

Studies Towards Low Oxidation State Taxanes

Reema Sadia

Thesis submitted to the University of Nottingham for the degree of MRes

September 2021

CONTENTS

Acknowledgement iv
Abbreviations v
Abstract vii
1. Introduction 1
1.1. Taxanes 1
1.2. Biosynthesis of taxanes skeleton 2
1.3. Biological activities of taxanes 8
1.3.1. Multi-drug resistant cancer (MDR) and P-glycoprotein (PgP) 9
1.4. Extracting taxanes 11
1.4.1. Production of taxadiene in *E. Coli* 11
1.4.2. Production of taxadiene in Yeast 13
1.4.3. Production of taxadiene in tomato plants 14
1.4.4. Production of taxadiene in tobacco 14
1.5. Synthesis of low oxidation state taxanes 15
1.5.1. Holton's synthesis of taxusin 15
1.5.2. Baran's synthesis of taxuyunnanine 16
1.5.3. Synthesis of taxanes by a Diels-Alder approach 17
1.5.4. Synthesis of taxadiene 22
1.6. Project aims and retrosynthesis 25
2. Results and Discussion 28
2.1. Synthesis of methyl farnesoate 28
2.1.1. *E,E*-methyl farnesoate 29
2.2. Synthesis of bromohydrin and C ring 30
2.2.1. Synthesis of C ring from *E,E*-methyl farnesoate 36
2.3. Synthesis of enone 38
2.4. Synthesis of tetra-substituted diene 40
2.4.1. Reformatsky reaction 41
2.5. Synthesis of dienophile 46
3. Conclusions and future work 51
4. Experimental 53
4.1. General experimental 53
4.2. Experimental procedure 54
References 88

DEDICATION

This thesis is dedicated to my beloved parents (Amir Bahadar and Shaheen Akhtar), my lovely husband (Saeed Ahmad) and my children (Eman Khan and Hashir Khan).

ACKNOWLEDGEMENT

First of all, I would like to extend my deepest gratitude to my research supervisor Prof. Chris Hayes, for giving me the opportunity to work on this topic. Without his guidance and support, I wouldn't have been able to achieve this milestone.

I am thankful to my colleagues Michael and Kyran for their help and invaluable advice whenever I needed it. I am particularly grateful to Kyran for reading my thesis and giving me his helpful suggestions.

My thanks also go to the technical team and other support staff at the School of Chemistry who facilitated me in completing my studies.

I would like to thank my husband Saeed, for his everlasting support and for being patient with the hours that research in Chemistry demands. Without his motivation and encouragement, I would not have been able to complete my studies. I greatly appreciate the support I received from my daughter Eman for being patient and a caring big sister to her brother when mummy was not around. I am also thankful to my son Hashir, who just turned 2 when I started my studies. He is the one who sacrificed the most for being away from me all day.

My gratitude also goes to my parents, brothers and sisters for their continued support, prayers and encouragement.

Finally, I would like to thank everyone who has facilitated me to complete my studies.

ABBREVIATIONS

Aq	Aqueous
Ar	Aromatic
br	Broad
Bu	Butyl
Conc	Concentrated
COSY	correlation spectroscopy
d	doublet
DCM	dichloromethane
DEPT	distortionless enhancement by polarisation transfer
DIBAL-H	diisobutylaluminium hydride
DMAPP	Dimethylallyl diphosphate
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
eq.	Equivalent
ESI	Electrospray ionisation
Et	Ethyl
GGPP	Geranylgeranyldiphosphate
GGPPS	Geranyl geranyldiphosphate synthase
GPP	geranyl diphosphate
h	Hour (s)
HMBC	Heteronuclear multiple bond correlation spectroscopy
HSQC	Heteronuclear spin quantum correlation spectroscopy
Hz	Hertz
IPP	Isopentenyl diphosphate
IR	Infrared
m	Multiplet
M	molar
MDR	Multidrug resistance

Me	Methyl
NBS	*N*-bromosuccinimide
NMR	Nuclear magnetic resonance
OCT	oxa-cyclotaxane
PGP	P-glycoprotein
ppm	parts per million
q	quartet
quin	quintet
r.t.	room temperature
RSM	recovered starting material
s	singlet
t	triplet
Taxol®	Paclitaxel – 'Taxol' registered trademark of Bristol-Myers Squibb
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMP	Tetramethyl piperidine
UV	Ultraviolet

ABSTRACT

This thesis outlines work towards the optimisation and production of taxadienone, a useful precursor to the low oxidation state taxanes and a member of the taxane family of natural products, through synthetic chemistry.

Chapter I Introduces the taxane family of natural products, their biosynthesis, biological activities and extraction.

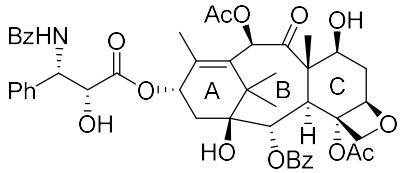
Chapter II describes our synthesis of taxadienone, using carbon building blocks from a sustainable source. We started our work with the formation of the C ring *via* an acid catalysed cyclisation of a polyene derived from the natural product, *E/Z* farnesol. A single isomer of farnesol was also used to study its effect on the diastereoselectivity of the cyclised product. Cyclisation was followed by the use of a novel indium-Reformatsky reaction to form a β-lactone which subsequently underwent decarboxylation to form a tetra-substituted diene. This was followed by the well-established Diels-Alder approach to construct taxadienone.

Chapter III provides an experimental section that gives detailed procedures and full characterisation data for the novel compounds discussed in the results and discussion.

1. INTRODUCTION

1.1. Taxanes

The taxanes are a large family of C-20 diterpenoid natural products originally identified from plants of the genus *Taxus,* such as *Taxus baccata* (European yew) and *Taxus brevifolia* (Pacific yew).[1,2,3] The slow growing botanical species of the *Taxus* genus are members of the *Taxaceae* family and are widely distributed throughout Europe, the Far East as well as Northern and Central America.[4,5] Initially scientists were specifically interested in the *Taxus baccata* because of its known toxicity, due to the accumulation of complex mixtures of taxane alkaloids in the needles and bark of the yew tree.[6] In 1856, Lucas carried out the first chemical extraction of this genus[7,8] and isolated a crude mixture called "taxine", which was suspected of being responsible for the yew's toxicity.[2] There has been a great deal of interest in these compounds since the discovery of Taxol® **1** (Figure **1**), a natural product and anticancer compound from *Taxus brevifolia,* by Wani and co-workers in 1967.[9,10]



1

Figure 1: Taxol®

Taxol® exhibits effective cytotoxicity *via* a novel mechanism of action and is currently licensed to use for the treatment of various kinds of cancers including breast, ovarian, bladder, esophageal, gastric, lung, prostate, head and neck and AIDS-related Kaposi's sarcoma.[11] Since the discovery of taxanes from *Taxus brevifolia,* over 400 of

these natural products have been isolated and characterised from various species of the *Taxus* genus[12,13] to contain a twenty-carbon skeleton with a common tricyclic 6.8.6 ring system (Figure **2**),[12] however, there are other known variations such as Taxol® bearing a fourth oxetane ring (Figure **1**).

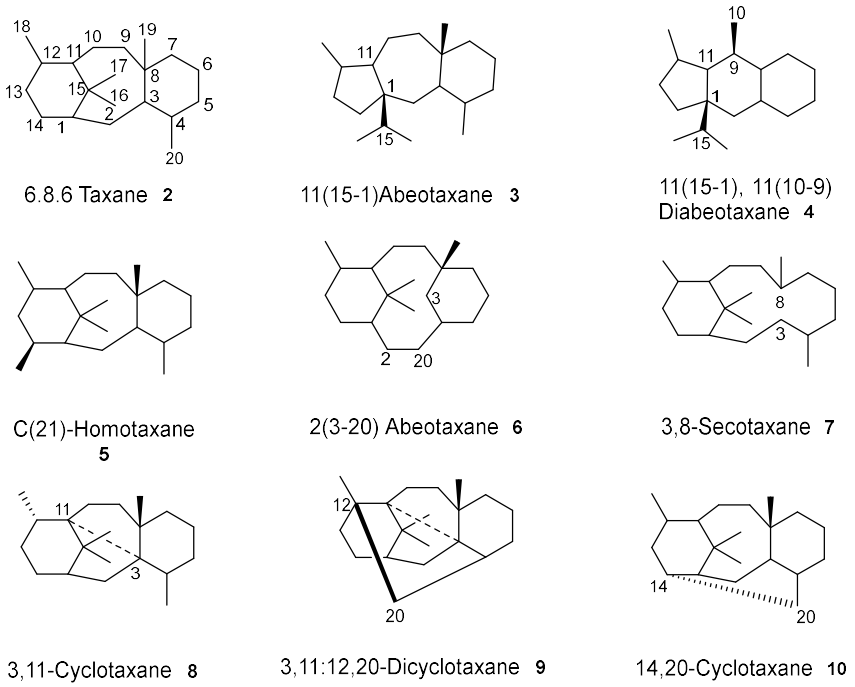
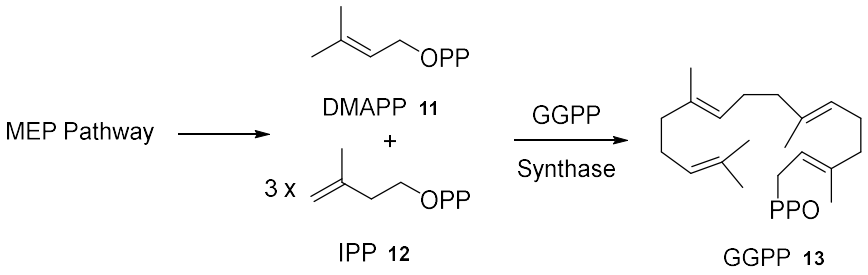


Figure 2: Carbon skeletons of the taxanes

1.2. Biosynthesis of taxanes skeleton

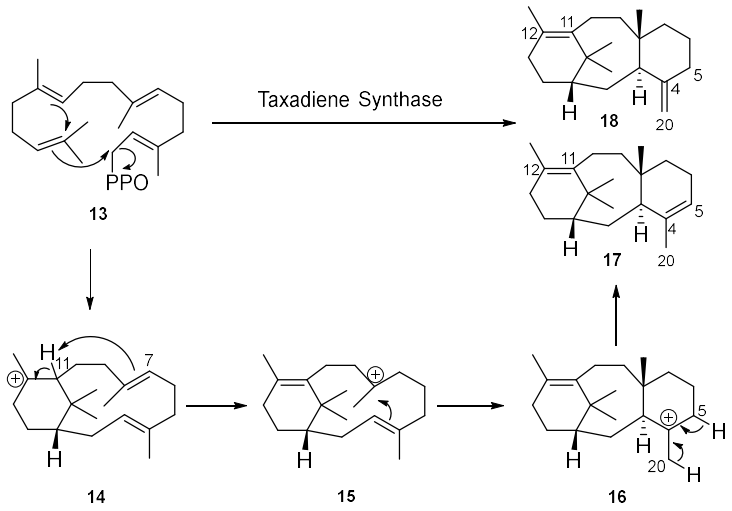
The biosynthesis of taxanes involves three main stages. The first step is the formation of geranylgeranyldiphosphate **13** (GGPP),[14,5] the precursor for all diterpenoids. This involves head-to-tail condensation of its building blocks (IPP and DMAPP), supplied from the methylerythritol phosphate pathway (MEP) occurring in the chloroplast[15] by the enzyme geranylgeranyldiphosphate synthase (GGPPS) to afford the C10

geranyl diphosphate (GPP), followed by C15 farnesyl diphosphate and then the C20 GGPP molecule (Scheme **1**).[16]



Scheme 1: Formation of GGPP

The linear precursor **13** is then cyclised by taxadiene synthase (Scheme **2**).[17,18] Cyclisation involves the loss of diphosphate from GGPP to give verticillenyl cation **14**, followed by a 11-7 H-shift to produce cation **15**. Closure of the taxane C ring followed by deprotonation from taxenyl cation **16** at the C20 gives the minor isomer taxa-4(20),11,(12)-diene **18**. Deprotonation from **16** at C5 affords the major isomer taxa-4(5),11,(12)-diene **17**.[19,20]

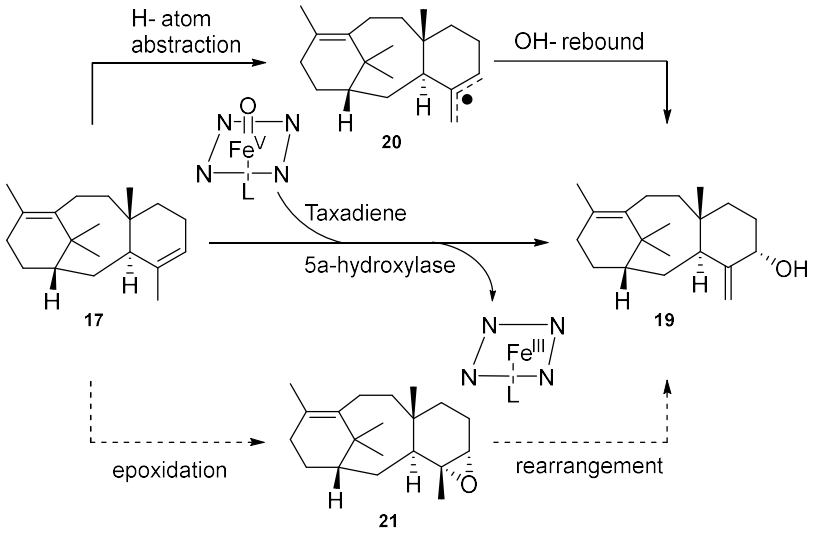


Scheme 2: Biosynthesis of taxadiene **17** and **18**

Taxadiene as a mixture of double bond isomers (**17** and **18**) is then transported to the endoplasmic reticulum where it undergoes a series of oxidations, mediated by

cytochrome P450 oxygenase and produce various taxane derivatives.[21,22] The exact sequence of all the oxidations is not well understood, however, it is thought that oxidation first occurs at C5 by the enzyme taxadiene 5α-hydroxylase[23] probably followed by oxidation at the C10, C2, C9, C13, C7 and C1 positions.[13]

Although taxadiene 5α-hydroxylase catalyses the oxidation of taxadiene **17** to 5α-hydroxytaxa-4(20)-11(12)-diene **19** (Scheme **3**), there are two proposed mechanisms for this biosynthetic oxidation by Williams and Croteau.[24] Initially, the enzyme promotes an oxidation-rearrangement process *via* hydrogen atom abstraction by the iron(V) oxo species which affords an allyl radical **20**. Hydroxylated product **19** is then formed following a rapid hydroxy rebound from the iron to the 5-α position.

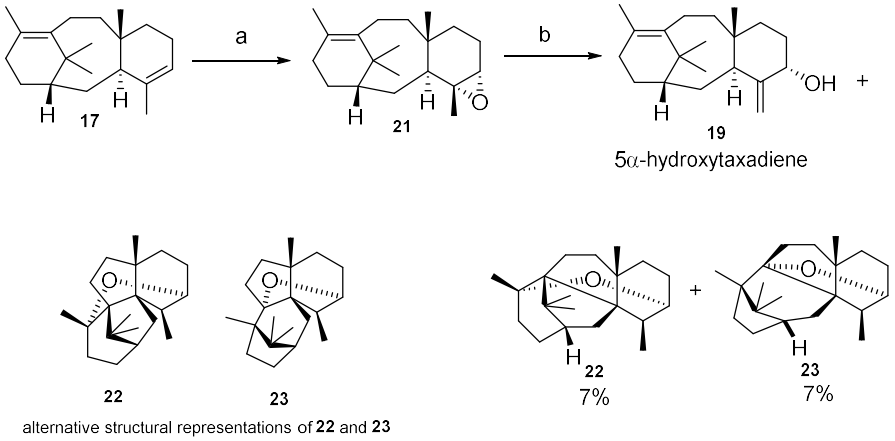


Scheme 3: 5α-hydroxylase mechanism

The second proposed oxidative mechanism proceeds *via* epoxide **21,** which rearranges with the loss of the proton at C20 to produce 5α-hydroxytaxa-4(20)-11(12)-diene **19**. The first mechanism (*via* an allyl radical) was favoured as both isomers of taxadiene **17** and **18** are converted to the same product **19**, no epoxide

intermediate has ever been isolated and it was presumed that a reduced iron(III) porphyrin was not Lewis acidic enough to rearrange an epoxide.[25,26]

However, research within the Hayes group supported the epoxide mechanism (Scheme **3**). While working on taxadiene **17** obtained from genetically modified tomatoes, Hayes suggested that taxa-4(5),11(12)-diene **17** undergoes oxidation *via* an epoxidation pathway (Scheme **4**).[14,21]

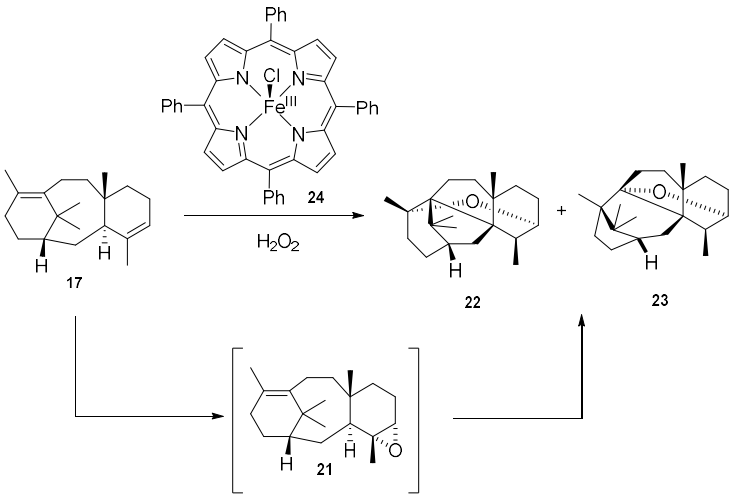


Scheme 4: 5α-hydroxylase mechanism

Reagents and conditions: **a**) DMDO (1.0 eq.), acetone/CH_2Cl_2, 63%. **b**) *p*TSA, C_6D_6, 17%.

During their synthetic work, they discovered that taxadiene **17** undergoes epoxidation regioselectively at the 4(5) olefin preferentially over the 11(12) alkene, possibly due to steric hindrance at the more substituted 11(12) double bond yielding epoxide **21**. Epoxide **21** was unstable to silica gel chromatography possibly due to the acidic nature of silica and was found to decompose into a complex mixture of products including oxa-cyclotaxane (OCT1 **22** and OCT2 **23**). To investigate the acid catalysed rearrangement of epoxide **21**, they treated **21** with acid to give the 5α-hydroxytaxadiene **19** along with OCT1 **22** and OCT2 **23** as minor products in a 1:1 ratio

(Scheme **4**). However, when epoxide **21** was treated with Fe^{III}(TPP)Cl in C_6D_6 at 25 °C for 72 hours, no 5α-hydroxytaxadiene **19** formation was observed. Instead, it was discovered that OCT1 **22** and OCT2 **23** were the major products in a 1:1 ratio (Scheme **5**), confirming that taxa-4(5),11(12)-diene **17** undergoes oxidation *via* an epoxidation pathway.



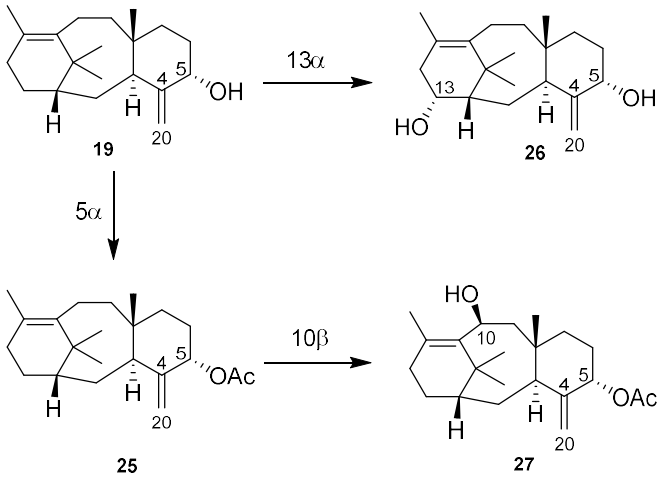
Scheme 5: Iron (III) porphyrin rearrangements of 4(5)-epoxytaxadiene **21**

Reagents and conditions: **a**) Fe^{III}(TPP)Cl (**24**), *d*6-benzene, r.t., 72 h. **22**:**23**-1:1

In 2016, Stephanopoulos published his work based on expressing taxadiene 5α-hydroxylase in a variety of organisms.[27] These organisms produced a range of oxidised taxanes including OCT1 **22**, OCT2 **23** and 5α-hydroxytaxadiene **19**. Stephanopoulos observed significantly different product distributions in each organism. He proposed that these organism-dependent product distributions cannot be accounted for by invoking the allyl radical **20** as a common intermediate. Instead, the observed product distributions are best explained by the formation of epoxide **21** that is subject to decomposition to different products, which is organism dependent.

This work supported Hayes' findings that epoxide **21** is an intermediate in the biosynthesis of taxanes.

Following oxidation at C5, taxadien-5-α-ol **19** can then be acetylated to give acetate **25**.[22,21] Acetate **25** is then oxidised at C10 to give hydroxylated product **27** by 10-β-hydroxylase enzyme at a slow rate.[21] The 13-α-hydroxylase also oxidizes **19** but uses acetate **25** as a substrate (Scheme **6**). Both C13α and C10β hydroxylases are supposed to be less selective in their roles and can interchange substrates.[20,28,29]



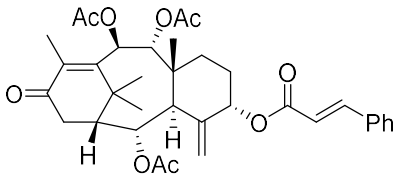
Scheme 6: Cytochrome P450-mediated hydroxylation

The C9 and C14 positions are believed to be oxidised in the middle of the pathway, with oxidation at C7, C2 and C1 occurring in the later stages.[13,21] The steps and enzymes involved in the next series of oxidations are not well understood. Similarly, the enzymes involved in the formation of the oxetane ring and the timing of its formation are unknown.[30,24] Once a position has been hydroxylated on the carbon skeleton it can be further functionalised to form substituted taxanes. This can occur from either oxidation of an alcohol to the carbonyl functionality, or the formation of

esters including acetyl, benzoyl and cinnamoyl. This unique biosynthesis is responsible for a large number of taxanes identified to date.[20,13]

1.3. Biological activities of taxanes

The biological activity of Taxol® is well-described in the literature[11,31] however, the biological properties of low oxidation state taxanes are less documented. Recently, research has been carried out to study the biological activities of some low oxidation state taxanes to determine how effective these compounds are in the treatment of multi drug resistant cancer. From the first use of cytotoxic drugs in cancer treatment, it has been obvious that drug resistance is a major problem in cancer therapies. Taxol® is the most studied and well-known member of the large family of taxanes and has been used extensively as a cytotoxic chemotherapy agent. However, it is now becoming clear that Taxol® is not the only member of taxanes that is biologically important, some other taxanes also show significant biological activity.[32] Taxinine **28** (Figure **3**) for example has been found to demonstrate considerable biological activities and can be used to reverse multidrug resistance.[20,32]



28

Figure 3: Taxinine

1.3.1. Multi-drug resistant cancer (MDR) and P-glycoprotein (PgP)

Drug resistance continues to be the main limiting factor in the treatment of patients with cancer.[33] Taxol® is currently considered to be one of the most important drugs used for the treatment of a range of different cancers, however, it is now becoming clear that some naturally occurring taxanes can also be used to tackle drug resistance.[32]

During chemotherapy, cancer cells can spontaneously develop resistance to anticancer drugs being used.[34] This is normally divided into two main categories. The first category involves cancer having a specific resistance to the anticancer drug being prescribed, caused by the specific mutations of the drug in the cell. In this case, treatment can still be effective with a different drug. The second category involves the resistance of cancer to a range of cancer drugs and is called multiple drug resistance (MDR). It can be challenging to find a suitable drug that is effective and not affected by the resistance mechanism.[34] Multi-drug resistance is thought to occur by the overexpression of cell efflux pumps, such as P-glycoprotein (PgP).[35,36] PgP is a transmembrane protein of the ATP binding cassette (ABC) family, which transports a variety of compounds out of the cell that includes anticancer drugs.[37,38] PgP is expressed on the capillaries of the brain, kidney, liver and small intestine and its biological function is considered as a defence mechanism against toxic materials within the cell.[39] Upon expression in the membrane of a cancer cell, it carries various kinds of anticancer agents from inside to the outside of the cell.[40] PgP contributes to the resistance by preventing sufficient accumulation of anticancer drugs within the cell, thus inhibiting their cytotoxic effects.[35,37] Apart from PgP, multi-drug resistance

protein 1 and breast cancer resistance protein are also known to cause multiple drug resistance.[34]

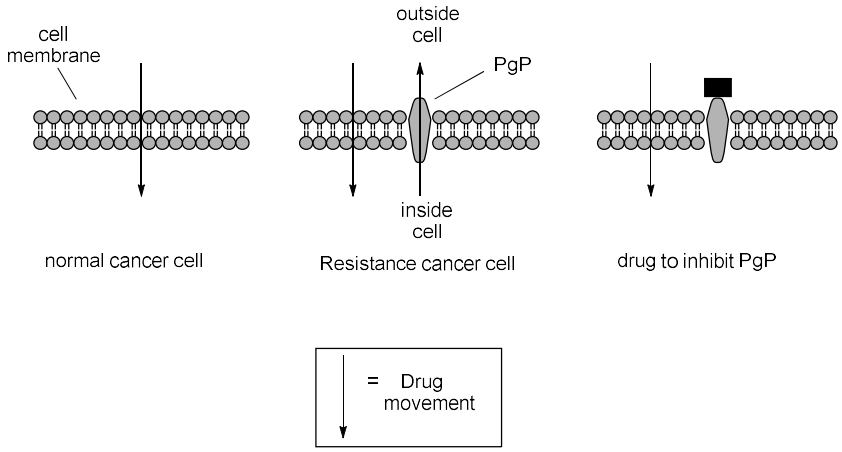


Figure 4: PgP pump inhibiting the movement of a drug

There are two ways to overcome the overexpression of PgP within cancer cells to resume successful chemotherapy. This could be either achieved by developing a drug that has not been affected by PgP or by directly inhibiting PgP (Figure **4**).[34]

Taxanes have been investigated for this purpose and it was found that some analogous show multi-drug resistance reversal activities.[40] Examples of taxanes that are effective PgP inhibitors are highlighted in Figure **5**.

