Studies Toward the Total Synthesis of Panduratin and Bicuculline Natural Products

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR ADMISSION TO THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

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This thesis is dedicated to my family.

"Families are the compass that guide us. They are the inspiration to reach great heights, and our comfort when we occasionally falter."

Brad Henry

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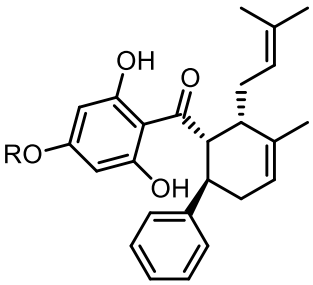
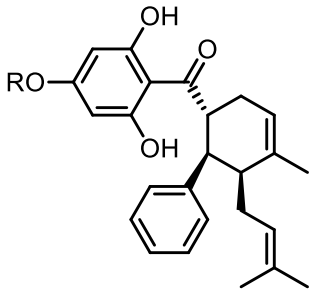
Abstract

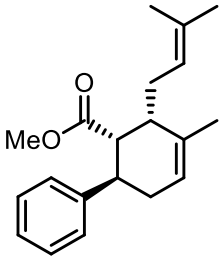
This thesis describes the total synthesis of racemic panduratin A (**8**), 4-hydroxypanduratin A (**9**), nicolaioidesin B (**20**) (isopanduratin A), 4-hydroxyisopanduratin A (**36**), panduratin H (**17**), panduratin I (**18**) and studies towards synthesis of bicuculline (**166**).



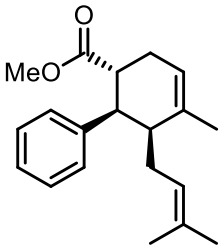
R = Me panduratin A (**8**)
R = H 4-hydroxypanduratin A (**9**)



R = Me nicolaioidesin B (**20**) (isopanduratin A)
R = H 4-hydroxyisopanduratin A (**36**)



panduratin H (**17**)



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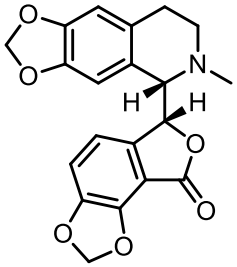
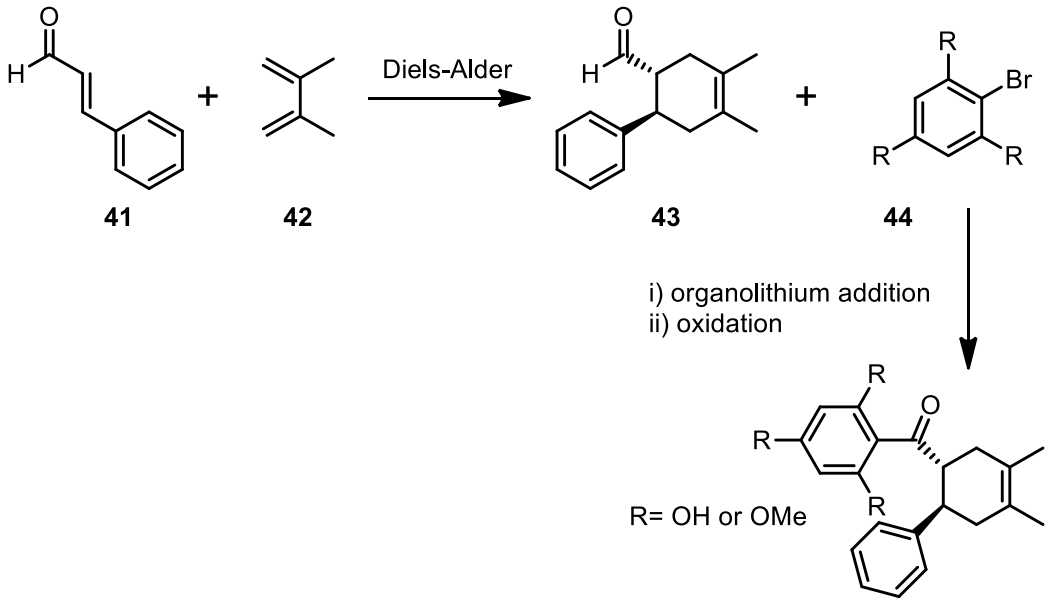


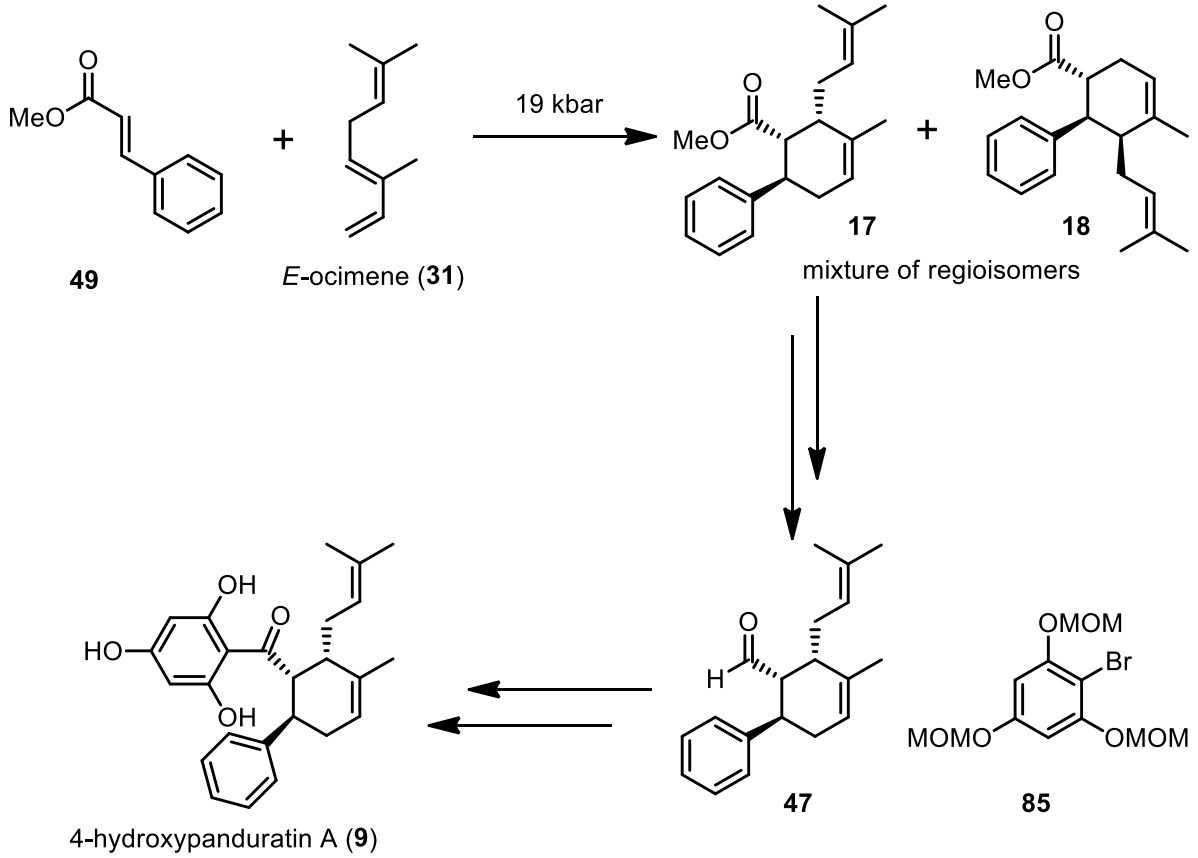
bicuculline (**166**)

The synthesis of the panduratin family members was achieved after first performing a model synthesis to successfully develop the required synthetic methodology. This involved a Diels-Alder reaction between cinnamaldehyde (**48**) and butadiene (**42**) followed by the addition of an organolithium derived from a bromobenzene.

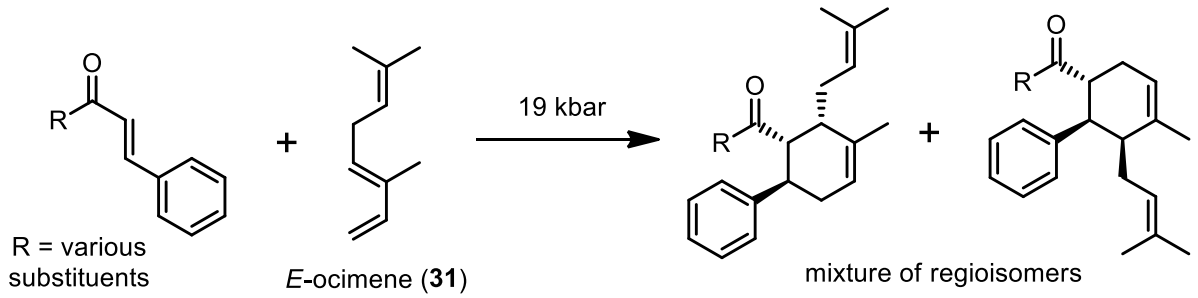


41 **42** **43** **44**

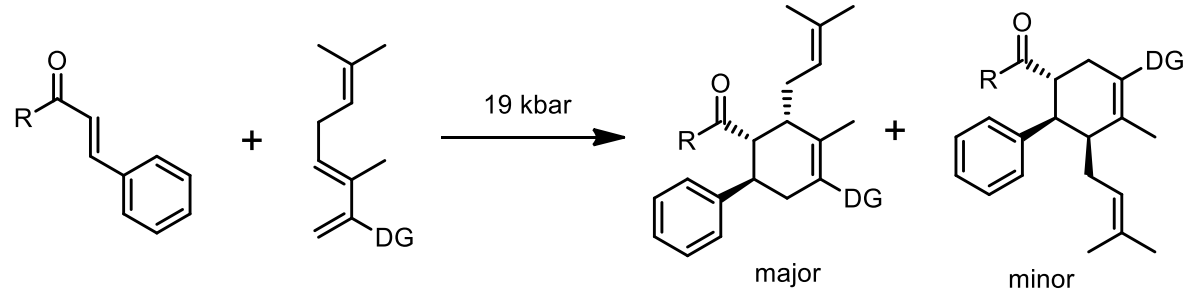
This developed methodology allowed the generation of many panduratin analogues as well as several panduratin family members. Some of the analogues were tested against the dengue fever serotype 2 (DEN-2) protease along with 4-hydroxypanduratin A (**9**).



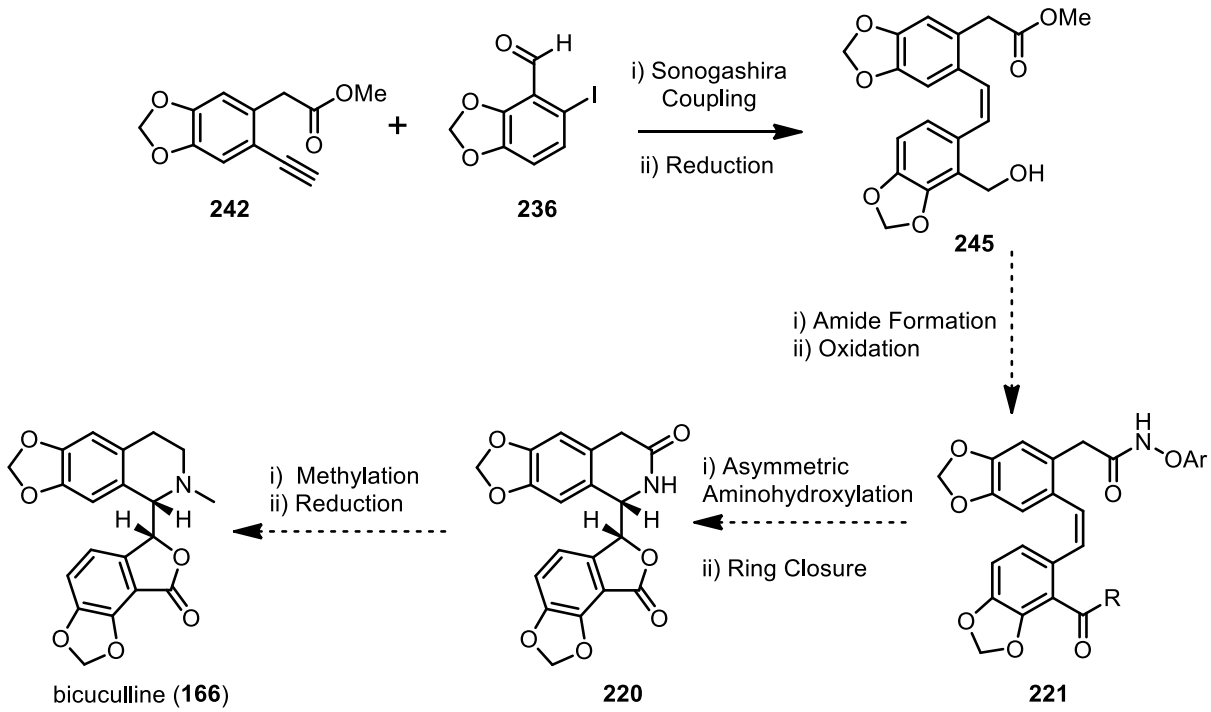
In addition to the synthesis of the panduratin family members and analogues, a regioselectivity study of high pressure Diels-Alder reactions between various cinnamates and *E*-ocimene (**31**) was also conducted to elucidate the steric and electronic factors responsible for the regioselectivity.



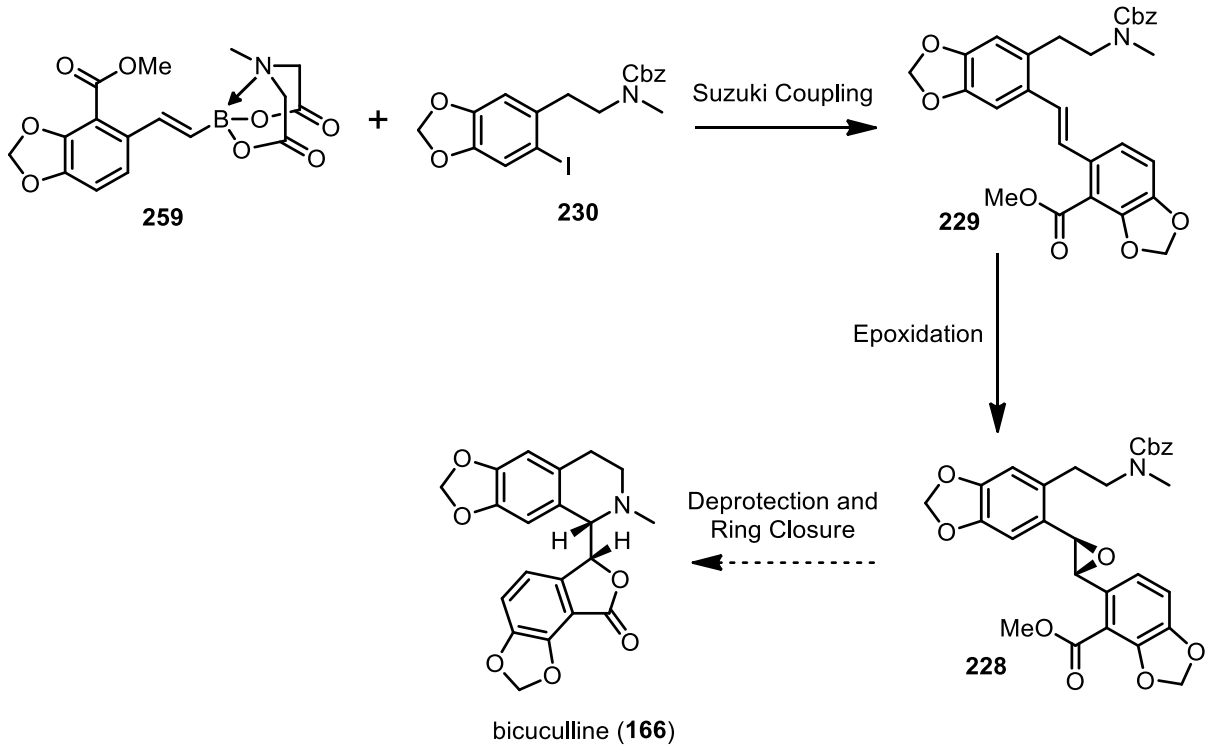
Following this study modified dienes with strong directing groups were synthesised in an attempt to shift the product distribution towards Diels-Alder product where the prenyl group was *ortho* to the electron withdrawing group of the cinnamate.



With respect to the synthesis of bicuculline (**166**) two approaches were employed. The first approach involved synthesis of a biaryl *Z*-alkene that could then undergo an intra-molecular tethered aminohydroxylation to afford the core of bicuculline. Biaryl alkene (**245**) was successfully synthesised through a Sonogashira coupling and subsequent reduction of the alkyne. Studies towards the remaining transformations remain ongoing.



The second approach to bicuculline (**166**) used a Suzuki coupling between MIDA boronate **259** and aryl iodide **230**. The *trans*-alkene **229** was then converted to the epoxide followed by deprotection of the amine to facilitate a ring closure resulting in a crude sample that has been postulated to be bicuculline (**166**). Investigations into alternative ring closure conditions and purification strategies are ongoing.



259 **230** **229** **228**

bicuculline (**166**)

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I would first like to thank Dr Malcolm McLeod for giving me the opportunity to work on this project all the assistance he has provided. His advice, guidance and support throughout the years was untiring and is greatly appreciated. I would also like to thank him for him patience and understanding while I wrote this thesis.

I must also thank the Otting and Coote research groups from ANU with who we collaborated with at many different times during this work. Laura de la Cruz from the Otting research group was instrumental in the testing of compounds against the dengue fever protease and also in the computational modelling of the protease. Likewise Junming Ho from Coote group performed all of the computational analysis of the frontier molecular orbitals of the dienophiles and dienes as well transition state calculations of the high pressure Diels-Alder reactions. I greatly appreciate their contribution to this work.

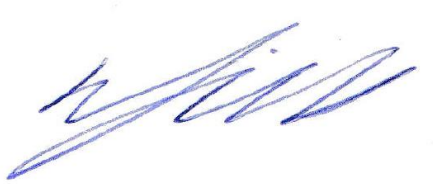
Thanks must also go to all the staff at the Research School of Chemistry. The equipment and technical assistance was always fantastic and made sure my work went as smooth as it could. Special thanks must go to all the NMR and mass spectroscopy staff who always strove to ensure the equipment was well maintained and delivered the best results possible.

A big thank you must also be said to the rest of the McLeod group who always provided assistance whenever it was needed and especially for their friendship. You all made the busy and stressful years as easy and enjoyable as possible.

Finally to my family and in particular my wife Sabrina. Thank you all for your love, patience and continual support. Words do not express how much I appreciate it. Everything I have ever achieved is because of all your support. Thank you

Declaration

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, nor material which to a substantial extent has been accepted for the award of any other degree or diploma at the Australian National University or any other educational institution, except where due acknowledgement is made in the thesis. Any contribution made to the research by others, with whom I have worked at the Australian National University, is explicitly acknowledged in the thesis.



Luke Alexander Pasfield

Abbreviations

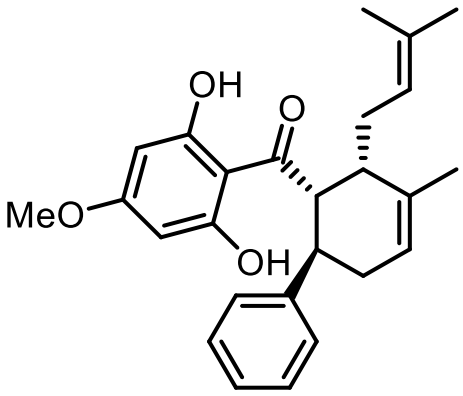
Ac	acetyl
ACN	acetonitrile
ADE	antibody dependent enhancement
AIBN	azobisisobutyronitrile
AgNP	silver nanoparticle
BHT	butylated hydroxytoluene
Bn	benzyl
b.p.	boiling point
br	broad
brine	saturated aqueous sodium chloride solution
Bu	butyl
BZs	benzodiazepines
°C	degree Celsius
calc.	calculated
Cbz	carboxybenzyl
CDI	1,1'-carbonyldiimidazole
d	doublet
Da	Dalton
DABCO	1,4-diazabicyclo[2.2. 2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
DEN	dengue
DG	directing group
DHF	dengue haemorrhagic fever
DIPEA	diisopropylethylamine
DMF	dimethylformamide

DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
ds	diastereoselectivity
DSS	dengue shock syndrome
ee	enantiomeric excess
EI	electron ionisation
ER	endoplasmic reticulum
ESI	electrospray ionisation
Et	ethyl
EtOH	ethanol
EWG	electron withdrawing group
g	gram
GABA	gamma aminobutyric acid
hr	hour(s)
hexanes	hexanes with b.p. 65 - 69°C
HIV	human immunodeficiency virus
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbit
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	Hertz
IPSP	inhibitory post synaptic potential
IR	infra-red spectroscopy
J	^{1}H-^{1}H coupling constant (in Hz)
L	litre
LDA	lithium diisopropyl amide
LHMDS	lithium hexamethyldisilazide

LRMS	low resolution mass spectrometry
LUMO	lowest unoccupied molecular orbit
M	molar
m	multiplet, medium
m.p.	melting point
m/z	mass to charge ratio
*m*CPBA	*meta* chloroperoxybenzoic acid
Me	methyl
MHz	megahertz
MIDA	*N*-methyliminodiacetic acid
min	Minute(s)
mL	millilitre
mm Hg	millimetre of mercury
mmol	millimole
mol	mole
MEM	methoxyethoxymethyl
MOM	methoxymethyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ph	phenyl
PMB	*para*-methoxybenzyl
ppm	parts per million
q	quartet
R	unspecified alkyl group
RNA	ribonucleic acid

RT	room temperature
s	singlet, strong
sat.	saturated
t	triplet
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
Tf	triflate
TFA	Trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	tetramethylsilane
TS	transition state
w	weak
W	Watts
WHO	World Health Organisation
WNV	West Nile Virus

Chapter 1 – Panduratins



panduratin A

Chapter 1 – Panduratins

1. Introduction

1.1 Dengue Fever

Dengue fever is an acute febrile disease caused by four closely related virus serotypes (DEN-1, DEN-2, DEN-3 and DEN-4) of the *Flaviviridae* family.[1-9] It is a mosquito-borne infection and thus is primarily found in tropical and sub-tropical areas with the principal transmitter of the dengue fever virus the *Aedes aeygpti* mosquito. According to the World Health Organisation (WHO), 40% of the world's population or 2.5 billion people, in over 100 countries, are at risk of dengue fever (**Figure 1.1**). The distribution of dengue fever is similar to that of malaria, another mosquito-borne disease; however, it is more prevalent in urban and sub-urban areas.

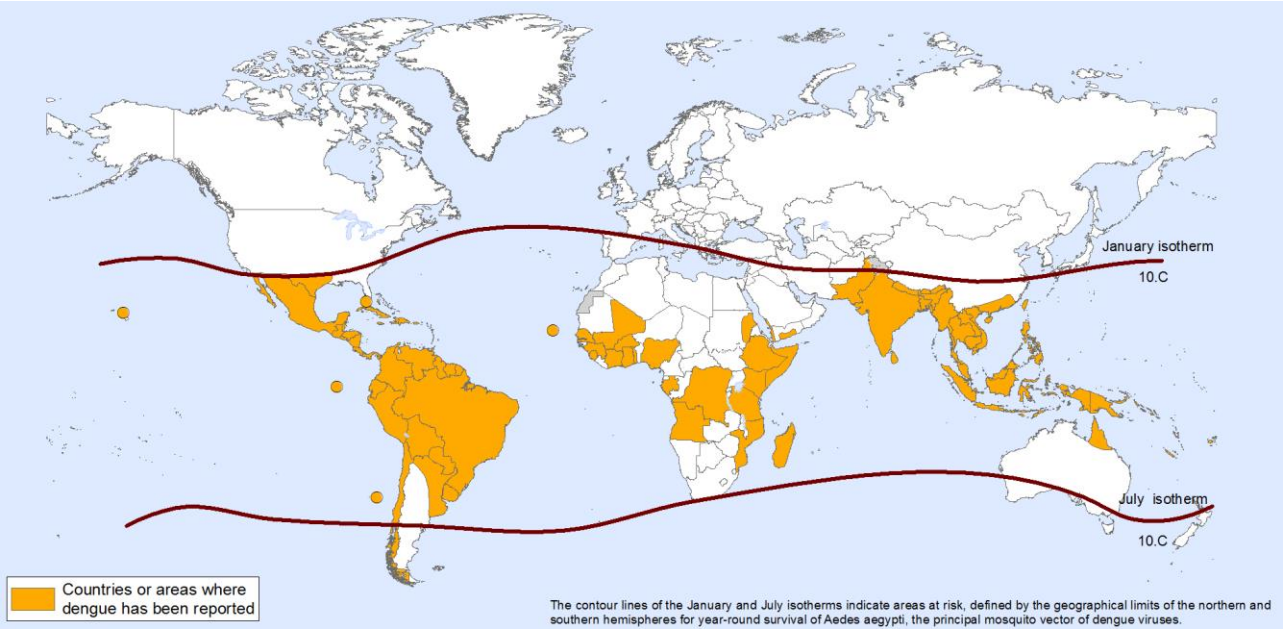


Figure 1.1 Worldwide dengue fever distribution.[9]

The dengue virus causes severe flu like symptoms as well as nausea, abdominal pain, vomiting and diarrhoea. Infection is also often indicated by a red rash, known as dengue rash, on the lower limbs and chest.[10] While dengue fever itself rarely causes death, complications called dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) can be lethal. In recent times DHF and DSS have become one of the leading causes of serious illness and death among children in Asian countries. It is estimated that 500 000 people a year are hospitalised, most of whom are children.[1] While generally only 2.5% of those infected die, without proper medical care this can exceed 20%.

Both DHF and DSS have been noted to be most common in areas where multiple serotypes of the dengue virus are found.[11] This is due to patients possessing pre-existing, but non-neutralising, antibodies to the dengue virus. Upon infection with another dengue serotype these antibodies can bind to the dengue virons and help adhere them to uninfected cells further facilitating the infection. This

process is termed antibody-dependent enhancement (ADE). For this reason infants born to dengue immune mothers are at risk to develop more severe dengue during a primary infection due to ADE.

The dengue virus is delivered to the blood stream of a recipient on being bitten by an infected mosquito (**Figure 1.2**).[3, 6, 12] After virus cell entry the nucleocapsid is uncoated and the positive strand RNA molecule is translated as a single polyprotein precursor on the endoplasmic reticulum (ER) and is processed into mature proteins by the host signal peptidase and by the viral NS3 serine protease that requires NS2B as a cofactor. The translated polypeptide consists of three structural (C, prM and E) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5) (**Figure 1.3**). Following further modification and folding the mature proteins replicate the viral genome and encase it in a nucleocapsid. This nucleocapsid then buds from the ER, through the golgi network and out of the cell to infect further cells.

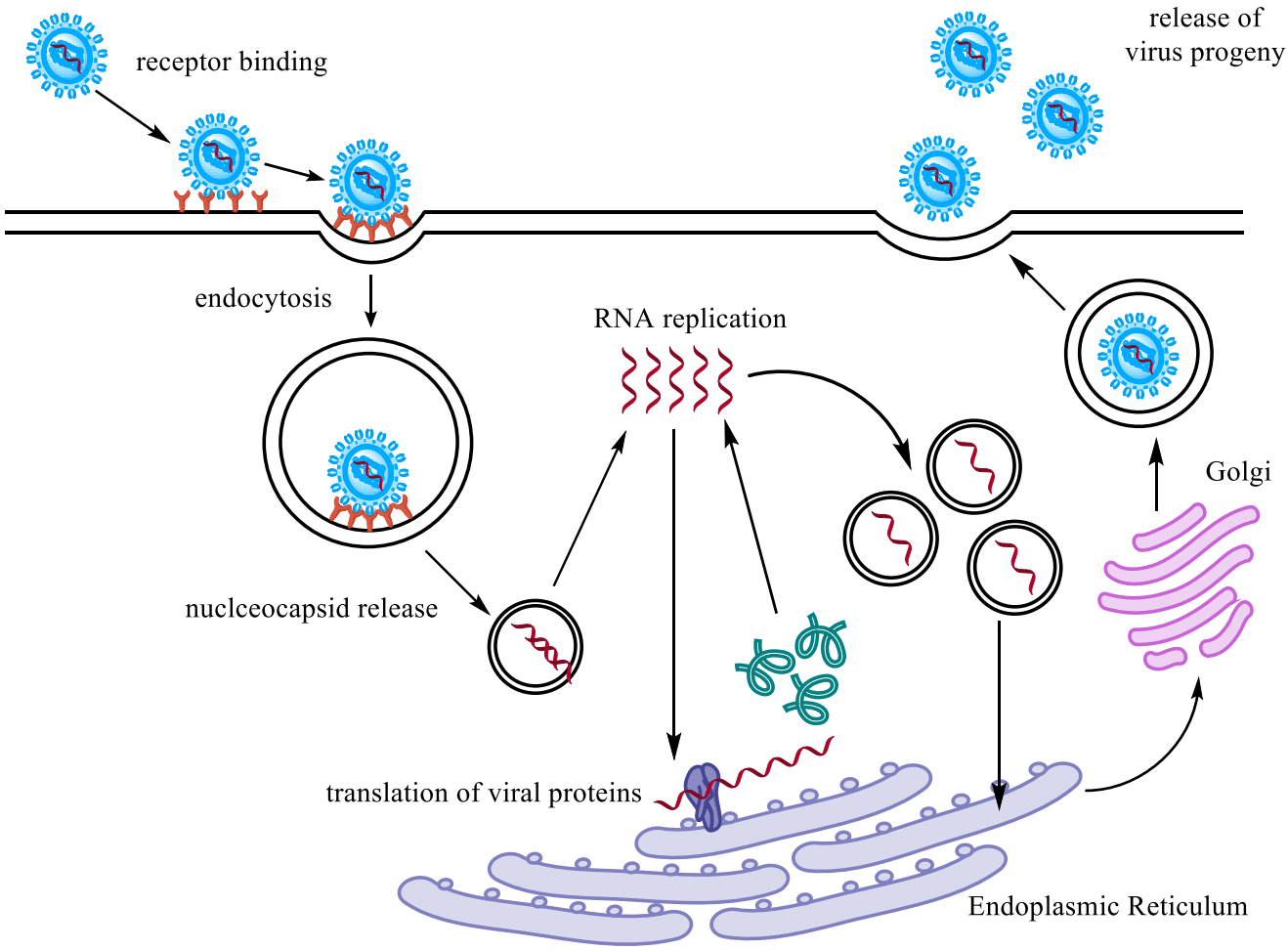


Figure 1.2 Dengue virus life cycle.[12]

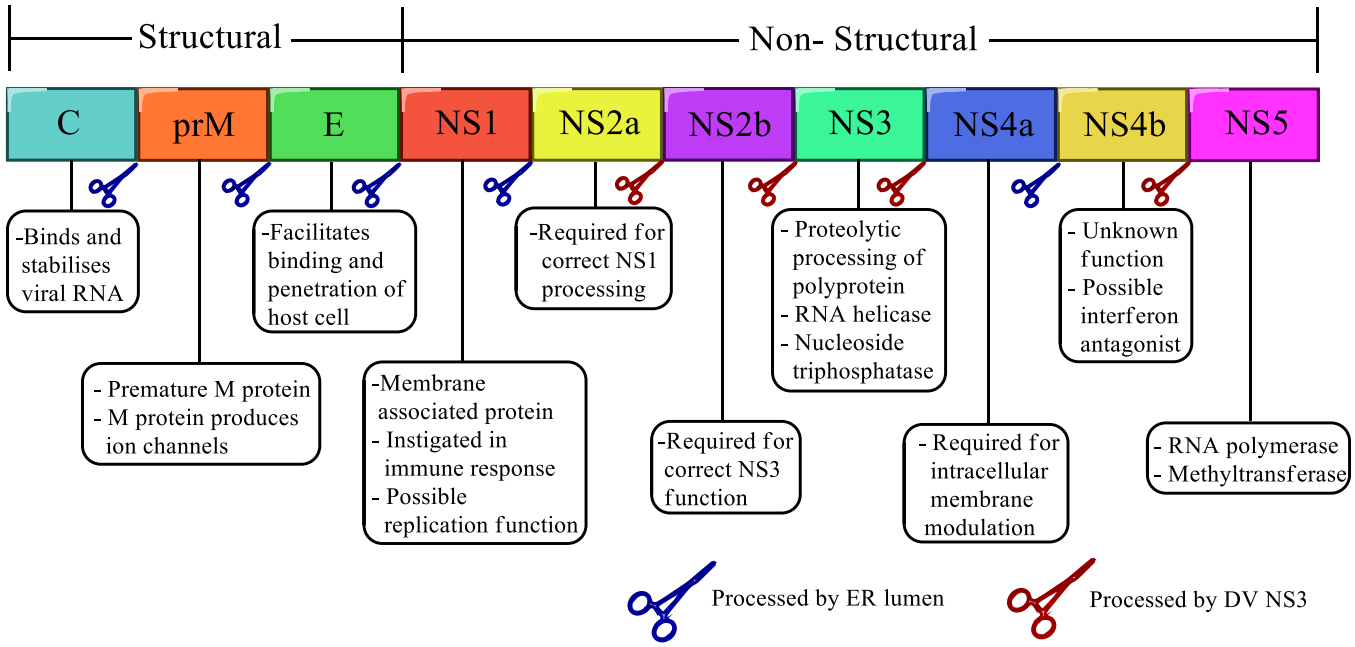


Figure 1.3 Dengue polyprotein processing.[11]

Given this protease is directly responsible for post-translational proteolytic processing of the polyprotein it is an ideal target. Drug design to potentially inhibit its action would halt viral replication.

The dengue NS2B/NS3 protease contains a trypsin-like catalytic triad containing a histidine, aspartic acid and serine residue. In 2012 Noble and co-workers published the first crystal structure of the dengue protease with an inhibitor bound (**Figure 1.4**).[13]

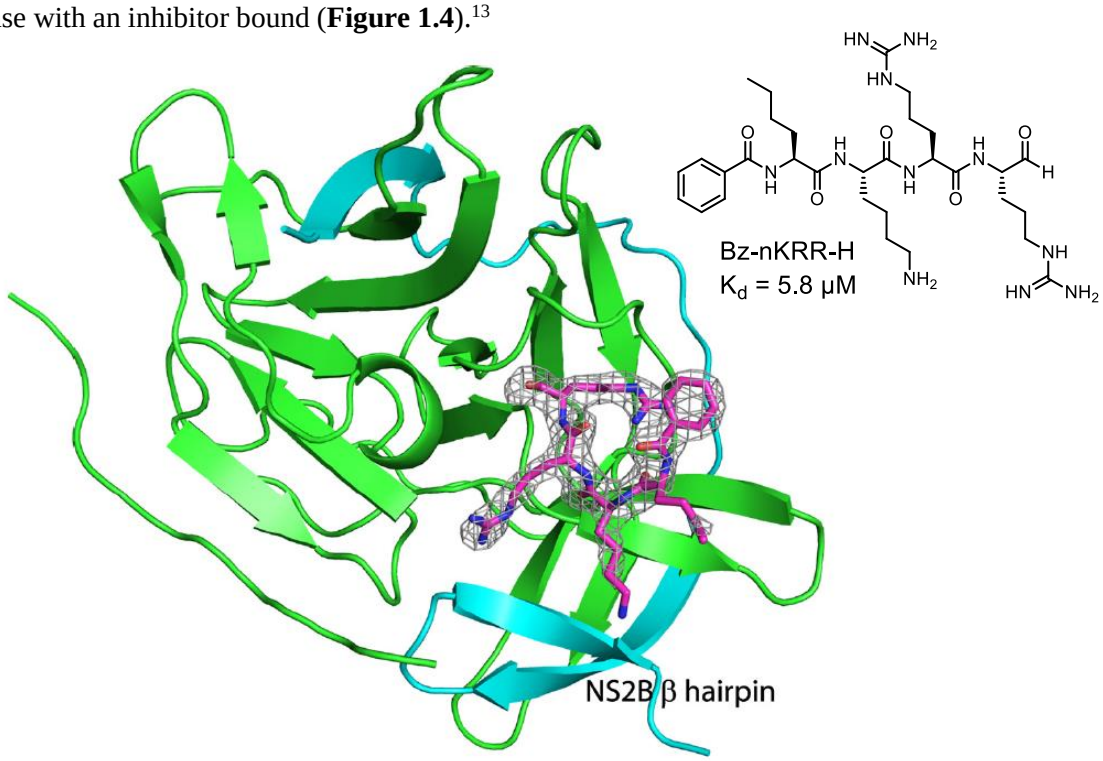


Figure 1.4 Crystal Structure of DEN-3 protease bound to Bz-nKRR-H (benzoyl-norleucine-Lys-Arg-Arg-aldehyde).[13]

This crystal structure shows that the NS2B plays a dual role; the *N*-terminus is inserted into the NS3 and stabilises it while the C-terminus forms part of the active site of the protease.[13] However the dengue protease without an inhibitor looks very different; while the *N*-terminus is still inserted into the NS3 the C-terminus is now far from the active site. Therefore it can be concluded that a substrate must be bound in the active site for the dengue NS2B/NS3 protease to change conformation with the NS2B protein wrapping around and closing the active site.

Prior to the publication Noble and co-workers of the crystal structure of the dengue protease with an inhibitor bound previously determined crystal structures of the West Nile virus (WNV) protease were used to predict the structure of the dengue protease with an inhibitor bound. WNV is a related flavivirus that has a similar NS2B/NS3 protease to dengue and have an amino-acid sequence about 40% similar. To this end crystal structures of WNV and the dengue protease (without inhibitor) were used in conjunction with NMR and computation techniques to predict the structure of the dengue NS2B/NS3 complex with an inhibitor bound (**Figure 1.5).**[13-16]

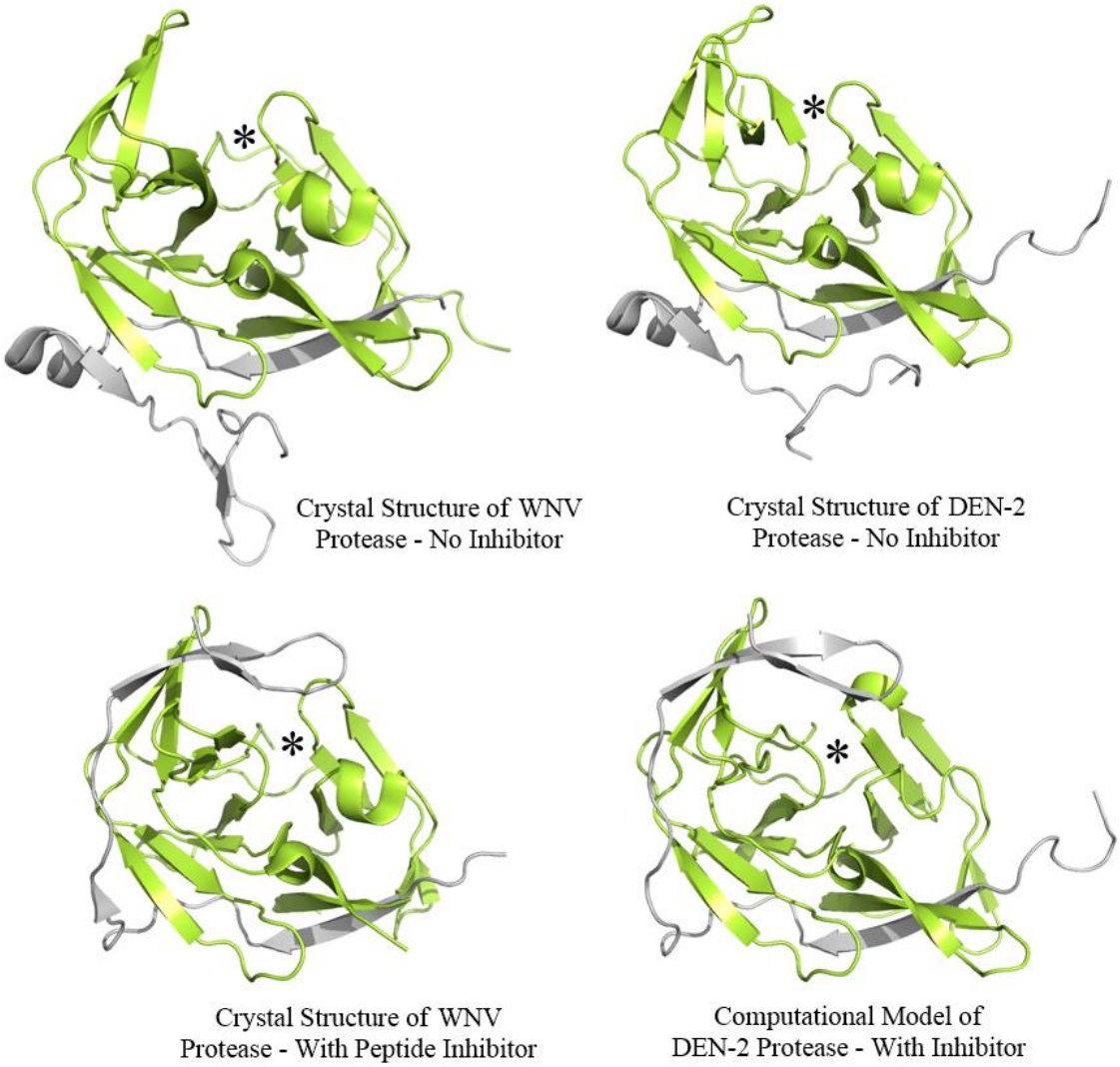


Figure 1.5 WNV and DEN-2 protease structures (active site located at position of asterisk).

Indeed this computational NMR predictive model of the dengue protease structure, by comparison to the WNV protease, was confirmed to be a powerful tool to visualise the dengue protease structure with potential inhibitors bound by the work of Noble and co-workers. Their publication confirmed that the structure and conformational changes of the WNV and dengue proteases are extremely similar when an inhibitor is bound (**Figure 1.6**).

Figure 1.6 DEN-3 protease in complex with Bz-nKRR-H (green) aligned with WNV protease bound to the same ligand (purple).[13]

With the confirmed computational model dengue protease in hand this now enabled the simulation of potential inhibitors in the active site to identify opportunities to modify and increase the binding of known inhibitors. This capability to computationally identify and develop inhibitors is especially import as there is currently no direct treatment for dengue fever available. There are no antiviral drugs in clinical use and currently treatment is limited to keeping patients well hydrated and managing fever and pain levels with appropriate medications.

With respect to vaccine development the greatest obstacle is producing one that induces a long lasting protective immune response against all four serotypes of dengue fever.[5, 11, 17-19] For instance while Dengvaxia® was licensed in 2015/2016 its efficacy against DEN-2 was consistently lower than other serotypes. Furthermore DENVax is a live attenuated vaccine in phase III clinical trials that while showing effectiveness against DEN-1 and DEN-2 displayed lower efficacy against DEN-3 and DEN-4.

Competitive inhibitors of the dengue NS2B/NS3 protease published thus far include peptides, Bowman-Birk inhibitors and synthetic compounds. Some peptidic inhibitors possessing a boronic acid or trifluoromethyl group developed thus far have shown binding affinities below 1 μM (**Figure 1.7**).[20-22] However the issue with peptide inhibitors as drug candidates is that they will most likely be broken down by other proteases before they can act as an inhibitor. They are also very polar compounds and so there are issues in their administration to patients.

Bz-Nle-Lys-Thr-Arg-OH	>500
Bz-Nle-Lys-Arg-Arg-OH	>500
Bz-Nle-Lys-Thr-Arg-NH_2	>500
Bz-Nle-Lys-Arg-Arg-NH_2	127.5
Bz-Nle-Lys-Arg-Arg-$NHSO_2CF_3$	>500
Bz-Nle-Lys-Thr-Arg-H	>500
Bz-Nle-Lys-Arg-Arg-H	5.8
Bz-Nle-Lys-Arg-Arg(OH)-CONH-Bn	178
Bz-Nle-Lys-Arg-Arg-Benzoxazole	82.9
Bz-Nle-Lys-Arg-Arg-Thiazole	42.8
Bz-Nle-Lys-Arg-Arg-CF_3	0.85
Bz-Nle-Lys-Arg-Arg-$B(OH)_2$	0.043

Figure 1.7 Some peptide inhibitors of DEN-2 protease and their binding affinities (μM).[20]

Bowman-Birk inhibitors (BBIs) are proteins abundant in dicotyledonous and monocotyledonous plants known to inhibit serine proteases (**Figure 1.8**).[11] They are typically 8 or 16 kDa in size and play a role a plant's defence against pests and pathogens. Most recently they have been identified as a prospective treatment for cancer, allergic disorders, inflammation and virus that employ serine proteases including dengue fever. However to date no specific K_d or K_i inhibition data has been published yet with regards to dengue fever.[23]

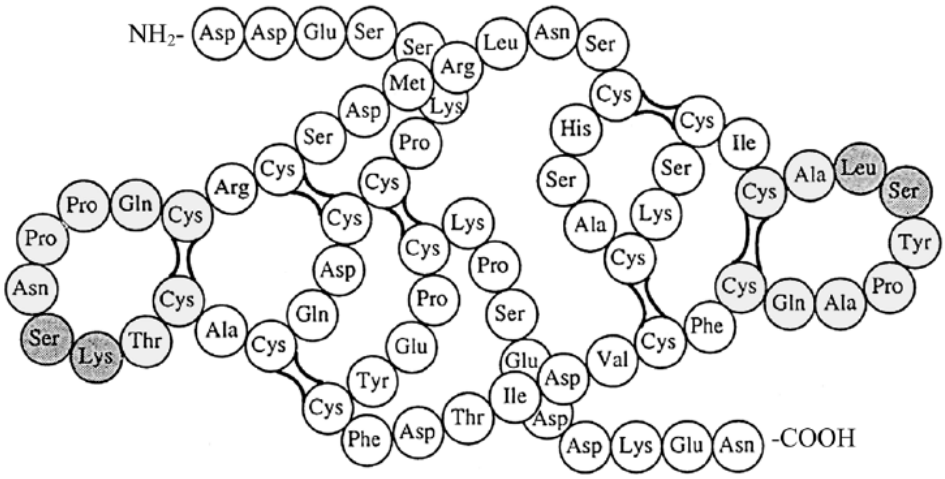


Figure 1.8 The primary structure of a soybean BBI also showing the seven disulfide bonds.[23]

Most work has been done on finding a synthetic compound to inhibit the dengue protease however none have been made yet that show inhibition values in the nM range. Some recent published examples can be seen in **Figure 1.9**. The challenge remains to find stable synthetic compounds that bind in <1 μM range.[3, 24-28]

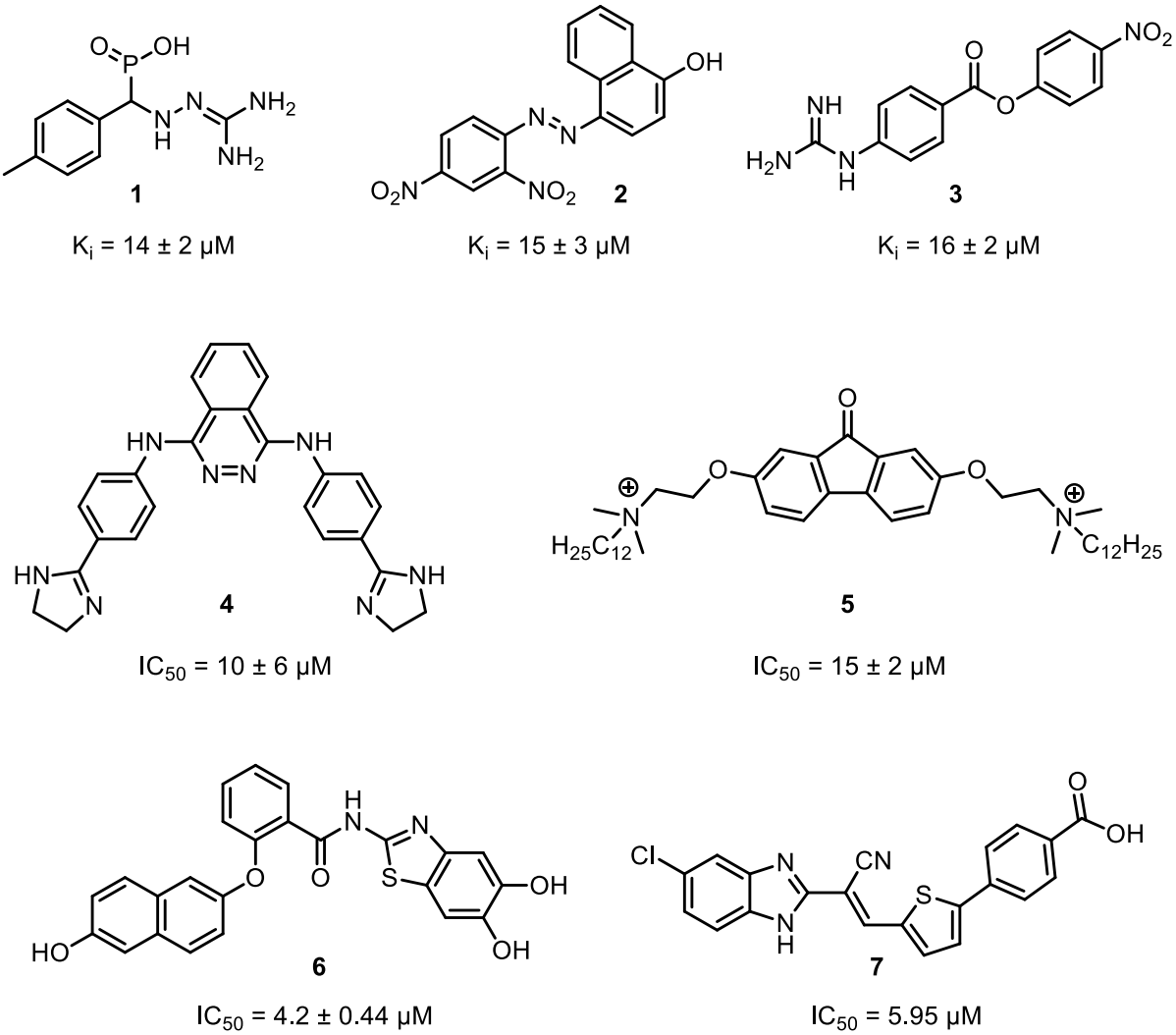


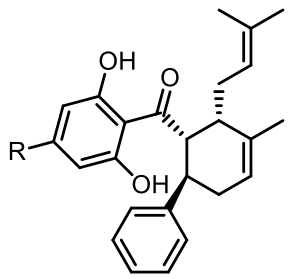
Figure 1.9 Recently published inhibitors of the DEN-2 protease.[24-29]

In 2006, Kiat and co-workers tested six compounds extracted from *Boesenbergia rotunda* against the DEN-2 protease for inhibition.[30] Of these six, panduratin A (**8**) and 4-hydroxypanduratin A (**9**) showed competitive inhibition of the protease with K_i values of 25 ± 8 and 21 ± 6 μM respectively. These low K_i values identify panduratin A (**8**) and 4-hydroxypanduratin A (**9**) as potential inhibitors of the dengue virus protease. Thus, a synthetic route to these compounds for further study, optimisation and testing was deemed highly desirable.

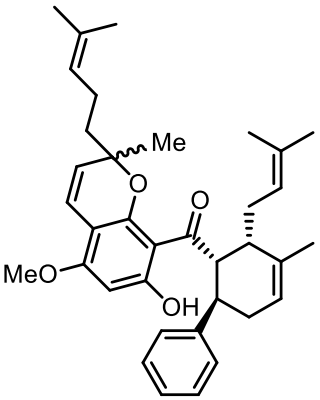
1.2 The Panduratin Family

Tuntiwachwuttikul and co-workers first isolated and elucidated the structure of panduratin A (**8**) in 1984 from *Boesenbergia rotunda* (also known as *Boesenbergia pandurata*) (**Figure 1.10**).[31] 4-Hydroxypanduratin A (**9**) was later isolated from the same source in 2001.[32] *Boesenbergia rotunda*, more commonly known as finger root, is a member of the ginger family (*Zingiberaceae*). It is found in Southeast Asia and has been used in traditional medicine to treat conditions such as diarrhoea, asthma, indigestion, dysentery and many other complaints.[33] Studies have also shown that the extracts have anti-HIV, antibacterial, antifungal, antitumor and insecticidal activity.[34]

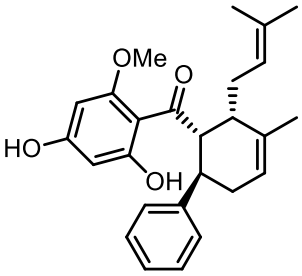
The key feature of panduratin family is a cyclohexene ring with 3 adjacent stereocentres. For panduratin A (**8**) this ring is tetra-substituted with methyl, prenyl, 2,6-dihydroxy-4-methoxybenzoyl and phenyl substituents. Other members of the family include 4-hydroxypanduratin A (**9**), panduratins B1 & B2 (**10** & **11**) and panduratins C-I (**12**-**18**).[35, 36] Panduratins B-F (**10**-**15**) differ from panduratin A (**8**) by virtue of their substitution on the benzoyl sidechain while panduratin G (**16**) has a different substitution pattern on the cyclohexene ring. The panduratins H (**17**) and I (**18**) have a methyl ester in place of the benzoyl moiety and differ from each other by their substitution pattern on the cyclohexene ring.



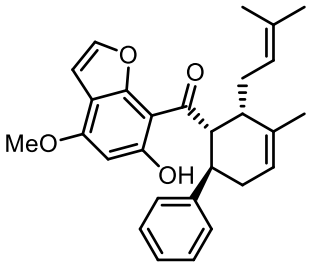
panduratin A R = OMe (**8**)
4-hydroxypanduratin A R = OH (**9**)



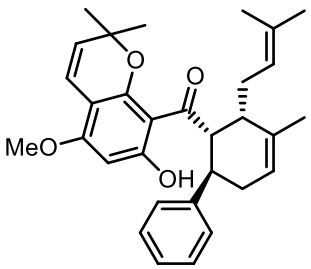
panduratin B1 (**10**) & B2 (**11**)



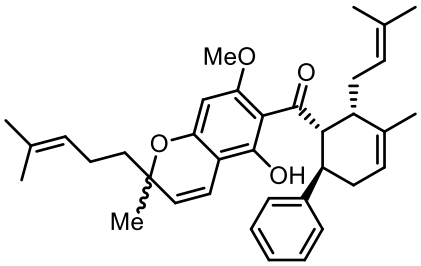
panduratin C (**12**)



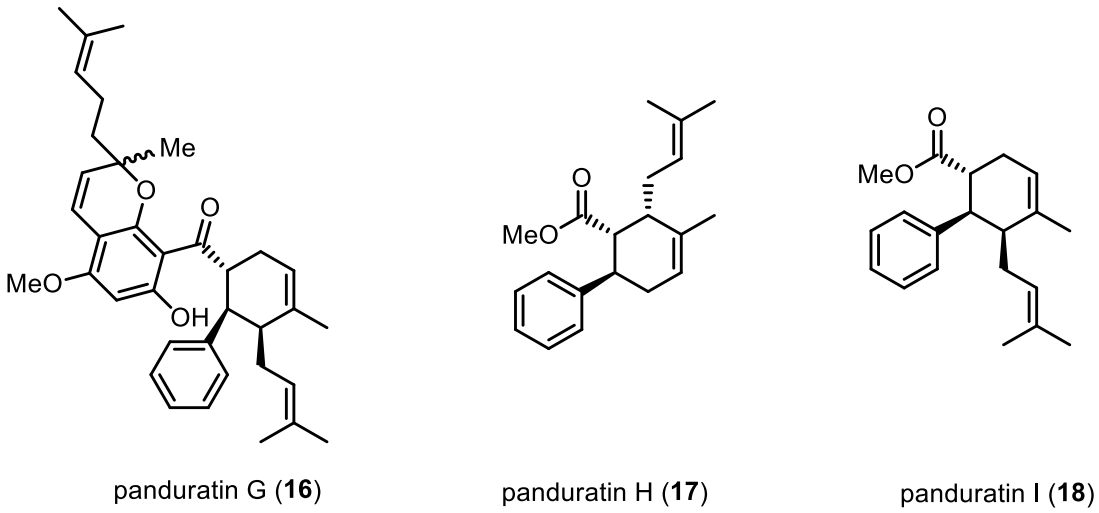
panduratin D (**13**)



panduratin E (**14**)



panduratin F (**15**)



panduratin G (**16**) panduratin H (**17**) panduratin I (**18**)

Figure 1.10 The panduratin family.

It should be noted that for of the above panduratins, except G and I, that the prenyl substituent is adjacent and *cis* with respect to the carbonyl. For panduratins G and I the prenyl substituent is adjacent and *cis* with respect to the phenyl group.

The biosynthesis of the panduratin family has not yet been determined and can only be speculated on. The members of the panduratin family do however, formally resemble products of a Diels-Alder reaction due to the presence of their cyclohexene core. A variety of naturally occurring polyketide derived chalcones have also been isolated from *Boesenbergia rotunda* and there is an abundance of unsaturated monoterpene oils found in nature which could act as dienophiles and dienes in Diels-Alder reactions, respectively. Whilst some enzymes have reported to catalyse various cycloadditions (Diels-Alderases), this is probably not the case with panduratin A (**8**).[37] Given it was isolated as a racemate, it seems to indicate that Diels-Alderases do not participate in the biosynthesis.

1.3 Related Compounds and Previous Syntheses

There are many related compounds to panduratin A (**8**), including nicolaioidesins A (**19**), B (**20**), C (**21**), as well as crinatusins C_1 (**22**) and C_2 (**23**) that have very similar structures (**Figure 1.11**).

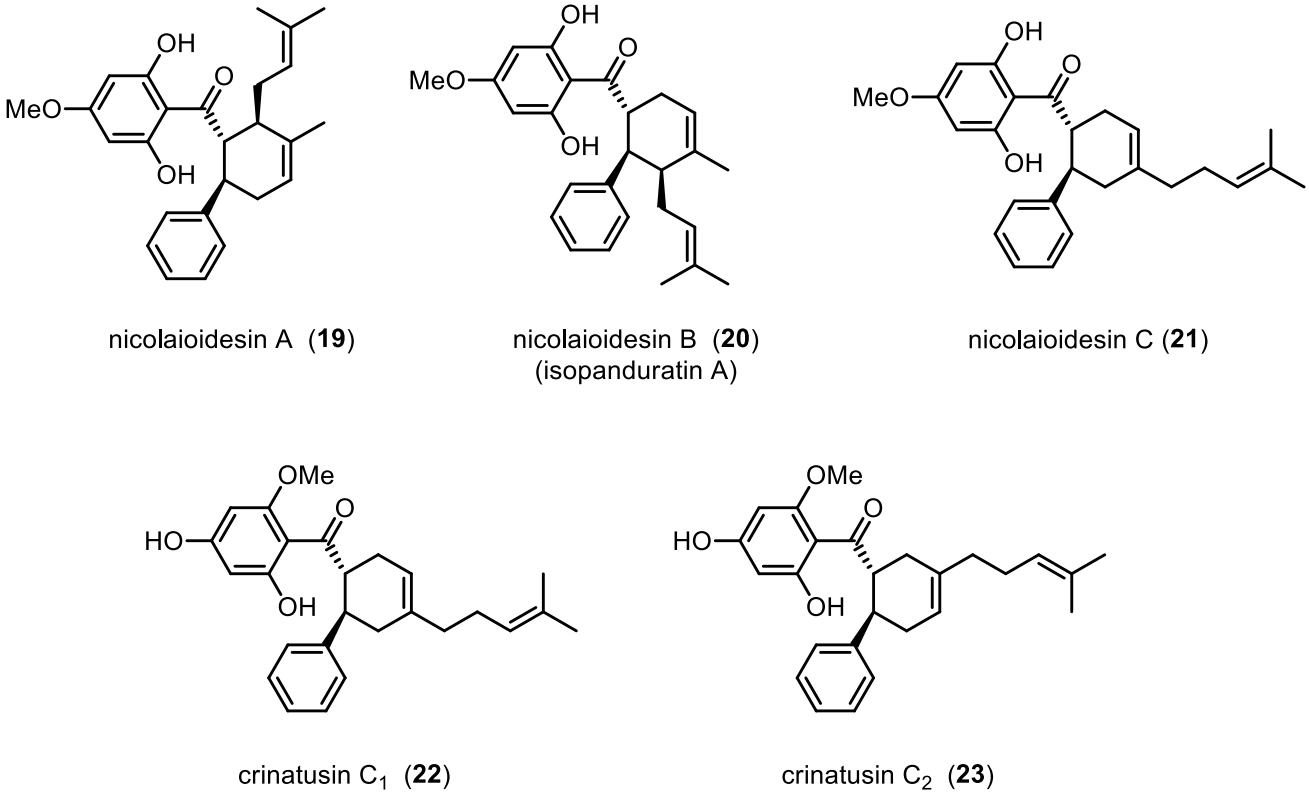
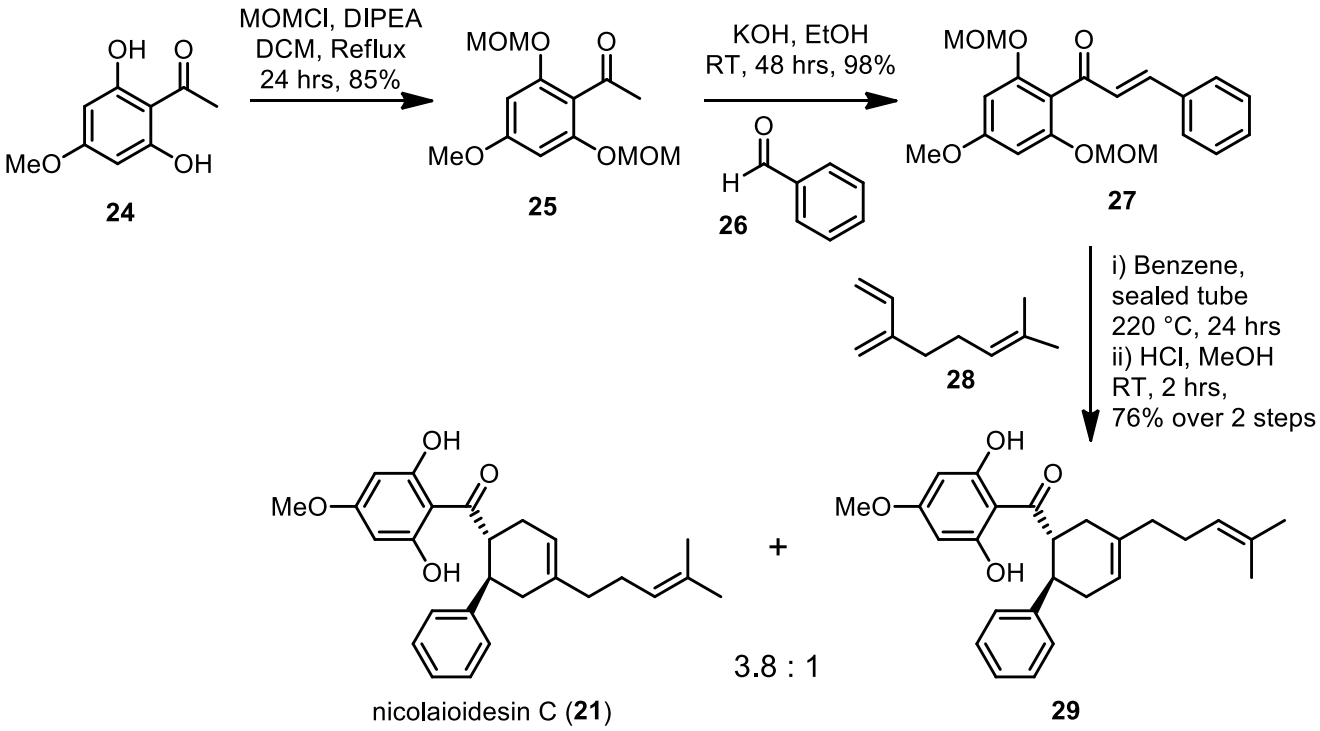


Figure 1.11 The nicolaioidensins and crinatusins.

These compounds all contain a cyclohexene core with similar substitutions on the ring. Of particular note is that nicolaioidesins A (**19**) only differs from panduratin A (**8**) in that the prenyl substituent is adjacent and *trans* with respect to the carbonyl.

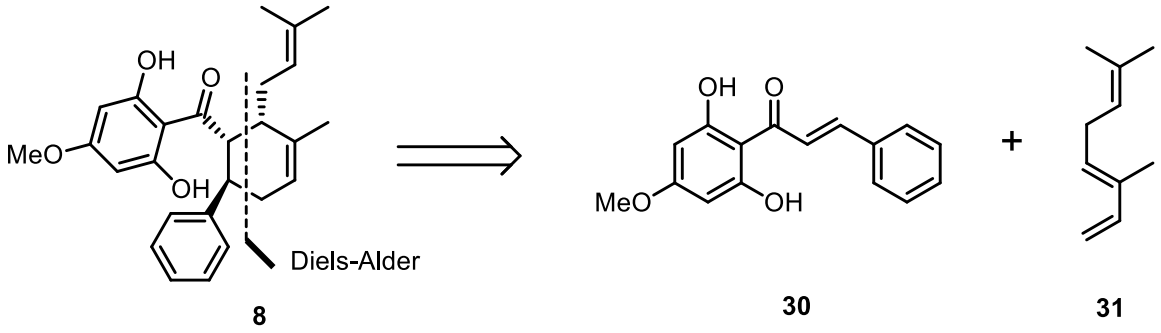
In 2008, Eun Mi Jung and Yong Rok Lee developed synthetic routes to nicolaioidesin C (**21**), crinatusin C_1 (**22**) and crinatusin C_2 (**23**).[34] Their general strategy was to take acetophenone **24** and protect the phenolic hydroxyls with methoxymethyl groups (MOM). These steps were followed by a Claisen-Schmidt reaction with benzaldehyde to generate a chalcone **27**. A normal electron demand Diels-Alder reaction was then performed between chalcone **27** and myrcene (**28**) followed by deprotection to give the desired natural product nicolaioidesin C (**21**) along with its regioisomer **29** in a ratio of 3.8:1 (**Scheme 1.1**). As expected nicolaioidesin C (**21**) was the major product with the 2-methylhex-2-ene orientated *para* with respect to the electron withdrawing group, whilst for regioisomer **29** this substituent was in a *meta* orientation.



Scheme 1.1 Synthesis of nicolaioidesin C (**21**) derived by Jung and Lee.[34]

1.4 Previous Syntheses of Panduratins

Similarly when looking at members of the panduratin family the cyclohexene core again suggests a synthetic disconnection of a Diels-Alder. In the case of panduratin A (**8**) this disconnection gives chalcone **30** and *E*-ocimene (**31**), a naturally occurring oil (**Scheme 1.2**).

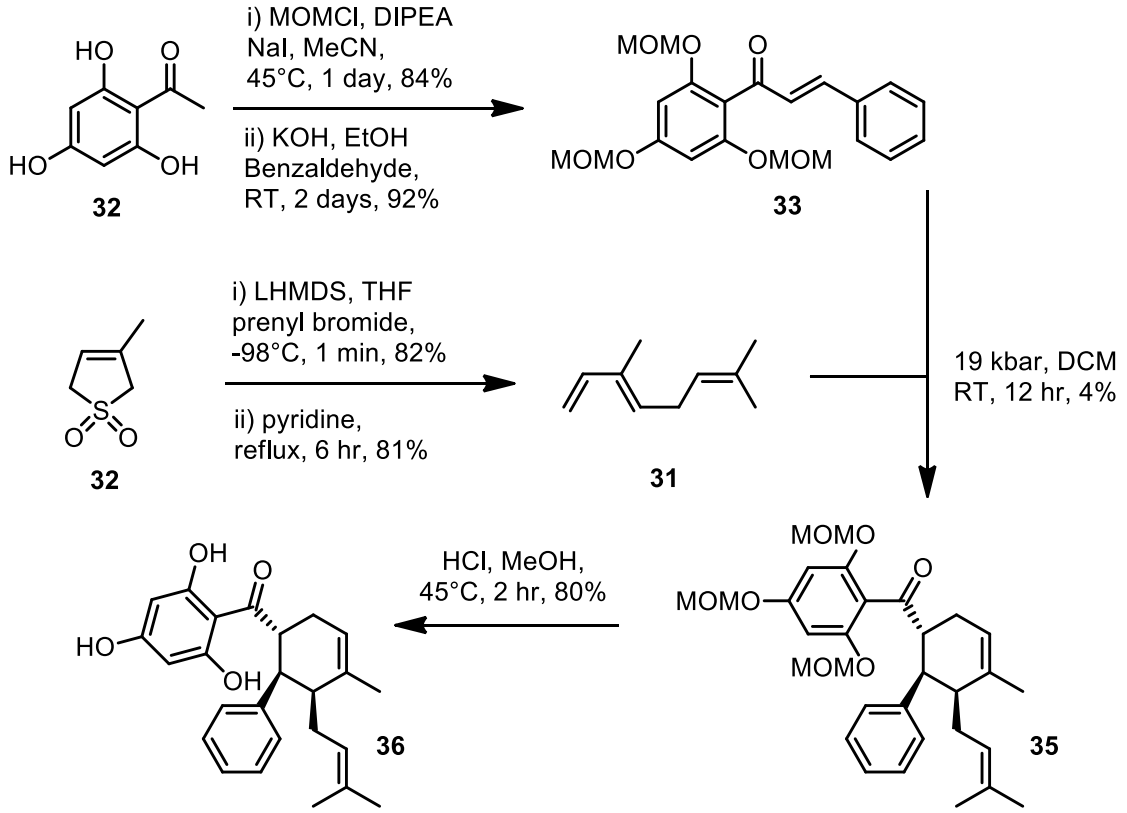


Scheme 1.2 Diels-Alder disconnection of panduratin A (**8**)

At the outset of work there were two syntheses of panduratin A (**8**) reported in the literature as well as our own synthesis of 4-hydroxyisopanduratin A (**9**) completed within the McLeod research group.

1.4.1 Pasfield and McLeod 4-hyrdoxyisopanduratin A Synthesis

In this candidate's Honours research preceeding this PhD the synthesis of the panduratins was first attempted. This previous work in our laboratory attempted to use the Diels-Alder disconnection and prepare both panduratin A (**8**) and 4-hydroxypanduratin A (**9**) for further testing against the dengue fever virus protease.[38] For the synthesis of 4-hydroxypanduratin A (**9**) protected chalcone **33** was prepared in a good yield from 2,4,6-trihydroxy acetophenone (**32**) via methoxymethyl (MOM) protection and a Claisen-Schmidt condensation with benzaldehyde (**Scheme 1.3**).



Scheme 1.3 Pasfield and McLeod synthesis of panduratin family member 4-hydroxyisopanduratin A (**36**)

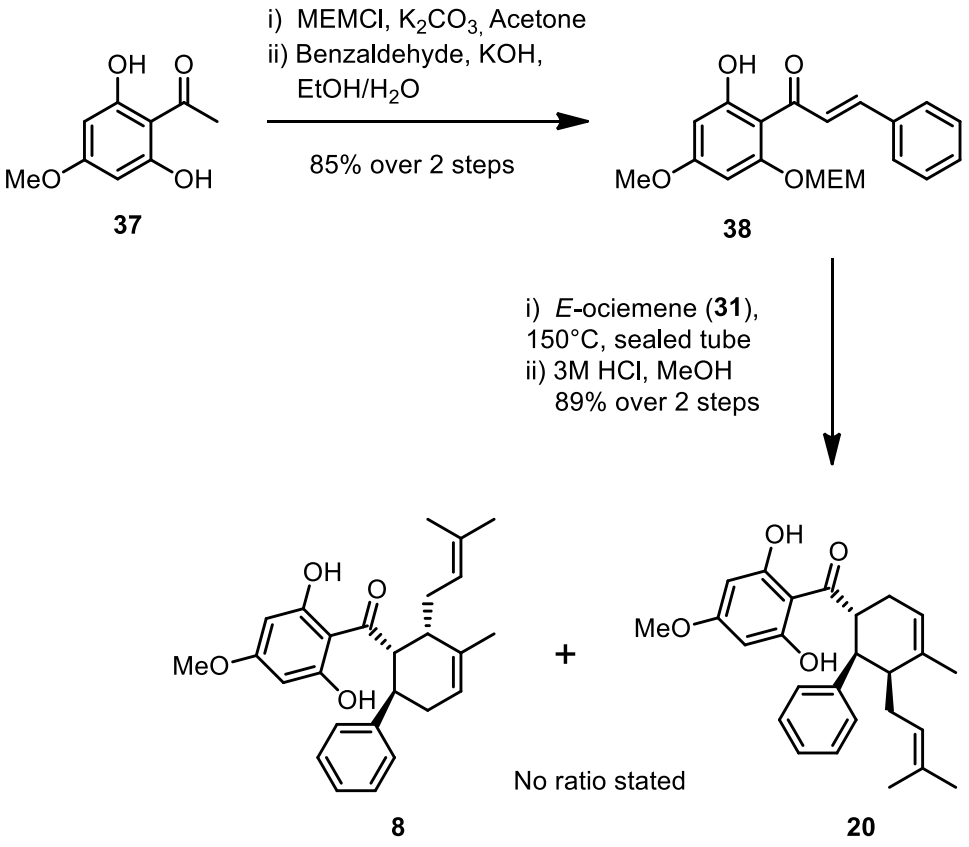
E-Ocimene (**31**) was also prepared from the selective alkylation of 3-methyl sulfolene (**32**).[39] The Diels-Alder reaction was then attempted between chalcone **33** and *E*-ocimene (**31**) without initial success. Typical conditions such as Lewis acid catalysis, high temperature sealed tube and microwave irradiation either resulted in no reaction or degradation of *E*-ocimene (**31**).

Whilst this Diels-Alder strategy seems a relatively straight forward, there are some synthetic challenges. Highly oxygenated chalcones are typically poor dienophiles due to their electron rich nature and steric bulk in cycloaddition reactions. Also the diene, *E*-ocimene (**31**), has been reported to undergo olefin isomerisation and polymerisation under acidic conditions.[40]

High pressure conditions were eventually found to promote the Diels-Alder reaction, however the only product isolated was adduct **35** in a low yield of 4%. After MOM deprotection comparison of the NMR data to that of the literature data indicated a regioisomer had been synthesised.[41] This regioisomer was actually in fact 4-hydroxyisopanduratin A (**36**) which is another member of the panduratin family. Furthermore this represented the first synthesis of this natural product. What could be deduced from this result was that it seemed the regioselectivity of the Diels-Alder was the opposite to what had been expected from examining related literature precedent.[42]

1.4.2 Rahman panduratin A Synthesis

In 2010 Rahman and co-workers completed the first synthesis of panduratin A (**8**).[43] Their approach was based on the Diels-Alder disconnection described above. The requisite monoprotected chalcone **38** was first synthesised over two steps from acetophenone **37** (**Scheme 1.4**).



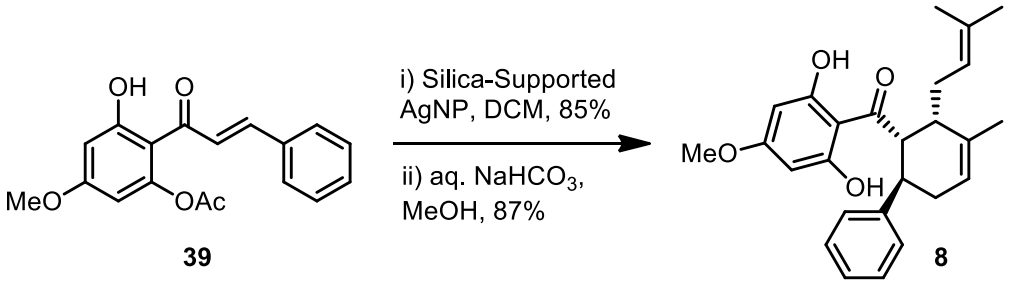
Scheme 1.4 Rahman's synthesis of panduratin A (**8**) and isopanduratin A (**20**).

This chalcone had a free hydroxyl group in the 2 position that was envisaged to act as an internal hydrogen bond donor to help further activate the chalcone towards the desired Diels-Alder reaction.

Submitting chalcone **38** with *E*-ocimene (**31**) neat to sealed tube conditions facilitated the Diels-Alder reaction and the following deprotection then gave panduratin A (**8**) and isopanduratin A (**20**) in a 89% yield over two steps. These regioisomeric products were stated to be inseparable and no ratio between the two was given. This outcome of the Diels-Alder reaction suggests there is an issue with regioselectivity of the reaction. Whether it is due to insufficient activation of the chalcone and/or the competing directing effects of the prenyl and methyl substituents of *E*-ocimene (**31**) was not clear.

1.4.3 Porco panduratin A Synthesis

A further synthesis of panduratin A (**8**) was achieved by Porco and co-workers who employed a similar chalcone approach as Rahman in their synthesis.[40] Using monoprotected chalcone **39**, synthesised in a 74% yield over 4 steps, and *E*-ocimene (**31**) in the presence of a silver nanoparticle (AgNP) catalyst, developed in their laboratory, they were able promote the cycloaddition. Subsequent deprotection of the acetyl group, then afforded panduratin A (**8**) (**Scheme 1.5**).

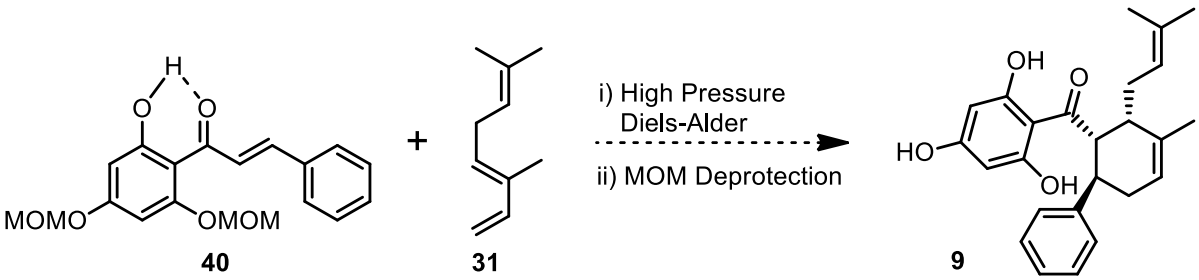


Scheme 1.5 Porco's synthesis of panduratin A (**8**).

The only by-product of the reaction was a small amount of nicolaioidesin A (**19**) a diastereoisomer of panduratin A (**8**) (see **Figure 1.8**). Interestingly, no other regioisomeric products were reported. Porco does however state in their paper that they believe these particular cycloadditions involve a step-wise process mediated by the AgNP's likely serving as an electron shuttle/redox catalyst. This proposal is obviously different to the concerted mechanism of the Diels-Alder reaction and thus could explain the different regioselectivity encountered by Rahman and our laboratory.

1.5 Revised Synthesis of Panduratin A

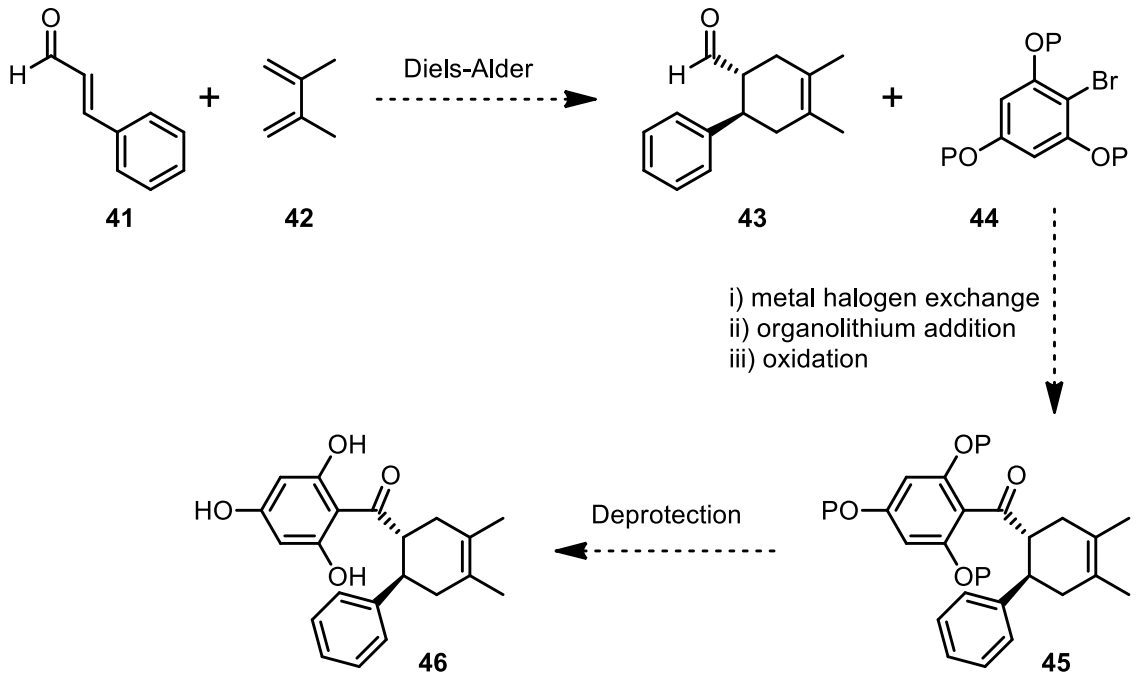
Having noted the successful Diels-Alder reactions employed by Rahman and formally by Porco using chalcones with a free phenol, it was postulated whether that the same could occur under high pressure conditions. The free phenol could act as an internal hydrogen bond donor that could further activate the chalcone and may also improve the yield and possibly give the desired regioselectivity (**Scheme 1.6**).



Scheme 1.6 Revised chalcone and *E*-ocimene (**31**) high pressure Diels-Alder.

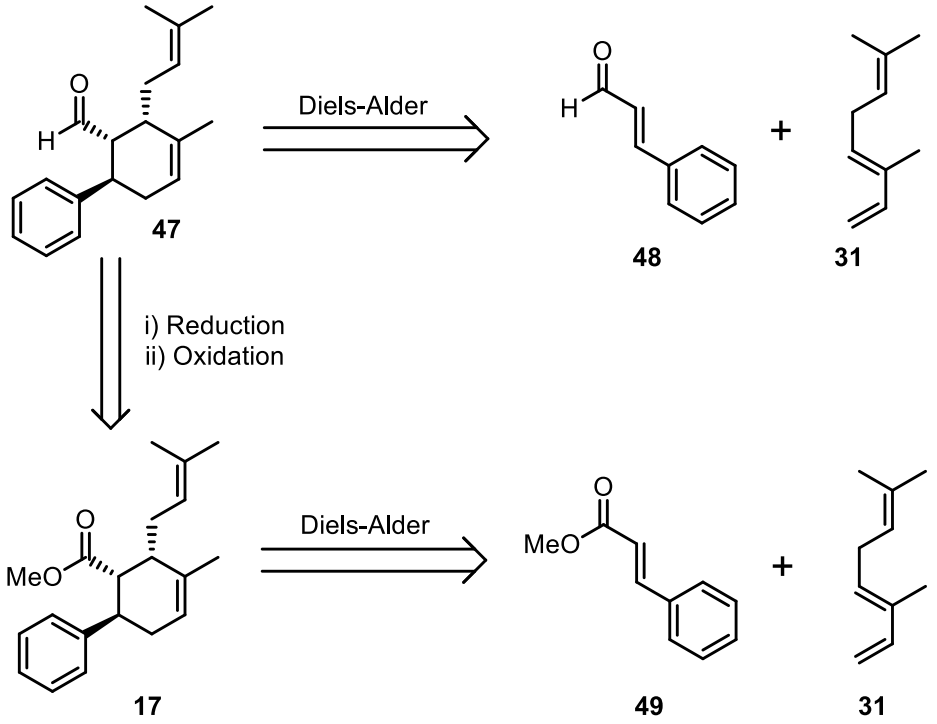
In addition, given the generally low reactivity of chalcones in the Diels-Alder and the inability to use traditional Lewis acids it was also sought to devise a new synthetic route to panduratin A (**8**) and 4-hydroxypanduratin A (**9**). It was envisioned that if the Diels-Alder could be performed earlier in the synthesis to construct the cyclohexene core and then further synthetic elaborations could elaborate this to the target compounds.

A model study, based on 4-hydroxypanduratin A (**9**) was devised to aid in the development of this strategy. Cinnamaldehyde (**41**) waschosen as the dienophile as the aldehyde group would provide enhanced activation of the alkene (**Scheme 1.7**).[44-46] Also for greater synthetic simplicity *E*-ocimene (**31**) could be replaced with 2,3,-dimethylbutadiene (**42**). This would allow the use of Lewis acid catalysis and there would be no issues of regioselectivity in the Diels-Alder reaction.



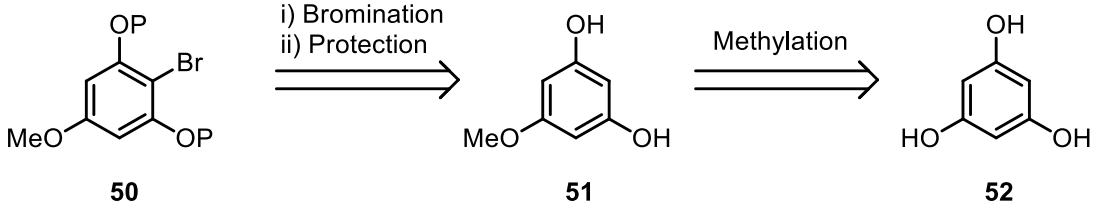
Scheme 1.7 Proposed strategy for model synthesis.

With aldehyde **43** in hand an organolithium addition with the appropriate bromobenzene **44**, followed by oxidation could be performed to introduce the benzoyl moiety. Deprotection would then afford the desired model compound **45**. If this strategy was successful then to apply it the synthesis of 4-hydroxypanduratin A (**9**) access to aldehyde **47** would be required, which possessed the prenyl and methyl substituents (**Scheme 1.8**). This could be achieved by a Diels-Alder reaction between cinnamaldehyde (**48**) and *E*-ocimene (**31**) or the reduction and oxidation of methyl ester (**17**), also accessible from a Diels-Alder reaction.



Scheme 1.8 Aldehyde **47** retrosynthesis.

For the synthesis of panduratin A (**8**) a slightly different bromobenzene fragment would be required (**Scheme 1.9**). Bromobenzene **50** could be prepared by the selective bromination and subsequent protection of 5-methoxyresorcinol (**51**), which in turn can be synthesised from the mono-methylation of phloroglucinol (**52**).



Scheme 1.9 Retrosynthetic plan for bromobenzene **50**.

While this synthetic strategy was designed to produce panduratin A (**8**) as a racemate, it is also desirable to develop a enantioselective synthesis. Biologically active chiral compounds often show greater activity for one enantiomer while the other is usually less effective or possibly even detrimental. Given that the dengue protease is a single enantiomer, it seems reasonable to expect that one enantiomer of panduratin A (**8**) would be a better inhibitor. Evidence to support this can be seen in the studies of Morikawa and co-workers who determined, following chromatographic separation of the naturally occurring material, that (-)-panduratin A (**8**) inhibits aminopeptidase N more effectively than (+)-panduratin A (**8**).[47] A synthetic problem though is that *E*-ocimene (**31**) is sensitive to Lewis acids which are used in many enantioselective Diels-Alder reactions. Thus an additional goal was to find suitable reaction conditions or modify our synthetic approach in order to complete an enantioselective synthesis of panduratin A (**8**).

