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Studies Towards the Synthesis of LL-Z1640-2
and Spirocyclic Systems

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Submitted in part fulfilment of the requirements for the degree of Doctor of Philosophy

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July 2010

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Abstract

Resorcylic acid lactones (RALs) are natural products, with some having been shown to be potent inhibitors of several protein kinases and mammalian cell proliferation and tumour growth in animals. LL-Z1640-2 (also known as 5Z-7-oxo-zeanol or C292) is a cis-enone RAL, isolated in 1978 from fungal broth and classified as an anti-protozoal agent. Later, in 1999, its cytokine releasing inhibiting activity was discovered, with subsequent data showing it could selectively and irreversibly inhibit transforming growth factor activating kinase-1 (TAK1) activity at low concentrations. It is also reported as having significant activity versus tumour necrosis factor-alpha (TNF-α) production in cells.

This thesis documents and describes the work undertaken towards a total synthesis of the 14-membered macrocycle, LL-Z1640-2. The presence of two internal bonds and three stereogenic centres poses a challenge synthetically, but this has been effectively overcome with the development of a flexible, economic and efficient synthesis, beginning from the commercially available starting materials, methyl 2,4,6-trihydroxybenzoate and 2-deoxy-D-ribose.

The original route relied on a Wittig olefination to introduce the E-double bond, with moderate selectivity and success. Later, an improved method was built upon, which utilised Grubbs mediated cross-metathesis to form the desired E-olefin in good yield and selectivity. Once the entire carbon framework had been established via a one-pot oxidation-Grignard addition of the appropriate alkyne unit, subsequent transformations enabled the formation of the seco-acid. This very successfully underwent Mitsunobu macrolactonisation, with complete inversion of the stereocentre, to afford the macrocyclic lactone. From this intermediate, the desired natural product LL-Z1640-2 could be generated in three steps.
A number of natural products and biologically important compounds contain spirocyclic pyran and piperidines ring systems as part of their overall structures. In 1996, pinnaic acid and halichlorine were isolated from their respective marine natural sources. It was subsequently shown that they exhibited inhibitory activity towards certain biological substances and for this reason they became targets for total synthesis. Characterised by an azaspiro[4.5]decane ring system, the difficulty in achieving total syntheses of such compounds is immense.

The aim of the project was to develop a concise method towards the generation of highly functionalised spirocyclic piperidine units. The regioselective aza-Achmatowicz oxidative rearrangement was used as the key step to rearrange α-amino furan building blocks into their respective enones. Importantly, this rearrangement was proven to be viable and to proceed with compounds possessing a terminal olefin, with no over-oxidation observed.

This thesis also describes the investigation and efforts made into the production of more functionalised units, as well as studies into the synthesis of the cores of halichlorine and polymaxenolide, again using the aza-Achmatowicz and Achmatowicz rearrangement respectively.
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Acknowledgements

I would like to take this opportunity to extend my thanks to my supervisor, Dr Rudi Marquez, for all his support, encouragement and guidance throughout my PhD. Many thanks also to my second supervisor, Dr Andrew Sutherland, for his help and advice throughout my time in the department.

I would also like to thank the staff who provided technical support at the University of Glasgow: Dr David Adam (NMR), Jim Tweedie (MS) and Ted Easdon.

Thank you to the past and present members of the RM group, who have helped to make PhD life so enjoyable - Murray, Mat, Jennifer, Mike, Phil, Frank, Ben, Alasdair, Seb, Kasia and Neil. A huge thank you goes to Anna from the JSC group for providing support, encouragement and most of all friendship.

I gratefully acknowledge Dr Ian Sword and the University of Glasgow for financial support.

Last, but by no means least, I must thank my family, especially Mum, Dad and Mark and also to Stephen, for being there every step of the way.

Suzannah
Author's Declaration

This thesis represents the original work of Suzannah Jane Harnor unless explicitly stated otherwise in the text. The research on which this thesis is based was carried out at the University of Glasgow in the Henderson and Raphael laboratories, under the supervision of Dr Rodolfo Marquez, during the period October 2006 to September 2009.

Suzannah J. Harnor

July 2010
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>4Å MS</td>
<td>4 Angstrom molecular sieves</td>
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<tr>
<td>Å</td>
<td>Angstrom</td>
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<tr>
<td>Allyl</td>
<td>2-propenyl</td>
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<tr>
<td>aq.</td>
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<td>Ar</td>
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<td>atm</td>
<td>atmosphere(s)</td>
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<td>bd</td>
<td>broad doublet</td>
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<tr>
<td>Bn</td>
<td>benzyl</td>
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<td>Boc</td>
<td>tert-butoxycarbonyl</td>
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<td>br</td>
<td>broad</td>
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<tr>
<td>Bu</td>
<td>butyl</td>
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<td>°C</td>
<td>degrees Celsius</td>
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<tr>
<td>CAN</td>
<td>ceric ammonium nitrate</td>
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<tr>
<td>cat.</td>
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<td>Cl</td>
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<td>COSY</td>
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<td>camphorsulfonic acid</td>
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<td>d</td>
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<td>DBU</td>
<td>1,8-diazabicyclo[5,4,0]undec-7-ene</td>
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<td>DDQ</td>
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<td>DEAD</td>
<td>diethyl azodicarboxylate</td>
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<td>distortionless enhancement through polarisation transfer</td>
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<td>DIPEA</td>
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<td>dimethyl sulfoxide</td>
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<td>FAB</td>
<td>fast atom bombardment</td>
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<td>flash column chromatography</td>
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<td>HF</td>
<td>hydrogen fluoride</td>
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<td>HRMS</td>
<td>high resolution mass spectrometry</td>
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HSQC  heteronuclear single quantum coherence  
HWE   Horner-Wadsworth-Emmons       
Hz    hertz                         
i    iso                           
IR    infrared                     
KHMDS potassium bis(trimethylsilyl)amide  
J    NMR spectra coupling constant   
µL    microlitre(s)                
L    litre(s)                      
lit.  literature                   
µM    micromolar                   
m    multiplet                     
M    molar (mol L⁻¹)               
mCPBA meta-chloroperoxybenzoic acid  
Me    methyl                       
MeOH  methanol                     
mg    milligram(s)                 
MHz   megahertz                    
min   minute(s)                    
µL    millilitre(s)                
mmol  millimole(s)                 
 mM   millimolar                    
 mol  mole(s)                      
MOM   methoxymethyl                
mp    melting point                
MS    mass spectroscopy/spectrum    
Ms    methanesulfonyl/mesyl         
MW    molecular weight             
 nBuLi n-butyllithium              
NMR  nuclear magnetic resonance    
oct. octet                         
p    para                          
Pd/C palladium on carbon           
PG    protecting group             
Ph    phenyl                       
PMB   p-methoxybenzyl              
ppm   parts per million            
PPTS  pyridinium p-toluenesulfonate  
Pyr   pyridine                     
q    quartet                       
qn    quintet                      
R    alkyl chain                   
RCM   ring closing metathesis      
rec. recovered                     
rt   room temperature              
s    singlet                       
sext. sextet                      
t    tertiary                      
t    triplet                      
TBAF  tetra-butylammonium fluoride 
TBAI  tetra-butylammonium iodide   
TBDMS/TBS tert-butyldimethylsilyl  
TBHP tert-butyl hydroperoxide
<table>
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<td>triethylamine</td>
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<tr>
<td><em>tert</em></td>
<td>tertiary</td>
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<td>TFAA</td>
<td>trifluoroacetic acid</td>
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<td>THF</td>
<td>tetrahydrofuran</td>
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<td>TIPS</td>
<td>triisopropylsily</td>
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<td>TLC</td>
<td>thin layer chromatography</td>
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<tr>
<td>TMS</td>
<td>trimethylsily</td>
</tr>
<tr>
<td>Ts</td>
<td><em>p</em>-toluenesulfonyl/tosyl</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>VO(acac)$_2$</td>
<td>vanadyl acetylacetonate</td>
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1 Introduction

1.1 Macrolides

Macrolides are a biologically important class of natural products, but for many years the synthesis of such compounds posed an insurmountable challenge to chemists due to their often complex structures. Over the last 20-30 years, new synthetic methodologies have been pioneered, enabling the total synthesis and subsequent biological evaluation of many of these significant natural products. The key step in the majority of cases is the formation of the large ring (macrocycle) and to date there are several reliable methods to execute this. Generally, a macrolide is defined as a molecule containing a large ring lactone in its structure,\(^1\) which can be thought of as being derived from seco acids through internal esterification (Figure 1). Additionally, those containing more than one ester linkage are also classified as macrolides.

![Figure 1: General Structure of Large Ring (Macrocyclic) Lactones (A) and Seco (Hydroxy) Acids (B).](image)

A large amount of investigation has been devoted into this class of compounds. They have been found to possess significant biological and physiological properties and many have the potential to be drug leads. The macrolide antibiotics\(^2\) feature a polysubstituted macrocyclic lactone, within a 12-16 membered framework. Examples of this class of antibiotics include erythromycin A and B, which both have 14-membered rings and leucomycin A, which has a 16-membered ring (Figure 2).
There is a wealth of information regarding the different types and classes of macrolides, but it is not feasible to document it all within the length of this thesis. Briefly, the polyene macrolide antibiotics\cite{3} possess strong anti-fungal activity, the cytochalasans\cite{4} are active metabolites isolated from marine microorganisms and exhibit antibiotic, antitumour and cytostatic action, the macrodiilides contain within their structure two ester linkages and the macrotetrolides have four ester linkages and are antibiotic and ionophoric. Alkaloids also can contain macrocyclic lactones and so can be thought of as macrolides, for example carpaine\cite{5} has a symmetrical 26-membered ring (Figure 3). β-Resorcyclic acid macrolides also exist with many members, but as they are the group that LL-Z-1640-2 belongs to they will be discussed in further depth.

1.2 Resorcylic Acid Lactones

Resorcylic acid lactones (RALs) have been known since 1953 when the first isolation of radicicol took place from Monocillium nordinii\cite{6} and was termed
Monorden. The isolation of zearalenone,\textsuperscript{[7]} LL-Z1640-2\textsuperscript{[8a]} and hypothemycin\textsuperscript{[9]} followed in subsequent years. Interestingly, the structures that were originally proposed for radicicol and hypothemycin were later found to be incorrect. When radicicol was isolated from \textit{Nectria radicicola}\textsuperscript{[10]} in 1964, the correct structure was elucidated and radicicol became the given name. In 2006, radicicol was found to be synthesised by fungi associated with a Sonoran desert plant.\textsuperscript{[11]} Initially, the biological activity of early discovered RALs did not attract immediate attention and it was only in latter years that they were held in greater esteem.

1.3 Biosynthesis of RALs

RALs are mycotoxins which are produced by different fungal strains via polyketide synthesis (Figure 4).\textsuperscript{[12]}

\begin{center}
\includegraphics[width=0.5\textwidth]{Figure4}
\end{center}

\textit{Figure 4: Biosynthesis of RALs.} The red carbons represent the two-carbon units that are added in each reiterative condensation.