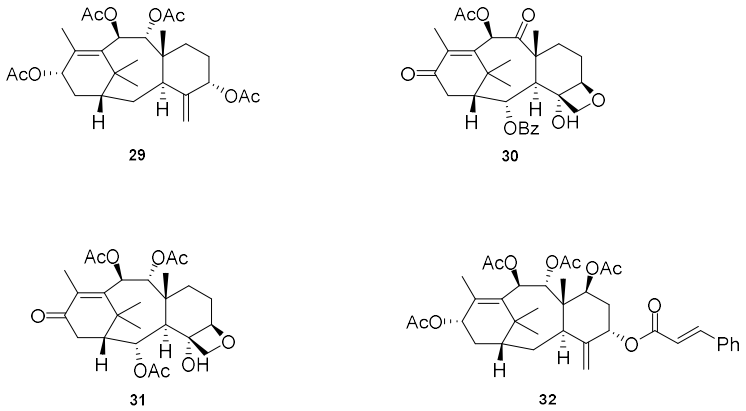


Figure 5: Taxanes that inhibit PgP

It is clear that taxanes display some useful biological properties however, the challenge is to find a method for sustainable production of taxanes derivatives.

1.4. Extracting taxanes

Initially extracted from *Taxus brevifolia* by Wani and co-workers with an overall yield of just 0.02%, a significant amount of research has been carried out on Taxol®.[9] Unfortunately, the availability of low oxidation state taxanes from the *Taxus* species is extremely low with approximately 1 mg of taxadiene **17** being isolated from 750 kg of yew bark, which places a huge amount of pressure on the natural resources. The low availability of taxanes from natural sources makes it very challenging to use them for extensive biological studies or the development of novel drugs. This shortage of taxanes through extraction and the impact of extraction on nature has led scientists to consider the possibility of obtaining taxanes either through semi-synthesis or total synthesis approaches. Without a sustainable source of taxadiene from a natural habitat, an alternative method of accessing taxadiene would be to produce it *in vivo*. Many research groups have used genetic modifications to produce taxadiene in a range of foreign organisms through genetic manipulations from yeast to tobacco.

1.4.1. Production of taxadiene in *E. Coli*

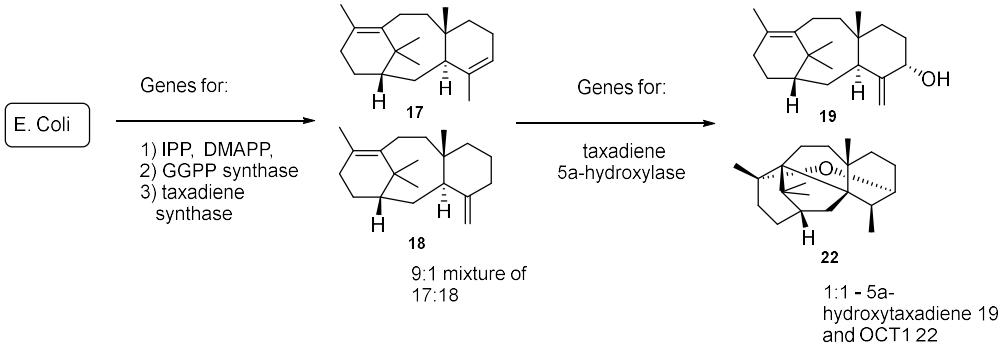
Croteau 1995

The enzyme taxadiene synthase (TS) was first purified and characterised by Croteau and co-workers in 1995.[17] After the successful isolation of the cDNA encoding

taxadiene synthase, he clone the enzyme into *E. Coli*. This approach, however, produced only microgram quantities of taxadiene, probably due to the poor solubility of taxadiene synthase hindering its activity.[41] Therefore, he produced a more soluble, truncated TS and published its crystal structure in 2011.[42] He expressed this in *E. Coli* which produced 1.3 mg/L of taxadiene. Although this adapted methodology improved the solubility, the obtained yield was still poor. It was postulated that the low yield of taxadiene **17** was due to a low expression of the pathway to produce GGPP. Later on, Boronat tried to improve the yield of taxadiene **17** by cloning the truncated TS into *Arabidopsis* (Thale Cress), which naturally produces high levels of GGPP. However, these plants experienced poor growth and produced sub-milligram quantities of taxadiene.[43]

Stephanopoulos 2010

In 2010, a breakthrough came when Stephanopolous expressed genes for the methylerythritol phosphate pathway to produce IPP **12** and DMAPP **11**, GGPP synthase and taxadiene synthase in *E. Coli* to afford taxadiene in yield of 1 g/L, as a 9:1 mixture of regioisomers **17**:**18** (Scheme **7**).[44] He also introduced a modified taxadiene 5α-hydroxylase in *E. Coli* to produce a 1:1 mixture of 5α-hydroxytaxadiene **19** and oxa-cyclotaxane (OCT) **22** in 21 mg/L and 24 mg/L respectively.



Scheme 7: Stephanolpoulos' production of taxadiene **17**, 5α-hydroxytaxadiene **19** and oxa-cyclotaxane (OCT1) **22** in *E.Coli*

1.4.2. Production of taxadiene in Yeast

Croteau and Jennewein 2006

In 2006, Croteau published his work expressing taxadiene synthase, taxadiene 5α-hydroxylase, an O-acetyl transferase and 10β-hydroxylase in *saccharomyces cerevisiae* (yeast), a strain known for the production of terpenoids.[45] Taxadiene **17** was produced in a small quantity (1.0 mg/L) along with sub milligram quantities of 5α-hydroxytaxadiene **19**. Surprisingly, no OCT **22** was produced and the next two biosynthetic steps using the O-acetal transferase and 10β-hydroxylase were unable to give any product. It was thought that the poor yield of the taxadiene 5α-hydroxylase step was limiting substrate availability for the next two enzymes. Despite this, in 2008 Jennewein published an improved yeast model with a yield of 8.7 mg/L of taxadiene **17**.[46]

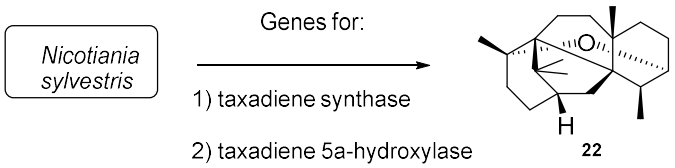
1.4.3. Production of taxadiene in tomato plants

In 2007 Fray and Hayes reported the production of a genetically modified tomato strain that produced 160 mg/kg of taxadiene.[47] The tomato line chosen was the mutant *yellow flesh* (locus r) which produces large amounts of GGPP **13** but lacks the enzyme phytoene synthase, which converts GGPP **13** to carotenoids and gives the tomatoes their red colour. The expression of natural taxadiene synthase in these plants results in stunted growth and retarded seed production, however, the production of taxadiene **17** was good. Though it was not as high as the subsequent work done by Stephanopoulos in *E.Coli* but was a major improvement on all other methods to date.

1.4.4. Production of taxadiene in tobacco

Tissier 2008

In 2008 Tissier expressed both taxadiene synthase and 5α-hydroxylase in tobacco (*Nicotiania sylvestris*).[25] Unfortunately, he found that taxadiene **17** was formed in only 2 mg/Kg and the unusual OCT **22** was formed as the only oxidised taxane (Scheme **8**).



Scheme 8: Tissier's unexpected production of oxa-cyclotaxane (OCT) **22** in *Nicotiania sylvestris*

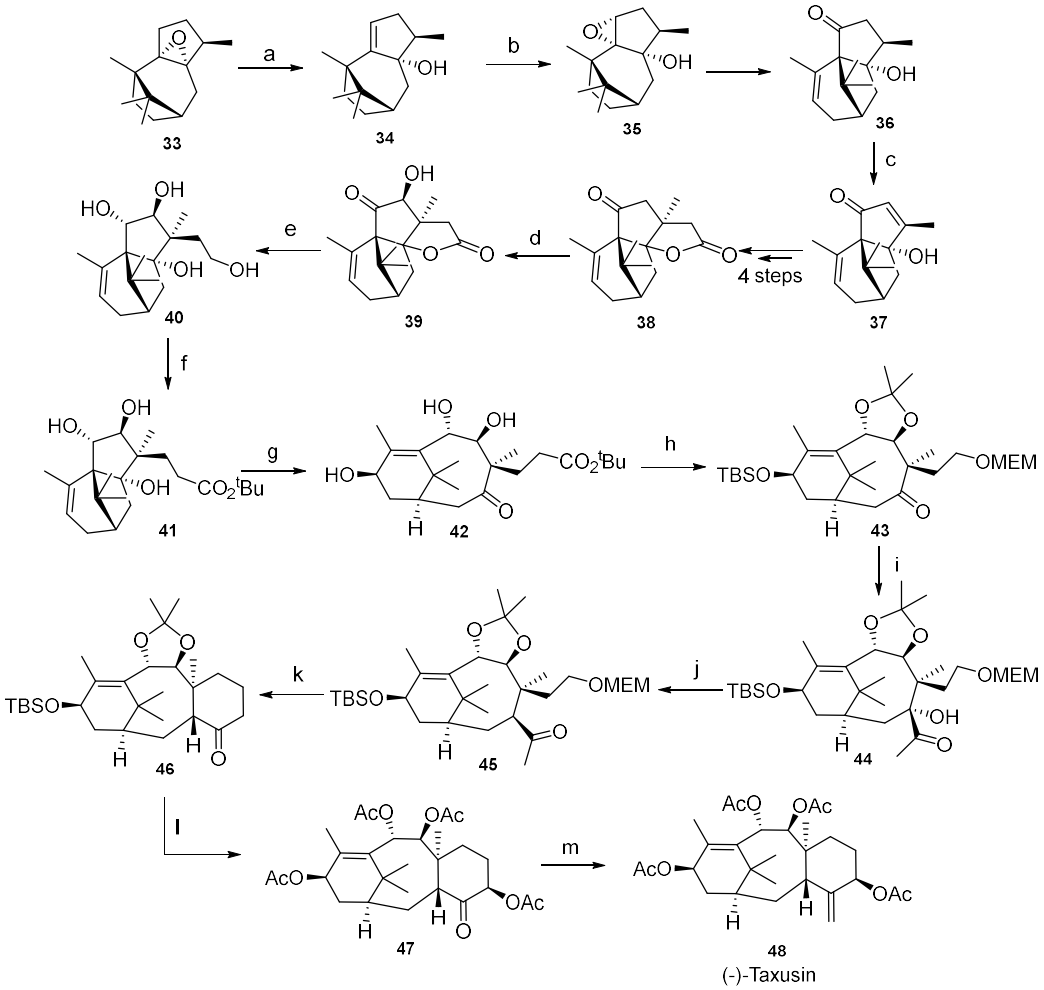
This contradicted Croteau's observation on his yeast model, which only isolated **19** with no OCT **22** formation.[45]

1.5. Synthesis of low oxidation state taxanes

There are many approaches towards the synthesis of taxane core throughout the literature. In 1988, Holton carried out the first synthesis of tricyclic natural taxane by synthesising (−)-Taxusin **48**, the enantiomer of natural product (+)-Taxusin.[48]

1.5.1. Holton's synthesis of taxusin

Holton started his synthetic route with (−)-patchoulene oxide **33**, a natural product (Scheme **9**). Ring-opening of **34** gave allylic alcohol which underwent epoxidation to give **35**. Acid catalysed rearrangement of **35**, followed by oxidation gave ketone **36**. Ketone **36** was then converted into enone **37** which was then transformed into hydroxy ketone **39** through lactone intermediate **38** in four steps. Hydroxy ketone **39** was then reduced to tetra-ol **40**. A and B rings of taxane core **42** were then obtained by the protection of tetra-ol **40**, followed by an oxidation and Grob rearrangement. Ring C was constructed by several steps that involved the deprotection of **45** before the formation of tosylate and subsequent C ring closure induced by an enolate nucleophile to obtain **46**. Alpha oxidation of **46** before protecting it as an acetate gave **47**. Finally, deprotection of **47** followed by acetylation and then Wittig olefination affords the unnatural enantiomer (−)-Taxusin **48**.

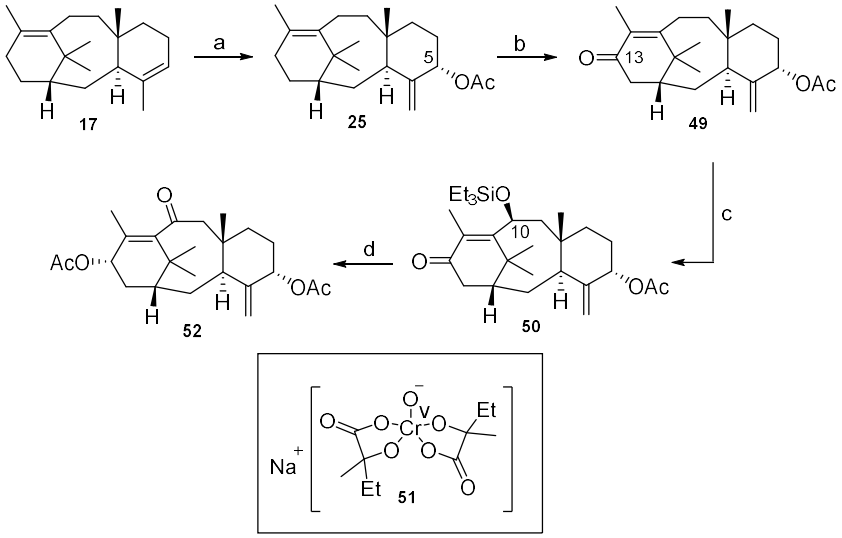


Scheme 9: Holton's synthesis of (−)-taxusin **48**

Reagents and conditions: **a**) ^{t}BuLi. **b**) ^{t}BuOOH, Ti(O^{i}Pr)$_4$, CH_2Cl_2, 98%. (2 steps) **c**) i) LDA, TMSCl, PhSeCl ii) H_2O_2, 95%. **d**) i) LDA, TMSCl ii) AcOOH, 92%. **e**) RedAl, 95%. **f**) ^{t}BuCOCl, 99%. **g**) i) AcOOH ii) Ti(OiPr)$_4$, 90%. **h**) i) 2,2-dimethoxypropane, TsOH ii) TBDMSOTf, pyridine iii) MEMCl, DIPEA, CH_2Cl_2, 97% (3 steps). **i**) i) α-methoxyvinyllithium, ii) AcOH, 90% j) SmI_2, 90%. **k**) i) $FeCl_3$, Ac_2O, NaOMe ii) Ts_2O, pyridine iii) ^{t}BuONa, 87% (3 steps). **l**) i) LDA, TMSCl ii) *m*-CPBA iii) TBAF, HCl vi) Ac_2O, 83% (4 steps). **m**) Ph_3PCH_2, 70%.

1.5.2. Baran's synthesis of taxuyunnanine

In 2014 Baran published his first synthesis studies into oxidation of taxadiene **17**, oxidising at C5, 13 and then 10.[49] This research resulted in the synthesis of the low oxidation state taxane (−)-taxuyunnanine D **52** (Scheme **10**).



Scheme 10: Baran's oxidation of taxadiene **17** to (−)-taxuyunnanine D **52**

Reagents and conditions: **a**) $Pd(OAc)_2$, benzoquinone, anisole, AcOH, 49%. **b**) **51**, MnO_2, 15-crown-5, 53%. **c**) i) NBS, benzoyl peroxide, ii) AgOTf, Et_3SiOH, toluene, 80%. **d**) i) DIBAL ii) Ac_2O, DMAP, Et_3N, 80%, iii) IBX, DMSO, 88%.

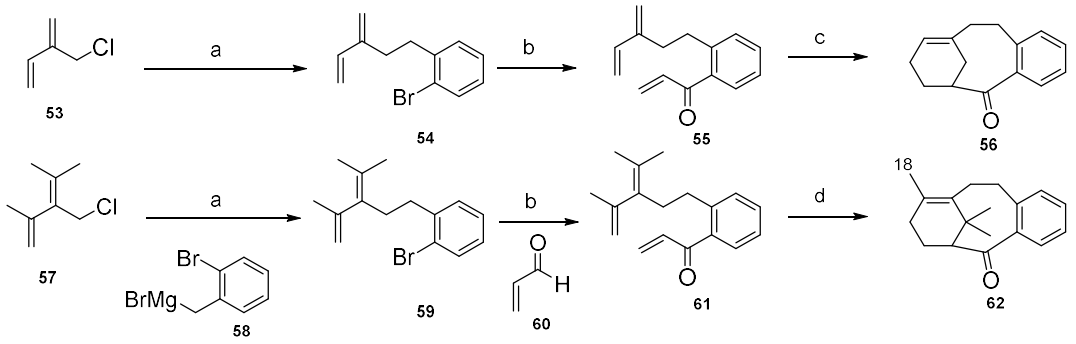
Baran used a palladium-catalysed acetoxylation to install C5 oxidation in a moderate yield of 49%. Treatment of **25** with chromium (V) reagent **51** then produced enone **49** in 53% yield. Allylic bromination followed by silver-mediated substitution with a silanol, then gave **50**. Reduction of intermediate **50** at the C13 carbonyl, followed by oxidation with IBX at C10 gave the natural product (−)-taxuyunnanine D **52** in 5 steps from taxadiene **17**.

1.5.3. Synthesis of taxanes by a Diels-Alder approach

An effective method for the synthesis of taxanes involves the application of a Diels-Alder reaction to form A and B rings of taxanes, as it allows the direct formation of 8 membered ring. The application of the Diels-Alder approach by various research groups is given below.

Shea's Diels-Alder

The first use of Diels-Alder reaction to form A and B rings of the taxane core was demonstrated by Shea in 1983.[50] He used a model system with an aromatic C ring for the formation of the A and B ring of the taxane skeleton (Scheme **11**).



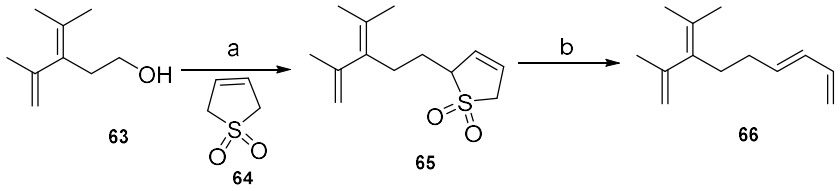
Scheme 11: Shea's Diels-Alder model system

Reagents and conditions: **a**) THF, 2 eq. **58**. **b**) i) ^{s}BuLi, **60** ii) PCC **c**) xylene, 185 °C, 70%. **d**) xylenes, 155 °C, 3.9 days, 70%.

In order to study the effects of dimethylation on the Diels-Alder reaction, he used *gem*-dimethylated diene **59** and desmethyl diene **54**. Dienes **54** and **59** are the key intermediates in Shea's synthesis. A solution of **53** and **57** in THF was treated with a solution of **58** in ether to give dienes **54** and **59** in 54% and 43% yields respectively. Dienes **54** and **59** are then converted into Diels-Alder precursors **55** and **61** *via* two steps. Heating of **55** and **61** in xylene then produced **56** and **62** respectively. Both reactions proceeded with almost identical yields of 70%, however, it is important to note that the rate of cyclisation was hindered by *gem*-dimethyl groups and the methyl group at C18. The desmethyl diene **55** underwent cyclisation in 1 h, whereas the time required for cyclisation of dimethylated diene **61** was 3.9 days.

Winkler's Diels-Alder

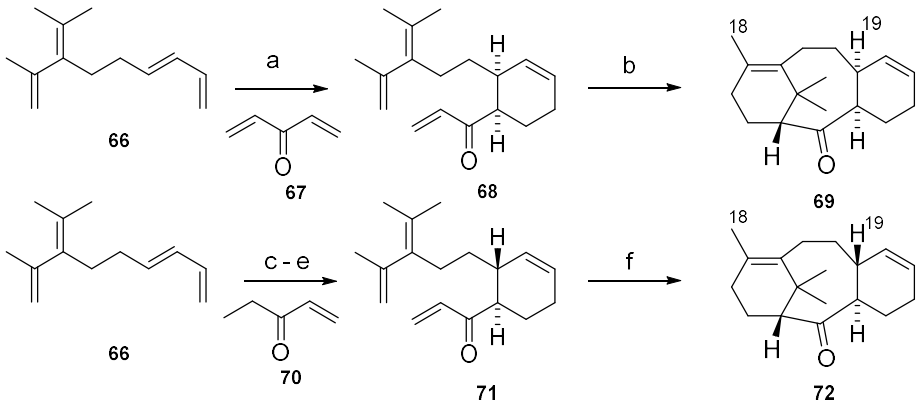
Following Shea's work, Winkler in 1997 used an alcohol **63** to synthesise diene **66** for his Diels-Alder reactions (Scheme **12**).[51] Alcohol **63** was converted into the corresponding mesylate, followed by treatment with sodium iodide to give the corresponding iodide, which then reacts with **64** to produce **65**. Intermediate **65** was then heated at reflux to give diene **66**.



Scheme 12: Winkler's synthesis of diene **66**

Reagents and conditions: **a**) i) MsCl, Et_3N, CH_2Cl_2, ii) NaI, Me_2CO, iii) **64**, LHMDS, THF. **b**) toluene, reflux.

Having successfully prepared diene **66**, a $ZnCl_2$-catalysed intermolecular Diels-Alder reaction with **67**, proceeding *via* an *endo*-transition state, gave *cis*-cyclohexene **68** (Scheme **13**). In a similar manner, intermolecular Diels-Alder reaction of diene **66** with **70** initially gave the *cis*-cyclohexene (*endo*-) product. The *cis*-cycloadduct was then isomerised to the *trans*-cyclohexene isomer by exposure to sodium methoxide. Finally, installation of the required enone was accomplished using a standard selenoxide elimination procedure to give the *trans*-cyclohexene **71** (Scheme **13**). The intramolecular Diels-Alder precursors (**68** and **71**) were then each treated with $BF_3{\cdot}Et_2O$ to afford the tricycles **69** and **72** respectively.



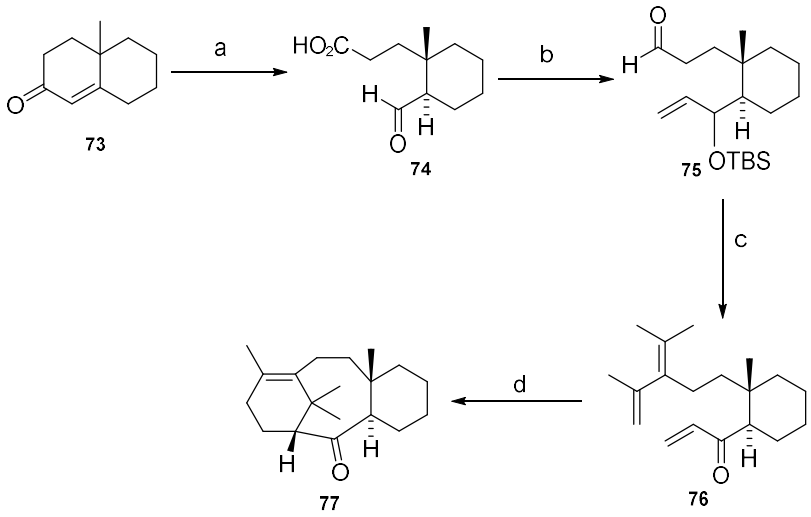
Scheme 13: Winkler's Diels-Alder model study

Reagents and conditions: **a**) $ZnCl_2$, CH_2Cl_2, **67**. **b**) 6 eq. BF_3•Et_2O, toluene, 0 °C, 82% . **c**) i) $ZnCl_2$, CH_2Cl_2, **70**. **d**) NaOMe, MeOH **e**) i) LHMDS, PhSeBr, ii) $NaIO_4$, $NaHCO_3$. **f**) 3 eq. BF_3•Et_2O, toluene, −35 °C, 66%.

Both cycloadditions (**68** to **69** and **71** to **72**) gave single stereoisomer products consistent with *endo*-transition states. Tricycle **69** (82%) was produced in higher yield than **72** (66%), thus suggesting that the *cis*-cyclohexene stereochemistry (**68**, Scheme **13**) leads to a more favourable transition state geometry than that available to the *trans*-cyclohexene isomer (**71**, Scheme **13**).

Jenkins' Diels-Alder

While Shea was working on the cyclisation of aromatic C-ring, Jenkins independently published the use of the Diels-Alder transformation on a model system with saturated C-ring (Scheme **14**).[52–55]



Scheme 14: Jenkins' Diels-Alder model

Reagents and conditions: **a**) i) Li, NH_3, ii) Et_3N, TMSCl, iii) O_3, CH_2Cl_2, MeOH. **b**) i) CH_2N_2, ii) vinyllMgBr, iii) TBSCl, iv) DIBAL. **c**) i) propenylMgBr, ii) CrO_3, py, iii) $Me_2C(SePh)_2$, BuLi, THF, iv) $SOCl_2$, Et_3N, CH_2Cl_2, v) HF, vi) CrO_3, py. **d**) 1 eq. $BF_3 \bullet Et_2O$, Toluene, −40 °C, 24 h, 58%.

