Studies Towards the Synthesis of the Palmerolides

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Supervisor: Dr. G. J. Florence
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I, Scott Eadie, hereby certify that this thesis, which is approximately 34000 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

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Date …………. signature of candidate ………………………

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Dedicated to my parents
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Abstract

In 2006, Baker reported the isolation of palmerolide A (14), a polyketide derived marine macrolide, from the Antarctic tunicate *Synoicum adareanum* collected in the shallow waters surrounding Anvers Island. This unique macrolide displayed potent levels of cytotoxic activity in the human melanoma cell lines (UACC-62, LC\textsubscript{50} = 18 nM and M14 LC\textsubscript{50} = 76 nM), while also inhibiting V-ATPase with an IC\textsubscript{50} of 2 nM. There have been eight further palmerolides isolated from *Synoicum adareanum*, which have been shown to possess cytotoxicity activity. The synthetic route devised (Scheme A), was a convergent approach synthesising palmerolide A (14) from three key subunits (91, 92 and 93), which could be coupled via a Horner-Wadsworth Emmons to give the C1-C14 subunit 94 followed by a Julia-Kocienski olefination and formation of the macrocycle 90. This approach offers both flexibility and convergence as alterations to the subunits would give access to other members of the palmerolide family and their analogues; as using the C15-C23 subunit (95) instead of the C15-C24 subunit (93) would give rise to palmerolide E (18). This thesis details the synthesis of these key fragments and efforts towards their coupling. The C1-C14 subunit synthesis is detailed in chapter 2; chapter 3 and 4 detail the synthesis of the C15-C23 subunit (95) for palmerolide E (18) and the C15-C24 subunit (94) for palmerolide A (14) respectively. Chapter 5 describes the unsuccessful Julia-Kocienski olefination between the C1-C14 subunit (94) and the C15-C24 subunit (95)
Scheme A
Compound Numbering

All compounds intended towards the total synthesis of palmerolide A (14) will be numbered according to the carbon chain of the natural product. This numbering is given on the structure.

The naming of the compounds in the experimental chapter uses IUPAC convention.
List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>α</td>
<td>alpha</td>
</tr>
<tr>
<td>p-ABSA</td>
<td>4-acetamidobenzenesulfonyl azide</td>
</tr>
<tr>
<td>Ac</td>
<td>acetate</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
</tr>
<tr>
<td>ATPH</td>
<td>aluminium tris-(2,6-diphenylphenoxide)</td>
</tr>
<tr>
<td>β</td>
<td>beta</td>
</tr>
<tr>
<td>BAIB</td>
<td>[bis(acetoxy)iodo]benzene</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane dimer</td>
</tr>
<tr>
<td>calc.</td>
<td>calculated</td>
</tr>
<tr>
<td>CSA</td>
<td>camphor sulfonic acid</td>
</tr>
<tr>
<td>C</td>
<td>carbon</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic</td>
</tr>
<tr>
<td>CBS</td>
<td>Corey-Bakshi-Shibata</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>DIP-Cl</td>
<td>B-chlorodiisopinocampheylborane</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin periodinane</td>
</tr>
<tr>
<td>d.r.</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DDQ</td>
<td>2, 3-dichloro-5, 6-dicyanobenzoquinone</td>
</tr>
<tr>
<td>(DHQ)$_2$PHAL</td>
<td>bis(dihydroquinino)phthalazine</td>
</tr>
<tr>
<td>DHQD</td>
<td>dihydroquinidine</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutyl aluminium hydride</td>
</tr>
<tr>
<td>DIAD</td>
<td>diisopropylazodicarboxylate</td>
</tr>
<tr>
<td>DIPEA</td>
<td>diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
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</table>
eq. equivalent
Et ethyl
γ gamma
g gram
HMDS hexamethyldisilazane
Hz hertz
HRMS high resolution mass spectrometry
h hours
IC₅₀ concentration required for 50% inhibition
ImH imidazole
IR infrared
LDA lithium diisopropylamide
L Litres
Mes mesityl
MeOH methanol
MOM methoxymethyl
MTPA α-methoxy-α-trifluoromethylphenylacetic acid
Me methyl
m milli; multiplet
mL millilitre
min minutes
M molarity
mol mole
μ micro
n normal
NMR nuclear magnetic resonance
Nu unspecified nucleophile
p para
ppm parts per million
pH -log[H⁺]
Ph phenyl
PTSH 1-phenyl-1H-tetrazole-5-thiol
PMB para-methoxybenzyl
i-Pr iso-propyl
H  proton
PPTS  pyridinium \( p \)-toluenesulfonate
pin  pinacol
RCM  ring closing metathesis
R  unspecified alkyl group
R_f  thin layer chromatography retention factor
s  singlet
\([\alpha]\)  specific rotation
\(t\)  tert (tertiary)
TBS  tert-butylidemethylsilyl
TBAF  tetrabutylammonium fluoride
THF  tetrahydrofuran
TEMPO  2, 2, 6, 6-tetramethyl-1-piperidinylxoy
tlc  thin layer chromatography
Ts  \( para \)-toluensulfonyl
TCA  trichloroacetimidate
TCCN  trichloroacetyl isocyanate
TES  triethyl silyl
TIPS  triisopropylsilyl
Tf  triflate
TMS  trimethylsilyl
\(t\)  triplet
UV  ultraviolet
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Introduction

1.1: Natural products in drug discovery

Nature has proven to be an extensive resource of structurally diverse secondary metabolites that can be isolated from both terrestrial and marine sources. Many of these secondary metabolites possess important functions directed to their host organism’s continual survival by acting as a defence against predators, parasites, diseases and also facilitating their reproductive processes. Due to this, secondary metabolites often exhibit unique and potent biological properties such as antibiotic, antifungal, cytotoxic and pesticidal activity, which can provide an extremely large library of potential lead agents for both pharmaceutical and agrochemical development.

The use of natural products in the search for biologically active compounds is a powerful method for the identification of lead compounds in the drug discovery process. To date 60–70% of pharmaceuticals in clinical use have natural product origins, from the pain killing drugs of morphine (1) and aspirin (2) to various anticancer agents of which 47% originate from natural products, with one of the most well known being Taxol (3) (Figure 1.1), which was isolated from the bark of the Pacific yew tree, *Taxus brevifolia*.3,4,5
Figure 1.1: Structures of morphine (1), aspirin (2) and Taxol (3).

Biologically active natural products can arise from many different sources. One area playing an ever-increasing role are compounds isolated from marine extracts.\textsuperscript{6} Two of the first notable discoveries from marine extracts were spongouridine (4) and spongothymidine (5), isolated by Bergmann from the Caribbean sponge Cryptotheca crypta in the early 1950s (Figure 1.2).\textsuperscript{7} These showed that for a nucleoside to have biological activity it did not require ribose or deoxyribose as the sugar unit and the base also could contain differing heterocycles.

Figure 1.2: Structure of spongouridine (4) and spongothymidine (5).

Due to the low abundance of many of these natural products, extraction from natural sources is often not practical, and as a result total synthesis remains the most viable option. Synthesis of natural products began in 1828 with the synthesis of urea (6) by Wöhler.\textsuperscript{8} Total synthesis has developed since then, through the continual development of new technologies and techniques for the
determination of compound structures and with the development of new reaction methodology. Now it is possible to synthesize highly complex molecules with many different stereocentres and functional groups such as dictyostatin (7) and erythronolide B (8, Figure 1.3).

Figure 1.3: Structure of urea (6), dictyostatin (7) and erythronolide B (8)

1.2: Classification of marine macrolides

Polyketides are secondary metabolites, which often display anticancer, antibiotic, antifungal, immunosuppressant and other biological properties. They have a generic 1,3–hydroxyl motif containing alternating carbonyl and methylene groups and are commonly biosynthesized via decarboxylative condensation of malonyl-CoA extender units via a Claisen condensation. The polyketide chains are assembled by multi-domain polyketide synthase enzymes (PKS’s).
One of the most prominent classes of polyketides are the macrolides. Macrolides are a class of compounds characterized by a macrocyclic lactone ring acting as a conformational constraint, which can be adorned with many stereocentres and a range of functional groups. These compounds can be isolated from a variety of sources and possess a diverse range of biological properties. Many marine macrolides, such as the spongistatins (9-13, Figure 1.4) have been shown to be potent against cell growth in numerous cancer cell lines, which has led to their development as possible lead structures in the discovery of new anticancer agents.

![Figure 1.4: Structure of spongistatins 1-6 (9-13)](image)

The study of how these macrolides interact with their corresponding protein targets could help provide many new opportunities in finding novel cancer treatments. As there is a low natural abundance of these macrolides, large scale harvesting is neither practical due to the associated financial costs nor ecologically acceptable. Therefore practical synthetic routes, in principal, have the most potential for supplying sufficient quantities of natural products to further investigate their activity and mode of interaction with their corresponding proteins. Due to their complex structures, synthesis still
presents a formidable challenge; in some cases the structure possesses in excess of thirty stereocentres, they can contain many di- or tri- substituted double bonds, and unusual structural motifs.

Total synthesis is also important for confirming, or in some cases determining the absolute and relative configuration of the target natural product. The common spectroscopic and crystallographic methods used to determine natural product structure may not have been able to fully assign the molecule or may have mis-assigned the relative and absolute configuration. The synthetic strategy devised must also be able to deliver sufficient quantities of pure material to enable further preclinical testing and biological evaluation, while also being flexible enough to allow access to structural analogues.

1.3: The palmerolides

1.3.1: Isolation of the palmerolides

Antarctica is one of the least accessible marine environments, due to its extreme isolation and severe climate. Predation and competition are the dominant forces that determine the species composition and distribution of such an ecosystem. Antarctica is home to many distinct organisms that produce novel secondary metabolites, possessing unique molecular structures with distinctive biological properties, essential for survival in this harsh environment. Its seas sustain a largely unexplored indigenous population of fauna and algae, due to the Antarctic polar front isolating this marine
ecosystem, for over 20 million years.\(^\text{15}\) During this time the Antarctic biota has evolved in a relatively stable system without the influence from other habitats. Due to this isolation, the Antarctic seas offer a unique collection of compounds, isolated from fauna that have evolved differently to organisms from more temperate climates. These species flourish in cold seas and have also developed unusual chemical defences to combat predators. Antarctic organisms are therefore of great interest in the search for novel compounds.\(^\text{16}\)

In 2006, Baker and co-workers isolated the palmerolide family from the circumpolar tunicate *Synoicum adareanum*, which is found in the shallow waters near Palmer station on Anvers Island.\(^\text{17}\) This family consists of nine polyketide-derived macrolides termed palmerolide A-H and K (14-22, Figure 1.5).\(^\text{18}\)
Figure 1.5: Palmerolide A-H and K (14-22)

Structurally each of the nine palmerolides A-H and K (14-22), are similar, each bearing a 20-membered macrolide, containing four \( E \)-olefins and four
stereocentres. Palmerolide A (14) bears an unsaturated N-acyl dienamide side chain bearing another stereocentre attached at C-19, whereas palmerolide E (18) supports a truncated C-19 enal side chain. The gross structure of palmerolide A (14) was assigned using a number of analytical techniques, including MS, and NMR spectroscopy.

Palmerolide D-G (17-22) are all presumed to have the same relative and absolute configuration as palmerolide A (14), assuming a common biogenesis. Palmerolide D (17) has been shown to bear an extended enamide side chain with the same macrolide core as palmerolide A, whereas palmerolide F (19) is a tautomer of palmerolide A (14) bearing the C29-C30 olefin at the C30-C32 terminus. Palmerolide G (20) is a geometric isomer of palmerolide A (14) with the (Z)-C23-C24 olefin. Palmerolide B (15) and H (21) both contain a carbamate moiety at C7 and a sulfonate at C11. Palmerolide K (22) contains the same structural variations as palmerolide C (16) in the macrolide core with hydroxyls at C8 and C9 and the carbamate at C10, but like palmerolide E (18) it lacks the enamide side chain while supporting a C19 enal side chain.

1.3.2: Structure of palmerolide A

Baker and co-workers attempted to establish the configuration of the C7 and C10 stereocentres through Mosher ester analysis,19 where the (R)- and (S)-MTPA esters of palmerolide A showed both the C7 and C10 to convey the (R) configuration which was later shown to be incorrect. The C11 stereocentre was then assigned based on the C10 Mosher ester analysis. This was achieved
using $J$-coupling based conformational analysis of the C10/C11 coupling constants which showed a gauche relationship between H10 and H11 based on the small $^3J_{HH}$ and large $^2J_{CH}$ for both H10/C11 and H11/C10 relationships (Figure 1.6).\textsuperscript{20}

<table>
<thead>
<tr>
<th>$^3J_{HH}$ (Hz)</th>
<th>$^2J_{CH}$ (Hz)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C10/C11

$\begin{array}{c}
\text{O} \\
\text{H}_9 \\
\text{C}_9 \\
\text{H}_{10} \\
\text{H}_{11} \\
\text{C}_{12} \\
\text{O} \\
\end{array}$

$\begin{array}{c}
\text{C11/H10: 5.5} \\
\text{C10/H11: 4.2} \\
\end{array}$

Figure 1.6: $J$-coupling based conformational analysis

This method, developed by Murata and co-workers, is based on heteronuclear spin-coupling constants ($^{2,3}J_{CH}$) as well as homonuclear ($^3J_{HH}$) coupling constants (Figure 1.7).\textsuperscript{20} In systems with conformational flexibility, the observed coupling constants exist as a weighted average for each conformer, so the most favourable conformer will govern the result. The dihedral angle dependence of proton to proton coupling constants ($^3J_{HH}$) and the Karplus relationship is frequently used to aid conformational analysis. This alone is inadequate for confident relative stereochemical determination, as two gauche rotamers cannot be distinguished, thus determination of the $^{2,3}J_{CH}$ coupling constants is necessary for stereochemical assignment.
The remote C19 and C20 stereocentres were assigned on the basis of nOe and ROESY correlation experiments, which was achievable due to the constraints placed in the macrolide by the four olefins.\textsuperscript{17}

The relative and absolute configuration of the five stereocentres, which was proposed by Baker and co-workers, was subsequently proved to be incorrect by De Brabander in 2007 (Figure 1.8).\textsuperscript{21} Total synthesis of the proposed diastereoisomer (23) showed that the synthetic compound’s \textsuperscript{1}H and \textsuperscript{13}C NMR spectra did not match the natural isolate. De Brabander then synthesised the diastereoisomer with inversion of the C19 and C20 stereocentres, which he believed to be the most tenuous assignments to give (24). This isomer was shown to have an identical NMR with the natural isolate but was found to be antipodal as the optical rotation and circular dichroism were essentially opposite, confirming the relative and absolute configuration as shown in (14).

Figure 1.7: Coupling constants size dependence on dihedral angle
The structural mis-assignment of the C7, C10 and C11 stereocentres by Baker and co-workers occurred due to a simple but common mistake in the Mosher ester analysis. In using Mosher acid chlorides in forming the MTPA ester, which under Cahn-Ingold priority gives a reversal of assignment in stereochemistry, so the (R)-MTPA acid chloride (25) gives the (S)-MTPA ester (26, Figure 1.9). Unfortunately, Baker and co-workers did not notice this not uncommon oversight and the assignments of the C7 and C10 stereocentres were erroneously reported as (R) instead of (S). This had a knock on effect throughout the structure, as the assignment of the C11 stereocentre was also reported incorrectly as J-based conformational analysis between the C10-C11 stereocentres was used to assign the relative stereochemistry. Therefore since the C10 stereocentre was mis-assigned as (R), the C11 was also mis-assigned as (R) when both should have been (S).
1.3.3: Structure of palmerolide C

Palmerolide C (16) contains significant structural variations within the macrolide core compared with palmerolide A (14). Until recently the absolute and relative configuration of the C8, C9 and C10 stereocentres were unknown but after work carried out within our group and in collaboration with Professor Baker, the macrolide was shown to have the $8R$, $9S$ and $10S$ configuration. This was achieved by comparison of the synthetic degradation fragments 27-30 with the natural equivalent (Figure 1.10).

![Figure 1.10: Degradation fragments 27-30 of palmerolide C (16)]
1.3.4: Malignant melanoma

Cancer is often thought of as a single disease, with each class having the same mechanism of action and behaving in the same manner, which is a common misconception. Instead cancer is the name given to a range of specific illnesses caused by the body’s cells displaying unregulated growth, which invade and destroy healthy tissue including organs. There are over 200 different types of cancer, which can occur from different causes and have differing symptoms, requiring different therapeutic strategies.

One of the most common cancers is skin cancer of which there are two main types, malignant melanoma and non-melanoma skin cancer. Malignant melanoma is the less common of the two but it is significantly more serious. Over the last thirty years malignant melanoma incidence rates have more than quadrupled, rising faster than any of the other more common cancers in both males and females (Graph 1.1). In 2008 approximately 12,000 new cases of malignant melanoma were diagnosed in the UK, and more than 98,800 non-melanoma skin cancers. In the same year around 2,560 people died from skin cancer, with 2,070 of these deaths from malignant melanoma and only around 500 from non-melanoma skin cancer.
The rates of malignant melanoma have been rising over the past thirty years, but due to early detection so are the survival rates which are amongst the highest for any cancer. The latest survival rates for malignant melanoma show that 81% of men and 90% of women survive the disease. However if it is not detected early enough the survival rates rapidly decrease. Patients with early stage melanoma (stage 0, I and IIA), when the tumours are thin and have no nodal spread, can be treated by surgery alone and have survival rates in excess of 95%. As tumor depth increases it becomes increasingly difficult to remove the entire tumor through surgery. Therefore the survival rates decrease, as the risk of developing nodal metastasis relates directly to tumor thickness. Patients with stage IIB and above melanoma are at risk of recurrence as there are currently no effective chemotherapies available.
Consequently further research into the understanding of this disease is required, as the process of melanoma pathogenesis is not fully understood. However a number of key genes and pathways have been implanted with the disease. It has been shown that the melanocortin receptor gene, *MC1R*, influences skin pigmentation, and polymorphisms are common within this gene. These variants have been linked to an increased risk of melanoma and also there is some evidence that polymorphisms in the oculocutaneous albinism gene, *OCA2*, may also increase risk.

**1.3.5: Bioactivity of the palmerolides**

Of the nine palmerolides isolated, A, C, and E (14, 16, 18) exhibited the most interesting biological profiles. Initial screening of palmerolide A (14) in the NCI 60 cell line panel revealed inhibition of human melanoma cell lines (UACC-62, LC<sub>50</sub> = 18 nM and M14 LC<sub>50</sub> = 76 nM) as well as activity against renal and colon cancer cell lines. Further screening of palmerolide A (14) revealed that it also inhibited V-ATPase (IC<sub>50</sub> = 2 nM), although the specific binding site within the V-ATPase protein is currently unknown.

The V-ATPase comprises a class of enzymes that are widely distributed throughout eukaryotes. These enzymes occur in many tissues of multicellular organisms. V-ATPases perform many diverse functions within eukaryotic organisms, such as receptor mediated endocytosis, intracellular targeting of lysosomal enzymes, protein processing and degradation and transport of small molecules. V-ATPases are proton-translocating pumps involved in the
regulation of pH for eukaryotic cells and are found in many intracellular compartments. The pumps work by transferring protons out of the cytoplasm into the organelle, where the hydrolysis of adenosine triphosphate (ATP) creates an electrochemical potential across the membrane that drives the transport of ions and solutes. It has been shown that V-ATPases are involved in the onset of diseases such as osteoporosis, diabetes, pancreatitis and melanoma.\(^\text{29}\)

Palmerolide A (14) has additionally demonstrated significant in vivo activity in the NCI’s hollow fibre assay. The NCI hollow fiber assay is a standard bioassay used by the National Cancer Institute to determine in vivo cytotoxicity of anticancer agents.\(^\text{30}\) The hollow fibre assay has established as a very efficient bioassay that can provide quantitative information of drug efficacy with minimum expenditures of time and materials. Palmerolide A (14) tested negative in COMPARE pattern recognition analyses during the NCI hollow fibre assay,\(^\text{18a}\) suggesting a novel mode of action as its mean-graph profiles did not reveal any significant correlations to the profiles of known antitumor compounds contained in the NCI’s standard agent database.\(^\text{30a}\)

Palmerolide E (18) was shown to possess similar activity to palmerolide A (14).\(^\text{18a}\) This information coupled with the relative instability of enamides at bodily pH suggests that in vivo palmerolide A (14) may be acting as a prodrug of the one carbon less palmerolide E (18). The similarity in activity between palmerolide A (14) and E (18) is believed to occur due to the C23 aldehyde in
palmerolide E’s acting as the unmasked enamide, suggesting the aldehyde performs a major role in the activity of these molecules. Palmerolide C (16) was also found (in the NCI 60 cell line panel) to inhibit human melanoma cell line UACC-62 with an LC$_{50}$ = 76 nM, which suggests the macrolide core is important to the activity.$^{18a}$

1.4: Salicylihalamide

In 1997, Boyd and co-workers reported the isolation of salicylihalamide A (31) and salicylihalamide B (32) from the marine sponge Haliclona, collected off the southwest Australian coast (Figure 1.11).$^{31}$ The structure was assigned on the basis of NMR and mass spectroscopy and the absolute stereochemistry was assigned by Mosher esters analysis. The salicylihalamides represent a novel class of macrocyclic benzolactones incorporating salicylic acid, and decorated with a highly unsaturated N-acyl enamine side chain.

Once again due to the failure to take into account the change of priority by the conversion of the Mosher’s acid chloride to the MTPA ester, the stereocentres at C12, C13 and C15 were assigned incorrectly.$^{32}$ As a result, the configuration of C13 is inverted to ($R$) and the biologically active forms are assigned as ($-$)-salicylihalamide A (33) and ($-$)-salicylihalamide B (34).
Screening of (-)-salicylihalamide A (33) showed some promising hits and had a unique cytotoxicity profile in the NCI 60-cell line human tumour screen. The mean GI<sub>50</sub> concentration was 15 nM across the NCI 60 cell line panel, with a sensitivity range of $\leq 10^3$. The melanoma cell lines were shown to have the highest average tumour-type subpanel sensitivity (GI<sub>50</sub> = 7 nM, TGI = 60 nM) and (-)-salicylihalamide A (33) has also been identified as a target for the V-ATPase enzyme (IC<sub>50</sub> < 1.0 nM).

Structure-activity relationships (SARs) studies carried out on (-)-salicylihalamide A showed the side-chain analogues 35–39 all maintain the ability to inhibit V-ATPase, with similar concentrations to those of 33 (Figure 1.12). The analogues 40 and 41 without the enamide suggest that the enamide side chain is irreversibly binding to the protein target, as the activities of these molecules are both dramatically reduced in in vitro testing. Smith and Zheng tested analogues 42, missing the C12 methyl and C13 hydroxyl, and 43 missing the C9-10 olefin, C12 methyl and C13 hydroxyl, which both retained some activity at reduced levels from 33. From these
results it was hypothesised that the structure of the macrolide is important for activity, but not decisive.\textsuperscript{33b/c}

![Structural analogues](image)

Figure 1.12: Structural analogues 35–43 of (-)-salicylihalamide A

Unlike other V-ATPase inhibitors (-)-salicylihalamide A (33) is able to discriminate between mammalian and non-mammalian V-ATPase, suggesting that it has a different binding site from classical V-ATPase inhibitors, such as bafilomycin A\textsubscript{1} (44, Figure 1.13).\textsuperscript{34}

![Structure of bafilomycin A\textsubscript{1}](image)

Figure 1.13: Structure of bafilomycin A\textsubscript{1} (44).

With both (-)-salicylihalamide A (33) and palmerolide A (14) having a macrolide core bearing an enamide side chain it is not inconceivable that they may share a similar mode of action. This is due to the similar \textit{N}-acyl enamide
side chain, which in the case for the former is necessary for the irreversible binding to the protein target. It is hypothesised that salicylihalamide inhibits V-ATPase via the enamide side chain forming a covalent bond with a lysine residue on the enzyme (Figure 1.14).\textsuperscript{34a,35} This is proposed to occur via the formation of an electrophilic N-acyliminium ion generated from the N-acyl enamide under acidic conditions, followed by attack of the active lysine residue. The adduct then fragments into a protein-imine complex with release of the amide side chain. Subsequent hydrolysis of this protein-imine complex could generate the aldehyde as found in palmerolide E (18).

![Figure 1.14: Interaction of enamide side chain with protein](image)

**1.5: Previous synthesis of palmerolide A**

To date there have been three total synthesis of palmerolide A, the first being completed in 2007 by De Brabander, followed by Nicolaou and Chen shortly after, then by Hall in 2009.\textsuperscript{21,36} There have also been several formal and partial syntheses completed.\textsuperscript{37}
1.5.1: De Brabander’s synthesis of palmerolide A

In 2007 De Brabander and co-workers synthesized the initially reported structure of palmerolide A (23) and the antipode (24) establishing the absolute and relative configuration. Their approach to assemble palmerolide A relied on a Suzuki cross-coupling reaction of vinyl iodide 45 and borane 46 to form the C15-16 bond, followed by esterification with enoic acid 47 (Scheme 1.1).\textsuperscript{21} Macrocyclization was to be achieved \textit{via} a Horner-Wadsworth Emmons olefination, and installation of the enamide side chain \textit{via} a Curtius rearrangement with trapping of the isocyanate with 2-methyl propenylmagnesium bromide to give palmerolide A (23).

![Scheme 1.1: De Brabander’s retrosynthesis of palmerolide A (23)](image)

In the assembly of 23, Suzuki coupling of vinyl iodide 48 and vinyl boronate 49 using catalytic palladium (0) provided diene 50 (Scheme 1.2).\textsuperscript{38} The diene was esterified with carboxylic acid 47 under Yamaguchi conditions,\textsuperscript{39} which after removal of the TES protecting groups gave diol 51. Selective oxidation of the primary alcohol 51 followed by an intramolecular Horner-Wadsworth Emmons macrocyclization and subsequent silyl protection gave macrolactone.
52. CBS reduction of the ketone introduced the C7 stereocentre,\textsuperscript{40} which after TBS protection gave 53. Ester hydrolysis of the C25-ester allowed the formation of acyl azide 54. Heating of acyl azide 54 promoted the Curtius rearrangement and treatment of the intermediate with 2-methyl propenylmagnesium bromide introduced the enamide side chain with high levels of efficiency to give 55. This allowed the introduction of the carbamate, which was followed by deprotection using TBAF to afford palmerolide A (23). The synthesis of the proposed structure of palmerolide A (23) was completed in a total of thirty-three steps, with a longest linear sequence of twenty-three steps with a 2.9\% yield.
Scheme 1.2: Assembly of palmerolide A (23)
1.5.2: Nicolaou and Chen’s synthesis of palmerolide A

Shortly after De Brabander completed his synthesis, Nicolaou and Chen completed their synthesis of the proposed structure of palmerolide A (23), and subsequently reported in 2008 the synthesis of the natural palmerolide A (14). They envisioned that they could assemble palmerolide A (14) from three fragments 56, 57 and 58 via a Stille coupling reaction to form the C15-16, esterification and a ring closing metathesis (Scheme 1.3). \(^{36a,b}\)

Scheme 1.3: Nicolaou and Chen’s retrosynthesis of palmerolide A (14)

The coupling of the C15-16 bond was achieved via Stille coupling between vinyl iodide 57 and vinyl stannane 59,\(^{41}\) which provided the tetraene 60 (Scheme 1.4). The carboxylic acid 61 was esterified with the newly formed tetraene 60 under Yamaguchi conditions to give ester 62.\(^{39}\) Introduction of the vinyl iodide was achieved by desilylation and oxidation of the primary hydroxyl, followed by a Takai olefination,\(^{42}\) which after removal of the two MOM protecting groups using boron trifluoride diethyl etherate gave 63. Exposure of adduct 63 to Grubbs II catalyst led to formation of the desired macrocycle 64 and finally installation of the enamide moiety was achieved via
a Buchwald Cu (I)-mediated reaction to give palmerolide A (14). In the synthesis of palmerolide A (14) there were a total of 28 steps, with a longest linear sequence of fifteen steps with a 1.7 % yield.

Scheme 1.4: Assembly of palmerolide A (14)
1.5.3: Hall’s synthesis of palmerolide A

In 2009, Hall and co-workers synthesised palmerolide A (14) utilising their organoboron chemistry to prepare fragment 65.\textsuperscript{43} They envisaged the synthesis of palmerolide A (14) would be achieved by coupling vinyl iodide 66 with olefin 67, \textit{via} hydroboration followed by a Suzuki coupling, then macrolactonisation under Yamaguchi conditions (Scheme 1.5).\textsuperscript{36c} Fragment 67 was to be accessed from pyran 65, which would originate from an Ireland-Claisen [3,3] rearrangement on alkenyl boronate substrate 68. This strategy was to exploit a boronate substituent as a masked alcohol and provide the differentiation of the C11 hydroxyl over the C10 and C7 hydroxyls.

Scheme 1.5: Hall’s retrosynthesis of palmerolide A (14)
The synthesis of fragment 67 began with acylation of alcohol 69, followed by formation of the enolsilane to trigger the Ireland-Claisen rearrangement (Scheme 1.6), which was oxidised with retention of stereochemistry. The carboxylic acid was esterified with diazomethane to produce 70 as a single stereoisomer. From pyran 70 there was a further eight steps in order to obtain fragment 71, which was coupled with 66 via a Suzuki coupling to form the C13-14 bond giving 72. The Yamaguchi macrolactonization of 72 was achieved firstly by selective hydrolysis of the methyl ester, followed by treatment of the adduct with 2,4,6-trichlorobenzoyl chloride, DMAP and triethylamine to provide the macrolide 73. The enoate side chain was transformed into the enamide via a Curtius rearrangement, following the conditions used by De Brabander in their synthesis of palmerolide A to give 14. The synthesis was completed via nucleophilic cleavage of the PMB ether, carbamate formation and deprotection to provide palmerolide A (14), in a longest linear sequence of twenty-one steps and 0.8% overall yield.
Scheme 1.6: Assembly of palmerolide A (14)

1.6: Structural analogues of palmerolide A

In 2008 Nicolaou synthesised a catalogue of palmerolide A analogues, which were subjected to biological evaluation against an array of tumour cells.\textsuperscript{45} Initially, diastereoisomers 23, 24, 74 and 75 of palmerolide A were
synthesised by inverting the stereocentres at C19 and C20, following the route proposed in their efforts to synthesise natural palmerolide A (14, Figure 1.15).\textsuperscript{36a,b}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{diastereoisomers.png}
\caption{Diastereoisomers 23, 24, 74 and 75 of palmerolide A synthesised by Nicolaou and Chen}
\end{figure}

These compounds were tested against a panel of cancer cells using Taxol 3 and natural palmerolide A 14 as standards. Both natural and synthetic palmerolide exhibited the same potent activity against all cell lines tested, whereas the antipodal palmerolide 24 was at least 100 fold less active. Inverting the stereochemistry at the C7, C10 and C11 to give 23; C7, C10, C11 and C19 to give 74; and C7, C10, C11 and C20 to give 75, all resulted in significant loss of activity (Table 1.1).\textsuperscript{45}
Cytotoxicity of selected palmerolides against various cancer cell lines (GI_{50} in \mu M)

<table>
<thead>
<tr>
<th></th>
<th>UACC-62</th>
<th>MCF-7</th>
<th>SF268</th>
<th>NCI-H460</th>
<th>IA9</th>
<th>PTX22</th>
<th>A8</th>
</tr>
</thead>
<tbody>
<tr>
<td>3: Taxol</td>
<td>0.022 ± 0.016</td>
<td>0.006 ± 0.001</td>
<td>0.026 ± 0.011</td>
<td>0.007 ± 0.001</td>
<td>0.006 ± 0.001</td>
<td>0.079 ± 0.001</td>
<td>0.021 ± 0.015</td>
</tr>
<tr>
<td>14: natural</td>
<td>0.057 ± 0.007</td>
<td>0.040 ± 0.007</td>
<td>0.030 ± 0.012</td>
<td>0.010 ± 0.001</td>
<td>0.038 ± 0.003</td>
<td>0.066 ± 0.007</td>
<td>0.018 ± 0.003</td>
</tr>
<tr>
<td>14: synthetic</td>
<td>0.062 ± 0.001</td>
<td>0.065 ± 0.011</td>
<td>0.048 ± 0.006</td>
<td>0.017 ± 0.004</td>
<td>0.059 ± 0.001</td>
<td>0.073 ± 0.005</td>
<td>0.049 ± 0.004</td>
</tr>
<tr>
<td>24: ent</td>
<td>8.077 ± 0.194</td>
<td>6.260 ± 0.174</td>
<td>9.475 ± 0.593</td>
<td>6.589 ± 0.054</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>8.844 ± 1.301</td>
</tr>
<tr>
<td>23</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td></td>
</tr>
<tr>
<td>74</td>
<td>5.398 ± 0.362</td>
<td>5.415 ± 0.247</td>
<td>6.830 ± 0.077</td>
<td>6.108 ± 0.134</td>
<td>&gt;10</td>
<td>7.052 ± 0.474</td>
<td>8.634 ± 1.860</td>
</tr>
<tr>
<td>75</td>
<td>8.129 ± 1.187</td>
<td>5.567 ± 0.255</td>
<td>7.961 ± 0.584</td>
<td>7.028 ± 0.192</td>
<td>7.131 ± 1.143</td>
<td>5.865 ± 0.590</td>
<td>6.145 ± 0.922</td>
</tr>
</tbody>
</table>

Table 1.1: Activity of palmerolide A diastereoisomers 23, 24, 74 and 75

Analogues 76–79, shown in figure 1.16, were synthesised via a similar method to the palmerolide diastereoisomers 23, 24, 74 and 75 but without the formation of the C11 carbamate. Protection of the C10 and C11 hydroxyls gave 80.