1.6 Structure Activity Relationship Studies

As previously mentioned, 4-hydroxypanduratin A (**9**) (K_i = 21 ± 8 µM) and panduratin A (**8**) (K_i = 25 ± 6 µM) were reported as competitive inhibitors of the dengue 2 protease. These compounds are thus suitable for optimisation of their structure activity relationships to improve their biological activity. The previously detailed model synthesis (see **Scheme 1.6**) is quite modular and thus allows variation of the different building blocks of panduratin A (**8**) (**Figure 1.14**).

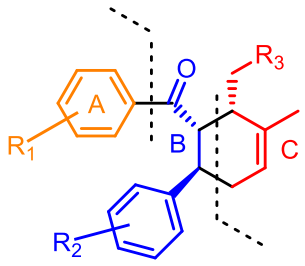
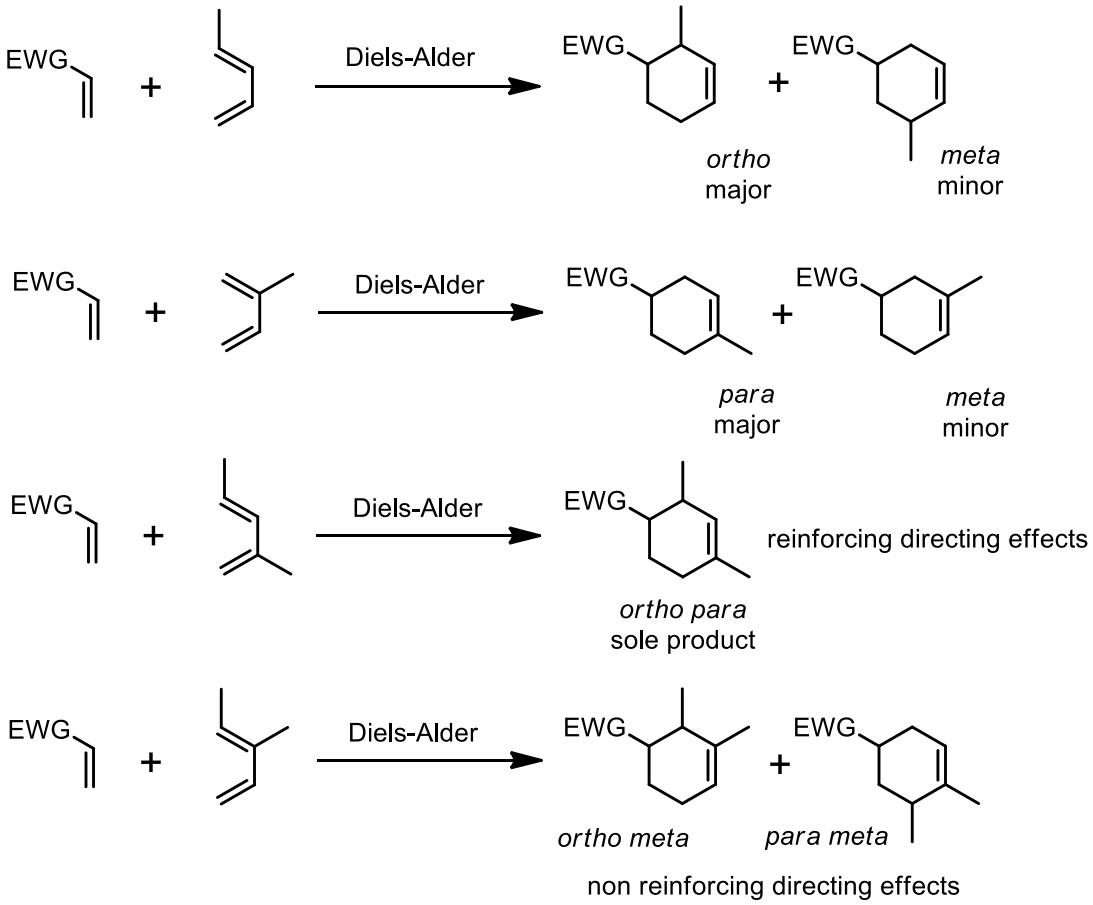


Figure 1.14 Panduratin A core structure showing key fragments (A, B and C) and areas of substitution variation (R^1, R^2 and R^3).

Variation of the substituents and their substitution patterns aimed to improve hydrophilicity, and provide additional interactions with hydrogen bond donor/acceptor groups or hydrophobic regions of the protein. These variations hoped to give access to compounds that bind with an inhibition constant <1 µM.

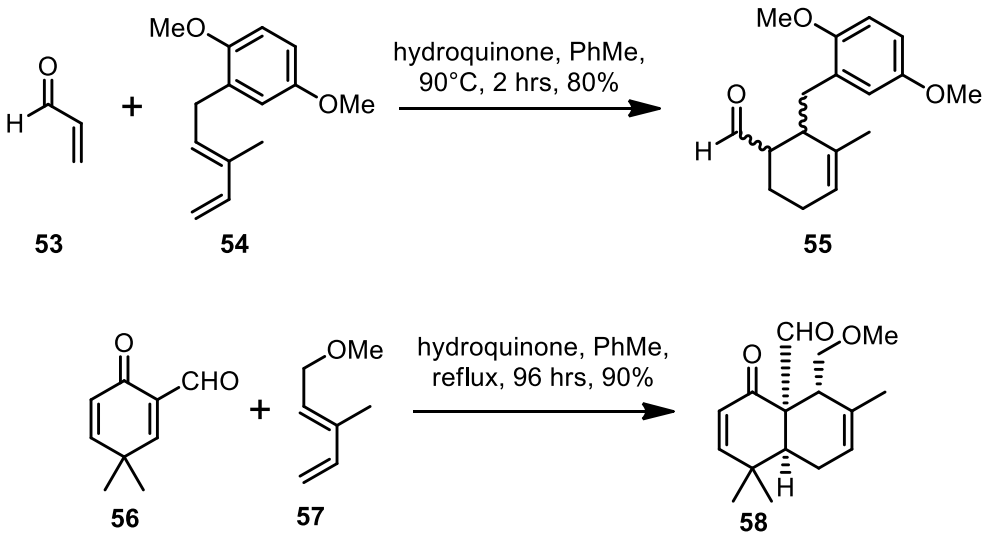
1.7 Diels-Alder Regioselectivity Study

There is still however the issue of regioselectivity in the Diels-Alder reaction between a cinnamate and *E*-ocimene (**31**). Since *E*-ocimene (**31**) is a 1,2 substituted diene the weakly donating substituents are non-reinforcing and thus compete with each other to be the dominant directing group in the Diels-Alder reaction (**Scheme 1.10**).



Scheme 1.10 Generally observed regioselectivity trends in the Diels-Alder reaction.

There was little data on the Diels-Alder regioselectivity of 1,2-substituted dienes in the literature. It was initially expected that the product would have the two alkyl substituents *ortho* and *meta* to the electron withdrawing group much like the regioselectivity of the thermal Diels-Alder reactions in **Scheme 1.11**.[42, 48] However as seen with our synthesis of 4-hydroxyisopanduratin A (**9**) the selectivity under high pressure conditions was the opposite of what was expected.



Scheme 1.11 Diels-Alder regioselectivity examples.[42, 48]

Thus it was desired to conduct a regioselectivity study on high pressure Diels-Alder reactions using different dienophiles and dienes (**Figures 1.12**). This would enable analysis of how their various steric and electronic factors influence the product distribution.

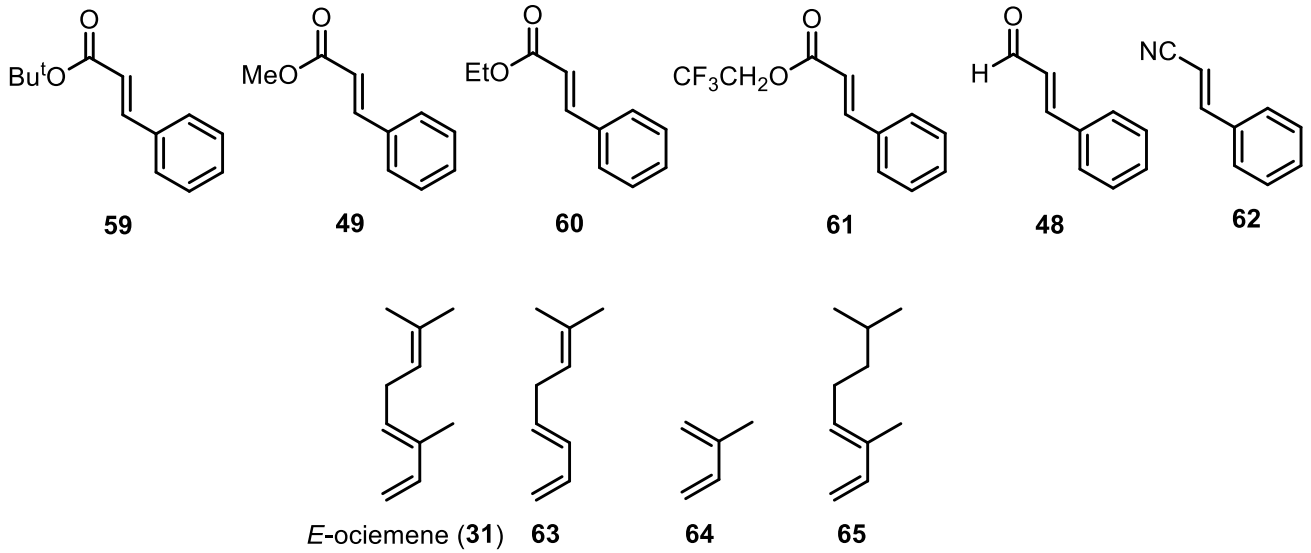


Figure 1.12 Dienophiles and dienes of interest.

The various dienophiles will be reacted with *E*-ocimene (**31**) to determine their effect on the regioselectivity. For example ethyl cinnamate (**60**) and 2,2,2-trichloroethyl cinnamate (**61**) are very similar in size but their electronics are very different with 2,2,2-trichloroethyl cinnamate (**61**) having a stronger electron withdrawing group. To differentiate steric affects then comparison between methyl cinnamate (**49**), ethyl cinnamate (**60**) and *tert*-butyl cinnamate (**59**) will inform if substituent size is having an impact on the regioselectivity.

In terms of the proposed dienes they have distinct differences to *E*-ocimene (**31**), diene **63** is missing the methyl in the 2 position of the diene while isoprene (**64**) is missing the prenyl chain in the 1 position. Comparison of the Diels-Alder adducts of these two dienes would hopefully give insight into which substituent in the diene dominates in terms of directing strength. Another possible factor in the regioselectivity is potential π stacking of the prenyl substituent with a phenyl ring on the dienophile in the Diels-Alder transition state. Using diene **65**, that has its prenyl chain saturated, any change in the regioselectivity can be observed, indicating if π stacking is a significant factor (**Figure 1.13**).

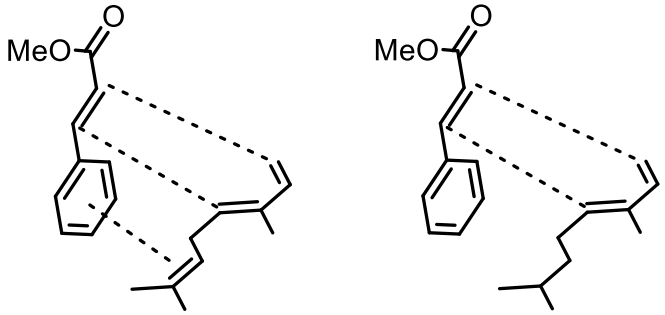
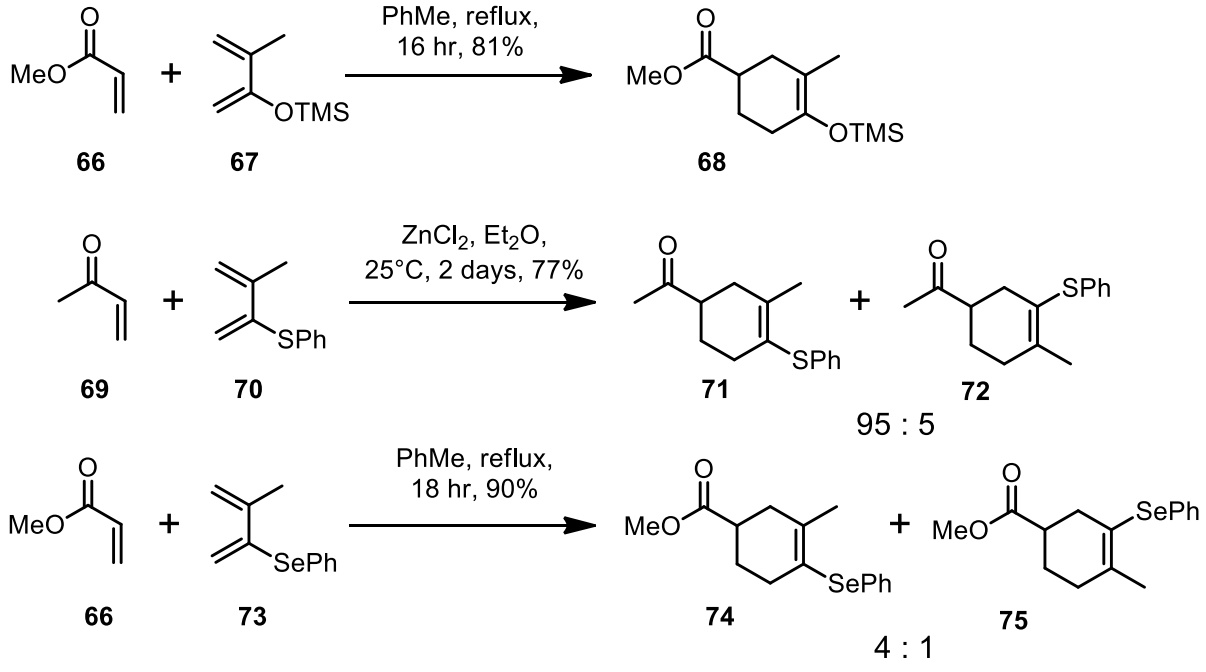


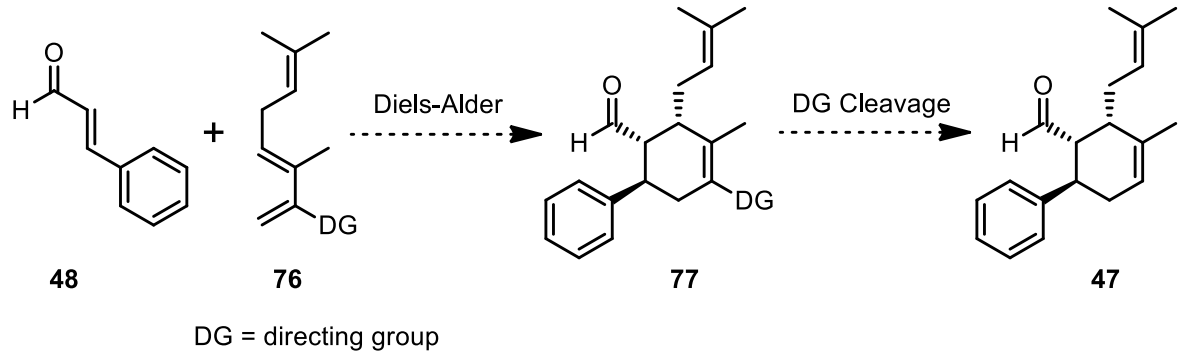
Figure 1.13 Potential π stacking interaction.

Should the regioselectivity of the Diels-Alder be unfavourable the application of a modified diene would be investigated. It has previously been shown in the literature that strong electron donating functional groups including group 16 elements such as oxygen, sulfur and selenium can be used to overcome the directing effect of other groups to provide the compound with the desired regioselectivity as the major product (**Scheme 1.12**).[49, 50] In these examples the directing groups are able to out-compete the methyl groups and favour the *para* position on the cyclohexene ring, with respect to the electron withdrawing group of the dienophile.



Scheme 1.12 Use of directing groups in Diels-Alder reactions.[49, 50]

Therefore, it was envisaged that by placing a strong directing group on the desired diene in conjunction with a strong activating group on the dienophile, this could override the regular regioselectivity to favour that required (**Scheme 1.13**). This directing group could then be removed at a later stage in the synthesis to give the desired cyclohexene core. An example directing group could be phenyl sulphide which could then potentially be reductively cleaved using Raney nickel.



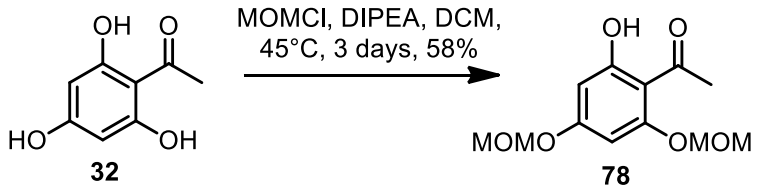
Scheme 1.13 Modified diene strategy.

Chapter 1 – Panduratins

2. Results and Discussion

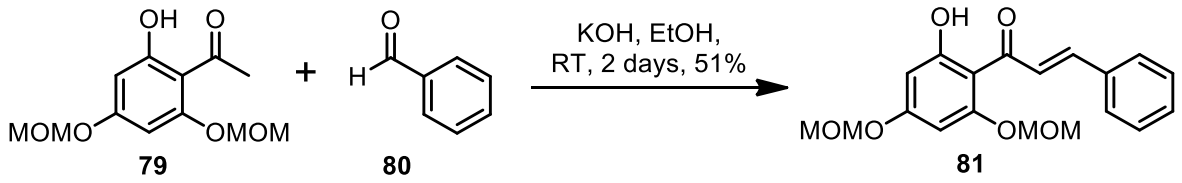
2.1 Revised Chalcone Diels-Alder

To test the idea of using a chalcone with a free phenol in a high pressure Diels-Alder reaction, first the required chalcone had to be prepared. To achieve this 2,4,6-trihydroxyacetophenone (**32**) reacted with 1.6 equivalents of methoxymethyl chloride to afford the desired doubly protected product (**Scheme 2.1**). Using in excess of 1.6 equivalents of methoxymethyl chloride (per acetopenone) started to impact the yield of the doubly protected product due to the increasing formation of the tris-protected product.



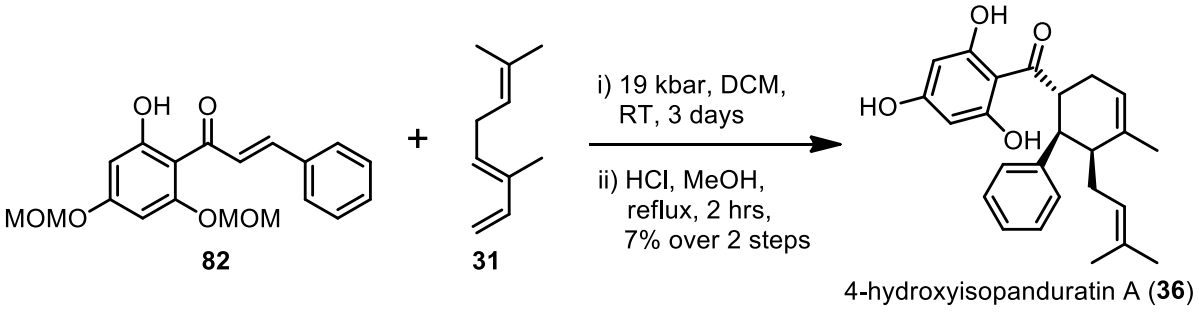
Scheme 2.1 MOM protection of 2,4,6-trihydroxyacetophenone (**32**).

This was followed with the bis protected acetophenone **78** being subjected it to a Claisen-Schmidt condensation with benzaldehyde to provide the desired doubly protected chalcone (**81**) (**Scheme 2.2**).



Scheme 2.2 Claisen-Schmidt condensation of doubly protected acetophenone **81**.

With the doubly protected chalcone now in hand it was then exposed it to high pressure conditions in conjunction with *E*-ocimene (**31**) to facilitate the Diels-Alder reaction (**Scheme 2.3**).

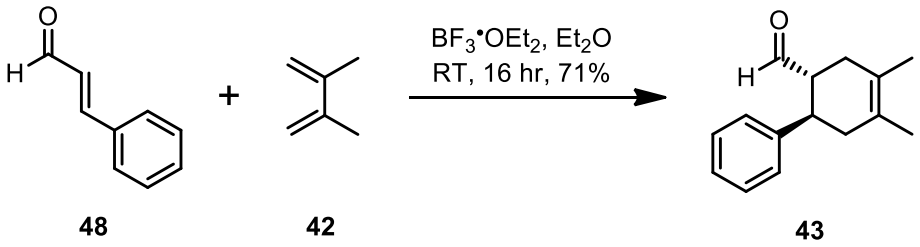


Scheme 2.3 High pressure Diels-Alder.

However once again only the undesired regioisomer 4-hydroxyisopanduratin A (**36**) as the sole isomer was produced in a low yield. Given Rahman and Porco had both been able to synthesis panduratin A (**8**) with similar chalcones it was clear that other factors were driving the selectivity of the high pressure reaction. This result reinforced that these chalcones had low reactivity under high pressure conditions and did not provide the desired regioisomer in order to prepare panduratin A (**8**) and 4-hydroxypanduratin A (**9**). Furthermore, this reinforced the need for a study of high pressure Diels-Alder reactivity.

2.2 4-Hydroxypanduratin A Model Synthesis

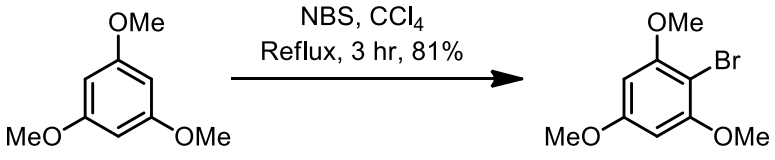
Work then began on the synthesis of the model compound to develop the required synthetic techniques for the organolithium addition approach. Firstly the cyclohexene core of the model compound was constructed using a Diels-Alder reaction between cinnamaldehyde (**48**) and 2,3-dimethylbutadiene (**42**) (**Scheme 2.4**). Using borontrifluoride diethyletherate as a Lewis acid the reaction proceeded smoothly to give Diels-Alder adduct **43** as a racemate in a yield of 71%.[45]



48 **42** **43**

Scheme 2.4 Diels-Alder reaction between cinnamaldehyde (**48**) and 2,3-dimethylbutadiene (**42**).

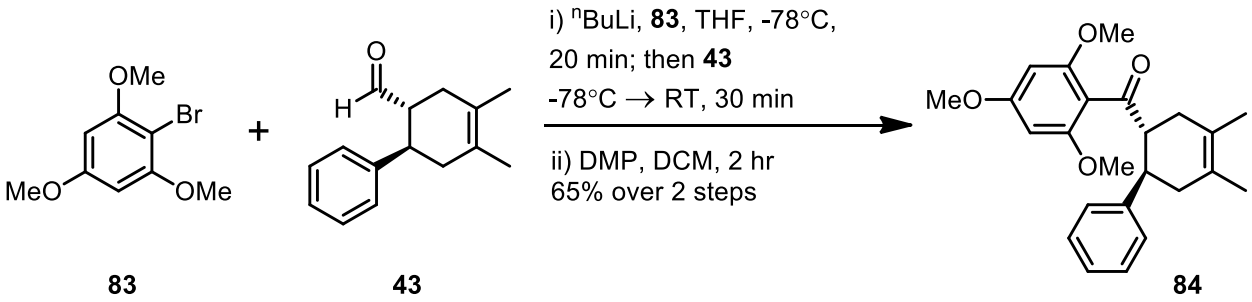
With aldehyde **43** in hand a protected bromobenzene for the organolithium addition was required. 2-Bromo-1,3,5-trimethoxybenzene (**83**) was chosen first and easily synthesised from the bromination of 1,3,5-trimethoxybenzene (**82**) (**Scheme 2.5**).[51]



82 **83**

Scheme 2.5 Bromination of 1,3,5-trimethoxybenzene (**82**).

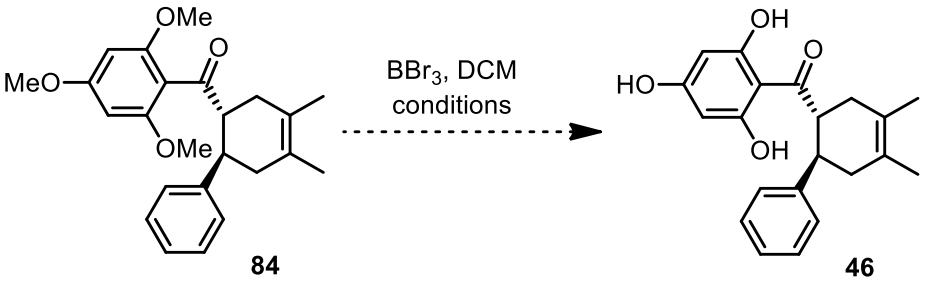
With both the aldehyde **43** and 2-bromo-1,3,5-trimethoxybenzene (**83**) in hand conditions for the organolithium addition were found that facilitated the addition giving a diastereomeric mixture of the alcohol products (**Scheme 2.6**). These products were then carried straight through to the oxidation step using Dess-Martin periodinane to afford the ketone product **84** in a yield of 65% over 2 steps as a racemic mixture.



83 **43** **84**

Scheme 2.6 Organolithium addition and oxidation.

All that was left now was to convert the methoxy groups to phenols in order to arrive at the desired model compound **46**. Investigation into the literature showed that the most successful conditions for this type of transformation used boron tribromide.[52] However applying these conditions to the trimethoxy compound **84** resulted in only the decomposition of starting material (**Scheme 2.7** & **Table 2.1**).



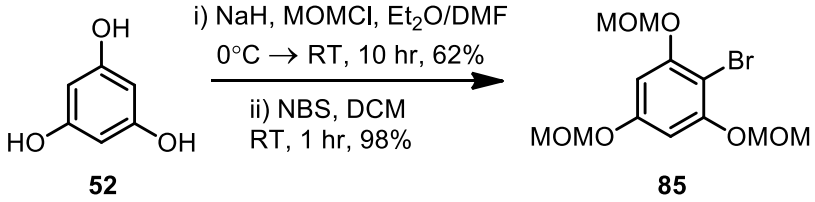
84 **46**

Scheme 2.7 Attempted demethylation.

Reaction Time (days)	Temperature (°C)	Result
2	0	Decomposition
2	-78	Decomposition
1	-78	Decomposition

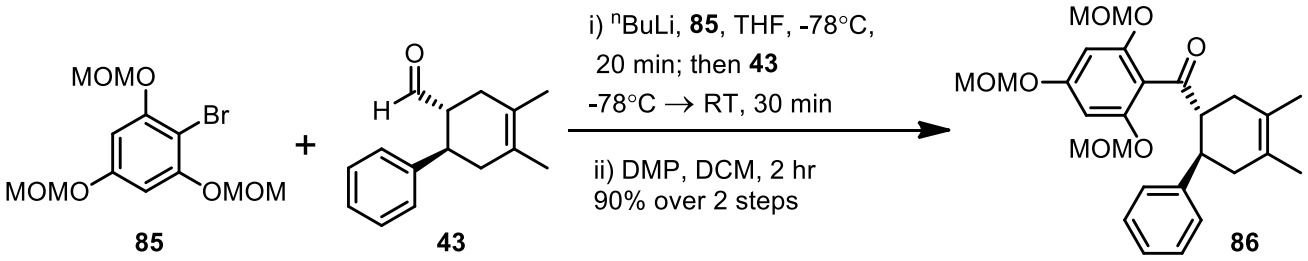
Table 2.1 Attempted demethylation.

Rather than persevering with the deprotection of trimethoxy compound **84** it was instead decided to change the protecting groups to something that would be easier to remove. Methoxymethyl (MOM) was chosen as the substitute protecting group and so an alternate bromobenzene needed to be synthesised. Starting from pholoroglucinol (**52**) the phenols were protected as the methoxymethyl ethers to afford 1,3,5-tris(methoxymethoxy)benzene in a yield of 62% (**Scheme 2.8**). NBS was then used as a brominating agent to give 2-bromo-1,3,5-tris(methoxymethoxy) benzene (**85**) in a near quantitative yield of 98%.[53]



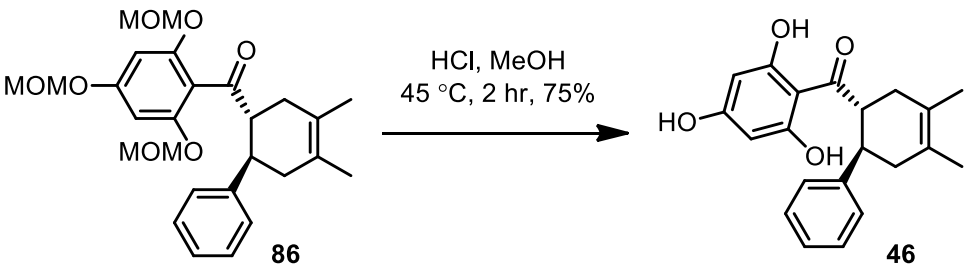
Scheme 2.8 MOM protection and bromination of phloroglucinol (**52**).

Having synthesised our alternate MOM protected bromobenzene **52** the organolithium addition and oxidation with aldehyde **43** was performed once again to give compound **86** in a high yield of 90% over steps (**Scheme 2.9**).



Scheme 2.9 Organolithium addition and oxidation.

With compound **86** in hand it was then sought to remove the MOM protecting groups. Using concentrated hydrochloric acid in methanol the MOM groups were successfully cleaved in a yield of 75% to afford model compound **46** (**Scheme 2.10**).



Scheme 2.10 MOM deprotection.

Having synthesised model compound **46** methodology was now in place for the synthesis of 4-hydroxypanduratin A (**9**) if the required aldehyde **47** could be prepared (**See Scheme 1.8**).

2.3 Analogue Synthesis

Along with model compounds **84** and **46**, other analogues where synthesised using the same synthetic strategy to begin looking at structure activity relationships (**Figure 2.1**). The compounds that were synthesised possessed various phenol substitutions, except compound **84**, on the benzoyl group with some methylated as well.

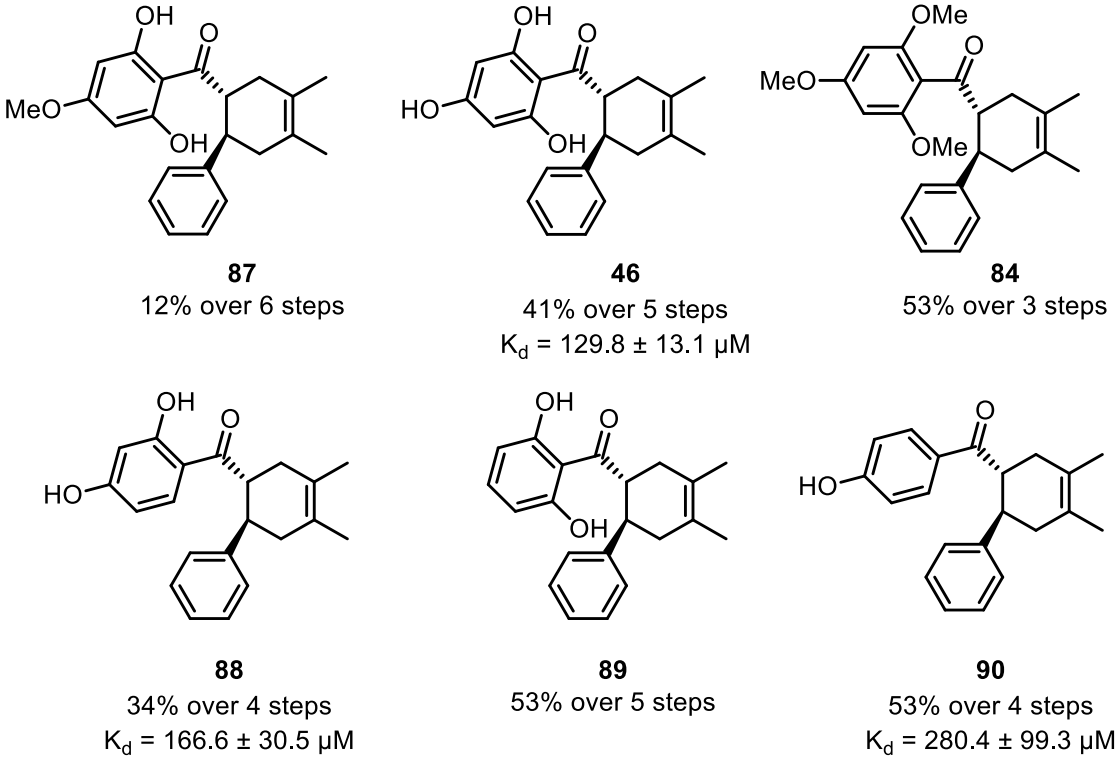


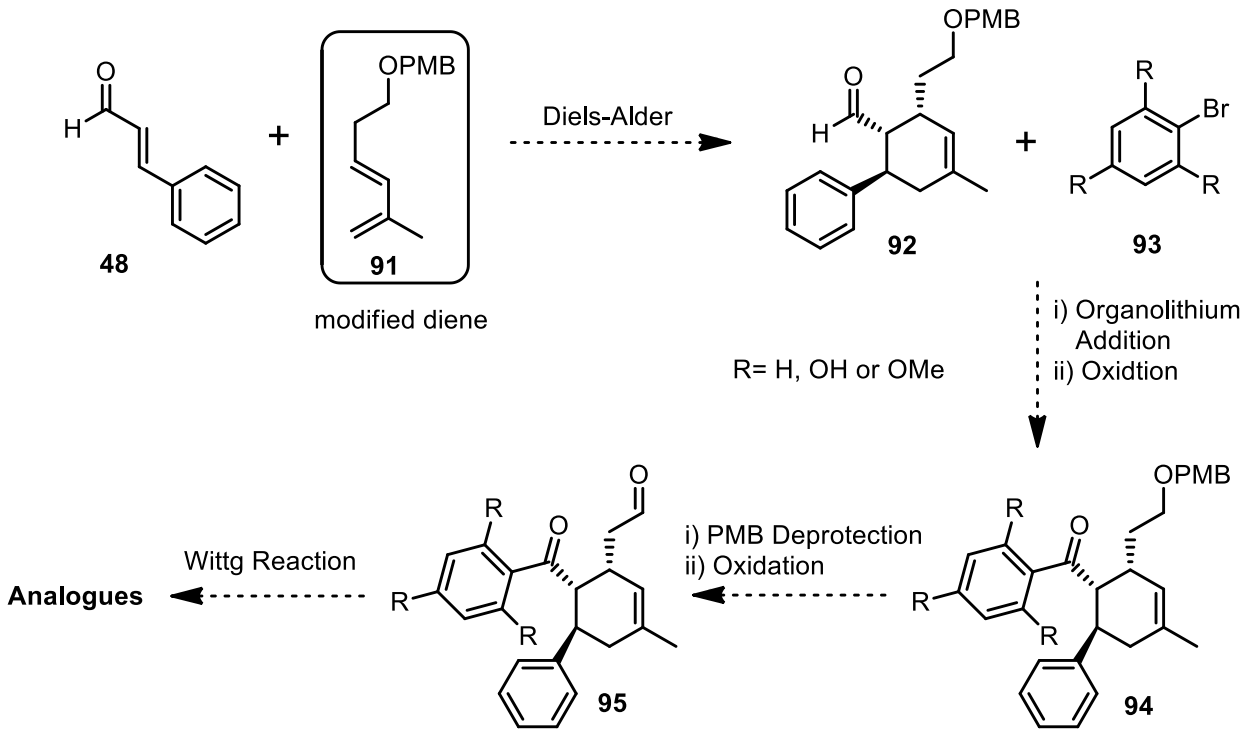
Figure 2.1 Analogues synthesised thus far and test results against the DEN-2 protease.

To test the binding of some of the compounds a fluorescence quenching assay was employed by the Otting research group at ANU to identify competitive binding to the DEN-2 NS3/NS2B protease.[54] The assay measured a decrease in fluorescence of the NS3/NS2B protease upon compound binding and this allowed determination of the binding affinity of the compounds. From the results it was clear to see that the phenols on the benzoyl ring are important for binding with the lowest K_d achieved of 129.8 ± 13.1 µM when all 3 phenols were present (model compound **46)**.

The K_d values can on first approximation be used to estimate K_i values. A qualitative comparison between the K_d values determined above and the K_i values reported by Kiat for 4-hydroxypanduratin A (**9**) (25 ± 8 µM and 21 ± 6 µM respectively) show that the model compound **46** was approximately 5 times weaker at binding to the NS3/NS2B protease.

The most notable difference between model compound **46** and 4-hydroxypanduratin A (**9**) is the presence of a prenyl substituent. This suggests the importance of this prenyl group (and possibly general carbon chains) ortho to the benzoyl ring for protein binding. Thus it was sought to devise methodology for the synthesis further analogues where there was the ability to vary the prenyl sidechain.

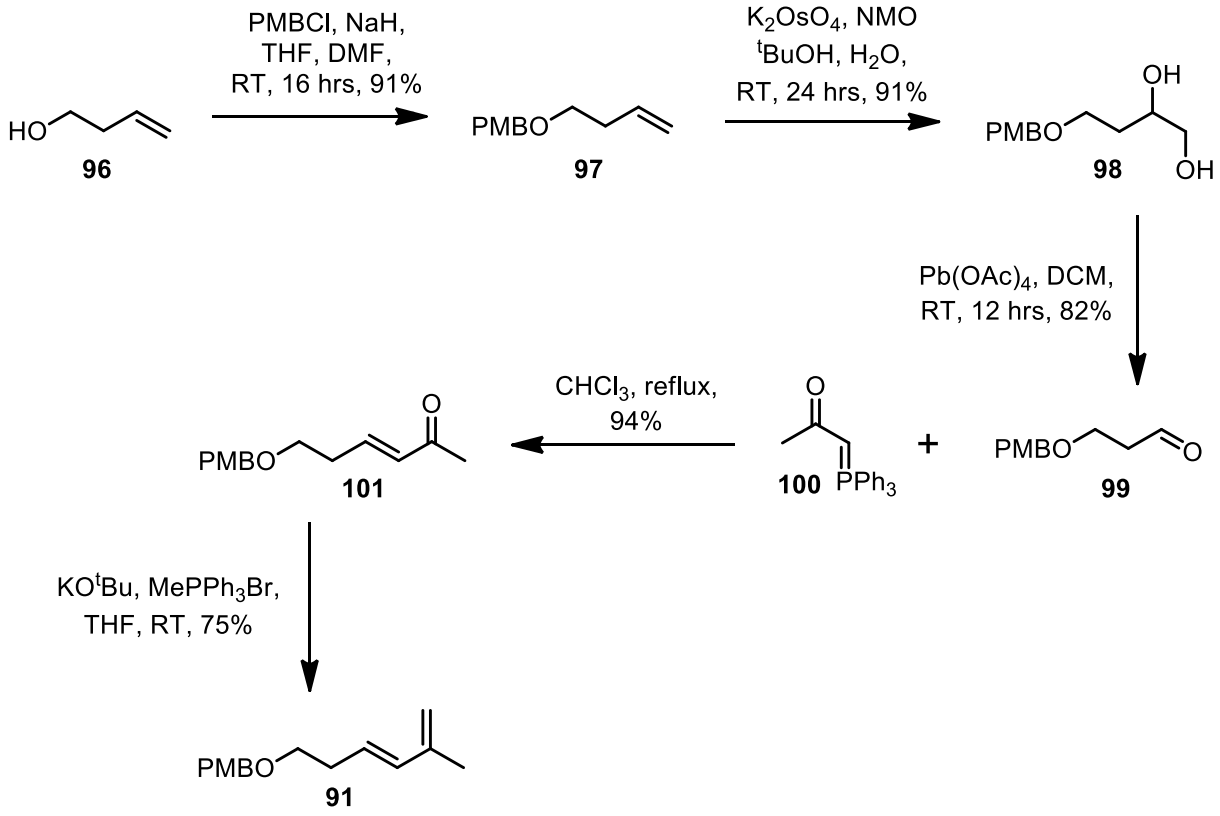
To achieve this it was envisaged that 2,3-dimethylbutadiene (**42**) could be replaced in the model synthetic strategy with a modified diene (**Scheme 2.11**). Specifically a diene that enabled modification of the prenyl group and also ensured that it provided the desired regioisomer from the Diels-Alder reaction.



Scheme 2.11 Proposed modified diene and analogue strategy.

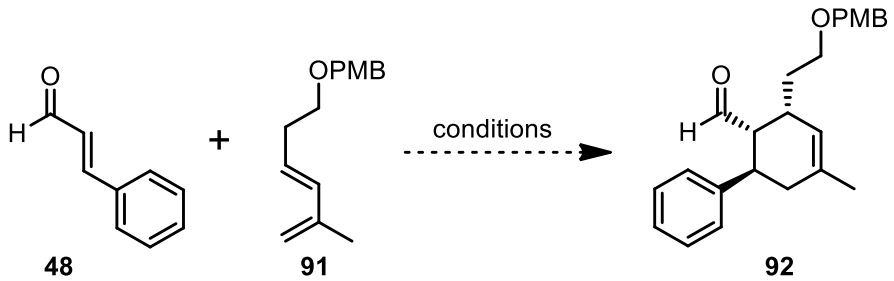
The proposed modified diene would allow various chains to be prepared through Wittig reactions after removal of the PMB group and ensuing oxidation. Furthermore migration of the methyl group to the 3' position on the diene should ensure the PMB protected substituent is *ortho* to the benzoyl group after the Diels-Alder reaction due to reinforcing directing effects.

To synthesise modified diene **91,** 3-butenyl alcohol (**96**) was protected as the PMB ether and then subsequently oxidised with osmium tetroxide to afford diol **98** (**Scheme 2.12**).[55, 56] Further oxidation of diol **98** was then performed with lead tetraacetate to produce aldehyde **99** in a good yield (68%) over 3 steps. A Wittig reaction was then performed between aldehyde **99** and commercially available ylide **100** to arrive at enone **101**. The desired diene **91** was then generated following a further Wittig reaction with methyltriphenylphosphonium bromide.



Scheme 2.12 Diene **91** synthesis.

With diene **91** now in hand it was now sought to perform the Diels-Alder reaction with cinnamaldehyde (**48**) to construct the cyclohexene core. Since a diene without the prenyl substituent was being used it was believed standard conditions such as Lewis acid promotion and sealed tube could be used to facilitate the Diels-Alder (**Scheme 2.13** & **Table 2.2**). However boron trifluoride diethyletherate or dimethyl aluminium chloride were unable to promote the reactions. Furthermore sealed tube conditions at high temperature simply resulted in starting material being reclaimed.

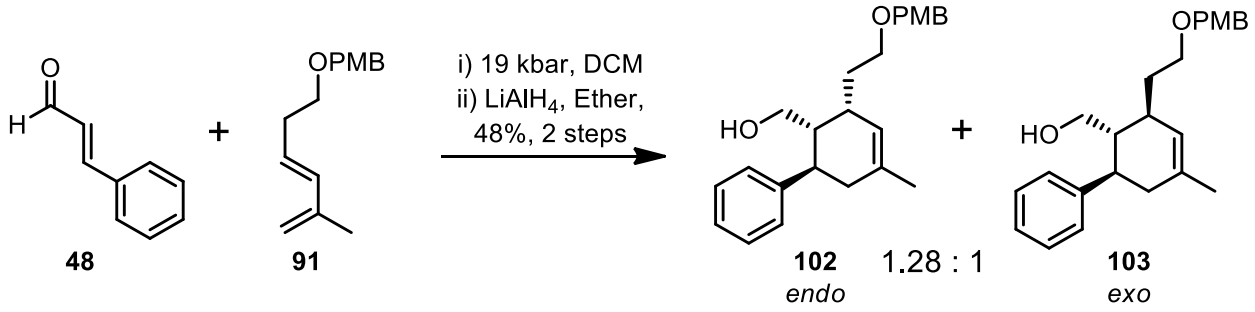


Scheme 2.13 Attempted Diels-Alder.

Conditions	Result
BF_3•OEt_2, OEt_2, RT, 16 hrs	no reaction
$AlMe_2Cl$, BHT, xylenes, RT, 1 day	no reaction
PhMe, sealed tube, 120°C, 2 days	no reaction
PhMe, sealed tube, 180°C, 2 days	no reaction

Table 2.2 Attempted Diels-Alder.

Given the trialled conditions were unsuccessful once again high pressure conditions were used to achieve the desired Diels-Alder reaction. Indeed under 19 kbar of pressure two Diels-Alder products were detected through crude ^{1}H-NMR, however these products were inseparable (**Scheme 2.14**). Reduction of the aldehyde to the corresponding alcohol did however allow separation and characterisation of the isomers.



Scheme 2.14 High pressure Diels-Alder and reduction.

What was found through ^{1}H-^{13}C HSQC and ^{1}H-NOE experiments was that whilst the desired regioisomer had been formed, the high pressure reaction had produced a mixture of the *endo* **102** (OPMB *cis* with respect to the hydroxymethyl substituent) and *exo* **103** products in a ratio of 1.28 : 1 respectively (**Figure 2.2**).

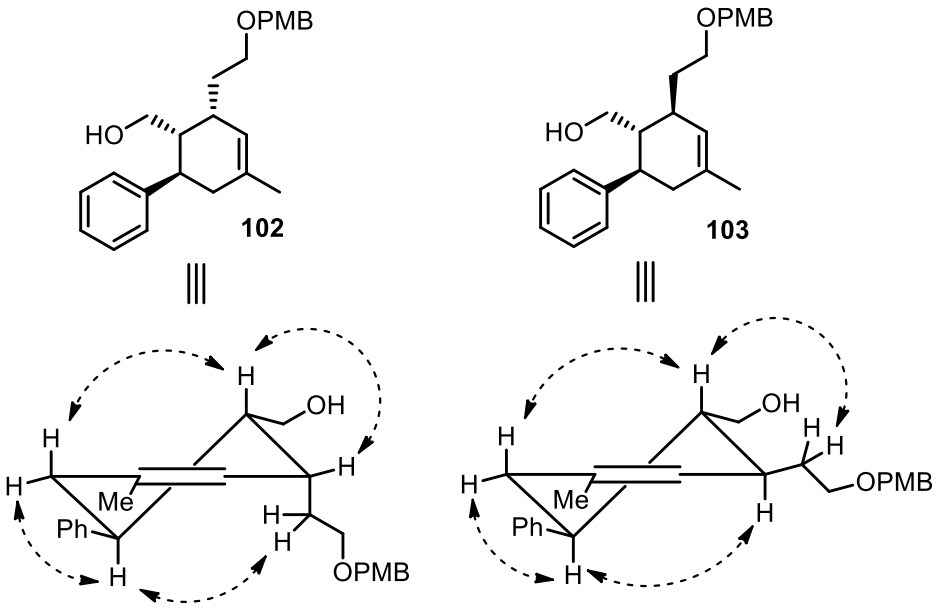
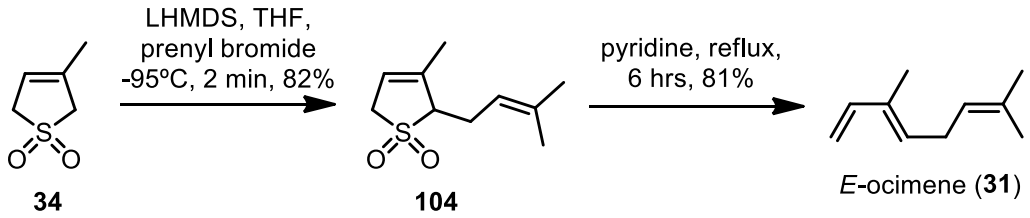


Figure 2.2 Observed NOEs for Diels-Alder adducts.

Given different selectivity issues now encountered with this modified diene it was decided to put analogue synthesis on hold and refocus efforts towards synthesising panduratin A (**8**) and 4-hydroxypanduratin A (**9**) for further testing against the dengue NS3/NS2B protease.

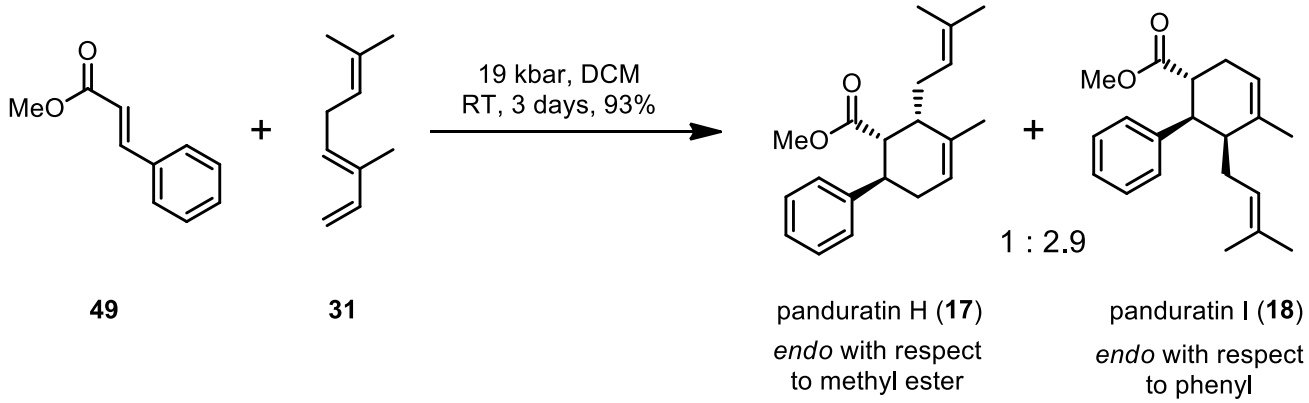
2.4 Synthesis of Panduratins

Work began on the synthesis of the panduratins by first synthesising *E*-ocimene (**31**) using the previous methodology developed in our lab. 3-Methyl sulfolene (**34**) was selectively alkylated at the 2' position with prenyl bromide followed by refluxing in pyridine to eliminate sulfur dioxide providing *E*-ocimene (**31**) in a good yield of 66% over two steps (**Scheme 2.15**).



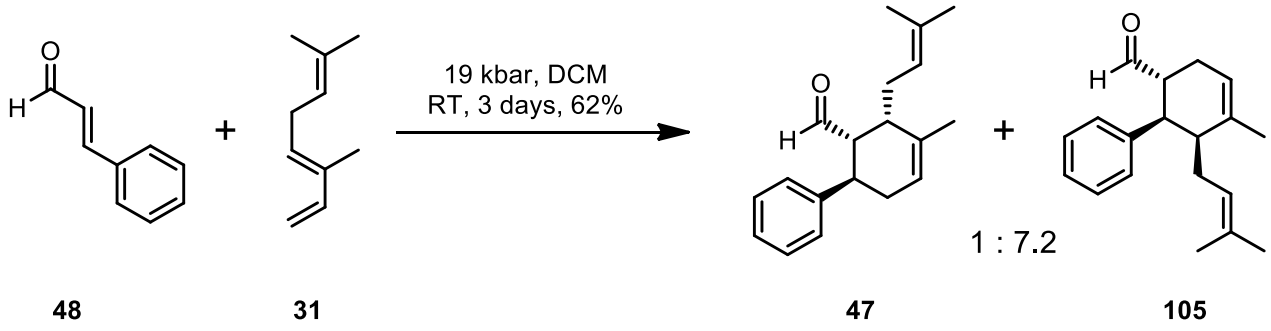
Scheme 2.15 *E*-ocimene (**31**) synthesis.

With *E*-ocimene (**31**) in hand methyl cinnamate (**49**) was chosen as the dienophile for the Diels-Alder in the hope of preparing panduratin H (**17**) and panduratin I (**18**). Subjecting these compounds to high pressure conditions successfully facilitated the Diels-Alder reaction providing the *endo* products panduratin H (**17**) and panduratin I (**18**) in a ratio of 1 : 2.9 and in a high yield of 93% (**Scheme 2.16**). It should be noted that these products have been termed *endo* as the prenyl substituent is *endo* with respect to the dienophile substituent that is adjacent or *ortho* to it. These products were only separable by high performance chromatography (HPLC), however this still constituted the first reported synthesis of these panduratins in just three synthetic steps.[38]



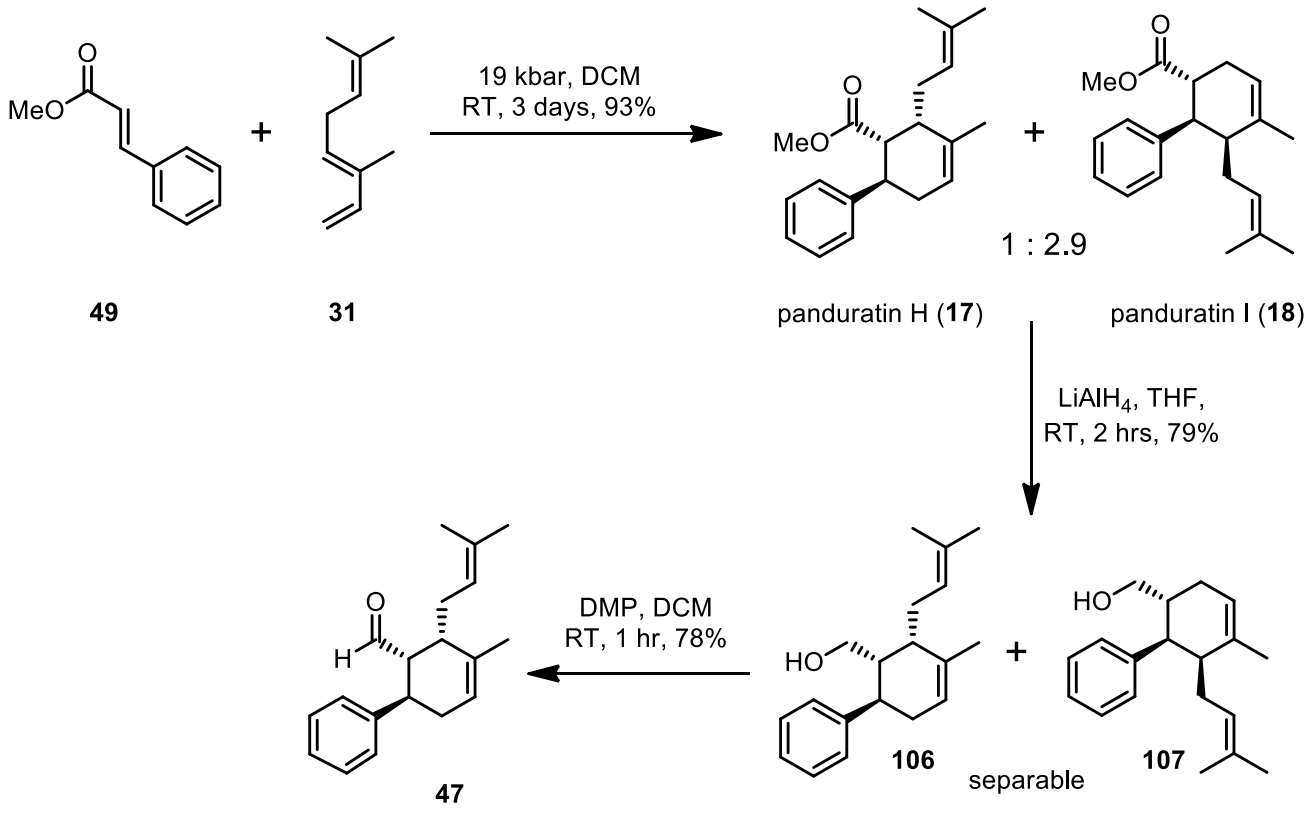
Scheme 2.16 Synthesis of panduratin H (**17**) and panduratin I (**18**).

Interestingly, this reaction with methyl cinnamate (**49**) and *E*-ocimene (**31**) was the first time the regioisomer with the prenyl substituent *ortho* and the methyl *meta* to the electron withdrawing group had been synthesised under high pressure conditions. It was speculated that the observed regioselectivity was due to the methyl ester group being a stronger electron withdrawing group (EWG) than the electron rich benzoyl group of the previously used chalcone. Hence it was proposed to investigate an even stronger electron withdrawing dienophile such as cinnamaldehyde (**48**) to shift the regioselectivity even further towards to the products where the prenyl group is *ortho* to the EWG. However reacting cinnamaldehyde (**48**) and *E*-ocimene (**31**) under high pressure conditions afforded both *endo* regioisomers in a ratio of 1 : 7.2 (methyl *meta : para* to EWG) which further favoured the undesired regioisomer where the methyl group was *meta* to the EWG (**Scheme 2.17**).



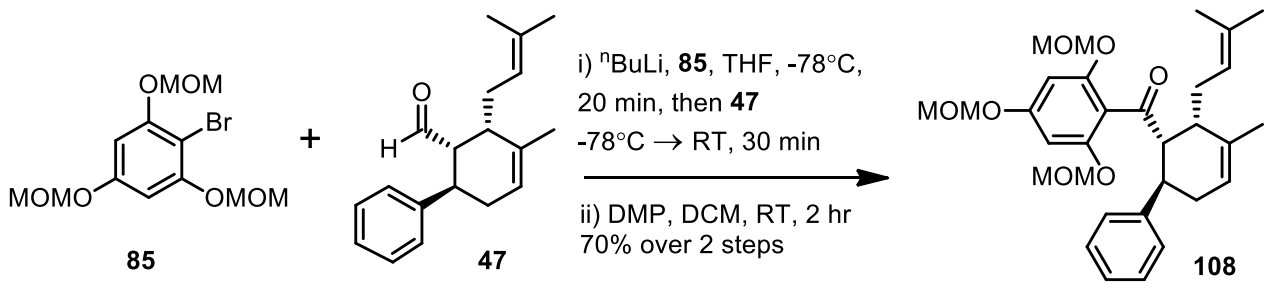
Scheme 2.17 Cinnamaldehyde (**48**) and *E*-ocimene (**31**) high pressure Diels-Alder

Clearly the selectivity of these high pressure Diels-Alder reactions required further investigation, however at this point it was decided to continue with our panduratin synthesis with the hope that enough panduratin A (**8**) and 4-hydroxypanduratin A (**9**) could be synthesised for further testing against the dengue fever protease. Since methyl cinnamate gave the best regioselectivity it was chosen for the synthesis. While HPLC was required to separate panduratin H (**17**) and panduratin I (**18**) it was found that they could be reduced to their corresponding alcohols and were then easily separable by flash column chromatography (**Scheme 2.18**). Alcohol **106** was then converted to the desired aldehyde **47** by oxidation with DMP.



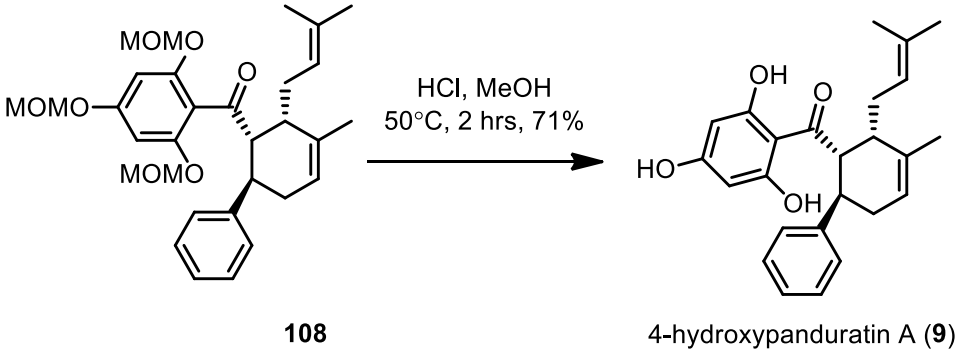
Scheme 2.18 Synthesis of aldehyde **47**.

Having now synthesised aldehyde **47** the organolithium addition with 2-bromo-1,3,5-tris(methoxymethoxy)benzene (**85**) was performed once again (**Scheme 2.19**)



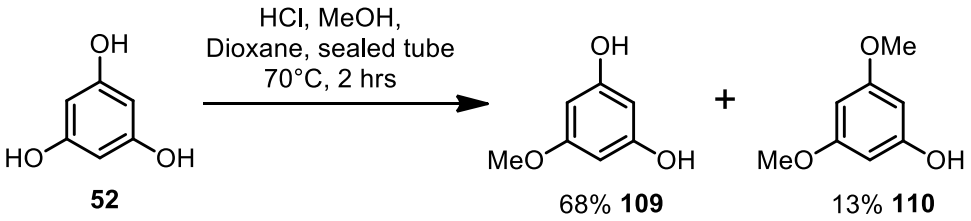
Scheme 2.19 Organolithium addition and oxidation.

Oxidation of the resultant alcohol product gave MOM protected 4-hydroxypanduratin A (**108**) in a 70% yield over 2 steps. Deprotection was then performed using concentrated hydrochloric acid in methanol to afford 4-hydroxypanduratin A (**9**) which matched the literature data (**Scheme 2.20**).[38]



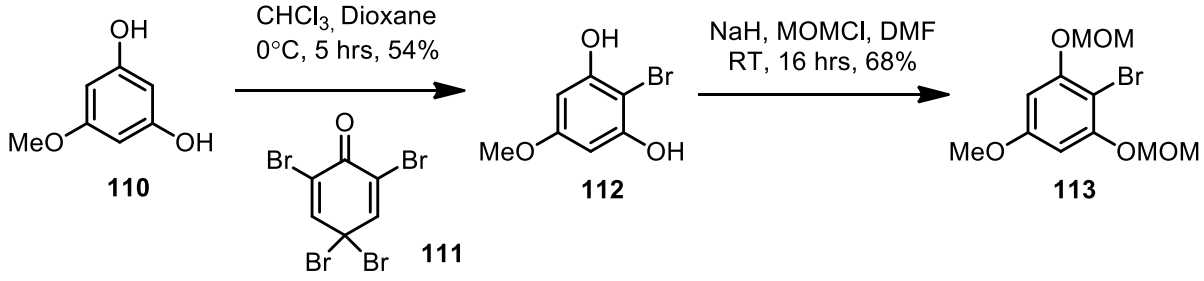
Scheme 2.20 MOM deprotection.

The next aim was to synthesis panduratin A (**8**) using the same strategy which would require 2-bromo-5-methoxy-1,3-bis(methoxymethoxy)benzene (**113**). Synthesis of this bromobenzene began with the methylation of phloroglucinol (**52**) (**Scheme 2.21**). With a hydrogen chloride saturated methanol solution 5-methoxyresorcinol (**109**) and 3,5-dimethoxyphenol (**110**) were generated in yields of 68% and 13% respectively.[57]



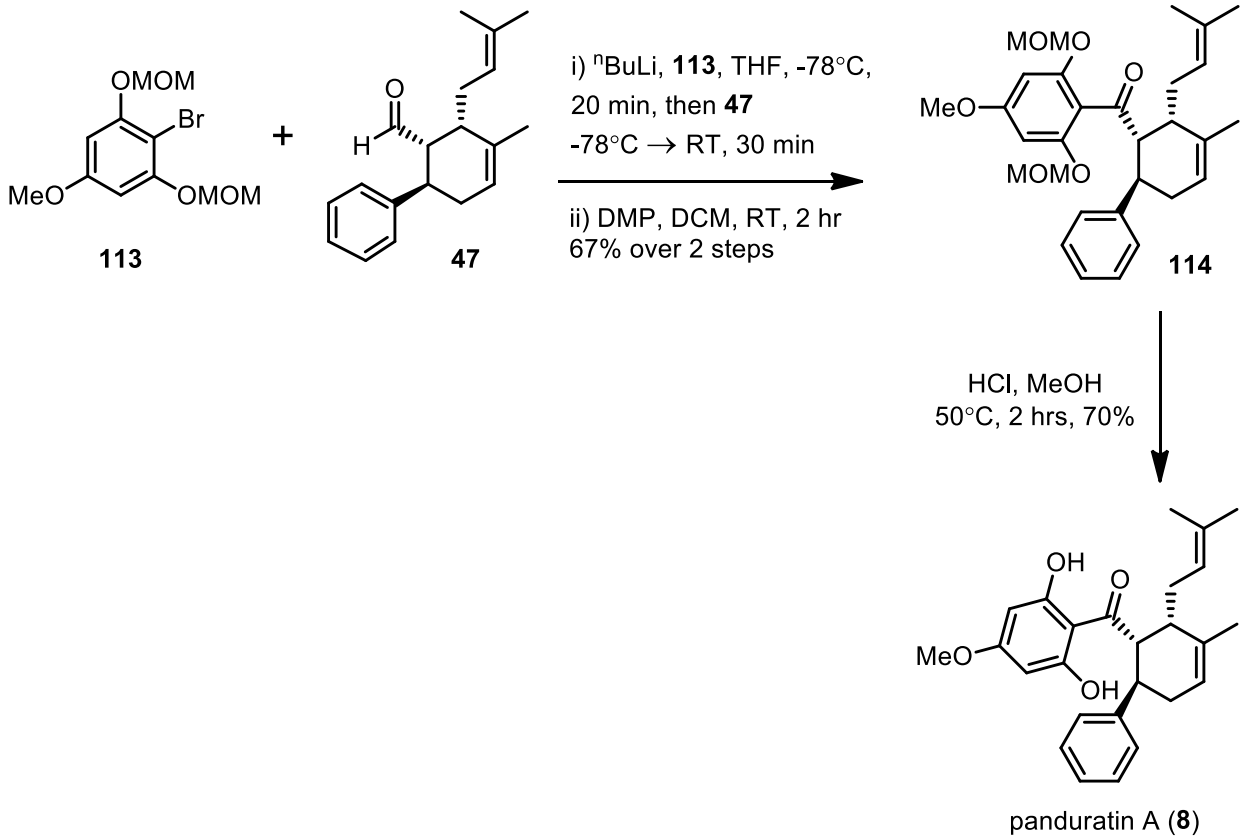
Scheme 2.21 Methylation of phloroglucinol (**52**).

5-Methoxyresorcinol (**109**) was then selectively brominated using 2,4,4,6-tetrabromo-2,5-cyclohexadienone (**111**) to give 2-bromo-5-methoxybenzene-1,3-diol (**112**) in a yield of 54% (**Scheme 2.22**).[58]



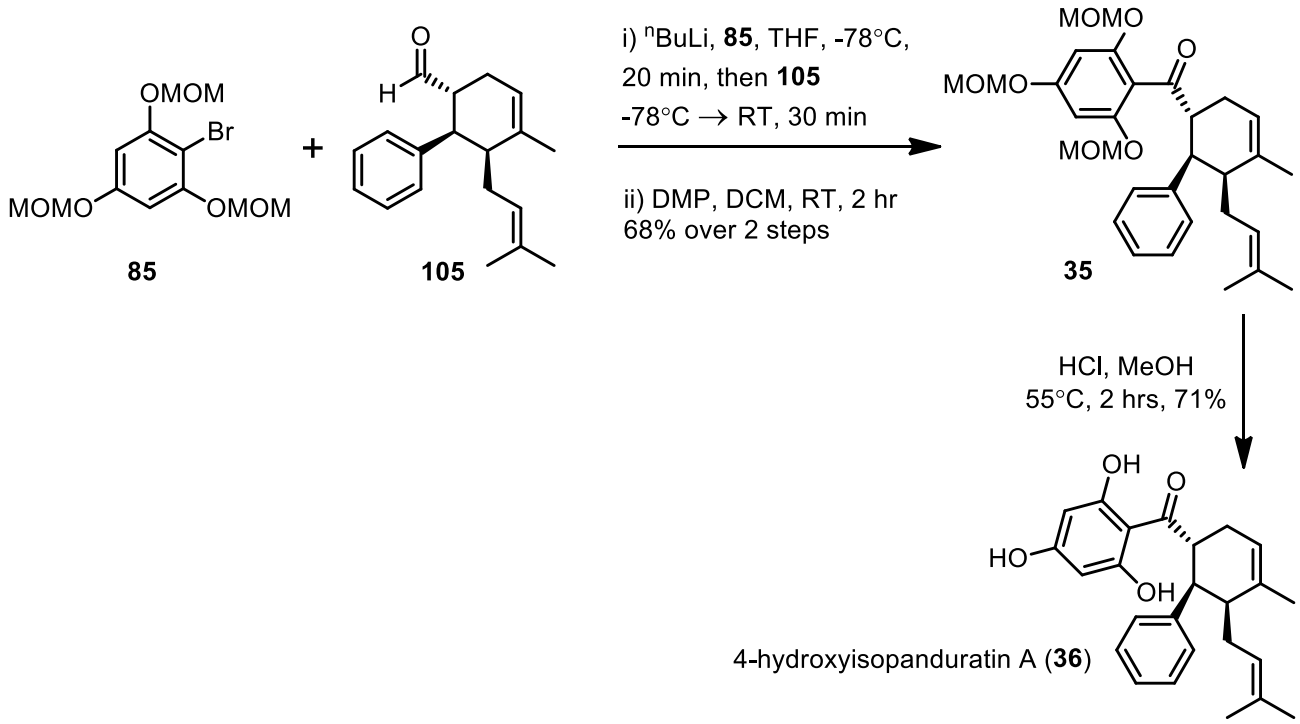
Scheme 2.22 Bromination and MOM protection of 5-methoxyresorcinol (**110**).

The phenols were then protected as the methoxymethyl ethers to afford 2-bromo-5-methoxy-1,3-bis(methoxymethoxy)benzene (**113**) which was then employed in the same organolithium addition, oxidation and deprotection steps to give panduratin A (**8**) (**Scheme 2.23**).



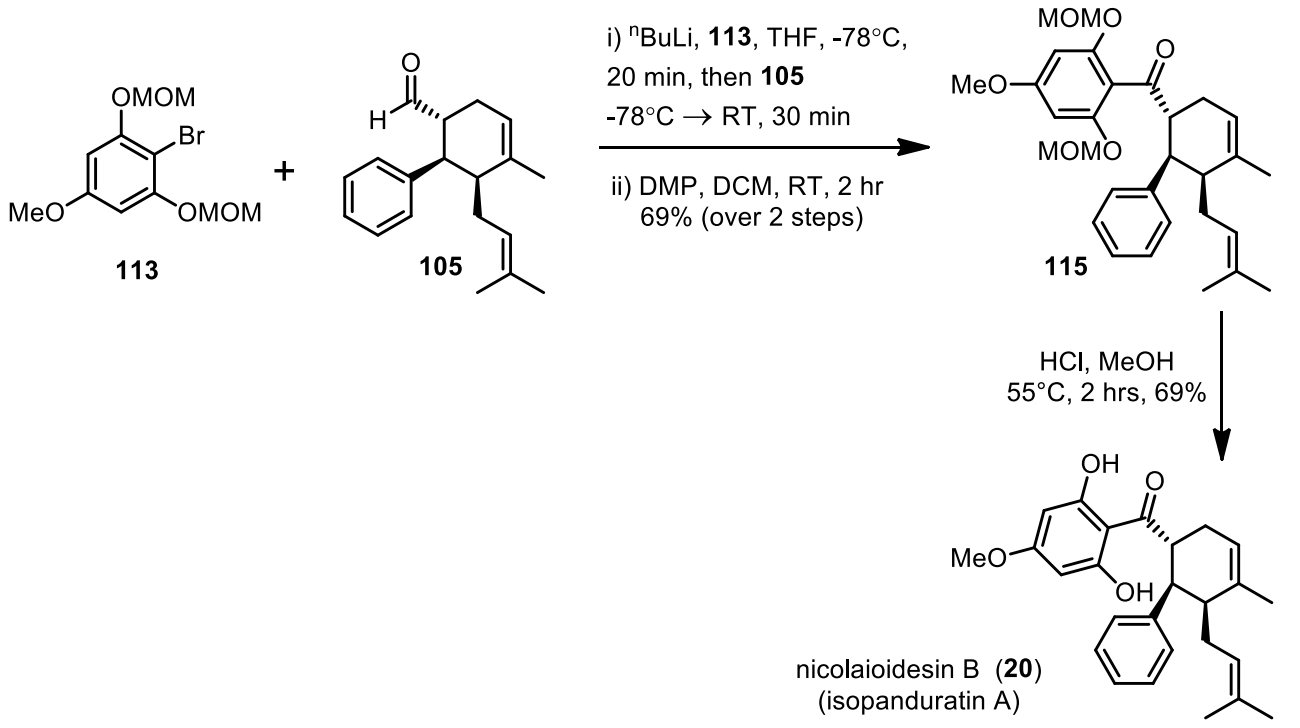
Scheme 2.23 Panduratin A (**8**) synthesis.

This synthetic methodology was also implemented to improve the previous synthesis of 4-hydroxyisopanduratin A (**36**). Using aldehyde **105** and 2-bromo-1,3,5-tris(methoxymethoxy)benzene (**85**) the same sequence of reactions were performed to afford 4-hydroxyisopanduratin A (**36**) (**Scheme 2.24**).



Scheme 2.24 4-Hydroxyisopanduratin A (**36**) synthesis.

Furthermore by using 2-bromo-5-methoxy-1,3-bis(methoxymethoxy)benzene (**113**) in the organolithium addition with aldehyde **105** nicolaioidesin B (**20**) (isopanduratin A) was successfully synthesised (**Scheme 2.25**). This represented the first reported synthesis of nicolaioidesin B (**20**) as a sole product and not as part of an inseparable mixture of regioisomers.[38, 43]



Scheme 2.25 Nicolaioidesin B (**20**) (isopanduratin A) synthesis.

With the panduratins now successfully synthesised a sample of 4-hydroxypanduratin A (**9**) was submitted to the Otting research group for NMR binding testing against a ^{15}N labelled DEN-2 NS3/NS2B protease. The consequent ^{1}H-^{15}N HSQC experiment of 4-hydroxypanduratin A (**9**) in the presence of the DEN-2 NS3/NS2B protease showed shifts in the signals which indicated that 4-hydroxypanduratin A (**9**) was indeed binding to the protease (**Figure 2.**).

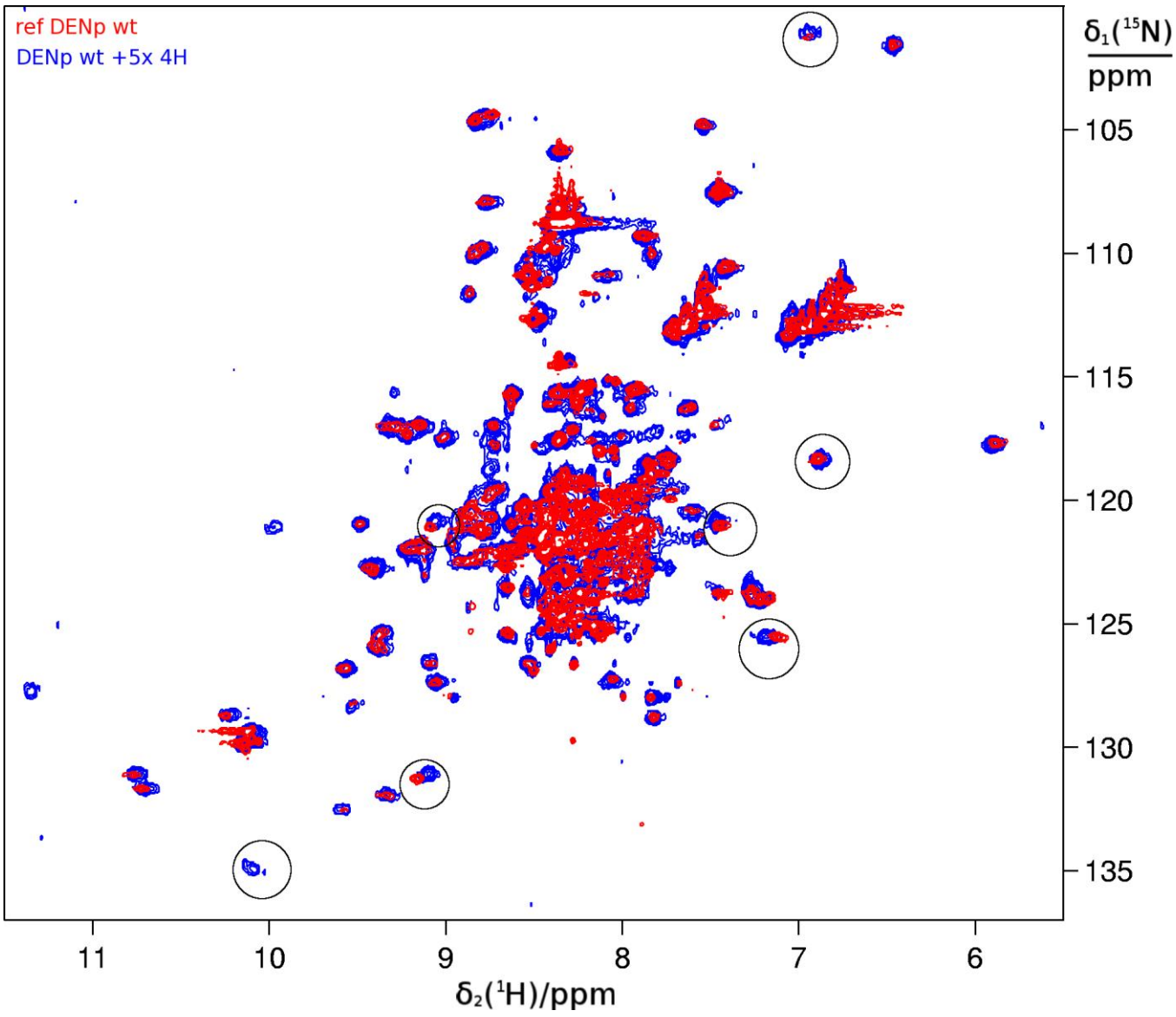


Figure 2.3 ^{1}H-^{15}N HSQC experiment of 4-hydroxypanduratin A (**9**) in the presence of the DEN-2 NS3/NS2B protease. Red signals are those of DEN-2 NS3/NS2B protease without ligand while blue represent the protease in the presence of 4-hydroxypanduratin A (**9**). The circles indicate the signals of protease residues that have shifted markedly.

Using the Otting group's computational NMR model of the DEN-2 NS3/NS2B protease the location of the residues that had shifted could be determined as well as the conformation of the protease (**Figure 2.4**).

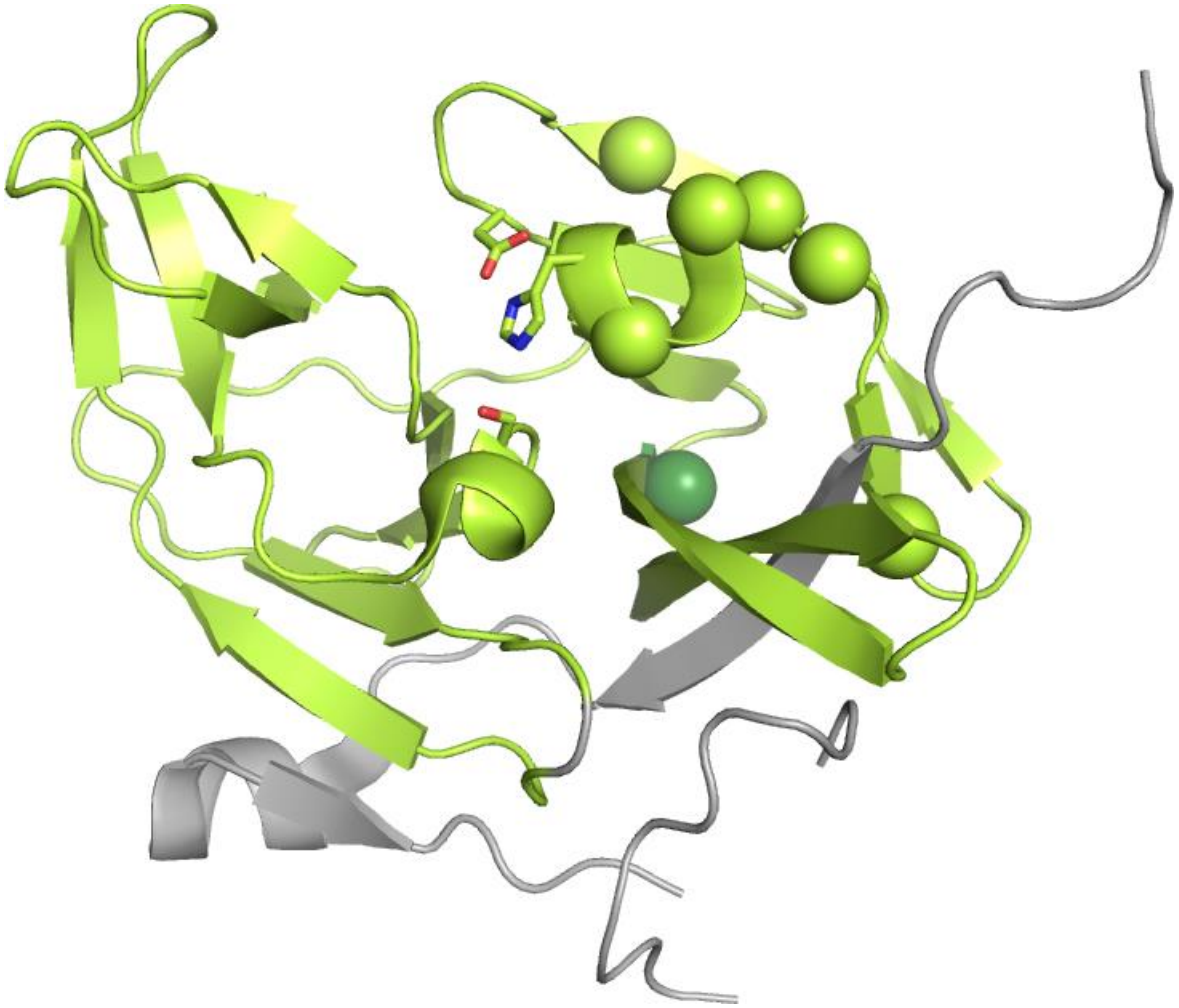


Figure 2.4 Computational NMR model of DEN-2 NS3/NS2B protease in the presence of 4-hydroxypanduratin A (**9**). The NS3 fragment is coloured green and shows the location of the catalytic triad, while NS2B is coloured grey. The green spheres indicate the α-carbons residues that have shifted in the ^{1}H-^{15}N HSQC due to 4-hydroxypanduratin A (**9**) binding.

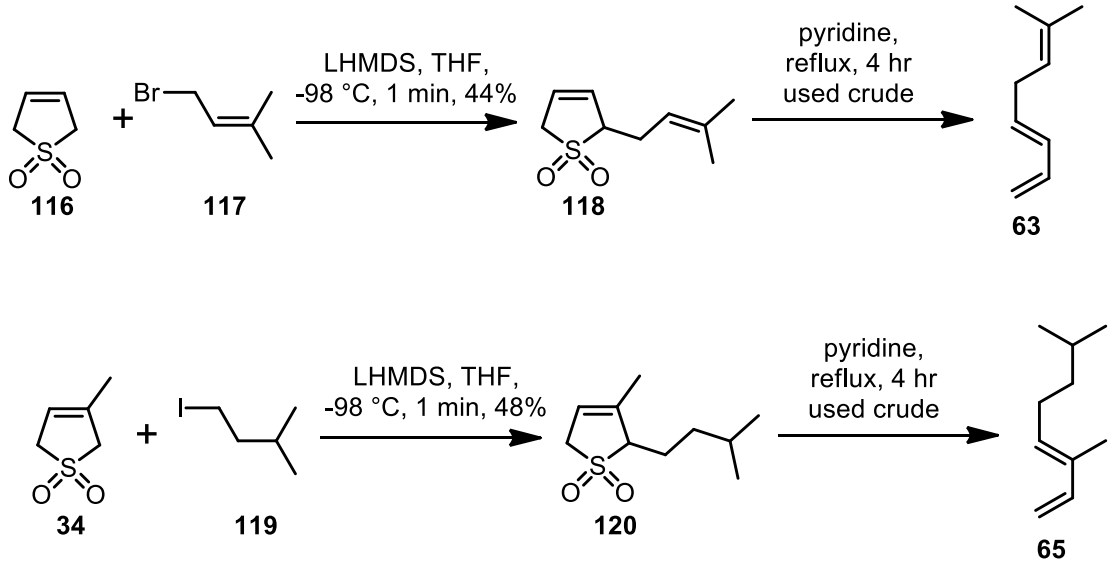
The computational model of the DEN-2 NS3/NS2B protease did show that residues near the catalytic triad had shifted which indicated that 4-hydroxypanduratin A (**9**) was binding in or near the active site. However what was most noticeable was that the binding of 4-hydroxypanduratin A (**9**) had failed to initiate the change of conformation of the protease complex that is typically observed when a substrate or inhibitor binds in the active site. As previously discussed (see page 6) the DEN-2 NS3/NS2B only undergoes a conformation change when a substrate is bound in the active site causing NS2B to wrap around and close the active site.

Furthermore in our hands samples of panduratin A (**8**) and 4-hydroxypanduratin A (**9**) were found to be poorly soluble in aqueous media. Addition of either of the two compounds from DMSO stock solutions to the protein sample caused precipitation of the panduratins. Panduratin A (**8**) even precipitated at a target concentration of 100 μM in 15% aqueous DMSO. It should also be noted that due to the poor sulbility of panduratin A (**8**) and 4-hydroxypanduratin A (**9**) the K_d values of these compounds against the DEN-2 NS3/NS2B protease could not be determined and compared to those reported by Kiat and co-workers.[30]

These results suggest that caution should be taken in adopting panduratin A (**8**) and 4-hydroxypanduratin A (**9**) as lead structures for the development of dengue virus NS2B-NS3 protease inhibitors.

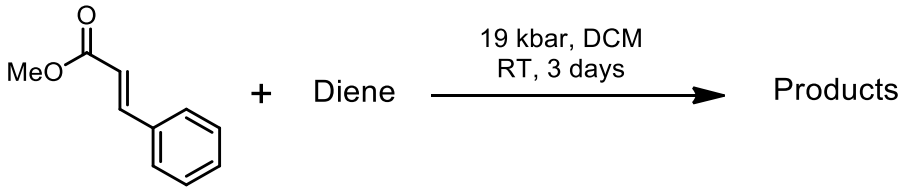
2.5 High Pressure Diels-Alder Regioselectivity Study

Having synthesised a range of panduratins our attention turned to investigating the factors influencing the regioselectivity of the high pressure Diels-Alder reaction. The first step was to try and determine what features of *E*-ocimene (**31**) were responsible for the regioselectivity under high pressure. It was proposed to use diene **63** (missing methyl group), isoprene (**64**) (missing prenyl group) and diene **65** (saturated prenyl group) as analogues of *E*-ocimene (**31**) for this study. While isoprene (**64**) was commercially available and *E*-ocimene (**31**) had already been previously prepared, dienes **63** and **65** were synthesised via the alkylation of a sulfolene with the appropriate alkyl halide (**Scheme 2.26**). It should be noted that due to the low boiling point of dienes **63** and **65** that extensive drying to remove hexane solvent resulted in very low yields. Consequently these dienes were used in the Diels-Alder reactions with some hexane solvents still present (crude).



Scheme 2.26 Sulfolene alkylation and elimination.