PKS's are type I polyketide synthases and are large multidomain enzymes that iteratively catalyse the condensation of nine units of malonates or thioacetates.\textsuperscript{[12]} The product of each condensation can then be processed by different modules to either reduce or dehydrate the $\beta$-ketone.

The biosynthesis involves two PKSs. The first assembles the first five acetate units, with further processing to arrive at the adequate oxidation state at each carbon and the second performs the remaining three condensations without carbonyl reduction. Ketones that are unreduced are highly reactive and take part in a cyclisation/aromatisation, the lactone then gets released \textit{via} a
cyclisation module on the second PKS.\textsuperscript{[13]} The functionality around the RAL macrocycle is dependent on the arrangement of modules in the first five condensations.

### 1.4 Biological Activity of the RALs

Originally, the properties of RALs did not attract much attention from chemists and it wasn't until the early 1990s that interest was renewed, mainly due to the selective kinase inhibitory action that some RALs possessed.

Zearalenone was found to have oestrogen agonistic properties, which were due to the direct interaction on the oestrogen receptor in competition with 17-estradiol.\textsuperscript{[14]} Interestingly, the macrocycle was able to adopt a conformation that mimicked a steroid\textsuperscript{[15]} and these properties further allowed it to be used as a bovine growth stimulant.

Radicicol has been found to be a potent and selective inhibitor of the molecular chaperone HSP90.\textsuperscript{[16,17]} When there is no HSP90 chaperone activity, clients of HSP90 are unfunctional and targeted for degradation. It has been shown through co-crystallisation studies that even though radicicol and ATP are not structurally similar, radicicol is a competitive ligand for the ATP binding site of HSP90.\textsuperscript{[18]}

There are some cis-enone RALs which irreversibly inhibit mitogen activated protein kinases (MAP kinases) and are competitive with ATP. The subject of protein kinases is vast and an immense amount of wide-ranging studies have been carried out in this field. Due to their importance and their biological connections with LL-Z1640-2, the protein kinases will be discussed in further depth.

### 1.5 MitogenActivated Protein Kinases (MAP Kinases)

Protein phosphorylation of amino acids in the human body is catalysed by kinases and likewise, dephosphorylation is phosphatase catalysed (Figure 5).
Mitogen activated protein kinases (MAP kinases) belong to the family of kinases that are responsible for controlling many cellular events. Although each has a unique character, a number of features are shared by all MAP kinases. They are activated by protein kinase cascades that contain at least two upstream kinases (Figure 6). These upstream kinases are members of the MAP kinase/ERK (extracellular signal-regulated kinase) kinase or MEK family. In order for MAP kinases to become highly active, they require tyrosine and threonine phosphorylation (catalysed by MEKs).[19,20]
Inhibitors of MAP kinases are interesting as the MAP kinases relay, amplify and integrate signals from a range of extracellular stimuli, in so doing regulating a cell’s response to its environment. The amplitude of the signal is controlled by three sequentially activated kinases, called a phosphorelay system. Generically, a stimulus turns on the activator which phosphorylates the first kinase (MAPKKK) which then phosphorylates the second kinase (MAPKK), which in turn phosphorylates the third kinase (MAPK) which phosphorylates a cytosolic protein or transcription factor.\(^{21}\)

There are at least three subfamilies of MAP kinases (ERKs, JNKs and p38 enzymes), with at least seventeen MAPKKKs, seven MAPKKs and twelve MAPKs. Importantly, the specificity of the cascades needs to be regulated. This is achieved by scaffolding proteins which organise and localise the cascades to provide a combinatorial arrangement and down stream signal which is unique.\(^{22}\)

The MAP kinases are intensely important in regulating cellular responses and it is for this reason that they are prime, viable drug targets. They are also hugely
important in determining the functions of specific MAP kinases in complex networks.

Radicicol A (Figure 7) was the first RAL to show inhibitory action towards a kinase. The mode of action is that it accelerates the degradation of specific mRNA sequences containing AU-rich elements (AREs).[23,24]

![Figure 7: Structures of cis-enone Containing RALs.](image)

Some macrolides contain an α,β-unsaturated ketone in the macrocycle, for example the cis-enones which include hypothemycin, radicicol, radicicol A, LL-783,277 and LL-Z1640-2 (Figure 7). These cis-enone RALs have been shown to inhibit mammalian cell proliferation and tumour growth in animals,[25-27] with other reports suggesting that cis-enone RALs inhibit selected protein kinases.[28] Researchers at Merck found that LL-783,277 and hypothemycin were potent and irreversible inhibitors of MEK1 (4 nM and 15 nM respectively), with the presence of their cis-enone being essential for the activity.[29] The irreversible inhibition can be accredited to a Michael addition onto the cis-enone of a cysteine residue which is present in the ATP-binding pocket of a subset of kinases (Figure 8).[28] LL-Z1640-2 was found to be a potent and irreversible inhibitor of TAK1 (IC_{50} 8.1 nM).[30]

![Figure 8: Proposed Mode of Action of the cis-enone RALs.](image) LL-783,277 is given as the example in this case.
1.6 Chemical Synthesis of the RALs

Constructing natural products synthetically provides challenges, both intellectually and practically, which many thrive on in order to discover and even invent new chemical reactions and strategies. Since the syntheses of urea and acetic acid in the early 1800’s, chemistry has evolved so much that high complexity of targets can be achieved. The macroles have in general; a large macrocyclic ring fused to resorcylic acid and for many years posed a challenge to synthetic chemists due to their complex structures. Over time, synthesis of these compounds has become more prevalent, with some having been synthesised and then re-synthesised to utilise new synthetic developments. As a consequence, long-standing, resistant molecules have finally succumbed to total synthesis.

Zearalenone\(^{[31]}\) (Figure 9), due to its marked anabolic and uterotrophic activities, held great interest and a number of syntheses to this molecule have been reported. Indeed, it was perhaps the first naturally occurring macrolide to be synthesised, with the first total synthesis published by chemists at Merck in 1968.\(^{[32]}\)

![Figure 9: Structure of Zearalenone.](image)

Leading up to the total synthesis of zearalenone, the Merck group investigated whether the macrocyclic ring could be formed by esterification of the seco-acid and from this, whether the natural product could be obtained. In order to test their hypothesis, they took natural zearalenone and prepared from it, the seco-acid derivative, by methylation of both phenolic groups and saponification. Preliminary experiments led to the knowledge that zearalenone could be obtained from the acyclic precursor by lactonisation followed by protection group removal. With the final stages completed, work began on the construction of the fragments which would join to form the seco-acid (Scheme 1).
Scheme 1: The Merck Synthesis of Zearalenone.

The aliphatic unit was obtained by condensation of 1 with 1-pentenylmagnesium bromide 2 followed by exposure to methanolic hydrogen chloride to afford the ketal 5, via 3 and 4. Reductive ozonolysis of the double bond and tosylation of the resulting alcohol 6 was followed by displacement of the tosylate with bromide ion and heating with triphenylphosphine to give the phosphonium salt 7. The aromatic unit, as its sodium salt, was obtained from 2,4-dimethoxyphthalic anhydride by partial reduction with lithium tri-t-butoxyaluminium hydride followed by diazomethane to afford the methyl ester 8, which was then converted to its sodium salt 9.

The phosphorane 10 and aldehyde 9 in DMSO were condensed to afford the seco-acid 11 in 55-60% yield. Cyclisation proceeded using trifluoroacetic anhydride in dilute benzene to give 12, which then underwent liberation of the phenolic group. The authors reported that this group was used as a handle to resolve the racemate 13 as 2-menthoxyacetate 14 gave natural zearalenone 13 after removal of the menthoxyacetate and the methyl ether (BBr₃).

1.7 LL-Z1640-2

LL-Z1640-2 (also known as C292_{8b} or 5Z-7-oxo-zeaenal) is a cis-enone resorcylic acid lactone that was first isolated in 1978 as an anti-protozoan agent from the culture broth of fungal strain f6024. As part of its structure it has a 14-
membered macrocycle, with two internal double bonds and three stereogenic centres (Figure 10).

Figure 10: Structure of LL-Z1640-2 (C292 or 5Z-7-oxo-zeaenol). The internal double bonds and stereogenic centres are highlighted.

1.8 Biological Activity of LL-Z1640-2

Originally, this compound did not capture a great deal of attention as it held no particularly interesting properties; it had no anabolic or oestrogen-like activity. However, a major breakthrough came when a screen for TAK1 inhibition revealed that this compound had an IC$_{50}$ of 8.1 nM.$^{[30]}$ Conversely, zearalenone and radicicol showed no appreciable activity. The same authors then proceeded to show that LL-Z1640-2 was competitive with ATP, as it targeted the ATP-binding pocket of kinases,$^{[12]}$ as well as being an irreversible inhibitor of a specific mitogen activated protein kinase, TAK1. On topical application to an animal model, LL-Z1640-2 was shown to effectively prevent inflammation.$^{[30]}$

1.9 Transforming Growth Factor Activating Kinase-1 (TAK1)

TAK1 is transforming growth factor activating kinase-1 and is a MAPKKK involved in the p38 signalling cascade for proinflammation signals such as cytokines (Figure 6 and Figure 11). LL-Z1640-2 is 50-fold less active against MEK1 (411 nM), whilst having no inhibitory effect on other MAP kinases, such as ASK1.$^{[33-35]}$ This renders this RAL a promising specific inhibitor of TAK1.
Figure 11: Position of TAK1 in a Summary of the Protein Kinase Cascade.

1.10 IC$_{50}$

For competition binding assays and functional antagonist assays the most common summary measure of the dose-response curve is IC$_{50}$. The IC$_{50}$ is defined as the half-maximal inhibitory concentration and it serves to measure how much of a particular substance/molecule is needed to inhibit a biological process by 50%. It is commonly used in pharmacological research as a measure of antagonist drug potency and is comparable with EC$_{50}$ for agonists. This is the concentration giving 50% of that compound’s maximal response. The IC$_{50}$ of a compound is calculated by plotting a dose-response curve relating concentration of the compound to the activity of the biological process. An example of a dose response curve is shown below (Figure 12).
1.11 Previous Syntheses of LL-Z1640-2

1.11.1 The First Total Synthesis - Tatsuta

Tatsuta, Takano, Sato and Nakano published the first total synthesis of LL-Z1640-2 in 2001[36], beginning from a carbohydrate starting material. In terms of the retrosynthesis (Scheme 2) they visualised the lactone core as originating from the Mukaiyama cyclisation[37] of seco-acid 16. They foresaw that a Tsuji hydrogenolysis[38] would enable them to reach the seco-acid. 17 is prepared through Sonogashira coupling[39] of 18 and 19. 19 is made from D-ribose 20 - the carbohydrate starting material and it was envisioned that the required stereochemistry of the two alcohols present in the final product would come from this compound.

Scheme 2: Tatsuta’s Retrosynthetic Analysis.
Tatsuta’s synthesis began with d-ribose 20 in which the anomeric hydroxyl was protected as a benzyl ether and the resulting triol 21 globally protected as MOM ethers to generate 22. Removal of the benzyl group, followed by reaction of the resulting lactol 23 with the lithiated acetylide, afforded diol 24. Selective pivaloylation of diol 24, yielded 25 as a single product. The authors note that only a trace of its diastereoisomer was observed.