Figure 1.16: Analogues of palmerolide A 76–80 synthesised by Nicolaou and Chen
Removing the carbamate from the C11 oxygen of palmerolide A resulted in an approximately 5-fold decrease of activity across most of the cell lines. The carbonate derivative 80 of decarbonated palmerolide 24 was also devoid of significant activity (Table 1.2).\(^{45}\)

<table>
<thead>
<tr>
<th></th>
<th>UACC-62</th>
<th>MCF-7</th>
<th>SF268</th>
<th>NCI-H460</th>
<th>IA9</th>
<th>PTX22</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>natural</td>
<td>0.057 ± 0.007</td>
<td>0.040 ± 0.007</td>
<td>0.030 ± 0.012</td>
<td>0.010 ± 0.001</td>
<td>0.038 ± 0.003</td>
<td>0.066 ± 0.007</td>
</tr>
<tr>
<td>76</td>
<td></td>
<td>8.768 ± 6.98</td>
<td>7.299 ± 0.430</td>
<td>9.638 ± 0.362</td>
<td>8.664 ± 0.494</td>
<td>&gt;10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>77</td>
<td></td>
<td>0.322 ± 0.088</td>
<td>0.200 ± 0.026</td>
<td>0.281 ± 0.118</td>
<td>0.075 ± 0.003</td>
<td>0.288 ± 0.017</td>
<td>0.627 ± 0.016</td>
</tr>
<tr>
<td>78</td>
<td></td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>79</td>
<td></td>
<td>&gt;10</td>
<td>8.257 ± 0.047</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>80</td>
<td></td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>

Table 1.2: Activity of palmerolide A analogues 76–80

The relationship between the polarity of the enamide functionality and the potency against the cell lines was then investigated. This was achieved by utilising the Buchwald copper catalysed coupling of the vinyl iodide with varying primary amides to give a selection of enamide analogues (81–86, Figure 1.17).\(^{36a,b,45}\)
Upon changing the enamide side chain, some interesting trends were shown. Exchanging the isoprene moiety in palmerolide A (14), with a methyl group 81 resulted in more than a 100-fold loss of activity, but when more polar groups were substituted such as in 82, 83 and 84 most of the activity was retained. However when the enamide side chain was converted to a nonpolar aromatic system as in 85 the compound exhibited almost a 10-fold increase in potency against several of the cells tested. When the isoprene substituent on the enamide of palmerolide A was altered to its saturated counterpart 86, its potency remained at similar levels (Table 1.3).
Cytotoxicity of selected palmerolides against various cancer cell lines (GI$_{50}$ in μM)

<table>
<thead>
<tr>
<th></th>
<th>UACC-62</th>
<th>MCF-7</th>
<th>SF268</th>
<th>NCI-H460</th>
<th>IA9</th>
<th>PTX22</th>
<th>A8</th>
</tr>
</thead>
<tbody>
<tr>
<td>14: natural</td>
<td>0.057 ± 0.007</td>
<td>0.040 ± 0.007</td>
<td>0.030 ± 0.012</td>
<td>0.010 ± 0.001</td>
<td>0.038 ± 0.003</td>
<td>0.066 ± 0.007</td>
<td>0.018 ± 0.003</td>
</tr>
<tr>
<td>81</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>7.291 ± 0.137</td>
<td>7.774 ± 1.094</td>
<td>&gt;10</td>
<td>6.700 ± 0.411</td>
</tr>
<tr>
<td>82</td>
<td>0.641 ± 0.000</td>
<td>0.755 ± 0.004</td>
<td>0.592 ± 0.007</td>
<td>0.430 ± 0.047</td>
<td>0.618 ± 0.051</td>
<td>0.741 ± 0.003</td>
<td>0.460 ± 0.042</td>
</tr>
<tr>
<td>83</td>
<td>0.735 ± 0.084</td>
<td>0.796 ± 0.166</td>
<td>0.491 ± 0.132</td>
<td>0.078 ± 0.001</td>
<td>0.378 ± 0.141</td>
<td>0.889 ± 0.029</td>
<td>0.072 ± 0.004</td>
</tr>
<tr>
<td>84</td>
<td>8.822 ± 0.083</td>
<td>7.397 ± 0.262</td>
<td>&gt;10</td>
<td>3.796 ± 0.306</td>
<td>7.944 ± 0.430</td>
<td>&gt;10</td>
<td>3.514 ± 1.379</td>
</tr>
<tr>
<td>85</td>
<td>0.009 ± 0.001</td>
<td>0.007 ± 0.000</td>
<td>0.007 ± 0.001</td>
<td>0.007 ± 0.000</td>
<td>0.009 ± 0.001</td>
<td>0.039 ± 0.002</td>
<td>0.006 ± 0.000</td>
</tr>
<tr>
<td>86</td>
<td>0.067 ± 0.000</td>
<td>0.071 ± 0.008</td>
<td>0.054 ± 0.000</td>
<td>0.061 ± 0.000</td>
<td>0.067 ± 0.002</td>
<td>0.081 ± 0.006</td>
<td>0.057 ± 0.001</td>
</tr>
</tbody>
</table>

Table 1.3: Activity of palmerolide A enamide analogues 81–86

In addition to the enamide analogues prepared, a number of macrolide analogues were prepared by varying the subunits used in the synthesis of palmerolide A. They synthesised the 20-membered macrolide without either the C7 hydroxyl 87, or C10 hydroxyl 88, but were unsuccessful in synthesising the macrolide missing both the C7 and C10 hydroxyls 89 (Figure 1.18).\(^{36a,b,45}\)

Figure 1.18: De-oxygenated analogues 87–89 synthesised by Nicolaou and Chen

---

\(^{36a,b,45}\)
It was shown that the analogue lacking the C10 hydroxyl \(87\) lost significant activity across the all cell lines tested but for \(88\) where the C7 hydroxyl was removed the potency was shown to be of comparable levels to palmerolide A (14, Table 1.4).\(^{45}\)

<table>
<thead>
<tr>
<th></th>
<th>UACC-62</th>
<th>MCF-7</th>
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</tr>
</thead>
<tbody>
<tr>
<td>14: natural</td>
<td>0.057 ± 0.007</td>
<td>0.040 ± 0.007</td>
<td>0.030 ± 0.012</td>
<td>0.010 ± 0.001</td>
<td>0.038 ± 0.003</td>
<td>0.066 ± 0.007</td>
<td>0.018 ± 0.003</td>
</tr>
<tr>
<td>87</td>
<td>6.979 ± 0.531</td>
<td>7.585 ± 0.252</td>
<td>8.764 ± 0.315</td>
<td>6.396 ± 0.106</td>
<td>7.135 ± 0.667</td>
<td>8.062 ± 0.037</td>
<td>6.691 ± 0.439</td>
</tr>
<tr>
<td>88</td>
<td>0.063 ± 0.001</td>
<td>0.074 ± 0.000</td>
<td>0.060 ± 0.004</td>
<td>0.055 ± 0.002</td>
<td>0.072 ± 0.001</td>
<td>0.076 ± 0.000</td>
<td>0.061 ± 0.013</td>
</tr>
</tbody>
</table>

Table 1.4: Activity of de-oxygenated palmerolide A analogues 87 and 88

From this data it can be concluded that the C7 hydroxyl is not essential for activity, as the potency of 88 was comparable to palmerolide A (14) in all the cell lines tested. It is shown that the C11 carbamate is needed for activity and when a non-polar aromatic substituent is appended on the enamide side chain such as 85, the potency increases.

### 1.7: Florence strategy for synthesis of the palmerolides

#### 1.7.1: Strategy for synthesis of palmerolide A

The primary objective of this project was to develop a flexible strategy for the synthesis of palmerolide A (14), in which the key subunits can be modified, allowing access to a wide range of novel analogues. The structure of palmerolide A (14) posed some interesting challenges for a synthetic
endeavour as the 20-membered macrocycle contains four stereocentres, four 
\((E)\)-olefins with a C11 carbamate group and a C19 unsaturated enamide side 
chain.

It was envisaged the most efficient way to achieve the synthesis was to devise 
a convergent approach, as it would allow the synthesis of palmerolide A (14), 
while also allowing access to other members of the palmerolide family and 
their analogues, through the alteration of the key subunits. Our strategy differs 
from previous synthesis as it has the functionality present at an early stage 
(Scheme 1.7), which has been shown to be difficult and costly to insert later 
on in the sequence.\textsuperscript{21,36} This route proposes a late stage enamide coupling \textit{via} 
a Buchwald coupling of the C24 vinyl iodide.\textsuperscript{46} The macrolide core 90 is 
dissected into three key subunits, the C1-C8 subunit 91, the C9-C14 subunit 92 and the C15-C24 subunit 93. The assembly of these subunits was to be 
achieved by coupling the C1-C8 \(\beta\)-ketophosphonate 91 with the C9-C14 aldehyde 92 \textit{via} a Horner-Wadsworth Emmons coupling to give the C1-C14 subunit 94. The C14-C15 bond would be introduced \textit{via} a Julia-Kocienski 
olefination of the elaborated C1-C14 subunit 94 and the C15-C24 sulfone 93 
followed by formation of the macrocycle 90 \textit{via} macrolactonisation.\textsuperscript{39} This 
approach offers both flexibility and high levels of convergence, as the order of 
the key bond couplings could be reversed if necessary, while all the key 
functionalities are present for the core coupling to minimise post-coupling 
operations. Through the application of this strategy it is envisaged that it will 
be possible to access palmerolide A (14) and other members of its family, 
through subtle changes in key subunits.
1.7.2: Strategy for synthesis of palmerolide E

This attractive aspect of our present approach will allow the synthesis of novel analogues through the variation of the key subunits or the enamide side chain, while also being applicable to other fragments of the palmerolide family. Palmerolide E (18) can be obtained via the route developed for palmerolide A (14), but by synthesising the alternative C15-C23 subunit 95 with a protected hydroxyl, instead of the C15-C24 vinyl iodide 94 (Scheme 1.8).
Scheme 1.8: Retrosynthesis of palmerolide E (18)
Results and Discussion

2.0: Synthesis of C1-C14 subunit

2.0.1: Retrosynthesis

Following the proposed retrosynthetic plan, the aim was to reduce the Weinreb amide 96 to its aldehyde then perform a Horner-Wadsworth Emmons reaction to couple the C1-C8 subunit (91) with the C9-C14 subunit (96), forming the desired C8-C9 (E)-olefin of C1-C14 fragment 97 (Scheme 2.1). The C7 ketone 97 was to be reduced to give the (7S)-hydroxyl, this would then be TBS-protected followed by removal of the C11 PMB-protecting group. Synthesis of the carbamate, then removal of the primary TBS-protecting group would give the C1-C14 subunit (98).

Scheme 2.1: Retrosynthesis of C1-C14 subunit 98
2.1: Synthesis of C1-C8 subunit

2.1.1: Retrosynthesis

It was envisaged that the preparation of the C1-C8 subunit 91 could be achieved using either of the retrosynthetic analysis outlined in Scheme 2.2. Starting from lactol 99, Wittig olefination would introduce the C1-C3 enoate. Oxidation of the primary alcohol 100 followed by formation of the acid chloride and addition of the lithium-anion of dimethyl methylphosphonate should furnish the requisite C1-C8 subunit 91. The alternative approach could utilize a cross metathesis reaction to introduce the C1-C3 (E)-enoate from 101. Conversion of 5-hexenoic acid 102 to the β-ketophosphonate via the acid chloride, followed by Grubbs cross metathesis with methyl acrylate would complete the synthesis of the C1-C8 subunit (91).

Scheme 2.2: Retrosynthesis of C1-C8 subunit 91
2.1.2: Synthesis of carboxylic acid 103

The initial route for the synthesis of the C1-C8 subunit 91 started with a Wittig olefination of tetrahydro-2H-pyran-2-ol 99 to introduce the C1-C3 enoate and provide ester 100. Treatment of 99 with methyl (triphenylphosphoranylidene) acetate in dichloromethane provided the ester 100 in good yield with 9 : 1, E : Z selectivity (Scheme 2.3). The resulting primary alcohol 100 was oxidised with TEMPO and BAIB in acetonitrile and water to give the carboxylic acid 103 in excellent yield.47

![Scheme 2.3: Synthesis of carboxylic acid 103](image)

A common problem with traditional methods for oxidising alcohols to carboxylic acids is that the reagents and conditions tend to be harsh. A milder method is the TEMPO oxidation, which can oxidise the alcohol to the aldehyde or the carboxylic acid depending on the solvent system used.48 In the reaction, TEMPO mediates the oxidation of the alcohol to the aldehyde, followed by regeneration using stoichiometric quantities of BAIB, so further oxidation can occur to give the carboxylic acid (Scheme 2.4).49
2.1.3: Attempted synthesis of C1-C8 subunit (91)

With the carboxylic acid 103 in hand, the acid chloride was synthesised via the reaction of 103 in dichloromethane with Ghosez reagent (104), a mild reagent for converting carboxylic acids into their corresponding acid chlorides.\textsuperscript{50} The crude acid chloride was reacted directly, without any purification, with the lithium anion of dimethyl methylphosphonate in tetrahydrofuran but unfortunately this did not form the desired β-ketophosphonate 91 and no starting acid 103 was recovered (Scheme 2.5).
2.1.4: Attempted synthesis of β-ketophosphonate 101

A similar route was also attempted with the introduction of the phosphonate to an acid chloride. TEMPO oxidation of 5-hexen-1-ol 105, in acetonitrile and water (1 : 1) gave carboxylic acid 102 in 80% yield.\(^{47}\) Carboxylic acid 102 was reacted with Ghosez reagent (104),\(^{50}\) to give the acid chloride, which was used directly in the reaction with dimethyl methylphosphonate and LiHMDS in tetrahydrofuran but again the β-ketophosphonate (101) was not formed and the starting acid 102 could not be recovered (Scheme 2.6).
2.1.5: Synthesis of β-ketophosphonate 101

Following the unsuccessful attempts to introduce the phosphonate by displacement, the C1-C8 subunit (91) synthesis was modified to have the phosphonate in place from the start of the sequence. Treatment of β-ketophosphonate 106 with sodium hydride and n-butyl lithium formed the dianion, which underwent alkylation with 4-bromobutene to afford the desired phosphonate 101 in excellent yield (Scheme 2.7).51

![Scheme 2.7: Synthesis of β-ketophosphonate 101](image)

2.1.6: Cross metathesis reaction

Cross metathesis reactions are a powerful method for forming carbon-carbon double bonds, they can tolerate many functional groups and are reactive towards a large range of olefins.52 Many metal catalysts have been developed for this purpose such as Schrock’s alkoxy imidomolybdenum complex (108),53 Grubbs I generation (109) and Grubbs II generation catalysts (107, Figure 2.1).54,55 Molybdenum catalysts are very active but they are unstable to air and are required to be prepared and used under an inert atmosphere. To combat this Grubbs and co-workers developed ruthenium alkylidenes, these catalysts are more stable and have proved to be compatible
with numerous functional groups, becoming benchmark catalysts for these transformations.

Grubbs ruthenium-based catalysts exhibit good reactivity in a variety of cross metathesis reactions. The electron rich phosphine ligands of the ruthenium metal centre in 107 and 109 increases metathesis reactivity, and the $N$-heterocyclic carbene ligand in 107 is believed to help to stabilise the ruthenium intermediate in the catalytic cycle.$^{54,55}$

With the appearance of well-defined catalysts, the mechanism of the olefin metathesis reaction was investigated thoroughly. After numerous kinetics experiments, Grubbs and co-workers were able to determine that the olefin metathesis reaction proceeds through a dissociative mechanism. The first step consists in the release of a phosphine from the catalyst (110) to provide the 14 electron species 111 (Scheme 2.8).$^{56,57}$ Ruthenium then coordinates with the olefin to give intermediate 112 which then forms metallocyclobutane 113. Retro [2+2] cycloaddition provides metal carbenoid 114 and following coordination with the second olefin gives intermediate 115, which then forms the second metallocyclobutane 116. A retro [2+2] cycloaddition provides the
cross-metathesis product 117 as well as the propagating species 118 that can re-coordinate with the olefin and re-enter the catalytic cycle.

Scheme 2.8: Dissociative mechanism for olefin cross metathesis

In its first applications, cross metathesis suffered from the fact that mixtures of products were obtained with low levels of selectivity. Indeed, a cross metathesis reaction can give six possible products not including the unreacted starting material (Scheme 2.9). This lack of selectivity had limited the utility of cross metathesis reactions in synthesis however, significant progress has been made in the recent years. Grubbs and co-workers have investigated cross-metathesis using different classes of olefins and described a general empirical model useful to predict product selectivity.\textsuperscript{58} By reacting an olefin
of high reactivity (electron rich) with an olefin of lower reactivity (electron poor), it is possible to achieve a selective cross-metathesis and to obtain products with excellent $E : Z$ ratios.

\[
\begin{align*}
R \equiv & \quad \equiv R' \\
-\text{C}_2\text{H}_4 & \\
\vdots & \\
R \equiv & \quad \equiv R' \\
R \equiv & \quad \equiv R' \\
& \quad \equiv R'
\end{align*}
\]

6 possible products

Scheme 2.9: Mixture of products in cross metathesis

**2.1.7: Synthesis of C1-C8 subunit (91) utilising cross metathesis**

Introduction of the C2-C3 ($E$)-enoate was then achieved via a cross metathesis reaction of phosphonate 101 with methyl acrylate and 1 mol\% of Grubbs II catalyst (107), which gave the C1-C8 subunit 91 in excellent yield with high levels of $E : Z$ selectivity (15 : 1, Scheme 2.10), as determined via $^1$H NMR spectroscopy.

\[
\begin{align*}
\text{Grubbs II cat. (107)} \\
\text{MeO-C} & \quad \text{(excess)} \\
\text{40 hours} & \quad 91\% \\
(E : Z = 15 : 1)
\end{align*}
\]

Scheme 2.10: Cross metathesis to synthesize C1-C8 subunit (91)

**2.1.8: Synthesis of C1-C8 subunit using catalyst 119**
The cross metathesis reaction shown in scheme 2.10 was also attempted using a similar ruthenium based catalyst developed by Prof. Steve Nolan (119, Figure 2.2) with the intention of either improving the yield or the $E : Z$ selectivity by the use of milder reaction conditions.\(^59\)

![Nolan-modified ruthenium catalyst 119](image)

Figure 2.2: Nolan-modified ruthenium catalyst 119

This reaction using catalyst 119 was completed using the same equivalents of reagents and 1 mol% of the catalyst. Initially when the reaction was left overnight at room temperature, there was 55% conversion with recovery of starting material, but when 119 was used in the same conditions as those used earlier in the Grubbs II cross metathesis, with heating under reflux for forty hours, the C1-C8 subunit 91 was produced with a yield of 79% and 10 : 1 $E : Z$ selectivity (Scheme 2.11).
Scheme 2.11: Modified cross metathesis reaction

In summary the synthesis of the C1-C8 subunit 91, was completed via an alkylation of the β-ketophosphonate 106 with 4-bromobutene, then a cross metathesis reaction of 101 using Grubbs II catalyst and methyl acrylate to give the C1-C8 subunit 91 in excellent yield and selectivity over the two steps (Scheme 2.12).

Scheme 2.12: Synthesis of C1-C8 subunit 91

With the C1-C8 subunit 91 in hand, the attention turned towards the synthesis of the C9-C14 subunit 96, so the Horner-Wadsworth Emmons reaction to form the C8-C9 olefin could be performed.
2.2: Synthesis of C9-C14 subunit

2.2.1: Retrosynthesis

It was proposed that the fully protected C9-C14 subunit 96 could be synthesised by the reaction sequence outlined in Scheme 2.13, where a Horner-Wadsworth Emmons reaction involving triethyl phosphonoacetate and the oxidized protected diol 120, would give enoate 121. Sharpless asymmetric dihydroxylation of enoate 121 would provide diol 122, which was expected to be monoprotected as its TBS-ether 123. It was anticipated that hydrogen bonding between the β-hydroxyl and ester group of diol 122 would ensure that protection would occur primarily on the α-hydroxyl group. Subsequent protection of the β-hydroxyl as its PMB-ether should provide the fully protected C9-C14 fragment 96. Formation of the Weinreb amide 96 then reduction would give the corresponding aldehyde to be used in the Horner-Wadsworth Emmons reaction with the C1-C8 subunit (91).

Scheme 2.13: Retrosynthesis of C9-C14 subunit 96
2.2.2: Synthesis of enoate 121

The synthesis of the C9-C14 subunit began from 1,4-butanediol 125, which was mono-protected as its TBS-ether 126, via careful control of the reaction equivalents, in excellent yield (Scheme 2.14). Swern oxidation gave the aldehyde, which was immediately followed by a Horner-Wadsworth Emmons reaction using the Masamune-Roush conditions, with triethyl phosphonoacetate 127, to provide enoate 121 in excellent yield over the two-step sequence with excellent $E:Z$ selectivity (30 : 1). The isomers could be separated with ease via column chromatography.

![Scheme 2.14: Synthesis of enoate 121](image)

2.2.3: Sharpless asymmetric dihydroxylation

The next stage involved a Sharpless asymmetric dihydroxylation to introduce the required syn-hydroxylation at C10-C11. Reacting AD-mix-$\alpha$ with enoate 121 and methanesulfonamide, gave the 1,2-diol 122 in excellent yield (Scheme 2.15).
Scheme 2.15: Sharpless asymmetric dihydroxylation of 122

The diastereoselectivity of this reaction is controlled by the choice of cinchona alkaloid ligand, either (DHQ)₂-PHAL (128) in AD-mix-α or (DHQD)₂-PHAL (129) in AD-mix-β (Figure 2.3).[^61^][^62^][^63^]

**Figure 2.3: Cinchona alkaloid ligands 128 and 129**

To determine which of the cinchona alkaloid ligands will give the desired stereochemical outcome the Sharpless mnemonic must be used (Scheme 2.16).[^62^][^63^] Employing AD-mix-α leads to high levels of α-facial selectivity and gives addition from below the plane, using the mnemonic, while AD-mix-β will give the opposite.
Scheme 2.16: Sharpless mnemonic for prediction of stereochemistry

When the Sharpless mnemonic is applied to the enoate 121 (Scheme 2.17), it can be seen that the ester functionality is acting as the large substituent and the side chain as the medium substituent. With the use of AD-mix-α the stereochemistry predicted is C10-(R) and C11-(S).

Scheme 2.17: Sharpless mnemonic applied for enoate 121

2.2.4: Selective protection of diol 122

With diol 122 in hand, the focus was turned to the selective protection of the α-hydroxyl. After considerable effort Murray found that reacting methyl-diol 130 with benzoyl chloride under basic conditions, using DMAP as a nucleophilic catalyst, for three hours at -78 °C, consumed all the starting
material and upon purification, 36% of the β-protected hydroxyl 131 and 49% of the α-protected hydroxyl 132 were found (Scheme 2.18).^64

Scheme 2.18: Attempted selective protection of diol 130

Further investigation of the reaction conditions found that the isolated yield could be improved to 79% by starting the reaction at -78 °C and allowing the reaction to progress at -50 °C for sixteen hours (Scheme 2.19). It is believed that the α-protected benzoate (132) forms first, as indicated by the higher yield of this product at shorter reaction times (3 h, 36%), and elevating the temperature and extending the reaction time, allows equilibration to the more thermodynamically stable β-protected benzoate (131).

Scheme 2.19: Selective benzoyl protection of diol 130

Application of this protocol to diol 122, was shown to give comparable yields under the same condition as the reaction with 130. This reaction was also
shown to work in a multigram scale where using 4.8 g of diol 122 gave the β-protected benzoate 133 in 77% yield (Scheme 2.20).

![Scheme 2.20: Selective benzoyl protection of diol 122](image)

2.2.5: Synthesis of the C9-C14 subunit (96)

The β-protected benzoate 133 was then protected as its TBS-ether via treatment of the unprotected α-hydroxyl with TBSCI and imidazole to give the orthogonally protected diol ester 134 in excellent yield. Conversion of 134 to deprotected Weinreb amide 135 occurred in excellent yield (Scheme 2.21).
Scheme 2.21: Synthesis of Weinreb amide 135

In the formation of Weinreb amide 135, the conditions are shown to also remove the benzoyl protecting group. These two transformations occur stepwise as the alkoxy group is the preferred leaving group from both tetrahedral intermediates (Scheme 2.22).

Scheme 2.22: Formation of the Weinreb amide
This left only the secondary C11-hydroxyl to be protected as its PMB-ether. Thus, treatment of alcohol 135 with PMBTCA and scandium triflate, provided the fully protected C9-C14 subunit (96) in good yield (Scheme 2.23).^65

![Scheme 2.23: PMB-protection to give the C9-C14 subunit (96)](image)

In summary the C9-C14 subunit (96) was synthesised via a Horner-Wadsworth Emmons reaction to give the enoate 121, then dihydroxylation to give diol 122. This was selectively β-protected as benzoyl ether 133 and after three further steps, gave the C9-C14 subunit (96) in 25% yield over 8 steps (Scheme 2.24).

![Scheme 2.24: Synthesis of C9-C14 subunit 96](image)

2.3: Synthesis of C1-C14 subunit

2.3.1: Horner-Wadsworth Emmons coupling

With both the C1-C8 subunit (91) and the C9-C14 subunit (96) in hand, the next step was to form the C8-C9 (E)-olefin of 97. The reaction was carried out
by treating the C9-C14 Weinreb amide (96) with DIBAL to give aldehyde 136 that was used directly in the Horner-Wadsworth Emmons reaction with the C1-C8 subunit (91) using K\textsubscript{2}CO\textsubscript{3} and 18-crown-6 to give the C1-C14 subunit (97) in a 71% yield over the two steps with good $E : Z$ selectivity (Scheme 2.25).

Scheme 2.25: Formation of C8-C9 ($E$)-olefin in C1-C14 subunit (97)
2.3.2: CSA deprotection of 97

The proposed strategy for the coupling of the C1-C14 subunit (98) with either the C15-C24 (93, palmerolide A) or the C15-C23 subunit (95, palmerolide E) requires that the primary TBS-ether group of 98 be cleaved in the presence of a secondary TBS. The resultant primary alcohol can then be oxidised to an aldehyde prior to performing the proposed Julia-Kocienski olefination with either 93 or 95, which would give the pre-cyclised skeleton of either palmerolide A or E, respectively.

The selective cleavage of the primary TBS-ether in the presence of the secondary TBS-ether of 97 proceeded using CSA in a 1:6 mixture of methanol : dichloromethane for one and a half hours giving 137 in excellent yield (Scheme 2.26). The time and ratios of methanol to dichloromethane had to be carefully monitored as if the reaction was left for too long, deprotection of the allylic C10-TBS ether was observed.

Scheme 2.26: Deprotection of C14-hydroxyl
2.3.3: Removal of PMB ether

With the removal of the primary TBS-protecting group shown to be successful, the deprotection of the C11 PMB-protecting group was investigated. This procedure has been shown to be problematic at later stages in previous palmerolide A syntheses, such as Hall’s synthesis of palmerolide A, where the deprotection of the C11-PMB and C7- and C10-TIPS had a combined yield of 16% for the two steps.\textsuperscript{36c} This was attributed to the benzyl ring of the PMB folding across the macrolide ring, which can interact with the diene contained within the macrolide core. Anticipating this, the deprotection was attempted before the Julia-Kocienski olefination with the C15-C24 subunit (93), as the C14-C15 and C16-C17 olefins were not yet in place. 97 was smoothly reacted with recrystallized DDQ to give the C11 deprotected subunit 138 in excellent yield (Scheme 2.27).

![Scheme 2.27: DDQ deprotection of 97](image)

DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) is a powerful and selective reagent for deprotections,\textsuperscript{67} though it can also be used as a reagent for oxidative couplings\textsuperscript{68} and the dehydrogenation of hydroaromatic
Deprotection of the $p$-methoxybenzyl ether proceeds via two single electron transfers with the methoxy group stabilising the intermediates, which is followed by a formal hydride transfer to give alcohol and $p$-methoxybenzaldehyde (Scheme 2.28).

Scheme 2.28: Mechanism of DDQ deprotection

2.3.4: Reduction of C7 ketone

The next challenge to overcome was the selective reduction of the C7 ketone. Our strategy required it to be reduced giving the $(7S)$-hydroxyl, which was expected to result from using $(R)$-CBS as De Brabander has utilised this method on macrolide 52 in his synthesis of palmerolide A (23, Scheme 1.2).
Initially the reduction was attempted with NaBH₄, to test that the ketone could be reduced to the alcohol (Scheme 2.29). This was completed by treating ketone 97, with NaBH₄ to give alcohol 139 in 83% yield as a 1:1 ratio of diastereoisomers.

Scheme 2.29: NaBH₄ reduction of C7 ketone 97

2.3.5: CBS reduction of C7 ketone

In 1987, E. J. Corey and co-workers developed the enantioselective reduction of an achiral ketone in the presence of a chiral borane.⁷⁰ One of these borane reagents is (R)-methyl oxazaborolidine (140, (R)-CBS, Figure 2.4), which can be used to reduce prochiral ketones to give the corresponding alcohols in high enantiomeric excess. Catalytic amounts of the CBS reagent are needed, and when treated with BH₃·THF in situ the diborane complex is formed, where it acts as both a Lewis acid and a chiral auxiliary.
After showing the reduction could be completed using NaBH₄, it was then attempted using \((R)\)-CBS (140) to introduce the desired C7-hydroxyl selectivity (Scheme 2.30). Initially the reaction was attempted using the same conditions used by De Brabander in his synthesis of palmerolide A (23), but this did not provide any alcohol (141) and the starting ketone (97) was not recovered. The reaction was also attempted under various conditions with different temperatures, time and equivalents of the reagents used (Table 2.1) but all the attempts were unsuccessful.

Scheme 2.30: Attempted \((R)\)-CBS reduction of C7 ketone 97
<table>
<thead>
<tr>
<th>Solvent</th>
<th>Time</th>
<th>(R)-CBS (eq)</th>
<th>BH$_3$·THF (eq)</th>
<th>Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>40 min</td>
<td>3</td>
<td>2</td>
<td>-40</td>
</tr>
<tr>
<td>THF</td>
<td>1 hr</td>
<td>3</td>
<td>3</td>
<td>-78</td>
</tr>
<tr>
<td>THF</td>
<td>4 hr</td>
<td>3</td>
<td>3</td>
<td>-78</td>
</tr>
<tr>
<td>THF</td>
<td>4 hr</td>
<td>3</td>
<td>3</td>
<td>-78 - -40</td>
</tr>
</tbody>
</table>

Table 2.1: Conditions used in (R)-CBS reduction of C7 ketone 97

2.3.6: Noyori hydrogenation

With the unsuccessful reduction using the (R)-CBS reagent (140), the attention was turned to a different method, which was to use a Noyori hydrogenation,\textsuperscript{71} with catalyst 142 (Figure 2.5) developed by Clark et al.\textsuperscript{72} The Noyori asymmetric hydrogenation is used for enantioselective hydrogenation of ketones, aldehydes and imines, using a chiral ruthenium catalyst.

![Catalyst 142](image)

Figure 2.5: Catalyst 142 used in Noyori hydrogenation

The hydrogenation of ketone 97 was attempted using 0.5% of catalyst 142, at 70 °C with KO'Bu under 30 bars of hydrogen in isopropyl alcohol, but
unfortunately this did not provide any of alcohol 141 (Scheme 2.31), and the hydrogenation was found to saturate both the C2-C3 and C8-C9 double bonds.

Scheme 2.31: Conditions used in attempted Noyori hydrogenation of ketone 97

### 2.3.7: DIP-Cl reduction of C7 ketone

The next attempt to reduce the C7 ketone was to use B-chlorodiisopinocampheylborane (Ipc₂BCl, known commercially as DIP-Cl) pioneered by Brown et al.\(^\text{73}\) DIP-Cl has been shown to be very effective for the asymmetric reduction of simple ketones, such as alkyl ketones, \(\alpha\)-hindered ketones and perfluoroalkyl ketones.\(^\text{74}\) Initially the reaction was attempted using (+)-DIP-Cl, as using the mnemonic shown it was quite difficult to distinguish which group would be the large substituent and which would be the small in subunit 97 (Figure 2.6).

Figure 2.6: Mnemonic used to determine selectivity using DIP-Cl
DIP-Cl efficiently reduces aromatic ketones to chiral secondary alcohols by de-hydroboration and loss of pinene (Scheme 2.32).\textsuperscript{75} The reduction proceeds via a six-membered cyclic, transition state where the β-hydrogen of the iso-pinocampheyl group is transferred to the carbonyl carbon and α-pinene is released.

