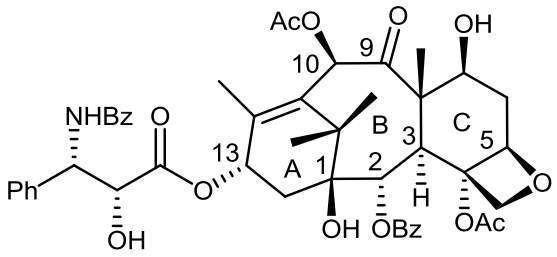
Towards the Synthesis of the ABC Tricycle of Taxol



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School of Chemistry
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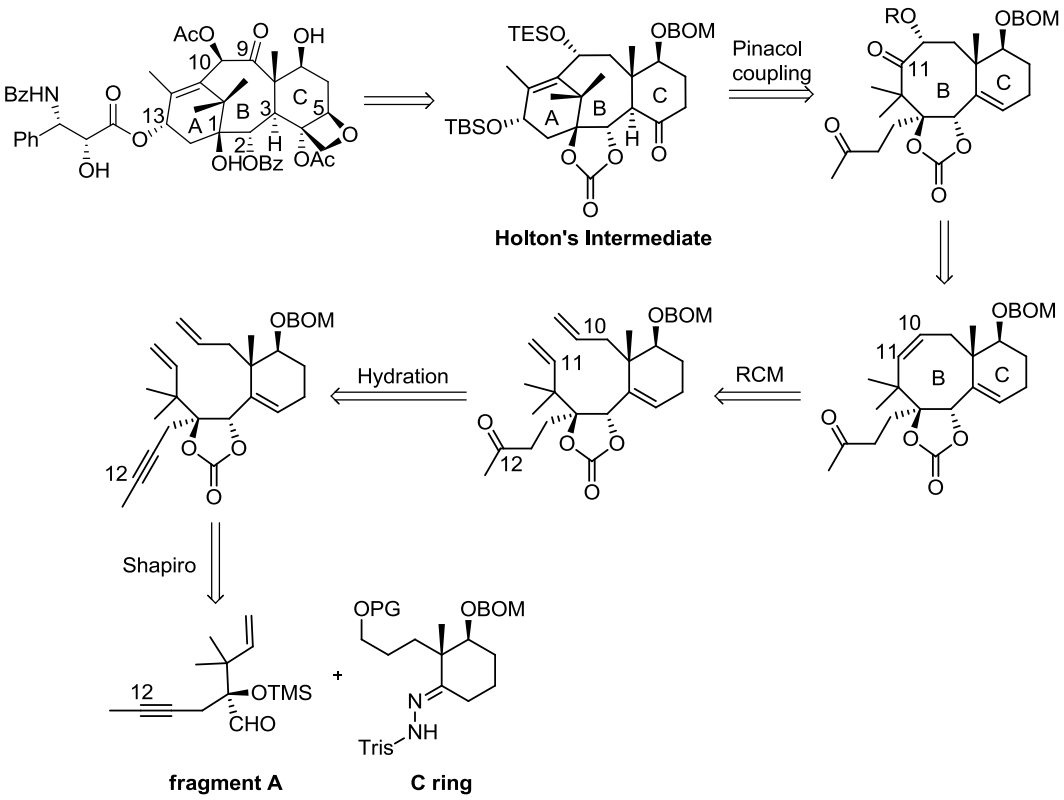
Abstract

Taxol is one of the world's most successful drugs used in the treatment of cancers. Isolated from the bark of the Pacific yew tree (*Taxus brevifolia*), it is a molecule of great interest within organic chemistry; with six total syntheses and a number of synthetic works having been published since its discovery.

A semi-convergent synthesis of an intermediate in Holton's synthesis was planned. The overall synthetic plan is shown below. The A ring would be installed by an intramolecular pinacol condensation. The BC bicycle would be closed by ring-closing metathesis at C10-C11. The ketone at C12 would be protected as an alkyne and the BC bicycle precursor would be obtained by coupling fragment A and the C ring.



This thesis describes the preparation of a model C ring, without the oxygenated functionality at C7, was successfully synthesised along with fragment A. Metathesis precursors were synthesised and gold hydration reactions were attempted.

Contents

Acknowledgements

Firstly, I would like to thank Dr Joëlle Prunet for all her help and support during this project. Her patience and understanding during the first two years of the project, when nothing seemed to be working, are greatly appreciated. The fact that she still manages to remain calm constantly amazes me.

I would also like to thank everyone I have worked with over the past three and a half years. Everyone in the Loudon and Raphael labs, both past and present including Michael, Anna, Lewis, Jo, Pooja and all the "frenchies" who I am constantly surrounded by. The 'Frunet' group are a great bunch of people and I hope we keep in touch in the future.

To everyone else in the department who has helped and encouraged me, Ted and Shaun from stores, Elizabeth, Alexis and all three Jims for their help and guidance on issues regarding the department, again many thanks.

Thanks also go to the volcano that erupted in 2010 and made me realise that you have to keep pushing and motivate yourself rather than just give up. Even to the woman who kicked a football at me, thus breaking my wrist, and keeping me out of the lab for two months.

Finally, I would like to thank my family and friends who have kept me sane during this period.

Author's Declaration

This thesis represents the original work of Antonia Wilkes unless stated otherwise within the text. The research was carried out at the University of Glasgow in the Raphael Laboratory under the supervision of Dr. Joëlle Prunet during the period of October 2009 to November 2012.

Abbreviations

Ac	Acetate
Aq.	Aqueous
Ar	Aromatic
Bn/Bz	Benzyl
BOM	Benzyloxymethyl
Br	Broad
Bu	Butyl
Cat.	Catalytic
CDI	Carbonyl diimidazole
Conc.	Concentrated
d	Doublet
DABCO	1, 4-Diazabicyclo[2.2.2]octane
DAMP	Dimethyl diazomethylphosphonate
DCE	Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
$(DHQD)_2AQN$	Hydroquinidine (anthraquinone-1, 4-diyl) diether
DIBAL	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMP	Dess-Martin Periodinane
DMSO	Dimethyl sulfoxide
DPC	Di-2-pyridyl carbonate
e.e.	Enantiomeric excess
EE	Ethoxyethyl
EI	Electron impact
Equiv.	Equivalent
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
g	Grams
h	Hours
^1H	Proton
HCl	Hydrochloric acid
Hex	Hexyl
Hz	Hertz

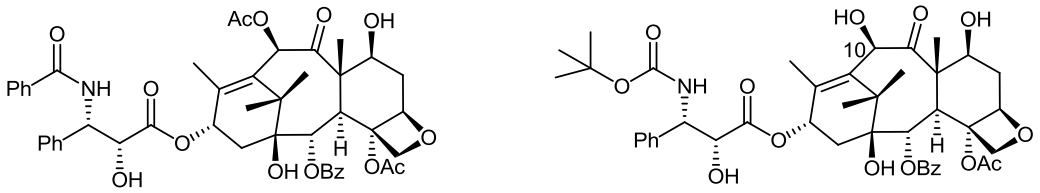
IBX	Iodoxybenzoic acid
Im	Imidazole
*i*Pr	Isopropyl
IR	Infrared
J	NMR spectra coupling constant
KHMDS	Potassium hexamethyldisilazide
M	Molar
m	Multiplet
m-CPBA	Chloroperbenzoic acid
Me	Methyl
MeOH	Methanol
Mg	Milligram(s)
Min	Minutes
mL	Millilitre(s)
MOM	Methoxymethyl
Mp	Melting point
N	Normal
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
PAM	Peptidylglycine monooxygenase
Ph	Phenyl
PMB	*p*-Methoxybenzyl
PPM	Parts per million
PTSA	*p*-Toluenesulfonic acid
Py	Pyridine
q	Quartet
quin	Quintet
s	Singlet
rt	Room temperature
t	Triplet
TBAF	Tetrabutylammonium fluoride
TESCl	Triethylsilyl chloride
Tris	Triisopropylbenzenesulfonyl
Troc	Trichloroethyl carbonate
Ts	Tosyl

Chapter I

Introduction

1.1 Generalities of Taxol

Paclitaxel, marketed as Taxol **1**, together with docetaxel (Taxotere **2**) are regarded as the top plant-based anti-cancer drugs in circulation in the world to date. Sales of both taxol and taxotere took over 3.15 billion US dollars in 2010 alone[1] and with 1 in 4 deaths in the United States a result of cancer,[2] sales are likely to keep increasing. Taxol is used to treat a variety of cancers including lung, ovarian, head and neck, and breast.[3] Since its anticancer properties were discovered, taxol (Scheme 1.01) and its derivatives have become key treatments in the fight against cancer.



Scheme 1.01 – Structure of Taxol and Taxotere

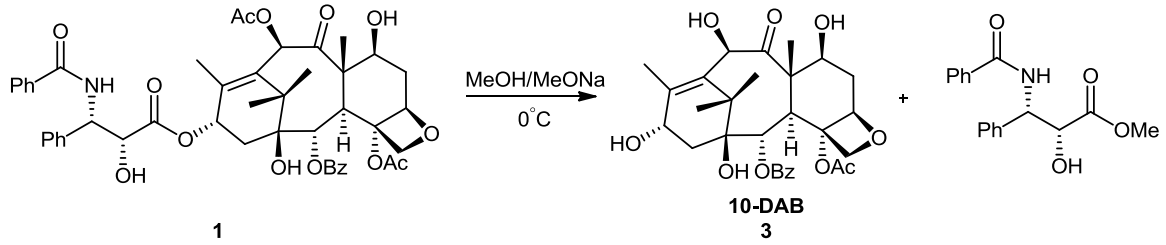
1.2 Discovery of Taxol[4]

In 1962, samples of bark, stem and needles were collected from the Pacific yew tree (*Taxus brevifolia*), as part of a program organised by the National Cancer Institute's (NCI) Cancer Chemotherapy National Service Centre (CCNSC). Plant samples were taken at random to be screened for anti-cancer properties and it was botanist Arthur Barclay who collected the samples from the evergreen tree *Taxus brevifolia*. At the time not much was known about the tree other than that it was poisonous.

In 1963, the crude extract from these woody samples was found to have cytotoxic activity against KB cells. It was not until 1966 that Dr Monroe Wall at the Research Triangle Institute (RTI), along with his colleague Mansukh Wani, discovered that extracts from the bark of the tree were active against leukemia in mice. Taxol was isolated in 1967, in a 0.01% yield, from the bark of the tree as the needles and wood contained much less taxol.

Wall and Wani set about characterising the isolated compound but admitted early failure in 1967; however, the slow process of determining the structure of taxol eventually paid off.

Using mass spectrometry, X-ray crystallography and NMR spectroscopy, Wall and Wani discovered that the structure of taxol was a large molecule connected to a small tail or side chain (Scheme 1.02). This work was then published in 1971 in the *Journal of American Chemical Society* stressing the anticancer activities of this newly isolated molecule.[5]



1 10-DAB 3

Scheme 1.02 – Cleavage of the side chain of taxol

The discovery of taxol at this point was discouraging as it had only shown to have modest activity against various leukaemias, it was insoluble in water and was isolated in very low yields from the bark of a slow growing yew tree. Further testing was therefore carried out by the NCI after Wall and Wani passed taxol onto them for further studies. In the early 1970s, results of bioassays carried out by the NCI proved to be crucial, especially toward the activity of taxol in a B16 mouse melanoma model. In 1977, taxol was selected as a development candidate following its good activity against MX-1 and NX-1 mammory and colon xenografts in mice.

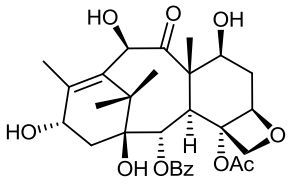
Its mechanism of action was discovered in 1979, by Susan Horwitz,[6] when she found that taxol prevented the replication of cancerous cells by stabilising microtubules and preventing their depolymerisation. As this was the first time this mode of action had ever been seen, the interest in taxol increased significantly.

Taxol entered Phase I and Phase II clinical trials in 1985. The trials showed the first signs that taxol was an efficient drug, exhibiting activity against melanomas in ovarian and breast cancers. In 1992 the Food and Drug Administration (FDA) agreed to the use of taxol against ovarian cancer[7] and for treatment of breast cancer[8] in 1994. Further clinical trials showed that taxol could also be effective in treating Kaposi's sarcoma, as well as the treatment of other cancers when taken in association with drugs such as cisplatin.

Taxol was playing a major part in the fight against cancer; however its availability was beginning to cause some problems. The clinical trials alone had consumed over 25,000

trees in order to extract taxol from the bark. This harvest was affecting the population of the tree in the north-western part of the United States, which was not popular with ecologists. It was becoming clear that harvesting taxol from the bark of the tree was not a possible long term option. A new source of taxol had to be found.

This new source came about when Pierre Potier and his group began collecting the needles of *Taxus baccata*, the European yew tree, and on analysing the samples found that they contained 10-deactylbaccatin III (10-DAB),[9] having the main structure of taxol without the side chain and the acetyl group at C10 (Scheme 1.03). Using 10-DAB from the needles of the tree proved to be a renewable source towards the synthesis of taxol and in 1988 Potier published the semi-synthesis of taxol[10] from 10-DAB isolated from the needles. During the semi-synthesis, Potier discovered an analogue of taxol, taxotere **2**.[11] This intermediate differs from taxol at the C10 position where the acetyl group is replaced by a hydroxyl group, which increases the solubility of taxotere in water. The side chain also differs from taxol as the benzoyl is replaced by a *tert*-butyloxycarbonyl. After its clinical phase I trial in 1990, taxotere was approved by the FDA in 1996 for the treatment of breast cancer and is currently marketed by Sanofi. Taxotere is produced by semi-synthesis, but taxol is produced by plant cell fermentation by Phyton Biotech, LLC, a DFB pharmaceuticals company for Bristol-Myers Squib.



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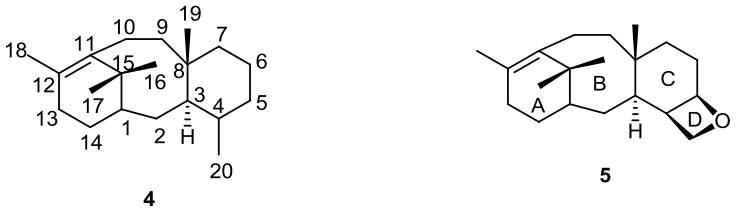
Scheme 1.03 – Structure of 10-DAB

1.3 Structure and nomenclature

Since the isolation of the first taxane in 1856, over 350 taxanes have been isolated and characterised.[12] Taxol is part of this large family of taxanes whose name comes from the genus *Taxus* of the yew tree, *Taxus brevifolia*. The majority of taxanes have a basic diterpene structure that consists of a pentamethyl [9.3.1.0] tricyclopentadecane skeleton (Scheme 1.04).

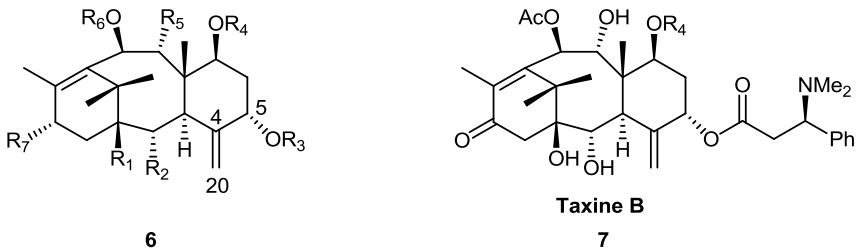


4 **5**

Scheme 1.04 – Pentamethyl [9.3.1.0] tricyclopentadecane skeleton

Taxanes can be classified into many different groups, which include the nature of the oxygenated functions found between C2 and C4; a select few are listed below.

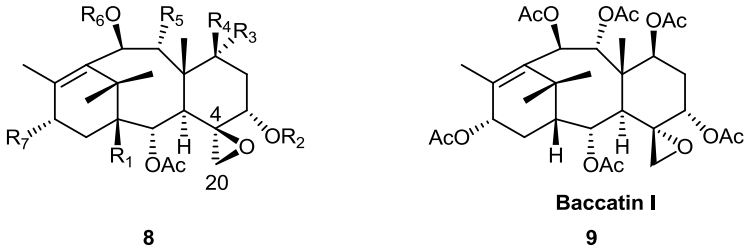
The first group of taxanes (Scheme 1.05) is characterised by an exocyclic double bond found between the C4 and C20 position, as well as an oxygenated functionality at C5 **6**. Taxine B **7** is a member of this group of taxanes, it is the major cardiotoxic agent found in the yew tree.



6 **Taxine B** **7**

Scheme 1.05 – Taxanes with a C4(20) double bond

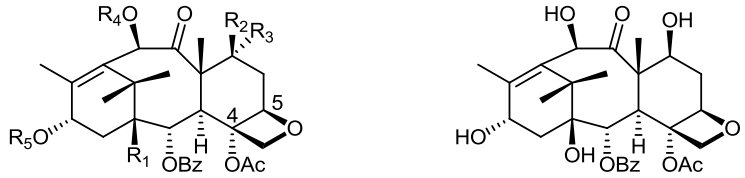
The second group of taxanes is characterised by an epoxide found between C4 and C20 **8** (Scheme 1.06). Baccatin I **9** is an example of these kinds of taxanes.



8 9

Scheme 1.06 – Taxanes with a C4(20) epoxide

The third group can be characterised by an oxetane ring found at the C4 and C5 positions **10** (Scheme 1.07). 10-Deacetylbaccatin III **3** (10-DAB) can be found in this group of taxanes.



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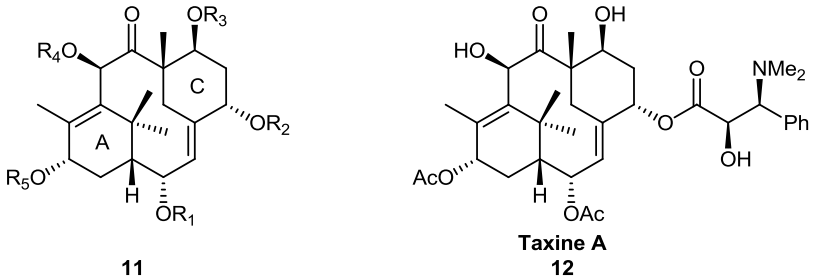
Scheme 1.07 – Taxanes with an oxetane ring

The final group we will mention is made up of taxanes that do not encompass the traditional ABC tricycle system. *Abeo*-taxoids **11** are thought to be formed from a transannular cyclisation different to that of normal taxoid biosynthesis. Taxine A **12** is an example of these class of taxanes.



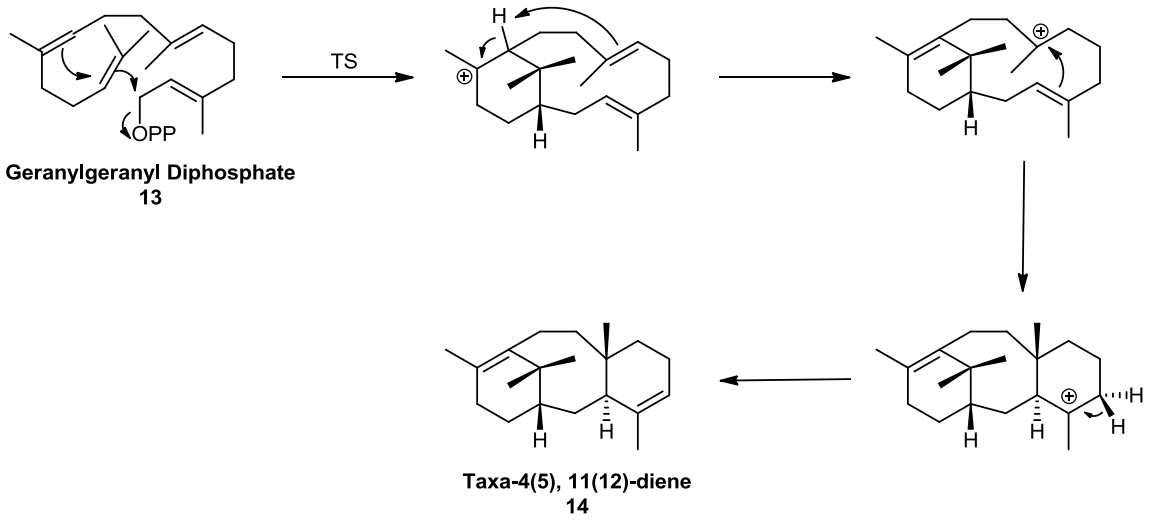
11 12

Scheme 1.08 – Abeo taxanes

1.4 Biosynthesis

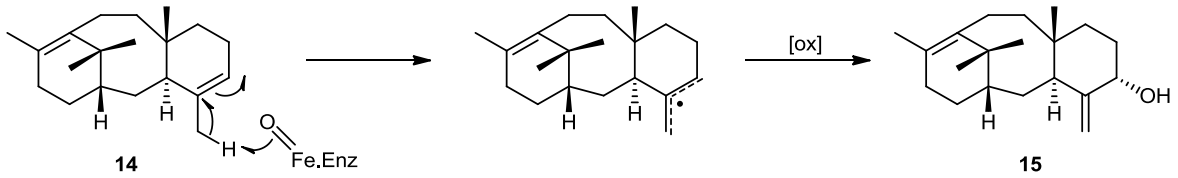
The biosynthesis of taxol has been studied in great detail in order to understand the production of the substance within the plant. Knowing this could then be used for the synthesis of taxol using cell cultures. The first few steps of the biosynthesis were discovered by Croteau.[13]

The first key step involved to synthesise taxol and other taxanes is the cyclisation of a diterpenoid precursor geranylgeranyl disphosphate **13** into taxa-4(5),11(12)-diene[3] **14** (Scheme 1.09) which is catalysed by the enzyme taxadiene synthase (TS). Many terpene synthases produce multiple products when undergoing plant secondary metabolism however, taxadiene synthase produces mainly taxa-4(5),11(12)-diene **14** with only small amounts of other taxadiene isomers being formed.[14]



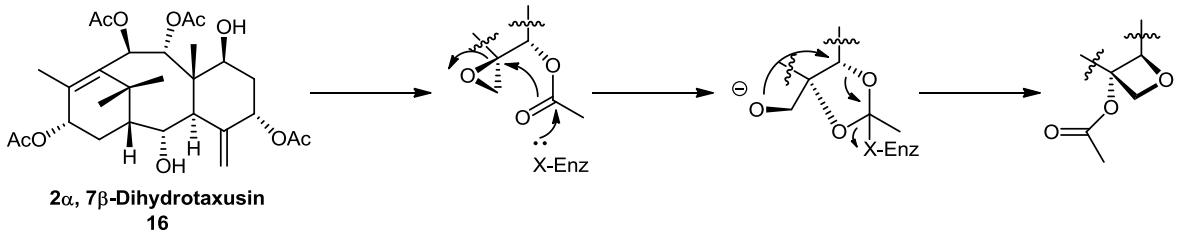
Scheme 1.09 – Formation of the taxol skeleton

The second key step in the biosynthesis is thought to be hydroxylation at the C5 position (Scheme 1.10). This occurs via an allylic rearrangement of the C4-C5 double bond **14** to the C4-C20 position **15** of the taxane ring using the enzyme cytochrome P450.



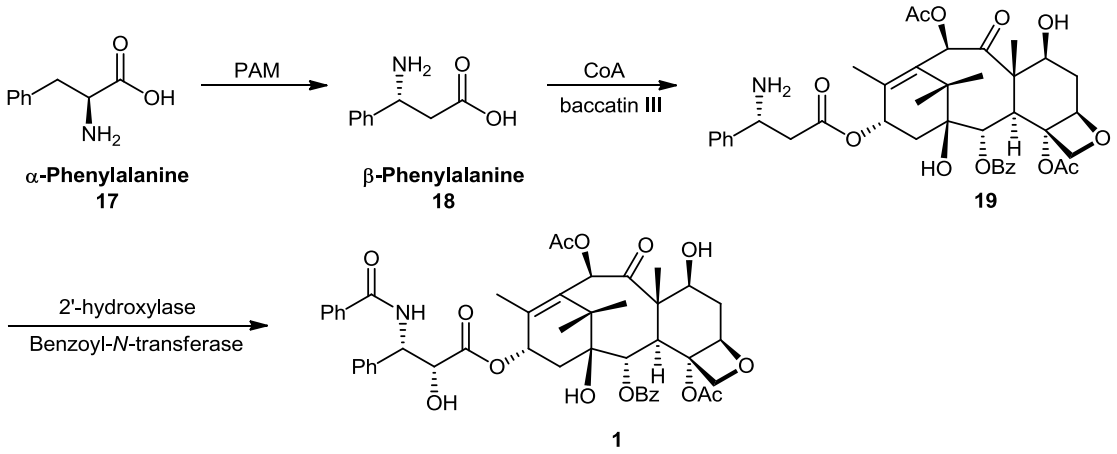
Scheme 1.10 – Oxidation at C5 with cytochrome P450

A number of oxidations take place followed by esterification giving 2α,7β-dihydrotaxusin **16**. The third key step is the formation of the oxetane ring, which occurs via an intramolecular exchange of the C5 α-acetoxy group (Scheme 1.11). Taxadien-5α-ol-*O*-acetyltransferase is the enzyme likely to be used during the formation of the oxetane ring.



Scheme 1.11 – Formation of the oxetane ring

The final steps involve the addition of the side chain to the taxane core which is essential for the biological activity of taxol. The natural amino acid α-phenylalanine **17** is converted into β-phenylalanine **18** by the enzyme Peptidylglycine Alpha-amidating Monooxygenase (PAM) (Scheme 1.12). CoA-ligase then activates β-phenylalanine to the corresponding CoA ester which is then transferred to baccatin III **19**. Hydroxylation at C2' and finally a benzoylation at C3' then gives taxol **1**.[15]

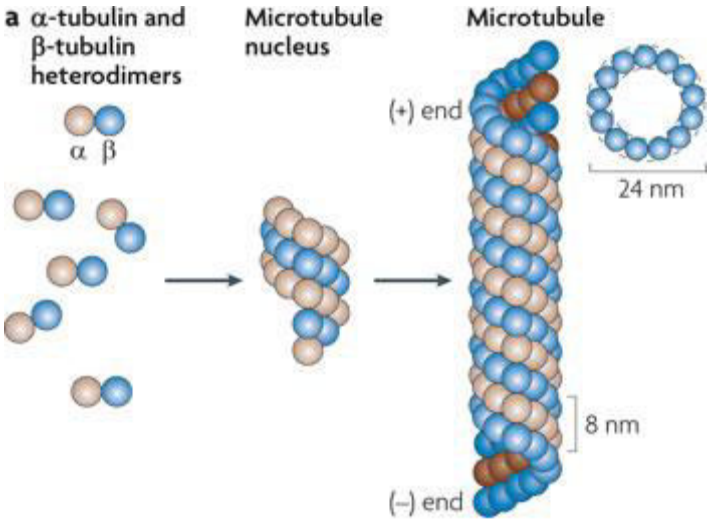


Scheme 1.12 – Biosynthesis of the Taxol side chain

1.5 Mode of Action

When the mode of action was discovered by Susan Horwitz in 1979,[16] it was found to be a unique one. Taxol is part of the same family of spindle poisons such as vinblastine and vincristine, both anticancer drugs, but its mode of action was different. Mitotic spindle poisons act on the cell cycle, blocking cell division at mitosis which results in cell apoptosis. However, taxol stabilises microtubule polymers, blocking mitosis, as chromosomes are unable to create the spindle during metaphase which evidently leads to cell apoptosis.

Microtubules are a component of the cell cytoskeleton and are made of tubulin. These hollow tubular polymers have an outer diameter of 24 nanometres, with an inner diameter of approximately 12 nanometres. They can grow up to 25 micrometres in length. Tubulin is a heterodimer consisting of an α-subunit and β-subunit. Microtubules are a result of the head to tail self assembly of these tubulin dimers which form protofilaments, these in turn form the walls of the microtubule (Scheme 1.13). Thirteen profilaments are needed to make a microtubule.

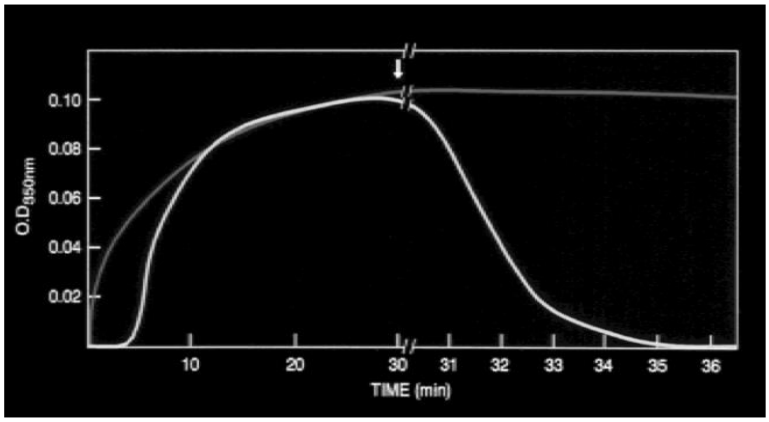


Scheme 1.13 – Structure of a microtubule[17]

(Picture from *Nat. Rev. Drug. Discov*, **2010**, ref 15)

Formation of microtubules is driven by guanosine triphosphate (GTP) binding and hydrolysis at the exchangeable site found on the β-subunit; it can also bind to the α-subunit but this is a non-exchangeable site. The two subunits are in equilibrium in the cell which is known as dynamic instability. Microtubules are assembled at 37 °C in the presence of GTP and dissembled when the temperature is lowered and/or in the presence of calcium ions.

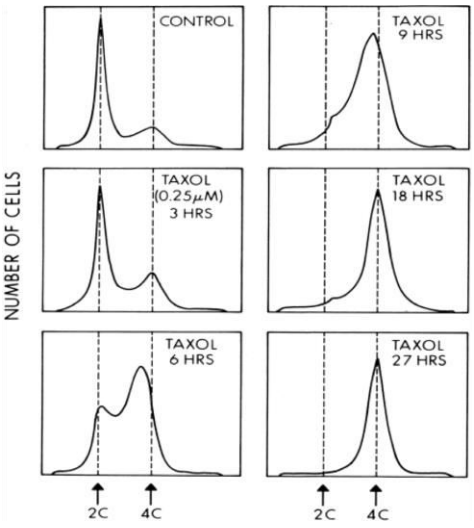
When spindle poisons such as vinblastine or vincristine bind to the β-subunit of tubulin, this affects the equilibrium of the cell and prevents polymerisation.[18] The mode of action of taxol is totally different to that of normal spindle poisons. Instead of preventing polymerisation, taxol promotes it and prevents depolymerisation of the microtubules. Taxol can even promote tubulin assembly in the absence of GTP and at lower temperatures. The most important discovery was that the microtubules formed in the presence of taxol were stable to depolymerisation in the presence of calcium ions and at 4 °C, when both these conditions would normally allow depolymerisation to occur (Scheme 1.14).



Scheme 1.14 – Stabilisation of microtubules

Taxol enhancing tubulin polymerisation and mictrotubule stabilisation
White line: no taxol added, Grey line: 10 µm taxol added. $CaCl_2$ (4 nM) is added at 30 min showing no destabilisation of the microtubule.
(Scheme from *J. Nat. Prod.* **2004**, *67*, 136-138)

Microtubules formed in the presence of taxol are narrower (22 nm outer diameter) than when formed under normal conditions due to only twelve protofilaments forming the microtubule. These abnormal microtubules are located near the poles of the spindle and do not organise themselves into the metaphase position (Scheme 1.15). Instead the abnormal microtubules replicate and form ball-shaped chromosomal masses; this lack of cellular organisation inhibits spindle formation and causes cell death.

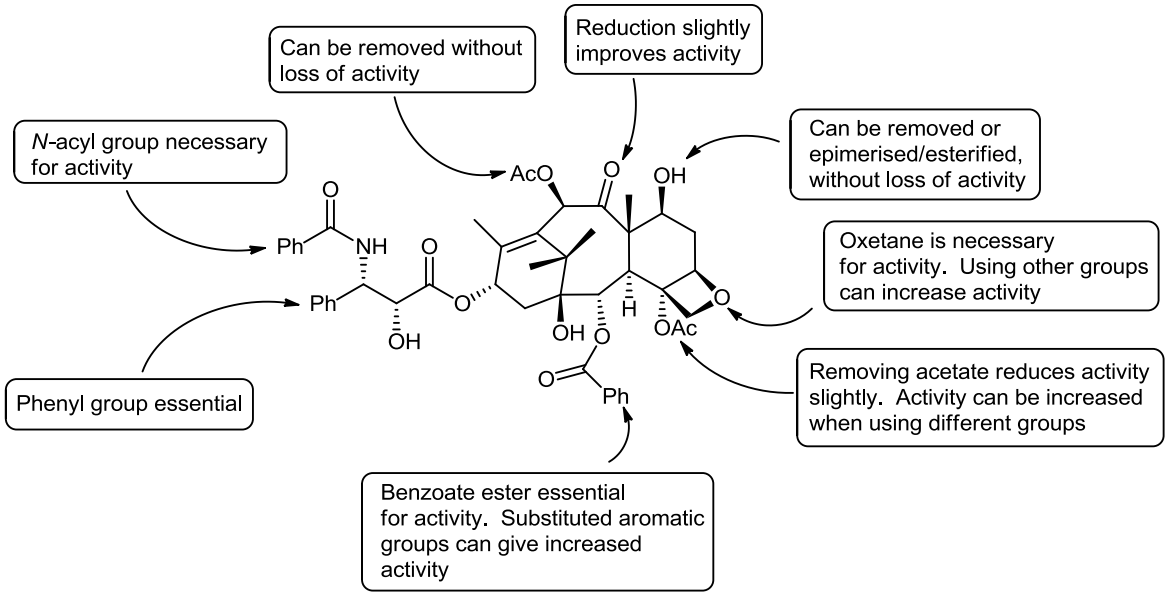


Scheme 1.15 – Taxol blocking cells during mitosis

DNA from diploids cells (2C) and tetraploid cells (4C) after treatment with taxol. DNA content did not change over the course of the experiment showing that taxol blocks cell division.
(Scheme from *J. Nat. Prod.* **2004**, *67*, 136-138)

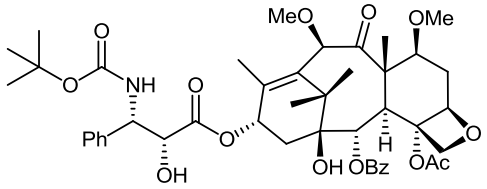
1.6 Structure and reactivity

There have been numerous studies on the structural activity of taxol in order to understand its biological activity and therefore create new analogues. Key points about the activity of taxol are shown below as detailed by Kingston[19] (Scheme 1.15). Changes made to the top half of the molecule tend not to affect its activity whereas changes made to the bottom half of the molecule affect its reactivity greatly. These changes would affect the way taxol binds to the β-tubulin subunit.



Scheme 1.16 – Structure-activity relationship

With the structural activity of taxol fully understood, this has led to novel analogues being synthesised, some of which are now available on the market as anti-cancer drugs, whilst some are still in clinical trials. One of these new analogues, cabazitaxel **20** (Scheme 1.17) is marketed by Sanofi as Jevtana[20] and was recently approved by the FDA as a therapy for patients with prostate cancer, which was previously treated with docetaxol (taxotere).



20

Scheme 1.17 – Cabazitaxel

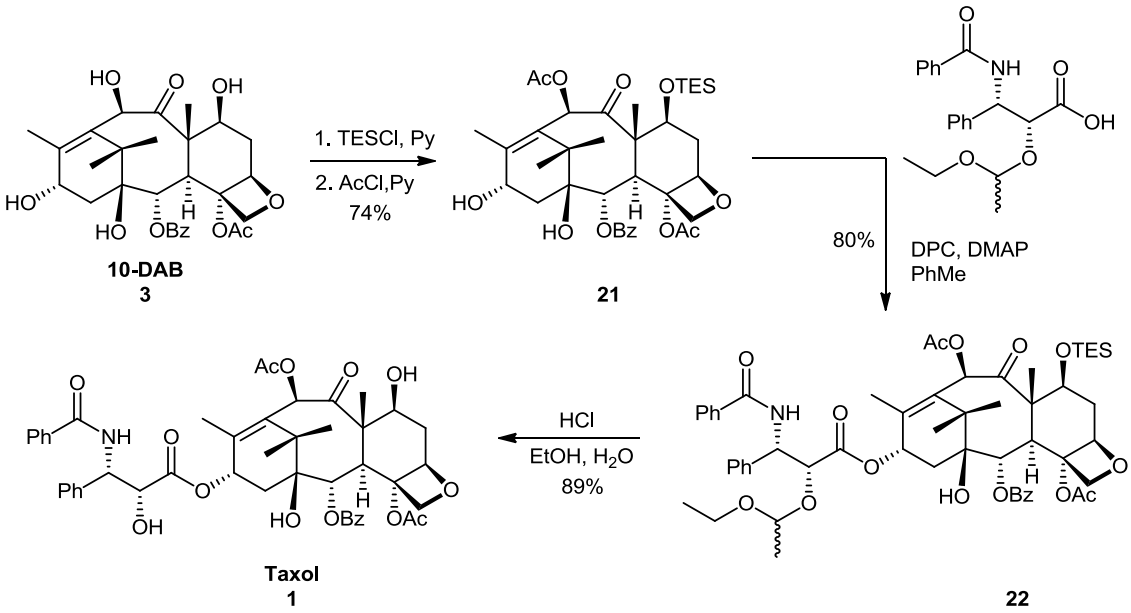
Cabazitaxel has the ability to cross the blood brain barrier, unlike taxol and taxotere and is undergoing further studies to be used as a treatment for other diseases/cancers.

1.7 Previous syntheses of taxol

Due to its complex structure, taxol has been the target of many organic chemists since its discovery. This interest has led to a variety of ways of synthesising taxol; numerous partial and total syntheses have been described. Most of the interest in synthesising taxol has not been applied to its synthesis in industry however; it has led the way for new analogues, such as taxotere and cabazitaxel, to be discovered.

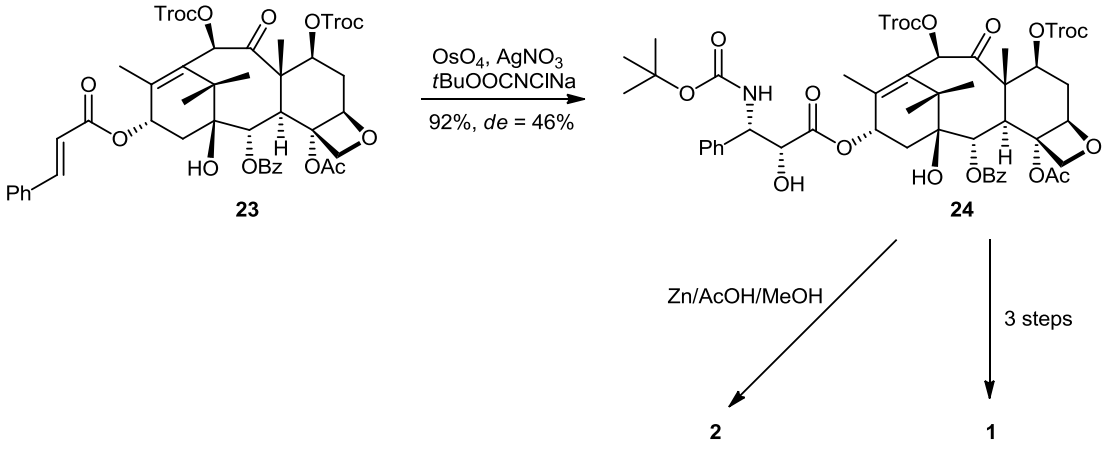
1.7.1 Semi-synthesis of taxol

Since taxol cannot be isolated in large yield from the bark of the yew tree, certain groups started looking into synthesising taxol from its more renewable source 10-DAB **3**. As mentioned before Potier and Greene[10] completed the semi-synthesis of taxol in 1988. The hydroxyl group at C7 was selectively protected to give 7-TES baccatin III **21** followed by addition of the side chain using di-2-pyridyl carbonate (DPC) **22**. Hydrolysis of the side chain then gave taxol in a good yield (Scheme 1.18).



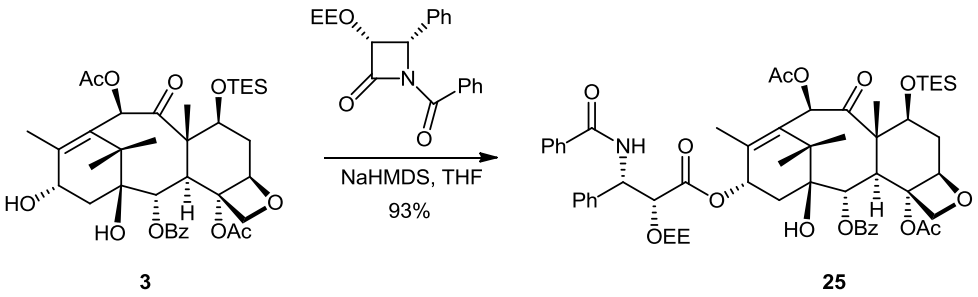
Scheme 1.18 – Semisynthesis by Potier and Greene

It was during this synthesis that Potier also synthesised taxotere.[21] Potier applied the Sharpless vicinal oxyamination reaction to a cinnamate taxane derivative he had synthesised in order to add the side chain. After some simple deprotections and removal of the trichloroethyloxycarbonyl group, taxotere was obtained (Scheme 1.19).



Scheme 1.19 – Potier semisynthesis of taxotere

Holton[22] and Ojima[23] also successfully added the side chain to 10-DAB **3**; they opened an optically pure β-lactam to give the side chain **25** (Scheme 1.20).



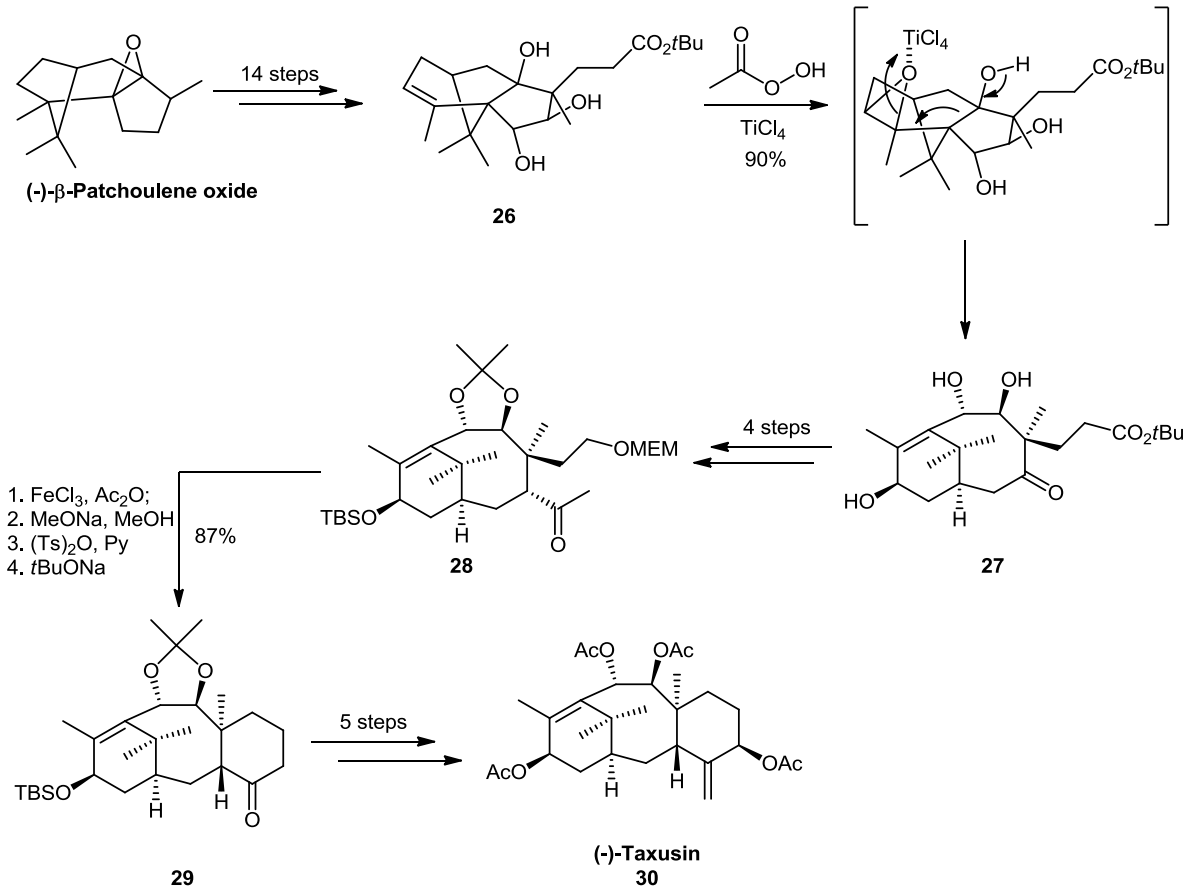
3 **25**

Scheme 1.20 – Semisynthesis by Holton and Ojima

1.7.2 Total syntheses of taxol

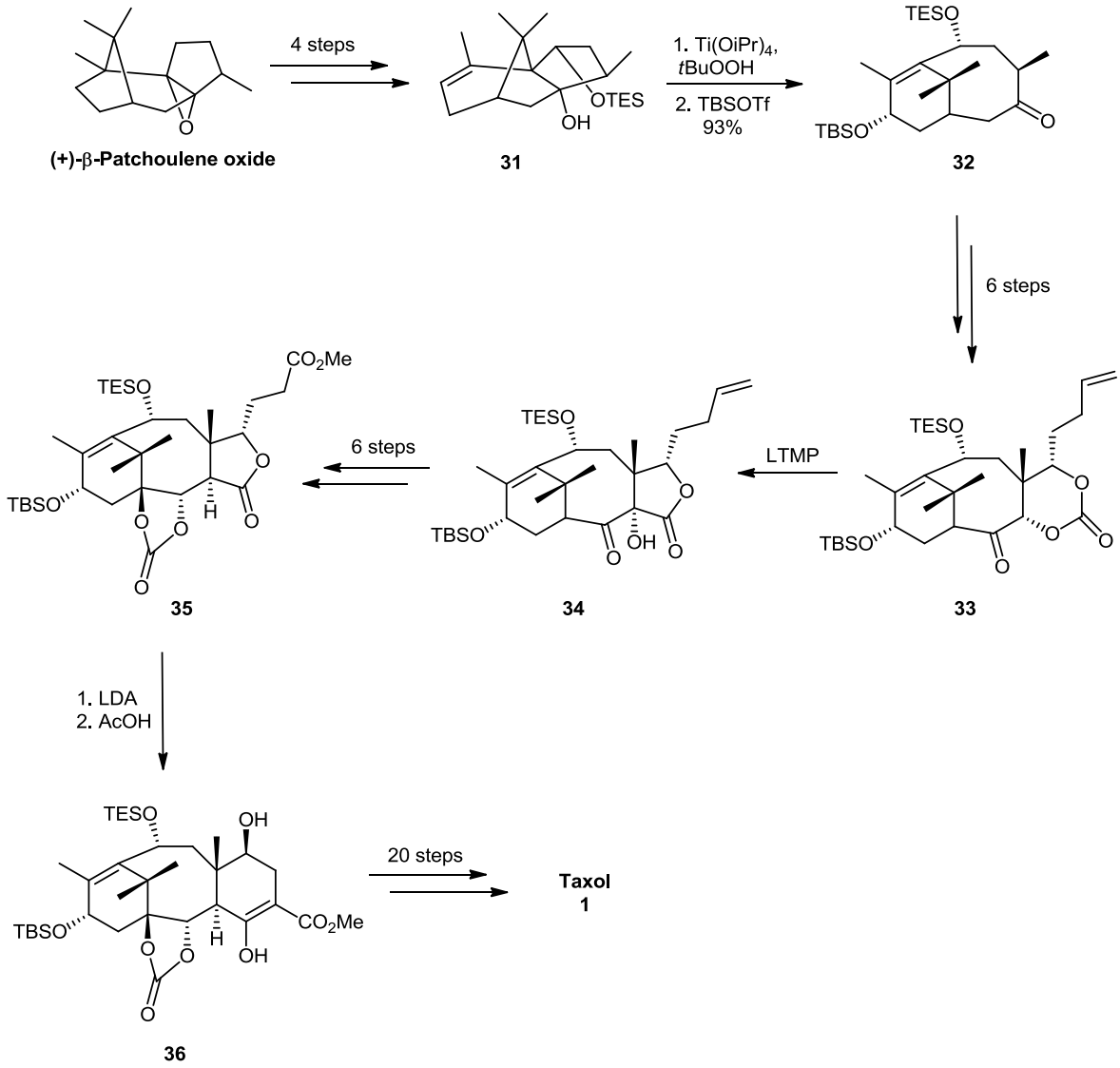
A. Fragmentation methods of synthesising taxol or taxane derivatives

The first breakthrough in the synthesis of taxol was achieved by Robert Holton. In 1984, he used work carried out by Buchi[24] to synthesise a derivative of β-patchouli oxide[25] which he would then skeletally rearrange. A few years later this work was then used to synthesise (-)-taxusin,[26] which has a skeletal system similar to taxol. Natural β-patchoulene oxide was converted to the homoallylic alcohol **26** in fourteen steps. This compound was then transformed to the epoxide, which when treated with titanium tetrachloride and peracetic acid to give the AB system **27** (Scheme 1.21). Using this method not only gave the AB bicycle but also placed five asymmetric centres on the molecule. The C ring was installed via an intramolecular nucleophilic substitution of the tosylate, synthesised from intermediate **28**. The final five steps were carried out to give (-)-taxusin **30** in a good yield.



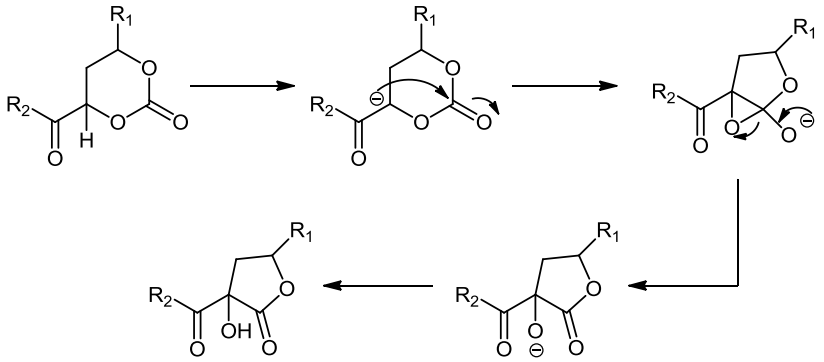
Scheme 1.21 – Holton synthesis of (-)-taxusin

Following on from the synthesis of (-)-taxusin, Holton completed the total synthesis of taxol in 1994,[27] using the same type of chemistry as had previously been carried out. The starting material for taxol was the unnatural enantiomer of β-patchoulene oxide, synthesised in twelve steps from (-)-camphor and described by Buchi.[28] The epoxide was transformed to the homoallylic alcohol **31** in four steps (Scheme 1.22).