Scheme 3: Tatsuta’s Synthesis of LL-Z1640-2. Reagents and Conditions: (a) CSA/BnOH, 80 °C, 89%; (b) MOMCl, i-Pr₂Net, MeCN, 50 °C, 4 h, 85%; (c) H₂, Pd(OH)₂, EtOH, 3 h, quant.; (d) TMS-acetylene, nBuLi, BF₃·OEt₂, THF, −78 °C → rt; (e) PivCl, pyridine, 0 °C, 1 h, 2 steps 48%.

Following TMS removal, the terminal alkyne 19 was coupled with iodobenzene 18 under palladium(0) mediated conditions to afford 26 (Scheme 4). Alkynol 26 was protected as the ethoxycarbonate 27 and then reduced with Lindlar’s catalyst to give the desired Z-olefin 17. Tsuji’s hydrogenolysis conditions[38] cleanly isomerised the olefin to yield the E-alkene 28.

Scheme 4: Tatsuta’s Synthesis of LL-Z1640-2. Reagents and Conditions: (a) TBAF, AcOH, THF, 2 h, quant.; (b) Pd(OAc)₂, Cul, PPh₃, Et₃N, 2 h, 85%; (c) ClCO₂Et, pyridine, 0 °C, 1 h, 98%; (d) H₂, Pd/BaCO₃, quinoline, EtOH, 30 min; (e) Pd₂(dba)₃CHCl₃, n-Bu₃P, HCOONH₄, 1.4-dioxane, 95 °C, 1 h, 2 steps 96%.
Pivaloyl group removal yielded the primary alcohol 29, which was oxidised to aldehyde 30. Treatment of aldehyde 30 with carbon tetrabromide and triphenylphosphine proceeded to give the dibromoolefin 31 (Scheme 5).

The dibromoolefin 31 was treated with nBuLi and the lithiated acetylide firstly produced; was captured with (S)-propylene oxide 32 to afford alcohol 33 (Scheme 6).

Lindlar’s reduction of alkyne 33 yielded Z-olefin 34. Saponification of the ester gave the seco-acid 16, which was cyclised under Mukaiyama conditions,\[^{[37]}\] to afford the lactone 36 in 50% yield over 3 steps (Scheme 7). Removal of the MOM protecting groups generated tetraol 37.
Scheme 7: Completion of Tatsuta’s Synthesis of LL-Z1640-2. Reagents and Conditions: (a) Et₃N, MeCN, 50 °C, 1 h, 3 steps, 47%; (b) 5% HCl-MeOH, 50 °C, 2 h, 76%; (c) Dess-Martin periodinane, CH₂Cl₂, 15 min, 62%.

The final step involved the selective oxidation of the allyl alcohol. Interestingly, the authors reported, after extensive experimentation, that DDQ and Dess-Martin periodinane were the only reagents found to selectively oxidise the alcohol in yields of 20% and 62% respectively. The authors claimed that ketone 15 was identical in all respects to the naturally isolated LL-Z1640-2.

1.11.2 The Second Total Synthesis – Sellès and Lett

In 2002, the second total synthesis of LL-Z1640-2 was published in two parts by Sellès and Lett. The first part focused on the stereospecific convergent synthesis of the precursors required for the formation of the 14-membered ring, either via intramolecular Suzuki coupling or an intermolecular Suzuki coupling followed by a macrolactonisation. The retrosynthetic analysis (Scheme 8) led to three subunits: the aromatic unit 38 and two enantiopure units 40 and 41.
The hypothesised approach is flexible and the 14-membered macrocycle can be formed either by an intramolecular Suzuki coupling or by a macrolactonisation (via acyl activation or Mitsunobu). The enantiopure units draw from readily available starting materials. The $\text{C}_4$-$\text{C}_7$-diol would come from the regio- and stereospecific opening of the epoxide by a carbamate derived from 43. This epoxy alcohol could be obtained through a Sharpless asymmetric epoxidation of the trans-disubstituted allylic alcohol.

Synthesis of the aromatic unit 38 began with 4-methoxysalicylic acid 46, which was selectively protected as the silyl ether 47, then treated with oxalyl chloride followed by diethylamine, to generate amide 48 (Scheme 9).
The presence of the TBS protective group prevented $\sigma$-metallation at position 3 of amide 48 by its steric effect and allowed conversion of the amide 48 into the methyl ester 51. The final aromatic unit 38 was obtained using conditions that avoided decarboxylation.

The synthesis of the enantiopure C\textsubscript{7}–C\textsubscript{10} subunit began with ethynyltrimethylsilane 52, which was lithiated and used to open the enantiopure (S)-propylene oxide 32. The free alcohol 53 was protected as the TBS ether 54 and specific deprotection of the TMS-alkyne using potassium carbonate in methanol gave alkyne 55 in a 76% overall yield (Scheme 10). Hydrozirconation with Schwartz' reagent\textsuperscript{[42]} was used to generate the (S)-E-vinyl iodide 56. Hydroboration of iodoalkyne 57 with Sia\textsubscript{2}BH generated the (S)-Z vinyl iodide 58.

Scheme 10: \textit{Lett’s Synthesis of LL-Z1640-2.} Reagents and Conditions: (a) Et\textsubscript{2}O, –78 °C, nBuLi, 30 min, then (S)-propylene oxide 32 and further addition of BF\textsubscript{3}-OEt\textsubscript{2}, in 50 min, –78 °C; (b) TBDMSCl, imidazole, DMF, rt; (c) K\textsubscript{2}CO\textsubscript{3}, MeOH, rt, 5 h; (d) Cp\textsubscript{2}ZrCl\textsubscript{2}, LiBHEt\textsubscript{3}, THF, rt, then 55, rt, 15 min and I\textsubscript{2} in THF; (e) nBuLi, THF, hexane, –78°C, 15 min, then I\textsubscript{2} in THF; (f) Sia\textsubscript{2}BH, THF, –20 °C → 0 °C, 3 h then AcOH, 65 °C, 3 h.

Epoxide 65 was obtained in seven steps from 2-butyne-1,4-diol 59 (Scheme 11). The authors note that the selective deprotection of TBS ether 63 was best carried out using DDQ.

Scheme 11: \textit{Lett’s Synthesis of LL-Z1640-2.} Reagents and Conditions: (a) Red-Al\textsuperscript{®}, toluene, THF, 0 °C–rt, overnight, 81%; (b) NaH, THF, rt, 1 h, then –78 °C, TBDMSCl, 36 h, 74%; (c) MsCl, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, –10 °C → rt, 30 min; (d) NaI, acetone, rt, 1 h; (e) TMS-alkyne 52, THF, nBuLi, –78 °C, 30 min, then 45 and HMPA (THF:HMPA = 10:1), rt, 4 h; (f) DDQ, MeCN:CH\textsubscript{2}O (9:1), rt, 2 h; (g) Ti(O\textsubscript{2}Pr\textsubscript{4}), (+)-DET, anhydrous CH\textsubscript{2}Cl\textsubscript{2}, tBuOOH (~ 3 M in isoctane), –25 °C, overnight.
Sharpless asymmetric epoxidation of enyne 64 with (+)-DET afforded the desired epoxyalcohol 65, as a single enantiomer. The epoxide 66 was opened in the presence of BF$_3$·OEt$_2$ to afford carbonate 67 in high yield (Scheme 12).

\[ \text{Scheme 12: Lett's Synthesis of LL-Z1640-2.} \]

Reagents and Conditions: (a) PhNCO, CH$_2$Cl$_2$, pyridine, rt, 1 h; (b) BF$_3$·OEt$_2$, Et$_2$O, –20°C, 2 h, then 1 N H$_2$SO$_4$, rt, overnight; (c) NaOMe, MeOH, rt, 8 h, then DOWEX 50 WX8 column eluted with MeOH; (d) TBDMSI, imidazole, DMF, rt, 1 h; (e) 2-methoxypropene, TsOH, CH$_2$Cl$_2$, rt, 1 h; (f) nBuLi, hexane, Et$_2$O, –30°C, 30 min, then TMSCl, –30°C → 10°C, 98%; (g) DDQ, MeCN:H$_2$O (9:1), rt, 2 h, 73%; (h) oxalyl chloride, DMSO, CH$_2$Cl$_2$, –78°C, 30 min, then 72, 30 min and Et$_3$N, –78°C → 0°C.

Simultaneous hydrolysis of the carbonate and TMS deprotection was achieved using sodium methoxide in methanol, to afford triol 68 in 93% yield. TBS protection (→69) and acetonide formation, followed by reprotction of terminal alkyne 70 with a TMS group (→71) all proceeded readily. Once again, DDQ was used to bring about the selective deprotection of TBS ether 72. These conditions minimised cleavage of the acetonide and TMS groups. Finally, the alcohol was converted to the aldehyde 73 under standard Swern conditions.

The synthesis of the C$_4$–C$_{10}$ fragment 79 began with the condensation of the two enantiopure fragments 58 and 73 to give a 60:40 mixture of the two C$_6$-epimeric diastereoisomers 74 (Scheme 13). Following deprotection of TMS-alkyne 74, the C$_6$-OH 75 was protected as the MPM ether 77. As the diastereoisomers were not easily separated, the authors carried forward this mixture to the macrocyclisation precursors.

As pointed out previously, the hypothesised approach was flexible and the macrocycle can be formed by one of two methods. If an intramolecular Suzuki
coupling\textsuperscript{[43]} were to be used for the formation of the macrocycle, then precursor 79 is needed. TBS ether 77 was deprotected using TBAF in THF and resulting alcohol 78 was coupled with benzoic acid 38 with DCC. The required ester 79 was obtained in 76% overall yield.

Scheme 13: Lett's Synthesis of LL-Z1640-2. Reagents and Conditions: (a) Et\textsubscript{2}O, –78 °C, then tBuLi/pentane, 15 min and further addition of 73 in pentane, –78 °C → 0 °C; (b) K\textsubscript{2}CO\textsubscript{3}, MeOH, rt, 5 h; (c) Et\textsubscript{2}O, CF\textsubscript{3}SO\textsubscript{3}H, rt, 4 h; (d) TBAF, THF, rt, 10 h; (e) DCC, DMAP, CH\textsubscript{2}Cl\textsubscript{2}, rt, 5 h.

For the alternative Mitsunobu macrolactonisation\textsuperscript{[44]} reaction, precursor 83 was required (Scheme 14).

Scheme 14: Lett's Synthesis of LL-Z1640-2. Reagents and Conditions: (a) Si\textsubscript{2}BH, THF, –25 °C → rt, 2 h, then aq. 2 M K\textsubscript{3}PO\textsubscript{4}, further addition of that mixture via cannula at rt to a solution of 51 and 15 mol% [Pd(OAc)\textsubscript{2}+4TFP] in DME; DME:H\textsubscript{2}O (~7:1), reflux, 8 h; (b) TBAF, THF, rt, 6 h, 93%; (c) 2 N NaOH:MeOH (1:3), reflux, overnight, 71%.

