SYNTHETIC APPROACHES TO THE BICYCLIC CORE OF TEO3.1, HAMIGERONE AND EMBELLISTATIN

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry at the University of Canterbury by Sarah Diane Lundy

August 2007
I would firstly like to thank Dr Jonathan Morris for the opportunity to undertake this research. Despite being away from the department for the last few years, you have continued to provide excellent supervision, guidance and support. I am also grateful for the many hours you have put into reviewing this thesis. Thank you to Professor Peter Steel for taking on the role as my supervisor after Jonathan’s departure to Adelaide, and for your assistance with proof-reading.

I am absolutely indebted to Andrew Muscroft-Taylor, the second to last member of the NZ branch of the Morris group. Your friendship, guidance, advice, support, crazy antics, and ‘bagel Fridays’ were crucial in me getting through this PhD.

Thanks also go to the previous members of the Morris Group. Regan and Darby for all their help in the lab in the early days, Jonno and Martin for always keeping me entertained in the office, and especially to Liesl for endless cups of tea, chocolate-chip biscuits and for her continued friendship and encouragement since leaving the department.

I am very grateful to Dr Emily Parker for being so supportive, encouraging and willing to welcome me into your group (not that you had much choice since I wasn’t moving!). Thanks to the members of the Parker group, especially Scott and Aidan, for their company in the office and the lab, and Penel, for bringing another female into 858 this year. Also thanks to the youngest member of the group, Jo, for breaking up my long afternoons of writing and corrections with chocolate and chats.

Many thanks go to the friendly academic and technical staff in the Chemistry Department. In particular, to Bruce Clark, Rob Stainthorpe and Dr Marie Squire for mass spectrometry analysis, Wayne Mackay and Rob McGregor for their expertise in repairing equipment and glassware, Professor Ward Robinson and Dr Chris Fitchett for X-Ray analysis, and to Dr’s Andy Pratt and Jan Wikaira for their advice and encouragement.

I am very grateful for the financial assistance I have received from the Bank of New Zealand Post Graduate Scholarship, NZIC Canterbury Branch Travel Scholarships, New Zealand Federation of
Graduate Women Sadie Balkind Award, and most importantly, the Foundation for Research, Science and Technology for a Top Achiever Doctoral Scholarship.

The friendships I have made over many years in this department mean a great deal to me. It’s always comforting to have someone to talk to who understands what you are going through. So thanks to the ‘Chem girls’ Anna, Andrea, Liesl, Marie and Malina for hours of gossip, to those crazy foreign post docs Florian and Jon for so many fun and entertaining nights out and many renditions of ‘Swing low, Sweet chariot’, and to Dave for distracting me with coffee and for taking over as chief supervisor of Chem 114 labs, otherwise I might have been there forever.

Huge thanks to Malina for always being there for me whenever I needed you. To Kama, Becs, Zack and Greg for their continued friendship and interest in what I am doing and thanks to Nicole, for always making my nails look beautiful after I had ruined them in the lab.

A special thank you goes to Marie. Your timing moving back to Christchurch, and to a job in the department, was perfect - just in time to run all my mass spec samples. Having you around for support, coffee and chocolate breaks and everything else has made this year so much easier. Bring on the Country Club plan!

Thank you to my brilliant family for your ongoing love and support. In particular, I would like to mention my Mum and Dad and my grandparents, my sister Renée, for always reminding me just how long I have been a student for and my cousins Jay and Tessa just for being themselves (and so their names are in this thesis). I would also like to thank the wonderful Dudley and Ginga (R.I.P) for always being excited to see me come home after a long day at uni.

And finally, a huge thanks to George, for always believing in me, supporting me and loving me, and for being what matters the most. And yes…you do have to call me Doctor now!
Abstract

This thesis describes synthetic studies directed towards the total synthesis of the natural products TEO3.1, hamigerone and embellistatin. Chapter One provides an overview, which details the role of antifungal natural products in the pharmaceutical and agrochemical industries, and describes the association between total synthesis and natural products. Three structurally related natural products TEO3.1, hamigerone and embellistatin are introduced as synthetic targets and a strategy for their synthesis is proposed involving an intramolecular Diels-Alder (IMDA) reaction, followed by addition-elimination chemistry.

Investigations into the application of the IMDA reaction to the synthesis of the bicyclic core are described in Chapter Two. A Julia olefination reaction was used to install the diene moiety and allowed for the successful synthesis of a model triene precursor. The IMDA cyclisation of the triene was shown to proceed with high endo-selectivity. However, efforts to generate the diene-containing bicyclic core failed and, as a result, this approach to the natural products was abandoned.

Chapter Three introduces the diene-regenerative Diels-Alder reaction as an alternative strategy for the direct installation of the diene moiety. The preparation of a model system is described, which established methodology for the efficient preparation of the pyrone-containing Diels-Alder substrate. Cyclisation of this material via a [4 + 2] cycloaddition reaction, followed by extrusion of carbon dioxide, proved a viable method for generating the desired cyclohexadiene system.

In Chapter Four, the previously established methodology is applied to the synthesis of the fully functionalised bicyclic core of TEO3.1, hamigerone and embellistatin. The preparation of the racemic Diels-Alder substrate and its successful cyclisation to the bicyclic core is described. An investigation into the preparation of chiral material is also discussed, as well as the description of a model study for the installation of the various side-chains of the natural products. The chapter concludes with a brief discussion of the future studies required to complete the total synthesis of the TEO3.1, hamigerone and embellistatin.
Table of Contents

Chapter One  Introduction

1.1  Natural Products  3
1.2  Natural Products as Pharmaceutical and Agrochemical Antifungal Agents  5
  1.2.1  Pharmaceuticals  5
  1.2.2  Agricultural Fungicides  11
  1.2.3  Summary  15
1.3  TEO3.1, Hamigerone, Embellistatin and Related Natural Products  16
1.4  The Role of Total Synthesis in the Development of Natural Products as Pharmaceutical Agents  19
1.5  Planning a Synthesis of the Target Molecules  22
1.6  Retrosynthetic Analysis  26
  1.6.1  Analogues  28
  1.6.2  Using an IMDA Reaction  29
1.7  Work Described in this Thesis  30
1.8  References for Chapter One  31

Chapter Two  Intramolecular Diels-Alder Synthesis of the Bicyclic Core

2.1  The Diels-Alder Reaction  39
2.2  The Intramolecular Diels-Alder Reaction  41
  2.2.1  Type I and Type II IMDA Reactions  42
  2.2.2  Examples of the Type I IMDA Reaction in Total Synthesis  43
2.3  Intramolecular Diels-Alder Strategy for the Synthesis of the Bicyclic Core  45
  2.3.1  Selectivity in the IMDA Reaction  47
2.4  Development of a Model System of the Bicyclic Core  52
  2.4.1  Synthesis of Triene 2.63  54
  2.4.2  The Julia Olefination Reaction  56
  2.4.3  Synthesis of the Substrates for the Julia Reaction  59
  2.4.4  The Julia Olefination Reaction and Isomer Separation  63
Chapter Three  A New Approach to the Synthesis of the Bicyclic Core

3.1 Introduction
   3.1.1 [4 + 2] Cycloaddition Reactions of 2-Pyrones

3.2 Diene-Regenerative Diels-Alder Strategy

3.3 Methods for the Preparation of 2-Pyrones
   3.3.1 General Methods
   3.3.2 Tandem Stille Reaction/Heterocyclisation
   3.3.3 Intramolecular Addition of Carboxylic Acids to Alkynes
   3.3.4 Comparison/Summary

3.4 Synthesis of the Pyrone System
   3.4.1 Preparation of Substrates for the Coupling Reaction
   3.4.2 Copper-Catalysed Coupling Reactions
   3.4.3 Formation of the Pyrone System Using ZnBr₂

3.5 Electrophilic Substitution of Pyrone 3.101

3.6 Diene-Regenerative Diels-Alder Reaction

3.7 Summary

3.8 References for Chapter Three

Chapter Four Synthesis of the Bicyclic Core of the Natural Products

4.1 Introduction

4.2 Methods for the Preparation of the Stereotriad

vii
4.2.1 Method A: Marshall and Adams 133
4.2.2 Method B: Poupon and co-workers 134
4.2.3 Method C: Breit and Zahn 136
4.2.4 Method D: Harada and co-workers/Chênevert and co-workers 138
4.2.5 Comparison of the Methods 139

4.3 Synthesis of Alkyne 4.25 141
4.3.1 Enzymatic Desymmetrisation 146

4.4 Development of a Racemic Synthesis of the Bicyclic Core 148
4.4.1 Elaboration to Pyrone 4.73 148
4.4.2 Construction of the Bicyclic Core via Diene-Regenerative Diels-Alder Reaction 149
4.4.3 Electrophilic Bromination 151

4.5 A Model System for the Introduction of the C-1 Side-Chain 153

4.6 Summary 155

4.7 Future Work 156
4.7.1 Enantioselective Synthesis of the Bicyclic Core 156
4.7.2 Introduction of the C-2 Side-Chain 157
4.7.3 Introduction of the C-1 Side-Chain – Completion of the Syntheses 158

4.8 References for Chapter Four 160

Chapter Five Experimental Details

5.1 General Experimental 165
5.1.1 Reagents and Solvents 165
5.1.2 Chromatography and Small-Scale Distillation 166
5.1.3 Spectroscopic Techniques 166
5.1.4 Nomenclature 167

5.2 Experiments Described in Chapter Two 168
5.3 Experiments Described in Chapter Three 196
5.4 Experiments Described in Chapter Four 209
5.5 X-Ray Crystallographic Data 229

5.6 References for Chapter Five 231
Abbreviations

Å  Angstrom(s)
AIDS  Acquired Immune Deficiency Syndrome
Ar  aryl
9-BBN  9-borabicyclo[3.3.1]nonane
BHT  3,5-di-tert-butyl-4-hydroxytoluene (butylated hydroxytoluene)
Bn  benzyl
BT  benzothiazole
Bu  butyl
Bz  benzoyl
COSY  correlation spectroscopy
δ  chemical shift in parts per million
d  doublet
2D NMR  two dimensional nuclear magnetic resonance spectroscopy
DBU  1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ  2,3-dichloro-5,6-dicyano-para-benzoquinone
DEAD  diethyl azodicarboxylate
DIBAL-H  diisobutylaluminium hydride
DMAP  4-dimethylaminopyridine
DME  1,2-dimethoxyethane
DMF  N,N-dimethylformamide
DMP  Dess-Martin periodinane
DMSO  dimethylsulfoxide
EDA  ethylenediamine
EI  electron impact
equiv  equivalent(s)
ES  electrospray
Et  ethyl
FT  Fourier transform
g  gram(s)
h  hour(s)
HMBC  heteronuclear multiple bond coherence
HMPA  hexamethylphosphoramide
HPLC  high performance liquid chromatography
HRMS  high resolution mass spectrometry
HSQC  heteronuclear single quantum coherence
Hz  Hertz
IBX  2-iodoxybenzoic acid
IMDA  Intramolecular Diels-Alder
i-Pr  isopropyl
IR  infrared
J  coupling constant
L  litre(s)
LDA  lithium diisopropylamide
LG  leaving group
Chapter One

Introduction
1.1 Natural Products

Naturally occurring compounds have traditionally served as the source of new leads for drug discovery, forming the basis for most early medicines. Well known examples of historically significant drugs from nature include the analgesic compounds morphine and acetylsalicylic acid (Aspirin) and the antibiotic penicillin.\textsuperscript{1}

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{natural_products.png}
\caption{Historically significant natural products.}
\end{figure}

The biodiversity inherent in nature provides a prolific source of structurally diverse secondary metabolites. Isolated from a variety of sources, including terrestrial plants, fungi and microbes and the marine environment, these natural products display a wide range of physiological and pharmaceutical properties attributable to their complex molecular architecture. A large number of these molecules have played a pivotal role in the development of medicinal agents for the treatment of disease. It is estimated that approximately 42\% of new drugs approved between 1981 and 2006, and 60-80\% of the antibacterial, anticancer and anti-HIV drugs were derived from natural products.\textsuperscript{2} Some examples of lead compounds from various sources that exhibit a wide range of pharmacological activities are shown in Figure 1.2.\textsuperscript{3}
Figure 1.2  Selected natural products from plant, marine and microbial sources.
1.2 Natural Products as Pharmaceutical and Agrochemical Antifungal Agents

As lead compounds, antifungal natural products are relevant to both the pharmaceutical and agrochemical industry. This thesis is concerned with a new class of natural products that have potent antifungal activity.

1.2.1 Pharmaceuticals

In recent years the number of life-threatening fungal infections has dramatically increased. Pathogens such as *Candida albicans*, *Cryptococcus neoformans*, *Pneumocystis carinii* and *Aspergillus fumigatus* have been implicated as the cause of considerable mortality in patients who are immunocompromised. Those at risk from fatal infections include AIDS patients, recipients of chemotherapy for the treatment of cancers, recipients of organ transplants and those with genetically impaired or drug suppressed immune systems. The most frequent cause of invasive fungal infections is *C. albicans* which causes candidaemia or candidiasis. *P. carinii* induces fungal pneumonia, which is the major cause of death amongst AIDS patients, and pulmonary aspergillosis caused by *A. fumigatus* is a prevalent cause of mortality in recipients of chemotherapy and organ transplant patients. Fungal meningitis caused by *C. neoformans* is the fourth most common life-threatening opportunistic infection in individuals with AIDS and is also prevalent amongst immunocompetent patients. Current treatments for serious fungal infections are hindered by both the number of drugs available and through the development of drug resistance by a number of strains of fungi. This intensifies both the desire and need to find new systemic fungicidal drugs for the treatment of serious fungal disease as well as for the management of prevalent topical fungal infections such as tinea pedis and candidiasis. Antifungal agents currently available for clinical use against invasive fungal infections belong to three major classes; polyenes, azoles and echinocandins. Below is a brief discussion of these families of compounds and some additional antifungal drugs.

The discovery of the polyene nystatin (fungicidin) in 1950 by Brown and Hazen represented a milestone in the development of antifungal agents. Following this discovery, amphotericin B was isolated in 1955 from the filamentous bacterium *Streptomyces nodosus*. Amphotericin B represents the first example of a commercially available drug for the treatment of systemic fungal
infections. These polyene compounds display selective activity against fungal cells through complexation with ergosterol and destabilisation of the fungal membrane, which leads to increased membrane permeability and thus, fungal cell death.\textsuperscript{7} Both amphotericin B and nystatin exhibit broad spectrum antifungal activity against most species of \textit{Candida} and \textit{Aspergillus}. Intravenous formulations of amphotericin B are generally administered for the treatment of systemic fungal infections such as those listed above, and also in immunocompromised patients exhibiting febrile symptoms, who do not respond to broad-spectrum antibiotics. The success of amphotericin B is balanced by its acute toxicity. In most cases serious reactions to the drug are evident approximately one to three hours following infusion. These include vomiting, headache, shortness of breath and fever but also severe and/or irreversible kidney damage, liver damage, anemia and cardiac failure. The gravity of these side effects can be reduced through the use of liposomal preparations of the drug.\textsuperscript{8} Despite over four decades of clinical use, resistance to amphotericin B remains rare.\textsuperscript{9} Free nystatin was never developed for systemic use due to its toxicological effects \textit{in vivo}; however, it is commercially available for the treatment of topical and oral fungal infections. Encapsulation of nystatin in liposomes has been found to produce tolerable toxicity and promising efficacy against invasive fungal infections. Whilst commercially these compounds are obtained through large-scale culture techniques, syntheses of these challenging polyene compounds have been reported, with the first total synthesis of amphotericin B being published by Nicolaou and co-workers in 1988.\textsuperscript{10}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{amphotericin_nystatin.png}
\caption{Polyene-based antifungal drugs.}
\end{figure}

There are a number of azole-based fungicidal drugs available for the treatment of both topical and more serious invasive fungal infections. Though these compounds are generally considered to be synthetic in origin, there is speculation that their drug prototype pathway can be traced back to the \textit{Streptomyces} metabolite azomycin.\textsuperscript{11} The mechanism of action of azole-based drugs derives
from the inhibition of an enzyme that converts lanosterol to ergosterol leading to ergosterol depletion and disruption of fungal cell membrane integrity. Fluconazole is commonly used for the treatment of candidiasis infections, meningitis caused by cryptococcal infection and in prophylaxis in patients with malignancy. It is inactive against *Aspergillus* infections and is susceptible to resistance problems. Itraconazole exhibits activity against a wider range of fungal infections including invasive infection caused by *Aspergillus*; however, it is also susceptible to resistance problems. Interestingly, there have been reports on its ability to inhibit angiogenesis (the formation of new blood vessels – *vide infra*), a target for anticancer therapies. Voriconazole is fast becoming the new standard for treatment of invasive *Aspergillus* infections based on a large randomised study which showed superior activity to amphotericin B. It has also been shown to be effective in treating candida infections of the bloodstream, as an empirical antifungal therapy in patients with unresolved fever and shows efficacy against emerging fungal pathogens such as *Fusarium* spp. and *Scedosporium apiospermum*. Fungal infections as a result of exposure to these moulds are becoming more common among immunocompromised patients, and they are generally resistant to other antifungal agents such as amphotericin B. Azole-based drugs are extensively used due to their reasonably good safety profile and limited side-effects, even after long periods of use.

![Figure 1.4 Azole-based antifungal drugs.](image_url)

The echinocandin family of antifungal drugs including caspofungin, micafungin (structure not shown) and anidulafungin, are a relatively new class of antifungal agents available for the
treatment of systemic fungal infections. These lipopeptide compounds are semi-synthetically derived from the natural products MK991, FK463 and LY303366 and display broad spectrum potent antifungal activity whilst exhibiting low toxicity. Their mode of action has been attributed to their ability to inhibit the synthesis of 1,3-β-D-glucan in the fungal cell wall. Caspofungin and micafungin were approved for clinical use in 2001 and 2002 respectively, for the treatment of Candida and Aspergillus infections. More recently, in February 2006, anidulafungin, which had completed Phase III trials for oral candidiasis in 2004 and began Phase III trials for the treatment of invasive Aspergillus and Candida infections, gained full FDA approval for the treatment of Candida infections. These compounds represent valuable new antifungal agents that can be used as viable alternatives to amphotericin B and fluconazole.

Figure 1.5  Echinocandin antifungal drugs.

There are a number of other antifungal drugs currently in use that are derived or loosely derived from natural products. These include compounds such as griseofulvin, 5-fluorocytosine (a nucleoside that is often used in combination with amphotericin B for the treatment of invasive fungal infections), allylamine-based compounds such as terbinafine, naftifine and butenafine.
and the thiocarbamate liranaftate\textsuperscript{23} which are all synthetic natural product mimics\textsuperscript{2} used to treat topical fungal infections.

\begin{center}
\includegraphics[width=\textwidth]{figure1_6.png}
\end{center}

\textbf{Figure 1.6} Other antifungal drugs in use today.

In 2005, Butler published a review detailing natural product-derived compounds which had advanced to clinical trials\textsuperscript{11}. These included:

\begin{itemize}
  \item the echinocandin compound, aminocandin\textsuperscript{24}, a semi-synthetic derivative of deoxymulundocandin\textsuperscript{25}, which had begun Phase I clinical trials against systemic fungal infections,
  \item a diascorbate salt of the polyene compound partricin A\textsuperscript{26} that exhibits activity comparable to amphotericin B, but is water soluble, that had advanced to Phase II clinical studies for systemic mycosis, and
  \item PLD-118\textsuperscript{27}, a natural product-derived compound based on the cyclic $\beta$-amino acid cispentacin\textsuperscript{28}, which has a dual mechanism of action not observed in any other antifungal clinical candidates or drugs. It inhibits fungal growth both through intercellular accumulation and through inhibition of the enzyme isoleucyl tRNA synthetase which disrupts fungal protein synthesis. Results from initial Phase II trials suggested that the drug was likely to be safe for HIV-infected patients for the treatment of oral candidiasis.
\end{itemize}

However, to date, whilst studies are still continuing, none of the aforementioned compounds have been approved by the FDA for pharmaceutical use.
The discussion above illustrates how, to a certain extent, most of the available drugs for the treatment of serious *Aspergillus* and *Candida* infections, and those being entered into trials, belong to three main families of compounds; polyenes, azoles and echinocandins. Between the years of 1981 and 2006, 29 new antifungal drugs were approved. Of these, 19 belonged to the azole family, three were the echinocandins discussed above, and four were allylamines including those pictured in Figure 1.6, leaving only three structurally diverse compounds. The table below summarises the drugs available and their spectrum and mode of action.
Table 1.1  Drugs available for the treatment of invasive fungal infections.

<table>
<thead>
<tr>
<th>Family</th>
<th>Antifungal drug</th>
<th>Spectrum</th>
<th>Mode of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyenes</td>
<td>Amphotericin B</td>
<td><em>Candida</em> spp., <em>Aspergillus</em> spp.</td>
<td>Binding to ergosterol and destabilization of cell membranes</td>
</tr>
<tr>
<td></td>
<td>Nystatin</td>
<td><em>Coccidioides immitis, Histoplasma capsulatum, Blastomyces dermatitidus</em></td>
<td></td>
</tr>
<tr>
<td>Azoles</td>
<td>Fluconazole</td>
<td><em>Cryptococcus</em> spp., many <em>Candida</em> spp.</td>
<td>Inhibition of cytochrome P450 14α-lanosterol demethylase</td>
</tr>
<tr>
<td></td>
<td>Itraconazole</td>
<td>Like fluconazole but with activity against <em>Aspergillus</em> spp. and other filamentous fungi</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
<td>Like fluconazole but with activity against <em>Aspergillus</em> and <em>Fusarium</em> spp.</td>
<td></td>
</tr>
<tr>
<td>Echinocandins</td>
<td>Caspofungin</td>
<td><em>Candida</em> spp., moderately active against <em>Aspergillus</em> spp.</td>
<td>Inhibition of the cell wall synthesis enzyme</td>
</tr>
<tr>
<td></td>
<td>Micafungin</td>
<td><em>Candida</em> spp., <em>Aspergillus</em> spp.</td>
<td>β-1,3 glucan synthase</td>
</tr>
<tr>
<td></td>
<td>Anidulafungin</td>
<td><em>Candida</em> spp., <em>Aspergillus</em> spp.</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5-Fluorocytosine</td>
<td><em>Cryptococcus</em> spp., <em>Candida</em> spp.</td>
<td>Impairment of nucleic acid biosynthesis</td>
</tr>
<tr>
<td></td>
<td>Terbinafine</td>
<td><em>Candida</em> spp., <em>Aspergillus</em> spp.</td>
<td>Inhibition of squalene epoxidase</td>
</tr>
</tbody>
</table>

1.2.2 Agricultural Fungicides

Whilst natural products have been the source of a number of antifungal pharmaceutical treatments, there are very few natural product-derived compounds that have been developed for agrochemical purposes. As insects, weeds and phytopathogenic fungi represent a significant cause of damage to agricultural crops as well as gardens, control of these pests is crucial. Whilst traditionally, synthetic pesticides have been used, the development of resistance to current pesticides opens up the need for alternatives. Other problems associated with synthetic pesticides include contamination of food, soil, water and air and other toxicological and environmental risks. Agrochemicals derived from natural products may be perceived as more environmentally compatible, thus addressing some of the environmental issues and, as natural products are inherently more structurally diverse than synthetically derived compounds, a wider range of structures and novel bioactivities may be accessible.

Some examples of natural product-inspired agricultural fungicides on the market today can be found in the strobilurin fungicides (Figure 1.8). These compounds are synthetic derivatives of the naturally occurring compound strobilurin A, a potent antifungal compound which was originally isolated from *Oudemansiella mucida* and *Strobiluris tenacellus*.Whilst the
naturally occurring compound proved powerful \textit{in vitro} it suffered problems \textit{in vivo} due to its volatility and photolability.\textsuperscript{31} Following a large amount of research into the synthesis of strobilurin A, and a series of approximately 1400 structurally modified analogues, azoxystrobin (Syngenta) and kresoxim-methyl (BASF) were released on the market in 1996.\textsuperscript{32} By 1998 azoxystrobin had become one of the top selling fungicides worldwide.\textsuperscript{33} It shows broad spectrum antifungal activity against all four classes of plant fungal pathogens and is deemed to be safe to birds, mammals, bees, earthworms and other beneficial insects.\textsuperscript{32} Other derivatives available on the market today include trifloxystrobin (Bayer), metominostrobin (Shionogi), pyraclostrobin (BASF) and picoxystrobin (Syngenta).\textsuperscript{32} The mode of action of these compounds is attributed to their ability to inhibit mitochondrial electron transfer by blocking the cytochrome b binding site.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{strobilurin}
\caption{Strobilurin based fungicides.}
\end{figure}

A number of groups are now pursuing natural products that exhibit activities of agricultural interest. In 2003 Hamann and co-workers reported on their efforts into the development of marine natural products as prototype agrochemical agents.\textsuperscript{34} They tested a number of recently isolated natural products for herbicidal, fungicidal and insecticidal activities. Some representative examples of their results from fungicidal assays are shown in \textbf{Figure 1.9}. A number of structurally diverse natural products were tested, all of which showed significant fungicidal
activity against one or more of the strains assayed, providing some interesting candidates for further investigation.

![Chemical structures]

Table 1.9 Examples of natural products assayed for fungicidal activity by Hamann and co-workers.

<table>
<thead>
<tr>
<th>compound</th>
<th>F. culmorum (head scab)</th>
<th>S. nodorum (wheat glume blotch)</th>
<th>Ph. Infestans (potato late blight)</th>
<th>Py. Grisei (rice blast)</th>
<th>Pu. Recondita (brown rust of wheat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>manzamine A</td>
<td>1</td>
<td>66</td>
<td>77</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>heteronemin</td>
<td>1</td>
<td>57</td>
<td>25</td>
<td>99</td>
<td>100</td>
</tr>
<tr>
<td>latrunculin B</td>
<td>101</td>
<td>103</td>
<td>91</td>
<td>59</td>
<td>67</td>
</tr>
<tr>
<td>(+)-aeroplysinin-1</td>
<td>2</td>
<td>0</td>
<td>68</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>halichondramide</td>
<td>102</td>
<td>106</td>
<td>104</td>
<td>58</td>
<td>67</td>
</tr>
<tr>
<td>sceptrin</td>
<td>8</td>
<td>36</td>
<td>72</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

% Growth inhibition at 10 ppm

Figure 1.9 Examples of natural products assayed for fungicidal activity by Hamann and co-workers.

In 1999 Jansen and co-workers reported the isolation of four novel metabolites, crocacin A-D, from the myxobacteria *Chondromyces crocatus* and *Chondromyces pediculatus*. These compounds moderately inhibit the growth of some gram-positive bacteria and are potent inhibitors of animal cell cultures and several yeasts and fungi. The high biological activity of crocacin A and D has led to them being earmarked as potential leads for agrochemicals. However, a major problem with crocacin A and D lies in their poor photostability, with 50% of the parent compound being lost in seven and 37 minutes respectively. In an effort to supply
material for further biological evaluation and provide an avenue for the construction of analogues to tackle the photostability issue, a number of total syntheses of crocacin A, C and D have been undertaken and reported since their discovery.\textsuperscript{37}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure10.png}
\caption{The crocacin family of natural products.}
\end{figure}

A report in 2007 by Crowley and co-workers reviewed the wide range of analogues of crocacin A and D that have been prepared by Zeneca Agrochemicals (now Syngenta) and discusses their activity in comparison with the natural products.\textsuperscript{36} Initially, analogues involving replacement of the \textit{Z}-double bonds with benzene rings and simplification of the complex side-chain were prepared with a typical example being 1.1 (Figure 1.11). Unfortunately, analogues of this type exhibited none of the biological activity observed in the parent compounds. Analogues of crocacin D, keeping the \textit{Z}-enamide glycine ester but varying the side-chain, led to the production of some compounds such as 1.2 that maintained some of the activity of the parent compound whilst exhibiting increased photostability. Replacing the \textit{Z}-enamide with mimics of this unusual group (see 1.3) illustrated the significance of this moiety on the activity of these compounds, as again, the potent antifungal activity of the parent compounds was not present in the analogues. The final group of analogues involved replacement of the glycine methyl ester. Whilst this group was found to be important for activity, it was also shown to be susceptible to hydrolysis by esterases in plants. Of these analogues, which involved replacement of the methyl ester with a number mimics, pyrazine 1.4 showed the best resistance to hydrolysis but was only weakly fungicidal. Disappointingly for the researchers, after a great body of work, none of the analogues proved to be superior to the natural products.
1.2.3 Summary

Immunocompromised patients worldwide are at increasing risk of systemic fungal infections from *Candida* spp. and *Aspergillus* spp. The modest range of compounds currently available for the treatment of these infections suffer from toxicity issues, in the case of amphotericin B, and emerging drug resistance to antifungal compounds, in particular those from the azole family, is of concern. The short review above illustrates that there is an ongoing need to pursue new antifungal agents with enhanced potency, broad spectrum of activity, reduced or limited toxicity and varied mode of action.

The agrochemical industry is also plagued by the problem of developing resistance to current pesticides. Concerns with contamination and toxicological and environmental risks posed by synthetic fungicides, has led to an increase in the popularity of natural products as a source of compounds that may be conceived as more environmentally compatible.

These factors highlight the need for discovering new compounds with pharmacologically and/or agriculturally relevant antifungal activity.
1.3 TEO3.1, Hamigerone, Embellistatin and Related Natural Products

During bioassay-guided isolation studies conducted by the Marine Chemistry group at the University of Canterbury in 2001, the metabolite TEO3.1 was isolated from the marine fungus TEO3, found in sea sediment on the shores of Lake Ellismere in the South Island of New Zealand. The compound displayed significant antifungal activity against a wide variety of fungi, with high potency against \textit{Aspergillus} species, including \textit{Aspergillus fumigatus}, a major cause of mortality amongst immunocompromised patients (\textit{vide supra}). In all cases, the activity was comparable to that of the known antifungal drug nystatin (Section 1.2.1). A number of other compounds with related structures, including TEO3.2-4, were also isolated. Structure elucidation by 2-dimensional NMR allowed the relative stereochemistry of four of the stereocentres to be assigned, but the absolute stereochemistry, and the stereochemistry of the epoxide moiety were not able to be determined.

![Structure of TEO3.1](image)

<table>
<thead>
<tr>
<th>fungus</th>
<th>TEO3-1 (30μg/disk)</th>
<th>Nystatin (23 μg/disk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{Aspergillus fumigatus}</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>\textit{Aspergillus niger}</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>\textit{Aspergillus ustus}</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>\textit{Cladosporium resinae}</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>\textit{Trichophyton mentagrophytes}</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>

![Figures 1.12](image)

\textbf{Figure 1.12}  Structure and activity of TEO3.1 and structures of other related compounds.
Literature searches for related compounds containing the bicyclic core of TEO3.1 led us to the report of the isolation of hamigerone and dihydrohamigerone by Breinholt and co-workers in 1997. These metabolites were isolated from the terrestrial fungus *Hamigera avellanea* during a search for compounds to inhibit the growth of the rice blast fungus *Pyricularia oryzae*. Following structure elucidation, isotopic enrichment studies were carried out to investigate the biosynthesis of these compounds, which were structurally unprecedented within the large class of known fungal metabolites. Isotopically enriched hamigerone samples were isolated from cultures of *H. avellanea* grown in the presence of variously $^{13}$C-labelled precursors. Analysis by $^{13}$C NMR spectroscopy clearly showed that hamigerone derives from ten acetate and five methionine-derived C$_1$ units as shown in Figure 1.13. *In vitro* assays with the plant pathogenic fungi *P. oryzae* and *Venturia inaequalis* (apple scab) showed that hamigerone possessed growth inhibitory activity comparable to commercial fungicides Prochloraz® and Bitertanol®, but that dihydrohamigerone only possessed marginal activity. Further testing indicated that hamigerone showed inferior ability, in comparison with the commercial fungicides, to protect rice plants against subsequent infection by *P. oryzae*. A patent entitled ‘Fungicides from *Hamigera Avellanea*’ was lodged by the researchers in 1996. As with TEO3.1, the stereochemistry of the epoxide moiety and the absolute configuration were unable to be determined.

![Figure 1.13](image-url)  
*Figure 1.13*  Structures of hamigerone and dihydrohamigerone and studies on the biosynthesis of hamigerone.
In 1999, Stierle and co-workers reported two polyketide derivatives, \textit{1.5} and \textit{1.6}, isolated from a \textit{Penicillium} species found on a healthy Pacific yew tree (\textit{Taxus brevifolia}).\textsuperscript{40} These compounds have a carbon skeleton and cyclisation pattern similar in structure to dihydrohamigerone. Although \textit{1.5} and \textit{1.6} are stereoisomers and might be converted by chemical or photochemical isomerisation none was observed, even after long term storage. Both compounds exhibited potent antifungal activity against the fungus \textit{Sclerotinia sclerotiorum}, a non-specific, omnivorous plant pathogen, and were non-toxic towards bacteria and other fungi.

![Figure 1.14 Structures of polyketide derivatives \textit{1.5} and \textit{1.6}.](image)

In a very recent paper, Kwon and co-workers reported the structure of embellistatin, a metabolite isolated from \textit{Embellisia chlamydospora},\textsuperscript{41} and previously from \textit{Culvularia lunata}.\textsuperscript{42} This compound contains the diene-containing bicyclic core evident in TEO3.1 and hamigerone and the heptatrienoic acid side chain found in \textit{1.5}. Embellistatin, reported previously as a microtubule polymerisation inhibitor,\textsuperscript{42} also shows anti-angiogenic activity both \textit{in vitro} and \textit{in vivo}.\textsuperscript{41} Angiogenesis is the process of new blood vessel formation, from existing vasculature, which is essential for embryonic development but also occurs during wound healing and tissue or organ regeneration.\textsuperscript{43} Angiogenesis also plays a central role in tumour development and metastasis, rheumatoid arthritis and diabetic retinopathy making its inhibition a promising target for the treatment of cancer and other angiogenesis associated diseases.\textsuperscript{44}

![Figure 1.15 Structure of Embellistatin.](image)
The potential pharmaceutical and agrochemical applications of this group of compounds sparked our interest in pursuing a synthetic route to these compounds that would also be applicable to the synthesis of non-natural analogues. Non-natural analogues of biologically active natural products provide a means through which to carry out detailed structure-activity relationships and to elucidate the mode of action. A synthetic route would also allow the absolute stereochemistry of the natural products, and the stereochemistry of the epoxide moiety in TEO3.1 and hamigerone, to be determined.

1.4 The Role of Total Synthesis in the Development of Natural Products as Pharmaceutical Agents

Before discussing how we would pursue a synthesis of the target molecules, it is important to consider whether total synthesis can play a role in the development of these compounds as pharmaceutical agents.

Traditionally, total synthesis of an isolated natural product was pursued as a means to confirm the postulated structural assignment of a compound. However, with the advanced spectroscopic techniques available today structural elucidation is generally completed prior to the pursuit of total or partial syntheses. This being said, unambiguous assignment of stereochemistry is often difficult or impossible to achieve by spectroscopic methodology alone. Generally, the synthesis of one or more of the possible stereoisomers is required to establish the correct structure. Increasingly, it is not uncommon for a total synthesis to be completed, only to find that the original structural assignment of the natural product was incorrect.\textsuperscript{45} Synthesis also plays an important role when sufficient material for the investigation of a lead compound is not available from a natural source, providing not only a source of the lead compound, but also an avenue for the construction of non-natural analogues. Synthetic analogues provide a basis for elucidating the mode of action of the compound through investigation of structure-activity relationships, and in many cases, provide compounds with enhanced biological activities when compared with the initial lead compound. As discussed in the previous section, more often than not it is a synthetic analogue of a natural product that advances to clinical or commercial use.
One natural product that has received a large amount of attention by prominent synthetic chemistry groups is discodermolide. In 1990, Gunasekera and co-workers reported the isolation and structure elucidation of (+)-discodermolide, derived from the deep sea marine sponge *Discodermia dissoluta*. Some years later in 1996, the groups of ter Haar and Schreiber published independent studies revealing the potent antimitotic activity of (+)-discodermolide, comparable to the proven anticancer agent Taxol™ (paclitaxel), with a similar mode of action involving binding to, and stabilising of, microtubule structures. Importantly, this compound exhibited potent antitumour activity against a wide range of cancer cell lines, including some Taxol-resistant cells.

![Structure of (+)-discodermolide.](image)

The limited availability of discodermolide from natural sources (0.002% w/w from the frozen sponge) provoked a number of groups to undertake its total synthesis in an effort to supply the practical quantities required to investigate the promising biological activity. The first total synthesis was published in 1996 by Schreiber and co-workers, followed by syntheses from the groups of Smith, Myles, Marshall and Paterson as well as a number of fragment syntheses.

In 2004, Novartis Pharmaceuticals were able to prepare 60 g of (+)-discodermolide in 26 linear steps and 1% overall yield utilising a hybrid synthetic scheme incorporating elements of the Paterson, Smith and Marshall routes.
The large-scale synthesis benefited from Schreiber and Smiths earlier identification of the common syn, anti stereotriad which is repeated three times in the linear polypropionate chain, allowing the synthesis to proceed from the common precursor 1.7, readily available from the (+)-S-Roche ester. Improvements by the groups of Smith\textsuperscript{52} and Paterson\textsuperscript{55a} aimed towards large scale production, have reduced the number of steps to 17 and 23 respectively whilst increasing the total overall yield to 9%. Numerous simplified structural analogues have also been prepared to assist in determining the biological profile of (+)-discodermolide. The significant quantities of this compound prepared \textit{via} the gram-scale synthesis has allowed (+)-discodermolide to progress to Phase I clinical trials.\textsuperscript{11}

As well as \textit{de-novo} synthesis being an attractive solution to the supply problem often associated with the development of natural products as drugs, semi-synthesis from a naturally available starting material can also be used. One example is the preparation of Taxol\textsuperscript{TM} (paclitaxel), a clinically proven anticancer agent, from 10-deacetylbaccatin III.\textsuperscript{57,58} The echinocandin-based
antifungal drug caspofungin (*vide supra*) is also prepared *via* semi-synthesis from naturally available pneumocandin B$_0$.$^{59}$

![Paclitaxel](image1.png)  
**Paclitaxel**  
from the bark of *Taxus brevifolia*

![10-Deacetylbaccatin III](image2.png)  
**10-Deacetylbaccatin III**  
from *Taxus baccata* needles

![Caspofungin](image3.png)  
**Caspofungin**

![Pneumocandin B$_0$](image4.png)  
**Pneumocandin B$_0$**

**Figure 1.17** Semi-synthetic preparations of pharmaceutical drugs from abundant natural compounds.

These examples highlight the major role that synthesis can play in the development of natural products.

### 1.5 Planning a Synthesis of the Target Molecules

As discussed in Section 1.3, the group of structurally related natural products TEO3.1, hamigerone and embellistatin exhibit interesting biological activities making them ideal target compounds for total synthesis. These natural products all contain the common structural motif of a functionalised cyclohexadiene bicyclic core (1.8). The point of difference between these natural products lies in the nature of the side chain at C-1. The absolute configuration of these compounds is unknown and the stereochemistry of the epoxide functionality of TEO3.1 and hamigerone could not be determined spectroscopically.
To the best of the author’s knowledge the bicyclic core 1.8 represents a relatively unique motif. Only two other natural products, Rulepidadiene B and the hydrated analogue Rulepidanol have been reported which display this carbon structural unit. 60 There have been no reported synthetic efforts towards these compounds.

![Figure 1.18 Core structure of the targeted natural products.]

One compound with a related structure is the marine-derived natural product tridachiahydropyrone isolated in 1996 by Gavagnin and co-workers from Tridachia crispate. 61 Synthetic efforts by Perkins and co-workers resulted in the synthesis of the putative structure of the natural product in 2005. However, comparing data from the synthetic compound with the natural compound led them to conclude that the true structure of tridachiahydropyrone must be a diastereoisomer of the proposed structure. The synthetic strategy to this compound involved the use of a novel cuprate addition-cyclisation reaction to form cyclohexanone 1.11 and the intramolecular cyclisation of 1.12 to pyrone 1.13, with simultaneous dehydration installing the diene. 62
Scheme 1.2 Perkins and co-workers synthesis of the proposed structure of tridachiahydropyrone.

Based upon the biosynthesis of hamigerone (Figure 1.13), it could be envisaged that these molecules could be prepared through electrocyclisation of polyene 1.15.

Scheme 1.3 Retrosynthesis via electrocyclisation.

When this project was initiated, there was little reported about the viability of such an approach. In the last three years, three examples have been reported utilising an electrocyclic approach for the synthesis of cyclohexadiene containing compounds. Funk and co-workers reported the facile electrocyclisation of hexatriene 1.16 into the corresponding cyclohexadiene 1.17 during the synthesis of indoles (Figure 1.19-A).\textsuperscript{63} The retinoid substrate 1.18 has been reported to undergo cyclisation to 1.19 by Nakanishi and co-workers (B).\textsuperscript{64} Recently, Jung and Min have reported the electrocyclisation of 1.20a into 1.21, involving initial isomerisation into the Z-isomer 1.20b.
However, it should be noted that they obtain the product where the ester substituent and the adjacent methyl group are *anti* to each other.

Figure 1.19  Reagents and yields: (i) Toluene, 110°C, 1h; (ii) MeOH, hv, sensitisier, 4h, 95%. (iii) hv, benzanthrone, THF, 5h; (iv) DMF, 154°C, 3 d, 64% (2 steps).

To synthesise the targeted natural products using such an electrocyclisation step would require the preparation of polyene substrate 1.15. A major obstacle in the synthesis of 1.15 would be the stereo-controlled formation of the two trisubstituted double bonds between C-8 and C-9 and C-10 and C-11, although it might be possible to achieve this using a photochemical isomerisation, as reported by Jung.

The major issue pertaining to the use of an electrocyclisation to generate the core structure 1.8 is the requirement to generate a *syn* relationship between the bridgehead proton and the adjacent C-1 side-chain. As noted earlier, when this project was initiated there was no precedent for this type of transformation. However, Nakanishi’s recent work indicates that a photochemically-induced electrocyclisation would be required to achieve the correct relative stereochemistry.
Adopting this strategy would also lead to a linear synthesis of the natural products, where we would be reliant upon the success of the proposed electrocyclisation following the synthesis of a suitable precursor. A linear synthesis would also not be as amenable to the synthesis of the non-natural analogues required to initiate structure-activity studies and to determine the mode of action of these compounds. As a consequence, we decided to develop an alternative pathway to TEO3.1, hamigerone and embellistatin.

![Figure 1.20 Substrate for electrocyclisation.](image)

1.6 Retrosynthetic Analysis

The aim of this work was to develop a synthesis of the three target molecules, and examine the role of the various side-chains to the biological activity. As noted earlier, all three molecules contain a common functionalised bicyclic core, thus we proposed that the synthesis of this group of related natural products would best be approached through the preparation of the common bicyclic carbon skeleton 1.22.

![Scheme 1.4 The common bicyclic core of TEO3.1, hamigerone and embellistatin.](image)

It was envisaged that this skeleton could then be elaborated with the various side chains of TEO3.1, hamigerone and embellistatin using a series of Wittig elongation-reduction-oxidation steps based on the synthesis of polyenes as described by Baldwin and co-workers (Scheme 1.5).
Scheme 1.5  Proposed routes for side-chain installation.
Approaching the synthesis in this modular fashion should provide a straightforward and rapid route that would allow for the preparation of non-natural analogues of the natural products for structure-activity studies.

1.6.1 Analogues

Possible analogues could include removal of some, or all of the functional groups on ring A of 1.22, variation of the side chain at C-2 or isomerisation of the diene moiety to form the motif inherent in dihydrohamigerone and 1.5 and 1.6. Analogues containing structural variations in the C-1 side chain could include removal of the methyl groups, variation of the terminal functionality and variation of the epoxide of TEO3.1 and hamigerone to the corresponding cyclopropane. Cyclopropanes are generally thought to be more stable in vivo, which could lead to an enhanced pharmacophore. Their preparation could also be used to probe the significance of the epoxide oxygen on the biological activity of these compounds.

**Figure 1.16** Potential analogues of the natural product targets.
1.6.2 Using an IMDA Reaction

Examining the common bicyclic core 1.22, we were intrigued by the possibility of utilising an intramolecular Diels-Alder approach, as this would allow for control of the stereochemistry required to generate the syn relationship between the C-1 ester substituent and the adjacent bridgehead proton. Elaboration of the IMDA adduct 1.32 to the desired diene moiety would then be addressed by utilising addition-elimination chemistry.

Scheme 1.6  Retrosynthesis of the bicyclic core 1.22.

The beauty of the IMDA reaction lies in its ability to generate polycyclic structures in a single step from acyclic precursors with high levels of regio- and stereo-control. The utility of this reaction can be seen in its application as the key step in the total synthesis of numerous complex natural products, examples of which will be discussed in Chapter Two.

To generate the key bicyclic skeleton 1.22 using the IMDA approach would require the synthesis of triene 1.33. It was anticipated that addition of the dienophile portion of the triene could be achieved through Wittig olefination of aldehyde 1.34, accessible via reduction of amide 1.35. Introduction of the C-8 stereogenic methyl group can be envisaged through the application of Evans chiral auxiliary chemistry to aldehyde 1.36. Appropriate selection of the base used for deprotonation of the chiral auxiliary should control the stereochemistry at C-8. Aldehyde 1.36 should be readily accessible from 1.37 via deprotection/oxidation chemistry. It is proposed that cross-coupling chemistry between two appropriately substituted entities, 1.38 and 1.39, should be amenable to the preparation of diene 1.37.
Scheme 1.7  Retrosynthesis of the IMDA substrate 1.33.

1.7  Work Described in this Thesis

The research described in this thesis involves the synthetic studies undertaken to form the cyclohexadiene containing bicyclic core common to the natural products TEO3.1, hamigerone and embellistatin. The initial aims of this research were as follows:

◊ To design and implement a method for the synthesis of the IMDA precursor which allows control of the stereochemistry of the groups in the tether.
◊ To investigate the selectivity of the IMDA cyclisation and the subsequent addition-elimination steps to form the bicyclic core of the natural products.
◊ To elaborate the bicyclic core with the appropriate side-chains to complete the syntheses of TEO3.1, hamigerone and embellistatin and to investigate the synthesis of non-natural analogues for structure-activity relationship studies.
1.8 References for Chapter One


Chapter One – Introduction

(21) Petranyi, G.; Ryder, N. S.; Stutz, A. Science 1984, 224, 1239-1241.


Chapter Two

Intramolecular Diels-Alder

Synthesis of the Bicyclic Core
2.1 The Diels-Alder Reaction

The $[4\pi + 2\pi]$ cycloaddition reaction was first recognised in 1928 when Diels and Alder reported the reaction of several dienes and dienophiles in a study that has had a significant impact on both mechanistic and synthetic organic chemistry. The reaction involves a concerted pericyclic reaction resulting in the formation of two new carbon $\sigma$-bonds and one $\pi$-bond.

\begin{align*}
\text{(A)} & \\
\begin{array}{c}
\text{endo} \\
\end{array} & \xrightarrow{\text{General Process:}} & \\
\text{(B)} & \\
\end{align*}

**Figure 2.1** The $[4 + 2]$ cycloaddition of cyclopentadiene and maleic anhydride discovered by Diels and Alder (A), and the general process for a Diels-Alder reaction (B).