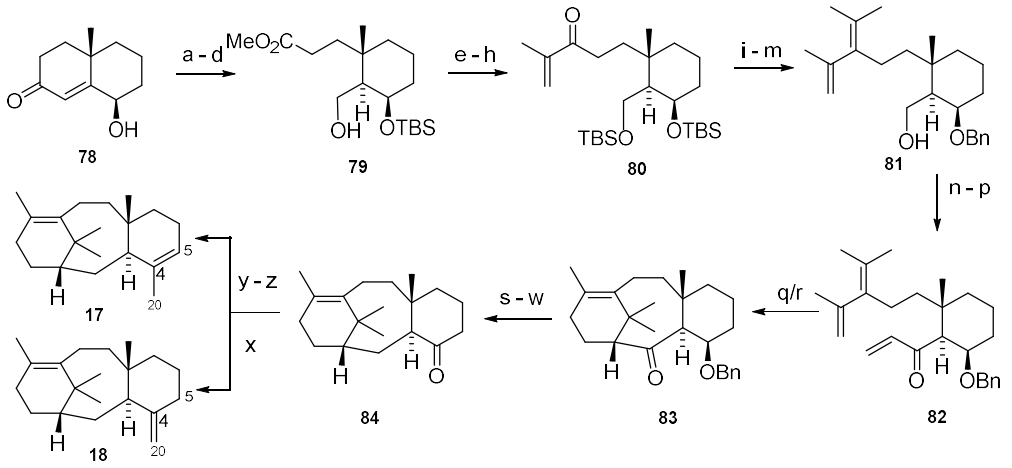
Jenkins started his work by using bicyclic enone **73** as a starting material for his Diels-Alder reaction to form the A and B rings. Reduction of **73**, followed by esterification and ozonolysis then gave **74**. Methylation of **74** followed by Grignard addition, protection and reduction produced **75**. In order to synthesise tetra-substituted diene **76**, he used the Krief-Reich reaction.[56] This sequence resulted in the formation of diene **76**, required for the Diels-Alder cycloaddition. Jenkins' Diels-Alder reaction with **76** required a 24 h reaction time using a strong Lewis acid to give 56% yield of the final product **77**.

1.5.4. Synthesis of taxadiene

The simplest taxane with a 6.8.6 ring system is taxadiene **17**. There are two published syntheses of taxadiene **17**. In 1995, Williams and co-worker published their first paper on the total synthesis of taxadiene.[57]

Williams' synthesis of taxadiene

Williams' synthesis is racemic and his synthesis was based on the work previously carried out by Jenkins using the Diels-Alder approach to form A and B rings (Scheme **15**).[52-55] He started his synthesis with bicyclic enone **78**, easily prepared from the condensation product of 2-methylcyclohexanone and methyl vinyl ketone. Protection of the secondary alcohol, followed by a reduction, a Baeyer-Villiger oxidation and treatment with sodium methoxide gave ester **79**. Protection of **79** followed by reduction, vinyl Grignard addition and oxidation gave enone **80**. A Krief-Reich reaction on **80** then gave tetra-substituted diene **81**.[56] Reduction of **81**, followed by vinyl Grignard addition and oxidation gave Diels-Alder precursor **82**. The Diels-Alder cycloaddition of **82** in the presence of a Lewis acid synthesised the taxane ring system **83**. A subsequent radical deoxygenation, deprotection and oxidation then produced ketone **84**. The ketone was then used to produce both taxadiene isomers *via* a Grignard addition and elimination to give **17**, or a Wittig olefination to give **18**.



Scheme 15: Williams' synthesis of taxadiene isomers **17** and **18**

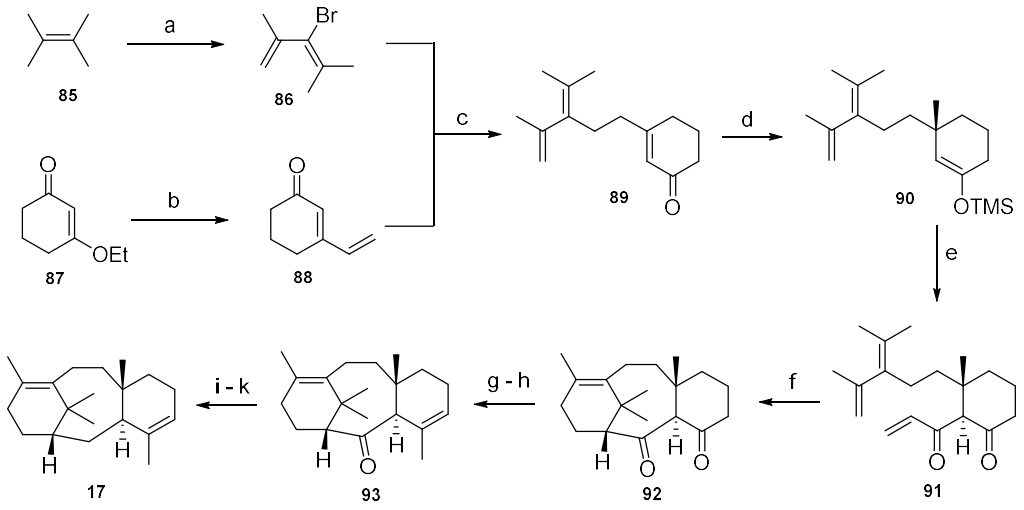
Reagents and conditions: **a**) TBSCl, imidazole, **b**) H_2, Pd/C, **c**) *m*CPBA, **d**) NaOMe. **e**) TBSCl, **f**) DIBAL, **g**) vinyl magnesium bromide, **h**) Dess-Martin periodinane, 65%. **i**) $Me_2C(SeMe_2)$, BuLi, quant., **j**) PI_3, Et_3N, 71% **k**) HF, 64%. **l**) $PhCH(OMe)_2$, PPTS, **m**) $LiAlH_4$, $AlCl_3$. **n**) Dess-Martin periodinane, 61%. **o**) vinyl magnesium bromide, quant. **p**) Dess-Martin periodinane, quant. **q**) 2 eq. $BF_3 \bullet Et_2O$, toluene, -23 °C, 48h, 28%. **r**) 6 eq. $BF_3 \bullet Et_2O$, toluene, 3 °C, 60%. **s**) $LiAlH_4$, **t**) PhOCSCl, NaHMDS, **u**) Bu_3SnH, AIBN, 53%, **v**) Na, NH_3. **w**) Dess-Martin periodinane, 56%. **x**) Ph_3PMeI, ^nBuLi, 80%. **y**) MeMgBr, $CeCl_3$, quant., **z**) Burgess reagent, 60%.

The advantage of using the Diels-Alder approach allows the formation of A and B rings with limited oxidation sites as compared to previous syntheses where a series of oxidations were involved. However, this route is quite long with 24 steps involved. Therefore, a shortened route is required to access both isomers.

Baran's synthesis of taxadiene

Baran and co-workers published their synthesis of taxadiene **17** with ketone **93** as an intermediate.[58,59] They also used the Diels-Alder approach to form A and B rings (Scheme **16**). They started their synthesis with tetramethylethylene **85**, which was reacted with bromoform, followed by rearrangement then gave bromodiene **86**. The addition of vinyl Grignard to ethoxy enone **87** then affords vinyl enone **88** in good

yield. Coupling of bromodiene **86** with vinyl enone **88** in a 1,6-conjugate addition gave **89**, resulting in the formation of diene and C ring of taxadiene. Subsequently, a 1,4-conjugate addition using trimethyl aluminium, followed by the treatment of TMSCl gave silyl enol ether **90**. Asymmetry was achieved by using a ligand developed by Alexakis.[60] A Mukaiyama aldol with acrolein was then employed to install the dienophile followed by oxidation and thus completed the formation of Diels-Alder precursor **91**. Baran applied the slow dilute addition of the Lewis acid within the Diels-Alder reaction to obtain **92** with 49% yield. An enol triflate formation, followed by a Negishi coupling with dimethylzinc gave taxadienone **93** in 84% yield. Taxadienone **93** was then successfully deoxygenated from a dissolving metal reduction of the corresponding acetate, to give taxadiene **17** in 18% overall yield.



Scheme 16: Baran's synthesis of taxadiene

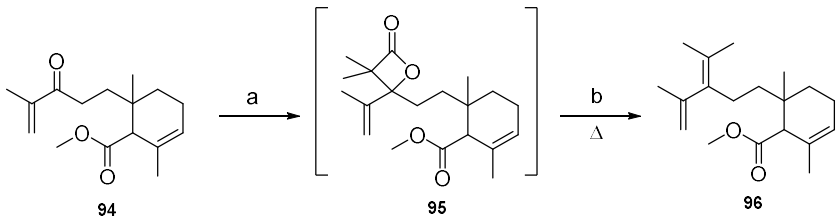
Reagents and conditions: **a**) i) ^{t}BuOK, $CHBr_3$ ii) $PhNMe_2$, 67%. **b**) vinyl magnesium bromide, 75%. **c**) i) ^{s}BuLi, ii) TMSCl, CuBr•DMS, 86%. **d**) i) Me_3Al, CuTC ii) TMSCl, 93%. **e**) i) $Gd(OTf)_3$, acrolein ii) CrO_3, 85% **f**) BF_3 •Et_2O, 47%. **g**) $PhNTf_2$, KHMDS **h**) Me_2Zn, $Pd(PPh_3)_4$, 84%. **i**) $LiAlH_4$, 72%. **j**) AcCl, 89%. **k**) Na, ^{t}BuOH, 82%.

Although Baran's synthetic route is enantioselective, the use of unsustainable starting material **85** is undesirable. Baran's Diels-Alder reaction used fewer approach than the synthetic methodology developed by Williams and the route has even been optimised for gram-scale. Although 15 chemical transformations have been involved to synthesise taxadiene, some steps were carried out without purification, resulting in the synthesis of taxadiene in overall 10 steps.

1.6. Project aims and retrosynthetic analysis

This project aims to develop a scalable route for the synthesis of low oxidation state taxanes from the renewable starting material, farnesol **98**. Hayes' previous synthesis towards low oxidation state taxanes originated from a mixture of *E/Z* isomers of farnesol, producing cyclised product in a 2:1 mixture of *trans*:*cis* isomers. We aim to investigate whether this diastereoselectivity will change if we use a single isomer of farnesol. Therefore, in this project we will be using *E*,*E* farnesol to study its behaviour in the key cyclisation step.

The installation of tetra-substituted alkene **96** is challenging. In this project, we also want to investigate and further explore the novel indium Reformatsky reaction, for the formation of tetra-substituted alkene (Scheme **17**) and to identify the resulting impurities.

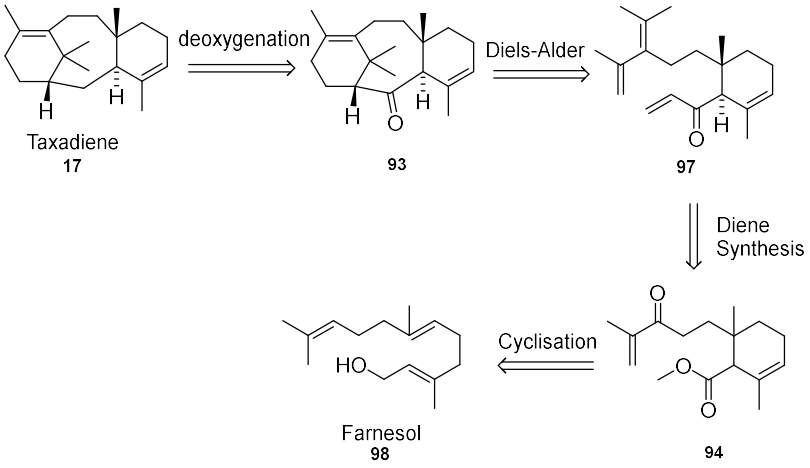


Scheme 17: Installation of diene using a Reformatsky reaction

Reagents and conditions: **a**) Ethyl-α-bromoisobutyrate, Indium, DMF. **b**) SiO_2, toluene, reflux.

We also aim to confirm that the Diels-Alder approach is low-yielding. However, prior to this, the route must be validated for its reliability and scalability. Therefore, this project will investigate the robustness of the synthetic route already developed in the Hayes group and will also focus on the optimisation of the existing route for the synthesis of novel and naturally occurring low oxidation state taxanes.

The planned retrosynthesis involves the use of the Diels-Alder cyclisation of **100** to form A and B rings. The Diels-Alder precursor would develop from the functionalisation of the C ring, which will be synthesised from the cyclisation of farnesol **98**, an inexpensive commercially available terpene obtained from plants. The use of farnesol **98** as the starting material would allow most of the carbon in taxadiene **17** to come from a green renewable source (Scheme **18**).

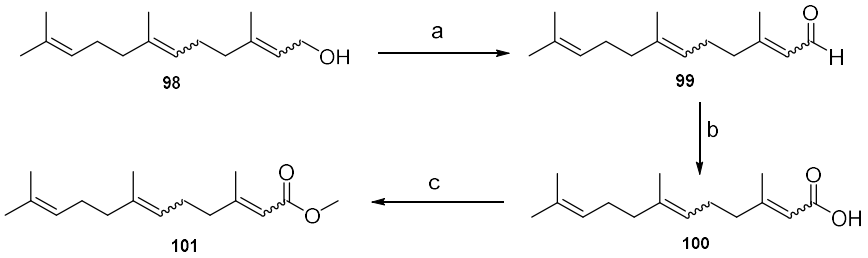


Scheme 18: Retrosynthetic analysis of taxadiene

2. RESULTS AND DISCUSSION

2.1. Synthesis of methyl farnesoate

Our route to access low oxidation state taxanes began following the work already carried out within the Hayes group which involved the use of *E/Z* farnesol **98**.[21,20] To access the route and to bring the material forward we used commercially available starting material *E/Z* farnesol **98**. Oxidation and protection of *E/Z* farnesol **98** produced *E/Z* methyl farnesoate **101** in three steps (Scheme **19**).



Scheme 19: Formation of *E/Z* methyl farnesoate **101** from *E/Z* farnesol **98**

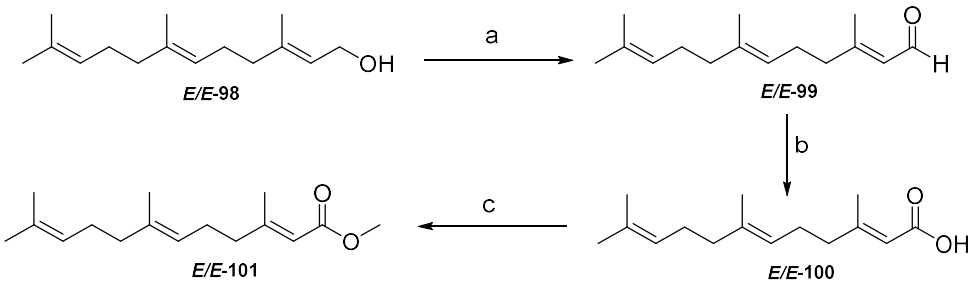
Reagents and conditions: **a**) MnO_2, 20 eq., CH_2Cl_2, r.t., 18 h. **b**) $NaH_2PO_4.2H_2O$, 4 eq. $NaClO_2$, 6 eq., 2-methyl-2-butene, ^tBuOH: H_2O (1:1), r.t., 18 h. **c**) CH_3I, K_2CO_3, 1.5 eq., DMF, r.t., 18 h, 74% over 3 steps.

The first step of synthesis involved the oxidation of *E/Z* farnesol **98** with manganese dioxide, a selective mild oxidant, in dichloromethane to afford *E/Z* farnesal **99**. *E/Z* farnesal **99** was subsequently oxidised using a Pinnick oxidation to give *E/Z* farnesoic acid **100**. These two reactions were carried out without purification. Esterification of **100** by methyl iodide in DMF affords *E/Z* methyl farnesoate **101** over 3 steps in 74% yield.[20] As we already know that *E/Z* methyl farnesoate **101** is a mixture of isomers,[20,21] and due to the presence of overlapping signals in the ^{1}HNMR spectrum, it is challenging to determine the exact ratio of isomers. However, by comparing the

spectroscopic data from *E/Z* methyl farnesoate **101** with the data from *E,E*-methyl farnesoate ***E/E*-101**, we estimated that *E/E* methyl farnesoate is the major isomer in the mixture of *E/Z* methyl farnesoate **101**.

2.1.1. *E,E*-methyl farnesoate

To study the effect of the double bonds' stereochemistry of methyl farnesoate in the key cyclisation step, a single isomer of *E,E*-methyl farnesoate ***E/E*-101** was synthesised. Commercially available *E,E*-farnesol ***E/E*-98** was used to synthesise *E,E*-methyl farnesoate ***E/E*-101**, following the same methodology used for the preparation of *E/Z* methyl farnesoate **101**. *E,E*-farnesol ***E/E*-98** was oxidised to *E,E*-farnesal ***E/E*-99** using manganese oxide, followed by the oxidation of *E,E*-farnesal ***E/E*-99** into *E,E*-farnesoic acid ***E/E*-100** and subsequently the protection of *E,E*-farnesoic acid ***E/E*-100** to *E,E*-methyl farnesoate ***E/E*-101** using methyl iodide in good yield over 3 steps (Scheme **20**).



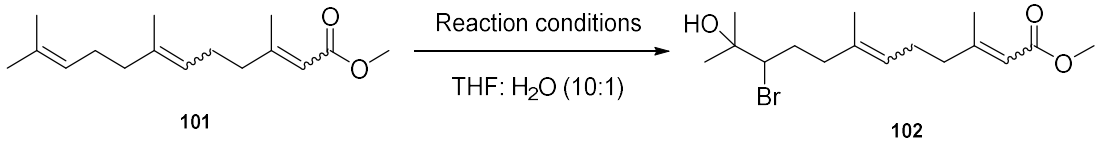
Scheme 20: Formation of *E,E*-methyl farnesoate ***E/E*-101** from *E,E*-farnesol ***E/E*-98**

Reagents and conditions: **a**) MnO_2, 20 eq., CH_2Cl_2, r.t., 18 h. **b**) $NaH_2PO_4.2H_2O$, 4 eq., $NaClO_2$, 6 eq., 2-methyl-2-butene, ^tBuOH: H_2O (1:1), r.t., 18 h. **c**) CH_3I, K_2CO_3, 1.5 eq., DMF, r.t., 18 h, 70% over 3 steps.

Pleasingly, the reaction gave *E,E*-methyl farnesoate ***E/E*-101** as a single isomer in 70% yield over 3 steps.

2.2. Synthesis of the bromohydrin and C ring

With the formation of *E/Z* methyl farnesoate **101**, the next step was the protection of terminal double bond to give *E/Z* bromohydrin **102** (Scheme **21**), before cyclisation with phosphoric acid to form the C ring of taxanes. Subjecting *E/Z* methyl farnesoate **101** to the original condition previously used in the Hayes group (Table **1**, entry **5**) found that the crude *E/Z* bromohydrin contained a by-product **103** (Scheme **22**) and also gave a low yield.



101 102

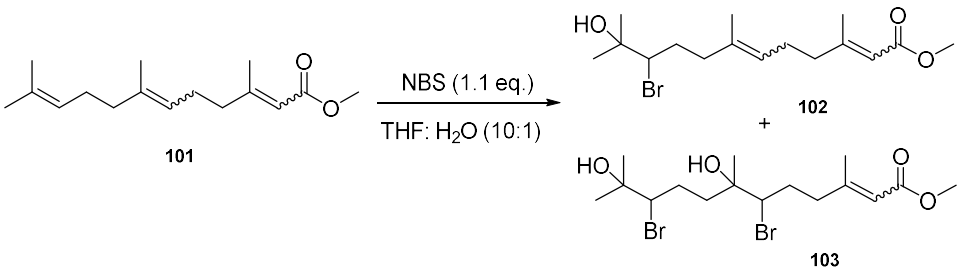
Scheme 21: Optimisation of bromohydrin **102**

Table 1: Optimisation of bromohydrin **102** formation

Entry	Reaction conditions	Reaction Concentration (M)	Time / h	Yield[a] / %	Recovered SM / %
1	NBS (0.97 eq.)	0.270	5	12	30
2	NBS (1 eq.)	0.276	5	56	26
3	NBS (1 eq.), (*conc*)	0.558	5	48	22
4	NBS (1 eq.)	0.276	18	38	23
5	NBS (1.1 eq.)	0.280	5	31	17

[a]isolated yield

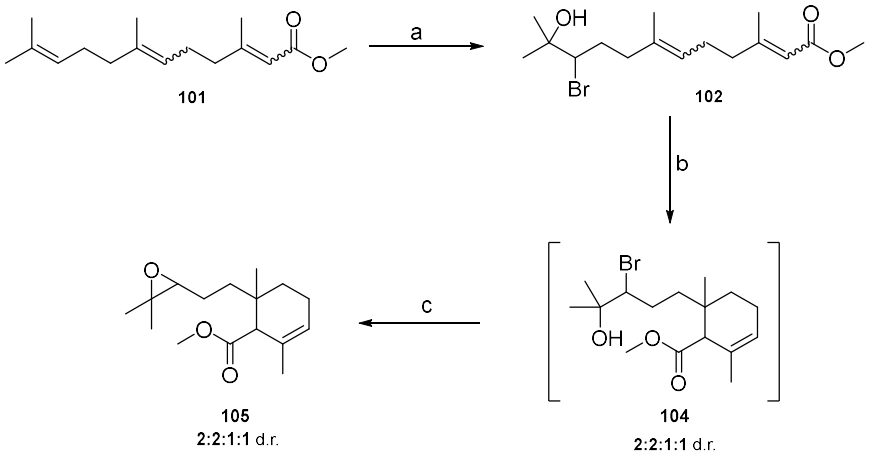
The formation of by-product **103** was suggested to be due to the over-addition of NBS. To prevent the formation of by-products and to optimise the reaction a series of reaction conditions were tested. By varying the reaction concentration and equivalents of NBS, it was found that using 1 eq. of NBS produced the highest yield of 56% (Table **1**, entry **2**).



Scheme 22: Formation of by-product

Purification of bromohydrin **102** was challenging possibly due to its decomposition on silica. This was solved by using a short column to minimize the interaction of **102** with silica.

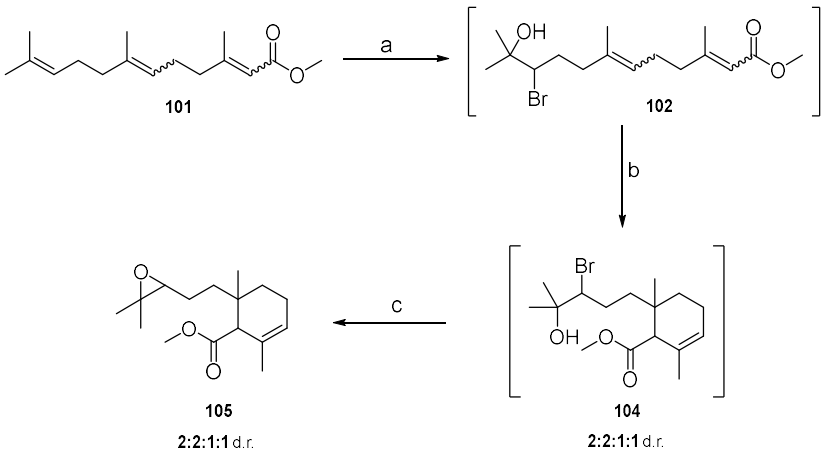
Following the method developed by Schwartz and Willbrand, *E/Z* bromohydrin **102** was treated directly with concentrated phosphoric acid to give cyclised bromohydrin **104**.[61] Cyclised bromohydrin **104** is 2:1 mixture of *trans:cis* cyclohexene isomers and also each one of these is a 1:1 mixture of alcohol diastereoisomers. Crude cyclised bromohydrin was then treated with potassium carbonate in methanol to afford epoxide **105**, with a yield of 48% over 2 steps (Scheme **23**).



Scheme 23: Cyclisation and epoxidation of methyl farnesoate using pure bromohydrin

Reagents and conditions: **a**) NBS, 1 eq., THF:H_2O (10:1), r.t., 5 h, dark, 55%. **b**) H_3PO_4 (15 M), r.t., 5 h. **c**) K_2CO_3, 2.3 eq., CH_3OH, r.t., 18 h, 48% over 2 steps. 2:2:1:1 d.r.

Attempting to increase the yield of cyclisation reaction, the duration of the reaction was increased from 5 h to 22 h, however, this had a negligible effect on the obtained yield. Pleasingly, it was discovered that subjecting crude bromohydrin **102** directly to the phosphoric acid induced cyclisation gave a 40% yield of epoxide **105** over 3 steps (Scheme **24**), an increased yield from 27% over 3 steps when purified bromohydrin **102** was treated with the same reaction conditions (Scheme **23**). It is important to note that the presence of a trace amount of phosphoric acid in the crude cyclised bromohydrin **104** dramatically decreased the yield of epoxide **105** in the final step, which was easily removed by a further aqueous workup.

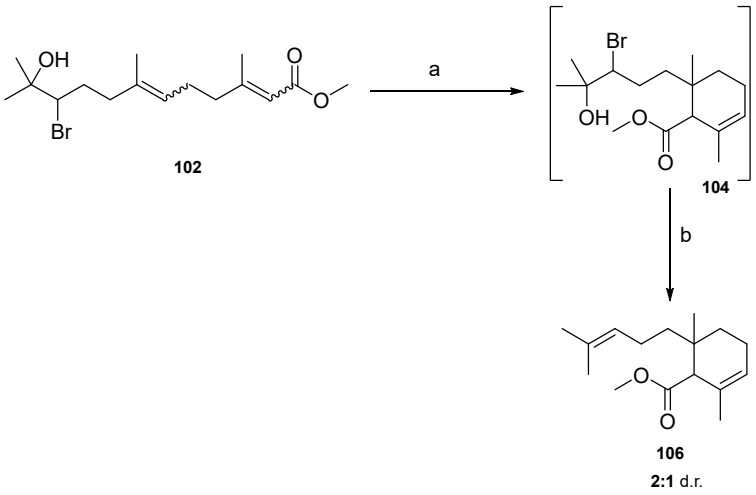


Scheme 24: Cyclisation and epoxidation of methyl farnesoate using crude bromohydrin

Reagents and conditions: **a**) NBS, 1 eq., THF:H_2O (10:1), r.t., 5 h, dark. **b**) H_3PO_4 (15 M), r.t., 5 h. **c**) K_2CO_3, 2.3 eq., CH_3OH, r.t., 18 h, 40% over 3 steps. 2:2:1:1 d.r.

