Synthetic Chemistry and Synthetic Biology Approaches to Low Oxidation State Taxanes

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Abbreviations

Ac	acetyl
acac	acetylacetonate
AIBN	2,2′-azobis(2-methylpropionitrile)
aq.	aqueous
Ar	aromatic
ATP	adenosine triphosphate
Bn	benzyl
BOM	benzyloxymethyl
br	broad
Bu	butyl
Bz	benzoyl
CMP	cytidine monophosphate
conc	concentrated
COSY	correlation spectroscopy
CTP	cytidine triphosphate
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DEAD	diethylazodicarboxylate
DEPT	distortionless enhancement by polarisation transfer
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMAPP	dimethylallyl diphosphate
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
EE	ethoxyethylacetal
eq.	equivalent
ESI	electrospray ionisation

Et	ethyl
Fe(PDP)	[*N*,*N*'-Bis(2-pyridylmethyl)]-2,2'-bipyrrolidinebis(acetonitrile)iron(II) hexafluoroantimonate
GGPP	geranylgeranyldiphosphate
h.	hour(s)
HMBC	heteronuclear multiple bond correlation spectroscopy
HSQC	heteronuclear spin quantum correlation spectroscopy
IBX	2-iodoxybenzoic acid
IPP	isopentenyl diphosphate
IR	infrared
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
m	meta
*m*CPBA	*3*-chloroperbenzoic acid
MDR	multi drug resistance
Me	methyl
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOSEY	nuclear Overhauser effect spectroscopy
OTf	triflate
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PGP	P-glycoprotein
Ph	phenyl
PMB	*para*-methoxybenzyl
ppm	parts per million
Pr	propyl
q	quartet

quin	quintet
r.t.	ambient temperature
RedAl	sodium bis(2-methoxyethoxy)aluminum hydride
RSM	recovered starting material
s	singlet
t	triplet
Taxol®	Paclitaxel – 'Taxol' registered trademark of Bristol-Myers Squibb
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl group
TBDPS	*tert*-butyldiphenylsilyl group
TBS	*tert*-butyldimethylsilyl group
TES	triethylsilyl group
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography
TMP	tetramethylpiperidine
TMS	trimethylsilyl
Troc	2,2,2-trichloroethyl carbonate
Ts	toluene sulfonyl
UV	ultraviolet

Abstract

This thesis details work towards the efficient production of low oxidation state taxanes either by synthetic biology or synthetic chemistry. With over 400 natural taxanes isolated to date, many low oxidation state taxanes have been eclipsed by the intense interest in Taxol®. Some of these low oxidation state taxanes have important medicinal properties, many are currently unexplored.

Chapter I introduces the taxane family of natural products, their biosynthesis and biological activity.

Chapter II documents our efforts to utilise synthetic biology to rapidly access low oxidation state taxanes. In this chapter we describe the semi-synthesis of a novel oxa-cyclotaxane (OCT2) and 5α-hydroxytaxadiene, both low oxidation state taxanes. Here we also report that taxadiene, extracted from genetically modified tomato fruit, can undergo epoxidation and rearrangement with a reduced iron porphyrin to form the same products encountered when taxadiene 5α-hydroxylase is expressed in foreign organisms. We conclude that the established free radical mechanism, based heavily on speculation, is most probably incorrect in favour of an epoxidation/ rearrangement mechanism.

Chapter III describes our chemical synthesis of low oxidation state taxanes utilising carbon building blocks from renewable sources. We make use of the well-established Diels-Alder approach to construct the A and B taxane rings simultaneously, culminating in the synthesis of the natural product 5α-hydroxytaxadiene. This chapter then goes on to present both our work towards an asymmetric synthesis of taxanes utilising Yamamoto's chiral Brønsted acid catalyst and our efforts in the manipulation of taxane oxidation both by reduction and C-H oxidation.

Work reported here has been the subject of the following publication:

Accessing low-oxidation state taxanes: Is taxadiene-4(5)-epoxide on the taxol biosynthetic pathway? N. A. Barton, B. J. Marsh, W. Lewis, N. Narraidoo, G. Seymour, R. Fray and C. J. Hayes, *Chem. Sci.*, **7**, 2016, 3102-3107.

Chapter I

Introduction to Taxanes

1.0 The Taxane Natural Products

The taxanes are a group of diterpenoid natural products isolated from plants of the genus *Taxus*, such as *Taxus baccata* (European Yew) and *Taxus brevifolia* (Pacific Yew). Scientists were initially interested in the *Taxus* species due to the known toxicity of *Taxus baccata*. The first chemical extractions of this genus were carried out by Lucas in 1856.[1] Lucas isolated a crude mixture he called "taxine" which seemed to account for the Yew's infamous toxicity. It was not until the start of the twentieth century that others isolated more of these compounds and determined their structures. There is a large array of different carbon skeletons known, however by far the most common is the 6.8.6 ring system **1** (Figure 1).[2]

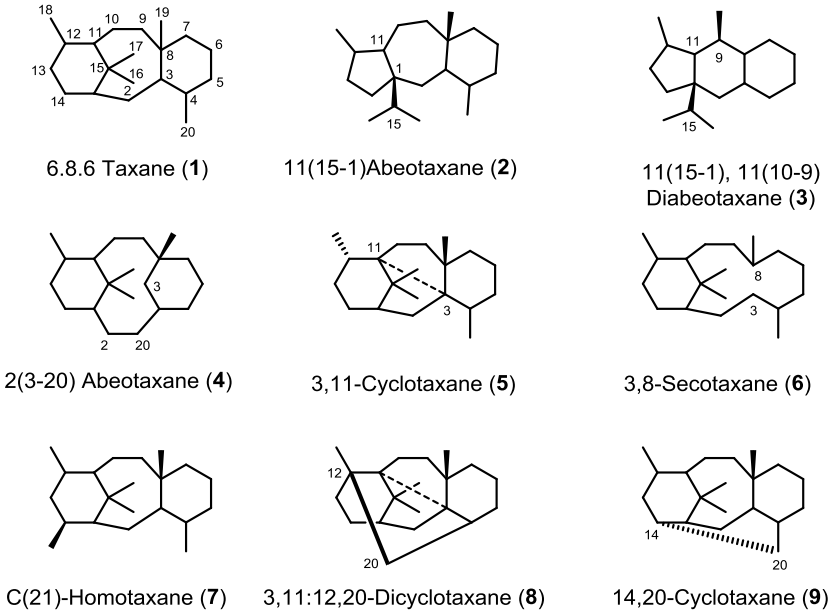
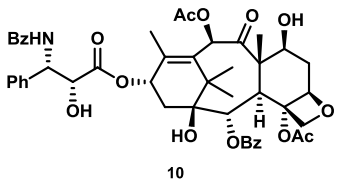


Figure 1: Common taxane carbon skeletons

Interest in these compounds was sparked by the isolation of Taxol® (**10**) in 1967 by Wani and co-workers from *Taxus brevifolia* in 0.02% yield.[3] Taxol® was reported to display

significant cytotoxicity in cancer cell lines. The structure of Taxol® **10** (Figure 2) was finally determined by NMR and X-ray crystallography in 1971.[3]



10

Figure 2: Taxol®

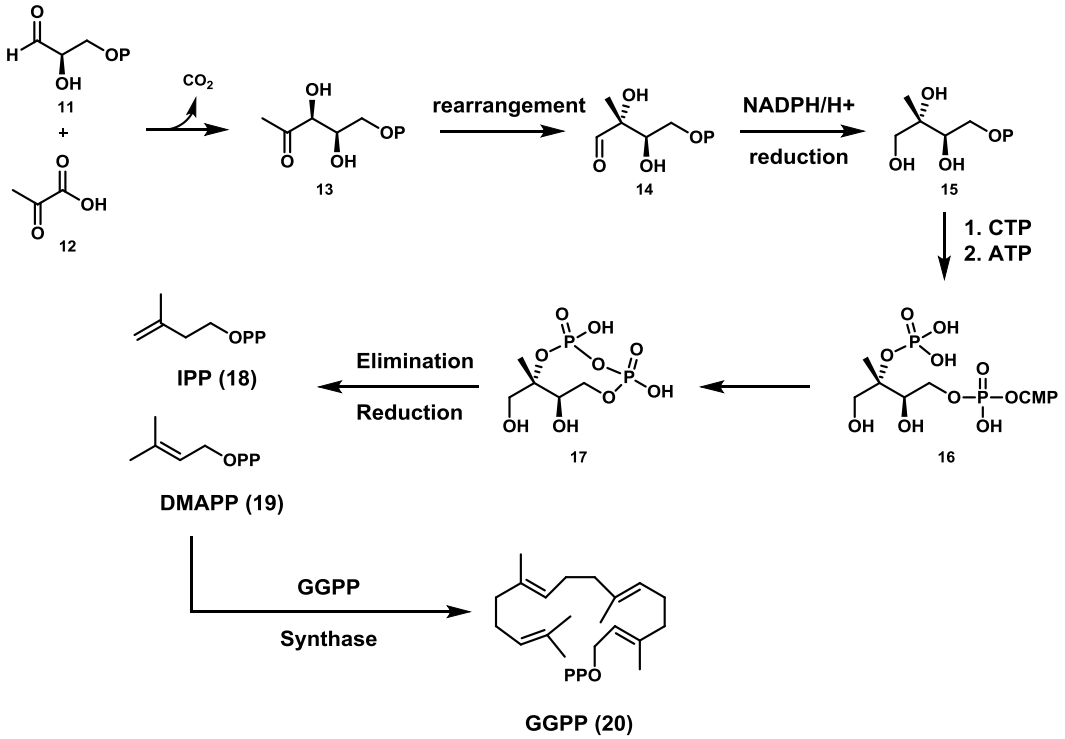
It was found that Taxol® catalyses tubulin polymerisation and stabilises microtubules, significantly inhibiting cell division.[4] Taxol® was developed further and is now a multi-million pound cancer drug routinely used for lung, head, neck, prostate, refractory ovarian, metastatic breast and cervical cancers as well as AIDS-related Kaposi's sarcoma.[5] Since the first discovery of taxanes from the genus *Taxus* over 400 naturally occurring compounds have been isolated and characterised.[2]

1.1 The Biosynthesis of Taxanes

The biosynthesis of taxanes occurs in three general stages. Firstly the carbon linear precursor geranylgeranyldiphosphate (GGPP) is produced, this is then cyclised by the enzyme taxadiene synthase and finally this skeleton is oxidised by a number of enzymes to produce a wide range of oxidised structures.

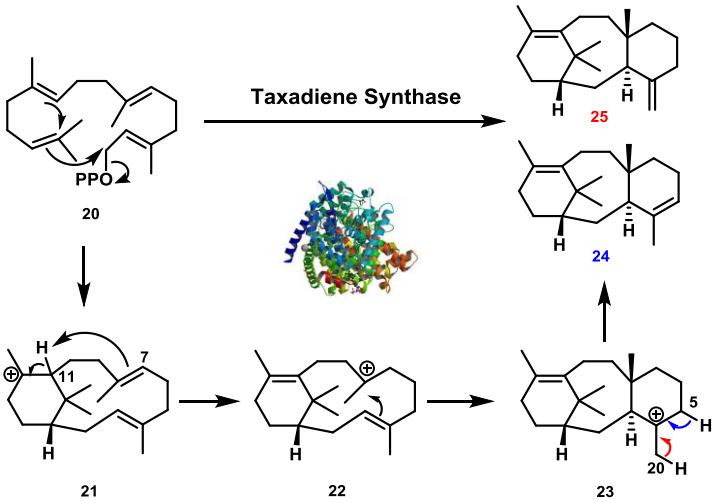
1.1.0 Biosynthesis of the Taxane Skeleton

The building blocks for the taxane skeleton are dimethyallyl diphosphate (DMAPP, **19**) and three units of isopentenyl diphosphate (IPP, **18**).[6] These are supplied by the methylerythritol phosphate pathway (MEP) contained within the chloroplasts (Scheme 1).[7]



Scheme 1: Production of GGPP **20**. CTP - Cytidine triphosphate CMP – Cytidine monophosphate ATP - Adenosine triphosphate, NADPH - Nicotinamide adenine dinucleotide phosphate.

Pyruvic acid is utilised for the synthesis of 1-Deoxy-D-xylulose 5-phosphate **13**. Following pinacol-type rearrangement and reduction, 2-C-methylerythritol 4-phosphate (MEP, **15**) is produced, this is phosphorylated twice to give **17**. Elimination of phosphate and reduction then gives IPP **18** and DMAPP **19**. These precursors are coupled by the enzyme geranylgeranyldiphosphate synthase (GGPPS) to give the linear precursor geranylgeranyldiphosphate (GGPP, **20**).[6] This linear precursor (GGPP, **20**) is later cyclised by the enzyme taxadiene synthase (Scheme 2).



Scheme 2: Action of taxadiene synthase on GGPP **20**.

Cyclisation of **20** with loss of diphosphate (OPP) gives the verticillenyl cation **21**, 11-7 H-shift then gives cation **22**, closure of the taxane C ring followed by deprotonation from either C20 or C5 gives taxa-4(5),11(12)-diene **24** or its isomer, taxa-4(20),11(12)-diene **25**.[8]

1.1.1 Biosynthetic Oxidation of Taxa-4(5),11(12)-diene

Following cyclisation, taxadiene, as a mixture of double bond isomers (**24** and **25**), translocates to the endoplasmic reticulum where it undergoes a series of oxidations catalysed by cytochrome P450 oxygenases.[9] The first of which is the C5 hydroxylation by the enzyme taxadiene 5α-hydroxylase.[10] This catalyses the oxidation of taxadiene **24** to 5α-hydroxytaxa-4(20)-11(12)-diene, the mechanism of which will be the subject of the second chapter of this thesis.

The exact order of the following oxidations is not well understood and has only been approximated by surveying functionalised isolated taxanes. However, following C5 oxidation the most likely order follows; C10, C9, C13, C2, C7 and C1.[6]

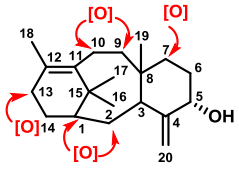


Figure 3: Enzymatic oxidation of the taxane skeleton

C13α and C10β hydroxylases, both identified by Croteau, are thought to be less selective in their roles and can interchange substrates.[11,12] The sequence and enzymes responsible for the next series of oxidations are currently unknown. The formation of the oxetane ring is also not fully understood.[13,14] An interesting hypothesis is that instead of site selective enzymatic oxidations the oxidation of taxanes is governed by their inherent structure. The enzymes may be promiscuous and the oxidation substrate controlled.

Throughout these oxidations intermediate hydroxyl groups can be intercepted by acyl transferase enzymes for production of acetyl, benzoyl and cinnamoyl substituted taxanes. They can also be oxidised further to ketones. This divergent biosynthesis accounts for the staggering number of unique taxanes isolated to date.[6]

1.2 Oxidation Pyramid of Taxanes

Rapid oxidation of the taxane skeleton by cytochrome P450 enzymes accounts for the very few low oxidation state taxanes isolated from the *Taxus* genus (those below Taxol® in Figure 4). This lack of extracted material along with the initial biological interest in Taxol ® has left over 400 lower oxidation state taxanes neglected by the chemistry and biology communities. There have been more syntheses of Taxol ® than syntheses of all other taxanes combined.

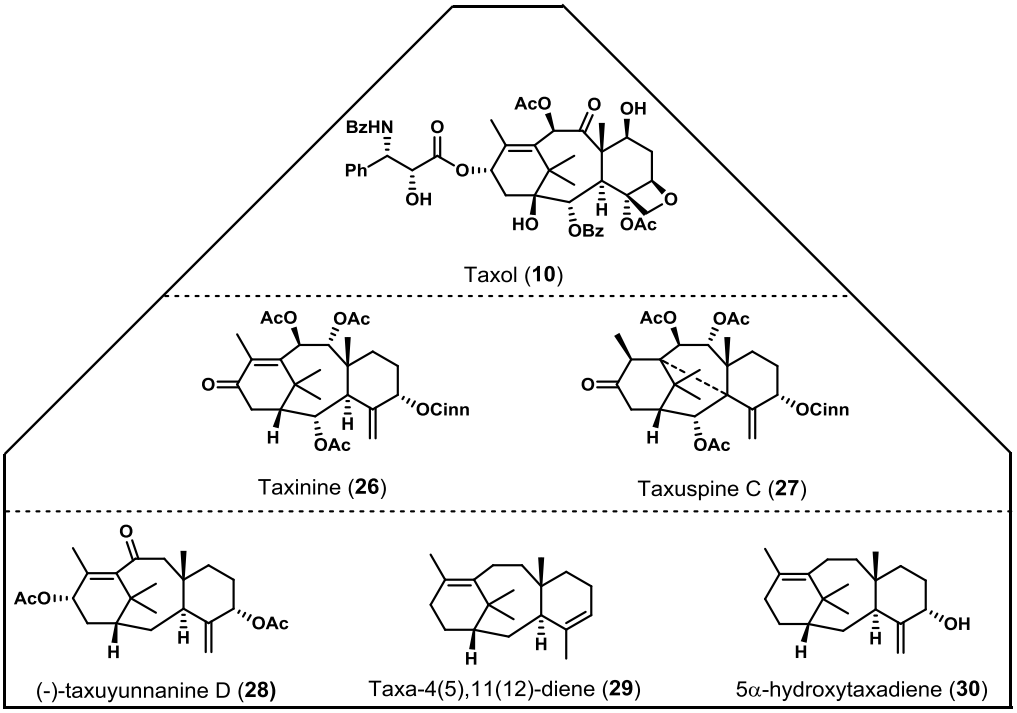


Figure 4: Taxane pyramid of oxidation levels.

Despite Taxol® taking much of the limelight, some low oxidation state taxanes have been found to hold significant biological activity. Taxinine **26** (Figure 4) for example has been shown to reverse multi drug resistance.[15]

1.3 Biological Activity of Low Oxidation State Taxanes

Recently efforts have been made to study the bioactivities of some low oxidation state taxanes. The main area of study is in the use of these compounds in the treatment of multi drug resistant cancer.

1.3.0 Low Oxidation State Taxanes and Multi-Drug Resistant Cancer (MDR)

From the first use of cytotoxic drugs in the treatment of cancer, drug resistance has been a major problem in treatment. Compounds such as Taxol® **10** have been used extensively as cytotoxic chemotherapy agents, but it is now becoming clear that low oxidation state taxanes can be used to combat drug resistance.[15]

During treatment, cancer can become resistant to the chemotherapy drug being used. This is normally due to two mechanisms: The cancer has specific resistance to the drug being used, caused by drug specific mutations in the cell, in which case a different drug may still be effective. Alternatively, the cancer can develop multi drug resistance. In this case, it can be challenging to find another drug that is effective.[16]

1.3.1 P-glycoprotein (PgP)

Multi-drug resistance is thought to occur due to the up regulation of cell efflux pumps such as P-glycoprotein (PgP).[17] PgP is a transmembrane protein of the ATP-binding cassette family, which can export a wide range of compounds out of the cell, particularly lipophilic, cytotoxic drugs. This efflux causes the levels of cytotoxic drug within the cell to drop below its therapeutic threshold, so rendering the drug ineffective.

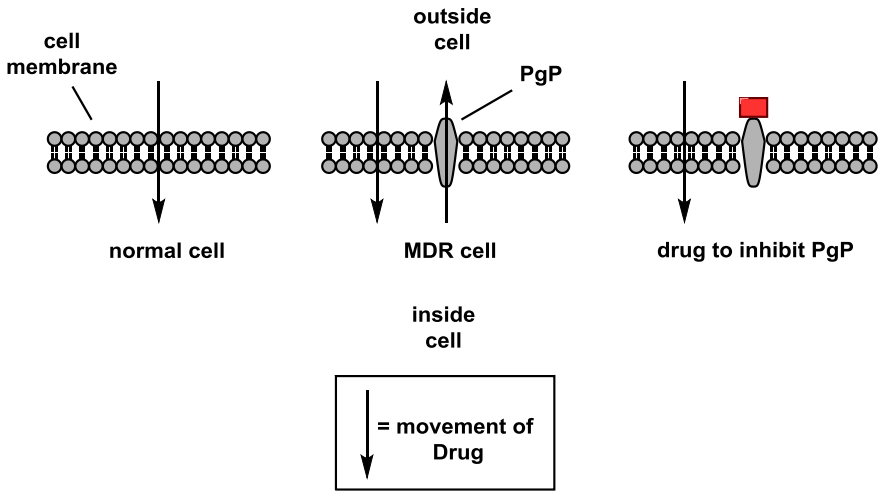


Figure 5: Effect of PgP pump inhibition on drug movement.

There are two ways of approaching the overexpression of PgP in cancer. A drug could be developed which was not affected by PgP and so could build up to cytotoxic levels within the cell without being removed. The other method would be to directly inhibit PgP alongside treatment with a chemotherapy drug.[16] (Figure 5)

Taxanes have be explored for this purpose and a number have been shown to either inhibit PgP, or not be effected by it.[18] Some PgP inhibitors are shown below.

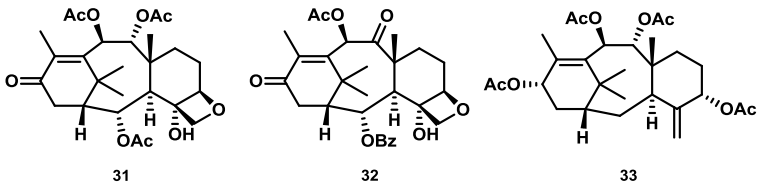
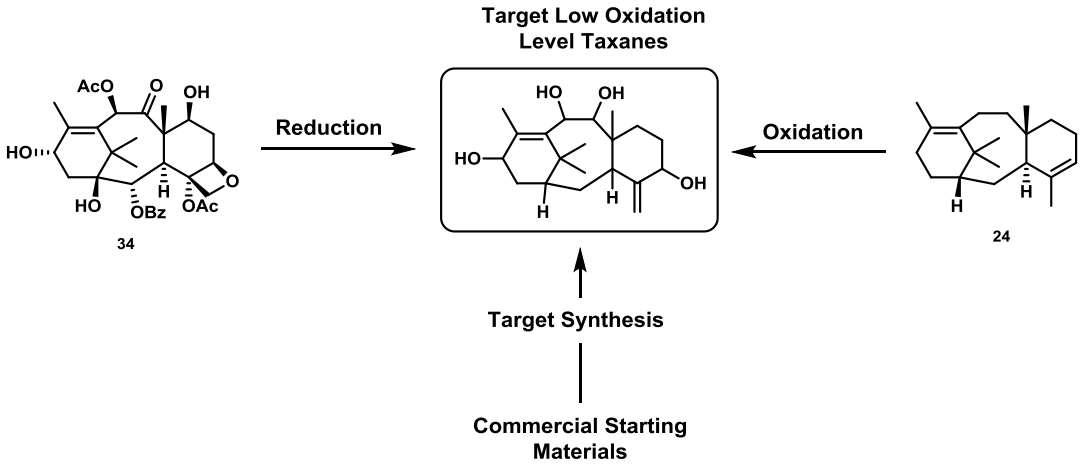


Figure 6: Taxanes that inhibit PgP.

It is clear that taxanes with low levels of oxidation are of interest in the area of MDR cancer, but their therapeutic uses have been studied beyond cancer, including as potential agents against Tuberculosis.[19]

Project Aims

There are clear incentives to explore the levels of oxidation between taxadiene and Taxol®. We were keen to investigate this relatively unexplored area. Accessing these compounds is however challenging.



Scheme 3: Strategies to access low oxidation state taxanes: oxidation, reduction or target synthesis.

There are three main strategies to access low oxidation state taxanes. The first, classic approach, would be the total synthesis of a particular target (target synthesis). This could be efficient but would potentially make it difficult to access a range of analogues for biological testing without a highly divergent route.

Using the second strategy, we could extract high oxidation state taxanes such as the widely available baccatin III **34** and then reduce this to a range of low oxidation taxanes. This has been attempted before but is normally limited to simple reduction of ketones and esters to alcohols. [20] It is very difficult to selectively remove oxidation completely.

The final strategy entails the iterative oxidation of simple carbon skeletons such as taxa-4(5),11(12)-diene **24** in order to access each oxidation level in turn. This could potentially provide hundreds of compounds for biological investigation. Our first step therefore, was

to access the simple carbon framework taxa-4(5),11(12)-diene **24**. This taxane is not widely available from plant extraction,[8] fortunately many groups have worked towards its production in foreign organisms.

Chapter II

Oxidation of Taxadiene and Implications for the Biosynthesis of Taxol®

2.0 Introduction

2.0.1 Producing Taxanes in Foreign Organisms

Since the discovery of Taxol® chemical biologists have been interested in producing taxanes in foreign organisms through genetic manipulations. Many groups have used genetic modifications to produce taxa-4(5),11(12)-diene **24** in a range of organisms.

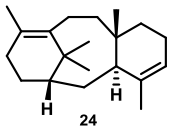


Figure 7: Taxa-4(5),11(12)-diene **24**.

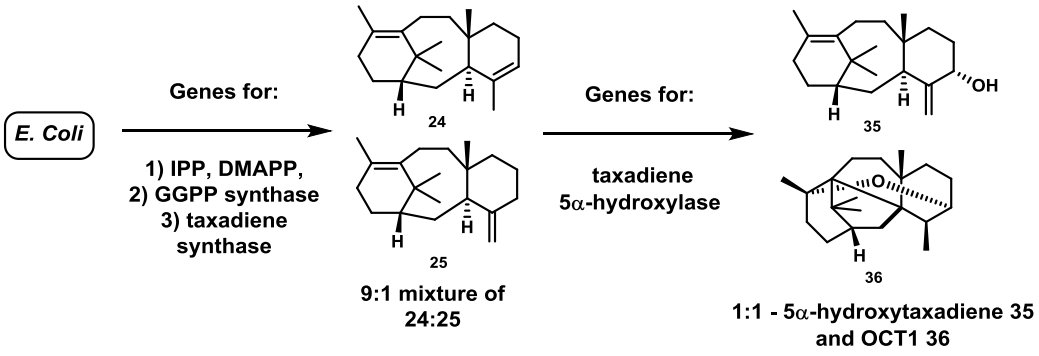
Production of Taxadiene in *E. Coli*

Croteau 1995

The first work in this area was conducted in 1995 by Croteau and co-workers with their purification and characterisation of the enzyme taxadiene synthase.[21] After successful isolation of the cDNA encoding taxadiene synthase, Croteau was able to clone the enzyme into *E. Coli*. This however suffered from poor solubility and produced only microgram quantities of taxadiene.[22] Truncating the cDNA, Croteau was able to produce a more soluble enzyme, solving the crystal structure in 2011[23] and expressing this in *E. Coli*, produced 1.3 mg/L of taxadiene. Although improved, this yield was poor. It was hypothesised that the low yield of taxadiene **24** was due to a low expression of the pathway to produce GGPP. Boronat attempted to improve this by cloning the truncated gene into *Arabidopsis* (Thale Cress) that produces large amount of GGPP. This however produced unhealthy plants and sub-milligram quantities of taxadiene.[24] All this work was vital in paving the way for a key discovery by Stephanopoulos in 2010.

Stephanopoulos 2010

Stephanopoulos expressed genes for the methylerythritol phosphate pathway to produce IPP and DMAPP, GGPP synthase and taxadiene synthase in *E. Coli*, producing taxadiene in a yield of 1 g/L, a significant improvement in the field.[25] Stephanopoulos went one step further expressing taxadiene 5α-hydroxylase in *E. Coli* to produce a mixture of 5α-hydroxytaxadiene **35** and oxa-cyclotaxane (OCT) **36** in 21 mg/L and 24 mg/L respectively.



Scheme 4: Stephanolpoulos' production of taxadiene **24**, 5α-hydroxytaxadiene **35** and oxa-cyclotaxane (OCT1) **36** in *E.Coli*.

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).[26] A small quantity of taxadiene was produced (1.0 mg/L) along with sub milligram quantities of 5α-hydroxytaxadiene **35.** Interestingly no OCT **36** was produced and the following two biosynthetic steps utilising the O-acetal transferase and 10β- hydroxylase failed to produce any product. It was reasoned that the poor yield of the taxadiene 5α-hydroxylase step was limiting substrate availability for the following two enzymes.

In 2008 Jennewein improved on this system and produced a yeast model that could provide 8.7 mg/L of taxadiene.[27]

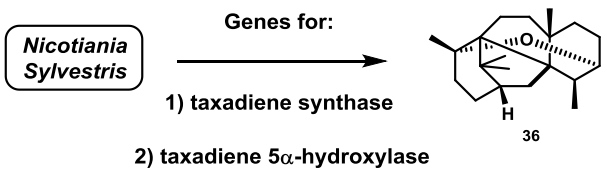
Production of Taxadiene in Tomato Plants

In 2007 Fray and Hayes reported the expression of taxadiene synthase in *yellow flesh* tomato fruit.[28] These plants produce large quantities of GGPP but lack the enzymes to produce carotenoids. The expression of natural taxadiene synthase produced plants that were infertile and displayed stunted growth, however production of taxadiene was observed at 160 mg / Kg. This was not as high as the subsequent work by Stephanopoulos in *E.Coli* but was a significant improvement on all other methods to date.

Production of Taxadiene in Tobacco

Tissier 2008

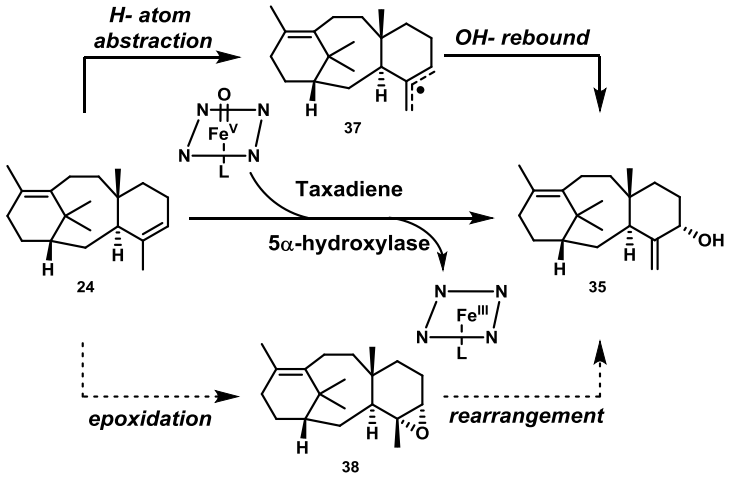
In 2008 Tissier expressed taxadiene synthase and 5α-hydroxylase in tobacco (*Nicotiania Sylvestris*).[29] Unfortunately, in combination, Tissier found that taxadiene **24** was formed in only 2 mg/Kg and OCT **36** was formed as the only oxidised taxane. This is at odds with Stephanopoulos' work in yeast that seems to suggest this transformation is possible, albeit inefficient.



Scheme 5: Tissier's unexpected production of oxa-cyclotaxane (OCT) **36** in *Nicotiania Sylvestris*.

2.0.2 Taxa-4(5),11(12)-diene 5α-hydroxylase

The first oxygenase in the biosynthetic pathway is the cytochrome P450, taxadiene 5α-hydroxylase.[10] This catalyses the oxidation of taxadiene **24** to 5α-hydroxytaxa-4(20)-11(12)-diene **35**. (Scheme 6) Williams and Croteau suggested two mechanisms for this biosynthetic oxidation.[14] Firstly, the enzyme promotes an oxidation-rearrangement process *via* hydrogen atom abstraction by the iron(V) oxo species. This gives an allyl radical **37**. Hydroxylated product **35** is then formed following rapid hydroxy rebound from the iron to the 5-α position.

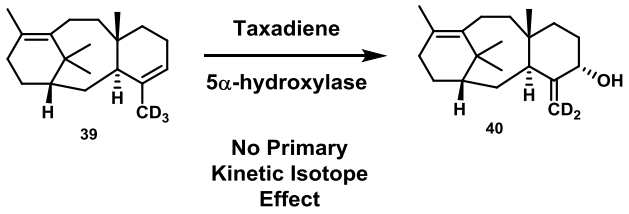


Scheme 6: 5α-hydroxylase mechanism.

A second suggestion was that the oxidation proceeds *via* epoxide **38**; C20 deprotonation and rearrangement then gives 5α-hydroxytaxa-4(20)-11(12)-diene **35**. The first mechanism (*via* an allyl radical) was favoured as both isomers of taxadiene **24** and **25** are converted to the same product **35**, 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.[29,30]

Croteau went on to conduct a kinetic isotope experiment using C20-$^{2}H_3$ taxa-4(5)-11(12)-diene. A KIE would be expected with a radical mechanism where an H atom abstraction

from C20 is probably rate limiting. In this experiment however, no primary kinetic isotope effect was observed.



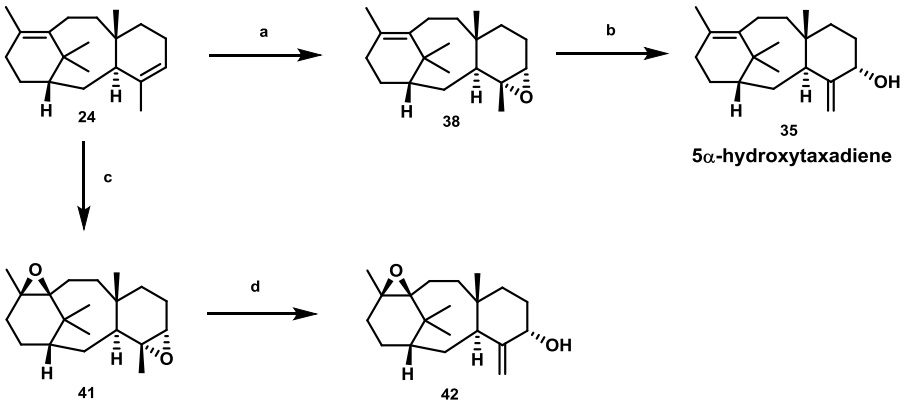
Scheme 7: Williams and Croteau kinetic isotope experiment.

In discussing this experiment Williams noted '[the experiment] unexpectedly revealed that the deuterated substrate yielded slightly more taxa-4(20),11(12)-dien-5α-ol than did the unlabelled substrate.' This would suggest a small inverse kinetic isotope effect. In fact, small (secondary) inverse kinetic isotope effects have been measured for epoxidation of deuterium labelled substrates both chemically with both mCPBA and cytochrome P450 enzymes.[31,32]

Despite this conflicting experimental evidence the radical mechanism for hydroxylation has become accepted in the literature. We suspected that the epoxide mechanism (Scheme 6) should not be discounted so readily on the basis of this limited experimental evidence. With our access to taxadiene from tomatoes we could explore the oxidation of taxadiene **24** to 5α-hydroxytaxa-4(20)-11(12)-diene **35.**

2.0.3 Epoxidation of Taxa-4(5),11(12)-diene

Our first step was to explore the epoxidation of taxadiene, having access to previously discounted epoxide **38** would help us explore its viability as an intermediate in the first biosynthetic oxidation of taxadiene. Previous work within the group succeeded in the epoxidation of taxadiene (Scheme 8).[33]



Scheme 8: Hayes epoxidation of taxadiene **24.**

Reagents and Conditions: **a)** DMDO, acetone/CH_2Cl_2, 63%. **b)** ^{n}BuLi, TMP, Et_2AlCl, PhMe, 60%. **c)** DMDO (2.0 eq.), acetone/CH_2Cl_2, 75%. **d))** ^{n}BuLi, TMP, Et_2AlCl, PhMe, 50%.

Hayes found that taxadiene **24** underwent epoxidation regioselectively at the 4(5) alkene over the 11(12) alkene. This is most probably due to steric hindrance at the more substituted 11(12) akene. This epoxide **38** could then be rearranged with Yamamoto's reagent to give the natural product 5α-hydroxytaxadiene **35.** An interesting observation at this stage was that epoxide **38**, which was discounted by Williams as an intermediate in Taxol biosynthetic pathway was particularly unstable to silica chromatography, decomposing to a complex mixture of products. If an excess of DMDO was used, taxadiene was epoxidised at both the 4(5) and 11(12) alkene to give bis-epoxide **41**. This compound was stable to silica chromatography and could be rearranged to the crystalline

epoxy alcohol **42**. A crystal structure of **42** confirmed the stereochemistry of the epoxidation.

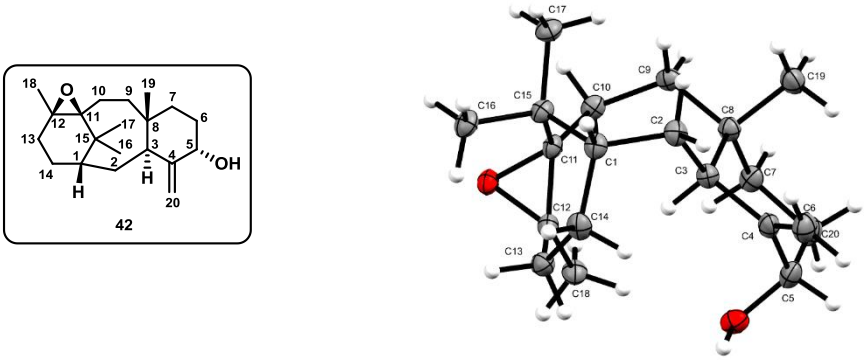


Figure 8: Crystal structure of epoxy alcohol **42**.

Oxidation occurs from the bottom face of the 4(5) alkene and the outside face of the 11(12) alkene. This structure displays beautifully the classic bowl shape of taxane natural products that controls the observed reactivity.

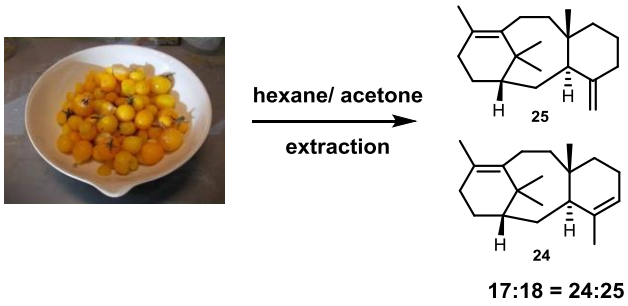
With the epoxidation of taxadiene completed within the Hayes group, we were ready to explore the intriguing instability of key epoxide **38** to silica gel and develop further routes to low oxidation state taxanes from taxadiene.

2.1 Results and Discussion

2.1.0 Extraction of Taxadiene

To obtain a sufficient quantity of taxadiene to complete synthetic studies we utilised genetically modified tomato fruit supplied by Fray and co-workers.[28] The procedure for extraction had been optimised within the group, improving on the original procedure using freeze dried fruit, we could now use wet fruit without any prior processing.[33]

We began by crushing the fresh/wet fruit before washing with acetone to removed excess water. This gave a waxy pulp which was then stirred in hexanes for 48 hours. The acetone washings were washed with hexane and the hexane then combined with the previous extract. This was dried over magnesium sulfate and the solvent evaporated under reduced pressure to yield a crude extract. This was then purified by silica gel chromatography to give on average 13 mg of taxadiene per 500 g of fresh fruit. Taxadiene was isolated as a 17:1 mixture of taxa-4(5),11(12)-diene **24** to taxa-4(20),11(12)-diene **25**.[28] (Scheme 9) This mixture will be referred to here as 'taxadiene **24**' for ease of discussion as this is the major component of the mixture (^{1}H NMR available in appendix I)



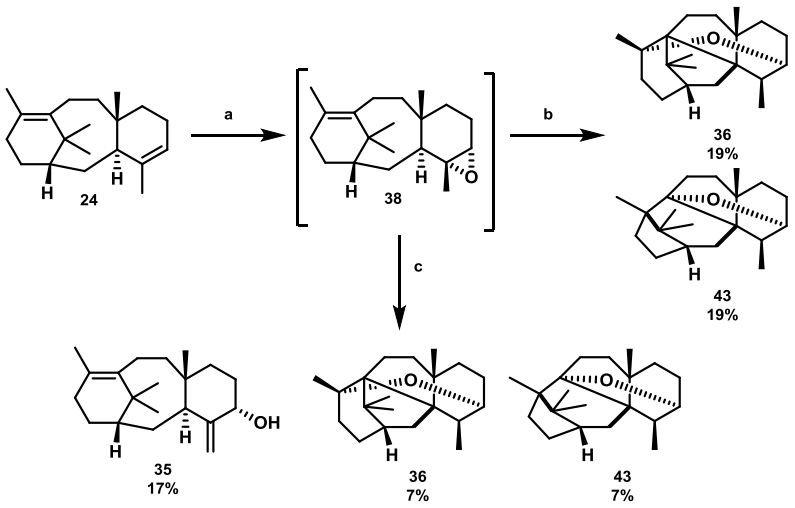
Scheme 9: Extraction of taxadiene **24** and **25.**

It is worth noting here that the mass of taxadiene recovered does vary within the year from batch to batch, this is presumably due to variation in plant health and growth.

2.1.1 Oxidation of Taxadiene

Epoxidation of the 4(5) alkene in taxadiene **24** had previously been studied in the group and it was found that the resulting 4(5) epoxide **38** was unstable on silica gel. This led us to investigate acid catalysed rearrangements of the epoxide.

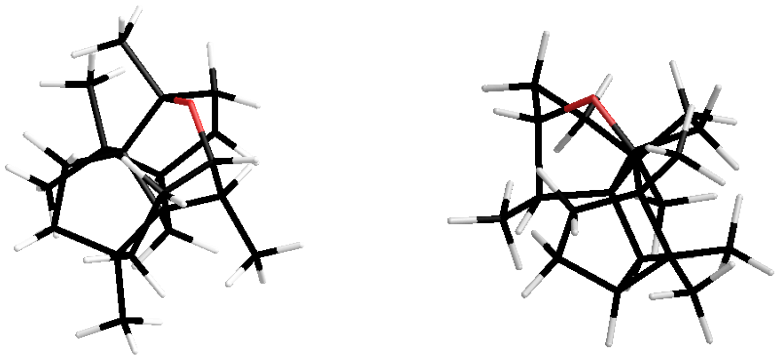
For our experiments we elected to use substoichiometric quantities (0.6 eq.) of dimethyldioxirane (DMDO) for the conversion to mono epoxide **38**, thus avoiding reaction at the 11(12) alkene. We also decided to carry out the reactions in *d*6-benzene for ease of monitoring and as an alternative to chloroform so that no additional acid was present.



Scheme 10: Acid rearrangements of 4(5)-epoxytaxadiene **38**.

Reagents and Conditions: **a)** DMDO (0.6 eq.), *d*6-benzene, r.t., 1 h. **b)** SiO_2, *d*6-benzene, 70 ˚C, 1 h., **36**-19%, **43**-19%. **c)** *p*-TSA (0.6 eq.), *d*6-benzene, r.t., 40 min., **35**-17%, **36**-7%, **43**-7%.

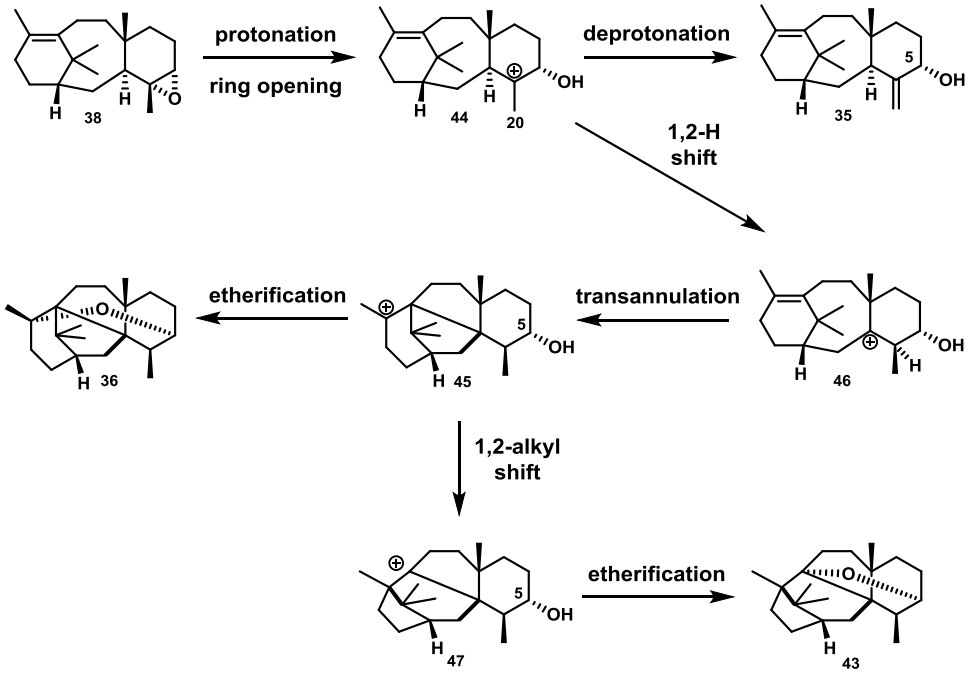
On treatment with 0.6 equivalents of DMDO (43.6 mM in acetone), taxadiene reacted to give a 1:4 mixture of unreacted taxadiene **24**: epoxide **38**. Discrepancies between this ratio and the quantity of DMDO added were common when working on a small scale. To initially test for any thermal decomposition of epoxide **38**, the mixture was subjected to heating at 70 ˚C. No decomposition of epoxide **38** was observed. The sample was then heated again to 70 ˚C in the presence of silica gel. After one hour complete conversion was seen by ^{1}H NMR to cyclic ethers **36** and **43**. This mixture was purified to give 19% yield of **36** and 19% yield of **43**. Cyclic ether **36** (oxa-cyclotaxane, OCT) has previously been isolated by Rontein and co-workers when expressing both taxadiene synthase and taxadiene 5α-hydroxylase together in tobacco plants.[29] Cyclic ether **43** is a new compound to the literature. We decided to investigate this rearrangement further. Hypothesising that a stronger acid could shift the product distribution we treated epoxide **38** with toluenesulfonic acid (*p*-TSA). This also gave equal quantities of **36** and **43** (7% each). However, the major compound from this reaction was 5α-hydroxytaxadiene **35** in 17% yield.



36 **43**

Figure 9: OCT1 **1** (**36**) and OCT2 (**43**) molecular models (ChemDraw3D, 2014) display the molecular complexity of these products that is difficult to represent in 2D drawings.

We propose compounds **35**, **36** and **43** are all formed from protonation of epoxide **38** followed by carbocation rearrangements (Scheme 11). Protonation of **38** followed by ring opening gives cation **44**, deprotonation at C20 of this intermediate gives 5α-hydroxytaxadiene **35**. Competing with deprotonation is a 1,2-hydride shift from the bridgehead which gives cation **46**. The 11(12) alkene then adds to this cation to give transannulation product **45**. Quenching the carbocation here with the C5 alcohol finally gives cyclic ether **36** (OCT1). Alternatively, a 1,2-alkyl shift from the bridgehead followed by quenching of cation **47** gives **43** (OCT2). On using a weak acid (silica) the 1,2 hydride shift from the bridgehead seems compete with deprotonation at the C20 methyl.

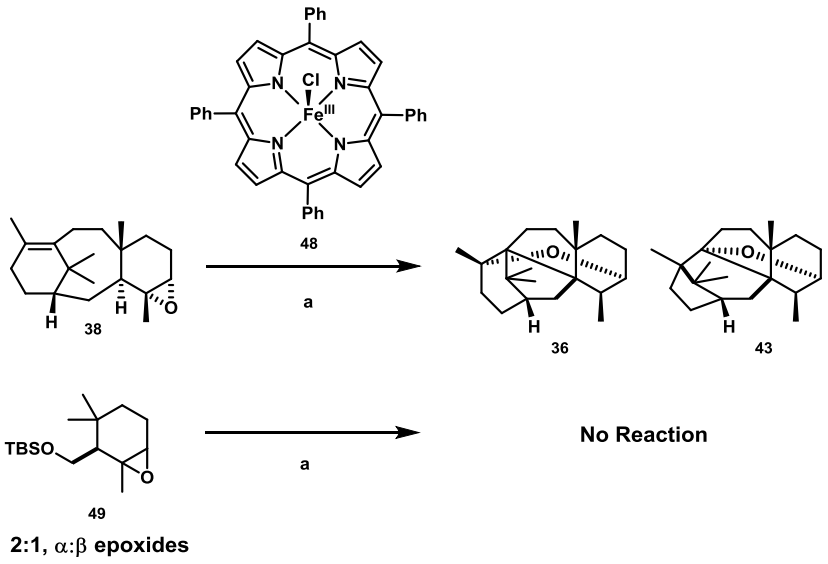


Scheme 11: Acid rearrangements of 4(5)-epoxytaxadiene **38**.

The fact that epoxide **38** rearranges easily even under weakly acidic conditions provides an explanation as to why no epoxide has previously been observed or isolated. The enhanced reactivity of epoxide **38** towards acid catalysed rearrangement caused us to reconsider the previously held assumption that iron (III) porphyrins and so by extension

taxadiene 5α-hydroxylase cannot mediate the rearrangement to **35**, **36**, or **43**. This previous assumption has led to the opinion that taxadiene 5α-hydroxylase oxidises taxadiene by a radical mechanism and not *via* an epoxidation.

To test this assumption we treated epoxide **38** in *d6*-benzene with a reduced iron (III) porphyrin (Fe(TPP)Cl, **48**) (Scheme 12).

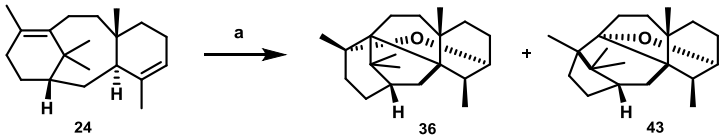


Scheme 12: Iron (III) porphyrin rearrangements of 4(5)-epoxytaxadiene **38** and the corresponding control experiment with terpene derived epoxide 49.

Reagents and Conditions: **a)** Fe(TPP)Cl (**48**), *d*6-benzene, r.t., 72 h. **36**:**43**-1:1 (^{1}H NMR).

After 72 h, ^{1}H NMR analysis showed complete conversion to a 1:1 mixture of cyclic ethers **36** and **43**. As a control experiment, epoxide **49**[34] was treated with **48** under identical conditions and no rearrangement was observed. This supports the long held belief that reduced iron porphyrins are not lewis acidic enough to open epoxides but also demonstrates that epoxide **38** is particularly prone to rearrangement.[30] This is mounting evidence that epoxide **38** cannot be discounted as an intermediate in the biosynthesis of taxanes.

As a further experiment we considered whether the iron porphyrin (Fe(TPP)Cl) could be used to epoxidise and rearrange taxadiene, so mimicking the action of taxadiene 5α-hydroxylase in tobacco.[29] Treatment of taxadiene **24** with Fe(TPP)Cl and hydrogen peroxide as a terminal oxidant gave slow conversion to products **36** and **43**.



Scheme 13: Biomimetic oxidation of taxadiene **24**.