Aryl bromide 38 underwent an intermolecular Suzuki coupling with the vinylidisiamylborane, prepared in situ from alkyne 80. In comparison to the previous method, the aromatic hydroxy acid is not used, but rather its precursor, the methyl ester 81 is used. Interestingly, the final methyl ester cleavage proved less than straight forward. This was eventually achieved in 71% yield.
from 82, using 13 equivalents of 2 N aq. NaOH in methanol under reflux to yield 83.

Once both cyclisation precursors were available, the cyclisation reactions were attempted. In the completion of the total synthesis, published as Part 2,\cite{41} the authors reported that the 14-membered macrocycle was achieved much more efficiently through the use of an intermolecular Suzuki coupling, followed by an intramolecular Mitsunobu macrolactonisation (Scheme 8 and Scheme 15).

Scheme 15: Retrosynthetic Analysis for Completion of the Synthesis.

Using a model system 84, the intramolecular Suzuki coupling of vinyldisiamylborane (generated \textit{in situ}) derived from the alkyne 79, was tested (Scheme 16). The best results were observed when acetone was added to destroy, \textit{in situ}, any excess Sia\textsubscript{2}BH that remained after hydroboration. Using these conditions, the macrolides 85 and 86 were obtained in 9% and 15% respectively. When the same conditions were applied to 87 and 88, no corresponding macrolides were seen.
Scheme 16: Lett's Synthesis of LL-Z1640-2. Reagents and Conditions: $\text{SiH}_2\text{BH}$, THF, $-20^\circ\text{C} \rightarrow \text{rt}$, 2 h, then addition of acetone and afterwards 2 M aq. $\text{K}_3\text{PO}_4$ at $-10^\circ\text{C} \rightarrow \text{rt}$, further addition of that mixture via cannula to a solution of 4 mol% [Pd(OAc)$_2$+4TFP] in DME, i.e. substrate 0.034 M in DME:H$_2$O (~30:1), reflux, 6 h.

The macrolactonisations were far more successful when using the Mitsunobu reaction and its associated conditions (Scheme 17). The transformations were all achieved at room temperature, under low dilution (0.007-0.01 M), with yields ranging from 64-70%. In these cases there were no inhibitory factors arising from steric interactions or ring strain. In the case of the macrolactonisation of 83, this proceeded readily in 67% yield.

As expected there was complete inversion of configuration at $\text{C}_{10}'$, further exemplified by comparison of the $^1\text{H}$ NMR spectra for product 86, being derived from either intramolecular Suzuki coupling or Mitsunobu macrolactonisation.
Scheme 17: Lett’s Synthesis of LL-Z1640-2. Reagents and Conditions: hydroxy acid 0.007 M in anhydrous toluene, PPh₃, DEAD, rt, 15 min.

All that remained was the conversion of 86 into the final target compound 15 (Scheme 18).

Scheme 18: Lett’s Completion of the Synthesis. Reagents and Conditions: (a) DDQ, CH₂Cl₂:pH 7 buffer (9:1), rt, 30 min, 94%; (b) p-TsOH, MeOH, rt, 4 h, 68%; (c) PCC, 2,5-DMP, CH₂Cl₂, 0 °C, 6 h; (d) Jones’ reagent, acetone, 0 °C, 10 min, 35%; (e) p-TsOH, CH₂Cl₂:MeOH (1:1), rt, 3 h, 30 min, 76%.
Firstly, MPM ether 86 was deprotected using DDQ in buffered conditions to afford the alcohols 94M and 94m (60:40) in 94% yield. When using a model system, the authors were readily able to oxidise the 6'-OH into the corresponding enone using activated MnO₂ in 70% yield, disappointingly, this could not be transferred to the 'real' system. The mixture of the epimers could not be oxidised even when using a large excess of active MnO₂ or by DDQ. An alternative was to prepare 95, but even this triol led to complex mixtures on oxidation with MnO₂. Fortunately, the authors tried PCC and on reacting 94M/94m with PCC in the presence of 2,5-dimethylpyrazole they observed a clear difference in the reactivity of the diastereoisomers. The major epimer 94M was converted quantitatively into the Z-enone 96 in 62% yield after chromatography, while the minor epimer 94m was unchanged and isolated in 23% yield after chromatography. The pure minor diastereoisomer was reacted under Jones' oxidation conditions to form the Z-enone 96 in 35% yield. Overall the Z-enone was isolated in 74% yield from 94 (60:40) mixture. Surprisingly, Swern oxidation of 94M gave the Z-enone 96 in 30% yield after chromatography. Finally, the acetonide was cleaved using p-TsOH in a 1:1 mixture of dichloromethane:methanol at room temperature, to generate LL-Z1640-2 15 in 76% yield (20% of 96 also recovered).

The syntheses presented by these two sets of authors are lengthy, containing steps that have needed careful establishment and much optimisation. At no time is there any mention of whether the steps that involve intricate conditions are readily reproducible, giving comparable yields. To their credit the syntheses are stereospecific, convergent and flexible. Indeed, Sellès and Lett go on to epoxidise the E₇,₈'-enone to afford hypothermecin. Another additional benefit is that they are able to carry through their 60:40 mixture of the two diastereoisomers 94M/94m, epimeric at C₆', through all the steps until the oxidation, which is the penultimate step of the synthesis, where they could isolate each epimer after chromatography.

1.11.3 Synthesis of the Aliphatic Subunit from Mannose

In 2007, Krohn and Shukov published their synthesis of the aliphatic subunit of LL-Z1640-2. This particular synthesis incorporated the Vasella reaction as a
key step and the synthesis proceeded via the ring-opening of a 6-iodo-4-deoxy-D-mannose unit. The Vasella reaction\textsuperscript{[46]} allows the conversion of halosugars into components having a carbonyl group tethered to an olefinic bond. The Vasella reaction is not uncommon and has been incorporated into previous total syntheses; of pentenomycin\textsuperscript{[47]} for example.

The authors hypothesised that mannose could be used to provide two of the required stereocentres present in LL-Z1640-2. Mannose is a simple and inexpensive, commercially available compound and as such is an ideal choice as a starting material for a total synthesis. For this particular synthesis, the authors prepared two 6-deoxy-6-iodomannose derivatives 100 and 102 from methyl-\(\alpha\)-D-mannopyranoside 97 (Scheme 19). This has been documented in depth in a previous publication by the same authors.\textsuperscript{[48]} The alcohols formed were then treated with iodine and triphenylphosphine to give 6-iodo sugars 100 and 102.

The iodo sugars 100 and 102 were then treated with activated zinc to initiate the Vasella ring-opening. Reaction of the deoxysugar 100 proceeded smoothly and gave aldehyde 103 in good yield using sonication (reaction of the mesylate 102, under the same conditions, gave a mixture of products, presumably due to an interaction of zinc with the mesylate group) (Scheme 20).

\begin{scheme}[H]
\centering
\includegraphics[width=\textwidth]{Scheme19.png}
\caption{Krohn’s Synthesis of LL-Z1640-2. Reagents and Conditions: (a) i) \(\text{H}_3\text{PO}_4/\text{AIBN}, \text{Et}_3\text{N}\), dioxane, reflux, 90%; ii) \(\text{p-TsOH}\), acetone, 90%; (b) \(\text{Ph}_3\text{P}, \text{I}_2\), rt, 90\%.

\end{scheme}
From their retrosynthesis the authors envisaged that the aldehyde could be coupled with either acetylene 104 or vinyl iodide 108. The acetylene unit was easily obtained and the Z-vinyl iodide could be accessed from the alkyne 104 through iodination and then stereoselective diimide reduction. The vinyl iodide and alkyne were each reacted in situ with nBuLi and then these lithium reagents reacted with the aldehyde 103. When the aldehyde 103 and vinyl lithium were reacted a complex mixture of products was seen. Conversely, when the aldehyde and lithiated alkyne were reacted a mixture of diastereomeric propargyl alcohols 105 was observed (1:2.3 by $^1$H NMR). Cleavage of the terminal TBS protecting group, followed by selective oxidation of the resulting diol 106, afforded ketone 107. Though not presented in the published paper, the authors identify this ketone as a late-stage building block towards 111 (Scheme 21). They predict that secondary alcohol 111 can be esterified with acid 110, followed by Z-selective reduction of the acetylene. Ring-closing metathesis of 109 would close the macrocycle to produce and finalise the synthesis of the required LL-Z1640-2.
The synthetic steps presented in this publication are neat and time efficient. The 6-iodo-4-deoxymannose derivative 100 was subjected to the Vasella ring-opening reaction, affording the δ,ε-hexenal 103. Coupling of the aldehyde to the acetylene is reliable and two subsequent, straightforward steps produces propargylic ketone 107.

1.11.4 Synthesis of the Complete LL-Z1640-2 Framework

In 2007, Marquez, Henry and Robertson published their fast and efficient, convergent synthesis of the complete LL-Z1640-2 framework.\(^{[49]}\) Their retrosynthetic analysis (Scheme 22) envisioned cleavage of the ester functionality and of the aryl double bond of the macrocyclic ring to produce the vinyl benzoic acid 113 and alcohol 115.

![Scheme 22: Marquez's Retrosynthetic Analysis.](image)

The commercially available and relatively inexpensive, methyl 2,4,6-trihydroxybenzoate 114 was used as the starting material for the synthesis of the vinyl benzoic acid unit 110 (Scheme 23). The C₄ position was methylated selectively through treatment with trimethylsilyl diazomethane to afford diol 117 in high yield. Monosilylation of the diol under standard conditions produced the TBS silyl ether 118, which was treated with triflic anhydride to yield triflate 119. The vinyl unit 120 was synthesised by subjecting the aryl triflate to a Stille coupling with vinyltributyltin. Saponification of the methyl ester 120 proceeded
to generate the free benzoic acid 110. Spontaneous desilylation was also observed during this step.

\[
\text{OH} \quad \text{OCH}_3 \quad \text{O} \quad \text{OH} \quad \text{H}_3\text{CO} \quad \text{OCH}_3 \quad \text{O} \quad \text{OH} \quad \text{TBSO} \quad \text{O} \quad \text{OTf} \quad \text{TBSO} \quad \text{H}_3\text{CO} \quad \text{OCH}_3 \quad \text{O} \quad \text{OTf} \quad \text{TBSO} \quad \text{O} \quad \text{OH} \quad \text{TBSO} \quad \text{H}_3\text{CO} \quad \text{OCH}_3 \quad \text{O} \quad \text{OH}
\]

\(114 \rightarrow 117 \rightarrow 118 \rightarrow 119 \rightarrow 120 \rightarrow 121 \rightarrow 122 \rightarrow 123 \rightarrow 124 \rightarrow 125 \rightarrow 126\)

Scheme 23: Marquez’s Synthesis Towards LL-Z1640-2. Reagents and Conditions: (a) TMS-CH\(_3\)N\(_2\), Et\(_2\)O, 90%; (b) TBDMSCl, Et\(_3\)N, CH\(_2\)Cl\(_2\), 80%; (c) Tf\(_2\)O, pyridine, 100%; (d) vinyltributyltin, Pd(PPh\(_3\))\(_4\), CH\(_2\)Cl\(_2\), 100%; (e) NaOH, 1,4-dioxane, 96%.