The Diels-Alder reaction has become a most useful and powerful tool for synthetic chemists and as a result it is the most widely studied and understood cycloaddition reaction. The power of the reaction is attributed to its ability to rapidly allow access to new cyclic structures from acyclic precursors, coupled with the stereospecific formation of up to four contiguous stereocenters, and a new double bond, in which the relative stereochemistry of groups present in the individual reaction partners are conserved in the product.

The initially observed intermolecular Diels-Alder reaction has been extended to include intramolecular reactions, hetero-Diels-Alder reactions, transannular reactions (TADA) and also a diene-regenerative Diels-Alder reaction that will be discussed further in Chapter 3. The Diels-Alder reaction has been widely employed in the synthesis of natural products due to its ability to greatly increase molecular complexity, and, for this reason it is commonly exploited as the key step during a synthetic strategy.
An early application of the Diels-Alder reaction in natural product synthesis can be found in the total synthesis of reserpine by Woodward in 1956.\(^7\) The first step of the sequence involved reaction of methyl 2,4-pentadienoate with benzoquinone to furnish the bicyclic system \(\text{2.1}\) stereospecifically via \textit{endo} cyclisation. In this single step, three of the stereocentres required for reserpine were generated, with the correct orientation. Stereoselective reaction at the double bond of ring E, controlled by the stereocentres already present, installed two additional stereocentres, providing \(\text{2.2}\), the key intermediate in Woodward’s synthetic sequence.

\[ \begin{align*} \text{2.1} & \quad \text{2.2} \\ \text{CO}_2\text{Me} + \text{H} & \quad \text{MeO}_2\text{C} \\ \text{endo} & \quad \text{anti} \\ \text{2.3} & \quad \text{reserpine} \end{align*} \]

\[ \text{Scheme 2.1} \quad \text{An example of the use of an intermolecular Diels-Alder reaction in natural product synthesis.} \]

The work carried out by E.J. Corey’s group provides a clear illustration of how the stereoselectivity of the Diels-Alder reaction can be controlled. The group exploited the Diels-Alder reaction as a new approach to the synthesis of prostaglandins in 1969 (\textbf{Figure 2.2}–\textbf{A}).\(^8\) Their synthesis was designed to; (a) control the stereochemistry, (b) allow the preparation of numerous analogues from a single precursor, and (c) allow optical resolution at an early stage. The Diels-Alder reaction of 5-methoxymethyl-1,3-cyclopentadiene \(\text{2.4}\) and 2-chloroacrylonitrile \(\text{2.5}\) provided the Diels-Alder adduct \(\text{2.6}\) as a mixture of stereoisomers differing in the \textit{exo-endo} orientation of the chloro and cyano groups. Both analogues were converted to the \textit{anti}-bicyclic ketone \(\text{2.7}\), which was then converted to various prostaglandins. In 1991, while developing a 3\(^{\text{rd}}\) generation synthesis of the prostaglandins, Corey and co-workers
illustrated the use of a chiral catalyst for a highly enantioselective Diels-Alder reaction.\textsuperscript{9} Chiral oxazaborolidine 2.8 was used as a Lewis-acid to control facial selectivity in the approach of the diene to the dienophile. The interaction favours coordination of the dienophile at the face of the boron which is cis to the 3-indolylmethyl substituent. As such, reaction of 2-bromoacrolein and 5-(benzylxoxymethyl)cyclopentadiene, in the presence of catalyst 2.8, provided the Diels-Alder adduct 2.9 in 81-83\% yield with 96:4 (R/S) enantioselectivity and 95:5 exo/endo diastereoselectivity. The resulting adduct could be readily transformed into the key prostaglandin intermediate 2.10.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Corey’s 1\textsuperscript{st} (A) and 3\textsuperscript{rd} (B) generation syntheses of prostaglandins.}
\end{figure}

\section{The Intramolecular Diels-Alder Reaction}

The use of the Diels-Alder reaction in an intramolecular fashion, that is when the diene and the dienophile are attached by a tether, was first reported in 1963 during the synthesis of \(\gamma\)-apopicropodophyllin (2.12).\textsuperscript{10} Over the next 10 years there was minimal interest in the area - a review by Carlson in 1974 cited just 15 papers on the subject.\textsuperscript{11} However, from that time on there has been an explosion of interest in the intramolecular Diels-Alder (IMDA) reaction and it has
since been used to great effect in the total syntheses of numerous natural products as a powerful means for the construction of polycyclic entities.

![Scheme 2.2](image)

Scheme 2.2  The first application of the IMDA reaction in natural product synthesis.

### 2.2.1 Type I and Type II IMDA Reactions

The IMDA can be described as type I or type II depending upon the nature of attachment of the dienophile to the diene. In the case of type I the attachment of the tether occurs terminally at C-1 and a *fused* ring system is produced. If attachment of the tether occurs at C-2, the IMDA reaction will generate a *bridged* bicyclic compound with a bridgehead double bond.

![Figure 2.3](image)

Figure 2.3  Type I and Type II IMDA connectivity and products.

The type I IMDA reaction, which generates a *fused* bicyclic system, has been extensively studied and has been utilised in the synthesis of a variety of natural products.\textsuperscript{12} There have been a number of reviews published on the subject and some of this work will be discussed in the context of this thesis. In contrast, the type II IMDA reaction has received much less attention as a synthetic tool\textsuperscript{13}, but has been successfully employed in the synthesis of taxanes, esperamicin,\textsuperscript{14} and phomoidrides A and B.\textsuperscript{15}
2.2.2 Examples of the Type I IMDA Reaction in Total Synthesis

The type I IMDA reaction has proven to be an exceptional method for the construction of polycyclic frameworks in natural product synthesis and the large numbers of examples present in the literature are testament to this. To illustrate the power of utilising the IMDA reaction as the key step in a synthetic sequence, we will examine two prominent total syntheses – colombiasin A and chlorothricolide.

The first example is the synthesis of (±)- and (-)-colombiasin A by Nicolaou and co-workers (Scheme 2.3). The synthesis opens with an intermolecular Diels-Alder reaction between 2.13 and 2.14, providing the endo-cycloadduct 2.15 as the sole product. Following elaboration to sulfone 2.16, sulfur dioxide extrusion under thermal conditions unmasked the diene 2.17 which underwent IMDA reaction with the quinone to generate the required endo scaffold 2.18 in 89% yield. This method was used to generate racemic colombiasin A. By utilising a chiral Lewis-acid catalyst in the initial Diels-Alder reaction 2.15 was generated in 94% enantiomeric excess and could be used to synthesise the natural enantiomer, (-)-colombiasin A.
In the second detailed example Roush and Sciotti utilised a remarkable sequence of simultaneous inter- and intramolecular Diels-Alder reactions as the key strategy in the enantioselective synthesis of (-)-chlorothricolide (Scheme 2.4).\(^{17}\) Diene 2.21 was synthesised by a Suzuki coupling between boronic acid 2.19 and vinyl iodide 2.20. Elaboration of 2.21 through a series of Horner-Wadsworth-Emmons type olefinations provided the IMDA substrate 2.22 containing six carbon-carbon double bonds. The key inter- and intramolecular Diels-Alder step was achieved by heating 2.22 and 2.23 in toluene. The expected doubly cyclised product 2.24 was obtained in 40-45% yield along with other cycloadduct isomers (19%) and the IMDA adduct 2.25, which could be recycled via independent intermolecular Diels-Alder reaction with 2.23 to provide additional 2.24 (total yield: 55-59% after one recycle). Of note is the fact that the intermolecular reaction occurred with complete regioselectivity for the upper conjugated triene portion of 2.22, and with high diastereofacial and exo-selectivity of the chiral dienophile 2.23. The C-9 trimethylsilyl group in 2.22 plays an important role in controlling the stereochemistry of the
IMDA reaction. The dual Diels-Alder adduct was elaborated via a series of steps to the desired natural product target (-)-chlorothricolide.

Scheme 2.4  Roush and Sciotti’s synthesis of (-)-chlorothricolide.

2.3 Intramolecular Diels-Alder Strategy for the Synthesis of the Bicyclic Core

As detailed in Chapter One, it was envisaged that an IMDA reaction of triene 1.33 could provide an avenue for the construction of the bicyclic core present in the synthetic target.
Following this key reaction, conversion of alkene 1.32 into the diene-containing bicyclic core 1.22 could be achieved through electrophilic addition to the alkene, followed by double elimination. It was proposed that triene 1.33 could be accessed from aldehyde 1.34 using a Wittig olefination reaction, with 1.34 being generated from alcohol 1.37. A Julia olefination reaction of substrates 1.38 and 1.39, where X and Y could be varied, should allow formation of conjugated diene 1.37. Since the nature of the sulfone and aldehyde substrate can dictate whether the desired (E,E) olefin is formed stereoselectively, it was felt that it would be advantageous for X and Y to be interchangeable.

The proposed strategy was designed to be flexible so that a range of compounds could be prepared to allow structure-activity relationship studies to be carried out. This also has the advantage of allowing the preparation of a simpler model system, which will enable the IMDA and addition-elimination steps to be examined without having to tackle the synthesis of the more complex substrate.
2.3.1 Selectivity in the IMDA Reaction

Before discussing our work on the IMDA approach to the bicyclic core, it is pertinent to comment on prior work on the stereoselectivity of the IMDA reaction. A number of research groups have investigated the exo/endo selectivity of triene substrates such as that proposed in Scheme 2.5.\(^\text{18}\) It is generally found that the presence of an ester substituent on the dienophile leads to little or no exo/endo selectivity in the case of thermal Diels-Alder reactions (Figure 2.4, entries 1-4 and Figure 2.5, entries 1 and 2).

However, Lygo and co-workers, during the course of their work on (±)-solanapyrones A and B have shown that cyclisation to the exo isomer can be favoured by changing the ester substituent to an amide, whereas the use of an imide (entry 9) resulted in the endo cycloadduct being favoured.\(^\text{18a}\)

![Figure 2.4](image)

**Figure 2.4** Substituent effects on exo/endo selectivity (Lygo).

During studies towards the synthesis of chlorothricolide, the Roush group showed that whilst Lewis-acid catalysed reactions with trienes of this type resulted in poor yields, due to Lewis-acid promoted decomposition reactions of the starting material, selectivity towards the trans-fused (Figure 2.5, entries 3-5) or cis-fused (entry 6) adducts could be achieved. Their work also showed that the presence of a substituent in the tether between the diene and the dienophile can enhance the formation of the cis-fused adduct vs. the trans-fused adduct, and that this preference is independent of dienophile stereochemistry (entries 7 and 8).\(^\text{19}\) After significant additional studies and some work based on the original findings of Wilson,\(^\text{20}\) they found that their desired
trans-fused adducts could be favoured by having a sterically bulky TMS group attached directly on the diene.\textsuperscript{21}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2_5.png}
\caption{Summary of Roush’s IMDA studies.}
\end{figure}
In subsequent studies towards the synthesis of the octahydropyrene substructure of kijanolide and tetrone Roush and Brown utilised a similar steric directing group strategy (Figure 2.6).\textsuperscript{22} They found that thermal cyclisation of triene 2.43 containing a brominated diene and a highly functionalised tether was highly selective for the desired adduct (entry 1), formed from the favoured transition state (\(A\)). The effect on selectivity due to the bromination of the diene and the orientation of the C-5 functionality were explored by thermal cyclisation of trienes 2.45 and 2.48 respectively. Replacing the C-9 steric directing bromo group with a hydrogen led to a lowered selectivity for the desired adduct, with some of the \textit{cis}-fused adduct formed through a now accessible transition state (\(B\)) (entry 2). Epimerisation of the C-5 acetate group had little effect on selectivity for the \textit{trans}-fused adduct (entry 3).

![Steric directing group studies by Roush and Brown.](image)

**Figure 2.6**  Steric directing group studies by Roush and Brown.
During the course of the experimental work detailed in this thesis being performed, several groups have since published their results on the stereoselectivity of similar IMDA reactions. MacMillan and co-workers reported the first enantioselective organocatalytic IMDA reaction which was used to complete the asymmetric synthesis of solanopyrone D.\textsuperscript{23} Cyclisation of triene 2.50, in the presence of catalytic amounts of 2.51, provided the cycloadduct 2.52 with high enantio- and diastereoselectivity. This cycloadduct was then elaborated \textit{via} a series of steps to solanopyrone D.

\textbf{Scheme 2.6}  The first example of an enantioselective organocatalytic IMDA reaction reported by MacMillan and co-workers.

During the synthesis of the lower segment of (+)-tubelactomycin A, Tadano and co-workers utilised a highly endo- and $\pi$-facial selective IMDA reaction to generate the stereochemistry required for the natural product.\textsuperscript{24} As such, cyclisation of triene 2.53, in the presence of the radical inhibitor butylated hydroxytoluene, provided the desired \textit{trans}-fused adduct 2.54 with 8:1 endo/exo ratio with complete $\pi$-facial selectivity. The \textit{trans}-orientated benzylidene substituent in the tether between the diene and the dienophile plays a critical role in the selectivity of the IMDA reaction, conformationally locking the transition states in a chair conformation leading to non-bonded interactions in the \textit{exo} transition state, making it unfavourable.
Scheme 2.7 A highly endo- and π-facial IMDA reaction reported by Tadano and co-workers.

An alternative synthesis of (+)-tubelactomycin A published by Tatsuta and co-workers also utilised a highly selective IMDA reaction. Thermal cyclisation of triene 2.56, followed by de-O-silylation afforded the required adduct 2.57 as a single product as expected from the favoured transition state. The IMDA adduct 2.57 could then be elaborated via a series of steps to provide the lower-half of (+)-tubelactomycin A.25

Scheme 2.8 Thermal cyclisation of 2.56 reported by Tatsuta and co-workers.
In 2006, Hoye and Dvornikovs reported the use of an IMDA reaction in the biomimetic total synthesis of (±)-UCS1025A.\textsuperscript{26} Thermal cyclisation of triene 2.58 provided two isomeric adducts in a 4:3 ratio that were inseparable by either normal or reversed-phase chromatography. Elaboration of the mixture into UCS1025A (2.61) and its diastereomer 2.62 allowed the assignment of the initial IMDA adducts as 2.59 and 2.60. Both result from an \textit{endo} mode of addition. Therefore, whilst substrate 2.58 favours \textit{endo} addition, facial selectivity for approach of the diene to the dienophile is virtually non-existent. This may be attributed to the remote nature of the stereocenters in 2.58.

![Scheme 2.9](image)

\textit{Scheme 2.9} \textit{Endo}-selective thermal cyclisation of 2.58 reported by Hoye and Dvornikovs.

### 2.4 Development of a Model System of the Bicyclic Core

As this project was initiated prior to Macmillan, Tadano and Hoye’s work in the area, we based our initial efforts on the work of Lygo and Roush. Thus, we decided to examine the Diels-Alder chemistry of triene 2.63. It was envisaged that the synthesis of triene 2.63, a model of the more complex triene required for the natural product synthesis, would provide an avenue to explore the selectivity of our IMDA cyclisation.
Chapter Two – IMDA synthesis of the bicyclic core

Scheme 2.10  Proposed model system.

Analysis of the chair-like transition states available to triene 2.63 reveals possible unfavourable interactions between the bulky C-5 TBS ether and H₉ (transition state C) and the C-5 TBS ether and H₃ and H₈ (transition state D). Due to the axial orientation of the C-5 TBS ether in transition state D there also exists an unfavourable 1,3 diaxial interaction between this group and H₇. Thus, these transition states may be significantly destabilised compared with transition states A and B, leading to endo being the favoured mode of cyclisation. Transition state B may also be slightly disfavoured relative to A as the bulky C-5 TBS ether would be in an axial orientation in transition state B, creating an unfavourable 1,3 diaxial interaction with H₇. As the stereocentres at C-2 and C-4a would be destroyed in the subsequent steps, elaboration of the IMDA adducts resulting from both transition states A and C via the proposed addition-elimination chemistry would provide the desired diene 2.65. Elaboration of the cycloadducts resulting from transition states B and D would provide the diastereomer 2.67.
2.4.1 Synthesis of Triene 2.63

The initial target to be synthesised for these studies was the IMDA substrate 2.63. The key reaction in this sequence is the formation of diene 2.72 through a Julia olefination reaction. The ability to generate alkenes by connective reactions that link two fragments is a highly valued tool in the area of natural product synthesis. Such methods must be not only regio- and stereospecific but also compatible with functionality inherent in the fragments. There are a number of methods available to facilitate alkene synthesis and the most applicable of these generally involve direct olefination of carbonyl compounds. Examples of these methods include the Wittig,\textsuperscript{27} Horner-Wittig\textsuperscript{28} and Horner-Wadsworth-Emmons\textsuperscript{29} reactions, Peterson\textsuperscript{30} and Johnson\textsuperscript{31} olefination reactions and both the classical\textsuperscript{32} and modified\textsuperscript{33,34} Julia olefination reactions.
Chapter Two – IMDA synthesis of the bicyclic core

Figure 2.8 Methodologies for the olefination of carbonyl compounds.

Of the methods available, the Julia olefination reaction would appear to be the most flexible. Disconnection of the C-4/5 double bond into two fragments via a retro-Julia reaction offers two complementary possibilities. Either of the two fragments 2.70 and 2.71 can be chosen as the aldehyde or sulfone derivative, or vice versa (Scheme 2.11).

The nature of each fragment can affect several aspects of the reaction. These include:

◊ difficulty with metallation of the sulfone,
◊ a lack of reactivity of one or both of the reaction partners,
◊ an unfavourable position of the equilibrium involving the addition reaction,
◊ competitive elimination of a leaving group β to the sulfone or the carbonyl compound,
◊ a competitive reduction of the carbonyl group by the anion of the sulfone, and
◊ control of the E or Z geometry of the newly formed alkene.35

To potentially circumvent any of these issues both an aldehyde and sulfone derivative of 2.70 and 2.71 will be prepared and their coupling investigated to determine which combination provides the greatest selectivity for the (E,E) diene over the (Z,E) diene in the best yield. Following the Julia olefination reaction, selective removal of the P1 protecting group of 2.72, followed by oxidation should provide aldehyde 2.73. Elaboration of 2.73 to the desired triene 2.63 should be achieved via addition of the enolate of N-methoxy-N-methyl acetamide followed by protection of
the free hydroxyl group as the TBS ether to give amide 2.74. Reduction to aldehyde 2.75 followed by a Wittig olefination reaction should provide triene 2.63.

![Scheme 2.11](image)

Scheme 2.11 Proposed route to model IMDA substrate 2.63.

### 2.4.2 The Julia Olefination Reaction

The classical Julia olefination reaction, first reported in 1973 by Marc Julia, involves the reductive elimination of a β-acyloxysulfone as the alkene-forming step. Following significant development by Lythgoe and Kocienski, the reaction has been utilised in a number of natural product syntheses. However, the reaction typically involves four synthetic manipulations: metallation of a phenylsulfone (I), addition of the metallated sulfone to an aldehyde (II), acylation of the formed β-alcoxysulfone (III) and finally reductive elimination of the β-acyloxysulfone with a single electron donor (IV). The reaction typically favours the formation of the E alkene.
In 1991 Sylvestre Julia found that replacement of the traditionally employed phenylsulfones with heteroarylsulfones lead to a profoundly altered reaction manifold. The use of heterocycles containing an electrophilic imine-like moiety leads to an alternative reaction pathway, which explains the observed enhanced reactivity. Four typically employed heterocyclic activators are illustrated in Figure 2.9.

The mechanism of the modified or one-pot Julia reaction begins with a first step analogous to the classical reaction, in that a metallated BT-sulfone adds to an aldehyde, however the resulting β-alkoxysulfone is inherently unstable and undergoes a facile Smiles rearrangement. The rearrangement, thought to occur via a spirocyclic intermediate, results in the transfer of the heterocycle from sulfur to oxygen generating a sulfinate salt. The alkene is generated directly through the spontaneous elimination of sulfur dioxide and lithium benzothiazolone.
Scheme 2.13  Mechanism of the modified Julia reaction.

The olefination reactions are generally performed under so-called Barbier conditions, which act to eliminate the undesirable side reaction of self-condensation of BT-sulfones (Figure 2.10-A). Under the Barbier protocol a non-nucleophilic base such as lithium diisopropylamide (LDA) or an alkali- (Na, Li or K) hexamethyldisilazide is added to a mixture of the sulfone and aldehyde at low temperature. In situ metallation of the sulfone and its addition to the carbonyl compound compete with self-condensation of the BT-sulfone. At low temperatures the extent of self-condensation is negligible for most linkage reactions so a premetallation protocol, whereby the sulfone is metallated before the addition of the aldehyde, can also be employed.

In general, reactions between simple alkyl BT-sulfones and saturated aliphatic aldehydes form non-conjugated 1,2-disubstituted alkenes with little or no stereochemical bias (Figure 2.10-B). However, one of the most synthetically useful reactions of BT-sulfones involves the formation of conjugated 1,2-disubstituted alkenes with a preference for the formation of the E isomer (C). There have been a number of applications of the modified Julia olefination in target-directed synthesis. Shortly following its disclosure Kocienski and co-workers employed the modified methodology to synthesise the conjugated triene segment of rapamycin (D). As such, triene 2.82 was prepared by the addition of lithiated BT-sulfone 2.81 to conjugated dienal 2.80 in THF. The triene was isolated in good yield and with excellent stereoselectivity for the E isomer (E:Z = 95:5). Their investigations also revealed that the nature of the base used to effect sulfone
deprotonation had a profound effect on the stereochemical outcome of the reaction (entries 1 and 2).

(A) Self-condensation of BT-sulfones

\[
\text{BT-SO}_2 \xrightarrow{\text{LDA (1.1eq), THF } -78^\circ C, 3h, 52\%} \text{product}
\]

(B) Stereorandom Julia olefination

\[
\text{BT-SO}_2 \xrightarrow{n-C_8 H_{17}CHO \text{ LDA, THF } -78^\circ C \text{ to rt}} n-C_8 H_{17} \text{ olefin } 48\%, E:Z = 49:51
\]

(C) Stereoselective Julia olefination

\[
\text{BT-SO}_2 \xrightarrow{\text{LDA, THF } -78^\circ C \text{ to rt}} \text{products with varying } E:Z \text{ ratios}
\]

(D) Kocienski’s synthesis of the triene fragment of Rapamycin

\[
\text{Entry} \quad \text{M} \quad \text{Yield} \quad E:Z \text{ ratio}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>M</th>
<th>Yield</th>
<th>E:Z ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Li</td>
<td>68%</td>
<td>95:5</td>
</tr>
<tr>
<td>2</td>
<td>Na</td>
<td>21%</td>
<td>78:22</td>
</tr>
</tbody>
</table>

Figure 2.10  Examples of the Julia olefination.

2.4.3 Synthesis of Substrates for the Julia Reaction

As discussed above, both complementary pairs of aldehyde and sulfone derivatives for the Julia coupling reaction will be prepared in order to investigate which pairing provides an optimum
yield of the desired diene with high selectivity for formation of the \((E,E)\) geometry. As such, the targets for synthesis are sulfone \(2.84\), which will be coupled with either aldehyde \(2.83a\) or \(2.83b\) to investigate the effect the protecting group has on the reaction, and sulfone \(2.85\) to be coupled with aldehyde \(2.86\).

**Scheme 2.14** Substrates for Julia olefination.

The synthesis of fragments \(2.83a\) and \(2.85\) began with the monoacylation of 1,4-butanediol following the method of Mattes and co-workers to give \(2.87a\).\(^{40}\) \(2.87b\) was prepared similarly through mono-protection with 4-methoxybenzyl bromide (PMB-Br) using sodium hydride in THF (Scheme 2.15). Aldehydes \(2.83a\) and \(2.83b\) were easily accessible through the oxidation of alcohols \(2.87a\) and \(2.87b\) using Dess-Martin periodinane.\(^{41}\) Reaction of \(2.87a\) under Mitsunobu conditions\(^{42,43}\) using 2-mercaptobenzothiazole, triphenylphosphine and diethyl azodicarboxylate (DEAD) in THF at room temperature afforded thioester \(2.88\). Synthesis of the desired sulfone \(2.85\) was achieved by oxidation of \(2.88\) with ammonium molybdate and hydrogen peroxide in ethanol.\(^{44}\)

**Scheme 2.15** Reagents and yields: (i) AcCl, pyridine, CH\(_2\)Cl\(_2\), 0°C to rt, 67%; (ii) PMB-Br, NaH, THF, 0°C, 50%; (iii) Dess-Martin periodinane, CH\(_2\)Cl\(_2\), rt, 1h, \(2.83a\)-91%, \(2.83b\)-91%; (iv) 2-mercaptobenzothiazole, DEAD, PPh\(_3\), THF, rt, 68%; (v) 50% H\(_2\)O\(_2\), (NH\(_4\))\(_6\)Mo\(_7\)O\(_{24}\).4H\(_2\)O, EtOH, 0°C to rt, 74%.
Fragments 2.84 and 2.86 were prepared starting from commercially available propane-1,3-diol (Scheme 2.16-A). Monosilylation with tert-butylimethylsilyl chloride under standard conditions,45 followed by oxidation with Dess-Martin periodinane gave aldehyde 2.90, which was used without purification in a Wittig reaction with phosphorane 2.91 or 2.92 in toluene to furnish 2.93 or 2.94. Both esters could be reduced to the corresponding alcohol 2.95 via treatment with diisobutylaluminium hydride at –78°C. Conversion to the desired aldehyde 2.86 was achieved through oxidation of 2.95 with Dess-Martin periodinane. Thioester 2.96 was prepared under Mitsunobu conditions as described for 2.88 however, attempted conversion to the sulfone target 2.84 using ammonium molybdate oxidation resulted in cleavage of the TBS ether due to residual acid formed during the reaction. The alcohol could be reprotected using TBSCI under standard conditions, however this resulted in moderate isolated yields of the desired material, which was contaminated with impurities despite purification by column chromatography. Attempts to buffer the reaction resulted in complex mixtures of products. The problem was circumvented through the use of the less acid-labile triisopropylsilyl (TIPS) protecting group in the same sequence (Scheme 2.16-B).
Scheme 2.16  Reagents and yields: (i) TBSCl, imidazole, THF, rt, 77%; (ii) Dess-Martin periodinane, CH$_2$Cl$_2$, rt, 1h, 92%; (iii) Me$_2$CC(=Me)=PPh$_3$ (2.91) or EtO$_2$CC(=Me)=PPh$_3$ (2.92), toluene, reflux, 2.93-75%, 2.94-70%; (iv) DIBAL-H, Et$_2$O, -78°C, 1h then 0°C, 1h, 89%; (v) Dess-Martin periodinane, CH$_2$Cl$_2$, rt, 1h, 98%; (vi) 2-mercaptobenzothiazole, DEAD, PPh$_3$, THF, rt, 89%; (vii) 50% H$_2$O$_2$, (NH$_4$)$_6$Mo$_7$O$_{24}$.4H$_2$O, EtOH, 0°C to rt, 54%; (viii) TBSCl, imidazole, THF, rt, 67%; (ix) TIPSCl, imidazole, THF, rt, 76%; (x) Dess-Martin periodinane, CH$_2$Cl$_2$, rt, 1h, 96%; (xi) EtO$_2$CC(=Me)=PPh$_3$ (2.92), toluene, reflux, 84%; (xii) DIBAL-H, Et$_2$O, -78°C, 1h then 0°C, 1h, 100%; (xiii) Dess-Martin periodinane, CH$_2$Cl$_2$, rt, 1h, 94%; (xiv) 2-mercaptobenzothiazole, DEAD, PPh$_3$, THF, rt, 73%; (xv) 50% H$_2$O$_2$, (NH$_4$)$_6$Mo$_7$O$_{24}$.4H$_2$O, EtOH, 0°C to rt, 55%.
2.4.4 The Julia Olefination Reaction and Isomer Separation

Initial studies carried out according to the Barbier protocol involved the addition of 1.2 equivalents of sodium hexamethyldisilazide to a solution of 2.83b and 2.104 in THF at –78°C. After three hours at this temperature and a further hour at room temperature standard work-up procedures provided the crude material, which was analysed by ¹H NMR spectroscopy to determine the ratio of the E and Z isomers (2.105a and 2.105b). It was found that the undesired Z isomer was formed predominantly in a ratio of 1:2.4. Extensive investigations using varied reaction conditions⁴⁶ failed to generate improved selectivity for the E isomer (Figure 2.11). Efforts to separate the E and Z isomers were quashed when deprotection of the PMB alcohols using either 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)⁴⁷ or cerium (III) chloride⁴⁸ resulted in decomposition of the E isomer and recovery of the PMB protected Z isomer.
Investigations into the acetate-protected substrates determined that the ratio of $E$ and $Z$ isomers was dependant upon the nature of the aldehyde and sulfone substrates (Scheme 2.17). The union of substrates 2.83a and 2.104 gave an inseparable mixture of alkenes 2.107a and 2.107b in which the $Z$ isomer predominated ($2.107a:b = 1:2.6$). However, subjecting substrates 2.85 and 2.102, in which the sulfone and aldehyde moieties have been interchanged, to the same conditions used to couple 2.83a and 2.104 led to an inseparable mixture of 2.107a and 2.107b in which the desired $E$ isomer was favoured ($2.107a:b = 3.9:1$). Similarly, coupling between 2.85 and TBS protected aldehyde 2.86 led to predominant formation of the $E$ isomer ($2.108a:b = 3.2:1$). Deprotection of
the acetate functionality with potassium carbonate in methanol resulted in a mixture of alcohols \(2.109a\) and \(2.109b\) or \(2.110a\) and \(2.110b\), which could be separated by chromatography.

The difference in selectivity observed when the aldehyde and sulfone moieties are interchanged may be explained by the nature of the sulfone substrates. Baudin and Julia have noted that metallated \(\beta\)-\(\gamma\)-unsaturated BT-sulfones condense with unbranched non-conjugated aliphatic aldehydes to give olefins with low to moderate \(Z\) selectivity (Figure 2.12-A). If we consider the mechanism for the reaction (B), when \(R^1\) is unsaturated, a mechanism for equilibration between the intermediate \textit{syn} and \textit{anti} \(\beta\)-alkoxy sulfones can occur via fragmentation to resonance.
stabilised α-metallated sulfones and carbonyl compounds, followed by subsequent re-addition. This equilibration, together with faster Smiles rearrangement/elimination for 2.112, provides a reasonable explanation for the observed $Z$ selectivity for coupling $\beta$$\gamma$-unsaturated BT-sulfones such as 2.104.

![Chemical diagram](image)

**Figure 2.12** Baudin and Julia’s observations for coupling of $\beta$$\gamma$-unsaturated BT-sulfones (A) and the mechanism for formation of $E$ and $Z$ alkenes (B).

During their synthesis of axinellamine A Seki and Mori also observed this difference in selectivity. Reaction of the $\beta$$\gamma$-unsaturated BT-sulfone 2.114 with aldehyde 2.113 led to the
formation of 2.115 favouring the formation of the Z isomer in a 6:4 ratio. However, reaction of unsaturated aldehyde 2.116 with sulfone 2.117 generated 2.115, now highly favouring the E isomer (Figure 2.13-A).

However, the situation is certainly more complex than this as there have been some examples from total synthesis where β-γ-unsaturated BT-sulfones have given high levels of E selectivity. Williams and co-workers observed the sole formation of the (E,E) diene 2.120 whilst working towards the synthesis of lankacyclinol (Figure 2.13-B). Low temperature deprotonation of β-γ-unsaturated BT-sulfone 2.119 with lithium diisopropylamide followed by addition of aldehyde 2.118 and immediate warming to ambient temperature saw formation of only the E isomer of 2.120 in 57% yield. Interestingly, their substrates 2.118 and 2.119 bear some similarity to the aldehyde and sulfones used in this synthesis (C).

(A)

(B)

(C)

Figure 2.13 Examples illustrating E/Z selectivity in the Julia Reaction.
2.4.5 Elaboration to the IMDA Substrate

With the diene portion of the substrate successfully in hand via the Julia olefination reaction, the desired triene could be prepared by elaboration of alcohol 2.110a. Smooth oxidation with Dess-Martin periodinane provided aldehyde 2.73 which was used without purification. Addition of aldehyde 2.73 to the enolate formed when \(N\)-methoxy-\(N\)-methylacetamide (2.121) was treated with lithium diisopropylamide (LDA) in THF at \(-78^\circ\text{C}\), followed by stirring at that temperature provided the crude aldol adduct 2.122 after workup. This crude adduct proved somewhat unstable towards purification by column chromatography so the free hydroxyl group was protected with tert-butyldimethylsilyl chloride under standard conditions prior to purification. This sequence provided the desired aldol adduct 2.74 in a yield of 67% over two steps. Conversion of the Weinreb amide to the aldehyde was achieved by treatment with diisobutylalumminium hydride in THF at \(-78^\circ\text{C}\). Aldehyde 2.75 was converted into the desired triene 2.63 through a Wittig reaction with phosphorane 2.123.

![Scheme 2.18](image_url)

**Scheme 2.18** Reagents and yields: (i) Dess-Martin periodinane, \(\text{CH}_2\text{Cl}_2\), rt, 1h, 80%; (ii) LDA, THF, \(N\)-methoxy-\(N\)-methylacetamide, \(-78^\circ\text{C}\), 15min then add 2.73, \(-78^\circ\text{C}\), 3h; (iii) TBSCI, imidazole, DMF, rt, 67% (2 steps); (iv) DIBAL-H, THF, \(-78^\circ\text{C}\), 2h, 100%; (v) \(\text{EtO}_2\text{CCH}=\text{PPh}_3\) (2.123), \(\text{CH}_2\text{Cl}_2\), rt, 69%.
2.5 The IMDA Reaction

The thermal Diels-Alder cyclisation of the IMDA substrate 2.63 was performed in toluene at ca. 160°C in a resealable Young’s tube for two days. Alternatively, the triene could be heated at reflux in xylenes to effect similar results. ¹H NMR spectroscopic analysis of the crude material indicated the presence of two products in an approximately 2:1 ratio and some small peaks attributed to a third product. The four possible products are shown below, with 2.64 and 2.66 resulting from endo cyclisation and 2.68 and 2.69 from exo cyclisation (see Section 2.3.1).

![Scheme 2.19 Possible products from IMDA cyclisation of triene 2.63.]

After purification of the crude reaction mixture by careful flash column chromatography two compounds were isolated in 19% and 9% yield along with 21% mixed material. These two compounds had similar ¹H NMR spectra (Figure 2.14). HSQC, HMBC and NOE experiments (vide infra) allowed the assignment of the ¹H and ¹³C chemical shifts for both the major and minor products. These data are shown in Figure 2.14 (omitting the chemicals shifts for the TBS groups). All protons are resolved in both products as a result of the rigid stereochemistry within the bicyclic molecule.
To ascertain the relationship between $H_1$ and $H_2$, $H_1$ and $H_{8a}$, and $H_{8a}$ and $H_{4a}$ coupling constant analysis and NOE studies of both compounds were carried out. The stereochemistry of the major
product was assigned on the basis of three key coupling constants ($J_{1,2} = 5.2$ Hz, $J_{1,8a} = 11.5$ Hz and $J_{4a,8a} = 11.4$ Hz) and NOE interactions between H$_1$ and H$_2$ and H$_1$ and H$_{4a}$. The large coupling constants between H$_1$ and H$_{8a}$, and H$_{4a}$ and H$_{8a}$, indicates an $180^\circ$ orientation between these protons, the smaller coupling constant between H$_1$ and H$_2$ indicates a $60^\circ$ orientation. In addition, irradiation at H$_1$ lead to NOE enhancements of the $^1$H NMR signals for both H$_2$ and H$_{4a}$. This enabled the conclusion that these protons had a syn relationship to each other due to their through-space correlation and thus, that the major product was the result of an endo cyclisation. The minor product also displayed the key coupling constants ($J_{1,2} = 5.3$ Hz and $J_{1,8a} = 11.7$ Hz) and similar NOE enhancements. From these findings, it was proposed that the two products were 2.64 and 2.66, both the result of endo cyclisation. If any exo products were present we would expect different coupling constants and NOE relationships.

![Figure 2.15](image)

Figure 2.15  Diagrams illustrating the relationship between protons in the endo and exo products.

Selective irradiation experiments also allowed the assignment of the signals for the diastereotopic protons at C-5, C-6 and C-8 by examining enhancements of signals when H$_7$ was irradiated.

![Figure 2.16](image)

Figure 2.16  Results of NOE studies from irradiation of H$_7$ (500 MHz) in adducts 2.64 and 2.66.
Serendipitously, both compounds crystallised as colourless plates which enabled the proposed structures of the two products to be confirmed by X-ray crystallography.

**Figure 2.17a** Crystallographic structure determined for the major IMDA product 2.64, [P-1, Z = 2, R = 15.7%], orientated to show the relationships between the key protons of the bicyclic system. The atom spheres are of an arbitrary radius.

**Figure 2.17b** Crystallographic structure determined for the minor IMDA product 2.66, [P-1, Z = 2, R = 25.0%], orientated to show the relationships between the key protons of the bicyclic system. The atom spheres are of an arbitrary radius.
The major product, 2.64, is formed from an *endo* cyclisation of triene 2.63 via transition state A which places the bulky C-5 TBS ether in an equatorial orientation. The minor product 2.66 is also formed from *endo* cyclisation this time through transition state B. This pathway is less favoured as the bulky C-5 TBS ether is placed in an axial orientation. The third product giving rise to the small peaks in the $^1$H NMR of the crude mixture, although not isolated, is likely to be the result of *exo* cyclisation. Thus, IMDA cyclisation of triene B occurs highly *endo* selectively, with moderate $\pi$-facial selectivity to provide the desired isomer 2.64 as the major product.

**Scheme 2.20**  Products from thermal cyclisation of triene 2.63.

### 2.6 Addition-Elimination Chemistry

With the desired IMDA adduct 2.64 in hand; attention was focused on methods available for the conversion of the alkene into the desired diene moiety. It was proposed that electrophilic addition to the alkene, followed by a double elimination would achieve this. There are a number of conditions available for the deoxygenation of epoxides to dienes and for conversion of dibromides to dienes *via* a double elimination of HBr. Some of the reported chemistry will be reviewed below.
2.6.1 Deoxygenation of Epoxides

Whilst carrying out the synthesis of allylsilanes, Carter and co-workers investigated the transformation of cyclohexene products, resulting from a Diels-Alder reaction, into the corresponding cyclohexadiene adducts controlling the positions of the two double bonds, relative to the position of the original.\textsuperscript{51} They reported the clean conversion of the Diels-Alder adduct \textit{2.124} into the corresponding epoxide \textit{2.125}. However, treatment of \textit{2.125} with 4-toluenesulfonic acid gave a mixture of products, with some material having one or both silyl groups removed.

\[ \text{Scheme 2.22} \quad \text{The formation of cyclohexadienes from alkenes reported by Carter and co-workers.} \]

In 1996 Hendrickson and coworkers reported the direct elimination of epoxides to form dienes using phosphonium anhydrides.\textsuperscript{52} Their procedure involves a one-pot reaction whereby the triphenylphosphonium anhydride trifluoromethanesulfonate (POP) reagent is first prepared from triphenylphosphine oxide and trifluoromethanesulfonic anhydride. The formed POP reagent precipitates in chlorocarbon solvents. Addition of the epoxide and triethylamine, followed by heating at reflux, generates diene products. Some examples of the epoxide substrates transformed are shown in Figure 2.18.
In 2001 Demir reported the tetramethyldiamidophosphoric acid chloride mediated epoxide-diene conversion. Previous reports regarding the hexamethylphosphoramide (HMPA)-mediated dehydration of alcohols to dienes implicated tetramethylamidophosphoric acid 2.126, formed from the hydrolysis of HMPA, as having an important role in the reaction. It was proposed that the acid would be formed from the corresponding acid chloride 2.127 under the conditions of the reaction and affect the desired deoxygenation of epoxides. The mechanism postulated by Demir and some examples are detailed in Figure 2.19. This provides a simple method for the conversion of epoxides to dienes using a commercially available reagent.
Chapter Two – IMDA synthesis of the bicyclic core

Proposed mechanism:

Figure 2.19  Examples of deoxygenation of epoxides with 2.124.

To investigate this strategy as a means for the installation of the diene moiety we first had to prepare the epoxide of the IMDA adduct. As such, epoxidation of 2.64 with m-chloroperbenzoic acid in dichloromethane proceeded cleanly to afford an inseparable mixture of two epoxides 2.128a and 2.128b in 3.8:1 ratio and with a yield of 87%. The structures of the major and minor products were assigned through selective NOE experiments. Selective irradiation of the signal for H₄ in the major product resulted in enhancement of the signal for the protons on the C-2 side-
Chapter Two – IMDA synthesis of the bicyclic core

chain. This provided evidence that these groups were on the same face of the bicycle. Enhancement of the signal for the C-3 methyl protons was also observed. Selective irradiation of the signal for H₄ in the minor component showed no enhancement of the protons on the C-2 side-chain but enhancement of the C-3 methyl protons signal was observed.

\[
\begin{align*}
\text{Scheme 2.23} & \quad \text{Reagents and yields: (i) } m\text{-CPBA, NaHCO}_3, \text{CH}_2\text{Cl}_2, 0^\circ\text{C to rt, 16h, 87%}. \\
& \quad \text{The inseparable mixture of epoxides 2.128a and 2.128b was treated with commercially available tetramethyldiamidophosphoric acid chloride and water and heated to } 140^\circ\text{C for 2 hours. Following work-up, analysis of the } ^1\text{H NMR spectrum of the crude material indicated that complete degradation of the starting material had occurred and no product or degradation product could be isolated. As it was felt that the reaction temperature may have been too harsh for the substrate, the reaction was repeated at room temperature. Whilst the } ^1\text{H NMR spectrum of the crude material showed no peak corresponding to H}_4 \text{ of the desired product 2.65, no starting material remained and a potential product was evident. Analysis of the integral values indicated that one or both of the silyl ether protecting groups had been hydrolysed as a result of the acidity of the reagent. However, on subjecting this material to column chromatography, none of the material apparent in the } ^1\text{H NMR spectrum of the crude material could be isolated.}
\end{align*}
\[
\begin{align*}
\text{Scheme 2.24} & \quad \text{Attempted deoxygenation of 2.128a and 2.128b with 2.127.}
\end{align*}
\]
2.128a & 2.128b

Crude reaction mixture

New peak

Figure 2.20  $^1$H NMR spectra (500 MHz) of 2.128a and 2.128b, and of the crude reaction mixture after treatment with 2.127.

At this point in the research program, positive results were being obtained using an alternative strategy for the synthesis of the bicyclic core (Chapter Three) so it was decided to discontinue investigations into the deoxygenation of epoxides 2.128a and 2.128b.

2.6.2 Dehydrobromination to form Dienes

It is well established that both potassium tert-butoxide$^{54}$ and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)$^{55}$ can be used to mediate dehydrobromination reactions, delivering a diene moiety. Sodium isopropoxide$^{56}$ and tetrabutylammonium fluoride (TBAF)$^{57}$ have also been reported to effect this transformation. Some recent examples are shown in Figure 2.21.
**Examples of dehydrobromination reagents:**

**DBU:**

Mehta and co-workers\(^ {55d} \)

\[
\begin{align*}
\text{OAc} & \quad \text{NBS, AIBN, CCl}_4 \\
\text{Br} & \quad \text{DBU, DMSO}
\end{align*}
\]

Watanabe and co-workers\(^ {55c} \)

\[
\text{Br} \quad \text{DBU, } \text{C}_6\text{H}_6
\]

Nitta and co-workers\(^ {55b} \)

\[
\text{Br} \quad \text{DBU, THF}
\]

**KO\text{-}t\text{-}Bu:**

Wege\(^ {54d} \)

\[
\text{Br} \quad \text{KO\text{-}t\text{-}Bu, THF}
\]

**NaO\text{-}i\text{-}Pr:**

Baeckvall and co-workers\(^ {56} \)

\[
\text{Br} \quad \text{NaO\text{-}i\text{-}Pr, triglyme}
\]

**TBAF:**

Paquette and Dura\(^ {57} \)

\[
\text{Br} \quad \text{TBAF, DMSO}
\]

**Figure 2.21** Examples of dehydrobromination to form dienes.

To transform the IMDA adduct 2.64 into the diene moiety using one of the methods discussed the dibromide analogue had to be prepared. Initially, bromination was attempted using bromine and tetraethylammonium bromide in dichloromethane,\(^ {45} \) however, this led to a complex mixture of
products including the desired product and a product where cleavage of the primary TBS ether had occurred. Reaction with bromine in dichloromethane also produced a similar mixture of products. Gratifyingly, when two equivalents of potassium carbonate were included with tetraethylammonium bromide and bromine clean conversion to a single product was observed. The same product was formed on reaction of 2.64 with pyridinium bromide perbromide and potassium carbonate in dichloromethane. It was proposed that, due to the mechanism of the bromination (formation of the bromonium ion followed by backside attack by Br⁻), only 2.129, one of the two possible products would form.

Scheme 2.25  
Reagents and yields: (i) Br₂, Et₄N⁺Br⁻, K₂CO₃, CH₂Cl₂, -78°C to rt, 16h, 83%.

Initial investigations of the dehydrobromination reaction were carried out under the conditions of Watanabe and co-workers; heating with DBU in benzene at 50°C. Following work-up, analysis of the ¹H NMR spectrum of the crude material showed complete consumption of the starting material had occurred to form a single product. However, rather than being consistent with the desired product 2.65, the spectrum showed the IMDA adduct 2.64 had been regenerated. Changing the conditions of the reaction to DBU in dichloromethane at 4°C had no affect on the outcome and the same adduct was generated.

If we consider the mechanism of dehydrobromination the lack of formation of the desired diene isn’t entirely unexpected. Dehydrohalogenations conducted in solution with a base, generally proceed via an E₂ mechanism which requires an anti relationship between the eliminating H and Br substituents. In the case of 2.129, we can see that while there is an anti relationship between H₄₈ and the adjacent Br, the relationship between H₂ and the adjacent Br is syn.
Figure 2.22  Attempted dehydrobromination of 2.129.

Treatment of 2.129 with both TBAF in dimethyl sulfoxide at 80°C or potassium tert-butoxide in THF at -78°C to 0°C provided complex mixtures of products from which no desired material could be isolated.

To generate an IMDA adduct with an anti relationship between both bromo substituents and their adjacent hydrogens (2.132) would require the synthesis of triene 2.130 containing the (E,Z) diene instead of the (E,E) diene in triene 2.63.
Figure 2.23 Comparison of adducts resulting from cyclisation of trienes 2.63 and 2.130.

There are very few examples of intramolecular Diels-Alder reactions published in the literature involving the cyclisation of a diene with a terminal Z olefin. Heckrodt and Mulzer purported that their cyclisation of 2.133 to produce adduct 2.134 was the first such example.\textsuperscript{61} To the best of the author’s knowledge, no examples are reported with longer side-chains on the terminal Z olefin.

Scheme 2.26 Heckrodt and Mulzer’s reported cyclisation of a diene containing a terminal Z olefin.

It was felt that pursuing the synthesis of the triene containing the \((E,Z)\) diene would not be the best approach towards a synthesis of the bicyclic core as it would require the successful IMDA cyclisation of triene 2.130 as well as the subsequent addition-elimination chemistry to then succeed. With promising results from concurrent work on an alternative strategy to the bicyclic core, the IMDA-addition/double elimination approach was abandoned.


2.7 **Summary**

A synthesis of the model IMDA triene system 2.63 was developed, which involved a key Julia olefination reaction for the formation of the diene portion. The olefination reaction showed varied selectivity for the \((E,E)\) and \((Z,E)\) dienes based on the nature of the sulfone and aldehyde coupling partners.