![Scheme 2.32: Mechanism for DIP-Cl reduction.]

Treating the ketone 97 with (+)-DIP-Cl in THF at -78 °C, then warming up the reaction mixture to room temperature and stirring for sixteen hours afforded a separable mixture of (7S : 7R) alcohols 141 and 143 in good yield (Scheme 2.33).

![Scheme 2.33: (+)-DIP-Cl reduction of C7 ketone 97]
2.3.8: Mosher ester analysis

To determine the selectivity of the (+)-DIP-Cl reduction, alcohol 143 was separately reacted with both (R)- and (S)-MTPA acids. This treatment of alcohol 143 in dichloromethane with the MTPA acid, \(N,N'\)-dicyclohexylcarbodiimide and DMAP at room temperature gave the MTPA esters 144 and 145 (Scheme 2.34).

Scheme 2.34: Synthesis of Mosher esters 144 and 145

The Mosher method uses \(\alpha\)-methoxy-\(\alpha\)-(trifluoromethyl)-phenylacetic acid (MTPA) esters for assigning the absolute configuration. It is based upon the assumption that the MTPA derivatives will adopt a preferred conformation in solution where the carbinol proton, ester carbonyl and trifluoromethyl group all sit in the same plane (Figure 2.7).\(^7\) Due to the diamagnetic effect of the
phenyl group when the MTPA group adopts this confirmation, the $^1$H NMR signals of Ha, Hb, and Hc in the (R)-MTPA ester appear upfield relative to the corresponding signals of the (S)-MTPA ester, while the Hx, Hy and Hz in the (R)-MTPA ester appear downfield. Therefore the absolute configuration can be assigned by calculating $\Delta \delta = -0.02$ for as many $^1$H NMR signals as possible for each of the (R)- and (S)-MTPA esters. Using this data it is possible to construct a molecular model showing that protons with $\delta > 0$ and protons with $\delta < 0$ lie on opposite sides of the MTPA plane, confirming the absolute configuration.

![Figure 2.7: Configurational models for Mosher ester analysis](image)

Comparison of the $^1$H NMR of 144 and 145 showed an upfield shift of the C$_8$-C$_{12}$ protons of 144 as the phenyl group shields them; conversely, the (R)-MTPA derivative 145 experienced an upfield shift on C$_2$-C$_6$ region (Table 2.2). Therefore, subtraction of the $^1$H NMR $\delta$ values for the (R)-MTPA ester from the (S)-MTPA ester gives a positive value for the C$_2$-C$_6$ region and a negative value in the C$_8$-C$_{12}$ region, allowing the assignment of the C7 stereocentre in the (+)-DIP-Cl reduction giving the 7R configuration as the major diastereoisomer.
Table 2.2: Mosher ester analysis of (+)-DIP-Cl reduction of 97

<table>
<thead>
<tr>
<th>Proton</th>
<th>$\delta S$ (ppm)</th>
<th>$\delta R$ (ppm)</th>
<th>$\delta S - \delta R$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>5.80</td>
<td>5.75</td>
<td>+0.05</td>
</tr>
<tr>
<td>3</td>
<td>6.87</td>
<td>6.88</td>
<td>+0.01</td>
</tr>
<tr>
<td>4</td>
<td>2.20</td>
<td>2.13</td>
<td>+0.07</td>
</tr>
<tr>
<td>5</td>
<td>1.47</td>
<td>1.35</td>
<td>+0.12</td>
</tr>
<tr>
<td>6</td>
<td>1.75</td>
<td>1.73</td>
<td>+0.02</td>
</tr>
<tr>
<td>7</td>
<td>4.31</td>
<td>4.29</td>
<td>+0.02</td>
</tr>
<tr>
<td>8</td>
<td>5.60</td>
<td>5.68</td>
<td>-0.08</td>
</tr>
<tr>
<td>9</td>
<td>5.86</td>
<td>5.96</td>
<td>-0.10</td>
</tr>
<tr>
<td>10</td>
<td>4.27</td>
<td>4.29</td>
<td>-0.02</td>
</tr>
<tr>
<td>11</td>
<td>3.28</td>
<td>3.30</td>
<td>-0.02</td>
</tr>
<tr>
<td>12</td>
<td>1.63</td>
<td>1.68</td>
<td>-0.05</td>
</tr>
</tbody>
</table>

With the reaction using (+)-DIP-Cl proving successful but giving the opposite selectivity needed, the reaction was attempted with (-)-DIP-Cl (Scheme 2.35). Under the same conditions treatment of 97 gave a 5 : 1 ratio in favour of what was assumed to be the desired 7S diastereoisomer 141.

Scheme 2.35: (-)-DIP-Cl reduction of C7 ketone 97
Mosher ester analysis was performed to confirm the selectivity of the (-)-DIP-Cl reduction, by treating alcohol 141 with both (R)- and (S)-MTPA acids, giving 146 and 147 (Scheme 2.36).

Scheme 2.36: Mosher ester analysis of 141

The two (R)- and (S)-Mosher ester derivatives 146 and 147 were subjected to the same $^1$H NMR analysis as 144 and 145 confirming the selectivity of the (-)-DIP-Cl reduction as 5 : 1 for 7S : 7R (Table 2.3, Figure 2.8), as subtraction of the $^1$H NMR $\delta$ values for the (R)-MTPA ester from the (S)-MTPA ester gives a negative value for the C$_2$-C$_6$ region and a positive value in the C$_8$-C$_{12}$ region.
<table>
<thead>
<tr>
<th>Proton</th>
<th>δS (ppm)</th>
<th>δR (ppm)</th>
<th>δS - δR (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>5.75</td>
<td>5.80</td>
<td>-0.05</td>
</tr>
<tr>
<td>3</td>
<td>6.87</td>
<td>6.87</td>
<td>0.00</td>
</tr>
<tr>
<td>4</td>
<td>2.12</td>
<td>2.20</td>
<td>-0.08</td>
</tr>
<tr>
<td>5</td>
<td>1.60</td>
<td>1.64</td>
<td>-0.04</td>
</tr>
<tr>
<td>6</td>
<td>1.75</td>
<td>1.81</td>
<td>-0.06</td>
</tr>
<tr>
<td>7</td>
<td>4.29</td>
<td>4.30</td>
<td>-0.01</td>
</tr>
<tr>
<td>8</td>
<td>5.68</td>
<td>5.62</td>
<td>+0.06</td>
</tr>
<tr>
<td>9</td>
<td>6.00</td>
<td>5.93</td>
<td>+0.07</td>
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<tr>
<td>10</td>
<td>4.35</td>
<td>4.31</td>
<td>+0.04</td>
</tr>
<tr>
<td>11</td>
<td>3.35</td>
<td>3.29</td>
<td>+0.06</td>
</tr>
<tr>
<td>12</td>
<td>1.65</td>
<td>1.61</td>
<td>+0.04</td>
</tr>
</tbody>
</table>

Table 2.3: Mosher ester analysis of (-)-DIP-Cl reduction of 97

Figure 2.8: $^1$H NMR comparison of (R)- and (S)-Mosher ester derivatives 146 and 147.
2.3.9: Synthesis of C1-C14 subunit 98

Using the conditions developed above it was attempted to synthesize the fully elaborated C1-C14 subunit (98). This was achieved by TBS protection of 141, giving 148 followed by deprotecting with recrystallised DDQ to remove the PMB-protecting group to give alcohol 149 in good yield. The free hydroxyl was then reacted with trichloroacetyl isocyanate, followed by treatment with potassium carbonate in methanol to give carbamate 150. This was followed by the selective deprotection of the primary TBS-protecting group using CSA in methanol and dichloromethane, in a 1:6 ratio, to give the fully elaborated C1-C14 subunit (98) in good yield (Scheme 2.38).

Scheme 2.38: Synthesis of the fully elaborated C1-C14 subunit 98
2.4: Conclusion

The C1-C14 subunit 98 was synthesised by reacting the C1-C8 subunit 91 with the reduced C9-C14 subunit 136 via a Horner-Wadsworth-Emmons to give the C8-C9 olefin 97. The selective reduction of the C7 ketone was shown to be successful using (-)-DIP-Cl, which was then protected as its TBS-ether 148. The PMB-ether was pre-emptively deprotected followed by formation of the carbamate 150 and deprotection of the primary TBS-ether to give the fully elaborated C1-C14 subunit 98 (Scheme 2.39) in seven steps and 19% overall yield.

Scheme 2.39: Synthesis of C1-C14 subunit 98
Results and Discussion

3.0: Synthesis of C15-C23 subunit for palmerolide E (18)

3.1: Retrosynthesis

The synthesis of the unsaturated C15-C23 subunit 95 (Scheme 3.1) was envisioned to begin with a Horner-Wadsworth Emmons olefination of the (S)-Roche ester derived aldehyde 152, to provide the trisubstituted enoate 153, which could be reduced to give the alcohol then protected as its TBS-ether 154. Elaboration of 154 to aldehyde 155 would then set the stage for the vinylogous Mukaiyama aldol reaction with silyl ketene acetal 156 under suitable Lewis acidic conditions, to generate the desired 1,2-syn adduct 157. Finally, TES-protection of the C19 alcohol followed by reduction and sulfone formation at the C15 terminus to give the C15-C23 subunit 95.
Scheme 3.1: Retrosynthesis of C15-C23 subunit 95

### 3.1.1: Horner-Wadsworth Emmons olefination

The synthesis of the C15-C23 subunit (95) began with PMB-protection of the free hydroxyl of (S)-Roche ester 158, using PMBTCA and PPTS to give 159 in good yield (Scheme 3.2).\textsuperscript{78} The Weinreb amide 160 was then formed by treating the protected Roche ester (159) with N,O-dimethyl hydroxylamine hydrochloride and \textit{iso}-propylmagnesium chloride, ensuring the temperature of the reaction did not rise above -15 °C, giving 160 in excellent yield. Synthesizing Weinreb amide 160 to gain access to aldehyde 152 was chosen over reducing the ester 159 to the corresponding alcohol followed by oxidation to the aldehyde in order to prevent epimerization of the C20 stereocentre.
Scheme 3.2: Synthesis of PMB-protected Weinreb amide 160

Olefin synthesis, employing phosphonium ylides was introduced by Wittig and Geissle in 1953. Shortly after in 1958, Horner disclosed a modified Wittig reaction employing phosphonate-stabilized carbanions. Wadsworth and Emmons investigated this further, showing that phosphonate-stabilized carbanions are more nucleophilic than their corresponding phosphonium ylides. The Horner-Wadsworth-Emmons reaction is the chemical reaction of stabilized phosphonate carbanions with aldehydes or ketones to produce predominantly E-olefins (Scheme 3.3). The reaction mechanism proceeds via the nucleophilic addition of the enolate to the aldehyde, which gives the two intermediates; the stereochemistry is set by steric control, where the antiperiplanar approach of the carbanion to the carbonyl group is favored when the smaller aldehydic hydrogen eclipses the bulky phosphoranyl moiety.
This places the ester group syn to the aldehyde $R'$ group. The resultant olefin can assume the more stable $E$-orientation, as interconversion between the intermediates is possible.

Scheme 3.3: Mechanism for Horner-Wadsworth Emmons reaction

The PMB-protected Weinreb amide 160 was treated with DIBAL to give aldehyde 152, which was used immediately and without purification, due to facile epimerization of the $\alpha$-chiral aldehyde. The crude aldehyde
152 was reacted in a Horner-Wadsworth Emmons reaction using triethyl 2-phosphonopropionate to give the $\alpha$, $\beta$-unsaturated ester 153 (Scheme 3.4).

![Scheme 3.4: Horner-Wadsworth Emmons reaction to synthesise $\alpha$, $\beta$-unsaturated ester 153](image)

The Horner-Wadsworth Emmons reaction of 152 was attempted using various bases and conditions. Initially it was attempted by treating of the aldehyde 152 with LiHMDS and triethyl 2-phosphonopropionate which gave the $\alpha$, $\beta$-unsaturated ester 153 ($E : Z = 1 : 4$) in a moderate yield for the two steps (Table 3.1). The selectivity of the reaction was determined by $^1$H NMR spectroscopy, which in this instance appears to be favoured as the reaction is under kinetic control.
<table>
<thead>
<tr>
<th>Base</th>
<th>Yield (%) from 160</th>
<th>$E : Z$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiHMDS</td>
<td>58</td>
<td>1 : 4</td>
</tr>
<tr>
<td>LiCl, Hünig’s base</td>
<td>65</td>
<td>4 : 1</td>
</tr>
<tr>
<td>Ba(OH)$_2$·H$_2$O, wet THF</td>
<td>70</td>
<td>9 : 1</td>
</tr>
</tbody>
</table>

Table 3.1: Conditions used in Horner-Wadsworth Emmons reaction of 152

Due to the excess formation of the undesired ($Z$)-isomer this reaction was attempted using the Masamune-Roush conditions. Treatment of aldehyde 152 with lithium chloride, Hünig’s base and triethyl 2-phosphonopropionate, gave a mixture of isomers of ester 153 ($E : Z = 4 : 1$) in a 65% yield for the two steps (Table 3.1). There is an increase in the $E : Z$ ratio as the thermodynamic product is now favoured.

Although a change in the selectivity of the reaction was observed, it was believed that the 4 : 1 ratio could be increased. Activated barium hydroxide has been shown to increase the ($E$)-selectivity in the Horner-Wadsworth-Emmons reaction. It has been hypothesised that the microcrystalline structure of the barium hydroxide is crucial to its catalytic activity with the reaction proceeding via an interfacial solid-liquid mechanism. The reaction was carried out by treating a mixture of activated barium hydroxide and triethyl 2-phosphonopropionate in tetrahydrofuran, with with aldehyde 152 in wet tetrahydrofuran, giving the desired ($E$)-regioisomer 153 in a good yield for the two steps and good selectivity ($E : Z = 9 : 1$, Table 3.1).
3.1.2: Synthesis of C19-C23 aldehyde 155

The synthesis of aldehyde 155 started with the reduction of ester 153, using DIBAL, to give alcohol 161 in excellent yield. This was followed by TBS protection of alcohol 161 to afford the di-protected fragment 154 (Scheme 3.5). Deprotection of the PMB ether, using DDQ in dichloromethane followed by oxidation using Dess-Martin periodinane gave aldehyde 155. The stage was now set to explore the introduction of silyl ketene acetal 156 in a vinylogous aldol reaction.

Scheme 3.5: Synthesis of aldehyde 155

Dess-Martin periodinane is a hypervalent iodine compound, which offers selective and mild oxidation of alcohols to their corresponding aldehydes and the product is easily separated from the iodo by-product. Dess-Martin periodinane works by displacement of an acetyl group by the alcohol (Scheme 3.6). A second acetate group then acts as a base, deprotonating the alcohol to form the aldehyde.
3.2: Aldol reaction

The next step of the sequence was to react the aldehyde (155) with silyl ketene acetal 156 to give the aldol adduct (157, Scheme 3.7). This was to be initially attempted using a vinylogous Mukaiyama aldol reaction.\textsuperscript{86}

3.2.1: Vinylogous Mukaiyama aldol

Formation of the desired 1,2-\textit{syn} adduct 157 was to be attempted utilising the substrate controlled vinylogous Mukaiyama aldol reaction with aldehyde 155 and silyl ketene acetal 156, prepared from methyl-3,3-dimethyl acrylate 161 (Scheme 3.8).
Scheme 3.8: Synthesis of silyl ketene acetal 156

Unfortunately treatment of aldehyde 155 with silyl ketene acetal 156 and BF$_3$·OEt$_2$ in dichloromethane at low temperature did not form any of the desired isomer (Scheme 3.9) giving only degradation of the starting material.$^{85b}$ The reaction was attempted under various conditions with varying equivalents of reagents and Lewis acid, but each attempt provided none of the aldol adduct (157) and no starting material was recovered, as the use of BF$_3$·OEt$_2$ led to degradation of the starting material in all cases (Table 3.2).

Scheme 3.9: Attempted vinylogous Mukaiyama aldol using BF$_3$·OEt$_2$
<table>
<thead>
<tr>
<th>Reagent (eq)</th>
<th>Lewis acid (eq)</th>
<th>Time (Min)</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTMS OMe (2)</td>
<td>BF₃·OEt (4)</td>
<td>10</td>
<td>-95</td>
<td>0</td>
</tr>
<tr>
<td>OTMS OMe (2)</td>
<td>BF₃·OEt (4)</td>
<td>15</td>
<td>-95 to -78</td>
<td>0</td>
</tr>
<tr>
<td>OTMS OMe (2)</td>
<td>BF₃·OEt (1)</td>
<td>30</td>
<td>-78</td>
<td>0</td>
</tr>
<tr>
<td>OTMS OMe (2)</td>
<td>BF₃·OEt (2)</td>
<td>10</td>
<td>-78</td>
<td>0</td>
</tr>
<tr>
<td>OTMS OMe (2)</td>
<td>BF₃·OEt (2)</td>
<td>30</td>
<td>-95</td>
<td>0</td>
</tr>
<tr>
<td>OTMS OMe (4)</td>
<td>BF₃·OEt (2)</td>
<td>30</td>
<td>-78</td>
<td>0</td>
</tr>
<tr>
<td>OTMS OMe (2)</td>
<td>BF₃·OEt (6)</td>
<td>30</td>
<td>-78</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3.2: Conditions attempted in vinylogous Mukaiyama aldol using BF₃·OEt₂

With the unsuccessful attempts of the vinylogous Mukaiyama aldol using BF₃·OEt₂, due to the degradation of the aldehyde 155, the reaction was attempted using TiCl₂(O’Pr)₂ (Scheme 3.10). This reaction was investigated using various conditions but again the starting material 155 was unrecoverable and the product 157 was not formed (Table 3.3).
Scheme 3.10: Attempted vinylogous Mukaiyama aldol of 156 and 155 using TiCl$_2$(O'Pr)$_2$

<table>
<thead>
<tr>
<th>Reagent (eq)</th>
<th>Lewis acid (eq)</th>
<th>Time (Min)</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTMS OMe (2)</td>
<td>TiCl$_2$(O'Pr)$_2$ (6)</td>
<td>180</td>
<td>-78</td>
<td></td>
</tr>
<tr>
<td>OTMS OMe (2)</td>
<td>TiCl$_2$(O'Pr)$_2$ (6)</td>
<td>90</td>
<td>-78</td>
<td></td>
</tr>
<tr>
<td>OTMS OMe (2)</td>
<td>TiCl$_2$(O'Pr)$_2$ (6)</td>
<td>180</td>
<td>-78</td>
<td></td>
</tr>
<tr>
<td>OTMS OMe (2)</td>
<td>TiCl$_2$(O'Pr)$_2$ (2)</td>
<td>180</td>
<td>-78</td>
<td></td>
</tr>
<tr>
<td>OTMS OMe (4)</td>
<td>TiCl$_2$(O'Pr)$_2$ (6)</td>
<td>180</td>
<td>-78</td>
<td></td>
</tr>
<tr>
<td>OTMS OMe (4)</td>
<td>TiCl$_2$(O'Pr)$_2$ (2)</td>
<td>180</td>
<td>-78</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.3: Conditions attempted in vinylogous Mukaiyama aldol using TiCl$_2$(O'Pr)$_2$

3.2.2: Lithium aldol

After the unsuccessful vinylogous Mukaiyama aldol with both BF$_3$·OEt$_2$ and TiCl$_2$(O'Pr)$_2$, a lithium aldol reaction with aldehyde 155 and acrylate 161 was
attempted to confirm that the aldol bond could be formed. Treatment of acrylate 161 with LDA and aldehyde 155 in tetrahydofuran at -78 °C gave a separable mixture of isomers ($\alpha : \gamma = 4 : 1$) in moderate yield (Scheme 3.11).

Scheme 3.11: Lithium aldol reaction of 155 and 161

The $\alpha$-regioisomer was favoured in this reaction as it proceeds via a Zimmerman-Traxler transition-state (Figure 3.1).

Figure 3.1: Zimmerman-Traxler transition-state

3.2.3: Yamamoto’s aluminium tris-(2,6-diphenylphenoxide) aldol

An alternative method to synthesise $\gamma$-aldol adducts is Yamamoto’s aldol reaction, which utilises aluminium tris-(2,6-diphenylphenoxide) (ATPH, 163, Figure 3.2) as a bulky Lewis acid.
Figure 3.2: Aluminium tris-(2,6-diphenylphenoxide) (163)

This proceeds by complexing the ATPH 163 Lewis acid to enolate 164, which reacts with aldehyde 165 to give the \( \gamma \)-aldol adduct 166 (or when no complexation with 163 occurs the \( \alpha \)-aldol adduct 167 is formed, Scheme 3.12). Direct aldol reactions of conjugated esters with aldehydes, initiated with LDA using ATPH (163) as the key reagent, have been shown to proceed with high \( \gamma \)-regioselectivities.\(^{88a,d}\) This can be explained by the large steric effects of the ATPH (163), which block attack via the \( \alpha \)-carbon by encapsulating the aldehyde substrate (164), therefore the \( \gamma \)-carbon is the preferred position of attack.

Scheme 3.12: Representation of Yamamoto’s aldol reaction
Using ATPH (163), a mixed aldol reaction between 3-methylbut-2-enal (168) and aldehyde 155 in toluene with LDA as a base, was attempted (Scheme 3.13). However this reaction did not produce the desired product (169) with the starting aldehyde 155 recovered.

Scheme 3.13: Attempted Yamamoto’s aldol reaction using ATPH (163), aldehyde 155 and 3-methylbut-2-enal (168)

Due to the unsuccessful reaction using 168, a similar reaction was tested again using ATPH reagent (163) but with methyl-3,3-dimethyl acrylate 161 (Scheme 3.14). This was carried out by treating acrylate 161 with a solution of ATPH 163 in toluene followed by the addition of aldehyde 155, this was left stirring for twenty minutes to allow complexation of the substrates to the ATPH after which LDA was added and the reaction was left at -78 °C for thirty minutes. This gave the product 157 in 55% yield with good γ-regioselectivity (α : γ = 1 : 7; γ-isomer d.r. = 4 : 1). The diastereomeric ratio was obtained via Mosher ester analysis explained below, while the α : γ regioselectivity of the reaction was established by 1H NMR spectroscopy.
Scheme 3.14: Yamamoto’s aldol reaction using ATPH 163, aldehyde 155 and methyl-3, 3-dimethyl acrylate 161

3.2.4: Felkin-Anh control

The selective introduction of the C19-hydroxyl stereocentre in 157 is proposed to arise from a stereoselective Felkin-Anh addition of the acrylate 161 to aldehyde 155. Using a Newman projection, the largest substituent is placed furthest from both the oxygen and hydrogen, with no eclipsing interactions; this gives the lowest energy conformation possible (Figure 3.3). The nucleophile attacks at 107° from the C=O bond with two possible trajectories of attack. The nucleophile selectively attacks past the small (S) substituent of the aldehyde (A) which is the least hindered path, giving the less stable product as the nucleophile reacts with the most reactive conformer. This is an example of the Curtin-Hammett principle, which states that it is the relative energies of the competing transition states that control selectivity, not the relative energies of the starting materials.
The absolute stereochemistry and selectivity of the aldol reaction was confirmed via Mosher ester analysis. The alcohol 157 was reacted with $N,N'$-dicyclohexylcarbodiimide, DMAP and both the ($R$)- and ($S$)-MTPA acids separately at room temperature to give the MTPA esters 170 and 171 respectively (Scheme 3.15). After analysis by $^1$H NMR spectroscopy, the aldol reaction was shown to have a diastereomeric ratio of 4 : 1 in favour of the ($R$)-diastereomer (Table 3.4).
Table 3.4: Mosher ester analysis of aldol adduct 157

<table>
<thead>
<tr>
<th>Proton</th>
<th>$\delta S$ (ppm)</th>
<th>$\delta R$ (ppm)</th>
<th>$\delta S - \delta R$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>5.80</td>
<td>5.75</td>
<td>+0.05</td>
</tr>
<tr>
<td>18a</td>
<td>2.29</td>
<td>2.21</td>
<td>+0.08</td>
</tr>
<tr>
<td>18b</td>
<td>2.13</td>
<td>2.07</td>
<td>+0.06</td>
</tr>
<tr>
<td>19</td>
<td>5.08</td>
<td>5.06</td>
<td>+0.02</td>
</tr>
<tr>
<td>20</td>
<td>2.72</td>
<td>2.78</td>
<td>-0.06</td>
</tr>
<tr>
<td>21</td>
<td>5.25</td>
<td>5.34</td>
<td>-0.09</td>
</tr>
<tr>
<td>23</td>
<td>4.01</td>
<td>4.03</td>
<td>-0.02</td>
</tr>
</tbody>
</table>

3.3: Alternate C15-C23 synthesis (172)

Due to the observed breakdown of aldehyde 155 during, in particular, the Mukaiyama aldol reaction, an alternative substrate (173) was synthesised with the TBS-protecting group replaced with a PMB-protecting group, which we believed would be less susceptible to deconstruct under the acidic Mukaiyama conditions. This was achieved via a similar route starting with TBS-protection of the (S)-Roche ester 158, and formation of the Weinreb amide 174 (Scheme 3.16). This was then reduced to the aldehyde using DIBAL and reacted under the same conditions used previously for the Horner-Wadsworth Emmons reaction giving 175, which after reduction of the ester and PMB-protection gave 176. Removal of the TBS-protecting group was facilitated with TBAF under standard conditions and oxidation using Dess-Martin periodinane gave 173, to be tested in both the Mukaiyama and Yamamoto aldol reaction.
Scheme 3.16: Synthesis of alternative C19-C23 aldehyde 173

3.3.1: Aldol reaction on PMB-protected aldehyde 173

Aldehyde 173 was subjected to both the vinylogous Mukaiyama aldol conditions previously tried on aldehyde 155. Treating aldehyde 173 with ketene acetal 156 and BF$_3$·OEt$_2$ at -78 °C again gave only degradation of the starting material (Scheme 3.17). The aldehyde (173) was also reacted using TiCl$_2$(OPr)$_2$ as the Lewis acid, but again this only broke down the starting material.
Scheme 3.17: Mukaiyama aldol reaction of aldehyde 173

Again due to the failure of the Mukaiyama aldol reaction, aldehyde 176 was reacted under Yamamoto’s protocol to see if the yield of the key aldol reaction could be improved. Aldehyde 176 was reacted with 161 under the conditions developed for TBS-protected aldehyde 155, to give the PMB-protected aldol adduct 172, albeit in a lower yield though with similar regioselectivity (α : γ = 1 : 6, γ-isomer d.r. = 4 : 1, Scheme 3.18).88

Scheme 3.18: Yamamoto’s aldol reaction using ATPH 163, aldehyde 173 and acrylate 161

Due to the lower yield observed with PMB-protected aldehyde 173 it was decided to continue with TBS-protected aldol adduct 157 to complete the synthesis of the C15-C23 subunit 95.
3.4: Completion of C15-C23 subunit 95

Taking forward 157, the final steps to provide the C15-C23 subunit 95 started with the protection of secondary alcohol 157 under standard conditions using TES-chloride and imidazole in dichloromethane to give 177 (Scheme 3.19). The resulting ester was reduced using DIBAL to give alcohol 178, and subsequent formation of the sulfone 95 via a Mitsunobu reaction to give the sulfide followed by oxidation completed the synthesis of the C15-C23 subunit (95).\textsuperscript{91,92}

![Scheme 3.19: Final steps to synthesise the C15-C23 subunit (95)](image)

3.5: Conclusion

The C15-C23 subunit 95 was synthesised starting from the (5)-Roche ester 158, which after PMB-protection and formation of the Weinreb amide gave 160. This was reduced using DIBAL and used in a Horner-Wadsworth Emmons reaction with activated barium hydroxide to give
ester 153. A further four steps generated aldehyde 155, which was used in a Yamamoto’s aldol reaction to give the $\gamma$-aldol adduct (157) with moderate diastereoselectivity. 157 was protected and reduced to give the free primary alcohol 178 and after formation of the sulfone finished the synthesis of the C15-C23 subunit (95) in a 9% overall yield over 13 steps (Scheme 3.20).

Scheme 3.20: Synthesis of C15-C23 subunit (95)
Results and Discussion

4.0: Synthesis of C15-C24 subunit for palmerolide A (14)

4.1: Retrosynthesis

The synthesis of the unsaturated C15-C24 subunit 93 was envisioned to arise via a similar method to the synthesis of the C15-C23 subunit 95, starting from the same (S)-Roche ester 158 through to previously synthesised alcohol 160, obtained from reduction of ester 153; alcohol 160 was to then be reacted in a Corey-Fuchs reaction followed by hydrostannation to form vinyl iodide 179 (Scheme 4.1). The vinyl iodide 179 was then to be reacted under the Yamamoto’s aldol conditions, developed for the synthesis of the C15-C23 subunit (95), to give 180 followed by TES-protection and sulfone formation to give the C15-C24 subunit 93.
Scheme 4.1: Retrosynthesis of C15-C24 subunit 93

4.2: Synthesis of vinyl iodide 192

With access to alcohol 160 established in the synthesis of the C15-C23 subunit (95) for palmerolide E, introduction of the terminal C23 vinyl iodide was required to give the C15-C24 subunit (93). This sequence started with oxidation of alcohol 160 with Dess-Martin periodinane to afford aldehyde 181 in 80% yield (Scheme 4.2).
4.2.1: Synthesis of alkyne 182

The initial attempt to synthesise alkyne 182 used a Corey-Fuchs reaction (Scheme 4.3). Treatment of aldehyde 181 with carbon tetrabromide, triphenylphosphine and zinc, was expected to give \textit{in situ} the dibromo intermediate 183, followed by formation of the alkyne with \textit{n}-BuLi, but unfortunately this protocol did not provide the any of the desired product 182, the dibromo intermediate 183 or return the starting aldehyde 181.

![Scheme 4.3: Attempted Corey-Fuchs reaction](image-url)
4.2.2: Seyferth-Gilbert reaction

With the failure of the Corey-Fuchs reaction our attention turned to an alternative alkynylation method: the Seyferth-Gilbert alkynylation. This homologation is a base promoted alkynylation, reacting the reagent (184) with an aldehyde to give the corresponding alkyne. It proceeds by deprotonation of the Seyferth-Gilbert reagent, which then adds to the carbonyl compound forming an alkoxide, this closes to give an oxaphosphetane. A cyclo-elimination yields a diazooalkene, which upon warming decomposes with loss of nitrogen to give the vinylidene carbene. This then undergoes a 1,2-migration to form the requisite alkyne (Scheme 4.4).

The Seyferth-Gilbert reagent can be prepared by two different methods, the first from reacting 185 with trimethyl phosphite to give 186, this is then
treated with hydrazine to give phosphonate 187; followed by formation of the Seyferth-Gilbert reagent 184 by reacting the amine 187 with sodium nitrite to generate the diazo phosphonate 184 (Scheme 4.5).[^95]

Scheme 4.5: First method to synthesise the Seyferth-Gilbert reagent (184)

Due to the poor yields and tricky synthesis associated with this route, an alternative route was investigated. This involved treating dimethyl methylphosphonate (188) with \( n\text{-BuLi} \) and 2,2,2-trifluoroethyl trifluoroacetate to give the intermediate 189, which after treatment with \( p\text{-ABSA} \) gave Seyferth-Gilbert reagent (184) in two steps and an improved overall yield of 46% (Scheme 4.6).[^96]

Scheme 4.6: Second method to synthesise the Seyferth-Gilbert reagent (184)
The Seyferth-Gilbert alkynylation was carried out by adding aldehyde 181 to a solution of dried potassium tert-butoxide and Seyferth-Gilbert reagent (184) in tetrahydrofuran, then stirred for 16 hours to successfully give the alkyne 182 in a 32% yield (Scheme 4.7).

![Scheme 4.7: Formation of alkyne 182 using Seyferth-Gilbert reagent](image)

**4.2.3: Bestmann-Ohira reaction**

Due to both the difficult synthesis of the Seyferth-Gilbert reagent (184) and the poor yielding alkynylation reaction, the Bestmann-Ohira reagent (190) was utilized which can be synthesised readily in one step by treating dimethyl (2-oxopropyl)phosphonate (106) with tosyl azide and sodium hydride giving the Bestmann-Ohira reagent (190) in a 69% yield (Scheme 4.8).  

![Scheme 4.8: Synthesis of Bestmann-Ohira reagent](image)
The mechanism of the Bestmann-Ohira reaction proceeds via a similar method to the Seyferth-Gilbert reaction, initially there is attack of the methanol into the β-ketophosphonate, followed by loss of methyl acetate to generate the deprotonated Seyferth-Gilbert reagent (Scheme 4.9), from there the reaction follows the same route as the Seyferth-Gilbert mechanism described above.

![Scheme 4.9: Bestmann-Ohira mechanism](image)

The reaction of aldehyde 181 with the Bestmann-Ohira reagent (190) was carried out by treating the reagent 190 with caesium carbonate in methanol, followed by addition of aldehyde 181 at 0 °C. The solution was warmed to room temperature upon which it was left stirring overnight giving alkyne 182 in a 58% yield. This route was preferred due to the ease of reagent synthesis (Scheme 4.10).

