated yield. It was eventually found that the most successful method was vacuum distillation of the crude mixture in order to distil off the vast majority of the solvent, with any remaining amount separated from the product by column chromatography. Using these purification methods brosiparin (**1.46**) was isolated as a white solid in a 75% yield. The process proved easily scalable, with up to 4 g of product being formed in one reaction.



Scheme 2.33 – Formation of brosiparin (1.46) using one-pot Wittig/*para*-Claisen/lactonisation

2.5.7 – Confirmation of the structure of brosiparin

The structure of the product of the tandem Wittig/*para*-Claisen rearrangement was confirmed to be that of brosiparin (**1.46**) using several different analytical methods. ^{1}H NMR spectroscopy data matched the peaks reported in the isolation paper. Both the ^{1}H and ^{13}C NMR spectra showed the characteristic signals of a coumarin ring system, with COSY, HSQC and HMBC giving further evidence that it had been formed. The coumarin ring protons at the C-2 and C-3 positions give a coupling constant of 9.5 Hz, a typical value for a (*Z*)-alkene, while HMBC spectrum shows cross-peaks between the C-2 proton and the carbonyl carbon, as well as the C-3 proton and C-5 carbon. HMBC and NOESY also helped to confirm the presence of the prenyl group at the 6-position of the ring. The nOe correlation between the CH_2 protons of the prenyl side chain and the CH_3 protons of the 7-methoxy group particularly supported this, along with the cross-peak between the prenyl CH_2 and H-5 on the coumarin ring (Figure **2.2**) (See experimental section for full 2D NMR data).



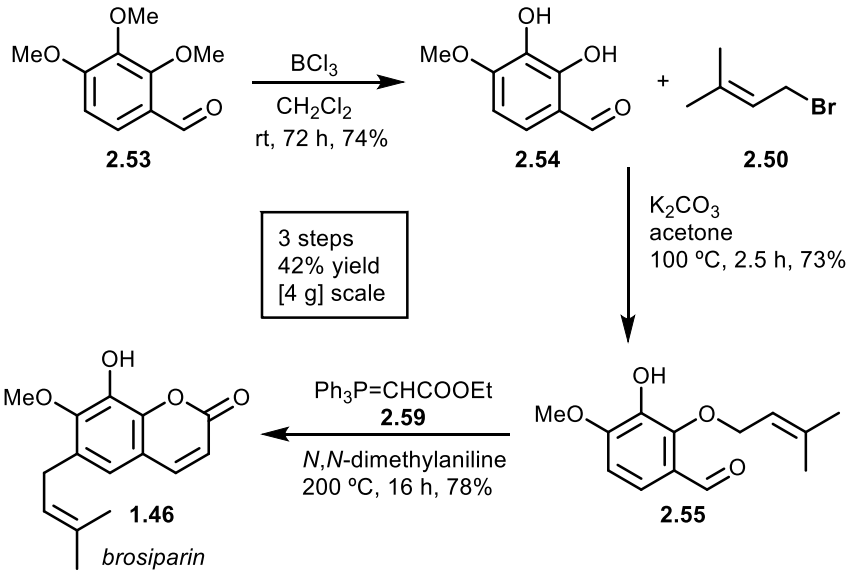
1.46
brosiparin

Figure 2.2 – Significant COSY (bold red bond) and NOESY (double-headed arrow) correlations of brosiparin (1.46)

HRMS and IR also suggested brosiparin (**1.46**) had been formed. The molecular ion in the mass spectrum (ESI^{+}) registered at *m/z* 261.10, which is consistent with the molecular formula of brosiparin (**1.46**), $C_{15}H_{17}O_4$, and the expected peaks in the IR spectrum, corresponding to C=C (1560-1620 cm^{-1}), C=O (~1700 cm^{-1}) and C–O (~1250 cm^{-1}) bonds were observed.[78]

2.6 - Conclusions

The first total synthesis of the coumarin natural product brosiparin (**1.46**) has been achieved in a three-step synthesis, all with high yields and easily scalable. Starting from inexpensive trimethoxybenzaldehyde, selective double demethylation gave compound **2.54**, before selective prenylation with prenyl bromide gave compound **2.55**. This compound then underwent a tandem Wittig olefination/*para*-Claisen/lactonisation rearrangement reaction at high temperature, to afford brosiparin (**1.46**). The synthesis was completed on a 4 g scale, in 42% overall yield.



Scheme 2.34 – Three-step synthesis of brosiparin (1.46)

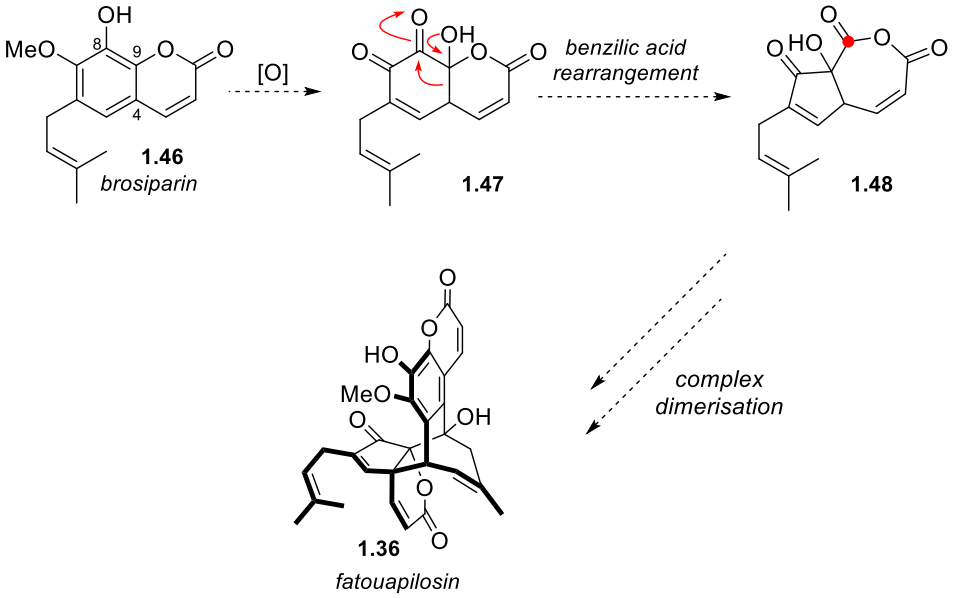
As this synthesis enabled the preparation of large quantities of brosiparin (**1.46**), we were able to move on and use brosiparin (**1.46**) as a testing ground to develop a method of oxidative ring contraction, both to apply to a range of substrates, but also to continue towards the synthesis of fatouapilosin (**1.36**).

Chapter 3 – Oxidation Chemistry of Brosiparin and Attempted Ring Contraction

3.1 Introduction

3.1.1 Aims

Following the synthesis of brosiparin (**1.46**), attention turned to the key step of the project – the oxidative ring contraction. In this step, it was envisioned that the oxidation would occur as shown in Scheme **3.1**, with oxidation proceeding via formation of *ortho*-quinone intermediate **1.47**, with hydroxylation at C-9. This would then be followed by a benzilic acid-type rearrangement of the molecule, with migration of the C-4–C-9 bond onto the C-8 carbonyl carbon, forming a 5-membered ring fused to a 7-membered ring (compound **1.48**).



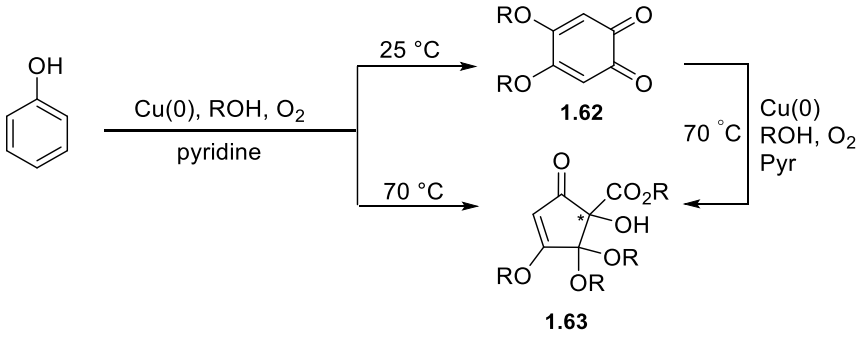
Scheme 3.1 – Proposed biosynthetic oxidative ring contraction of brosiparin (1.46)

The other objective of the project was to apply the developed oxidative ring contraction methodology to a vast range of phenol-derived substrates, ideally using renewable, inexpensive and abundant metals as catalysts.

3.2 Initial Oxidation Trials

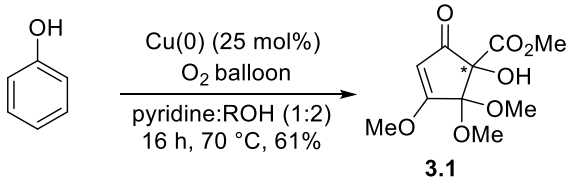
3.2.1 Cu(0)-mediated Oxidation

The initial oxidation trials would utilise the conditions reported by Rossi in his copper-catalysed ring contraction of phenol (Scheme **3.2**).[23]



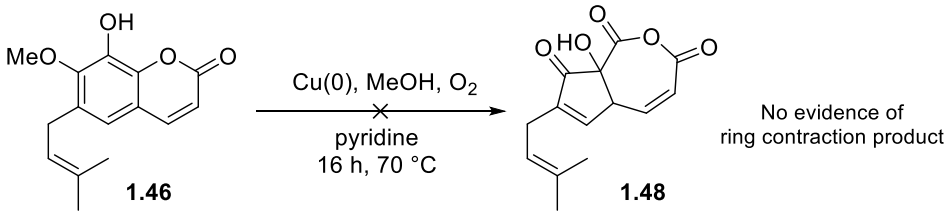
Scheme 3.2 – Rossi's copper-catalysed oxidative ring contraction of phenol

We initially repeated the reaction Rossi reported using phenol, copper powder, oxygen gas and pyridine (Scheme **3.3**). Despite the reduced oxygen pressure in our set-up compared to that of Rossi, the substituted cyclopentenone compound **3.1** was successfully formed in a comparable yield (measured from ^{1}H NMR spectra of crude reaction mixture).



Scheme 3.3 – Repeat of Rossi's copper-catalysed oxidative ring contraction of phenol

Encouraged by this result, the oxidative ring contraction of brosiparin (**1.46**) was attempted under the same conditions. Unfortunately, degradation of the starting material was observed when the reaction was carried out at 70 °C, and no reaction was observed at room temperature (Scheme **3.4**).

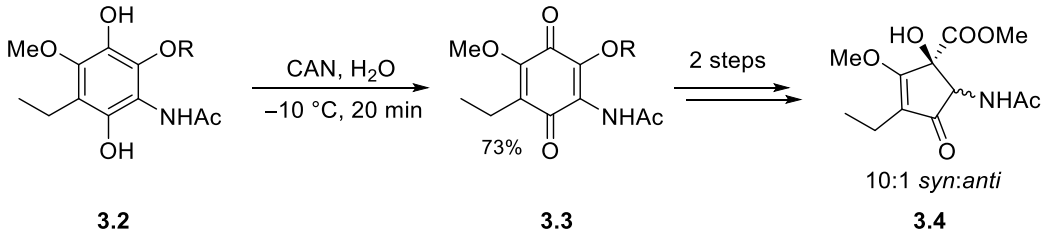


Scheme 3.4 – Attempted copper-catalysed oxidative ring contraction of brosiparin (1.46)

As these conditions had proved unsuccessful, we decided to investigate the reactivity of brosiparin (**1.46**) with a range of other oxidising agents that had previously been used for phenolic oxidations. Once the behaviour of brosiparin (**1.46**) had been established, we would be better equipped to identify suitable base metal catalysed conditions. We speculated that we may have needed to separate the oxidative ring contraction into two steps, with initial oxidation to the quinone followed by a ring contraction step.

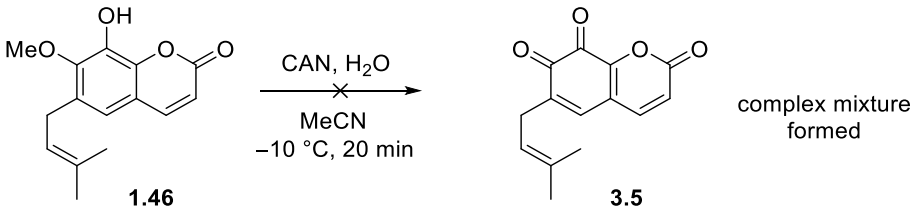
3.2.2 Attempted oxidation using Ce(IV)

In the total synthesis of mccrearamycins A-D, Thorson and co-workers carried out a ring contraction of 6-membered *para*-quinone **3.3** to cyclopentenone **3.4** by trialling both a range of basic conditions and Lewis acid catalysts (discussed further below in section **3.5.1**).[29] *para*-Quinone **3.3** was prepared by oxidation of precursor **3.2** using ceric ammonium nitrate (CAN) as an oxidising agent (Scheme **3.5**). CAN is widely used in organic synthesis as an oxidant for functional groups such as alcohols, ethers, thioethers, as well as for the synthesis of quinones from oxygenated aromatic compounds.[104-106]



Scheme 3.5 – Use of CAN by Thorson to prepare *para*-quinone and subsequent ring contraction

Thorson's conditions were trialled on brosiparin (**1.46**), in an attempt to oxidise to the *ortho*-quinone compound **3.5** but analysis of the ^{1}H NMR spectrum showed a complex mixture of unidentifiable products (Scheme **3.6**).



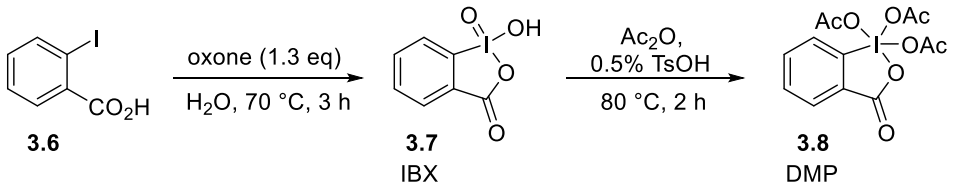
Scheme 3.6 – Attempted oxidation of brosiparin (1.46) using CAN

3.3 - Use of hypervalent iodine reagents

3.3.1 Background

In recent years, the use of hypervalent iodine reagents for oxidation chemistry has become more prevalent as an alternative to reagents based on toxic heavy metals.[107-108] They are attractive oxidising agents due to their stability, selectivity, low toxicity and ease of handling. Compounds exist with iodine in the +3 oxidation state (iodinanes) or the +5 oxidation state (periodinanes). Hypervalent iodine reagents can be used to carry out a number of different transformations, including C–C and C–heteroatom bond formations. A number of established procedures have also been developed for the oxidation of alcohols to carbonyls, and the oxidation of phenols, which is particularly relevant to this project.[107-110]

Examples of ubiquitous periodinane compounds include 2-iodoxybenzoic acid (IBX) (**3.7**), which is synthesised from 2-iodobenzoic acid (**3.6**) and is commonly used to oxidise alcohols to aldehydes,[111-112] and Dess–Martin periodinane (DMP) (**3.8**), an IBX derivative with increased reactivity and solubility in organic solvents. It can be formed from IBX (**3.7**) using acetic anhydride and tosic acid (Scheme **3.7**).[113]



Scheme 3.7 – Preparation of establiblished iodinane reagents

Many examples of iodinane reagents are derived from iodobenzene, including iodosobenzene (**3.9**), (dichloroiodo)benzene (**3.10**) and (difluoroiodo)benzene (**3.11**). Two iodinane reagents that have been extensively reported to oxidise phenols to quinones

are (diacetoxyiodo)benzene (PIDA, **3.13**) and [bis(trifluoroacetoxy)iodo]benzene (PIFA, **3.14**) (Figure **3.1**).[109, 114-116]

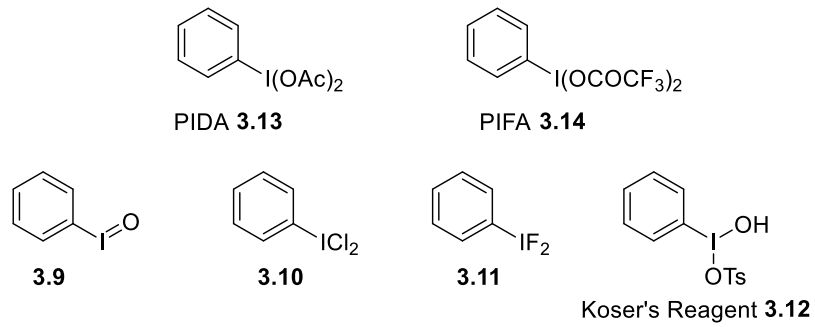
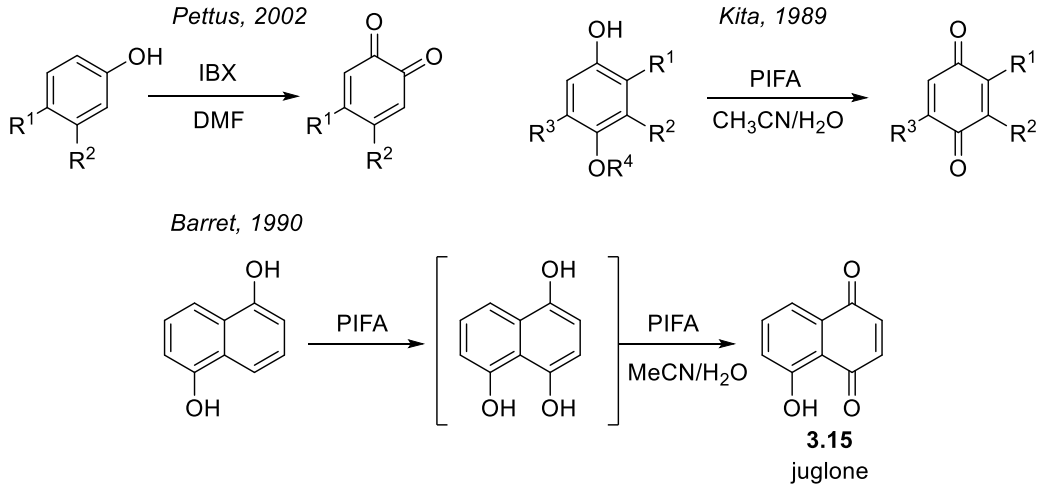


Figure 3.1– Iodinane reagents

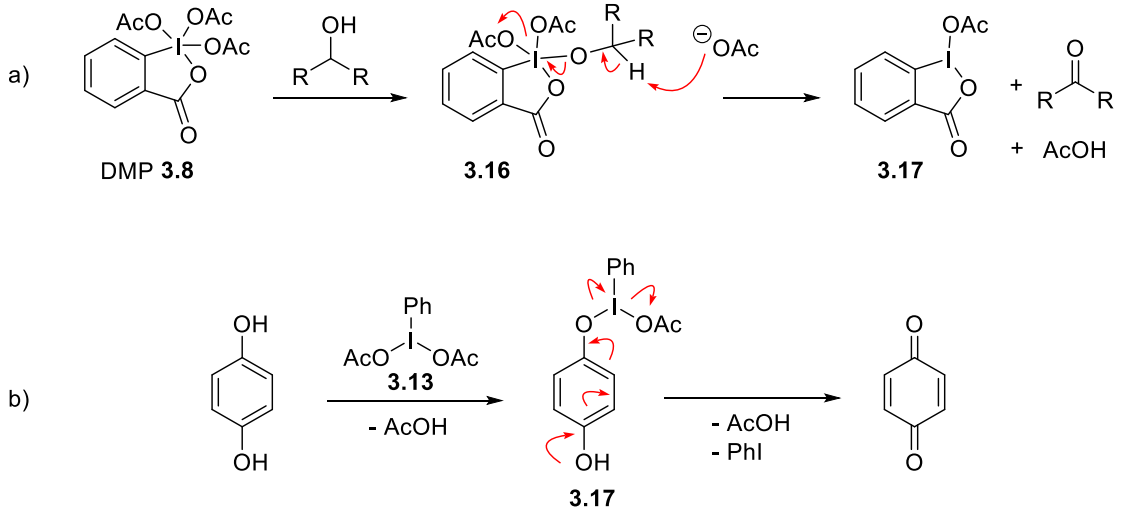
The oxidations of phenols using the hypervalent iodine reagents described above have been extensively studied, including Pettus's use of IBX to directly oxidise electron-rich phenols to *ortho*-quinones (Scheme **3.8**).[117] Another particularly relevant example is the work of Kita, who used PIFA to form *para*-quinones,[118] a reaction which was applied by Barret in the total synthesis of juglone (**3.15**) (Scheme **3.8**).[119]



Scheme 3.8 – Previous examples of phenol oxidation using hypervalent iodine reagents

Iodine(V) oxidation of alcohols, for example with DMP (**3.8**), proceeds as shown in scheme **3.9a**. Initial ligand exchange from the iodine centre gives a diacetoxyalkoxyperiodinane species **3.16**, releasing an acetate anion, which can then act as base and deprotonate the α-hydrogen of the alcohol. This results in the breakdown of species **3.16** to give the carbonyl compound, iodinane compound **3.17** and acetic acid.

The mechanism of iodine(III) oxidation of 1,4-dihydroxyphenol using PIDA is also shown, and begins with a similar ligand exchange step, with coordination of the 1-hydroxy group to the iodine to form intermediate **3.18**. Delocalisation of the lone pair from the 4-hydroxy group onto the ring then leads to *para*-quinone formation, and loss of the iodine species as iodobenzene (Scheme **3.9b**). Numerous examples of this kind of oxidative dearomatisation using reagents such as PIDA (**3.13**) or PIFA (**3.14**) exist, often involving addition of a nucleophilic species *para*- to the hydroxyperiodinane group.[120-121]



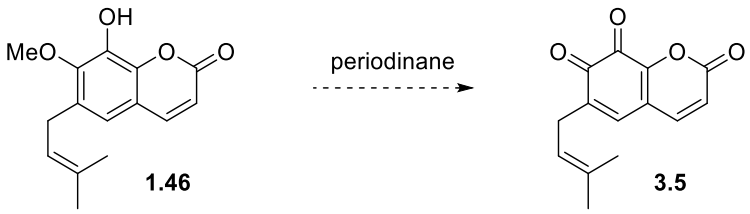
Scheme 3.9 – a) Mechanism of oxidation by I(V) (DMP) and b) I(III) (PIDA, 3.13) species

3.3.2 Initial oxidation of brosiparin with periodine reagents

The oxidation of brosiparin (**1.46**) with a number of different hypervalent iodine reagents was attempted (Table **3.1**). Subjecting brosiparin (**1.46**) to two equivalents of DMP and sodium bicarbonate, following a protocol reported by Beaudry and co-workers,[122] resulted in no reaction at room temperature, with only unreacted starting material observed (entry *a*). The temperature was therefore increased to 70 °C and the solvent changed from dichloromethane to the higher boiling dichloroethane. This time a reaction did occur, but attempts to purify and analyse the resulting complex mixture proved unsuccessful (entry *b*). Oxidation of brosiparin (**1.46**) with IBX (**3.7**), using conditions

described by Beaudry at room temperature and 70 °C (entries *c* and *d*) also resulted in a complex and inseperable mixture of products.[122]

Table 3.1 – Reactions of brosiparin (1.46) with DMP (3.8) and IBX (3.7)

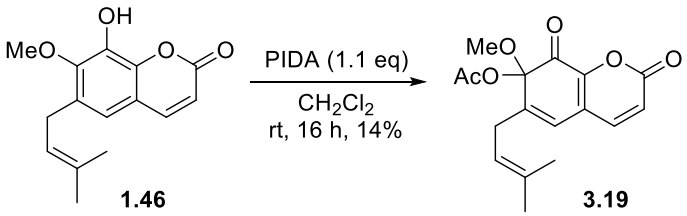


1.46 **3.5**

Entry	*Reagent(s)*	*Solvent*	*Time (h)*	*Temp (°C)*	*Result*
a	DMP, $NaHCO_3$	CH_2Cl_2	16	rt	No reaction
b	DMP, $NaHCO_3$	$(CH_2Cl)_2$	4	70	Complex mixture
c	IBX	EtOAc	16	rt	Complex mixture
d	IBX	EtOAc	16	70	Complex mixture

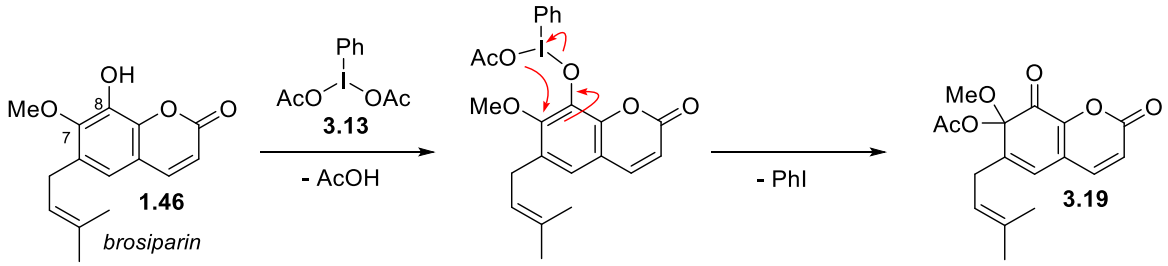
3.3.3 Oxidations to masked *ortho*-quinone using PIDA

At this point, our attention turned to the use of iodinane reagents, containing iodine in the +3 oxidation state. PIDA (**3.13**) and PIFA (**3.14**), shown in Figure **3.1** above, have been used extensively for the oxidation of phenols to quinones and related compounds.[107] The reaction of brosiparin (**1.46**) with 1.1 equivalents of PIDA (**3.13**) was initially carried out at room temperature using dichloromethane as solvent, following a procedure described by Poupon and co-workers.[123] The ^{13}C NMR spectrum showed that an extra peak corresponding to a carbonyl group was present, suggesting that an oxidation reaction had indeed occurred. Further examination of NMR data, along with mass spectrometry, identified the formation of a mixed ketal, giving a masked *ortho*-quinone compound **3.19** (Scheme **3.10**). The formation of the mixed acetal group meant that C-7 was now a stereogenic centre, causing the methylene protons of the prenyl group to be diastereotopic and show as two separate peaks in the ^{1}H NMR spectrum. Unfortunately the masked *ortho*-quinone **3.19** was formed in a low yield, and also proved unstable to silica gel column chromatography, and therefore difficult to purify.



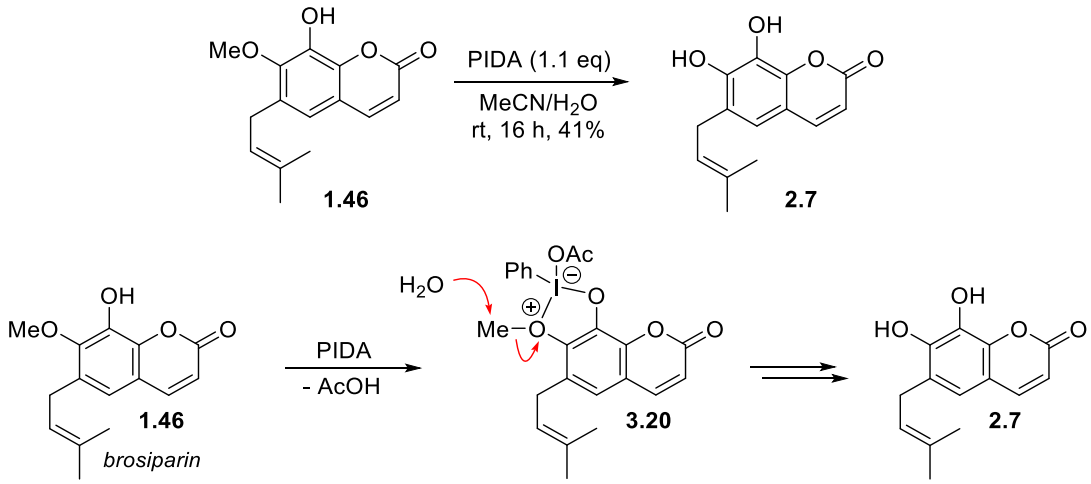
Scheme 3.10 - Formation of mixed-acetal masked quinone compound 3.19

We proposed that the reaction proceeded in a similar manner to the known PIDA oxidation mechanism (see Scheme **3.9**). Initial coordination of the hydroxyl group to the iodine, is followed by intramolecular addition of the acetate group at the C-7 position to form the mixed acetal (**3.19**), as well as the carbonyl at C-8, with the iodine species lost as iodobenzene.



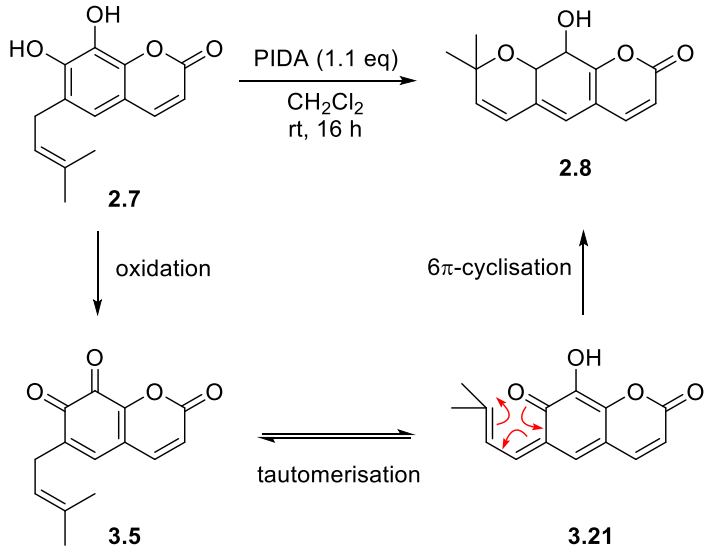
Scheme 3.11 - Proposed mechanism of oxidation of brosiparin with PIDA in CH_2Cl_2

Previous work in the Lawrence group had found success with a protocol reported by Novak and Glover - using an acetonitrile:water mixture (1:1) as solvent, so we applied these conditions to the oxidation of brosiparin (**1.46**).[124] Unexpectedly, however, the reaction resulted in the demethylation of brosiparin (**1.46**), to give the prenylated coumarin diol compound **2.7**. The reaction took place in reasonable yield and the product proved straightforward to isolate by column chromatography, though unfortunately is not at the oxidation level required for our synthesis. This result is likely to be due to the coordination of the I(III) centre to the methoxy group to give intermediate **3.20** (Scheme **3.12**), then hydrolysis of the methoxy group by water. Compound **2.7** is itself a natural product, fipsomin, recently isolated by Akihara and co-workers from the the fruits of *Ficus nipponica*, and this is, to the best of our knowledge, the first total synthesis of this natural product.[125]



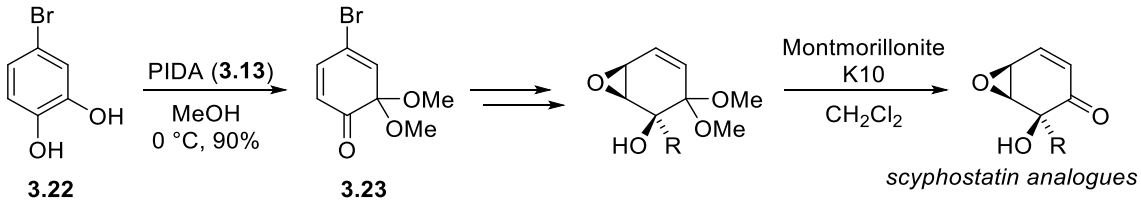
Scheme 3.12 – Demethylation of brosiparin (1.46) to produce fipsomin (2.7) using PIDA (3.13) in MeCN:H_2O

Fipsomin (**2.7**) was then subjected to Poupon's conditions, oxidation with PIDA (**3.13**) in dichloromethane, and gave tricyclic compound (**2.8**), where the prenyl group had cyclised onto the oxygen at C-7 to form a 6-membered ring (Scheme **3.13**). The tricylic coumarin-derived backbone of **2.8** was similar to that of luvangetin (**2.2**) and xanthyletin (**1.5**), both coumarin-derived natural products isolated alongside brosiparin (**1.46**) (see section **2.1.2**). We speculated that this result was due to the initial oxidation of fipsomin (**2.7**) to *ortho*-quinone **3.5**, which would undergo tautomerisation to give compound **3.21**, before 6π-cyclisation to form cyclised compound **2.8** (Scheme **3.13**). The presence of the methyl group on brosiparin (**1.46**) seemingly prevents this cyclisation from occurring.



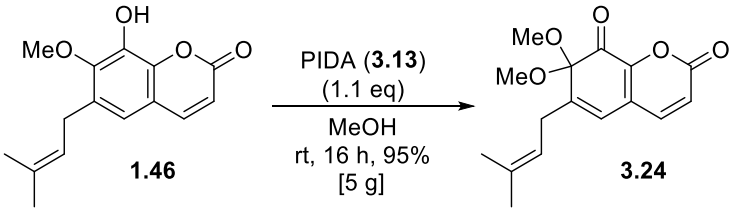
Scheme 3.13 – Oxidation and 6π-cyclisation of fipsomin (2.7) to give tricyclic compound 2.8

Taylor and co-workers reported the synthesis of scyphostatin analogues from 4-bromoguiacol (**3.22**), in which the oxidation of the starting material was carried out using PIDA (**3.13**) in methanol. This resulted in formation of a dimethyl acetal masked quinone (**3.23**), which was purified by column chromatography, which indicated its greater stability than the mixed ketal (**3.19**) that we had previous synthesised. This selective *in situ* protection enabled functionalisation of the carbonyl position, before eventual cleavage of the acetal group to reveal the second carbonyl group (Scheme **3.14**).



Scheme 3.14 – PIDA (3.13) oxidation in methanol in the synthesis of scyphostatin analogues

These conditions were then applied to the oxidation of brosiparin (**1.46**) (Scheme **3.15**). Initially the reaction was left overnight, where a colour change from colourless to yellow was observed, and TLC analysis of the reaction mixture indicated that there was no starting material remaining. Analysis of the crude reaction mixture by ^{1}H and ^{13}C NMR spectroscopy showed a similar oxidation to the reaction in dichloromethane, with a carbonyl group at the C-8 position, but this time a dimethyl acetal was observed at C-7, giving a similar masked *ortho*-benzoquinone compound (**3.24**) to that reported by Taylor. Complete conversion of the starting material was observed and the product was isolated in very high yield (95%), following purification by column chromatography. Further experimentation showed that the reaction was complete within two hours. The reaction was also able to be carried out on a multi-gram scale with no decrease in the isolated yield.



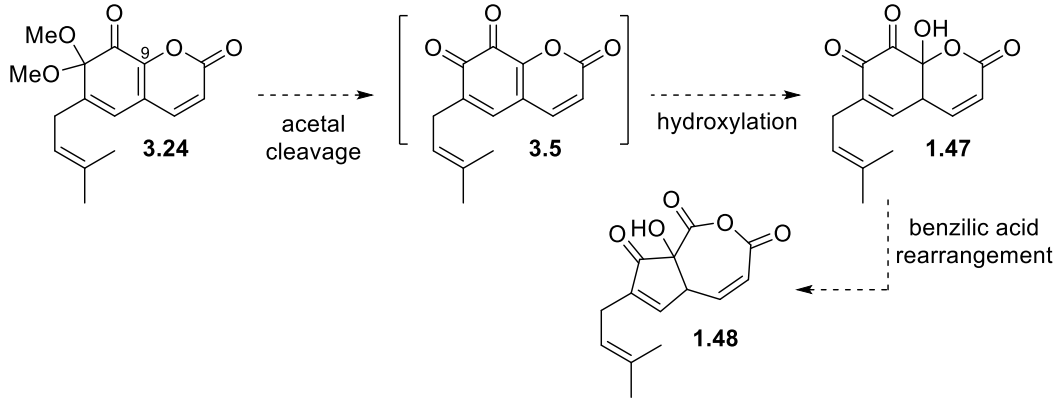
Scheme 3.15 – PIDA (3.13) oxidation of brosiparin (1.46) in methanol to form masked *ortho*-benzoquinone compound 3.24

In summary, the oxidation conditions trialled, using cerium, copper and iodine reagents did not lead directly the the desired *ortho*-quinone compound, and subsequent ring contraction. Other unsuccessful oxidising agents trialled on small-scale included Fremy's salt and iron chloride. However the use of the hypervalent iodine reagent PIDA (**3.13**) allowed us to oxidise brosiparin (**1.46**) to a masked *ortho*-quinone compound, the nature of which varied depending on which solvent was used. In dichloromethane mixed acetal compound **3.19** was formed, but proved unstable and difficult to isolate, whereas in methanol dimethoxyacetal-containing masked *ortho*-quinone **3.24** was successfully formed in high yield and on large scale.

3.4 – Attempted Acetal Cleavage

3.4.1 – Use of Lewis Acid catalysts

With practical quantities of masked *ortho*-quinone **3.24** available, attention turned towards the planned ring contraction. The initial step would be to attempt to cleave the dimethyl acetal group to reveal the *ortho*-quinone **3.5**. Subsequent hydroxylation at the C-9 position is needed to give compound **1.47**, which would be primed to undergo the ring contraction by a benzilic acid-type rearrangement (Scheme **3.16**)

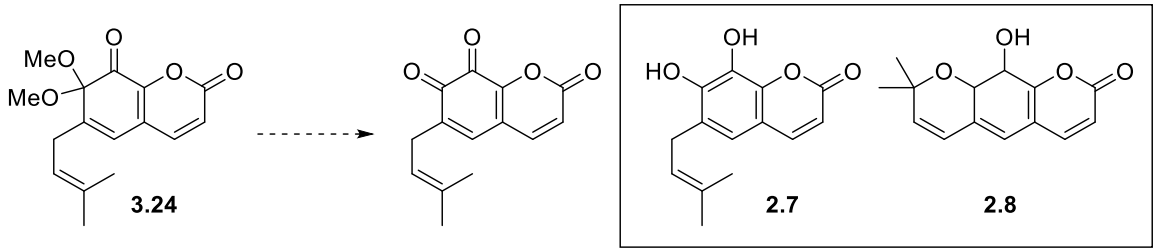


Scheme 3.16 – Proposed route to ring contraction from masked *ortho*-benzoquinone 3.24

A number of different methods for the cleavage of dimethyl acetals have previously been reported in the literature. The most common method is via acid-catalysed hydrolysis, using Brønsted acids such as toluenesulfonic acid, trifluoroacetic acid, acetic acid and Montmorillonite K10.[126-129] In recent years, however, a number of examples have been published describing the use of lanthanide-based Lewis acid catalysts to cleave acetal

groups.[130-131] These reactions can be carried out under very mild conditions and have been shown to be more environmentally friendly than previous methods.[130] Lanthanide triflates have been shown to effectively cleave alkyl and cyclic acetals, so erbium and ytterbium triflates (which were readily available within the lab) were initially screened, along with other Lewis acids (bismuth iodide and indium triflate) for the acetal cleavage of compound **3.24**.[132-134]

Table 3.2 – Attempted cleavage of acetal of 3.24 using lanthanide triflates



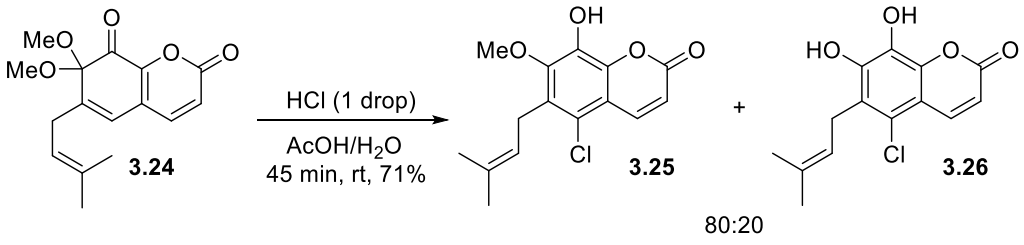
Entry	*Reagent*	*Equiv.*	*Solvent*	*Temp*	*Time*	*Product*
a	$Er(OTf)_3$	0.1	$MeCN/H_2O$	rt	16 h	No rxn
b	$Er(OTf)_3$	0.1	$MeCN/H_2O$	rt	16 h	No rxn
c	$Yb(OTf)_3$	0.1	$MeCN/H_2O$	rt	72 h	No rxn
d	$Yb(OTf)_3$	0.1	$MeCN/H_2O$	rt	72 h	No rxn
e	$Er(OTf)_3$	0.1	$MeCN/H_2O$	80 °C	12 h	**2.8**
f	$Yb(OTf)_3$	0.1	$MeCN/H_2O$	80 °C	12 h	**2.8**
g	BiI_3	0.05	H_2O	100 °C	20 h	**2.7/2.8**
h	$In(OTf)_3$	0.1	acetone	rt	24 h	**2.7/2.8**

As can be seen in table **3.2**, the results were similar for all the different Lewis acids used. At room temperature, with 0.1 equivalents of catalyst in acetonitrile/water, no reaction was observed after 16 hours (entries *a* and *b*), or even when the reaction was left for several days (entries *c* and *d*). The reaction was repeated, but the mixture was heated to 80 °C (entries *e* and *f*), and it was clear from TLC analysis that the elevated temperature enabled consumption of the starting material, with a new spot appearing. From extensive analysis of the ^{1}H and ^{13}C NMR spectra, it was clear that a cyclisation reaction of the prenyl side chain had occurred, giving tricyclic compound **2.8**, the same product

observed from the PIDA oxidation of fipsomin (**2.7**). This cyclisation is proposed to occur by the same 6π-cyclisation mechanism as in the oxidation of fipsomin (**2.7**), with acetal cleavage resulting in *ortho*-quinone **3.5**, which can undergo tautomerisation, followed by cyclisation (Scheme **3.13**, above). The key indicators from the NMR analysis was the loss of the prenyl alkene and methylene peaks, but the presence of a new pair of cycloalkene peaks with J = 9.9 Hz, characteristic of a (*Z*)-alkene. When using either indium triflate and bismuth iodide (entries *g* and *h*) as the catalyst, a mixture of compounds was observed. Cyclised compound **2.8** had formed, again presumably via 6π-cyclisation of the *ortho*-quinone, but a significant amount of an unexpected reduction had also occurred following cleavage of the acetal, as the dihydroxy coumpound fipsomin (**2.7**) was also observed.[134-135]

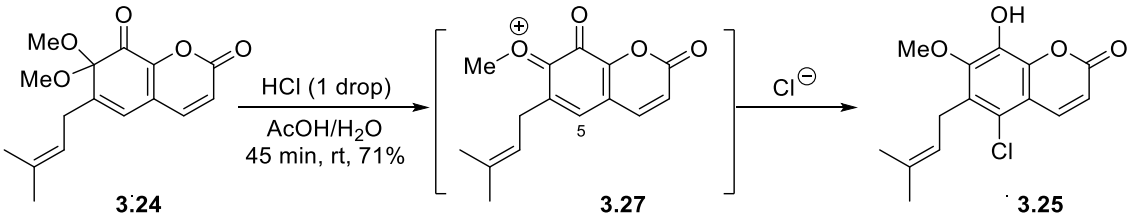
3.4.2 – Use of Brønsted acids

Brønsted acid conditions were also screened for the acetal cleavage. When the reaction of masked *ortho*-quinone **3.24** with acetic acid, water and one drop of concentrated HCl took place, a mixture of compounds **3.25** and **3.26** were formed, both of which contained a chloro- group at the 5-position of the coumarin ring system. Compound **3.25** was the major product of the two, containing a methoxy group at C-7 and a hydroxyl group at C-8, the result of partial hydrolysis of the dimethyl acetal. The NMR spectra suggested substitution of the 5-position on the ring, and the use of mass spectrometry indicated the presence of a chloro group, therefore enabling elucidation of the structure. The yield was low, as a significant amount of demethylated dihydroxyl compound **3.26** had also formed (in a 1:4 ratio to compound **3.25**).



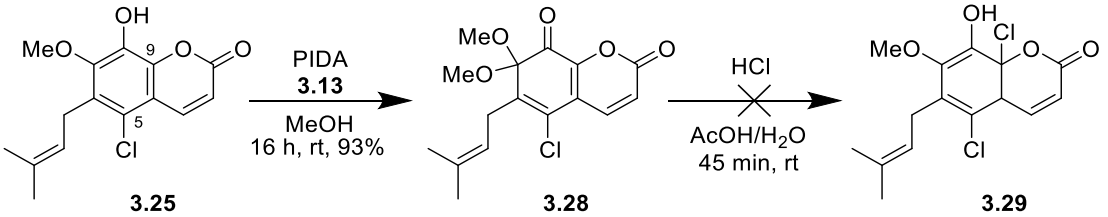
Scheme 3.17 - Acetal cleavage and C-5 halogenation of masked *ortho*-quinone 3.24

We proposed that the reaction proceeded via initial cleavage of the acetal to give the *ortho*-quinone type oxonium intermediate **3.27**. Subsequent nucleophilic chloride addition to the C-5 position, followed by tautomerisation and re-aromatisation, would lead to the product (Scheme **3.18**).



Scheme 3.18 – Proposed mechanism of acetal cleavage and C-5 chlorination of masked *ortho*-quinone 3.24

Looking back at our proposed mechanism for the oxidative ring-contraction (Scheme **3.1** above), the ideal step following formation of the *ortho*-quinone was hydroxylation at the C-9 position of the coumarin ring system. It seemed from the result in Scheme **3.18** that nucleophilic addition to the coumarin system preferentially occurs at the C-5 position, however, so it was necessary to devise a plan to circumvent this issue. It was envisioned that a compound with a substituent at the C-5 position, therefore blocking it from nucleophilic addition, may undergo the desired functionalisation at C-9. Ideally, we would then be able to remove the C-5 substituent later in the synthesis. Our hypothesis was tested using the C-5 halogenated compound **3.25**. Oxidation with PIDA (**3.13**) in methanol, using the conditions described above, was carried out to give the C-5 chlorinated masked *ortho*-quinone compound **3.28** in high yield (Scheme **3.19**). Compound **3.28** was then submitted to the acetal cleavage conditions using acetic acid, water and HCl, which we hoped would cleave the acetal and chlorinate the C-9 position in a single step. Unfortunately the reaction proved unsuccessful, with only a complex mixture of degradation products formed.

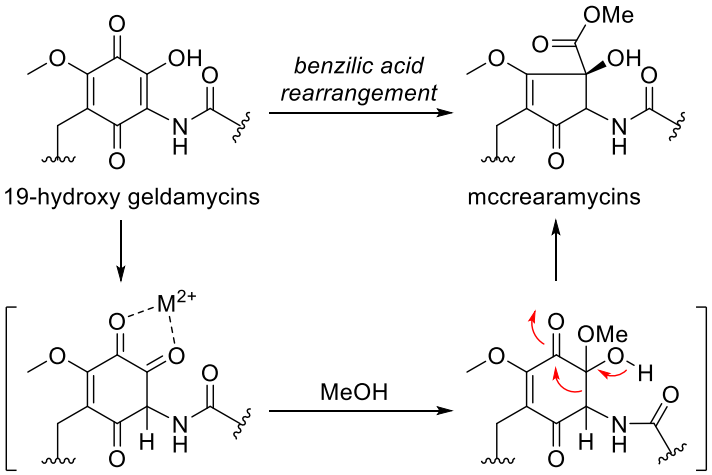


Scheme 3.19 – Attempt to direct hydroxylation to the C-9 of the coumarin

3.5 – Attempts to carry out ring-contraction of masked *ortho*-quinone 3.24

3.5.1 – Thorson's use of Metal Salts and Basic Conditions

An example of the use of the benzilic acid rearrangement in total synthesis was published by Thorson in 2017, in the synthesis of mccrearamycins A-D, which were isolated from abandoned coal mine microbes, along with geldanamycins B-G.[29] These natural products contain a cyclopentenone unit which is derived from the benzilic acid rearrangement of the 19-hydroxy geldanamycin quinone core. The conditions Thorson described for the preparation of *para*-quinones using CAN were previously trialled in section 3.2.2,[29] but now we wanted to focus on the subsequent ring contraction step. Thorson proposed a metal-mediated mechanism for this transformation (Scheme **3.20**) and trialled the use of a number of different transition metal salts on a model quinone system, as well as bases known to promote benzilic acid rearrangements.

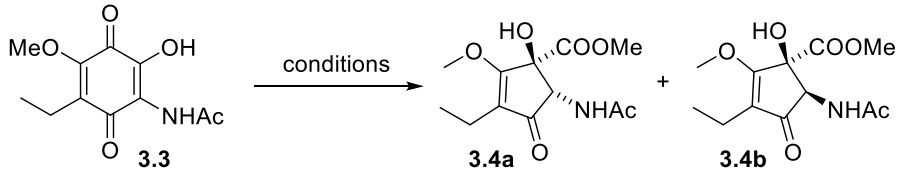


Scheme 3.20 – Proposed benzilic acid rearrangement mechanism in Thorson's synthesis of mccrearamycins A-D

Thorson found that the optimum conditions trialled were cobalt(II) chloride (2 equivalents), in methanol with the reaction heated to 80 °C for 16 hours (Table **3.3**). This successfully gave the cyclopentenone product **3.4a** in a high diastereomeric ratio and yield. Other metals salts used were copper(II) chloride and nickel(II) chloride, which both gave an "undefined mixture" of products, and silver(I) triflate, which produced a higher ratio of the undesired isomer. Other relatively successful results were obtained

with bases such as DBU, triethylamine and Hünig's base, which all gave compound **3.4a** in reasonable yield, but with less stereoselectivity than $CoCl_2$

Table 3.3 – Thorson's benzilic acid rearrangement model studies [29]



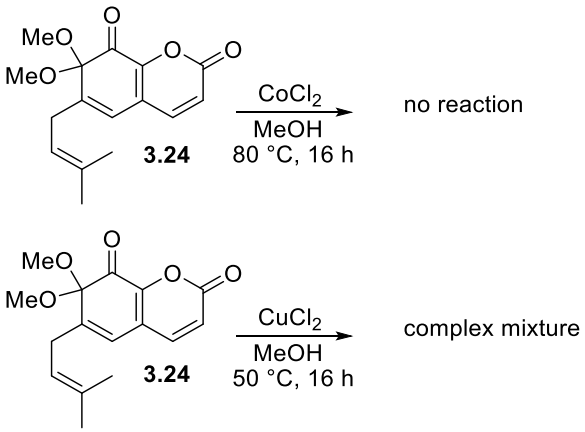
Entry	*Additive (2 eq)*	*Solvent*	*Temp*	*Ratio (3.4a:3.4b)*	*Yield*
a	$CoCl_2$	$MeOH/CH_2Cl_2$	50 °C	>10:1	73%
*b**	$CoCl_2$	MeOH	50 °C	>10:1	82%
c	$CoCl_2$	MeOH	80 °C	>10:1	85%
d	$CuCl_2$	$MeOH/CH_2Cl_2$	50 °C	-	'Undefined mixture'
e	$NiCl_2$	$MeOH/CH_2Cl_2$	50 °C	-	'Undefined mixture'
f	AgOTf	$MeOH/CH_2Cl_2$	50 °C	1:5	39%
g	DBU	$MeOH/CH_2Cl_2$	50 °C	2:1	51%
h	Triethylamine	$MeOH/CH_2Cl_2$	50 °C	5:1	60%
i	DIPEA	$MeOH/CH_2Cl_2$	50 °C	4:1	55%

*Run for 40 hours, all other reactions 16 hours.

3.5.2 – Application of Thorson's conditions to our system

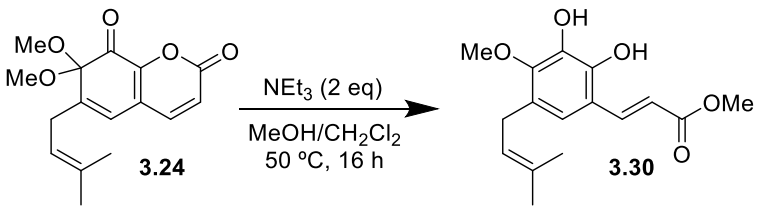
Thorson's conditions were trialled on our system, the masked *ortho*-quinone compound **3.24**, in the hope that we could effect a ring contractive benzilic acid rearrangement reaction. However, when the reaction was carried out at 50 °C and at 80 °C only unreacted starting material was observed. Even when another 2 equivalents of $CoCl_2$ was added, no reaction took place. This is likely due to the nature of the substrate, as Thorson was able to form the required *ortho*-quinone compound, whereas the attempted methoxy acetal cleavage of **3.24** did not successfully form the *ortho*-quinone. If the reaction does indeed progress with metal coordination to the two carbonyl groups, this may explain

why no reaction takes place. It is possible that a one-pot reaction, using the acetal cleavage conditions described previously (Table **3.3**), along with $CoCl_2$ may enable the formation of the *ortho*-quinone, followed by chelation by the metal, which may prevent the previously observed cyclisation of the prenyl group. The reaction was also carried out with copper chloride, but as with Thorson, only a complex mixture of compounds was produced (Scheme **3.21**).



Scheme 3.21 – Reaction of 3.24 with metal salts using's Thorson's conditions

A very different result was observed when the reaction was carried out using the basic conditions Thorson reported, with two equivalents of triethylamine used, in a methanol/dichloromethane solvent mixture. After analysis by 2D NMR spectroscopy and mass spectrometry it was concluded that the product formed was compound **3.30**, formed by ring-opening of the coumarin lactone with methanol (scheme **3.22**). A key piece of evidence for the ring-opening was the coupling constants (J = 16 Hz) of the alkene now indicating the presence of an (*E*)-alkene rather than a (*Z*)-alkene, which would not be possible in a 6-membered ring.

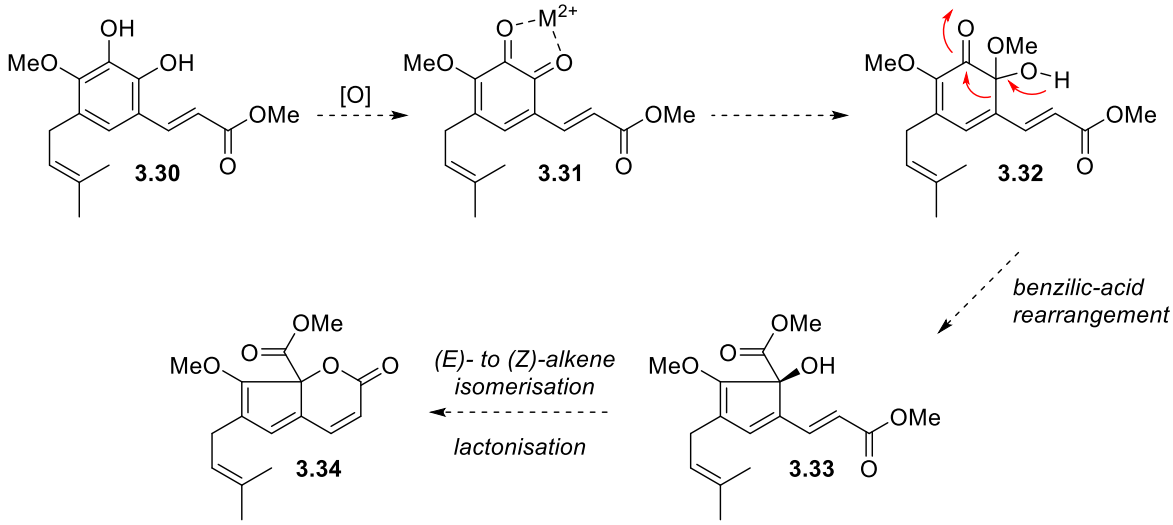


Scheme 3.22 – Ring opening of 3.24 using triethylamine in $MeOH/CH_2Cl_2$

3.6 - Synthesis and Reactions of a ring-opened brosiparin derivative

3.6.1 – Design of synthetic route based on ring-contraction prior to coumarin formation

Although it was not the product we were hoping to form in this reaction, isolating the ring-opened form of brosiparin **3.30** led us to re-think our route to the product of the ring contraction of brosiparin (Scheme **3.1**, compound **1.48**). We speculated that the formation of an *ortho*-quinone **3.31** (at C-8 and C-9) from compound **3.30** may be much more likely than the *ortho*-quinone compound targeted from brosiparin (**1.46**). Thorson's proposed mechanism suggests this may then be able to undergo benzilic acid rearrangement. If the desired compound **3.31** could be formed, Thorson's and other benzilic acid rearrangement conditions would be trialled, in the hope of achieving the ring contraction to give compound **3.33**. A subsequent ring closing of the ester would re-form the lactone, giving compound **3.34**. The coumarin formation occurs at high temperatures in the initial synthesis of brosiparin (**1.46**), so it was proposed that heating compound **3.33** would enable this similar ring-closing step (Scheme **3.23**).

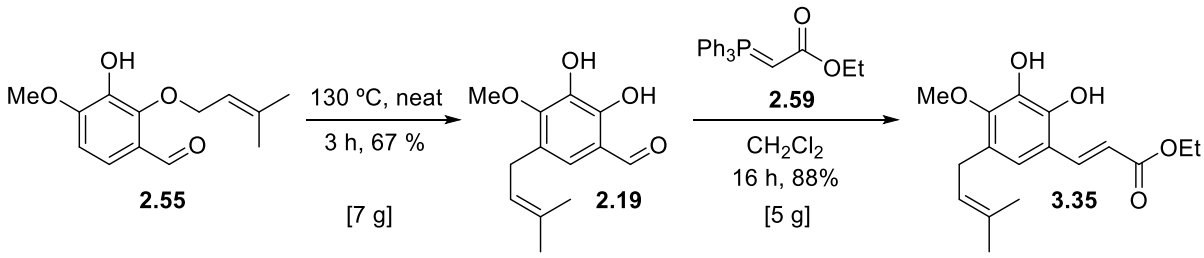


Scheme 3.23 – Proposed route to ring contraction from ring opened compound 3.30

3.6.2 – Synthesis of ring-opened brosiparin **3.35**

The formation of the ring-opened form of brosiparin (**3.30**) using NEt_3 proved to be difficult on large scale, due to the formation and subsequent removal of unwanted triethylamine salts. We therefore developed an alternative approach, by altering the original synthesis of brosiparin (**1.46**) to successfully synthesise ring-opened equivalent **3.35** in high yield, which contained an ethyl ester rather than the methyl ester in

compound **3.30**. The first two steps, double demethylation, and prenylation, to give compound **2.55** were the same as in the synthesis of brosiparin (see section **2.6**). The *para*-Claisen rearrangement was then carried out neat at 130 °C, using the same conditions reported by Hamada, and trialled in early attempts to form brosiparin (**1.46**) (Chapter 2, Scheme **2.9**), to give compound **2.19**, in which the position of the prenyl group on the ring was confirmed by 2D NMR analysis. HMBC data showed cross-peaks between the proton at the unsubstituted position of the aryl ring and both the aldehyde carbon and the prenyl CH_2 carbon. The NOESY spectrum showed cross-peaks between the methoxy and prenyl CH_2 protons, and between the aldehyde proton and the aryl proton, which enabled us to confirm the structure (see section **5.6** for spectra). Wittig olefination of the aldehyde of compound **2.19** was then carried out at room temperature using the same phosphorane reagent **2.59**, resulting in compound **3.35** in high yield. The lower temperature of the reaction meant we could replace the high boiling solvent *N*,*N*-dimethylaniline with dichloromethane and prevented the closing of the lactone ring, which was key to the synthesis of brosiparin (**1.46**). The synthesis of **3.35** was easily scalable, with the last step carried out on a five gram scale.



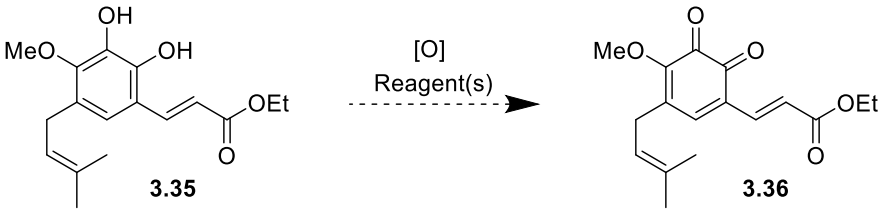
Scheme 3.24 – Synthesis of ring-opened brosiparin equivalent 3.35

3.6.3 – Oxidation reactions of ring-opened brosiparin (**3.35**)

There are numerous examples of oxidation reactions of catechols to *ortho*-quinones, and a number of these were trialled on the substrate **3.35** (Table **3.4**). Oxidising agents such as *ortho*- and *para*-chloranil, silver oxide, CAN and IBX have been reported to oxidise catechols to quinones,[123, 136-138] so these were initially tested (entries *a*-*c*). Disappointingly, all gave either no reaction or a complex mixture of inseperable compounds. Rossi's copper(0) and oxygen conditions were trialled, but once again these attempts resulted in a complex mixture of products (entries *d*-*g*) . A different copper-catalysed phenolic oxidation procedure has been reported by Lumb, which used $CuPF_6$ along with a *N*,*N'*-di-*tert*-butyl ethylenediamine (DBED) ligand in the presence of

molecular oxygen.[139] However, when these conditions were used with substrate **3.35**, no reaction occurred, with only unreacted starting material observed (entry *h*). We turned next to our optimised conditions for the oxidation of brosiparin (**1.46**) (see Scheme **3.15**), using PIDA (**3.13**), which had also been previously shown by Kita to be capable of oxidising a 1,2-catechol to the respective *ortho*-quinone (entry *i*).[107] The reaction was carried out at room temperature, using 1.2 equivalents of PIDA in methanol, and TLC analysis seemed to indicate the clean formation of a new product after 40 minutes, so the reaction was quenched. However ^{1}H NMR analysis of the crude material after work-up showed a complex mixture of degradation products.

Table 3.4 – Oxidation condition trialled on substrate 3.35



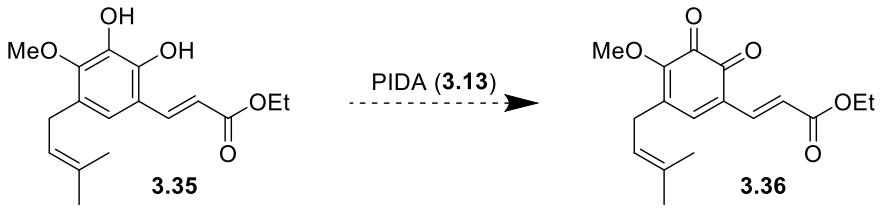
3.35 **3.36**

Entry	***Reagent(s)***	***Equiv.***	***Solvent***	***Temp***	***Time***	***Result***
a	*p*-chloranil	1.2	Et_2O	−20 °C	16 h	complex mixture
b	*o*-chloranil	1.2	Et_2O	−20 °C	16 h	complex mixture
c	Ag_2O	2.5	CH_3CN	rt	16 h	complex mixture
d	IBX	2	$CHCl_3$/MeOH (9:1)	rt	30 min	complex mixture
e	CAN	2	CH_3CN/H_2O (1:1)	−10 °C	25 min	complex mixture
f	Cu(0), O_2	0.25	Pyr/MeOH	rt	90 min	complex mixture
g	Cu(0), O_2	0.25	Pyr/MeOH	70 °C	90 min	complex mixture
h	$CuPF_6$, DBED, O_2	0.2, 0.4	CH_2Cl_2	rt	16 h	no reaction
i	PIDA	1	MeOH	rt	40 min	complex mixture

As the TLC analysis had suggested clean formation of a new product in the reaction of compound **3.35** with PIDA (**3.13**), we decided to investigate further. The reaction was, therefore, carried out in deuterated methanol, with regular aliquots taken for analysis by

^{1}H NMR spectroscopy. After 10 minutes, the ^{1}H NMR spectrum showed clear formation of another product in 42% conversion, with similar, slightly shifted peaks as would be expected if the *ortho*-quinone formation had occurred (Table **3.5**, entry a). ^{13}C NMR of the aliquot gave a clearer indication that this was the case, showing two new signals corresponding to carbonyl groups (δ 177.9 and 175.8 ppm). However, when further aliquots were taken over time, the NMR spectra showed less of the quinone with respect to the starting material, which indicated that the product was unstable, and broke down easily (entries *b* and *c*). Many *ortho*-quinone compounds have been previously reported to be unstable due to their high electrophilicity and they are known to readily undergo reactions including Diels–Alder-type dimerisations.[140-142] Quenching the reaction after 10 minutes did not help, as the product has seemingly broken down by the time it was analysed after work-up, despite the aliquot NMR showing some conversion. Reactions with a larger excess of PIDA (**3.13**) showed increased conversion, but the stability issues remained (entries *d* and *e*). When the reaction was carried out at −78 °C, the rate of formation of quinone **3.36** was slower (29% conversion after 1 hour), but the compound was stable over a longer time period (entries *f-h*). However, when the sample was warmed to room temperature, a complex mixture was once again observed.

Table 3.5 – Further investigation into the oxidation of substrate 3.35 with PIDA

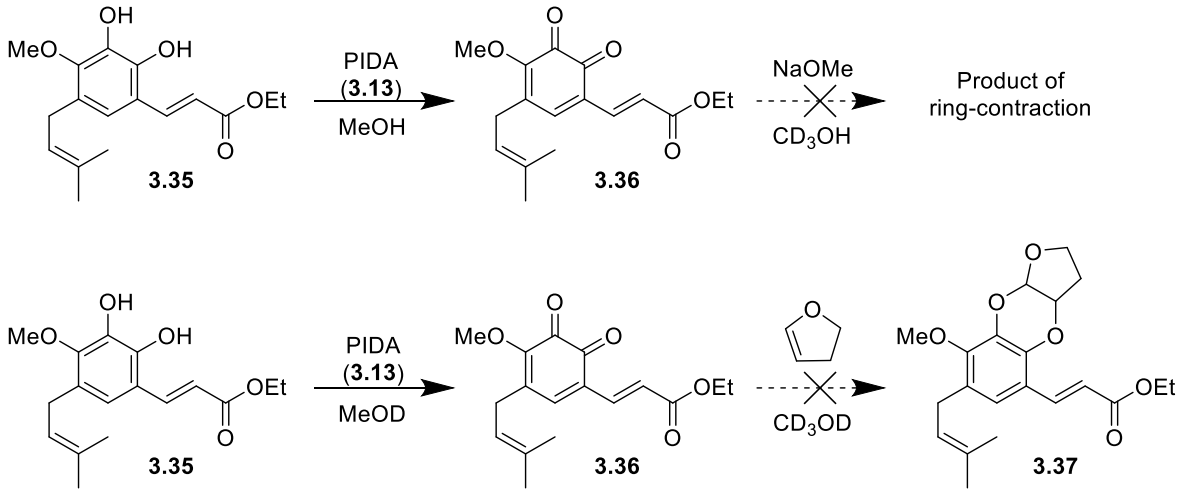


Entry	*Reagent(s)*	*Eq.*	*Solvent*	*Temp*	*Time*	*Conversion**
a	PIDA	1	MeOH	rt	10 min	42%
b	PIDA	1	MeOH	rt	30 min	33%
c	PIDA	1	MeOH	rt	60 min	14%
d	PIDA	5	MeOH	rt	5 min	65%
e	PIDA	5	MeOH	rt	20 min	complex mixture
f	PIDA	5	MeOH	−78 °C	30 min	19%

g	PIDA	5	MeOH	−78 °C	60 min	29%
h	PIDA	5	MeOH	−78 °C	120 min	29%

*with respect to starting material

Due to the instability of the *ortho*-quinone at room temperature, we speculated that it may be possible to carry out the ring contraction at low temperature *in situ*, by adding in sodium methoxide. However, initial studies, in which sodium methoxide was added to the reaction mixture when TLC analysis showed formation of the quinone, only resulted in a complex mixture, from which it was not possible to identify any products of a ring contraction. Other methods trialled to attempt to trap the *ortho*-quinone **3.36** included the addition of 2,3-dihydrofuran, in the hope of carrying out an inverse electron demand Diels–Alder reaction. However this approach also proved unsuccessful (Scheme **3.25**), with no evidence from NMR spectroscopy that we had been able to trap *ortho*-quinone **3.36**.



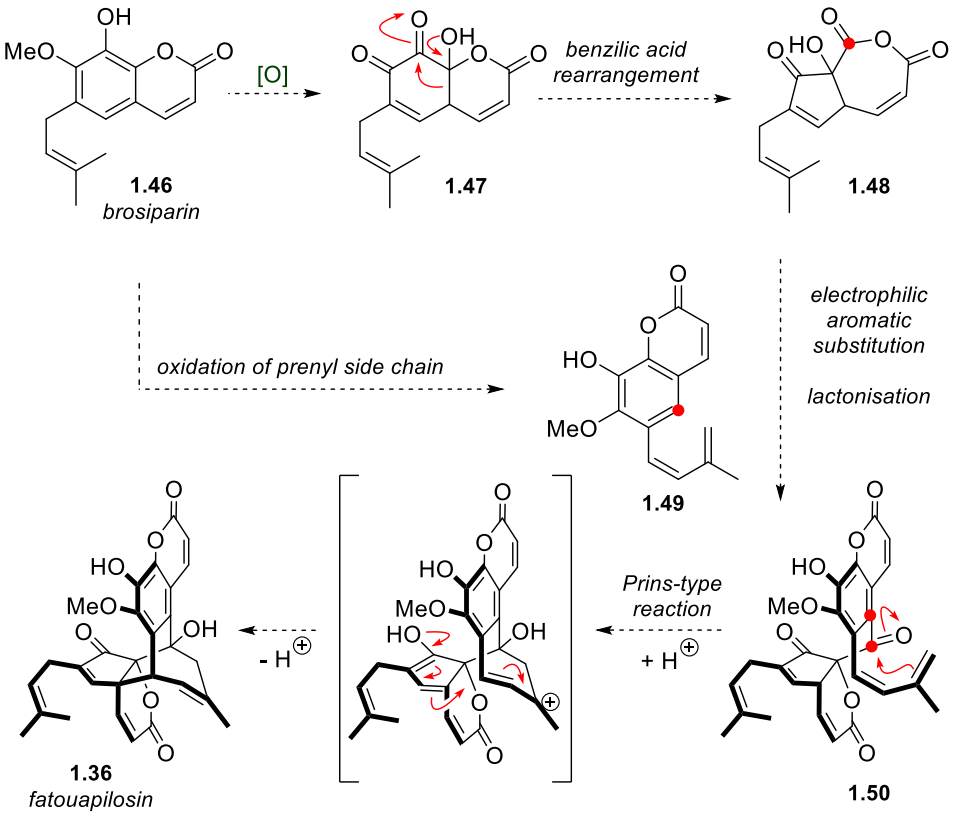
Scheme 3.25 – Attempts to trap unstable quinone

3.7 – Alternative Biosynthetic Approach

3.7.1 – Example of BF_3-mediated aryl-aryl bond formation

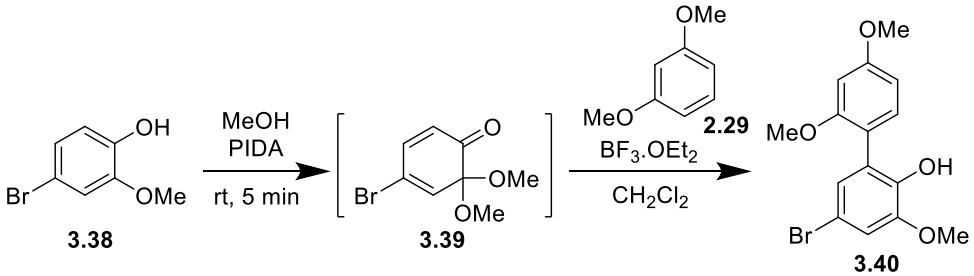
All attempts to progress with the synthesis of fatouapilosin (**1.36**) had thus far been following our proposed biosynthetic pathway (Scheme **3.26**), in which the oxidative ring contraction step was followed by a C–C bond formation between the ring contracted compound **1.48** and brosiparin derivative **1.49** (which contains an oxidised prenyl group),

to give compound **1.50**. It was proposed this step could occur by electrophilic aromatic substitution, followed by lactonisation.



Scheme 3.26 – Proposed biosynthesis of fatouapilosin (1.36)

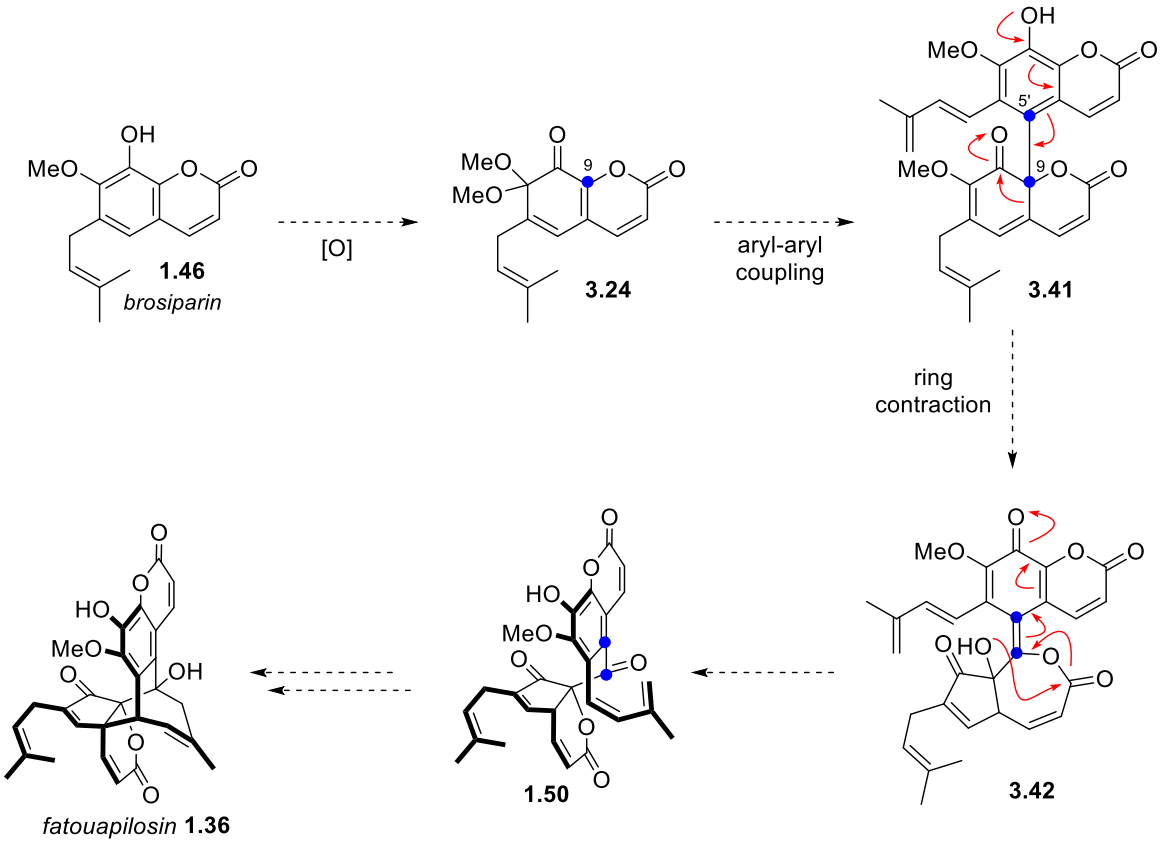
However, a recently published article by Peddinti came to our attention, in which they developed a synthesis of oxygenated biaryl compounds by coupling methoxyphenols with electron-rich arenes (Scheme **3.27**).[143] The first step is analogous to the oxidation of brosiparin (**1.46**) with PIDA in methanol, where the methoxyphenol starting material **3.38** is oxidised to the masked *ortho*-benzoquinone **3.39**. An electron-rich arene (eg. dimethoxybenzene (**2.29**)) (2 equivalents) and $BF_3{\cdot}Et_2O$ are subsequently added at −30 °C, and a new C–C aryl-aryl bond is formed at the 2-position, adjacent to the carbonyl group of the masked *ortho*-benzoquinone. A range of different biaryl compounds were formed in this way.



Scheme 3.27 – BF_3-mediated coupling of methoxyphenols

3.7.2 – Alternative proposed biosynthetic pathway to fatouapilosin

By reordering the steps in our proposed biosynthesis (Scheme **3.28**), it was proposed that this C–C bond forming transformation could be applied to the synthesis of fatouapilosin (**1.36**). After oxidation of brosiparin (**1.46**) to masked *ortho*-quinone **3.24**, Peddinti's aryl-aryl coupling step would be used to react compound **3.24** and the brosiparin isoprene-derivative **1.49** to give compound **3.41**, which would then be subjected to benzilic acid rearrangement conditions in an attempt to undergo a selective ring contraction to give compound **3.42**. The same Prins reaction initially proposed could then occur, leading to fatouapilosin (**1.36**).