Scheme 1.22 – Total synthesis of taxol by Holton

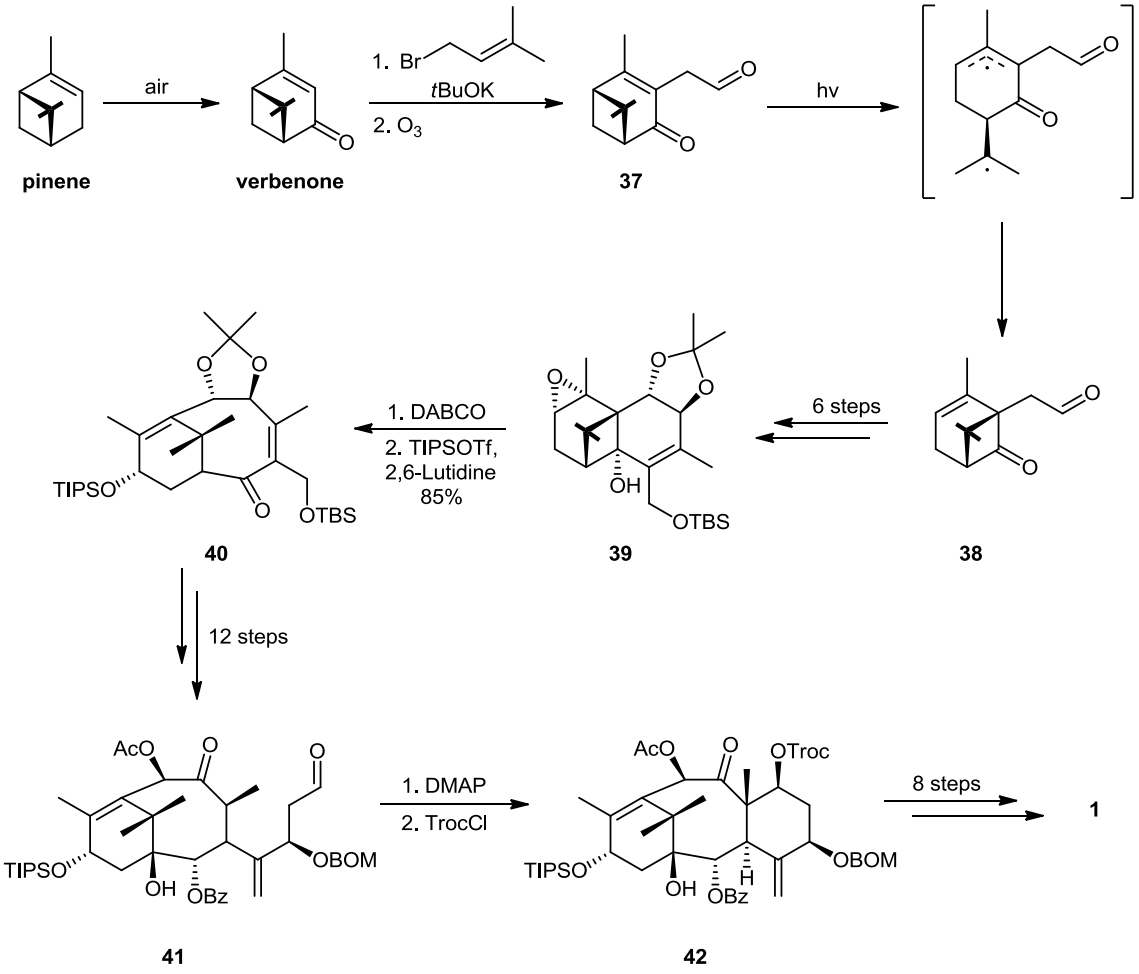
This was then subjected to the same fragmentation as described in the synthesis of taxusin. Ketone **32** was then transformed into the carbonate **33**, using lithium 2,2,6,6-tetramethylpiperidide (LTMP), which was followed by a Chan rearrangement[29] (Scheme 1.23) to give **34**, before the hydroxylactone was transformed into ester **35**. To form the C ring a Dieckmann condensation was carried out giving **36** and following a further twenty steps the synthesis of taxol was complete.



Scheme 1.23 - Chan rearrangement

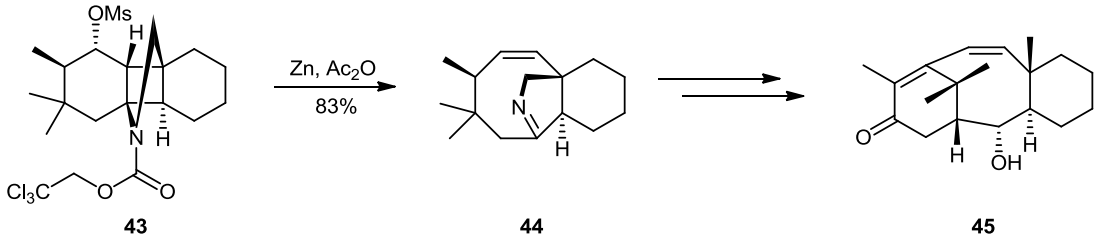
It was not only Holton who synthesised taxol starting from a natural product, Wender synthesised taxol from pinene,[30] an abundant and inexpensive starting material. Pinene is easily oxidised in air giving verbenone which was then converted to the keto-aldehyde **37** by addition of prenyl bromide followed by selective ozonolysis of the more electron rich double bond (Scheme 1.24). Photochemical rearrangement of **37** gave the chrysanthenone derivative **38**, and a further six steps gave the intermediate **39.**

Transformation to **40** was carried out using a fragmentation method similar to that of the rearrangement carried out by Holton, which gave Wender the AB bicycle skeleton of taxol. This bicycle is slightly more functionalised than Holton's as it features the oxygenated positions at C2 and C9. This was then transformed into the keto-aldehyde **41** in twelve steps. An intramolecular aldol reaction formed the C ring **42**, giving the oxygenated C7 position with good stereoselectivity. It took a further eight steps to complete the synthesis of taxol **1**.



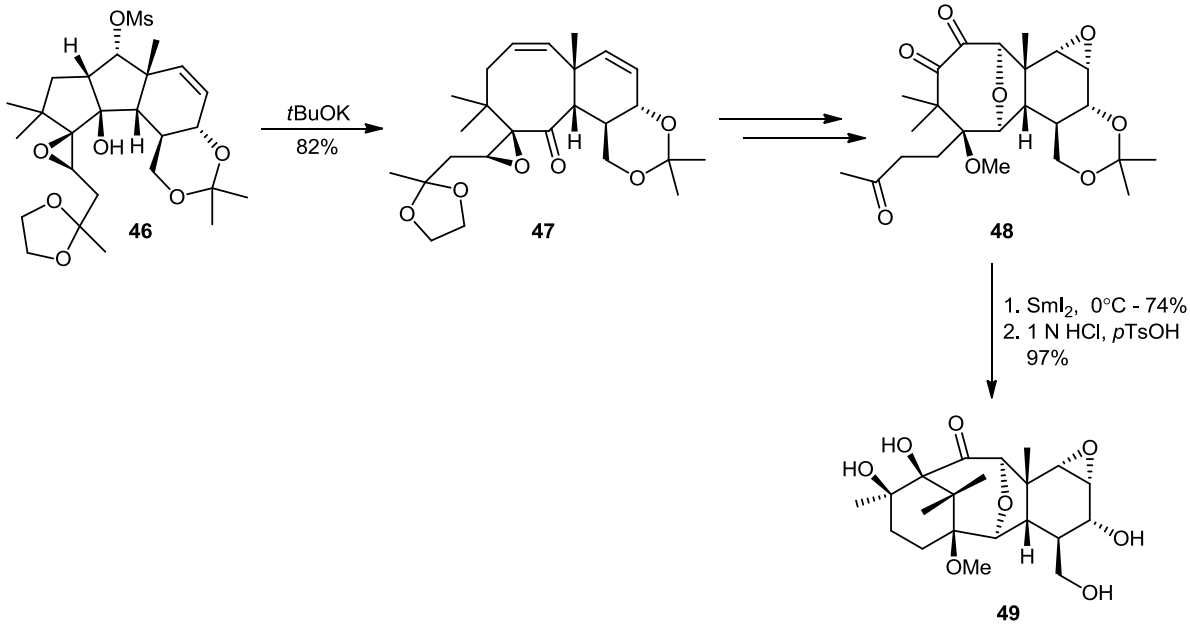
Scheme 1.24 – Total synthesis of taxol by Wender

Using this kind of fragmentation has led to two total syntheses of taxol but other methods have also been applied. Ring-opening methods were studied by Swindell and Arseniyadis. Swindell[31] carried out a Grob fragmentation using zinc[32] to give the BC bicycle of taxol from an intermediate synthesised using photochemistry (Scheme 1.25).



Scheme 1.25 – Grob fragmentation by Swindell to form the BC bicycle

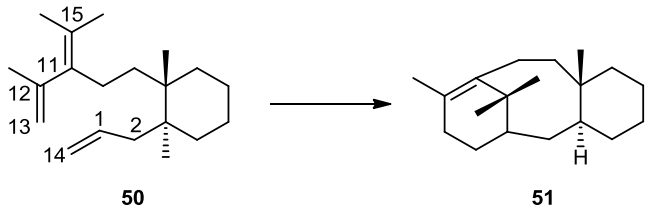
Arseniyadis[33] also carried out a Grob fragmentation in order to synthesise the BC bicycle of taxol in 2005. The fragmentation precursor gave the BC bicycle **47** in good yield. The A ring was closed using a samarium(II) iodide-mediated aldol reaction which produced a highly functional tricyclic taxoid skeleton **49** (Scheme 1.26).



Scheme 1.26 – Synthesis of the BC bicycle by Arseniyadis

B. Syntheses of taxol or its derivatives using the Diels-Alder reaction

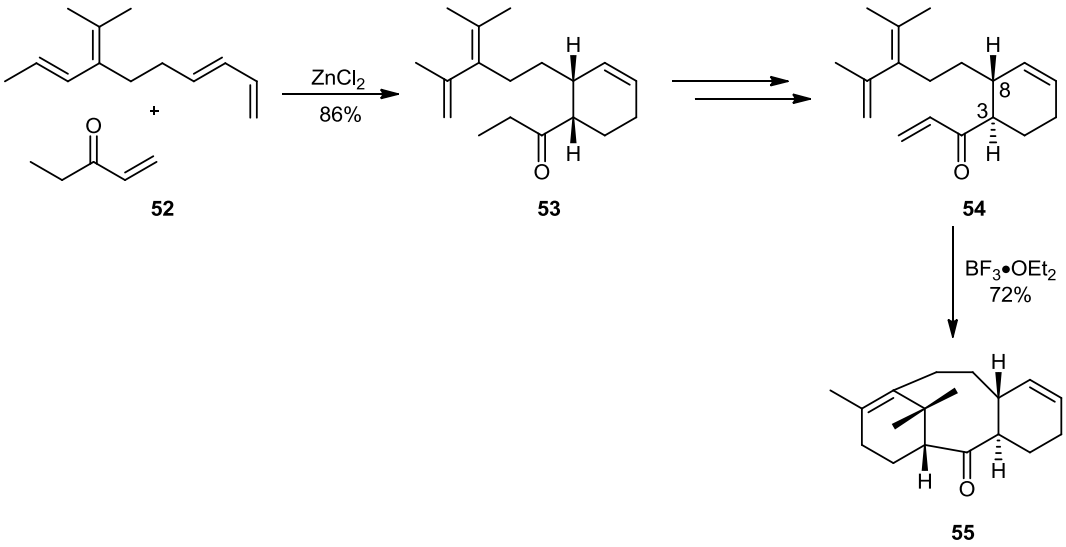
Diels-Alder reactions are more commonly used during the synthesis of polycyclic compounds; however intramolecular Diels-Alder (IMDA) reactions[34] have been applied to only a few syntheses toward the taxane skeleton. In 1983 both Sakan[35] and Shea used IMDA reactions to synthesise the ABC tricycle of a simple taxane. Shea[36] planned an IMDA reaction using a trienone as the precursor (Scheme 1.27).



Scheme 1.27 – Planned IMDA reaction by Shea

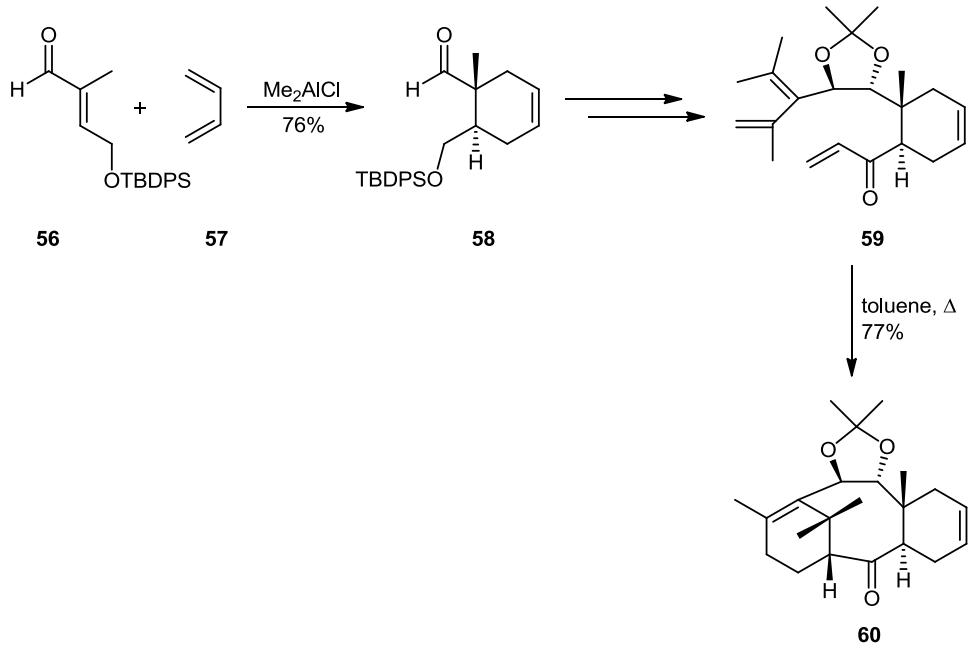
Many groups have studied this reaction although the problem was how to install the C ring using the Diels-Alder reaction. Winkler[37] was the first to accomplish this and installed

the A and C rings of taxane using Diels-Alder cycloaddition reactions. The second Diels-Alder reaction gave the ABC taxane tricycle **55** in a highly stereoselective fashion (Scheme 1.28).



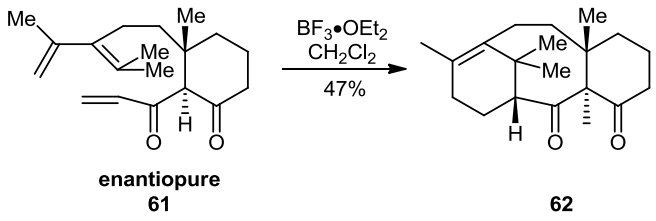
Scheme 1.28 – Synthesis of the taxane tricycle by Winkler

The examples discussed so far do not have highly functionalised skeletons; however Shea, using work from Winkler, has synthesised a more functionalised taxane skeleton whilst synthesising taxusin. This skeleton has the methyl at C8 present and a C9-C10 diol is in place.[38] The C ring was incorporated using a Lewis acid-catalysed IMDA reaction of an aldehyde and butadiene (Scheme 1.29).



Scheme 1.29 – Taxusin tricycle by Shea

More recently Baran[39] carried out a large scale (3.2 g) Diels-Alder reaction when working toward the synthesis of taxadienone, a simplified taxane intermediate which allows easy access to the taxane family skeleton. The desired diketone **62** was synthesised in a moderate yield from the enantiopure precursor **61** (Scheme 1.30).



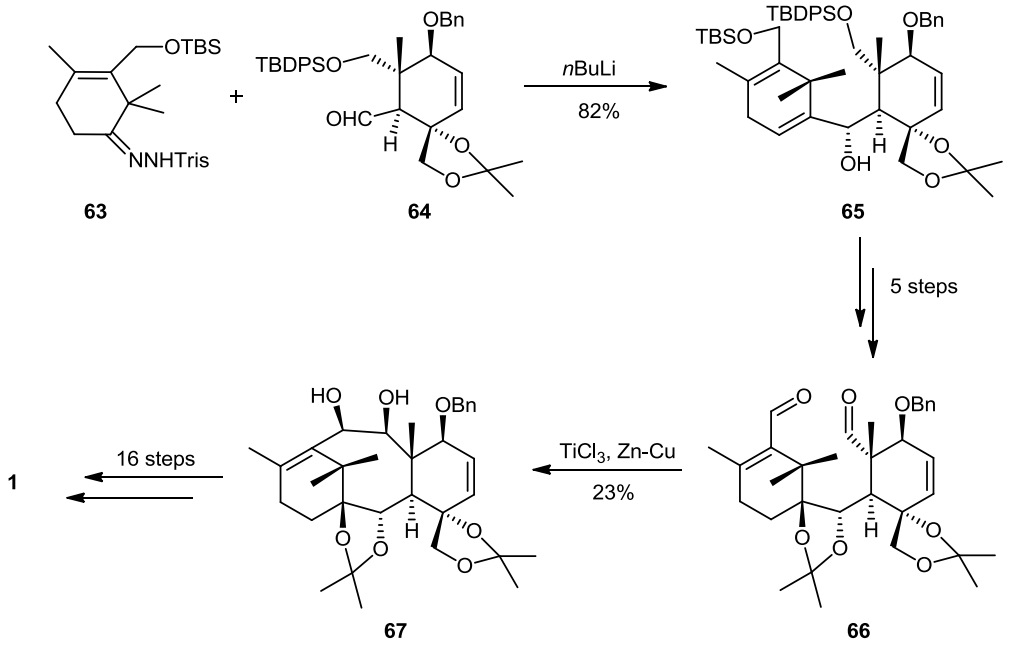
Scheme 1.30 – Diels-Alder reaction towards taxadienone by Bara

C. Convergent syntheses of taxol

The above methods are useful if only the basic skeletal frame of taxol is required. However, in order to synthesise taxol many steps are needed in order to add the necessary functionality. Many groups have developed a number of strategies towards the synthesis of taxol but a more convergent approach, where the functionalised A and C fragments are attached and then used to form the B ring, may seem more favourable. Most of these convergent approaches close the B ring between either C9-C10 or C10-C11.

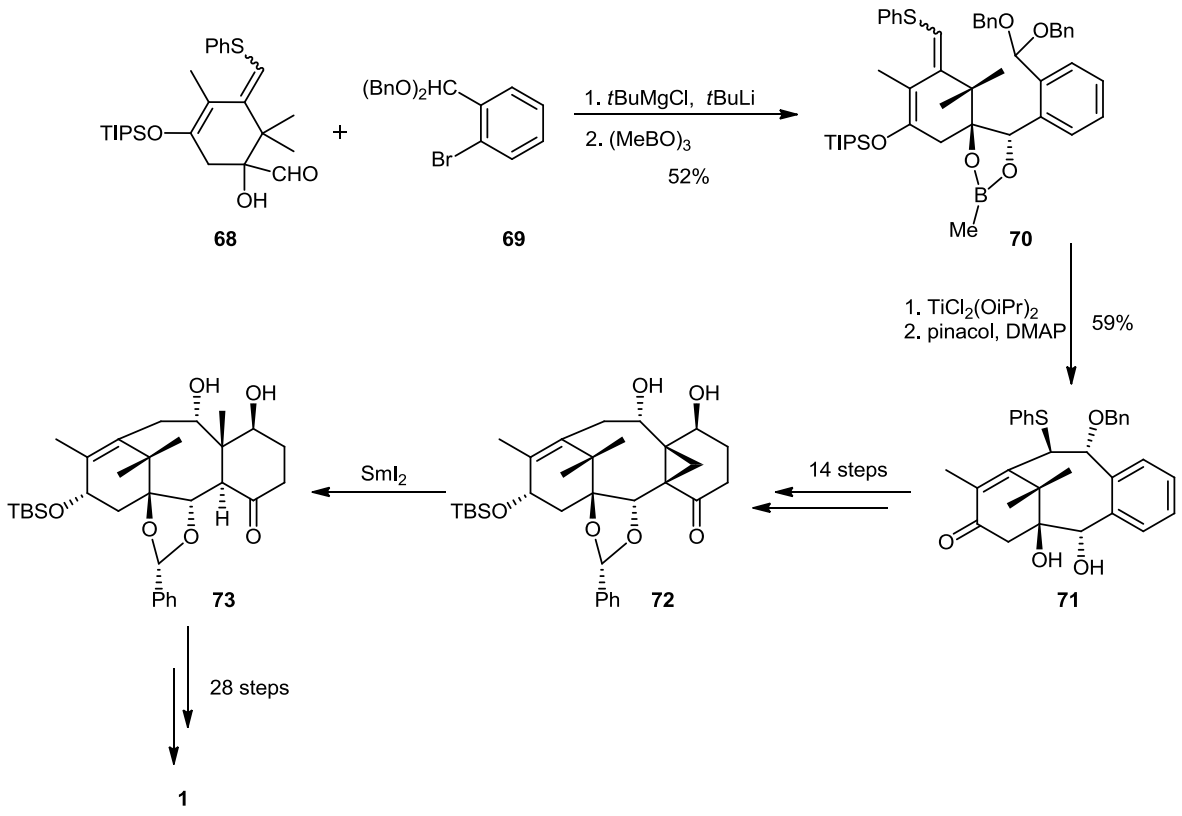
Coupling between C9-C10

In 1994, Nicolaou[40] synthesised taxol using a convergent synthesis. The first key step is a Shapiro coupling carried out between the A ring hydrazone **63** and the C ring aldehyde **64**. This is then transformed in five steps to give the dialdehyde **66,** which undergoes a McMurry coupling in order to obtain the ABC tricycle **67**. Taxol **1** is obtained after a further sixteen steps as the side chain and functionalities at C13 and C5 still need to be added (Scheme 1.31).



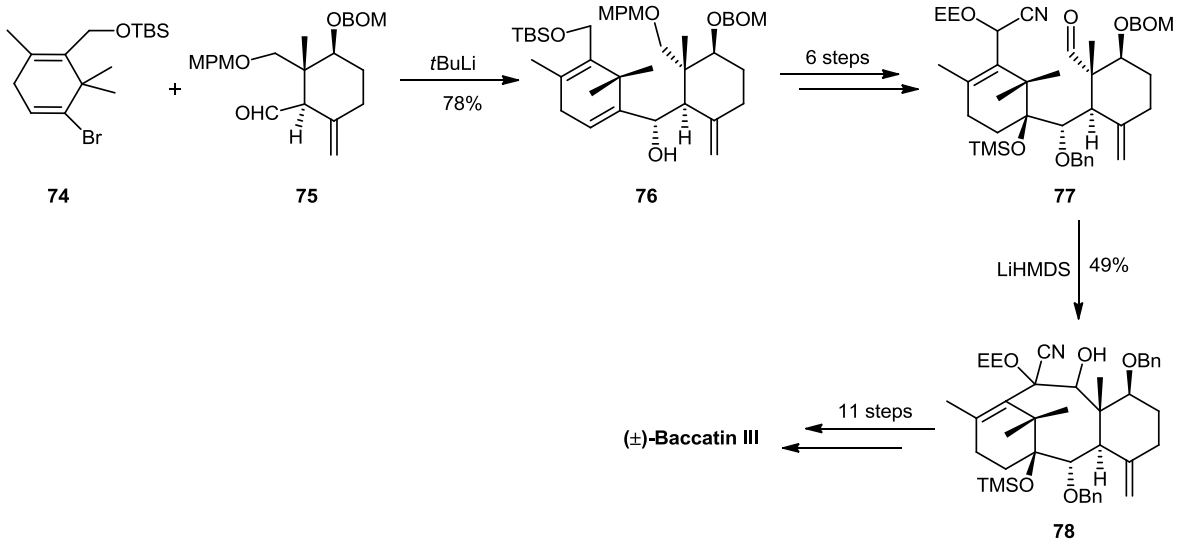
Scheme 1.31 – Synthesis of taxol by Nicolaou

Kuwajima also proposed a coupling reaction between C9 and C10 in order to synthesise taxol. The synthesis planned for a Mukaiyama aldol reaction between a vinyl sulfide and an acetal, which would be catalysed by a Lewis acid. This strategy allowed Kuwajima to synthesise not only taxol[41] but taxusin[42] as well. The synthesis, like Nicolaou's, starts with the C ring **69**, which is lithiated and added to the A ring **68** to give precursor **70**. A Mukaiyama aldol reaction then takes place to give the ABC tricycle skeleton **71** with an aromatic C ring. The methyl group at the C8 position was introduced by the ring opening of the cyclopropane **72** after treatment with samarium diiodide to give **73**. Twenty-eight more steps were needed in order to complete the total synthesis of taxol (Scheme 1.32).



Scheme 1.32 – Formal synthesis of taxol by Kuwajima

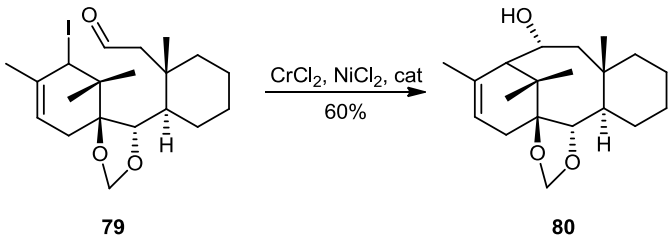
Closing the B ring between C9-C10 was also used in a formal synthesis of taxol by Takahashi[43] in 2006. Coupling between the A ring **74** and C ring **75** gave intermediate **76**, which was transformed in a further six steps to give **77**. This intermediate undergoes an intramolecular alkylation of the protected cyanohydrin to give **78** in a moderate yield. It then takes a further eleven steps to synthesise Baccatin III, thus completing the formal synthesis (Scheme 1.33).



Scheme 1.33 – Synthesis of Baccatin III by Takahashi

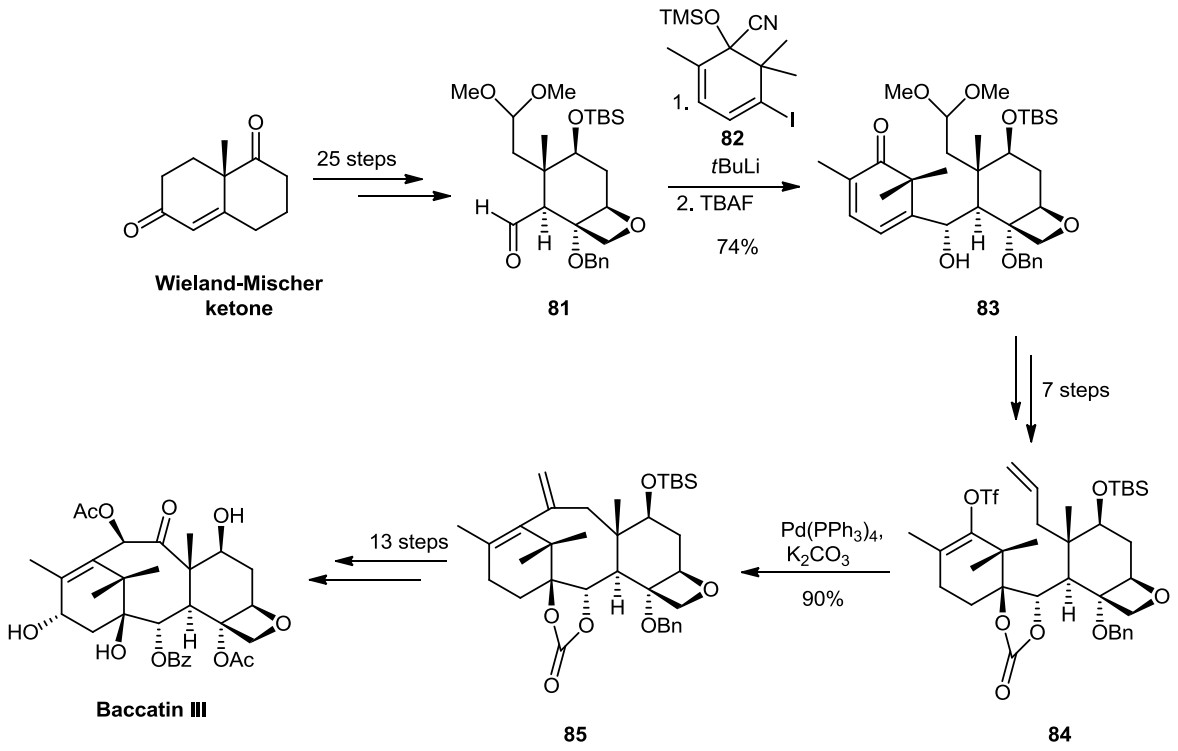
Coupling between C10-C11

Kishi[44] was the first to use a transition metal-mediated coupling to form the B ring between C10-C11. This was achieved using Ni(II) and Cr(II) chloride[45] to form the ring via an intramolecular coupling between the vinyl iodide and the aldehyde (Scheme 1.34).



Scheme 1.34 – Closure of the B ring by Kishi

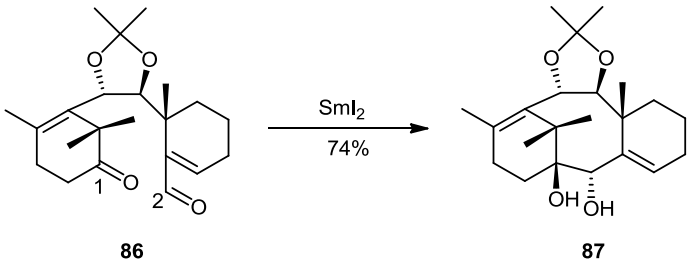
Closure of the B ring between C10 and C11 was also carried out by Danishefsky[46] in 1995 during his approach to the total synthesis of taxol. After transforming the Wieland-Mischer ketone to the C ring and preparing the A ring, **81** and **82** were coupled together using the vinyl lithiated species of **82** to give **83**. Transformation to **84** in seven steps then allowed for a Heck coupling to take place in order to close the B ring of the taxane skeleton giving **85**. After a further thirteen transformations, Baccatin III **3** was synthesised and this was transformed into taxol (Scheme 1.35).



Scheme 1.35 – Synthesis of taxol by Danishefsky

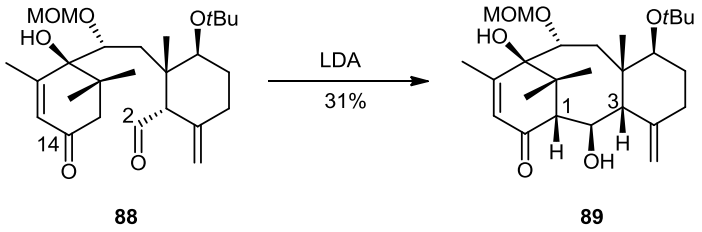
Coupling between C1-C2

Other routes of forming the eight-membered B ring of taxol have been studied; these examples look at closing the ring between C1 and C2. Swindell[47] proposed a pinacol coupling using samarium diiodide between a ketone at C1 and an aldehyde at C2. This was carried out on an intermediate without the oxygen functionalisation at C7 but did incorporate the methyl group at C8 (Scheme 1.36).



Scheme 1.36 – Closure of the B ring using a pinacol coupling

Arseniyadis[48] synthesised the B ring using an aldol reaction between an aldehyde at C2 and a ketone at C14. Despite giving a poor yield, this ABC tricycle has some functionalisation but lacks the oxygen functionality at C1 and generates the wrong diastereomer at C3 (Scheme 1.37).

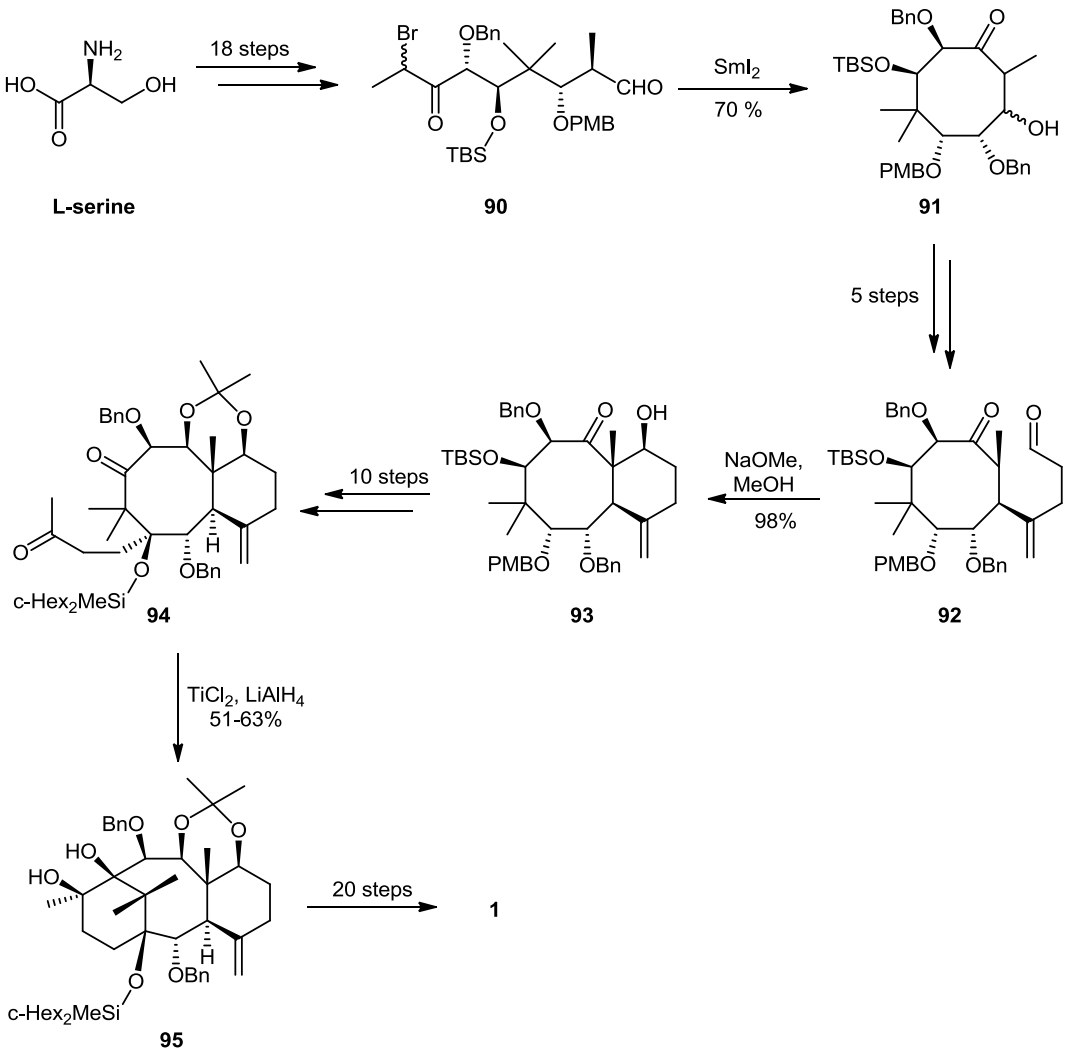


88 89

Scheme 1.37 – Closure of the B ring using an aldol reaction

D. Other examples towards taxol

The last of the six total syntheses of taxol falls under this category. Mukaiyama[49] synthesised taxol using a linear synthesis based on forming the B ring and adding the rest of the structure around it. L-Serine was transformed in eighteen steps to give the aldehyde **90.** The B ring was then formed by an intramolecular Reformatsky reaction using samarium diiodide to give **91**. This was then transformed in five steps to give **92**, which underwent an aldol reaction to form the BC bicycle **93** in good yield**.** A further ten transformations led to **94**, which underwent a pinacol coupling using titanium chloride in order to form the A ring **95**. A further twenty steps resulted in the synthesis of taxol **1** (Scheme 1.38).



Scheme 1.38 –Total synthesis of taxol by Mukaiyama

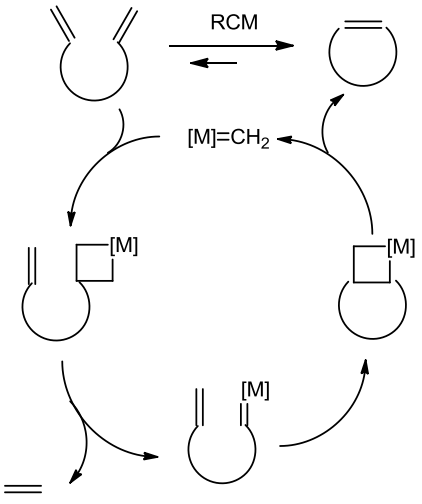
There are many different ways to synthesise the ABC tricycle of taxol, some more successful than others. Despite these previous attempts no one has synthesised taxol using olefin metathesis. This could be a key development in synthesising the B ring with all its functionalities and could lead to other new analogues of taxol being discovered.

1.8 Cyclooctene formation using metathesis reactions

1.8.1 Introduction to metathesis

Metathesis comes from the Greek meaning 'change of position' and it promotes skeletal rearrangements between carbon atoms.[50] It is a powerful tool used in synthetic organic chemistry. In 2006, the Nobel prize for Chemistry was won by three researchers who had worked on the metathesis reaction. Yves Chauvin[51] studied the mechanism of the reaction whilst Richard Schrock[52] and Robert Grubbs[53] developed catalysts that increased the efficiency of the reaction.

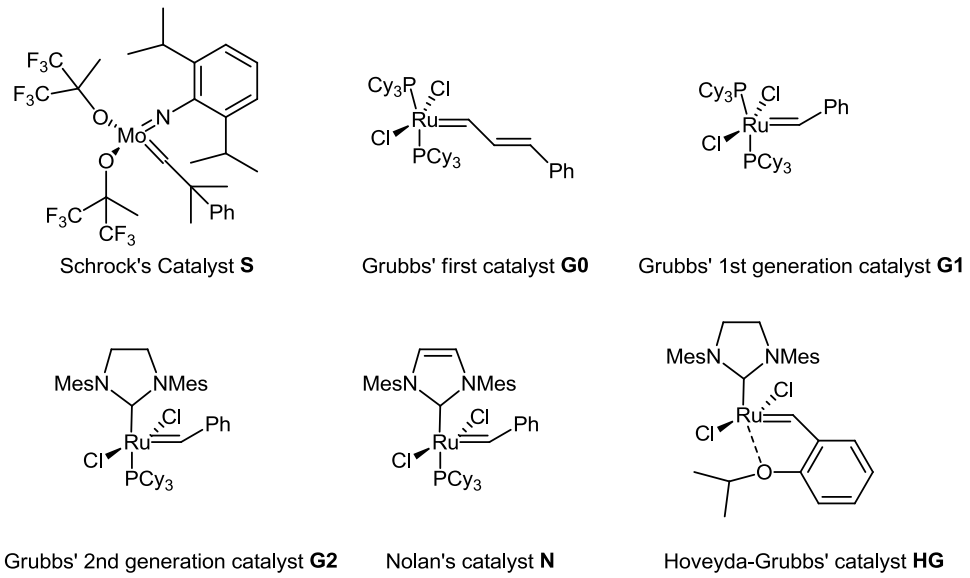
Olefin metathesis can be classified into four groups: cross-metathesis (CM), ring-closing metathesis (RCM), ring opening metathesis (ROM) and acyclic diene metathesis (ADMET). Cross metathesis allows C1=C2 and C3=C4 to be transformed into C1=C3 and C2=C4 and all reactions are, in principle, reversible. The most commonly used type of metathesis is RCM, where terminal alkenes react using a catalyst to generate a cyclic olefin (Scheme 1.39). A smaller olefin is released during this reaction.



Scheme 1.39 – RCM catalytic cycle

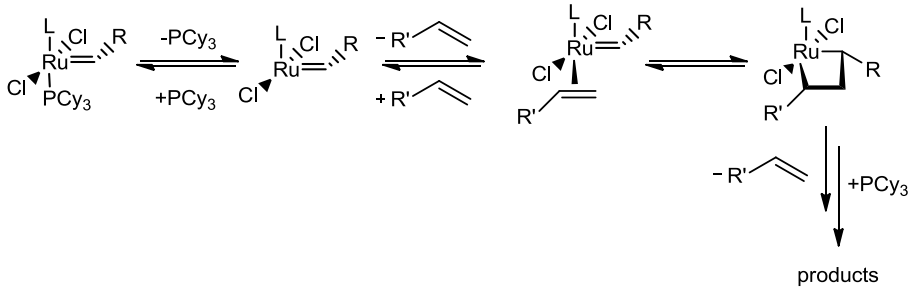
The mechanism of this reaction was discovered by Chauvin[54] in 1971 and as shown above, involves a sequence of [2+2] cycloadditions/cycloreversions of the metallic carbene and metallacyclobutane. The steps in the mechanism are reversible, however the reaction entropically favours the catalytic process as the ethylene group produced is highly volatile. Since the discovery of the mechanism many catalysts have been developed in order to

improve the reaction. The first catalysts, designed by Schrock between 1980 and 1990, were compounds containing either tungsten or molybdenum as these were found to be efficient in catalysing the reaction. However, these catalysts had their drawbacks, they were highly sensitive to air and moisture and they reacted with other functional groups present in the substrate. Grubbs developed a number of catalysts containing ruthenium, which were more stable in air and did not react with the other functional groups present in the substrate (Scheme 1.40).



Scheme 1.40 – Metathesis catalysts

Grubbs' catalysts contain the neutral ruthenium atom in an oxidation state (II) and have sixteen electrons in the external orbital. The metal ion is normally coordinating one or more electron rich phosphine species, such as PCy_3. Grubbs proposed a slightly more detailed mechanism than Chauvin, suggesting the electron-rich phosphine atom participates using a dissociation-association pathway.[55] The first step is the dissociation of a phosphine ligand, this then generates the active carbene species that has fourteen electrons. The metal complex enters the catalytic cycle and forms an adduct with the olefin which contains sixteen electrons. The metallocyclobutane which is then formed is a new active species containing fourteen electrons, dissociation then allows the release of the metathesis product (Scheme 1.41).

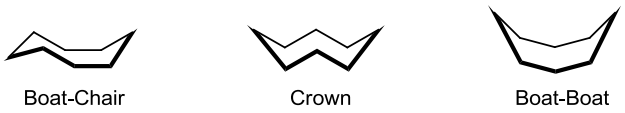


Scheme 1.41 – Metathesis mechanism by Grubbs

1.8.2 Formation of cyclooctenes by ring-closing metathesis[56]

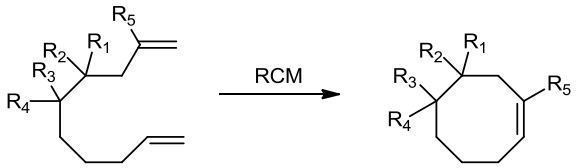
Synthesising eight-membered rings from acyclic precursors is a challenging problem faced by organic chemists. This is due to the amount of strain and the number of transannular interactions which are entropically unfavourable when forming the ring.

Conformations of an eight membered ring can be separated into three groups:[57] boat-chair, crown and boat-boat (Scheme 1.42). The interconversion between the conformations depends on the substituents found on the ring. The boat-chair conformation represents the most stable conformer as transannular interactions are minimised.



Scheme 1.42 – Conformations of cyclooctene

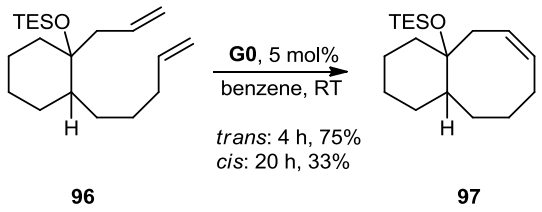
Ring-closing metathesis has become a powerful and versatile tool for the selective formation of cyclic compounds. Grubbs[58] was the first to use metathesis methods in an attempt to synthesise an eight-membered ring in 1995 (Scheme 1.43). The initial work was not successful and produced only dimerisation products, despite the reactions being carried out at high dilution.



R_1	R_2	R_3	R_4	R_5	Catalyst	Yield
Me	OTES	H	H	H	**G0**	0%
H	H	CO_2Et	CO_2Et	H	**S/G1**	0%
H	H	CO_2Et	CO_2Et	Me	**S/G1**	0%

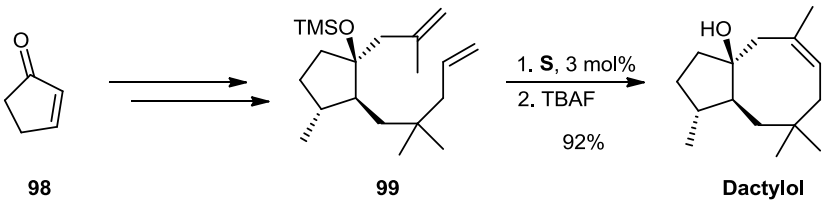
Scheme 1.43 – First tests by Grubbs

Despite these early failures, cyclisation could be realised by introducing conformational constraints, such as a ring that was already in place or using sterically hindered 1,2-disubstitents. An example of this was carried out by Grubbs, that involved a 1,2-*trans*-disubstitued cyclohexane (Scheme 1.44). It was presumed that the two olefins reacted due to their proximity as a resultant of the fused ring constrains. The *cis*-disubstituted isomer was a poorer substrate and gave a lower yield of the desired cycloocetene, together with some starting material and some side products.



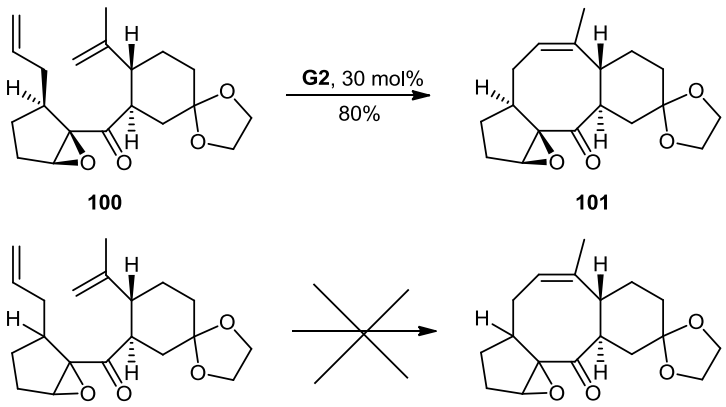
Scheme 1.44 – Influence of conformational restraints

Fürstner then applied this theory towards his synthesis of dactylol.[59] The eight-membered ring was formed in the presence of a fused five-membered ring and a *gem*-dimethyl group (Scheme 1.45) giving the product in an excellent yield.



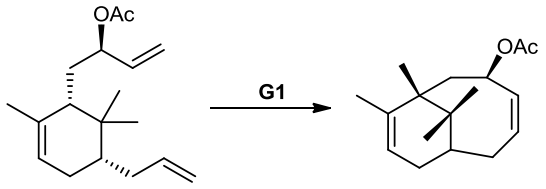
Scheme 1.45 – Synthesis of Dactylol by Fürstner

Tori[60] tested ring-closing metathesis reactions on four diastereomers that had an epoxide present, in his attempt to synthesise YW3699. Under the same conditions, only one diastereomer cyclised in an excellent yield; however the other three cyclisations were unsuccessul (Scheme 1.46). This shows the importance of the configuration of the molecule and shows that there are difficulties when cyclising some highly substituted molecules.



Scheme 1.46 – Cyclisation attempts by Tori

Syntheses using RCM to obtain the B ring of taxol have been attempted previously. The first has been carried out by Blechert when he was synthesising a model AB bicycle.[61] The precursor of the metathesis was obtained from (-)-β-pinene which was transformed to the enantiomerically pure A ring building block. Two diastereoemers were formed and under metathesis conditions using Grubbs' first catalyst, only one cyclised successfully, giving the desired AB bicycle model (Scheme 1.47).

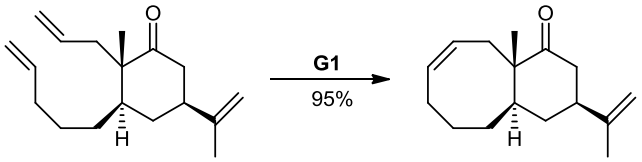


102 **103**

β-OAc 0%
α-OAc 59%

Scheme 1.47 – Synthesis of model AB bicycle by Blechert

Srikrishna[62] also carried out a successful metathesis reaction when synthesising a model BC ring of taxol. This simplified bicycle with no functionality at C1-C2 and no *gem*-dimethyl groups present, gave the cyclised product in excellent yield (Scheme 1.48).



104 **105**

Scheme 1.48 – Metathesis of BC bicycle by Srikrishna

These two examples show that metathesis reactions can be successfully applied when synthesising the B-ring of taxol. The problem remains that some key functionalities of taxol are missing and whether or not ring-closing metathesis would occur on a more substituted precursor.