Reagents and Conditions: **a)** Fe(TPP)Cl (10 mol%), H_2O_2 (1 eq.) CH_2Cl_2 , r.t., 72 h. **36**-5% **43**-3%.

This experiment completes in the lab the full transformation that is observed when taxadiene 5α-hydroxylase is expressed in tobacco. We have already shown that epoxide **38** can be rearranged with a reduced iron porphyrin to **36** and **43**. Here we observe the same products, suggesting that epoxide **38** is most probably an intermediate in this reaction and therefore epoxide **38** is also a likely intermediate in the oxidation of taxadiene by taxadiene 5α-hydroxylase.

<u>Stephanopoulos 2016</u>

Publishing almost simultaneously with our efforts in 2016, Stephanopoulos also suggested epoxide **38** as an intermediate in the biosynthesis of Taxol.[35] Stephanopoulos expressed taxadiene 5α-hydroxylase in three different host organisms; a bacteria, *E. coli* and two different yeasts, *Y. lipolytica* and *S. cerevisiae*. These three different organisms were then cultured in both rich and minimal media. This provided six different environments for the oxidation pathway. Taxadiene **24** was supplemented exogenously and the product distributions determined by GCMS. These organisms produced a range of oxidised taxanes including OCT1 **36**, OCT2 **43** and 5α-hydroxytaxadiene **35**. Stephanopoulos observed

significantly different product distributions between each organism and even between each media with the same organism. Stephanopoulos proposed that this difference in enzyme selectivity between each organism and environment is not due to a change in the enzyme itself, rather the formation of a reactive intermediate (epoxide **38**) that is subject to decomposition to different products dependant on the cellular environment.

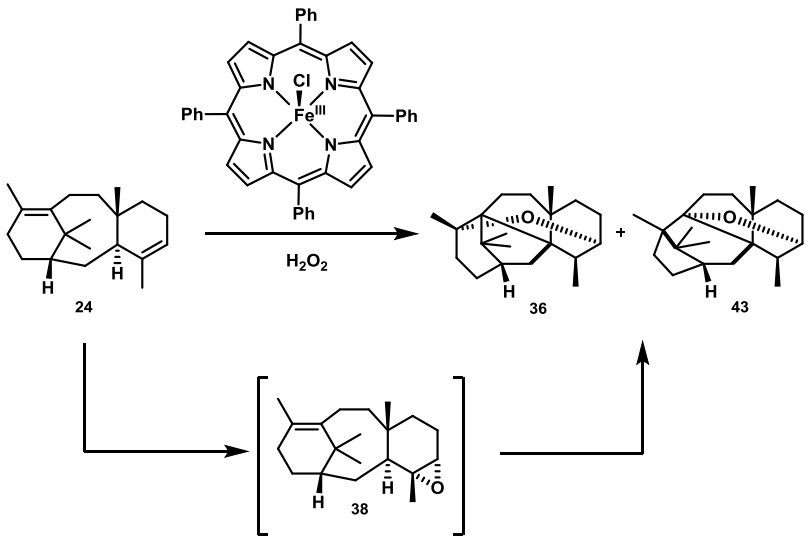
To further explore the idea of the environmental decomposition of epoxide **38** Stephanopoulos expressed both taxadiene synthase and taxadiene 5α-hydroxylase in *E. coli* and cultured the bacteria under three different conditions. To each culture was added either dodecane, diisononyl phthalate (DINP), or a solid C18 chromatography resin. Each culture gave significantly different product distributions. Dodecane and diisononyl phthalate could feasibly interact directly with taxadiene 5α-hydroxylase and change the enzymes selectivity. C18 chromatography resin however has a large particle size (40-60 μm), this is far too large to enter the cell. This supports once again the hypothesis that 5α-hydroxytaxadiene **35**, OCT1 **36** and OCT2 **43** are products of the rearrangement of epoxide **38** and this occurs away from the enzymatic site.

Stephanopoulos conducted a further experiment. A culture of *E.coli* that previously produced a range of products (OCT1, OCT2, 5α-hydroxytaxadiene) when supplemented with taxa-4(5),11(12)-diene **24** was instead supplemented with purified taxa-4(20),11(12)-diene **25.** In this experiment only 5α-hydroxytaxadiene was produced. This isomer of taxadiene cannot feasibly undergo oxidation *via* an epoxidation pathway. This has been used previously as an argument in support of both isomers of taxadiene **24** and **25** undergoing oxidation *via* a radical pathway. This experiment however suggests that the two isomers of taxadiene (**24** and **25**) undergo different oxidation pathways. Taxa-4(20),11(12)-diene **25** appears to oxidise through the radical pathway proposed by Williams. Whereas, there is now significant evidence from both our work and that of

Stephanopoulos that taxa-4(5),11(12)-diene **24** undergoes oxidation *via* an epoxidation pathway.

2.2 Conclusion and Future Work

This chapter has detailed our investigations into the first oxidation step in the biosynthesis of taxanes. We have found an oxidation in the laboratory that mimics the action of taxadiene-5α-hydroxylase in tobacco.[29] This work which is supported by the recent work of Stephanopoulos suggests that epoxide **38** should be considered the likely intermediate in the mechanism of taxadiene-5α-hydroxylase. We have also isolated in the course of this work cyclic ether **43**, a low oxidation state taxane, which Stephanopoulos also detected.



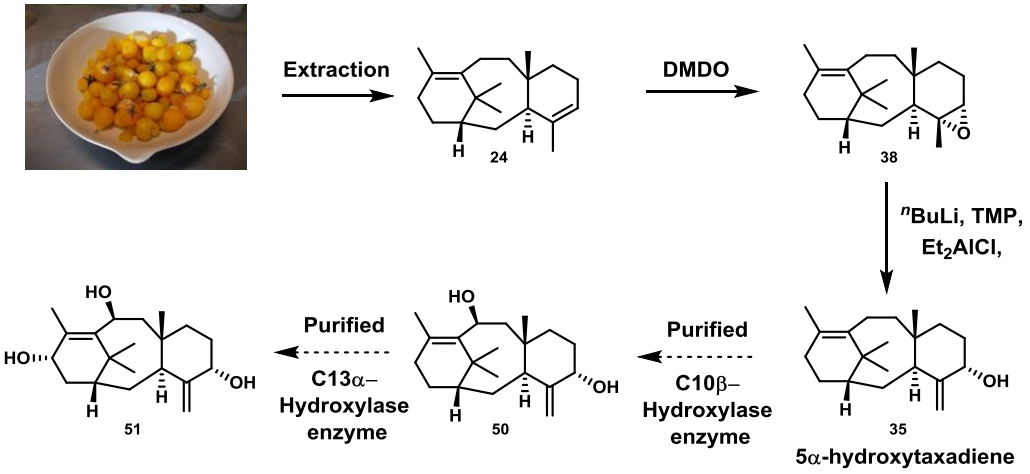
Scheme 14: Biomimetic oxidation of taxadiene.

Our hypothesis is that taxadiene 5α-hydroxylase produces epoxide **38** that then undergoes facile rearrangement to 5α-hydroxy taxadiene catalysed by weak acid. In the

environment of the *Taxus* plant this process is seems reasonably selective for 5α-hydroxy taxadiene but in other organisms this rearrangement is not selective.

It is clear from this work that utilising synthetic biology for the production of low oxidation state taxanes is challenging. A number of groups have found it difficult to replicate the transformation of taxadiene into 5α-hydroxy taxadiene in foreign organisms.

Our future work in this area would progress towards using genetically modified tomatoes to access higher oxidation state taxanes. This could include the use of a combined chemical synthesis and synthetic biology approach. (Scheme 15)



Scheme 15: Combined synthetic chemistry- synthetic biology approach.

The use of purified C13 and C10 hydroxylase enzymes produced from sequences already characterised by Croteau[11,12] could allow the use of enzymes as synthetic reagents for the next oxidation steps.

With challenges still to be overcome in the synthetic biology approach to low oxidation state taxanes we turned our attention to chemical synthesis of the taxane skeleton with the intention of accessing higher oxidation state taxanes.

Chapter III

The Total Synthesis of Low Oxidation State Taxanes

3.0 Introduction

3.0.1 Total Syntheses Taxanes

This chapter will start with a short review of the relevant taxane syntheses in the literature beginning with highly oxidised compounds before moving onto the synthesis of less oxidised natural products with the 6,8,6 ring system, such as taxa-4(5),11(12)-diene **24**.

High Oxidation State Taxanes

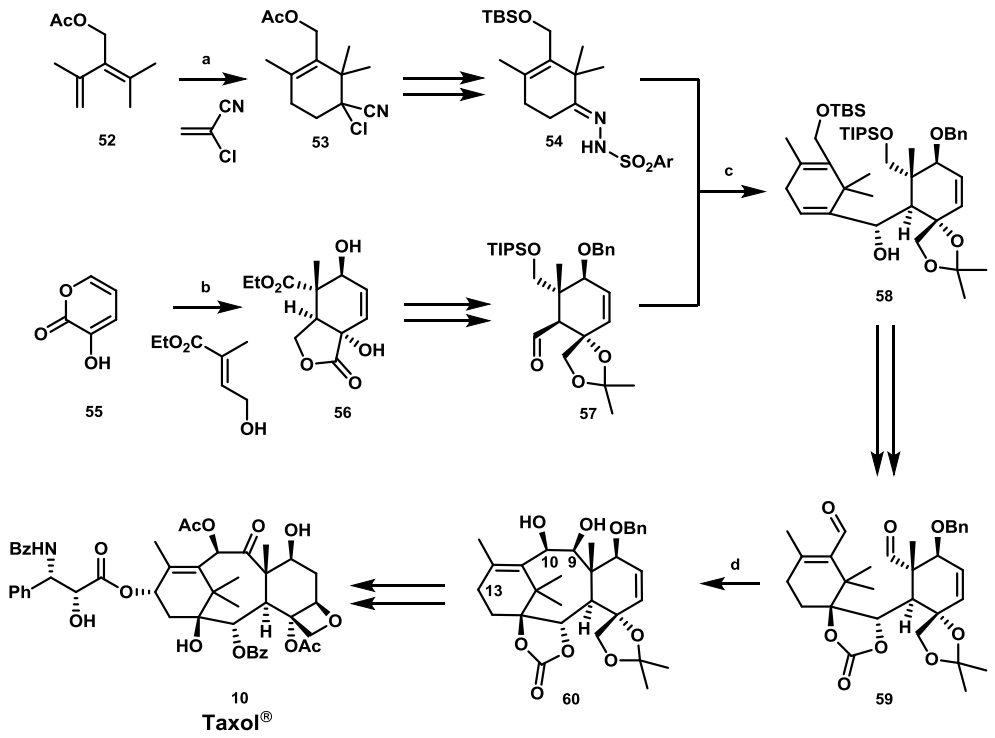
Synthesis of Taxol®

Following its isolation in 1967 and initial characterisation as a potent anticancer agent, the first taxane to receive significant attention from the synthesis community was Taxol® (**10**) this triggered many chemists to begin work towards its total synthesis. This area developed rapidly during the late 20th and early 21st century culminating in the total synthesis of Taxol® initially reported in 1994, independently by the groups of Nicolaou[36–39] and Holton.[40] Taxol® has been prepared ten times since its isolation, with seven total syntheses,[40–48] and three formal syntheses.[49–52]

Although we aim to synthesise low oxidation state taxanes it is important to take into consideration these landmark syntheses of Taxol®. These syntheses vary in the approach to the taxane skeleton, the popular approaches will be exemplified below. For our purposes it is important to recognise that all of these routes involve the introduction of oxidation early on, to facilitate carbon-carbon bond forming reactions.

Formation of A and C rings Followed by B Ring

The most popular approach to Taxol® has been the formation of the A and C rings followed by coupling to form the 8 membered B ring. This is exemplified in Nicolaou's synthesis (Scheme 16).



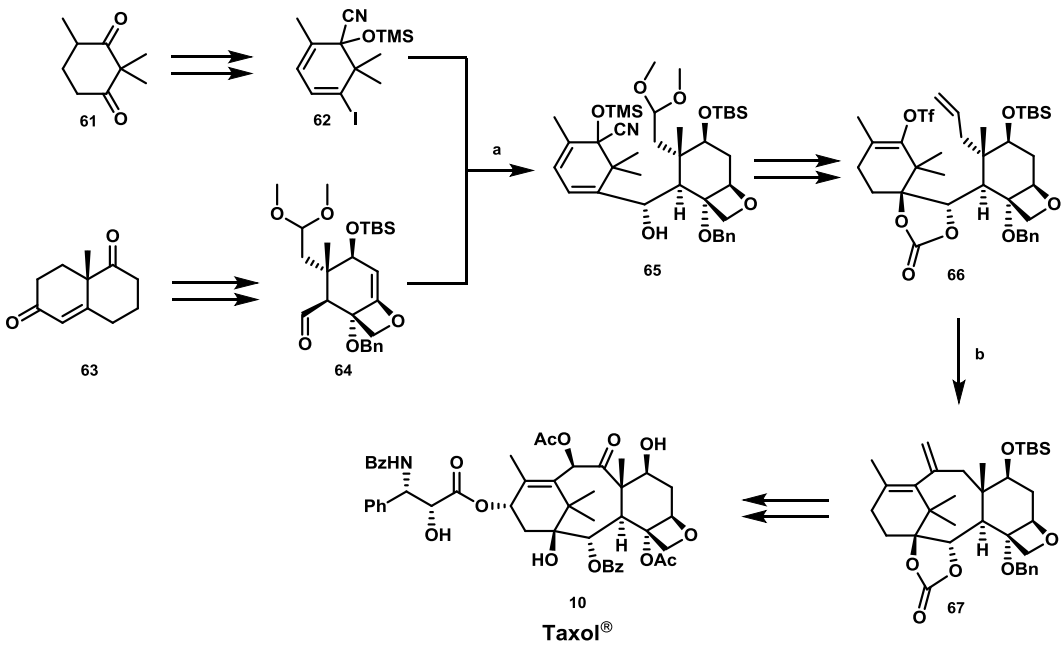
Scheme 16: Nicolaou's synthesis of Taxol® **10**.

Reagents and Conditions: **a)** PhH, 80% **b)** i) $PhB(OH)_2$ ii) 2,2-dimethyl-1,3-propanediol, 79% **c)** BuLi, 82% **d)** $(TiCl_3)_2$•DME, Zn-Cu, 23%.

Nicolaou began his synthesis with an uncatalysed Diels-Alder reaction to give cyano chloride **53.** This was then converted in a number of steps to tosyl hydrazone **54**, the taxane A ring fragment. An initial Diels-Alder reaction of **55** followed by a number of functional group interconversions and protections gave aldehyde **57**, the C ring fragment. A Shapiro reaction was then used to link **54** and **57** to give **58** which was converted to **59** over a number of steps. Intermediate **59** was then set up for a McMurry coupling to fully

furnish the B ring of Taxol® with C9 and C10 oxidation in place (**60**). Further work including C13 oxidation gave Taxol® **10**.

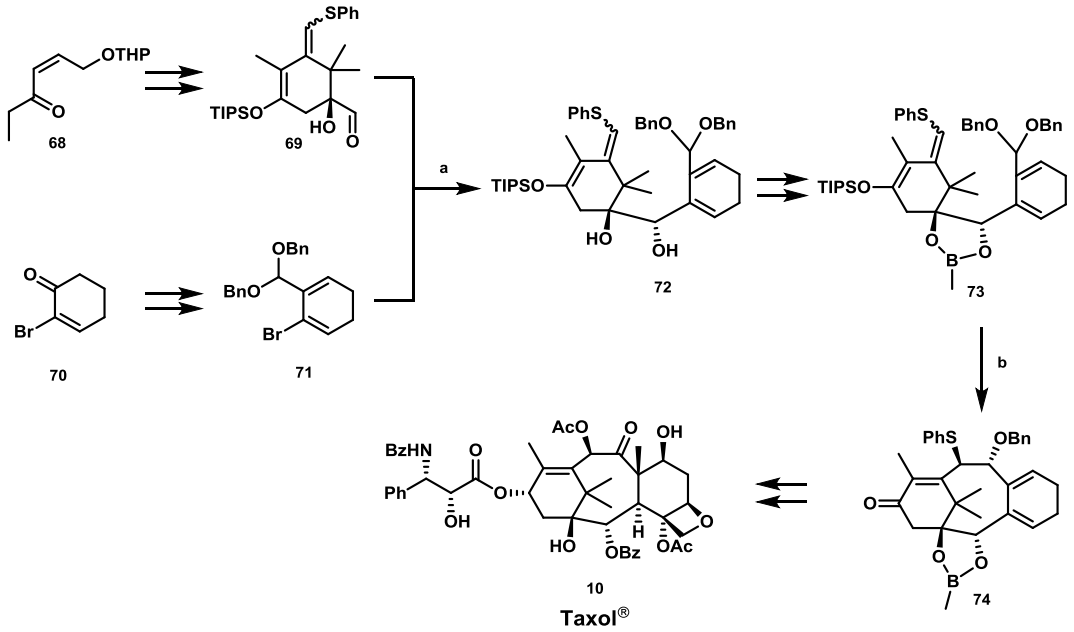
Danishefsky, Kuwajima and Takahashi also utilised this approach in their syntheses. Danishefsky used an organolithium addition to couple A ring precursor **62** with C ring precursor aldehyde **64**, giving **65** in excellent yield (Scheme 17). The second key step was then an intramolecular palladium catalysed cross-coupling between a vinyl triflate and an alkene in **66** to give taxane skeleton **67** in moderate yield. A number of additional steps then furnished Taxol® **10**.[43]



Scheme 17: Danishefsky's synthesis of Taxol® **10**.

Reagents and Conditions: **a)** ^{t}BuLi, 93% **b)** $Pd(PPh_3)_4$, K_2CO_3, 49%.

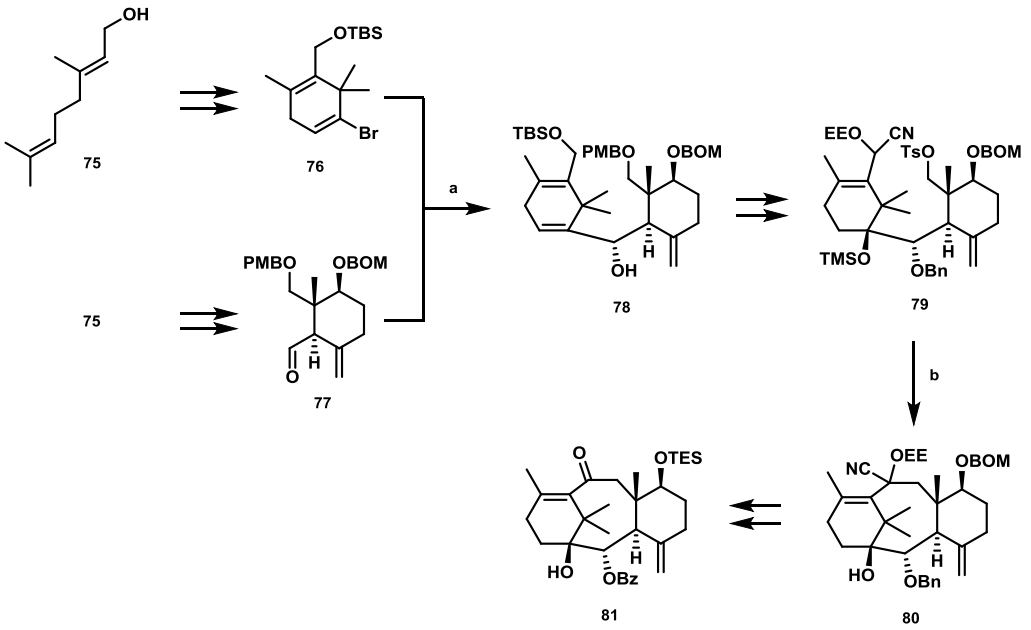
Kuwajima followed a similar approach, this time utilising an organolithium addition followed by a Mukaiyama aldol to form the ABC ring system.[47]



Scheme 18: Kuwajima's synthesis of Taxol® **10**.

Reagents and Conditions: **a)** ^{t}BuMgCl, 68% **b)** $TiCl_2(O^{i}Pr)$, 59%.

Takahashi also use an organolithium addition to couple the A and C rings in his partially automated, formal synthesis of Taxol®. He then formed the B ring **80** *via* an α-cyanoanion cyclisation (Scheme 19). Takahashi's synthesis obtained taxane **81**, an intermediate in Danishefsky's total synthesis.[49] Interestingly and rather pleasingly, Takahashi used geraniol **75** as starting material for his synthesis of both the A and C ring precursors.



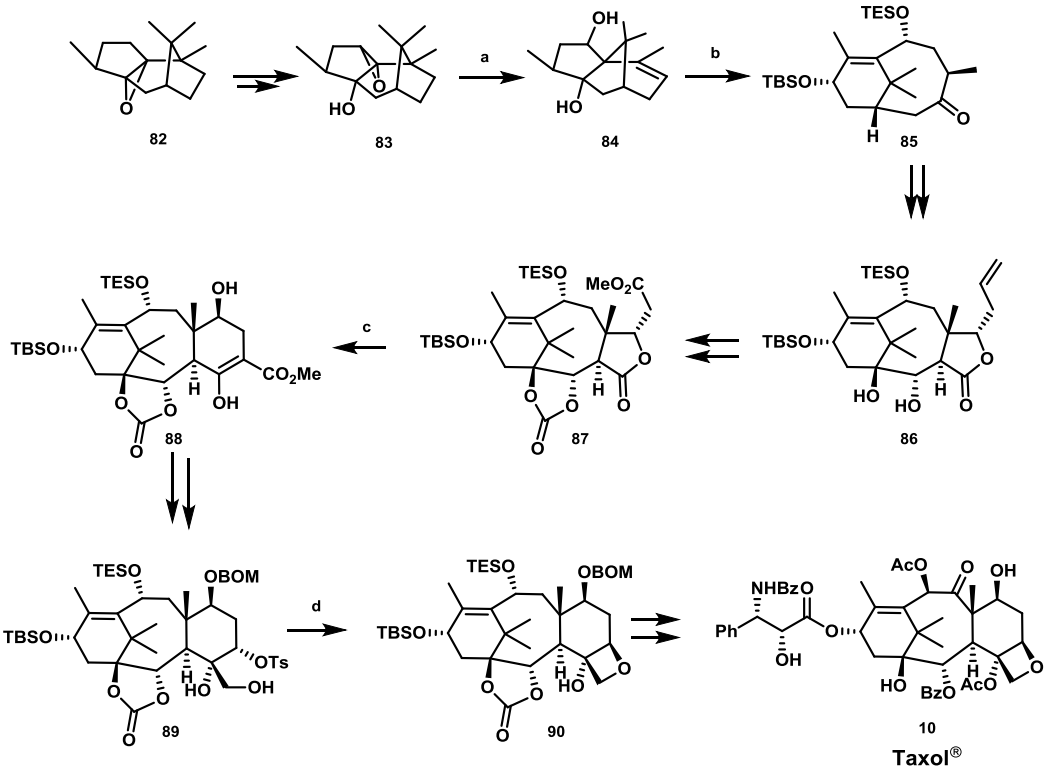
Scheme 19: Takahashi's formal synthesis of Taxol® **10**.

Reagents and Conditions: **a)** ^{t}BuLi, $CeCl_3$, 78% **b)** LiHMDS, 49%.

This approach of forming the A and C rings followed by coupling to obtain the B ring is popular as it allows for a highly convergent route and both A and C rings can be heavily functionalised before coupling.

Grobb Fragmentation Approach

Holton and Wender both utilised a Grobb fragmentation to form the challenging eight membered B ring. As with the other approaches, oxidation is introduced throughout the synthesis.



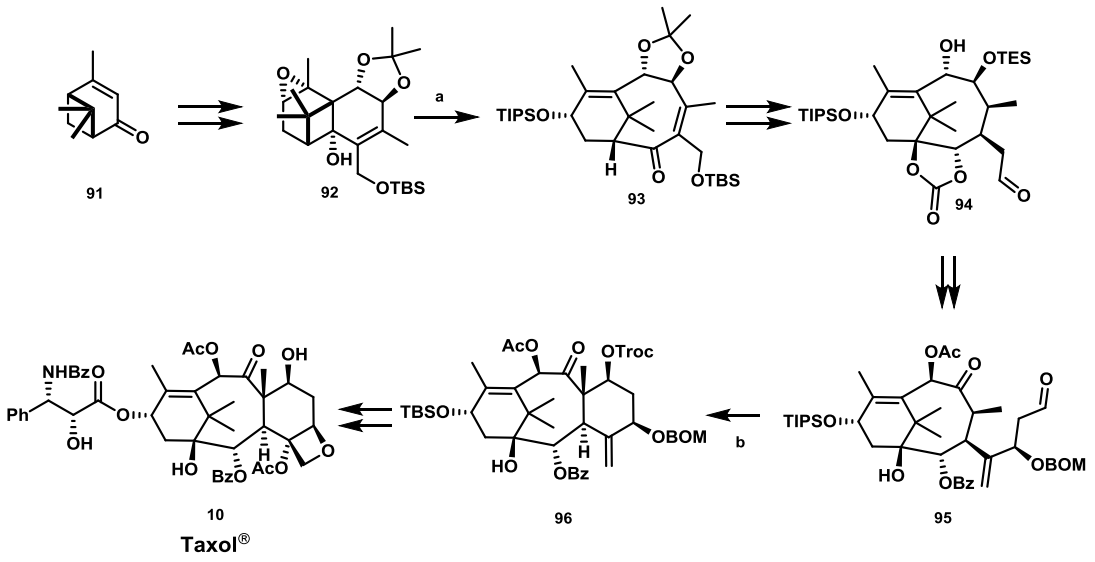
Scheme 20: Holtons's synthesis of Taxol® **10**.

Reagents and Conditions: **a)** $BF_3{\cdot}Et_2O$, TfOH, 70% **b)** i) TESCl, Et_3N. ii) ^{t}BuOOH, Ti(^{i}PrO)$_4$. Iii) TBSOTf, 94% (3 steps). **c)** LDA, THF, 84%. **d)** DBU, PhMe, 85%.

Holton used the starting material (-)-patchoulene oxide **82** for his synthesis of Taxol®.[40,42] Ring opening of the epoxide followed by epoxidation gave **83**. Boron trifluoride etherate and triflic acid prompted a rearrangement of **83** to furnish the taxane A ring, compound **84**. Protection and epoxidation of **84** then gave the Grobb fragmentation product **85.** This was a highly efficient synthesis of both the A and B rings of Taxol® in a small number of

steps. Ketone **85** was converted in a number of steps to lactone **87** which underwent a Dieckmann condensation to give the taxane C ring **88**. Further functionalisation gave **89**, which was set-up for a nucleophilic displacement of the tosylate to give oxetane **90.** From here, oxidation and attachment of the side chain furnished Taxol® **10**.

Wender utilised a similar approach to Holton but using the natural product verbenone **91** as starting material (Scheme 21).[45,53,54] Grobb fragmentation of **92** gave the A and B ring compound **93** in good yield. Further synthesis set up the molecule for an aldol addition to close the C ring. Ketone **95** was treated with DMAP and TrocCl to furnish the completed taxane skeleton **96** in reasonable yield. From **96**, formation of the oxetane and side chain addition gave Taxol® **10**.



Scheme 21: Wenders's synthesis of Taxol® **10** from verbenone **91**.

Reagents and Conditions: **a)** i) *m*CPBA ii) DABCO, 85% (two steps) **b)** DMAP, TrocCl, 62%.

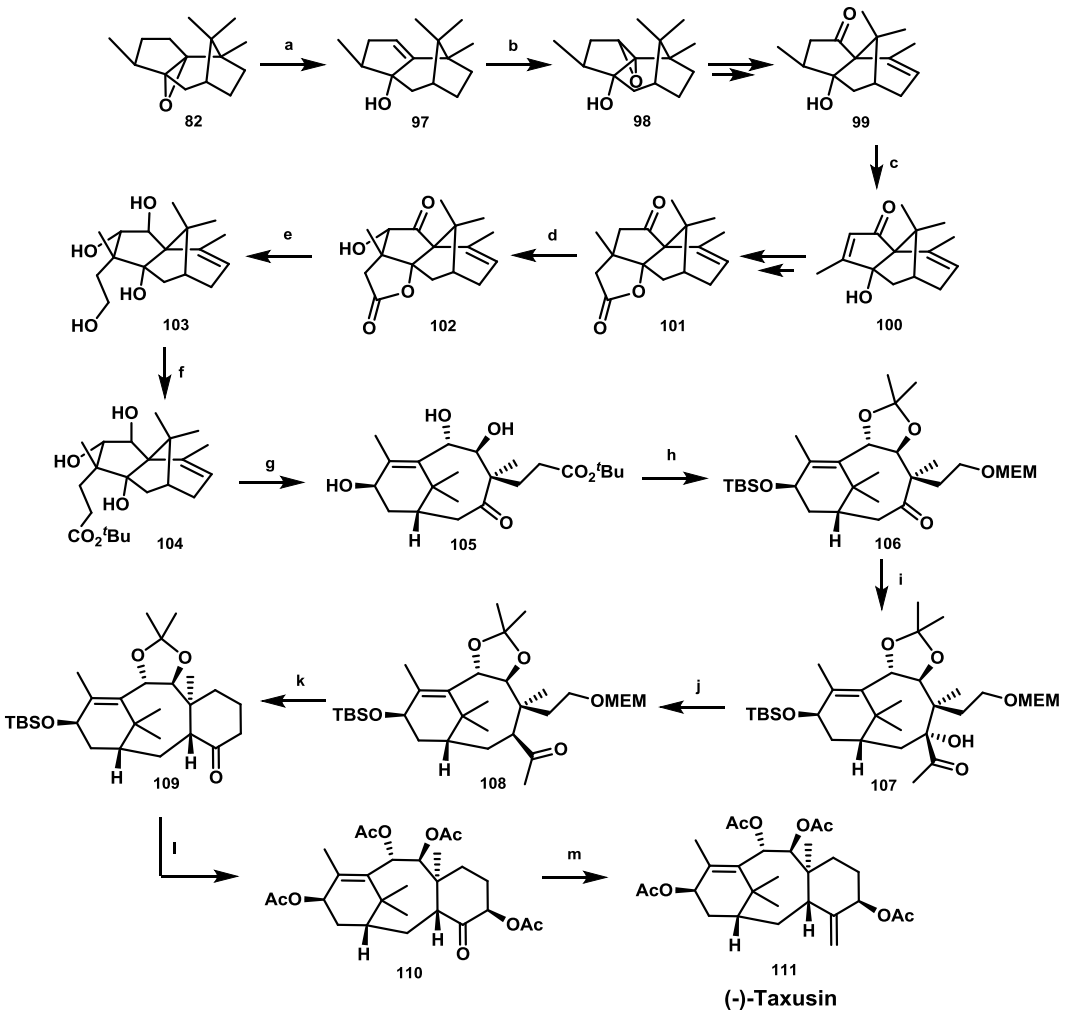
It is clear that these classic syntheses of Taxol® are not amenable to our aims. Nicolaou's first 6:8:6 ring system intermediate contains six sites of oxidation and Holton's seven, this oxidation would have to be later removed to produce low oxidation state taxanes.

Low Oxidation State Taxanes

(-)-Taxusin

The first synthesis of a relatively low oxidation state taxane with the characteristic 6,8,6 ring system was achieved by Holton in 1988 with the synthesis of (-)-taxusin **111**, the enantiomer of the natural product (+)-taxusin.[55]

Holton's synthesis started with the same natural product as his work on Taxol®, (-)-patchoulene oxide **82**. In similar steps to his synthesis of Taxol®, ring opening of the epoxide of **82** gave **97** followed by epoxidation gave **98**. Epoxide **98** underwent a key acid catalysed rearrangement to form the taxane A ring followed by oxidation with PDC to give ketone **99**. Ketone **99** was converted to enone **100** using phenyl selenyl chloride followed by hydrogen peroxide. Four further steps converted **100** through to lactone **101**, which was promptly oxidised further to hydroxy ketone **102**, which was reduced to tetra-ol **103**. Protection of **103** followed by another oxidation and Grobb rearrangement gave the A and B rings of the taxane skeleton (**105**). Further steps set up the structure to close the C ring. Holton deprotected **108** before making the tosylate and ring closing with an enolate nucleophile to give **109**. Alpha-oxidation of **109** followed by protection as the acetate gave **110**. Global deprotection followed by acetylation and Wittig olefination gave (-)-taxusin **111**.



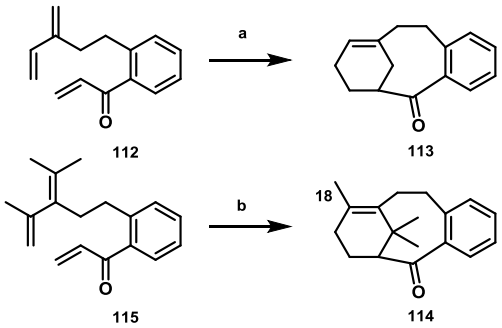
Scheme 22: Synthesis of (-)-taxusin **111** by Holton

Reagents and Conditions: **a)** ^{t}BuLi **b)** ^{t}BuOOH, Ti(O^{i}Pr)4, 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) $Ti(O^{i}Pr)_4$, 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%.

Although this was a synthesis of the unnatural enantiomer, (-)-taxusin, Holton did note that preparation of the opposite enantiomer of patchoulene **82** using Buchi's preparation would lead to (+)-taxusin.[56]

Diels-Alder Approach

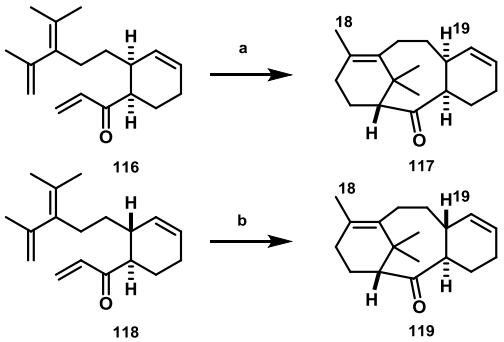
One very efficient method for the synthesis of low oxidation state taxanes is to form both the A and B rings *via* a Diels-Alder cycloaddition. This avoids the need to incorporate excessive oxidation for carbon bond formation. Shea proposed this method in 1983, completing studies on a model system with an aromatic C ring.[57]



Scheme 23: Shea's aromatic C ring Diels-Alder model

Reagents and Conditions: **a)** xylene, 185 ˚C, 1 h., 70%. **b)** xylene, 155 ˚C, 3.9 days, 70%.

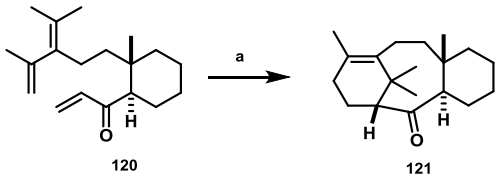
It is interesting to note here how the *gem*-dimethyl groups and C18 methyl appear to inhibit the rate of cyclisation. The unmethylated Diels-Alder precursor cyclises in 1 h, whereas the methylated requires nearly 4 days. Shea went on to produce a number of 6,8,6 ring systems with this Diels-Alder approach.[58,59] Shea's findings were complimented later by the work of Winkler in 1997.[60] Using Diels-Alder precursors with the *gem*-dimethyl group but lacking the C19 methyl gave good yields and interestingly a *cis*-diasteromeric precursor cyclised in higher yield than a *trans*- precursor (Scheme 24).



Scheme 24: Winkler's aromatic 19-H model system

Reagents and Conditions: **a)** 6 eq. BF_3•Et_2O, PhMe, 0 ˚C, 24 h., 82% **b)** 3 eq. BF_3•Et_2O, PhMe, -35 ˚C, 24 h., 66%.

At the same time as Shea's work, Jenkins was exploring the cyclisation of a completely saturated C-ring model system.[61–64]



Scheme 25: Jenkins' model system.

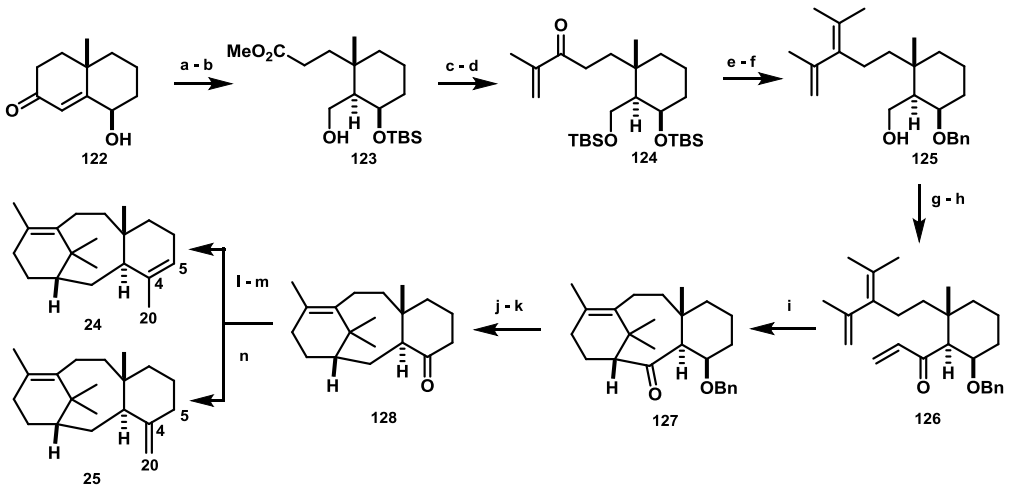
Reagents and Conditions: **a)** 1 eq. BF_3•Et_2O, PhMe, -40 ˚C, 24 h., 58%.

With this Diels-Alder approach well documented in the literature it has been used for the synthesis of a number of low oxidation state taxanes.

Syntheses of Taxadiene

The simplest taxane with the iconic 6,8,6 ring system is taxadiene **24**. When this research project was started in the Hayes group, there was only one published synthesis of **24**. This was the route developed by Williams and co-workers in 1995.[65] (Scheme 26)

Williams' Synthesis of Taxadiene



Scheme 26: Williams' synthesis of both taxadiene isomers **24** and **25**.

Reagents and Conditions: **a)** i) TBSCl, imidazole ii) H_2, Pd/C, 62%. **b)** i) mCPBA ii) NaOMe, 77%. **c)** i) TBSCl ii) DIBAL, 71%. **d)** i) vinyl magnesium bromide ii) Dess-Martin periodinane, 65%. **e)** $Me_2C(SeMe_2)$, BuLi, quant. **f)** i) PI_3, Et_3N ii) HF, 64%. **g)** i) $PhCH(OMe)_2$, PPTS ii) $LiAlH_4$, $AlCl_3$ iii) Dess-Martin periodinane, 61%. **h)** i) vinyl magnesium bromide, quant. ii) Dess-Martin periodinane, quant. **i)** 2 eq. $BF_3 \bullet Et_2O$, 28%. **j)** i) $LiAlH_4$ ii) PhOCSCl, NaHMDS iii) Bu_3SnH, AIBN, 53%. **k)** i) Na, NH_3 ii) Dess-Martin periodinane, 56%. **l)** MeMgBr, $CeCl_3$, quant. **m)** Burgess reagent, 60%. **n)** Ph_3PMeI, ^{n}BuLi, 80%.

During their studies to elucidate the mechanism of taxadiene 5α-hydroxylase (Chapter II), Williams and Croteau needed to access both isomers of taxadiene **24** and **25** (4(5) and 4(20) alkenes) and be able to install radio labelling at the C20 position at a late stage. This meant it was necessary to design a divergent route, synthesising first ketone **128** that would allow them to access both isomers of the natural product and functionalise C5.

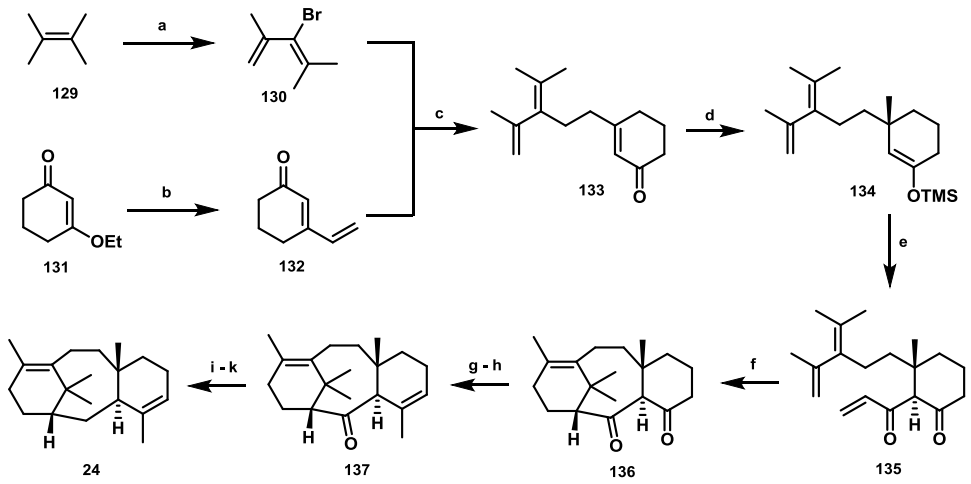
Williams started his synthesis with bicyclic enone **122**, easily prepared from the condensation product of 2-methylcyclohexanone and methyl vinyl ketone. Protection of the secondary alcohol which would later manifest as the C20 position followed by reduction, Baeyer-Villiger and treatment with sodium methoxide gave ester **123**. Protection followed by reduction, vinyl Grignard addition and oxidation gave enone **124**. A Krief-Reich reaction on enone **124** gave tetrasubstituted diene **125**.[66] Another reduction,

vinyl Grignard addition and oxidation then gave Diels-Alder precursor **126**. The Diels-Alder cycloaddition proceeded smoothly under Lewis acid catalysis to give the taxane ring system **127**, which, following radical deoxygenation, deprotection and oxidation gave ketone **128**. This was then used to produce both taxadiene isomers *via* a Grignard addition and elimination to give **24** or a Wittig olefination to give **25**.

As discussed previously the advantage of the Diels-Alder approach is that it can be used to form both A and B rings with limited sites of oxidation. This worked well here, however at 24 steps Williams' synthesis is long, most probably due to the need to have a divergent last step.

Baran's Synthesis of Taxadiene

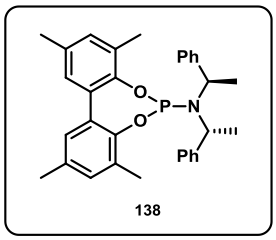
Whilst our group was working towards a synthesis of taxadiene 24, Baran published a short, efficient route to taxadiene, once again utilising the Diels-Alder approach to the A and B rings.[67,68]



Scheme 27: Baran's synthesis of taxadiene **24**.

Reagents and Conditions: **a)** i) ^{t}BuOK, $CHBr_3$ ii) $PhNMe_2$, Δ, 67%. **b)** vinyl magnesium bromide, 75%. **c)** i) ^{s}BuLi, ii) TMSCl, CuBr•DMS, 86%. **d)** i) Me_3Al, CuTC, Ligand **138** 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% (two steps) **i)** $LiAlH_4$, 72%. **j)** KH, AcCl, 89%. **k)** Na, ^{t}BuOH, 82%.

Baran's route starts with commercially available olefin **129**, reaction with bromoform and base followed by thermal rearrangement gave bromodiene **130**. Addition of vinyl Grignard to ethoxy enone **131** gave vinyl enone **132** in good yield. At this stage bromodiene **130** was coupled with vinyl enone **132** in a 1,6 conjugate addition to give **133**. This was followed by a 1,4 conjugate addition of trimethyl aluminium and quench with TMSCl to give silyl enol ether **134**. Asymmetry was achieved in this reaction using a phosphoramidite ligand **138** developed by Alexakis.[69]



138

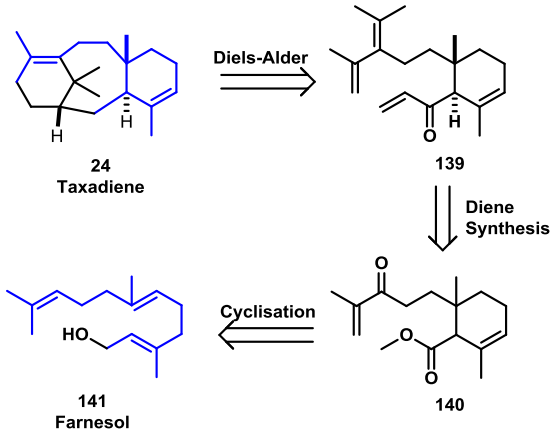
Figure 10: Alexakis phosphoramidite ligate **138** for asymmetric conjugate addition.

A Mukaiyama aldol with acrolein followed by oxidation of the resulting alcohol, was then employed to install the dienophile and complete the synthesis of Diels-Alder precursor **135**. Baran used a slow addition of dilute Lewis acid in the Diels-Alder cyclisation to give the taxane ring system **136** in 49% yield. Enol triflate formation followed by Negishi reaction gave taxadieneone **137** in 84% yield. Taxadienone **137** was then successfully deoxygenated by dissolving metal reduction of the corresponding acetate, to give taxadiene **24** in 18% overall yield.

Baran's synthesis of taxadiene, although 15 chemical 'transformations' has been highly optimised with a number of steps being carried out before purification. Adjusting for this provides a synthesis of taxadiene **24** in around 10 steps. Baran's route to taxadienone **137** has been further optimised on a process scale by the chemistry group at AMRI, USA.[70]

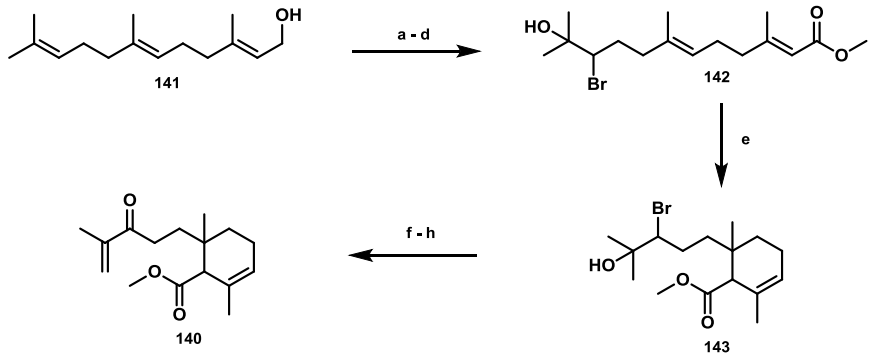
Hayes Formal Synthesis of Taxadiene

The initial plan within the Hayes group was to shorten Williams' route with taxadiene **24** as the target compound to then attempt oxidations to higher oxidation state taxanes.[33] Our initial retrosynthetic planning aimed to utilise as many carbons from sustainable sources as possible, choosing farnesol **141** as starting material allowed for 15 of the 20 carbons in the final product to come from a sustainable source (plant product). (Scheme 28)



Scheme 28: Retrosynthetic analysis. Carbons originating from farnesol are in blue.

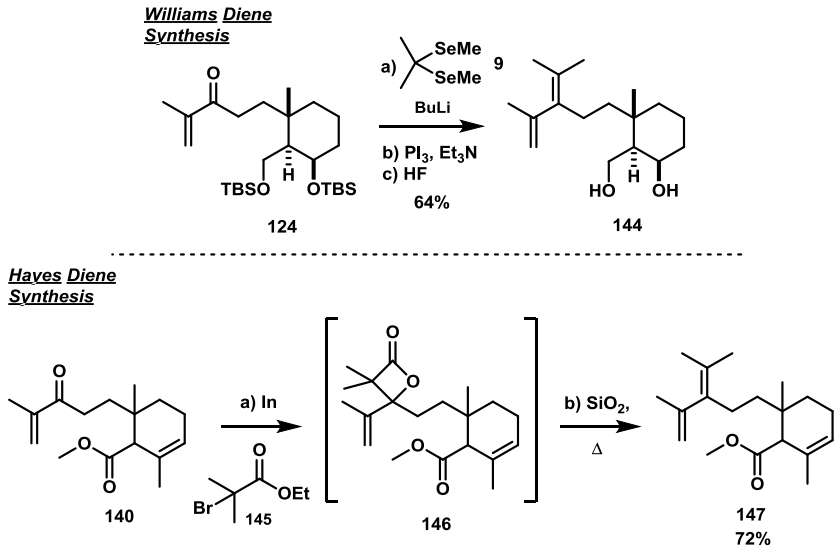
Farnesol **141** was oxidised to farnesoic acid, protected as the methyl ester and converted to the bromohydrin **142** in good overall yield. Brønsted acid mediated cyclisation of bromohydrin **142** with concentrated phosphoric acid gave cyclohexene **143.** This cyclisation gave a 2:2:1:1 mixture of diastereoisomers (*cis*: *trans*, 1:2) which were inseparable at this stage. Treatment of **143** with base followed by rearrangement of the epoxide and oxidation gave enone **140**.[71]



Scheme 29: Hayes synthesis of enone **140**.

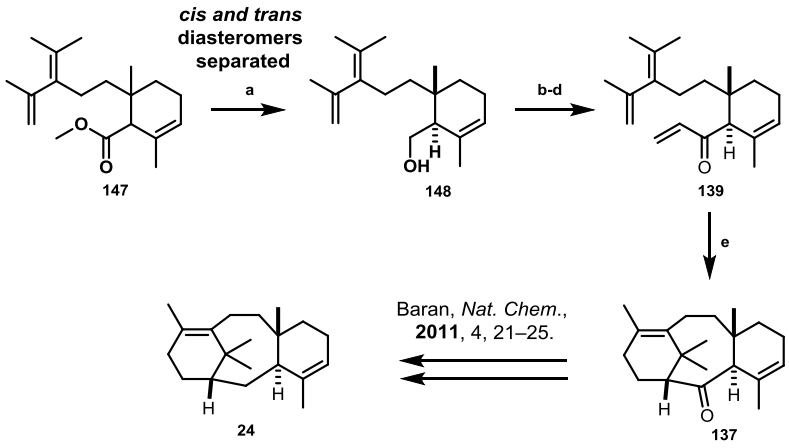
Reagents and Conditions: **a)** MnO_2, 86%. **b)** $NaH_2PO_4 \bullet 2H_2O$, 2-methyl-2-butene, $NaClO_2$, 90%. **c)** MeI, K_2CO_3, 97%. **d)** NBS, 61%. **e)** H_3PO_4, 75%. **f)** K_2CO_3, 88%. **g)** ^{n}BuLi, TMP, Et_2AlCl, 98%. **h)** Dess-Martin periodinane, pyridine, 97%.