![Scheme 4.10: Bestmann-Ohira synthesis of PMB-protected alkyne 182](image)
4.2.4: Synthesis of vinyl iodide 192

With alkyne 182 in hand the next challenge in the C15-C24 subunit synthesis was the formation of the vinyl iodide; this was expected to be achieved via a hydrostannylation reaction of 182. Hydrostannylation reactions are palladium (II) catalysed syn-addition of the alkyl tin to an alkyne, which leads to a vinyl-stannane. They are carried out under mild conditions and can tolerate the presence of a wide variety of functional groups and have been shown to give good regio- and stereo-control.

The hydrostannation was realised by treating alkyne 182 with tributyltin hydride and catalytic palladium(II) to give the vinyl stannane intermediate, after the solvent was removed the intermediate was reacted with iodine in dichloromethane to give the vinyl iodide 191 in moderate yield (Scheme 4.11).

![Scheme 4.11: Synthesis of PMB-protected vinyl iodide 191](image)

The PMB-protecting group of vinyl iodide 191 then had to be removed to facilitate the subsequent aldol reaction; the deprotection was achieved by treating vinyl iodide 191 with DDQ to give alcohol 192 in good yield (Scheme 4.12).
Scheme 4.12: DDQ deprotection of PMB-protected vinyl iodide 191

4.3: Alternate C19-C24 subunit (192) synthesis

In an attempt to increase the yield of vinyl iodide 192, the alternative TBS-protected vinyl iodide (193) was synthesised alongside the PMB-protected vinyl iodide (191). This was accomplished starting from the analogous alcohol 195, which could be readily oxidised using Dess-Martin periodinane to give the corresponding aldehyde, which was treated with the Bestmann-Ohira reagent (190),96 giving alkyne (195, Scheme 4.13). Hydrostannylation of alkyne 195 followed by iodination gave the TBS-protected vinyl iodide (193) in a disappointing 33% yield over the 3 steps.97

Scheme 4.13: Synthesis of TBS-protected vinyl iodide 193
4.3.1: Takai olefination

Due to the poor yields observed for the formation of both PMB- and TBS-protected alkynes 182 and 194 and the subsequent vinyl iodides 192 and 193, the Takai olefination was investigated as an alternative. This involves the treatment of an aldehyde with chromium (II) chloride and iodoform to synthesise the vinyl iodide.\(^99\)

In the reaction mechanism proposed by Takai, chromium(II) is oxidized to chromium(III) upon replacing iodine from iodoform to give A, this is repeated to give di-chromium intermediate B. This geminal carbodianion complex reacts with the aldehyde in a 1,2-addition across one of the carbon-chromium bonds to give C and in the next step both chromium bearing groups engage in an elimination reaction to generate the desired vinyl iodide D (Scheme 4.14).\(^98\)

![Scheme 4.14: Takai olefination mechanism](image-url)
The Takai olefination was carried out on the TBS-protected aldehyde, by addition of a solution of the aldehyde and iodoform in dioxane to a solution of chromium(II) chloride in THF (Scheme 4.15). This solution was left to stir overnight giving vinyl iodide 193 in a pleasing 70% yield over the two steps with good $E : Z$ selectivity, which was established via $^1$H NMR spectroscopy.

![Scheme 4.15: Synthesis of TBS-protected vinyl iodide 193 via a Takai olefination](image)

With the improved formation of the vinyl iodide via a Takai olefination, the TBS-protected vinyl iodide 193 was deprotected using TBAF to give the previously synthesised alcohol 192, in good yield (Scheme 4.16).

![Scheme 4.16: TBAF deprotection of TBS-protected vinyl iodide 193](image)
4.4: Completion of C15-C24 subunit (93)

4.4.1: Yamamoto’s aldol reaction

With the deprotected vinyl iodide 192 in hand, the attention was turned to the aldol reaction between the oxidised alcohol 192 and 3,3-dimethyl acrylate (161), to introduce the diene and the C19 stereocentre. This was achieved using the same conditions developed in the synthesis of the C15-C23 subunit (95), with Dess-Martin periodinane oxidation to give the aldehyde 179 in good yield, followed by Yamamoto’s aldol reaction using 3,3-dimethyl acrylate (161), ATPH (163), and LDA giving vinyl iodide γ-aldol adduct (180), in moderate yield with 7 : 1 γ : α selectivity and a 3 : 1 syn : anti ratio (Scheme 4.17).
Scheme 4.17: Synthesis of vinyl iodide aldol adduct 180

4.4.2: Final steps towards the C15-C24 subunit (93)

After the aldol reaction, the free hydroxyl of aldol adduct 180 was protected as its TES-ether, by reacting the alcohol 180 with TES-chloride and imidazole, to give 196 (Scheme 4.18). Ester 196 was reduced to alcohol 197 using DIBAL at -78 °C. This was then transformed to the sulfone 93, via a Mitsunobu reaction to give the sulfide intermediate followed by oxidation to give the sulfone in good yield over the two steps, completing the synthesis of the C15-C24 subunit (93).90,91
Scheme 4.18: Final steps completing the synthesis of the C15-C24 subunit (93)

4.5: Conclusion

The C15-C24 subunit (93) was synthesised via a similar method to the synthesis of the C15-C23 subunit (95), but included formation of vinyl iodide 195. This was achieved via a Takai olefination, which after Yamamoto’s aldol reaction and formation of the sulfone gave the C15-C24 subunit (93) in a 6% overall yield over the 14 steps (Scheme 4.19).

Scheme 4.19: Synthesis of the C15-C24 subunit (93)
5.0: Attempted synthesis of C1-C23 subunit for palmerolide E (198)

5.1: Retrosynthesis

To form the macrolide core of palmerolide E (198) the C1-C14 subunit (98) had to be coupled with the C15-C23 subunit (95). This was envisaged to be achieved via a Julia-Kocienski olefination between the oxidised C1-C14 subunit (199) with the C15-C23 subunit (95) to form the C14-C15 olefin of 198 (Scheme 5.1).

Scheme 5.1: Retrosynthesis of C1-C23 subunit (198)
5.2: C1-C14 subunit (98) coupling with C15-C23 subunit (95)

5.2.1: Classical Julia olefination

In 1973, Julia and Paris reported an alkene bond construction protocol via a reductive elimination of β-acyloxsulfonyl (Scheme 5.2). This olefination relied on the formation of a sulfonyl anion by deprotonation of the phenyl sulfone, followed by the addition of an aldehyde to give the β-acyloxsulfone, which after acylation then reductive elimination gives the olefin. This method gave access to the alkene functionality in a stereoselective manner with (E)-selective products.

![Scheme 5.2: Classical Julia olefination mechanism](image)

5.2.2: Modified Julia olefination

In the 1990’s, Julia and co-workers reported a modified Julia olefination reaction substituting the phenylsulfone for a heteroaryl sulfone derivative (Figure 5.1). Benzothiazol-2-ylsulfones (BT sulfone) and a further three major modifications of the sulfone heterocycle have been reported, which all display various degrees of reactivity and stereoselectivity.
Figure 5.1: Heterocyclic variants of the modified Julia olefination

In comparison with the phenyl sulfone, the BT-sulfone protocol gives rise to the alkene product via an alternative pathway (Scheme 5.3).\textsuperscript{105,106} The reaction commences with the deprotonation of BT-sulfone, and the resulting anion acts as the nucleophilic partner in the reaction manifold. This species subsequently adds to the electrophilic carbonyl component, forming a transient $\beta$-alkoxysulfone intermediate. The alkoxide, attacks the electrophilic C=N bond of the benzothiazole portion of the molecule in an intramolecular fashion. This series of consecutive reactions results in a putative spirocyclic intermediate that selectively breaks down via an overall Smiles rearrangement to afford the alkene together with loss of sulfur dioxide and elimination of metallated benzothiazolone.

Scheme 5.3: Mechanistic rationale for modified Julia olefination
The stereoselectivity of the modified Julia olefination is dependent upon the R’ and R” substituents of both the sulfone and carbonyl components. When the R’ and R” groups are non-conjugated alkyl substituents, the resultant alkene product displays little or no stereocontrol. This is attributable to the poor diastereoselective addition of the aldehyde to the sulfone component. Alternatively, when the R’ group is a vinyl or aryl substituent and the R” substituent is an alkyl group, the (Z)-alkene product dominates. This outcome can be explained by the stabilization of the metallated sulfone by the conjugated R’ group, which allows the β-alkoxysulfone to undergo reversible retroaddition/addition reactions, which leads to the equilibration of the diastereomeric alkoxides (Scheme 5.3).

5.2.3: Modified Julia-Kocienski olefination

In 1998, Kocienski and co-workers reported a 1-phenyl-1H-tetrazol-5-yl (PT) sulfone as an alternative to the BT-sulfone for the modified Julia olefination. Using the PT-sulfone there is reduced tendency to self-condense providing a greater selectivity for the E-alkene. Kocienski tested the effect of both solvent polarity and base counterion on the outcome of the olefination reaction. An analogous trend to the BT-sulfone was observed; increased solvent polarity enhanced the tendency towards the formation of E-alkenes (DME > THF > Et₂O > PhMe), as did increasing the size of the counterion (Li⁺ < Na⁺ < K⁺).
The mechanism of the modified Julia-Kocienski follows that of the BT-sulfone (Scheme 5.4),\textsuperscript{104} initial deprotonation with base forms the lithium anion \( \text{E} \) and subsequent addition of a carbonyl gives the two β-alkoxysulfones \( \text{F} \) and \( \text{G} \). However, unlike the BT-sulfone, the addition of the aldehyde to the PT-sulfone predominantly forms the \textit{anti}-adduct \( \text{G} \), due to the bulky nature of the phenyl substituent. The Smiles rearrangement orients the \( \text{R} \) groups in a \textit{syn}-arrangement \( \text{H} \) to reduce the steric clash with the phenyl group and subsequent elimination of the sulfur dioxide and the PT group gives an \textit{E}-alkene.
Scheme 5.4: Mechanism of modified Julia-Kocienski olefination
5.2.4: Attempted synthesis of C14-C15 olefin

To set the stage for the Julia-Kocienski olefination alcohol 98 had to be oxidised to the aldehyde 199. This was achieved by treating alcohol 98 with Dess-Martin periodinane to give the aldehyde 199 (Scheme 5.5).

Scheme 5.5: Dess-Martin periodinane oxidation of alcohol 98

The Julia-Kocienski olefination was attempted by treating the C15-C23 sulfone (95) with LiHMDS at -78 °C for ten minutes then addition of the freshly prepared aldehyde 199, the reaction mixture was left stirring at -78 °C for four hours, but unfortunately this did not give any of the C1-C23 product (198) and no starting aldehyde was recovered (Scheme 5.6). This reaction was attempted using various conditions and different bases but none tested provided the C1-C23 subunit 198 (Table 5.1).
Scheme 5.6: Attempted Julia-Kocienski olefination between the C1-C14 aldehyde (199) and the C15-C23 sulfone (95)

Table 5.1: Conditions attempted in the Julia-Kocienski olefination between the C1-C14 aldehyde (199) and the C15-C23 sulfone (95)

<table>
<thead>
<tr>
<th>Sulfone (eq)</th>
<th>Aldehyde (eq)</th>
<th>Base (eq)</th>
<th>Time</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>LiHMDS 1.5</td>
<td>4 hours</td>
<td>-78</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.2</td>
<td>LiHMDS 1.5</td>
<td>6 hours</td>
<td>-78</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.2</td>
<td>NaHMDS 1.7</td>
<td>4 hours</td>
<td>-78</td>
<td></td>
</tr>
</tbody>
</table>

5.3: Conclusion

We believe the unsuccessful attempts at the Julia-Kocienski olefination, were due to the small scale of the reaction and moisture being present in the reaction mixture. Hence it is hoped that this can be rectified by increasing the scale of the reaction, or if needed by swapping the substituents and placing the sulfone on the C1-C14 subunit and the aldehyde on the C15-C23 subunit.
Unfortunately due the lack of material this reaction between the C1-C14 aldehyde (199) and the C15-C23 sulfone (95) could not be repeated and tested on a larger scale.
Summary and Future Work

6.1 Final steps towards palmerolide E (18)

Once the problems with the Julia-Kocienski olefination, between aldehyde 199 and the C15-C23 subunit (95) have been overcome, there would be a further four steps to complete the synthesis of palmerolide E (18); involving TES-deprotection, macrolactonization, deprotection of the three TBS-protected alcohols and oxidation of the primary alcohol to the aldehyde, which would give palmerolide E (18) in a longest linear sequence of twenty steps (Scheme 6.1)
Scheme 6.1: Final steps towards the synthesis of palmerolide E (18)

6.2 Final steps towards palmerolide A (14)

The synthesis of palmerolide A (14) is expected to be completed following a similar route devised for the synthesis of palmerolide E (18, Scheme 6.2). A Julia-Kocienski olefination between aldehyde 199 and the C15-C24 subunit (93), followed by TES-deprotection and macrolactonization should furnish macrolide 201, which after a global deprotection and introduction of the enamide would give palmerolide A (14), in a longest linear sequence of twenty steps.
Scheme 6.2: Final steps towards the synthesis of palmerolide A (14)

6.3 Summary

In the synthesis of palmerolide A (14), the coupling between the C1-C8 fragment (91) and the C9-C14 fragment (96) was achieved. Further elaboration gave the C1-C14 subunit (98), which can also be used in the synthesis of palmerolide E (18). The synthesis of both the C15-24 subunit (93) for palmerolide A and the C15-C23 subunit (95) for palmerolide E, have been completed with the investigation into the Julia-Kocienski coupling of these fragments with the oxidised C1-C14 subunit (199) under investigation. Although neither synthesis of palmerolide A or E were completed, significant
progress was made and useful information into the key fragments was obtained during these studies.
Experimental

7.1: General experimental details

All reactions were performed in flame dried glassware under a positive pressure of argon, with magnetic stirring unless otherwise stated.

7.2: General procedures

\(^1\text{H NMR spectra}\) were recorded on the following instruments: Bruker Avance 300 (300.1 MHz) instrument, Bruker Avance II 400 (400.1 MHz) instrument or Bruker Avance 500 (499.9 MHz) instrument. An internal reference of $\delta_{\text{H}}$ 7.27 and 7.16 was used for the residual protons in CDCl$_3$ and C$_6$D$_6$ respectively. The chemical shift data for each signal are given as $\delta$ in units of parts per million (ppm) relative to tetramethylsilane (TMS) where $\delta_{\text{TMS}} = 0.00$ ppm. The multiplicity of each signal is indicated by: s (singlet); br s (broad singlet); d (doublet); t (triplet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dddd (doublet of doublet of doublet of doublets); ddt (doublet of doublet of triplets); q (quartet); qd (quartet of doublets); or m (multiplet). The number of protons (n) for a given resonance is indicated by nH. Coupling constants ($J$) are quoted in Hz, they are recorded to the nearest 0.1 Hz and are uncorrected. Assignments were determined either on the basis of unambiguous chemical shift, coupling pattern or by analogy to fully interpreted spectra.


$^{13}$C NMR spectra were recorded on a Bruker Avance 300 (75.5 MHz) instrument, Bruker Avance II 400 (100.6 MHz) instrument or Bruker Avance 500 (125.7 MHz) at probe temperature using an internal deuterium lock. The chemical shift data for each signal are reported in ppm on the $\delta$ scale ($\delta_{TMS} = 0$). The solvent peak was used as a reference value for $^{13}$C NMR: CDCl$_3 =$ 77.00 or C$_6$D$_6 =$ 128.06.

IR spectra were recorded on a Perkin-Elmer Paragon Series 1000 FTIR spectrometer as thin films. Absorption maxima ($\nu_{\text{max}}$) are reported in wavenumbers (cm$^{-1}$).

Optical rotations were recorded on a Perkin-Elmer Model 341 automatic polarimeter instrument at the sodium D line (589 nm), in cells with a path length of 1 cm and are reported as: $[\alpha]_T^\circ$, concentration (c in g/100 mL) and solvent, where T is temperature in $^\circ$C.

HRMS and LRMS (High and Low resolution mass spectrometry) were recorded using a Thermofisher LTQ Orbitrap XL mass spectrometer, Finnigan MAT 900 XLT mass spectrometer, Micromass Quattro II mass spectrometer, Water ZQ4000 mass spectrometer or a Thermofisher DSQ-II mass spectrometer by EPSRC national mass spectrometry service (Swansea, UK) using Electron Impact (EI), Electron Ionisation (ES), Chemical Ionisation (CI), Fast Atom Bombardment (FAB) or Atmospheric Pressure Chemical Ionisation (APCI) techniques. Other spectra were recorded on a Thermo Fisher Q Exactive mass spectrometer or a Waters micromass LCT.
mass spectrometer by the University of St Andrews mass spectrometry service (School of Chemistry and Biomolecular Sciences).

*Analytical thin layer chromatography* (TLC) was carried out on E. Merck precoated (25 µm) silica gel 60 F254 plates. Reagent grade ethyl acetate, hexanes (commercial mixture), dichloromethane and methanol were purchased and used as is for chromatography. Visualisation was by absorption of UV light, or thermal development after dipping in either an aqueous solution of potassium permanganate, an ethanolic solution of phosphomolybdic acid (PMA) or an anisaldehyde dip.

*Flash column chromatography* was carried out on silica gel 60 (E. Merck, 40-63 µm) under a positive pressure of compressed air.

*Kugelrohr bulb-to-bulb distillations* were carried out using a Büchi B-585 machine. Boiling points are the actual oven temperatures.

*Reagents and Solvents* were purified by standard means. Dimethyl sulfoxide (DMSO) was dried over CaH₂, distilled under high vacuum and stored over 4Å molecular sieves. Methanol was distilled from magnesium methoxide in a recycling still under nitrogen. Ethyl acetate was purified by washing with 5% Na₂CO₃, and saturated aqueous CaCl₂ and dried with MgSO₄. Dichloromethane, tetrahydrofuran (THF), diethyl ether and toluene were dried by passage through two columns of alumina using an M-BRAUN SPS-800 solvent purification system. Anhydrous N,N-dimethylformamide was
purchased from Aldrich UK and dried by distillation from 4 Å molecular sieves onto 4 Å molecular sieves under an atmosphere of argon. Triethylamine (Et₃N) and BF₃·Et₂O were distilled from CaH₂ under Ar. Oxalyl chloride was distilled from CaH₂ into potassium carbonate under argon. All other reagents were purchased from Acros UK, Aldrich UK, Fisher UK or Molekula. All other chemical were used as received, except otherwise stated in the experimental procedure. Aqueous solutions of sodium bicoarbonante (NaHCO₃), sodium chloride (brine), potassium sodium tartrate and ammonium chloride (NH₄Cl) were saturated. All experiments were performed under anhydrous conditions and an inert atmosphere of argon, using a vacuum manifold with argon passed through calcium chloride and self-indicating silica gel. Hexane refers to n-hexane and petroleum ether to the fraction boiling between 40 and 60 °C. Room temperature refers to the temperature of approximately 22 °C.
7.3: Preparation of reagents

Methyl 2-(triphenylphosphoranylidene) acetate (200)\(^\text{107}\)

![Structural formula of methyl 2-(triphenylphosphoranylidene) acetate (200)](image)

To a stirred solution of triphenylphosphine (18.0 g, 68.6 mmol) in ethyl acetate (120 mL), was added a solution of methyl bromoacetate (6.50 mL, 68.6 mmol) in ethyl acetate (30 mL). The solution was left to stir for 14 h at room temperature upon which a white precipitate formed. The precipitate was filtered off, washed with diethyl ether (30 mL) and the filtrate was dried over MgSO\(_4\). The mixture was dissolved in dichloromethane (150 mL), separated with 1 M NaOH (100 mL) and vigorously shaken. The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 40 mL). The combined organic layers were washed with brine, dried over MgSO\(_4\) then concentrated in vacuo to give the product 200 (21.7 g, 95%) as a white powder.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.70–7.43 (15\text{H}, \text{Ar-}H), 3.53 (3\text{H}, \text{s, O-CH}_3)\) and 2.91 (1H, s, C-CH\(_3\)).
**1-Hydroxy-1,2-benziodoxol-3 (1H)-one 1-oxide (201)**

![OH](image)

2-Iodobenzoic acid (50.0 g, 200 mmol) was added to a solution of Oxone (181.0 g, 290 mmol) in water (650 mL). The reaction mixture was warmed to 75 °C then stirred at this temperature for 3 h, after which the suspension was cooled to 5 °C and left stirring at this temperature for 2 h. The mixture was filtered, then rinsed with water (6 x 100 mL) and acetone (2 x 100 mL), the precipitate was dried at room temperature for 16 h to give the product 201 (48.5 g, 87%) as a white crystalline solid.

**1,1,1-Triacetoxy-1-dihydro-1,2-benziodoxol-3 (1H)-one (202)**

![AcO](image)

1-Hydroxy-1,2-benziodoxol-3 (1H)-one 1-oxide 201 (48.5 g, 170 mmol) was added to a solution of Ac₂O (200 mL) and TsOH·H₂O (500 mg). The mixture was heated to 80 °C and stirred at this temperature for 3 h, then cooled to 0 °C. The cold mixture was filtered, and then rinsed with diethyl ether (5 x 50 mL). The resulting white crystalline solid 202 (59.5 g, 81%) was transferred to an argon flushed dark flask, and stored in a freezer.
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.29 (1H, d, $J$ = 8.1 Hz, Ar-H), 8.09 (1H, t, $J$ = 8.1 Hz, Ar-H), 7.93-7.90 (2H, m, Ar-H), 2.32 (3H, s, CH$_3$) and 1.99 (6H, s, 2 x CH$_3$).

**Diazomethyl dimethylphosphonate (184)$^{94,95}$**

![Diazomethyl dimethylphosphonate (184)](image)

**Method A:**

A solution of N-(bromomethyl)phthalimide 185 (10.0 g, 41.7 mmol), trimethyl phosphite (5.40 mL, 45.8 mmol) in xylene (20 mL) was heated under reflux for 5 h. The solvent was partially reduced in vacuo and the resulting solid was filtered and dried under vacuum to give 186 (10.9 g, 93%) as a white powder.

To a solution of 186 (8.40 g, 31.0 mmol) in ethanol (130 mL), was added hydrazine (2.65 mL, 54.6 mmol). The reaction mixture was refluxed for 1.5 h. The un-reacted phosphonate 186 was filtered off; the mixture was concentrated under reduced pressure and distilled (120 °C, 0.5 mbar) to give 187 (530 mg, 12%) as a colourless oil.

To a solution of 187 (500 g, 3.60 mmol) in dichloromethane (10 mL) at -5 °C, was added a solution of aqueous NaNO$_2$ (300 mg, 4.30 mmol) in water (3 mL), followed by acetic acid (430 mg, 7.20 mmol). The reaction mixture was stirred for 4 h at 0 °C. The reaction was quenched with aqueous potassium...
carbonate (4 mL), extracted with dichloromethane (3 x 10 mL), dried over potassium carbonate, filtered and reduced under pressure. The product was purified by distillation (87 °C, 0.5 mbar) to give the diazomethyl dimethylphosphonate 184 (380 mg, 70%) as a colourless oil.

Method B:
A mixture of dimethyl methylphosphonate 188 (2.00 g, 16.1 mmol) in THF (40 mL) was cooled to -78 °C, and n-butyl lithium (1.6 M in hexane, 10.1 mL, 16.1 mmol) was slowly added to the mixture and stirred for 30 min. 2,2,2-Trifluoroethyl trifluoroacetate (3.20 mL, 24.2 mmol) was added and the mixture was warmed to room temperature over 15 min. The mixture was partitioned between diethyl ether (250 mL) and 3M HCl (10 mL), and the organic layer was washed with aqueous NaHCO₃, brine, dried over MgSO₄ and concentrated under reduced pressure. The residue 189 was dissolved in acetonitrile (40 mL), followed by the addition of 4-acetamidobenzenesulfonyl azide (4.10 g, 16.1 mmol). The solution was cooled to 0 °C and triethylamine (2.20 mL, 16.1 mmol) was slowly added. The solution was stirred for 16 h at room temperature and the solvent was then removed under reduced pressure. The crude residue was suspended in chloroform (20 mL) filtered and washed with chloroform (10 mL). Column chromatography (1 : 9, hexane : ethyl acetate) of the concentrated filtrate gave the product 184 (1.12 g, 46%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃) δ 3.97 (1H, d, J = 10.6 Hz, CH) and 3.82 (6H, d, J = 10.5 Hz, O-CH₃).
Dimethyl 1-diazo-2-oxopropyl phosphonate (190)$^{96}$

![Chemical Structure](image)

A solution of TsCl (8.00 g, 42.0 mmol) and sodium azide (2.73 g, 42.0 mmol) in acetone (120 mL) and water (120 mL) was stirred at 0 °C for 2 h. The acetone was evaporated, and the reaction mixture was extracted from diethyl ether (3 x 80 mL), and the organic phase was dried in Na$_2$SO$_4$. Evaporation of the solvent gave tosyl azide (8.10 g, 98%) as a colourless oil.

A solution of NaH (990 mg, 41.5 mmol) in THF (150 mL) was cooled to 0 °C. Dimethyl (2-oxopropyl)phosphonate $^{106}$ (6.26 ml, 37.7 mmol) in THF (50 mL) was added and the resulting mixture was stirred at 0 °C for 1 h after which tosyl azide (8.10 g, 37.7 mmol) was added and left to stir for 30 min. The reaction mixture was purified by column chromatography (1 : 9, hexane : ethyl acetate) to afford Bestmann-Ohiro reagent $^{190}$ (5.10 g, 69%) as a colourless oil.

$^1$H NMR (300 MHz, CDCl$_3$) δ 3.86 (6H, d, $J = 11.9$ Hz, 2 x O-CH$_3$) and 2.28 (3H, s, CH$_3$).

$(Z)$-Trimethyl (1-methoxy-3-methyl-1, 3-butadienyloxy)silane (156)$^{110}$

![Chemical Structure](image)
A solution of $n$-butyl lithium (1.6 M in hexane, 32.9 mL, 52.5 mmol) was added to a solution of diisopropylamine (6.90 mL, 52.6 mmol) in THF (60 mL) at -78 °C. The mixture was stirred for 30 min and methyl-3,3-dimethyl acrylate 161 (5.00 g, 43.8 mmol) and TMSCl (7.60 mL, 56.94 mmol) were added sequentially over 15 min intervals. After 30 min the mixture was warmed to room temperature, stirred for a further 2 h, and quenched with NaHCO$_3$ (40 mL). The organic portions were extracted with dichloromethane (3 x 40 mL) and the combined organic extracts were dried over MgSO$_4$. The solvent was removed under reduced pressure and the residue was purified by Kugelrohr distillation (40 °C, 0.5 mbar) to afford the silyl enol ether 156 (5.11 g, 63%) as a colourless oil.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.78 (1H, dt, $J$ = 2.7, 0.8 Hz, H$_{4a}$), 4.53 (1H, dq, $J$ = 2.7, 1.4 Hz, H$_{4b}$), 4.26 (1H, s, CH$_2$), 3.54 (3H, s, OCH$_3$), 1.93 (3H, dd, $J$ = 1.4, 0.7 Hz, CH$_3$) and 0.22 (9H, s, SiCH$_3$).

4-Methoxybenzyl-2,2,2-trichloroacetimidate (203)$^{111}$

To a solution of 4-methoxybenzyl alcohol (34.0 g, 250 mmol) in a KOH (300 mL, 100g in 100 mL of H$_2$O) and dichloromethane (300 mL) solution was added TBA·H$_2$SO$_4$ (870 mg, 2.56 mmol). This was cooled to -10 °C upon which TCCN (29.6 mL, 294.4 mol) was added, the resulting mixture was
warmed to room temperature then left to stir for 1 h. The product was extracted with dichloromethane (3 x 100 mL), dried over Na₂SO₄, the solvent removed under reduced pressure and the residue was purified by Kugelrohr distillation (150 °C, 0.5 mbar) to give the product 203 (53.2 g, 77%) as a pale orange oil.

$^{1}$H NMR $\delta$ (300 MHz, CDCl₃) $\delta$ 7.38 (2H, d, $J = 8.8$ Hz, ArH), 6.92 (2H, d, $J = 8.8$ Hz, ArH), 5.30 (2H, s, CH₂) and 3.83 (3H, s, OCH₃).

7.4: Experimental for Chapter 2

Tetrahydro-2H-pyran-2-ol (99)$^{112}$

Concentrated HCl (15.0 mL, 95.1 mmol) was added to a stirring solution of 3,4-dihydro-2H-pyran (40.0 g, 476 mmol) in water (440 mL) at 0 °C over 10 min. The solution was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched with aqueous NaHCO₃, the product extracted with dichloromethane (3 x 100 mL), dried over MgSO₄ and concentrated under reduced pressure. The product was subsequently purified using Kugelrohr distillation (80 °C, 2 mbar) to give the product 99 (27.1 g, 56%) as a colourless oil.
\( R_f 0.71 \) (20\% ethyl acetate : petroleum ether); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \)

4.84-4.80 (1H, m, \( H_1 \)), 4.46 (1H, d, \( J = 4.6 \text{ Hz}, O-H \)), 3.98–3.89 (1H, m, \( H_{5\alpha} \)), 3.51–3.43 (1H, m, \( H_{5\beta} \)), 1.83–1.69 (2H, m, \( H_2 \)) and 1.51–1.42 (4H, m, \( H_3 \) and \( H_4 \)).

**(E)-Methyl-7-hydroxyhept-2-enoate (100)**

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

To a stirred solution of carbomethoxymethyl triphenylphosphonium 200 (9.20 g, 27.4 mmol) in THF (100 mL) was added, 2-tetrahydro-2H-pyran-2-ol 99 (2.00 g, 19.6 mmol) and the mixture was heated under reflux for 3 h. The solvent was removed under reduced pressure, and the concentrate was stirred for 45 min in a 7 : 3 mixture of diethyl ether and petroleum ether (40 mL). The resulting suspension was filtered and washed with the same mixture (10 mL). The crude mixture was concentrated under reduced pressure and the residue was purified by column chromatographed (4 : 1, hexane : ethyl acetate) to give the product 100 (2.03 g, 66\%, \( E : Z = 9 : 1 \)) as a colourless oil.

\( R_f 0.55 \) (50\% ethyl acetate : petroleum ether); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \)

6.96 (1H, dt, \( J = 15.8, 6.8 \text{ Hz}, H_3 \)), 5.82 (1H, dt, \( J = 15.7, 1.6 \text{ Hz}, H_2 \)), 3.71 (3H, s, O-CH\(_3\)), 3.68-3.61 (2H, m, \( H_7 \)), 2.27–2.20 (2H, m, \( H_4 \)) and 1.68–1.48 (4H, m, \( H_5 \) and \( H_6 \)).
(E)-7-Methoxy-7-oxo-hept-5-enoic acid (103)\textsuperscript{114}

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{OH}
\end{align*}
\]

To a solution of TEMPO (100 mg, 640 µmol) and BIAB (2.06 g, 6.41 mmol) in a mixture of acetonitrile and water (14 mL, 1 : 1), (E)-methyl-7-hydroxyhept-2-enoate 100 (500 mg, 3.20 mmol) was added at 0 °C. The solution was allowed to warm to room temperature where it was stirred for 12 h. The reaction was quenched with aqueous NH\textsubscript{4}Cl (10 mL), extracted with dichloromethane (3 x 15 mL) and dried over sodium sulfate. The residue was purified by column chromatography (1 : 9, hexane : ethyl acetate) to provide the carboxylic acid 103 (0.54 g, 98%) as a colourless oil.

\[R_f\] 0.51 (50% ethyl acetate : petroleum ether); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\)

11.07 (1H, br s, C(O)-OH), 6.94 (1H, dt, \(J = 15.6, 6.9\) Hz, H\textsubscript{5}), 5.84 (1H, dt, \(J = 15.7, 1.5\) Hz, H\textsubscript{6}), 3.70 (3H, s, O-CH\textsubscript{3}), 2.36 (2H, t, \(J = 7.3\) Hz, H\textsubscript{2}) 2.26 (2H, ddt, \(J = 7.4, 7.0, 1.6\) Hz, CH\textsubscript{4}) and 1.79 (2H, tt, \(J = 7.4, 7.3\) Hz, H\textsubscript{3})

5-Hexenoic acid (103)\textsuperscript{115}

\[
\begin{align*}
\text{O} & \\
\text{H} & \quad \text{OH}
\end{align*}
\]

To a solution of TEMPO (625 mg, 4.0 mmol) and BIAB (12.9 g, 40.0 mmol) in a mixture of acetonitrile and water (100 mL, 1 : 1), 5-hexen-1-ol 105 (2.00
g, 20.0 mmol) was added at 0 °C. The solution was allowed to warm to room temperature where it was stirred for 14 h. The reaction was quenched with aqueous NH₄Cl (100 mL), extracted with dichloromethane (3 x 100 mL) and dried over sodium sulfate. The residue was purified by column chromatography (1 : 9, hexane : ethyl acetate) to provide the carboxylic acid 103 (1.21 g, 80%) as a colourless oil.