With the successful preparation of the triene system the IMDA reaction was investigated under thermal cyclisation conditions. The cyclisation was observed to proceed with high *endo* selectivity and with moderate \(\pi\)-facial selectivity to provide two products 2.64 and 2.66.

Addition chemistry allowed the successful preparation of epoxides 2.128a and 2.128b and dibromide 2.129. However, attempts at elimination chemistry failed to provide any diene from treatment of the epoxides with tetramethyldiamidophosphoric acid chloride, or from treatment of dibromide 2.129 with DBU, TBAF or potassium tert-butoxide.

It is anticipated that this strategy could be successful if an IMDA adduct with an *anti* relationship between both bromo substituents and their adjacent hydrogens could be generated. However, this requires a successful IMDA cyclisation with a terminal Z olefin as part of the diene system. With promising results obtained using an alternative IMDA process, it was decided to discontinue work in this area.
2.8 References for Chapter Two


Chapter Two – IMDA synthesis of the bicyclic core


Chapter Three

A New Approach to the Synthesis of the Bicyclic Core
3.1 Introduction

The lack of success in converting the model intramolecular Diels-Alder reaction product into the diene system required for the synthesis of the bicyclic core of the natural products TEO3.1, hamigerone and embellistatin (Chapter Two) meant that an alternative route to these compounds had to be developed. It was proposed that the best approach would be to investigate methods for the direct synthesis of the diene moiety without the subsequent addition-elimination manipulations that were required for the original IMDA approach. Examination of the literature found some examples where the [4 + 2] cycloaddition reaction between a 2-pyrone tethered to a dienophile, followed by extrusion of carbon dioxide, had been applied to the synthesis of cyclohexadiene type compounds (vide infra). It was proposed that this so called “diene-regenerative” Diels-Alder reaction could be utilised as the key step in the formation of the bicyclic core as a means for the direct installation of the desired diene moiety. Chapter Three will investigate whether the approach is applicable to the synthesis of the bicyclic core of TEO3.1, hamigerone and embellistatin.

IMDA route (Chapter Two):

Diene-Regenerative Diels-Alder strategy:

Figure 3.1 An alternative approach to the synthesis of the bicyclic core.
3.1.1 [4 + 2] Cycloaddition Reactions of 2-Pyrones

In 1931, three years after they first reported the [4 + 2] cycloaddition reaction between dienes and dienophiles, Diels and Alder reported the use of 2-pyrones as the diene component of the reaction.\(^1\) The use of 2-pyrones as dienes has augmented the considerable synthetic utility of the Diels-Alder reaction and has been the subject of several reviews.\(^2\) Most applications of 2-pyrones as dienes occur in the preparation of aromatised fused systems using either alkynes, or an olefin appropriately substituted with a group that can be easily eliminated, as the dienophile. Cycloaddition with an alkyne initially generates the highly strained intermediate 3.4 that readily undergoes extrusion of carbon dioxide to form aromatic products (3.5). Cycloaddition with an alkene leads to the more stable and sometimes isolable intermediate 3.6. Extrusion of carbon dioxide regenerates a diene moiety in the form of a dihydrobenzene (3.7). Commonly, aromatic products are then formed via the loss of HX (3.8). However, formation of a dihydrobenzene adduct provides an attractive method for the construction of the bicyclic core.

\[
\text{Scheme 3.1} \quad \text{Diels-Alder reactions of 2-pyrones.}
\]

Cycloadditions of this type have been widely utilised for the preparation of many interesting natural products and biologically important compounds. The majority of examples involve the formation of aromatic products, such as the syntheses of pachybasin, helminthosporin and chrysophanol.\(^3\) Rapid entry to these natural products was achieved through reaction of 6-methoxy-4-methyl-2\(H\)-pyran-2-one (3.9) with dienophilic quinones (3.10) (Figure 3.2-A). Aromatic products have also been prepared exploiting microwave activation, rather than conventional thermal conditions. For example, Loupy and co-workers performed cycloadditions of 3-carbomethoxy-2-pyrene (3.11) with acetylenic dienophiles comparing conventional heating
in solvents and solvent-free microwave assisted conditions. Summarised in Figure 3.2-B, they showed that shorter reaction times, improved yield and varied selectivity could be achieved with microwave assisted reactions.\(^4\)

\[
\text{(A)}
\]

\[
\begin{align*}
\text{3.9} & \quad \text{3.10} \\
+ & \quad \text{1. heat} \\
& \quad \text{2. Ag}_2\text{O, MgSO}_4 \\
& \quad \text{3. HBr, HOAc} \\
\end{align*}
\]

\text{pachybasin} \ (R^1 = R^2 = H) \\
\text{helminthosporin} \ (R^1 = R^2 = \text{OH}) \\
\text{chryosophanol} \ (R^1 = H, R^2 = \text{OH})

\[
\text{(B)}
\]

\[
\begin{align*}
\text{3.11} & \quad \text{R} \\
+ & \quad \text{3.12} \\
& \quad \text{3.13} \\
\end{align*}
\]

\[
\begin{array}{|c|c|c|c|c|c|}
\hline
R & Activation & Medium & Temp (°C) & Time (h) & Yield & 3.12:3.13 ratio \\
\hline
\text{CO}_2\text{Et} & \text{heat} & \text{xylenes} & 140 & 30 & 50 & 20:80 \\
& \text{microwave} & \text{xylenes (3 mL)} & 120 & 2 & 7 & 28:72 \\
& \text{heat} & \text{no solvent} & 120 & 24 & 19 & 42:58 \\
& \text{microwave} & \text{no solvent} & 120 & 2 & 80 & 31:69 \\
\text{Ph} & \text{heat} & \text{toluene} & 250 & 24 & 60 & 65:35 \\
& \text{heat} & \text{no solvent} & 150 & 3 & 19 & 100:0 \\
& \text{heat} & \text{no solvent} & 150 & 24 & 44 & 100:0 \\
& \text{microwave} & \text{no solvent} & 150 & 3 & 64 & 100:0 \\
\hline
\end{array}
\]

Figure 3.2 Examples of the use of 2-pyrones as dienes in the Diels-Alder reaction.

A more recent example utilising the [4 + 2] cycloaddition of an alkyne and a 2-pyrene can be seen in the total synthesis of (\(\pm\))-haouamine by Baran and Burns.\(^5\) One major challenge in the synthesis of the target molecule is the generation of the bent aromatic ring. The researchers proposed that forming a non-aromatic conformational mimic of the bent aromatic ring that could undergo subsequent aromatisation could provide a solution. The proposed pyrone-alkyne Diels-Alder reaction would lead to a cyclohexadiene in a boat configuration which would aromatise on loss of carbon dioxide. To this end, the Diels-Alder substrate 3.16 was prepared in seven steps from readily available starting materials 3.14 and 3.15. After extensive experimentation 3.16 was converted into (\(\pm\))-haouamine upon microwave irradiation in dichlorobenzene at 250°C for ten hours, followed by acetate hydrolysis with potassium carbonate. This macrocyclisation proceeded...
with high atropselectivity (10:1, separable by HPLC) and provided 21% yield of synthetic (±)-haouamine along with 30% recovered 3.16.

![Scheme 3.2](image)

Scheme 3.2 Synthesis of (±)-haouamine A reported by Baran and Burns.

There have also been numerous examples where isolable bicyclocadducts have been used as a rich source of highly-functionalised building blocks. This involves careful planning to achieve cycloadditions at low temperatures to avoid extrusion of carbon dioxide. One solution is to utilise geometrically constrained, highly reactive 2-pyrone or dienophiles. Substitution of the pyrone ring with electron withdrawing groups and the dienophile with electron donating groups or *vice versa*, or employing high pressure conditions can be also be used to achieve this. During their synthesis of epipodophyllotoxin Jones and Thompson utilised the reaction between 3.17 and dimethyl fumarate (3.18) in acetonitrile at 50°C to give a 5:1 mixture of the *exo* and *endo* cycloadducts 3.19 and 3.20. The *endo* adduct 3.20, isolated in 76% yield, could be elaborated in four steps to epipodophyllotoxin (Scheme 3.3).
Scheme 3.3 An example of the isolation of bicycloadducts in the synthesis of epipodophyllotoxin.

In a significantly fewer number of cases, the reaction has been utilised to form a dihydrobenzene, that is, to ‘regenerate’ the diene moiety, as is required for this synthesis. In 1985 Noguchi and co-workers reported the intramolecular \([4 + 2]\) cycloaddition of the 6-substituted pyrone 3.21 in toluene at 150°C.\(^7\) At this temperature, the initially formed cycloadduct readily underwent extrusion of carbon dioxide to provide 1,3-cyclohexadiene derivatives as products. These intramolecular reactions were shown to proceed in good yield (66-72%) with retention of stereochemistry of the dienophile moiety. The products were immediately reacted via an intermolecular Diels-Alder reaction with selected dienophiles (Figure 3.3-A) as they were found to be unstable. On standing at room temperature for three weeks both dimerisation and aromatisation products were detected. In addition, they have also reported a similar reaction between 2-pyrone-6-carboxamides (3.25) and tethered dienophiles of varying chain lengths. They observed similar results forming 6-5, 6-6 and 6-7 fused ring systems with the reaction temperature required to promote cyclisation increasing with increasing ring size (B).\(^8\)
Martin and co-workers employed a similar strategy towards the synthesis of the indole alkaloids (±)-reserpine and (±)-α-yohimbine. The 6-substituted pyrone 3.29 underwent an intramolecular [4 + 2] cycloaddition reaction heating in xylenes under reflux, followed by extrusion of carbon dioxide, to afford the cyclohexadiene product 3.30. This key intermediate could be elaborated, via a series of functional group manipulations, to provide both alkaloids.
Yamaguchi and co-workers utilised a more complex 6-substituted 2-pyrone when tackling the synthesis of various alkaloid systems.\(^\text{10}\) A three component coupling reaction between 3.31, 3.32 and allyltributyltin in the presence of molecular sieves gave the Diels-Alder substrate 3.33 in 90-97% isolated yield. An intramolecular Diels-Alder reaction and subsequent extrusion of carbon dioxide was achieved by heating in toluene under reflux. This afforded the tetracyclic system 3.34 which could be elaborated to various alkaloid compounds. Following the same sequence using 3.35 in the coupling reaction in place of 3.31 provided access to the pentacyclic scaffold 3.37.
Scheme 3.5  Alkaloid scaffold synthesis.

An application of this methodology, using an intermolecular reaction, can be seen in the synthesis of (±)-10-epijuneol.\textsuperscript{11} Reaction of 3-carbomethoxy-2-pyrone (3.11) with α-terpinene, followed by carbon dioxide extrusion, provided the bicycle 3.40 in 64% yield. This was elaborated through a series of steps to provide the desired metabolite.

Scheme 3.6  The synthesis of (±)-10-epijuneol by Hatsui and co-workers.

### 3.2 Diene-Regenerative Diels-Alder Strategy

Given the lack of success in converting the IMDA product 2.64 into the required diene moiety, the proposed diene-regenerative Diels-Alder reaction, which would install the diene without the need for further manipulation, provides an attractive alternative route to the key bicyclic target. To utilise this key reaction, a 2-pyrone substrate with a tether connecting the dienophile had to be prepared. [4 + 2] cycloaddition of the dienophile to the pyrone diene, followed by extrusion of
carbon dioxide should install the desired diene moiety. Control of the stereochemistry of the dienophile, following the precedent of Noguchi and co-workers,\(^7\) should establish the required syn relationship between the bridgehead proton and the C-1 ester functionality following cyclisation and extrusion of carbon dioxide. Thus, the preparation of a 2-pyrone substituted at the 6-position with a chain containing the E-dienophile (3.41) would be required. The tether between the pyrone and the dienophile would incorporate the two methyl groups with the stereochemistry required for the natural products as well as the oxygenation at C-7. It was envisaged that the side-chain at the C-2 position of pyrone 3.41 could be introduced via reaction of brominated pyrone 3.43 with methoxy allyl bromide based upon known copper-mediated chemistry (Scheme 3.7 – Route A).\(^{12}\) Alternatively, following cyclisation of the brominated pyrone 3.43 to cyclohexadiene 3.42, halogen-lithium exchange, followed by reaction with methoxy allyl bromide could be investigated as a means for introducing the side-chain (Route B). It is anticipated that the bromo functionality could be introduced via an electrophilic substitution to the key intermediate 3.44.
Scheme 3.7  Proposed routes to the bicyclic core.

As a preliminary investigation to ascertain whether the diene-regenerative cyclisation reaction would be successful and also to investigate methods for the efficient preparation of the pyrone substrate (3.44) the synthesis of a simpler system (3.56a) was undertaken. This system lacks the functionality in the A ring, and the side-chain at C-2. It was proposed that both the brominated and the non-brominated bicycles, 3.55b and 3.55a, could be prepared from pyrone 3.56a.
Scheme 3.8  Retrosynthesis of bicycles 3.55a and 3.55b.

3.3 Methods for the Preparation of 2-Pyrroles

To prepare the required pyrone substrate 3.56a the challenge lies not only in the construction of the pyrone ring itself but also in the placement of substituents at the correct positions on the ring. Whilst there are a variety of methods available to prepare 2-pyrroles, the choice is limited by the ease of construction of the required precursors. Some general methods will be briefly discussed followed by an in-depth discussion of two methods: the tandem Stille reaction/heterocyclisation and the intramolecular addition of carboxylic acids to alkynes.

3.3.1 General Methods

A review by Afarinkia and Vinader in 2003 details numerous methods for the synthesis of 2-pyrroles. Of particular interest for this thesis are methods involving the formation of one, two or three new bonds to generate 2-pyrroles from acyclic precursors. An example of the formation of three bonds is the reaction between two equivalents of an alkyne and carbon dioxide (Figure 3.4-A). The pyrone is assembled by forming one new carbon-oxygen bond and two new carbon-carbon bonds in the presence of a nickel catalyst. 2-Pyrroles can also be assembled by formation of two new bonds, either one carbon-oxygen and one carbon-carbon as illustrated by the addition of enolates to propynoates (B), or two carbon-carbon bonds via a [4 + 2] cycloaddition reaction (C). The assembly of 2-pyrroles by the formation of one new carbon-carbon bond can be
achieved through a Horner-Wittig reaction (D).\textsuperscript{17} Section 3.3.3 will address the preparation of 2-pyrones via the formation of one carbon-oxygen bond. Other methods for the synthesis of 2-pyrones include ring transformations, aromatisation reactions and substituent modification reactions.\textsuperscript{13}

(A) \textit{Formation of three bonds}

\begin{equation}
\text{TMS} \equiv \equiv \text{OEt} \xrightarrow{\text{Ni(cod)}_2, \text{dppb}, \text{CO}_2} 80\% \xrightarrow{\rho-\text{TsOH}} 90\% \text{EtO}
\end{equation}

(B) \textit{Formation of two bonds: one C-O and one C-C}

\begin{equation}
\text{MeO}_2\text{C} \equiv \text{CH}_2\text{OBz} + \text{CO}_2\text{Me} \xrightarrow{52\%} \text{MeO}_2\text{C} \equiv \text{CH}_2\text{OBz}
\end{equation}

(C) \textit{Formation of two C-C bonds}

\begin{equation}
\text{Cl} \xrightarrow{\text{rt}} 75\% \xrightarrow{75\%} \text{MeO}_2\text{C} \equiv \text{N}\text{Et}_2
\end{equation}

(D) \textit{Formation of one new C-C bond}

\begin{equation}
\text{Et} \xrightarrow{73\%} \text{NaH, DME, rt} \text{Et}
\end{equation}

\textbf{Figure 3.4} Methods for the formation of 2-pyrones from acyclic precursors.

3.3.2 \textbf{Tandem Stille Reaction/Heterocyclisation}

In 2005 Cherry and co-workers reported the formation of 2-pyrones and 3-substituted isocoumarins through reaction of \textit{Z}-vinylic iodides or 2-iodobenzoic acids with allenyltributyltin reagents in the presence of palladium acetate, triphenylphosphine and tetrabutylammonium bromide.\textsuperscript{18} Various substrates were investigated with a selection outlined in the table below.
Chapter Three – A New Approach to the Synthesis of the Bicyclic Core

The authors proposed a mechanism for the reaction based upon their experimental observations and what is known about palladium chemistry. The mechanism is applicable to both the 2-pyrone and isocoumarin synthesis but is shown only for the 2-pyrone case. The first step involves the reduction of palladium acetate to palladium(0), the actual catalyst for the reaction. Oxidative addition of palladium(0) to the vinylic iodide, followed by transmetallation and reductive elimination provides the Stille reaction adduct. Complexation with palladium activates the allene to nucleophilic 6-exo-dig attack by the carboxylate functional group. The cycle is then completed by protonolysis to afford the desired pyrone product.

Selected examples of substituted pyrones:

<table>
<thead>
<tr>
<th>Iodide</th>
<th>Allenylstannane</th>
<th>2-pyrone</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Iodide" /></td>
<td><img src="image2" alt="Allenylstannane" /></td>
<td><img src="image3" alt="2-pyrone" /> (83%)</td>
</tr>
<tr>
<td><img src="image4" alt="Iodide" /></td>
<td><img src="image5" alt="Allenylstannane" /></td>
<td><img src="image6" alt="2-pyrone" /> (85%)</td>
</tr>
<tr>
<td><img src="image7" alt="Iodide" /></td>
<td><img src="image8" alt="Allenylstannane" /></td>
<td><img src="image9" alt="2-pyrone" /> (84%)</td>
</tr>
<tr>
<td><img src="image10" alt="Iodide" /></td>
<td><img src="image11" alt="Allenylstannane" /></td>
<td><img src="image12" alt="2-pyrone" /> (82%)</td>
</tr>
</tbody>
</table>

Figure 3.5   Tandem Stille reaction/heterocyclisation.
Figure 3.6  Proposed mechanism of the tandem Stille reaction/heterocyclisation.

To utilise this chemistry for the synthesis of the desired substrate 3.56a, would require preparation of allenyltributyltin adduct 3.58.

Scheme 3.9  Retrosynthetic analysis of 3.56a.

A general method for the preparation of allenylstannanes is shown in Figure 3.7-A. Mesylation of a propargyl alcohol, followed by \textit{anti}-S_N2’ displacement with the cuprate formed from equimolar quantities of Bu$_3$SnLi and CuBr.SMe$_2$ provides the desired allenylstannane moiety. Mukai and Takahashi have prepared a number of allenylstannanes \textit{via} this method (B)$^{19}$ as have others.$^{20,21}$ In terms of this synthesis, the allenyltributyltin compound 3.58 could be prepared
from 1-heptyne-3,7-diol (3.61) which is accessible in two steps from commercially available δ-valerolactone (3.60) via the method of Marshall and co-workers\(^{22}\). Allenylstannane 3.58 would be generated by protection of the primary alcohol of 3.61, followed by mesylation of the secondary alcohol and then reaction of 3.63 with Bu₃SnLi and CuBr.SMe₂ (C).

**Figure 3.7** Formation of allenylstannanes.

### 3.3.3 Intramolecular Addition of Carboxylic Acids to Alkynes

Over the past decade there have been numerous methods reported for the synthesis of 2-pyrones utilising halolactonisation\(^{23}\) or transition metals (Ag, Hg, Pd) to promote the intramolecular addition of carboxylic acids to alkynes\(^{24}\). In many cases, these reactions have suffered from poor regioselectivity, with mixtures of 2-pyrones and 5-alkylidenefuranones being obtained (Figure 3.8-A). This problem of regioselectivity has been addressed by Larock and co-workers in 1999 and more recently by Negishi and co-workers in 2002. Larock demonstrated that both substituted isocoumarins and 2-pyrones could be prepared by treating \(\beta\)-halo-\(\alpha,\beta\)-unsaturated esters with
internal alkynes in the presence of a palladium catalyst. However in some cases, when non-symmetrical alkynes were employed, two pyrone regioisomers were obtained ($B$).\textsuperscript{25}

\begin{equation}
(A)
\end{equation}

Negish and co-workers have reported the catalytic and selective conversion of ($Z$)-2-en-4-ynoic acids into 2-pyrone when zinc bromide was used or ($Z$)-5-alkylidene furanones when the reaction was carried out in the presence of silver carbonate. This presented a new development in this type of cyclisation as it is the first example of a catalyst being use to convert ($Z$)-2-en-4-ynoic acids into 2-pyrone as the major product in high yields. Previous reports of catalysis have utilised a variety of silver salts (AgClO$_4$, AgNO$_3$, AgOTf, Ag$_2$CO$_3$) which led to the formation of 2-pyrone, but only as a minor component to ($Z$)-5-alkylidene furanones.\textsuperscript{26} Some examples of the substrates employed are shown in Figure 3.9.\textsuperscript{27}
Chapter Three – A New Approach to the Synthesis of the Bicyclic Core

CO₂H

R

ZnBr₂ (5-10 mol%)  
THF, 23°C

Ag₂CO₃ (5 mol%)  
DMF, 23°C

Examples:

R

CO₂H

∑

O

O

R

O

R

R

3.64

3.65

<table>
<thead>
<tr>
<th>R</th>
<th>Ratio of 3.64:3.65 with ZnBr₂</th>
<th>Ratio of 3.64:3.65 with Ag₂CO₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-Hex</td>
<td>94.6 (95%)</td>
<td>4.96 (96%)</td>
</tr>
<tr>
<td>i-Pr</td>
<td>96.4 (98%)</td>
<td>5.95 (99%)</td>
</tr>
<tr>
<td>Cyclohexyl</td>
<td>96.4 (92%)</td>
<td>3:97 (95%)</td>
</tr>
<tr>
<td>t-Bu</td>
<td>66:34 (93%)</td>
<td>2:98 (95%)</td>
</tr>
<tr>
<td>Ph</td>
<td>50:50 (94%)</td>
<td>2:98 (94%)</td>
</tr>
</tbody>
</table>

Figure 3.9  Formation of 2-pyrone with ZnBr₂ or (Z)-5-alkylidene-furanones (3.65) with Ag₂CO₃ as reported by Negishi and co-workers.

The researchers speculated that polarisation of the unsaturated bonds in (Z)-2-en-4-ynoic acids would favor the formation of 2-pyrone via a Lewis acid-catalysed polar process, whereas transition metal-catalysed processes would favor the formation of (Z)-5-alkylidene-furanones via a 5-exo cyclisation.

Scheme 3.10 Proposed mechanism for the formation of 2-pyrone and (Z)-5-alkylidene-furanones.
To generate the desired pyrone 3.56a utilising this strategy, the synthesis of (Z)-2-en-4-ynoic acid 3.66 or 3.67 is required. It was proposed that this class of compound could be generated through a coupling reaction between alkyne 3.68 or 3.69 and iodide 3.70, followed by ester hydrolysis.

Scheme 3.11 Retrosynthesis of pyrone 3.56a.

3.3.4 Comparison/Summary

Two methods have been outlined for the formation of the desired pyrone moiety; the tandem Stille reaction/heterocyclisation and the zinc bromide-catalysed intramolecular addition of carboxylic acids to alkynes. When weighing the merits of each method it was essential to consider the ease of construction of the precursors for the model system in addition to those required for the synthesis of the bicyclic system of the natural product. In the first instance, the allenylstannane precursor 3.58 could be relatively easily prepared from 3.61, a readily accessible substrate. The required iodide is also easily prepared. However, if this method was to be utilised in the synthesis of the natural product the tetrasubstituted 6-heptyn-1-ol 3.71, analogous to 3.61, would have to be prepared. The application of this methodology would rely upon the successful manipulation of alkyne 3.71 into the corresponding allenyl stannane 3.72. In contrast, applying a zinc bromide-catalysed cyclisation to prepare the model system would necessitate the preparation of the (Z)-2-en-4-ynoic acid precursor 3.66 or 3.67. These could be constructed through coupling of the readily accessible iodide 3.70 with alkynes 3.68 or 3.69, followed by ester hydrolysis. Alkynes 3.68 and 3.69 should be readily prepared via straightforward routes. Applying this method to the synthesis of the model system would require preparation of the trisubstituted 6-heptyn-1-ol 3.73 as the main precursor to the (Z)-2-en-4-ynoic acid 3.74. After surveying both methods, it was decided to focus attentions towards pyrone formation via the zinc bromide-catalysed cyclisation due to two considerations. Firstly, the formation of allenylstannanes and their subsequent conversion to 2-pyr ones has, at present, been restricted to relatively simple aliphatic model systems. In contrast, the Sonogashira chemistry required for the coupling of the
terminal alkyne and vinyl iodide as utilised in the zinc bromide-catalysed cyclisation route has been extensively explored.\textsuperscript{28} Secondly, performing the cyclisation with a catalytic amount of zinc bromide is advantageous as it removes the need to separate by-products associated with Stille stannane chemistry. This would make the strategy more amenable to the large-scale synthesis required for the development of the natural products as drug targets.
Figure 3.10  Comparison of the methods for pyrone formation.
3.4 Synthesis of the Pyrone System

3.4.1 Preparation of Substrates for the Coupling Reaction

To form the required (Z)-2-en-4-ynoic acids 3.66 or 3.67, we need to prepare alkynes 3.77, 3.69 and 3.82 so that they can be coupled with iodide 3.70 (Scheme 3.12-A). Accordingly, treatment of 5-hexyn-1-ol with 4-toluenesulfonyl chloride in pyridine at 0°C afforded tosylate 3.76. Reaction of 3.76 with sodium cyanide in dimethylsulfoxide at 90°C provided the desired nitrile 3.78, which was reduced to the corresponding aldehyde 3.79 through dropwise addition of diisobutylaluminium hydride at -78°C. Wittig elongation with phosphorane 3.80 or 3.81 provided alkynes 3.82 and 3.69 in 67% and 54% yields respectively. The silyl-protected alkyne 3.77 was prepared by reaction of 5-hexyn-1-ol with tert-butyldimethylsilyl chloride.

Iodides 3.70 and 3.83 were both prepared from ethyl 2-butynoate, which can be prepared in four steps from commercially available ethyl bromoacetate via the method of Boers and co-workers. Iodide 3.70 is prepared by reaction with sodium iodide in glacial acetic acid at 70°C. Reaction of ethyl 2-butynoate with iodine and catalytic copper(I) iodide in acetonitrile furnished diiodide 3.83 (B).  

Scheme 3.12  Reagents and yields: (i) p-TsCl, pyridine, 0°C to 4°C, 65%; (ii) TBSCl, imidazole, DMF, rt, 84%; (iii) NaCN, DMSO, 70°C, 2h, 85%; (iv) DIBAL-H, Et₂O, addition over 2h at -78°C, 93%; (v) t-BuO₂CCH=PPh₃ (3.80) or EtO₂CCH=PPh₃ (3.81), toluene, reflux, 3.82-67%, 3.69-54%; (vi) NaI, HOAc, 70°C, 84%; (vii) I₂, Cul, MeCN, reflux, 88%. 
3.4.2 Copper-Catalysed Coupling Reactions

In recent years there has been significant interest in developing copper-catalysed cross-coupling reactions.\textsuperscript{32,33} Utilising copper in place of traditional metals such as palladium provides an economic attraction for large scale synthesis as it removes the need for additional, often expensive ligands. Copper catalysts may also alleviate problems associated with catalyst sensitivity to exogenous oxygen and moisture and improve functional group tolerance. In 2001 Venkataraman and co-workers reported mild synthetic protocols for the formation of aryl-carbon, aryl-nitrogen and aryl-oxygen bonds based on the soluble, well-defined copper catalysts 3.84 and 3.85 (Figure 3.11).\textsuperscript{32i}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{copper-catalysts.png}
\caption{Structures of copper catalysts reported by Venkataraman and co-workers.}
\end{figure}

These catalysts are easily prepared and stable to both air and moisture. Further work from this group has lead to the publication of additional catalysts (3.86 and 3.87) as well as extending the scope of these reactions to include the formation of 1,3-enynes,\textsuperscript{32c} aryl-sulfur bonds\textsuperscript{32g} and diaryl-selenides.\textsuperscript{32c} Selected examples of their work are detailed in Figure 3.12.
Chapter Three – A New Approach to the Synthesis of the Bicyclic Core

Aryl-nitrogen bond forming:

\[
\text{Ph-N} + \text{Ph-X} \xrightarrow{3.85 (10 \text{ mol\%})} \text{Ph-NPh} \\
\text{KOT-Bu, toluene, 110°C} \\
X = \text{I, 6h, 78\%} \\
X = \text{Br, 36h, 73\%} \\
X = \text{Cl, 36h, 49\%}
\]

Aryl-oxygen bond forming:

\[
\text{Ph-CH} + \text{Br-Ph} \xrightarrow{3.85 (10 \text{ mol\%})} \text{Ph-CHPh} \\
\text{Cs_2CO_3, toluene, 110°C} \\
36h, 99\%
\]

Aryl-carbon bond forming:

\[
\text{Ph} + \text{I-Ph} \xrightarrow{3.84 (10 \text{ mol\%})} \text{Ph-Ph} \\
\text{K_2CO_3, toluene, 110°C} \\
24h, 74\%
\]

Formation of 1,3 enynes:

\[
\text{Ph-CH} + \text{Ph-CO_2Et} \xrightarrow{\text{Cu cat. (10 mol\%)}} \text{Ph-CHCO_2Et} \\
\text{Cs_2CO_3, toluene, 110°C} \\
24h, 76\% \\
3.86 \\
3.87 \\
3.84 \\
3.85 \\
74\%
\]

Aryl-sulfur bond forming:

\[
\text{Ph-I} + \text{HS-Ph} \xrightarrow{\text{Cul (10 mol\%)}} \text{Ph-S-Ph} \\
\text{NaOT-Bu, toluene, 110°C, 94\%}
\]

Formation of diaryl selenides

\[
\text{Ph-I} + \text{HSe-Ph} \xrightarrow{\text{Cul (10 mol\%)}} \text{Ph-Se-Ph} \\
\text{K_2CO_3, toluene, 110°C, 84\%}
\]

Figure 3.12  Examples of the use of catalysts 3.84-3.87 for coupling reactions reported by Venkataraman and co-workers.

The research group of Buchwald has also published a significant body of work, 47 journal articles to date, on various copper-catalysed reactions including the coupling of aryl halides with phenols, alkylamines, aliphatic alcohols, thiols, primary alkylamines, secondary phosphines and phosphites and amides and carbamates. 34 These reactions generally involve copper(I) iodide and
various co-ligands as catalysts, in the presence of a base at elevated temperatures. The scope has also been extended to include reactions at room temperature\textsuperscript{35} and coupling to haloimidazopyridines.\textsuperscript{36}

\textbf{Aryl-oxygen bond forming:}

\[
\begin{align*}
\text{MeO} & \quad + \quad \text{HO} \quad \text{MeO} \\
\text{I} & \quad \text{CuI (10 mol\%)} \\
\text{toluene, 110°C, 86\%}
\end{align*}
\]

\textbf{Aryl-nitrogen bond forming:}

\[
\begin{align*}
\text{MeO} & \quad + \quad \text{H}_2\text{NBn} \\
\text{I} & \quad \text{CuI (5 mol\%)} \\
\text{Cs}_2\text{CO}_3 & \quad \text{toluene, 110°C, 86\%}
\end{align*}
\]

\textbf{Aryl-sulfur bond forming:}

\[
\begin{align*}
\text{I} & \quad + \quad \text{HS} \quad \text{S} \\
\text{CuI (5 mol\%)} & \quad \text{toluene, 80°C, 91\%}
\end{align*}
\]

\textbf{Aryl-phosphorus bond forming:}

\[
\begin{align*}
\text{I} & \quad + \quad \text{O} \quad \text{P} \\
\text{OMe} & \quad \text{CuI (5 mol\%)} \\
\text{toluene, 110°C, 85\%}
\end{align*}
\]

\textbf{Ligands:}

\[
\begin{align*}
\text{3.88} & \quad \text{3.89} & \quad \text{3.90}
\end{align*}
\]

\textbf{Figure 3.13} Examples of copper-catalysed reactions from Buchwald’s group.

Three of the catalysts reported by Venkataraman were chosen for initial study \([\text{Cu(phen)(PPh}_3]\text{Br}) (3.84), [\text{Cu(phen)(PPh}_3]_2\text{NO}_3 (3.86)\text{ and [Cu(bipy)(PPh}_3]\text{Br}) (3.87).\text{ These were readily prepared using the reported methods.}^{32c, f}\text{ The coupling of various alkynes with iodides 3.70 and 3.83 were investigated using either potassium carbonate or cesium carbonate as the base. These results are summarised below.}
Figure 3.14  Results from studies on copper-catalysed coupling of various alkynes with iodides 3.70 and 3.83.

The use of potassium carbonate as a base proved to be disappointing, providing clean conversion but low yields of the desired products. For this system, the [Cu(phen)(PPh₃)Br] catalyst (3.84) gave the best yields. Comparable yields were obtained with the [Cu(bipy)(PPh₃)Br] catalyst (3.87), but removing impurities associated with the catalyst was more challenging. Switching to cesium carbonate produced the desired alkyne products in moderate to good yield depending upon the nature of the R group and the catalyst used. Based on the superior yields, the (Z)-2-en-4-ynoic acids 3.94 and 3.95 were selected for elaboration to the pyrone system. As discussed at the beginning of the chapter, it is anticipated that the C-2 side-chain could be introduced via functionalisation of a C-2 halogen. Thus, it was decided to investigate whether it would be possible to incorporate the halogen prior to formation of the pyrone. However, disappointingly the diiodide 3.83 failed to couple with the alkyne, providing only decomposition of 3.83.
3.4.3 Formation of the Pyrone System Using ZnBr₂
Before cyclisation to the pyrone could be carried out, the C-1 ethyl ester had to be hydrolysed to the carboxylic acid. To this end, substrate 3.94 presented a problem in that the C-11 ethyl ester would also be hydrolysed. As it has been reported that methyl esters can be selectively cleaved in the presence of ethyl esters by treatment with sodium cyanide in hexamethylphosphoramide (HMPA) at 75°C, compound 3.97 was prepared from alkyne 3.69 and iodide 3.96, which was prepared analogously to 3.70 from methyl-2-butynoate. However, treatment of 3.97 under the reported conditions failed to yield any of the desired carboxylic acid 3.67. Only decomposition of the starting material was observed. Stirring with 1M aqueous sodium hydroxide solution in 1:1 methanol/THF provided diacid 3.98 as a white solid in 89% yield.

Scheme 3.13  Reagents and yields: (i) [Cu(phen)(PPh₃)Br], Cs₂CO₃, toluene, 110°C, 57%; (ii) NaCN, HMPA, 75°C; (iii) 1M NaOH, 1:1 THF/MeOH, rt, 89%.

Hydrolysis of 3.95 was achieved cleanly with 1M aqueous lithium hydroxide solution in 1:1 methanol/THF to provide 3.99 in 51% yield.

Scheme 3.14  Reagents and yields: (i) 1M LiOH, 1:1 THF/MeOH, rt, 51%.

The (Z)-2-en-4-ynoic acids 3.98 and 3.99 were treated with a 20 mol% solution of zinc bromide in THF at room temperature. The cyclisations proceeded slowly and were best monitored by
removing a small sample for analysis by $^1$H NMR spectroscopy. While the cyclisation of diacid 3.98 led to a mixture of products, the major product 3.100 was isolated in 54% yield after a reaction time of 72 hours. Pleasingly, the ester substrate 3.99 cyclised cleanly affording the desired pyrone adduct 3.101 in 77% yield following purification.

Scheme 3.15  Reagents: (i) ZnBr$_2$ (20 mol%), THF, rt, 72h, 3.100 54%, 3.101 77%.

### 3.5 Electrophilic Substitution of Pyrone 3.101

With a model pyrone system in hand attentions were focused on an electrophilic substitution reaction to install the bromine at C-3. It is known that 2-pyrones are isoelectronic with phenoxide and thus, readily undergo electrophilic substitution at C-3 and C-5 (analogous to the 2- and 4-substituted products from phenol), a property bought about by the resonance contributors shown in Figure 3.15.

![Resonance contributors to 2-pyrone (A) and phenoxide (B).](image)

Some examples of the conditions used for electrophilic substitution of 2-pyrones and isocoumarins with Br$^+$ are shown in Figure 3.16. Bromination of 2-pyrone at C-3 was achieved in 57% yield by heating with bromine in carbon tetrachloride under reflux.$^{12}$ Isocoumarin 3.102 was brominated efficiently with bromine in glacial acetic acid at 60°C.$^{39}$ N-Bromosuccinimide has also been utilised as the source of Br$^+$ for this substitution either alone, in the case of isocoumarins 3.104$^{40}$ and 3.106,$^{41}$ or in the presence of a base (3.108).$^{42}$
Due to the presence of the alkene in the side-chain of pyrone 3.101 it was reasoned that heating with bromine under reflux could present problems not only with bromination of the alkene but also with a heat-promoted Diels-Alder cyclisation. Based on the successful bromination of 3.104 with \(N\)-bromosuccinimide, leaving the terminal alkene intact, 3.101 was treated with \(N\)-bromosuccinimide, adding one equivalent initially. After 48 hours starting material remained so an additional 0.5 equivalents was added. This was repeated again at 96 hours. After an additional 24 hours the desired brominated pyrone 3.110 was isolated in 75% yield with no bromination of the alkene observed.

Scheme 3.16  Reagents and yields: (i) \(N\)-bromosuccinimide, THF, rt, 4 days, 75%.
3.6 Diene-Regenerative Diels-Alder Reaction

With the successful preparation of pyrones 3.101 and 3.110 complete, attention was turned to investigating the crucial diene-regenerative cyclisation reaction. Following the conditions of Noguchi and co-workers, pyrone 3.101 was heated in a sealed tube in toluene at 150°C. After 48 hours, complete consumption of the starting material was achieved and 1H NMR spectroscopic analysis of the crude material showed the presence of one major and two minor components. Unfortunately, these were inseparable by column chromatography. In an attempt to alleviate this problem, alternative conditions were considered. To avoid the need for a sealed tube reaction, 3.101 was heated in xylenes under reflux and a similar mixture of products to that observed in the sealed tube was obtained. Carrying out the reaction in the presence of a radical inhibitor, butylated hydroxytoluene did not change the product distribution. However, gratifyingly, carrying out the reaction in the presence of Proton-Sponge® resulted in clean conversion to a single product. The 1H NMR spectrum of this compound is shown in Figure 3.17. During the acquisition of a 13C NMR spectrum in CDCl3, the appearance of a number of additional peaks was noted. After a week in CDCl3, complete degradation of the initially formed compound was observed. The 1H NMR spectrum of this product was identical to the major product of the reactions performed in the absence of Proton-Sponge®. The two singlets attributed to the alkenyl protons at C-2 and C-4 have shifted downfield from 5.18 and 5.42 to 5.44 and 5.76 and the distinctive signals for the protons at C-1 and C-8a have completely disappeared. It was proposed that isomerisation of the initially formed Diels-Alder adduct 3.111 into 3.112 was occurring catalysed by residual acid in the CDCl3 that was used as the solvent for NMR spectroscopy. To avoid this issue, CDCl3 doped with 0.1% d5-pyridine was used when acquiring spectra of these compounds.

\[ \text{Scheme 3.17} \quad \text{Reagents and yields: (i) Proton-Sponge® (30 mol%), xylenes, reflux, 48h, 72%; (ii) cat. H}^+ \text{.} \]
Figure 3.17 $^1$H NMR spectra (500 MHz) and $^{13}$C NMR spectra (75 MHz) of the desired Diels-Alder adduct 3.111 and the product derived from acid-catalysed isomerisation.

Full 2-dimensional NMR spectroscopic analysis of the product confirmed the desired dihydrobenzene adduct 3.111 had been formed. Some of the important HMBC correlations that distinguish 3.111 from its isomer 3.112 are shown in Figure 3.18 along with the $^{13}$C chemical shift data assigned for 3.111 from HSQC and HMBC experiments. The relative stereochemistry
at C-1 and C-8a was confirmed through the observation of a pronounced large coupling constant of 13 Hz between protons H-8a and H-1. The Karplus Rules state that diaxial protons will have coupling constants around 10-13 Hz due to their 180° orientation; diequatorial protons or those in an equatorial/axial relationship have coupling constants around 2-5 Hz corresponding to a dihedral angle of approximately 60°. Thus, the coupling constant of 13 Hz is consistent with a diaxial relationship. This confirmed the trans orientation of H-1 and H-8a, and the retention of dienophile stereochemistry, as observed by Noguchi and co-workers.

Figure 3.18  Important HMBC correlations, assigned 13C chemical shift data and key coupling constants for 3.111.

Adduct 3.111 proved to be unstable, which is a property of dihydrobenzenes previously noted by Noguchi. On standing at room temperature, or even storing at cooler temperatures (4°C or 0°C), some aromatisation product 3.113 was detected. This impurity could not be removed by flash column chromatography.

Figure 3.19  1H NMR spectrum (500 MHz) showing observed aromatisation of 3.111 (♦ indicates peaks due to 3.113).
Subjecting the brominated pyrone 3.110 to the conditions optimised for 3.101 (Proton-Sponge® (30 mol%/xylenes) led to clean conversion to the desired dihydrobenzene adduct 3.114. Both the $^1$H NMR and $^{13}$C NMR spectrum bore close resemblance to those obtained for 3.111. Notable differences include the downfield shifts of the signals for H$_1$, from 2.88 ppm in 3.111 to 3.21 ppm in 3.114, and for the methyl substituent (1.70 ppm in 3.111 to 1.85 ppm in 3.114) due to the adjacent bromine substituent.

![Figure 3.20](image)

The brominated dihydrobenzene adduct 3.114 displayed similar acid sensitivity and susceptibility to aromatisation to 3.111. Conservation of the dienophile stereochemistry was again confirmed by the large vicinal coupling constant between H-1 and H-8a; the value of 9.5 Hz being indicative of a *trans* coplanar orientation.
3.7 Summary

Using the strategy outlined in Scheme 3.11 the synthesis of the diene-regenerative Diels-Alder substrate 3.101 was realised using a key copper-catalysed coupling reaction, and the intramolecular addition of a carboxylic acid to an alkyne to form the desired pyrone.

The [4 + 2] cycloaddition reaction followed by extrusion of carbon dioxide was achieved by heating 3.101 in xylenes under reflux, with Proton-Sponge® playing a crucial role in preventing acid-catalysed isomerisation of the desired dihydrobenzene adduct. This pathway successfully installs the diene moiety required for the bicyclic core.

Electrophilic addition of Br⁺ to pyrone 3.101 was carried out, and subsequent cyclisation of this compound provided the brominated dihydrobenzene adduct 3.114. This key substitution provides a means for the introduction of the side-chain at C-2 in the natural product.

The success of this model system indicates that the proposed strategy should be readily adapted to the synthesis of the bicyclic core of the natural products TEO3.1, hamigerone and embellistatin.
3.8 References for Chapter Three


(32) From the Venkataraman group see: (a) Saejueng, P.; Bates, C. G.; Venkataraman, D. Synthesis 2005, 1706-1712; (b) Bates, C. G.; Saejueng, P.; Doherty, M. Q.; Venkataraman, D.


Prepared from methyl bromoacetate as per reference 21.


Chapter Four

Synthesis of the Bicyclic Core of the Natural Products
4.1 Introduction

As has been described in Chapter Three, a successful synthesis of a model system of the bicyclic core of TEO3.1, hamigerone and embellistatin has been developed (Scheme 4.1). Having determined that the diene-regenerative Diels-Alder reaction was applicable to the direct installation of the desired diene moiety, our attention turned to the application of this methodology to the synthesis of the fully functionalised bicyclic core of the natural products.

Scheme 4.1  Summary of the synthesis of the model system.

As indicated in Chapter One, the goal was to prepare the fully functionalised bicyclic compound 1.22, upon which the side-chains could then be appended. Accordingly, the retrosynthetic analysis for the fully functionalised bicyclic core is displayed in Scheme 4.2. It is proposed that the pyrone system 4.2, analogous to that employed successfully in the model system, would undergo [4 + 2] cycloaddition, followed by carbon dioxide extrusion to provide the desired “diene-regenerated” product. The bromo group required to install the C-2 side-chain of the natural products would be introduced by bromination of pyrone 4.4 with N-bromosuccinimide, followed by cyclisation to give 4.1. In addition, the de-bromo derivative 4.3 could be prepared from pyrone 4.4. Installation of the dienophile should be achieved through a Wittig reaction with aldehyde 4.5, prepared from 4.6 via selective deprotection of the primary protecting group and oxidation. Intramolecular addition of the carboxylic acid functionality of 4.7 to the alkyne, catalysed by zinc bromide, should provide access to pyrone 4.6. A copper-catalysed coupling of iodide 3.70 and alkyne 4.8, followed by ester hydrolysis should provide 4.7. The various
synthetic approaches to alkyne 4.8 will be discussed in Section 4.2 (vide infra). This synthetic sequence depicted below differs from that used in the model system as installation of the dienophile to the side-chain is to be carried out following formation of the pyrone. This reduces the complexity of the alkyne substrate 4.8 required for the copper-catalysed coupling reaction.

Scheme 4.2  Retrosynthesis of the bicyclic core 1.22.
One issue arising from this strategy is the facial selectivity of the diene-regenerative Diels-Alder reaction. Introducing stereochemistry into the tether between the pyrone and the dienophile means that two diastereoisomers could result from the cyclisation reaction. As shown in Scheme 4.3, approach of the dienophile to the pyrone as shown in pathway A would generate the desired bicyclic core with all substituents on the same side, as is required for the natural product. In the transition state all of the substituents in the chain would be equatorial. However, if the dienophile added to the pyrone as depicted in pathway B, a diastereomer of the bicyclic core where the substituents of the dienophile are on the opposite face to the methyl groups in the tether would be formed. When the transition state is considered, however, it can be seen that pathway B would be unlikely to occur as all of the substituents would have to occupy axial positions.

Scheme 4.3  Possible products from diene-regenerative Diels-Alder reaction of pyrone 4.4.

4.2  Methods for the Preparation of the Stereotriad

To generate the fully functionalised core, the stereochemistry of the methyl groups in the A ring must be controlled. However, it was felt that it would be better to generate the C-7 ketone at the very end of the synthesis, so as to avoid any chemoselectivity issues. Accordingly, a stereotriad needs to be generated. Adaptation of the sequence developed in Chapter Three to prepare the bicyclic core of the natural product requires access to an alkyne that contains three contiguous stereogenic centres. This can be either the anti, anti stereotriad or the syn, syn stereotriad. It was decided to pursue the anti, anti stereotriad as it would result in a bicyclic adduct where all the substituents are on the same side of the molecule.
Scheme 4.4  Retrosynthesis to the syn, syn or anti, anti stereotriad.

A search of the literature revealed a number of reported methods to construct the anti, anti stereotriad which could be elaborated to alkyne 4.15. Four different approaches that utilise various chemistries for the construction of the stereotriad will be discussed in detail, considering the number of steps and ease of approach of each method. Method A, reported by Marshall and Adams, involves the addition of the chiral allenylzinc reagent derived from mesylate (R)-4.16 to chiral aldehyde (R)-4.17 to generate the desired stereotriad in one step. Method B involves the desymmetrisation of chiral ketone 4.18, prepared in six steps from diethyl 4-oxopimelate, using a commercially available chiral base. An anti-selective hydroformylation reaction is the key step in the preparation of the stereotriad by method C, and diastereoselective double hydroboration of diene 4.20, followed by a chemoenzymatic desymmetrisation, provides the basis for generating the stereotriad via method D. All of these methods involve the generation of the acetylene in the final step and all would be applicable to the synthesis of alkyne 4.15.
Figure 4.1 Methods for the preparation of the anti, anti stereotriad.