The challenge of installing the tetrasubstituted diene **147** prompted the development of a novel indium Reformatsky-decarboxylation sequence (Scheme 30). This was a significant improvement over the Krief-Reich reaction used by Williams that required toxic selenium reagents. Subjecting enone **140** first to an indium Reformatsky reaction to give a *beta*-lactone **146** followed by treatment with silica and heating prompted decarboxylation to diene **147** in 72% over two steps.[72]



Scheme 30: Williams Krief-Reich reaction and Hayes Reformatsky-decarboxylation approach to tetra-substituted diene **147**.

Ester **147** was then reduced to the alcohol **148**. At this stage *cis* and *trans* diastereoisomers were separable by column chromatography. The *trans* compound was isolated and subjected to a reduction, Grignard addition and oxidation to furnish the Diels-Alder precursor **139**. After a significant effort in optimisation, enone **139** was treated with boron trifluoride etherate under dilute conditions to give taxadieneone **137** in 20% yield. At this stage Baran published his synthesis of taxadiene.[67,68] (Scheme 27) Taxadienone **137** was a common intermediate in both the Hayes and Baran routes. Therefore, even though taxadiene **24** was not pursued further, with Baran's conditions for deoxygenation at C2 the Hayes route was rendered a formal synthesis of taxadiene **24**.

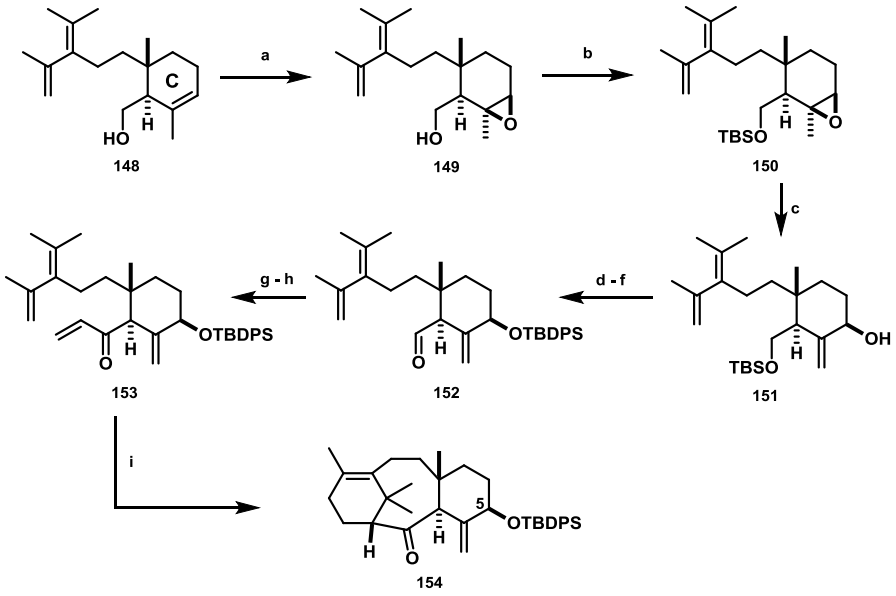


Scheme 31: Hayes formal synthesis of taxadiene **24**.

Reagents and Conditions: **a)** DIBAL-H, 59%. **b)** $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 87%. **c)** vinyl magnesium bromide, 83%. **d)** $(COCl)_2$, DMSO, Et_3N, 78%. **e)** $BF_3 \bullet Et_2O$, 20%.

Hayes Synthesis of a C2 and C5 Oxidised Taxane

The Hayes route was later adapted towards the synthesis of a C5 oxidised taxane **154** with an exocyclic 4(20) double bond (Scheme 32).[33]



Scheme 28: Hayes' synthesis of a C2 and C5 oxidised taxane **154.**

Reagents and Conditions: **a)** $VO(acac)_2$, ^tBuOOH, 69%. **b)** TBSCl, Imidazole, 99%. **c)** ^nBuLi, TMP, Et_2AlCl, 96%. **d)** TBDPSCl, Imidazole, 81%. **e)** PTSA, 88%. **f)** $(COCl)_2$, DMSO, Et_3N, 84%. **g)** vinyl magnesium bromide, 75%. **h)** $(COCl)_2$, DMSO, Et_3N, 55%. **i)** $BF_3 \bullet Et_2O$, 65%.

Oxidation on the C ring was installed early on using a regio- and stereoselective vanadium catalysed epoxidation to give epoxide **149**, followed by protection and rearrangement to allylic alcohol **151**. Using chemistry developed in the synthesis of taxadieneone **137**, the dienophile was installed to give Diels-Alder precursor **153**. The Diels-Alder reaction worked well here giving the C5 oxidised taxane **154** in 65% yield.

With the synthesis of simple taxane ring systems precedented in the literature we wanted then reviewed the extent to which low oxidation state taxanes could be oxidised. The chemical oxidation of taxanes in the literature is often concerned with already highly oxidised taxanes such as the oxidation of C13 in many Taxol® syntheses. There are

however some studies on the oxidation of low oxidation state taxanes such as taxadiene **24** and **25**.

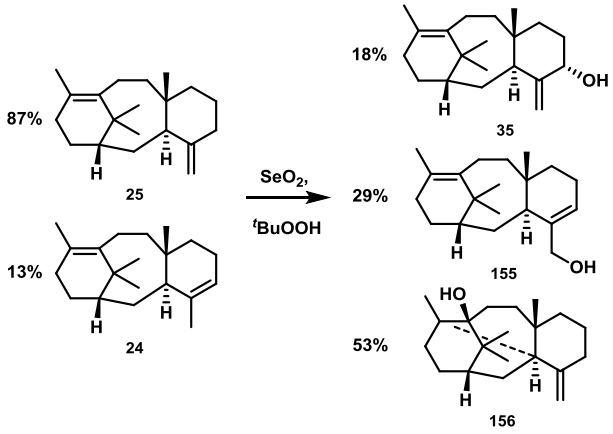
3.0.2 Chemical Oxidation of Taxanes

The oxidation of the taxane skeleton in nature is undertaken by a range of cytochrome P450 oxygenase enzymes. Oxidation occurs at allylic positions and completely unactivated carbon centres. In sparsely functionalised molecules such as taxadiene **24** these oxidations are a significant challenge.[73]

Literature Taxane Oxidations and Potential Methods

Selenium Dioxide Oxidations

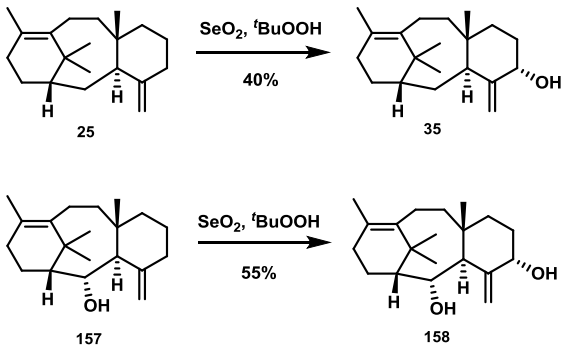
Allylic C-H bonds are the most activated on the carbon skeleton and therefore potentially the simplest to oxidise. Williams and Scott have both used selenium dioxide to perform allylic oxidations of taxanes.[74,75] Scott oxidised a mixture of taxa-4(5)-11(12)-diene **24** and taxa-4(20)-11(12)-diene **25** to a mixture of products.



Scheme 33: Scott's allylic oxidation.

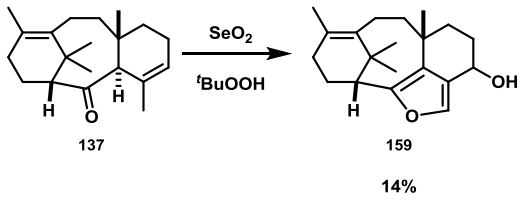
Williams oxidised synthetic taxadiene **25** and **157** successfully to the corresponding 5α-hydroxy compounds **35** and **158** (scheme 34). Interestingly he obtained complete regio-

control with selenium dioxide reacting at the least sterically hindered, albeit the less substituted 4,20 alkene. He also obtained complete stereo-control with in both cases forming only the 5α- alcohol.



Scheme 34: William's allylic oxidation of taxanes

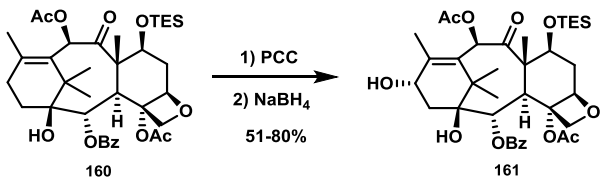
Scott's conditions have been repeated by Hayes on taxadiene **24** giving the same mixture of products. When subjecting taxadieneone **137** (Scheme 35) to Scott's conditions the unusual furan **159** was formed. The stereochemistry of the alcohol in this product was not determined at the time.[33]



Scheme 35: Scott's conditions applied to taxadieneone **137**.

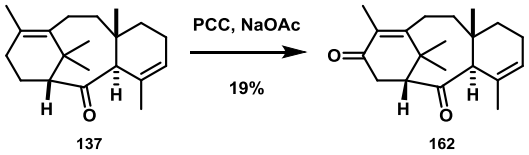
Pyridinium Chlorochromate Oxidations

Pyridinium chlorochromate (PCC) has also been used to oxidise taxane **160** by numerous groups including Nicolaou, Danishefsky and Takahashi in their syntheses of Taxol®.[41,43,49]



Scheme 36: Nicolaou, Danishefsky and Takahashi's oxidations with PCC.

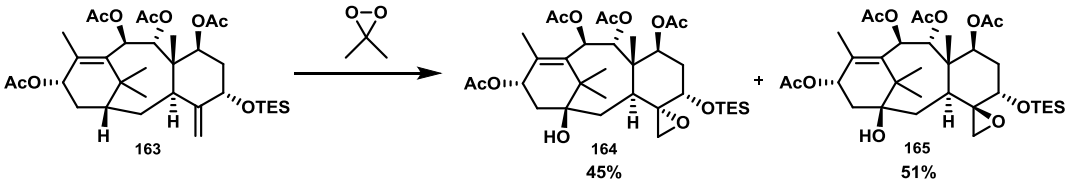
In these reactions, oxidation has occurred selectively at C13 of the carbon skeleton in contrast to selenium dioxide which reacts at the C5 position. Hayes has shown that treatment of low oxidation state taxanes such as taxadieneone **137** with PCC gave C13 oxidation, all be it in low yield.



Scheme 37: Hayes oxidation with PCC.

Peroxide Based Oxidations

Oxidations at completely unactivated centres have also been attempted on taxanes *via* C-H insertion or H atom abstraction. Oxidation at C1 was achieved in pioneering work by Oritani using dimethyl dioxirane (DMDO).[76]

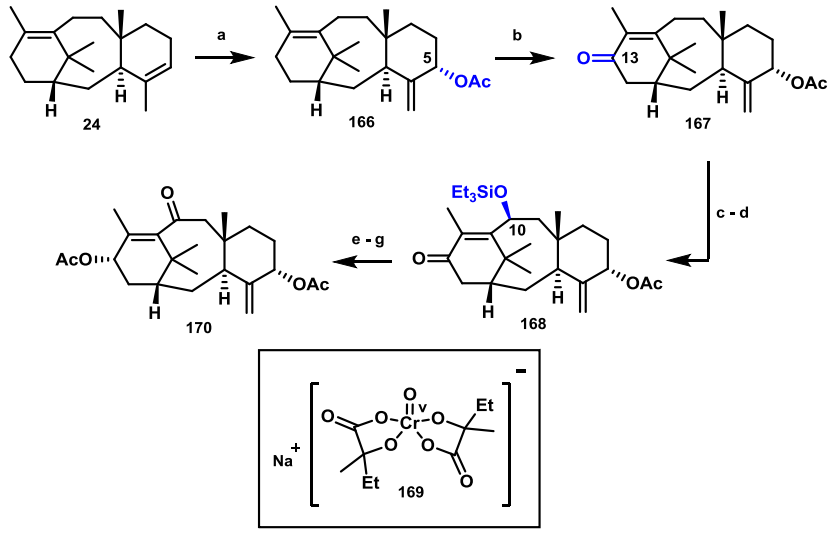


Scheme 38: C1 oxidation using DMDO

Interestingly, the C20-4 alkene of **163** was also epoxidisied in the reaction however the C11-12 alkene was left untouched.

In 2014 Baran published his first oxidations of taxadiene **24** oxidising at C5, 13 and 10.[77] This work culminated in the synthesis of the low oxidation state taxane (-)-taxuyunnanine D **170** (Scheme 72).

Baran utilised a palladium catalysed acetoxylation to install C5 oxidation in 49% yield. After screening hundreds of conditions, it was found that treatment of **166** with chromium (V) reagent **169** gave enone **167** in reasonable yield. Allylic bromination followed by a displacement with a silanol gave **168**, reduction of the C13 carbonyl, followed by oxidation of the C10 alcohol then gave the natural product (-)-taxuyunnanine D **170**.



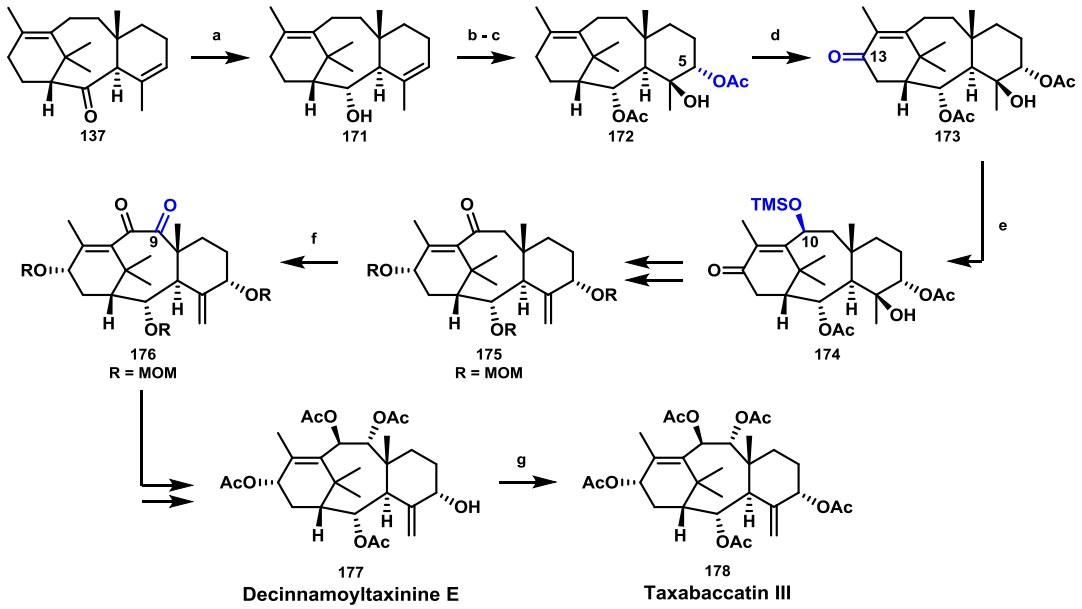
Scheme 39: Baran's oxidation of taxadiene **24** to (-)-taxuyunnanine D **170**. Key oxidations are highlighted in blue.

Reagents and Conditions: **a)** $Pd(OAc)_2$, benzoquinone, anisole, AcOH, 49%. **b) 169**, MnO_2, 15-crown-5, 53%. **c)** NBS, benzoyl peroxide, **d)** AgOTf, Et_3SiOH, toluene, 80%. **e)** i) DIBAL ii) Ac_2O, DMAP, Et_3N, 80%. **g)** IBX, DMSO, 88%.

Baran's work indicates that it is possible to oxidise the low oxidation state taxanes with methods already described within the literature. However, it is apparent that a significant

amount of optimisation (>100 reagents screened per step) was required to develop the reactions for these substrates.

Baran extended this work in 2016 to synthesise a further two natural products decinnamoyltaxinine E **177** and taxabaccatin III **178** on route to Taxol®.[78]



Scheme 40: Baran's synthesis of decinnamoyltaxinine E (**177**) and taxabaccatin III (**178**). Key oxidations are highlighted in blue.

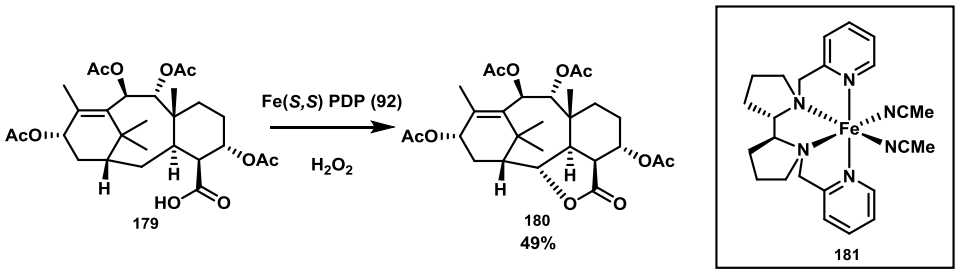
Reagents and Conditions: **a)** Na°, ^{i}PrOH, 63%. **b)** i) $VO(acac)_2$, TBHP ii) NaOH 3 M aq., 67% (two steps). **c)** Ac_2O, Et_3N, DMAP, 89%. **d) 213**, MnO_2, 15-crown-5, ^{t}BuOMe, 50%. **e)** i) NBS, benzoyl peroxide, CCl_4, ii) TMSOH, *2,6,*-ditertbutyl pyridine, toluene, 79%. **f)** i) Et_2NLi, MoOPh. ii) $Cu(OAc)_2$, MeOH, 77%. **g)** $Cu(OTf)_2$, Ac_2O, 87%.

Deccinnamoyltaxinine E **177** and taxabaccatin III **178** both have oxidation at the C2 position. For Baran this meant that starting with taxadieneone **137** and reducing the ketone would be far more efficient than starting with taxadiene **24** and having to install C2 oxidation later. Baran was successful in reduction of ketone **137** with sodium in refluxing isopropanol giving alcohol **171** with the natural α-stereochemistry. Oxidation of the C5 position and an epoxidation - hydrolysis sequence gave a diol which was then protected to give **172**. Using chromium catalyst **169** again to oxidise C13 to enone **173**,

followed by radical bromination and displacement gave C10 oxidised taxane **174**. After numerous functional group manipulations **175** was oxidised, first to the α-hydroxy-ketone using Vedej's reagent,[79] then oxidised again to the dione **176**. With oxidation at positions C5, C13, C10 and C9 in place, protecting group manipulations and reductions gave Decinnamoyltaxinine E **177** to which addition of an acetate group gave taxabaccatin III **178**.

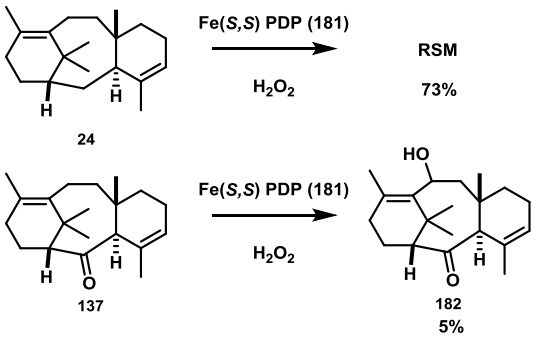
White's Non-Heme Iron Catalysts

Non-heme iron was first shown to oxidise C-H bonds by Fenton in 1894 using $Fe(SO_4)_2$ and H_2O_2.[80] White has recently developed an iron catalyst **181** (Fe(*S,S*) PDP) (Scheme 41) that has been shown to oxidise C-H bonds.[81–83] White also showed that **181** can be used in directed C-H oxidations using taxane **179** as a substrate.[82]



Scheme 41: Directed oxidation at C2 using White's Catalyst

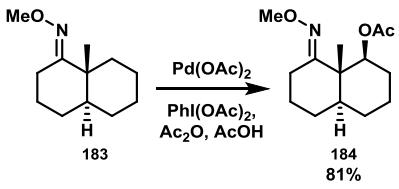
White's catalyst has been used previously by Hayes on extracted taxadiene with variable success. Taxadiene **24** did not undergo any oxidation with 73% starting material recovered. However, taxadieneone **137** did react to a mixture of products, with C10 oxidised product **182** isolated in 5% yield, the stereochemistry at C10 was not determined at the time of synthesis.[33]



Scheme 42: Hayes oxidations with White's catalyst

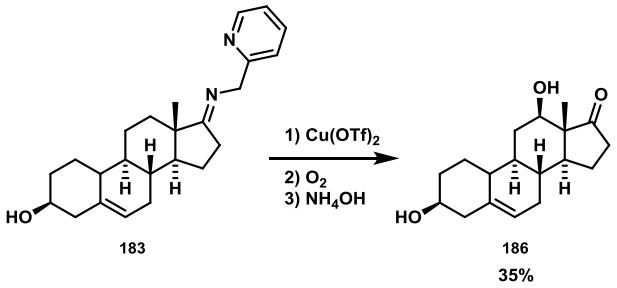
Alternative C-H Oxidation Approaches

One method for obtaining selectivity in C-H oxidation reactions is to install a directing group into the substrate. Interactions between this functional group and the metal catalyst or oxidant can direct C-H insertion or H atom abstraction to a specific site on the taxane skeleton. Work published by Sanford exemplifies this approach.[84]



Scheme 43: Sanford oxime directed C-H oxidation

Sanford used a methyl-oxime to direct a palladium catalysed C-H oxidation across the ring system of **183**. Schonecker has published a similar method using an amino pyridine group to direct a copper catalysed C-H oxidation.



183 186

35%

Scheme 44: Schonecker amino pyridine directed C-H oxidation.

Directed oxidations are an attractive option to obtain selective oxidation, however to carry out the reaction we would need to install the directing group and then remove it afterwards. This is not a particularly atom-efficient method.

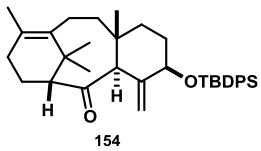
Exploring allylic oxidation of the taxane skeleton is vital as nearly every site of oxidation in Taxol® could be accomplished with the correct combination of allylic oxidation and alpha-keto oxidation as demonstrated by Baran.

With precedent for the oxidation of low oxidation state taxanes we embarked on our synthetic work towards the minimally oxidised taxane skeleton.

3.1 Results and Discussion

3.1.0 Synthesis of the Taxane Skeleton

The aims for our synthetic work were initially to access the 6,8,6 ring system as quickly as possible. We identified the C2 and C5 oxidised taxane **154** as an appropriate starting point for oxidation and reduction studies.

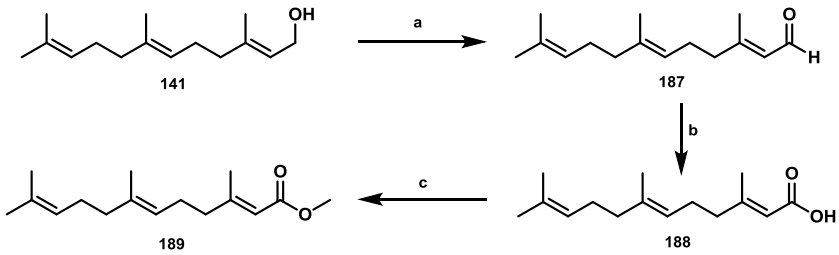


154

Figure 11: Initial synthetic target.

Synthesis of the C Ring

Synthetic work started following the route developed within the Hayes group.[33] This began with the three-step oxidation and protection of farnesol **141** to methyl farnesate **189** (Scheme 45).



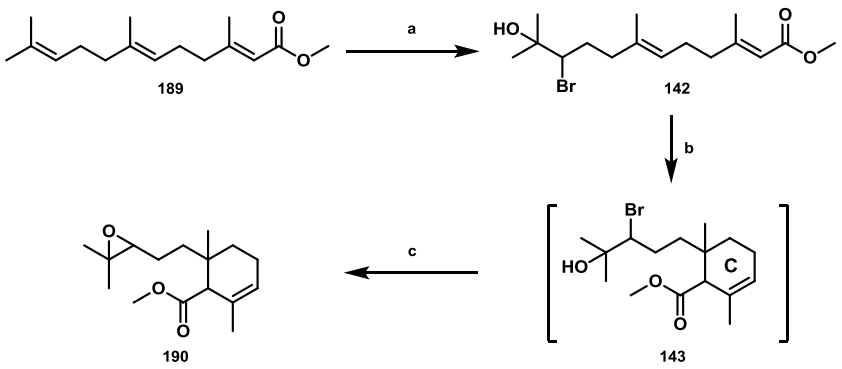
141 187 189 188

Scheme 45: Three-step oxidation of farnesol **141** to methyl farnesate **189**.

Reagents and Conditions: **a)** MnO_2, CH_2Cl_2, r.t., 18 h. **b)** $NaH_2PO_4 \bullet 2H_2O$, 2-methyl-2-butene, $NaClO_2$, ^tBuOH: H_2O (1:1), r.t., 18 h. **c)** MeI, K_2CO_3, DMF, r.t., 18 h., 67% over 3 steps.

In the first step, farnesol **141** was oxidised using manganese dioxide in dichloromethane to give farnesal **187**. Here it was found that the quantity of manganese dioxide could be reduced from twenty equivalents to sixteen without issue. Oxidation of aldehyde **187**

using a Pinnick oxidation gave acid **188**, which was treated with methyl iodide to give methyl farnesate **189** in 67% yield over three steps.[85] These reactions were robust enough to allow material to be passed through the three steps without purification on a 60 g scale. With methyl farnesate in hand, the next step was to functionalise the terminal alkene before treatment with phosphoric acid to form the taxane C ring.



Scheme 46: Formation of epoxide **190** from methyl farnesate **189**.

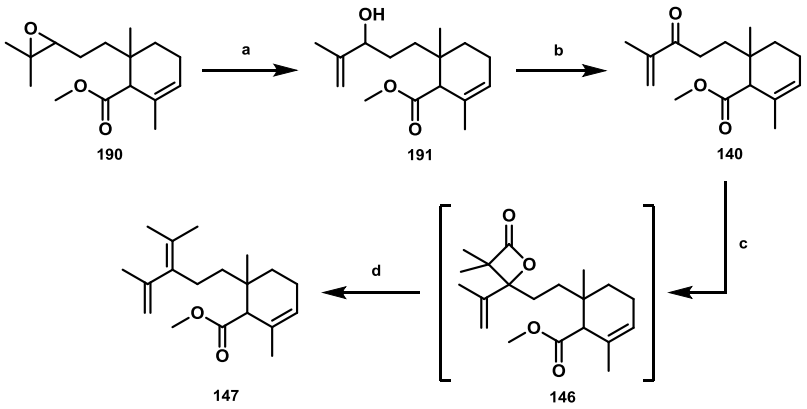
Reagents and Conditions: **a)** NBS, THF:H_2O (10:1), r.t., 5 h, dark. 55%. **b)** H_3PO_4 (15 M), r.t., 5 h. **c)** K_2CO_3, MeOH, r.t., 18 h., 53% over two steps, 2:2:1:1 d.r.

Using chemistry developed by Schwartz and Willbrand, the terminal alkene of methyl farnesate **189** was first converted to the bromohydrin by treatment with NBS in THF/water to give a reasonable yield of **142**. Direct treatment of **142** with concentrated phosphoric acid gave the cyclised product **143**.[86] Purification of both bromohydrin **142** and **143** proved challenging probably due to alkylation of these compounds on silica. It was found that purification of **143** was not necessary to obtain reasonable yields in the last step. Treatment of crude **143** with potassium carbonate in methanol gave the epoxide **190** in 53% yield over 2 steps. This sequence formed the taxane C ring rapidly and in reasonable yields, 10-15 g of epoxide **190** could be obtained and this intermediate was well set for further chemistry. In addition to this all 15 carbons from our sustainable starting material (farnesol **141**) are conserved in this material.

Epoxide **190** was later found to be a 2:2:1:1 mixture of diastereoisomers, with a 2:1 ratio of *trans*:*cis* diastereomers. The epoxide stereocenter was unimportant as this would be removed later in the synthesis. This ratio of isomers was determined by separation and independent characterisation later in the synthesis.[33] As the diastereoisomers were inseparable at this stage epoxide **190** was carried through to install the diene.

Synthesis of the tetra-Substituted Diene 110

The next stage of the synthesis involved converting epoxide **190** to diene **147** in four steps. Epoxide **190** was first rearranged to the allylic alcohol **191** using Yamamoto's reagent in 80% yield (scheme 31).[71]



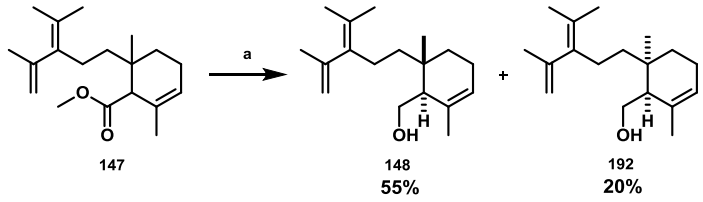
Scheme 47: Synthesis of diene **147**.

Reagents and Conditions: **a)** ^{n}BuLi, TMP, Et_2AlCl, toluene, 0 °C, 3 h., 88%. **b)** Dess-Martin periodinane, pyridine, CH_2Cl_2, r.t., 30 min., 70%. **c)** Ethyl-α-bromoisobutyrate, In, DMF, 80 °C to r.t., 3 h. **d)** SiO_2, toluene, 110 °C, 1 h., 62% over two steps.

Oxidation of the allylic alcohol **191** with Dess-Martin periodinane then gave enone **140** in reasonable yield. Using an indium Reformatsky reaction, enone **140** was converted to lactone **146** (stereochemistry undetermined). Treatment of this crude lactone with silica prompted decarboxylation to diene **147** in 62% yield over 2 steps.[33]

Separation of Diastereoisomers and Synthesis of (±)-cis-8-epi-2-oxo-taxa-(4,5)-(11,12)-diene (127)

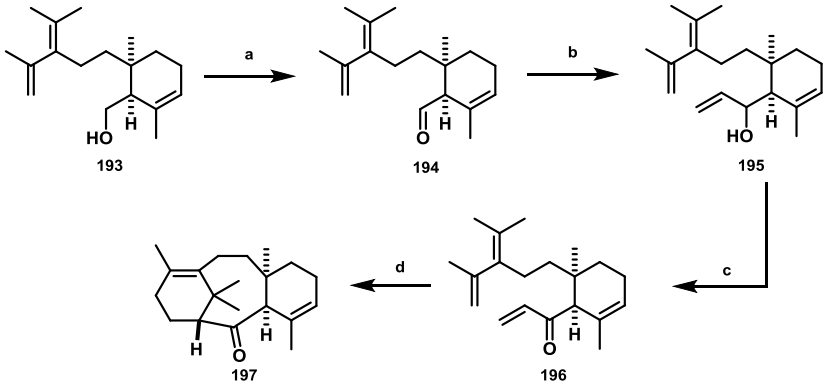
With the diene in place, ester **147** was reduced to the alcohol. At this stage the *trans* and *cis* diastereoisomers **148** and **192** could be separated by conventional silica gel chromatography. Both these diastereomers could lead to taxanes of interest. Initially *cis* diastereoisomer **192** was taken forward to produce the previously unreported *cis*-taxadienone **197**.



Scheme 48: Reduction of ester **147**.

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

Work began with the addition of the last two carbon atoms in the taxane skeleton in the form of a vinyl group, followed by a key Diels-Alder reaction using conditions published by Baran and co-workers.[68]



Scheme 49: Synthesis of (±)-*cis*-8-epi-2-oxo-taxa-(4,5)-(11,12)-diene **197**.

Reagents and Conditions: **a)** $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 4 h., 95%. **b)** vinyl magnesium bromide, THF, -78 °C, 2 h., 77%. **c)** $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 4 h., 44%. **d)** $BF_3 \bullet Et_2O$ (3.65 eq.), CH_2Cl_2, 0 °C, 6 h., 60%.

In the first instance, alcohol **193** was oxidised *via* a Swern oxidation to aldehyde **194** in good yield. Vinyl magnesium bromide addition then gave allylic alcohol **195**. Another Swern oxidation furnished the Diels-Alder precursor, enone **196**. The key Diels-Alder reaction then gave *cis*-taxadiene **197** in 60% yield. A crystal structure was obtained to confirm the stereochemistry of **197**.

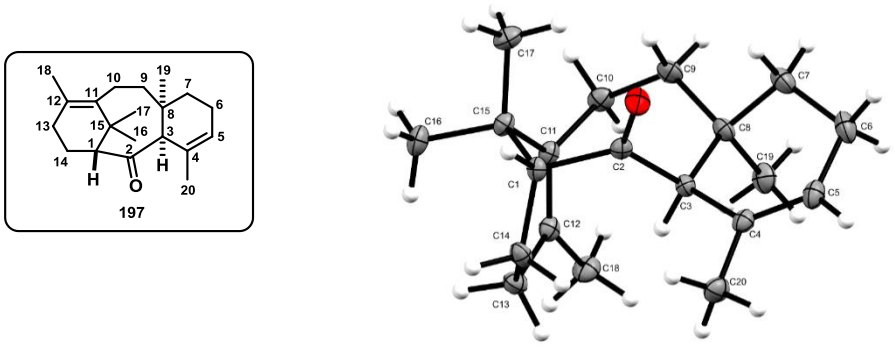
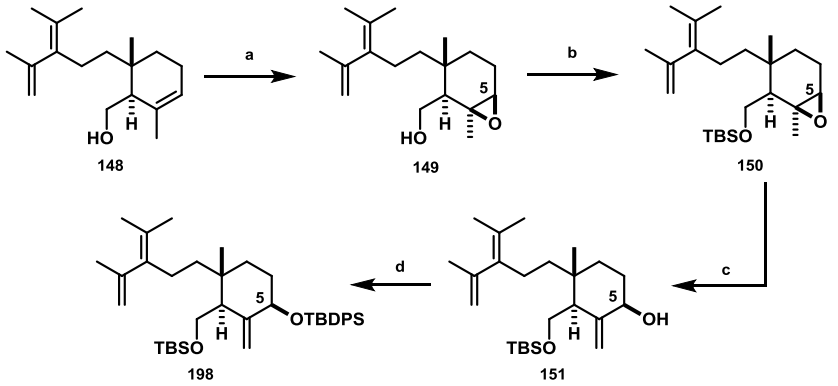


Figure 12: Crystal structure of (±)-*cis*-8-epi-2-oxo-taxa-(4,5)-(11,12)-diene **197**.

Synthesis of 5α-hydroxytaxadienone

With the un-natural diastereomeric alcohol used for the synthesis of (±)-*cis*-8-epi-2-oxo-taxa-(4,5)-(11,12)-diene **197**, we now utilised *trans* alcohol **148** to produce taxanes bearing the natural *trans* fused rings system. We decided to install oxidation at C5 of the taxane skeleton through a vanadium catalysed epoxidation of **148**.



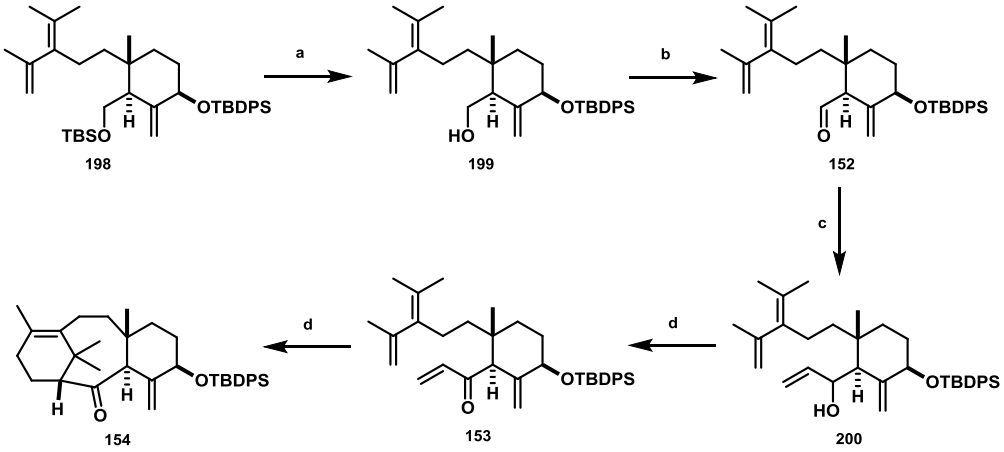
Scheme 50: Oxidation and protection of the C ring.

Reagents and Conditions: **a)** $V(acac)_3$, ^tBuOOH, CH_2Cl_2, r.t., 3.5 h., 89%. **b)** TBSCl, Imidazole, DMF, r.t., 4 h., 81%. **c)** ^nBuLi, TMP, Et_2AlCl, toluene, 0 °C, 4 h., 75%. **d)** TBDPSCl, Imidazole, r.t., 5 h., 76%.

Although vanadyl (IV) acetylacetonate ($VO(acac)_2$) has become the 'go to' reagent for this transformation, Vanadium (III) acetylacetonate ($V(acac)_3$) was found to catalyse the epoxidation of homo-allylic alcohol **148** in excellent yield and with complete diastereocontrol.

Vanadium (III) has been reported in the epoxidation of alkenes with *tert*-butyl hydrogen peroxide in an initial screen of transition metals carried out by Brill and co-workers in 1965.[87] It appears that after this, vanadyl acetylacetonate became more popular simply because it was chosen to study the mechanism of the epoxidation reaction in subsequent literature.[88] Brill and co-workers suggested that vanadium (III) is oxidised in situ to vanadium (IV) which then carries out the reaction.

Following the epoxidation of **148** to **149** in good yield, the free alcohol of **149** was protected as the *tert*-butyldimethylsilyl ether to give **150** in 81% yield. Protected alcohol **150** was then converted in 75% yield to allylic alcohol **151** using Yamamoto's reagent and subsequently protected with a *tert*-butyldiphenylsilyl group to give the bis-silyl ether compound **198**.



Scheme 51: Synthesis of silyl protected taxane **154**.

Reagents and Conditions: **a)** $TsOH \cdot H_2O$, $EtOH:H_2O$ (1:1), r.t., 5 h., 60%. **b)** $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ˚C, 1.5 h., 84%. **c)** vinyl magnesium bromide, THF, 0 ˚C, 1 h., 76%. **d)** $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ˚C, 3.5 h., 72%. **e)** $BF_3 \cdot Et_2O$ (2 eq.), PhMe, 0 °C, 6 h., 65%.

The apparently simple deprotection of **198** with acid to selectively remove the *tert*-butyldimethylsilyl group proved challenging. After significant optimisation it was found that reaction with 0.5 equivalents of toluenesulfonic acid at ambient temperature for 5 h in a 1:1 mixture of ethanol : water gave best results, with a yield of 60% and quantitative recovery of mass. Leaving the reaction for too long degraded the product, resulting in lower yields and poor recovery of starting material. We believe that the solvent mixture is key here to obtain high yields, the use of methanol to replace ethanol increased the rate of reaction and more decomposition was observed.

Subsequent oxidation of alcohol **199** followed by Grignard addition and further oxidation gave Diels-Alder precursor **153**. This was then treated with boron trifluoride etherate in toluene to furnish taxane **154** in 62% yield.

Comparing Diels-Alder Reactions

It is interesting to pause here and compare the Diels-Alder reactions reported in this thesis and in the literature (Figure 13). [33,63,65,67]

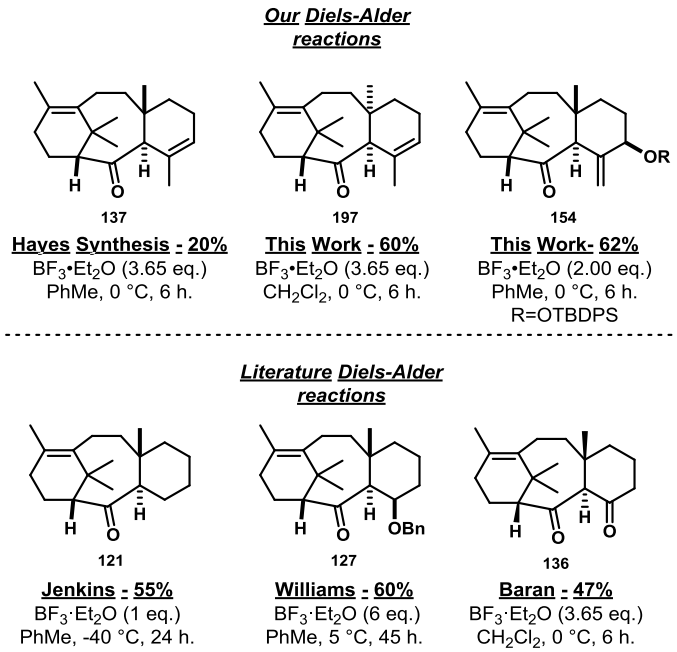


Figure 13: Comparison of Diels-Alder products from Hayes and this work (top) and literature (bottom)

Although each substrate was optimized independently it is clear that the natural *trans*-substrate with the 4(5) alkene is reluctant to cyclise, giving only 20% yield of **137**. When we progressed to substrates with a diasteromeric ring system **197** or an exocyclic alkene **154** we obtained yields comparable to the best in the literature. A possible explanation for this is that the internal 4(5) alkene significantly shifts the diene and dienophile out of the optimum conformation for the cycloaddition. A review of the literature on successful Diels-Alder reactions appears to support this hypothesis. (Figure 13) Jenkins, Williams and

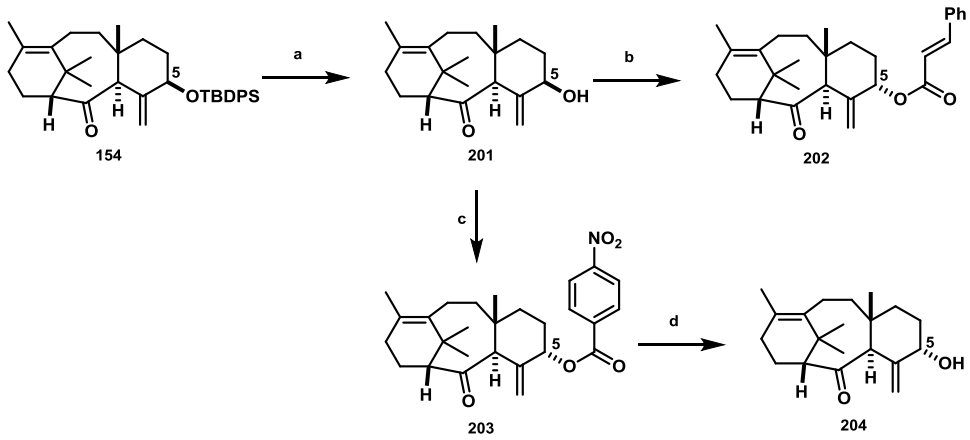
Baran all had no internal alkene in their Diels-Alder precursors and all obtained reasonable yields.

3.1.1 Functionalisation of Diels- Alder Products

With a C2 and C5 oxidised taxane **154** in hand, we proceeded to modify this structure to obtain different low oxidation state taxanes.

Inverting C5 Stereochemistry

Our first aim was to invert the alcohol at C5 to the natural α- stereochemistry.



Scheme 52: Deprotection and inversion of C5 stereochemistry.

Reagents and Conditions: **a)** TBAF, THF, r.t., 18 h., 95%. **b)** *trans*-cinnamic acid, PPh_3 , DEAD, THF, 0 ˚C, 3 h., 58%. **c)** *p*-nitrobenzoic acid, PPh_3, DEAD, THF, 0 ˚C to r.t., 2 h., 80%. **d)** K_2CO_3, MeOH, THF, r.t., 3 h., 75%.

Treatment of *tert*-butyldiphenylsilyl protected taxane **154** with tetra-butylammonium fluoride (TBAF) gave deprotected β alcohol **201**. This was then reacted under Mitsunobu conditions with cinnamic acid to give the corresponding 5α-cinnamoyltaxa-4(20)-11(12)-dien-2-one **202**.[89,90] Cinnamic acid was chosen here as it is a common side chain found in naturally occurring taxanes.[91] Using the same conditions with *p*-nitrobenzoic acid gave **203** a crystalline solid. Pleasingly the crystal structure of **203** showed that the Mitsunobu

reaction had proceeded with inversion at C5 to give the correct α- stereochemistry (Figure 14).

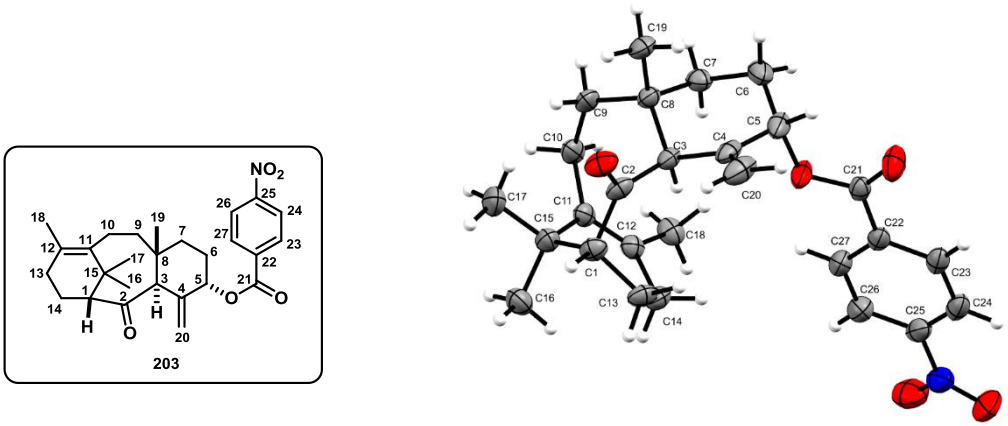


Figure 14: Crystal structure of **203** showing C5-α-stereochemistry.

We could not obtain a crystal structure of the cinnamoyl ester **202** to confirm the stereochemistry, however comparison of the total coupling constant in the ^{1}H NMR for the C5-H signal between **201**, **202** and **203** suggested that the cinnamoyl ester **202** had the same stereochemistry at C5 as ester **203**. The sum of the C5-H coupling constants for the Mitsunobu products was significantly less than that of the β alcohol starting material **201** (Figure 16). This is consistent with the loss of a *trans*-diaxial coupling constant between C5-Hα and C6-Hβ in **201**.

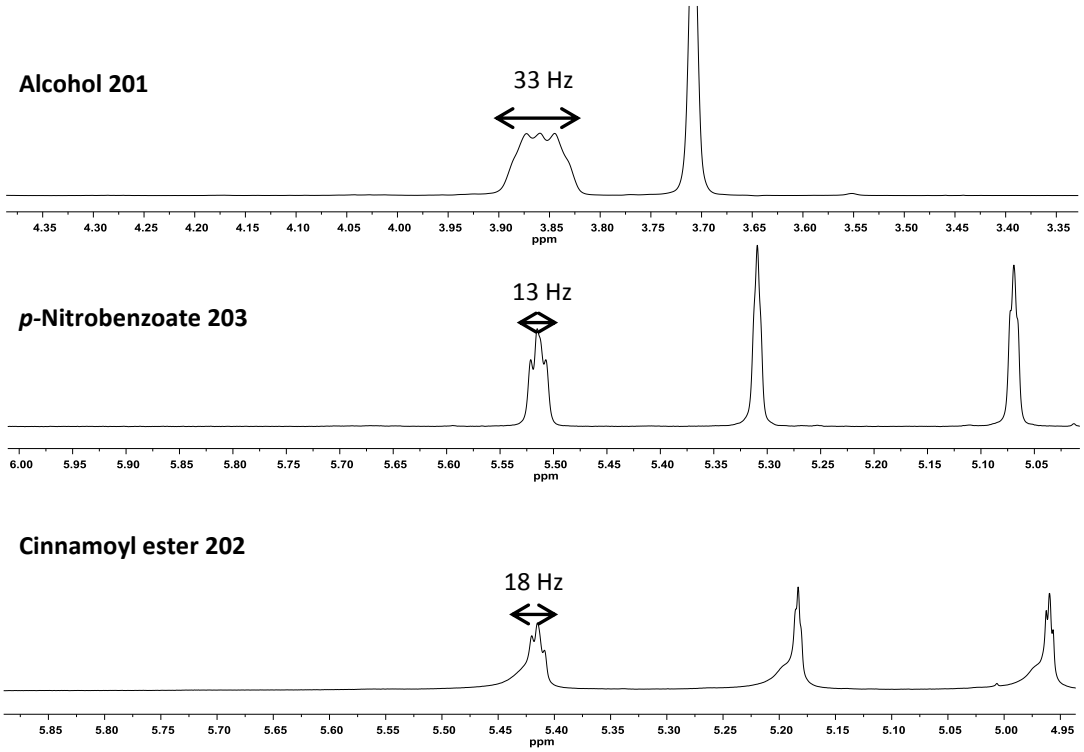


Figure 15: C5-H ^{1}H NMR signal from **201, 202, 203** illustrating total coupling constant.

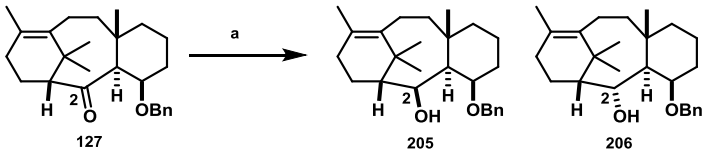
Deprotection of **203** by methanolysis gave 5α-hydroxytaxadieneone **204**. With a synthetic sequence for inverting C5 stereochemistry our attention shifted further functionalisation at C2.

Reducing C2 Ketone

There are no known natural taxanes that have a ketone at the C2 position.[91] Therefore, initial work began attempting to reduce the C2 ketone to the correct α stereochemistry.

Literature C2 Reductions

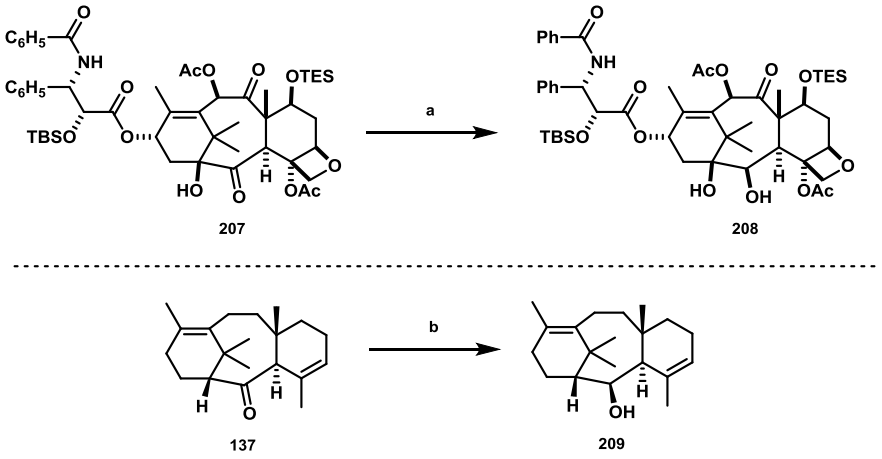
A number of groups have attempted to reduce a ketone at C2 stereoselectively, with varying success. Williams only obtained a 1:1.3 mixture of α and β alcohols when **127** was reduced with sodium in his synthesis of taxadiene.[74]



Scheme 53: Williams reduction of **127** at C2.