In their original procedure, Schwartz and Willbrand used hexane as a co-solvent with phosphoric acid for the cyclisation step.[61] To study the effect of hexane on cyclisation, two parallel reactions were designed: one with hexane and one without hexane and the products were purified. It was found that the yield of epoxide **105** from cyclised bromohydrin was increased by 4% when hexane was used as a co-solvent. Therefore, we decided to use hexane as a co-solvent in the cyclisation step. As cyclised bromohydrin **104** was a mixture of 4 diastereoisomers, it was hard to determine the stereochemistry. Furthermore, bromohydrins **102** and **104** were unstable on the silica due to the presence of the bromine group, which could affect the yield of epoxide **105**. Therefore, we decided to synthesise alkene **106** from *E/Z* bromohydrin **102**, following the method developed by Schwartz and Willbrand,[61] so that we could establish the *cis*:*trans* ratio of the cyclohexene fragment. Alkene **106** could be easily purified through column chromatography which would make it easy to compare the

yields of epoxide **105** and alkene **106** (Scheme **25**). Following the cyclisation, crude cyclised bromohydrin **104** was then reduced using zinc dust and acetic acid, giving ester **106**. The yield of alkene **106** was the same as the yield of epoxide **105**, however, the reaction did not go to completion. Previously in the group, they managed to separate the *cis* and *trans* isomers of alkene **106**[21] however, by trying the solvent system they used, we did not achieve a complete separation through column chromatography, however, by comparing the data with previously published data in the group the ratio of *trans:cis* isomer is 2:1.[21] As this alkene **106** was not the main focus of the project, so we proceeded with the synthetic work towards the epoxide **105**, to access low oxidation state taxanes.

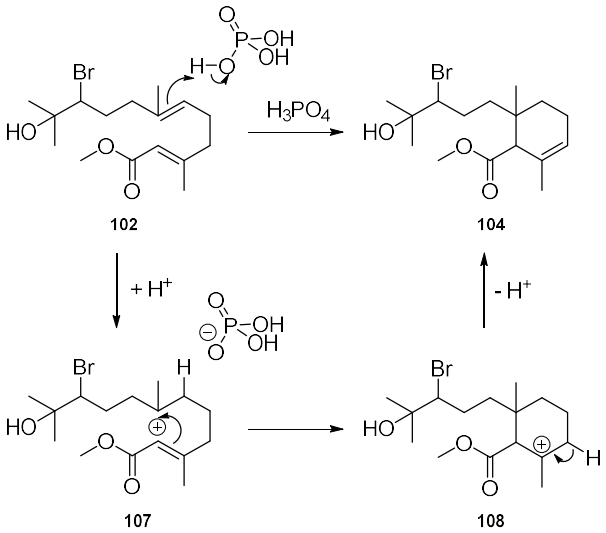


Scheme 25: Formation of a cyclised alkene

Reagents and conditions: **a**) H_3PO_4 (15 M), r.t., 5 h. **b**) Zn, 10 eq., AcOH, Et_2O, reflux, 18 h, 41% over 2 steps.

With the formation of epoxide **105**, the C ring of taxane was obtained in reasonable yield and all the 15 carbons from *E/Z* farnesol **98** were preserved. The epoxide **105** was a 2:2:1:1 mixture of diastereoisomers, with a 2:1 ratio of *trans*:*cis* cyclohexene

isomer and also each one of these was a 1:1 mixture of epoxide diastereoisomers. Although it should be noted that the epoxide stereocenter was irrelevant as this would be removed later in the synthesis. This ratio of isomers was confirmed by comparing the data with previously unpublished data in the group.[21] A proposed mechanism for cyclisation is given below (Scheme **26**).

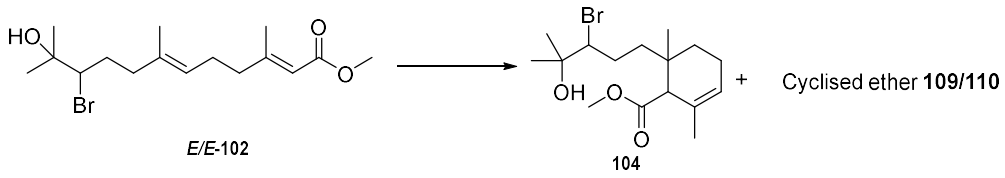


Scheme 26: Proposed mechanism of cyclisation with phosphoric acid

It was proposed that this reaction proceeds through protonation of the most electron-rich double bond in **102**, producing a carbocation intermediate **107**. The conjugate base of the catalyst (the anion) may remain in close proximity to the substrate (cation **107**) to allow the addition of second alkene to the carbocation. The addition of the second alkene to this carbocation affords a second tertiary carbocation **108**. This can then lose a proton to give the final cyclised product **104**.

2.2.1. Synthesis of C ring from *E,E*-methyl farnesoate

With the synthesis of epoxide **105** from *E/Z* methyl farnesotae **101** attention was then turned to synthesising epoxide from *E/E* methyl farnesoate **E/E-101**, to study the effect of a single isomer in the cyclisation step. *E,E*-methyl farnesoate **E/E-101** was subjected to the optimised conditions used for *E/Z* methyl farnesoate **101** and was converted into *E/E* bromohydrin ***E/E*-102** using NBS in (10:1) THF:H_2O resulting in the protection of terminal alkene (Scheme **28**). The crude bromohydrin ***E/E*-102** was then cyclised by concentrated phosphoric acid. Unfortunately, the yield of the reaction was very low, and it also formed a by-product **109/110** (Scheme **27**). Interestingly, this by-product was not present in the cyclisation step from *E/Z* methyl farnesoate **101**.



Scheme 27: Cyclisation of *E,E*-methyl farnesoate

Reagents and conditions: **a**) NBS, 1 eq., THF:H_2O (10:1), r.t., 5 h, dark. **b**) H_3PO_4 (15 M), r.t., 5 h.

We could not establish from spectroscopic data whether this cyclised ether was **109** or **110** (Figure **6**).

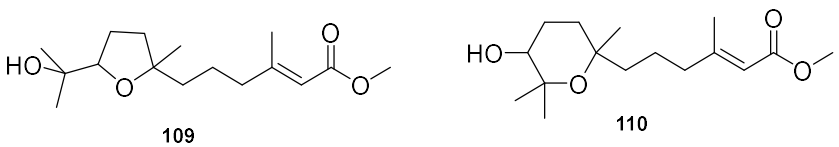
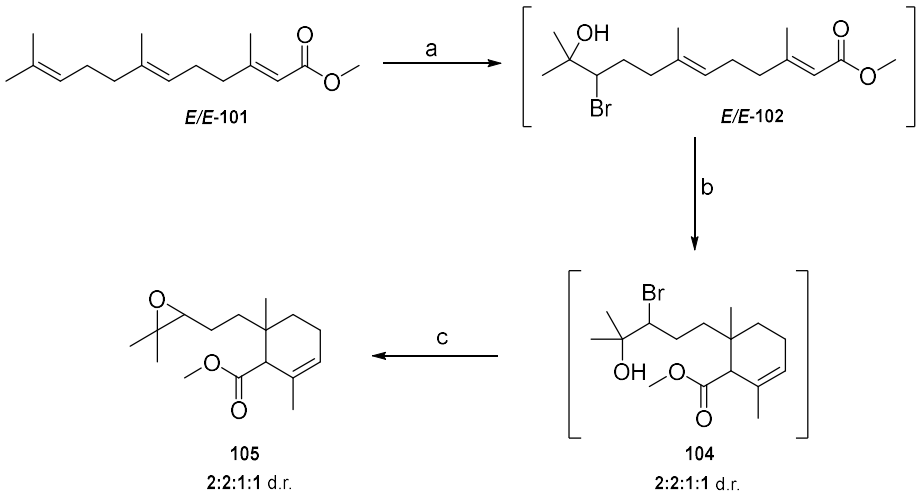


Figure 6: Possible structures of cyclised ether by-product

The reaction was optimised by increasing the time of the cyclisation step from 5 h to 22 h. It is postulated that the cyclised ether was produced due to the fact that the *E,E* isomer is slow to react in the cyclisation reaction.

The crude cyclised bromohydrin was then subjected to epoxidation using potassium carbonate (Scheme **28**).



Scheme 28: Formation of epoxide from *E,E*-methyl farnesoate

Reagents and conditions: **a**) NBS, 1 eq., THF:H_2O (10:1), r.t., 5 h, dark. **b**) H_3PO_4 (15 M), r.t., 22. **c**) K_2CO_3, 2.3 eq., CH_3OH, r.t., 18 h. 24% over three steps, 2:2:1:1 d.r.

The epoxide **105** was formed in an overall yield of 24% over 3 steps, which was low as compared to the yield of epoxide **105** from the *E/Z* isomer. When we compare the obtained data from this epoxide with the data of epoxide obtained from *E/Z* isomer, unfortunately, it was the same mixture of diastereoisomers (Figure **7**), meaning that the *E,E*-alkene geometry of the starting material gave no improvement on the stereochemical outcomes of the phosphoric acid-induced cyclisation reaction.

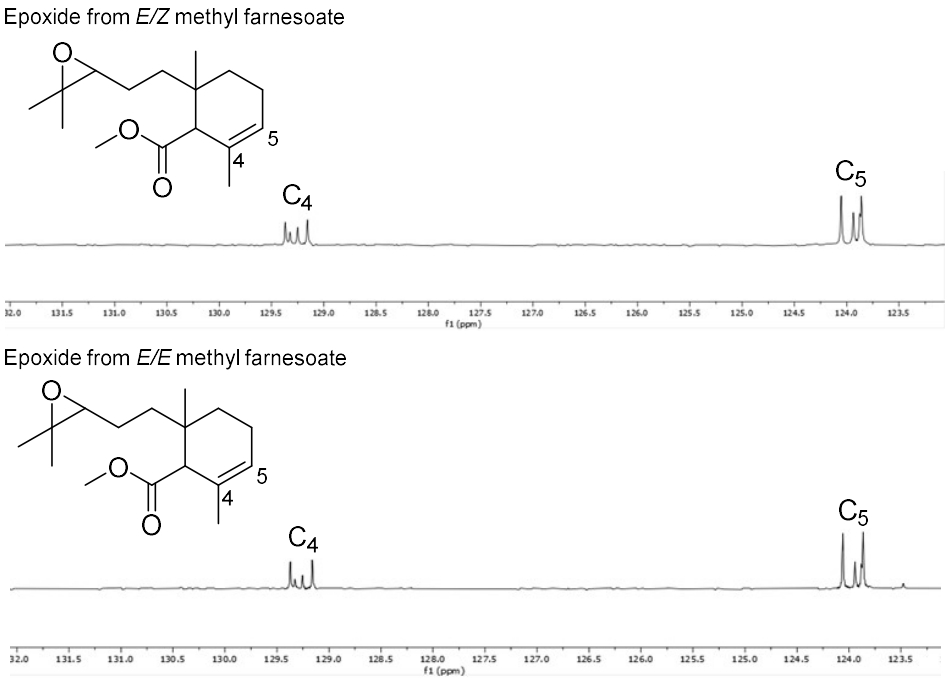


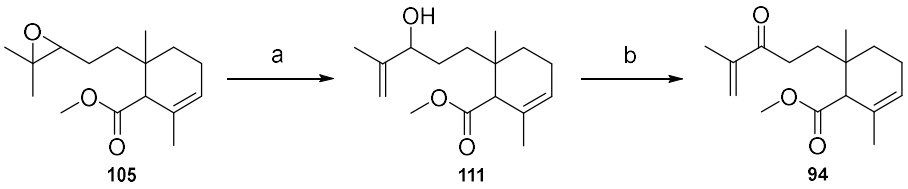
Figure 7: Carbon NMR for epoxide **105** highlighting signals for C4 and C5, indicating the same ratios of isomers

The yield of the epoxide **105** was lower from *E/E* methyl farnesoate **E/E-101** as compared to *E/Z* methyl farnesoate **101**, however, this could be improved if we use other isomers of methyl farnesoate. Unfortunately, at this stage we didn't have time to make the other geometrical isomers of methyl farnesoate, therefore, we decided to shift our interest to the original *E/Z* methyl farnesoate **101**.

2.3. Synthesis of enone 94

As the diastereoisomers were inseparable at this stage, epoxide **105** was taken forward as a mixture for the installation of diene. The next step involved the rearrangement of epoxide into allylic alcohol **111** using Yamamoto's reagent,[62] in an

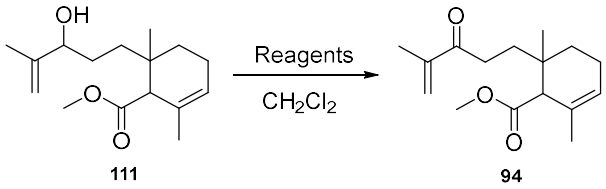
excellent yield of 93%, followed by oxidation of the allylic alcohol producing enone **94** (Scheme **29**).



Scheme 29: Formation of enone

Reagents and conditions: **a**) ^{n}BuLi, 3 eq., TMP, 3 eq., Et_2AlCl, 3 eq., toluene, 0 °C, 3 h, 93%. **b**) Dess-Martin periodinane, 2.1 eq., CH_2Cl_2, r.t., 2 h, 90%.

Initially, manganese dioxide was used to convert allylic alcohol **111** into enone **94**, however, the reaction required long durations and was low yielding (Scheme **30**). Different conditions were tried but unfortunately, it did not increase the yield of enone **94** (Table **2**, entries **1** and **2**). Similarly, Swern oxidation was also low-yielding and proceeded with the recovery of starting material (Table **2**, entry **3**). Therefore, Dess-Martin periodinane was applied to allylic alcohol **111**, synthesising enone **94** in an excellent yield of 90% (Table **2,** entry **4**).



Scheme 30: Optimisation of enone synthesis

Table 2: Optimisation of enone synthesis

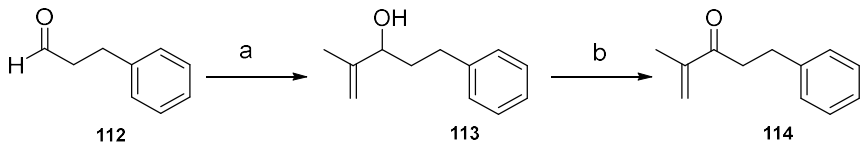
Entry	Reagents / conditions	Time / h	Yield[a] / %	Recovered SM / %
1	MnO_2, r.t.,	18	50	22
2	MnO_2, reflux	18	40	9
3	Swern, −78 °C	3	31	53
4	DMP, r.t.,	2	90	-

[a]isolated yield

While working with commercially available Dess Martin we were unable to separate the Dess Martin oxidation by-product from enone **94**, even when applying alternative work-up procedures. Upon further investigation, it was found that freshly produced Dess-Martin periodinane overcame the purification issue and produced enone **94** in an excellent yield of 90% (Table **2**, entry **4**).

2.4. Synthesis of the tetra-substituted diene 96

With the formation of enone **94**, the next step of the synthetic route was to convert the enone functionality into tetra-substituted diene. In order to access the reaction and to conserve our stock of enone **94**, we decided to use a model enone **114**, which was prepared from aldehyde **112** in good yield over two steps (Scheme **31**).



112 113 114

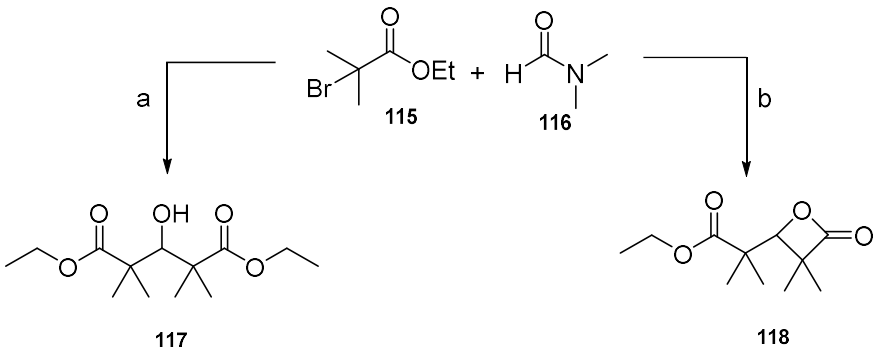
Scheme 31: Synthesis of model system

Reagents and conditions: **a**) isopropenylMgBr, THF, 0 °C, 2 h, 48%. **b**) Dess-Martin periodinane, 1.3 eq., CH_2Cl_2, r.t., 2 h, 90%.

A simple Grignard addition to aldehyde **112** using isopropenylmagnesium bromide at 0 °C, followed by oxidation of allylic alcohol **113** with Dess Martin periodinane allowed us to rapidly access enone **114** in good yield over two steps.

2.4.1. Reformatsky reaction

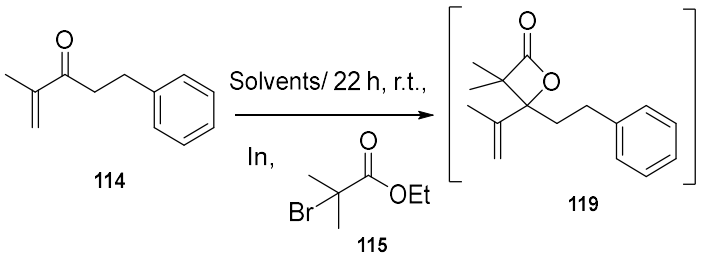
The resultant enone **114** was then subjected to an indium Reformatsky reaction to form β-lactone **119**. Trialling the reaction conditions previously used within the group,[21] unfortunately, produced β-lactone **119** in low yield and formed an unknown complex mixture of by-products, which were inseparable from β-lactone **119**. Numerous attempts were made to optimise the β-lactone formation: heating for 1 h at 80 °C followed by stirring at room temperature for 2 h, stirring for 1 h at room temperature followed by stirring for 2 h at 80 °C, as well as stirring overnight at room temperature were all assessed. The latter condition gave a reasonable yield but was still seen to produce unknown by-products. A detailed analysis of the crude β-lactone's NMR spectrum allowed the determination of the reaction's by-products, and it was found that the solvent (DMF) was responsible for the formation of the observed impurities. In order to investigate this, a control experiment involving ethyl α-bromoisobutyrate **115**, indium powder and DMF **116** without the addition of enone **114**, was performed which along with other impurities gave another β-lactone **118**. Pleasingly, we found that at elevated temperature the reaction gave β-lactone **118** as a by-product however, at room temperature it forms an alcohol **117** as a major by-product (Scheme **32**).



Scheme 32: By-products of indium Reformatsky reaction

Reagents and conditions: **a**) In, 2 h, r.t., **b**) In, 1 h, 80 °C, 2 h, r.t.

After determining and characterising the obtained impurities, once again we shifted our interest towards the optimisation of β-lactone **119**. In the original paper, Schick had used DMF:THF 1:2 ratio for his formation of β-lactone **119**.[63] As DMF was participating in the reaction and producing minor impurities, the use of various solvent systems were assessed (Scheme **33**). Varying ratios of DMF:THF were trialled, and it was discovered that a 1:2 ratio of THF:DMF gave the greatest conversion of β-lactone **119** (Table **3**, entry **5**).

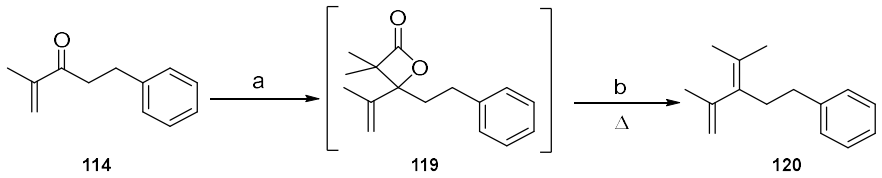


Scheme 33: Formation and optimisation of β-lactone

Table 3: Optimisation of β-lactone **119**

Entry	Solvents	Mass recovery / %	Products (isolated yield)/ * indicates ratio from crude ^{1}H NMR Spectrum)
1	DMF	Pure	**114** (12%), (61%) **119**
2	THF	117 (crude)	**114** (1.7: 1)*** 119**
3	THF:DMF (1:1)	140 (crude)	No reaction, (**RSM**), Unreacted **115***
4	THF:DMF (2:1)	144 (crude)	No reaction, (**RSM**), Unreacted **115***
5	THF:DMF (1:2)	129 (crude)	**114** (1: 9.4)*** 119**
6	DMF, **115** (1.5 eq.)	89 (crude)	(**RSM**), No formation of **119**

With the formation and optimisation of β-lactone **119**, the next step was the treatment of this crude lactone with silica to form diene **120** (Scheme **34**).[64]

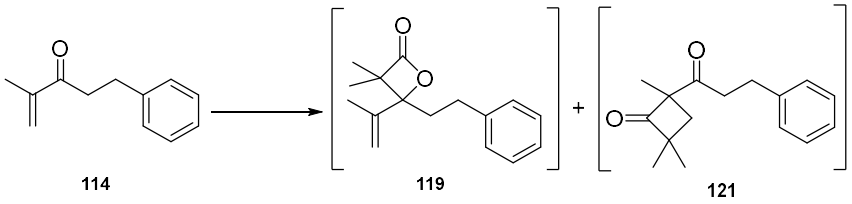


Scheme 34: Diene formation

Reagents and conditions: **a**) Ethyl-α-bromoisobutyrate, 2 eq., In, 2 eq., DMF: THF (2:1), r.t., 22 h. **b**) SiO_2, toluene, 110 °C, 4 h, 70% over two steps.

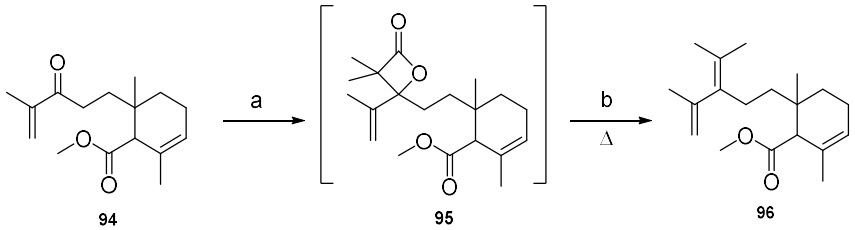
Previous research within the Hayes group performed the decarboxylation step in 1 h,[21,20] however, by using β-lactone **119** as a crude mixture, the reaction did not go to completion and give some unreacted β-lactone. To solve this, we increased the time of the decarboxylation step from 1 h to 4 h. Pleasingly this gave an excellent yield (70%) of the desired diene **120**, from which the by-products were easily removed by

column chromatography. The reaction also yielded a small amount of unreacted enone **114** and the undesired cyclobutanone **121** resulted from competitive 1,4 addition (Scheme **35**). Pleasingly, it was found that the optimal conditions for the formation of diene **120** over two steps were from the DMF:THF 2:1 solvent system, followed by the decarboxylation of crude β-lactone for 4 h.



Scheme 35: Formation of cyclobutanone

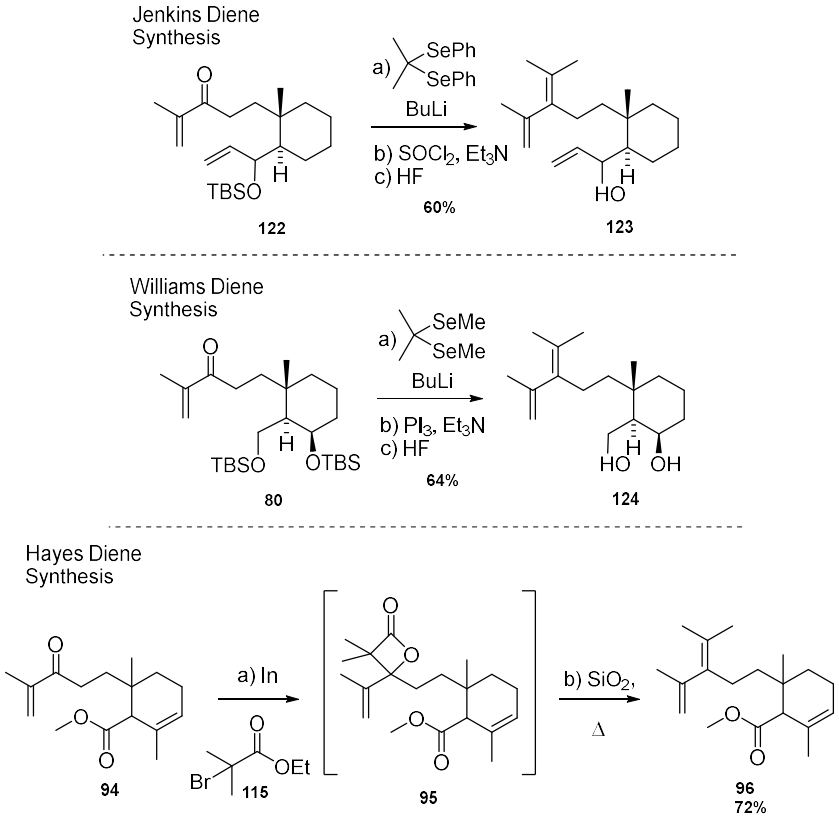
After finding the optimal reaction conditions for the model diene system, attention was turned to the synthesis of diene **96**. Subjecting the enone **94** to the obtained optimised conditions produced a low yield of 38% over 2 steps, along with 15% recovery of starting material. Therefore, it was decided to use a different condition in order to improve the yield, by stirring the enone **94** in DMF at 80 °C for 30 min, followed by 3 h at room temperature to afford β-lactone **95**, which on treating with silica at reflux for 1 h, produced diene **96** in 41% yield over 2 steps (Scheme **36**), along with 16% recovery of starting material. This condition had a negligible effect on the yield of diene **96** however, it reduced the time required for β-lactone formation from 22 h to 3 h.



Scheme 36: Synthesis of diene **96**

Reagents and conditions: **a**) Ethyl-α-bromoisobutyrate, 2 eq., In, 2 eq., DMF, 80 °C to r.t., 3 h. **b**) SiO_2, toluene, 110 °C, 1 h, 41% over two steps.

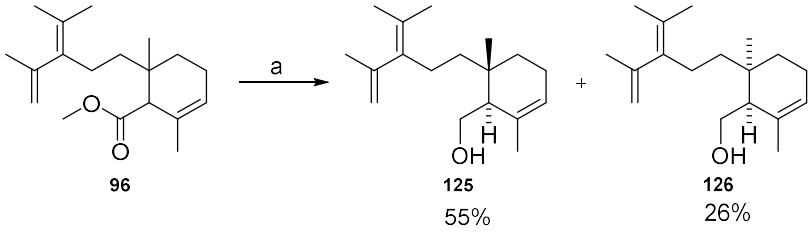
This resulted in the formation of tetra-substituted diene **96** through a novel indium Reformatsky-decarboxylation sequence. This was a significant improvement over the Krief-Reich reaction used by Williams and Jenkins that required toxic selenium reagents (Scheme **37**).