4.2.1 Method A: Marshall and Adams

During the total synthesis of bafilomycin V₁ Marshall and Adams reported the synthesis of alkyne 4.25 containing the anti, anti stereotriad.¹ The synthesis commenced with addition of the allenylzinc reagent derived from mesylate (R)-4.16 to aldehyde (R)-4.17.² The addition proceeded at -20°C to give the anti, anti triad 4.21 in 70% yield, along with a small amount of the anti, syn isomer that could be separated by chromatography. Anti, anti alcohol 4.21 was protected as the TBS ether in near quantitative yield. Transformation of the terminal alkyne into the aldehyde was achieved by employing a two-step hydroboration-homologation sequence. Treatment of 4.22 with freshly prepared dicyclohexylborane at low temperature, followed by treatment with basic hydrogen peroxide furnished the desired aldehyde 4.23 (81%), along with alcohol 4.24 (12%) that could be recycled through oxidation with Dess-Martin periodinane. Attempts to convert 4.23 to the desired alkyne were unsuccessful using both the Corey-Fuchs protocol³ and Savignac’s dichlorophosphonate reagent⁴ due to extensive decomposition and cleavage of the TBS ethers. Successful homologation was achieved using the Seyferth-Gilbert diazophosphonate reagent⁵ to provide alkyne 4.25. This method has also been used for the construction of the corresponding syn, syn stereotriad during the synthesis of leptofuranin D.⁶

Thus, this method provides a three step sequence to the desired alkyne from (R)-4.16 and (R)-4.17, compounds available in one or two steps respectively from commercially available starting materials. Whilst this appears to be a viable method for the synthesis of alkyne 4.25, as the chiral precursors to make (R)-4.16 and (R)-4.17 are available from a commercial source, the expense
involved in obtaining these materials in sufficient quantity for this synthesis [For example \((R)-(+)\)-3-butyn-2-ol $1254.60 for 5 g and \((R)\)-methyl-3-hydroxy-2-methylpropionate $204.51 for 5 g] would far exceed the available budget for this project.

Scheme 4.5 Reagents and yields: (i) MsCl, Et$_3$N, CH$_2$Cl$_2$, -78°C, 1h, 95%; (ii) a) TBSCl, DMAP, imidazole, DMF, rt, 83%; b) Dibal-H (1.1 eq), toluene, -78°C, 62%; (iii) Pd(OAc)$_2$, PPh$_3$, Et$_2$Zn, THF, -20°C, 70%; (iv) TBSTf, 2,6-lutidine, CH$_2$Cl$_2$, 0°C, 96%; (v) \((c$-$C$_6$H$_11$)$_2$BH, DME, 0°C to rt then H$_2$O$_2$, NaOH; (vi) Dess-Martin Periodinane, CH$_2$Cl$_2$, rt, 95%; (vii) \((EtO)$_2$P(O)CHN$_2$, KOr-Bu, THF, -78°C to 0°C, 96%.

4.2.2 Method B: Poupon and Co-Workers

In 2003 Poupon and co-workers reported the synthesis of a similar alkyne fragment to Marshall and Adams during their work on the enantioselective synthesis of the C$_1$-C$_{11}$ fragment of bafilomycin A$_1$. The key step towards formation of alkyne 4.33 was the desymmetrisation of meso dimethyl ketone 4.18 with a chiral base. The desired dimethyl ketone was prepared in seven steps from commercially available diethyl 4-oxopimelate (4.26). Treatment of 4.18 with the chiral base \((R,R)-4.29 could be carried out under two sets of conditions; internal quench, where the ketone is added to a mixture of base and trimethylsilylchloride (TMSCl), or external quench, where the base is added to the ketone followed by TMSCl. The base is generated by treating the
hydrochloride salt of 4.29 with two equivalents of n-butyllithium. This provides lithium chloride in the reaction mixture, which is crucial in obtaining good enantiomeric excess. The chiral base required for the reaction is commercially available as the hydrochloride salt from Sigma-Aldrich Chemical Company or can be prepared using the literature procedure described by Marshall and Lebreton. As is illustrated in Scheme 4.6 the yield of 4.30 for the external quench method is higher than for the internal method but with a slight decrease in enantiomeric excess. Elaboration of 4.30 to alkyne 4.33 was achieved in seven steps. A key reaction in this sequence was the use of Ohira’s reagent in the conversion of aldehyde 4.32 into the alkyne. This reagent is easier to make and store in comparison with the Seyferth-Gilbert reagent.

Scheme 4.6 Reagents: (i) a) (CH$_2$OH)$_2$, p-TsOH, benzene, reflux; b) NaH, THF, reflux; (ii) a) NaH, THF, 0°C; t-BuLi, -78°C, HMPA; MeI, -78°C to rt; b) NaOH/EtOH, reflux; (iii) a) L-selectride, THF, -78°C; b) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, 0°C; c) p-TsOH, acetone, reflux; (iv) n-BuLi, TMSCl, THF, -110°C to -78°C; (v) a) O$_3$, CH$_2$Cl$_2$/MeOH, -78°C; NaBH$_4$, -78°C to rt; b) CH$_2$N$_2$, Et$_2$O; (vi) a) PivCl, pyridine; b) DIBAL-H, THF, -78°C to -20°C; c) IBX, THF, DMSO; (vii) a) CH$_3$C(O)C(N$_2$)P(O)-(OMe)$_2$, K$_2$CO$_3$, MeOH, 0°C to rt; b) DIBAL-H, toluene, -78°C.
It was felt that this sequence was quite lengthy and required the use of a relatively expensive starting material. However, an alternative method for the preparation of dimethyl ketone 4.18 can be devised based on literature methods. The four step sequence would commence from readily available 2,6-dimethylphenol which could be oxidised to the corresponding quinone 4.34 using bromine and hydrogen peroxide under acidic conditions.\(^{11}\) Hydrogenation of 4.34 using a 5% rhodium on alumina catalyst would provide a 2:1 mixture of the isomeric diols 4.35a and 4.35b.\(^ {12}\) Oxidation of these diols using chromic oxide,\(^ {13}\) followed by protection of the free hydroxyl group as the TBS ether would provide an alternative route to compound 4.18. If method B was selected to prepare the anti, anti stereotriad, this alternative preparation of 4.13 could be employed to shorten the sequence.

![Scheme 4.7](image)

**Scheme 4.7** Alternative preparation of compound 4.18.

### 4.2.3 Method C: Breit and Zahn

During their work on the assembly of polypropionate subunits, Breit and Zahn reported the synthesis of alkyne 4.44.\(^ {14}\) The key step in their synthesis was a stereoselective hydroformylation reaction of the substituted 1,3-dioxane 4.19 to construct the stereotriad. Preparation of 4.19 was achieved in four steps from ethyl acetate and methacrolein (4.37). Addition of the lithium enolate of ethyl acetate to 4.37 furnished the unsaturated \(\beta\)-hydroxy ester 4.38. This was transformed into the lithium enolate and treated with excess methyl iodide in hexamethylphosphoramide (HMPA) to provide allyl alcohol 4.39 with high diastereoselectivity. Reduction of 4.39 to the
corresponding diol 4.40, followed by protection of the free hydroxyl groups as a benzylidene acetal afforded the desired substituted 1,3-dioxane 4.19. Subjecting 4.19 to the conditions for hydroformylation provided aldehyde 4.41 in good yield with excellent selectivity for the anti, anti isomer. This aldehyde was then elaborated to the C₅-C₁₁ building block of bafilomycin A₁. As such, Corey-Fuchs chain elongation of 4.41 furnished alkyne 4.43, which was deprotected to form our alkyne of interest 4.44.¹⁵

![Scheme 4.8](image)

**Scheme 4.8** Reagents and yields: (i) LDA, -78°C, THF then 4.37, -78°C, 70%; (ii) LDA, -50°C, THF then MeI/HMPA, -20°C, 85%; (iii) LiAlH₄, Et₂O, 0°C, 69%; (iv) PhCH(OMe)₂, p-TsOH, CH₂Cl₂, 72%; (v) 0.7 mol% [Rh(CO)₂acac/4 P(OPh)₃], toluene, 70°C, 20 bar (H₂/CO, 1:1), 36 h, 80%; (vi) CBr₄, PPh₃, CH₂Cl₂, 0°C, 67%; (vii) n-BuLi, THF, -78°C to rt then H₂O, 95%; (viii) 80% HOAc, THF, 50°C, 40%.
4.2.4 Method D: Harada and Co-Workers / Chênevert and Co-Workers

In 1993 Harada and co-workers reported the diastereoselective double hydroboration of diene 4.20 (available in two steps from isopropenyl magnesium bromide\textsuperscript{16}) with 9-borabicyclo[3.3.1]nonane (4.45).\textsuperscript{17} This provided the \textit{anti, anti} diol 4.46\textsubscript{a} in a 4:1 ratio over the \textit{syn, anti} diol 4.46\textsubscript{b}. Some years later in 2003, Chênevert and co-workers reported the enzyme catalysed stereoselective acylation of 4.46\textsubscript{a} with vinyl acetate in the presence of \textit{Candida rugosa} lipase, to give the alcohol 4.47 in high yield and high enantiomeric excess.\textsuperscript{16} They found that the addition of intact molecular sieves to trap the by-product acetaldehyde was essential to achieve high enantioselectivity and that the reaction could be performed on a several gram scale. To elaborate 4.47 into the desired \textit{anti, anti} stereotriad via this route would require protection of the free hydroxyl group as the TBS ether followed by conversion of the acetate functionality of 4.48 into a suitable leaving group, which could be alkylated to form alkyne 4.25.

Scheme 4.9

Reagents and yields: (i) a) Mg, THF, \(\Delta\) 1h then ethyl formate, \(\text{Et}_2\text{O}\), rt then reflux 1h; b) TBSCl, imidazole, DMF, rt, 24 h, 53\% from 2-bromopropane; (ii) 4.45, THF, -85\(^\circ\)C to rt then 6M NaOH and 30\% \(\text{H}_2\text{O}_2\), -10\(^\circ\)C to rt, 69\% 4.46\textsubscript{a}, 17\% 4.46\textsubscript{b}; (iii) \textit{Candida rugosa} lipase, vinyl acetate, 4Å mol. sieves, hexane, 94\%.
4.2.5 Comparison of the Methods

In choosing a method for the synthesis of the required alkyne fragment there were a number of factors to consider. Whilst method A (Marshall and Adams), discussed in Section 4.2.1, provides the shortest route to the anti, anti stereotriad containing alkyne 4.25, it requires expensive starting materials that exceed the resources available for this project. The method of Poupon and co-workers (method B - Section 4.2.2) would require 16 steps to generate alkyne 4.33 or 13 steps if the proposed alternative preparation of 4.18 was used. Utilising the method of Breit and Zahn (Section 4.2.3) would shorten the sequence to nine steps, but includes the challenging homologation step requiring a stainless steel autoclave pressurised under a hydrogen/carbon monoxide atmosphere. Therefore, it was decided to pursue the synthesis of alkyne 4.25 using the diastereoselective double hydroboration reported by Harada and co-workers, as this would allow us to explore the proposed sequence, plus provide us with the opportunity to obtain chiral material using the chemoenzymatic desymmetrisation reaction using Candida rugosa lipase reported by Chênevert and co-workers (Section 4.2.4). The desired alkyne should be prepared in eight steps from 2-bromopropene.

In selecting this synthetic route, a method for the introduction of an acetylene unit to the stereotriad 4.49 had to be investigated. There are a number of reagents that can be used to add an intact acetylene unit to a molecule via displacement of an appropriate leaving group (OTs, OTf, I). In 1964 Beumel and Harris published a method for the preparation and isolation of lithium acetylide ethylenediamine (EDA) complex (4.50).18 Today, this complex is commercially available and provides a convenient source of monolithium acetylide. In the examples shown in Figure 4.2, the alkyne group is introduced through nucleophilic displacement of a tosylate,19 or an iodide20 in DMSO in good yield. Monolithium acetylide can also be prepared in situ from acetylene gas and lithium in ammonia.21 Trimethylsilyl acetylene has been employed as a means of introducing the acetylene unit. Treatment with n-butyllithium provides lithium trimethylsilylacetylide which is coupled to the desired substrate, followed by removal of the trimethylsilyl group. The example below shows displacement of a triflate, followed by treatment with potassium hydroxide to remove the TMS group.22 Transition metal (Cu or Pd) catalysed coupling of ethynyl magnesium bromide has also be used to introduce an acetylene unit.23
Figure 4.2  Methods for the introduction of an acetylene unit.
4.3 Synthesis of Alkyne 4.25

The synthesis of alkyne 4.25 commenced from freshly distilled 2-bromopropene, prepared in two steps from methacrylic acid.24 Following the method of Tullis and co-workers,25 ethyl formate was added to freshly prepared vinyl Grignard 4.51 to provide alcohol 4.52. This was protected as the TBS ether prior to purification to give 4.20 in a yield of 82% from 2-bromopropene. The diastereoselective double hydroboration reaction was carried out using the modified Harada procedure25 to furnish the meso diol 4.46a in 69% yield.

Initial investigations into the chemoenzymatic desymmetrisation reaction carried out according to the procedure of Chênevert and co-workers proved disappointing. Despite extended reaction times and gentle heating of the reaction mixture, no desired product could be isolated. The quality of the enzyme was questioned, as it was not a lyophilized powder as stated on the bottle. In order to allow the synthesis to continue, it was decided to proceed with a racemic synthesis and return to the desymmetrisation when a second batch of enzyme could be obtained.

Protection of meso diol 4.46a as the di-TBS ether under standard conditions afforded a mixture of three products. The desired primary alcohol 4.52a was isolated in 46% yield along with the secondary alcohol 4.52b, where silyl migration has occurred, in 31% yield and recovered starting material (26%). Silyl migration generally occurs under basic conditions and proceeds intramolecularly via a five-coordinate silicon (4.53).26 The most common migrations are 1,2- and 1,3-migrations although migrations that span many atoms are possible given the proper orientation within a molecule. The TBS group has been observed to migrate frequently while the more stable TBDPS and TIPS groups migrate less frequently; a property that could be exploited at a later date. Attempts to recycle 4.52b into 4.52a by treating with sodium hydride were unsuccessful.
Scheme 4.10  Reagents and yields: (i) Mg, THF, Δ, 2.5 h (ii) ethyl formate, THF, r.t, 16 h; (iii) TBSCl, imidazole, DMF, rt, 82% (2 steps); (iv) 9-BBN, THF, -78°C to rt then 3M NaOH, 50% H₂O₂, 0°C to rt, 69%; (v) Candida rugosa lipase, 4Å mol. sieves, vinyl acetate, hexane, rt; (vi) TBSCl, imidazole, DMF, rt, 4.52a 43%, 4.52b 31%, 4.46a 26%.

With a moderate yield of the desired alcohol 4.52a in hand it was decided to proceed with the synthesis of alkyne (rac)-4.25 in the hopes that the problems associated with the TBS protection would be avoided when utilising material from a successful chemoenzymatic desymmetrisation reaction.

Scheme 4.11  Racemic and enantioselective syntheses of 4.25.
The two-step process to convert alcohol 4.52a into alkyne 4.25 commenced with tosylation of 4.52a with 4-toluenesulfonyl chloride to generate 4.54 in 75% yield. Treatment of this compound with lithium acetylide EDA complex to nucleophilically displace the tosylate afforded what initially appeared to be only the desired compound. Purification of the crude material by careful flash chromatography led to the isolation of two compounds with closely related 1H NMR spectra. Full 2-dimensional NMR analysis indicated that the second product was the desired alkyne 4.25 which was isolated in 32% yield. The 1H NMR spectrum of the side product was almost identical to that assigned to 4.25 but without the signal for the acetylenic proton (H1) at 1.93 ppm.

![1H NMR spectra](image.png)

Figure 4.3 1H NMR spectra (500 MHz) of 4.25 and the side product.

It was proposed that this side product may be the result of silyl transfer to the alkyne, and thus could have three possible structures; the fully silylated 4.55, primary alcohol 4.56 or secondary alcohol 4.58. The presence of the silyl group on the alkyne was confirmed through an HMBC correlation between C-1 and the methyl substituents of the TBS group. Alkyne 4.55 was assigned as the structure of the side product based upon the integral values of the SiC(CH3)3 and SiCH3 signals in the 1H NMR spectrum and the number of SiCH3 signals in the 13C NMR spectrum. Five distinct peaks were present between -5.5 ppm and -4.0 ppm attributable to the non-equivalent methyl groups on the TBS ethers and the methyl groups on the silylated alkyne. To confirm this assignment the side product was treated with Dess-Martin periodinane. No oxidation to aldehyde 4.57 or ketone 4.59 was observed, thus confirming 4.55 as the structure of the side
product. This silylated acetylene was isolated in 29% yield along with some material that was a mixture of 4.25 and 4.55.

*Possible side-products:*

![Chemical structures](image)

*Important HMBC correlations:*

*Selected region of $^{13}$C NMR spectrum (75 MHz) of 4.55:*

![NMR spectrum](image)

**Figure 4.4** Determination of the structure of the side product.

Semmelhack and co-workers observed a similar result when carrying out nucleophilic displacement of a tosylate group. They found that side reactions including elimination as well as silyl transfer to the alkyne anion led to a modest yield of their desired material 4.61.

**Scheme 4.12** The reaction studied by Semmelhack and co-workers.
To increase the yield of the desired alkyne \( \text{4.25} \), a two-step recycling procedure was carried out. The side product \( \text{4.55} \) was globally deprotected with tert-butylammonium fluoride to give diol \( \text{4.62} \) with the alkyne desilylated. Re-protection of the hydroxyl groups as TBS ethers under standard conditions allowed the isolation of an additional 18% of \( \text{4.25} \). Recycling of the mixed material provided an additional 12% of the desired material, to give an overall yield of 62% from \( \text{4.54} \).

\[
\begin{align*}
\text{OTBS} & \quad \text{OH} \\
\text{TBSO} & \quad \text{\textcircled{O}} \\
\text{4.52a} & \\
\text{ii} & \quad \text{OTBS} \\
\text{TBSO} & \quad \text{\textcircled{O}} \\
\text{4.54} & \\
\text{OH} & \quad \text{HO} \\
\text{TBSO} & \quad \text{\textcircled{O}} \\
\text{4.25} & \\
\text{iii} & \quad \text{HO} \\
\text{4.62} & \\
\text{OH} & \quad \text{HO} \\
\text{TBSO} & \quad \text{\textcircled{O}} \\
\text{4.55} & \\
\text{i} & \quad \text{OTBS} \\
\text{TBSO} & \quad \text{\textcircled{O}} \\
\text{4.52a} & \\
\end{align*}
\]

**Scheme 4.13** Reagents and yields: (i) \( p\)-TsCl, DMAP, Et\(_3\)N, CH\(_2\)Cl\(_2\), 0°C, 75%; (ii) \( \text{4.50} \), DMSO, rt, \( \text{4.25} \) 32%, \( \text{4.55} \) 29%; (iii) TBAF, THF, rt, 97%; (iv) TBSCl, imidazole, DMF, rt, 80%.

The recycling procedure provided a yield of \( \text{4.25} \) that was sufficient to continue with the synthesis. It was felt that it was best to focus on completion of the fully functionalised bicyclic core before tackling the optimisation of each step of the pathway. In anticipation of future studies, it was proposed that slow nucleophilic displacement of the tosylate group of \( \text{4.54} \) was occurring competitively with deprotonation and intermolecular nucleophilic attack on the oxygen-silicon bond leading to silyl group transfer to the terminal alkyne. Methods that could be investigated to improve the yield of the reaction could include the use of a more facile leaving group ( triflate or iodide) or the addition of trimethylsilyl acetylene, followed by selective removal of the TMS group with potassium carbonate in methanol as an alternative approach for the installation of the alkyne.
4.3.1 Enzymatic Desymmetrisation

Whilst developing the racemic synthesis of the fully functionalised bicyclic core that would provide the correct relative stereochemistry, it was decided to concurrently focus on the optimisation of the chemoenzymatic desymmetrisation reaction, with the aim of being able to generate one enantiomer of the bicyclic core that could be elaborated to the natural products to allow the absolute stereochemistry of TEO3.1, hamigerone and embellistatin to be determined. Upon receiving a new batch of Candida rugosa lipase, diol 4.46a was subjected to the conditions described by Chênevert and co-workers (Figure 4.5-A). However, again, in our hands the formation of product could not be replicated. Investigations into the literature found a number of examples of acylations using different sources of lipase under varying conditions. Using Lipase PS-30 from Pseudomonas cepacia with vinyl acetate as the acyl donor, Danishefsky and co-workers resolved racemic glycals of varying complexity.\(^{28}\) Their reactions were carried out in 1,2-dimethoxyethane using a large excess of vinyl acetate over varying time periods. An example of their work is depicted in Figure 4.5-B. Resolution of hydroxyl ester 4.63 has also been reported by Kanerva and Sundholm using the same lipase in tetrahydrofuran with three equivalents of vinyl acetate (Figure 4.5-C).\(^{29}\) Lipase from Pseudomonas fluorescens has been reported for the desymmetrisation of 2,4-dimethylpentan-1,4-diol in 1.5 equivalents of neat vinyl acetate\(^{30}\) and for the acylation of α-pyranoside 4.66 in a large excess of vinyl acetate at 35°C (Figure 4.5-D and E).\(^{31}\)
In an effort to achieve the enzymatic desymmetrisation of 4.46a various reaction conditions were trialed. Subjecting 4.46a to enzymatic acylation with lipase from Candida rugosa in either 1,2-
dimethoxyethane with excess vinyl acetate or in tetrahydrofuran with five equivalents of vinyl acetate, in the presence of molecular sieves at 35°C, showed no conversion to the desired material even after a reaction time of seven days. However, gratifyingly, when vinyl acetate was employed as both the solvent and the acylating agent in the presence of molecular sieves at 35°C an approximately 40% conversion to 4.47 was observed after seven days. This could be separated from the remaining starting material by flash column chromatography to provide a 33% yield of 4.47 and 49% yield of recovered starting material. The optical rotation of this compound was not able to be measured due to a problem with the polarimeter. Whilst this result was promising, this material has not yet been elaborated to the bicyclic core.

4.4 Development of a Racemic Synthesis of the Bicyclic Core

4.4.1 Elaboration to Pyrone 4.73

With the desired alkyne 4.25 in hand, elaboration to pyrone 4.73 was initiated utilising the copper-mediated coupling reaction optimised for the model system. As such, coupling alkyne 4.25 and iodide 3.70 in the presence of [Cu(phen)(PPh₃)Br] catalyst (3.84) and cesium carbonate produced the desired adduct 4.68 in 55% yield. Hydrolysis of the ethyl ester using the model system conditions (1M aqueous lithium hydroxide solution in 1:1 THF/MeOH) led to a 1:2 mixture of the desired acid 4.69 and the corresponding methyl ester. Changing the solvent from methanol to the less nucleophilic isopropyl alcohol furnished the desired acid in 77% yield. Intramolecular addition of the carboxylic acid to the alkyne catalysed by zinc bromide provided pyrone 4.70. Selective deprotection of the primary TBS ether using 4-toluenesulfonic acid in methanol provided alcohol 4.71 which was oxidised to aldehyde 4.72 using Dess-Martin periodinane. Wittig elongation with 1-(ethoxycarbonyl)methylenetriphenylphosphorane afforded pyrone 4.73, the substrate for the diene-regenerative Diels-Alder reaction.
Scheme 4.14  Reagents and yields: (i) [Cu(phen)(PPh₃)Br], Cs₂CO₃, toluene, 110°C, 48h, 55%; (ii) 1M LiOH, 1:1 THF/i-PrOH, rt, 18h, 77%; (iii) ZnBr₂(20 mol%), THF, rt, 72h, 61%; (iv) p-TsOH, MeOH, 0°C, 2h then rt 2h, 90%; (v) Dess-Martin Periodinane, CH₂Cl₂, rt, 1h, 87%; (vi) EtO₂CCH=PPh₃, CH₂Cl₂, rt, 50%.

4.4.2 Construction of the Bicyclic Core via Diene-Regenerative Diels-Alder Reaction

Following the successful preparation of pyrone 4.73 attention was turned to the crucial diene-regenerative Diels-Alder reaction to construct the bicyclic core. Applying the conditions optimised for the model system, 4.73 was refluxed in xylenes in the presence of Proton-Sponge®. ¹H NMR spectroscopic analysis of the crude material showed the formation of a single product. Full analysis of the purified material using 2-dimensional NMR spectroscopy (HSQC and HMBC) and selective NOE experiments (vide infra) confirmed the desired bicyclic adduct 4.74 had been formed and allowed the assignment of the ¹H and ¹³C chemical shifts.
Scheme 4.15  Reagents and yields: (i) Proton-Sponge®, xylenes, reflux, 48h, 81%.

Figure 4.6  $^1$H NMR spectrum (500 MHz), important HMBC correlations and assigned $^{13}$C chemical shift data for 4.74.

To confirm the relationship between the protons in the molecule, and thus confirm the formation of the desired diastereoisomer, coupling constants and NOE interactions were examined. The $^1$H NMR signal for $\text{H}_{8a}$ appears as an apparent triplet with a coupling constant of 11 Hz. This indicates an 180° dihedral angle with both adjacent protons $\text{H}_1$ and $\text{H}_8$. Selective irradiation of the signal for $\text{H}_{8a}$ produced NOE enhancements of the signals for $\text{H}_{5A}$ and the 8-CH$_3$ group, but no enhancement of the signals for $\text{H}_1$ or $\text{H}_8$. This confirmed the diaxial orientation and hence, both the retention of dienophile stereochemistry as observed in the model system and the anti relationship between $\text{H}_8$ and $\text{H}_{8a}$. The $^1$H NMR signal for $\text{H}_{5A}$ appears as a doublet of doublets with coupling constants of 3.9 Hz and 13.5 Hz, the latter suggesting a diaxial coupling.
Irradiation of the signal for H$_{5A}$ showed no enhancement of the signal for H$_6$, whereas irradiation at H$_{5B}$ did. This confirmed the diaxial relationship between H$_{5A}$ and H$_6$ and the assignment of the signals for the diastereotopic protons at C-5. Irradiation of the $^1$H NMR signal for H$_7$ led to NOE enhancements of the signals for both H$_6$ and H$_8$. This through-space correlation confirmed the syn relationship between these protons, and thus, the retention of the stereotriad stereochemistry.

<table>
<thead>
<tr>
<th>Irradiated Proton</th>
<th>Enhanced Proton(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H$_7$</td>
<td>H$_6$, H$_8$, 6-CH$_3$, 8-CH$_3$</td>
</tr>
<tr>
<td>H$_1$</td>
<td>H$_6$, H$_8$, 8-CH$_3$</td>
</tr>
<tr>
<td>H$_{5A}$</td>
<td>H$_{5A}$, 8-CH$_3$</td>
</tr>
<tr>
<td>H$_6$</td>
<td>H$<em>7$, H$</em>{5B}$, H$_8$, 6-CH$_3$</td>
</tr>
<tr>
<td>H$_8$</td>
<td>H$_7$, H$_1$, H$_6$, 8-CH$_3$</td>
</tr>
<tr>
<td>H$_{5A}$</td>
<td>H$<em>{5B}$, H$</em>{8a}$</td>
</tr>
<tr>
<td>H$_{5B}$</td>
<td>H$_{5A}$, H$_4$, H$_6$, 6-CH$_3$</td>
</tr>
</tbody>
</table>

Figure 4.7  Results of selective irradiation experiments and spectrum showing irradiation of H$_7$ (500 MHz).

4.4.3 Electrophilic Bromination

With the successful preparation of pyrone 4.73 achieved, attention was turned to the installation of the C-2 bromo substituent that would allow addition of the three carbon side-chain required at this position. As the formation of the pyrone ring was achieved earlier in the synthetic sequence than for the model system, initial attempts focused on bromination of pyrone 4.70 under the conditions described for the model system. As such, 4.70 was treated with N-bromosuccinimide in THF at room temperature. Analysis of the $^1$H NMR spectrum of the reaction mixture showed a complex mixture of products, with evidence that the TBS ethers were being removed. N-Bromosuccinimide in aqueous DMSO has been reported to remove of TBS ethers$^{26}$ and under these conditions, the removal of primary TBS ethers in the presence of secondary TBS ethers has been observed by Yamamoto and co-workers during their work on chiral β-lactams.$^{32}$
As an alternative, pyrone 4.73, analogous to 3.101 that was successfully brominated during the model system work, was subjected to the conditions described above. Bromination proceeded slowly. After 1 week, analysis of a sample by $^1$H NMR spectroscopy indicated an approximately 1:1 mixture of starting material to product, along with a third component. Purification of the mixture allowed a small sample of the desired pyrone to be isolated and both a $^1$H NMR spectrum and mass spectrum to be obtained. However, due to time constraints and a lack of available material, the reaction conditions were not optimised and no yield of the product is reported.

Figure 4.8 Reaction of 4.70 with N-bromosuccinimide (A) and an example of selective TBS ether cleavage with NBS (B).

Figure 4.9 Bromination of pyrone 4.73 and a $^1$H NMR spectrum (500 MHz) of the reaction product 4.78.
This slow reaction time is in stark contrast to that observed in the model system. Thus, further investigations need to be carried out to determine the optimum point in the sequence to introduce the C-2 bromo substituent.

### 4.5 A Model System for the Introduction of the C-1 Side-Chain

Whilst the synthesis of the bicyclic core was being developed, a model study was conducted to investigate the introduction of the C-1 side-chain of TEO3.1, based on the sequence reported by Baldwin and co-workers.\(^{33}\) This sequence was attractive as it allows access to a range of analogues, plus it would allow us to utilise the Sharpless asymmetric epoxidation to prepare both possible stereoisomers of the side-chain.

Accordingly, benzaldehyde was reacted with phosphorane \(2.92\) to provide alkene \(4.79\). Reduction of the ester to the corresponding alcohol, followed by oxidation with Dess-Martin periodinane gave the aldehyde. A second Wittig elongation with \(2.92\) provided diene \(4.80\) in 35% yield for the three-step sequence. Reduction of ester \(4.80\) with diisobutylaluminium hydride at \(-78^\circ\text{C}\) provided allylic alcohol \(4.81\) in 91% yield. Oxidation of allylic alcohol \(4.81\) was achieved with \(m\)-chloroperbenzoic acid to afford the epoxide in 52% yield. Oxidation of \(4.82\) to the corresponding aldehyde, followed by a Horner-Wadsworth-Emmons (HWE) reaction with diethyl phosphonoacetamide (\(4.83\)) completed the model system (\(4.84\)) for the installation of the side-chain of TEO3.1.

The corresponding cyclopropane analogue \(4.86\) could also be prepared using this approach. As such, cyclopropanation of \(4.81\) was achieved using the method of Charette and co-workers, whereby the complex \(\text{Zn(CH}_2\text{I)}_2\text{DME}\) is formed from pre-chelation of diethylzinc to 1,2-dimethoxyethane followed by addition of diiodomethane.\(^{34}\) This methodology afforded the cyclopropane \(4.85\) in 55% yield. Oxidation of \(4.85\) to the corresponding aldehyde, followed by HWE reaction with \(4.83\) furnished the cyclopropane analogue \(4.86\) in 58% yield for the two-step sequence.
Scheme 4.16  Reagents and yields: (i) \( \text{EtO}_2\text{CC(Me)=PPh}_3 \) (2.92), toluene, reflux, 79%; (ii) (a) DIBAL-H, Et\(_2\)O, -78°C, 1h then 0°C, 1h; (b) Dess-Martin periodinane, CH\(_2\)Cl\(_2\), rt, 1h; (c) EtO\(_2\)CC(Me)=PPh\(_3\) (2.92), toluene, reflux, 35% (3 steps); (iii) DIBAL-H, Et\(_2\)O, -78°C, 1h then 0°C, 1h, 94%; (iv) \( m\)-CPBA, CH\(_2\)Cl\(_2\), 0°C, 3h, 52%; (v) (a) Dess-Martin periodinane, pyridine, CH\(_2\)Cl\(_2\), rt, 4h; (b) \( (\text{EtO})_2\text{P(=O)CH}_2\text{CONH}_2 \) (4.83), \( n\)-BuLi, THF, -78°C, 5 min then aldehyde, -78°C to rt, 30 min, 44% (2 steps); (vi) 1.5 equiv Zn(CH\(_2\))\(_2\).DME, CH\(_2\)Cl\(_2\), -20°C to rt, 3 days, 55%; (vii) (a) TPAP, NMO, mol. sieves, CH\(_2\)Cl\(_2\), rt, 4h; (b) \( (\text{EtO})_2\text{P(=O)CH}_2\text{CONH}_2 \) (4.83), \( n\)-BuLi, THF, -78°C, 5 min then aldehyde, -78°C to rt, 1 h, 58% (2 steps).

Figure 4.10  \(^1\text{H} \) NMR spectra (500 MHz) of epoxide 4.84 and cyclopropane 4.86.

This brief study into the generation of the C-1 side-chain indicates that this sequence should allow us to access the desired systems readily, plus allow the generation of a range of analogues.
4.6 Summary

Based on the chemistry established in Chapter Three for the model system, a racemic synthesis of the diene-regenerative Diels-Alder substrate 4.73 was successfully achieved. The [4 + 2] cycloaddition reaction, followed by extrusion of carbon dioxide in the presence of Proton-Sponge®, established a successful route to the bicyclic core of the targeted natural products.

The proposed enantioselective synthesis was postponed due to a failure to replicate the chemoenzymatic desymmetrisation of 4.46a with lipase from Candida rugosa as reported by Chênevert and co-workers. Studies involving variation of the reaction conditions found that employing vinyl acetate as both the solvent and the acylating agent led to the formation of the desired material albeit at a low percentage conversion.

Investigations were also made regarding the introduction of a C-2 bromo substituent to the pyrone. Whilst a sample of the desired bromo derivative was prepared, time constraints and a lack of material prevented the reaction conditions being optimised and the diene-regenerative Diels-Alder reaction being carried out.

A short model study was performed introducing the C-1 side-chain of TEO3.1 onto a benzene ring. An analogue with the side-chain epoxide replaced by a cyclopropane was also prepared.
4.7 **Future Work**

To complete the synthesis of TEO3.1, hamigerone and embellistatin there are three areas which need to be addressed; the development of an enantioselective synthesis of the bicyclic core, the introduction of the side-chain at C-2 and the introduction of the side-chain at C-1. In order to continue the development of these natural products as lead compounds with potential pharmaceutical and agricultural applications the preparation of a number of analogues would also be required.

4.7.1 **Enantioselective Synthesis of Bicyclic Core**

To determine the absolute stereochemistry of the natural products, the synthesis of one of the possible enantiomers would need to be achieved and optical rotation data compared to that of the isolated natural products. With further optimisation of the enzymatic desymmetrisation reaction of 4.46a, enough material should be accessible to generate the (S,R,S,S) enantiomer of the bicyclic core and elaborate it to the natural products (Figure 4.11). If required, the synthetic strategy could be easily adapted to generate the opposite enantiomer of the bicyclic core by preparing the key stereotriad-containing alkyne 4.25 with the opposite stereochemistry (Figure 4.12).

![Figure 4.11 Possible enantiomers of the bicyclic core.](image-url)
4.46a 4.47 4.48

Figure 4.12  Building blocks for the enantioselective synthesis of the bicyclic core.

4.7.2 Introduction of C-2 Side-Chain

Although preliminary studies have provided a method for the preparation the brominated pyrone 4.78, it will be necessary to optimise this reaction to acquire the significant quantities of this material necessary to carry out the diene-regenerative Diels-Alder reaction. Following cyclisation, investigations into the conditions required for the introduction of the side-chain at C-2 would begin. It is proposed that this could be achieved in one of two ways. Halogen-lithium exchange of bromo adduct 4.89, followed by addition of methoxy allyl bromide should provide enol ether 4.90 which could be hydrolysed to the corresponding ketone upon treatment with acid. It is hoped that this step would also remove the TBS ether, which could then be oxidised to the ketone functionality required for the natural products. This would provide 4.87, an analogue with the C-1 side-chain removed.
Scheme 4.17 Proposed method for the introduction of the C-2 side-chain.
An alternative method for the introduction of the side-chain would involve conversion of the bromopyrone 4.78 into the corresponding cuprate 4.91 utilising known copper pyrone chemistry.\textsuperscript{35} Addition of methoxy allyl bromide should provide the diene-regenerative Diels-Alder substrate 4.92 with the C-2 side-chain functionality pre-included. Following cyclisation, this material could be elaborated in two steps to the same C-1 truncated analogue of the natural products.

Scheme 4.18 Proposed method for pre-inclusion of C-2 side-chain.

4.7.3 Introduction of C-1 Side-Chain – Completion of the Syntheses
Introduction of the C-1 side-chain should be readily achieved using the method outlined in Chapter One and briefly investigated in Section 4.5. For embellistatin this would entail a series of reduction-oxidation-Wittig elongation steps, followed by a global deprotection, oxidation to install the C-7 ketone functionality and hydrolysis to reveal the terminal carboxylic acid.
Scheme 4.19  Proposed method to complete the synthesis of embellistatin.

To complete the synthesis of TEO3.1 and hamigerone the stereochemistry of the epoxide moiety in the side-chain must be established. To this end, Sharpless asymmetric epoxidation chemistry would be used to stereoselectively generate both possible isomers of TEO3.1 and hamigerone and optical rotation data compared with that reported for the natural products.

Scheme 4.20  Proposed method to complete the synthesis of TEO3.1 and hamigerone and establish the stereochemistry of the epoxide moiety.
4.8 References for Chapter Four


Chapter Five

Experimental Details
5.1 General Experimental

5.1.1 Reagents and Solvents

Reagents and solvents used in reactions were purified according to well established methods. In particular, anhydrous tetrahydrofuran (THF) and diethyl ether (Et₂O) were freshly distilled from sodium benzenophenone ketyl immediately prior to use. Toluene, dichloromethane (CH₂Cl₂), pyridine, N,N-diisopropylamine, triethylamine and ethyl formate were freshly distilled from calcium hydride. N,N-Dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were sequentially dried over two batches of freshly activated 4Å molecular sieves (2 x 24 h), before being stored under argon over a third batch of 4Å molecular sieves. Prior to use, the DMF solvent was evacuated (~0.1 mmHg) for 15 min to remove residual dimethylamine. Acetyl chloride was refluxed with PCl₅ to remove traces of acetic acid then distilled. m-Chloroperbenzoic acid (m-CPBA) was recrystallised from CH₂Cl₂. N-Bromosuccinimide (NBS) was recrystallised from H₂O. The petroleum ether used consisted of the fraction with a boiling range of 50-70°C. Solutions of n-butyllithium in hexanes were titrated in THF with standardised 2-butanol, using 1,10-phenanthroline as an indicator. Sodium bis(trimethylsilyl)amide was titrated with 2-butanol using 2,2’-bipyridine as an indicator. The Dess-Martin periodinane (DMP) was prepared according to the modified procedures of Ireland and Liu. 1-(Methoxycarbonyl) ethyldenetriphenylphosphorane and 1-(ethoxycarbonyl) ethyldenetriphenylphosphorane were prepared in two steps from the corresponding alkyl 2-bromopropionate according to literature procedure. 1-(Ethoxycarbonyl) methylenetriphenylphosphorane and 1-(tert-butoxycarbonyl) methylenetriphenylphosphorane were prepared in two steps from the corresponding alkyl bromoacetate according to literature methods. 4-Methoxybenzyl bromide (PMB-Br) was prepared immediately prior to use by shaking a solution of 4-methoxybenzyl alcohol in Et₂O (10 mL of Et₂O per g of alcohol) with an equal volume of hydrobromic acid (HBr). N-Methoxy-N-methyl acetamide was prepared according to the method of Gimbert and co-workers. Lithium diisopropylamide (LDA) was prepared in situ according to the procedure described by Leonard and co-workers. Ethyl 2-butynoate and methyl 2-butynoate were prepared following the procedure of Boers and co-workers. The copper catalysts [Cu(phen)(PPh₃)Br], [Cu(phen)(PPh₃)₂]NO₃ and [Cu(bipy)(PPh₃)Br] were prepared according to literature procedures. 2-Bromopropene was prepared according to the method of Braude and Evans.
Diethyl phosphonoacetamide was prepared from triethylphosphonoacetate according to the method of Kagara and co-workers.\textsuperscript{10}

Unless otherwise stated, all reactions were performed in oven- or flame-dried glassware under an atmosphere of argon or nitrogen with the reaction temperature referring to the external bath temperature. All organic extracts were washed with brine and dried over anhydrous sodium or magnesium sulfate. After filtration of the solutions to remove the solids, the solvents were evaporated under reduced pressure on a Büchi rotary evaporator (~12 mmHg). When necessary, a high vacuum pump (~0.1 mmHg) was used to remove the last traces of solvent from purified compounds.

### 5.1.2 Chromatography and Small-Scale Distillation

Analytical thin-layer chromatography (TLC) was conducted on aluminium-backed Merck Kieselgel KG60F\textsubscript{254} silica plates or plastic-backed Macherey-Nagel Polygram\textsuperscript{®} SIL G/UV\textsubscript{254} silica plates. The developed TLC plates were visualised under short- or long-wave ultraviolet (UV) light followed by staining with aqueous potassium permanganate dip.

Flash chromatography was routinely carried out upon Merck Silica 60 (40-63 μm) using the procedure of Still and co-workers.\textsuperscript{11} Solvents used for chromatography were purified by simple distillation.

Small scale (bulb-to-bulb) distillation was performed under low vacuum (~10-12 mmHg) or high vacuum (~0.1 mmHg) in a Büchi Kugelrohr apparatus.

### 5.1.3 Spectroscopic Techniques

The $^1$H NMR spectra were obtained on either a Varian UNITY 300 or Varian INOVA 500 spectrometer, operating at 300 MHz and 500 MHz respectively, at 23°C. The $^{13}$C NMR spectra were recorded on a Varian UNITY 300 NMR spectrometer operating at 75 MHz, typically with a delay (d1) of 1-3 seconds. 2D NMR experiments were carried out on a Varia INOVA 500 spectrometer fitted with an Inverse Detection Probe and Pulsed Field Gradient Driver, operating at 500 MHz. Assignments of $^1$H and $^{13}$C signals were determined on the basis of COSY, HSQC, HMBC or CIGAR experiments. In some cases, difference-NOE or 1D NOESY experiments were employed if uncertainty regarding structural assignments remained.
Chemical shifts are reported in parts per million (ppm) on the $\delta$ scale, and were referenced to residual protonated solvent peaks: CDCl$_3$ referenced to CHCl$_3$ at $\delta_H$ 7.25 and CDCl$_3$ at $\delta_C$ 77.0. Tetramethylsilane (TMS) was used as an internal standard at $\delta_H$ 0.0. For acid sensitive compounds 0.1% v/v C$_5$D$_5$N (deuteriopyridine) was added to the CDCl$_3$ solvent.

Infrared spectra (IR) were obtained on a Shimadzu FTIR-8201 PC spectrometer. Spectra of oils were run neat on KBr plates. Spectra of solids were obtained from KBr pellets or solid materials were dissolved in a minimum amount of CH$_2$Cl$_2$, applied to the plates as a solution and then evaporated under a N$_2$ stream. Values of selected peaks are reported in wavenumbers (cm$^{-1}$).

High Resolution Electron Impact Mass Spectrometry (HREIMS) was carried out on a Kratos MS80RFA Mass spectrometer operating in electron ionisation (EI) mode at 70 eV, using a 4 kV accelerating potential and 250$^\circ$C source temperature. High Resolution Electrospray Ionisation Mass Spectra (HRESIMS) were obtained from a Micromass LCT spectrometer with a probe voltage of 3200 V and temperature of 120$^\circ$C. A nebuliser gas flow of 160 L/hr and desolvation gas flow of 520 L/hr were used in conjunction with a source temperature set at 80$^\circ$C. The carrier solvent was 50% MeCN/H$_2$O at 20 $\mu$L/min (for direct injection mode). A 10 $\mu$L injection of sample was made from a 10 $\mu$g/mL solution. Positive ESI mass spectra were recorded after the addition of sodium iodide or formic acid to the sample prior to analysis. Only molecular ions (M$^+$) and other major fragments are reported.

Melting points (mp) were obtained using a Büchi 510 Cambridge Instruments Gallen$^\text{TM}$ III hot stage melting point apparatus and are uncorrected.

### 5.1.4 Nomenclature

The nomenclature used in this thesis is in accordance with the IUPAC recommendations.$^{12}$
5.2 Experiments described in Chapter Two

4-Acetoxybutan-1-ol (2.87a):

Following the method of Mattes and co-workers\textsuperscript{13} acetyl chloride (11.5 mL, 0.16 mol) was added dropwise at 0°C to a solution of butane-1,4-diol (30 mL, 0.33 mol) and pyridine (13 mL, 0.16 mol) in CH\textsubscript{2}Cl\textsubscript{2} (30 mL). The mixture was stirred overnight at room temperature followed by removal of the solvent under reduced pressure. Purification of the crude material \textit{via} flash chromatography on silica, eluting with 80% Et\textsubscript{2}O/petroleum ether provided the title compound as a colourless oil (14.41 g, 67%). Values from the \textsuperscript{1}H NMR spectrum were in close agreement with the reported values.\textsuperscript{14}

\textbf{1H NMR} (500 MHz, CDCl\textsubscript{3}): \(\delta\) 1.57 (m, 2H), 1.67 (m, 2H), 1.99 (s, 3H, COCH\textsubscript{3})), 2.31 (br s, 1H, OH), 3.60 (t, \(J = 6.4\) Hz, 2H, H-1), 4.04 (t, \(J = 6.5\) Hz, 2H, H-4).

\textbf{13C NMR} (75 MHz, CDCl\textsubscript{3}): \(\delta\) 20.9 (COCH\textsubscript{3}), 24.9 (C-2), 28.9 (C-3), 62.0 (C-1), 64.2 (C-4), 171.3 (C=O).

\textbf{FTIR} (KBr, cm\textsuperscript{-1}): 3396, 2947, 2876, 1738, 1717, 1367, 1248, 1047.

4-(4'-Methoxybenzyloxy)butan-1-ol (2.87b):

A solution of butane-1,4-diol (1 mL, 11 mmol) in THF (2 mL) was added \textit{via} cannula to a suspension of NaH (0.35 g, 15 mmol) in THF (10 mL) at 0°C. After stirring at this temperature for 30 min a solution of 4-methoxybenzyl bromide (2.4 g, 12 mmol) in THF (2 mL) was added. The reaction mixture was warmed slowly to room temperature and stirred overnight. Following dilution with H\textsubscript{2}O (15 mL), the aqueous layer was extracted with EtOAc (x3) and the combined organic extracts washed with brine, dried and concentrated. Purification of the crude material \textit{via} flash chromatography on silica gel, eluting with 50% EtOAc/petroleum ether, afforded the title compound as a colourless oil (1.00 g, 43%). Values from the \textsuperscript{1}H NMR spectrum were in close agreement with the reported values.\textsuperscript{15}
**1H NMR** (500 MHz, CDCl3): $\delta$ 1.68 (m, 4H, H-2 and H-3), 3.49 (t, $J = 5.8$ Hz, 2H, H-4), 3.63 (t, $J = 5.8$ Hz, 2H, H-1), 3.80 (s, 3H, OCH$_3$), 4.45 (s, 2H, OCH$_2$Ar), 6.88 (d, $J = 8.7$ Hz, 2H, ArH), 7.26 (d, $J = 8.7$ Hz, 2H, ArH).