Reagents and Conditions: **a)** Na˚, Et_2O, -40 ˚C, 79%, **205:206 – 1:1.3**.

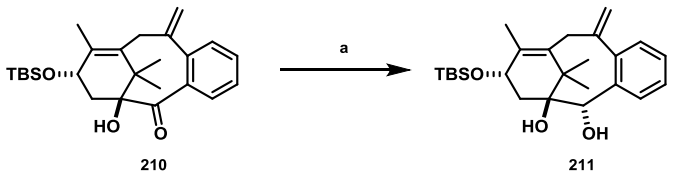
Kingston found that reduction of his highly oxidised taxane with sodium borohydride gave exclusively the β alcohol.[92] This seems to be the preferred stereochemistry when reducing with hydride reductants as Baran and Hayes confirmed with their reductions of taxadieneone **137** with lithium aluminium hydride.



Scheme 54: Kingston's and Baran's reductions at C2.

Reagents and Conditions: **a)** Na˚, EtOH, Et_2O, 0 ˚C, 60%. **b)** $LiAlH_4$, Et_2O, -78 ˚C to r.t., 72%.

In stark contrast to these reports, in his synthesis of an aromatic C ring model system for Taxol ® Wender managed to reduce a C2 ketone to the correct α-stereochemistry. This may be due to the lack of a C19 bridgehead methyl group in this system which would otherwise block the top face of the ring system or direction by the adjacent C1 hydroxyl group.



210 211

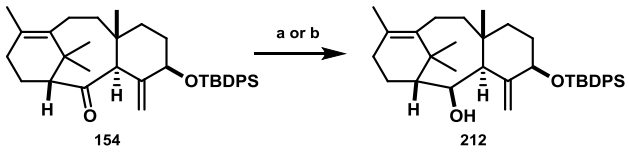
Scheme 55: Wender's ketone reduction.

Reagents and Conditions: **a)** $NaBH_4$, THF: MeOH, r.t., 1 h., 78%. **b)** $LiAlH_4$, Et_2O, -78 ˚C to r.t., 12 h., 72%.

Reviewing the literature, it appears that the reduction at C2 is highly substrate dependent. This is due to the range of conformations the 8 membered B ring can adopt. In some substrates such as **210** the taxane can form a more folded structure, opening the top face and allowing nucleophilic attack at the ketone.

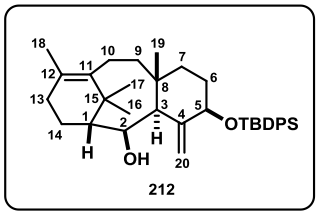
Our Reductions of the C2 Ketone

We set out first to use Williams's conditions for ketone reduction as these seemed to give the best selectivity for the desired α stereochemistry. We chose ketone **154** as this was our most abundant taxane substrate. Unfortunately Williams's conditions gave only 30% reduction to exclusively the β-alcohol, switching to diisobutylaluminium hydride (DIBAL-H) gave the same β-alcohol all be it in higher yield. The stereochemistry of **212** was confirmed by x-ray crystallography (Figure 16).



Scheme 56: Our reduction of ketone **117**.

Reagents and Conditions: **a)** Na˚, EtOH, Et_2O, -40 ˚C, 2 h. 30%. **b)** DIBAL-H, CH_2Cl_2, 0 ˚C, 0.5 h., 66%.



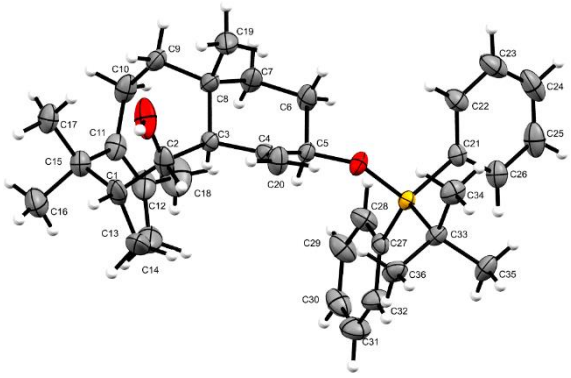
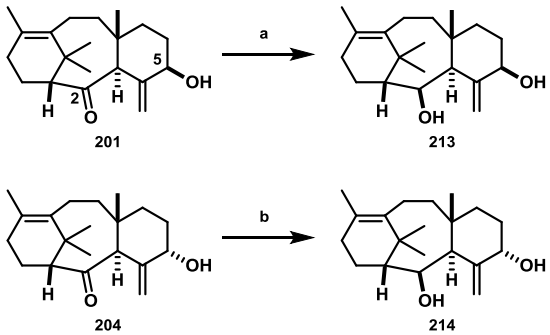


Figure 16: Crystal structure of alcohol **212.**

It is clear from this crystal structure that the C2 position is significantly hindered by both the C19 methyl and *gem*-dimethyl groups on the top face and by the inherent bowl shape of the taxane blocking the bottom face.

As we cannot significantly change the inherent shape of the taxane ring system, we hypothesised that the bulky OTBDPS substituent at C5 might affect the conformation of the B ring enough to change the stereochemical course of the reduction. To test this we proceeded to subject both the C5-α and C5-β alcohol substrates to Williams' conditions.



Scheme 57: Our reductions of **201** and **204**.

Reagents and Conditions: **a)** Na˚, EtOH, Et_2O, -45 ˚C, 2 h. 1:1.3 (**201**:**213**) **b)** Na˚, EtOH, Et_2O, -45 ˚C, 2 h. 1:4 (**204**:**214**).

Both reduction conditions in scheme 41 did not go to full conversion. With the diol products difficult to separate from the ketone starting material we were only able to obtain crude mixtures. Fortunately, diol **213** was later obtained pure enough for x-ray crystallography to confirm the C2-β stereochemistry (Figure 18). The coupling constants in the ^1H NMR for the C2-H signal for **213** and **214** were almost identical and this was sufficient to show that **214** was also the C2-β alcohol (Figure 17). Our adjustments to the substrate did not appear to stereochemical course of the reduction.

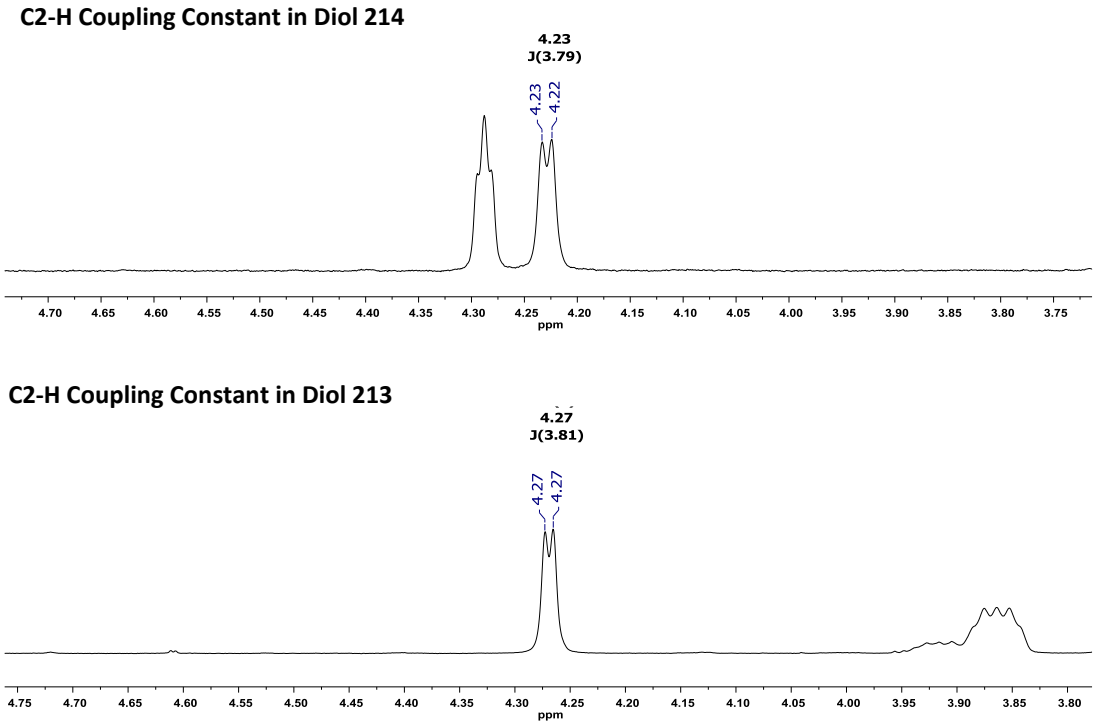
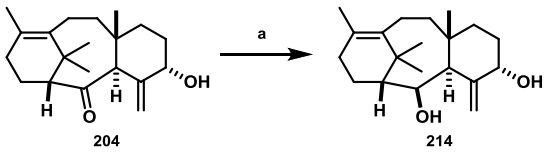


Figure 17: Comparison of C2-H coupling constants for diols **213** and **214** showing they most likely have the same stereochemistry.

In an attempt to improve the yield of the reduction we elected to use sodium/ ammonia for the reduction of ketone **204**. Although increasing to full conversion with these conditions, diol **214** was once again the exclusive product, formed this time in 70% yield.

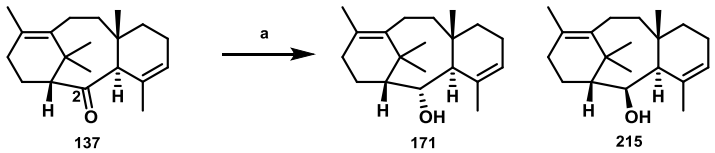


Scheme 58: Reduction of **204**.

Reagents and Conditions: **a)** Na˚, NH_3, MeOH, Et_2O, -45 ˚C, 2 h., 70%

In 2016 Baran published his reduction of taxadieneone **137** using sodium in isopropyl alcohol to obtain 63% of the desired C2 α- alcohol **171** (Scheme 59). We were able to repeat this work on a sample of our sample of taxadieneone **137**, obtaining α-alcohol **171**

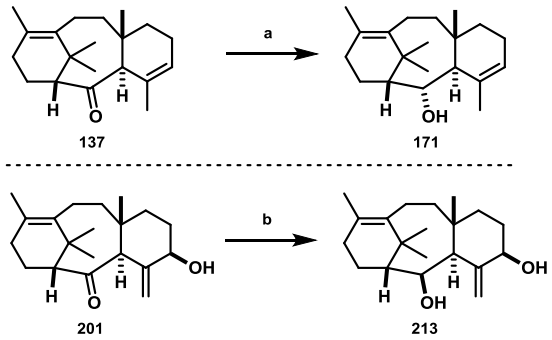
in 43% yield (Scheme 60). Unlike Baran, we were not able to detect any of the epimeric alcohol **215** in our experiment. This may be due to the vast difference in the scale of reactions, Baran used 2.85 g for his reduction, we used 10 mg.



Scheme 59: Baran's reduction of **100**.

Reagents and Conditions: **a)** Na˚, IPA, 80 ˚C, 3 h., 63% **171**, 11% **215**.

Unfortunately using Baran's conditions on our C ring oxidised substrate, alcohol **201**, gave once again poor conversion with the undesired stereochemistry. It is interesting to note Baran's use of high temperature in this reduction (80 ˚C) this may be significantly adjusting the conformation of the B ring to allow for reduction from the top face.



Scheme 60: Our reduction of **100** and **131**.

Reagents and Conditions: **a)** Na˚, IPA, 80 ˚C, 3 h., 43%. **b)** Na˚, IPA, 80 ˚C, 3 h., 1:4.4 (**201**:**213**)

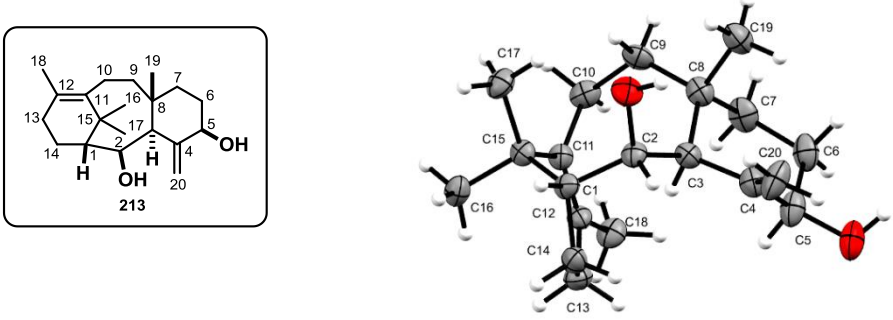


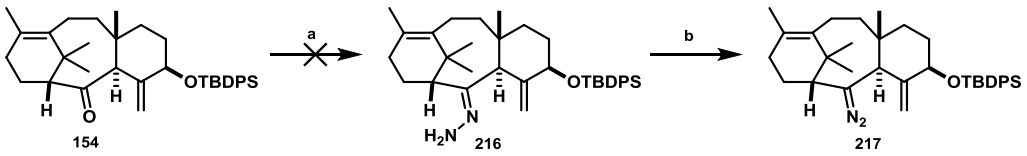
Figure 18: Crystal structure of diol **213** to confirm stereochemistry.

Our results confirm that the reduction at C2 is highly substrate dependent. With no oxidation in the C ring of the taxane the reduction seems to give the desired α alcohol whereas when the C ring is oxidised and contains an alkene, as in our substrate, the stereoselectivity of the reduction is switched to give the β alcohols. This effect seems unchanged by adjusting C5-stereochemistry.

Alternative Inversion Strategies for C2 Oxidation

With evidence that we were unlikely to be able to reduce the C2 ketone to the correct stereochemistry we attempted a number of alternative strategies.

Initially we attempted to synthesise diazo **217**. This compound could then act as a precursor to a C2 metal carbenoid which we hoped would allow us to explore OH insertion chemistry from the least hindered α face of the taxane ring system, thus giving a C2-α alcohol. Unsurprisingly this strategy is unprecedented in the literature.



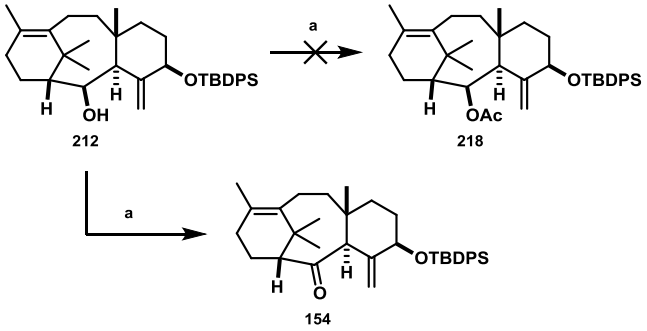
Scheme 61: Attempted hydrazone formation.

Reagents and Conditions: **a)** N_2H_4, 100 ˚C, 24 h. **b)** MnO_2.

Unfortunately despite extremely forcing conditions (hydrazine 100 ˚C) ketone **154** would not form the corresponding hydrazone. This is probably because of the high levels of steric hindrance at the C2 position already discussed previously. This problem persisted when we attempted to invert the corresponding C2 alcohol **212** under Mitsunobu conditions.[93,94] Unfortunately this only resulted in recovery of starting material.

Deoxygenation of C2 β-Alcohol: Total Synthesis of 5a-hydroxytaxadiene

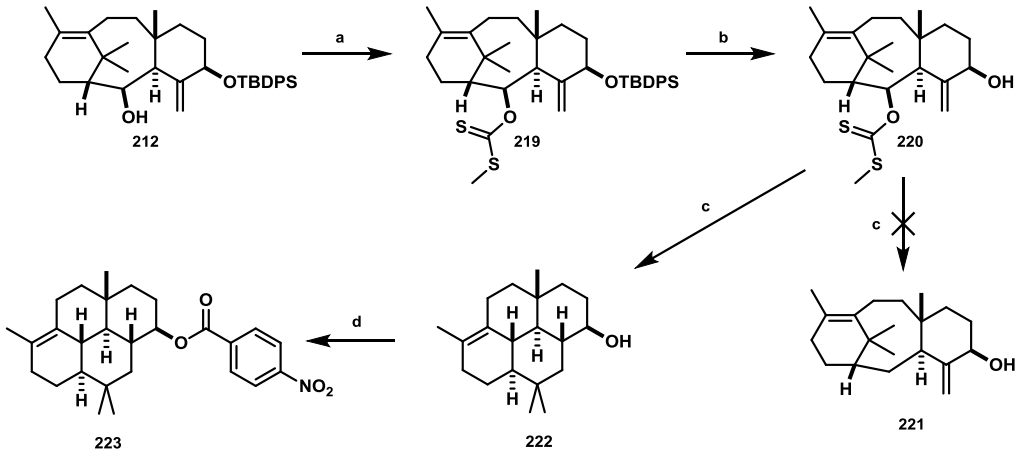
With the ketone and alcohol at C2 proving challenging to manipulate, we shifted attention to the reduction of this position. We first attempted to repeat the conditions used by Baran for his deoxygenation of taxadienone **137** by preparing the corresponding acetate **218** and then reducing this with sodium metal (Scheme 26). Unfortunately, we found preparing the acetate challenging. Using potassium hydride the reaction suffered from poor conversion < 5% and clean material was not isolated. We changed base to use potassium hexamethyldisilazide (KHMDS), however this resulted in oxidation back to the corresponding ketone (Scheme 62) presumably with reduction of acetyl chloride to acetaldehyde. We can envisage this reaction proceeding through a similar mechanism to the well-known Oppenauer oxidation.[95] Modifications to the Oppenauer reaction have been reported where the original Lewis acid aluminium triisopropoxide is replaced with a potassium alkoxide base.[96]



Scheme 62: Oppenauer oxidation during attempted acetate formation.

Reagents and Conditions: **a)** KHMDS, AcCl, -15 ˚C to r.t., 1 h., 50%.

Following these initial challenges, our attention turned to radical deoxygenation. One of the few reactions we could perform with alcohol **212** was the formation of the corresponding xanthate **219** (Scheme 63).



Scheme 63: Attempted Barton-McCombie deoxygenation of **212.**

Reagents and Conditions: **a)** i) KHMDS, CS_2, -78 ˚C to r.t., 1 h. ii) MeI, RT, 1 h. 89%. **b)** TBAF, THF, r.t., 26 h., 65%. **c)** $^{n}Bu_3SnH$ (1.2 eq.), AIBN, PhH, 80 ˚C, 2 h., 58%. **d)** *p*-nitrobenzoic acid, DMAP, DCC, r.t., 24 h., 48%.

Treatment of alcohol **212** with potassium hexamethyldisilazide, carbon disulphide and then methyl iodide furnished the desired methyl xanthate **219** in good yield. Deprotection of the C5 silyl group with TBAF gave alcohol **220**, which was then subjected to the classic Barton-McCombie conditions for deoxygenation. Xanthate **220** was treated with tributyltin hydride and azobisisobutyronitrile in benzene at reflux.[97] Unfortunately, instead of isolating the reduction product 5β-hydroxytaxadiene **221**, the novel tetradecahydropyrenol **222** was formed as the major product. Formation of the *p*-nitrobenzoate **223** allowed confirmation of connectivity and stereochemistry by x-ray crystallography.

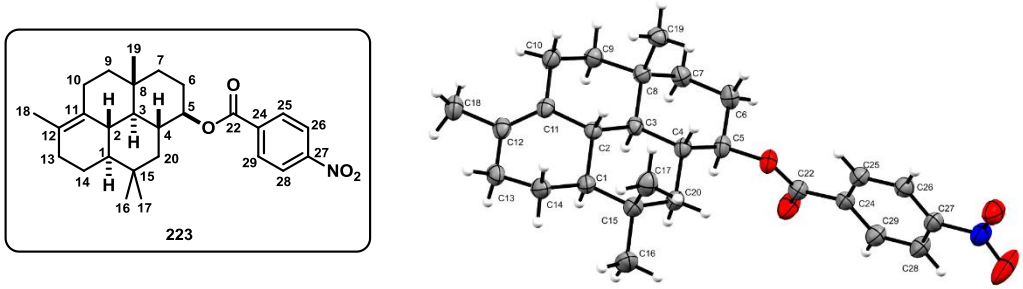
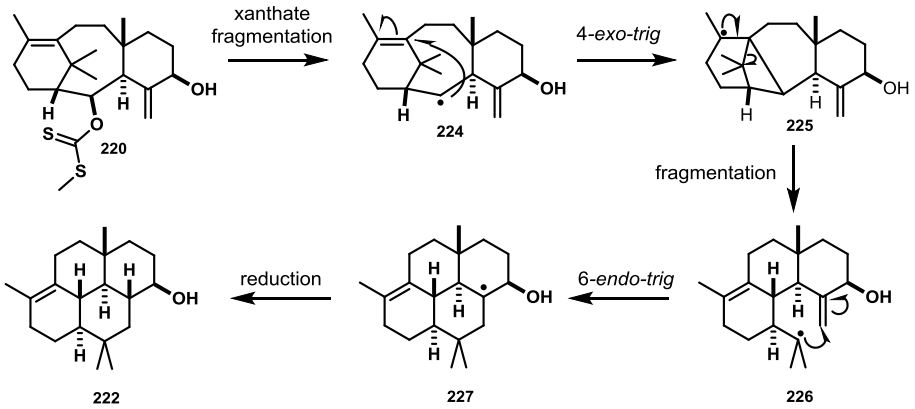


Figure 19: Crystal structure of **223.** Displayed with taxane numbering to aid discussion.

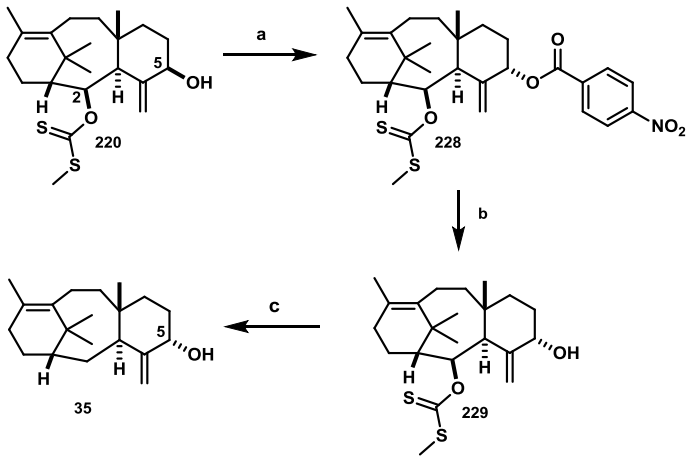
Although no mechanistic work was undertaken here, we propose that decahydropyrenol **222** is formed *via* a highly substituted cyclobutane **225** (Scheme 64).



Scheme 64: Proposed mechanism for the formation of decahydropyrenol **222**.

Following the addition of a tributyltin radical to xanthate **220**, fragmentation occurs through the established mechanism to give an carbon centred radical at C2 (**224**). At this point rapid addition of this radical to the 11(12) alkene in a 4-exo-trig process gives the heavily substituted cyclobutane **225**. This in turn fragments to give another stabilised tertiary radical **226**, which then adds in a 6-endo-trig manner to the 4(20) alkene. The subsequent radical (**227**) is then reduced to give the observed decahydropyrenol **222**.

With undesired product **222** identified, we could be guided in our approach to the reduction of **220**.



Scheme 65: Optimised Barton-McCombie deoxygenation

Reagents and Conditions: **a)** *p*-nitrobenzoic acid, DEAD, PPh_3, THF, 0 ˚C to r.t., 1 h., 63%. **b)** $LiOH{\cdot}H_2O$, $THF{:}H_2O$, r.t., 14 h., 69 %. **c)** $^{n}Bu_3SnH$ (10 eq.), AIBN, PhH, 80 ˚C, 2 h., 34%.

Due to limited quantities of alcohol **220** available we elected to employ our Mitsunobu inversion sequence first before final reduction of the xanthate. Therefore, Mitsunobu inversion of alcohol **220** with *p*-nitrobenzoic acid gave *p*-nitrobenzoate **228**, hydrolysis with lithium hydroxide then gave C5-α alcohol **229** (scheme 65).

Our approach to reduction of xanthate **229** was then to use a large excess of tributyltin hydride in the hope that we would increase the rate of reduction of the C2 radical, out-

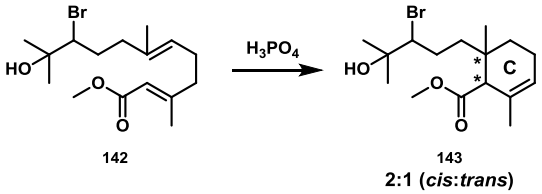
competing the 4-exo-trig cyclisation that ultimately leads to decahydropyrenol **222**. With 10 equivalents of tributyltin hydride this was successful and we could isolate the desired natural product 5α-hydroxytaxa-4(20),11(12)-diene **35**. Data for **35** matched the literature and our sample made from epoxidation and rearrangement of taxadiene **24**.

Now with two methods for accessing the low oxidation state taxane 5α-hydroxytaxa-4(20),11(12)-diene either by oxidation and rearrangement of taxadiene derived from genetically modified tomatoes (chapter II) or through chemical synthesis from farnesol (chapter III) our attention shifted to the development of an enantioselective synthetic route to these compounds.

3.1.2 Asymmetric Synthesis

The syntheses of the unnatural diastereomers or enantiomers of taxanes such as *cis*-taxadienone **197** (Scheme 33) are rare in the literature. Despite apparent aims to provide analogues for biological testing the large majority of taxane syntheses focus exclusively on pursuing natural products. The diasteromeric and enantiomeric analogues are of vital importance if taxanes are to be fully explored for medicinal purposes. The ability to access two enantiomeric series of our taxanes would provide vital analogues previously unexplored.

We first considered strategies available to us. Since the intramolecular Diels-Alder reaction is diastereoselective, the formation of the first (C) ring in our synthesis is the stereo-defining step. Currently the formation of the C ring (Scheme 66) is racemic and produces the product as a 2:1 mixture of *trans*:*cis* isomers.



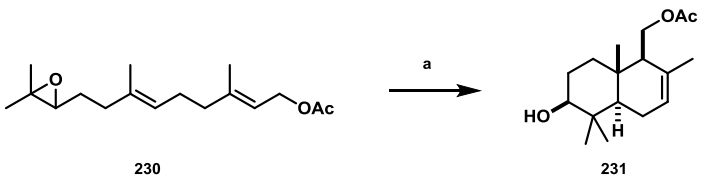
Scheme 66: Racemic and poorly diastereoselective cyclisation.
* Denotes permanent stereocenters.

Asymmetric C-ring Cyclisation

In nature, a range of terpenoids are enzymatically synthesised by cationic cyclisations, an example of which, the cyclisation of geranylgeranyl pyrophosphate (GGPP) by taxadiene synthase was given in the introduction to this thesis.[98] This is a remarkable process, forming multiple rings and quaternary centres with absolute control of stereochemistry.

Since the advent of the Stork-Eschenmoser hypothesis,[99–101] cation initiated polyene cyclisations have attracted much attention.[102] The Stork-Eschenmoser hypothesis states that in a cationic polyene cyclisation, each double bond undergoes a stereospecific, concerted anti-addition with the molecule arranged in a chair like transition state. Therefore the use of a polyene with *trans*-alkenes leads to a cyclised product with *trans*-ring junctions.

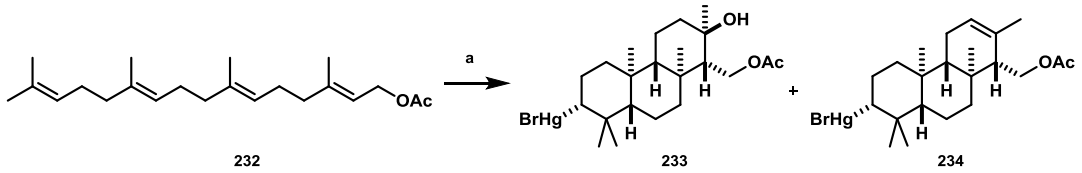
An example of early work in this area is the report by Van-Tamelen that treatment of epoxide **230** with boron trifluoride etherate prompted cyclisation to give a single diastereoisomer of **231** in 85% yield.[103]



Scheme 67: Van-Tamelen's cationic cyclisation.

Reagents and Conditions: **a)** $BF_3{\cdot}Et_2O$, PhH, 85%.

Others have extended this work using Lewis acids and mercury salts on un-oxidised substrates, such as the work of Hayashi (Scheme 68).[104] Hayashi found that geranylgeranyl acetate **232** cyclises in the presence of mercury (II) triflate and *N,N*-dimethylaniline to give tricyclic products **233** and **234**.



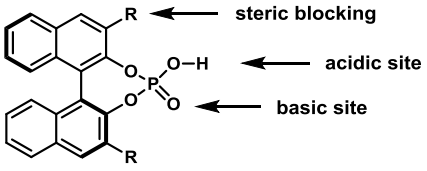
232 233 234

Scheme 68: Hayashi's mercury promoted cyclisation

Reagents and Conditions: **a)** $Hg(OTf)_2$, $PhNMe_2$, $MeNO_2$, then KBr aq., 16% **233**, 17% **234**.

These examples (Scheme 67 and 68) are however, diastereoselective cyclisations, the current state of art is to render these processes enantioselective.

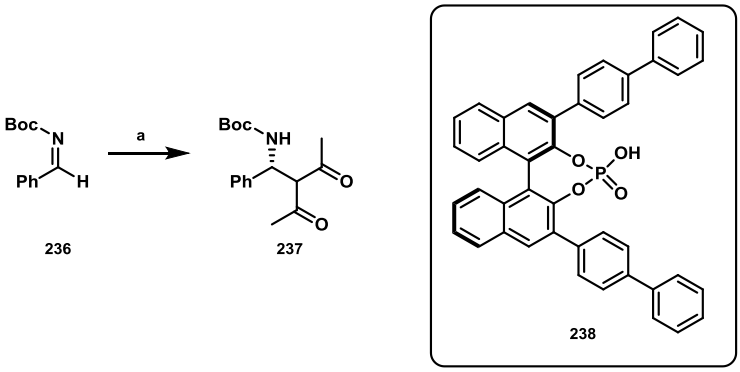
Chiral BINOL phosphoric acids, whose general structure is depicted below (**235**) have been found to be particularly effective in this area. Rather than activating the substrate with a Lewis acid they catalyse the cyclisation by forming a cation *via* protonation of the substrate.[105–108]



235

Figure 20: General structure of BINOL phosphoric acids.

The first use of these BINOL phosphoric acids in synthesis was reported by Terada in 2004 using BINOL phosphoric acid **238**for an asymmetric Mannich reaction.[109]



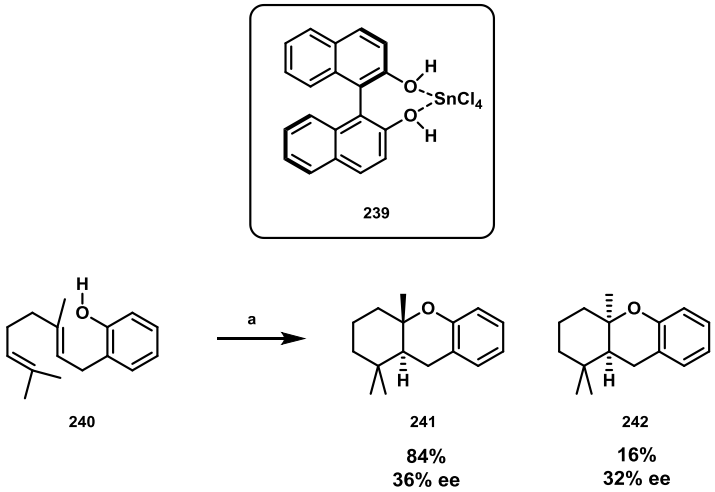
Scheme 69: Terada's asymmetric Mannich reaction.

Reagents and Conditions: **a) 238** (2 mol%), acac, CH_2Cl_2, r.t., 1 h., 88%, 90% *ee*.

Since Terada's first report in this area, the field of BINOL Brønsted acids has grown, with the chiral acids and their derivatives being applied to a wide range of chemistries.[105,106,108,110]

Yamamoto's Binaphyl (BINOL) – Tin Chloride Catalyst

Yamamoto reported in 1999 a binaphol (BINOL) – tin chloride catalyst **239** for enantioselective polyene cyclisations.[111]

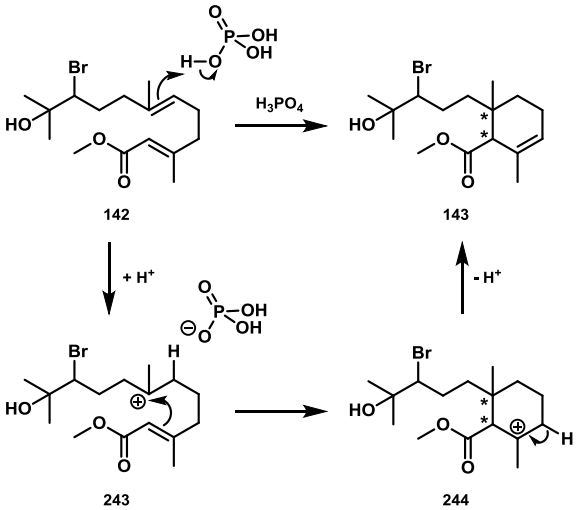


Scheme 70: Yamamoto's asymmetric polyene cyclisation

Reagents and Conditions: **a)** Catalyst **239** (1 eq.), CH_2Cl_2, -78 ˚C, 24 h.

The addition of a Lewis acid to a chiral Brønsted acid increases its acidity facilitating protonation of the terminal olefin in **240**. Yamamoto went on to modify this approach to create a range of chiral bisphenol catalysts.[112,113]

We considered again our current cyclisation following the work of Willbrand.[86] We can propose that this reaction proceeds through protonation of the most electron rich double bond in **142** (Scheme 71) producing a carbocation intermediate **243**. Addition of the second alkene to this carbocation gives a second tertiary carbocation **244**. This can then lose a proton to give the final cyclised product **143**.

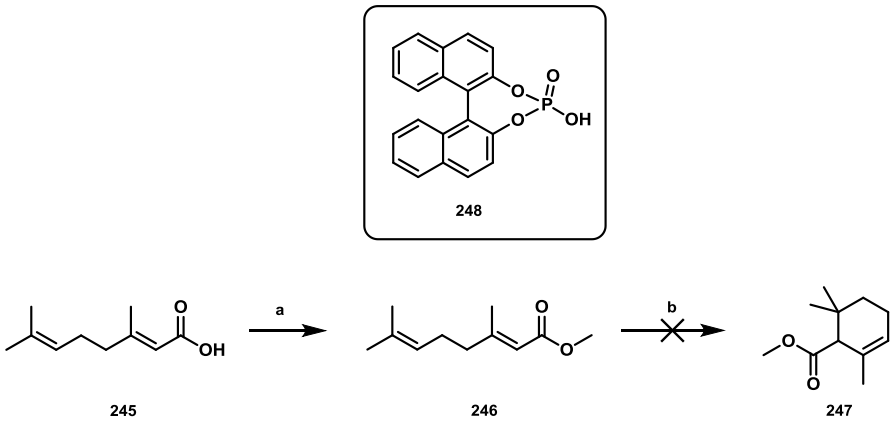


Scheme 71: Proposed mechanism of our cyclisation with phosphoric acid.

Although only a proposal, this mechanism suggests that the use of a chiral Brønsted acid may be beneficial. By protonating the alkene **142**, the conjugate base of the catalyst (the anion) may remained in close proximity to the substrate (cation **243**) to allow for an asymmetric addition of the second alkene to the carbocation. With this in mind we explored the use of chiral Brønsted acids in our system.

BINOL Phosphoric Acids

We first synthesised a model system to simplify the substrate by removing the terminal stereocenter. Methylation of geranoic acid **245** provided methyl geranoate **246** in good yield. We first attempted to cyclise **246** using 10 mol% of the commercially available racemic phosphoric acid **248** in toluene to determine if this acid is capable of promoting cyclisation. Unfortunately acid **248** gave no conversion to cyclo-methylgeranoate **247**.



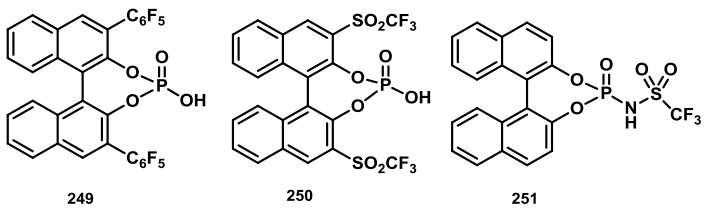
Scheme 72: Reaction of methylgeranoate with BINOL phosphoric acid catalysts.

Reagents and Conditions: **a)** MeI, K_2CO_3, DMF, r.t., 24 h., 92%. **b)** BINOL cat. **248** (10 mol%), PhMe, r.t., 18 h.

A significant challenge with these chiral acids is the moderation of their acidity. We believe that catalyst **248** with a pKa of 13-14 in acetonitrile and 3.37 in DMSO is simply not acidic enough to protonate the terminal alkene of methyl geranoate **245**.[110,114] With this in mind we worked to increase the acidity of our catalysts.

One way of doing this is to introduce electron withdrawing groups *ortho* to the phosphate in the napthyl ring giving potential catalysts **249** and **250** (Figure 21). In addition to this Yamamoto has developed a strong Brønsted acid by exchanging the phosphoric acid

moiety for a *N*-triflylphosphoramide.[115] When applied to BINOL phosphoric acids this should render our simplified catalyst **251** significantly more acidic. [116,117]

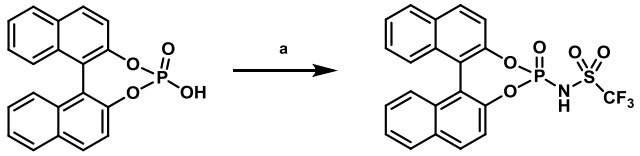


249 250 251

Figure 21: BINOL catalysts with increased acidity.

Catalyst Synthesis

Triflimide Catalyst **252** was synthesised from the simple BINOL phosphoric acid **248** in one step following a procedure reported by Nagorny.[118]



248 252

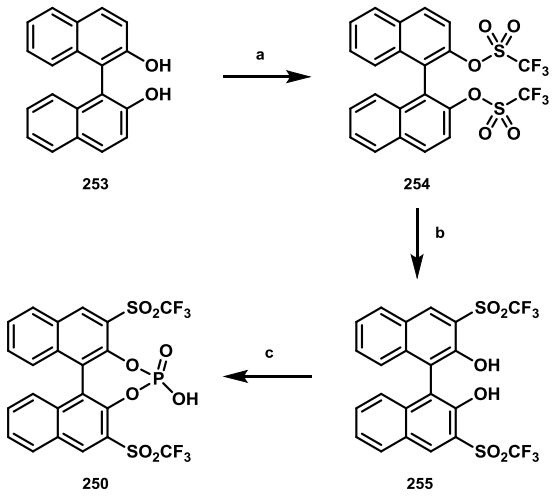
Scheme 73: Synthesis of triflimide catalyst **252**.

Reagents and Conditions: **a)** i) $(COCl)_2$, DMF, CH_2Cl_2, 0 ˚C, 24 h. ii) Trifluoromethylsulfonamide, DMAP, Et_3N, MeCN, r.t., 8 h., 30% (2 steps).

Catalyst **250** was synthesised in three steps using a thia-Fries rearrangement. Reaction of racemic BINOL **253** with triflic anhydride gave **254** in good yield.[119] Triflate **254** was then rearranged using the thia-Fries rearrangement developed by Lloyd-Jones.[120] This involved the sequential addition of lithium diisopropylamide (LDA) to **254** to give triflone **255** in 18% yield. BINOL **255** was then converted to the corresponding phosphoric acid **250** by reaction with phosphorus oxychloride in pyridine. This reaction proved quite challenging.

The product was first obtained as the pyridinium salt which required repeated washing with 6 M hydrochloric acid to give the free acid in 14% yield.

Fluorinated catalyst **249**, first reported by Terada in 2001, was kindly donated to us by the Woodward group in Nottingham.[121]

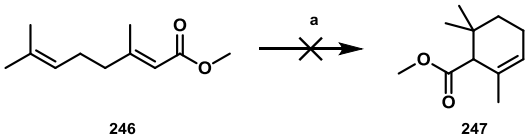


Scheme 74: Synthesis of triflone catalyst **250**.

Reagents and Conditions: **a)** $(Tf)_2O$, Et_3N, CH_2Cl_2, -78 ˚C to r.t., 2 h., 88%. **b)** i) LDA, THF, -78 ˚C to r.t., 1 h., ii) LDA, THF, -78 ˚C to r.t., 1 h., 18%. **c)** i) $POCl_3$, pyridine, 95 ˚C, 1 h. ii) H_2O, 95 ˚C, 1 h., 14%.

BINOL Brønsted Acid Cyclisations

All three of the new BINOL acid catalysts were tested on our model system methyl geranoate **246**.



Scheme 75: Reaction of methylgeranoate with BINOL phosphoric acid catalysts.

Reagents and Conditions: **a)** BINOL cat. (10 mol%), PhMe, r.t., 18 h.

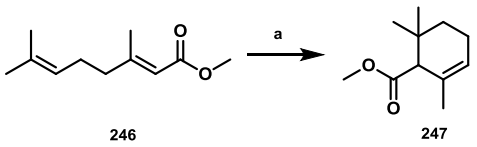
Unfortunately none of the BINOL acid catalysts reacted with methyl geranoate. The reactions were subsequently heated to 50 ˚C and still no product was observed. This may be an indication that despite some of these catalysts being particularly acidic, they were still not acidic enough to protonate the terminal olefin of **246**.

A solution to this problem may be to use a chiral Brønsted acid with an achiral Lewis acid to increase its acidity.

Yamamoto's Tin Chloride Catalyst

We decided to utilise Yamamoto's chiral BINOL/$SnCl_4$ catalyst for our cyclisation. Unfortunately, treatment of bromohydrin **142** with Yamamoto's catalyst gave only decomposition. This is not surprising considering the harsh conditions of the reaction coupled with a sensitive tertiary alcohol substrate.

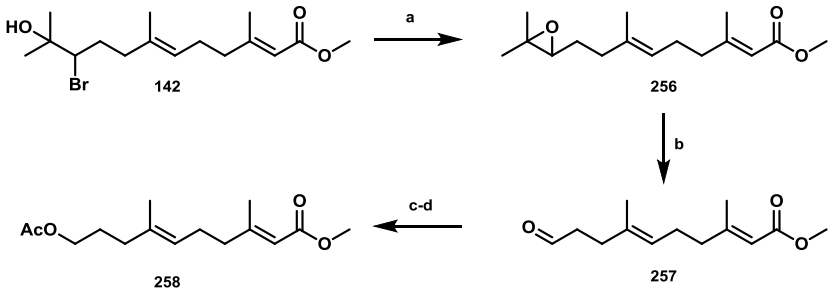
We went on to test Yamamoto's catalyst on our model system, methyl geranoate **246**. After optimisation to reduce the catalyst loading from 100 to 15 mol% we were able to cyclise methyl geranoate to give **247** in 50% yield. At this stage we used only racemic BINOL to test the reactivity of the system.



Scheme 76: Methyl geranoate cyclisation with Yamamoto's catalyst.

Reagents and Conditions: **a)** (±) BINOL (15 mol%), $SnCl_4$ (15 mol%), CH_2Cl_2, -78 ˚C to r.t., 18 h., 50%.

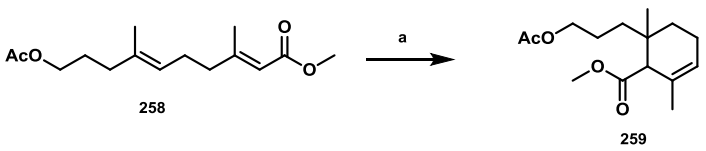
Although promising, cyclised product **247** has only one stereocenter and limited functionality. To extend this method to a more realistic system we synthesised ester **258**.



Scheme 77: Synthesis of ester **258**.

Reagents and Conditions: **a)** K_2CO_3, MeOH, r.t., 12 h., 99%. **b)** H_5IO_6, Et_2O, r.t., 1 h., 96%. **c)** $NaBH_4$, MeOH, 10 min., 82%. **d)** Ac_2O, DMAP, CH_2Cl_2, r.t., 18 h., 92%. **e)** (±) BINOL (15 mol%), $SnCl_4$ (15 mol%), CH_2Cl_2, -78 ˚C to r.t., 18 h., 50% conversion, inseparable from starting material.

Ring closure of bromohydrin **142** to epoxide **256** followed by periodic acid cleavage, reduction and protection gave **258** in good overall yield. Initial application of our previous conditions with 15 mol% catalyst gave a low conversion (50%). Increasing the catalyst loading to 20 mol% gave complete conversion to the desired cyclised product **259**, albeit in modest yield (33%).



Scheme 78: Cyclisation of ester **258**.

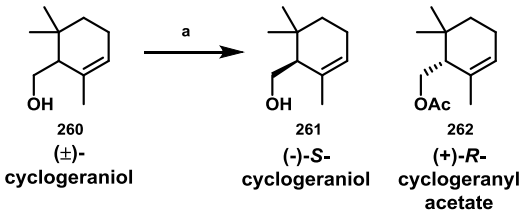
Reagents and Conditions: **a)** (±) BINOL (20 mol%), $SnCl_4$ (20 mol%), CH_2Cl_2, -78 ˚C to r.t., 18 h., 33%., 1:1.4 d.r.

Cyclohexene **259** was found to be a mixture of diastereoisomers in a 1:1.4 ratio (^{1}HNMR). Although these could be partly separated by silica gel chromatography it was not possible to assign relative stereochemistry by ^{1}H NOSEY NMR.

With the Yamamoto's organocatalyst failing to provide diastereocontrol of the cyclisation we decided to move on and attempt a kinetic resolution later in our synthesis. This had the advantage of being easy to set up and would allow us to access both enantiomers of the taxane system.

Kinetic Resolution with Lipase

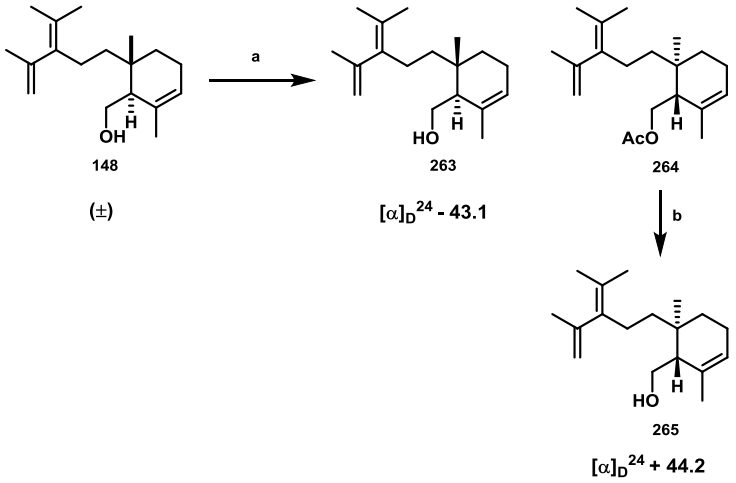
A lipase resolution (*Pseudomonas cepacia*) was used by Vidari to resolve cyclogeraniol **260** in his synthesis of α-ionones.[122]



Scheme 79: Vidari's lipase resolution of cyclogeraniol.

Reagents and Conditions: **a)** *Pseudomonas cepacia*, vinyl acetate, hexanes/Et_3N (2.8:1), 4-Å-molecular sieves, 0 ˚C, 5 days, 58% conversion, **261** - 95% *ee*, **262** – 68% *ee*.

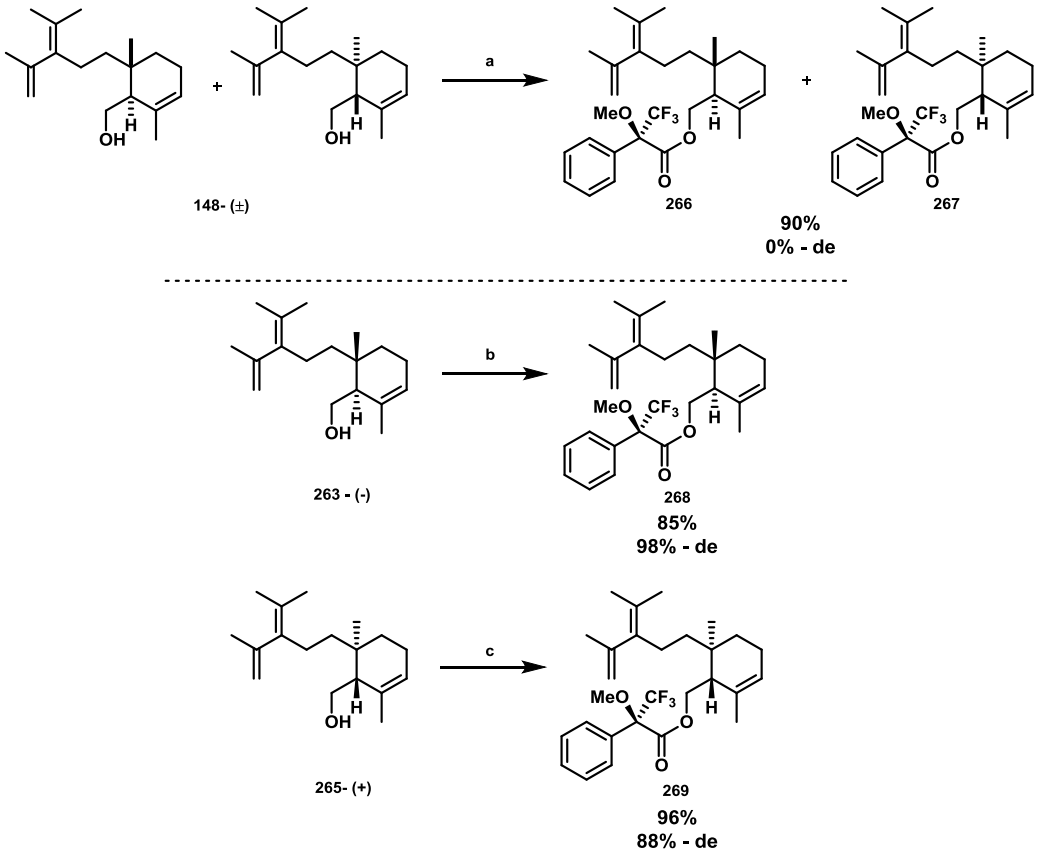
We identified alcohol **148** (Scheme 80) as a similar substrate to **260** to test a lipase resolution. After testing the reaction following Vidari's procedure at 0 ˚C for 5 days we observed low conversion to the acetate product. Optimisation of this procedure by warming to ambient temperature and allowing the reaction to continue for 6 days gave 58% yield of acetate **264**.