Chapter II

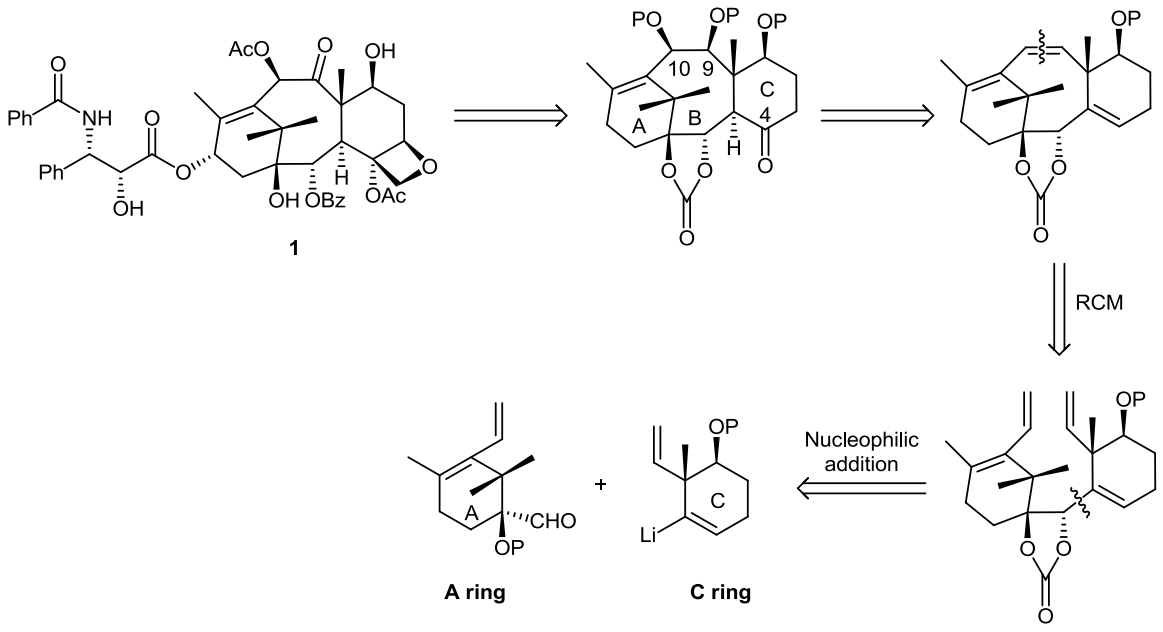
Towards Taxol- Synthesis of fragment A and ring C

2.1 Previous work in the lab

2.1.1 First approach to taxol

When the project started there were no publications about the total synthesis of taxol or the formation of cyclooctene rings using ring-closing metathesis. A convergent synthesis was planned where the A and C rings would be prepared and coupled together before closing the B ring; a strategy employed used by Nicolaou in his total synthesis of taxol.

Ring-closing metathesis between C9 and C10 would close the B ring and give the ABC tricycle. The metathesis precursor would be obtained from the addition of the A ring to a vinyllithiated C ring. The oxygenated functionalities would then be added by means of a dihydroxylation at C9-C10 and a hydroboration/oxidation sequence at C4 (Scheme 2.01).

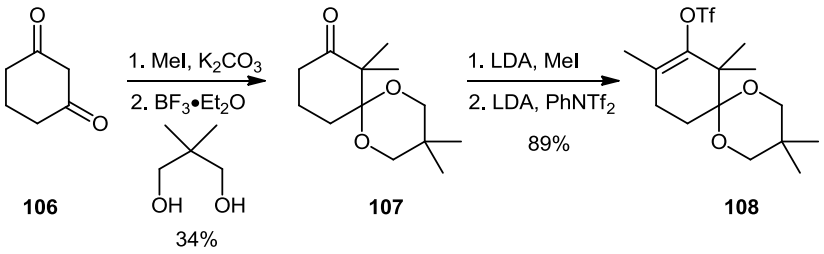


Scheme 2.01 – Proposed retrosynthesis

2.1.2 Work by Benoît Muller[63]

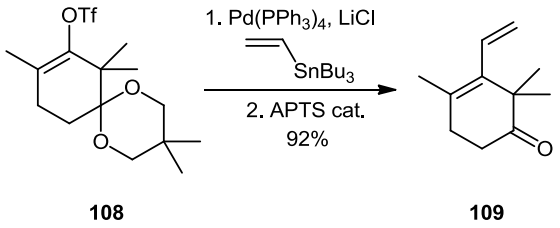
A. Synthesis of the A ring

A racemic model A ring with double bond functionality was synthesised.[64] 1,3-Cyclohexanedione **106** was dimethylated and one ketone was protected giving **107**. Another methylation procedure was then carried out followed by triflate formation which gave the precursor to the A ring **108** (Scheme 2.02).



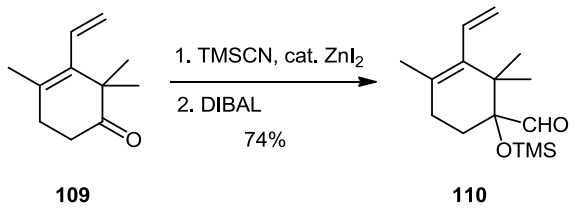
Scheme 2.02 – Synthesis of the vinyltriflate precursor

Compound **108** then underwent a coupling reaction with vinylbutylstannane, which was followed by the hydrolysis of the cyclic ketal to produce the dienone **109** (Scheme 2.03).



Scheme 2.03 – Synthesis of dienone **109**

Ketone **109** was then subjected to a cyanation reaction using trimethylsilyl cyanide in the presence of a catalytic amount of zinc iodide. The cyanohydrin obtained was then reduced to the aldehyde using diisobutylaluminium hydride to give the A ring **110** (Scheme 2.04).



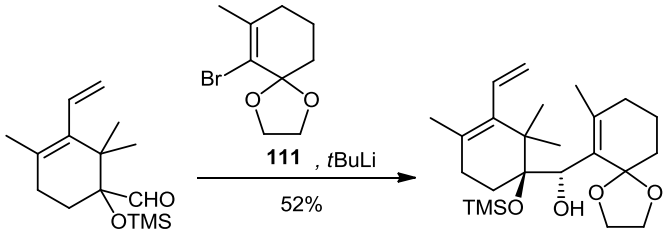
109 **110**

Scheme 2.04 – A ring aldehyde **110**

With the A ring successfully synthesised it could now be coupled with the model C ring.

B. First coupling of the A and C rings

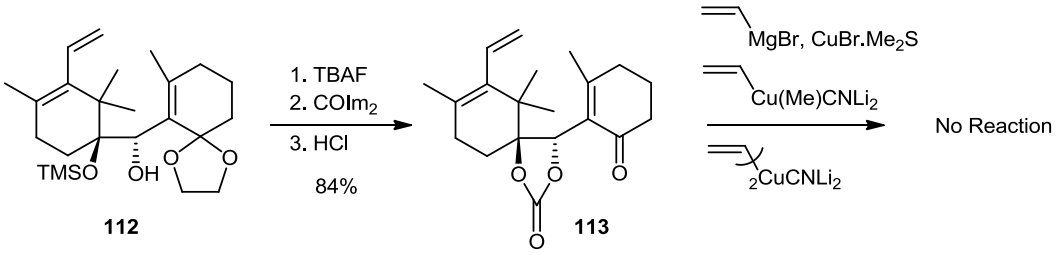
The first couplings took place using the vinylbromide **111**, which can easily be synthesised from 3-methylcyclohexanone.[65] The coupling using *tert*-butyllithium gave only the *trans* product **112** (Scheme 2.05); this unusual selectivity will be discussed later on.



110 **112**

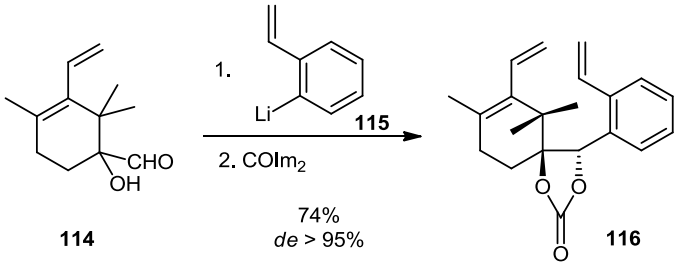
Scheme 2.05 – Coupling of A and C rings

Deprotection of the trimethysilyl ether gave the diol which was then transformed to the carbonate. The spiroketal was deprotected to reveal ketone **113**. This was to be followed by a Michael addition of a vinyl group to synthesise the precursor for the metathesis reaction. The Michael addition was unsuccessful, possibly due to steric hindrance around the enone (Scheme 2.06).



Scheme 2.06 – Michael addition trials

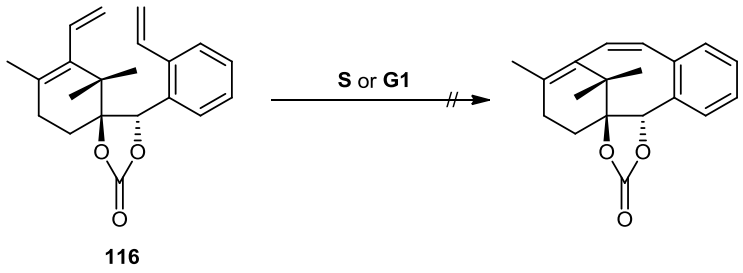
A simpler model was then used to test the metathesis reaction. A lithium derivative of 2-bromostyrene **115** was added to the A ring. The selectivity of the reaction was poor and a ratio of 2:1, in favour of the *cis* isomer, was obtained. This could be resolved by carrying out the coupling on the α-hydroxy aldehyde **114**, as the *trans* isomer **116** is the major product obtained after protection of the diol as a carbonate (Scheme 2.07).



Scheme 2.07 – Model metathesis precursor

C. Test metathesis reactions: closing the B ring

A ring-closing metathesis reaction was carried out with the trienic carbonate however, in the presence of either Schrock or Grubbs first generation catalysts (and regardless of the temperature) no reaction occurred (Scheme 2.08). There are several possible explanations to why this reaction was not working. One reason could be the deactivation of the double bonds due to conjugation, it could also be because of the strain that would be present if the B ring was successfully formed, as well as the strain from *gem*-dimethyl group.



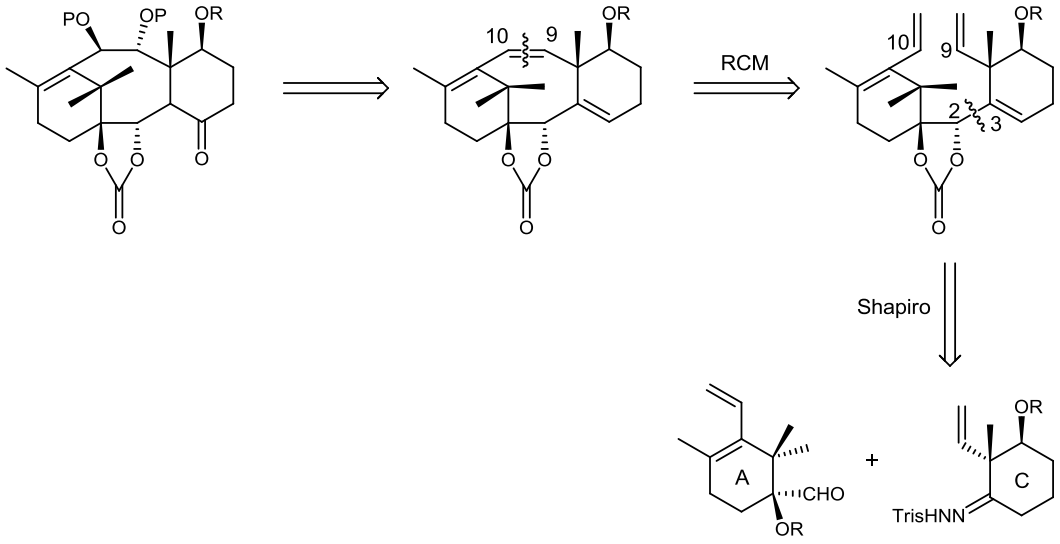
Scheme 2.08 – Metathesis tests

Despite the metathesis reactions failing to form the B ring, the A ring had been synthesised successfully.

2.1.3 Work by Damien Bourgeois[66]

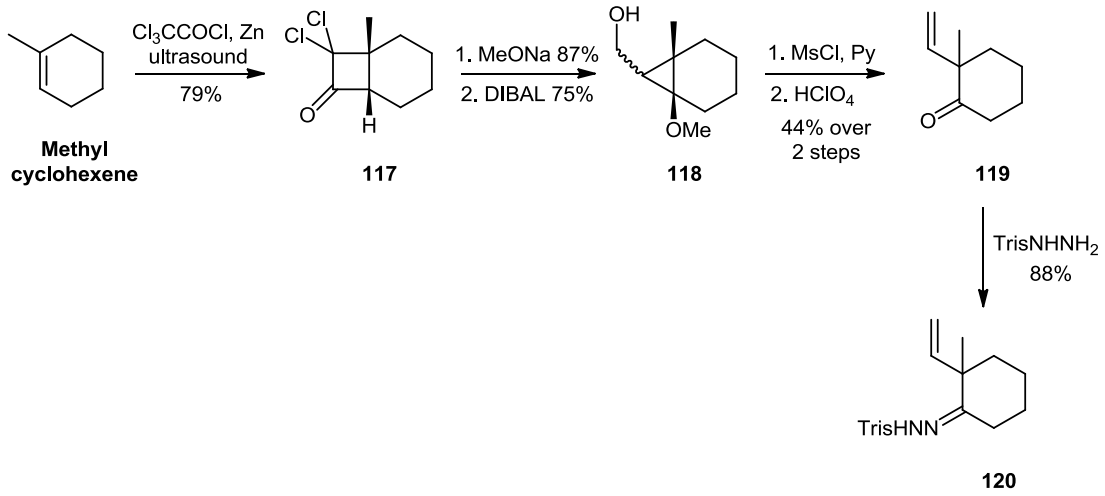
A. Convergent approach

A convergent retrosynthesis was then envisaged, synthesising taxol from a tricyclic compound. The B ring would be closed between C9 and C10 by ring-closing metathesis, whilst the precursor would be obtained by coupling the A and C rings (Scheme 2.09).



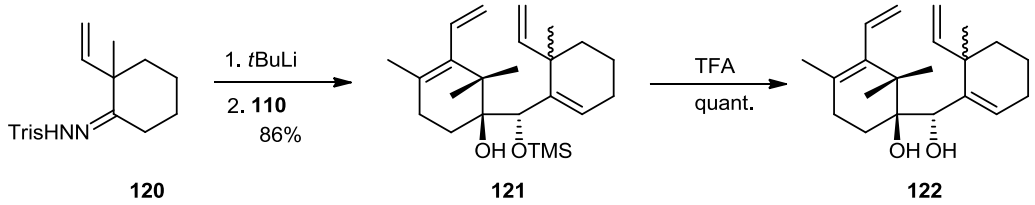
Scheme 2.09 – Retrosynthesis for convergent approach

A model C ring was synthesised using methyl cyclohexene, which was transformed into **117** following a [2+2] cycloaddition. Compound **117** underwent ring rearrangement and reduction to give **118**, which was subjected to elimination, then oxidation, giving **119**. Compound **119** was then transformed to the hydrazone **120** (Scheme 2.10).



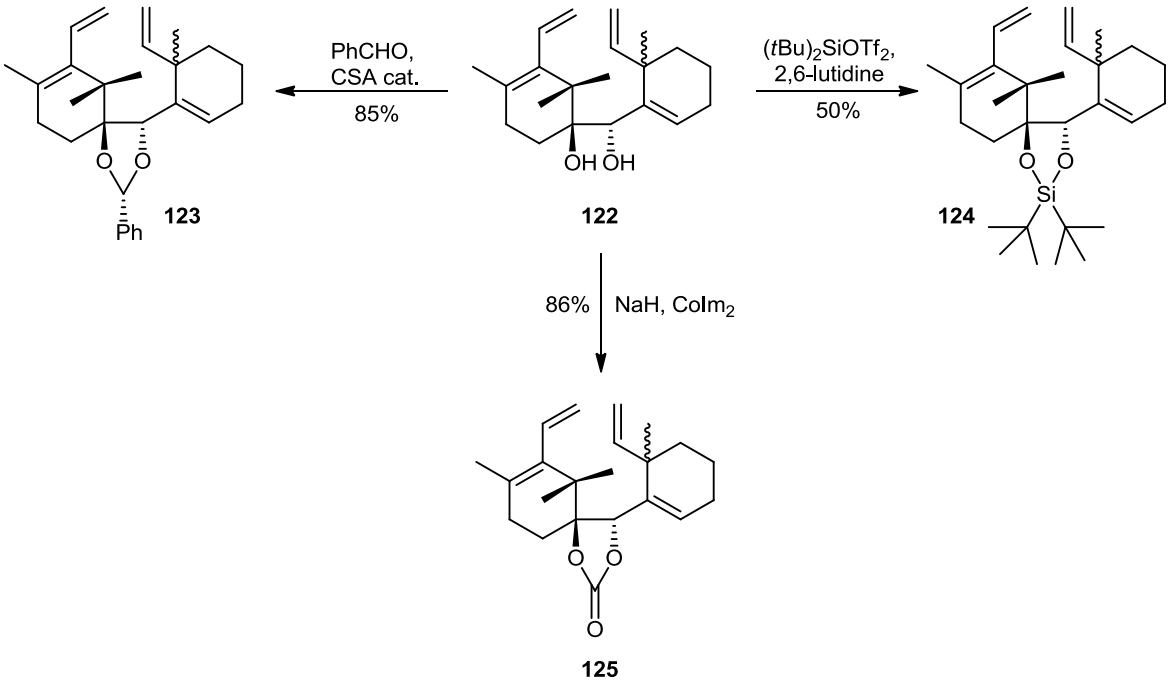
Scheme 2.10 – Synthesis of the model C ring

Compound **120** was then coupled together with **110** to give Shapiro adduct **121** in an excellent yield. Deprotection of the trimethylsilyl group gave **122** (Scheme 2.11).



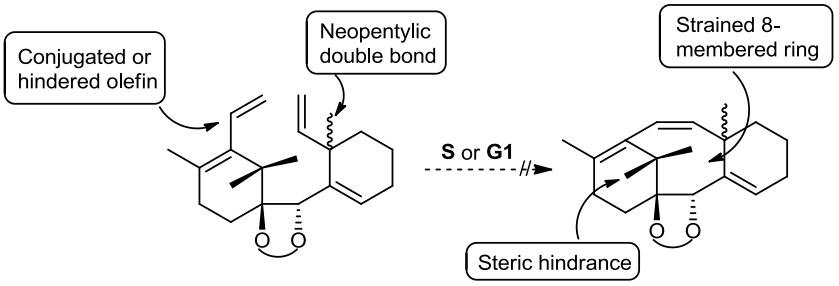
Scheme 2.11 – Synthesis of diol **122** from the Shapiro reaction

Compound **122** was then transformed into different metathesis precursors by protecting the diol with different groups (Scheme 2.12).



Scheme 2.12 – Preparation of metathesis precursors

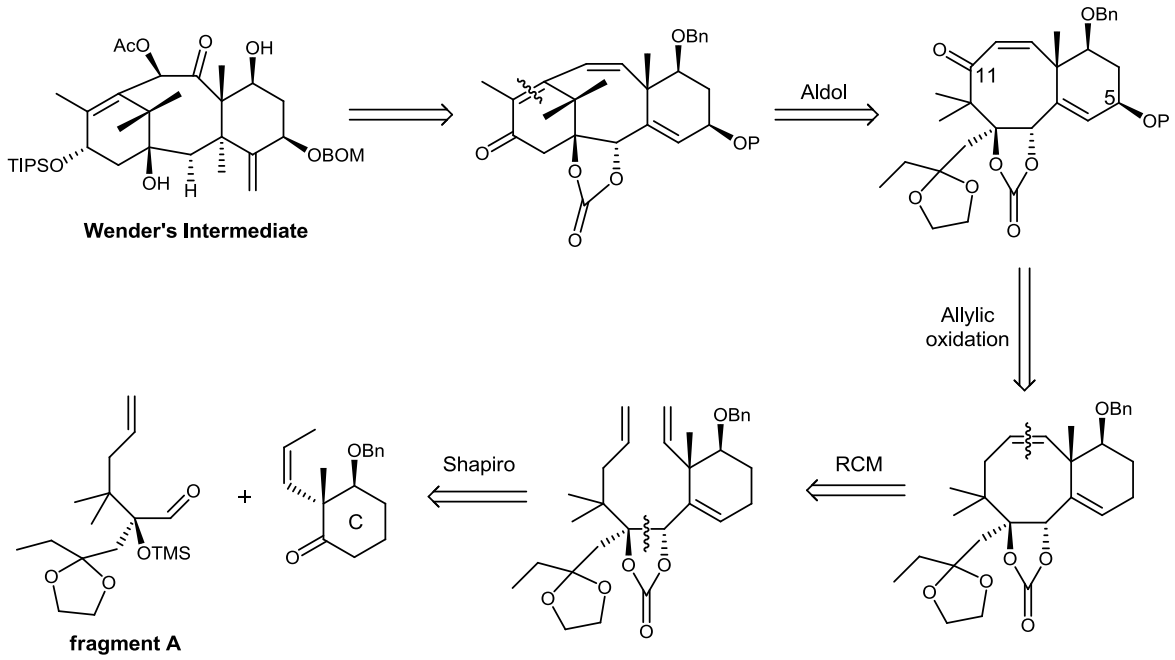
Despite using different catalysts and substoichiometric amounts (up to 50% of these catalysts) the metathesis reactions using precursors **123**, **124** and **125** were unsuccessful and starting material was recovered (Scheme 2.13). The catalyst did not react with either double bond, not even the one at C9, which is not conjugated as was previously. However, the neopentylic double bond disfavours the metathesis reaction as it is sterically hindered, which could explain the lack of reactivity.



Scheme 2.13 – Failed metathesis reactions

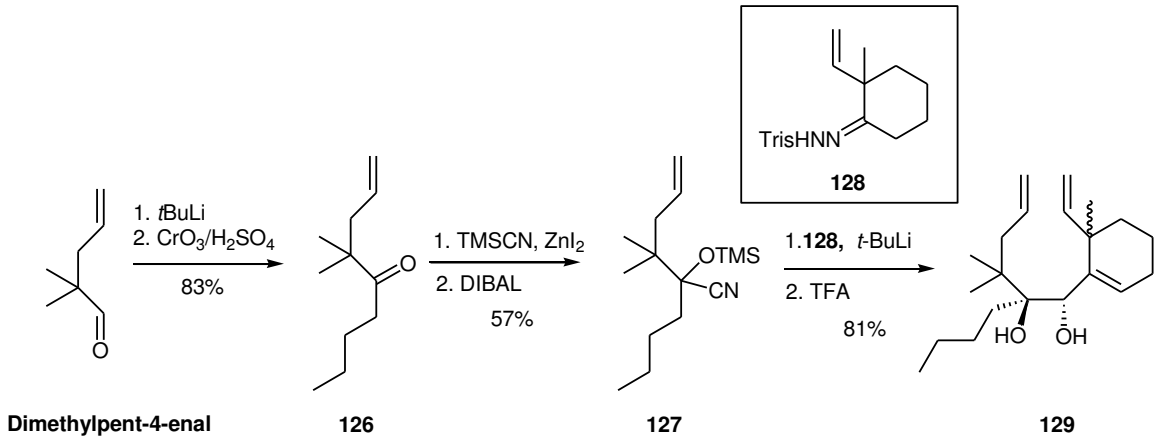
B. Semi-convergent approach

A semi-convergent synthesis was then proposed, preparing taxol from a highly advanced intermediate previously described by Wender. The A ring would be formed by an intramolecular aldol reaction, whilst the two oxygenated functions at C5 and C11 would be generated by a double allylic oxidation to give the desired oxygenated functionalities of the BC bicycle. The B ring would be formed using ring-closing metathesis and the precursor would be prepared from a Shapiro coupling of fragment A and the C ring (Scheme 2.14).



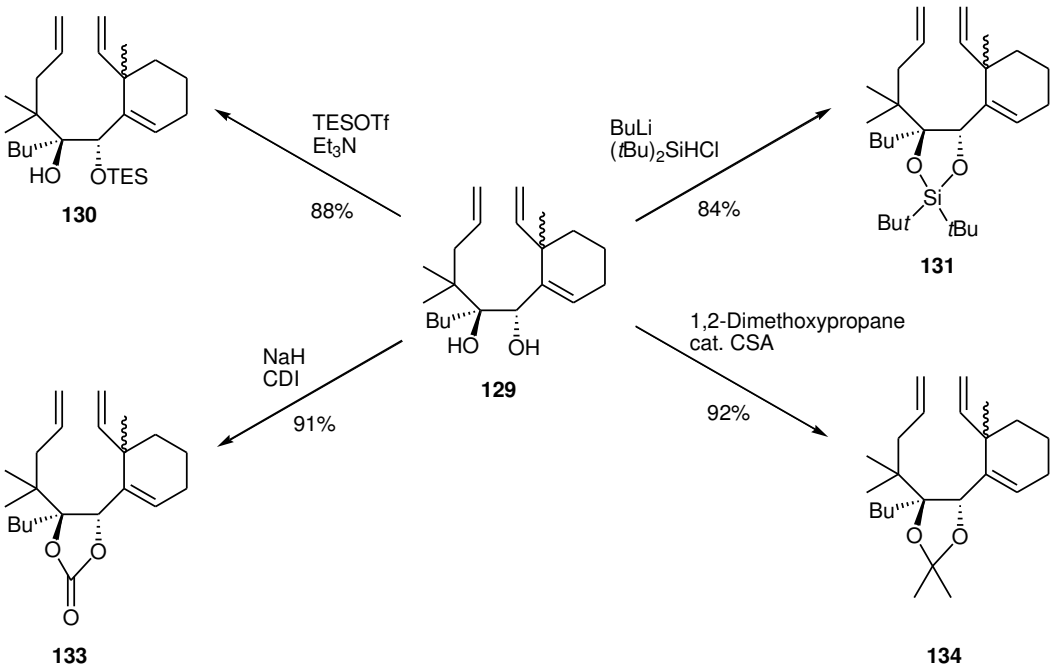
Scheme 2.14 – Semi-convergent retrosynthesis

Fragment A was first synthesised; the ketal functionality was removed so that the Shapiro reaction could be tested on a simpler model. The model fragment was prepared by adding *t*-butyllithium to commercially available 2,2-dimethylpent-4-enal. This was then oxidised using Jones' conditions to give the ketone **126.** Cyanation of **126** and reduction of the corresponding cyanohydrin then gave the aldehyde **127** which was used in the Shapiro reaction with hydrazone **128,** previously synthesised, to give the BC bicycle skeleton **129** with high stereoselectivity after deprotection of the trimethyl silyl group (Scheme 2.15).



Scheme 2.15 – Synthesis of diol **129**

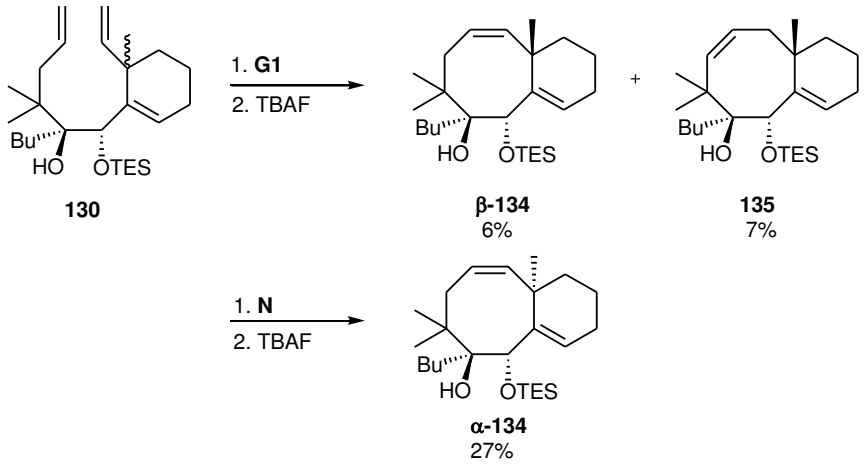
The viability of the metathesis reaction, resulting in the formation of the B ring, was tested. Several metathesis precursors were prepared using various protecting groups for the diol (Scheme 2.16).



Scheme 2.16 – Synthesis of different metathesis precursors

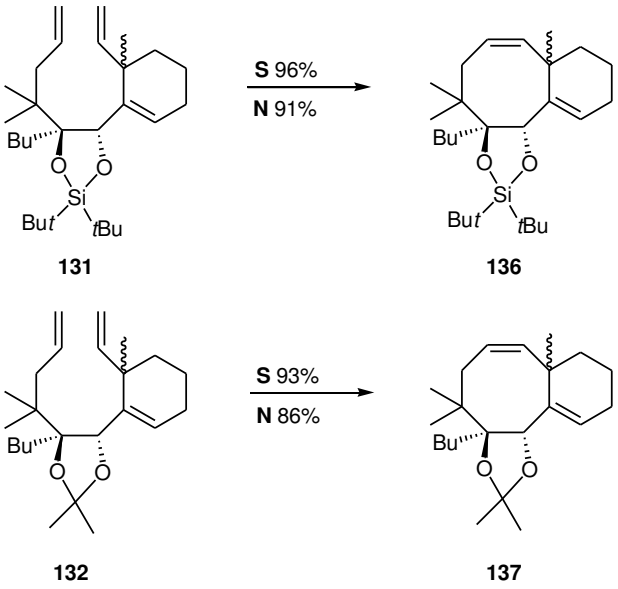
The first metathesis precursor to be tested was **130**. Using Grubbs' first generation catalyst only the taxol-like isomer cyclised giving the desired ring closing between C9 and C10. Its bicyclic isomer was also formed, resulting from migration of the double bond to the C10-C11 position. This isomer is more thermodynamically stable (ΔG = 3kcal mol^{-1}). The yields of the reactions were however quite low. When using Nolan's catalyst, the only

diastereomer that did cyclise had the wrong stereochemistry at C8 for taxol[67] (Scheme 2.17).



Scheme 2.17 – Metathesis with mono-protected diol **130**

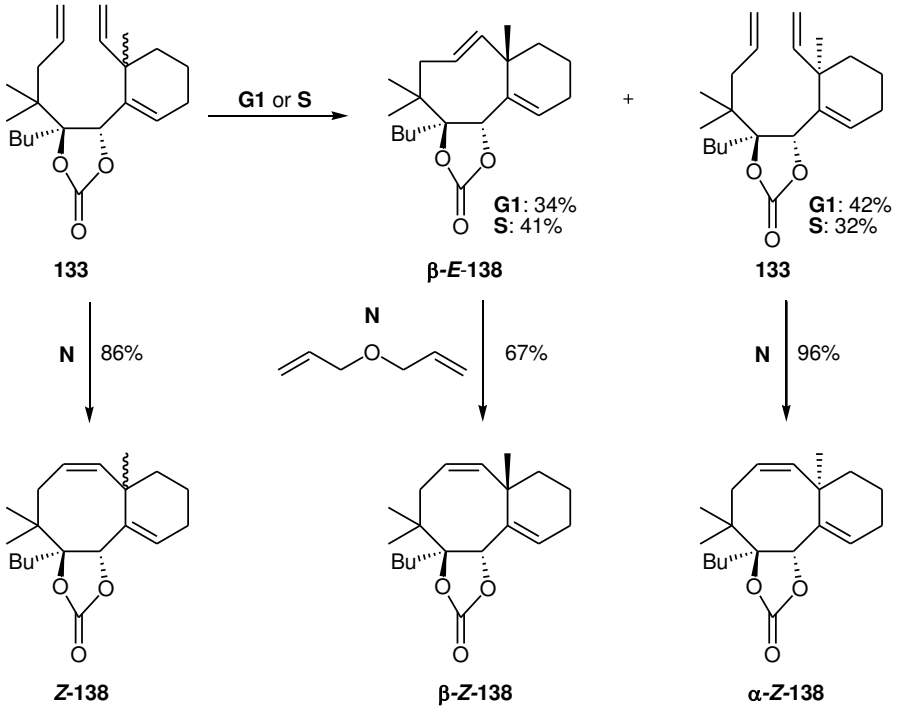
Ring-closing metathesis was then tested on cyclic silylene **131** and acetonide **132**. These two precursors cyclise efficiently using either Schrock's or Nolan's catalysts. Grubbs' first-generation catalyst did not produce any cyclisation products (Scheme 2.18).



Scheme 2.18 – Metathesis reactions with silylene **131** and acetonide **132**

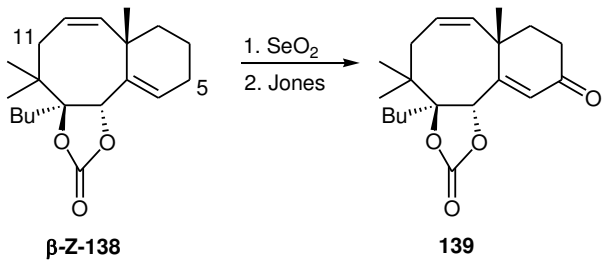
Using the carbonate protected diol **133**, in the presence of Grubbs' first generation catalyst or Schrock's catalyst, only one isomer cyclised. Despite the desired taxol-like isomer forming, the geometry of the double bond is *trans.* This was the first case of a *trans* cyclooctene ring being formed by ring-closing metathesis.[68] Metathesis using Nolan's

catalyst gave the *cis* diastereomer and in the presence of allyl ether; the *trans* diastereomer could be transformed to the *cis* diastereomer (Scheme 2.19).



Scheme 2.19 – Metathesis reactions with carbonate protected diol

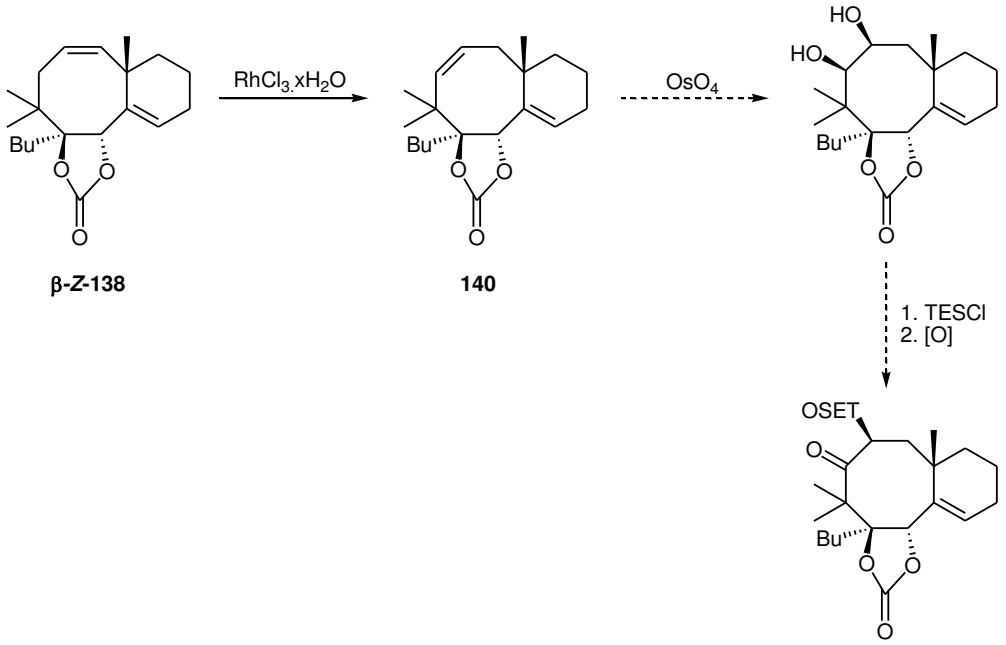
Bicycle **β-*Z*-138** was then subjected to an oxidation using selenium dioxide and then Jones' reagent in order to generate the oxygen functionalities at C5 and C11. Oxidation at C11 proved to be difficult and failed, most probably due to the steric hinderance of the bulky *gem*-dimethyl group (Scheme 2.20).



Scheme 2.20 – Oxidation at C5

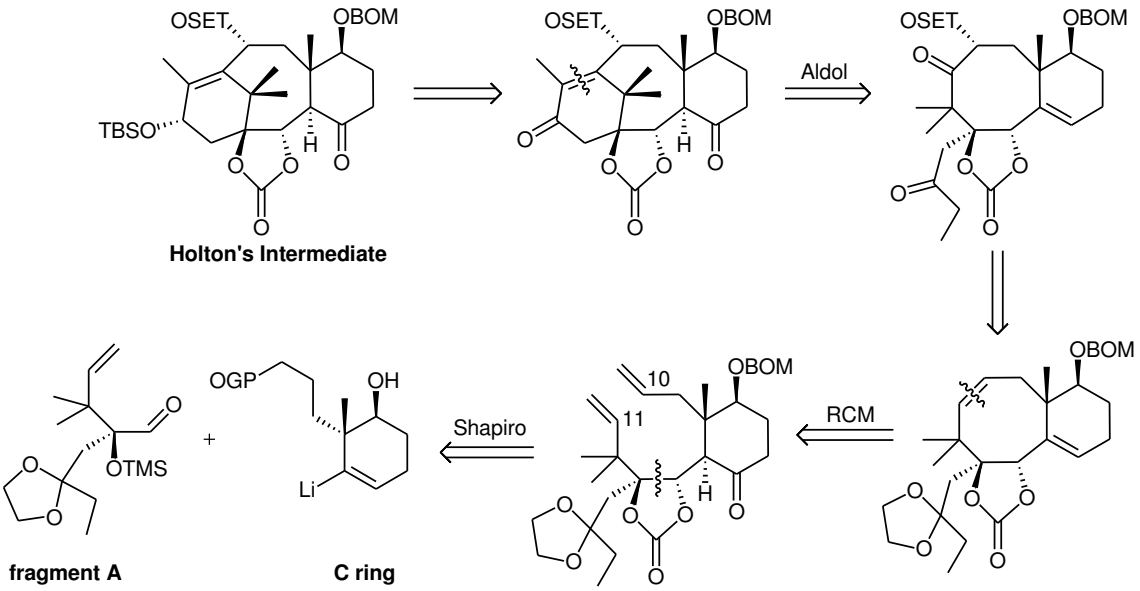
In order to install the oxygen functionality at C11, it could be possible to take advantage of the more stabilised isomer with the alkene between C10 and C11 on the BC bicycle. The bicycle **β-Z-138** could be isomerised to **140** with rhodium(III) chloride. Dihydroxylation of the alkene followed by selective monoprotection of the diol before oxidation would take

place. This would then produce a ketone in the C11 position, which would give the functionality necessary to form the A ring (Scheme 2.21).



Scheme 2.21 – Possible route to achieve functionality at C11

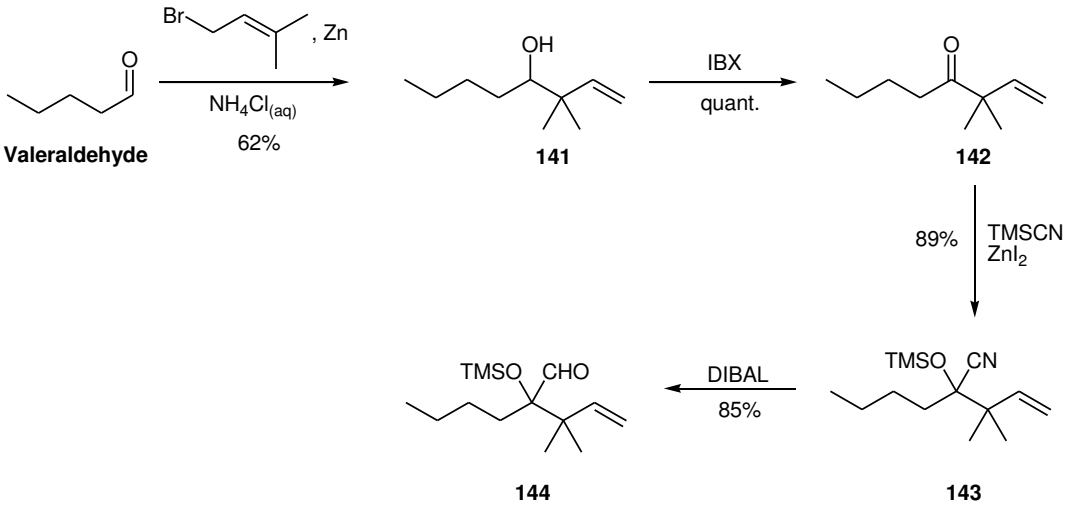
A simpler option would be to synthesise the BC bicycle using ring-closing metathesis between C10 and C11, instead of isomerising the alkene between C9 and C10. A new semi-convergent synthesis was designed, starting from an intermediate used by Holton in his taxol synthesis. The A ring would be closed using an intramolecular aldol condensation. The BC bicycle would again be formed using metathesis methods, and the precursor would be prepared from a new C ring and fragment A using a Shapiro reaction (Scheme 2.22).



Scheme 2.22 – Modified semi-convergent retrosynthesis

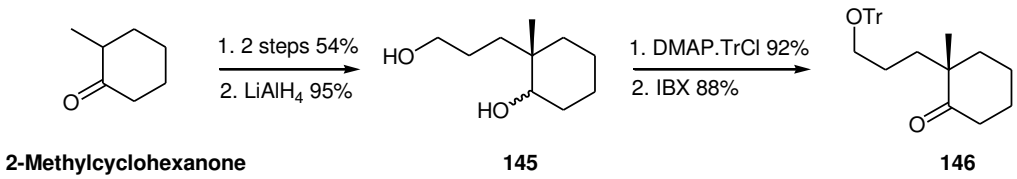
2.1.4 Work by Stéphanie Schiltz[69]

Fragment A was synthesised without any functionality at C13 and a 7-deoxy model C ring was prepared. The commercially available starting material was valeraldehyde. This was subjected to a Barbier reaction to give the alcohol **141**, which was oxidised to give ketone **142.** A cyanation reaction was carried out giving **143**, which was reduced to the aldehyde **144**, thus completing the synthesis of fragment A (Scheme 2.23).



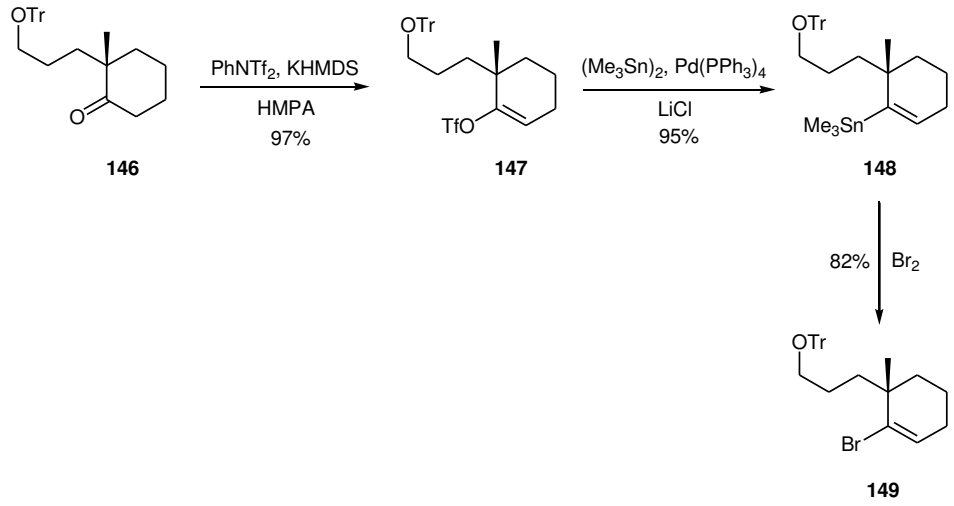
Scheme 2.23 – Synthesis of racemic model fragment A

The C ring precursor was synthesised employing an enantioselective Michael addition of an enantiopure enamine to methyl acrylate in order to define the stereochemistry of the methyl group at C8.[70] 2-Methylcyclohexanone was transformed in five steps to **146**, this will be discussed in more detail later (Scheme 2.24).



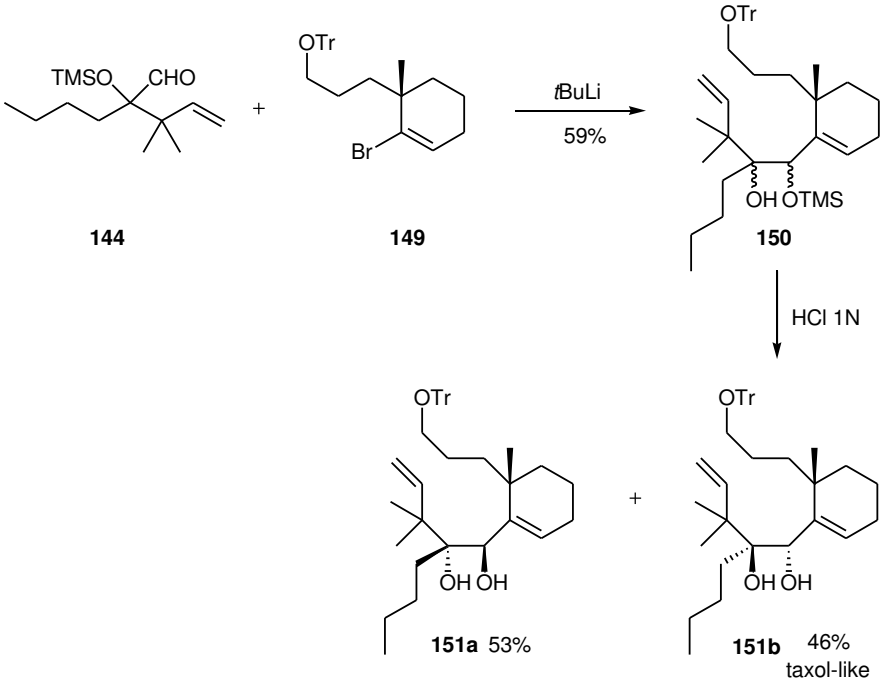
Scheme 2.24 – Synthesis of ketone **146**

The Shapiro reaction proved to be difficult to optimise, so a different method was designed. The ketone **146** was transformed into the vinyltriflate, which was submitted to a Stille coupling with hexamethyldistannane to give **148**. The vinyl bromide **149** was synthesised by a tin-bromide exchange (Scheme 2.25).



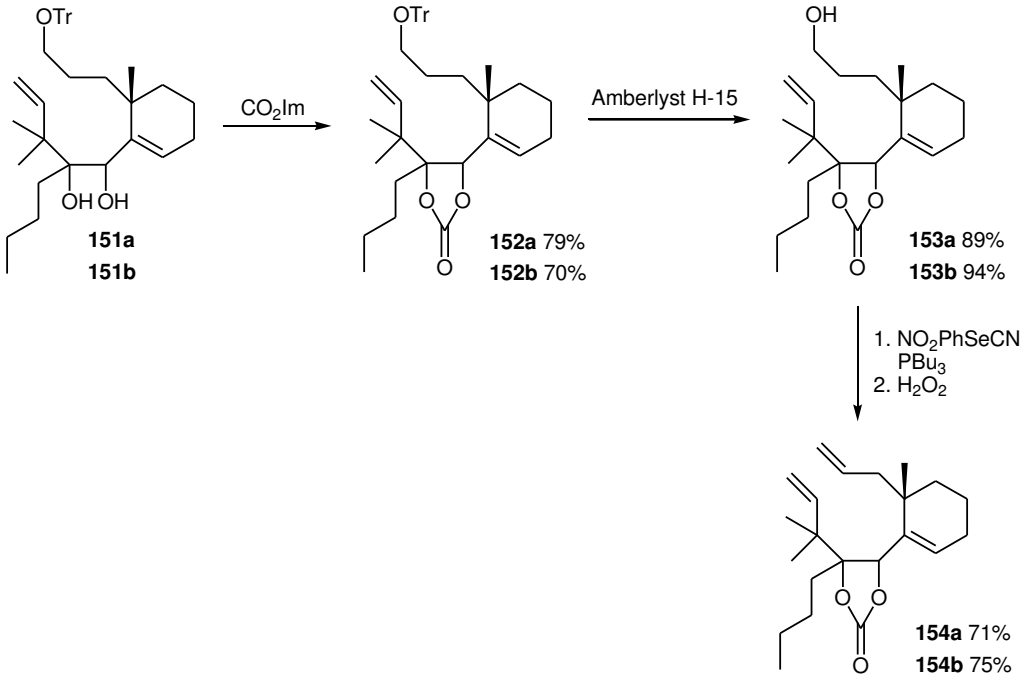
Scheme 2.25 – Synthesis of the vinyl bromide **149**

The vinyl bromide was then coupled with aldehyde **144** using *tert*-butyllithium to form the BC bicycle skeleton **150**. This produced two diastereomers in a 1:1 mixture, which were inseparable, in a 59% yield. Treatment with acid then gave the two diols **151a** and **151b**, which were separated using flash column chromatography (Scheme 2.26). **151b** is the isomer which possesses the required relative configuration for taxol.



Scheme 2.26 – Synthesis of diols **151a** and **151b**

Both diastereomers were transformed separately into metathesis precursors. The diols were protected as carbonates using carbonyl diimidazole. The trityl protecting group was removed using Amberlyst H-15 to give the alcohols **153a** and **153b**. Using Grieco's reaction then gave the desired trienic carbonates **154a** and **154b** (Scheme 2.27).



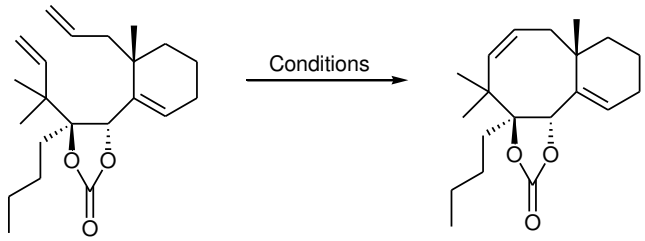
Scheme 2.27 – Synthesis of trienes **154a/b**

The two trienic carbonates were then subjected to ring-closing metathesis. The non taxol-like isomer **154a** did not cyclise when using Grubbs' first or second generation catalyst (Scheme 2.28). Prolonged reaction time led to decomposition of the material.

154a

Scheme 2.28 – Metathesis of the trienic compound **154a**

However, when triene **154b** was treated with a catalytic quantity (30 mol%) of Grubbs' first generation catalyst in 1,2-dichloroethane, the BC bicycle **155b** was formed. The single isomer gave the thermodynamic (*Z*) product in a 65% yield. Using Grubbs' second-generation catalyst, or Nolan's catalyst, proved to be more efficient and gave better yields with lower catalyst loadings, as well as reduced reaction times (Scheme 2.29).



154b **155b**

Cat.	Quantity	Solvent	Temperature	Time	Yield
G1	30 mol%	DCE	20 °C	5 days	65%
G2	10 mol%	DCE	80 °C	1 h	69%
N	5 mol%	DCE	80 °C	1 h	72%

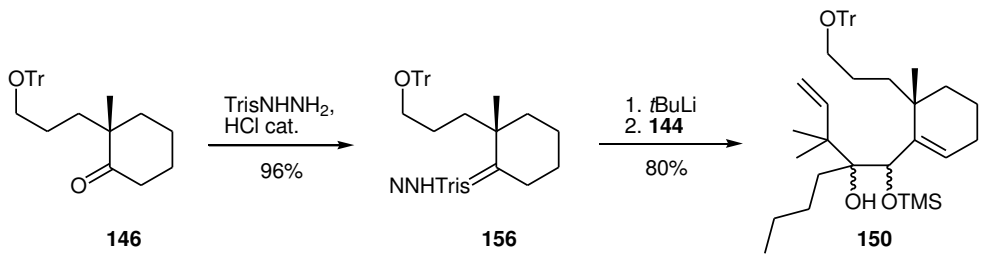
Scheme 2.29 – Metathesis with triene **154b**

With the success of the model C10-C11 route completed, work then continued toward the synthesis of fragments A and C that were necessary to synthesise taxol.