**13C NMR** (75 MHz, CDCl3): $\delta$ 26.7 (C-2), 30.2 (C-3), 55.2 (OCH$_3$), 62.6 (C-1), 70.0 (C-4), 72.7 (OCH$_2$Ar), 113.8 (ArH), 129.3 (ArH), 130.1 (Ar), 159.2 (Ar).

**FTIR** (KBr, cm$^{-1}$): 3388, 2939, 2864, 1612, 1513, 1466, 1443, 1364, 1303, 1249, 1174, 1097, 1064, 1035.

4-Acetoxybutanal (2.83a):

A solution of alcohol 2.87a (0.2 g, 1.5 mmol) in CH$_2$Cl$_2$ (2 mL) was added, via cannula, to a solution of Dess-Martin periodinane (0.71 g, 1.7 mmol) in CH$_2$Cl$_2$ (8 mL) at room temperature. After stirring for 1 h at room temperature the reaction mixture was diluted with Et$_2$O (10 mL), then stirred for ~10 min with 1M aqueous NaOH solution (5 mL) to dissolve the white precipitate. The organic layer was removed, and the aqueous portion extracted with Et$_2$O (x2). The combined organic portions were washed with 1M aqueous NaOH solution, then brine, dried and concentrated to provide 2.83a as a colourless oil (0.17 g, 91%), which was used without further purification. Values from the $^1$H NMR spectrum were in close agreement with the reported values.$^{13}$

**1H NMR** (500 MHz, CDCl3): $\delta$ 1.95 (m, 2H, H-3), 2.02 (s, 3H, COCH$_3$), 2.52 (td, $J = 7.2$, 1.3 Hz, 2H, H-2), 4.07 (t, $J = 6.4$ Hz, 2H, H-4), 9.77 (t, $J = 1.3$ Hz, 1H, H-1).

**13C NMR** (75 MHz, CDCl3): $\delta$ 20.8 (COCH$_3$), 21.2 (C-3), 40.4 (C-2), 63.3 (C-4), 170.9 (C=O), 201.2 (C-1).

**FTIR** (KBr, cm$^{-1}$): 2962, 2901, 1740, 1682, 1441, 1389, 1367, 1244, 1049.

4-(4’-Methoxybenzyloxy)butanal (2.83b):

A solution of alcohol 2.87b (0.72 g, 3.4 mmol) in CH$_2$Cl$_2$ (5 mL) was added, via cannula, to a solution of Dess-Martin periodinane (1.6 g, 3.8 mmol) in CH$_2$Cl$_2$ (20 mL) at room temperature.
After stirring for 1 h at room temperature the reaction mixture was diluted with Et₂O (30 mL), then stirred for ~10 min with 1M aqueous NaOH solution (30 mL) to dissolve the white precipitate. The organic layer was removed, and the aqueous portion extracted with Et₂O (x2). The combined organic portions were washed with 1M aqueous NaOH solution, then brine, dried and concentrated to provide 2.83b as a pale yellow oil (0.65 g, 91%), which was used without further purification. Values from the ¹H NMR spectrum were in close agreement with the reported values.¹⁶

¹H NMR (500 MHz, CDCl₃): δ 1.92 (m, 2H, H-3), 2.52 (dt, J = 1.6, 7.1 Hz, 2H, H-2), 3.46 (t, J = 6.1 Hz, 2H, H-4), 3.79 (s, 3H, OCH₃), 4.40 (s, 2H, OCH₂OPMB), 6.86 (d, J = 8.7 Hz, 2H, ArH), 7.23 (d, J = 8.7 Hz, 2H, ArH), 9.76 (t, J = 1.6 Hz, 1H, H-1).

¹³C NMR (75 MHz, CDCl₃): δ 22.5 (C-3), 40.9 (C-2), 55.2 (OCH₃), 68.8 (C-4), 72.6 (OCH₂Ar), 113.7 (ArH), 129.2 (ArH), 130.3 (Ar), 159.1 (Ar), 202.3 (C-1).

FTIR (KBr, cm⁻¹): 2937, 2860, 2839, 1724, 1614, 1514, 1464, 1442, 1362, 1302, 1248, 1175, 1097, 1034.

4-Acetoxybutylthio benzothiazole (2.88):
Chapter Five – Experimental Details

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.82 (m, 2H, H-3), 1.91 (m, 2H, H-2), 2.04 (s, 3H, COCH$_3$), 3.38 (t, $J = 7.2$ Hz, 2H, H-1), 4.12 (t, $J = 6.4$ Hz, 2H, H-4), 7.28 (t, $J = 7.6$ Hz, 1H, ArH), 7.40 (t, $J = 7.6$ Hz, 1H, ArH), 7.74 (d, $J = 8.0$ Hz, 1H, ArH), 7.86 (d, $J = 8.0$ Hz, 1H, ArH).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 20.8 (COCH$_3$), 25.8 (C-2), 27.5 (C-3), 32.8 (C-1), 63.7 (C-4), 120.8 (ArH), 121.3 (ArH), 124.1 (ArH), 125.9 (ArH), 135.0 (Ar), 153.1 (Ar), 166.6 (N=CS$_2$), 171.0 (C=O).

FTIR (KBr, cm$^{-1}$): 2955, 1738, 1460, 1427, 1365, 1309, 1240, 1047.

HRMS (ES): calc C$_{13}$H$_{16}$NO$_2$S$_2$ (MH$^+$): 282.0622; obs. 282.0629.

4-Acetoxybutylsulfonyl benzothiazole (2.85):

Ammonium molybdate (35.1 g, 28 mmol) was added to a solution of 50% aqueous H$_2$O$_2$ solution (32.8 mL, 570 mmol) at 0°C. An ice cold solution of thioester 2.88 (19.8 g, 71 mmol) in aqueous ethanol (100 mL) was added to the resulting bright yellow complex, and the mixture further diluted with the addition of 700 mL of ice cold aqueous ethanol. The cloudy yellow reaction mixture was warmed slowly to room temperature and stirred overnight. The reaction mixture was diluted with Et$_2$O and washed with water and brine. The organic layer was removed and the aqueous washings extracted with Et$_2$O (x2). The combined organic extracts were washed with brine, dried and concentrated under reduced pressure. Purification of the crude material via flash chromatography on silica, eluting with 80% Et$_2$O/petroleum ether provided the title compound as a white solid (16.5 g, 74%).

Mp: 53-54°C.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.79 (m, 2H, H-3), 1.97 (m, 2H, H-2), 1.99 (s, 3H, COCH$_3$), 3.54 (m, 2H, H-1), 4.05 (t, $J = 6.2$ Hz, 2H, H-4), 7.61 (m, 2H, ArH), 8.01 (d, $J = 7.4$ Hz, 1H, ArH), 8.20 (d, $J = 7.6$ Hz, 1H, ArH).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 19.2 (C-2), 20.7 (COCH$_3$), 27.0 (C-3), 54.0 (C-1), 63.0 (C-4), 122.3 (ArH), 125.3 (ArH), 127.6 (ArH), 128.0 (ArH), 136.6 (Ar), 152.5 (Ar), 165.5 (N=CS$_2$), 170.8 (C=O).
FTIR (KBr, cm$^{-1}$): 2955, 1734, 1474, 1427, 1366, 1327, 1242, 1150, 1049.

HRMS (ES): calc. C$_{13}$H$_{16}$NO$_4$S$_2$ (MH$^+$): 314.0521; obs. 314.0520.

3-(tert-Butyldimethylsilyloxy)propan-1-ol (2.89):

Following the method of Hall and co-workers,$^{17}$ imidazole (7.6 g, 0.12 mol) and tert-butyldimethylsilyl chloride (18.02 g, 0.12 mol) were successively added to a solution of propane-1,3-diol (40 mL, 0.6 mol) in THF (300 mL) at 0°C. After stirring overnight at room temperature the reaction mixture was diluted with CH$_2$Cl$_2$, washed with water (x5), dried and concentrated. Purification of the crude material via flash chromatography on silica, eluting with 30% EtOAc/petroleum ether, provided the product as a colourless oil (17.54 g, 77% yield). Values from the $^1$H NMR spectrum were in close agreement with the reported values.$^{17}$

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.05 (s, 6H, SiCH$_3$), 0.88 (s, 9H, SiC(CH$_3$)$_3$), 1.76 (qn, $J = 5.6$ Hz, 2H, H-2), 3.78 (t, $J = 5.6$ Hz, 2H, H-1 or H-3), 3.81 (t, $J = 5.6$ Hz, 2H, H-1 or H-3).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ -5.5 (SiCH$_3$), 18.1 (SiC(CH$_3$)$_3$), 25.8 (SiC(CH$_3$)$_3$), 34.2 (C-2), 62.2 (C-1 or C-3), 62.8 (C-1 or C-3).

FTIR (KBr, cm$^{-1}$): 3364, 2932, 2858, 1474, 1258, 1096, 1007.

HRMS (EI): calc. C$_5$H$_{13}$O$_2$Si (M$^+$- t-Bu): 133.0685; obs. 133.0689.

3-(tert-Butyldimethylsilyloxy)propanal (2.90):

A solution of alcohol 2.89 (14.3 g, 75 mmol) in CH$_2$Cl$_2$ (20 mL) was added, via cannula, to a solution of Dess-Martin periodinane (35 g, 83 mmol) in CH$_2$Cl$_2$ (330 mL) at room temperature. After stirring for 1 h at room temperature the reaction mixture was diluted with Et$_2$O (300 mL), then stirred for $\sim$10 min with 1M aqueous NaOH solution (300 mL) to dissolve the white precipitate. The organic layer was removed, and the aqueous portion extracted with Et$_2$O (x2). The combined organic portions were washed with 1M aqueous NaOH solution, then brine, dried and concentrated to provide 2.90 as a pale yellow oil (12.96 g, 92%), which was used without
further purification. Values from the $^1$H NMR spectrum were in close agreement with the reported values.$^{18}$

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.05 (s, 6H, SiCH$_3$), 0.86 (s, 9H, SiC(CH$_3$)$_3$), 2.58 (dt, $J = 2.1$, 6.0 Hz, 2H, H-2), 3.97 (t, $J = 6.0$ Hz, 2H, H-3), 9.78 (t, $J = 2.1$, 1H, H-1).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ -5.5 (SiCH$_3$), 18.2 (SiC(CH$_3$)$_3$), 25.8 (SiC(CH$_3$)$_3$), 46.5 (C-2), 57.3 (C-3), 202.0 (C-1).

FTIR (KBr, cm$^{-1}$): 2955, 2862, 1728, 1466, 1389, 1258, 1103.

Methyl (E)- 5-(tert-butyldimethylsilyloxy)-2-methylpent-2-enoate (2.93):

1-(Methoxycarbonyl) ethyldenetriphenylphosphorane (2.91) (26 g, 75 mmol) was added in one portion to a solution of aldehyde 2.90 (12.96 g, 69 mmol) in toluene (400 mL). The reaction mixture was refluxed for 18 h before being cooled to room temperature. Toluene was removed under reduced pressure and petroleum ether added to the residue. The precipitated triphenylphosphine oxide was removed via filtration and the filtrate concentrated. Purification of the crude material via flash chromatography on silica eluting with 7% Et$_2$O/petroleum ether provided 2.93 as a colourless oil (13.23 g, 75%).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.03 (s, 6H, SiCH$_3$), 0.87 (s, 9H, SiC(CH$_3$)$_3$), 1.83 (s, 3H, CH$_3$), 2.39 (m, 2H, H-4), 3.68 (t, $J = 6.7$ Hz, 2H, H-5), 3.71 (s, 3H, CO$_2$CH$_3$), 6.76 (m, 1H, H-3).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ -5.4 (SiCH$_3$), 12.5 (CH$_3$), 18.3 (SiC(CH$_3$)$_3$), 25.9 (SiC(CH$_3$)$_3$), 32.4 (C-4), 51.7 (CO$_2$CH$_3$), 61.7(C-5), 129.0 (C-2), 138.8 (C-3), 168.5 (C-1).

FTIR (KBr, cm$^{-1}$): 2955, 2862, 1720, 1651, 1466, 1389, 1258, 1103.

HRMS (ES): calc. C$_{13}$H$_{27}$O$_3$Si (MH$^+$) 259.1729; obs. 259.1739.
Ethyl \((E)-5-\text{tert-butyldimethylsilyloxy})-2\text{-methylpent-2-enoate (2.94):}\)

\[
\text{CH}_3\text{CO}_2\text{CH}_2\text{CH} = \text{CH}_2 + \text{Ph}_3\text{P} + \text{Si(CH}_3)_2\text{O} \rightarrow \text{CH}_3\text{CO}_2\text{CH}_2\text{CH} = \text{CH}_2 + \text{O} + \text{Ph}_3\text{P} + \text{Si(CH}_3)_2\text{O}
\]

The ethyl ester was prepared as described above from aldehyde 2.90 (4.62 g, 23 mmol) and 1-(ethoxycarbonyl) ethylidenetriphenylphosphorane (2.92) (9.0 g, 25 mmol). Flash chromatography on silica eluting with 5% EtO\_2/ petroleum ether gave the title compound as a colourless oil (4.38 g, 70%). Values from the \(^1\)H NMR spectrum were in agreement with the reported values.\(^{19}\)

\(^1\)H NMR (500 MHz, CDCl\_3): \(\delta 0.04\) (s, 6H, Si\(\text{C(CH}_3)_3\)), \(0.88\) (s, 9H, Si\(\text{C(CH}_3)_3\)), \(1.27\) (t, \(J = 7.1\) Hz, 3H, CO\(\text{O}_2\text{CH}_2\text{CH}_3\)), \(1.83\) (s, 3H, CH\(3\)), \(2.39\) (m, 2H, H-4), \(3.69\) (t, \(J = 6.7\) Hz, 2H, H-5), \(4.17\) (q, \(J = 7.1\) Hz, 2H, CO\(\text{O}_2\text{CH}_2\text{CH}_3\)), \(6.76\) (m, 1H, H-3).

\(^{13}\)C NMR (75 MHz, CDCl\_3): \(\delta -5.4\) (Si\(\text{CH}_3\)), \(12.5\) (CH\(3\)), \(14.2\) (CO\(\text{O}_2\text{CH}_2\text{CH}_3\)), \(18.3\) (Si\(\text{C(CH}_3)_3\)), \(25.9\) (Si\(\text{C(CH}_3)_3\)), \(32.4\) (C-4), \(60.4\) (CO\(\text{O}_2\text{CH}_2\text{CH}_3\)), \(61.7\) (C-5), \(129.2\) (C-2), \(138.5\) (C-3), \(168.0\) (C-1).

FTIR (KBr, cm\(^{-1}\)): 2957, 2931, 2896, 2858, 1713, 1464, 1257, 1105.

HRMS (EI): calc. C\(_{13}\)H\(_{25}\)O\(_3\)Si (M\(^+\) - Me): 257.1573; obs. 257.1570.

\((E)-5-\text{tert-Butyldimethylsilyloxy})-2\text{-methylpent-2-en-1-ol (2.95):}\)

DIBAL-H (139 mL of a 1M solution in hexanes, 139 mmol) was slowly added to a solution of ester 2.94 (12.01 g, 46 mmol) in Et\(_2\)O (450 mL) at -78°C. After stirring at -78°C for 1 h the reaction mixture was warmed to 0°C and stirred for an additional 1 h. The reaction was quenched by the slow addition of methanol and then stirred with saturated aqueous Na/K tartrate solution for \(\sim 2\) h until the layers cleared and separated. The organic layer was removed and the aqueous layer extracted with EtOAc (x3). The combined organics were washed with brine, dried and concentrated to provide 2.95 as a colourless oil (9.47 g, 89%), which was used without further purification. Values from the \(^1\)H NMR spectrum were in close agreement with the reported values.\(^{19}\)
$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.04 (s, 6H, SiCH$_3$), 0.87 (s, 9H, SiC(CH$_3$)$_3$), 1.66 (s, 3H, CH$_3$), 2.26 (m, 2H, H-4), 3.60 (t, $J = 7.1$ Hz, 2H, H-5), 3.99 (s, 2H, H-1), 5.41 (m, 1H, H-3).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ -5.3 (SiCH$_3$), 13.8 (CH$_3$), 18.3 (SiC(CH$_3$)$_3$), 25.9 (SiC(CH$_3$)$_3$), 31.4 (C-4), 62.7 (C-5), 68.8 (C-1), 122.1 (C-3), 136.6 (C-2).

FTIR (KBr, cm$^{-1}$): 3348, 2932, 2858, 1474, 1258, 1096, 1007.

HRMS (EI): calc. C$_8$H$_{17}$O$_2$Si (M$^+$ - t-Bu): 173.0998; obs. 173.0999.

$(E)$-5-(tert-Butyldimethylsilyloxy)-2-methylpent-2-enal (2.86):

A solution of alcohol 2.95 (9.01 g, 39 mmol) in CH$_2$Cl$_2$ (40 mL) was added, via cannula, to a solution of Dess-Martin periodinane (18.2 g, 43 mmol) in CH$_2$Cl$_2$ (200 mL) at room temperature. After stirring for 1 h at room temperature the reaction mixture was diluted with Et$_2$O (250 mL), then stirred for ~10 min with 1M aqueous NaOH solution (250 mL) to dissolve the white precipitate. The organic layer was removed, and the aqueous portion extracted with Et$_2$O (x2). The combined organic portions were washed with 1M aqueous NaOH solution, then brine, dried and concentrated to provide 2.86 as a pale yellow oil (8.73 g, 98%), which was used without further purification. Values from the $^1$H NMR spectrum were in close agreement with the reported values.$^{20}$

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.04 (s, 6H, SiCH$_3$), 0.87 (s, 9H, SiC(CH$_3$)$_3$), 1.74 (s, 3H, CH$_3$), 2.55 (m, 2H, H-4), 3.76 (t, $J = 6.3$ Hz, 2H, H-5), 6.54 (m, 1H, H-3), 9.40 (s, 1H, H-1).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ -5.4 (SiCH$_3$), 9.3 (CH$_3$), 18.2 (SiC(CH$_3$)$_3$), 25.8 (SiC(CH$_3$)$_3$), 32.6 (C-4), 61.3 (C-5), 140.5 (C-2), 151.3 (C-3), 195.2 (C-1).

FTIR (KBr, cm$^{-1}$): 2955, 2932, 2858, 1693, 1647, 1474, 1258, 1103, 1057.

HRMS (EI): calc. C$_8$H$_{15}$O$_2$Si (M$^+$ - t-Bu): 171.0841; obs. 171.0843.
(E)-2-(5-(tert-Butyldimethylsilyloxy)-2-methylpent-2-enylthio)benzothiazole (2.96):

A solution of DEAD (1.12 mL, 7.2 mmol) in THF (2 mL) was added dropwise to a mixture of alcohol 2.95 (1.56 g, 6.5 mmol), triphenylphosphine (1.91 g, 7.2 mmol) and 2-mercaptobenzothiazole (1.20 g, 7.2 mmol) in THF (20 mL) at room temperature. The mixture was stirred overnight and the solvent removed under reduced pressure. 20% EtOAc/petroleum ether (30 mL) was added to the residue and the precipitated triphenylphosphine oxide was removed via filtration. The filtrate was concentrated and the crude material purified by flash chromatography on silica, eluting with 50% Et2O/petroleum ether, to provide the title compound as a pale yellow oil (1.97 g, 80%).

1H NMR (500 MHz, CDCl3): \( \delta \) 0.02 (s, 6H, SiCH3), 0.87 (s, 9H, SiC(CH3)3), 1.79 (s, 3 3H, CH3), 2.25 (m, 2H, H-4), 3.57 (t, \( J = 6.9 \) Hz, 2H, H-5), 3.99 (s, 2H, H-1), 5.57 (m, 1H, H-3), 7.28 (m, 1H, ArH), 7.40 (m, 1H, ArH), 7.74 (d, \( J = 8.0 \) Hz, 1H, ArH), 7.86 (d, \( J = 8.0 \) Hz, 1H, ArH).

13C NMR (75 MHz, CDCl3): \( \delta \) -5.3 (SiCH3), 15.5 (CH3), 18.3 (SiC(CH3)3), 25.9 (SiC(CH3)3), 32.0 (C-4), 43.0 (C-1), 62.4 (C-5), 120.9 (ArH), 121.5 (ArH), 124.2 (ArH), 126.0 (ArH), 126.8 (C-3), 131.2 (C-2), 135.3 (Ar), 153.1 (Ar), 167.1 (N=CS2).

FTIR (KBr, cm\(^{-1}\)): 2932, 2862, 1466, 1427, 1249, 1103.


TIPS protected sequence:

3-(Triisopropylsilyloxy)propan-1-ol (2.98):

Imidazole (0.64 g, 9.4 mmol) and triisopropylsilyl chloride (2 mL, 9.4 mmol) were successively added to a solution of propane-1,3-diol (3.4 mL, 47 mmol) in DMF (25 mL) at 0°C. After stirring overnight at room temperature the reaction mixture was diluted with CH2Cl2, washed with water (x5), dried and concentrated. Purification of the crude material via flash chromatography on silica, eluting with 20% EtOAc/petroleum ether, provided the product as a colourless oil (1.63 g,
76% yield). The spectroscopic data obtained for 2.98 was in agreement with the reported literature values.\(^{21}\)

\(\text{\(^1\)H NMR}\) (500 MHz, CDCl\(_3\)): \(\delta\) 1.08 (m, 21H, SiCH(CH\(_3\))\(_2\) and SiCH(CH\(_3\))\(_2\)), 1.78 (m, 2H, H-2), 3.81 (t, \(J = 5.5\) Hz, 2H, H-1 or H-3), 3.91 (t, \(J = 5.5\) Hz, 2H, H-1 or H-3).

\(\text{\(^{13}\)C NMR}\) (75 MHz, CDCl\(_3\)): \(\delta\) 11.7 (SiCH(CH\(_3\))\(_2\)), 17.9 (SiCH(CH\(_3\))\(_2\)), 34.1 (C-2), 62.8 (C-1 or C-3), 63.7 (C-1 or C-3).

\(\text{FTIR}\) (KBr, cm\(^{-1}\)): 3352, 2945, 2893, 2868, 1464, 1107, 1069, 1015.

\(\text{HRMS (EI)}\): calc. C\(_9\)H\(_{21}\)O\(_2\)Si (M\(^+\) - i-Pr): 189.1311; obs. 189.1318.

3-(Triisopropylsilyloxy)propanal (2.99):

\[
\text{HO} \quad \text{OTIPS} \quad \text{OHC} \quad \text{OTIPS}
\]

A solution of alcohol 2.98 (1.5 g, 6.4 mmol) in CH\(_2\)Cl\(_2\) (2 mL) was added, via cannula, to a solution of Dess-Martin periodinane (3.02 g, 7.1 mmol) in CH\(_2\)Cl\(_2\) (30 mL) at room temperature. After stirring for 1 h at room temperature the reaction mixture was diluted with Et\(_2\)O (30 mL), then stirred for \(~10\) min with 1M aqueous NaOH solution (30 mL) to dissolve the white precipitate. The organic layer was removed, and the aqueous portion extracted with Et\(_2\)O (x2). The combined organic portions were washed with 1M aqueous NaOH solution, then brine, dried and concentrated to provide 2.99 as a colourless oil (1.43 g, 96%), which was used without further purification. \(\text{\(^1\)H NMR}\) data was in agreement with the reported literature values.\(^{22}\)

\(\text{\(^1\)H NMR}\) (500 MHz, CDCl\(_3\)): \(\delta\) 1.04 (m, 21H, SiCH(CH\(_3\))\(_2\) and SiCH(CH\(_3\))\(_2\)), 2.60 (dt, \(J = 6.1, 2.2\) Hz, 2H, H-2), 4.07 (t, \(J = 6.1\) Hz, 2H, H-3), 9.82 (t, \(J = 2.2\) Hz, 1H, H-1).

\(\text{\(^{13}\)C NMR}\) (75 MHz, CDCl\(_3\)): \(\delta\) 11.8 (SiCH(CH\(_3\))\(_2\)), 17.9 (SiCH(CH\(_3\))\(_2\)), 46.7 (C-2), 57.9 (C-3), 202.2 (C-1).

\(\text{FTIR}\) (KBr, cm\(^{-1}\)): 2943, 2866, 1728, 1466, 1389, 1111, 1069.
Ethyl (E)-5-(triisopropylsilyloxy)-2-methylpent-2-enoate (2.100):

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{PPh}_3 \quad \begin{array}{c}
\text{OHC} \\
\text{OTIPS}
\end{array} \\
2.92 & \quad + \quad \begin{array}{c}
\text{OHC} \\
\text{OTIPS}
\end{array} \\
2.99 & \quad \rightarrow \quad \begin{array}{c}
\text{EtO}_2\text{C} \\
\text{OTIPS}
\end{array} \\
2.100 &
\end{align*}
\]

The ethyl ester was prepared, as described for the preparation of 2.93, from aldehyde 2.99 (1.3 g, 5.6 mmol) and 1-(ethoxycarbonyl) ethylidenetriphenylphosphorane (2.92) (2.24 g, 6.2 mmol). Flash chromatography on silica eluting with 5% Et₂O/petroleum ether gave the title compound as a colourless oil (1.48 g, 84%).

\[^{1}\text{H NMR} \ (500 \text{ MHz, CDCl}_3): \delta \ 1.05 \ (m, \ 21H, \ Si\text{CH(CH}_3)_2 \ \text{and SiCH(CH}_3)_2), \ 1.27 \ (t, \ J = 7.1 \ Hz, \ 3H, \ OCH}_2\text{CH}_3), \ 1.84 \ (s, \ 3H, \ CH}_3), \ 2.42 \ (m, \ 2H, \ H-4), \ 3.77 \ (t, \ J = 6.7 \ Hz, \ 2H, \ H-5), \ 4.17 \ (q, \ J = 7.1 \ Hz, \ 2H, \ OCH}_2\text{CH}_3), \ 6.81 \ (m, \ 1H, \ H-3).\]

\[^{13}\text{C NMR} \ (75 \text{ MHz, CDCl}_3): \delta \ 11.9 \ (\text{SiCH(CH}_3)_2), \ 12.5(\text{CH}_3), \ 14.2 \ (\text{OCH}_2\text{CH}_3), \ 17.9 \ (\text{SiCH(CH}_3)_2), \ 32.5 \ (\text{C-4}), \ 60.4 \ (\text{OCH}_2\text{CH}_3), \ 62.0 \ (\text{C-5}), \ 129.1 \ (\text{C-2}), \ 138.6 \ (\text{C-3}), \ 168.1 \ (\text{C-1}).\]

\[^{\text{FTIR}} \ (\text{KBr, cm}^{-1}): \ 2943, \ 2893, \ 2866, \ 1713, \ 1462, \ 1277, \ 1246, \ 1211, \ 1107.\]

\[^{\text{HRMS}} \ (\text{EI}): \ \text{calc.} \ \text{C}_14\text{H}_{27}\text{O}_3\text{Si} (\text{M}^+ - \text{i-Pr}: 271.1729; \ \text{obs.} \ 271.1732.\]

\((E)-2\text{-Methyl-5-(triisopropylsilyloxy)pent-2-en-1-ol} \ (2.101):

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \begin{array}{c}
\text{OTIPS}
\end{array} \\
2.100 & \quad \rightarrow \quad \begin{array}{c}
\text{HO} \\
\text{OTIPS}
\end{array} \\
2.101 &
\end{align*}
\]

DIBAL-H (12.0 mL of a 1M solution in toluene, 12 mmol) was slowly added to a solution of ester 2.100 (1.23 g, 3.9 mmol) in Et₂O (50 mL) at –78°C. After stirring at –78°C for 1 h the reaction mixture was warmed to 0°C and stirred for an additional 1 h. The reaction was quenched by the slow addition of methanol and then stirred with saturated aqueous Na/K tartrate solution for ~2 h until the layers cleared and separated. The organic layer was removed and the aqueous layer extracted with EtOAc (x3). The combined organics were washed with brine, dried and concentrated to provide 2.101 as a colourless oil (1.12 g, 100%), which was used without further purification. \[^{1}\text{H NMR data was in agreement with the reported literature values.}\]

\[^{1}\text{H NMR} \ (500 \text{ MHz, CDCl}_3): \delta \ 1.05 \ (m, \ 21H, \ Si\text{CH(CH}_3)_2 \ \text{and SiCH(CH}_3)_2), \ 1.68 \ (s, \ 3H, \ CH}_3), \ 2.30 \ (m, \ 2H, \ H-4), \ 3.68 \ (t, \ J = 7.1 \ Hz, \ 2H, \ H-5), \ 4.00 \ (s, \ 2H, \ H-1), \ 5.44 \ (t, \ J = 7.1 \ Hz, \ 1H, \ H-3).\]
\(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)): \(\delta\) 12.0 (SiCH(CH\(_3\))\(_2\)), 13.8 (CH\(_3\)), 18.0 (SiCH(CH\(_3\))\(_2\)), 31.6 (C-4), 62.9 (C-5), 68.9 (C-1), 122.3 (C-3), 136.5 (C-2).

\textbf{FTIR} (KBr, cm\(^{-1}\)): 3230, 2944, 2926, 2894, 2867, 1466, 1383, 1110, 1070, 1014.


\((E)-2\)-methyl-5-(triisopropylsilyloxy)pent-2-enal (2.102):

A solution of 2.101 (0.45 g, 17 mmol) in CH\(_2\)Cl\(_2\) (2 mL) was added, via cannula, to a solution of Dess-Martin periodinane (0.77 g, 18 mmol) in CH\(_2\)Cl\(_2\) (10 mL) at room temperature. After stirring for 1 h at room temperature the reaction mixture was diluted with Et\(_2\)O (15 mL), then stirred for \(\sim\)10 min with 1M aqueous NaOH solution (15 mL) to dissolve the white precipitate. The organic layer was removed, and the aqueous portion extracted with Et\(_2\)O (x2). The combined organic portions were washed with 1M aqueous NaOH solution, then brine, dried and concentrated to provide 2.102 as a pale yellow oil (0.42 g, 94%), which was used without further purification. Values from the \(^1\text{H NMR}\) spectrum were in agreement with the reported literature values.\(^{23}\)

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)): \(\delta\) 1.05 (m, 21H, SiCH(CH\(_3\))\(_2\) and SiCH(CH\(_3\))\(_2\)), 1.76 (s, 3H, CH\(_3\)), 2.58 (m, 2H, H-4), 3.85 (t, \(J = 6.3\) Hz, 2H, H-5), 6.60 (t, \(J = 7.2\) Hz, 1H, H-3), 9.41 (s, 1H, H-1).

\(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)): \(\delta\) 9.3 (CH\(_3\)), 11.9 (SiCH(CH\(_3\))\(_2\)), 17.9 (SiCH(CH\(_3\))\(_2\)), 32.8 (C-4), 61.7 (C-5), 140.4 (C-2), 151.5 (C-3), 195.3 (C-1).

\textbf{FTIR} (KBr, cm\(^{-1}\)): 2943, 2893, 2866, 1692, 1464, 1109.

\((E)-2\)-(2-Methyl-5-(triisopropylsilyloxy)pent-2-enylthio)benzothiazole (2.103):

\textbf{DEAD} (0.32 mL, 2.02 mmol) in THF (2 mL) was added dropwise to a mixture of alcohol 2.101 (0.5 g, 1.83 mmol), triphenylphosphine (0.53 g, 2.02 mmol) and 2-mercaptobenzothiazole (0.34
g, 2.02 mmol) in THF (4 mL) at room temperature. The mixture was stirred overnight and the solvent removed under reduced pressure. 20% EtOAc/petroleum ether was added to the residue and the precipitated triphenylphosphine oxide was removed via filtration. The filtrate was concentrated and the crude material purified by flash chromatography on silica, eluting with 5% Et₂O/petroleum ether, to provide the title compound as a pale yellow oil (0.56 g, 73%).

\(^1\)H NMR (500 MHz, CDCl₃): \(\delta\) 1.04 (m, 21H, SiCH(CH₃)₂ and SiCH(CH₃)₂), 1.80 (s, 3H, CH₃), 2.29 (m, 2H, H-4), 3.64 (t, \(J = 6.9\) Hz, 2H, H-5), 4.00 (s, 2H, H-1), 5.61 (dt, \(J = 1.1, 7.2\) Hz, 1H, H-3), 7.29 (m, 1H, ArH), 7.40 (m, 1H, ArH), 7.74 (d, \(J = 7.3\) Hz, 1H, ArH), 7.87 (d, \(J = 8.1\) Hz, 1H, ArH).

\(^13\)C NMR (75 MHz, CDCl₃): \(\delta\) 11.9 (SiC(CH₃)₂), 15.4 (CH₃), 18.0 (SiCH(CH₃)₂), 32.1 (C-4), 43.1 (C-1), 62.6 (C-5), 120.9 (ArH), 121.5 (ArH), 124.2 (ArH), 126.0 (ArH), 127.0 (C-3), 131.0 (C-2), 135.3 (Ar), 153.2 (Ar), 167.3 (N=CS₂).

FTIR (KBr, cm\(^{-1}\)): 2943, 2892, 2865, 1462, 1428, 1384, 1239, 1107, 1072, 1017.

HRMS (ES): calc C₂₂H₃₅NOS₂Si (MH\(^{+}\)): 422.2007; obs. 422.2009.

\((E)\)-2-(2-Methyl-5-(triisopropylsiloxyl)pent-2-enylsulfonyl)benzothiazole (2.104):

\[ \text{Ammonium molybdate (0.7 g, 0.56 mmol) was added to a 50\% aqueous H}_2\text{O}_2 \text{ solution (0.75 mL, 26 mmol) at 0°C. An ice cold solution of thioester 2.103 (0.65 g, 1.54 mmol) in aqueous ethanol (15 mL) was added to the resulting bright yellow complex, and the mixture was further diluted by the addition of 10 mL of ice cold aqueous ethanol. The cloudy yellow reaction mixture was warmed slowly to room temperature and stirred overnight. The reaction mixture was diluted with Et}_2\text{O and washed with water and brine. The organic layer was removed and the aqueous washings extracted with Et}_2\text{O (x2). The combined organic extracts were washed with brine, dried and concentrated under reduced pressure. Purification via flash chromatography on silica, eluting with 15\% EtOAc/petroleum ether provided the title compound as a colourless oil (0.39 g, 55%).} \]
1H NMR (500 MHz, CDCl3): δ 0.97 (m, 21H, SiCH(CH3)2 and SiCH(CH3)2), 1.85 (s, 3H, CH3), 2.17 (m, 2H, H-4), 3.35 (t, J = 7.2 Hz, 2H, H-5), 4.15 (s, 2H, H-1), 5.32 (t, J = 7.2 Hz, 1H, H-3), 7.60 (m, 2H, ArH), 7.98 (d, J = 7.4 Hz, 1H, ArH), 8.21 (d, J = 6.8 Hz, 1H, ArH).

13C NMR (75 MHz, CDCl3): δ 11.8 (SiC(CH3)2), 16.9 (CH3), 17.9 (SiCH(CH3)2), 32.3 (C-4), 62.0 (C-5), 64.5 (C-1), 122.2 (ArH), 123.7 (C-2), 125.4 (ArH), 127.6 (ArH), 127.9 (ArH), 133.9 (C-3), 136.8 (Ar), 152.6 (Ar), 165.5 (N=CS2).

FTIR (KBr, cm\(^{-1}\)): 2943, 2866, 2892, 1473, 1389, 1334, 1316, 1164, 1136, 1106, 1070.

HRMS (ES): calc C22H35NO3S2Si (MH\(^+\)): 454.1906; obs. 454.1908.

**Julia Coupling Experiments:**

Triisopropyl((3E,5E)-9-(4-methoxybenzyloxy)-4-methylnona-3,5-dienyloxy)silane (2.105a)/triisopropyl((3E,5Z)-9-(4-methoxybenzyloxy)-4-methylnona-3,5-dienyloxy)silane (2.105b):

A 1M solution of NaN(TMS)\(_2\) in THF (264 μL, 0.26 mmol) was added dropwise to a solution of sulfone 2.104 (109 mg, 0.24 mmol) and aldehyde 2.83b (50 mg, 0.24 mmol) in THF (2 mL) at –78°C. The reaction mixture was stirred at –78°C for 3 h, warmed to room temperature, and stirred for an additional 1 h. After quenching with saturated aqueous NH\(_4\)Cl solution the aqueous layer was extracted with Et\(_2\)O (x3) and the combined organic extracts washed with brine, dried and concentrated under reduced pressure. Purification of the crude material *via* flash chromatography on silica, eluting with 10% EtOAc/petroleum ether provided an inseparable mixture (2.105a:2.105b = 1:1.3) of the two title dienes as a colourless oil (57 mg, 52%).

1H NMR (500 MHz, CDCl3): δ 1.05 (s, 21H, SiCH(CH3)2 and SiCH(CH3)2), 1.68 (m, 2H, H-8), 1.72 (s, 1.3H, CH3, a), 1.77 (s, 1.7H, CH3, b), 2.17 (m, 0.86H, H-7, a), 2.35 (m, 3.14H, H-7, b and H-2), 3.44 (m, 2H, H-2), 3.68 (m, 2H, H-1), 3.79 (s, 3H, OCH3), 4.41 (s, 2H, OCH2Ar), 5.26 (td, J = 7.3, 11.7 Hz, 0.57H, H-6, b), 5.37 (m, 1H, H-3), 5.54 (m, 0.43H, H-6, a), 5.81 (d, J =
12.0 Hz, 0.57H, H-5, b), 6.05 (d, J = 15.6 Hz, 0.43H, H-5, a), 6.87 (m, 2H, ArH), 7.25 (m, 2H, ArH).

$^{13}$C NMR (75 MHz, CDCl$_3$): δ 11.9 (SiCH(CH$_3$)$_2$), 12.5 (CH$_3$, a), 16.8 (CH$_3$, b), 17.9 (SiCH(CH$_3$)$_2$), 25.3 (C-7, b), 29.3 (C-7, a), 29.6 (C-8, a), 30.3 (C-8, b), 32.07 (C-2, b), 32.12 (C-2, a), 55.1 (OCH$_3$), 62.9 (C-1, b), 63.0 (C-1, a), 69.4 (C-9, a), 69.5 (C-9, b), 72.4 (OCH$_2$Ar, a), 72.5 (OCH$_2$Ar, b), 113.6 (ArH), 126.3 (C-3, a), 126.5 (C-3, b), 127.0 (C-6, a), 128.9 (C-6, b), 129.06 (ArH), 129.09 (ArH), 129.11 (ArH), 130.6 (ArH), 133.1 (C-5, b), 134.1 (C-4, b), 134.9 (C-4 a), 135.1 (C-5, a), 159.0 (ArH).

FTIR (KBr, cm$^{-1}$): 2943, 2893, 2866, 1614, 1514, 1464, 1302, 1248, 1173, 1103, 1072, 1040.

HRMS (ES): calc. C$_{27}$H$_{47}$O$_3$Si (MH$^+$) 447.3294; obs. 447.3310.

Preparation of (4$^E$,6$^E$)-9-(Triisopropylsilyloxy)-6-methylnona-4,6-dien-1-ol (2.109a) and (4$^Z$,6$^E$)-9-(Triisopropylsilyloxy)-6-methylnona-4,6-dien-1-ol (2.109b):

(a) Method One

A 1M solution of NaN(TMS)$_2$ in THF (132 μL, 0.13 mmol) was added dropwise to a solution of sulfone 2.104 (48.7 mg, 0.11 mmol) and aldehyde 2.83a (29.2 mg, 0.22 mmol) in THF (2 mL) at –78°C. The reaction mixture was stirred at –78°C for 3 h, warmed to room temperature, and stirred for an additional 1 h. After quenching with saturated aqueous NH$_4$Cl solution, the aqueous
layer was extracted with Et$_2$O (x3) and the combined organic extracts washed with brine, dried and concentrated under reduced pressure. Purification of the crude material via flash chromatography on silica, eluting with 15% Et$_2$O/petroleum ether provided an inseparable mixture (2.107a:2.107b = 1:2.6) of the two title dienes as a colourless oil (18.8 mg, 47%).

Method Two

A 1M solution of NaN(TMS)$_2$ in THF (3.2 mL, 3.2 mmol) was added dropwise to a solution of sulfone 2.85 (0.91 g, 2.9 mmol) and aldehyde 2.102 0.78 g, 2.9 mmol) in THF (25 mL) at –78°C. The reaction mixture was stirred at –78°C for 3 h, warmed to room temperature, and stirred for an additional 1 h. After quenching with saturated aqueous NH$_4$Cl solution, the aqueous layer was extracted with Et$_2$O (x3) and the combined organic extracts washed with brine, dried and concentrated under reduced pressure. Purification of the crude material via flash chromatography on silica, eluting with 15% Et$_2$O/petroleum ether provided an inseparable mixture (2.107a:2.107b = 3.9:1) of the two title dienes as a colourless oil (0.47 g, 45%).

(4E,6E)-6-Methyl-9-(triisopropylsilyloxy)nona-4,6-dienyl acetate (2.107a) and (4Z,6E)-6-Methyl-9-(triisopropylsilyloxy)nona-4,6-dienyl acetate (2.107b):

$^1$H NMR (500 MHz, CDCl$_3$): δ 1.05 (s, 21H, SiCH(CH$_3$)$_2$ and SiCH(CH$_3$)$_2$), 1.72 (m, 5H, CH$_3$ and H-2), 2.03 (s, 3H, COCH$_3$), 2.15 (m, 1.6H, H-3, a), 2.31 (m, 0.4H, H-3, b), 2.37 (m, 2H, H-8), 3.67 (t, J = 7.2 Hz, 2H, H-9), 4.05 (t, J = 6.7 Hz, 0.4H, H-1, b), 4.06 (t, J = 6.7 Hz, 1H, H-1, a), 5.24 (td, J = 7.3, 11.6 Hz, 0.20H, H-4, b), 5.39 (t, J = 7.4 Hz, 1H, H-7), 5.53 (m, 0.80H, H-4, a), 5.83 (d, J = 11.9 Hz, 0.20H, H-5, b), 6.06 (d, J = 16.0 Hz, 0.80H, H-5, a).

$^{13}$C NMR (75 MHz, CDCl$_3$): δ 12.0 (SiCH(CH$_3$)$_2$), 12.5 (CH$_3$, a), 16.8 (CH$_3$, b), 18.0 (SiCH(CH$_3$)$_2$), 21.0 (COCH$_3$), 25.0 (C-3, b), 28.5 (C-2), 29.1 (C-3, a), 32.2 (C-8), 63.0 (C-9), 64.0 (C-1), 126.1 (C-4, a), 126.8 (C-7), 128.0 (C-4, b), 133.7 (C-6, a), 133.9 (C-6, b), 134.8 (C-5, b), 135.6 (C-5, a), 171.1 (C=O).

FTIR (KBr, cm$^{-1}$): 2943, 2893, 2866, 1744, 1464, 1240, 1105.

HRMS (ES): calc. C$_{21}$H$_{41}$O$_3$Si (MH$^+$) 369.2825; obs. 369.2809.

b) Potassium carbonate (80 mg, 0.58 mmol) was added to a mixture of the acetates 2.107a and 2.107b (0.36 g, 0.97 mmol) in aqueous methanol (12 mL) at room temperature. After stirring for 1.5 h the methanol was removed under reduced pressure and the remaining residue partitioned
between Et₂O and water. The organic layer was removed and the aqueous extracted with Et₂O (x2). The combined organic extracts were washed with brine, dried and concentrated under reduced pressure. Purification via flash chromatography on silica, eluting with 30% EtOAc/petroleum ether, afforded the separation of the two isomers yielding 2.109a (73 mg, 24%), 2.109b (18 mg, 6%) and a mixture of isomers (0.18 g, 58%) as colourless oils.

(4E,6E)-9-(Triisopropylsilyloxy)-6-methylnona-4,6-dien-1-ol (2.109a):

\[ ^1H \text{ NMR (500 MHz, CDCl}_3\text{):} \delta 1.06 \text{ (m, 21H, SiCH(CH}_3\text{)}_2 \text{ and SiCH(CH}_3\text{)}_2 \text{), 1.66 (m, 2H, H-2),} \]
\[ 1.73 \text{ (s, 3H, CH}_3\text{), 2.17 \text{ (m, 2H, H-3), 2.37 \text{ (m 2H, H-8), 3.65 (t, J = 6.50 Hz, 2H, H-1), 3.67 (t, J = 7.1 Hz, 2H, H-9) 5.39 (t, J = 7.4 Hz, 1H, H-7), 5.56 (m, 1H, H-4), 6.08 (d, J = 15.6 Hz, 1H, H-5).} \]

\[ ^13C \text{ NMR (75 MHz, CDCl}_3\text{):} \delta 12.0 \text{ (SiCH(CH}_3\text{)}_2\text{), 12.5 (CH}_3\text{), 18.0 (SiCH(CH}_3\text{)}_2\text{), 29.1 (C-8), 32.2 (C-3), 32.5 (C-2), 62.5 (C-1), 63.0 (C-9), 126.7 (C-7), 126.9 (C-4), 134.9 (C-6), 135.3 (C-5).} \]

FTIR (KBr, cm⁻¹): 3335, 2943, 2893, 2866, 1464, 1383, 1105, 1069.
HRMS (ES): calc. C₁₉H₃₉O₂Si (MH⁺) 327.2719; obs. 327.2715.

(4Z,6E)-9-(Triisopropylsilyloxy)-6-methylnona-4,6-dien-1-ol (2.109b):

\[ ^1H \text{ NMR (500 MHz, CDCl}_3\text{):} \delta 1.05 \text{ (m, 21H, SiCH(CH}_3\text{)}_2 \text{ and SiCH(CH}_3\text{)}_2 \text{), 1.64 (m, 2H, H-2),} \]
\[ 1.77 \text{ (s, 3H, CH}_3\text{), 2.33 \text{ (m, 2H, H-3 and H-8), 3.64 (t, J = 6.5 Hz, 2H, H-9), 3.69 (t, J = 7.0 Hz, 2H, H-1)), 5.28 (td, J = 7.4, 11.7 Hz, 1H, H-4), 5.37 (t, J = 7.3 Hz, 1H, H-7), 5.83 (d, J = 11.7 Hz, 1H, H-5).} \]

\[ ^13C \text{ NMR (75 MHz, CDCl}_3\text{):} \delta 12.0 \text{ (SiCH(CH}_3\text{)}_2\text{), 16.9 (CH}_3\text{), 18.0 (SiCH(CH}_3\text{)}_2\text{), 25.0 (C-3), 32.1 (C-8), 33.2 (C-2), 62.5 (C-1), 63.0 (C-9), 126.7 (C-7), 128.8 (C-4), 133.4 (C-5), 134.0 (C-6).} \]

FTIR (KBr, cm⁻¹): 3350, 2943, 2866, 1464, 1105, 1069.
HRMS (ES): calc. C₁₉H₃₉O₂Si (MH⁺) 327.2719; obs. 327.2707.
Preparation of (4\text{E}, 6\text{E})-9-(\text{tert}-Butyldimethylsilyloxy)-6-methylnona-4,6-dien-1-ol (2.110\text{a}) and (4\text{Z}, 6\text{E})-9-(\text{tert}-Butyldimethylsilyloxy)-6-methylnona-4,6-dien-1-ol (2.110\text{b}):

(a) A 1M solution of NaN(TMS)$_2$ in THF (3.74 mL, 3.74 mmol) was added dropwise to a solution of sulfone 2.85 (1.06 g, 3.4 mmol) and aldehyde 2.86 (0.78 g, 3.4 mmol) in THF (30 mL) at $-78^\circ$C. The reaction mixture was stirred at $-78^\circ$C for 3 h, warmed to room temperature, and stirred for an additional 1 h. After quenching with saturated aqueous NH$_4$Cl solution, the aqueous layer was extracted with Et$_2$O (x3) and the combined organic extracts washed with brine, dried and concentrated under reduced pressure. Purification of the crude material via flash chromatography on silica, eluting with 20% Et$_2$O/petroleum ether provided an inseparable mixture (2.108\text{a}:2.108\text{b} = 3.2:1) of the two title dienes as a colourless oil (0.72 g, 65%).