(L)-(+)—Diethyl tartrate 116 was used as the starting material for the synthesis of the C\(_{1'}\)—C\(_{10'}\) aliphatic unit (Scheme 24). The tartrate was protected as the dimethyl ketal (\(\rightarrow 121\)) and then the diester reduced to the corresponding diol. Selective silylation provided TBS ether 122, which then underwent Swern oxidation to generate aldehyde 123. Corey-Fuchs olefination gave alkyne 124, which was then alkynated with (S)-propylene oxide 32 under highly activated conditions. This resulted in the formation of internal alkynol 125 as a single diastereoisomer, after which silylation gave the bis-TBS silyl ether 126.

\[
\text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \quad \text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \quad \text{OH} \quad \text{OCH}_3 \quad \text{O} \quad \text{OH} \quad \text{H}_3\text{CO} \quad \text{OCH}_3 \quad \text{O} \quad \text{OH} \quad \text{TBSO} \quad \text{O} \quad \text{OTf} \quad \text{TBSO} \quad \text{O} \quad \text{OTf} \quad \text{TBSO} \quad \text{O} \quad \text{OH} \quad \text{TBSO} \quad \text{H}_3\text{CO} \quad \text{OCH}_3 \quad \text{O} \quad \text{OH} \quad \text{TBSO} \quad \text{H}_3\text{CO} \quad \text{OCH}_3 \quad \text{O} \quad \text{OH}
\]

\(116 \rightarrow 121 \rightarrow 122 \rightarrow 123 \rightarrow 124 \rightarrow 125 \rightarrow 126\)

Scheme 24: Marquez’s Synthesis Towards LL-Z1640-2. Reagents and Conditions: (a) 2-Methoxypropene, \(p\)-TsOH, CH\(_2\)Cl\(_2\), 97%; (b) i) LiAlH\(_4\), THF; ii) NaH, TBDMSCl, THF, 89%; (c) Swern, 100%; (d) i) CBr\(_4\), PPh\(_3\), CH\(_2\)Cl\(_2\); ii) \(n\)BuLi, Et\(_2\)O, 79%; (e) (S)-propylene oxide, \(n\)BuLi, BF\(_3\)-OEt\(_2\), THF, 76%; (f) TBDMSCl, Et\(_3\)N, DMAP, CH\(_2\)Cl\(_2\), 97%.

The outstanding steps of the C\(_{1'}\)—C\(_{10'}\) unit started with the selective deprotection of the primary TBS silyl ether, which yielded the primary alcohol 127 (Scheme...
A one-pot oxidation-allylation progressed to give the homoallylic alcohol 128 as a 1:1 mixture of diastereoisomers. At this stage the authors did not attempt to control the stereochemistry of allylation as the aim was to access LL-Z1640-2, as well as its C9 anomer for biological evaluation purposes. The next step was to convert the alkyne unit into the Z-alkene that is present in LL-Z1640-2. Attempts at hydrogenation using a Pd/BaSO4 catalyst poisoned with quinoline, regrettably led to the over-reduced alkane 129.

The observed over-reduction prompted an assessment of the synthetic route and as a consequence changes were made. In the modified approach the bis-TBS ether 126 was selectively reduced to yield the Z-olefin 131 with complete stereocontrol (Scheme 26). Primary TBS removal (→132), followed by a one-pot oxidation-allylation procedure provided the required C1—C10 fragments 133 of LL-Z1640-2 and 9-epi-LL-Z1640-2.
In order to introduce the remaining units of the framework, the free alcohol 133 was protected as the PMB ether and the secondary TBS silyl ether carefully removed to afford the secondary alcohol 135 (Scheme 27). Reaction of alcohol 135 with vinyl benzoic acid 110 generated the esters 136 and 137 cleanly in good yield. This served to complete the entire frameworks of both LL-Z1640-2 and 9-epi-LL-Z1640-2 respectively.

Scheme 27: Marquez’s Synthesis Towards LL-Z1640-2. Reagents and conditions: (a) NaH, PMBCl, TBAI, THF, 100%; (b) HF–pyr/pyridine, 97%; (c) 110, DCC, 67%.

The authors conclude that their two-directional chain functionalisation synthesis is fast, high-yielding and flexible, producing not only the complete framework of LL-Z1640-2 but also that of its C9- epimer, 9-epi-LL-Z1640-2.

1.11.5 The Third Total Synthesis – Winssinger’s Modular Approach

In 2007, a third total synthesis of LL-Z1640-2 was published, whereby a modular approach was developed. The authors devised a retrosynthesis (Scheme 28) in which the enone would be introduced at a late stage to avoid isomerisation to the trans-isomer.

The cis-alkene would originate from a vinyl lithium addition onto an aldehyde. Three fragments, 138, 139 and 140, would be used to construct the main body of the structure, the order in which they could be coupled possible by means of any permutation. Despite this the authors needed a starting point and so rationally presumed that coupling the two non-aromatic fragments, 138 and 140, first would allow them to use a fluorinated protecting group for the alcohol, facilitating the use of fluorous isolation technology. A distinct advantage of this technique is that multiple components can be tagged and taken through a synthesis as a mixture, with fluorous chromatography performed at the end to resolve the mixture.

For the synthesis of the aromatic fragment 143 (Scheme 29), carboxylic acid 141 was protected with a 2-(trimethylsilyl)ethyl group by esterification with 2(trimethylsilyl)ethanol. Selenide 143 was then formed by treatment of ester 142 with LDA and then coupled with diphenyldiselenide.

Scheme 29: Winssinger’s Synthesis of LL-Z1640-2. Reagents and Conditions: (a) Oxalyl chloride, DMF, CH₂Cl₂, 0 °C, 1 h, then 2-(trimethylsilyl)ethanol, Et₃N, DMAP, rt, 1 h, 96-98%; (b) LDA, diphenyldiselenide, THF, –78 °C, 1 h, 89-91%.
Aldehyde 147 was obtained from the ketal-protected deoxyribose 144\textsuperscript{[51]} by reduction with lithium aluminium hydride and the crude diol 145 selectively silylated on the less sterically hindered alcohol with a TBS protecting group (\(\rightarrow\)146). The remaining alcohol was oxidised using an immobilised version of IBX, giving aldehyde 147, which was used without work-up or purification (Scheme 30).

\begin{equation}
\text{Scheme 30: Winssinger's Synthesis of LL-Z1640-2. Reagents and Conditions: (a) LiAlH}_4, THF, 0^\circ\text{C} \rightarrow \text{rt, 2 h, 95%; (b) TBDPSCI, imidazole, DMF, 23^\circ\text{C}, 2 h, 66%; (c) PS-IBX, CH}_2\text{Cl}_2, \text{rt, 2 h, 100%}.}
\end{equation}

The remaining fragment was synthesised beginning from (R)-2-hydroxypentane 148 with fluorous PMB trichloroacetimidate 149 to afford 150 (Scheme 31). Cross-metathesis of alkene 150 with vinyl borolane 151, in the presence of Grubbs second generation catalyst, afforded the trans-product 152 in good selectivity (>20:1 E:Z). The vinylborane could be transformed into the cis-vinyl bromide 153 through treatment with bromine and sodium methoxide.
Transmetallation of the bromide with tBuLi and addition onto the crude aldehyde 155 afforded alcohol 154, which was protected as the EOM ether to yield 155 as a mixture of diastereoisomers (3:1). Conversion of the silyl-protected hydroxyl group into the iodide proceeded smoothly to afford 156, which was then alkylated with the aromatic fragment 143. The resulting selenide was oxidised and eliminated to afford 157. The crude reaction mixture was loaded onto a fluorous-silica column to remove the non-fluorous tagged components from the desired compound. The seco-acid 158 was obtained after the sequential removal of the PMB and TMSE ester protecting groups.

The final steps of the synthesis incorporate the key macrolactonisation which was accomplished through a Mitsunobu reaction using fluorous-tagged triphenyl phosphine and diazodicarboxylate (Scheme 32). The desired compound 159 was gained after a fluorous solid-phase extraction. The usage of boron trichloride enabled the simultaneous deprotection of the EOM and acetonide groups as well as the cleavage of the ortho-phenol. The formed allylic alcohol 95 was
selectively oxidised with a polymer-bound IBX to afford LL-Z1640-2 15 after filtration.

Scheme 32: Winssinger's Completion of the Synthesis of LL-Z1640-2. Reagents and Conditions: (a) $R^3$Ph$_3$P, $R^1$DEAD, toluene (10 mM), rt, 2 h, 81%; (b) BCl$_3$, CH$_2$Cl$_2$, 0 °C, 15 min, 86%; (c) PS-IBX, CH$_2$Cl$_2$, rt, 1 h, >90%.

This synthesis is concise and advantageous in its use of fluoro chemistry and polymer-bound reagents, enabling the process to be suitable for high-throughout synthesis.

1.12 Inflammation

Inflammation is the body's immediate response to damage to its tissues and cells by pathogens (infection), noxious stimuli (chemicals) or physical injury. It is characterised by redness, swelling, heat and pain in a tissue.\(^{[52]}\)

There are two classifications of inflammation: acute and chronic. Acute inflammation is a short-term response, resulting in healing. Leukocytes penetrate the damaged region, repairing the tissue. Chronic inflammation is a prolonged response that involves active inflammation, tissue destruction and attempts at tissue repair. The persistency is associated with many chronic human conditions, including allergy, cancer, arthritis and autoimmune diseases,\(^{[52]}\) some of which can be treated with non-steroidal anti-inflammatory drugs (NSAIDs).\(^{[53]}\)

In response to damage of body tissues, mast cells release histamine. Although there are other substances involved in the inflammatory response, histamine is thought to be responsible for most of the effects. Histamine acts to increase
blood flow to damaged tissues, causing the heat and redness. It also makes the blood capillaries more 'leaky', resulting in fluid oozing out of them and into the tissues, causing localised swelling. The pain associated with inflammation is attributed to the stimulation of nerve endings by inflammatory chemicals.

1.13 Inflammatory Disorders

1.13.1 Rheumatoid Arthritis

Rheumatoid arthritis is a non-specific autoimmune disorder, where the immune system acts against and damages joints and surrounding soft tissues. The reasons why these autoimmune disorders develop are unclear, but genetic factors may play a role. An autoimmune disorder may primarily affect a specific organ or cell type, or may affect various organs. In the case of arthritis, it is the inflammation of a joint, characterised by pain, swelling and stiffness. The arthritis may involve one joint or many and can vary in severity from a mild ache and stiffness to severe pain and joint deformity. Rheumatoid arthritis is the most severe type of inflammatory joint disease and as shown in Figure 13, the joints most commonly affected are those in the hands, wrists, feet and arms, which become extremely stiff, painful and deformed.