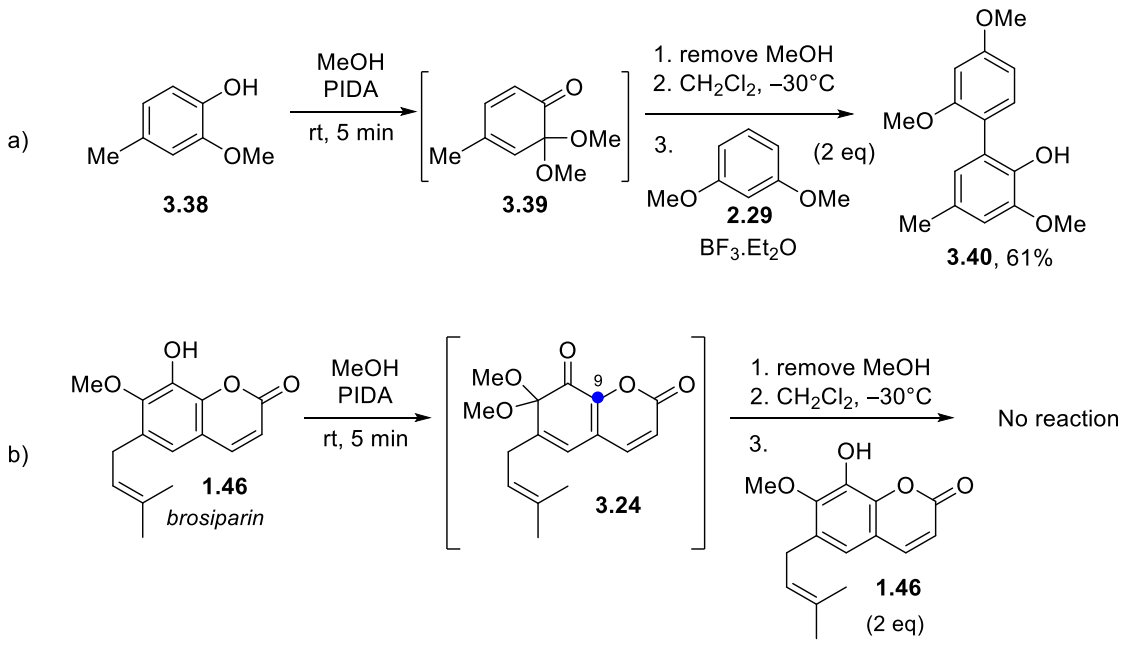


Scheme 3.28 – Modified proposed route to fatouapilosin

3.7.3 – Formation of new C–C bond from coumarin ring

A test reaction was carried out using a simplified substrate (Scheme **3.29a**), which successfully formed the same biaryl product **3.40**, in comparable yield to that reported by Peddinti.[143] Following this, a coupling reaction of masked *ortho*-quinone **3.24** with brosiparin **1.46** as the electron-rich arene was attempted – the objective being to form a new C–C bond at the C-9 position adjacent to the carbonyl group of the masked *ortho*-

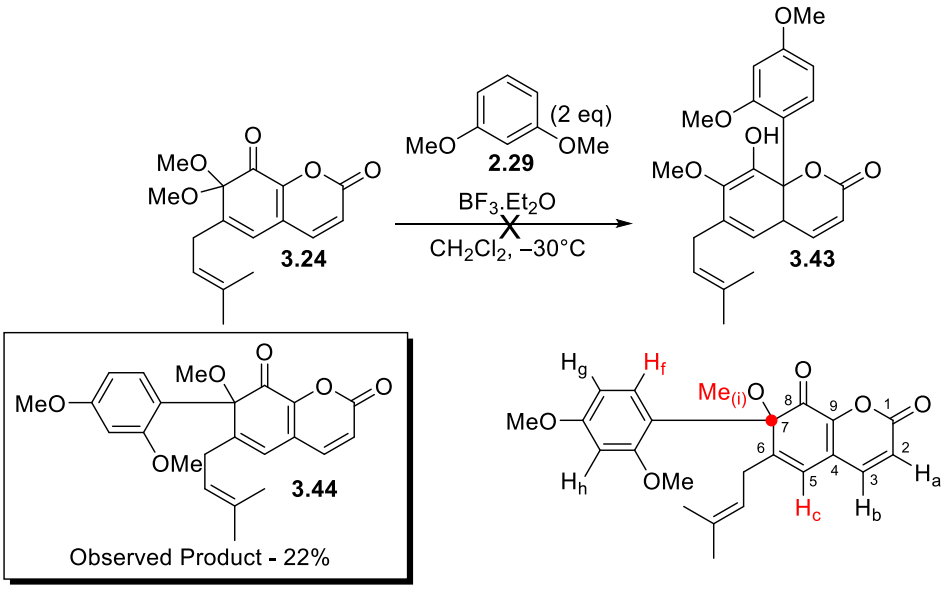
quinone **3.24** (Scheme **3.28** above). This would ideally undergo electrophilic aromatic substitution onto the one free position on the aromatic ring of brosiparin (**1.46**) (C-5). Unfortunately, no reaction took place, with only unreacted starting material observed by ^{1}H NMR analysis, even when reaction times and equivalents of brosiparin (**1.46**) were increased (Scheme **3.29b**).



Scheme 3.29 – a) Attempted aryl-aryl coupling reactions using Peddinti's substrate (3.38) and b) using brosiparin

We decided to further explore the reaction by attempting to couple masked *ortho*-quinone **3.24** with a model nucleophile – electron-rich arene, 1,3-dimethoxybenzene (**2.29**). The result of this was a complex mixture of compounds including a significant amount of unreacted starting material, but through column chromatography it was possible to isolate the major product in a 22% yield (Scheme **3.30**). From initial analysis it was clear that the newly formed compound was indeed as a result of aryl-aryl coupling, with a new C–C bond formed, and it was assumed that the desired reaction may have occurred. However, upon further analysis of the 2D NMR spectroscopy data, it was clear from the chemical shifts of the carbons at C-9 and C-7 that rather than the desired C–C bond formation at C-9 to give compound **3.43**, we had instead observed aryl-aryl coupling at C-7, effectively substituting one of the methoxy groups to give biaryl compound **3.44**. An important indicator that compound **3.44** had been formed, rather than **3.43**, was the presence of the additional carbonyl signal in the ^{13}C NMR spectrum. Additionally, the

prenyl CH_2 appeared to be diastereotopic, in the same manner as seen earlier for mixed acetal compound **3.19** (section **3.3**) suggesting a stereogenic centre at C7. Analysis of the HMBC spectrum helped to confirm this, as cross-peaks were observed between the C7-carbon and the C7 methoxy protons (H_i), as well as C7 and H_c on the coumarin ring, and C7 and H_f on the aryl ring (all indicated in red in Scheme **3.30**, see section **5.6** for spectra).

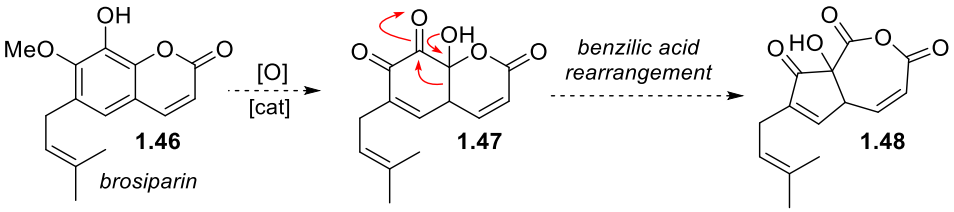


Scheme 3.30 – Formation of mixed acetal 3.44

NMR analysis of the crude reaction mixture provided no evidence of any other products resulting from C–C bond formation. As with the previous reactions of the masked *ortho*-quinone compound **3.24**, the main issue seemed to be that it does not seem to be predisposed to react at the desired C-9 position under any conditions. As a result, we decided not to proceed further with this reaction using the masked *ortho*-quinone substrate **3.24**. Although we had not achieved the coupling reaction we had aimed for, this was still an interesting result, and this type of aryl-aryl coupling using a coumarin ring system is a novel transformation that has the potential to be further explored in the future.

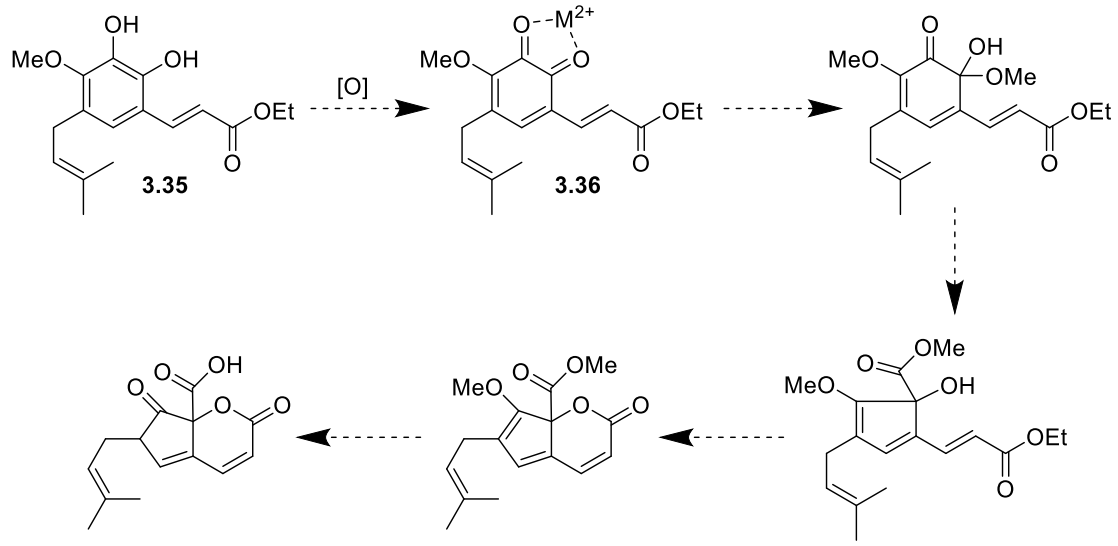
3.8 – Conclusions and Future Work

The main aim of this part of the project was to carry out the key step in the total synthesis of fatouapilosin (**1.36**), an oxidative ring contraction. We hoped to develop methodology for oxidative ring contraction by a benzilic acid rearrangement-type rearrangement, using brosiparin (**1.46**) as the substrate, and ideally using base metal catalysis (Scheme **3.31**). Initial trials based on Rossi's ring contraction of phenol proved unsuccessful, yielding only a complex inseparable mixture, so other oxidising agents known for preparing quinone-type compounds were explored.



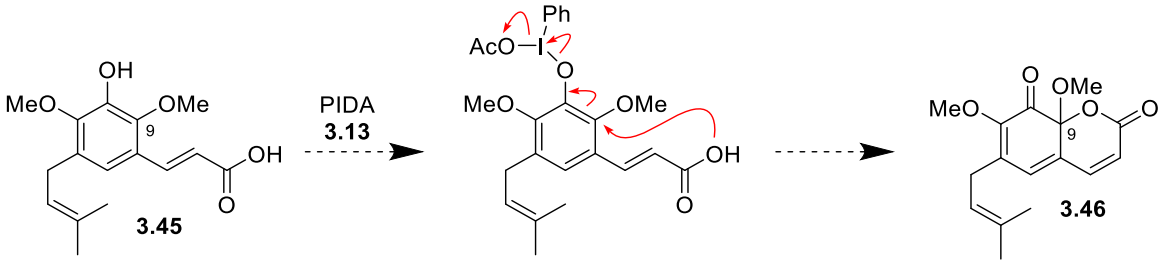
Scheme 3.31 – Proposed oxidative ring contraction of brosiparin

The use of hypervalent iodine reagents, such as PIDA (**3.13**), led to the successful formation of a masked *ortho*-quinone containing a dimethyl acetal (**3.24**). Attempts to cleave the acetal and reveal the *ortho*-quinone predominantly resulted in unwanted cyclisation of the prenyl group onto the newly exposed oxygen, however C-5 halogenation was observed in the presence of acetic acid, water and HCl to give compound **3.25**. Unfortunately, attempts to tune the substrate and the reaction conditions did not result in successful functionalisation at C-9. An alternative route to fatouapilosin (**1.36**), with a C–C bond formation step before the ring contraction, was attempted and although the oxidised form of brosiparin (**3.24**) was successfully coupled to another aryl substrate, we were not able to selectivity form the new bond at the C-9 position. As most of the issues seemed to lie with the reactivity of the coumarin ring system of the substrate, particularly in attempting to carry out reactions at the C-9 ring junction, a ring-opened form of brosiparin (**3.35**) was synthesised in four steps and used as a substrate for oxidation reactions. An altered biosynthetic pathway was proposed, with the ring contraction step taking place before cyclisation (Scheme **3.32**) Unfortunately, the resulting quinone compound was unstable and could not be isolated, despite a number of attempts to trap the intermediate or to carry out a ring contraction *in situ*.



Scheme 3.32 - Proposed reaction pathway from the ring-opened form of brosiparin (3.35)

Future work within this project would likely further explore the proposed biosynthetic pathway from the ring-opened form of brosiparin (**3.35**). Further methods of trapping the *ortho*-quinone compound **3.36** could be explored, such as the addition of a metal species into the previously trialled oxidation with PIDA (**3.13**), which may be able to coordinate to and therefore stabilise the observed *ortho*-quinone species (Scheme **3.32** above). Another route that could be investigated is the formation of a ring-opened variant of brosiparin containing a free carboxylic acid on the alkene side chain (**3.45**), and a methoxy group at the C-9 (Scheme **3.33**). It is speculated that upon oxidation of compound **3.45** with PIDA (**3.13**), the free acid may act as a nucleophile, and cyclise to form compound **3.46**, which would be functionalised at the C-9 position, and potentially primed to undergo a ring contraction in basic conditions (Scheme **3.33**).



Scheme 3.33 – Proposed one-pot oxidation and cyclisation of ring-opened compound 3.45

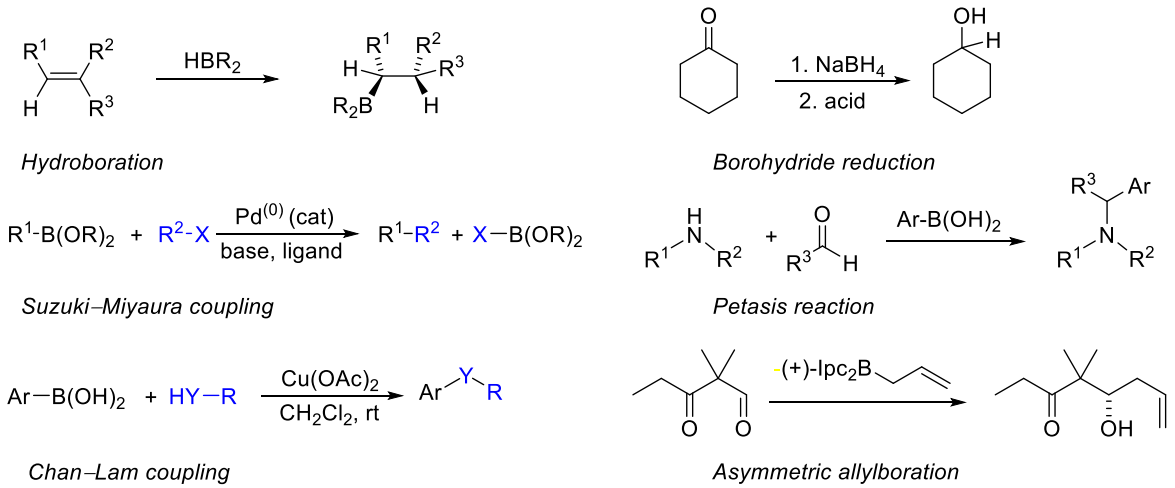
Overall, despite the lack of success with regards to the targeted ring contraction reaction of brosiparin (**1.46**), we were able to carry out a number of interesting oxidative transformations which gave us significant insight into the reactivity of the coumarin derived substrate. As stated above, a key strategy moving forward is the oxidation and ring contraction of a ring-opened brosiparin derivative, followed by cyclisation. This may be a better strategy for the thus far unsuccessful functionalisation of the C-9 position.

Chapter 4 – Borane-catalysed Enantioselective Reduction by Transborylation

4.1 - Introduction

4.1.1 – Organoboron Chemistry

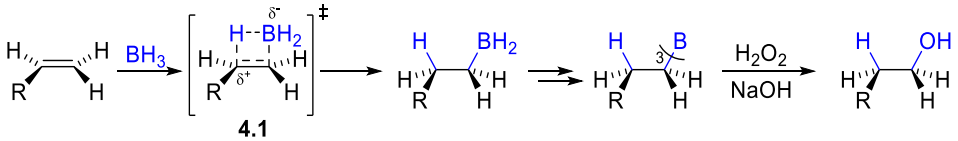
In 1979, Herbert C. Brown was awarded the Nobel Prize for the 'development of the use of boron-containing compounds into important reagents in organic synthesis.'[144] His pioneering work in this field established organoboron chemistry as a fundamental area of organic chemistry. The ease of synthesis, and the flexibility, reactivity and stereochemical control of organoboron reagents, has led to the development of a wide range of transformations in synthetic chemistry. Key examples include hydroboration and allylboration - both of which form an organoborane intermediate from which a range of a functional groups can be introduced - as well as the reduction of ketones with borohydrides, and cross-coupling reactions (Scheme **4.1**).[145-146] Specific cross-coupling transformations include the Suzuki-Miyaura reaction, in which new C–C bonds are formed by the palladium-catalysed coupling of organoboronic acids with halides, and the Chan-Lam reaction, where secondary aryl amines or aryl ethers are formed by the copper-catalysed reaction of aryl boronic acids with an alcohol or amine (Scheme **4.1**).[147-149] Both of these reactions are widely used in pharmaceutical synthesis.[150] The Petasis reaction, a variation of the Mannich reaction in which substituted amines are formed from the reaction of amines and aldehydes with an alkenyl- or arylboronic acid, is another important transformation involving the use of organoboron reagents.[151]



Scheme 4.1 – Examples of organoboron reactions used in organic synthesis

4.1.2 – Hydroboration

The addition of a B–H bond of an organoborane compound to a C=C, C=O, C=N or C≡C bond is known as hydroboration, a transformation initially developed by Brown in 1957.[145] The reaction proceeds in a concerted manner, to give the anti-Markovnikov product, the opposite to an addition of HX to an alkene. The alkene adds at the least-substituted (and therefore less hindered) carbon into the vacant *p*-orbital of the electrophilic boron, and the B–H hydrogen adds to the more substituted carbon of the alkene. The transition state structure (**4.1**) shows a partial negative charge on boron, with a partial positive charge being supported by the more substituted alkene carbon (Scheme **4.2**). BH_3 is commonly used in hydroboration reactions, and will react with three molecules of the alkene to give a trialkylborane species.



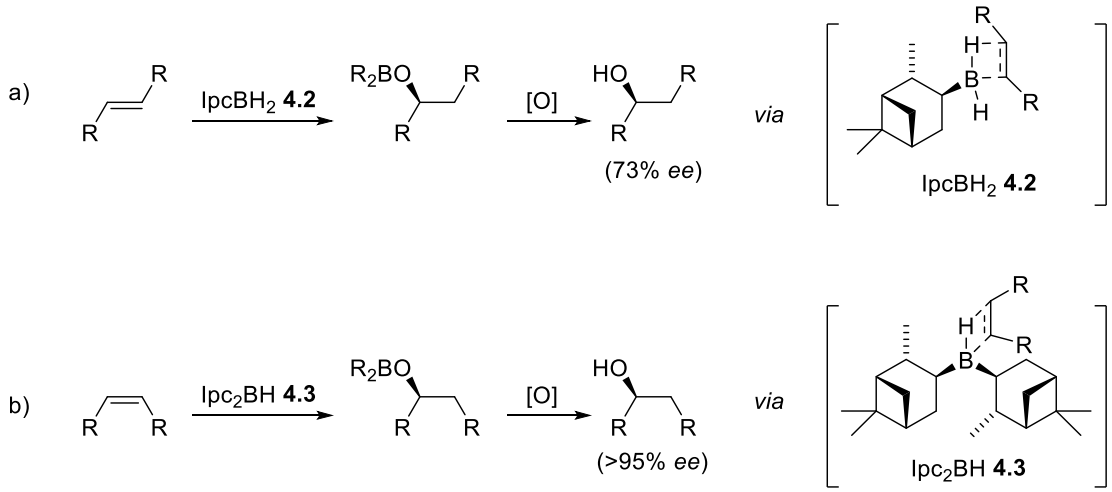
Scheme 4.2 – Hydroboration and subsequent oxidation of olefins

The intermediate organoborane compound can go on to form a number of different compounds containing a variety of functional groups. The most common reaction of this type is the hydroboration-oxidation sequence, in which the intermediate is reacted with basic hydrogen peroxide, leading to the formation of anti-Markovnikov alcohols (Scheme **4.2**).[152] The analogous addition of amines or halides to the organoborane intermediate has been shown to result in amines or alkyl halide products.[153-155] This transformation can also take place on alkynes, resulting in the formation of aldehydes (from a terminal alkyne), or ketones (from an internal alkyne).[156]

4.1.3 – Asymmetric Hydroboration

The hydroboration of alkenes has been carried out in an asymmetric fashion, using a number of different enantiopure organoboron reagents. Brown developed mono- and di*iso*pinocampheylborane ($IpcBH_2$ (**4.2**) and Ipc_2BH (**4.3**), respectively), by the reaction of α-pinene with BH_3, then prepared enantiomeric allylic boranes from olefin substrates that were readily oxidised to the corresponding alcohols in high enantiomeric excess

(Scheme **4.3**).[157] A drawback of these boranes was that $IpcBH_2$ (**4.2**) only favours enantioselective hydroboration of (*E*)-alkenes and Ipc_2BH (**4.3**) favours (*Z*)-alkenes, and neither are effective with trisubstituted alkenes, or 1,1-disubstituted alkenes.[158] Ipc_2BH (**4.3**) also has a tendency to disproportionate to $IpcBH_2$ (**4.2**) in certain solvents, which leads to a decrease in enantioselectivity of the reaction as the two boranes give products with opposite stereochemistry during hydroboration.[157]



Scheme 4.3 – Asymmetric hydroboration of alkenes using a) $IpcBH_2$ and b) Ipc_2BH

Masamune reported C_2-symmetric borane **4.4** (2,5-dimethylborolane), which successfully mediated the enantioselective reduction of (*E*)-, (*Z*)- and trisubstituted alkenes, giving the corresponding alcohol products in very high enantioselectivity.[159] 1,1-Disubstituted alkenes once again proved very challenging, with very poor *ee* values reported. This is rationalised by the transition-state structure (Figure **4.1**), which shows that the alkene hydrogen occupies the position closest to the methyl of the borolane, and the selectivity is lost when R=H. Masamune's borane (**4.4**) has not been widely used due to the 9-step synthesis, which involves both the difficult separation of diastereomers and the resolution of the racemic *trans*-borolane.[159] Vedejs and co-workers developed a tetrahydroazaborine complex, which was able to hydroborate (*Z*)-alkenes with high enantioselectivity (84-86% *ee*) in the presence of TMSCl, which abstracted a hydride to give active species **4.5**. However, this system proved to be far less effective for the asymmetric hydroboration of (*E*)-alkenes and, once again, 1,1-disubstituted alkenes (>5% *ee*) (Figure **4.1**). The development of borane **4.6** by Soderquist, derived from *B*-H-9-BBN (**4.7**), went some way to improving the issue of enantioselective hydroboration of 1,1-disubstituted alkenes, with substrates reduced with moderate to high

enantioselectivity.[160] The reason for this is due to steric factors, as the alkene will approach in a manner so that its larger substituent will be remote from the C-10 substituent on Soderquist's borane (Figure **4.1**). Despite this significant step forward, the reliable reduction of 1,1-disubstituted alkenes in high enantioselectivity remains a work in progress.[158]

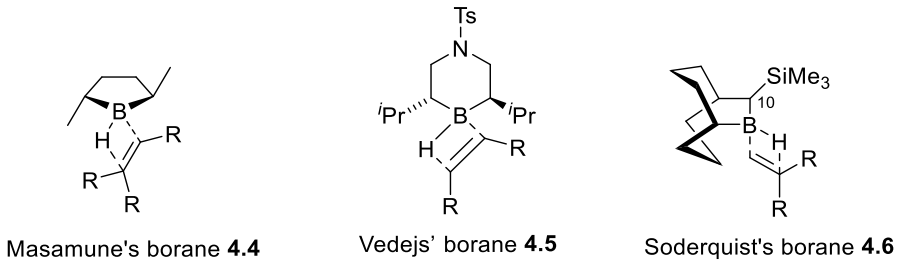
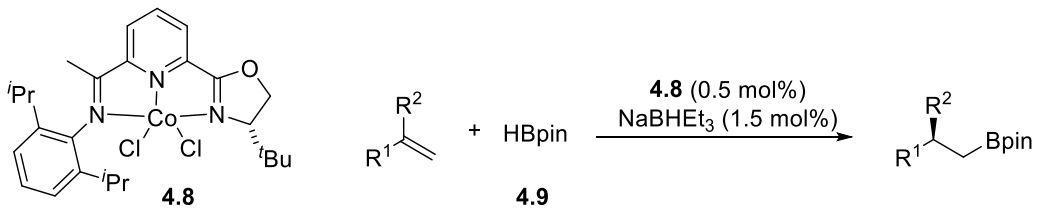


Figure 4.1 - Asymmetric hydroboration of alkenes with Masamune, Vedejs and Soderquist's boranes

Transition metals have been reported to catalyse the asymmetric hydroboration of alkenes. Lu and co-workers have developed a cobalt complex with enantiopure iminopyridine oxazoline ligands (**4.8**), which has been used for the regio- and enantioselective reduction of 1,1-disubstituted aryl alkenes (Scheme **4.4**).[161] Other examples include the work of Hayashi and co-workers, who reported the use of a rhodium-BINAP complex for the asymmetric hydroboration of styrenes, and Luna and co-workers, who developed a chiral iridium catalyst for the hydroboration of *meso*-substrates.[162-163] Major drawbacks of these systems include the use of expensive, unsustainable and toxic metals, and well as the need to develop and synthesis chiral ligands. Moving forward, an analogous transformation using less expensive, more abundant and non-toxic catalysts would be highly desirable.



Scheme 4.4 – Cobalt-catalysed asymmetric hydroboration

4.1.4 – Boronic Esters

The difficulties in the handling and storage of organoborane compounds, due to their air- and moisture sensitivity has led to the development of air and moisture-stable boronic esters as alternative synthetic building blocks.[164] The Lewis acidic boron centre is stabilised by the oxygen atoms of the ester, which can donate electron density into the empty *p*-orbital of the boron atom (Figure **4.2a**). Particularly well-studied examples of boronic esters include catecholborane (HBcat) (**4.10)** and pinacolborane (HBpin) (**4.9)** (Figure **4.2b**).[165-167] Studies have shown that HBpin (**4.9)** has increased stability compared to HBcat (**4.10)**, in which the oxygen lone-pair can also delocalise onto the conjugated π-system, therefore competing with donation to the boron centre.

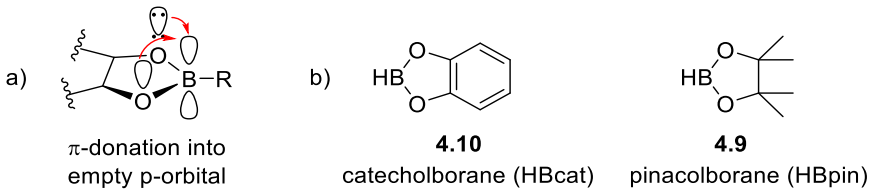
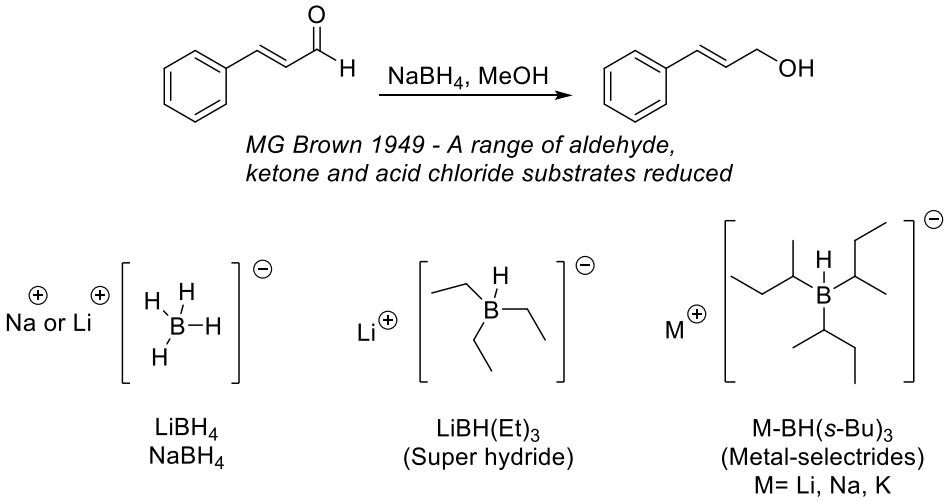


Figure 4.2a) – Stabilisation of boron centre of boronic ester b) Examples of boronic esters

4.1.5 – Hydroboration of Carbonyls

4.1.5.1 – Metal Borohydrides

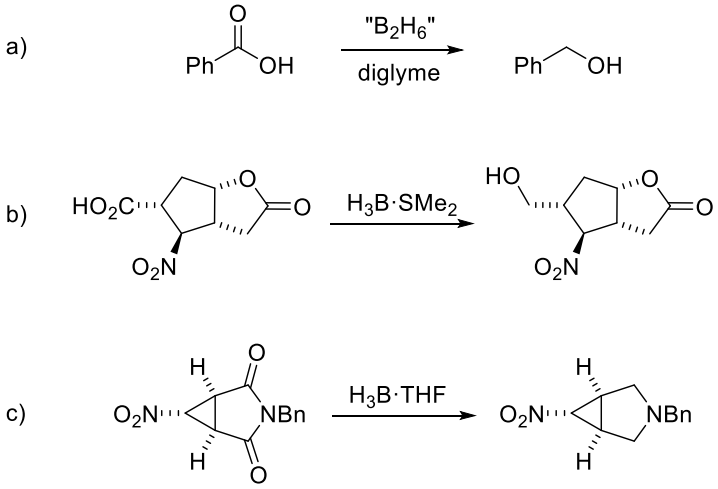
A further important transformation that can be carried out using boron reagents is the reduction of carbonyl-containing compounds such as ketones, aldehydes and amides. The use of inorganic borohydride compounds for this purpose is very well established and ubiquitous within organic chemistry. Commonly used reagents include sodium borohydride, which reduces ketones, aldehydes and acid chlorides, and lithium borohydride, a stronger reducing agent that can also reduce esters and amides to alcohols and primary amines respectively (Scheme **4.5**).[168] Further examples include $LiBH(Et)_3$ (Super-Hydride), which is stronger still, and will reduce difficult substrates such as sterically hindered ketones, and metal-selectrides, which can reduce 1,2 or 1,4-enones, lactones and ketones with high selectivity (Scheme **4.5**) .[169-170]



Scheme 4.5 – Metal borohydride reagents used for the reduction of carbonyls

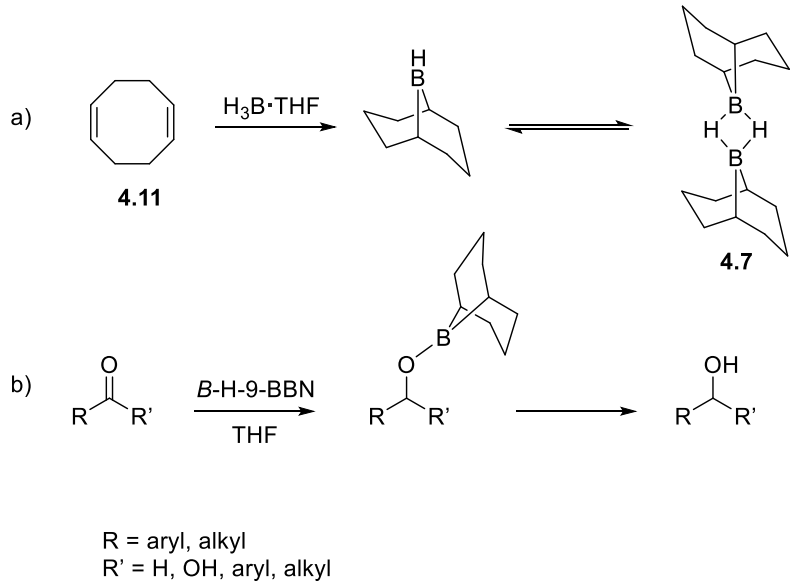
4.1.5.2 – Organoboranes

Numerous examples also exist of commercial borane compounds being used for the reduction of carbonyl compounds, such as aldehydes, carboxylic acids and nitrile groups to the corresponding alcohols or amines using diborane, which was reported by Brown and Rao (Scheme **4.6a**).[171] Diborane was generated *in situ*, from $NaBH_4$ and $BF_3.OEt_2$. Borane adducts have also been commonly used; with $H_3B{\cdot}SMe_2$ and $H_3B{\cdot}THF$ having been shown to effectively reduce carboxylic acids and amides (Scheme **4.6b** and **4.6c**).[172] When coordinated to amines, such as pyridine, NEt_3 and H_2N*t*-Bu, BH_3 has been shown to reduce imines, oximes and enamines.[173]



Scheme 4.6 – a) Use of diborane to reduce carbonyl groups; b) use of $H_3B{\cdot}SMe_2$ to reduce carboxylic acids; c) use of $H_3B{\cdot}THF$ to reduce amides

Brown has also reported the reduction of a range of aldehydes, ketones, carboxylic acids, esters and lactones by the organoborane compound 9-borabicyclo[3.3.1]nonane (**4.7**) (*B*-H-9-BBN) (Scheme **4.7b**).[174] This compound was initially prepared by the reaction of 1,5-cyclooctadiene (**4.11**) with $H_3B{\cdot}THF$, but is now commercially available. It is generally present as the hydride-bridged dimer (**4.7**) (Scheme **4.7a**).

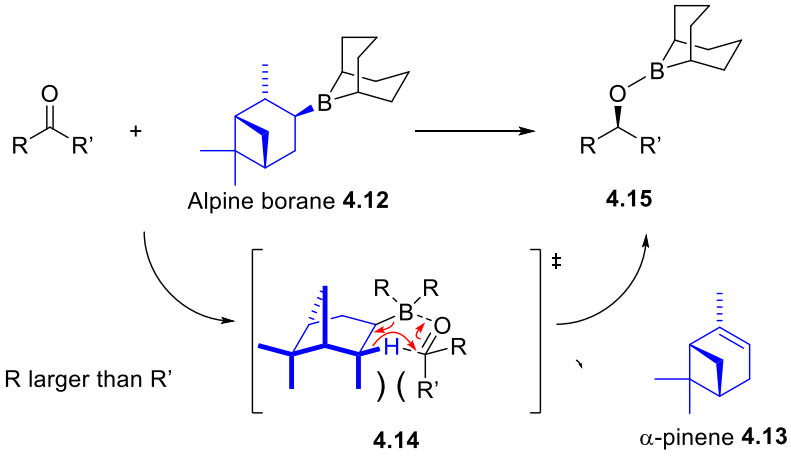


Scheme 4.7 – a) Synthesis of *B*-H-9-BBN (4.7) and b) use in carbonyl reduction

4.1.5.3 – Asymmetric Ketone Reduction – Ipc-based reagents

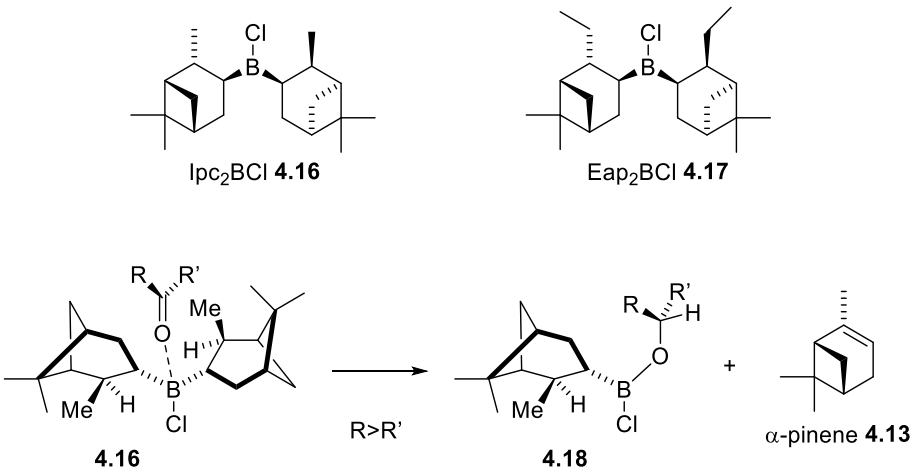
As with alkenes, a number of enantioselective borane reductions of carbonyl compounds have been reported. Midland and co-workers developed a procedure for the enantioselective reduction of carbonyls (mostly ketones) to alcohols using the Ipc-derived reagent Alpine borane (**4.12**) (Scheme **4.8**). Alpine borane (**4.12**) is synthesised by heating the inexpensive starting materials α-pinene (**4.13**) and *B*-H-9-BBN (**4.7**) in THF.[175] The Midland reduction proved sluggish with simple ketones such as acetophenone, and gave products in low *ee*, but when a less sterically demanding group such as a propargylic- or nitrile-substituted ketone was used as the substrate, the enantioselectivity and reactivity were vastly increased.[176] Alpine borane (**4.12**) does not contain a B–H bond, so the hydride must be delivered from elsewhere on the molecule. As a result of this, the reaction proceeds through a 6-membered chair-like transition state, in which the carbonyl oxygen is coordinated to the boron (transition state structure **4.14**). This mechanism is analogous to a Meerwein-Pondorf-Verley reduction, where a hydride is transferred from an aluminium alkoxide species. As the boron-oxygen bond forms, the

α-pinene C=C bond reforms, and the hydrogen adjacent to the boron is simultaneously delivered to the electrophilic carbon of the carbonyl group. This results in the enantioselective formation of a borinic ester (such as **4.15**), and the regeneration of α-pinene (**4.13**), which can be recovered and recycled.



Scheme 4.8 – Midland's asymmetric reduction of carbonyl compounds with Alpine borane (4.12)

Brown has also developed a series of boranes based on diisopinocampheylborane, including Ipc_2BCl (**4.16**) and Eap_2BCl (**4.17**) (Scheme **4.9**). The presence of an electronegative chloride on boron rather than hydrogen helped to make the boron centre more Lewis acidic, thereby enabling the compound to be a stronger reducing agent. These sterically hindered R_2BCl derivatives were also more stable to dissociation, resulting in compounds such as borinic ester (**4.18**), when compared to R_3B derived compounds.[177] As a result the reaction times were much faster compared to those using Alpine borane (**4.12**), and both Ipc_2BCl (**4.16**) and Eap_2BCl (**4.17**) were successfully able to reduce a much wider range of carbonyl compounds with very high enantioselectivity. Ipc_2BCl (**4.16**) was particularly effective for the asymmetric reduction of cyclic and aromatic ketones (98% *ee* for both), but less so for acyclic ketones (32% *ee*). Replacing the methyl group on the α-pinene (**4.13**) in Ipc_2BCl (**4.16**) with an ethyl group, to give Eap_2BCl (**4.17**), increased the enantiomeric excess to >99% for the reduction of the same cyclic and aromatic ketones (along with heterocylic and α-halo ketones) but, significantly, showed improved enantioselectivity when reducing acylic ketones (95% *ee*).[177-178]

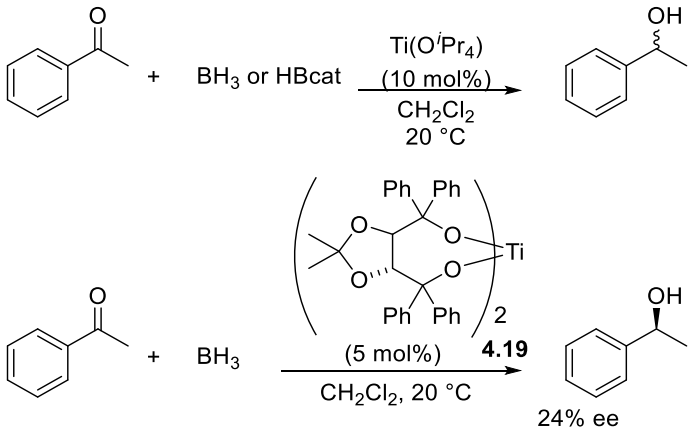


Scheme 4.9 – Brown's diisopinocampheylborane based boranes for carbonyl reduction

4.1.6 – Catalytic Hydroboration of Carbonyls

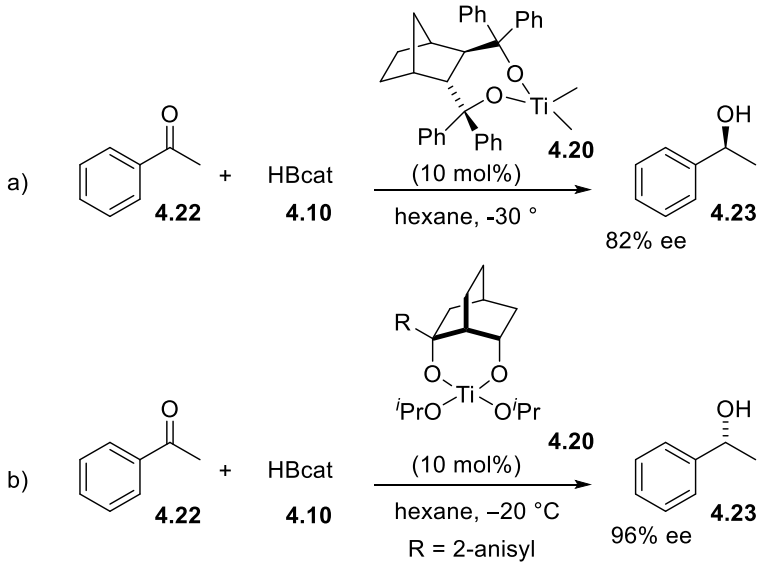
4.1.6.1 – Transition-Metal Catalysts

Several examples exist of transition metal complexes being used as catalysts for the hydroboration of ketones and aldehydes. Early examples of this include the use of titanium alkoxides. Building on their use of stoichiometric $TiCl_4$ to accelerate ketone reduction,[179] DiMare and co-workers discovered that $Ti(O^iPr)_4$ could be used in a substoichiometric amount (5 mol%) for the hydroboration of acetophenone with BH_3 or HBcat (**4.10**) (Scheme **4.10**). They also used titanium-TADDOL complex **4.19** to develop an asymmetric ketone reduction, however the *ee* was fairly low (24%).[180]



Scheme 4.10 – DiMare's use of titanium alkoxides to catalyse hydroboration of acetophenone

Independent work carried out by the groups of Wandrey and Frejd improved the enantioselectivity of this transformation, as they were able to develop enantioenriched titanium catalysts **4.20** (scheme **4.11a**) and **4.21** (Scheme **4.11b**) respectively, which were generated *in situ* from the reaction of $Ti(O^iPr)_4$ with TADDOL-analogous ligands.[181-182] The hydroboration of acetophenone (**4.22**) using HBcat (**4.10**) in the presence of 10 mol% of either titanium catalyst **4.20** or **4.21** resulted in the successful formation of 1-phenylethanol (**4.23**) with high enantioselectivity (Scheme **4.11**).



Scheme 4.11 – a) Wandrey and b) Frejd's titanium-catalysed enantioselective hydroboration of acetophenone

An iminooxazoline (IMOX) zinc(II) complex **4.24** has been developed by Umani-Ronchi, Cozzi and co-workers by mixing Zn(OTf) and an IMOX ligand, and used to catalyse the hydroboration of a range ketones by HBcat, giving the alcohols in high conversion and *ee* (82%).[183] Cozzi then developed zinc complex **4.25**, which improved the enantioselectivity of the reaction (93% *ee*).[184] Several other zinc(II) complexes have been reported, including one derived from Zn(II) monohydride and stabilised by an NHC ligand to give zinc complex **4.26**, which has been used for the hydroboration of benzophenone with HBpin (**4.9**) (Figure **4.3**).[185]

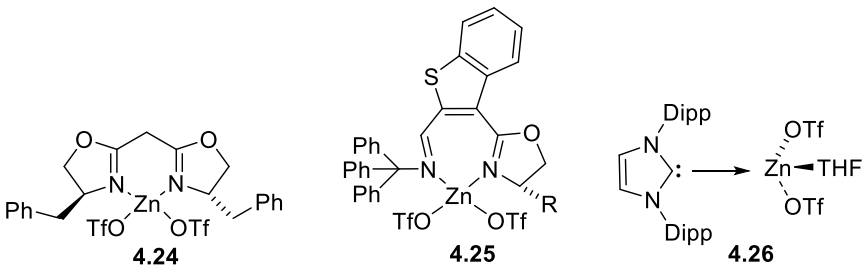
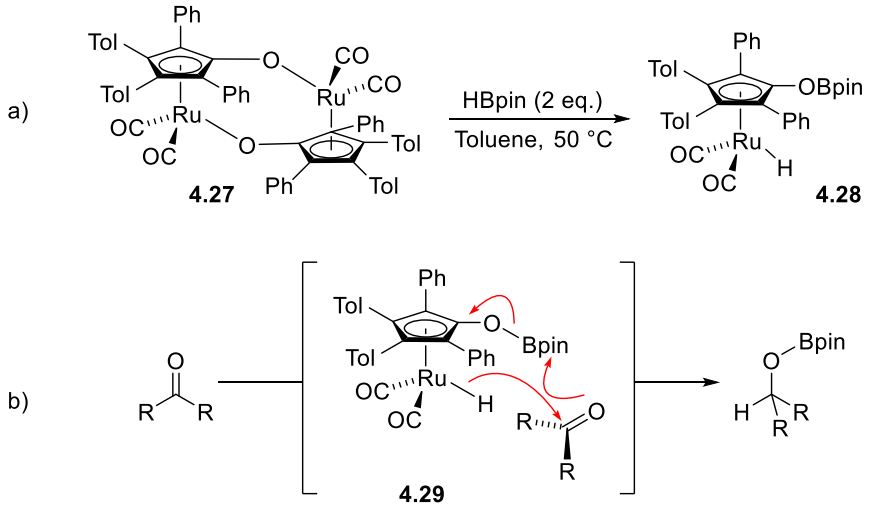


Figure 4.3 – Zinc-catalysts used for enantioselective hydroboration of ketones

The ruthenium-based Shvo catalyst has previously been shown to be effective for the hydrogenation of alkenes, carbonyls and imines.[186] A boron substituted derivative **4.28** was prepared *in situ* by addition of HBpin (**4.10**) to ruthenium dimer **4.27** (Scheme **4.12a**). Borylated complex **4.28** was reported to effectively catalyse the hydroboration of aldehydes, ketones and imines. The proposed mechanism involves concerted formation of the new C–H and O–B bonds (transition state structure **4.29**) (Scheme **4.12b**), with the catalyst subsequently regenerated by HBpin.[187]

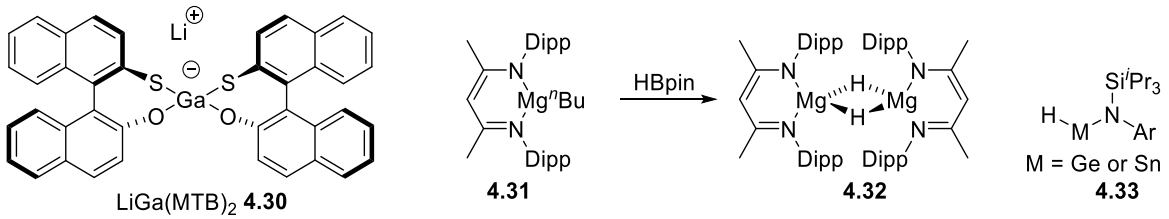


Scheme 4.12 – a) Preparation of boron-substituted Shvo's catalyst (4.28); b) Use of catalyst 4.28 in the hydroboration of ketones

4.1.6.2 – Main-Group Catalysts

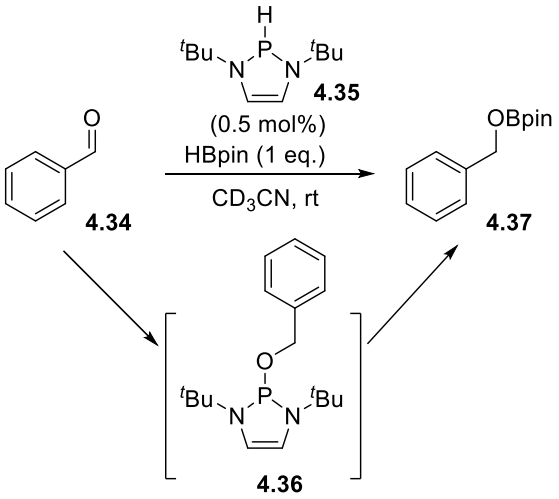
The replacement of toxic and expensive transition metal catalysts with cheaper and more abundant main group elements has been a major area of research across chemistry in recent years, and a number of systems have been developed using p-block compounds for the catalysis of hydroboration reactions.[188] $LiGa(MTB)_2$ (**4.30**), generated *in situ* from $LiGaH_4$ and 2-hydroxy-2'-mercapto-1,1'-binapthyl was reported to catalyse the

reduction of prochiral ketones in high yields and enantioselectivity.[189] Hill and co-workers developed a magnesium-based complex (**4.31**), which was proposed to react with HBpin (**4.9**) to form dimeric magnesium-hydride active species **4.32**.[190] The hydroboration of aldehydes and ketones was carried out in high yields (91-99%) with very low catalyst loadings (0.1-0.5 mol%). Jones and co-workers used germanium(II) and tin(II) hydrides to catalyse the hydroboration of aldehydes and ketones with HBpin (**4.9**).[191]



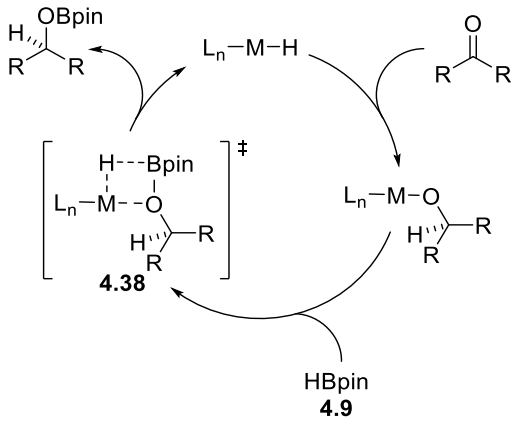
Scheme 4.13 – Main-group compounds used for hydroboration of aldehydes and ketones

Kinjo and co-workers developed a metal-free catalytic hydroboration of carbonyl compounds. The hydridic P–H bond in 1,3,2-diazophospholene (**4.35**) had previously been shown to react with carbonyl compounds.[192] The reaction of benzaldehyde (**4.34**) with diazaphospholene **4.35** gave benzyloxydiazaphospholene **4.36**, which upon reaction with stoichiometric HBpin (**4.9**) gave the hydroborated aldehyde **4.37** and regenerated diazaphospholene **4.35**. Subsequently it was shown that sub-stoichiometric amounts of diazaphospholene **4.35** (0.5-10 mol%) and HBpin (**4.9**) could be used to catalyse the hydroboration of aldehydes and ketones (Scheme **4.14**).[193]



Scheme 4.14 – Phosphorus catalysed hydroboration of carbonyls

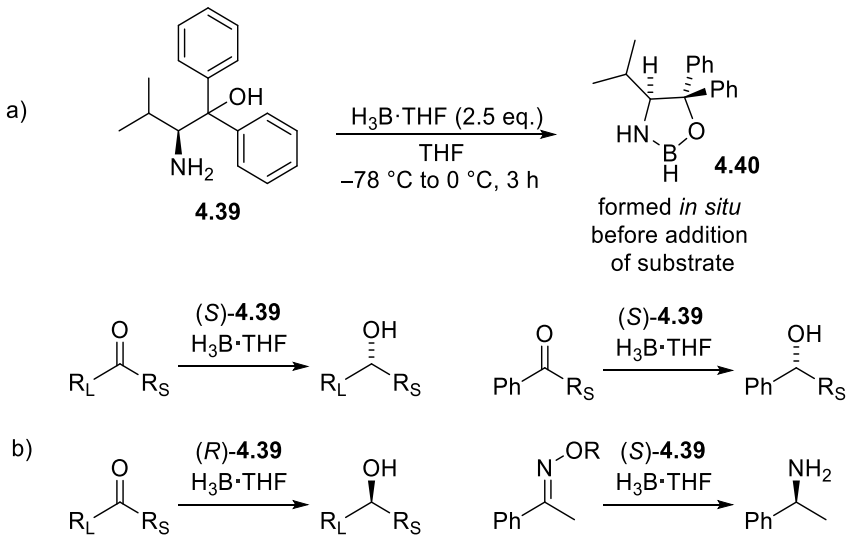
Mechanistic studies, both experimental and computational, have been carried out on the above transformations, which generally suggest a common initial insertion of an M–H hydride to the C=O bond, followed by σ-bond metathesis (transition state structure **4.38**) between the alkoxide and HBpin (**4.9**), to give the *O*-borylated alcohol and regenerate the catalyst (Scheme **4.15**).



Scheme 4.15 - General σ-bond metathesis mechanism for the hydroboration of carbonyls

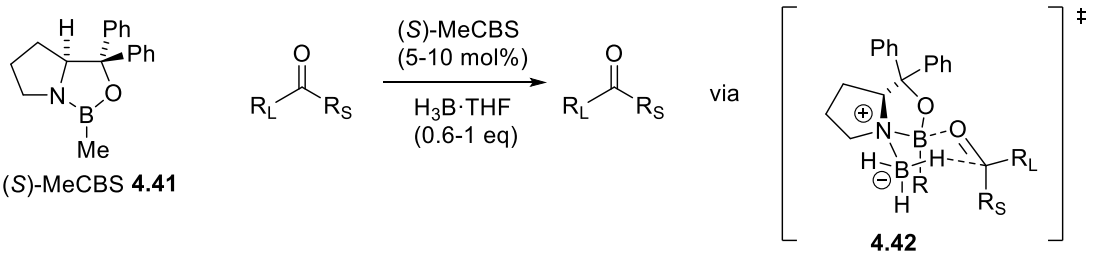
4.1.6.3 – Borane Catalysts - CBS reduction

Possibly the most well-known example of enantioselective main-group catalysed hydroboration of carbonyl compounds is the Corey-Bakshi-Shibata (CBS) reduction, sometimes also known as the Corey-Itsuno reduction. Itsuno first reported the use of an enantiopure alkoxyamine-borane complex for the asymmetric reduction of ketones in 1981.[194] The (*S*)-valine derived reagent **4.39** was pre-mixed with $H_3B{\cdot}THF$ to prepare the oxazaborolidine compound **4.40** *in situ*, before addition of the ketone (Scheme **4.16a**). Itsuno's reagent (**4.40**) was shown to stoichiometrically reduce ketones with defined large and small groups, to give alcohols in very high enantioselectivity, as well as oxime ethers to give amine products (Scheme **4.16b**).



Scheme 4.16 – a) Formatiom of Itsuno's reagent (*S*)-4.40; b) Use of (*S*)-4.40 in the asymmetric reduction of ketones and oxime ethers

In the subsequent years, Corey and co-workers built upon the work carried out by Itsuno to prepare an oxazaborolidine compound Me-CBS (**4.41**), derived from proline (both (*R*) and (*S*) enantiomers were synthesised), that could be used in sub-stoichiometric amounts for asymmetric ketone reduction in the presence of stoichiometric $H_3B{\cdot}THF$ (Scheme **4.17**).[195-196] The proline-based rigid bicylic structure of the catalyst leads to higher *ee* values of the alcohols formed compared to the more flexible ring system of Itsuno's reagent (**4.40**). The high yields and enantioselectivity obtained in the reaction, along with the high stability (due to the B–C bond vs B–H) and ease of preparation of the catalyst, have enabled the CBS reduction to be widely utilised within organic chemistry, both in industry and in a number of natural product syntheses.[196-198]



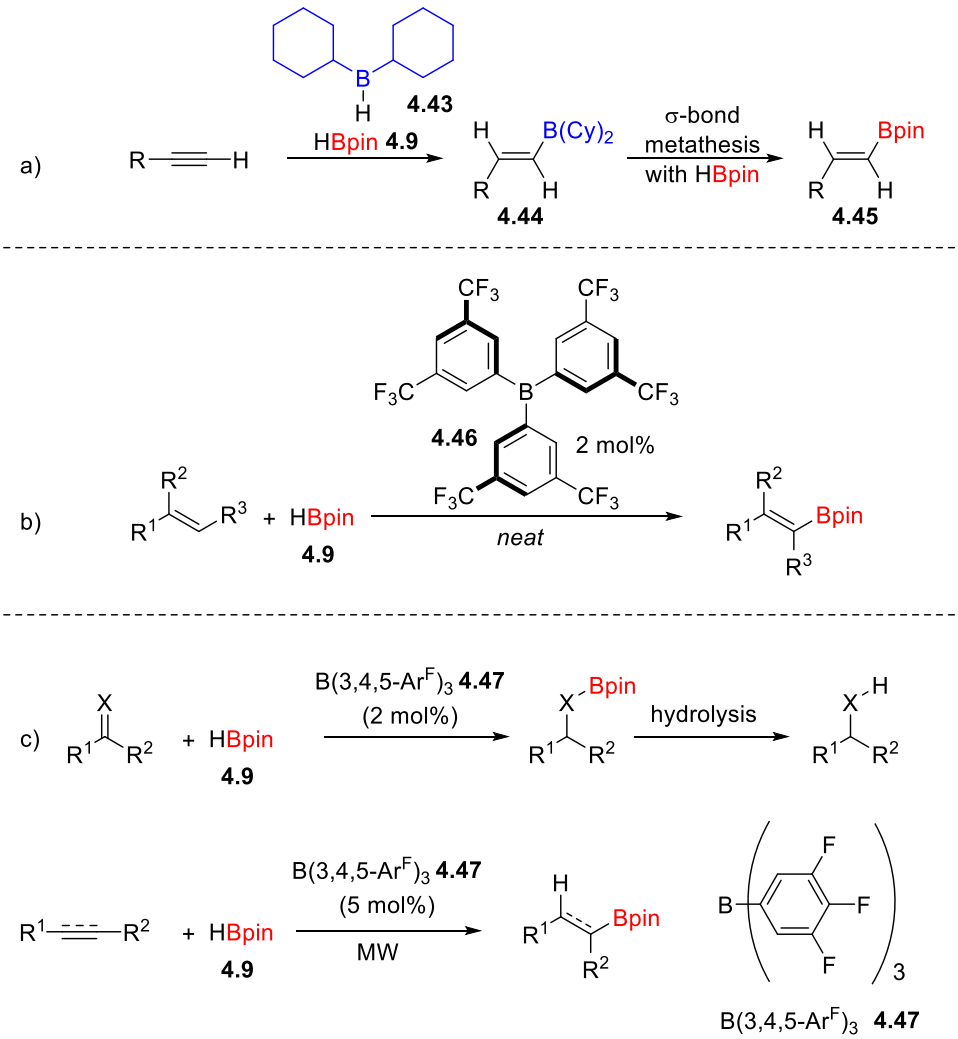
Scheme 4.17 – CBS reduction of ketones

Corey proposed that the mechanism of CBS reduction proceeds initially by coordination of BH_3 to the nitrogen of the CBS catalyst (**4.41**), which enhances the Lewis acidity of

the CBS boron, and therefore activates the coordinated BH_3 as a hydride donor. The CBS-borane complex then binds to the ketone at the lone pair closer to the smaller ketone substituent, which is more sterically accessible, thus determining the selectivity of the reaction. Face-selective hydride transfer from borane to the ketone then occurs through a six-membered transition state (Scheme **4.17**, transition state structure **4.42**). CBS reduction has been shown to successfully reduce a wide range of different substrates, including aryl-alkyl ketones, diaryl and dialkyl ketones, cyclic and acyclic enones, ynones, and ketones containing heteroatoms.[199-200]

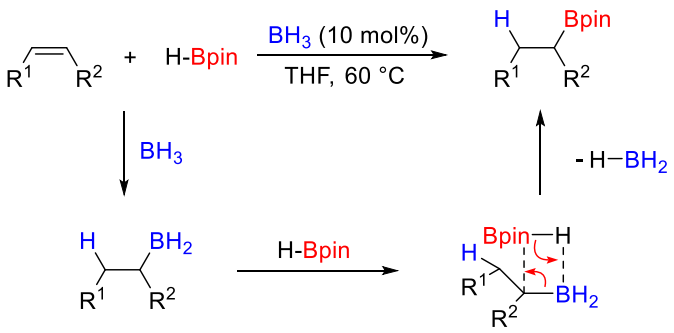
4.1.7 – 'Transborylation' in borane-catalysed hydroboration

Hoshi, Shirakawa and co-workers, using substoichiometric dicyclohexylborane (**4.43**) and stoichiometric HBpin (**4.9**), have also reported the use of boron compounds as active catalysts for the hydroboration of alkynes (Scheme **4.18a)**.[201] The proposed mechanism suggested hydroboration of the alkyne with dicyclohexylborane to give alkenyl borane **4.44**, which then underwent σ-bond metathesis with HBpin (**4.9**), to form the boronic ester compound **4.45** and regenerate dicyclohexylborane (**4.43**). Oestreich and co-workers have reported the boron-catalysed hydroboration of alkene substrates using tris[3,5-bis(trifluoromethyl)phenyl]borane (BAr^F_3) (**4.46) (**Scheme **4.18b)**,[202] while Melen and co-workers have carried out the hydroboration of aldehydes, ketones and imines using tris(3,4,5-trifluorophenyl)borane (**4.47**) as a catalyst (Scheme **4.18c**).[203] The use of microwave irradiation enabled the hydroboration of alkenes and alkynes with the same borane catalyst (**4.47**).



Scheme 4.18 – Boron-catalysed hydroboration of alkynes and alkenes by a) Hoshi b) Oestreich and c) Melen

Work previously carried out within the Thomas group has shown that the hydroboration of alkene and alkyne substrates with HBpin (**4.9**) can be catalysed by 10 mol% BH_3.[204] The proposed mechanism is analogous to that of Hoshi and Shirakawa, with initial hydroboration of the unsaturated carbon-carbon bond to form a trialkylborane, which subsequently undergoes boron-carbon σ-bond metathesis with HBpin (**4.9**), to form an alkyl pinacolboronic ester and regenerate the BH_3 catalyst (Scheme **4.19**).



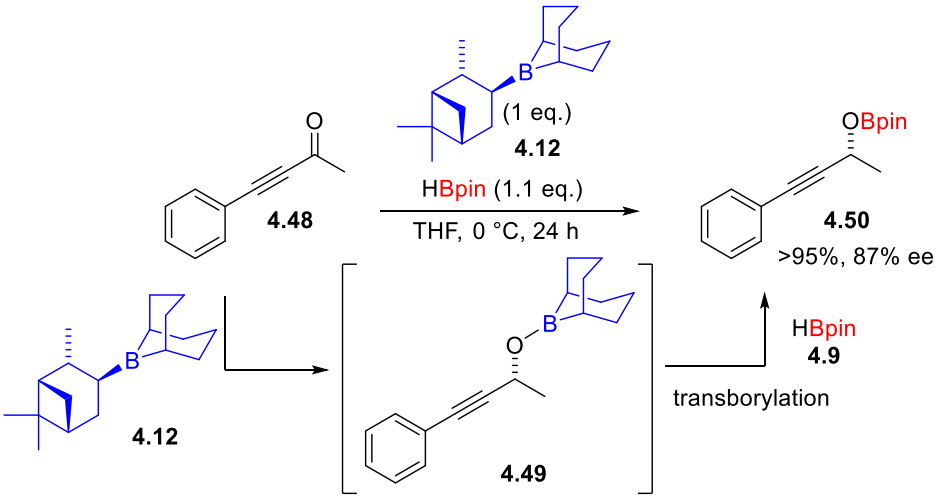
Scheme 4.19 – BH_3-catalysed hydroboration of alkenes by HBpin

The transfer of the substrate from one boron species to another by σ-bond metathesis was termed 'transborylation'. As the use of boron-catalysis had proven successful in the racemic hydroboration of alkenes and alkynes, it was proposed that the use of enantioenriched boron catalysts and prochiral substrates could enable the development of the catalytic asymmetric hydroboration of alkenes and carbonyls with HBpin (**4.9**), to prepare enantioenriched boronic- and borate-ester containing compounds.

4.1.8 – Attempted alkene and ketone hydroboration using transborylation

Initial investigations within the Thomas group focused on the use of established enantiopure borane reagents as catalysts for both hydroboration of alkenes and carbonyl compounds. Ipc_2BH (**4.3**) was shown to have some success catalysing the hydroboration of terminal alkenes, but unfortunately not with prochiral substrates, such as secondary alkenes. Attempts to catalyse the hydroboration of alkenes using Soderquist's borane (**4.6**) have also thus far proven unsuccessful, with further studies still in progress. Stoichiometric amounts of Ipc_2BCl (**4.16**) showed successful hydroboration of carbonyl substrates to form a borinic ester intermediate, but the subsequent σ-bond metathesis with HBpin did not occur, meaning the process could not be made catalytic. Alpine borane (**4.12**), previously shown to enantioselectively reduce propargylic ketones, was the next compound investigated. The hydroboration of a prochiral propargylic ketone **4.48** to the borate ester **4.50** (then the corresponding alcohol) using stoichiometric Alpine borane (**4.12**) in the presence of HBpin (**4.9**) proceeded with high conversion (>95%) and enantioselectivity (87% *ee*) at 0 °C, and ^{11}B NMR studies gave strong evidence that transborylation was occurring (Scheme **4.20**). A clear peak indicating formation of the borinic ester intermediate **4.49** was observed upon addition of the substrate to Alpine

borane (**4.12**). When HBpin was added, the borinic ester was consumed and a new peak appeared corresponding to the borate ester **4.50** appeared.[205]

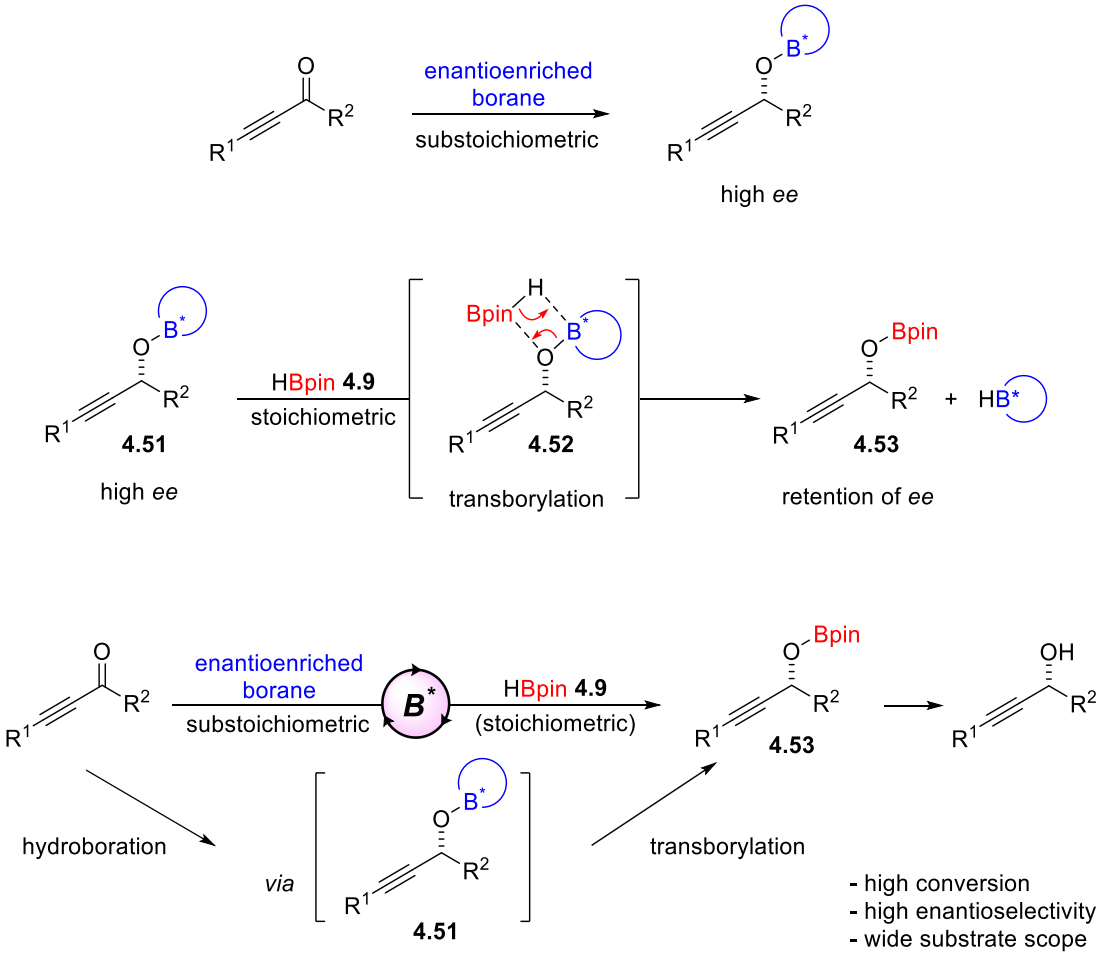


Scheme 4.20 – Successful enantioselective hydroboration of propargylic ketone 4.48 with stoichiometric Alpine borane (4.12)

4.1.9 – Project Aims

Preliminary work within the Thomas group showed the proof of concept that the enantioselective hydroboration of propargylic ketones can be carried out using an enatiopure borane and HBpin (**4.9**).[205] The aim at this point was to carry out the enantioselective hydroboration of a ketone substrate using a substoichiometric amount of the chiral borane reagent (Scheme **4.21**). Turnover of the borane catalyst would be achieved by the addition of stoichiometric HBpin (**4.9**), enabling a boron-boron exchange, or transborylation type mechanism (transition state structure **4.52**), giving a boronate ester (**4.53**). Enantioselectivity would be retained from borinic ester (**4.51**), and the enantiopure catalyst would be regenerated. The enantioselectivity of the hydroboration would be measured by conversion of the boronic ester to the respective alcohol, and analysis by chiral HPLC. Once a procedure had been optimised, the aim was to explore the reaction scope, by trialling a range of different carbonyl compounds. Insight into, and confirmation of, the reaction mechanism would be sought using ^{1}H and ^{11}B NMR spectroscopy. As the initial results were obtained using Alpine borane as the enantiopure borane source, the optimisation would begin at the same point, however a number of chiral borane reagents would be trialled if necessary. The propargylic ketone 4-phenyl-3-butyn-2-one (**4.48**) would continue to be used as the model substrate for

optimisation. Work into the analogous borane-catalysed hydroboration of alkenes would also be carried out separately within the research group.



Scheme 4.21 – Project aims

4.2 - Alpine Borane

As earlier discussed, the Alpine borane-mediated reduction of simple ketones such as acetophenone was very sluggish compared to the reduction of aldehydes, with reactions taking several days to go to completion. Carrying out the reaction under reflux shortened the reaction time, but also lowered the enantioselectivity. Midland proposed that this sluggishness could be explained by the transition state structure. For ketones, an alkyl group occupies a pseudo-axial position, resulting in a steric clash with the methyl group of Alpine borane (**4.12**), which slows the reaction (Figure **4.4b**).[175-176] This is avoided with aldehydes, as the hydrogen is pseudo-axial (Figure **4.4a**). Less sterically encumbered ketone species, such as propargylic ketones, were successfully reduced

however (Figure **4.4c**), as the alkyne does not clash with the methyl group of Alpine borane (**4.12**).

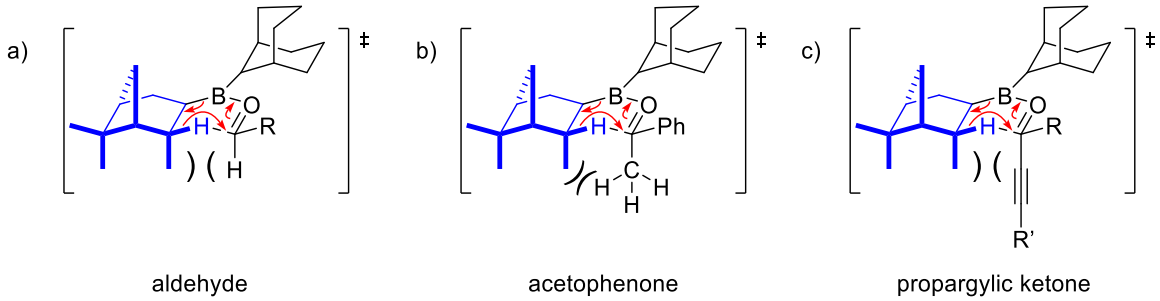
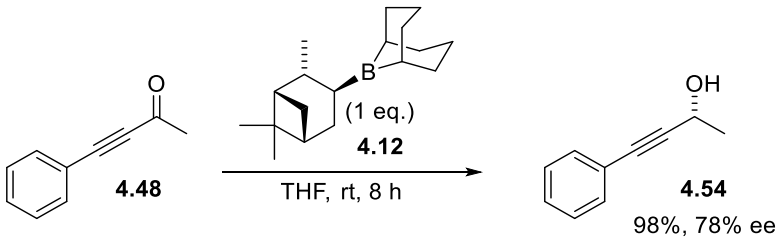


Figure 4.4 – Transition states for reduction of a) aldehydes, b) acetophenone and c) propargylic ketones with Alpine borane (4.12)

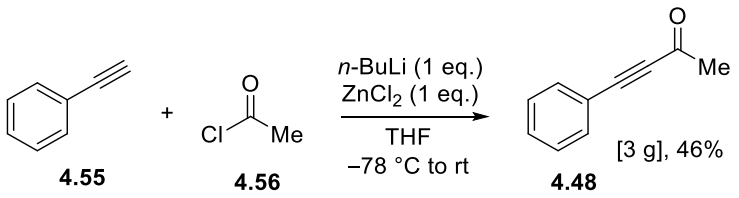
A range of these substrates were trialled by Midland, including 4-phenyl-3-butyn-2-one (**4.48**) which was to be reduced to the respective alcohol **4.54** in >95% yield and 78% *ee* (Scheme **4.42**).[175] This was the substrate used in the successful reduction with stoichiometric Alpine borane (**4.12**) and HBpin, so we continued with it for further studies.



Scheme 4.22 – Alpine borane-mediated reduction of 4-phenyl-3-butyn-2-one (4.48)

Due to the small quantities in which propargylic ketone **4.48** was commercially available, as well as its lengthy delivery period, we decided to synthesise according to a literature procedure reported by Dos Santos and co-workers.[206] Phenylacetylene (**4.55**) was deprotonated using *n*-butyllithium at −70 °C, before zinc(II) chloride and acetyl chloride (**4.56**) were added to the reaction mixture, which was stirred at room temperature for 40 minutes. Small amounts of an impurity arising from the ring opening of THF by *n*-BuLi were present in the crude reaction mixture, and proved difficult to remove by column chromatography. However, by controlling the temperature more carefully during the *n*-BuLi addition, this problem was solved. The isolated yield was 46%, which was lower

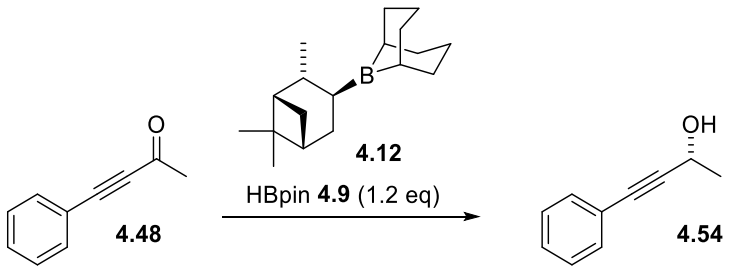
than reported in literature, but the reaction was able to be scaled up, with up to 3 g of product formed each time.



Scheme 4.23 – Formation of 4-phenyl-3-butyn-2-one (4.48)

The studies into the catalytic reduction of propargylic ketone **4.48** with Alpine borane (**4.12**) began with repetition of the stoichiometric reaction, with 100 mol% of Alpine borane used, along with 1.2 equivalents of HBpin at 0 °C, before a range of different conditions were trialled, altering the catalyst loading, time and temperature of the reaction (Table **4.1**). Each reaction was quenched by opening to the atmosphere and addition of SiO_2, the conversion was measured by NMR yield using 20 mol% of 1,3,5-trimethoxybenzene as internal standard, then the alcohol product purified by column chromatography before analysis by chiral HPLC.

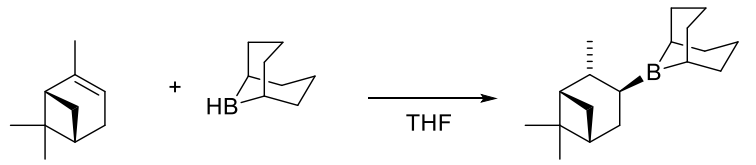
Table 4.1 – Studies into the catalytic reduction of propargylic ketone 4.48 with commercial Alpine borane (4.12)



Entry	*Catalyst (mol%)*	*HBpin (eq.)*	*Time (h)*	*Temp (°C)*	*Yield (%)*	*ee (%)*
a	100	1.2	16	0	79	38
b	30	1.2	16	0	69	20
c	100	1.2	40	0	86	30
d	30	1.2	40	0	95	25
e	100	1.2	16	−40	49	15
f	30	1.2	16	−40	18	24
g	100	1.2	16	−10	74	31
h	30	1.2	16	−10	24	13
i	30	1.2	40	−10	61	15

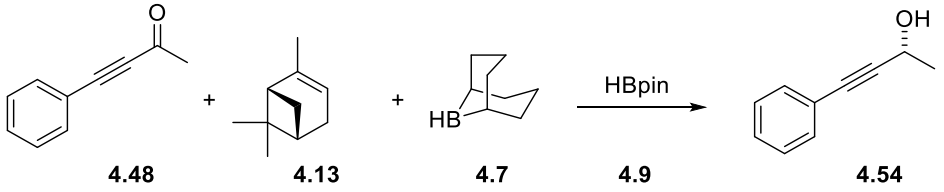
Repetition of the conditions previously trialled in the group, using stoichiometric Alpine borane (**4.12**) (Table **4.1**, entry *a*) gave a very different result; a comparable yield, but the alcohol was obtained in significantly lower enantiomeric excess (38% compared to 87%). Going from stoichiometric to substoichiometric catalyst loading (30 mol%), the yield dropped slightly to 69%, and the enantioselectivity also decreased. An increase in reaction time from 16 h to 40 h (entries *c* and *d*) saw an increase in yield, but no significant change in *ee*. Concerned by the lack of enantioselectivity in the reaction, we decreased the temperature and carried out reactions at −10 °C and -40 °C (entries *e-i*). Disappointingly no increase in enantioselectivity was observed at lower temperatures for reactions with either stoichiometric or sub-stoichiometric Alpine borane (**4.12**). An alternative approach was investigated, with Alpine borane (**4.12**) formed *in situ* from α-pinene (**4.13**) and *B*-H-9-BBN (**4.7**) rather than the commercial catalyst used (Scheme **4.24**). Again, reactions were trialled using differing amounts of catalyst, as well as different reaction temperatures. In all cases α-pinene (**4.13**) and *B*-H-9-BBN (**4.7**) were

stirred together in THF for 2 hours, before the addition of substrate and HBpin, and the pre-mix temperature was also altered (Table **4.2**).



Scheme 4.24 – Synthesis of Alpine borane (4.12)

Table 4.2 – Studies into the catalytic reduction of propargylic ketone 4.48 with Alpine borane (4.12) formed *in situ*

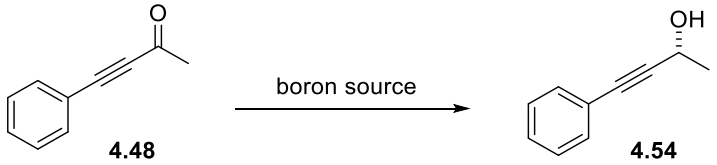


Entry	***B-H-9-BBN (mol%)***	***α-pinene (mol%)***	***HBpin (eq.)***	***Time (h)***	***Temp (°C)***	***Yield (%)***	***ee (%)***
a	100	100	1.2	16	0	84	24
b	30	30	1.2	16	0	78	21
c	100	100	1.2	16	0	74	3
d	30	30	1.2	16	0	87	9
e	100	100	1.2	16	25	58	9
f	30	30	1.2	16	25	75	9

Before addition of substrate, *B*-H-9-BBN and α-pinene pre-mixed for 16 hours at 0 °C (entries *a, b, e, f*), or 25 °C (entries *c and d*)

Unfortunately, results proved very similar to those obtained with commercial Alpine borane (**4.12**), with the alcohol product being formed in high yield but with low enantioselectivity (Table **4.2**, entries *a* and *b*). The *ee* was lower still when the catalyst was pre-mixed at room temperature (entries *c* and *d*), and when the reaction was carried out at room temperature (entries *e* and *f*). It was hypothesised that the low enantiomeric excess could be due to the reduction being carried out by an achiral borane; ie. HBpin (**4.9**) or *B*-H-9-BBN (**4.7**). To investigate this possibility, control reactions were carried out, as detailed in Table **4.3**.