Scheme 80: Lipase resolution of alcohol **148** (absolute stereochemistry unknown - assigned arbitrarily for convenience of discussion)

Reagents and Conditions: **a)** *Pseudomonas cepacia*, vinyl acetate, hexanes/Et_3N (2.8:1), 4-Å-molecular sieves, r.t., 6 days, **263 -** 48%, $[\alpha]_D^{24}$ - 43.1, **264** – 58%. **b)** LiOH·H_2O, THF/H_2O (2:1), r.t., 18 h., 51%, $[\alpha]_D^{24}$ + 44.2.

Following lipase resolution, acetate **264** was hydrolysed to alcohol **265**. Mosher's ester analysis was then used to determine the enantiomeric purity of both alcohols **263** and **265**.[123] Although this method can be used to determine absolute stereochemistry by NMR, in this case **148** is a primary alcohol and too far from the stereocenters in question to determinate absolute configuration.[124]



Scheme 81: Mosher's ester analysis on alcohols **263** and **265**, *d.e* determined by ^{1}HNMR.

Reagents and Conditions: **a)** (*R*)-Mosher's acid, DCC, DMAP, CH_2Cl_2, r.t., 24 h., 90%, 0% *de*. **b)** (*R*)-Mosher's acid, DCC, DMAP, CH_2Cl_2, r.t., 18 h., 85%, 98% *de*. **c)** (*R*)-Mosher's acid, DCC, DMAP, CH_2Cl_2, r.t., 18 h., 96%, 88% *de*.

To determine whether there would be any kinetic resolution in the coupling reaction with Mosher's acid, racemic alcohol (±)-**148** was first subjected to the ester coupling reaction conditions for 24 h. This reaction proceeded in 90% yield giving as expected no resolution (1:1 mixture of diastereoisomers, 0% de). Treatment of each enantioenriched alcohol **263** and **265** with these conditions for only 18 h. gave esters **268** and **269.** Integration of the cyclohexene alkenic protons allowed determination of *de* for these esters and so *ee* for the corresponding alcohols (Figure 22).

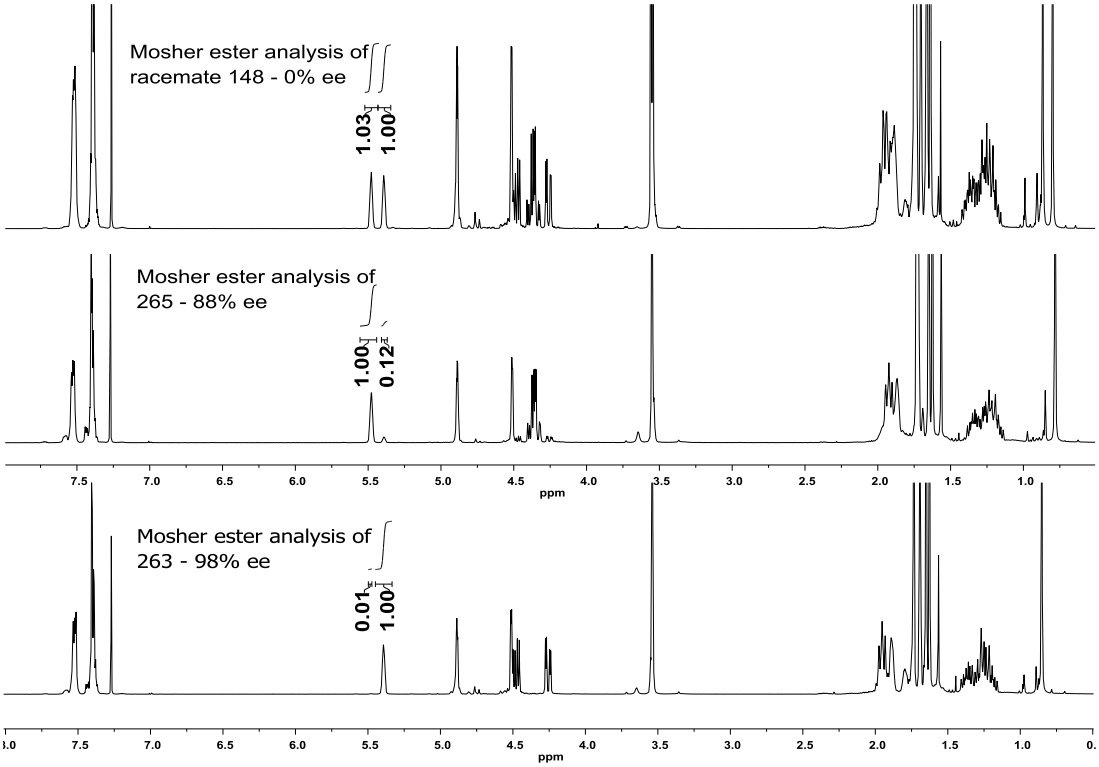


Figure 22: ^{1}HNMR of Mosher's esters **266/267**, **268** and **269**. Integration of the 4-H alkenic peaks was used for the determination of diasteromeric excess. **269** = 1:0.12 *dr* = 88% *de*. **268** = 1:0.01 – 98% *de*.

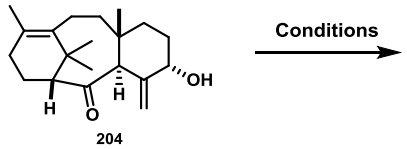
Having run the lipase kinetic resolution over 50% conversion, we observed an excellent enantioenrichment (98% *ee*) of the remaining alcohol **263** from the reaction and pleasingly a reasonable enrichment (88% *ee*) of alcohol **265**.

These preliminary results were pleasing as they showed that we could potentially access both enantiomeric series of our taxanes, immediately doubling the range of analogues we could prepare. There is still work on-going work to develop an enantioselective synthesis of our low oxidation state taxanes, however, further investigations concerned the oxidation of our taxanes to obtain further analogues for biological testing.

3.1.3 Our Oxidations of Synthetic Taxanes

Oxidation studies commenced on a range of substrates. These were chosen based on availability of material at each stage of the synthesis. A range of conditions for allylic oxidation using peroxides were tested with alcohol **204** as a substrate. These conditions were expected to oxidise at either C13 or C10.

Table 1: Allylic oxidation of **204** using peroxides.



204

Entry	Conditions[a]	Solvent	Result
1[125]	Fe(TPP)Cl, H_2O_2	CH_2Cl_2	No Reaction
2[126]	Fe(*S,S*)-PDP, H_2O_2, AcOH	MeCN	Decomposition
3[127]	CuI, $^tBuOOCOPh$	PhH	Decomposition
4[128]	$Pd(OAc)_2$, ^tBuOOH, K_2CO_3	CH_2Cl_2	Decomposition
5[129]	$Co(acac)_2$, ^tBuOOH	PhH	Decomposition

a) Please see references for experimental detail.

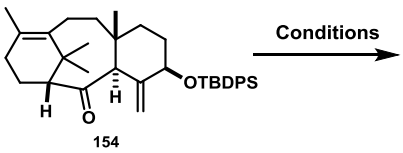
Entry 1 using Fe(TPP)Cl and hydrogen peroxide were conditions used previously for the oxidation of taxadiene (chapter II) however here we hoped to access the ability of iron porpyrins to promote C-H abstraction and OH rebound.[125] Unfortunately **204** was unreactive under these conditions. We then went on to try White's catalyst ($[Fe(PDP][SbF_6]_2$). This however gave mostly decomposition with some evidence by ^{13}C NMR of epoxidation of the 11(12) alkene, a common problem for this catalyst.

We moved on to try other peroxide/metal catalyst based methods. The classic conditions for this process are the Karasch conditions (Entry 3). This uses *tert*-butylbenzoylperoxide, an active peroxide that decomposes in the presence of copper (I) salts to produce *tert*-butoxide radicals. These then abstract a hydrogen atom from the substrate. Radical recombination of the benzoate radical with the alkyl radical produced then gives the desired oxidation product.

Unfortunately all the conditions attempted using peroxides failed to give clean conversion to oxidised products. We suspect this is due to the unselective oxidation on the taxane skeleton. This accompanied by any side reactions/rearrangements associated with alkyl radicals gives a vast range of possible products which can all undergo further oxidation in an uncontrolled manner.

To continue oxidation studies we changed substrate to silyl ether **154**. This compound was available in larger quantities and with a protected alcohol would allow us to explore more conditions without the concern of oxidising alcohol **204**to the corresponding ketone.

Table 2: Allylic oxidation of **154.**

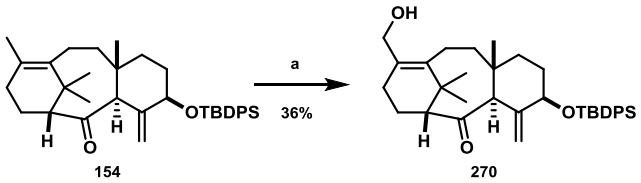


154

Entry	Conditions[a]	Solvent	Result
1[130]	$Pd(OAc)_2$, $Cu(OAc)_2$, BQ	AcOH	No Reaction
2	SeO_2	CH_2Cl_2	36% C18 oxidation

a) Please see references for experimental detail. BQ = Benzoquinone

Classical palladium acetoxylation conditions (Entry 1) failed to oxidise the substrate giving only recovered starting material. Pleasingly, selenium dioxide was found to oxidise taxane **154** at C18.



a) SeO_2 (2 eq.), CH_2Cl_2, r.t., 10 days.

Scheme 82: Allylic oxidation of **154** using selenium dioxide

At this point we decided to use this alcohol to direct oxidation selectively on the taxane skeleton utilising C-H oxidation chemistry developed by Sanford.[131] Unfortunately oxidation of this alcohol to the aldehyde gave only a mixture of products.

As expected the selective C-H oxidation of these sparsely functionalised molecules is challenging.

3.2 Conclusions and Future Work

In this chapter we have described the synthesis of a range of low oxidation state taxanes, presented work towards an asymmetric synthesis of the taxane ring system and explored the C-H oxidation of low oxidation state taxanes.

3.2.0 Synthesis of Taxanes

The synthesis of a range of low oxidation state taxanes have been described, examples of which are shown below.

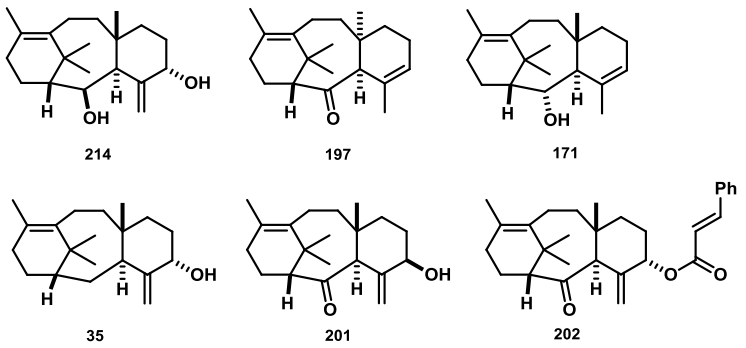
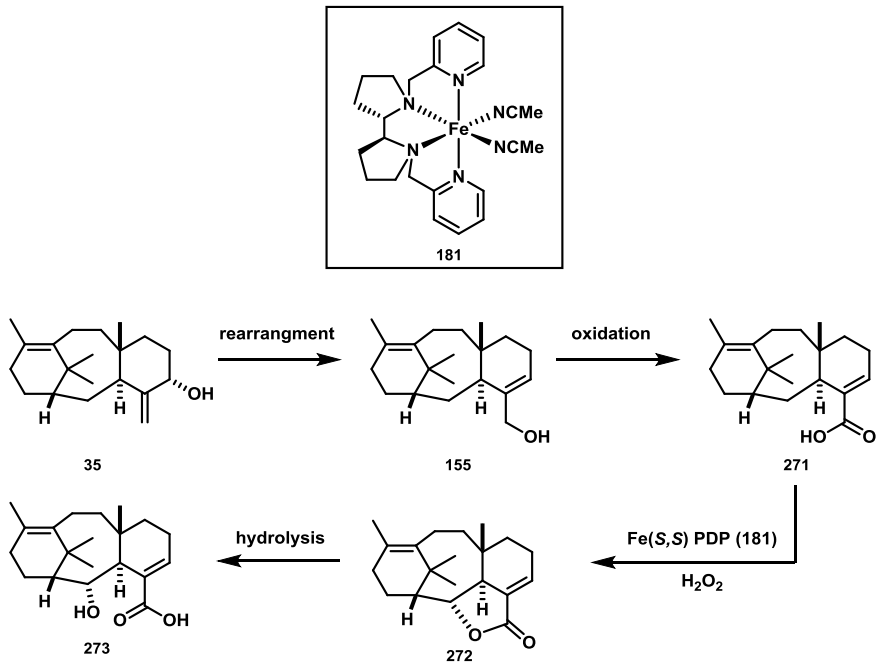


Figure 23: Low oxidation state taxanes; 5α,2β-hydroxytaxadiene **214**, *cis*-taxadieneone **197**, 2α-hydroxytaxadiene **171**, 5α-hydroxytaxadiene **35**, 5β-hydroxytaxadienone **201** and 5α-cinnamoyltaxadienone **202**.

We have prepared taxanes with oxidation at both the C2 and C5 positions and with both internal and external alkene isomers finally culminating in the total synthesis of 5α-hydroxytaxadiene **35**.

We have shown that to achieve an efficient Diels-Alder cycloaddition we require an exocyclic alkene in the C ring. Unfortunately, this same exocyclic alkene then appears to impede our ability to reduce the C2 ketone to the correct stereochemistry.

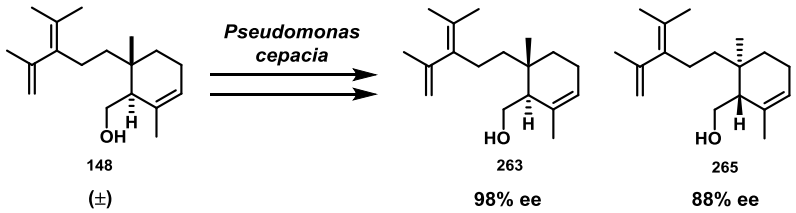
Future work in this area could involve the installation of C2 oxidation by directed C-H oxidation. White has used an iron catalyst for this purpose, as reviewed previously in this thesis.[82]



Scheme 83: Route to C2-α-alcohol.

3.2.1 Asymmetric Synthesis of Taxanes

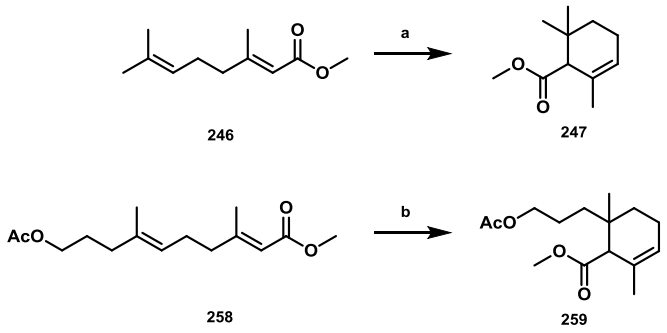
Preliminary studies towards an asymmetric synthesis have showed promise. We have shown that we can access both enantiomeric series of alcohol **148** by a lipase resolution, giving alcohols **263** and **265**with excellent levels of enantiomeric enrichment.



Scheme 84: Lipase resolution of alcohol **148**.

The disadvantage of the lipase approach is that if we chose to pursue one enantiomeric series then half of our material would be wasted. A far more efficient approach is to

render the cyclisation asymmetric through catalysis. We have conducted preliminary work in this area with initial success using a BINOL-$SnCl_4$ catalyst system developed by Yamamoto for polyene cylisations.[111]



Scheme 85: Cyclisations with Yamamoto's catalyst.

Reagents and Conditions: **a)** (±) BINOL (15 mol%), $SnCl_4$ (15 mol%), CH_2Cl_2, -78 ˚C to r.t., 18 h., 50%. **b)** (±) BINOL (20 mol%), $SnCl_4$ (20 mol%), CH_2Cl_2, -78 ˚C to r.t., 18 h., 33%., 1:1.4 d.r.

The simple model system methyl geranoate cyclised in 50% yield to give **247** and the more complex acetate **258** was shown to cyclise to give **259** in 33% yield. Unfortunately the latter cyclisation was not diastereoselective.

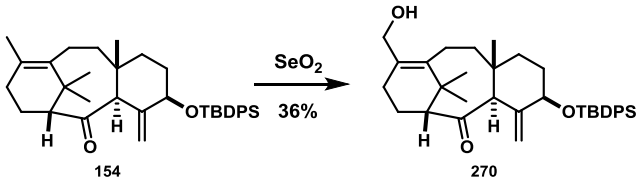
Future work in this area will concentrate on developing a diastereoselective and eventually enantioselective cyclisation of polyenes. Initial studies could investigate the role of the acetate protecting group in **258**. Acetate groups can provide neighbouring group participation and so changing this group may be beneficial to the stereoselectivity.

3.2.2 Oxidations of Taxanes

Initial oxidation studies into the taxanes have been challenging. The difficultly with the C-H oxidation of taxanes was exemplified by Baran when surveying hundreds of reagents for a single oxidation step in his synthesis of (-)-taxuyunnanine D.[68]

Decomposition of the starting material appears to occur in the majority of reactions trialled. This may be due to a combination of the harsh conditions sometimes necessary to oxidise a C-H bond and the small scale experiments were conducted on. With access to more material we may be able to screen more reagents at a larger, more manageable scale.

Despite these problems we have found a method for the selective oxidation at C18 using selenium dioxide.



Scheme 86: Successful oxidation of taxane **154.**

Further manipulations of alcohol **270** were unfortunately unsuccessful, however this is a good result, showing that selective oxidation is possible.

Final Conclusions

Reported in this thesis are our efforts towards low oxidation state taxanes by both synthetic biology and chemical synthesis. Undoubtedly the best way to produce high oxidation state taxanes such as Taxol® is through the synthetic biology approach. It would be an incredible achievement of total synthesis to provide a more efficient route to Taxol® in the lab.

In the case of low oxidation state taxanes the choice between approaches is not so clear. Synthetic biology is, seemingly, the most efficient way to produce the simple taxane skeleton. Nature is also undoubtedly the best at asymmetric synthesis, as of yet it seems that chemical synthesis cannot compete with the tomato plant. However the oxidations of these products within an organism *via* the introduction of additional hydroxylase enzymes has been incredibly challenging and remains a problem with a synthetic biology approach. This is undoubtedly where chemical synthesis takes the lead.

The discovery of selective C-H oxidations takes time and effort, but once developed they overcome the bottle neck in the synthetic biology approach, as Baran has shown with his oxidations of taxadiene, producing oxidised taxanes on a relatively large scale. Chemical synthesis also has the advantage of producing un-natural analogues such as our *cis*-taxadieneone, unobtainable through synthetic biology.

We must therefore conclude that developing both approaches side by side should lead us to a position where we can produce enough material in plants to develop and scale reactions in the lab capable of accessing a wide range of natural and unnatural taxanes. These analogues, as discussed, are vital to explore the true medicinal potential of the taxane family.

Experimental

General Experimental

All starting materials obtained from suppliers were used without purification unless otherwise stated. Diethyl ether and THF were obtained from a solvent purification system. Dichloromethane was distilled from calcium hydride under lab atmosphere. Toluene, triethylamine, tetramethylpiperidine, diisopropylamine and TMSCl were distilled from calcium hydride under an argon atmosphere. DMSO was distilled from calcium hydride under reduced pressure. Pyridine was distilled from potassium hydroxide under an argon atmosphere. DMF was distilled from calcium sulphate under reduced pressure. Butyl lithium was titrated before use using a Gilman double titration.[132] Petrol refers to petroleum ether fraction boiling between 40 – 60 °C. Water refers to deionised water. Brine refers to a saturated solution of sodium chloride in water. Ether refers to diethyl ether. 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 a solution of vanillin, nin-hydrin or basic potassium permanganate. Column chromatography was carried out using a stationary phase of Merck silica gel 60, 35-70 µm particles. All reactions were carried out in flame-dried glassware under argon unless otherwise stated.

NMR spectra were recorded on either a Bruker DPX 400 MHz, AV 400 MHz, AV(III) 400 MHz, AV(III) 400 HD MHz or AV(III) 500 MHz NMR spectrometer. All spectra were obtained at 298 K as a dilute solution in the specified deuterated solvent. Spectra were recorded on the δ scale in ppm and referenced to the residual solvent peak ($CHCl_3$ δ^H 7.27, $CDCl_3$ δ^C 77.10; CHD_2OD δ^H 3.31, CD_3OD δ^C 49.00; d6-DMSO δ^H 2.50, δ^C 39.52; C_6D_6 δ^H 7.15, δ^C 128.06). The multiplicity of each signal is designated by the following abbreviations: s,

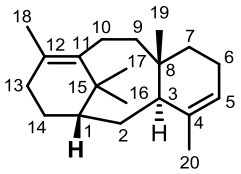
singlet; d, doublet; t, triplet; q, quartet; quin, quintet. *J* values are reported in Hertz (Hz) to one decimal place. All assignments made are with the aid of DEPT sequences and correlation techniques: COSY, HMBC, HSQC, NOSEY.

Infrared spectra were recorded on a Perkin-Elmer 1600 FT spectrometer as thin films on NaCl plates, as dilute solutions in the specified solvent or using a attenuated total reflection (ATR) adapter. Characteristic signals are quoted as wavenumber in cm^{-1}. High resolution mass spectra (HRMS) were recorded on a MicroTOF 61 spectrometer using electrospray ionisation (ESI), electron ionisation (EI) or field de-adsorption ionisation (FDI) in both positive and negative modes. Melting points were determined on a Stuart SMP3 apparatus and are uncorrected. Specific rotations were measured on a Bellingham ADP440+ polarimeter at a wavelength of 589 nm and a path length of 1 dm. Concentrations are given in g/100 mL.

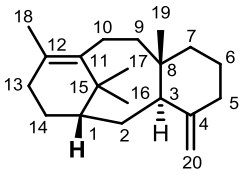
A single crystal of the appropriate compound was selected and mounted on MicroMounts (MiTeGen) using perfluoropolyether oil (Lancaster) on a GV1000, Atlas or XtaLAB Pro: Kappa single diffractometer. The crystal was kept at 90 K or 120 K during data collection. Using Olex2,[133] the structure was solved with the olex2.solve[134] structure solution program using Charge Flipping or direct methods and refined with the ShelXL[135] refinement package using Least Squares minimisation.

Dimethyl dioxirane (DMDO) was prepared using the procedure described by Jeyaraman.[136]

Isolation of taxa-4(5),11(12)-diene (**24**) and taxa-4(20),11(12)-diene (**25**)



24



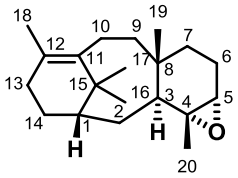
25

Tomato fruit provided by the Fray group[28] (577 g) were crushed with a pestle and mortar. The resulting pulp was placed in a Büchner funnel and washed with acetone (3 x 75 mL). The acetone washings were combined and extracted with hexane (4 x 250 mL). The acetone-washed fruit pulp was then transferred to a round bottomed flask and stirred with hexane (500 mL) for 3 days. The hexane was decanted and the combined hexane extracts from acetone wash and hexane extraction were dried ($MgSO_4$) and the solvent concentrated in *vacuo* to give an orange oil. Purification by silica gel chromatography (pentane) gave taxadiene **24** and **25** (13.0 mg) as a colourless oil. Taxadiene was isolated as an inseparable 17:1 mixture of 4(5):4(20) alkene isomers. R_f 0.60 (pentane); $[\alpha]^{23}_D$ = + 110.03 (c 0.8, $CHCl_3$) (lit: $[\alpha]^{20}_D$ = + 135 (c 0.32, $CHCl_3$); ν_{max} cm^{-1} ($CHCl_3$) 2955, 2927, 2855, 1460, 1376, 1254, 1176, 1108, 1084, 1029, 967; ^{1}H NMR ($CDCl_3$, 400 MHz) (data for the major 4(5)-isomer) 5.30 (1H, br. s, 5-H), 2.63 (1H, ddd, *J* 15.0, 10.5, 5.5, 10-Ha), 2.53 (1H, br. s, 3-H), 3.37-2.27 (1H, m, 13-Ha), 2.20-2.00 (3H, m, 6-Ha, 14-Ha, 10-Hb), 1.93-1.79 (3H, m, 6-Hb, 9-Ha, 13-Hb), 1.76-1.56 (5H, m, 1-H, 2-Ha, 7-H_2), 1.70 (3H, br. s, 14-Hb), 1.67 (3H, s, 18-H_3), 1.43 (1H, ddd, *J* 15.0, 6.5, 5.5, 9-Hb), 1.34 (3H, s, 16-H_3 or 17-H_3), 1.22-1.18 (1H, m, 2-Hb), 1.04 (3H, s, 16-H_3 or 17-H_3), 0.84 (3H, s, 19-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) (data for the major 4(5)- isomer) 138.5 (C), 137.7 (C), 129.6 (C), 121.1 (CH), 44.3 (CH), 41.4

(CH_2), 39.8 (CH), 39.0 (C), 38.5 (CH_2), 37.3 (C), 30.7 (CH_3), 29.8 (CH_2), 28.4 (CH_2), 26.3 (CH_3), 24.5 (CH_2), 24.0 (CH_3), 23.2 (CH_2), 22.7 (CH_2), 21.7 (CH_3), 21.5 (CH_3); HRMS *m/z* (EI^+) 272.2498 (M^+, $C_{20}H_{32}^+$ requires 272.2499).

Data consistent with that previously reported.[137]

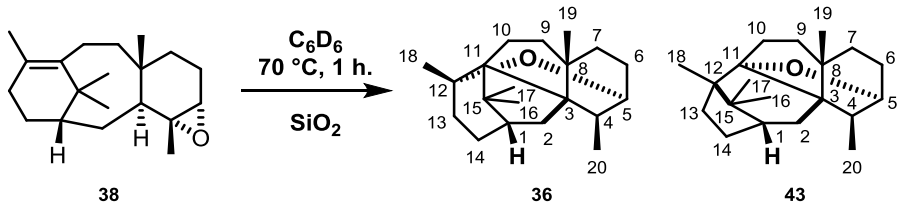
Taxadiene-4(5)-epoxide (**38**)



Taxadiene-4(5)-epoxide was synthesised before each rearrangement reaction to avoid decomposition. Data for previously reported, isolated epoxide is given below for reference purposes.[33,125]

$[\alpha]^{23}_D$ = + 99.36 (c 0.4, C_6D_6); ν_{max} cm^{-1} ($CHCl_3$) 3010, 2928, 2856, 1602, 1459, 1379, 1330, 1239, 1165, 1131, 1052, 1021, 965; ^1H NMR (500 MHz, C_6D_6) 2.69-2.62 (2H, m, 5-H, 10-Ha), 2.41 (1H, dd, *J* 6.0, 2.4, 3-H), 2.30-2.23 (1H, m, 13-Ha), 2.09-1.98 (3H, m, 10-Hb, 13-Hb, 14-Ha), 1.95-1.86 (2H, m, 6-Ha, 9-Ha), 1.77-1.68 (1H, m, 7-Ha), 1.74 (3H, s, 18-H_3), 1.68-1.45 (5H, m, 1-H, 2-H_2, 6-Hb, 14-Hb), 1.29 (3H, s, 16-H_3 or 17-H_3), 1.12 (3H, s, 20-H_3), 1.09 (3H, s, 16-H_3 or 17-H_3), 1.04-0.99 (1H, m, 9-Hb), 0.84-0.80 (1H, m, 7-Hb), 0.58 (3H, s, 19-H_3); ^{13}C NMR (125 MHz, C_6D_6) 137.2 (C), 131.2 (C), 61.3 (CH), 60.6 (C), 44.3 (CH), 41.0 (CH), 40.3 (CH_2), 39.9 (C), 37.1 (C), 33.3 (CH_2), 31.6 (CH_3), 30.4 (CH_2), 28.2 (CH_2), 25.9 (CH_3), 25.3 (CH_2), 24.5 (CH_3), 23.7 (CH_2), 23.0 (CH_2), 22.8 (CH_3), 22.0 (CH_3); HRMS *m/z* (ESI^+) 289.2518 ($M + H^+$, $C_{20}H_{33}O$ requires 289.2526), 311.2341 ($M + Na^+$, $C_{20}H_{32}ONa$ requires 311.2345).

Rearrangement of Taxadiene-4(5)-epoxide (**38**) with Silica Gel

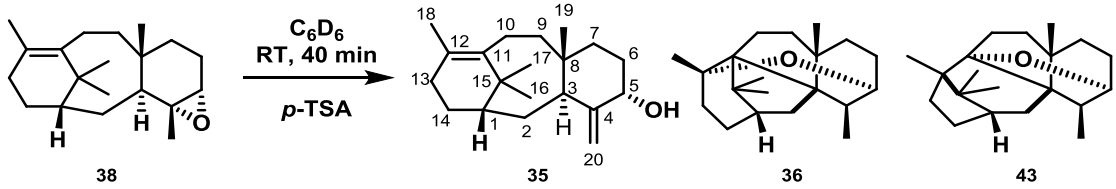


38 **36** **43**

Dimethyldioxirane (524 µL of a 42.0 mM solution in acetone, 22.0 µmol,), was added to a stirring solution of taxadiene (10.0 mg, 36.7 µmol) in *d6*-benzene (0.70 mL) at 8 °C under argon. After 10 min the reaction was allowed to warm to ambient temperature and stirred for 1 h. The reaction was then concentrated in *vacuo*. Analysis by ^{1}H NMR (C_6D_6) showed a 1:4 ratio of unreacted taxadiene:epoxide **38** (Data of epoxide consistent with that previously reported). This crude mixture was dissolved in *d6*-benzene (0.7 ml) and heated to 70 ^{o}C for 1 h. After cooling to ambient temperature, analysis by ^{1}H NMR (C_6D_6) showed no decomposition of starting epoxide **38**. Silica gel (100 mg) was added and the reaction was heated at 70 ˚C for 1 h. After cooling to ambient temperature, the reaction mixture was filtered and analysis by ^{1}H NMR (C_6D_6) showed complete conversion to **36** and **43**. Concentration in *vacuo* and purification by silica gel chromatography (pentane to 1:9, ether:pentane) afforded recovered taxadiene as a colourless oil (1.2 mg), followed by **43** (2.0 mg, 19%) as a colourless oil. R_f 0.75 (1:9, ether:pentane); $[\alpha]^{20}_{D}$ = + 31.5 (c 0.09, C_6D_6); ^{1}H NMR (500 MHz, C_6D_6) 4.02 (1H, app. t, *J* 5.2, 5-H), 2.36-2.26 (2H, m, 4-H, 13-Ha), 2.13 (1H, dd, *J* 14.8, 10.2, 10-Ha), 2.02 (1H, ddd, *J* 14.8, 12.2, 8.7, 10-Hb), 1.86-1.66 (5H, m, 2-Hb, 6-H_2, 9-Ha, 14-Ha), 1.58-1.50 (2H, m, 1-H, 7-Ha), 1.42 (1H, ddd, *J* 14.3, 12.0, 4.5, 13-Hb), 1.36-1.21 (4H, m, 2-Hb, 7-Hb, 9-Hb, 14-Hb), 1.16 (3H, s, 18-H_3), 0.95 (3H, s, 16-H_3 or 17-H_3), 0.93 (3H, s, 19-H_3), 0.88 (3H, s, 16-H_3 or 17-H_3), 0.86 (3H, d, 20-H_3); ^{13}C NMR (125 MHz, C_6D_6) 96.9 (C), 76.4 (CH), 52.5 (C), 50.3 (C), 50.0 (C), 46.1 (CH), 44.0 (CH_2), 43.2 (C), 42.4 (CH), 37.7 (CH_2), 33.3 (CH_2), 33.3 (CH_2), 28.8 (CH_2), 28.0 (CH_2), 27.1 (CH_3), 26.8 (CH_2), 26.4 (CH_3), 19.8 (CH_3), 16.4 (CH_3), 9.1 (CH_3); HRMS *m/z* (ESI^{+}) 289.2526 (M + H^{+}, $C_{20}H_{33}O$

requires 289.2526). Further elution gave **36** (2.0 mg, 19%) as a colourless oil. R_f 0.33 (1:9, ether:pentane); $[\alpha]^{21}_D$ = + 12.4 (c 0.8, $CHCl_3$); ν_{max} cm^{-1} ($CHCl_3$) 3054, 2958, 2930, 1601, 1466, 1376, 1239, 1152, 1107, 1070, 1043, 1030, 1003, 856; ^1H NMR (400 MHz, $CDCl_3$) 3.98 (1H, dd, *J* 9.0, 3.5, 5-H), 2.49 (1H, qd, *J* 7.0, 3.5, 4-H), 2.25 (1H, dd, *J* 13.0, 5.0, 2-Ha), 2.15-1.79 (8H, m, 6-H_2, 7-Ha, 9-Ha, 10-Ha, 13-H_2, 14-Ha), 1.77-1.73 (1H, m, 1-H), 1.70-1.51 (2H, m, 14-Hb, 9-Hb), 1.41-1.33 (3H, m, 2-Hb, 7-Hb, 10-Hb), 1.23 (3H, s, 18-H_3), 1.15 (3H, d, 20-H_3), 1.07 (3H, s, 19-H_3), 1.05 (3H, s, 16-H_3 or 17-H_3), 0.96 (3H, s, 16-H_3 or 17-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 80.1 (C), 69.6 (CH), 65.7 (C), 53.1 (C), 47.8 (CH_2), 45.9 (C), 45.8 (CH), 42.6 (C), 38.9 (CH_2), 37.4 (CH_2), 37.0 (CH), 36.3 (CH_2), 30.1 (CH_3), 30.1 (CH_2), 28.7 (CH_3), 28.0 (CH_3), 28.0 (CH_2), 27.3 (CH_2), 26.7 (CH_3), 15.2 (CH_3); HRMS m/z (ESI^+) 311.2335 (M + Na^+, $C_{20}H_{32}ONa$ requires 311.2345), 289.2522 (M + H^+, $C_{20}H_{33}O$ requires 289.2526). The spectroscopic data for **36** are consistent with that reported previously.[29]

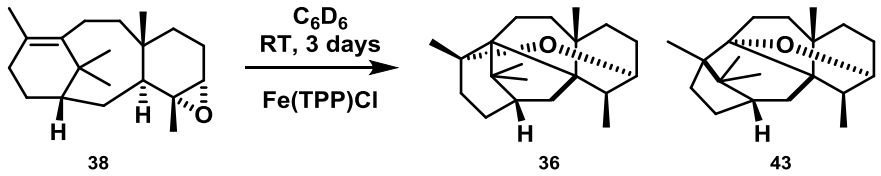
<u>Rearrangement of Taxadiene-4(5)-epoxide **38** with pTSA</u>



Dimethyldioxirane (1.36 mL of a 43.6 mM solution in acetone, 59.5 µmol) was added dropwise to a stirring solution of taxadiene (27.0 mg, 99.1 µmol) in *d6*-benzene (1.89 mL) at 8 °C under argon. The reaction was stirred for 10 min, allowed to warm to ambient temperature and stirred for 1 h. The reaction was concentrated in *vacuo*. Analysis by ^1H NMR (C_6D_6) showed a 1:4.7 ratio of unreacted taxadiene:epoxide **38**. This crude mixture was dissolved in *d6*-benzene (1.89 mL) and *p*-toluenesulphonic acid monohydrate (11.0 mg, 59.5 µmol) was added. The reaction was stirred under argon at ambient temperature

for 40 min before dilution with ether (5 mL) followed by water (5 mL). The layers were separated and the aqueous layer extracted with ether (3 x 5 mL). The combined organic layers were washed with brine (2 x 5 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Analysis by ^1H NMR (C_6D_6) showed complete conversion of epoxide **38**, and appearance of characteristic signals corresponding to **36, 43** and taxa-4(20),11(12)-dien-5α-ol **35**. Purification by silica gel chromatography (pentane to 1:9, ether:pentane) afforded recovered taxadiene (13.0 mg) as a colourless oil, **43** (2.0 mg, 7%) as a colourless oil and **36** (2.0 mg, 7%). as a colourless oil. Further elution then gave taxa-4(20),11(12)-dien-5α-ol **35** (5.0 mg, 17%). R_f 0.18 (1:9, ether:pentane); $[\alpha]^{21}_D$ = + 108.03 (c 0.5, $CHCl_3$); ν_{max} cm^{-1} ($CHCl_3$) 3603, 3079, 3055, 3008, 2982, 2930, 1643, 1601, 1461, 1378, 1296, 1240, 1125, 1107, 1054, 1018, 999, 986, 965, 941, 924, 902; ^1H NMR (400 MHz, $CDCl_3$) 4.94 (1H, dd, *J* 1.5, 1.0, 20-Ha), 4.65 (1H, dd, *J* 1.5, 1.0, 20-Hb), 4.26 (1H, t, *J* 3.0, 5-H), 3.32 (1H, ddt, *J* 5.5, 2.0, 1.5, 3-H), 2.85 (1H, td, *J* 13.5, 5.0, 10-Ha), 2.40-2.25 (2H, m, 6-Ha, 13-Ha), 2.25-1.97 (3H, m, 9-Ha, 14-Ha, 10-Hb), 1.94-1.86 (1H, m, 13-Hb) 1.84 (3H, s, 18-H_3), 1.79-1.74 (3H, m, 1-H, 7-Ha, OH), 1.65 (1H, ddd, *J* 15.5, 5.5, 2.0, 2-Ha), 1.56 (1H, ddd, *J* 15.5, 5.0, 2.0, 2-Hb), 1.35 (3H, s, 16-H_3 or 17-H_3), 1.31-1.20 (3H, m, 7-Hb, 9-Hb, 14-Hb), 1.05 (3H, s, 16-H_3 or 17-H_3), 1.02-0.97 (1H, m, 6-Hb), 0.62 (3H, s, 19-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 155.9 (C), 136.8 (C), 130.6 (C), 108.7 (CH_2), 74.6 (CH), 43.5 (CH), 40.05 (C), 39.96 (CH_2), 39.2 (C), 35.4 (CH), 32.7 (CH_2), 30.8 (CH_3), 30.17 (CH_2), 30.12 (CH_2), 28.0 (CH_2), 25.5 (CH_3), 24.7 (CH_2), 22.9 (CH_2), 22.1 (CH_3), 21.3 (CH_3); HRMS *m/z* (ESI^+) 311.2336 (M + Na^+, $C_{20}H_{32}ONa$ requires 311.2345), 289.2521 (M + H^+, $C_{20}H_{33}O$ requires 289.2526). The spectroscopic data for **36** and **43** matched that reported above. Data for 5α-hydroxytaxadiene **35** consistent with that previously reported.[125]

Rearrangement of Taxadiene-4(5)-epoxide **38** with Fe(TPP)Cl



38 36 43

Dimethyldioxirane (361 µL of a 51.0 mM solution in acetone, 18.4 µmol) was added dropwise to a stirring solution of taxadiene (10.0 mg, 36.7 µmol) in *d6*-benzene (0.70 mL) at 8 ˚C under argon. The reaction was stirred for 10 min, warmed to ambient temperature and stirred for 2 h. The reaction was then concentrated in *vacuo*. Analysis by ^{1}H NMR (C_6D_6) showed a 1:1.4 ratio of unreacted taxadiene:epoxide **38**. This crude mixture was dissolved in *d6*-benzene (0.70 mL) and tetraphenylporphyrin iron (III) chloride (26.0 mg, 36.7 µmol) added. The reaction was stirred under argon at ambient temperature for 3 days before dilution with ether (10 mL) followed by water (10 mL). The layers were separated and the aqueous layer extracted with ether (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Analysis by ^{1}H NMR (C_6D_6) showed complete conversion of epoxide **38**, and appearance of characteristic signals corresponding to **36** and **43** (1:1 by ^{1}H NMR shown below).

^{1}H NMRs (400 MHz, C_6D_6):

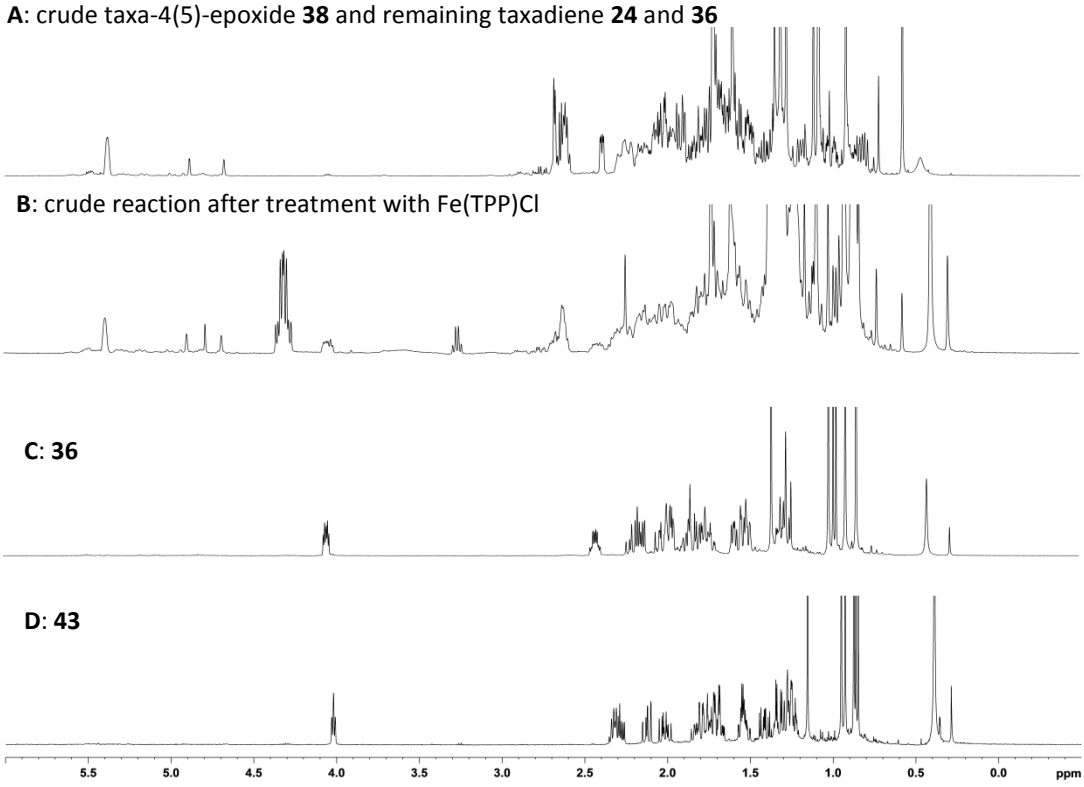
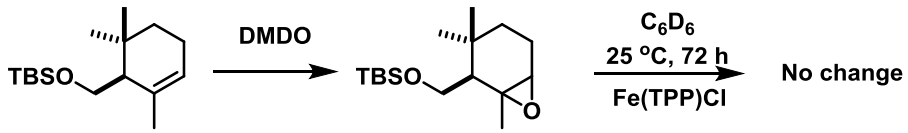


Figure 21: ^{1}HNMR experiment for rearrangement with Fe(TPP)Cl.

Oxidation of Taxadiene **24** with Fe(TPP)Cl and H_2O_2

Tetraphenylporphyrin Iron (III) chloride **48** (2.6 mg, 3.67 µmol) was added to a stirring solution of taxadiene (17:1 isomeric mixture) (10.0 mg, 36.7 µmol) in anhydrous dichloromethane (0.5 mL). Aqueous hydrogen peroxide (30% w/w, 3.7 µL, 36.7 µmol) was added and the reaction stirred for 3 days at ambient temperature under argon. Water (3 mL) was added to the reaction and the layers separated. The organic layer was dried ($MgSO_4$) and concentrated in *vacuo*. Analysis by ^{1}H NMR showed a complex mixture of products. Purification by silica gel chromatography (1:9, ether:pentane) afforded **43** as a colourless oil (0.3 mg, 3%). Further elution gave **36** (0.5 mg, 5%). The spectroscopic data for **36** and **43** matched that reported above.

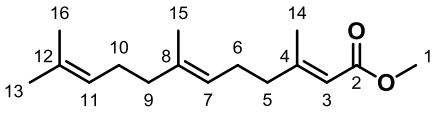
Control experiment for the Fe(TPP)Cl rearrangement of epoxide **49**



2:1; α:β epoxides

Dimethyldioxirane (363 μL, 18.6 μmol) was added dropwise to a stirring solution of alkene[25] (10.0 mg, 37.2 μmol) in dichloromethane (0.70 mL) at 0 °C under argon. The reaction was stirred for 10 min, warmed to ambient temperature and stirred for 1 h. Concentration in *vacuo* and analysis by ^{1}H NMR showed a ratio of 1:0.7 (starting material: epoxide). The crude reaction mixture was dissolved in dichloromethane (0.70 mL), cooled to 0 °C, and a further portion of dimethyldioxirane (580 μL of a 51.3 mM solution in acetone, 29.8 μmol) was added dropwise. The reaction was warmed to ambient temperature, stirred for 20 min, and then concentrated *in vacuo* to give crude epoxide **49** (9.0 mg) as a 2:1 mixture of diastereoisomers. Epoxide **49** (9.0 mg) was dissolved in anhydrous dichloromethane (0.70 mL) and tetraphenylporphyrin iron (III) chloride (26.0 mg, 37.2 μmol) was added. The reaction was stirred under argon at ambient temperature for 3 days. The reaction was diluted with ether (5 mL), then water (5 mL), and the separated aqueous layer was extracted with ether (3 x 5 mL). The combined organic layers were then washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Analysis by ^{1}H NMR showed no change to the epoxide **49**.

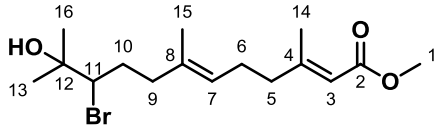
Methyl Farnesate (**189**)



Activated manganese dioxide (78.0 g, 0.90 mol) was added to a stirring solution of farnesol (10.0 g, 45.0 mmol) in anhydrous dichloromethane (113 mL). The reaction was stirred at ambient temperature for 18 h. The reaction was then filtered through a plug of celite and the solvent concentrated in *vacuo* to give crude farnesal **187** (9.14 g) as a colourless oil. Purity determined by TLC, R_f 0.25 (1:4, ether:petrol). Sodium chlorite (22.4 g, 247 mmol) was added portion-wise to a stirring solution of crude farnesal (9.14 g, 41.2 mmol), sodium dihydrogen orthophosphate dihydrate (25.7 g, 165 mmol) and 2-methyl-2-butene (28.0 mL, 247 mmol) in ^{t}BuOH : water (1:1 v/v, 409 mL). A stopper was placed in the flask and the reaction was stirred for 18 h at ambient temperature. The reaction was then concentrated in *vacuo* and brine (100 mL) added. The solution was extracted with ethyl acetate (4 x 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in *vacuo* to give crude farnesoic acid **188** (9.76 g) as a colourless oil. Purity determined by TLC, R_f 0.35 (1:4, EtOAc : petrol). Methyl iodide (3.90 mL, 62.0 mmol) was added dropwise to a stirring solution of crude farnesoic acid (9.76 g, 41.3 mmol) and potassium carbonate (8.55 g, 61.9 mmol) in anhydrous *N,N*-dimethylformamide (53.0 mL). The reaction was stirred at ambient temperature for 18 h. Water (100 mL) and brine (100 mL) were added to the reaction and the aqueous layer extracted with ether (4 x 100 mL). The combined organic layers were washed with brine (3 x 30 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:4, ether : petrol) gave the title compound **189** (7.52 g, 67% over 3 steps) as a colourless oil. R_f 0.65 (1:4, ether :

petrol); ν_{max} (thin film)/cm^{-1} 2926, 1721, 1650; ^{1}H NMR (400 MHz, $CDCl_3$) 5.70 (1H, s, 3-H), 5.15-5.08 (2H, m, 7-H, 11-H), 3.71 (3H, s, 1-H_3), 2.21-2.18 (7H, m, 5-H_2, 10-H_2, 14-H_3), 2.14-1.98 (4H, m, 9-H_2, 6-H_2), 1.73-1.69 (3H, m, 13-H_3), 1.63 (6H, s, 16-H_3, 15-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 167.3 (C), 160.2 (C), 136.2 (C), 131.4 (C), 124.2 (CH), 122.9 (CH), 115.2 (CH), 50.8 (CH_3), 41.2 (CH_2), 39.7 (CH_2), 26.7 (CH_2), 25.8 (CH_2), 25.3 (CH_3), 18.9 (CH_3), 17.7 (CH_3), 16.0 (CH_3); HRMS *m/z* (EI$^+$) 251.1650 (M + H$^+$, $C_{16}H_{27}O_2$ requires 251.1933).

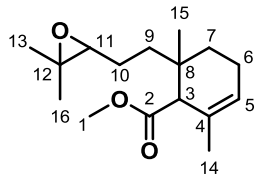
(±)-Methyl-11-bromo-12-hydroxy-4,8,12-trimethyldodeca-3,7-dienoate (**142**)



N-bromosuccinimide (5.87 g, 33.0 mmol) was added to a stirring solution of methyl farnesate **189** (7.52 g, 30.0 mmol) in THF : water (10:1, v/v, 107 mL) at 0 °C. The reaction was covered with aluminium foil and stirred in the dark at ambient temperature for 5 h. The reaction was concentrated in *vacuo* and diluted with water (50 mL). The aqueous layer was then extracted with ether (4 x 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in *vacuo* to give the crude product. This was loaded onto a short silica gel column eluting with a rapid flow of ether : petrol (1:1) to give the title compound **142** (5.72 g, 55%) as an orange oil. R_f 0.2 (1:2, ether : petrol); ν_{max} (thin film)/cm^{-1} 3475, 2978, 2949, 1709, 1649; ^{1}H NMR (400 MHz, $CDCl_3$) 5.67 (1H, br. s, 3-H), 5.16 (1H, br. s, 7-H), 3.93 (1H, dd, *J* 11.5, 2.0, 11-H), 3.68 (3H, s, 1-H_3), 2.37-2.07 (9H, m, 6-H_2, 9-H_2, 10-Ha, 14-H_3, OH), 2.07-1.70 (3H, m, 5-H_2, 10-Hb), 1.69-1.50 (3H, m, 15-H_3), 1.36-1.27 (6H, m, 13-H_3, 16-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 167.3 (C), 159.8 (C), 134.3 (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), 25.8 (CH_2), 25.9 (CH_3), 18.9 (CH_3), 15.8 (CH_3); HRMS *m/z* (ESI$^+$) 369.1027 (M + Na$^+$,

$C_{16}H_{27}{}^{79}BrO_3Na$ requires 369.1036) 371.1019 ($M + Na^+$, $C_{16}H_{27}{}^{81}BrO_3Na$ requires 371.1015).