Figure 13: Common Target Sites for Rheumatoid Arthritis.\(^{[54]}\)

The symptoms occur most commonly in women but can also arise in younger people. Overall, women are affected two to three times more than men. The
onset of the disease is gradual, with mild fever and aches and pains preceding specific joint symptoms, though in some, joint inflammation can develop suddenly. As well as the joint being affected, the structures around the joint may also become inflamed, resulting in weakness of the tendons, ligaments and surrounding muscles. The finger joints are the most commonly affected, resulting in a weak grip.\(^{[55]}\)

With respect to the pathogenesis of rheumatoid arthritis,\(^{[56]}\) monocytes are attracted to the affected joint, where they differentiate into macrophages and become activated. In addition to interleukin-1 (IL-1), they also secrete tumour-necrosis factor (TNF), which increases the expression of adhesion molecules on endothelial cells, which recruit more cells to the joint. IL-1 and TNF induce synovial fibroblasts to express cytokines, chemokines and growth factors, which contribute to cartilage and bone destruction (Figure 14).
1.13.2 Osteoarthritis

Osteoarthritis (OA) is a form of arthritis also known as degenerative arthritis and is the most common type, resulting from general mechanical stress and ‘wear and tear’ on the joints. It is thought that metabolic and genetic factors may also contribute. It is characterised by degeneration and degradation of the cartilage that lines joints which leads to joint space narrowing (JSN), painful joint disruption and loss of function or by formation of osteophytes (bony outgrowths), which lead to pain and stiffness of the affected joint.\textsuperscript{[55,57]}
generally evolves in middle age, but it most prevalently troubles the older generation, affecting three times as many women as men. Injury to a joint in earlier life can attribute to the development of osteoarthritis. Osteoarthritis causes pain, swelling, creaking and stiffness of one or more joints, the hands, hips, knees and spine being most commonly affected as shown in Figure 15.

Figure 15: Common target sites for Osteoarthritis.\textsuperscript{[58]}

OA involves the entire joint organ, including the subchondral bone, menisci, ligaments, muscle, capsule and synovium. If pain prevents the joint from being used regularly, weakness and shrinkage of the muscles surrounding the joint results. The affected joints become enlarged and distorted by osteophytes, which are responsible for the characteristic gnarled appearance of hands affected by osteoarthritis. In the United Kingdom, there are an estimated 8.5 million people affected by OA.\textsuperscript{[59]} In the United States there are an estimated 20-40 million people affected; with over 250,000 knee replacements and over 150,000 hip replacements carried out annually.\textsuperscript{[57]} Due to improvements in MRI imaging, there is an increased understanding of the other tissues in the pathophysiology of OA (Figure 16).
Traditionally thought of as a non-inflammatory disease, Dr. Abramson and colleagues at NYU Medical Centre in the United States have reported that "OA cartilage produces inflammatory mediators such as nitric oxide, prostaglandin E2 and other pro-inflammatory cytokines locally which leads to joint deterioration." There is a general belief that interleukin-1 (IL-1) plays a central role in the pathogenesis, with data being retrieved from animal susceptibility models, models of IL-1-targeted therapy, genetic association studies and elevated IL-1 gene expression in whole blood from patients with multi-joint osteoarthritis.

### 1.13.3 Crohn's disease

Inflammatory bowel disease is a general term for chronic inflammatory disorders affecting the small and/or large intestine. Crohn's disease most commonly affects those in adolescence and early adulthood and arises due to specific conditions - inflammation affecting any part of the gastrointestinal tract from the mouth to the anus, causing pain, fever, diarrhoea and loss of weight. The
site of inflammation is most commonly the terminal ileum, which becomes thick due to continued chronic inflammation and deep, penetrating ulcers may form. The disease tends to be irregular; areas of the intestine that lie between diseased areas may appear normal but in fact could be mildly affected. The cause is unknown, but it may arise from an abnormal allergic reaction or response to a viral or bacterial agent. The diagnosis can be determined firstly by displayed symptoms of spasmic pain in the abdomen, diarrhoea and sickness, followed by a physical examination which could reveal tender abdominal swellings. The disease is chronic and the symptoms fluctuate over years, in some cases eventually subsiding. Many other patients require surgery, whilst some remain in normal health with the disease being localised.

1.13.4 Cancer and Inflammation

The recognised connection between the development of cancer and inflammation has long been known.\textsuperscript{[60,61]} Long-term inflammation leads to the development of dysplasia, an abnormal alteration in a tissue owing to abnormality in the function of the component cells, leading to cancer. Epidemiological studies estimate that nearly 15\% of worldwide cancer cases can be related to microbial infections.\textsuperscript{[62,63]} Further evidence has come from the use of NSAIDs in the prevention of spontaneous tumour formation in people with familial adenomatous polyposis (FAP), an autosomal dominant genetic disorder.\textsuperscript{[64]}

The formation of reactive oxygen and nitrogen species can occur at the site of inflammation. These species have the potential to damage DNA, proteins and cell membranes, favouring carcinogenesis. It is also known that chronic inflammation often results in repeated cycles of damage and compensating cell proliferation. As a consequence, the number of cells that are dividing increases and therefore there are more cells that are available for DNA damage, promoting the growth of malignant cells.\textsuperscript{[65]} In the article, \textit{Why Cancer and Inflammation},\textsuperscript{[66]} it is suggested that cancer and inflammation are related by epidemiology, histopathology, inflammatory profiles and the efficacy of anti-inflammatory drugs in prophylaxis. The association is non-trivial and therefore
cannot be reduced to one theory, but lines of evidence show that the inflammatory system positively affects tumour development and growth.

1.14 Tumour Necrosis Factor-alpha (TNF-α) and Alzheimer’s Disease

In the brains of those patients with Alzheimer's disease, neuroinflammation with over-expression of cytokines is a standard characteristic. Tumour necrosis factor-alpha (TNF-alpha or TNF-α) is a proinflammatory cytokine and numerous studies have proven it be involved in the pathogenesis of the disease. Over recent years it has become known that excess TNF-alpha plays a pivotal role in Alzheimer's disease. Etanercept, a potent anti-TNF therapeutic, was firstly used to treat rheumatoid arthritis, acting by binding to TNF-alpha and blocking its interaction with cell surface TNF-alpha receptors. The result is that the effects that excess TNF-alpha exerts are reduced. The drug has duly been used to treat other inflammatory disorders in which TNF-alpha takes part.

In 2006, in a pilot study, it was reported that treatment with Etanercept was effective in the treatment of mild to severe Alzheimer’s. These findings encouraged further studies and new, exceptional conclusions were reported in 2008. In the study by Tobinick and Gross in 2006, there was noticeable clinical improvement in Alzheimer’s disease patients within minutes of administration of the drug. It is important to note that a novel method of administration was used called perispinal extrathecal into the posterior neck. This serves to improve delivery of the drug to the brain via the cerebrospinal venous system.

In the most recently published study, Tobinick and Gross were able to take an individual patient with late onset Alzheimer’s disease and use cognitive tests to evaluate the rapid effect after treatment. The most obvious sign of an improvement came when observing the results of the Montreal cognitive assessment. One day before treatment the patient was unable to complete parts of the test; becoming agitated and overwhelmed by his inability to do so. His score was seven out of a possible thirty. Two hours after administration, his score increased to fifteen out of thirty and he was able to answer questions with
less frustration and perform simple calculations. Seven weeks and fourteen days after receiving his last dose of perispinal Etanercept, his score was fourteen, with noticeable improvement in the tasks (Figure 17).

**Figure 17: Tobinick and Gross’ Most Definitive Study Results.** The Montreal Cognitive Assessment shows rapid and sustained improvement in Visuospatial/Executive function following perispinal etanercept administration. Reproduced from Reference 68 with permission from the original publisher (BioMed Central).
Tobinick and Gross conclude that TNF-alpha is of critical importance in the regulation of synaptic transmission in the brain. They attribute this to the extreme rapidity of the effect and the potency and selectivity of Etanercept as an anti-TNF-alpha agent. Synaptic dysfunction is important in the pathogenesis of Alzheimer's disease and TNF-alpha mediates this and the associated cognitive and behavioural impairment. By using Etanercept they can rapidly neutralise the excess TNF-alpha and bring it to normal physiological levels, thereby alleviating the cognitive difficulties in patients by allowing normal cross-talk between regions of the brain. Clearly this is an intensely significant breakthrough in the study of Alzheimer’s disease and the results presented can be utilised to set up further studies.

It has been shown that LL-Z1640-2 has significant activity versus TNF-alpha production in cells, with an IC$_{50}$ of 6 nM.\textsuperscript{[70]} This leads to the hypothesis that LL-Z1640-2 could be an antagonist and as such, a possible drug lead for the treatment of Alzheimer’s disease. If it can indeed reduce the levels of TNF-alpha in cells, then this is analogous to the mode of action of Etanercept, proven to be successful in improving the cognitive function in patients with Alzheimer's disease.

### 1.15 Targeting TAK1

One of the major roles of TAK1 is to mediate some of the intracellular actions of proinflammatory cytokines. When it becomes activated, TAK1 is believed to switch on several protein-kinase cascades, including those that activate stress-activated protein kinase 2a, which is also called p38$\alpha$, but is more often abbreviated to SAPK2a/p38$\alpha$.

At the head of three proinflammatory kinase cascades lie TAK1 and its associated regulatory subunits TAB1 and TAB2 and the structurally related TAB3.\textsuperscript{[71,72]} In 2003, Cohen and colleagues showed that SAPK2a/p38$\alpha$ exerted feedback control on TAK1 via TAB1.\textsuperscript{[72]} They also discovered that the down regulation of TAK1 by SAPK2a/p38$\alpha$ was not just a feedback control device for limiting the activation of SAPK2a/p38$\alpha$, but could also limit the activation of IKK
and JNK. This would synchronise three signalling pathways that play key roles in the inflammatory response.

![Figure 18: A representation of the feedback control of TAK1 activity by SAPK2a/p38α, highlighting how it implicates the regulation of JNK and NF-κB.][71]

Reproduced with permission.

Figure 18A shows how SAPK2a/p38α downregulates TAK1, via the phosphorylation of TAB1. In Figure 18B, SAPK2a/p38α is inhibited by SB203580, which stops the feedback control of TAK1. This causes the upregulation of the JNK and IKK pathways. These findings and those in associated publications, has led to the belief that the downregulation of TAK1 by SAPK2a/p38α may be a critical factor for the development of anti-inflammatory drugs. Presently, there are compounds that are more potent than SB 203580, which are undergoing clinical trials for the treatment of rheumatoid arthritis and other chronic inflammatory diseases. Ultimately, it is reasonable to suggest that the inhibition of TAK1 activity may be effective in preventing inflammation and tissue destruction endorsed by proinflammatory cytokines.

1.16 Retrosynthetic Analysis

For this approach towards the total synthesis of LL-Z1640-2, it was important to utilise and build upon findings obtained through previous work carried out by past members of the Marquez research group. The retrosynthetic analysis is
shown in Scheme 33, highlighting the key disconnections. A distinct advantage is that the synthesis begins from readily available starting materials, which are easily handled and manipulated to form the key fragments required for the coupling reactions.

Scheme 33: Initial Retrosynthetic Analysis.