(4\text{E}, 6\text{E})-9-(\text{tert}-Butyldimethylsilyloxy)-6-methylnona-4,6-dienyl acetate (2.108\text{a}) and (4\text{Z}, 6\text{E})-9-(\text{tert}-Butyldimethylsilyloxy)-6-methylnona-4,6-dienyl acetate (2.108\text{b}):

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.04 (s, 6H, SiCH$_3$), 0.88 (s, 9H, SiC(CH$_3$)$_3$), 1.72 (m, 5 H, CH$_3$ and H-2), 2.03 (s, 3H, COCH$_3$), 2.15 (m, 2H, H-3), 2.31 (m, 2H, H-8), 3.61 (t, $J = 6.9$ Hz, 2H, H-9), 4.05 (t, $J = 6.7$ Hz, 0.48H, H-1, b), 4.06 (t, $J = 6.7$, 1.52H, H-1, a), 5.25 (m, 0.24H, H-4, b), 5.36 (t, $J = 7.4$ Hz, 1H, H-7), 5.53 (m, 0.76H, H-4, a), 5.83 (d, $J = 11.9$ Hz, 0.24H, H-5, b), 6.06 (d, $J = 15.6$ Hz, 0.76H, H-5, a).
$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ -5.3 (SiCH$_3$), 12.5 (CH$_3$, a), 16.8 (CH$_3$, b), 18.3 (Si(CH$_3$)$_3$), 21.0 (COCH$_3$), 25.0 (C-3, b), 25.9 (Si(CH$_3$)$_3$), 28.5 (C-2), 29.1 (C-3, a), 31.9 (C-8, b), 32.0 (C-8, a), 62.75 (C-9, a), 62.69 (C-9, b), 64.0 (C-1), 126.2 (C-4, a), 126.6 (C-7, b), 126.7 (C-7, a), 128.1 (C-4, b), 133.7 (C-6, a), 134.1 (C-6, b), 135.0 (C-5, b), 135.5 (C-5, a), 171.2 (C=O).

**FTIR** (KBr, cm$^{-1}$): 2955, 2930, 2897, 2858, 2361, 2341, 1744, 1742, 1472, 1470, 1443, 1389, 1364, 1242, 1099.

**HRMS** (EI): calc. C$_{14}$H$_{25}$O$_3$Si (M+ - t-Bu): 269.1573; obs. 269.1573.

b) Potassium carbonate (0.56 g, 4.1 mmol) was added to a mixture of the acetates 2.108a and 2.108b (2.22 g, 6.8 mmol) in aqueous methanol (90 mL) at room temperature. After stirring for 1.5 h the methanol was removed under reduced pressure and the remaining residue partitioned between Et$_2$O and water. The organic layer was removed and the aqueous extracted with Et$_2$O (x2). The combined organics were washed with brine, dried and concentrated under reduced pressure. Purification via flash chromatography on silica, eluting with 30% EtOAc/petroleum ether afforded the separation of the two isomers yielding 2.110a (1.35 g, 70%), 2.110b (0.09 g, 5%) and a mixture of isomers (0.32 g, 17%) as colourless oils.

**(4E,6E)-9-(tert-Butyldimethylsilyloxy)-6-methylnona-4,6-dien-1-ol (2.110a):**

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.04 (s, 6H, SiCH$_3$), 0.88 (s, 9H, SiC(CH$_3$)$_3$), 1.66 (m, 2H, H-2), 1.72 (s, 3H, CH$_3$), 2.17 (m, 2H, H-8), 2.34 (m, 2H, H-3), 3.60 (t, $J$ = 7.1 Hz, 2H, H-9), 3.64 (t, $J$ = 6.5 Hz, 2H, H-1), 5.36 (t, $J$ = 7.4 Hz, 1H, H-7), 5.56 (m, 1H, H-4), 6.07 (d, $J$ = 15.5 Hz, 1H, H-5).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ -5.3 (SiCH$_3$), 12.6 (CH$_3$), 18.3 (SiC(CH$_3$)$_3$), 25.9 (Si(CH$_3$)$_3$), 29.1 (C-8), 32.0 (C-3), 32.5 (C-2), 62.5 (C-1), 62.8 (C-9), 126.5 (C-7), 126.9 (C-4), 135.0 (C-6), 135.3 (C-5).

**FTIR** (KBr, cm$^{-1}$): 3352, 2928, 2858, 2361, 2341, 1473, 1389, 1258, 1099.

**HRMS** (ES): calc. C$_{16}$H$_{33}$O$_2$Si (MH$^+$) 285.2250; obs. 285.2239.

**(4E,6E)-9-(tert-Butyldimethylsilyloxy)-6-methylnona-4,6-dien-1-ol (2.110b):**

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.04 (s, 6H, SiCH$_3$), 0.88 (s, 9H, SiC(CH$_3$)$_3$), 1.64 (td, $J$ = 13.7, 6.7 Hz, 2H, H-2), 1.76 (s, 3H, CH$_3$), 2.31 (m, 4H, H-3 and H-8), 3.63 (m, 4H, H-1 and H-9), 5.29 (m, 1H, H-4), 5.34 (t, $J$ = 7.3 Hz, 1H, H-7), 5.83 (d, $J$ = 11.6 Hz, 1H, H-5).
Chapter Five – Experimental Details

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ -5.3 (SiCH$_3$), 16.9 (CH$_3$), 18.3 (SiC(CH$_3$)$_3$), 24.9 (C-3), 25.9 (SiC(CH$_3$)$_3$), 31.9 (C-8), 33.1 (C-2), 62.5 (C-1), 62.8 (C-9), 126.5 (C-7), 128.8 (C-4), 133.4 (C-5), 134.1 (C-6).

FTIR (KBr, cm$^{-1}$): 3356, 2932, 2858, 1258, 1099, 1007.

HRMS (ES): calc. C$_{16}$H$_{33}$O$_2$Si (MH$^+$) 285.2250; obs. 285.2258.

(4E,6E)-9-(tert-Butyldimethylsilyloxy)-6-methylnona-4,6-dienal (2.73):

A solution of alcohol 2.110a (2.50 g, 9.1 mmol) in CH$_2$Cl$_2$ (10 mL) was added, via cannula, to a solution of Dess-Martin periodinane (7.72 g, 18 mmol) and Na$_2$CO$_3$ (2.9 g, 27 mmol) in CH$_2$Cl$_2$ (65 mL) at room temperature. After stirring for 3 h at room temperature the reaction mixture was diluted with Et$_2$O (80 mL), then stirred for ~10 min with 1M aqueous NaOH solution (80 mL) to dissolve the white precipitate. The organic layer was removed, and the aqueous portion extracted with Et$_2$O (x2). The combined organic portions were washed with 1M aqueous NaOH solution, H$_2$O, then brine, dried and concentrated to provide 2.73 as a pale yellow oil (2.05 g, 80%), which was used without further purification.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.04 (s, 6H, SiCH$_3$), 0.88 (s, 9H, SiC(CH$_3$)$_3$), 1.71 (s, 3H, CH$_3$), 2.33 (m, 2H, H-8), 2.42 (m, 2H, H-3), 2.53 (m, 2H, H-4), 3.60 (t, $J = 7.1$ Hz, 2H, H-9), 5.38 (t, $J = 7.3$ Hz, 1H, H-7), 5.55 (m, 1H, H-4), 6.08 (d, $J = 15.6$ Hz, 1H, H-5), 9.77 (t, $J = 1.6$ Hz, 1H, H-1).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ -5.3 (SiCH$_3$), 12.5 (CH$_3$), 18.4 (SiC(CH$_3$)$_3$), 25.4 (C-3), 25.9 (SiC(CH$_3$)$_3$), 32.0 (C-8), 43.6 (C-2), 62.7 (C-9), 125.0 (C-4), 127.3 (C-7), 134.8 (C-6), 136.0 (C-5), 202.2 (C-1).

FTIR (KBr, cm$^{-1}$): 2932, 2862, 2716, 1728, 1466, 1389, 1250, 1103.

HRMS (ES): calc. C$_{16}$H$_{31}$O$_2$Si (MH$^+$) 283.2093; obs. 283.2085.
Preparation of (6E,8E)-3,11-bis(tert-Butyldimethylsilyloxy)-N-methoxy-N,8-dimethylundeca-6,8-dienamide (2.74):

(a) A solution of LDA was prepared at –78°C from N,N-diisopropylamine (810 μL, 8.0 mmol) and n-BuLi (5.5 mL of a 1.6M solution in hexanes, 8.8 mmol) in THF (35 mL). A solution of N-methoxy-N-methyl acetamide (2.121) (1.05 g, 10.2 mmol) in THF (5 mL) was added dropwise to this solution at –78°C. After stirring for 15 min a solution of aldehyde 2.73 (2.05 g, 7.3 mmol) in THF (5 mL) was added dropwise and the reaction mixture stirred at –78°C for 3 h. The reaction was quenched by the addition of saturated aqueous NH₄Cl solution and warmed to room temperature. The reaction mixture was extracted with Et₂O and the combined extracts washed with brine, dried and concentrated to provide the aldol adduct 2.122 as a pale yellow oil (3.12 g). This compound proved unstable to purification via column chromatography, so was used immediately in the next step.

(6E,8E)-11-(tert-Butyldimethylsilyloxy)-3-hydroxy-N-methoxy-N,8-dimethylundeca-6,8-dienamide (2.122):

³¹H NMR (500 MHz, CDCl₃): δ 0.03 (s, 6H, SiCH₃), 0.87 (s, 9H, SiC(CH₃)₃), 1.52 (m, 1H, H-4), 1.64 (m, 1H, H-4), 1.71 (s, 3H, CH₃), 2.20 (m, 2H, H-5), 2.33 (m, 2H, H-10), 2.44 (m, 1H, H-2), 2.65 (m, 1H, H-2), 3.17 (s, 3H, NCH₃), 3.59 (t, J = 7.2 Hz, 2H, H-11), 3.67 (s, 3H, NOCH₃), 4.03 (m, 1H, H-3), 5.34 (t, J = 7.2 Hz, 1H, H-9), 5.56 (m, 1H, H-6), 6.08 (d, J = 15.5 Hz, 1H, H-7).

¹³C NMR (75 MHz, CDCl₃): δ -5.3 (SiCH₃), 12.5 (CH₃), 18.3 (SiC(CH₃)₃), 25.9 (SiC(CH₃)₃), 28.8 (C-5), 31.8 (NCH₃), 32.0 (C-10), 36.3 (C-4), 38.1 (C-2), 61.2 (NOCH₃), 62.8 (C-11), 67.3 (C-3), 126.3 (C-9), 127.0 (C-6), 135.1 (C-8), 135.2 (C-7), 173.8 (C-1).

FTIR (KBr, cm⁻¹): 3449, 2932, 2862, 1651, 1466, 1443, 1389, 1258, 1103.

(b) The crude aldol adduct (2.79 g) was dissolved in DMF (8 mL) and \textit{tert}-butyldimethylsilyl chloride (2.19 g, 14.0 mmol) and imidazole (1.91 g, 28.0 mmol) were added sequentially. The reaction mixture was stirred at room temperature for 40 h, diluted with H$_2$O and extracted with Et$_2$O (x3). The combined extracts were washed with brine, dried and the solvent removed \textit{in-vacuo}. The crude material was purified by flash chromatography on silica, eluting with 20% EtOAc/petroleum ether to provide 2.74 as a colourless oil (2.43 g, 81%).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.02 (s, 3H, SiCH$_3$), 0.04 (s, 6H, SiCH$_3$), 0.06 (s, 3H, SiCH$_3$), 0.86 (s, 9H, SiC(CH$_3)_3$), 0.88 (s, 9H, SiC(CH$_3)_3$), 1.59 (m, 2H, H-4), 1.72 (s, 3H, CH$_3$), 2.15 (m, 2H, H-5), 2.33 (m, 2H, H-10), 2.40 (m, 1H, H-2), 2.71 (m, 1H, H-2), 3.16 (s, 3H, NCH$_3$), 3.60 (t, $J = 7.2$ Hz, 2H, H-11), 3.67 (s, 3H, NOC(CH$_3$)$_3$), 4.24 (m, 1H, H-3), 5.34 (t, $J = 7.4$ Hz, 1H, H-9), 5.55 (dt, $J = 15.5$, 6.9 Hz, 1H, H-6), 6.05 (d, $J = 15.5$ Hz, 1H, H-7).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ -5.3 (SiCH$_3$), -4.7 (SiCH$_3$), -4.6 (SiCH$_3$), 12.5 (CH$_3$), 18.0 (SiC(CH$_3)_3$), 18.4 (SiC(CH$_3)_3$), 25.8 (SiC(CH$_3)_3$), 25.9 (SiC(CH$_3)_3$), 28.4 (C-5), 32.0 (NCH$_3$ and C-10), 37.8 (C-4), 39.6 (C-2), 61.3 (NOCH$_3$), 62.8 (C-11), 69.1 (C-3), 126.2 (C-9), 127.4 (C-6), 134.8 (C-7), 135.1 (C-8), 172.4 (C-1).

FTIR (KBr cm$^{-1}$): 2957, 2930, 2897, 2858, 1670, 1474, 1387, 1256, 1097.

HRMS (ES): calc. C$_{26}$H$_{54}$NO$_4$Si$_2$ (MH$^+$): 500.3591; obs. 500.3549.

\textbf{(6E,8E)-3,11-bis(\textit{tert}-Butyldimethylsilyloxy)-8-methylundeca-6,8-dienal (2.75):}

\begin{center}
\begin{tikzpicture}

\node (A) at (0,0) {\textit{OTBS} N \textit{OMe}};
\node (B) at (1,0) {\textit{OTBS}};
\node (C) at (0,-1) {\textit{TBSO} K \textit{OMe}};
\node (D) at (1,-1) {\textit{TBSO}};
\draw (A) -- (B);
\draw (C) -- (D);
\end{tikzpicture}
\end{center}

DIBAL-H (13.2 mL of a 1M solution in hexanes, 13.2 mmol) was added dropwise over 30 min to a solution of amide 2.74 (2.2 g, 4.4 mmol) in THF (75 mL) at $-78^\circ$C. The reaction mixture was stirred at this temperature for 2 h., quenched with MeOH and poured into a mixture of saturated aqueous Na/K tartrate solution and Et$_2$O, which was stirred vigorously until the layers cleared (~1 h). The organic portion was removed and the aqueous portion extracted with ether (x2). The combined extracts were washed with brine, dried and the solvent removed under reduced
pressure to provide the aldehyde as a pale yellow oil (1.98g, 100%). This was used directly without further purification.

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta \) 0.037 (s, 6H, Si\(\text{CH}_3\)), 0.044 (s, 3H, Si\(\text{CH}_3\)), 0.07 (s, 3H, Si\(\text{CH}_3\)), 0.87 (s, 9H, SiC(\(\text{CH}_3\))\(_3\)), 0.88 (s, 9H, SiC(\(\text{CH}_3\))\(_3\)), 1.62 (m, 2H, H-4), 1.72 (s, 3H, \(\text{CH}_3\)), 2.13 (m, 2H, H-5), 2.34 (m, 2H, H-10), 2.52 (m, 2H, H-2), 3.60 (t, \(J = 7.1\) Hz, 2H, H-11), 4.19 (m, 1H, H-3), 5.36 (t, \(J = 7.5\) Hz, 1H, H-9), 5.52 (m, 1H, H-6), 6.05 (d, \(J = 15.60\) Hz, 1H, H-7), 9.80 (t, \(J = 2.5\) Hz, 1H, CHO).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta \) -5.3 (Si\(\text{CH}_3\)), -4.7 (Si\(\text{CH}_3\)), -4.4 (Si\(\text{CH}_3\)), 12.6 (\(\text{CH}_3\)), 18.0 (SiC(\(\text{CH}_3\))\(_3\)), 18.4 (SiC(\(\text{CH}_3\))\(_3\)), 25.8 (SiC(\(\text{CH}_3\))\(_3\)), 25.9 (SiC(\(\text{CH}_3\))\(_3\)), 28.4 (C-5), 32.0 (C-10), 37.7 (C-4), 50.7 (C-2), 62.8 (C-11), 67.7 (C-3), 126.56 (C-6), 126.64 (C-9), 135.0 (C-8), 135.2 (C-7), 202.2 (C-1).

FTIR (KBr, cm\(^{-1}\)): 2932, 2893, 2862, 1728, 1466, 1381, 1258, 1103.

HRMS (ES): calc. C\(_{24}\)H\(_{49}\)O\(_3\)Si\(_2\) (MH\(^+\)) 441.3220; obs. 441.3221.

(\(2E,8E,10E\))-Ethyl 5,13-bis(tert-butyldimethylsilyloxy)-10-methyltrideca-2,8,10-trienoate (\(2.63\)):

\[ \text{Ph}_3\text{P}=\text{CO}_2\text{Et} \quad 2.123 \]

1-(Ethoxycarbonyl) methylenetriphenylphosphorane (\(2.123\)) (1.55 g, 4.3 mmol) was added in one portion to a solution of aldehyde \(2.75\) (1.70 g, 3.9 mmol) in CH\(_2\)Cl\(_2\) (100 mL) at room temperature. After stirring for 16 h the solvent was removed \textit{in-vacuo} and petroleum ether added to the residue. The precipitated triphenylphosphine oxide was removed by filtration and the filtrate concentrated \textit{in-vacuo} to provide the crude material. Purification of the crude material \textit{via} flash chromatography on silica, eluting with 5% EtOAc/petroleum ether, afforded the title triene as a colourless oil (1.38 g, 69%).
\[ ^1H \text{NMR} \ (500 \text{ MHz, CDCl}_3): \ \delta \ 0.03 \ (s, \ 9H, \ \text{SiCH}_3), \ 0.04 \ (s, \ 3H, \ \text{SiCH}_3), \ 0.877 \ (s, \ 9H, \ \text{SiC(CH}_3)_3), \ 1.27 \ (t, \ J = 7.1 \text{ Hz}, \ 3H, \ \text{OCH}_2\text{CH}_3), \ 1.52 \ (m, \ 2H, \ \text{H-6}), \ 1.72 \ (s, \ 3H, \ \text{CH}_3), \ 2.11 \ (m, \ 2H, \ \text{H-7}), \ 2.34 \ (m, \ 4H, \ \text{H-4 and H-12}), \ 3.60 \ (t, \ J = 7.1 \text{ Hz}, \ 2H, \ \text{H-13}), \ 3.78 \ (m, \ 1H, \ \text{H-5}), \ 4.17 \ (q, \ J = 7.1 \text{ Hz}, \ 2H, \ \text{OCH}_2\text{CH}_3), \ 5.35 \ (t, \ J = 7.1 \text{ Hz}, \ 1H, \ \text{H-11}), \ 5.52 \ (\text{td}, \ J = 15.5, \ 6.9 \text{ Hz}, \ 1H, \ \text{H-8}), \ 5.82 \ (dt, \ J = 15.6, \ 1.4 \text{ Hz}, \ 1H, \ \text{H-2}), \ 6.04 \ (d, \ J = 15.5 \text{ Hz}, \ 1H, \ \text{H-9}), \ 6.94 \ (m, \ 1H, \ \text{H-3}). \]

\[ ^{13}C \text{NMR} \ (75 \text{ MHz, CDCl}_3): \ \delta \ -5.3 \ (\text{SiCH}_3), \ -4.53 \ (\text{SiCH}_3), \ -4.49 \ (\text{SiCH}_3), \ 12.5 \ (\text{CH}_3), \ 14.3 \ (\text{OCH}_2\text{CH}_3), \ 18.1 \ (\text{SiC(CH}_3)_3), \ 18.4 \ (\text{SiC(CH}_3)_3), \ 25.8 \ (\text{SiC(CH}_3)_3), \ 25.9 \ (\text{SiC(CH}_3)_3), \ 28.6 \ (\text{C-7}), \ 32.0 \ (\text{C-12}), \ 37.1 \ (\text{C-6}), \ 40.1 \ (\text{C-4}), \ 60.1 \ (\text{OCH}_2\text{CH}_3), \ 62.8 \ (\text{C-13}), \ 70.8 \ (\text{C-5}), \ 123.3 \ (\text{C-2}), \ 126.3 \ (\text{C-11}), \ 127.2 \ (\text{C-8}), \ 134.9 \ (\text{C-9}), \ 135.1 \ (\text{C-10}), \ 145.8 \ (\text{C-3}), \ 166.4 \ (\text{C}=\text{O}). \]

\[ \text{FTIR (KBr, cm}^{-1}): \ 2932, \ 2862, \ 1728, \ 1466, \ 1366, \ 1258, \ 1180, \ 1103. \]

\[ \text{HRMS (ES): calc. C}_{28}\text{H}_{55}\text{O}_4\text{Si}_2 \ (\text{MH}^+) \ 511.3639; \ \text{obs.} \ 511.3618. \]

Ethyl 7-(\text{tert-butyldimethylsilyloxy})-2-(2-(\text{tert-butyldimethylsilyloxy})ethyl)-3-methyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate (2.64 and 2.66):

A solution of 2.63 (1.57 g, 3.1 mmol) in xylenes (50 mL) was heated at reflux for 48h. After cooling to room temperature the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with 5% Et\text{2}O/petroleum ether, yielding 2.66 (0.14 g, 9%), 2.64 (0.31 g, 19%) and a mixture of isomers (0.24 g, 15%) as colourless oils. Upon storing at 4°C, 2.64 and 2.66 both crystallised to afford colourless plates.

2.64:

\[ \text{Mp:} \ 53-56^\circ \text{C} \]

\[ ^1H \text{NMR (500 MHz, CDCl}_3): \ \delta \ 0.01 \ (s, \ 6H, \ \text{SiCH}_3), \ 0.04 \ (s, \ 3H, \ \text{SiCH}_3), \ 0.05 \ (s, \ 3H, \ \text{SiCH}_3), \ 0.87 \ (s, \ 18H, \ \text{SiC(CH}_3)_3), \ 0.93 \ (m, \ 1H, \ \text{H-8}_b), \ 1.03 \ (\text{ddd}, \ J = 3.7, \ 13.3, \ 26.1 \text{ Hz}, \ 1H, \ \text{H-5}_\text{A}), \ 1.26 \ (t, \ J = 7.1 \text{ Hz}, \ 3H, \ \text{OCH}_2\text{CH}_3), \ 1.33 \ (m, \ 2H, \ \text{H-6}_b \text{ and H-8}_a), \ 1.47 \ (m, \ 1H, \ \text{CH}_2\text{CH}_2\text{OTBS}), \ 1.58 \]
(m, 1H, H-4a), 1.68 (s, 3H, CH₃), 1.70 (m, 1H, H-5B), 1.83-1.92 (m, 2H, H-6A and CH₂CH₂OTBS), 2.11 (m, 1H, H-8A), 2.28 (m, 1H, H-2), 2.50 (dd, J = 5.2, 11.5 Hz, 1H, H-1), 3.37 (dd, J = 9.1, 15.7 Hz, 1H, CH₂CH₂OTBS), 3.49 (ddd, J = 4.5, 7.4, 10.0 Hz, 1H, CH₂CH₂OTBS), 3.64 (m, 1H, H-7), 4.06 (qd, J = 7.1, 10.9 Hz, 1H, OCH₂CH₃), 4.16 (qd, J = 7.1, 10.9 Hz, 1H, OCH₂CH₃), 5.13 (s, 1H, H-4).

**¹³C NMR** (75 MHz, CDCl₃): δ -5.4 (SiCH₃), -5.3 (SiCH₃), -4.64 (SiCH₃), -4.58 (SiCH₃), 14.2 (OCH₂CH₃), 18.20 (SiC(CH₃)₃), 18.24 (SiC(CH₃)₃), 21.9 (CH₃), 25.9 (SiC(CH₃)₃), 30.8 (C-5), 33.8 (CH₂CH₂OTBS), 35.3 (C-8a), 36.2 (C-6), 38.0 (C-2), 39.1 (C-8), 41.9 (C-4a), 49.3 (C-1), 60.0 (OCH₂CH₃), 62.3 (CH₂CH₂OTBS), 71.5 (C-7), 125.4 (C-4), 136.2 (C-3), 173.6 (C=O).

**FTIR** (KBr, cm⁻¹): 2932, 2862, 1728, 1466, 1381, 1250, 1173, 1096.

**HRMS** (ES): calc. C₂₈H₅₅O₄Si₂ (MH⁺) 511.3639; obs. 511.3660.

2.66:

**Mp**: 42-44°C

**¹H NMR** (500 MHz, CDCl₃): δ 0.01 (s, 9H, SiCH₃), 0.06 (s, 3H, SiCH₃), 0.86 (s, 9H, SiC(CH₃)₃), 0.89 (s, 9H, SiC(CH₃)₃), 1.00 (dt, J = 2.0, 12.2 Hz, 1H, H-8A), 1.25 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.41-1.44 (m, 2H, H-5 and H-6B), 1.46-1.54 (m, 2H, H-5 and CH₂CH₂OTBS), 1.60 (m, 1H, H-4a), 1.67 (m, 1H, H-6A), 1.69 (s, 3H, CH₃), 1.86-1.95 (m, 3H, H-8B, H-8a and CH₂CH₂OTBS), 2.31 (m, 1H, H-2), 2.45 (dd, J = 5.3, 11.7 Hz, 1H, H-1), 3.42 (m, 1H, CH₂CH₂OTBS), 3.51 (m, 1H, CH₂CH₂OTBS), 4.06 (m, 2H, OCH₂CH₃ and H-7), 4.14 (m, 1H, OCH₂CH₃), 5.13 (s, 1H, H-4).

**¹³C NMR** (75 MHz, CDCl₃): δ -5.32 (SiCH₃), -5.28 (SiCH₃), -5.0 (SiCH₃), -4.9 (SiCH₃), 14.3 (OCH₂CH₃), 18.0 (SiC(CH₃)₃), 18.2 (SiC(CH₃)₃), 21.9 (CH₃), 25.8 (SiC(CH₃)₃), 25.9 (SiC(CH₃)₃), 27.2 (C-5), 31.0 (C-8a), 33.7 (CH₂CH₂OTBS), 34.2 (C-6), 36.9 (C-8), 38.6 (C-2), 42.8 (C-4a), 49.7 (C-1), 59.8 (OCH₂CH₃), 62.2 (CH₂CH₂OTBS), 67.0 (C-7), 126.7 (C-4), 135.6 (C-3), 173.7 (C=O).

**FTIR** (KBr, cm⁻¹): 2932, 2862, 1736, 1466, 1381, 1250, 1173, 1103, 1042.

**HRMS** (ES): calc. C₂₈H₅₅O₄Si₂ (MH⁺) 511.3639; obs. 511.3642.
Ethyl 3,4-epoxy-7-(tert-butyldimethylsilyloxy)-2-(2-(tert-butyldimethylsilyloxy)ethyl)-3-methyldecahydronaphthalene-1-carboxylate (2.128a and 2.128b):

\[
\begin{align*}
&\text{2.128a} \quad \text{2.128b} \\
&\begin{array}{c}
\text{OTBS} \\
\text{CO}_2\text{Et} \\
\text{H} \\
\text{OTBS} \\
\text{O} \\
\text{O} \\
\text{OTBS} \\
\text{CO}_2\text{Et} \\
\text{H} \\
\text{OTBS} \\
\text{O} \\
\text{O} \\
\text{OTBS} \\
\text{CO}_2\text{Et} \\
\text{H} \\
\text{OTBS} \\
\end{array}
\end{align*}
\]

\(m\)-Chloroperbenzoic acid (14 mg, 78 \(\mu\)mol) was added to a solution of 2.64 (20 mg, 39 \(\mu\)mol) in CH\(_2\)Cl\(_2\) (2 mL) at 0°C. The resulting solution was stirred for 2 h at 0°C and then warmed to room temperature overnight. The solution was diluted with CH\(_2\)Cl\(_2\) and washed with 1:1 saturated aqueous NaHCO\(_3\) solution/saturated aqueous Na\(_2\)S\(_2\)O\(_3\) solution. The aqueous portion was extracted with additional CH\(_2\)Cl\(_2\) (x2) and the combined organic extracts dried and concentrated \textit{in-vacuo} to provide an inseparable mixture of the diastereomeric products (2.128a: 2.128b, 3.5:1) as a white solid (17.9 mg, 87%).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 0.00 (s, 3H, SiCH\(_3\)), 0.01 (s, 3H, SiCH\(_3\)), 0.016 (s, 3H, SiCH\(_3\)), 0.024 (s, 3H, SiCH\(_3\)), 0.85 (s, 9H, Si(C(CH\(_3\)))\(_3\)), 0.86 (s, 9H, Si(C(CH\(_3\)))\(_3\)), 0.87 (m, 1.22H, H-5 and H-6 \textit{b}), 1.19 (m, 0.22H, H-8a, \textit{b}), 1.226 (t, \(J = 7.1\) Hz, 0.66H, OCH\(_2\)CH\(_3\)), 1.230 (t, \(J = 7.1\) Hz, 2.34H, OCH\(_2\)CH\(_3\), \textit{a}), 1.33 (s, 0.66H, CH\(_3\), \textit{b}), 1.35 (s, 2.34H, CH\(_3\), \textit{a}), 1.38 (m, 3.6H, H-4a, H-6 \textit{a}, H-8 and H-8a \textit{a}), 1.57 (m, 1H, CH\(_2\)CH\(_2\)OTBS), 1.75 (m, 1.78H, CH\(_2\)CH\(_2\)OTBS and H-6 \textit{a}), 1.81 (m, 0.22H, H-6, \textit{b}) 1.96 (m, 1H, H-8), 2.07 (dd, \(J = 2.0, 10.0\) Hz, 1H, H-5), 2.19 (q, \(J = 4.4\) Hz, 0.22H, H-2, \textit{b}), 2.30 (dd, \(J = 6.1, 10.7\) Hz, 0.78H, H-1, \textit{a}), 2.39 (q, \(J = 5.8\) Hz, 0.78H, H-2, \textit{a}), 2.57 (dd, \(J = 4.3, 11.2\) Hz, 0.22H, H-1, \textit{b}), 2.63 (s, 0.22H, H-4, \textit{b}), 2.81 (s, 0.78H, H-4, \textit{a}), 3.53 (m, 2H, H-7 and CH\(_2\)CH\(_2\)OTBS), 3.66 (m, 1H, CH\(_2\)CH\(_2\)OTBS), 4.08 (m, 2H, CO\(_2\)CH\(_2\)CH\(_3\)).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) -5.41 (SiCH\(_3\)), -5.38 (SiCH\(_3\)), -4.71 (SiCH\(_3\), \textit{a}), -4.69 (SiCH\(_3\), \textit{b}), -4.66 (SiCH\(_3\), \textit{a}), -4.62 (SiCH\(_3\), \textit{b}), 14.1 (OCH\(_2\)CH\(_3\), \textit{a}), 14.2 (OCH\(_2\)CH\(_3\), \textit{b}), 18.1 (Si(C(CH\(_3\)))\(_3\), 18.2 (Si(C(CH\(_3\)))\(_3\), \textit{a}), 18.3 (Si(C(CH\(_3\)))\(_3\), \textit{b}), 21.7 (CH\(_3\), \textit{b}), 24.3 (CH\(_3\), \textit{a}), 25.8 (Si(C(CH\(_3\)))\(_3\), \textit{a}), 25.85 (Si(C(CH\(_3\)))\(_3\), \textit{b}), 25.88 (Si(C(CH\(_3\)))\(_3\), \textit{a}), 25.94 (Si(C(CH\(_3\)))\(_3\), \textit{b}), 27.4 (C-6, \textit{a}), 29.2 (C-6, \textit{b}), 30.1 (C-8a, \textit{a}, 30.3 (CH\(_2\)CH\(_2\)OTBS, \textit{b}), 30.4 (CH\(_2\)CH\(_2\)OTBS, \textit{a}), 34.4 (C-8a, \textit{b}), 34.6 (C-2, \textit{a}), 36.0 (C-8, \textit{a}), 36.3 (C-8, \textit{b}), 37.4 (C-2, \textit{b}) 38.9 (C-5, \textit{a}), 39.4 (C-5, \textit{b}), 41.5 (C-4a, \textit{b}), 42.2 (C-4a, \textit{a}), 45.4 (C-1, \textit{b}), 49.3 (C-1, \textit{a}), 60.0 (OCH\(_2\)CH\(_3\), \textit{b}), 60.1 (OCH\(_2\)CH\(_3\), \textit{a}), 60.2 (C-3, \textit{a}), 61.1
(CH₂CH₂OTBS, a), 62.0 (C-3, b), 62.6 (CH₂CH₂OTBS, b), 63.0 (C-4, b), 63.8 (C-4, a), 70.9 (C-7, a), 71.2 (C-7, b), 172.5 (C=O, a), 173.6 (C=O, b).

FTIR (KBr, cm⁻¹): 2930, 2858, 1734, 1464, 1379, 1256, 1094.

HRMS (ES): calc. C₂₈H₅₅O₅Si₂ (MH⁺) 527.3588; obs. 527.3564.

Ethyl 3,4-dibromo-7-(tert-butyldimethylsilyloxy)-2-(2-(tert-butyldimethylsilyloxy)ethyl)-3-methyldecahydronaphthalene-1-carboxylate (2.129):

Tetraethylammonium bromide (0.21 g, 0.98 mmol) was added to a solution of 2.64 (0.05 g, 0.098 mmol) in CH₂Cl₂ (2 mL) at room temperature. The reaction mixture was cooled to -78°C and bromine (10 μL, 0.2 mmol) was added. After warming slowly to room temperature and stirring overnight the reaction mixture was diluted with EtOAc and washed with saturated aqueous Na₂S₂O₃ solution. The aqueous portion was extracted with additional EtOAc (x2) and the combined organics extracts washed with brine, dried and concentrated in-vacuo to afford 2.129 as a cream solid (54.5 mg, 83%).

¹H NMR (500 MHz, CDCl₃): δ 0.00 (s, 3H, SiCH₃), 0.01 (s, 3H, SiCH₃), 0.03 (s, 3H, SiCH₃), 0.04 (s, 3H, SiCH₃), 0.86 (s, 9H, SiC(CH₃)₃), 0.87 (s, 9H, SiC(CH₃)₃), 1.00 (q, J = 11.5 Hz, 1H, H-5), 1.27 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.38 (m, 1H, H-6), 1.51 (dd, J = 3.3, 13.5 Hz, 1H, H-8), 1.64 (ddd, J = 3.3, 13.8, 16.5 Hz, 1H, H-8), 1.89 (m, 3H, CH₂CH₂OTBS, H-6 and H-8), 2.12 (m, 3H, CH₂CH₂OTBS, H-4a and H-8), 2.22 (s, 3H, CH₃), 2.50 (br s, 1H, H-2), 3.07 (dt, J = 4.8, 9.9 Hz, 1H, CH₃CH₂OTBS), 3.14 (dd, J = 4.5, 11.5 Hz, 1H, H-1), 3.43 (ddd, J = 3.7, 6.3, 9.9 Hz, 1H, CH₃CH₂OTBS), 3.59 (ddd, J = 4.2, 10.6, 15.0 Hz, 1H, H-7), 4.00 (qd, J = 7.1, 10.8 Hz, 1H, OCH₂CH₃), 4.19 (qd, J = 7.1, 10.8 Hz, 1H, OCH₂CH₃), 4.43 (s, 1H, H-4).

¹³C NMR (75 MHz, CDCl₃): δ -5.42 (SiCH₃), -5.36 (SiCH₃), -4.6 (SiCH₃), 14.1 (OCH₂CH₃), 18.1 (SiC(CH₃)₃), 18.2 (SiC(CH₃)₃), 25.88 (SiC(CH₃)₃), 25.90 (SiC(CH₃)₃), 30.7(C-8 and C-8a),
31.9 (CH$_2$CH$_2$OTBS), 33.1 (CH$_3$), 35.3 (C-6), 39.6 (C-5), 41.5 (C-4a), 46.0 (C-2), 49.6 (C-1),
60.4 (OCH$_2$CH$_3$), 62.8 (CH$_2$CH$_2$OTBS), 64.5 (C-4), 70.4 (C-7), 76.0 (C-3), 173.3 (C=O).

**FTIR** (KBr, cm$^{-1}$): 2929, 2858, 1724, 1384, 1258, 1096, 735.

5.3 **Experiments Described in Chapter Three**

Hex-5-ynyl 4-methylbenzenesulfonate (3.76):

\[
\text{3.75} \quad \rightarrow \quad \text{3.76}
\]

Following the method of Davison and co-workers\textsuperscript{24} 4-toluenesulfonyl chloride (44.5 g, 0.23 mol) was added in one portion to a stirred solution of 5-hexyn-1-ol (3.75) (20 g, 0.21 mol) in pyridine (400 mL) at 0°C. After stirring for 18 h at 4°C saturated aqueous NaHCO\(_3\) solution (800 mL) was added at 0°C. The mixture was poured into additional saturated aqueous NaHCO\(_3\) solution (800 mL) and extracted with Et\(_2\)O (3 x 800 mL). The combined organic extracts were washed with 2M aqueous HCl solution (3 x 800 mL), H\(_2\)O (800 mL) and brine, dried and the solvent removed under reduced pressure. Purification of the crude material via flash chromatography on silica eluting with 30% EtOAc/petroleum ether, provided the title compound as a colourless oil (34.3 g, 65%). Values from the \(^1\)H NMR spectrum were in close agreement with the reported values.\textsuperscript{24}

\(^1\)H NMR (500MHz, CDCl\(_3\)): \(\delta\) 1.53 (dt, \(J = 7.0, 14.4\) Hz, 2H, H-3), 1.75 (m, 2H, H-2), 1.90 (t, \(J = 2.6\) Hz, 1H, H-6), 2.14 (dt, \(J = 7.0, 2.6\) Hz, 2H, H-4), 2.43 (s, 3H, ArCH\(_3\)), 4.03 (t, \(J = 6.3\) Hz, 2H, H-1), 7.33 (d, \(J = 8.0\) Hz, 2H, ArH), 7.77 (d, \(J = 8.0\) Hz, 2H, ArH).

\(^13\)C NMR (75MHz, CDCl\(_3\)): \(\delta\) 17.6 (C-4), 21.5 (ArCH\(_3\)), 24.1 (C-3), 27.6 (C-2), 68.9 (C-6), 69.8 (C-1), 83.3 (C-5), 127.7 (ArH), 129.8 (ArH), 132.9 (ArC), 144.7 (ArC).

FTIR (KBr, cm\(^{-1}\)): 3294, 2955, 1736, 1597, 1450, 1358, 1180, 1096, 1018.

Hept-6-ynenitrile (3.78):

\[
\text{3.76} \quad \rightarrow \quad \text{3.78}
\]

A stirred solution of 3.76 (34.3 g, 0.14 mol) and sodium cyanide (9.5 g, 0.19 mol) in DMSO (150 mL) was heated at 90°C for 2 h. After cooling to room temperature, the reaction mixture was poured into H\(_2\)O (360 mL) and extracted with Et\(_2\)O (x3). The combined organic extracts were washed with H\(_2\)O (x3) and brine, dried and the solvent removed in-vacuo. The pale yellow product was distilled under low vacuum to provide the title compound as a colourless oil (12.77 g, 85%). Values from the \(^1\)H NMR spectrum were in close agreement with the reported values.\textsuperscript{24}
Chapter Five – Experimental Details

1H NMR (500MHz, CDCl3): δ 1.65 (m, 2H, H-4), 1.78 (m, 2H, H-3), 1.96 (t, J = 2.6 Hz, 1H, H-7), 2.23 (td, J = 6.8, 2.6 Hz, 2H, H-5), 2.36 (t, J = 7.1 Hz, 2H, H-2).

13C NMR (75MHz, CDCl3): δ 16.6 (C-2), 17.5 (C-5), 24.1 (C-3), 27.0 (C-4), 69.2 (C-7), 82.9 (C-6), 119.3 (C-1).

FTIR (KBr, cm⁻¹): 3294, 2947, 2245, 1427, 1334.

Hept-6-ynal (3.79):

DIBAL-H (75 mL of a 1M solution in hexanes, 75 mmol) was added dropwise via syringe pump over a 1 h period to a solution of 3.78 (4.00 g, 37 mmol) in Et₂O (240 mL) at −78°C. After stirring at -78°C for 2 h the reaction was quenched by the careful addition of saturated aqueous NH₄Cl solution (60 mL), 1M aqueous HCl solution (60 mL) and saturated aqueous Na/K tartrate solution (60 mL) and the mixture allowed to warm to room temperature and vigorous stirring continued until the layers cleared. The organic layer was removed and the aqueous layer extracted with EtOAc (x3). The combined extracts were washed with brine, dried and concentrated to provide the title aldehyde as a colourless oil (3.80 g, 93%). The aldehyde proved relatively unstable and was used without further purification. Values from the 1H NMR spectrum were in close agreement with the reported values.25

1H NMR (500MHz, CDCl3): δ 1.54 (m, 2H, H-4), 1.73 (m, 2H, H-3), 1.93 (t, J = 2.6 Hz, 1H, H-7), 2.19 (dt, J = 2.6, 7.0 Hz, 2H, H-5), 2.44 (dt, J = 1.6, 7.4 Hz, 2H, H-2), 9.75 (t, J = 1.6 Hz, 1H, H-1).

13C NMR (75MHz, CDCl3): δ 18.1 (C-5), 21.0 (C-3), 27.7 (C-4), 43.2 (C-2), 68.7 (C-7), 83.7 (C-6), 202.2 (C-1).

FTIR (KBr, cm⁻¹): 3296, 2941, 2864, 1724, 1460, 1246.
Chapter Five – Experimental Details

(E)-tert-Butyl non-2-en-8-ynoate (3.82):

\[ \text{CHO} \quad 3.79 \quad \text{Ph}_3\text{P} \quad \text{CO}_2\text{t-Bu} \quad \rightarrow \quad \text{CHO} \quad 3.80 \quad \text{CO}_2\text{t-Bu} \]

1-(tert-Butoxycarbonyl) methylenetriphenylphosphorane (3.80) (3.5 g, 9.3 mmol) was added in one portion to a solution of aldehyde 3.79 (0.93 g, 8.5 mmol) in toluene (50 mL). The reaction mixture was refluxed for 18 h before being cooled to room temperature and the toluene removed under reduced pressure. Petroleum ether added to the residue and the precipitated triphenylphosphine oxide was removed via filtration and the filtrate concentrated. Purification of the crude material via flash chromatography on silica, eluting with 5% EtOAc/petroleum ether, provided 3.82 as a colourless oil (1.19 g, 67%).

\[ ^1\text{H NMR (500MHz, CDCl}_3\):} \, \delta \, 1.46 \, (s, \, 9H, \, C(CH}_3)_3), \, 1.54 \, (m, \, 4H, \, H-5 \, \text{and} \, H-6), \, 1.93 \, (t, \, J = 2.7 \, Hz, \, 1H, \, H-9), \, 2.18 \, (m, \, 4H, \, H-4 \, \text{and} \, H-7), \, 5.73 \, (dt, \, J = 15.6, \, 1.5 \, Hz, \, 1H, \, H-2), \, 6.82 \, (dt, \, 1H, \, J = 15.6, \, 6.9 \, Hz, \, H-3).
\]

\[ ^{13}\text{C NMR (75MHz, CDCl}_3\):} \, \delta \, 18.1 \, (C-7), \, 27.0 \, (C-5), \, 27.8 \, (C-6), \, 28.1 \, (C(CH}_3)_3), \, 31.4 \, (C-4), \, 68.5 \, (C-9), \, 80.0 \, (C(CH}_3)_3), \, 84.0 \, (C-8), \, 123.2 \, (C-2), \, 147.3 \, (C-3), \, 166.0 \, (C-1).
\]

\[ \text{FTIR (KBr, cm}^{-1}\):} \, 3302, \, 2978, \, 2939, \, 2862, \, 1713, \, 1651, \, 1458, \, 1366, \, 1296, \, 1258, \, 1165.
\]

\[ \text{HRMS (EI):} \, \text{calc.} \, C_{12}H_{17}O_2 \, (M^+ - \text{Me}): \, 193.1228; \, \text{obs.} \, 193.1220; \, \text{calc.} \, C_9H_{12}O_2 \, (M^+ - \text{t-Bu}): \, 152.0837; \, \text{obs.} \, 152.0839.
\]

(E)-Ethyl non-2-en-8-ynoate (3.69):

\[ \text{CHO} \quad 3.79 \quad \text{Ph}_3\text{P} \quad \text{CO}_2\text{Et} \quad \rightarrow \quad \text{CHO} \quad 3.81 \quad \text{CO}_2\text{Et} \]

Using the method described above for 3.82, 3.69 was prepared from 3.79 (0.46 g, 4.2 mmol) and 1-(ethoxycarbonyl) methylenetriphenylphosphorane (3.81) (1.6 g, 4.6 mmol) in toluene (25 mL). Purification of the crude material via flash chromatography on silica gel, eluting with 5% EtOAc/petroleum ether provided the title compound as a colourless oil (0.45 g, 60%).

\[ ^1\text{H NMR (500MHz, CDCl}_3\):} \, \delta \, 1.26 \, (t, \, J = 7.1 \, Hz, \, 3H, \, OCH}_2\text{CH}_3), \, 1.55 \, (m, \, 4H, \, H-5 \, \text{and} \, H-6), \, 1.93 \, (t, \, J = 2.7 \, Hz, \, 1H, \, H-9), \, 2.19 \, (m, \, 4H, \, H-4 \, \text{and} \, H-7), \, 4.15 \, (q, \, J = 7.1 \, Hz, \, 2H, \, OCH}_2\text{CH}_3), \, 5.80 \, (d, \, J = 14.5 \, Hz, \, 1H, \, H-2), \, 6.93 \, (m, \, 1H, \, H-3).
\]
\(^{13}\text{C NMR}\) (75MHz, CDCl\(_3\)): \(\delta\) 14.1 (OCH\(_2\)CH\(_3\)), 18.1 (C-7), 26.9 (C-5), 27.7 (C-6), 31.5 (C-4), 60.1 (OCH\(_2\)CH\(_3\)), 68.5 (C-9), 83.9 (C-8), 121.5 (C-2), 148.6 (C-3), 166.5 (C-1).

\(\text{FTIR}\) (KBr, cm\(^{-1}\)): 3300, 2981, 2939, 2864, 1720, 1655, 1447, 1367, 1309, 1269, 1188, 1148, 1097, 1043.

\(\text{HRMS}\) (EI): calc. C\(_9\)H\(_{11}\)O\(_2\) (M\(^+\)-Et): 151.0759; obs. 151.0754.