Methyl cinnamate (**49**) was chosen as the dienophile for the high pressure Diels-Alder with these dienes as the methoxy ^{1}H-NMR signals of the products would appear in a clear window of the spectrum to allow accurate integration and consequent product ratio determination (**Scheme 2.27** & **Table 2.3**).



Scheme 2.27 High pressure Diels-Alder with dienes of interest.

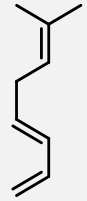
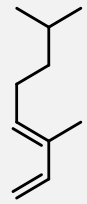
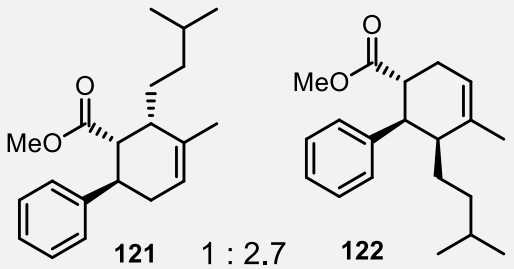
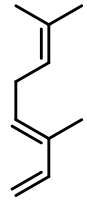
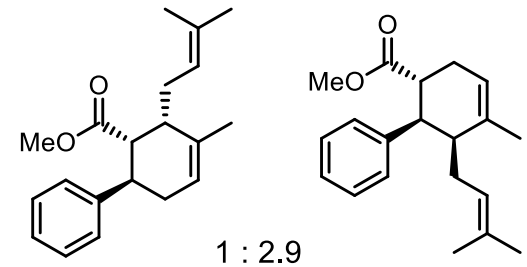
Diene	Yield (%)	Products
 **63**	63	Mixture of Products* 2 : 1.3 : 1 : 1.5
 **64**	decomposition	-
 **65**	71	 **121** 1 : 2.7 **122**
 *E*-ocimene (**31**)	93	 panduratin H (**17**) 1 : 2.9 panduratin I (**18**)

Table 2.3 High pressure Diels-Alder with dienes analogues.

*Please see the following paragraph and Figure 2.5 for further explanation

Diene **63** gave a mixture of four Diels-Alder adducts in the ratio of 2 : 1.3 : 1 : 1.5. These products were not individually separable, even by HPLC or after reduction to their alcohols, and thus their structure could not be ascertained. After analysis of their H-NMR spectra looking specifically at the cyclohexene proton shifts and multiplicity, it was postulated the four compounds were composed of two pairs of closely related regioisomers. Given there was a large separation in the methyl ester signals in each regioisomer pair, it was suggested that this was due to each pair containing an *endo* and *exo* product (**Figure 2.5**). However it was not possible to confidently assign signals to the compounds and consequently the structures could not be matched to the product distribution.

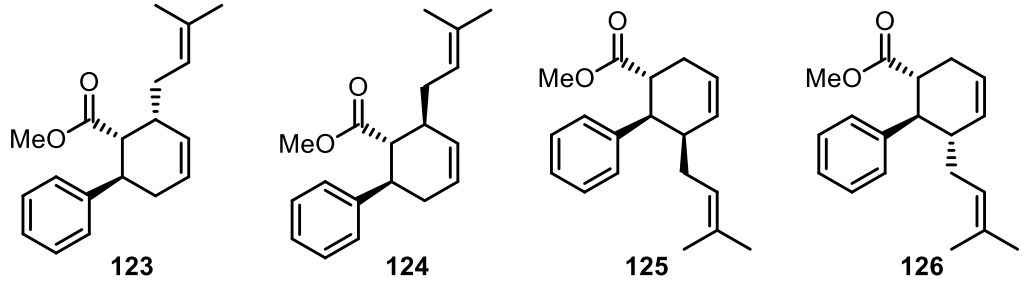


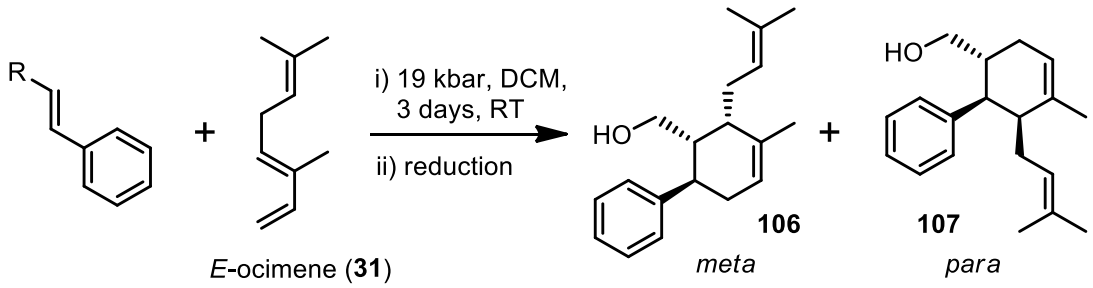
Figure 2.5 Speculated products of Diels-Alder with diene **63**.

With respect to the high pressure reaction with isoprene (**64**) this only resulted in decomposition and so once again it could not be determined what the relative directing strengths of the prenyl and methyl substituents on *E*-ocimene (**31**) were.

Subjection of diene **65** to the high pressure conditions yielded adducts **121** and **122** in a ratio of 1:2.7. Whilst there was a small change in the ratio from using *E*-ocimene (**31**) (1:2.9) it was not significant enough to suggest appreciable π stacking was taking place in the transition state.

Despite the inseparable mix and decomposition of isoprene (**64**) it can still be proposed that the methyl group of *E*-ocimene (**31**) is required to be in the 2' position of the diene to ensure that only *endo* products are produced. This is further supported by the previously synthesised modified diene (**91**) (see **Scheme 2.14** & **Figure 2.2**), that had the methyl in the 3'position of the diene, also producing a mixture of *endo* and *exo* products. Furthermore the high pressure reaction with diene **65** shows that the prenyl group does not seem to be participating in π stacking with the benzene ring of the cinnamates. However dispersion forces between the alkyl group and phenyl substituent could be contributing to the observed regioselectivity.

Having studied *E*-ocimene (**31**) analogues it was then decided to look at the dienophiles and determine how the size and strength of the electron withdrawing substituent impacts the regioselectivity of the high pressure Diels-Alder with *E*-ocimene (**31**). In addition to methyl cinnamate (**49**) and cinnamaldehyde (**48**) other dienophiles were both subjected to high pressure conditions with *E*-ocimene (**31**) (**Scheme 2.28** & **Table 2.4**).



Scheme 2.28 High pressure reactions with *E*-ocimene (**31**). The product where the methyl group is *meta* to the methanol substituent in termed *meta* and likewise for the *para* product.

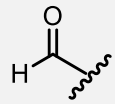
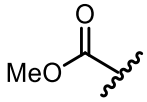
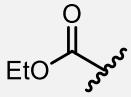
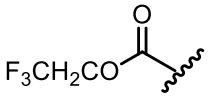
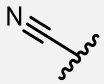
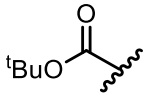
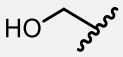
R =	**Yield (%)**	**Ratio (*meta*: *para*)[a]**
	62	1 : 7.2
	73[c]	1 : 2.9
	68[c]	1 : 3.1
	56[c]	1 : 2.4
	64[b]	1: 9.5
	63[c]	1 : 8.9
	trace product	only trace *meta*

Table 2.4 Product distributions for high pressure reactions with *E*-ocimene (**31**). a) ratio of regioisomers determined by 400 MHz ^{1}H-NMR spectroscopy of the crude reaction mixture. b) ratio determined after reduction to aldehyde. c) ratio determined after reduction to alcohol.

For the methyl cinnamate (**49**) reaction the resultant products were panduratin H (**17**) and panduratin I (**18**) in a ratio of 1:2.9 respectively where the major product had the methyl substituent *para* to the ester group. When the high pressure Diels-Alder was repeated with cinnamaldehyde (**49**) in place of methyl cinnamate (**49**) a product ratio of 1:7.2 was obtained where once again the major product had the methyl substituent *para* to the EWG. Therefore it initially seemed a stronger activating group

(ie. aldehyde) resulted in the regioselectivity being even further towards the *para* product. However the trifluoroethyl activating group (also a strong EWG) produced a product ratio of 1 : 2.4 which was less justified than weaker EWGs such as the methyl and ethyl esters (1 : 2.9 & 1 : 3.1). Therefore another theory was that smaller EWGs such as an aldehyde or nitrile (1 : 9.5) strongly favoured the formation the product whereby the methyl was *para* to the EWG. However when the large *tert*-butyl cinnamate group was reacted under high pressure conditions it also produced a heavily justified product ratio (1 : 8.9) similar to the much smaller than the aldehyde and nitrile EWGs.

Despite there not being a clear steric or electronic factor influencing the regioselectivity, the major product in all of the reactions had the methyl substituent *para* to the EWG. Therefore from these results it can at least be concluded that the,

- The C3-methyl group appears to dominate the regioselectivity over the prenyl group with the methyl *para* regioisomers favoured in all examples using *E*-ocimene (**31**). The results confirm that the methyl and prenyl substituents are non-reinforcing.
- The C3-methyl also appears to favour *endo* products over *exo*. In all instances that *E*-ocimene (**31**) is used only *endo* products are observed. However dienes without this C3-methyl seem to lack selectivity in high pressure Diels-Alder reactions. Diene **63** with prenyl alone appears to give mixtures with little selectivity suggesting little or no control over regioselectivity (see **Scheme 2.27** and **Table 2.3**). However this could not be confirmed unequivocally as structures and ratios were not assigned. Furthermore Diene **91** is reinforcing where a single regioisomer forms but is a mixture of *endo* and *exo* (see **Scheme 2.14** and **Figure 2.2**).
- The the size or strength of the EWG does not allow prediction of the product distribution. Only that methyl *para* products are favouired when using using *E*-ocimene (**31**).

To better understand the observed results computational analysis of the frontier molecular orbitals of the dienophiles and the *E*-ocimene (**31**) was conducted in collaboration with the Coote Research group (**Figure 2.6**).

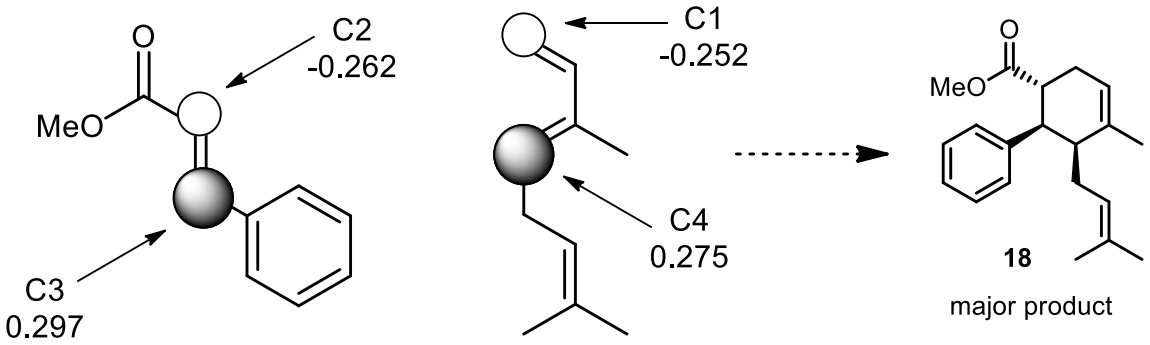


Figure 2.6 The 2Pz atomic orbital coefficients of methyl cinnamate (**49**) and *E*-ocimene (**31**) calculated at the B3LYP/6-31G(d) level of theory.

Taking methyl cinnamate (**49**) and *E*-ocimene (**31**) alignment of the larger diene HOMO (2Pz atomic orbital) coefficient with that of the corresponding dienophile LUMO coefficient predicts the formation of methyl ester **18** as the major regioisomer. As this prediction matched the observed regioselectivity of the high pressure Diels-Alder reaction, further computational analysis of the 2Pz atomic orbital coefficients of the employed dienophiles was conducted (**Table 2.5**).

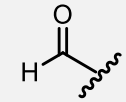
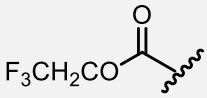
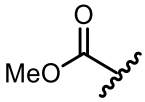
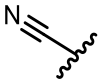
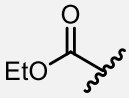
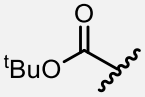
R =	**C3 2Pz**	**C2 2Pz**	**Δ**	**R =**	**C3 2Pz**	**C2 2Pz**	**Δ**
	0.308	-0.228	0.536		0.309	-0.251	0.560
	0.297	-0.262	0.559		0.306	-0.288	0.594
	0.295	-0.263	0.558		0.307	-0.245	0.552

Table 2.5 Atomic orbital coefficients of the 2p orbitals of various dienophiles calculated at the B3LYP/6-31G(d) level of theory.

Looking at **Table 2.5** the magnitude of the 2Pz coefficients typically match the observed regioselectivity with, for example, the high 2Pz values of the aldehyde, nitrile and *tert*-butyl ester groups resulting in the product distribution being justified towards the methyl being in a *para* position to the EWG. However the trifluoroethyl group did not conform to this trend as it had the largest C3 coefficient but only modest selectivity. Furthermore the magnitude of difference between the C3 and C2 2Pz coefficients similarly does not predict the reaction regioselectivity. For example the aldehyde EWG had the lowest difference (0.536) and the nitrile highest (0.594) yet these EWGs both strongly favoured the methyl *para* regioisomers (1:7.2 and 1:9.5 respectively).

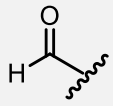
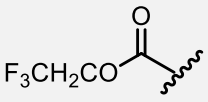
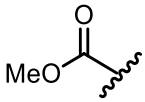
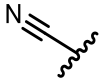
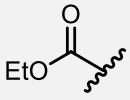
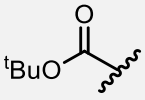
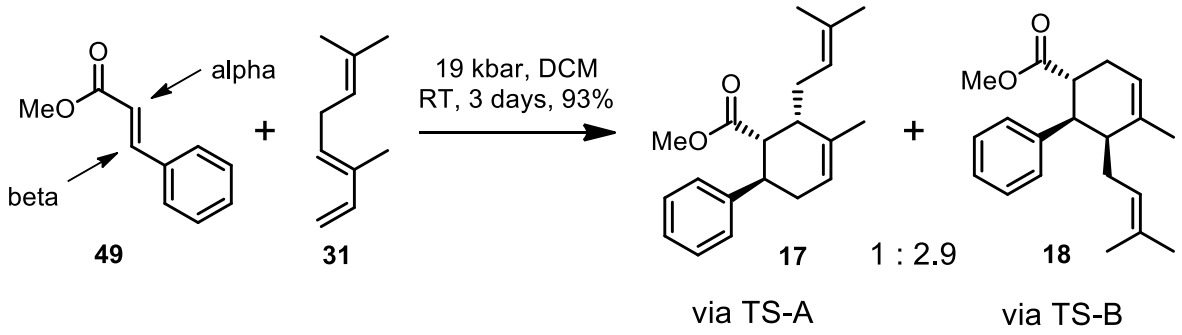
R =	**E_{HL}**	**R =**	**E_{HL}**
	368.62		364.94
	392.25		365.47
	394.88		377.28

Table 2.6 HOMO-LUMO energy gap of various dienophiles and *E*-ocimene (**31**) calculated at the B3LYP/6-31G(d) level of theory.

Further orbital calculations were investigated such as the energy gap between the HOMO of the dienophile and the LUMO (E_{HL}) of *E*-ocimene (**31**) (**Table 2.6**). From **Table 2.6** it can be seen that the aldehyde and nitrile groups have a small E_{HL} which matched the observed regioselectivity being justified towards the methyl being in a *para* position to the EWG (1:7.2 and 1:9.5 respectively). However the trifluoroethyl group actually had the lowest E_{HL} value and actually had shown the lowest amount of the methyl *para* product (1:2.4) compared to the other EWGs. Furthermore the *tert*-butyl group had an intermediate E_{HL} value yet exhibited a strong preference for methyl *para* product (1:8.9). What was clear at this stage was that electronic factors were not solely responsible for explaining the product distribution of the high pressure Diels-Alder reactions between cinnamates and *E*-ocimene (**31**).

At this point it was proposed to investigate the transition states (TS) of these high pressure Diels-Alder reactions as the reaction volumes and developing bond lengths of the cyclohexenyl moiety have been suggested as regioselectivity indicators of the Diels-Alder reaction.[59, 60] In particular reaction volumes are very influential under high pressure conditions with the smallest transition state typically leading to the major product. This is indeed why *exo* Diels-Alder adducts are rarely observed under high pressure conditions as their TS typically have a larger volume than their equivalent *endo* TS.

Once again in collaboration with the Coote research group modelling the TS of methyl cinnamate (**49**) and *E*-ocimene (**31**) was first investigated (**Scheme 2.29** & **Figures 2.7**-**2.8**).



Scheme 2.29 Modelling of the transitions states (TS) for methyl cinnamate (**49**) and *E*-ocimene (**31**). The TS for the prenyl *ortho* and *endo* with respect to the carbonyl is termed TS-A, and for the prenyl *ortho* and *endo* with respect to the phenyl TS-B.

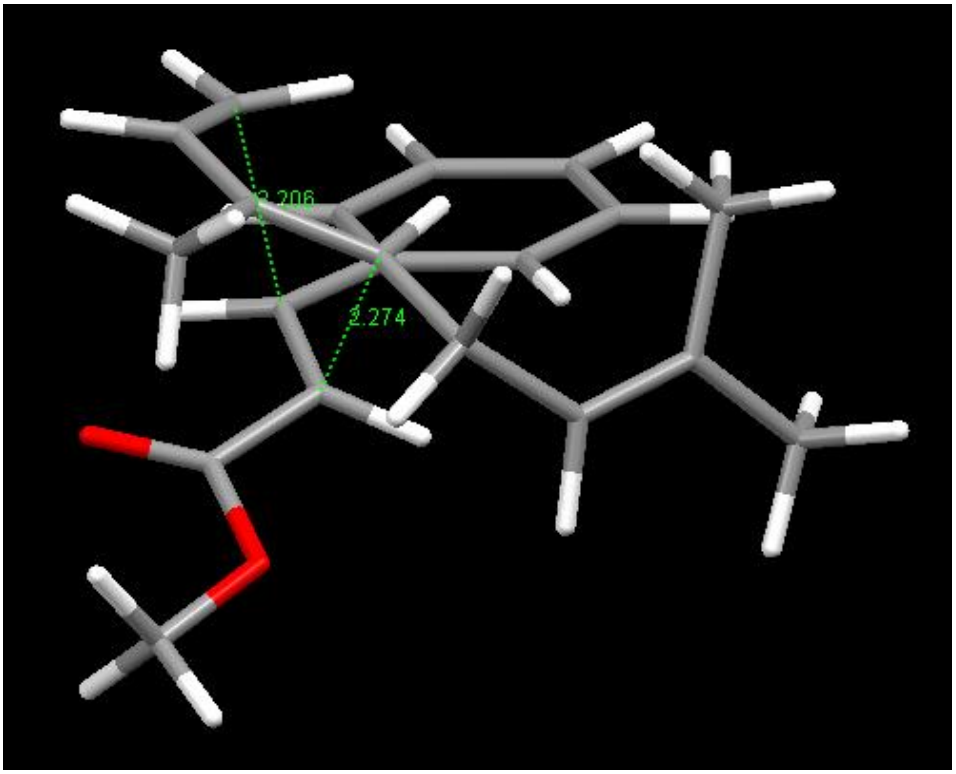


Figure 2.7 TS-A of methyl cinnamate (**49**) and *E*-ocimene (**31**).

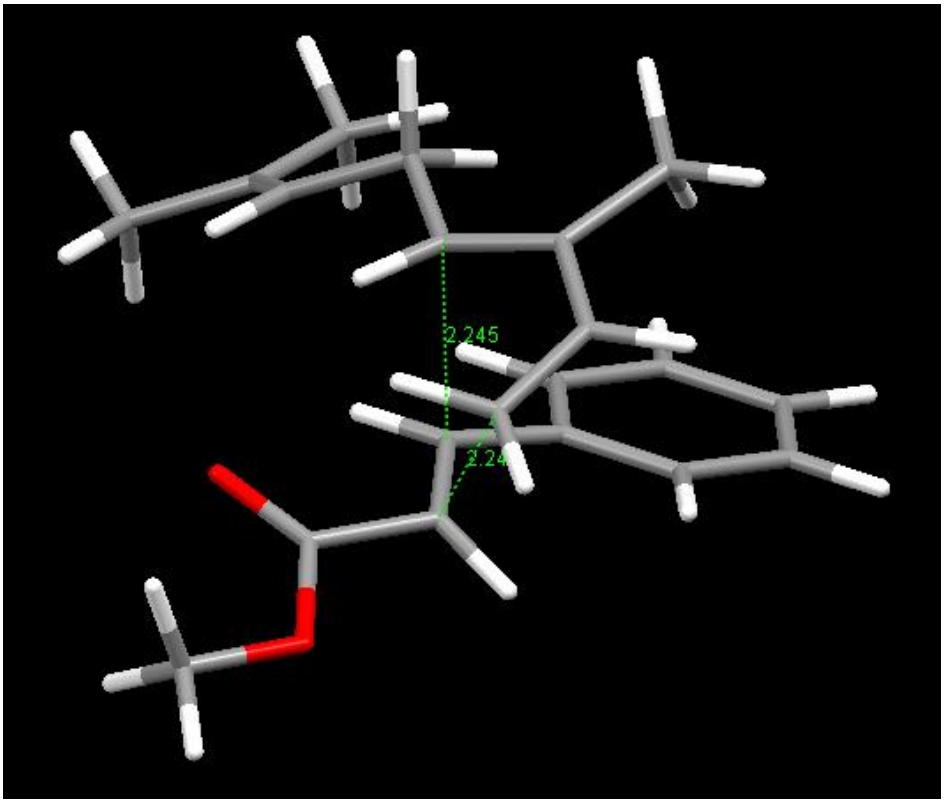
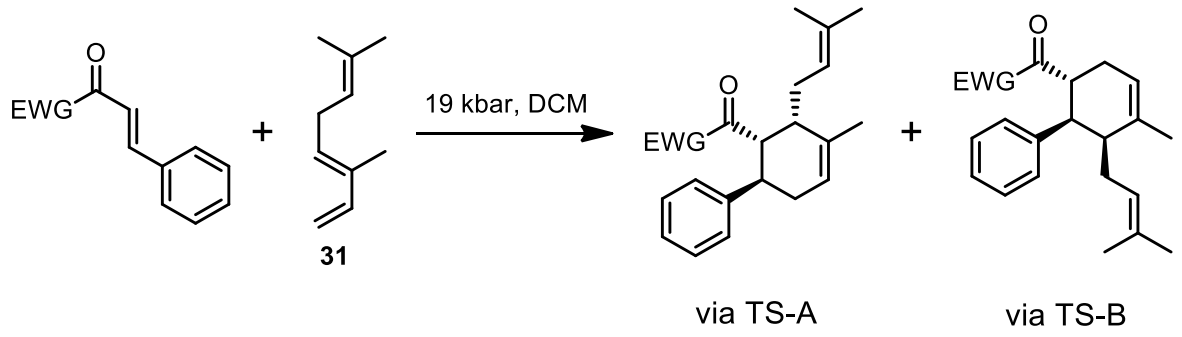


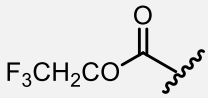
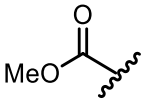
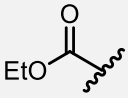
Figure 2.8 TS-B of methyl cinnamate (**49**) and *E*-ocimene (**31**).

The modelling of methyl cinnamate (**49**) and *E*-ocimene (**31**) was successful using a M06-2X/6-31G* level of theory. The reaction volume of TS-A was found to be 239.092 cm^3/mol and the developing bond length *(R)* at the alpha and beta carbons of methyl cinnamate were 2.2741 and 2.2061 angstroms respectively. With respect to TS-B the volume was 237.101 cm^3/mol and the developing bond length *(R)* at the alpha and beta carbons were 2.24431and 2.2449 respectivley. Therefore from this modelling it was shown that TS-A had the shortest developing bonds, yet TS-B had the smaller volume.

The TS modelling of the other dienophiles was then performed in an effort to identify a trend in the obtained data (**Scheme 2.30** & **Table 2.7**).



Scheme 2.30 Modelling of the transitions states (TS) of various dienophiles and *E*-ocimene (**31**) at a M06-2X/6-31G* level of theory.

EWG =	**Transition State**	**r beta (Å)**	**r alpha (Å)**	**Volume (cm^3/mol)**
 1 : 2.4	TS-A	2.18577	2.28281	229.879
	TS-B	2.21776	2.27168	284.323
 1 : 2.9	TS-A	2.2061	2.2741	239.092
	TS-B	2.2449	2.24431	237.101
 1 : 3.1	TS-A	2.2288	2.23748	311.512
	TS-B	2.2427	2.24656	289.575

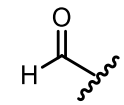
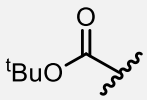
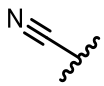
 1 : 7.2	TS-A	2.132	2.377	245.759
	TS-B	2.189	2.311	194.673
 1 : 8.9	TS-A	2.21142	2.28137	270.797
	TS-B	2.24457	2.24297	272.148
 1 : 9.5	TS-A	2.249	2.237	248.137
	TS-B	2.262	2.233	230.737

Table 2.7 Developing bond lengths and reaction volumes of the Diels-Alder reaction TS at a M06-2X/6-31G* level of theory.

Of particular note from this data was that r-beta is shorter for TS-A than TS-B in all cases. This can perhaps be explained by the *E*-ocimene (**31**) coefficient being smaller at this end and so a closer approach is required for bonding. With respect to the reaction volumes in most cases the volume correctly predicted that the reaction would progress via TS-B, although with the exception of the trifluoroethyl and *tert*-butyl esters.

Reflecting on all the data, including the observed reaction regioselectivity and computational data, there did not appear to be a single factor that on its own explained the Diels-Alder regioselectivity that was being observed for high pressure reactions (**Table 2.8**). For example the trifluoroethyl ester EWG had the largest C3 2Pz coefficient (0.309) and yet formed less of the methyl *para* product compared to the ethyl ester EWG (0.95). Furthermore, with respect to TS volumes there was very little difference between TS-A and TS-B for the tert-butyl ester EWG (-1.351 cm^3/mol) and yet the methyl *para* product was still strongly favoured. Therefore it seems apparent that multiple factors must be influencing the regioselectiviely of the Diels-Alder reaction.

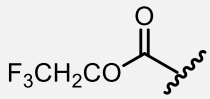
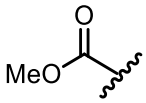
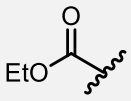
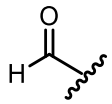
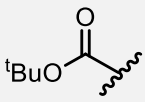
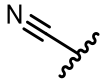
R =	Ratio (methyl *meta*: *para*)	C3 2Pz	C2 2Pz	TS-A Volume (cm^3/mol)	TS-B Volume (cm^3/mol)	Volume Δ (A – B)
	1 : 2.4	0.309	-0.251	229.879	284.323	-54.444
	1 : 2.9	0.297	-0.262	239.092	237.101	1.991
	1 : 3.1	0.295	-0.263	311.512	289.575	21.937
	1 : 7.2	0.308	-0.228	245.759	194.673	51.117
	1 : 8.9	0.307	-0.245	270.797	272.148	-1.351
	1: 9.5	0.306	-0.288	248.137	230.737	17.400

Table 2.8 Observed regioselectivity, C3 2Pz coefficients and TS volumes of various dienophiles.

The closest approximation that could be deduced was that each of the aldehyde, nitrile and *tert*-butyl ester EWGs had a high C3 2Pz coefficient (ie. greater than 0.300) and this resulted in an observed regioselectivity heavily shifted to the methyl *para* product (via TS-B) in comparison to the methyl and ethyl ester EWGs. The exception to this trend is the trifluoroethyl ester group which favours the methyl *para* product the least of all the dienophiles, however this could be explained by its TS reaction volume. For the trifluoroethyl ester group TS-A, which leads to the methyl *para* product, is nearly 20% smaller than TS-B and perhaps explains why it doesn't exhibit a regioisomer ratio similar to that of the aldehyde, nitrile and *tert*-butyl ester EWGs. Therefore whilst a clear single factor for the product distribution has not been identified, a combination of electronic and steric factors between the dienophile and *E*-ocimene (**31**) is influencing the regioselectivity of the high pressure Diels-Alder reaction.

Soon after this study ocimene became commercially available from Sigma-Aldrich as a mix of the *E*:*Z* isomers in a ratio of 2.4 : 1. While this wasn't a pure source of *E*-ocimene (**31**) it was believed that *E*-ocimene (**31**) would react in preference given that the 1,3-diene s-*cis* conformation required for the Diels-Alder reaction had an energy much lower than that of *Z*-ocimene (**127**) (**Figure 2.9**).

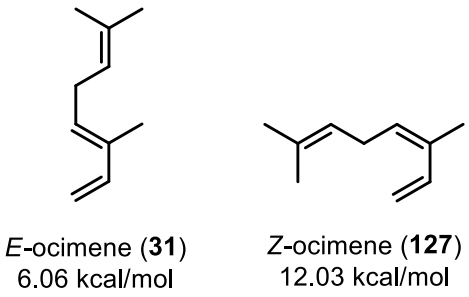
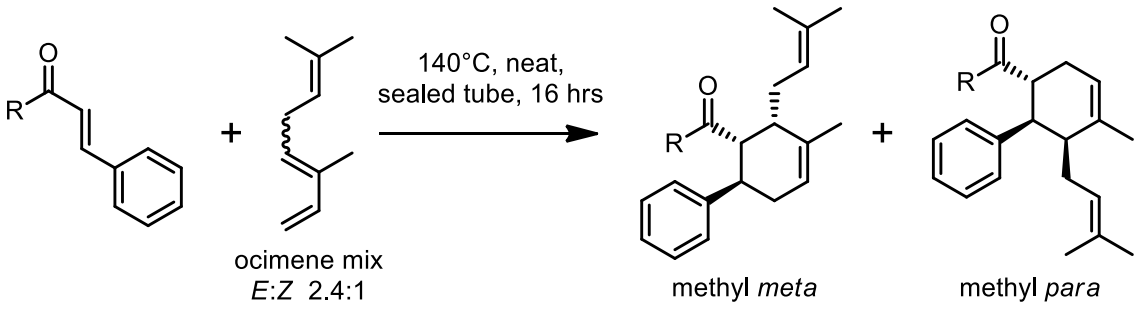


Figure 2.9 Energy of s-*cis* conformations of *E*-ocimene (**31**) and *Z*-ocimene (**127**).[43]

Thus it was decided to use this ocimene source in place of the laboratory synthesised pure *E*-ocimene (**31**) to attempt sealed tube reactions consisting of just cinnamate and the ocimene mix without solvent in the hope of finding a faster and cheaper route to the cyclohexene core of the panduratins (**Scheme 2.31** & **Table 2.9**).



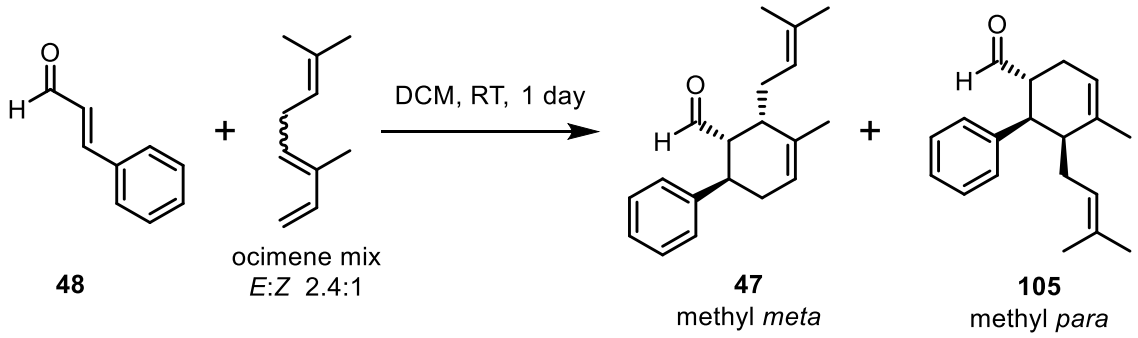
Scheme 2.31 Thermal Diels-Alder.

R=	Yield	Thermal Ratio (methyl *meta*:*para*)	High Pressure Ratio (methyl *meta*:*para*)
OMe	83%	1 : 2.8	1 : 2.9
H	59%	4 products 4.1 : 8.1 : 3.4 : 1*	1 : 7.2
			100% *E*-ocimene

Table 2.9 Thermal Diels-Alder. *These products were not isolated and identified.

Surprisingly it was found that whilst regioselectivity was the same for methyl cinnamate (**49**), in the case of cinnamaldehyde (**48**) thermal conditions afforded four products. These products could only be partially separated, however anaylsis of the crude ^{1}H-NMR spectra indicated that these were likely *endo* and *exo* products of the two regioisomers.

Given this thermal result for cinnamaldehyde (**48**) it was thought it would be prudent to repeat the high pressure Diels-Alder at various pressures with the ocimene mix instead of pure *E*-ocimene (**31**) to ascertain at which point the ratio returned to what was previously observed (**Scheme 2.32** & **Table 2.10**). It was postulated that given *endo* Diels-Alder transition states typically have a lower reaction volumes than the *exo* equivalents that when high pressure was applied only *endo* products would be observed once again.



Scheme 2.32 Varied pressure Diel-Alder reactions with ocimene mix.

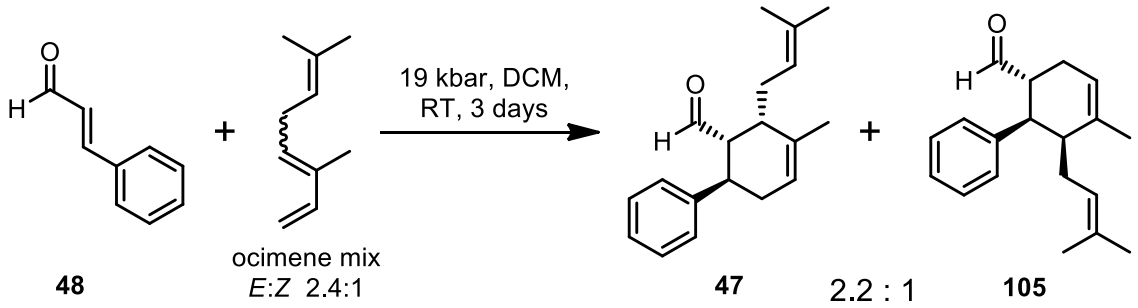
Pressure	Ratio (methyl *meta*:*para*)	Yield (%)
3 kbar	-	no rxn
9 kbar	4.5 : 1	8
13 kbar	3.0 : 1	66
19 kbar	2.3 :1	95

Table 2.10 Varied pressure Diel-Alder reactions with ocimene mix.

By conducting high pressure reactions at various pressures it was found that the regioisomer ratio shifted as the pressure was changed. Using the ocimene mixture and increasing the pressure resulted in the ratio shifting towards the methyl *para* product **105**, however at 19 kbar the ratio was still favoured the methyl *meta* product **47** and had not moved back to the expected ratio of 1 : 7.2 which had been previously. This was a greatly unexpected result and it was unclear at this stage what was causing the change in regioselectivity. After comparing the reactions the following factors were identified as possible contributors to the observed change.

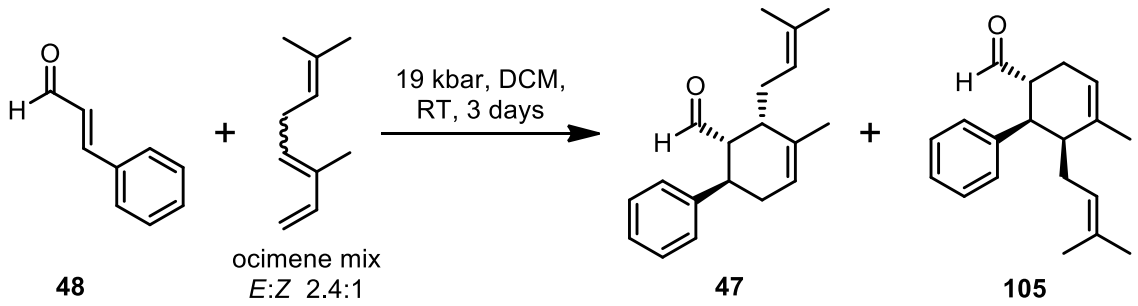
- Reaction time – previous high pressure reactions were for 3 days where repeated high pressure reactions and thermal reactions were for only 1 day.
- More equivalents of ocimene – high pressure conditions used 4 equivalents of *E*-ocimene while the thermal conditions were performed in a neat ocimene mixture.
- A possible sulfolene impurity – the high pressure reaction may still have some sulfolene impurity present from the synthesis of *E*-ocimene, however the ocimene mixture has no sulfolene present.
- A solvent effect – dichloromethane was used as solvent for high pressure reactions while the thermal reactions were performed in neat ocimene mixture
- A mix of ocimene *E*/*Z* isomers – the previous high pressure reactions used pure E-ocimene whilst the thermal conditions used a mixture of the *E* and *Z* isomers.

The first variable tested was reaction time wherein the high pressure reaction was repeated for 3 days with the ocimene mixture (**Scheme 2.33**).



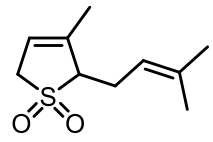
Scheme 2.33 High pressure reaction of ocimene mixture for 3 days.

The longer reaction time resulted in a ratio of 2.2 : 1 with the the methyl *meta* cyclo adduct still the major product. This ratio was virtually the same as previously observed (2.3 : 1) for the one day reaction. Given that the reaction time did not appear to be a factor the equivalents of ocimene and the possible sulfolene impurity were then investigated (**Scheme 2.34** & **Table 2.11**).



Scheme 2.34 Varied equivalents of ocimene and addition of sulfone impurity.

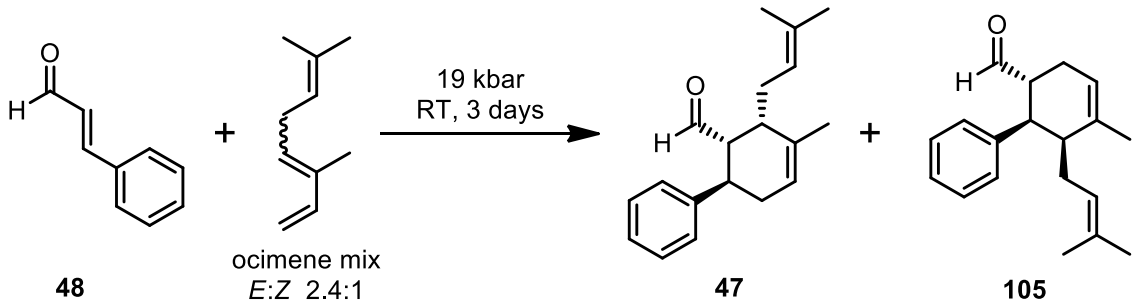
Eq	Ratio	Yield (%)
10	2.3 : 1	100%
4	2.2 : 1	92%
4 (+1 eq sulfolene **104**)	2.1 : 1	82%
1	2.2 : 1	42%



sulfolene **104**

Table 2.11 Varied equivalents of ocimene and addition of sulfone impurity.

As can be seen from the results as the equivalents of ocimene were lowered there was no significant change in the ratio of the regioisomeric products. Furthermore addition of an equivalent sulfolene **104** did not affect the ratio in any substantial way. Still unclear as to the cause of the shift in product distribution our attention turned to investigating the impact of the choice of solvent for the high pressure reaction. These reactions were always carried out in dichloromethane and so a more polar solvent (acetonitrile) and a more non-polar solvent (hexane) were chosen for comparison (**Scheme 2.35** & **Table 2.12**).



48 **47** **105**

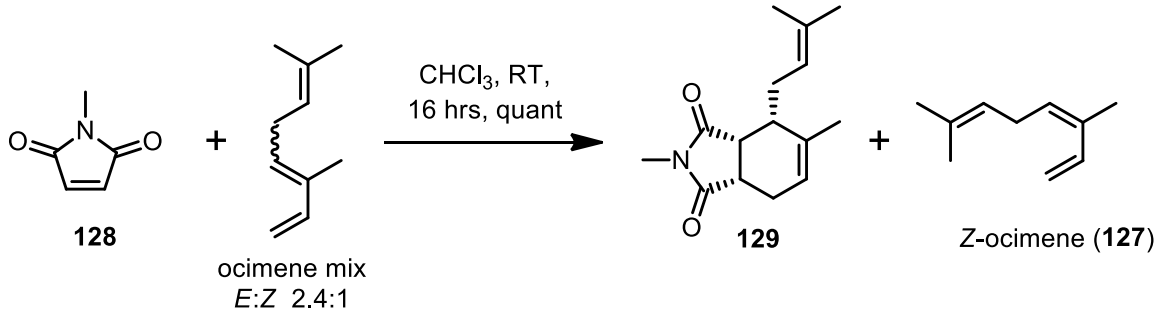
Scheme 2.35 Varied equivalents of ocimene and addition of sulfone impurity.

Solvent	Ratio	Yield (%)
MeCN	2.4 : 1	84
DCM	2.2 : 1	87
Hexane	2.2 : 1	79

Table 2.12 Varied equivalents of ocimene and addition of sulfone impurity.

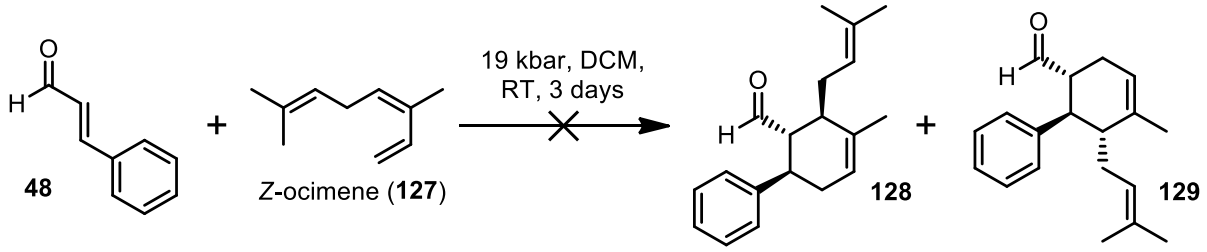
Once again no appreciable change in the ratio was observed when solvents of different polarity were employed in the reaction. The remaining factor to now examine was the effect of the presence of *Z*-ocimene (**127**) in the reaction. In order to explore this it was first sought to purify a sample of *Z*-ocimene (**127**) from the mixture to confirm it was not participating in the Diels-Alder reaction under high pressure conditions. This was believed to be very unlikely as the *Z* isomer of ocimene experiences unfavourable steric interactions and a resulting high energy when adopting the s-*cis* conformation required for a Diels-Alder reaction (**Figure 2.9**).

Pure *Z*-ocimene (**127**) was prepared by adding *N*-methylmaleimide (**128**) to the ocimene mixture in chloroform. The maleimide reacted preferentially with *E*-ocimene (**31**) to afford the corresponding Diels-Alder adduct and leaving unreacted *Z*-ocimene (**127**) which was then separated (**Scheme 2.36**).



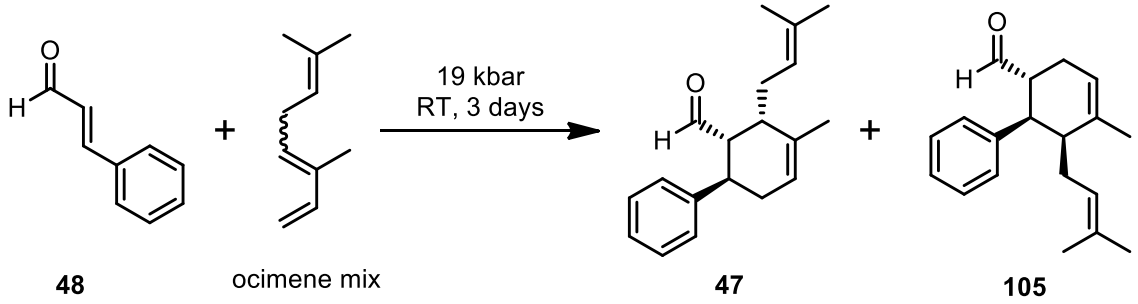
Scheme 2.36 Isolation of pure *Z*-ocimene (**127**).

With pure *Z*-ocimene (**127**) in hand it was then submitted to high pressure conditions with cinnamaldehyde (**48**) (**Scheme 2.37**).



Scheme 2.37 Reactivity of under high pressure conditions.

As expected no Diels-Alder adducts, or any other products, were observed to form from the reaction mixture. The only variable left to explore was the ratio of *E*/*Z* ocimene in the high pressure reaction. To investigate this pure *E*-ocimene (**31**) was added to ocimene mixture in order to change the ratio (**Scheme 2.38** & **Table 2.13**).



Scheme 2.38 Varied ratio of ocimene isomers.

***E* : *Z* ocimene**	**Product Ratio (47 : 105)**	**Yield (%)**
2.4 : 1 (71% *E*)	2.2 : 1	87
3.5 : 1 (78% *E*)	1.5 : 1	78
8.7 : 1 (90% *E*)	1.1 : 1	82
100% *E*	1 : 7.2	62

Table 2.13 Varied ratio of ocimene isomers.

Surprisingly, as the ratio of *E*-ocimene (**31**) in the mixture rose the ratio of the regioisomer products shifted towards the methyl *para* product **105**. In particular it was found that the addition of just 10% Z-ocimene (**127**) had a strong effect and shifted the product distribution from greatly favouring the methy *para* product **105** to almost a 50:50 mixture. Furthermore, given these reactions are using 4 equivalents of ocimene then the *Z*-ocimene (**127**) appears to be exerting its effects sub-stoichiometrically.

A possible explanation of this result would be that the *Z*-ocimene (**127**) is somehow participating in the transition state of the Diels-Alder reaction between *E*-ocimene (**31**) and cinnamaldehyde (**48**). This could in turn effect the volume of the transition state which under high pressure conditions has been known to influence the product distribution. Further computational modelling of the transition state may be useful to elucidate the influence of the *Z*-ocimene (**127**) on the observed regioisomer ratio. However, modelling may prove difficult if this interaction is actually ter-molecular (three molecules) or maybe greater where only two actually react.

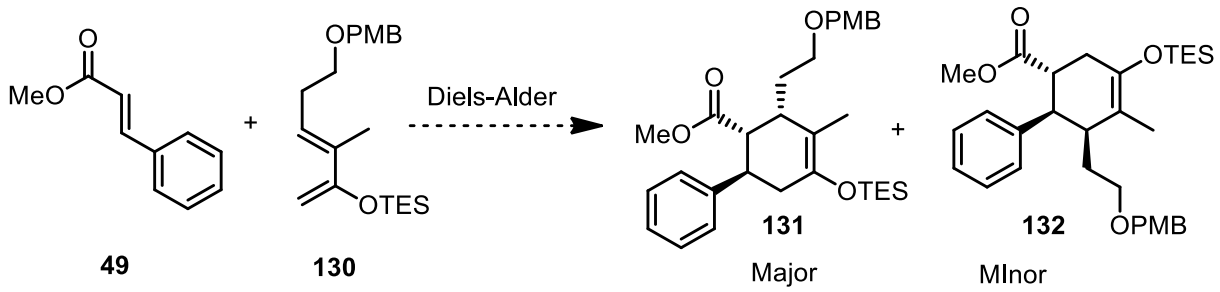
While it is still unclear what exactly is causing this shift in regioselectivity, this surprising result could be used more efficiently access panduratin A and related natural products. This could be achieved by using a mix of *E*/*Z* ocimene that comprises at least 29% *Z*-ocimene (**127**) in the high pressure reaction to improve the yield of the desired methyl *meta* product **105**.

Nevertheless, whilst it appeared the regioisomer ratio could be influenced using a mixture of ocimene *E*/*Z* isomers what was clear was that the regioselectivity of the high pressure reaction was influenced by both electronic and steric factors. Despite this it was sought to explore whether the electronic properties of a stronger directing group on a modified diene could shift the product distribution to a sole Diels-Alder product.

2.6 Directing Diene Strategy.

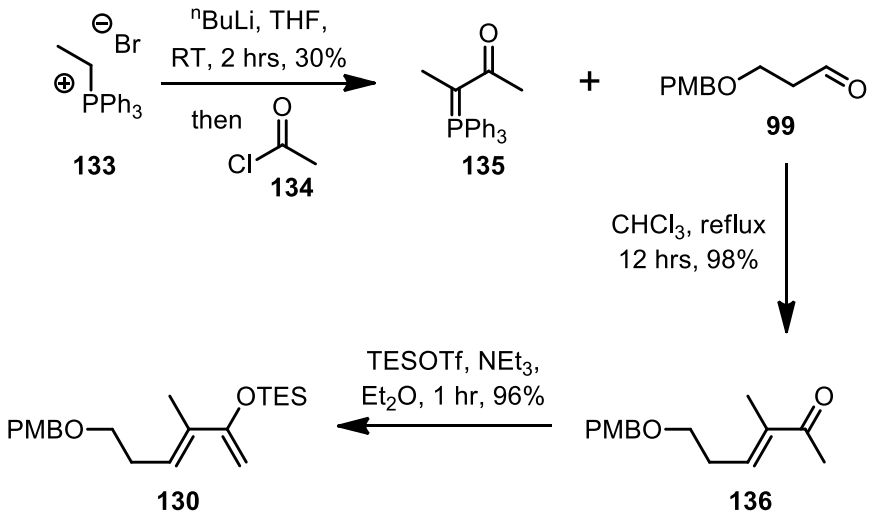
Elements from Group 16 of the periodic table have been used extensively as directing groups in Diels-Alder reactions and so it was sought to synthesis modified dienes with oxygen, sulfur or selenium electron donating groups (see **Scheme 1.12**).

It was first decided to trial a diene with an oxygen directing group to influence the regioselectivity in the Diels-Alder reaction. Diene **130** was envisaged that possessed a triethylsilyl ether in the 3 position of the diene such that it would favour an orientation *para* to the electron withdrawing group and give the desired regioisomer (**Scheme 2.39**). Furthermore once again the prenyl group was replaced with a PMB protected alcohol so that Lewis acid catalysis could potentially be used without isomerisation or polymerisation of the diene.



Scheme 2.39 Proposed oxygen directing diene strategy.

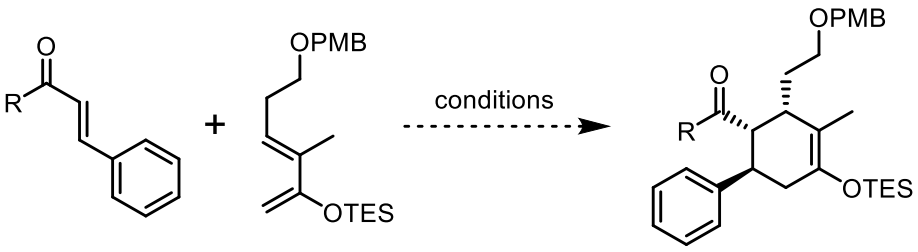
Synthesis of the silyloxy diene began by generating stabilised ylide **135** from ethyltriphenylphosphonium bromide (**133**) and acetyl chloride (**134**) (**Scheme 2.40**).[61]



Scheme 2.40 Oxysilane diene synthesis.

Stabilised ylide **135** then underwent a Wittig reaction with previously prepared aldehyde **99** to afford enone **136** as solely the *E* isomer in a high yield of 98%.[62] With enone **136** in hand it was then silylated by trapping its requisite enolate with triethylsilyltriflate.

Having successfully synthesised the target diene Diels-Alder reactions were then attempted (**Scheme 2.41** & **Table 2.14**).

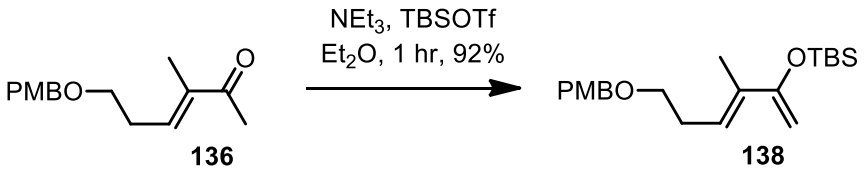


Scheme 2.41 Attempted Diels-Alder reactions.

R =	Conditions	Result
H	BF_3•Et_2O, Et_2O, 0°C, 16 hrs	enone **136**
H	140°C sealed tube, PhMe, 2 days	no reaction
MeO	$ZnBr_2$, MeCN, RT, 16 hrs	enone **136**
MeO	Me_2AlCl, DCM, -30 °C, 16 hrs	enone **136**
MeO	140°C sealed tube, PhMe, 2 days	no reaction

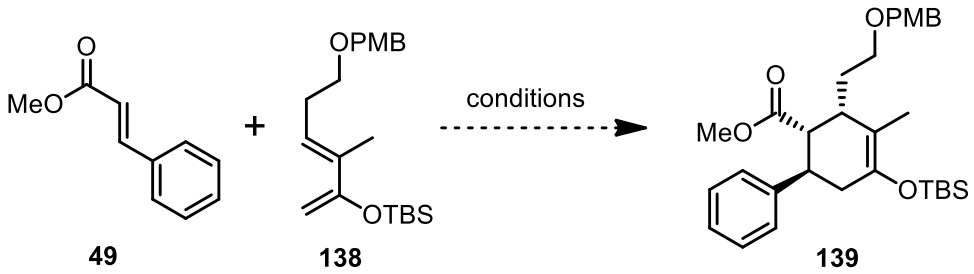
Table 2.14 Attempted Diels-Alder reactions.

Despite attempting a range of reaction conditions the Diels-Alder reaction could not be effected with the lability of the triethylsilyl group in the presence of a Lewis acid also a concern. As a result, a more stable silyl ether such as the *tert*-butyldimethylsilyl group was investigated. Similar conditions were used to generate this compound from enone **136** (**Scheme 2.42**).



Scheme 2.42 Silylation with TBSOTf

With diene **138** the Diels-Alder reaction was once again trialled (**Scheme 2.43** & **Table 2.15**).



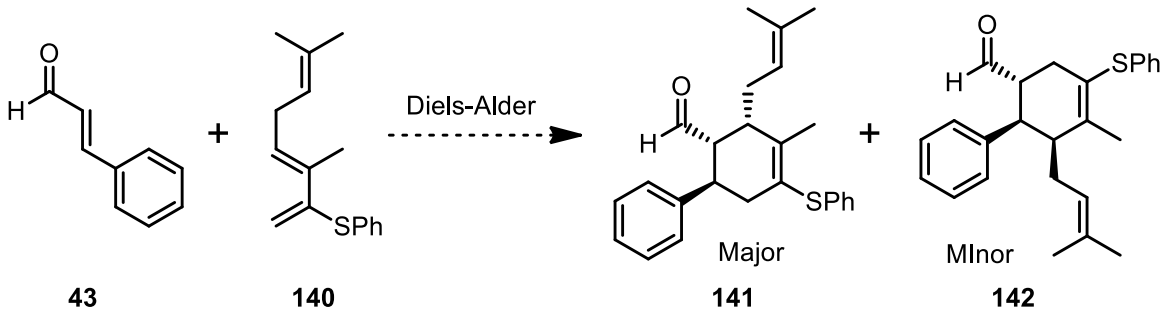
Scheme 2.43 Attempted Diels-Alder reactions.

Conditions	**Result**
BF_3•Et_2O, Et_2O, 0°C, 16 hrs	enone **136**
$ZnBr_2$, MeCN, RT, 16 hrs	enone **136**
Me_2AlCl, DCM, -30°C, 16 hrs	enone **136**
140°C sealed tube, PhMe, 2 days	no reaction
160°C sealed tube, xylenes, 2 days	no reaction
19 kbar, DCM, RT, 3days	no reaction

Table 2.15 Attempted Diels-Alder reactions.

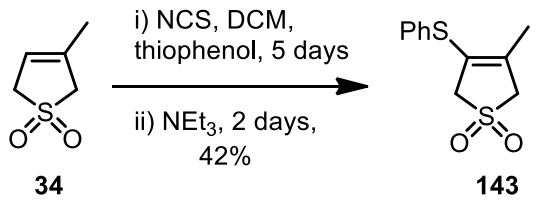
Once again the Diels-Alder was unsuccessful with diene **138**, even under high pressure conditions which has previously always provided a Diels-Alder adduct.

Instead of investigating further Diels-Alder conditions with diene **138** it was decided to instead trial a diene possessing a sulfur directing group to favour the formation of our desired regioisomer product. Sulfur diene **140** was proposed with the thio ether group expected to prefer a *para* orientation to the electron withdrawing group in the Diels-Alder reaction (**Scheme 2.44**). This sulfur group could then potentially be reductively cleaved at a later stage of the synthesis.[63-65]



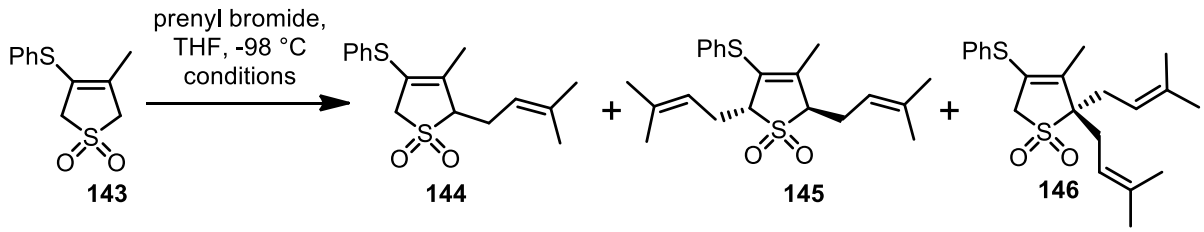
Scheme 2.44 Sulfur as a directing group in the Diels-Alder reaction.

Synthesis of sulfur diene **140** began with preparation of sulfolene **143** from 3-methylsulfolene (**34**) in a yield of 42% (**Scheme 2.45**).[49]



Scheme 2.45 Sulfolene **143** synthesis.[49]

It was then sought to selectively alkylate sulfolene **143** in the 5 position with prenyl bromide using conditions developed in our laboratory for similar reactions. However using these conditions a low yield of the desired alkylated sulfolene **144** and dialkylated sulfolenes **145** and **146** were obtained (**Scheme 2.46** & **Table 2.16**)

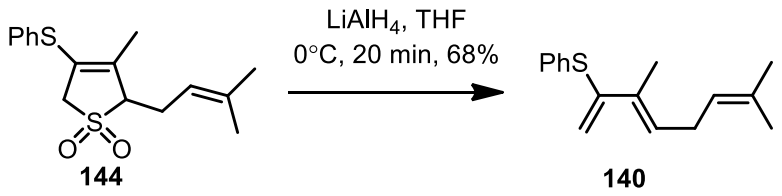


Scheme 2.46 Optimisation of sulfolene alkylation.

Base	Base Eq	Additive	Yield (%)144:145:146
LHMDS	1.2	-	36 : 12 :5
LHMDS	1	-	39 : 8: 2
n-BuLi	1	HMPA	53 : 0 : 0
n-BuLi	1.5	HMPA	57 : 0 : 0

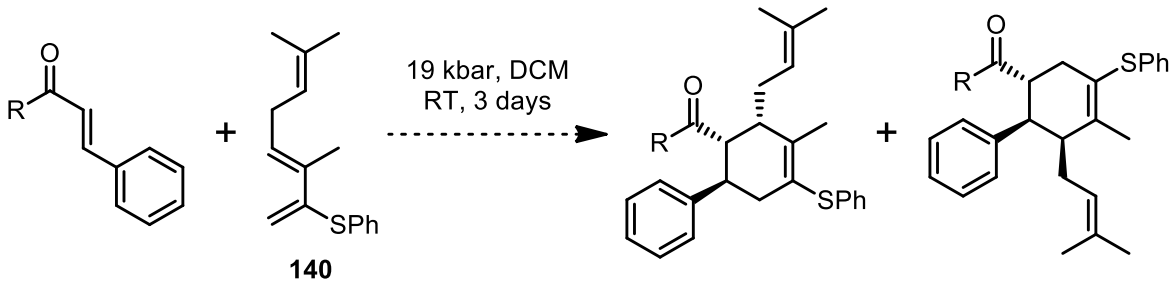
Table 2.16 Optimisation of sulfolene alkylation.

Eventually conditions were found using n-butyl lithium and HMPA to give alkylated sulfolene **144** as the sole product in a yield 57%.[66, 67] Elimination of sulfur dioxide using lithium aluminium hydride then afforded the desired diene **140** (**Scheme 2.47**).



Scheme 2.47 Sulfur dioxide elimination.

Diene **140** was then subjected to high pressure conditions with both methyl cinnamate (**49**) and cinnamaldehyde (**48**) (**Scheme 2.48** & **Table 2.17**).



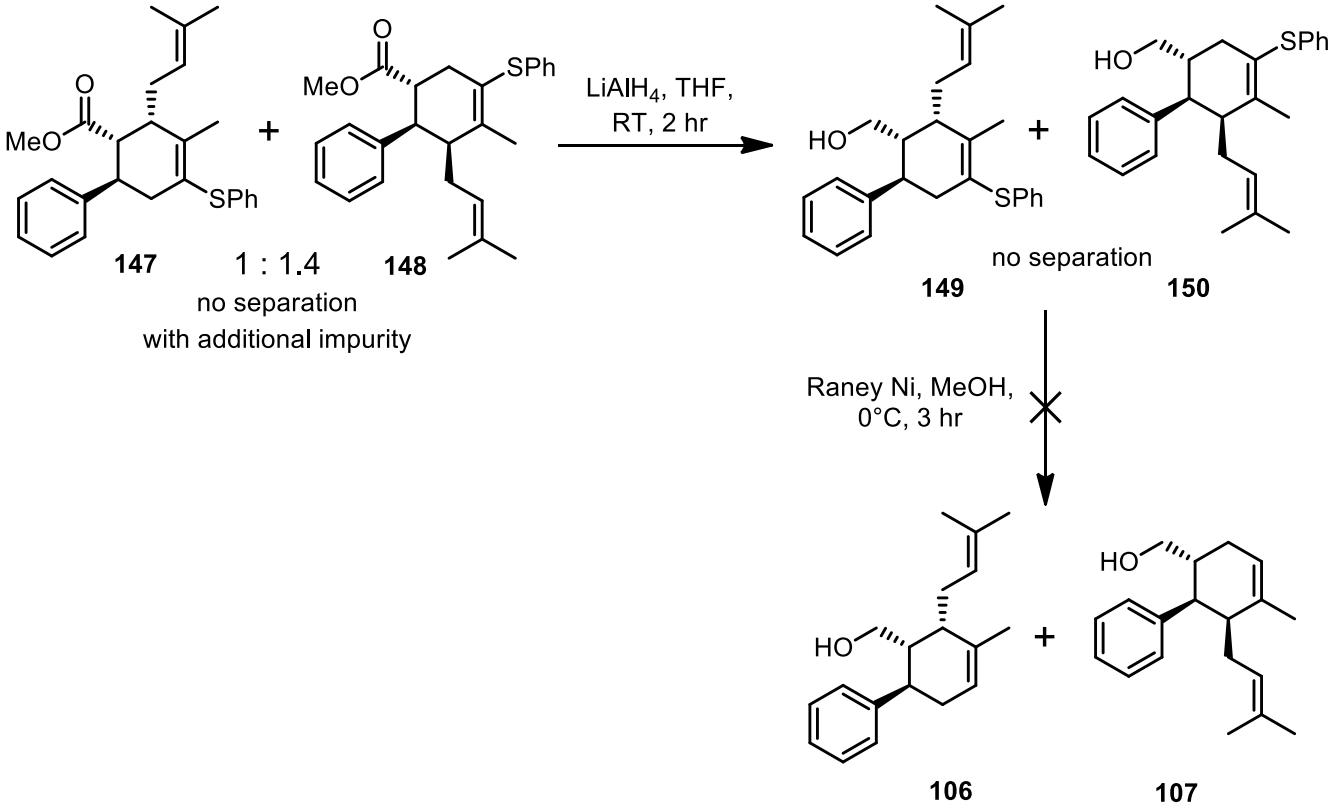
Scheme 2.48 Diels-Alder reactions with diene **140**.

R =	**Result**	**Comment**
OMe	2 inseparable products in the ratio of 1 : 1.4 (*para* : *meta*)	Unknown inseparable impurity also present
H	4 inseparable products in the ratio of 1.6 : 1.7 : 1 : 0.1	-

Table 2.17 Diels-Alder reactions with diene **140**.

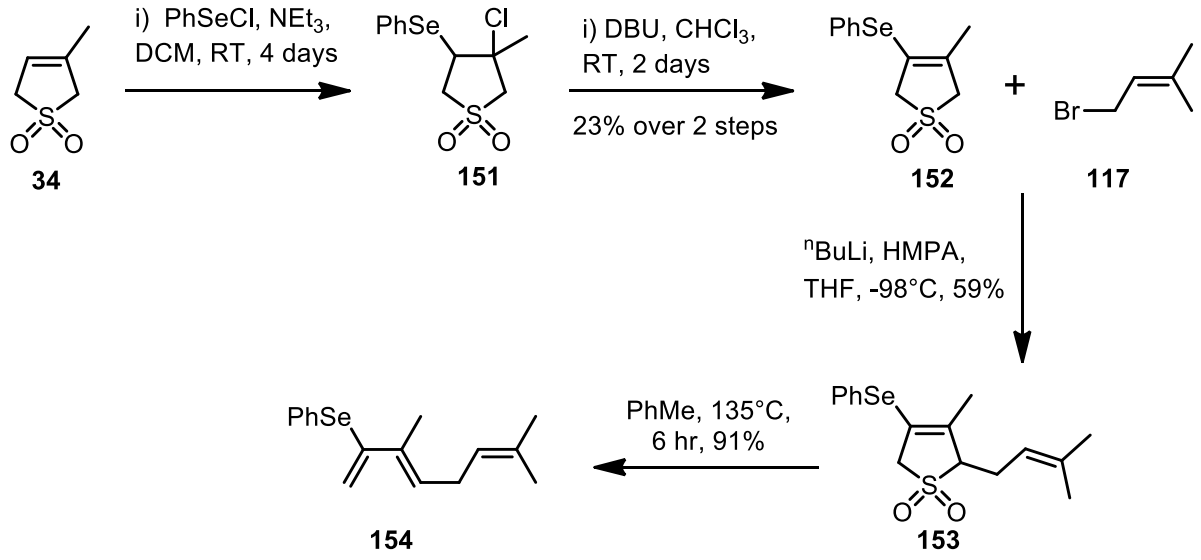
Reaction with methyl cinnamate (**49**) gave 2 inseparable products in the ratio of 1 : 1.4 where the major product had the sulphur substituent *meta* to the ester group. Whilst the regioselectivity had slightly improved when compared to pure *E*-ocimene (**31**), the stronger activating aldehyde was then tested. Again Diels-Alder products were able to be isolated however an inseparable mixture was again obtained with 4 products present in the ratio of 1.6 : 1.7 : 1 : 0.1. The ^{1}H-NMR spectra obtained were however too complex to accurately assign product structures.

In an attempt to separate the products of the methyl cinnamate (**49**) Diels-Alder lithium aluminium hydride was used to reduce the methyl ester groups to the corresponding alcohols (**Scheme 2.49**). However these products were also inseparable. Raney nickel was also used in an attempt cleave the sulfur directing group, however no cleaved products were observed.[63-65]



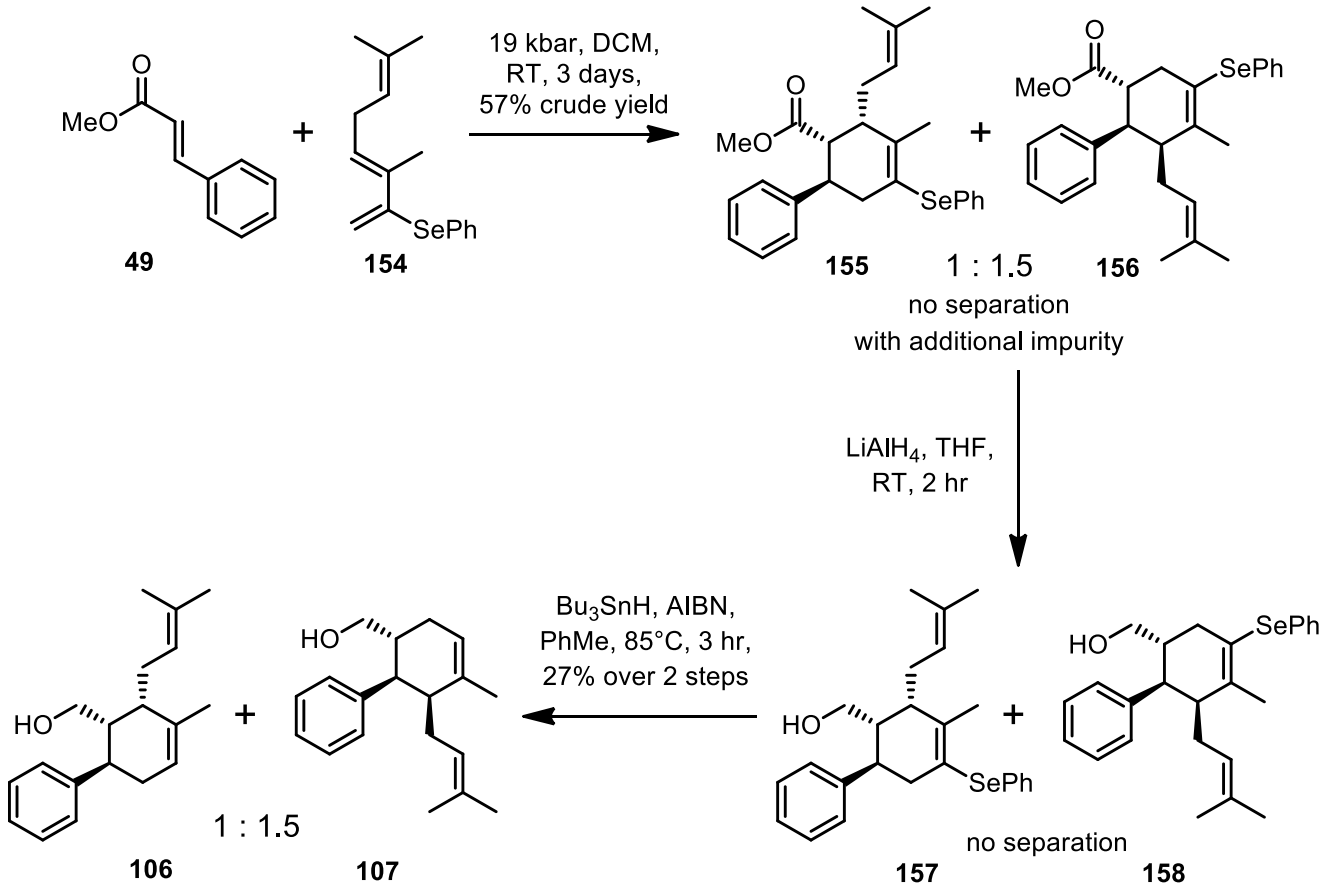
Scheme 2.49 Attempted separation of Diels-Alder adducts.

Given the inability to separate, purify and characterise the products product obtained using sulfur diene **140** it was decided to try selenium instead as a Diels-Alder directing group. The required selenium diene **154** was synthesised in a similar manner by first taking 3-methyl sulfolene (**34**) and performing an electrophilic addition with phenylselenyl chloride followed by elimination in the presence of DBU (**Scheme 2.50**).[68-71]



Scheme 2.50 Synthesis of selenium diene **154**.

Sulfolene **152** was then alkylated with prenyl bromide followed by elimination of sulfur dioxide by heating in toluene. With selenium diene **154** in hand high pressure conditions were used to facilitate the Diels-Alder reaction given there had been no success with thermal or Lewis acid conditions with the earlier silyl ether variant (**Scheme 2.51**).



Scheme 2.51 High pressure Diels-Alder with selenium diene **154**.

High pressure conditions were able to generate the desired Diels-Alder adducts in ratio of 1 : 1.5 with an additional unknown impurity still present. This was a very similar result to that achieved using sulfur diene **140**, however in this case the regioisomers were able to be separated and purified after reduction of the methyl ester and reductive cleavage of the phenylselenyl group. Whilst the regioselectivity of the Diels-Alder reaction had not been reversed, it had certainly been shifted towards the desired methyl *meta* isomer in comparison to pure *E*-ocimene (**31**).

Overall, the directing group strategy was unable to provide the desired methyl *meta* product as the major regioisomer of the Diels-Alder reaction. Under thermal, Lewis acid and high pressure conditions silyloxy dienes **130** and **138** were unreactive, or prone to conversion to their corresponding enone. With respect to sulfur diene **140** the Diels-Alder was able to be achieved under high pressure conditions. However, the methyl *meta* product was still the minor product and there was an additional inseparable

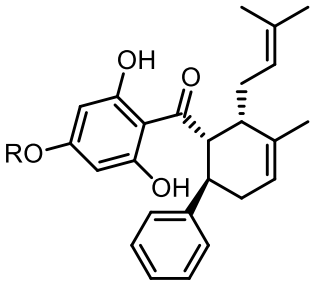
impurity present. Only selenium diene **154** was able to participate in the Diel-Alder reaction, and following reduction of the methyl ester, allow separartion and purification of the two regiosimers from each other. However whilst there was slight improvement in the regioselectivity (now 1:1.5 methyl *meta* : *para*), the additional synthetic steps and low yields did not suggest that this approach using the selenium diene should be incorporated into the panduratin synthetic strategy.

Chapter 1 – Panduratins

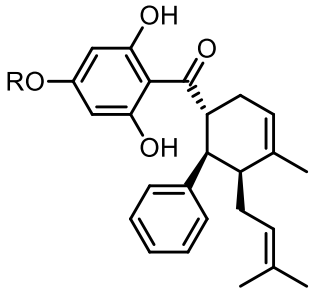
3. Conclusions & Future Work

3. Conclusions and Future Work

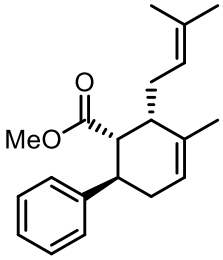
The work reported in this thesis constituted an efficient total synthesis of panduratin A (**8**), 4-hydroxypanduratin A (**9**), nicolaioidesin B (**20**) (isopanduratin A), 4-hydroxyisopanduratin A **(36**), panduratin H (**17**) and panduratin I (**18**).



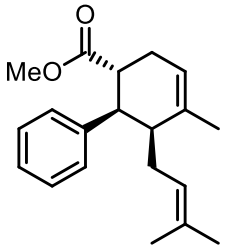
R = Me panduratin A (**8**)
R = H 4-hydroxypanduratin A (**9**)



R = Me nicolaioidesin B (**20**) (isopanduratin A)
R = H 4-hydroxyiso panduratin A (**36**)

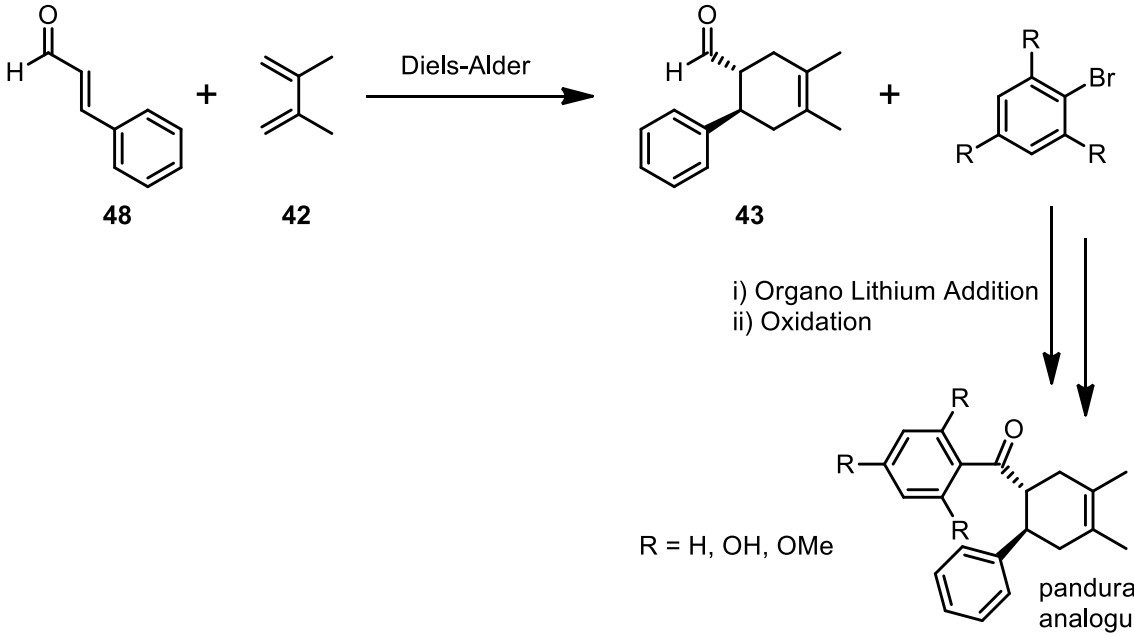


panduratin H (**17**)



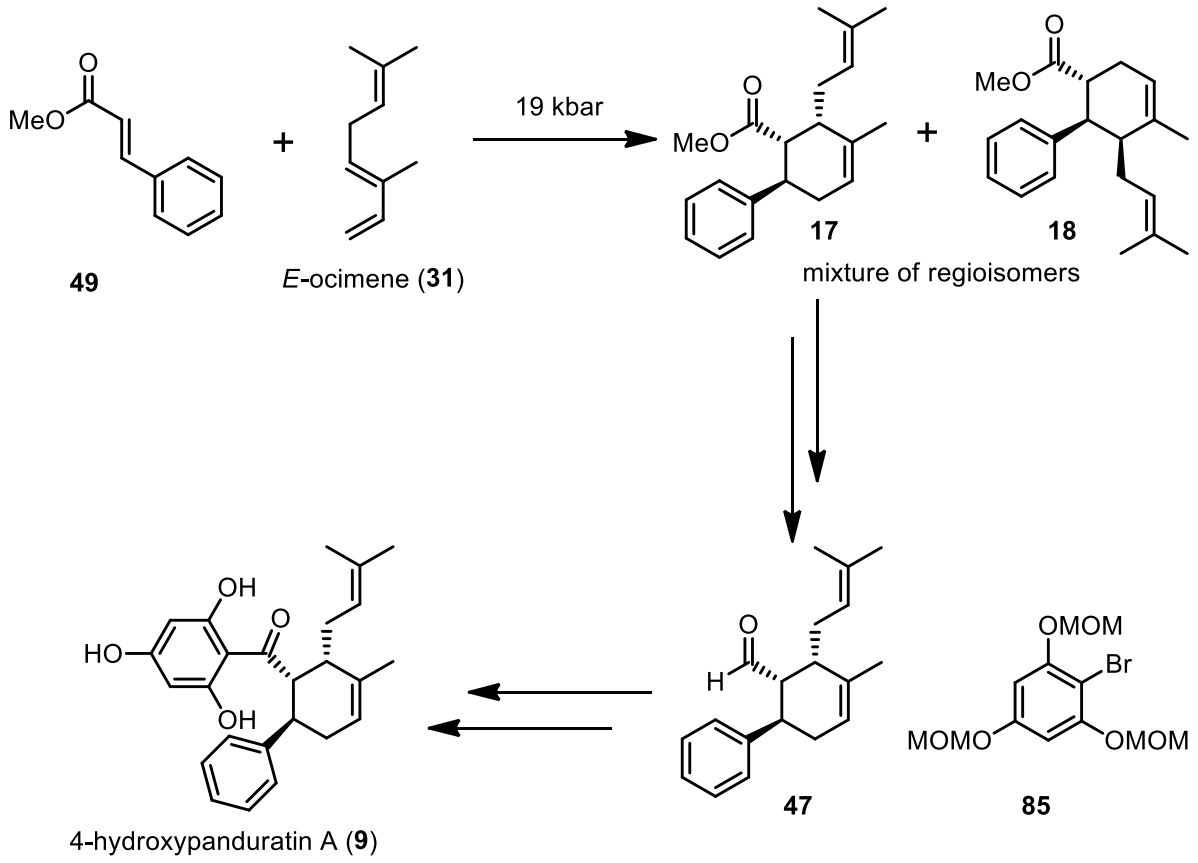
panduratin I (**18**)

The synthesis of the panduratin family members was achieved after first performing a model synthesis to successfully develop the required synthetic methodology. This involved Lewis acid catalysed Diels-Alder reaction between cinnamaldehyde (**48**) and a diene, followed by addition of an organolithium derived from a bromobenzene and oxidation.



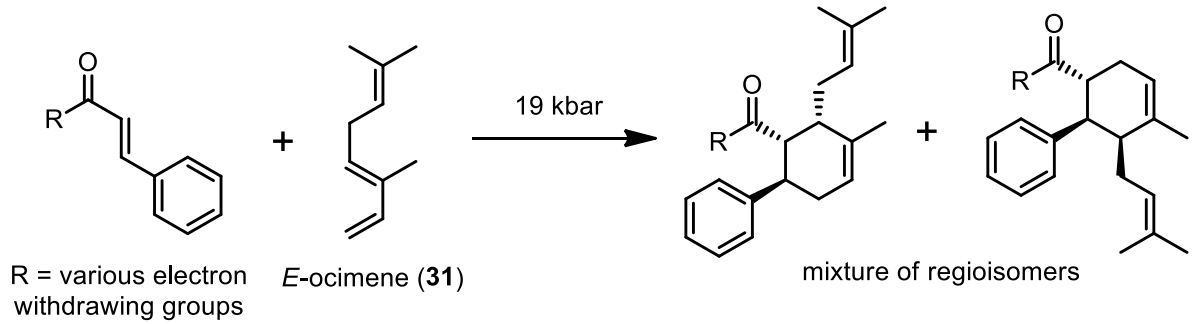
48 **42** **43**

Using this developed synthetic methodology many panduratin analogues as well as several panduratin family members were successfully generated. This included the first reported total synthesis of 4-hydroxypanduratin A (**9**), 4-hydroxyisopanduratin A **(36**), panduratin H (**17**) and panduratin I (**18**). Furthermore, this work constituted the first total synthesis of a pure sample of nicolaioidesin B (**20**) (isopanduratin A).



Some of the panduratin analogues were tested against the DEN-2 protease along with panduratin A (**8**) and 4-hydroxypanduratin A (**9**). However the analogues and tested panduratins A only showed moderate binding the DEN-2 protease and in the case 4-hydroxypaduratin A (**9**) was unable to affect the conformation change of the protease typically observed when a compound is bound in the active site. Furthermore panduratin A (**8**) and 4-hydroxypanduratin A (**9**) exhibited poor aqueous solubility frequently precipitating out of solution. These results suggest that caution should be taken in adopting panduratin A (**8**) and 4-hydroxypanduratin A (**9**) as lead structures for the development of dengue virus NS2B-NS3 protease inhibitors. Future work around the synthesis and development of dengue fever protease inhibitors will likely focus on different lead natural products or small molecules that have exhibited strong binding to the active site.

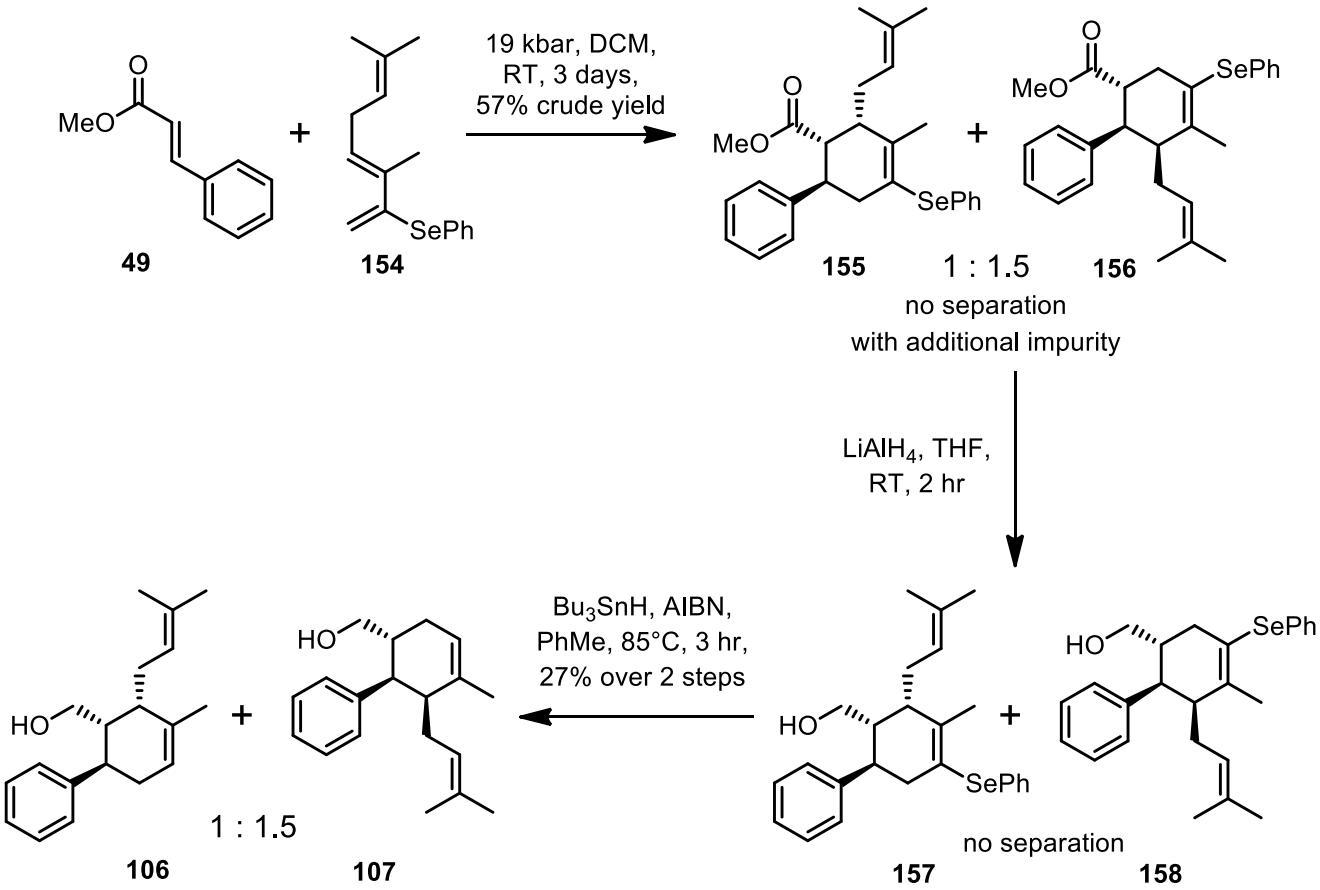
In addition to the synthesis of the panduratin family members and analogues a regioselectivity study of high pressure Diels-Alder reactions between various cinnamates and *E*-ocimene (**31**) was also conducted to elucidate the steric and electronic factors responsible for the regioselectivity.