Table 4.3 – Control reactions to investigate low enantioselectivity of reduction

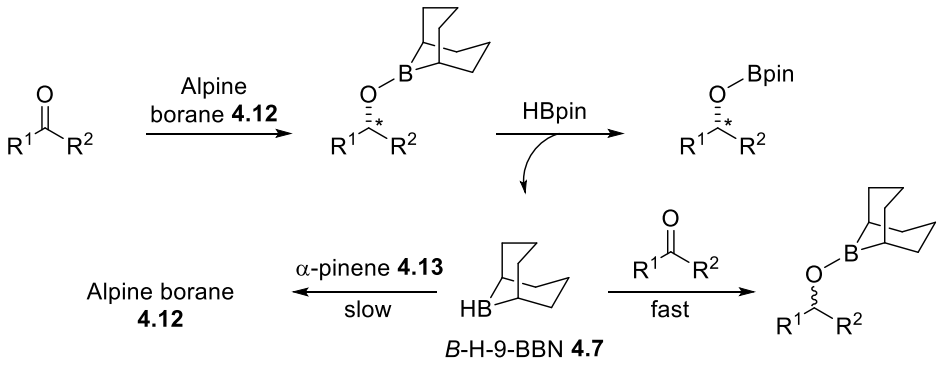


4.48 4.54

Entry	*Catalyst. (mol%)*	*HBpin (eq.)*	*B-H-9-BBN) (eq.)*	*Time (h)*	*Temp (°C)*	*Yield (%)*	*ee (%)*
a	100	0	0	3	0	43	81
b	100	1.2	0	3	0	75	39
c	0	1.2	0	3	0	26	-
d	0	0	1	3	0	37	-

*all reactions carried out by Joanne Dunne

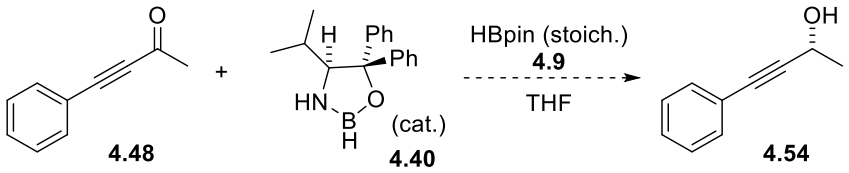
The reaction of propargylic ketone **4.48** with stoichiometric Alpine borane (**4.12**) in the absence of HBpin (**4.9**) was carried out (Table **4.3**, entry *a*), giving the product in a lower yield than previously observed, which can be explained by the shorter reaction time and the absence of HBpin (**4.9**), but crucially, in a much higher enantiomeric excess of 81%. This reaction was run in parallel with entry *b*, with the only difference being the addition of 1.2 equivalents of HBpin (**4.9**) (as in table **4.2**, entry *a*), which as before, gave a relatively high yield but a much lower *ee* (39% compared to 81%). A control reaction with HBpin in the absence of Alpine borane (**4.12**) was carried out (entry *c*), and resulted in 26% conversion to the alcohol **4.54** in 3 hours. This was evidence that a non-enantioselective 'background reaction' of hydroboration of substrate **4.48** with HBpin (**4.9**) was taking place, resulting in the decrease in the *ee* of the product. Control reaction with one equivalent of *B*-H-9-BBN (**4.7**) in the absence of Alpine borane (**4.12**) and HBpin also led to significant conversion (entry *d*), suggesting that the non-enantioselective reduction of the substrate with free *B*-H-9-BBN (**4.7**), formed during the reaction, could also be contributing to the decrease in enantioselectivity (Scheme **4.25**). From these results, we hypothesised that the regeneration of the catalyst was slow, which led to the enantioselective reduction by Alpine borane (**4.12**) being outcompeted by background HBpin (**4.9**) reduction, as well as allowing for *B*-H-9-BBN (**4.7**) to directly hydroborate the ketone substrate (**4.48**). We decided to explore the use of alternative chiral borane compounds as catalysts in order to prevent these issues.



Scheme 4.25 – Background reduction of ketone due to slow regeneration of catalyst

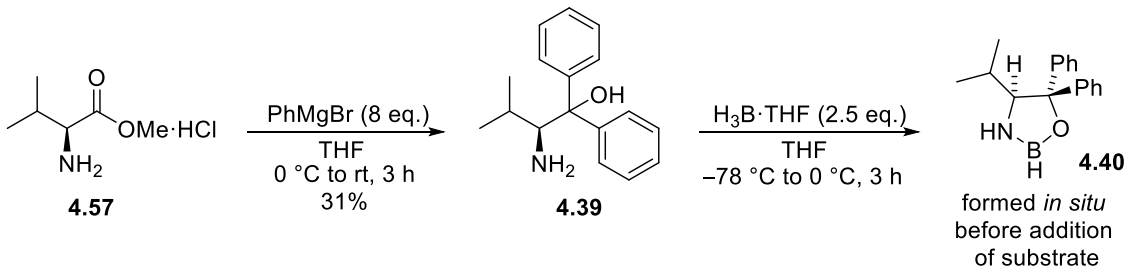
4.3 - Itsuno's Catalyst

As previously discussed (see section **4.1.5.3**), Itsuno reported the synthesis and use of an (*S*)-valine-derived chiral alkoxyamine-borane complex (**4.40**) for the asymmetric reduction of a range of carbonyl containing compounds, including ketones. Itsuno's work was further developed by Corey and co-workers in the CBS reduction; in which a similar oxazaborolidine reagent (**4.42**) is used sub-stoichiometrically and regenerated with BH_3. Itsuno's reagent (**4.40**) has previously only been reported in the stoichiometric reduction of carbonyl compounds, but we proposed that it could potentially be used sub-stoichiometrically along with HBpin (**4.9**), and could undergo a similar transborylation type mechanism to that earlier proposed (Scheme **4.26**).[194-195]



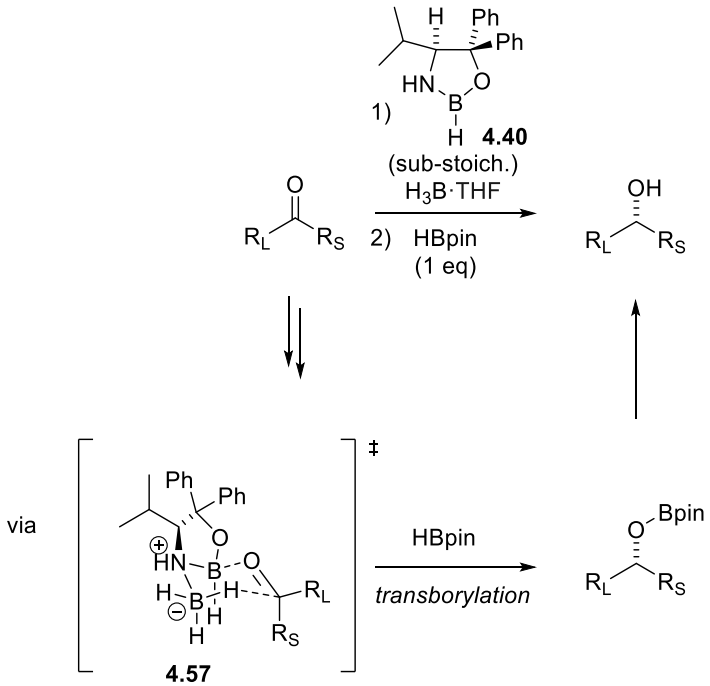
Scheme 4.26 – Proposed catalytic use of Itsuno's catalyst with HBpin in asymmetric ketone reduction

Itsuno's reagent is commonly formed *in situ*, by mixing the ligand **4.39** with an excess of $H_3B{\cdot}THF$ for 3 hours, prior to the addition of the carbonyl substrate. Ligand **4.39** was formed in one step by the reaction of (*S*)-valine methyl ester hydrochloride (**4.57**) with a large excess of phenyl magnesium bromide (Scheme **4.27**).



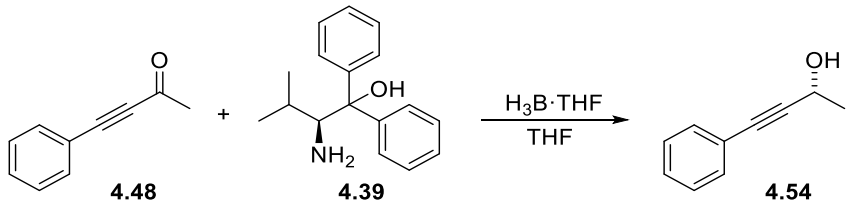
Scheme 4.27 – Synthesis of ligand 4.39 and formation of Itsuno's reagent 4.40

We proposed that reduction using Itsuno's reagent **4.40** and HBpin (**4.9**) would initially proceed by a mechanism analogous to the CBS reduction, with coordination of BH_3 to the nitrogen of the oxazaborolidine (which activates BH_3 as a hydride donor) followed by coordination of the endocylic boron to the ketone substrate at the most sterically accessible oxygen lone pair. Hydride transfer through a six-membered transition state structure (**4.57**) would then be followed by transborylation with HBpin, to form a boronic ester and reform the active catalytic species (Scheme **4.28**).



Scheme 4.28 – Proposed reduction of ketones by substoichiometric Itsuno's reagent (4.40) and HBpin

Table 4.4 – Studies into the catalytic reduction of ketones with Itsuno's reagent (4.40)



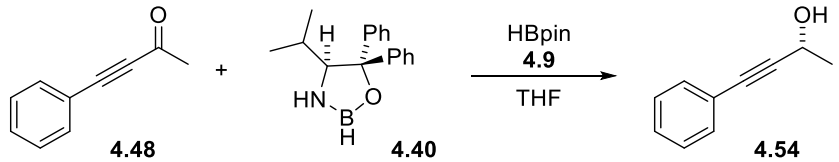
4.48 **4.39** **4.54**

Entry	*Substrate*	*Ligand (4.39) (eq.)*	*H_3B·THF (eq.)*	*Time (h)*	*Temp (°C)*	*Yield (%)*	*ee (%)*
a	**4.48**	1.25	2.5	16	25	>95	30
b	**4.48**	1.25	2.5	16	0	88	43
c	**4.48**	1	1	16	25	<10	-
d	**4.48**	1	0.5	16	25	<10	-
*e**	**4.48**	1	1	16	25	<10	-
*f**	**4.48**	1	0.5	16	25	<10	-

***4.48** and H_3B·THF pre-mixed for 8 hours

The reduction of propargylic ketone **4.48** was attempted using conditions reported by Itsuno, with 1.2 equivalents of ligand **4.39** mixed with 2.5 equivalents of H_3B·THF and stirred for 3 hours, before the addition of the substrate. Conversion to alcohol (**4.54**) was very high (Table **4.4**, entries *a* and *b*), but the enantioselectivity was fairly low relative to that reported by Itsuno. It was hypothesised that the BH_3 could be contributing to the reduction, and decreasing the enantioselectivity, so the number of equivalents of BH_3 was reduced to 1 (entry *c*) or 0.5 (entry *d*) in an attempt to prevent this. Unfortunately, in both these cases the conversion to alcohol **4.54** decreased to less than 10%. The use of less BH_3 seemed to prevent background reduction of the ketone, but also may have prevented the formation of Itsuno's reagent (**4.40**). The pre-mix time for the ligand and H_3B·THF was extended to 8 hours (entries *e* and *f*) but unfortunately there was no difference in the result.

Table 4.5 – Attempted reduction with Itsuno's reagent and HBpin



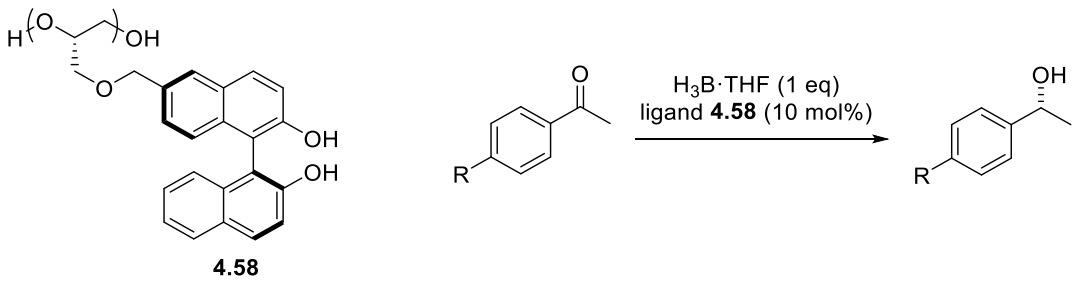
4.48 **4.40** **4.54**

Entry	*Ligand (eq.)*	*4.39*	*$H_3B{\cdot}THF$ (eq.%)*	*HBpin (eq.)*	*Time (h)*	*Temp (°C)*	*Yield (%)*	*ee (%)*
a	1.25		5	0	16	25	43	40
b	1.25		5	0	16	0	30	60
c	1.25		5	1	16	25	82	7
d	1.25		5	1	16	0	68	15

To solve this problem, we attempted to synthesise Itsuno's reagent (**4.40**) first, by mixing ligand **4.39** with a larger excess of $H_3B{\cdot}THF$ (5 equivalents), before removing any excess BH_3 under vacuum, then adding the substrate and THF to the catalyst, which was kept under inert atmosphere. Reaction at room temperature between substrate (**4.48**) and Itsuno's reagent, gave a low conversion (Table **4.5**, entry *a*), but slightly higher *ee* than the analogous reaction where Itsuno's reagent (**4.40**) was formed *in situ* (Table **4.4**, entry *c*). When the temperature was decreased to 0 °C (entry *b*), the conversion was slightly lower, but the *ee* of the product increased to 60%. Encouraged by this, one equivalent of HBpin (**4.9**) was added to the reaction, in an attempt to increase the conversion while maintaining enantioselectivity (entries *c* and *d*). Although a significant increase in the conversion was observed, the *ee* of the product was much lower than the analogous reactions without HBpin (**4.9**) (entries *a* and *b*), suggesting that background reduction of the substrate by HBpin (**4.9**) was occurring at a faster rate than reduction by Itsuno's reagent (**4.40**), and therefore the reduction was not enantioselective.

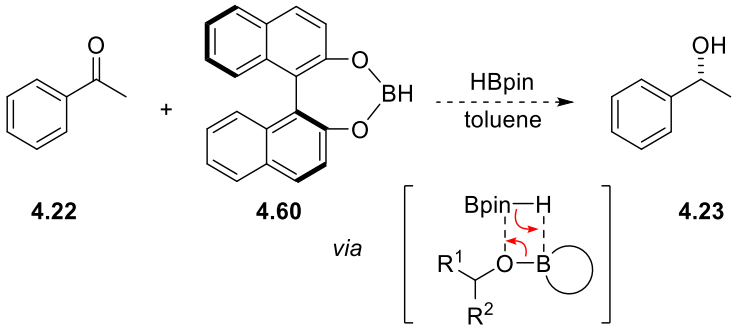
4.4 - Binol

An example of the use of borane complexes containing binapthol (BINOL) derived ligands for the asymmetric reduction of ketones has been reported by Yang and co-workers, who developed a complex containing polyether ligand (**4.58**) with $H_3B{\cdot}THF$. This complex, formed *in situ*, was used to reduce a wide range of substituted pro-chiral ketones.[207]

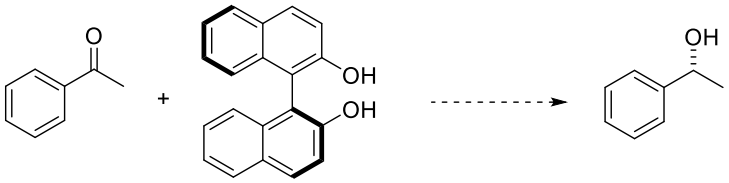


Scheme 4.29 – Previous use of BINOL-derived borane reagents for asymmetric ketone reduction

We thought it may be possible to replicate Yang's conditions, and to carry out the reduction of acetophenone (**4.22**) using catalytic (*S*)-BINOL (**4.59**) along with stoichiometric $H_3B{\cdot}THF$, with the borane complex (**4.60**) formed *in situ*. If this was successful we would investigate reducing the amount of BH_3 used, and adding stoichiometric HBpin (**4.9**) in an attempt to carry out transborylation (Scheme **4.30**).



Scheme 4.30 – Proposed asymmetric reduction of ketones with a BINOL-borane complex (4.60) and HBpin (4.9)



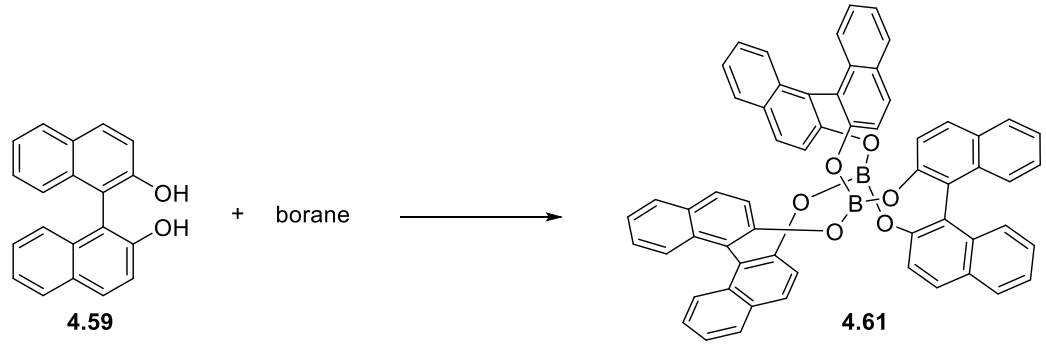
4.22 4.59 4.23

Table 4.6 – Studies into catalytic reduction with BINOL-borane complex and HBpin

Entry	*(S)-BINOL (eq.)*	*H_3B·THF (eq.)*	*Solvent*	*HBpin (eq.)*	*Time (h)*	*Temp (°C)*	*Yield (%)*	*ee (%)*
a	0.1	1	Toluene	0	16	25	82	-
b	0.1	1	THF	0	16	25	52	-
c	0.1	1	Toluene	0	16	0	70	-
d	0.2	1	Toluene	0	16	25	89	-
e	0.2	1	Toluene	0	16	0	75	-
f	0.1	0.1	Toluene	1.2	16	25	15	-
g	0.1	0.1	Toluene	1.2	16	0	5	-

Despite very high yields, all reactions carried out using 10 mol% (*S*)-BINOL and stoichiometric BH_3 unfortunately gave no enantioselectivity in the alcohol product, either at room temperature (Table **4.6**, entry *a*) or at 0 °C (entries *c* and *e*). Doubling the catalyst loading made no difference, with the *ee* values obtained still extremely low (entries *d* and *e*). We speculated that the high conversions observed were due to background reduction with BH_3. The amount of H_3B·THF was therefore reduced, and one equivalent of HBpin added to the reaction, but the same low enantioselectivity was observed, and the conversion also significantly decreased. This further suggested that H_3B·THF or HBpin, rather than the chiral borane species, was carrying out the reduction. It may have been the case that the BINOL-borane is not being formed, with the rate of H_3B·THF reduction of the substrate being faster than the rate of BINOL-borane (**4.60**) formation. We decided to move on to other borane catalysts, but later became aware of another reported use of BINOL-borane type complexes by Thormeier and co-workers, which suggested that when unsubstituted BINOL (**4.59**) was complexed with BH_3, 'propeller' compounds (**4.61**) were formed (Scheme **4.31**).[208] If this were the case, excess BH_3 would be available to carry out the reduction in a non-enantioselective manner. Future work could potentially explore this further, by altering the ratio of BH_3 to ligand, or by investigating the coordination of primary amines to the boron, which was also reported by Thormeier

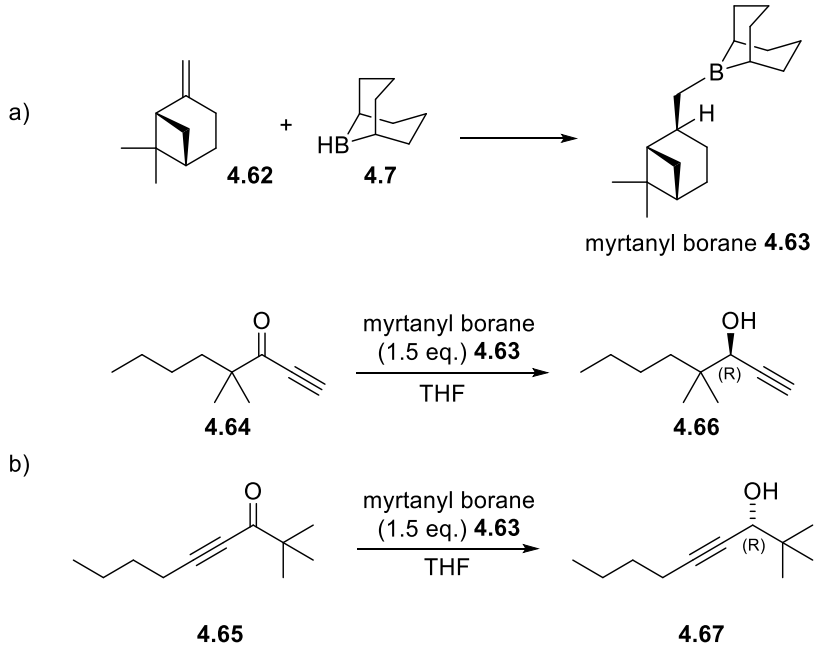
and prevented formation of propeller complexes, but only resulted in moderate enantioselectivity.



Scheme 4.31 – Formation of bis-borate propeller complexes from BINOL

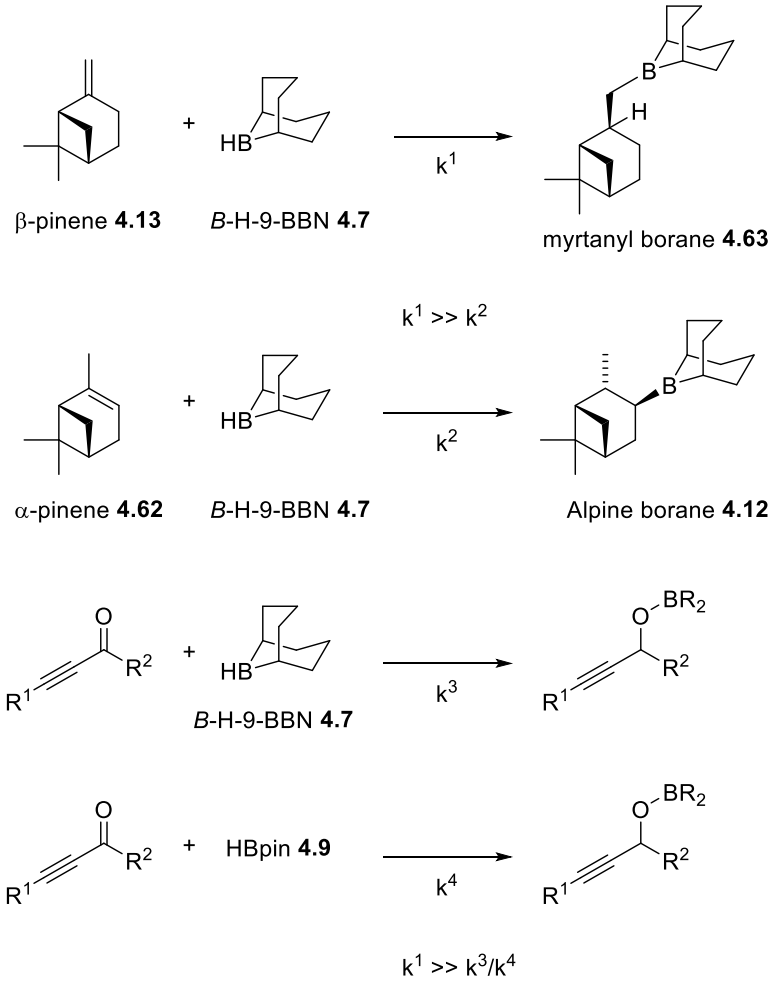
4.5 - Myrtanyl borane

As well as Alpine borane (**4.12**), Midland reported the preparation and use of myrtanyl borane (**4.63**) as a reagent for the asymmetric reduction of ketones, particularly hindered acetylenic ketones such as 2,2-dimethyl-4-nonyn-3-one (**4.64**), and 4,4-dimethyl-1-ocytn-3-one (**4.65**), both of which were reduced to give the respective (*R*)-alcohols (**4.66** and **4.67**) in high yield and enantiomeric excess (Scheme **4.32b**). Myrtanyl borane (**4.63**) is synthesised in the same manner as Alpine borane (**4.12**), but with β-pinene (**4.62**) rather than α-pinene (**4.13**). (Scheme **4.32a**)[209]



Scheme 4.32 – a) Synthesis of myrtanyl borane (4.63) and b) use in asymmetric ketone reduction

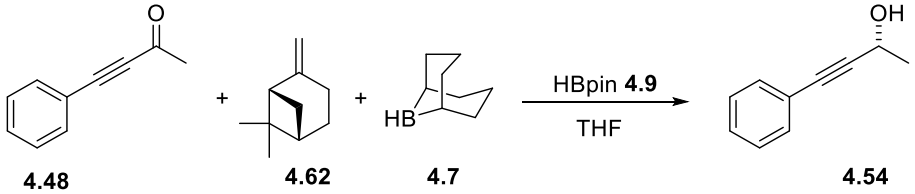
The alkene in β-pinene (**4.62**) is exocylic, making it more accessible than the endocyclic alkene of α-pinene, which suggests myrtanyl borane (**4.63**) may be able to re-form at a faster rate during the reaction than Alpine borane (**4.12**), therefore preventing any reduction by free *B*-H-9-BBN. If the catalyst did re-form faster, this would also likely reduce the amount of background reduction by HBpin (**4.9)**, which is known to proceed slower than the rate of reduction by the chiral borane (Scheme **4.33**).



Scheme 4.33 – Predicted rates of hydroboration of α-pinene (4.12) and β-pinene (4.62), as well as background reduction

If our hypothesis was correct, use of myrtanyl borane (**4.63**) should lead to the reduction proceeding with much higher enantioselectivity. Reactions would be carried out using the same conditions as for those when Alpine borane was formed *in situ* (table **4.7**), with β-pinene and *B*-H-9-BBN (**4.7**) pre-mixed before the addition of the substrate **4.48** and then HBpin (**4.49**).

Table 4.7 – Studies into catalytic reduction of ketone 4.48 using myrtanyl borane 4.63 and HBpin



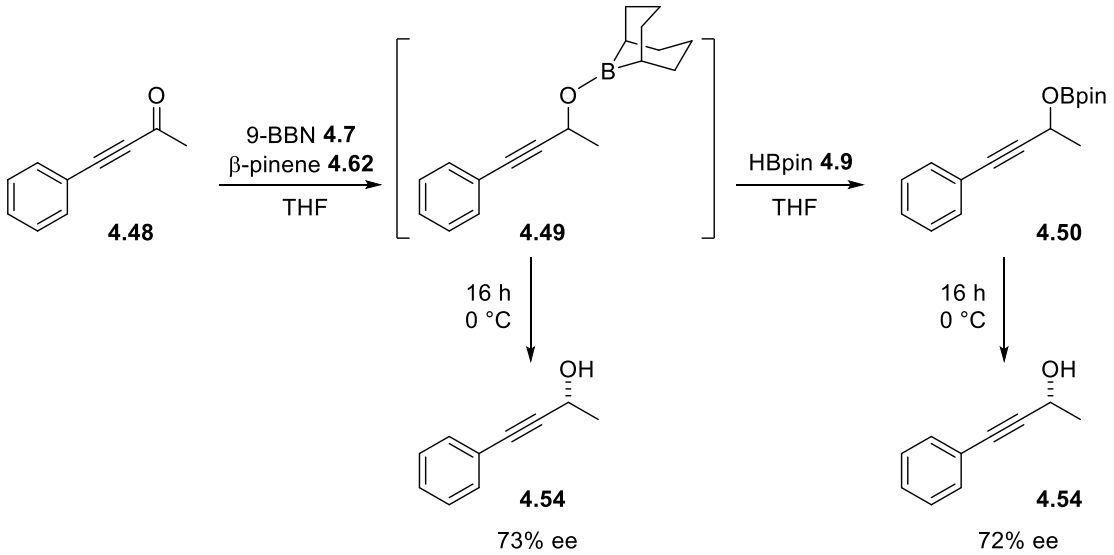
4.48 4.62 4.7 4.54

Entry	*B-H-9-BBN (mol%)*	*β-pinene (mol%)*	*Mix time (h)*	*HBpin (eq.)*	*Time (h)*	*Yield (%)*	*ee (%)*
a	100	100	2	0	16	35	75
b	100	100	2	1.2	16	93	74
c	20	20	2	1.2	16	88	68
d	20	20	6	1.2	16	90	66
e	20	20	16	1.2	16	95	72
f	20	100	16	1.2	16	92	71
g	10	20	16	1.2	16	42	72
h	20	20	16	1.2	6	44	70

*Temperature 0 °C for all reactions

The initial reaction, carried out using stoichiometric *B*-H-9-BBN (**4.7**) and β-pinene (**4.62**), pre-mixed for 2 hours, saw the successful reduction of ketone **4.48** to alcohol **4.54** in low yield, but in good enantioselectivity (entry *a*). When 1.2 equivalents of HBpin (**4.9**) were added the yield increased significantly to 93%, but crucially the *ee* was maintained (entry *b*). The catalytic reaction, using 20 mol% *B*-H-9-BBN (**4.7**) and β-pinene (**4.62**) with 1.2 equivalents of HBpin (**4.9**) (entry *c*) showed high conversion and retention of the high enantioselectivity seen in the stoichiometric reaction. This result supported our predictions that the catalyst formation (and therefore regeneration) was much faster for Myrtanyl borane (**4.63**) than for Alpine borane (**4.12**), preventing any background reduction of the substrate with *B*-H-9-BBN (**4.7**); ie. the asymmetric reduction by the catalyst was outcompeting any reduction by HBpin (**4.9**) or *B*-H-9-BBN (**4.7**). Increasing the catalyst pre-mix time saw no significant change in results, with conversion and enantioselectivity still high, again suggesting the rate of catalyst formation was faster than the formation of Alpine borane (**4.12**) (entries *d* and *e*). Use of excess β-pinene (**4.62**) with respect to *B*-H-9-BBN (**4.7**) (to potentially mop up any free *B*-H-9-BBN (**4.7**), thus preventing background reduction) (entry *f*) also had no significant effect on the results. To ensure the enantioselectivity was retained from the borinic ester

intermediate **4.49** through the transborylation step, a reaction was carried out in which an aliquot was removed from the reaction prior to the addition of HBpin (**4.9**), then both solutions were stirred for 16 hours and quenched at the same time. Similarly high *ee* values were observed for both products, confirming retention of enantioselectivity (Scheme **4.34**).



Scheme 4.34 – Comparison of *ee* of alcohol from intermediate 4.49 and alcohol from borate ester 4.50

4.6 - Mechanistic Studies

In order to obtain further mechanistic insight into the transformation, we carried out a study on the stoichiometric reduction of propargylic ketone **4.48** using ^{11}B NMR spectroscopy. Use of ^{11}B NMR spectra after the catalyst formation, after addition of the substrate, and after addition of HBpin, would allow the observation of the formation and disappearance of each relevant boron-containing species in the reaction, as in each compound the boron is in a significantly different environment and would show up as a distinct peak (Figure **4.5**).

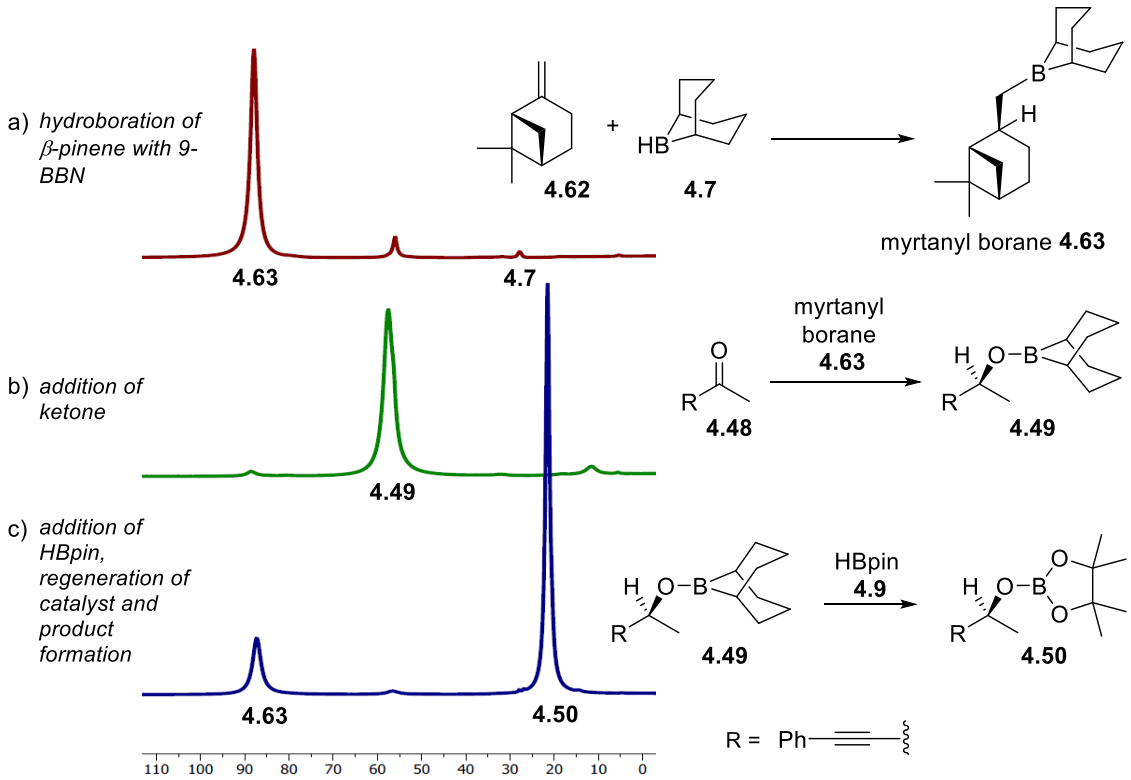
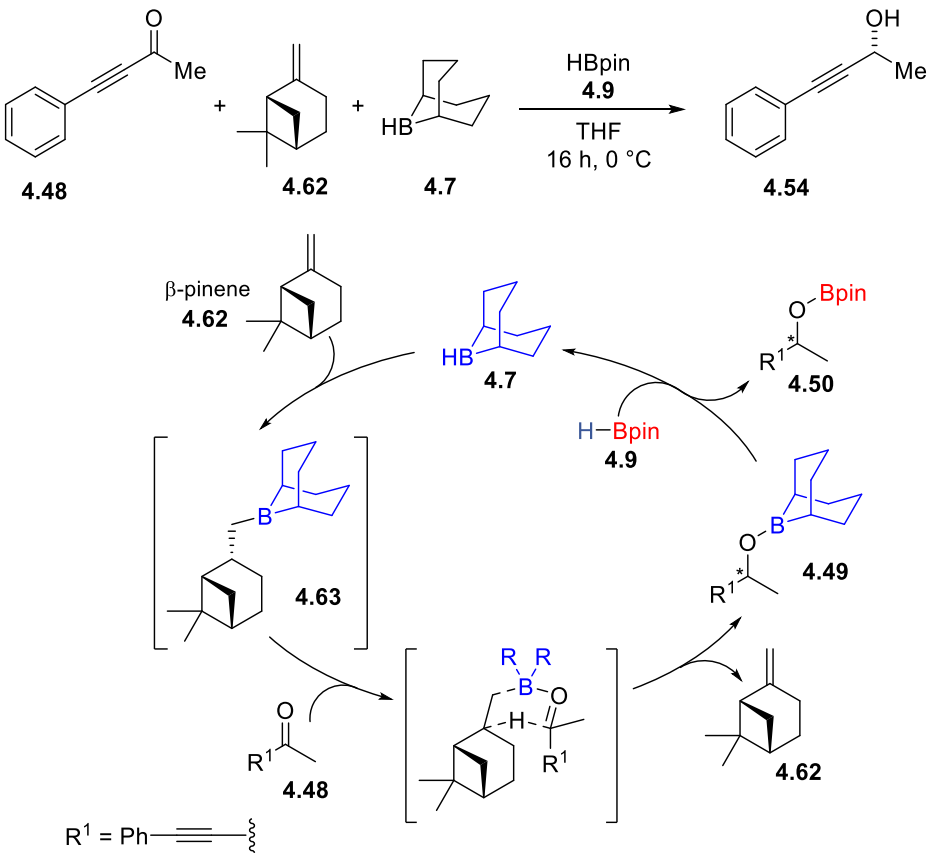


Figure 4.5 – Mechanistic study of Myrtanyl borane catalysed reduction of ketones

The ^{11}B NMR spectrum, taken after the hydroboration of β-pinene with *B*-H-9-BBN (**4.7**) (Figure **4.5a**), to form the catalyst, showed a very clear peak at 88 ppm, corresponding to myrtanyl borane (**4.63**). Trialkyl borane species characteristically appear between 80-90 ppm, and *B*-H-9-BBN is known to appear at 28 ppm in $CDCl_3$, so the NMR gives strong evidence that the catalyst has been formed, with only a small amount of *B*-H-9-BBN (**4.7**) observed.[210-211] After addition of the ketone substrate (Figure **4.5b**), almost total consumption of the catalyst is observed, along with a new peak at 58 ppm - in the region where borinic esters are usually observed - corresponding to the borinic ester **4.49**, formed by hydroboration of ketone **4.48** by myrtanyl borane (**4.63**).[211] After addition of HBpin (**4.9**), a new peak at 21 ppm was observed, corresponding to boronate ester **4.50**, formed from borinic acid **4.49** by boron-boron exchange, with the peak again corresponding with NMR data previously reported for borate ester species (Figure **4.5c**).[211] The observed peak at 88 ppm indicated regeneration of the myrtanyl borane catalyst (**4.63**), and the absence of a clear *B*-H-9-BBN (**4.7**) peak suggested the rate of re-formation of the catalyst was fast, therefore reducing the possibility of background reduction, as any liberated *B*-H-9-BBN (**4.7**) had already been used up. This study gave us the evidence we needed to confidently suggest that the proposed transborylation

mechanism, and catalyst regeneration from β-pinene (**4.63**) and liberated *B*-H-9-BBN (**4.7**) were indeed occurring. The full proposed catalytic cycle (Scheme **4.35**), shows catalyst formation, hydroboration by a Meerwein-Pondorf-Verley type mechanism, transborylation with HBpin, then regeneration of the catalyst.

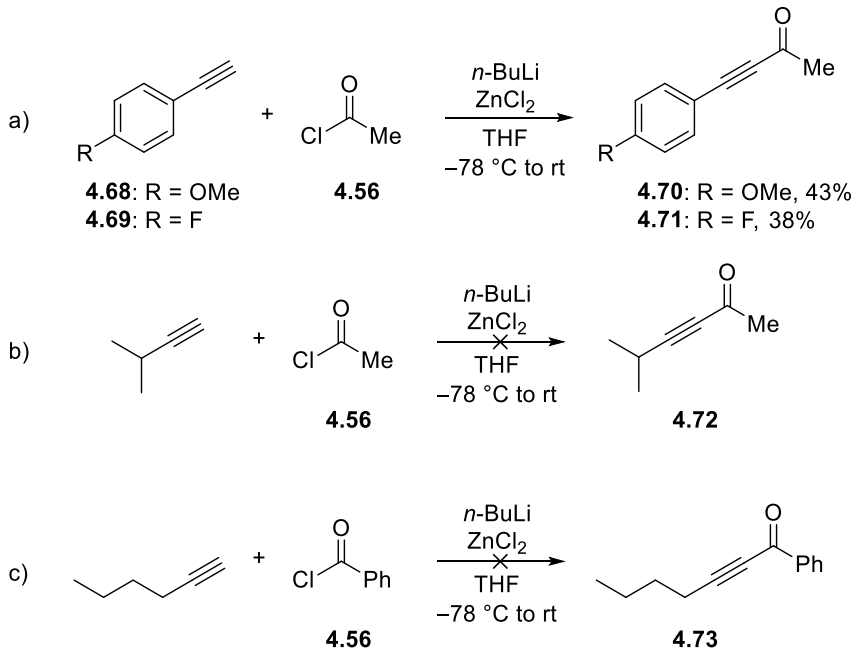


Scheme 4.35 – Proposed catalytic cycle for ketone reduction by Myrtanyl borane 4.63

4.7 - Substrate Scope

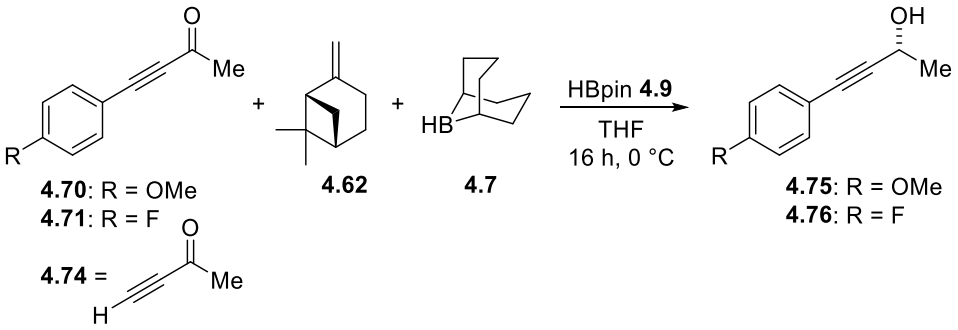
Once the reaction conditions had been optimised (see table **4.7**, entry *e*), and the mechanism determined (Scheme **4.35**), we aimed to increase the substrate scope. As discussed earlier (see section **4.2**), the very sluggish reduction of sterically encumbered compounds, such as acetophenone (**4.22**) by Alpine borane (**4.12**) and myrtanyl borane (**4.63**), meant that we were restricted to propargylic ketones. However, by altering the groups adjacent to the alkyne, and adjacent to the ketone, it would still be possible to test the reduction with a variety of different functionalities, and hopefully to show a high functional group tolerance for the reaction. Midland reported the reduction of a wide

range of propargylic ketone substrates with stoichiometric Alpine borane (**4.12**) and myrtanyl borane (**4.63**), including those containing alkyl- and aryl-groups, as well as alkenes and esters, both of which were not reduced by the borane reagent.[212] The compounds trialled differed from the original propargylic ketone substrate (**4.48**) by inclusion of an electron-donating methoxy- (**4.70**) or an electron-withdrawing fluoro- (**4.71**) group on the phenyl ring, *para*- to the alkyne (Scheme **4.36a**). The two propargylic ketone substrates were synthesised using the same route previously described (see section **4.2**), in comparable yields to that of 4-phenyl-3-butyn-2-one (**4.48**). Using the same method, we attempted to synthesise substrates containing different groups on the alkyne, such as an *iso*-propyl substituent (**4.72**), and hexyl-substituent (**4.73**), however both of these reactions were unsuccessful (Scheme **4.36b** and **4.36c**). Alternative methods for the synthesis of both of these have been reported in the literature, so these could potentially be investigated in the future.[213-214]



Scheme 4.36 – a) Attempted formation of propargylic ketone substrates containing *para*-substituted aromatic rings; b) containing an iso-propyl substituent; c) containing a hexyl-substituent

Table 4.8 – Reduction of propargylic ketones with Myrtanyl borane (4.63)

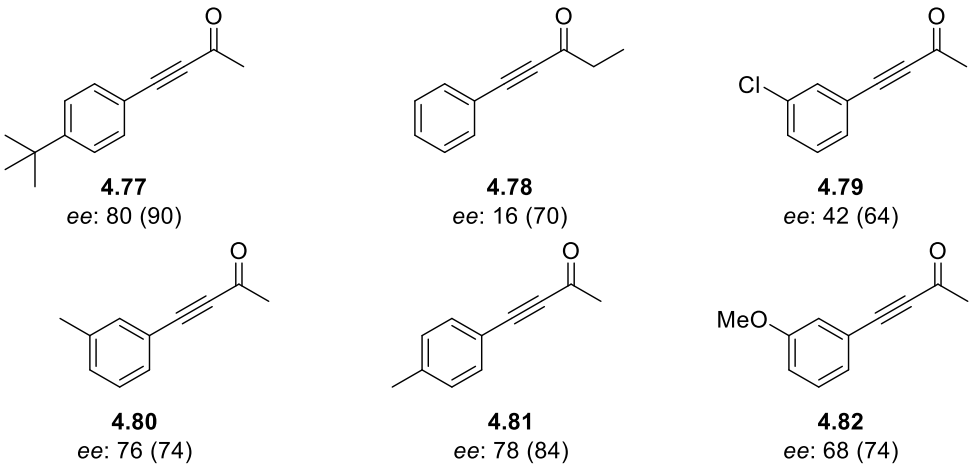


Entry	*Substrate (mol%)*	*Catalyst (mol%)*	*Mix time (h)*	*HBpin (eq.)*	*Time (h)*	*Temp (°C)*	*Yield (%)*	*ee (%)*
a	**4.70**	100	2	1.2	16	0	89	70
b	**4.71**	100	2	1.2	16	0	81	67
c	**4.70**	20	2	1.2	16	0	52	56
*d**	**4.71**	20	2	1.2	16	0	68	66
e	**4.74**	100	2	1.2	16	0	0	-

*reaction d carried out by Kieran Nicholson

Reduction of ketones **4.70** and **4.71** was carried out using the optimised Myrtanyl borane conditions, initially with stoichiometric catalyst and HBpin. The methoxy-substituted ketone **4.70** was successfully reduced in high yield and *ee* (Table **4.8**, entry *a*), as was the fluoro-substituted ketone (**4.71**) (Entry *b*). When the catalyst loading was reduced to 20%, both substrates were successfully reduced enantioselectively, though with a decrease in yield. For the methoxy-containing alcohol product (**4.75**) the *ee* also decreased slightly between the stoichiometric and catalytic reactions, giving an enantiospecificity (or es) of 80% (entry *c*). The *ee* of fluoro-substituted alcohol (**4.76**) however, was retained from the stoichiometric to the catalytic reaction with a very high es value (>95%). These results show that the transformation was tolerant of both electron-donating and electron-withdrawing groups on the aromatic ring. Commercially available propargylic ketone **4.74**, containing a terminal alkyne, was also trialled, but reduction was unsuccessful, with none of the alcohol product observed. Within the group a number of other propargylic ketone substrates have now successfully been reduced (Figure **4.6**, work carried out by Joanne Dunne and Kieran Nicholson). These include compounds

bearing a tertiary butyl group *para*-to the alkyne (**4.77**), with chloro- (**4.79**) and methoxy- (**4.82**) groups in the *meta* position of the ring, and a methyl group in either the *meta* (**4.80**) or *para* (**4.81**) position on the ring. Ethyl-substituted ketone (**4.78**) was also reduced, where the group on the other side of the ketone was altered. Further substrates are currently being investigated, including compounds without aryl groups, and compounds containing amine groups.

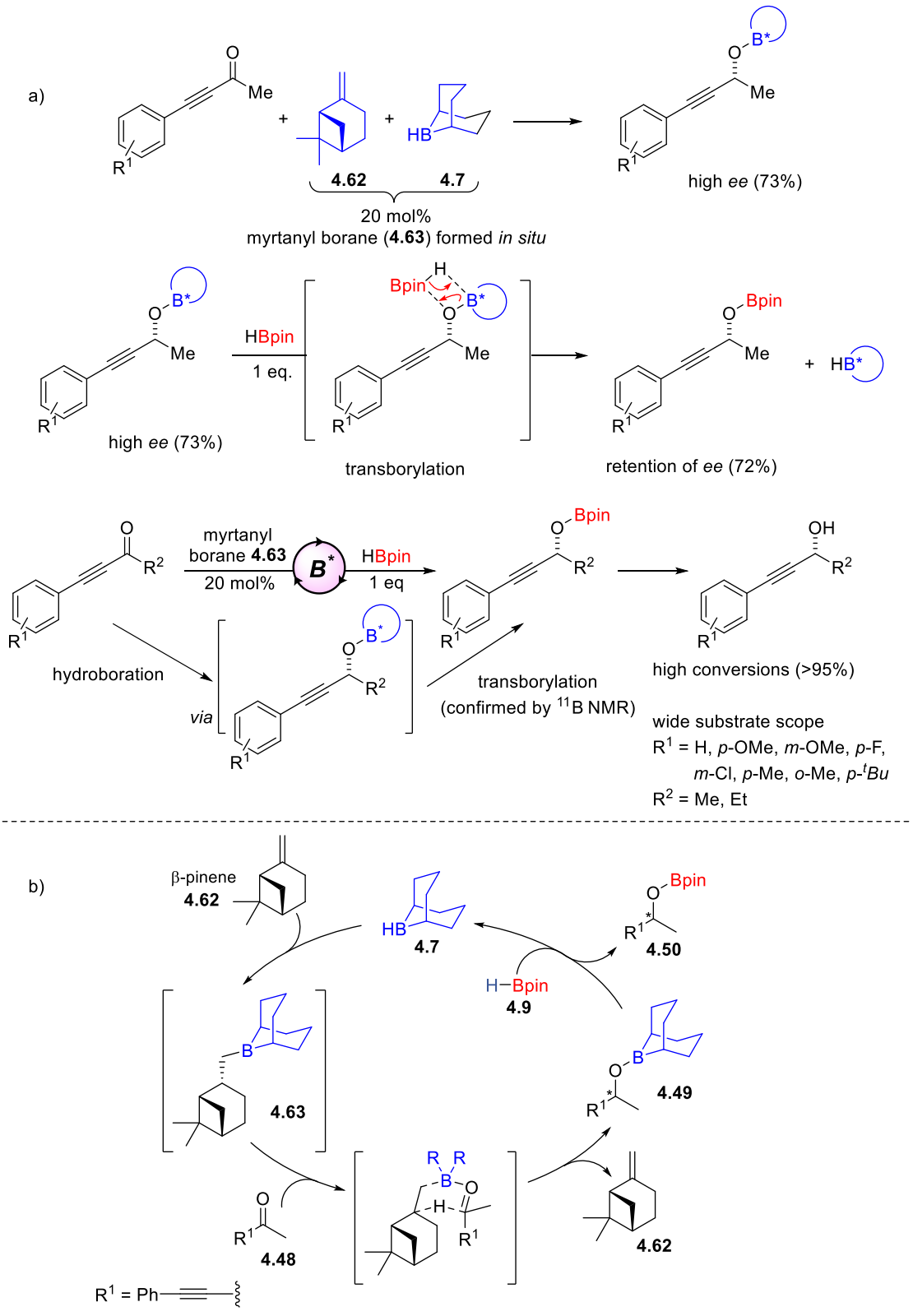


* *ee* with 20 mol% catalyst, *ee* with stoichiometric catalyst in brackets

Figure 4.6 – Further substrates successfully reduced within the Thomas group

4.8 - Conclusions and Future Work

In conclusion, a process to carry out the chiral borane-catalysed asymmetric reduction of propargylic ketones, using stoichiometric HBpin (**4.9**) to enable turnover of the catalyst by boron-boron exchange, has been successfully developed and optimised. Investigations into the use of Alpine borane (**4.12**), Itsuno's catalyst (**4.40**), and a BINOL-borane species (**4.60**) all resulted in either low, or a complete lack of enantioselectivity. This was mainly due to inefficient or slow catalyst formation, which led to the non-enantioselective background reduction by either HBpin, *B*-H-9-BBN or BH_3 outcompeting reduction by the chiral species. Myrtanyl borane (**4.63**) however, prepared in situ from β-pinene (**4.62**) and *B*-H-9-BBN (**4.7**), proved to be an effective catalyst, as the 1,1-disubstitued exocyclic alkene of β-pinene (**4.62**) was hydroborated at a much faster rate than the endocyclic alkene of α-pinene, which prevented significant background reduction by HBpin (**4.9**) or *B*-H-9-BBN (**4.7**). 20 mol% of the catalyst was used alongside stoichiometric HBpin to successfully carry out the reduction of propargylic ketone **4.48** in high yield (95%) and high enantioselectivity (72% *ee*), which compared well with previous literature reductions using Myrtanyl borane (Scheme **4.37**). Importantly, high retention of enantioselectivity was observed from the stoichiometric reduced to the catalytic reduction.



Scheme 4.37 – a) Asymmetric Myrtanyl borane (4.63)-catalysed reduction of propargylic ketones by transborylation with HBpin (4.9) and b) Mechanism of the reaction

Mechanistic studies using ^{11}B NMR spectroscopy strongly suggested hydroboration of the ketone substrate by myrtanyl borane (**4.63**) to form a chiral borinic ester, was followed by transborylation with HBpin (**4.9**), giving a borate ester and releasing *B*-H-9-BBN (**4.7**), which regenerated the catalyst. A range of propargylic ketone substrates, containing alkyl-, methoxy- and halide- substituted aryl groups, have been reduced in high conversion and enantioselectivity. Future work aims to extend the substrate scope to propargylic ketones containing ether-, thioether- and amine- substituted aryl groups, as well as substrates with alkyl groups on the alkyne. The propargylic ketones shown in Figure **4.7** have been prepared, and investigations into their reduction is ongoing. Further future work aims to show that the reduction can be widely applied to substrates bearing a range of functional groups. The application of our system, along with other chiral borane catalysts, to other unsaturated compounds such as ketones and imines will be investigated.

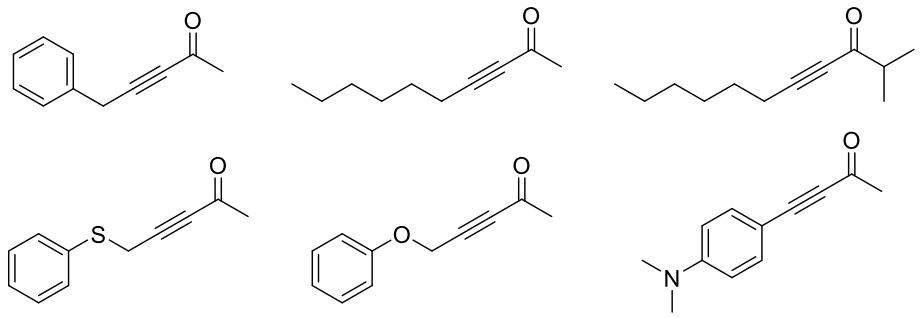


Figure 4.7 – Substrates synthesised to be trialled in the future

Chapter 5 - Experimental Procedures & Characterisation

5.1 - General Experimental

Experimental Procedures, Glassware and Reagents

Unless stated otherwise, reactions were carried out under anhydrous conditions, under a positive pressure of nitrogen, using flame-dried glassware and with magnetic stirring. Reagents and solvents were purchased from commercially available sources and utilised without further purification, unless stated otherwise.

NMR spectra

^{1}H NMR spectra were recorded at 600 MHz, 500MHz, and 400 MHz using a, Bruker AVANCE 600, Bruker AVANCE 500, Bruker PRO 500 or Bruker AVANCE 400 spectrometer. Residual solvent peaks were used as an internal reference for ^{1}H NMR spectra ($CDCl_3$ δ 7.26 ppm, CD_3OD δ 3.31 ppm). Multiplicities are indicated by app. (apparent), br. (broad), s (singlet), d (doublet), t (triplet), q (quartet), quin. (quintet), sext. (sextet), sept. (septet). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Assignment of proton signals was assisted by ^{1}H-^{1}H COSY, HSQC and HMBC experiments. ^{13}C NMR spectra were recorded at 125 MHz, using a Bruker AVANCE 500, or Bruker PRO 500 spectrometer. Solvent peaks were used as an internal reference for ^{13}C NMR spectra ($CDCl_3$ δ 77.2 ppm, CD_3OD δ 49.0 ppm). ^{13}C NMR peaks are generally reported to 1 decimal place. Assignment of carbon signals was assisted by ^{1}H-^{1}H COSY, HSQC, HMBC and NOESY experiments.

IR spectra

Infrared spectra were recorded using a Shimadzu IR Affinity-1 fourier transform IR spectrophotometer as neat samples, using Pike MIRacle ATR accessory. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}).

Mass spectrometry

High resolution mass spectra were recorded on a Bruker microTOF instrument using Electrospray Ionisation (ESI+).

Chromatography

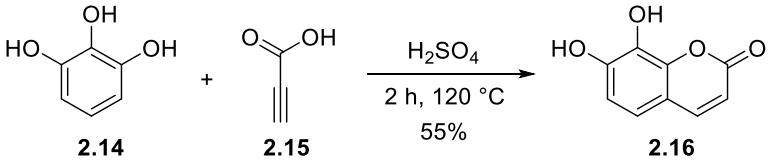
Reactions were monitored by thin-layer chromatography (TLC), using silica gel plates (Merck Kieselgel 60 F254). Visualisation was effected by quenching of UV fluorescence (λ_{max} = 254 nm) and by staining with a standard solution of *p*-anisaldehyde, vanillin or $KMnO_4$ followed by heating. Merck silica gel 60 (230-400 mesh) was used for flash chromatography. Petroleum ether refers to petroleum ether 40-60. Analytical chiral HPLC was conducted using an Agilent 1100 series system using a G1313 autosampler, a multiwavelength detector and a binary pump. A Chiralcel ODH column was used for all samples, with column length 250 mm, internal diameter 4.6 mm and particle size 5 μm. For all runs the solvent flow rate was 1 mL/min and the run time 20 minutes.

Melting Point

Melting points were measured on a Gallenkamp Melting Point System or a Stanford Research Systems OptiMelt MPA100.

5.2 – Chapter 2 Experimental Procedures

5.2.1 – 7,8-Dihydroxycoumarin



2.14 **2.15** **2.16**

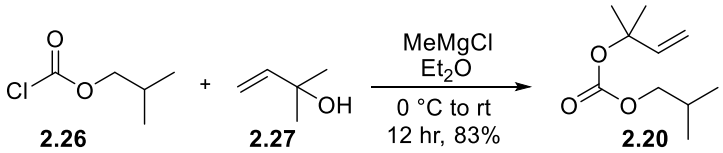
Prepared using a literature procedure.[88] H_2SO_4 (1 drop) was added to a mixture of pyrogallol (**2.14**) (1.00 g, 7.94 mmol) and propiolic acid (**2.15**) (1.00 mL, 15.9 mmol) and the resulting red/brown suspension stirred for 2 hours at 120 °C, before cooling and dissolving in EtOAc (50 mL). The mixture was then washed with 5% $NaHCO_3$ (6 × 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude orange/brown powder was triturated several times with Et_2O to remove soluble impurities, to give the product 7,8-dihydroxycoumarin (**2.16**) as an off-white powder (0.78 g, 4.38 mmol, 55%). All spectroscopic data matched literature values.[88]

^{1}H NMR (500 MHz, CD_3OD) δ 7.84 (d, *J* = 9.5 Hz, 1H, Ar*H*), 7.00 (d, *J* = 8.5 Hz, 1H, Ar*H*), 6.83 (d, *J* = 8.5 Hz, 1H, Ar*H*), 6.19 (d, *J* = 9.5 Hz, 1H, Ar*H*) ppm;

^{13}C NMR (125 MHz, CD_3OD) δ 162.0 (C), 149.7 (C), 145.2 (CH), 143.6 (C), 132.1 (C), 118.8 (CH), 112.4 (C), 112.3 (CH), 110.7 (CH) ppm.

MP – 253-255 °C (lit[88] 255-256 °C)

5.2.2 – Isobutyl 2-methylbut-3-en-2-yl carbonate



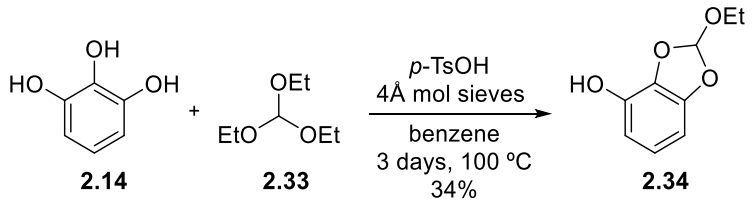
2.26 **2.27** **2.20**

Prepared using a literature procedure.[90] To a suspension of methylmagnesium chloride (3 M in THF, 7.80 mL, 23.4 mmol) in diethyl ether (36 mL), was added 2-methyl-3-buten-2-ol (**2.27**) (1.88 mL, 18.0 mmol) in diethyl ether (6 mL), and the mixture stirred at 0 °C for 30 minutes. A 0 °C solution of isobutyl chloroformate (**2.26**) (3.30 mL, 27.0 mmol) in diethyl ether (36 mL) was then added dropwise, and the reaction mixture stirred at room temperature for 15 hours before being quenched with NH_4Cl (50 mL) and the aqueous layer extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to afford isobutyl 2-methylbut-3-en-2-yl carbonate (**2.20**) as a clear liquid (2.78 g, 14.9 mmol, 83%). All spectroscopic data matched literature values.[89-90]

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.13 (dd, *J* = 17.5, 10.9 Hz, 1H, *H*C=CH_2), 5.24 (dd, *J* = 17.5, 0.8 Hz, 1H, C=C*H*$_a$H$_b$), 5.15 (dd, *J* = 10.9, 0.8 Hz, 1H, C=CH$_a$*H*$_b$), 3.88 (d, *J* = 6.8 Hz, 2H, O–C*H*$_2$), 1.98 (dp, *J* = 13.4, 6.7 Hz, 1H, C*H*$(CH_3)_2$, 1.58 (s, 6H, 2 × C*H*$_3$), 0.96 (d, *J* = 6.8 Hz, 6H, CH(C*H*$_3)_2$) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.6 (C), 141.9 (CH), 113.5 (CH), 82.0 (C), 73.4 (CH_2), 27.8 (CH_2), 26.3 (2 × CH_3), 19.0 (2 × CH_3) ppm.

5.2.3 – 2-Ethoxy-4-hydroxybenzo[1,3]dioxole



Compound **2.34** was prepared using a modified literature procedure.[215] TsOH (0.37 g, 1.98 mmol) was added to a solution of pyrogallol (**2.14**) (5.00 g, 39.7 mmol), triethylorthoformate (**2.33**) (10.0 mL, 59.5 mmol) and 4Å molecular sieves in benzene (100 mL). The mixture was heated under reflux for 3 days with the red/purple liquid turning black. The reaction mixture was then cooled and filtered through celite before being purified by column chromatography (1:1 DCM:Hexane) to afford orthoester-protected compound **2.34** as a dark red oil (2.50 g, 13.7 mmol, 34 %). All spectroscopic data matched literature values.[215-216]

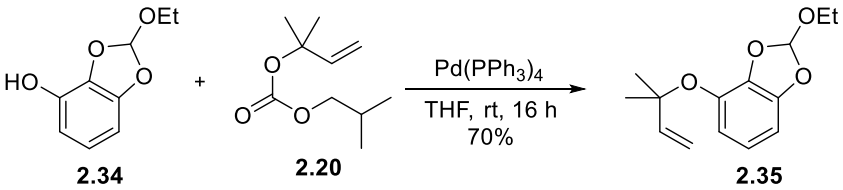
^{1}H NMR (500 MHz, CD_3OD) δ 6.85 (s, 1H, $O_{(3)}$–C*H*), 6.70 (dd, *J* = 8.4, 7.8 Hz, 1H, Ar*H*), 6.45 (dd, *J* = 8.4, 1.0 Hz, 1H, Ar*H*), 6.42 (dd, *J* = 7.9, 1.1 Hz, 1H, Ar*H*), 3.73 (q, *J* = 7.1 Hz, 2H, O–CH_2), 1.24 (t, *J* = 7.1 Hz, 3H, CH_3) ppm;

^{13}C NMR (126 MHz, CD_3OD) δ 147.2 (C), 132.9 (C), 121.4 (CH), 118.7 (CH), 110.5 (CH), 106.9 (C), 99.7 (CH), 58.7 (CH_2), 13.8 (CH_3) ppm;
(minor impurities at 140.5 and 145.8 ppm from starting material)

IR (Neat, cm^{-1}) 3365(br), 2982, 2940, 2718, 2357, 1700, 1616, 1506, 1477, 1376, 1250, 999;

HRMS (ESI+) *m/z* = 183.0652 (calculated $[M+H]^+$ ($C_9H_{11}O_4$) 183.0657).

5.2.4 – 2-Ethoxy-4-((2-methylbut-3-en-2-yl)oxy)benzo[1,3]dioxole



2.34 **2.20** **2.35**

Compound **2.35** was prepared using a modified literature procedure.[89] Orthoester compound **2.34** (0.10 g, 0.55 mmol) and *iso*butyl 2-methylbut-3-en-2-yl carbonate (**2.20**) (0.15 g, 0.82 mmol) were stirred in THF (10 mL), before addition of $Pd(PPh_3)_4$ (4.0 mg, 6.0 μmol). The mixture was stirred at room temperature for 1.5 h then quenched with saturated aq. NH_4Cl (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (3 × 20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Column chromatography (6:1 hexane:ethyl acetate) gave reverse-prenylated compound **2.35** as a yellow oil (98 mg, 0.39 mmol, 70%).

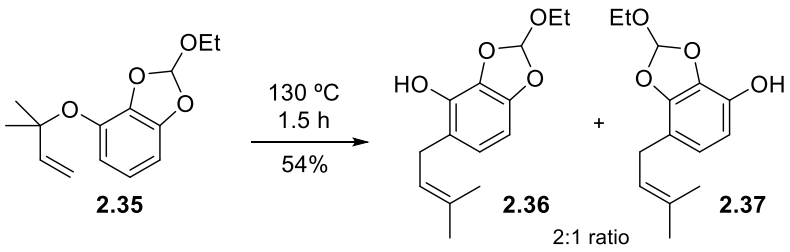
^{1}H NMR (500 MHz, CD_3OD) δ 6.87 (s, 1H, C*H*), 6.73 (app. t, *J* = 8.1 Hz, 1H, Ar*H*), 6.61 (ddd, *J* = 7.9, 6.4, 1.1 Hz, 2H, 2 × Ar*H*), 6.16 (dd, *J* = 17.6, 10.9 Hz, 1H, *H*C=CH_2), 5.17 (dd, *J* = 17.6, 1.1 Hz, HC=CH_aH$_b$), 5.08 (dd, *J* = 10.9, 1.1 Hz, 1H, HC=CH_a*H*$_b$), 3.71 (qd, *J* = 7.1, 0.8 Hz, 2H, O–CH_2), 1.44 (s, 6H, 2 × CH_3), 1.23 (t, *J* = 7.1 Hz, 3H, CH_2CH_3) ppm;

^{13}C NMR (126 MHz, CD_3OD) δ 147.2 (C), 143.5 (C), 138.7 (C), 138.3 (C), 120.5 (CH), 118.7 (CH), 118.3 (CH), 112.7 (CH), 103.4 (CH), 81.2 (C), 58.9 (CH_2), 25.6 (CH_3), 25.5 (CH_3), 13.8 (CH_3) ppm;

IR (Neat, cm^{-1}) 2980, 1630, 1485, 1460, 1350, 1250, 1125, 1060, 1001;

HRMS (ESI+) *m/z* = 250.1200 (calculated $[M]^+$ ($C_{14}H_{18}O_4$) 250.1205).

5.2.5 – 2-Ethoxy-5-(3-methylbut-2-en-1-yl)benzo[1,3]dioxol-4-ol (2.36) and 2-ethoxy -7-(3-methylbut-2-en-1-yl)benzo[1,3]dioxol-4-ol (2.37)



Compounds **2.36** and **2.37** were prepared using a modified literature procedure.[89] Compound **2.35** (75 mg, 0.30 mmol, neat) was heated to 130 °C for 1.5 hours, before being cooled to RT and the resulting dark red/brown solid purified by column chromatography (5:1 hexane:ethyl acetate) to afford both the desired product **2.36** (9 mg, 0.037 mmol, 18%), and compound **2.37** resulting from migration of the orthoester protecting group to the newly free hydroxyl group (21 mg, 0.084 mmol, 36%).

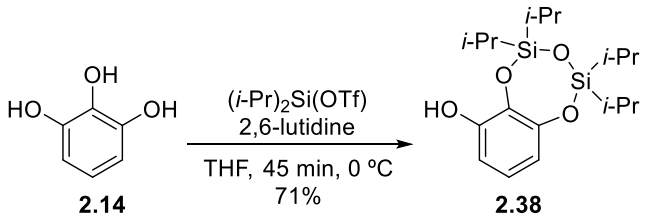
Compound 2.36 - ^{1}H NMR (500 MHz, Methanol-d_4) δ 6.86 (s, 1H, C*H*), 6.56 (d, *J* = 8.0 Hz, 1H, Ar*H*), 6.33 (d, *J* = 8.0 Hz, 1H, Ar*H*), 5.28 (t, *J* = 7.3 Hz, 1H, *H*C=C), 3.72 (q, *J* = 7.3 Hz, 2H, CH_2CH$_3$), 3.26 (d, *J* = 7.3 Hz, 2H, ArCH_2), 1.72 (dd, *J* = 9.0, 1.4 Hz, 6H, 2 × CH_3), 1.24 (t, *J* = 7.1 Hz, 3H, CH$_2$CH_3) ppm;

^{13}C NMR (126 MHz, CD$_3$OD) δ 145.1 (C), 137.7 (C), 133.3 (C), 131.2 (C), 124.0 (C), 123.0 (CH), 121.0 (CH), 118.9 (CH), 99.0 (CH), 58.6 (CH$_2$), 25.5 (CH$_2$), 22.3 (CH$_3$), 15.3 (CH$_3$), 13.0 (CH$_3$) ppm;
(impurity peaks between 14-32 ppm likely due to hexane)

Compound 2.37 - ^{1}H NMR (500 MHz, CD$_3$OD) δ 6.88 (s, 1H, C*H*), 6.51 (d, *J* = 8.5, 1H, Ar*H*), 6.37 (d, *J* = 8.5, 1H, Ar*H*), 5.27 (ddt, *J* = 8.8, 6.0, 1.4, 1H, *H*C=C), 3.71 (q, *J* = 7.1, 2H, CH_2CH$_3$), 3.22 (m, 2H, ArCH_2), 1.73 (d, *J* = 1.2 Hz, 6H, 2 × CH_3), 1.24 (t, *J* = 7.1, 3H, CH$_2$CH_3) ppm;

^{13}C NMR (126 MHz, Methanol-d_4) δ 144.7 (C), 138.2 (C), 132.5 (C), 131.7 (C), 122.0 (CH), 121.5 (CH), 118.6 (CH), 114.1 (C), 110.2 (CH), 58.6 (CH$_2$), 27.0 (CH$_2$), 24.4 (CH$_3$), 16.4 (CH$_3$), 13.9 (CH$_3$) ppm.

5.2.6 – 2,2,4,4-Tetraisopropylbenzo[1,3,5,2,4]trioxadisilepin-6-ol



Compound **2.38** was prepared according to a literature procedure.[220] Diisopropylsilyl bis(trifluoromethanesulfonate) (0.375 mL, 1.27 mmol) was added to a stirred solution of pyrogallol (**2.14**) (100 mg, 0.19 mmol) and 2,6-lutidine (0.275 mL, 2.37 mmol) in tetrahydrofuran at 0 °C over 10 minutes, before the mixture was stirred for 45 minutes. The reaction was warmed to room temperature before the solvent was removed under reduced pressure. Purification by column chromatography (20:1:1 petroleum ether:toluene:MeO^{t}Bu) gave the siloxane protected compound **2.38** as a colourless oil (209 mg, 0.57 mmol, 71%).

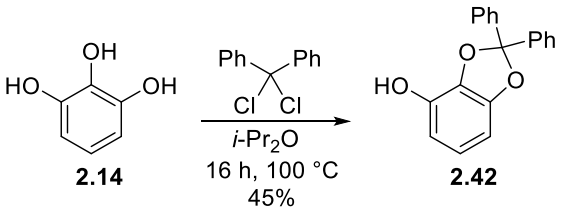
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78, (app. t, *J* = 8.2 Hz, 1H, Ar*H*), 6.62 (dd, *J* = 8.1, 1.6 Hz, 1H, Ar*H*), 6.52 (dd, 8.2, 1.6 Hz, 1H, Ar*H*), 5.48 (s, 1H, O*H*), 1.15-1.09 (m, 28H, 4 × C*H*(CH_3)$_2$, 24 × CH(C*H*$_3$)$_2$) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.1 (C), 144.8 (C), 133.1 (C), 122.0 (CH), 113.5 (CH), 108.4 (CH), 17.0 (8 × CH_3), 13.1 (4 × CH) ppm;

IR (Neat, cm^{-1}) 3241(br), 2945, 2868, 1587, 1491, 1468, 1358, 1290, 1225, 1188, 1052, 1011;

HRMS (ESI+) *m/z* = 369.1929 (calculated for $[M+H]^+$ ($C_{18}H_{33}O_4Si_2$) 369.1917).

5.2.7 – 2,2-Diphenylbenzo[1,3]dioxol-4-ol



Compound **2.42** was prepared using a modified literature procedure.[217] Dichlorodiphenylmethane (13.7 g, 11.5 mL, 57.7 mmol) was added to pyrogallol (**2.14**) (5.00 g, 38.2 mmol) in diisopropyl ether (600 mL) and the reaction mixture was heated at 100 °C for 30 min. The solvent was removed under vacuum, before purification by column chromatography (9:1 petroleum ether:ethyl acetate) to give protected compound **2.42** as a dark red/brown oil (5.02 g, 0.45 mmol, 45%).

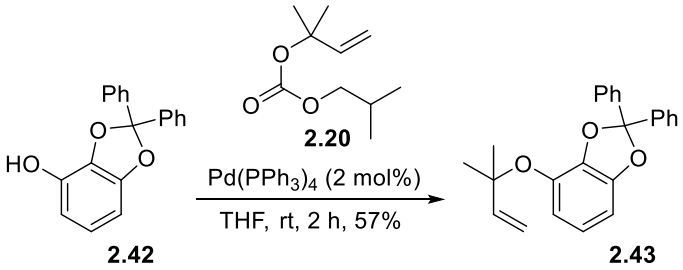
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63-7.58 (m, 4H, 4 × Ar*H*), 7.42-7.38 (m, 6H, 6 × Ar*H*), 6.75 (app. t, *J* = 8.1 Hz, 1H, Ar*H*), 6.56 (dd, *J* = 7.9, 1.0 Hz, 1H, Ar*H*), 6.51 (dd, *J* = 8.4, 1.0 Hz, 1H, Ar*H*), 4.75 (s, 1H, O*H*) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.2 (C), 140.0 (2 × C), 139.3 (C), 133.8 (C), 129.2 (2 × CH), 128.3 (4 × CH), 126.4 (4 × CH), 122.1 (CH), 117.3 (C), 110.8 (CH), 102.0 (CH) ppm;

IR (Neat, cm^{-1}) 3354(br), 3061, 1703.1, 1641, 1614, 1496, 1469, 1449, 1358, 1319, 1252, 1206, 1055, 1045, 1015;

HRMS (ESI+) *m/z* = 291.1028 (calculated for $[M+H]^+$ ($C_{19}H_{15}O_3$) 291.1021).

5.2.8 – 4-((2-Methylbut-3-en-2-yl)oxy)-2,2-diphenylbenzo[1,3]dioxole



Compound **2.43** was prepared using a modified literature procedure.[89] To a stirred solution of protected compound **2.42** (60 mg, 0.21 mmol) and isobutyl 2-methylbut-3-en-2-yl carbonate (**2.20**) (57 mg, 0.31 mmol), in THF (10 mL), tetrakis(triphenylphosphine)palladium(0) (4.8 mg, 4.1 μmol) was added. The mixture was stirred at room temperature for 2 h, then quenched with saturated aq. NH_4Cl (20 mL). The reaction mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (3 × 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate = 2:1) to give compound **2.43** (74 mg, 0.21 mmol, 57 %) as a light brown oil.

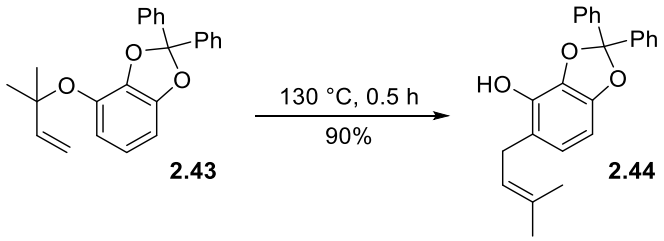
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63-7.59 (m, 4H, Ar*H*), 7.41-7.36 (m, 6H, Ar*H*), 6.70 (t, *J* = 8.1 Hz, 1H, Ar*H*), 6.66 (dd, *J* = 7.8. 1.5 Hz, 1H, Ar*H*), 6.59 (dd, *J* = 8.1, 1.5 Hz, 1H, Ar*H*), 6.17 (dd, *J* = 17.5, 10.9 Hz, 1H, *H*C=CH_2), 5.12 (dd, *J* = 17.5, 1.0 Hz, 1H, HC=C*H*$_a$H$_b$), 5.00 (dd, *J* = 10.9, 1.0 Hz, 1H, HC=CH$_a$*H*$_b$), 1.46 (s, 6H, 2 × C*H*$_3$) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5 (C), 143.8 (C), 140.4 (2 × C), 140.0 (CH), 139.0 (C), 129.0 (2 × CH), 128.1 (4 × CH), 126.4 (4 × CH), 120.8 (CH), 118.9 (CH), 117.4 (C), 113.5 (CH), 104.2 (CH_2), 81.4 (C), 26.6 (2 × CH_3) ppm;

IR (Neat, cm^{-1}) 2980, 1741, 1628, 1483, 1450, 1356, 1248, 1251, 1128, 1073, 1016;

HRMS (ESI+) *m/z* = 359.1619 (calculated for $[M+H]^+$ ($C_{24}H_{23}O_3$) 359.1647).

5.2.9 – 5-(3-Methylbut-2-en-1-yl)-2,2-diphenylbenzo[1,3]dioxol-4-ol



Compound **2.44** was prepared using a modified literature procedure.[89] Compound **2.43** (135 mg, 0.376 mmol) was heated neat to 130 ºC for 30 minutes, before being cooled to rt, then purified by column chromatography (8:1 petroleum ether:ethyl acetate) to afford the desired product **2.44** as a yellow oil (122 mg, 0.340 mmol, 90%).