\textit{tert-}Butyl(hex-5-ynyloxy)dimethylsilane (3.77):

\[
\begin{align*}
\text{3.75} & \quad \rightarrow \quad \text{3.77} \\
& \quad \text{OH} \quad \text{OTBS}
\end{align*}
\]

Imidazole (0.89 g, 13 mmol) and \textit{tert-}butyldimethylsilyl chloride (1.5 g, 10 mmol) were successively added to a solution of 5-hexyn-1-ol (3.75) (1 g, 10 mmol) in THF (45 mL) at room temperature. After stirring overnight the reaction mixture was diluted with petroleum ether and filtered through a silica gel plug. The silica was washed with 10% EtOAc/petroleum ether and the filtrate concentrated to provide the crude material. Purification \textit{via} flash chromatography on silica, eluting with 30% EtOAc/petroleum ether, provided the title compound as a colourless oil (1.79 g, 84% yield). Values from the \(^1\text{H NMR}\) spectrum were in close agreement with the reported values.\(^{26}\)

\(^1\text{H NMR}\) (500MHz, CDCl\(_3\)): \(\delta\) 0.03 (s, 6H, SiCH\(_3\)), 0.87 (s, 9H, SiC(CH\(_3\))\(_3\)), 1.60 (m, 4H, H-2 and H-3), 1.92 (t, \(J = 2.6\) Hz, 1H, H-6) 2.20 (td, \(J = 2.6, 6.9\) Hz, 2H, H-4), 3.61 (t, \(J = 6.0\) Hz, 2H, H-1).

\(^{13}\text{C NMR}\) (75MHz, CDCl\(_3\)): \(\delta\) -5.3 (SiCH\(_3\)), 18.2 (SiC(CH\(_3\))\(_3\)), 18.3 (C-4), 24.9 (C-3), 25.9 (SiC(CH\(_3\))\(_3\)), 31.8 (C-2), 62.6 (C-1), 68.2 (C-6), 84.5 (C-5).

\(\text{FTIR}\) (KBr, cm\(^{-1}\)): 3321, 2932, 2858, 2338, 1256, 1107.

\(\text{HRMS}\) (ES): calc. C\(_{12}\)H\(_{25}\)OSi (MH\(^+\)) 213.1675; obs. 213.1674.

\((Z)-\text{Ethyl 3-iodobut-2-enoate (3.70)}\):

\[
\begin{align*}
\text{3.70} & \quad \rightarrow \quad \text{3.70} \\
& \quad \text{CO}_2\text{Et} \quad \text{CO}_2\text{Et}
\end{align*}
\]

A mixture of ethyl 2-butynoate (1.00 g, 9 mmol), NaI (2.15 g, 14 mmol) and HOAc (3.5 g, 58 mmol) was heated at \(70^\circ\text{C}\) for 15 h. The brown reaction mixture was transferred, whilst hot, to a
separating funnel containing H₂O (80 mL) and Et₂O (80 mL). The organic layer was removed and the aqueous layer extracted with Et₂O (x2). The combined organic extracts were washed with saturated aqueous NaHCO₃ solution, saturated aqueous Na₂S₂O₃ solution and brine, dried and concentrated to provide the title compound as a pale yellow oil (1.82 g, 84%). Values from the H NMR spectrum were consistent with those reported in the literature.²⁷

**¹H NMR** (500MHz, CDCl₃): δ 1.26 (t, J = 7.1 Hz, 3H, OCH₂C₃H₇), 2.69 (d, J = 1.4 Hz, 3H, H-4), 4.17 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 6.25 (q, J = 1.4 Hz, 1H, H-2).

**¹³C NMR** (75MHz, CDCl₃): δ 14.1 (OCH₂CH₃), 36.4 (C-4), 60.4 (OCH₂CH₃), 113.1 (C-3), 125.5 (C-2), 164.2 (C-1).

**FTIR** (KBr, cm⁻¹): 2982, 2939, 2363, 2241, 1728, 1627, 1433, 1308, 1259, 1178, 1047.


**(Z)-methyl 3-iodobut-2-enoate (3.96):**

A mixture of methyl 2-butynoate (0.73 g, 7.4 mmol), NaI (1.80 g, 12 mmol) and HOAc (2.8 g, 50 mmol) was heated at 70°C for 15 h. The brown reaction mixture was transferred, whilst hot, to a separating funnel containing H₂O (60 mL) and Et₂O (60 mL). The organic layer was removed and the aqueous layer extracted with Et₂O (x2). The combined organic extracts were washed with saturated aqueous NaHCO₃ solution, saturated aqueous Na₂S₂O₃ solution and brine, dried and concentrated to provide the title compound as a pale yellow oil (1.19 g, 70%). Values from the H NMR spectrum were consistent with those reported in the literature.²⁸

**¹H NMR** (500MHz, CDCl₃): δ 2.72 (d, J = 1.5 Hz, 3H, H-4), 3.73 (s, 3H, OCH₃), 6.28 (q, J = 1.5 Hz, 1H, H-2).

**¹³C NMR** (75MHz, CDCl₃): δ 36.5 (C-4), 51.5 (OCH₃), 113.7 (C-3), 125.1 (C-2), 164.7 (C-1).
**Copper Couplings: General Procedure**

Solutions of alkyne (1 equiv) and iodide (1.1 equiv) in toluene were added, *via* cannula to a long-necked round bottom flask containing a solution of Cu(Phen)(PPh3)Br (10 mol %) and Cs2CO3 (2 equiv) in toluene. The reaction mixture was stirred at 110°C until consumption of iodide starting material was complete, as monitored by 1H NMR spectroscopy. After cooling to room temperature the mixture was filtered through a pad of Celite and the solvent removed *in-vacuo*. Purification of the crude material was achieved *via* flash chromatography on silica gel eluting with 10% EtOAc/petroleum ether (3.95 and 3.92), 20% EtOAc/petroleum ether (3.97 and 3.94), 30% EtOAc/petroleum ether (3.93) and 70% EtOAc/petroleum ether (3.91).

![Chemical Structures](image)

(2Z,10E)-12-tert-Butyl 1-ethyl 3-methyldodeca-2,10-dien-4-ynedioate (3.95):

Using the general procedure, coupling of 3.82 (1.27 g, 6.1 mmol) and 3.70 (1.61 g, 6.7 mmol) in toluene (45 mL) provided the title compound as a pale yellow oil (1.41 g, 73%) following purification.

1H NMR (500MHz, CDCl3): δ 1.25 (t, J = 7.1 Hz, 3H, OCH2C6H3), 1.45 (s, 9H, C(CH3)3), 1.60 (m, 4H, H-7 and H-8), 2.00 (s, 3H, CH3), 2.19 (m, 2H, H-9), 2.44 (m, 2H, H-6), 4.16 (q, J = 7.1 Hz, 2H, OCH2CH3), 5.74 (dt, J = 15.6, 1.6 Hz, 1H, H-11), 5.91 (s, 1H, H-2), 6.83 (dt, J = 15.6, 6.9 Hz, 1H, H-10).

13C NMR (75MHz, CDCl3): δ 14.3 (OCH2CH3), 19.7 (C-6), 25.7 (CH3), 27.2 (C-7 or C-8), 28.0 (C-7 or C-8), 28.1 (C(CH3)3), 31.4 (C-9), 59.9 (OCH2CH3), 79.99 (C-4), 80.05 (C(CH3)3), 102.2 (C-5), 123.2 (C-11), 123.4 (C-2), 135.6 (C-3), 147.4 (C-10), 165.2 (C-1), 166.0 (C-12).

FTIR (KBr, cm⁻¹): 2978, 2932, 2893, 2222, 1713, 1651, 1620, 1450, 1373, 1288, 1219, 1157, 1096, 1049.

(2Z,10E)-Diethyl 3-methyldodeca-2,10-dien-4-ynedioate (3.94):
Using the general procedure, coupling of 3.69 (43.7 mg, 0.2 mmol) and 3.70 (53.0 mg, 0.22 mmol) in toluene (2 mL) provided the title compound as a pale yellow oil (41.7 mg, 71%) following purification.

$^1$H NMR (500MHz, CDCl$_3$): $\delta$ 1.26 (t, $J$ = 7.1 Hz, 3H, OCH$_2$CH$_3$), 1.27 (t, $J$ = 7.1 Hz, 3H, OCH$_2$CH$_3$), 1.61 (m, 4H, H-7 and H-8), 2.00 (s, 3H, CH$_3$), 2.22 (m, 2H, H-9), 2.44 (m, 2H, H-6), 4.16 (q, $J$ = 7.1 Hz, 4H, 2 x OCH$_2$CH$_3$), 5.83 (d, $J$ = 15.6 Hz, 1H, H-11), 5.92 (s, 1H, H-2), 6.94 (dt, $J$ = 15.6, 6.9 Hz, 1H, H-10).

$^{13}$C NMR (75MHz, CDCl$_3$): $\delta$ 14.2 (OCH$_2$CH$_3$), 14.3 (OCH$_2$CH$_3$), 19.7 (C-6), 25.7 (CH$_3$), 27.1 (C-7 or C-8), 27.8 (C-7 or C-8), 31.6 (C-9), 59.9 (OCH$_2$CH$_3$), 60.1 (OCH$_2$CH$_3$), 80.1 (C-4), 102.1 (C-5), 121.5 (C-11), 123.4 (C-2), 135.6 (C-3), 148.7 (C-10), 165.1 (C-1), 166.6 (C-12).

FTIR (KBr, cm$^{-1}$): 2982, 2939, 1720, 1655, 1620, 1447, 1369, 1271, 1223, 1153, 1047.

HRMS (ES): calc. C$_{17}$H$_{25}$O$_4$ (MH$^+$) 293.1753; obs. 293.1751.

(2Z,10E)-12-Ethyl 1-methyl 3-methyldodeca-2,10-dien-4-ynedioate (3.97):
Using the general procedure, coupling of 3.69 (0.3 g, 1.7 mmol) and 3.83 (0.44 g, 1.9 mmol) in toluene (10 mL) provided the title compound as a pale yellow oil (0.26 g, 57%) following purification.

$^1$H NMR (500MHz, CDCl$_3$): $\delta$ 1.27 (t, $J$ = 7.1 Hz, 3H, OCH$_2$CH$_3$), 1.62 (m, 4H, H-7 and H-8), 2.00 (s, 3H, CH$_3$), 2.22 (m, 2H, C-9), 2.46 (m, 2H, C-6), 3.70 (s, 3H, OCH$_3$), 4.17 (q, $J$ = 7.1 Hz, 2H, OCH$_2$CH$_3$), 5.82 (d, $J$ = 15.7 Hz, 1H, H-11), 5.93 (s, 1H, H-2), 6.95 (m, 1H, H-10).

$^{13}$C NMR (75MHz, CDCl$_3$): $\delta$ 14.3 (OCH$_2$CH$_3$), 19.7 (C-6), 25.7 (CH$_3$), 27.1 (C-7 or C-8), 27.8 (C-7 or C-8), 31.6 (C-9), 51.2 (OCH$_3$), 60.1 (OCH$_2$CH$_3$), 80.1 (C-4), 102.3 (C-5), 121.6 (C-11), 123.0 (C-2), 136.0 (C-3), 148.7 (C-10), 165.6 (C-1), 166.7 (C-12).

FTIR (KBr, cm$^{-1}$): 2945, 1720, 1655, 1620, 1447, 1369, 1271, 1223, 1157, 1045.

HRMS (ES): calc. C$_{16}$H$_{23}$O$_4$ (MH$^+$) 279.1596; obs. 279.1583.
(Z)-Ethyl 9-hydroxy-3-methyl non-2-en-4-ynoate (3.91):
Using the general procedure, but with K₂CO₃ instead of Cs₂CO₃, coupling of 3.75 (22.6 mg, 0.21 mmol) and 3.70 (55.0 mg, 0.23 mmol) in toluene (2 mL) provided the title compound as a pale yellow oil (12.7 mg, 30%) following purification.

1H NMR (500MHz, CDCl₃): δ 1.26 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.72 (m, 4H, H-7 and H-8), 2.00 (s, 3H, CH₃), 2.49 (t, J = 6.4 Hz, 2H, H-6), 3.68 (t, J = 6.1 Hz, 2H, H-9), 4.16 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 5.92 (s, 1H, H-2).

13C NMR (75MHz, CDCl₃): δ 14.3 (OCH₂CH₃), 19.7 (C-6), 24.5 (C-7), 25.7 (CH₃), 31.7 (C-8), 60.6 (OCH₂CH₃), 62.2 (C-9), 80.3 (C-4), 102.7 (C-5), 123.4 (C-2), 135.9 (C-3), 165.3 (C-1).

FTIR (KBr, cm⁻¹): 3400, 2939, 2869, 2220, 1711, 1618, 1447, 1377, 1259, 1225, 1157, 1049.

HRMS (ES): calc. C₁₂H₁₉O₃ (MH⁺) 211.1334; obs. 211.1339.

(Z)-Ethyl 9-(tert-butyldimethylsilyloxy)-3-methyl non-2-en-4-ynoate (3.92):
Using the general procedure, coupling of 3.77 (0.13 g, 0.62 mmol) and 3.70 (0.16 g, 0.68 mmol) in toluene (5 mL) provided the title compound as a colourless oil (0.10 g, 50%) following purification.

1H NMR (500MHz, CDCl₃): δ 0.02 (s, 6H, SiCH₃), 0.87 (s, 9H, Si(CH₃)₃), 1.26 (t, J = 7.2 Hz, 3H, OCH₂CH₃), 1.64 (m, 4H), 2.00 (s, 3H, CH₃), 2.46 (m, 2H), 3.62 (t, J = 6.0 Hz, 2H), 4.17 (q, J = 7.2 Hz, 2H, OCH₂CH₃), 5.90 (s, 1H, H-2).

13C NMR (75MHz, CDCl₃): δ -5.3 (SiCH₃), 14.3 (OCH₂CH₃), 18.3 (Si(CH₃)₃), 19.8 (C-6), 24.9 (C-7), 25.8 (CH₃), 25.9 (Si(CH₃)₃), 32.0 (C-8), 59.9 (OCH₂CH₃), 62.6 (C-9), 79.9 (C-4), 102.8 (C-5), 123.3 (C-2), 136.7 (C-3), 165.2 (C-1).

FTIR (KBr, cm⁻¹): 2982, 2939, 1720, 1620, 1447, 1377, 1225, 1155, 1049.
HRMS (ES): calc. C₁₈H₃₃O₃Si (MH⁺) 325.2199; obs. 325.2207.
(Z)-Ethyl 9-cyano-3-methylnon-2-en-4-ynoate (3.93):
Using the general procedure, coupling of 3.78 (42 mg, 0.38 mmol) and 3.70 (110 mg, 0.42 mmol) in toluene (5 mL) provided the title compound as a pale yellow oil (36 mg, 43%) following purification.

\[ ^1H \text{NMR} \ (500\text{MHz, CDCl}_3): \delta 1.26 \ (t, J = 7.1 \text{ Hz}, 3\text{H, OCH}_2\text{CH}_3), 1.75 \ (m, 2\text{H, H-7}), 1.86 \ (m, 2\text{H, H-8}), 2.00 \ (s, 3\text{H, CH}_3), 2.41 \ (t, J = 7.1 \text{ Hz}, 2\text{H, H-9}), 2.51 \ (t, J = 6.7 \text{ Hz}, 2\text{H, H-6}), 4.16 \ (q, J = 7.1 \text{ Hz}, 2\text{H, OCH}_2\text{CH}_3), 5.94 \ (s, 1\text{H, H-2}). \]

\[ ^{13}\text{C NMR} \ (75\text{MHz, CDCl}_3): \delta 14.2 \ (\text{OCH}_2\text{CH}_3), 16.7 \ (\text{C-9}), 19.1 \ (\text{C-6}), 24.3 \ (\text{C-8}), 25.6 \ (\text{CH}_3), 27.0 \ (\text{C-7}), 59.9 \ (\text{OCH}_2\text{CH}_3), 80.7 \ (\text{C-4}), 100.8 \ (\text{C-5}), 119.5 \ (\text{C}=\text{N}), 123.8 \ (\text{C-2}), 135.3 \ (\text{C-3}), 165.1 \ (\text{C-1}). \]

\[ \text{FTIR (KBr, cm}^{-1})\ : \ 2935, 2858, 1705, 1620, 1447, 1377, 1225, 1155, 1051. \]

\[ \text{HRMS (ES): calc. C}_{13}\text{H}_{18}\text{NO}_2 \ (\text{MH}^+) \ 220.1338; \text{ obs.} \ 220.1333. \]

(2Z,10E)-3-methyldodeca-2,10-dien-4-ynedioic acid (3.98):
A solution of 3.97 (0.10 g, 0.36 mmol), 1M aqueous NaOH solution (4.5 mL) and 1:1 THF/MeOH (15 mL) was stirred at room temperature overnight. After diluting with H\(_2\)O (10 mL), the solution was acidified to pH = 1 by the addition of 1M aqueous HCl solution and extracted with EtOAc (x3). The combined organic extracts were washed with brine, dried and concentrated to a white solid (0.08 g, 89%).

\[ ^1H \text{NMR} \ (500\text{MHz, CDCl}_3): \delta 1.60 \ (m, 2\text{H, H-7}), 1.71 \ (m, 2\text{H, H-8}), 2.04 \ (s, 3\text{H, CH}_3), 2.26 \ (q, J = 7.0 \text{ Hz}, 2\text{H, H-9}), 2.48 \ (t, J = 6.3 \text{ Hz}, 2\text{H, H-6}), 5.90 \ (d, J = 15.7 \text{ Hz}, 1\text{H, H-11}), 5.96 \ (s, 1\text{H, H-2}), 7.15 \ (m, 1\text{H, H-10}). \]

\[ ^{13}\text{C NMR} \ (75\text{MHz, CDCl}_3): \delta 19.7 \ (\text{C-6}), 25.8 \ (\text{CH}_3), 26.4 \ (\text{C-8}), 27.8 \ (\text{C-7}), 32.1 \ (\text{C-9}), 80.2 \ (\text{C-4}), 104.0 \ (\text{C-5}), 120.8 \ (\text{C-11}), 123.0 \ (\text{C-2}), 138.4 \ (\text{C-3}), 151.9 \ (\text{C-10}), 170.6 \ (\text{C-1}), 172.5 \ (\text{C-12}). \]

\[ \text{FTIR (KBr, cm}^{-1})\ : \ 3071, 2939, 2866, 2222, 1695, 1423, 1256. \]

\[ \text{HRMS (ES): calc. C}_{13}\text{H}_{17}\text{O}_4 \ (\text{MH}^+) \ 237.1127; \text{ obs.} \ 237.1136. \]
(2Z,10E)-12-tert-Butoxy-3-methyl-12-oxododeca-2,10-dien-4-ynoic acid (3.99):

A solution of \(3.95\) (1.5 g, 4.7 mmol), 1M aqueous LiOH solution (19 mL, 19 mmol) and 1:1 THF/MeOH (36 mL) was stirred overnight at room temperature. After diluting with H\(_2\)O (50 mL) the solution was carefully neutralised by the addition of 1M aqueous HCl solution and extracted with EtOAc (x3). The combined organic extracts were washed with brine, dried and concentrated. Purification of the crude material via flash chromatography on silica, eluting with 30% EtOAc/petroleum ether, provided the title compound as a cream solid (0.68 g, 51%).

\[\text{Mp}: 60-64^\circ\text{C}.\]

\(^1\text{H NMR}\) (500MHz, CDCl\(_3\)): \(\delta\) 1.47 (s, 9H, C(CH\(_3\))\(_3\)), 1.61 (m, 4H, H-7 and H-8), 2.04 (s, 3 H, CH\(_3\)), 2.20 (m, 2H, H-9), 2.46 (t, \(J = 6.2\) Hz, 2H, H-6), 5.76 (d, \(J = 15.5\) Hz, 1H, H-11), 5.97 (s, 1H, H-2), 6.85 (dt, \(J = 15.5, 6.7\) Hz, 1H, H-10).

\(^{13}\text{C NMR}\) (75MHz, CDCl\(_3\)): \(\delta\) 19.8 (C-6), 25.8 (CH\(_3\)), 27.0 (C-7), 27.6 (C-8), 28.1 (C(CH\(_3\))\(_3\)), 31.4 (C-9), 79.8 (C-4), 80.2 (C(CH\(_3\))\(_3\)), 104.1 (C-5), 123.22 (C-2), 123.24 (C-11), 137.2 (C-3), 147.6 (C-10), 166.3 (C-12), 168.6 (C-1).

\(\text{FTIR}\) (KBr, cm\(^{-1}\)): 2982, 2943, 2909, 2866, 2835, 2584 (OH dil), 2341, 1701, 1616, 1454, 1369, 1319, 1261, 1219, 1165, 1142.

\(\text{HRMS}\) (EI): calc. C\(_{13}\)H\(_{16}\)O\(_4\) (M\(^+\) - t-Bu): 236.1049; obs. 236.1048.

\((\text{E})\)-tert-Butyl 7-(4-methyl-6-oxo-6H-pyran-2-yl)hept-2-enoate (3.101):

A 1M solution of ZnBr\(_2\) in THF (0.41 mL, 4.1 mmol) was added to a solution of \(3.99\) (0.60 g, 2.1 mmol) in THF (25 mL). The reaction mixture was stirred at room temperature for 48 h and concentrated. Purification of the crude material via flash chromatography on silica, eluting with 30% EtOAc/petroleum ether, provided the title compound as a colourless oil (0.47 g, 77%).
1H NMR (500MHz, CDCl3): δ 1.45 (s, 9H, C(CH3)3), 1.47 (m, 2H, H-5), 1.66 (td, J = 7.7, 15.7 Hz, 2H, H-6), 2.10 (d, J = 1.0 Hz, 3H, CH3), 2.17 (q, J = 7.1 Hz, 2H, H-4), 2.44 (t, J = 7.7 Hz, 2H, H-7), 5.71 (d, J = 15.5 Hz, 1H, H-2), 5.81 (s, 1H, H-3’), 5.93 (s, 1H, H-5’), 6.80 (td, J = 6.9, 15.5 Hz, 1H, H-3).

13C NMR (75MHz, CDCl3): δ 21.3 (C(CH3)), 26.3 (C-6), 27.3 (C-5), 28.0 (C(CH3)3), 31.5 (C-4), 33.3 (C-7), 80.1 (C(CH3)3), 105.8 (C-3’), 110.6 (C-5’), 123.4 (C-2), 146.9 (C-3), 156.1 (C-4’), 163.2 (C-6’), 164.2 (C-2’), 165.9 (C-1).

FTIR (KBr, cm⁻¹): 2978, 2936, 2866, 1732, 1647, 1562, 1458, 1407, 1369, 1319, 1292, 1253, 1165, 1026.


**(E)-tert-Butyl 7-(5-bromo-4-methyl-6-oxo-6H-pyran-2-yl)hept-2-enoate (3.110):**

\[ \text{N-Bromosuccinimide (0.30 g, 1.7 mmol) was added to a solution of 3.101 (0.50 g, 1.7 mmol) in THF (15 mL) at room temperature. The reaction mixture was stirred for 48 h at this temperature at which time TLC analysis indicated the presence of unreacted 3.101. An additional 0.15 g (0.85 mmol) of NBS was added and stirring continued. After 48 h an additional 0.1 g (0.56 mmol) of NBS was added. After a further 48 h the reaction mixture was diluted with CH2Cl2, washed with saturated aqueous NaHCO3 solution and brine, dried and the solvent removed in-vacuo. The crude material was purified via flash chromatography on silica gel, eluting with 30% EtOAc/petroleum ether to provide the title compound as a white solid (0.48 g, 75%).} \]

1H NMR (500 MHz, CDCl3): δ 1H 1.44 (s, 9H, C(CH3)3), 1.46 (m, 2H, H-5), 1.65 (td, J = 7.6, 15.5 Hz, 2H, H-6), 2.16 (q, J = 7.0 Hz, 2H, H-4), 2.23 (s, 3H, CH3), 2.42 (t, J = 7.6 Hz, 2H, H-7), 5.70 (d, J = 15.5 Hz, 1H, H-2), 5.89 (s, 1H, H-3’), 6.78 (m, 1H, H-3).

13C NMR (75 MHz, CDCl3): δ 23.3 (CH3), 26.3 (C-6), 27.3 (C-5), 28.1 (C(CH3)3), 31.5 (C-4), 33.0 (C-7), 80.2 (C(CH3)3), 106.6 (C-3’), 108.7 (C-5’), 123.5 (C-2), 146.8 (C-3), 154.5 (C-4’), 159.3 (C-6’), 162.5 (C-2’), 165.9 (C-1).
**Chapter Five – Experimental Details**

**FTIR** (KBr, cm\(^{-1}\)): 2978, 2934, 1780, 1728, 1645, 1535, 1458, 1393, 1367, 1294, 1256, 1217, 1165.

**HRMS (ES):** calc. C\(_{17}\)H\(_{24}\)O\(_4\)Br (MH\(^+\)) 371.0858; obs. 371.0870.

**tert-Butyl 3-methyl-1,5,6,7,8,8a-hexahydronaphthalene-1-carboxylate (3.111):**

![Chemical Structure](image)

A solution of 3.101 (0.17 g, 0.57 mmol) and Proton Sponge\(^\circledR\) (0.04 g, 0.17 mmol) in xylenes (20 mL) was refluxed vigorously for 48 h. The solvent was removed *in-vacuo* and the crude material purified *via* flash chromatography on silica, eluting with 10% EtOAc/petroleum ether, to provide the title compound as a colourless oil (0.10 g, 72%).

**\(^1\)H NMR** (500MHz, CDCl\(_3\) with 0.1% d\(_5\)-pyridine): \(\delta\) 1.15 (dq, \(J = 3.5, 12.6\) Hz, 1H, H-8\(_B\)), 1.35 (m, 2H, H-6 and H-7), 1.46 (s, 9H, C(CH\(_3\))\(_3\)), 1.70 (s, 3H, CH\(_3\)), 1.78 (m, 2H, H-6 and H-7), 1.87 (m, 1H, H-8\(_A\)), 2.07 (t, \(J = 14.0\) Hz, 1H, H-5\(_A\)), 2.31 (d, \(J = 16.1\) Hz, 1H, H-5\(_B\)), 2.60 (t, \(J = 13.1\) Hz, 1H, H-8a), 2.88 (d, \(J = 12.8\) Hz, 1H, H-1), 5.18 (s, 1H, H-2), 5.42 (s, 1H, H-4).

**\(^{13}\)C NMR** (75MHz, CDCl\(_3\) with 0.1% d\(_5\)-pyridine): \(\delta\) 21.4 (CH\(_3\)), 26.1 (C-6 or C-7), 27.4 (C-6 or C-7), 28.1 (C(CH\(_3\))\(_3\)), 34.3 (C-5), 35.5 (C-8), 37.5 (C-8a), 49.8 (C-1), 80.4 (OC(CH\(_3\))\(_3\)), 115.0 (C-2), 119.8 (C-4), 131.6 (C-3), 141.4 (C-4a), 174.3 (C=O).

**FTIR** (KBr, cm\(^{-1}\)): 2978, 2932, 2856, 1728, 1450, 1366, 1273, 1150.

**HRMS (ES):** calc. C\(_{16}\)H\(_{25}\)O\(_2\) (MH\(^+\)) 249.1855; obs. 249.1863.
tert-Butyl 2-bromo-3-methyl-1,5,6,7,8,8a-hexahydronaphthalene-1-carboxylate (3.114):

![Structural formula](image)

A solution of 3.110 (0.20 g, 0.54 mmol) and Proton Sponge® (0.04 g, 0.16 mmol) in xylenes (20 mL) was refluxed vigorously for 48 h. The solvent was removed in-vacuo and the crude material purified via flash chromatography on silica, eluting with 5% EtOAc/petroleum ether, to provide the title compound as a colourless oil (0.13 g, 74%).

**1H NMR** (500MHz, CDCl₃ with 0.1% d₅-pyridine): δ 1.27-1.31 (m, 3H, H-6, H-7 and H-8), 1.47 (s, 9H, C(CH₃)₃), 1.76-1.82 (m, 3H, H-6, H-7 and H-8), 1.85 (d, J = 2.1 Hz, 3H, CH₃), 2.01 (m, 1H, H-5), 2.27 (m, 1H, H-5), 2.62 (m, 1H, H-8a), 3.21 (dd, J = 1.9, 9.5 Hz, 1H, H-1), 5.40 (t, J = 1.9 Hz, 1H, H-4).

**13C NMR** (75MHz, CDCl₃ with 0.1% d₅-pyridine): δ 21.8 (CH₃), 26.1 (C-7), 27.9 (C(CH₃)₃), 28.1 (C-6), 34.2 (C-5), 35.4 (C-8), 42.8 (C-8a), 58.1 (C-1), 81.2 (C(CH₃)₃), 112.6 (C-2), 119.4 (C-4), 131.2 (C-3), 141.0 (C-4a), 172.8 (C=O).

**FTIR** (KBr, cm⁻¹): 2980, 2930, 2856, 1732, 1367, 1256, 1148, 847.

**HRMS** (ES): calc. C₁₆H₂₃O₂BrCs (MCs⁺) 458.9936; obs. 458.9946.
5.4 Experiments Described in Chapter Four

**tert-Butyl(2,4-dimethylpenta-1,4-dien-3-yloxy)dimethylsilane (4.20):**

\[
\begin{align*}
\text{Br} & \quad \text{a} \quad \text{OH} \quad \text{b} \quad \text{OTBS} \\
\text{4.52} & \quad \text{4.20}
\end{align*}
\]

(a) According to the procedure of Tullis and co-workers\(^2^9\) a solution of freshly distilled 2-bromopropene (18.45 g, 0.15 mol) in THF (60 mL) was added slowly *via* an addition funnel, keeping the temperature of the solution at gentle reflux, to a solution of magnesium turnings (4 g, 0.16 mol) in THF (40 mL). The resulting mixture was refluxed for 2.5 h and cooled to room temperature. A solution of ethyl formate (4 mL, 0.05 mol) in THF (15 mL) was added slowly keeping the reaction temperature just below reflux. Following addition, the reaction mixture was stirred overnight at room temperature, heated at reflux for 1 h and then cooled to 0°C before H\(_2\)O (80 mL) was slowly added. The organic phase was decanted off and saturated NH\(_4\)Cl solution (80 mL) added to the remaining solids. The combined aqueous phases were extracted with Et\(_2\)O (x3) and the combined extracts washed with brine, dried and concentrated to provide alcohol 4.52 as a yellow oil that was used without purification.

(b) The crude alcohol (5.68 g) was dissolved in DMF (30 mL) and *tert*-butyldimethylsilyl chloride (7.50 g, 0.05 mol) and imidazole (7.15 g, 0.11 mol) were added. The reaction mixture was stirred at room temperature for 40 h, diluted with H\(_2\)O and extracted with Et\(_2\)O (x3). The combined extracts were washed with brine, dried and the solvent removed *in-vacuo*. The crude material was purified by flash chromatography on silica, eluting with petroleum ether to provide the product as a colourless oil (9.31 g, 82% over two steps). Values from the \(^1\)H NMR spectrum were consistent with those reported in the literature.\(^2^9\)

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 0.03 (s, 6H, Si\(\text{CH}_3\)), 0.90 (s, 9H, Si\(\text{C}(\text{CH}_3)_3\)), 1.58 (s, 6H, C-2 and C-4 \(\text{CH}_3\)), 4.39 (s, 1H, H-3), 4.84 (m, 2H, H-1 and H-6), 5.00 (m, 2H, H-1 and H-6).

\(^1^3\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) -5.2 (Si\(\text{CH}_3\)), 17.5 (C-2 and 4 \(\text{CH}_3\)), 18.3 (Si\(\text{C}(\text{CH}_3)_3\)), 25.8 (Si\(\text{C}(\text{CH}_3)_3\)), 80.1 (C-3), 111.1 (C-1), 145.6 (C-2).

FTIR (KBr, cm\(^{-1}\)): 2957, 2932, 2887, 2858, 1474, 1462, 1252, 1097, 1005.

HRMS (ES): calc. C\(_{13}\)H\(_{27}\)OSi (MH\(^+\)) 227.1831; obs. 227.1842.
(2R,3S,4S)-3-(tert-Butyldimethylsilyloxy)-2,4-dimethylpentane-1,5-diol (4.46a):

According to the method of Tullis and co-workers, a solution of 9-BBN (200 mL of a 0.5M solution in THF, 0.1 mol) was added dropwise over 2 h to a solution of 4.20 (7.5 g, 0.033 mol) in THF (60 mL) at -78°C. The resulting white slurry was slowly warmed to room temperature overnight and then stirred at this temperature for an additional 30 h. After cooling to 0°C, a solution of 3M aqueous NaOH solution (110 mL, 0.33 mol) was added dropwise, followed by dropwise addition of 50% aqueous H₂O₂ solution (28.5 mL, 0.5 mol). The reaction mixture was stirred at 0°C for 45 min and for 1 h at room temperature. After addition of saturated aqueous K₂CO₃ solution (250 mL) the phases were separated and the aqueous layer extracted with CH₂Cl₂ (x3). The combined extracts were washed with brine, dried and concentrated. Purification of the crude material by flash chromatography on silica gel eluting with 40% EtOAc/petroleum ether provided the title compound as a white solid (6.00 g, 69%). Values from the ¹H NMR spectrum were consistent with those reported in the literature.

Mp: 44-46°C (lit. 45-45.5°C)

¹H NMR (500 MHz, CDCl₃): δ 0.12 (s, 6H, SiCH₃), 0.91 (s, 9H, SiC(CH₃)₃), 0.98 (d, J = 7.1 Hz, 6H, 2-CH₃ and 4-CH₃), 1.93 (m, 2H, H-2 and 4), 2.27 (br s, 2H, OH), 3.62 (m, 4H, H-1 and H-5), 3.70 (dd, J = 4.9, 4.9 Hz, 1H, H-3).

¹³C NMR (75 MHz, CDCl₃): δ -4.2 (SiCH₃), 15.1 (2-CH₃ and 4-CH₃), 18.2 (SiC(CH₃)₃), 26.0 (SiC(CH₃)₃), 38.9 (C-2 and C-4), 65.4 (C-1 and C-5), 79.7 (C-3).

FTIR (KBr, cm⁻¹): 2930, 2858, 2361, 2341, 1462, 1362, 1254, 1092, 1022.

HRMS (ES): calc. C₁₃H₃₁O₃Si (MH⁺) 263.2042; obs. 263.2043.
3,5-Bis(tert-butyldimethylsilyloxy)-2,4-dimethylpentan-1-ol and 1,5-bis(tert-butyldimethylsilyloxy)-2,4-dimethylpentan-3-ol (4.52a):

\[
\begin{align*}
&\text{HO} &\rightarrow &\text{TBSO} \\
&\text{OTBS} 4.46a &+ &\text{TBSO} \text{OTBS} 4.52a &+ &\text{OH} 4.52b
\end{align*}
\]

Diol 4.46a (5.7 g) was dissolved in DMF (30 mL) and tert-butyldimethylsilyl chloride (3.32 g, 0.02 mol) and imidazole (1.50 g, 0.02 mol) were successively added. The reaction mixture was stirred at room temperature for 40 h, diluted with H₂O and extracted with Et₂O (x3). The combined extracts were washed with brine, dried and the solvent removed in-vacuo. Purification of the crude material by flash chromatography on silica, eluting with 20% EtOAc/petroleum ether followed by 40% EtOAc/petroleum ether, provided the desired product 4.52a as a colourless oil (3.52 g, 43%) along with the side product 4.52b as a colourless oil (2.61 g, 31%) and some recovered starting material (1.53 g, 26%).

4.52a:

\( ^1H \text{ NMR} (500 \text{ MHz, CDCl}_3) \): \( \delta \) 0.02 (d, \( J = 2.50 \text{ Hz} \), 6H, Si\( CH_3 \)), 0.08 (s, 3H, Si\( CH_3 \)), 0.10 (s, 3H, Si\( CH_3 \)), 0.88 (s, 9H, SiC\( (CH_3)_3 \)), 0.90 (m, 12H, SiC\( (CH_3)_3 \) and 4-\( CH_3 \)), 1.00 (d, \( J = 7.1 \text{ Hz} \), 3H, 2-\( CH_3 \)), 1.89 (m, 1H, H-2), 1.93 (m, 1H, H-4), 3.45 (dd, \( J = 6.4, 10.0 \text{ Hz} \), 1H, H-5), 3.57 (m, 2H, H-1 and H-5), 3.69 (dd, \( J = 4.0, 11.0 \text{ Hz} \), 1H, H-1), 3.76 (dd, \( J = 4.4, 5.4 \text{ Hz} \), 1H, H-3).

\( ^{13}C \text{ NMR} (75 \text{ MHz, CDCl}_3) \): \( \delta \) -5.5 (Si\( CH_3 \)), -5.4 (Si\( CH_3 \)), -4.31 (Si\( CH_3 \)), -4.26 (Si\( CH_3 \)), 12.8 (4-\( CH_3 \)), 16.5 (2-\( CH_3 \)), 18.2 (SiC\( (CH_3)_3 \)), 25.9 (SiC\( (CH_3)_3 \)), 26.0 (SiC\( (CH_3)_3 \)), 35.9 (C-2), 41.5 (C-4), 65.0 (C-5), 66.1 (C-1), 78.7 (C-3).

\( \text{FTIR} (\text{KBr}, \text{ cm}^{-1}) \): 3355, 2957, 2930, 2885, 2858, 1474, 1464, 1389, 1362, 1256, 1088, 1030.

\( \text{HRMS (ES)} \): calc. C\(_{19}\)H\(_{45}\)O\(_3\)Si\(_2\) (MH\(^+\)) 377.2907; obs. 377.2914.

4.52b:

\( ^1H \text{ NMR} (500\text{MHz, CDCl}_3) \): \( \delta \) 0.02 (s, 6H, Si\( CH_3 \)), 0.03 (s, 6H, Si\( CH_3 \)), 0.88 (s, 18H, SiC\( (CH_3)_3 \)), 0.92 (d, \( J = 6.9 \text{ Hz} \), 6H, 2-\( CH_3 \) and 4-\( CH_3 \)), 1.85 (m, 2H, H-2 and H-4), 3.38 (m, 2H, H-1 and H-5), 3.58 (t, \( J = 4.9 \text{ Hz} \), 1H, H-3), 3.69 (m, 2H, H-1 and H-5).
13C NMR (75MHz, CDCl3): δ -5.4 (SiCH3), -5.3 (SiCH3), -4.1 (SiCH3), 14.8 (2-CH3 and 4-CH3), 18.3 (SiC(CH3)3), 26.0 (SiC(CH3)3), 25.1 (SiC(CH3)3), 39.7 (C-2 and C-4), 65.2 (C-1 and C-5), 76.1 (C-3).

FTIR (KBr, cm⁻¹): 2957, 2930, 2858, 2885, 1474, 1464, 1258, 1087.


3,5-Bis(tert-butyldimethylsilyloxy)-2,4-dimethylpentyl-4-methylbenzenesulfonate (4.54):

4-Toluenesulfonyl chloride (2.1 g, 11 mmol), 4-dimethylaminopyridine (0.1 g, 0.8 mmol) and Et3N (3.3 mL, 24 mmol) were successively added to a solution of 4.52a (3.0 g, 8 mmol) in CH2Cl2 (40 mL) at 0°C. After warming to room temperature and stirring overnight the reaction mixture was diluted with EtOAc and washed with 1M aqueous HCl solution and saturated aqueous NaHCO3 solution. The aqueous portions were extracted with additional EtOAc (x2) and the combined extracts washed with brine, dried and the solvent removed under reduced pressure. Purification of the crude material via flash chromatography on silica gel, eluting with 20% EtOAc/petroleum ether, provided the title compound as a colourless oil (3.2 g, 75%).

1H NMR (500 MHz, CDCl3): δ -0.05 (s, 3H, SiCH3), -0.01 (s, 3H, SiCH3), -0.000 (s, 6H, SiCH3), 0.80 (s, 9H, SiC(CH3)3), 0.81 (d, J = 7.0 Hz, 3H, 4-CH3), 0.86 (s, 9H, SiC(CH3)3), 0.92 (d, J = 6.9 Hz, 3H, 2-CH3), 1.75 (m, 1H, H-4), 2.03 (m, 1H, H-2), 2.43 (s, 3H, ArCH3), 3.37 (dd, J = 6.4, 10.0 Hz, 1H, H-5), 3.52 (dd, J = 6.2, 10.0 Hz, 1H, H-5), 3.55 (dd, J = 4.2, 5.3 Hz, 1H, H-3), 3.77 (dd, J = 8.9, 9.5 Hz, 1H, H-1), 4.17 (dd, J = 4.3, 9.5 Hz, 1H, H-1), 7.32 (d, J = 8.0 Hz, 2H, ArH), 7.77 (d, J = 8.3 Hz, 2H, ArH).

13C NMR (75 MHz, CDCl3): δ -5.5 (SiCH3), -5.4 (SiCH3), -4.4 (SiCH3), -4.1 (SiCH3), 13.5 (4-CH3), 15.8 (2-CH3), 18.18 (SiC(CH3)3), 18.21 (SiC(CH3)3), 21.6 (ArCH3), 25.9 (SiC(CH3)3), 26.0 (SiC(CH3)3), 35.5 (C-2), 40.4 (C-4), 64.8 (C-5), 73.1 (C-1), 75.8 (C-3), 128.0 (ArH), 129.7 (ArH), 133.1 (ArC), 144.6 (ArC).

FTIR (KBr, cm⁻¹): 2957, 2930, 2858, 2885, 1474, 1464, 1366, 1254, 1190, 1178, 1097, 1036.

HRMS (ES): calc. C26H51O5Si2S (MH⁺) 531.2996; obs. 531.2998.
5,7-Bis(tert-butyldimethylsilyloxy)-4,6-dimethylhept-1-yne (4.25):

Lithium acetylide ethylenediamine complex (1.7 g, 15.3 mmol) was added to a solution of tosylate 4.54 (3.0 g, 5.7 mmol) in DMSO (30 mL). After stirring at room temperature for 36 h the brown reaction mixture was poured into a vigorously stirring mixture of EtOAc and brine. The organic layer was removed and the aqueous layer extracted with EtOAc (x2). The combined extracts were washed with H₂O and brine, dried and solvent removed under reduced pressure. Purification of the crude material via flash chromatography on silica gel, eluting with 3% Et₂O/petroleum ether, provided the title compound as a pale yellow oil (0.70 g, 32%) as well as the TBS acetylide 4.55 (0.65 g, 23%) and some 4.25:4.55 mixture (0.49 g). 4.55 and the 4.25:4.55 mixture could be recycled as detailed below to give an additional 0.66 g (30%) of 4.25.

Representative recycling procedure:
A solution of TBS acetylide 4.55 (0.65 g, 1.3 mmol) in THF (85 mL) was treated with TBAF (11.7 mL of a 1M solution in THF, 11.7 mmol). After stirring at room temperature for 48 h the reaction mixture was quenched with H₂O and the aqueous mixture extracted with Et₂O (x3). The combined organic extracts were washed with brine, dried and solvent removed under reduced pressure. Purification of the crude material via flash chromatography on silica gel, eluting with 70% EtOAc/petroleum ether provided diol 4.62 as a colourless oil (0.20 g, 97%).

Diol 4.62 (0.20 g, 1.28 mmol) was dissolved in DMF (5 mL) and tert-butyldimethylsilyl chloride (0.77 g, 5.12 mmol) and imidazole (0.70 g, 10.2 mmol) were added. The reaction mixture was stirred at room temperature for 72 h, diluted with H₂O and extracted with Et₂O (x3). The combined extracts were washed with brine, dried and the solvent removed in-vacuo. Purification
of the crude material by flash chromatography on silica, eluting with 5% Et₂O/petroleum ether provided the title compound (4.25) as a colourless oil (0.39 g, 80%).

5,7-Bis(tert-butyldimethylsilyloxy)-4,6-dimethylhept-1-yne (4.25):

\( ^1H \text{ NMR} (500 \text{ MHz, CDCl}_3): \delta \ 0.02 \ (s, 6H, \text{SiCH}_3), 0.05 \ (s, 3H, \text{SiCH}_3), 0.06 \ (s, 3H, \text{SiCH}_3), 0.882 \ (s, 9H, \text{SiC(CH}_3)_3), 0.884 \ (s, 9H, \text{SiC(CH}_3)_3), 0.92 \ (d, J = 7.0 \text{ Hz, 3H, 6-CH}_3), 1.04 \ (d, J = 6.9 \text{ Hz, 3H, 4-CH}_3), 1.82 \ (m, 1H, H-6), 1.89 \ (m, 1H, H-4), 1.93 \ (t, J = 2.7 \text{ Hz, 1H, H-1}), 2.07 \ (ddd, J = 2.7, 9.1, 16.8 \text{ Hz, 1H, H-3}), 2.32 \ (ddd, J = 2.7, 4.3, 16.8 \text{ Hz, 1H, H-3}), 3.40 \ (dd, J = 7.1, 6.9 \text{ Hz, 1H, H-5}), 3.65 \ (dd, J = 7.1, 9.9 \text{ Hz, 1H, H-7}).

\( ^{13}C \text{ NMR} (75 \text{ MHz, CDCl}_3): \delta \ -5.4 \ (\text{SiCH}_3), -5.3 \ (\text{SiCH}_3), -4.0 \ (\text{SiCH}_3), 14.3 \ (6-\text{CH}_3), 17.5 \ (4-\text{CH}_3), 18.3 \ (\text{SiC(CH}_3)_3), 21.3 \ (\text{C-3}), 25.9 \ (\text{SiC(CH}_3)_3), 26.1 \ (\text{SiC(CH}_3)_3), 35.8 \ (\text{C-4}), 40.0 \ (\text{C-6}), 65.0 \ (\text{C-7}), 76.9 \ (\text{C-5}), 84.2 \ (\text{C-2}).

\( \text{FTIR (KBr, cm}^{-1}): 3323, 2957, 2930, 2858, 2178, 1474, 1462, 1389, 1362, 1254, 1082, 1032.

\( \text{HRMS (ES): calc. C}_{21}H_{45}O_2Si_2 (MH^+) 385.2958; \text{obs. 385.2949.}

1-((tert-Butyldimethylsilyl)-5,7-bis(tert-butyldimethylsilyloxy)-4,6-dimethylhept-1-yne (4.55):

\( ^1H \text{ NMR} (500 \text{ MHz, CDCl}_3): \delta \ 0.01 \ (s, 6H, \text{SiCH}_3), 0.04 \ (d, J = 7.2 \text{ Hz, 6H, SiCH}_3), 0.06 \ (s, 6H, \text{SiCH}_3), 0.87 \ (s, 18H, CH}_3), 0.89 \ (d, J = 7.3 \text{ Hz, 3H, 6-CH}_3), 0.91 \ (s, 9H, \text{SiC(CH}_3)_3), 1.01 \ (d, J = 6.9 \text{ Hz, 3H, 4-CH}_3), 1.82 \ (m, 1H, H-6), 1.88 \ (m, 1H, H-4), 2.12 \ (dd, J = 8.5, 17.0 \text{ Hz, 1H, H-3}), 2.33 \ (dd, J = 4.9, 17.0 \text{ Hz, 1H, H-3}), 3.37 \ (dd, J = 7.3, 9.9Hz, 1H, H-7), 3.55 \ (dd, J = 4.9, 4.9 \text{ Hz, 1H, H-5}), 1.07 \ (d, J = 5.4, 9.9 \text{ Hz, 1H, H-7}).

\( ^{13}C \text{ NMR} (75 \text{ MHz, CDCl}_3): \delta \ -5.4 \ (\text{SiCH}_3), -5.3 \ (\text{SiCH}_3), -4.4 \ (\text{SiCH}_3), -4.0 \ (\text{SiCH}_3), -3.9 \ (\text{SiCH}_3), 14.7 \ (6-\text{CH}_3), 17.4 \ (4-\text{CH}_3), 18.3 \ (\text{SiC(CH}_3)_3), 18.4 \ (\text{SiC(CH}_3)_3), 23.0 \ (\text{C-3}), 26.0 \ (\text{SiC(CH}_3)_3), 26.12 \ (\text{SiC(CH}_3)_3), 26.14 \ (\text{SiC(CH}_3)_3), 36.4 \ (\text{C-4}), 39.7 \ (\text{C-6}), 65.0 \ (\text{C-7}), 77.1 \ (\text{C-5}), 83.4 \ (\text{C-1}), 107.5 \ (\text{C-2}).