This study trialled various electronic and steric attributes on a range of dienophiles and *E*-ocimene (**31**) as well as computationally modelling the orbitals and transition states of the reaction. What this study found was found was that,

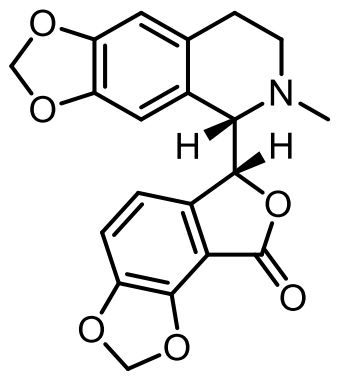
- The C3-methyl group appears to dominate the regioselectivity over the prenyl group with the methyl *para* regioisomers favoured in all examples using *E*-ocimene (**31**). The results confirm that the methyl and prenyl substituents are non-reinforcing.
- The C3-methyl also appears to favour *endo* products over *exo*. In all instances that *E*-ocimene (**31**) is used only *endo* products are observed. However dienes without this C3-methyl seem to lack selectivity in high pressure Diels-Alder reactions.
- The size or strength of the EWG does not allow prediction of the product distribution. Only that methyl *para* products are favoured when using *E*-ocimene (**31**).
- Computational modelling or orbital coefficients and TS volumes indicated that no single factor was responsible for the observed selectivity under high pressure conditions. The closest approximation was that dienophiles that had a C3 2Pz coefficient greater than 0.300, and where TS-B was smaller than TS-A, greatly favoured the methyl *para* product.
- The use of a mixture of *E*/*Z* ocimene in the high pressure Diels-Alder reaction surprisingly shifted the ratio of the regioisomer products towards the methyl *para* product. In particular it was found that the addition of just 10% Z-ocimene (**127**) had a strong effect and shifted the product distribution from greatly favouring the methyl *para* product to almost a 50:50 mixture.

Following this study modified dienes with strong directing groups were synthesised in an attempt to justify the product distribution towards Diels-Alder product where the methyl group was *para* to the electron withdrawing group of the cinnamate. The diene with a selenium directing group was the only one that underwent a Diels-Alder reaction, gave an improved product distribution and was then able to be cleaved. However the overall the additional steps and low yields did not justify incorporating this approach into the panduratin synthesis.



Whilst the overall aim to synthesis panduratin A (**8**) and 4-hydroxypanduratin A (**9**) natural products was successful, a highly selective Diels-Alder reaction was not achieved. Future work will focus on employing the use of *Z*-ocimene (**127**) to justify the product distribution towards the methyl *meta* products. In addition further high pressure reaction with various dienophiles and computational analysis will be used to elucidate how *Z*-ocimene (**127**) is having such a strong influence in the high pressure Diels-Alder reactions.

Chapter 2 – Bicuculline



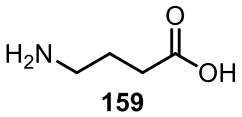
bicuculline

Chapter 2 – Bicuculline

1. Introduction

1.1 GABA Receptors

One of the major inhibitory molecules required for neurotransmitters in the mature vertebrate central nervous system is GABA (gamma-aminobutyric acid) which is an agonist of GABA receptors (**Figure 1.1**).[72-83] This neurotransmitter, is essential for the overall balance between neuronal excitation and inhibition that is vital to normal brain function. If GABA receptors are too active it can lead to coma, depression, low blood pressure, sedation or sleep, while if they are not active enough it can result in a range of conditions including convulsions, anxiety, high blood pressure, restlessness and insomnia.



159

Figure 1.1 GABA.

GABA receptors are ligand-gated chloride ion channels that consist of 5 protein subunits arranged around a central pore. Each of these subunits have large extracellular domains which comprise the binding sites for GABA and other molecules such as benzodiazepines (BZs) which enhance the effect of GABA (**Figure 1.2**). In particular the $GABA_A$ receptor may be comprised of 16 subunits including α1-6, β1-3, γ1-3, δ, ε, π, θ. Ligands of the $GABA_A$ receptor bind at the interface of an α- and an adjacent β- or γ- subunit. For example GABA binds at the α- β- subunit interface while BZ binds at the α- γ- subunit interface.

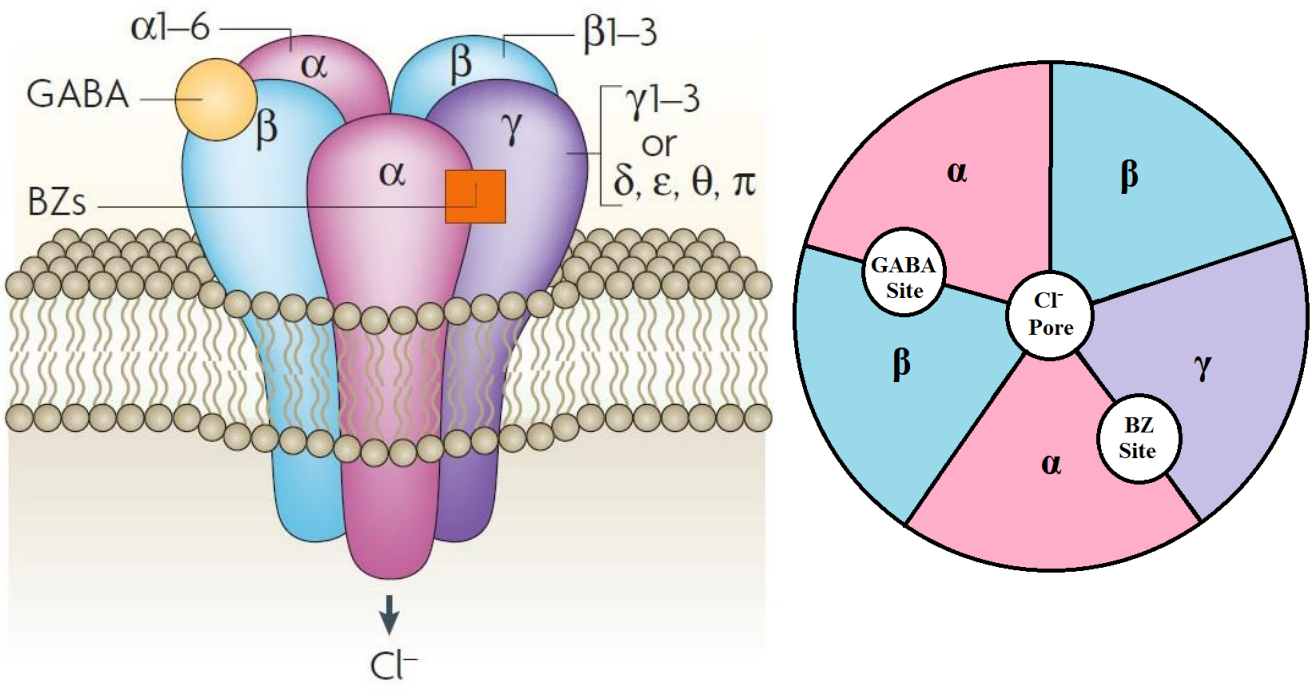


Figure 2.2 Structure of the $GABA_A$ receptor.

Given the range of possible subunits a huge number of $GABA_A$ receptors can potentially be formed, and in some cases more than eight subunit isoforms have been found to be expressed in a single cell. For instance if just the α, β and γ subunits are considered then there are 30 possible pentameric receptors (**Figure 1.3**). The major adult isoform is generally accepted to be composed of α_2, β_2 and γ_1 subunits.

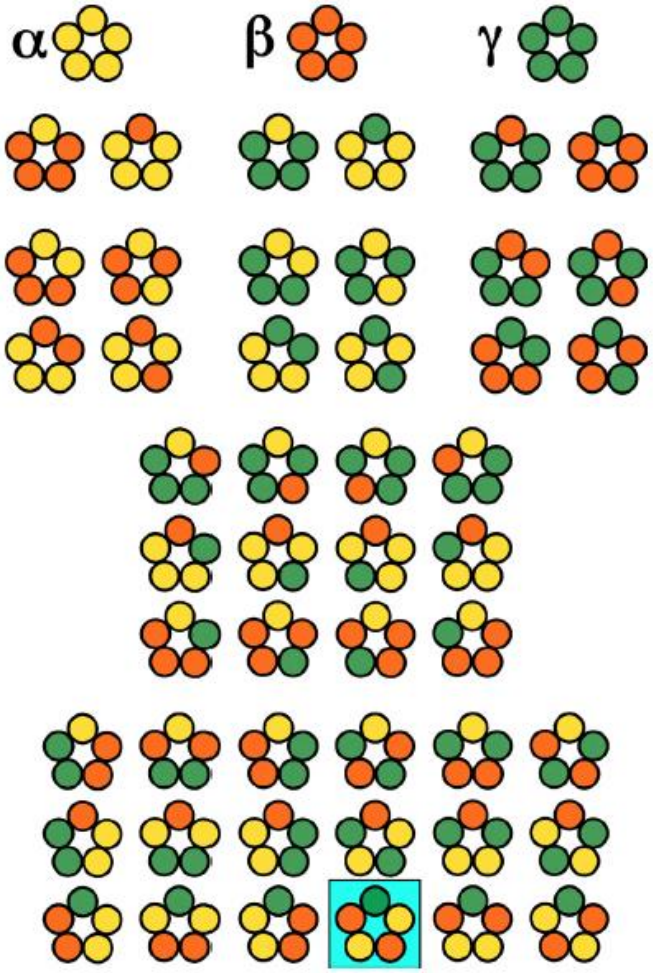


Figure 1.3 Possible arrangements in a pentamer of subunits taken from three different types, α (yellow), β (red) and γ (green). There are three homomeric receptors, 18 receptors composed of two subunits, and 30 receptors composed of three different subunits. The receptor on the blue square represents the current consensus of the subunit arrangement in $\alpha_2\beta_2\gamma_1$ $GABA_A$ receptors as seen from the cell exterior.

When no GABA is bound to the $GABA_A$ receptor it is in a closed conformation and no chloride ions are allowed to flow throw the channel. When two GABA molecules do bind to the receptor it changes in conformation allowing chloride ions to flow through and contribute to the early part of the inhibitory post-synaptic potential (IPSP) (**Figure 1.4**).

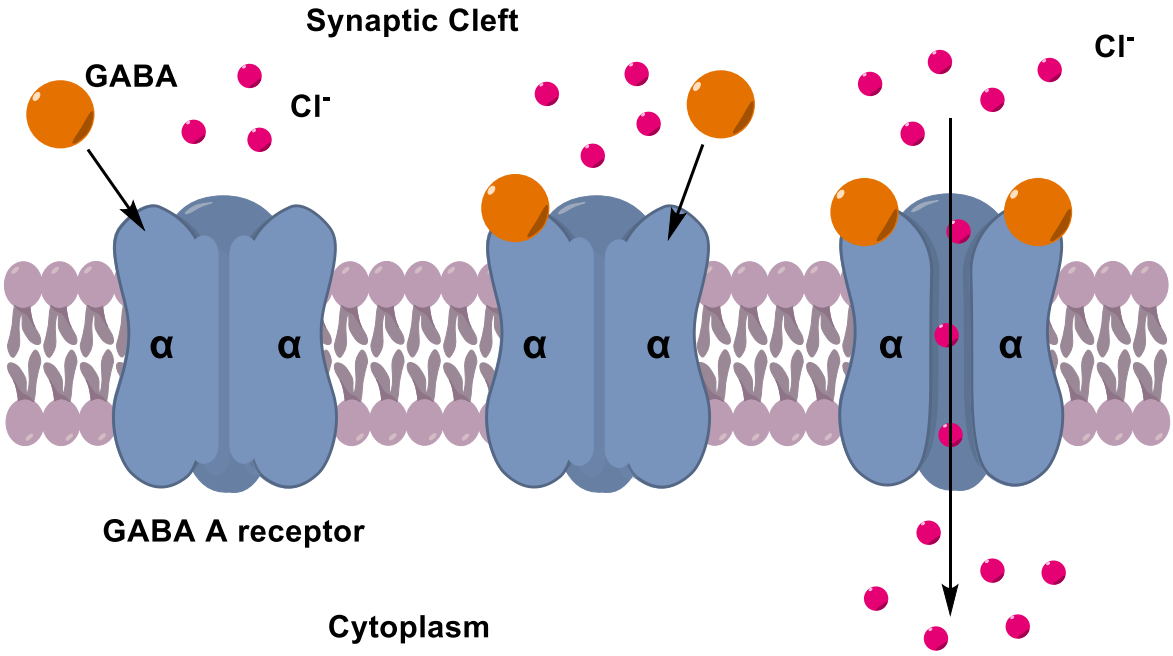


Figure 1.4 GABA binding to the $GABA_A$ receptor.

The IPSP is a synaptic potential that makes neurons less likely to generate an action potential. Typically when a neuron receives an impulse (or is excited (E)) it exceeds threshold and an action potential is generated (spike, **Figure 1.5**). However when the $GABA_A$ receptor is activated and chloride ions follow into the cytoplasm of the neuron the potential is inhibited (I). As a result when the neuron is next excited it does not reach the threshold and thus no action potential is generated.

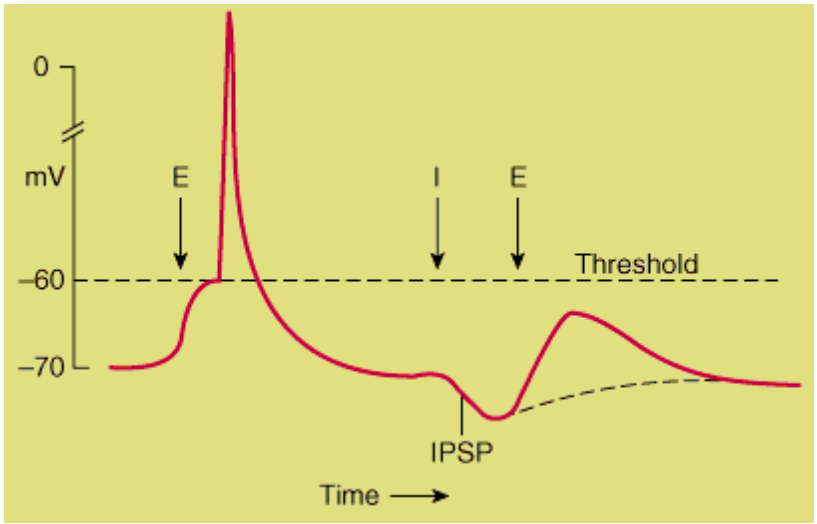


Figure 1.5 Inhibition of a post-synaptic potential. In the above graph E represents and excitation event while I represents inhibition.

Therefore it can be seen that if the $GABA_A$ receptors are over active and allow too much chloride through then neurons will unlikely be able to generate action potential leading to conditions such as coma, depression and others. As such many $GABA_A$ receptor antagonists are being developed as potential therapeutics for $GABA_A$ receptor mediated conditions (**Figure 1.6**).[78, 79]

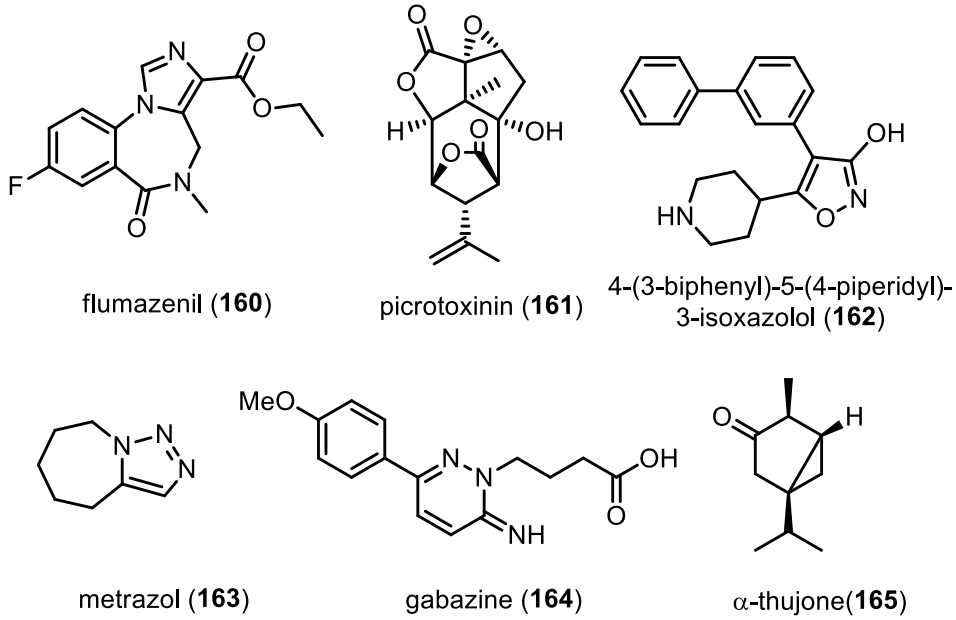


Figure 1.6 Known $GABA_A$ antagonists.

1.2 Phthalideisoquinoline Alkaloids

The phthalideisoquinoline alkaloids are a family of compounds of which many inhibit the $GABA_A$ receptor.[84, 85] This family may be divided in two broad groups including the classical phthalideisoquinolines possessing an intact tetracyclic skeleton such as bicuculline (**166**) and the secophthalideisoquinolines where the B ring has been cleaved to afford a dimethylamino side chain such as aobamidine (**167**) (**Figure 1.7**).

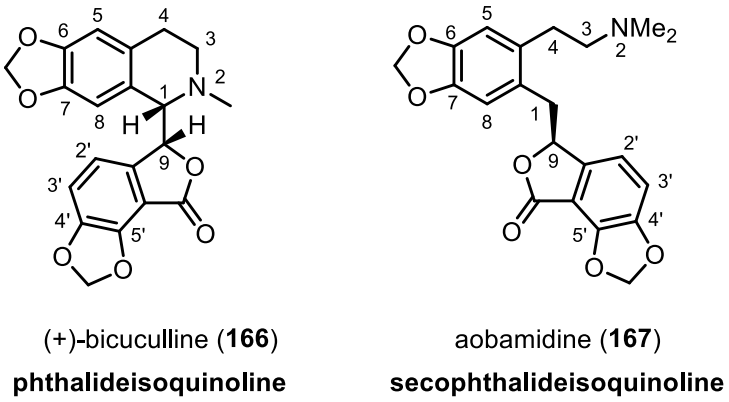
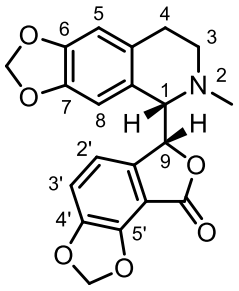
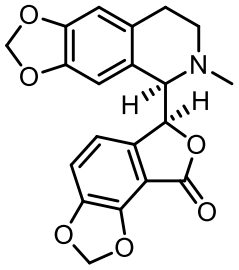


Figure 1.7 Phthalideisoquinoline and secophthalideisoquinoline structures.

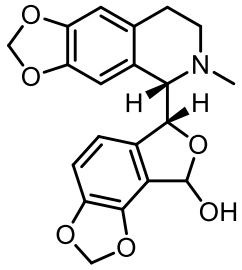
Further members of the phthalideisoquinoline family are shown in **Figure 1.8**. These members mainly differ in the presence/number of methylenedioxy, methoxy and hydroxyl groups on the phenyl rings as well as the absolute stereochemistry across the phthalideisoquinoline bridge.



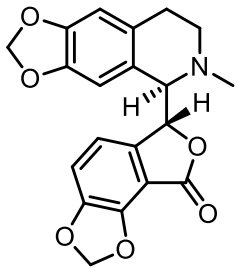
(+)-bicuculline (**1S9R-166**)



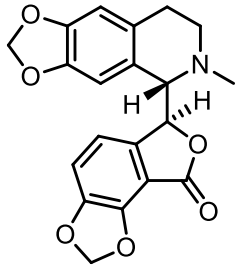
(-)-bicuculline (**1R9S-166**)



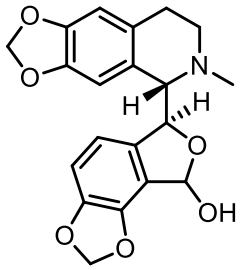
(+)-egenine (**168**)



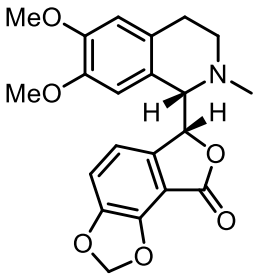
(-)-capnoidine (**169**)



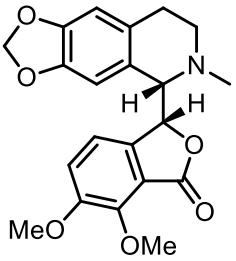
(+)-adlumidine (**170**)



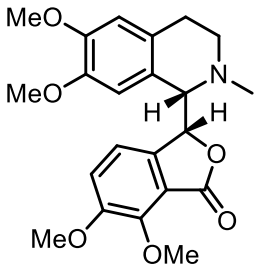
(+)-corytensine (**171**)



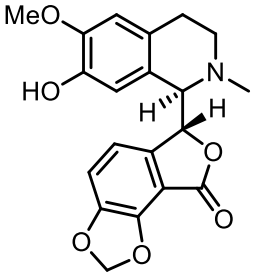
(+)-corlumine (**172**)



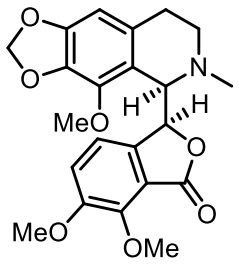
(+)-hydrastine (**173**)



(+)-cordrastine (**174**)



(-)-severtzine (**175**)



(-)-narcotine (**176**)
(noscapine)

Figure 1.8 Phthalideisoquinoline family members.

Of particular interest in this phthalideisoquinolines family is (+)-bicuculline (**166**) which was isolated from *Dicentra cucullaria* in 1932.[86] Bicuculline (**166**) is known to be a competitive antagonist at $GABA_A$ receptors and has been used to probe GABA mediated synaptic inhibition.[87] Studies have shown bicuculline (**166**) to act as a competitive antagonist that binds at the orthosteric site resulting in stabilisation of the receptor in a closed state. Below **Figure 1.9** shows bicuculline along with some structure activity relationships that are presently known.

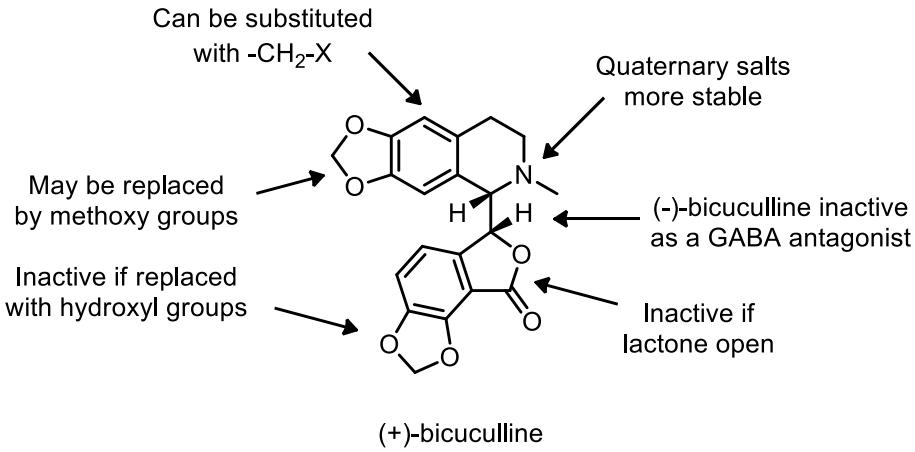
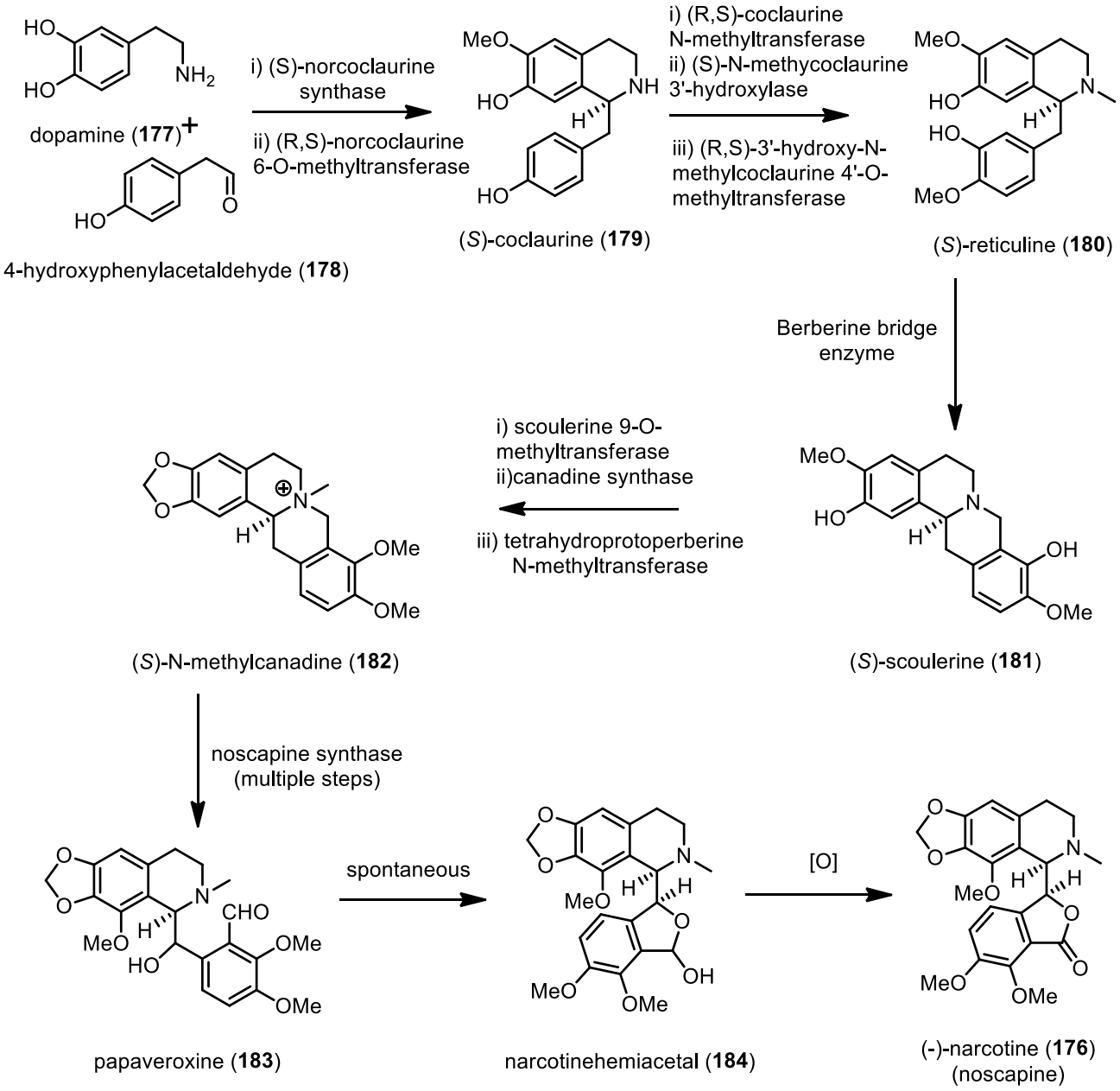


Figure 1.9 Summary of bicuculline structure features that contribute to the GABA receptor antagonist properties.

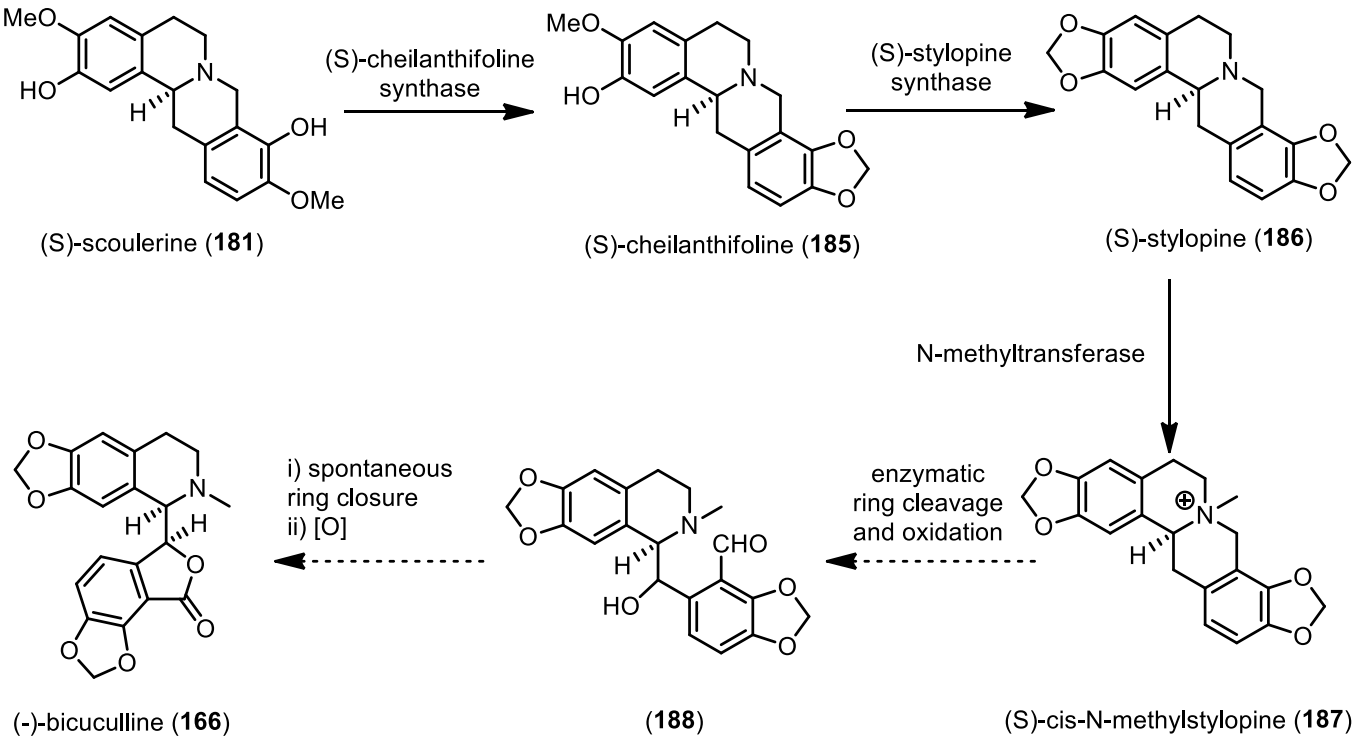
Given bicuculline is a selective inhibitor of $GABA_A$ receptors it is a desirable target to develop synthetic pathways towards in order to generate further analogues which may be useful in treating a wide range of GABA mediated conditions such as convulsions, anxiety, schizophrenia and others. Furthermore given the diversity in receptor subunits there is a great need to develop selective antagonists capable of binding to particular GABA subtypes.

At present the biosynthesis of bicuculline (**166**) is unknown, however the biosynthetic pathway of a related compound (-)-narcotine (**176**) has been determined (**Scheme 1.1**).[88, 89] To begin with, dopamine (**177**) and 4-hydroxyphenylacetaldehyde (**178**) are condensed to form the required isoquinoline ring followed by oxidation and methylation to arrive at *(S)*-reticuline (**180**). The berberine bridge enzyme then generates a further isoquinoline ring to form *(S)*-scoulerine (**181**). Methylation and methylene dioxy bridge formation is then followed by a ring cleavage to afford papaveroxine (**183**) which then under goes spontaneous ring closure and oxidation to arrive at (-)-narcotine (**176**).



Scheme 1.1 (-)-narcotine (**176**) biosynthesis.

Given (-)-narcotine (**176**) differs from (-)-bicuculline (**166**) simply in a methoxy substitution of the A ring and a methylene dioxy bridge on the D ring, it is proposed that the biosynthesis of (-)-bicuculline (**166**) proceeds through another known pathway before the lactone ring is formed. Specifically it is proposed that methylene dioxy bridges are formed on *(S)*-scoulerine (**181**) by *(S)*-cheilanthifoline (**185**) synthase and *(S)*-stylopine (**186**) synthase followed by methylation to form *(S)*-cis-*N*-methylstylopine (**187**) (**Scheme 1.2**). Subsequent enzymatic ring cleavage and stereoselective oxidation to form the reactive aldehyde group in compound **118** would then result in spontaneous ring closure which after oxidation would generate (-)-bicuculline (**166**).



Scheme 1.2 Proposed biosynthesis of bicuculline from scoulerine (**181**).

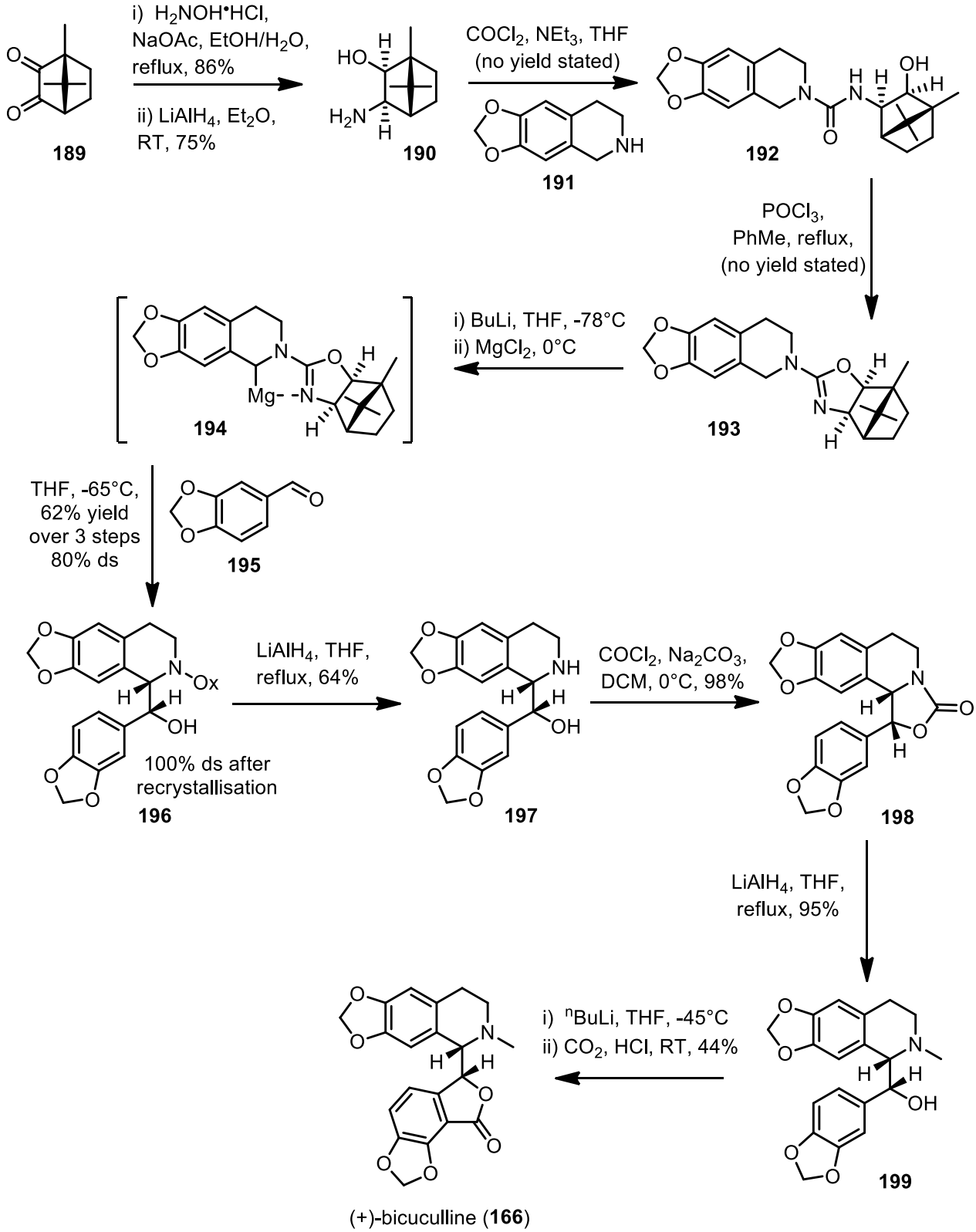
1.3 Previous Syntheses of Bicuculline

At the time of writing there were six reported synthesises of bicuculline (**166**) that have adopted many different synthetic strategies.[90-95] Two example synthesises are those successfully completed by Gawley and Santos.

1.3.1 Gawley Synthesis

In 1990 Gawley and co-workers reported the synthesis of many phthalideisoquinolines, including bicuculline, by exploiting the asymmetric addition of chiral dipole-stabilised organometallics to benzaldehydes (**Scheme 1.3**).[93, 96, 97] Their synthesis begun with dione **189** which after oxime formation and reduction afforded chiral auxiliary **190**. This was followed by reaction with amine **191**, phosgene and subsequent cyclisation to form chiral oxazoline **192**. At this point Gawley and co-workers used their previously developed conditions to convert chiral oxazoline **194** to its Grignard derivative. This reacted with piperonal (**195**) to form isoquinoline adduct **196** in a yield of 62% and with 80% diastereoselectivity. Subsequent reduction with lithium aluminium hydride to remove the chiral auxiliary was followed by reaction with phosgene to form oxazolidinone **198**. Further reduction, directed metalation with butyl lithium and reaction with carbon dioxide formed the required lactone to arrive at (+)-bicuculline (**166**). Overall the Gawley synthesis consisted of 9 steps and achieved good

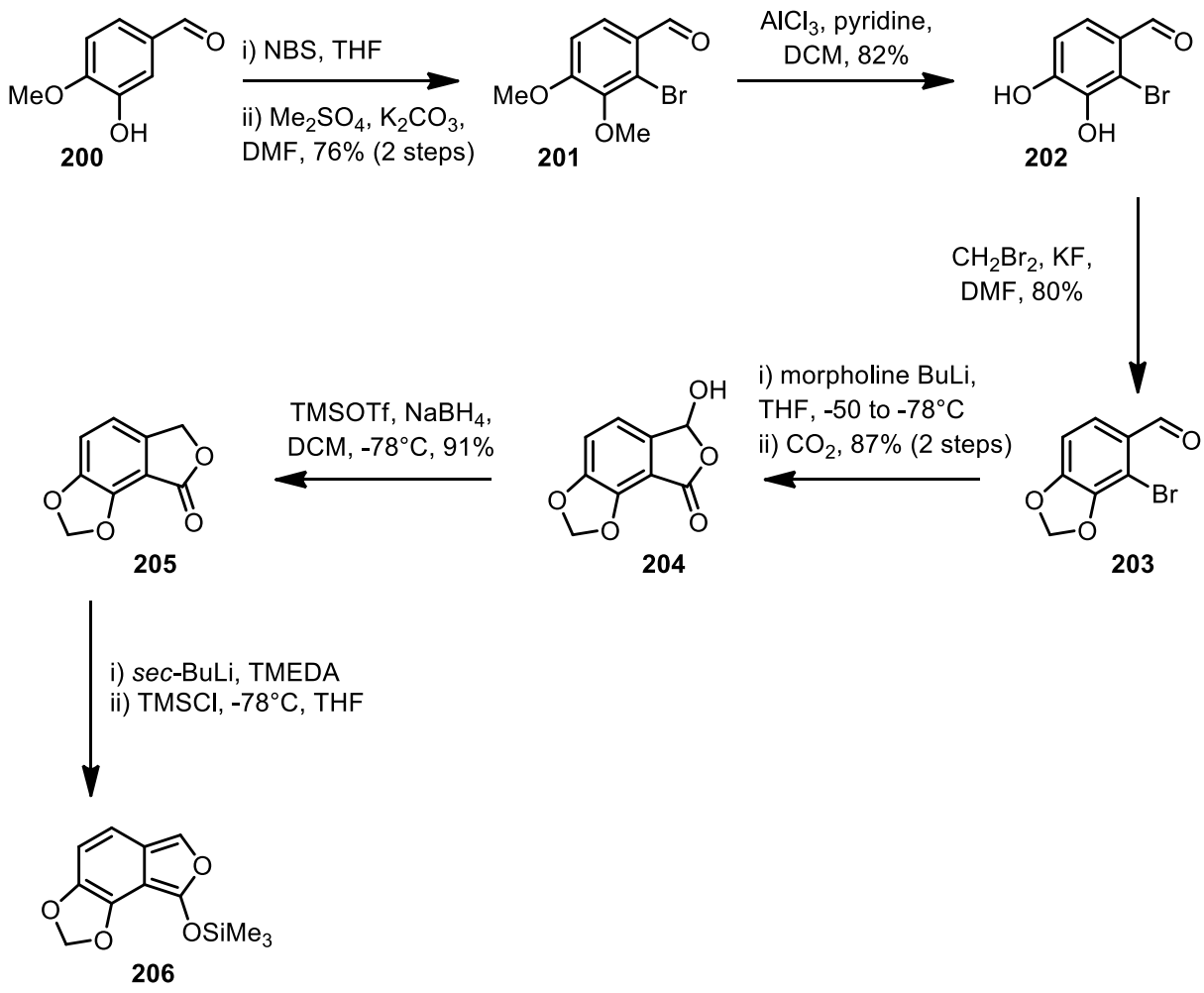
diastereoselectivity with reasonable yields. However this synthesis did require stoichiometric amounts of chiral auxiliaries from the very start, and two steps required the use of highly toxic phosgene.



Scheme 1.3 Gawley synthesis of bicuculline (**166**).

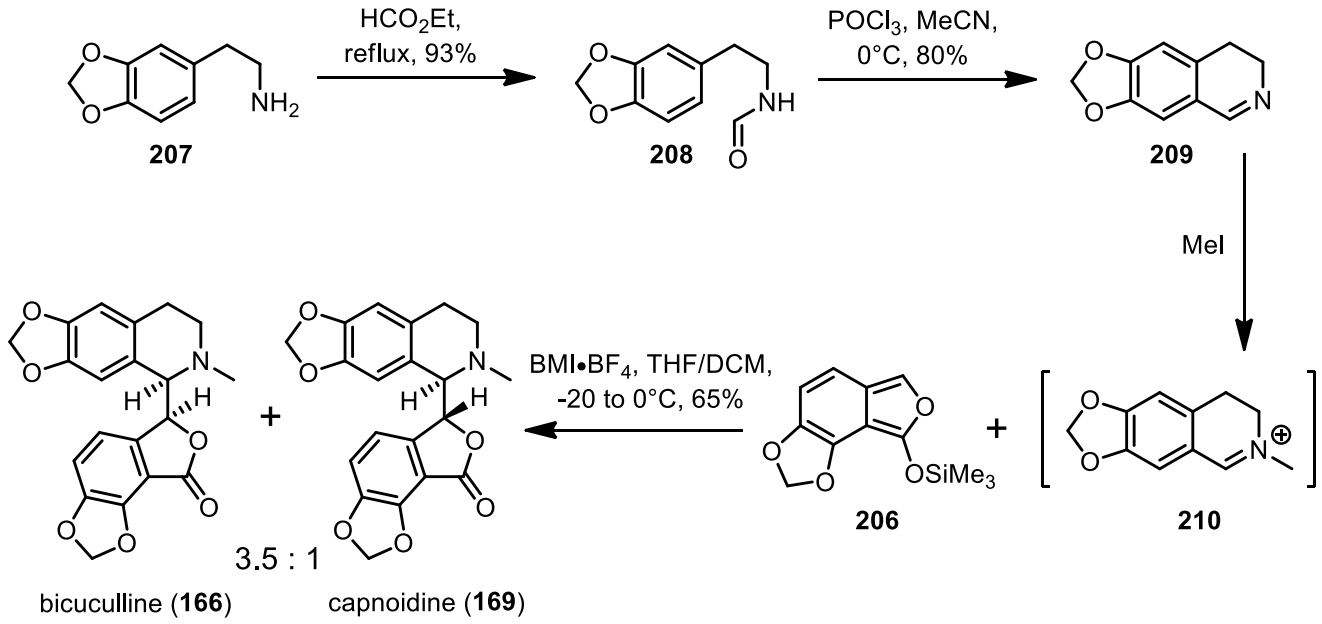
1.3.2 Santos Synthesis

In 2010 Santos and co-workers reported a diastereoselective strategy for the synthesis of noscapine (**176**), bicuculline (**166**), egenine (**168**), capnoidine (**169**) and corytensine (**171**).[90] This approach used the addition of a 1-silyloxy-isobenzofuran to an iminium ion. Starting from isovanillin exposure to NBS and ensuing methylation using dimethylsulfate afforded bromobenzaldehyde **201** in a yield of 76% (**Scheme 1.4**). Aluminium trichloride was then used to demethylate and expose the free phenols which were in turn reacted with dibromomethane to form the methylenedioxy ring. With bromoaldehyde **203** in hand lithium morpholide and n-butyllithium was used to produce an *ortho*-lithiated intermediate which was in turn reacted with dry ice to furnish hydroxy lactone **204**. Next, exposure to TMSOTf gave the resulting oxonium ion which was reduced with sodium borohydride in a yield of 91%. Finally to the resulting lactone was added sec-BuLi and TMEDA followed by trimethylsilyl chloride to afford the required silyloxy-isobenzofuran **206** which was unstable and thus was used without further purification.



Scheme 1.4 Santos synthesis of bicuculline (**166**).

With 1-silyloxy-isobenzofuran **206** in hand the required iminium ion was synthesised in 4 steps from 3,4-methylenedioxy-phenethylamine (**207**) (**Scheme 1.5**). Firstly, 3,4-methylenedioxy-phenethylamine (**207**) was reacted with ethyl formate to produce formamide **208** in a yield of 93%. Then through a Bischler-Napieralski cyclization using phosphoryl chloride in acetonitrile and ensuing exposure to methyl iodide imine **210** was successfully generated. With both intermediates synthesised the addition of silyloxy-isobenzofuran **206** to iminium **210** was performed using 1-methyl-3-butylimidazolium tetrafluoroborate (BMI•BF_4) in tetrahydrofuran/dichloromethane to afford bicuculline (**166**) and capnoidine (**169**) in ratio of 3.5:1 and a yield of 65%.



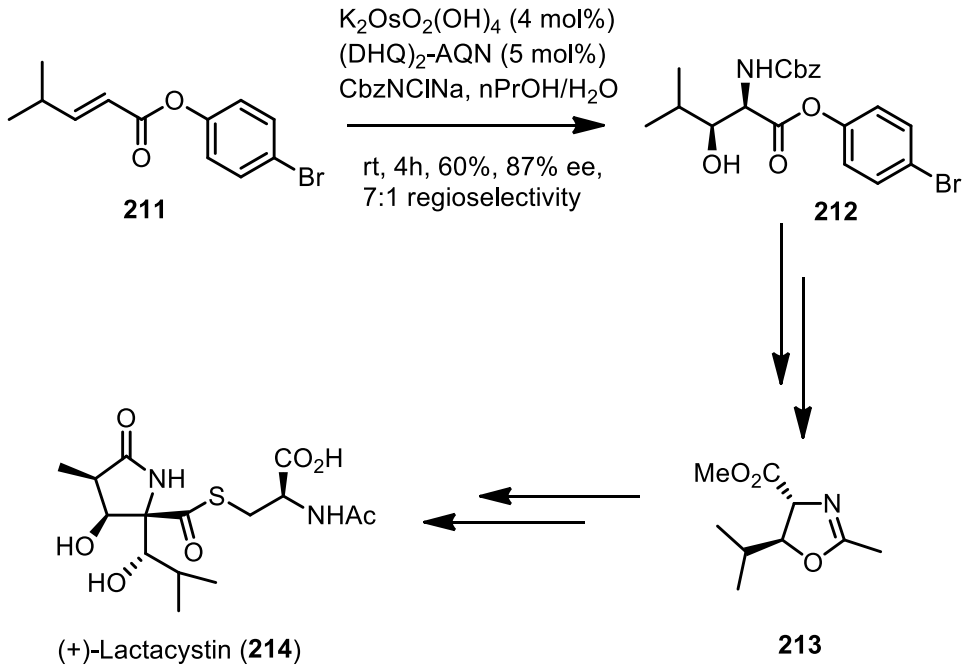
Scheme 1.5 Santos synthesis of bicuculline (**166**) continued.

It is important to note that it was found through model studies that an additive such as BMI•BF_4 or caesium fluoride was required to improve the diastereoselectivity as without them poor selectivity's of 1.1-1.4 : 1 was achieved. Thus Santos was able to prepare racemic bicuculline (**166**) and capnoidine (**169**) (3.5:1) in 7 steps with an overall yield of 26%.

1.4 Retrosynthetic Approaches

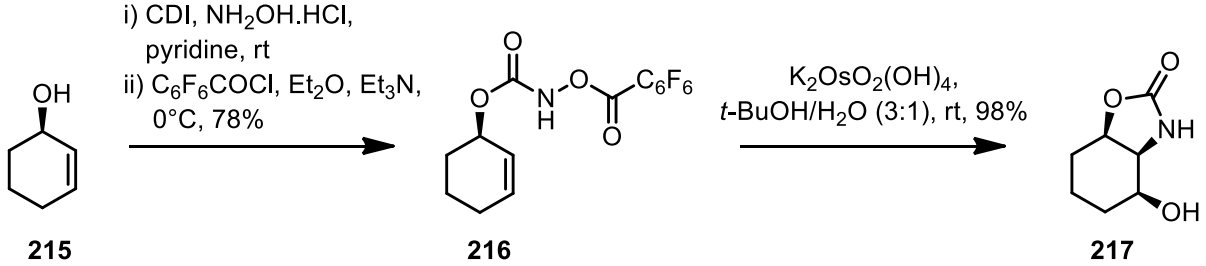
1.4.1 Intramolecular Aminohydroxylation Retrosynthetic Approach

The Sharpless aminohydroxylation is a reaction that allows the sy*n*-selective addition to prepare 1,2-amino alcohols from alkenes using the salts of *N*-halo-sulfonamides, -amides and -carbamates in conjunction with an OsO_4 as a catalyst. This reaction has been used extensively in natural product synthesis to construct heterocyclic rings such as in the Panek synthesis of (+)-lactacystin (**214**) (**Scheme 1.6**).[98]



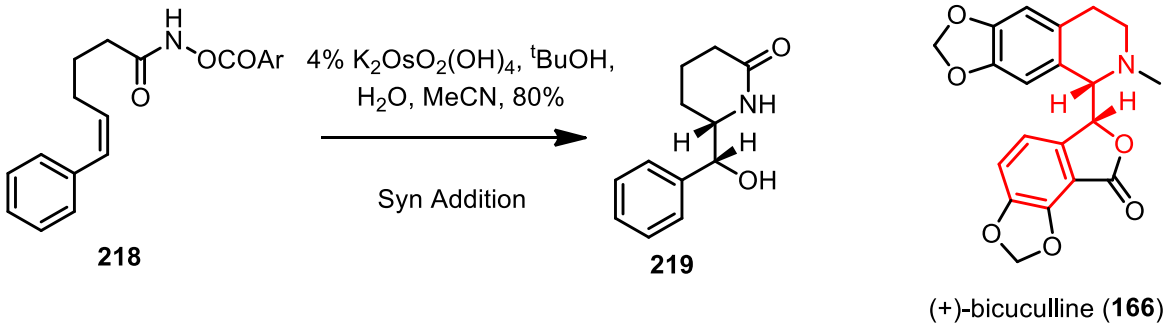
Scheme 1.6 Panek synthesis of (+)-lactacystin (**214**)

In 2007 Donohoe and co-workers reported improved reaction conditions for tethered aminohydroxylation reactions extending its scope to substrates containing an allylic alcohol (**Scheme 1.7**).[99, 100] This approach allowed the regioselectivity to be controlled during the aminohydroxylation of unsymmetrical alkenes.



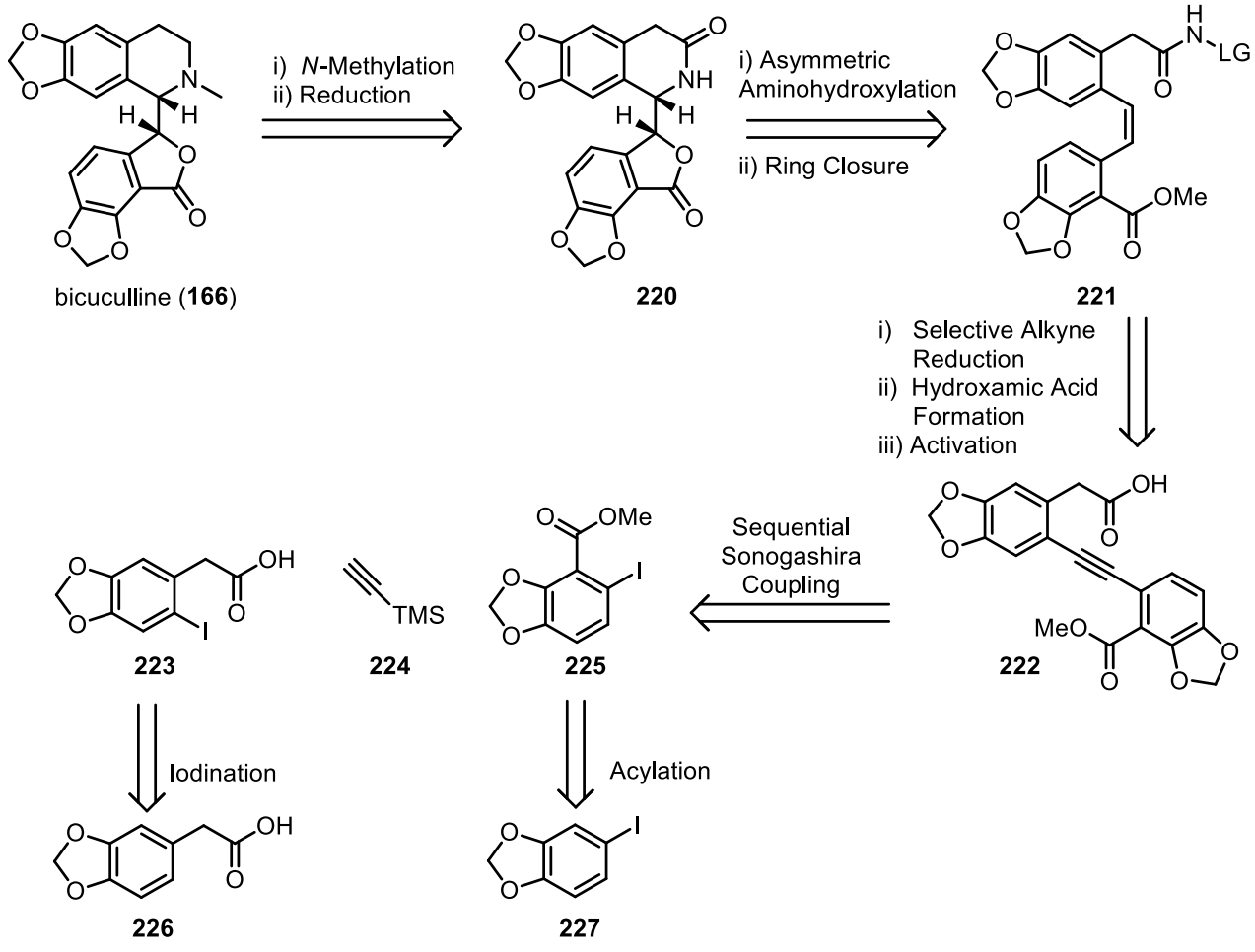
Scheme 1.7 Tethered Aminohydroxylation by Donohoe.

Furthermore Donohoe showed that this chemistry could be employed to generate six membered lactams (**Scheme 1.8**). We recognised that these tethered aminohydroxylation reactions on an appropriately functionalised *Z*-alkene could be employed to generate the core of bicuculline (**166**) with good regioselectivity. Furthermore, it may also be possible to use chiral ligands to control the enantioselectivity of the reaction.



Scheme 1.8 Lactam formation by tethered aminohydroxylation.

As a result, a retrosynthetic analysis was undertaken that encompassed the late formation of the isoquinoline ring and lactone by using a tethered aminohydroxylation reaction with a *Z*-alkene and subsequent methylation and oxidation (**Scheme 1.9**).

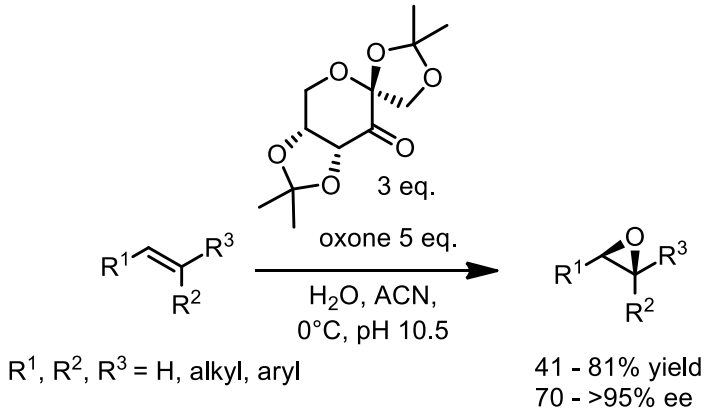


Scheme 1.9 Intramolecular aminohydroxylation retrosynthetic approach.

The tethered aminohydroxylation substrate **221** would be synthesised by selective reduction of alkyne **222** followed by conversion of the carboxylic acid to the hydroxamic acid followed by acylation. This would be preceded by a Sonogashira coupling between aryl iodides **223** and **225** with trimethylsilylacetylene. Aryl iodides **223** and **225** would be synthesised from carboxylic acid **226** and aryl iodide **227** respectively. The advantages of this proposed strategy are that it is a convergent synthesis that would allow the generation of a wide range of bicuculline analogues by employing different aryl iodides prior to Sonogashira coupling. Furthermore different dihydroquinidine-derived chiral ligands have the potential to control enantioselectivity in the late stage tethered aminohydroxylation reaction to access both enantiomers of bicuculline and its analogues.

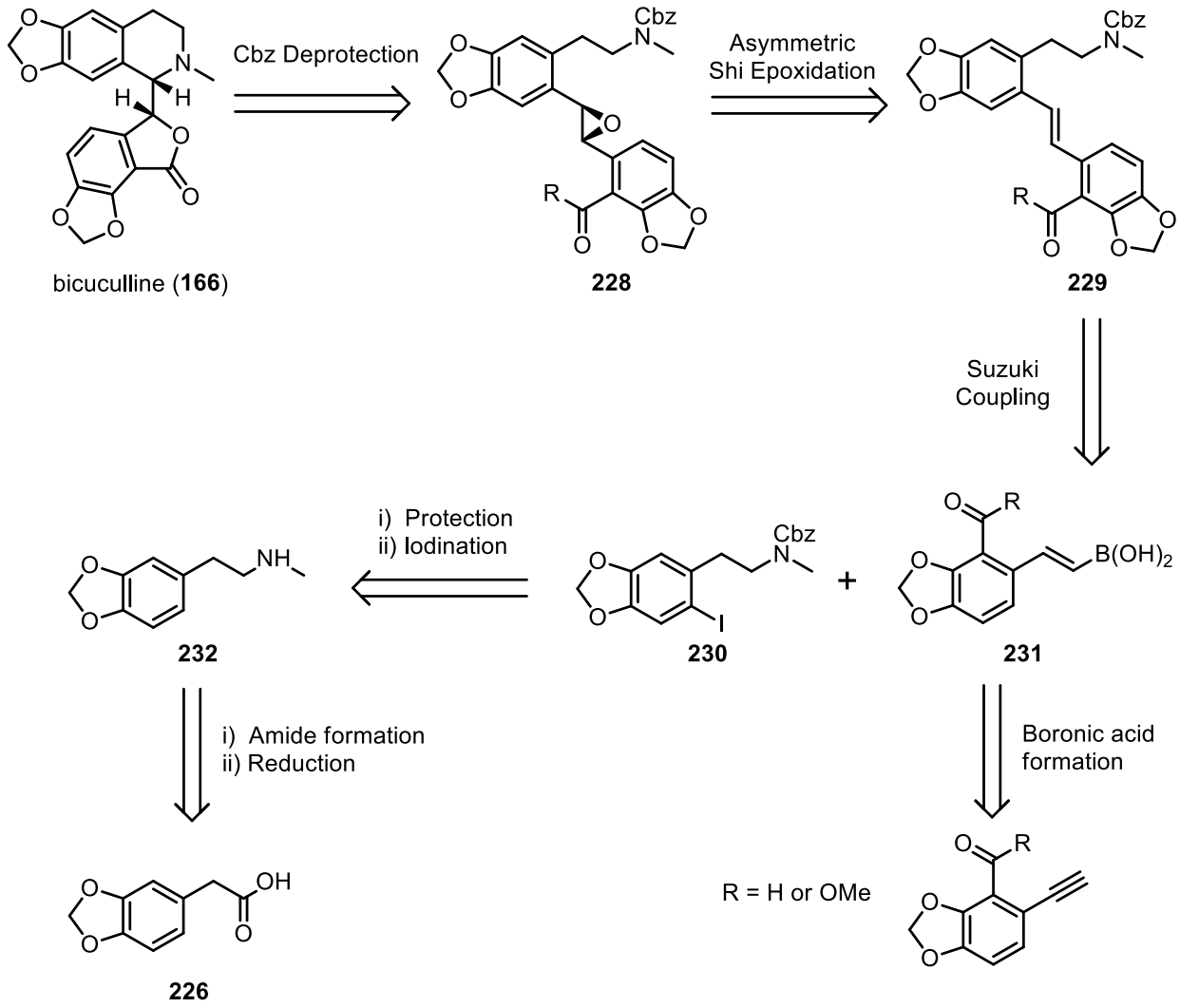
1.4.2 Epoxidation Retrosynthesis

The Shi epoxidation is an effective asymmetric epoxidation reaction that affords good yields and high enantioselectivity (**Scheme 1.10**).[101] This reaction employs a cheap and readily available D-fructose derived ketone catalyst that works with a wide range of substrates.



Scheme 2.10 Asymmetric Shi epoxidation.

It was envisaged the Shi epoxidation could also be used to generate the appropriate bridge stereochemistry of bicuculline (**166**) from a *trans* alkene. Asymmetric epoxidation of *trans* alkene **229** would provide epoxide **228** which after deprotection could be cyclised to afford bicuculline (**166**) (Scheme **1.11**). The required *trans* alkene **229** could be formed through a Suzuki coupling between aryl iodide **230** and boronic acid **231**. Aryl iodide **230** could be synthesised from homopiperonylic acid (**226**) through amide formation, reduction, protection and iodination while boronic acid **231** could be formed from the previously synthesised aryl alkyne.



Scheme 2.11 Asymmetric Shi epoxidation retrosynthetic approach

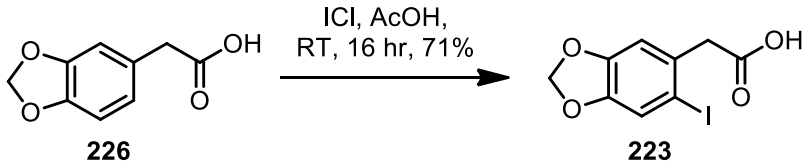
This approach would once again be a convergent synthesis that would allow the generation of a wide range of bicuculline analogues including their enantiomers by selecting the appropriate Shi catalyst.

Chapter 2 – Bicuculline

2. Results and Discussion

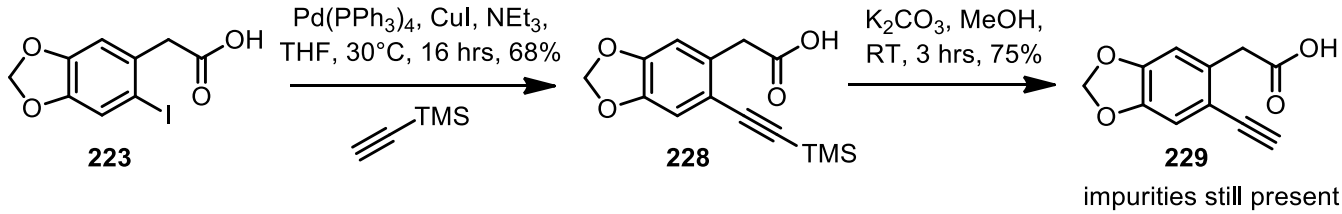
2.1 Aminohydroxylation Approach

Initially work on the aminohydroxylation synthesis of bicuculline (**166**) started by preparing the required coupling partners for the Sonogashira reaction. This began by taking homopiperonylic acid (**226**) and iodinating it with iodine monochloride in the presence of acetic acid to afford aryl iodide **223** in a yield of 71% (**Scheme 2.1**).[102, 103]



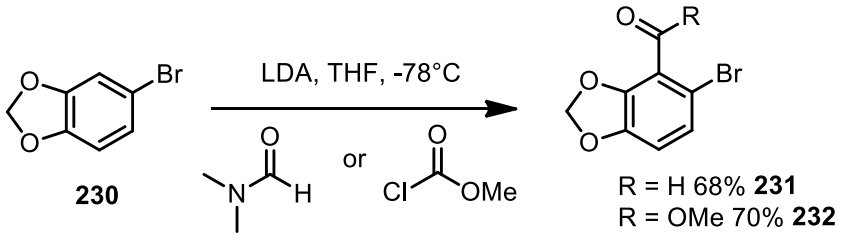
Scheme 2.1 Iodination of homopiperonylic acid (**226**).

With aryl iodide **223** in hand it was then coupled to trimethylsilylacetylene followed by removal of the trimethylsilyl group using potassium carbonate in methanol to arrive at alkyne **229** (**Scheme 2.2**). However despite attempts to purify alkyne **229** by flash chromatography and recrystallisation, impurities were still present in the samples.



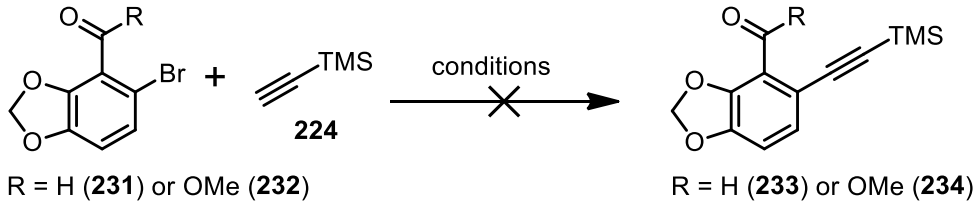
Scheme 2.2 Coupling of acetylene to aryl iodide **223**.

Given that purifying alkyne **229** had proved to be difficult it was decided to instead first couple trimethylsilylacetylene to the other coupling partner. Efforts towards this began by using LDA to ortho lithiate 5-bromo-1,3-benzodioxole (**230**) followed by reaction with either DMF or methyl chloroformate to arrive at aryl bromides **231** and **232** (**Scheme 2.3**).[104]



Scheme 2.3 Synthesis of aryl bromides **231** and **232**.

Having synthesised aryl bromides **231** and **232** Sonogashira coupling with trimethylsilylacetylene was then attempted under standard conditions, however these aryl bromides proved to be unreactive with the starting material reclaimed (**Scheme 2.4** & **Table 2.1**).[105-108]

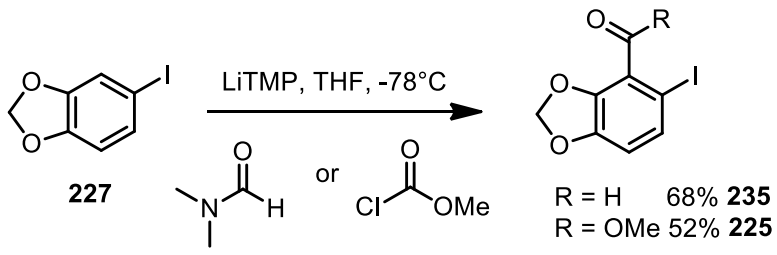


Scheme 2.4 Attempted coupling with trimethylsilylacetylene.

Conditions	Result
$Pd(PPh_3)_2Cl_2$, CuI (0.05 eq), TEA, THF, RT, 16 hrs	no reaction
$Pd(PPh_3)_2Cl_2$, CuI (0.05 eq), TEA, THF, 50°C, 16 hrs	no reaction
$Pd(PPh_3)_4$, CuI (0.1 eq), TEA, THF, RT, 16 hrs	no reaction
$Pd(PPh_3)_4$, CuI (0.1 eq), TEA, THF, 50°C, 16 hrs	no reaction

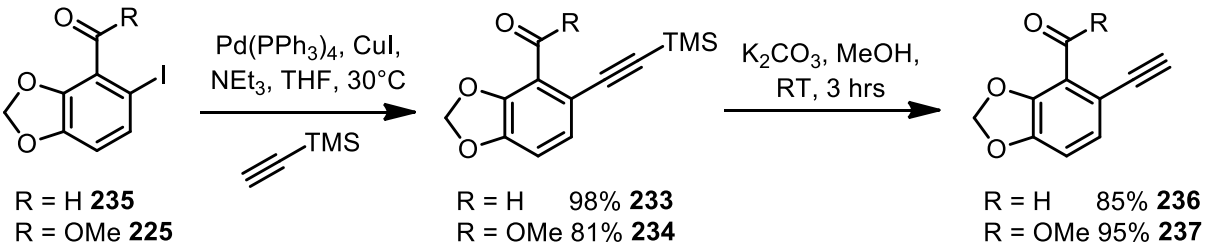
Table 2.1 Attempted coupling with trimethylsilylacetylene.

Rather than persisting and trying to find more reactive conditions it was decided to instead prepare the equivalent aryl iodides which are known to be more reactive in coupling reactions. Therefore, in a similar manner, 5-iodo-1,3-benzodioxole (**227**) was reacted with LiTMP followed by DMF or methyl chloroformate to afford aryl iodides **235** and **225** (**Scheme 2.5**).



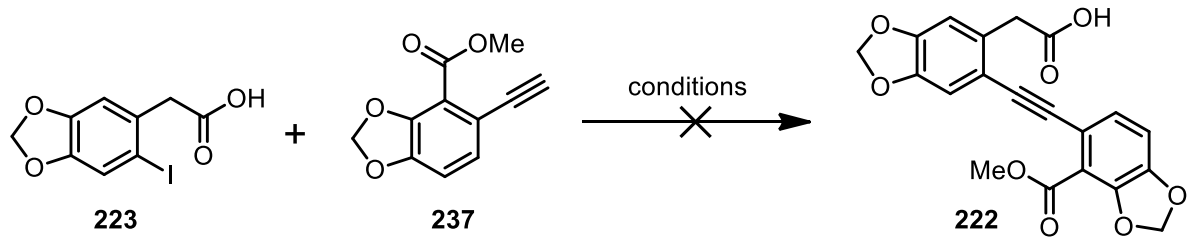
Scheme 2.5 Synthesis of aryl iodides **235** and **225**.

Having now synthesised aryl iodides **235** and **225** the coupling with trimethylsilylacetylene was attempted once again. This time the couplings proceeded readily affording TMS alkynes **233** and **234** in high yields of 98% and 81% respectively (**Scheme 2.6**). The TMS groups were then subsequently removed with potassium carbonate in methanol to arrive at aryl alkynes **236** and **237** in high yields once again.



Scheme 2.6 Coupling of acetylene to aryl iodides **235** and **225**.

With the required coupling partners in hand the second Sonogashira coupling was now attempted. It was first trialled with aryl alkyne **237** and aryl iodide **223** under standard coupling conditions, however no product was observed to form (**Scheme 2.7** & **Table 2.2**).

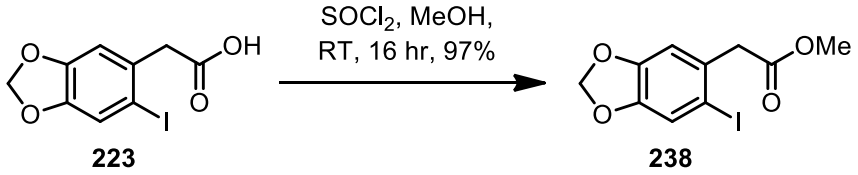


Scheme 2.7 Attempted coupling between aryl iodide **223** and alkyne **237**.

Conditions	Result
$Pd(PPh_3)_4$, CuI (0.1 eq), TEA, THF, RT, 16 hrs	no reaction
$Pd(PPh_3)_4$, CuI (0.1 eq), TEA, THF, 30°C, 16 hrs	no reaction
$Pd(PPh_3)_4$, CuI (0.1 eq), TEA, THF, DMF, 50°C, 16 hrs	no reaction

Table 2.2 Attempted coupling between aryl iodide **223** and alkyne **237**.

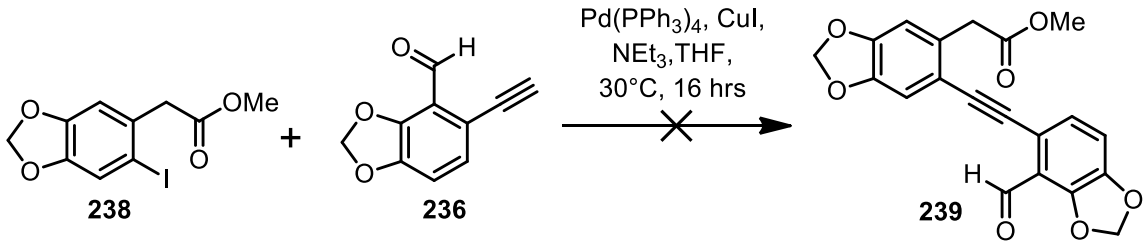
It was speculated that the carboxylic group of aryl iodide **223** may be sequestering the palladium catalyst and preventing it from entering the required catalytic cycle. To circumvent this issue it was decided to try protecting the carboxylic acid either as a benzyl or methyl ester. Consequently aryl iodide **223** was reacted with thionyl chloride and methanol to afford the corresponding methyl ester in a high yield of 97% (**Scheme 2.8**).



223 **238**

Scheme 2.8 Synthesis of methyl ester protected aryl iodide **223**.

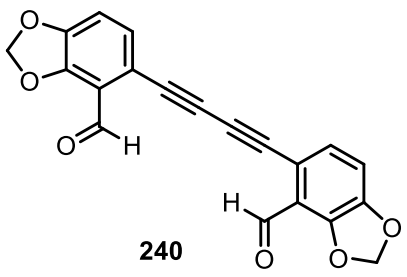
Having now protected the carboxylic acid group the Sonogashira reaction was once again attempted using aryl alkyne **236** as it was considered to be the most reactive given the presence of the aldehyde group (**Scheme 2.9**). Unfortunately using the previous standard coupling conditions no product was observed to form.



238 **236** **239**

Scheme 2.9 Attempted coupling between aryl iodide **238** and alkyne **236**.

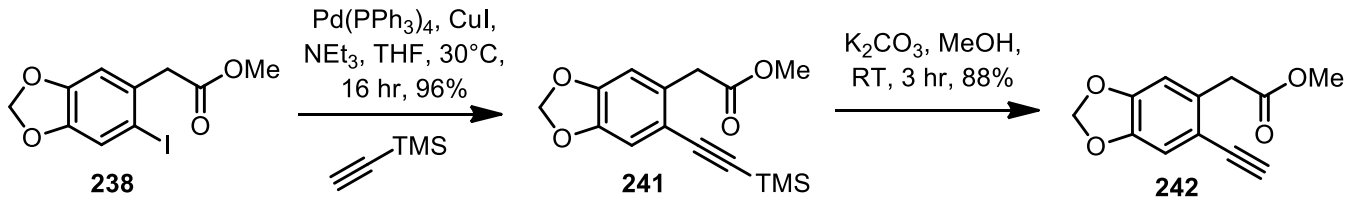
However it was noted from TLC sampling of the reaction that much of the aryl alkyne **236** starting material had been consumed and upon closer inspection of the reaction mixture with high resolution mass spectroscopy, a strong peak at *m/z* 346.0475 was found which was suspected to be a dimer produced through a Glaser coupling side reaction (**Figure 2.1**).



240

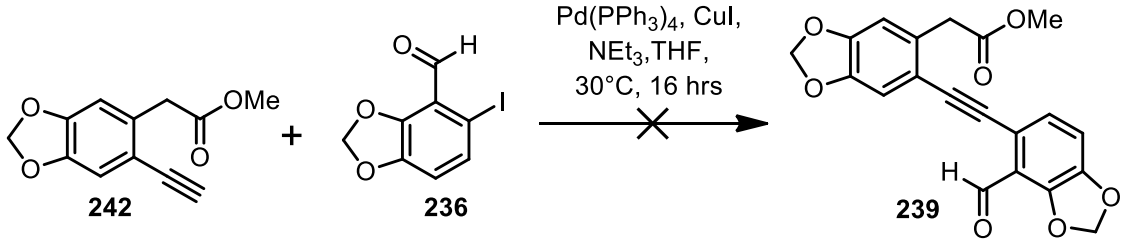
Figure 2.1 Suspected Glaser coupling product.

It was postulated that aryl alkyne **236** was too reactive due to the aldehyde group and thus it was proposed to couple the alkyne first to methyl ester protected aryl iodide **238** to prevent formation of Glaser products. Consequently aryl iodide **238** was coupled to trimethylsilylacetylene in a high yield of 96% followed by removal of the TMS group (**Scheme 2.10**).



Scheme 2.10 Coupling of acetylene to aryl iodide **238**.

With aryl alkyne **242** in hand the Sonogashira coupling was once again attempted using standard conditions (**Scheme 2.11**).



Scheme 2.11 Attempted coupling between aryl iodide **236** and alkyne **242**.

However a similar result was obtained in that none of the desired product was formed and high resolution mass spectroscopy again confirmed the presence of alkyne dimers suspected to be formed through a Glaser coupling side reaction (**Figure 2.2**).

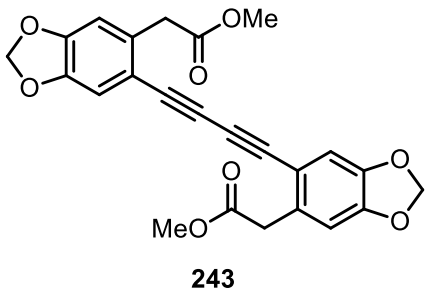
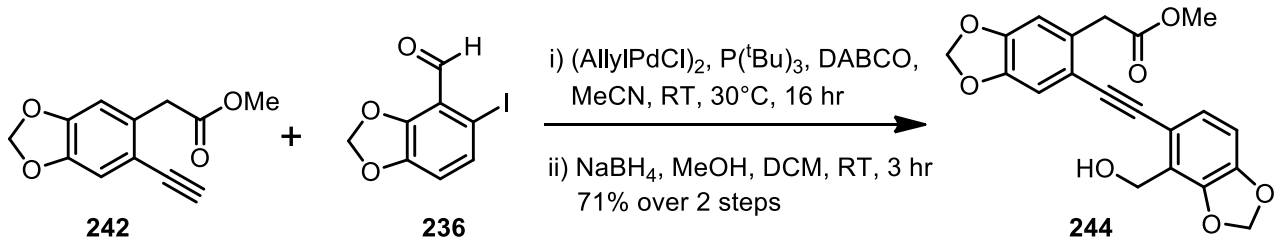


Figure 2.2 Suspected Glaser coupling product.

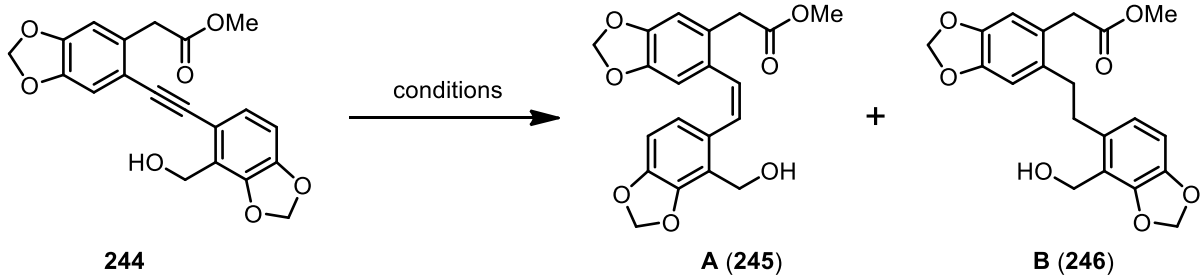
The Glaser reaction is an oxidative homo-coupling of terminal alkynes using a copper catalyst in the presence of oxygen and is a common side reaction of Sonogashira couplings. Given that copper is required for the Glaser reaction the literature was consulted to identify Sonogashira conditions that did not require the presence of copper. Conditions were subsequently found that employed $(AllylPdCl)_2$ and P(*t*-Bu)$_3$ to provide the active Pd(0) catalyst that facilitated the required coupling without the need for copper (**Scheme 2.12**).[109]



Scheme 2.12 Copper free coupling of alkyne **242** and aryl iodide **236**.

Whilst the fully coupled product could be detected by NMR and mass spectroscopy in the reaction mixture it was found to be unstable during efforts to purify it. As a result it was decided to reduce the aldehyde group to the corresponding primary alcohol directly after the Sonogashira coupling. Consequently sodium borohydride was used as the reducing agent to arrive at alkyne **244** in a yield of 71% over two steps that was easily purified and characterised.

With alkyne **244** in hand attention now turned our attention to the selective reduction required to form *cis*-alkene **245**. Initial attempts used activated zinc powder as well as Rieke zinc reducing conditions, however none of the desired *cis*-alkene **245** was obtained (**Scheme 2.13** & **Table 2.3**).[110-112] With Zinc conditions unsuccessful, hydrogenation using Lindlar catalyst was attempted to affect the *Z*-selective reduction.[113-115]



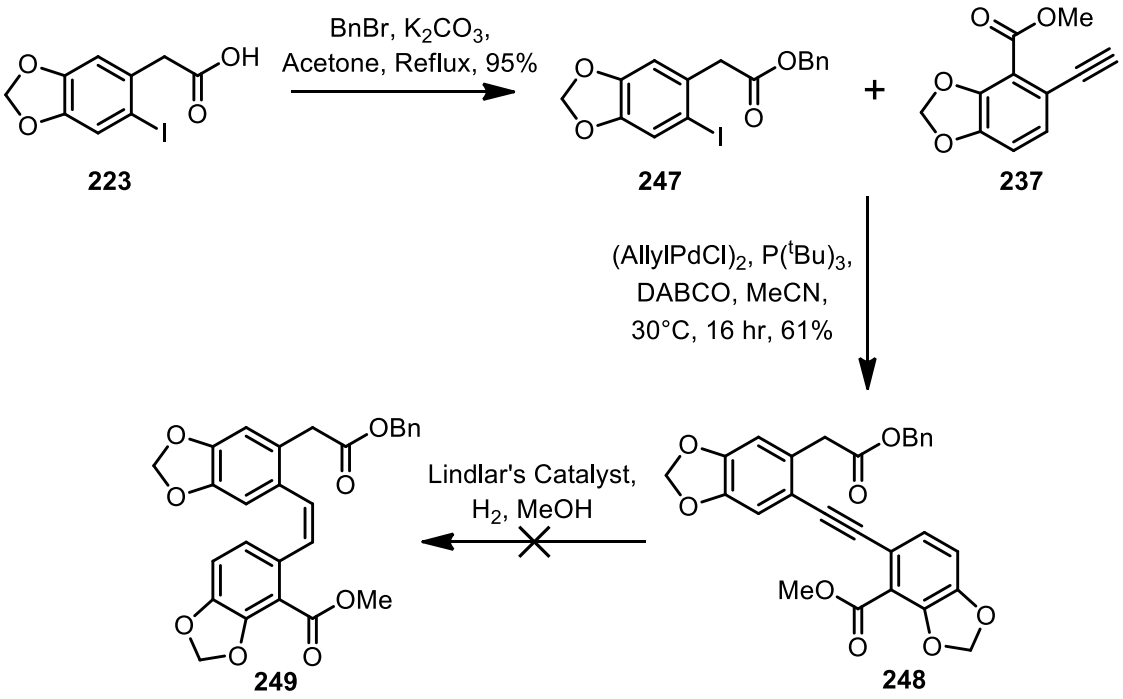
Scheme 2.13 Selective reduction of alkyne **244**.

Reagents	Result
Zinc, Dibromoethane, EtOH	no reaction
Zinc, Dibromoethane, CuBr, LiBr, EtOH	no reaction
Rieke Zinc, THF, 0°C, 16 hrs	no reaction
Rieke Zinc, THF, 25°C → 50°C, 16 hrs	no reaction
H_2, Lindlar catalyst, Quinoline, Benzene, 16 hrs	no reaction
H_2, Lindlar catalyst, Toluene, 16 hrs	56% **A** : 8% **B**
H_2, Lindlar catalyst, MeOH, 3 days	82% **A**

Table 2.3 Selective reduction of alkyne **244**.

The Lindlar catalyst with quinolone and benzene was unable to perform the reduction and while using toluene instead as the solvent afforded 56% of the *cis*-alkene **245**, it also produced some of the fully reduced alkane. With methanol as the solvent an 82% yield of *cis*-alkene **245** was obtained on a 20 mg scale. However as the scale of the reaction was increased towards 100 mg the yield dropped off markedly and more and more of alkyne **244** would remain unreduced.

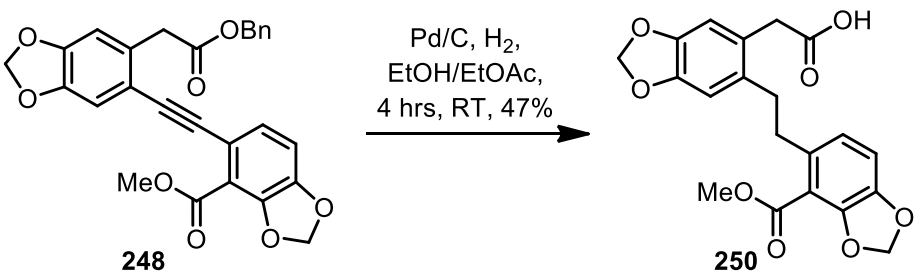
Given the instability of the aldehyde group and alkyne's resistance to selective reduction it was thought the synthetic approach should be redesigned (**Scheme 2.14**).



Scheme 2.14 Revised synthetic approach.

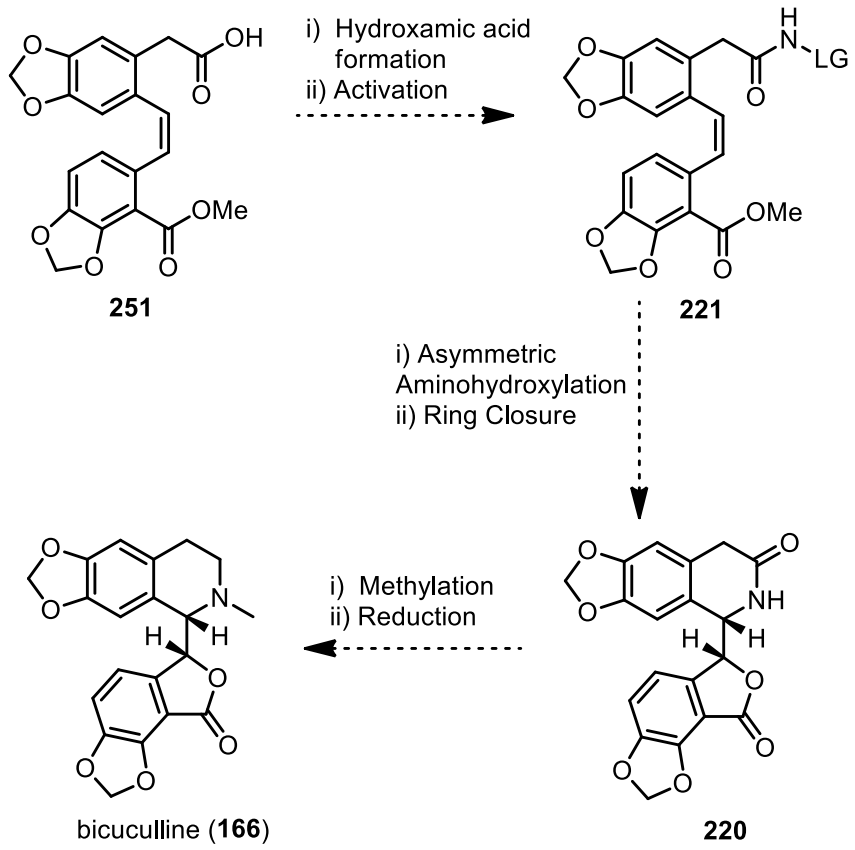
Specifically it was envisaged that a methyl ester group could replace the aldehyde removing the need for reduction, and that a benzyl group could be used to protect the carboxylic acid group instead allowing for selective deprotection and elaboration to the tethered aminohydroxylation precursor. Furthermore an advantage of using the benzyl group would be that it could possibly be cleaved at the same time as the alkyne reduction removing the need for a subsequent deprotection step. To this end aryl iodide **223** was reacted with benzyl bromide to obtain benzyl protected compound **247** in a high yield. The copper free Sonogashira reaction was then used to couple aryl iodide **247** with alkyne **237** to arrive at alkyne **248**. Lindlar reduction was then attempted using the previously successful conditions, however none of the desired *cis* alkene **249** was produced.