An efficient approach was envisaged that would afford the final product 15 from the macrolactonisation of seco-acid 160. No issues were foreseen with this type of lactonisation, despite it serving to form a large-ring macrocycle. The precedent in the literature for this has already been demonstrated and discussed previously in this introduction. Seco-acid 160 could result from a series of transformations from alkyne 161. Alkyne 161 is obtained through the addition of alkyne 164 to terminal alcohol 162, itself a product of a Wittig olefination between aromatic fragment 163 and sugar moiety 144. It is hoped that this choice of reaction would enable the key trans-alkene to be formed in high selectivity.

The aromatic fragment 163 could be synthesised from the readily available starting material, methyl 3-oxobutanoate, in five steps, while the sugar moiety 144 could also be easily prepared in one protection step from 2-deoxy-D-ribose. The alkyne unit 164 is available from S-(+)-propylene oxide 32, with the added
advantage that the second protection step is carried out on the crude material, so discarding the need for any purification on a highly volatile material.

The proposed route is robust and allows flexibility in the choice of orthogonal protecting group on fragments 163 and 164. Following the Wittig olefination and introduction of the alkyne unit, the target compound 15 should be accessible in seven steps.
2 Results and Discussion

2.1 General Information

For the purposes of the following results and discussion section, the carbon atoms in the structure of the final product have been assigned accordingly. This enables the reader to interpret and distinguish between the correct fragments and specific parts of the molecule being discussed. The assignment is documented in Figure 19 below.

![Figure 19: Structural Assignment of LL-Z1640-2.](image)

2.2 Synthesis of the Aromatic Fragment

2.2.1 Retrosynthetic Analysis of (3-Acetoxy-5-methoxy-2-methoxycarbonylbenzyl)-triphenylphosphonium bromide, 165

The proposed retrosynthetic analysis of (3-acetoxy-5-methoxy-2-methoxycarbonylbenzyl)-triphenylphosphonium bromide 165 is shown in Scheme 34. The salt was thought of as originating from the bromide 166, which in turn could originate from the methoxy unit 167. Methoxy unit 167 is a result of acetate protection of phenol 168, itself a product of selective capping of the \textit{para}-hydroxyl of diol 169 with a methyl group. The diol could be prepared from the cyclisation and aromatisation of methyl acetoacetate 170.
Thus, the key step in this synthetic strategy is the first reaction, whereby methyl acetoacetonate is used to produce the aromatic product. The next four steps after aromatisation were thought to be straightforward and no potential pitfalls were envisioned.

2.2.2 Synthesis of Methyl 2-acetoxy-6-bromomethyl-4-methoxybenzoate, 166

The synthesis of the aromatic fragment 166 began with methyl acetoacetonate 170, which was efficiently converted into the aromatic unit 169 using established conditions. This reaction proceeded well and resulted in high yields.

Scheme 35: Synthesis of the Aromatic Fragment 166. Reagents and Conditions: (a) NaH, nBuLi, THF, –78 °C → rt–reflux, 16 h, 65%; (b) TMS diazomethane, CHCl₃:MeOH, 0 °C, 3 h then rt, 16 h, 89%; (c) Ac₂O, pyridine, DMAP, Et₃N, CH₂Cl₂, 0 °C → rt, 2 h, 97%; (d) 1,3-dibromo-5,5-dimethylhydantoin, benzoyl peroxide, CCl₄, reflux, 3.5 h, 95%.
The mechanism for this first transformation is worth discussing due to its relative complexity (Scheme 36). Deprotonation of $\beta$-ketoester $A$ gives enolate $B$, which can attack the ketone of a second $\beta$-ketoester unit. Treatment of intermediate anion $C$ with $n$-butyllithium removes the acidic hydrogen α to the ketone to give $D$. B-elimination of the hydroxyl group of $E$ then gives the condensation product $F$. Deprotonation then generates enolate $G$, which upon attack onto the adjacent ester gives cyclic hemiacetal intermediate $H$, which then collapses into the tricarbonyl unit $I$. Compound $J$ is formed by tautomerisation of the 1,3-dione $I$.

![Scheme 36: Mechanism by which Methyl 2,4-dihydroxy-6-methylbenzoate (169) is Formed.](image)

Selective methylation of $169$ was achieved in 89% yield with TMS diazomethane in a mixture of chloroform and methanol.\textsuperscript{[49b]} The mechanism is thought to proceed as shown in Scheme 37. TMS diazomethane $171$ deprotonates the alcohol para to the ester functionality (presumably due to less steric hindrance and lack of H-bonding) and methanol attacks the δ+ silicon. Hydrogen transfers from oxygen to diazomethane as silicon leaves. The phenolic anion then attacks the CH$_3$ group, giving product $168$ and releasing nitrogen.
Protection of the remaining phenol proceeded under standard acetylation conditions to afford the fully protected aryl unit 167 in 97% yield. The final step was bromination of the methyl group, which proceeded using 1,3-dibromo-5,5-dimethylhydantoin to afford 166 in 95% yield.[49b]

The proposed mechanism is shown in Scheme 38 and the first step is the homolytic cleavage of the radical initiator, benzoyl peroxide 172, to give two radical units 173. Radical 173 reacts with aryl unit 167 to generate radical 174. This goes on to react with 1,3-dibromo-5,5-dimethylhydantoin 175 to give desired product 166 and new radical 176, which can go on to react with a second molecule of 167 to form radical 174 and 177. These react together to generate product 166 and new radical 178.
**Scheme 38: Radical Bromination of 167.**

### 2.3 Synthesis of the Sugar Fragment

The synthesis of the carbohydrate unit 144 was previously established\(^{[75]}\) and began with 2-deoxy-\(\beta\)-ribose 179, which initially was ketal protected (Scheme 39) using Horton’s conditions.\(^{[51]}\) However, their high yields were not reproducible, although the ratio of \(\alpha\)- and \(\beta\)-anomers matched those reported. In Horton’s procedure, dimethylformamide is used as the solvent due to the poor solubility of 2-deoxy-\(\beta\)-ribose. This suffices to an extent for those reactions on a smaller scale, but as this is one of the initial steps in a total synthesis, the reaction calls to be carried out on a large scale. Evidently, using vast volumes of DMF is prohibitive, both in terms of its toxicity but also due to the difficulty in removing it from the final product. In due course, it was discovered that switching to ethyl acetate as the solvent for the reaction, greatly improved the yields. In addition, ethyl acetate is readily removed under vacuum, circumventing any unnecessary decomposition of product. The protection yield was significantly improved when a catalytic amount of pyridinium \(p\)-
toluenesulfonate (PPTS) was used and ethyl acetate was employed as the solvent. After purification, the desired ketal protected product 144 was isolated in 62% yield.

![Scheme 39: Ketal Protection of 2-deoxy-D-ribose. Reagents and Conditions: (a) 2-Methoxypropene, PPTS, EtOAc, –10 °C, 2.5 h then rt, 16 h, 62%.

2.4 Coupling of the Aromatic and Sugar Fragments

The C1—C2 olefin present in the target compound possesses the E-configuration and whilst there are many ways by which olefins can be formed it is essential in this case that the chosen reaction generates an olefin with high E-selectivity.

2.4.1 Controlling the Geometry of Olefins

Geometrical isomers of alkenes are different compounds and they often have very different biological, chemical and physical properties. Experimentally they pose problems as they can be very difficult to separate by chromatography or distillation and as a consequence chemists have discovered and developed methods to make olefins as single isomers.

There are elimination reactions that can be employed to give single geometrical isomers as the product and they fall into four main classes:

1. Only one geometrical isomer is possible, for example, in a six-membered ring only a cis-double bond can exist.
2. The geometrical isomers are in equilibrium and the more stable E-alkene is formed.
3. The reaction is stereoselective and the E-alkene is formed as the main product by kinetic controls.
4. The reaction is stereospecific and the alkene geometry depends on the stereochemistry of the starting materials and the mechanism of the reaction.

Most common are reactions that fall into class 3 in the above list. Predominantly E-alkenes can be formed by stereoselective elimination reactions.
E1 elimination reactions give mainly the $E$-alkene as the transition state is lower in energy than that leading to the $Z$-alkene. An example is the treatment of $2$-pentyl bromide with base (Scheme 40), which leads to three times as much $E$-alkene as $Z$-alkene, due to the lower energy of the transition state.

Scheme 40: Stereoselective Formation of $E$-Alkenes. Adapted from Reference 119.

2.4.2 Wittig Olefination

The Wittig reaction is arguably the most important and effective reaction used to generate $E$- and $Z$-alkenes.\textsuperscript{[77,78]} The formation of the olefin comes from the reaction of aldehydes (fast) and ketones (slow) with the ylide generated from a phosphonium salt (Scheme 41).

Scheme 41: General Scheme for the Wittig Olefination

The phosphorus ylide is prepared from a triaryl- or trialkylphosphine and a primary or secondary alkyl halide, followed by deprotonation with a suitable base. Depending on the nature of the $R$ substituents, there are three different types of ylide:

Type 1 - "Stabilised" - The alkyl halide has at least one strong electron withdrawing group
Type 2 - "Semi-stabilised" - Have at least one aryl or alkenyl substituents as the $R$ groups
Type 3 - "Unstabilised" - Have only alkyl substituents.
The overall geometry of the olefin is dependent on the reactivity of the ylide. "Stablilised" ylides give rise to predominantly $E$-alkenes with aldehydes and are not as reactive as "unstabilised" ylides, which give rise mainly to $Z$-alkenes. "Semi-stablilised" ylides generate alkenes with intermediate selectivity.

Mechanistically, the addition of the ylide $B$ to the carbonyl $A$ is thought to lead to a zwitterionic intermediate betaine $D$, which closes to the four-membered cyclic oxaphosphetane $E$. If the betaine possesses the cis-configuration the reaction from the reactive ylide to the cis-oxaphosphetane, then the major $Z$-alkene $F$ is fast. The reaction to the $trans$-betaine is slower, but the collapse is fast to form the minor $E$-alkene.

Scheme 42: General Mechanism for the Wittig Reaction.

Improvements have been established to enable better selectivity of the Wittig reaction. In the Schlosser modification of Wittig,$^{79,80}$ $E$-alkenes are made in a one-pot synthesis from "unstabilised" ylides and carbonyl compounds.

Mechanistically (Scheme 43), the addition of the ylide $A$ to the carbonyl compound $B$, at $-78$ °C, leads to the formation of the cyclic cis-oxaphosphetane $C$. $Cis$-oxaphosphetane $C$ is deprotonated with alkyl/aryl lithium to give the $cis$-lithiobetaine $D$. Treatment of $D$ with phenyllithium generates the $cis$-$\beta$-oxido P-ylide $E$, which equilibrates to the $trans$-$\beta$-oxido P-ylide $F$, which is more thermodynamically stable. The $trans$-ylide $F$ is then treated with an $H^+$ donor to give the pure $trans$-lithiobetaine $G$ and then with $t$BuOK to generate the $trans$-oxaphosphetane $I$ via the $trans$-betaine $H$. This $trans$-oxaphosphetane $I$ then collapses to the desired $E$-alkene $J$. 
When it came to the coupling of the aromatic fragment and the sugar derivative, the choice of method was considered carefully. It was decided that a Wittig olefination using a stabilised ylide would yield the desired double bond geometry. The corresponding Wittig salt 165 was generated in one step from the bromide 166 (Scheme 44).