2.1.5 Work by Cong Ma[71a]

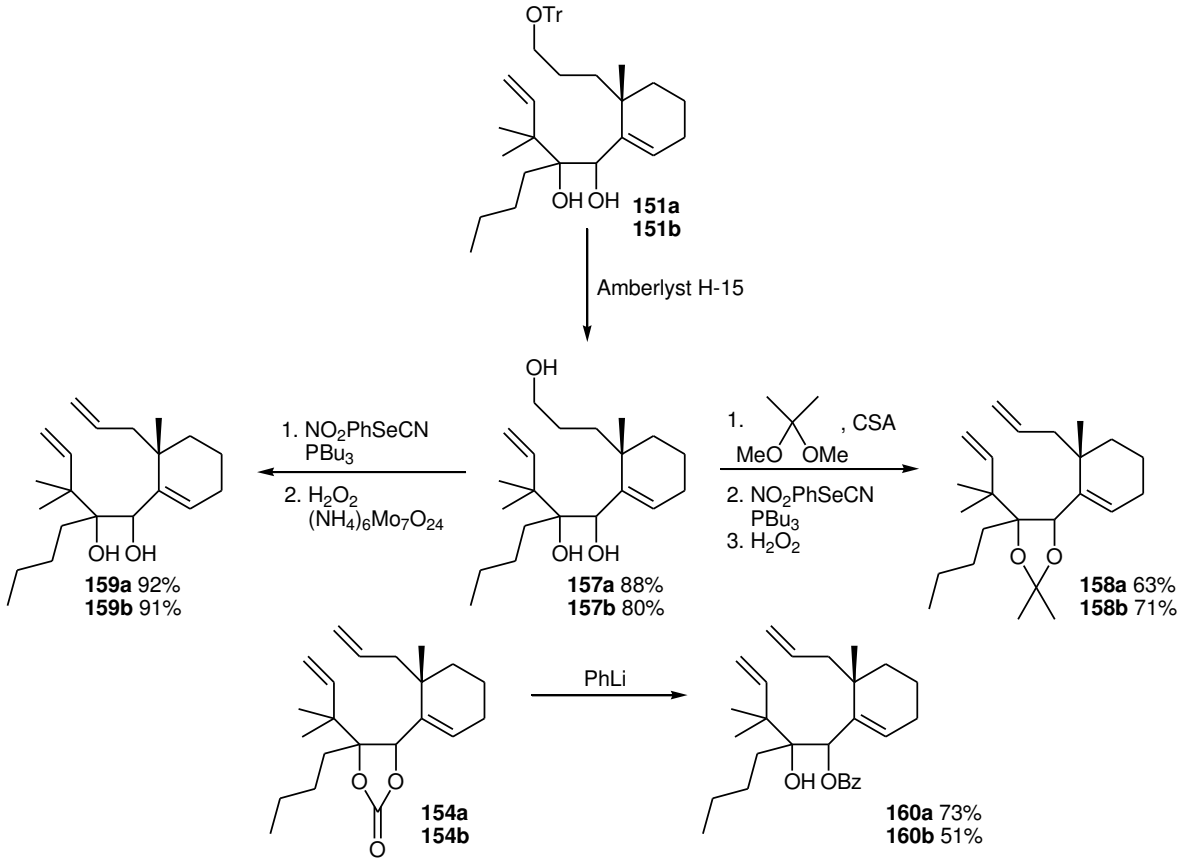
A. Optimisation of the metathesis[72]

The first aim was to improve the cyclisation reaction. A number of different diols were studied. The ketone **146** was transformed into the hydrazone, and a Shapiro reaction took place to give the BC bicycle skeleton in good yield (Scheme 2.30).



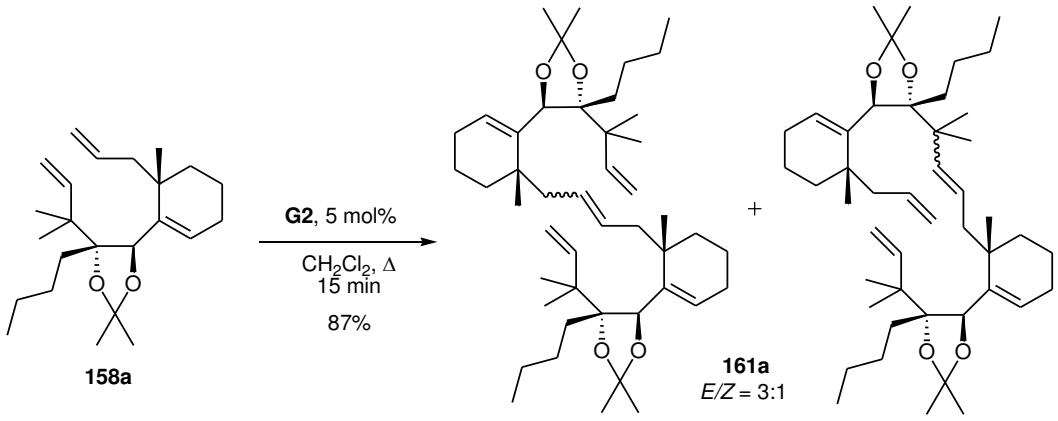
Scheme 2.30 – Synthesis of **150** by a Shapiro coupling

After removal of the trimethylsilyl group, the two diols were separated. The trityl groups were removed using Amberlyst H-15 to give triols **157a** and **157b**. Trienes **158a** and **158b** were formed by protecting the diol with acetonide, whilst trienes **159a** and **159b** were formed by directly eliminating the primary alcohol using Grieco's conditions. Ammonium molybdate is used in the Grieco reaction so oxidation of the double bond between C3-C4 is prevented. The carbonates **154a** and **154b** were opened using phenyllithium to obtain the benzoates **160a** and **160b** (Scheme 2.3`).



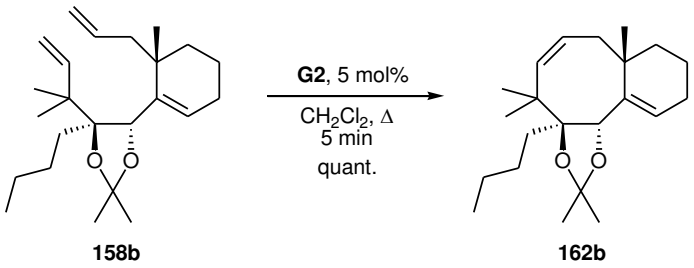
Scheme 2.31 – Synthesis of metathesis precursors

With a variety of precursors now available, the metathesis reaction was studied. The acetonide precursors were reacted with Grubbs' second-generation catalyst. After fifteen minutes in dichloromethane at reflux, the isomer **158a** gave a mixture of dimeric products, the head-head and head-tail (Scheme 2.32). Prolonged reaction time did not produce any cyclisation product.



Scheme 2.32 – Metathesis with **158a**

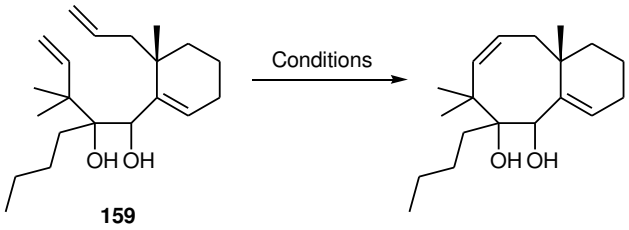
Cyclisation of the isomer **158b** under the same conditions was extremely rapid and the BC bicycle was obtained in a quantitative yield after five minutes (Scheme 2.33).



Scheme 2.33 – Metathesis with **158b**

The diol precursors were tested but only **159b** gave the desired cyclisation product when using Grubbs' second-generation cataylst. The other isomer degraded (Table 1).

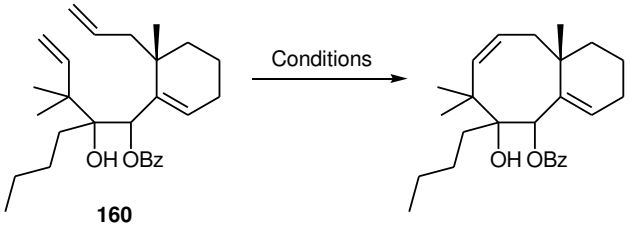
Table 1 – Metathesis with **159a/b**



Isomer	Catalyst	Solvent	Temperature	Result
a	**G2**	Toluene	110 °C	degradation
b	**G1**	Toluene	110 °C	degradation
b	**G2**	CH_2Cl_2	40 °C	quant.

Both of the benzoate precursors cyclised when using either Grubbs' first or second-generation catalyst (Table 2).

Table 2 – Metathesis with **160a/b**



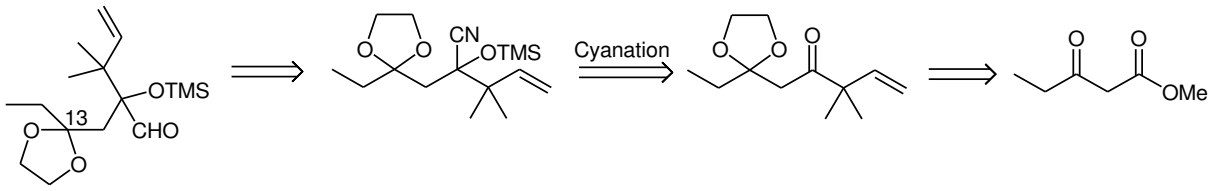
160

Isomer	Catalyst	Solvent	Temperature	Duration	Result
a	**G1**	$CH_3CH_2Cl_2$	80 °C	36 h	71%
a	**G2**	CH_2Cl_2	40 °C	18 h	84%
b	**G1**	CH_2Cl_2	40 °C	12 h	78%
b	**G2**	CH_2Cl_2	20 °C	15 min	quant.

With tests on a number of precursors complete, the synthesis of fragments A and C necessary to synthesise the ABC tricycle of taxol was undertaken.

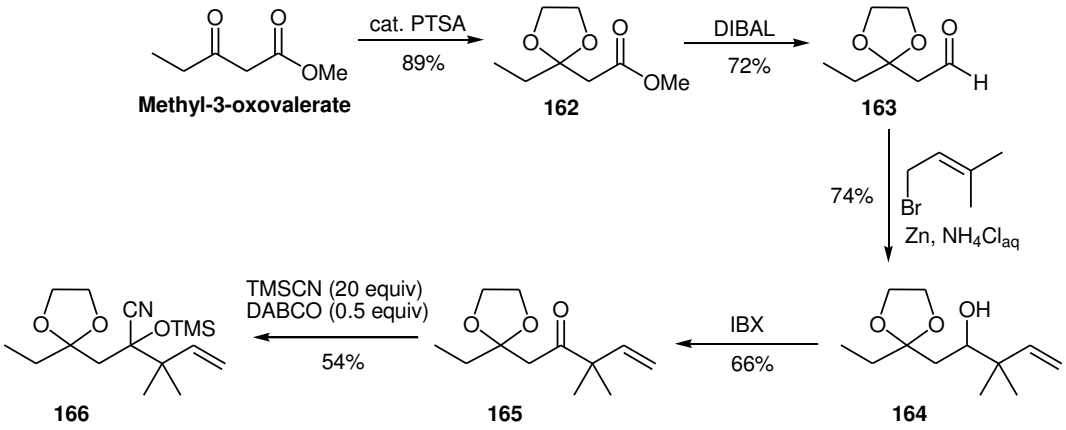
B. Synthesis of fragment A

The starting material was commercially available methyl-3-oxovalerate and the carbonyl at C13 would be protected as a ketal (Scheme 2.34).



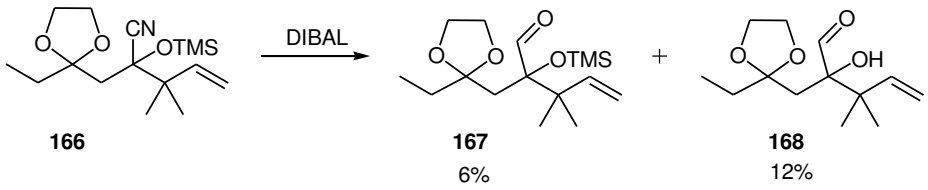
Scheme 2.34 – Fragment A retrosynthesis

Methyl-3-oxovalerate was transformed to the ketal **162** in the presence of *p*-toluenesulfonic acid, followed by the reduction of the ketal ester to give the aldehyde **163**. The *gem*-dimethyl group was installed by a Barbier reaction giving **164** followed by oxidation of the alcohol to give **165**. Cyanation and trimethylsilyl protection of **165** gave **166** (Scheme 2.35).



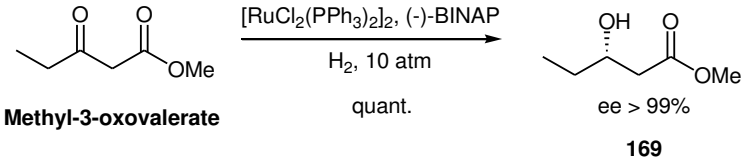
Scheme 2.35 – Synthesis of cyanohydrins **166**

Reduction of **166** with diisobutylaluminium hydride only gave a low yield of the desired aldehyde **167** and its derivative resulting from removal of the trimethylsilyl group (Scheme 2.36). The bulky ketal group, which is sterically hindered, was most likely to have affected the yield of the reaction.



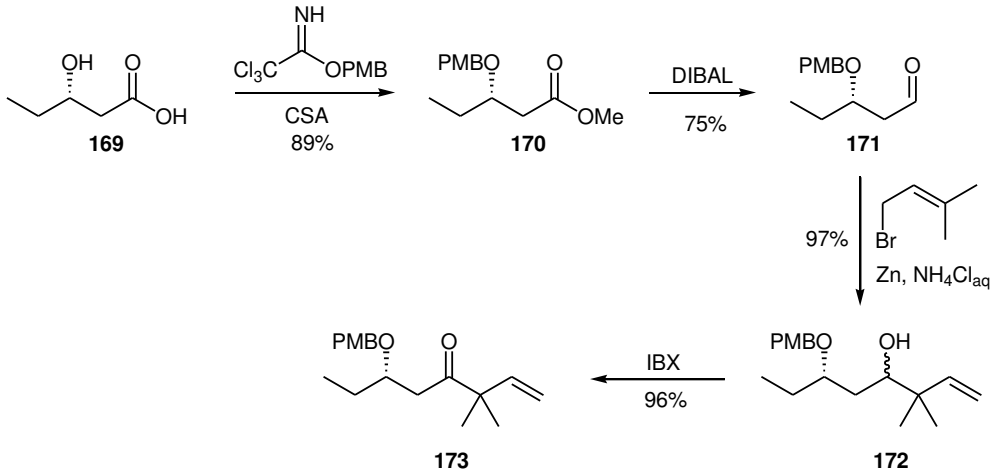
Scheme 2.36 – Formation of **167**

A new route was then envisaged, this time masking the ketone as a protected secondary alcohol. Methyl-3-oxovalerate was subjected to an enantioselective reduction using a high pressure hydrogen atmosphere (ten atm) in the presence of a ruthenium catalyst and (-)-BINAP.[73] The product was obtained with an excellent enantiomeric excess (Scheme 2.37).



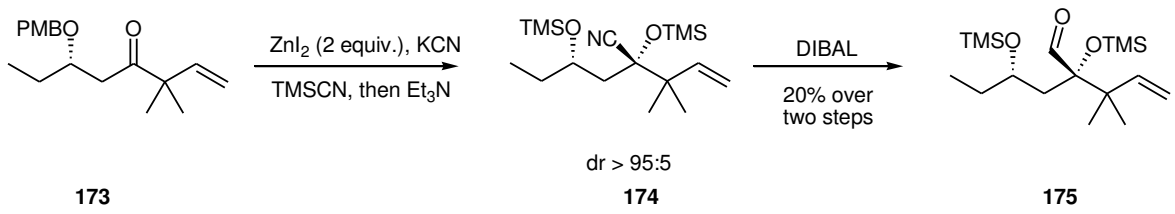
Scheme 2.37 – Enantioselective reduction

The alcohol was then protected as the *para*-methoxybenzyl ether. The ester was reduced to the aldehyde **171** using diisobutylaluminium hydride. A Barbier reaction then took place forming the homoallylic alcohol as a 1:1 mixture of diastereomers, which were oxidised to the ketone **173** (Scheme 2.38).



Scheme 2.38 – Synthesis of ketone **173**

A cyanation reaction then took place with ketone **173** using trimethylsilyl cyanide and potassium cyanide. Two equivalents of zinc iodide were used for the *in situ* deprotection of the *para*-methyloxybenzyl ether and to form the cyanohydrin **174**, which was obtained as a single diastereomer**.** The cyanide was then reduced to give the aldehyde **175** but it was difficult to isolate and a 20% yield was achieved only once (Scheme 2.39).



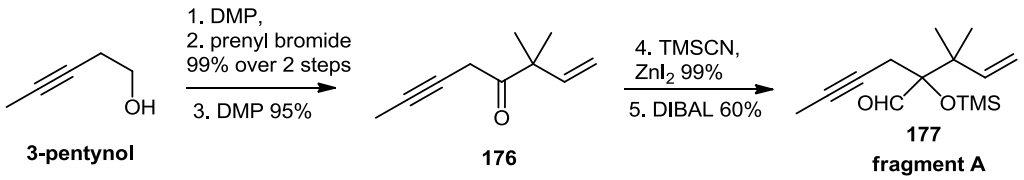
Scheme 2.39 – Synthesis of aldehyde **175**

This aldehyde was not a successful candidate for the Shapiro reaction due to the irreproducibility of its synthesis. A different strategy was then looked at but this time only the racemic fragment was synthesised.

C. New fragment A route

This time the ketone at C12 was masked as an alkyne. This alkyne would then undergo a hydroboration or gold hydration to unmask the ketone at a later stage. The new fragment A started from commercially available 3-pentynol.

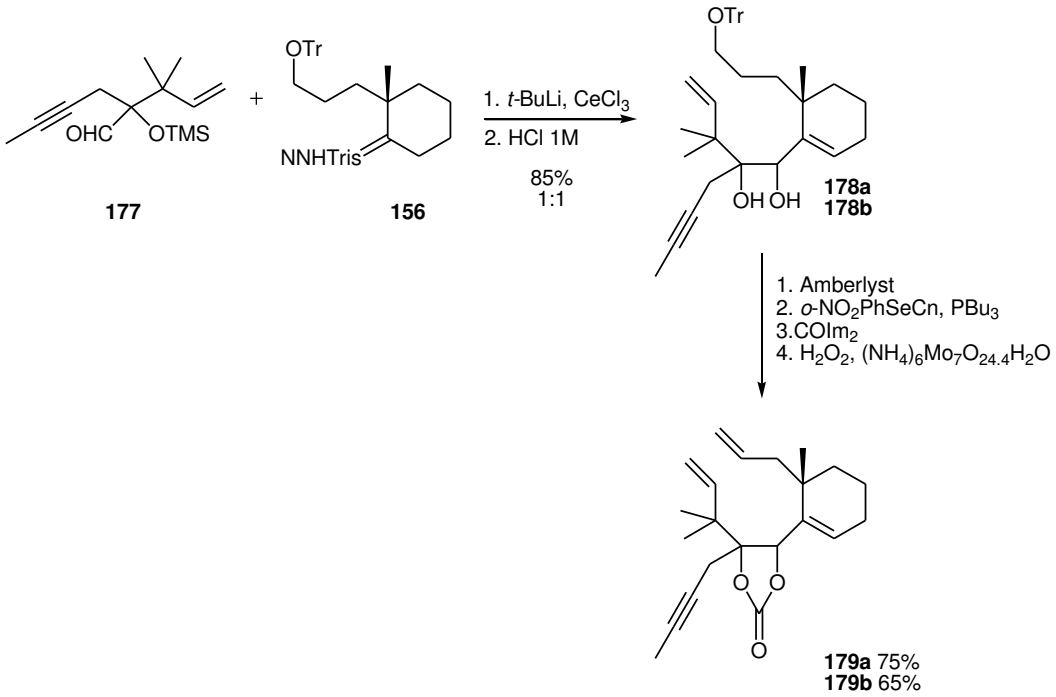
3-Pentynol was transformed into aldehyde **177** in five steps which will be discussed in detail later (Scheme 2.40).



Scheme 2.40 – Synthesis of racemic fragment A

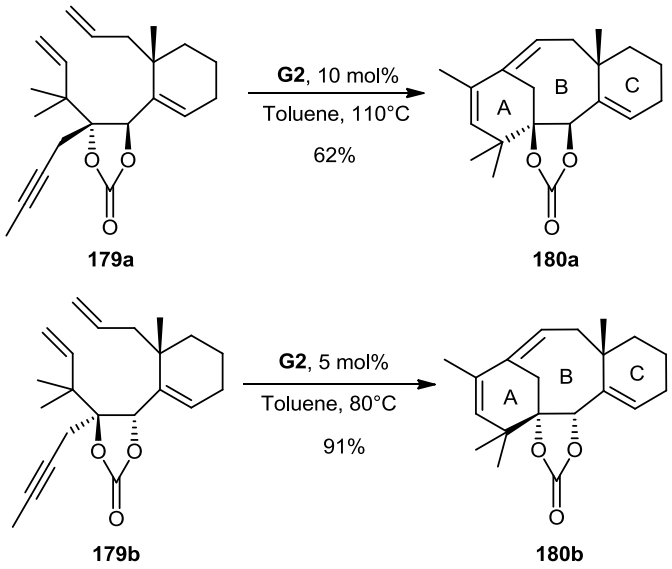
D. Towards 7-deoxytaxol

Racemic fragment A **177** was then coupled together with the model C ring **156** in a Shapiro reaction. Cerium trichloride titrated with butyllithium[74] was used in order to produce better yields of the coupling; this will be discussed in detail later. After hydrolysis of the trimethylsilyl ether, the two diasteromers were separated giving **178a** and **178b**. The two diols were then transformed into metathesis precursors **179a** and **179b** in four steps without any intermediate purifications (Scheme 2.41).



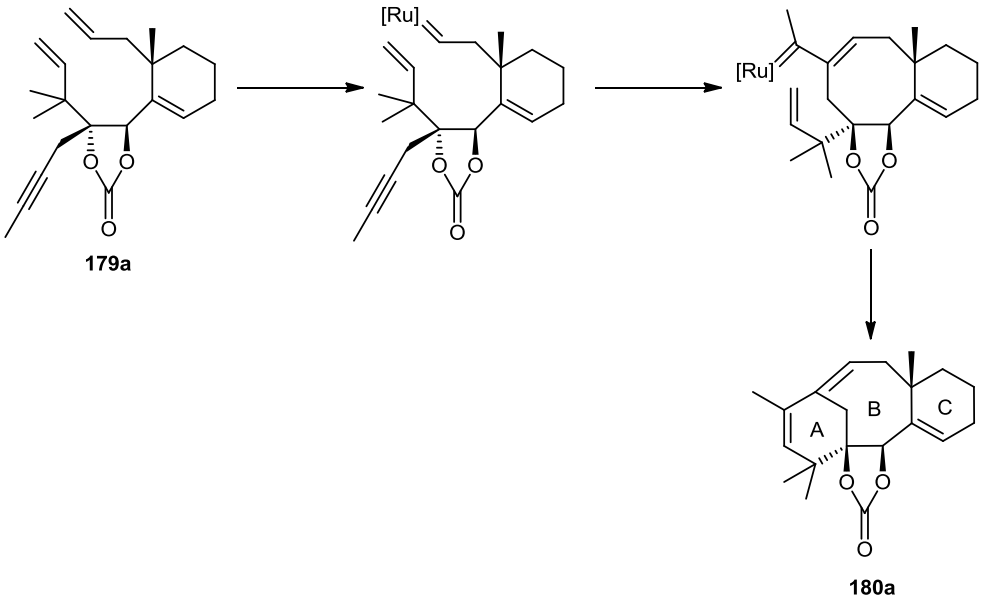
Scheme 2.41 – Synthesis of metathesis precursors

The reaction with the two precursors using Grubbs' second-generation catalyst did give a cyclised product just not the desired one. Both isomers had undergone ene-yne-ene metathesis rather than the desired ene-ene metathesis. This did however give a version of the ABC tricycle of taxol but with the *gem*-dimethyl group in the wrong position (Scheme 2.42).



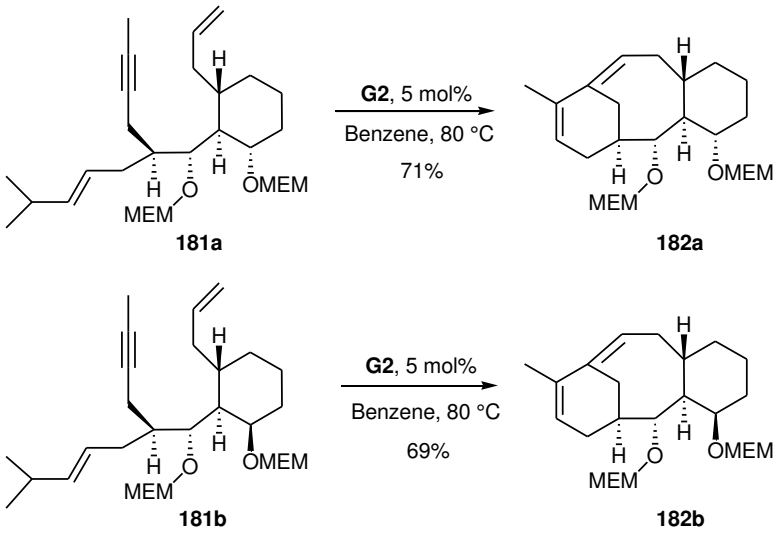
Scheme 2.42 – Ene-yne-ene metathesis

Carbene formation starts at C10 and rotation around the C1 bond is followed by ene-yne metathesis to close the B ring; the A ring is then closed by ene-ene metathesis (Scheme 2.43).



Scheme 2.43 – Cyclisation mechanism

This ene-yne-ene reaction has been observed before by Granja.[75] In the presence of Grubbs' second-generation catalyst, he formed the ABC tricycles (without the *gem*-dimethyl group or the methyl at C8 position) from a simple skeleton in good yields (Scheme 2.44). These models possess the wrong stereochemistry at C1 for taxol.



Scheme 2.44 – Synthesis of the ABC tricycle by Granja

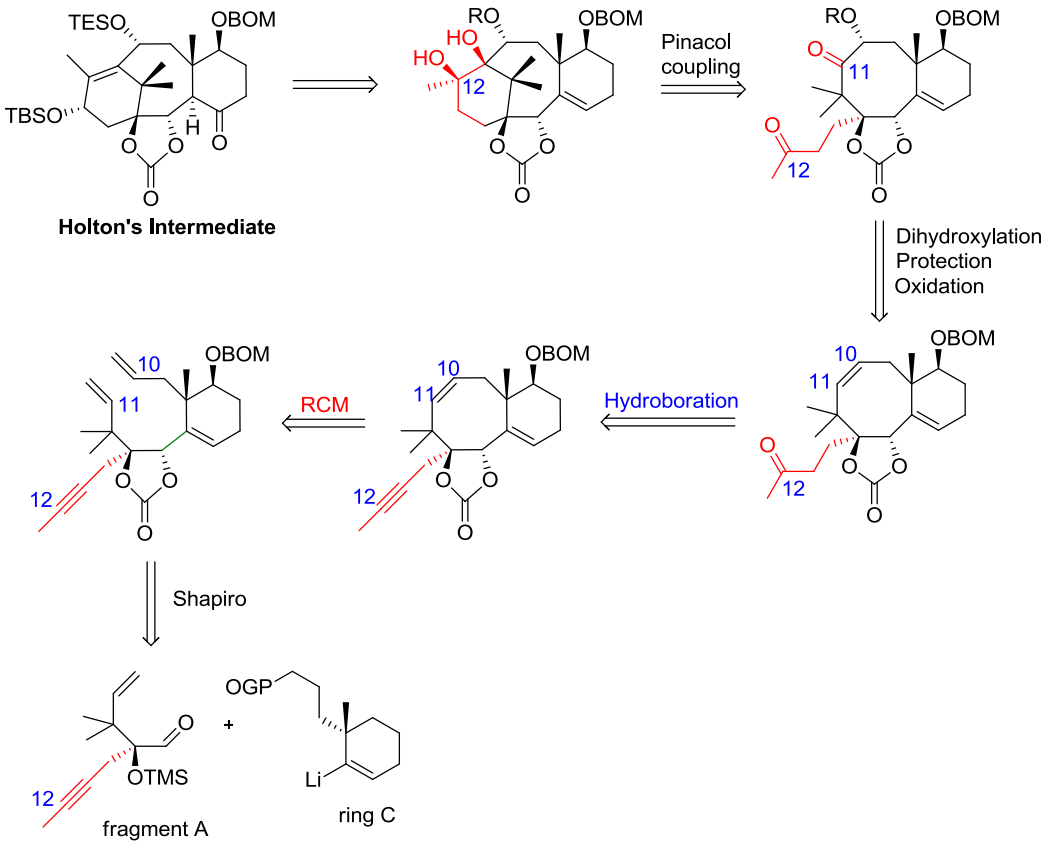
In order to obtain the desired BC ring system, the alkyne needs to be transformed to the ketone before the ring-closing metathesis takes place.

2.2 Aim of the project

The aim of this project is to work towards the synthesis of the model 7-deoxy ABC tricycle of taxol. Studies will be a continuation from work previously carried out in the lab by past members of the group. I will be looking to close the B ring between C10 and C11 using RCM and avoid ene-yne-ene metathesis as seen previously. The precursor to the metathesis reaction will be formed from a Shapiro coupling of two precursors: the A fragment and the C ring.

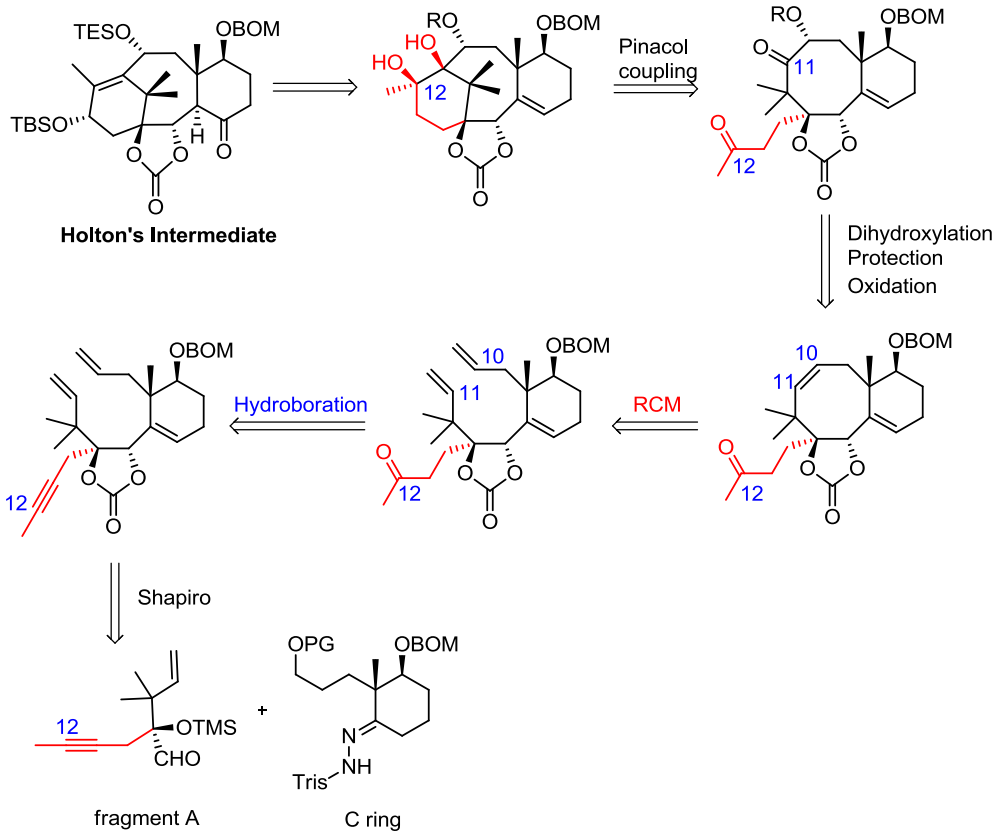
2.3 Modified retrosynthesis

The previous retrosynthesis (Scheme 2.45) planned for ring-closing metathesis to take place before the unmasking of the ketone but as discussed, this allows ene-yne-ene metathesis to occur.



Scheme 2.45 – Retrosynthesis of Cong Ma's work

The retrosynthesis has therefore been modified so that the ring-closing metathesis and hydroboration/hydration steps have been switched. By unmasking the ketone before the metathesis step, the BC ring should close leaving the ketone at C12 ready to use to form the A ring at a later stage by a pinacol coupling with the ketone at C11 (Scheme 2.46).

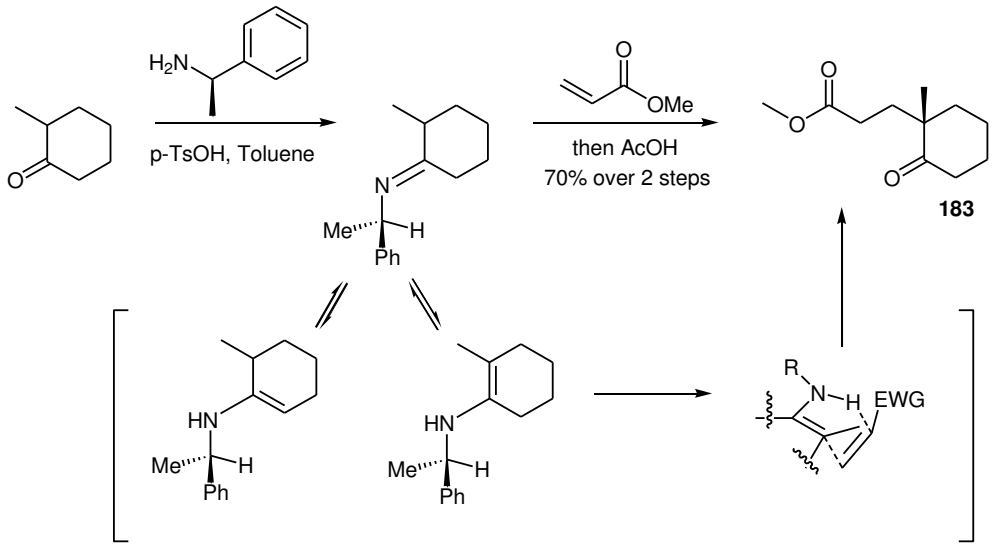


Scheme 2.46 – Modified retrosynthesis

2.4 Towards the Shapiro coupling

2.4.1 Synthesis of the model C ring

A model 7-deoxy C ring was prepared in an enantiopure form through a chiral intermediate previously reported by d'Angelo[70] (Scheme 2.47) and enantiopure product **183** was obtained in good yield.



Scheme 2.47 – Proposed enantioselectivity control of chiral imine formation by d'Angelo

This procedure was modified from the one previously used[71a] as that described purifying the enamine by distillation before adding the methyl acrylate. This however proved to be difficult as distillation was not clean and prolonged heating degraded the enamine. The enamine was concentrated and used crude for the reaction with methyl acrylate.

D'Angelo proposed that the addition of chiral imines to electrophilic alkenes proceeds through a compact complex, where the tautomeric equilibrium of imine to enamine minimises the main steric interactions. This was confirmed by deuterated experiments. In the more substituted enamine, the *syn* N-H bond and double bond favoured internal concerted proton transfer, which is also stabilised by hyperconjugation of the methyl group. Attack is favoured from the less hindered face of the enamine (*anti* to the bulky phenyl group), in its energetically favoured conformation (Figure 2.01).

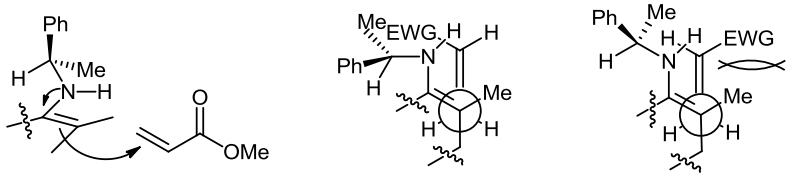
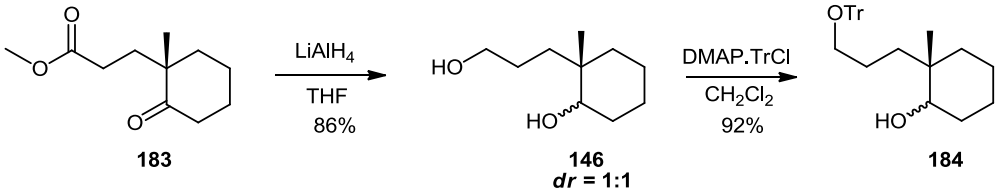


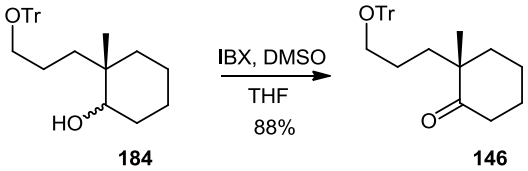
Figure 2.01 – Approach from one face only

Reduction of the keto ester **183** was then carried out using lithium aluminium hydride as described in the literature to give **146** as a 1:1 mixture of diastereomers.[76] This was then followed by selective protection of the primary alcohol as the trityl ether **184** (Scheme 2.48).



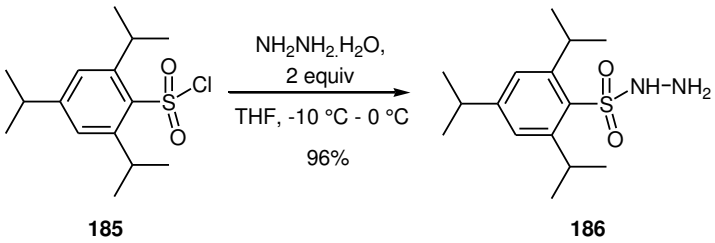
Scheme 2.48 – Formation of trityl ether **184**

The trityl ether was obtained in good yield and the secondary alcohol underwent oxidation to the ketone using iodoxybenzoic acid in tetrahydrofuran and dimethylsulfoxide, which was stirred overnight at room temperature. This gave the protected ketone **146** in good yield (Scheme 2.49).



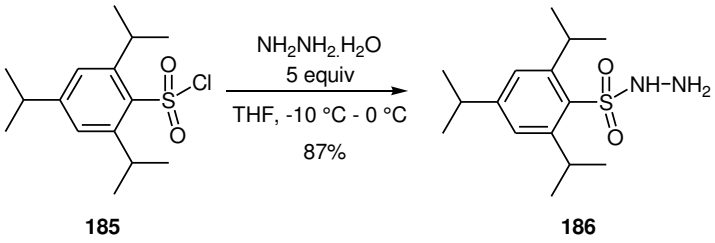
Scheme 2.49 – Oxidation of primary alcohol **184**

In order to carry out the Shapiro reaction, the hydrazone needed to be synthesised. Trisyl hydrazine was prepared from a literature procedure (Scheme 2.50).[77]



Scheme 2.50 - Literature procedure

The reaction using the literature precedent was repeated but the yields were still very low. Test reactions were carried out in order to synthesise the hydrazine in good yields as it is cheaper to make than purchase. A number of different tests were carried out, mainly varying the number of equivalents of hydrazine hydrate added to the sulfonyl chloride. Results showed that adding five equivalents of hydrazine hydrate to the triisopropylsulfonyl chloride at -10 °C gave better yields and a pure white solid was formed (Scheme 2.51).



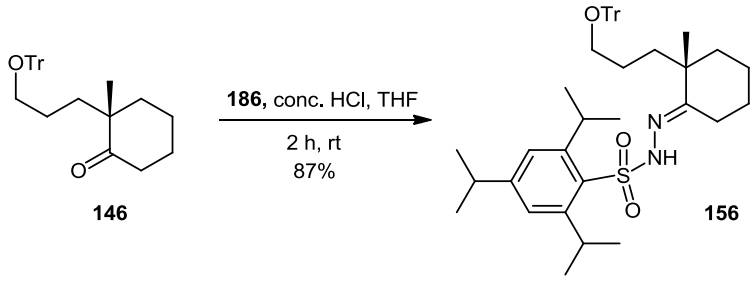
Scheme 2.51 - Modified hydrazine synthesis

Formation of the trisylhydrazone from ketone **146** was then attempted. When using the conditions previously developed in the group,[71a] the yield was only 30% (entry 1). In order to improve the yield of this reaction, different variables were tested (**Table 3**).

Table 3 – Test conditions for hydrazone formation using 1.44 mmol ketone **146**

Entry	Equivalents of hydrazine	THF mL	Amount of conc. HCl added (drops)	Reaction Time	Yield
1	1.0	5.0	2	1 h	30%
2	1.0	5.0	4	1 h	40%
3	1.1	5.0	4	1 h	42%
4	1.1	5.0	0	2 h	-
5	1.1	5.0	2	2 h	38%
6	1.1	5.0	4	16 h	-
7	1.2	5.0	4	2 h	53%
8	1.1	5.0	4	2 h	71%
9	1.1	10.0	4	2 h	87%

The number of equivalents of hydrazine added was varied, and the best result was found to be when 1.1 equivalents were used (entries 2 vs 3 and 7 vs 8). Varying the number of drops of concentrated acid to the reaction was crucial, too little or none and the reaction would not work (entries 4 and 5), too much and the reagents degraded. Degradation was also a result of prolonged stirring (entry 6). Adding 10 mL of tetrahydrofuran to the hydrazone and the ketone and ensuring they were completely dissolved before adding the acid gave the best result as after work up the yield had improved to 87% (entry 9) (Scheme 2.52).



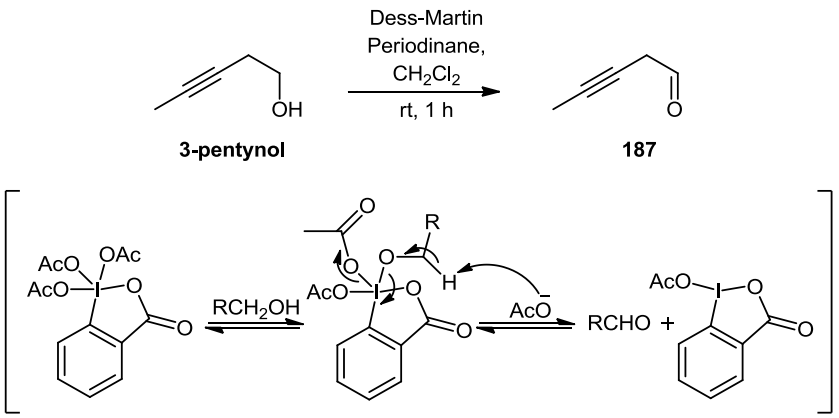
Scheme 2.52 – Synthesis of hydrazone using optimised conditions

A three-gram scale up was carried out however a low yield of 34% was obtained. It was decided to carry out the reaction on a one-gram scale but carrying out multiple reactions at one time. Material could then be brought through and purified together in one column.

With the hydrazone successfully synthesised, fragment A needed to be completed so that we had the two fragments for the Shapiro coupling.

2.4.2 Synthesis of fragment A

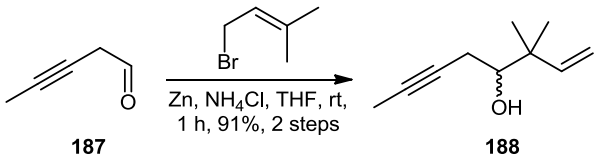
The starting material, 3-pentynol, was oxidised using Dess-Martin periodinane (DMP) which produced the desired aldehyde **187** (Scheme 2.53). The iodoxy salt was precipitated out by cooling the solution to -78 °C and adding pentane.[78] The crude product was recovered by filtering off the iodoxy salt through a silica gel plug and concentrated under vacuum. The desired aldehyde is known to be unstable and has a low boiling point, which resulted in the loss of the aldehyde through the vacuum. The reaction was repeated and concentration was again attempted, this time with ice in the water bath. Despite the cooled bath, the aldehyde was again lost through the vacuum.



Scheme 2.53 – DMP oxidation

To prevent further loss, the aldehyde was not concentrated but left in solution. 3-Pentynol was again oxidised using Dess-Martin periodinane and cooled to -78 °C to precipitate out the iodoxy salt. Pentane was not added as the aldehyde would already be diluted and this may affect the Barbier reaction that was to be carried out. After filtration of the iodoxy salt, the crude aldehyde was left in solution.

The diluted aldehyde was used in the Barbier reaction, which was carried out at room temperature (Scheme 2.54).



Scheme 2.54 – Barbier reaction to form **188**

The first attempt at this reaction gave a 60% yield, which may be a result of the diluted reagent. The reaction was repeated using the same conditions as before, only to give a yield of 30%. This dramatic decrease in the yield was thought to be due to the use of inactivated zinc dust. The reaction was repeated again using activated zinc dust and the yield improved to 60%; however, another problem had occurred.

The Barbier reaction uses 1-bromo-3-methylbut-2-ene, which has to be freshly prepared as it decomposes quickly. The first time it was prepared a brown crude oil was obtained, which was then purified by distillation to give a clear oil. This was then placed in the fridge overnight. When retrieving the product the next day the clear oil had turned brown, showing signs of decomposition even when refrigerated. This was thought to be a contributing factor to the low yields obtained during these early reactions.

The solution to this was to use freshly prepared 1-bromo-3-methylbut-2-ene. This proved to be more difficult than first thought. The hydrobromic acid was added to the cooled 2-methyl-3-buten-2-ol dropwise over half an hour. This gave a clearer crude product before distillation but again problems started to occur. Small distillation apparatus was used to reduce the loss of distilled product; however, the crude product would not distill over and excessive heating led to further decomposition. Different sized distillation apparatus was used, as well as carrying out the distillation under vacuum. Despite a few attempts at each of these methods pure 1-bromo-3-methylbut-2-ene could not be obtained.

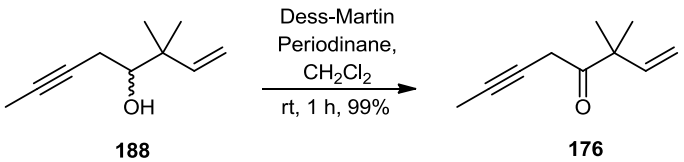
The ^{1}H NMR spectrum of the crude product showed that it was cleaner when the hydrobromic acid was added dropwise to a cooled solution of methyl-3-buten-2-ol and did not require further purification. The crude product was then used, in slight excess, in the Barbier reaction with the diluted aldehyde in dichloromethane.

Another possible problem was that as the crude aldehyde **187** was diluted in solution and it could not be analysed for purity or yield by NMR techniques. It was also possible that the

oxidation reaction of 3-pentynol may not have been complete or even successful. First attempts at the oxidation of the alcohol were analysed by TLC, however the aldehyde spot was hard to see and the DMP reagent was seen as a large spot on the TLC plate. The first few attempts gave low to moderate yields, which did not correspond to the yield obtained in the procedure that was being followed. The DMP reagent was then examined.

DMP was synthesised from IBX, previously synthesised and analysed for purity using NMR. After workup the DMP reagent was analysed by ^{1}H NMR techniques and was found to have some IBX impurities. The reagent was washed with ether and analysed by ^{1}H NMR again. The reagent was pure and was then used to oxidise the alcohol. On adding two drops of water to the reaction the DMP is activated and the mixture would normally warm up. However, on some occations this did not happen. Additional DMP reagent was added and sometimes more drops of water were added. The TLC plate was not clear when more DMP is added as it shows up as the largest spot, masking any starting material and product spots. In order to improve the purity of the DMP the acetic anhydride used to synthesise it from IBX was distilled as it was thought that this could be affecting the quality of the reagent. The freshly distilled acetic anhydride was used to synthesise DMP again and this seemed to improve the quality of the reagent. On ordering a fresher bottle of acetic anhydride it was found that it did not need to be purified further and a purer batch of DMP was synthesised. This was then used to oxidise the alcohol successfully, as seen by TLC once the DMP residues were removed and a small aliqot of the dilute aldehyde was obtained. This was then used in the Barbier reaction.

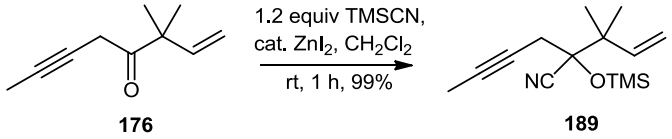
Despite the Barbier reaction being carried out in a mixture of solvents, the yield over two steps improved to 91% and gave the desired racemic alcohol **188**. This alcohol was oxidised using Dess-Martin periodinane and gave the ketone **176** in an excellent yield (Scheme 2.55).



188 **176**

Scheme 2.55 – DMP oxidation to give the ketone

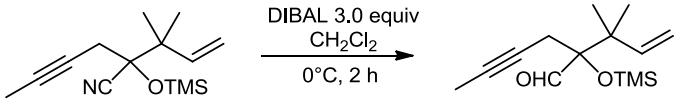
The ketone was then transformed into the racemic protected cyanohydrin[79] **189** (Scheme 2.56) in an excellent yield. Cyanation was carried out using catalytic zinc iodide and trimethylsilyl cyanide.



176 **189**

Scheme 2.56 – Synthesis of racemic nitrile

The racemic nitrile was then reduced with diisobutylaluminium hydride to give racemic aldehyde **177** (Scheme 2.57) following the procedure as carried out by Ma.[71a] This is when we noticed problems starting to occur.

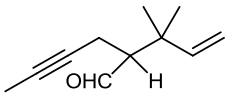


189 **177**

Scheme 2.57 - DIBAL reduction of racemic nitrile

This reaction should have given the desired aldehyde and when analysing the ^{1}H NMR spectrum, should show an aldehyde peak around 9.60 ppm. However, the ^{1}H NMR spectrum of the first reaction showed two aldehyde peaks and starting material. This did not correspond to the previous results obtained in the group. The two compounds containing aldehydes were hard to separate by flash column chromatography as the Rf values were very similar. The reaction was repeated with only two equivalents of DIBAL but again, the same two aldehyde peaks appeared on the NMR spectrum.