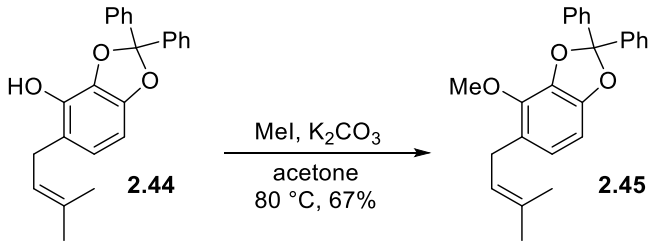
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62-7.59 (m, 4H, Ar*H*), 7.41-7.37 (m, 6H, Ar*H*), 6.59 (d, *J* = 8.0 Hz, 1H, Ar*H*), 6.46 (d, *J* = 8.0 Hz, 1H, Ar*H*), 5.31 (t, *J* = 7.2 Hz, 1H), 4.99 (s, 1H, O*H*), 3.30 (d, *J* = 7.2 Hz, 2H, CH_2), 1.53 (s, 6H, 2 × CH_3) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6 (C), 140.2 (2 × C), 137.9 (C), 133.7 (C), 129.1 (2 × CH), 128.2 (4 × CH), 126.4 (4 × CH), 122.7 (C), 122.4 (CH), 121.7 (CH), 118.4 (C), 117.4 (C), 101.1 (CH), 28.9 (CH_2), 25.8 (CH_3), 17.8 (CH_3) ppm;

IR (Neat, cm^{-1}) 3451(br), 2913, 1638, 1476, 1449, 1317, 1258, 1206, 1136, 1061, 1043, 1018, 947, 851, 760, 701, 640;

HRMS (ESI+) *m/z* = 359.1618 (calculated for $[M+H]^+$ ($C_{24}H_{23}O_3$) 359.1647).

5.2.10 – 4-Methoxy-5-(3-methylbut-2-en-1-yl)-2,2-diphenylbenzo[1,3]dioxole



Compound **2.45** was prepared according to a literature procedure.[218] Methyl iodide (0.350 mL, 5.58 mmol) was added to a stirred solution of **2.44** (100 mg, 0.279 mmol) and potassium carbonate (771 mg, 5.58 mmol) in acetone (15 mL), and the reaction heated to 80 °C for 2 hours. The mixture was cooled, filtered, then purified by column chromatography (10:1 petroleum ether:dichloromethane) to give methylated compound **2.45** as a clear oil (89 mg, 0.24 mmol, 67%).

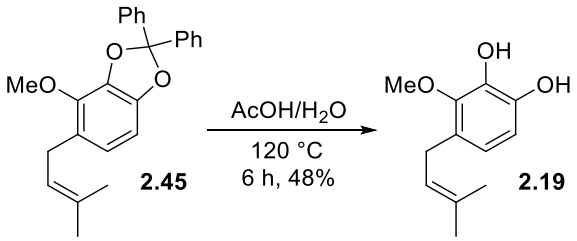
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63-7.59 (m, 4H, Ar*H*), 7.41-7.36 (m, 6H, Ar*H*), 6.60 (d, 1H, *J* = 8.0 Hz, 1H, Ar*H*), 6.53 (d, *J* = 8.0 Hz, 1H, Ar*H*), 5.24 (t, *J* = 7.3 Hz, 1H, *H*C=C), 4.08 (s, 3H, OCH_3), 3.24 (d, *J* = 7.3 Hz, 2H, CH_2), 1.73 (s, 3H, CH_3), 1.71 (s, 3H, CH_3) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.2 (C), 141.4 (C), 140.4 (2 × C), 136.4 (C), 131.9 (C), 129.0 (2 × CH), 128.2 (4 × CH), 127.1 (C), 126.4 (4 × CH), 123.1 (CH), 121.5 (CH), 116.6 (C), 102.5 (CH), 59.7 (CH_3), 28.5 (CH_2), 25.8 (CH_3), 17.7 (CH_3) ppm;

IR (Neat, cm^{-1}) 3205, 2912, 1628, 1470, 1449, 1375, 1360, 1256, 1207, 1070, 1045, 1020;

HRMS (ESI+) *m/z* = 373.1782 (calcd. for $[M+H]^+$ ($C_{25}H_{25}O_3$) 373.1804).

5.2.11 – 3-Methoxy-4-(3-methylbut-2-en-1-yl)benzene-1,2-diol



Compound **2.19** was prepared according to a literature procedure.[219] A solution of compound **2.45** (20 mg, 0.054 mmol) in glacial acetic acid (0.75 mL) and water (0.15 mL) was heated to reflux for 6 hours. After cooling, the mixture was concentrated under reduced pressure, before purification by column chromatography afforded the deprotected product **2.19** as a clear oil (11 mg, 0.053 mmol, 48%).

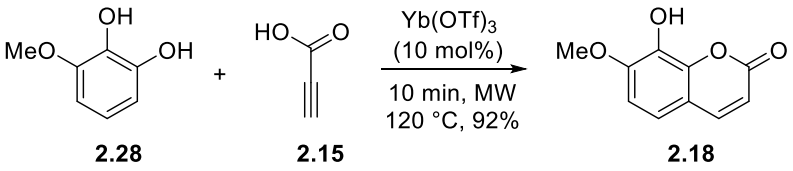
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (d, *J* = 8.4 Hz, 1H, Ar*H*), 6.63 (d, *J* = 8.4 Hz, 1H, Ar*H*), 5.27 (t, *J* = 7.3 Hz, 1H, *H*C=C), 3.83 (s, 3H, OCH_3), 3.30 (d, *J* = 7.3 Hz, 2H, CH_2), 1.73 (s, 3H, CH_3), 1.71 (s, 3H, CH_3) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.5 (C), 142.9 (C), 136.5 (C), 132.5 (C), 126.3 (C), 123.1 (CH) 120.6 (CH), 111.4 (CH), 61.3 (CH_3), 27.9 (CH_2), 25.9 (CH_3), 18.0 (CH_3) ppm;

IR (Neat, cm^{-1}) 3377(br), 2936, 1616, 1506, 1466, 1267, 1202, 1050, 986;

HRMS (ESI+) *m/z* = 208.1071 (calculated for $[M]^+$ ($C_{12}H_{16}O_3$) 208.1099).

5.2.12 – 8-Hydroxy-7-methoxy-2*H*-chromen-2-one



2.28 **2.15** **2.18**

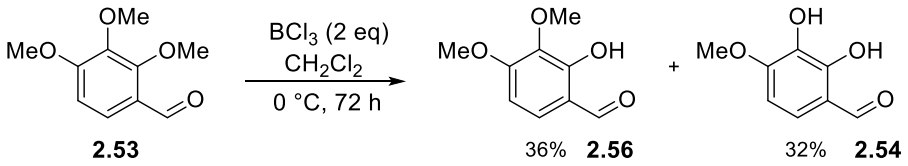
Compound **2.18** was prepared according to a modified literature procedure.[97] A sealed microwave tube containing a mixture of 3-methoxycatechol (**2.28**) (200 mg, 1.43 mmol), propiolic acid (**2.15**) (0.440 mL, 7.15 mmol), and $Yb(OTf)_3$ (88.7 mg, 0.143 mmol) was put in the MW apparatus and irradiated at 200 W (120 °C) for 10 min. The crude solid obtained was diluted with Et_2O and the resulting suspension filtered under vacuum to separate the catalyst, the precipitate washed several times with Et_2O. The filtrate was washed twice with a 5% aq. $NaHCO_3$ solution (10 mL) dried over $MgSO_4$ and evaporated to dryness under vacuum yielding the 7-methoxy-8-hydroxycoumarin (**2.18**) (253 mg, 1.32 mmol, 92%) as a light brown solid. All spectroscopic data matched literature values.[97]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 9.6 Hz, 1H, Ar*H*), 7.04 (d, *J* = 8.6 Hz, 1H, Ar*H*), 6.89 (d, *J* = 8.6 Hz, 1H, Ar*H*), 6.29 (d, *J* = 9.5 Hz, 1H, Ar*H*), 4.01 (s, 3H, OCH_3) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.2 (C), 149.6 (C), 143.8 (CH), 142.1 (C), 132.9 (C), 118.8 (CH), 113.7 (CH), 113.6 (C), 107.8 (CH), 56.6 (CH_3) ppm.

MP – 167-170 °C (Lit[221] 169-171 °C)

5.2.13 – 2-Hydroxy-3,4-dimethoxybenzaldehyde (2.56) and 2,3-dihydroxy-4-methoxybenzaldehyde (2.54)



2.53 36% **2.56** 32% **2.54**

The reaction was carried out according to a modified literature procedure.[100] Boron trichloride (1 M in CH_2Cl_2, 20.4 mL, 20.4 mmol) was added dropwise to a solution of trihydroxybenzaldehyde (**2.53**) (2.0 g, 10.2 mmol) in dichloromethane (40 mL) at 0 °C. The resulting mixture was stirred for 3 days at 0 °C to give a brown solution, before being quenched with water (40 mL) and extracted with dichloromethane (2 × 100 mL). The combined organic extracts were washed with brine (2 × 100 mL), dried (Na_2SO_4) and the solvent removed under vacuum to give a purple solid. This was purified by column chromatography (3:1 petroleum ether:EtOAc) to give two major products. **2.54** (0.55 g, 3.27 mmol, 32%) was isolated as a yellow/white solid, and **2.56** (0.67 g, 3.68 mmol, 36%), which was a white solid. All spectroscopic data matched literature values.[100]

2.56 - **^{1}H NMR** (500 MHz, $CDCl_3$) δ 11.21 (s 1H, O*H*), 9.78 (s, 1H, C*H*O), 7.31 (d, *J* = 8.7 Hz, 1H, Ar*H*), 6.63 (d, *J* = 8.7 Hz, 1H, Ar*H*), 3.98 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 194.9 (CH), 159.4 (C), 155.8 (C), 136.2 (C), 130.2 (CH), 116.6 (C), 104.0 (CH), 60.8 (CH_3), 56.3 (CH_3) ppm.

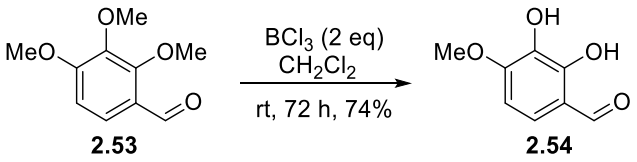
MP - 72-75 °C (lit[222] 70-80 °C)

2.54 - **^{1}H NMR** (500 MHz, $CDCl_3$) δ 11.13 (s, 1H, O*H*), 9.78 (s, 1H, C*H*O), 7.17 (d, *J* = 8.7 Hz, 1H, Ar*H*), 6.64 (d, *J* = 8.7 Hz, 1H, Ar*H*), 5.47 (s, 1H, O*H*), 4.01 (s, 3H, OCH_3) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 195.2 (CH), 153.0 (C), 149.1 (C), 133.1 (C), 126.1 (CH), 116.1 (C), 103.7 (CH), 56.4 (C) ppm.

MP - 90-91 °C (lit[100] 93-95 °C)

5.2.14 – 2,3-Dihydroxy-4-methoxybenzaldehyde



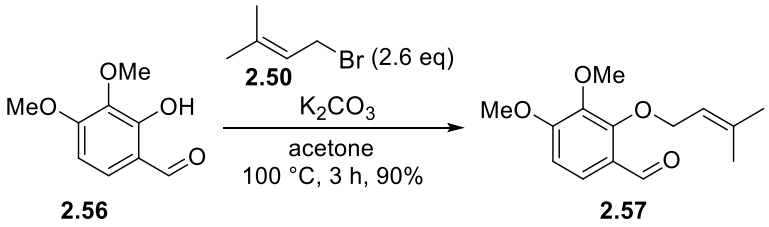
2.53 **2.54**

Boron trichloride (200 mL, 202.5 mmol) was added dropwise to a solution of trihydroxybenzaldehyde **2.53** (20.0 g, 102 mmol) in dichloromethane (600 mL) at 0 °C. The resulting mixture was stirred for 2 days at room temperature to give a brown solution, before being quenched with water (500 mL) and extracted with dichloromethane (2 × 600 mL). The combined organic extracts were washed with brine (2 × 500 mL), dried (Na_2SO_4) and the solvent removed under vacuum to give a purple solid. This was purified by column chromatography (3:1 petroleum ether:EtOAc) to give **2.54** (12.7 g, 75.5 mmol, 74 %), which was isolated as a yellow/white solid. All spectroscopic data matched literature values.[100]

2.54 - **^{1}H NMR** (500 MHz, $CDCl_3$) δ 11.13 (s, 1H, O*H*), 9.78 (s, 1H, C*H*O), 7.17 (d, *J* = 8.7 Hz, 1H, Ar*H*), 6.64 (d, *J* = 8.7 Hz, 1H, Ar*H*), 5.47 (s, 1H, O*H*), 4.01 (s, 3H, OCH_3) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 195.2 (CH), 153.0 (C), 149.1 (C), 133.1 (C), 126.1 (CH), 116.1 (C), 103.7 (CH), 56.4 (C) ppm.

5.2.15 – 3,4-Dimethoxy-2-((3-methylbut-2-en-1-yl)oxy)benzaldehyde

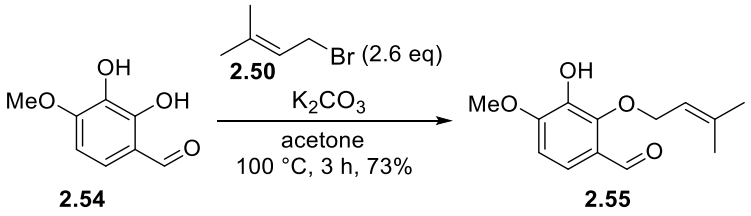


Compound **2.57** was prepared according to a literature procedure.[99] Prenyl bromide (**2.50**) (0.825 mL, 1.79 mmol) was added dropwise to a stirred solution of compound **2.56** (500 mg, 2.74 mmol) and potassium carbonate (470 mg, 3.40 mmol) in acetone (30 mL), and the mixture heated to reflux for 3 hours. The resulting dark yellow solution was filtered and the solvent removed under vacuum, before the resulting solid was taken up in Et_2O (10 mL), washed with NaOH (2M, 10 mL) and water (10 mL). Drying with Na_2SO_4, and evaporation of solvent under vacuum gave compound **2.57** as a yellow solid (617 mg, 2.46 mmol, 90%). All spectroscopic data matched literature values.[99]

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.26 (s, 1H, C*H*O), 7.63 (d, *J* = 8.8 Hz, 1H, Ar*H*), 6.78 (d, *J* = 8.8 Hz, 1H, Ar*H*), 5.54 (t, *J* = 7.5 Hz, 1H, *H*C=C), 4.72 (d, *J* = 7.5 Hz, 2H, CH_2), 3.96 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 1.78 (s, 3H, CH_3), 1.69 (s, 3H, CH_3) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 189.2 (CH), 159.0 (C), 155.9 (C), 142.0 (C), 140.0 (C), 124.2 (C), 119.9 (CH), 119.4 (CH), 107.5 (CH), 71.1 (CH_2), 60.9 (CH_3), 56.2 (CH_3), 25.8 (CH_3), 18.0 (CH_3) ppm.

5.2.16 – 3-Hydroxy-4-methoxy-2-((3-methylbut-2-en-1-yl)oxy)benzaldehyde



Compound **2.55** was prepared according to a modified literature procedure.[99] Prenyl bromide (**2.50**) (4.80 mL, 41.6 mmol) was added dropwise to a stirred solution of compound **2.54** (7.00 g, 41.6 mmol) and potassium carbonate (5.7 g, 41.6 mmol) in acetone (400 mL), and the mixture heated to reflux for 3 hours. The resulting dark yellow solution was filtered and the solvent removed under vacuum, before purification by column chromatography (4:1 petroleum ether:EtOAc) to give compound **2.55** as a yellow solid (7.12 g, 30.2 mmol, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.24 (s, 1H, C*H*O), 7.44 (d, *J* = 8.7 Hz, 1H, Ar*H*), 6.77 (d, *J* = 8.7 Hz, 1H, Ar*H*), 5.68 (s, 1H, O*H*), 5.56 (t, *J* = 7.5 Hz, 1H, *H*C=C) 4.72 (d, *J* = 7.5 Hz, 2H, CH_2) 3.99 (s, 3H, OCH_3), 1.78 (s, 3H, CH_3), 1.67 (s, 3H, CH_3) ppm;

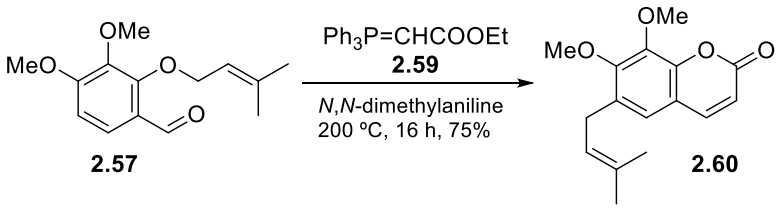
^{13}C NMR (126 MHz, $CDCl_3$) δ 189.3 (CH), 152.6 (C), 148.7 (C), 140.5 (C), 138.5 (C), 124.0 (C), 120.3 (CH), 119.3 (CH), 106.5 (CH), 71.0 (CH_2), 56.4 (CH_3), 25.8 (CH_3), 18.0 (CH_3) ppm;

IR (Neat, cm^{-1}) 3173(br), 2970, 2937, 1661, 1587, 1572, 1497, 1462, 1281, 1244, 1221, 1080;

HRMS (ESI+) *m/z* = 237.1121 (calculated for $[M+H]^+$ ($C_{13}H_{17}O_4$) 237.1127);

MP 63–66 °C.

5.2.17 – 7,8-Dimethoxy-6-(3-methylbut-2-en-1-yl)-2*H*-chromen-2-one

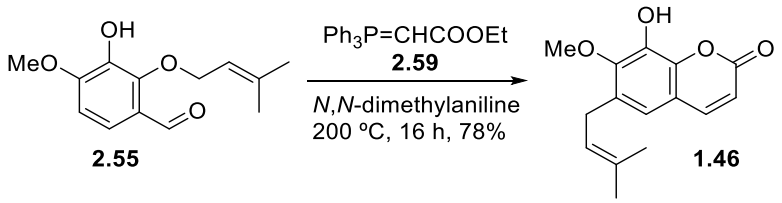


Compound **2.60** was prepared according to a literature procedure.[99] A solution of prenylated compound **2.57** (50 mg, 0.21 mmol), and phosphorane **2.59** (84 mg, 0.24 mmol) was heated for 12 hours at 200 °C in *N,N*-dimethylaniline (4 mL). The resulting dark brown solution was cooled, and the solvent removed under vacuum, before water (10 mL) and ethyl acetate (10 mL) were added. The aqueous layer was further extracted by EtOAc (2 × 10 mL), before the combined organic extracts were washed with HCl (1M, 10 mL) and water (10 mL), dried (Na_2SO_4) and the solvent removed under vacuum, to give the crude product **2.60** as a brown oil (43.2 mg, 0.16 mmol). All spectroscopic data matched literature values.[99]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (d, *J* = 9.5 Hz, 1H, Ar*H*), 6.85 (s, 1H, Ar*H*) 6.31 (d, *J* = 9.5 Hz, 1H, Ar*H*), 5.26 (t, *J* = 7.5 Hz, 1H, *H*C=C), 4.03 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 3.35 (d, *J* = 7.5 Hz 2H, CH_2), 1.78 (d, *J* = 1.3 Hz, 3H, CH_3), 1.74 (s, 3H, CH_3) ppm;

^{13}C NMR (151 MHz, $CDCl_3$) δ 160.5 (C), 146.9 (C), 143.7 (CH), 140.0 (C), 133.4 (C), 131.9 (C), 129.6 (C), 122.1 (CH), 121.9 (CH), 115.3 (C), 114.4 (CH), 61.4 (CH_3), 59.3 (CH_3) 28.4 (CH_2), 25.8 (CH_3), 16.2 (CH_3) ppm.

5.2.18 – 8-Hydroxy-7-methoxy-6-(3-methylbut-2-en-1-yl)-2*H*-chromen-2-one



Compound **1.46** was prepared according to a modified literature procedure.[99] A solution of prenylated compound **2.55** (5.00 g, 21.2 mmol), and phosphorane **2.59** (8.30 g, 23.8 mmol) was heated for 12 hours at 200 °C in *N,N*-dimethylaniline (250 mL). The resulting dark brown solution was cooled, and the solvent removed under vacuum, before water (200 mL) and ethyl acetate (200 mL) were added. The aqueous layer was further extracted by EtOAc (2 × 200 mL), before the combined organic extracts were washed with HCl (1M, 200 mL) and water (200 mL), dried (Na_2SO_4) and the solvent removed under vacuum, to give the crude product as a brown oil. Column chromatography was carried out, to give brosiparin (**1.46**) (4.31 g, 16.55 mmol, 78%) as an off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 9.5 Hz, 1H, Ar*H*), 6.85 (s, 1H, Ar*H*), 6.32 (d, *J* = 9.5 Hz, 1H, Ar*H*), 5.99 (s, 1H, O*H*), 5.28 (t, *J* = 7.2, 1H, *H*C=C), 3.99 (s, 3H, OCH_3), 3.39 (d, *J* = 7.2 Hz, 2H, CH_2) 1.78 (s, 3H, CH_3) 1.75 (s, 3H, CH_3) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.1 (C), 148.1 (C), 144.0 (CH), 141.4 (C), 136.2 (C), 133.5 (C), 131.9 (C), 121.9 (CH), 118.4 (CH), 114.7 (C), 114.4 (CH), 60.9 (CH_3), 28.3 (CH_2), 25.8 (CH_3), 17.9 (CH_3) ppm;

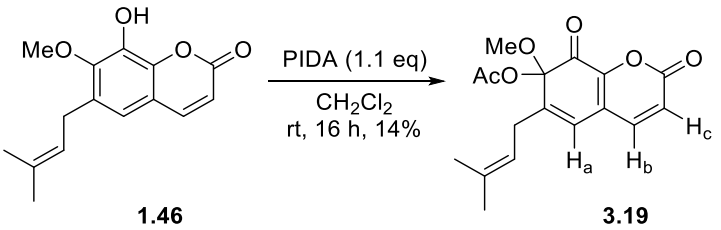
IR (Neat, cm^{-1})3363(br), 3092, 2990, 2911, 2832, 1711, 1607, 1570, 1447, 1418, 1257, 1180, 1087, 995;

HRMS (ESI+) *m/z* = 261.1121 (calculated for $[M+H]^+$ ($C_{15}H_{17}O_4$) 261.1127);

MP 74–76 °C

5.3 – Chapter 3 Experimental Procedures

5.3.1 - 7-Methoxy-6-(3-methylbut-2-en-1-yl)-2,8-dioxo-7,8-dihydro-2*H*-chromen-7-yl acetate



1.46 **3.19**

The reaction was carried out using a modified literature procedure.[123] (Diacetoxy)iodobenzene (372 mg, 1.15 mmol) was added to a solution of brosiparin (**1.46**) (200 mg, 0.77 mmol) in dichloromethane (8 mL) at room temperature, and the reaction stirred for 16 hours. The resulting red/brown solution was quenched with saturated aq. $NaHCO_3$ (10 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried with Na_2SO_4, filtered and the solvent removed under vacuum. Purification by column chromatography (6:1 petroleum ether:EtOAc) gave compound **3.19** as a brown oil (51 mg, 0.16 mmol, 14%).[123]

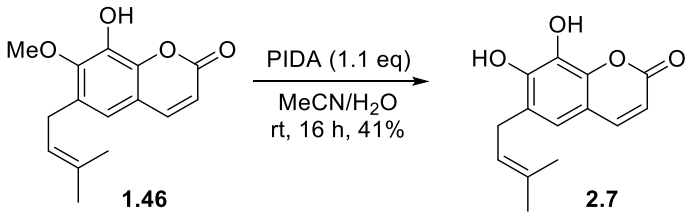
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, J = 9.5 Hz, 1H, H_b), 6.63 (d, J = 9.5 Hz, 1H, H_c), 6.07 (t, J = 1.9 Hz, 1H, H_a), 5.19 (ddp, J = 7.2, 5.7, 1.4 Hz, 1H, HC=C), 3.47 (s, 3H, OCH_3), 2.99 (dd, J = 18.1, 7.2 Hz, 1H, CH_aH$_b$), 2.87 (dd, J = 18.1, 7.2, Hz, 1H, CH$_a$$H_b$), 2.14 (s, 3H, OC(O)C$H_3$), 1.80 (d, J = 1.4 Hz, 3H, CH_3), 1.65 (s, 3H, CH_3) ppm;

^{13}C NMR (150 MHz, $CDCl_3$) δ 183.1 (C), 169.8 (C), 158.6 (C), 145.1 (C), 142.4 (CH), 137.4 (C), 135.9 (C), 123.3 (CH), 122.1 (C), 118.8 (CH), 118.5 (CH), 95.1 (C), 51.2 (CH_3), 28.4 (CH_2), 25.8 (CH_3), 20.3 (CH_3), 17.7 (CH_3) ppm;

IR (Neat, cm^{-1}) 3370, 1713, 1624, 1572, 1449, 1408, 1335, 1123, 910;

HRMS (ESI+) *m/z* = 319.1170 (calculated for $[M+H]^+$ ($C_{17}H_{18}O_6$) 319.1182).

5.3.2 – 7,8-Dihydroxy-6-(3-methylbut-2-en-1-yl)-2*H*-chromen-2-one



1.46 2.7

The reaction was carried out according to a modified literature procedure.[124] (Diacetoxy)iodobenzene (142 mg, 0.440 mmol) was added to a solution of brosiparin (**1.46**) (100 mg, 0.400 mmol) in acetonitrile:water (1:1, 4 mL) at room temperature, and the reaction stirred for 16 hours. The resulting red/brown solution was quenched with saturated aq. $NaHCO_3$ (5 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried with Na_2SO_4, filtered and the solvent removed under vacuum. Purification by column chromatography (4:1 petroleum ether:EtOAc) gave compound (**2.7**) as a white solid (44 mg, 0.18 mmol, 41%). All spectroscopic data matched literature values.[125]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 9.5 Hz, 1H, Ar*H*), 6.85 (s, 1H, Ar*H*), 6.22 (d, *J* = 9.5 Hz, 1H, Ar*H*), 5.33 (t, *J* = 7.3 Hz, 1H, *H*C=C), 3.39 (d, *J* = 7.3 Hz, 2H, CH_2), 1.79 (s,, 3H, CH_3), 1.75 (s, 3H, CH_3) ppm;

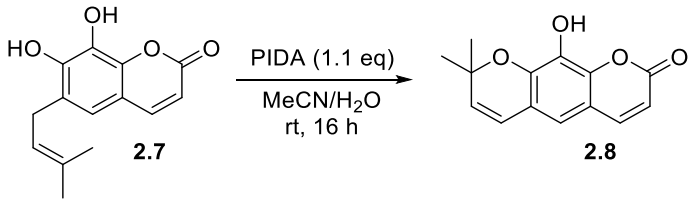
^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9 (C), 145.9 (C), 144.8 (CH), 141.0 (C), 133.9 (C), 129.6 (C), 125.5 (C), 121.2 (CH), 119.0 (CH), 112.1 (CH), 111.3 (C) 27.9 (CH_2), 25.8 (CH_3), 17.8 (CH_3) ppm;

IR (Neat, cm^{-1}) 3345(br), 1685, 1625, 1605, 1582, 1508;

HRMS (ESI+) *m/z* = 247.0965 (calculated for $[M+H]^+$ ($C_{14}H_{15}O_4$) 247.0971).

MP – 162-164 °C (Lit[99] 161.7-161.9 °C)

5.3.3 – 10-Hydroxy-8,8-dimethyl-2*H*,8*H*-pyrano[3,2-g]chromen-2-one



The reaction was carried out using a modified literature procedure.[124] (Diacetoxy)iodobenzene (17 mg, 0.053 mmol) was added to a solution of demethylbrosiparin **2.7** (12 mg, 0.049 mmol) in dichloromethane (0.5 mL) at room temperature, and the reaction stirred for 16 hours. The resulting red/brown solution was quenched with saturated aq. $NaHCO_3$ (1 mL) and extracted with ethyl acetate (2 × 2 mL). The combined organic layers were dried with Na_2SO_4, filtered and the solvent removed under vacuum to give compound **2.8** as a brown oil (7 mg). The material was not fully purified, but the spectra obtained were enough to fully characterise the compound.

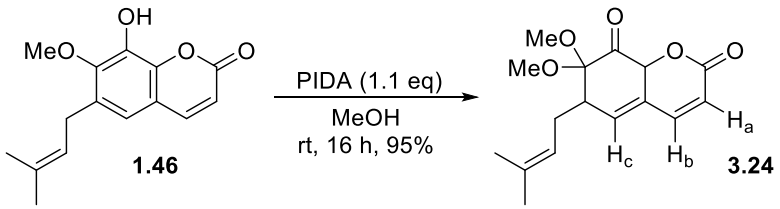
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 9.5 Hz, 1H, Ar*H*), 6.72 (s, 1H, Ar*H*), 6.36 (d, *J* = 10.0 Hz, 1H, Ar*H*), 6.26 (d, *J* = 9.5 Hz, 1H, Ar*H*), 5.72 (d, *J* = 10.0 Hz, 1H, Ar*H*), 1.51 (s, 6H, 2 × C*H*$_3$) ppm;
(Impurities present at 7.75, 7.31 and 7.12 ppm due to iodobenzene)

^{13}C NMR (125 MHz, $CDCl_3$) δ 160.3 (C), 143.9 (CH), 143.1 (C), 142.7 (C), 132.0 (C), 131.2 (CH), 121.0 (CH), 118.3 (C), 115.5 (CH), 113.2 (CH), 112.8 (C), 78.3 (C), 28.3 (2 × CH_3) ppm;
(Impurites present at 137.6, 130.4, 127.6, 94.7 due to iodobenzene)

IR (Neat, cm^{-1}) 3395(br), 2922, 2853, 1717, 1651, 1620, 1582, 1452, 1234, 1134, 1038;

HRMS (ESI+) *m/z* = 245.0819 (calculated for $[M+H]^+$ ($C_{14}H_{13}O_4$) 245.0814)

5.3.4 – 7,7-Dimethoxy-6-(3-methylbut-2-en-1-yl)-2*H*-chromene-2,8(7*H*)-dione



The reaction was carried out using a modified literature procedure.[126] (Diacetoxy)iodobenzene (6.80 g, 21.2 mmol) was added to a solution of brosiparin **1.46** (5 g, 19.3 mmol) in methanol (200 mL) at room temperature, and the reaction stirred for 16 hours. The resulting red/brown solution was quenched with saturated aq. $NaHCO_3$ (250 mL) and extracted with ethyl acetate (2 × 250 mL). The combined organic layers were dried with Na_2SO_4, filtered and the solvent removed under vacuum. Purification by column chromatography (6:1 petroleum ether:EtOAc) gave compound **3.24** as a light brown solid (5.31 g, 18.3 mmol, 95%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, J = 9.5 Hz, 1H, H_b), 6.65 (d, J = 9.5 Hz, 1H, H_a), 6.12 (t, J = 2.0 Hz, 1H, H_c), 5.26 (t, J = 7.3 Hz, 1H, HC=C), 3.29 (s, 6H, 2 × OCH_3), 3.01 (dt, J = 7.3, 2.0 Hz, 2H, CH_2), 1.84 (s, 3H, CH_3), 1.68 (s, 3H, CH_3) ppm;

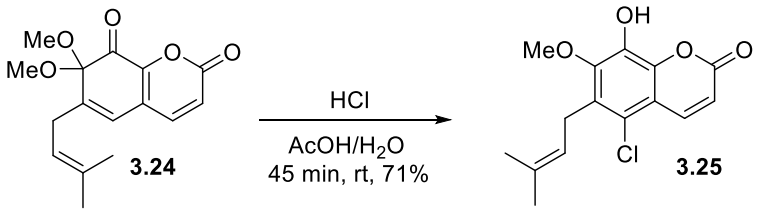
^{13}C NMR (150 MHz, $CDCl_3$) δ 187.3 (C), 158.4 (C), 148.0 (C), 145.0 (C), 142.3 (CH), 135.8 (C), 123.6 (CH), 122.4 (C), 119.3 (CH), 118.8 (CH), 95.4 (C), 51.0 (2 × CH_3), 27.9 (CH_2), 25.8 (CH_3), 17.8 (CH_3) ppm;

IR (Neat, cm^{-1}) 3418, 1771, 1744, 1682, 1406, 1373, 1342, 1246, 1211, 1190, 1155, 1128, 1105, 1088;

HRMS (ESI+) m/z = 291.1239 (calculated for $[M+H]^+$ ($C_{16}H_{19}O_5$) 291.1227);

MP – 88 °C (degradation).

5.3.5 – 5-Chloro-8-hydroxy-7-methoxy-6-(3-methylbut-2-en-1-yl)-2*H*-chromen-2-one



The reaction was carried out using a modified literature procedure.[225] One drop of concentrated HCl was added to a solution of oxidised compound **3.24** (200 mg, 0.689 mmol) in acetic acid (2 mL) and water (2-3 drops) and the reaction stirred at room temperature for 45 minutes, before the mixture was poured into ice water, and the resulting white precipitate filtered to give a crude mixture of compounds. These were subsequently separated by column chromatography (5:1 petroleum ether:EtOAc) to give compound **3.25** as an off-white solid (144 mg, 0.489 mmol, 71 %).

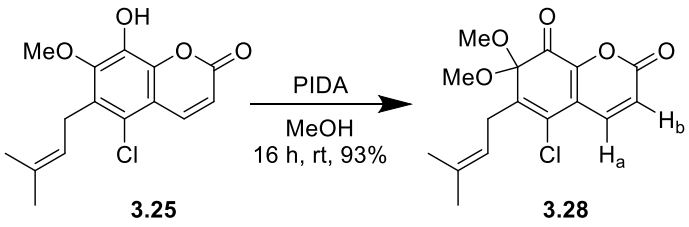
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (d, *J* = 9.8 Hz, 1H, Ar*H*), 6.40 (d, *J* = 9.8 Hz, 1H, Ar*H*), 5.13 (t, *J* = 6.9 Hz, 1H, *H*C=C), 4.00 (s, 3H, OCH_3), 3.56 (d, *J* = 6.9 Hz, 2H, CH_2), 1.83 (s, 3H, CH_3), 1.72 (s, 3H, CH_3) ppm;

^{13}C NMR (150 MHz, $CDCl_3$) δ 159.3 (C), 148.4 (C), 141.96 (C), 141.20 (CH), 135.34 (C), 133.05 (C), 130.77 (C), 121.31 (C), 120.74 (CH), 114.91 (CH), 112.23 (C), 61.21 (CH_3), 27.01 (CH_2), 25.74 (CH_3), 18.04 (CH_3) ppm;

IR (Neat, cm^{-1}) 3423(br), 2974, 2920, 1669, 1584, 1458, 1373, 1306, 1198, 1155, 997;

HRMS (ESI+) *m/z* = 295.0716 (calculated for $[M+H]^+$ $C_{15}H_{16}ClO_4$ 295.0737)

5.3.6 – 5-Chloro-7,7-dimethoxy-6-(3-methylbut-2-en-1-yl)-2*H*-chromene-2,8(7*H*)-dione



3.25 **3.28**

The reaction was carried out using a modified literature procedure.[126] (Diacetoxy)iodobenzene (126 mg, 0.39 mmol) was added to a solution of para-substituted brosiparin derivative **3.25** (100 mg, 0.36 mmol) in methanol (10 mL) at room temperature, and the reaction stirred for 45 minutes. The resulting dark red/brown solution was quenched with saturated aq. $NaHCO_3$ (10 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried with Na_2SO_4, filtered and the solvent removed under vacuum. Purification by column chromatography (3:1 petroleum ether:EtOAc) gave compound **3.28** as a light brown oil (102 mg, 0.33 mmol, 93%).

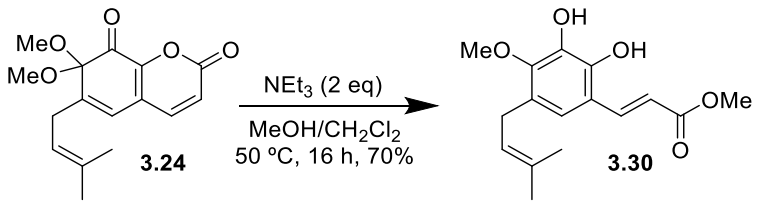
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 9.8 Hz, 1H, H_a), 6.71 (d, *J* = 9.8 Hz, 1H, H_b), 5.23 (t, *J* = 7.1 Hz, 1H, *H*C=C), 3.27 (s, 6H, 2 × OCH_3), 3.21 (d, *J* = 7.1 Hz, 2H, CH_2), 1.76 (d, *J* = 1.3 Hz, 6H, 2 × CH_3) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 185.4 (C), 157.8 (C), 145.4 (C), 142.2 (C), 139.9 (CH), 134.0 (CH), 124.8 (C), 122.9 (CH), 121.7 (C), 118.6 (CH), 96.3 (C), 51.4 (2 × CH_3), 28.3 (CH_2), 25.7 (CH_3), 18.0 (CH_3) ppm;
(Minor impurities between 20-35 ppm likely due to hexane)

IR (Neat, cm^{-1}) 3441, 1621, 1601, 1443, 1369, 1148, 1132, 980;

HRMS (ESI+) *m/z* = 347.0636 (calculated for $[M+Na]^+$ ($C_{16}H_{17}ClO_5Na$) 347.0662).

5.3.7 – Methyl (*E*)-3-(2,3-dihydroxy-4-methoxy-5-(3-methylbut-2-en-1-yl)phenyl) acrylate



Compound **3.30** was prepared using a modified literature procedure.[29] Compound **3.24** (50 mg, 0.172 mmol) was dissolved in a mixture of methanol and dichloromethane (1:1, 2 mL), before the slow addition of triethylamine (0.48 µL, 0.345 mmol). The resulting mixture was heated at 50 °C for 16 hours, before being cooled and quenched by addition of NH_4Cl (10 mL). The aqueous layer was extracted with dichloromethane (3 × 10 mL), dried (Na_2SO_4), filtered and the solvent removed under vacuum to afford a compound **3.30** as a red/brown oil. The material was not fully purified, but the spectra obtained were enough to characterise the compound.

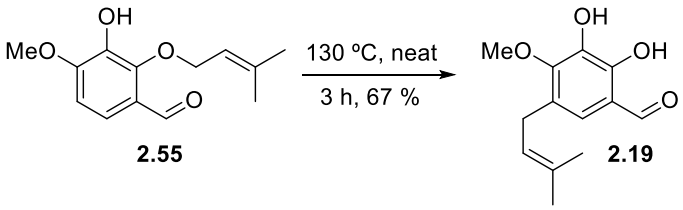
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, *J* = 16.1 Hz, 1H, *H*C=CH), 6.82 (s, 1H, Ar*H*), 6.53 (d, *J* = 16.1 Hz, 1H, HC=C*H*), 5.27 (t, *J* = 7.3 Hz) 1H, HC=C(CH_3)$_2$), 3.85 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.30 (d, *J* = 7.3 Hz, CH_2) 1.76 (d, *J* = 1.4 Hz, 6H, 2 × CH_3), 1.74 (s, 3H, CH_3) ppm;

^{13}C NMR (150 MHz, $CDCl_3$) δ 168.1 (C), 148.8 (C), 144.7 (C), 140.1 (CH), 136.2 (C), 133.1 (C), 126.1 (C), 122.4 (CH), 121.0 (CH), 117.9 (CH) 117.8 (C), 61.3 (CH_3), 51.6 (CH_3), 27.7 (CH_2), 25.8 (CH_3), 17.9 (CH_3) ppm;

IR (Neat, cm^{-1}) 3365(br), 2976, 2928, 1691, 1612, 1490, 1368, 1263, 1175, 1034, 945;

HRMS (ESI+) *m/z* = 293.1366 (calculated for $[M+H]^+$ ($C_{16}H_{21}O_5$) 293.1389)

5.3.8 – 2,3-Dihydroxy-4-methoxy-5-(3-methylbut-2-en-1-yl)benzaldehyde



2.55 **2.19**

Compound **2.19** was prepared using a modified literature procedure.[89] *O*-prenylated compound **2.55** (10.0 g, 42.0 mmol, neat) was heated to 130 °C for 3 hours, with the reaction followed by TLC, before being cooled to RT and the resulting dark red/brown solid purified by column chromatography (4:1 hexane:ethyl acetate) to afford the desired product **2.19** (6.62 g, 28.1 mmol, 67%) as a clear/yellow oil.

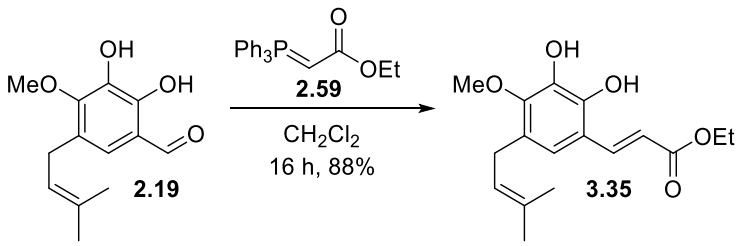
^{1}H NMR (500 MHz, $CDCl_3$) δ 11.16 (s, 1H, O*H*), 9.77 (s, 1H, C*H*O), 6.94 (s, 1H, Ar*H*), 5.53 (s, 1H, O*H*), 5.27 (t, *J* = 7.3 Hz 1H, *H*C=C), 4.04 (s, 3H, OCH_3), 3.31 (d, *J* = 7.3 Hz, 2H, CH_2), 1.78 (s, 3H, CH_3), 1.74 (s, 3H_3) ppm;

^{13}C NMR (150 MHz, $CDCl_3$) δ 195.6 (CH), 151.5 (C), 148.6 (C), 136.6 (C), 133.3 (C), 127.1 (C), 124.2 (CH), 122.05 (CH), 116.3 (C), 60.5 (CH_3), 28.0 (CH_2), 25.8 (CH_3), 17.8 (CH_3) ppm.
(Impurity at 30.9 ppm due to acetone)

IR (Neat, cm^{-1}) 3420(br), 2930, 2858, 1645, 1506, 1452, 1310, 1276, 1248, 1105;

HRMS (ESI+) *m/z* = 237.1133 (calculated for $[M+H]^+$ ($C_{13}H_{17}O_4$) 237.1121).

5.3.9 – Ethyl (*E*)-3-(2,3-dihydroxy-4-methoxy-5-(3-methylbut-2-en-1-yl)phenyl) acrylate



Compound **3.35** was prepared using a modified literature procedure.[224] Aldehyde **2.19** (4.50 g, 19.08 mmol) was dissolved in dry dichloromethane (250 mL), before the addition of phosphorane **2.59** (7.32 g, 21.0 mmol**)**. The reaction was stirred at room temperature for 16 hours, before the solvent was removed under vacuum, and the resulting residue purified by column chromatography (3:1 petroleum ether:ethyl acetate) to give compound **3.35** (5.13 g, 17.1 mmol, 88%) as a red/brown oil.

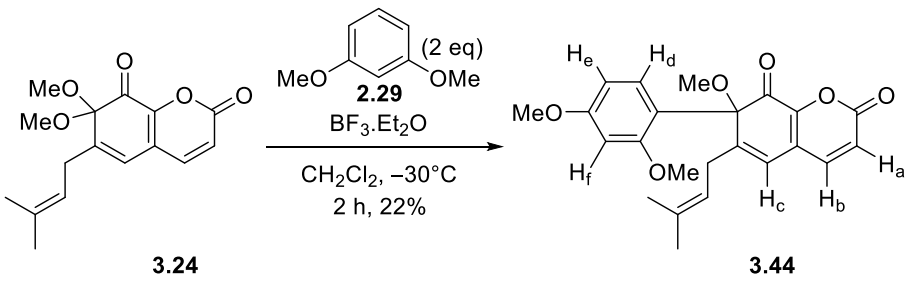
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, *J* = 16.1 Hz, 1H, *H*C=CH), 6.86 (s, 1H, Ar*H*), 6.58 (d, *J* = 16.1 Hz, 1H, HC=C*H*), 5.72 (s, 1H, O*H*), 5.55 (s, 1H, O*H*), 5.26 (t, *J* = 7.3 Hz, 1H, *H*C=C$(CH_3)_2$), 4.28 (q, *J* = 7.1 Hz, 2H, C$H_2$$CH_3$), 3.84 (s, 3H, OC$H_3$), 3.30 (d, *J* = 7.3 Hz, 2H, CH_2), 1.78 (d, *J* = 1.3 Hz, 3H, CH_3), 1.75 (s, 3H, CH_3), 1.36 (t, *J* = 7.1 Hz, 3H, CH_2CH_3) ppm;

^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8 (C), 146.7 (C), 142.9 (C), 139.9 (CH), 136.3 (C), 133.1 (C), 126.2 (C), 122.3 (CH), 120.9 (CH), 118.2 (CH), 117.8 (C), 61.3 (CH_2), 60.4 (CH_3), 27.7 (CH_2), 25.8 (CH_3), 17.9 (CH_3), 14.4 (CH_3) ppm;

IR (Neat, cm^{-1}) 3366(br), 2976, 2932, 1690, 1612, 1497, 1462, 1368, 1263, 1175, 1131, 1034, 988;

HRMS (ESI+) *m/z* = 307.1499 (calculated for $[M+H]^+$ ($C_{17}H_{23}O_5$) 307.1540).

5.3.10 – 7-(2,4-Dimethoxyphenyl)-7-methoxy-6-(3-methylbut-2-en-1-yl)-2*H*-chromene-2,8(7*H*)-dione



3.24 **3.44**

The reaction was carried out using a modified literature procedure.[143] Masked *ortho*-quinone **3.24** (25 mg, 0.086 mmol) was dissolved in dry CH_2Cl_2 (2 mL), then 1,3-dimethoxybenzene (25 µL, 0.172 mmol) and $BF_3.Et_2O$ (21 µL, 0.172 mmol) were added at −30 °C. The mixture was stirred at this temperature for 2 hours, and followed by TLC, during which time a colour change from yellow to red was observed. The reaction was quenched with saturated aq. $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (2 × 10 mL), before being dried (Na_2SO_4), filtered and the solvent removed under vacuum. This afforded a crude residue which was purified by column chromatography (2:1 petroleum ether:EtOAc) to give compound **3.44** (7.5 mg, 0.019 mmol, 22%) as a red/brown oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.7 Hz, 1H, H_d), 7.47 (d, *J* = 9.6 Hz, 1H, H_b), 6.65 (d, *J* = 9.5 Hz, 1H, ArH_a), 6.58 (dd, 8.7, 2.4, 1H, ArH_e), 6.35 (d, *J* = 2.4 Hz, 1H, ArH_f), 6.24 (t, *J* = 1.8 Hz, 1H, H_c) 5.06 (ddp, *J* = 7.5, 5.8, 1.4 Hz, 1H, *H*C=C$(CH_3)_2$), 3.82 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.25 (s, 3H, OCH_3), 2.80 (dd, *J* = 18.2, 7.5 Hz, 1H, CH_aH$_b$), 2.46 (dd, *J* = 18.2, 7.5 Hz, 1H, CH$_a$$H_b$), 1.74 (d, *J* = 1.4 Hz, 3H, CH_3), 1.50 (s, 3H, CH_3) ppm;

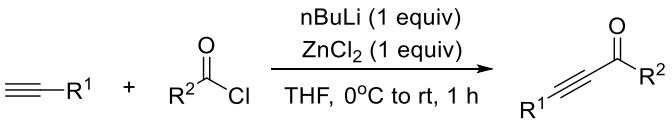
^{13}C NMR (150 MHz, $CDCl_3$) δ ppm; 193.2 (C), 106.7 (C), 159.1 (C), 155.8 (C), 147.5 (C), 146.9 (C), 143.0 (CH), 134.9 (C), 128.6 (CH), 122.6 (C), 122.3 (CH), 121.6 (C), 119.6 (CH), 118.7 (CH), 105.0 (CH), 98.8 (CH), 81.3 (C), 55.6 (CH_3), 55.4 (CH_3), 51.8 (CH_3), 29.0 (CH_2), 25.7 (CH_3), 17.6 (CH_3) ppm;

IR (Neat, cm^{-1}) 2922, 2853, 1730, 1611, 1452, 1439, 1259, 1207, 907;

HRMS (ESI+) *m/z* = 397.1632 (calculated for $[M+H]^+$ ($C_{23}H_{25}O_6$) 397.1646).

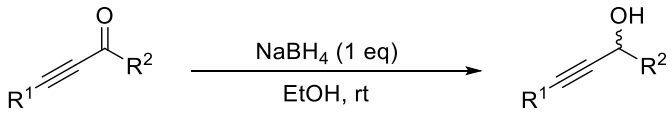
5.4 – Chapter 4 Experimental Procedures

5.4.1 - General Procedure for the synthesis of propargylic ketones



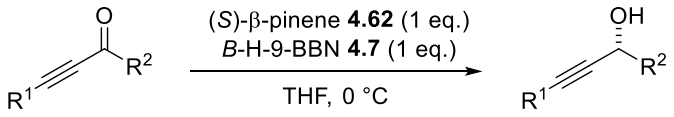
Propargylic ketones were synthesised according to the following modified literature procedure.[206] A solution of the terminal alkyne (20 mmol, 1 equiv.) in THF (100 mL), was cooled to −78 °C under an argon atmosphere, before *n*-BuLi (15 mL, 1.6 M, 20 mmol, 1 equiv.) was added dropwise using a syringe over approximately 5 minutes. The mixture was allowed to warm to 0 °C and stirred for 40 minutes, before being cooled to −78 °C and zinc(II) chloride (28 mL, 0.7 M, 20 mmol, 1 equiv) added dropwise using a syringe over approximately 10 minutes. The mixture was allowed to warm to room temperature over 15 minutes, before being cooled to −78 °C and acyl chloride (20 mmol, 1 equiv.) added in a dropwise fashion. The solution was then warmed to room temperature and stirred for 1 hour, then diluted with n-hexane (25 mL) and washed with NaOH (2 M in H_2O, 25 mL) and brine (3 x 25 mL). Subsequent drying with $MgSO_4$, filtration and concentration under vacuum afforded the crude propargylic ketone, which was purified by flash column chromatography.

5.4.2 - General Procedure for preparation of racemic propargylic alcohols



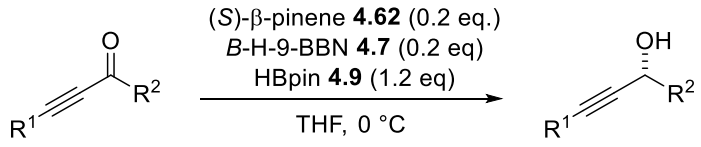
The relevant propargylic ketone substrate (0.5 mmol, 1 equiv) and $NaBH_4$ (0.5 mmol, 1 equiv) were stirred in ethanol (2 mL) at room temperature for 2.5 hours and the reaction followed by TLC. The reaction was quenched with water (2 mL) and extracted with ethyl acetate (2 × 5 mL). The crude product was purified by flash column chromatography, and the pure sample analysed by HPLC to provide reference retention times.

5.4.3 - General Procedure for stoichiometric hydroboration of propargylic ketones



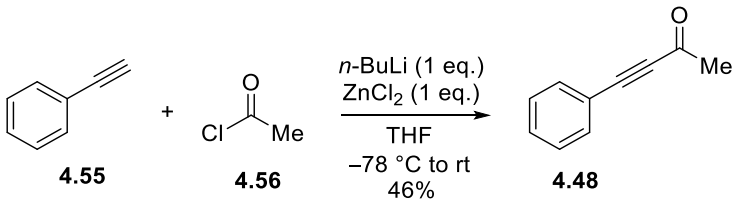
Stoichiometric reduction of propargylic ketones was carried out using the optimised *B*-H-9-BBN procedure. (1 mL, 0.5 M, 0.5 mmol, 1 equiv) and (*S*)-β-pinene (78 µl, 0.5 mmol, 1 equiv) were stirred under argon at room temperature for 2 hours. Propargylic ketone (0.5 mmol, 1 equiv) was added and the solution was stirred at 0 ºC overnight. The reactions were quenched with SiO_2 (0.3 g, 5 mmol, 10 equiv) and filtered then concentrated *in vacuo*. Conversion was measured using trimethoxybenzene as internal standard (16.8 mg, 0.1 mmol). The crude product was purified by flash column chromatography.

5.4.4 - General Procedure for sub-stoichiometric hydroboration of propargylic ketones



Sub-stoichiometric reduction of propargylic ketones was carried out using the optimised *B*-H-9-BBN procedure. *B*-H-9-BBN (0.2 mL, 0.1 M, 0.5 mmol, 0.2 equiv) and (*S*)-β-pinene (16 µl, 0.1 mmol, 0.2 equiv) were stirred under argon at room temperature for 2 hours. Propargylic ketone (0.5 mmol, 1 equiv) and HBpin (87 µl) were added and the solution was stirred at 0 °C overnight. Conversion was measured using trimethoxybenzene as internal standard (16.8 mg, 0.1 mmol). The reactions were quenched with SiO_2 (0.3 g, 5 mmol, 10 equiv) and filtered then concentrated under reduced pressure. The crude product was purified by flash column chromatography.

5.4.5 – 4-Phenylbut-3-yn-2-one

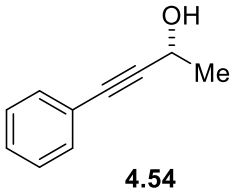


According to the general procedure for preparation of propargylic ketones (**5.4.1**), phenyl acetylene (**4.55**) (5.5 mL, 50 mmol), *n*-BuLi (1.6 M in hexanes, 31.3 mL, 50 mmol), ZnCl (0.7 M in THF, 70 mL, 50 mmol) and acetyl chloride (**4.56**) (3.75 mL, 50 mmol) were reacted in THF (250 mL). The crude product was purified by flash column chromatography (hexane/diethyl ether 20:1) to give 4-phenylbut-3-yn-2-one (**4.48**), (3.3 g, 23.0 mmol, 46%) as a yellow oil. All spectroscopic data matched literature values.[206]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62-7.58 (m, 2H 2 × Ar*H*), 7.51-7.46 (m, 1H, Ar*H*), 7.44-7.38 (m, 2H, 2 × Ar*H*), 2.48 (s, 3H, CH_3) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 184.6 (C), 133.0 (2 × CH), 130.7 (CH), 128.6 (2 × CH), 120.0 (C), 90.3 (C), 88.3 (C), 32.8 (CH_3) ppm.

5.4.6 – (*R*)-4-Phenylbut-3-yn-2-ol



4.54

Prepared according to the general procedure for both stoichiometric (**5.4.3**) and sub-stoichiometric (**5.4.4**) reductions. The crude product was purified by flash column chromatography (hexane/ diethyl ether 5:1) to give alcohol **4.54**, 4-phenyl-but-3-yn-2-ol, for both the stoichiometric (0.068 g, 0.46 mmol, 93%, 73% *ee*), and sub-stoichiometric reaction (0.069 g, 0.48 mmol, 95%, 71% *ee*) as a colourless oil. All spectroscopic data matched literature values.[229]

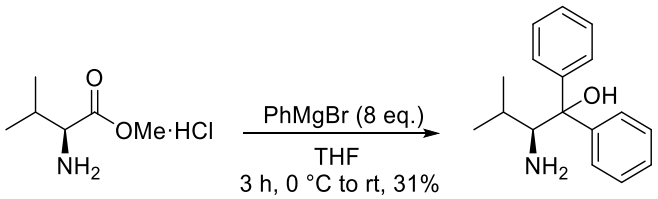
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.43 (m, 2H, 2 × Ar*H*), 7.35-7.32 (m, 3H, 3 × Ar*H*), 4.79 (qd. *J* = 6.6, 5.3 Hz, 1H, C*H*(OH)), 2.24 (d, *J* = 5.2 Hz, 1H, O*H*) 1.89 (d, *J* = 6.6 Hz, 3H, CH_3) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 131.7 (2 × CH), 128.4 (CH), 128.3 (2 × CH), 122.6 (C), 90.9 (C), 84.0 (C), 58.9 (CH), 24.4 (CH_3) ppm.

HPLC (IPA:hexane, 20:80) Stoichiometric reduction: R_t (major) = 5.05 min, 86.6%, R_t (minor) = 9.01 min, 13.4%; 73% e.e. Sub-stoichiometric reduction: R_t (major) = 5.04 min, 85.7%, R_t (minor) = 8.89 min, 14.3%; 71% e.e. Retention times matched the reported literature values, as well as those observed for the racemic sample.[230]

[α]$_D$ = +22.7 (c = 0.22, $CDCl_3$) (Measured by Kieran Nicholson)

5.4.7 – (*S*)-2-Amino-3-methyl-1,1-diphenylbutan-1-ol



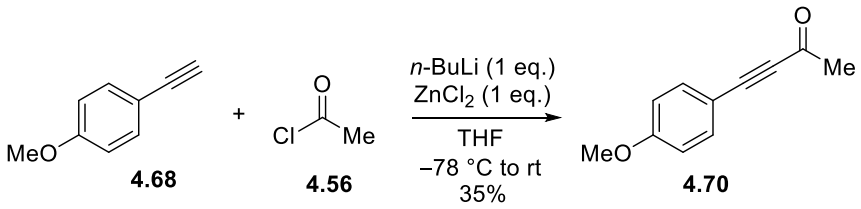
4.57 **4.39**

Compound **4.39** was prepared according to a literature procedure.[227] (*S*)-Valine methyl ester hydrochloride (**4.57**) (5 g, 29.8 mmol) was added portionwise to a solution of phenylmagnesium bromide (3.0 M, 60 mL, 239 mmol) in THF (30 mL) at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 3 hours, before being poured slowly into ice-cold ammonium chloride solution (100 mL). Diethyl ether (50 mL) and ethyl acetate (50 mL) were added to the mixture, before the layers were separated, and the aqueous phase extracted with TBME (100 mL). The combined organic layers were acidified with HCl (35%, ~5 mL) at 0 °C. The resulting precipitate formed was filtered off, rinsed with TBME (20 mL) and taken up in dichloromethane (100 mL) and water (100 mL). The solution was then stirred at 0 °C and basified with sodium hydroxide (35%, ~6 mL). The layers were again separated, and the aqueous layer extracted with dichloromethane (100 mL), before the combined organic layers were washed with water (50 mL) and brine (50 mL). The mixture was dried with Na_2SO_4 and concentrated to give the product (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (**4.39**) as a white amorphous solid (2.36 g, 9.25 mmol, 31%). All spectroscopic data matched literature values [228]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 8.5, 1.3 Hz, 2H, 2 × Ar*H*), 7.52 (dd, *J* = 8.5, 1.3 Hz, 2H, 2 × Ar*H*), 7.36 – 7.29 (m, 4H, 4 × Ar*H*), 7.23 – 7.16 (m, 2H, 2 × Ar*H*), 3.87 (d, *J* = 2.2 Hz, 1H, C*H*(NH_2)), 1.79 (spt, *J* = 7.0, 2.2 Hz, 1H, C*H*(CH_3)$_2$), 0.96 (d, *J* = 7.0 Hz, 3H, CH_3), 0.92 (d, *J* = 7.0 Hz, 3H, CH_3) ppm;

^{13}C NMR (150 MHz, $CDCl_3$) δ 147.8 (C), 144.8 (C), 128.4 (2 × CH), 128.0 (2 × CH), 126.6 (CH), 126.3 (CH), 126.0 (2 × CH), 125.5 (2 × CH), 79.7 (C), 60.3 (CH), 27.8 (CH), 23.0 (CH_3), 16.1 (CH_3) ppm.

5.4.8 – 4-(4-Methoxyphenyl)but-3-yn-2-one

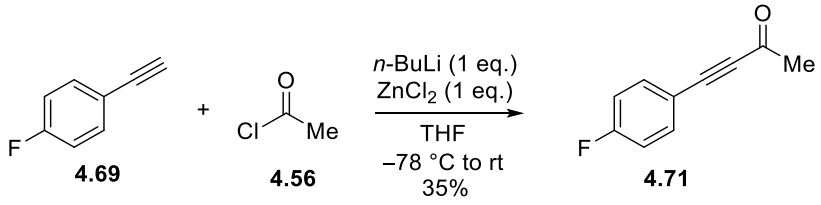


According to the general procedure for preparation of propargylic ketones (**5.4.1**), 4-ethynylanisole (**4.68**) (0.2 mL, 1.5 mmol), *n*-BuLi (1.6 M in hexanes, 0.96 mL, 1.5 mmol), ZnCl (0.7 M in THF, 2.2 mL, 1.5 mmol) and acetyl chloride (**4.56**) (0.11 mL, 1.5 mmol) were reacted in THF (10 mL). The crude product was purified by flash column chromatography (hexane/ethyl acetate 10:1) to give 4-(4-methoxyphenyl)but-3-yn-2-one (**4.70**) (0.099 g, 0.57 mmol, 38%) as a pale solid. All spectroscopic data matched literature values.[225]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dt, *J* = 9.1, 2.7 Hz, 2H, 2 × Ar*H*), 6.92 (dt, *J* = 9.1, 2.7 Hz, 2H, 2 × Ar*H*), 3.87 (s, 3H, OCH_3), 2.45 (s, 3H, CH_3) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 184.6 (C), 161.7 9 (C), 136.1 (2 × CH), 114.4 (2 × CH), 111.7 (C), 91.5 (C), 88.3 (C), 55.4 (CH_3), 32.6 (CH_3) ppm.

5.4.9 – 4-(4-Fluorophenyl)but-3-yn-2-one



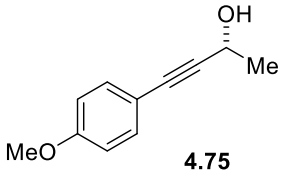
According to the general procedure for preparation of propargylic ketones (**5.4.1**), 1-ethynylfluorobenzene (0.17 mL, 1.5 mmol), *n*-BuLi (1.6 M in hexanes, 0.96 mL, 1.5 mmol), $ZnCl_2$ (0.7 M in THF, 2.2 mL, 1.5 mmol) and acetyl chloride (0.11 mL, 20 mmol) were reacted. The crude product was purified by flash column chromatography (hexane/ethyl acetate 10:1) to give 4-(4-fluorophenyl)but-3-yn-2-one (**4.71**) (0.092 g, 0.57 mmol, 38%) as a yellow oil. All spectroscopic data matched literature values.[228]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dddd, *J* = 8.7, 5.3, 2.7, 1.9 Hz, 2H, 2 × Ar*H*)), 7.11 (dddd, *J* = 8.7, 8.5, 2.7, 1.9 Hz, 2H, 2 × Ar*H*), 2.47 (s, 3H, CH_3) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 184.4 (C), 164.0 (d, $^{1}J_{CF}$ = 253 Hz, C), 135.3 (d, $^{3}J_{CF}$ = 9.0 Hz, 2 × CH), 116.3 (d, $^{2}J_{CF}$ = 22.3 Hz, CH), 89.2 (C), 88.2 (d, $^{4}J_{CF}$ = 1.5 Hz), 32.7 (CH_3) ppm;

^{19}F NMR (377 MHz, $CDCl_3$) δ −106.3 (tt, *J* = 8.5, 5.3 Hz) ppm.

5.4.10 – (*R*)-4-(4-Methoxyphenyl)but-3-yn-2-ol



4.75

Prepared according to the general procedure for both stoichiometric and sub-stoichiometric reactions. The crude product was purified by flash column chromatography (hexane/diethyl ether 5:1) to give alcohol **4.75**, 4-(4-methoxyphenyl)but-3-yn-2-ol, for stoichiometric (0.078 g, 0.44 mmol, 89%, 70% ee) and sub-stoichiometric (0.046 g, 0.26 mmol, 52%, 56% ee) reactions as a colourless oil. Spectroscopic data matched literature values.[231]

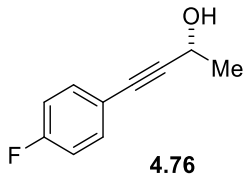
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.8 Hz, 2H, 2 × Ar*H*), 6.86 (d, *J* = 8.8 Hz, 2H, 2 × Ar*H*), 4.77 (q, *J* = 6.6 Hz, 1H, C*H*(OH)), 3.83 (s, 3H, O*H*), 1.60 (d, *J* = 6.6 Hz, 3H, CH_3) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7 (C), 133.1 (2 × CH), 114.7 (C), 113.9 (2 × CH), 89.6 (C), 83.9 (C), 58.9 (CH), 55.3 (CH_3), 24.9 (CH_3) ppm.

HPLC (IPA:hexane, 20:80) Stoichiometric reduction: R_t (major) = 5.90 min, 85%, R_t (minor) = 13.8 min, 15%; 70% e.e. Sub-stoichiometric reduction: R_t (major) = 5.86 min, 78%, R_t (minor) = 13.6 min, 22%; 56% e.e. Retention times matched those observed for the racemic sample.

[α]$_D$ = +36.1 (c = 2.24, $CDCl_3$) (measured by Kieran Nicholson)

5.4.11 – (*R*)-4-(4-Fluorophenyl)but-3-yn-2-ol



4.76

Prepared according to the general procedure for both stoichiometric (**5.4.3**) and sub-stoichiometric (**5.4.4**) reductions. The crude product was purified by flash column chromatography (hexane/diethyl ether 5:1) to give alcohol **4.76**, 4-(4-fluorophenyl)but-3-yn-2-ol, for stoichiometric (0.066 g, 0.41 mmol, 81%, 67% ee) and sub-stoichiometric (0.056 g, 0.34 mmol, 68%, 66% ee) reactions as a colourless oil. Spectroscopic data matched literature values.[231]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (dddd, *J* = 8.7, 5.3, 2.7, 1.9 Hz, 2H, 2 × Ar*H*), 7.05 – 6.98 (dddd, *J* = 8.7, 8.5, 2.7, 1.9 Hz, 2H, 2 × Ar*H*), 4.76 (qd, *J* = 5.3, 6.6 Hz, 1H, C*H*(OH)), 1.95 (br, d, *J* = 5.3 Hz, 1H, O*H*), 1.57 (d, *J* = 6.6 Hz, 2H, CH_3) ppm;

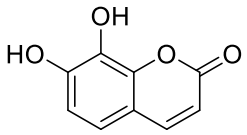
^{13}C NMR (126 MHz, $CDCl_3$) δ 162.6 (d, $^{1}J_{CF}$ = 253 Hz, 2 × C), 133.5 (d, $^{3}J_{CF}$ = 9.0 Hz, 2 × CH), 118.7 (C), 115.6 (d, $^{2}J_{CF}$ = 22.3 Hz, CH), 90.7 (C), 83.0 (C), 58.8 (CH), 24.4 (CH_3) ppm;

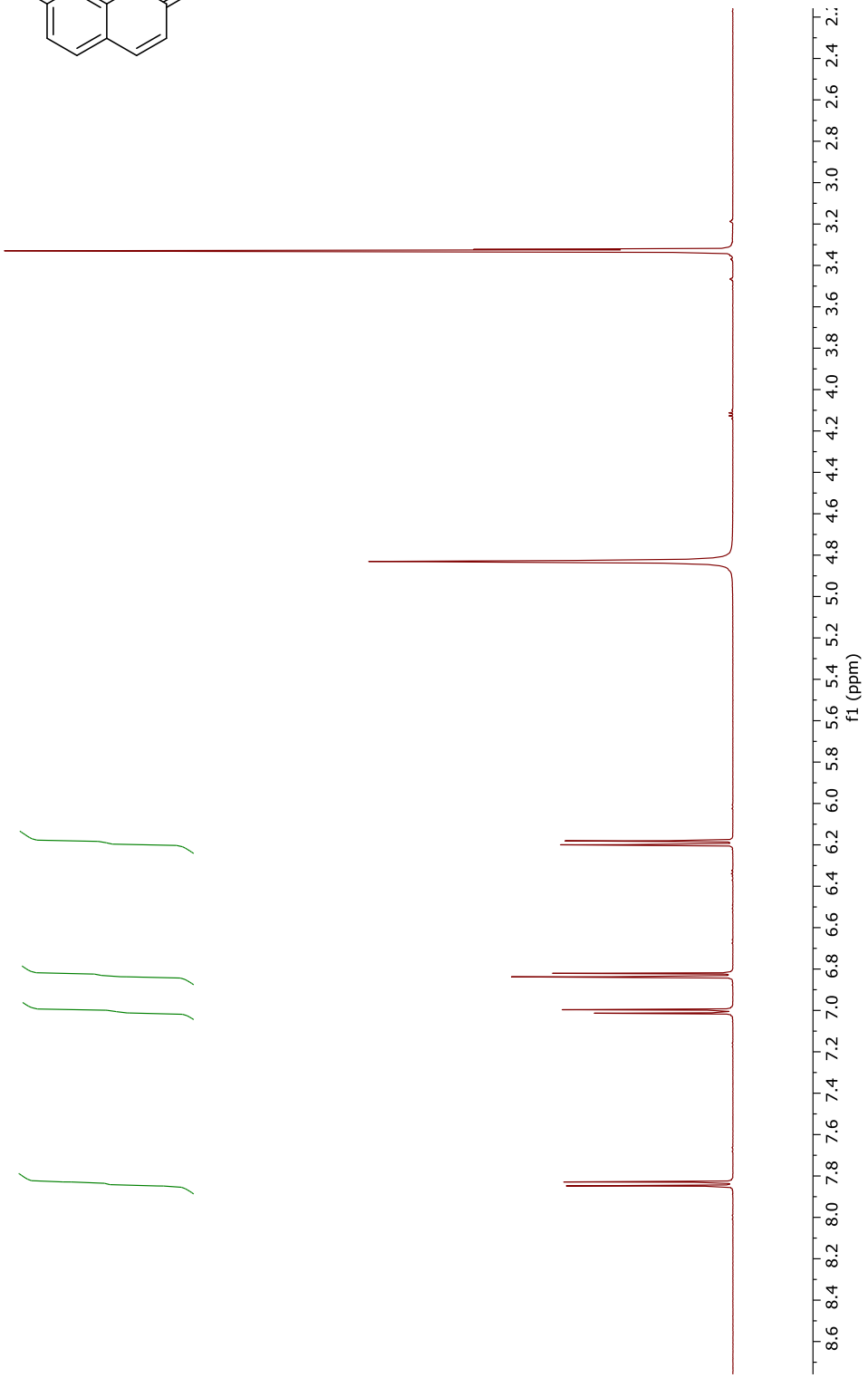
^{19}F NMR (472 MHz, $CDCl_3$) δ -110.9 (tt, *J* = 8.5, 5.3 Hz) ppm.

HPLC (IPA:hexane, 20:80) Stoichiometric reduction: R_t (major) = 7.55 min, 83.5%, R_t (minor) = 10.2 min, 16.5%; 67% e.e. Sub-stoichiometric reduction: R_t (major) = 7.45 min, 83%, R_t (minor) = 10.1 min, 17%; 66% e.e. Retention times matched those observed for the racemic sample.