Given alkyne **248**'s further resistance to reduction more forcing conditions were sought to achieve the desired transformation. Standard Pd/C was chosen and whilst it did cleave the benzyl protecting group as hoped it also fully reduced the alkyne to the corresponding alkane (**Scheme 2.15**).



Scheme 2.15 Reduction with Pd/C.

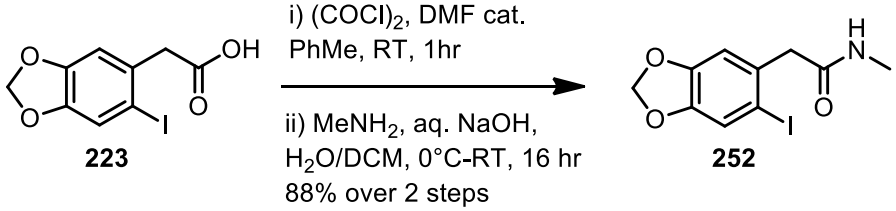
In the future, if a reducing agent or conditions can be found that only hydrogenate the alkyne to the *cis* alkene and also remove the benzyl group then the synthesis will be in its final stages. With *cis* alkene **249** in hand reaction with hydroxylamine and acylation would then be followed by the tethered aminohydroxylation reaction (**Scheme 2.16**). Subsequent ring closure, methylation and reduction would then provide bicuculline (**166**).



Scheme 2.16 Work remaining to complete aminohydroxylation synthesis.

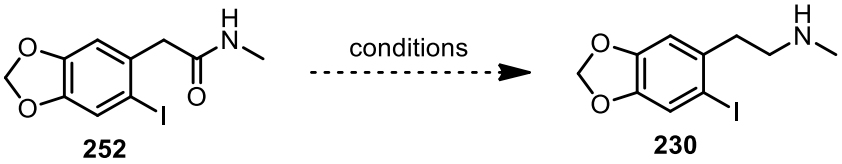
2.2 Epoxidation Approach

Whilst work took place on the asymmetric aminohydroxylation strategy studies also began on the epoxidation approach. Synthesis began on the coupling partner that would become the A and B ring of bicuculline by taking carboxylic acid **223** and treating it with oxalyl chloride to generate the corresponding acyl chloride followed by reaction with methylamine to afford amide **252** in a high yield (**Scheme 2.17**).[116]



Scheme 2.17 Amide **252** synthesis.

The next step required reduction of the amide to corresponding amine, however even after trialling a range of reduction conditions the amide proved to be unreactive (**Scheme 2.18** & **Table 2.4**).[117, 118]

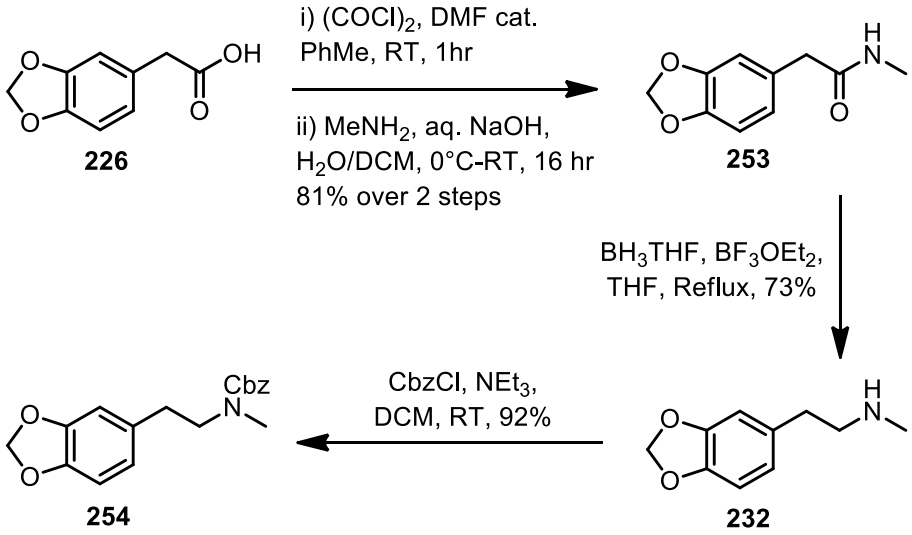


Scheme 2.18 Attempted reduction of amide **252**.

Conditions	Result
BH_3•THF, THF, Reflux	<10% conversion*
BH_3•THF, BF_3•OEt_2, THF, RT	<10% conversion*
BH_3•THF, BF_3•OEt_2, Reflux	<10% conversion*
$NaBH_4$, THF, RT	no reaction
$NaBH_4$, BF_3•OEt_2,THF	no reaction

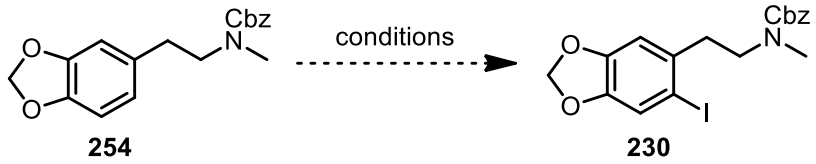
Table 2.4 Attempted reduction of amide **252**. *Conversion of the amide to the amine was calculated by ^{1}H-NMR anaylsis of the reaction mixture.

As a result it was decided to attempt the formation of the amine first followed by subsequent protection and iodination. To this end homopiperonylic acid (**226**) was subjected to the same oxalyl chloride and methylamine conditions previously used (**Scheme 2.19**). Amide **253** was then treated with BH_3•THF to afford the required amine **232** in a yield of 73%. The free amine was then protected with a carboxybenzyl group in preparation for iodination.



Scheme 2.19 Cbz protected amine synthesis.

With protected amine **254** in hand standard iodination conditions with NIS were initially investigated, but the substrate was not very reactive to these conditions (**Scheme 2.19** & **Table 2.5**). Eventually conditions were found using molecular iodine and silver trifluoroacetate to afford aryl iodide **230** in a good yield of 76%.[119]

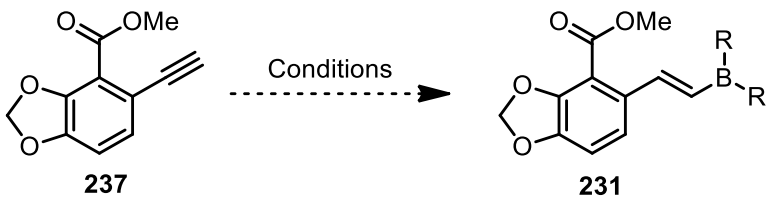


Scheme 2.19 Iodination of Cbz protected amine **230**.

Conditions	Result
NIS (1 eq), TFA (1 eq), MeCN	51% conversion*
NIS (1.3 eq), TFA (1.3 eq), MeCN	61% conversion*
I_2 (1 eq), $AgOOCCF_3$ (1 eq), $CHCl_3$	55% conversion*
I_2 (1.3 eq), $AgOOCCF_3$ (1.3 eq), $CHCl_3$	76% conversion*
I_2 (2 eq), $AgOOCCF_3$ (2 eq), $CHCl_3$	76% yield

Table 2.5 Iodination of Cbz protected amine **254**. *Conversion of the amide to the amine was calculated by ^{1}H-NMR anaylsis of the reaction mixture.

Having synthesised the first coupling partner for the Suzuki reaction attention then turned to the required boronic acid or boronate ester **231**. Taking previously synthesised aryl alkyne **237** first refluxing in THF with pinacol borane was attempted, however this only resulted in decomposition of the starting material (**Scheme 2.20** & **Table 2.6**). Numerous other hydroboration conditions and reagents were trialled in an attempt to form a boronic acid or boronate ester that could be used in the coupling, but these resulted in either no reaction or decomposition of aryl alkyne **237**.[120-126]



Scheme 2.20 Attempted boronic acid or ester formation.

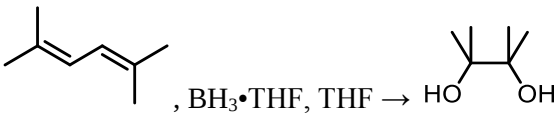
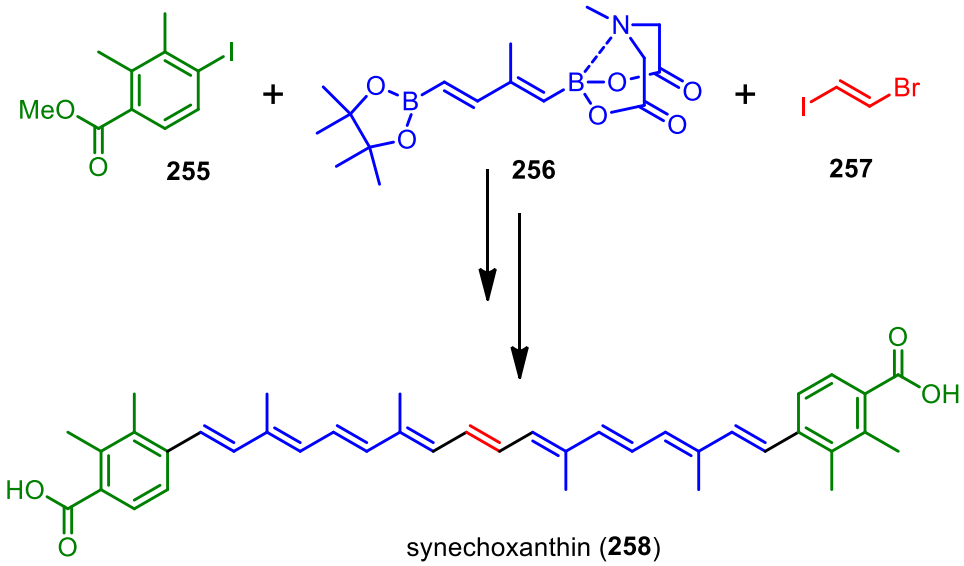
Conditions	R =	Result
Pinacol borane, THF, reflux	-OC(CH$_3$)$_2$C(CH$_3$)$_2$O-	decomp
Pinacol borane, Zr(Cp)$_2$HCl, THF, RT	-OC(CH$_3$)$_2$C(CH$_3$)$_2$O-	no prod
Catechol borane, THF, reflux	OH	decomp
 , BH$_3$•THF, THF →	-OC(CH$_3$)$_2$C(CH$_3$)$_2$O-	no prod
 , BH$_3$•THF, THF →	-OCH$_2$CH$_2$NHCH$_2$CH$_2$-	no prod
BHBr$_2$•SMe$_2$, DCM, reflux → H$_2$O	OH	decomp

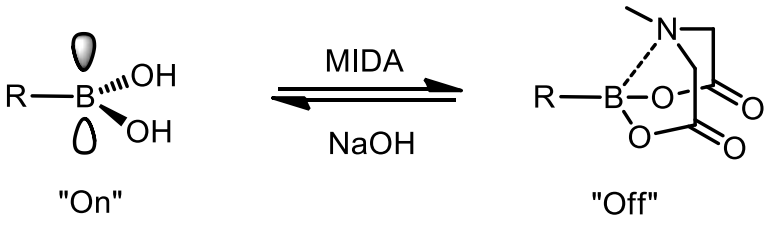
Table 2.6 Attempted boronic acid or ester formation.

After researching boronic acid and ester formation in the literature an iterative cross coupling technique developed by Burke and co-workers was found to construct complex natural product polyenes under mild conditions (**Scheme 2.21**).[127-131]



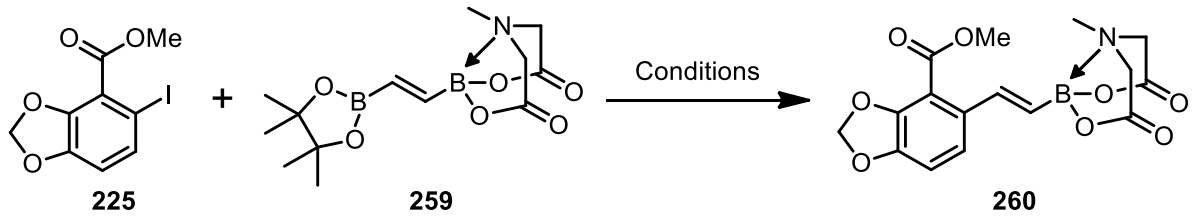
Scheme 2.21 Burke and co-workers iterative cross-coupling synthesis of synechoxanthin (**258**).

This technique used *N*-methyliminodiacetic acid (MIDA) protected boronic acids that are unreactive until the MIDA group is removed with sodium hydroxide, and this allows the sequential addition of coupling partners in a very controllable manner (**Scheme 2.22**).



Scheme 2.22 MIDA protected boronic acids.

Whilst it was not needed to construct a complex polyene system, it was envisaged that these MIDA compounds and the mild conditions used in this approach could be employed to couple an ethylene unit to the aromatic iodide components. To this end aryl iodide **225** was reacted with commercially available diboronate ester **259** in the presence of $Pd(OAc)_2$, XPhos and caesium carbonate to yield MIDA boronate **260** in moderate yield of 68% (**Scheme 2.23** & **Table 2.7**). The yield of this reaction could be raised to 90% by employing $Pd_2(dba)_2$ as the catalyst and using tripotassium phosphate in place of caesium carbonate.

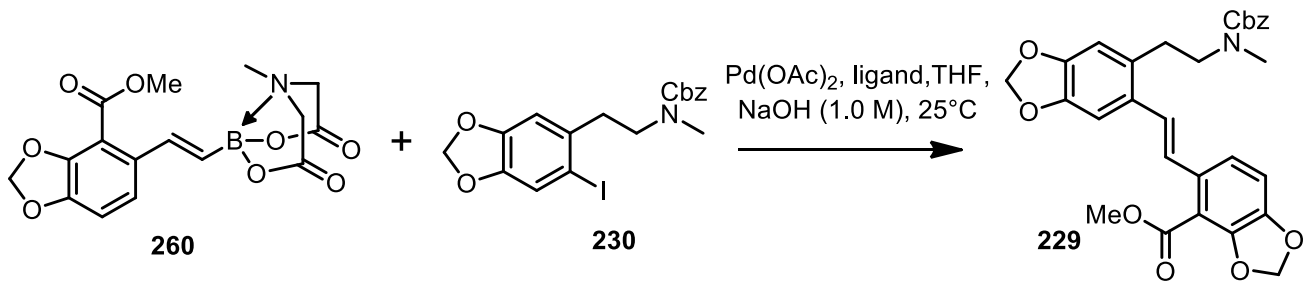


Scheme 2.23 MIDA boronate coupling.

Conditions	Yield
$Pd(OAc)_2$, XPhos, $CsCO_3$, THF	68%
$Pd(OAc)_2$, XPhos, K_3PO_4, THF	72%
$Pd_2(dba)_3$, XPhos, K_3PO_4, THF	90%

Table 2.7 MIDA boronate coupling.

With MIDA boronate **260** in hand this was then coupled with aryl iodide **230** by using NaOH to deprotect the MIDA boronate to form the desired stilbene **229** (**Scheme 2.24** & **Table 2.8**). Initially this only gave a modest yield of 60% (88% brsm), however by optimising the choice of ligand as well as the equivalents of MIDA boronoate and NaOH the yield was raised to 87% with complete consumption of the starting material.

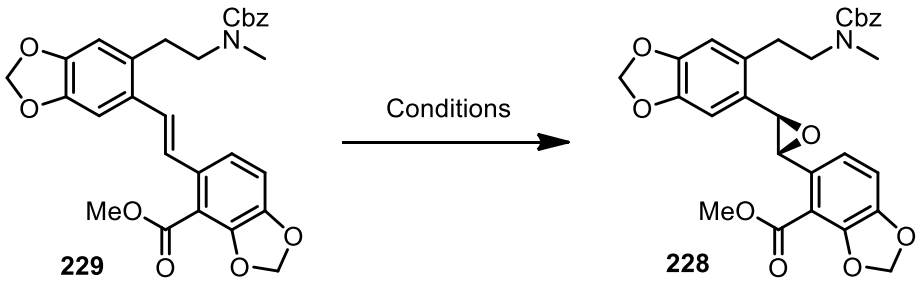


Scheme 2.24 MIDA boronate coupling.

Ligand	Boronate Eq	NaOH Eq	Yield
XPhos	1.2	3.6	60% (88% brsm)
XPhos	1.5	4.5	62% (90% brsm)
SPhos	1.2	3.6	47% (81% brsm)
SPhos	1.9	9.5	77% (91% brsm)
SPhos	2.0	10	87%

Table 2.8 MIDA boronate coupling.

Having synthesised stilbene **229** it was now time to investigate the Shi epoxidation in order to install the desired stereochemistry across the bridge. However, before employing the Shi epoxidation it was deemed prudent to first test the reactivity of stilbene **229** under standard epoxidation conditions such as with *m*CPBA. Indeed what was discovered was that the alkene was fairly unreactive and 5 equivalents of freshly purified *m*CPBA was required to achieve 74% conversion (**Scheme 2.25** & **Table 2.9**).[132-138] In particular the reaction required the addition of a mild base such as sodium bicarbonate to convert *m*CPBA to its conjugate base and improve its nucleophilicity. Attempts to purify and characterise the epoxide product resulted in degradation and loss of the material.

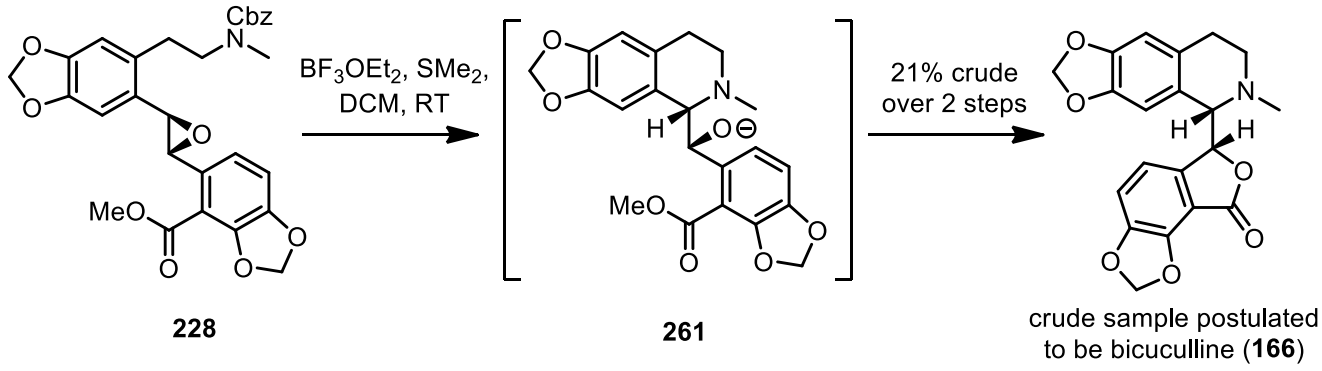


Scheme 2.25 Epoxidation of stilbene **229**.

Conditions	Eq	Time (hr)	Result
*m*CPBA (tech), DCM	1.2	3	trace in MS
*m*CPBA (tech), DCM	1.5	3	decomp
*m*CPBA (tech), DCM, $NaHCO_3$	1.5	16	trace in ^{1}H-NMR
*m*CPBA (>99%), DCM	1.5	3	decomp
*m*CPBA (>99%), DCM, $NaHCO_3$ (0.5 M)	1.5	16	55% conversion
*m*CPBA (>99%), DCM, $NaHCO_3$ (0.5 M)	2.5	16	72% conversion
*m*CPBA (>99%), DCM, $NaHCO_3$ (0.5 M)	5	16	74% conversion

Table 2.9 Epoxidation of stilbene **229**.

Given epoxide **228** could not be easily purified, it was decided to use crude samples and attempt to form the isoquinoline and lactone rings of bicuculline (**166**) by deprotecting the carbamate. Initially conditions used BF_3·OEt_2 and dimethyl sulfide were attempted to not only liberate the amine of epoxide **228** but also promote lactone ring closure after nucleophilic attack on the epoxide by the free amine (**Scheme 2.26**).[139, 140]



Scheme 2.26 Deprotection of amine and subsequent lactone formation.

These conditions did produce a few milligrams of a crude sample, which if it was indeed bicuculline (**166**) would equate to a low yield of 21%. Unfortunately this reaction could not be reproduced despite further purification of the reagents as well as various reaction times and temperatures. Furthermore, attempts to further purify the crude sample by recrystallisation, flash chromatography and HPLC failed to remove impurities.

Comparison of the crude sample ^{1}H-NMR to that of stilbene **228** did show some positive indications that the epoxidation and ring closure had been successful (**Figure 2.3**).

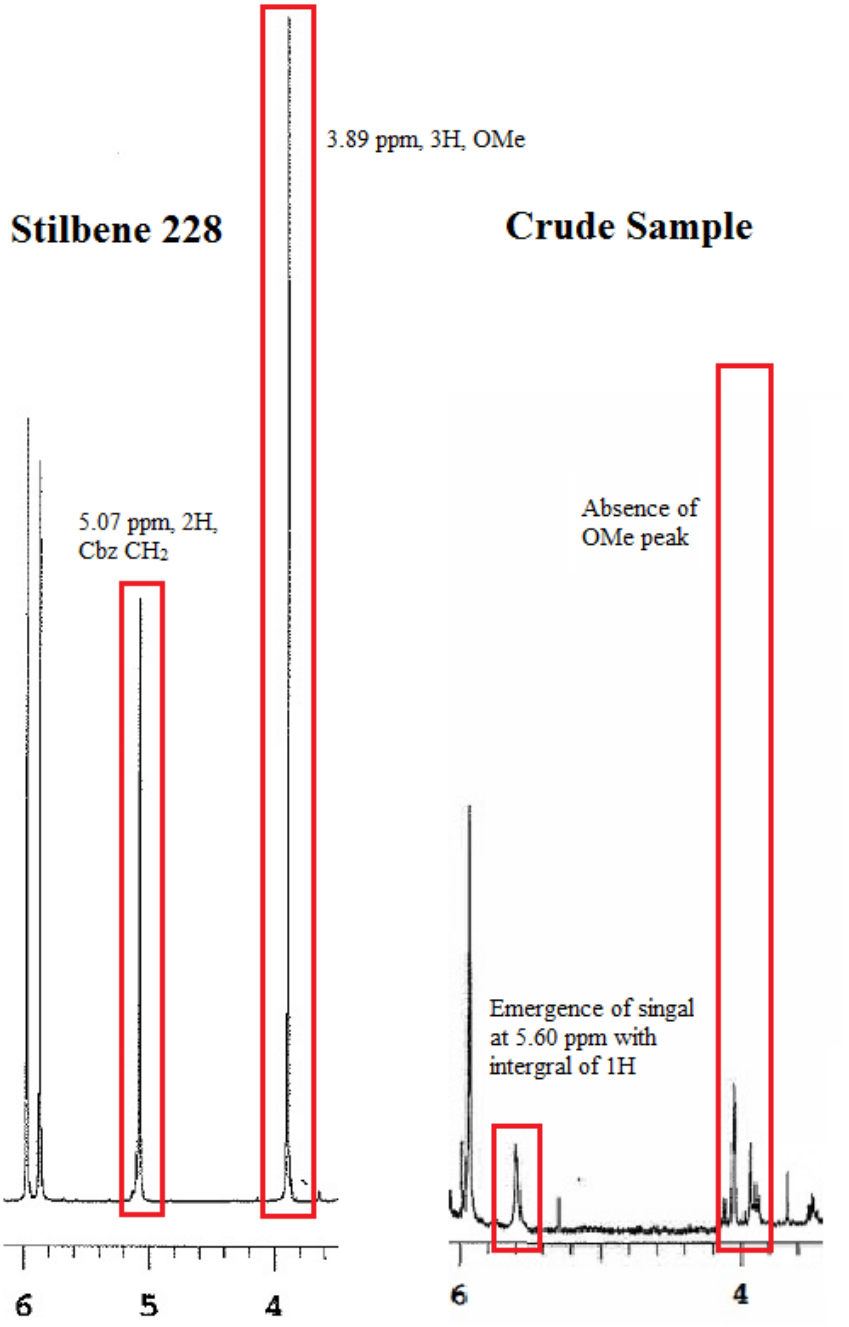


Figure 2.3 ^{1}H-NMR comparison between stilbene **229** and crude sample.

For instance the methyl ester signal was no longer present perhaps indicating that the oxyanion generated from the epoxide opening had formed the lactone ring, eliminating the methoxy group. Furthermore, a new signal integrating for 1H was observed at 5.60 ppm which was at a shift consistent with the proton of the lactone CH in phthalide ring systems. Given this evidence it was decided to further compare the ^{1}H-NMR of the crude sample with those reported for bicuculline (**166**) in the literature (**Figure 2.4** & **Table 2.10**).

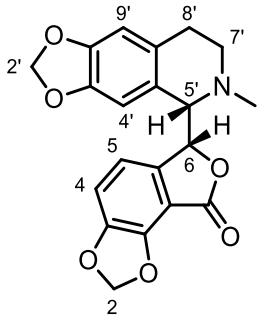


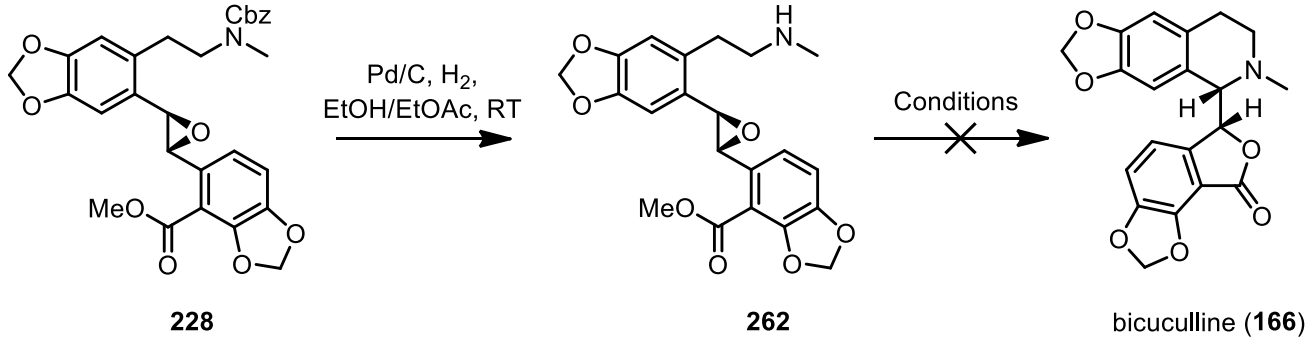
Figure 24 Bicuculline (**166**).

Assignment	Soriano[90]	Allan and Apostopoulos[141]	Crude Sample
H4	6.91, 1H	6.92, 1H	6.92, 1H
H4’	6.58, 1H	6.58, 1H	6.58, 1H
H9’	6.47, 1H	6.47, 1H	6.44, 1H
H5	6.19, 1H	6.19, 1H	6.22, 1H
H2	6.17, 2H	6.15, 2H	6.16, 2H
H2’	5.92, 2H	5.93, 2H	5.93, 2H
H6	5.56, 1H	5.56, 1H	5.60, 1H
H5’	4.05, 1H	4.03, 1H	4.05, 1H
N-Me	2.54, 3H	2.55, 3H	2.56, 3H
H7’a	2.90-2.83, 1H	2.96-1.68, 4H	2.95-2.83, 1H
H7’b & H8’a	2.62-2.51, 2H		2.62-2.52, 2H
H8’b	2.31-2.23, 1H		2.29-2.25, 1H

Table 2.10 Comparison of reported bicuculline (**166**) ^{1}H-NMR signals and crude sample.

In addition to the ^{1}H-NMR data, high resolution ESI mass spectrometry detected a m/z peak at 368.1134 which eactly matched the expected exact mass for bicuculline (**166**) ($C_{20}H_{18}NO_6$, $[M+H]^+$). Furthemore the IR spectra of the crude sample showed a new peak with strong initenstity at 1762 cm^{-1}, which suggests the presence the desired γ-lactone (C=O in γ-lactone: 1780-1760 cm^{-1} (s)).[142]

As can be seen the crude sample largely correlated with the ^{1}H-NMR of bicuculline (**166**), and high resolution mass spectrometry and IR anaylsis supported this assignment. However given the inability to reproduce the reaction and also to purify the sample alternate synthetic strategies were investigated. Therefore, in an effort to produce a pure sample of bicuculline (**166**) it was decided to first remove the carboxybenzyl protecting group followed by ring closure in a stepwise fashion. To this end removal of the protecting group was achieved using Pd/C under a hydrogen atmosphere and was confirmed by crude ^{1}H-NMR analysis on the reaction mixture (**Scheme 2.27** & **Table 2.10**). Crude ^{1}H-NMR anaylsis of the reaction mixture indicated the loss of the Ph$\underline{CH_2}$ signal at around 5 ppm and no apparent hydrogenolysis of the epoxide. Purification of the subsequent unprotected epoxide **262** was not attempted given it has already proved to be unstable. With crude unprotected epoxide **262** in hand various conditions where trialled to promote nucleophilic attack of the free amine and subsequent lactone formation.[143, 144]



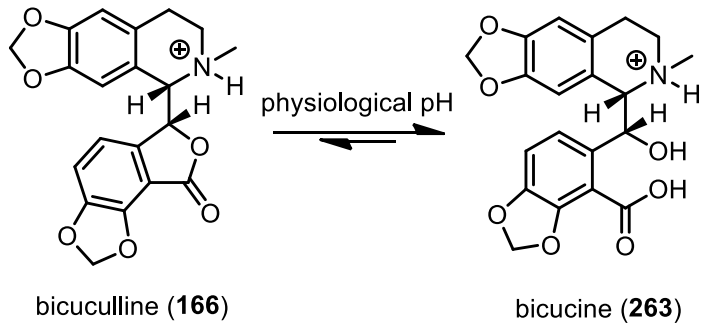
Scheme 2.27 Attempted Cbz deprotection and subsequent lactone formation.

Conditions	Result
BF_3·OEt_2, DCM, RT, 16 hrs	decomp
TFA, DCM, -78°C→ RT, 16 hrs	decomp
DMF, 100°C, 16 hrs	decomp
TMSI, LiI, $CHCl_3$, RT, 5 hrs	decomp

Table 2.10 Attempted Cbz deprotection and subsequent lactone formation.

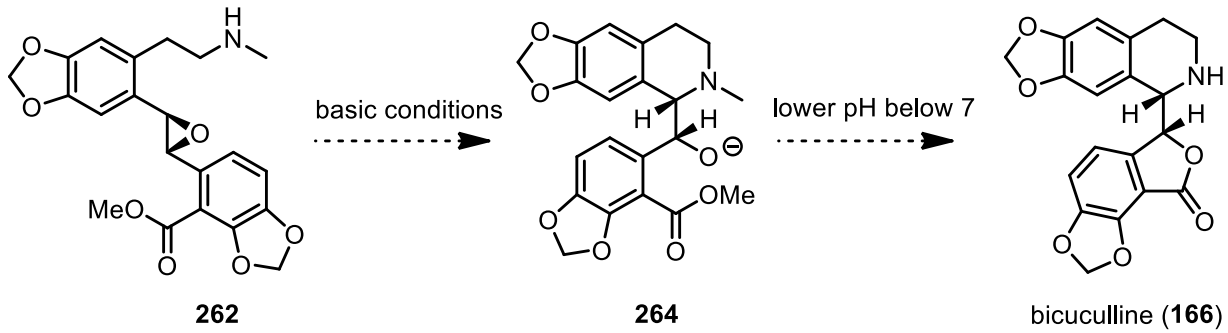
Unfortunately the trialled conditions resulted in decomposition of the starting material and high resolution mass spectrometry was unable to confirm the presence of a molecular ion consistent with bicuculline (**166**).

After looking into the literature again around the stability of bicuculline (**161**) it was found that it exists in equilibrium with bicucine (**263**) which is favoured at physiological pH (**Scheme 2.28**).[87] Furthermore it was disclosed that bicucine (**263**) is slowly converted to bicuculline (**166**) at acidic pH.



Scheme 2.28 Equilibrium between bicuculline (**166**) and bicucine (**263**).

Therefore it was proposed that future attempts at forming the lactone ring of bicuculline (**166**) employ basic conditions first to form the isoquinoline ring, followed by lowering the pH below to promote the formation of the lactone ring (**Scheme 2.29**).



Scheme 2.29 Proposed strategy for future attempts at lactone formation.

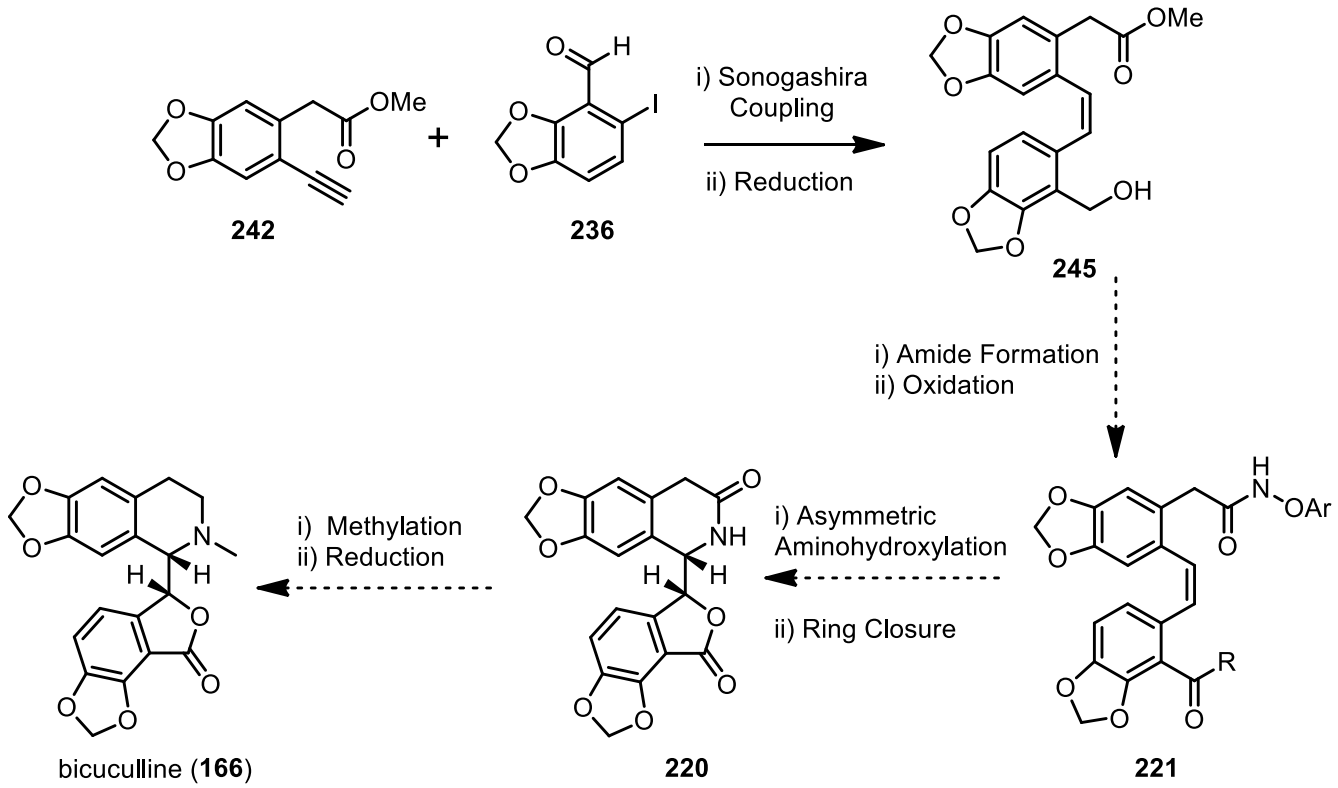
Unfortunately due to a lack of material and time this work was unable to be completed as part of this body of research.

Chapter 2 – Bicuculline

3. Conclusions & Future Work

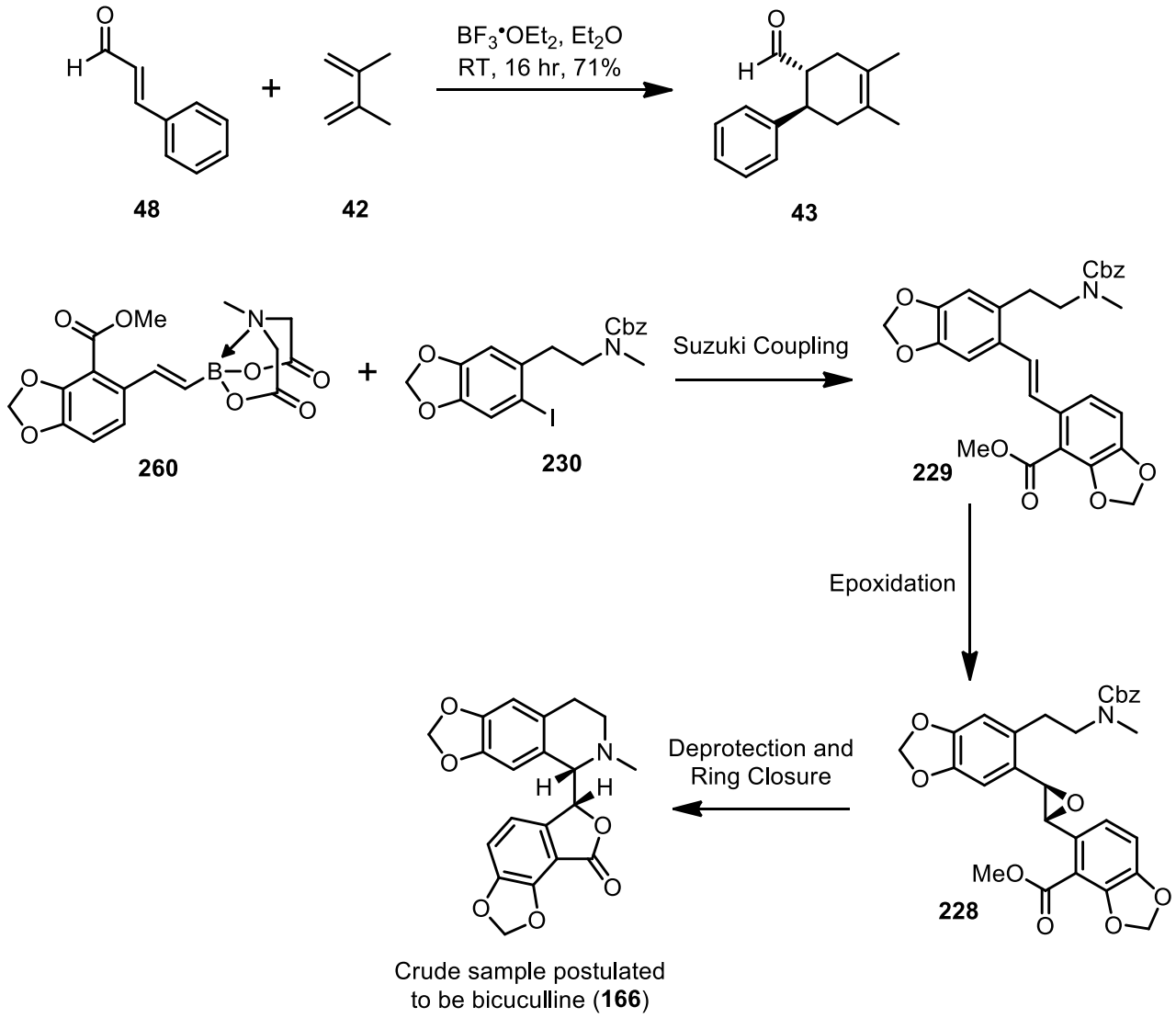
3. Conclusions and Future Work

With respect to the synthesis of bicuculline (**166**) two approaches were employed. The first approach involved synthesis of a biaryl *cis*-alkene that could then undergo an intra-molecular tethered aminohydroxylation to afford the core of bicuculline. Biaryl alkene (**245**) was successfully synthesised through a Sonogashira coupling and subsequent reduction of the alkyne.

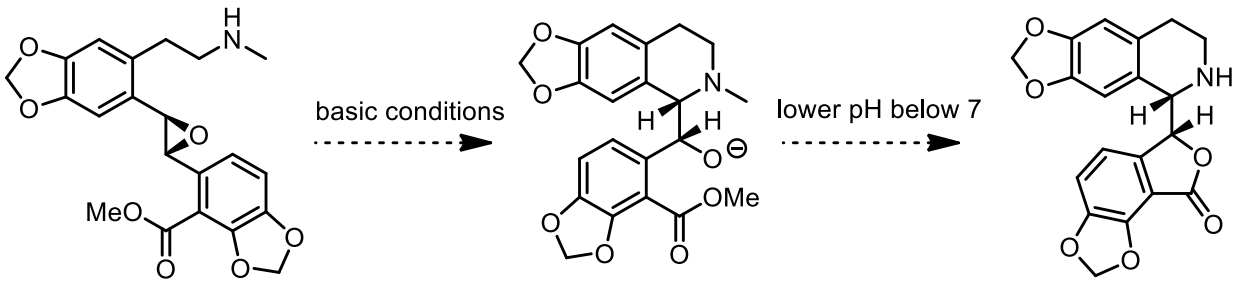


Whilst the Lindlar reaction conditions were able to selectively reduce the alkyne to the *cis* alkene, this rection was not scalable. Future work on this approach will entail the search for appropriately balanced reducing conditions such that the alkyne is efficiently transformed to the subsequent *cis* alkene on a scale suitable for further synthetic transormations. Alternatively the MIDA boronates employed in the epoxide approach could bed used to couple an ethene moiety between the two aryl fragments in a *cis* fashion. Once the desired alkene **221** is synthesised on a suitable scale then further synthetic transformations will be devised to prepare the *cis* alkene for the intramolecular amino hydroxylation required to form the dihydroisoquinoline ring system. Following the intramolecular amino hydroxylation reduction and subsequent methylation of the amide will provide bicuculline (**166**). Unfortuntately this approach was not pursured due to time constraits and focus was instead turned to the second approach that employed an epoxide precusor.

The second approach to bicuculline (**166**) used a Suzuki coupling between MIDA boronate **259** and aryl iodide **230**. The *trans*-alkene **229** was then converted to the epoxide followed by deprotection of the amine to facilitate a ring closure resulting in a crude sample that was postulated to be bicuculline (**166**).



Given a pure sample of bicuculline (**166**) was not produced future work will focus on optimising the final ring closure to afford a pure sample for full characterisation. Other possible stragtegies to achieve this could include forming the dihydroisoquinoline ring of bicuculline (**166**) under basic conditions first, followed by lowering the pH below to promote the formation of the lactone ring.



262 **264** bicuculline (**166**)

Additionally alternate protecting groups that are more easily removed could be investigated for the amine group such as Fmoc or Boc. Furthemore stronger electron withdrawing groups could be employed in place of the methyl on the ester group as this would make carbonyl more electrophilic.

Upon successful preparation of a pure sample of bicuculline (**166**) further work will include investigation into the application of an asymmetric Shi epoxidation in order to achieve and enantioselective synthesis.

Experimental

General Experimental

Infrared absorption (IR) spectra were obtained using with a Perkin-Elmer Spectrum One FTIR spectrometer. Compounds were prepared as a thin film between 0.5 cm sodium chloride plates. Absorption maxima (ν_{max}) are expressed in wavenumbers (cm–1). 1H Nuclear magnetic resonance spectra were recorded using a Varian Mercury 300 (300 MHz), Varian Mercury 400 (400 MHz) or Bruker 800 (800 MHz) spectrometer at 25°C, and are recorded in parts per million (ppm) downfield shift from tetramethylsilane (δTMS = 0), using residual chloroform (δ 7.26) or methanol (δ 3.31) solvent as internal reference. The data is reported as chemical shift (δH), relative integral, multiplicity (s = singlet, br = broad, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (J Hz), and assignment. ^{13}C Nuclear magnetic resonance spectra were recorded using a Varian Mercury 300 (75 MHz) or Varian Mercury 400 (100 MHz) spectrometer at 25°C with complete proton decoupling. Data is expressed in parts per million (ppm) downfield relative to tetramethylsilane (δTMS = 0) using deuterated chloroform (δ 77.00) solvent as an internal reference and is reported as chemical shift (δC). High and low resolution electron ionization (EI) mass spectra were recorded using a Micromass VG Autospec mass spectrometer. Low and high resolution electrospray ionization (ESI) mass spectra were recorded using a Micromass ZMD LR mass spectrometer or a Waters LCT Premier XE mass spectrometer respectively. Preparative HPLC was performed on a Waters preparative HPLC system consisting of a 600E solvent delivery system, in-line degasser and 2996 diode array detector. Samples were injected manually via a Rheodyne 7725i injection valve fitted with a 5 mL loop and separated on a Waters XBridge C18 5 µm 150 mm x 4.6 mm eluted at 1 mL min^{-1}. The system was interfaced with Empower 2 software for instrument control and data acquisition. Analytical thin layer chromatography (TLC) was performed using 0.2 mm thick aluminium backed pre-coated silica gel plates (Merck Kieselgel 60 F254). Flash chromatography was carried out using Merck Kieselgel 60 (230–400 mesh ASTM), under a positive pressure of nitrogen. Solvent compositions were mixed v/v as specified. High pressure reactions were carried out in a PSIKA high pressure reactor. All solvents and reagents were purified according to standard literature procedures.[145]

General Method A – Organolithium Addition

Bromobenzene (9 mmol) and tetrahydrofuran (30 mL) were added to a flask and cooled to -78°C under a nitrogen atmosphere. Butyllithium (9 mmol) was then added dropwise over 5 minutes and the resulting solution stirred for 30 minutes. A solution of aldehyde (3 mmol) in tetrahydrofuran (5 mL) was then added dropwise over 5 minutes followed by stirring at -78°C for 15 minutes. After this the reaction was allowed to warm to room temperature and stirred for a further 30 minutes followed by quenching with saturated aqueous ammonium chloride (50 mL). Extraction with diethyl ether (3x30 mL), drying over

magnesium sulfate and purification by column chromatography gave a mixture of the product alcohol diastereomers.

General Procedure B – Dess-Martin Oxidation

Alcohol (3 mmol), Dess-Martin periodinane (6 mmol) and dichloromethane (30 mL) were added to a flask and stirred at room temperature for 1 hr. The reaction was then evaporated on to silica under reduced pressure and purified by column chromatography to afford the requisite carbonyl compound.

General Procedure C – High Pressure Diels-Alder

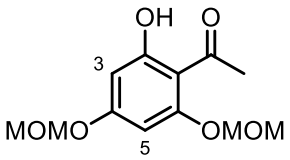
Dienophile (2 mmol), diene (8 mmol) and dichloromethane (3 mL) were added to a pressure vessel and sealed. The vessel was then pressurised to 19 kbar for 3 days at room temperature. After relieving the pressure the reaction mixture was transferred to a flask and the dichloromethane evaporated under reduced pressure. The resulting residue was then purified and analysed or subjected to reducing conditions.

General Procedure D – Reduction of Diels-Alder Residues

The Diels-Alder residue derived from general procedure C was dissolved in tetrahydrofuran (30 mL) and cooled to 0°C with rapid stirring. Lithium aluminium hydride (95% w/w, 12 mmol) was then added portionwise over 30 mins. The reaction was then left for 3 hrs followed by dropwise quenching with water and then 2 M hydrochloric acid solution. A saturated solution of potassium sodium tartrate (60 mL) was then added and the mixture stirred vigorously for 2 hrs. Extraction of the resulting mixture with ether (3x30 mL) was followed by washing the combined organic layers with water (40 mL) and brine (40 mL). Evaporation on to silica under reduced pressure and purification by column chromatography afforded the requisite alcohol.

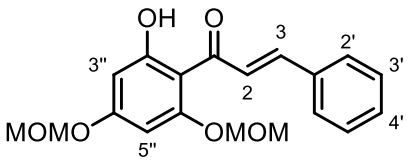
Synthetic Methods and Characterisation

2-Hydroxy-4,6-bis(methoxymethoxy)acetophenone (**32**)



2,4,6-Trihydroxyacetophenone monohydrate (1.53 g, 8.24 mmol), diisopropylethylamine (7.11 mL, 40.8 mmol), and dry dichloromethane (30 mL) were added and allowed to stir. Methoxymethyl chloride (976 µL, 12.9 mmol) was then added slowly over 2 minutes and then the solution was heated at 45 °C with stirring for 3 days. The reaction mixture was then quenched with water (20 mL) and extracted with ethyl acetate (3×30 mL). Drying over magnesium sulfate, filtration, concentration under reduced pressure and purification via silica gel chromatography using ethyl acetate : hexane (3:7) gave 2-hydroxy-4,6-bis(methoxymethoxy)acetophenone (**32**) as a bright yellow solid (1.23 g, 58%); $\mathbf{R_f}$ (EtOAc:Hex ; 3:7) 0.35; **m.p.** 48-49 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 13.73 (1H, s, OH), 6.27 (1H, d, *J* = 2.4 Hz, H5), 6.25 (1H, d, *J* = 2.4 Hz, H3), 5.26 (2H, s, $CH_3O\underline{CH_2}O$), 5.17 (2H, s, $CH_3O\underline{CH_2}O$), 3.52 (3H, s, $\underline{CH_3}OCH_2O$), 3.47 (3H, s, $\underline{CH_3}OCH_2O$), 2.66 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 203.2, 166.8, 163.4, 160.3, 106.9, 97.1, 94.4, 94.0 (2C), 56.7, 56.4, 33.0; **IR** (thin film) υ_{max} = 3422 (m), 2958 (m), 2932 (m), 1622 (s), 1597 (s), 1434 (m), 1363 (m), 1268 (m), 1151 (s) cm^{-1}; **LRMS** (EI^+) *m/z* = 256 ($M^{+\bullet}$, 100%); **HRMS** (EI^+) calc. for $C_{12}H_{16}O_6$ ($M^{+\bullet}$) 256.0947, found 256.0943.

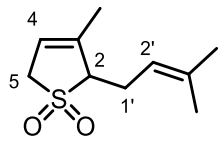
(*E*)-1-(2-Hydroxy-4,6-bis(methoxymethoxy)phenyl)-3-phenylprop-2-en-1-one (**78**)



To a solution of 2-hydroxy-4,6-bis(methoxymethoxy)acetophenone (853 mg, 3.33 mmol) in ethanol (20 mL) was added potassium hydroxide (1.50 g, 26.6 mmol) followed by stirring for 30 min. Benzaldehyde (408 µL, 4.00 mmol) was then added and the reaction left for 2 days to stir at room temperature. It was then acidified to pH 5 with 2 M hydrochloric acid, extracted with ethyl acetate (3×25 mL) and dried over magnesium sulfate. Filtration, concentration under reduced pressure and purification via silica gel chromatography using ethyl acetate : hexane (3:7) afforded (*E*)-1-(2-Hydroxy-4,6-bis(methoxymethoxy)phenyl)-3-phenylprop-2-en-1-one (**78**) as a bright yellow solid (586 mg,

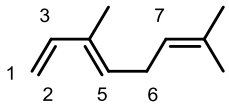
51%); **R_f** (EtOAc:Hex ; 2:3) 0.46;; **m.p.** 39-56 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 13.83 (1H, s, OH), 7.93 (1H, d, *J* = 15.6 Hz, H3), 7.79 (1H, d, *J* = 15.6 Hz, H2), 7.62-7.57 (2H, m, H2'), 7.42 (3H, m, H3' & H4'), 6.32 (1H, d, *J* = 2.4 Hz, H5''), 6.25 (1H, d, *J* = 2.4 Hz, H3''), 5.30 (2H, s, $CH_3O\underline{CH_2}O$), 5.19 (2H, s, $CH_3O\underline{CH_2}O$), 3.54 (3H, s, $\underline{CH_3}OCH_2O$), 3.49 (3H, s, $\underline{CH_3}OCH_2O$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 192.9, 167.3, 163.5, 159.8, 142.5, 135.4, 130.2, 128.9, 128.3, 127.3, 107.5, 97.4, 95.1, 94.7, 94.0, 56.9, 56.5; **IR** (thin film) υ_{max} = 2956 (w), 2924 (w), 1630 (vs), 1579 (s), 1448 (w), 1340 (m), 1209 (m), 1150 (s) cm^{-1}; **LRMS** (EI^+) *m/z* = 344 ($M^{+\bullet}$, 80%), 131 (100%); **HRMS** (EI^+) calc. for $C_{19}H_{20}O_6$ ($M^{+\bullet}$) 344.1260, found 344.1256.

(±)-2-Methyl-4-(3-methyl-3-sulfolen-2-yl)but-2-ene (**104**)[146]



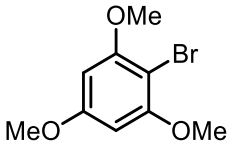
3-Methyl sulfolene (3.46 g, 26.2 mmol), prenyl bromide (1.53 mL, 13.1 mmol) and tetrahydrofuran (50 mL) were added to a flask and under a nitrogen atmosphere and cooled to -95ºC with stirring. LHMDS (26.2 mL, 26.2 mmol) was then slowly added over 1 minute and the reaction allowed to stir for a further minute. Quenching with a saturated solution of ammonium chloride (30 mL) was then followed by extraction with diethyl ether (3x20 mL). The combined organic layers were then dried over magnesium sulfate, filtered, concentrated under reduced pressure and purified via silica gel chromatography using diethyl ether : hexane (2:3) to afford (±)-2-methyl-4-(3-methyl-3-sulfolen-2-yl)-2-butene (**104**) as a clear yellow oil (2.15 g, 82%); **R_f** (Ether:Hex ; 2:3) 0.19; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.68 (1H, m, H4), 5.21 (1H, m, H2'), 3.67 (2H, m, H5), 3.50 (1H, t, *J* = 6.0 Hz, H2), 2.55 (2H, m, H1'), 1.85 (3H, s, CH_3), 1.72 (3H, s, CH_3), 1.66 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 138.6, 135.3, 118.3, 117.0, 67.2, 55.6, 26.4, 25.7, 18.1, 17.8; **IR** (thin film) υ_{max} = 2970 (m), 2920 (m), 2856 (m), 1730 (w), 1671 (w), 1442 (m) 1380 (m), 1303 (s) cm^{-1}; **LRMS** (EI^+) *m/z* = 200 ($M^{+\bullet}$, 10%), 135 ($[M\text{-}SO_2\text{-}H]^{+\bullet}$, 100%); **HRMS** ($EI^+$) calc. for $C_{10}H_{16}O_2S$ ($M^{+\bullet}$) 200.0871, found 200.0873, calc. for $C_{10}H_{15}$ ($[M\text{-}SO_2H]^{+\bullet}$) 135.1174, found 135.1172.

(*E*)-Ocimene (**31**)[40]



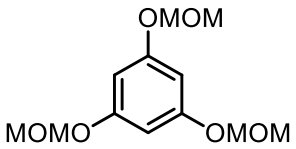
2-Methyl-4-(3-methyl-3-sulfolen-2-yl)-2-butene (**104**) (403 mg, 2.01 mmol) and pyridine (20 mL) were added to a flask and heated at reflux for 6 hours with stirring. After cooling to room temperature the reaction was extracted with 30-40 petroleum spirits (20 mL) and washed with 2 M hydrochloric acid solution (4x20 mL). The petroleum spirit layer was then washed through a silica gel plug and concentrated under reduced pressure to give *E*-ocimene (**31**) as a clear colourless oil (222 mg, 81%); **R_f** (Ether:Hex ; 2:3) 0.75; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 6.37 (1H, dd, *J* = 17.4 & 11.1 Hz, H3), 5.46 (1H, t, *J* = 7.8 Hz, H5), 5.16-5.07 (2H, m, H2 & H7), 4.94 (1H, d, *J* = 10.5 Hz, H1), 2.84 (2H, t, *J* = 7.5 Hz, H6), 1.77 (3H, s, CH_3), 1.71 (3H, s, CH_3), 1.65 (3H, s, CH_3); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 141.6, 133.8, 132.3, 131.9, 122.3, 110.7, 27.4, 25.8, 17.8, 11.7; **IR** (thin film) υ_{max} = 2975 (s), 2926 (s), 2857 (m), 1789 (w), 1640 (m), 1606 (m), 1448 (m), 1376 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 136 ($M^{+\bullet}$, 45%), 93 (100%).

2-Bromo-1,3,5-trimethoxybenzene (**83**)[51]



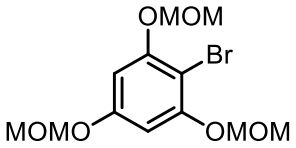
To a solution of 1,3,5-trimethoxybenzene (7.50 g, 44.6 mmol) in carbon tetrachloride (40 mL) was added NBS (6.61 g, 37.2 mmol) and the reaction mixture heated at reflux for 3 hrs. After cooling the reaction mixture was filtered, concentrated under reduced pressure and purified via silica gel chromatography using ethyl acetate : hexane (3:17) to give 2-bromo-1,3,5-trimethoxybenzene (**83**) as a white solid (7.45 g, 81%); **R_f** (EtOAc:Hex ; 1:4) 0.28; **m.p.** 85-86°C (lit. m.p. 84-86°C); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.17 (2H, s, CH), 3.87 (6H, s, CH_3O), 3.81 (3H, s, CH_3O); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 160.4, 157.4, 91.9, 91.6, 56.3, 55.5; **IR** (thin film) υ_{max} = 2941 (m), 2838, (m), 1586 (s), 1452 (s), 1384 (m), 1339 (m), 1227 (s), 1122 (s) cm^{-1}; **LRMS** (EI^+) *m/z* = 246 ($C_9H_{11}O_3{}^{79}Br$, $M^{+\bullet}$, 98%), 248 ($C_9H_{11}O_3{}^{81}Br$, $M^{+\bullet}$, 97%); **HRMS** (EI^+) calc. for ($C_9H_{11}O_3{}^{79}Br$ ($M^{+\bullet}$) 245.9892, found 245.9890, calc. for $C_9H_{11}O_3{}^{81}Br$ ($M^{+\bullet}$) 247.9871, found 247.9873.

1,3,5-Tris(methoxymethoxy)benzene (**264**)[53]



Sodium hydride 60% dispersion in mineral oil (5.70 g, 143 mmol) and hexane (40 mL) were added to a flask and stirred vigorously at room temperature for 30 minutes. The mixture was then allowed to settle and the majority of the hexane removed by pipette. Dimethylformamide (80 mL) was added to the flask followed by cooling to 0°C. Phloroglucinol (4.50 g, 35.7 mmol) was then added portion wise over 10 minutes followed by methoxymethylchloride (8.97 mL, 118 mmol) dropwise over 10 minutes. After warming to room temperature the resulting solution was stirred for 16 hours and then diluted with water (100 mL). Extraction with ether (3x50 mL), drying over magnesium sulfate, concentration under reduced pressure and purification by silica gel chromatograhy using ethyl acetate : hexane (1:4) afforded 1,3,5-tris(methoxymethoxy)benzene (**264**) as a clear colourless oil (5.68 g, 62%); $\mathbf{R_f}$ (EtOAc:Hex ; 1:4) 0.22; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.41 (3H, s, CH), 5.13 (6H, s, $CH_3O\underline{CH_2}O$), 3.47 (9H, s, $\underline{CH_3}OCH_2O$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 158.9, 98.4, 94.5, 56.1; **IR** (thin film) υ_{max} = 2955 (w), 2901 (m), 2827 (m), 1598 (s), 1471 (m), 1439 (w), 1399 (m), 1314 (w) cm^{-1}; **LRMS** (EI^+) *m/z* = 258 ($M^{+\bullet}$, 55%), 45 ($CH_3OCH_2^+$, 100%) ; **HRMS** (EI^+) calc. for $C_{12}H_{18}O_6$ ($M^{+\bullet}$) 258.1103, found 258.1116.

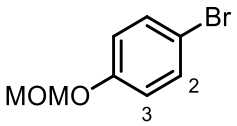
2-Bromo-1,3,5-tris(methoxymethoxy)benzene (**85**)[53]



To a solution of 1,3,5-tris(methoxymethoxy)benzene (**264**) (5.68 g, 22.0 mmol) in dichloromethane (60 mL) was added NBS (4.11 g, 23.1 mmol) followed by stirring at room temperature for 1 hour. The reaction was then evaporated on to silica under reduced pressure and purified by silica gel chromatography using ethyl acetate : hexane (3:17) to give 2-bromo-1,3,5-tris(methoxymethoxy)benzene (**85**) as a white solid (7.34 g, 98%); $\mathbf{R_f}$ (EtOAc:Hex ; 1:4) 0.20; **m.p.** 35-40 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.60 (2H, s, CH), 5.23 (4H, s, $CH_3O\underline{CH_2}O$), 5.14 (2H, s, $CH_3O\underline{CH_2}O$), 3.52 (6H, s, $\underline{CH_3}OCH_2O$), 3.47 (3H, s, $\underline{CH_3}OCH_2O$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 157.7, 155.2, 98.5, 96.1, 95.1, 94.6, 56.4, 56.1; **IR** (thin film) υ_{max} = 2957 (m), 2907 (m), 2828 (m), 1588 (vs), 1469 (m), 1392 (s), 1307 (w), 1232 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 336 ($C_{12}H_{17}O_6{}^{79}Br$, $M^{+\bullet}$,

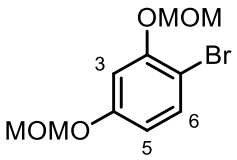
100%), 338 ($C_{12}H_{17}O_6{}^{81}Br$, $M^{+\bullet}$, 100%); **HRMS** (EI^+) calc. for $C_{12}H_{17}{}^{79}BrO_6$ ($M^{+\bullet}$) 336.0209, found 336.0208, calc. for $C_{12}H_{17}{}^{81}BrO_6$ ($M^{+\bullet}$) 338.0188, found 338.0192.

1-Bromo-4-(methoxymethoxy)benzene (**265**)[147]



A solution of 4-bromophenol (3.02 g, 17.4 mmol), in tetrahydrofuran (50 mL) was cooled to 0°C followed by the addition of sodium hydride 60% dispersion in mineral oil (1.05 g, 26.2 mmol) portionwise over 1 hour. Methoxymethylchloride (1.99 mL, 26.2 mmol) was then added dropwise over 10 minutes and the reaction stirred for 1 hour at 0°C. Dilution with water (80 mL) was then followed by extraction with ethyl acetate (3x50 mL). The combined organic layers were washed with brine (60 mL), dried over magnesium sulfate, filtered and purified via column chromatography using ethyl acetate : hexane (1:9) to afforded 1-bromo-4-(methoxymethoxy)benzene (**265**) as a clear colourless oil (3.12 g, 83%); $\mathbf{R_f}$ (EtOAc:Hex ; 1:9) 0.39; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.37 (2H, m, H2), 6.92 (2H, m, H3), 5.13 (2H, s, $CH_3O\underline{CH_2}O$), 3.54 (3H, s, $\underline{CH_3}OCH_2O$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 156.3, 132.2, 118.0, 114.1, 94.4, 56.0; **IR** (thin film) υ_{max} = 2955 (m), 2902 (m), 2862 (w), 1590 (m), 1488 (s), 1405 (w), 1234 (s), 1153 (s) cm^{-1}; **LRMS** (EI^+) *m/z* = 216 ($C_8H_9O_2{}^{79}Br$, $M^{+\bullet}$, 58%), 218 ($C_8H_9O_2{}^{81}Br$, $M^{+\bullet}$, 55%), 84 (100%); **HRMS** (EI^+) calc. for $C_8H_9O_2{}^{79}Br$ ($M^{+\bullet}$) 215.9786, found 215.9784, calc. for $C_8H_9O_2{}^{81}Br$ ($M^{+\bullet}$) 217.9765, found 217.9769.

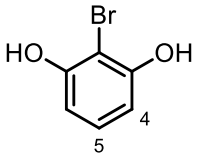
1-Bromo-2,4-bis(methoxymethoxy)benzene (**266**)[148]



Sodium hydride 60% dispersion in mineral oil (1.84 g, 46.0 mmol) and hexanes (40 mL) were added to a flask and stirred vigorously at room temperature for 30 minutes. The mixture was then allowed to settle and the majority of the hexane was removed by pipette. Dimethylformamide (40 mL) was added to the flask followed by cooling to 0°C. 4-Bromoresorcinol (2.17 g, 11.5 mmol) was then added portionwise over 10 minutes followed by methoxymethylchloride (2.62 mL, 34.4 mmol) dropwise over 10 minutes. After warming to room temperature the resulting solution was stirred for 16 hours and then diluted with water (100 mL). Extraction with ether (3x40 mL), drying over magnesium sulfate,

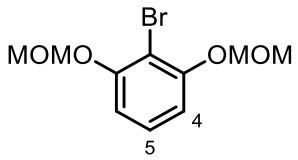
concentration under reduced pressure and purification by silica gel chromatograhy using diethyl ether : hexane (1:4) afforded 1-bromo-2,4-bis(methoxymethoxy)benzene (**266**) as a pale yellow oil (2.64 g, 83%); $\mathbf{R_f}$ (Ether:Hex ; 3:7) 0.26; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.41 (1H, d, *J* = 8.4 Hz, H6), 6.87 (1H, d, *J* = 2.8 Hz, H3), 6.63 (1H, dd, *J* = 8.8 & 2.8 Hz, H5), 5.23 (2H, s, $CH_3O\underline{CH_2}O$), 5.14 (2H, s, $CH_3O\underline{CH_2}O$), 3.52 (3H, s, $\underline{CH_3}OCH_2O$), 3.47 (3H, s, $\underline{CH_3}OCH_2O$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 157.5, 154.3, 133.2, 110.5, 105.3, 104.7, 95.1, 94.5, 56.4, 56.1; **IR** (thin film) υ_{max} = 2957 (m), 2904 (m), 2827 (w), 1587 (s), 1481 (s), 1393 (m), 1275 (m), 1218 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 276 ($C_{10}H_{13}O_4{}^{79}Br$, $M^{+\bullet}$, 100%), 278 ($C_{10}H_{13}O_4{}^{81}Br$, $M^{+\bullet}$, 100%); **HRMS** (EI^+) calc. for $C_{10}H_{13}O_4{}^{79}Br$ ($M^{+\bullet}$) 275.9997, found 276.0003, calc. for $C_{10}H_{13}O_4{}^{81}Br$ ($M^{+\bullet}$) 277.9977, found 277.9983.

2-Bromoresorcinol (**267**)[149]



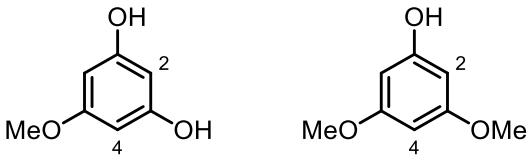
Bromine (3.83 mL, 74.4 mmol) was slowly added to resorcinol (2.48 g, 22.5 mmol) in chloroform (40 mL) over 5 minutes at room temperature. After refluxing for 1 hour the solvent was removed by rotary evaporation and the residue dissolved in methanol (10 mL) and water (55 mL). A solution of sodium sulfite (5.67 g, 45.0 mmol) and sodium hydroxide (1.80 g, 45.0 mmol) in water (65 mL) was added and stirred for 18 hours at room temperature. The reaction was then acidified to pH 5 with 1 M hydrochloric acid followed by extraction with diethyl ether (3x50 mL). The combined organic layers were dried over magnesium sulfate, concentrated under reduced pressure and then purified by silica gel chromatography using ethyl acetate : hexane (3:17) to give 2-bromoresorcinol (**267**) as pale orange crystals (3.66 g, 86%); $\mathbf{R_f}$ (EtOAc:Hex ; 3:7) 0.22; **m.p.** 83-84°C (lit. m.p. 84-85°C); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.09 (1H, t, *J* = 8.0 Hz, H5), 6.60 (2H, d, *J* = 8.0 Hz, H4), 5.48 (2H, br s, OH); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 152.9, 129.0, 108.1, 99.3; **IR** (thin film) υ_{max} = 3392 (m, br), 3051 (w), 3027 (w), 1601 (m), 1585 (m), 1465 (s), 1339 (w), 1232 (m) cm^{-1}; **LRMS** (ESI^-) *m/z* = 187 ($C_6H_5O_2{}^{79}Br$, $[M-H]^-$, 5%), 189 ($C_6H_5O_2{}^{81}Br$, $[M-H]^-$, 4%), 79 (Br^-, 100%); **HRMS** (ESI^-) calc. for $C_6H_4O_2{}^{79}Br$ ($[M-H]^-$) 186.9395, found 186.9393, calc. for $C_6H_4O_2{}^{81}Br$ ($[M-H]^-$) 188.9374, found 188.9373.

2-Bromo-1,3-bis(methoxymethoxy)benzene (**268**)



Sodium hydride 60% dispersion in mineral oil (2.00 g, 49.8 mmol) and hexanes (40 mL) were added to a flask and stirred vigorously at room temperature for 30 minutes. The mixture was then allowed to settle and the majority of the hexane was removed by pipette. Dimethylformamide (40 mL) was added to the flask followed by cooling to 0°C. 2-Bromo resorcinol (**267**) (3.15 g, 16.6 mmol) was then added portionwise over 20 minutes followed by methoxymethylchloride (3.16 mL, 41.6 mmol) dropwise over 10 minutes. After warming to room temperature the resulting solution was stirred for 16 hours and then diluted with water (100 mL). Extraction with ether (3x50 mL), drying over magnesium sulfate, concentration under reduced pressure and purification by silica gel chromatograhy using diethyl ether : hexane (1:4) gave 2-bromo-1,3-bis(methoxymethoxy)benzene (**268**) as a pale orange oil (4.28 g, 93%); **R_f** (Ether:Hex ; 1:1) 0.48; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.17 (1H, t, *J* = 8.4 Hz, H5), 6.83 (2H, d, *J* = 8.0 Hz, H4), 5.24 (4H, s, $CH_3O\underline{CH_2}O$), 3.51 (6H, s, $\underline{CH_3}OCH_2O$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 154.9, 128.1, 109.4, 103.8, 95.0, 56.3; **IR** (thin film) υ_{max} = 2957 (m), 2905 (m), 2826 (m), 1594 (m), 1573 (m), 1470 (s), 1440 (m), 1255 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 276 ($C_{10}H_{13}O_4{}^{79}Br$, $M^{+\bullet}$, 100%), 278 ($C_{10}H_{13}O_4{}^{81}Br$, $M^{+\bullet}$, 98%); **HRMS** (EI^+) calc. for $C_{10}H_{13}O_4{}^{79}Br$ ($M^{+\bullet}$) 275.9997, found 275.9995, calc. for $C_{10}H_{13}O_4{}^{81}Br$ ($M^{+\bullet}$) 277.9977, found 277.9964.

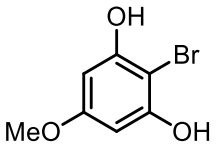
5-Methoxyresorcinol (**109**) & 3,5-dimethoxyphenol (**110**)[57]



Dry hydrogen chloride gas was bubbled through methanol (40 mL) for 30 minutes to give a saturated solution. Phloroglucinol dihydrate (3.11 g, 19.2 mmol), 1,4-dioxane (15 mL) and the saturated hydrogen chloride solution were then added to a sealed tube. After heating to 70°C, with stirring, for 2 hours the tube was allowed to cool, purged with nitrogen gas and the solution then neutralised with saturated aqueous sodium bicarbonate solution. The aqueous layer was then extracted with ethyl acetate (3×40 mL), the organic layers combined, washed with brine (20 mL) and dried over magnesium sulfate. Filtration, concentration under reduced pressure and purification via silica gel chromatography using ethyl acetate : hexane (3:7) afforded 5-methoxyresorcinol (**109**) as an off white solid (1.84 g, 68%); **R_f**

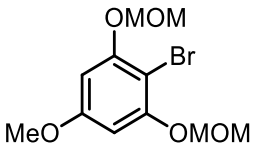
(EtOAc:Hex ; 3:7) 0.15; **m.p.** 76-77 °C (lit. m.p. 77-78°C); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.01 (2H, d, *J* = 2.0 Hz, H4), 5.96 (1H, t, *J* = 2.4 Hz, H2), 4.78 (2H, s, OH), 3.75 (3H, s, CH_3O); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 161.8, 157.4, 95.6, 94.4, 55.3; **IR** (thin film) υ_{max} = 3391 (s), 2974 (m), 2942 (m), 2846 (w), 1610 (s), 1508 (m), 1370 (m), 1306 (m) cm^{-1}; **LRMS** (ESI^-) *m/z* = 139 ($[M-H]^-$, 6%), 124 (100%); **HRMS** (ESI^-) calc. for $C_7H_7O_3$ ($[M-H]^-$) 139.0395, found 139.0394. A second fraction afforded 3,5-dimethoxyphenol (**110**) a viscous pale orange oil (385 mg, 13%); $\mathbf{R_f}$ (EtOAc:Hex ; 3:7) 0.35; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.08 (1H, t, *J* = 2.0 Hz, H4), 6.03 (2H, d, *J* = 1.6 Hz, H2), 5.10 (1H, br s, OH), 3.75 (6H, s, CH_3O); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 161.6, 157.3, 94.2, 93.2, 55.3; **IR** (thin film) υ_{max} = 3401 (m), 2959 (w), 2841 (w), 1602 (s), 1501 (m), 1342 (w), 1202 (s), 1151 (s) cm^{-1}; **LRMS** (ESI^-) *m/z* = 153 ($[M-H]^-$, 28%), 138 (100%); **HRMS** (ESI^-) calc. for $C_8H_9O_3$ ($[M-H]^-$) 153.0552, found 153.0550.

2-Bromo-5-methoxybenzene-1,3-diol (**112**)[58, 150]



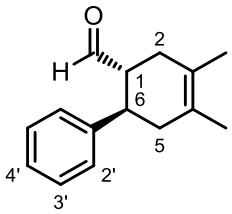
To a solution of 5-methoxyresorcinol (**109**) (1.92 g, 13.7 mmol) in chloroform (100 mL) and dioxane (5 mL) at 0°C was added portionwise over 1 hour a solution of 2,4,4,6-tetrabromo-2,5-cyclohexadienone (6.79 g, 16.6 mmol) in chloroform (20 mL). The resulting reaction mixture was stirred at 0 °C for 5 hours and then concentrated under reduced pressure. Purification via silica gel chromatography using dichloromethane followed by recrystallisation from dichloromethane gave 2-bromo-5-methoxybenzene-1,3-diol (**112**) as white crystals (1.60 g, 54%); $\mathbf{R_f}$ (DCM) 0.13; **m.p.** 74-77°C (lit. m.p. 73-75°C); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.22 (2H, s, CH), 5.41 (2H, s, OH), 3.75 (3H, s, CH_3O); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 160.7, 153.3, 94.7, 90.6, 55.5; **IR** (thin film) υ_{max} = 3453 (m), 2940 (w), 2849 (w), 1597 (vs), 1506 (m), 1444 (m), 1368 (m), 1323 (w) cm^{-1}; **LRMS** (ESI^-) *m/z* = 217 ($C_7H_6O_3{}^{79}Br$, $[M-H]^-$, 22%), 219 ($C_7H_6O_3{}^{81}Br$, $[M-H]^-$, 21%), 122 (100%); **HRMS** (ESI^-) calc. for $C_7H_6O_3{}^{79}Br$ ($[M-H]^-$) 216.9500, found 216.9500, calc. for $C_7H_6O_3{}^{81}Br$ ($[M-H]^-$) 218.9480, found 218.9482.

2-Bromo-5-methoxy-1,3-bis(methoxymethoxy)benzene (**113**)[151]



Sodium hydride 60% dispersion in mineral oil (557 mg, 13.9 mmol) and hexanes (60 mL) were added to a flask and stirred vigorously at room temperature for 30 minutes. The mixture was then allowed to settle and the majority of the hexane removed by pipette. Dimethylformamide (30 mL) was added to the flask followed by cooling to 0°C. 2-Bromo-5-methoxybenzene-1,3-diol (**112**) (1.02 g, 4.66 mmol) was then added portionwise over 20 minutes followed by methoxymethylchloride (881 µL, 11.6 mmol) dropwise over 10 minutes. After warming to room temperature the resulting solution was stirred for 16 hours and then diluted with water (60 mL). Extraction with ether (3x50 mL), drying over magnesium sulfate, concentration under reduced pressure and purification by silica gel chromatograhy using diethyl ether : hexane (1:4) gave 2-bromo-5-methoxy-1,3-bis(methoxymethoxy)benzene (**113**) as a clear colourless oil (946 mg, 66%); $\mathbf{R_f}$ (Ether:Hex ; 3:7) 0.26; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.46 (2H, s, CH), 5.22 (4H, s, $CH_3O\underline{CH_2}O$), 3.77 (3H, s, CH_3O), 3.51 (6H, s, $\underline{CH_3}OCH_2O$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 160.0, 155.1, 96.2, 95.0, 94.6, 56.2, 55.4; **IR** (thin film) υ_{max} = 2963 (s), 2911 (s), 2831 (m), 1605 (s), 1537 (w), 1482 (s), 1391 (m), 1303 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 306 ($C_{11}H_{15}O_5{}^{79}Br$, $M^{+\bullet}$, 100%), 308 ($C_{11}H_{15}O_5{}^{81}Br$, $M^{+\bullet}$, 98%); **HRMS** (EI^+) calc. for $C_{11}H_{15}O_5{}^{79}Br$ ($M^{+\bullet}$) 306.0103, found 306.0103, calc. for $C_{11}H_{15}O_5{}^{81}Br$ ($M^{+\bullet}$) 308.0082, found 308.0066.

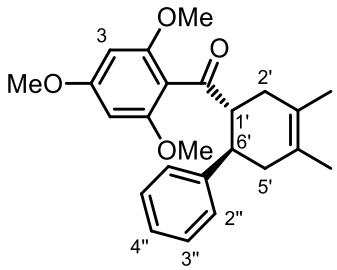
(±)-(1'*R*,6'*R*)-3,4-Dimethyl-6-phenyl-3-cyclohexene-1-carbaldehyde (**43**)



Cinnamaldehyde (2.34 g, 17.7 mmol), 2,3-diemthylbutadiene (8.02 mL, 70.9 mmol) and diethyl ether (50 mL) were added to a flask followed dropwise addition of borontrifluoride diethyletherate (445 µL, 3.54 mmol). The reaction was allowed to stir for 16 hours at room temperature followed by dilution with water (30 mL) and extraction with diethyl ether (3x40 mL). The combined organic layers were evaporated on to silica and purified by column chromatography using diethyl ether : hexane (1:9) to afford (±)-(1'*R*,6'*R*)-3,4-dimethyl-6-phenyl-3-cyclohexene-1-carbaldehyde (**43**) as a pale yellow oil (2.67 g, 71%); $\mathbf{R_f}$ (Ether:Hex ; 1:9) 0.26; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.47 (1H, d, *J* = 2.8 Hz, CHO),

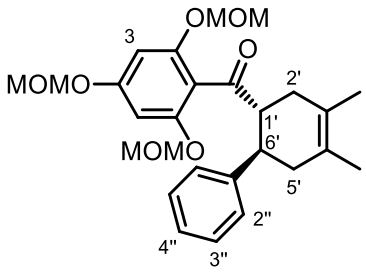
7.33-7.19 (5H, m, H2', 3' & 4'), 3.09 (1H, ddd, *J* = 10.4, 8.8 & 6.4, H6), 2.81 (1H, dddd, *J* = 12.8, 8.4, 5.2, 2.4 Hz, H1), 2.34-2.24 (3H, m, H2 & 5β), 2.09 (1H, dd, *J* = 17.2 & 4.4 Hz, H5α), 1.71 (3H, d, *J* = 0.8 Hz, CH_3), 1.67 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 204.5, 143.6, 128.8, 127.5, 126.8, 125.7, 123.5, 52.2, 41.5, 39.6, 31.1, 18.9 (2C); **IR** (thin film) υ_{max} = 2908 (s), 2832 (s), 2715 (m), 1724 (s), 1602 (m), 1494 (s), 1453 (s), 1383 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 214 ($M^{+\bullet}$, 38%), 107 (100%); **HRMS** (EI^+) calc. for $C_{15}H_{18}O$ ($M^{+\bullet}$) 214.1358, found 214.1358.

(±)-(1'*R*,6'*R*)-(2,4,6-Trimethoxyphenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl)methanone (**84**)



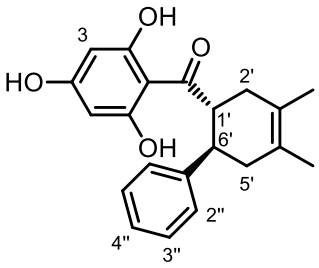
General procedure A using 2-bromo-1,3,5-trimethoxybenzene (**83**) (3.05 g, 12.4 mmol), butyl lithium (5.30 mL, 13.2 mmol) and (±)-(1'*R*,6'*R*)-3, 4-dimethyl-6-phenyl-3-cyclohexene-1-carbaldehyde (**43**) (887 mg, 4.14 mmol) and purification by column chromatography using diethyl ether : hexane (2:3) gave the alcohol products; **R_f** (Ether:Hex ; 1:1) 0.13 & 0.17; The alcohol products were then submitted to general procedure B with DMP (2.00 g, 4.71 mmol). Purification by column chromatography using diethyl ether : hexane (1:1) gave (±)-(1'*R*,6'*R*)-(2,4,6-trimethoxyphenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl)methanone (**84**) as a white solid (722 mg, 65% over 2 steps); **R_f** (Ether:Hex ; 3:2) 0.26; **m.p.** 122-128°C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.17-7.06 (5H, m, H2'', H3'' & H4'''), 5.94 (2H, s, H3), 3.78 (3H, s, CH_3O), 3.58 (6H, s, CH_3O), 3.55, (1H, ddd, *J* = 10.4, 10.4 & 5.6 Hz, H6'), 3.14 (1H, ddd, *J* = 9.6, 9.6 & 6.0 Hz), 2.42-2.10 (4H, m, H2' & H5'), 1.66 (3H, s, CH_3), 1.63 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 205.9, 162.2, 158.6, 145.1, 127.9, 127.6, 125.6, 124.8, 124.7, 113.9, 90.2, 55.6, 55.3, 53.2, 43.4, 40.9, 34.4, 18.8, 18.6; **IR** (thin film) υ_{max} = 2910 (m), 2838 (m), 1690 (m), 1605 (vs), 1586 (s), 1493 (w), 1454 (s), 1227 (s) cm^{-1}; **LRMS** (EI^+) *m/z* = 380 ($M^{+\bullet}$, 100%); **HRMS** (EI^+) calc. for $C_{24}H_{28}O_4$ ($M^{+\bullet}$) 380.1988, found 380.1997.

(±)-(1'*R*,6'*R*)-(2,4,6-Tris(methoxymethoxy)phenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl) methanone (**86**)



General procedure A using 2-bromo-1,3,5-tris(methoxymethoxy)benzene (**85**) (3.22 g, 9.58 mmol), butyl lithium (3.83 mL, 9.58 mmol) and (±)-(1'*R*,6'*R*)-3,4-dimethyl-6-phenyl-3-cyclohexene-1-carbaldehyde (**43**) (684 mg, 3.19 mmol) and purification by column chromatography using diethyl ether : hexane (2:3) gave the alcohol products; $\mathbf{R_f}$ (Ether:Hex ; 1:1) 0.20 & 0.26; The alcohol products were then submitted to general procedure B using DMP (2.65 g, 6.25 mmol) and purification by column chromatography using diethyl ether : hexane (2:3) gave (±)-(1'*R*,6'*R*)-(2,4,6-tris(methoxymethoxy)phenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl) (**86**) as a clear colourless oil (1.36 g, 90% over 2 steps); $\mathbf{R_f}$ (Ether:Hex ; 1:1) 0.30; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.28-7.08 (5H, m, H2'', 3'' & 4''), 6.43 (2H, s, H3), 5.11 (2H, s, $CH_3O\underline{CH_2}O$), 4.98-4.92 (4H, m, $CH_3O\underline{CH_2}O$), 3.57 (1H, ddd, *J* = 10.0, 10.0 & 6.0 Hz, H6'), 3.46 (3H, s, $\underline{CH_3}OCH_2O$), 3.37 (6H, s, $\underline{CH_3}OCH_2O$), 3.22 (1H, ddd, *J* = 9.6, 9.6 & 5.6 Hz, H1'), 2.35-2.13 (4H, m, H2' & 5'), 1.63 (6H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 204.8, 159.4, 155.7, 145.4, 128.0, 127.7, 125.7, 125.1, 124.1, 116.2, 96.7, 94.5, 94.4, 56.1, 53.4, 42.2, 40.4, 34.2, 18.7, 18.6; **IR** (thin film) υ_{max} = 3270 (m), 2912 (m), 2833 (w), 1629 (s), 1601 (s), 1519 (m), 1453 (m), 1237 (s); **LRMS** (EI^+) *m/z* = 470 ($M^{+\bullet}$, 5%), 184 (100%); **HRMS** (EI^+) calc. for $C_{27}H_{34}O_7$ ($M^{+\bullet}$) 470.2305, found 470.2304.