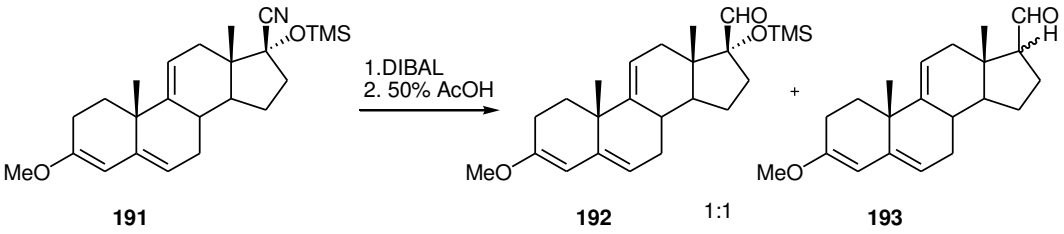
A small amount of the desired aldehyde and the second aldehyde compound were eventually separated. Analysis by ^{1}H NMR showed that the trimethylsilyl group had been cleaved. This could have occurred during the work up, when silica was added to the diluted reaction mixture and left in the freezer overnight. This had not happened in previous reaction where this work up had been used and therefore needed to be investigated further. However, the side product was identified, using COSY ^{1}H NMR, as the over-reduced silyl ether **190** (Scheme 2.58).



190

Scheme 2.58 – Side product

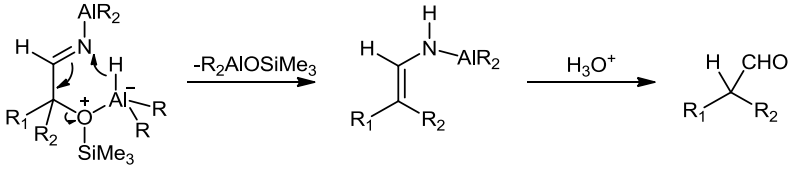
When studying the literature, this side product was not uncommon when using diisobutylaluminium hydride to reduce protected cyanohydrins. Reid and Debiak-Krook[80] had also encountered this over-reduced product whilst they were investigating the synthesis of corticoids. They reduced a nitrile group to the corresponding aldehyde, using diisobutylaluminium hydride in dichloromethane, which gave them the over-reduced side product and the desired product as a 1:1 mixture (Scheme 2.59).



191 **192** **193**

Scheme 2.59 – Over reduction as seen by Reid and Debiak-Krook

They mentioned that solvent choice for this reaction was crucial. In non chelating solvents such as dichloromethane or toluene, they discovered the level of the deoxy impurity ranged from 10 to 40%. They also discovered that when using tetrahydrofuran, the level of impurity was less than 1% but the reaction was very slow. They claimed the degree of over-reduction leading to the side product correlated with the Lewis basicity of the solvent, indicating that complexation of the silyloxy by some aluminium species was probably involved in the reaction. It was thought that the complexation occured through a second equivalent of diisobutylaluminium hydride, followed by an intramolecular conjugate hydride displacement (Scheme 2.60) that would give the enamine, which would produce the side product upon work up.



Scheme 2.60 – Mechanism for the formation of **190**

The over-reduction problem had also occurred in an earlier synthesis of fragment A at the start of the project. The problem had been overcome by using ether as a solvent instead of dichloromethane.[69]

In order to stop or even reduce the amount of side product being formed, different variables were tested. **Table 4** shows a selection of reactions of the tests carried out.

Table 4 – Test reactions carried out to reduce amount of side product **190** formed using DIBAL reagent supplied by Aldrich

Entry	Solvent	Temperature (time left at temperature)	Equivalents of DIBAL (solvent supplied in)	Work up	Ratio of product 177 to side product 190	Conversion from starting material
1	CH_2Cl_2	0 °C (2 h)	2 (CH_2Cl_2)	Silica	-	-
2	CH_2Cl_2	0 °C (2 h)	2 (CH_2Cl_2)	HCl (aq)	-	-
3	CH_2Cl_2	0 °C (2 h)	2 (CH_2Cl_2)	NH_4Cl (aq)	1:2	93
4	CH_2Cl_2	0 °C (2 h)	(Fresh bottle) 2 (CH_2Cl_2)	NH_4Cl (aq)	1:3	83
5	CH_2Cl_2	-40 °C (2 h)	2 (CH_2Cl_2)	NH_4Cl (aq)	1:3	80
6	CH_2Cl_2	-40 °C (2 h)	(Titrated DIBAL) 2 (CH_2Cl_2)	NH_4Cl (aq)	1:4	76
7	CH_2Cl_2	0 °C (2 h)	1 (CH_2Cl_2)	NH_4Cl (aq)	No reaction	-
8	Et_2O	-78 °C (2 h)	2 (CH_2Cl_2)	NH_4Cl (aq)	No reaction	-
9	Et_2O	0 °C (2 h)	2 (CH_2Cl_2)	NH_4Cl (aq)	No reaction	-
10	Et_2O	0 °C (2 h)	2 (Hexane)	NH_4Cl (aq)	No reaction	-
11	Et_2O	-40 °C to 20 °C (4 h)	2 (CH_2Cl_2)	NH_4Cl (aq)	No reaction	-
12	Et_2O	-40 °C to 20 °C (16 h)	2 (CH_2Cl_2)	NH_4Cl (aq)	No reaction	-
13	THF	0 °C (2 h)	2 (Cyclohexane)	NH_4Cl (aq)	No reaction	-
14	THF	0 °C (6 h)	2 (Cyclohexane)	NH_4Cl (aq)	No reaction	-
15 (Fresh **189**)	THF	0 °C – 20 °C (16 h)	2 (Cyclohexane)	NH_4Cl (aq)	No reaction	-
16	Hexane	0 °C (2 h)	2 (Hexane)	NH_4Cl (aq)	No reaction	-
17	Hexane	0 °C (2 h)	2 + 2 after 2 h (Hexane)	NH_4Cl (aq)	No reaction	-
18	Hexane	0 °C (2 h)	2 (Cyclohexane)	NH_4Cl (aq)	No reaction	-
19	Hexane	0 °C (2 h)	2 (Hexane)	NH_4Cl (aq)	No reaction	-

Before actually isolating any product, the work up had to be optimised (entries 1-3). Using silica gel to remove any excess diisobutylaluminium hydride was leaving a sticky aluminium residue. The product might have been trapped in this sticky residue. The work up was carried out using 1M aqueous hydrochloric acid, which removed any aluminium salts from the organic layer. Another alternative work up was using saturated ammonium chloride. This was added to the quenched reaction mixture and left to stir at 0 °C for one hour until the aluminium salts precipitated out. This was preferred over the hydrochloric acid work up, as the salt could be seen forming and produced a cleaner crude ^{1}H NMR spectrum.

A fresh bottle of reagent was then used, to ensure a good quality of the reagent (entry 4), but the same result was obtained.

The next variable to be changed was the temperature of the reaction (entries 5 and 6). The nitrile was dissolved in dichloromethane and diisobutylaluminium hydride was added to the reaction at -40 °C, however over-reduction still occurred.

As the second equivalent of diisobutylaluminium hydride was causing the over-reduction, the reaction was carried out using only one equivalent to see if only the product was obtained (entry 7). This reaction was unsuccessful and only starting material was recovered.

Having examined the literature paper by Reid and Debiak, we decided to run the reaction in diethyl ether at different temperatures (entry 8-12). The diisobutylaluminium hydride was added at -40 °C and the reaction was monitored by TLC every thirty minutes; however, after two hours no reaction had taken place. The reaction was left to warm to room temperature overnight and after work up the product and side product were still present. Reactions attempted in THF at diverse temperatures also gave no product (entries 13-15). Ether and THF complex to the diisobutylaluminium hydride and reduces its ability to react with the nitrile. We therefore decided to use non-complexing solvents for further attempts (entries 17-19), but once again, no reaction was observed.

We then questioned the quality of the diisobutylaluminium hydride reagent. Two test reactions were carried out in hexane, as this was the solvent that the diisobutylaluminium hydride was supplied in. One bottle of diisobutylaluminium hydride was from Aldrich and the other from Fisher (Table 5). Both were new bottles so that a fair comparison could be

carried out. The hexane was freshly distilled onto molecular sieves to remove any moisture present. Both reactions containing the nitrile were cooled in hexane to -78 °C. Two equivalents of diisobutylaluminium hydride were added dropwise to the reactions, which were then allowed to warm to room temperature and stirred for two hours. The reactions were quenched with ethyl acetate and diluted with diethyl ether. Ammonium chloride was added and stirred at 0 °C for forty five minutes to remove any excess diisobutylaluminium hydride. The reactions were filtered over celite and dried over sodium sulfate. Once the solvent had been evaporated, the crude products were analysed.

Table 5 - Test reactions carried out to reduce amount of side product **190** formed using DIBAL reagent supplied from Fisher

Entry	**Solvent**	**Temperature (time left at temperature)**	**Equivalents of DIBAL (solvent supplied in)**	**Work up**	**Ratio of product 177 to side product 190**	**Conversion from starting material**
20	Hexane	0 °C (2 h)	2 (Hexane) Fresh bottle	$NH_4Cl_{(aq)}$	3:1	90
21	Hexane	0 °C (2 h)	2 (Hexane)	$NH_4Cl_{(aq)}$	No reaction	-
22	Hexane	0 °C (2 h)	2.5 (Hexane)	$NH_4Cl_{(aq)}$	No reaction	-
23	Hexane	0 °C (2 h)	2 (Hexane Fresh bottle)	$NH_4Cl_{(aq)}$	3:1	93

The reaction using the bottle supplied by Aldrich, which was also the diisobutylaluminium hydride used in all the above test reactions, had over-reduced the cyanide as it had done previously. The Fisher bottle had reduced the cyanide to the desired aldehyde with only a small amount of side product present (entry 20).

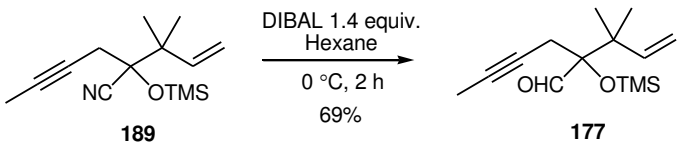
A second reduction was then carried out using the Fisher diisobutylaluminium hydride in hexane. This reaction was unsuccessful and the starting material was recovered (entry 21). The same result was observed when using 2.5 equivalents of DIBAL (entry 22). The diisobutylaluminium hydride had only been open for four days, which shows that this

reaction is sensitive to the reagents used and also indicates the importance of the quality of the diisobutylaluminium hydride.

As this reaction is very sensitive, to reduce the amount of diisobutylaluminium hydride waste, a large scale reduction was carried out using three grams of racemic nitrile and a new bottle of diisobutylaluminium hydride from Fisher. Using the same conditions as above the larger scale reduction was successful however, some side product was still formed but after purification the aldehyde was obtained in a 70% yield (entry 23). Racemic fragment A had been synthesised successfully.

A larger scale reduction was carried out after this using approximately five grams of racemic nitrile however, this reaction was not as clean and once again the side product was present. The largest scale that this reaction should carried out on should be no more than three grams in order to obtain the best results.

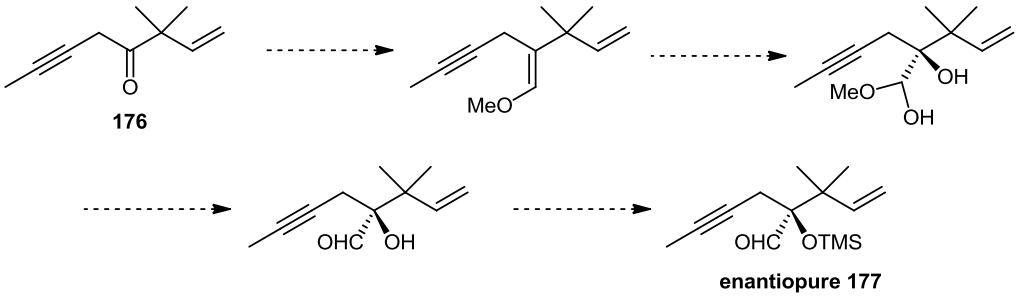
Finally, to prevent formation of the side product, 1.4 equivalents of fresh diisobutylaluminium hydride were used. This gave the desired aldehyde **177** in a 69% yield without any side product being formed (Scheme 2.61). These were the best conditions for the reduction of the nitrile.



189 **177**

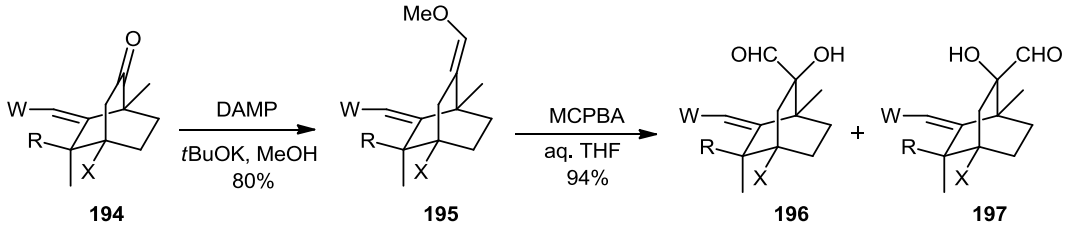
Scheme 2.61 – Optimised conditions for reduction of the nitrile

This reaction optimisation was very time consuming, as nitrile **189** had to be resynthesised several times. As the aldehyde of fragment A was proving to be difficult to synthesise, an alternative route was also devised in parallel. This would also create an enantiopure fragment A. This route would start with ketone **176** which would be converted into the methyl enol ether, followed by a Sharpless asymmetric dihydroxylation. The hemiacetal would then be hydrolysed to the corresponding aldehyde using acid. Finally, the alcohol would be protected as the trimethylsilyl ether thus giving possible access to the enantiopure fragment A (Scheme 2.62).



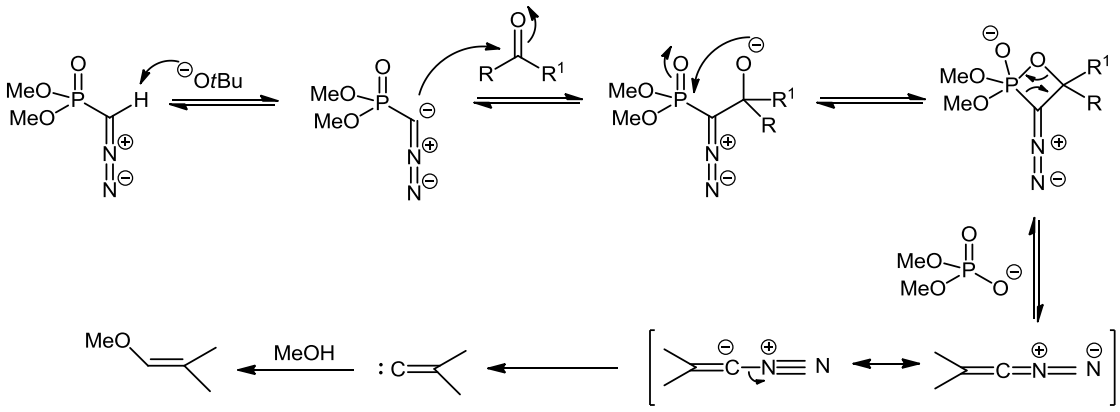
Scheme 2.62 – Retrosynthesis of enantiopure fragment A

The start of this route was based on a precedent by Martin *et al*[81] who were looking at synthesising the AB ring system of taxane diterpenes. The group synthesised the aldehyde **197** by converting the ketone **194** into the enol ether **195** using dimethyl diazomethylphosphate (DAMP) in methanol in the presence of potassium *tert*-butoxide (Scheme 2.63).



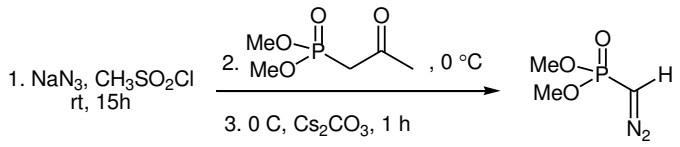
Scheme 2.63 – Converting ketone **194** into the corresponding aldehyde by Martin

This reaction using ketones, leads to methyl enol ethers by trapping the intermediate carbene with residual methanol (Scheme 2.64).



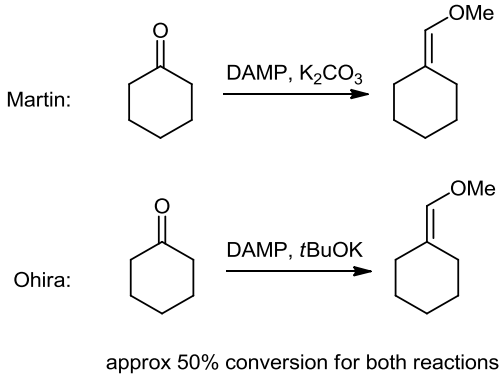
Scheme 2.64 – Mechanism of DAMP

To convert the ketone to the methyl enol ether, the Seyferth/Gilbert reagent had to be synthesised. This was done following a procedure by Maehr *et al*[82] and was chosen due to its one-pot procedure (Scheme 2.65).



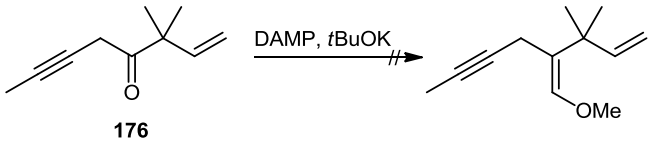
Scheme 2.65 – Preparation of Seyferth/Gilbert reagent

Once the reagent had been synthesised, it was used in a test reaction with cyclohexanone. The first test reaction was carried out using the conditions in the Martin paper using cyclohexanone, dimethyl diazomethylphosphonate (DAMP), potassium-*tert*-butoxide and methanol. The ^{1}H NMR spectrum showed that the reaction had been somewhat successful with approximately 50% conversion to the desired product. Whilst looking into this new approach, another paper was found where Ohira[83] had tested the dimethyl diazomethylphosphonate reagent on cyclohexanone using slightly different conditions to Martin. A second test reaction was carried out using the conditions in the Ohira paper, which used potassium carbonate instead of potassium-*tert*-butoxide as the base (Scheme 2.66). ^{1}H NMR spectrum showed an approximate 50% conversion for this reaction as well.



Scheme 2.66 – Test reactions using Martin and Ohira conditions

The reaction was then carried out with ketone **176** using Ohira's conditions (Scheme 2.67). The crude ^{1}H NMR spectrum showed that the product was decomposing. The reaction was repeated, this time using cesium carbonate as the base but again the crude ^{1}H NMR spectrum showed decomposition.



176

Scheme 2.67 – Attempted conversion of the ketone to the methyl enol ether

This route to synthesise the enantiopure fragment A using the Gilbert/Seyferth reagent was not worth continuing with so we pursued the synthesis using racemic fragment A which would be used in the subsequent Shapiro coupling.

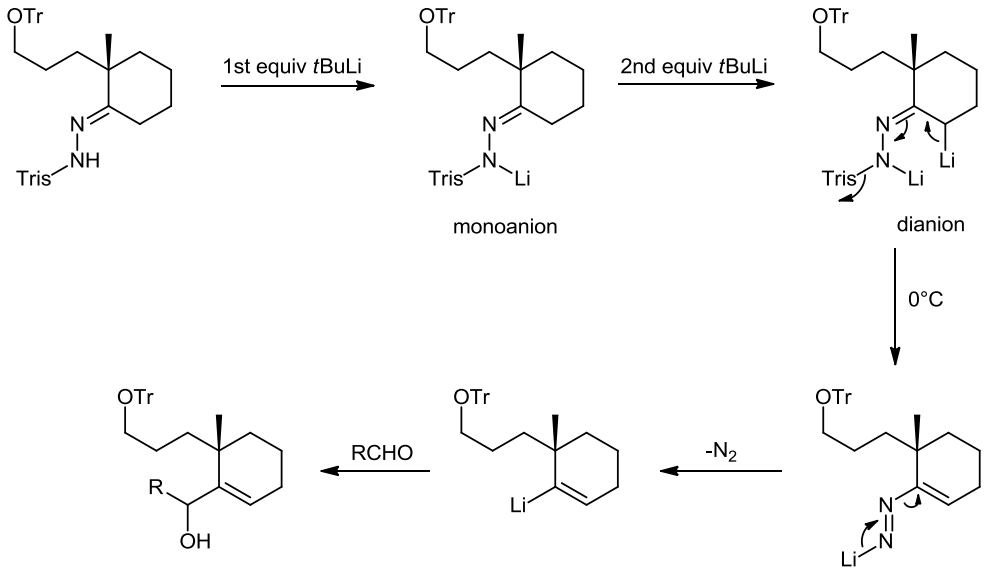
Chapter III

Towards 7-deoxy taxol and ring-closing metathesis

3.1 Shapiro coupling

The Shapiro reaction transforms ketones to alkenes through an intermediate hydrazone.[84] This reaction was utilised by Chamberlin[85] who reported a method that generated a variety of vinyllithium derivatives that could be trapped using an assortment of electrophilic reagents.

The Shapiro reaction is very sensitive and previously within the group it has been difficult to optimise. The key step in the reaction is the formation of the second anion (Scheme 3.01), detected by a colour change from red (monoanion) to dark red (dianion).



Scheme 3.01 – Mechanism of Shapiro reaction

Test Shapiro reactions were carried out using hydrocinnamaldehyde and the C ring hydrazone. *tert*-Butyllithium was added to a cooled solution of hydrazone in tetrahydrofuran, the solution turned red but doubt about the colour of the reaction led to the addition of two extra equivalents of *tert*-butyllithium (entry 1, Table 3.1). Addition of excess *tert*-butyllithium results in the addition of *t*-butyl lithium to the aldehyde.

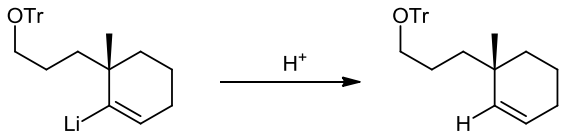
Table 3.1 – Test Shapiro reactions using hydrocinnamaldehyde

Entry	Amount of solvent per 500 mg hydrazone	Equivalents of *t*BuLi	Aldehyde purified	Reaction time	Result
1	1.0 mL	2.0 (+ 2.0)	No	30 min	Addition of *t*-butyllithium to aldehyde
2	1.0 mL	2.0	No	30 min	Alkene **199**
3	4.0 mL	2.0	No	30 min	Alkene **199**
4	4.0 mL	2.0	No	5 h	Alkene **199**
5	1.5 mL	2.15	Yes	30 min	Alkene **199**
6*	1.5 mL	2.15	Yes	2 h	Product 61%

* C ring was azeotroped with toluene

The reaction was repeated again, but this time only two equivalents of *tert*-butyllithium were added, hydrocinnamaldehyde was then added, however this reaction was also unsuccessful (see entry 2, Table 3.1).

We thought any moisture present in the system might affect the reaction as this would promote the formation of the alkene **199**, a side product formed if the vinyl anion does not react with the aldehyde but is instead protonated (Scheme 3.02). This alkene has very distinct peaks in the ^{1}H NMR spectrum, found at around 5.31 ppm (d) and 5.25 ppm (ddd) representing the two alkene protons. This allows for the easy identification of the alkene product in the spectrum.



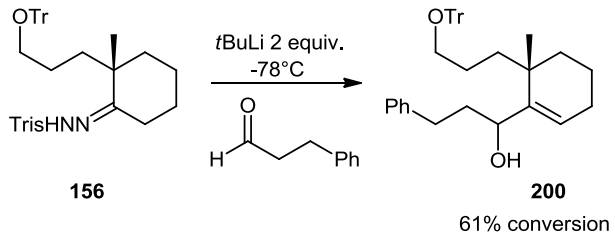
198 **199**

Scheme 3.02 – Side product of Shapiro reaction

The concentration of the reaction was then varied (see entries 3 and 4, Table 3.1). The reaction was also left stirring for longer to give the reagents time to react; again these reactions failed.

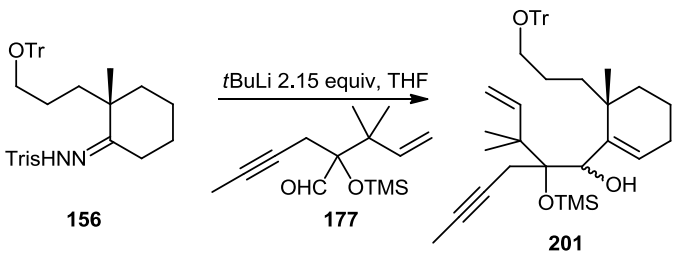
The aldehyde was purified to remove any excess moisture that could affect the reaction. Addition of the freshly distilled aldehyde to the reaction mixture showed no reaction had taken place once analysed by ^{1}H NMR. A slight excess of *tert*-butyllithium (2.15 equivalents) was added to ensure that the two deprotonations were taking place.

The hydrazine was azeotroped with toluene then placed under vacuum for four hours to remove any moisture present. *tert*-Butyllithium (2.15 equivalents) was added to the dried hydrazone before the aldehyde was added at -78 °C. After work up, the crude ^{1}H NMR spectrum showed that the desired aldehyde had been formed and conversion was calculated using the ratio of starting material to product from the spectrum (Scheme 3.03).



Scheme 3.03 – Successful test reaction with hydrocinnamaldehyde

After the success of the test reaction, we carried out Shapiro reactions with fragment A (Scheme 3.04).



Scheme 3.04 – Shapiro reaction using fragment A

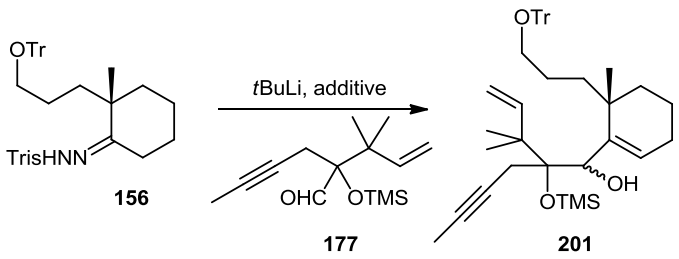
In all cases, the aldehyde was freshly prepared and all the starting materials were thoroughly dried under vacuum after azeotroping with toluene. Different conditions were

investigated to see if the yield of the reaction could improve. Some of these can be found in Table 3.2.

Table 3.2 – Results of early Shapiro reactions carried out

Entry	**Equivalents of hydrazone in THF (mL)**	**Equivalents of *t*BuLi**	**Equivalents of $CeCl_3$**	**Reaction time at -78 °C**	**Yield of mixture after removal of 199**
1	1.5 (4 mL)	3.0	-	5 h	-
2	1.2 (1.5 mL)	2.1	-	2 h	-
3	1.2 (1.5 mL)	2.1	1.2	2 h	13%
4	1.2 (1.5 mL)	2.1	1.2	30 min	24%
5	1.1 (1.5 mL)	2.1	1.2	30 min	-
6	1.1 (2 mL)	2.1	1.2	30 min	21%
7	1.1 (3 mL)	2.1	1.2	30 min	33%
8	1.2 (3 mL)	2.1	1.2	30 min	24%
9	1.2 (3 mL)	2.1	1.2	1 h	19%
10	1.2 (3 mL)	2.15	1.2	1 h	20%
11	1.2 (3 mL)	2.15	1.2	30 min	29%
12	1.2 (6 mL)	2.15	1.2	30 min	35%
13	1.2 (6 mL)	2.15	1.3	30 min	30%
14	1.2 (3 mL)	2.15	1.3	30 min	23%
15	1.2 (4 mL)	2.15	1.3	30 min	17%
16	1.2 (4.5 mL)	2.15	1.3	30 min	-
17	1.2 (5 mL)	2.15	1.2	1 h	45%

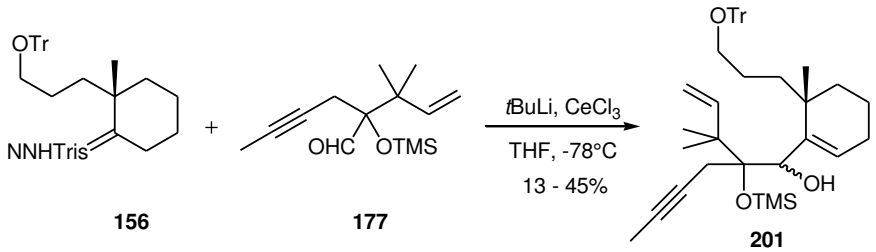
The first few attempts at the Shapiro reaction were carried out without any cerium trichloride (entries 1, 2) as test reactions. Previous work in the group[71a] had shown that in order to increase the yield of the reaction, it was necessary to increase the nucleophilicity of the vinyl anion by transmetallating it with cerium trichloride (Scheme 3.05).



Additive	Time after addition	Yield
None	-	20%
$CeCl_3$	30 min	85%

Scheme 3.05 – Improved yield by addition of $CeCl_3$ (Cong Ma)

Anhydrous cerium trichloride was dried using a literature procedure[74] and tetrahydrofuran was added. The cerium trichloride was stirred vigorously in tetrahydrofuran, between two and four hours, to create a suspension. The suspension was cooled to -78 °C and titrated with *tert*-butyllithium to give a yellow coloured solution. This was then added *via* cannula to the dianion (Scheme 3.06).



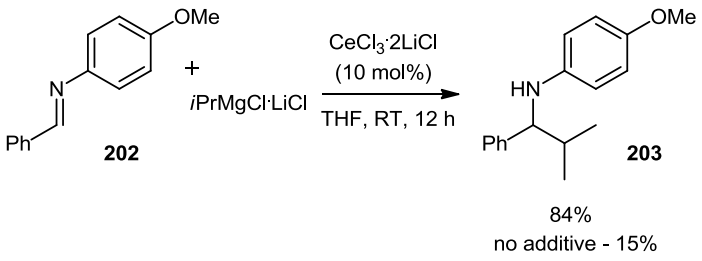
Scheme 3.06 – Shapiro reaction with $CeCl_3$

The cerium trichloride used was in anhydrous bead form. These were supplied in a vial with an inert atmosphere and were weighed into the reaction flask under argon before the flask was sealed, under an inert atmosphere, and then weighed. Tetrahydrofuran was then added to the beads and they were stirred vigourously for two hours under argon before being titrated with *tert*-butyllithium. At first the beads were not thought to be crushed enough to create a good enough suspension and so they were left stirring vigorously for four hours. The reactions using the anhydrous cerium trichloride beads were not producing the desired diastereomers in good yields, and so after being weighed they were placed under vacuum to remove any moisture that might have been present. The solvent was then added and the solution was stirred vigourously (entries 3-9).

Depsite best efforts, the yields were still low and so we switched to using the cheaper powdered version, cerium trichloride heptahydrate (entries 11-17). This was dried by heating under vacuum for set time periods and then heating under vacuum overnight. This was then cooled, tetrahydrofuran was added and the powder was stirred vigourously for four hours before being titrated with *tert*-butyllithium. The yields improved slightly but not enough to ensure that a moderate to good yield was being obtained. Adding more equivalents of cerium trichloride was thought to improve the nucleophilicity of the vinyl anion, but this could also have led to more moisture being present in the system and more *tert*-butyllithium added to titrate it with. Both factors could have been affecting the reaction.

Despite transmetallation of the vinyl anion, the yield of the Shapiro reaction still remained low. The maximum yield of the two diastereomers formed was 45%, with the alkene being obtained as the major product in 50% yield relative to the aldehyde.

Titrating the cerium trichloride with *tert*-butyllithium should remove any water present. However, a literature procedure was discovered where two equivalents of lithium chloride were added to the cerium trichloride.[86] This promoted the addition of more hindered nucleophiles and claimed to minimise any side reactions occurring (Scheme 3.07).



Scheme 3.07 – Use of LiCl to improve reaction yields by Knochel

Two equivalents of lithium chloride were added to the cerium trichloride, which was heated and stirred under vacuum overnight. Addition of the lithium chloride allows the normally insoluble cerium trichloride to dissolve. When this suspension was added to the dianion the solution turned black and after work up the crude ^{1}H NMR spectrum showed a number of signals.

Adding more solvent or reagent could increase the amount of moisture in the system (entries 4-14). The aldehyde **177** and hydrazone **158** were both azeotroped with toluene

and dried under vacuum before being added to the reaction. At first only for one hour but this was extended up to eight hours. In order to reduce the amount of moisture in the solvent molecular sieves were added and left for at least two to four hours under an inert atmosphere. As well as using solvent from a departmental still, freshly distilled solvent from the laboratory was used, but again this led to no improvement in the yield of the reaction.

Another factor that could have affected the reaction is the freshness of the aldehyde. The first few times the reaction was carried out the aldehyde had been in the fridge, where again it could have collected moisture or even start to degrade (entries 1-3). Before the aldehyde was used it was analysed for any signs of degradation using ^{1}H NMR. The issues with synthesising the aldehyde and the hydrazone at first meant that both were not as fresh as could be. More starting material was brought forward to see if the freshly synthesised hydrazone and aldehyde would help to increase the yield of the reaction (entries 4-18). This did not seem to have any effect on the reaction and low yields of the two diastereomers continued to be isolated.

At first the reaction was carried out quite concentrated as it is thought that the reaction is sensitive. This was affecting the yield of the reaction and so using a different procedure [71a] was followed, this time carrying out the reaction in a more diluted concentration. This did improve the separation and work up, as well as visualising the colour change of the hydrazone once adding the *tert*-butyllithium, but the reaction yields were still low despite following a procedure that claimed an 80% yield.

By varying the number of equivalents of hydrazine and *tert*-butyl lithium used it was thought that this would allow the aldehyde to react with an increased percentage of the vinyl anion. The negative impact by doing this is that with more hydrazone present there is an increased risk that more undesired alkene **199** will be formed.

The *tert*-butyllithium was titrated before every experiment (entries 1-18) in order to obtain its concentration. As with the diisobutyllithium before, older bottles could possibly have affected the reaction with the increase in solids forming in the bottle. The older bottles may also have affected the rate of the deprotonation of the hydrazone, despite allowing extra volume for a decrease in its concentration. This could lead to over or reduced addition of the reagent and therefore affect the formation of the vinyl anion.

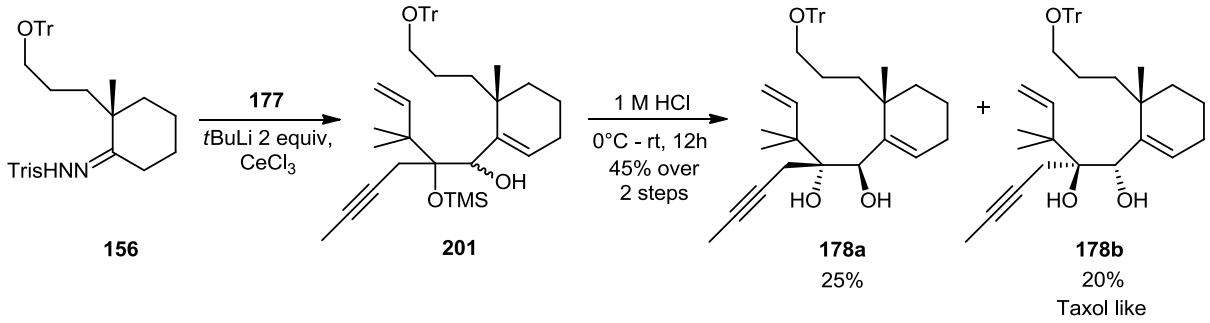
The number of equivalents of aldehyde was varied from 1 to 1.2; this was seen not to have reacted with the vinyl anion by TLC after work up. Most of the unreacted aldehyde could not be recovered as its rf value was very similar to that of the alkene **199** and the two products came off the column together, even though attempts at separating them off with specific eluents were carried out.

The first procedure we were following[71b] left the reaction stirring for five hours, whereas the second procedure said for thirty minutes.[71a] The time the reagents had to react could have affected the result, most likely in our case it did not, as the alkene had already formed thus reducing the amount of vinyl anion the aldehyde could react with. We varied the time of the reaction to see if we could get close to the yields acquired in the two procedures, however we were not successful.

After the coupling experiments the crude mixture was purified. The TLC plate of the crude mixture showed up to six or seven spots. The three nearest the top of the plate were the undesired alkene **199**, unreacted aldehyde and an unknown fraction. These were easily removed together, but were never separated individually. The two inseparable diastereomers were the next fraction to come off, followed by three other unknown compounds. The number of spots present on the TLC plate showed that this reaction is not clean and that side reactions are occurring and are affecting the yield of the reaction.

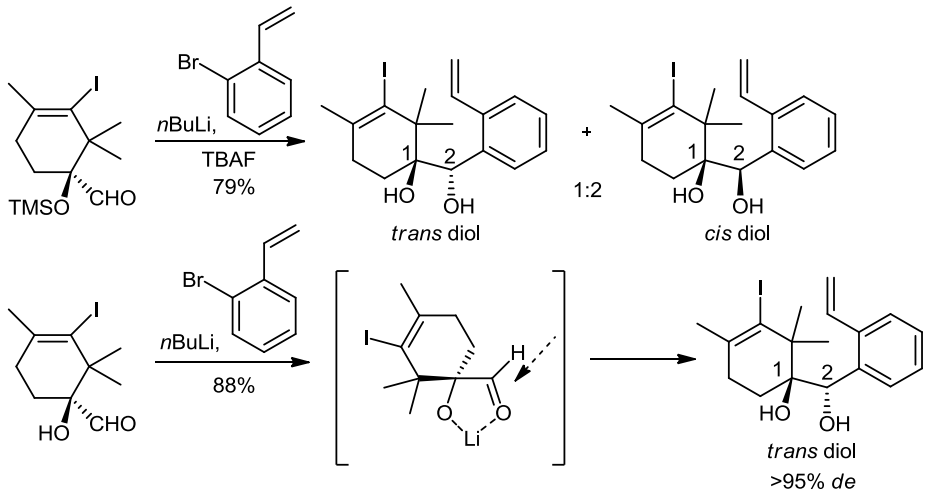
At this point where it seemed like we were making progress we ran out of material and more had to be brought through. We continued carrying out Shapiro reactions with the conditions in Scheme 3.06 despite the low yields and formation of the unwanted alkene **199,** but this could be removed by flash column chromatography leaving the two diastereomers.

The mixture of diastereomers was then dissolved in tetrahydrofuran and subjected to mild acidic conditions to remove the protecting trimethylsilyl group. Separation by flash column chromatography gave the two *trans* diols **178a** and **178b** (Scheme 3.08).



Scheme 3.08 - Separation of the two diastereomers

Danishefsky[87] was the first to study the diastereoselectivity of the addition of nucleophiles to aldehydes at the C2 position in order to obtain the C1-C2 diol of taxol. When adding a siloxy aldehyde to a lithiated styrene, the *trans* diol was obtained, in a 1:2 ratio, with the *cis* diol. Reacting an α-hydroxy aldehyde with the lithiated styrene gave the *trans* diol exclusively. This was due to chelation of the lithium by the two oxygens of the substrate (Scheme 3.09).



Scheme 3.09 – *Trans* diol formation by Danishefsky[87] using lithium chelation

The *cis* 1,2-diol can be obtained through a transition state following the polar Felkin-Ahn model. The siloxy group is orthogonal to the carbonyl group in the transition state; this lowers the energy of the lowest unoccupied molecular orbital of the π system rendering it more reactive. The overlap between σ* C-OSi is π* C=O are at maximum when in this conformation (Figure 3.01).

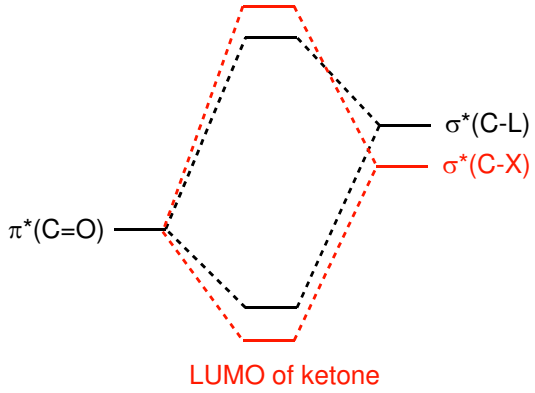
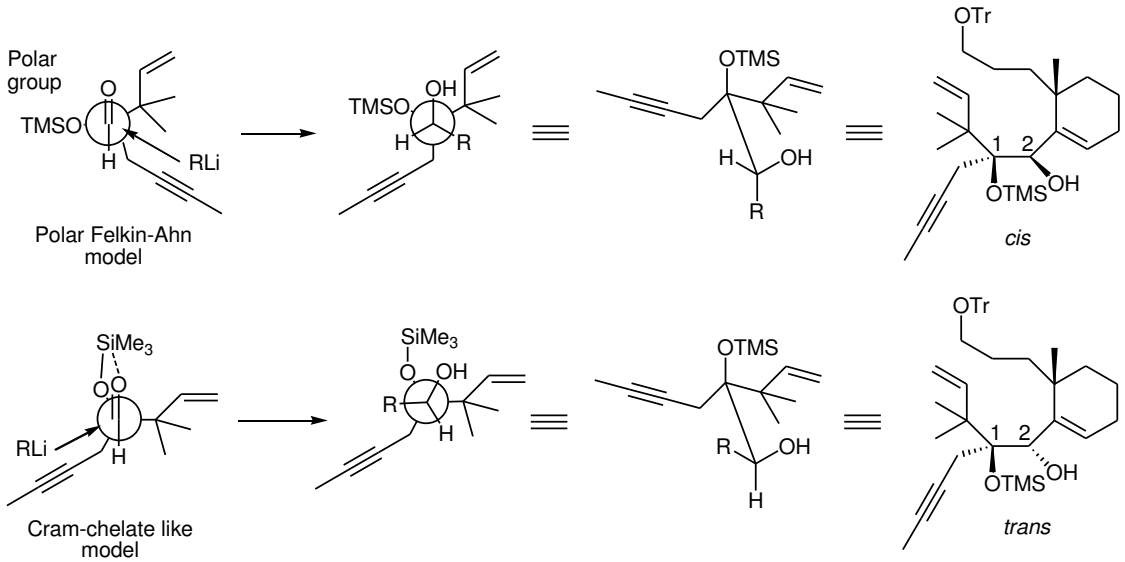


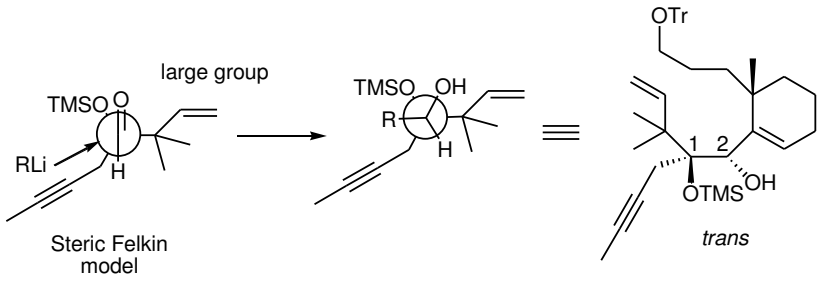
Figure 3.01 – Lowering of energy of the LUMO

To obtain the *trans* diol the Cram-chelate could be involved, as there could be complexation between the siloxy group and the carbonyl group, but this is unlikely. Both transitions are shown below in Scheme 3.10.



Scheme 3.10 – Selectivity models

Another possibility is that the *trans* product can be obtained via the steric Felkin transition state, where the largest group, in this case the chain, which contains the *gem*-dimethyl group, is positioned perpendicularly to the aldehyde. This would give the more stable conformer that the nucleophile can attack giving the *trans* product (Scheme 3.11).

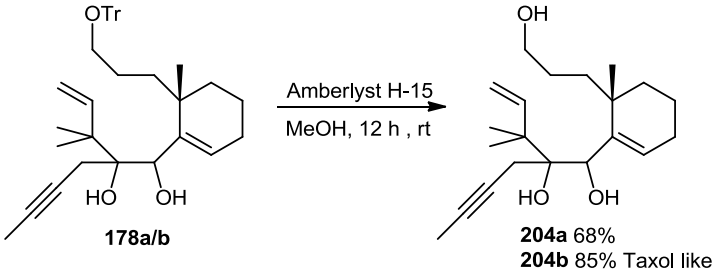


Scheme 3.11 – Steric Felkin model giving the *trans* product

With the two *trans* diols separated, the corresponding metathesis precursors could be synthesised.

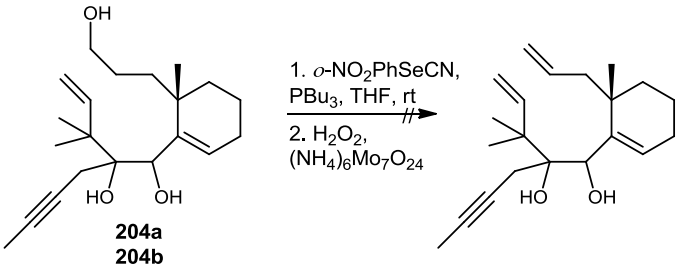
3.2 Synthesis of Metathesis Precursors

Both diastereomers had the trityl protecting group removed under acidic conditions using Amberlyst H-15 (Scheme 3.12) giving triols **204a** and **204b** in moderate to good yields.



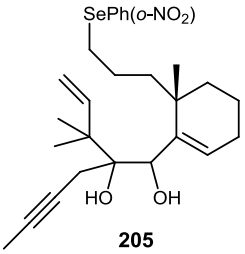
Scheme 3.12 – Removal of the trityl group

The next step was to transform the primary hydroxyl group to the terminal olefin. This had previously been done using Grieco's method.[88] Both triols were subjected to Grieco's conditions however following work up the desired product was not obtained (Scheme 3.13).



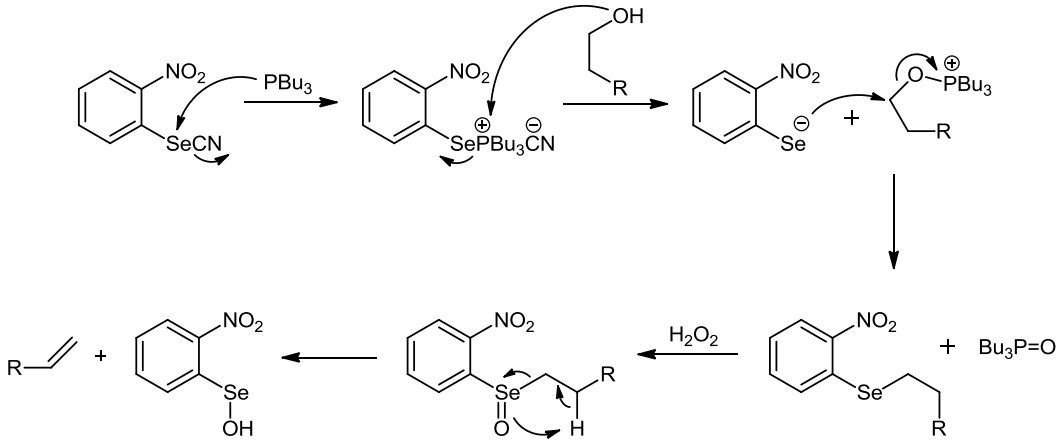
Scheme 3.13 – Attempt at Grieco reaction

The crude ^{1}H NMR spectrum showed that two sets of aryl peaks were present. One from the excess *o*-nitrophenylselenocyanate and the other from the selenium ether formed in the first step of the reaction (Scheme 3.14).



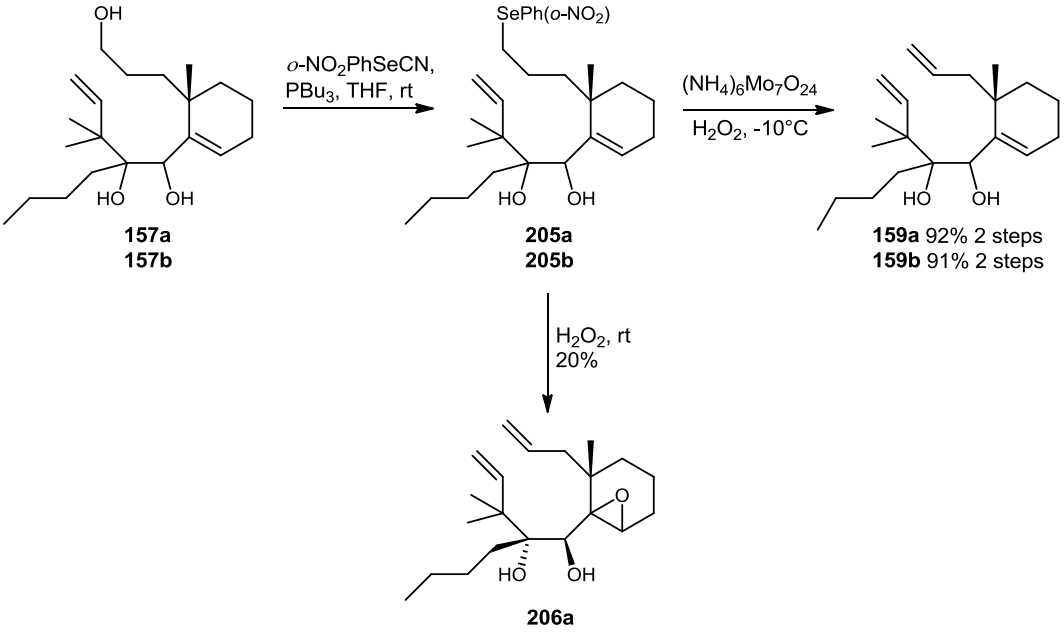
Scheme 3.14 – Selenium ether obtained from Grieco reaction

The Grieco elimination is carried out in two steps; the first forms a selenium ether. The alcohol reacts with *o*-nitrophenylselenocyanate and tributylphosphine to form a selenide in a nucleophilic substitution on the electron deficient selenium. In the second step the selenide is oxidised, using hydrogen peroxide, to the selenoxide followed by its elimination (Scheme 3.15).



Scheme 3.15 – Grieco olefination mechanism

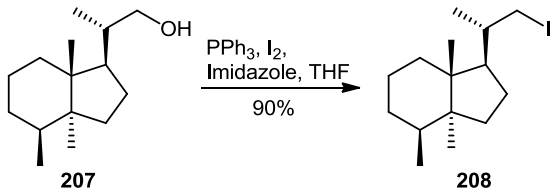
In our case, elimination of the selenoxide had not occurred. We had planned to add only hydrogen peroxide to the intermediate selenyl ether; however previous work[71a] on a model system, with a butyl side chain, had shown that this could lead to the epoxidation of the double bond between C3 and C4 (Scheme 3.16). To avoid epoxidation, a premixed solution of ammonium molybdate and hydrogen peroxide was added to the selenyl ether.