Scheme 37: Williams and Jenkins Krief-Reich reactions and Hayes Reformatsky-decarboxylation approach to tetra-substituted diene **96**

2.5. Synthesis of dienophile 97

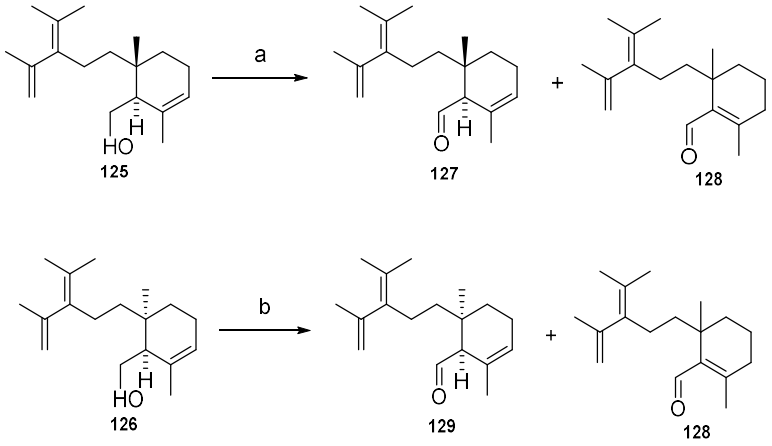
Having developed a robust synthesis of diene **96**, the next task was the installation of the dienophile. Reduction of ester **96** with DIBAL-H gave *trans* alcohol **125** and *cis* alcohol **126** in good yields. Pleasingly, the alcohol diastereoisomers **125** and **126** were separable by column chromatography (Scheme **38**).



Scheme 38: Reduction of ester **96**

Reagents and conditions: **a**) DIBAL-H, CH_2Cl_2, 0 °C, 2.5 h.

Both these diastereomers could lead to taxanes of interest, the natural with *trans* chemistry and unnatural with *cis* chemistry. To add the last two carbon atoms in the taxane skeleton and obtain the Diels-Alder precursors, alcohols **125** and **126** were oxidised using Swern oxidation producing the desired aldehydes **127** and **129** in good yields of 64% and 55% respectively. Interestingly, we noticed that Swern oxidation was also producing conjugated aldehyde **128**, possibly *via* isomerisation of aldehydes **127** and **129** under basic conditions (Scheme **39**).

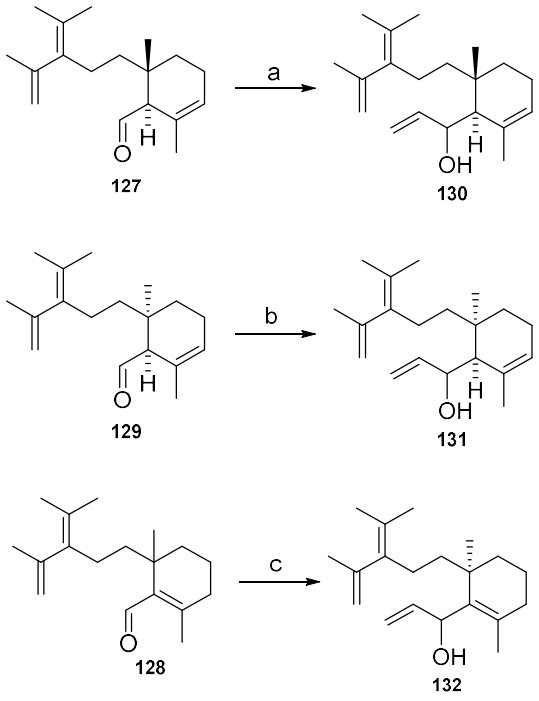


Scheme 39: Oxidation of alcohol **125** and **126**

Reagents and conditions: **a**) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 3 h, (**127**) 64%, (**128)** 2%. **b**) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 3 h, (**129**) 55%, (**128**) 13%.

Cis alcohol **128** was difficult to handle as one of the reactions converted all of the *cis* alcohol **128** into conjugated aldehyde **128** in 61% yield with no formation of *cis* aldehyde **129**.

A Diels-Alder cyclisation of taxane precursor with a double bond in the 3(4) position as the conjugated aldehyde **128**, has not been reported in the literature. Therefore, we decide to subject conjugated aldehyde **128** to Grignard addition along with aldehydes **127** and **129**. Grignard addition to the *trans* aldehyde **127** and *cis* aldehyde **129** gave allylic alcohols **130** and **131** (stereochemistry undetermined) in 87% and 36% yields respectively (Scheme **40**).

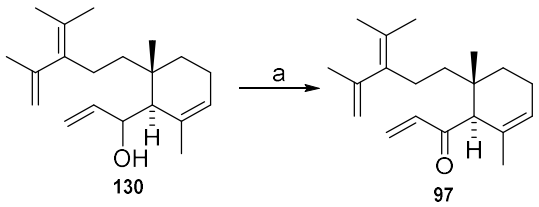


Scheme 40: Grignard addition to aldehydes **127**, **129** and **128**

Reagents and conditions: **a**) vinyl magnesium bromide, THF, −78 °C, 2 h, 87%. **b**) vinyl magnesium bromide, THF, −78 °C, 2 h, 36%. **c**) vinyl magnesium bromide, THF, −78 °C, 2 h, 4%.

However, the conjugated aldehyde **128** only gave a 4% yield of allylic alcohol **132** (Scheme **40**), possibly due to the impurities in the starting material.

Due to the small quantities of *cis* alcohol **131** and alcohol **132** we decided to stop working on them, and thus we took *trans* alcohol **130** forward and subject it to the subsequent Swern oxidation, which produced enone **97** in a good yield of 68% (Scheme **41**), along with 25% recovery of starting material.

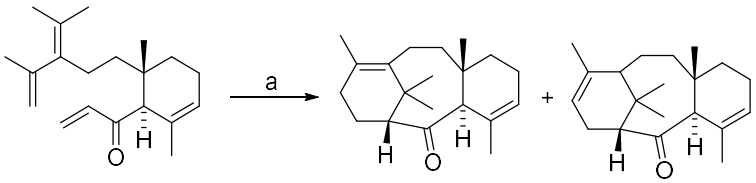


130 97

Scheme 41: Synthesis of Diels-Alder precursor

Reagents and conditions: **a**) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 3 h, 85%.

With the formation of enone **97**, the next step was to use a Diels-Alder reaction to form taxadienone **93**. To avoid intermolecular reaction, we decided to keep the overall concentration of the reaction very low (0.004 M). The Diels-Alder precursor, enone **97** was then added slowly by using a syringe pump to a dilute solution of boron trifluoride etherate which gave the desired *trans* taxadienone **93** in 31% yield, along with 11% recovery of starting material (Scheme **42**).



97 93 133

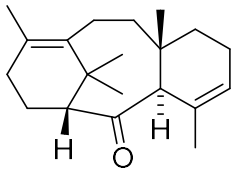
Scheme 42: Synthesis of *trans* taxadienone **93**

Reagents and conditions: **a**) $BF_3 \bullet Et_2O$ (3.65 eq.), toluene, 0 °C, 6 h, 35%.

The reaction also gave a small amount of **133**, possibly due to the isomerisation of taxadienone **93** under the Lewis acidic conditions. Repeating the reaction under the same conditions gave nearly the same yield, showing that the yield is easily reproducible.

3. CONCLUSIONS AND FUTURE WORK

In conclusion, many of the original aims of this work were achieved. Having established a successful synthetic route towards low oxidation state taxanes, starting from the commercially available and renewable *E/Z*-farnesol **98**, taxadienone **93** was efficiently synthesised (Figure **8**).



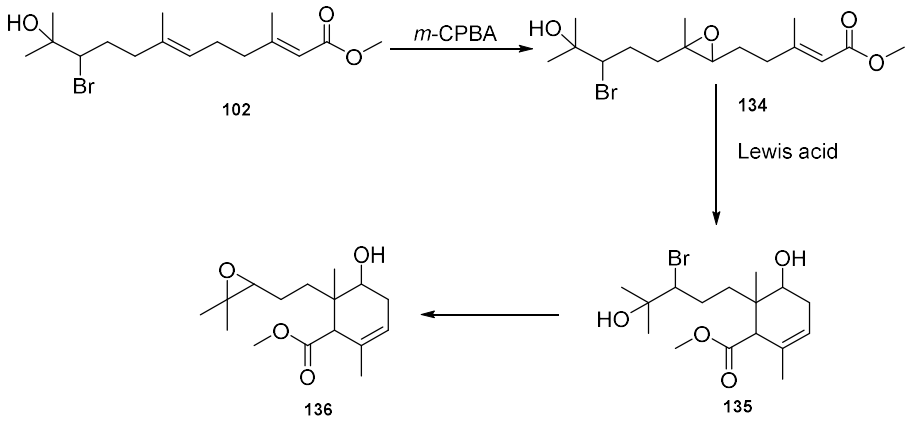
93

Figure 8: Taxadienone

During the course of this synthesis, a new method for the conversion of enone **94** to tetra-substituted diene **96** was developed. The successful high-yield formation of tetra-substituted diene **96** through a novel indium Reformatsky-decarboxylation sequence is preferable over the Krief-Reich reaction the only other alternative, using toxic selenium reagents.

An approach using *E,E*-farnesol was attempted, however, the same diastereomeric ratio was obtained, when compared with epoxide from *E/Z*-farnesol, in the phosphoric acid catalysed cyclisation step. The other isomers of methyl farnesoate could be synthesised to access their behaviour in the key cyclisation step.

Future work in this area would involve the formation of epoxide **134**, followed by cyclisation to determine the diastereomeric ratio of the cyclised product (Scheme **43**).



Scheme 43: Epoxidation followed by cyclisation approach

This could be done by reacting bromohydrin **102** with *m*-CPBA to form epoxide **134**, which could then be treated with Lewis acid to obtain the cyclised product **135**.

4. EXPERIMENTAL

4.1. General experimental

All the starting materials were obtained from commercial suppliers and were used without further purification unless otherwise stated. Anhydrous THF and toluene were obtained from a solvent purification system. Anhydrous DMSO was obtained from commercial suppliers. DCM was freshly distilled from calcium hydride under the lab atmosphere. Tetramethylpiperidine and triethylamine were distilled from calcium hydride under reduced pressure. DMF was distilled under reduced pressure from calcium sulphate and stored under an argon atmosphere before use. Pyridine was distilled from potassium hydroxide under an argon atmosphere. The concentration of *n*-butyllithium was determined by titration, under argon, against a 0.1 M solution of *N*-benzylbenzamide (211 mg, 1.00 mmol) in THF (10 mL). All reactions were carried out in oven-dried glassware under an argon atmosphere. Petrol refers to petroleum ether fraction with a boiling point between 40–60 °C. Ether refers to diethyl ether. Water refers to deionised water and was used for the preparation of all the aqueous solutions. Saturated brine refers to an aqueous saturated solution of sodium chloride. Analytical thin layer chromatography was carried out using Merck silica gel pre-coated sheets SIL G/UV254, which were visualised under UV light before staining with either an acidic solution of vanillin in ethanol or basic potassium permanganate. Column chromatography was carried out using a stationary phase of Merck silica gel 60, 35-70 μm particles, with the eluent specified.

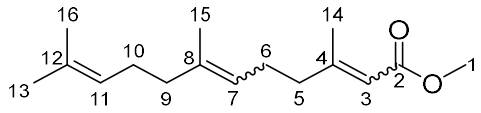
Infrared spectra were recorded on a Bruker ALPHA FT-IR spectrometer. Characteristic signals are quoted as wavenumber over the range of 4000 to 400 cm^{-1}.

NMR spectra were recorded on either a Bruker AV 400 MHz, AV(II) 400 MHz, AV(III) 400 HD MHz, or AV 500 MHz NMR spectrometer. Spectra were obtained at 298 K as a dilute solution in a deuterated solvent. The spectra were recorded on the δ scale in ppm referenced to chloroform ($CDCl_3$: δ_H 7.26, δ_C 77.2). All Assignments were made with the aid of DEPT sequences and correlation techniques such as COSY, HMQC, HMBC. The multiplicity of each signal is designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet; app, apparent; br, broad. Coupling Constants, *J* values are reported in Hertz (Hz) to one decimal place.

High resolution mass spectra (HRMS) were routinely recorded on a MicroTOF 61 mass spectrometer using electrospray ionisation (ESI) in both positive and negative modes. The compound nomenclature was generated using the software Chemdraw 19.1. When available, trivial names were used for simple compounds. The atom numbering system used in the description of ^{1}H NMR spectra aims at giving a clear description of peak assignments and does not always reflect the systematic numbering given in the compound name.

4.2. Experimental procedure

<u>*E/Z* methyl Farnesoate (101)</u>

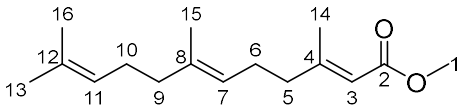


To a stirring solution of *E/Z* farnesol **98** (7.00 g, 31.5 mmol, 1 eq.) in anhydrous CH_2Cl_2 (79 mL), activated manganese dioxide (54.6 g, 628 mmol, 20 eq.) was added. The

reaction mixture was stirred at room temperature for 18 h and was then filtered through celite using ether (150 mL) and the filtrate was concentrated *in vacuo* to give crude *E/Z* farnesal as a colourless oil (6.70 g, 30.5 mmol), which was used in the next step without further purification. Purity determined by TLC, R_f 0.46 (1:4, ether:pentane). Sodium dihydrogen orthophosphate dihydrate (19.5 g, 125 mmol, 4 eq.) and 2-methyl-2-butene (20.5 mL) were then added to a stirring solution of crude *E/Z* farnesal (6.70 g, 30.5 mmol, 1 eq.), in ^{t}BuOH:water (1:1, *v/v*; 300 mL) followed by the portion-wise addition of sodium chlorite (16.5 g, 182 mmol, 6 eq.). The reaction mixture was stirred at room temperature for 18 h and was then concentrated *in vacuo* to remove THF. Brine (50 mL) was added, and the resultant aqueous layer was extracted with ethyl acetate (4 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give crude *E/Z* farnesoic acid as a colourless oil (7.60 g, 32.0 mmol), which was used in the next step without further purification. Purity determined by TLC, R_f 0.79 (1:4, EtOAc:pentane). Iodomethane (3.0 mL) was added dropwise to a stirring solution of crude *E*/*Z* farnesoic acid (7.60 g, 32.0 mmol, 1 eq.) and potassium carbonate (6.70 g, 48.5 mmol, 1.5 eq.) in anhydrous DMF (42 mL). The reaction mixture was then stirred at room temperature for 18 h. Water (50 mL) was added to the reaction mixture followed by brine (50 mL) and the aqueous layer was extracted with ether (4 x 50 mL). The combined organic extracts were then washed with brine (3 x 40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (1:4, ether:pentane) gave the *title compound* as a colourless oil (5.85 g, 23.4 mmol, 74% over 3 steps). R_f 0.82 (1:4, ether:pentane); IR (ATR) $\nu_{max,}$ cm^{-1} 2915, 2855, 1719, 1649, 1434, 1378, 1357, 1325, 1277, 1221, 1145, 1109, 1058, 1030, 921; Only the signals observed for the major isomer are reported

here. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (1H, s, 3-H), 5.09 (2H, br. s, 7-H, 11-H), 3.68 (3H, s, 1-H_3), 2.17-2.15 (7H, m, 5-H_2, 10-H_2, 14-H_3), 2.07-1.95 (4H, m, 9-H_2, 6-H_2), 1.67 (3H, s, 13-H_3), 1.60 (6H, br. s, 16-H_3, 15-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4 (C), 160.3 (C), 136.3 (C), 131.5 (C), 124.2 (CH), 122.9 (CH), 115.3 (CH), 50.9 (CH_3), 41.0 (CH_2), 39.8 (CH_2), 32.1 (CH_2), 26.8 (CH_2), 25.8 (CH_3) 18.9 (CH_3) 17.8 (CH_3), 16.1 (CH_3); HRMS (ESI$^+$) *m/z* found 251.2001 (M+H$^+$, $C_{16}H_{27}O_2$ requires 251.2006) and 273.1824 (M + Na$^+$, $C_{16}H_{26}O_2Na$ requires 273.1825). All data agreed with that previously reported.[65]

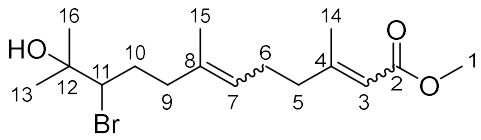
<u>*E*,*E*-methyl Farnesoate (*E*/*E*-101)</u>



To a stirring solution of *E*,*E*-farnesol **110** (4.00 g, 17.9 mmol, 1 eq.) in anhydrous CH_2Cl_2 (45.2 mL), activated manganese dioxide (31.2 g, 350 mmol, 20 eq.) was added. The reaction mixture was stirred at room temperature for 18 h and the resultant solution was then filtered through celite using ether (50 mL). The filtrate was then concentrated *in vacuo* to give crude *E*,*E*-farnesal as a colourless oil (3.99 g, 18.0 mmol), which was used in the next step without further purification. Purity determined by TLC, R_f 0.45 (1:4, ether:pentane). Sodium dihydrogen orthophosphate dihydrate (11.3 g, 72.8 mmol, 4 eq.) and 2-methyl-2-butene (12.0 mL) were added to a stirring solution of crude *E*,*E*-farnesal (3.99 g, 18.0 mmol, 1 eq.) in ^{t}BuOH:water (1:1 *v/v*; 179 mL), followed by the portion-wise addition of sodium chlorite (9.78 g, 108 mmol, 6 eq.). The reaction mixture was stirred at room temperature for 18 h and the

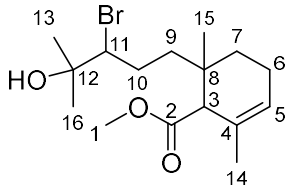
resultant solution was then concentrated *in vacuo* to remove THF. Brine (50 mL) was added to the reaction mixture and the resultant solution was extracted with ethyl acetate (4 x 50 mL). The combined organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo* to give crude *E*,*E*-farnesoic acid as a colourless oil (4.00 g, 16.9 mmol), which was used in the next step without further purification. Purity determined by TLC, R_f 0.58 (1:4, EtOAc:pentane). Iodomethane (1.53 mL) was added dropwise to a stirring solution of crude *E*,*E*-farnesoic acid (4.00 g, 16.9 mmol, 1 eq.) and potassium carbonate (3.62 g, 26.1 mmol, 1.5 eq.) in anhydrous DMF (22 mL). The reaction mixture was then stirred at room temperature for 18 h. Water (40 mL) was added, followed by the addition of brine (40 mL) and the aqueous layer was extracted with ether (4 x 30 mL). The combined organic extracts were then washed with brine (3 x 25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (1:4, ether:pentane) gave the *title compound* as a colourless oil (3.10 g, 12.5 mmol, 70% over 3 steps). R_f 0.79 (1:4, ether:pentane). IR (ATR) $\nu_{max,}$ cm^{-1} 2921, 2854, 1719, 1648, 1434, 1382, 1357, 1325, 1278, 1221, 1144, 1109, 1057, 1030, 918; ^1H NMR (400 MHz, $CDCl_3$) δ 5.66 (1H, s, 3-H), 5.08 (2H, br. s, 7-H, 11-H), 3.68 (3H, s, 1-H_3), 2.16 (7H, m, 5-H_2, 10-H_2, 14-H_3), 2.09-1.96 (4H, m, 9-H_2, 6-H_2) 1.68 (3H, s, 13-H_3), 1.60 (6H, br. s, 15-H_3, 16-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4 (C), 160.3 (C), 136.3 (C), 131.5 (C), 124.3 (CH), 123.0 (CH), 115.3 (CH), 50.9 (CH_3), 41.0 (CH_2), 39.8 (CH_2), 26.8 (CH_2), 26.0 (CH_2), 25.8 (CH_3), 18.9 (CH_3) 17.8 (CH_3), 16.1 (CH_3); HRMS (ESI^+) *m/z* found 251.2003 ($M+H^+$, $C_{16}H_{27}O_2$ requires 251.2006).

(*E*/*Z*)-methyl-11-bromo-12-hydroxy-4,8,12-trimethyldodeca-3,7-dienoate (102)



To a stirring solution of *E*/*Z* methyl farnesoate **101** (2.70 g, 10.8 mmol, 1 eq.) in THF:H_2O (10:1, *v/v*; 39 mL), NBS (1.95 g, 10.8 mmol, 1 eq.) was added at 0 °C. The reaction mixture was then covered with aluminium foil and stirred in the dark for 5 h at room temperature. THF was evaporated *in vacuo* and the reaction mixture was diluted with water (50 mL). The aqueous layer was extracted with ether (4 x 50 mL) and the combined organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo.* The crude material was then purified by using a short column (1:2, ether:petrol) to give the *title compound* as a pale oil (2.10 g, 6.08 mmol, 56%). R_f 0.42 (1:2, ether: pentane); IR (ATR) $\nu_{max,}$ cm^{-1} 3469, 2974, 2948, 1717, 1647, 1435, 1378, 1360, 1327, 1288, 1223, 1147, 1057, 960; Only the signals observed for the major isomer are reported here. ^1H NMR (400 MHz, $CDCl_3$) δ 5.67 (1H, br. s, 3-H), 5.16 (1H, br. s, 7-H), 3.94 (1H, dd, *J* = 11.5, 2.0, 11-H), 3.68 (3H, s, 1-H_3), 2.35-2.07 (9H, m, 6-H_2, 9-H_2, 10-H^a, 14-H_3, OH), 2.01-1.75 (3H, m, 5-H_2, 10-H^b), 1.68-160 (3H, m, 15-H_3), 1.36-1.32 (6H, m, 13-H_3, 16-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3 (C), 159.8 (C), 134.2 (C), 124.6 (CH), 115.4 (CH), 72.4 (C), 70.5 (CH), 50.8 (CH_3), 40.7 (CH_2), 38.1 (CH_2), 32.0 (CH_2), 26.6 (CH_3), 25.9 (CH_2), 25.8 (CH_3), 18.8 (CH_3) 15.8 (CH_3); HRMS (ESI^+) *m/z* found 347.1200 (M + H^+, $C_{16}H_{27}{}^{79}BrO_3$ requires 347.1216) and 369.1031 (M + Na^+, $C_{16}H_{26}{}^{79}BrO_3Na$ requires 369.1036). All data agreed with that previously reported.[61]

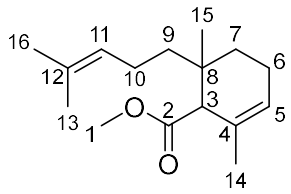
Methyl-6-(4-hydroxy-4-methylpentyl)-2,6-dimethylcyclohex-2-ene-1-carboxylate (104)



Phosphoric acid (33.0 mL, 495 mmol of a 15 M aqueous solution) was added dropwise to *E/Z* bromohydrin **102** (950 mg, 2.70 mmol). The reaction was stirred at room temperature for 5 h. The reaction mixture was then quenched with portion-wise addition of ice water (50 mL) and the resultant aqueous layer was extracted with ether (4 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give crude product which was then purified by using a short column (1:2, ether:pentane) to give the *title compound* as a yellow oil (729 mg, 2.09 mmol, 77%). R_f 0.30 (1:2, ether:pentane); IR (ATR) $\nu_{max,}$ cm^{-1} 3488, 2932, 1718, 1648, 1433, 1379, 1324, 1289, 1219, 1192, 1149, 1043, 1010, 955; ^1H NMR (400 MHz, $CDCl_3$, 2:1 mixture of *trans*:*cis* diastereoisomers, The presence of * indicates the data for the *cis*-isomer where distinguishable from the *trans*-isomer) δ 5.64 (1H, s, 5-H)*, 5.55 (1H, br. s, 5-H), 3.94-3.85 (1H, m, 11-H), 3.70 (3H, s, 1-H_3)*, 3.68 (3H, s, 1-H_3), 2.69 (1H, s, 3-H)*, 2.64 (1H, s, 3-H), 2.16-1.94 (3H, m, 6-H_2, OH), 1.91-1.73 (3H, m, 7-H^a/H^b, 9-H^a/H^b, 10-H^a/H^b), 1.64 (3H, s, 14-H_3), 1.36 (3H, s, 13-H_3/16-H_3), 1.34 (3H, s, 13-H_3/16-H_3), 1.31-1.05 (3H, m, 3H, m, 7-H^a/H^b, 9-H^a/H^b, 10-H^a/H^b), 0.90 (3H, s, 15-H_3), 0.89 (3H, s, 15-H_3)*; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3 (C), 129.7 (C), 124.2 (CH), 124.1 (CH), 124.0 (CH), 123.9 (CH), 72.8 (CH), 72.7 (C), 72.3 (C), 56.1 (CH_3), 55.9 (CH_3), 55.7 (CH_3), 51.7 (CH), 51.6 (CH), 40.1 (CH_2), 37.8 (CH_2), 37.6 (CH_2), 34.3 (C), 29.4 (CH_2), 28.9 (CH_2), 28.5 (CH_2), 28.2 (CH_2), 28.0 (CH_2),26.8 (CH_3), 26.1 (CH_3), 26.0 (CH_3), 25.7

(CH_3), 24.3 (CH_3), 23.1 (CH_3), 23.0 (CH_3), 22.9 (CH_3), 22.5 (CH_3), 22.5 (CH_2), 22.4 (CH_2); HRMS (ESI^+) *m/z* found 369.1036 ($M + Na^+$, $C_{16}H_{27}{}^{79}BrO_3Na$ requires 369.1036). All data agreed with that previously reported.[21,61]

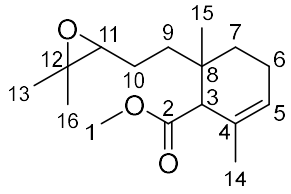
Methyl-2,6-dimethyl-6-(4-methylpent-3-en-1-yl)cyclohex-2-ene-1-carboxylate (106)



Phosphoric acid (35 mL, 525 mmol of a 15 M aqueous solution) was added dropwise to a stirring solution of *E*/*Z* bromohydrin (1.00 g, 2.90 mmol) in hexane (5 mL). The reaction was stirred at room temperature for 5 h. The reaction mixture was then quenched with portion-wise addition of ice water (50 mL) and the resultant aqueous layer was extracted with ether (4 x 50 mL). The combined organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product as a yellow oil (970 mg, 2.70 mmol), which was used in the next step without further purification. Purity determined by TLC, R_f 0.30 (1:2, ether:pentane). The yellow oil was dissolved in ether (40 mL) and glacial acetic acid (4.2 mL) was added dropwise to the stirring solution at room temperature, followed by zinc dust (2.00 g, 30.5 mmol). The resulting mixture was then heated to reflux under argon for 18 h. The mixture was cooled, filtered and the filtrate was washed successively with water (30 mL) then saturated aqueous sodium hydrogen carbonate (30 mL). The organic layer was then dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (1:9, ether:petrol) gave the *title compound* as a colourless oil (358 mg, 1.40 mmol, 49%). R_f 0.52 (1:9, ether:petrol); IR (ATR) $\nu_{max,}$ cm^{-1} 2963, 2916, 2855,

1735, 1649, 1432, 1377, 1324, 1287, 1218, 1189, 1141, 1061, 1042, 1008, 913; ^{1}H NMR (400 MHz, $CDCl_3$, 2:1 mixture of *trans*:*cis* diastereoisomers, The presence of * indicates the data for the *cis*-isomer where distinguishable from the *trans*-isomer) δ 5.58 (1H, s, 5-H), 5.06 (1H, t, *J* = 6.0 Hz, 11-H), 3.68 (3H, s, 1-H_3), 3.67 (3H, s, 1-H_3)*, 2.68 (1H, s, 3-H), 2.64 (1H, s, 3-H)*, 2.32 - 1.94 (4H, m, 6-H_2, 10-H_2), 1.93 - 1.84 (1H, m, 7-H^a/H^b)*, 1.83- 1.74 (1H, m, 7-H^a/H^b), 1.66 (3H, s, 13-H_3), 1.65 - 1.61 (3H, m, 14-H_3), 1.59 (3H, s, 16-H_3), 1.43- 1.23 (2H, m, 7-H^a/H^b and 9-H^a/H^b), 1.22-1.09 (1H, m, 9-H^a/H^b), 0.90 (3H, s, 15-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4 (C), 131.3 (C), 131.0 (C), 129.4 (CH), 129.3 (CH_2), 124.8 (CH), 124.6 (CH), 123.9 (CH), 123.9 (CH), 72.8 (CH), 72.7 (C), 72.3 (C), 56.1 (CH), 55.7 (CH), 51.4 (CH_3), 40.6 (CH_2), 40.4 (CH_2) 34.7 (C), 34.4 (C), 28.6 (CH_2), 28.5 (CH_2), 25.7 (CH_3), 24.0 (CH_3), 23.0 (CH_3), 22.9 (CH_3), 22.8 (CH_3), 22.7 (CH_3), 22.5 (CH_2), 22.4 (CH_2), 22.0 (CH_2), 17.5 (CH_3); HRMS (ESI^+) *m/z* found 251.2002 ($M+H^+$, $C_{16}H_{27}O_2$ requires 251.2006) and 273.1824 ($M + Na^+$, $C_{16}H_{26}O_2Na$ requires 273.1825). All data agreed with that previously reported.[61]

Methyl-8-(11,12-epoxy-12-methylpentyl)-4,8-dimethylcyclohex-4-eneoate (97)



Method 1:

Potassium carbonate (585 mg, 4.23 mmol, 2.3 eq.) was added to a stirring solution of cyclised bromohydrin **104** (650 mg, 1.87 mmol, 1 eq.) in methanol (5 mL). The reaction mixture was then stirred at room temperature for 18 h and then quenched

with water (30 mL). The resultant aqueous layer was extracted with ether (4 x 30 mL). The combined organic layers were then dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography (1:4, ether:pentane) gave the *title compound* (2:2:1:1 mixture of diastereoisomers) as a colourless oil (444 mg, 1.66 mmol, 89%).