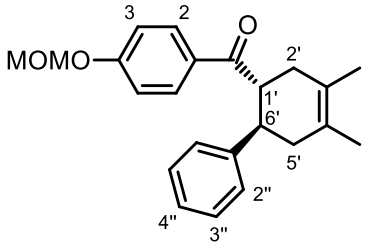
(±)-(1'*R*,6'*R*)-(2,4,6-Trihydroxyphenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl)methanone (**87**)



(±)-(1'*R*,6'*R*)-(2,4,6-tris(methoxymethoxy)phenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl) (**86**) (235 mg, 0.500 mmol), methanol (15 mL) and 8 drops of concentrated hydrochloric acid were added to a flask and heated at 45 ºC with stirring for 2 hours. The reaction mixture was then neutralised with a

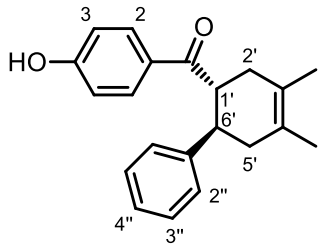
saturated sodium bicarbonate solution, extracted with ethyl acetate (2x30 mL) and dried over magnesium sulfate. Filtration, concentration under reduced pressure and purification via silica gel chromatography using diethyl ether : hexane (1:1) afforded (±)-(1'*R*,6'*R*)-(2,4,6-trihydroxyphenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl)methanone (**87**) as a pale yellow oil (126 mg, 75%); $\mathbf{R_f}$ (Ether:Hex ; 1:1) 0.11; **^{1}H-NMR** (400 MHz, CD_3OD) δ 7.19-7.02 (5H, m, H2'', H3'' & H4''), 5.73 (2H, s, H3), 4.62 (1H, ddd, *J* = 10.4, 10.4 & 4.8 Hz, H6'), 3.18 (1H, ddd, *J* = 11. 2, 9.2, 7.2 Hz, H1'), 2.39 (1H, dd, *J* = 16.0, 4.8 Hz, H5'α), 2.18-2.13 (3H, m, H2' & 5'β), 1.68 (3H, s, CH_3), 1.65 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, CD_3OD) δ 210.0, 165.9, 165.5, 146.8, 129.1, 128.4, 126.8, 126.2, 125.6, 106.1, 95.8, 51.4, 44.6, 42.7, 37.7, 18.9, 18.8; **IR** (thin film) υ_{max} = 3391 (w), 2907 (m), 2829 (w), 1701 (m), 1605 (s), 1451 (m), 1217 (m), 1154 (s) cm^{-1}; **LRMS** (ESI^+) *m/z* = 249 ($[M+Na]^+$, 55%), 121 (100%); **HRMS** (ESI^+) calc. for $C_{12}H_{18}O_4Na$ ($[M+Na]^+$) 249.1103, found 249.1103.

(±)-(1'*R*,6'*R*)-(4-Methoxymethoxyphenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl)methanone (**269**)



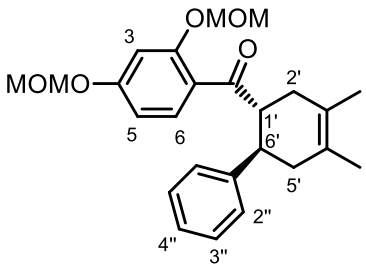
General procedure A using 1-bromo-4-(methoxymethoxy)benzene (**265**) (3.12 g, 14.4 mmol), butyl lithium (5.76 mL, 14.4 mmol) and (±)-(1'*R*,6'*R*)-3,4-dimethyl-6-phenyl-3-cyclohexene-1-carbaldehyde (**43**) (1.02 g, 4.80 mmol) and purification by column chromatography using ethyl acetate : hexane (1:4) gave the alcohol products; $\mathbf{R_f}$ (EtOAc:Hex ; 1:4) 0.11 & 0.17; The alcohol products were then submitted to general procedure B using DMP (4.07 g, 9.60 mmol) and purification by column chromatography using ethyl acetate : hexane (1:4) gave (±)-(1'*R*,6'*R*)-(4-methoxymethoxyphenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl)methanone (**269**) as a yellow oil (1.61 g, 95% over 2 steps); $\mathbf{R_f}$ (EtOAc:Hex ; 1:4) 0.24; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.83 (2H, m, H2), 7.25-7.14 (4H, m, H2'' & 3''), 7.05 (1H, m, H4''), 6.99 (2H, m, H3), 5.19 (2H, s, $CH_3O\underline{CH_2}O$), 3.96 (1H, ddd, *J* = 10.8, 10.8 & 6.0 Hz, H6'), 3.46 (3H, s, $\underline{CH_3}OCH_2O$), 3.28 (1H, ddd, *J* = 11.2, 8.0, 8.0 Hz, H1'), 2.35-2.21 (4H, m, H2' & H5'), 1.67 (6H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 201.8, 160.8, 144.8, 131.1, 130.2, 128.3, 127.3, 126.0, 125.6, 124.1, 115.6, 94.0, 56.2, 46.9, 42.8, 40.8, 37.1, 18.7, 18.6; **IR** (thin film) υ_{max} = 2903 (m), 2832 (m), 1671 (s), 1600 (s), 1508 (m), 1419 (m), 1311 (m), 1235 (s); **LRMS** (EI^+) *m/z* = 350 ($M^{+\bullet}$, 5%), 165 (100%); **HRMS** (EI^+) calc. for $C_{23}H_{26}O_3$ ($M^{+\bullet}$) 350.1882, found 350.1881.

(±)-(1'*R*,6'*R*)- (4-Hydroxyphenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl)methanone (**90**)



(±)-(1'*R*,6'*R*)-(4-methoxymethoxyphenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl)methanone (**269**) (1.60 g, 4.52 mmol), methanol (40 mL) and 8 drops of concentrated hydrochloric acid were added to a flask and heated at 40 ºC with stirring for 2 hours. The reaction mixture was then neutralised with saturated sodium bicarbonate solution, extracted with ethyl acetate (2x30 mL) and dried over magnesium sulfate. Filtration, concentration under reduced pressure and purification via silica gel chromatography using ethyl acetate : hexane (1:4) afforded (±)-(1'R,6'R)-(4-hydroxyphenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl)methanone (**90**) as white crystals (932 mg, 67%); $\mathbf{R_f}$ (EtOAc:Hex ; 1:4); **m.p.** 83-88°C; **^{1}H-NMR** (400 MHz, CD_3OD) δ 7.77 (2H, m, H2), 7.19 (2H, d, *J* = 7.6 Hz, H2''), 7.11 (2H, t, *J* = 7.6 Hz, H3''), 7.01 (1H, t, *J* = 7.6 Hz, H4''), 6.76 (2H, m , H3), 4.09 (1H, m, H6'), 3.15 (1H, ddd, *J* = 11.6, 11.6 & 6.0 Hz, H1'), 2.35-2.16 (4H, m, H2' & 5'), 1.68 (6H, s, CH_3); **^{13}C-NMR** (100 MHz, CD_3OD) δ 204.8, 163.8, 146.0, 132.0, 130.2, 129.2, 128.6, 127.1, 126.6, 125.1, 116.2, 47.8, 44.8, 42.0, 38.3 (2C); **IR** (thin film) υ_{max} = 3233 (m), 2912 (m), 2833 (m), 1648 (m), 1597 (s), 1578 (s), 1493 (w), 1285 (m), ; **LRMS** (ESI^+) *m/z* = 307 ($[M+H]^+$, 38%), 121 (100%); **HRMS** (ESI^+) calc. for $C_{21}H_{23}O_2$ ($[M+H]^+$) 307.1698, found 307.1698.

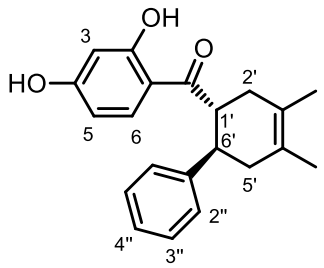
(±)-(1'*R*,6'*R*)-(2,4-Bis(methoxymethoxy)phenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl) methanone (**270**)



General procedure A using 1-bromo-2,4-bis(methoxymethoxy)benzene (**266**) (953 mg, 3.44 mmol), butyl lithium (1.38 mL, 3.44 mmol) and (±)-(1'*R*,6'*R*)-3,4-dimethyl-6-phenyl-3-cyclohexene-1-carbaldehyde (**43**) (243 mg, 1.15 mmol) and purification by column chromatography using diethyl ether : hexane (2:3) gave the alcohol products; $\mathbf{R_f}$ (Ether:Hex ; 2:3); The alcohol products were then submitted to general procedure B with DMP (830 mg, 1.96 mmol) and purification by column chromatography

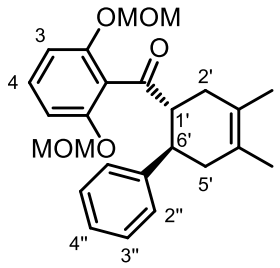
using diethyl ether : hexane (3:7) gave (±)-(1'*R*,6'*R*)-(2,4-bis(methoxymethoxy)phenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl)methanone (**270**) as a clear colourless oil (294 mg, 62% over 2 steps); $\mathbf{R_f}$ (Ether:Hex ; 1:4) 0.17; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.16-7.12 (4H, m, H2'' & 3''), 7.08-7.04 (2H, m, H6 & 4''), 6.72 (1H, d, *J* = 2.4 Hz, H3), 6.51 (1H, dd, *J* = 8.8 & 2.4 Hz, H5), 5.22-5.18 (2H, m, $CH_3O\underline{CH_2}O$) 5.14 (2H, s, $CH_3O\underline{CH_2}O$), 3.93 (1H, ddd, *J* = 10.8, 7.6 & 7.6 Hz, H6'), 3.48 (3H, s, $\underline{CH_3}OCH_2O$), 3.45 (3H, s, $\underline{CH_3}OCH_2O$), 3.18 (1H, ddd, *J* = 10.8, 7.6 & 7.6, H1'), 2.31 (2H, d, *J* = 7.6 Hz, H5'), 2.22 (2H, d, *J* = 8.0 Hz, H2'), 1.67 (3H, s, CH_3), 1.65 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 205.2, 160.8, 156.7, 144.8, 131.4, 128.0, 127.6, 125.9, 125.1, 124.6, 124.4, 108.7, 102.7, 94.5, 94.2, 56.4, 56.2, 52.0, 43.7, 40.6, 35.8, 18.7, 18.7; **IR** (thin film) υ_{max} = 2908 (w), 2829 (w), 1670 (w), 1602 (s), 1493 (w), 1248 (m), 1154 (s), 1009 (s) cm^{-1}; **LRMS** (EI^+) *m/z* = 410 ($M^{+\bullet}$, 3%), 248 (100%); **HRMS** (EI^+) calc. for $C_{25}H_{30}O_5$ ($M^{+\bullet}$) 410.2093, found 410.2093.

(±)-(1'*R*,6'*R*)-(2,4-Dihydroxyphenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl)methanone (**88**)



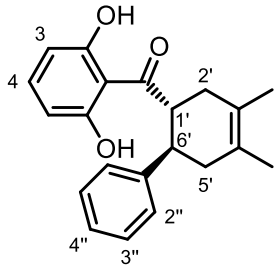
(±)-(1'*R*,6'*R*)-(2,4-bis(methoxymethoxy)phenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl) methanone (**270**) (269 mg, 656 µmol), methanol (15 mL) and 5 drops of concentrated hydrochloric acid were added to a flask and heated at 40ºC with stirring for 2 hours. The reaction mixture was then neutralised with saturated sodium bicarbonate solution, extracted with ethyl acetate (2x30 mL) and dried over magnesium sulfate. Filtration, concentration under reduced pressure and purification via silica gel chromatography using ethyl acetate : hexane (1:4) afforded (±)-(1'*R*,6'*R*)-(2,4-dihydroxyphenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl)methanone (**88**) as a clear colourless oil (140 mg, 66%); $\mathbf{R_f}$ (EtOAc:Hex ; 1:4); **^{1}H-NMR** (400 MHz, CD_3OD) δ 7.81 (1H, d, *J* = 9.2 Hz, H6), 7.19 (2H, m, H2''), 7.13 (2H, m, H3''), 7.04 (1H, tt, *J* = 6.8 & 1.6 Hz, H4''), 6.31 (1H, dd, *J* = 9.2 & 2.4 Hz, H5), 6.12 (1H, d, *J* = 2.4 Hz, H3), 4.02 (1H, ddd, *J* = 10.8, 10.8 & 5.2 Hz, H6'), 3.18 (1H, ddd, *J* = 11.2, 11.2 & 5.6 Hz, H1'), 2.36-2.17 (4H, m, H2' & H5'), 1.69 (6H, s, CH_3); **^{13}C-NMR** (100 MHz, CD_3OD) δ 208.9, 166.8, 166.7, 145.8, 133.7, 129.2, 128.6, 127.2, 126.7, 125.1, 114.2, 109.2, 103.6, 47.3, 44.6, 41.9, 38.4, 18.9, 18.8; **IR** (thin film) υ_{max} = 3338 (m), 2909 (m), 2836 (m), 1629 (vs), 1601 (s), 1443 (m), 1375 (m), 1239 (m) cm^{-1}; **LRMS** (ESI^-) *m/z* = 321 ($[M-H]^+$, 38%), 121 (100%); **HRMS** (ESI^-) calc. for $C_{21}H_{21}O_3$ ($[M-H]^-$) 321.1491, found 321.1489.

(±)-(1'*R*,6'*R*)- (2,6-Bis(methoxymethoxy)phenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl) methanone (**271**)



General procedure A using 2-bromo-1,3-bis(methoxymethoxy)benzene (**268**) (2.45 g, 8.83 mmol), butyl lithium (3.81 mL, 8.83 mmol) and (±)-(1'*R*,6'*R*)-3,4-dimethyl-6-phenyl-3-cyclohexene-1-carbaldehyde (**43**) (631 mg, 2.94 mmol) and purification by column chromatography using diethyl ether : hexane (3:7) gave the alcohol products; $\mathbf{R_f}$ (Ether:Hex ; 1:1) 0.22 & 0.28; The alcohol products were then submitted to general procedure B with DMP (1.87 g, 4.41 mmol) and purification by column chromatography using diethyl ether : hexane (3:7) gave (±)-(1'*R*,6'*R*)- (2,6-bis(methoxymethoxy)phenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl)methanone (**271**) as a pale yellow oil (1.04 g, 86% over 2 steps); $\mathbf{R_f}$ (Ether:Hex ; 2:3) 0.31; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.28-7.09 (6H, m, H4, H2'', H3'' & H4''), 6.72 (2H, d, *J* = 8.4 Hz, H3), 5.01-4.94 (4H, m, $CH_3O\underline{CH_2}O$), 3.57 (1H, ddd, *J* = 10.0, 10.0 & 5.6 Hz, H6'), 3.37 (6H, s, $\underline{CH_3}OCH_2O$), 3.26 (1H, ddd, *J* = 9.6, 9.6 & 5.6, H1'), 2.36-2.15 (4H, m, H2' & H5'), 1.63 (6H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 205.3, 154.7, 145.4, 130.6, 128.0, 127.7, 125.7, 125.2, 123.9, 122.0, 108.0, 94.3, 56.1, 53.4, 41.8, 40.2, 33.9, 18.7, 18.6; **IR** (thin film) υ_{max} = 2904 (m), 2829 (w), 1703 (m), 1595 (m), 1464 (m), 1400 (w), 1248 (m), 1154 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 410 ($M^{+\bullet}$, 3%), 181 (100%); **HRMS** (EI^+) calc. for $C_{25}H_{30}O_5$ ($M^{+\bullet}$) 410.2093, found 410.2097.

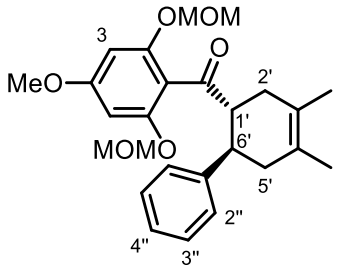
(±)-(1'*R*,6'*R*)- (2,4-Dihydroxyphenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl)methanone (**89**)



(±)-(1'*R*,6'*R*)-(2,6-bis(methoxymethoxy)phenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl) methanone (**271**) (995 mg, 2.42 mmol), methanol (30 mL) and 10 drops of concentrated hydrochloric acid were added to a flask and heated at 55ºC with stirring for 2 hours. The reaction mixture was then

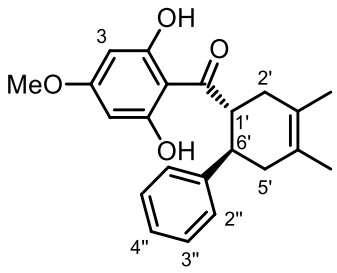
neutralised with saturated sodium bicarbonate solution, extracted with ethyl acetate (2x40 mL) and dried over magnesium sulfate. Filtration, concentration under reduced pressure and purification via silica gel chromatography using diethyl ether : hexane (3:7) afforded (±)-(1'*R*,6'*R*)-(2,4-dihydroxyphenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl)methanone (**89**) as a bright yellow solid (600 mg, 77%); $\mathbf{R_f}$ (Ether:Hex ; 3:7) 0.22; **m.p.** 98-103°C; **^{1}H-NMR** (400 MHz, CD_3OD) δ 7.16 (2H, d, *J* = 7.2 Hz, H2''), 7.11-6.99 (4H, m, H4, H3'' & H4''), 6.27 (2H, d, *J* = 8.4 Hz, H3), 4.65 (1H, ddd, *J* = 11.2, 11.2 & 5.2 Hz, H6'), 3.21 (1H, m, H1'), 2.43 (1H, m, H5'β), 2.20-2.13 (3H, m, H2' & H5'α), 1.65 (3H, s, CH_3), 1.62 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, CD_3OD) δ 212.4, 162.9, 146.4, 136.7, 129.1, 128.3, 126.8, 126.6, 125.4, 112.1, 108.3, 52.4, 44.7, 42.3, 37.2, 18.9 (2C); **IR** (thin film) υ_{max} = 3252 (m), 2910 (m), 2833 (m), 1626 (s), 1582 (s), 1449 (s), 1378 (w), 1221 (s) cm^{-1}; **LRMS** (ESI^-) *m/z* = 321 ($[M-H]^+$, 100%); **HRMS** (ESI^-) calc. for $C_{21}H_{21}O_3$ ($[M-H]^-$) 321.1491, found 321.1491.

(±)-(1'*R*,6'*R*)-(4-Methoxy-2,6-bis(methoxymethoxy)phenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl)methanone (**272**)



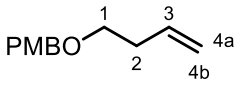
General procedure A using 2-bromo-5-methoxy-1,3-bis(methoxymethoxy)benzene (**113**) (456 mg, 1.49 mmol), butyl lithium (0.642 mL, 1.49 mmol) and (±)-(1'*R*,6'*R*)-3,4-dimethyl-6-phenyl-3-cyclohexene-1-carbaldehyde (**43**) (159 mg, 0.743 mmol) and purification by column chromatography using diethyl ether : hexane (1:1) gave the alcohol products; $\mathbf{R_f}$ (Ether:Hex ; 1:1) 0.13 & 0.17; The alcohol products were then submitted to general procedure B with DMP (473 mg, 1.11 mmol) and purification by column chromatography using diethyl ether : hexane (2:3) gave (±)-(1'*R*,6'*R*)-(4-methoxy-2,6-bis(methoxymethoxy)phenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl)methanone (**272**) as a clear colourless oil (194 mg, 71% over 2 steps); $\mathbf{R_f}$ (Ether:Hex ; 1:1) 0.28; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.24-7.18 (4H, m, H2'' & H3''), 7.10 (1H, t, *J* = 7.2 Hz, H4''), 6.30 (2H, s, H3), 4.98-4.92 (4H, m, $CH_3O\underline{CH_2}O$), 3.75 (3H, s, CH_3O), 3.58 (1H, ddd, *J* = 10.0, 10.0 & 5.2 Hz, H6'), 3.34 (6H, s, $\underline{CH_3}OCH_2O$), 3.22 (1H, ddd, *J* = 10.0, 10.0 & 6.0 Hz, H1'), 2.36-2.13 (4H, m, H2' & H5'), 1.63 (6H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 204.9, 161.9, 156.0, 145.4, 127.9, 127.7, 125.7, 125.1, 124.1, 115.2, 94.5 (2C), 56.1, 55.3, 53.4, 42.3, 40.5, 34.3, 18.7, 18.6; **IR** (thin film) υ_{max} = 2908 (m), 2833 (w), 1698 (m), 1606 (s), 1590 (s), 1451 (m), 1392 (m), 1216 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 440 ($M^{+\bullet}$, 10%), 211 (100%); **HRMS** (EI^+) calc. for $C_{26}H_{32}O_6$ ($M^{+\bullet}$) 440.2199, found 440.2193.

(±)-(1'*R*,6'*R*)-(2,6-Dihydroxy-4-methoxyphenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl) methanone (**87**)



(±)-(1'*R*,6'*R*)-(4-methoxy-2,6-bis(methoxymethoxy)phenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl)methanone (**272**) (274 mg, 0.777 mmol), methanol (20 mL) and 4 drops of concentrated hydrochloric acid were added to a flask and heated at 55ºC with stirring for 2 hours. The reaction mixture was then neutralised with saturated sodium bicarbonate solution, extracted with ethyl acetate (2x40 mL) and dried over magnesium sulfate. Filtration, concentration under reduced pressure and purification via silica gel chromatography using diethyl ether : hexane (1:1) afforded (±)-(1'*R*,6'*R*)-(2,6-dihydroxy-4-methoxyphenyl)(3',4'-dimethyl-6'-phenylcyclohex-3'-en-1'-yl) methanone (**87**) as a clear oil (195 mg, 71%); $\mathbf{R_f}$ (Ether:Hex ; 1:1) 0.26; **^{1}H-NMR** (400 MHz, CD_3OD) δ 7.18-7.11 (4H, m, H2'' & H3''), 7.03 (1H, t, *J* = 6.8 Hz, H4''), 5.84 (2H, s, H3), 4.62 (1H, ddd, *J* = 10.0, 10.0 & 4.8 Hz, H6'), 3.72 (3H, s, CH_3), 3.19 (1H, m, H1'), 2.40 (1H, m, H5'β), 2.19-2.13 (3H, m, H2' & H5'α), 1.68 (3H, s, CH_3), 1.65 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, CD_3OD) δ 210.4, 167.3, 165.4, 146.8, 129.1, 128.4, 126.8, 126.3, 125.6, 106.8, 94.3, 55.8, 51.6, 44.7, 42.6, 37.6, 18.9, 18.8; **IR** (thin film) υ_{max} = 3233 (w), 2907 (w), 2830 (w), 1622 (vs), 1571 (s), 1403 (m), 1235 (s), 1207 (s) cm^{-1}; **LRMS** (ESI^+) *m/z* = 353 ($[M+H]^+$, 15%), 375 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{22}H_{25}O_4$ ($[M+H]^+$) 353.1753, found 353.1752, calc. for $C_{22}H_{24}O_4Na$ ($[M+Na]^+$) 375.1572, found 375.1572.

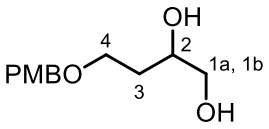
1-((But-3-enyloxy)methyl)-4-methoxybenzene (**97**)[55]



Sodium hydride 60% in mineral oil (5.27 g, 132 mmol) and hexane (30 mL) were added to a flask and stirred vigorously at room temperature for 30 minutes. The mixture was then allowed to settle and the majority of the hexane removed by pipette. Dimethylformamide (120 mL) was added to the flask followed by 3-buten-1-ol (4.18 g, 58.0 mmol) in THF (15 mL). The solution was stirred 1.5 hours after which *para*-methoxybenzyl chloride (7.15 mL, 52.7 mmol) was added and the mixture stirred overnight. The reaction was then quenched with a saturated solution of ammonium chloride (50 mL) and extracted with ethyl acetate (3x50 mL). The organic extracts were combined, washed with brine (40 mL), dried

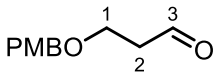
over magnesium sulfate, concentrated under reduced pressure and purified by silica gel chromatograhy using diethyl ether : hexane (1:9) to afford 1-((but-3-enyloxy)methyl)-4-methoxybenzene (**97**) as a clear colourless oil (9.09 g, 91%); $\mathbf{R_f}$ (Ether:Hex ; 1:9) 0.33; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.26 (2H, m, ArH), 6.87 (2H, m, ArH), 5.83 (1H, m, H3), 5.12-5.02 (2H, m, H4a & H4b), 4.45 (2H, s, $ArCH_2$), 3.80 (3H, s, CH_3O), 3.49 (2H, t, *J* = 6.8 Hz, H1), 2.36 (2H, m, H2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 159.1, 135.3, 130.5, 129.2, 116.3, 113.7, 72.5, 69.3, 55.2, 34.2; **IR** (thin film) υ_{max} = 2934 (m), 2907 (m), 2855 (m), 1641 (w), 1613 (s), 1513 (s), 1360 (m), 1248 (s) cm^{-1}; **LRMS** (EI^+) *m/z* = 192 ($M^{+\bullet}$, 25%), 121 (100%); **HRMS** (EI^+) calc. for $C_{12}H_{16}O_2$ ($M^{+\bullet}$) 192.1150, found 192.1157.

4-(4-Methoxybenzyloxy)butane-1,2-diol (**98**)[56]



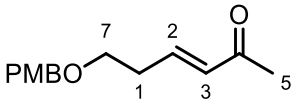
1-((But-3-enyloxy)methyl)-4-methoxybenzene (**97**) (9.09 g, 47.3 mmol) was dissolved in a mixture of 2-methyl propenol (100 mL) and water (100 mL). Potassium osmate dihydrate (523 mg, 1.42 mmol) and *N*-methylmorpholine oxide (11.1 g, 94.6 mmol) were added and the mixture stirred at room temperature for 24 hours. The reaction was then quenched with saturated sodium thiosulfate (50 mL) and ethyl acetate (50 mL). The mixture was stirred vigorously for 3 hours and the layers separated. The aqueous phase was extracted with ethyl acetate (3x50 mL) and the combined organic extracts washed with brine (40 mL), dried over magnesium sulfate, concentrated under reduced pressure and purified by silica gel chromatograhy using ethyl acetate : hexane (4:1) to afford 4-(4-methoxybenzyloxy)butane-1,2-diol (**98**) as a pale yellow oil (9.77 g, 91%); $\mathbf{R_f}$ (EtOAc:Hex ; 4:1) 0.11; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.25 (2H, m, ArH), 6.89 (2H, m, ArH), 4.46 (2H, s, $ArCH_2$), 3.90 (1H, m, H2), 3.80 (3H, s, OCH_3), 3.70-3.58 (3H, m, H1a & H4), 3.49 (1H, m, H1b), 3.22-3.14 (1H, m, OH), 2.39 (1H, m, OH), 1.88-1.67 (2H, m, H3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 159.3, 129.8, 129.3, 113.8, 72.7, 71.2, 67.8, 66.5, 55.2, 32.7; **IR** (thin film) υ_{max} = 3369 (m), 2919 (m), 2863 (m), 1612 (m), 1513 (s), 1302 (w), 1248 (s) 1090 (m) cm^{-1}; **LRMS** (ESI^+) *m/z* = 249 ($[M+Na]^+$, 55%), 121 (100%); **HRMS** (ESI^+) calc. for $C_{12}H_{18}O_4Na$ ($[M+Na]^+$) 249.1103, found 249.1103.

3-(4-Methoxybenzyloxy)propanal (**99**)[62]



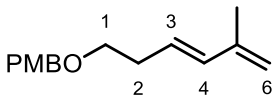
Diol **98** (3.18 g, 14.1 mmol) was dissolved in dichloromethane (100 mL) and the solution cooled to 0°C. Anhydrous sodium carbonate (3.28 g, 30.9 mmol), was then added followed by lead (IV) acetate (12.5 g, 28.2 mmol) and the mixture warmed up to room temperature and stirred for 12 hours. The orange mixture was then filtered through a pad of celite, concentrated and diluted with diethyl ether (50 mL). The mixture was again filtered through a pad of celite washing with ether (20 mL) and concentrated under reduced pressure. Purification by silica gel chromatograhy using ethyl acetate : hexane (2:3) afforded 3-(4-methoxybenzyloxy)propanal (**99**) as a clear colourless oil (2.25 g, 82%); $\mathbf{R_f}$ (EtOAc:Hex ; 2:3) 0.33; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.75 (1H, t, *J* = 2 Hz, CHO), 7.24 (2H, m, ArH), 6.87 (2H, m, ArH), 4.44 (2H, s, $ArCH_2$), 3.78 (3H, s, OCH_3), 3.77 (2H, t, *J* = 6.0 Hz, H1), 2.65 (2H, dt, *J* = 6.0 & 1.6 Hz, H2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 201.09, 159.2, 129.8, 129.2, 113.7, 72.7, 63.4, 55.1, 43.7; **IR** (thin film) υ_{max} = 2905 (m), 2861 (m), 2732 (w), 1724 (s), 1612 (m), 1513 (s), 1362 (m), 1247 (s) cm^{-1}; **LRMS** (EI^+) *m/z* = 194 ($M^{+\bullet}$, 30%), 121 (100%); **HRMS** (EI^+) calc. for $C_{11}H_{14}O_3$ ($M^{+\bullet}$) 194.0943, found 194.0945.

(*E*)-6-((4-Methoxybenzyl)oxy)hex-3-en-2-one (**101**)



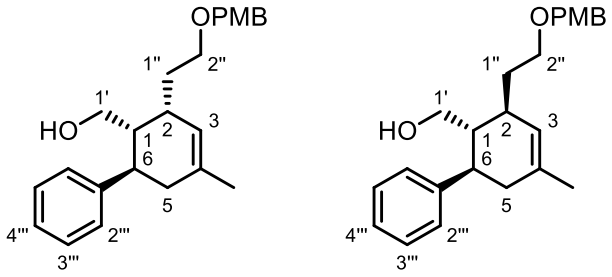
3-(4-Methoxybenzyloxy)propanal (**99**) (3.61 g, 18.6 mmol) and (triphenylphosphoranlidene)-2-propane (7.70 g, 24.2 mmol) were dissolved in chloroform (100 mL) and heat at reflux for 12 hours. The solution was then allowed to cool and then evaporated on to silica under reduced pressure. Flash column chromatography using ethyl acetate : hexane (1:1) then afforded (*E*)-6-((4-methoxybenzyl)oxy)hex-3-en-2-one (**101**) as a clear oil (4.76 g, 84%); $\mathbf{R_f}$ (EtOAc:Hex ; 1:1) 0.46; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.25 (2H, m, ArH), 6.88 (2H, m, ArH), 6.81 (1H, dt, *J* = 16.4, & 6.4 Hz, H2), 6.12 (1H, dt, *J* = 16.0, 1.6 Hz, H3), 4.46 (2H, s, $ArCH_2$), 3.80 (3H, s, OMe), 3.57 (2H, t, *J* = 6.8 Hz, H7), 2.51 (2H, dtd, *J* = 12.8, 6.4 & 1.6 Hz, H1), 2.24 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 198.3, 159.2, 144.8, 132.5, 130.0, 129.2, 113.7, 72.6, 67.8, 55.1, 32.7, 26.7; **IR** (thin film) υ_{max} = 2934 (m), 2858 (m), 1696 (m), 1674 (s), 1612 (s), 1513 (s), 1360 (m), 1248 (vs) cm^{-1}; **LRMS** (EI^+) *m/z* = 234 ($M^{+\bullet}$, 5%), 203 (100%); **HRMS** (EI^+) calc. for $C_{14}H_{18}O_3$ ($M^{+\bullet}$) 234.1256, found 234.1253.

(*E*)-1-Methoxy-4-(((5-methylhexa-3,5-dien-1-yl)oxy)methyl)benzene (**91**)



Methyltriphenylphosphonium bromide (4.02 g, 11.2 mmol) in tetrahydrofuran (50 mL) was treated with potassium *tert*-butoxide (1.10 g, 9.76 mmol) at room temperature and then heated at 60°C for 4 hours. After cooling to room temperature a solution of (*E*)-6-((4-methoxybenzyl)oxy)hex-3-en-2-one (**101**) (1.76 g, 7.51 mmol) in tetrahydrofuran (15 mL) was added followed by stirring for 18 hours at 25°C. The solution was then evaporated on to silica under reduced pressure and was purified by flash column chromatography using ethyl acetate : hexane (1:1) to afford (*E*)-1-methoxy-4-(((5-methylhexa-3,5-dien-1-yl)oxy)methyl)benzene (**91**) as a clear colourless oil (1.31 g, 75%); $\mathbf{R_f}$ (EtOAc:Hex ; 1:1) 0.58; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.26 (2H, m, ArH), 6.87 (2H, m, ArH), 6.20 (1H, d, *J* = 15.6 Hz, H4), 5.66 (1H, dt, *J* = 15.6 & 7.2 Hz, H3), 4.88 (2H, s, H6), 4.45 (2H, s, $PhCH_2$), 3.80 (3H, s, OMe), 3.50 (2H, t, *J* = 7.2 Hz, H1), 2.41 (2H, m, H2), 1.83 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 159.1, 141.9, 134.5, 130.5, 129.2, 126.8, 114.8, 113.7, 72.5, 69.5, 55.2, 33.2, 18.6; **IR** (thin film) υ_{max} = 2935 (s), 2854 (s), 1611 (s), 1513 (vs), 1455 (m), 1301 (m), 1247 (vs), 1094 (s) cm^{-1}; **LRMS** (EI^+) *m/z* = 232 ($M^{+\bullet}$, 5%), 137 (100%); **HRMS** (EI^+) calc. for $C_{15}H_{20}O_2$ ($M^{+\bullet}$) 232.1463, found 232.1466.

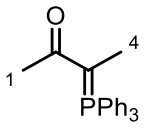
(±)-((1*R*,2*R*,6*R*)-4-Methyl-6-phenyl-cyclohex-3-en-1-yl)methanol (**102**) & (±)- ((1*R*,2*S*,6*R*)-4-methyl-6-phenyl-cyclohex-3-en-1-yl)methanol (**103**)



Cinnamaldehyde (289 mg, 2.18 mmol), (*E*)-1-methoxy-4-(((5-methylhexa-3,5-dien-1-yl)oxy)methyl)benzene (**91**) (1.01 g, 4.37 mmol) and dichloromethane (4 mL) were added to a pressure vessel and sealed. The vessel was then pressurised to 19 kbar for 3 days at room temperature. After relieving the pressure the reaction mixture was transferred to a flask and the dichloromethane evaporated under reduced pressure. The resulting residue was then redissolved in diethyl ether (30 mL) and cooled to 0°C. Lithium aluminium hydride (8.72 mL, 1.0 M in diethyl ether) was then added dropwise over 15 min and the reaction then left to stir for 30 min. Ethyl acetate was then added dropwise until the excess lithium aluminium hydride had been quenched and the bubbling subsided. A saturated

aqueous solution of potassium sodium tartrate (50 mL) was then added followed by stirring for 2 hours. Extraction of the mixture with diethyl ether (3x30 mL) was followed by washing the combined organic layers with brine (2x20 mL) and evaporation on to silica under reduced pressure. Purification by flash column chromatography using dichloromethane afforded (±)-((1*R*,2*R*,6*R*)-4-methyl-6-phenyl-cyclohex-3-en-1-yl)methanol (**102**) as a clear colourless oil (215 mg, 27%); $\mathbf{R_f}$ (Ether:Hex ; 3:2) 0.35; **^{1}H-NMR** (800 MHz, $CDCl_3$) δ 7.20 (2H, dd, *J* = 7.2 & 7.2 Hz, H3'''), 7.15 (2H, d, *J* = 8.8 Hz, ArH), 7.13-7.09 (3H, m, H2''' & H4'''), 6.79 (2H, d, *J* = 8.8 Hz, ArH), 5.01 (1H, s, H3), 4.36 (2H, m, $ArCH_2$), 3.72 (3H, s, OMe), 3.51-3.49 (1H, m, H2''a), 3.44-3.41 (1H, m, H2''b), 3.38-3.35 (1H, m, H1'a), 3.27-3.25 (1H, m, H1'b), 2.74 (1H, dt, *J* = 8.8 & 6.4 Hz, H6), 2.33 (1H, br s, H2), 2.13-2.03 (3H, m, H1 & H5), 1.90 (1H, br s, OH), 1.83-1.78 (1H, m, H1''a), 1.61 (3H, s, CH_3), 1.44-1.40 (1H, m, H1''b); **^{13}C-NMR** (200 MHz, $CDCl_3$) δ 159.2, 145.0, 133.0, 130.3, 129.4, 128.5, 127.6, 126.3, 125.1, 113.8, 72.8, 68.8, 55.3, 44.2, 39.6, 37.9, 32.3, 30.9, 30.4, 23.3; **IR** (thin film) υ_{max} = 3435 (w), 2910 (m), 2870 (m), 1721 (w), 1612 (m), 1513 (s), 1453 (w), 1248 (s) cm^{-1}; **LRMS** (ESI^+) *m/z* = 389($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{24}H_{30}O_3Na$ ($[M+Na]^+$) 389.2093, found 389.2093. A further fraction afforded (±)- ((1*R*,2*S*,6*R*)-4-methyl-6-phenyl-cyclohex-3-en-1-yl)methanol (**103**) as a clear colourless oil (168 mg, 21%); $\mathbf{R_f}$ (Ether:Hex ; 3:2) 0.20; **^{1}H-NMR** (800 MHz, $CDCl_3$) δ 7.30 (2H, dd, *J* = 8.0 & 8.0 Hz, H3'''), 7.26 (2H, d, *J* = 8.0 Hz, ArH), 7.2-7.19 (3H, m, H2''' & H4'''), 6.87 (2H, d, *J* = 8.0 Hz, ArH), 5.35 (1H, br s, H3), 4.44 (2H, m, $ArCH_2$), 3.79 (3H, s, OMe), 3.59-3.52 (3H, m, H1'a & H2''), 3.30 (1H, d, *J* = 12.0 Hz, H1'b), 2.82 (1H, ddd, *J* = 11.2, 11.2 & 5.6 Hz, H6), 2.41 (1H, s, H2), 2.20 (1H, m, H5a), 2.08 (1H, dd, *J* = 17.2 & 4.4 Hz, H5b), 1.95-1.91 (1H, m, H1''a), 1.68 (3H, s, CH_3), 1.63-1.58 (2H, m, H1 & H1''b), 1.49 (1H, br s, OH) ; **^{13}C-NMR** (200 MHz, $CDCl_3$) δ 159.1, 145.2, 133.1, 130.5, 129.2, 128.6, 127.7, 126.3, 125.0, 113.8, 72.7, 68.1, 61.8, 55.2, 45.6, 43.3, 39.2, 34.5, 33.7, 23.3; **IR** (thin film) υ_{max} = 3418 (w), 2916 (s), 2857 (s), 1724 (w), 1612 (m), 1513(s), 1453 (w), 1248 (s) cm^{-1}; **LRMS** (ESI^+) *m/z* = 389($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{24}H_{30}O_3Na$ ($[M+Na]^+$) 389.2093, found 389.2090.

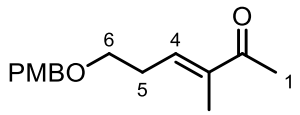
3-(Triphenylphosphoranylidene)butan-2-one (**135**)[61]



Ethyltriphenylphosphonium bromide (7.30 g, 19.7 mmol) in tetrahydrofuran (100 ml) was stirred at room temperature under nitrogen while butyl lithium in hexane (12.9 ml, 20.6 mmol) was added dropwise over 5 minutes. After 30 minutes a solution of acetyl chloride (700 µl, 9.83 mmol) in tetrahydrofuran (5 ml) was added and after a further 2 hours the mixture added to water (50 mL). Extraction with diethyl ether (3x50 mL), washing the combined extracts with water (3x50 mL), drying

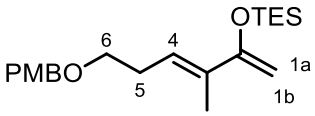
over magnesium sulfate and evaporation gave a yellow oil which crystallised on standing. Recrystallisation from diethyl ether gave 3-(triphenylphosphoranylidene)butan-2-one (**135**) as a pale yellow solid (991 mg, 30%); **m.p.** 217-220 °C (lit. m.p. 215-218°C); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.70-7.43 (15H, m, PPh_3), 2.13 (3H, s, H1), 1.65 (3H, d, *J* = 15.6 Hz, H4);

(*E*)-6-(4-Methoxybenzyloxy)-3-methylhex-3-en-2-one (**136**)



Aldehyde **99** (9.19 mg, 4.73 mmol) and the stabilised ylide 3-(triphenylphosphoranylidene)butan-2-one (**135**) (1.89 g, 5.68 mmol) were dissolved in chloroform (60 mL) and heated at reflux for 12 hours. The yellow solution was then allowed to cool, concentrated under reduced pressure and purified by silica gel chromatograhy using ethyl acetate : hexane (2:3) to afford (*E*)-6-(4-methoxybenzyloxy)-3-methylhex-3-en-2-one (**136**) as a colourless oil (1.15 g, 98%); **R_f** (EtOAc:Hex ; 2:3) 0.37; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.26 (2H, m, ArH), 6.89 (2H, m, ArH), 6.65 (1H, dt, *J* = 7.2 & 1.2 Hz, H4), 4.47 (2H, s, $ArCH_2$), 3.81 (3H, s, OCH_3), 3.57 (2H, t, *J* = 6.8 Hz, H6), 2.54 (2H, qd, *J* = 7.6 & 0.8 Hz, H5), 2.30 (3H, s, H1), 1.77 (3H, d, *J* = 0.8 Hz, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 199.7, 159.2, 139.9, 138.9, 130.2, 129.2, 113.8, 72.6, 68.1, 55.2, 29.7, 25.4, 11.3; **IR** (thin film) υ_{max} = 2932 (m), 2858 (m), 1667 (vs), 1612 (s), 1513 (s), 1365 (m), 1248 (s), 1097 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 248 ($M^{+\bullet}$, 2%), 121 (100%); **HRMS** (EI^+) calc. for $C_{15}H_{20}O_3$ ($M^{+\bullet}$) 248.1412, found 248.1414.

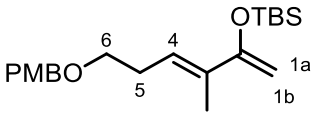
(*E*)-Triethyl(6-(4-methoxybenzyloxy)-3-methylhexa-1,3-diene-2-yloxy)silane (**137**)



To a 0 °C solution of enone **136** (707 mg, 2.85 mmol) and triethyl amine (516 µL, 3.70 mmol) in diethyl ether (30 mL), was added triethylsilyl trifluoromethanesulfonate (773 µL, 3.42 mmol). After stirring for 1 hour the reaction mixture was concentrated under reduced pressure and purified by silica gel chromatograhy using ethyl acetate : hexane (2:3) to afford (*E*)-triethyl(6-(4-methoxybenzyloxy)-3-methylhexa-1,3-diene-2-yloxy)silane (**137**) as a colourless oil (996 mg, 96%); **R_f** (EtOAc:Hex ; 2:3) 0.63; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.26 (2H, m, ArH), 6.87 (2H, m, ArH), 6.04 (1H, t, *J* = 6.8 Hz, H4), 4.45 (2H, s, $ArCH_2$), 4.40 (1H, s, H1a), 4.26 (1H, s, H1b), 3.79 (3H, s, OCH_3), 3.49 (2H, t, *J* = 7.2 Hz, H6), 2.44 (2H, q, *J* = 7.6 Hz, H5), 1.76 (3H, s, CH_3), 0.98 (9H, t, *J* = 8.4 Hz, $SiCH_2\underline{CH_3}$), 0.71 (6H,

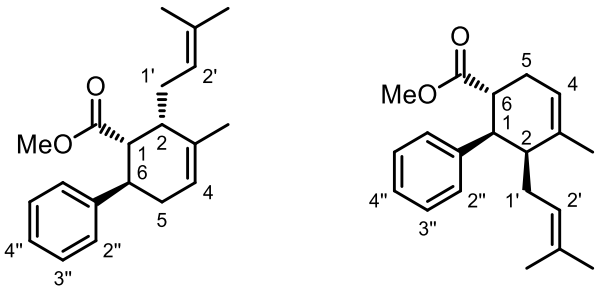
q, *J* = 8.0 Hz, Si<u>CH$_2$</u>CH$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 159.1, 157.1, 132.5, 130.6, 129.2, 124.1, 113.7, 90.8, 72.6, 69.5, 55.2, 29.0, 13.3, 6.7, 4.9; **IR** (thin film) υ_{max} = 2954 (m), 2911 (m), 2876 (m), 1612 (w), 1513 (s), 1301 (m), 1248 (s), 1100 (m) cm^{-1}; **LRMS** (EI$^+$) *m/z* = 362 ($M^{+\bullet}$, 10%), 85 (100%); **HRMS** (EI$^+$) calc. for $C_{21}H_{34}O_3Si$ ($M^{+\bullet}$) 362.2277, found 362.2279.

(*E*)-*tert*-Butyl(6-(4-methoxybenzyloxy)-3-methylhexa-1,3-dien-2-yloxy)dimethylsilane (**138**)



To a 0°C solution of enone **136** (294 mg, 1.18 mmol) and triethyl amine (214 µL, 1.53 mmol) in diethyl ether (20 mL), was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (326 µL, 1.42 mmol). After stirring for 1 hour the reaction mixture was concentrated under reduced pressure and purified by silica gel chromatograhy using ethyl acetate : hexane (1:4) to afford (*E*)-*tert*-butyl(6-(4-methoxybenzyloxy)-3-methylhexa-1,3-dien-2-yloxy)dimethylsilane (**138**) as a clear colourless oil (397 mg, 92%); **R_f** (EtOAc:Hex ; 1:4) 0.39; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.26 (2H, d, J = 9.2 Hz, ArH), 6.87 (2H, m, ArH), 6.03 (1H, t, *J* = 7.2 Hz, H4), 4.45 (2H, s, $ArCH_2$), 4.41 (1H, s, H1a), 4.25 (1H, s, H1b), 3.80 (3H, s, OCH_3), 3.49 (2H, t, *J* = 7.2 Hz, H6), 2.44 (2H, q, *J* = 7.2 Hz, H5), 1.76 (3H, s, CH_3), 0.96 (9H, s, $Si(CH_3)_2C(\underline{CH_3})_3$), 0.16 (6H, s, $Si(\underline{CH_3})_2C(CH_3)_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 159.1, 157.2, 132.6, 130.6, 129.2, 124.3, 113.7, 91.2, 72.6, 69.5, 55.3, 29.0, 25.9, 18.3, 13.3, -4.7; **IR** (thin film) υ_{max} = 2955 (s), 2857 (s), 1612 (m), 1594 (m), 1513 (s), 1360 (m), 1249 (s), 1100 (m) cm^{-1}; **LRMS** (EI$^+$) *m/z* = 362 ($M^{+\bullet}$, 3%), 85 (100%); **HRMS** (EI$^+$) calc. for $C_{21}H_{34}O_3Si$ ($M^{+\bullet}$) 362.2277, found 362.2271.

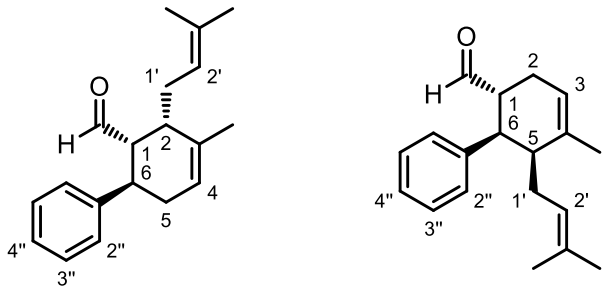
(±)-Panduratin H (**17**) & (±)-panduratin I (**18**)[35]



Methyl cinnamate (601 mg, 3.71 mmol), *E*-ocimene (2.02 g, 14.8 mmol) and dichloromethane (2 mL) were added to a pressure vessel, sealed and pressurised to 19 kbar for 3 days. The reactions was then diluted with dichloromethane (20 mL), evaporated on to silica, purified by column chromatography using diethyl ether : hexane (1:9) and then preparative HPLC on Waters Xbridge C18, 60% acetonitrile,

40% water: ret. time 31.1 min to afford (±)-panduratin H (**17**) as a clear colourless oil (257 mg, 23%); $\mathbf{R_f}$ (Ether:Hex ; 1:4) 0.44; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.26 (2H, m, H3''), 7.20-7.13 (3H, m, H2'' & H4''), 5.42 (1H, br s, H4), 5.06 (1H, m, H2'), 3.40 (3H, s, OCH_3), 3.19 (1H, ddd, *J* = 12.0, 10.4 & 6.4 Hz, H6), 3.08 (1H, dd, *J* = 12.4, 4.8 Hz, H1), 2.45 (1H, dd, *J* = 10.4 & 5.2 Hz, H2), 2.40-2.23 (2H, m, H1'), 2.20-2.13 (1H, m, H5a), 2.08-1.99 (1H, m, H5b), 1.78 (3H, s, CH_3), 1.67 (3H, s, CH_3), 1.60 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 173.8, 145.9, 136.3, 132.0, 128.3, 127.1, 126.0, 123.8, 121.0, 51.0, 49.1, 42.6, 37.1, 35.1, 29.2, 25.9, 22.6, 17.9; **IR** (thin film) υ_{max} = 2966 (m), 2949 (m), 2914 (m), 1741 (vs), 1494 (w), 1434 (m), 1301 (w), 1157(s); **LRMS** (EI^+) *m/z* = 298 ($M^{+\bullet}$, 60%), 169 (100%); **HRMS** (EI^+) calc. for $C_{20}H_{26}O_2$ ($M^{+\bullet}$) 298.1933, found 298.1935. A further fraction gave (±)-panduratin I (**18**) as a colourless oil (772 mg, 70%); $\mathbf{R_f}$ (Ether:Hex ; 1:4) 0.39; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.26 (2H, m, H3''), 7.19-7.14 (3H, m, H2'' & H4''), 5.45 (1H, br s, H4), 4.81 (1H, m, H2'), 3.49 (3H, s, OCH_3), 3.33 (1H, dd, *J* = 11.2 & 5.2 Hz, H1), 3.18 (1H, ddd, *J* = 11.2, 9.6 & 6.4 Hz, H6), 2.44 (1H, m, H5β), 2.32 (1H, m, H5α), 2.23 (1H, dd, *J* = 10.8 & 5.2 Hz, H2), 1.99-1.86 (2H, m, H1'), 1.74 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.34 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 176.5, 142.3, 137.6, 131.0, 128.2, 128.1, 126.1, 123.4, 119.5, 51.5, 46.3, 44.5, 39.9, 29.5, 27.6, 25.8, 22.9, 17.7; **IR** (thin film) υ_{max} = 2966 (m), 2950 (m), 2913 (m), 1739 (vs), 1496 (w), 1435 (m), 1265 (m), 1162 (s); **LRMS** (EI^+) *m/z* = 298 ($M^{+\bullet}$, 60%), 169 (100%); **HRMS** (EI^+) calc. for $C_{20}H_{26}O_2$ ($M^{+\bullet}$) 298.1933, found 298.1935.

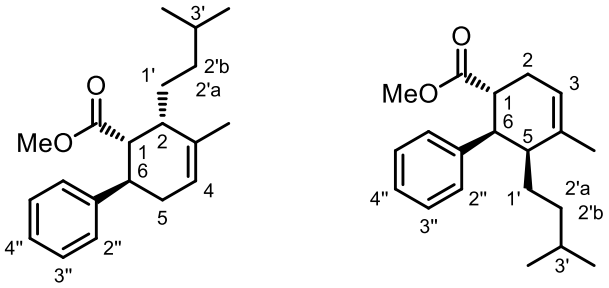
(±)-(1'*R*,2'*S*,6'*R*)-3-Methyl-2-(3'-methylbut-2'-en-1'-yl)-6-phenyl-3-cyclohexene-1-carbaldehyde (**47**) & (±)-(1'*R*,5'*S*,6'*R*)-4-methyl-5-(3'-methylbut-2'-en-1'-yl)-6-phenyl-3-cyclohexene-1-carbaldehyde (**105**)



Cinnamaldehyde (917 mg, 6.94 mmol), *E*-ocimene (3.79 g, 27.8 mmol) and dichloromethane (3 mL) were added to a pressure vessel, sealed and pressurised to 19 kbar for 3 days. The reactions was then diluted with dichloromethane (20 mL), evaporated on to silica and purified by column chromatography using diethyl ether : hexane (1:9) to afford as (±)-(1'*R*,2'*S*,6'*R*)-3-methyl-2-(3'-methylbut-2'-en-1'-yl)-6-phenyl-3-cyclohexene-1-carbaldehyde (**47**) a clear colourless oil (144 mg, 8%); $\mathbf{R_f}$ (Ether:Hex ; 1:4) 0.54; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.46 (1H, d, *J* = 3.6 Hz, CHO), 7.28 (2H, m, H2''), 7.18 (3H, H3'' & H4''), 5.49 (1H, br s, H3), 5.05 (1H, m, H2'), 3.35 (1H, ddd, *J* = 10.8, 10.8 & 6.0 Hz, H1), 2.81 (1H, ddd, *J* = 10.8, 4.4 & 3.6 Hz, H6), 2.52-2.40 (2H, m, H5 & H2β), 2.31 (2H, t, *J* = 5.6 Hz, H1'), 2.17-

2.10 (1H, m, H2α), 1.78 (3H, s, CH_3), 1.66 (3H, s, CH_3), 1.60 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 205.80, 144.0, 136.3, 132.3, 128.7, 127.7, 126.6, 123.7, 121.6, 55.3, 42.2, 36.9, 34.0, 28.9, 25.7, 22.2, 18.0; **IR** (thin film) υ_{max} = 2964 (m), 2914 (m), 1725 (s), 1604 (w), 1493 (m), 1447 (m), 1209 (w), 748 (m); **LRMS** (EI^+) *m/z* = 268 ($M^{+\bullet}$, 80%), 91 (100%); **HRMS** (EI^+) calc. for $C_{19}H_{24}O$ ($M^{+\bullet}$) 268.1827, found 268.1824. A further fraction afforded (±)-(1'*R*,5'*S*,6'*R*)-4-methyl-5-(3'-methylbut-2'-en-1'-yl)-6-phenyl-3-cyclohexene-1-carbaldehyde (**48**) as a clear colourless oil (630 mg, 54%); **R_f** (Ether:Hex ; 1:4) 0.48; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.42 (1H, d, *J* = 3.6 Hz, CHO), 7.27 (2H, m, H3''), 7.20-7.16 (3H, m, H2'' & H4''), 5.50 (1H, m, H3), 4.85 (1H, m, H2'), 3.35 (1H, dd, *J* = 10.4 & 5.2 Hz, H6), 2.99 (1H, dddd, *J* = 10.4, 7.2, 7.2 & 3.2 Hz, H1), 2.28-2.22 (3H, m, H2 & H5), 1.97 (2H, dd, J = 11.6 & 6.4, H1'), 1.75 (3H, s, CH_3), 1.57 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 204.1, 141.1, 137.9, 131.42, 128.8, 128.2, 126.4, 122.9, 119.2, 46.5, 44.0, 43.5, 27.3, 25.7, 24.5, 22.7, 17.5; **IR** (thin film) υ_{max} = 2964 (m), 2913 (m), 1724 (s), 1602 (w), 1495 (m), 1452 (m), 1377 (m), 750 (m); **LRMS** (EI^+) *m/z* = 268 ($M^{+\bullet}$, 80%), 91 (100%); **HRMS** (EI^+) calc. for $C_{19}H_{24}O$ ($M^{+\bullet}$) 268.1827, found 268.1824.

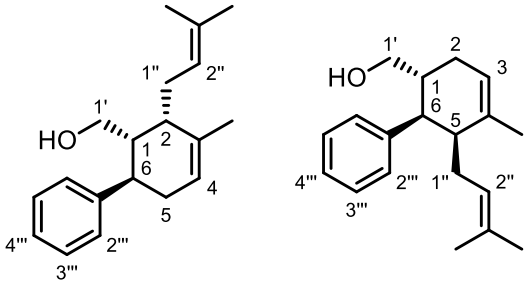
(±)-(1'R,2'*S*,6'*R*)-3-Methyl-2-isopentyl-4-methyl -6-phenylcyclohexa-3-en-1-yl-1-methanoate (**121**) & (±)-(1'*R*,5'*S*,6'*R*)-4-methyl-5-isopentyl-4-methyl -6-phenylcyclohexa-en-1-yl-1-methanoate (**122**)



2-Isopentyl-3-methyl-2,5-dihydrothiophene 1,1-dioxide (**120**) (1.37 g, 6.79 mmol) and pyridine (20 mL) were added to a flask and heated at reflux for 6 h with stirring. After cooling to room temperature the reaction was extracted with 30-40 petroleum spirits (20 mL) and washed with 2 M hydrochloric acid solution (4x20 mL). The petroleum spirit layer was then washed through a silica gel plug and concentrated under reduced pressure to give (*E*)-3,7-dimethylocta-1,3-diene (**65**) which was used without further purification. Methyl cinnamate (316 mg, 1.70 mmol), crude (*E*)-3,7-dimethylocta-1,3-diene (**65**) and dichloromethane (2 mL) were added to a pressure vessel, sealed and pressurised to 19 kbar for 3 days. The reactions was then diluted with dichloromethane (20 mL), evaporated on to silica and purified by column chromatography using diethyl ether : hexane (1:9) to afford (±)-(1'*R*,2'*S*,6'*R*)-3-methyl-2-isopentyl-4-methyl -6-phenylcyclohexa-3-en-1-yl-1-methanoate (**121**) (97.9 mg, 19%); **R_f** (Ether:Hex ; 1:4) 0.55; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.26 (2H, m, H3''), 7.20-7.14 (3H, m, H2''), 5.41 (1H, m, H4), 3.44 (3H, s, OMe), 3.17-3.07 (2H, m, H1), 2.37-2.31 (1H, m, H6), 2.07-1.99 (1H, m,

H2), 1.76 (3H, s, CH_3), 1.70-1.59 (2H, m, H5), 1.52-1.32 (3H, m, H1'& H3'), 1.28-1.19 (1H, m, 2'a), 1.11-1.02 (1H, m, H2'b), 0.87 (3H, d, *J* = 2.4 Hz, CH_3), 0.85 (3H, d, *J* = 2.4 Hz, CH_3); **LRMS** (EI^+) *m/z* = 300($M^{+\bullet}$, 20%), 137 (100%); **HRMS** (EI^+) calc. for $C_{20}H_{28}O_2$ ($M^{+\bullet}$) 300.2089, found 300.2085. A further fraction gave (±)-(1'*R*,5'*S*,6'*R*)-4-methyl-5-isopentyl-4-methyl -6-phenylcyclohexa-en-1-yl-1-methanoate (**122**) (265 mg, 52%); $\mathbf{R_f}$ (Ether:Hex ; 1:4) 0.52; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.28-7.15 (5 H, m, H2'', H3'' & H4''), 5.39 (1H, br s, H4), 3.50 (3H, s, CH_3O), 3.33 (1H, dd, *J* = 11.6 & 5.6 Hz, H6), 3.10 (1H, ddd, *J* = 11.6, 9.6 & 6.0 Hz, H1), 2.43-2.27 (2H, m, H2), 2.06 (1H, d, *J* = 4.4 Hz, H5), 1.74 (3H, s, CH_3), 1.33-1.10 (2H, m, H2'a & H3'), 0.95-0.78 (2H, m, H1'), 0.65 (6H, m, CH_3), 0.48 (1H, m, H2'b); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 176.5, 142.3, 138.1, 128.1, 128.0, 126.1, 118.7, 51.5, 46.1, 44.4, 40.4, 38.2, 29.5, 28.3, 27.4, 22.7, 22.4, 22.3; **IR** (thin film) υ_{max} = 2952 (m), 2868 (w), 1739 (s), 1453 (w), 1264 (w), 1161 (w), 1032 (w), 701 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 300($M^{+\bullet}$, 20%), 137 (100%); **HRMS** (EI^+) calc. for $C_{20}H_{28}O_2$ ($M^{+\bullet}$) 300.2089, found 300.2085.

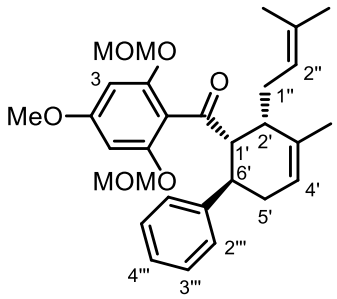
(±)-(1'*R*,2'*S*,6'*R*)-3-Methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl-1-methanol (**106**) & (±)-(1'*R*,5'*S*,6'*R*)-4-Methyl-5-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl-1-methanol (**107**)



To a solution of panduratin H (**17**) and panduratin I (**18**) (251 mg, 0.841 mmol) in tetrahydrofuran (20 mL) was added 1 M lithium aluminium hydride in tetrahydrofuran (3.37 mL, 3.37 mmol) dropwise over 5 minutes. After 1 hr of stirring at room temperature the reaction was cooled to 0 °C and ethyl acetate (10 mL) was added dropwise over 10 minutes. The reaction was then diluted with diethyl ether (80 mL) and a saturated solution of potassium sodium tartrate (80 mL) and stirred vigorously for 30 minutes. The diethyl ether layer was then separated and the aqueous layer re-extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed with brine (50 mL) and evaporated on to silica with purification by column chromatography using diethyl ether : hexane (1:4) affording (±)-(1'*R*,2'*S*,6'*R*)-3-methyl-(3-methylbut-2-en-1-yl)-6-phenyl-3-cyclohexene-1-methol (**106**) as a colourless oil (45.5 mg, 20%); **Rf** (Ether:Hex ; 3:7) 0.20; **1H-NMR** (400 MHz, CDCl3) δ 7.27 (2H, m, H3''), 7.20-7.17 (3H, t, J = 8.4 Hz, H2'' & H4''), 5.45 (1H, br s, H4), 5.28 (1H, m, H2''), 3.38-3.26 (2H, m, H1'), 2.79 (1H, ddd, J = 10.8, 10.8 & 6.4 Hz, H6), 2.33-2.15 (6H, m, H1, H2 H5 & H1''), 1.78 (3H, s, CH3), 1.71 (3H, s, CH3), 1.68 (3H, s, CH3), (OH not observed); **13C-NMR** (100 MHz, CDCl3) δ 145.0, 137.2, 132.0,

128.5, 127.6, 126.3, 124.6, 121.2, 63.4, 45.0, 40.5, 39.0, 34.9, 27.7, 25.8, 22.7, 18.0; **IR** (thin film) υmax = 3350 (m), 2963 (s), 2911 (s), 1602 (w), 1452 (m), 1376 (w), 1048 (m), 757 (m); **LRMS** (ESI+) m/z = 293 ([M+Na]+, 58%), 102 (100%); **HRMS** (ESI+) calc. for C19H26ONa ([M+Na]+), 293.1881, found 293.1881. A second fraction afforded (±)-(1'*R*,5'*S*,6'*R*)-4-methyl-5-(3-methylbut-2-en-1-yl)-6-phenylcyclohexa-3-en-1-yl-1-methanol (**107**) as a colourless oil (134 mg, 59%); Rf (Ether:Hex ; 3:7) 0.15; **1H-NMR** (400 MHz, CDCl3) δ 7.28 (2H, m, H3'''), 7.20-7.16 (3H, m, H2''' & H4'''), 5.48 (1H, s, H3), 4.90 (1H, m, H2''), 3.60 (1H, m, H1'a), 3.42 (1H, m, H1'b), 2.92 (1H, dd, J = 9.6 & 4.8 Hz), 2.36-2.24 (2H, m, H1 & H2a), 2.15 (1H, m, H5), 2.06-1.99(3H, m, H2b & H1''), 1.73 (3H, s, CH3), 1.58 (3H, s, CH3), 1.34 (3H, s, CH3), (OH not observed); 13C-NMR (100 MHz, CDCl3) δ 142.4, 137.1, 130.9, 129.3, 128.0, 126.0, 123.6, 121.1, 66.1, 46.1, 44.1, 35.0, 28.1, 27.5, 25.8, 22.8, 17.7; **IR** (thin film) υmax = 3326 (m), 2962 (s), 2913 (s), 1494 (m), 1452 (s), 1376 (m), 1032 (m), 703 (s); **LRMS** (ESI+) m/z = 293 ([M+Na]+, 100%); **HRMS** (ESI+) calc. for C19H26ONa ([M+Na]+), 293.1881, found 293.1884.

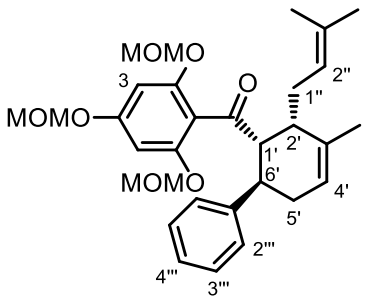
(±)-(1'*R*,2'*S*,6'*R*)-3-Methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-enyl)(4-methoxy-2,6-bis(methoxymethoxy) phenyl)methanone (**114**)



2-Bromo-5-methoxy-1,3-bis(methoxymethoxy)benzene (**113**) (230 mg, 748 µmol) and tetrahydrofuran (15 mL) were added to a flask and cooled to -78°C under a nitrogen atmosphere. Butyl lithium (575 µL, 1.6 M, 748 µmol) was then added dropwise over 5 min and the resulting solution stirred for 30 min. A solution of (±)-(1'*R*,2'*S*,6'*R*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenyl-3-cyclohexene-1-carbaldehyde (**47**) (66.9 mg, 249 µmol) in tetrahydrofuran (5 mL) was then added dropwise over 5 min followed by stirring at -78°C for 15 min. After this the reaction was allowed to warm to room temperature and stirred for a further 30 minutes followed by quenching with a saturated solution of ammonium chloride (30 mL). Extraction with diethyl ether (3 x 30 mL), drying over magnesium sulfate and purification by column chromatography using diethyl ether : hexane (3:7))gave a mixture of the alcohol diastereomer products; $\mathbf{R_f}$ (Ether:Hex ; 1:1) 0.11 & 0.22; The alcohol products, Dess-Martin periodinane (211 mg, 498 µmol) and dichloromethane (15 mL) were added to a flask and stirred at room temperature for 1 hr. The reaction was then evaporated on to silica under reduced pressure and purified

by column chromatography using diethyl ether : hexane (3:7) to afford (±)-(1'*R*,2'*S*,6'*R*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-enyl)(4-methoxy-2,6-bis(methoxymethoxy)phenyl) methanone (**114**) as colourless oil (87.5 mg, 71% over 2 steps); $\mathbf{R_f}$ (Ether:Hex ; 1:1) 0.19; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.31 (2H, d, *J* = 8.0 Hz, H2'''), 7.23 (2H, t, *J* = 8.0 Hz, H3'''), 7.10 (1H, t, *J* = 7.2 Hz, H4'''), 6.36 (2H, s, H3), 5.40 (1H, br s, H4'), 5.11 (1H, m, H2''), 5.01 (4H, s, $\underline{CH_2}OCH_3$), 3.84 (1H, dd, *J* = 10.8 & 3.2 Hz, H1'), 3.77 (3H, s, OCH_3), 3.48 (1H, m, H6'), 3.38 (6H, s, $CH_2O\underline{CH_3}$), 2.51 (1H, m, H5'β), 2.35 (3H, m, H2' & H1''), 2.17 (1H, m, 5'α), 1.72 (3H, s, CH_3), 1.67 (3H, s, CH_3), 1.61 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 203.3, 161.8, 156.5, 146.8, 138.3, 130.9, 128.2, 127.7, 125.5, 124.6, 120.6, 114.8, 94.9, 94.5, 58.2, 56.1, 55.4, 407, 36.8, 34.5, 29.6, 25.8, 23.6, 18.0; **IR** (thin film) υ_{max} = 2960 (m), 2912 (m), 1695 (m), 1605 (vs), 1452 (m), 1391 (w), 1215 (m), 1151 (vs); **LRMS** (EI^+) *m/z* = 494 ($M^{+\bullet}$, 2%), 197 (100%); **HRMS** (EI^+) calc. for $C_{30}H_{38}O_6$ ($M^{+\bullet}$) 494.2668, found 494.2669.

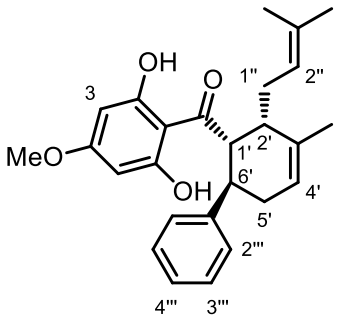
(±)-(1'*R*,2'*S*,6'*R*)-3-Methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-enyl)(2,4,6-tris(methoxymethoxy) phenyl)methanone (**108**)



1,3,5-tris(methoxymethoxy)benzene (**85**) (277 mg, 823 µmol) and tetrahydrofuran (15 mL) were added to a flask and cooled to -78°C under a nitrogen atmosphere. Butyl lithium (514 µL, 1.6M, 823 µmol) was then added dropwise over 5 min and the resulting solution stirred for 30 min. A solution of (±)-(1'*R*,2'*S*,6'*R*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenyl-3-cyclohexene-1-carbaldehyde (**47**) (55.2 mg, 206 µmol) in tetrahydrofuran (5 mL) was then added dropwise over 5 min followed by stirring at -78 °C for 15 min. After this the reaction was allowed to warm to room temperature and stirred for a further 30 min followed by quenching with a saturated solution of ammonium chloride (30 mL). Extraction with diethyl ether (3 x 30 mL), drying over magnesium sulfate and purification by column chromatography using diethyl ether : hexane (3:7))gave a mixture of the alcohol diastereomer products; $\mathbf{R_f}$ (Ether:Hex ; 1:1) 0.20 & 0.28; The alcohol products, Dess-Martin periodinane (131 mg, 309 µmol) and dichloromethane (15 mL) were added to a flask and stirred at room temperature for 1 hr. The reaction was then evaporated on to silica under reduced pressure and purified by column chromatography using diethyl ether : hexane (3:7) to afford (±)-(1'*R*,2'*S*,6'*R*)-3-methyl-2-(3-

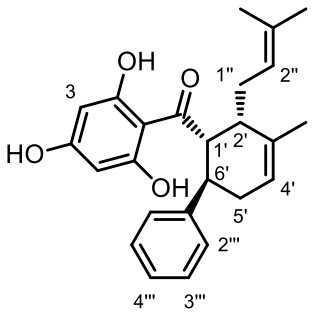
methylbut-2-en-1-yl)-6-phenylcyclohex-3-enyl)(2,4,6-tris(methoxymethoxy)phenyl)methanone (**108**) as colourless oil (78.9 mg, 73% over 2 steps); $\mathbf{R_f}$ (Ether:Hex ; 1:1) 0.37; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.31 (2H, d, *J* = 7.6 Hz, H2'''), 7.23 (2H, t, *J* = 7.2 Hz, H3'''), 7.11 (1H, t, *J* = 7.2 Hz, H4'''), 6.48 (2H, s, H3), 5.41 (1H, br s, H4'), 5.13 (3H, s, H2'' & $\underline{CH_2}OCH_3$), 5.00 (4H, s, $\underline{CH_2}OCH_3$), 3.81 (1H, dd, *J* = 11.2 & 3.2 Hz, H1'), 3.52-3.47 (4H, m, H6' & $CH_2O\underline{CH_3}$), 3.37 (6H, s, $CH_2O\underline{CH_3}$), 2.51 (1H, m, H5'β), 2.36-.2.33 (3H, m, H2' & H1''), 2.17 (1H, m, H5'α), 1.73 (3H, s, CH_3), 1.67 (3H, s, CH_3), 1.61 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 203.3, 159.4, 156.3, 146.7, 138.3, 130.9, 128.3, 127.7, 125.5, 124.6, 120.7, 115.9, 97.0, 94.5, 94.4, 58.3, 56.3, 56.2, 40.6, 36.7, 34.4, 29.6, 25.8, 23.6, 18.0; **IR** (thin film) υ_{max} = 2959 (m), 2911 (m), 1697 (m), 1605 (s), 1451 (w), 1217 (w), 1155 (s), 1050 (vs); **LRMS** (EI^+) *m/z* = 524 ($M^{+\bullet}$, 3%), 389 (100%); **HRMS** (EI^+) calc. for $C_{31}H_{40}O_7$ ($M^{+\bullet}$) 524.2774, found 524.2794.

(±)-Panduratin A (**8**)[40]



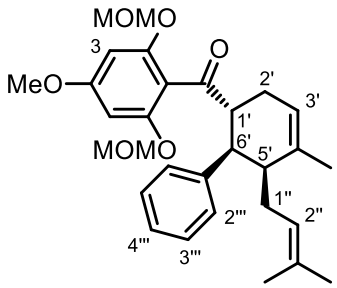
(±)-(1'*R*,2'*S*,6'*R*)-3-Methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-enyl)(4-methoxy-2,6-bis(methoxymethoxy) phenyl)methanone (**114**) (83.4 mg, 169 µmol), methanol (10 mL) and 2 drops of concentrated hydrochloric acid were added to a flask and heated at 50ºC with stirring for 2 hrs. The reaction mixture was then neutralised with saturated sodium bicarbonate solution, extracted with ethyl acetate (2 x 30 mL) and dried over magnesium sulfate. Filtration, concentration under reduced pressure and purification via silica gel chromatography using diethyl ether : hexane (3:7) afforded (±)-panduratin A (**8**) as a yellow solid (48.3 mg, 70%); $\mathbf{R_f}$ (Ether:Hex ; 1:1) 0.35; **m.p.** 154-156 °C; **^{1}H-NMR** (400 MHz, CD_3OD) δ 7.18-7.16 (4H, m, H2''' & H3'''), 7.05 (1H, m, H4'''), 5.88 (2H, s, H3), 5.41 (1H br s, H4'), 4.88 (1H, under H_2O peak, H2''), 4.77 (1H, dd, *J* = 11.6 & 4.4, H1'), 3.74 (3H, s, OMe), 3.38 (1H, ddd, *J* = 10.8, 10.8, 6.4 Hz, H6'), 2.65 (1H, m, H2'), 2.36-2.24 (2H, m, H5'b & H1''b), 2.08-1.95 (2H, m, H5'a & H1''a), 1.77 (3H, s, CH_3), 1.50 (6H, s, CH_3); **^{13}C-NMR** (100 MHz, CD_3OD) δ 208.1, 167.0, 165.4, 148.5, 138.4, 132.4, 129.2, 128.3, 126.4, 125.7, 122.0, 107.2, 94.4, 55.76, 55.0, 43.4, 38.4, 37.1, 29.8, 25.9, 23.0, 18.1; **IR** (thin film) υ_{max} = 3401 (s), 2964 (w), 2914 (w), 1627 (s), 1581 (m), 1424 (w), 1231 (m), 1162 (m) cm^{-1}; **LRMS** (ESI^-) *m/z* = 405 ($[M-H]^-$, 100%); **HRMS** (ESI^-) calc. for $C_{26}H_{29}O_4$ ($[M-H]^-$) 405.2066, found 405.2066.

(±)-4-Hydroxypanduratin A (**9**)[32]



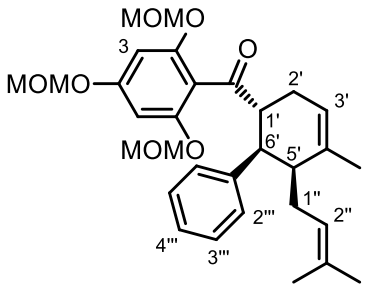
(±)-(1'*R*,2'*S*,6'*R*)-3-Methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-enyl)(2,4,6-tris(methoxymethoxy)phenyl)methanone (**108**) (69.7 mg, 141 µmol), methanol (10 mL) and 2 drops of concentrated hydrochloric acid were added to a flask and heated at 50ºC with stirring for 2 hrs. The reaction mixture was then neutralised with saturated sodium bicarbonate solution, extracted with ethyl acetate (2 x 30 mL) and dried over magnesium sulfate. Filtration, concentration under reduced pressure and purification via silica gel chromatography using diethyl ether : hexane (2:3) afforded (±)-4-hydroxypanduratin A (**9**) as a pale yellow oil (39.3 mg, 71%); $\mathbf{R_f}$ (Ether:Hex ; 1:1) 0.17; **^{1}H-NMR** (400 MHz, CD_3OD) δ 7.18-7.17 (4H, d, *J* = 4.4 Hz, H2''' & H3'''), 7.05 (1H, m, H4'''), 5.78 (2H, s, H3), 5.40 (1H, br s, H4'), 4.91 (1H, under H_2O peak, H2''), 4.76 (1H, dd, *J* = 12.0, 4.8 Hz, H1'), 3.37 (1H, ddd, *J* = 10.4, 10.4, 6.4, H6'), 2.65 (1H, m, H2'), 2.36-2.22 (2H, m, H5'b & H1''b), 2.08-1.94 (2H, m, H5'a & H1''a), 1.77 (3H, s, CH_3), 1.51 (6H, s, CH_3); **^{13}C-NMR** (100 MHz, CD_3OD) δ 207.8, 165.5, 148.6, 138.4, 132.2, 129.1, 128.2, 126.4, 125.7, 121.9, 106.5, 95.8, 54.8, 43.8, 38.4, 37.1, 29.9, 25.9, 23.0, 18.0; **IR** (thin film) υ_{max} = 3400 (vs), 2958 (w), 2913 (w), 1623 (s), 1597 (m), 1492 (w), 1436 (w), 1216 (w) cm^{-1}; **LRMS** (ESI^-) *m/z* = 391 ($[M-H]^-$, 100%); **HRMS** (ESI^-) calc. for $C_{25}H_{27}O_4$ ($[M-H]^-$) 391.1909, found 391.1909.

(±)-(1'*R*,5'*S*,6'*R*)-3-Methyl-2-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)(4-methoxy-2,6-bis(methoxymethoxy) phenyl)methanone (**115**)



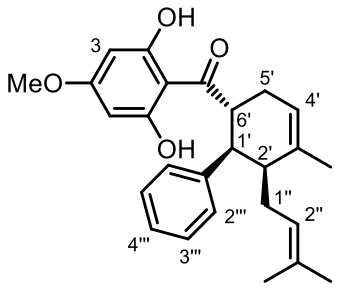
2-Bromo-5-methoxy-1,3-bis(methoxymethoxy)benzene (**113**) (229.7 mg, 748 µmol) and tetrahydrofuran (20 mL) were added to a flask and cooled to -78°C under a nitrogen atmosphere. Butyl lithium (575 µL, 1.3 M, 748 µmol) was then added dropwise over 5 min and the resulting solution stirred for 30 min. A solution of (±)-(1'*R*,5'*S*,6'*R*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenyl-3-cyclohexene-1-carbaldehyde (**105**) (66.9 mg, 249 µmol) in tetrahydrofuran (5 mL) was then added dropwise over 5 min followed by stirring at -78°C for 15 min. After this the reaction was allowed to warm to room temperature and stirred for a further 30 min followed by quenching with a saturated solution of ammonium chloride (30 mL). Extraction with diethyl ether (3 x 20 mL), drying over magnesium sulfate and purification by column chromatography using diethyl ether : hexane (1:3) gave a mixture of the alcohol diastereomer products; $\mathbf{R_f}$ (Ether:Hex ; 1:1) 0.11 & 0.19; The alcohol products, Dess-Martin periodinane (158 mg, 374 µmol) and dichloromethane (10 mL) were added to a flask and stirred at room temperature for 1 hr. The reaction was then evaporated on to silica under reduced pressure and purified by column chromatography using diethyl ether : hexane (3:7) to afford (±)-(1'*R*,5'*S*,6'*R*)-3-methyl-2-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)(4-methoxy-2,6-bis(methoxymethoxy) phenyl)methanone (**115**) as colourless oil (85.0 mg, 69% over 2 steps); $\mathbf{R_f}$ (Ether:Hex ; 1:1) 0.39; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.23-7.08 (5H, m, H2''', H3''', H4'''), 6.37 (2H), 5.48 (1H, s, H3'), 5.05 (2H, m, $\underline{CH_2}OCH_3$), 4.99 (2H, m, $\underline{CH_2}OCH_3$), 4.87 (1H, t, *J* = 6.4 Hz, H2''), 3.79 (3H, s, OMe), 3.71 (1H, dd, *J* = 16 & 7.2 Hz, H6'), 3.47-3.42 (7H, m, H1' & $CH_2O\underline{CH_3}$), 2.35-2.32 (3H, m, H2' & H5'), 2.04-1.90 (2H, m, H1''), 1.74 (3H, s, CH_3), 1.55 (3H, s, CH_3), 1.25 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 204.8, 162.0, 156.2, 143.2, 137.2, 130.9, 129.0, 127.6, 125.6, 123.6, 120.6, 115.1, 94.8, 94.7, 56.2, 55.4, 48.4, 45.5, 43.5, 27.8, 27.0, 25.7, 22.7, 17.5; **IR** (thin film) υ_{max} = 2960 (w), 2913 (w), 1698 (m), 1606 (s), 1452 (w), 1153 (s), 1048 (s), 924 (w) cm^{-1}; **LRMS** (EI^+) *m/z* = 494 ($M^{+\bullet}$, 2%), 255 (100%); **HRMS** (EI^+) calc. for $C_{30}H_{38}O_6$ ($M^{+\bullet}$) 494.2668, found 494.2673.

(±)-(1'*R*,5'*S*,6'*R*)-3-Methyl-2-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)(2,4,6-tris(methoxymethoxy) phenyl)methanone (**35**)



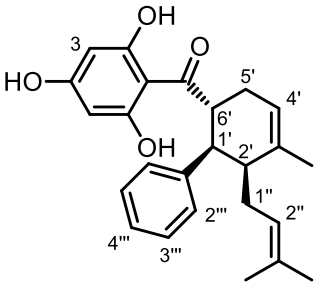
2-Bromo-1,3,5-tris(methoxymethoxy)benzene (**85**) (136 mg, 406 µmol) and tetrahydrofuran (10 mL) were added to a flask and cooled to -78°C under a nitrogen atmosphere. Butyl lithium (162 µL, 1.6 M, 406 µmol) was then added dropwise over 5 min and the resulting solution stirred for 30 min. A solution of (±)-(1'*R*,5'*S*,6'*R*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenyl-3-cyclohexene-1-carbaldehyde (**105**) (36.3 mg, 135 µmol) in tetrahydrofuran (5 mL) was then added dropwise over 5 min followed by stirring at -78°C for 15 min. After this the reaction was allowed to warm to room temperature and stirred for a further 30 min followed by quenching with a saturated solution of ammonium chloride (30 mL). Extraction with diethyl ether (3 x 20 mL), drying over magnesium sulfate and purification by column chromatography using diethyl ether : hexane (1:3))gave a mixture of the alcohol diastereomer products; $\mathbf{R_f}$ (Ether:Hex ; 1:1) 0.11 & 0.19; The alcohol products, Dess-Martin periodinane (83.2 mg, 196 µmol) and dichloromethane (5 mL) were added to a flask and stirred at room temperature for 1 hr. The reaction was then evaporated on to silica under reduced pressure and purified by column chromatography using diethyl ether : hexane (3:7) to afford (±)-(1'*R*,5'*S*,6'*R*)-3-methyl-2-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)(2,4,6-tris(methoxymethoxy) phenyl)methanone (**35**) as colourless oil (50.3 mg, 71% over 2 steps); $\mathbf{R_f}$ (Ether:Hex ; 2:3) 0.17; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.24-7.16 (4H, m, H2''' & H3'''), 7.11(1H, m, H4'''), 6.50 (2H, s, H3), 5.47 (1H, s, H3'), 5.15 (2H, s, $\underline{CH_2}OCH_3$), 5.06 (2H, m, $\underline{CH_2}OCH_3$), 5.00 (2H, m, $\underline{CH_2}OCH_3$), 4.87 (1H, m, H2''), 3.69 (1H, dd, *J* = 8.4 & 7.2 Hz, H6'), 3.50-3.42 (10H, m, H1' & $CH_2O\underline{CH_3}$), 2.35-2.34 (3H, m, H2' & H5'), 1.97 (2H, m, H2''), 1.75 (3H, s, CH_3), 1.55 (3H, s, CH_3), 1.24 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ; **IR** (thin film) υ_{max} = 2959 (m), 2912 (m), 1700 (m), 1605 (s), 1451 (m), 1216 (m), 1155 (s), 1050 (s) cm^{-1}; **LRMS** (EI^+) *m/z* = 524 ($M^{+\bullet}$, 1%), 285 (100%); **HRMS** (EI^+) calc. for $C_{31}H_{40}O_7$ ($M^{+\bullet}$) 524.2774, found 524.28.

(±)-Isopanduratin A (**20**)[43]



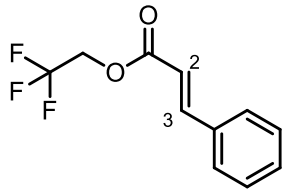
(±)-(1'*R*,5'*S*,6'*R*)-3-Methyl-2-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)(4-methoxy-2,6-bis(methoxymethoxy) phenyl)methanone (**115**) (71.3 mg, 175 µmol), methanol (10 mL) and 4 drops of concentrated hydrochloric acid were added to a flask and heated at 50ºC with stirring for 2 hrs. The reaction mixture was then neutralised with saturated sodium bicarbonate solution, extracted with ethyl acetate (2 x 20 mL) and dried over magnesium sulfate. Filtration, concentration under reduced pressure and purification via silica gel chromatography using diethyl ether : hexane (35:65) afforded (±)-isopanduratin A (**20**) as a pale yellow oil (49.1 mg, 69%); $\mathbf{R_f}$ (Ether:Hex ; 2:3) 0.07;**^{1}H-NMR** (400 MHz, CD_3OD) δ 7.18-7.11 (4H, m, H2''' & H3'''), 7.09-7.05 (1H, m, H4'''), 5.93 (2H, s, H3), 5.49 (1H, s, H4'), 4.92 (1H, m, H6'), 4.88 (1H, m, H2''), 3.77 (3H, s, OMe), 3.51 (1H, dd, *J* = 11.6 & 5.2 Hz), 2.61 (1H, m, H5'), 2.24 (1H, m, H2'), 2.07-1.83 (3H, m, H5' & H1''), 1.75 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.34 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, CD_3OD) δ 211.2, 167.4, 165.5, 144.9, 138.6, 131.4, 129.4, 129.0, 126.7, 124.8, 121.4, 106.8, 94.5, 55.8, 47.6, 47.0, 44.6, 31.9, 29.0, 26.1, 23.3, 18.0; **IR** (thin film) υ_{max} = 3292 (w), 2964 (w), 2913 (w), 1625 (vs), 1575 (s), 1377 (w), 1211 (s), 1079 (w) cm^{-1}; **LRMS** (ESI^-) *m/z* = 405 ($[M-H]^-$, 40%), 113 (100%); **HRMS** (ESI^-) calc. for $C_{26}H_{29}O_4$ ($[M-H]^-$) 405.2066, found 405.2067.

(±)-4-hydroxyisopanduratin A (**36**)[41]



(±)-(1'*R*,5'*S*,6'*R*)-3-Methyl-2-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)(2,4,6-tris(methoxymethoxy) phenyl)methanone (**35**) (40.0 mg, 76.2 µmol), methanol (10 mL) and 4 drops of concentrated hydrochloric acid were added to a flask and heated at 50ºC with stirring for 2 hrs. The reaction mixture was then neutralised with saturated sodium bicarbonate solution, extracted with ethyl acetate (2 x 20 mL) and dried over magnesium sulfate. Filtration, concentration under reduced pressure and purification via silica gel chromatography using diethyl ether : hexane (35:65) afforded (±)-4-hydroxyisopanduratin A (**36**) as a pale yellow oil (21.1 mg, 71%); $\mathbf{R_f}$ (Ether:Hex ; 2:3) 0.07; **^{1}H-NMR** (800 MHz, CD_3OD) δ 7.19-7.06 (5H, m, H2''', H3''' & H4'''), 5.81 (2H, s, H3), 4.92 (1H, ddd, *J* = 11.1, 11.1 & 6.1 Hz, H6'), 4.88 (1H, under H_2O peak, H2''), 3.50 (1H, dd, *J* = 11.7 & 5.0 Hz, H1'), 2.60 (1H, m, H5'β), 2.24 (1H, m, H2'), 2.05-1.96 (2H, m, H1''), 1.86 (1H, m, 5'α), 1.75 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.34 (3H, s, CH_3); **^{13}C-NMR** (200 MHz, CD_3OD) δ 210.8, 166.1, 145.0, 138.6, 131.4, 129.5, 129.0, 126.7, 124.9, 121.5, 106.1, 95.9, 47.6, 47.1, 44.4, 31.9, 29.1, 26.1, 23.3, 17.9; **IR** (thin film) υ_{max} = 3235 (w), 2918 (w), 2853 (w), 1627 (s), 1599 (s), 1451 (m), 1202 (m), 1073 (m) cm^{-1}; **LRMS** (ESI^-) *m/z* = 392 ($[M-H]^-$, 10%), 153 (100%); **HRMS** (ESI^-) calc. for $C_{25}H_{27}O_4$ ($[M-H]^-$) 391.1909, found 391.1899.