Scheme 3.16 – Previous work on the Grieco reaction

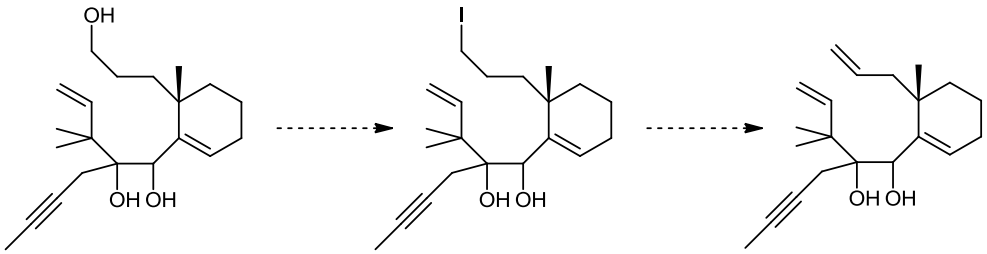
The selenyl ether was subjected to the solution containing hydrogen peroxide and ammonium molybdate; however no reaction occured.

We then investigated a different route to prepare the terminal alkene. Variations of the Appel reaction using iodine, imidazole and triphenylphosphine are an effective way to transform an alcohol into the corresponding alkyl iodide. These conditions are mild and effective as shown by examples in the literature. One example of this was carried out by Fall whilst synthesising vitamin D intermediates (Scheme 3.17).[89]



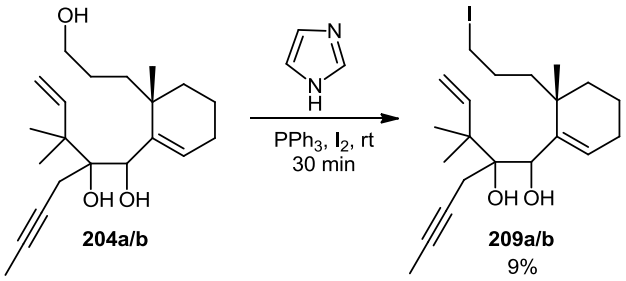
Scheme 3.17 – Iodination of an alcohol by Fall

Our new strategy was to perform this same variation of the Appel reaction to form the alkyl iodide before an elimination reaction, using sodium hydride, would give the alkene (Scheme 3.18).



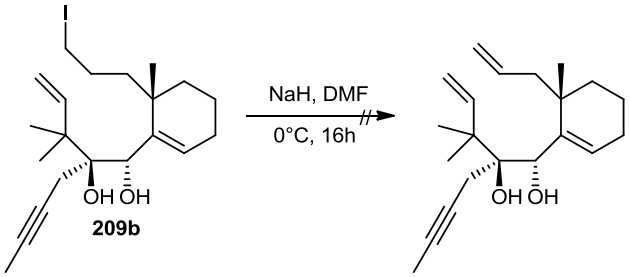
Scheme 3.18 – Planned Appel reaction route to triene

Preparation of the iodide was not as successful as we had hoped for. On addition of the iodine to triols **204a** and **204b**, the brown solution turned clear indicating some form of reaction; however the product was only obtained in 9% yield after work up (Scheme 3.19). The low yield was most likely obtained as the iodine could have reacted with the alkene in the starting material.



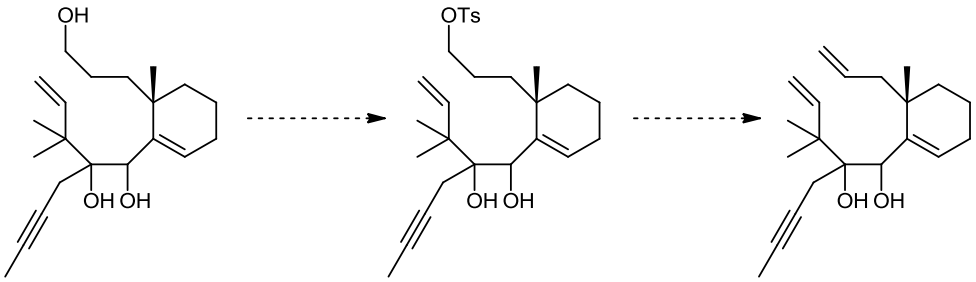
Scheme 3.19 – Appel reaction

Despite the low yield we wanted to test the elimination reaction and so the small amount of taxol-like iodide product **209b** was subjected to sodium hydride (Scheme 3.20). However, the small scale of the reaction made it difficult to distinguish if any product had formed.



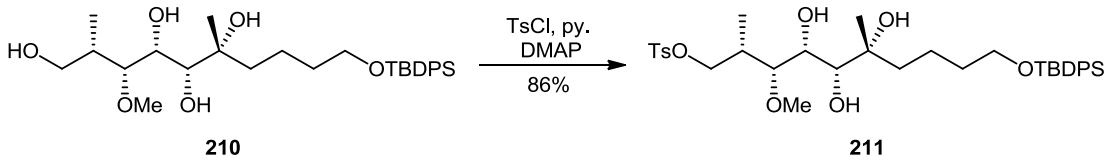
Scheme 3.20 – Attempt at obtaining trienic compound

Despite attempting the reaction multiple times, the yield of the alkyl iodide obtained was never greater than 9%. Another method was then proposed to form the desired trienic compound, which would involve transforming the primary alcohol into a tosylate followed by elimination (Scheme 3.21).



Scheme 3.21 – Proposed method to form trienic compound

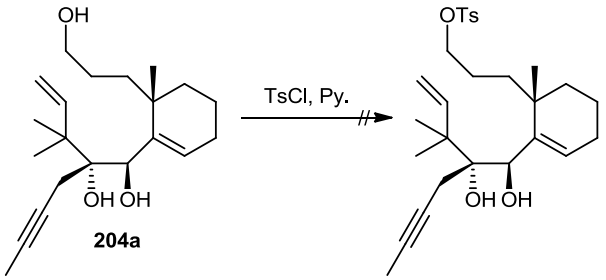
The conditions for this reaction were found in a procedure by Nishiyama[90] who carried out tosylation of a primary alcohol in the presence of secondary alcohols which were unaffected (Scheme 3.22).



210 **211**

Scheme 3.22 – Nishiyama tosylation

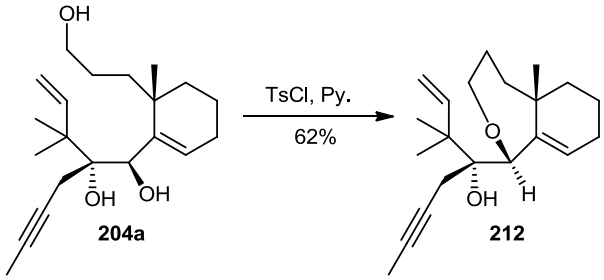
The non taxol-like triol **204a** was dissolved in pyridine and recrystallised tosyl chloride was added. After work up, the crude ^{1}H NMR spectrum showed fewer proton signals than expected and showed that the desired product had not been formed (Scheme 3.23).



204a

Scheme 3.23 – Failed attempt at tosylation

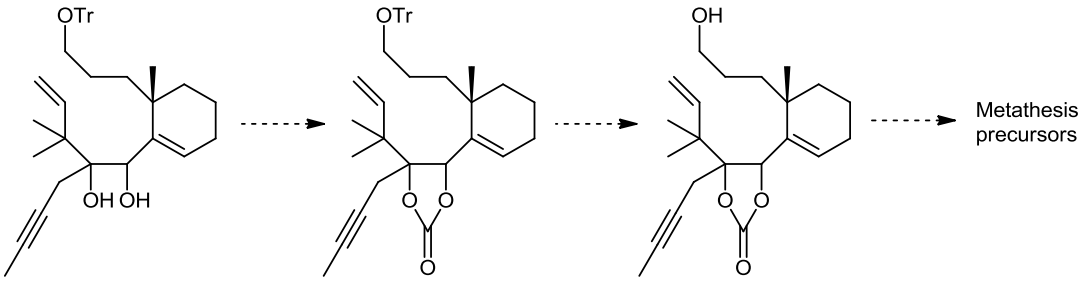
The product that had been formed during the reaction was a seven-membered cyclic ether (Scheme 3.24).



204a **212**

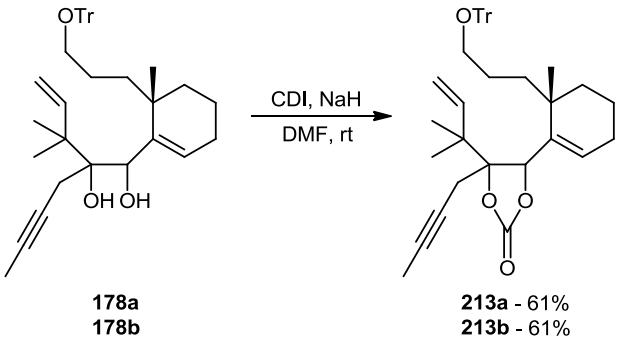
Scheme 3.24 – Seven membered cyclic ether

As none of the attempts at synthesising the trienic compound were successful, we decided to go back an earlier stage of the synthesis regarding the diol and protect it as a carbonate in order to synthesise the metathesis precursor (Scheme 3.25).



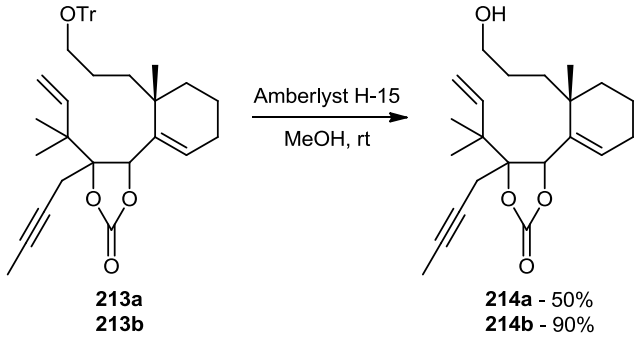
Scheme 3.25 – New procedure towards metathesis precursors

Diols **178a** and **178b** were subjected to carbonyl diimadazole and sodium hydride. After stirring at room temperature for thirty minutes and following work up, carbonates **213a** and **213b** were obtained in good yields (Scheme 3.26).



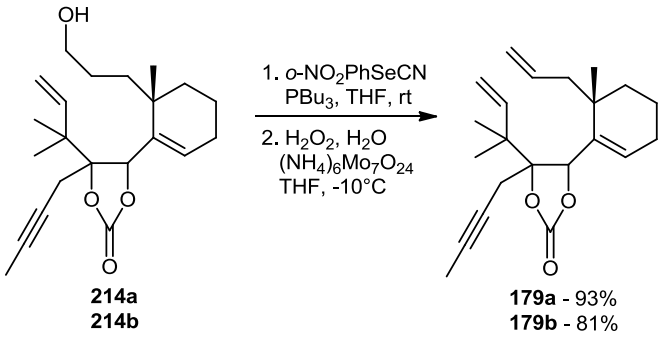
Scheme 3.26 – Protection of the diol using carbonate ester

Both carbonates were subjected to Amberlyst H-15 and stirred overnight at room temperature. The resulting alcohols **213a** and **213b** were obtained in good to excellent yields (Scheme 3.27).



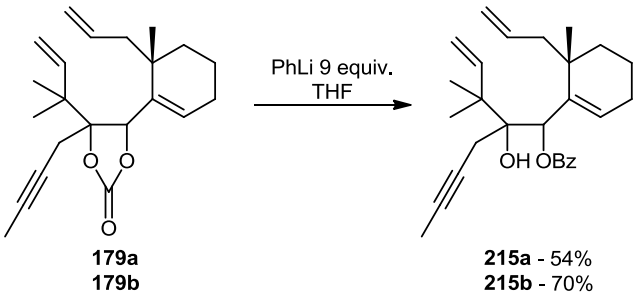
Scheme 3.27 – Removal of the trityl ether

The alcohols **214a** and **214b** were then subjected to the Grieco reaction which was carried out in two stages as before. The trienic compounds were obtained in good yields (Scheme 3.28)



Scheme 3.28 – Trienic compounds

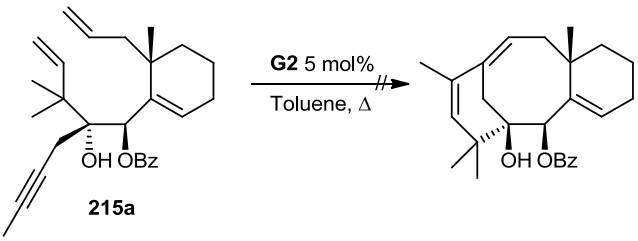
The two trienic compounds had already been used as metathesis precursors by Dr Cong Ma, so we investigated transforming these compounds into the benzoate esters before ring-closing metathesis to evaluate the influence of the diol protecting group on the outcome of the metathesis reaction. The two compounds were subjected to nine equivalents of phenyllithium once dissolved in tetrahydrofuran. After stirring for one and a half hours at -78 °C the reaction was quenched and following work up gave the desired benzoate (Scheme 3.29).



Scheme 3.29 – Transformation of carbonates to benzoate esters

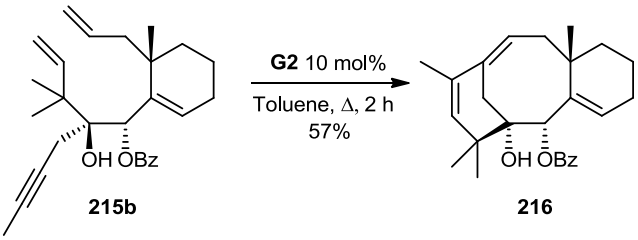
The benzoate esters were then subjected to ring-closing metathesis using Grubbs' second-generation catalyst.

The undesired isomer **215a** was dissolved in toluene and Grubbs' second-generation catalyst was added. After monitoring by TLC and stirring overnight, analysis of the crude product by ^{1}H NMR showed that it had degraded (Scheme 3.30).



Scheme 3.30 – Degradation of non taxol-like isomer

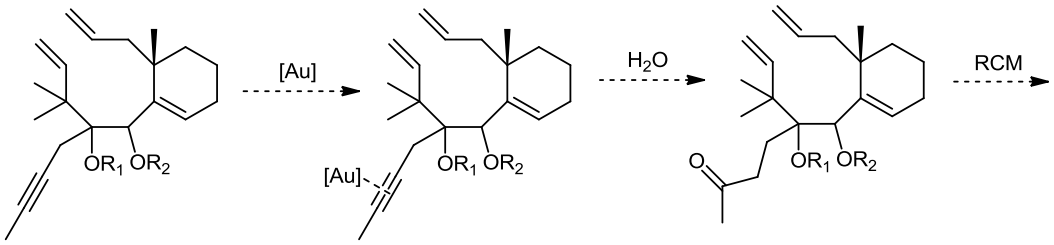
The taxol-like isomer **215b** was dissolved in toluene and Grubbs' second-generation catalyst was added and after monitoring the reaction for one hour, TLC showed complete conversion of the starting material. Purification of the crude product gave the isotaxane **216** containing the benzoate ester in a moderate yield (Scheme 3.31).



Scheme 3.31 – Formation of the isotaxane **216**

These results are consistent with the model studies carried out previously in the group. Despite ene-ene metathesis normally occurring more easily than ene-yne metathesis,[91] in this case it was disfavoured because of the steric hinderance of the olefin at C11 due to the neighbouring *gem*-dimethyl group.

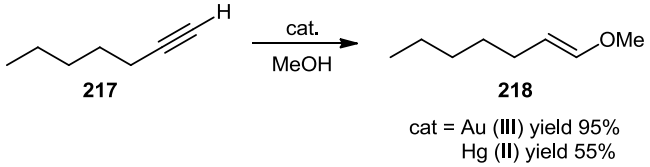
In order to avoid the ene-yne metathesis we planned to unmask the ketone using a gold hydration reaction (Scheme 3.32).



Scheme 3.32 – Planned route to avoid ene-yne metathesis

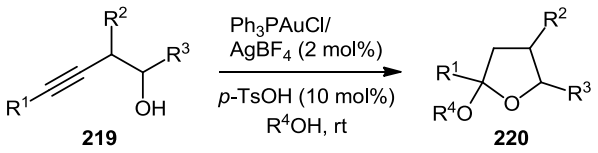
Carbonyls can be synthesised by the addition of water to alkynes. Hydration of alkynes has been known since 1881, when Kucherov[92] discovered that using mercury (II) salts under mild conditions could catalyse the hydration of alkynes. This reaction is however unsuitable for modern methods due to the toxicity of mercury-based compounds and alternative catalysts have since been discovered.[93]

In 1976, the catalytic hydration of alkynes using gold (III) catalysts was observed by Norman.[94] Reactions had previously been carried out in the presence of a mercury catalyst but using a gold (III) catalyst significantly improved the yields (Scheme 3.33).



Scheme 3.33 – Catalytic hydration of alkynes[94]

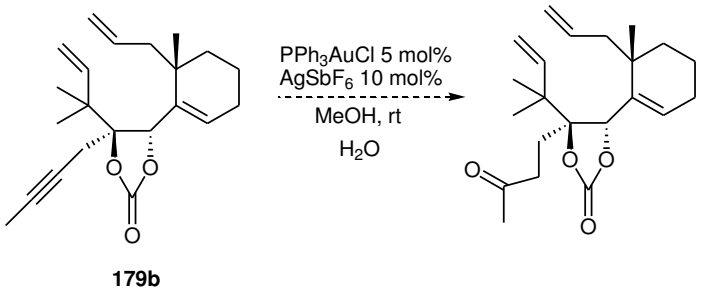
Gold (I) catalysts are not sensitive to water or air and were reported as being powerful catalysts that could be used to promote the hydration of alkynes.[95] Krause used a gold (I) catalyst to promote an intramolecular version of this reaction[96] (Scheme 3.34).



Scheme 3.34 – Intramolecular hydration of an alkyne by Krause

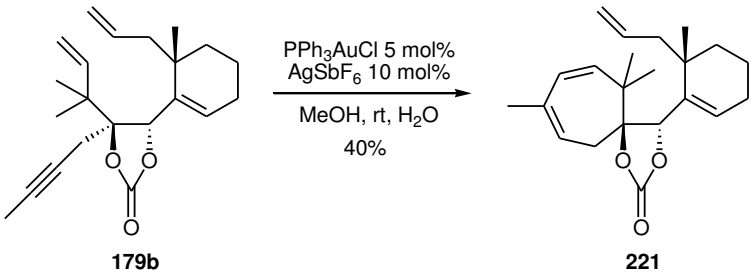
Our metathesis precursor has a similar structure to that used by Krause in relation to the position of the alkyne and the alcohol, which may result in the formation of the hemi acetal if the tertiary alcohol is unprotected.

However, we still possessed some carbonate **179b** and decided to subject this to the hydration conditions as a comparison. The alcohol that would attack the gold-coordinated alkyne is now protected and we thought that the alkyne would be transformed to give the ketone (Scheme 3.35).



Scheme 3.35 – Planned unmasking of the alkyne from the carbonate

The carbonate **179b** was dissolved in methanol and the gold (I) catalyst was added along with two drops of water. After work up and separation of the catalyst, starting material was recovered. The reaction had not worked as the gold (I) catalyst is not active enough on its own. The reaction was repeated with the addition of 10 mol% silver (I) hexafluoroantimonate to activate the catalyst by forming an active cationic gold species. After stirring at room temperature for thirty minutes the reaction was quenched. The resulting product was not what we had been expecting (Scheme 3.36).



Scheme 3.36 – Product formed after hydration of carbonate

The resulting structure of **221** was tentatively assigned using both ^{1}H and ^{13}C NMR techniques. When comparing the ^{1}H NMR spectrum of **221** with the starting material **179b**, peaks in the region 5.0 ppm to 6.2 ppm had significantly changed (Figure 3.02).

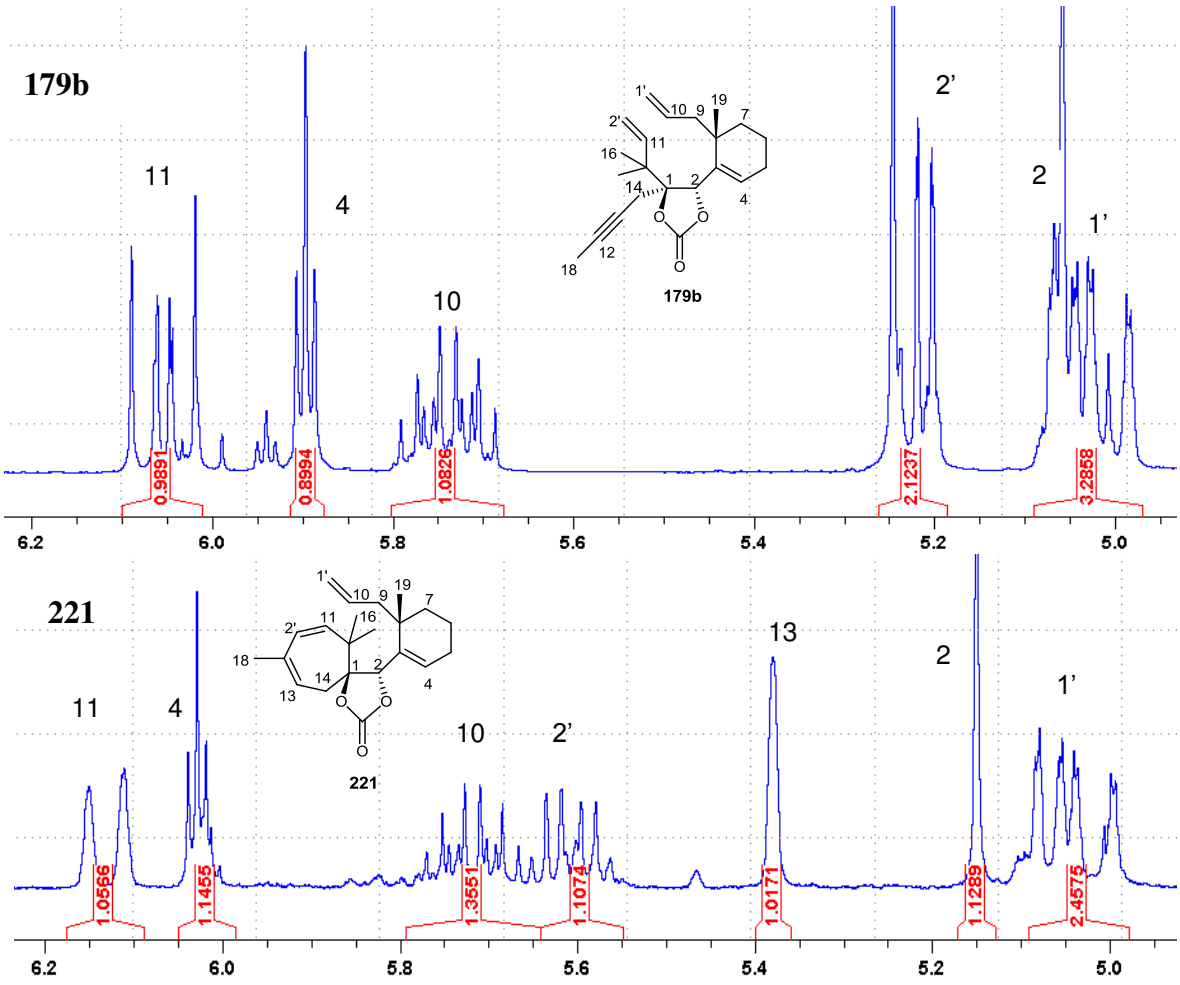


Figure 3.02 – Comparison of ^{1}H NMR spectra for compounds **179b** and **221**

H-10 and H-1' are almost unaffected, and H-2 and H-4 only have a slight difference in their chemical shifts. However, H-11 and H-2' are have completely different aspect and chemical shifts.

Another difference between the spectra of compounds **221** and **179b** was regarding the protons at C14. The ^{1}H NMR spectrum of **179b** shows the C14 protons coupled to the methyl group of either C16 or C17, resulting in two doublets of quartets. However; the peaks found in the ^{1}H NMR spectrum of **221** appear to be a doublet and a broad doublet (Figure 3.03).

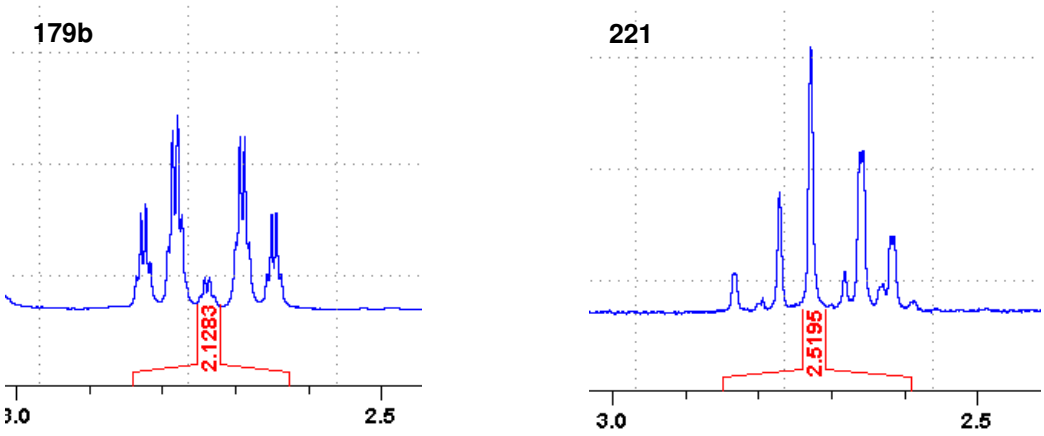
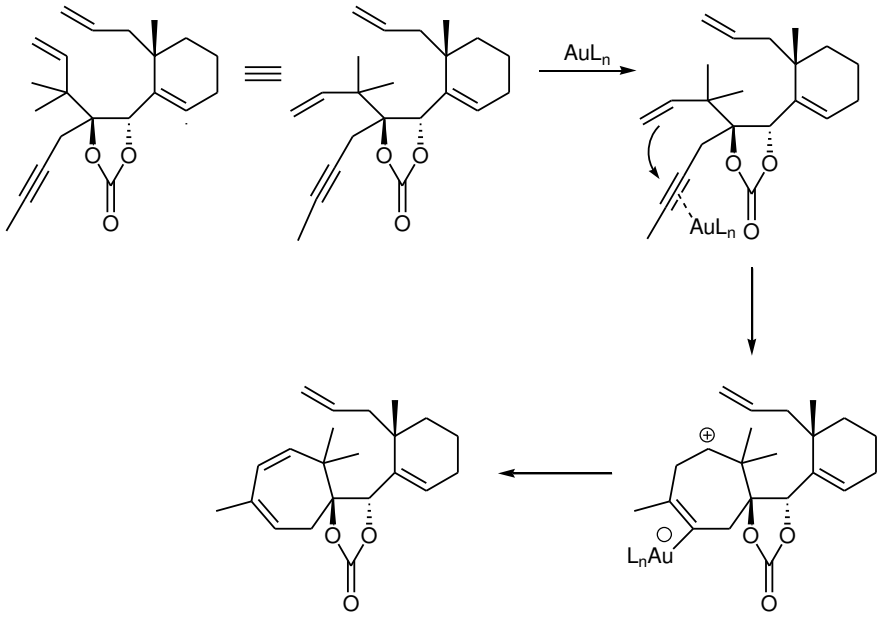


Figure 3.03 – C14 peaks from the ^{1}H NMR spectra of compounds **179b** and **221**

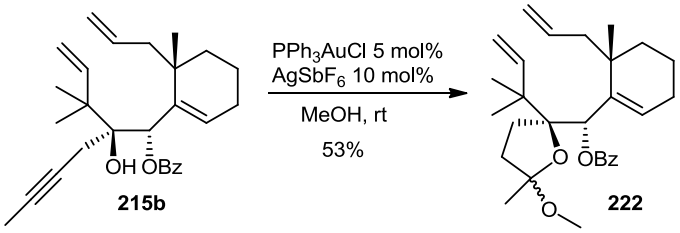
The COSY spectrum showed that the peaks found at 6.15 ppm, 5.60 ppm and 1.74 ppm all coupled together and had broad signals. We thought these peaks represented protons H-11, H-2' and H-18 respectively. The peak at 5.40 ppm was coupled with peaks found at 2.65 ppm and 1.74 ppm, which could respresent protons H-13, H-14 and H-18 respectively. The two protons found at 2.75 ppm and 2.65 ppm were also coupled together, respresenting the two protons at H-14. ^{13}C NMR (^{13}C, DEPT and HSQC) analysis confirmed the possible structure of **221** containing a seven-membered ring. Mass spectrometry showed that compounds **179b** and **221** have the same mass showing a rearrangement of atoms has taken place.

The mechanism for the formation of the seven-membered ring is simple compared to some other gold cyclisation pathways. The gold (I) catalyst coordinates to the alkyne, followed by the attack of the alkene. The seven-membered ring is formed and deprotonation/protodeauration leads to the product (Scheme 3.37).



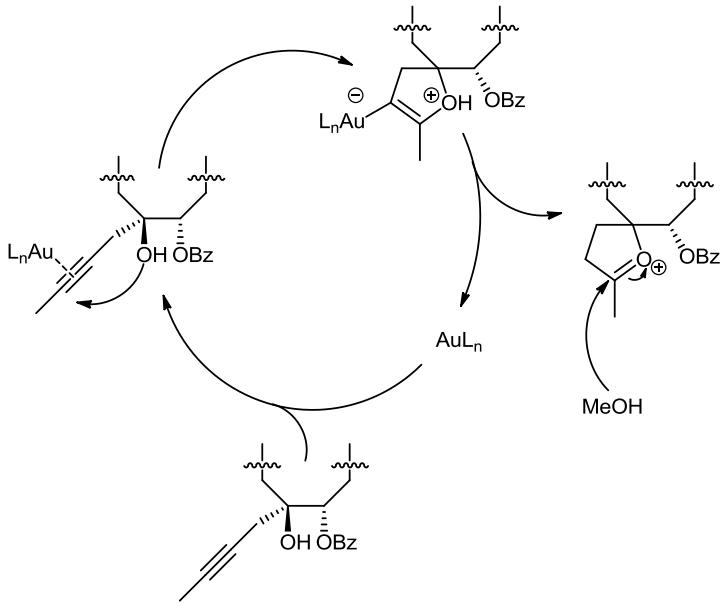
Scheme 3.37 – Formation of seven-membered ring

The taxol-like metathesis precursor **215b** was then dissolved in methanol and the gold (I) catalyst was added. The resulting product was a mixture of diastereomers of hemiacetal **222** (Scheme 3.38).



Scheme 3.38 - Formation of the hemiacetal

A mechanism suggested by Krause[96] can be used to explain the formation of the hemiacetal (Scheme 3.39). The gold catalyst coordinates to the alkyne; this is followed by nucleophilic attack of the oxygen to form the cyclic gold complex. Protodemetallation then occurs and releases the gold catalyst back into the cycle. Nucleophilic attack by the methanol and loss of a proton then affords the product.



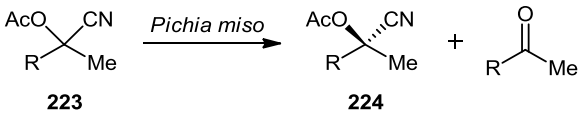
Scheme 3.39 – Formation of the hemiacetal as suggested by Krause

The two diasteromers **222** were then subjected to a ring-closing metathesis reaction to see if the BC bicycle could be closed avoiding ene-yne metathesis. Due to the small scale of the reaction, it was hard to tell if the BC bicycle had been formed. The ^{1}H NMR spectrum was also hard to analyse due to the presence of the two diasteromers. Due to time constraints we were not able to repeat this reaction on a larger scale.

3.3 Synthesis of enantiopure fragment A

We wanted to improve the yield of the Shapiro reaction and form only the taxol-like isomer. This would be obtained by synthesising an enantiopure version of fragment A.

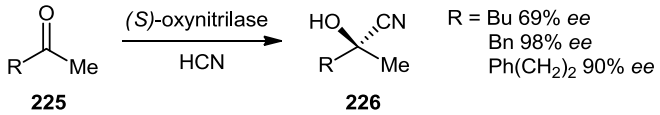
There are several methods reported in the literature for the enantioselective cyanation of ketones. The first was discovered by Sugai who carried out an enzymatic hydrolysis of a racemic α-acetoxy nitrile using the microorganism *Pichia miso* IAM 4682. The microorganism isolates the non-hydrolysed enantiomer in its enantioenriched form[97] (Scheme 3.40).



223 **224**

Scheme 3.40 – Sugai enzymatic enantioselective cyanation

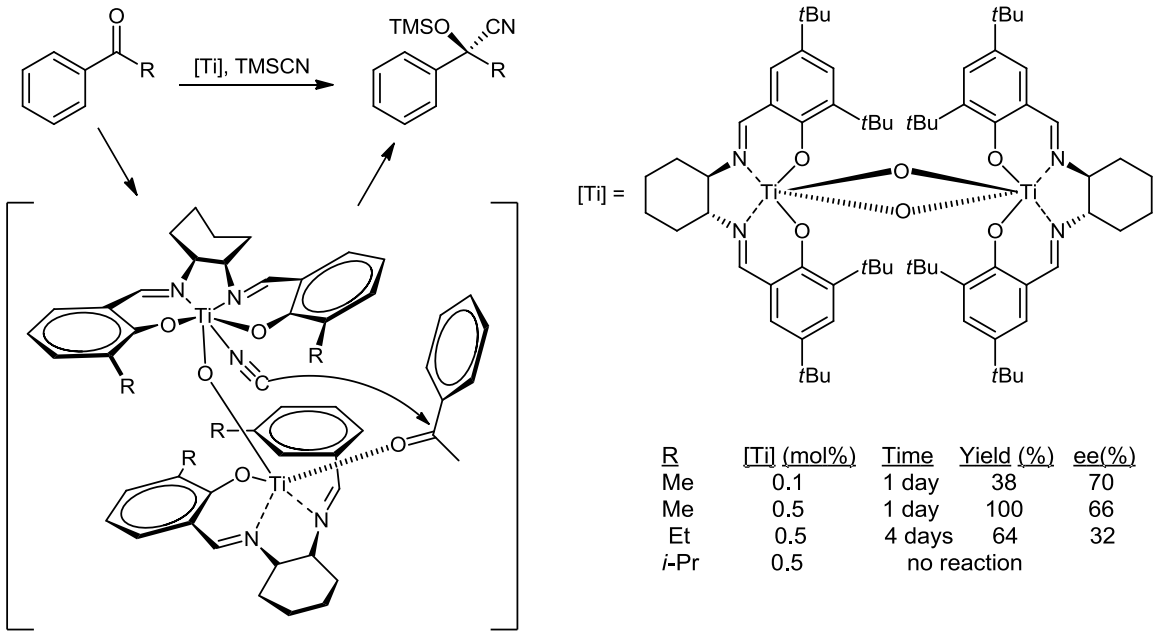
Similarly, Effenberger[98] and co-workers discovered that using (*R*)- and (*S*)-oxynitrilases, isolated from rubber trees, could also directly catalyse the enantioselective cyanation of aldehydes and ketones. This reaction was limited by its scale and its poor conversion rates (Scheme 3.41).



225 **226**

Scheme 3.41 – Effenberger enzymatic enantioselective cyanation

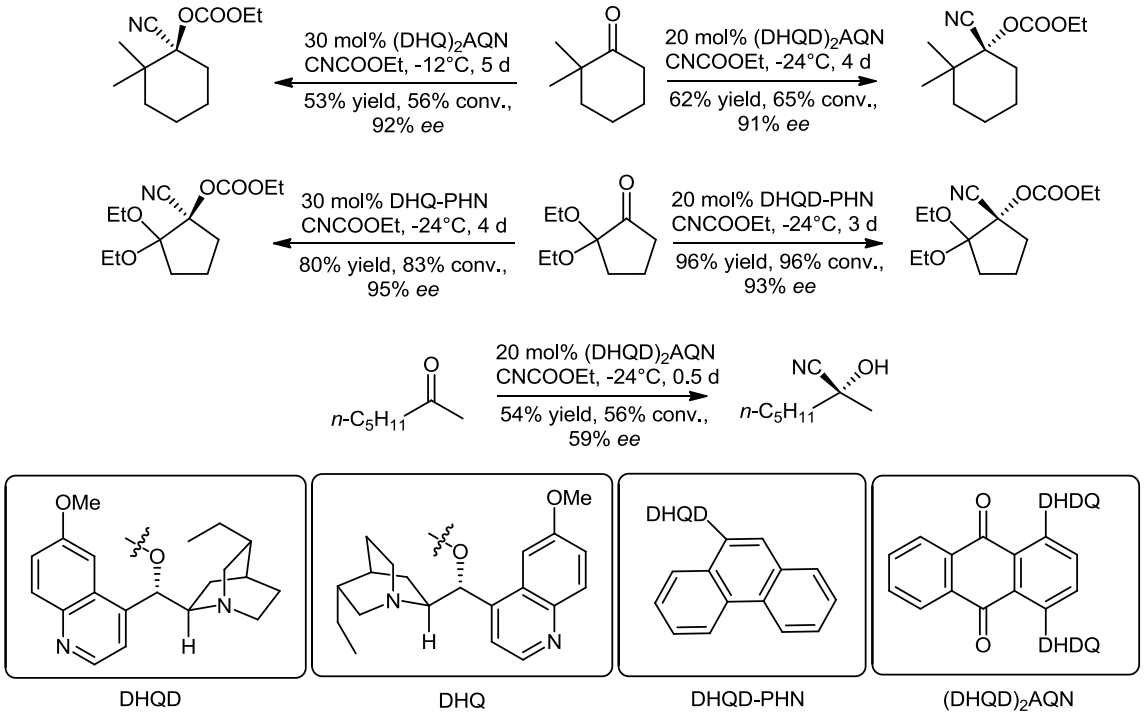
Methods using titanium catalysts have also been effective. One example involved a tetradentate ligand, salen, which was developed by Timofeeva.[99] In the presence of this catalyst, aromatic ketones could be transformed to siloxy cyanohydrins, with good enantiomeric excesses (Scheme 3.42).



R	[Ti] (mol%)	Time	Yield (%)	ee(%)
Me	0.1	1 day	38	70
Me	0.5	1 day	100	66
Et	0.5	4 days	64	32
i-Pr	0.5	no reaction		

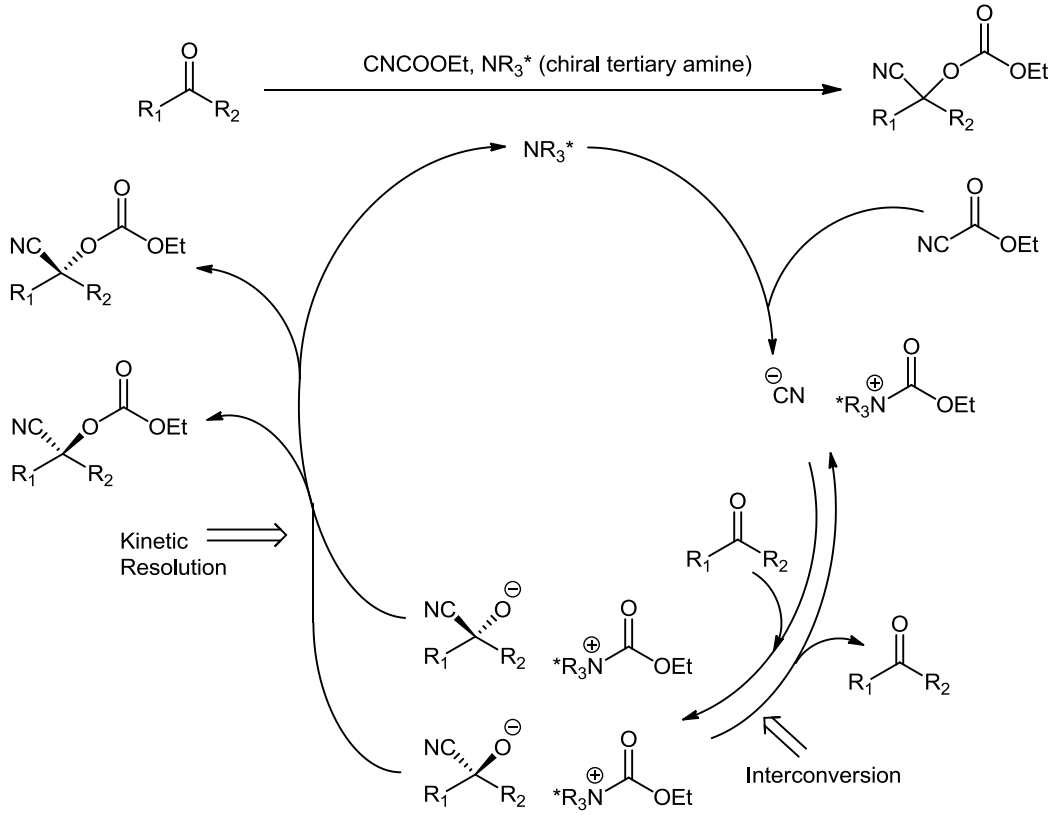
Scheme 3.42 – Enantioselective cyanation using titanium catalyst salen

Lewis bases have also been used to catalyse the cyanation reaction. Deng and co-workers[100] performed an enantioselective cyanation with tertiary chiral amines using a ligand developed by Sharpless.[101] Using either the DHQD or DHQ derived ligand, (*R*)- or (*S*)- cyanohydrins were produced in excellent enantiomeric excesses (Scheme 3.43). Cyanation of α-dialyoxy ketones could also be performed using trimethylsilyl cyanide instead of ethyl cyanoformate.[102]



Scheme 3.43 – Enantioselective cyanation using chiral amines

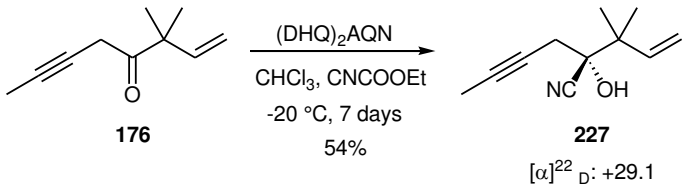
Deng[103] proposed a mechanism for the reaction involving kinetic resolution to explain the enantioselectivity of the different substrates (Scheme 3.44). The kinetic resolution step is the final formation of the carbonates. If the rate of interconversion is slower than that of the kinetic resolution step, the enantiomeric excess decreases. α-Dialkoxy ketones are attacked more easily due to the effects of the electron-withdrawing group, which therefore increases the rate of interconversion. High enantiomeric excesses are obtained when using α-dialkoxy ketones in cyanation reactions.



Scheme 3.44 – Proposed mechanism of the enantioselective cyanation by chiral amines

We decided to use Deng's method for the cyanation of our highly sterically hindered ketone as it seemed efficient and the catalyst could be purchased directly from a chemical supplier.

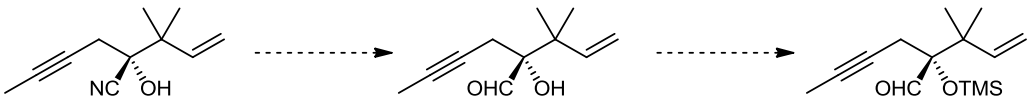
Ketone **176** was subjected to a reaction with 20 mol% of $(DHQ)_2AQN$ and ethyl cyanoformate. After seven days standing in the freezer at -20 °C, the desired non racemic cyanohydrin was obtained in a 30% yield. A second reaction was carried out, this time adding 30 mol% of the catalyst, and after work up gave the desired cyanhydrin in a 54% yield (Scheme 3.45).



Scheme 3.45 – Enantioselective cyanation of ketone **176**

The specific rotation was calculated as +29.1 (*c* 1.2, CH_2Cl_2) for compound **227**. This reaction had been carried out previously in the group on **176** but using the ligand $(DHQD)_2AQN$, producing the undesired enantiomer. The specific rotation for the enantiomer was -74.1 (*c* 1.7, CH_2Cl_2) and the *ee* was determined to be 99% by chiral HPLC. This result proves that we have synthesised the desired enantiomer of **227**, however the lower specific rotation could mean either that the compound is not enantiopure or that there are traces of the chiral catalyst present. Chiral HPLC will need to be carried out on compound **227** to determine its enantiopurity.

If time had allowed the enantiopure cyanohydrin would have been subjected to a reduction using diisobutylaluminium hydride, followed by the alcohol being protected with a trimethylsilyl ether to avoid polymerisation that could occur as seen in the previous work.[71a] This enantiopure fragment A would have then been used in a Shapiro reaction to give only the taxol-like isomer (Scheme 3.46).

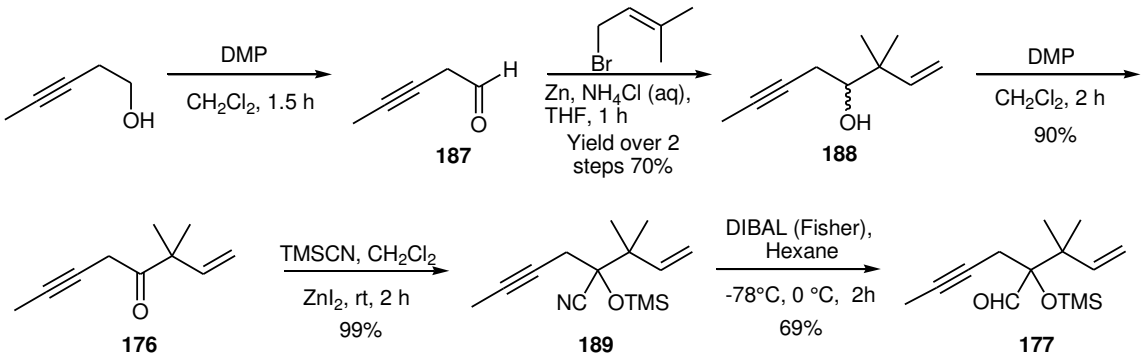


Scheme 3.46 – Future work on enantiopure fragment A

4.1 Conclusions and future work

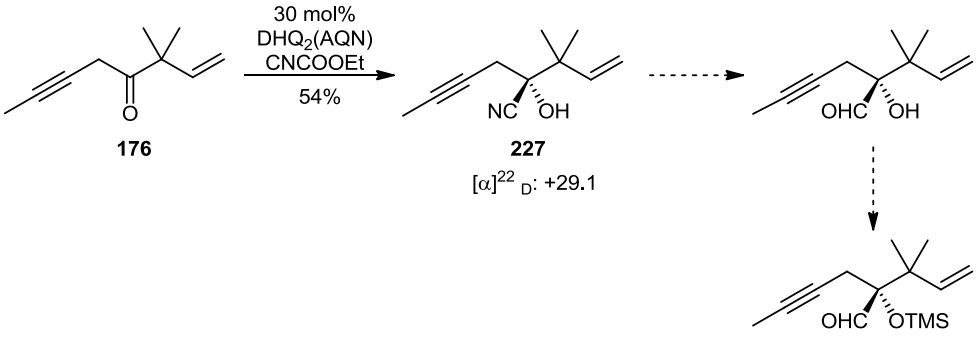
4.1.1 Conclusions

Fragment A has been synthesised and the reproducibility and conditions of the nitrile reduction have been studied in detail (Scheme 4.01).



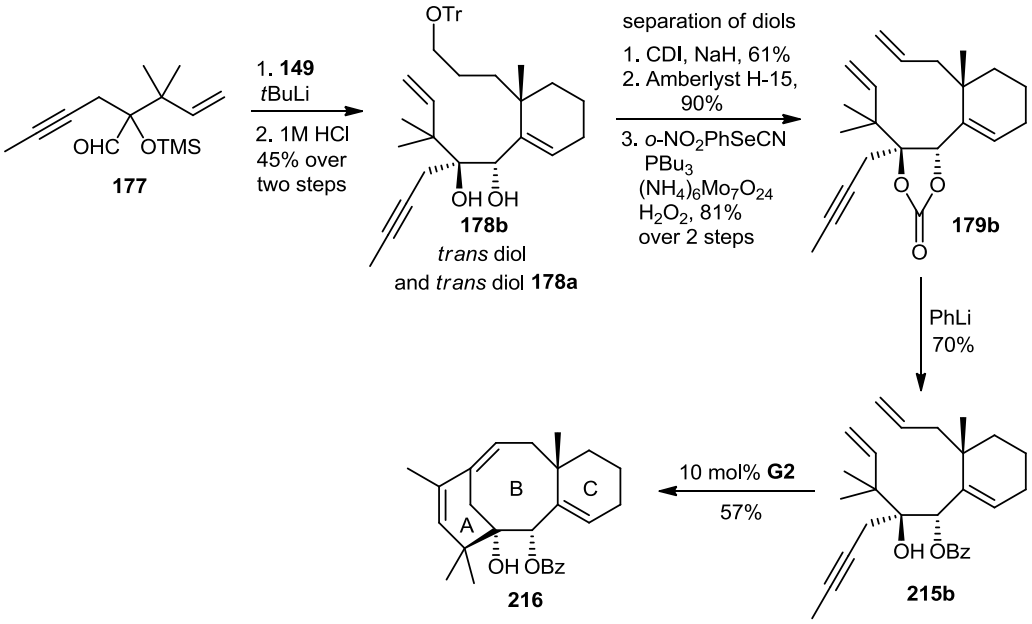
Scheme 4.01 – Synthesis of fragment A

The start of a synthesis of enantiopure fragment A has been carried out and the end synthesis planned (Scheme 4.02).



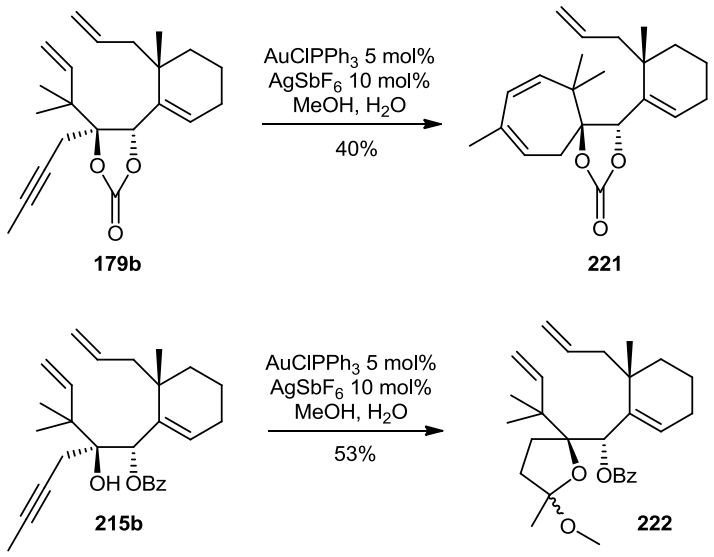
Scheme 4.02 – Beginning of enantiopure synthesis of fragment A

Optimisation of the Shapiro reaction has been carried out despite being time consuming only led to moderate yield of the desired products. An isotaxane has been synthesised with the benzoate ester precursor (Scheme 4.03). Isotaxanes are precursor to analogues of taxol not available by semi synthesis, which might exhibit interesting biological activities.