Method 2:

Phosphoric acid (7.50 mL, 112 mmol of a 15 M aqueous solution) was added dropwise to *E*/*Z* bromohydrin **102** (400 mg, 1.15 mmol). The reaction was stirred at room temperature for 5 h. The reaction mixture was then quenched with portion-wise addition of ice water (20 mL) and the resultant aqueous layer was extracted with ether (4 x 20 mL). The combined organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo* to give crude cyclised bromohydrin as an orange oil (249 mg, 720 μmol), which was used in the next step without further purification. Purity determined by TLC, R_f 0.21 (1:2, ether: petrol). Potassium carbonate (228 mg, 1.64 mmol, 2.3 eq.) was added to a stirring solution of crude cyclised bromohydrin (249 mg, 720 μmol, 1 eq.) in methanol (1.65 mL). The reaction mixture was then stirred at room temperature for 18 h and was quenched with water (20 mL). The resultant aqueous layer was then extracted with ether (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography (1:4, ether:petrol) gave the *title compound* (2:2:1:1 mixture of diastereoisomers) as a colourless oil (147 mg, 554 μmol, 48% over 2 steps).

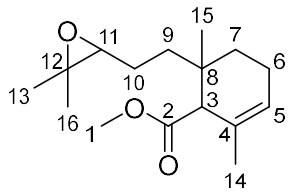
Method 3:

To a stirring solution of *E*/*Z* methyl farnesoate **101** (600 mg, 2.40 mmol, 1 eq.) in THF:H_2O (10:1, *v/v*; 10 mL), NBS (426 mg, 2.40 mmol, 1 eq.) was added at 0 °C. The

reaction mixture was then covered with aluminium foil and stirred in the dark for 5 h at room temperature. THF was evaporated *in vacuo* and the reaction mixture was diluted with water (20 mL). The aqueous layer was then extracted with ether (4 x 20 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give crude bromohydrin as a pale oil (680 mg, 1.95 mmol), which was used in the next step without further purification. Purity determined by TLC, R_f 0.25 (1:2, ether: petrol). Phosphoric acid (13.0 mL, 195 mmol of a 15 M aqueous solution) was added dropwise to *E*/*Z* bromohydrin (680 mg, 1.95 mmol). The reaction was stirred at room temperature for 5 h. The reaction mixture was then quenched with portion-wise addition of ice water (20 mL) and the resultant aqueous layer was extracted with ether (4 x 20 mL). The combined organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo* to give crude cyclised bromohydrin as an orange oil (487 mg, 1.40 mmol), which was used in the next step without further purification. Purity determined by TLC, R_f 0.20 (1:2, ether:petrol). Potassium carbonate (450 mg, 3.20 mmol, 2.3 eq.) was added to a stirring solution of crude cyclised bromohydrin (487 mg, 1.40 mmol, 1 eq.) in methanol (3.2 mL). The reaction mixture was then stirred at room temperature for 18 h and was quenched with water (20 mL). The resultant aqueous layer was then extracted with ether (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography (1:4, ether:petrol) gave the *title compound* (2:2:1:1 mixture of diastereoisomers) as a colourless oil (250 mg, 940 μmol, 40% over 3 steps). R_f 0.27 (1:4, ether:petrol); IR (ATR) $\nu_{max,}$ cm^{-1} 2948, 2874, 1719, 1648, 1434, 1375, 1324, 1278, 1221, 1147, 1091, 1039, 918; ^1H NMR (400 MHz, $CDCl_3$) (2:2:1:1 mixture of diastereoisomers) δ 5.58 (1H, br. s, 5-H) 3.67 (3H, br. s, 1-H_3), 2.68-2.62 (2H, m, 3-H,

11-H), 2.15-1.97 (2H, m, 6-H_2), 1.90-1.76 (1H, m, 7-H^a), 1.63 (3H, br. s, 14-H_3), 1.60-1.40 (4H, m, 9-H_2, 10-H_2), 1.29 (3H, s, 13-H_3 /16-H_3), 1.25 (3H, s, 13-H_3 /16-H_3), 1.22-1.11 (1H, m, 7-H^b), 0.89 (3H, s, 15-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3 (C), 129.5 (C), 129.2 (C), 124.1 (CH), 123.9 (CH), 64.9 (CH), 64.7 (CH), 58.4 (C), 56.2 (CH), 55.8 (CH), 51.5 (CH_3), 37.0 (CH_2), 35.0 (CH_2), 34.6 (CH_2), 34.3 (C), 28.6 (CH_2), 25.0 (CH_3), 24.1 (CH_3), 23.5 (CH_3), 23.1 (CH_2), 22.8 (CH_3), 22.5 (CH_2), 18.7 (CH_3); HRMS (ESI^+) *m/z* found 267.1961 ($M + H^+$, $C_{16}H_{27}O_3$ requires 267.1955).[21]

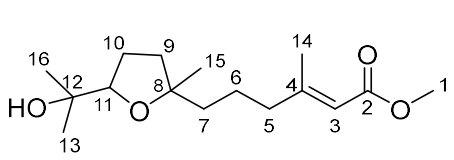
Methyl-8-(11,12-epoxy-12-methylpentyl)-4,8-dimethylcyclohex-4-eneoate (97)

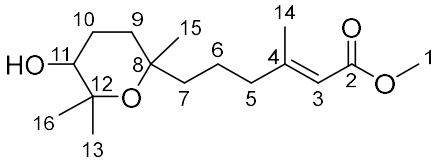


To a stirring solution of *E*,*E*-methyl farnesoate ***E/E*-98** (750 mg, 3.00 mmol, 1 eq.) in THF:water (10:1, *v/v*; 11.2 mL), NBS (534 mg, 3.00 mmol, 1 eq.) was added at 0 °C. The reaction mixture was then covered with aluminium foil and stirred in the dark for 5 h at room temperature. THF was evaporated *in vacuo* and the reaction mixture was diluted with water (25 mL). The aqueous layer was extracted with ether (4 x 25 mL). The combined organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo* to give crude bromohydrin as a yellow oil (835 mg, 2.40 mmol), which was used in the next step without further purification. Purity determined by TLC, R_f 0.35 (1:2, ether:pentane). Phosphoric acid (15.8 mL, 237 mmol of a 15 M aqueous solution) was added dropwise to crude bromohydrin (835 mg, 2.4 mmol, 1 eq.). The reaction mixture was stirred at room temperature for 18 h and was then quenched with

portion-wise addition of ice water (40 mL). The resultant aqueous layer was then extracted with ether (4 x 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give crude cyclised bromohydrin as an orange oil (708 mg, 2.03 mmol), which was used in the next step without further purification. Purity determined by TLC, R_f 0.32 (1:2, ether:pentane). Potassium carbonate (654 mg, 4.73 mmol, 2.3 eq.) was added to a stirring solution of crude cyclised bromohydrin (708 mg, 2.03 mmol, 1 eq.) in methanol (4.6 mL). The reaction was stirred at room temperature for 18 h and was then quenched with water (25 mL). The resultant aqueous layer was extracted with ether (4 x 25 mL). The combined organic layers were then dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography (1:4, ether:pentane) first gave the *title compound* as a colourless oil (2:2:1:1 mixture of diastereoisomers) (190 mg, 713 μmol, 24% over 3 steps). R_f 0.42 (1:4, ether:pentane); IR (ATR) $\nu_{max,}$ cm^{-1} 2959, 2926, 1721, 1648, 1433, 1378, 1358, 1323, 1285, 1221, 1189, 1145, 1042, 1023, 891; ^1H NMR (500 MHz, $CDCl_3$) (2:2:1:1 mixture of diastereoisomers) δ 5.58 (1H, br. s, 5-H) 3.68 (3H, br. s, 1-H_3), 2.68-2.62 (2H, m, 3-H, 11-H), 2.17-2.01 (2H, m, 6-H_2), 1.89-1.76 (1H, m, 7-H^a), 1.63 (3H, br. s, 14-H_3), 1.60-1.37 (4H, m, 9-H_2, 10-H_2) 1.35-1.31 (1H, m, 7-H^b), 1.30 (3H, s, 13-H_3/16-H_3), 1.25 (3H, s, 13-H_3/16-H_3), 0.89 (3H, s, 15-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2 (C), 129.3 (C), 129.1 (C), 124.0 (CH), 123.8 (CH), 64.6 (CH), 64.5 (CH), 58.3 (C), 56.1 (CH), 55.7 (CH), 51.4 (CH_3), 36.9 (CH_2), 34.8 (CH_2), 34.8 (CH_2), 34.1 (C), 28.5 (CH_2), 24.9 (CH_3), 24.0 (CH_3), 23.9 (CH_3), 23.3 (CH_2), 22.9 (CH_3), 22.3 (CH_2), 18.6 (CH_3); HRMS (ESI^+) *m/z* found 267.1954 ($M + H^+$, $C_{16}H_{27}O_3$ requires 267.1955) and 289.1777 ($M + Na^+$, $C_{16}H_{27}0_3Na$ requires 289.1774), followed by the by-product **109/110** as colourless oil (31 mg, 100 μmol, 5%);

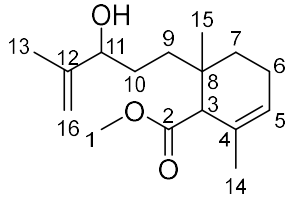
Methyl(*E*)-6-(5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl)-3-methylhex-2-enoate (109) OR methyl (E)-6-(5-hydroxy-2,6,6-trimethyltetrahydro-2H-pyran-2-yl)-3-methylhex-2-enoate (110)





R_f 0.12 (1:4, ether:pentane); IR (ATR) $\nu_{max,}$ cm^{-1} 3484, 2967, 2947, 2870, 1717, 1648, 1434, 1375, 1357, 1323, 1280, 1221, 1147, 1059, 1030, 949; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (1H, br. s, 3-H), 3.70-3.74 (1H, m, 11-H), 3.68 (3H, br. s,1-H_3),2.19-2.17 (2H, m, 5-H_2) 2.15 (3H, s, 14-H_3), 1.89-1.65 (4H, m, 9-H_2, 10-H_2), 1.57-1.43 (5H, m, 6-H_2, 7-H_2, OH), 1.20 (3H, s, 15-H_3), 1.18 (3H, s, 13-H_3/16-H_3), 1.11 (3H, s, 13-H_3/16-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3 (C), 160.3 (C), 115.4 (CH), 85.8 (CH), 82.9 (C), 70.7 (C), 50.9 (CH_3), 41.3 (CH_2), 40.8 (CH_2), 37.5 (CH_2), 27.7 (CH_3), 26.7 (CH_3), 26.6 (CH_2), 24.1 (CH_3), 22.3 (CH_2), 18.8 (CH_3); HRMS (ESI^+) *m/z* found 285.2065 (M + H^+, $C_{16}H_{29}O_4$ requires 285.2060) and 307.1891 (M + Na^+, $C_{16}H_{28}O_4Na$ requires 370.1880).

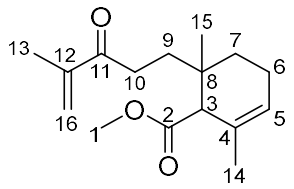
Methyl-8-(11-hydroxy-12-methylpent-12-enyl)-4,8-dimethylcyclohex-4-eneoate (111)



To a stirring solution of tetramethylpiperidine (1.05 mL) in anhydrous toluene (11 mL), ^{n}BuLi (2.25 M in hexanes, 2.9 mL) was added dropwise at 0 °C. The solution was stirred at 0 °C for 45 min before the dropwise addition of diethyl aluminium chloride

(1 M in hexanes, 6.5 mL). After a further 45 min epoxide **97** (560 mg, 2.10 mmol) in toluene (6 mL) was added to the reaction mixture and was stirred for 1.5 h at 0 °C under argon. Saturated aqueous sodium bicarbonate (20 mL) was then added portion-wise, followed by water (15 mL). The resultant aqueous layer was extracted with ether (3 x 40 mL). The combined organic extracts were then washed with brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (1:1, ether:petrol) gave the *title compound* (2:2:1:1 mixture of diastereoisomers) as a colourless oil (521 mg, 1.95 mmol, 93%). R_f 0.42 (1:1, ether: petrol); IR (ATR) $\nu_{max,}$ cm^{-1} 3430, 2930, 2874, 1723, 1650, 1447, 1433, 1379, 1324, 1238, 1212, 1191, 1144, 1058, 1020, 898; ^1H NMR (400 MHz, $CDCl_3$) (2:2:1:1 mixture of diastereoisomers) δ 5.57 (1H, br. s, 5-H), 4.92 (1H, s, 16-H^a), 4.84 (1H, s, 16-H^b), 4.01-3.95 (1H, m, 11-H), 3.67 (3H, s, 1-H_3), 2.67-2.63 (1H, m, 3-H), 2.10 -1.98 (2H, m, 6-H_2), 1.82 -1.74 (1H, m, 10-H^a), 1.71 (3H, s, 13-H_3), 1.62 (3H, s, 14-H_3), 1.57-1.47 (2H, m, OH, 10-H^b), 1.32-1.06 (4H, m, 7-H_2, 9-H_2), 0.88 (3H, s, 15-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4 (C), 147.6 (C), 147.4 (C), 129.4 (C), 129.23(C), 124.1 (CH), 124.0 (CH), 111.6 (CH_2), 111.5 (CH_2), 111.1 (CH_2), 76.7 (CH), 76.6 (CH), 76.5 (CH), 56.2 (CH), 55.9 (CH), 51.5 (CH_3), 36.5 (CH_2), 36.4 (CH_2), 34.5 (CH_2), 34.2 (CH_2), 29.0 (CH_2), 28.6 (CH_2), 24.1 (CH_3), 23.0 (CH_3), 22.8 (CH_3), 22.5 (CH_2), 22.4 (CH_2), 17.5 (CH_3); HRMS (ESI^+) *m/z* found 289.1784 ($M + Na^+$, $C_{16}H_{27}O_3Na$ requires 289.1774).[20,21]

Methyl-8-(12-methyl-11-oxopent-12-enyl-4,8-dimethylcyclohex-4-eneoate (94)



Method 1:

To a stirring solution of allylic alcohol **111** (250 mg, 938 μmol, 1 eq.) in CH_2Cl_2 (10 mL) Dess-Martin periodinane (796 mg, 1.87 mmol, 2.1 eq.) was added. The reaction mixture was stirred at room temperature for 2 h and then quenched with saturated aqueous sodium thiosulphate (25 mL). The resultant aqueous layer was then extracted with ether (4 x 25 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (3 x 40 mL) and then dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (1: 4, ether:pentane) gave the *title compound* (2:1 mixture of *trans*:*cis* diastereoisomers) as a colourless oil (223 mg, 844 μmol, 90%).

Method 2:

To a stirring solution of oxalyl chloride (35.0 μL, 463 μmol, 2 eq.) in anhydrous CH_2Cl_2 (2.75 mL), Anhydrous dimethyl sulfoxide (65 μL, 844 μmol, 4 eq.) was added dropwise at −78 °C. After 30 min alcohol **111** (58 mg, 22.0 μmol, 1 eq.) in anhydrous CH_2Cl_2 (2 mL) was then added dropwise. The reaction mixture was stirred at −78 °C for 1.5 h. Triethylamine (220 μL, 1.57 mmol, 7.2 eq.) was added dropwise and the reaction was stirred for a further 1 h at −78 °C. Saturated aqueous sodium bicarbonate (10 mL) was added, and the layers separated. The aqueous layer was extracted with

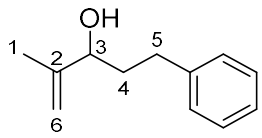
dichloromethane (3 x 10 mL). The combined organic layers were then washed with brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (1:4, ether:petrol) gave the *title compound* (2:1 mixture of *trans*:*cis* diastereoisomers) as a colourless oil (18 mg, 68 μmol, 31%).

Method 3:

To a stirring solution of allylic alcohol **111** (45.0 mg, 170 μmol, 1 eq.) in anhydrous CH_2Cl_2 (550 μL), activated manganese dioxide (38.0 mg, 4.37 mmol, 25 eq.) was added. The reaction was stirred at room temperature for 18 h and the solution was then filtered through celite using ether (40 mL) and the filtrate was then concentrated *in vacuo*. Purification by column chromatography (1:4, ether:petrol) gave the *title compound* (2:1 mixture of *trans*:*cis* diastereoisomers) as a colourless oil (22 mg, 83 μmol, 49%). R_f 0.35 (1:4, ether:petrol); IR (ATR) $\nu_{max,}$ cm^{-1} 2925, 1731, 1675, 1449, 1630, 1449, 1432, 1378, 1324, 1240, 1215, 1189, 1144, 1085, 1042, 1013, 930; ^1H NMR (400 MHz, $CDCl_3$) (2:1 mixture of *trans*:*cis* diastereoisomers, The presence of * indicates the data for the *cis*-isomer where distinguishable from the *trans*-isomer) δ 5.97 (1H, s, 16-H^a*), 5.95 (1H, s, 16-H^a), 5.77 (1H, s, 16-H^b), 5.58 (1H, s, 5-H), 3.68 (3H, s, 1-H_3), 3.66 (3H, s, 1-H_3*), 2.68-2.63 (3H, m, 3-H, 10-H_2), 2.16-1.99 (2H, m, 6-H_2), 1.87 (3H, s, 13-H_3), 1.85-1.79 (1H, m, 7-H^a), 1.65 (3H, s, 14-H_3), 1.57-1.43 (2H, s, 9-H_2), 1.33-1.19 (1H, m, 7-H^b), 0.90 (3H, s, 15-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2 (C), 174.3 (C), 174.2 (C), 144.6 (C), 129.3 (C), 124.5 (CH_2), 124.5 (CH_2), 124.0 (CH), 56.0 (CH), 55.7 (CH), 51.7 (CH_3), 51.6 (CH_3), 35.3 (CH_2), 34.6 (C), 34.2 (C), 33.0 (CH_2), 32.1 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 24.0 (CH_3), 23.1 (CH_3), 22.7 (CH_3), 22.5

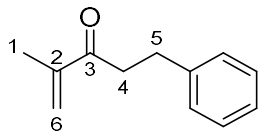
(CH_2), 17.9 (CH_3); HRMS (ESI^+) *m/z* found 265.1803 ($M + H^+$, $C_{16}H_{25}O_3$ requires 265.1798).[20,21]

2-methyl-5-phenylpent-1-en-3-ol (113)



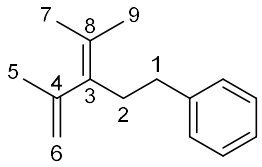
To a stirring solution of 3-phenylpropionaldehyde **112** (3.00 g, 22.4 mmol, 1eq.) in anhydrous THF (45 mL), isopropenyl magnesium bromide (58 mL, 0.5 M in THF) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 h under argon and then was quenched with saturated aqueous ammonium chloride (50 mL). The resultant aqueous layer was extracted with ether (4 x 40 mL) and the combined organic layers were then washed with brine (2 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography (1:4, ether:pentane) gave the *title compound* as a colourless oil (1.90 g, 10.8 mmol, 48%). R_f 0.28 (1:4, ether:pentane); IR (ATR) $\nu_{max,}$ cm^{-1} 3349, 3063, 3026, 2939, 2860, 1649, 1603, 1495, 1452, 1372, 1298, 1152, 1029, 899; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.26 (2H, m, Ar-H), 7.26-7.17 (3H, m, Ar-H), 4.98 (1H, dd, *J* = 1.9, 1.0, 6-H^a /H^b), 4.88 (1H, d, *J* = 1.7, 6-H^a /H^b), 4.12 (1H, m, 3-H), 2.77 - 2.61 (2H, m, 5-H_2), 1.93 -1.88 (2H, m, 4-H_2), 1.75 (3H, d, *J* = 1.4, 1-H_3), 1.62-1.53 (1H, m, OH); ^{13}C NMR (100 MHz, CDCl3) δ 147.5 (C), 142.1 (C), 128.5 (CH), 128.5 (CH), 125.9 (CH), 111.3 (CH2), 75.4 (CH), 36.7 (CH2), 32.0 (CH2), 17.7 (CH3); HRMS (ESI^+) *m/z* found 176.1175 ($M + H^+$, $C_{12}H_{16}O$ requires 176.1196). All data agreed with that previously reported.[66]

2-methyl-5-phenylpent-1-en-3-one (114)



To a stirring solution of allylic alcohol **113** (1.29 g, 7.30 mmol, 1eq.) in CH_2Cl_2 (37 mL), Dess Martin periodinane (4.05 g, 9.52 mmol, 1.3 eq.) was added. The reaction was stirred at room temperature for 2 h and quenched with saturated aqueous sodium thiosulphate (50 mL). The resultant aqueous layer was extracted with ether (4 x 50 mL) and the combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (1:4, ether:pentane) gave the *title compound* as a colourless oil (1.15 g, 6.60 mmol, 90%). R_f 0.59 (1:4, ether:pentane); IR (ATR) $\nu_{max,}$ cm^{-1} 3062, 3026, 2954, 2924, 1674, 1630, 1603, 1494, 1451, 1410, 1366, 1178, 1088, 1070, 1030, 981; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.25 (2H, m, Ar-H), 7.21 (3H, m, Ar-H), 5.95 (1H, s, 6-H^a/H^b), 5.76 (1H, s, 6-H^a/H^b), 3.04-3.00 (1H, m, 4-H_2), 2.96-2.92 (2H, m, 5-H_2), 1.89 (3H, s, 1-H_3); ^{13}C NMR (100 MHz, CDCl3) δ 201.1 (C), 144.5 (C), 141.5 (C), 128.6 (CH), 128.3 (CH), 126.2 (CH), 124.7 (CH_2), 39.4 (CH_2), 30.5 (CH_2), 17.7 (CH_3); HRMS (ESI^+) *m/z* found 175.1111 (M + H^+, $C_{12}H_{15}O$ requires 175.1117) and 197.0922 (M + Na^+, $C_{12}H_{14}NaO$ requires 197.0937). All data agreed with that previously reported.[67]

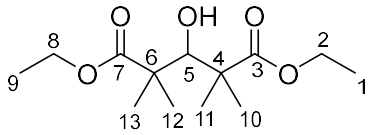
(4-methyl-3-(prop-1-en-2-yl)pent-3-en-1-yl)benzene (120)



To a stirring solution of enone **115** (150 mg, 860 μmol, 1 eq.) in DMF:THF (2:1, *v/v;* 1.5 mL), ethyl α-bromo isobutyrate (253 μL, 1.72 mmol, 2 eq.) was added followed by indium powder (198 mg, 1.72 mmol, 2 eq.). The reaction was stirred at room temperature for 22 h and was then quenched with hydrochloric acid (1M, 10 mL). The aqueous layer was extracted with ether (4 x 10 mL) and the combined organic layers were then washed with water (15 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give crude β-lactone **119** (272 mg) which was used in the next step without further purification. Purity determined by TLC, R_f 0.26 (1:9, ether:pentane). Crude β-lactone **119** (272 mg, 1.10 mmol) was then diluted with toluene (12 mL) and silica gel (0.8 g) was added. The stirring mixture was heated at reflux for 4 h. The resulting solution was concentrated *in vacuo* and the silica gel was loaded directly onto a column. Purification by column chromatography (1:9, ether:pentane) first gave the *title compound* as a colourless oil (120 mg, 600 μmol, 70% over 2 steps). R_f 0.90 (1:9, ether:pentane); IR (ATR) $\nu_{max,}$ cm^{-1} 3073, 3026, 2916, 2856, 1631, 1603, 1495, 1444, 1370, 1167, 1154, 1122, 1085, 1061, 1029, 1006, 893; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.32 (2H, m, Ar-H), 7.30-7.22 (3H, m, Ar-H), 5.06 (1H, dq, *J* = 2.6, 1.3, 6-H^a /H^b), 4.70 (1H, d, *J* = 2.7, 6-H^a /H^b), 2.74-2.66 (2H, m, 1-H_2), 2.49-2.40 (2H, m, 2-H_2), 1.88 (3H, d, *J* = 1.3, 5-H_3), 1.76 (3H, s, 7 /9-H_3), 1.70 (3H, s, 7 /9-H_3); ^{13}C NMR (100 MHz, CDCl3) δ 146.5 (C), 142.8 (C), 136.0 (C), 129.1 (CH), 128.5 (CH) 128.3 (CH), 125.8 (CH), 125.7 (CH), 113.5 (CH_2), 34.9 (CH_2), 33.4 (CH_2), 22.9 (CH_3), 21.8 (CH_3), 19.6 (CH_3); The

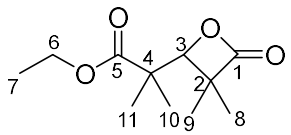
compound did not ionise under the ESI-HRMS conditions used.[21] Diene **120** was followed by the recovered starting material **114** (10 mg, 57 μmol, 7%), further eluting gave alcohol **117** as a colourless oil (60.0 mg, 230 μmol, 26%);

Diethyl 3-hydroxy-2,2,4,4-tetramethylpentanedioate (117)



R_f 0.10 (1:9, ether:pentane); IR (ATR) $\nu_{max,}$ cm^{-1} 3450, 2980, 2935, 1722, 1695, 1461, 1388, 1367, 1300, 1258, 1207, 1139, 1115, 1095, 1055, 1024, 982; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (1H, d, *J* = 9.8, OH), 4.13 (4H, qq, *J* = 6.9, 3.7 Hz, 2-H_2, 8-H_2), 3.88 (1H, d, *J* = 9.7, 5-H), 1.26 (6H, d, *J* = 7.2, 1-H_3, 9-H_3), 1.20 (6H, s, 10-H_3, 11-H_3), 1.16 (6H, s, 12-H_3, 13-H_3); ^{13}C NMR (101 MHz, CDCl3) δ 178.2 (C), 81.7 (CH), 60.91 (CH_2), 46.2 (C), 23.6 (CH_3), 22.9 (CH_3), 13.9 (CH_3); HRMS (ESI^+) *m/z* found 261.1694 ($M + H^+$, $C_{13}H_{25}O_5$ requires 261.1697) and 283.1518 ($M + Na^+$, $C_{13}H_{24}NaO_5$ requires 283.1516).