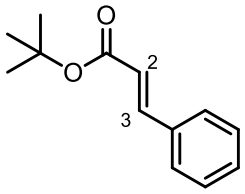
(*E*)-Trifluoroethyl cinnamate (**61**)



2,2,2- Trifluoroethanol (941 µL, 13.1 mmol), triethylamine (2.49 mL, 17.9 mmol) and ethyl acetate (80 mL) were added to a flask and stirred at room temperature. Cinnamoyl chloride (1.98 g, 11.9 mmol) was then added portion-wise over 30 minutes and the reaction then stirred for a further 2 hours. The reaction was then filtered to remove the triethylamine hydrochloride salt and the mixture evaporated on to silica under reduced pressure. Purification by silica gel chromatography using diethyl ether : hexane (1:4) afforded (*E*)-trifluoroethyl cinnamate (**61**) as a clear colourless oil (2.33 g, 85%); $\mathbf{R_f}$ (Ether:Hex ;

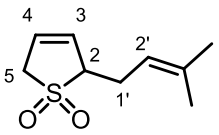
2:3) 0.55; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.79 (1H, d, *J* = 15.6 Hz, H3), 7.58-7.53 (2H, m, Ar), 7.43-7.38 (3H, m, Ar), 6.49 (1H, d, *J* = 16.0 Hz, H2), 4.60 (2H, q, *J* = 8.8 Hz, CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 165.2, 147.1, 133.9, 130.9, 129.0, 128.3, 121.7, 115.9, 60.4 (q, *J* = 36.4 Hz); **IR** (thin film) υ_{max} = 3031 (w), 2972 (w), 1735 (vs), 1637 (s), 1578 (w), 1497 (w), 1451 (m) 1411 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 230 ($M^{+\bullet}$, 70%), 131 (100%); **HRMS** (EI^+) calc. for $C_{11}H_9O_2{}^{19}F_3$ ($M^{+\bullet}$) 230.0555, found 230.0556.

(*E*)-*tert*-Butyl cinnamate (**59**)



Cinnamic acid (3.28 g, 22.1 mmol), EDC (5.15 g, 33.2 mmol), DMAP (3.24 g, 26.5 mmol) and dichloromethane(40 mL) were added to a flask and stirred at room temperature. *tert*-Butyl alcohol(4.19 mL, 44.2 mmol) was then added and the reaction refluxed overnight under a nitrogen atmosphere. After filtering through celite the reaction was evaporated on to silica under reduced pressure. Purification by silica gel chromatography using diethyl ether hexane (1:9) then afforded (*E*)-*tert*-butyl cinnamate (**59**) as a colourless oil (2.69 g, 82%); $\mathbf{R_f}$ (Ether:Hex ; 1:4) 0.64; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.59 (1H, d, *J* = 16 Hz, H3), 7.51-7.47 (2H, m, Ar), 7.37-7.33 (3H, m, Ar), 6.37 (1H, d, *J* = 16 Hz, H2), 1.53 (9H, s, ^{t}Bu); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 166.2, 143.4, 134.5, 129.9, 128.7, 127.8, 120.1, 80.4, 28.1; **IR** (thin film) υ_{max} = 2977 (m), 2931 (w), 1707 (s), 1637 (s), 1578 (w), 1449 (m), 1367 (m), 1207 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 204 ($M^{+\bullet}$, 25%), 148 (100%); **HRMS** (EI^+) calc. for $C_{13}H_{16}O_2$ ($M^{+\bullet}$) 204.1150, found 204.1149.

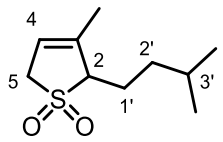
2-(3'-Methylbut-2'-en-1'-yl)-2,5-dihydrothiophene 1,1-dioxide (**118**)



Sulfolene (4.24 g, 35.9 mmol), prenyl bromide (2.78 mL, 23.9 mmol) and tetrahydrofuran (30 mL) were added to a flask and under a nitrogen atmosphere and cooled to -95ºC with stirring. LHMDS (28.7 mL, 28.7 mmol) was then slowly added over 1 minute and the reaction allowed to stir for a further minute. Quenching with a saturated solution of ammonium chloride (30 mL) was then followed by extraction with diethyl ether (3x20 mL). The combined organic layers were then dried over magnesium sulfate,

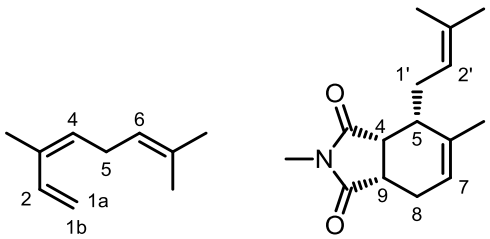
filtered, concentrated under reduced pressure and purified via silica gel chromatography using diethyl ether : hexane (2:3) to afford (±)-2-(3-methylbut-2-en-1-yl)-2,5-dihydrothiophene 1,1-dioxide (**118**) as a clear colourless oil (1.98 g, 44%); $\mathbf{R_f}$ (Ether:Hex ; 2:3) 0.11; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.03 (2H, s, H3 & H4), 5.19 (1H, m, H2'), 3.80-3.65 (3H, m, H2 & H5), 2.63 (1H, ddd, *J* = 14.8, 6.4 & 6.4 Hz, H1'a), 2.36 (1H, ddd, *J* = 15.6, 7.6 & 7.6 Hz. H1'b), 1.74 (3H, s, CH_3), 1.65 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 135.9, 130.1, 122.9, 118.1, 64.4, 55.6, 27.2, 25.7, 17.9; **IR** (thin film) υ_{max} = 2972 (m), 2917 (m), 1672 (w), 1441 (m), 1305 (s), 1244 (s), 1135 (s), 820 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 121 ($[M\text{-}SO_2H]^{+\bullet}$, 90%), 40 (100%); **HRMS** (EI^+) calc. for C_9H_{13} ($[M\text{-}SO_2H]^{+\bullet}$) 121.1017, found 121.1021.

2-Isopentyl-3-methyl-2,5-dihydrothiophene 1,1-dioxide (**120**)



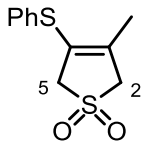
3-Methyl sulfolene (2.18 g, 16.5 mmol), 1-iodo-3-methylbutane (4.34 mL, 33.0 mmol) and tetrahydrofuran (70 mL) were added to a flask and under a nitrogen atmosphere and cooled to -95ºC with stirring. LHMDS (16.5 mL, 16.5 mmol) was then slowly added over 10 minutes and the reaction allowed to stir for a further 10 minutes followed by warming to room temperature and another 30 minutes of stirring. Quenching with a saturated solution of ammonium chloride (30 mL) was then followed by extraction with diethyl ether (3x20 mL). The combined organic layers were then dried over magnesium sulfate, filtered, concentrated under reduced pressure and purified via silica gel chromatography using diethyl ether : hexane (2:3) to afford (±)-2-isopentyl-3-methyl-2,5-dihydrothiophene 1,1-dioxide (**120**) as a clear colourless oil (1.60 g, 48%); $\mathbf{R_f}$ (Ether:Hex ; 2:3) 0.20; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.68 (1H, t, *J* = 1.6 Hz, H4), 3.69 (2H, m, H5), 3.47 (1H, t, *J* = 6.4 Hz, H2), 1.87-1.81 (5H, m, H1' & CH_3), 1.60 (1H, m, H3'), 1.49 (1H, m, H2'a), 1.37 (1H, m, H2'b), 0.93 (3H, d, *J* = 6.4 Hz, CH_3), 0.92 (3H, d, *J* = 6.8 Hz, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 138.5, 116.9, 67.4, 55.8, 35.2, 28.0, 25.3, 22.4, 22.1, 18.0; **IR** (thin film) υ_{max} = 2955 (s), 2929 (m), 2871 (m), 1468 (w), 1305 (vs), 1246 (w), 1150 (w), 1120 (s) cm^{-1}; **LRMS** (EI^+) *m/z* = 202 ($M^{+\bullet}$, 1%), 138 ($[M\text{-}SO_2]^{+\bullet}$, 40%), 81 (100%); **HRMS** (EI^+) calc. for $C_{10}H_{18}O_2S$ ($M^{+\bullet}$) 202.1028, found 202.1033, calc. for $C_{10}H_{18}$ ($[M\text{-}SO_2]^{+\bullet}$) 138.1409, found 138.1406.

(*Z*)-Ocimene (**127**) & (±)-(4*R*,5*S*,9S)-2,6-dimethyl-5-(3'-methylbut-2'-en-1-yl)-4,5,8,8,9-tetrahydro-isoindole-1,3-dione (**129**)



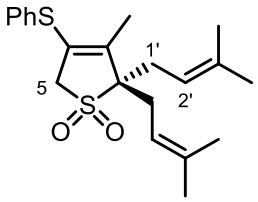
N-Methylmaleimide (2.64 g, 23.8 mmol), ocimene mix (3.24 g, 23.8 mmol, 2.4:1 ; *E*:*Z*) and chloroform (50 mL) were added to a flask and stirred overnight at room temperature. The chloroform was then evaporated off under reduced pressure and the resulting residue redissolved in 30-40 petroleum spirit (60 mL). The solution was then passed through a silica plug followed by further rinsing of the flask with 30-40 petroleum spirit (2 x 60 mL) The combined 30-40 petroleum spirit was then evaporated under reduced pressure to afford (*Z*)-Ocimene (**127**) as a clear colourless oil (940 mg, quantitative); $\mathbf{R_f}$ (Ether:Hex ; 3:7) 0.89; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.82 (1H, dd, *J* = 17.2 & 10.4 Hz, H2), 5.36 (1H, t, *J* = 7.2 Hz, H4), 5.21 (1H, d, *J* = 17.2 Hz, H1a), 5.14-5.09 (2H, m, H1b & H6), 2.87 (2H, dd, *J* = 6.8 & 6.8 Hz, H5), 1.82 (3H, s, CH_3), 1.71 (3H, s, CH_3), 1.65 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 133.6, 132.0, 131.9, 129.6, 122.5, 113.5, 26.4, 25.6, 19.7, 17.7; **IR** (thin film) υ_{max} = 2971 (m), 2927 (m), 2857 (m), 1594 (w), 1440 (m), 1377 (m), 1107 (m), 986 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 135 ($[M-H]^{+\bullet}$, 90%), 203 (100%); **HRMS** (EI^+) calc. for $C_{10}H_{15}$ ($[M-H]^{+\bullet}$) 135.1174, found 135.1174. The silica plug was then washed with ethyl acetate (3 x 60 mL) and the combined washings evaporated on to silica. Purification by flash column chromatography using diethyl ether : hexane (3:7) then afforded (±)-(4*R*,5*S*,9S)-2,6-dimethyl-5-(3'-methylbut-2'-en-1-yl)-4,5,8,8,9-tetrahydro-isoindole-1,3-dione (**129**) as a pale yellow oil (4.18 g, quantitative); $\mathbf{R_f}$ (Ether:Hex ; 3:7) 0.21; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.52 (1H, m, H7), 5.13 (1H, m, H2'), 3.06 (1H, dd, *J* = 8.8 & 5.2 Hz, H4), 2.99 (1H, ddd, *J* = 9.6, 8.0 & 2.8, H9), 2.88 (3H, s, NMe), 2.57-2.47 (2H, m, H8a & H1'a), 2.36-2.27 (2H, m, H5 & H1'b), 2.20 (1H, m, H8b), 1.70 (3H, s, CH_3), 1.68 (3H, s, CH_3), 1.64 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 180.36, 178.6, 140.6, 133.6, 122.5, 120.5, 43.0, 39.9, 39.8, 26.7, 25.8, 24.5, 24.0, 20.8, 17.9; **IR** (thin film) υ_{max} = 2963 (m), 2915 (m), 2854 (w), 1773 (m), 1700 (vs), 1434 (s), 1382 (s), 1283 (s) cm^{-1}; **LRMS** (ESI^+) *m/z* = 270 ($[M+Na]^+$, 70%), 302 (100%); **HRMS** (ESI^+) calc. for $C_{15}H_{21}O_2NNa$ ($[M+Na]^+$) 270.1470, found 270.1472.

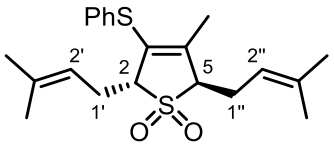
3-Methyl-4-(phenylthio)-2,5-dihydrothiophene 1,1-dioxide (**143**)[49]

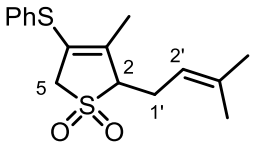


To a rapidly stirring solution of NCS (19.6 g, 147 mmol) in dichloromethane (160 mL) at room temperature was added thiophenol (approx.. 5 mL of 15.1 mL, 147 mmol). The solution was then gently warmed to 30°C until an orange colour developed. After cooling to 0 °C the remaining thiophenol was added dropwise over 15 minutes. The reaction was then allowed to warm to room temperature and stirred for 30 minutes. 3-Methyl sulfolene (20.4 g, 154 mmol) was then added to the reaction followed by stirring for 4 days at room temperature and then 1 day at reflux. After cooling to 0°C freshly distilled triethylamine (23.3 mL, 167 mmol) was then added dropwise over 15 minutes and the resulting mixture stirred for 2 days at 25°C. The solution was then diluted with diethyl ether (200 mL) and washed sequentially with water (100 mL), 1 M hydrochloric acid (100 mL), brine (100 mL) and a saturated solution of sodium bicarbonate (100 mL). The organic layer was then dried over magnesium sulfate, filtered and concentrated under reduced pressure. Cooling in the freezer overnight gave crystals in a light orange oil. A cold solution of 65% diethyl ether in hexanes was added with rapid stirring for 4 minutes followed by filtration to afford 3-methyl-4-(phenylthio)-2,5-dihydrothiophene 1,1-dioxide (**143**) as pale yellow crystals (15.4 g, 42%); $\mathbf{R_f}$ (Ether:Hex ; 1:4) 0.06; **m.p.** 38-70°C (lit. m.p. 67-68°C); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.34-7.31 (5H, m, ArH), 3.92-3.91 (2H, m, H5), 3.73-3.71 (2H, m, H2), 2.09-2.07 (3H, m, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 135.1, 131.7, 131.0, 129.5, 127.9, 123.1, 61.4, 59.0, 16.6; **IR** (thin film) υ_{max} = 3057 (w). 2973 (w), 2920 (w), 1582 (m), 1478 (s), 1439 (s) cm^{-1}; **LRMS** (EI^+) *m/z* = 240 ($M^{+\bullet}$, 100%); **HRMS** (EI^+) calc. for $C_{11}H_{12}O_2S_2$ ($M^{+\bullet}$) 240.0279, found 240.0280.

3-Methyl-2,2-bis(3'-methylbut-2'-en-1'-yl)-4-(phenylthio)-2,5-dihydrothiophene 1,1-dioxide (**146**), *trans*-3-methyl-2,5-bis(3'-methylbut-2'-en-1'-yl)-4-(phenylthio)-2,5-dihydrothiophene 1,1-dioxide (**145**) & 3-methyl-2-(3'-methylbut-2'-en-1'-yl)-4-(phenylthio)-2,5-dihydrothiophene 1,1-dioxide (**144**)





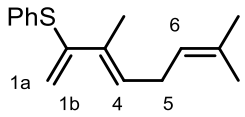


Procedure 1: 3-Methyl-4-(phenylthio)-2,5-dihydrothiophene 1,1-dioxide (**143**) (883 mg, 3.68 mmol) and tetrahydrofuran (20 mL) were added to a flask and under a nitrogen atmosphere and cooled to -95ºC with stirring. Prenyl bromide (856 µL, 7.35 mmol) was then added followed by the dropwise addition of LHMDS (4.42 mL, 4.42 mmol) over 5 minutes. The reaction was stirred for 3 minutes, warmed to room temperature and stirred for a further 10 minutes. Quenching with a saturated solution of ammonium chloride (30 mL) was then followed by extraction with diethyl ether (3x20 mL). The combined organic layers were then dried over magnesium sulfate, filtered, concentrated under reduced pressure and purified via silica gel chromatography using diethyl ether : hexane (1:4) to afford 3-methyl-2,2-bis(3-methylbut-2-en-1-yl)-4-(phenylthio)-2,5-dihydrothiophene 1,1-dioxide (**146**) as a clear colourless oil (61.2 mg, 4%); $\mathbf{R_f}$ (Ether:Hex ; 1:4) 0.35; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.34-7.25 (5H, m, Ar-H), 5.25 (2H, m, H2'), 3.50 (2H, m, H5), 2.68 (2H, dd, *J* = 15.2 & 8.0 Hz, H1'a), 2.55 (2H, dd, *J* = 15.2 & 6.4 Hz, H1'b), 2.00 (3H, t, *J* = 2.4 Hz, CH_3), 1.75 (6H, s, CH_3), 1.66 (6H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 143.1, 136.3, 132.0, 131.0, 129.4, 127.7, 122.2, 117.3, 73.6, 57.2, 31.7, 26.1, 18.0, 14.5; **IR** (thin film) υ_{max} = 2968 (w), 2915 (w), 1582 (w), 1378 (w), 1440 (w), 1307 (s), 1210 (w), 1136 (s) cm^{-1}; **LRMS** (EI^+) *m/z* = 376 ($M^{+\bullet}$, 10%), 307 (100%); **HRMS** (EI^+) calc. for $C_{21}H_{28}O_2S_2$ ($M^{+\bullet}$) 376.1531, found 376.1532. A further fraction gave *trans*-3-methyl-2,5-bis(3-methylbut-2-en-1-yl)-4-(phenylthio)-2,5-dihydrothiophene 1,1-dioxide (**145**) as a pale yellow oil (221 mg, 16%); $\mathbf{R_f}$ (Ether:Hex ; 1:4) 0.30; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.32-7.2 (5H, m, Ar-H), 5.58 (1H, m, H2''), 5.16 (1H, m, H2'), 3.67 (1H, t, *J* = 5.6 Hz, H5), 3.57 (1H, m, H2), 2.75-2.60 (3H, m, H1'' & H1'a), 2.46 (1H, m, H1'b), 2.04 (3H, s, CH_3), 1.78 (3H, s, CH_3), 1.70 (3H, s, CH_3), 1.63 (3H, s, CH_3), 1.45 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 142.1, 135.8, 135.3, 133.0, 129.3, 129.1, 126.9, 126.8, 118.4, 118.1, 68.3, 65.8, 26.5, 26.2, 25.9, 25.7, 18.0, 17.6, 16.0; **IR** (thin film) υ_{max} = 2969 (w), 2914 (w), 1582 (w), 1440 (w), 1377 (w), 1307 (s), 1128 (w), 743 (w) cm^{-1}; **LRMS** (EI^+) *m/z* = 376 ($M^{+\bullet}$, 40%), 69 (100%); **HRMS** (EI^+) calc. for $C_{21}H_{28}O_2S_2$ ($M^{+\bullet}$) 376.1531, found 376.1530. A further fraction gave 3-methyl-2-(3-methylbut-2-en-1-yl)-4-(phenylthio)-2,5-dihydrothiophene 1,1-dioxide (**144**) as a pale yellow oil (408 mg, 36%); $\mathbf{R_f}$ (Ether:Hex ; 1:4) 0.22; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.35-7.27 (5H, m, ArH), 5.25-5.20 (1H, m, H2'), 3.74 (1H, dt, *J* = 6.4, 0.8 Hz, H2), 3.61 (2H, s, H5),

2.70-2.58 (2H, m, H1'), 2.05 (3H, s, CH_3), 1.75 (3H, s, CH_3), 1.68 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 139.7, 136.0, 131.9, 130.8, 129.5, 127.7, 122.6, 117.8, 70.0, 57.8, 27.0, 25.9, 18.0, 15.9; **IR** (thin film) υ_{max} = 2971 (m), 2914 (m), 1582 (m), 1477 (s), 1440 (s), 1312 (vs), 1131 (vs), 1088 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 308 ($M^{+\bullet}$, 20%), 131 (100%); **HRMS** (EI^+) calc. for $C_{16}H_{20}O_2S_2$ ($M^{+\bullet}$) 308.0905, found 308.0906.

Procedure 2: 3-Methyl-4-(phenylthio)-2,5-dihydrothiophene 1,1-dioxide (**143**) (1.42 g, 5.92 mmol), hexamethylphosphoramide (4.12 mL, 23.7 mmol) and tetrahydrofuran (40 mL) were added to a flask and cooled to -98°C. Butyllithium (2.55 mL, 5.92 mmol) was then added dropwise over 5 minutes. After 3 minutes of stirring prenyl bromide (3.45 mL, 29.6 mmol) was added and the reaction left to stir for 20 minutes. The reaction was then allowed to warm to room temperature followed by quenching with a saturated solution of ammonium chloride (30 mL) and extraction with diethyl ether (3x20 mL). The combined organic layers were then dried over magnesium sulfate, filtered, concentrated under reduced pressure and purified via silica gel chromatography using diethyl ether : hexane (3:17) to afford (±)-3-methyl-2-(3-methylbut-2-en-1-yl)-4-(phenylthio)-2,5-dihydrothiophene 1,1-dioxide (**144**) as a pale yellow oil (1.75 g, 57%).

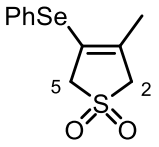
(*E*)-(3,7-dimethylocta-1,3,6-trien-2-yl)(phenyl)sulfane (**140**)



To a solution of 1 M lithium aluminium hydride (39.9 mL, 39.9 mmol), in tetrahydrofuran was added a solution of 3-methyl-2-(3-methylbut-2-en-1-yl)-4-(phenylthio)-2,5-dihydrothiophene 1,1-dioxide (**144**) (1.51 g, 4.90 mmol) in tetrahydrofuran (10 mL) dropwise over 20 minutes. The solution was then stirred at room temperature for 20 minutes followed by cooling to -78°C. The reaction was then quenched with the dropwise addition of ethyl acetate (10 mL) over 10 minutes followed by dilution with diethyl ether (50 mL) and a saturated solution of potassium sodium tartrate (50 mL). After vigorous stirring for 30 minutes the organic layer was separated and the aqueous layer re-extracted with diethyl ether (2x50 mL). The combined organic layers were concentrated under reduced pressure, the residue redissolved in hexanes (20 mL) and passed through a silica plug to afford (*E*)-(3,7-dimethylocta-1,3,6-trien-2-yl)(phenyl)sulfane (**140**) as a clear colourless oil (926 mg, 77%); **R_f** (Ether:Hex ; 1:4) 0.69; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.34-7.17 (5H, m, Ar-H), 6.04 (1H, dt, *J* = 7.2 & 0.8 Hz, H4), 5.45 (1H, s, H1b), 5.14 (1H, s, H1a), 5.02 (1H, m, H6), 2.76 (2H, t, *J* = 7.2 Hz, H5), 1.85 (3H, s, CH_3), 1.66 (3H, s, CH_3), 1.57 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 146.0, 134.9, 132.2, 132.1, 131.4, 130.7, 128.8, 126.8, 121.8, 114.9, 27.7, 25.6, 17.7, 14.9; **IR** (thin film) υ_{max} = 2970 (m), 2914 (m), 1581 (m), 1478

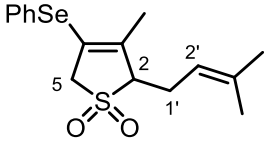
(m), 1439 (m), 1376 (w), 1088 (w), 1024 (w) cm^{-1}; **LRMS** (EI^+) *m/z* = 244 ($M^{+\bullet}$, 50%), 119 (100%); **HRMS** (EI^+) calc. for $C_{16}H_{20}S$ ($M^{+\bullet}$) 244.1286, found 244.1287.

3-Methyl-4-(phenylseleno)-2,5-dihydrothiophene 1,1-dioxide (**152**)



Phenylselenyl chloride (1.19 g, 6.24 mM), 3-methyl sulfolene (784 mg, 5.94 mM) and dichloromethane (20 mL) were added to a flask and stirred at room temperature for 2 days. Triethylamine (911 µL) was then added followed by another 2 days of stirring at 30°C. After quenching with a saturated solution of ammonium chloride (40 mL) dilution with dichloromethane (30 mL) was followed by separation of the organic layer. The aqueous layer was extracted again with dichloromethane (40 mL) and the combined organic layers were evaporated under reduced pressure. The resulting residue was then redissolved in chloroform (20 mL) followed by the addition of 1,8-diazabicycloundec-7-ene (4 drops) and stirred for 2 days at room temperature. The reaction was then diluted with diethyl ether (50 mL) and the organic layer separated followed by washing with 1 M hydrochloric acid solution (3 x 30 mL). Evaporation on to silica under reduced pressure and purification by flash column chromatography using diethyl ether : hexane (1:1) afforded 3-methyl-4-(phenylseleno)-2,5-dihydrothiophene 1,1-dioxide (**152**) as brown solid (400 mg, 23%). $\mathbf{R_f}$ (Ether:Hex ; 1:1) 0.21; **m.p.** 71-73°C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.47-7.45 (2H, m, ArH), 7.33-7.30 (3H, m, ArH), 3.87 (2H, s, H2), 3.72 (2H, s, H5), 2.03 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 134.9, 133.4, 129.5, 128.2, 126.9, 119.1, 61.0 (2C), 18.2; **IR** (thin film) υ_{max} = 2967 (w), 2916 (w), 1576 (w), 1475 (w), 1437 (w), 1312 (s), 1240 (s), 1132 (s) cm^{-1}; **LRMS** (EI^+) *m/z* = 288 ($M^{+\bullet}$, 55%), 67 (100%); **HRMS** (EI^+) calc. for C11H12O_2SSe ($M^{+\bullet}$) 287.9723, found 287.9723.

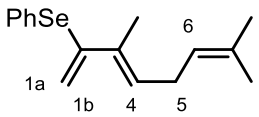
3-Methyl-2-(3'-methylbut-2'-en-1'-yl)-4-(phenylseleno)-2,5-dihydrothiophene 1,1-dioxide (**153**)



3-Methyl-4-(phenylseleno)-2,5-dihydrothiophene 1,1-dioxide (**152**) (729 mg, 2.54 mmol), hexamethylphosphoramide (1.77 mL, 10.2 mmol) and tetrahydrofuran (60 mL) were added to a flask and cooled to -98°C. Butyllithium (1.59 mL, 2.54 mmol) was then added dropwise over 5 minutes.

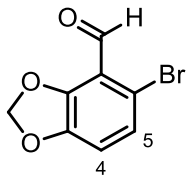
After 3 minutes of stirring prenyl bromide (1.48 mL, 12.7 mmol) was added and the reaction left to stir for 20 minutes. The reaction was then allowed to warm to room temperature followed by quenching with a saturated solution of ammonium chloride (30 mL) and extraction with diethyl ether (3x20 mL). The combined organic layers were then dried over magnesium sulfate, filtered, concentrated under reduced pressure and purified via silica gel chromatography using diethyl ether : hexane (3:7) to afford 3-methyl-2-(3'-methylbut-2'-en-1'-yl)-4-(phenylseleno)-2,5-dihydrothiophene 1,1-dioxide (**153**) as a pale yellow oil (532.3 mg, 59%); $\mathbf{R_f}$ (Ether:Hex ; 1:1) 0.37; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.47-7.32 (2H, m, ArH), 7.32-7.28 (3H, m, ArH), 5.20 (1H, m, H2'), 3.70 (1H, t, *J* = 6.0 Hz, H2), 3.62 (2H, m, H5), 2.63-2.60 (2H, m, H1'), 2.02 (3H, s, CH_3), 1.74 (3H, s, CH_3), 1.67 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 139.3, 135.9, 133.6, 129.7, 128.3, 127.2, 119.0, 117.9, 69.8, 59.9, 27.1, 25.9, 18.0, 17.7; **IR** (thin film) υ_{max} = 2967 (m), 2909 (m), 1642 (m), 1576 (m), 1438 (m), 1309 (s), 1228 (m), 1129 (s) cm^{-1}; **LRMS** (EI^+) *m/z* = 356 ($M^{+\bullet}$, 25%), 131 (100%); **HRMS** (EI^+) calc. for $C_{16}H_{20}O_2SSe$ ($M^{+\bullet}$) 355.9852, found 355.9852.

(*E*)-(3,7-dimethylocta-1,3,6-trien-2-yl)(phenyl)selane (**154**)



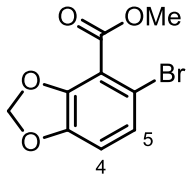
3-Methyl-2-(3'-methylbut-2'-en-1'-yl)-4-(phenylseleno)-2,5-dihydrothiophene 1,1-dioxide (**153**) (219 mg, 616 µmol) and toluene (15 mL) were added to a flask and refluxed for 6 hours. After allowing the reactions to cool to room temperature the mixture was passed through a silica plug and washed with hexane (3x15 mL). The resulting solution was then evaporated under educed pressure to afford (*E*)-(3,7-dimethylocta-1,3,6-trien-2-yl)(phenyl)selane (**154**) as a clear yellow oil (164 mg, 91%); $\mathbf{R_f}$ (Ether:Hex ; 1:1) 0.70; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.49-7.46 (2H, m, ArH), 7.27-7.22 (3H, m, ArH), 5.94 (1H, t, *J* = 6.8 Hz, H4), 5.71 (1H, s, H1b), 5.24 (1H, s, H1a), 5.02 (1H, m, H6), 2.77 (2H, dd, *J* = 7.2 & 7.2 Hz, H5), 1.86 (3H, s, CH_3), 1.67 (3H, s, CH_3), 1.59 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 144.1, 133.9, 133.3, 132.3, 131.5, 130.3, 129.1, 127.3, 121.8, 116.6, 27.8, 25.6, 17.7, 15.0; **IR** (thin film) υ_{max} = 2970 (m), 2923 (m), 1667 (w), 1578 (m), 1476 (s), 1437 (s), 1376 (m), 1021 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 292 ($M^{+\bullet}$, 30%), 119 (100%); **HRMS** (EI^+) calc. for $C_{16}H_{20}Se$ ($M^{+\bullet}$) 292.0730, found 292.0730.

6-Bromo-2,3-(methylenedioxy)benzaldehyde (**231**)[104]



To a flask was added diisopropyl amine (1.40 mL, 9.95 mmol) and tetrahydrofuran (20 mL) followed by cooling to -78°C under nitrogen. Butyllithium (1.31 M, 7.02 mL, 9.13 mmol) was then slowly added over 10 minutes and the mixture allowed to stir for 15 minutes. 1-Bromo-3,4-(methylenedioxy)benzene (1.00 mL, 8.30 mmol) was then added dropwise at such a rate to maintain the temperature below -70°C. After stirring for 15 minutes dimethylformamide (770 µL, 9.95 mmol) was added and the reaction left to stir for a further 15 minutes at -78°C. The reaction was then allowed to warm to room temperature and after stirring for 30 minutes was quenched with water (30 mL) and diluted with ethyl acetate (30 mL). The organic layer was separated followed by washing with 1 M hydrochloric acid solution (2x40 mL), sodium carbonate (2x40 mL) and brine (40 mL). Concentration under reduced pressure gave a crude residue which was recrystallised from isopropyl acetate to afford 6-bromo-2,3-(methylenedioxy)benzaldehyde (**231**) (1.30 g, 68%) as pale yellow crystals; $\mathbf{R_f}$ (Ether:Hex ; 2:3) 0.38; **m.p.** 159-162°C (lit. m.p. 160-162°C); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.29 (1H, s, CHO), 7.11 (1H, d, *J* = 8.4 Hz, H4), 6.85 (1H, d, *J* = 8.4 Hz, H5), 6.17 (2H, s, OCH_2O); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 190.4, 149.4, 148.7, 126.2, 117.3, 115.6, 113.6, 103.4; **IR** (thin film) υ_{max} = 2930 (w), 1679 (s), 1586 (w), 1454 (s), 1398 (m), 1243 (vs), 1115 (m), 1017 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 228 ($C_8H_5O_3{}^{79}Br$, $M^{+\bullet}$, 100%), 230 ($C_8H_5O_3{}^{81}Br$, $M^{+\bullet}$, 98%); **HRMS** (EI^+) calc. for $C_8H_5O_3{}^{79}Br$ ($M^{+\bullet}$) 227.9422, found 227.9421, calc. for $C_8H_5O_3{}^{81}Br$ ($M^{+\bullet}$) 229.9402, found 229.9408.

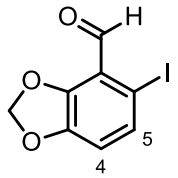
Methyl 6-bromo-2,3-(methylenedioxy)benzoate (**232**)



To a flask was added diisopropyl amine (1.40 mL, 9.95 mmol) and tetrahydrofuran (20 mL) followed by cooling to -78°C under nitrogen. Butyl lithium (1.31 M, 7.02 mL, 9.13 mmol) was then slowing added over 10 minutes and the mixture allowed to stir for 15 minutes. 1-Bromo-3,4-(methylenedioxy)benzene (1.00 mL, 8.30 mmol) was then added dropwise at such a rate to maintain the temperature below -70°C. After stirring for 15 minutes methyl chloroformate (769 µL, 9.95 mmol)

was added and the reactions left to stir for a further 15 minutes at -78°C. The reaction was then allowed to warm to room temperature and after stirring for 30 minutes was quenched with water (30 mL) and diluted with ethyl acetate (30 mL). The organic layer was separated followed by washing with 1 M hydrochloric acid solution (2x40 mL), saturated sodium carbonate (2x40 mL) and brine (40 mL). Concentration under reduced pressure and purification by flash column chromatography using diethyl ether : hexane (1:9) afforded methyl 6-bromo-2,3-(methylenedioxy)benzoate (**232**) (1.54 g, 70%) as a pale yellow solid; $\mathbf{R_f}$ (Ether:Hex ; 1:9) 0.09; **m.p.** 58-59 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.05 (1H, d, *J* = 8.0 Hz, H4), 6.72 (1H, d, *J* = 8.4 Hz, H5), 6.05 (2H, s, OCH_2O), 3.94 (3H, s, OMe); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 164.0, 147.6, 147.4, 126.0 (2C), 115.9, 110.9, 102.3, 52.4; **IR** (thin film) υ_{max} = 2953 (m), 2905 (m), 1733 (vs), 1626 (m), 1451 (vs), 1342 (m), 1276 (vs), 1137 (s) cm^{-1}; **LRMS** (ESI^+) *m/z* = 281 ($C_9H_7O_4{}^{79}Br$ $[M+Na]^+$, 35%), 283 ($C_9H_7O_4{}^{81}Br$, $[M+Na]^+$, 30%), 343 (100%); **HRMS** (ESI^+) calc. for $C_9H_7O_4{}^{79}BrNa$ ($[M+Na]^+$) 280.9425, found 280.9425, calc. for $C_9H_7O_4{}^{81}BrNa$ ($[M+Na]^+$) 282.9405, found 282.9409.

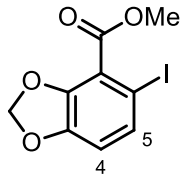
6-Iodo-2,3-(methylenedioxy)benzaldehyde (**235**)[104]



2,2,6,6-Tetramethylpiperidine (3.94 mL, 23.2 mmol) and tetrahydrofuran (50 mL) were added to a flask under nitrogen and cooled to -78°C. Butyllithium (1.5 M, 14.2 mL, 21.2 mmol) was then added dropwise over 5 min and the reaction allowed to warm to 0°C. After stirring for 30 min the reaction was once again cooled to -78°C followed by the dropwise addition over 15 minutes of 1-iodo-3,4-(methylenedioxy)benzene (2.50 mL, 19.3 mmol) and subsequent stirring for a further 30 min. Dimethylformamide (1.80 mL, 23.2 mmol) was then added dropwise over 5 min and the reaction left to stir at -78°C for 15 min and then allowed to warm to room temperature with stirring for a further 30 min. The reaction was then quenched with water (60 mL) and extracted with ethyl acetate (3x30 mL). The combined organic layers were then washed with 1 M hydrochloric acid solution (50 mL), saturated sodium carbonate (30 mL) and brine (30 mL). Concentration under reduced pressure gave a crude residue which was recrystallised from cyclohexane to afford 6-iodo-2,3-(methylenedioxy)benzaldehyde (**235**) (3.63 g, 68%) as pale yellow crystals. $\mathbf{R_f}$ (Ether:Hex ; 2:3) 0.36; **m.p.** 163-166°C (lit. m.p. 162-165°C); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.05 (1H, s, CHO), 7.41 (1H, d, *J* = 8.0 Hz, H4), 6.73 (1H, d, *J* = 8.0 Hz, H5), 6.16 (2H, s, OCH_2O); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 194.0, 149.8, 149.2, 133.3, 118.1, 114.4, 103.1, 86.3; **IR** (thin film) υ_{max} = 2926 (w), 1671 (s), 1581 (m), 1448 (s), 1392 (m) 1240

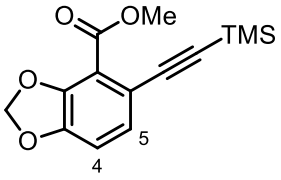
(vs), 1108 (m), 1017 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 276 ($M^{+\bullet}$, 100%); **HRMS** (EI^+) calc. for $C_8H_5O_3I$ ($M^{+\bullet}$) 275.9283, found 275.9284.

Methyl 6-iodo-2,3-(methylenedioxy)benzoate (**236**)



2,2,6,6-Tetramethylpiperidine (7.86 mL, 46.2 mmol) and tetrahydrofuran (100 mL) were added to a flask under nitrogen and cooled to -78°C. Butyl lithium (28.2 mL, 42.4 mmol) was then added dropwise over 5 min and the reaction allowed to warm to 0°C. After stirring for 30 min the reaction was once again cooled to -78°C followed by the dropwise addition over 15 minutes of 5-iodo-1,3-benzodioxole (5.00 mL, 38.5 mmol) and subsequent stirring for a further 30 min. Methyl chloroformate (3.58 mL, 46.2 mmol) was then added dropwise over 5 min and the reaction left to stir at -78°C for 15 min and then allowed to warm to room temperature with stirring for a further 30 min. The reaction was then quenched with water (100 mL) and extracted with ethyl acetate (3x50 mL). The combined organic layers were then washed with 1 M hydrochloric acid solution (50 mL), saturated sodium carbonate (50 mL) and brine (50 mL). Concentration under reduced pressure and purification by flash column chromatography using diethyl ether : hexane (1:9) afforded methyl 6-iodo-2,3-(methylenedioxy)benzoate (**236**) (6.11g, 52%). $\mathbf{R_f}$ (Ether:Hex ; 1:9) 0.19; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.36 (1H, d, *J* = 8.4 Hz, H4), 6.62 (1H, d, *J* = 8.0 Hz, H5), 6.04 (2H, s, OCH_2O) 3.94 (3H, s, OMe); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 165.0, 148.5, 147.4, 133.3, 119.0, 112.0, 102.2, 81.4, 52.6; **IR** (thin film) υ_{max} = 2951 (w), 2903 (w), 1729 (s), 1619 (w), 1448 (s), 1273 (s), 1239 (s), 1041 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 306 ($M^{+\bullet}$, 100%); **HRMS** (EI^+) calc. for $C_9H_7O_4I$ ($M^{+\bullet}$) 305.9389, found 305.9393.

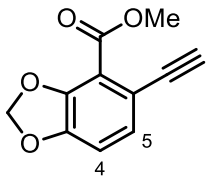
Methyl 6-(trimethylsilyl)ethynyl-2,3-(methylenedioxy)benzoate (**234**)



Methyl 6-iodo-2,3-(methylenedioxy)benzoate (**236**) (2.27 g, 7.45 mmol), palladium tetrakis (triphenylphosphine) (430 mg, 373 µmol), copper iodide (142 mg, 745 µmol) and tetrahydrofuran (50 mL) were added to a flask and stirred under nitrogen. Triethylamine was then added (3.12 mL, 22.4

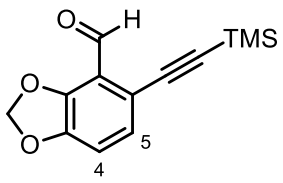
mmol) followed by trimethylsilylacetylene (1.59 mL, 11.1 mmol) and the reaction left to stir for 16 hours at 30°C. The reaction was then quenched with a saturated solution of ammonium chloride (75 mL) followed by extraction with diethyl ether (3x30 mL). The combined organic layers were then concentrated under reduced pressure and purified by flash column chromatography using diethyl ether : hexane (3:7) to give methyl 6-(trimethylsilyl)ethynyl-2,3-(methylenedioxy)benzoate (**234**) (1.67 g, 81%) as a pale yellow oil. **R_f** (EtOAc:Hex ; 3:7) 0.38; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.09 (1H, d, *J* = 7.6 Hz, H5), 6.82 (1H, d, *J* = 7.6 Hz, H4), 6.08 (2H, s, OCH_2O), 3.92 (3H, s, OMe), 0.24 (9H, s, TMS); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 164.4, 148.4, 147.6, 128.6, 115.7, 115.6, 110.5, 102.7, 102.3, 96.8, 52.1, 0.1; **IR** (thin film) υ_{max} = 2956 (w), 2899 (w), 2153 (m), 1731 (s), 1462 (vs), 1274 (s), 1248 (s), 1053 (s) cm^{-1}; **LRMS** (EI^+) *m/z* = 276 ($M^{+\bullet}$, 96%), 231 (100%); **HRMS** (EI^+) calc. for $C_{14}H_{16}O_4Si$ ($M^{+\bullet}$) 276.0818, found 276.0821.

Methyl 6-ethynyl-2,3-(methylenedioxy)benzoate (**237**)



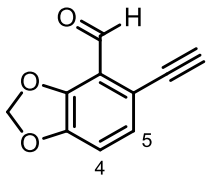
Methyl 6-(trimethylsilyl)ethynyl-2,3-(methylenedioxy)benzoate (**234**) (1.11 g, 4.01 mmol), potassium carbonate (55.4 mg, 401 µmol) and methanol (50 mL) were added to a flask and stirred at room temperature for 3 hours. The reaction was then diluted with water (50 mL) followed by extraction with dichloromethane (3x40 mL) and washing with brine (50 mL). The combined organic layers were evaporated on to silica under reduced pressure and purified by flash column chromatography using diethyl ether : hexane (3:7) to afford methyl 6-ethynyl-2,3-(methylenedioxy)benzoate (**237**) (775 mg, 95%) as a brown solid. **R_f** (Ether:Hex ; 3:7) 0.18; **m.p.** decomp > 96°C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.13 (1H, d, *J* = 8.0 Hz, H4), 6.85 (1H, d, *J* = 8.4 Hz, H5), 6.09 (2H, s, OCH_2O), 3.94 (3H, s, OMe), 3.20 (1H, s, C≡CH); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 164.3, 148.7, 147.8, 129.1, 115.6, 114.9, 110.7, 102.3, 81.5, 79.7, 52.2; **IR** (thin film) υ_{max} = 3248 (m), 2956 (w), 2919 (w), 1713 (vs), 1449 (s), 1243 (s), 1054 (m), 921 (w) cm^{-1}; **LRMS** (EI^+) *m/z* = 204 ($M^{+\bullet}$, 100%); **HRMS** (EI^+) calc. for $C_{11}H_8O_4$ ($M^{+\bullet}$) 204.0423, found 204.0426.

6-(Trimethylsilyl)ethynyl-2,3-(methylenedioxy)benzaldehyde (**233**)



2-Carboxaldehyde-1-iodo-3,4-(methylenedioxy)benzene (**235**) (1.00 g, 3.64 mmol), palladium tetrakis (triphenylphosphine) (210 mg, 182 µmol), copper iodide (69.3 mg, 364 µmol) and tetrahydrofuran (30 mL) were added to a flask and stirred under nitrogen. Triethylamine was then added (2.54 mL, 18.2 mmol) followed by trimethylsilyl acetylene (776 µL, 5.45 mmol) and the reaction left to stir for 16 hours at 30°C. The reaction was then quenched with a saturated solution of ammonium chloride (50 mL) followed by extraction with diethyl ether (3x30 mL). The combined organic layers were then concentrated under reduced pressure and purified by flash column chromatography using diethyl ether : hexane (15:85) to give 3-carboxaldehyde-4-(2-(trimethylsilyl)ethyny)-1,2-(methylenedioxy)benzene (**233**) (874 mg, 98%) as a pale yellow oil. $\mathbf{R_f}$ (Ether:Hex ; 2:3) 0.36; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.38 (1H, s, CHO), 7.04 (1H, d, *J* = 8.0 Hz, H5), 6.86 (1H, d, *J* = 8.0 Hz, H4), 6.11 (2H, s, OCH_2O), 0.21 (9H, s, TMS); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 190.1, 149.0, 147.4, 127.7, 119.1, 118.4, 112.4, 103.0, 100.1, 99.7, 0.3; **IR** (thin film) υ_{max} = 2959 (w), 2901 (w), 2150 (m), 1695 (s), 1615 (m), 1462 (vs), 1243 (s), 1069 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 246 ($M^{+\bullet}$, 55%), 231 (100%); **HRMS** (EI^+) calc. for $C_{13}H_{14}O_3Si$ ($M^{+\bullet}$) 246.0712, found 246.0719.

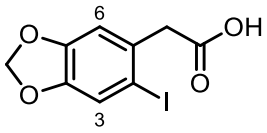
6-Ethynyl-2,3-(methylenedioxy)benzaldehyde (**236**)



6-(Trimethylsilyl)ethynyl-2,3-(methylenedioxy)benzaldehyde (**235**) (871 mg, 3.54 mmol), potassium carbonate (48.9 mg, 354 µmol) and methanol (30 mL) were added to a flask and stirred at room temperature for 3 hours. The reaction was then diluted with water (40 mL) followed by extraction with dichloromethane (3x30 mL) and washing with brine (40 mL). The combined organic layers were evaporated on to silica under reduced pressure and purified by flash column chromatography using diethyl ether : hexane (3:7) to afford 6-ethynyl-2,3-(methylenedioxy)benzaldehyde (**236**) (527 mg, 85%) as a brown solid. $\mathbf{R_f}$ (Ether:Hex ; 3:7) 0.13; **m.p.** 136-156°C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.44 (1H, s, CHO), 7.15 (1H, d, *J* = 8.0 Hz, H5), 6.95 (1H, s, *J* = 8.0 Hz, H4), 6.18 (2H, s, OCH_2O), 3.33 (1H, s,

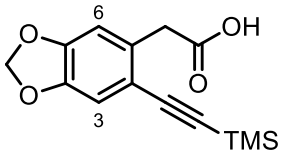
C≡CH); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 189.7, 149.5, 147.8, 128.3, 119.6, 117.1, 112.6, 103.2, 82.1, 79.3; **IR** (thin film) υ_{max} = 3266 (m), 2929 (w), 1677 (s), 1615 (m), 1465 (s), 1403 (m), 1249 (s), 1072 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 174 ($M^{+\bullet}$, 100%); **HRMS** (EI^+) calc. for $C_{10}H_6O_3$ ($M^{+\bullet}$) 174.0317, found 174.0317.

2-Iodo-4,5-methylenedioxyphenylacetic acid (**223**)



Iodine monochloride (1.55 mL, 30.9 mmol) was dissolved in acetic acid (20 mL) and added to a stirring solution of homopiperonylic acid (5.07 g, 28.1 mmol) in acetic acid (20 mL). The reaction was then allowed to stir for 16 hrs at room temperature followed by the addition of water (30 mL) and sodium metabisulfite until a yellow colour persisted. Water (60 mL) was then added slowly over 30 min and the reaction left to stir for 2 hrs. Filtration of the reaction mixture, washing with water (3x30 mL) and drying afforded 2-iodo-4,5-methylenedioxyphenylacetic acid (**223**) as a white solid (6.11 g, 71%). **R_f** (EtOAc:Hex ; 1:1) 0.05; **m.p.** 179-186 °C; **^{1}H-NMR** (400 MHz, CD_3OD) δ 7.26 (1H, s, H3), 6.87 (1H, s, H6), 5.97 (2H, s, OCH_2O), 3.71 (2H, s, CH_2); **^{13}C-NMR** (100 MHz, CD_3OD) δ 174.5, 150.0, 149.0, 132.9, 119.3, 111.7, 103.2, 89.5, 46.6; **IR** (thin film) υ_{max} = 3317 (m), 3012 (m), 2910 (m), 1697 (vs), 1484 (s), 1407 (m), 1226 (s), 1034 (m) cm^{-1}; **LRMS** (ESI^+) *m/z* = 329 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_9H_7O_4Na$ ($[M+H]^+$) 328.9287, found 328.9286.

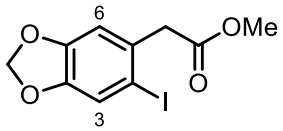
4,5-Methylenedioxy-2-(2-(trimethylsilyl)ethynyl)phenylacetic acid (**228**)



2-Iodo-4,5-methylenedioxyphenylacetic acid (**223**) (197 mg, 643 µmol), palladium tetrakis (triphenylphosphine) (37.2 mg, 32.2 µmol), copper iodide (12.2 mg, 64.3 µmol) and tetrahydrofuran (10 mL) were added to a flask and stirred under nitrogen. Triethylamine was then added (269 µL, 1.93 mmol) followed by trimethylsilylacetylene (137 µL, 965 µmol) and the reaction left to stir for 16 hours at 30°C. The reaction was then quenched with a saturated solution of ammonium chloride (50 mL) and the resulting mixture acidified with 2 M hydrochloric acid solution followed by extraction with ethyl acetate (3x30 mL). The combined organic layers were then concentrated under reduced pressure and

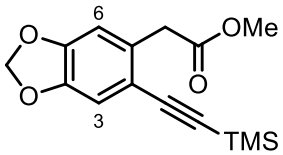
purified by flash column chromatography using ethyl acetate : hexane (3:2) to give 4,5-methylenedioxy-2-(2-(trimethylsilyl)ethynyl)phenyl acetic acid (**228**) (120 mg, 68%) as a brown oil. $\mathbf{R_f}$ (EtOAc:Hex ; 3:2) 0.36; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.91 (1H, s, H3), 6.73 (1H, s, H6), 5.96 (2H, s, OCH_2O), 3.78 (2H, s, CH_2), 0.22 (9H, s, TMS), (OH not observed); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 177.5, 148.1, 146.6, 130.7, 116.6, 111.6, 110.2, 102.7, 101.5, 97.9, 39.4, -0.1; **IR** (thin film) υ_{max} = 2959 (m), 2899 (m), 2152 (m), 1712 (s), 1483 (vs), 1407 (w), 1250 (m), 1039 (m) cm^{-1}; **LRMS** (ESI^-) *m/z* = 275 ([M-H]$^-$, 3%), 231 (100%); **HRMS** (ESI^-) calc. for $C_{14}H_{15}O_4Si$ ([M-H]$^-$) 275.0740, found 275.0741.

Methyl 2-iodo-4,5-methylenedioxyphenyl acetate (**238**)



2-Iodo-4,5-methylenedioxyphenylacetic acid (**223**) (1.51 g, 4.95 mmol) and methanol (50 mL) were added to a flask and cooled to 0°C with stirring. Thionyl chloride (575 µL, 7.92 mmol) was then added dropwise over 15 minutes and the reaction then allowed to warm to room temperature followed by stirring for 16 hours. The solvent was then removed under reduced pressure and the resulting residue purified by flash column chromatography using ethyl acetate : hexane (3:7) to give methyl 2-iodo-4,5-methylenedioxyphenyl acetate (**238**) (1.54 g, 97%) as a white solid. $\mathbf{R_f}$ (EtOAc:Hex ; 1:1) 0.55; **m.p.** 56-60°C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.23 (1H, s, H3), 6.79 (1H, s, H6), 5.95 (2H, s, OCH_2O), 3.70 (5H, m, CH_2 & OMe); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 171.0, 148.4, 147.5, 130.6, 118.5, 110.3, 101.7, 88.7, 52.1, 45.7; **IR** (thin film) υ_{max} = 2955 (w), 2906 (w), 1733 (s), 1647 (s), 1487 (s), 1389 (m), 1339 (s), 1116 (s) cm^{-1}; **LRMS** (EI^+) *m/z* = 320 ($M^{+\bullet}$, 80%), 261 (100%); **HRMS** (EI^+) calc. for $C_{10}H_9O_4I$ ($M^{+\bullet}$) 319.9546, found 319.9543.

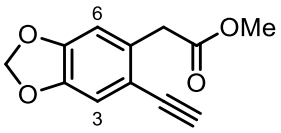
Methyl 4,5-methylenedioxy-2-(2-(trimethylsilyl)ethynyl)phenyl acetate (**241**)



Methyl 2-iodo-4,5-methylenedioxyphenyl acetate (**238**) (350 mg, 1.09 mmol), palladium tetrakis (triphenylphosphine) (63.0 mg, 54.5 µmol), copper iodide (20.8 mg, 109 µmol) and tetrahydrofuran (10 mL) were added to a flask and stirred under nitrogen. Triethylamine was then added (760 µL, 5.45 mmol) followed by trimethylsilyl acetylene (234 µL, 1.64 mmol) and the reaction left to stir for 16

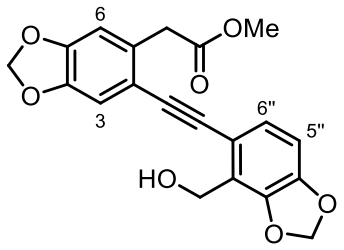
hours at 30°C. The reaction was then quenched with a saturated solution of ammonium chloride (30 mL) followed by extraction with diethyl ether (3x20 mL). The combined organic layers were then concentrated under reduced pressure and purified by flash column chromatography using diethyl ether : hexane (3:7) to give methyl 4,5-methylenedioxy-2-(2-(trimethylsilyl)ethynyl)phenyl acetate (**241**) (304 mg, 96%) as a pale yellow oil. $\mathbf{R_f}$ (Ether:Hex ; 1:1) 0.55; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.88 (1H, s, H3), 6.72 (1H, s, H6), 5.93 (2H, s, OCH_2O), 3.74 (2H, s, CH_2), 3.68 (3H, s, OMe), 0.22 (9H, s, TMS); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 171.5, 148.1, 146.4, 131.5, 116.3, 111.5, 110.1, 102.9, 101.4, 97.4, 51.9, 39.4, 0.14; **IR** (thin film) υ_{max} = 2956 (m), 2899 (w), 2151 (m), 1741 (s), 1617 (w), 1484 (vs), 1331 (m), 1250 (s) cm^{-1}; **LRMS** (EI^+) *m/z* = 290 ($M^{+\bullet}$, 100%); **HRMS** (EI^+) calc. for $C_{15}H_{18}O_4Si$ ($M^{+\bullet}$) 290.0974, found 290.0975.

Methyl 2-ethynyl-4,5-methylenedioxyphenyl acetate (**242**)



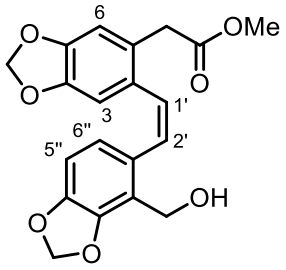
Methyl 4,5-methylenedioxy-2-(2-(trimethylsilyl)ethynyl)phenyl acetate (**241**) (304 mg, 1.05 mmol), potassium carbonate (14.5 mg, 105 µmol) and methanol (20 mL) were added to a flask and stirred at room temperature for 3 hours. The reaction was then diluted with water (20 mL) followed by extraction with dichloromethane (3x15 mL) and washing with brine (20 mL). The combined organic layers were evaporated on to silica under reduced pressure and purified by flash column chromatography using diethyl ether : hexane (1:4) to afford methyl 2-ethynyl-4,5-methylenedioxyphenyl acetate (**242**) (202 mg, 88%) as a brown oil. $\mathbf{R_f}$ (Ether:Hex ; 2:3) 0.38; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.93 (1H, s, H3), 6.76 (1H, s, H6), 5.97 (2H, s, OCH_2O), 3.78 (2H, s, CH_2), 3.71 (3H, s, OMe), 3.19 (1H, s, C≡CH); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 171.5, 148.4, 146.5, 131.5, 115.2, 112.0, 110.1, 101.5, 81.2, 80.2, 52.1, 39.2; **IR** (thin film) υ_{max} = 3248 (m), 2956 (w), 2915 (w), 2097 (w), 1720 (s), 1613 (w), 1489 (s), 1272 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 218 ($M^{+\bullet}$, 70%), 159 (100%); **HRMS** (EI^+) calc. for $C_{12}H_{10}O_4$ ($M^{+\bullet}$) 218.0579, found 218.0578.

Methyl 2-[2'-(2"-methanol-3",4"-methendioxybenzene-1-yl)ethynyl]-4,5-methylenedioxyphenyl acetate (**239**)



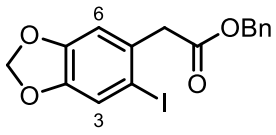
6-Iodo-2,3-(methylenedioxy)benzaldehyde (**235**) (1.97 g, 7.14 mmol), allylpalladium(II) chloride dimer (65.3 mg, 178 µmol) and acetonitrile (20 mL) were added to a flask and stirred under nitrogen. Tri-*tert*-butylphosphine (10% wt in Hex, 2.18 mL, 714 µmol), methyl 2-ethynyl-4,5-methylenedioxyphenyl acetate (**242**) (1.87 g, 8.57 mmol) and 1,4-diazabicyclo[2.2.2]octane (1.60 g, 14.3 mmol) were then added, in that order, and the reaction stirred for 16 hours at 30°C. The reaction was then quenched with a saturated aqueous solution of ammonium chloride (30 mL) followed by extraction with ethyl acetate (3x20 mL). The combined organic fractions were transferred to a clean reaction flask and concentrated under reduced pressure to afford a crude residue. Sodium borohydride (324 mg, 8.57 mmol), methanol (40 mL) and dichloromethane were then added to flask and the reactions stirred for 3 hours at room temperature. Quenching with a saturated aqueous solution of ammonium chloride (30 mL) was followed by extraction with ethyl acetate (3x20 mL) and the combined organic layers were evaporated under reduced pressure. Purification by flash column chromatography using ethyl acetate : hexane (1:1) afforded methyl 2-[2'-(2"-methanol-3",4"-methendioxybenzene-1-yl)ethynyl]-4,5-methylenedioxyphenyl acetate (**239**) (1.87 g, 71% over 2 steps) as a yellow/orange solid. **R_f** (EtOAc:Hex ; 1:1) 0.29; **m.p.** 139-158°C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.07 (1H, d, *J* = 8.0 Hz, H6'), 6.96 (1H, s, H3), 6.80 (1H, s, H6), 6.75 (1H, d, *J* = 7.6 Hz, H5') 6.03 (2H, s, OCH_2O), 5.99 (2H, s, OCH_2O), 4.83 (2H, s, CH_2OH), 3.81 (2H, s, $ArCH_2$), 3.68 (3H, s, OMe), (OH not observed); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 171.9, 148.1, 147.8, 146.7, 146.1, 130.4, 126.8, 123.2, 116.4, 116.0, 111.5, 110.3, 108.0, 101.6 (2C), 90.0, 89.7, 57.9, 52.4, 40.1; **IR** (thin film) υ_{max} = 3498 (s), 2952 (w), 2907 (w), 1725 (s), 1631 (w), 1486 (vs), 1336 (m), 1244 (s) cm^{-1}; **LRMS** (EI^+) *m/z* = 368 ($M^{+\bullet}$, 100%); **HRMS** (EI^+) calc. for $C_{20}H_{16}O_7$ ($M^{+\bullet}$) 368.0896, found 368.0896.

Methyl *cis*-2-[2'-(2"-methanol-3",4"-methendioxybenzen-1-yl)ethenyl]-4,5-methylenedioxyphenyl acetate (**245**)



Methyl 2-[2'-(2"-methanol-3",4"-methendioxybenzene-1-yl)ethynyl]-4,5-methylenedioxyphenyl acetate (**239**) (354 mg, 960 µmol), Lindlar's catalyst (40 mg, 5% Pd) and methanol (40 mL) were added to a flask and stirred vigorously at room temperature. The flask was then flushed with hydrogen and after stirring for 3 days under a constant atmosphere of hydrogen the reaction was filtered through a plug of celite. The celite was then washed with ethyl acetate (2x30 mL) and the washings added to the reaction mixture. After evaporation under reduced pressure the resulting material was purified by flash column chromatography using ethyl acetate : hexane (2:3) to afford methyl *cis*-2-[2'-(2"-methanol-3",4"-methendioxybenzen-1-yl)ethenyl]-4,5-methylenedioxyphenyl acetate (**245**) as a pale yellow oil (292 mg, 82%); $\mathbf{R_f}$ (EtOAc:Hex ; 1:1) 0.23; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.74-6.70 (2H, m, H3 & H1'), 6.61-6.57 (3H, m, H2' & H5'' & H6''), 6.50 (1H, s, H6), 5.98 (2H, s, OCH_2O), 5.89 (2H, s, OCH_2O), 4.66 (2H, s, CH_2OH), 3.66 (3H, s, OMe), 3.55 (2H, s, $ArCH_2$), 1.60 (1H, s, OH); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 172.0, 146.9, 146.6, 146.5, 146.2, 130.2, 129.8, 128.8, 128.2, 125.9, 123.1, 120.4, 110.5, 109.5, 108.0, 101.2, 101.0, 57.2, 52.1, 38.8; **IR** (thin film) υ_{max} = 3429 (w), 2952 (w), 2894 (w), 1733 (s), 1484 (vs), 1332 (m), 1250 (s), 1038 (s) cm^{-1}; **LRMS** (EI^+) *m/z* = 370 ($M^{+\bullet}$, 100%); **HRMS** (EI^+) calc. for $C_{20}H_{18}O_7$ ($M^{+\bullet}$) 370.1053, found 370.1051.

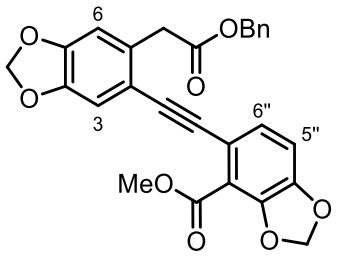
Benzyl 2-iodo-4,5-(methylenedioxy)phenylacetate (**247**)



2-Iodo-4,5-methylenedioxyphenylacetic acid (**223**) (629 mg, 2.06 mmol), benzyl bromide (269 µL, 2.26 mmol), potassium carbonate (285 mg, 2.06 mmol) and acetone (15 mL) were added to a flask and refluxed for 16 hours. After allowing the reaction to cool it was diluted with water (30 mL) and extracted with ethyl acetate (2x30 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium hydrogencarbonate (30 mL) and evaporated on to silica under reduced pressure. Purification by flash column chromatography using ethyl acetate : hexane (3:7) gave benzyl 2-iodo-4,5-

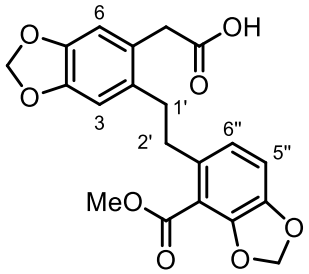
(methylenedioxy)phenylacetate (**247**) (779 mg, 95%) as white crystals; $\mathbf{R_f}$ (EtOAc:Hex ; 3:7) 0.27; **m.p.** 88-91°C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.34-7.28 (5H, m, Ph), 7.23 (1H, s, H3), 6.78 (1H, s, H6), 5.92 (2H, s, OCH_2O), 5.15 (2H, s, CH_2), 3.74 (2H, s, CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 170.3, 148.3, 147.5, 135.6, 130.5, 128.4, 128.1 (2C), 118.4, 110.3, 101.6, 88.7, 66.6, 45.8; **IR** (thin film) υ_{max} = 2954 (w), 2896 (w), 1735 (s), 1480 (vs), 1326 (m), 1230 (s), 1150 (s), 1037 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 396 ($M^{+\bullet}$, 50%), 261 (100%); **HRMS** (EI^+) calc. for $C_{16}H_{13}O_4I$ ($M^{+\bullet}$) 395.9859, found 395.9859.

Benzyl 2-[2'-(2''carboxymethyl-3",4"-methendioxybenzen-1-yl)ethynyl]-4,5-methylenedioxyphenyl acetate (**248**)



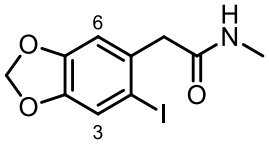
Benzyl 2-iodo-4,5-methylenedioxyphenylacetate (**247**) (634 mg, 1.60 mmol), allylpalladium(II) chloride dimer (14.6 mg, 40.0 µmol) and acetonitrile (10 mL) were added to a flask and stirred under nitrogen. Tri-*tert*-butylphosphine (10% wt in Hex, 490 µL, 160 µmol), methyl -3- carboxylate-4-ethyny-1,2-(methylenedioxy)benzene (**237**) (490 mg, 2.40 mmol) and 1,4-diazabicyclo[2.2.2]octane (359 mg, 3.20 mmol) were then added, in that order, and the reaction stirred for 16 hours at 30°C. The reaction was then quenched with a saturated aqueous solution of ammonium chloride (30 mL) followed by extraction with ethyl acetate (3x20 mL). The combined organic fractions were washed with brine (20 mL) and evaporated on to silica under reduced pressure. Purification by flash column chromatography using ethyl acetate : hexane (1:1) afforded benzyl 2-[2'-(2''carboxymethyl-3",4"-methendioxybenzen-1-yl)ethynyl]-4,5-methylenedioxyphenylacetate (**248**) as a brown solid (464 mg, 61%); $\mathbf{R_f}$ (EtOAc:Hex ; 1:1) 0.19; **m.p.** 123-129°C **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.32-7.25 (5H, m, ArH), 7.03 (1H, d, *J* = 8.4 Hz, H6''), 6.96 (1H, s, H3), 6.80-6.78 (2H, m, H6 & H5''), 6.07 (2H, s, OCH_2O), 5.95 (2H, s, OCH_2O), 5.13 (2H, OCH_2Ar), 3.92 (2H, s, $ArCH_2$), 3.89 (3H, s, OMe); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 171.2, 164.3, 148.1, 148.0, 147.8, 146.5, 135.8, 130.9, 128.3 (2C), 128.0 (2C), 116.7, 116.1, 114.6, 111.4, 110.7, 110.1, 102.2, 101.4, 90.7, 90.1, 66.5, 52.1, 39.5; **IR** (thin film) υ_{max} = 2951 (w), 2903 (w), 1728 (s), 1614 (w), 1486 (vs), 1373 (m), 1241 (vs), 1151 (m) cm^{-1}; **LRMS** (EI^+) *m/z* = 472 ($M^{+\bullet}$, 80%), 322 (100%); **HRMS** (EI^+) calc. for $C_{27}H_{20}O_8$ ($M^{+\bullet}$) 472.1158, found 472.1171.

2-[2'-(2''Carboxymethyl-3",4"-methendioxybenzen-1-yl)ethanyl]-4,5-methylenedioxyphenylacetic acid (**250**)



Benzyl 2-[2'-(2''carboxymethyl-3",4"-methendioxybenzen-1-yl)ethynyl]-4,5-methylenedioxyphenyl acetate (**248**) (113 mg, 239 µmol) was added to a flask along with palladium on carbon (10 mg, 10%), ethanol (10 mL) and ethyl acetate (10 mL). The flask was then flushed with hydrogen and after stirring for 4 hours under a constant atmosphere of hydrogen the reaction was filtered through a plug of celite. The celite was then washed with ethyl acetate (2x30 mL) and the combined washings evaporated under reduced pressure and the resulting material purified by flash column chromatography using ethyl acetate : hexane : acetic acid (70:29:1) to afford 2-[2'-(2''carboxymethyl-3",4"-methendioxybenzen-1-yl)ethanyl]-4,5-methylenedioxyphenylacetic acid (**250**) as a yellow oil (43.4 mg, 47%); $\mathbf{R_f}$ (EtOAc:Hex:AcOH ; 70:29:1) 0.25; **^{1}H-NMR** (400 MHz, CD_3OD) δ 6.84 (1H, d, *J* = 8.0 Hz, H5''), 6.70 (1H, d, *J* = 8.0 Hz, H6''), 6.68 (1H, s, H3), 6.64 (1H, s, H6), 5.99 (2H, s, OCH_2O), 5.88 (2H, s, OCH_2O), 3.87 (3H, s, OMe), 3.51 (2H, s, CH_2), 2.94 (2H, m, H2'), 2.74 (2H, m, H1'); **^{13}C-NMR** (100 MHz, CD_3OD) δ 176.2, 167.5, 148.9, 148.1, 147.9, 147.3, 136.1, 135.0, 127.3, 124.6, 114.9, 111.7, 111.4, 110.6, 103.0, 102.1, 52.5, 39.1, 36.6, 36.3; **IR** (thin film) υ_{max} = 3435 (m), 2928 (w), 2875 (w), 1717 (vs), 1444 (m), 1254 (s), 1039 (m), 927 (m) cm^{-1}; **LRMS** (ESI^-) *m/z* = 385 ($[M-H]^-$, 30%), 309 (100%); **HRMS** (ESI^+) calc. for $C_{20}H_{18}O_8Na$ ($[M+Na]^+$) 409.0899, found 409.0891.

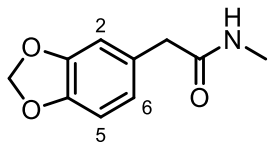
2-Iodo-4,5-methylenedioxyphenyl-*N*-methyl acetamide (**252**)



A solution of 2-iodo-4,5-methylenedioxyphenyl acetic acid (**223**) (546 mg, 1.78 mmol), oxalyl chloride (184 µL, 2.14 mmol) and 3 drops of *N*,*N*-dimethylformamide in toluene (10 mL) was stirred at room temperature for 1 hr. The solvent was then evaporated under reduced pressure to give crude 2-iodo-4,5-methylenedioxyphenylacetyl chloride which was redissolved in dichloromethane (10 mL) and cooled to 0°C. A solution of methylamine (40% in H_2O, 360 mg, 4.63 mmol) in 2 M sodium hydroxide (10 mL) was then added dropwise over 1 hr. After allowing the reaction to warm to room temperature it

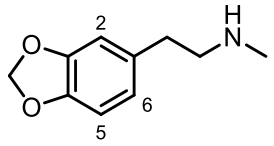
was stirred for 16 hrs followed by extraction with dichloromethane (3x20 mL). The combined organic layers were then washed with 2 M hydrochloric acid solution (40 mL), saturated sodium bicarbonate solution (40 mL) and water (40 mL). Concentration under reduced pressure and purification by flash column chromatography using ethyl acetate : hexane (3:2) gave 2-iodo-4,5-methylenedioxyphenyl-*N*-methyl acetamide (**252**) as a white solid (502 mg, 88% over 2 steps); $\mathbf{R_f}$ (EtOAc:Hex ; 7:3) 0.13; **m.p.** 176-178°C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.27 (1H, s, H3), 6.86 (1H, s, H6), 5.99 (2H, s, OCH_2O), 5.43 (1H, s, NH), 3.63 (2H, s, CH_2), 2.79 (3H, d, *J* = 4.4 Hz, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 170.2, 148.9, 147.9, 131.4, 118.8, 110.5, 101.9, 88.9, 48.3, 26.5; **IR** (thin film) υ_{max} = 3287 (m), 2906 (w), 2803 (w), 1649 (s), 1561 (w), 1477 (s), 1386 (m), 1229 (s) cm^{-1}; **LRMS** (ESI^+) *m/z* = 342 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{10}H_{10}O_3NINa$ ($[M+Na]^+$) 341.9603, found 341.9604.

3,4-Methylenedioxyphenyl-*N*-methylacetamide (**253**)



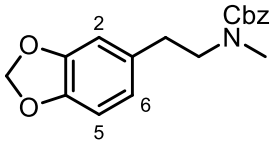
A solution of (3,4-methylenedioxy)phenyl acetic acid (5.11 g, 28.3 mmol), oxalyl chloride (2.92 mL, 34.0 mmol) and 3 drops of *N*,*N*-dimethylformamide in toluene (60 mL) was stirred at room temperature for 1 hr. The solvent was then evaporated under reduced pressure to give crude (3,4-methylenedioxy)phenyl acetyl chloride which was redissolved in dichloromethane (60 mL) and cooled to 0°C. A solution of methylamine (40% in H_2O, 5.71 g, 73.6 mmol) in 2 M sodium hydroxide (30 mL) was then added dropwise over 1 hr. After allowing the reaction to warm to room temperature it was stirred for 16 hrs followed by extraction with dichloromethane (3x40 mL). The combined organic layers were then washed with 2 M hydrochloric acid solution (50 mL), saturated sodium bicarbonate solution (50 mL) and water (50 mL). Concentration under reduced pressure and purification by flash column chromatography using ethyl acetate gave 3,4-methylenedioxyphenyl-*N*-methyl acetamide (**253**) as a yellowish solid (4.97 g, 91%); $\mathbf{R_f}$ (EtOAc) 0.17; **m.p.** 98-100°C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.76 (1H, d, *J* = 8.0 Hz, H5), 6.74 (1H, d, *J* = 1.6 Hz, H2), 6.69 (1H, dd, *J* = 7.6 & 1.6 Hz, H6), 5.94 (2H, s, OCH_2O), 5.92 (1H, br s, NH), 3.45 (2H, s, CH_2), 3.75 (3H, d, *J* = 4.8 Hz, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 171.7, 147.9, 146.7, 128.5, 122.4, 109.6, 108.4, 101.0, 43.0, 26.3; **IR** (thin film) υ_{max} = 3315 (s), 3078 (w), 3035 (w), 2976 (w), 2943 (w), 2909 (m), 1642 (s), 1556 (s) cm^{-1}; **LRMS** (ESI^+) *m/z* = 194 ($[M+H]^+$, 75%), 135 (100%); **HRMS** (ESI^+) calc. for $C_{10}H_{12}O_3N$ ($[M+H]^+$) 194.0817, found 194.0815.

N-Methyl-3,4-(methylenedioxy)phenylethylamine (**232**)



To a solution of (3,4-methylenedioxy)phenyl-*N*-methylacetamide (**253**) (7.14 g, 36.9 mmol) in tetrahydrofuran (200 mL) was added BH_3•THF (1.0 M, 185 mL, 185 mmol) and the reaction refluxed for 16 hrs. The solution was then allowed to cool followed by careful quenching with 1 M hydrochloric acid solution until bubbling had subsided a 6 M hydrochloric acid solution was then added and the mixture heated to 50°C for 1 hr. After cooling the mixture was basified with 2 M sodium hydroxide solution followed by extraction with ethyl acetate (3x60 mL). The combined organic layers were washed with brine (50 mL), concentrated under educed pressure and purified by flash column chromatography using dichloromethane : methanol : ammonia solution (90:9:1) to afford *N*-methyl-3,4-(methylenedioxy)phenethylamine (**232**) as a pale yellow oil (6.26 g, 95%); $\mathbf{R_f}$ (DCM:MeOH:NH_3 ; 90:9:1) 0.20; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.73 (1H, d, *J* = 8.0 Hz, H5), 6.70 (1H, d, *J* = 1.2 Hz, H2), 6.65 (1H, dd, *J* = 7.6 & 1.6 Hz, H6), 5.92 (2H, s, OCH_2O), 2.80 (2H, m, NCH_2), 2.72 (2H, m, $ArCH_2$), 2.43 (3H, s, *N*-Me), 1.59 (1H, s, NH); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 147.6, 145.8, 133.7, 121.5, 109.0, 108.2, 100.7, 53.3, 36.2, 35.8; **IR** (thin film) υ_{max} = 3391 (m), 2940 (m), 2893 (m), 1631 (w), 1489 (s), 1443 (s), 1248 (s), 1040 (s) cm^{-1}; **LRMS** (ESI^+) *m/z* = 180 ($[M+H]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{10}H_{14}O_2N$ ($[M+H]^+$) 180.1025, found 180.1026.

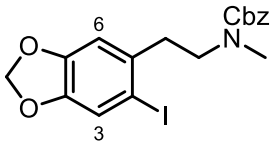
Benzyl *N*-methyl-3,4-(methylenedioxy)phenylethylcarbamate (**254**)



N-Methyl-3,4-(methylenedioxy)phenethylamine (**232**) (1.25 g, 6.98 mmol) was dissolved in dichloromethane (30 mL) and cooled to 0°C. Triethylamine (2.92 mL, 20.9 mmol) was then added followed by benzyl chloroformate (1.49 mL, 10.5 mmol) dropwise over 10 min. The reaction was then allowed to warm to room temperature and stirred for a further 16 hrs. After pouring into water (50 mL) the reaction was extracted with dichloromethane (2x30 mL) and the combined organic layers washed with 2 M hydrochloric acid solution (2x30 mL) and water (30 mL). Evaporation under reduced pressure and purification by flash column chromatography gave benzyl *N*-methyl-3,4-(methylenedioxy)phenylethylcarbamate (**254**) as a pale yellow oil (2.02 g, 92%); $\mathbf{R_f}$ (EtOAc:Hex ; 1:1)

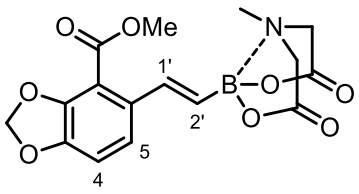
0.26; **^{1}H-NMR** (300 MHz, $CDCl_3$, 52°C) δ 7.32-7.22 (5H, m, Ph), 6.68-6.55 (3H, m, H2, H5 & H6), 5.83 (2H, s, OCH_2O), 5.09 (2H, s, OCH_2Ar), 3.43 (2H, t, *J* = 6.9 Hz, NCH_2), 2.84 (3H, s, *N*-Me), 2.71 (2H, t, *J* = 7.5 Hz, $ArCH_2$); **^{13}C-NMR** (75 MHz, $CDCl_3$, 52°C) δ 155.9, 147.6, 146.0, 136.9, 132.6, 128.3, 127.7, 127.6, 121.5, 109.0, 108.1, 100.6, 66.8, 50.8, 34.6, 34.0; **IR** (thin film) υ_{max} = 2935 (m), 2894 (m), 1699 (s), 1489 (s), 1246 (m), 1192 (m), 1039 (m), 927 (m) cm^{-1}; **LRMS** (ESI^+) *m/z* = 314 ($[M+H]^+$, 5%), 336 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{14}H_{20}O_4N$ ($[M+H]^+$) 314.1392, found 314.1397.

Benzyl *N*-methyl-2-iodo-4,5-(methylenedioxy)phenylethylcarbamate (**230**)



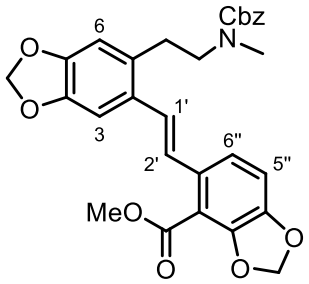
To a stirring solution of benzyl-*N*-methyl-3,4-(methylenedioxy)phenylethylcarbamate (**254**) (218 mg, 696 µmol) and Silver(I) trifluoroacetate (308 mg, 1.39 mmol) in chloroform (20 mL) was added iodine (353 mg, 1.39 mmol) portionwise over 30 minutes. The mixture was then stirred overnight followed by filtering through celite. The solution was then washed with 5% aqueous sodium thiosulfate (3x30 mL) and evaporated on to silica. Purification by flash column chromatography using ethyl acetate : hexane (3:7) afforded benzyl *N*-methyl-2-iodo-4,5-(methylenedioxy)phenylethylcarbamate (**230**) (233 mg, 76%) as an off white solid; **R_f** (EtOAc:Hex ; 2:3) 0.31; m.p. 85-87°C; **^{1}H-NMR** (300 MHz, $CDCl_3$, 52°C) δ 7.36-7.24 (5H, m, Ph), 7.17 (1H, s, H3), 6.65 (1H, s, H6), 5.88 (2H, s, OCH_2O), 5.11 (2H, s, OCH_2Ar), 3.42 (2H, t, *J* = 6.9 Hz, NCH_2), 2.90-2.85 (5H, m, *N*-Me & $ArCH_2$); **^{13}C-NMR** (75 MHz, $CDCl_3$, 52°C) δ 156.1, 148.6, 147.1, 136.9, 134.9, 128.4 (2C), 127.8, 118.6, 109.7, 101.5, 87.5, 67.0, 49.4, 38.9, 34.9; **IR** (thin film) υ_{max} = 2936 (m), 2897 (m), 1699 (s), 1474 (s), 1363 (m), 1228 (s), 1039 (m), 932 (m) cm^{-1}; **LRMS** (ESI^+) *m/z* = 462 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{18}H_{18}O_4NINa$ ($[M+Na]^+$) 462.0178, found 462.0178.

Methyl (*E*)-6-(vinyl-2-boronic acid MIDA ester)-2,3-(methylenedioxy)benzoate (**260**)



To a vial under nitrogen was added tris(dibenzylideneacetone)dipalladium (343 mg, 375 µmol), XPhos (715 mg, 1.50 mmol) and tetrahydrofuran (20 mL) and the solution allowed to stir for 20 minutes at room temperature. To a separate flask was added methyl 6-iodo-2,3-(methylenedioxy)benzoate (**236**) (2.29 g, 7.50 mmol), trans-2-(pinacol boronate)vinylboronic acid MIDA ester (2.78 g, 9.00 mmol), finely ground potassium phosphate (5.41 g, 25.5 mmol) and tetrahydrofuran (60 mL) followed by stirring at room temperature. The catalyst solution was then transferred by syringe to the other flask and the reaction stirred at 30°C for 40 hours in a low light environment. After filtering the reaction through a pad of celite the resulting solution was concentrated under reduced pressure and purified by flask column chromatography using ethyl acetate to afford methyl (*E*)-6-(vinyl-2-boronic acid MIDA ester)-2,3-(methylenedioxy)benzoate (**259**) as a white solid (2.44 g, 90%); $\mathbf{R_f}$ (EtOAc) 0.13; **m.p.** 191-201°C; **^{1}H-NMR** (400 MHz, CD_3CN) δ 7.19-7.12 (2H, m, H4 & H1'), 6.95 (1H, d, *J* = 8.0 Hz, H5), 6.04 (2H, s, OCH_2O), 6.00 (1H, d, *J* = 18.0 Hz, H2'), 3.98 (2H, d, *J* = 17.6 Hz, $COCH_a$), 3.84-3.80 (5H, m, OMe & $COCH_b$), 2.81 (3H, s, NMe); **^{13}C-NMR** (100 MHz, CD_3CN) δ 169.3, 166.4, 148.9, 148.2, 141.0, 133.3, 121.4, 113.9, 111.4, 103.3, 62.3, 52.7, 47.7, 25.1; **IR** (thin film) υ_{max} = 2985 (w), 2947 (w), 1740 (s), 1609 (w), 1454 (m), 1285 (m), 1131 (m), 1001 (m) cm^{-1}; **LRMS** (ESI^+) *m/z* = 384 ($[M+Na]^+$, 30%), 379 (100%); **HRMS** (ESI^+) calc. for $C_{16}H_{16}O_8NNa$ ($[M+H]^+$) 384.0867, found 384.0865.

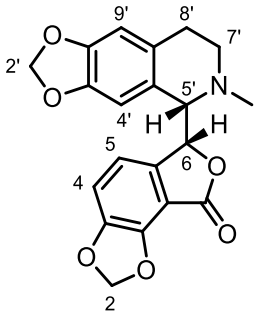
Benzyl *N*-methyl-2-[2''-carboxymethyl-3",4"-methendioxybenzen-1-yl)ethynyl]-4,5-(methylene dioxy)phenylethylcarbamate (**229**)



To a flask was added palladium acetate (22.3 mg, 99.5 µmol), SPhos (81.7 mg, 199 µmol) and tetrahydrofuran (10 mL) and the resulting solution was stirred at room temperature for 10 minutes under nitrogen. Benzyl *N*-methyl-2-iodo-4,5-(methylenedioxy)phenylethylcarbamate (**230**) (874 mg, 1.99 mmol), methyl (*E*)-6-(vinyl-2-boronic acid MIDA ester)-2,3-(methylenedioxy)benzoate (**259**) (1.44 g,

3.98 mmol) and tetrahydrofuran (70 mL) were added to a separate flask and stirred at room temperature under nitrogen. The catalyst solution was then added in one portion followed by aqueous sodium hydroxide solution (1.0 M, 19.9 mL, 19.9 mmol). The reaction was then left to stir for 24 hours at 25°C in a low light environment. The reaction mixture was then poured into aqueous phosphate buffer (1.0 M, pH 7.5, 80 mL) and extracted with diethyl ether (3 x 40 mL). After washing the combined organic layers with brine (50 mL) and concentration under reduced pressure the resulting residue was purified by flash column chromotograghy using ethyl acetate : hexane (2:3) to afford benzyl *N*-methyl-2-[2''-carboxymethyl-3",4"-methendioxybenzen-1-yl)ethynyl]-4,5-(methylene dioxy)phenylethylcarbamate (**229**) as a yellow/brown oil (899 mg, 87%); $\mathbf{R_f}$ (EtOAc:Hex ; 2:3) 0.24; **^{1}H-NMR** (300 MHz, $CDCl_3$, 52°C) δ 7.35-7.24 (9H, m, Ph, H3, H1', H2' & H5''), 6.83 (1H, s, H6''), 6.58 (1H, s, H6), 5.97 (2H, s, OCH_2O), 5.87 (2H, s, OCH_2O), 5.07 (2H, s, $PhCH_2$), 3.89 (3H, s, OMe), 3.42 (2H, t, *J* = 6.9 Hz, CH_2CH_2NMe), 2.90-2.84 (5H, m, CH_2CH_2NMe & *N*-Me); **^{13}C-NMR** (75 MHz, $CDCl_3$, 52°C) δ 165.4, 155.9, 147.7, 147.3, 147.2, 146.7, 136.9, 132.3, 130.7, 130.2, 128.2, 127.6, 127.4 (2C), 126.7, 120.0, 112.6, 110.8, 109.7, 105.7, 101.7, 100.8, 66.7, 51.8, 50.8, 34.9, 31.7; **IR** (thin film) υ_{max} = 2950 (w), 2899 (w), 1714 (s), 1482 (s), 1460 (vs), 1251 (s), 1129 (m) 1049 (m) cm^{-1}; **LRMS** (ESI^+) *m/z* = 540 ($[M+Na]^+$, 90%), 493 (100%); **HRMS** (ESI^+) calc. for $C_{29}H_{27}NO_8Na$ ($[M+Na]^+$) 540.1634, found 540.1633.