Scheme 4.03 – Synthesis of an isotaxane

The ketone at C12 was unmasked using a gold hydration reaction attempts using the carbonate precursor led to the formation of a seven memebered ring, whilst the benzoate precursor formed the hemiketal, (Scheme 4.04).

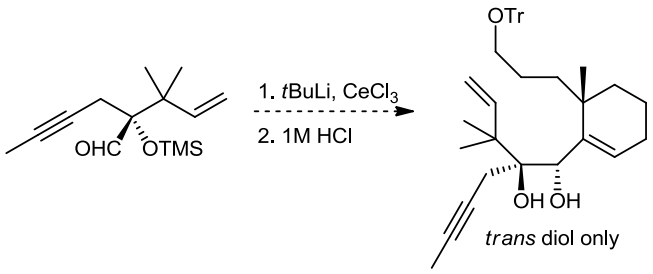


Scheme 4.04 – Hydration reactions and products

4.1.2 Future work

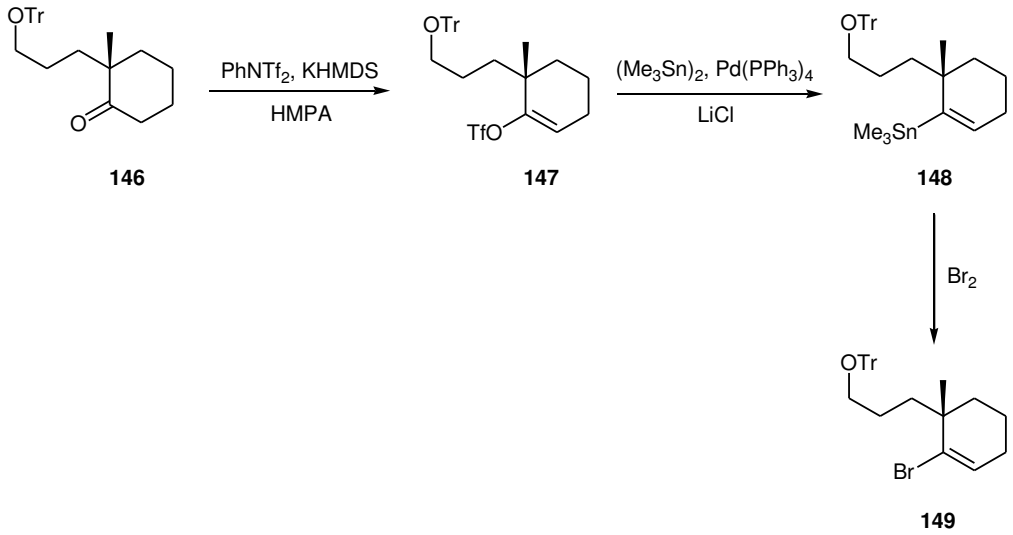
The Shapiro coupling has caused a number of problems, with time and resources wasted. To move forward either the two reactants must be modified or a new coupling procedure must be attempted. Depsite following a published procedure, the results cannot be repeated and this has affected our planned synthesis.

If the enantiopure fragment A is synthesised successfully, this would be coupled with the hydrazone using the Shapiro reaction, however with previous problems this reaction had caused, a new route could be planned.



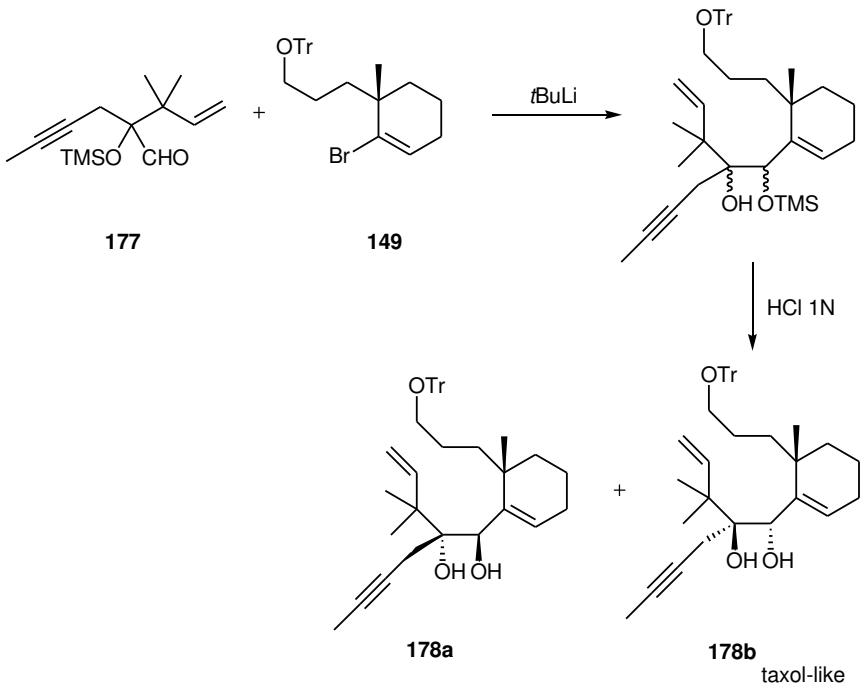
Scheme 4.05 – Enantiopure fragment A completion and coupling

Following work performed by Schiltz in the group,[69] the C ring ketone **146** could be transformed into the vinyl bromide so that a tin-bromide exchange could take place (Scheme 4.06).



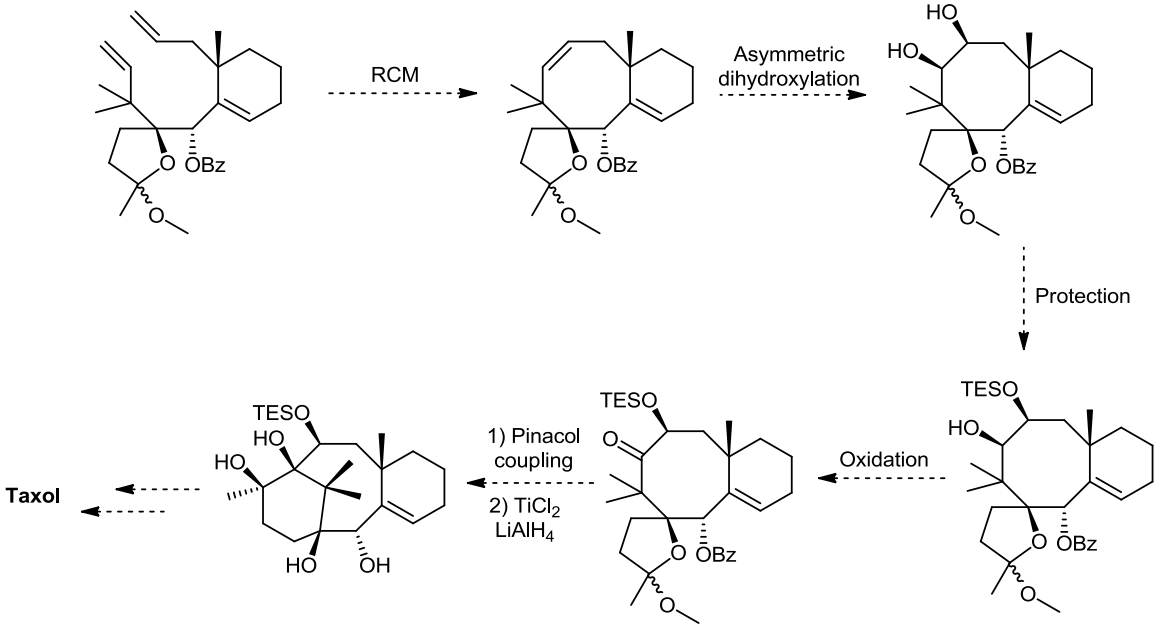
Scheme 4.06 – Transformation of the **146** to the vinyl bromide **149**

The vinyl bromide would then undergo a halogen-lithium exchange, followed by a coupling reaction with fragment A **177**, as previously carried out by Schiltz with aldehyde **144**. The sterics of the alkyne group might affect the reaction, but it would be worth attempting to see if an improved yield could be obtained (Scheme 4.07).



Scheme 4.07 – Coupling of the vinyl bromide **149** and aldehyde **177**

RCM reactions need to be carried out on the hemiketal benzoate ester; this could then be followed by a Sharpless asymmetric dihydroxylation and selective protection of one alcohol. Oxidation of the remaining alcohol to the ketone which would then be used to perform a pinacol coupling, however the hemiketal will need to be opened for this be to achieved.



Scheme 4.06 – Work towards taxol

Chapter IV

Experimental Details

General Experimental

NMR

NMR spectra were recorded on a Bruker 400 MHz Spectrospin spectrometer (^{1}H NMR at 400 MHz and ^{13}C NMR at 400 MHz or 500 MHz). Chemical shifts are reported in ppm. ^{1}H NMR spectra were recorded with $CDCl_3$ as solvent using (δ = 7.26) as internal standard, and for ^{13}C NMR spectra, the chemical shifts are reported relative to the central resonance of $CDCl_3$ (δ = 77.16). Signals in NMR spectra are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), sextet (sext), septet (sept), multiplet (m), broad (b) or combination of these, which refers to the spin-spin coupling pattern observed. DEPT 135, DEPT 90 and two-dimensional (COSY, HSQC) NMR spectroscopy were used where appropriate to assist the assignment of signals in the ^{1}H and ^{13}C NMR spectra. Taxol numbering used for NMR assignment.

IR and Mass Spectrometry

Infrared spectra were obtained neat using a SHIMADZU spectrometer. High resolution mass spectra were recorded under EI, FAB, CI and ES conditions by the analytical services at the University of Glasgow. Elemental analyses were carried out on an Exeter Analytical Elemental Analyser EA 440.

Chromatography

Column chromatography was performed under pressure using Fisher matrix silica 60. Macherey-Nagel aluminium-backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised using UV light or by staining with potassium permanganate (3 g of potassium permanganate, 20 g potassium carbonate, 5 mL 5% aqueous sodium hydroxide and 300 mL water) or a acidic ethanolic anisaldehyde solution (formed by dissolving 15 g of anisaldehyde in 250 mL ethanol and 2.5 mL conc. sulfuric acid).

Solvents and Reagents

Liquid reagents were distilled prior to use if needed. All reagents were purchased from commercial suppliers and used without further purification unless otherwise stated.

General Reaction Conditions

Reactions involving air-sensitive agents and dry solvents were performed in glassware dried in an oven 120 °C or flame dried prior to use. These reactions were carried out with the exclusion of air using an argon atmosphere. Brine refers to a saturated solution of sodium chloride in distilled water.

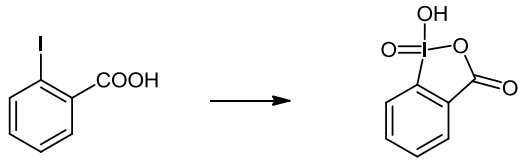
Nomenclature

IUPAC nomenclature was used for all compounds (determined by reaxys).

NMR spectra descriptions are numbered using a chain extension or numbering used for Taxol.

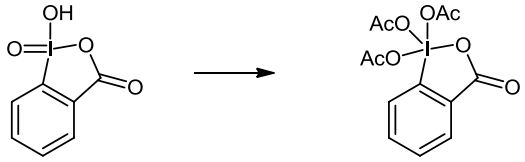
Known compounds have already been fully characterised.[71a]

Preparation of 2-Iodoxybenzoic acid (IBX).[104]



2-Iodobenzoic acid (30.0 g, 121 mmol) was added to a solution of oxone (144.8 g, 235.5 mmol, 2.0 equiv) in deionised water (500 mL) in a 1 L flask. The reaction mixture was warmed to 73 °C over 20 min and was stirred for 3 h. The suspension was then cooled between 0-5 °C and stirred for 1.5 h. The white powder was filtered through a sintered glass funnel and washed with deionised water (4x100 mL) and acetone (2x100 mL) before being left to dry at room temperature for 16 h (no inert atmosphere necessary). The product was obtained as a white solid (29.6 g, 88%).

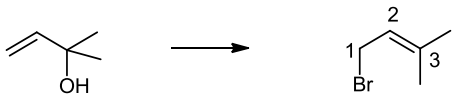
Preparation of Dess-Martin Periodinane (DMP).[105]



2-Iodoxybenzoic acid (29.5 g, 105 mmol) was added to a solution of *p*-toluenesulfonic acid (0.16 g) in acetic anhydride (120 mL). This was stirred at 80 °C for 2 h before the mixture was cooled in an ice/water bath. The cold mixture was filtered through a sintered glass funnel and rinsed with anhydrous ether (250 mL). The resulting white solid was transferred to an argon flushed round bottom flask and stored in the freezer. The product was obtained as a white solid (38.4 g, 86% yield).

Problems with the DMP reagent can occur if it is not washed with enough ether. If IBX residues are present the reagent does not work as well.

Preparation of 1-Bromo-3-methyl-2-butene.[106]



First attempt

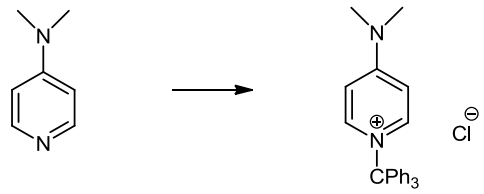
2-Methyl-3-buten-2-ol (20.0 g, 232 mmol) was cooled to 0 °C in a round bottom flask. Hydrobromic acid (93 mL, 48% aq.) was slowly introduced into the reaction flask and the resulting mixture was stirred at 0 °C for 30 min. The two layers were separated and the aqueous layer was extracted with dichloromethane. The organic layers were combined and washed with water, brine, dried over anhydrous magnesium sulfate before being filtered and concentrated *in vacuo* (no heat in the water bath which was filled with ice water). Distillation of the crude product, as suggested in the method, caused the product to turn brown, showing signs of degradation. This was seen in an uninterpretable ^{1}H NMR spectrum.

Second attempt

2-Methyl-3-buten-2-ol (20.0 g, 232 mmol) was cooled to 0 °C in a round bottom flask. Hydrobromic acid (93 mL, 48% aq.) was added dropwise to the flask and the resulting mixture was stirred at 0 °C for 30 min. The two layers were separated and the aqueous layer was extracted with dichloromethane. The organic layers were combined and washed with water, brine, dried over anhydrous magnesium sulfate before being filtered and concentrated *in vacuo* (no heat in the water bath which was filled with ice water). The crude product was obtained as a colourless oil (27.6 g, 79%).

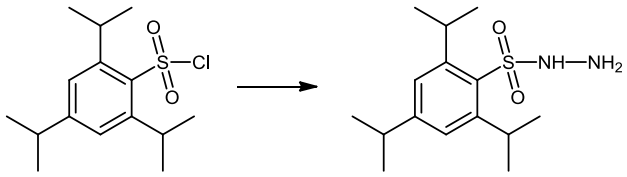
^{1}H NMR (δ_H): 5.53 (tsept, 1H, J = 8.5 Hz, 1.4 Hz, H-2), 4.02 (d, 2H, J = 8.5 Hz, H-1), 1.78 (s, 3H, Me-3), 1.73 (s, 3H, Me-3).

Preparation of 4-dimethylamino-*N*-triphenylmethyl pyridinium chloride.[107]



Freshly recrystallised trityl chloride (3.00 g, 11.0 mmol, 1.10 equiv – from toluene) and 4-dimethylaminopyridine (1.22 g, 10.0 mmol) in dichloromethane (30 mL) were stirred for 30 min at room temperature. Addition of diethyl ether (100 mL) precipitated the product which was filtered and washed with more diethyl ether. The white solid was dried under vacuum for 2 h. The product was obtained as a dry white solid (3.90 g, 98%).

Preparation of 2,4,6-Triisopropylbenzenesulfonohydrazine (186).[77]



185 **186**

First attempt

Two equivalents of hydrazine hydrate were added dropwise to a solution of sulfonyl chloride in tetrahydrofuran at -10 °C. This was warmed to 0 °C and stirred for three hours. The crude mixture was kept cold whilst the work up was carried out using ice-cold brine and removing the solvent *in vacuo* at 15 °C. The white solid that was meant to form was yellow. On analysis by ^{1}H NMR, the yellow solid proved to be mostly starting material.

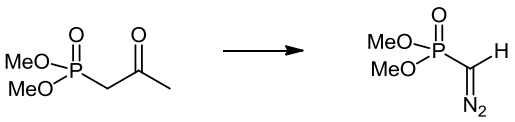
Second attempt

2,4,6-Triisopropylbenzenesulphonochloride **185** (10.7 g, 35.0 mmol) in tetrahydrofuran (40 mL) was cooled to -10 °C and hydrazine hydrate (5.0 mL, 180 mmol, 5.0 equiv) was added dropwise over 30 min. The reaction was then warmed to 0 °C and stirred at this temperature for 3 h. Water was added to dissolve any precipitated solids in the flask. The mixture was transferred to a separating funnel and the aqueous layer was discarded. The

organic layer was washed with ice cold brine and was then dried over sodium sulfate at 0 °C for 1.5 h (placed in the fridge). Sodium sulfate was filtered off and the solution was concentrated *in vacuo* (water bath at less than 15 °C – ice added to bath). The white solid was washed several times with petroleum ether before being titurated with ice cold water and dried under vacuum for 2 h. The product was obtained as a dry white solid (9.10 g, 87%) which was stored in the freezer at -20 °C.

^{1}H NMR: 7.19 (s, 2H, Ar), 5.44 (br s, 1H, NH), 4.12 (sept, 2H, J = 6.9 Hz, CH (*o*)), 3.26 (br s, 2H, NH_2) 2.88 (sept, 1H, J = 6.9 Hz, CH (*p*)), 1.25 (d, 12H, J = 6.9 Hz, $(CH_3)_2$ (*o*)), 1.24 (d, 6H, J = 6.9 Hz, $(CH_3)_2$ (*p*)).

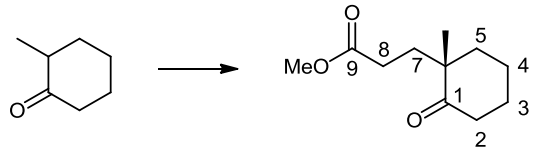
Preparation of Dimethyl (diazomethyl)phosphonate (DAMP).[82]



A mixture of sodium azide (1.68 g, 25.8 mmol, 1.20 equiv), acetonitrile (30 mL) and mesyl chloride (1.83 mL, 1.10 equiv) was stirred overnight at room temperature. The mixture was cooled in an ice bath and dimethyl 2-oxopropylphosphonate (2.50 g, 21.5 mmol) was added. After 10 min, cesium carbonate (7.10 g, 1.00 equiv) was added and the mixture was stirred in the ice bath for 1 h. The ice bath was then removed and the reaction mixture was stirred at room temperature for 2 h before being cooled to 0 °C. Methanol (10 mL) was added within 5 min and the reaction was stirred for 4.5 h at 0 °C. The ice bath was then removed and the mixture was diluted with toluene, stirred for a further 5 min and then filtered through celite. The filter cake was washed with toluene several times. The crude product was diluted further with toluene and concentrated *in vacuo* until the mixture had reduced by half. The oily layer was separated from the top straw coloured layer by decanting it off carefully. The oily layer was then washed with several portions of toluene and added to the decanted layer. The solvent was then removed *in vacuo* and the product was then co evaporated with hexane and toluene to give a straw-coloured oil (2.94 g, 91%).

^{1}H NMR: (δ_H): 3.76 (d, 1H, J = 11.0 Hz), 3.77 (d, 6H, J = 11.7 Hz).

Methyl 3-[(1*S*)-1-Methyl-2-oxocyclohexyl]propanoate (183).



2-methylcyclohexanone **183**

2-Methylcyclohexanone (10 mL, 82.3 mmol), (*R)*-(+)-α-methylbenylamine (10 mL, 84.5 mmol, 1.10 equiv) and *p*-TsOH (30.0 mg, 0.2 mol%) were dissolved in toluene (50 mL). The mixture was heated to reflux with a Dean-Stark apparatus attached. After 3 h, once cool, the solvent was removed *in vacuo*, and methyl acrylate (8.0 mL, 85 mmol, 1.1 equiv) was added. The resulting mixture was stirred at room temperature for ten days. The reaction was quenched with 10% aqueous acetic acid (30 mL) and the aqueous and organic layers were separated. The aqueous layer was extracted with diethyl ether and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (ethyl acetate/petroleum ether: 1/9) which gave **183** as a pale yellow oil (9.98 g, 70%).

$[\alpha]^{22}_{D}$: -9.25 (*c* 1.2, CH_2Cl_2).

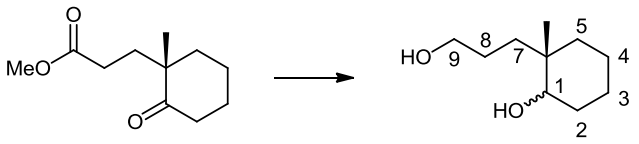
^{1}H NMR (δ_H): 3.66 (s, 3H, OMe), 2.42-2.36 (m, 2H, H-8), 2.15 (ddd, 1H, *J* = 16.3, 11.2, 5.3 Hz, H-2), 2.04 (ddd, 1H, *J* = 16.2, 11.1, 5.2 Hz, H-2), 1.75 (m, 8H, H-3, H-4, H-5 and H-7), 1.06 (s, 3H, Me-6).

^{13}C NMR (δ_C): 214.3 (C-1), 173.1 (C-9), 50.7 (OMe), 47.0 (C-6), 38.3, 37.8, 31.6, 28.0, 26.5 (CH_2), 21.4 (Me-6), 20.0 (CH_2).

MS: 199 $(M+H)^+$, 168.

IR (film): 2939, 2862, 1728, 1705, 1435, 1373, 1303, 1257, 1172, 1126 cm^{-1}.

(2*S*)-2-(3-Hydroxypropyl)-2-methylcyclohexan-1-ol (145).



183 **145**

A solution of keto ester **183** (8.63 g, 43.4 mmol) in tetrahydrofuran (60 mL) was added dropwise to a suspension of lithium aluminium hydride (4.12 g, 108 mmol, 2.50 equiv) in tetrahydrofuran (100 mL) at 0 °C. The resulting mixture was allowed to warm to room temperature and stir overnight. After cooling to 0 °C, saturated aqueous ammonium chloride was added dropwise until the fizzing stopped and the aluminium salts had crashed out giving a white solid. The white salts were filtered off over a pad of celite and washed thoroughly with diethyl ether. The aqueous and organic layers were separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to give **145** as a 1:1 mixture of diastereomers as a colourless oil (6.41 g, 86%).

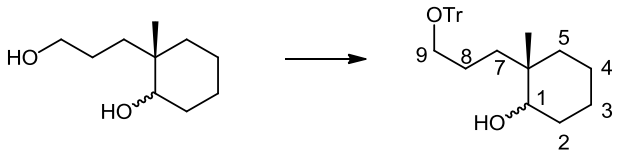
^{1}H NMR (δ_H): 3.62 (m, 2H, H-9), 3.44-3.33 (m, 1H, H-1), 1.97-1.76 (m, 2H, OH), 1.72-1.22 (m, 11H, H-2, H-3, H-4, H-5, H-7, H-8), 1.08-0.98 (m, 1H, CH_2) 0.98 (s, 1.7H, Me-6), 0.86 (s, 1.3H, Me-6).

^{13}C NMR (δ_C): 76.7 (C-1), 75.2 (C-1), 63.0 (C-9), 63.0 (C-9), 36.2 (CH_2), 35.8 (CH_2), 34.2 (CH_2), 33.4 (CH_2), 29.7 (CH_2), 28.8 (CH_2), 25.5 (CH_2), 25.3 (CH_2), 23.5 (CH_2), 22.8 (Me-6), 22.1 (CH_2), 20.4 (CH_2), 20.3 (CH_2), 16.3 (Me-6).

MS: 199 $(M+H)^+$, 168.

IR (film): 3271, 2931, 2862, 1450, 1373, 1342, 1118, 1057 cm^{-1}**.**

(2*S*)-2-Methyl-2-[3-(triphenylmethoxy)propyl]cyclohexan-1-ol (184).



145 **184**

To a solution of **145** (5.20 g, 30.1 mmol) in dichloromethane (90 mL) was added 4-dimethylamino-*N*-triphenylmethyl pyridinium chloride (13.6 g, 33.9 mmol, 1.10 equiv). The resulting mixture was refluxed overnight. Once cool, diethyl ether (300 mL) was added and the resulting white salts were filtered off. The solution was dried over anhydrous magnesium sulfate, filtered and dried *in vacuo*. The crude oil was purified by flash column chromatography (diethyl ether/petroleum ether: 3/7) to give a white sticky oil **184** as a 1:1 mixture of diastereomers (11.5 g, 92%).

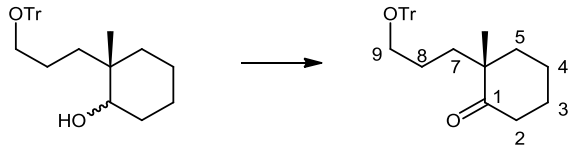
^{1}H NMR (δ_{H}): 7.51-7.47 (m, 6H, H-Ar), 7.33-7.27 (m, 6H, H-Ar), 7.29-7.22 (m, 3H, H-Ar), 3.44-3.34 (m, 1H, H-1), 3.14-3.03 (m, 2H, H-9), 1.75-1.15 (m, 12H, CH_2), 0.96 (s, 1.5H, Me-6), 0.89 (s, 1.5H, Me-6) .

^{13}C NMR (δ_{C}): 144.5 (C-Ar), 127.8 (C-Ar), 126.8 (C-Ar), 126.0 (C-Ar), 85.5 (CPh_3), 63.1(C-1), 64.8 (C-9), 36.9 (C-6), 34.9 (CH_2), 34.1 (CH_2), 30.4 (CH_2), 29.6 (CH_2), 24.0 ($CH_{2)}$, 21.2 (Me-6), 17.1 (CH_2).

MS: 243 ($^{+}CPh_3$).

IR (film): 3063, 2931, 1705, 1489, 1450, 1219, 1157, 1080, 1033, 1003 cm^{-1}.

(2*S*)-2-Methyl-2-[3-(triphenylmethoxy)propyl]cyclohexan-1-one (146).



184 **146**

A solution of 2-iodoxybenzoic acid (9.33 g, 33.3 mmol, 1.20 equiv) in dimethyl sulfoxide (90 mL) was added to a solution of the crude mixture of diastereomers **184** (11.5 g, 27.7 mmol) in tetrahydrofuran (90 mL). The resulting mixture was stirred at room temperature overnight. Water was added and the organic phase was diluted with diethyl ether. The resulting white salts were filtered off and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified via flash column chromatography (diethyl ether/petroleum ether: 1/9) to afford **146** as a white solid (10.0 g, 88% yield).

M.p: 116-118 °C.

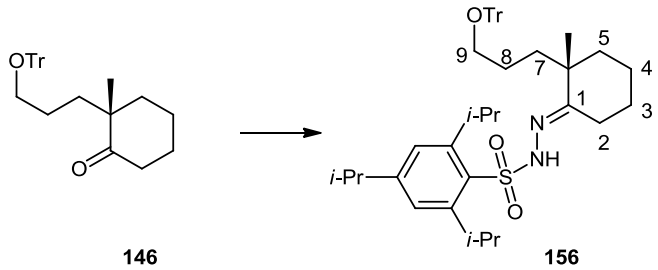
^{1}H NMR (δ_{H}): 7.44-7.40 (m, 6H, H-Ar), 7.31-7.27 (m, 6H, H-Ar), 7.24-7.20 (m, 3H, H-Ar), 3.08-3.00 (m, 2H, H-9), 2.44-2.28 (m, 2H, H-2), 1.94-1.84 (m, 1H, CH_2), 1.79-1.70 (m, 4H, CH_2), 1.69-1.54 (m, 3H, CH_2), 1.46-1.31 (m, 2H, CH_2), 1.04 (s, 3H, Me-6).

^{13}C NMR (δ_{C}): 215.1 (C-1), 143.5 (C-Ar), 127.8 (C-Ar), 126.8 (C-Ar), 126.0 (C-Ar), 85.5 (CPh_3), 63.1 (C-9), 47.5 (C-8), 38.4 (C-6), 37.8 (C-2), 33.1 (CH_2), 26.6 (CH_2), 23.6 (CH_2), 21.6 (Me-6), 20.2 (CH_2).

MS: 243 ($^{+}CPh_3$).

IR (film): 3063, 2931, 1705, 1489, 1450, 1219, 1157, 1080, 1033, 1003, 748, 694 cm^{-1}**.**

N'-[(1*E*,2*S*)-2-Methyl-2-[3-(triphenylmethoxy)propyl]cyclohexylidene]-2,4,6-*tris*(propan-2-yl)benzene-1-sulfonohydrazide (156).



146 **156**

First attempt

The hydrazine was then reacted with ketone **146** and concentrated hydrochloric acid in order to form the hydrazone. The experimental conditions used previously[71a] were applied to the reaction: one equivalent of the ketone and hydrazine were dissolved in five mL tetrahydrofuran. Two drops of concentrated hydrochloric acid were then added to the reaction and it was left to stir at room temperature for one hour. After work up and purification, the yield was 30%.

Second attempt

To a solution of ketone **146** (1.00 g, 2.42 mmol) in tetrahydrofuran (10 mL) was added triisopropylbenzenesulfonohydrazine **186** (0.90 g, 2.7 mmol, 1.1 equiv). The solution was stirred until both solids had dissolved. Concentrated hydrochloric acid (4 drops) were added to the solution, which was then stirred for 2 h at room temperature. The reaction was quenched with saturated aqueous sodium hydrogencarbonate. The two phases were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (diethyl ether/petroleum ether: 20/80) and gave **156** as a white solid (1.45 g, 87%).

M.p: 74-77 °C.

^{1}H NMR (δ_H): 7.40-7.36 (m, 7H, N-H, H-Ar), 7.30-7.26 (m, 9H, H-Ar), 7.10 (s, 2H, H-Ar'), 4.19 (septet, 2H, *J* = 6.7 Hz, ArC**H**$(CH_3)_2$), 2.91 (dt, 2H, *J* = 6.2, 1.2 Hz, H-9), 2.81

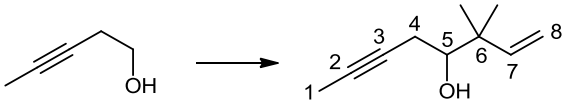
(septet, 1H, *J* = 6.9 Hz, ArC**H**$(CH_3)_2$), 2.34 (dt, 1H, *J* = 14.6, 4.6 Hz, H-2), 1.97-1.89 (m, 1H, H-2), 1.76-1.69 (m, 2H, CH_2), 1.65-1.53 (m, 4H, CH_2), 1.48-1.36 (m, 3H, CH_2), 1.22 (2d, 12H, *J* = 6.7 Hz, ArCH(C**H**$_3)_2$), 1.18 (2d, 6H, *J* = 6.9 Hz, ArCH(C**H**$_3)_2$), 1.08-1.02 (m, 1H, CH_2), 0.88 (s, 3H, Me-6).

^{13}C NMR (δ_C): 162.5 (C-1), 152.1 (C-Ar'), 150.3 (C-Ar'), 143.6 (C-Ar), 130.7 (C-Ar'), 127.9 (C-Ar), 126.8 (C-Ar), 126.0 (C-Ar), 122.5 (C-Ar'), 85.6 (CPh_3), 63.1 (C-9), 41.0 (C-6), 38.4 (CH_2), 33.7, 33.2 (Ar**C**H$(CH_3)_2$), 29.9, 29.0, 24.9, 23.9, 23.9, 23.4 (ArCH(**C**$H_3)_2$), 23.3 (CH_2), 22.6 (CH_2), 22.0 (CH_2), 20.0 (CH_3).

MS: 691 $(M-H)^-$.

IR (film): 2924, 2862, 2623, 2407, 2291, 2252, 2191, 2075, 1982, 1597, 1458, 1319, 1157, 1072, 1018 cm^{-1}**.**

3,3-Dimethyl-oct-1-en-6-yn-4-ol ((±)-188).



3-pentynol **188**

First attempt

A solution of 3-pentynol (0.9 mL, 9.75 mmol) in dichloromethane (5 mL) was added to a stirred solution of Dess-Martin periodinane (4.55 g, 10.7 mmol, 1.10 equiv) in dichloromethane (25 mL). Water (1 drop) was added to the mixture. After stirring for 1 h at room temperature, the reaction was cooled to -78 °C and pentane was added (10 mL). This was then filtered through a pad of silica gel and the crude product was concentrated *in vacuo* at room temperature. No crude product was obtained as it had been lost through the vacuum. The reaction was repeated, but this time the product was concentrated *in vacuo* between 5 and 10 °C. The crude product was still lost through the vacuum.

Second attempt

A solution of 3-pentynol (5.0 mL, 59 mmol) in dichloromethane (20 mL) was added to a stirred solution of Dess-Martin periodinane (30.0 g, 71.3 mmol, 1.20 equiv) in dichloromethane (120 mL). Water (2 drops) was added to the mixture. After stirring for 1 h at room temperature, the reaction was cooled to -78 °C and filtered through a pad of silica gel. The crude product was left dissolved in dichloromethane. Tetrahydrofuran (75 mL) was added to the crude mixture before an excess of freshly prepared 1-bromo-3-methylbut-2-ene (15 mL, 71.3 mmol, 1.20 equiv) was added. Saturated aqueous ammonium chloride (75 mL) was added to the mixture before being cooled to 0 °C and zinc dust (11.6 g, 178.2 mmol, 3.00 equiv) was added slowly. The mixture was warmed to room temperature and stirred vigorously for 1 h (no inert atmosphere is necessary). After 1 h the reaction mixture was filtered through a pad of celite and the two phases were separated. The aqueous layer was extracted with diethyl ether before the combined organic fractions were washed with brine, dried over anhydrous magnesium sulfate and filtered. The solvent was removed *in vacuo* and the product was purified by flash column chromatography (diethyl ether/petroleum ether: 5/95) which gave a pale yellow oil (8.23 g, 91% over two steps).

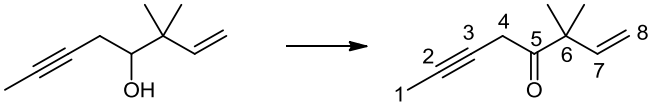
^{1}H NMR (δ_H): 5.85 (dd, 1H, *J* = 17.5 10.8 Hz, H-7), 5.08-5.01 (m, 2H, H-8), 3.45 (dt, 1H, *J* = 10.0, 3.1 Hz, H-5), 2.36 (dq, 1H, *J* = 16.5, 2.6 Hz, H-4), 2.20-2.09 (m, 2H, H-4, OH), 1.80 (t, 3H, *J* = 2.5 Hz, H-1), 1.03 (s, 3H Me-6), 1.02 (s, 3H, Me-6).

^{13}C NMR (δ_C): 144.6 (C-7), 113.2 (C-8), 78.3 (C-3), 76.7 (C-5), 76.5 (C-2), 41.1 (C-6), 23.1 (C-4), 23.0 (Me-6), 22.7 (Me-6), 3.7 (C-1).

MS: 154.3 $(M+H)^+$, 135.3.

IR (film): 3506, 3082, 2966, 2920, 2874, 1793, 1728, 1693, 1465, 1450, 1415, 1377, 1365, 1273, 1068, 1041 cm^{-1}.

3,3-Dimethyloct-1-en-6-yn-4-one (176).



188 176

A solution of **(±)-188** (8.22 g, 54.0 mmol) in dichloromethane (20 mL) was added to a solution of Dess-Martin periodinane (27.5 g, 64.8 mmol, 1.20 equiv) in dichloromethane (150 mL). Water (2 drops) was also added to the mixture. After stirring at room temperature for 2 h, the reaction mixture was cooled to -78 °C. The cold mixture was filtered through a pad of silica gel and the crude product was concentrated *in vacuo*. The product was purified by flash column chromatography (diethyl ether/petroleum ether: 3/97) which gave a pale yellow oil (8.00 g, 99%).

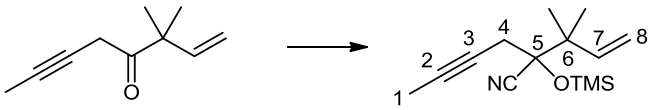
^{1}H NMR (δ_H): 5.91 (dd, 1H, *J* = 17.2 10.3 Hz, H-7), 5.19-5.15 (m, 2H, H-8), 3.36 (q, 2H, *J* = 2.5 Hz, H-4), 1.83 (t, 3H, *J* = 2.5 Hz, H-1), 1.25 (s, 3H, Me-6), 1.25 (s, 3H, Me-6).

^{13}C NMR (δ_C): 207.1 (C-5), 142.0 (C-7), 115.1 (C-8), 80.1 (C-3), 71.6 (C-2), 50.9 (C-6), 29.4 (C-4), 23.7 (Me-6), 3.8 (C-1).

MS: 151.3 $(M+H)^+$, 121.2.

IR (film): 2974, 2924, 1720, 1635, 1465, 1442, 1365, 1319, 1234, 1207, 1126, 1060, 1018 cm^{-1}.

2-(2-Methylbut-3-en-2-yl)-2-[(trimethylsilyl)oxy]hex-4-ynenitrile ((±)-189).



176 189

To a stirred solution of ketone **176** (8.14 g, 54.1 mmol) and zinc iodide (2.59 g, 8.12 mmol, 0.15 equiv) in dichloromethane (80 mL) was added trimethylsilyl cyanide (8.2 mL, 65

mmol). The mixture was stirred at room temperature overnight. Excess solvent and trimethylsilyl cyanide were removed *in vacuo* using a bleach and sodium hydroxide (1 M) trap. The crude residue was purified by flash column chromatography (diethyl ether/petroleum ether: 2/98) and gave a pale yellow oil (12.2 g, 99%).

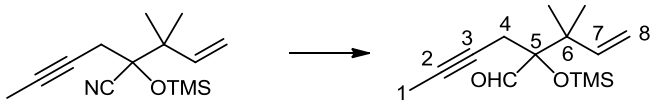
^{1}H NMR (δ_H): 5.95 (dd, 1H, *J* = 17.4 Hz, 10.9 Hz, H-7), 5.14-5.09 (m, 2H, H-8), 2.63 (dq, 1H, *J* = 16.8 Hz, 2.5 Hz, H-4), 2.44 (dq, 1H, *J* = 16.8 Hz, 2.5 Hz, H-4), 1.81 (t, 3H, *J* = 2.6 Hz, H-1), 1.18 (s, 3H, Me-6), 1.13 (s, 3H, Me-6), 0.29 (s, 9H, H-TMS).

^{13}C NMR (δ_C): 141.7 (C-7) 119.8 (C-N), 115.2 (C-8), 80.5 (C-3) 79.2 (C-2), 74.4 (C-5), 45.4 (C-6), 28.7 (C-4), 22.8 (Me-6), 22.1 (Me-6), 3.8 (C-1), 1.64 (C-TMS).

MS: 150.2 $(M+H)^+$.

IR (film): 3087, 2969, 2926, 2249, 1640, 1465, 1379, 1255, 1139, 1004 cm^{-1}.

2-(2-Methylbut-3-en-2-yl)-2-[(trimethylsilyl)oxy]hex-4-ynal ((±)-177).



189 **177**

First attempt

Nitrile **(±)-189** (220 mg, 0.88 mmol) was dissolved in dichloromethane (10 mL) and cooled to -78 °C. DIBAL (2.21 mL, 1 M in hexanes, 2.21 mmol, 2.50 equiv, Aldrich) was then added dropwise. The reaction mixture was warmed to 0 °C and stirred for 2 h. The reaction was quenched with ethyl acetate, diluted with diethyl ether and allowed to warm to room temperature. Silica was added to the solution, which was then placed at -20 °C overnight. After completion of the reaction, the mixture was warmed to room temperature and the silica was filtered off. Solvents were evaporated under reduced pressure. The crude ^{1}H NMR of the product showed many signals and after attempting purification the desired product was not obtained.

Second attempt

Nitrile **(±)-189** (230 mg, 0.90 mmol) was dissolved in dichloromethane (10 mL) and cooled to -78 °C. DIBAL (2.23 mL, 1 M in hexanes, 2.23 mmol, 2.50 equiv, Aldrich) was then added dropwise. The reaction mixture was warmed to 0 °C and stirred for 2 h. The reaction was quenched with ethyl acetate, diluted with diethyl ether and allowed to warm to room temperature. The reaction was quenched with 1 M aq HCl (5 mL) and stirred for 1 h. Solvents were evaporated under reduced pressure. The crude ^{1}H NMR spectrum of the product again showed many signals and purification was not carried out.

Third attempt

Nitrile **(±)-189** (3.00 g, 12.0 mmol) was dissolved in hexane (275 mL) and cooled to -78 °C. Fresh diisobutylaluminium hydride (17.0 mL, 1 M in hexanes, 1.40 equiv, Fisher) was added dropwise and the reaction mixture was allowed to warm to 0 °C. The mixture was stirred at 0 °C for 2 h. The reaction was quenched with ethyl acetate and diluted with diethyl ether. Saturated aqueous ammonium chloride was added to the mixture and stirred at 0 °C for 45 min until a precipitate started to form. The mixture was filtered through celite and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (diethyl ether/petroleum ether: 1/99) which gave a colourless oil **177** (1.87 g, 69%).

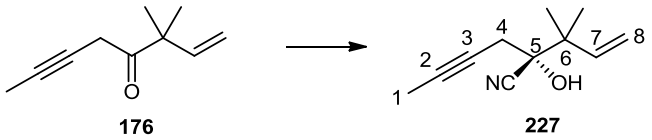
^{1}H NMR (δ_H): 9.63 (s, 1H, CHO), 5.96 (dd, 1H, *J* = 17.5 10.8, Hz, H-7), 5.09-4.98 (m, 2H, H-8), 2.75 (dq, 1H, *J* = 16.8, 2.6 Hz, H-4), 2.37 (dq, 1H, *J* = 16.8, 2.6 Hz, H-4), 1.72 (t, 3H, *J* = 2.6 Hz, H-1), 1.03 (s, 6H, Me-6), 0.21 (s, 9H, H-TMS).

^{13}C NMR (δ_C): 202.6 (CHO), 141.6 (C-7), 112.3 (C-8), 84.8 (C-3), 77.8 (C-2), 73.8 (C-5), 43.1 (C-6), 22.1 (C-4), 22.5 (Me-6), 20.5 (Me-6) 2.2 (C-1), 1.3 (C-TMS).

MS: 253.4 $(M+H)^+$, 223.3, 171.3.

IR (film): 3070, 2957, 2852, 2102, 1647, 1460, 1332, 1242, 1155, 1016 cm^{-1}.

(2*R*)-2-Hydroxy-2-(2-methylbut-3-en-2-yl)hex-4-ynenitrile (227).



176 227

To a stirred solution of ketone **176** (0.60 g, 4.10 mmol) in chloroform (0.2 M) at -20 °C was added $(DHD)_2AQN$ (1.10 g, 1.30 mmol, 30 mol%) and ethyl cyanoformate (0.80 mL, 8.2 mmol, 2.0 equiv). The resulting mixture was allowed to stand at that temperature in a freezer for 7 days without stirring. Aqueous hydrochloric acid (1 M, 10 mL) was added to the reaction mixture. The mixture was extracted with ether and the organic phase was washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The product was purified by flash column chromatography (diethyl ether/petroleum ether: 3/97) which gave the enantioenriched alcohol **227** as a yellow oil (0.40 g, 54%). Potassium carbonate was added to the aqueous layer to adjust the pH of the solution to between 9-11. The resulting solution was extracted with ethyl acetate (100 mL), and the organic layer was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to give the recovered $(DHD)_2AQN$) (0.88 g, 80%).

$[\alpha]^{22}_{D}$: +29.1 (*c* 1.2, CH_2Cl_2).

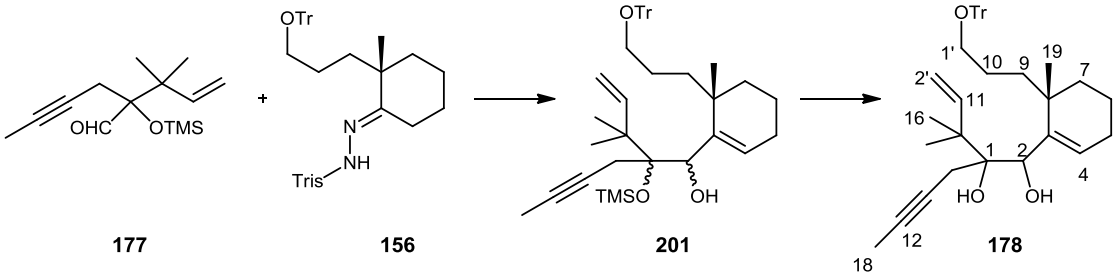
^{1}H NMR (δ_H): 5.96 (dd, 1H, *J* = 17.5 Hz, 10.9 Hz, H-7), 5.22-5.11 (m, 2H, H-8), 3.12 (s, 1H, OH), 2.64 (dq, 1H, *J* = 16.6 Hz, 2.5 Hz, H-4), 2.53 (dq, 1H, *J* = 16.7 Hz, 2.5 Hz, H-4), 1.85 (t, 3H, *J* = 2.5 Hz, H-1), 1.22 (s, 3H, Me-6), 1.20 (s, 3H, Me-6).

^{13}C NMR (δ_C): 139.9 (C-7), 119.2 (C-N), 114.8 (C-8), 81.5 (C-3), 75.5 (C-2), 70.9 (C-5), 42.3 (C-6), 27.1 (C-4), 21.4 (Me-6), 20.9 (Me-6), 2.7 (C-1).

HRMS Calcd for $C_{11}H_{15}NO$: 177.1154. Found: 177.1151.

IR (film): 3493, 2976, 2355, 1761, 1640, 1465, 1419, 1386, 1094, 1065 cm^{-1}.

(1*R*,2*R*)-1-[(6*S*)-6-Methyl-6-[3-(triphenylmethoxy)propyl]cyclohex-1-en-1-yl]-2-(2-methylbut-3-en-2-yl)hex-4-yne-1,2-diol 178a and (1*S*,2*S*)-1-[(6*S*)-6-Methyl-6-[3-(triphenylmethoxy)propyl]cyclohex-1-en-1-yl]-2-(2-methylbut-3-en-2-yl)hex-4-yne-1,2-diol 178b.



177 156 201 178

First attempt

To a stirred solution of hydrazone **156** (1.00 g, 1.44 mmol) in tetrahydrofuran (10 mL) at -78 °C was added *tert*-butyllithium (3.60 mL, 1.6 M in pentane, 3.87 mmol, 3.00 equiv dropwise. The solution turned red and was stirred at -78 °C for 30 min until the colour turned dark red. The temperature was then allowed to warm to 0 °C to allow nitrogen evolution. After 5 min, once bubbling has stopped, the solution was again cooled to -78 °C. A pre-cooled solution of aldehyde **((±)-177)** (355 mg, 1.29 mmol, 0.9 equiv) in tetrahydrofuran (5 mL) was added dropwise and the resulting mixture was stirred at -78 °C for 5 h. The reaction was quenched with saturated aqueous sodium hydrogencarbonate (10 mL). The phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. Starting material was recovered.

Second attempt

To a stirred solution of hydrazone **156** (1.00 g, 1.44 mmol) in tetrahydrofuran (10 mL) at -78 °C was added *tert*-butyllithium (1.88 mL, 1.6 M in pentane, 3.05 mmol, 2.10 equiv) dropwise. The solution turned red and was stirred at -78 °C for 30 min until the colour turned dark red. The temperature was then allowed to warm to 0 °C to allow nitrogen evolution. After 5 min, once bubbling has stopped, the solution was again cooled to -78 °C. A solution of cerium (III) chloride (419 mg, 1.70 mmol, 1.2 equiv) in tetrahydrofuran (5 mL) was stirred for 4 h at room temperature, after which time it was cooled to -78 °C

and titrated with *tert*-butyllithium until the solution turned yellow. This was then added dropwise to the previous solution at -78 °C and stirred for a further 30 min. A pre-cooled solution of aldehyde **((±)-177)** (355 mg, 1.29 mmol, 0.9 equiv) in tetrahydrofuran (5 mL) was added dropwise and the resulting mixture was stirred at -78 °C for 1 h. The reaction was quenched with saturated aqueous sodium hydrogencarbonate (10 mL). The phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. Purification of the crude product using flash column chromatography (diethyl ether/petroleum ether:1/99) gave compound **201** as a yellow oil and as a 1:1 inseparable mixture of diastereomers (120 mg, 13%).

Third attempt

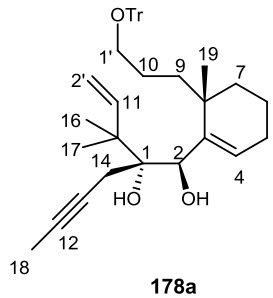
To a stirred solution of hydrazone **156** (1.00 g, 1.44 mmol) in tetrahydrofuran (10 mL) at -78 °C was added *tert*-butyllithium (1.93 mL, 1.6 M in pentane, 3.10 mmol, 2.15 equiv dropwise. The solution turned red and was stirred at -78 °C for 30 min until the colour turned dark red. The temperature was then allowed to warm to 0 °C to allow nitrogen evolution. After 5 min, once bubbling has stopped, the solution was again cooled to -78 °C. Two equivalents of lithium chloride (123.6 mg, 2.88 mmol) were added to cerium trichloride (355 mg, 1.44 mmol). This was heated and stirred under vacuum overnight before being dissolved in tetrahydrofuran (5 mL), this was stirred for 4 h at room temperature, after which time it was cooled to -78 °C and titrated with *tert*-butyllithium. The solution turned black and not yellow. The aldehyde was not added and the reaction was abandoned.