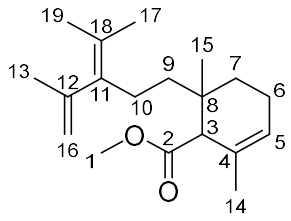
Ethyl 2-(3,3-dimethyl-4-oxooxetan-2-yl)-2-methylpropanoate (118)



To a stirring solution of ethyl α-bromo isobutyrate (334 mg, 1.72 mmol, 1 eq.) in DMF (1.5 mL), indium powder (198 mg, 1.72 mmol, 1 eq.) was added. The reaction was stirred at 80 °C for 1 h, followed by stirring at room temperature for 2 h. The reaction mixture was then quenched with hydrochloric acid (1M, 10 mL) and the aqueous layer was extracted with ether (4 x 10 mL). The combined organic layers were washed with

water (15 mL), dried over Na_2SO_4 and concentrated *in vacuo.* Purification by column chromatography (1:4, ether: pentane) gave the *title compound* as a colourless oil (25.0 mg, 120 μmol, 7%). R_f 0.25 (1:4, ether:pentane); IR (ATR) $\nu_{max,}$ cm^{-1} 2977, 2936, 2877, 1825, 1721, 1467, 1392, 1368, 1300, 1265, 1239, 1146, 1100, 1057, 1028, 980; ^1H NMR (400 MHz, $CDCl_3$) δ 4.35 (1H, s, 3-H), 4.18 (2H, q, *J* = 7.1 Hz, 6-H_2), 1.49 (3H, s, 8-H_3), 1.35 (3H, s, 9-H_3), 1.32-1.25 (6H, s, 10-H_3, 11-H_3), 1.24 (3H, s, 7-H_3); ^{13}C NMR (101 MHz, CDCl3) δ 175.1 (C), 175.0 (C), 86.1 (CH), 61.1 (CH_2), 54.1 (C), 43.8 (C), 26.1 (CH_3), 25.1 (CH_3), 19.3 (CH_3), 16.8 (CH_3), 14.1 (CH_3); HRMS (ESI^+) *m/z* found 215.1277 ($M + H^+$, $C_{11}H_{19}O_4$ requires 215.1278) and 237.1102 ($M + Na^+$, $C_{11}H_{18}NaO_4$ requires 237.1097).

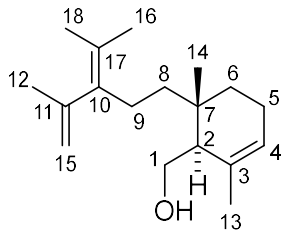
Methyl-8-(12-methyl-11-(prop-1-enyl)pent-12-enyl)-4,8-dimethylcyclohex-4-eneoate (96)

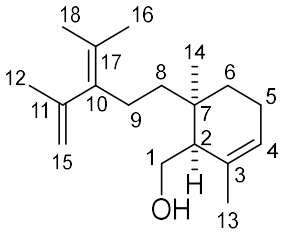


To a stirring solution of enone **94** (542 mg, 2.05 mmol, 1 eq.) in DMF (6 mL), ethyl α-bromoisobutyrate (620 μL, 4.10 mmol, 2 eq.) was added followed by indium powder (470 mg, 4.10 mmol, 2 eq.) at room temperature. The reaction was stirred at 80 °C for 30 min before being allowed to cool to room temperature and stirred for 3 h. The reaction mixture was then quenched with hydrochloric acid (1M, 25 mL) and the aqueous layer was extracted with ether (4 x 25 mL). The combined organic layers were washed with water (25 mL), dried over Na_2SO_4 and concentrated *in vacuo.*

Purification by silica gel chromatography (1:9 rising to 1:4, ether:petrol) first gave recovered starting material. R_f 0.35 (1:4, ether:pentane) then crude fractions containing β-lactone. R_f 0.20 (1:4, ether:pentane).These fractions containing β-lactone (614 mg, 1.83 mmol) were combined, concentrated *in vacuo* followed by dilution with toluene (15 mL). Silica gel (1.8 g) was added and the stirring mixture was heated at reflux for 1 h. The resultant solution was concentrated *in vacuo* and silica gel was loaded directly onto a column. Purification by column chromatography (1:9, ether:pentane) gave the *title compound* (2:1 mixture of *cis* : *trans* diastereoisomers) as a colourless oil (242 mg, 835 μmol, 41% over 2 steps). R_f 0.74 (1:9, ether:pentane); IR (ATR) $\nu_{max,}$ cm^{-1} 2913, 2856, 1735, 1631, 1445, 1432, 1378, 1324, 1286, 1240, 1214, 1189, 1143, 1079, 1040, 1008, 892; ^1H NMR (400 MHz, $CDCl_3$) (2:1 mixture of *trans*: *cis* diastereoisomers, The presence of * indicates the data for the *cis*-isomer where distinguishable from the *trans*-isomer) δ 5.58 (1H, s, 5-H), 4.89 (1H, s, 16-H^a), 4.51 (1H, dd, *J* = 7.1, 2.7 Hz, 16-H^b), 3.67 (3H, s, 1-H_3), 3.65 (3H, s, 1-H_3*), 2.69 (1H, s, 3-H), 2.63 (1H, s, 3-H*), 2.14-1.98 (4H, m, 6-H_2, 10-H_2), 1.92-1.77 (1H, m, 9-H^a), 1.74 (3H, s, 13-H_3), 1.64 (6H, br. s, 17-H_3, 19-H_3), 1.62 (3H, s, 14-H_3), 1.42-1.23 (2H, m, 7-H^a, 9-H^b), 1.21-1.08 (1H, m, 7-H^b), 0.90 (3H, s, 15-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6 (C), 174.5 (C), 146.7 (C), 146.6 (C), 136.8 (C), 136.6 (C), 129.5 (C), 129.4 (C), 124.9 (C), 124.7 (C), 124.0 (CH), 113.1 (CH_2), 113.1 (CH_2), 56.0 (CH), 55.7 (CH), 51.5 (CH_3), 51.5 (CH_3), 39.2 (CH_2), 36.9 (CH_2), 34.7 (C), 34.4 (C), 28.8 (CH_2), 28.7 (CH_2), 25.3 (CH_2), 24.9 (CH_2), 24.0 (CH), 23.1 (CH_3), 23.0 (CH_3), 22.8 (CH_3), 22.6 (CH_3), 22.6 (CH_3), 22.5 (CH_2), 21.9 (CH_3), 21.8 (CH_3), 19.5 (CH_3), 19.5 (CH_3); HRMS (ESI^+) *m/z* found 291.2323 (M + H^+, $C_{19}H_{31}O_2$ requires 291.2319) and 313.2149 (M + Na^+, $C_{19}H_{31}NaO_2$ requires 313.2138).[20,21]

(±)-*trans*-2-(hydroxymethyl)-7-(11-methyl-10-(prop-1-enyl)pent-11-enyl)-3,7-dimethylcyclohex-3-ene (125) and (±)-*cis*-2-(hydroxymethyl)-7-(11-methyl-10-(prop-1-enyl)pent-11-enyl)-3,7-dimethylcyclohex-3-ene (126)

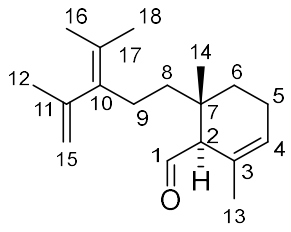




To a stirring solution of ester **96** (282 mg, 970 μmol, 1 eq.) in anhydrous CH_2Cl_2 (5 mL), DIBAL-H (1.2 M in toluene, 1.6 mL, 1.94 mmol, 2 eq.) was added dropwise at 0 °C. The reaction was stirred for 2.5 h at 0 °C. Methanol (5 mL) was then added dropwise followed by aqueous hydrochloric acid (1 M, 20 mL). The reaction was allowed to warm to room temperature and extracted with ether (3 x 20 mL). The combined organic layers were then washed with brine (3 x 30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by silica gel chromatography (1:9, ether:pentane) gave firstly the recovered starting material (50.0 mg, 172 μmol, 18%), followed by *cis*-diastereoisomer **126** (65.0 mg, 247 μmol, 26%) as a colourless oil. R_f 0.35 (1:9, ether:pentane); IR (ATR) $\nu_{max,}$ cm^{-1} 3380, 2960, 2913, 2873, 2855, 1630, 1444, 1373, 1274, 1219, 1192, 1158, 1125, 1069, 1024, 1005, 967.49; ^1H NMR (400 MHz, $CDCl_3$) 5.61 (1H, br. s, 4-H), 4.93-4.92 (1H, m, 15-H^a), 4.59-4.56 (1H, m, 15-H^b), 3.77-3.69 (2H, m, 1-H_2), 2.20-2.09 (1H, app. td, *J* 13.0, 4.5, 9-H^a), 2.04-1.93 (3H, m, 5-H_2, 9-H^b), 1.77 (3H, s, 13-H_3), 1.74-1.67 (3H, m, 12-H_3), 1.73 (1H, br. s, 2-H), 1.67 (3H, s, 16-H_3 /18-H_3), 1.65 (3H, s, 16-H_3 /18-H_3), 1.60-1.58 (1H, m, 6-H^a), 1.47-1.36 (1H, app. td, J 13.0, 4.5 Hz, 8-H^a), 1.33-1.20 (2H, m, 6-H^b, 8-H^b), 0.87 (3H, s, 14-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 146.7 (C), 136.9 (C), 131.8 (C), 124.7 (CH), 124.5 (C), 113.1 (CH_2), 60.7 (CH_2), 50.5 (CH), 38.7 (CH_2), 34.2 (C), 30.6 (CH_2), 24.8 (CH_2), 23.2 (CH_3), 23.0 (CH_3), 22.8 (CH_3),

22.7 (CH_2), 21.7 (CH_3), 19.5 (CH_3); HRMS (ESI^+) *m/z* found 263.2370 ($M + H^+$, $C_{18}H_{31}O$ requires 263.2369) and 285.2192 ($M + Na^+$, $C_{18}H_3NaO$ requires 285.2189). Further elution gave *trans*-diastereoisomer **125** (137 mg, 522 μmol, 55%) as a colourless oil. R_f 0.23 (1:9, ether:pentane); IR (ATR) $\nu_{max,}$ cm^{-1} 3326, 3073, 2960, 2912, 2875, 2855, 1631, 1444, 1372, 1316, 1274, 1227, 1208, 1154, 1123, 1045, 1021, 969; ^1H NMR (400 MHz, $CDCl_3$) 5.60 (1H, br. s, 4-H), 4.92-4.87 (1H, m, 15-H^a), 4.53-4.51 (1H, d, *J* = 2.7, 15-H^b), 3.75-3.73 (2H, m, 1-H_2), 2.03-1.92 (4H, m, 5-H_2, 9-H_2), 1.85-1.73 (7H, m, 13-H_3, 12-H_3, 2-H), 1.67-1.61 (7H, m, 6-H^a, 16-H_3, 18-H_3), 1.34-1.15 (4H, m, 6-H^b, 8-H_2, OH), 1.01 (3H, s, 14-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 146.7 (C), 136.9 (C), 131.6 (C), 124.7 (CH), 124.5 (C), 112.8 (CH_2), 61.4 (CH_2), 50.4 (CH), 37.2 (CH_2), 34.2 (C), 30.4 (CH_2), 25.4 (CH_2), 24.1 (CH_3), 22.8 (CH_3), 22.7 (CH_3), 22.7 (CH_2), 21.7 (CH_3), 19.4 (CH_3); HRMS (ESI^+) *m/z* found 263.2375 ($M + H^+$, $C_{18}H_{31}O$ requires 263.2369) and 285.2173 ($M + Na^+$, $C_{18}H_{30}NaO$ requires 285.2189).[20,21]

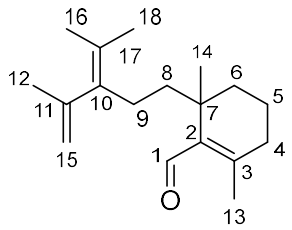
(±)-*trans*-7-(11-methyl-7-(prop-1-enyl)pent-11-enyl)-3,7-dimethylcyclohex-3-en-2-al (127)



To a stirring solution of oxalyl chloride (93 μL, 1.0 mmol, 2 eq.) in anhydrous CH_2Cl_2 (6 mL), anhydrous dimethyl sulfoxide (155 μL, 2.18 mmol, 4 eq.) was added dropwise at −78 °C under argon. After 30 min *trans*-alcohol **125** (140 mg, 533 μmol, 1 eq.) in anhydrous CH_2Cl_2 (3 mL) was added dropwise. The reaction was stirred at −78 °C for 1.5 h. Anhydrous triethylamine (550 μL, 3.94 mmol, 7 eq.) was added dropwise. The

reaction was then stirred for a further 1 h at −78 °C. Saturated aqueous sodium bicarbonate (10 mL) was added and the layers separated. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (1:4, ether:pentane) first gave the *title compound* (95 mg, 364 μmol, 68%) as a colourless oil. R_f 0.69 (1:9, ether:petrol); IR (ATR) $\nu_{max,}$ cm^{-1} 2960, 2915, 2856, 1717, 1672, 1631, 1443, 1378, 1309, 1276, 1225, 1207, 1153, 1134, 1072, 1018, 937; ^1H NMR (400 MHz, $CDCl_3$) 9.50 (1H, d, *J* 5.0, 1-H), 5.73 (1H, br. s, 4-H), 4.89 (1H, s, 15-H^a), 4.52 (1H, s, 15-H^b), 2.48 (1H, d, *J* 5.0, 2-H), 2.18-2.12 (2H, m, 5-H_2), 2.12-1.98 (2H, m, 9-H_2), 1.73 (3H, s, 12-H_3), 1.72-1.62 (1H, m, 6-H^a), 1.64 (3H, s, 16-H_3 /18-H_3), 1.63 (3H, s, 16-H_3 /18-H_3), 1.58 (3H, d, *J* 1.5, 13-H_3), 1.53-1.40 (1H, dd, *J* 13.5, 5.5, 6-H^b), 1.31-1.18 (2H, m, 8-H_2), 0.98 (3H, s, 14-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 202.3 (CH), 146.4 (C), 136.3 (C), 126.8 (C), 125.7 (CH), 125.9 (C), 113.1 (CH_2), 62.4 (CH), 36.5 (CH_2), 34.0 (C), 30.0 (CH_2), 24.6 (CH_2), 24.0 (CH_3), 22.8 (CH_2), 22.5 (CH_3), 22.4 (CH_3), 21.7 (CH_3), 19.4 (CH_3); HRMS (ESI^+) *m/z* found 261.2208 ($M + H^+$, $C_{18}H_{29}O$ requires 261.2213) and 283.2026 ($M + Na^+$, $C_{18}H_{28}NaO$ requires 283.2032), followed by aldehyde **128** (4.0 mg, 15 μmol, 2%);

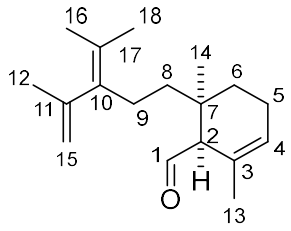
3,7-dimethyl-7-(11-methyl-10-(prop-16-en-16-yl)pent-9-enyl)cyclohex-2-enecarbaldehyde (128)



Yellow oil; R_f 0.34 (1:9, ether:pentane); IR (ATR) $\nu_{max,}$ cm^{-1} 3073, 2916, 2865, 2756, 1715, 1671, 1631, 1611, 1445, 1371, 1322, 1289, 1265, 1210, 1122, 1045, 1006, 957;

^{1}H NMR (400 MHz, $CDCl_3$) 10.1 (1H, s, 1-H), 4.89 (1H, dq, *J* = 2.5, 1.5, 15-H^{a}), 4.89 (1H, s, 15-H^{a}), 4.52 (1H, d, *J* 2.0, 15-H^{b}), 2.27-2.16 (2H, m, 4-H_2), 2.10 (3H, s, 13-H_3), 1.97-1.85 (2H, m, 5-H, 8-H^{a}), 1.78-1.76 (1H, m, 9-H), 1.73 (3H, d, *J* = 1.5, 15-H_3), 1.71-1.61 (1H, m, 6-H^{a}), 1.62 (3H, s, 16-H_3 /18-H_3), 1.61 (3H, s, 16-H_3 /18-H_3), 1.58-1.56 (2H, m, 5-H_2 /9-H_2), 1.32-1.16 (1H, m, 8-H^{b}), 1.32-1.26 (1H, m, 6-H^{b}) 1.19 (3H, s, 14-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 192.1 (CH), 156.6 (C), 146.7 (C), 139.6 (C), 136.7 (C), 124.6 (C), 112.8 (CH_2), 37.8 (CH_2), 36.1 (C), 35.8 (CH_2), 35.5 (CH_2), 26.2 (CH_3), 26.2 (CH_2), 22.7 (CH_3), 21.7 (CH_3), 19.5 (CH_3), 19.5 (CH_3), 18.4 (CH_2); HRMS (ESI^{+}) *m/z* found 261.2203 (M + H^{+}, $C_{18}H_{29}O$ requires 261.2213) and 283.2020 (M + Na^{+}, $C_{18}H_{28}NaO$ requires 283.2032).[21]

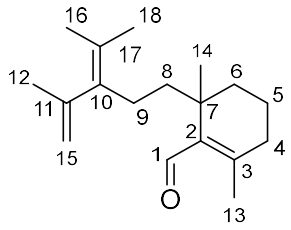
(±)-*cis*-7-(11-methyl-7-(prop-1-enyl)pent-11-enyl)-3,7-dimethylcyclohex-3-en-2-al (129)



To a stirring solution of oxalyl chloride (43.0 µL, 480 µmol, 2 eq.) in anhydrous CH_2Cl_2 (3 mL), anhydrous dimethyl sulfoxide (70 µL, 1.0 mmol, 4 eq.) was added dropwise at −78 °C under argon. After 30 min *cis*-alcohol **126** (64.0 mg, 243 µmol, 1 eq.) in anhydrous CH_2Cl_2 (2.5 mL) was added dropwise to the reaction mixture. The resulting solution was stirred at −78 °C for 1.5 h. Anhydrous triethylamine (250 µL, 1.80 mmol, 7 eq.) was added dropwise and the resulting solution was stirred for a further 1 h at −78 °C. Saturated aqueous sodium bicarbonate (10 mL) was then added and the

layers separated. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic layers were then washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by silica gel chromatography (1:9, ether:pentane) first gave the *title compound* **129** (35 mg, 134 μmol, 55%) as a colourless oil. R_f 0.69 (1:9, ether:petrol); IR (ATR) $\nu_{max,}$ cm^{-1} 2964, 2915, 2854, 1715, 1669, 1630, 1443, 1374, 1328, 1282, 1253, 1222, 1179, 1152, 1129, 1073, 1019, 993; ^1H NMR (400 MHz, $CDCl_3$) 9.44 (1H, d, *J* 5.5, 1-H), 5.72 (1H, br. s, 4-H), 4.89 (1H, s, 15-H^a), 4.51 (1H, d, *J* 2.0, 15-H^b), 2.43 (1H, d, *J* 5.5, 2-H), 2.20-2.12 (2H, m, 5-H_2), 2.10-2.04 (2H, m, 9-H_2), 1.72 (3H, s, 12-H_3), 1.72-1.65 (1H, m, 6-H^a), 1.63 (3H, s, 16-H_3 /18-H_3), 1.63 (3H, s, 16-H_3 /18-H_3), 1.58 (3H, d, *J* 1.5, 13-H_3), 1.45 (1H, dd, *J* 13.5, 5.5, 6-H^b), 1.32-1.16 (2H, m, 8-H_2), 0.89 (3H, s, 14-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 201.4 (CH), 146.2 (C), 136.2 (C), 126.6 (C), 125.9 (CH), 125.0 (C), 113.2 (CH_2), 62.6 (CH), 39.3 (CH_2), 34.3 (C), 30.1 (CH_2), 24.1 (CH_2), 22.8 (CH_2), 22.6 (CH_3), 22.4 (CH_3), 22.3 (CH_3), 21.7 (CH_3), 19.4 (CH_3); HRMS (ESI^+) *m/z* found 283.2036 ($M + Na^+$, $C_{18}H_{28}NaO$ requires 283.2032), followed by the conjugated aldehyde **128** (8 mg, 30 μmol, 13%);

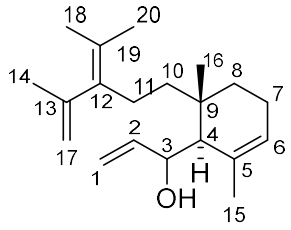
3,7-dimethyl-7-(11-methyl-10-(prop-16-en-16-yl)pent-9-enyl)cyclohex-2-enecarbaldehyde (128)



Yellow oil; R_f 0.34 (1:9, ether:pentane); IR (ATR) $\nu_{max,}$ cm^{-1} 3073, 2916, 2865, 2756, 1715, 1671, 1631, 1611, 1445, 1371, 1322, 1289, 1265, 1210, 1122, 1045, 1006, 957;IR ^1H NMR (400 MHz, $CDCl_3$) 10.1 (1H, s, 1-H), 4.89 (1H, dq, *J* = 2.5, 1.5, 15-H^a), 4.89 (1H, s, 15-H^a), 4.52 (1H, d, *J* 2.0, 15-H^b), 2.27-2.16 (2H, m, 4-H_2), 2.10 (3H, s, 13-

H_3), 1.97-1.85 (2H, m, 5-H, 8-H^a), 1.78-1.76 (1H, m, 9-H), 1.73 (3H, d, *J* = 1.5, 15-H_3), 1.71-1.61 (1H, m, 6-H^a), 1.62 (3H, s, 16-H_3 /18-H_3), 1.61 (3H, s, 16-H_3 /18-H_3), 1.58-1.56 (2H, m, 5-H_2 /9-H_2), 1.32-1.16 (1H, m, 8-H^b), 1.32-1.26 (1H, m, 6-H^b) 1.19 (3H, s, 14-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 192.1 (CH), 156.6 (C), 146.7 (C), 139.6 (C), 136.7 (C), 124.6 (C), 112.8 (CH_2), 37.8 (CH_2), 36.1 (C), 35.8 (CH_2), 35.5 (CH_2), 26.2 (CH_3), 26.2 (CH_2), 22.7 (CH_3), 21.7 (CH_3), 19.5 (CH_3), 19.5 (CH_3), 18.4 (CH_2); HRMS (ESI$^+$) *m/z* found 261.2203 (M + H^+, $C_{18}H_{29}O$ requires 261.2213) and 283.2020 (M + Na^+, $C_{18}H_{28}NaO$ requires 283.2032).[21]