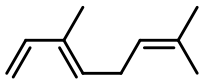
Crude sample – postulated to be (±)-Bicuculline (**166**)[90, 141]



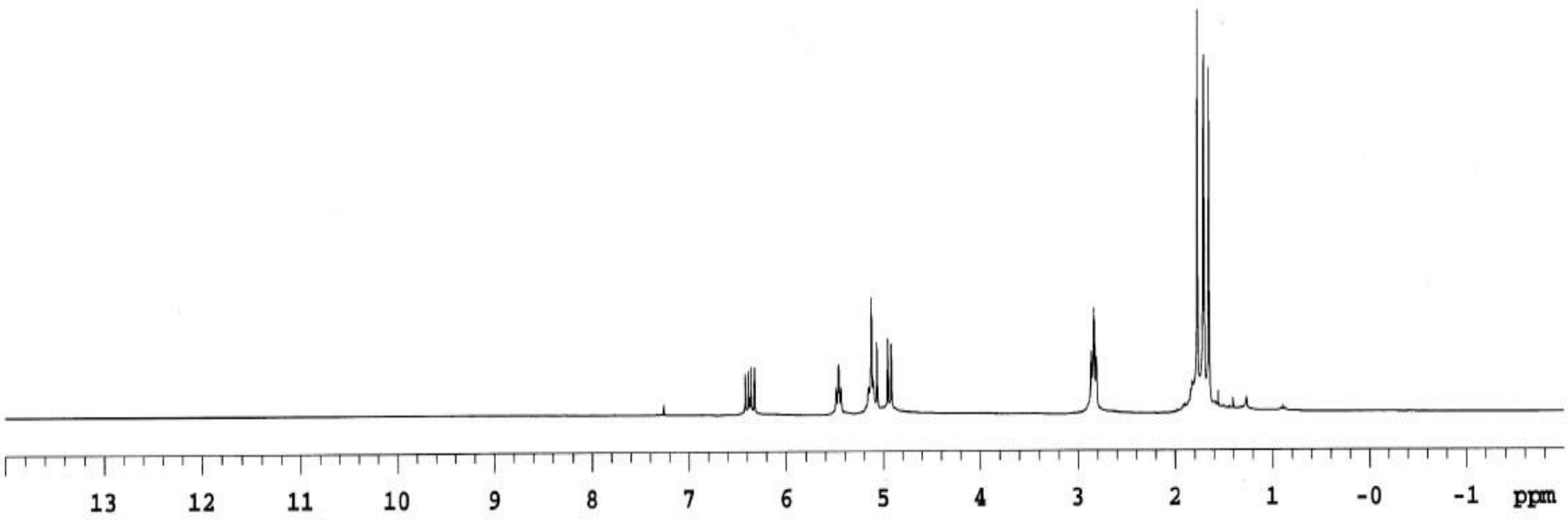
Benzyl *N*-methyl-2-[2''-carboxymethyl-3",4"-methendioxybenzen-1-yl)ethynyl]-4,5-(methylene dioxy)phenylethylcarbamate (**229**) (64.2 mg, 124 µmol), dichloromethane (10 mL) and aqueous sodium bicarbonate solution (0.5 M, 5 mL) were added to a flask and stirred rapidly. *m*CPBA (53.4 mg, 310 µmol) as a solutions in dichloromethane (3 mL) was then slowly added over 10 minutes and the reaction left to stir for 16 hours at room temperature. After dilution with diethyl ether (20 mL) the mixture was allowed to separate and the organic layer collected. Following washing with a saturated solution of aqueous sodium sulfite (3x15 mL) and an aqueous solution of sodium hydroxide (0.1 M, 20 mL) the solution was evaporated under reduced pressure to afford a crude sample of the epoxide product (47.3 mg). This crude product was redissolved in dichloromethane (5 mL) followed by the addition of

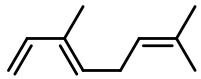
dimethyl sulfide (130 µL, 1.77 mmol) and boron trifluoride diethyl etherate (109 µL. 887 µmol) and stirred at room temperature for 2 hours. After a second addition of dimethyl sulfide (130 µL, 1.77 mmol) the reaction was stirred for another 2 hours and then poured into water (10 mL) and aqueous ammonium hydroxide (10%, 10 mL). The mixture was extracted with dichloromethane (3x10 mL) and the combined organic layers washed with brine (15 mL) and water (15 mL). Evaporation under reduced pressure afforded a crude sample postulated to be (±)-bicuculline (**166**) as a yellow oil (9.7 mg, 21% over 2 steps); $\mathbf{R_f}$ (DCM:Hex:MeOH ; 5:4.5:0.5) 0.2; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.92 (1H, d, *J* = 7.6 Hz, H4), 6.58 (1H, s, H4'), 6.44 (1H, s, H9'), 6.22 (1H, d, *J* = 8 Hz, H5), 6.16 (2H, d, *J* = 4 Hz, 2) 5.93 (2H, d, *J* = 2.8 Hz, H2'), 5.60 (1H, s, H6), 4.05 (1H, d, *J* = 3.6 Hz, H5'), 2.95-2.83 (1H, m, H7'a), 2.62-2.56 (5H, m, H7'b & H8'b & *N*-Me), 2.29-2.25 (1H, m, H8'b); **IR** (thin film) υ_{max} = 2918 (w), 2854 (w), 1762 (s), 1650 (w), 1502 (m), 1476 (vs), 1252 (s), 1037 (s) cm^{-1}; **LRMS** (ESI^+) *m/z* = 368 ($[M+H]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{20}H_{18}NO_6$ ($[M+H]^+$) 368.1134, found 368.1134.

Spectra

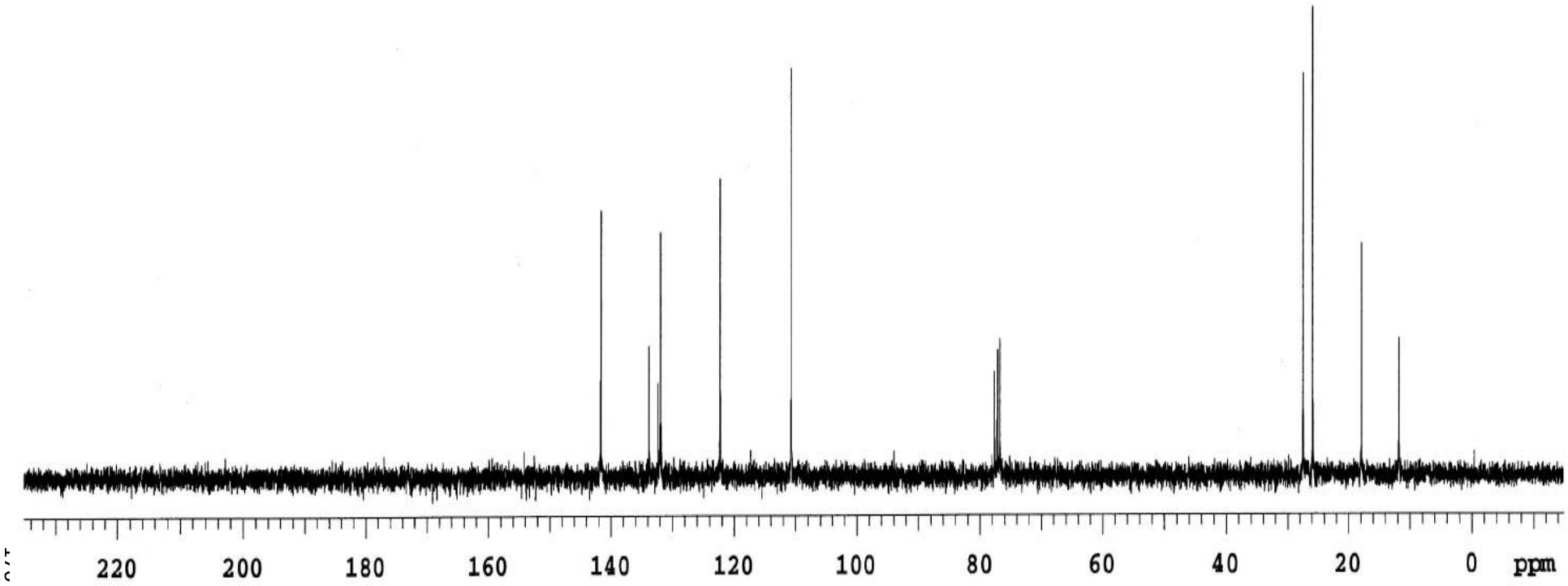


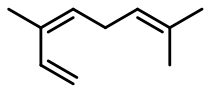
E-ocimene (**31**)
^{1}H-NMR spectrum
300 MHz, $CDCl_3$



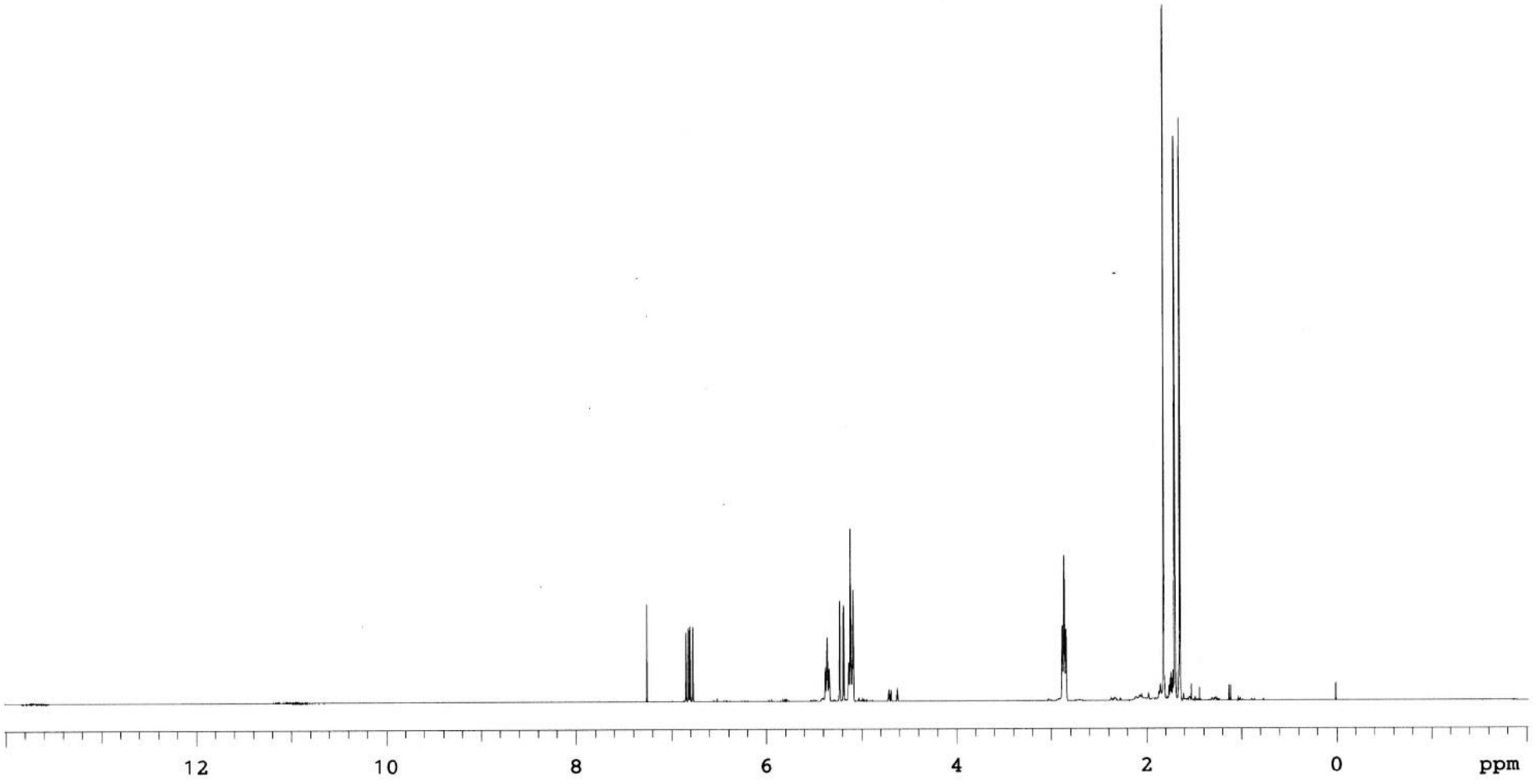


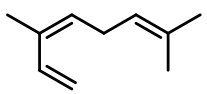
E-ocimene (**31**)
^{13}C-NMR spectrum
100 MHz, $CDCl_3$



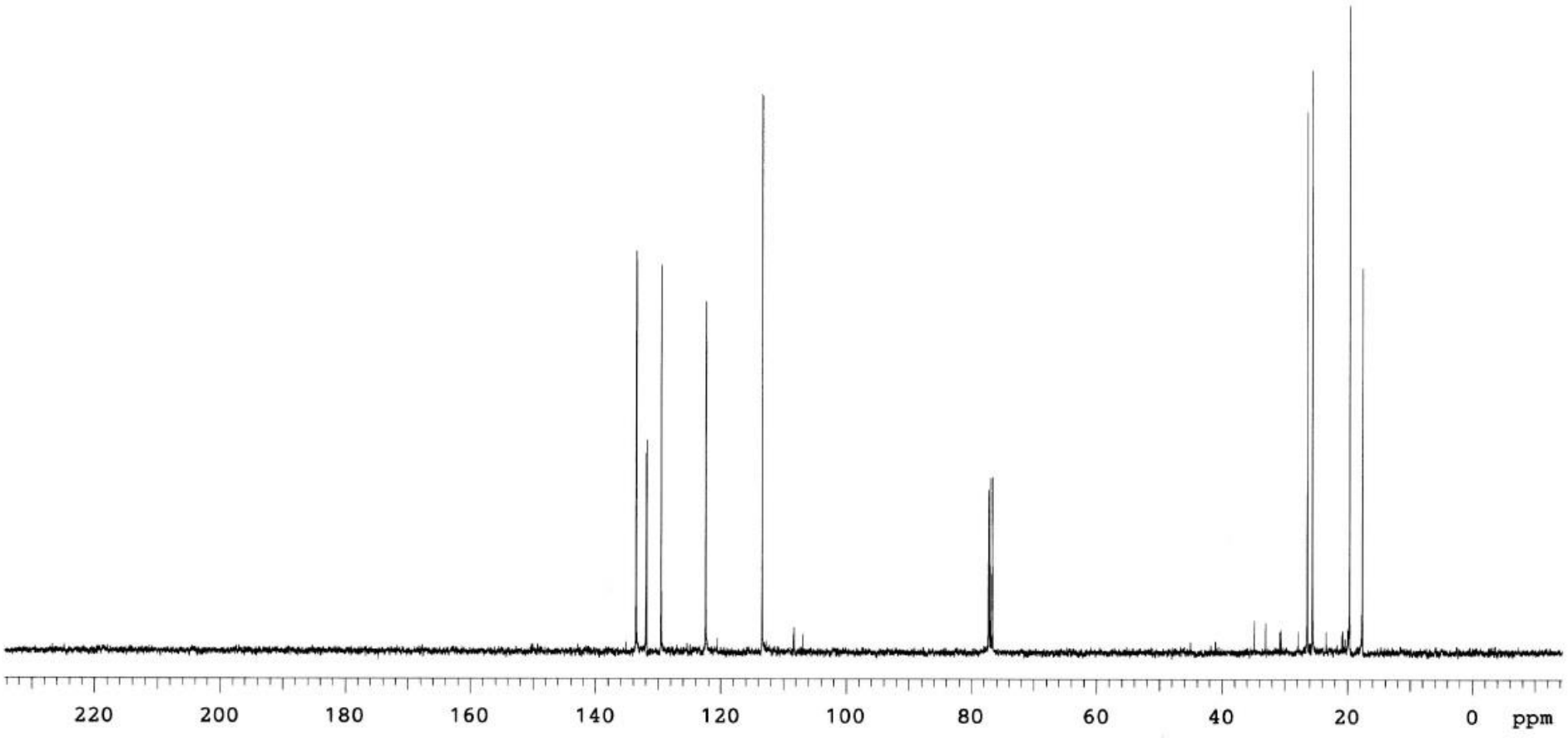


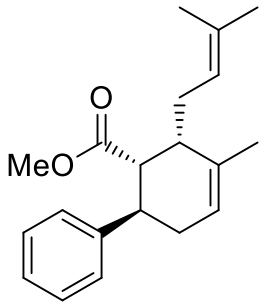
Z-ocimene (**127**)
^{1}H-NMR spectrum
400 MHz, $CDCl_3$





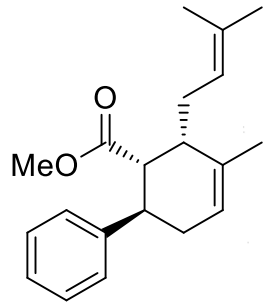
Z-ocimene (**127**)
^{13}C-NMR spectrum
100 MHz, $CDCl_3$



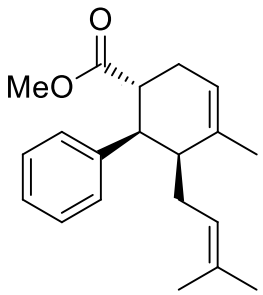


panduratin H (**17**)

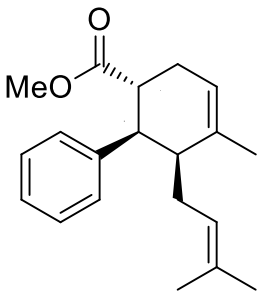
^{1}H-NMR spectrum, 400MHz, $CDCl_3$



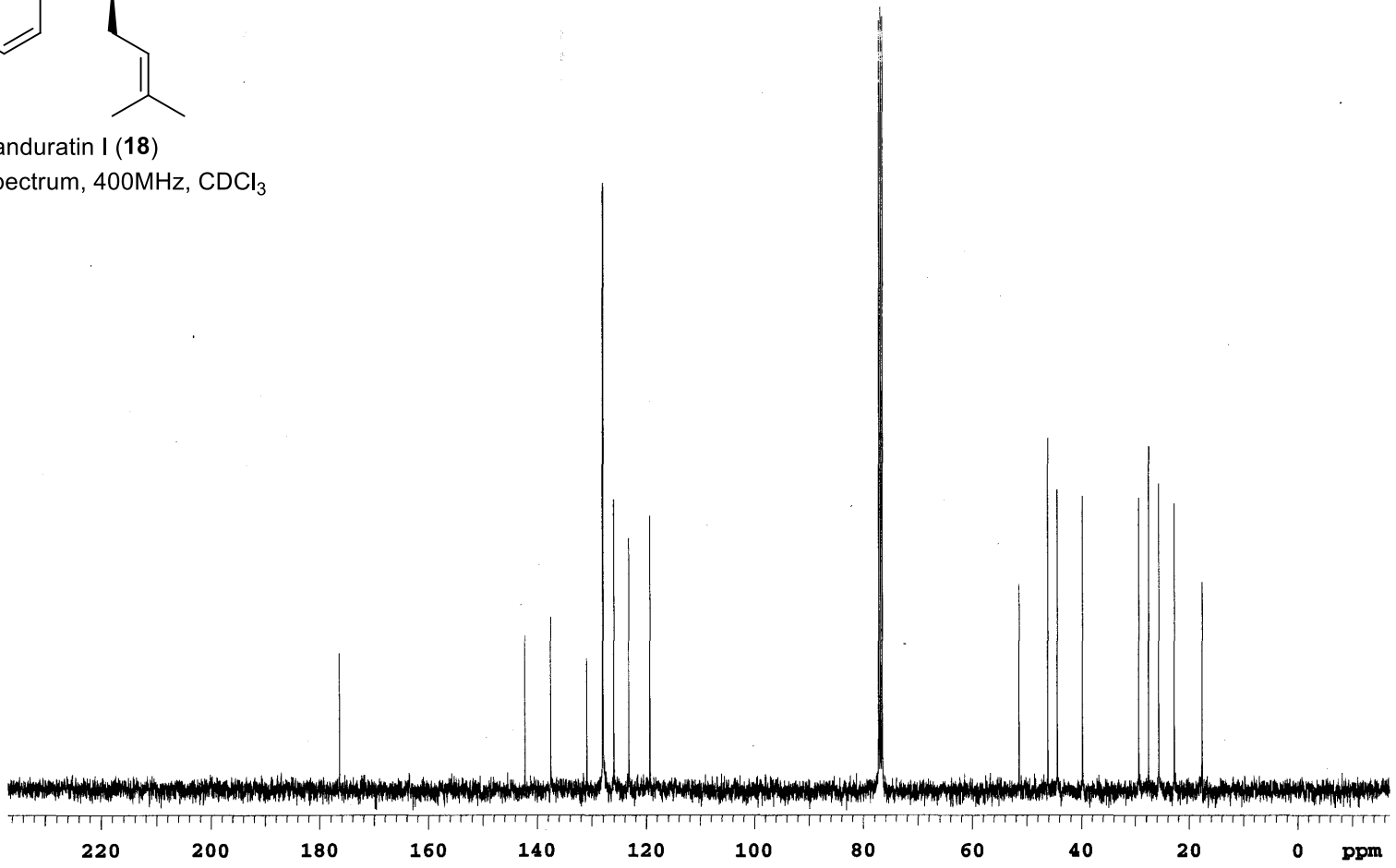
panduratin H (**17**)
^{13}C-NMR spectrum, 100MHz, $CDCl_3$

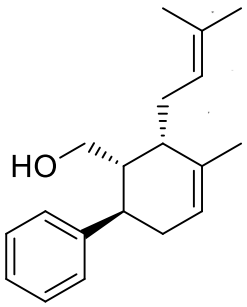


panduratin I (**18**)
^{1}H-NMR spectrum, 400MHz, $CDCl_3$

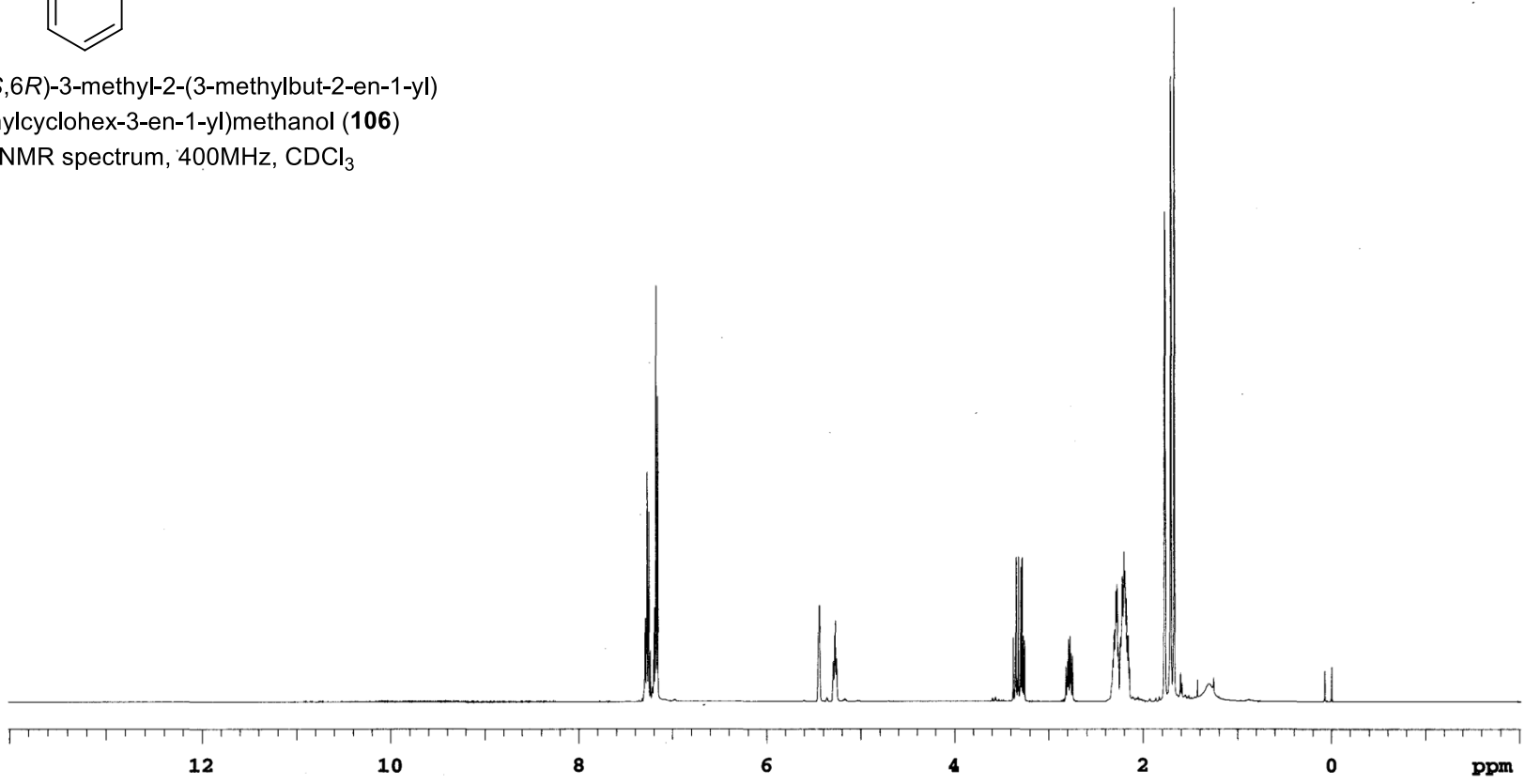


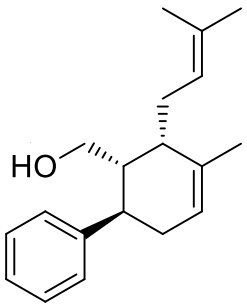
panduratin I (**18**)
^{13}C-NMR spectrum, 400MHz, $CDCl_3$



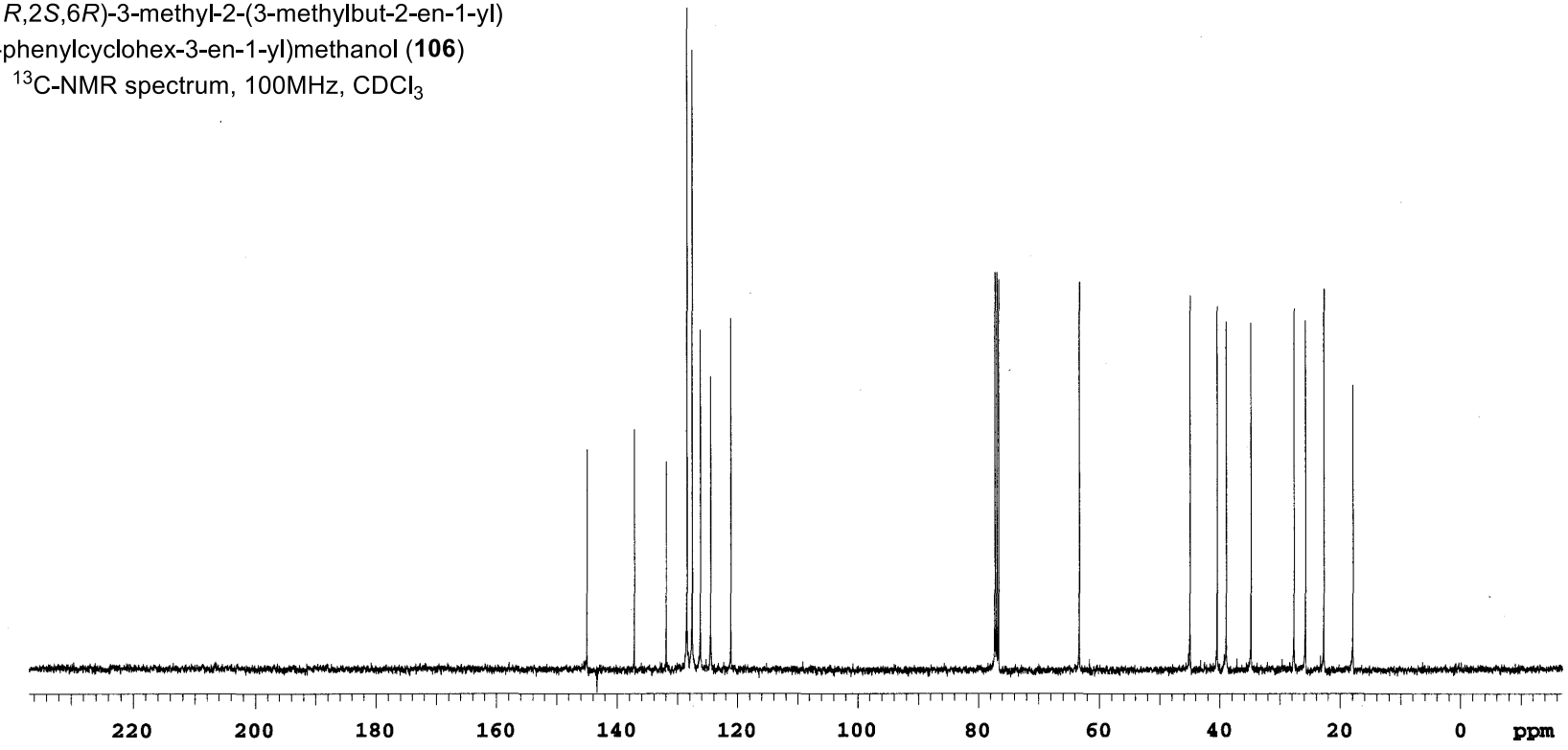


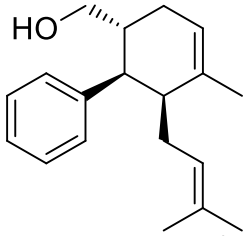
(±)-((1*R*,2*S*,6*R*)-3-methyl-2-(3-methylbut-2-en-1-yl)
-6-phenylcyclohex-3-en-1-yl)methanol (**106**)
^{1}H-NMR spectrum, 400MHz, $CDCl_3$



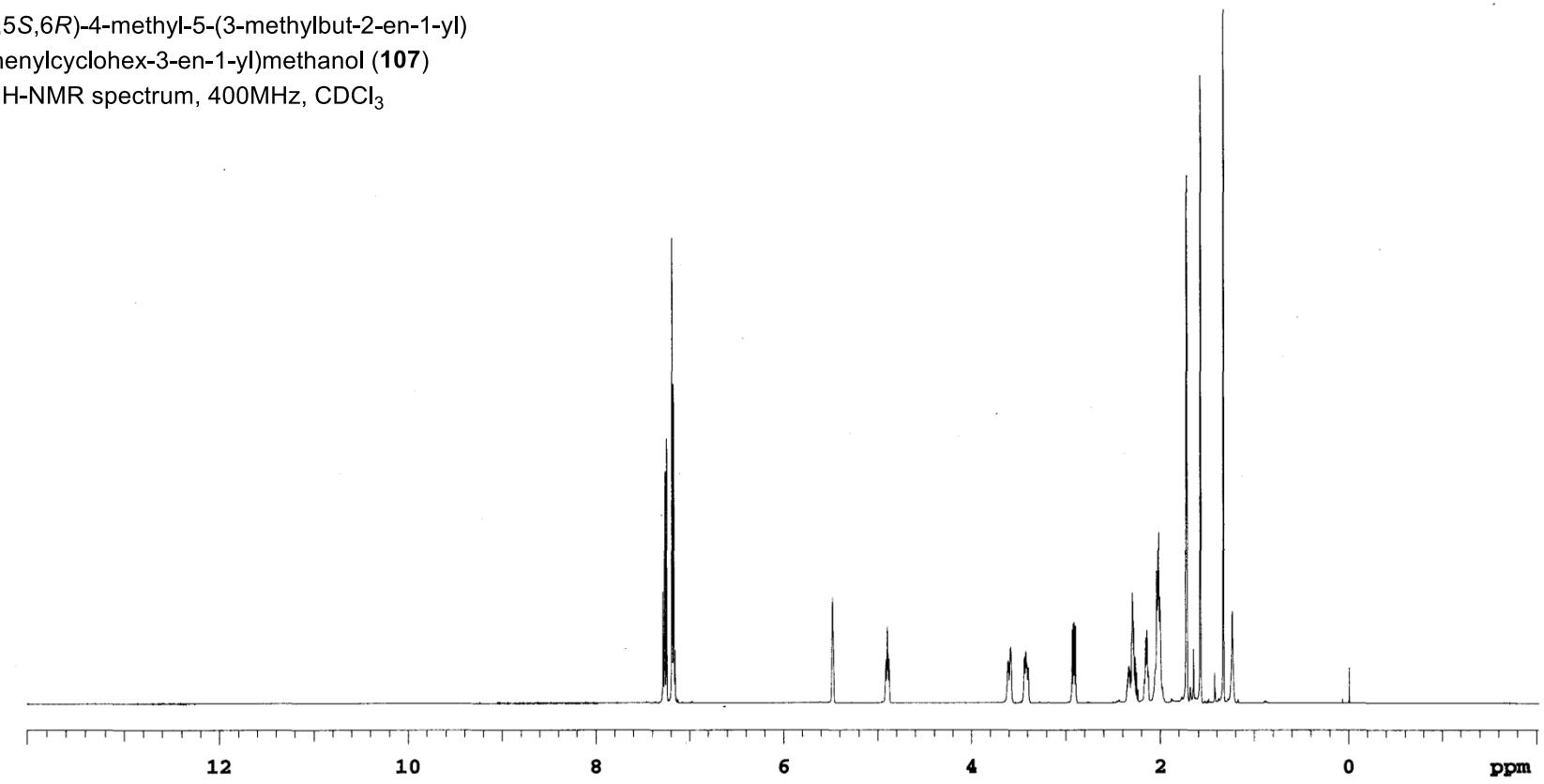


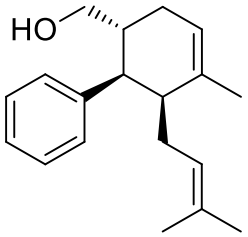
(±)-((1*R*,2*S*,6*R*)-3-methyl-2-(3-methylbut-2-en-1-yl)
-6-phenylcyclohex-3-en-1-yl)methanol (**106**)
^{13}C-NMR spectrum, 100MHz, $CDCl_3$



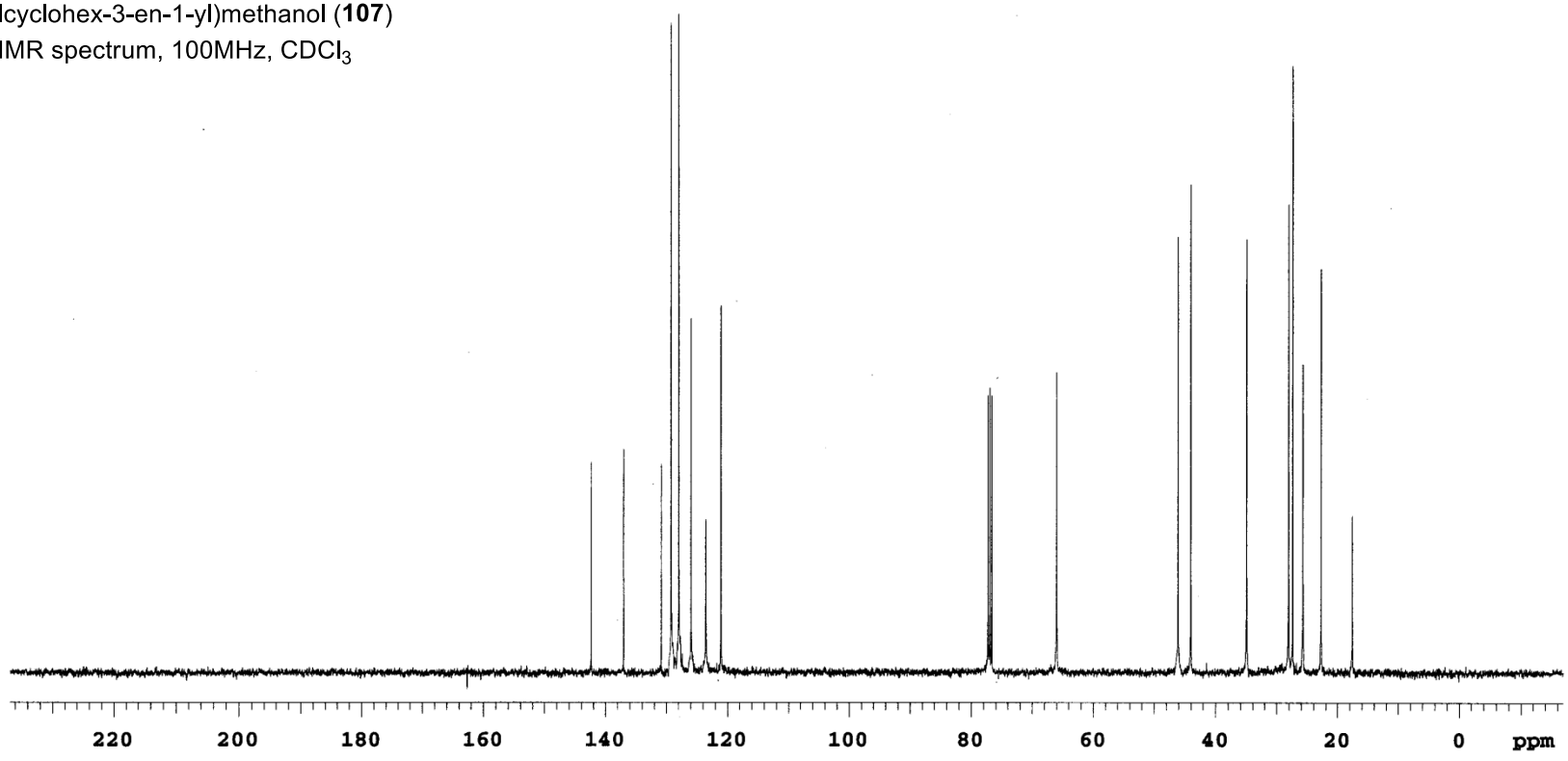


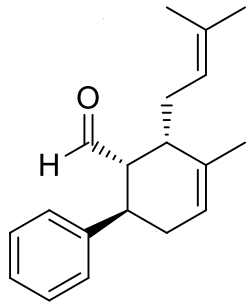
(±)-((1*R*,5*S*,6*R*)-4-methyl-5-(3-methylbut-2-en-1-yl)
-6-phenylcyclohex-3-en-1-yl)methanol (**107**)
^{1}H-NMR spectrum, 400MHz, $CDCl_3$



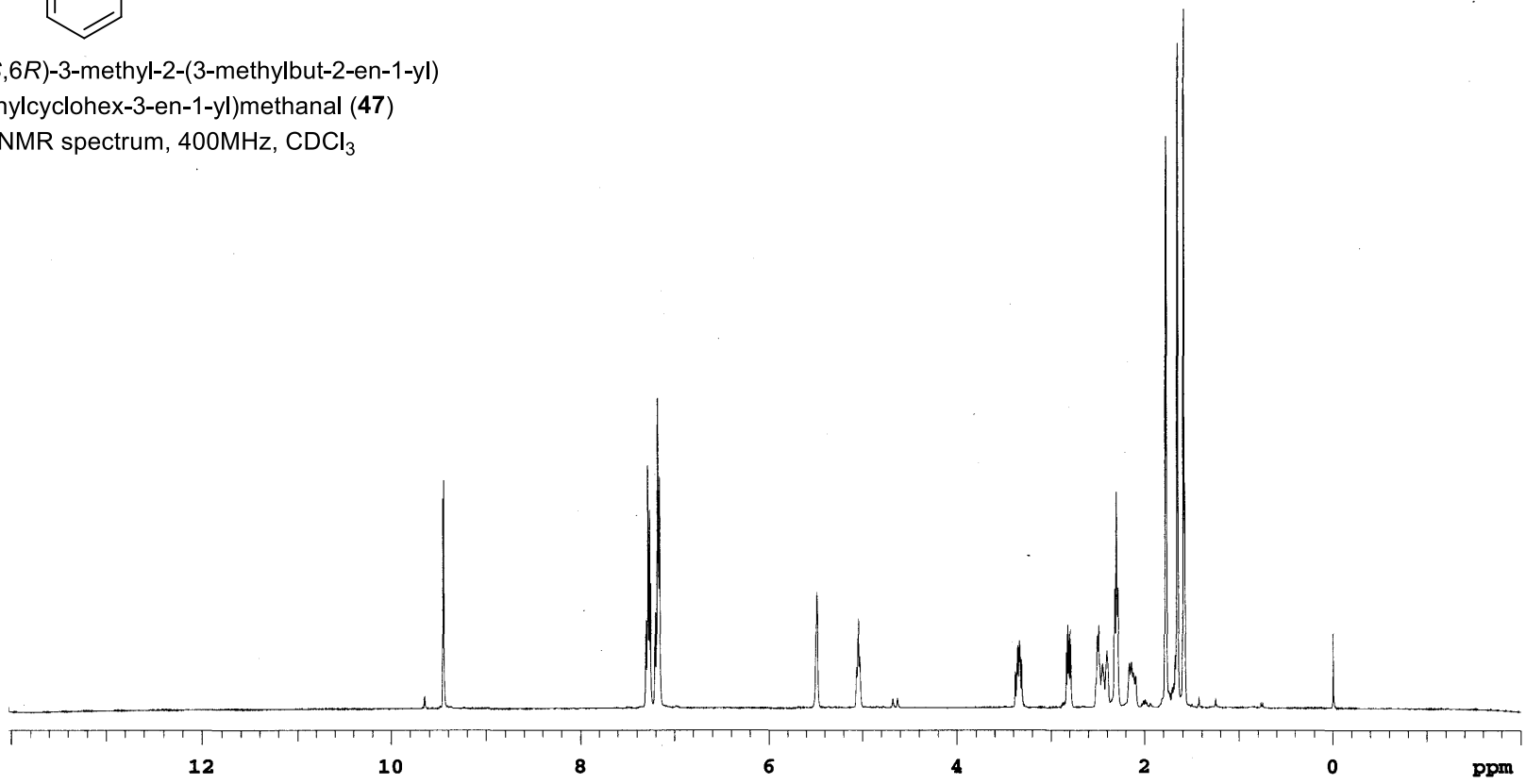


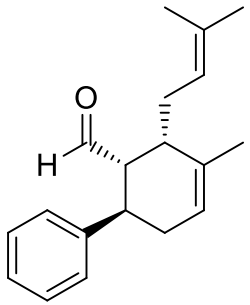
(±)-((1*R*,5*S*,6*R*)-4-methyl-5-(3-methylbut-2-en-1-yl)
-6-phenylcyclohex-3-en-1-yl)methanol (**107**)
^{13}C-NMR spectrum, 100MHz, $CDCl_3$



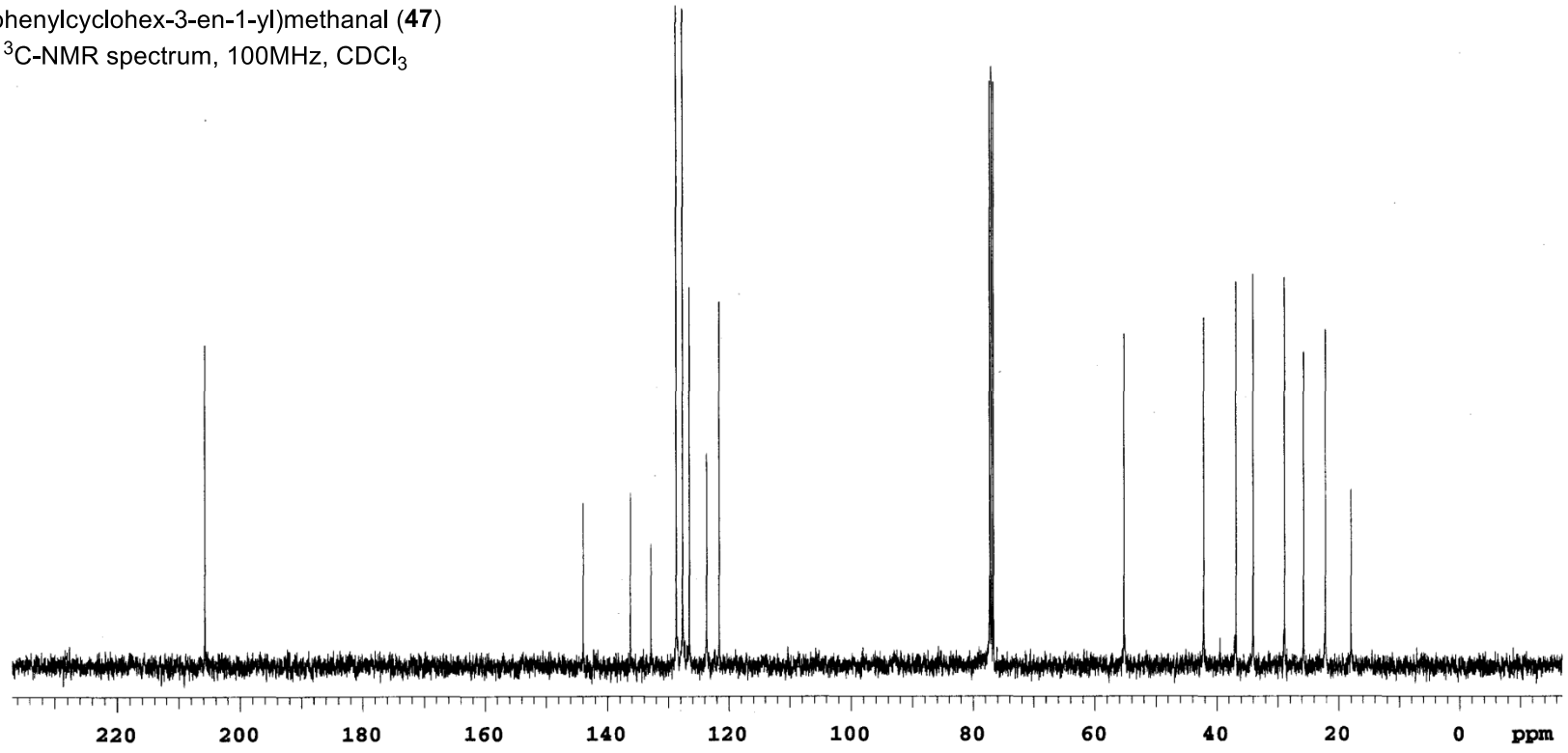


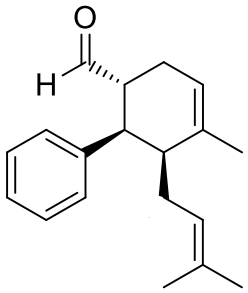
(±)-((1*R*,2*S*,6*R*)-3-methyl-2-(3-methylbut-2-en-1-yl)
-6-phenylcyclohex-3-en-1-yl)methanal (**47**)
^{1}H-NMR spectrum, 400MHz, $CDCl_3$



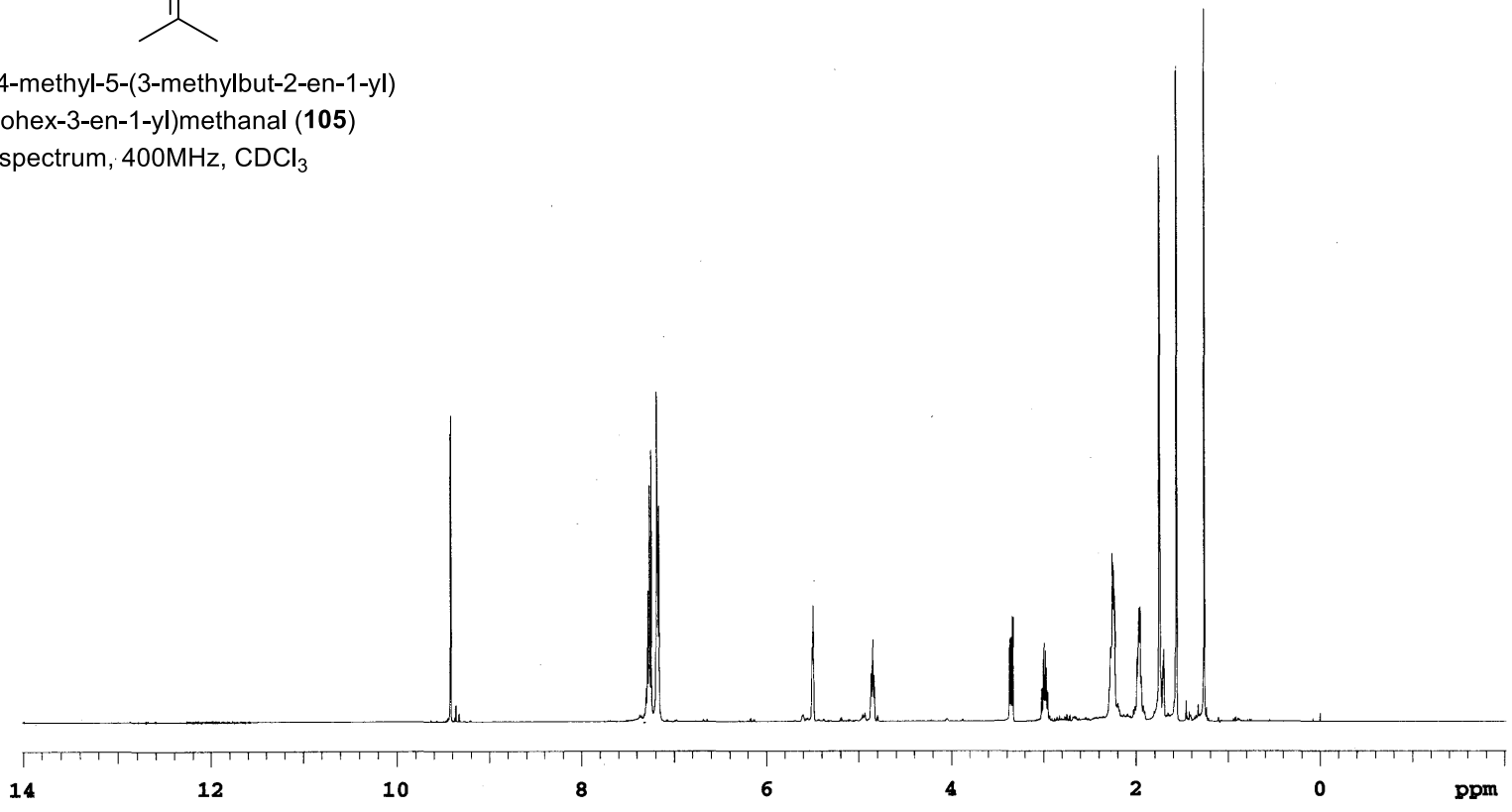


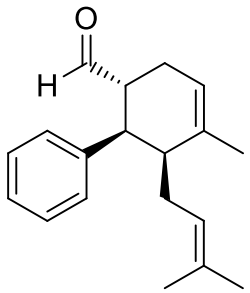
(±)-((1*R*,2*S*,6*R*)-3-methyl-2-(3-methylbut-2-en-1-yl)
-6-phenylcyclohex-3-en-1-yl)methanal (**47**)
^{13}C-NMR spectrum, 100MHz, $CDCl_3$



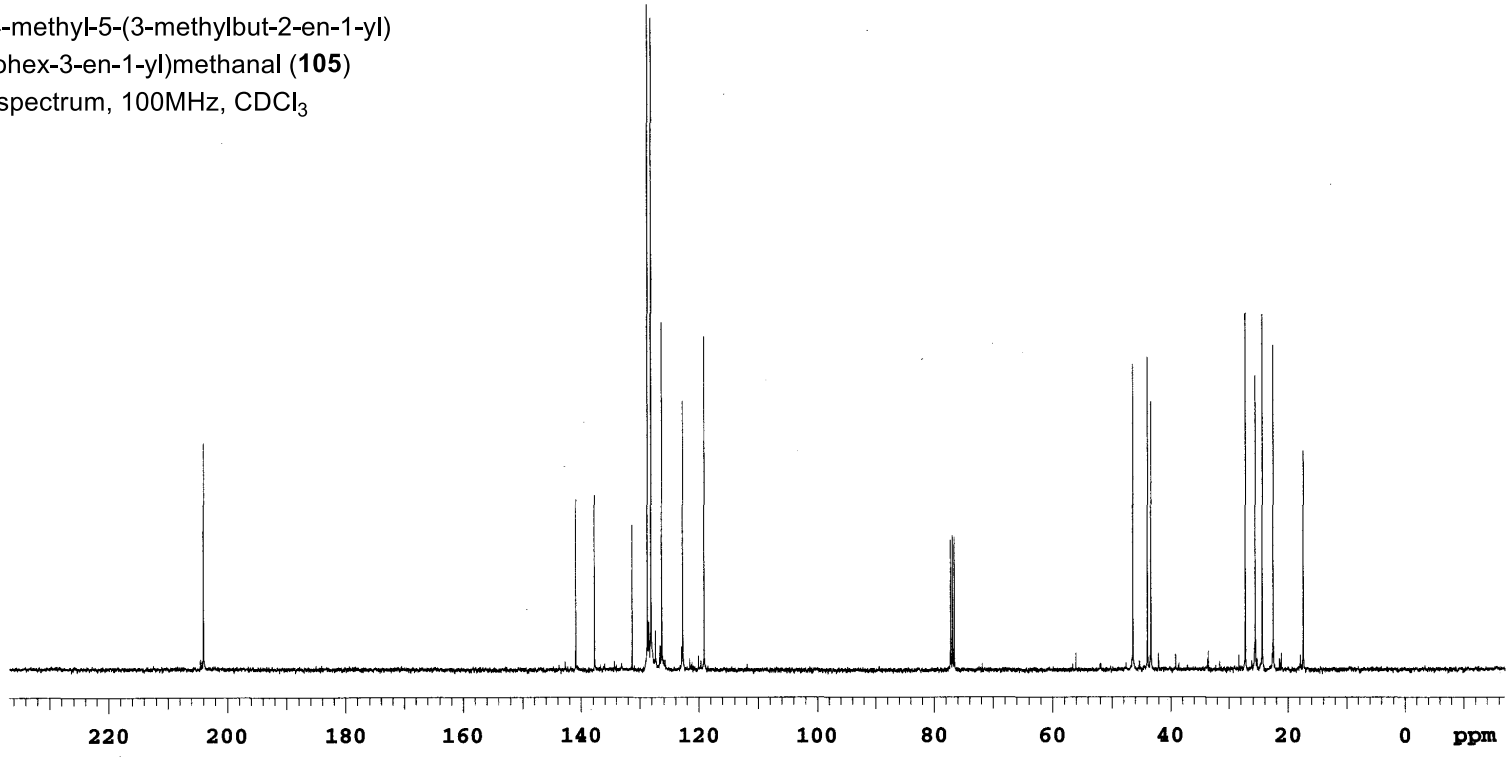


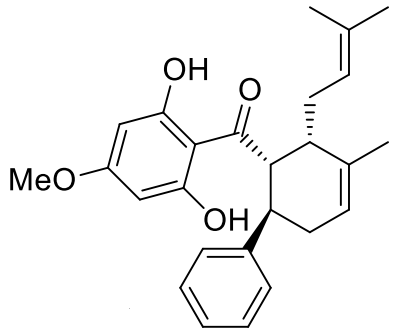
(±)-((1*R*,5*S*,6*R*)-4-methyl-5-(3-methylbut-2-en-1-yl)
-6-phenylcyclohex-3-en-1-yl)methanal (**105**)
^{1}H-NMR spectrum, 400MHz, $CDCl_3$



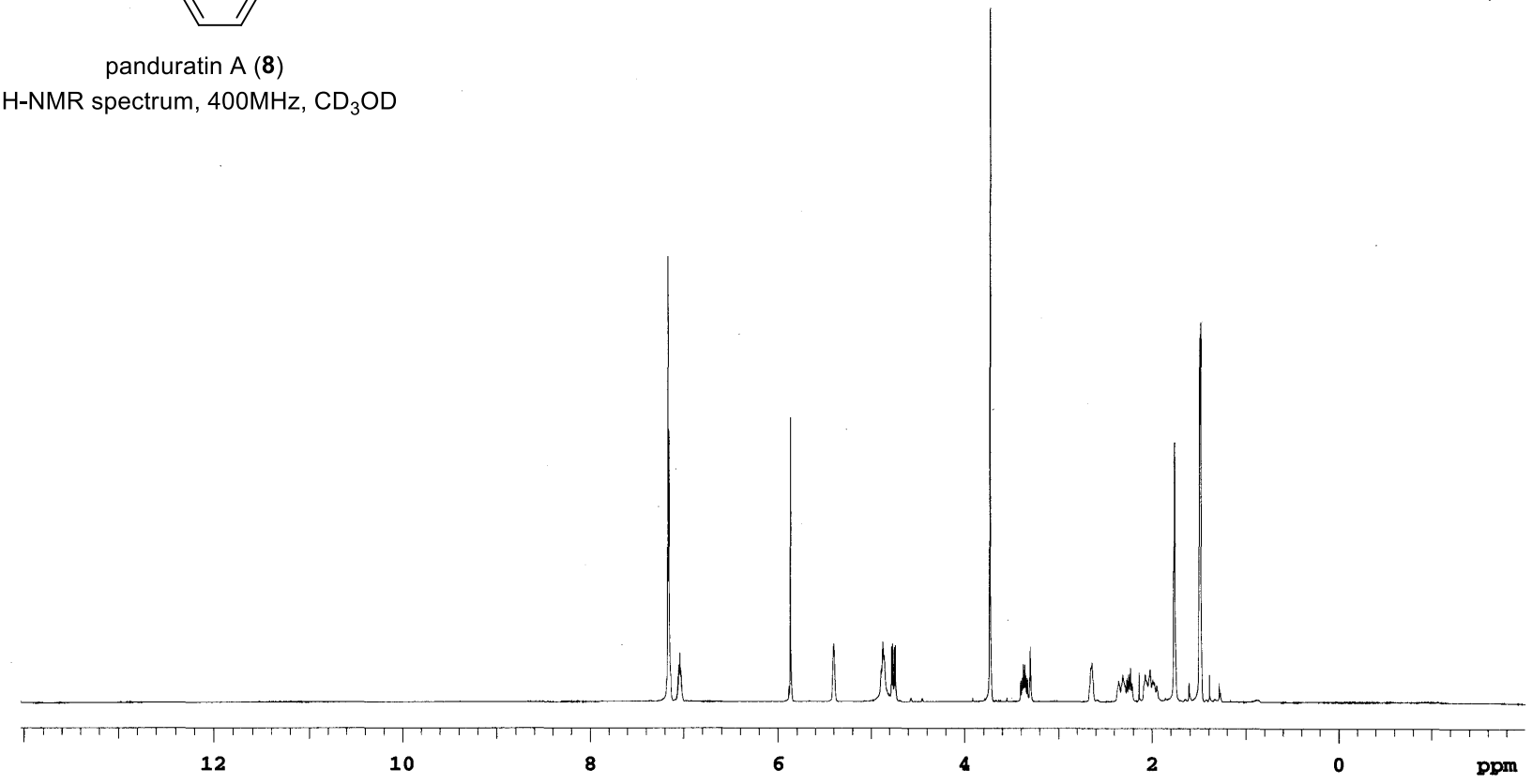


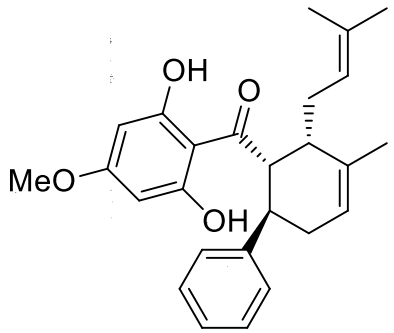
(±)-((1*R*,5*S*,6*R*)-4-methyl-5-(3-methylbut-2-en-1-yl)
-6-phenylcyclohex-3-en-1-yl)methanal (**105**)
^{13}C-NMR spectrum, 100MHz, $CDCl_3$



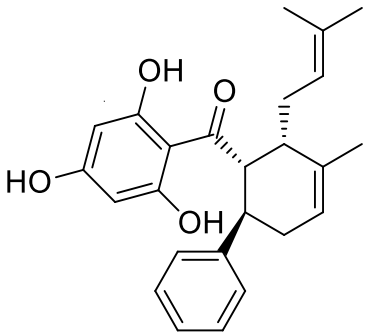


panduratin A (**8**)
^{1}H-NMR spectrum, 400MHz, CD_3OD

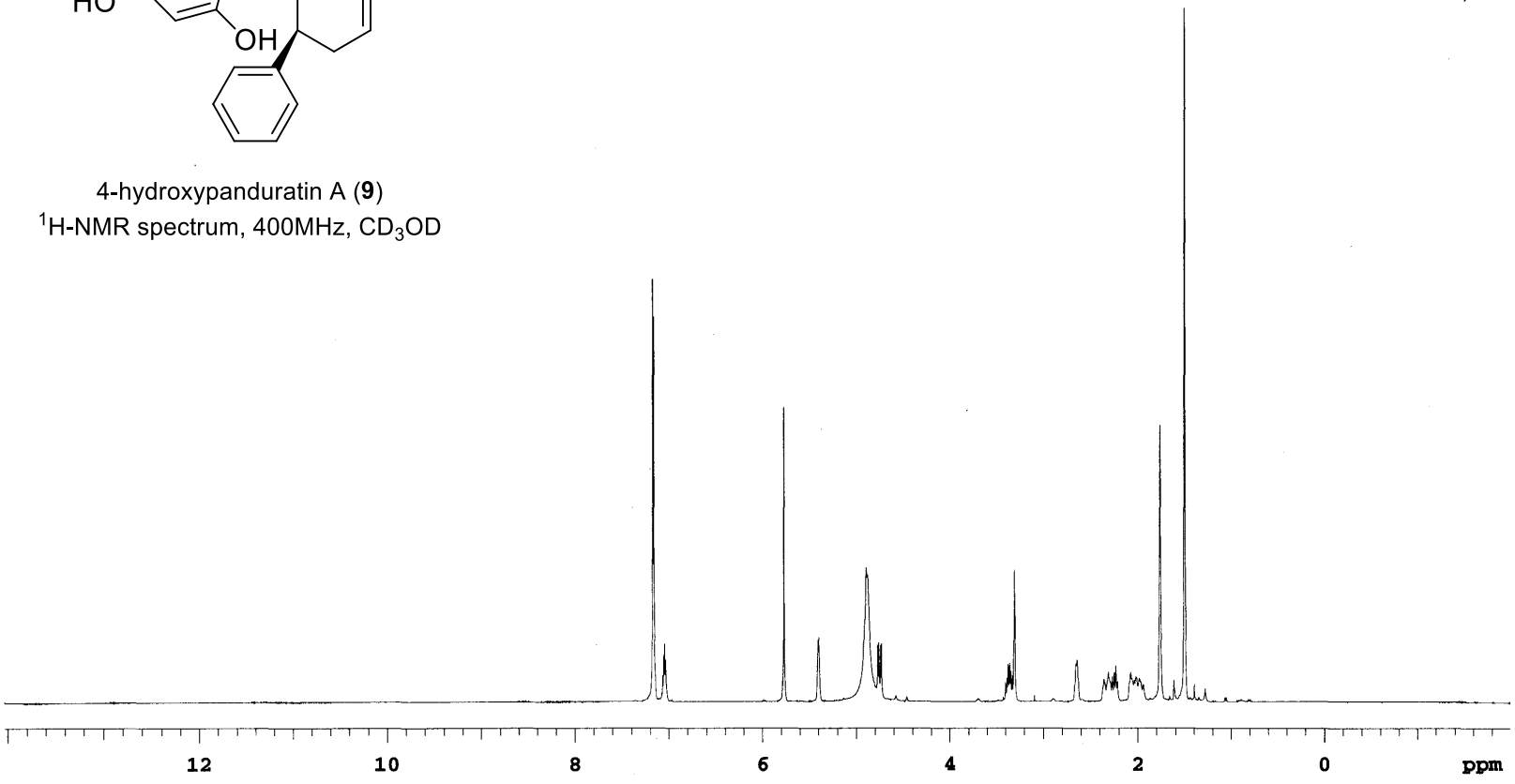


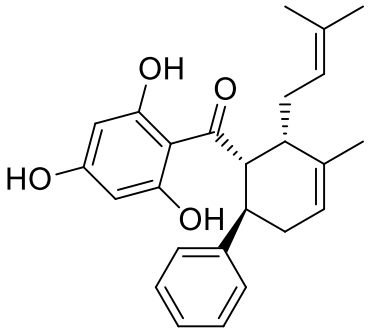


panduratin A (**8**)
^{13}C-NMR spectrum, 100MHz, CD_3OD

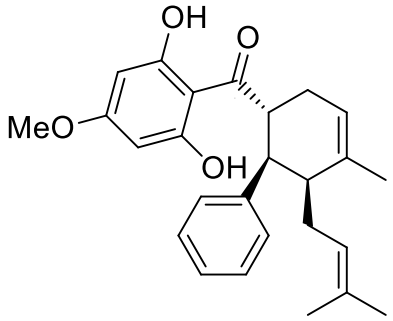


4-hydroxypanduratin A (**9**)
^{1}H-NMR spectrum, 400MHz, CD_3OD

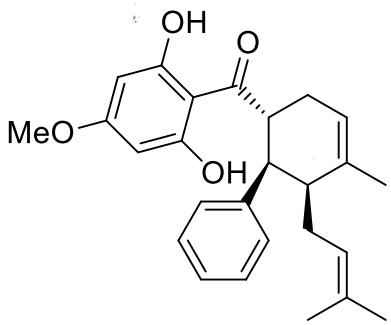




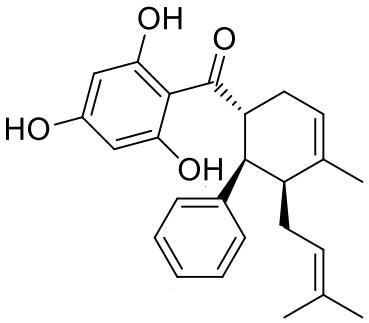
4-hydroxypanduratin A (**9**)
^{13}C-NMR spectrum, 100MHz, CD_3OD



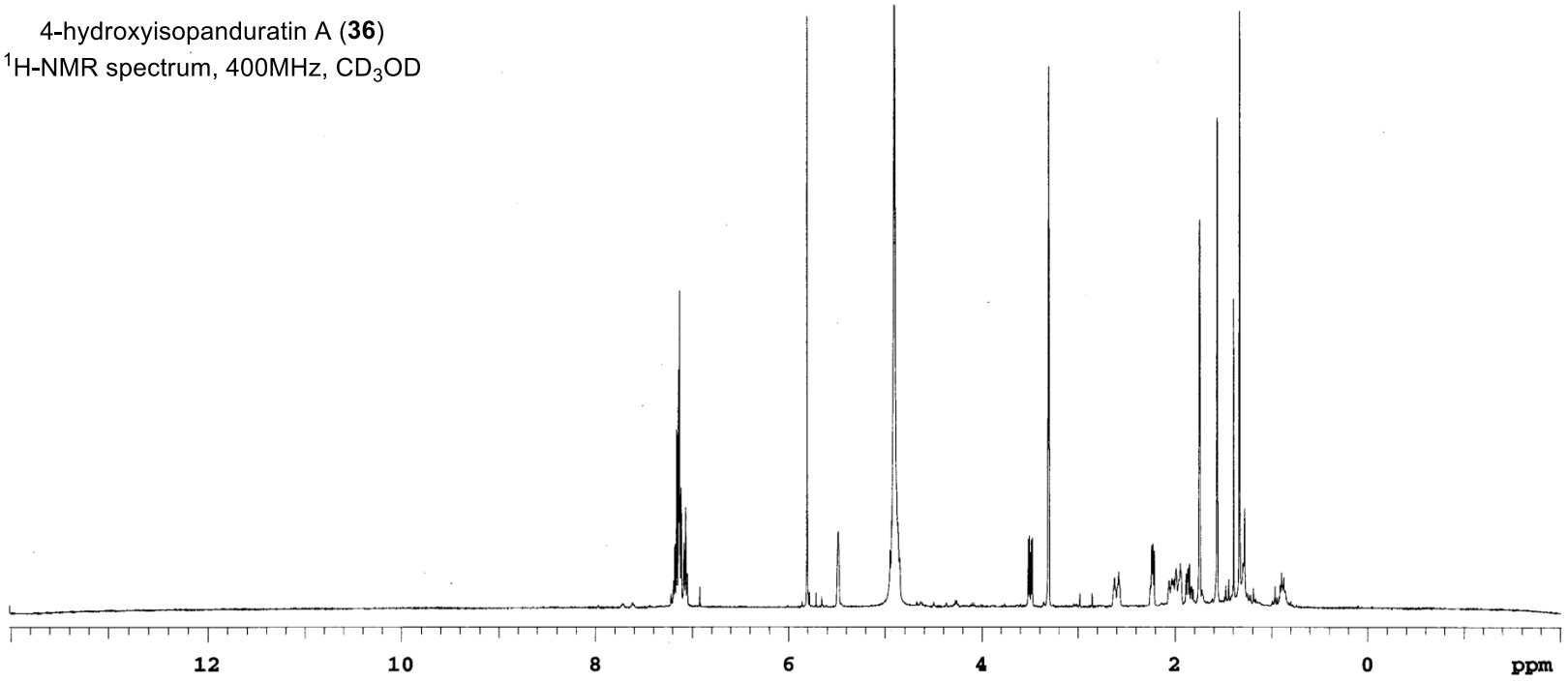
isopanduratin A (nicolaioidesin B) (**20**)
^{1}H-NMR spectrum, 400MHz, CD_3OD

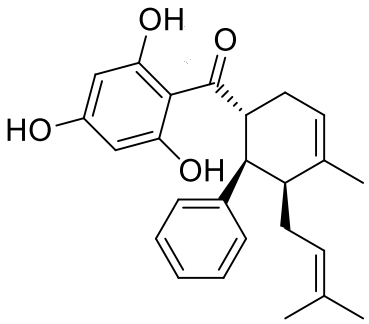


isopanduratin A (nicolaioidesin B) (**20**)
^{13}C-NMR spectrum, 100MHz, CD_3OD

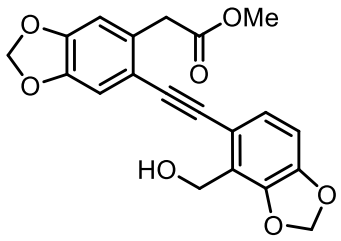


4-hydroxyisopanduratin A (**36**)
^{1}H-NMR spectrum, 400MHz, CD_3OD



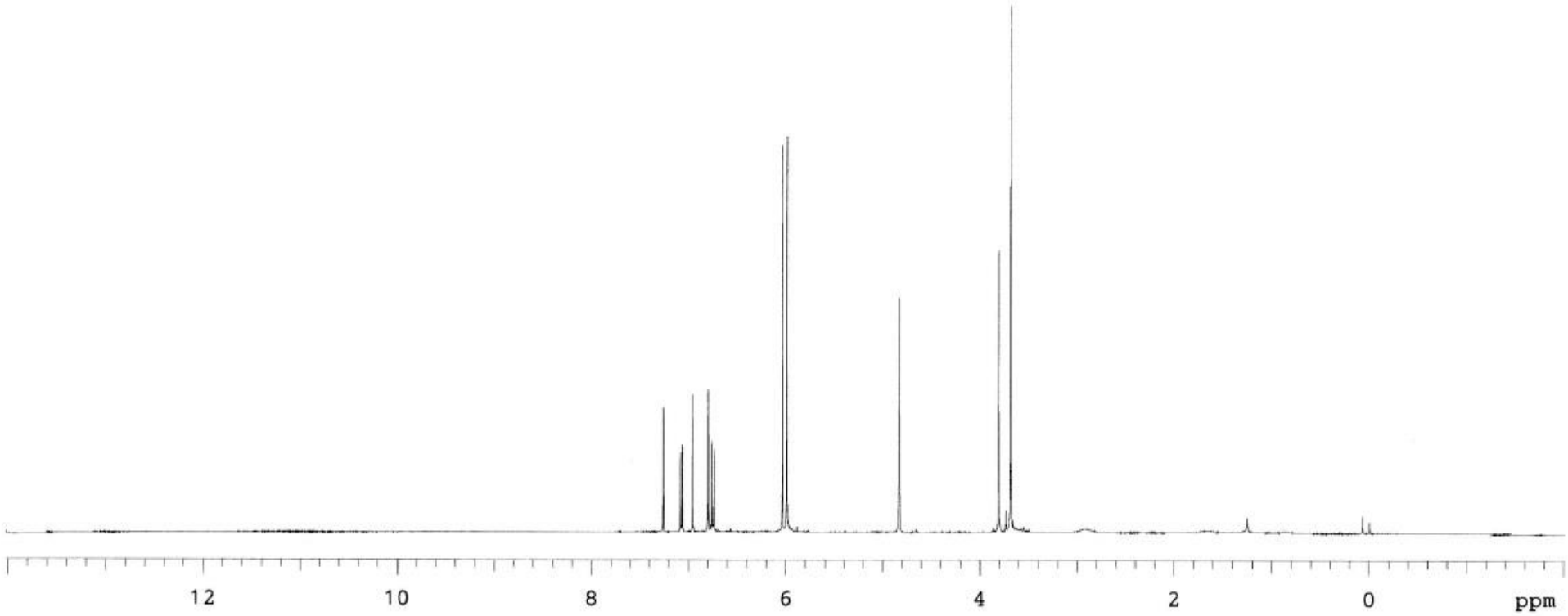


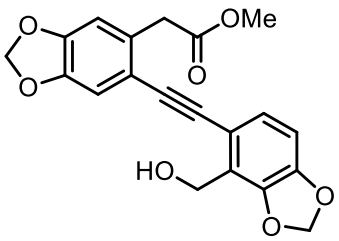
4-hydroxyisopanduratin A (**36**)
^{13}C-NMR spectrum, 100MHz, CD_3OD



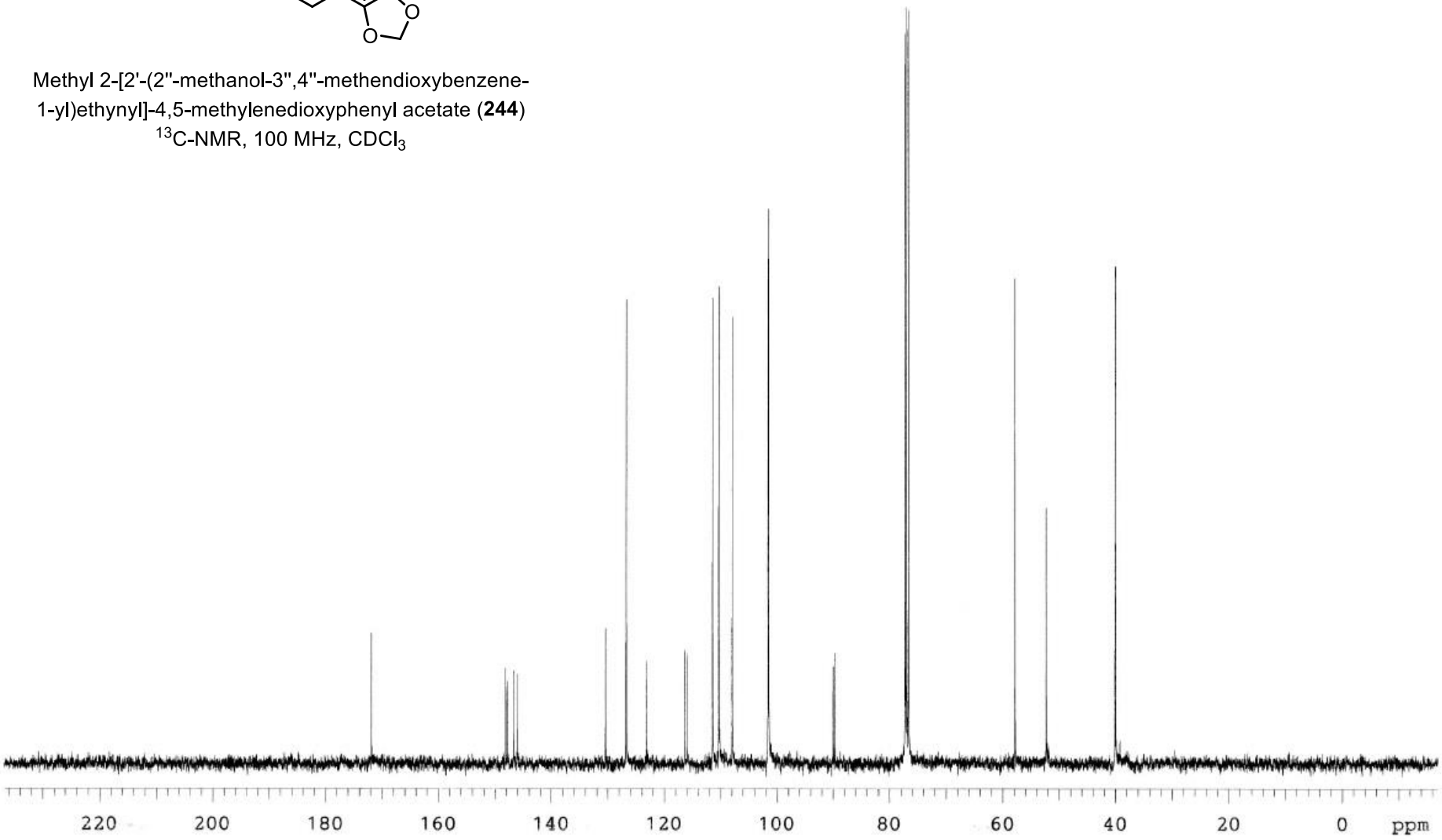
Methyl 2-[2'-(2''-methanol-3'',4''-methendioxybenzene-1-yl)ethynyl]-4,5-methylenedioxyphenyl acetate (**244**)

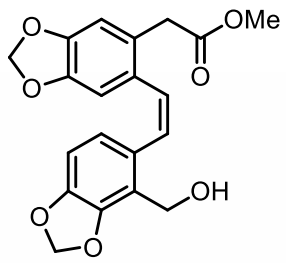
^{1}H-NMR,400 MHz, $CDCl_3$





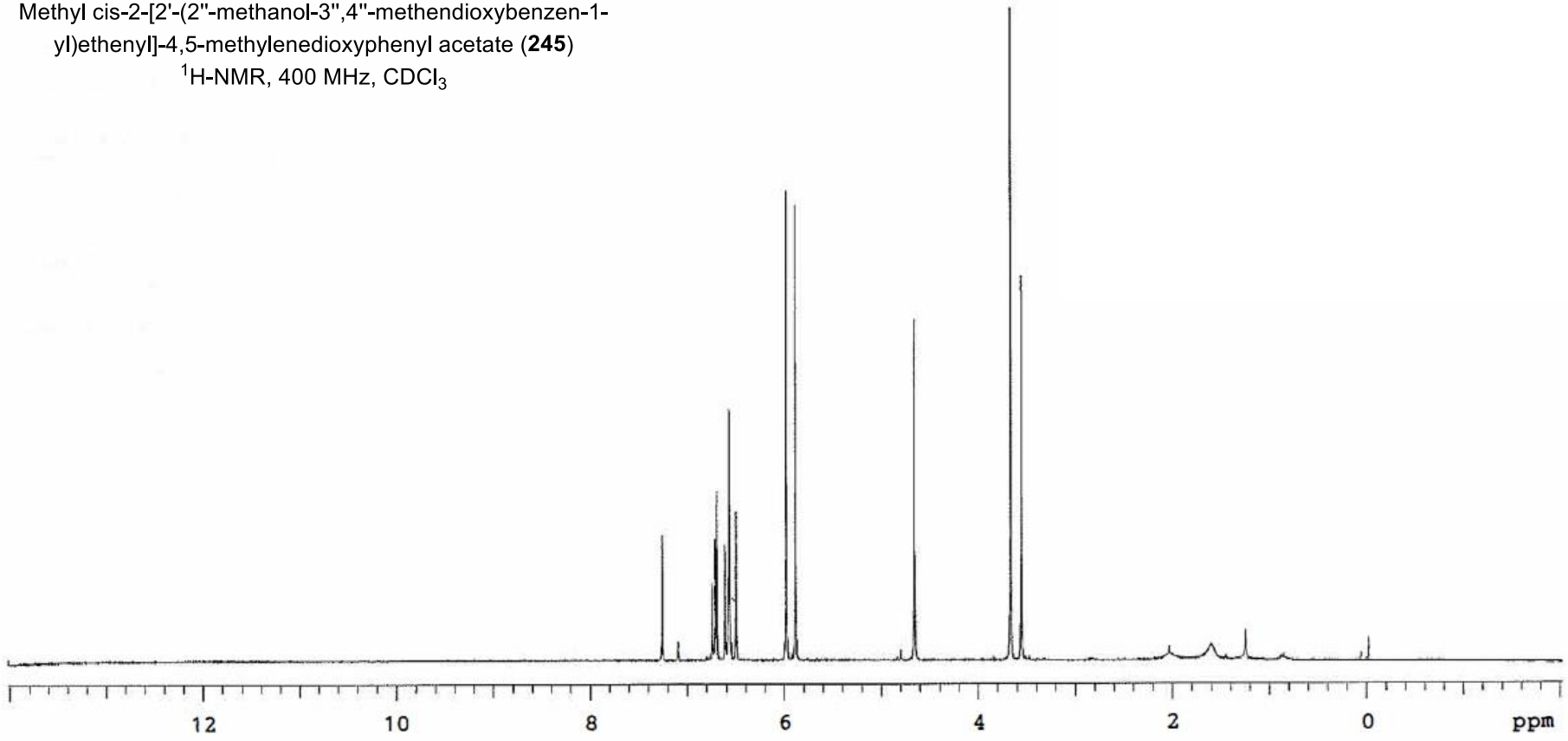
Methyl 2-[2'-(2''-methanol-3'',4''-methendioxybenzene-1-yl)ethynyl]-4,5-methylenedioxyphenyl acetate (**244**)
^{13}C-NMR, 100 MHz, $CDCl_3$

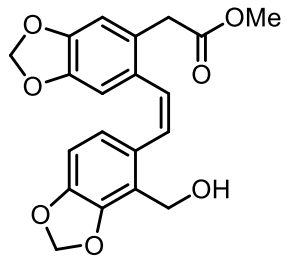




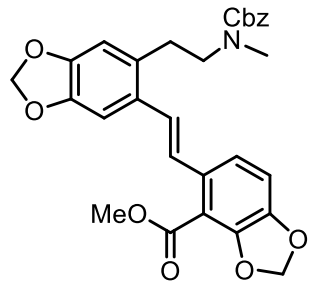
Methyl cis-2-[2'-(2''-methanol-3'',4''-methendioxybenzen-1-yl)ethenyl]-4,5-methylenedioxyphenyl acetate (**245**)

^{1}H-NMR, 400 MHz, $CDCl_3$



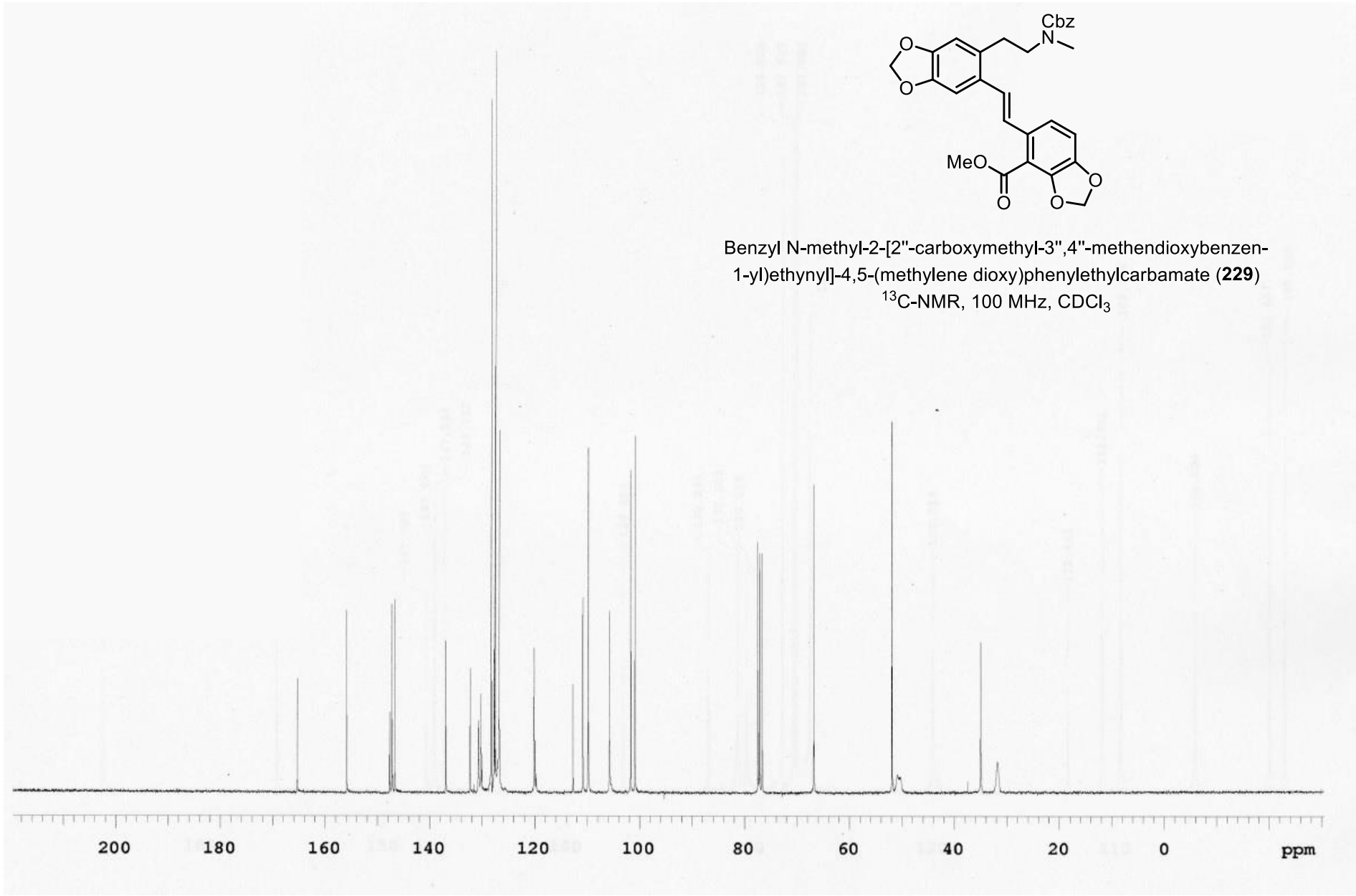


Methyl cis-2-[2'-(2''-methanol-3'',4''-methendioxybenzen-1-yl)ethenyl]-4,5-methylenedioxyphenyl acetate (**245**)
^{13}C-NMR, 100 MHz, $CDCl_3$

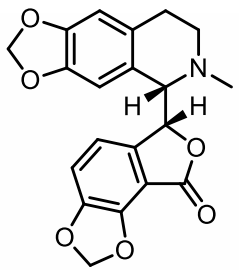


Benzyl N-methyl-2-[2''-carboxymethyl-3'',4''-methendioxybenzen-1-yl)ethynyl]-4,5-(methylene dioxy)phenylethylcarbamate (**229**)

^{1}H-NMR, 400 MHz, $CDCl_3$



Benzyl N-methyl-2-[2''-carboxymethyl-3'',4''-methendioxybenzen-1-yl)ethynyl]-4,5-(methylene dioxy)phenylethylcarbamate (**229**)
^{13}C-NMR, 100 MHz, $CDCl_3$



(±)-Bicuclline (**166**)
^{1}H-NMR, 400 MHz, $CDCl_3$

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