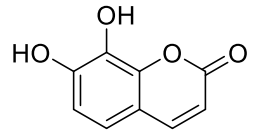
5.5 - NMR Spectra Chapter 2 – Brosiparin Synthesis

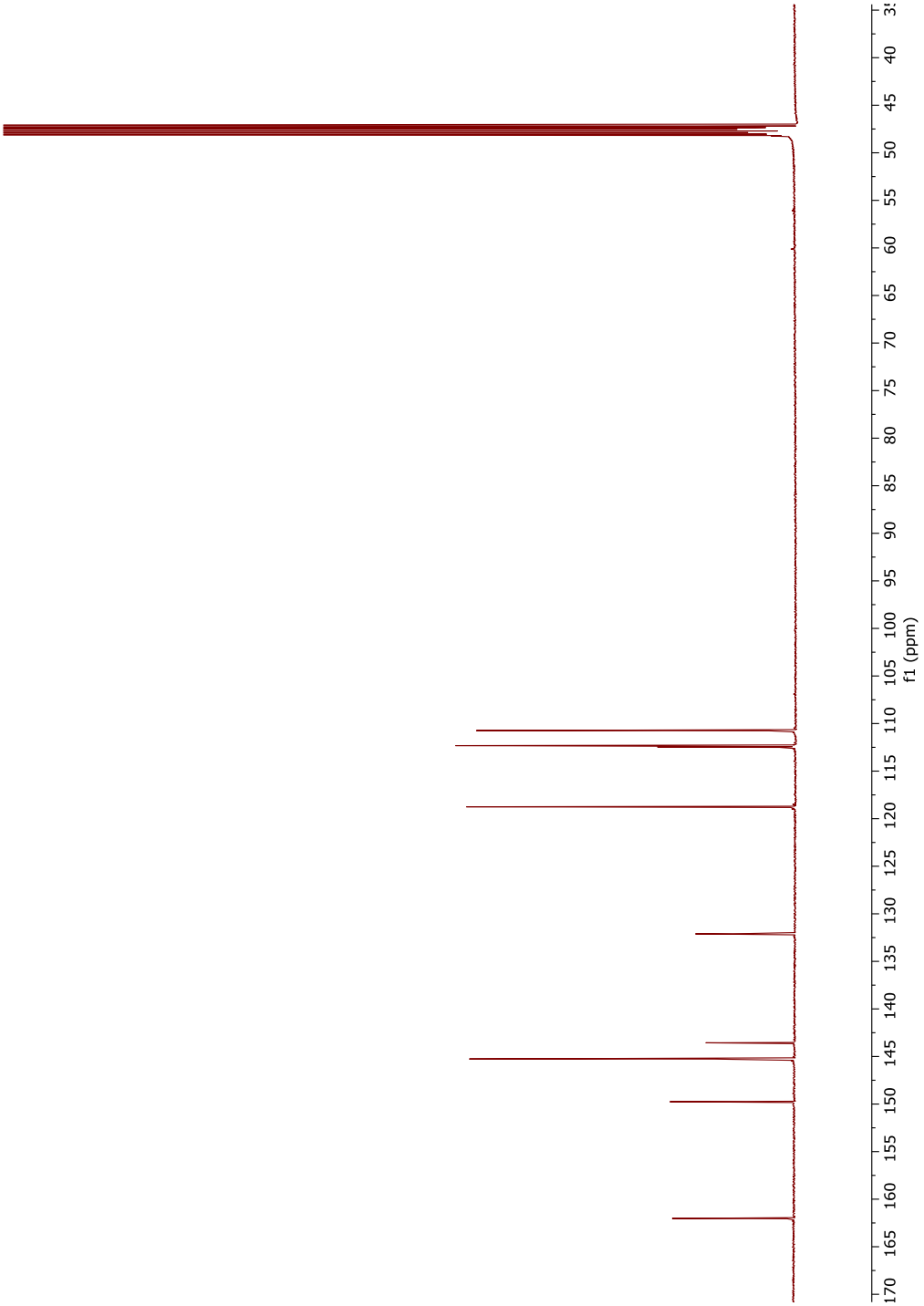
5.5.1 ^{1}H NMR Spectrum of compound 2.16 (500 MHz, MeOD)



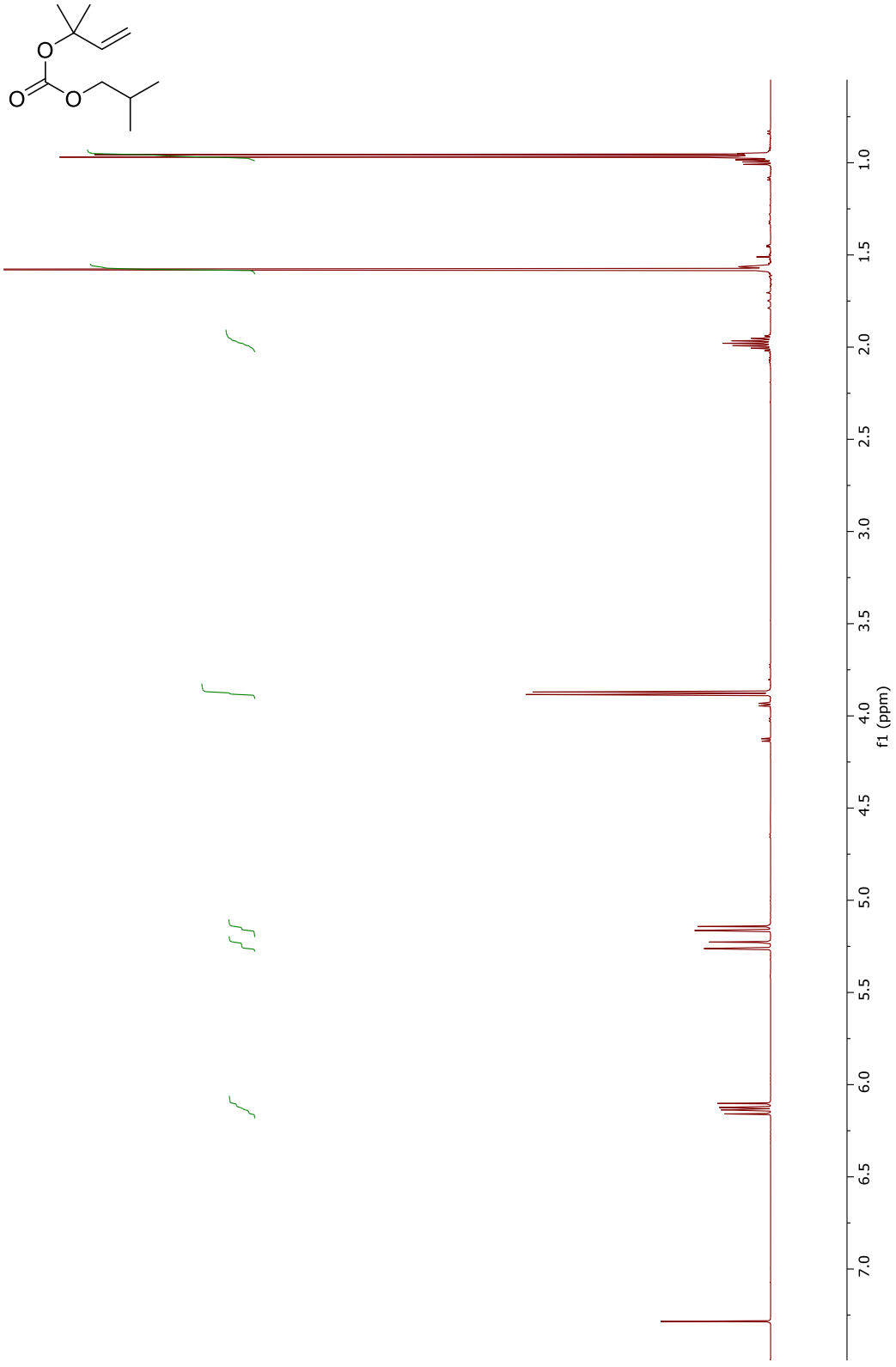


5.5.2 ^{13}C NMR Spectrum of compound 2.16 (125 MHz, MeOD)

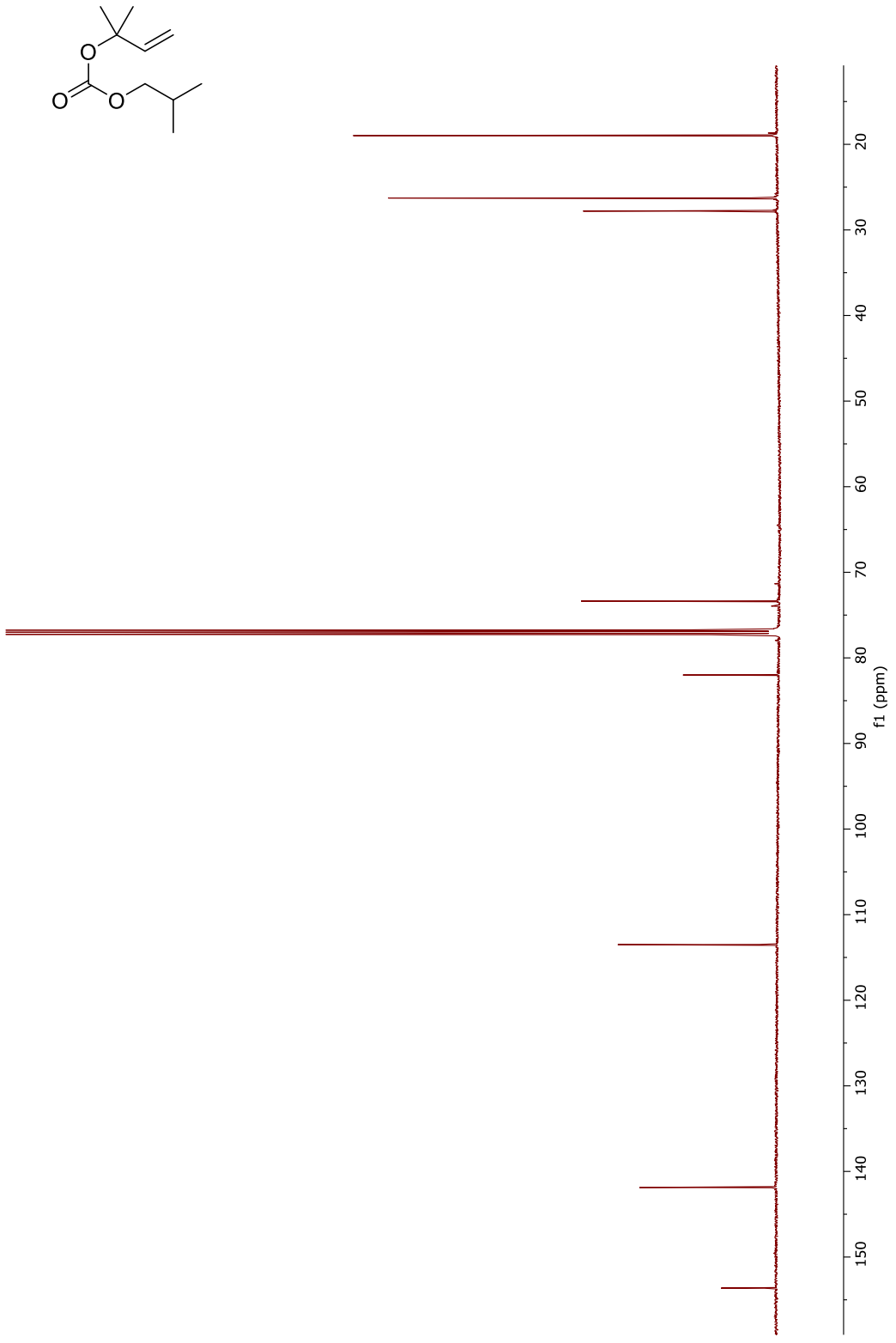




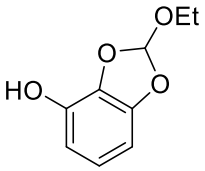
5.5.3 ^{1}H NMR Spectrum of compound 2.20 (500 MHz, $CDCl_3$)

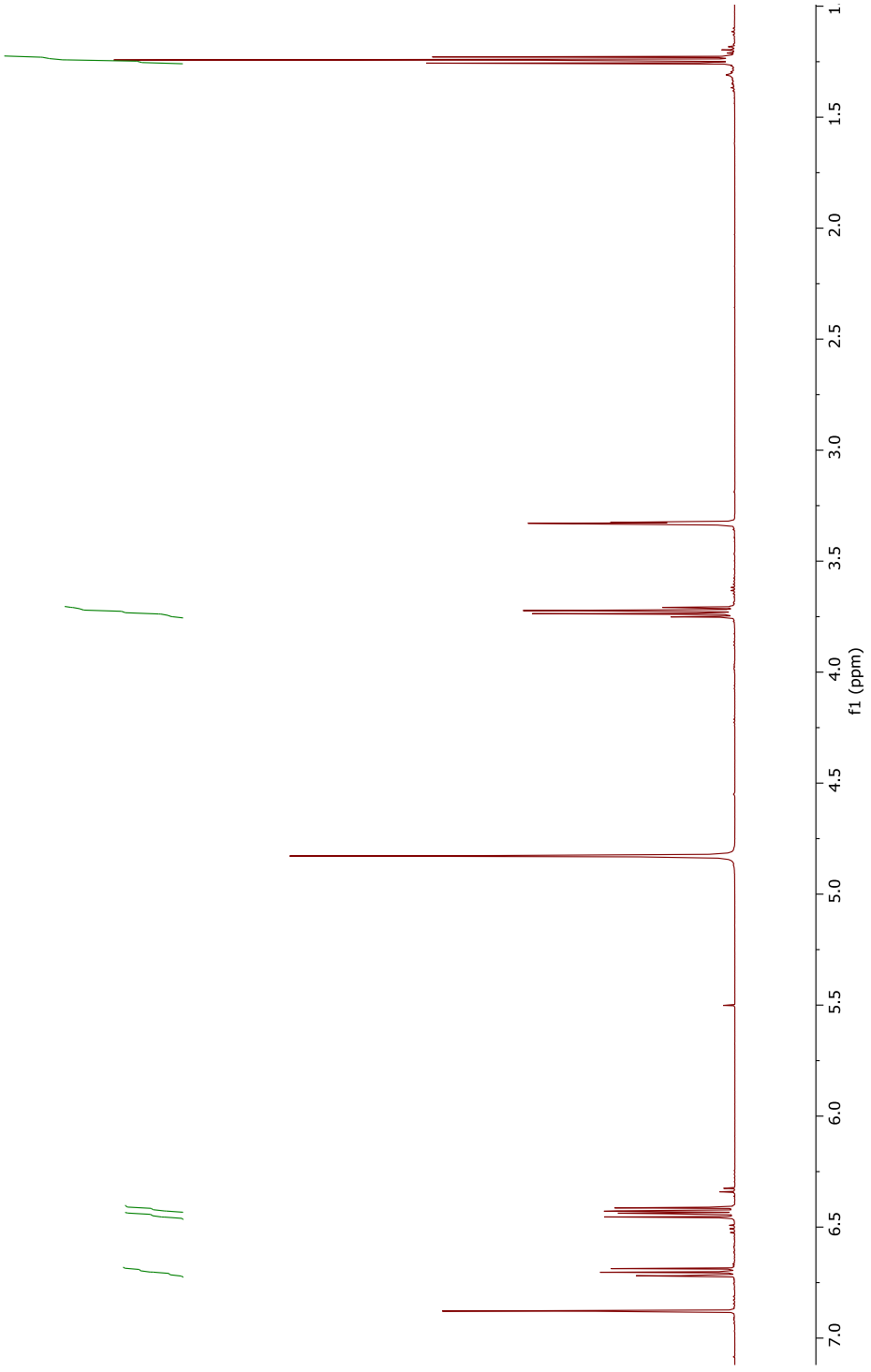


5.5.4 ^{13}C NMR Spectrum of compound 2.20 (125 MHz, $CDCl_3$)

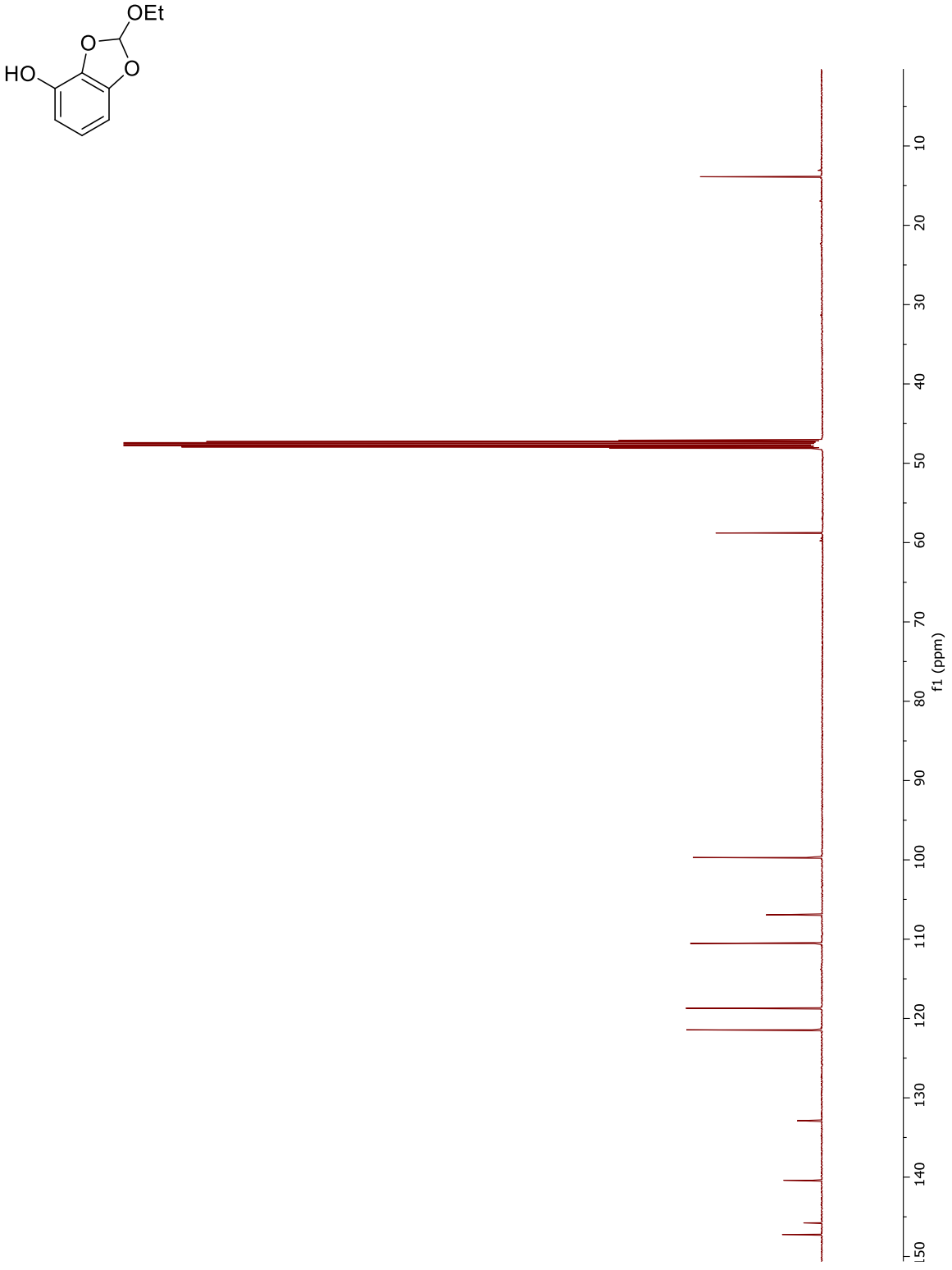


5.5.5 ^{1}H NMR Spectrum of compound 2.34 (500 MHz, MeOD)

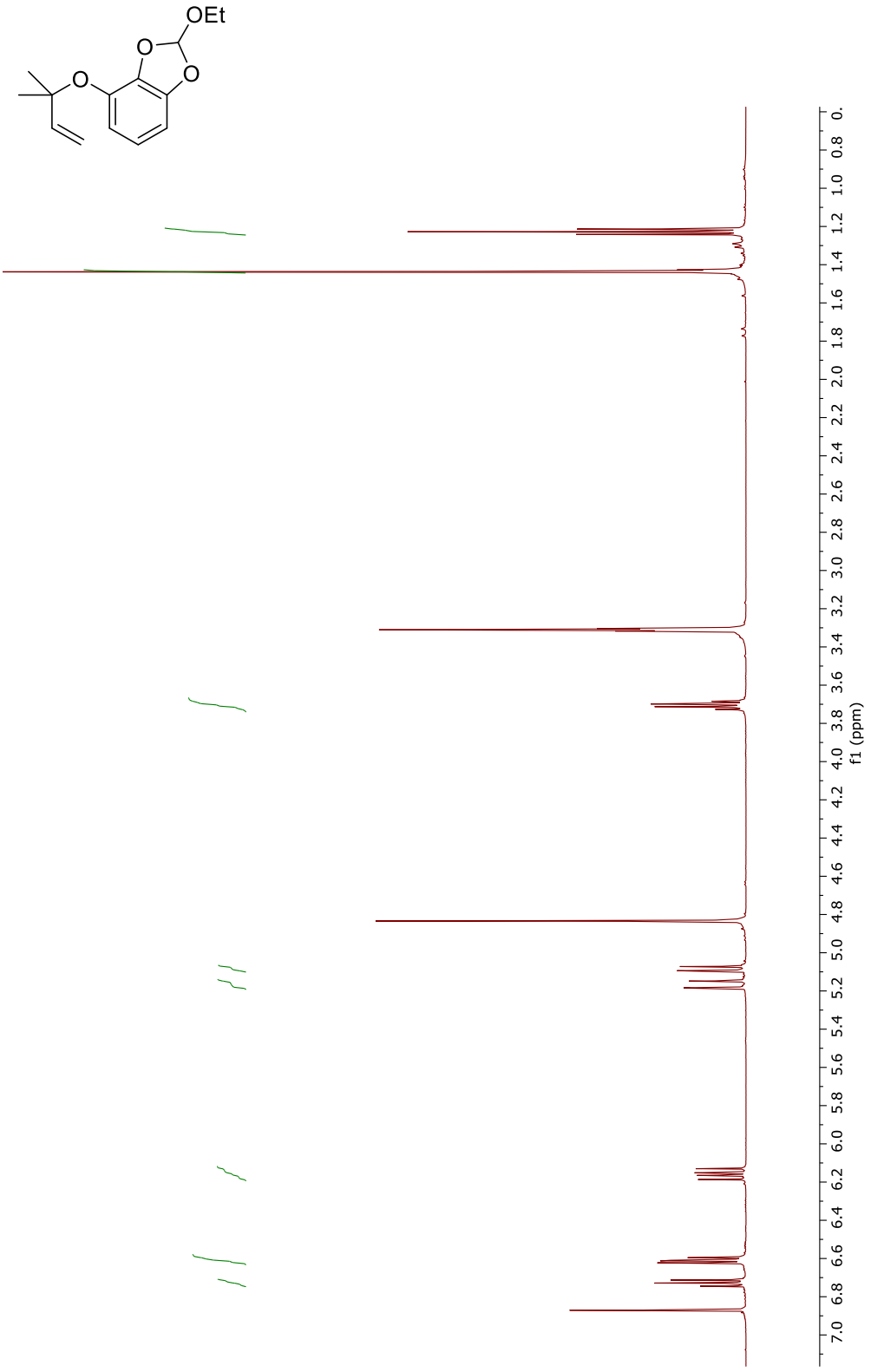




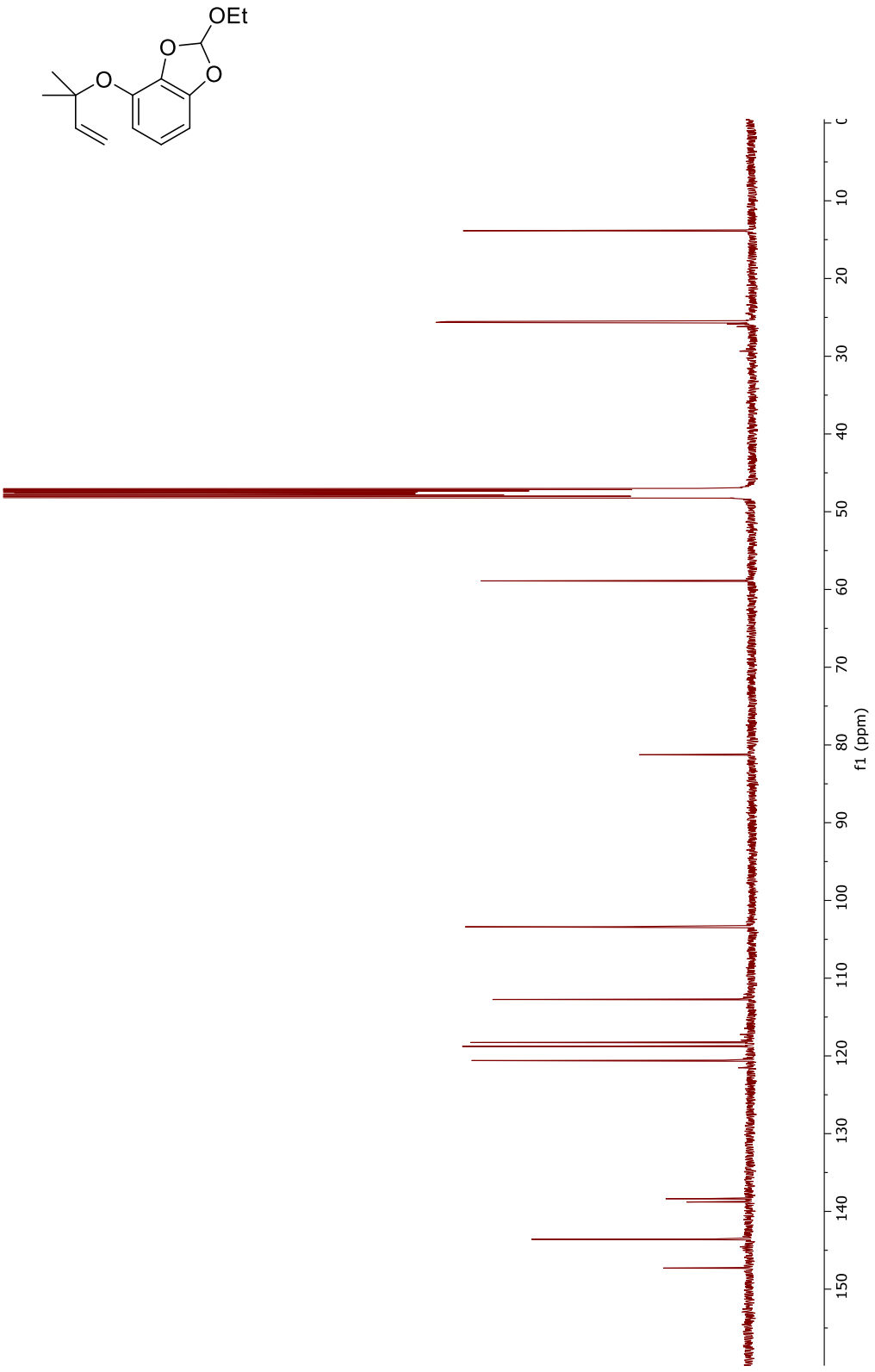
5.5.6 ^{13}C NMR Spectrum of compound 2.34 (125 MHz, MeOD)



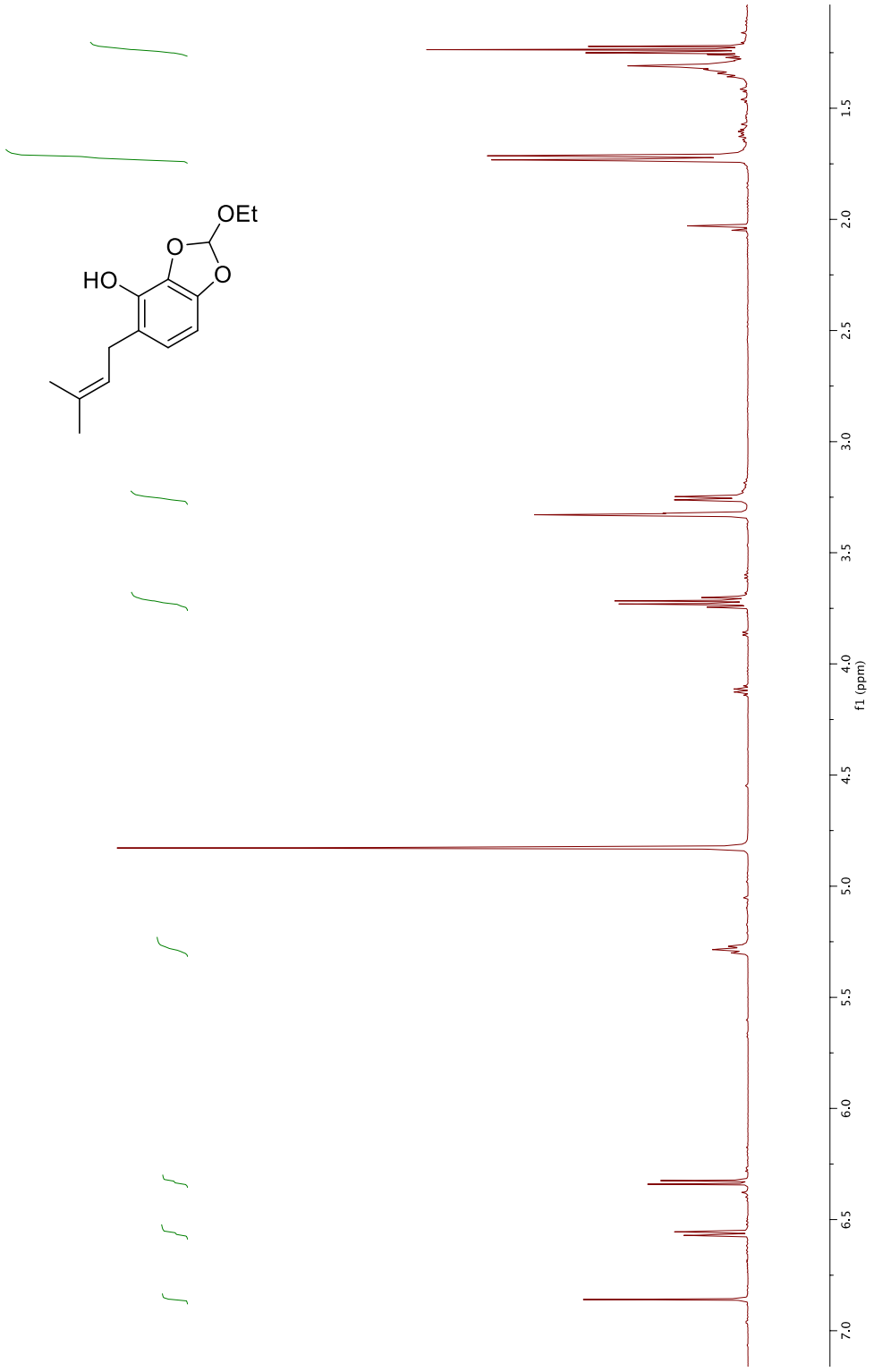
5.5.7 ^{1}H NMR Spectrum of compound 2.35 (500 MHz, MeOD)



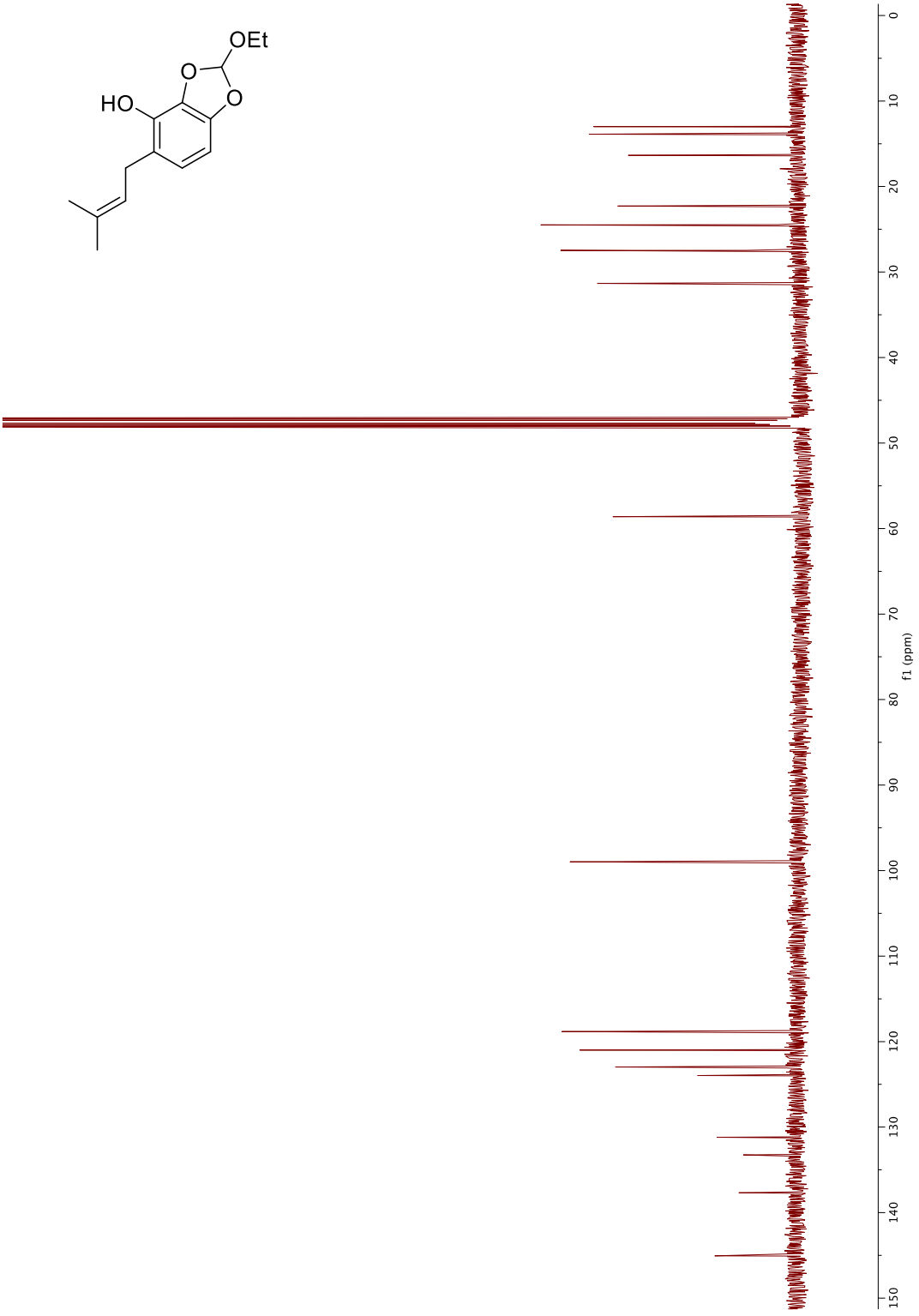
5.5.8 ^{13}C NMR Spectrum of compound 2.35 (125 MHz, MeOD)



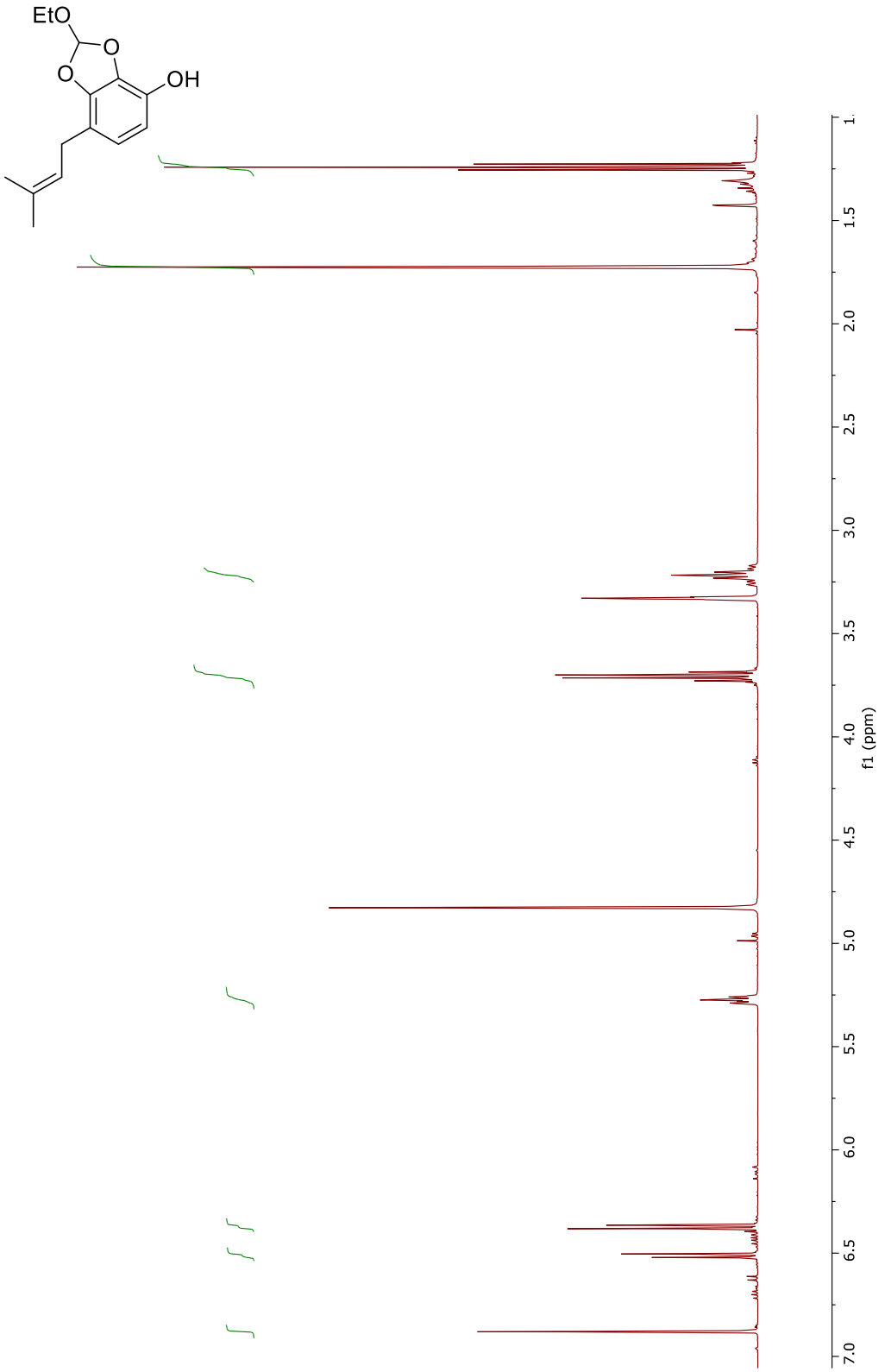
5.5.9 ^{1}H NMR Spectrum of compound 2.36 (500 MHz, MeOD)



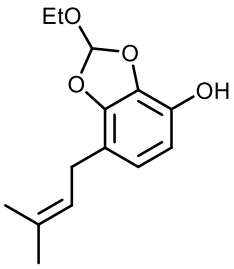
5.5.10 ^{13}C NMR Spectrum of compound 2.36 (125 MHz, MeOD)

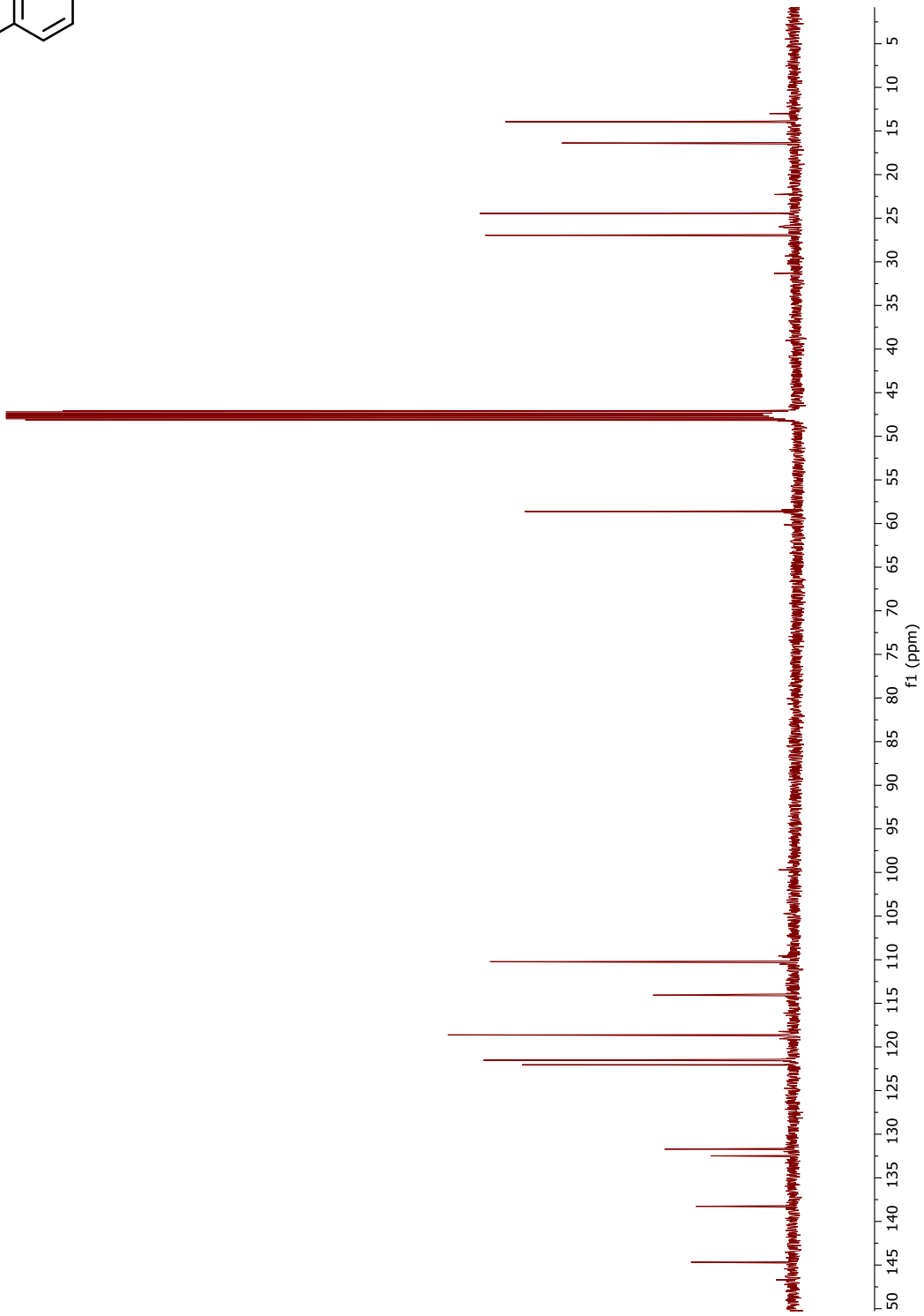


5.5.11 ^{1}H NMR Spectrum of compound 2.37 (500 MHz, MeOD)

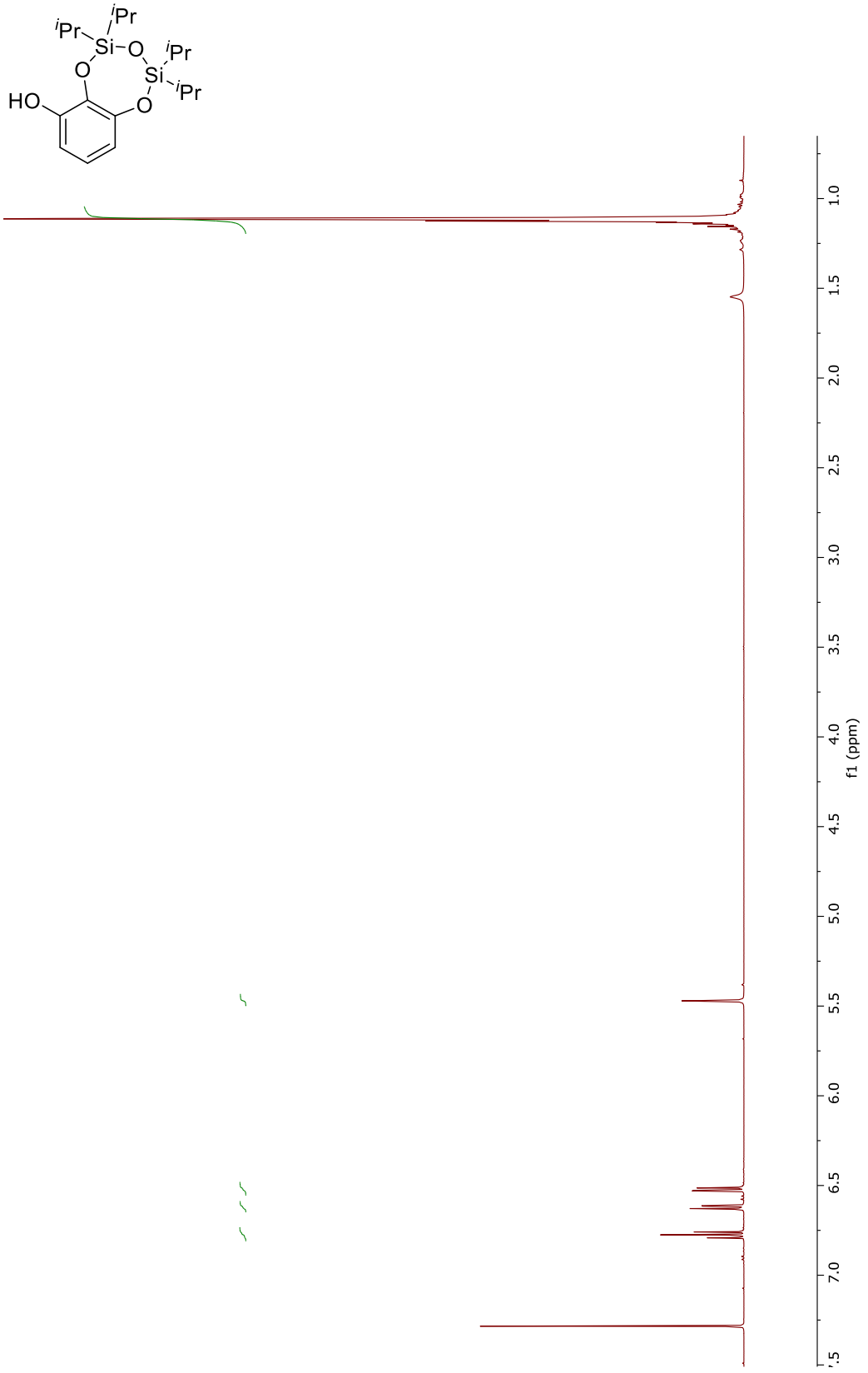


5.5.12 ^{13}C NMR Spectrum of compound 2.37 (125 MHz, MeOD)

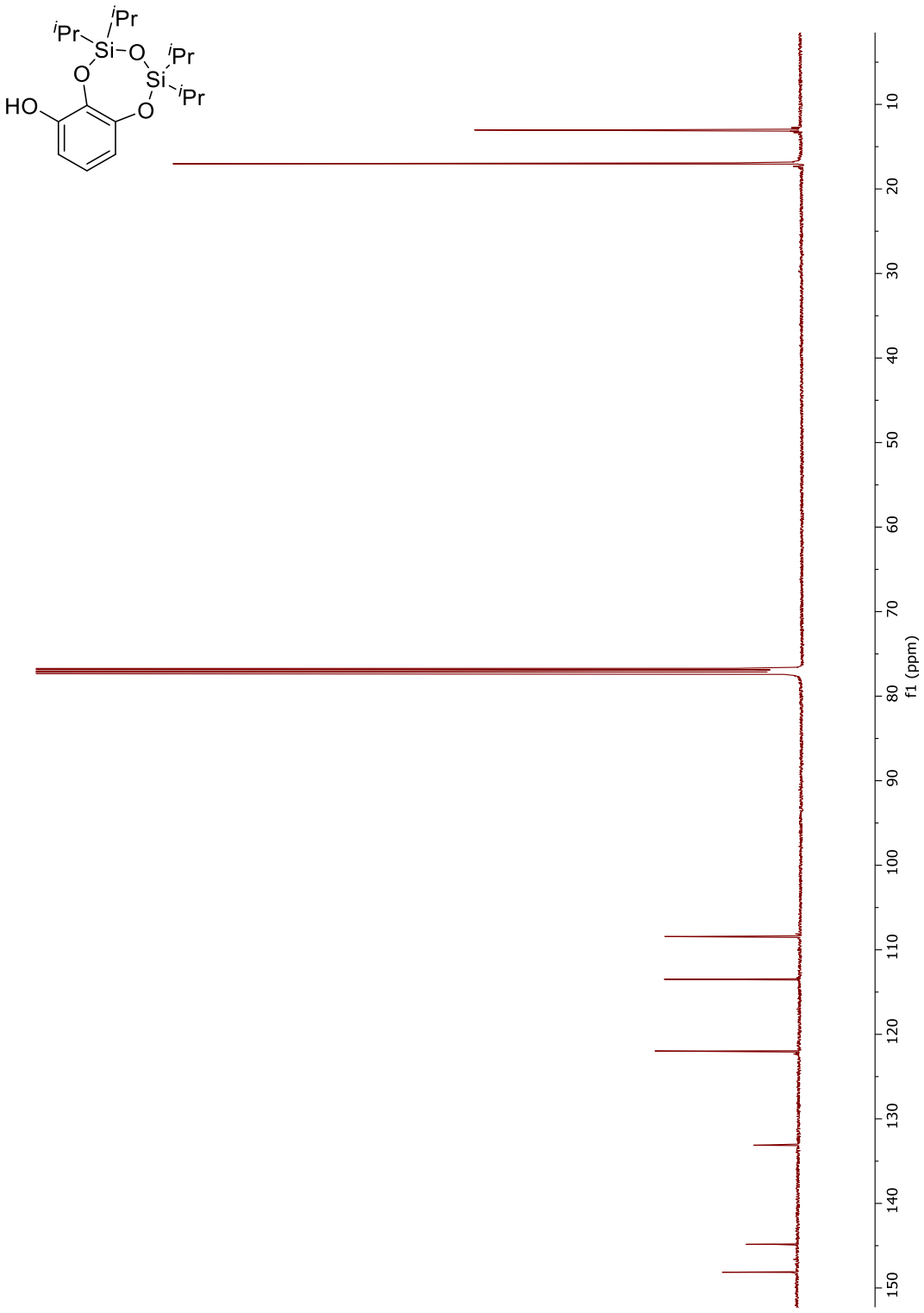




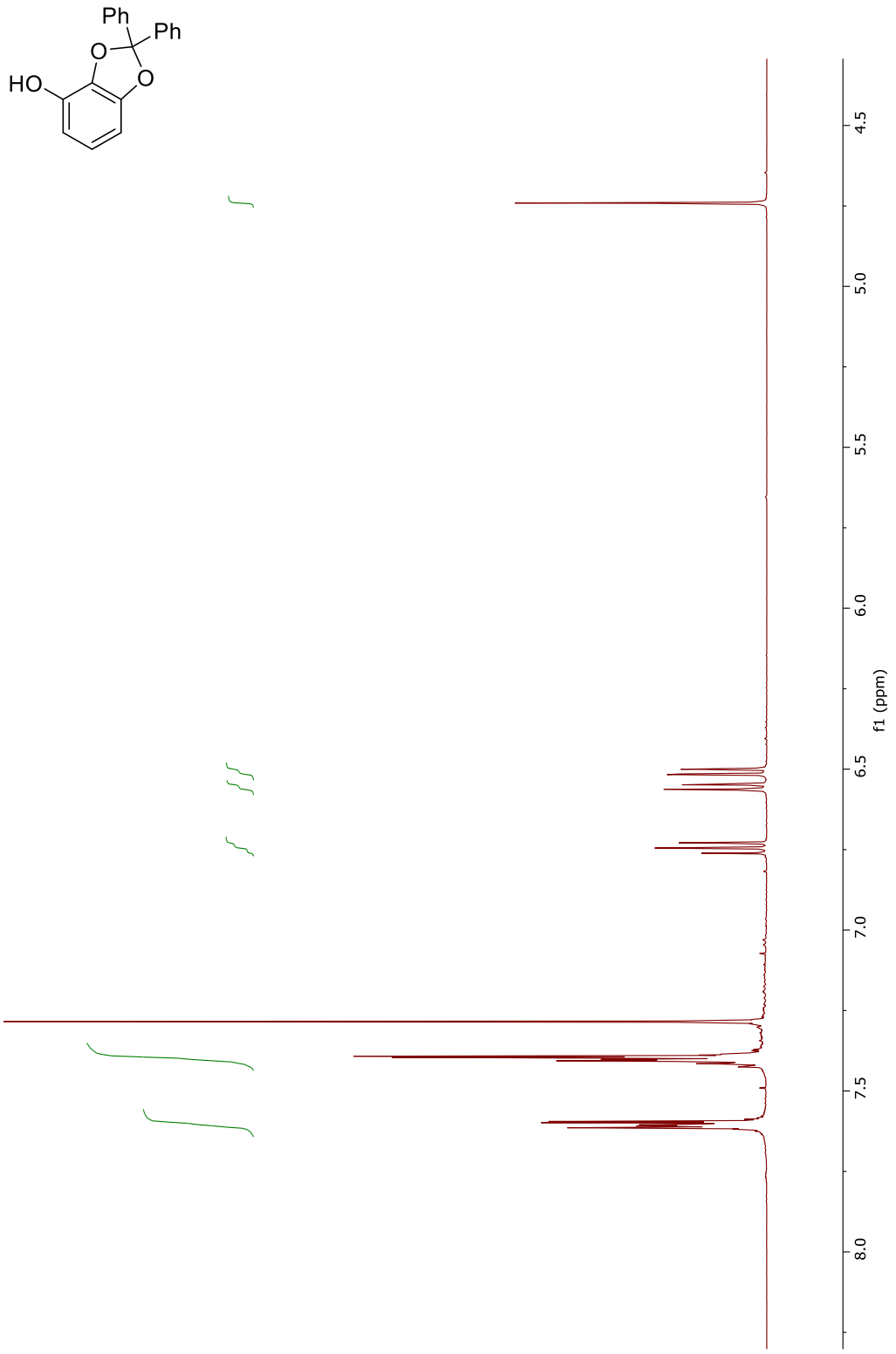
5.5.13 ^{1}H NMR Spectrum of compound 2.38 (500 MHz, $CDCl_3$)



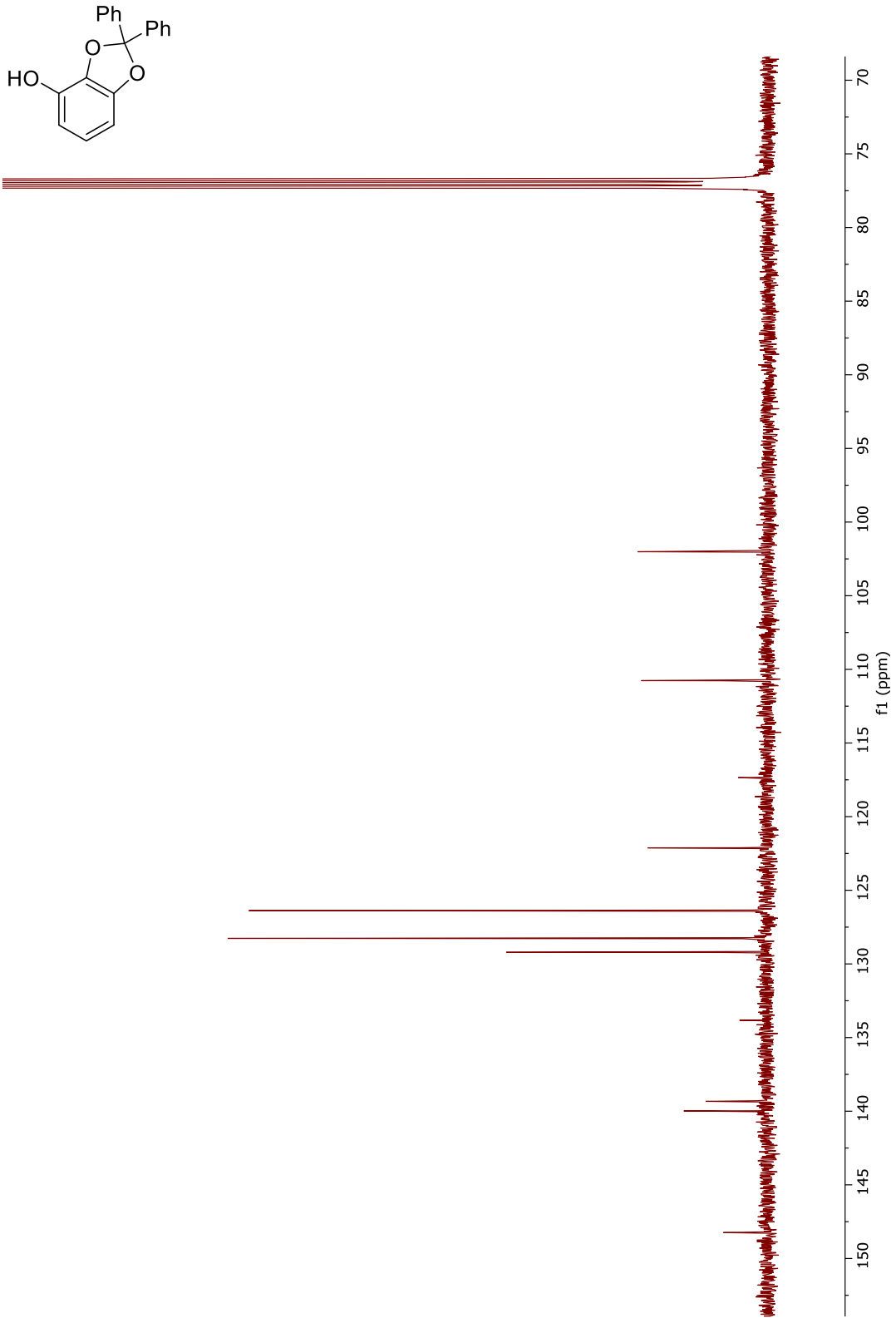
5.5.14 ^{13}C NMR Spectrum of compound 2.38 (125 MHz, $CDCl_3$)



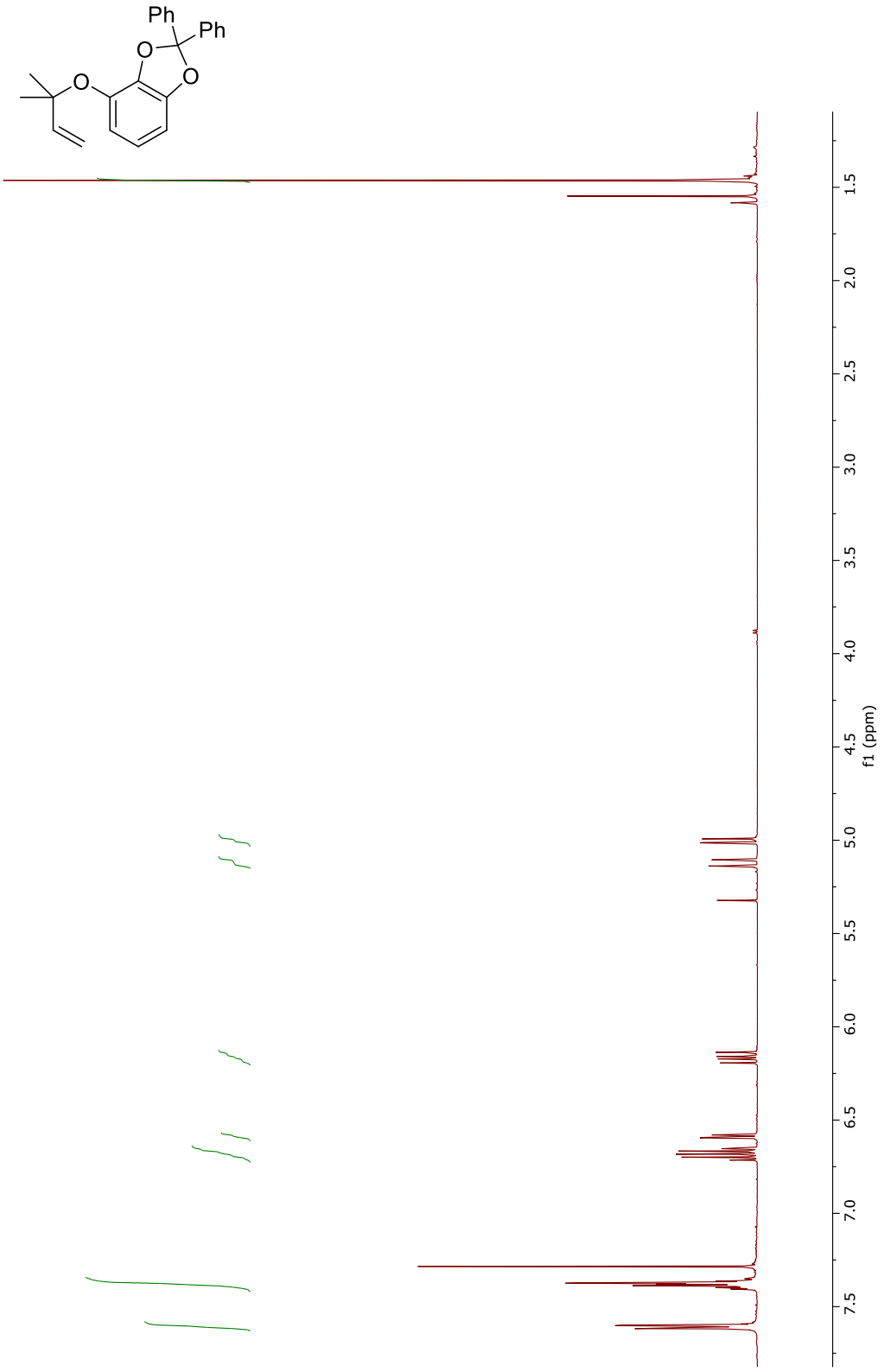
5.5.15 ^{1}H NMR Spectrum of compound 2.42 (500 MHz, $CDCl_3$)



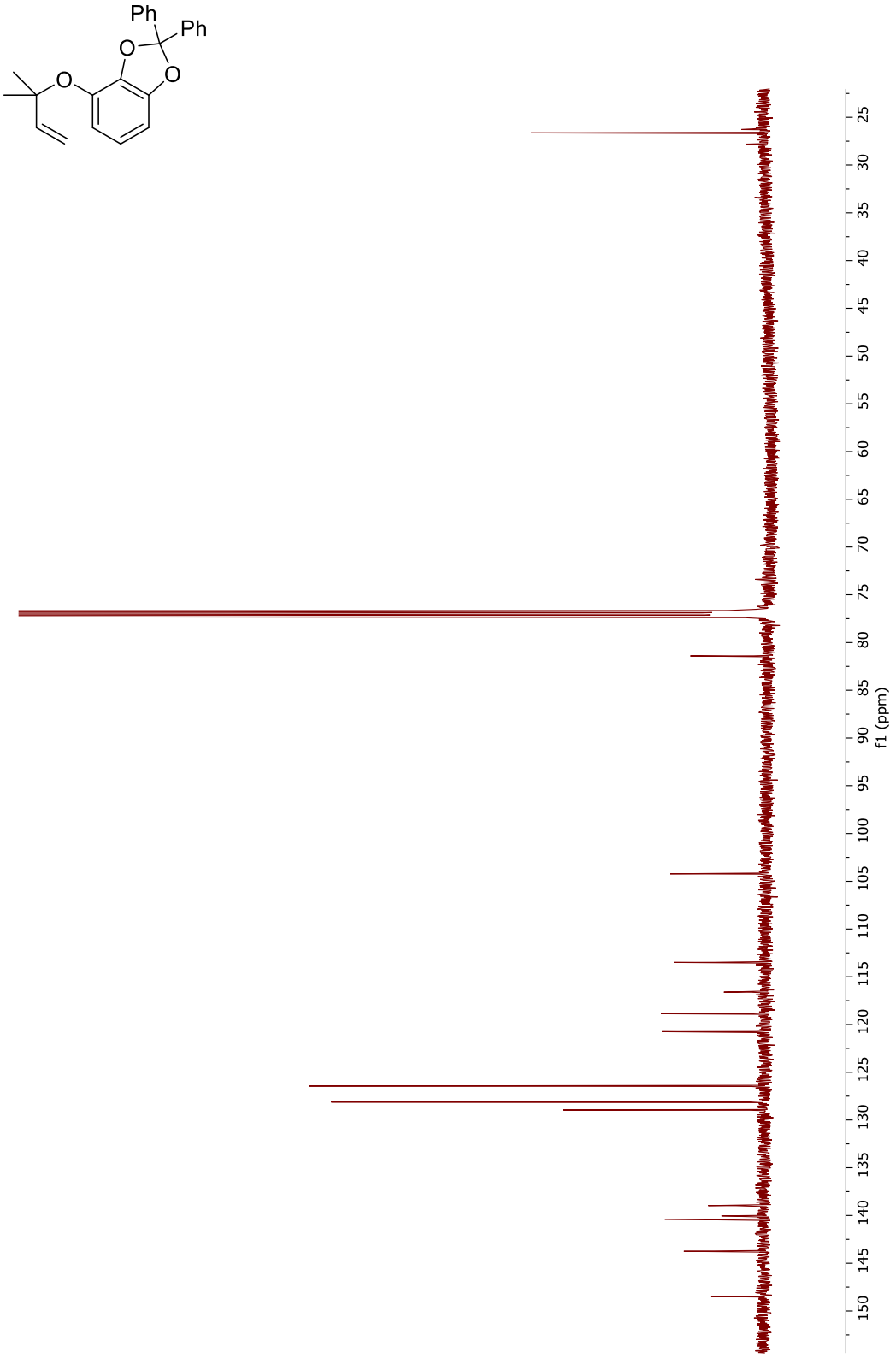
5.5.16 ^{13}C NMR Spectrum of compound 2.42 (125 MHz, $CDCl_3$)



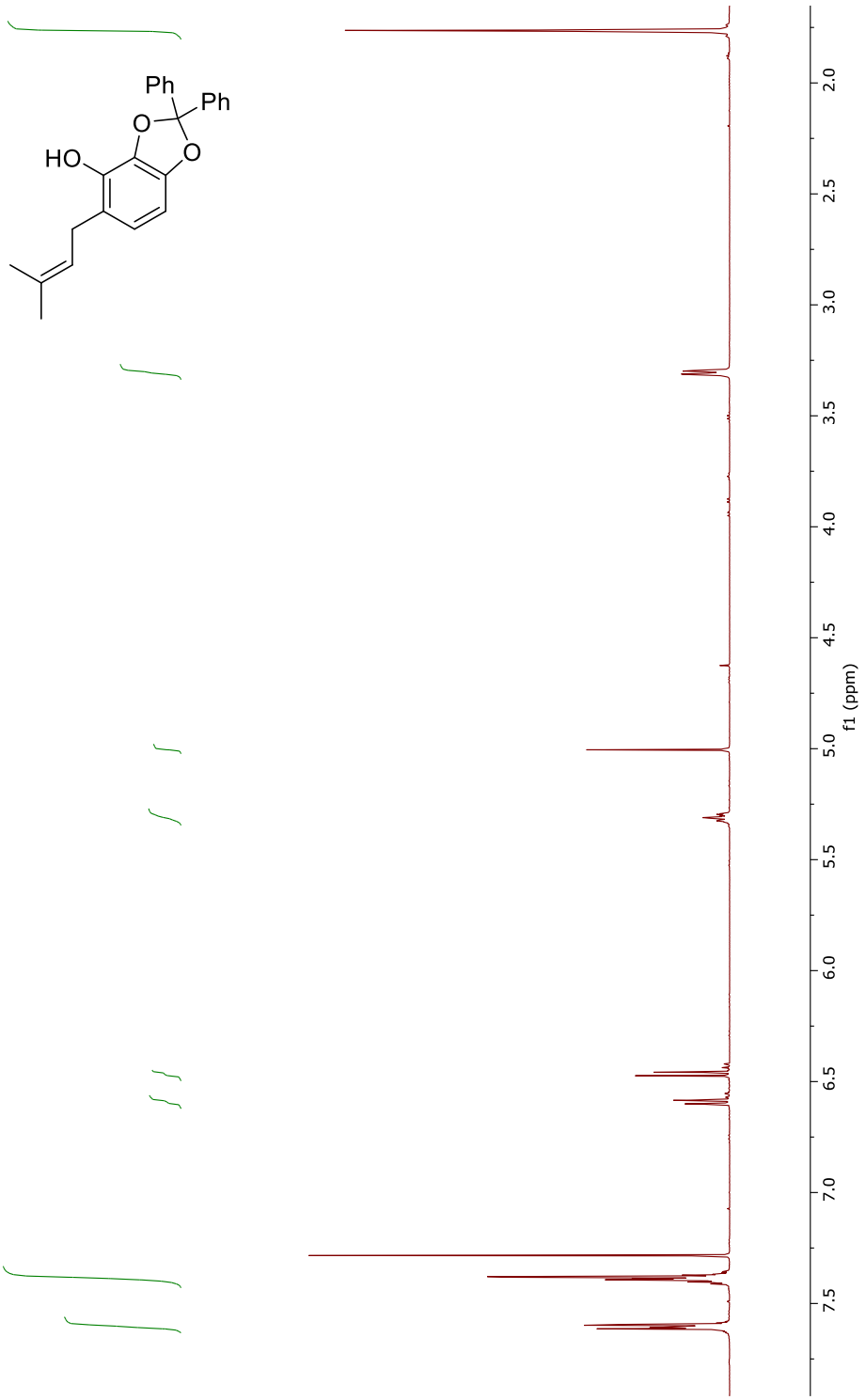
5.5.17 ^{1}H NMR Spectrum of compound 2.43 (500 MHz, $CDCl_3$)



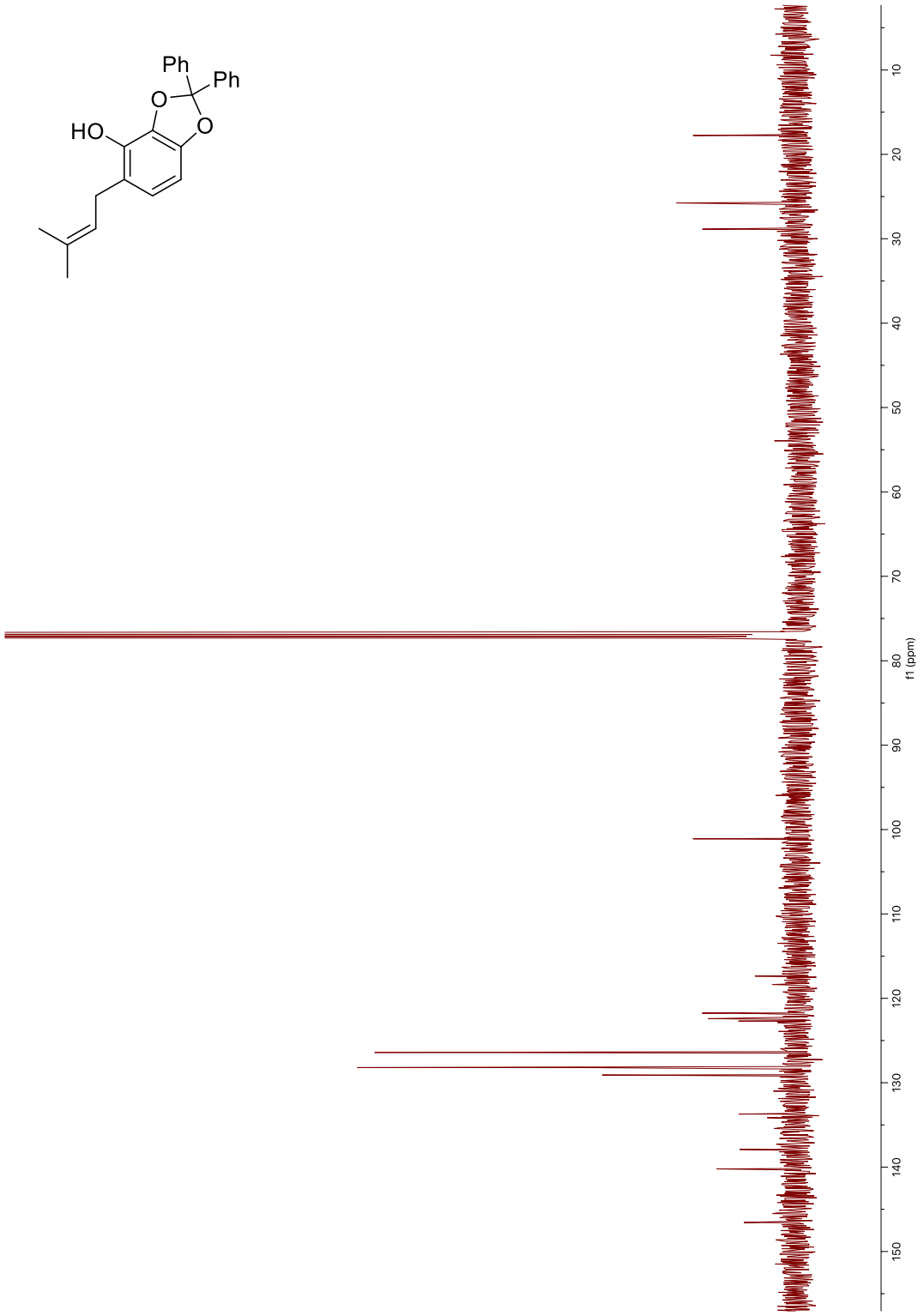
5.5.18 ^{13}C NMR Spectrum of compound 2.43 (125 MHz, $CDCl_3$)



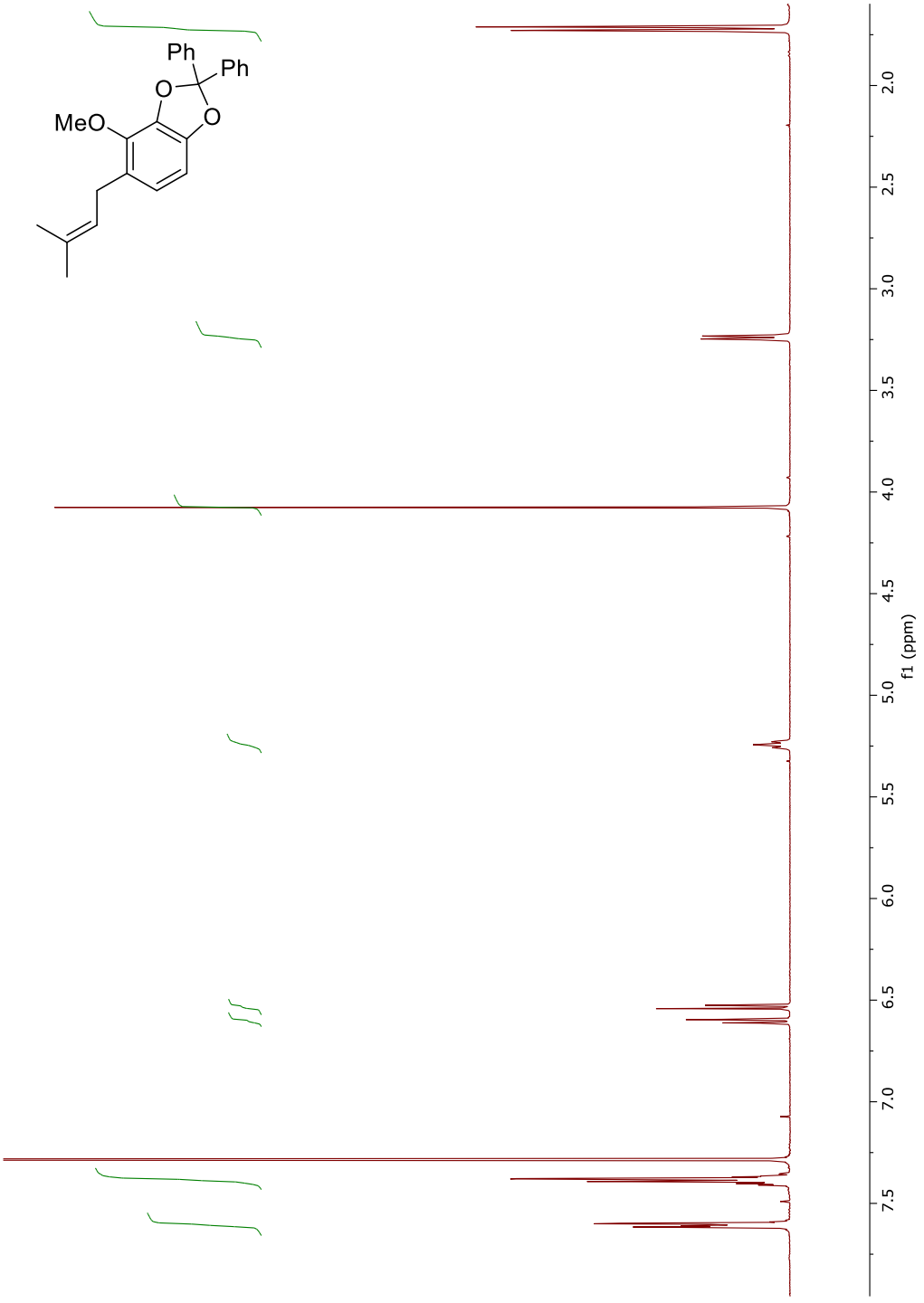
5.5.19 ^{1}H NMR Spectrum of compound 2.44 (500 MHz, $CDCl_3$)



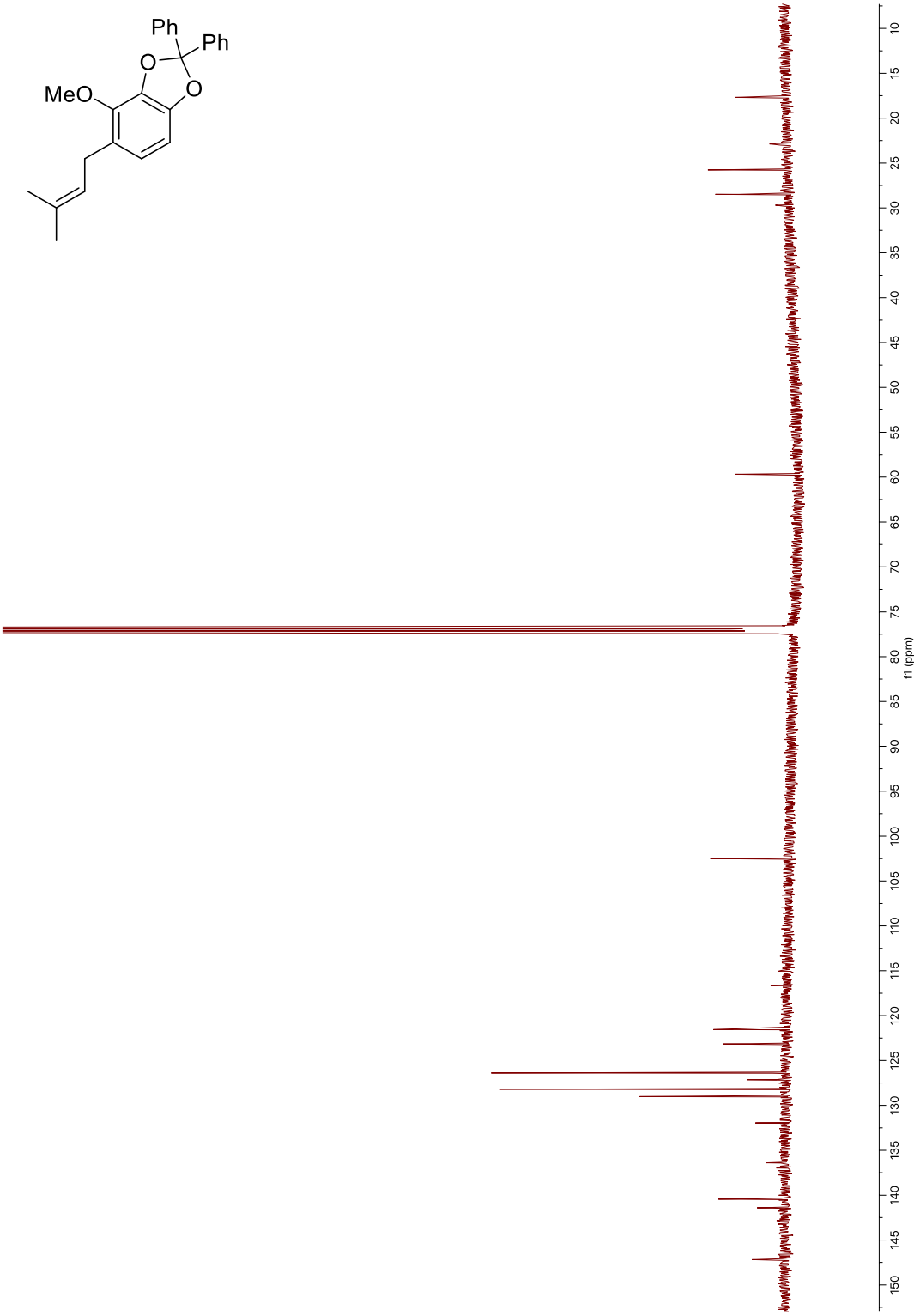
5.5.20 ^{13}C NMR Spectrum of compound 2.44 (125 MHz, $CDCl_3$)



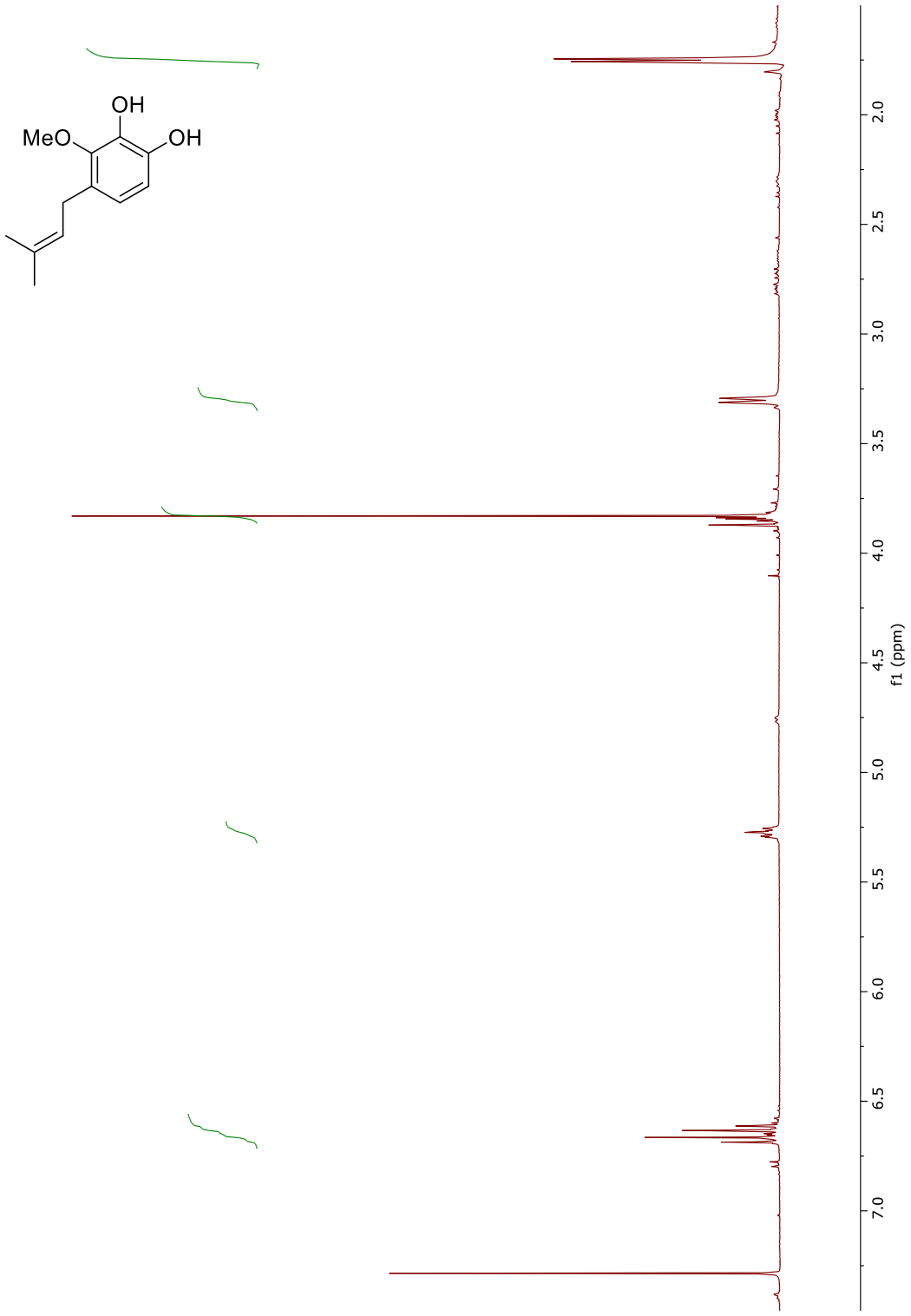
5.5.21 ^{1}H NMR Spectrum of compound 2.45 (500 MHz, $CDCl_3$)