R₉ 0.39 (20% ethyl acetate : petroleum ether); ¹H NMR (300 MHz, CDCl₃) δ 11.82 (1H, br s, OH), 5.83-5.73 (1H, m, H₅), 5.07-4.99 (2H, m, H₆), 2.37 (2H, t, 7.6 Hz, H₂), 2.15-2.09, (2H, m, H₄) and 1.74 (2H, tt, 7.6, 7.6 Hz, H₃).

Dimethyl-2-oxohept-6-enylphosphonate (101)

To a suspension of NaH (520 mg, 21.6 mmol, 60% dispersion in mineral oil) in THF (30 mL), dimethyl-2-oxypropylphosphonate 106 (1.70 mL, 12.0 mmol) was added drop wise, at room temperature. The resulting mixture was stirred for 1.5 h prior to the addition of a solution of n-butyl lithium in hexane (8.25 mL of a 1.6 M in hexane, 13.2 mmol) at 0 °C. The solution was stirred for 20 min and 4-bromobutene (1.40 mL, 14.4 mmol) was added. The resulting mixture was warmed to room temperature and stirred for a further 3 h. The reaction was quenched with 2M HCl (8 mL), extracted with dichloromethane (3 x 15 mL), the combined organic extracts were washed.
with brine (20 mL) and dried over MgSO$_4$. The solvent was removed under reduced pressure and column chromatography (1 : 9, hexane : ethyl acetate) afforded the product 101 (2.45 g, 95%) as a colourless oil.

$R_f$ 0.47 (5% MeOH : CH$_2$Cl$_2$); IR (thin film) 2957, 1713, 1360, 1252, 1184, 1018, 825 and 808 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.70 (1H, ddt, $J = 10.3, 8.6, 6.9$ Hz, H$_6$), 4.99–4.89 (2H, m, H$_7$), 3.72 (6H, d, $J = 11.2$ Hz, PO-CH$_3$ x 2), 3.03 (2H, d, $J = 22.8$ Hz, H$_1$), 2.57 (2H, t, $J = 7.3$ Hz, H$_3$), 2.00 (2H, dt, $J = 7.2, 7.2$ Hz, H$_5$) and 1.63 (2H, tt, $J = 7.3, 7.3$ Hz, H$_4$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 201.6, 137.8, 115.1, 52.9, 52.9, 43.2, 41.9, 32.7 and 22.3; HRMS (ES$^+$) calc. For C$_9$H$_{18}$O$_4$P [M + H]$^+$ 221.0937, found 221.0937.

**Methyl-8-(dimethoxyphosphoryl)-7-oxooct-(2E)-enoate (91)**

![Methyl-8-(dimethoxyphosphoryl)-7-oxooct-(2E)-enoate (91)](image)

**Method A:**

To a solution of dimethyl-2-oxohept-6-enylphosphonate 101 (2.20 g, 9.99 mmol) in dichloromethane (30 mL) was added methyl acrylate (30 mL) and Grubbs II catalyst 107 (100 mg, 118 µmol). The solution was heated under reflux for 16 h upon which a further portion of Grubb’s second-generation catalyst 107 (100 mg, 118 µmol) was added and this was left stirring at this temperature for a further 24 h. The solution was concentrated under reduced
pressure and purified by column chromatography (1 : 9, hexane : ethyl acetate) to yield the olefin 91 (2.78 g, 94 %, \(E : Z = 15 : 1\)) as a brown oil.

**Method B:**

To a solution of dimethyl-2-oxohept-6-enylphosphonate 101 (180 mg, 820 \(\mu\)mol) in dichloromethane (3 mL) was added a solution of methyl acrylate (3 mL) and a solution of the Nolan-modified ruthenium catalyst 119 (10.0 mg, 8.81 \(\mu\)mol) in dichloromethane (5 mL). The solution was heated under reflux for 16 h upon which a further portion of the Nolan-modified ruthenium catalyst 119 (10.0 mg, 8.81 \(\mu\)mol) was added and this was left stirring at this temperature for a further 24 h. The solution was concentrated under reduced pressure and purified by column chromatography (1 : 9, hexane : ethyl acetate) to yield the olefin 91 (170 mg, 79 %, \(E : Z = 10 : 1\)) as a brown oil.

\(R_f\) 0.59 (5% MeOH : CH\(_2\)Cl\(_2\)); \textbf{IR} (thin film) 2957, 1713, 1653, 1437, 1254, 1182, 1018, 829 and 814 \(\text{cm}^{-1}\); \textbf{\(^1\)H NMR} (300 MHz, CDCl\(_3\)) \(\delta\) 6.90 (1H, dt, \(J = 15.6, 7.0\) Hz, \(H_3\)), 5.81 (1H, dt, \(J = 15.7, 1.5\) Hz, \(H_2\)), 3.76 (6H, d, \(J = 11.3\) Hz, PO-CH\(_3\) \(\times 2\)), 3.76 (3H, s, C(O)O-CH\(_3\)), 3.06 (2H, d, \(J = 22.9\) Hz, \(H_8\)), 2.63 (2H, t, \(J = 7.2\) Hz, \(H_6\)), 2.20 (2H, ddt, \(J = 1.6, 7.1, 7.1\) Hz, \(H_4\)) and 1.74 (2H, tt, \(J = 7.3, 7.2\) Hz, \(H_5\)); \textbf{\(^{13}\)C NMR} (75 MHz, CDCl\(_3\)) \(\delta\) 202.2, 147.2, 134.2, 124.0, 52.1, 50.5, 42.0, 39.6, 25.4 and 20.5; \textbf{HRMS} (ES\(^+\)) calc. For \(\text{C}_{11}\text{H}_{20}\text{O}_{6}\text{P}\) [M + H]\(^+\) 279.0992, found 279.0996.
4-(tert-Butyldimethylsilyl)oxy-butan-1-ol (126)\textsuperscript{116}

\[
\text{TBSO}\begin{array}{c}\cdots\end{array}\text{OH}
\]

To a solution of 1,4-butanediol 125 (19.7 mL, 222 mmol), triethylamine (13.4 mL, 96.2 mmol) and DMAP (900 mg, 7.36 mmol) in dichloromethane (80 mL) at room temperature was slowly added a solution of TBSCI (11.2 g, 74.3 mmol) in dichloromethane (20 mL). After 16 h, the reaction solution was quenched with brine (100 mL) and the organics were extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with water (200 mL), brine (100 mL), dried (MgSO\(_4\)), filtered and concentrated under reduced pressure. Purification by column chromatography (7 : 3, hexane : ethyl acetate) provided alcohol 126 (25.8 g, 86\%) as a colourless oil.

\(R_f\) 0.43 (50\% EtOA : petroleum ether); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.70-3.62 (4H, m, H\(_1\) + H\(_4\)), 2.54 (1H, t, \(J = 5.4\) Hz, OH), 1.71-1.60 (4H, m, H\(_2\) + H\(_3\)), 0.91 (9H, s, Si-C(CH\(_3\))\(_3\)), 0.08 (6H, m, Si-CH\(_3\)).

4-(tert-Butyldimethylsilyl)oxy-butanal (204)\textsuperscript{115}

\[
\text{TBSO}\begin{array}{c}\cdots\end{array}\text{O} \quad \text{H}
\]
To a solution of oxalyl chloride (6.78 mL, 78.4 mmol) in dichloromethane (100 mL) at -78 °C was slowly added DMSO (6.66 mL, 94.2 mmol). After 30 min, a solution of alcohol 126 (8.00 g, 39.2 mmol) in dichloromethane (50 mL) was added dropwise. After 2 h, triethylamine (19.1 mL, 274 mmol) was added and the slurry was allowed to attain room temperature. After 1 h, an aqueous solution of NH₄Cl (100 mL) was added and the organics were extracted with dichloromethane (3 × 100 mL). The combined organic extracts were washed with water (100 mL), brine (100 mL), dried (MgSO₄), filtered and concentrated under reduced pressure to give the crude aldehyde 204, which was used without further purification.

Rf 0.71 (25% ethyl acetate : petroleum ether); \(^1\)H NMR (400 MHz, CDCl₃) δ 9.80 (1H, t, J = 1.7 Hz, CHO), 3.66 (2H, t, J = 5.9 Hz, H₄), 2.51 (2H, dt, J = 1.7, 7.2 Hz, H₂), 1.87 (2H, m, H₃), 0.89 (9H, s, Si-(CH₃)₃) and 0.05 (6H, m, Si-CH₃).

\((E)-\text{Ethyl 6-}(\text{tert-butyldimethylsilyl})\text{oxy-hex-2-enoate (121)}\)\(^{115}\)

\[
\text{TBSO} \begin{array}{c}
\text{O}
\end{array} \begin{array}{c}
\text{Et}
\end{array} \]

To a solution of triethyl phosphonoacetate 127 (9.36 mL, 51.0 mmol), lithium chloride (11.1 g, 262 mmol) and Hünig’s base (4.30 mL, 35.2 mmol) in acetonitrile (100 mL) at room temperature was added a solution of freshly prepared aldehyde 204 (39.2 mmol) in acetonitrile (50 mL). After 18 h, water (100 mL) was added and the organics were extracted with ethyl acetate (3 ×
100 mL). The combined extracts were dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (9 : 1, hexane : ethyl acetate) provided (E)-enoate 121 (7.10 g, 70% over two steps, $E : Z = 30 : 1$) as a colourless oil.

$\text{R}_f$ 0.52 (25% ethyl acetate : petroleum ether); $^1\text{H NMR}$ (400 MHz, CDCl₃) $\delta 7.00$ (1H, dt, $J = 15.7, 7.0$ Hz, H₃), $5.84$ (1H, dt, $J = 15.7, 1.6$ Hz, H₂), 4.19 (2H, q, $J = 7.9$ Hz, OCH₂), 3.47 (2H, t, $J = 6.1$ Hz, H₆), 2.28 (2H, ddt, $J = 1.6, 8.4, 7.0$ Hz, H₄), 1.72-1.63 (2H, m, H₅), 1.29 (3H, t, $J = 7.2$ Hz, OCH₂CH₃), 0.90 (9H, s, Si-C(CH₃)₃) and 0.05 (6H, m, Si-CH₃).

(2R, 35)-Ethyl-6-(tert-butyldimethylsilyl)oxy-2, 3-dihydrohexanoate (122)

To a solution of enoate 121 (6.81 g, 26.4 mmol) in t-BuOH : H₂O (1 : 1, 120 mL) at 0 °C was added methanesulfonamide (5.01 g, 52.7 mmol) and AD-mix-α (39.6 g, 1.5 g/mmol of 128). The solution was allowed to attain room temperature, and after 16 h, sodium thiosulfate (78.6 g, 316 mmol) was added. After 1 h, water (100 mL) and dichloromethane (100 mL) were added and the organics were extracted with dichloromethane (3 × 100 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Purification by column chromatography (3 : 2, hexane : ethyl acetate) provided diol 122 (7.52 g, 93%) as a colourless oil.
$R_f$ 0.43 (50% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ -15.1 (c 1.1, CHCl$_3$); IR (thin film) 3412, 2955, 2854, 1747, 1472, 1256, 1100, 837 and 777 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.29 (2H, q, $J = 7.1$ Hz, OCH$_2$) 4.07 (1H, d, $J = 2.2$ Hz, H$_2$), 3.97-3.92 (1H, m, H$_3$), 3.74-3.65 (2H, m, H$_6$), 1.75-1.69 (4H, m, H$_4$ + H$_5$), 1.32 (3H, t, $J = 7.1$ Hz, OCH$_2$CH$_3$), 0.90 (9H, s, Si-C(CH$_3$)$_3$) and 0.08 (6H, m, Si-CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.4, 73.6, 72.3, 63.3, 61.2, 31.0, 29.0, 25.9, 18.3, 14.2 and -5.4; HRMS (ES$^+$) calc. for C$_{14}$H$_{31}$O$_5$Si ([M+H]$^+$) 307.1935, found 307.1938.

(2$R$, 3$S$)-6-(tert-Butyldimethylsilyl)oxy-2-hydroxy-1-ethoxy-1-oxohexan-3-yl benzoate (133)

![Structure](image)

To a solution of diol 122 (4.81 g, 16.5 mmol), triethylamine (5.76 mL, 41.4 mmol) and DMAP (60.0 mg, 570 µmol) in dichloromethane (70 mL) at -78 °C was added benzoyl chloride (1.95 mL, 16.9 mmol) dropwise. After 1 h, the reaction solution was allowed to attain -50 °C. After a further 16 h, an aqueous solution of NaHCO$_3$ (100 mL) was added, and the organics were extracted with dichloromethane (3 × 80 mL). The combined organic extracts were dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure. Purification by column chromatography (19 : 1, hexane : ethyl acetate) provided benzoate 133 (5.06 g, 77%) as a colourless oil.
Rf 0.51 (25% ethyl acetate : petroleum ether); [α]D20 -209 (c 1.0, CHCl3); IR (thin film) 3493, 2954, 2858, 1748, 1723, 1452, 1271, 1110, 835, 777 and 712 cm⁻¹; ¹H NMR (400 MHz, CDCl3) δ 8.02-7.99 (2H, m, Ar-H), 7.60-7.54 (1H, m, Ar-H), 7.47-7.41 (2H, m, Ar-H), 5.46 (1H, dt, J = 7.0, 2.2 Hz, H3), 4.35 (1H, dd, J = 7.5, 2.2 Hz, H2), 4.18 (2H, q, J = 7.2 Hz, OCH2CH3), 3.70-3.65 (2H, m, H6), 3.11 (1H, d, J = 7.4, OH), 2.00-1.92 (2H, m, H4), 1.70-1.62 (2H, m, H3), 1.21 (3H, t, J = 7.2 Hz, OCH2CH3), 0.90 (9H, s, Si-C(CH3)3), 0.05 (3H, m, Si-CH3) and 0.04 (3H, m, Si-CH3); ¹³C NMR (100 MHz, CDCl3) δ 172.9, 165.8, 133.3, 129.9, 129.8, 128.5, 74.8, 71.9, 62.8, 62.3, 28.7, 27.3, 26.1, 18.4, 14.2 and -5.2; HRMS (ES⁺) calc. for C21H35O6Si ([M+H]⁺) 411.2197, found 411.2184.

(2R, 3S)-2, 6-Bis(tert-butyldimethylsilyloxy)-1-ethoxy-1-oxohexan-3-yl benzoate (134)

![TBSO-OTBS-OEt-OEt](image)

To a solution of TBSCl (2.44 g, 16.2 mmol) and imidazole (2.20 g, 32.3 mmol) in DMF (5 mL) at 0 °C was added a solution of alcohol 133 (4.27 g, 10.8 mmol) in DMF (4 mL). After 14 h, a saturated solution of NH₄Cl (10 mL) was added and the organics were extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with water (40 mL) and brine (20 mL), then dried (Na2SO₄), filtered and concentrated under
reduced pressure. Purification by column chromatography (99 : 1 to 19 : 1, hexane : ethyl acetate) provided bis-TBS-ether 134 (4.80 g, 87%) as a colourless oil.

$R_f$ 0.47 (10% ethyl acetate : petroleum ether); $[\alpha]^{20}_D$ -3.0 (c 1.0, CHCl$_3$); IR (thin film) 2955, 2858, 1762, 1724, 1473, 1271, 837, 778 and 711 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.06-8.03 (2H, m, Ar-H), 7.58-7.52 (1H, m, Ar-H), 7.46-7.40 (2H, m, Ar-\text{H}), 5.40-5.34 (1H, dt, $J = 7.1, 3.9$ Hz, \text{H}_3), 4.41 (1H, d, $J = 4.0$ Hz, \text{H}_2), 4.13 (2H, q, $J = 7.2$ Hz, OCH$_2$CH$_3$), 3.68-3.60 (2H, m, \text{H}_6), 1.94-1.83 (2H, m, \text{H}_4), 1.66-1.59 (2H, m, \text{H}_5), 1.18 (3H, t, $J = 7.3$ Hz, OCH$_2$CH$_3$), 0.93 (9H, s, Si-C(CH$_3$)$_3$), 0.89 (9H, s, Si-C(CH$_3$)$_3$), 0.11 (3H, m, Si-CH$_3$), 0.06 (3H, m, Si-CH$_3$) and 0.04 (6H, m, 2 x Si-CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 171.3, 166.1, 133.0, 130.3, 129.8, 128.4, 75.2, 73.4, 62.8, 61.1, 29.0, 26.7, 26.0, 25.8, 22.8, 18.3, 14.2, -4.8 and -5.2; HRMS (ES$^+$) calc. for C$_{27}$H$_{49}$O$_6$Si$_2$ ([M+H]$^+$) 525.3068, found 525.3049.

(2R,3S)-2,6-Bis(tert-butyldimethylsilyl)oxy-3-hydroxy-N-methoxy-N-methyl hexanamide (135)

To a solution of ethyl-ester 134 (3.18 g, 6.21 mmol) and N,O-dimethyl hydroxylamine hydrochloride (900 mg, 9.11 mmol) in THF (75 mL) at -30 ºC was slowly added iso-propylmagnesium chloride (13.9 mL, 27.9 mmol, 2M in
THF). The reaction solution was allowed to attain room temperature and after 6 h a saturated solution of NH₄Cl (70 mL) was added. The organics were extracted with dichloromethane (3 × 80 mL) and the combined organic extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Purification by column chromatography (4 : 1, hexane : ethyl acetate) provided Weinreb amide 135 (2.31 g, 85%) as a colourless oil.

**R**f 0.40 (40% ethyl acetate : petroleum ether); [α]°D -12.5 (c 1.1, CHCl₃); **IR** (thin film) 2930, 2857, 1726, 1646, 1473, 1387, 1255, 1098, 837, 778 and 706 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 4.48 (1H, d, J = 3.6 Hz, H₂), 3.83-3.77 (1H, m, H₃), 3.71 (3H, s, NOC₃H₃), 3.68-3.63 (2H, m, H₆), 3.57 (3H, s, NCH₃), 1.78-1.53 (4H, m, H₄ + H₅), 0.94 (9H, s, Si-C(CH₃)₃), 0.90 (9H, s, Si-C(CH₃)₃), 0.13 (3H, s, Si-CH₃), 0.09 (3H, s, Si-CH₃) and 0.05 (6H, s, 2 × Si-CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ 170.0, 72.5, 63.0, 61.2, 61.0, 33.8, 30.4, 29.1, 26.0, 25.8, 18.4, 18.3, -4.6, -5.3 and -5.3; **HRMS** (ES⁺) calc. for C₂₀H₄₆NO₅Si₂ ([M+H]⁺) 436.2905, found 436.2909.

**(2R,3S)-2,6-Bis(tert-butyldimethylsilyl)oxy-3-(p-methoxybenzyl)oxy-N-methoxy-N-methyl hexanamide (96)**

![Chemical Structure](image)

To a solution of alcohol 135 (2.00 g, 4.60 mmol) and PMBTCA (1.62 g, 5.74 mmol) in toluene (40 mL) at 0 °C was added scandium (III) triflate
(134 mg, 240 µmol). After 6 h, the reaction mixture was filtered, and the filtrand was washed with hexane (3 x 30 mL). The filtrate was concentrated under reduced pressure. Purification by column chromatography (19 : 1, hexane : ethyl acetate) provided PMB ether 96 (1.96 g, 77%) as a colourless oil.

\[ R_f 0.57 \text{ (25\% ethyl acetate : petroleum ether); } [\alpha]_D^{20} -0.9 \text{ (c 1.0, CHCl}_3) \text{; } \text{IR} \text{ (thin film) 2930, 2857, 1726, 1646, 1473, 1387, 1255, 1098, 837, 778 and 706 cm}^{-1} \text{; } \text{1H NMR (400 MHz, CDCl}_3) \delta 7.27 \text{ (2H, d, } J = 8.6 \text{ Hz, Ar-H}, 6.86 \text{ (2H, } d J = 8.6 \text{ Hz, Ar-H}, 4.74-4.55 \text{ (2H, m, OCH}_3\text{H}_n\text{PhOMe + } H_2), 4.52 \text{ (1H, d, } J = 11.0 \text{ Hz, OCH}_3\text{H}_n\text{PhOMe}), 3.80 \text{ (3H, s, NOCH}_3), 3.75-3.65 \text{ (4H, m, NCH}_3), 3.60-3.53 \text{ (2H, m, H}_6), 3.20 \text{ (3H, br s, ArOCH}_3), 1.78-1.41 \text{ (4H, m, H}_s + H_4), 0.93 \text{ (9H, s, Si-C(CH}_3)_3), 0.88 \text{ (9H, s, Si-C(CH}_3)_3), 0.10 \text{ (3H, s, Si-CH}_3), 0.1 \text{ (3H, s, Si-CH}_3) \text{ and 0.03 (6H, s, 2 × Si-CH}_3); } \text{13C NMR (100 MHz, CDCl}_3) \delta 159.1, 131.0, 129.7, 113.7, 80.5, 72.9, 63.1, 55.3, 29.2, 27.3, 26.0, 25.9, 18.3, -4.7, -5.0 \text{ and -5.3; } \text{HRMS (ES}^-) \text{ calc. for C}_{28}H_{54}NO_6Si_2 ([M+H]^-) 556.3479, found 556.3484.}
To a solution of Weinreb amide 96 (1.02 g, 1.88 mmol) in THF (20 mL) at -78 °C was added DIBAL (3.6 mL, 3.60 mmol, 1 M in dichloromethane). After 1 h, the reaction solution was transferred to a stirring aqueous solution of Rochelle salt (30 mL) via cannula. After 3 h, the organics were extracted with dichloromethane (3 × 30 mL) and the combined organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure, to give aldehyde 136 which was used without further purification.

A mixture of 18-crown-6 (700 mg, 2.66 mmol), ground K₂CO₃ (3.66 g, 26.6 mmol) in toluene (50 mL) was stirred for 1 h at room temperature prior to the introduction of a solution of the freshly prepared aldehyde 136 in toluene (10 mL), followed by a solution of C1-C8 phosphonate 91 (2.10 g, 15.2 mmol) in toluene (10 mL). After 20 h, an aqueous solution of NH₄Cl (50 mL) was added and the organics were extracted with dichloromethane (3 × 50 mL) and the combined organic extracts were washed with water (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by column chromatography (9 : 1, hexane : ethyl
acetate) provided dienoate 97 (861 mg, 71% over two steps, E : Z = 6 : 1) as a colourless oil.

$R_f$ 0.33 (25% ethyl acetate : petroleum ether); $[\alpha]_{D}^{20}$ -11.8 (c 1.0, CHCl$_3$); IR (thin film) 2929, 2856, 1722, 1674, 1514, 1247, 1093, 1035, 837 and 775 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.29-7.26 (2H, m, Ar-H), 7.01-6.81 (4H, m, Ar-H, H$_3$ + H$_6$), 6.29 (1H, dd, $J$ = 15.7, 1.7 Hz, H$_8$), 5.85 (1H, dt, $J$ = 15.5, 1.4 Hz, H$_2$), 4.58-4.41 (3H, m, OCH$_2$Ph + H$_{10}$), 3.82 (3H, s, OCH$_3$), 3.74 (3H, s, OCH$_3$), 3.62-3.52 (2H, m, H$_{11}$ + H$_{14a}$), 3.45-3.36 (1H, m, H$_{14b}$), 2.59 (2H, t, $J$ = 7.5 Hz, H$_6$), 2.29-2.18 (2H, m, H$_4$), 1.85-1.59 (6H, m, H$_{12}$ + H$_{13}$ + H$_5$), 0.90 (9H, s, Si-C(CH$_3$)$_3$), 0.88 (9H, s, Si-C(CH$_3$)$_3$) and 0.04-0.01 (12H, m, 4 × Si-CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 199.4, 166.9, 158.9, 148.6, 146.0, 130.4, 129.6, 129.5, 129.4, 121.5, 113.8, 81.8, 80.4, 72.4, 63.1, 55.3, 51.4, 39.0, 31.4, 29.5, 29.1, 27.2, 26.0, 25.8, 22.3, 18.1, -4.8, -5.0 and -5.3; HRMS (ES$^+$) calc. for C$_{35}$H$_{64}$NO$_7$Si$_2$ ([M+NH$_4$]$^+$) 666.4221, found 666.4216.

(2$E$, 8$E$, 10S, 11S)-Methyl-10-((tert-butyldimethylsilyl)oxy)-14-hydorxy-11-(4-methoxy benzyl)oxy-7-oxotetradeca-2, 8-dienoate (137)
To a solution of silyl ether 97 (20.0 mg, 31.0 µmol) in dichloromethane : methanol (1.4 mL, 6 : 1) at room temperature was added CSA (1.00 mg, 3.10 µmol). The reaction mixture was left to stir for 1.5 h, then quenched with a saturated solution of NaHCO₃ (1 mL), extracted with diethyl ether and dried over Na₂SO₄. The mixture was filtered and the resulting solution was concentrated under reduced pressure, and then purified by column chromatography (7 : 3, hexane : ethyl acetate) to give the primary alcohol 137 (13.6 mg, 81%) as a colourless oil.

Rf 0.31 (50% ethyl acetate : petroleum ether); [α]_D^20 -10.3 (c 1.0, CHCl₃); IR (thin film) 2953, 2928, 2856, 1717, 1653, 1456, 1254, 1035, 839 and 779 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.29-7.27 (2H, m, Ar-H), 6.30 (1H, dd, J = 1.8, 16.0 Hz, H₈), 5.85 (1H, dt, J = 1.5, 15.7 Hz, H₃), 4.61-4.49 (3H, m, OCH₂Ph + H₁₀), 3.81 (3H, s, OMe), 3.70 (3H, s, OMe), 3.60-3.57 (2H, m, H₁₁ + H₁₄a), 3.44-3.40 (1H, m, H₁₄b), 3.20 (1H, br s, OH), 2.60 (2H, t, J = 7.5 Hz, H₅), 2.29-2.18 (2H, m, H₄), 1.82-1.56 (6H, m, H₁₂ + H₁₃ + H₉), 0.92 (9H, s, Si-C(CH₃)₃), 0.05 (3H, s, Si-CH₃) and 0.03 (3H, s, Si-CH₃); ¹³C NMR (126 MHz, CDCl₃) δ 199.4, 167.0, 159.4, 148.6, 145.6, 132.1, 129.8, 121.5, 113.9, 113.7, 81.8, 80.3, 72.5, 62.8, 55.3, 51.5, 39.1, 31.4, 29.7, 29.4, 25.9, 22.2, 18.2, -4.8 and -5.0; HRMS (ES⁺) calc. for C₂₉H₅₀NO₇Si ([M+NH₄]⁺) 552.3351, found 552.3343.
(2E, 8E, 10S, 11S)-Methyl-10, 14-bis((tert-butyldimethylsilyl)oxy)-11-hydorxy-7-oxotetradeca-2, 8-dienoate (138)

To a solution of PMB ether 97 (19 mg, 28 µmol) in dichloromethane (1.0 mL) and pH 7 buffer (100 µL) at 0 °C, was added recrystallised DDQ (13 mg, 82 µmol). The solution was stirred at room temperature for 2 h and quenched with NaHCO₃ (2 mL), extracted with dichloromethane (3 x 2 mL). The solution was concentrated under reduced pressure and purified by column chromatography (4 : 1 to 7 : 3, hexane : ethyl acetate) to yield the alcohol 138 (12 mg, 81%) as a colourless oil.

R_f 0.22 (50% ethyl acetate : petroleum ether); [α]_D̊ +0.90 (c 1.0, CHCl₃); IR (thin film) 3393, 2933, 2928, 2856, 1720, 1661, 1472, 1462, 1254, 1096, 834 and 775 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.94 (1H, dt, J = 15.7, 7.0 Hz, H₃), 6.85 (1H, dd, J = 5.2, 15.9 Hz, H₉), 6.25 (1H, dd, J = 1.6, 16.0 Hz, H₈), 5.83 (1H, dt, J = 15.7, 1.6 Hz, H₂), 4.25 (1H, ddd, J = 4.3, 5.0, 1.5 Hz, H₁₀), 3.72 (3H, s, OMe), 3.69-3.60 (2H, m, H₁₁ + H₁₄a), 3.55-3.51 (1H, m, H₁₄b), 3.20 (1H, br s, OH), 2.59 (2H, t, J = 7.2 Hz, H₆), 2.26-2.20 (2H, m, H₄), 1.83-1.55 (6H, m, H₁₂ + H₁₃ + H₅), 0.91 (9H, s, Si-C(CH₃)₃), 0.88 (9H, s, Si-
C(CH$_3$)$_3$) and 0.07-0.04 (12H, m, 4 × Si-CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 199.4, 166.9, 145.8, 129.7, 121.6, 75.1, 74.5, 63.2, 51.4, 39.2, 31.6, 29.7, 29.6, 29.3, 25.9, 22.2, 18.3, 18.2, -5.0 and -5.4; HRMS (ES$^+$) calc. for C$_{27}$H$_{53}$O$_6$Si$_2$ ([M+H]$^+$) 529.3375, found 529.3369.

(2E, 7R, 8E, 10S, 11S)-Methyl-10, 14-bis((tert-butyldimethylsilyl)oxy)-7-hydroxy-11-((4-methoxy benzyl)oxy)tetradeca-2, 8-dienoate (143)

To a solution of (+)-DIP-Cl (161 mg, 500 µmol) in THF (5.0 mL) at -78 °C, was added a solution of ketone 97 (32.0 mg, 50.0 µmol) in THF (5.0 mL). The reaction was warmed to room temperature and left to stir for 16 h, when it was quenched with NH$_4$Cl (6 mL), extracted with diethyl ether (3 x 5 mL) and dried over MgSO$_4$ to give a mixture of diastereoisomers (7S : 7R = 1 : 3). The product was purified by column chromatography (17 : 3, hexane : ethyl acetate) to give (7R)-alcohol 143 (20.6 mg, 66%) as a colourless oil.

$R_f$ 0.32 (30% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ -1.5 (c 1.1, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.28-7.25 (2H, m, Ar-H), 6.96 (1H, dt, $J = 15.6, 7.0$ Hz, H$_3$), 6.88 (2H, d, $J = 8.8$ Hz, Ar-H), 5.83 (1H, dt, $J = 1.6, 15.6$ Hz,
H2, 5.75-5.71 (2H, m, H6 + H9), 4.61-4.48 (2H, m, OCH2Ph), 4.30-4.28 (1H, m, H10), 4.17-4.10 (1H, m, H7), 3.81 (3H, s, OMe), 3.73 (3H, s, OMe), 3.67-3.55 (2H, m, H11 + H14a), 3.34-3.30 (1H, m, H14b), 2.25-2.20 (2H, m, H4), 1.90-1.47 (8H, m, H12 + H13 + H6 + H5), 0.90 (18H, s, 2 × Si(CH3)3) and 0.05-0.03 (12H, m, 4 × Si-CH3).

(R)-MTPA ester of 143 (144)

To a solution of alcohol 143 (3 mg, 4.70 µmol), DCC (2.0 mg, 9.4 µmol) and DMAP (2 mg) in dichloromethane (2.0 mL) at room temperature was added (+)-(R)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (2.2 mg, 9.4 µmol). After 6 h, the crude reaction mixture was purified directly by column chromatography (19 : 1, hexane : ethyl acetate) to give (R)-MTPA ester 144 (2.3 mg, 57%).

Rf 0.42 (20%, ethyl acetate : hexane); 1H NMR (400 MHz, CDCl3) δ 7.50-7.47 (2H, m, Ar-H), 7.42-7.38 (3H, m, Ar-H), 7.28-7.25 (2H, m, Ar-H), 6.90-6.87 (3H, m, Ar-H + H3), 5.97-5.95 (1H, m, H9), 5.75 (1H, dt, J = 1.6, 15.5 Hz, H2), 5.69-5.68 (1H, m, H8), 4.61-4.48 (2H, m, OCH2Ph), 4.30-4.27 (2H, m, H7 + H10), 3.81 (3H, s, OMe), 3.73 (3H, s, OMe), 3.58-3.55 (1H, m, H14a),

150
3.47 (3H, d, J = 1.1 Hz, MTPA-OCH₃), 3.34-3.28 (1H, m, H₁₁ + H₁₄b), 2.15-2.10 (2H, m, H₄), 1.85-1.34 (8H, m, H₁₂ + H₁₃ + H₆ + H₅), 0.90 (18H, s, 2 × Si-C(CH₃)₃) and 0.05-0.03 (12H, m, 4 × Si-CH₃).

**(S)-MTPA ester of 143 (145)**

![MTPA ester structure]

To a solution of alcohol 143 (3 mg, 4.70 µmol), DCC (2.0 mg, 9.4 µmol) and DMAP (2 mg) in dichloromethane (2.0 mL) at room temperature was added (+)-(S)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (2.2 mg, 9.4 µmol). After 6 h, the crude reaction mixture was purified directly by column chromatography (19 : 1, hexane : ethyl acetate) to give (S)-MTPA ester 145 (2.1 mg, 51%).