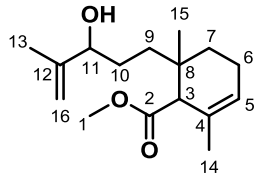
Methyl-8-(11,12-epoxy-12-methylpentyl)-4,8-dimethylcyclohex-4-eneoate (**190**)



Phosphoric acid (15 M, 197 mL) was added to bromohydrin **142** (5.7 g, 16 mmol). The reaction was stirred for 5 h at ambient temperature before quenching with portionwise addition of ice water (200 mL) over 30 min. The resulting aqueous solution was extracted with ether (3 x 200 mL). The combined organic layers were then dried ($MgSO_4$) and concentrated in *vacuo* to give the crude cyclised bromohydrin **143** as a yellow oil (6.19 g). Rf 0.33 (1:2, ether: petrol). Potassium carbonate (5.67 g, 41.0 mmol) was added to a solution of crude bromohydrin **143** (6.19 g) in methanol (40 mL). The reaction was stirred at ambient temperature for 18 h. Water (100 mL) was added to the reaction and the aqueous layer extracted with ether (3 x 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:4, ether: petrol) gave the title compound **190** (2:2:1:1 mixture of diastereoisomers) (2.33 g, 53% over 2 steps) as a colourless oil. R_f 0.66 (1:1, ether : petrol); ν_{max} ($CHCl_3$)/cm^{-1} 2965, 2929, 1731; ^1H NMR (400 MHz, $CDCl_3$) (2:2:1:1 mixture of diastereoisomers) 5.56 (1H, br. s, 5-H), 3.65 (3H, s, 1-H_3), 2.64-2.61 (2H, m, 3-H, 11-H), 2.17-1.97 (2H, m, 6-H_2), 1.90-1.75 (1H, m, 7-Ha), 1.63 (3H, s, 14-H_3), 1.60-1.34 (4H, m, 9-H_2, 10-H_2), 1.34-1.30 (1H, m, 7-Hb), 1.28 (3H, s, 13-H_3 or 16-H_3), 1.24 (3H, s, 13-H_3 or 16-H_3), 0.87 (3H, s, 15-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 174.1 (C), 129.3 (C), 129.2 (C), 124.0 (CH), 123.8 (CH), 64.6 (CH), 64.5 (CH), 58.4 (C), 55.9 (CH), 55.7 (CH), 51.5 (CH_3), 36.8 (CH_2), 34.8 (CH_2), 34.6 (CH_2), 34.2 (C), 28.5 (CH_2), 24.8

(CH_3), 24.0 (CH_3), 23.4 (CH_3), 23.3 (CH_2), 22.8 (CH_3), 22.4 (CH_2), 18.6 (CH_3); HRMS *m/z* (ESI^+) 267.1956 ($M + H^+$, $C_{16}H_{27}O_3$ requires 267.1955).

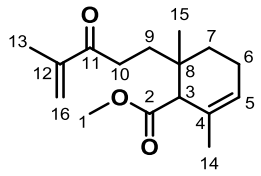
Methyl-8-(11-hydroxy-12-methylpent-12-enyl)-4,8-dimethylcyclohex-4-eneoate (**191**)



^{n}BuLi (1.95 M in hexanes, 11.5 mL) was added dropwise to a stirring solution of tetramethylpiperidine (3.80 mL, 23.0 mmol) in anhydrous toluene (39.0 mL) at 0 °C. The solution was stirred at 0 °C for 40 min before diethylaluminium chloride (1 M in hexanes, 22.5 mL) was added dropwise. After a further 40 min epoxide **190** (2.00 g, 7.50 mmol) was added as a solution in toluene (20 mL). The reaction was stirred at 0 °C under argon for 1.5 h. Saturated aqueous sodium bicarbonate (20 mL) was added portionwise, followed by further dilution with water (10 mL). The aqueous layer was extracted with ether (2 x 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:1, ether:petrol) gave the title compound **191** (2:2:1:1 mixture of diastereoisomers) (1.69 g, 88%) as a colourless oil. R_f 0.35 (1:1, ether : petrol); ν_{max} ($CHCl_3$)/cm^{-1} 3607, 2929, 1726, 1676, 1602, 1434, 1239; ^{1}H NMR (400 MHz, $CDCl_3$) (2:2:1:1 mixture of diastereoisomers) 5.50 (1H, br. s, 5-H), 4.83 (1H, app. s, 16-Ha), 4.74 (1H, app. s, 16-Hb), 3.91-3.80 (1H, m, 11-H), 3.59 (3H, s, 1-H_3), 2.60-2.55 (1H, m, 3-H), 2.00-1.85 (2H, m, 6-H_2), 1.85-1.68 (1H, m, 10-Ha), 1.63 (3H, s, 13-H_3), 1.55 (3H, s, 14-H_3), 1.51-1.40 (2H, m, OH, 10-Hb), 1.40-1.07 (4H, m, 7-H2, 9-H_2), 0.81 (3H, s, 15-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 174.3 (C), 147.4 (C), 147.2 (C), 129.3 (C), 129.2 (C), 124.0 (CH), 123.8 (CH), 111.4 (CH_2), 111.1 (CH_2), 110.8 (CH_2), 76.8 (CH), 76.5 (CH), 76.3 (CH), 55.8 (CH), 55.7 (CH), 51.4 (CH_3), 36.4 (CH_2), 36.2 (CH_2), 34.4 (CH_2), 34.0

(CH_2), 28.8 (CH_2), 28.6 (CH_2), 24.1 (CH_3), 22.9 (CH_3), 22.7 (CH_3), 22.4 (CH_2), 22.3 (CH_2), 17.3 (CH_3); HRMS *m/z* (ESI^+) 289.1755 ($M + Na^+$, $C_{16}H_{26}O_3Na$ requires 289.1774).

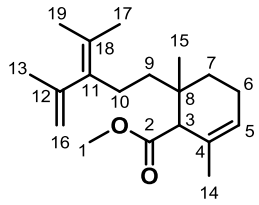
Methyl-8-(12-methyl-11-oxopent-12-enyl)-4,8-dimethylcyclohex-4-eneoate (**140**)



Dess-Martin periodinane (9.33 g, 22.0 mmol) was added to a stirring solution of allylic alcohol **191** (2.90 g, 11.0 mmol) and anhydrous pyridine (1.78 mL, 22.0 mmol) in anhydrous dichloromethane (106 mL). The reaction was stirred at ambient temperature for 30 min. Saturated aqueous sodium thiosulphate (30 mL) was added and the aqueous layer extracted with ether (4 x 30 mL). The combined organic layers were washed with saturated aqueous sodium thiosulphate (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:4, ether:petrol) gave the title compound **140** (2:1 mixture of *cis* : *trans* diastereoisomers) (2.04 g, 70%) as a colourless oil. R_f 0.65 (1:1, ether : petrol); ν_{max} ($CHCl_3$)/cm^{-1} 2954, 1729, 1667, 1435, 1382, 1239; ^1H NMR (400 MHz, $CDCl_3$) (2:1 mixture of *trans*: *cis* diastereoisomers, * data for *cis* where distinguishable from the *trans*-isomer) 5.98 (1H, app. s, 16-Ha*), 5.96 (1H, app. s, 16-Ha), 5.77 (1H, app. s, 16-Hb), 5.59 (1H, s, 5-H), 3.69 (3H, s, 1-H_3), 3.66 (3H, s, 1-H_3*), 2.80-2.63 (3H, m, 3-H and 10-H_2), 2.18-1.99 (2H, m, 6-H_2), 1.88 (3H, s, 13-H_3), 1.87-1.80 (1H, m, 7-Ha), 1.70-1.65 (2H, m, 9-H_2), 1.64 (3H, s, 14-H_3), 1.33-1.22 (1H, m, 7-Hb), 1.40-1.07 (4H, m, 6-H_2, 12-H_2), 0.91 (3H, s, 15-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 202.2 (C), 202.1 (C), 174.1 (C), 144.5 (C), 129.2 (C), 124.4 (CH_2), 124.4 (CH_2), 123.8 (CH), 55.8 (CH), 55.6 (CH), 51.6 (CH_3), 51.5 (CH_3), 35.1 (CH_2), 34.5 (C), 34.0 (C), 32.9 (CH_2), 32.7 (CH_2), 31.7 (CH_2),

28.8 (CH_2), 28.6 (CH_2), 23.9 (CH_3), 23.0 (CH_3), 22.6 (CH_3), 22.4 (CH_2), 17.7 (CH_3); HRMS *m/z* (ESI^+) 265.1782 ($M + H^+$, $C_{16}H_{25}O_3$ requires 265.1798).

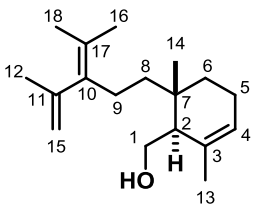
Methyl-8-(12-methyl-11-(prop-1-enyl)pent-12-enyl)-4,8-dimethylcyclohex-4-eneoate (**147**)

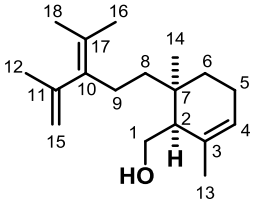


Indium powder (1.73 g, 15.1 mmol) was added to a stirring solution of enone **140** (2.00 g, 7.54 mmol) and ethyl α-bromoisobutyrate (2.20 mL, 15.0 mmol) in anhydrous N,N-dimethylformamide (10.8 mL) at ambient temperature. The reaction was heated at 80 °C for 30 min, before being allowed to cool to ambient temperature and stirred for 3 h. Hydrochloric acid (1 M aq., 5 mL) was added and the solution extracted with ether (2 x 100 mL). The organic layers were washed with brine (20 mL), ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:9 rising to 1:4, ether:petrol) gave first recovered starting material. R_f 0.32 (1:4, ether:petrol) then crude fractions containing β-lactone. R_f 0.20 (1:4, ether:petrol). These fractions were combined, concentrated in *vacuo* and the remaining oil dissolved in toluene (40 mL). Silica gel (4.40 g) was added and the reaction heated at reflux for 1 h. The reaction was then concentrated in *vacuo* and loaded directly onto a silica gel column. Purification by silica gel chromatography (1:9 rising to 1:4, ether:petrol) gave the title compound **147** (2:1 mixture of *cis* : *trans* diastereoisomers)(1.36 g, 62% over 2 steps) as a colourless oil. R_f 0.33 (1:4, ether : petrol); ν_{max} ($CHCl_3$)/cm^{-1} 2954, 1732, 1667, 1602, 1240; ^1H NMR (400 MHz, $CDCl_3$) (2:1 mixture of *trans*: *cis* diastereoisomers, * data for *cis* where distinguishable from the *trans*-isomer)

5.55 (1H, br. s, 5-H), 4.87 (1H, br. s, 16-Ha), 4.51-4.47 (1H, m, 16-Hb), 3.65 (3H, s, 1-H_3), 3.62 (1H, s, 1-H_3*), 2.68 (1H, s, 3-H), 2.61 (1H, s, 3-H*), 2.10-1.98 (4H, m, 6-H_2, 10-H_2), 1.89-1.75 (1H, m, 9-Ha), 1.74 (3H, s, 13-H_3), 1.63 (6H, br. s, 17-H_3, 19-H_3), 1.60 (3H, s, 14-H_3), 1.38-1.21 (2H, m, 7-Ha, 9-Hb), 1.21-1.10 (1H, m, 7-Hb), 0.90-0.87 (3H, m, 15-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 174.3 (C), 174.2 (C), 146.5 (C), 136.7 (C), 136.5 (C), 129.3 (C), 125.3 (C), 123.9 (CH), 112.9 (CH_2), 55.9 (CH), 55.6 (CH), 51.3 (CH_3), 39.1 (CH_2), 36.8 (CH_2), 34.0 (C), 34.3 (C), 28.7 (CH_2), 25.2 (CH_2), 24.8 (CH_2), 23.9 (CH), 23.0 (CH_3), 22.9 (CH_3), 22.8 (CH_3), 22.6 (CH_3), 22.5 (CH_2), 21.7 (CH_3), 19.3 (CH_3); HRMS *m/z* (ESI^+) 313.2121 (M + Na^+, $C_{19}H_{30}O_2Na$ requires 313.2138).

(±)-*trans*-2-(hydroxymethyl)-7-(11-methyl-10-(prop-1-enyl)pent-11-enyl)-3,7-dimethylcyclohex-3-ene (**148**) and (±)-*cis*-2-(hydroxymethyl)-7-(11-methyl-10-(prop-1-enyl)pent-11-enyl)-3,7-dimethylcyclohex-3-ene (**192**)

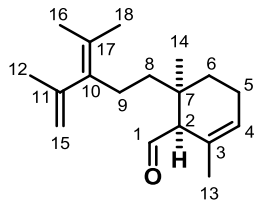




DIBAL-H (1.5 M in toluene, 10.2 mL, 15.4 mmol) was added dropwise to a stirring solution of ester **147** (2.23 g, 7.68 mmol) in anhydrous dichloromethane (38 mL) at 0 °C. The reaction was stirred for 2.5 h at 0 °C. Methanol (10 mL) was added dropwise followed by aqueous hydrochloric acid (1 M, 20 mL). The reaction was allowed to warm to ambient temperature and extracted with ether (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:9 rising to 1:4, ether:petrol) gave firstly *cis*-diastereoisomer **192** (407 mg, 20%) as a colourless oil. R_f 0.62 (1:1, ether:petrol); ν_{max} ($CHCl_3$)/cm^{-1} 3625,

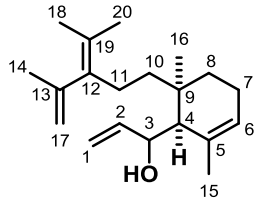
3560, 2916, 1630; ^{1}H NMR (400 MHz, $CDCl_3$) 5.64 (1H, br. s, 4-H), 4.97-4.94 (1H, m, 15-Ha), 4.61-4.59 (1H, m, 15-Hb), 3.80-3.70 (2H, m, 1-H_2), 2.18 (1H, app. td, *J* 13.0, 4.5, 9-Ha), 2.10-1.89 (3H, m, 5-H_2, 9-Hb), 1.80 (s, 3H, 13-H_3), 1.78-1.76 (3H, m, 12-H_3), 1.73 (1H, br. s, 2-H), 1.68 (3H, s, 16-H_3 or 18-H_3), 1.67 (3H, s, 16-H_3 or 18-H_3), 1.65-1.58 (1H, m, 6-Ha), 1.44-1.35 (1H, app. td, J 13.0, 4.5 Hz, 8-Ha), 1.38-1.20 (2H, m, 6-Hb, 8-Hb), 0.89 (3H, s, 14-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 146.7 (C), 137.0 (C), 131.8 (C), 124.7 (CH), 124.5 (C), 113.1 (CH_2), 60.8 (CH_2), 50.6 (CH), 38.8 (CH_2), 34.3 (C), 30.7 (CH_2), 24.9 (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 *m/z* (ESI^+) 285.2183 (M + Na^+, $C_{18}H_{30}ONa$ requires 285.2189). Further elution gave *trans*-diatereoisomer **148** (1.10 g, 55%) as a colourless oil. R_f 0.48 (1:1, ether : petrol); ν_{max} ($CHCl_3$)/cm^{-1} 3623, 3075, 3011, 2916, 1631; ^{1}H NMR (400 MHz, $CDCl_3$) 5.60 (1H, br. s, 4-H), 4.92-4.89 (1H, m, 15-Ha), 4.55-4.53 (1H, m, 15-Hb), 3.76 (2H, br. s, 1-H_2), 2.06-1.96 (4H, m, 5-H2, 9-H_2), 1.85-1.73 (7H, m, 13-H_3, 12-H_3, 2-H), 1.69-1.61 (7H, m, 6-Ha, 16-H_3, 18-H_3), 1.39-1.20 (4H, m, 6-Hb, 8-H_2, OH), 1.03 (3H, s, 14-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 146.7 (C), 137.0 (C), 131.7 (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), 22.9 (CH_3), 22.8 (CH_3), 22.7 (CH_2), 21.8 (CH_3), 19.2 (CH_3); HRMS *m/z* (ESI^+) 285.2164 (M + Na^+, $C_{18}H_{30}ONa$ requires 285.2189).

(±)-*cis*-7-(11-methyl-7-(prop-1-enyl)pent-11-enyl)-3,7-dimethylcyclohex-3-en-2-al (**194**)



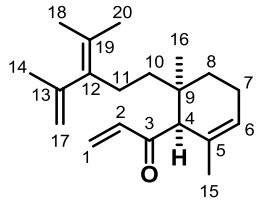
Anhydrous dimethyl sulfoxide (551 µL, 7.75 mmol) was added dropwise to a solution of oxalyl chloride (393 µL, 4.65 mmol) in anhydrous dichloromethane (13.0 mL) at –78 °C. After 30 min *cis*-alcohol **193** (407 mg, 1.55 mmol) was added dropwise as a solution in anhydrous dichloromethane (4.50 mL). The reaction was stirred for 1.5 h. at –78 °C. Triethylamine (1.63 mL, 11.6 mmol) was added dropwise. 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 5 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:4, ether:petrol) gave the title compound **194** (383 mg, 95%) as a colourless oil. R_f 0.63 (1:4, ether : petrol); ν_{max} ($CHCl_3$)/cm^{-1} 2930, 1713, 1602, 1458, 1380, 1241, 909; ^{1}H NMR (400 MHz, $CDCl_3$) 9.44 (1H, d, *J* 5.5, 1-H), 5.73 (1H, br. s, 4-H), 4.95-4.90 (1H, m, 15-Ha), 4.51 (1H, d, *J* 2.0, 15-Hb), 2.43 (1H, d, *J* 5.5, 2-H), 2.18-2.12 (2H, m, 5-H_2), 2.12-2.06 (2H, m, 9-H_2), 1.73 (3H, s, 12-H_3), 1.72-1.65 (1H, m, 6-Ha), 1.64 (3H, s, 16-H_3 or 18-H_3), 1.63 (3H, s, 16-H_3 or 18-H_3), 1.58 (3H, d, *J* 1.5, 13-H_3), 1.43 (1H, app. dd, *J* 13.5, 5.5, 6-Hb), 1.38-1.18 (2H, m, 8-H_2), 0.89 (3H, s, 14-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 201.4 (CH), 146.8 (C), 136.8 (C), 126.6 (C), 125.9 (CH), 125.0 (C), 112.9 (CH_2), 62.7 (CH), 39.4 (CH_2), 34.3 (C), 30.2 (CH_2), 24.2 (CH_2), 22.9 (CH_2), 22.7 (CH_3), 22.5 (CH_3), 22.4 (CH_3), 21.7 (CH_3), 19.5 (CH_3); HRMS *m/z* (ESI^+) 261.2187 (M + H^+, $C_{18}H_{29}O$ requires 261.2213).

(±)-*cis*-4-(3-hydroxyprop-1-enyl)-9-(13-methyl-12-(prop-1-enyl)pent-13-enyl)-5,9-dimethylcyclohex-5-ene (**195**)



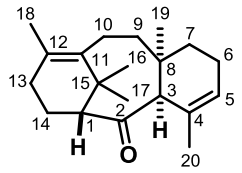
Vinyl magnesium bromide (0.7 M in THF, 4.00 mL, 2.80 mmol) was added dropwise to a stirring solution of aldehyde **194** (365 mg, 1.40 mmol) in anhydrous THF (14.0 mL) at -78 °C. The reaction was stirred for 2 h at -78 °C, after which another batch of vinyl magnesium bromide (0.7 M in THF, 4.00 mL, 2.80 mmol) 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 10 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:20, ether:petrol) gave the title compound **195** (310 mg, 77%) as a colourless oil. R_f 0.70 (1:20, ether:petrol); ν_{max} ($CHCl_3$)/cm^{-1} 3625, 3561, 2961, 1630, 1447, 1377, 1193; ^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), 5.28 (1H, app. dt, *J* 17.0, 2.0, 1-Ha), 5.05 (1H, app. dt, *J* 10.5, 2.0, 1-Hb), 4.92 (1H, dq, *J* 3.0, 1.5, 17-Ha), 4.59-4.54 (1H, m, 17-Hb), 4.39-4.36 (1H, m, 3-H) 2.15 (1H, app. td, *J* 13.0, 4.0 Hz, 11-Ha), 2.09-2.01 (2H, m, 7-H_2), 2.00-1.90 (1H, m, 11-Hb), 1.84-1.74 (4H, m, 8-Ha, 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), 1.59 (1H, br. s, OH), 1.51 (1H, app. td, *J* 13.0, 5.0, 10-Ha), 1.27 (1H, app. td, *J* 13.0, 4.0, 10-Hb), 1.20-1.13 (1H, m, 8-Hb), 0.87 (3H, s, 16-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 146.5 (C), 143.9 (CH), 136.7 (C), 130.8 (C), 126.8 (CH), 124.7 (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), 25.9 (CH_3), 24.8 (CH_2), 23.3 (CH_2), 22.8 (CH_3), 22.6 (CH_3), 21.7 (CH_3), 19.5 (CH_3); HRMS *m/z* (ESI^+) 311.2327 ($M + Na^+$, $C_{20}H_{32}ONa$ requires 311.2345)

(±)-*cis*-4-(3-oxoprop-1-enyl)-9-(13-methyl-12-(prop-1-enyl)pent-13-enyl)-5,9-dimethyl-cyclohex-5-ene (**196**)



Anhydrous dimethyl sulfoxide (273 µL, 3.84 mmol) was added dropwise to a solution of oxalyl chloride (162 µL, 1.92 mmol) in anhydrous dichloromethane (11.0 mL) at –78 °C. After 1 h at -78 °C, *cis*-alcohol **195** (277 mg, 0.96 mmol) was added dropwise as a solution in anhydrous dichloromethane (3.00 mL). The reaction was stirred for 2 h. at –78 °C. Triethylamine (1.07 mL, 7.48 mmol) was added dropwise. The reaction was allowed to warm to ambient temperature and stirred for a further 1 h. Saturated aqueous sodium bicarbonate (10 mL) was added and the layers separated. The aqueous layer was extracted with dichloromethane (3 x 5 mL). The organic layer was washed with brine (10 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:20, ether: petrol) gave the title compound **196** (122 mg, 44%) as a colourless oil. R_f 0.47 (1:20, ether : petrol); ν_{max} ($CHCl_3$)/cm^{-1} 2913, 1684, 1668, 1630, 1454, 1376; ^{1}H NMR (400 MHz, $CDCl_3$) 6.57 (1H, dd, *J* 17.0, 10.5, 2-H), 6.23 (1H, dd, *J* 17.0, 1.5, 1-Ha), 5.67 (1H, dd, *J* 10.5, 1.5, 1-Hb), 5.62 (1H, br. s, 6-H), 4.85 (1H, br. s, 17-Ha), 4.45 (1H, d, *J* 2.0, 17-Hb), 2.97 (1H, s, 4-H), 2.23-1.98 (4H, m, 7-H_2, 11-H_2), 1.80-1.72 (1H, m, 8-Ha), 1.70 (3H, s, 14-H_3), 1.61 (3H, s, 18-H_3 or 20-H_3), 1.60 (3H, s, 18-H_3 or 20-H_3), 1.58 (3H, br. s, 15-H_3), 1.37-1.22 (2H, m, 8-Hb, 10-Ha), 1.08 (1H, ddd, *J* 13.5, 10.5, 6.5, 10-Hb), 0.94 (3H, s, 16-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 202.7 (C), 146.5 (C), 136.7 (CH), 136.5 (C), 130.1 (C), 127.5 (CH_2), 124.7 (C), 124.0 (CH), 113.0 (CH_2), 61.2 (CH), 39.1 (CH_2), 35.6 (C), 28.5 (CH_2), 24.9 (CH_2), 23.6 (CH_3), 23.5 (CH_3), 22.8 (CH_3), 22.5 (CH_2), 21.7 (CH_3), 19.4 (CH_3); HRMS *m/z* (ESI^+) 309.2175 ($M + Na^+$, $C_{20}H_{30}ONa$ requires 309.2189)

(±)-*cis*-8-epi-2-oxo-taxa-(4,5)-(11,12)-diene (**197**)

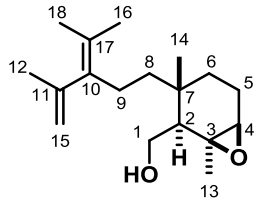


A solution of enone **196** (122 mg, 0.42 mmol) in anhydrous, degassed dichloromethane (30.5 mL) was added by syringe pump over 5 h to a solution of boron trifluoride etherate (189 μL, 1.53 mmol) in anhydrous, degassed dichloromethane (22.0 mL) at 0 °C. After addition, the reaction was stirred for a further 1 h at 0 °C. Saturated aqueous sodium bicarbonate (5 mL) was added and the layers separated. The organic layer was washed with brine (3 x 20 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:40, ether:petrol) gave the title compound **197** (72.0 mg, 60%) as a colourless solid. R_f 0.34 (1:40 ether : petrol); mp 53-55 °C ($CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3006, 2920, 1678, 1460, 1392, 1379, 1335, 1306; ^{1}H NMR (400 MHz, $CDCl_3$) 5.52 (1H, br. s, 5-H), 2.94 (1H, s, 3-H), 2.81 (1H, app. td, *J* 13.5, 5.5, 10-Ha), 2.54-2.36 (1H, m, 13-Ha, 1-H), 2.17-1.95 (6H, m, 10-Hb, 13-Hb, 14-H_2, 6-H2), 1.84 (3H, s, 18-H_3), 1.81-1.69 (2H, m, 7-Ha, 9-Ha), 1.53 (3H, s, 20-H_3), 1.27 (3H, s, 16-H_3 or 17-H_3), 1.21-1.13 (1H, m, 9-Hb), 1.10 (3H, s, 16-H_3 or 17-H_3), 0.90 (3H, s, 19-H_3), 0.88-0.79 (1H, m, 7-Hb); ^{13}C NMR (100 MHz, $CDCl_3$) 217.9 (C), 136.7 (C), 131.1 (C), 129.7 (C), 123.8 (CH), 62.6 (CH), 57.0 (CH), 40.3 (CH_2), 37.7 (C), 37.8 (C), 32.9 (CH_2), 29.9 (CH_3), 28.6 (CH_2), 24.9 (CH_2), 24.9 (CH_3), 24.7 (CH_3), 23.4 (CH_3), 22.0 (CH_2), 22.0 (CH_3), 18.3 (CH_2); HRMS *m/z* (ESI^+) 287.2361 ($M + H^+$, $C_{20}H_{31}O$ requires 287.2369).

Crystallographic Data

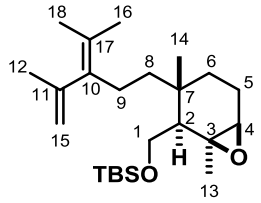
Empirical formula	$C_{20}H_{30}O$
Formula weight	286.44
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	8.2764(2)
b/Å	10.1676(2)
c/Å	19.2712(5)
α/°	90
β/°	95.673(3)
γ/°	90
Volume/Å^3	1613.74(7)
Z	4
ρ_{calc}mg/mm^3	1.179
m/mm^{-1}	0.526
F(000)	632.0
Crystal size/mm^3	0.4995 × 0.4382 × 0.3592
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection	9.224 to 151.616°
Index ranges	$-9 \leq h \leq 10$, $-12 \leq k \leq 12$, $-24 \leq l \leq 24$
Reflections collected	40872
Independent reflections	3355 [R_{int} = 0.0263, R_{sigma} = 0.0093]
Data/restraints/parameters	3355/0/195
Goodness-of-fit on F^2	1.054
Final R indexes [I>=2σ (I)]	R_1 = 0.0379, wR_2 = 0.0987
Final R indexes [all data]	R_1 = 0.0384, wR_2 = 0.0992
Largest diff. peak/hole / e Å^{-3}	0.32/-0.20

(±)-*trans*-2-(hydroxymethyl)-3,4-epoxy-7-(11-methyl-10-(prop-1-enyl)pent-11-enyl)-3,7-dimethylcyclohexane (**149**)



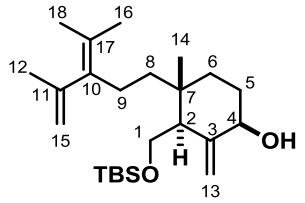
Tert-butylhydrogen peroxide (455 µL, 3.28 mmol) was added to a stirring solution of *trans*-alcohol **148** (613 mg, 2.34 mmol) and vanadium (III) acetylacetonate (17.0 mg, 0.047 mmol) in anhydrous dichloromethane (25.0 mL) at ambient temperature. The reaction was stirred for 3.5 h before brine (20 mL) was added. The organic layer was then washed with saturated aqueous sodium bicarbonate (100 mL), saturated aqueous sodium thiosulphate (100 mL), ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:4 rising to 1:1, ether:petrol) gave the title compound **149** (579 mg, 89%) as a colourless oil. R_f 0.25 (1:1, ether : petrol); ν_{max} ($CHCl_3$)/cm^{-1} 3617, 3515, 2932, 1630, 1446; ^{1}H NMR (400 MHz, $CDCl_3$) 4.94-4.90 (1H, m, 15-Ha), 4.56-4.53 (1H, m, 15-Hb), 3.98 (1H, dd, *J* 11.5, 3.7, 1-Ha), 3.86-3.77 (1H, m, 1-Hb), 3.01 (1H, br. s, 4-H), 2.79 (1H, br. s, OH), 2.06-1.90 (3H, m, 5-Ha, 9-H_2), 1.86-1.79 (1H, m, 5-Hb), 1.76 (3H, s, 12-H_3), 1.66 (6H, s, 16-H_3, 18-H_3), 1.58-1.47 (2H, m, 2-H, 6-Ha), 1.39 (3H, s, 15-H_3), 1.30-1.14 (2H, m, 8-H_2), 1.03 (1H, app. dd, *J* 14.0, 6.1, 6-Hb), 0.92 (3H, s, 14-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 146.5 (C), 136.5 (C), 124.8 (C), 113.1 (CH_2), 62.2 (CH_2), 60.4 (C), 59.8 (CH), 46.5 (CH), 37.5 (CH_2), 32.8 (C), 27.6 (CH_2), 25.6 (CH_3), 24.9 (CH_2), 23.0 (CH_3), 22.8 (CH_3), 22.6 (CH_3), 21.4 (CH_2), 19.5 (CH_3); HRMS *m/z* (ESI^+) 301.2120 (M + Na^+, $C_{18}H_{30}O_2Na$ require 301.2143).

(±)-*trans*-2-(tert-butyldimethylsilyloxymethyl)-7-(11-methyl-10-(prop-1-enyl)pent-11-enyl)-3,4-epoxy-3,7-dimethylcyclohexane (**150**)



tert-Butyldimethylsilyl chloride (351 mg, 2.33 mmol) was added to a stirring solution of alcohol **149** (539 mg, 1.94 mmol) and imidazole (264 mg, 3.88 mmol) in anhydrous *N,N*-dimethylformamide (8.20 mL) at ambient temperature. The reaction was stirred for 4 h at ambient temperature. Water (20 mL) was added before extraction with ether (3 x 30 mL). The organic layer was then washed with brine (3 x 20 mL), dried ($MgSO_4$) and concentrated in *vacuo* to give the title compound **150** (618 mg, 81%) as a colourless oil. Rf 0.64 (1:4, ether : petrol); ν_{max} (thin film)/cm^{-1} 2958, 2877, 1458, 1415, 1153; ^{1}H NMR (400 MHz, $CDCl_3$) 4.92 (1H, dq, *J* 2.9, 1.4, 15-Ha), 4.58-4.56 (1H, m, 15-Hb), 3.72 (1H, dd, *J* 9.9, 7.1, 1-Ha), 3.66 (1H, dd, *J* 9.9, 6.0, 1-Hb), 2.91 (1H, br. s, 4-H), 2.09-1.90 (2H, m, 9-H_2), 1.90-1.78 (2H, m, 5-H_2), 1.76 (3H, s, 12-H_3), 1.70-1.60 (7H, m, 16-H_3, 18-H_3, 2-H), 1.37 (3H, s, 13-H_3), 1.30-1.12 (3H, s, 8-H_2, 6-Ha), 0.97-0.85 (10H, m, 6-Hb, $OSiMe_2{}^tBu$), 0.81 (1H, s, 14-H_3), 0.11-0.05 (6H, m, $OSiMe_2{}^tBu$); ^{13}C NMR (100 MHz, $CDCl_3$) 146.6 (C), 136.7 (C), 124.6 (C), 113.0 (CH_2), 61.4 (CH_2), 59.3 (CH), 59.1 (C), 47.9 (CH), 37.2 (CH_2), 32.7 (C), 26.2 (CH_3), 26.0 (CH_3), 25.8 (CH_3), 25.7 (CH_2), 24.9 (CH_2), 23.6 (CH_3), 22.8 (CH_3), 21.7 (CH_3), 21.7 (CH_2), 19.5 (CH_3), 18.2 (C), -5.3 (CH_3), -5.4 (CH_3); HRMS *m/z* (ESI^+) 415.3021 (M + Na^+, $C_{24}H_{44}O_2SiNa$ requires 415.3008); 393.3198 (M + H^+, $C_{24}H_{45}O_2Si$ requires 393.3183).

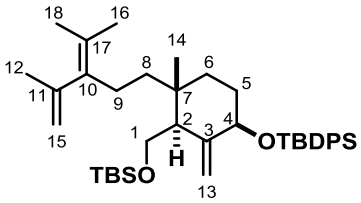
(±)-*trans*-2-(tert-butyldimethylsilyloxymethyl)-7-(11-methyl-10-(prop-1-enyl)pent-11-enyl)-7-methyl-3-methylenecyclohexan-4-ol (**151**)



^{n}BuLi (2.5 M in hexanes, 2.24 mL, 5.60 mmol) was added dropwise to a stirring solution of tetramethylpiperidine (0.95 mL, 5.60 mmol) in anhydrous toluene (24.0 mL) at 0 °C. The solution was stirred at 0 °C for 40 min before diethylaluminium chloride (1 M in hexanes, 5.6 mL, 5.60 mmol) was added dropwise. After a further 40 min epoxide **150** (960 mg, 2.44 mmol) was added as a solution in anhydrous toluene (6.0 mL). The reaction was stirred at 0 °C for 2 h. Saturated aqueous sodium bicarbonate (10 mL) was added portionwise followed by further dilution with water (10 mL). The aqueous layer was extracted with ether (2 x 15 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:9 rising to 1:4, ether:petrol) gave first recovered starting material **150** (120 mg) followed the title compound **151** (716 mg, 75%) as a colourless oil.. R_f 0.10 (ether:petrol; 1:9); ν_{max} (thin film)/cm^{-1} 3373, 2931, 2858, 1632, 1470, 1258, 1090; ^{1}H NMR (400 MHz, $CDCl_3$) 5.12 (1H, d, *J* 1.0, 13-Ha), 4.88 (1H, d, *J* 2.5, 15-Ha), 4.84 (1H, d, *J* 1.0, 13-Hb), 4.51 (1H, d, *J* 2.5, 15-Hb), 4.10-4.07 (1H, m, 4-H), 3.94 (1H, dd, *J* 10.0, 6.3, 1-Ha), 3.69 (1H, dd, *J* 10.0, 4.0, 1-Hb), 3.64 (1H, br. s, OH), 2.05 (1H, dd, *J* 6.3, 4.0, 2-H), 2.04-1.90 (2H, m, 9-H_2), 1.80-1.69 (5H, m, 5-Ha, 6-Ha, 12-H_3), 1.69-1.57 (7H, m, 5-Hb, 16-H_3, 18-H_3), 1.37-1.12 (3H, m, 6-Hb, 8-H_2), 0.91 (3H, s, 14-H_3), 0.92 (9H, s, OSiMe$_2$*^{t}Bu*), 0.09 (3H, s, OSi*Me$_2$*^{t}Bu), 0.07 (3H, s, OSi*Me$_2$*^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) 149.3 (C), 146.6 (C), 136.7 (C), 124.7 (C), 113.0 (CH_2), 71.5 (CH), 63.9 (CH_2), 51.9 (CH), 38.0 (CH_2), 36.1 (C), 30.6 (CH_2), 30.0 (CH_2), 25.9 (CH_3), 25.1 (CH_2), 22.8 (CH_3), 22.7 (CH_3), 21.7 (CH_3), 19.5 (CH_3), 18.2 (CH_3),

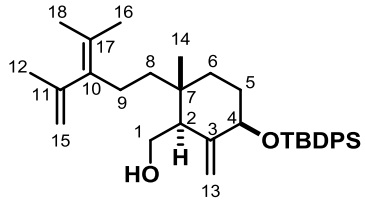
-5.5 (CH_3), -5.7 (CH_3); HRMS *m/z* (ESI^+) 415.2984 (M + Na^+, $C_{24}H_{44}O_2SiNa$ requires 415.3003)

(±)-*trans*-2-(tert-butyldimethylsilyloxymethyl)-4-(tert-butyldiphenylsilyloxy)-7-(11-methyl-10-(prop-1-enyl)pent-11-enyl)-7-methyl-3-methylenecyclohexane (**198**)



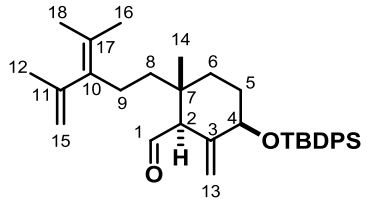
tert-Butyldiphenylsilyl chloride (137 µL, 0.52 mmol) was added to a stirring solution of alcohol **151** (104 mg, 0.26 mmol) and imidazole (70 mg, 1.4 mmol) in anhydrous N,N-dimethylformamide (1.7 mL). The reaction was stirred at ambient temperature for 5 h. Water (3 mL) was added and the solution extracted with ether (3 x 5 mL). The organic layer was washed with brine (10 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:9, ether:petrol) gave the title compound **198** (120 mg, 76%) as a colourless oil. R_f 0.87 (1:9, ether:petrol); ν_{max} (thin film)/cm^{-1} 2929, 2857, 1472, 1112, 909; ^{1}H NMR (400 MHz, $CDCl_3$) 7.84-7.70 (4H, m, ArH), 7.5-7.34 (6H, m, ArH), 5.44 (1H, br. s, 13-Ha), 4.97 (1H, br. s, 13-Hb), 4.93 (1H, br. s, 15-Ha), 4.57 (1H, d, *J* 2.0, 15-Hb), 4.10 (1H, dd, *J* 8.5, 4.5, 4-H), 3.94 (1H, dd, *J* 10.5, 4.5, 1-Ha), 3.88 (1H, dd, *J* 10.5, 7.0, 1-Hb), 2.12-1.88 (3H, m, 2-H, 9-H_2), 1.79 (3H, s, 12-H_3), 1.70 (3H, s, 16-H_3), 1.68 (3H, s, 18-H_3), 1.63-1.27 (6H, m, 5-H_2, 6-H_2, 8-H_2), 1.18 (9H, s, $OSiMe_2{}^tBu$), 0.98 (9H, s, $OSiMe_2{}^tBu$), 0.89 (3H, s, 14-H_3), 0.13 (3H, s, $OSiMe_2{}^tBu$), 0.12 (3H, s, $OSiMe_2{}^tBu$); ^{13}C NMR (100 MHz, $CDCl_3$) 148.8 (C), 146.7 (C), 136.9 (C), 135.9 (CH), 135.8 (CH), 134.8 (C), 134.2 (C), 129.6 (CH), 129.5 (CH), 127.6 (CH), 127.5 (CH), 124.4 (C), 112.9 (CH_2), 74.6 (CH), 61.2 (CH_2), 52.2 (CH), 39.2 (CH_2), 36.7 (C), 33.6 (CH_2), 32.6 (CH_2), 27.1 (CH_3), 25.9 (CH_3), 25.1 (CH_3), 22.9 (CH_3), 21.7 (CH_3), 19.4 (C), 18.2 (C), -5.4 (CH_3), -5.3 (CH_3); HRMS *m/z* (ESI^+) 653.4168 (M + Na^+, $C_{40}H_{62}O_2Si_2Na$ requires 653.4181).

(±)-*trans*-2-(hydroxymethyl)-4-(tert-butyldiphenylsilyloxy)-7-(11-methyl-10-(prop-1-enyl)pent-11-enyl)-7-methyl-3-methylenecyclohexane (**199**)



p-Toluenesulfonic acid (146 mg, 0.765 mmol) was added to a stirring solution of bisprotected alcohol **198** (966 mg, 1.53 mmol) in ethanol : THF (1.4 mL, 1:1) under argon at ambient temperature, and the resulting solution was stirred at ambient temperature for 5 h. The reaction was then quenched with saturated aqueous sodium hydrogen carbonate (20 mL), extracted with ether (3 x 20 mL) and the combined organic extractions were washed with brine (20 mL) and dried ($MgSO_4$) then concentrated in *vacuo*. Purification by silica gel chromatography (1:9, ether:petrol) afforded firstly returned starting material **198** (390 mg, 40%) then the mono deprotected product **199** (493 mg, 60%) as a colourless oil. Rf 0.25 (1:9, ether:petrol); ν_{max} (thin film)/cm^{-1} 3431, 2932, 2856, 1428, 1112, 909; ^{1}H NMR (400 MHz, $CDCl_3$) 7.76-7.62 (4H, m, ArH), 7.48-7.34 (6H, m, ArH), 5.16 (1H, br. s, 13-Ha), 4.91 (2H, br. s, 13-Hb, 15-Ha), 4.48 (1H, d, *J* 2.5, 15-Hb), 4.17 (1H, app. t, *J* 5.0, 4-H), 3.96 (1H, app. t, *J* 10.0, 1-Ha), 3.73 (1H, dd, *J* 10.0, 4.0, 1-Hb), 2.10 (1H, dd, *J* 10.0, 4.0, 2-H), 2.01-1.85 (2H, m, 9-H_2), 1.71 (3H, s, 12-H_3), 1.62 (3H, s, 16-H_3), 1.60 (3H, s, 18-H_3), 1.58-1.42 (2H, m, 5-H_2), 1.29-1.14 (4H, m, 6-H_2, 8-H_2), 1.11 (9H, s, $OSiPh_2{}^tBu$), 0.88 (3H, s, 14-H_3); ^{13}C NMR (400 MHz, $CDCl_3$) 148.0 (C), 146.8 (C), 136.6 (C), 135.9 (CH), 134.1 (C), 133.6 (C), 129.8 (CH), 127.9 (CH), 127.6 (CH), 124.7 (C), 113.0 (CH_3), 74.2 (CH), 61.4 (CH_2), 52.9 (CH), 41.4 (C), 40.9 (CH_2), 33.8 (C), 27.0 (CH_3), 23.9 (CH_2), 22.6 (CH_3), 22.1 (CH_3), 19.0 (CH_3); HRMS *m/z* (ESI^+) 539.3302 (M + Na^+, $C_{34}H_{48}O_2SiNa$ requires 539.3316).

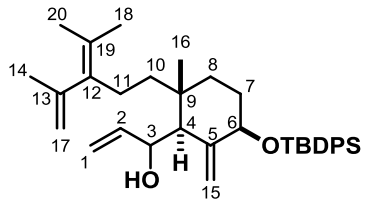
(±)-4-(tert-butyldiphenylsilyloxy)-7-methyl-7-(11-methyl-10-(prop-1-en-2-yl)pent-11-enyl)-3-methylenecyclohexane-2-carbaldehyde (**152**)



Anhydrous DMSO (835 µL, 11.8 mmol) was added dropwise to a stirring solution of oxalyl chloride (498 µL, 5.88 mmol) in anhydrous dichloromethane (20.0 mL) under argon at -78°C, and the resulting solution stirred at -78°C for 30 min. Alcohol **199** (1.52 g, 2.94 mmol) was added dropwise as a solution in anhydrous dichloromethane (15 mL), and the resulting solution was stirred at -78 °C for 1 h. Anhydrous triethylamine (2.05 mL, 14.7 mmol) was then added to the solution at -78 °C, and the resulting mixture stirred at ambient temperature for 30 min. The reaction was then quenched by the addition of saturated aqueous sodium hydrogen carbonate (20 mL) and the aqueous layer extracted with ether (3 x 20 mL). The combined organic extractions were dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:5, ether:petrol,) afforded the aldehyde **152** (92.0 mg, 84%) as a colourless oil. R_f 0.80 (1:5, ether:petrol); ν_{max} (thin film, NaCl)/cm^{-1} 3072, 2931, 2857, 1718, 1646, 1471, 1427, 1373, 1191, 1111, 1055, 991, 894, 822; ^{1}H NMR (400 MHz, $CDCl_3$) 10.1 (1H, d, *J* 4.5, 1-H), 7.75-7.70 (2H, m, ArH), 7.63-7.61 (2H, m, ArH), 7.46-7.35 (6H, m, ArH), 5.04 (1H, s, 13-Ha), 4.86-4.85 (2H, m, 13-Hb and 15-Ha), 4.47 (1H, d, *J* 2.0, 15-Hb), 4.17 (1H, t, *J* 4.5, 4-H), 2.68 (1H, d, *J* 4.5, 2-H), 2.00-1.88 (3H, m, 6-Ha and 9-H_2), 1.70 (3H, br s, 12-H_3), 1.62 (3H, s, 16-H_3 or 18-H_3), 1.59 (3H, s, 16-H_3 or 18-H_3), 1.56-1.51 (2H, m, 5-H_2), 1.33-1.28 (1H, m, 6-Hb), 1.24-1.15 (2H, m, 8-H_2), 1.09 (3H, s, 14-H_3), 1.10 (9H, s, *t*BuPh$_2$Si); ^{13}C NMR (100 MHz, $CDCl_3$) 203.2 (CH), 146.4 (C), 144.8 (C), 136.2 (C), 136.0 (CH), 135.9 (CH), 134.1 (C), 133.3 (C), 129.7 (CH), 127.6 (CH), 127.5 (CH), 125.0 (C), 113.7 (CH_2), 113.1 (CH_2), 72.8 (CH), 64.2 (CH), 37.3 (CH_2),

36.3 (C), 30.5 (CH_2), 30.3 (CH_2), 27.0 (CH_3), 24.6 (CH_2), 22.9 (CH_3), 22.7 (CH_3), 21.7 (CH_3), 19.4 (CH_3), 19.2 (C); HRMS *m/z* (ESI^+) 537.3160 ($M+Na^+$, $C_{34}H_{46}O_2SiNa$ requires 537.3159).

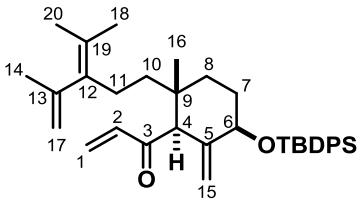
(±)-6-(tert-butyldiphenylsilyloxy)-9-methyl-9-(13-methyl-12-(prop-1-en-2-yl)pent-13-enyl)-5-methylenecyclohexyl)-4-prop-1-en-3-ol (**200**)



Vinyl magnesium bromide (1 M in THF, 6.22 mL, 6.22 mmol,) was added dropwise to a stirring solution of aldehyde **152** (1.60 g, 3.11 mmol) in anhydrous THF (10.0 mL) under argon at -78 °C, and the resulting solution was stirred for 1 h at -78 °C, then quenched by the addition of saturated aqueous ammonium chloride (5 mL). The aqueous layer was extracted with ether (3 x 10 mL), and the combined organic extractions were dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:30, ether:petrol;) afforded the title compound **200** (1.28 g, 76%) as a colourless oil (10:1 d.r, unassigned relative stereochemistry). R_f 0.10 (1:30, ether:petrol;); ν_{max} (thin film, NaCl)/cm^{-1} 3358, 3011, 2961, 2933, 1472, 1112; ^1H NMR (400 MHz, $CDCl_3$) 7.75-7.67 (4H, m, ArH), 7.49-7.38 (6H, m, ArH), 5.93 (1H, ddd, *J* 17.0, 10.5, 5.0, 2-H), 5.23 (1H, ddd, *J* 17.0, 2.0, 1.5, 1-Ha), 5.11 (1H, ddd, *J* 10.5, 2.0, 1.5, 1-Hb), 5.02 (1H, d, *J* 11.0, O*H*), 4.98 (1H, dd, *J* 2.5, 0.5, 15-Ha), 4.84 (1H, dd, *J* 2.5, 0.5, 15-Hb), 4.82 (1H, dq, *J* 2.5, 1.0, 17-Ha), 4.45-4.40 (2H, m, 3-H and 17-Hb), 4.22 (1H, t, *J* 2.5, 6-H), 2.27 (1H, td, *J* 13.0, 6.0, 7-Ha), 2.11 (1H, d, *J* 2.5, 4-H), 1.93 (1H, td, *J* 12.5, 5.0, 11-Ha), 1.84 (1H, td, *J* 12.5, 5.0, 11-Hb), 1.69 (3H, br s, 14-H_3), 1.61 (3H, s, 18-H_3 or 20-H_3), 1.58 (3H, s, 18-H_3 or 20-H_3), 1.32-1.28 (3H, m, 8-Ha and 10-H_2), 1.19-1.08 (2H, m, 7-Hb and 8-Hb), 1.16 (3H, s, 14-H_3), 1.12 (9H, s, ^{t}BuPh$_2$Si); ^{13}C NMR (100 MHz, $CDCl_3$) 146.6 (C), 143.9 (C), 142.4 (CH), 136.7 (C), 136.2 (CH), 136.1 (C),

133.2 (C), 132.7 (C), 130.1 (CH), 129.9 (CH), 127.7 (CH), 127.5 (CH), 124.5 (C), 120.0 (CH_2), 113.3 (CH_2), 112.8 (CH_2), 73.4 (CH), 72.1 (CH), 56.7 (CH), 37.4 (C), 36.0 (CH_2), 29.1 (CH_2), 28.0 (CH_2), 27.1 (CH_3), 25.1 (CH_2), 23.9 (CH_3), 22.7 (CH_3), 21.7 (CH_3), 19.4 (CH_3), 19.1 (C); HRMS *m/z* (ESI^+) 565.3475 ($M+Na^+$, $C_{36}H_{50}O_2SiNa$ requires 565.3472).