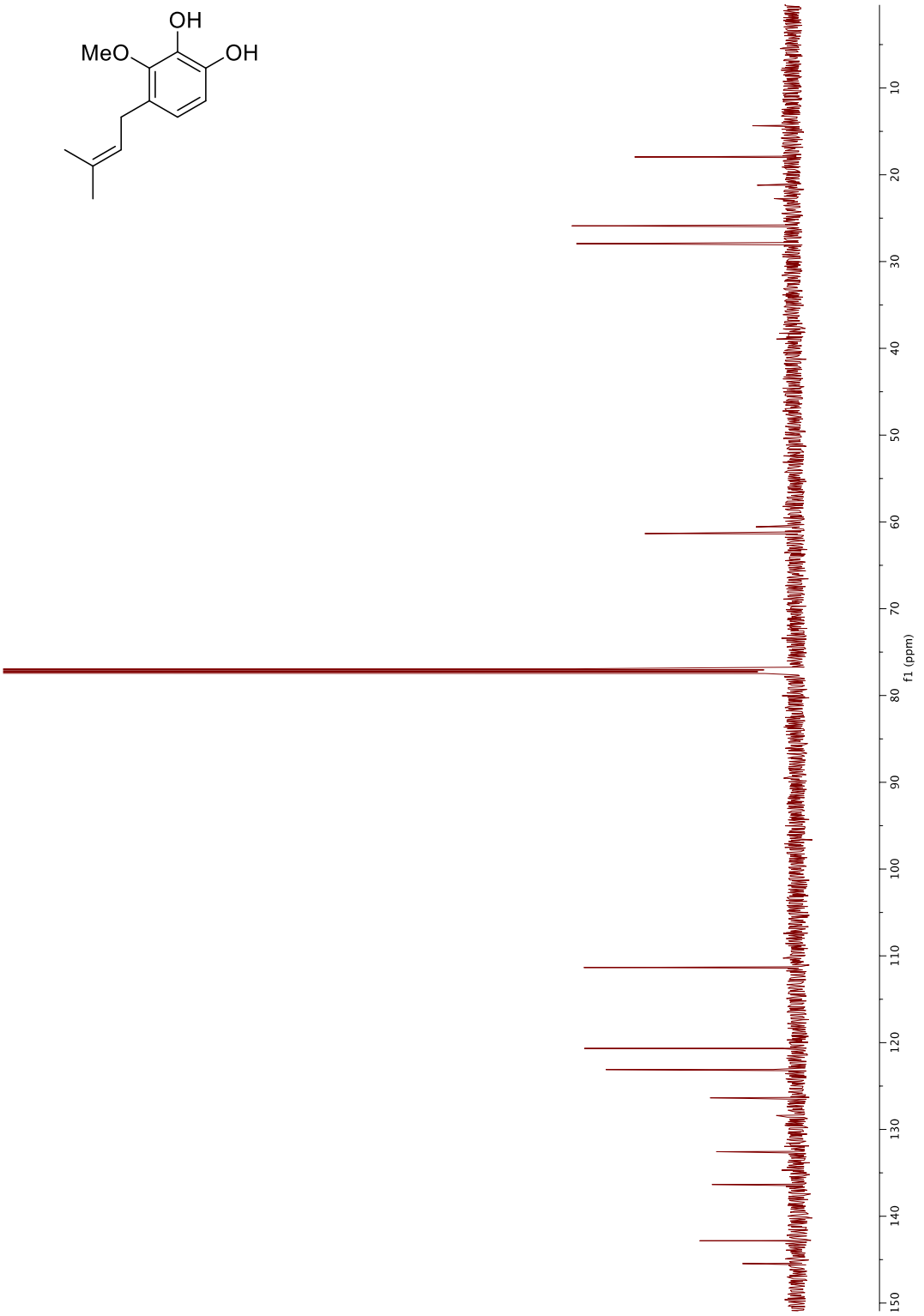
5.5.22 ^{13}C NMR Spectrum of compound 2.45 (125 MHz, $CDCl_3$)



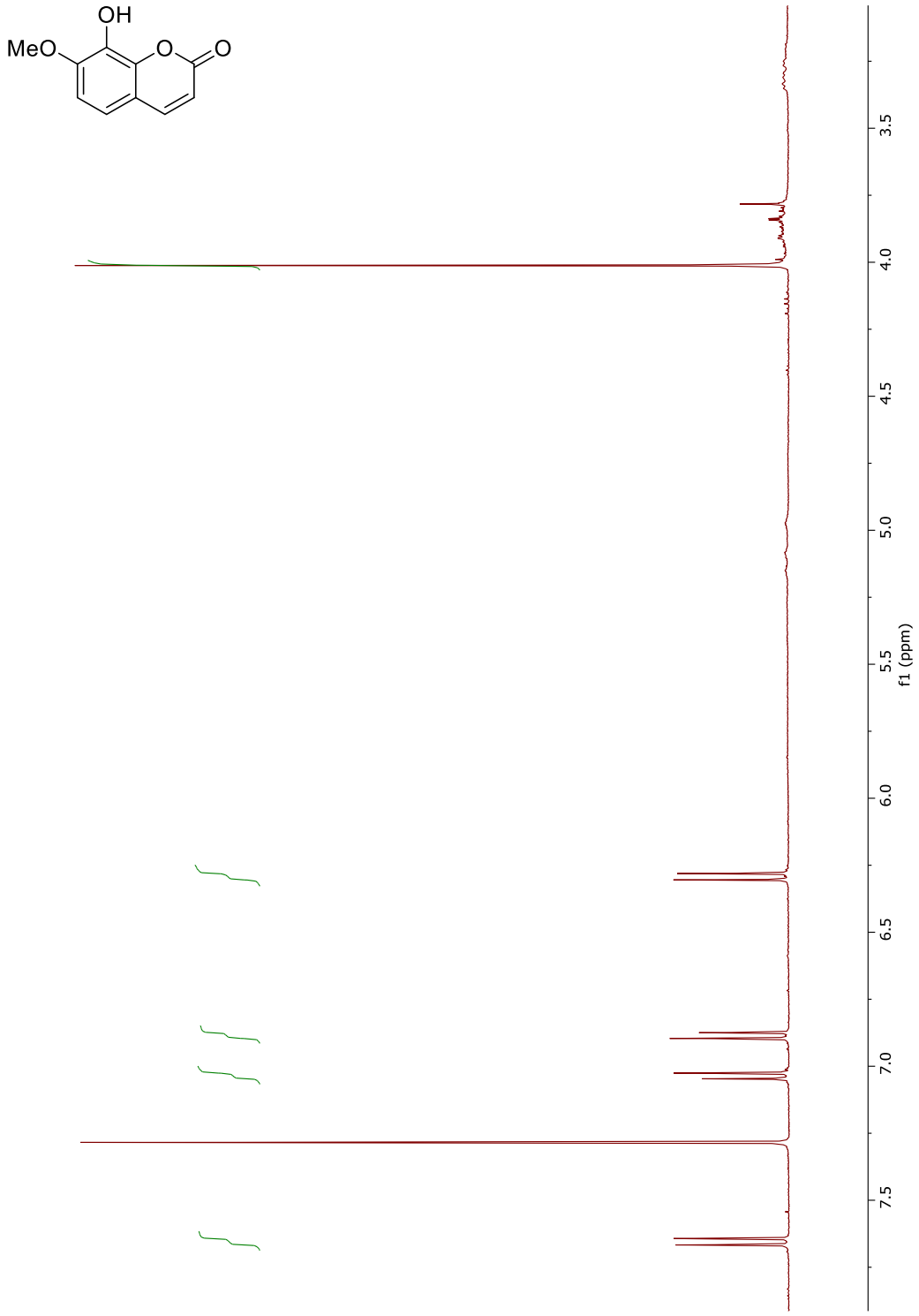
5.5.23 ^{1}H NMR Spectrum of compound 2.19 (500 MHz, $CDCl_3$)



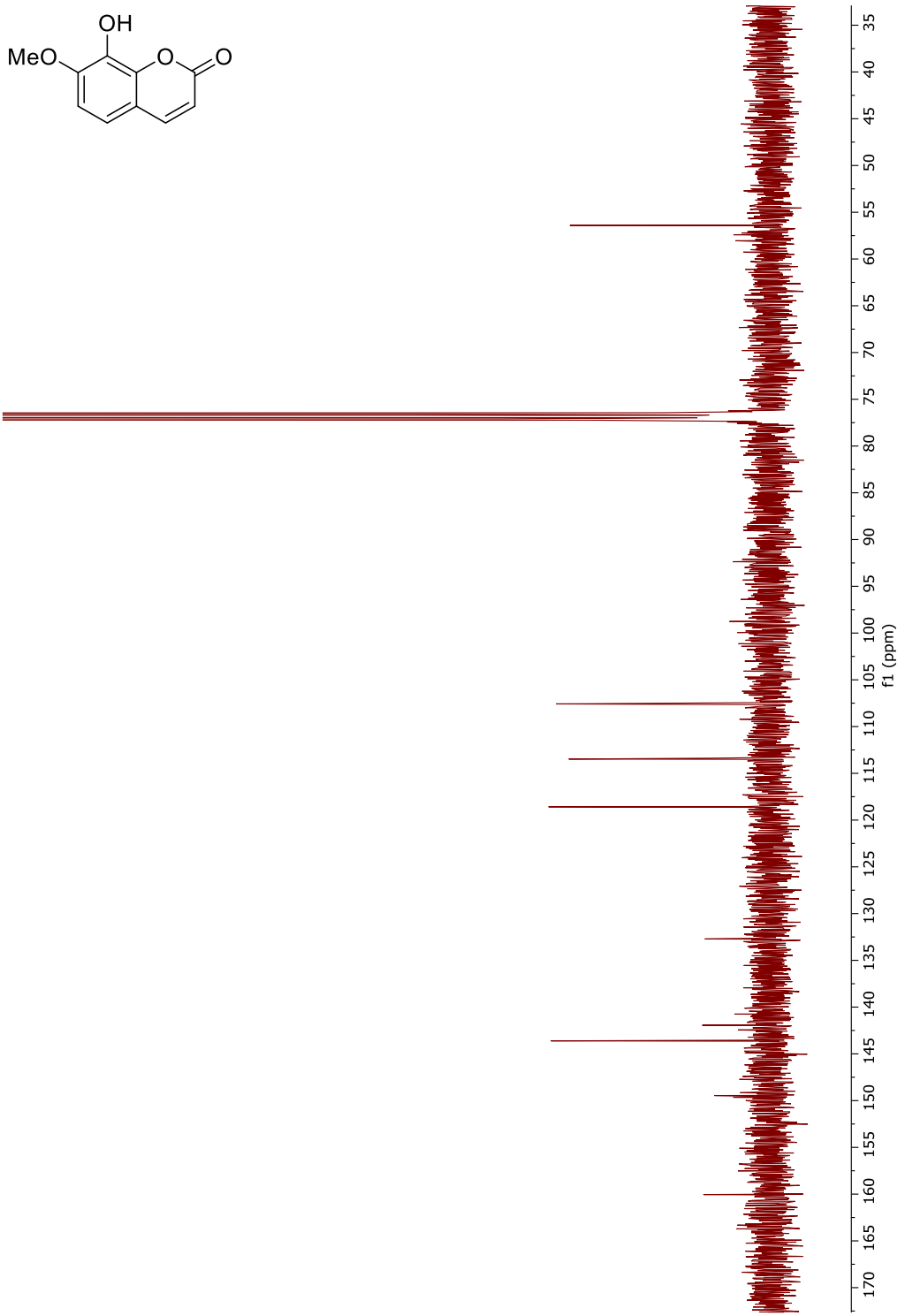
5.5.24 ^{13}C NMR Spectrum of compound 2.19 (125 MHz, $CDCl_3$)



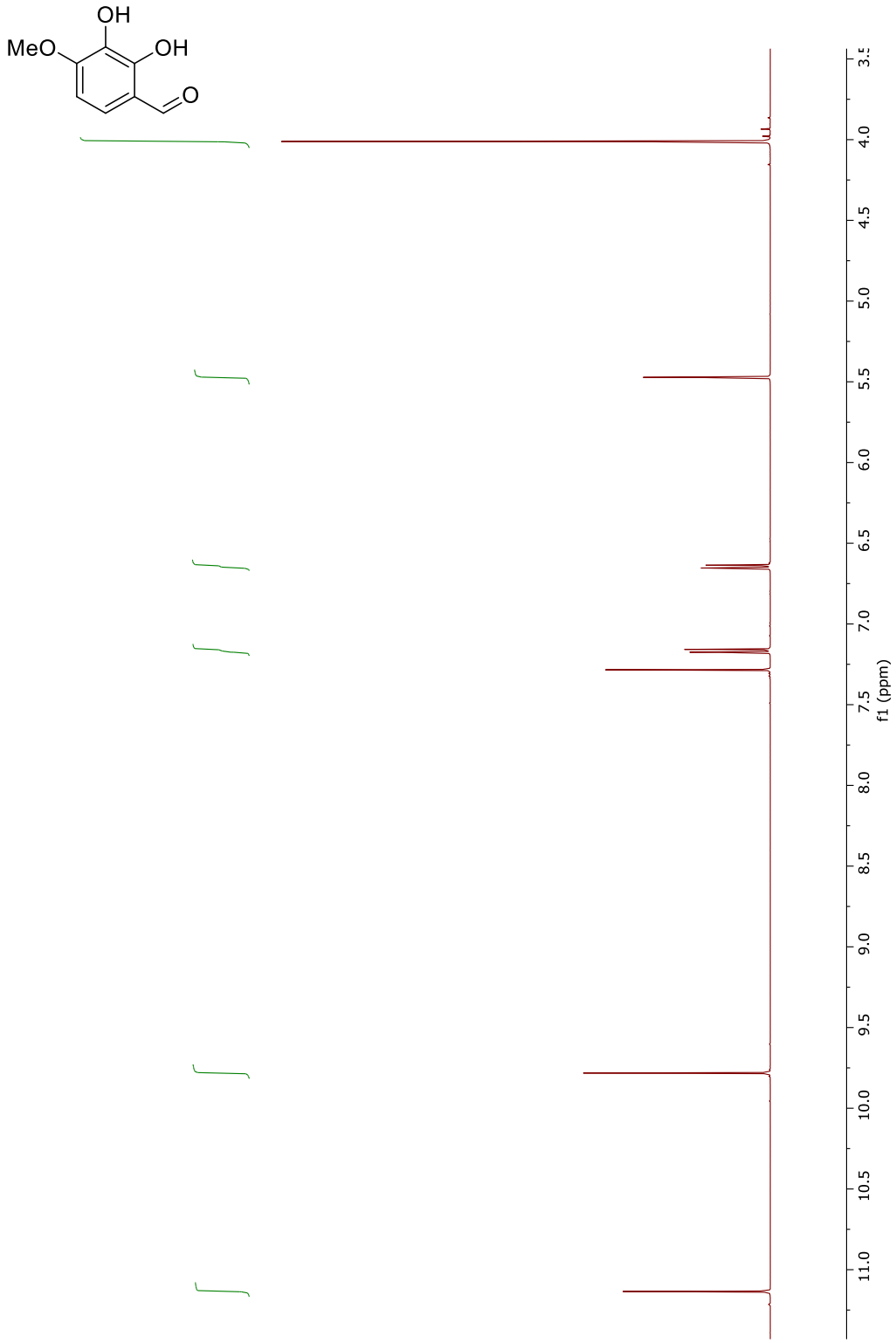
5.5.25 ^{1}H NMR Spectrum of compound 2.18 (500 MHz, $CDCl_3$)



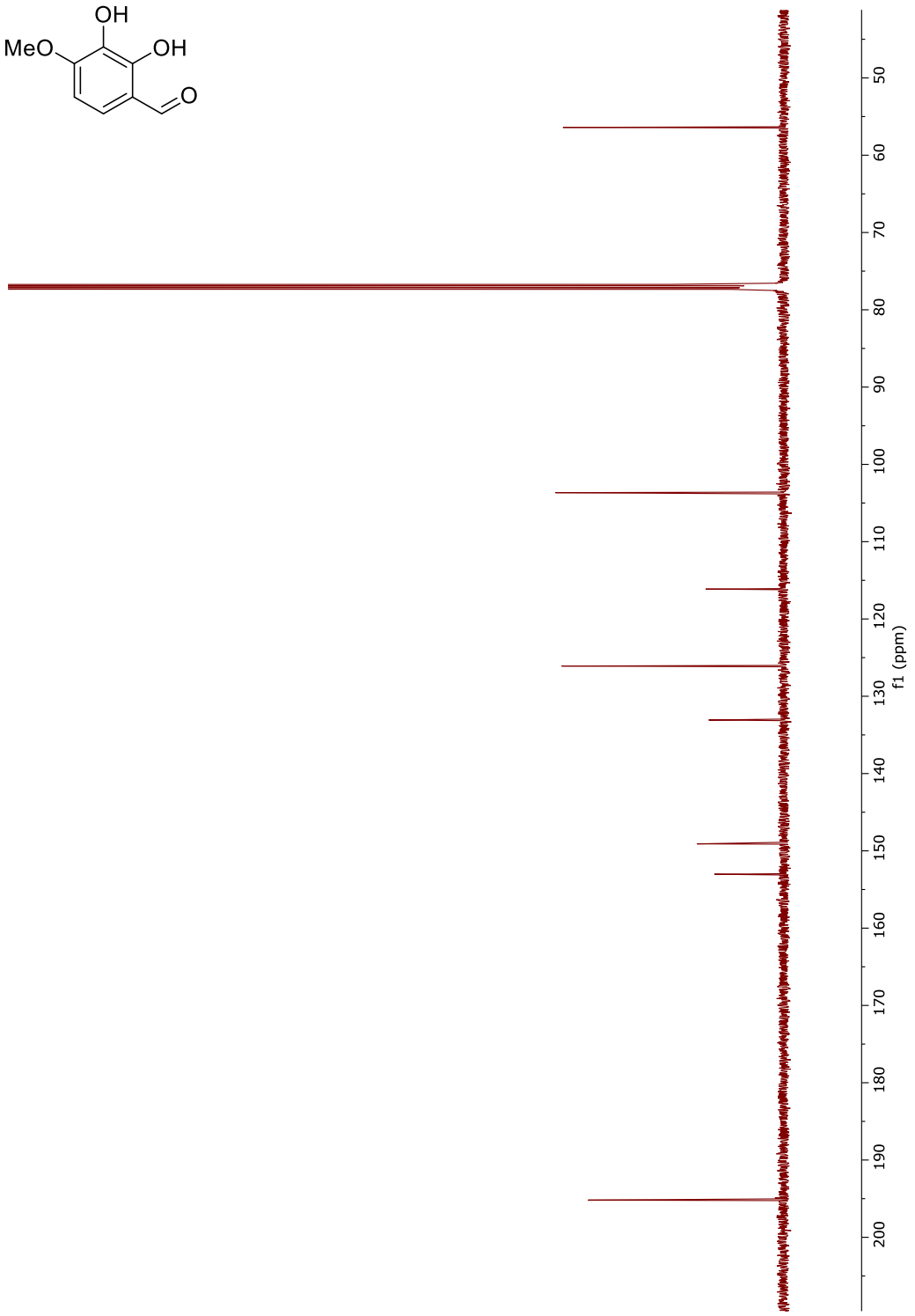
5.5.26 ^{13}C NMR Spectrum of compound 2.18 (125 MHz, $CDCl_3$)



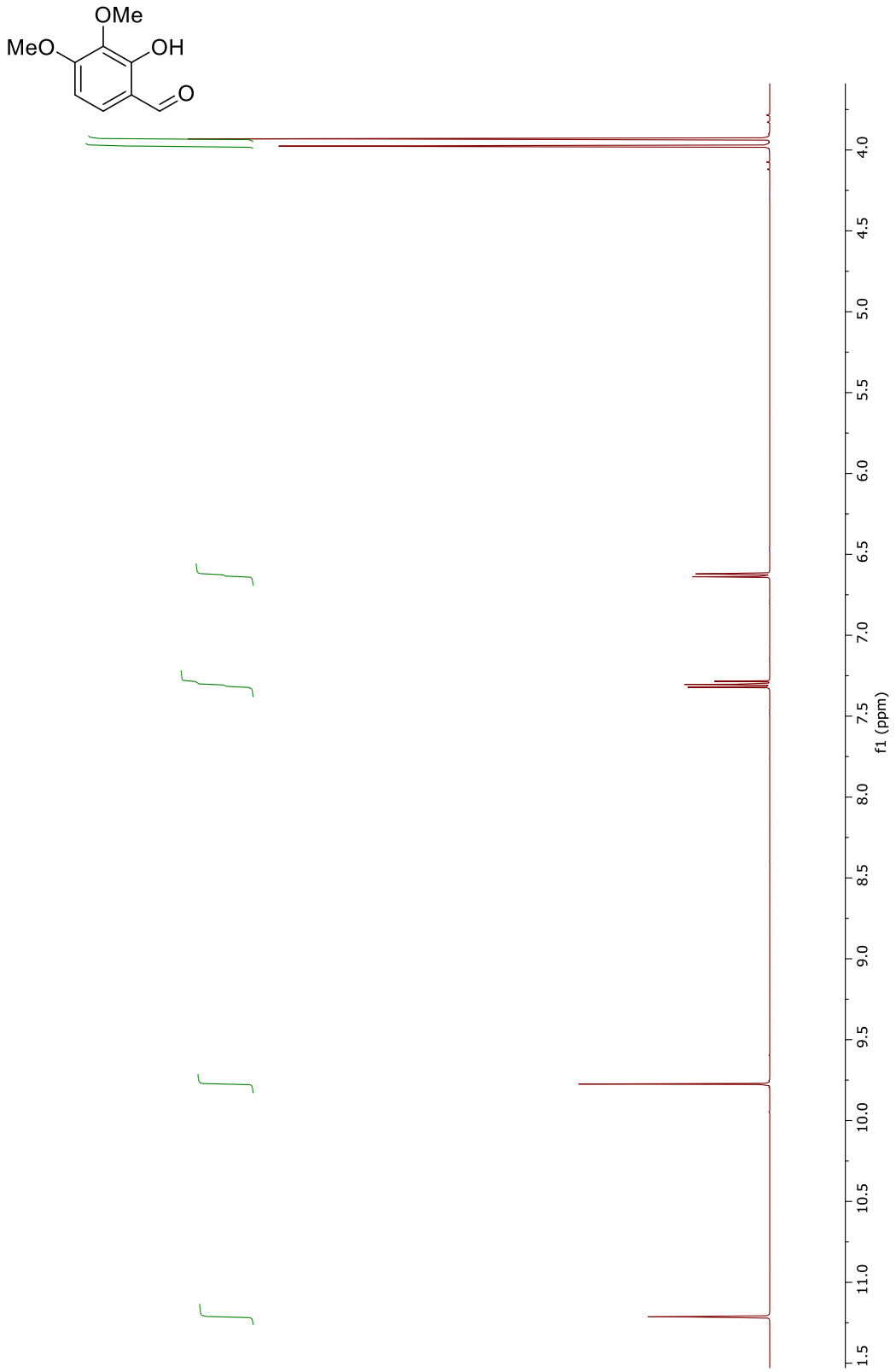
5.5.27 ^{1}H NMR Spectrum of compound 2.54 (500 MHz, $CDCl_3$)



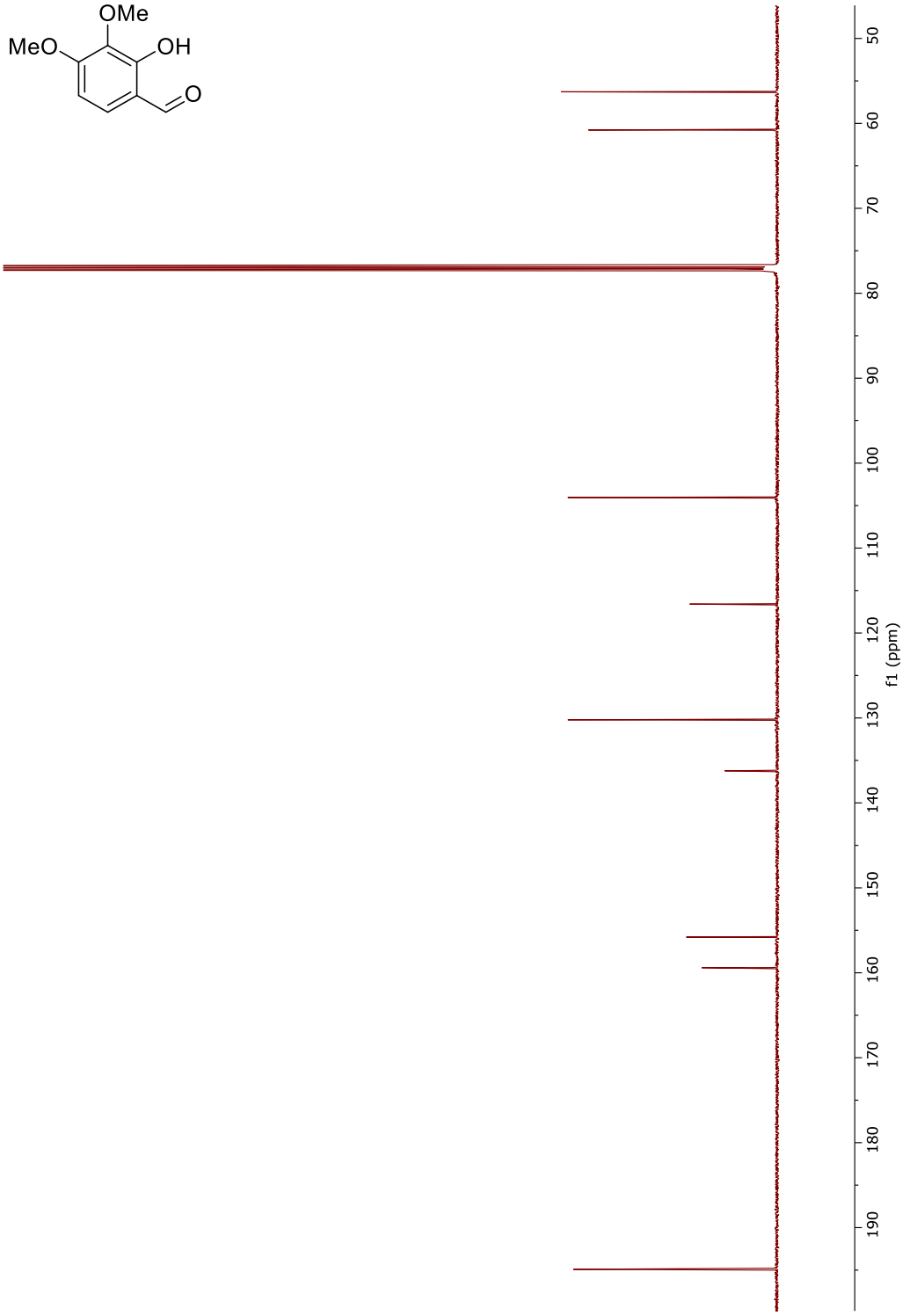
5.5.28 ^{13}C NMR Spectrum of compound 2.54 (125 MHz, $CDCl_3$)



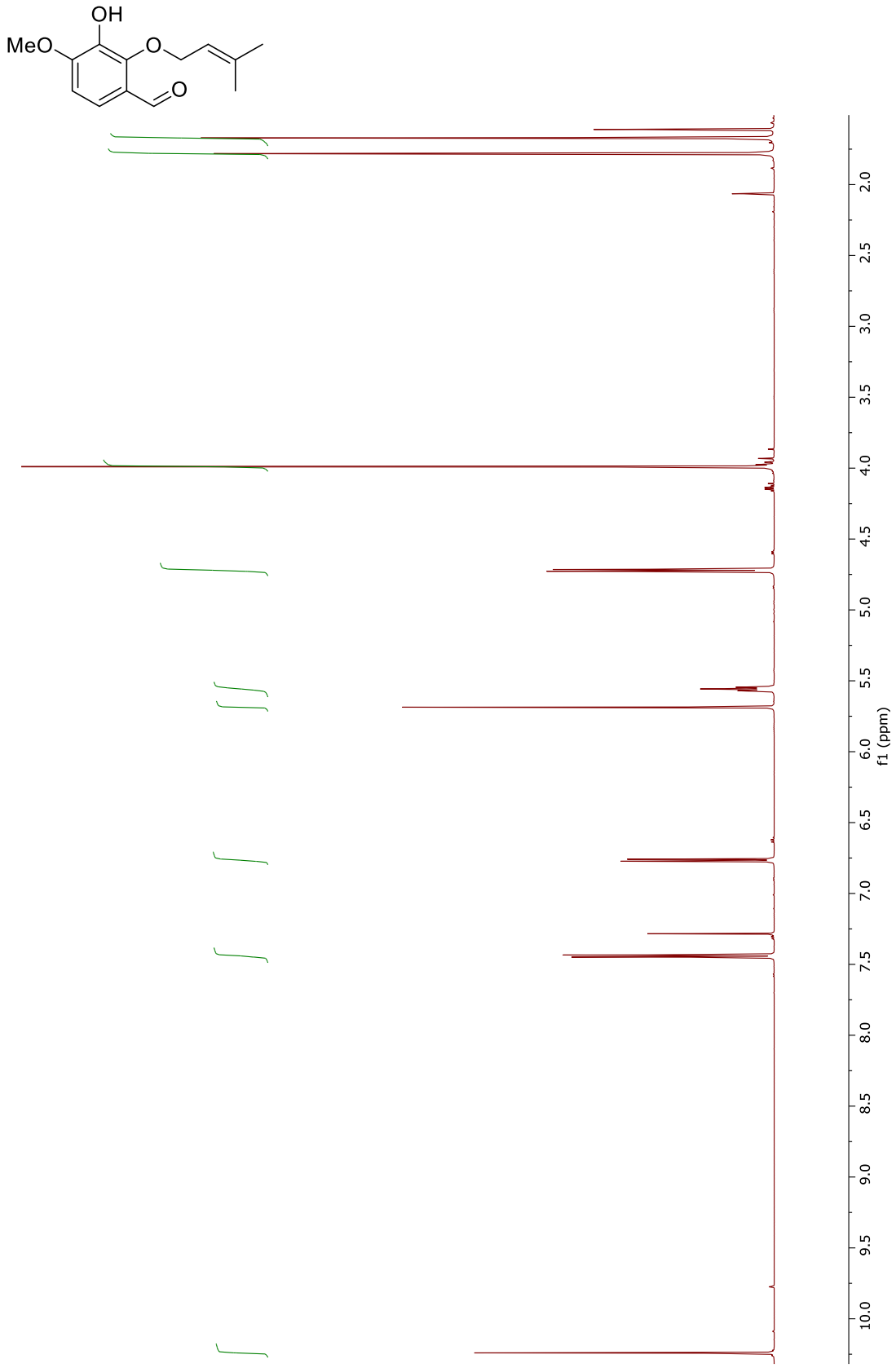
5.5.29 ^{1}H NMR Spectrum of compound 2.56 (500 MHz, $CDCl_3$)



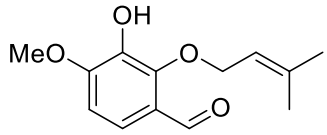
5.5.30 ^{13}C NMR Spectrum of compound 2.56 (125 MHz, $CDCl_3$)

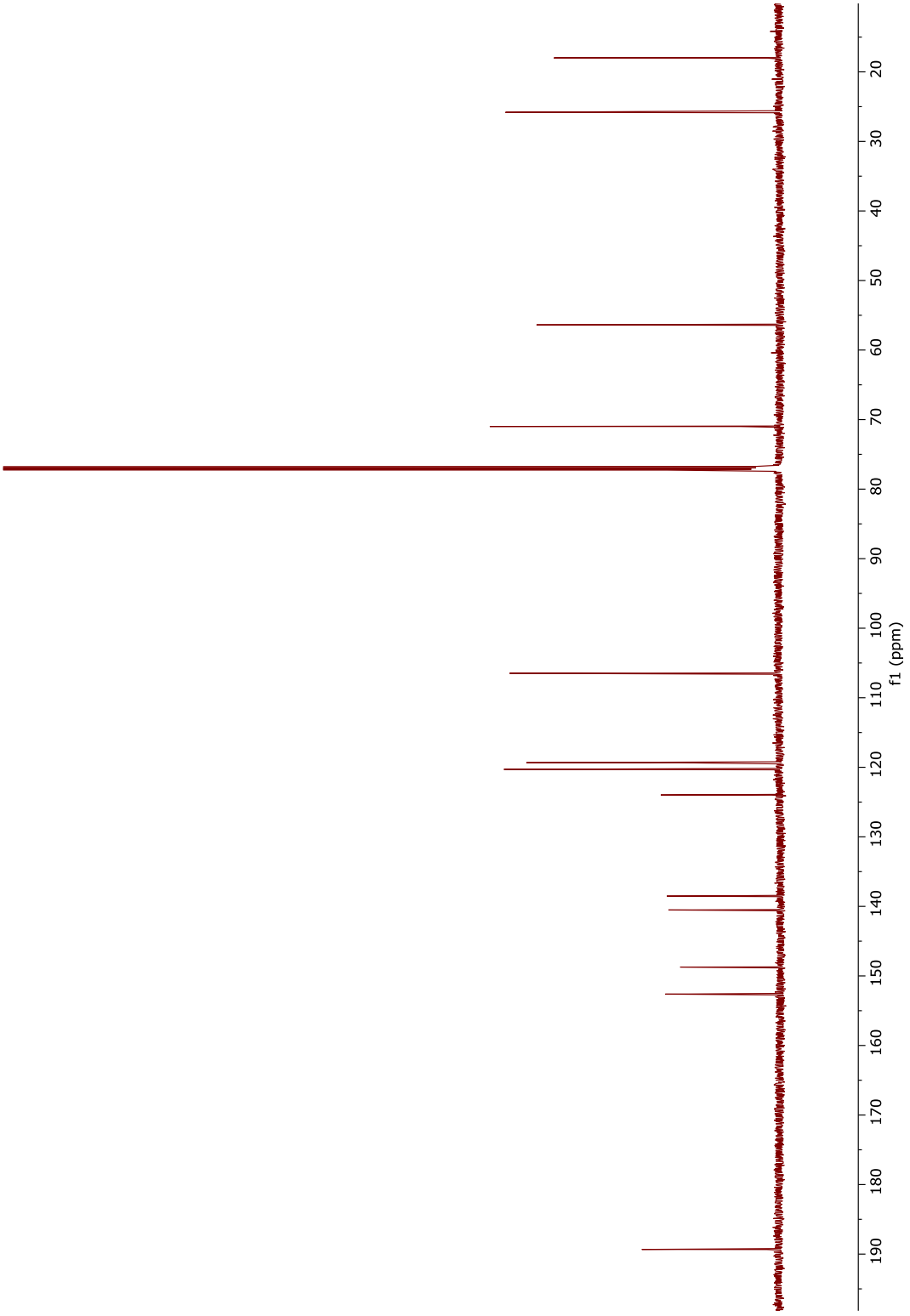


5.5.31 ^{1}H NMR Spectrum of compound 2.55 (500 MHz, $CDCl_3$)

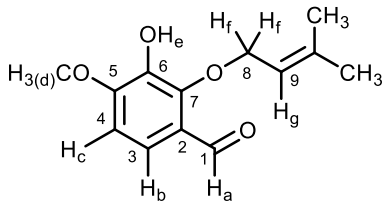


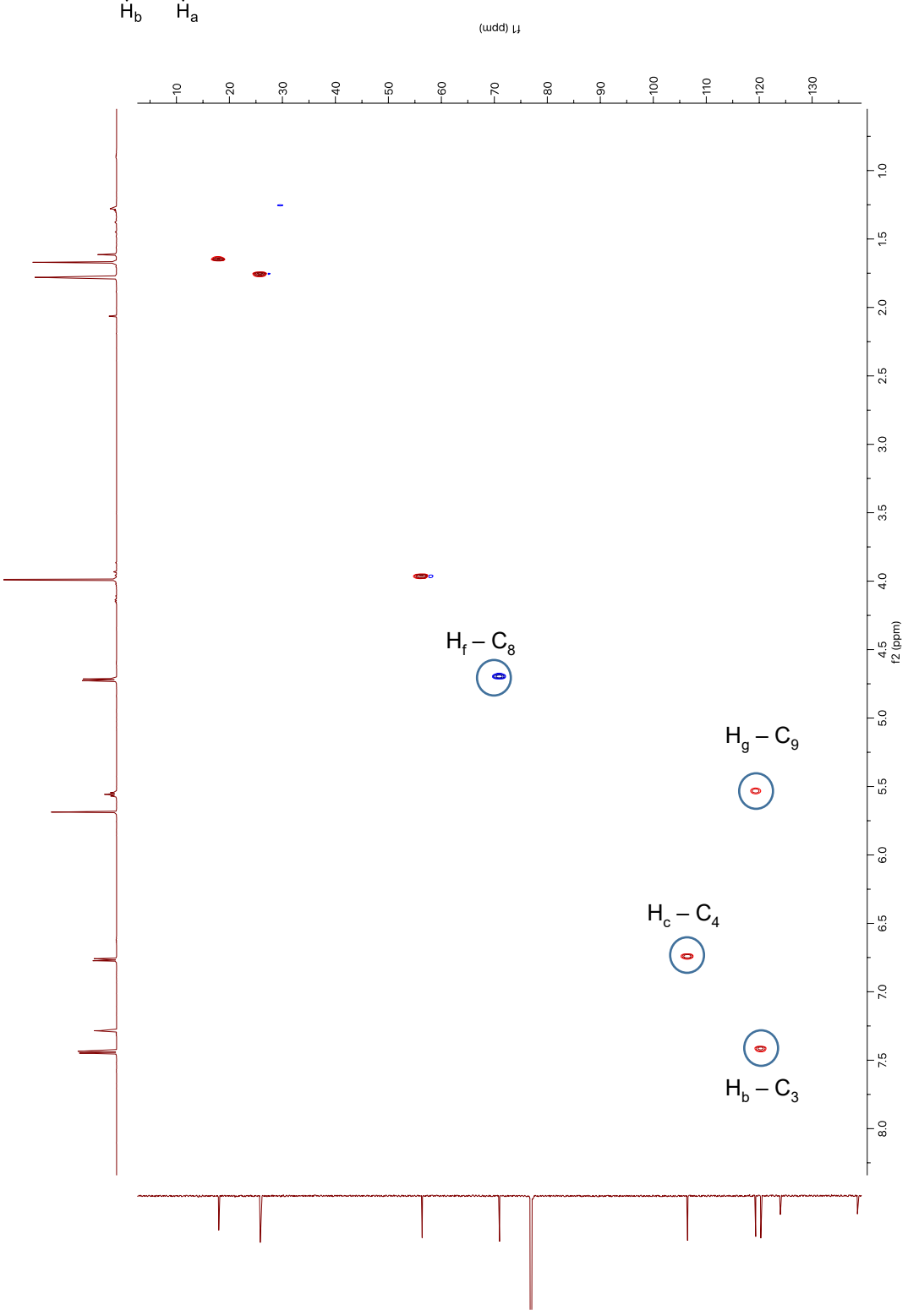
5.5.32 ^{13}C NMR Spectrum of compound 2.55 (125 MHz, $CDCl_3$)



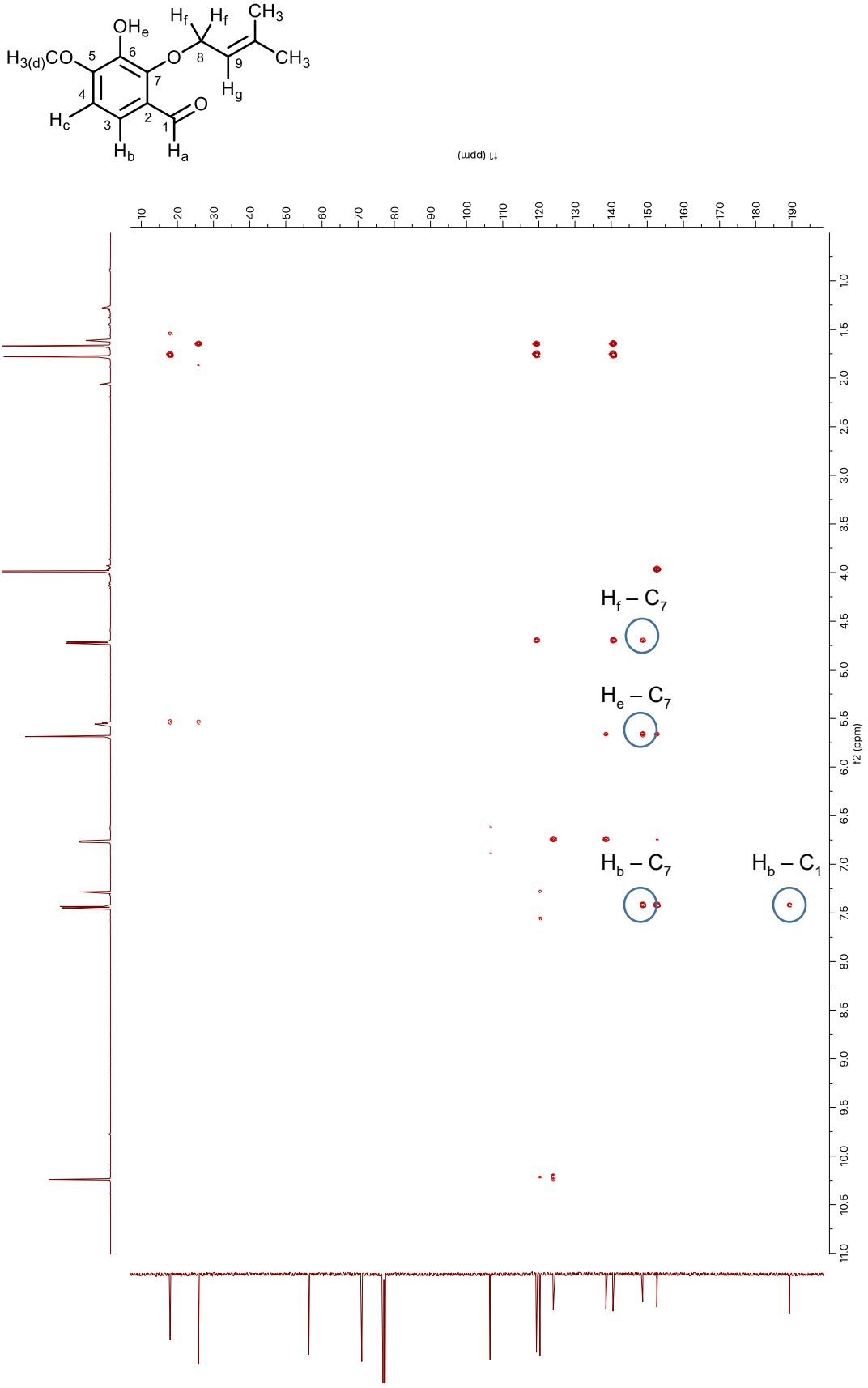


5.5.33 ^{1}H-^{13}C HSQC Spectrum of compound 2.55 (500 MHz, $CDCl_3$)

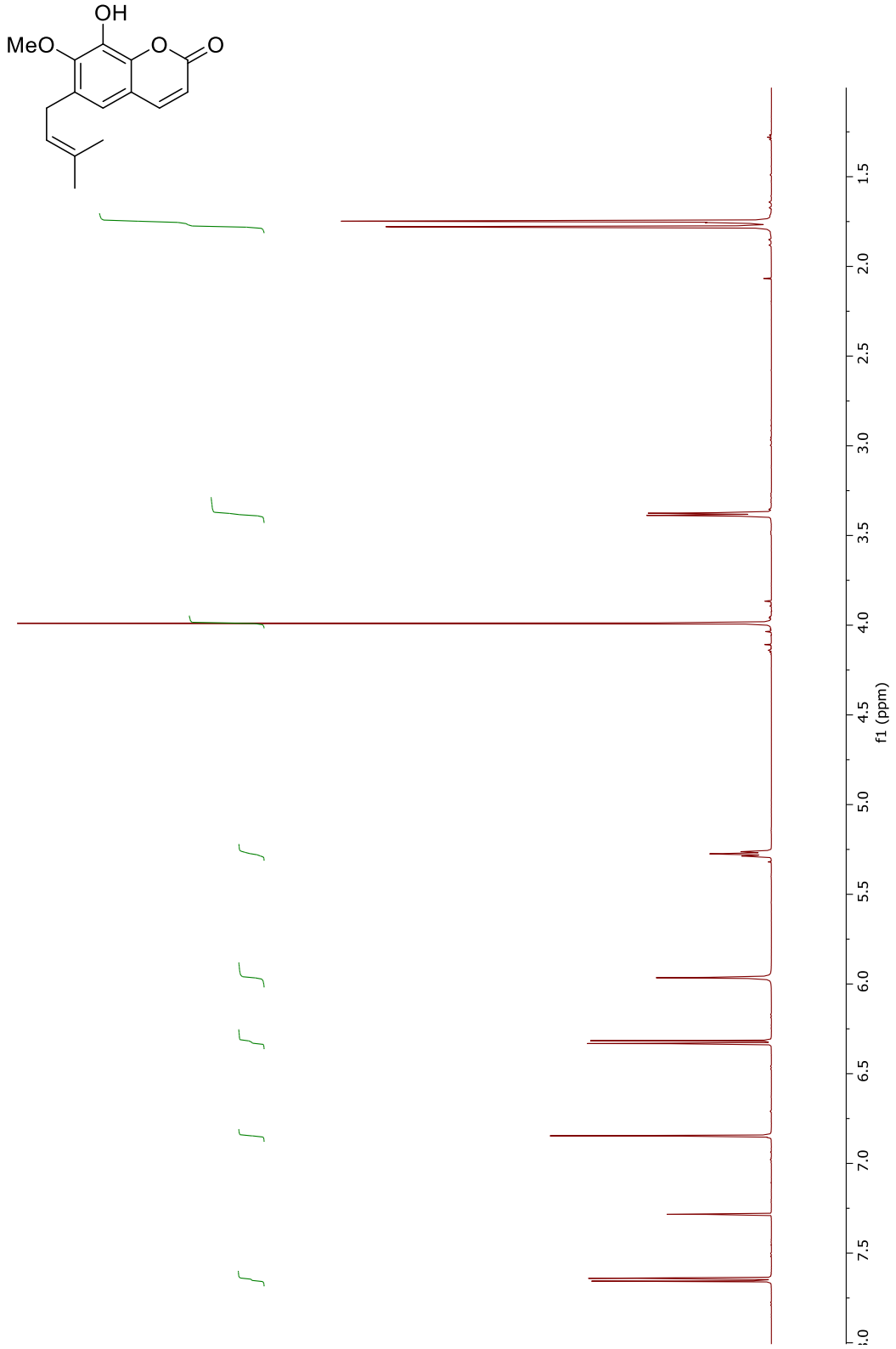




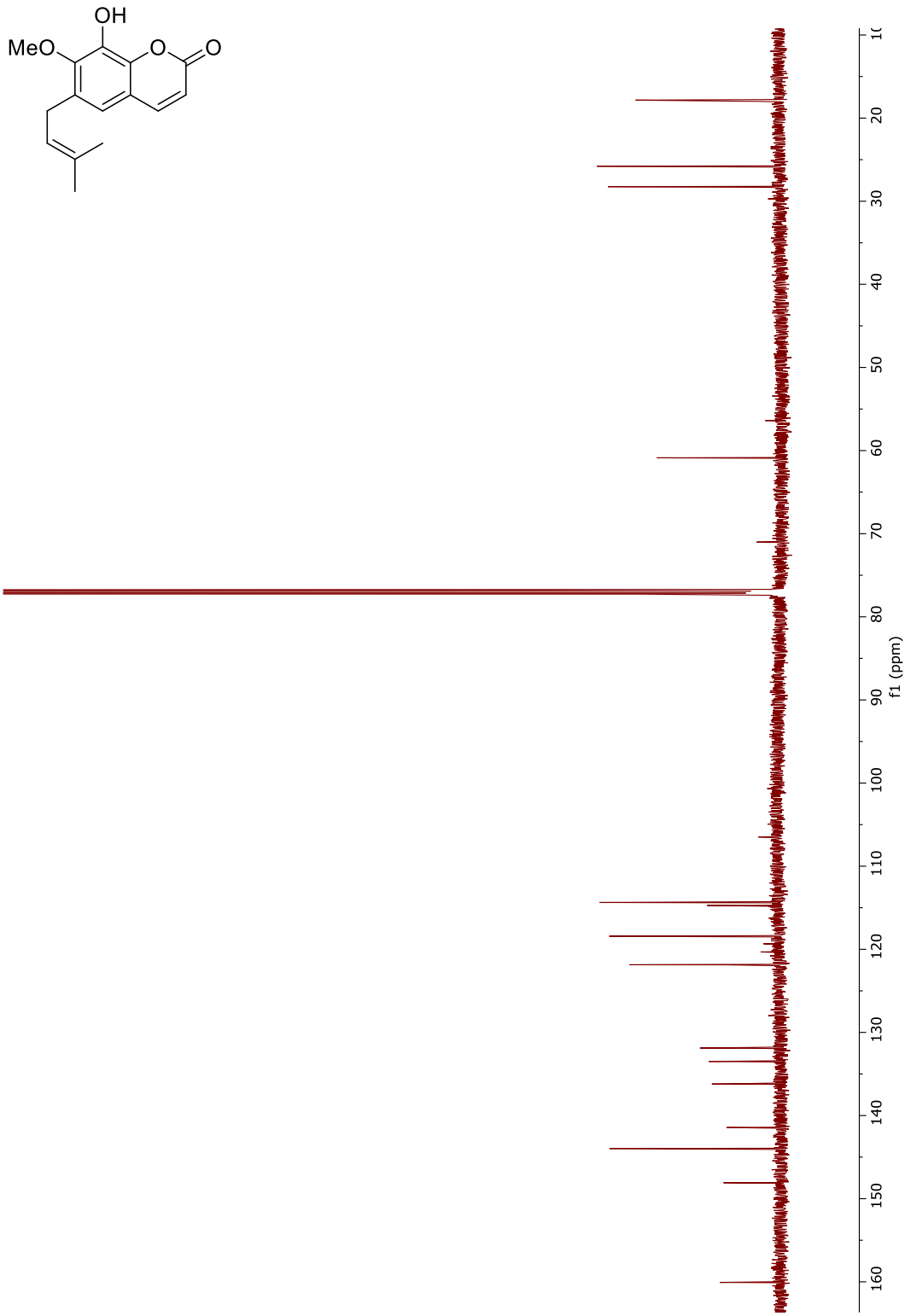
5.5.34 ^{1}H-^{13}C HMBC spectrum of compound 2.55 (500 MHz, $CDCl_3$)



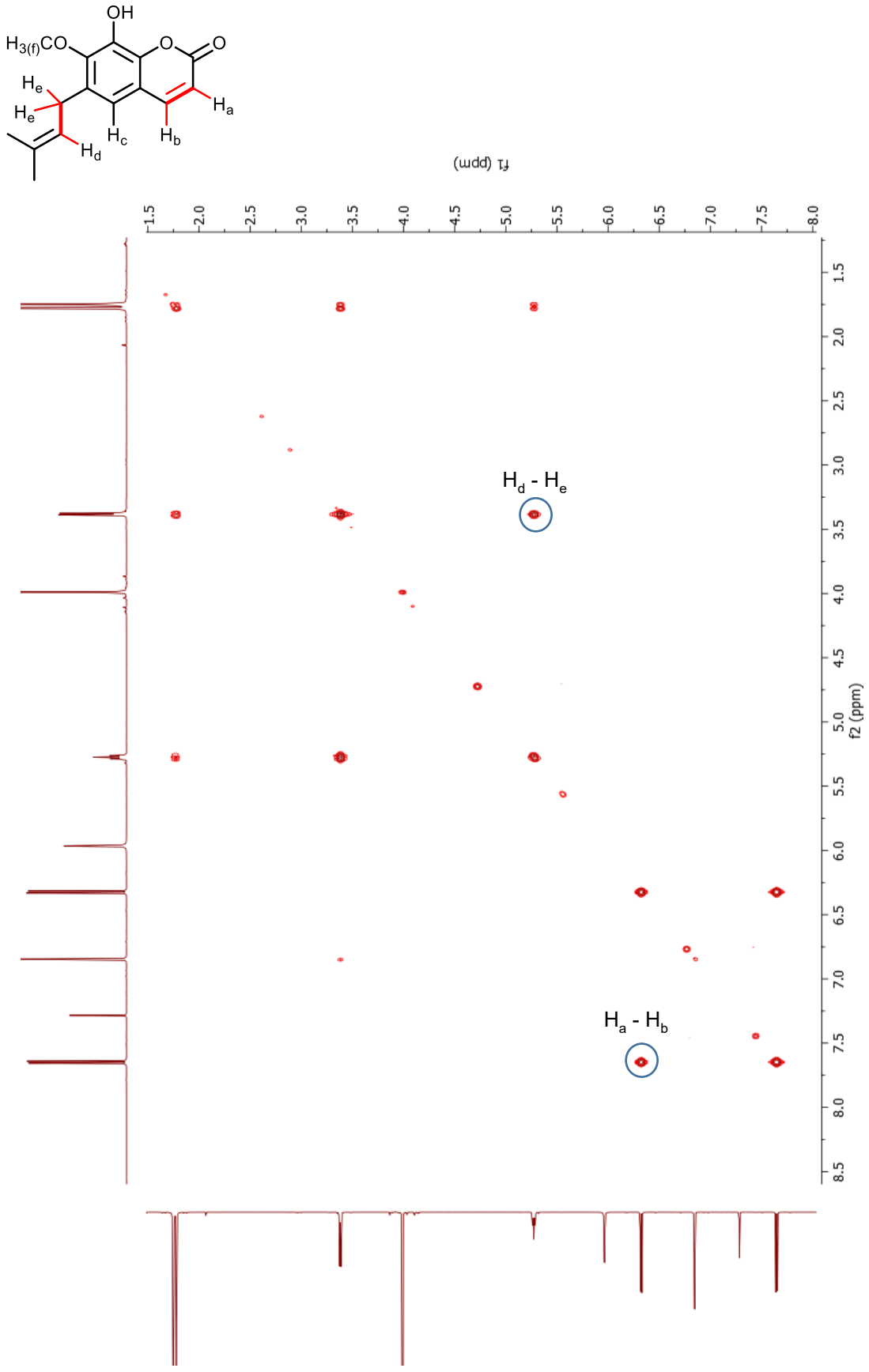
5.5.35 ^{1}H NMR Spectrum of brosipain 1.46(500 MHz, $CDCl_3$)



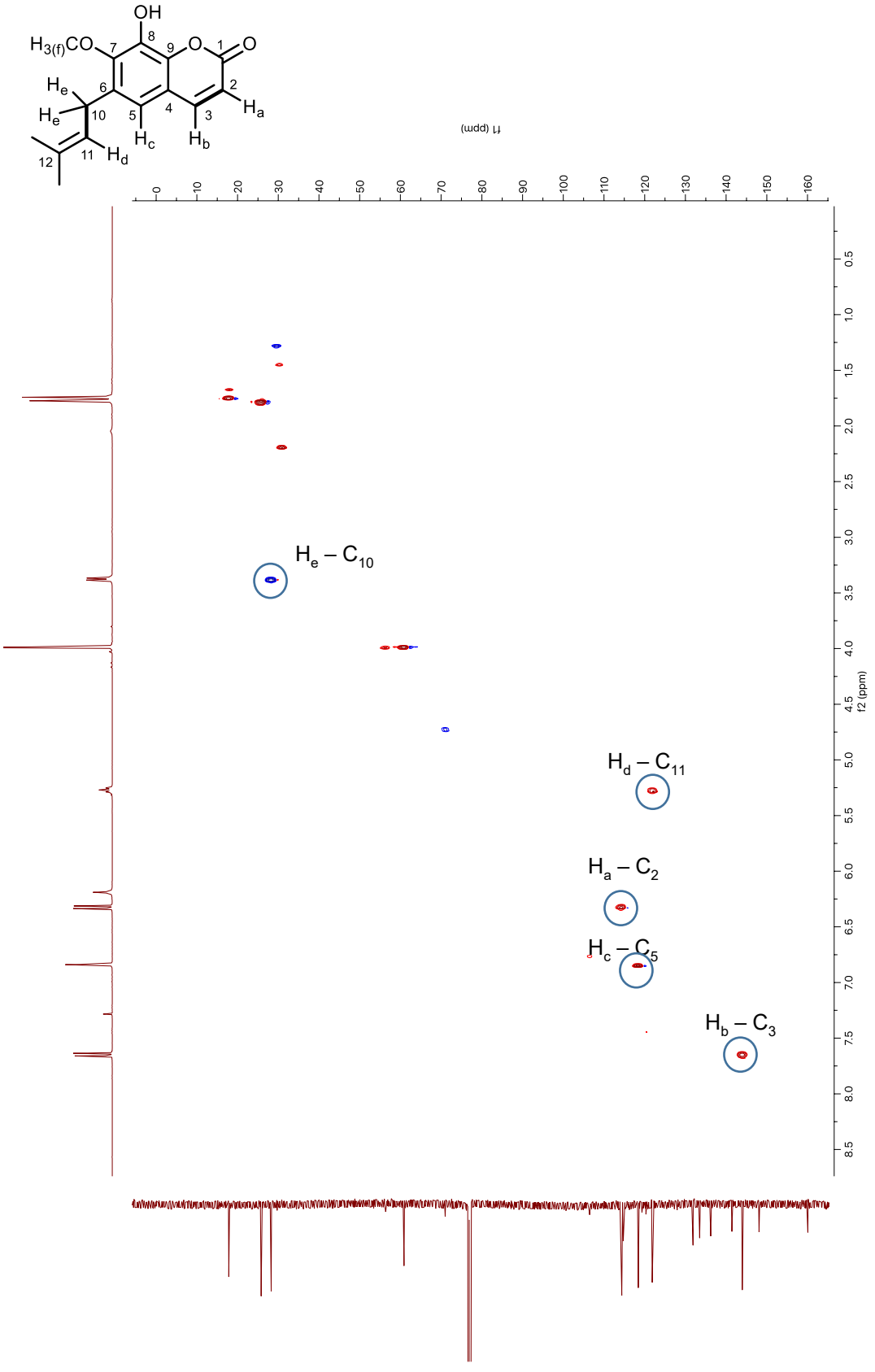
5.5.36 ^{13}C NMR Spectrum of brosiparin 1.46 (125 MHz, $CDCl_3$)



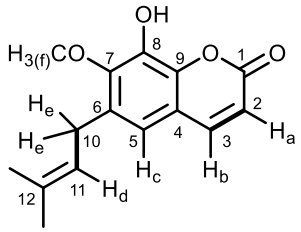
5.5.37 ^{1}H-^{1}H COSY Spectrum of brosiparin 1.46 (500 MHz, $CDCl_3$)

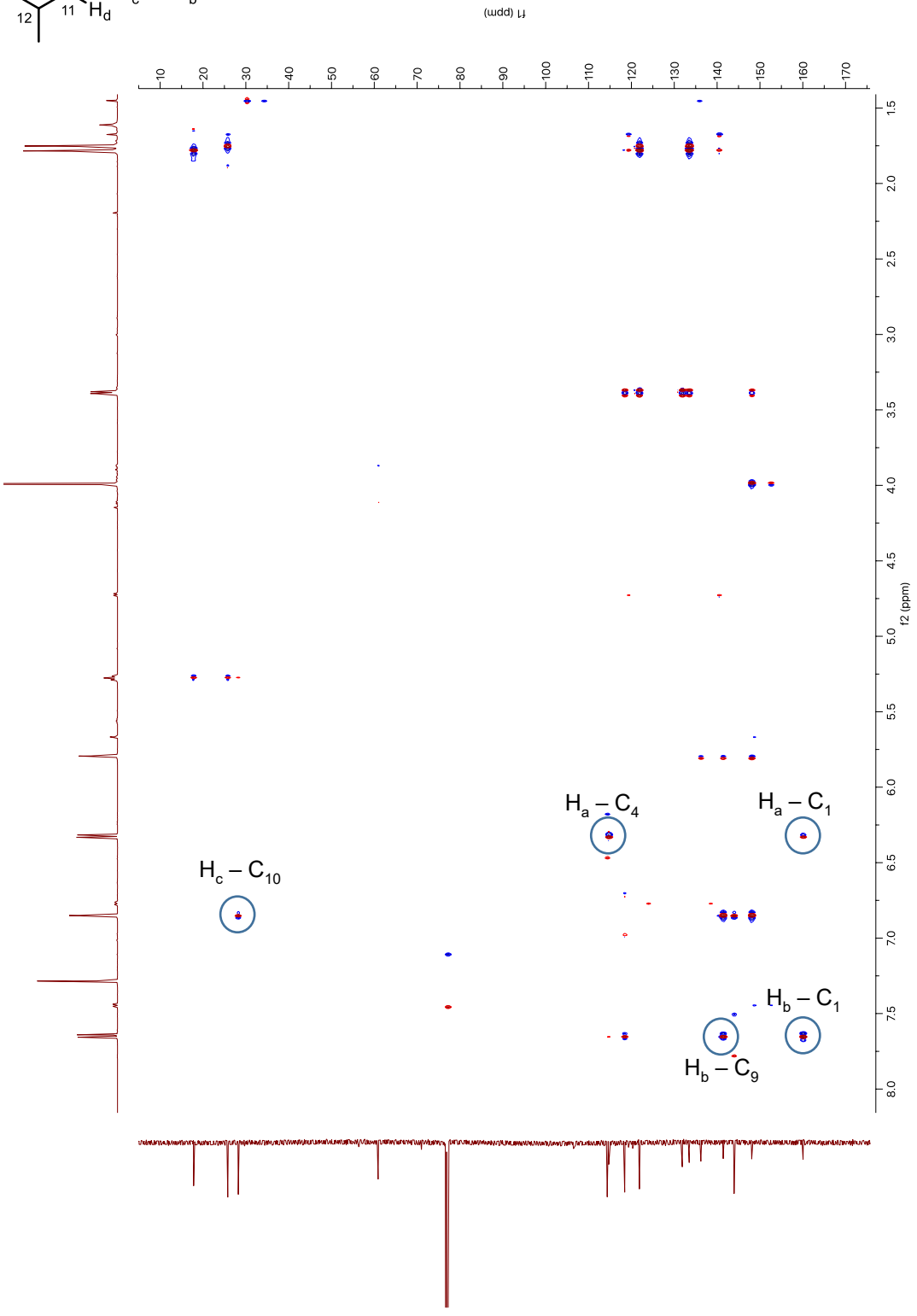


5.5.38 ^{1}H-^{13}C HSQC Spectrum of brosiparin 1.46 (500 MHz, $CDCl_3$)

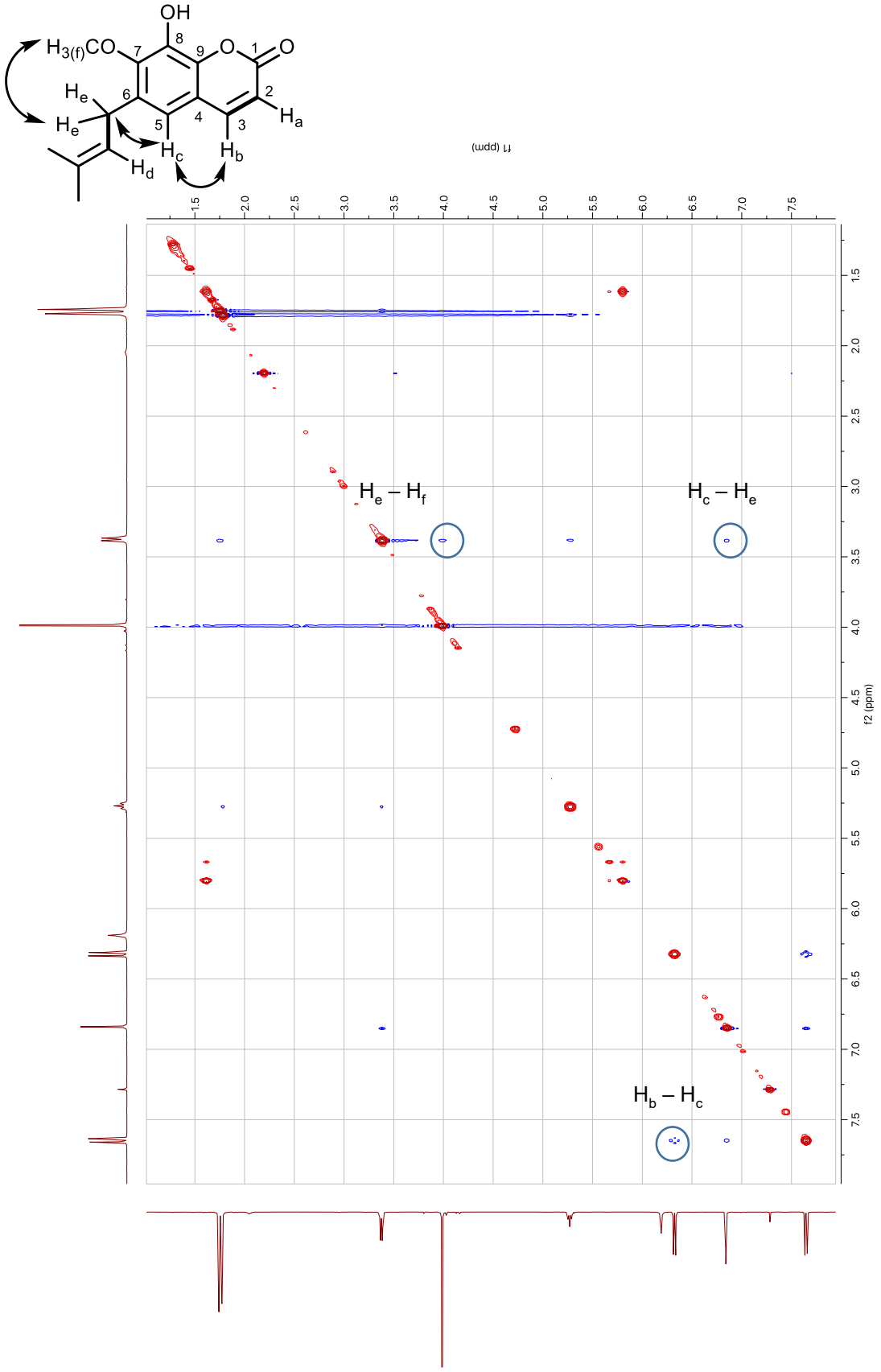


5.5.39 ^{1}H-^{13}C HMBC spectrum of brosiparin 1.46 (500 MHz, $CDCl_3$)



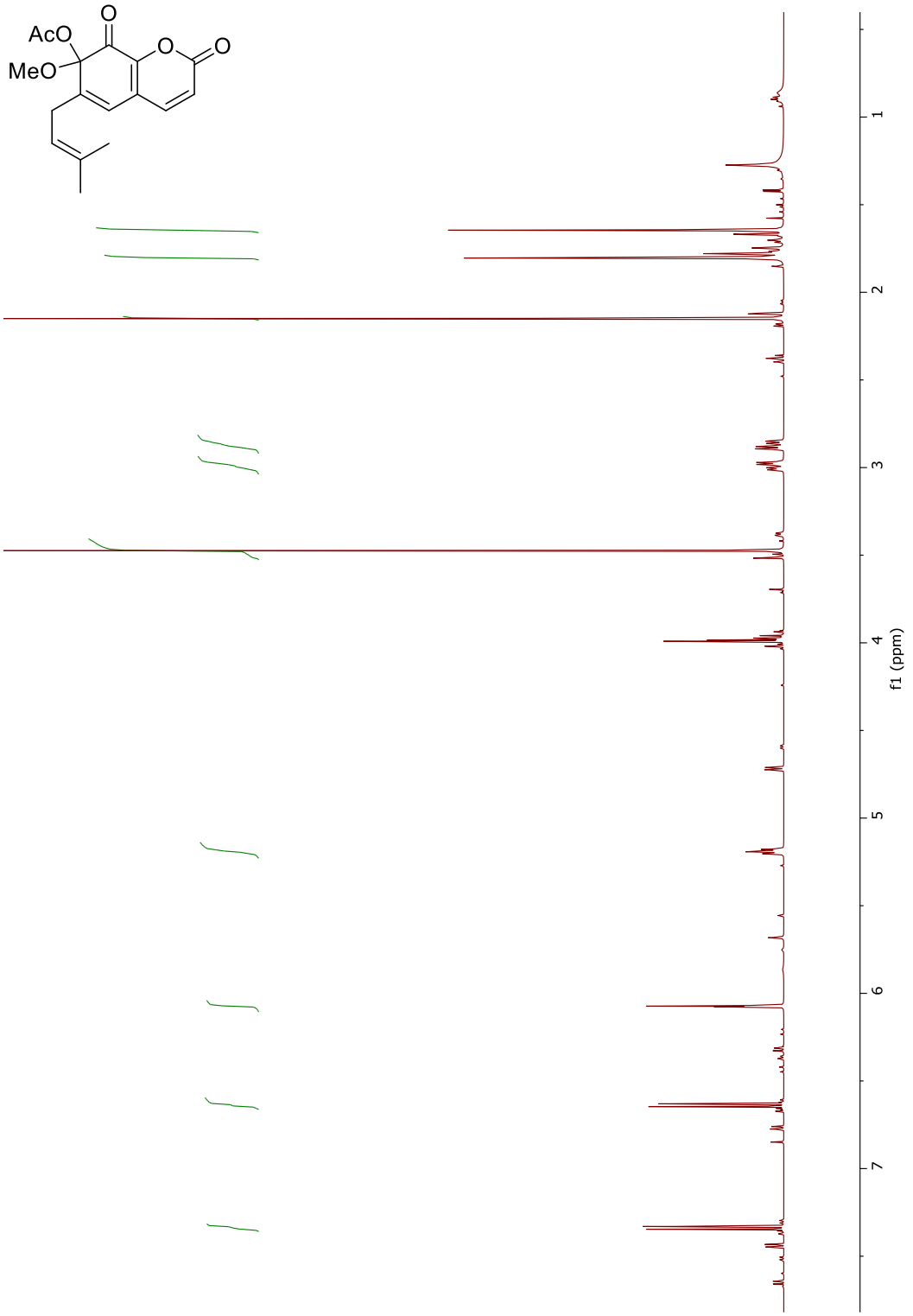


5.5.40 ^{1}H-^{1}H NOESY Spectrum of brosiparin 1.46 (500 MHz, $CDCl_3$)

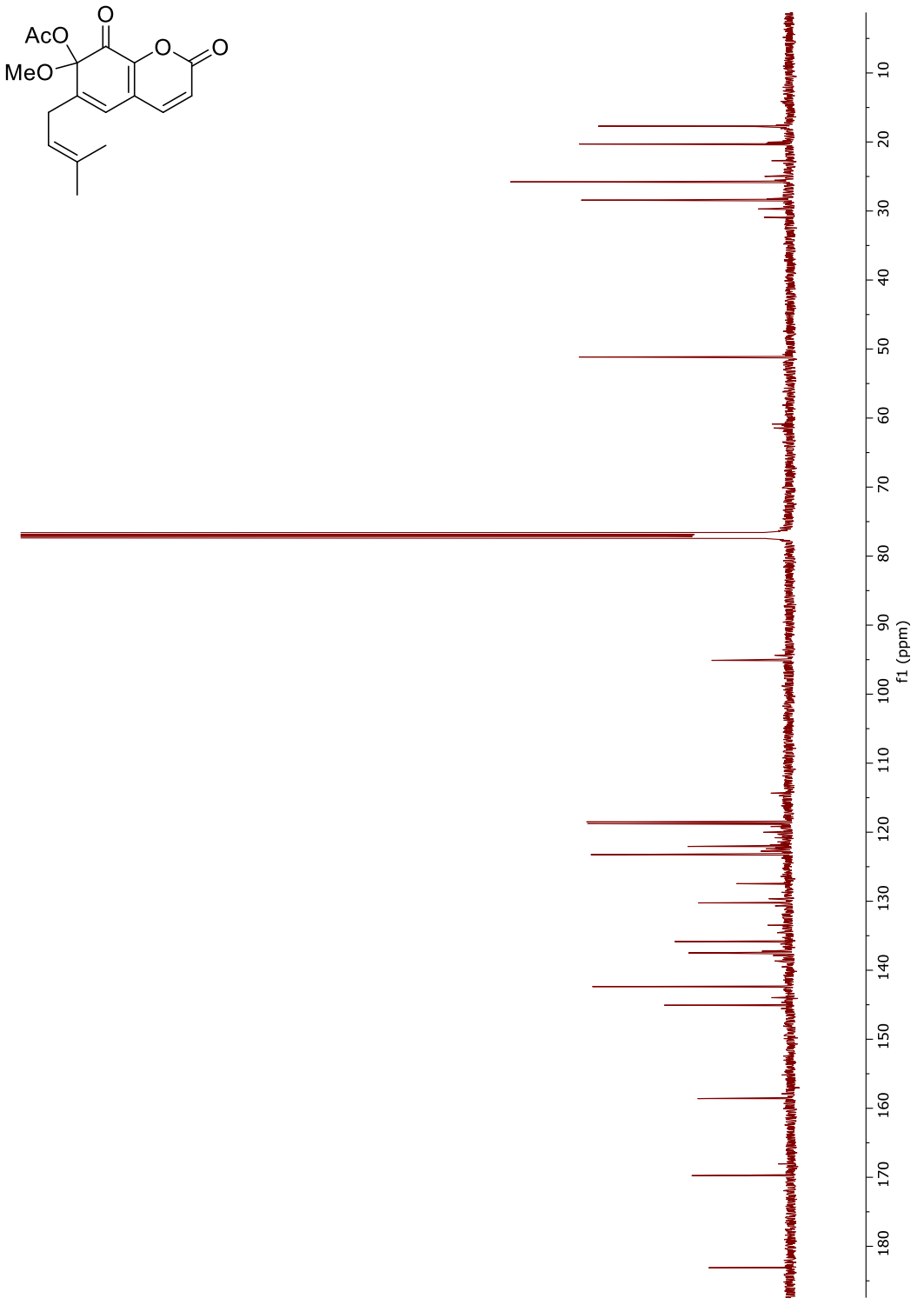


5.6 - NMR Spectra Chapter 3 – Oxidation Chemistry of Brosiparin

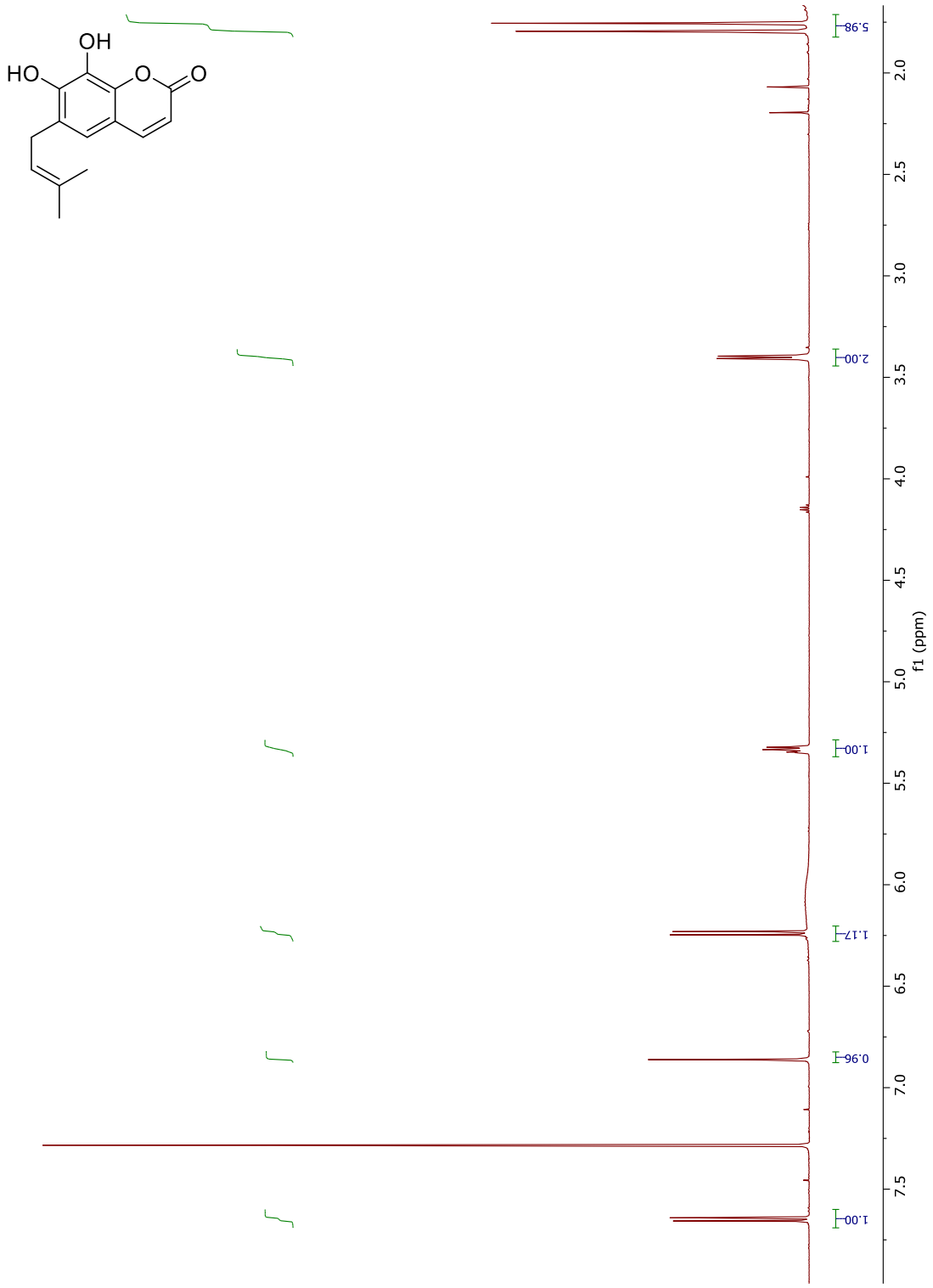
5.6.1 ^{1}H NMR Spectrum of compound 3.19 (600 MHz, $CDCl_3$)