Rᶠ 0.43 (20%, ethyl acetate : hexane); **¹H NMR** (400 MHz, CDCl₃) δ 7.49-7.47 (2H, m, Ar-H), 7.41-7.37 (3H, m, Ar-H), 7.28-7.25 (2H, m, Ar-H), 6.90-6.86 (3H, m, Ar-H + H₃), 5.87-5.86 (1H, m, H₆), 5.80 (1H, dt, J = 1.4, 15.0 Hz, H₂), 5.69-5.67 (1H, m, H₈), 4.56-4.45 (2H, m, OCH₂Ph), 4.32-4.30 (1H, m, H₇), 4.28-4.27 (1H, m, H₁₀), 3.80 (3H, s, OMe), 3.75 (3H, s, OMe), 3.56-3.54 (1H, m, H₁₄a), 3.50 (3H, d, J = 1.3 Hz, MTPA-OCH₃), 3.30-3.26 (1H, m,
$\text{H}_{11} + \text{H}_{(\text{ab})}$, 2.21-2.19 (2H, m, $\text{H}_4$), 1.90-1.40 (8H, m, $\text{H}_{12} + \text{H}_{13} + \text{H}_5 + \text{H}_6$), 0.90 (18H, s, $2 \times \text{Si-CH}_3$) and 0.05-0.03 (12H, m, $4 \times \text{Si-CH}_3$).

(2E, 7S, 8E, 10S, 11S)-Methyl-10, 14-bis(tert-butyl(dimethyl)silyl)oxy)-7-hydroxy-11-((4-methoxy benzyl)oxy)tetradeca-2, 8-dienoate (141)

$$\text{MeO}$$

$$\text{O}$$

$$\text{TBSO}$$

$$\text{TBSO}$$

$$\text{OPMB}$$

To a solution of (-)-DIP-Cl (2.50 g, 7.71 mmol) in THF (40 mL) at -78 °C, was added a solution of ketone 97 (500 mg, 771 µmol) in THF (20 mL). The reaction was warmed to room temperature and left to stir for 16 h, when it was quenched with NH$_4$Cl (30 mL), extracted with diethyl ether (3 x 30 mL) and dried over MgSO$_4$ to give a mixture of diastereoisomers ($7\text{S} : 7\text{R} = 5 : 1$). The product was purified by column chromatography (17 : 3, hexane : ethyl acetate) to give (7S)-alcohol 141 (350 mg, 69%) as a colourless oil.

$R_f$ 0.35 (30% ethyl acetate : hexanes); $[\alpha]_D^{20}$ -8.2 (c 1.0, CHCl$_3$); IR (thin film) 3402, 2951, 2928, 2857, 1742, 1514, 1247, 1093, 833 and 775 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.28-7.25 (2H, m, Ar-$\text{H}$), 6.96 (1H, dt, $J = 15.6, 6.8 \text{ Hz}$, H$_5$), 6.88 (2H, d, $J = 8.3 \text{ Hz}$, Ar-$\text{H}$), 5.83 (1H, dt, $J = 1.5, 1.55 \text{ Hz}$, H$_2$), 5.74-5.69 (2H, m, H$_8 + \text{H}_9$), 4.63-4.49 (2H, m, OCH$_3$-$\text{Ph}$), 4.32-4.29 (1H, m, H$_{10}$),
4.15-4.10 (1H, m, H7), 3.82 (3H, s, OMe), 3.74 (3H, s, OMe), 3.66-3.56 (2H, m, H11 + H14a), 3.37-3.31 (1H, m, H14b), 2.27-2.20 (2H, m, H4), 1.92-1.50 (8H, m, H12 + H13 + H6 + H5), 0.91 (18H, s, 2 × Si-(CH3)3) and 0.06-0.04 (12H, m, 4 × Si-CH3); 13C NMR (75 MHz, CDCl3) δ 167.4, 159.6, 149.7, 134.5, 131.1, 130.8, 130.0, 121.5, 114.1, 82.7, 73.2, 72.7, 72.5, 63.7, 55.6, 51.7, 45.3, 36.8, 32.4, 30.0, 29.9, 26.2, 26.2, 24.3, 18.4, -4.4 and -4.9; HRMS (ES+) calc. for C35H66NO7Si2 ([M+NH4]+) 668.4367, found 669.4391.

(R)-MTPA ester of 141 (146)

To a solution of alcohol 141 (3 mg, 4.70 µmol), DCC (2.0 mg, 9.4 µmol) and DMAP (2 mg) in dichloromethane (2.0 mL) at room temperature was added (+)-(R)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (2.2 mg, 9.4 µmol). After 6 h, the crude reaction mixture was purified directly by column chromatography (19 : 1, hexane : ethyl acetate) to give (R)-MTPA ester 146 (2.7 mg, 67%).

Rf 0.40 (20%, ethyl acetate : hexane); 1H NMR (400 MHz, CDCl3) δ 7.51-7.48 (2H, m, Ar-H), 7.37-7.32 (3H, m, Ar-H), 7.28-7.25 (2H, m, Ar-H), 6.88-6.87 (3H, m, Ar-H + H3), 5.93-5.92 (1H, m, H9), 5.80 (1H, dt, J = 1.5, 15.4
Hz, H_2), 5.63-5.61 (1H, m, H_6), 4.54-4.41 (2H, m, OCH_2Ph), 4.31-4.29 (2H, m, H_7 + H_10), 3.82 (3H, s, OMe), 3.73 (3H, s, OMe), 3.58-3.55 (1H, m, H_{14a}), 3.49 (3H, d, J = 1.2 Hz, MTPA-OCH_3), 3.30-3.26 (1H, m, H_{11} + H_{14b}), 2.21-2.19 (2H, m, H_4), 1.98-1.52 (8H, m, H_{12} + H_{13} + H_6 + H_5), 0.90 (18H, s, 2 × Si-C(CH_3)_3) and 0.05-0.03 (12H, m, 4 × Si-CH_3).

((S)-MTPA ester of 141 (147)

To a solution of alcohol 141 (3 mg, 4.70 µmol), DCC (2.0 mg, 9.4 µmol) and DMAP (2 mg) in dichloromethane (2.0 mL) at room temperature was added (+)-(S)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (2.2 mg, 9.4 µmol). After 6 h, the crude reaction mixture was purified directly by column chromatography (19 : 1, hexane : ethyl acetate) to give (S)-MTPA ester 147 (2.3 mg, 56%).

R_f 0.42 (20%, ethyl acetate : hexane); ^1H NMR (400 MHz, CDCl_3) δ 7.52-7.48 (2H, m, Ar-H), 7.39-7.35 (3H, m, Ar-H), 7.28-7.25 (2H, m, Ar-H), 6.88-6.86 (3H, m, Ar-H + H_3), 6.01-5.99 (1H, m, H_9), 5.75 (1H, dt, J = 1.6, 15.5 Hz, H_2), 5.69-5.67 (1H, m, H_8), 4.65-4.54 (2H, m, OCH_2Ph), 4.36-4.33 (1H, m, H_{10}), 4.30-4.28 (1H, m, H_7), 3.79 (3H, s, OMe), 3.74 (3H, s, OMe), 3.55-
3.52 (1H, m, H\textsubscript{14a}), 3.45 (3H, d, J = 1.1 Hz, MTPA-OC\textsubscript{3}H\textsubscript{3}), 3.36-3.30 (1H, m, H\textsubscript{11} + H\textsubscript{14b}), 2.14-2.10 (2H, m, H\textsubscript{4}), 1.90-1.52 (8H, m, H\textsubscript{12} + H\textsubscript{13} + H\textsubscript{6} + H\textsubscript{5}), 0.90 (18H, s, 2 × Si-(CH\textsubscript{3})\textsubscript{3}) and 0.05-0.03 (12H, m, 4 × Si-CH\textsubscript{3}).

\((2E, 7S, 8E, 10S, 11S)\)-Methyl-7, 10, 14-tris((\textit{tert}-butyldimethylsilyl)oxy-11-((4-methoxy benzyl)oxy)tetradeca-2, 8-dienoate (148)

\[
\text{MeO} \quad \begin{array}{c}
\text{TBSO} \\
\text{TBSO} \\
\text{OPMB} \\
\text{OTBS}
\end{array}
\]

To a solution of alcohol 141 (285 mg, 440 µmol) in dichloromethane (5 mL) at room temperature, was added imidazole (57 mg, 670 µmol), TBSCI (100 mg, 585 µmol) and DMAP (5.0 mg) The mixture was stirred at room temperature for 16 h, and quenched with ammonium chloride (5 mL), the product extracted with dichloromethane (3 x 5 mL) and the combined organic extracts were dried over MgSO\textsubscript{4}. The crude residue was purified using column chromatography (19 : 1, hexane : ethyl acetate) to afford the silyl enol ether 148 (301 mg, 89%) as a colourless oil.

\(R_f\) 0.57 (20% ethyl acetate : petroleum ether); \([\alpha]_D^{19}\) -13.0 (c 2.1, CHCl\textsubscript{3}); \textbf{IR} (thin film) 3309, 2950, 2929, 2850, 1732, 1517, 1247, 1093, 1030, 835 and 775 cm\(^{-1}\); \textbf{\textit{H NMR}} (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.27-7.25 (2H, m, Ar-H), 6.99-6.92
(1H, m, H₃), 6.87 (2H, d, J = 8.3 Hz, Ar-H), 5.81 (1H, dt, J = 1.5, 15.5 Hz, H₂), 5.69-5.59 (2H, m, H₈ + H₉), 4.62-4.47 (2H, m, OCH₂Ph), 4.29-4.27 (1H, m, H₁₆), 4.15-4.11 (1H, m, H₁₇), 3.81 (3H, s, Ar-OMe), 3.73 (3H, s, OMe), 3.61-3.49 (2H, m, H₁₁ + H₁₄a), 3.31-3.27 (1H, m, H₁₄b), 2.23-2.16 (2H, m, H₄), 1.75-1.44 (8H, m, H₁₂ + H₁₃ + H₆ + H₅), 0.92 (9H, s, Si-C(CH₃)₃), 0.89 (9H, s, Si-C(CH₃)₃), 0.88 (9H, s, Si-C(CH₃)₃) and 0.04-0.01 (18H, m, 6 × Si-CH₃);

¹³C NMR (100 MHz, CDCl₃) δ 167.5, 159.0, 149.4, 134.1, 131.1, 129.3, 128.8, 120.9, 113.6, 82.4, 72.9, 72.8, 72.2, 63.4, 55.3, 51.3, 37.8, 32.2, 29.7, 29.5, 29.5, 26.1, 26.0, 25.9, 23.7, 18.4, 18.2, -4.6, -4.8 and -5.3; HRMS (ES⁺) calc. for C₄₁H₈₀NO₇Si₃ ([M+NH₄]⁺) 782.5232, found 782.5224.

(2E, 7S, 8E, 10S, 11S)-Methyl-7, 10, 14-tris((tert-butyldimethylsilyl)oxy-11-hydroxytetradeca-2, 8-dienoate (149)

To a solution of PMB ether 148 (150 mg, 196 µmol) in dichloromethane (2 mL) and pH 7 buffer (200 µL) at 0 °C, was added recrystallised DDQ (133 mg, 588 µmol). The solution was stirred at room temperature for 3 h and quenched with NaHCO₃ (40 mL), extracted with dichloromethane (3 x 30 mL), and dried over Na₂SO₄. The solution was concentrated under
reduced pressure and purified by column chromatography (4 : 1 to 7 : 3, hexane : ethyl acetate) to yield the alcohol 149 (96 mg, 76%) as a colourless oil.

\( R_f \) 0.18 (50% ethyl acetate : petroleum ether); \( [\alpha]_D^{20} +4.0 \) (c 1.0, CHCl₃); \textbf{IR} (thin film) 3418, 2921, 2847, 1719, 1277, 1126, 835 and 766 cm⁻¹; \textbf{¹H NMR} (400 MHz, CDCl₃) δ 6.95 (1H, dt, \( J = 6.9, 15.7 \) Hz, \( H_3 \)), 5.82 (1H, dt, \( J = 1.5, 15.7 \) Hz, \( H_2 \)), 5.69-5.50 (2H, m, \( H_8 + H_9 \)), 4.16-4.11 (1H, m, \( H_{10} \)), 3.91-3.86 (1H, m, \( H_7 \)), 3.73-3.63 (5H, m, OMe, \( H_{11} + H_{14a} \)), 3.43-3.37 (1H, m, \( H_{14b} \)), 2.23-2.18 (2H, m, \( H_4 \)), 1.74-1.48 (8H, m, \( H_{12} + H_{13} + H_6 + H_5 \)), 0.90 (9H, s, Si-C(CH₃)₃), 0.89 (18H, s, 2 x Si-C(CH₃)₃), 0.09 (6H, s, 2 x Si-CH₃) and 0.05-0.02 (12H, m, 4 x Si-CH₃); \textbf{¹³C NMR} (100 MHz, CDCl₃) δ 167.3, 149.4, 136.6, 129.4, 121.2, 75.1, 72.4, 63.0, 53.6, 51.6, 37.6, 32.3, 29.9, 29.7, 29.7, 26.0, 26.0, 25.9, 23.6, 18.3, 18.2, -4.3, -4.6 and -4.7; \textbf{HRMS} (ES⁻) calc. for \( C_{33}H_{72}NO_6Si_3 ([M+NH_4]^+) \) 662.4667, found 662.4651.

\( (2E, 7S, 8E, 10S, 11S)\)-Methyl-7, 10, 14-tris((tert-butyldimethylsilyl)oxy-11-(carbamoyloxy)tetradeca-2, 8-dienoate (150)
To a solution of alcohol 149 (80 mg, 154 µmol) in dichloromethane (2 mL), trichloroacetyl isocyanate (185 µL, 1.55 mmol) was added. The reaction mixture was stirred for 1 h at room temperature, upon which the solvent was removed under vacuo, then redissolved in methanol (5.0 mL). To this dried potassium carbonate (145 mg, 1.05 mmol) was added, and this was left to stir for 16 h at room temperature, upon which it was quenched with water (5 mL), extracted with dichloromethane (3 x 5 mL) and dried over Na₂SO₄. The mixture was purified using column chromatography (7 : 3, hexane : ethyl acetate) to give carbamate 150 (74 mg, 69%) as a colourless oil.

\[ R_f \] 0.29 (40% ethyl acetate : petroleum ether); \[ [\alpha]_D^{10} \] -14.0 (c 0.2, CHCl₃); IR (thin film) 2953, 2928, 2855, 1717, 1707, 1506, 1065, 1051, 835 and 775 cm⁻¹; \[ ^1H \text{ NMR} \] (400 MHz, CDCl₃) δ 6.95 (1H, dt, \( J = 6.9, 15.8 \) Hz, \( H_3 \)), 5.83 (1H, dt, \( J = 1.5, 15.7 \) Hz, \( H_2 \)), 5.71-5.53 (2H, m, \( H_8 + H_9 \)), 4.75-4.58 (3H, m, NH₂ + \( H_{11} \)), 4.24 (1H, t, \( J = 5.2 \) Hz, \( H_{10} \)), 4.14-4.04 (3H, m, \( H_7 + H_{14} \)), 3.73 (3H, s, OMe), 2.24-2.19 (2H, m, \( H_4 \)), 1.71-1.48 (8H, m, \( H_{12} + H_{13} + H_6 + H_5 \)), 0.90 (18H, s, 2 x Si-C(CH₃)₃), 0.89 (9H, s, Si-C(CH₃)₃), 0.08 (6H, s, 2 x Si-CH₃) and 0.05-0.03 (12H, m, 4 x Si-CH₃); \[ ^{13}C \text{ NMR} \] (100 MHz, CDCl₃) δ 167.4, 156.6, 150.0, 135.6, 128.0, 121.1, 76.9, 73.1, 72.6, 65.2, 51.6, 37.7, 32.3, 30.0, 29.9, 29.9, 26.0, 26.0, 25.9, 23.7, 18.4, 18.3, -4.4, -4.7 and -4.8; HRMS (ES⁺) calc. for C₃₄H₇₀NO₇Si₃ ([M+H]⁺) 688.4460, found 688.4463.
(2E, 7S, 8E, 10S, 11S)-Methyl 7, 10-bis((tert-butylidemethylsilyl)oxy-11-(carbamoyloxy)-14-hydroxytetradeca-2, 8-dienoate (98)

To a solution of silyl ether 150 (50 mg, 72 µmol) in dichloromethane : methanol (2.5 mL, 6 : 1) at room temperature was added CSA (2.0 mg, 11.1 µmol). The reaction mixture was left to stir for 2 h, then quenched with sodium bicarbonate (3 mL), extracted with dichloromethane (3 x 5 mL) and dried over Na₂SO₄. The mixture was filtered and the resulting solution was concentrated under reduced pressure, then purified by column chromatography (3 : 2, hexane : ethyl acetate) to give the primary alcohol 98 (41.4 mg, 80%) as a colourless oil.

Rf 0.28 (50% ethyl acetate : petroleum ether); [α]D²⁰⁻8.4 (c 0.1, CHCl₃); IR (thin film) 3466, 3364, 2979, 2929, 2854, 1714, 1366, 1312, 1278, 1188, 1128, 835 and 775 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.96 (1H, dt, J = 6.9, 15.7 Hz, H₃), 5.83 (1H, dt, J = 1.5, 15.7 Hz, H₂), 5.70-5.53 (2H, m, H₈ + H₉), 4.75-4.58 (3H, m, NH₂ + H₁₁), 4.26-4.22 (1H, m, H₁₀), 4.17-4.11 (1H, m, H₇), 4.06-4.04 (2H, m, H₁₄), 3.73 (3H, s, OMe), 2.23-2.20 (2H, m, H₆), 1.73-1.45 (8H, m, H₁₂ + H₁₃ + H₆ + H₅), 0.90 (18H, s, 2 x Si-C(CH₃)₃), and 0.05-0.03
(12H, m, 4 × Si-CH\textsubscript{3}); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 166.8, 156.5, 148.5, 130.9, 129.4, 121.9, 77.4, 75.8, 74.8, 63.0, 52.8, 32.8, 32.0, 30.8, 29.5, 26.1, 26.0, 21.9, 18.4, 18.3, -4.4 and -4.5; HRMS (ES\textsuperscript{+}) calc. for C\textsubscript{28}H\textsubscript{56}NO\textsubscript{7}Si\textsubscript{2} ([M+H]\textsuperscript{+}) 574.3595, found 574.3591.

7.5: Experimental for Chapter 3

(2S)-Methyl-3-(para-methoxybenzyl)-2-methylpropanoate (159)

\[
\begin{align*}
\text{MeO} & \quad \text{OPMB} \\
\end{align*}
\]

To a solution of (S)-Roche ester 158 (10.0 g, 84.6 mmol) in dichloromethane (200 mL) at 0 °C, PMBTCA (28.7 g, 101.6 mmol) was added followed by careful addition of PPTS (1.00 g, 4.23 mmol). After 3 h at 0 °C the reaction was warmed to room temperature, then left stirring for 16 h, upon which it was quenched with NH\textsubscript{4}Cl (200 mL), washed with dichloromethane (3 x 150 mL) and dried over MgSO\textsubscript{4}. Purification by column chromatography (9 : 1, hexane : ethyl acetate) provided PMB ether 159 (17.1 g, 85%) as a colourless oil.

\(R_f\) 0.60 (30% ethyl acetate : petroleum ether); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.31 (2H, d, \(J = 8.7\) Hz, Ar-H), 6.91 (2H, d, \(J = 8.6\) Hz, Ar-H), 4.49 (2H, s, OCH\textsubscript{2}PhOMe), 3.82 (3H, s, PhOCH\textsubscript{3}), 3.79 (1H, dd, \(J = 9.1, 7.3\) Hz, H\textsubscript{3a}).
To a solution of (S)-Roche ester 158 (10.0 g, 84.6 mmol) in dichloromethane (200 mL) at room temperature, was added imidazole (8.64 g, 127 mmol) and TBSCl (15.3 g, 101.6 mmol). The mixture was stirred at room temperature for 16 h, and quenched with NH₄Cl (300 mL) and the product was extracted with dichloromethane (3 x 150 mL), washed with brine (150 mL) and water (150 mL). The combined organic extracts were dried over MgSO₄. The crude residue was purified using column chromatography (9 : 1, hexane : ethyl acetate) to afford the silyl ether 205 (15.9 g, 98%) as a colourless oil.

\( R_f 0.50 \) (20% ethyl acetate : petroleum ether); \( ^1H \text{ NMR} \) (400 MHz, CDCl₃) \( \delta \) 3.78 (1H, dd, \( J = 9.7, 6.9 \text{ Hz, } H_{3a} \)) 3.69-3.63 (4H, m, \( H_{3b} + OCH_3 \)), 2.66 (2H, ddq, \( J = 13.1, 7.0, 6.1 \text{ Hz, } H_2 \)), 1.15 (3H, d, \( J = 7.0 \text{ Hz, CHCH}_3 \)), 0.88 (9H, s, Si-C(CH₃)₃), and 0.05 (6H, m, 2 × Si-CH₃).
To a solution of PMB-protected Roche ester 159 (16.0 g, 67.1 mmol) and \(N, O\)-dimethyl hydroxylamine hydrochloride (10.5 g, 107 mmol) in THF (300 mL) at -30 °C was slowly added \(\text{iso}-\text{propylmagnesium chloride}\) (89.2 mL, 178.4 mmol, 2M in THF). The reaction solution was stirred at this temperature for 3 h upon which a saturated solution of NH\(_4\)Cl (300 mL) was added. The organics were extracted with dichloromethane (3 x 200 mL) and the combined organic extracts were dried over Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. Purification by column chromatography (4 : 1, hexane : ethyl acetate) provided Weinreb amide 160 (16.9 g, 94%) as a colourless oil.

\(R_f\) 0.53 (30% ethyl acetate : petroleum ether); \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\)

- 7.24 (2H, d, \(J = 8.6\) Hz, Ar-H), 6.87 (2H, d, \(J = 8.6\) Hz, Ar-H), 4.45 (2H, s, OCH\(_3\)PhOMe), 3.81 (3H, s, PhOCH\(_3\)), 3.71-3.67 (4H, m, H\(_{3a} + \text{NOC\(_3\)}\)), 3.40 (1H, dd, \(J = 8.9, 5.8\) Hz, H\(_{3b}\)), 3.31-3.19 (4H, m, H\(_2 + \text{NCH\(_3\)}\)) and 1.11 (3H, d, \(J = 6.9\) Hz, CCH\(_3\)).
(2S)-3-(tert-Butyldimethylsilyloxy)-N-methoxy-2, N-dimethyl propanamide (174)\textsuperscript{117}

To a solution of TBS-protected Roche ester 205 (15.0 g, 64.6 mmol) and \textit{N,O-}
dimethyl hydroxylamine hydrochloride (9.50 g, 96.9 mmol) in THF (300 mL) at -30 °C was slowly added \textit{iso}-propylmagnesium chloride (146 mL, 291 mmol, 2M in THF). The reaction solution was stirred at this temperature for 3 h upon which a saturated solution of NH\textsubscript{4}Cl (300 mL) was added. The organics were extracted with dichloromethane (3 x 200 mL) and the combined organic extracts were dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated under reduced pressure. Purification by column chromatography (9 : 1, hexane : ethyl acetate) provided Weinreb amide 174 (15.5 g, 92% yield) as a colourless oil.

\[ R_f 0.48 \text{ (20\% ethyl acetate : petroleum ether); } \]  \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \)

3.84 (1H, dd, \( J = 9.5, 8.1\) Hz, \textit{H}_{3a}), 3.72 (3H, s, NOCH\textsubscript{3}), 3.54 (1H, dd, \( J = 9.5, 6.1\) Hz, \textit{H}_{3b}), 3.25-3.10 (4H, m, \textit{H}_{2} + NCH\textsubscript{3}), 1.08 (3H, d, \( J = 7.0\) Hz, CCH\textsubscript{3}), 0.88 (9H, s, Si-C(CH\textsubscript{3})\textsubscript{3}), and 0.05 (6H, m, \( 2 \times \text{Si-CH}_{3} \)).
(2S)-3-(para-methoxybenzyl)-2-methylpropanal (152)\textsuperscript{116}

![Chemical Structure](image)

To a solution of Weinreb amide 160 (10.0 g, 37.4 mmol) in dichloromethane (100 mL) at -78 °C, was added DIBAL (75.0 mL, 75.0 mmol, 1 M in dichloromethane). The mixture was stirred for 3 h and quenched with aqueous potassium sodium tartrate (200 mL), and the mixture was stirred for a further 2 h. The crude product was extracted with diethyl ether (3 x 100 mL), which was washed with brine, dried over MgSO\textsubscript{4} and the solvent was removed under reduced pressure to give the crude aldehyde 152, which was used without further purification in the next step.

\[ R_f \text{ 0.48 (20\% ethyl acetate : petroleum ether)}; \textsuperscript{1}H \text NMR (400 MHz, CDCl}_3) \delta \]

9.64 (1H, d, \( J = 1.6 \text{ Hz, H}_1 \)), 7.16 (2H, d, \( J = 8.7 \text{ Hz, ArH}_1 \)), 6.81 (2H, d, \( J = 8.7 \text{ Hz, ArH}_2 \)), 3.73 (3H, s, PhOC\textsubscript{H}_3) 3.58 (1H, dd, \( J = 9.4, 6.7 \text{ Hz, H}_{3a} \)), 3.53 (1H, dd, \( J = 9.4, 5.3 \text{ Hz, H}_{3a} \)), 2.61-2.53 (1H, m, H\textsubscript{2}), 1.05 (3H, d, \( J = 7.1 \text{ Hz, CCH}_3 \)).

(2\textit{E}, 4\textit{S})-Ethyl-5-(para-methoxybenzyl)-2,4-dimethylpent-2-enoate

(153)\textsuperscript{116}

![Chemical Structure](image)

164
Method A:

Triethyl-2-phosphonopropionate (2.44 mL, 11.4 mmol) was added to a stirring solution of LiHMDS (1.0 M in hexane, 12.4 mL, 12.4 mmol) in THF (50 mL) at -78 °C. The solution was left to stir for 20 min before the crude aldehyde 152 (9.20 mmol) was slowly added. The solution was warmed to -40 °C and stirred for 17 h. The reaction was quenched with NH₄Cl (25 mL), extracted with dichloromethane (3 x 20 mL) and the combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by column chromatography (4 : 1, hexane : ethyl acetate) to give ester 153 (1.56 g, 58% over two steps, E : Z = 4 : 1) as a colourless oil.

Method B:

LiCl (900 mg, 19.2 mmol) was flame dried prior to use. A mixture of acetonitrile (70 mL) and LiCl, was cooled at 0 °C, and triethyl-2-phosphonopropionate (2.3 mL, 10.6 mmol) and Hünig’s base (3.4 mL, 19.2 mmol) were added. The mixture was maintained at 0 °C for 20 min, and the crude aldehyde 152 (9.50 mmol) was added. The mixture was warmed to room temperature and stirred for 13 h, prior to the addition of water (40 mL). The organic portions were extracted with ethyl acetate (3 x 20 mL). The combined organic layers was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography (4 : 1, hexane : ethyl acetate) to give ester 153 (1.81 g, 65% over two steps, E : Z = 4 : 1) as a colourless oil.
Method C:

To a stirring solution of activated barium hydroxide (11.6 g, 35.7 mmol) in THF (150 mL), triethyl-2-phosphonopropionate (11.7 mL, 67.2 mmol) was added. The mixture was stirred for 30 min at room temperature, and the crude aldehyde 152 (37.4 mmol), in wet THF (40 : 1, THF : water, 100 mL) was added. The mixture was stirred at room temperature for 16 h, the mixture was filtered, and the crude product extracted with dichloromethane (3 x 100 mL), washed with NaHCO$_3$ (150 mL) and dried over MgSO$_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (4 : 1, hexane : ethyl acetate) to give ester 153 (7.60 g, 70% over two steps, E : Z = 9 : 1) as a colourless oil.

$R_f$ 0.69 (20% ethyl acetate : petroleum ether); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$

7.25 (2H, d, $J = 8.8$ Hz, ArH), 6.88 (2H, d, $J = 8.7$ Hz, ArH), 6.59 (1H, dq, $J = 9.7$, 1.4 Hz, H$_3$), 4.45 (2H, s, OCH$_2$Ar), 4.19 (2H, q, $J = 7.2$ Hz, OCH$_2$CH$_3$), 3.81 (3H, s, ArOCH$_3$), 3.36 – 3.31 (2H, m, H$_3$), 2.89–2.78 (1H, m, H$_4$), 1.87 (3H, d, $J = 1.5$ Hz, =CCH$_3$), 1.30 (3H, t, $J = 7.2$ Hz, OCH$_2$CH$_3$) and 1.04 (3H, d, $J = 6.8$ Hz, CCH$_3$).

**(2S)-3-(tert-butyldimethylsilyloxy)-2-methylpropanal (206)**

![Chemical Structure](image)
To a solution of Weinreb amide 174 (10.3 g, 40.3 mmol) in dichloromethane (100 mL) at -78 °C, was added DIBAL (82.0 mL, 82.0 mmol, 1 M in dichloromethane). The mixture was stirred for 3 h, quenched with aqueous potassium sodium tartrate (60 mL), then the mixture was stirred for a further 2 h. The crude product was extracted with diethyl ether (3 x 100 mL), which was washed with brine (100 mL), dried over MgSO₄ and the solvent was removed under reduced pressure to give crude aldehyde 206, which was used without further purification in the next step.

Rf 0.60 (20% ethyl acetate : Hexanes); $^1$H NMR (300 MHz, CDCl₃) δ 9.74 (1H, d, $J = 1.6$ Hz, H₁), 3.86 (1H, dd, $J = 10.2, 5.2$ Hz, H₃a), 3.80 (1H, dd, $J = 10.2, 6.3$ Hz, H₃b), 2.60-2.47 (1H, m, H₂), 1.09 (3H, d, $J = 7.0$ Hz, CH₃), 0.87 (9H, s, Si(CH₃)₃) and 0.05 (6H, s, Si(CH₃)₂).

(2E, 4S)-Ethyl-5-(tert-butyldimethylsilyloxy)-2,4-dimethylpent-2-enoate (175)$^{119}$

To a stirring solution of activated barium hydroxide (12.1 g, 38.3 mmol) in THF (200 mL), triethyl-2-phosphonopropionate (12.5 mL, 72.3 mmol) was added. The mixture was stirred for 30 min at room temperature, and the TBS-protected crude aldehyde 206 (40.3 mmol), in wet THF (40 : 1, THF : water, 100 mL) was added. The mixture was stirred at room temperature for 16 h, after which it was filtered and washed with hexane (3 x 80 mL), followed by
the addition of NH₄Cl (150 mL). The crude product was extracted with dichloromethane (3 x 100 mL), washed with NaHCO₃ (150 mL) and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by column chromatography (9 : 1, hexane : ethyl acetate) to give a mixture of E and Z regioisomers of 175 (8.31 g, 72% over two steps, E : Z = 9 : 1).

Rₚ 0.45 (20% ethyl acetate : petroleum ether); ¹H NMR (400 MHz, CDCl₃) δ 6.56 (1H, dq, J = 9.8, 1.4 Hz, H₃), 4.20 (2H, q, J = 7.2 Hz, OCH₂), 3.87 (1H, dd, J = 5.2, 10.1 Hz, H₃a), 3.81 (1H, dd, J = 10.1, 6.3 Hz, H₃b), 2.75-2.64 (1H, m, H₄), 1.87 (3H, d, J = 1.3 Hz, =CCH₃), 1.30 (3H, d, J = 7.3 Hz, OCH₂CH₃), 1.02 (3H, d, J = 6.8 Hz, CCH₃), 0.88 (9H, s, Si-C(CH₃)₃), and 0.05 (6H, m, 2 × Si-CH₃).

(2E, 4S)-5-(para-Methoxybenzyl)-2,4-dimethylpent-2-en-1-ol (160)₁²⁰

To a solution of PMB-protected ester 153 (6.70 g, 22.9 mmol) in dichloromethane (60 mL) at -78 °C, was added DIBAL (46.0 mL, 46.0 mmol, 1 M in dichloromethane). The mixture was stirred for 3 h upon which aqueous potassium sodium tartrate (100 mL) was added, and the mixture was stirred for a further 4 h. The crude product was extracted with diethyl ether (3 x 60 mL), which was washed with brine (60 mL), dried over Na₂SO₄ and the
solvent was removed under reduced pressure. The crude residue was purified using column chromatography (1 : 1, hexane : ethyl acetate) to yield alcohol 160 (4.64 g, 81%) as a colourless oil.