\( \text{FTIR (KBr, cm}^{-1}): 2957, 2930, 2858, 2174, 1472, 1464, 1256, 1082.

\( \text{HRMS (ES): calc. C}_{27}H_{59}O_2Si_3 (MH^+) 499.3823; \text{obs. 499.3808.}

2,4-Dimethylhept-6-yn-1,3-diol (4.62):

\( ^1H \text{ NMR} (500 \text{ MHz, CDCl}_3): \delta \ 0.97 \ (d, J = 7.0 \text{ Hz, 3H, 2-CH}_3), 1.07 \ (d, J = 6.9 \text{ Hz, 3H, 4-CH}_3), 1.86 \ (m, 1H, H-2), 1.93 \ (m, 1H, H-4), 1.98 \ (t, J = 2.7 \text{ Hz, 1H, H-7}), 2.26 \ (m, 1H, H-5), 2.39 \ (m,
Chapter Five – Experimental Details

1H, H-5), 2.84 (br s, 1H, OH), 3.05 (br s, 1H, OH), 3.42 (dd, \( J = 5.9, 5.9 \) Hz, 1H, H-3), 3.62 (dd, \( J = 6.2, 10.8 \) Hz, 1H, H-1), 3.82 (dd, \( J = 3.4, 10.8 \) Hz, 1H, H-1).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 14.4 (2-CH\(_3\)), 16.7 (4-CH\(_3\)), 20.2 (C-5), 35.3 (C-4), 36.4 (C-2), 67.0 (C-1), 69.6 (C-7), 80.6 (C-3), 83.5 (C-6).

FTIR (KBr, cm\(^{-1}\): 3302, 2966, 2934, 2880, 2118, 1458, 1050.


\((2S,3R,4R)-3-\text{(Tert-butylidemethylsilyloxy)}-5\text{-hydroxy-2,4-dimethylpentyl acetate (4.47)}:\)

\[
\text{HO} \begin{array}{c}
\text{SiC} \text{(CH}_3\text{)}_3
\end{array}\text{OH} \quad \begin{array}{c}
\text{HO}
\end{array}\begin{array}{c}
\text{SiC} \text{(CH}_3\text{)}_3
\end{array}\text{OAc}
\]

A solution of diol 4.46a (0.15 g, 0.57 mmol), \textit{Candida Rugosa} lipase (5 mg) and 4Å molecular sieves (0.5 g) in vinyl acetate (20 mL) was stirred at 40°C. After 7 days the reaction mixture was filtered through Celite, rinsing with 20 mL of Et\(_2\)O. The filtrate was concentrated under reduced pressure and the crude material purified via flash column chromatography on silica gel eluting with 40% EtOAc/petroleum ether to provide the title compound as a colourless oil (0.06 g, 33%) along with recovered starting material (0.07 g, 49%). Values from the \(^1\)H NMR spectrum were consistent with those reported in the literature.\(^{31}\)

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 0.07 (s, 3H, SiCH\(_3\)), 0.11 (s, 3H, SiCH\(_3\)), 0.90 (s, 9H, SiC(CH\(_3\))\(_3\)), 0.99 (d, \( J = 6.1 \) Hz, 3H, 2-CH\(_3\)), 1.00 (d, \( J = 6.3 \) Hz, 3H, 4-CH\(_3\)), 1.89 (m, 1H, H-4), 2.05 (s, 3H, COCH\(_3\)), 2.07 (m, 1H, H-2), 3.59-3.65 (m, 3H, H-3 and H-5), 3.91 (dd, \( J = 7.1, 11.0 \) Hz, 1H, H-1), 4.17 (dd, \( J = 5.5, 11.0 \) Hz, 1H, H-1).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) -4.4 (SiCH\(_3\)), -4.1 (SiCH\(_3\)), 14.0 (2-CH\(_3\)), 15.9 (4-CH\(_3\)), 18.2 (SiC(CH\(_3\))\(_3\)), 20.9 (COCH\(_3\)), 26.0 (SiC(CH\(_3\))\(_3\)), 37.3 (C-4), 37.6 (C-2), 65.5 (C-5), 66.4 (C-1), 78.4 (C-3), 170.9 (C=O).

FTIR (KBr, cm\(^{-1}\): 3454, 2959, 2931, 2858, 1741, 1474, 1390, 1371, 1254, 1092, 1034.

HRMS (ES): calc. C\(_{13}\)H\(_{33}\)O\(_4\)Si (MH\(^+\)) 305.2148; obs. 305.2146.
(Z)-Ethyl 8,10-bis(tert-butyldimethylsilyloxy)-3,7,9-trimethyldec-2-en-4-ynoate (4.68):

\[
\text{TBSO} \quad \text{OTBS} \quad \begin{array}{c} \text{4.25} \\ + \end{array} \quad \begin{array}{c} \text{3.70} \\ \text{CO}_2\text{Et} \end{array} \quad \rightarrow \quad \text{TBSO} \quad \text{OTBS} \quad \begin{array}{c} \text{4.68} \\ \text{CO}_2\text{Et} \end{array}
\]

Solutions of alkyne 4.25 (0.69 g, 1.8 mmol) and iodide 3.70 (0.47 g, 2.0 mmol) in toluene (2 mL) were added, via cannula to a solution of Cu(Phen)(PPh₃)Br (0.11 g, 0.18 mmol) and Cs₂CO₃ (1.17 g, 3.6 mmol) in toluene (16 mL) in a long-necked round bottom flask. The reaction mixture was stirred at 110°C until complete consumption of iodide as monitored by ¹H NMR spectroscopy. After approximately 48 h the reaction mixture was cooled to room temperature and filtered through a pad of Celite and the solvent removed in-vacuo. Purification of the crude material via flash chromatography on silica gel, eluting with 10% EtOAc/petroleum ether, provided the title compound as a pale yellow oil (0.35 g, 55%).

¹H NMR (500 MHz, CDCl₃): δ 0.02 (s, 6H, Si(CH₃)₃), 0.048 (s, 3H, Si(CH₃)₂), 0.053 (s, 3H, Si(CH₃)), 0.879 (s, 9H, Si(C(CH₃)₃), 0.884 (s, 9H, Si(C(CH₃)₃), 0.92 (d, J = 7.0 Hz, 3H, 9-CH₃), 1.09 (d, J = 6.9 Hz, 3H, 7-CH₃), 1.26 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.84 (m, 1H, H-9), 1.97 (m, 1H, H-7), 2.01 (d, J = 1.4 Hz, 3H, 3-CH₃), 2.32 (dd, J = 9.2, 17.2 Hz, 1H, H-6), 2.59 (dd, J = 4.4, 17.2 Hz, 1H, H-6), 3.40 (dd, J = 7.2, 9.9 Hz, 1H, H-10), 3.58 (dd, J = 4.8, 4.8 Hz, 1H, H-8), 3.66 (dd, J = 5.5, 9.9 Hz, 1H, H-10), 4.17 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 5.91 (d, J = 1.4 Hz, 1H, H-2).

¹³C NMR (75 MHz, CDCl₃): δ -5.4 (Si(CH₃)), -5.3 (Si(CH₃)), -4.0 (Si(CH₃)), -3.9 (Si(CH₃)), 14.29 (OCH₂CH₃), 14.34 (9-CH₃), 17.8 (7-CH₃), 18.2 (Si(C(CH₃)₃), 18.4 (Si(C(CH₃)₃), 22.8 (C-6), 25.8 (Si(C(CH₃)₃), 25.9 (Si(C(CH₃)₃), 26.1 (3-CH₃), 36.0 (C-7), 40.1 (C-9), 59.9 (OCH₂CH₃), 65.1 (C-10), 77.1 (C-8), 80.7 (C-4), 102.8 (C-5), 123.1 (C-2), 135.7 (C-3), 165.2 (C-1).

FTIR (KBr, cm⁻¹): 2957, 2930, 2858, 2230, 1728, 1622, 1472, 1464, 1257, 1221, 1153, 1082.

(Z)-8,10-Bis(tert-butyldimethylsilyloxy)-3,7,9-trimethyldec-2-en-4-ynoic acid (4.69):

A solution of 4.68 (0.34 g, 0.66 mmol), 1M aqueous LiOH solution (5 mL, 5 mmol) and 1:1 THF/i-PrOH (10 mL) was stirred overnight at room temperature. After diluting with H$_2$O (10 mL) the solution was carefully acidified by the addition of 1M aqueous HCl solution and extracted with EtOAc (x3). The combined organic extracts were washed with brine, dried and concentrated. Purification of the crude material via flash chromatography on silica, eluting with 20% EtOAc/petroleum ether, provided the title compound as a colourless oil (0.24 g, 77%).

$^1$H NMR (500 MHz, CDCl$_3$): δ 1H 0.02 (s, 3H, SiC$_3$H$_3$), 0.03 (s, 3H, SiC$_3$H$_3$), 0.05 (s, 3H, SiC$_3$H$_3$), 0.06 (s, 3H, SiC$_3$H$_3$), 0.08 (s, 9H, SiC(CH$_3$)$_3$), 0.89 (s, 9H, SiC(CH$_3$)$_3$), 0.91 (d, J = 7.0 Hz, 3H, 9-CH$_3$), 1.07 (d, J = 6.9 Hz, 3H, 7-CH$_3$), 1.85 (m, 1H, H-9), 1.98 (m, 1H, H-7), 2.05 (d, J = 1.4 Hz, 3H, 3-CH$_3$), 2.35 (dd, J = 8.9, 17.4 Hz, 1H, H-6), 2.58 (dd, J = 4.3, 17.4 Hz, 1H, H-6), 3.41 (dd, J = 7.0, 9.9 Hz, 1H, H-10), 3.57 (dd, J = 4.9, 4.9 Hz, 1H, H-8), 3.66 (dd, J = 5.6, 9.9 Hz, 1H, H-10), 5.96 (d, J = 1.4 Hz, 1H, H-2).

$^{13}$C NMR (75 MHz, CDCl$_3$): δ -5.4 (SiCH$_3$), -5.3 (SiCH$_3$), -4.01 (SiCH$_3$), -3.96 (SiCH$_3$), 14.3 (9-CH$_3$), 17.7 (7-CH$_3$), 18.3 (SiC(CH$_3$)$_3$), 18.4 (SiC(CH$_3$)$_3$), 22.9 (C-6), 25.8 (3-CH$_3$), 25.9 (SiC(CH$_3$)$_3$), 26.1 (SiC(CH$_3$)$_3$), 35.9 (C-7), 40.1 (C-9), 65.0 (C-10), 77.8 (C-8), 80.3 (C-4), 105.0 (C-5), 122.9 (C-2), 137.6 (C-3), 168.9 (C-1).

FTIR (KBr, cm$^{-1}$): 3099, 2957, 2930, 2858, 2216, 1695, 1616, 1472, 1464, 1254, 1082.

HRMS (ES): calc. C$_{25}$H$_{49}$O$_4$Si$_2$ (MH$^+$) 469.3169; obs. 469.3185.

6-(3,5-Bis(tert-butyldimethylsilyloxy)-2,4-dimethylpentyl)-4-methyl-2H-pyran-2-one (4.70):

ZnBr$_2$ (153 μL of a 1M solution in THF, 0.15 mmol) was added to a solution of 4.69 (0.24 g, 0.51 mmol) in THF (5 mL) The reaction mixture was stirred at room temperature for 72 h and
concentrated. Purification of the crude material via flash chromatography on silica, eluting with 20% EtOAc/petroleum ether, provided the title compound as a colourless oil (0.15 g, 61%).

\[ ^1H \text{NMR} (500 \text{ MHz, CDCl}_3): \delta 0.01 \text{ (s, 6H, SiCH}_3\text{)}, 0.04 \text{ (s, 3H, SiCH}_3\text{)}, 0.05 \text{ (s, 3H, SiCH}_3\text{)}, 0.87 \text{ (s, 9H, SiC(CH}_3\text{)}_3\text{)}, 0.89 \text{ (m, 12H, SiC(CH}_3\text{)}_3\text{ and 2’-CH}_3\text{)}, 0.92 \text{ (d, } J = 6.9 \text{ Hz, 3H, 4’-CH}_3\text{)}, 1.79 \text{ (td, } J = 6.4, 12.9 \text{ Hz, 1H, H-4’)}, 2.09 \text{ (s, 3H, 4-CH}_3\text{)}, 2.13 \text{ (m, 2H, H-1’ and H-2’)}, 2.71 \text{ (d, } J = 11.4 \text{ Hz, 1H, H-1’)}, 3.43 \text{ (dd, } J = 6.8, 9.8 \text{ Hz, 1H, H-5’)}, 3.53 \text{ (dd, } J = 2.2, 6.1 \text{ Hz, 1H, H-3’)}, 3.63 \text{ (dd, } J = 5.3, 9.8 \text{ Hz, 1H, H-5’)}, 5.80 \text{ (s, 1H, H-5)}, 5.91 \text{ (s, 1H, H-3)}. \]

\[ ^{13}C \text{NMR (75 MHz, CDCl}_3\text{): } \delta -5.44 \text{ (SiCH}_3\text{)}, -5.35 \text{ (SiCH}_3\text{)}, -3.99 \text{ (SiCH}_3\text{)}, -3.95 \text{ (SiCH}_3\text{)}, 14.1 \text{ (C-4’ CH}_3\text{)}, 17.9 \text{ (C-2’ CH}_3\text{)}, 18.2 \text{ (SiC(CH}_3\text{)}_3\text{)}, 18.4 \text{ (SiC(CH}_3\text{)}_3\text{)}, 21.4 \text{ (C-4 CH}_3\text{)}, 25.9 \text{ (SiC(CH}_3\text{)}_3\text{)}, 26.1 \text{ (SiC(CH}_3\text{)}_3\text{)}, 34.0 \text{ (C-2’)}, 35.7 \text{ (C-1’)}, 40.4 \text{ (C-4’)}, 65.1 \text{ (C-5’)}, 77.3 \text{ (C-3’)}, 106.9 \text{ (C-5)}, 110.5 \text{ (C-3)}, 156.0 \text{ (C-4)}, 163.4 \text{ (C-2)}, 164.7 \text{ (C-4)}. \]

\[ \text{FTIR (KBr, cm}^{-1}\text{): 2957, 2930, 2858, 1736, 1647, 1564, 1254, 1080.} \]

\[ \text{HRMS (ES): calc. C}_{25}\text{H}_{49}\text{O}_4\text{Si}_2 \text{ (MH}^+) \text{ 469.3169; obs. 469.3177.} \]

6-(3-(tert-Butyldimethylsilyloxy)-5-hydroxy-2,4-dimethylpentyl)-4-methyl-2H-pyran-2-one (4.71): 

4-Toluenesulfonic acid (4.1 mg, 10 mol%) was added to a solution of 4.70 (100 mg, 0.21 mmol) in MeOH (5 mL) at 0°C. The reaction mixture was stirred at this temperature for 2 h then warmed to room temperature and stirred for an additional 2 h. The mixture was diluted with EtOAc (10 mL) and washed with 1:1 saturated aqueous NaHCO\textsubscript{3} solution/brine (10 mL). The aqueous washings were extracted with additional EtOAc (x2) and the combined organic portions washed with brine, dried and solvent removed under reduced pressure. Purification of the crude material via flash chromatography on silica gel, eluting with 50% EtOAc/petroleum ether, provided the title compound as a colourless oil (67.9 mg, 90%).
**Chapter Five – Experimental Details**

1H NMR (500 MHz, CDCl3): δ 0.09 (s, 3H, SiCH3), 0.11 (s, 3H, SiCH3), 0.91 (s, 9H, SiC(CH3)3), 0.93 (d, J = 6.6 Hz, 2'-CH3), 0.99 (d, J = 7.1 Hz, 4'-CH3), 1.87 (m, 1H, H-4'), 2.11 (s, 3H, 4-CH3), 2.11 (m, 1H, H-1'), 2.17 (m, 1H, H-2'), 2.74 (dd, J = 3.0, 13.3 Hz, 1H, H-1’), 3.54 (dd, J = 3.6, 5.5 Hz, 1H, H-3’), 3.63 (dd, J = 1.5, 5.9 Hz, 2H, H-5’), 5.82 (s, 1H, H-5), 5.94 (s, 1H, H-3).

13C NMR (75 MHz, CDCl3): δ -4.03 (SiCH3), -3.97 (SiCH3), 15.8 (4’-CH3), 16.8 (2’-CH3), 18.3 (SiC(CH3)3), 21.4 (4-CH3), 26.1 (SiC(CH3)3), 36.0 (C-2’), 36.2 (C-1’), 38.2 (C-4’), 65.7 (C-5’), 80.2 (C-3’), 107.0 (C-5), 110.7 (C-3), 156.0 (C-4), 163.2 (C-2), 164.0 (C-6).

FTIR (KBr, cm⁻¹): 3435, 2957, 2930, 2856, 1728, 1643, 1560, 1462, 1251, 1080.


3-(tert-Butyldimethylsilyloxy)-2,4-dimethyl-5-(4-methyl-6-oxo-6H-pyran-2-yl)pentanal (4.72):

Dess Martin periodinane (68 mg, 0.16 mmol) was added to a solution of 4.71 (51.2 mg, 0.14 mmol) in CH2Cl2 (2 mL) at room temperature. After stirring for 1.5 h, the reaction mixture was diluted with Et2O (10 mL) then stirred for ~10 min with 1M aqueous NaOH solution (10 mL) to dissolve the white precipitate. The organic layer was removed, and the aqueous portion extracted with Et2O (x2). The combined organic portions were washed with 1M aqueous NaOH solution and brine, dried and concentrated to provide the title compound as a colourless oil (44.3 mg, 87%), which was used without further purification.

1H NMR (500 MHz, CDCl3): δ 0.06 (s, 3H, SiCH3), 0.08 (s, 3H, SiCH3), 0.88 (d, J = 6.7 Hz, 3H, 4-CH3), 0.89 (s, 9H, SiC(CH3)3), 1.14 (d, J = 7.1 Hz, 3H, 2-CH3), 2.12 (s, 3H, 4’-CH3), 2.19 (m, 2H, H-4 and H-5), 2.54 (m, 1H, H-2), 2.72 (dd, J = 3.1, 13.3 Hz, 1H, H-5), 3.81 (dd, J = 4.5, 4.5 Hz, 1H, H-3), 5.83 (s, 1H, H-5’), 5.95 (s, 1H, H-3’), 9.75 (d, J = 2.5 Hz, 1H, H-1).
\( ^{13}C \) NMR (75 MHz, CDCl\(_3\): \( \delta \) -4.3 (Si\(\text{CH}_3\)), -4.1 (Si\(\text{CH}_3\)), 11.6 (2-\(\text{CH}_3\)), 16.1 (4-\(\text{CH}_3\)), 18.2 (Si\(\text{C}(\text{CH}_3)_3\)), 21.4 (4'-\(\text{CH}_3\)), 25.9 (Si\(\text{C}(\text{CH}_3)_3\)), 35.8 (C-4), 36.5 (C-5), 50.3 (C-2), 77.4 (C-3), 107.2 (C-5'), 110.9 (C-3'), 156.0 (C-4'), 163.1 (C-6'), 163.3 (C-2'), 204.2 (C-1).

**FTIR** (KBr, cm\(^{-1}\)): 2932, 2856, 1730, 1645, 1562, 1254, 1074.

**HRMS** (ES): calc. \( \text{C}_{19}\text{H}_{33}\text{O}_4\text{Si} \) (MH\(^+\)) 353.2148; obs. 353.2140.

\((E)-\text{Ethyl-5-}(\text{tert-butyldimethylsilyloxy})-4,6\text{-dimethyl-7-}(4\text{-methyl-6-oxo-6H-pyran-2-yl})\text{-hept-2-enoate (4.73):}\)

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{PPh}_3 \quad 2.123 \quad + \quad \text{O} \\
\text{4.72} & \quad \text{OTBS} & \quad \rightarrow \quad \text{EtO}_2\text{C} \\
\text{4.73} & \quad \text{OTBS}
\end{align*}
\]

1-(Ethoxycarbonyl) methylenetriphenylphosphorane (2.123) (44.0 mg, 0.13 mmol) was added, in one portion to a solution of 4.72 (40.4 mg, 0.12 mmol) in CH\(_2\)Cl\(_2\) (4 mL) at room temperature. After stirring for 56 h the solvent was removed \textit{in-vacuo} and petroleum ether added to the residue. The precipitated triphenylphosphine oxide was removed by filtration and the filtrate concentrated to provide the crude material. Purification by flash chromatography on silica, eluting with 30% EtOAc/petroleum ether, afforded the title compound as a colourless oil (24.4 mg, 50%).

\( ^1\text{H} \) NMR (500 MHz, CDCl\(_3\)): \( \delta \) 0.03 (s, 3H, Si\(\text{CH}_3\)), 0.04 (s, 3H, Si\(\text{CH}_3\)), 0.86 (d, \( J = 6.4 \) Hz, 3H, 6-\(\text{CH}_3\)), 0.89 (s, 9H, Si\(\text{C}(\text{CH}_3)_3\)), 1.08 (d, \( J = 7.0 \) Hz, 3H, 4-\(\text{CH}_3\)), 1.27 (t, \( J = 7.1 \) Hz, 3H, O\(\text{C}(\text{CH}_3)_2\)), 2.10 (s, 2H, H-6 and H-7), 2.51 (m, 1H, H-4), 2.71 (m, 1H, H-7), 3.46 (dd, \( J = 3.8 \), 4.8 Hz, 1H, H-5), 4.17 (q, \( J = 7.1 \) Hz, 2H, O\(\text{C}(\text{CH}_2)_2\)), 5.77 (dd, \( J = 1.1 \), 15.8 Hz, 1H, H-2), 5.80 (s, 1H, H-3’), 5.92 (s, 1H, H-5’), 6.99 (dd, \( J = 8.2 \), 15.8 Hz, 1H, H-3).

\( ^{13}C \) NMR (75 MHz, CDCl\(_3\)): \( \delta \) -3.9 (Si\(\text{CH}_3\)), -3.8 (Si\(\text{CH}_3\)), 14.2 (O\(\text{C}(\text{CH}_2)_2\)), 17.1 (4-\(\text{CH}_3\)), 17.2 (6-\(\text{CH}_3\)), 18.3 (Si\(\text{C}(\text{CH}_3)_3\)), 21.4 (4'-\(\text{CH}_3\)), 26.1 (Si\(\text{C}(\text{CH}_3)_3\)), 35.6 (C-6), 36.1 (C-7), 41.1 (C-4), 60.2 (O\(\text{C}(\text{CH}_2)_2\)), 79.5 (C-5), 107.0 (C-3’), 110.7 (C-5’), 121.0 (C-2), 151.6 (C-3), 156.0 (C-4’), 163.2 (C-6’), 164.0 (C-8), 166.5 (C-1).

**FTIR** (KBr, cm\(^{-1}\)): 2957, 2932, 2856, 1728, 1647, 1562, 1462, 1254, 1180, 1034.

**HRMS** (ES): calc. \( \text{C}_{23}\text{H}_{39}\text{O}_5\text{Si} \) (MH\(^+\)) 423.2567; obs. 423.2569.
Ethyl-7-(tert-butyldimethylsilyloxy)-3,6,8-trimethyl-1,5,6,7,8,8a-hexahyronaphthalene-1-carboxylate (4.74):

A solution of 4.73 (11.6 mg, 0.027 mmol) and Proton sponge® (1.8 mg, 30 mol %) in xylenes (2 mL) was refluxed vigorously for 48 h. The solvent was removed in-vacuo and the crude material purified via flash chromatography on silica, eluting with 10% EtOAc/petroleum ether, to provide the title compound as a colourless oil (8.3 mg, 81%).

\(^1\)H NMR (500 MHz, CDCl\(_3\) with 0.1% d\(_5\)-pyridine): \(\delta\) 0.05 (s, 6H, SiCH\(_3\)), 0.86 (d, \(J = 6.9\) Hz, 3H, 8-CH\(_3\)), 0.92 (d, \(J = 6.9\) Hz, 3H, 6-CH\(_3\)), 0.94 (s, 9H, Si(CH\(_3\))\(_3\)), 1.25 (t, \(J = 7.1\) Hz, OCH\(_2\)CH\(_3\)), 1.48 (m, 1H, H-8), 1.62 (m, 1H, H-6), 1.69 (t, \(J = 2.0\) Hz, 3H, 3-CH\(_3\)), 1.90 (dd, \(J = 3.9, 13.5\) Hz, 1H, H-5\(_A\)), 2.32 (m, 1H, H-5\(_B\)), 3.03 (dd, \(J = 11.0, 11.0\) Hz, 1H, H-8a), 3.11 (m, 1H, H-1), 3.64 (m, 1H, H-7), 4.15 (m, 2H, OCH\(_2\)CH\(_3\)), 5.09 (s, 1H, H-2), 5.39 (s, 1H, H-4).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\) with 0.1% d\(_5\)-pyridine): \(\delta\) -3.3 (SiCH\(_3\)), 14.2 (OCH\(_2\)CH\(_3\)), 16.8 (8-CH\(_3\)), 18.6 (SiC(CH\(_3\))\(_3\)), 19.4 (6-CH\(_3\)), 21.5 (3-CH\(_3\)), 26.3 (SiC(CH\(_3\))\(_3\)), 36.8 (C-8a), 37.0 (C-5), 39.1 (C-6), 45.8 (C-8), 46.0 (C-1), 60.7 (OCH\(_2\)CH\(_3\)), 77.5 (C-7), 114.3 (C-2), 118.5 (C-4), 131.4 (C-3), 141.0 (C-4a), 175.5 (C=O).

FTIR (KBr, cm\(^{-1}\)): 2957, 2930, 2856, 1740, 1462, 1366, 1252, 1153, 1036.

HRMS (ES): calc. C\(_{22}\)H\(_{39}\)O\(_3\)Si (MH\(^+\)) 379.2668; obs. 379.2664.
(E)-Ethyl-7-(5-bromo-4-methyl-6-oxo-6H-pyran-2-yl)-5-(tert-butyldimethylsilyloxy)-4,6-dimethylhept-2-enoate (4.78):

\[
\text{EtO}_2\text{C} \quad \text{OTBS} \\
\text{4.73} \\
\text{EtO}_2\text{C} \quad \text{OTBS} \\
\text{4.78}
\]

\[N\text{-Bromosuccinimide (2.8 mg, 16 } \mu \text{mol) was added to a solution of 4.73 (6.7 mg, 16 } \mu \text{mol) in THF (1 mL) at room temperature. The reaction mixture was stirred for 48 h at this temperature at which time TLC analysis indicated the presence of unreacted 4.73. An additional 1.4 mg (8 } \mu \text{mol) of NBS was added and stirring continued. After 48 h an additional 1.4 mg (8 } \mu \text{mol) of NBS was added. After a further 48 h the reaction mixture was diluted with CH}_2\text{Cl}_2, \text{ washed with saturated aqueous NaHCO}_3 \text{ solution and brine, dried and the solvent removed in-vacuo.} \text{ }^1\text{H NMR analysis of the crude material indicated a mixture of 4.73, 4.78 and an unidentified side-product. Small scale purification via flash chromatography on silica gel, eluting with 30}\% \text{ EtOAc/petroleum ether provided a small sample of the title compound (~1.0 mg) that was used to obtain }^1\text{H NMR and mass spectral data.}
\]

\[^1\text{H NMR (500 MHz, CDCl}_3\text{): } \delta 0.05 \text{ (s, 3H, SiC}_3\text{H}_3\text{), 0.06 (s, 3H, SiC}_3\text{H}_3\text{), 0.87 (m), 0.90 (s, 9H, SiC(C}_3\text{H}_3)_3\text{), 1.08 (d, } J = 6.9 \text{ Hz, 3H, CH}_3\text{), 1.28 (t, } J = 7.1 \text{ Hz, 3H, OCH}_2\text{CH}_3\text{), 2.10 (m, 2H), 2.26 (s, 3H, CH}_3\text{), 2.52 (m, 1H), 2.72 (m, 1H), 3.47 (dd, } J = 4.1, 4.1 \text{ Hz, 1H, H-5), 4.18 (q, } J = 7.1 \text{ Hz, 2H, OCH}_2\text{CH}_3\text{), 5.78 (dd, } J = 1.2, 15.8 \text{ Hz, 1H, H-2), 5.89 (s, 1H, H-3’), 7.00 (dd, } J = 8.1, 15.8 \text{ Hz, 1H, H-3}).
\]

\[^{\text{HRMS (ES): calc. C}_{23}\text{H}_{38}\text{O}_5\text{SiBr (MH}^+)\text{ 501.1672; obs. 501.1688.}}\]
Model system for Side-Chain Installation:

\((E)-\text{Ethyl 2-methyl-3-phenylacrylate (4.79)}:\)

\[
\begin{align*}
\text{CHO} & \quad \text{CO}_2\text{Et} \\
\end{align*}
\]

1-(Ethoxycarbonyl) ethylenetriphenylphosphorane (2.92) (5.2 g, 14 mmol) was added in one portion to a solution of benzaldehyde (1.0 g, 9.6 mmol) in toluene (60 mL). The reaction mixture was refluxed for 18 h before being cooled to room temperature. Toluene was removed under reduced pressure and petroleum ether added to the residue. The precipitated triphenylphosphine oxide was removed via filtration and the filtrate concentrated. Purification of the crude material via flash chromatography on silica eluting with 5% Et₂O/petroleum ether provided 4.79 as a colourless oil (1.44 g, 79%). Values from the \(^1\)H NMR spectrum were in close agreement with the reported values.\(^{32}\)

\(^1\)H NMR (500 MHz, CDCl₃): \(\delta 1.35 (t, J = 7.1 \text{ Hz}, 3\text{H}, \text{OCH}_2\text{C}_\text{H}_3), 2.11 (s, 3\text{H}, \text{CH}_3), 4.27 (q, J = 7.1 \text{ Hz}, 2\text{H}, \text{OCH}_2\text{C}_\text{H}_3), 7.30-7.40 (m, 5\text{H}, \text{ArH}), 7.70 (s, 1\text{H}, \text{H-3}).\)

\(^{13}\)C NMR (75 MHz, CDCl₃): \(\delta 14.0 (\text{CH}_3), 14.3 (\text{OCH}_2\text{CH}_3), 60.8 (\text{OCH}_2\text{CH}_3), 128.2 (\text{ArH}), 128.3 (\text{ArH}), 128.6 (\text{C-2}), 129.6 (\text{ArH}), 135.9 (\text{Ar}), 138.6 (\text{C-3}), 168.6 (\text{C-1}).\)

HRMS (EI): calc. C\(_{12}\)H\(_{14}\)O\(_2\) (M\(^+\)) 190.0994; obs. 190.0994.

\((2E,4E)-\text{Ethyl 2,4-dimethyl-5-phenylpenta-2,4-dienoate (4.80)}:\)

DIBAL-H (23 mL of a 1M solution in hexanes, 23 mmol) was slowly added to a solution of ester 4.79 (1.44 g, 7.6 mmol) in Et₂O (80 mL) at −78°C. After stirring at −78°C for 1 h the reaction mixture was warmed to 0°C and stirred for an additional 1 h. The reaction was quenched by the slow addition of methanol and then stirred with saturated aqueous Na/K tartrate solution for ~2 h until the layers cleared and separated. The organic layer was removed and the aqueous layer extracted with EtOAc (x3). The combined organic fractions were washed with brine, dried and concentrated to provide the alcohol as a colourless oil (1.17 g), which was used without further purification.
A solution of the alcohol (1.17 g) in CH₂Cl₂ (5 mL) was added, via cannula, to a solution of Dess-Martin periodinane (3.6 g, 8.4 mmol) in CH₂Cl₂ (20 mL) at room temperature. After stirring for 1 h at room temperature the reaction mixture was diluted with Et₂O (25 mL), then stirred for ~10 min with 1M aqueous NaOH solution (25 mL) to dissolve the white precipitate. The organic layer was removed, and the aqueous portion extracted with Et₂O (x2). The combined organic portions were washed with 1M aqueous NaOH solution and brine, dried and concentrated to provide the aldehyde as a pale yellow oil (0.91g), which was used without further purification.

1-(Ethoxycarbonyl) ethylidenetriphenylphosphorane (2.92) (4.1 g, 11 mmol) was added in one portion to a solution of the aldehyde (0.91 g) in toluene (60 mL). The reaction mixture was refluxed for 18 h before being cooled to room temperature. Toluene was removed under reduced pressure and petroleum ether added to the residue. The precipitated triphenylphosphine oxide was removed via filtration and the filtrate concentrated. Purification of the crude material via flash chromatography on silica eluting with 5% Et₂O/petroleum ether provided 4.80 as a colourless oil (0.59 g, 35% over three steps).

1H NMR (500 MHz, CDCl₃): δ 1.32 (t, J = 7.1 Hz, 3H, OCH₂C₃H₃), 2.09 (s, 6H, 2-CH₃ and 4-CH₃), 4.22 (q, J = 7.1 Hz, 2H, OCH₂C₃H₃), 6.61 (s, 1H, H-5), 7.24-7.34 (m, 6H, H-3 and ArH).

13C NMR (75 MHz, CDCl₃): δ 14.2 (2-CH₃), 14.3 (OCH₂C₃H₃), 18.3 (4-CH₃), 60.7 (OCH₂C₃H₃), 126.9 (C-2), 127.1 (ArH), 128.2 (ArH), 129.2 (ArH), 134.2 (Ar), 134.4 (C-5), 137.0 (C-4), 143.1 (C-3), 168.9 (C-1).


(2E,4E)-2,4-Dimethyl-5-phenylpenta-2,4-dien-1-ol (4.81):

DIBAL-H (7.8 mL of a 1M solution in hexanes, 7.8 mmol) was slowly added to a solution of ester 4.80 (0.59 g, 2.6 mmol) in Et₂O (30 mL) at −78°C. After stirring at −78°C for 1 h the reaction mixture was warmed to 0°C and stirred for an additional 1 h. The reaction was quenched by the slow addition of methanol and then stirred with saturated aqueous Na/K tartrate solution for ~2 h until the layers cleared and separated. The organic layer was removed and the aqueous
layer extracted with EtOAc (x3). The combined organics were washed with brine, dried and concentrated. Purification of the crude material via flash chromatography on silica eluting with 30% EtOAc/petroleum ether provided the title compound as a colourless oil (0.45 g, 94%).

**1H NMR** (500 MHz, CDCl₃): δ 1.42 (s, 1H, O-H), 1.90 (s, 3H, 2-CH₃), 2.00 (s, 3H, 4-CH₃), 4.10 (s, 2H, H-1), 6.05 (s, 1H, H-2), 6.39 (s, 1H, H-4), 7.19-7.39 (m, 5H, Ar-H).

**13C NMR** (75 MHz, CDCl₃): δ 15.6 (2-CH₃), 18.8 (4-CH₃), 69.3 (C-1), 126.3 (C-5), 128.1 (Ar-H), 129.0 (Ar-H), 129.7 (Ar-H and C-3), 134.9 (C-4), 136.0 (Ar), 137.9 (C-2).

**HRMS** (EI): calc. C₁₃H₁₆O (M⁺) 188.1201; obs. 188.1206.

**Epoxy-2,4-dimethyl-5-phenylpent-4-en-1-ol (4.82):**

(m-Chloroperbenzoic acid (0.26 g, 1.5 mmol) was added to a solution of 4.80 (0.28 g, 1.5 mmol) in CH₂Cl₂ (20 mL) at 0°C. The resulting solution was stirred for 3 h at 0°C and calcium hydroxide (1 g) and Na₂SO₄ (1 g) added. The mixture was filtered and the filtrate concentrated *in-vacuo*. Purification of the crude material via flash chromatography on silica eluting with 50% EtOAc/petroleum ether provided the title compound as a white solid (0.16 g, 52%).

**1H NMR** (500 MHz, CDCl₃): δ 1.25 (s, 3H, 2-CH₃), 1.92 (s, 3H, 4-CH₃), 3.65 (s, 1H, H-3), 3.72 (d, J = 12.4 Hz, 1H, H-1), 3.83 (d, J = 12.4 Hz, 1H, H-1), 6.48 (s, 1H, H-5), 7.22-7.34 (m, 5H, Ar-H).

**13C NMR** (75 MHz, CDCl₃): δ 13.1 (4-CH₃), 15.9 (2-CH₃), 62.4 (C-2), 63.4 (C-3), 65.0 (C-1), 126.1 (C-5), 126.5 (Ar-H), 128.2 (Ar-H), 128.9 (Ar-H), 131.4 (C-4), 137.0 (Ar).

**HRMS** (EI): calc. C₁₃H₁₆O₂ (M⁺) 204.1150; obs. 204.1150.
(2E,6E)-4,5-Epoxy-4,6-dimethyl-7-phenylhepta-2,6-dienamide (4.84):

A solution of the 4.82 (0.16 g, 0.78 mmol) in CH₂Cl₂ (2 mL) was added, via cannula, to a solution of Dess-Martin periodinane (0.36 g, 0.85 mmol) and pyridine (390 μL, 4.7 mmol) in CH₂Cl₂ (14 mL) at room temperature. After stirring for 4 h at room temperature the reaction mixture was diluted with Et₂O (15 mL), then stirred for ~10 min with 1M aqueous NaOH solution (10 mL) to dissolve the white precipitate. The organic layer was removed, and the aqueous portion extracted with Et₂O (x2). The combined organic portions were washed with 1M aqueous NaOH solution and brine, dried and concentrated to provide the aldehyde as a pale yellow oil (0.15 g), which was used without further purification.

A solution of n-BuLi (590 μL of a 1.6M solution in hexanes, 0.94 mmol) was added dropwise to a solution of diethyl phosphonoacetamide (4.83) (0.17 g, 0.86 mmol) in THF (4 mL) at -78°C. After stirring for 5 min a solution of the aldehyde (0.15 g) in THF (2 mL) was added via cannula. After an additional 30 min at -78°C the solution was warmed to room temperature and quenched with H₂O (5 mL). The aqueous mixture was extracted with EtOAc (x3) and the combined organic portions washed with brine, dried and the solvent removed under reduced pressure. Purification of the crude material via flash chromatography on silica, eluting with 10% MeOH/CH₂Cl₂ provided the title compound as a white solid (83.4 mg, 44% over two steps).

¹H NMR (500 MHz, CDCl₃): δ 1.36 (s, 3H, 4-CH₃), 1.90 (s, 3H, 6-CH₃), 3.39 (s, 1H, H-5), 5.70 (s, 1H, NH₂), 5.95 (s, 1H, NH₂), 6.09 (d, J = 15.2 Hz, 1H, H-2), 6.47 (s, 1H, H-7), 6.87 (d, J = 15.2 Hz, 1H, H-3), 7.20-7.35 (m, 5H, ArH).

¹³C NMR (75 MHz, CDCl₃): δ 14.3 (4-CH₃), 15.7 (6-CH₃), 61.1 (C-4), 68.8 (C-5), 122.6 (C-2), 126.7 (ArH), 127.0 (C-7), 128.2 (ArH), 128.9 (ArH), 130.6 (C-6), 136.7 (Ar), 146.5 (C-3), 167.3 (C-1).

HRMS (ES): calc. C₁₅H₁₈NO₂ (MH⁺) 244.1338; obs. 244.1344.
**Chapter Five – Experimental Details**

(4E)-2,3-Cyclopropyl-2,4-dimethyl-5-phenylpent-4-en-1-ol (4.85):

\[
\begin{align*}
&\text{4.81} \quad \text{OH} \\
&\text{4.85} 
\end{align*}
\]

A solution of Et₂Zn (1.0 mL of a 1.57M solution in THF, 1.6 mmol) was added dropwise to a solution of 1,2-dimethoxyethane (166 μL, 1.6 mmol) in CH₂Cl₂ (12 mL) at -20°C. After stirring for 15 min at this temperature CH₂I₂ (265 μL, 3.3 mmol) was added, then, after an additional 15 min stirring a solution of 4.81 (0.18 g, 1.1 mmol) was added via cannula. The reaction mixture was warmed to room temperature, stirred for 3 days then quenched with saturated aqueous NH₄Cl solution. The aqueous portion was extracted with CH₂Cl₂ (x3) and the combined organic portions washed with brine, dried and solvent removed under reduced pressure. Purification of the crude material via flash chromatography on silica, eluting with 30% EtOAc/petroleum ether, provided the title compound as a colourless oil (0.12 g, 55%).

\(^{1}\text{H NMR}\) (500 MHz, CDCl₃): δ 0.74 (m, 2H, CH₂), 1.09 (s, 3H, 2-CH₃), 1.50 (m, 1H, H-3), 1.94 (s, 3H, 4-CH₃), 3.50 (m, 2H, H-1), 6.24 (s, 1H, H-5), 7.18-7.34 (m, 5H, ArH).

\(^{13}\text{C NMR}\) (75 MHz, CDCl₃): δ 14.6 (6-CH₃), 14.7 (CH₂), 19.8 (4-CH₃), 24.6 (C-2), 31.3 (C-3), 71.8 (C-1), 126.0 (ArH), 126.1 (C-5), 128.0 (ArH), 128.8 (ArH), 136.4 (Ar), 138.2 (C-4).


(2E,6E)-4,5-Cyclopropyl-4,6-dimethyl-7-phenylhepta-2,6-dienamide (4.86):

\[
\begin{align*}
&\text{4.85} \quad \text{OH} \\
&\text{4.86} \quad \text{CONH₂} 
\end{align*}
\]

A solution of TPAP (7.4 mg, 7 mol%) in CH₂Cl₂ (1 mL) was added to a solution of 4.85 (62 mg, 0.3 mmol), N-methylmorpholine-N-oxide (50 mg, 0.44 mmol) and 4Å molecular sieves (50 mg) in CH₂Cl₂ (3 mL) at room temperature. After stirring at this temperature for 4 h the reaction mixture was filtered through a short pad of silica gel, eluting with EtOAc. The filtrate was concentrated under reduced pressure to provide the aldehyde as a pale yellow oil that was used without further purification.
A solution of $n$-BuLi (590 $\mu$L of a 1.6M solution in hexanes, 0.94 mmol) was added dropwise to a solution of diethyl phosphonoacetamide (4.83) (0.17 g, 0.86 mmol) in THF (4 mL) at -78°C. After stirring for 5 min a solution of the aldehyde (0.15 g) in THF (2 mL) was added via cannula. After an additional 10 min at -78°C the solution was warmed to room temperature over 1 h then quenched with $H_2O$ (5 mL). The aqueous mixture was extracted with EtOAc (x3) and the combined organic portions washed with brine, dried and the solvent removed under reduced pressure. Purification of the crude material via flash chromatography on silica gel, eluting with 10% MeOH/CH$_2$Cl$_2$ provided the title compound as a white solid (41.9 mg, 58% over two steps).

$^1$H NMR (500 MHz, CD$_3$OD): $\delta$ 1.14 (dd, $J = 4.9, 6.7$ Hz, 1H, CH$_2$), 1.18 (s, 3H, 4-C$_H$$_3$), 1.24 (dd, $J = 4.9, 8.3$ Hz, 1H, CH$_2$), 1.89 (s, 3H, 6-C$_H$$_3$), 1.90 (m, 1H, H-5), 5.95 (d, $J = 15.4$ Hz, 1H, H-2), 6.29 (s, 1H, H-7), 6.52 (d, $J = 15.4$ Hz, 1H, H-3), 7.16-7.32 (m, 5H, ArH).

$^{13}$C NMR (75 MHz, CD$_3$OD): $\delta$ 15.2 (4-C$_H$$_3$), 20.2 (6-C$_H$$_3$), 21.0 (CH$_2$), 25.8 (C-4), 38.3 (C-5), 119.3 (C-2), 127.6 (ArH), 128.5 (C-7), 129.4 (ArH), 130.2 (ArH), 136.7 (C-6), 139.6 (Ar), 156.1 (C-3), 171.7 (C-1).

HRMS (ES): calc. C$_{16}$H$_{20}$NO (MH$^+$) 242.1545; obs. 242.1538.
5.5 X-Ray Crystallographic Data

Table 5.1 lists the crystallographic data and X-ray experimental details for the two crystal structures described in this thesis. Complete crystallographic data and structure refinement tables including atomic coordinates, anisotropic displacement parameters and hydrogen atom coordinates are available from the Chemistry Department of the University of Canterbury.

All measurements were made with a Bruker-Nonius APEX II diffractometer irradiating the sample with graphite monochromated MoK$\alpha$ ($\lambda = 0.71073$ Å) radiation. Data collection, cell determination and data reduction were all performed with the APEX package of software.\textsuperscript{33} Intensities were corrected for Lorentz and polarisation effects and for absorption using SADABS.\textsuperscript{34} The structures were solved by direct methods using the SHELXTL program.\textsuperscript{35} All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed at calculated ideal positions and refined using a riding model.
Table 5.1  Crystal data and X-ray experimental details for 2.64 and 2.66.

<table>
<thead>
<tr>
<th>Compound</th>
<th>2.64</th>
<th>2.66</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C$<em>{28}$H$</em>{54}$O$_4$Si$_2$</td>
<td>C$<em>{28}$H$</em>{54}$O$_4$Si$_2$</td>
</tr>
<tr>
<td>Formula weight</td>
<td>510.89</td>
<td>510.89</td>
</tr>
<tr>
<td>Temperature (K)</td>
<td>123(2) K</td>
<td>293(2) K</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Triclinic</td>
<td>Triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P-1</td>
<td>P-1</td>
</tr>
<tr>
<td>Unit cell dimensions:</td>
<td>a (Å) 8.602(2)</td>
<td>b (Å) 11.941(3)</td>
</tr>
<tr>
<td></td>
<td>c (Å) 15.885(3)</td>
<td>α (°) 92.938(13)</td>
</tr>
<tr>
<td></td>
<td>β (°) 94.974(13)</td>
<td>γ (°) 104.442(15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Volume(Å$^3$) 1569.6(6)</td>
</tr>
<tr>
<td></td>
<td>Z</td>
<td>Density (calculated) (Mg/m$^3$) 1.022</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Absorption coefficient (mm$^{-1}$) 0.101</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F(000) 536</td>
</tr>
<tr>
<td></td>
<td>Crystalsize (mm) 0.7 x 0.36 x 0.02</td>
<td>0.7 x 0.5 x 0.2</td>
</tr>
<tr>
<td></td>
<td>Theta range for data collection (°) 1.29 to 25.25</td>
<td>2.53 to 30.00.</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>8506</td>
<td>1643</td>
</tr>
<tr>
<td>Independent reflections [R(int)]</td>
<td>5281 [0.1297]</td>
<td>1577 [0.0240]</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>5281 / 0 / 319</td>
<td>1577 / 0 / 307</td>
</tr>
<tr>
<td>Goodness-of-fit on F$^2$</td>
<td>1.423</td>
<td>2.553</td>
</tr>
<tr>
<td>$R_1$ [I&gt;2σ(I)]</td>
<td>0.1565</td>
<td>0.2497</td>
</tr>
<tr>
<td>wR$_2$ (all data)</td>
<td>0.4730</td>
<td>0.5566</td>
</tr>
</tbody>
</table>


5.6 References for Chapter Five


(33) Bruker-Nonius, Apex V2.02, 2005-2006.