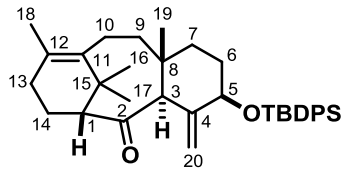
(±)-6-(tert-butyldiphenylsilyloxy)-9-methyl-9-(13-methyl-12-(prop-1-en-2-yl)pent-13-enyl)-5-methylenecyclohexyl)prop-1-en-3-one (**153**)



Anhydrous DMSO (639 µL, 9.00 mmol) was added dropwise to a stirring solution of oxalyl chloride (380 µL, 4.50 mmol) in anhydrous dichloromethane (7.0 mL) under argon at -78 °C, and the resulting solution stirred at -78 °C for 30 min. Alcohol **200** (1.22 g, 2.25 mmol, 10:1 mixture of diastereomers) was added dropwise as a solution in anhydrous dichloromethane (3.00 mL), and the resulting solution was stirred at -78 °C for 3 h. Anhydrous triethylamine (1.25 mL, 9.00 mmol) was then added at -78 °C, and the resulting solution stirred at -78 °C for 1 h. The reaction was then quenched by the addition of saturated aqueous sodium hydrogen carbonate (20 mL) and the aqueous layer extracted with dichloromethane (3 x 30 mL). The combined organic extractions were dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:30, ether: petrol) afforded enone **153** (882 mg, 72%) as a colourless oil. R_f 0.57 (1:9, ether:petrol); ν_{max} (thin film, NaCl)/cm^{-1} 3073, 3053, 3010, 2858, 1702, 1679, 1486, 1445, 1110, 909; ^1H NMR (400 MHz, $CDCl_3$) 7.74-7.68 (4H, m, ArH), 7.46-7.35 (6H, m, ArH), 6.22 (1H, dd, *J* 17.5, 10.5, 2-H), 6.05 (1H, dd, *J* 17.5, 1.5, 1-Ha), 5.60 (1H, dd, *J* 10.5, 1.5, 1-Hb), 5.48 (1H, s, 15-Ha), 4.84 (1H, dq, *J* 2.5, 1.0, 17-Ha), 4.61 (1H, s, 15-Hb), 4.45 (1H, dq, *J* 2.5, 1.0, 17-Hb),

4.08 (1H, dd, *J* 10.5, 5.0, 6-H), 3.06 (1H, s, 4-H), 1.96 (1H, td, *J* 13.0, 5.5, 11-Ha), 1.81 (1H, td, *J* 13.0, 5.5, 11-Hb), 1.67 (3H, dd, *J* 1.0, 1.0, 14-H_3), 1.61 (3H, s, 18-H_3 or 20-H_3), 1.56 (3H, s, 18-H or 20-H_3), 1.69-1.58 (2H, m, 7-H_2), 1.42-1.20 (4H, m, 8-H_2 and 10-H_2), 1.12 (12H, s, 14-H_3 and ^{t}BuPh$_2$Si); ^{13}C NMR (100 MHz, $CDCl_3$) 198.6 (C), 146.4 (C), 146.1 (C), 137.4 (CH), 136.3 (C), 135.9 (CH), 135.8 (CH), 134.3 (C), 133.9 (C), 129.7 (CH), 129.6 (CH), 127.5 (CH), 127.5 (CH), 126.6 (CH_2), 124.8 (C), 113.0 (CH_2), 109.3 (CH_2), 74.6 (CH), 59.6 (CH), 39.5 (CH_2), 38.3 (C), 35.7 (CH_2), 33.0 (CH_2), 27.0 (CH_3), 25.4 (CH_2), 22.7 (CH_3), 21.7 (CH_3), 19.5 (CH_3), 19.4 (CH_3), 19.3 (C); HRMS *m/z* (ESI$^+$) 563.3315 (M+Na$^+$, $C_{36}H_{48}O_2SiNa$ requires 563.3316).

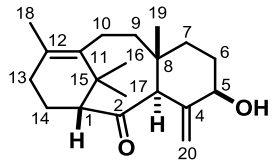
(±)-5β-(tert-butyldiphenylsilyloxy)-taxa-4(20),11(12)-dien-2-one (**154**)



A solution of *trans*-enone **153** (24.0 mg, 44.4 µmol) in anhydrous toluene (2.30 mL) was added via syringe pump over 5 h to a stirring solution of BF_3•OEt_2 (11.0 µL, 88.8 µmol) in anhydrous toluene (4.80 mL) at 0 °C under argon, and once the addition was complete the reaction solution was stirred for a further 1 h at 0 °C. The reaction was then quenched with cold saturated aqueous sodium hydrogen carbonate solution (20 mL). The aqueous layer was extracted with dichloromethane (3 x 20 mL), and the combined organic extractions washed sequentially with water (30 mL) then brine (30 mL). The organic layer was then dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:40, ether:petrol) afforded the title compound **154** (15.0 mg, 62%) as a colourless solid. R_f 0.32 (1:9, ether:pentane); m.p. 128-133 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3072, 3052, 3010, 2859, 1692, 1462, 1391, 1110, 909; ^{1}H NMR (400 $CDCl_3$), 7.71-7.66 (4H, m,

ArH), 7.44-7.34 (6H, m, ArH), 5.37 (1H, s, 20-Ha), 4.88 (1H, s, 20-Hb), 3.80 (1H, t, *J* 7.5, 5-H), 3.50 (1H, s, 3-H), 2.74 (1H, td, *J* 13.5, 5.5, 13-Ha), 2.40-2.30 (2H, m, 1-H and 10-Ha), 2.80-2.40 (1H, m, 13-Hb), 1.89-1.73 (2H, m, 14-Ha and 7-Ha), 1.66-1.53 (4H, m, 6-Ha, 9-H_2 and 10-Hb), 1.58 (3H, s, 18-H_3), 1.43-1.20 (5H, m, 7-Hb, 14-Hb and 16-H_3 or 17-H_3), 1.10 (9H, s, ^{t}BuPh$_2$Si), 1.07 (3H, s, 16-H_3 or 17-H_3), 1.10-0.99 (1H, m, 6-Hb), 0.91 (3H, s, 19-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 213.1 (C), 144.8 (C), 137.3 (C), 135.8 (CH), 135.7 (CH), 134.4 (C), 133.8 (C), 131.0 (C), 129.6 (CH), 127.50 (CH), 127.46 (CH), 106.6 (CH_2), 74.6 (CH), 62.1 (CH), 53.2 (CH), 41.4 (C), 38.8 (C), 38.5 (CH_2), 36.6 (CH_2), 33.0 (CH_2), 29.7 (CH_3), 29.0 (CH_2), 27.0 (CH_3), 25.0 (CH_3), 25.0 (CH_2), 23.3 (CH_3), 22.1 (CH_3), 19.4 (C), 17.9 (CH_2); HMRS *m/z* (ESI$^+$) 563.3301 (M+Na$^+$, $C_{36}H_{48}O_2SiNa$ requires 563.3316).

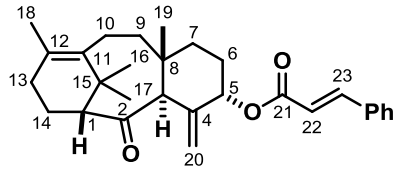
(±)-5β-hydroxy-taxa-4(20),11(12)-dien-2-one (**201**)



TBAF (1M in THF, 562 µL, 562 µmol,) was added to a solution of protected allylic alcohol **154** (152 mg, 281 µmol) in anhydrous THF (1.50 mL) at 0 °C under argon. The reaction was allowed to warm to ambient temperature after 10 min and stirred for a further 18 h. The reaction was then diluted with water (10 mL) and extracted with ether (3 x 10 mL) and the combined organic extractions dried ($MgSO_4$) and the solvent concentrated in *vacuo*. Purification by silica gel chromatography (1:1, ether:pentane) afforded the title compound **201** (81.0 mg, 95%) as a colourless oil. R_f 0.20 (1:1, ether:pentane); ν_{max} cm^{-1} ($CHCl_3$) 3603, 301, 2984, 2925, 2903, 1691, 1458, 1392, 1115; ^{1}H NMR (400 MHz, $CDCl_3$) 5.08 (1H, app. dt, *J* 2.0, 1.0, 20-Ha), 4.88 (1H, br. s, 20-Hb), 3.9 (1H, dd, *J* 9.0, 2.0, 5-H), 3.75 (1H, br. s, 3-H), 2.88 (1H, td, *J* 13.5, 5.5, 10-Ha), 2.57-2.47 (1H, m, 13-Ha), 2.43 (1H, d,

J 8.5, 1-H), 2.20-2.12 (1H, m, 10-Hb), 2.05-1.91 (4H, m, 6-Ha, 7-Ha, 13-Hb and 14-Ha), 1.88 (3H, s, 18-H_3), 1.86-1.79 (1H, m, 9-Ha), 1.69-1.50 (3H, m, 6-Hb, 14-Hb and O*H*), 1.34 (1H, ddd, *J* 15.5, 5.5, 2.5, 9-Hb), 1.29 (3H, s, 16-H_3), 1.23-1.19 (1H, m, 7-Hb), 1.13 (3H, s, 17-H_3), 0.95 (3H, s, 19-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 213.2 (C), 145.8 (C), 137.4 (C), 131.0 (C), 105.3 (CH_2), 72.6 (CH), 62.2 (CH), 53.4 (CH), 41.4 (C), 38.9 (CH_2), 38.5 (C), 36.6 (CH_2), 32.8 (CH_2), 29.7 (CH_3), 29.2 (CH_2), 25.1 (CH_3), 25.0 (CH_2), 23.3 (CH_3), 22.3 (CH_3), 18.0 (CH_2); HRMS (ESI$^+$) *m/z* 325.2139 (M+Na$^+$, $C_{20}H_{30}O_2Na$ requires 325.2138).

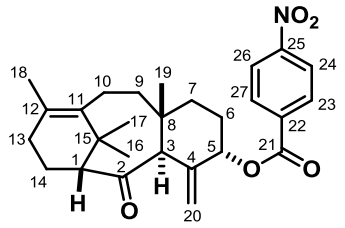
(±)-taxa-4(20),11(12)-dien-2-one-5α-cinnamate (**202**)



Diethylazodicarboxylate (9.0 µL, 54.6 µmol) was added dropwise to a stirring solution of alcohol **201** (11.0 mg, 36.4 µmol), *trans* cinnamic acid (8.0 mg, 54.6 µmol) and triphenylphosphine (14.0 mg, 54.6 µmol) in anhydrous THF (200 µL) at 0 °C. The reaction was stirred at 0 °C for 3 h under argon. The reaction was quenched with water (5 mL) and extracted with ether (3 x 2 mL). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (3 ml), brine (3 ml), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (pentane rising to 1:1, ether:pentane, then ether) afforded the title compound **202** (9.0 mg, 58%) as a colourless solid. R_f 0.60 (1:4, ether:pentane); ^{1}H NMR (500 MHz, $CDCl_3$) 7.76 (1H, d, *J* 15.9, 22-H), 7.57-7.55 (2H, m, ArH), 7.45-7.42 (3H, m, ArH), 6.53 (1H, d, *J* 15.9, 23-H), 5.44 (1H, m, 5-H), 5.21 (1H, br. s, 20-Ha), 4.99 (1H, t, *J* 1.0, 20-Hb), 4.35 (1H, br. s, 3-H), 2.96 (1H, td, *J* 13.7, 5.5, 10-Ha), 2.57-2.52 (1H, m, 13-Ha), 2.42 (1H, d, *J* 8.4, 1-H), 2.25-2.17 (2H, m, 6-Ha and 10-Hb), 2.11-2.07 (1H, m, 13-Hb), 2.06 (3H, s, 18-H_3), 2.01-1.90 (3H, m, 7-H_2 and 14-

Ha), 1.86 (1H, m, 9-Ha), 1.64 (1H, ddd, *J* 15.4, 9.8, 5.8, 14-Hb), 1.37-1.34 (1H, m, 9-Hb), 1.30 (3H, s, 16-H_3), 1.14-1.11 (1H, m, 6-Hb), 1.13 (3H, s, 17-H_3), 0.97 (3H, s, 19-H_3); ^{13}C NMR (125 MHz, $CDCl_3$) 214.1 (C), 166.0 (C), 145.1 (CH), 141.2 (C), 137.1 (C), 134.4 (C), 133.0 (C), 131.3 (C), 130.4 (CH), 129.0 (CH), 128.0 (CH), 118.2 (CH), 114.8 (CH_2), 77.18 (CH), 75.1 (CH), 62.4 (CH), 50.6 (CH), 41.2 (C), 39.4 (CH_2), 38.5 (C), 33.8 (CH_2), 29.7 (CH_3), 29.5 (CH_2), 27.9 (CH_2), 25.3 (CH_2), 25.0 (CH_3), 22.9 (CH_3), 21.9 (CH_3), 18.1 (CH_2); HRMS *m/z* (ESI$^+$) 455.2584 (M+Na$^+$, $C_{29}H_{36}O_3Na$ requires 455.2557).

(±)-taxa-4(20),11(12)-dien-2-one-5α-nitrobenzoate (**203**)



Diethylazodicarboxylate (21.0 µL, 132 µmol) was added dropwise to a stirring solution of alcohol **201** (10.0 mg, 33.1 µmol), *p*-nitrobenzoic acid (22.0 mg, 132 µmol) and triphenylphosphine (35.0 mg, 132 µmol) in anhydrous THF (350 µL) at 0 °C. The reaction was stirred allowed to warm to ambient temperature and stirred 2 h under argon. The reaction was quenched with water (4 mL) and extracted with ether (3 x 2 mL). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (2 ml), brine (2 ml), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:1.8, ether:pentane) afforded the title compound **203** (12.0 mg, 80%) as a colourless solid. R_f 0.75 (1:1.5, ether:pentane); ν_{max} cm^{-1} ($CHCl_3$) 3007, 2983, 2933, 2860, 1721, 1690, 1608, 1530, 1461, 1347, 1098. ^{1}H NMR (400 MHz, $CDCl_3$) 8.35-8.31 (2H, m, ArH), 8.23-8.19 (2H, m, ArH), 5.53-5.50 (1H, m, 5-H), 5.31 (1H, s, 20-Ha), 5.07 (1H, s, 20-Hb) 4.17 (1H, s, 3-H), 2.87 (1H, td, *J* 13.7, 5.5, 10-Ha), 2.42 (1H, d, *J* 8.5, 1-

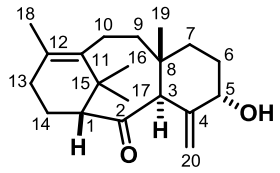
H), 2.41-2.34 (1H, m, 13-Ha), 2.26-2.13 (2H, m, 10-Hb, 14-Ha), 2.12-1.99 (2H, m, 6-H_2), 1.93-1.84 (2H, m, 9-Ha, 7-Ha), 1.82 (3H, s, 18-H_3), 1.64-1.48 (2H, m, 13-Hb, 7-Hb), 1.41-1.34 (1H, m, 9-Hb), 1.27 (3H, s, 16-H_3 or 17-H_3), 1.25-1.16 (1H, m, 14-Hb), 1.08 (3H, s, 16-H_3 or 17-H_3), 0.98 (3H, s, 19-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) 213.7 (C), 164.3 (C), 150.5 (C), 140.4 (C), 137.4 (C), 136.2 (C), 130.7 (CH), 130.6 (CH), 130.7 (C), 123.5 (CH), 116.9 (CH_2), 62.4 (CH), 50.9 (CH), 41.15 (C), 39.5 (CH_2), 38.5 (C), 34.1 (CH_2), 29.6 (CH_3), 29.3 (CH_2), 27.7 (CH_2), 25.2 (CH_2), 25.0 (CH_3), 22.9 (CH_3), 22.0 (CH_3), 18.1 (CH_2). HRMS *m/z* (ESI^+) 474.2275 ($M+Na^+$, $C_{27}H_{33}NO_5Na$ requires 474.2256).

Crystallographic Data

Empirical formula	$C_{27}H_{33}NO_5$
Formula weight	451.54
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	18.5482(4)
b/Å	8.49438(11)
c/Å	15.3266(2)
α/°	90
β/°	105.4335(18)
γ/°	90
Volume/Å^3	2327.71(7)
Z	4
ρ_{calc}g/cm^3	1.288
μ/mm^{-1}	0.712
F(000)	968.0
Crystal size/mm^3	0.1777 × 0.0985 × 0.0252
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.894 to 148.694

Index ranges	$-23 \leq h \leq 21, -10 \leq k \leq 10, -19 \leq l \leq 19$
Reflections collected	22915
Independent reflections	4699 [R_{int} = 0.0219, R_{sigma} = 0.0143]
Data/restraints/parameters	4699/0/302
Goodness-of-fit on F^2	1.025
Final R indexes [I>=2σ (I)]	R_1 = 0.0374, wR_2 = 0.0958
Final R indexes [all data]	R_1 = 0.0422, wR_2 = 0.0997
Largest diff. peak/hole / e $Å^{-3}$	0.23/-0.20

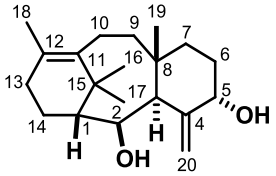
(±)-5α-hydroxy-taxa-4(20),11(12)-dien-2-one (**204**)



Potassium carbonate (46.0 mg, 333 µmol) was added to a stirring solution of ester **203** (50 mg, 111 µmol) in 2:1 mixture of methanol: THF (1.5 mL) at ambient temperature. The reaction was stirred for 3 h. Water (5 ml) was added, followed by extraction with ether (3 x 10 ml). The combined organic layers were washed with brine (10 ml), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:1.5, ether: pentane) afforded the title compound **204** (25.0 mg, 75%) as a colourless oil. R_f 0.25 (1:1.5, ether: pentane); ν_{max} cm^{-1} ($CHCl_3$) 3690, 3631, 3010, 2984, 2936, 2858, 1687, 1602, 1460, 1391, 1241, 1015, 933; ^{1}H NMR (500 MHz, $CDCl_3$) 4.95 (1H, app. t, *J* 1.3, 20-Ha), 4.78 (1H, app. t, *J* 1.7, 20-Hb), 4.49 (1H, s, 3-H), 4.23 (1H, br. s, 5-H), 2.94 (1H, td, *J* 13.7, 5.6, 10-Ha), 2.54-2.45 (1H, m, 13-Ha), 2.41 (1H, d, *J* 8.5, 1-H), 2.26 (1H, td, *J* 13.3, 4.6, 7-Ha), 2.18-2.12 (1H, m, 10-Hb), 2.07 (1H, ddd, *J* 18.3, 10.0, 2.0, 13-Hb), 2.00-1.92 (4H, m, 14-Ha, 18-H_3), 1.91-1.72 (3H, m, 6-H_2, 9-Ha), 1.65 (1H, m, 14-Hb), 1.33-1.25 (4H, m, 16-H_3 or 17-H_3, 9-Hb), 1.12 (3H, s, 16-H_3 or 17-H_3), 0.98 (1H, ddd, *J* 13.3, 5.0, 2.3, 7-Hb), 0.91 (3H, s, 19-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 214.7 (C), 146.8 (C), 136.3 (C), 131.9 (C), 111.1 (CH_2), 72.9 (CH), 62.6

(CH), 49.3 (CH), 39.4 (CH_2), 38.5 (C), 33.1 (CH_2), 29.8 (CH_3), 29.8 (CH_3), 29.7 (C), 29.1 (CH_2), 25.2 (CH_2), 25.1 (CH_2), 22.8 (CH_3), 21.6 (CH_3), 18.3 (CH_2); HRMS (ESI^+) *m/z* 325.2130 ($M+Na^+$, $C_{20}H_{30}O_2Na$ requires 325.2143).

(±)-5α,2β-hydroxy-taxa-4(20),11(12)-diene (**214**)



Sodium/ Ammonia Reduction

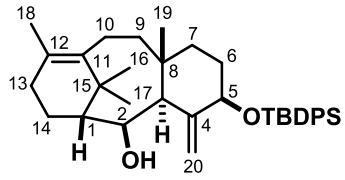
Sodium metal (300 mg, 13.0 mmol) was added portionwise to a solution of ketone **204** (2.0 mg, 6.61 µmol) in 10:1, liquid ammonia and methanol (5.5 mL) at -45 ˚C until a blue coloured solution persisted for 10 min. (In total 0.3 g, 13.0 mmol of sodium added). The reaction was then stirred for 2 h at -45 ˚C. The reaction was then allowed to warm to ambient temperature. After the ammonia had evaporated methanol (5 ml) was added carefully to the residue. The solvent was then concentrated in *vacuo*. Water was then added (5 ml) and extracted with ether (3 x 5 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo* to afford the title compound **214** (1.4 mg, 70%) as a colourless oil. ^1H NMR (500 MHz, $CDCl_3$) 5.06 (1H, s, 20-Ha), 4.82 (1H, s, 20-Hb), 4.28 (1H, t, *J* 2.6, 5-H), 4.23 (1H, app. d, *J* 3.8, 2-H), 3.45 (1H, s, 3-H), 2.88 (1H, td, *J* 13.6, 5.3, 10-Ha), 2.63-2.56 (1H, m, 9-Ha), 2.36-2.28 (2H, m, 13-Ha, 7-Ha), 2.25-2.10 (2H, m, 10-Hb, 14-Ha), 1.93-1.72 (6H, m, 13-Hb, 6-H_2, 18-H_3), 1.63 (3H, s, 16-H_3 or 17-H_3), 1.36-1.25 (1H, m, 9-Hb) 1.19-1.12 (1H, m, 14-Hb), 1.09 (3H, s, 16-H_3 or 17-H_3), 0.97 (3H, s, 19-H_3), 0.94-0.82 (1H, m, 7-Hb); ^{13}C NMR (125 MHz, $CDCl_3$) 156.6 (C), 149.9 (C), 136.7 (C), 108.9 (CH_2), 82.9 (CH), 74.6 (CH), 51.8 (CH), 39.9 (CH_2), 39.2 (CH), 39.3 (CH_3), 38.6 (C), 35.2 (CH_2), 32.7 (CH_3),

29.7 (CH_2), 29.02 (CH_2), 26.2 (CH_3), 25.4 (CH_3), 25.1 (CH_2), 23.2 (CH_2), 21.1 (CH_3); HRMS (ESI^+) *m/z* 327.2308 ($M+Na^+$, $C_{20}H_{32}O_2Na$ requires 327.2300).

Sodium / Ether Reduction

Sodium metal (2.5 mg, 109 µmol) was added portionwise to a solution of ketone **204** (2.0 mg, 6.60 µmol) in diethyl ether (0.50 mL) at -40 ˚C. After 0.5 h. ethanol (0.25 ml) was added dropwise. After 1 h. the above procedure was repeated another two times by addition of sodium followed by 0.5 h. wait and another addition of ethanol. After 1 h. additional stirring after the last addition, the reaction was quenched by dropwise addition of methanol (5 mL), followed by warming to ambient temperature. Hydrochloric acid (1 M aq., 1 mL) was then added and the solution extracted with ether (3 x 2 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo* to give the crude product (5 mg) as a colourless oil. ^1H NMR of the crude product showed 1:4 ratio of starting ketone **204** : title compound **214**. Purification by silica gel chromatography (pentane to 1:10 ether:pentane) was unsuccessful. Data for the title compound in the crude product was consistent with that reported above.

(±)-5β-(tert-butyldiphenylsilyloxy)-2β-hydroxy-taxa-4(20),11(12)-diene (**212**)



DIBAL-H Reduction

DIBAL-H (74.0 µL of a 1.5 M solution in toluene, 111 µmol) was added dropwise to a solution of ketone **154** (30.0 mg, 55.0 µmol) in CH_2Cl_2 (0.50 mL) at 0 ˚C under argon. The reaction was stirred for 0.5 h. at 0 ˚C before methanol (1.0 mL) was added dropwise

followed by water (5 ml). The aqueous layer was then extracted with ether (3 x 10 ml). Combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:4, ether:petrol) afforded the title compound **212** (20.0 mg, 66%) as a colourless oil. R_f 0.2 (1:4, ether : petrol); ν_{max} cm^{-1} ($CHCl_3$) 3613, 3052, 3010, 2931, 2859, 1488, 1427, 1260, 1106, 1006; ^1H NMR (500 MHz, $CDCl_3$) 7.61-7.54 (4H, m, ArH), 7.32-7.21 (6H, m, ArH), 5.35 (1H, s, 20-Ha), 4.71 (1H, s, 20-Hb), 4.17 (1H, app. t, *J* 3.5, 2-H), 3.66-3.61 (1H, m, 5-H), 2.55 (1H, td, *J* 13.5, 5.2, 10-Ha), 2.44-2.36 (1H, m, 13-Ha), 2.30 (1H, s, 3-H), 2.05-1.97 (1H, m, 9-Ha), 1.95-1.86 (1H, m, 10-Hb), 1.75-1.7 (1H, m, 1-H), 1.55-1.44 (6H, m, 6-H_2, 14-Ha, 18-H_3), 1.34 (3H, s, 16-H_3 or 17-H_3), 1.30-1.22 (1H, m, 9-Hb), 1.18-1.10 (1H, m, 13-Hb), 0.99 (9H, s, OSi^t*Bu*), 0.90 (3H, s, 16-H_3 or 17-H_3), 0.84 (3H, s, 19-H_3), 0.82-0.75 (2H, m, 7-Hb, 14-Hb); ^{13}C NMR (125 MHz, $CDCl_3$) 155.7 (C), 137.6 (C), 135.8 (CH), 135.7 (CH), 134.6 (C), 129.5 (CH), 128.3 (CH), 127.4 (CH), 104.29 (CH_2), 83.5 (CH), 76.0 (CH), 51.5 (CH), 43.9 (CH), 39.9 (C), 39.1 (CH_2), 38.7 (C), 38.0 (CH_2), 33.44 (CH_2), 32.58 (CH_3), 28.9 (CH_2), 27.1 (CH_3), 26.0 (CH_3), 24.8 (CH_2), 21.5 (CH_3), 22.7 (CH_2), 19.4 (C), 0.80 (CH_3); HRMS (ESI^+) *m/z* 565.3475 ($M+Na^+$, $C_{36}H_{50}O_2SiNa$ requires 565.3478).

Sodium Reduction

Sodium metal (2.8 mg, 122 µmol) was added portionwise to a solution of ketone **154** (4.0 mg, 7.4 µmol) in diethyl ether (1.0 mL) at -40 ˚C. After 0.5 h. ethanol (0.5 ml) was added dropwise. After 1 h. the above procedure was repeated another two times by addition of sodium followed by 0.5 h. wait and another addition of ethanol. After 1 h. additional stirring after the last addition, the reaction was quenched by dropwise addition of methanol (5 mL), followed by warming to ambient temperature. Hydrochloric acid (1M aq., 1 mL) was then added and the solution extracted with ether (3 x 2 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel

chromatography (pentane to 1:10 ether:pentane) gave the title compound **212** (1.2 mg, 30%). Data was consistent with that reported above.

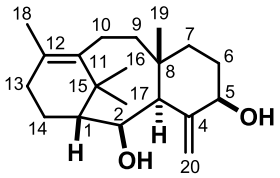
Crystallographic Data

Empirical formula	$C_{36}H_{50}O_2Si$
Formula weight	542.85
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	9.3532(3)
b/Å	14.8184(4)
c/Å	22.9582(8)
α/°	90
β/°	99.627(4)
γ/°	90
Volume/Å^3	3137.20(18)
Z	4
ρ_{calc}g/cm^3	1.149
μ/mm^{-1}	0.873
F(000)	1184.0
Crystal size/mm^3	0.227 × 0.163 × 0.09
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.13 to 148.65
Index ranges	$-10 \leq h \leq 11$, $-11 \leq k \leq 18$, $-24 \leq l \leq 28$
Reflections collected	12993
Independent reflections	6227 [R_{int} = 0.0325, R_{sigma} = 0.0377]
Data/restraints/parameters	6227/10/360
Goodness-of-fit on F^2	1.077
Final R indexes [I>=2σ (I)]	R_1 = 0.0692, wR_2 = 0.1645

Final R indexes [all data] $R_1 = 0.0751$, $wR_2 = 0.1690$

Largest diff. peak/hole / e $Å^{-3}$ 0.52/-0.36

(±)-5β,2β-hydroxy-taxa-4(20),11(12)-diene (**213**)



Sodium/IPA reduction

Sodium metal (14.0 mg, 693 µmol) was added in 5 equal portions over 1 h to a solution of ketone **201** (6.0 mg, 19.8 µmol) in isopropanol (1.0 mL) at 80 ˚C under argon. After stirring for 3 h. the reaction was not complete. A further addition of sodium metal (14.0 mg, 693 µmol) was added in 5 equal portions over 30 min. 30 min after the last addition the solution had solidified. Isopropanol (2.0 mL) was added followed by saturated aqueous ammonium chloride (4 mL) and the solution extracted with ether (3 x 2 mL). The combined organic layers were washed with water (5 mL), brine (5 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:2.5 ether:petrol) gave the title compound **213** (2.7 mg) as a mixture with starting material **201** (**201**: **213**, 1:4). *data for starting ketone where distinguishable from the title compound. R_f 0.4 (1:2.5, ether: petrol); M.p 198-202 ˚C; ν_{max} cm^{-1} ($CHCl_3$) 3610, 3026, 3011, 2928, *1710, 1363, 909; ^1H NMR (500 MHz, $CDCl_3$) 5.18 (1H, d, *J* 1.80, 20-Ha), 5.09 (0.25H, s, 20-Ha*), 4.90 (0.25H, s, 20-Hb*), 4.88 (1H, s, 20-Hb), 4.27 (1H, d, *J* 3.8, 2-H), 3.89-3.83 (1H, m, 5-H), 3.76 (0.26H, s, 3-H*), 2.82 (1H, app. td, *J* 13.6, 5.2, 10-Ha), 2.65-2.58 (2H, m, 9-Ha, 3-H), 2.37-2.38 (1H, m, 13-Ha), 2.25-2.18 (1H, m, 10-Hb), 2.17-2.07 (1H, m, 14-Ha), 2.06-1.88 (2H, m, 6-Ha, 7-Ha), 1.79-1.71 (4H, m, 18-H_3, 13-Hb), 1.63 (3H, s, 16-H_3 or 17-H_3), 1.57-1.46 (1H, m, 6-Hb), 1.40-1.34 (1H, m, 9-Hb), 1.31 (0.83H, s, 16-H_3 or 17-H_3*), 1.15 (0.83H, s, 16-H_3 or 17-

H_3*), 1.14-1.08 (2H, m, 14-Hb, 7-Hb), 1.08 (3H, s, 16-H_3 or 17-H_3), 0.98 (3H, s, 19-H_3), 0.96 (0.83, s, 19-H_3*); ^{13}C NMR (126 MHz, $CDCl_3$) 213.4 (C)* 165.6 (C), 137.8 (C), 128.3 (C), 102.9 (CH_2), 83.4 (CH), 74.2 (CH), 51.8 (CH), 44.2 (CH), 39.9 (C), 39.4 (CH), 38.8 (C), 33.2 (CH_2), 32.7 (CH_3), 29.1 (CH_2), 26.3 (CH_3), 26.2 (CH_3), 25.1 (CH_2), 22.9 (CH_2), 21.8 (CH_3); HRMS (ESI$^+$) *m/z* 327.2290 (M+Na^+, $C_{20}H_{32}O_2Na$ requires 327.2295).

Crystallographic Data

Empirical formula	$C_{20}H_{32}O_2$
Formula weight	304.45
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	7.4996(4)
b/Å	14.3479(10)
c/Å	31.6938(16)
α/°	90
β/°	95.361(5)
γ/°	90
Volume/Å^3	3395.4(3)
Z	8
ρ_{calc}g/cm^3	1.191
μ/mm^{-1}	0.572
F(000)	1344.0
Crystal size/mm^3	0.193 × 0.043 × 0.025
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.33 to 133.188
Index ranges	$-8 \leq h \leq 8$, $-17 \leq k \leq 17$, $-3 \leq l \leq 37$
Reflections collected	5935
Independent reflections	5935 [R_{int} = ?, R_{sigma} = 0.0625]
Data/restraints/parameters	5935/17/410

Goodness-of-fit on F^2 1.173

Final R indexes [I>=2σ (I)] $R_1 = 0.1137$, $wR_2 = 0.2861$

Final R indexes [all data] $R_1 = 0.1374$, $wR_2 = 0.2975$

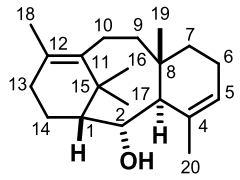
Largest diff. peak/hole / e $Å^{-3}$ 0.52/-0.42

Sodium/Ether Reduction

Sodium metal (4.0 mg, 164 µmol) was added portionwise to a solution of ketone **201** (3.0 mg, 9.9 µmol) in diethyl ether (0.75 mL) at -40 ˚C. After 0.5 h. ethanol (0.30 ml) was added dropwise. After 1 h. the above procedure was repeated another two times by addition of sodium followed by 0.5 h. wait and another addition of ethanol. After 1 h. additional stirring after the last addition, the reaction was quenched by dropwise addition of methanol (5 mL), followed by warming to ambient temperature. Hydrochloric acid (1 M aq., 3 mL) was then added and the solution extracted with ether (3 x 3 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo* to give the crude product (1 mg) as a colourless oil. ^{1}H NMR of the crude product showed 1:1.3 ratio of starting ketone **201**: title compound **213**. Purification by silica gel chromatography (pentane to 1:10 ether:pentane) was unable to isolate product from starting material.

Data for the title compound in the crude product was consistent with that reported above.

(±)-2α-hydroxy-taxa-(4,5)-(11,12)-diene (**171**)

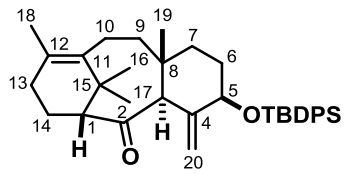


Sodium metal (28.0 mg, 1.35 mmol) was added in 5 equal portions over 1 h to a solution of ketone **137** (11.0 mg, 38.4 µmol) in isopropanol (384 µL) at 80 ˚C under argon. After

stirring for 3 h. saturated aqueous ammonium chloride (5 mL) was added and the solution extracted with ether (3 x 5 mL). The combined organic layers were washed with water (2 mL), brine (3 mL), dried ($MgSO_4$) and concentrated in *vacuo* to afford the title compound **171** (4.8 mg, 43%) as a colourless oil. R_f 0.3 (1:4, ether: petrol); ν_{max} cm^{-1} ($CHCl_3$) 3010, 2921, 1460, 1232, 1014, 785; ^1H NMR (500 MHz, $CDCl_3$) 5.62 (1H, app. d, *J* 7.04, 5-H), 4.22 (1H, s, 2-H), 2.62 (1H, br. s, 3-H), 2.60-2.53 (1H, m, 10-Ha), 2.40-2.32 (1H, m, 13-Ha), 2.24-2.16 (1H, m, 10-Hb), 2.13-2.02 (1H, m, 6-Ha), 2.02-1.89 (6H, m, 14-H_2, 20-H_3, 13-Hb), 1.87-1.76 (2H, m, 6-Hb, 1-H), 1.68 (3H, s, 18-H_3), 1.60-1.54 (1H, m, 7-Ha), 1.50-1.37 (5H, m, 16-H_3 or 17-H_3, 9-H_2), 1.27-1.21 (1H, m, 7-Hb), 1.08 (3H, s, 16-H_3 or 17-H_3), 1.04 (3H, s, 19-H_3); ^{13}C NMR (126 MHz, $CDCl_3$) 136.2 (C), 136.1 (C), 131.0 (C), 126.3 (CH), 72.5 (CH), 53.0 (CH), 46.8 (CH), 42.0 (CH_2), 41.5 (CH_2), 38.5 (C), 37.8 (C), 30.7 (CH_2), 29.5 (CH_2), 27.0 (CH_3), 26.8 (CH_3), 24.1 (CH_3), 22.6 (CH_3), 22.3 (CH_2), 21.7 (CH_3) 18.3 (CH_2); HRMS (ESI^+) *m/z* 311.2337 ($M+Na^+$, $C_{20}H_{32}ONa$ requires 311.2351).

Data consistent with that previously reported.[78]

Attempted Acetylation of C2 Alcohol (Oppenauer Oxidation) (**154**)

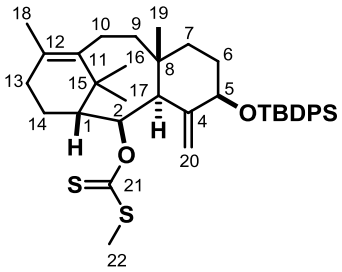


KHMDS (0.5 M in PhMe, 442 µL, 221 µmol) was added dropwise to a solution of alcohol **212** (20.0 mg, 36.8 µmol) in THF (200 µL) at -15 ˚C. The reaction was stirred for 10 min at -15 ˚C before being allowed to warm to ambient temperature and stirred for 30 min. The reaction was then cooled to -15 ˚C and freshly distilled acetyl chloride (8.0 µL, 110 µmol) added dropwise. After 10 min at -15 ˚C the solution was allowed to warm to ambient temperature and stirred for 1 h. Saturated aqueous sodium hydrogen carbonate (2 mL) was added and the resulting solution extracted with ether (3 x 5 mL). The combined

organic layers were dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (pentane to 1:40 ether:petrol) gave the title compound **154** (10.0 mg, 50%) as a colourless oil.

All data was consistent with that previously reported.

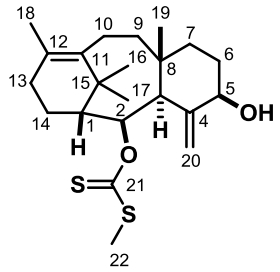
(±)-5β-(tert-butyldiphenylsilyloxy)-taxa-4(20),11(12)-dien-2β-*O*-methylxanthate (**219**)



KHMDS (830 µL of a 0.5 M solution in toluene, 414 µmol) was added dropwise to a solution of alcohol **212** (45.0 mg, 82.9 µmol) and carbon disulphide (50.0 µL, 829 µmol) in THF (1.7 mL) at -78 ˚C. The reaction was stirred for 5 min at -78 ˚C before allowing to warm to ambient temperature and stirring for 1 h. Methyl iodide (26.0 µL, 414 µmol) was added dropwise and the reaction stirred for 1 h. Water (3 mL) was then added and the aqueous layer extracted with ether (3 x 2 mL). Combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. Filtration through a short plug of silica and washing the plug with hexane afforded the title compound **219** (46.0 mg, 89%) as a yellow gum. R_f 0.8 (1:4, ether : petrol); ν_{max} cm^{-1} ($CHCl_3$) 2992, 2947, 2850, 1462, 1430, 1391, 1115, 1102, 1060, 904; ^1H NMR (400 MHz, $CDCl_3$) 7.75-7.66 (4H, m, ArH), 7.48-7.34 (6H, m, ArH), 6.04 (1H, d, *J* 4.0, 2-H), 5.47 (1H, s, 20-Ha), 4.86 (1H, s, 20-Hb), 3.78-3.73 (1H, m, 5-H), 2.79-2.66 (6H, m, 3-H, 10-Ha, 22-H_3), 2.58-2.47 (1H, m, 9-Ha), 2.33 (1H, dd, *J* 9.0, 4.0, 1-H), 2.22-2.13 (2H, m, 10-Hb, 13-Ha), 2.10-1.98 (1H, m, 7-Ha), 1.73-1.55 (3H, m, 6-H_2, 14-Ha), 1.47 (3H, s, 18-H_3), 1.43-1.32 (5H, m, 16-H_3 or 17-H_3, 13-Hb, 9-Hb), 1.11 (9H, s, OSi^t*Bu*), 1.06-0.92 (5H, m, 7-Hb, 14-Hb, 16-H_3 or 17-H_3), 0.9 (3H, s, 19-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) 214.8 (C), 153.8 (C), 137.5 (C), 135.8 (CH), 135.7 (CH), 134.5 (C), 133.9 (C), 129.6

(CH), 128.9 (C), 127.5 (CH), 105.9 (CH_2), 92.5 (CH), 75.9 (CH), 45.9 (CH), 43.9 (CH), 40.4 (CH_2), 39.2 (CH_2), 38.1 (C), 37.9 (C), 33.3 (CH_2), 32.1 (CH_3), 28.7 (CH_2), 27.12 (CH_3), 26.0 (CH_3), 25.5 (CH_3), 25.0 (CH_2) 21.6 (CH_2), 21.6 (CH_3), 19.5 (CH_3); HRMS (FDI^+) *m/z* 632.3147 (M^+, $C_{38}H_{52}O_2S_2Si$ requires 632.3172).

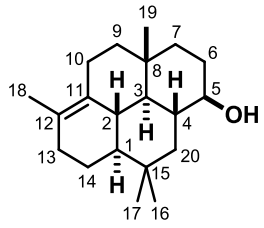
(±)-5β-hydroxy-taxa-4(20),11(12)-dien-2β-*O*-methylxanthate (**220**)



TBAF·$3H_2O$ (203 mg, 644 µmol) was added to a solution of silyl ether **219** (100 mg, 161 µmol) in THF (0.5 mL) at ambient temperature. The reaction was stirred for 26 h. Water (3 mL) was added and the solution extracted with ether (3 x 2 mL). The combined organic layers were washed with water (3 mL), brine (2 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:2, ether : petrol) afforded the title compound **220** (41 mg, 65%) as a yellow oil. R_f 0.2 (1:2.5, ether : petrol); ν_{max} cm^{-1} ($CHCl_3$) 3329, 2998, 2923, 2885, 1459, 1427, 1378, 1238, 1055, 1002; ^{1}H NMR (400 MHz, $CDCl_3$) 6.11 (1H, d, *J* 4.0, 2-H), 5.12 (1H, s, 20-Ha), 4.86 (1H, s, 20-Hb), 3.9-3.82 (1H, m, 5-H), 2.97 (1H, s, 3-H), 2.86 (1H, app. td, *J* 13.5, 5.3, 10-Ha), 2.66-2.56 (4H, m, 22-H_3, 9-Ha), 2.38 (1H, dd, *J* 9.5, 4.0, 1-H), 2.36-2.21 (2H, m, 10-Hb, 13-Ha), 2.18-2.06 (1H, m, 14-Ha), 2.05-1.95 (2H, m, 6-Ha, 7-Ha), 1.86-1.76 (4H, m, 18-H_3, 13-Hb), 1.54-1.42 (5H, m, 16-H_3 or 17-H_3, 6-Hb, 9-Hb), 1.28-1.12 (2H, m, 14-Hb, 7-Hb), 1.03 (3H, s, 16-H_3 or 17-H_3), 0.90 (3H, s, 19-H_3); ^{13}C NMR (126 MHz, $CDCl_3$) 214.8 (C), 154.6 (C), 137.7 (C) 128.8 (C), 104.3 (CH_2), 92.2 (CH), 74.0 (CH), 46.0 (CH), 44.3 (CH), 40.4 (CH_3), 39.4 (CH_2), 38.2 (C), 38.0 (CH_2), 32.9 (CH_2), 32.1

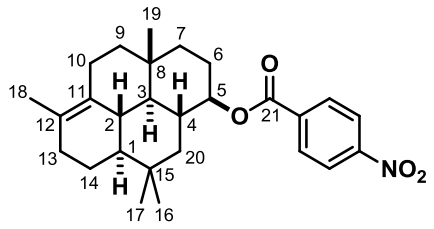
(CH_3), 29.0 (CH_2), 26.0 (CH_3), 25.6 (CH_3), 25.1 (CH_2), 21.8 (CH_2), 19.5 (CH_3); HRMS (ESI^+) *m/z* 417.1895 ($M+Na^+$, $C_{22}H_{34}O_2S_2Na$ requires 417.1898).

(±)-5β-hydroxy-15,8,12-tetramethyltetradecahydropyr-(11,12)-ene (**222**)



A round bottomed flask with reflux condenser was charged with xanthate **220** (19.0 mg, 48.2 μmol), tributyltin hydride (28.0 μL, 96.4 μmol), AIBN (0.8 mg, 4.8 μmol) and freshly distilled benzene (482 μL). This solution was subjected to three freeze-pump-thaw cycles before placing under argon and heated at reflux for 2 h. The reaction was concentrated in *vacuo* and the residue purified by silica gel chromatography (pentane rising to 1:2, ether: pentane) to afford the title compound **222** (8.0 mg, 58%) as a colourless oil. R_f 0.3 (1:2, ether: petrol); ν_{max} cm^{-1} ($CHCl_3$) 3619, 3629, 3013, 2944, 2919, 2883, 1716, 1658, 1470, 1448, 1381, 1365, 1309, 1089, 1026; ^1H NMR (500 MHz, $CDCl_3$) (product contains impurities, signals are marked 'impurity') 2.89 (1H, ddd, *J* 14.9, 10.0, 5.1, 5-H), 2.53 (1H, ddd, *J* 15.2, 4.6, 2.5, 10-Ha), 2.09-1.99 (1H, m, 13-Ha), 1.97-1.84 (3H, m, 10-Hb, 13-Hb, 20-Ha), 1.80-1.72 (1H, m, 2-H), 1.70-1.54 (7H, m, 14-Ha, 18-H_3, 6-Ha, impurity), 1.53-1.43 (1H, m, 6-Hb), 1.38-1.24 (5H, m, 4-H, 9-Ha, 7-Ha, impurity), 1.11-0.96 (5H, m, 14-Hb, 9-Hb, 7-Hb, impurity), 0.95-0.89 (4H, m, 16-H_3 or 17-H_3, 1-H), 0.85 (3H, s, 19-H_3), 0.78 (3H, s, 16-H_3 or 17-H_3), 0.45-0.40 (2H, m, 3-H, impurity); ^{13}C NMR (126 MHz, $CDCl_3$) 130.8 (C), 124.5 (C), 76.1 (CH), 51.5 (CH), 48.8 (CH), 45.2 (CH_2), 40.8 (CH_2), 39.5 (CH_2), 39.1 (CH), 37.7 (CH), 33.6 (CH_2), 32.3 (C), 32.0 (C), 30.9 (CH_2), 30.5 (CH_3), 27.8 (CH_2, impurity), 26.8 (CH_2, impurity), 24.2 (CH_2), 23.0 (CH_2), 20.0 (CH_3), 19.1 (CH_3), 16.9 (CH_2, impurity), 16.3 (CH_3), 13.4 (CH_3, impurity); HRMS (ESI^+) *m/z* 311.2338 ($M+Na^+$, $C_{20}H_{32}ONa$ requires 311.2345).

(±)-15,8,12-tetramethyltetradecahydropyr-(11,12)-en-5β-nitrobenzoate (**223**)

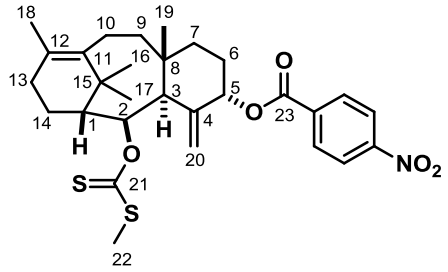


N,N-Dimethylaminopyridine (400 µg, 3.0 µmol) and *p*-nitrobenzoic acid (5.0 mg, 30.0 µg) were added to a solution of alcohol **222** (6.0 mg, 21 µmol) in CH_2Cl_2 (150 µL) at ambient temperature. *N,N'*-dicyclohexylcarbodiimide (6.2 mg, 30 µmol) was added and the reaction stirred for 24 h. Water (2 mL) was added and the solution extracted with ether (3 x 2 mL). The combined organic layers were washed with brine (2 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:2, ether : petrol) afforded the title compound **223** (4.4 mg, 48%) as a yellow solid. Slow evaporation of a solution in pentane gave a crystalline sample. R_f 0.6 (1:1.5, ether : petrol); M.p 179-181 ˚C (decomp); ν_{max} cm^{-1} ($CHCl_3$) 3015, 2922, 2852, 1718, 1529, 1349, 1279, 1117, 1104; ^1H NMR (500 MHz, $CDCl_3$) 8.35-8.33 (4H, m, ArH), 4.71 (1H, ddd, *J* 11.3, 10.2, 5.1, 5-H), 2.64-2.56 (1H, m, 10-Ha), 2.15-1.72 (7H, m, 13-Ha, 13-Hb, 10-Hb, 6-Ha, 6-Hb, 14-Ha, 2-H, 4-H), 1.65 (3H, s, 18-H_3), 1.59 (1H, m, 20-Ha), 1.54-1.45 (2H, m, 7-Ha, 9-Ha), 1.35-1.23 (4H, m, 7-Hb, impurity), 1.16-1.06 (2H, m, 14-Hb, 9-Hb, 19-H_3), 1.03-0.95 (1H, m, 1-H), 0.92-0.83 (6H, m, 16-H_3, 17-H_3), 0.77 (1H, app. t, *J* 11.5, 3-H); ^{13}C NMR (126 MHz, $CDCl_3$) 164.5 (C), 150.5 (C), 136.3 (C), 130.8 (CH), 130.6 (C), 125.7 (C), 123.6 (CH), 80.6 (CH), 51.9 (CH), 48.8 (CH), 45.1 (CH_2), 40.6 (CH_2), 39.1 (CH_2), 37.7 (CH), 36.4 (CH), 34.0 (C), 33.6 (CH_2), 32.3 (C), 30.5 (CH_3), 27.2 (CH_2), 23.9 (CH_2), 23.0 (CH_2), 20.2 (CH_3), 19.3 (CH_3), 16.6 (CH_3); HRMS (FD^+) *m/z* 437.2563 (M^+,$C_{27}H_{35}NO_4$ requires 437.2561).