\( R_f \) 0.63 (50% ethyl acetate : petroleum ether); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \)

\[ 7.28 \text{ (2H, d, } J = 8.8 \text{ Hz, Ar-H)}, \]

\[ 6.91 \text{ (2H, d, } J = 8.7 \text{ Hz, Ar-H)}, \]

\[ 5.26 \text{ (1H, dq, } J = 9.2, 1.4 \text{ Hz, } H_3), \]

\[ 4.47 \text{ (2H, s, OCH}_2\text{Ar),} \]

\[ 4.00 \text{ (2H, s, } H_4), \]

\[ 3.83 \text{ (3H, s, ArOCH}_3\text{),} \]

\[ 3.33 \text{ (1H, dd, } J = 9.2, 6.7 \text{ Hz, CH}_3\text{a),} \]

\[ 3.28 \text{ (1H, dd, } J = 9.3, 6.9 \text{ Hz, CH}_3\text{b),} \]

\[ 2.86-2.68 \text{ (1H, m, } H_4), \]

\[ 1.71 \text{ (3H, d, } J = 1.3 \text{ Hz, } =\text{CH}_3\text{) and} \]

\[ 1.01 \text{ (3H, d, } J = 6.7 \text{ Hz, } \text{CH-CH}_3\text{).} \]

(2E, 4S)-5-(tert-Butyldimethylsilyloxy)-2,4-dimethylpent-2-en-1-ol (195)\(^{118}\)

\[
\text{HO-}\begin{array}{c}
  \text{CH}_2
  \end{array}\text{-OTBS}
\]

To a solution of TBS-protected ester 175 (6.90 g, 23.9 mmol) in dichloromethane (50 mL) at -78 °C, was added DIBAL (48.0 mL, 48.0 mmol, 1 M in dichloromethane). The mixture was stirred for 3 h upon which aqueous potassium sodium tartrate (100 mL) was added, and the mixture was stirred for a further 4 h. The crude product was extracted with dichloromethane (3 x 50 mL), which was washed with brine (50 mL), dried over MgSO\(_4\) and the solvent was removed under reduced pressure. The crude residue was purified using column chromatography (4 : 1, hexane : ethyl acetate) to yield alcohol 195 (5.26 g, 90%) as a colourless oil.
\( R_f \) 0.30 (30% ethyl acetate : petroleum ether); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \)

5.14 (1H, dq, \( J = 9.4, 1.3 \text{ Hz}, \text{H}_3 \)), 3.93 (2H, d, \( J = 4.4 \text{ Hz}, \text{H}_1 \)), 3.42 (1H, dd, \( J = 9.7, 6.1 \text{ Hz}, \text{H}_{5a} \)), 3.34 (1H, dd, \( J = 9.8, 7.1 \text{ Hz}, \text{H}_{5b} \)), 2.62-2.47 (1H, m, \( \text{H}_4 \)), 2.34 (1H, br s, OH), 1.65 (3H, d, \( J = 1.4 \text{ Hz}, \text{=CCH}_3 \)), 0.92 (3H, d, \( J = 6.7 \text{ Hz}, \text{CCH}_3 \)), 0.86 (9H, s, Si-C(CH\(_3\))\(_3\)), and 0.01 (6H, m, 2 \( \times \) Si-CH\(_3\)).

\((2E, 4R)-1-(\text{tert-Butyldimethylsilyloxy})-5-(\text{para-methoxybenzyl})-(2, 4)-\text{dimethyl-pent-3-ene (154)}^{119}\)

To a solution of alcohol 160 (4.25 g, 16.9 mmol) in dichloromethane (60 mL) at room temperature, was added imidazole (1.83 g, 25.5 mmol) and TBSCI (3.20 g, 20.4 mmol). The mixture was stirred at room temperature for 16 h, and quenched with ammonium chloride (60 mL) and the product was extracted with dichloromethane (3 x 60 mL). The combined organic extracts were dried over MgSO\(_4\). The crude residue was purified using column chromatography (9 : 1, hexane : ethyl acetate) to afford silyl ether 154 (5.73 g, 93%) as a colourless oil.

\( R_f \) 0.48 (10% ethyl acetate : petroleum ether); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \)

7.27 (2H, d, \( J = 8.6 \text{ Hz}, \text{Ar-H} \)), 6.89 (2H, d, \( J = 8.7 \text{ Hz}, \text{Ar-H} \)), 5.22 (1H, dq, \( J = 9.2, 1.3 \text{ Hz}, \text{H}_3 \)), 4.44 (2H, s, OCH\(_2\)Ar), 4.02 (2H, s, H\(_1\)), 3.81 (3H, s, OCH\(_3\)), 3.33 (1H, dd, \( J = 9.1, 6.0 \text{ Hz}, \text{CH}_{5a} \)), 3.24 (1H, dd, \( J = 9.1, 7.5 \text{ Hz}, \text{CH}_{5b} \)), 2.80–2.69 (1H, m, \( \text{H}_4 \)), 1.64 (3H, d, \( J = 1.3 \text{ Hz}, \text{=CCH}_3 \)), 1.01 (3H, d, \( J \)
= 6.7 Hz, CH-CH₃), 0.93 (9H, s, Si-C(CH₃)₃), and 0.08 (6H, m, 2 × Si-CH₃).

(2E, 4R)-5-(tert-Butyldimethylsilyloxy)-1-(para-methoxybenzyl)-(2, 4)-dimethyl-pent-3-ene (176)

![Diagram of compound](attachment:image.png)

To a solution of alcohol 195 (2.00 g, 8.2 mmol) in THF (50 mL), NaH (450 mg, 11.1 mmol, 60% dispersion in mineral oil) was added at 0 ºC. After 30 min a solution of PMBCl (1.9 mL, 13.8 mmol) in THF (20 mL) was added and the resulting mixture was stirred for 3 h at 0 ºC. The reaction was quenched with saturated aqueous NH₄Cl (50 mL), and the product extracted with diethyl ether (3 x 50 mL). The resulting solution was dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by column chromatography (9 : 1 to 4 : 1, hexane : ethyl acetate) gave PMB-protected ether 176 (1.67 g, 56%) as a pale yellow oil.

Rᵢ 0.42 (30% ethyl acetate : petroleum ether); \(^1\)H NMR (400 MHz, CDCl₃) δ 7.26 (2H, d, J = 8.6 Hz, Ar-H), 6.86 (2H, d, J = 8.6 Hz, Ar-H), 5.19 (1H, dq, J = 9.3, 1.2 Hz, H₃), 4.36 (2H, s, OCH₂Ar), 3.85 (2H, s, H₁), 3.76 (3H, s, OCH₃), 3.49-3.33 (2H, m, CH₃), 2.64–2.52 (1H, m, H₄), 1.68 (3H, d, J = 1.3 Hz, =CCH₃), 0.96 (3H, d, J = 6.7 Hz, CH-CH₃), 0.88 (9H, s, Si-C(CH₃)₃), and 0.03 (6H, m, 2 × Si-CH₃); \(^13\)C NMR (75 MHz, CDCl₃) δ 159.1, 134.9, 130.9, 129.1, 127.2, 113.7, 75.0, 72.5, 68.6, 55.3, 36.4, 32.6, 25.9, 17.7, 13.7 and -5.2; HRMS (ES⁺) Calcd. For C₂₁H₄₀NO₃Si 382.2772, found [M + NH₄]⁺
To a solution of PMB ether (4.90 g, 13.4 mmol) in dichloromethane (100 mL) and pH 7 buffer (10 mL) at 0 °C, was added DDQ (4.20 g, 18.0 mmol). The solution was stirred for 2 h and quenched with NaHCO₃ (1000 mL), extracted with dichloromethane (3 x 300 mL), washed with brine and dried over MgSO₄. The solution was concentrated under reduced pressure and purified by column chromatography (19 : 1, hexane : ethyl acetate) to yield alcohol (2.85 g, 87 % yield) as a colourless oil.

\[ R_f \ 0.25 \ (10\% \ ethyl \ acetate : \ petroleum \ ether) ; \ \^H \ NMR \ (400 \ MHz, \ CDCl_3) \ \delta \]

5.17 (1H, dq, \( J = 9.6, 1.4 \) Hz, \( H_3 \)), 3.96 (2H, s, \( H_1 \)), 3.47 (1H, dd, \( J = 10.4, 6.1 \) Hz, \( CH_5a \)), 3.36 (1H, dd, \( J = 10.5, 7.9 \) Hz, \( CH_5b \)), 2.71 − 2.60 (1H, m, \( H_4 \)), 1.65 (3H, d, \( J = 1.4 \) Hz, =CCH₃), 0.95 (3H, d, \( J = 6.8 \) Hz, CCH₃), 0.91 (9H, s, SiCCH₃) and 0.07 (6H, s, SiCH₃).

(2S, 3E)-5-(para-Methoxybenzyl)-2,4-dimethylpent-3-en-1-ol (208)
TBAF (8.3 mL, 8.3 mmol, 1 M in THF) was added to a solution of TBS ether 176 (1.50 g, 4.1 mmol) in THF (15 mL) at 0 °C. After 6 h the reaction mixture was quenched with saturated aqueous NH₄Cl (20 mL), extracted with diethyl ether (3 x 20 mL) and dried over MgSO₄. The resulting solution was concentrated under reduced pressure and purified by column chromatography (4 : 1, hexane : ethyl acetate) to yield alcohol 208 (923 mg, 89%) as a colourless oil.

*RF* 0.28 (20% ethyl acetate : petroleum ether); *¹H NMR* (400 MHz, CDCl₃) δ 7.27 (2H, d, *J* = 8.6 Hz, Ar-H), 6.88 (2H, d, *J* = 8.7 Hz, Ar-H), 5.21 (1H, dq, *J* = 9.5, 1.2 Hz, H₃), 4.41 (2H, s, OCH₂Ar), 3.89 (2H, s, H₁), 3.81 (3H, s, OCH₃), 3.48 (1H, dd, *J* = 10.4, 6.1 Hz, CH₅a), 3.38 (1H, dd, *J* = 10.5, 7.7 Hz, CH₅b), 2.74–2.59 (1H, m, H₄), 1.72 (3H, d, *J* = 1.3 Hz, =CCH₃) and 0.97 (3H, d, *J* = 6.7 Hz, CH-CH₃).

**(2S, 3E)-5-(tert-Butyldimethylsilyloxy)-2,4-dimethylpent-3-enal (155)**

![Chemical Structure](image)

**Method A:**

To a solution of oxalyl chloride (156 mg, 1.23 mmol) in dichloromethane (5.0 mL) was cooled to -78 °C and a solution of DMSO (114 mg, 1.47 mmol) in dichloromethane (2.0 mL) was added dropwise over 5 min. The solution was left stirring for a further 10 min, upon which the alcohol 207 (150 mg,
614 µmol) in dichloromethane (2.0 mL) was added dropwise. The solution was left stirring at -78 °C for 1.5 h, prior to the addition of triethylamine (435 mg, 4.30 mmol) in dichloromethane (2.0 mL). The solution was warmed to room temperature and quenched with water (5 mL), extracted with dichloromethane (3 x 5 mL). The organic layer was dried over MgSO₄ and concentrated under reduced pressure. The residue was passed through a column (9 : 1, hexane : ethyl acetate) to yield aldehyde 155, which was used immediately without further purification.

**Method B:**

Dess-Martin periodinane (2.25 g, 6.84 mmol) was added to a solution of alcohol 207 (1.00 g, 4.10 mmol) in dichloromethane (30 mL). The solution stirred for 2 h then quenched with sodium thiosulfate (25 mL). The product was extracted with dichloromethane (3 x 30 mL) and dried over MgSO₄. The product was purified by filtration through Celite®, and washing with excess petroleum ether, to give aldehyde 155, which was used immediately without further purification.

\[ R_f \ 0.55 \ (10\% \ ethyl \ acetate : \ petroleum \ ether); \ ^1H \ NMR \ (300 \ MHz, \ CDCl_3) \ \delta \ 9.51 \ (1H, d, J = 1.9 \ Hz, H_1), 5.29 \ (1H, dq, J = 9.1, 1.4 \ Hz, H_3), 4.07 \ (2H, s, H_5), 3.36 - 3.25 \ (1H, m, H_2), 1.68 \ (3H, d, J = 1.2 \ Hz, =CHCH_3), 1.18 \ (3H, d, J = 7.0 \ Hz, CHCH_3), 0.92 \ (9H, s, SiCH_3) \ and \ 0.08 \ (6H, s, SiCH_3). \]
(2S, 3E)-5-(para-Methoxybenzyl)-2,4-dimethylpent-3-enal (173)

Dess-Martin periodinane (830 mg, 2.00 mmol) was added to a solution of alcohol 208 (250 mg, 1.00 mmol) in dichloromethane (4 mL). The solution stirred for 2 h then quenched with sodium thiosulfate (5 mL). The product was extracted with dichloromethane (3 x 5 mL) and dried over MgSO₄. The product was purified by filtration through Celite®, and washing with excess petroleum ether, to give aldehyde 173, which was used immediately without further purification.

R_{r} 0.38 (10% ethyl acetate : petroleum ether); ^{1}H NMR (400 MHz, CDCl₃) δ 9.52 (1H, d, J = 1.8 Hz, H₁), 7.27 (2H, d, J = 8.6 Hz, ArH), 6.87 (2H, d, J = 8.7 Hz, ArH), 5.30 (1H, dq, J = 9.5, 1.2 Hz, H₃), 4.41 (2H, s, OCH₂Ar), 3.91 (2H, s, H₅), 3.79 (3H, s, OCH₃), 3.36-3.18 (1H, m, H₂), 1.73 (3H, d, J = 1.4 Hz, =CCH₃) and 1.18 (3H, d, J = 6.9 Hz, CH-CH₃).

(2R, 3S, 4R, 5E)-Methyl 7-(tert-butyldimethylsilyl)oxy-3-hydroxy-(4, 6)-dimethyl-2-(prop-1-en-2-yl)hept-5-enoate (162)
A solution of \( n \)-butyl lithium (52 ml, 0.83 mmol, 1.6 M in hexane) was added to a solution of diisopropylamine (110 mL, 830 µmol) in THF (5 mL) at -78 °C. The mixture was stirred for 30 min where methyl-3,3-dimethyl acrylate 161 (70 mg, 620 µmol) in THF (2 mL) was added. After 30 min a solution of aldehyde 155 (409 µmol) in THF (1 mL) was added. The mixture was left to stir for 1 h and quenched with \( \text{NH}_4 \text{Cl} \) (5 mL), the organic portions were extracted with diethyl ether (3 x 5 mL) and the combined organic extracts were dried over \( \text{Na}_2\text{SO}_4 \). The solution was concentrated under reduced pressure and purified by column chromatography (14 : 1, hexane : ethyl acetate) to give aldol adduct 162 (78 mg, 53%, \( \alpha : \gamma = 4 : 1 \)) as a colourless oil.

\( R_f \) 0.32 (10% ethyl acetate : petroleum ether); \([\alpha]^{20}_D +21.4 \) (c 1.0 CHCl\(_3\)); \( \text{IR} \) (thin film) 3450, 3442, 2970, 2926, 1714, 1651, 1447, 1280, 1180, 1015, 949, and 867 cm\(^{-1}\); \( ^1\text{H NMR} \) (300 MHz, CDCl\(_3\)) \( \delta 5.26 (1\text{H, dq, } J = 9.7, 1.4 \text{ Hz}, \text{H}_5), 5.07-5.05 (1\text{H, m, } \text{C} = \text{CH}_3), 4.96-4.95 (1\text{H, m, } \text{C} = \text{CH}_2), 4.00 (2\text{H, s, H}_7), 3.91 (1\text{H, ddd, } J = 7.1, 6.8, 3.3 \text{ Hz, H}_3), 3.70 (3\text{H, s, OCH}_3), 3.21 (1\text{H, d, } J = 6.6 \text{ Hz, H}_4), 2.56-2.50 (1\text{H, m, H}_2), 2.43 (1\text{H, d, } J = 3.3 \text{ Hz, OH}), 1.84-1.83 (3\text{H, m, } =\text{C-CH}_3), 1.60 (3\text{H, d, } J = 1.2 \text{ Hz, } =\text{C}_6\text{-CH}_3), 1.04 (3\text{H, d, } J = 6.7 \text{ Hz, C}_4\text{-CH}_3), 0.91 (9\text{H, s, SiCCH}_3) \) and \( 0.07 (6\text{H, m, SiCH}_3) \); \( ^{13}\text{C NMR} \) (75 MHz, CDCl\(_3\)) \( \delta 174.2, 140.7, 134.8, 127.3, 115.1, 75.0, 68.5, 55.7, 52.1, 35.7, 30.1, 26.0, 21.6, 15.2, 13.7 \) and \(-5.1\); \( \text{HRMS (ES}^+) \) calc. for \( \text{C}_{19}\text{H}_{40}\text{O}_4\text{SiN ([M+NH}_4]^+) \) 374.2721, found 374.2719.
(2E, 5R, 6R, 7E)-Methyl 9-(tert-butyldimethylsilyl)oxy-5-hydroxy-(3, 6, 8)-trimethyl-nona-2, 7-dienoate (157)

To a solution of freshly prepared ATPH 163 (6.80 mmol) in toluene (15 mL) at -78 °C was added a solution of methyl-3,3-dimethyl acrylate 161 (480 mg, 4.10 mmol) in toluene (5 mL); after 15 min a solution of aldehyde 155 (2.05 mmol) in toluene (5 mL) was added. The mixture was stirred for 20 min upon which a solution of n-butyl lithium (2.8 mL, 4.50 mmol, 1.6 M in hexane) and diisopropylamine (643 µL, 4.50 mmol) in THF (15 mL) was added. After 30 min at -78 °C, a saturated solution of NH₄Cl (30 mL) was added, and the mixture was filtered through Celite®. The organic portions were extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were dried over Na₂SO₄. The solution was concentrated under reduced pressure and purified by column chromatography (14 : 1, hexane : ethyl acetate) to give aldol adduct 157 (402 mg, 55% over two steps, α : γ = 1 : 7, d.r = 4 : 1) as a colourless oil.

$R_f$ 0.30 (10% ethyl acetate : petroleum ether); $[\alpha]_D^{20} +7.5$ (c 1.1 CHCl₃); IR (thin film) 3402, 2951, 1742, 1614, 1447, 1223, 1050 and 933 cm⁻¹; $^1$H NMR (400 MHz, CDCl₃) δ 5.84 (1H, q, $J = 1.3$ Hz, H₂), 5.30 (1H, dq, $J = 9.9, 1.4$ Hz, H₇), 4.04 (2H, s, H₆), 3.70 (3H, s, OCH₃), 3.53-3.47 (1H, m, H₅), 2.55-
2.49 (1H, m, H₆), 2.30 (1H, dd, J = 12.8, 2.4 Hz, H₄a), 1.97 (1H, dd, J = 12.0, 5.6 Hz, H₄b), 1.93 (3H, d, J = 1.3 Hz, =C₃-CH₃), 1.64 (3H, d, J = 1.4 Hz, C₈-CH₃), 1.08 (3H, d, J = 6.8 Hz, C₆-CH₃), 0.91 (9H, s, SiCCH₃) and 0.07 (6H, s, SiCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 168.5, 135.6, 132.8, 126.2, 113.9, 74.6, 70.3, 52.0, 39.1, 34.2, 31.1, 26.3, 20.9, 16.3, 12.7 and -5.2; HRMS (ES⁺) calc. for C₁₉H₄₀O₄SiN ([M+NH₄⁺]⁺) 374.2721, found 374.2721.

(R)-MTPA ester of 157 (171)

To a solution of alcohol 157 (5 mg, 14.0 µmol), DCC (5.9 mg, 38.0 µmol) and DMAP (2 mg) in dichloromethane (2.0 mL) at room temperature was added (+)-(R)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (6.5 mg, 38.0 µmol). After 6 h, the crude reaction mixture was purified directly by column chromatography (19 : 1, hexane : ethyl acetate) to give (R)-MTPA ester 171 (3.6 mg, 41%).

R₁ 0.27 (10%, ethyl acetate : hexane); ¹H NMR (400 MHz, CDCl₃) δ 7.50-7.48 (2H, m, Ar-H), 7.43-7.37 (3H, m, Ar-H), 5.75 (1H, q, J = 1.3 Hz, H₂), 5.34 (1H, dq, J = 9.8, 0.6 Hz, H₇), 5.06 (1H, dt, J = 7.7, 5.8 Hz, H₅), 4.03 (2H, s, H₆), 3.66 (3H, s, OCH₃), 3.48 (3H, d, J = 1.1 Hz, MTPA-OCH₃), 2.79-2.77
(1H, m, H₆), 2.21 (1H, m, H₄a), 2.07 (1H, m, H₄b), 2.17 (3H, d, J = 1.3 Hz, C₃-CH₃), 1.74 (3H, d, J = 1.3 Hz, C₈-CH₃) and 1.03 (3H, d, J = 6.8 Hz, C₆-CH₃).

(S)-MTPA ester of 157 (170)

To a solution of alcohol 157 (5 mg, 14.0 µmol), DCC (5.9 mg, 38.0 µmol) and DMAP (2 mg) in dichloromethane (2.0 mL) at room temperature was added (+)-(R)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (6.5 mg, 38.0 µmol). After 6 h, the crude reaction mixture was purified directly by column chromatography (19 : 1, hexane : ethyl acetate) to give (S)-MTPA ester 170 (3.7 mg, 43%).

Rᵣ 0.30 (10%, ethyl acetate : hexane); ¹H NMR (400 MHz, CDCl₃) δ 7.49-7.47 (2H, m, Ar-H), 7.41-7.37 (3H, m, Ar-H), 5.80 (1H, q, J = 1.1 Hz, H₂), 5.25 (1H, dq, J = 10.1, 0.8 Hz, H₇), 5.10-5.07 (1H, m, H₅), 3.68 (3H, s, OCH₃), 3.51 (3H, d, J = 1.2 Hz, MTPA-OCH₃), 2.73-2.71 (1H, m, H₆), 2.29 (1H, m, H₄a), 2.13 (1H, m, H₄b), 2.19 (3H, d, J = 1.3 Hz, C₃-CH₃), 1.67 (3H, d, J = 0.9 Hz, C₈-CH₃) and 0.94 (3H, d, J = 6.8 Hz, C₆-CH₃).
(2E, 5R, 6R, 7E)-Methyl 9-(para-methoxybenzyl)-5-hydroxy-(3, 6, 8)-trimethyl-nona-2, 7-dienoate (172)

To a solution of freshly prepared ATPH 163 (3.30 mmol) in toluene (5 mL) at -78 °C was added a solution of methyl-3,3-dimethyl acrylate 161 (230 mg, 2.00 mmol) in toluene (1 mL) and a solution of aldehyde 173 (1.00 mmol) in toluene (1 mL) was added. The mixture was stirred for 20 min upon which a solution of n-butyl lithium (1.4 mL, 2.2 mmol, 1.6 M in hexane) and diisopropylamine (308 µL, 2.2 mmol) in THF (5 mL) was added. After 30 min at -78 °C, a saturated solution of NH₄Cl (8 mL) was added, and the mixture was filtered through Celite®. The organic portions were extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over Na₂SO₄. The solution was concentrated under reduced pressure and purified by column chromatography (14 : 1, hexane : ethyl acetate) to give aldol adduct 172 (184 mg, 52% over two steps, α : γ = 1 : 6, d.r = 4 : 1) as a colourless oil.

*R* 0.35 (20% ethyl acetate : petroleum ether); [α]²⁰0 +8.2 (c 1.0 CHCl₃); IR (thin film) 3475, 2948, 1715, 1644, 1435, 1223, 1059, 950 and 755 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.31 (2H, d, J = 8.7 Hz, Ar-Η), 6.91 (2H, d, J = 8.6 Hz, Ar-Η), 5.82 (1H, q, J = 1.2 Hz, Η₂), 5.09 (1H, dq, J = 10.0, 1.4 Hz, Η₂), 4.49 (2H, s, OCH₂PhOMe), 4.03 (2H, s, Η₆), 3.82 (3H, s, PhOCH₃), 3.58
(3H, s, OCH$_3$), 3.38-3.32 (1H, m, H$_5$), 2.35-2.29 (1H, m, H$_6$), 2.10 (1H, dd, J = 13.4, 2.3 Hz, H$_{4a}$), 2.04 (3H, d, J = 1.3 Hz, =C$_3$-CH$_3$), 1.86 (1H, dd, J = 13.7, 8.8 Hz, H$_{4b}$), 1.61 (3H, d, J = 1.4 Hz, C$_8$-CH$_3$) and 1.01 (3H, d, J = 6.7 Hz, C$_6$-CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 169.2, 159.0, 135.0, 133.9, 131.1, 128.8, 126.2, 114.3, 113.6, 79.2, 75.1, 74.6, 53.6, 52.0, 39.1, 31.1, 20.9, 16.3 and 12.7; HRMS (ES$^+$) calc. for C$_{21}$H$_{34}$O$_5$N ([M+NH$_4^+$]) 380.2431, found 380.2428.

(2$^E$, 5$^R$, 6$^R$, 7$^E$)-Methyl 9-(tert-butyldimethylsilyl)oxy-5-(((triethylsilyl)oxy)-(3, 6, 8)-trimethyl-nona-2, 7-dienoate (177)

![Chemical Structure](image_url)

To solution of alcohol 157 (300 mg, 841 μmol) in dichloromethane (5 mL) at 0 °C was added TESCl (228 μL, 1.25 mmol), imidazole (170 mg, 2.45 mmol) and DMAP (5.0 mg, 40.0 μmol). The reaction mixture was allowed to warm to room temperature then stirred for 16 h and quenched with saturated aqueous NH$_4$Cl (5 mL), extracted with dichloromethane (3 x 5 mL) and dried over MgSO$_4$. The resulting solution was concentrated under reduced pressure and purified using column chromatography (9 : 1, hexane : ethyl acetate) to give silyl enol ether 177 (364 mg, 92%) as a colourless oil.

$R_f$ 0.28 (15% ethyl acetate : petroleum ether); $[\alpha]_D^{20} +19.2$ (c 1.0 CHCl$_3$); IR (thin film) 2950, 2929, 2850, 1732, 1617, 1435, 1225, 1082, 755 and 725 cm$^{-1}$;
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.81 (1H, q, $J = 1.3$ Hz, H$_2$), 5.22 (1H, dq, $J = 9.9, 1.3$ Hz, H$_7$), 4.14-4.08 (1H, m, H$_5$), 4.03 (2H, s, H$_9$), 3.63 (3H, s, OCH$_3$), 2.79-2.73 (1H, m, H$_6$), 2.27-2.22 (2H, m, H$_4$), 1.96 (3H, d, $J = 1.3$ Hz, =C$_3$-CH$_3$), 1.64 (3H, d, $J = 1.3$ Hz, C$_9$-CH$_3$), 1.13 (3H, d, $J = 6.6$ Hz, C$_6$-CH$_3$), 0.96-0.95 (6H, m, Si-(CH$_2$CH$_3$)$_3$), 0.91 (9H, s, Si-C(CH$_3$)$_3$), 0.54-0.48 (9H, m, Si-(CH$_2$CH$_3$)$_3$) and 0.07 (6H, s, Si-CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.6, 140.7, 132.8, 126.2, 115.6, 74.8, 70.8, 51.3, 46.9, 42.8, 32.0, 25.6, 18.5, 16.1, 12.8, 7.8, 5.9 and -5.0; HRMS (ES$^+$) calc. for C$_{25}$H$_{54}$O$_4$Si$_2$N ([M+NH$_4$]$^+$) 488.3586, found 488.3581.

(2$^E$, 5$R$, 6$R$, 7$E$)-9-(tert-Butyldimethylsilyl)oxy-5-((triethylsilyl)oxy)-(3, 6, 8)-trimethyl-nona-2, 7-dien-1-ol (178)

To a solution of ester 177 (280 mg, 5.94 µmol) in dichloromethane (2 mL) at -78 °C, was added DIBAL (1.18 mL, 1.18 mmol, 1 M dichloromethane). The mixture was stirred for 2 h and quenched with aqueous potassium sodium tartrate (5 mL), and the mixture was stirred for a further 4 h. The crude product was extracted with diethyl ether (3 x 5 mL), dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The crude residue was purified using coloumn chromatography (3 : 2, hexane : ethyl acetate) to yield alcohol 178 (234 mg, 89%) as a colourless oil.
$R_f$ 0.46 (40% ethyl acetate : petroleum ether); $[\alpha]_{D}^{20} +10.8 \text{ (c} 0.5 \text{ CHCl}_3); \text{IR}$ (thin film) 3418, 2951, 2921, 1457, 1008, 946 and 755 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.33-5.30 (1H, m, H$_2$), 5.24 (1H, dq, $J$ = 9.9, 1.3 Hz, H$_2$), 4.14-4.09 (1H, m, H$_3$), 4.00 (2H, s, H$_2$), 3.91 (2H, d, $J$ = 6.8 Hz, H$_1$), 2.81-2.78 (1H, m, H$_6$), 2.29-2.25 (2H, m, H$_4$), 1.69 (3H, d, $J$ = 1.3 Hz, $\text{=C}_{\text{3}}$-CH$_3$), 1.60 (3H, d, $J$ = 1.2 Hz, C$_{\text{8}}$-CH$_3$), 1.16 (3H, d, $J$ = 6.8 Hz, C$_{\text{6}}$-CH$_3$), 0.95-0.94 (6H, m, Si-(CH$_2$CH$_3$)$_3$), 0.90 (9H, s, Si-C(CH$_3$)$_3$), 0.58-0.52 (9H, m, Si-(CH$_2$CH$_3$)$_3$) and 0.05 (6H, s, Si-CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.9, 133.8, 125.6, 124.2, 74.1, 71.5, 58.9, 45.9, 37.9, 29.6, 26.1, 18.5, 15.4, 12.1, 7.3, 5.7 and -5.2; HRMS (ES$^+$) calc. for C$_{24}$H$_{51}$O$_3$Si$_2$ ([M+H]$^+$) 443.3371, found 443.3368.

(2E, 5R, 6R, 7E)-9-(tert-Butyldimethylsilyl)oxy-5-((triethylsilyl)oxy)-1-(sulfanyl-1-phenyl-1H-1, 2, 3, 4-tetrazol-5-yl)-(3, 6, 8)-trimethyl-nona-2, 7-diene (210)

To a solution of alcohol 178 (100 mg, 225 µmol) at 0 ºC in THF (2 mL) was added 1-H-mercaptophenyltertrazole (60 mg, 264 µmol), triphenylphosphine (82 mg, 302 µmol) followed by DIAD (45 µL, 302 µmol) drop-wise. The reaction mixture was warmed up to room temperature and left to stir for 2 h before aqueous NH$_4$Cl (2 mL) was added, upon which the
resulting mixture was extracted with ethyl acetate (3 x 5 mL), and dried over 
Na$_2$SO$_4$. The solution was concentrated under reduced pressure and purified 
by column chromatography (9 : 1, hexane : ethyl acetate) to give sulfide 210 
(108 mg, 80%) as a colourless oil.

$R_f$ 0.37 (20% ethyl acetate : petroleum ether); $[\alpha]_{D}^{20} +26.1$ (c 0.5 CHCl$_3$); IR 
(thin film) 3042, 2966, 2927, 2875, 1595, 1500, 1385, 1240, 1018, 950, 759, 755 and 742 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.19-7.17 (2H, m, Ar-$H$), 6.90-6.88 (3H, m, Ar-$H$), 5.29-5.26 (1H, m, H$_2$), 5.19 (1H, dq, $J = 9.8, 1.3$ Hz, $H_7$), 4.10-4.04 (1H, m, H$_3$), 3.99 (2H, s, H$_9$), 3.87 (2H, d, $J = 7.2$ Hz, H$_1$), 2.75-2.70 (1H, m, H$_8$), 2.26-2.21 (2H, m, H$_4$), 1.72 (3H, d, $J = 1.2$ Hz, $=C_3$-$CH_3$), 1.60 (3H, d, $J = 1.2$ Hz, C$_8$-$CH_3$), 1.02 (3H, d, $J = 7.0$ Hz, C$_6$-$CH_3$), 0.94-0.93 (6H, m, Si-(CH$_2$CH$_3$)$_3$), 0.89 (9H, s, Si-C(CH$_3$)$_3$), 0.56-0.51 (9H, m, Si-(CH$_2$CH$_3$)$_3$) and 0.05 (6H, s, Si-CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 154.5, 139.8, 134.1, 133.8, 129.7, 129.6, 125.2, 123.6, 119.8, 74.8, 71.8, 45.8, 38.2, 31.9, 30.2, 25.5, 16.9, 15.4, 12.2, 7.0, 5.5 and -4.9; HRMS (ES$^+$) calc. 
for C$_{31}$H$_{55}$N$_4$O$_2$SSi$_2$([M+H]$^+$) 603.3579, found 603.3577.

(2$E$, 5$R$, 6$R$, 7$E$)-9-((tert-Butyldimethysilyl)oxy-5-((triethysilyl)oxy)-1-
(sulfonyl-1-phenyl-1H-1, 2, 3, 4-tetrazole)-(3, 6, 8)-trimethyl-nona-2, 7-
diene (95)

$$\text{TBSO} \quad \text{TESO}$$
A mixture of ammonium molybdate (33 mg, 26 µmol) and hydrogen peroxide (47 µL, 1.2 mmol, 30% v/v) was allowed to stir at 0 °C for 15 min. Half of the resulting yellow solution was added dropwise at 0 °C to a solution of sulfide 210 (70 mg, 116 µmol) in ethanol (1 mL). The reaction mixture was stirred for 1 h at room temperature before the remaining resultant oxidant was added, and stirred for 16 h. The reaction mixture was the diluted with ethanol (1 mL) then filtered. The filtrate was portioned between water (1 mL) and dichloromethane (2 mL) followed by extraction with dichloromethane (3 x 2 mL). The organic phases were dried over Na₂SO₄, filtered and concentrated by reduced pressure. Purification by column chromatography (9 : 1, hexane : ethyl acetate) provided sulfone 95 (60 mg, 82%) as a colourless oil.