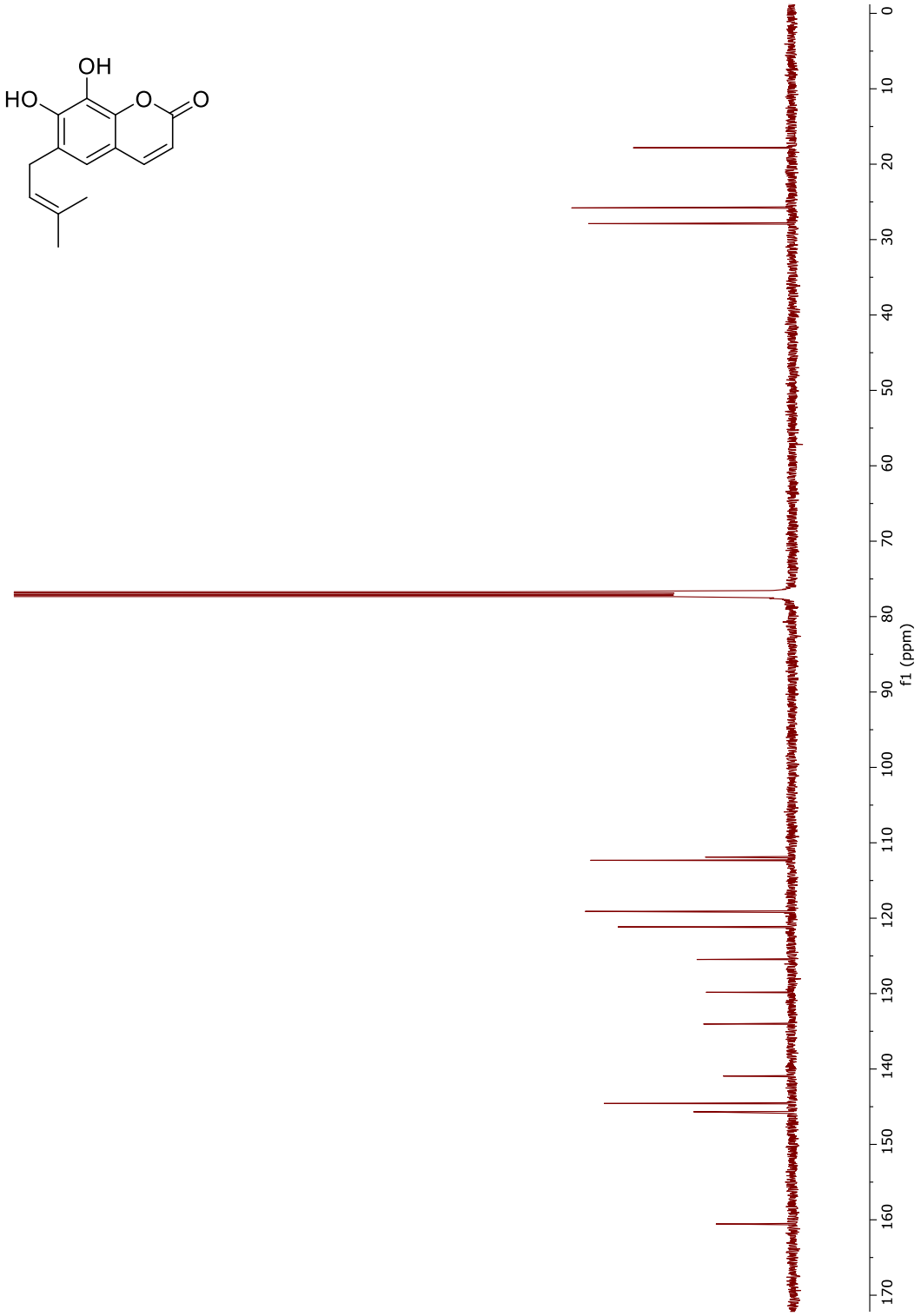
5.6.2 ^{13}C NMR Spectrum of compound 3.19 (125 MHz, $CDCl_3$)



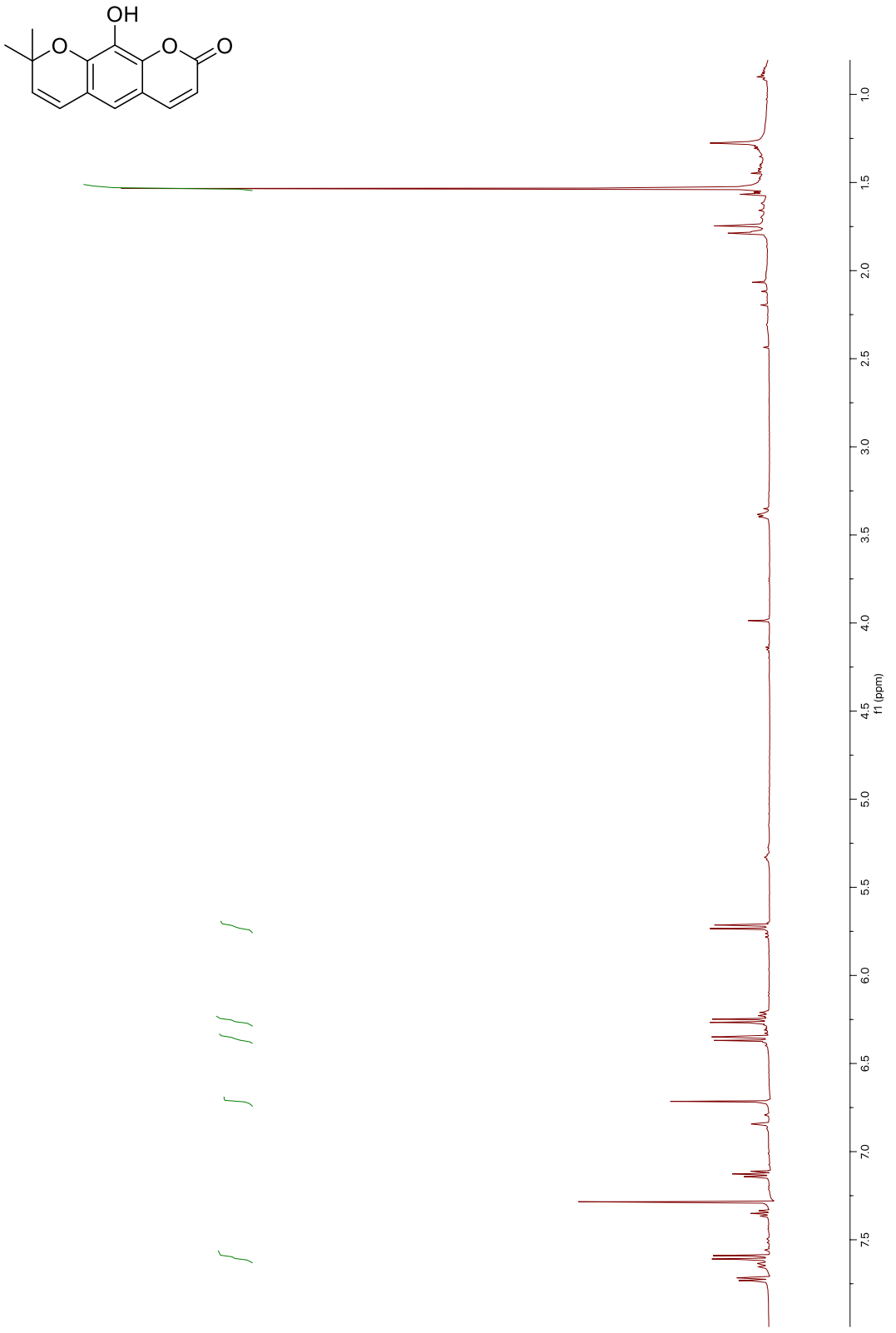
5.6.3 ^{1}H NMR Spectrum of compound 2.7 (600 MHz, $CDCl_3$)



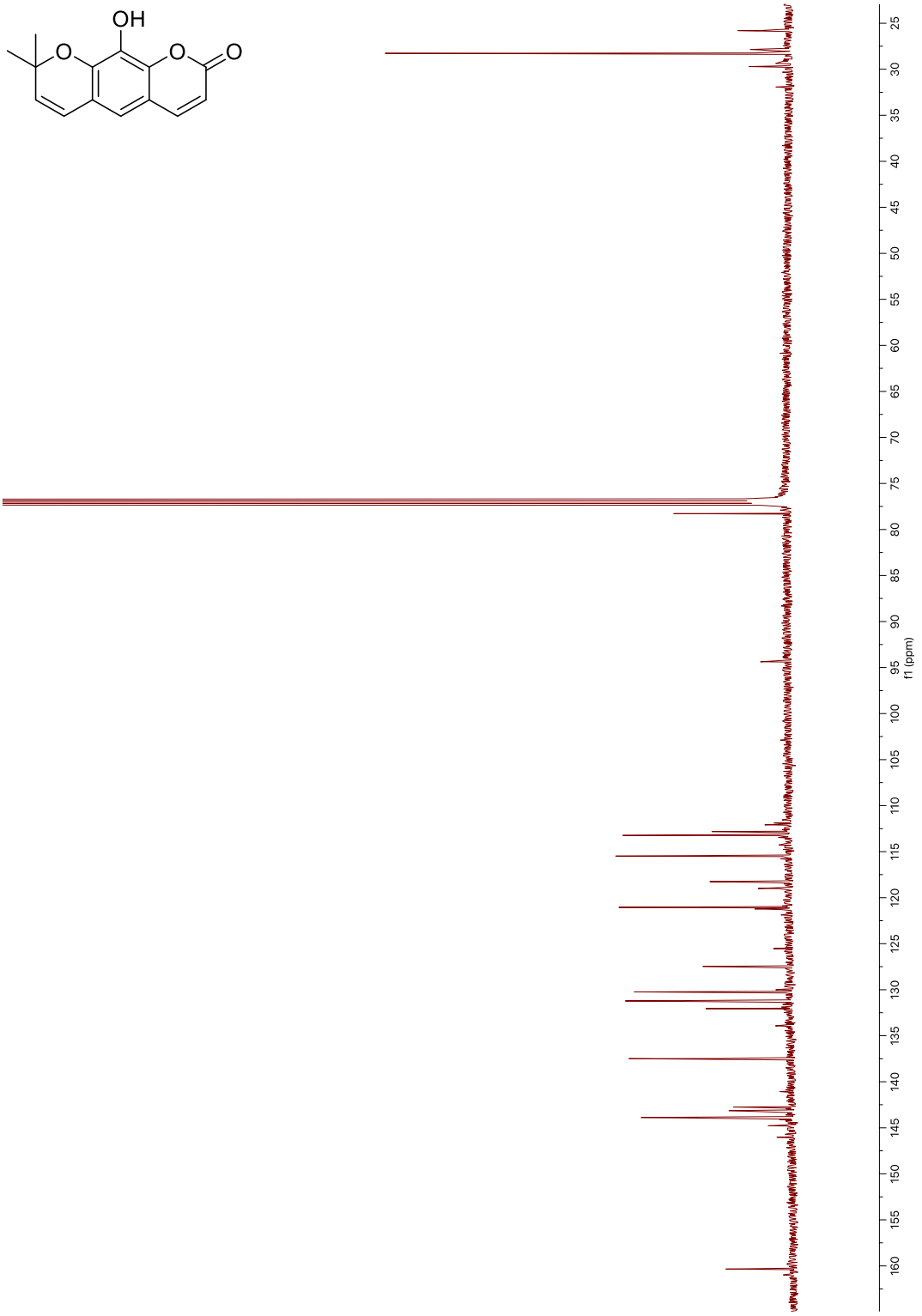
5.6.4 ^{13}C NMR Spectrum of compound 2.7 (600 MHz, $CDCl_3$)



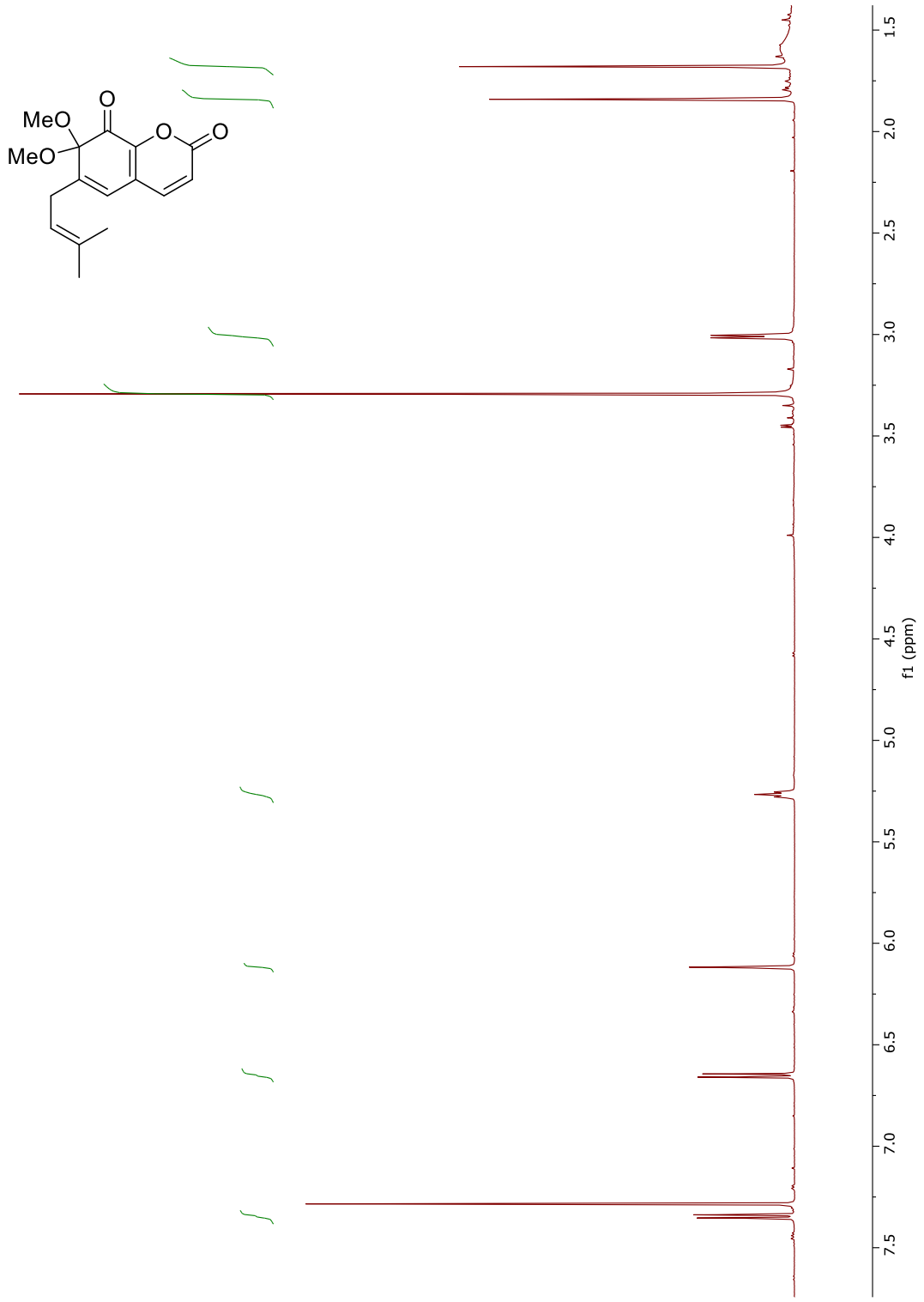
5.6.5 ^{1}H NMR Spectrum of compound 2.8 (600 MHz, $CDCl_3$)



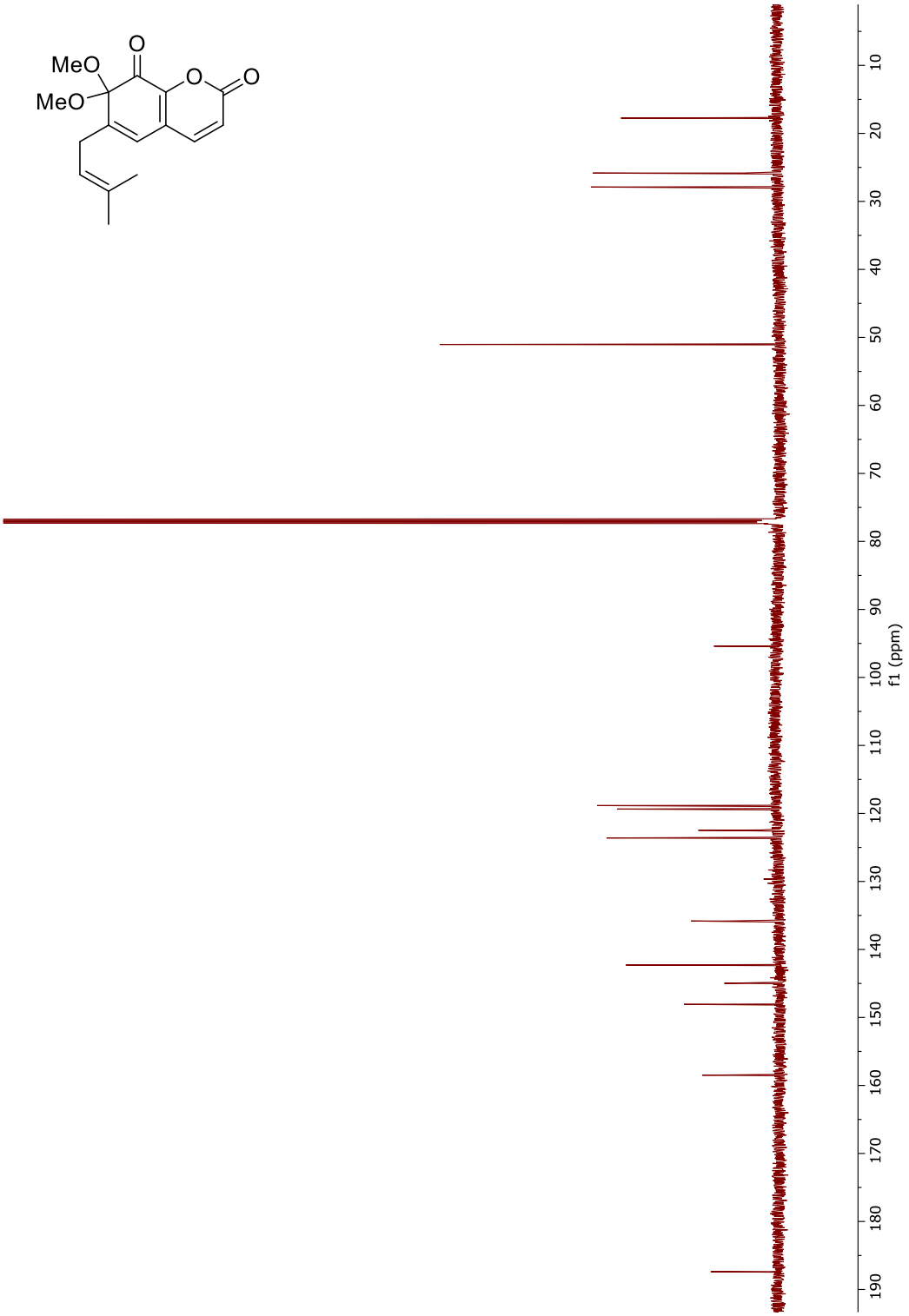
5.6.6 ^{13}C NMR Spectrum of compound 2.8 (125 MHz, $CDCl_3$)



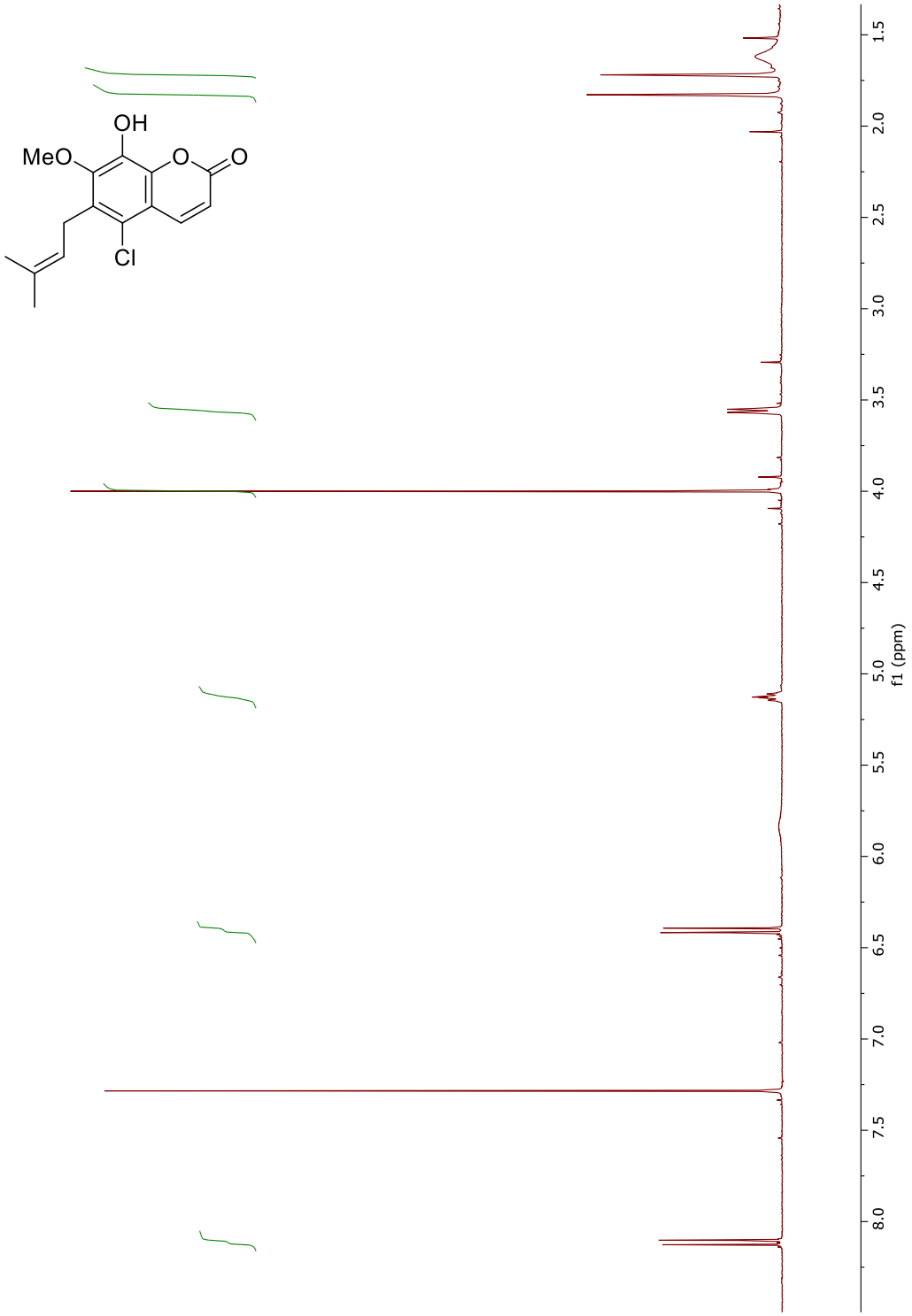
5.6.7 ^{1}H NMR Spectrum of compound 3.24 (600 MHz, $CDCl_3$)



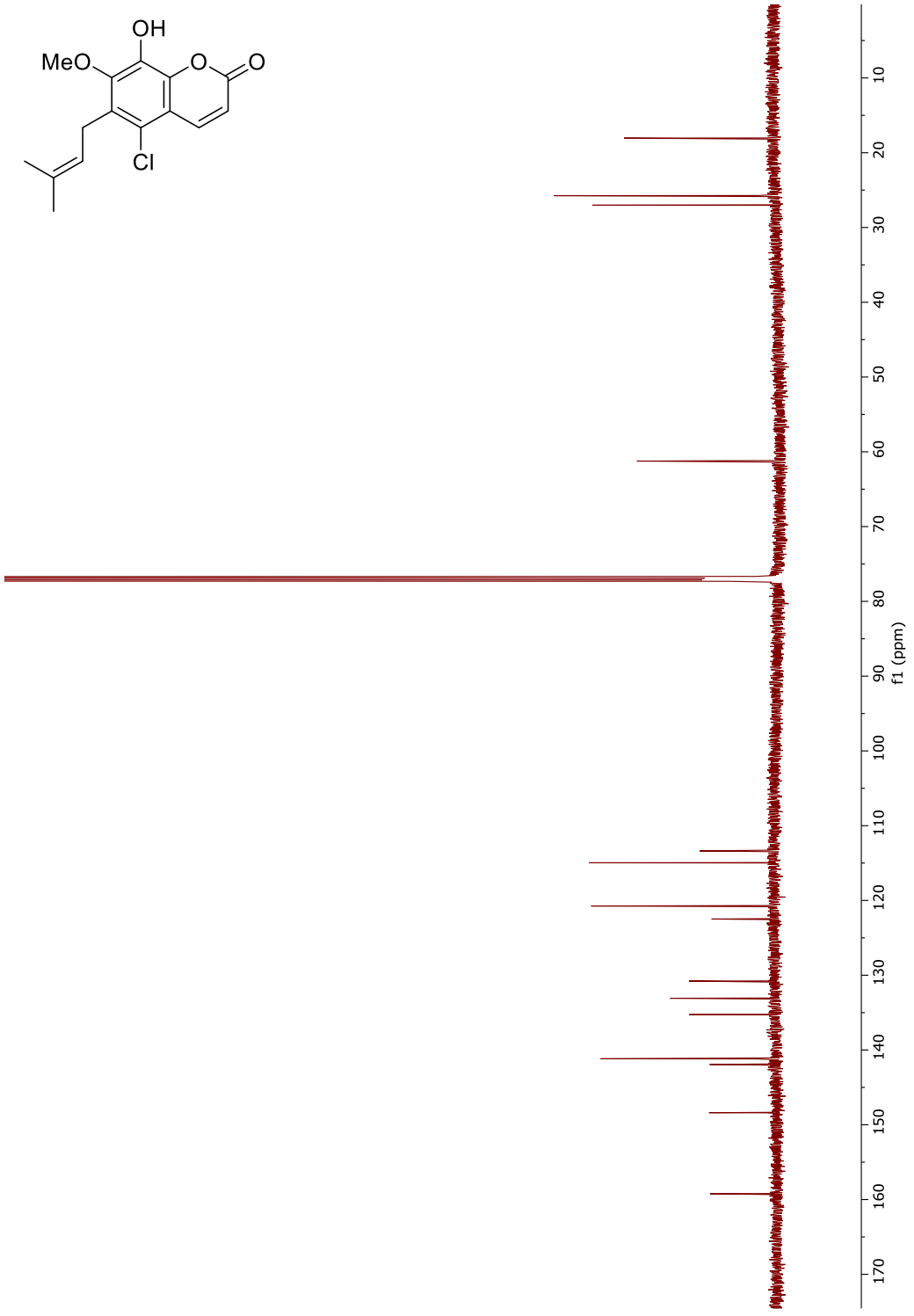
5.6.8 ^{13}C NMR Spectrum of compound 3.24 (600 MHz, $CDCl_3$)



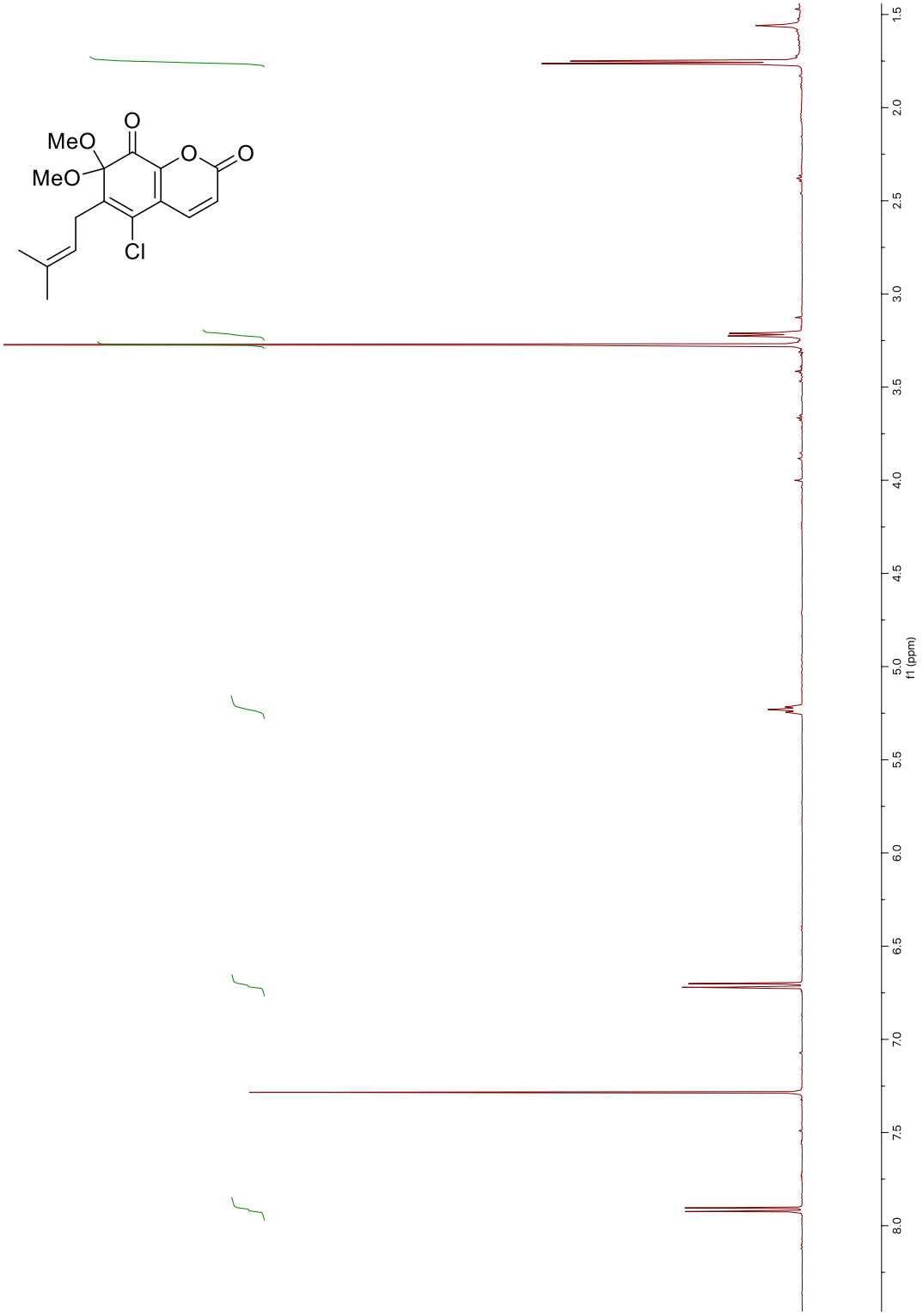
5.6.9 ^{1}H NMR Spectrum of compound 3.25 (600 MHz, $CDCl_3$)



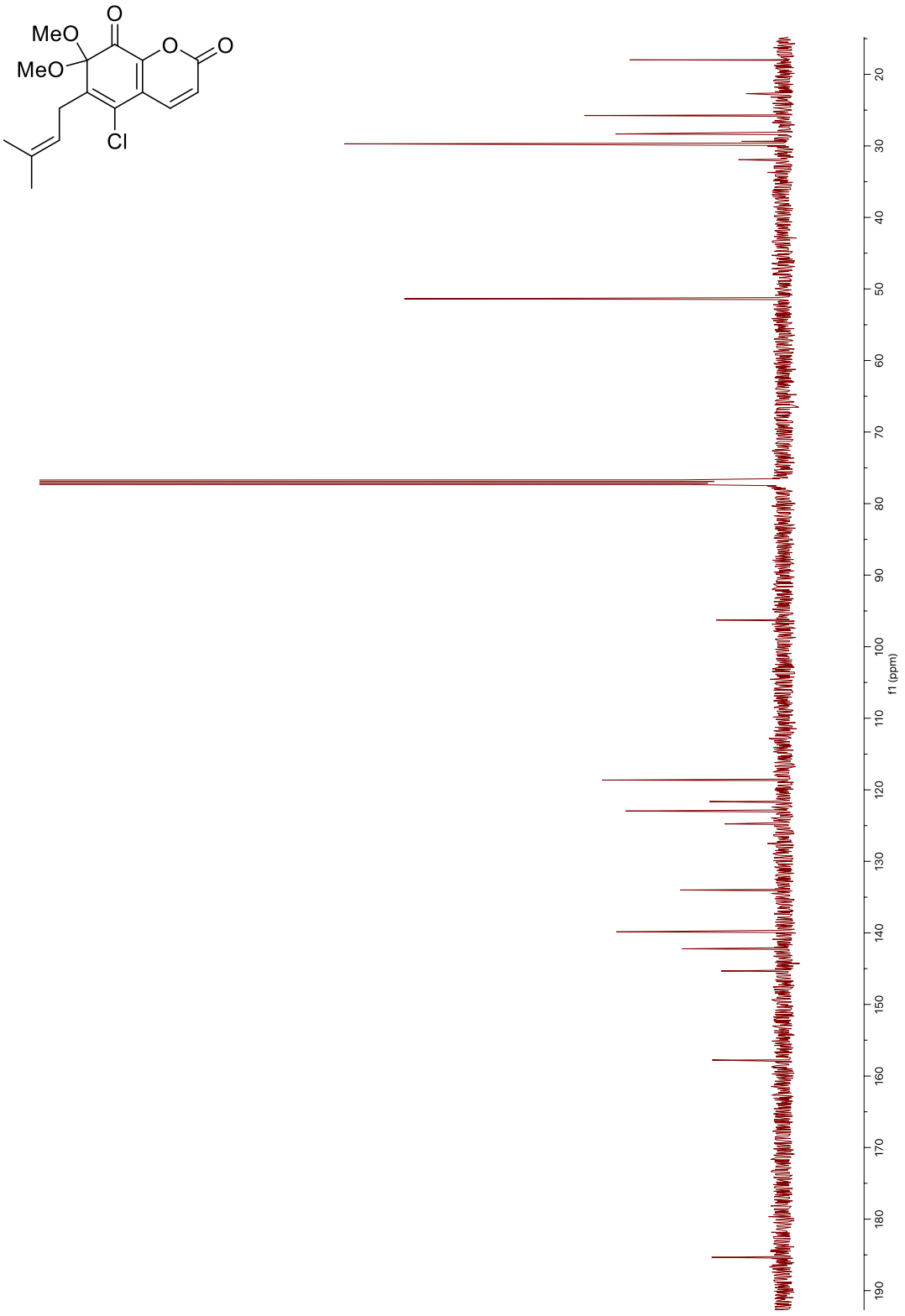
5.6.10 ^{13}C NMR Spectrum of compound 3.25 (600 MHz, $CDCl_3$)



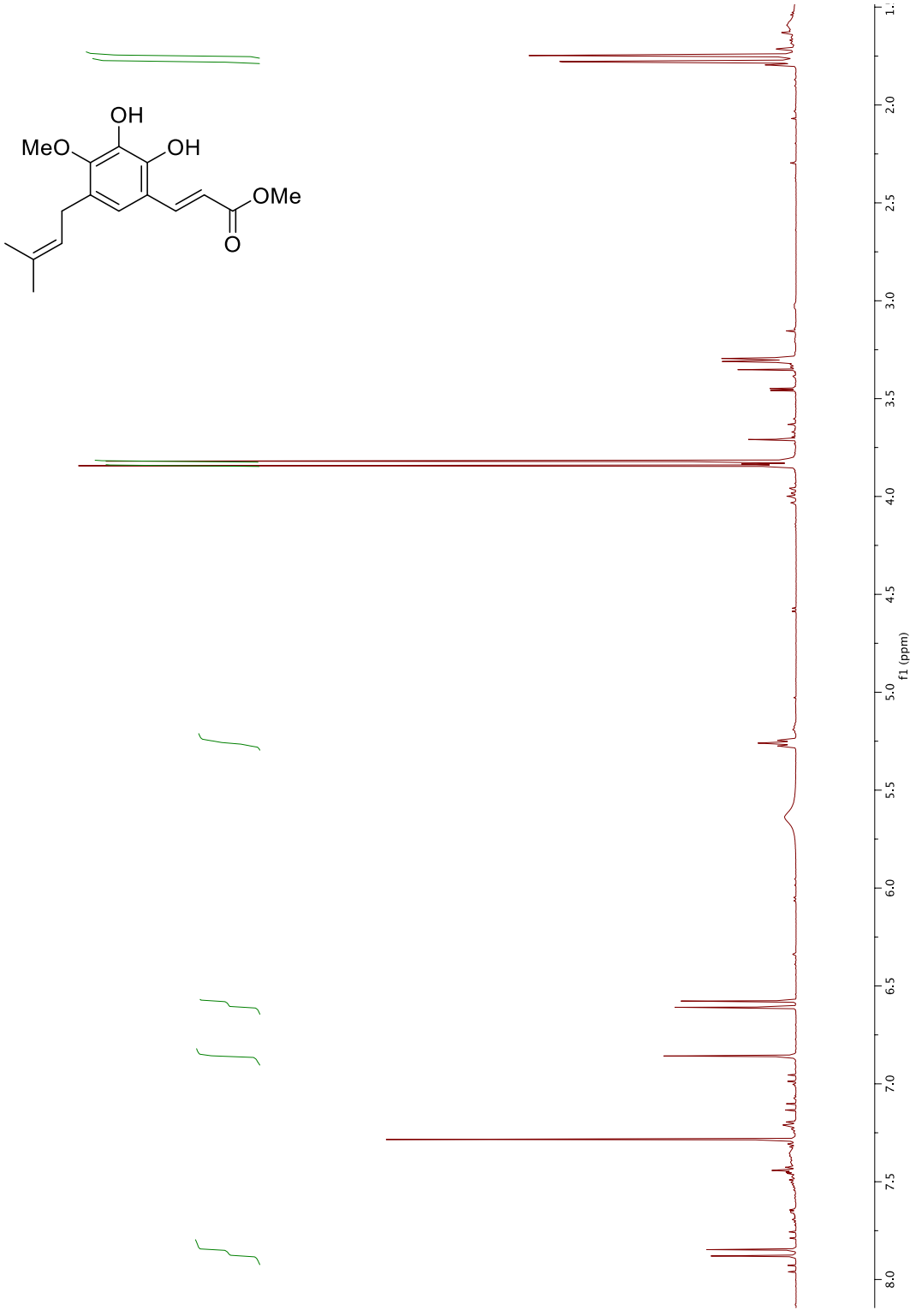
5.6.11 ^{1}H NMR Spectrum of compound 3.28 (600 MHz, $CDCl_3$)



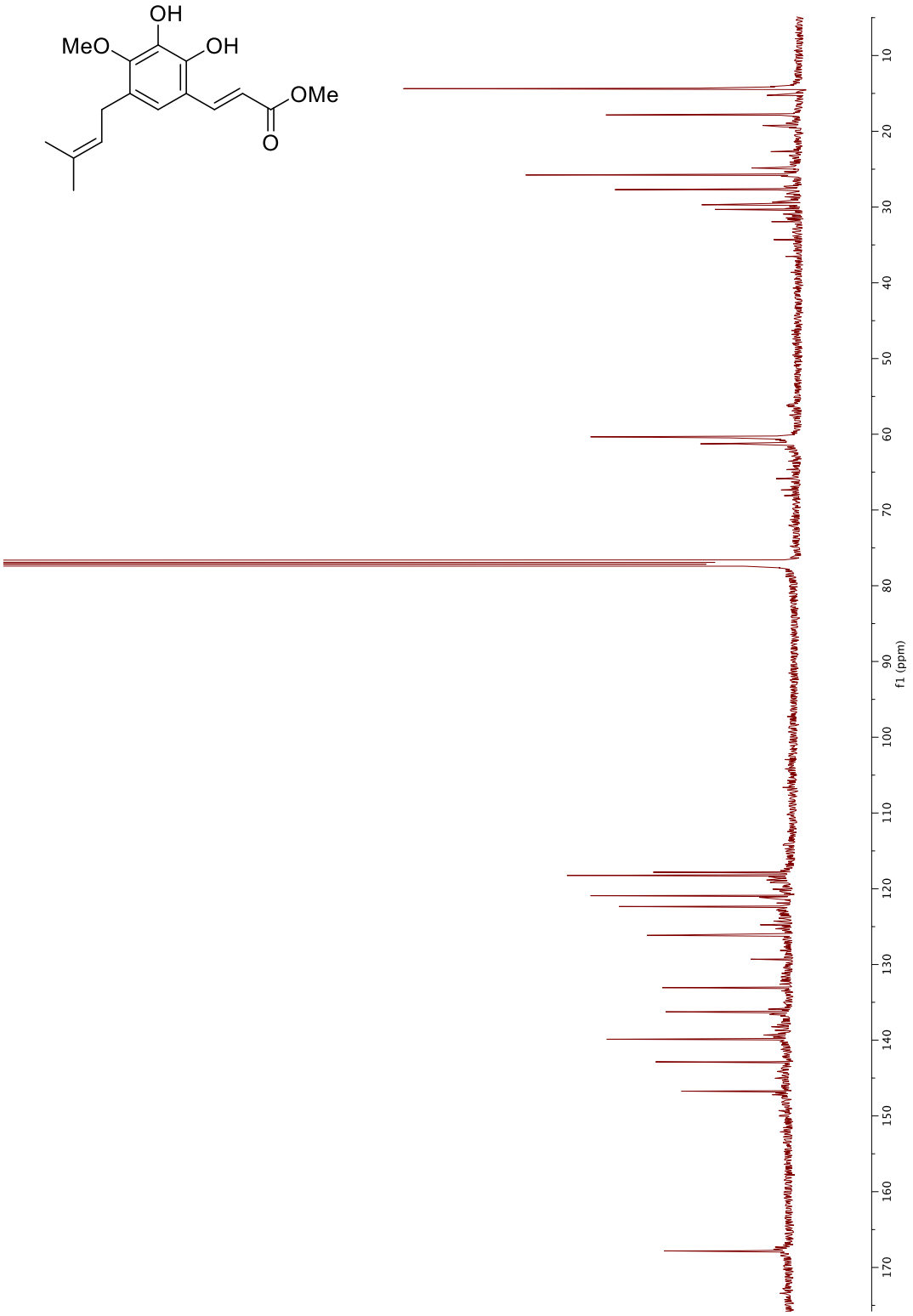
5.6.12 ^{13}C NMR Spectrum of compound 3.28 (600 MHz, $CDCl_3$)



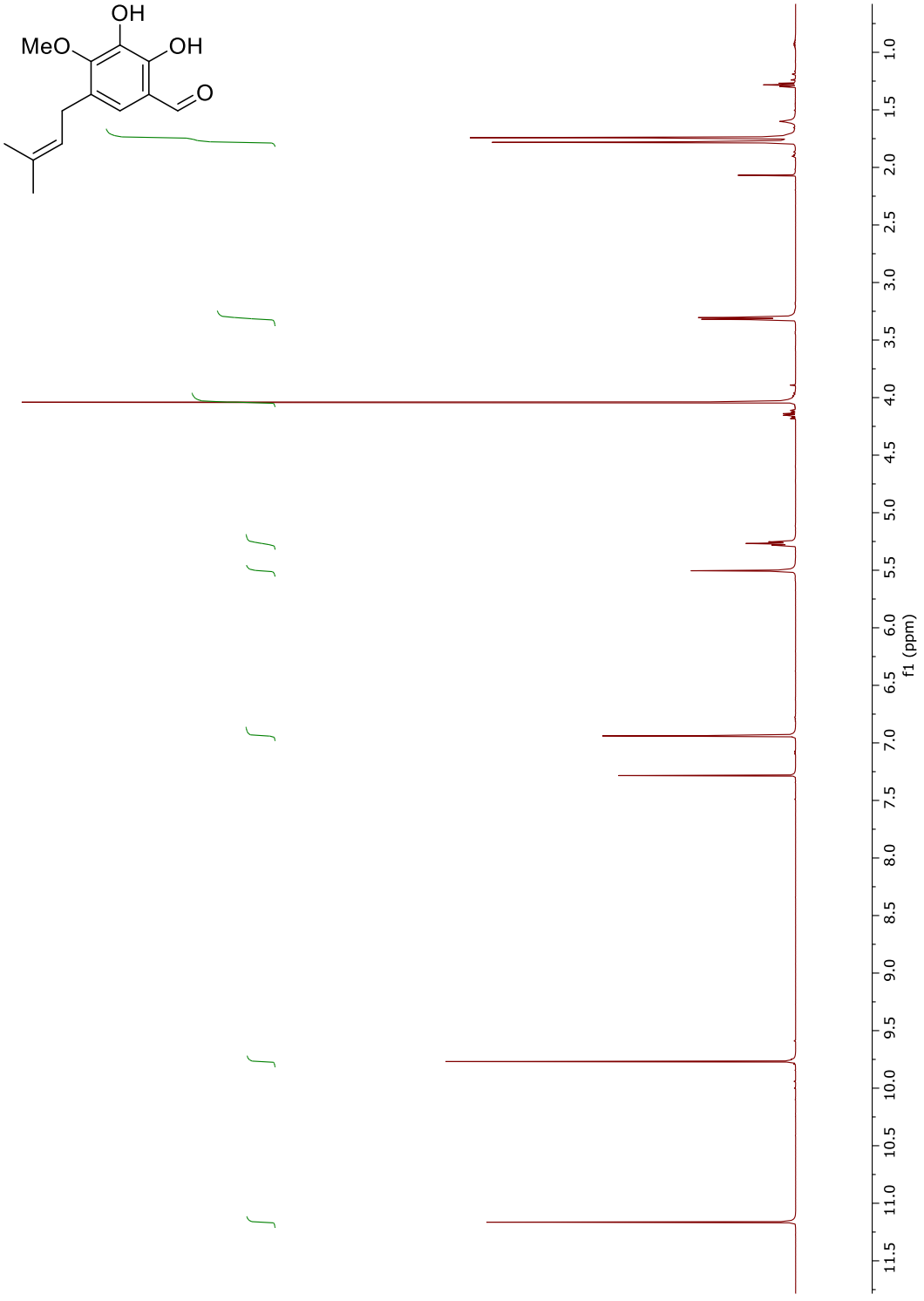
5.6.13 ^{1}H NMR Spectrum of compound 3.30 (500 MHz, $CDCl_3$)



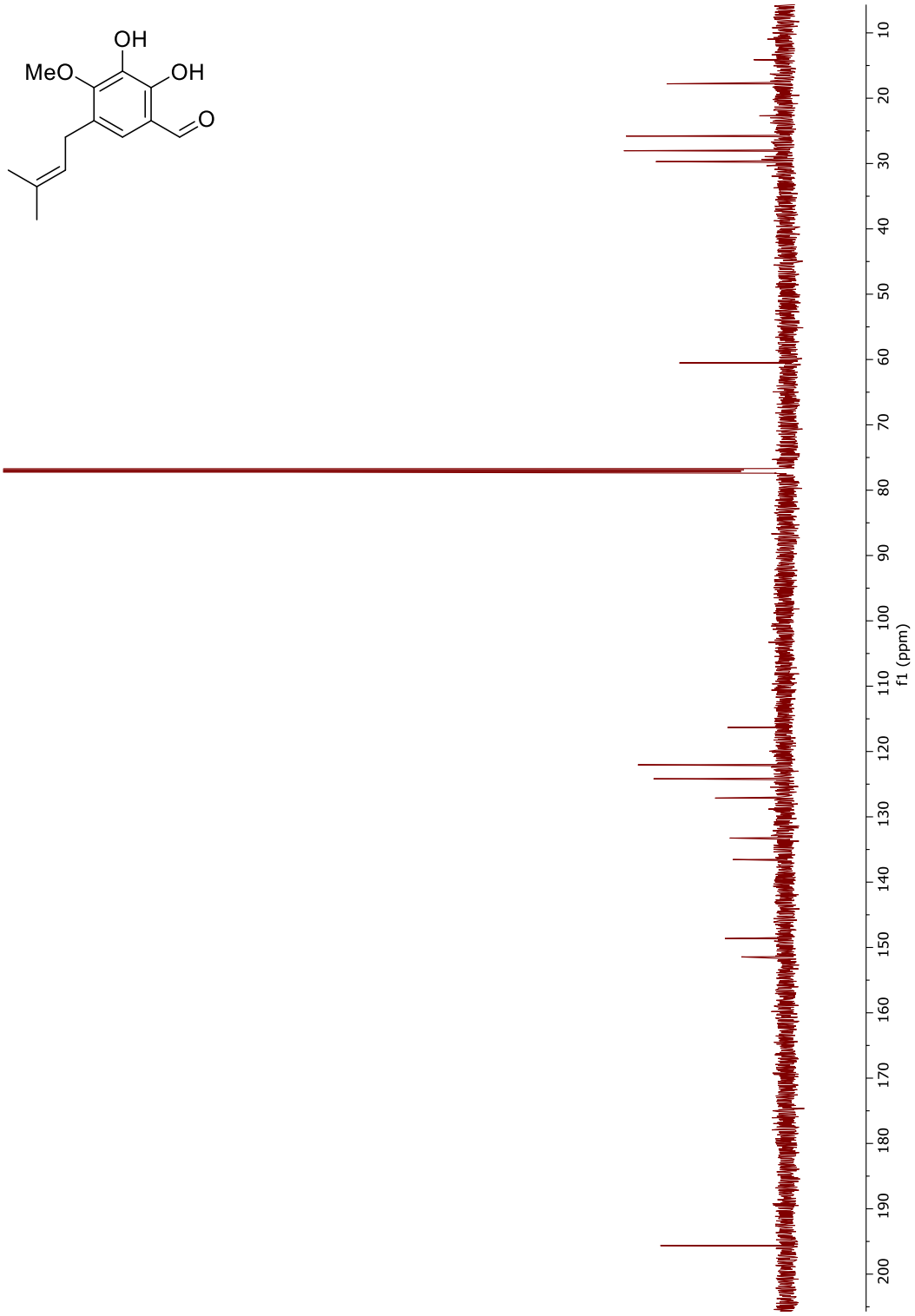
5.6.14 ^{13}C NMR Spectrum of compound 3.30 (125 MHz, $CDCl_3$)



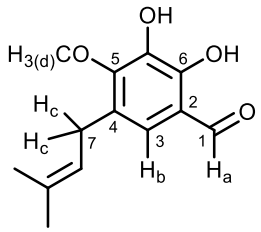
5.6.15 ^{1}H NMR Spectrum of compound 2.19 (500 MHz, $CDCl_3$)

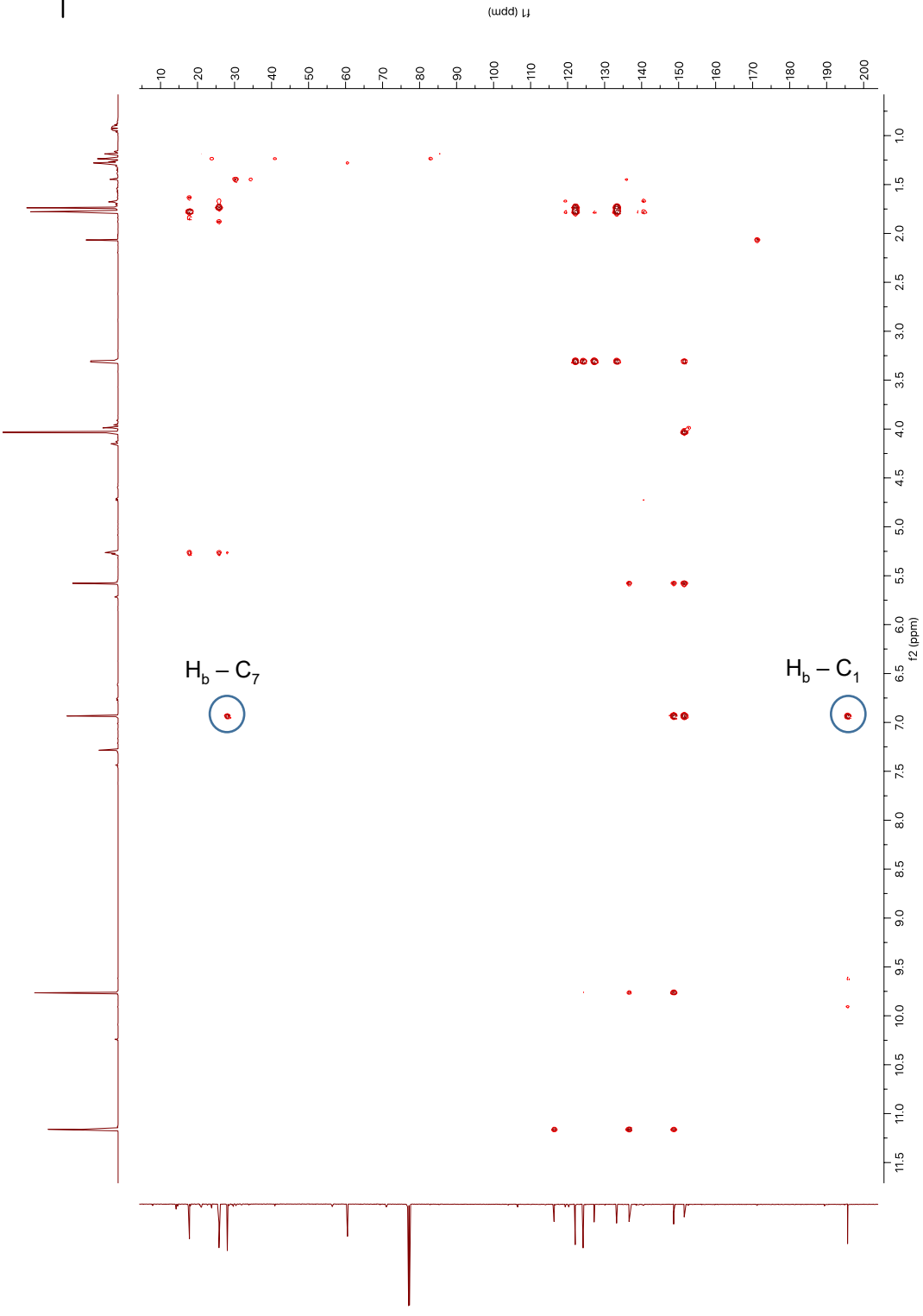


5.6.16 ^{13}C NMR Spectrum of compound 2.19 (125 MHz, $CDCl_3$)

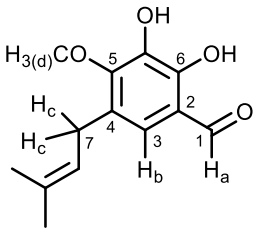


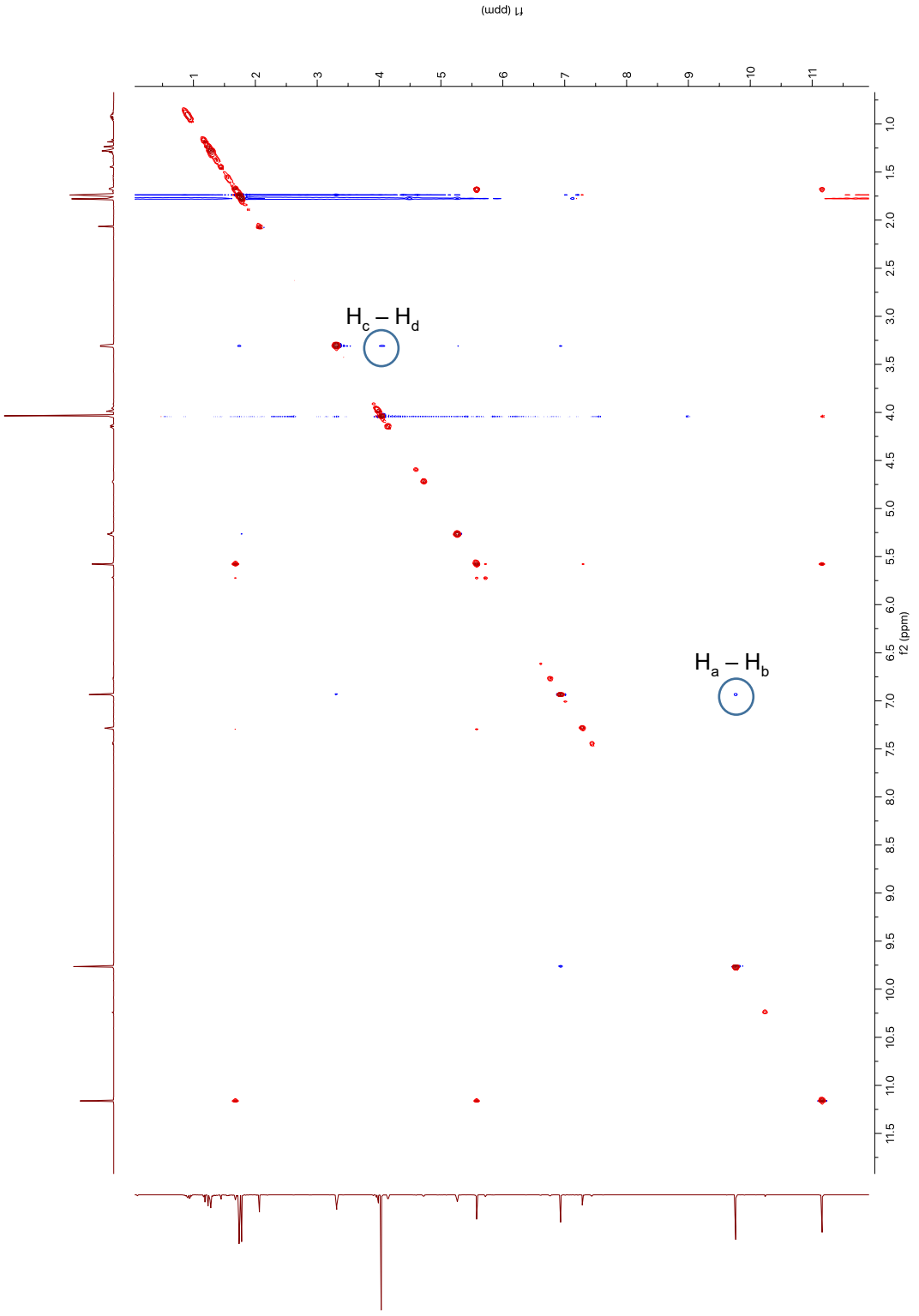
5.6.17 ^{1}H-^{13}C HMBC spectrum of compound 2.19 (500 MHz, $CDCl_3$)



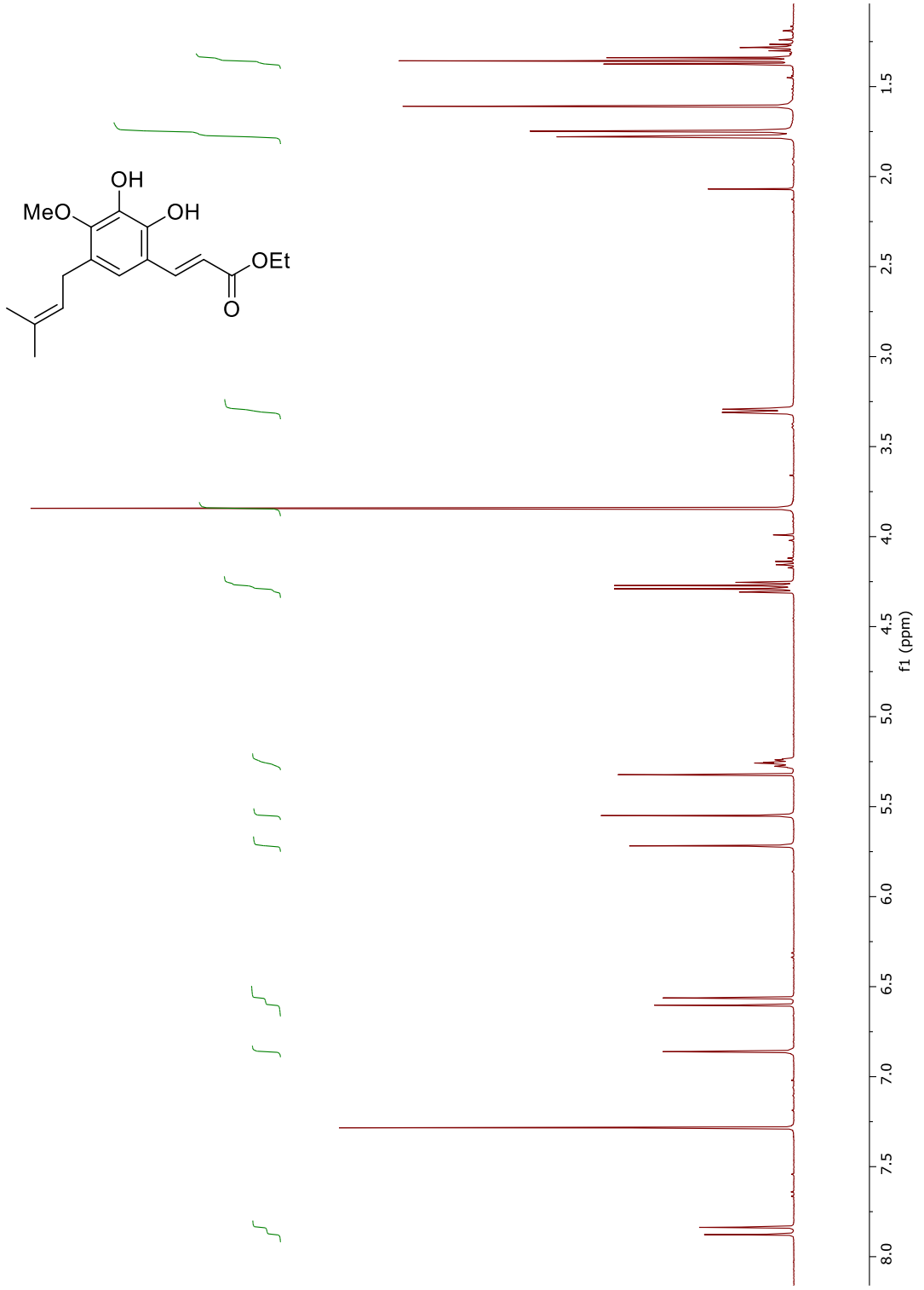


5.6.18 ^{1}H-^{1}H NOESY spectrum of compound 2.19 (500 MHz, $CDCl_3$)

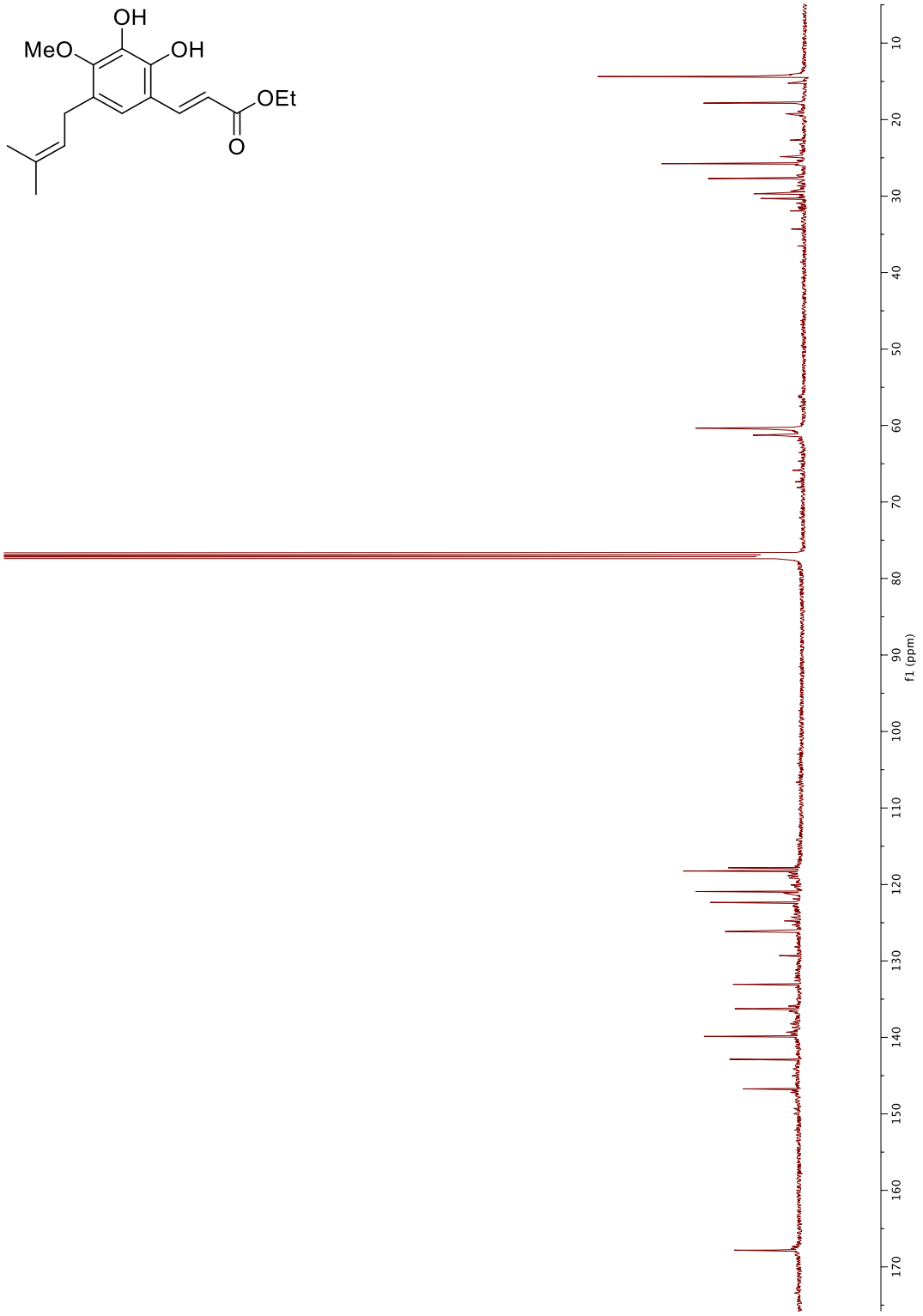




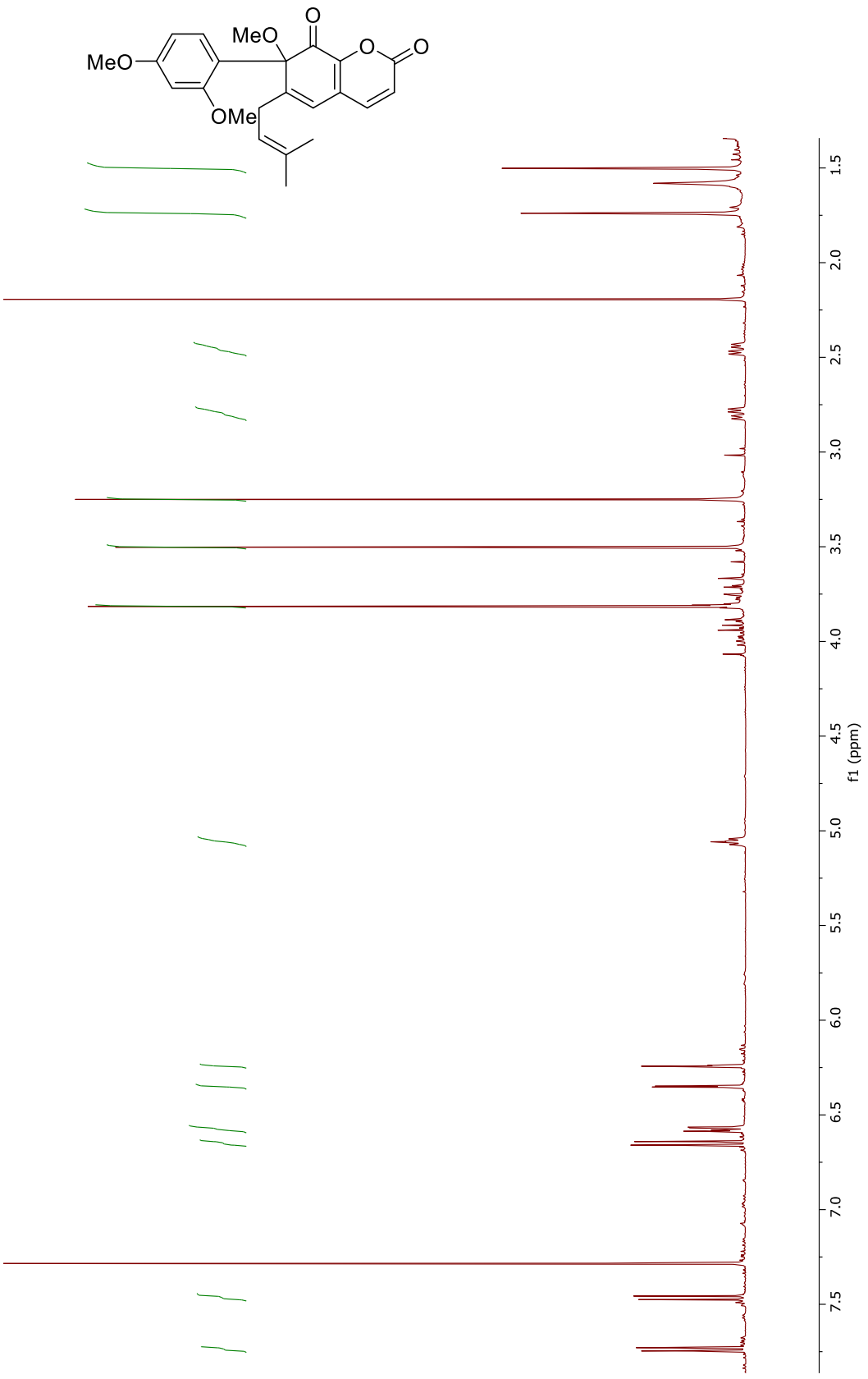
5.6.19 ^{1}H NMR Spectrum of compound 3.35 (500 MHz, $CDCl_3$)



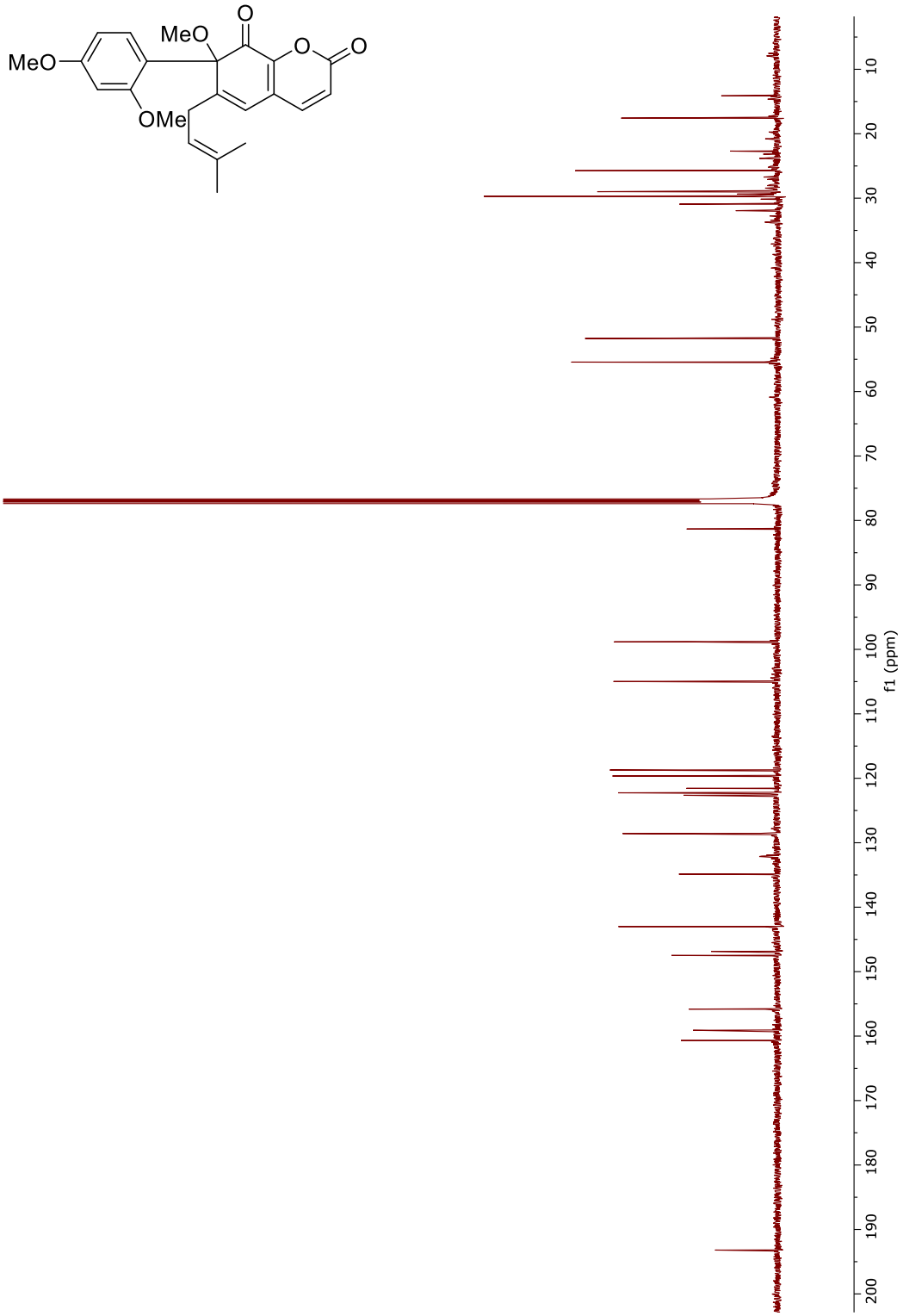
5.6.20 ^{13}C NMR Spectrum of compound 3.35 (125 MHz, $CDCl_3$)



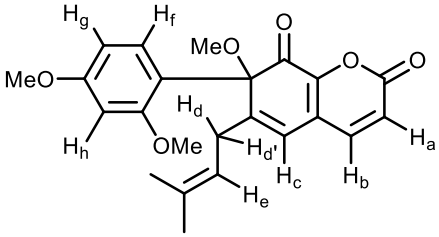
5.6.21 ^{1}H NMR Spectrum of compound 3.44 (500 MHz, $CDCl_3$)

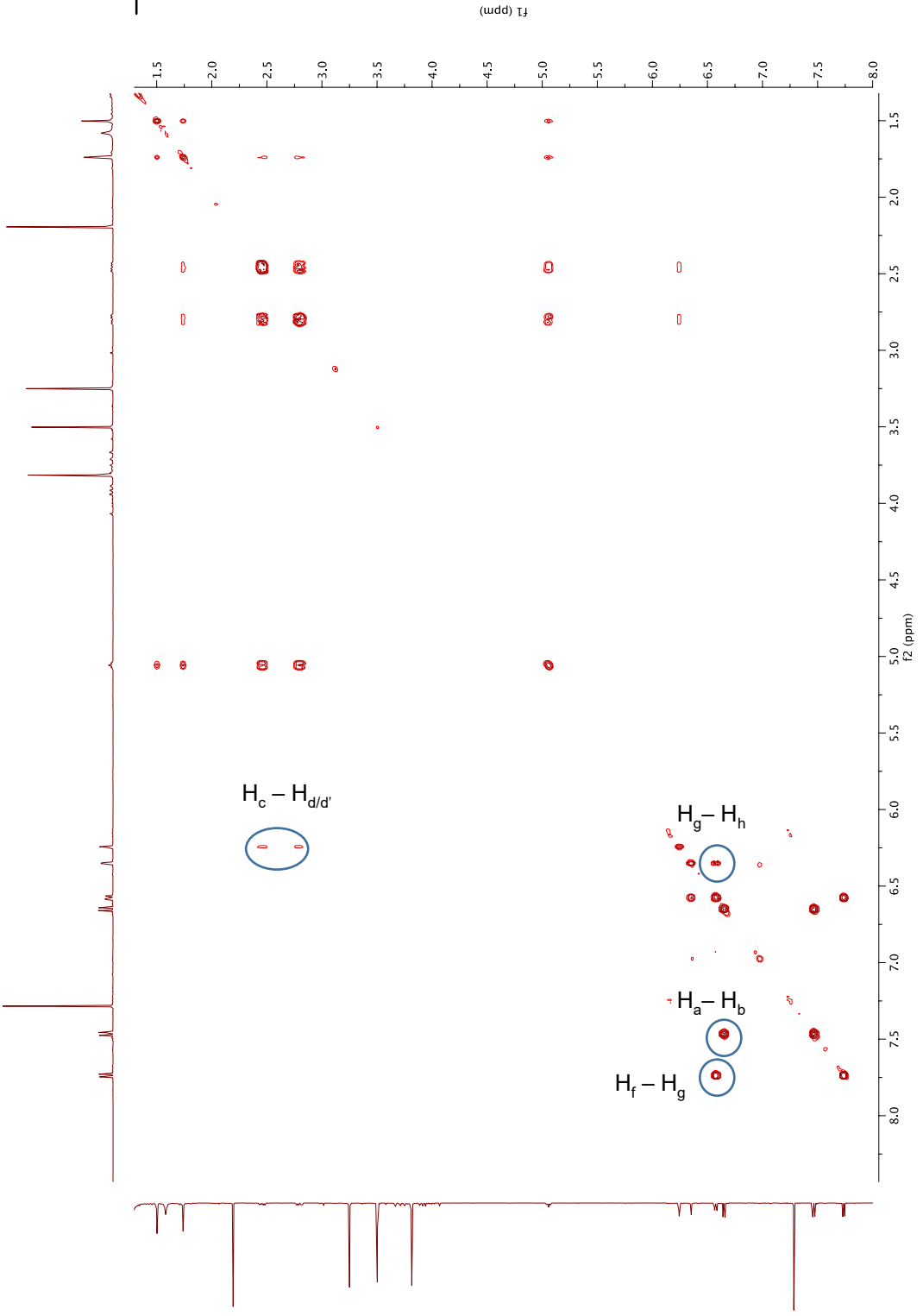


5.6.22 ^{13}C NMR Spectrum of compound 3.44 (125 MHz, $CDCl_3$)