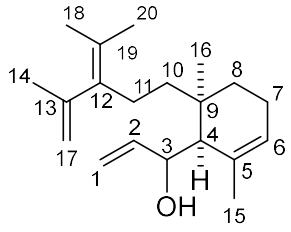
(±)-*trans*-4-(5,9-dimethyl-9-(13-methyl-12-(prop-19-en-19-yl)pent-17-enyl)cyclohex-5-enyl)prop 1-en-3-ol (130)



To a stirring solution of *trans* aldehyde **127** (177 mg, 679 μmol, 1 eq.) in anhydrous THF (8.0 mL), vinyl magnesium bromide (1 M in THF, 1.4 mL, 1.42 mmol, 2 eq.) was added dropwise at −78 °C. The reaction was stirred for 2 h at −78 °C, after which another batch of vinyl magnesium bromide (1 M in THF, 1.4 mL, 1.42 mmol, 2 eq.) was added dropwise at −78 °C. The reaction was stirred for a further 20 min before quenching with saturated aqueous ammonium chloride (30 mL). The aqueous layer was then extracted with ether (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated in *vacuo*. Purification by silica gel chromatography (1:20, ether:pentane) gave a single isomer of *the title compound* **130** (stereochemistry undetermined) (171 mg, 593 μmol, 87%) as a colourless oil. R_f

0.17 (1:20, ether:pentane); IR (ATR) $\nu_{max,}$ cm^{-1} 3469, 3073, 2959, 2912, 2872, 2723, 2326, 2074, 1795, 1657, 1631, 1562, 1544, 1511, 1443, 1400, 1374, 1348, 1326, 1275, 1202, 1139, 1106, 1080, 1052, 990; ^{1}H NMR (400 MHz, $CDCl_3$) 6.02-5.94 (1H, ddd, *J* 17.0, 10.5, 4.0, 2-H), 5.70 (1H, br. s, 6-H), 5.28 (1H, app. dt, *J* 17.0, 2.0, 1-H^a), 5.08 (1H, app. dt, *J* 10.5, 2.0, 1-H^b), 4.90 (1H, dq, *J* 3.0, 1.5, 17-H^a), 4.52-4.51 (1H, m, 17-H^b), 4.44-4.40 (1H, m, 3-H), 2.05-1.95 (4H, m, 7-H_2, 11-H_2), 1.87-1.77 (2H, m, 4-H, 8-H^a), 1.74 (3H, s, 14-H_3), 1.71 (3H, br. s, 15-H_3), 1.64 (3H, s, 18-H_3 / 20-H_3), 1.63 (3H, s, 18-H_3 / 20-H_3), 1.60 (1H, br. s, OH), 1.31-117 (3H, m, 8-H^b, 10-H_2), 1.02 (3H, br. s, 16-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 146.5 (C), 144.0 (CH), 136.8 (C), 130.8 (C), 126.7 (CH), 124.5 (C), 112.8 (CH_2), 112.1 (CH_2), 69.7 (CH), 53.8 (CH), 37.4 (CH_2), 34.9 (C), 29.4 (CH_2), 25.6 (CH_3), 25.6 (CH_2), 24.8 (CH_3), 23.1 (CH_2), 22.7 (CH_3), 21.7 (CH_3), 19.4 (CH_3); HRMS (ESI^+) *m/z* found 311.2333 ($M + Na^+$, $C_{20}H_{32}NaO$ requires 311.2345).[21]

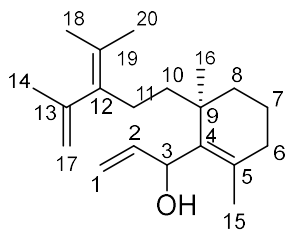
(±)-*cis*-4-(5,9-dimethyl-9-(13-methyl-12-(prop-19-en-19-yl)pent-17-enyl)cyclohex-5-enyl)prop 1-en-3-ol (131)



To a stirring solution of *cis* aldehyde **129** (31.0 mg, 121 μmol, 1 eq.) in anhydrous THF (2.0 mL), vinyl magnesium bromide (1 M in THF, 25.0 μL, 254 μmol, 2 eq.) was added dropwise at −78 °C. The reaction was stirred for 2 h at −78 °C, after which another batch of vinyl magnesium bromide (1 M in THF, 25.0 μL, 254 μmol, 2 eq.) was added dropwise at −78 °C. The reaction was stirred for a further 20 min before quenching

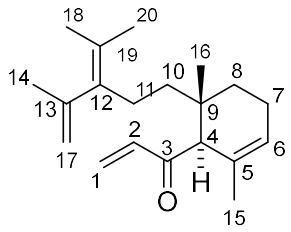
with saturated aqueous ammonium chloride (15 mL). The aqueous layer was then extracted with ether (3 x 15 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated in *vacuo*. Purification by silica gel chromatography (1:20, ether:petrol) gave *the title* compound (13 mg, 43 μmol, 36%) as a colourless oil. R_f 0.57 (1:20, ether:petrol); IR (ATR) $\nu_{max,}$ cm^{-1} 3453, 3073, 2915, 2854, 2726, 2332, 2185, 2052, 1711, 1670, 1631, 1577, 1541, 1442, 1372, 1229, 1210, 1159, 1108, 1078, 1026, 990; ^1H NMR (400 MHz, $CDCl_3$) 5.97 (1H, ddd, *J* 17.0, 10.5, 4.0, 2-H), 5.70 (1H, br. s, 6-H), 5.30 (1H, app. dt, *J* 17.0, 2.0, 1-H^a), 5.05 (1H, app. dt, *J* 10.5, 2.0, 1-H^b), 4.92 (1H, dq, *J* 3.0, 1.5, 17-H^a), 4.58-4.52 (1H, m, 17-Hb), 4.39-4.36 (1H, m, 3-H) 2.15 (1H, app. td, *J* 13.0, 4.0 Hz, 11-H^a), 2.09-2.01 (2H, m, 7-H_2), 2.00-1.90 (1H, m, 11-H^b), 1.84-1.74 (4H, m, 8-H^a, 14-H_3), 1.70 (3H, br. s, 15-H_3), 1.67 (3H, s, 18-H_3 or 20-H_3), 1.66 (3H, s, 18-H_3 or 20-H_3), 1.60 (1H, br. s, OH), 1.51 (1H, app. td, *J* 13.0, 5.0, 10-H^a), 1.43 (3H, s, 14-H_3) 1.27 (1H, app. td, *J* 13.0, 4.0, 10-H^b), 1.20-1.13 (1H, m, 8-H^b), 0.87 (3H, s, 16-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 146.4 (C), 143.9 (CH), 136.7 (C), 130.8 (C), 126.8 (CH), 125.5 (C), 124.6 (C) 113.2 (CH_2), 112.3 (CH_2), 68.8 (CH), 53.3 (CH), 39.4 (CH_2), 34.9 (C), 30.2 (CH_2), 25.8 (CH_3), 24.7 (CH_2), 23.2 (CH_2), 23.1 (CH_3), 22.8 (CH_3), 21.7 (CH_3), 19.5 (CH_3); HRMS (ESI^+) *m/z* found 311.2339 ($M + Na^+$, $C_{20}H_{32}NaO$ requires 311.2345).[21]

(±)-*trans*-4-(-5,9-dimethyl-9-(13-methyl-12-(prop-19-en-19-yl)pent-12-enyl)cyclohex-4enyl)prop-1-en-3-ol (132)



To a stirring solution of aldehyde **128** (67.0 mg, 251 μmol, 1 eq.) in anhydrous THF (5.0 mL), vinyl magnesium bromide (1 M in THF, 55.0 μL, 514 μmol, 2 eq.) was added dropwise at −78 °C. The reaction was stirred for 2 h at −78 °C, after which another batch of vinyl magnesium bromide (1 M in THF, 55 μL, 514 μmol, 2 eq.) was added dropwise at −78 °C. The reaction was stirred for a further 20 min before quenching with saturated aqueous ammonium chloride (15 mL). The aqueous layer was then extracted with ether (3 x 10 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated in *vacuo*. Purification by silica gel chromatography (1:20, ether:petrol) gave *the title* compound (4 mg, 13 μmol 5%) as a colourless oil. R_f 0.20 (1:9, ether:pentane); IR (ATR) $\nu_{max,}$ cm^{-1} 3384, 3073, 2924, 2856, 2724, 2172, 2038, 1981, 1707, 1630, 1443, 1372, 1260, 1203, 1185, 1122, 1098, 986; ^1H NMR (400 MHz, $CDCl_3$) 6.08 (1H, ddd, *J* = 17.0, 10.5, 4.0, 2-H), 5.25 (1H, d, *J* = 7.5, 1-H^a), 5.10 (1H, app. dt, *J* 10.5, 1.8, 1-H^b), 4.89 (1H, app. dt, *J* = 2.9, 1.5, 17-H^a), 4.79 (1H, d, *J* = 4.5, 3-H), 4.55-4.47 (1H, m, 17-H^b), 2.06-1.88 (4H, m, 6-H_2, 11-H_2) 1.76 (3H, s, 15-H_3), 1.73 (3H, s, 14-H_3), 1.63 (6H, s, 18-H_3 and 20-H_3), 1.62-1.53 (4H, m, 7-H_2, 8-H^a and OH), 1.41 (3H, m, 8-H^b, 10-H_2), 1.11 (3H, s, 16-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 146.6 (C), 140.8 (CH), 139.2 (C), 136.8 (C), 133.6 (C), 124.5 (C), 113.6 (CH_2) 112.9 (CH_2), 70.8 (CH), 38.1 (CH_2), 37.5 (C), 35.1 (CH_2), 33.7 (CH_2), 25.6 (CH_2), 25.1 (CH_3), 22.8 (CH_3), 21.7 (CH_3), 21.1 (CH_3) 19.4 (CH_3), 19.1 (CH_2); HRMS (ESI^+) *m/z* found 311.2339 (M + Na^+, $C_{20}H_{32}NaO$ requires 311.2345).[21]

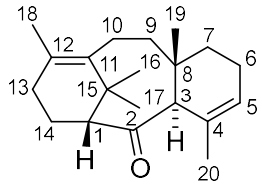
(±)-*trans*-4-(3-oxoprop-1-enyl)-9-(13-methyl-12-(prop-1-enyl)pent-13-enyl)-5,9-dimethyl-cyclohex-5-ene (97)



To a solution of oxalyl chloride (140 μL, 1.45 mmol) in anhydrous dichloromethane (9.0 mL), anhydrous dimethyl sulfoxide (230 μL, 2.90 mmol) was added dropwise at − 78 °C. After 1 h *trans*-alcohol **130** (209 mg, 725 μmol) in anhydrous dichloromethane (5 mL) was added dropwise. The reaction was then stirred at −78 °C for 2 h. Triethylamine (820 μL, 5.07 mmol) was added dropwise and the reaction was allowed to warm to room temperature and stirred for a further 1 h. Saturated aqueous sodium bicarbonate (20 mL) was added and the layers separated. The aqueous layer was extracted with dichloromethane (3 x 15 mL). The organic layer was washed with brine (25 mL), dried over $MgSO_4$ and concentrated in *vacuo*. Purification by silica gel chromatography (1:20, ether:petrol) gave *the title* compound **97** (141 mg, 492 μmol, 68%) as a colourless oil. R_f 0.30 (1:20, ether:petrol); IR (ATR) $\nu_{max,}$ cm^{-1} 3073, 2961, 2912, 2873, 2854, 1746, 1688, 1672, 1631, 1608, 1443, 1396, 1378, 1346, 1318, 1274, 1241, 1208, 1146, 1119, 1083, 1025, 988; ^{1}H NMR (400 MHz, $CDCl_3$) 6.58 (1H, dd, *J* 17.0, 10.5, 2-H), 6.27 (1H, dd, *J* 17.0, 1.5, 1-H^a), 5.72 (1H, dd, *J* 10.5, 1.5, 1-H^b), 5.64 (1H, br. s, 6-H), 4.91 (1H, br. s, 17-H^a), 4.52 (1H, d, *J* 2.0, 17-H^b), 3.06 (1H, s, 4-H), 2.13-1.98 (4H, m, 7-H_2, 11-H_2), 1.75 (3H, s, 14-H_3), 1.74-1.64 (1H, m, 8-H^a) 1.66 (6H, s, 18-H_3 and 20-H_3), 1.54 (3H, br. s, 15-H_3), 1.45-1.17 (3H, m, 8-Hb, 10-Ha, and 10-H^b), 0.84 (3H, s, 16-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 202.9 (C), 146.5 (C), 137.0 (CH), 136.4 (C), 130.0 (C), 127.6 (CH_2), 124.8 (C), 124.0 (CH), 113.0 (CH_2), 59.6 (CH), 37.5 (CH_2),

35.0 (C), 28.8 (CH_2), 25.1 (CH_2), 24.3 (CH_3), 23.4 (CH_3), 22.7 (CH_3), 22.4 (CH_2), 21.7 (CH_3), 19.4 (CH_3); HRMS (ESI^+) *m/z* found 287.2360 ($M + H^+$, $C_{20}H_{31}O$ requires 287.2369) and 309.2192 ($M + Na^+$, $C_{20}H_{30}ONa$ requires 309.2189).[21]

(±)-*trans*-8-epi-2-oxo-taxa-(4,5)-(11,12)-diene (93)



A solution of enone **97** (46.0 mg, 160 μmol, 1 eq.) in anhydrous toluene (8.5 mL) was added by syringe pump over 5 h to a solution of boron trifluoride etherate (72 μL, 584 μmol, 3.65 eq.) in anhydrous degassed toluene (31.5 mL) at 0 °C. After addition, the reaction was stirred for a further 1 h at 0 °C. Saturated aqueous sodium bicarbonate (50 mL) was added. The aqueous layer was extracted with dichloromethane (3 x 50 mL) and the combined organic layers were washed with water (50 mL), then brine (50 mL). The organic layer was then dried over $MgSO_4$ and concentrated in *vacuo*. Purification by silica gel chromatography (1:20, ether:petrol) gave *the title* compound **93** (14 mg, 48.9 μmol, 31%) as a white solid. R_f 0.35 (1:20 ether: pentane); mp 126-130 °C; IR (ATR) $\nu_{max,}$ cm^{-1} 2994, 2974, 2954, 2908, 2847, 1682, 1456, 1440, 1387, 1374, 1363, 1321, 1290, 1274, 1253, 1221, 1206, 1177, 1117, 1093, 1077, 1030, 997; ^1H NMR (400 MHz, $CDCl_3$) 5.57 (1H, m, 5-H), 3.31 (1H, s, 3-H), 2.59 (1H, dd, *J* = 10.0, 4.5, 1-H), 2.55-2.45 (2H, m, 10-H^a, 13-H^a), 2.26 (1H, ddd, *J* = 16.0, 12.5, 4.0, 10-H^b), 2.19-2.06 (2H, m, 6-H^a, 13-H^b), 2.04-1.96 (2H, m, 14-H_2), 1.87-1.72 (2H, m, 6-H^b, 9-H^a), 1.80 (3H, s, 18-H_3), 1.49 (3H, s, 20-H_3) 1.36-1.30 (2H, m, 7-

H^a, 9-H^b), 1.30-1.24 (1H, m, 7-H^b), 1.20 (3H, s, 16-H_3 /17-H_3), 1.08 (3H, s, 16-H_3/ 17-H_3), 0.91 (3H, s, 19-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 218.1 (C), 136.9 (C), 133.4 (C), 130.7 (C), 124.9 (CH) 64.9 (CH), 56.0 (CH), 43.6 (CH_2), 40.8 (CH_2), 38.6 (C), 37.4 (C), 29.0 (CH_3), 28.4 (CH_2), 27.7 (CH_3), 23.8 (CH_3), 23.7 (CH_2), 22.2 (CH_3), 21.9 (CH_2), 20.7 (CH_3), 18.7 (CH_2); HRMS (ESI^+) *m/z* found 287.2353 ($M + H^+$, $C_{20}H_{31}O$ requires 287.2369) and 309.2188 ($M + Na^+$, $C_{20}H_{30}ONa$ requires 309.2189).[21]

REFERENCES

1 S. Malik, R. M. Cusidó, M. H. Mirjalili, E. Moyano, J. Palazón and M. Bonfill, *Process Biochem.*, 2011, **46**, 23–34.

2 Y. F. Wang, Q. W. Shi, M. Dong, H. Kiyota, Y. C. Gu and B. Cong, *Chem. Rev.*, 2011, **111**, 7652–7709.

3 Q. Zhang, Z. Yang, Q. Wang, S. Liu, T. Zhou, Y. Zhao and M. Zhang, *J. Am. Chem. Soc.*, 2021, **143**, 7088–7095.

4 N. Narraidoo, PhD Thesis, University of Nottingham, 2011.

5 O. Besumbes, S. Sauret-Güeto, M. a Phillips, S. Imperial, M. Rodríguez-Concepción and A. Boronat, *Biotechnol. Bioeng.*, 2004, **88**, 168–75.

6 G. Appendino, *Alkaloids Chem. Biol. Perspect.*, 1996, **11**, 237–268.

7 H. Lucas, *Arch. Pharm.,* 1856, **135**, 145–149.

8 C. R. Wilson, J. M. Sauer and S. B. Hooser, *Toxicon.*, 2001, **39**, 175–185.

9 M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon and A. T. Mcphail, *J. Am. Chem. Soc.*, 1971, **93**, 2325–2327.

10 J. Guerra-Bubb, R. Croteau and R. M. Williams, *Nat. Prod. Rep.*, 2012, **29**, 683–696.

11 G. M. Cragg, *Med. Res. Rev.*, 1998, **18**, 315–331.

12 Q. W. Shi and H. Kiyota, *Chem. Biodivers.*, 2005, **2**, 1597–1623.

13 R. Croteau, R. E. B. Ketchum, R. M. Long, R. Kaspera and M. R. Wildung, *Phytochem. Rev.*, 2006, **5**, 75–97.

14 N. A. Barton, B. J. Marsh, W. Lewis, N. Narraidoo, G. B. Seymour, R. Fray and C. J. Hayes, *Chem. Sci.*, 2016, **7**, 3102–3107.

15 W. Eisenreich, B. Menhard, P. J. Hylands, M. H. Zenk and A. Bacher, *Proc. Natl. Acad. Sci.*, 1996, **93**, 6431–6436.

16 Q. Wang, S. Quan and H. Xiao, *Bioresour. Bioprocess.*, 2019, **6**, 1–13.

17 M. Hezari, N. G. Lewis and R. Croteau, *Arch. Biochem. Biophys.*, 1995, **322**, 437–444.

18 X. Lin, M. Hezari, A. E. Koepp, H. G. Floss and R. Croteau, *Biochemistry.*, 1996, **35**, 2968–2977.

19 A. E. Koepp, M. Hezari, J. Zajicek, B. S. Vogel, R. E. LaFever, N. G. Lewis and R. Croteau, *J. Biol. Chem.*, 1995, **270**, 8686–8690.

20 B. Marsh, PhD Thesis, University of Nottingham, 2016.

21 N. A. Barton, PhD Thesis, University of Nottingham, 2013.

22 A. L. Wheeler, R. M. Long, R. E. B. Ketchum, C. D. Rithner, R. M. Williams and R. Croteau, *Arch. Biochem. Biophys.*, 2001, **390**, 265–278.

23 S. Jennewein, R. M. Long, R. M. Williams and R. Croteau, *Chem. Biol.*, 2004, **11**, 379–387.

24 J. Hefner, S. M. Rubenstein, R. E. B. Ketchum, D. M. Gibson, R. M. Williams and R. Croteau, *Chem. Biol.*, 1996, **3**, 479–489.

25 D. Rontein, S. Onillon, G. Herbette, A. Lesot, D. Werck-Reichhart, C. Sallaud and A. Tissier, *J. Biol. Chem.*, 2008, **283**, 6067–6075.

26 D. C. Liebler and F. P. Guengerich, *Biochemistry.*, 2002, **22**, 5482–5489.

27 S. Edgar, K. Zhou, K. Qiao, J. R. King, J. H. Simpson and G. Stephanopoulos, *Chem. Biol.*, 2016, **11**, 460–469.

28 A. Schoendorf, C. D. Rithner, R. M. Williams and R. B. Croteau, *Proc. Natl. Acad. Sci. U. S. A.*, 2001, **98**, 1501–1506.

29 S. Jennewein, C. D. Rithner, R. M. Williams and R. B. Croteau, *Proc. Natl. Acad. Sci. U. S. A.*, 2001, **98**, 13595–13600.

30 D. Willenbring and D. J. Tantillo, *Russ. J. Gen. Chem.*, 2008, **78**, 723–731.

31 P. B. Schiff, J. Fant and S. B. Horwitz, *Nature*, 1979, **277**, 665–667.

32 I. Ojima, P. Y. Bounaud, C. Takeuchi, P. Pera and R. J. Bernacki, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 189–194.

33 N. Vasan, J. Baselga and D. M. Hyman, *Nature.*, 2019, **575**, 299–309.

34 E. Galletti, M. Magnani, M. L. Renzulli and M. Botta, *ChemMedChem.*, 2007, **2**, 920–942.

35 A. K. Nanayakkara, C. A. Follit, G. Chen, N. S. Williams, P. D. Vogel and J. G. Wise, *Sci. Rep.*, 2018, **8**, 1–18.

36 J. G. Reeve, G. L. Koch and P. R. Twentyman, *Br. J. Cancer.*, 1987, **56**, 143–145.

37 R. Callaghan, F. Luk and M. Bebawy, *DRUG Metab. Dispos. Drug Metab Dispos.*, 2014, **42**, 623–631.

38 R. Hayeshi, C. Masimirembwa, S. Mukanganyama and A. L. B. Ungell, *Eur. J. Pharm. Sci.*, 2006, **29**, 70–81.

39 F. Staud, M. Ceckova, S. Micuda and P. Pavek, *Methods Mol. Biol.*, 2010, **596**, 199–222.

40 T. Hasegawa, J. Bai, S. Zhang, J. Wang, J. Matsubara, J. Kawakami, A. Tomida, T. Tsuruo, K. Hirose, J. Sakai, M. Kikuchi, M. Abe and M. Ando, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 1122–1126.

41 C. and A. I. S. Q, Haung. C. A. Roessner, R, *Bioorg. Med. Chem.*, 2001, **9**, 2237–2242.

42 M. Köksal, Y. Jin, R. M. Coates, R. Croteau and D. W. Christianson, *Nature*, 2011, **469**, 116–120.

43 Ó. Besumbes, S. Sauret-Güeto, M. A. Phillips, S. Imperial, M. Rodríguez-Concepción and A. Boronat, *Biotechnol. Bioeng.*, 2004, **88**, 168–175.

44 B. P. and S. G. P. K. Ajikumar, W. H. Xiao, K. E. J. Tyo, Y. Wang, F. Simeon, E. Leonard, O. Mucha, T. H. Phon, *Science.*, 2010, **330**, 70–74.

45 J. M. Dejong, Y. Liu, A. P. Bollon, R. M. Long, S. Jennewein, D. Williams and R. B. Croteau, *Biotechnol. Bioeng.*, 2006, **93**, 212–224.

46 B. Engels, P. Dahm and S. Jennewein, *Metab. Eng.*, 2008, **10**, 201–206.

47 K. Kovacs, L. Zhang, R. S. T. Linforth, B. Whittaker, C. J. Hayes and R. G. Fray, *Transgenic Res.*, 2007, **16**, 121–126.

48 R. A. Holton, R. R. Juo and H. B. Kim, *J. Am. Chem. Soc.*, 1988, **110**, 6558–6560.

49 N. C. Wilde, M. Isomura, A. Mendoza and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 4909–4912.

50 K. J. Shea and P. D. Davis, *Angew. Chem. Int. Ed.,* 1983, **22**, 419–426.

51 J. D. Winkler, H. S. Kim, S. Kim, K. Ando and K. N. Houk, *J. Org. Chem.,* 1997, **62**, 2957–2962.

52 R. V Bonnert and P. R. Jenkins, *J. Chem. Soc. Perkin Trans. I.*, 1989, **1**, 413–418.

53 P. A. Brown and P. R. Jenkins, *J. Chem. Soc. Perkin Trans. I.,* 1986, **3**, 1303–1309.

54 R. V Bonnert and P. R. Jenkins, *J. Chem. Soc. Chem. Commun.*, 1987, **20**, 1540–1541.

55 P. A. Brown, P. R. Jenkins, J. Fawcett and D. R. Russell, *J. Chem. Soc., Chem. Commun.*, 1984, **253**, 84–85.

56 A. Krief, *Tetrahedron*, 1980, **36**, 2531–2640.

57 S. M. Rubenstein and R. M. Williams, *J. Org. Chem.*, 1995, **60**, 7215–7223.

58 A. Mendoza, Y. Ishihara and P. S. Baran, *Nat. Chem.*, 2012, **4**, 21–25.

59 Y. Ishihara, A. Mendoza and P. S. Baran, *Tetrahedron*, 2013, **69**, 5685–5701.

60 M. Vuagnoux-d'Augustin and A. Alexakis, *Chem. Eur. J.*, 2007, **13**, 9647–9662.

61 M. A. Schwartz and A. M. Willbrand, *J. Org. Chem.*, 1985, **50**, 1359–1365.

62 A. Yasuda, S. Tanaka, K. Oshima, H. Yamamoto and H. Nozaki, *J. Am. Chem. Soc.*, 1974, **96**, 6513–6514.

63 H. Schick, R. Ludwig, K. H. Schwarz, K. Kleiner and A. Kunath, *J. Org. Chem.*, 1994, **59**, 3161–3164.

64 R. L. Danheiser and J. S. Nowick1, *J. Org. Chem.*, 1991, **56**, 1176–1185.

65 K. Mori, M. Ohki and M. Matsui, *Agric. Biol. Chem.*, 1971, **35**, 1139–1141.

66 M. Takahashi, M. Mclaughlin, G. C. Micalizio, M. Takahashi, M. Mclaughlin and G. C. Micalizio, *Ang. Chem. Int. Ed.*, 2009, **48**, 3648–3652.

67 J. I. Matsuo, T. Kozai, O. Nishikawa, Y. Hattori and H. Ishibashi, *J. Org. Chem.*, 2008, **73**, 6902–6904.