**Rf** 0.25 (20% ethyl acetate : petroleum ether); [α]D²⁰⁰ +21.5 (c 0.1 CHCl₃); **IR** (thin film) 3049, 2955, 2927, 2870, 1498, 1449, 1354, 1015, 950, 755 and 739 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 7.74-7.68 (2H, m, Ar-H), 7.63-7.61 (3H, m, Ar-H), 5.04-4.98 (1H, m, H₂), 4.94-4.88 (1H, m, H₇), 4.11-4.06 (2H, m, H₁), 3.89-3.85 (1H, m, H₃), 3.40 (2H, s, H₉), 2.84-2.74 (1H, m, H₆), 2.58-2.51 (2H, m, H₄), 1.56 (3H, d, J = 1.3 Hz, =C₃-CH₃), 1.27(3H, d, J = 1.2 Hz, C₈-CH₃), 1.01-0.93 (9H, m, C₆-CH₃ + Si-(CH₂CH₃)₃), 0.90 (9H, s, Si-C(CH₃)₃), 0.63-0.56 (9H, m, Si-(CH₂CH₃)₃) and 0.05-0.03 (6H, m, Si-CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ 154.0, 136.8, 134.7, 133.5, 129.7, 129.7, 125.2, 123.9, 110.0, 74.1, 71.8, 58.7, 45.9, 39.2, 30.7, 25.9, 16.8, 16.0, 12.6, 6.8, 5.2 and 5.2; **HRMS** (ES⁺) calc. for C₃₁H₅₈N₅O₄SSi₂ ([M+NH₄]+) 652.3743, found 652.3741.
7.6: Experimental for Chapter 4

(2E, 4S)-5-(tert-Butyldimethysilyloxy)-2, 4-dimethylpent-2-enal (209)\textsuperscript{121}

Method A:

Dess-Martin periodinane (7.30 g, 17.2 mmol) was added to a solution of alcohol 195 (2.10 g, 8.60 mmol) in dichloromethane (50 mL). The solution was stirred for 2.5 h, and quenched with sodium thiosulfate (50 mL). The product was extracted with ethyl acetate (3 x 30 mL), and dried over MgSO\textsubscript{4}. The product was purified by filtration through Celite\textsuperscript{®}, to give aldehyde 209 which was used without further purification.

Method B:

To a solution of alcohol 195 (2.00 g, 8.18 mmol) in dichloromethane (100 mL) was added MnO\textsubscript{2} (7.10 g, 82.0 mmol) at room temperature. The resulting mixture was stirred for 3 h where a further MnO\textsubscript{2} (7.10 g, 184.0 mmol) was added. After 3 h the mixture was filtered through Celite\textsuperscript{®}, and crude aldehyde 209 was used without further purification.

\( R_f \) 0.39 (10% ethyl acetate : petroleum ether); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \)

- 9.40 (1H, s, H\textsubscript{1}),
- 6.32 (1H, dq, \( J = 9.7, 1.3 \) Hz, H\textsubscript{3}),
- 3.59 (1H, dd, \( J = 9.9, 6.0 \) Hz, H\textsubscript{5a}),
- 3.54 (1H, dd, \( J = 9.9, 6.5 \) Hz, H\textsubscript{5b}),
- 2.89 (1H, ddd, \( J = 12.6, 9.7, 6.6 \) Hz, H\textsubscript{2}).
Hz, \( H_2 \)), 1.77 (3H, d, \( J = 1.4 \) Hz, \(-\text{C-CH}_3\)), 1.06 (3H, d, \( J = 6.8 \) Hz, -CH-CH\(_3\)), 0.87 (9H, s, Si-C(CH\(_3\))\(_3\)), 0.04 (3H, s, Si-CH\(_3\)) and 0.03 (3H, s, Si-CH\(_3\)).

\((2E, 4S)-5-(\text{para-Methoxybenzyl})-2, 4\text{-dimethylpent-2-enal (181)}\)\(^{122}\)

![Aldehyde Structure](image)

Dess-Martin periodinane (1.96 g, 4.63 mmol) was added to a solution of alcohol 160 (580 mg, 2.32 mmol) in dichloromethane (30 mL). The solution was stirred for 2 h, and quenched with sodium thiosulfate (20 mL). The product was extracted with ethyl acetate (3 x 20 mL), and dried over MgSO\(_4\). The product was purified by filtration through Celite\(^\circledR\), and washed with excess petroleum ether, to give aldehyde 181 which was used without further purification.

\( R_f \) 0.70 (20% ethyl acetate : petroleum ether); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \)

9.33 (1H, s, \( H_1 \)), 7.16 (2H, d, \( J = 8.7 \) Hz, \( \text{CH}_2\)-Ar-\( H \)), 6.81 (2H, d, \( J = 8.6 \) Hz, O-Ar-\( H \)), 6.27 (1H, dq, \( J = 13.4, 9.4 \) Hz, \( H_3 \)), 4.38 (2H, s, O-\( \text{CH}_2\)-Ar), 3.74 (3H, s, Ar-O-\( \text{CH}_3\)), 3.30–3.37 (2H, m, \( H_5 \)), 2.89–3.00 (1H, m, \( H_4 \)), 1.70 (3H, d, \( J = 1.3 \) Hz, \(-\text{C-CH}_3\)) and 1.01 (3H, d, \( J = 6.8 \) Hz, CH-\( \text{CH}_3\))
(3E, 5S)-6-( tert-Butyldimethylsilyloxy)-3,5-dimethyl-3-hexen-1-ynylidene (194)\(^{123}\)

\[
\begin{align*}
\text{H} & \quad \begin{array}{c}
\text{OTBS}
\end{array} \\
\end{align*}
\]

**Method A:**
To a solution of dry potassium tert-butoxide (530 mg, 4.75 mmol) in THF (20 mL) at -78 °C, was added Gilbert reagent 184 (715 mg, 4.75 mmol) in THF (8 mL). After 5 min a solution of crude aldehyde 209 (3.96 mmol) in THF (8 mL) was added and the solution was stirred at -78 °C for 16 h, followed by 3 h at room temperature. The reaction was quenched with water (80 mL), and the product was extracted with dichloromethane (3 x 50 mL), washed with brine (50 mL) and dried over MgSO\(_4\). The solution was concentrated under reduced pressure and the crude residue was purified by column chromatography (9 : 1, hexane : ethyl acetate) to afford alkyne 194 (482 mg, 51% over two steps) as a colourless oil which was used immediately in the following reaction.

**Method B:**
A solution of dimethyl (1-diazo-2-oxopropyl)-phosphonate 190 (2.10 g, 10.8 mmol), crude aldehyde 209 (3.60 mmol) and Cs\(_2\)CO\(_3\) (4.80 g, 14.4 mmol) in methanol (30 mL) was stirred at 0 °C for 1 h, then at room temperature for 16 h. The reaction mixture was quenched with saturated aqueous NH\(_4\)Cl (40 mL) and extracted with diethyl ether (3 x 40 mL). The
organic phase was dried with Na$_2$SO$_4$. Evaporation of the solvent under reduced pressure followed by column chromatography (9 : 1, hexane : ethyl acetate) yielded alkyne 194 (590 mg, 69% over two steps) as a colourless oil which was used immediately in the following reaction.

$R_f$ 0.61 (20% ethyl acetate : petroleum ether); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$

5.20 (1H, dq, J = 9.1, 1.4 Hz, H$_4$), 4.00 (1H, s, H$_1$), 3.49-3.35 (2H, m, H$_6$), 2.64–2.54 (1H, m, H$_5$), 1.70 (3H, d, J = 1.4 Hz, -C-CH$_3$), 0.97 (3H, d, J = 6.7 Hz, -C-CH$_3$), 0.90 (9H, s, Si-C(CH$_3$)$_3$) and 0.05 (6H, s, 2 x Si-CH$_3$).

(3E, 5S)-6-(para-Methoxybenzyl)-3, 5-dimethyl-3-hexen-1-ynylidene (182)

Method A:

To a solution of dry potassium tert-butoxide (300 mg, 2.41 mmol) in THF (10 mL) at -78 °C, was added Gilbert reagent 184 (520 mg, 2.41 mmol) in THF (4 mL). After 5 min a solution of crude aldehyde 181 (2.0 mmol) in THF (4 mL) was added and the solution was stirred at -78 °C for 16 h, followed by 3 h at room temperature. The reaction was quenched with water (50 mL), and the product was extracted with dichloromethane (3 x 20 mL), washed with brine (50 mL) and dried over MgSO$_4$. The solution was concentrated under reduced pressure and the crude residue was purified by column chromatography (9 : 1, hexane : ethyl acetate) to afford alkyne 182 (150 mg,
32% over two steps) as a colourless oil which was used immediately in the following reaction.

**Method B:**

A solution of dimethyl (1-diazo-2-oxopropyl)-phosphonate 190 (1.10 g, 5.70 mmol), aldehyde 181 (1.90 mmol) and Cs$_2$CO$_3$ (2.50 g, 7.60 mmol) in methanol (15 mL) was stirred at 0 ºC for 1 h, then at room temperature for 16 h. The reaction mixture was quenched with saturated aqueous NH$_4$Cl (20 mL) and extracted with diethyl ether (3 x 20 mL). The organic phase was dried with Na$_2$SO$_4$. Evaporation of the solvent followed by column chromatography (9 : 1, hexane : ethyl acetate) yielded the alkyne 182 (270 mg, 58% over two steps) as a colourless oil which was used immediately in the following reaction.

$R_f$ 0.16 (20% ethyl acetate : petroleum ether); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.27 (2H, d, $J = 8.6$ Hz, CH$_2$-Ar-H), 6.83 (2H, d, $J = 8.6$ Hz, O-Ar-CH), 5.16 (1H, dq, $J = 9.2$, 1.3 Hz, H$_3$), 4.36 (2H, s, O-CH$_2$-Ar), 3.86 (1H, s, H$_6$), 3.70 (3H, s, O-CH$_3$), 3.25-3.14 (2H, m, H$_1$), 2.69–2.62 (1H, m, H$_2$), 1.61 (3H, d, $J = 1.4$ Hz, Me$_4$) and 0.91 (3H, d, $J = 6.7$ Hz, Me$_2$).

(1$E$, 3$E$, 5$S$)-6-(tert-Butyldimethylsilyloxy)-1-iodo-3, 5-dimethyl-1, 3-hexadiene (193)
Method A:

In a dark environment at room temperature, a solution of alkyne 194 (200 mg, 850 µmol) in THF (7 mL) and PdCl₂(PPh₃)₂ (33.0 mg, 43.0 µmol) was prepared. The mixture was stirred for 2 h and Bu₃SnH (520 µL, 1.10 mmol) was added drop wise. The mixture was stirred for 10 min then concentrated under reduced pressure. Dichloromethane (8 mL) was added and the mixture was cooled to -78 °C, prior to the addition of a solution of iodine (400 mg) in dichloromethane (2 mL). After 10 min, the solution was warmed to room temperature and stirred for a further 2 h. The solution was concentrated under reduced pressure, and the crude material 193 was directly subjected to TBAF deprotection.

Method B:

In a dark environment a solution of crude aldehyde 209 (4.10 mmol) and iodoform (4.80 g, 12.3 mmol) in dioxane (100 mL) was added to a solution of CrCl₂ (5.10 g, 41.0 mmol) in THF (100 mL) at room temperature. The reaction was left stirring for 16 h, upon which aqueous NaHCO₃ (300 mL) was added and this mixture was filtered through Celite®. The product was then extracted with ethyl acetate (3 x 200 mL), dried over Na₂SO₄ and the crude material 193 was directly subjected to TBAF deprotection.

Rf 0.76 (10% ethyl acetate/Hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.03 (1H, d, J = 14.6 Hz, H₂), 6.15 (1H, d, J = 14.6 Hz, H₁), 5.27 (1H, d, J = 9.5 Hz, H₄), 3.45-3.41 (2H, m Hz, H₆), 2.64 (1H, m, H₃), 1.74 (3H, d, J = 1.3 Hz, =C-CH₃), 0.97 (3H, d, J = 6.7 Hz, -CH-CH₃), 0.88 (9H, s, Si-C(CH₃)₃), 0.03
(3H, s, Si-CH₃) and 0.02 (3H, s, Si-CH₃).

**1E, 3E, 5S)-6-(para-Methoxybenzyl)-1-iodo-3, 5-dimethyl-1, 3-hexadiene (191)**

![OPMB](image)

In a dark environment at room temperature, a solution of alkyne 182 (400 mg, 1.60 mmol) in THF (10 mL) and PdCl₂(PPh₃)₂ (68.0 mg, 97.0 µmol) was prepared. The mixture was stirred for 5 min and Bu₃SnH (1.0 mL, 3.8 mmol) was added dropwise. The mixture was stirred for 10 min then concentrated under reduced pressure. Dichloromethane (10 mL) was added and the mixture was cooled to -78 °C, prior to the addition of a solution of iodine (820 mg) in dichloromethane (5 mL). After 10 min, the solution was warmed to room temperature and stirred for a further 10 min. The solution was concentrated under reduced pressure, and the crude material 191 was directly subjected to DDQ deprotection.

Rₚ 0.54 (10% ethyl acetate : petroleum ether); **¹H NMR** (300 MHz, CDCl₃) δ 7.20 (2H, d, J = 8.6 Hz, ArH), 7.15 (1H, d, J = 14.7 Hz, H₂), 6.83 (2H, d, J = 8.6 Hz, ArH), 6.76 (1H, d, J = 14.7 Hz, H₁), 5.13 (1H, dq, J = 9.2, 1.3 Hz, H₄), 4.36 (2H, s, OCH₂Ar), 3.70 (3H, s, OCH₃), 3.25-3.14 (2H, m, H₆), 2.69–2.62 (1H, m, H₅), 1.61 (3H, d, J = 1.3 Hz, =CHCH₃) and 0.91 (3H, d, J = 6.7 Hz, CHCH₃).
(1E, 3E, 5S)-1-Iodo-3, 5-dimethyl-1, 3-hexadiene-6-ol (192)

\[
\begin{align*}
\text{OH} \\
\end{align*}
\]

**Method A:**

TBAF (8.20 mL, 8.20 mmol, 1 M in THF) was added slowly to a solution of TBS-protected vinyl iodide 193 (4.10 mmol) in THF (30 mL) at 0 °C. After 2 h the reaction mixture was quenched with saturated aqueous NH₄Cl (30 mL), extracted with ethyl acetate (3 x 30 mL) and dried over MgSO₄. The resulting solution was concentrated under reduced pressure and purified by column chromatography (19 : 1, hexane : ethyl acetate) to yield alcohol 192 (860 mg, 83%) as a pale yellow oil.

**Method B:**

To a solution of PMB ether 191 (530 µmol) in dichloromethane (5 mL) and pH 7 buffer (0.5 mL) at 0 °C, was added DDQ (240 mg, 1.06 mmol). The solution was stirred for 2 h and quenched with NaHCO₃ (100 mL), extracted with dichloromethane (3 x 30 mL) and dried over MgSO₄. The solution was concentrated under reduced pressure and purified by column chromatography (19 : 1, hexane : ethyl acetate) to yield alcohol 192 (64.0 mg, 79%) as a pale yellow oil.

\[ R_f 0.30 \] (10% ethyl acetate/Hexane), \[ [\alpha]_D^{20} +40.8 \] (c 0.7, CHCl₃); \[ \text{IR} \] (thin film) 3374, 2959, 2926, 2870, 1726, 1707, 1451, 1178, 1035, 1018, 960 and 752 cm⁻¹; \[ \text{¹H NMR} \] (400 MHz, CDCl₃) δ 7.06 (2H, dd, \( J = 14.7, 0.8 \) Hz, \( \text{H}_2 \)).
6.22 (1H, dd, J = 14.7, 0.6 Hz, H₁), 5.27 (1H, dt, J = 9.6, 0.6 Hz, H₄), 3.55-3.49 (1H, m, H₆a), 3.44-3.39 (1H, m, H₆b), 2.78-2.67 (1H, m, H₅), 1.78 (3H, d, J = 1.3 Hz, =C-CH₃) and 0.98 (3 H, d, J = 6.7 Hz, -CH-CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 149.6, 136.5, 136.0, 74.5, 67.6, 35.7, 16.8 and 12.5; HRMS (ES⁺) calc. for C₈H₁₄I [M+H]^⁺ 253.0084, found 253.0079.

(1E, 3E, 5S)-1-Iodo-3, 5-dimethyl-1, 3-hexadiene-6-al (179)

Dess-Martin periodinane (1.00 g, 2.38 mmol) was added to a solution of alcohol 192 (300 mg, 1.20 mmol) in dichloromethane (5 mL). The solution was stirred for 2.5 h, and quenched with sodium thiosulfate (5 mL). The product was extracted with dichloromethane (3 x 5 mL), and dried over MgSO₄. The product was purified by filtration through Celite®, and washed with excess dichloromethane, which was removed under vacuo, to give crude aldehyde 179 that was used without further purification.

R_f 0.47 (10% ethyl acetate : petroleum ether); ¹H NMR (400 MHz, C₆D₆) δ 9.05 (1H, d, J = 1.6, H₁), 6.81 (1H, dd, J = 14.7, 0.8 Hz, H₂), 5.91 (1H, dd, J = 14.7, 0.6 Hz, H₄), 4.73 (1H, ddt, J = 9.2, 1.3, 0.7 Hz, H₅), 2.69 (1H, ddd, J = 9.0, 7.1, 1.8 Hz, H₆), 1.19 (3H, d, J = 1.3 Hz, =C-CH₃) and 0.79 (3H, d, J = 6.9 Hz, =CH-CH₃).
To a solution of ATPH 163 (3.95 mmol) in toluene (3 mL) at -78 °C was added a solution of methyl-3,3-dimethyl acrylate 161 (270 mg, 2.38 mmol) in toluene (1 mL); after 15 min a solution of crude aldehyde 180 (1.20 mmol) in toluene (1 mL) was added. The mixture was stirred for 20 min upon which a solution of n-butyl lithium (1.65 mL, 2.62 mmol, 1.6 M in hexane) and diisopropylamine (365 µL, 2.62 mmol) in THF (3 mL) was added. After 30 h at -78 °C, a saturated solution of NH₄Cl (5 mL) was added, and the mixture was filtered through Celite® and washed with diethyl ether. The organic portions were extracted with diethyl ether (3 x 5 mL) and the combined organic extracts were dried over Na₂SO₄. The solution was concentrated under reduced pressure and purified by column chromatography (14 : 1, hexane : ethyl acetate) to give aldol adduct 180 (220 mg, 51% over two steps, α : γ = 1 : 7, d.r. = 3 : 1) as a pale yellow oil.

R_f 0.26 (10% ethyl acetate : petroleum ether); [α]_D^{20} +17.7 (c 1.0, CHCl₃); IR (thin film) 3475, 2948, 1715, 1644, 1435, 1223, 1151, 1059 and 950 cm⁻¹; ^1H NMR (400 MHz, C₆D₆) δ 6.92 (1H, dd, J = 14.7, 0.8 Hz, H₂), 5.91 (1H, dd, J = 14.7, 0.7 Hz, H₃), 5.80 (1H, dd, J = 2.1, 1.2 Hz, H₄), 4.89 (1H, d, J = 10.0 Hz, H₅), 3.44 (3H, s, OCH₃), 3.16-3.23 (1H, m, H₆), 2.21-2.11 (1H, m, H₇),
2.18 (H, d, J = 1.2 Hz, C\textsubscript{8}-CH\textsubscript{3}), 1.95 (1H, dd, J = 13.6, 2.3 Hz, H\textsubscript{7a}), 1.75 (1H, dd, J = 13.6, 9.8 Hz, H\textsubscript{7b}), 1.31 (3H, d, J = 1.2 Hz, C\textsubscript{3}-CH\textsubscript{3}) and 0.87 (3H, d, J = 6.7 Hz, C\textsubscript{5}-CH\textsubscript{3}); \textsuperscript{13}C NMR (100 MHz, C\textsubscript{6}D\textsubscript{6}) δ 166.6, 157.2, 149.8, 136.5, 134.8, 118.1, 74.7, 73.1, 50.6, 46.7, 39.4, 19.0, 16.2 and 12.1; HRMS (ES\textsuperscript{+}) calc. for C\textsubscript{14}H\textsubscript{25}IO\textsubscript{3}N [M+NH\textsubscript{4}]\textsuperscript{+} 382.0874, found 382.0869.

\textit{(1E, 3E, 5R, 6R, 8E)-Methyl 6-((triethylsilyl)oxy)-1-iodo-3, 5, 8-trimethyldeca-2, 3, 8-trienoate} (196)\textsuperscript{22a,124}

\[ \text{To solution of alcohol 180 (175 mg, 480 µmol) in dichloromethane (3 mL) at room temperature was added TESCl (105 mg, 705 µmol), imidazole (100 mg, 1.48 mmol) and DMAP (6.0 mg). The reaction mixture was stirred for 16 h and quenched with saturated aqueous NH}_4Cl (3 mL), extracted with dichloromethane (3 x 5 mL) and dried over MgSO\textsubscript{4}. The resulting solution was concentrated under reduced pressure and purified using column chromatography (9 : 1, hexane : ethyl acetate) to give silyl enol ether 196 (198 mg, 87%) as a pale yellow oil.}

\textbf{R}\textsubscript{f} 0.69 (10% ethyl acetate : petroleum ether); [\alpha]\textsubscript{D}\textsuperscript{20} +33.6 (c 0.5, CHCl\textsubscript{3}); \textbf{IR} (thin film) 2953, 2911, 2876, 1720, 1647, 1435, 1223, 1150, 1087, 1008, 739 and 725 cm\textsuperscript{-1}; \textbf{H} NMR (400 MHz, C\textsubscript{6}D\textsubscript{6}) δ 7.02 (1H, dd, J = 14.6, 0.7 Hz, H\textsubscript{2}), 5.93 (1H, d, J = 14.6 Hz, H\textsubscript{1}), 5.87 (1H, q, J = 1.1 Hz, H\textsubscript{9}), 5.12 (1H, dd,
\[ J = 9.7, 0.4 \text{ Hz, } H_4, 3.64 \text{ (1H, dt, } J = 6.6, 5.4 \text{ Hz, } H_6, 3.44 \text{ (3H, s, OCH}_3) \],

2.46-2.39 (1H, m, H_5), 2.25 (3H, d, \( J = 1.3 \text{ Hz, } C_8-\text{CH}_3 \)), 2.10-2.08 (1H, td, \( J = 6.10, 0.95 \text{ Hz, } H_{7a} \)), 2.07 (1 H, d, \( J = 0.8 \text{ Hz, } H_{7b} \)), 1.36 (3H, d, \( J = 1.2 \text{ Hz, } C_5-\text{CH}_3 \)), 0.96 (6H, m, Si-(CH_2CH_3)_3), 0.89 (3H, d, \( J = 6.8 \text{ Hz, } C_3-\text{CH}_3 \)), 0.56 (9H, m, Si-(CH_2CH_3)_3); \(^{13}\text{C NMR} \text{ (100 MHz, } C_6D_6) \delta 166.6, 156.5, 149.9, 137.2, 134.4, 118.7, 74.7, 74.5, 50.6, 46.9, 38.5, 19.5, 15.6, 12.1, 7.2 \text{ and } 5.6; \]

HRMS (ES\(^+\)) calc. for C\(_{20}\)H\(_{39}\)I\(_3\)SiN [M+NH\(_4\)]\(^+\) 496.1738, found 496.1734.

\((1E, 3E, 5R, 6R, 8E)-6-((\text{Triethylsilyl})\text{oxy)-1-iodo-3, 5, 8-trimethyldeca-2,} 3, 8-\text{trien-1-ol (197)}\]\(^{22a,124}\)

\[
\begin{array}{c}
\text{TESO} \\
\text{HO}
\end{array}
\]

To a solution of ester 196 (160 mg, 345 \( \mu \text{mol} \)) in dichloromethane (2 mL) at -78 °C, was added DIBAL (690 \( \mu \text{L}, 690 \mu \text{mol, 1 M in dichloromethane} \)). The mixture was stirred for 2 h and quenched with aqueous potassium sodium tartrate (5 mL) was added, and the mixture was stirred for a further 4 h. The crude product was extracted with diethyl ether (3 x 5 mL), dried over Na\(_2\)SO\(_4\) and the solvent was removed under reduced pressure. The crude residue was purified using column chromatography (4 : 1, hexane : ethyl acetate) to yield alcohol 197 (127 mg, 81%) as a as a pale yellow oil.

\( R_f \) 0.29 (20% ethyl acetate : petroleum ether); \([\alpha]_D^{20} +18.5 \text{ (c } 0.7, \text{ CHCl}_3 \)); IR (thin film) 3342, 2955, 2911, 1457, 1003, 948, 744 and 725 \text{ cm}^{-1}; \(^1\text{H NMR} \)
(400 MHz, C$_6$D$_6$) $\delta$ 7.07 (1H, dd, $J = 14.6$, 0.8 Hz, H$_2$), 5.93 (1H, dd, $J = 14.6$, 0.6 Hz, H$_1$), 5.38 (1H, ddd, $J = 7.8$, 5.4, 1.2 Hz, H$_9$), 5.27 (1H, d, $J = 9.8$ Hz, H$_4$), 3.94 (2H, d, $J = 6.8$ Hz, H$_{10}$), 3.70-3.64 (1H, m, H$_6$), 2.52-2.48 (1H, m, H$_5$), 2.14 (2H, qd, $J = 13.6$, 6.2 Hz, H$_7$), 1.51 (3H, d, $J = 0.7$ Hz, C$_8$-CH$_3$), 1.41 (3H, d, $J = 1.3$ Hz, C$_3$-CH$_3$), 1.01-0.97 (6H, m, Si-(CH$_2$CH$_3$)$_3$ + C$_5$-CH$_3$) and 0.58 (9H, m, Si-(CH$_2$CH$_3$)$_3$); $^{13}$C NMR (100 MHz, C$_6$D$_6$) $\delta$ 150.0, 138.3, 135.0, 133.9, 129.0, 74.7, 74.2, 59.3, 45.9, 37.8, 16.9, 15.1, 12.1, 7.3 and 5.6; HRMS (ES$^+$) calc. for C$_{19}$H$_{39}$IO$_2$SiN [M+NH$_4$]$^+$ 468.1789, found 468.1787.

(1$E$, 3$E$, 5$R$, 6$R$, 8$E$)-6-((Triethylsilyl)oxy)-1-iodo-10-(sulfanyl-1-phenyl 1$H$-1, 2, 3, 4-tetrazol-5-yl) 3, 5, 8-trimethyldeca-2, 3, 8-triene (210)$^{22a,124}$

To a solution of alcohol 197 (80 mg, 176 µmol) at 0 ºC in THF (2 mL) was added 1-$H$-mercaptophenyltertrazole (42 mg, 232 µmol), triphenylphosphine (61 mg, 232 µmol) followed by DIAD (32 µL, 232 µmol) dropwise. The reaction mixture was warmed up to room temperature and left to stir 2 h before aqueous NH$_4$Cl (5 mL) was added, upon which the resulting mixture was extracted with ethyl acetate (3 x 5 mL), and dried over Na$_2$SO$_4$. The solution was concentrated under reduced pressure and purified by column chromatography (19 : 1, hexane : ethyl acetate) to give sulfide 210 (84 mg, 79%) as a pale yellow oil.
$R_f$ 0.54 (10% ethyl acetate : petroleum ether); $\left[\alpha\right]_{D}^{20} +58.5 \; (c \; 1.0, \; CHCl_3)$; IR (thin film) 3068, 2955, 2911, 2875, 1597, 1500, 1384, 1234, 1092, 1015, 950, 759, 742 and 725 cm$^{-1}$; $^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ 7.19-7.17 (2H, m, Ar-H$_2$), 7.05 (1H, dd, $J = 14.6, 0.7$ Hz, H$_2$), 6.93-6.87 (3H, m, Ar-H$_3$), 5.95 (1H, dd, $J = 14.6, 0.5$ Hz, H$_1$), 5.37 (1H, td, $J = 7.9, 1.1$ Hz, H$_9$), 5.22 (1H, dt, $J = 9.8, 0.5$ Hz, H$_{10}$), 3.90 (2H, dq, $J = 14.6, 7.9$ Hz, H$_{10}$), 3.62 (1H, dt, $J = 6.2, 1.3$ Hz, H$_8$), 2.46-2.24 (1H, m, H$_5$), 2.07 (2H, ddt, $J = 20.2, 13.9, 6.6$ Hz, H$_7$), 1.58 (3H, d, $J = 1.3$ Hz, C$_8$-CH$_3$), 1.40 (3H, d, $J = 1.2$ Hz, C$_5$-CH$_3$), 0.96 (6H, m, Si-(CH$_2$CH$_3$)$_3$), 0.92 (3H, d, $J = 6.8$ Hz, C$_5$-CH$_3$) and 0.58-0.53 (9H, m, Si-(CH$_2$CH$_3$)$_3$); $^{13}$C NMR (100 MHz, C$_6$D$_6$) $\delta$ 154.1, 150.0, 139.8, 138.0, 134.3, 134.0, 129.6, 123.9, 120.8, 74.5, 74.3, 45.8, 37.7, 31.6, 16.9, 15.0, 12.1, 7.3 and 5.6; HRMS (ASAP) calc. for C$_{26}$H$_{40}$I$_4$N$_4$SSi [M+H]$^+$ 611.1731, found 611.1729.

(1$E$, 3$E$, 5$R$, 6$R$, 8$E$)-6-((Triethylsilyl)oxy)-1-iodo-10-(sulfonyl-1-phenyl -1H-1, 2, 3, 4-tetrazol-5-yl) 3, 5, 8-trimethyldeca-2, 3, 8-triene (93)$^{22a,124}$

A mixture of ammonium molybdate (20 mg, 15.0 µmol) and hydrogen peroxide (25 µL, 650 µmol, 30% v/v) was allowed to stir at 0 ºC for 15 min. Half of the resulting yellow solution was added dropwise, at 0 ºC, to a solution of sulfide 210 (40 mg, 65 µmol) in ethanol (1 mL). The reaction
mixture was stirred for 1 h at room temperature before the remaining resultant oxidant was added, and stirred for 16 h. The reaction mixture was the diluted with ethanol (1 mL) then filtered. The filtrate was portioned with water (1 mL) then extracted with dichloromethane (3 x 1 mL). The organic phases were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by column chromatography (19 : 1, hexane : ethyl acetate) provided sulfone 93 (33 mg, 78%) as a as a pale yellow oil.

\[ R_f \, 0.41 \, (10\% \text{ ethyl acetate : petroleum ether}) \]; \[ [\alpha]_{D}^{20} +33.6 \, (c \, 0.5, \text{CHCl}_3) \]; \text{IR} (thin film) 3069, 2955, 2925, 2875, 1498, 1461, 1343, 1156, 1107, 1015, 950, 761 and 739 cm\(^{-1}\); \textbf{\textit{\textsuperscript{1}H NMR}} (400 MHz, C₆D₆) \( \delta \) 7.33-7.26 (2H, m, Ar-H), 7.05 (1H, dd, \( J = 14.6, 0.8 \, \text{Hz, H}_2 \)), 6.87-6.85 (3H, m, Ar-H), 5.94 (2H, dd, \( J = 14.6, 0.5 \, \text{Hz, H}_1 \)), 5.29 (1H, td, \( J = 7.9, 0.9 \, \text{Hz, H}_9 \)), 5.22 (1H, d, \( J = 9.3 \, \text{Hz, H}_4 \)), 4.08 (2H, dd, \( J = 7.9, 3.0 \, \text{Hz, H}_{10} \)), 3.63 (1H, td, \( J = 6.5, 4.1 \, \text{Hz, H}_6 \)), 2.38-2.35 (1H, m, H₅), 2.10 (1H, dd, \( J = 13.6, 6.9 \, \text{Hz, H}_{7a} \)), 2.01 (1H, dd, \( J = 13.6, 6.1 \, \text{Hz, H}_{7b} \)), 1.50 (3H, d, \( J = 1.2 \, \text{Hz, C}_8{\text{-CH}_3} \)), 1.39 (3H, d, \( J = 1.2 \, \text{Hz, C}_3{\text{-CH}_3} \)), 1.01-0.89 (6H, m, Si-(CH₂CH₃)₃), 0.86 (3H, d, \( J = 6.7 \, \text{Hz, C}_5{\text{-CH}_3} \)) and 0.60-0.48 (9H, m, Si-(CH₂CH₃)₃); \textbf{\textit{\textsuperscript{13}C NMR}} (100 MHz, C₆D₆) \( \delta \) 154.0, 149.8, 146.8, 136.6, 134.8, 133.5, 131.0, 129.4, 125.4, 111.0, 74.6, 72.6, 56.2, 45.9, 39.2, 17.0, 16.3, 12.1, 7.2 and 6.9; \textbf{HRMS} (ES\(^+\)) calc. for C₂₆H₄₃IO₃N₅SSi [M+NH₄\(^+\)] 660.1895, found 660.1893.
References


63 Murray, R. *Unpublished results.*


124 Procedure carried out in unison with Dr. Wlochal.
Appendix: Selected $^1$H and $^{13}$C NMR spectra
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