Fourth attempt

To a stirred solution of hydrazone **156** (1.00 g, 1.44 mmol) in tetrahydrofuran (10 mL) at -78 °C was added *tert*-butyllithium (1.93 mL, 1.6 M in pentane, 3.10 mmol, 2.15 equiv dropwise. The solution turned red and was stirred at -78 °C for 30 min until the colour turned dark red. The temperature was then allowed to warm to 0 °C to allow nitrogen evolution. After 5 min, once bubbling has stopped, the solution was again cooled to -78 °C. A solution of cerium (III) chloride (355 mg, 1.44 mmol) in tetrahydrofuran (5 mL) was stirred for 4 h at room temperature, after which time it was cooled to -78 °C and titrated with *tert*-butyllithium until the solution turned yellow. This was then added dropwise to the previous solution at -78 °C and stirred for a further 30 min. A pre-cooled

solution of aldehyde **((±)-177)** (355 mg, 1.29 mmol, 0.9 equiv) in tetrahydrofuran (5 mL) was added dropwise and the resulting mixture was stirred at -78 °C for 1 h. The reaction was quenched with saturated aqueous sodium hydrogencarbonate (10 mL). The phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. Purification of the crude product using flash column chromatography (diethyl ether/petroleum ether:1/99) gave a yellow oil as an inseparable mixture of 1:1 diastereomers (415 mg, 45%). The crude mixture of two inseparable diastereomers was dissolved in tetrahydrofuran (10 mL) and cooled to 0 °C and 1 M aqueous hydrochloric acid (0.60 mL, 0.60 mmol, 2.0 equiv) was added. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated aqueous sodium hydrogencarbonate, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography (diethyl ether/petroleum ether: 10/90) which allowed separation of the two diastereomers, undesired alcohol **178a** as a colourless oil (98.0 mg, 50%) and desired alcohol **178b** as a colourless oil (78.0 mg, 41%).

(1*R*,2*R*)-1-[(6*S*)-6-Methyl-6-[3-(triphenylmethoxy)propyl]cyclohex-1-en-1-yl]-2-(2-methylbut-3-en-2-yl)hex-4-yne-1,2-diol 178a.



178a

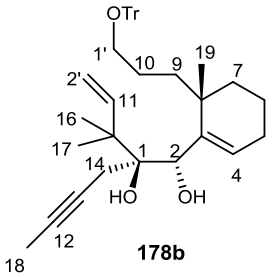
^{1}H NMR (δ_H): 7.47-7.42 (m, 6H, H-Ar), 7.31-7.26 (m, 6H, H-Ar), 7.24 – 7.20 (m, 3H, H-Ar), 6.27–6.18 (m, 2H, H-4, H-11), 5.07-5.01 (m, 2H, H-2'), 4.22 (d, 1H, *J* = 5.9 Hz, H-2), 3.14 (s, 1H, OH (C-1)), 3.08-3.04 (m, 2H, H-1'), 2.52-2.48 (m, 2H, H-14), 2.16 (d, 1H, *J* = 6.4 Hz, OH (C-2)), 2.07-1.98 (m, 2H, H-5), 1.78 (t, 3H, *J* = 2.6 Hz, H-18), 1.70-1.51 (m, 6H, CH_2), 1.49-1.41 (m, 2H, CH_2), 1.20 (s, 3H, H-16 or H-17), 1.17 (s, 3H, H-17 or H-16), 0.98 (s, 3H, H-19).

^{13}C NMR (δ_C): 145.8 (C-3), 145.3 (C-Ar), 143.7 (C-11), 127.9 (C-Ar), 127.4 (C-4), 126.7 (C-Ar), 125.8 (C-Ar), 111.4 (C-2'), 85.6 (CPh_3), 78.4, 76.4, 75.6 (C-13, C-12, C-1), 68.2 (C-2), 64.8 (C-1'), 45.5 (C-15), 36.2 (C-8), 35.9 (C-5), 34.5 (CH_2), 25.3 (CH_2), 25.2 (CH_2), 24.9 (C-14), 23.8 (C-19), 22.9 (C-16 or C-17), 22.4 (C-16 or C-17), 17.8 (CH_2), 2.7 (C-18).

MS: 577 $(M+H)^+$, 559.

IR (film): 3517, 2920, 2867, 1490, 1448, 1152, 1115, 1088, 1070 cm^{-1}**.**

(1*S*,2*S*)-1-[(6*S*)-6-Methyl-6-[3-(triphenylmethoxy)propyl]cyclohex-1-en-1-yl]-2-(2-methylbut-3-en-2-yl)hex-4-yne-1,2-diol 178b.



178b

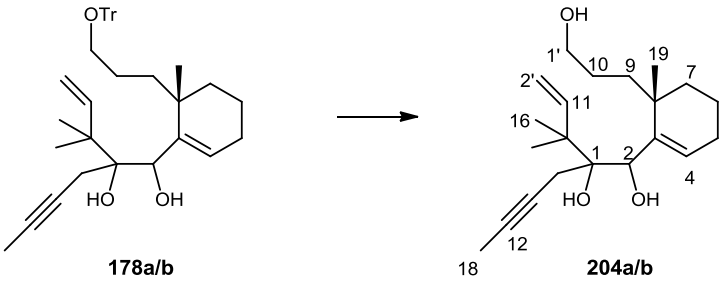
^{1}H NMR (δ_H): 7.45-7.43 (m, 6H, H-Ar), 7.32-7.27 (m, 6H, H-Ar), 7.25-7.20 (m, 3H, H-Ar), 6.26-6.16 (m, 2H, H-4, H-11), 5.05-4.93 (m, 2H, H-2'), 4.24 (d, 1H, *J* = 6.4 Hz, H-2), 3.09 (s, 1H, OH (C-1)), 3.04 (t, 2H, *J* = 6.1 Hz, H-1'), 2.52-2.43 (m, 2H, H-14), 2.05-1.99 (m, 3H, H-5, OH (C-2)), 1.66 (t, 3H, *J* = 2.8 Hz, H-18), 1.62-1.48 (m, 5H, CH_2), 1.45-1.37 (m, 3H, CH_2), 1.18 (s, 3H, H-16 or H-17), 1.15 (s, 3H, H-17 or H-16), 1.07 (s, 3H, H-19).

^{13}C NMR (δ_C): 146.6 (C-3), 145.8 (C-Ar), 143.7 (C-11), 127.8 (C-Ar), 126.8 (C-Ar), 126.6 (C-4), 125.9 (C-Ar), 111.4 (C-2'), 85.6 (Ph_3C), 78.5, 76.5, 75.6 (C-13, C-12, C-1), 68.9 (C-2), 64.8 (C-1'), 45.6 (C-15), 35.9 (C-8), 35.0 (C-5), 34.2 (CH_2), 25.4 (CH_2), 25.0 (C-19), 24.2 (CH_2), 23.6 (C-14), 22.9 (C-16 or C-17), 22.5 (C-16 or C-17), 17.7 (CH_2), 2.6 (C-18).

MS: 577 $(M+H)^+$, 559.

IR (film): 3517, 2922, 1448, 1379, 1002 cm^{-1}**.**

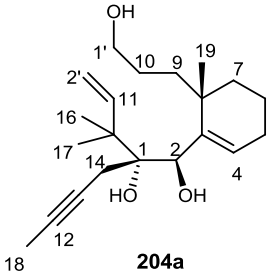
(1*R*,2*R*)-1-[(6*S*)-6-(3-Hydroxypropyl)-6-methylcyclohex-1-en-1-yl]-2-(2-methylbut-3-en-2-yl)hex-4-yne-1,2-diol 204a and (1*S*,2*S*)-1-[(6*S*)-6-(3-Hydroxypropyl)-6-methylcyclohex-1-en-1-yl]-2-(2-methylbut-3-en-2-yl)hex-4-yne-1,2-diol 204b.



To a solution of **178a** (103 mg, 0.30 mmol) in methanol (5 mL) was added Amberlyst (500 mg). The mixture was stirred at room temperature overnight. The Amberlyst was filtered off and washed thoroughly with ethyl acetate before the solvent was removed *in vacuo*. Purification of the product by column chromatography (ethyl acetate/petroleum ether: 25/75) gave **204a** as a colourless oil (41.0 mg, 68%).

The same procedure was used with **178b** (95.0 mg, 0.16 mmol) and gave the desired carbonate **204b** as a colourless oil (46.0 mg, 85%).

(1*R*,2*R*)-1-[(6*S*)-6-(3-Hydroxypropyl)-6-methylcyclohex-1-en-1-yl]-2-(2-methylbut-3-en-2-yl)hex-4-yne-1,2-diol 204a.



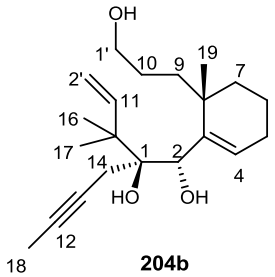
^{1}H NMR (δ_H): 6.30-6.23 (m, 2H, H-4, H-11), 5.09-5.06 (m, 2H, H-2'), 4.28 (d, 1H, *J* = 4.2 Hz, H-2), 3.61 (t, 2H, *J* = 6.6 Hz, H-1'), 3.05 (s, 1H, OH (C-1)), 2.53-2.50 (m, 2H, H-14), 2.06-2.00 (m, 3H, H-5, OH (C-2)), 1.79 (t, 3H, *J* = 2.7 Hz, H-18), 1.66-1.59 (m, 2H, CH_2), 1.57-1.50 (m, 4H, CH_2), 1.40-1.32 (m, 2H, CH_2), 1.24 (s, 3H, H-16 or H-17), 1.20 (s, 3H, H-17 or H-16), 1.09 (s, 3H, H-19).

^{13}C NMR (δ_C): 146.3 (C-3), 144.9 (C-11), 128.9 (C-4), 112.6 (C-2'), 79.6, 77.1, 76.2 (C-13, C-12, C-1), 68.7 (C-2), 62.9 (C-1'), 46.4 (C-15), 37.4 (C-8), 35.9 (C-5), 35.2 (CH_2), 27.1 (CH_2), 26.9 (CH_2), 26.1 (C-19), 25.9 (C-14), 23.8 (C-16 or C-17), 23.2 (C-17 or C-16), 18.8 (CH_2), 3.7 (C-18).

MS: 335 $(M+H)^+$.

IR (film): 3636, 3456, 3082, 2924, 2868, 2735, 2669, 1723, 1633, 1460, 1416, 1383, 1236, 1063, 1004 cm^{-1}.

(1*S*,2*S*)-1-[(6*S*)-6-(3-Hydroxypropyl)-6-methylcyclohex-1-en-1-yl]-2-(2-methylbut-3-en-2-yl)hex-4-yne-1,2-diol 204b.



204b

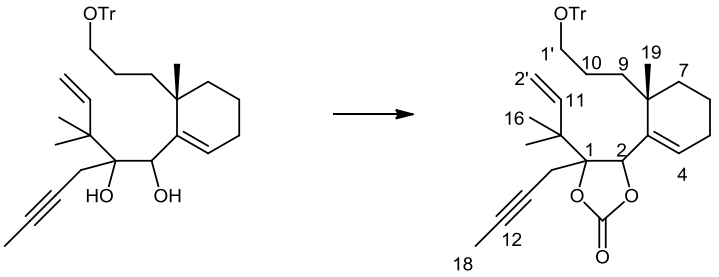
^{1}H NMR (δ_H): 6.29 (t, 1H, *J* = 4.1 Hz, H-4), 6.21 (dd, 1H, *J* = 17.8, 10.5 Hz, H-11), 5.08-5.04 (m, 2H, H-2'), 4.23 (s, 1H, H-2), 3.72-3.67 (m, 1H, H-1'), 3.64-3.50 (m, 2H, OH, H-1'), 3.05 (s, 1H, OH), 2.52-2.45 (m, 2H, H-14), 2.03-1.97 (m, 2H, H-5), 1.75 (t, 3H, *J* = 2.6 Hz, H-18), 1.73-1.65 (m, 1H, CH_2), 1.60-1.51 (m, 4H, CH_2), 1.44-1.33 (m, 3H, CH_2), 1.19 (s, 3H, H-16 or H-17), 1.17 (s, 3H, H-17 or H-16), 0.99 (s, 3H, H-19).

^{13}C NMR (δ_C): 147.1 (C-3), 146.8 (C-11), 127.7 (C-4), 112.6 (C-2'), 79.3, 77.5, 76.6 (C-13, C-12, C-1), 69.8 (C-2), 63.8 (C-1'), 46.4 (C-15), 36.6 (C-8), 35.3 (C-5), 35.0 (CH_2), 27.1 (CH_2), 26.2 (CH_2), 25.8 (C-19), 25.1 (C-14), 23.7 (C-16 or C-17), 23.3 (C-17 or C-16), 18.5 (CH_2), 3.7 (C-18).

MS: 335 $(M+H)^+$.

IR (film): 3636, 3533, 2932, 2867, 1460, 1380, 1117, 1048, 1008 cm^{-1}.

(4*R*,5*R*)-4-(But-2-yn-1-yl)-5-[(6*S*)-6-methyl-6-[3-(triphenylmethoxy)propyl]cyclohex-1-en-1-yl]-4-(2-methylbut-3-en-2-yl)-1,3-dioxolan-2-one 213a and (4*S*,5*S*)-4-(But-2-yn-1-yl)-5-[(6*S*)-6-methyl-6-[3-(triphenylmethoxy)propyl]cyclohex-1-en-1-yl]-4-(2-methylbut-3-en-2-yl)-1,3-dioxolan-2-one 213b.

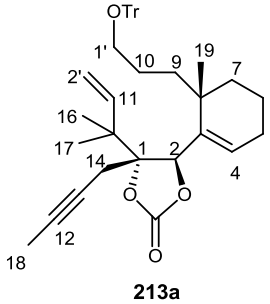


178a/b **213a/b**

To a solution of **178a** (300 mg, 0.52 mmol) in dimethylformamide (10 mL) was added sodium hydride (70 mg, 60% in mineral oil, 1.7 mmol, 2.5 equiv) and carbonyl diimidazole (0.50 g, 2.6 mmol, 5.0 equiv). The mixture was stirred at room temperature for 30 min before being quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with diethyl ether and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the product by flash column chromatography (diethyl ether/petroleum ether: 20/80) gave **213a** as a thick white oil (185 mg, 61%).

The same procedure was used with **178b** (300 mg, 0.52 mmol) and gave the desired carbonate **213b** as a white solid (190 mg, 61%).

(4*R*,5*R*)-4-(But-2-yn-1-yl)-5-[(6*S*)-6-methyl-6-[3-(triphenylmethoxy)propyl]cyclohex-1-en-1-yl]-4-(2-methylbut-3-en-2-yl)-1,3-dioxolan-2-one 213a.



213a

$[\alpha]^{24}_{D}$: +21.5 (*c* 0.2, CH_2Cl_2).

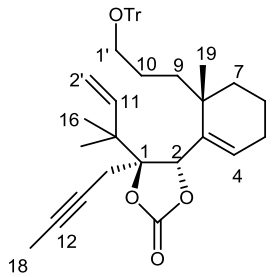
^{1}H NMR (δ_H): 7.46-7.42 (m, 6H, H-Ar), 7.32-7.27 (m, 6H, H-Ar), 7.25–7.20 (m, 3H, H-Ar), 6.04–5.94 (m, 2H, H-4, H-11), 5.19-5.13 (m, 2H, H-2'), 4.94 (s, 1H, H-2), 3.07-3.02 (m, 2H, H-1'), 2.81-2.65 (m, 2H, H-14), 2.15-2.07 (m, 2H, H-5), 1.75 (t, 3H, *J* = 2.5 Hz, H-18), 1.67-1.52 (m, 5H, CH_2), 1.41-1.30 (3H, m, CH_2), 1.21 (s, 3H, H-16 or H-17), 1.19 (s, 3H, H-16 or H-17), 0.99 (s, 3H, H-19).

^{13}C NMR (δ_C): 154.0 (C=O), 143.4 (C-3), 140.9 (C-11), 137.4 (C-Ar), 132.5 (C-4), 127.8 (C-Ar), 126.8 (C-Ar), 125.9 (C-Ar), 115.0 (C-2'), 85.5 (CPh_3), 78.2, 76.7, 76.3 (C-13, C-12, C-1), 73.1 (C-2), 63.2 (C-1'), 45.3 (C-15), 36.0 (CH_2), 35.8 (CH_2), 34.2 (C-8), 25.9 (C-19), 24.9 (C-5), 23.3 (CH_2), 22.5 (C-14), 21.9 (C16 or 17), 20.4 (C16 or C-17), 17.5 (CH_2), 2.8 (C-18).

HRMS Calcd for $C_{41}H_{46}O_4Na$: 625.3288. Found: 625.3262.

IR (film): 3057, 2935, 2866, 1799, 1448, 1195, 1174, 1060, 1041, 1003 cm^{-1}.

(4*S*,5*S*)-4-(But-2-yn-1-yl)-5-[(6*S*)-6-methyl-6-[3-triphenylmethoxy)propyl]cyclohex-1-en-1-yl]-4-(2-methylbut-3-en-2-yl)-1,3-dioxolan-2-one 213b.



213b

[**α**]^{24} **D**: +4.5 (*c* 0.2, CH_2Cl_2).

^{1}H NMR (δ_H): 7.47-7.42 (m, 6H, H-Ar), 7.34-7.28 (m, 6H, H-Ar), 7.27–7.21 (m, 3H, H-Ar), 5.99–5.88 (m, 2H, H-4, H-11), 5.17-5.03 (m, 2H, H-2'), 5.01 (s, 1H, H-2), 3.04 (t, 2H, *J* = 6.3 Hz, H-1'), 2.84-2.62 (m, 2H, H-14), 2.15-2.09 (m, 2H, H-5), 1.65 (t, 3H, *J* = 2.5 Hz, H-18), 1.63-1.53 (m, 5H, CH_2), 1.47-1.30 (3H, m, CH_2), 1.18 (s, 3H H-16 or H-17), 1.18 (s, 3H H-16 or H-17), 1.09 (s, 3H, H-19).

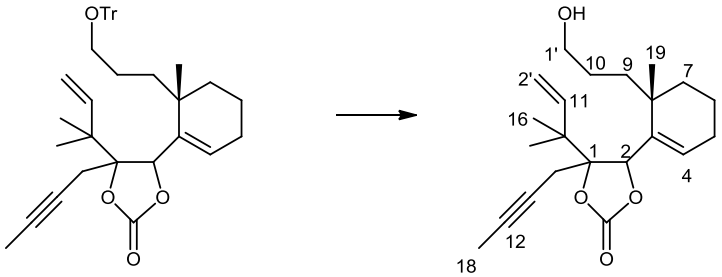
^{13}C NMR (δ_C): 153.8 (C=O), 143.3 (C-3), 140.9 (C-11), 139.2 (C-Ar), 130.8 (C-4), 127.6 (C-Ar), 126.8 (C-Ar), 126.0 (C-Ar), 114.9 (C-2'), 85.5 (CPh_3), 78.2 (C-13), 77.4 (C-1),

76.3 (C-12), 73.0 (C-2), 63.2 (C-1'), 45.2 (C-15), 35.5 (CH_2), 34.9 (CH_2), 33.7 (C-8), 24.8 (C-19), 23.8 (C-5), 23.3 (CH_2), 22.5 (C-14), 21.9 (C16 or 17), 20.3 (C16 or C-17), 17.2 (CH_2), 2.7 (C-18).

HRMS Calcd for $C_{41}H_{46}O_4Na$: 625.3288. Found: 625.3267.

IR (film): 3517, 2922, 1448, 1379, 1002 cm^{-1}.

(4*R*,5*R*)-4-(but-2-yn-1-yl)-5-[(6*S*)-6-(3-hydroxypropyl)-6-methylcyclohex-1-en-1-yl]-4-(2-methylbut-3-en-2-yl)-1,3-dioxolan-2-one 214a and (4*S*,5*S*)-4-(but-2-yn-1-yl)-5-[(6*S*)-6-(3-hydroxypropyl)-6-methylcyclohex-1-en-1-yl]-4-(2-methylbut-3-en-2-yl)-1,3-dioxolan-2-one 214b.

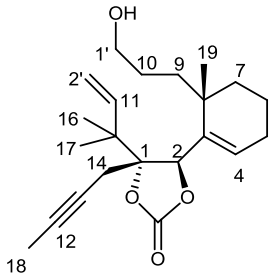


213a/b **214a/b**

To a solution of **213a** (185 mg, 0.30 mmol) in wet methanol (7 mL) was added Amberlyst H-15 (300 mg). The mixture was stirred overnight at room temperature. The resin was filtered off and washed thoroughly with ethyl acetate. The solvent was then removed *in vacuo*. The crude mixture was purified by flash column chromatography (diethyl ether/petroleum ether: 20/80) and gave **214a** as a colourless oil (55.0 mg, 50%).

The same procedure was used with **213b** (190 mg, 0.31 mmol) and gave the desired alcohol **214b** as a colourless oil (102 mg, 90%).

(4*R*,5*R*)-4-(But-2-yn-1-yl)-5-[(6*S*)-6-(3-hydroxypropyl)-6-methylcyclohex-1-en-1-yl]-4-(2-methylbut-3-en-2-yl)-1,3-dioxolan-2-one 214a.



214a

$[\alpha]^{21.9}_{D}$: +2.6 (*c* 0.1, CH_2Cl_2).

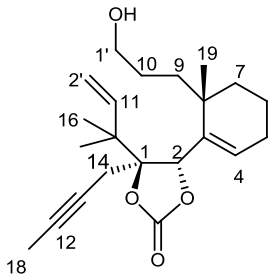
^{1}H NMR (δ_H): 6.08–5.94 (m, 2H, H-4, H-11), 5.22 (m, 2H, H-2'), 4.99 (s, 1H, H-2), 3.69-3.54 (m, 2H, H-1'), 2.76 (dq, 1H, *J* = 17.5, 2.6 Hz, H-14), 2.69 (dq, 1H, *J* = 17.5, 2.6 Hz, H-14), 2.19-2.05 (m, 2H, H-5), 1.74 (t, 3H, *J* = 2.7 Hz, H-18), 1.67-1.40 (m, 9H, OH, CH_2), 1.22 (s, 3H, H-16 or H-17), 1.21 (s, 3H, H-16 or H-17), 1.00 (s, 3H, H-19).

^{13}C NMR (δ_C): 154.0 (C=O), 140.9 (C-3), 137.3 (C-11), 132.7 (C-4), 115.1 (C-2'), 88.1, 78.2, 76.7, (C-13, C-12, C-1) 73.1 (C-2), 63.2 (C-1'), 45.4 (C-15), 35.9 (CH_2), 35.5 (CH_2), 34.2 (CH_2), 26.0 (C-8), 25.9 (C-19), 24.9 (C-5), 22.5 (C-14), 21.9 (C16 or 17), 20.3 (C16 or C-17), 17.4 (CH_2), 2.7 (C-18).

HRMS Calcd for $C_{22}H_{32}O_4Na$: 383.2193. Found: 383.2174.

IR (film): 3483, 2935, 2872, 2332, 1799, 1464, 1344, 1199, 1043, 927, 767 cm^{-1}**.**

(4S,5S)-4-(but-2-yn-1-yl)-5-[(6S)-6-(3-hydroxypropyl)-6-methylcyclohex-1-en-1-yl]-4-(2-methylbut-3-en-2-yl)-1,3-dioxolan-2-one 214b.



214b

$[\alpha]^{21.9}_{D}$: +9.0 (*c* 0.1, CH_2Cl_2).

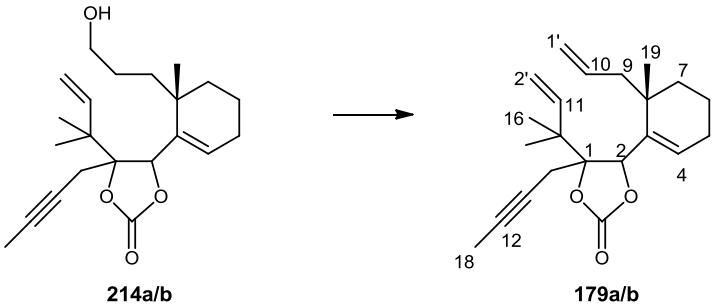
^{1}H NMR (δ_H): 6.07–5.98 (dd, 1H, *J* = 17.4, 10.7 Hz, H-11), 5.85 (t, 1H, *J* = 3.9 Hz H-4), 5.24-5.16 (m, 2H, H-2'), 5.02 (s, 1H, H-2), 3.61-3.53 (m, 2H, H-1'), 2.78 (dq, 1H, *J* = 17.4, 2.6 Hz, H-14), 2.67 (dq, 1H, *J* = 17.4, 2.6 Hz, H-14), 2.13-2.04 (m, 2H, H-5), 1.72 (t, 3H, *J* = 2.5 Hz, H-18), 1.59-1.43 (m, 5H, CH_2), 1.42-1.30 (m, 3H, CH_2), 1.21 (s, 3H, H-16 or H-17), 1.19 (s, 3H, H-16 or H-17), 1.06 (s, 3H, H-19).

^{13}C NMR (δ_C): 153.9 (C=O), 141.0 (C-3), 139.1 (C-11), 130.8 (C-4), 115.0 (C-2'), 88.1, 78.3, 77.7 (C-13, C-12, C-1), 73.0 (C-2), 62.4 (C-1'), 45.2 (C-15), 35.5 (CH_2), 34.5 (CH_2), 33.9 (CH_2), 25.9 (C-8), 24.8 (C-19), 23.9 (C-5), 22.6 (C-14), 21.9 (C16 or 17), 20.2 (C16 or C-17), 17.2 (CH_2), 2.7 (C-18).

HRMS Calcd for $C_{22}H_{32}O_4Na$: 383.2193. Found: 383.2179.

IR (film): 3421, 2939, 2870, 1797, 1417, 1344, 1201, 1057, 927, 767 cm^{-1}**.**

(4*R*,5*R*)-4-(But-2-yn-1-yl)-5-[(6*S*)-6-methyl-6-(prop-2-en-1-yl)cyclohex-1-en-1-yl]-4-(2-methylbut-3-en-2-yl)-1,3-dioxolan-2-one 179a and (4*S*,5*S*)-4-(But-2-yn-1-yl)-5-[(6*S*)-6-methyl-6-(prop-2-en-1-yl)cyclohex-1-en-1-yl]-4-(2-methylbut-3-en-2-yl)-1,3-dioxolan-2-one 179b.



214a/b **179a/b**

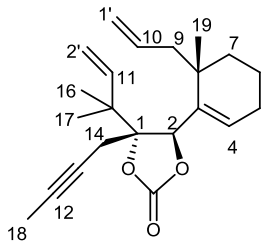
To a solution of **214a** (50 mg, 0.13 mmol) in tetrahydrofuran (3 mL) was added *o*-nitrophenylselenocyanate (74 mg, 0.33 mmol, 2.4 equiv) and tributylphosphine (80 µL, 0.33 mmol, 2.4 equiv). The mixture was stirred at room temperature for 20 min before being quenched with water. The aqueous layer was extracted with diethyl ether and the combined organic extracts were washed with brine, dried over anhydrous magnesium

sulfate, filtered and concentrated *in vacuo*. The crude brown oil was used without further purification.

A solution of ammonium molybdate (86 mg) in water (6 mL), and 30% aqueous hydrogen peroxide (3 mL) was prepared. This solution (1.7 mL) was added at -10 °C to a solution of the crude brown oil in tetrahydrofuran (3 mL). The mixture was stirred at this temperature for 20 min (no longer). The reaction was quenched with water and the aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (diethyl ether/petroleum ether: 5/95) and gave **179a** as a pale yellow oil (44.0 mg, 93% yield).

The same procedure was used with **214b** (44.0 mg, 0.15 mmol) and gave the desired triene **179b** as a pale yellow oil (42.0 mg, 81%).

(4*R*,5*R*)-4-(But-2-yn-1-yl)-5-[(6*S*)-6-methyl-6-(prop-2-en-1-yl)cyclohex-1-en-1-yl]-4-(2-methylbut-3-en-2-yl)-1,3-dioxolan-2-one 179a.



179a

$[\alpha]^{22}_{D}$: +19.4 (*c* 1.2, CH_2Cl_2).

^{1}H NMR (δ_H): 6.03 (dd, *J* = 17.8, 10.6 Hz, 1H, H-11), 5.95 (t, 1H, *J* = 4.0 Hz, H-4), 5.81–5.69 (m, 1H, H-10), 5.26-5.19 (m, 2H, H-2'), 5.10-5.00 (m, 3H, H-1', H-2), 2.78 (dq, 1H, *J* = 17.5, 2.6 Hz, H-14), 2.70 (dq, 1H, *J* = 17.5, 2.6 Hz, H-14), 2.30-2.23 (m, 1H, H-9), 2.17-2.09 (m, 3H, H-5, H-9), 1.74 (t, 3H, *J* = 2.6 Hz, H-18), 1.67-1.55 (m, 2H, CH_2), 1.43-1.32 (m, 2H, CH_2) 1.23 (s, 3H, H-16 or H-17), 1.22 (s, 3H H-16 or H-17), 1.01 (s, 3H, H-19).

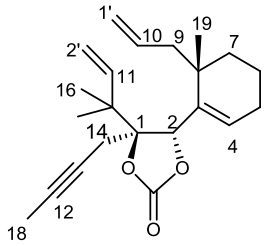
^{13}C NMR (δ_C): 154.0 (C=O), 141.9 (C-11), 137.3 (C-3), 133.1 (C-10), 132.3 (C-4), 117.1 (C-1'), 115.0 (C-2'), 88.0, 78.2, 76.8 (C-13, C-12, C-1), 76.3 (C-2), 45.4 (C-15), 44.1 (C-

8), 36.0 (C-9), 34.7 (C-5), 25.1 (C-6), 24.7 (C-19), 22.5 (C-14), 22.0 (C16 or 17), 20.3 (C16 or C-17), 17.2 (C-7), 2.7 (C-18).

MS: 343 $(M+H)^+$, 281.

IR (film): 2933, 2850, 1801, 1448, 1325, 1193, 1043, 1109 cm^{-1}**.**

(4*S*,5*S*)-4-(But-2-yn-1-yl)-5-[(6*S*)-6-methyl-6-(prop-2-en-1-yl)cyclohex-1-en-1-yl]-4-(2-methylbut-3-en-2-yl)-1,3-dioxolan-2-one 179b.



179b

$[\alpha]^{21.9}{}_D$: -66.4 (*c* 1.1, CH_2Cl_2).

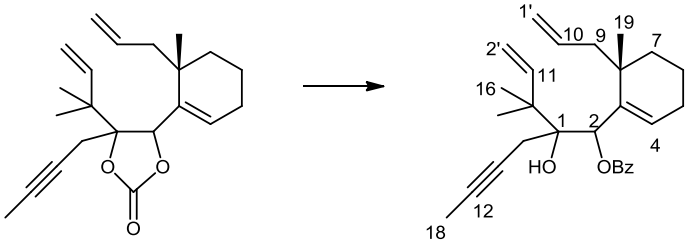
^{1}H NMR (δ_H): 6.05 (dd, *J* = 17.5, 10.2 Hz, 1H, H-11), 5.89 (t, 1H, *J* = 4.0 Hz, H-4), 5.79–5.68 (m, 1H, H-10), 5.26-5.18 (m, 2H, H-2'), 5.08-4.96 (m, 3H, H-1', H-2), 2.79 (dq, 1H, *J* = 17.5, 2.6 Hz, H-14), 2.70 (dq, 1H, *J* = 17.5, 2.6 Hz, H-14), 2.23-2.15 (m, 1H, H-9), 2.14-2.01 (m, 3H, H-5, H-9), 1.73 (t, 3H, *J* = 2.6 Hz, H-18), 1.68-1.53 (m, 1H, CH_2), 1.38-1.29 (m, 3H, CH_2) 1.23 (s, 3H, H-16 or H-17), 1.22 (s, 3H H-16 or H-17), 1.07 (s, 3H, H-19).

^{13}C NMR (δ_C): 153.8 (C=O), 141.0 (C-11), 138.7 (C-3), 133.2 (C-10), 131.3 (C-4), 117.0 (C-1'), 115.0 (C-2'), 88.1, 78.5, 77.5 (C-13, C-12, C-1), 73.1 (C-2), 45.3 (C-15), 42.9 (C-8), 36.1 (C-9), 34.0 (C-5), 24.9 (C-6), 24.1 (C-19), 22.7 (C-14), 22.1 (C16 or 17), 20.4 (C16 or C-17), 17.1 (C-7), 2.7 (C-18).

MS: 343 $(M+H)^+$, 281.

IR (film): 3421, 2976, 2860, 1803, 1450, 1325, 1193, 1041 cm^{-1}**.**

(1*R*,2*R*)-2-Hydroxy-1-[(6*S*)-6-methyl-6-(prop-2-en-1-yl)cyclohex-1-en-1-yl]-2-(2-methylbut-3-en-2-yl)hex-4-yn-1-yl benzoate 215a and (1*S*,*2S)*-2-Hydroxy-1-[(6*S*)-6-methyl-6-(prop-2-en-1-yl)cyclohex-1-en-1-yl]-2-(2-methylbut-3-en-2-yl)hex-4-yn-1-yl benzoate 215b.

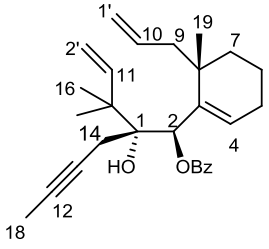


179a/b **215a/b**

To a solution of **179a** (46 mg, 0.13 mmol) in tetrahydrofuran (3 mL) at -78˚C was added phenyllithium (1.72 mL, 0.7 M in ether, 1.17 mmol, 9.0 equiv). The mixture was stirred at this temperature for 1.5 h before being quenched with saturated aqueous sodium hydrogen carbonate. The aqueous phase was extracted with diethyl ether and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography (diethyl ether/petroleum ether: 5/95) gave **215a** as a pale yellow oil (30 mg, 54 %).

The same procedure was used with **179b** (42 mg, 0.12 mmol) and gave the desired benzoate **215b** as a pale yellow oil (36 mg, 70%).

(1*R*,2*R*)-2-Hydroxy-1-[(6*S*)-6-methyl-6-(prop-2-en-1-yl)cyclohex-1-en-1-yl]-2-(2-methylbut-3-en-2-yl)hex-4-yn-1-yl benzoate 215a.



215a

$[\alpha]^{24}_{D}$: +65.0 (*c* 0.6, CH_2Cl_2).

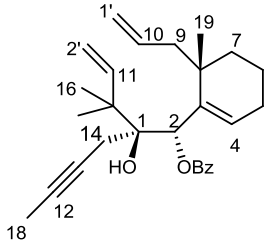
^{1}H NMR (δ_H): 8.00 (d, 2H, *J* = 7.5 Hz, H-Ar), 7.54 (t, 1H, *J* = 7.5 Hz, H-Ar), 7.43 (t, 2H, *J* = 7.5 Hz, H-Ar), 6.44 (t, 1H, *J* = 4.0 Hz, H-4), 6.09 (dd, 1H, *J* = 17.7, 10.8 Hz, H-11), 5.81 (s, 1H, H-2), 5.74-5.62 (m, 1H, H-10), 5.01-4.92 (m, 2H, H-2'), 4.89 (d, 1H, *J* = 17.7 Hz, H-1'), 4.71 (d, 1H, *J* = 10.7 Hz, H-1'), 2.89 (s, 1H, OH), 2.67 (dq, 1H, *J* = 17.0, 2.6 Hz, H-14), 2.56 (dq, 1H, *J* = 17.0, 2.6 Hz, H-14), 2.46 (m, 1H, H-9), 2.16-2.07 (m, 3H, H-5, H-9), 1.82 (t, 3H, *J* = 2.6 Hz, H-18), 1.65-1.50 (m, 4H, H-6, H-7), 1.22 (s, 3H, H-16 or H-17), 1.14 (s, 3H, H-16 or H-17), 1.11 (s, 3H, H-19).

^{13}C NMR (δ_C): 163.9 (C=O), 144.6 (C-11) 141.5 (C-3), 134.3 (C-10), 131.8 (C-4), 131.0 (C-Ar), 130.3 (C-Ar), 129.0 (C-Ar), 127.5 (C-Ar), 116.2 (C-1'), 110.5 (C-2'), 79.5, 77.0, 76.3 (C-13, C-12, C-1), 74.9 (C-2), 45.0 (C-15), 43.2 (C-8), 36.0 (C-9), 34.2 (C-5), 25.5 (C-6), 24.9 (C-19), 24.5 (C-14), 23.3 (C16 or 17), 22.0 (C16 or C-17), 17.1 (C-7), 2.9 (C-18).

HRMS Calcd for $C_{28}H_{37}O_3$: 421.6029. Found: 421.6021. MS: 421 $(M+H)^+$, 299.

IR (film): 3541, 3064, 2931, 2864, 1712, 1446, 1311, 1267, 1105 cm^{-1}.

(1*S*,2*S*)-2-Hydroxy-1-[(6*S*)-6-methyl-6-(prop-2-en-1-yl)cyclohex-1-en-1-yl]-2-(2-methylbut-3-en-2-yl)hex-4-yn-1-yl benzoate 215b.



215b

$[\alpha]^{24}_D$: -33.2 (*c* 1.2, CH_2Cl_2).

^{1}H NMR (δ_H): 8.00 (d, 2H, *J* = 7.7 Hz, H-Ar), 7.55 (t, 1H, *J* = 7.7 Hz, H-Ar), 7.44 (t, 2H, *J* = 7.7 Hz, H-Ar), 6.39 (t, 1H, *J* = 4.0 Hz, H-4), 6.09 (dd, 1H, *J* = 17.4, 10.6 Hz, H-11), 5.85 (s, 1H, H-2), 5.83-5.75 (m, 1H, H-10), 5.05-4.97 (m, 2H, H-2'), 4.97 (d, 1H, *J* = 17.6 Hz, H-1'), 4.91 (d, 1H, *J* = 10.7 Hz, H-1'), 2.88 (s, 1H, OH), 2.63 (dq, 1H, *J* = 17.0, 2.6 Hz, H-14), 2.56 (dq, 1H, *J* = 17.0, 2.6 Hz, H-14), 2.47-2.39 (m, 1H, H-9), 2.25-2.17 (m, 1H, H-9),

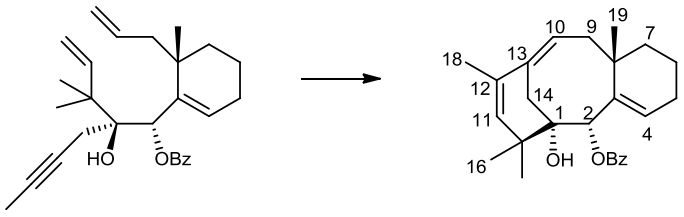
2.14-2.04 (m, 2H, H-5), 1.81 (t, 3H, *J* = 2.6 Hz, H-18), 1.66-1.51 (m, 4H, H-6, H-7), 1.24 (s, 3H, H-16 or H-17), 1.17 (s, 3H, H-16 or H-17), 1.12 (s, 3H, H-19).

^{13}C NMR (δ_C): 164.0 (C=O), 144.8 (C-11) 141.6 (C-3), 134.3 (C-10), 131.9 (C-4), 131.0 (C-Ar), 130.2 (C-Ar), 128.8 (C-Ar), 127.4 (C-Ar), 116.4 (C-1'), 110.9 (C-2'), 79.5, 77.2, 76.7 (C-13, C-12, C-1), 75.0 (C-2), 44.9 (C-15), 43.4 (C-8), 35.8 (C-9), 34.8 (C-5), 25.8 (C-6), 24.9 (C-19), 24.6 (C-14), 23.2 (C16 or 17), 22.2 (C16 or C-17), 17.0 (C-7), 2.8 (C-18).

HRMS Calcd for $C_{28}H_{37}O_3$: 421.6029. Found: 421.6021.

IR (film): 3543, 2931, 2359, 1716, 1450, 1315, 1269, 1111 cm^{-1}**.**

(1*S*,2*S*,8*S*,10*E*)-1-Hydroxy-8,12,14,14-tetramethyltricyclo[9.3.1.0{3,8}]pentadeca- 3,10,12-trien-2-yl benzoate 216.



215b **216**

To a thoroughly degassed solution of **215b** (14 mg, 33 μmol) in toluene (3 mL) was added second generation Grubbs' catalyst (1.4 mg, 1.6 μmol, 5 mol%). The mixture was stirred at reflux and monitored by TLC. After 1 h the mixture was cooled and the solvent was removed *in vacuo* and the crude mixture was purified by flash column chromatography and gave **216** as a colourless oil (diethyl ether/petroleum ether: 8 mg, 57%).

$[\alpha]^{24}_{D}$: +14.8 (*c* 0.8, $CHCl_3$).

^{1}H NMR (δ_H): 8.00 (d, 2H, *J* = 7.8 Hz, H-Ar), 7.56 (t, 1H, *J* = 7.8 Hz, H-Ar), 7.45 (t, 2H, *J* = 7.8 Hz, H-Ar), 6.12 (m, 1H, H-4), 5.77 (t, 1H, *J* = 8.0 Hz, H-10), 5.47 (s, 1H, H-2), 4.97 (m, 1H, H-11), 2.84 (dd, 1H, *J* = 12.7, 8.4 Hz, H-9), 2.66 (d, 1H, *J* = 11.4 Hz, H-14), 2.33

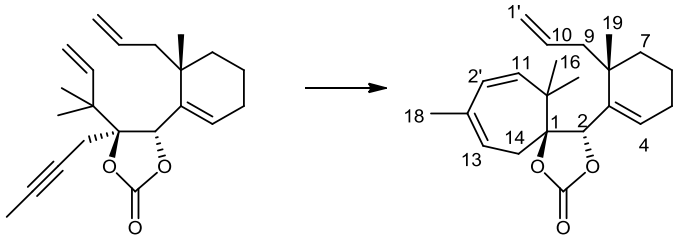
(s, 1H, OH), 2.29 (d, 1H, *J* = 11.6 Hz, H-14), 2.18 (dt, 1H, *J* = 18.4, 5.3 Hz, H-5), 2.05-1.93 (m, 1H, H-5), 1.80 (s, 3H, H-18), 1.71 (dd, 1H, *J* = 12.9, 7.5 Hz, H-9), 1.63-1.57 (m, 2H, H-6, H-7), 1.46-1.35 (m, 2H, H-6, H-7), 1.19 (s, 3H, H-16 or H-17), 1.13 (s, 3H, H-16 or H-17), 0.89 (s, 3H, H-19).

^{13}C NMR (δ_C): 163.4 (C=O), 143.1 (C-11), 138.0 (C-3), 132.8 (C-13), 132.0 (C-10), 130.8 (C-4), 130.0 (C-Ar), 128.5 (C-Ar), 127.9 (C-Ar), 127.6 (C-Ar), 121.5 (C-12), 78.1 (C-1), 72.0 (C-2), 42.2 (C-15), 42.0 (C-8), 40.8 (C-7), 38.3 (C-9), 33.5 (C-14), 26.5 (C-19), 25.8 (C-5), 25.0 (C-16 or C-17), 23.6 (C16 or C-17), 17.5 (C-6), 16.9 (C-18).

HRMS Calcd for $C_{26}H_{32}O_3$: 392.2351. Found: 392.2348.

IR (film): 3542, 2927, 1718, 1451, 1320, 1266, 1113, 1068 cm^{-1}**.**

(4*S*,5*S*)-6,6,9-Trimethyl-4-[(6S)-6-methyl-6-(prop-2-en-1-yl)cyclohex-1-en-1-yl]-1,3-dioxaspiro[4.6]undeca-7,9-dien-2-one 221.



179b **221**

To a solution of **179b** (33.0 mg, 96.4 mmol) in methanol (2 mL) with 2 drops of water was added $AuClPPh_3$ (2.4 mg, 4.8 µmol, 5 mol%) and $AgSbF_6$ (3.3 mg, 9.6 µmol, 10 mol%). The reaction was stirred for 30 min at room temperature before being quenched with water. The aqueous layer was extracted with diethyl ether and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography (diethyl ether/petroleum ether: 5/95) gave the product **221** as a yellow oil (14.0 mg, 40%).

$[\alpha]^{24}_{D}$: -54.9 (*c* 1.0, $CHCl_3$).

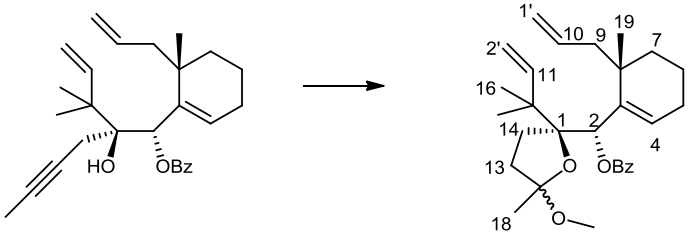
^{1}H NMR (δ_H): 6.13 (br d, 1H, *J* = 15.8 Hz, H-11), 6.02 (t, 1H, *J* = 4.0 Hz, H-4), 5.77-5.66 (m, 1H, H-10), 5.65-5.55 (dq, 1H, *J* = 15.6, 6.7 Hz, H-2'), 5.38 (br s, 1H, H-13), 5.14 (br s, 1H, H-2), 4.98 (m, 2H, H-1'), 2.85-2.59 (m, 2H, H-14), 2.15-2.06 (m, 3H, H-5, H-9), 2.05-1.98 (m, 1H, H-9), 1.78 (d, 3H, *J* = 6.6 Hz, H-18), 1.69-1.56 (m, 4H, H-6, H-7), 1.19 (s, 3H, H-19), 1.11 (2s, 6H, H-16, H-17).

^{13}C NMR (δ_C): 154.2 (C=O), 140.9 (C-11), 135.5 (C-3), 134.1 (C-10), 132.7 (C-12), 129.4 (C-13), 126.9 (C-4), 126.3 (C-2'), 117.3 (C-1'), 95.6 (C-1), 75.0 (C-2), 50.7 (C-8), 43.2 (C-9), 39.2 (C-7), 36.0 (C-15), 33.9 (C-14), 24.8 (C-5), 24.0 (C-18), 23.9 (C-16 or C-17), 19.1 (C16 or C-17), 17.3 (C-19), 17.2 (C-6).

HRMS Calcd for $C_{22}H_{30}O_3$: 342.2195. Found: 342.2192.

IR (film): 3020, 2935, 1785, 1447, 1331, 1215, 1175, 1052 cm^{-1}**.**

(*S*)-[(2*S*)-5*RS*-Methoxy-5-methyl-2-(2-methylbut-3-en-2-yl)oxolan-2-yl][(6*S*)-6-methyl-6-(prop-2-en-1-yl)cyclohex-1-en-1-yl]methyl Benzoate 222.



215b **222**

To a solution of **215b** (13 mg, 30 µmol) in methanol (2 mL) with 2 drops of water was added $AuClPPh_3$ (2.4 mg, 4.8 µmol, 5 mol%) and $AgSbF_6$ (3.3 mg, 9.6 µmol, 10 mol%). The reaction was stirred for 30 min at room temperature before being quenched with water. The aqueous layer was extracted with diethyl ether and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography (diethyl ether/petroleum ether: 5/95) gave the hemiketal **222** as a mixture of 1:1.5 diastereomers as a yellow oil (1:1.5/ minor (md): major (Md)) (7 mg, 53%).

^{1}H NMR (δ_H): 8.07 (dd, 2H, *J* = 8.1 Hz, H-Ar (md)), 8.07 (dd, 2H, *J* = 7.8 Hz, H-Ar (Md)), 7.55-7.50 (m, 2H, H-Ar (Md, md)), 7.41-7.40 (m, 4H, H-Ar (Md, md)), 6.24-6.15 (m, 2H, H-4 (Md), H-11 (Md)), 6.12 (dd, 1H, *J* = 17.6, 10.8 Hz, H-11 (md)), 6.05 (t, 1H, *J* = 3.9 Hz, H-4 (md)), 5.89-5.78 (m, 3H, H-10 (Md, md), H-2 (md)), 5.70 (s, 1H, H-2 (Md)), 5.07-4.99 (m, 4H, H-2' (Md, md)), 4.98-4.89 (m, 2H, H-1' (md)), 4.82 (d, 1H, *J* = 17.7 Hz, H-1' (Md)), 4.67 (d, 1H, *J* = 10.5 Hz, H-1' (Md)), 3.32 (s, 3H, OMe (Md)), 3.22 (s, 3H, OMe (md)), 2.66-2.59 (m, 1H, H-14 (md)), 2.57-2.51 (m, 1H, H-14 (Md)), 2.28-2.21 (m, 2H, H-14, H-13 (md)), 2.17-2.11 (m, 2H, H-14, H-13 (Md)), 2.06-2.00 (m, 5H, H-13, H-9, H-5 (md)), 2.00-1.94 (m, 5H, H-13, H-9, H-5, (Md)), 1.61-1.57 (m, 4H, H-6, H-7 (Md), (md)), 1.55 (s, 6H, H-18, H-19, (md)), 1.55-1.52 (m, 4H, H-6, H-7 (Md), (md)), 1.51 (s, 6H, H-18, H-19, (Md)), 1.16 (s, 6H, H-16, H-17 (md)), 1.12 (d, 6H, H-16, H-17 (Md)).

^{13}C NMR (δ_C): 166.8 (C=O), 166.4 (C=O), 147.0 (C-11), 146.3 (C-11), 143.9 (C-3), 135.7 (C-10), 135.2 (C-10), 132.6 (C-4), 132.5 (C-4), 131.7 (C-Ar), 130.5 (C-Ar), 129.8 (C-Ar), 129.7 (C-Ar), 128.3 (C-Ar), 117.5 (C-1'), 117.1 (C-1'), 109.1 (C-2'), 94.4 (C-12), 93.8 (C-12), 79.6 (C-1), 77.7 (C-1), 74.0 (C-2), 73.5 (C-2), 50.3 (OMe), 49.5 (OMe), 45.2 (C-8), 43.9 (C-8), 39.3 (C-9), 37.1 (C-15), 37.0 (C-15), 35.6 (C-13), 31.5 (C-5), 31.4 (C-5), 30.1 (C-7), 30.0 (C-7), 25.9 (C-19), 25.7 (C-19), 25.5 (C-14), 25.4 (C-14), 25.2 (C-18), 24.3 (C-18), 24.0 (C-16 or C-17), 23.0 (C-16 or C-17), 22.1 (C-16 or C-17), 18.0 (C-6), 17.9 (C-6).

HRMS Calcd for $C_{29}H_{40}O_4Na$: 475.2819. Found: 475.2810.

IR (film): 2916, 2849, 1715, 1461, 1376, 1315, 1217, 1176, 1097, 1068 cm^{-1}**.**

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