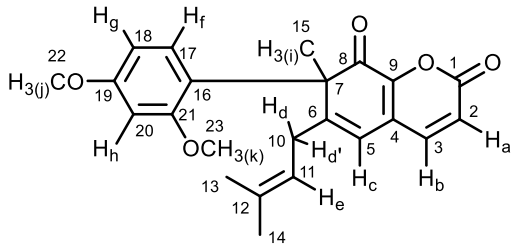


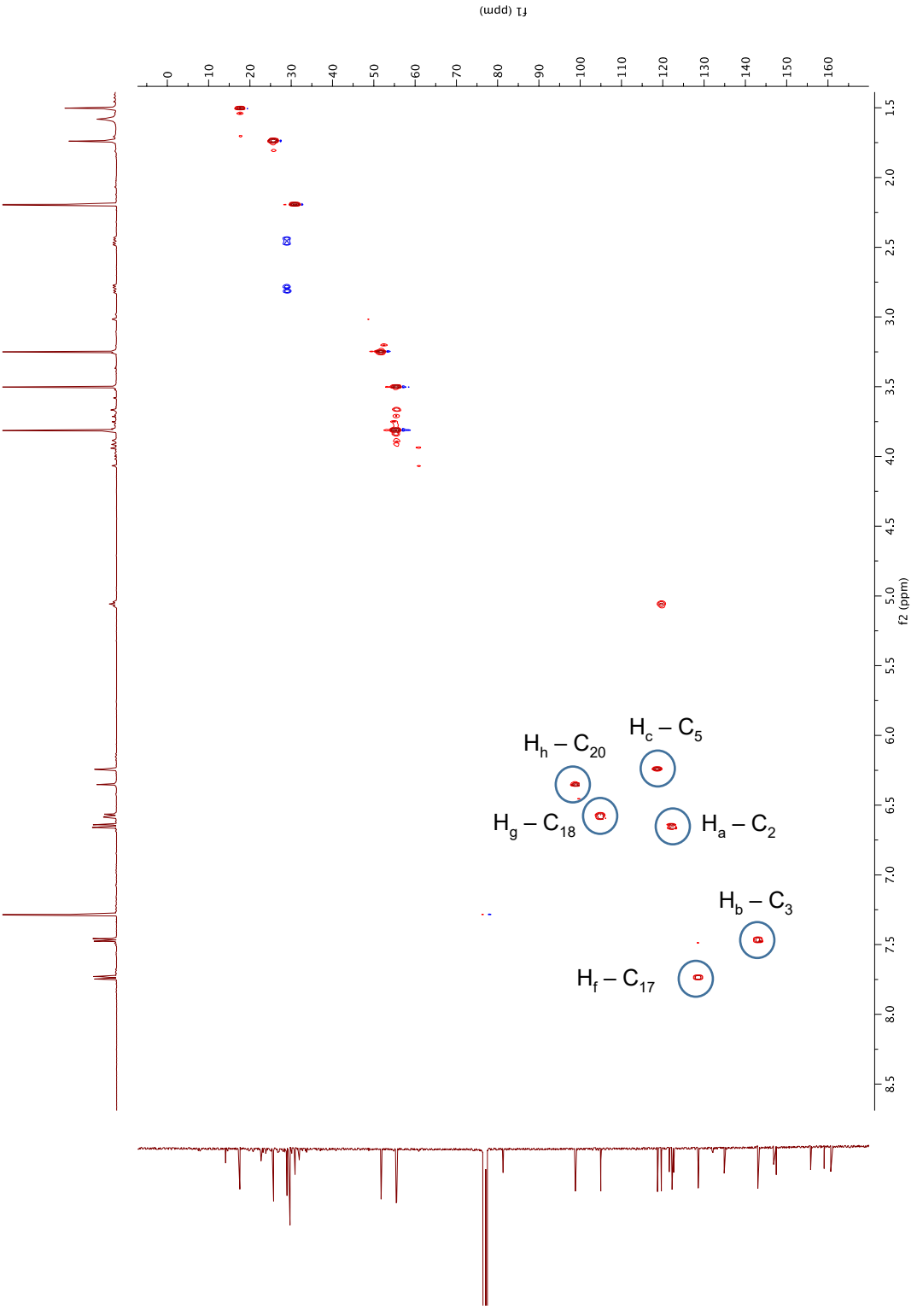
5.6.23 ^{1}H-^{1}H COSY spectrum of compound 3.44 (500 MHz, $CDCl_3$)



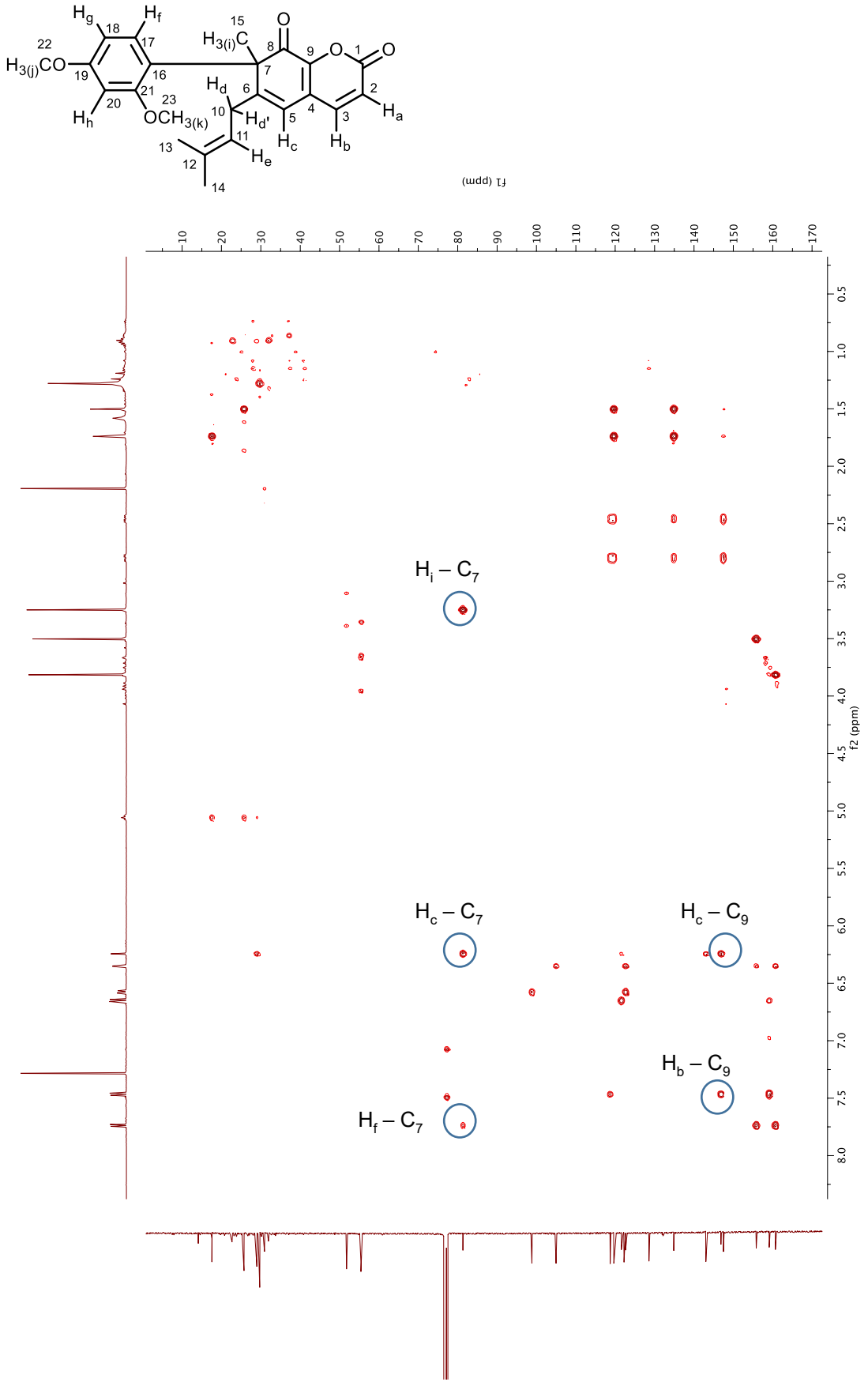


5.6.24 ^{1}H-^{13}C HSQC spectrum of compound 3.44 (500 MHz, $CDCl_3$)



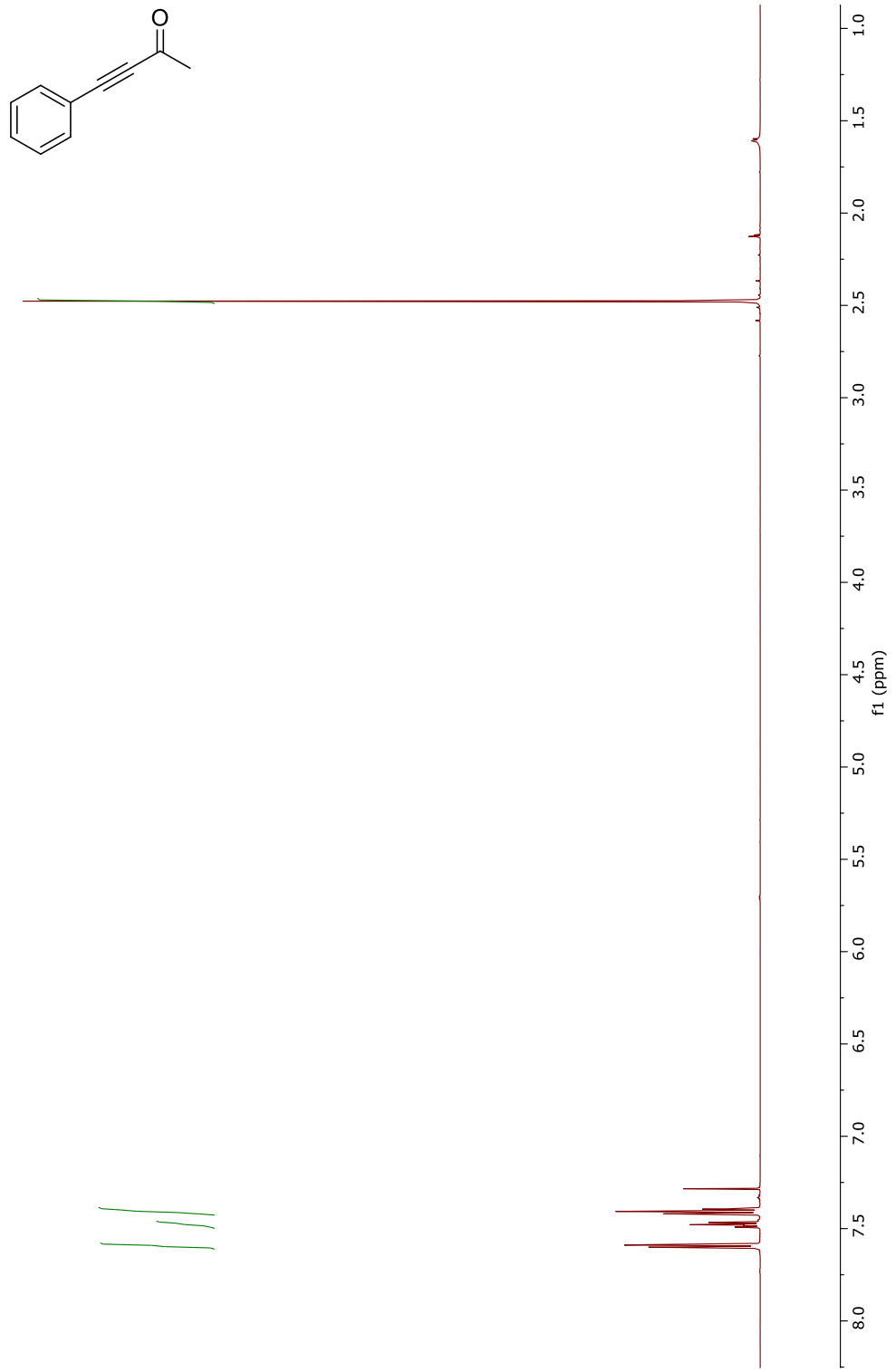


5.6.25 ^{1}H-^{13}C HMBC spectrum of compound 3.44 (500 MHz, $CDCl_3$)

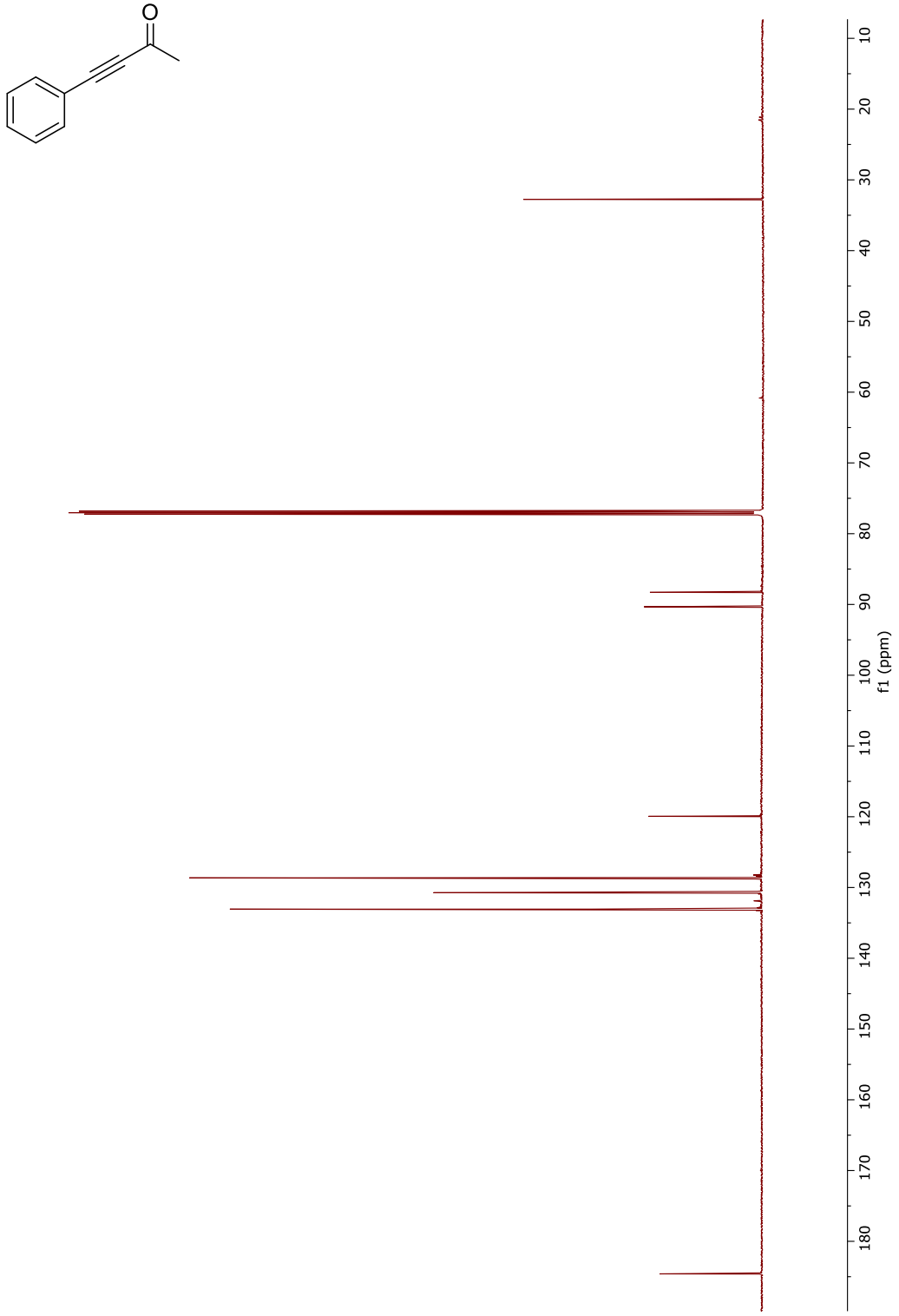


5.7 - NMR Spectra Chapter 4 – Transborylation

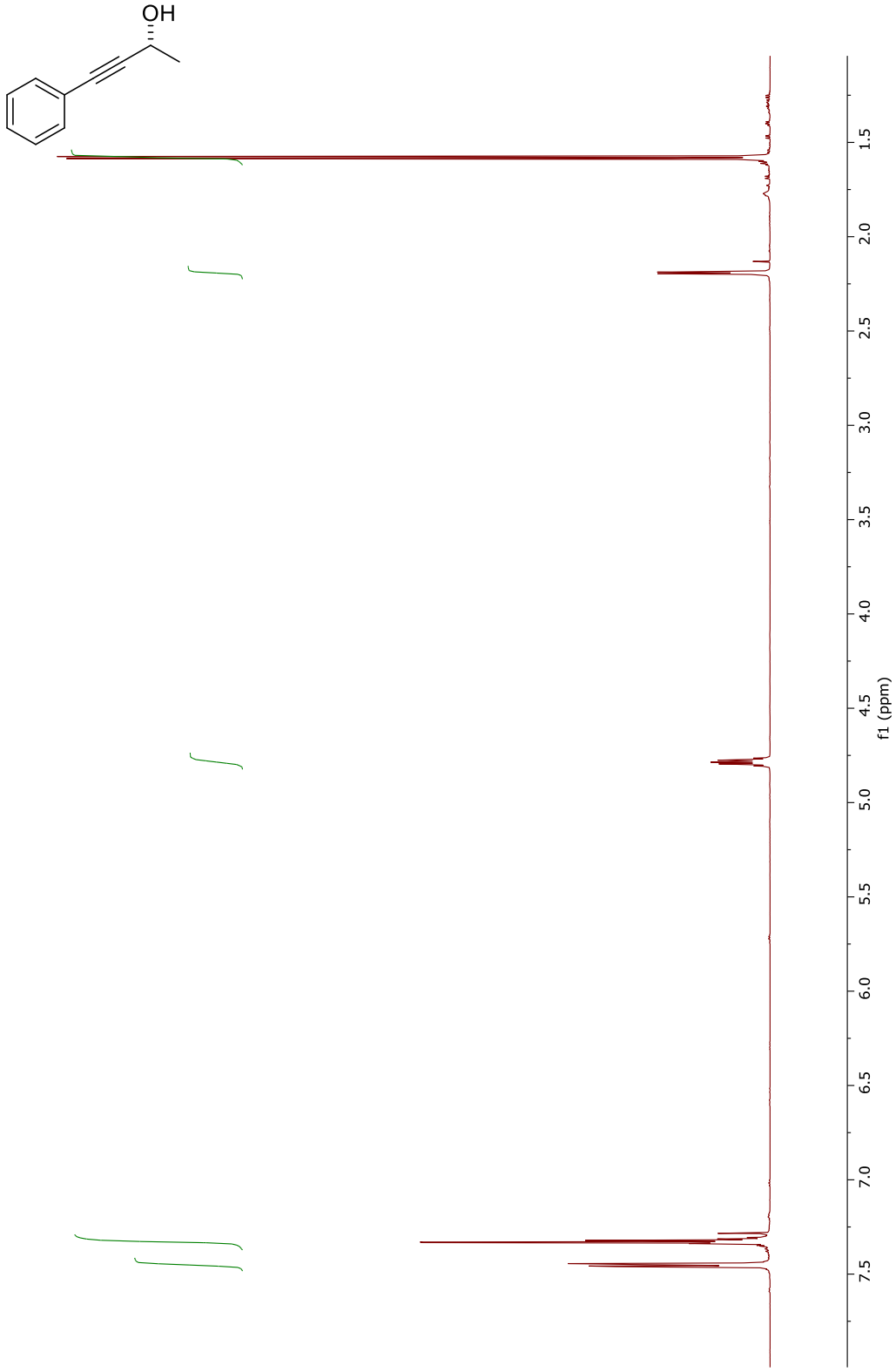
5.7.1 ^{1}H NMR Spectrum of compound 4.48 (500 MHz, $CDCl_3$)



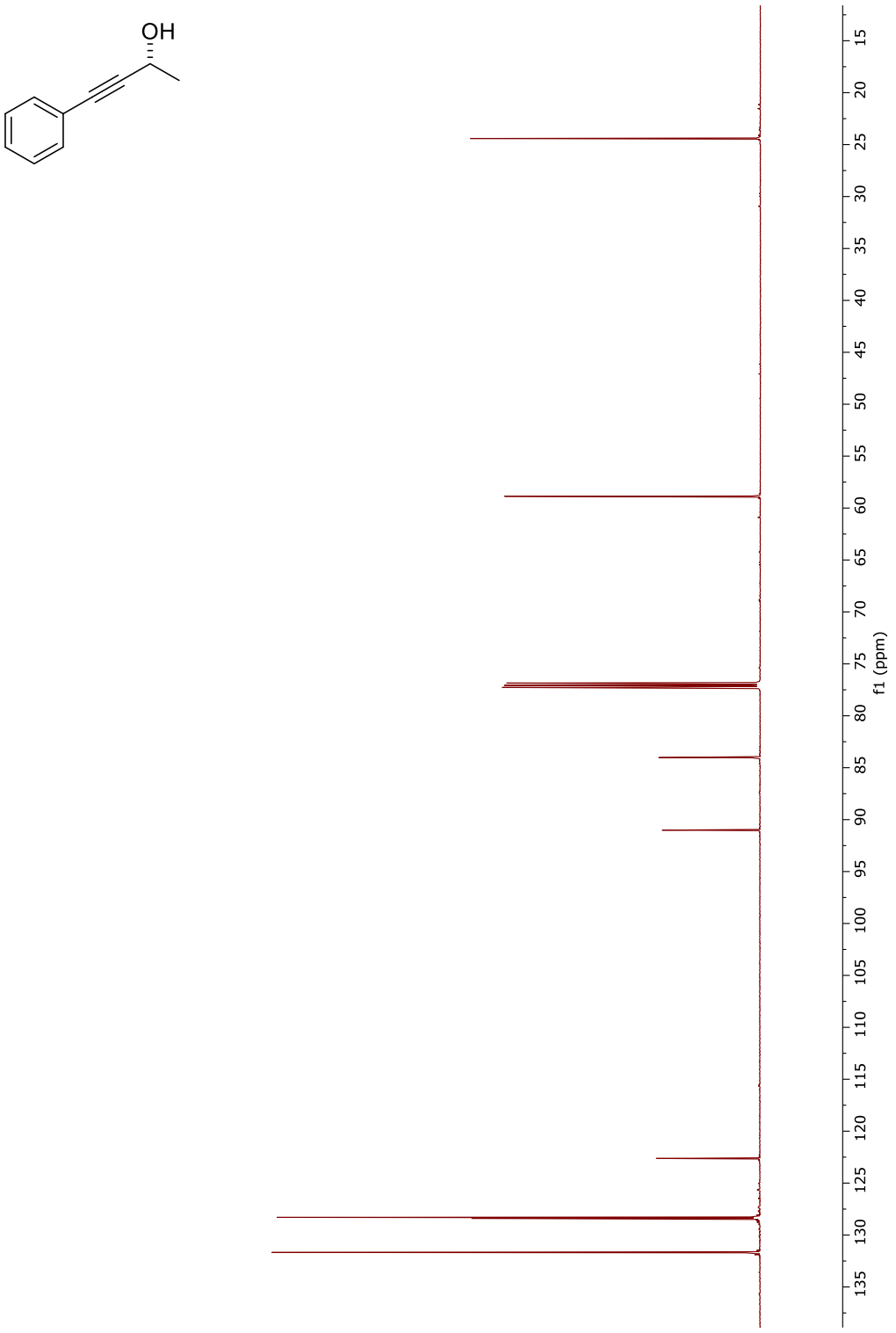
5.7.2 ^{13}C NMR Spectrum of compound 4.48 (500 MHz, $CDCl_3$)



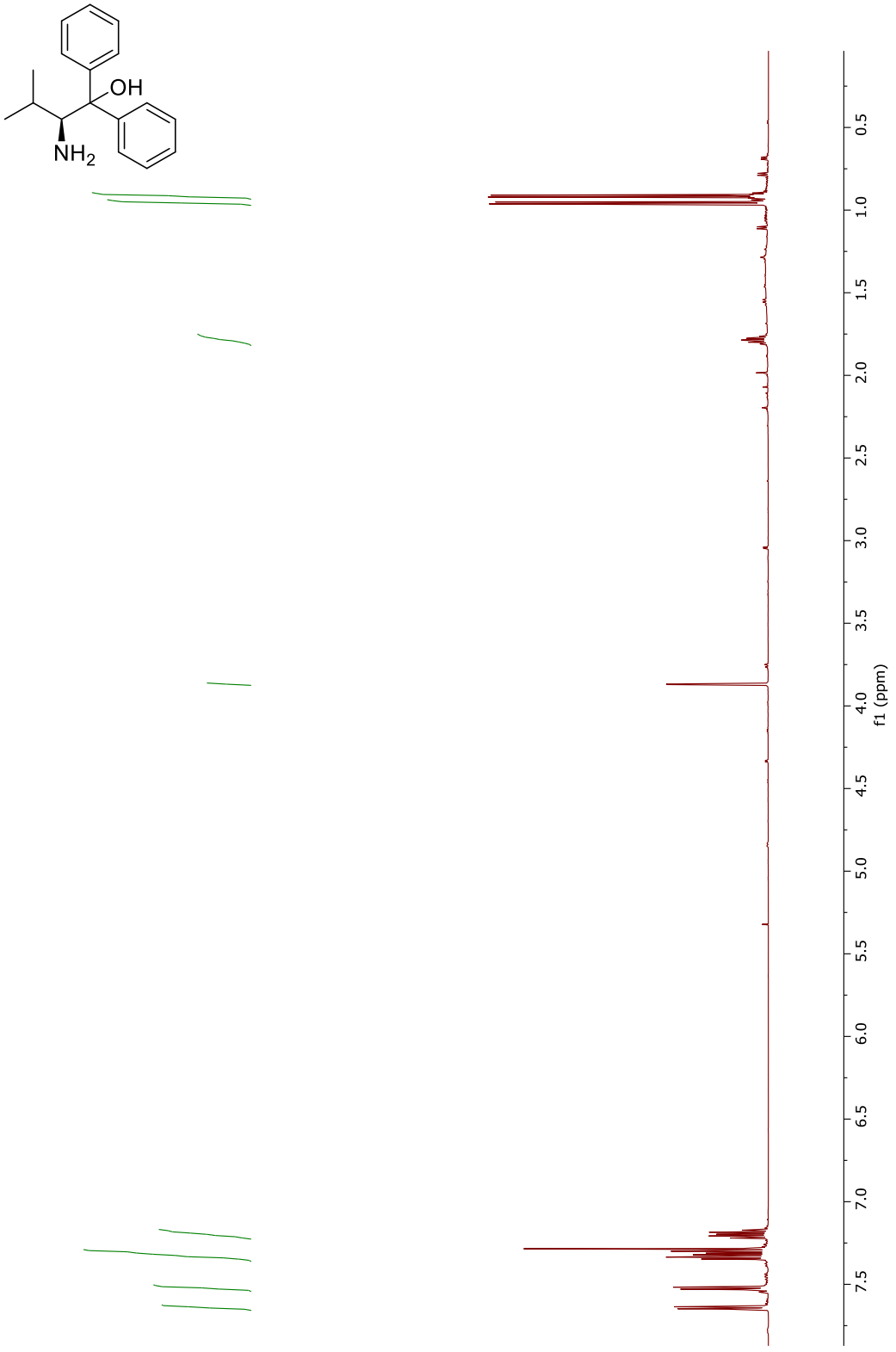
5.7.3 ^{1}H NMR Spectrum of compound 4.54 (500 MHz, $CDCl_3$)



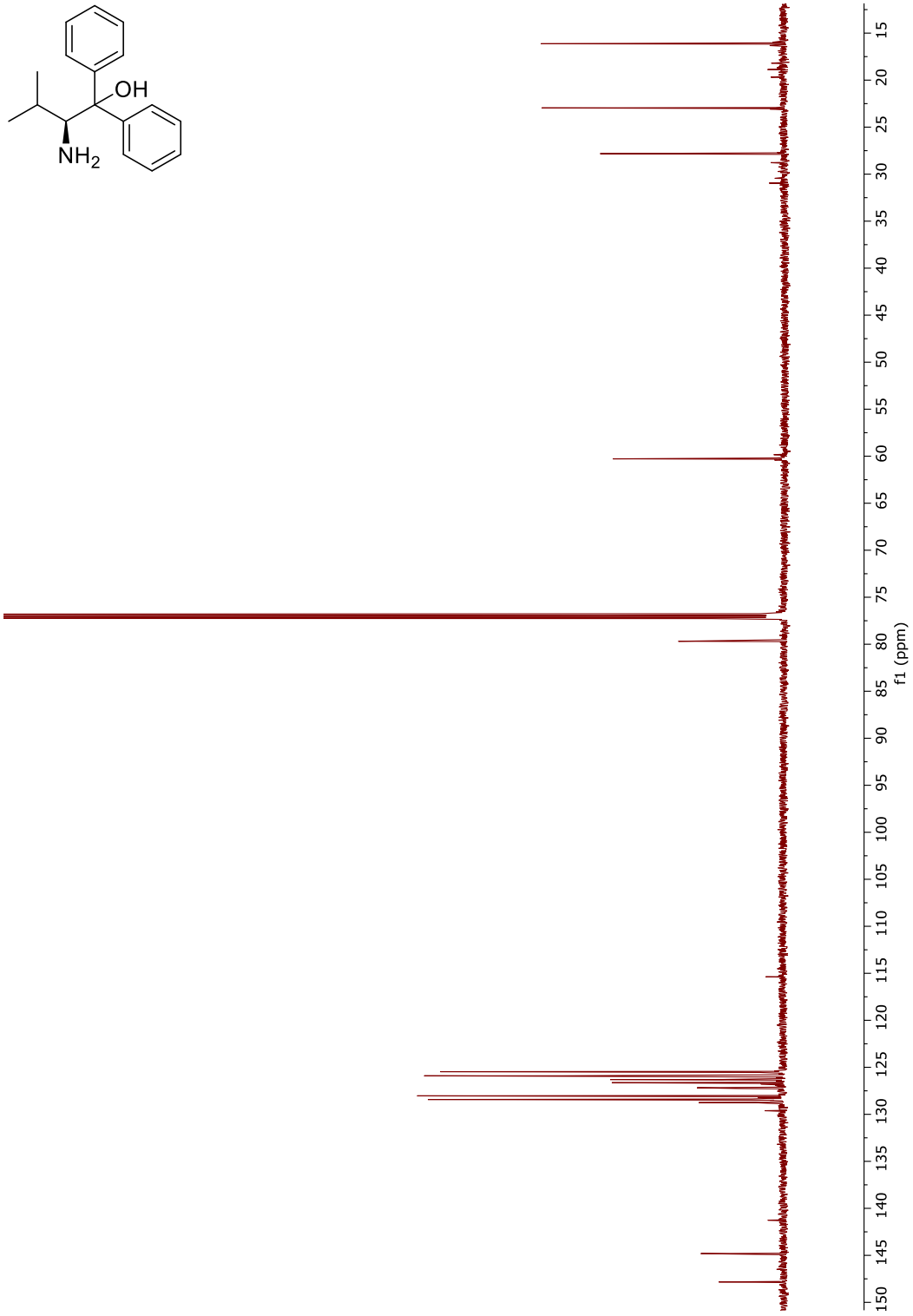
5.7.4 ^{13}C NMR Spectrum of compound 4.54 (500 MHz, $CDCl_3$)



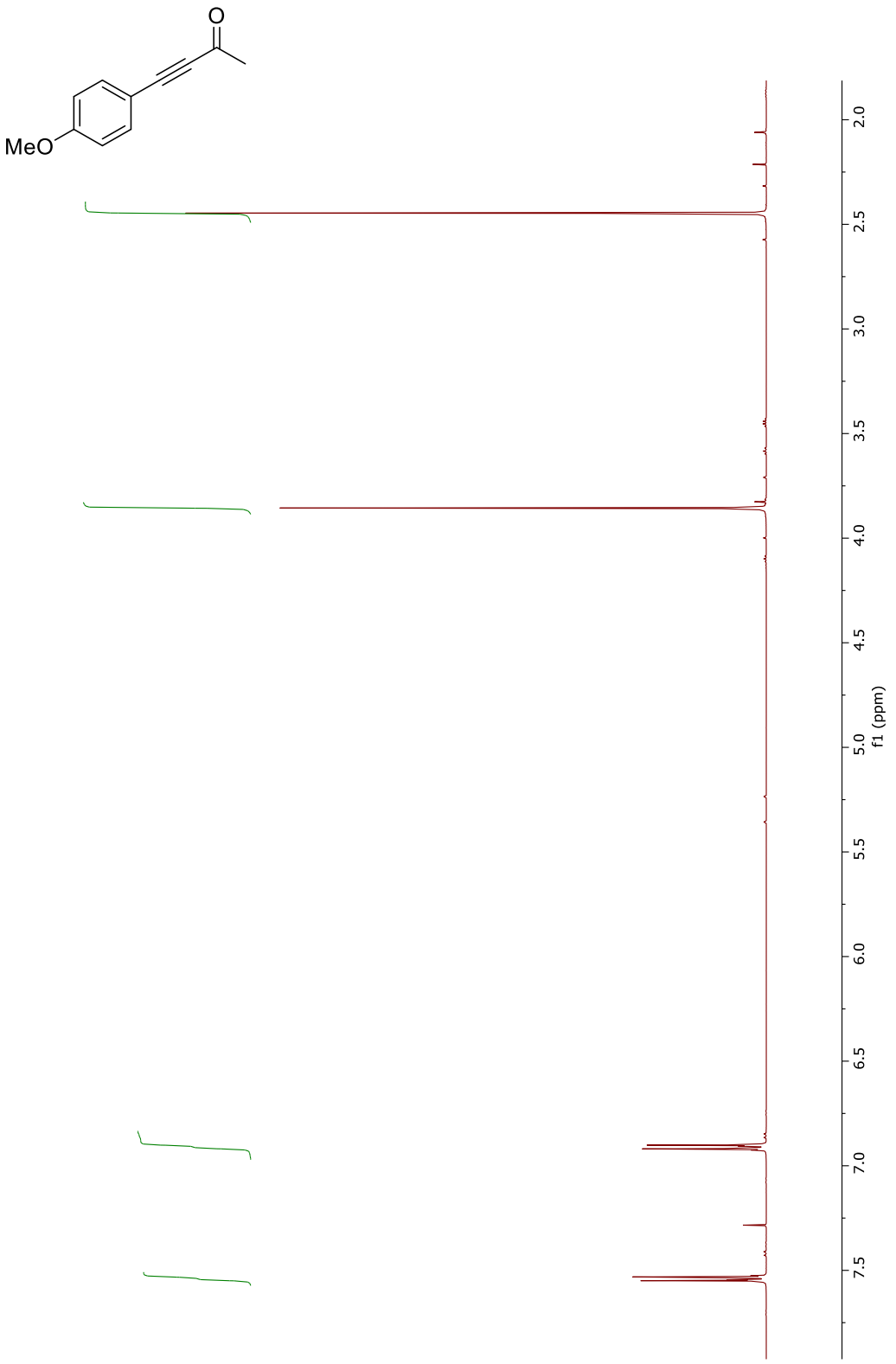
5.7.5 ^{1}H NMR Spectrum of compound 4.39 (500 MHz, $CDCl_3$)



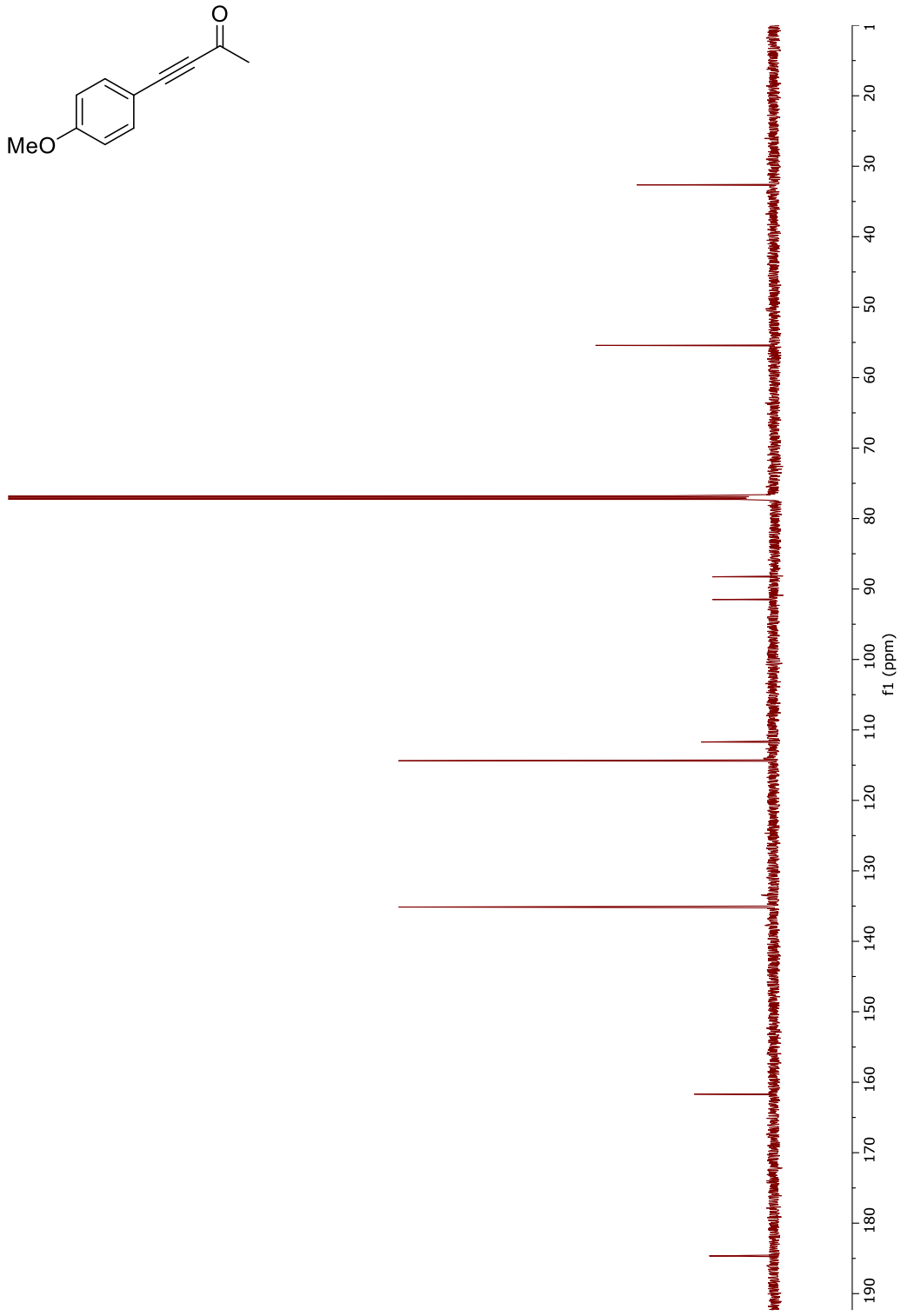
5.7.6 ^{13}C NMR Spectrum of compound 4.39 (500 MHz, $CDCl_3$)



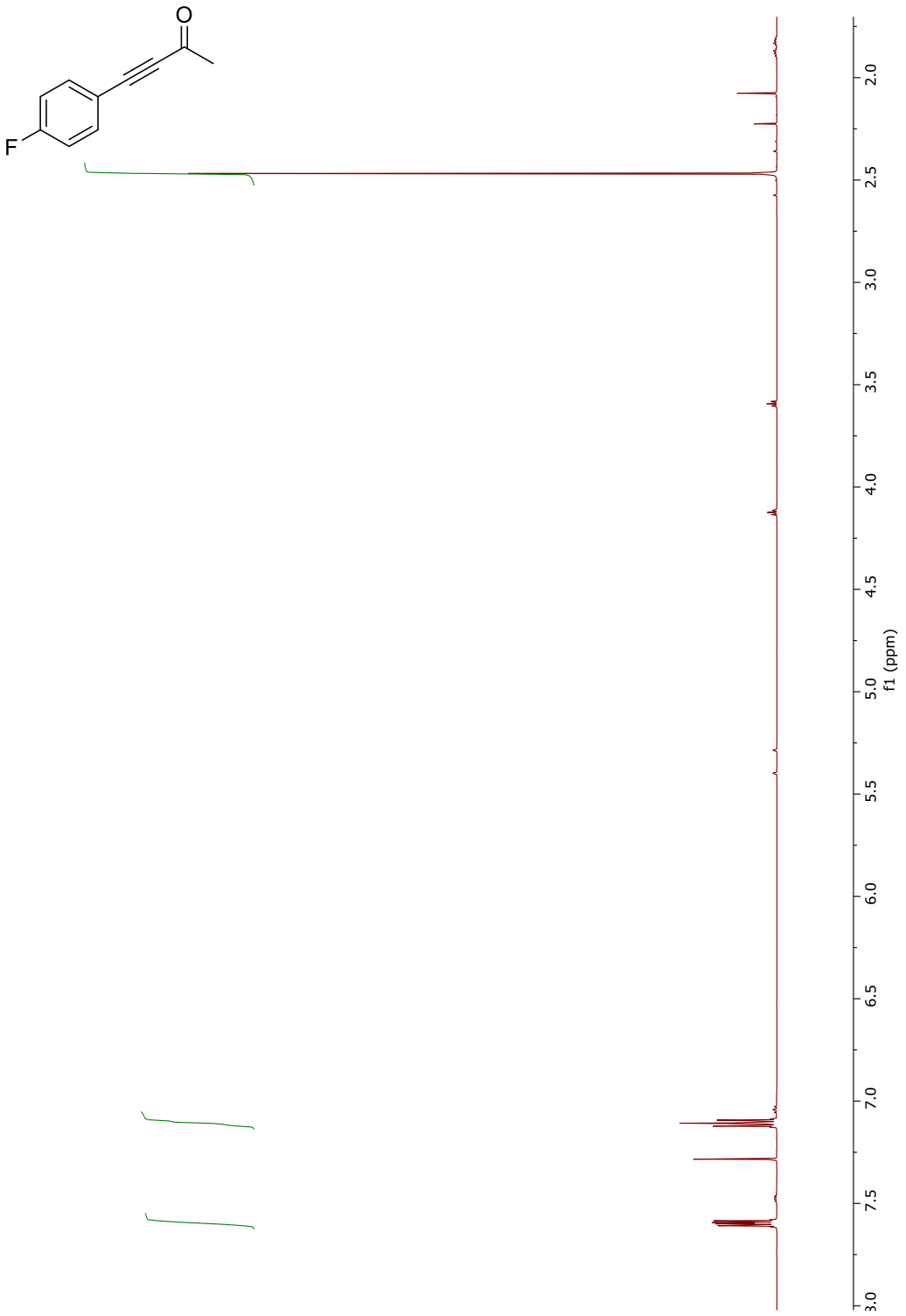
5.7.7 ^{1}H NMR Spectrum of compound 4.70 (500 MHz, $CDCl_3$)



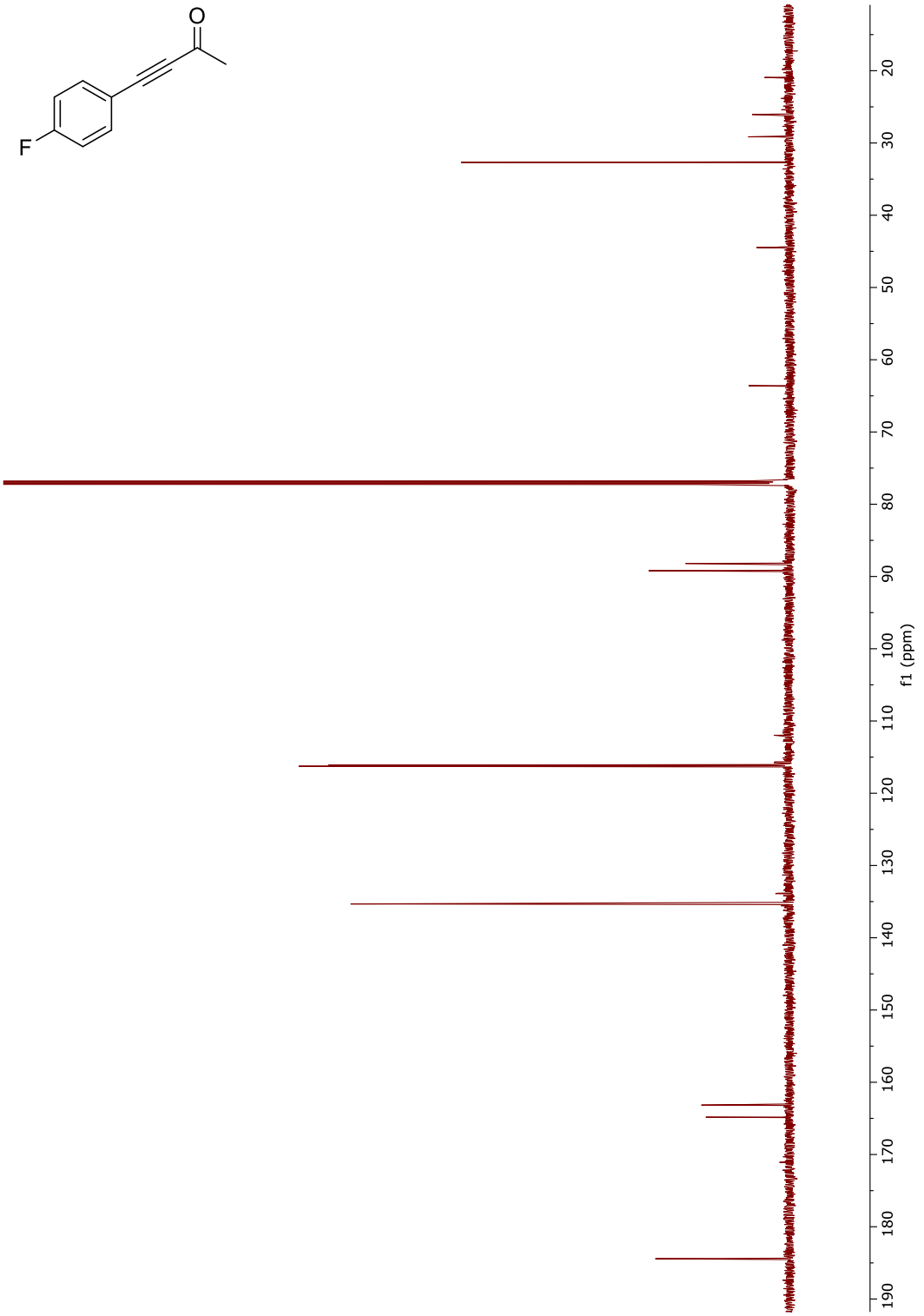
5.7.8 ^{13}C NMR Spectrum of compound 4.70 (500 MHz, $CDCl_3$)



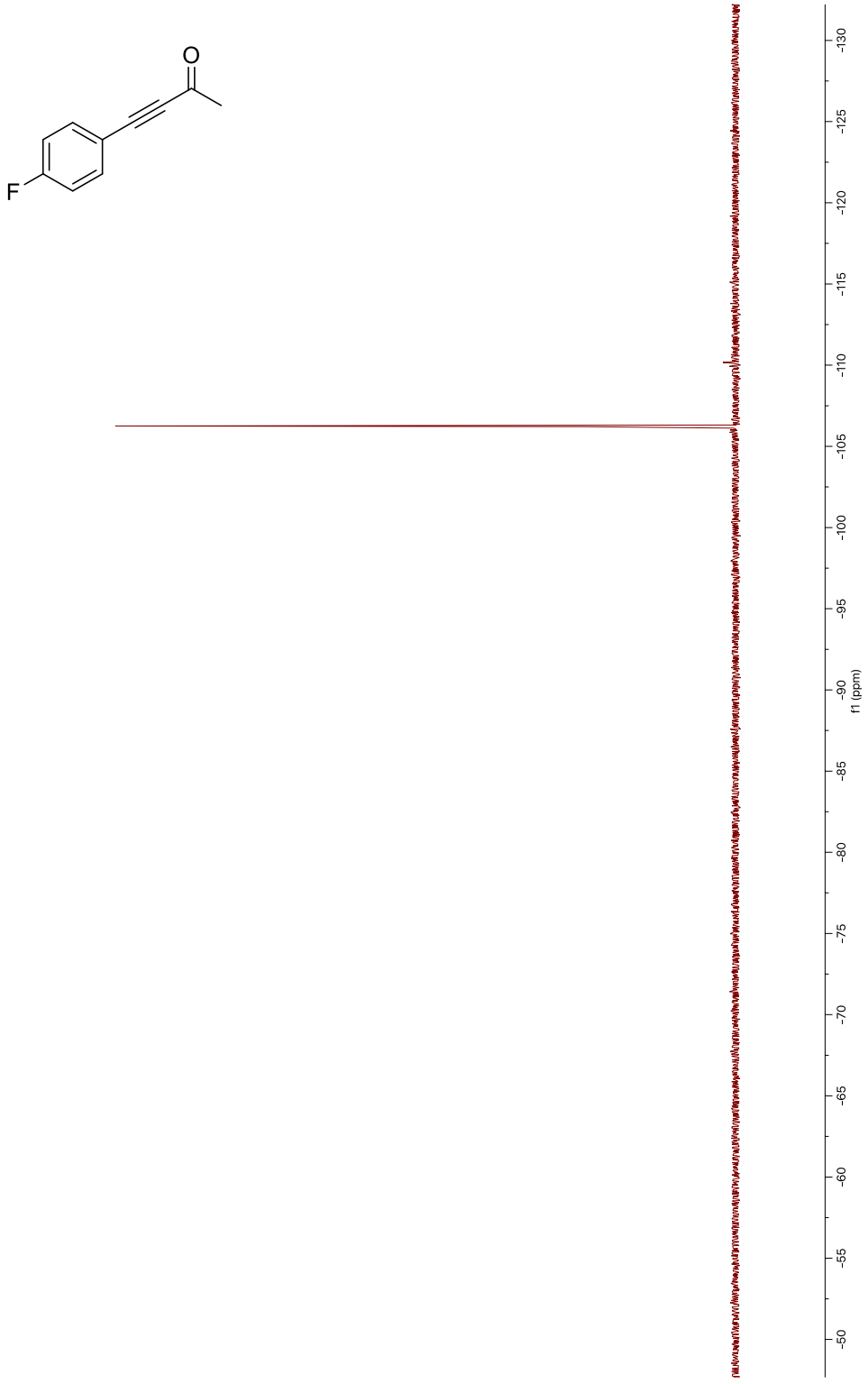
5.7.9 ^{1}H NMR Spectrum of compound 4.71 (500 MHz, $CDCl_3$)



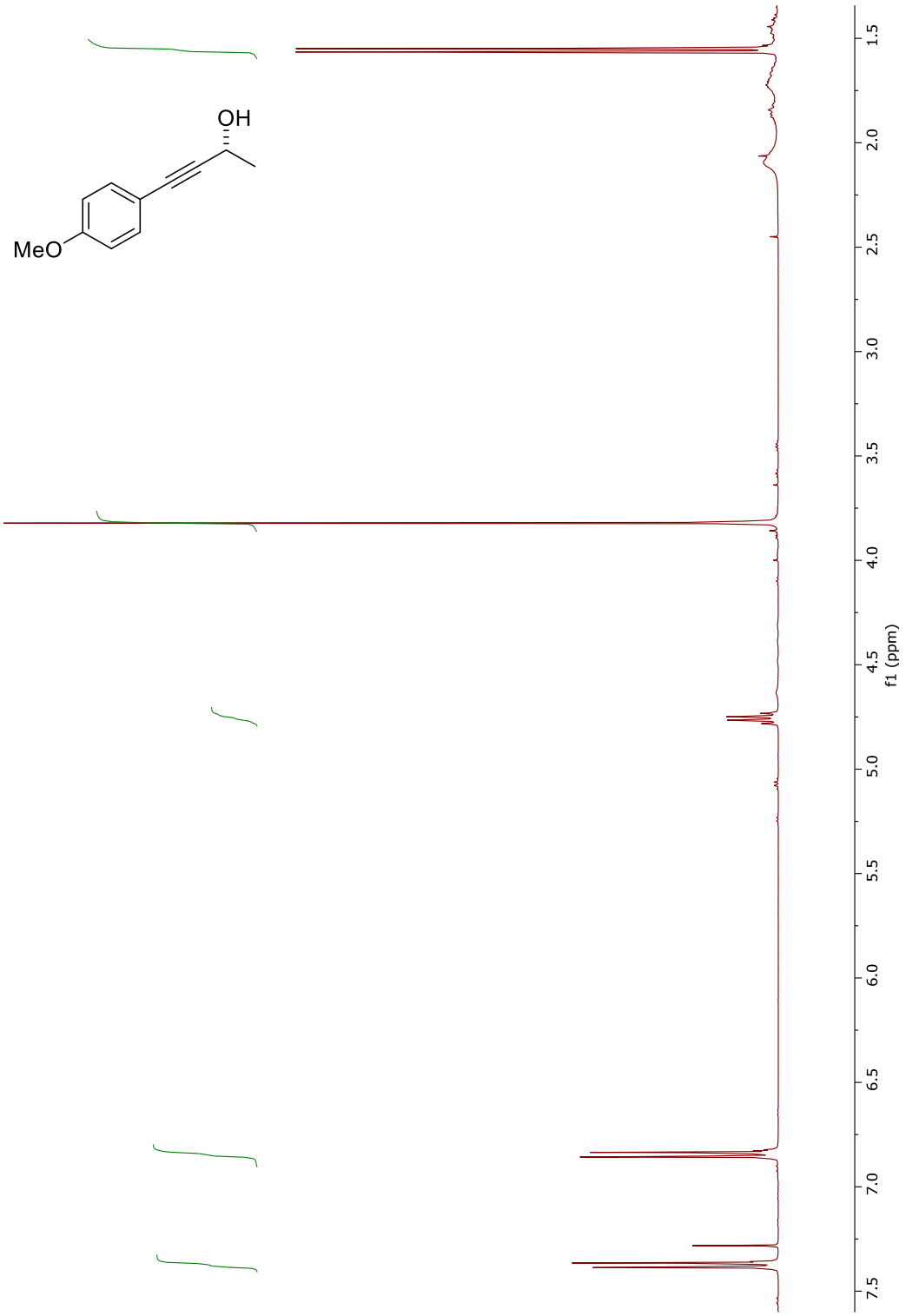
5.7.10 ^{13}C NMR Spectrum of compound 4.71 (500 MHz, $CDCl_3$)



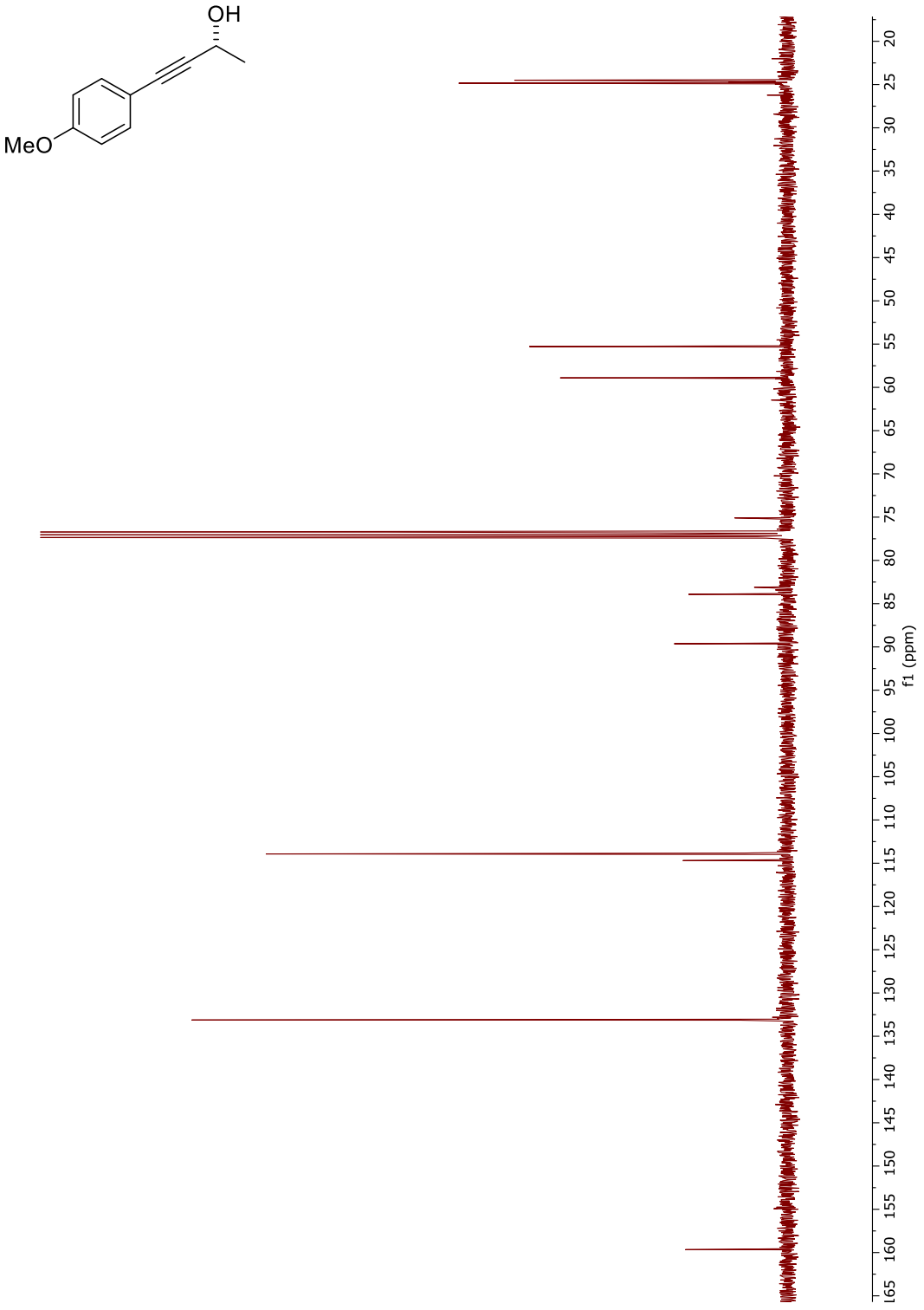
5.7.11 ^{19}F NMR Spectrum of compound 4.71 (377 MHz, $CDCl_3$)



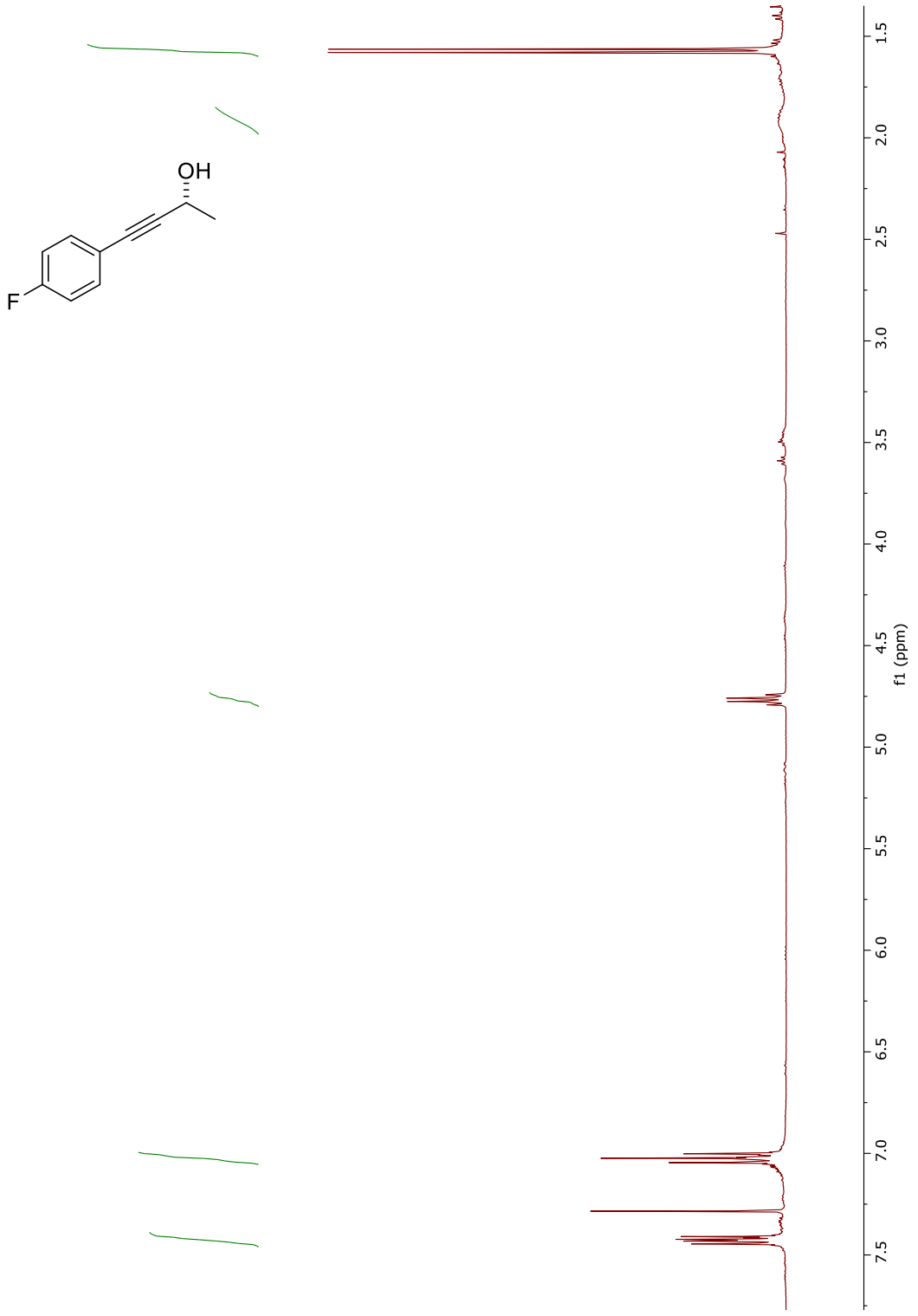
5.7.12 ^{1}H NMR Spectrum of compound 4.75 (500 MHz, $CDCl_3$)



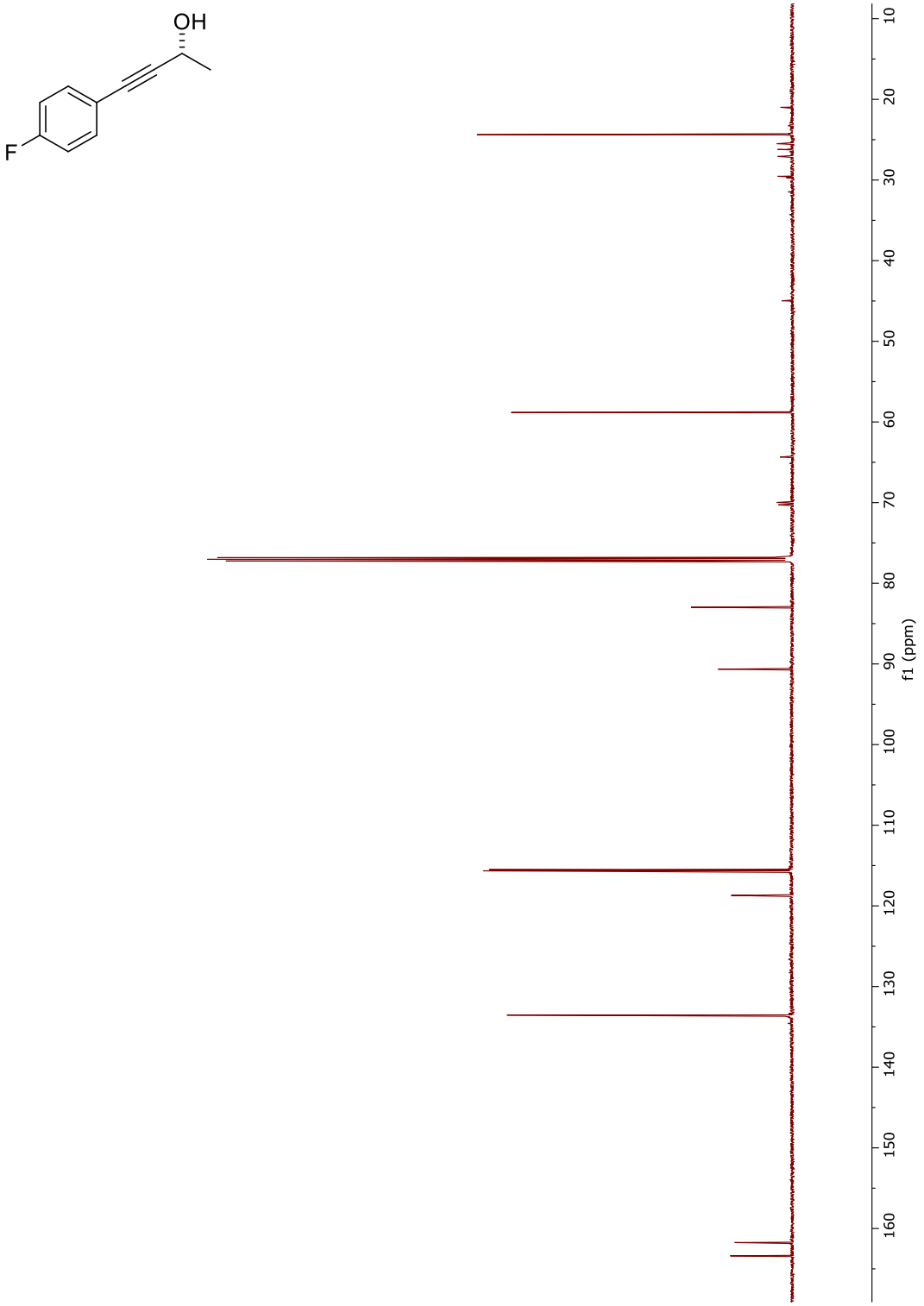
5.7.13 ^{13}C NMR Spectrum of compound 4.75 (500 MHz, $CDCl_3$)



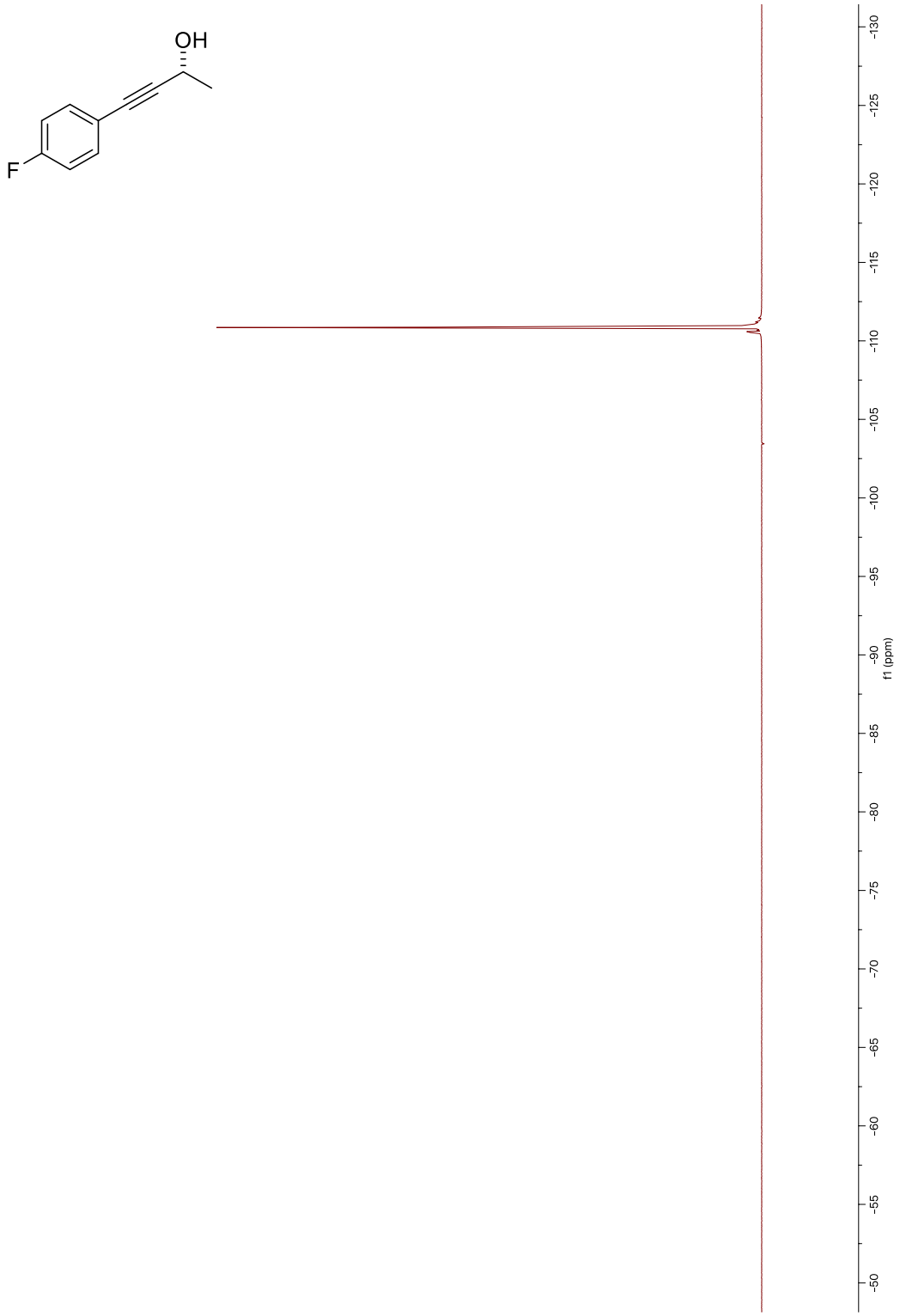
5.7.14 ^{1}H NMR Spectrum of compound 4.76 (500 MHz, $CDCl_3$)



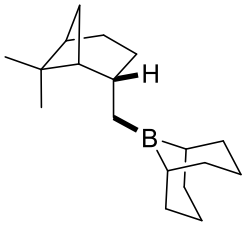
5.7.15 ^{13}C NMR Spectrum of compound 4.76 (500 MHz, $CDCl_3$)

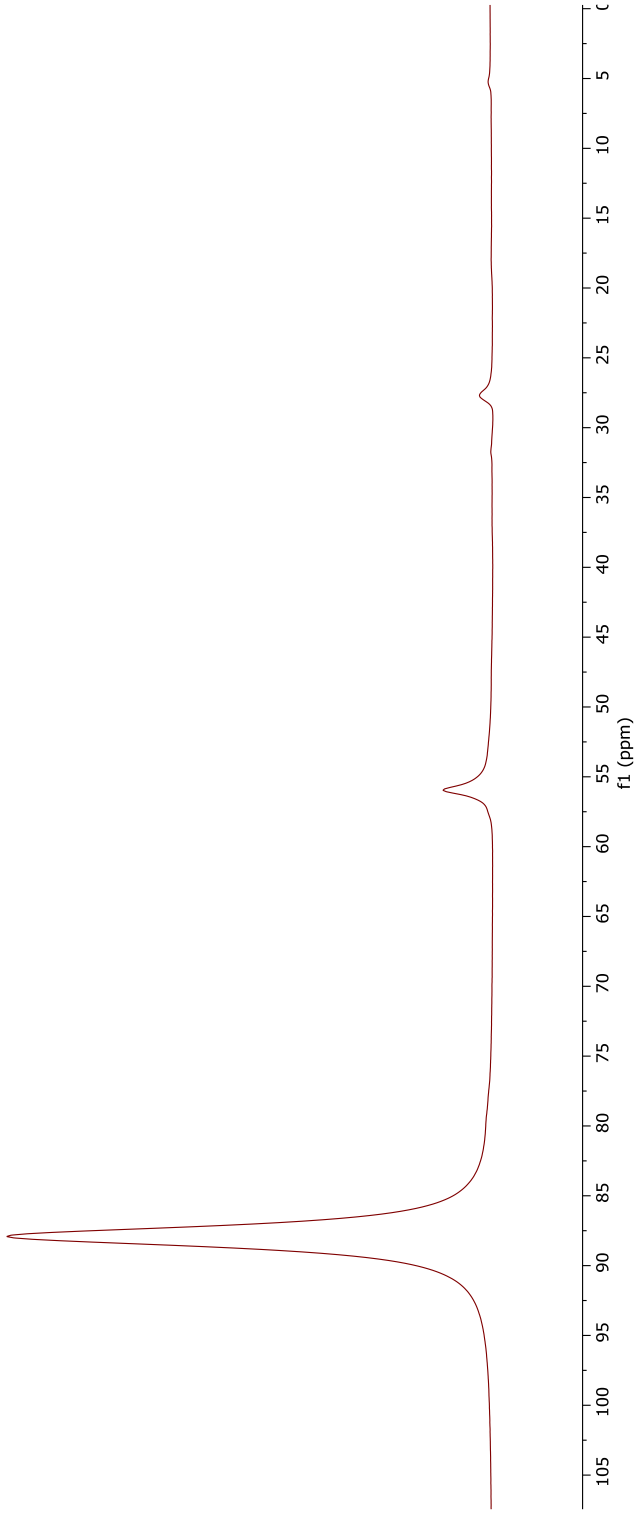


5.7.16 ^{19}F NMR Spectrum of compound 4.76 (472 MHz, $CDCl_3$)

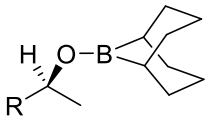


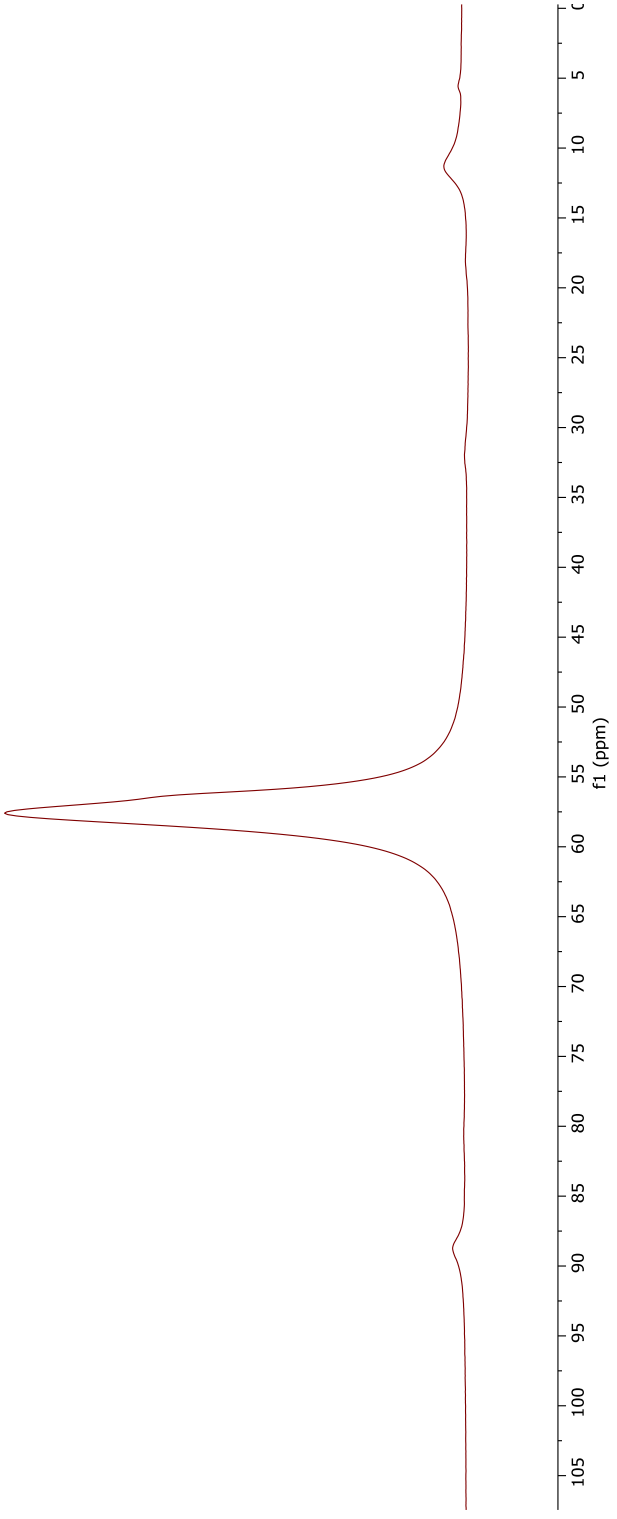
5.7.17 ^{11}B NMR of B-pinene + 9-BBN to give myrtanyl borane 4.63



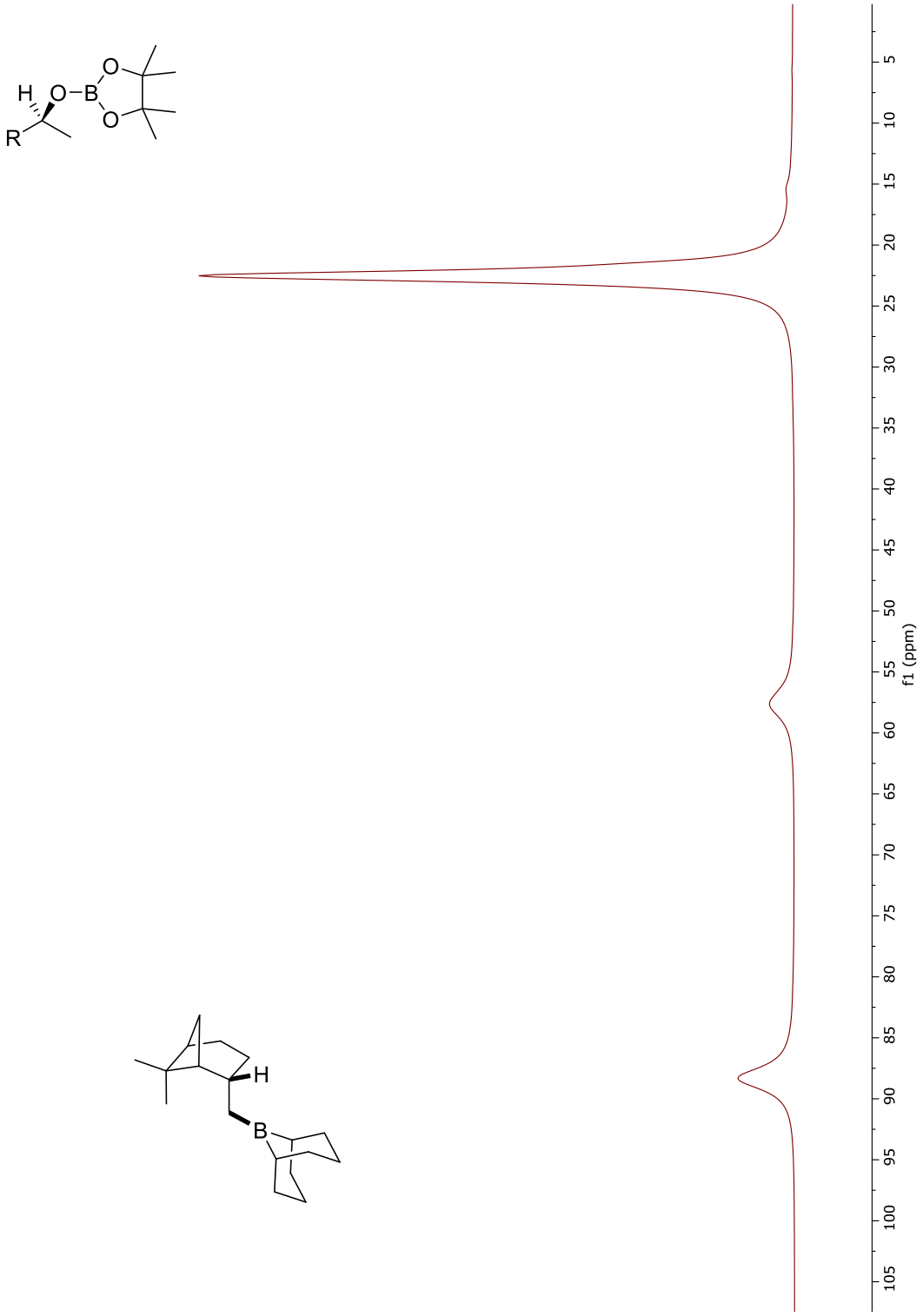


5.7.18 ^{11}B NMR of Myrtanyl borane + substrate to give borinic ester 4.49





5.7.19 ^{11}B NMR of borinic ester 4.49 + HBpin to give borate ester 4.50 and regenerate myrtanyl borane 4.63



Chapter 6 – References

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