Crystallographic Data

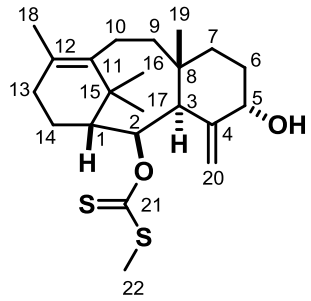
Empirical formula	$C_{29.5}H_{41}NO_4$
Formula weight	473.63
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	16.9860(6)
b/Å	6.1603(2)
c/Å	27.0282(9)
α/°	90
β/°	95.691(3)
γ/°	90
Volume/Å^3	2814.26(16)
Z	4
ρ_{calc}g/cm^3	1.118
μ/mm^{-1}	0.578
F(000)	1028.0
Crystal size/mm^3	0.215 × 0.128 × 0.047
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	10.468 to 148.67
Index ranges	$-18 \leq h \leq 20$, $-7 \leq k \leq 7$, $-33 \leq l \leq 29$
Reflections collected	20759
Independent reflections	5679 [R_{int} = 0.0302, R_{sigma} = 0.0253]
Data/restraints/parameters	5679/0/293
Goodness-of-fit on F^2	1.053
Final R indexes [I>=2σ (I)]	R_1 = 0.0464, wR_2 = 0.1295
Final R indexes [all data]	R_1 = 0.0576, wR_2 = 0.1405
Largest diff. peak/hole / e Å^{-3}	0.23/-0.30

(±)-2β-*O*-methyl-xanthate-taxa-4(20),11(12)-dien-5α-*p*-nitrobenzoate (**228**)



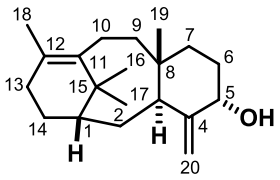
Diethylazodicarboxylate (38.0 µL, 224 µmol) was added to a solution of the alcohol **220** (24.0 mg, 61.0 µmol), triphenylphosphine (64.0 mg, 224 µmol) and *p*-nitrobenzoic acid (41.0 mg, 244 µmol) in THF (0.6 mL) at 0 ˚C. The reaction was stirred for 10 min and then allowed to warm to ambient temperature and stirred for 1 h. Water (2 mL) was added and the solution extracted with ether (3 x 3 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (4 mL) dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:9, ether: petrol) afforded the title compound **228** (21.0 mg, 63%) as a yellow solid. R_f 0.5 (1:9, ether: petrol); M.p 180-182 ˚C (decomp); ν_{max} cm^{-1} ($CHCl_3$) 3061, 3038, 3021, 1719, 1425, 1347, 1330, 1273, 1221, 1057; ^{1}H NMR (400 MHz, $CDCl_3$) 8.32 (2H, d, *J* 8.9, ArH), 8.20 (2H, d, *J* 8.9, ArH), 6.07 (1H, d, *J* 4.0, 2-H), 5.53 (1H, s, 5-H), 5.33 (1H, s, 20-Ha), 5.09 (1H, s, 20-Hb), 3.44 (1H, s, 3-H), 2.87 (1H, app. td, *J* 13.5, 5.3, 10-Ha), 2.71-2.60 (4H, m, 22-H_3, 9-Ha), 2.44 (1H, dd, *J* 9.4, 4.0, 1-H), 2.16-2.36 (3H, m, 10-Hb, 13-Ha, 14-Ha), 2.12-2.00 (3H, m, 6-H_2, 7-Ha), 1.74 (3H, s, 18-H_3), 1.52-1.42 (5H, m, 16-H_3 or 17-H_3, 13-Hb, 9-Hb), 1.21-1.06 (2H, m, 7-Ha, 14-Hb), 1.00 (3H, s, 16-H_3 or 17-H_3), 0.98 (3H, s, 19-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) 214.9 (C), 164.5 (C), 150.5 (C), 148.6 (C), 137.7 (C), 136.3 (C), 130.7 (CH), 128.4 (C), 123.5 (CH), 115.5 (CH_2), 91.5 (CH), 79.3 (CH), 46.0 (CH), 41.7 (CH), 40.5 (C), 40.1 (CH_2), 38.0 (C), 36.2 (CH_2), 31.8 (CH_3), 29.0 (CH_2), 28.0 (CH_2), 26.0 (CH_3), 25.3 (CH_2), 25.2 (CH_3), 21.9 (CH_2), 21.5 (CH_3), 19.5 (CH_3); HRMS (ESI^+) *m/z* 566.2006 ($M+Na^+$, $C_{29}H_{37}NO_5S_2Na$ requires 566.2011).

(±)-5α-hydroxy-taxa-4(20),11(12)-dien-2β-*O*-methylxanthate (**229**)



Lithium hydroxide monohydrate (2.0 mg, 44.2 µmol) was added to a solution of ester **228** (12.0 mg, 22.1 µmol) in THF: water (2:1, 200 µL) at ambient temperature. The reaction was stirred for 14 h. The reaction was diluted with ether (1 mL) and water (1 mL). The layers were separated and the aqueous layer extracted with ether (3 x 1 mL). The combined organic layers were washed with brine (1 mL), dried ($MgSO_4$) and concentrated in *vacuo* to afford the title compound **229** (6.0 mg, 69%) as a yellow oil. R_f 0.4 (1:2, ether: petrol); ν_{max} cm^{-1} ($CHCl_3$) 3685, 3604, 3036, 3007, 2924, 1601, 1463, 1213, 1056; ^{1}H NMR (500 MHz, $CDCl_3$) 6.09 (1H, d, *J* 4.1, 2-H), 4.99 (1H, s, 20-Ha), 4.82 (1H, d, *J* 1.5, 20-Hb), 4.27 (1H, app. t, *J* 2.9, 5-H), 3.79 (1H, s, 3-H), 2.93 (1H, app. td, *J* 13.5, 5.4, 10-Ha), 2.63 (3H, s, 22-H_3), 2.64-2.55 (1H, m, 9-Ha), 2.40-2.21 (4H, m, 1-H, 7-Ha, 13-Ha, 10-Hb), 2.19-2.08 (1H, m, 14-Ha), 1.98-1.89 (1H, m, 13-Hb), 1.87 (3H, s, 18-H_3), 1.85-1.69 (2H, m, 6-H_2), 1.45 (3H, s, 16-H_3 or 17-H_3) 1.45-1.37 (1H, m, 9-Hb), 1.29-1.23 (1H, m, 14-Hb), 1.04 (3H, s, 16-H_3 or 17-H_3), 1.00-0.93 (1H, m, 7-Hb), 0.89 (3H, s, 19-H_3); ^{13}C NMR (126 MHz, $CDCl_3$) 215.1 (C), 154.8 (C), 136.6 (C), 129.8 (C), 110.3 (CH_2), 92.2 (CH), 74.6 (CH), 46.1 (CH), 40.8 (C), 39.9 (CH_2), 39.5 (CH), 38.0 (C), 35.2 (CH_2), 32.2 (CH_3), 30.0 (CH_2), 28.9 (CH_2), 26.0 (CH_3), 25.2 (CH_2), 25.0 (CH_3), 22.1 (CH_2), 21.3 (CH_3), 19.5 (CH_3); HRMS (ESI^+) *m/z* 417.1891 ($M+Na^+$, $C_{22}H_{34}O_2S_2Na$ requires 417.1898).

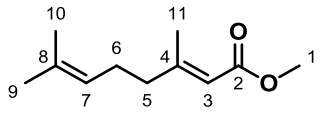
(±)-5α-hydroxytaxa-(4,20)-(11,12)-diene (**35**)



A round bottomed flask with reflux condenser was charged with xanthate **229** (6.0 mg, 15.2 µmol), tributyltin hydride (45.0 µL, 152 µmol), AIBN (<1 mg, approx. 1.5 µmol) and freshly distilled benzene (152 µL). This solution was subjected to three freeze-pump-thaw cycles before placing under argon and heated at reflux for 2 h. The reaction was concentrated in *vacuo* and the residue purified by silica gel chromatography (pentane rising to 1:2, ether: pentane) to afford the title compound **35**(1.5 mg, 34%) as a colourless oil. R_f 0.3 (1:2, ether: petrol); ν_{max} cm^{-1} ($CHCl_3$) 3612, 2998, 2967, 2928, 2857, 1666, 1447, 1380, 986; ^1H NMR (500 MHz, $CDCl_3$) 4.94 (1H, br. s, 20-Ha), 4.65 (1H, br. s, 20-Hb), 4.26 (1H, br. s, 5-H), 3.32 (1H, m, 3-H), 2.85 (1H, app. td, *J* 13.5, 5.3, 10-Ha), 2.38-2.22 (2H, m, 13-Ha, 7-Ha), 2.12-1.97 (3H, m, 9-Ha, 10-Hb, 14-Ha), 1.94-1.86 (1H, m, 13-Hb), 1.84 (3H, s, 18-H_3) 1.79-1.73 (3H, m, 6-Ha, 1-H, O*H*), 1.67-1.56 (2H, m, 2-H), 1.35 (3H, s, 16-H_3 or 17-H_3), 1.30-1.18 (3H, m, 9-Hb, 6-Hb, 14-Hb), 1.05 (3H, s, 16-H_3 or 17-H_3), 1.02-0.97 (1H, m, 7-Hb), 0.61 (3H, s, 19-H_3); ^{13}C NMR (126 MHz, $CDCl_3$) 155.9 (C), 136.9 (C), 130.7 (C), 108.8 (CH_2) 74.7 (CH), 43.6 (CH), 40.1 (C), 40.0 (CH_2), 39.3 (C), 35.5 (CH), 32.7 (CH_2), 30.9 (CH_3), 30.2 (CH_2), 30.2 (CH_2), 28.1 (CH_2), 25.5 (CH_3), 24.8 (CH_2), 23.0 (CH_2), 22.2 (CH_3), 21.4 (CH_3); HRMS (EI^+) *m/z* 288.2447 (M^+, $C_{20}H_{32}O$ requires 288.2448).

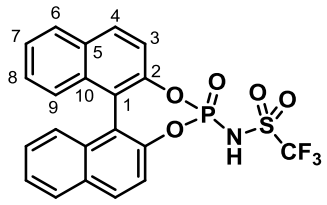
Data consistent with that previously reported.[74]

Methyl Geranoate (**246**)



Methyl iodide (2.77 mL, 44.6 mmol) was added dropwise to a solution of geranoic acid (5.00 g, 29.7 mmol) and potassium carbonate (6.16 g, 44.6 mmol) in DMF (30.0 mL) at ambient temperature. The reaction was stirred for 24 h. before the addition of water (200 mL). The resulting solution was extracted with ether (3 x 200 mL) and the combined organic layers washed with water (2 x 200 mL), brine (100 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:4, ether: petrol) to give the title compound **246** (5.00 g, 92%) as a colourless oil; R_f 0.80 (1:4, ether: petrol); ν_{max} ($CHCl_3$)/cm^{-1} 2970, 2950, 2917, 2857, 1710, 1648, 1347, 1241, 1151; ^1H NMR (400 MHz, $CDCl_3$) 5.70 (1H, br. s, 3-H), 5.09 (1H, br. s, 7-H), 3.70 (3H, s, 1-H_3), 2.18 (7H, br. s, 6-H_2, 5-H_2, 11-H_3), 1.71 (3H, s, 9-H_3 or 10-H_3), 1.63 (3H, s, 9-H_3 or 10-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 167.3 (C), 160.5 (C), 132.5 (C), 122.9 (CH), 115.2 (CH), 50.8 (CH_3), 41.9 (CH_2), 26.1 (CH_2), 26.0 (CH_3), 18.8 (CH_3), 17.6 (CH_3); HRMS *m/z* (ESI^+) 205.1206 (M + Na^+, $C_{11}H_{18}O_2Na$ requires 205.1199).

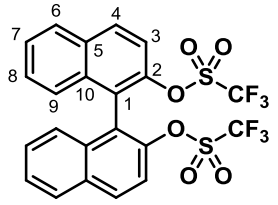
1,1'-binaphthyl-2,2'-phosphoryltriflimide (**252**)



Oxalyl chloride (1.23 mL, 14.4 mmol) was added dropwise to a stirring suspension of BINOL phosphoric acid (1.00 g, 2.87 mmol) and DMF (20.0 µL, 260 µmol) in CH_2Cl_2 (15 mL) at 0 ˚C. The reaction was stirred for 24 h. before concentration in *vacuo*. The residue was

dissolved in acetonitrile (32.6 mL) and cooled 0 ˚C. Trifluoromethylsulfonamide (857 mg, 5.75 mmol) was added to the solution followed by DMAP (700 mg, 5.75 mmol) and triethylamine (799 μL, 5.75 mmol). The reaction was allowed to warm to ambient temperature and stirred for 8 h. Concentration in *vacuo* followed by purification by silica gel chromatography (1:1, ether: CH_2Cl_2) gave the title compound **252** (430 mg, 30%) as a brown solid. M.p 120-122 ˚C (decomp); ν_{max} (ATR)/cm^{-1} 1282, 1187, 1155, 1093, 1068, 960; ^{1}H NMR (500 MHz, d^6-DMSO, resonance for CF_3 not found) 8.17 (1H, d, *J* 8.8, 3-H), 8.12-8.07 (1H, m, 6-H), 7.56-7.49 (2H, m, 4-H, 7-H), 7.40-7.34 (1H, m, 8-H), 7.27-7.22 (1H, m, 9-H); ^{13}C NMR (125 MHz, d^6-DMSO) 148.8 (C), 147.7 (C), 132.1 (C), 131.4 (C), 131.1 (CH), 129.1 (CH), 127.1 (CH), 126.6 (CH), 125.8 (CH), 122.2 (CH); ^{19}F NMR (376 MHz, d^6-DMSO) -78.59; ^{31}P NMR (162 MHz, d^6-DMSO) 2.17; HRMS *m/z* (ESI$^+$) 502.0105 (M + Na^+, $C_{21}H_{13}F_3NO_5PSNa$ requires 502.0102).

1,1'-Bi-2,2'-naphthol-bis(trifluoromethanesulfonate) (**254**)

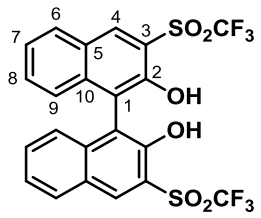


Triflic anhydride (2.59 mL, 15.4 mmol) was added dropwise to a solution of BINOL (2.00 g, 6.99 mmol) and triethylamine (2.90 mL, 20.9 mmol) in CH_2Cl_2 (17 mL) at -78 ˚C. The reaction was allowed to warm to ambient temperature and stirred for 2 h. Concentration in *vacuo* and purification by silica chromatography (1:9, EtOAc:Et_2O) gave the title compound **254** (3.38 g, 88%) as a cream solid. M.p 89-92 ˚C (lit 82-83 ˚C)[138]; ν_{max} (ATR)/cm^{-1} 1417, 1207, 1173, 1136, 955, 829; ^{1}H NMR (500 MHz, d^6-DMSO) 8.44 (1H, d, *J* 8.5, 3-H), 8.38 (1H, d, *J* 8.4, 6-H), 7.82 (1H, d, *J* 8.5, 4-H), 7.72-7.67 (1H, m, 7-H), 7.54-7.50 (1H, m, 8-H), 7.12 (1H, d, *J* 8.5, 9-H); ^{13}C NMR (125 MHz, d^6-DMSO) 145.4 (C), 133.4 (CH), 132.8 (C),

132.6 (C), 129.1 (CH), 128.9 (CH), 128.0 (CH), 126.3 (CH), 122.7 (C), 119.6 (CH), 118.0 (C, q, *J* 320.2, CF_3); ^{19}F NMR (376 MHz, d^6-DMSO) -74.63; HRMS *m/z* (ESI^+) 572.9867 ($M + Na^+$, $C_{22}H_{12}F_6O_6S_2Na$ requires 572.9877).

Data consistent with that previously reported[138]

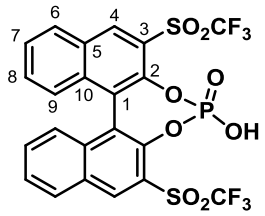
1,1'-Bi-(3,3'-bis(trifluoromethanesulfone)-2,2'-napthol (**255**)



^{n}BuLi (1.45 M in hexanes, 2.50 mL, 3.64 mmol) was added dropwise to a solution of *N,N*-isopropyl amine (659 µL, 3.78 mmol) in THF (14.5 mL) at -78 ˚C. Following addition the reaction was allowed to warm to ambient temperature and stirred for 1 h. The reaction was then cooled to -78 ˚C and BINOL bistriflate **254** (2.00 g, 3.64 mmol) in THF (14.5 mL) added dropwise. The reaction was allowed to warm to ambient temperature. In another flask ^{n}BuLi (1.45 M in hexanes, 2.50 mL, 3.64 mmol) was added dropwise to a solution of *N,N*-isopropyl amine (659 µL, 3.78 mmol) in THF (14.5 mL) at -78 ˚C. Following addition the reaction was allowed to warm to ambient temperature and stirred for 1 h. This was then added to the reaction mixture at -78 ˚C before allowing this solution to warm to ambient temperature and stirred for 1 h. Hydrochloric acid (2 M aq., 200 mL) was added and the resulting solution extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and concentrated in *vacuo*. Purification by silica gel chromatography (1:1, ether:petrol) gave a yellow solid which was recrystallized from toluene to give the title compound **255** (403 mg, 18%) as a yellow solid. M.p 75-78 ˚C; ν_{max} (ATR)/cm^{-1} 3451, 1617, 1574, 1349, 1202, 1116, 1020; ^1H NMR (500 MHz, d^6-DMSO) 10.51 (1H, br. s, OH) 8.96 (1H, s, 4-H), 8.33 (1H, d, *J* 7.9, 9-H), 7.57-7.46 (2H, m, 7-H, 8-H), 6.90

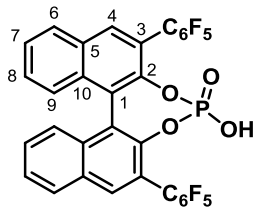
(1H, d, *J* 8.35, 6-H); ^{13}C NMR (125 MHz, d^6-DMSO) 152.5 (C), 138.6 (C), 137.9 (CH), 132.1 (CH), 131.3 (CH), 127.3 (C), 125.3 (CH), 123.8 (CH), 121.0 (C), 120.3 (C, q, *J* 327.5, CF_3) 116.1 (C); ^{19}F NMR (376 MHz, d^6-DMSO) -78.5; HRMS *m/z* (ESI$^-$) 548.9913 (M - H$^+$, $C_{22}H_{11}F_6O_6S_2$ requires 548.9907).

1,1'-Bi-(3,3'-bis(trifluoromethanesulfone)-2,2'-napthylphosphoric acid (**250**)



Phosphorus oxychloride (40.0 µL, 432 µmol) was added dropwise to a suspension of triflone **255** (170 mg, 309 µmol) in pyridine (396 µL) at ambient temperature. The reaction was heated at 95 ˚C for 1 h. After cooling to ambient temperature, water (67.0 µL, 3.71 mmol) was added and the reaction heated again at 95 ˚C for 1 h. After cooling to ambient temperature, hydrochloric acid (6 M aq., 5 mL) was added followed by CH_2Cl_2 (5 mL). This suspension was sonicated for 10 min. The layers were then separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were then washed with hydrochloric acid (6 M aq., 10 x 20 mL), brine (10 mL) and concentrated in *vacuo*. The residue was triturated with pentane to give the title compound **250** (26 mg, 14%) as a yellow solid. M.p 99-102 ˚C; ν_{max} (ATR)/cm^{-1} 1370, 1358, 1205, 1177, 1042, 1023, 981; ^{1}H NMR (500 MHz, d^6-DMSO) 9.20 (1H, s, 4-H), 8.51 (1H, d, *J* 8.3, 9-H), 7.71 (1H, app. t, *J* 7.7, 8-H), 7.64 (1H, app. t, *J* 7.7, 7-H), 7.10 (1H, d, *J* 8.5, 6-H); ^{13}C NMR (125 MHz, d^6-DMSO) 146.2 (C), 139.2 (CH), 136.4 (C), 132.6 (CH), 131.6 (CH), 129.2 (C), 127.6 (CH), 126.2 (CH), 124.0 (C), 122.4 (C), 120 (C, q, *J* 327.2, CF_3); ^{19}F NMR (376 MHz, d^6-DMSO) -80.25; ^{31}P NMR (162 MHz, d^6-DMSO) 0.52 ; HRMS *m/z* (ESI$^-$) 610.9470 (M - H$^+$, $C_{22}H_{10}F_6O_8PS_2$ requires 610.9464).

1,1'-Bi-(3,3'-pentafluorophenyl)-2,2'-napthylphosphoric acid (**249**)



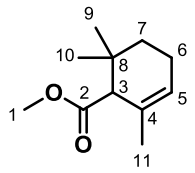
The title compound **249** was provided by Woodward and co-workers at Nottingham University, School of Chemistry. It was synthesised following the method described by Terada.[121]

M.p 103-105 ˚C; ν_{max} (ATR)/cm^{-1} 1521, 1493, 1438, 1230, 1028, 988; ^{1}H NMR (500 MHz, d^{6}-DMSO) 8.38 (1H, s, 4-H), 8.19 (1H, d, *J* 7.5, 9-H), 7.64 (1H, app. t, *J* 7.5, 8-H), 7.53 (1H, t, *J* 8.5, 7-H) 7.38 (1H, d, *J* 8.5, 6-H); ^{13}C NMR (125 MHz, d^{6}-DMSO, resonances from C_6F_5 group weak and complex in the region 145.7-136.1 ppm) 146.2 (C), 133.5 (CH), 132.7 (C), 130.6 (C), 129.5 (CH), 128.7 (CH), 126.7 (CH), 126.4 (CH), 122.5 (C), 119.3 (C); ^{19}F NMR (376 MHz, d^{6}-DMSO) -139.16 (1F, dd, *J* 24.5, 7.5), -140.07 (1F, dd, *J* 24.5, 7.5), -154 (1F, app. t, *J* 23.0), -162.75 (1F, app. td, *J* 23.0, 6.5), -163.78 (1F, app. td, *J* 24.5, 23.0, 8.0); ^{31}P NMR (162 MHz, d^{6}-DMSO) 2.28; HRMS *m/z* (ESI^-) 679.0174 ($M - H^+$, $C_{32}H_{10}F_{10}O_4O_4P$ requires 679.0163).

General Procedure for Chiral BINOL Bronsted Acid Cyclisations

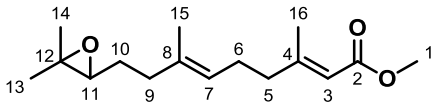
BINOL Acid (10 mol%) was added in one portion to a stirring solution of methyl geranoate (see table) in toluene (1 M in alkene). The reaction was stirred for 36 h. at ambient temperature. No product formation was observed by TLC (1:15, ether:petrol). Water was added (4 mL) and the resulting solution extracted with ether (3 x 3 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in *vacuo*. ^{1}H NMR analysis of the crude reaction mixture showed only methyl geranoate and no indication of cyclisation.

Methyl-4,8,8-trimethylcyclohex-4-ene-3-carboxylate (**247**)



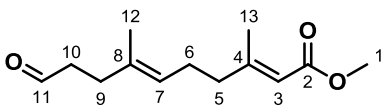
Tin tetrachloride (1 M CH_2Cl_2, 75.0 µL, 75.0 µmol,) was added dropwise to a solution of (±)-BINOL (21.0 mg, 75.0 µmol) in CH_2Cl_2 (1.0 mL) at -78 ˚C. After 5 min methyl geranoate **246** (91.0 mg, 500 µmol) was added dropwise as a solution in CH_2Cl_2 (0.5 mL). Following addition the reaction was allowed to warm to ambient temperature and stirred for 18 h. Pyridine (60.0 µL) was added followed by saturated aqueous sodium bicarbonate (10 mL). The resulting solution was extracted with ether (3 x 10 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:9, ether: petrol) to give the title compound **247** (46.0 mg, 50%) as a colourless oil; R_f 0.80 (1:4, ether: petrol); ν_{max} ($CHCl_3$)/cm^{-1} 3008, 2954, 2872, 1725, 1451, 1329, 1242, 1159; ^{1}H NMR (400 MHz, $CDCl_3$) 5.61 (1H, br. s, 5-H), 3.70 (3H, s, 1-H_3), 2.62 (1H, s, 3-H), 2.15-1.98 (2H, m, 6-H_2), 1.76-1.88 (1H, m, 7-Ha), 1.67 (3H, s, 11-H_3), 1.17-1.25 (1H, m, 7-Hb), 0.99-0.93 (6H, m, 9-H_3, 10-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 174.4 (C), 129.5 (C), 123.7 (CH), 56.9 (CH), 51.3 (CH_3), 31.8 (C), 31.0 (CH_2), 27.5 (CH_3), 27.1 (CH_3), 22.9 (CH_3), 22.7 (CH_2); HRMS *m/z* (ESI^+) 205.1208 (M + Na^+, $C_{11}H_{18}O_2Na$ requires 205.1199).

(±)-Methyl-11,12-epoxy-farnesate (**256**)



Potassium carbonate (2.85 g, 20.7 mmol) was added to a stirring solution of bromohydrin **142** (2.76 g, 7.95 mmol) in methanol (40 mL). The reaction was stirred for 12 h. Water (200 mL) was added and the solution extracted with ether (3 x 100 mL). The combined organic layers were washed with water (20 mL), brine (50 mL), dried ($MgSO_4$) and concentrated in *vacuo* to give the title compound **256** (2.09 g, 99%) as a colourless oil. R_f 0.6 (1:1, ether: petrol); ν_{max} (ATR)/cm^{-1} 3028, 3010, 2966, 1711, 1649, 1437, 1380, 1237, 1154, 907; ^{1}H NMR (400 MHz, $CDCl_3$) 5.67 (1H, s, 3-H), 5.14 (1H, br. s, 7-H), 3.69 (3H, s, 1-H_3), 2.73-2.67 (1H, m, 11-H), 2.21-2.11 (10H, m, 5-H_2, 6-H_2, 9-H_2, 10-Ha, 16-H_3), 1.66-1.57 (4H, m, 10-Hb, 15-H_3), 1.31 (3H, d, *J* 4.5, 14-H_3 or 13-H_3), 1.27 (3H, d, *J* 4.5, 14-H_3 or 13-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 167.3 (C), 135.4 (C), 124.4 (CH), 123.6 (C), 115.4 (CH), 64.2 (CH), 58.5 (C), 50.9 (CH_3), 41.1 (CH_2), 28.6 (CH_2), 27.5 (CH_2), 25.8 (CH_2), 25.0 (CH_3), 23.4 (CH_3), 18.9 (CH_3), 16.1 (CH_3); HRMS *m/z* (ESI^+) 289.1776 (M + Na^+, $C_{16}H_{26}O_3Na$ requires 289.1780).

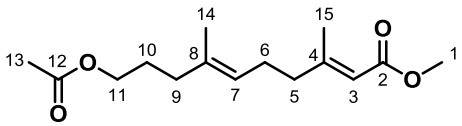
Methyl-4,8-dimethyl-11-oxodeca-3,7-dienoate (**257**)



Epoxide **256** (2.09 g, 7.85 mmol) was added dropwise as a solution in ether (26 mL) to a suspension of periodic acid (2.32 g, 10.2 mmol) in ether (56 mL) at ambient temperature. The reaction was stirred for 1 h. then washed with water (200 mL), brine (50 mL), dried ($MgSO_4$) and concentrated in *vacuo* to afford the title compound **257** (1.69 g, 96%) as a

colourless oil. R_f 0.5 (1:1, ether: petrol); ν_{max} (ATR)/cm^{-1} 3028, 3019, 2950, 1718, 1649, 1437, 1235, 1154; ^{1}H NMR (400 MHz, $CDCl_3$) 9.79 (1H, d, *J* 13.6, 11-H), 5.69 (1H, br. s, 3-H), 5.19-5.12 (1H, m, 7-H), 3.72 (3H, s, 1-H_3) 2.57-2.51 (2H, m, 10-H_2), 2.40-2.31 (2H, m, 9-H_2), 2.24-2.16 (7H, m, 5-H_2, 6-H_2, 13-H_3) 1.71 (3H, s, 12-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 202.4 (CH), 167.2 (C), 134.2 (C), 125.1 (CH), 124.0 (C), 115.4 (CH), 50.8 (CH_3), 42.2 (CH_2), 40.9 (CH_2), 31.8 (CH_2), 25.8 (CH_2), 23.0 (CH_3), 18.8 (CH_3); HRMS *m/z* (ESI^+) 247.1308 (M + Na^+, $C_{13}H_{20}O_3Na$ requires 247.1305).

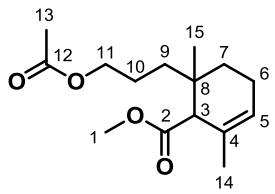
Methyl-11-acetoxy-4,8-dimethyldeca-3,7-dienoate (**258**)



Sodium borohydride (285 mg, 7.53 mmol) was added portionwise to a solution of aldehyde **257** (1.69 g, 7.53 mmol) in methanol (30 mL) at ambient temperature. The reaction was stirred for 10 min. then cooled to 0 ˚C and water (200 mL) added. The resulting solution was allowed to warm to ambient temperature and extracted with ether (4 x 50 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated in *vacuo* to give the alcohol product (1.39 g, 82%) as a colourless oil. R_f 0.2 (1:1, ether: petrol); ν_{max} (ATR)/cm^{-1} 3623, 3524, 3034, 3012, 2949, 1711, 1649, 1437, 1385, 1204, 1153; ^{1}H NMR (400 MHz, $CDCl_3$) 5.67 (1H, s, 3-H), 5.12 (1H, br. s, 7-H_3), 3.70 (3H, s, 1-H_3), 3.63 (2H, app. q, *J* 6.3, 11-H_2), 2.21-2.15 (7H, m, 13-H_3, 6-H_2, 5-H_3), 2.13-2.04 (2H, m, 9-H_2), 1.70-1.61 (5H, 10-H_2, 12-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 167.3 (C), 135.9 (C), 124.2 (CH), 123.4 (C), 115.4 (CH), 62.9 (CH_2), 50.9 (CH_3), 41.1 (CH_2), 30.9 (CH_2), 25.8 (CH_2), 28.1 (CH_2), 19.0 (CH_3), 16.0 (CH_3); HRMS *m/z* (ESI^+) 249.1466 (M + Na^+, $C_{13}H_{20}O_3Na$ requires 249.1461). This product was immediately protected without purification.

DMAP (16.0 mg, 133 µmol) was added to a solution of the alcohol (300 mg, 1.33 mmol) and acetic anhydride (150 µL, 1.59 mmol) in CH_2Cl_2 (6.7 mL) at ambient temperature. The reaction was stirred for 18 h. Water (10 mL) was added and the resulting solution extracted with ether (3 x 10 mL). The combined organic layers were washed with hydrochloric acid (1 M aq., 2 x 5 mL), dried ($MgSO_4$) and concentrated in *vacuo* to give the title compound **258** (330 mg, 92%) as a colourless oil. R_f 0.7 (1:1, ether: petrol); ν_{max} (ATR)/cm^{-1} 2943, 1736, 1715, 1434, 1223, 1146, 1034; ^{1}H NMR (400 MHz, $CDCl_3$) 5.67 (1H, s, 3-H), 5.16-5.09 (1H, m, 7-H), 4.04 (2H, app. td, *J* 6.6, 2.8, 11-H_2), 3.69 (3H, s, 1-H_3), 2.25 (3H, s, 13-H_3), 2.20-2.14 (7H, m, 15-H_3, 6-H_2, 5-H_2), 2.11-2.02 (5H, m, 14-H_3, 9-H_2), 1.77-1.68 (2H, m, 10-H_2); ^{13}C NMR (100 MHz, $CDCl_3$) 167.2 (C), 159.9 (C), 135.0 (C), 124.5 (C), 124.6 (CH), 115.3 (CH), 64.1 (CH_2), 50.8 (CH_3), 41.0 (CH_2), 35.7 (CH_2), 25.8 (CH_2), 25.9 (CH_2), 21.0 (CH_3), 22.2 (CH_3), 18.9 (CH_3); HRMS *m/z* (ESI^+) 291.1571 (M + Na^+, $C_{15}H_{24}O_4Na$ requires 291.1567).

Methyl 8-(11-acetoxypropyl)-4,8-dimethylcyclohex-4-ene-3-carboxylate (**259**)

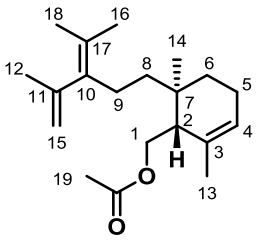


Tin tetrachloride (1 M, CH_2Cl_2, 75.0 µL, 75.0 µmol,) was added dropwise to a solution of (±)-BINOL (21.0 mg, 75.0 µmol) in CH_2Cl_2 (1.2 mL) at -78 ˚C. After 5 min ester **258** (100 mg, 373 µmol) was added dropwise as a solution in CH_2Cl_2 (0.5 mL). Following addition the reaction was allowed to warm to ambient temperature and stirred for 18 h. Pyridine (6.0 µL) was added followed by saturated aqueous sodium bicarbonate (10 mL). The resulting solution was extracted with ether (3 x 5 mL), dried ($MgSO_4$) and concentrated in *vacuo*.

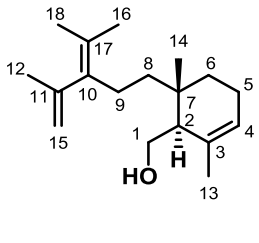
^{1}HNMR analysis of this mixture showed a 1:1.4 mixture of diastereoisomers. Purification by silica gel chromatography (1:4, ether:petrol) gave first a single diastereomer of the title compound **259** (15.0 mg, 15%) as a colourless oil. Rf 0.43 (1:4, ether: petrol); ν_{max} (ATR)/cm^{-1} 2950, 1732, 1448, 1364, 1236, 1148, 1030, 942; ^{1}H NMR (400 MHz, $CDCl_3$) 5.58 (1H, br. s, 5-H), 4.02 (2H, app. td, *J* 6.8, 2.0, 11-H_2), 3.68 (3H, s, 1-H), 2.65 (1H, s, 3-H), 2.11-1.92 (5H, m, 6-H_2, 13-H_3), 1.84-1.76 (1H, m, 7-Ha), 1.63 (3H, br. s, 14-H_3), 1.62-1.56 (2H, m, 10-H_2), 1.42-1.16 (3H, 9-H_2, 7-Hb), 0.89 (3H, s, 15-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 174.3 (C), 171.2 (C), 129.4 (C), 124.0 (CH), 65.1 (CH_2), 55.8 (CH), 51.5 (CH_3), 34.5 (CH_2), 34.2 (C), 28.5 (CH_2), 24.0 (CH_3), 23.1 (CH_2), 23.0 (CH_3), 22.4 (CH_2), 21.1 (CH_3); HRMS *m/z* (ESI$^+$) 291.1573 (M + Na$^+$, $C_{15}H_{24}O_4Na$ requires 291.1567). Further elution gave the second diastereoisomer as a mixture with the first (18 mg, 18%) as a colourless oil. Rf 0.42 (1:4, ether: petrol); ν_{max} (ATR)/cm^{-1} 2950, 1732, 1433, 1381, 1234, 1148, 1031; ^{1}H NMR (400 MHz, $CDCl_3$, *denotes resonances from other diastereoisomer) 5.58 (1H, br. s, 5-H), 4.01 (2H, app. t, *J* 6.8, 11-H_2), 3.68 (3H, s, 1-H), 2.66 (1H, s, 3-H*), 2.63 (1H, s, 3-H), 2.12-1.96 (5H, m, 6-H_2, 13-H_3), 1.89-1.76 (1H, m, 7-Ha), 1.74-1.56 (5H, m, 10-H_2, 14-H_3), 1.42-1.14 (3H, 9-H_2, 7-Hb), 0.89 (3H, s, 15-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) (1:0.4 mixture of diastereoisomers, * data for other diastereoisomer where distinguishable) 174.3 (C), 171.2 (C), 129.3 (C), 124.0 (CH), 65.2 (CH_2), 65.1 (CH_2*), 56.1 (CH), 55.8 (CH*), 51.6 (CH_3), 51.5 (CH_3*), 36.7 (CH_2), 34.5 (C), 28.8 (CH_2) 28.5 (CH_2*), 24.0 (CH_3*), 23.1 (CH_3), 22.98 (CH_3*), 22.81 (CH_3), 22.76 (CH_2), 22.5 (CH_2), 22.4 (CH_2), 22.38 (CH_2*), 21.1 (CH_3); HRMS *m/z* (ESI$^+$) 291.1570 (M + Na$^+$, $C_{15}H_{24}O_4Na$ requires 291.1567)

Lipase Resolution:

3,7-dimethyl-7-(11-methyl-10-(prop-1-en-2-yl)pent-11-enyl)cyclohex-3-enyl)-2-methyl acetate (**264**) and (-)-3,7-dimethyl-7-(11-methyl-10-(prop-1-en-2-yl)pent-11-enyl)cyclohex-3-enyl)-2-methanol (**263**)



264



263

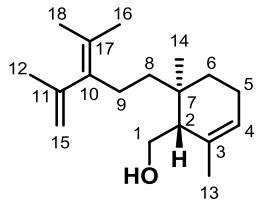
Lipase (37.0 mg, *pseudomonas cepacia*, CAS: 9001-62-1) was added to a solution of vinyl acetate (136 µL, 1.48 mmol) and alcohol **148** (50.0 mg, 191 µmol) in triethylamine/ hexane (2.71 mL, 1:2.6). Activated 4 Å molecular sieves were added and the flask stoppered. The reaction was stirred for 6 days at ambient temperature, filtered and then concentrated in *vacuo*. Purification by silica gel chromatography (1:2.5, ether: petrol) gave first acetate **264** (34.0 mg, 58%) as a colourless oil. R_f 0.69 (1:1, ether : petrol); ν_{max} ($CHCl_3$)/cm^{-1} 2962, 2914, 2857, 1740, 1445, 1365, 1229, 1027, 968; ^1H NMR (400 MHz, $CDCl_3$) 5.45 (1H, br. s, 4-H), 4.89 (1H, dq, *J* 2.99, 1.51, 15-Ha), 4.53-4.51 (1H, m, 15-Hb), 4.19 (1H, dd, *J* 11.68, 5.91, 1-Ha), 4.05 (1H, dd, *J* 11.68, 3.50, 1-Hb), 2.04 (3H, s, 19-H_3), 2.03-1.93 (4H, m, 5-H_2, 9-H_2), 1.93-1.88 (1H, m, 2-H), 1.75 (3H, dd, *J* 1.51, 0.91, 12-H_3), 1.73 (3H, app. d, *J* 1.90, 13-H_3), 1.66-1.63 (6H, m, 16-H_3, 18-H_3), 1.52-1.43 (1H, m, 6-Ha), 1.36-1.21 (3H, m, 6-Hb, 8-H_2), 0.93 (3H, s, 14-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 171.1 (C), 146.7 (C), 136.8 (C), 132.1 (C), 124.6 (C), 123.3 (CH), 112.9 (CH_2), 64.3 (CH_2) 47.0 (CH) 36.9 (CH_2), 34.2 (C), 29.7 (CH_2), 25.4 (CH_2), 23.7 (CH_3), 23.1 (CH_3), 22.8 (CH_2) 22.7 (CH_3), 21.7 (CH_3), 21.2 (CH_3), 19.4 (CH_3); HRMS *m/z* (ESI^+) 327.2297 (M + Na^+, $C_{20}H_{32}O_2Na$ requires 327.2295). Further elution gave alcohol **263** (24.0 mg, 48%) as a colourless oil. R_f 0.35 (1:1, ether : petrol); $[\alpha]^{25}_D$ = - 43.1 (*c* = 1.0, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3356, 2961, 2912, 2856,

1444, 1372, 1046, 1021; ^{1}H NMR (400 MHz, $CDCl_3$) 5.60 (1H, br. s, 4-H), 4.90-4.89 (1H, m, 15-Ha), 4.53-4.51 (1H, m, 15-Hb), 3.77-3.73 (2H, br. s, 1-H_2), 2.03-1.96 (4H, m, 5-H_2, 9-H_2), 1.76-1.73 (7H, m, 13-H_3, 12-H_3, 2-H), 1.66-1.59 (7H, m, 6-Ha, 16-H_3, 18-H_3), 1.36-1.17 (4H, m, 6-Hb, 8-H_2), 1.02 (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), 22.9 (CH_3), 22.8 (CH_3), 22.7 (CH_2), 21.8 (CH_3), 19.4 (CH_3); HRMS *m/z* (ESI^+) 285.2185 ($M + Na^+$, $C_{18}H_{30}ONa$ requires 285.2189).

The absolute stereochemistry of these products is unknown, stereochemistry drawn is only for convenience of discussion.

Acetate Hydrolysis:

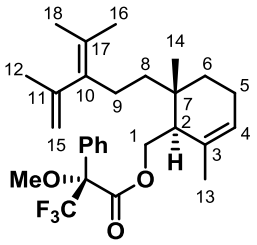
(+)-3,7-dimethyl-7-(11-methyl-10-(prop-1-en-2-yl)pent-11-enyl)cyclohex-3-enyl)-2-methanol (**265**)



$LiOH{\cdot}H_2O$ (5.2 mg, 123 µmol) was added to a stirring solution of acetate **264** (34.0 mg, 112 µmol) in THF/H_2O (1 mL, 2:1) at ambient temperature. The reaction was stirred for 18 h. before water was added (5 mL) and the resulting solution extracted with ether (3 x 5 mL). The combined organic layers were then washed with brine (5 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:2, ether: petrol) gave first recovered starting material **264** (2.6 mg), followed by the title compound **265** (15.0 mg, 51%) as a colourless oil. R_f 0.38 (1:1, ether : petrol); $[\alpha]^{24}_D$ = + 44.2 (*c* = 1.0, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3325, 2960, 2912, 2855, 1444, 1372, 1274, 1019; ^{1}H NMR (400 MHz, $CDCl_3$) 5.60 (1H, br. s, 4-H), 4.89 (1H, s, 15-Ha), 4.52 (1H, s, 15-Hb), 3.77-3.74 (2H, br. s, 1-H_2),

2.04-1.94 (4H, m, 5-H_2, 9-H_2), 1.78-1.70 (7H, m, 13-H_3, 12-H_3, 2-H), 1.69-1.59 (7H, m, 6-Ha, 16-H_3, 18-H_3), 1.36-1.16 (4H, m, 6-Hb, 8-H_2), 1.01 (3H, s, 14-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 146.8 (C), 137.0 (C), 131.8 (C), 124.8 (CH), 124.6 (C), 112.9 (CH_2), 61.5 (CH_2), 50.5 (CH), 37.2 (CH_2), 34.3 (C), 30.5 (CH_2), 25.5 (CH_2), 24.2 (CH_3), 23.0 (CH_3), 22.9 (CH_3), 22.8 (CH_2), 21.8 (CH_3), 19.5 (CH_3); HRMS *m/z* (ESI^+) 285.2186 (M + Na^+, $C_{18}H_{30}ONa$ requires 285.2189).

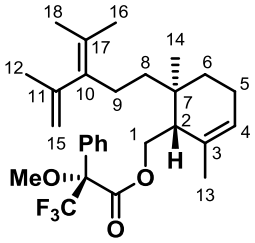
3,7-dimethyl-7-(11-methyl-10-(prop-1-en-2-yl)pent-11-enyl)cyclohex-3-enyl)-2-methyl-(R)-trifluoromethoxyphenylpropanoate (**268**)



DMAP (1.20 mg, 9.90 µmol) was added to a solution of alcohol **263** (26.0 mg, 99.1 µmol), (*R*)-(+)-α-Methoxy-α-trifluoromethylphenylacetic acid (23.0 mg, 99.1 µmol) and dicyclohexylcarbodiimide (DCC) (22.0 mg, 109 µmol) in CH_2Cl_2 (500 µL) at ambient temperature. The reaction was stirred for 18 h. before being cooled to -20 ˚C (freezer) and rapidly filtered. The filtrate was concentrated in *vacuo* and the residue purified by silica gel chromatography (1:4, ether: petrol) to give the title compound **268** (40 mg, 85%) as a colourless oil. Mixture of diastereoisomers 1:0.01 d.r.; R_f 0.63 (1:4, ether : petrol); ν_{max} ($CHCl_3$)/cm^{-1} 3022, 3015, 2917, 2856, 1743, 1498, 1379, 1273, 1189, 1122, 1019; ^{1}H NMR (400 MHz, $CDCl_3$) 7.58-7.49 (2H, m, ArH), 7.45-7.34 (3H, m, ArH), 5.39 (1H, s, 4-H), 4.90-4.86 (1H, m, 15-Ha), 4.51 (1H, br. s, 15-Hb), 4.48 (1H, dd, *J* 11.7, 5.5, 1-Ha), 4.26 (1H, dd, *J* 11.7, 2.8, 1-Hb), 3.54 (3H, s, OMe), 1.99-1.87 (5H, m, 5-H_2, 9-H_2, 2-H), 1.74 (3H, s, 12-H_3), 1.69 (3H, s, 13-H_3), 1.64 (3H, s, 16-H_3 or 18-H_3), 1.61 (3H, s, 16-H_3 or 18-H_3), 1.41-1.16 (4H, m, 6-H_2, 8-H_2), 0.85 (14-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 166.7 (C), 146.7 (C), 136.8 (C),

132.3 (C), 130.9 (CH), 129.6 (CH), 128.4 (CH), 127.5 (CH), 127.4 (CH), 124.7 (C), 124.2 (CH), 123.4 (q, *J* 288.4, CF_3), 113.0 (CH_2), 65.9 (CH_2), 55.5 (CH_3), 47.2 (CH), 36.8 (CH_2), 34.1 (C), 29.6 (CH_2), 25.5 (CH_2), 23.8 (CH_3), 22.8 (CH_2), 22.6 (CH_3), 22.5 (C), 22.6 (CH_3), 21.8 (CH_3), 19.5 (CH_3); HRMS *m/z* (ESI^+) 501.2584 ($M + Na^+$, $C_{28}H_{37}F_3O_3Na$ requires 501.2592).

3,7-dimethyl-7-(11-methyl-10-(prop-1-en-2-yl)pent-11-enyl)cyclohex-3-enyl)-2-methyl-(R)-trifluoromethoxyphenylpropanoate (**269**)



DMAP (0.8 mg, 6.1 µmol) was added to a solution of alcohol **265** (16.0 mg, 61.0 µmol), (*R*)-(+)-α-Methoxy-α-trifluoromethylphenylacetic acid (14 mg, 61 µmol) and dicyclohexylcarbodiimide (DCC) (13.8 mg, 67.0 µmol) in CH_2Cl_2 (300 µL) at ambient temperature. The reaction was stirred for 18 h. before being cooled to -20 ˚C (freezer) and rapidly filtered. The filtrate was concentrated in *vacuo* and the residue purified by silica gel chromatography (1:4, ether: petrol) to give the title compound **269** (28.0 mg, 96%) as a colourless oil. Mixture of diastereoisomers 1:0.12 d.r.; R_f 0.62 (1:4, ether: petrol); ν_{max} ($CHCl_3$)/cm^{-1} 2917, 2856, 1743, 1450, 1272, 1195, 1123, 1018; ^{1}H NMR (400 MHz, $CDCl_3$) 7.56-7.48 (2H, m, ArH), 7.44-7.36 (3H, m, ArH), 5.48 (1H, s, 4-H), 4.90-4.87 (1H, m, 15-Ha), 4.50 (1H, br. s, 15-Hb), 4.41-4.31 (2H, m, 1-Ha), 3.56 (3H, s, OMe), 1.99-1.84 (5H, m, 5-H_2, 9-H_2, 2-H), 1.73 (6H, br. s, 12-H_3, 13-H_3), 1.64 (3H, s, 16-H_3 or 18-H_3), 1.62 (3H, s, 16-H_3 or 18-H_3) 1.40-1.12 (4H, m, 6-H_2, 8-H_2), 0.78 (14-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 166.7 (C), 146.7 (C), 136.8 (C), 132.3 (C), 131.4 (CH), 129.6 (CH), 128.4 (CH), 127.3 (CH), 127.4 (CH), 124.7 (C), 124.2 (CH), 123.4 (q, *J* 288.9, CF_3), 113.0 (CH_2), 65.9 (CH_2), 55.6 (CH_3), 47.2 (CH),

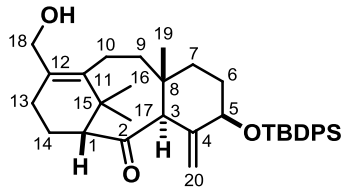
36.9 (CH_2), 34.1 (C), 29.5 (CH_2), 25.5 (CH_2), 23.7 (CH_3), 22.8 (C), 22.8 (CH_3), 22.6 (CH_3), 21.8 (CH_3), 19.5 (CH_3); HRMS *m/z* (ESI^+) 501.2585 ($M + Na^+$, $C_{28}H_{37}F_3O_3Na$ requires 501.2592).

Control – Mosher's Analysis of Racemic Alcohol (**148**)

DMAP (1.0 mg, 7.60 µmol) was added to a solution of alcohol **148** (20.0 mg, 76.0 µmol), (*R*)-(+)-α-Methoxy-α-trifluoromethylphenylacetic acid (18.0 mg, 76.0 µmol) and dicyclohexylcarbodiimide (DCC) (17.0 mg, 84.0 µmol) in CH_2Cl_2 (381 µL) at ambient temperature. The reaction was stirred for 24 h. before being cooled to -20 ˚C (freezer) and rapidly filtered. The filtrate was concentrated in *vacuo* and the residue purified by silica gel chromatography (1:9, ether: petrol) to give a mixture of esters (33.0 mg, 90%) as a colourless oil. ^{1}HNMR showed mixture of **266** and **267** diastereoisomers 1:1.03 d.r.

Data for mixture consistent with data of individual components above.

(±)-5β-(tert-butyldiphenylsilyloxy)-18-hydroxytaxa-(4,20)-(11,12)-dien-2-one (**270**)



Selenium dioxide (8.2 mg, 73.9 µmol) was added to a stirring solution of silyl ether **154** (20.0 mg, 36.9 µmol) in CH_2Cl_2 (150 µL) at ambient temperature. The reaction was sealed and stirred for 10 days. Saturated sodium thiosulphate solution (3 ml) was added followed by extraction with ether (3 x 5 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. Purification by silica gel chromatography (1:4, ether:petrol) afforded firstly recovered starting material **154** (5.7 mg) followed by the title compound

270 (7.5 mg, 36%) as a colourless oil. R_f 0.4 (1:4, ether: petrol); ν_{max} cm^{-1} ($CHCl_3$) 3617, 3052, 2933, 2859, 1692, 1473, 1428, 1110, 1008; ^1H NMR (400 MHz, $CDCl_3$) 7.71-7.64 (4H, m, ArH), 7.46-7.33 (6H, m, ArH), 5.43 (1H, br. s, 20-Ha), 4.85 (1H, br. s, 20-Hb), 4.12 (1H, d, *J* 11.4, 18-Ha), 3.94 (1H, dd, *J* 11.4, 4.1, 18-Hb), 3.90-3.84 (1H, m, 5-H), 3.66 (1H, s, 3-H), 2.84 (1H, td, *J* 13.6, 5.6, 10-Ha), 2.39 (1H, d, *J* 8.7, 2.4, 1-H), 2.43-2.31 (1H, m, 13-Ha), 2.12-2.05 (1H, m, 10-Hb), 2.02-1.86 (2H, m, 13-Hb, 14-Ha), 1.79-1.70 (1H, m, 9-Ha), 1.66-1.59 (2H, m, 6-H_2), 1.47-1.37 (1H, m, Hb), 1.27-1.12 (5H, m, 16-H_3 or 17-H_3, 7-H_2), 1.09 (3H, s, 16-H_3 or 17-H_3), 1.08 (9H, s, OSi^t*Bu*), 0.90-0.89 (4H, 9-Hb, 19-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) 212.8 (C), 145.3 (C), 141.6 (C), 135.9 (CH), 135.9 (CH), 134.4 (C), 134.4 (C), 129.6 (CH), 127.4 (CH), 106.4 (CH_2), 74.0 (CH), 63.4 (CH_2), 62.2 (CH), 53.0 (CH), 41.4 (C), 38.9 (C), 37.8 (CH_2), 33.0 (CH_2), 29.5 (CH_3), 27.0 (CH_3), 25.06 (CH_2), 25.05 (CH_2), 25.04 (CH_3), 23.4 (CH_3), 19.4 (C), 17.7 (CH_2); HRMS (ESI^+) *m/z* 579.3258 ($M+Na^+$, $C_{36}H_{48}O_3SiNa$ requires 579.3270).

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Appendix

^{1}H NMR (400 MHz, $CDCl_3$) - Taxa-4(5),11(12)-diene (**17**) and Taxa-4(20),11(12)-diene (**18**)