Triphenylphosphonium salt 165 is a stabilised ylide due to the negative charge being stabilised by further conjugation and by the phosphorus atom. This stabilised ylide is not very reactive and as a consequence the reaction progresses slowly, via the trans-oxaphosphetane, to generate the E-alkene. Stabilised ylides have been shown to react with lactols efficiently and the concept of carrying out Wittig chemistry on lactols is well known. Wittig approaches and reactions of stabilised ylides with lactols have been commonly used to form C-glycosides\(^{[81]}\) and to synthesise lactones\(^{[82]}\) and 2-substituted tetrahydrofurans.\(^{[83]}\) The protected sugar 144 has masked aldehyde character of C\(_1\), which is exploited under Wittig conditions (Scheme 45).
Reaction of ylide 165 and lactol 144 afforded the desired alkene 184. However, the selectivity was disappointing and as determined by $^1$H NMR spectroscopy the E:Z-ratio was 3:2, matching preliminary results obtained within the group.[49b] Unfortunately, the isomers were inseparable and in addition, it was discovered that approximately 10% of a deacetylated side-product 185, was also present in the inseparable mixture. The instability of the acetate group to the reaction conditions meant that our choice of protection group had to be modified. In an alternative approach, the Wittig olefination reaction was repeated, but on this occasion sodium methoxide was added directly to the reaction mixture in order to ensure complete cleavage of the acetate protecting group. The overall yield over the 2 steps was determined as 40%. With diol 185 in hand, the primary hydroxyl was protected selectively as its silyl ether 186 in 65% yield. This then enabled the protection of the remaining aryl hydroxyl as the PMB ether 187 in excellent 90% yield using standard conditions (Scheme 46).
2.4.3 Horner-Wadsworth-Emmons Olefination

The Horner-Wadsworth-Emmons olefination\cite{84} is another reaction that can be used to generate alkenes with excellent E-selectivity. In general terms, it is the reaction between an aldehyde or ketone and a phosphonate ester (Scheme 47). It is important to note that the reaction does not proceed in the case of β-hydroxy phosphonates as no elimination takes place.

The first step of the mechanism shown in Equation [1], Scheme 48, is the formation of the phosphonate carbanion from the phosphonate ester. The base can be nBuLi, NaH or NaOMe for example, which deprotonates the acidic hydrogen first, to then allow the addition of the aldehyde or ketone. The addition of the carbanion to the carbonyl can occur syn- or anti-periplanar, to form either the trans- (Equation [2]) or cis-oxaphosphetane (Equation [3]) intermediate. The formation of the trans-oxaphosphetane is favoured as the bulky substituents are kept as far apart as possible on opposite sides of the ring. Elimination gives the E-alkene and is faster than elimination to the Z-alkene by

Scheme 46: Wittig Olefination of 165 and 144. Reagents and Conditions: (a) NaH, THF:DMF, 80 °C, 30 min; (b) NaOMe, rt, 15 min, 40%; (c) TBDMSCl, imidazole, DMF, rt, 3 h, 65%; (d) PMBCl, TBAI, K₂CO₃, DMF, 80 °C, 18 h, 90%.

Scheme 47: General Reaction Scheme for the Horner-Wadsworth-Emmons Olefination.
way of the steric crowding in the syn-transition state. Equilibration of the two oxaphosphetane diastereoisomers as a result of the starting material replenishing the supply of anti-diastereoisomer, causing the E-alkene to be formed almost exclusively. The E-selectivity is further maximised by increasing the size of the alkyl group of the phosphonate.\(^{[85]}\)


In an attempt to improve the E-selectivity of the reaction a Horner-Wadsworth-Emmons olefination was carried out. This first required the generation of the phosphonate ester, which would then be coupled with lactol 144.

The phosphonate ester was obtained via an Arbuzov (or Michaelis-Arbuzov) reaction,\(^{[86]}\) whereby the bromide 166 was treated with triethyl phosphite under microwave irradiation conditions to obtain phosphonate ester 189 in 58% yield. The choice to use microwave chemistry was advantageous in this case as it reduced not only the reaction time, but also reduced the safety risk associated with heating a reaction to elevated temperature for a prolonged period.

Mechanistically, nucleophilic attack (\(S_N2\)) by the phosphorus on the alkyl halide of 166 is followed by dealkylation of the trialkoxyphosphonium salt 188 to generate phosphonate ester 189 (Scheme 49).
Scheme 49: Mechanism of Formation of 189 via the Arbuzov Reaction.

2.4.4 Microwave Reactions

Microwave chemistry originated in the 1950s, but only gained prominence in 1986. Microwave methodology is the application of microwave irradiation to a reaction. It has become increasingly popular due to benefits such as reaction rate acceleration, shorter reaction times, milder reaction conditions and higher yields, as well as operational simplicity and lower energy usage.

Microwaves act as high frequency electric fields and usually will heat polar molecules in a solvent or conducting ions in a solid. With conventional heating the walls of the reactor heat quickly, but the core takes a prolonged time to achieve the target temperature. Microwave heating directly targets the compounds in the mixture throughout their volume, enabling the advantages mentioned above. The modern microwaves, manufactured by companies such as Biotage, are powerful but safe and easy to use, indeed some are even automated. The temperature range is typically 40 to 250 °C, with a pressure range of 0-20 bar. Different vial sizes are available enabling the user to begin with milligrams and scale up to grams if necessary.

With the phosphonate ester 189 in hand, the Horner-Wadsworth-Emmons reaction was attempted under conditions published by Schauer and Helquist. Helquist's reaction conditions have the advantage of being mild and require a tertiary amine base in the presence of a Lewis acid, instead of the strong bases originally used. Helquist's work revealed that zinc(II) triflate is an effective promoter of mild Horner-Wadsworth-Emmon reactions with diprotic substances.
Scheme 50: Horner-Wadsworth-Emmons of Phosphonate Ester 189 and Lactol 144. Reagents and Conditions: Zn(OTf)$_2$, DBU, TMEDA, THF, rt, 18 h.

Unfortunately, the HWE coupling under Helquist's optimised conditions gave mixed results. The $^1$H NMR spectrum showed that 184 was present as a mixture of inseparable E- and Z-isomers in low yield, together with the deacetylated product 185. This disappointing result prompted us to pursue the initial Wittig olefination approach. This provided us with a way to carry material forward in an attempt to progress with the total synthesis. The differentially protected diol 187 gave us an excellent starting point from which to incorporate the entire carbon framework of LL-Z1640-2.

2.5 Synthesis of the Alkyne Fragment

2.5.1 Retrosynthetic Analysis of (S)-(−)-tert-butyldimethyl(pent-4-yn-2-yloxy)silane, 55

From our original retrosynthesis of LL-Z1640-2, we had realised the importance that the alkyne unit to be coupled to the aldehyde had the correct stereochemistry already in place. Literature precedent indicated that this would be easily achievable through a straightforward approach (Scheme 51).[89]

Scheme 51: Retrosynthetic Analysis of the Alkyne Fragment 164. PG equals a suitable protecting group.
2.5.2 Synthesis of \((S)-(-)-\text{tert-butylidimethyl(pent-4-yn-2-yloxy)silane, 55}\)

\((S)-(+)-\text{Propylene oxide}\) is commercially available, but extremely hazardous and particular care is needed when handling this compound. \((S)-(+)-\text{Propylene oxide} 32\) can be synthesised from ethyl \((S)-\text{lactate} 191\), according to Golding’s procedure (Scheme 52).\(^{[90]}\) We chose not to do this, as we were mindful of the safety aspects in producing such a compound.

![Scheme 52: Golding's Synthesis of \((S)-(+)-\text{Propylene oxide}\).](image)

Reagent and Conditions: (a) LiAlH\(_4\); (b) 33% HBr in AcOH; (c) C\(_5\)H\(_{11}\)ONa, C\(_5\)H\(_{11}\)OH.

Commercially sourced \((S)-\text{propylene oxide} 32\) was added to a stirred suspension of lithium acetylide ethylenediamine complex to afford the crude alcohol 190 in quantitative yield. In order to maintain our orthogonal protecting group strategy, the free alcohol was protected as its TBS silyl ether to generate the desired optically pure alkyne fragment 55 in 78% yield.

![Scheme 53: Synthesis of the Alkyne Fragment 55.](image)

Reagents and Conditions: (a) lithium acetylide ethylenediamine complex, DMSO, 0°C → rt, 48 h, 100%; (b) TBDMSCl, imidazole, DMF, rt, 16 h, 78%.

2.6 Synthesis of the \(C_{1'}—C_{10'}\) Carbon Framework

2.6.1 Addition of the Alkyne Fragment

There is literature precedent for the enantioselective synthesis of propargylic alcohols by the direct addition of terminal alkynes to aldehydes and this had the potential to be exploited in this synthesis.
Before Carreira published his conditions,\textsuperscript{[91,92]} the methods available for asymmetric synthesis of optically active propargylic alcohols were nucleophilic addition of metallated acetylenes to aldehydes or ynone reduction, with both the metallated acetylene and ynone requiring prior preparation. In 2000, Carreira published the synthesis of optically active propargylic alcohols 195 (up to 99\% e.e.) under mild conditions at room temperature using $N$-methylephedrine 194 as a chiral additive (Scheme 54).\textsuperscript{[91]}

![Scheme 54: Carreira’s Synthesis of Propargylic Alcohols Using a Chiral Additive.](image)

The authors initially found that in the presence of Zn(OTf)$_2$ and an amine base, terminal acetylenes underwent addition to aldehydes at room temperature in good yields. They hypothesised that a zinc(II) alkynylide was generated \textit{in situ}, comparing it to the reaction of Cu(I) salts and amine bases with terminal acetylenes. With this success, they then went on to use inexpensive, commercially available chiral additives as ligands for Zn(II). In summary, they found that $N$-methylephedrine, an amino alcohol, was the most effective to give the optically active adduct.

The coupling sequence began with protected compound 187 which was deprotected using TBAF to generate alcohol 196 in 94\% yield (Scheme 55). Alcohol 196 was then subjected to standard Swern conditions to produce aldehyde 197, confirmed by the strong, characteristic signal in the $^1$H NMR spectrum.

![Scheme 55: Synthesis of Aldehyde 197. Reagents and Conditions: (a) TBAF, THF, 0 °C → rt, 2 h, 94\%; (b) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, −78 °C → rt.](image)
Unfortunately, this particular aldehyde proved unstable and started decomposing almost immediately, rendering it unusable for the addition to the alkyne unit. It also meant that large quantities could not be made and then stored for future use. In order to circumvent this problem, a new method was devised. As part of the new Swern oxidation procedure, triethylamine would be added at $-78 \, ^\circ\text{C}$ and the reaction mixture allowed to warm to room temperature before being stirred for a further 30 minutes. It was hypothesised that at this stage the aldehyde need not be isolated, but rather it could be added directly to a second, simultaneously running reaction. This second reaction would contain the other reagents needed for the overall addition reaction (Scheme 56). The freshly prepared aldehyde 197 was added to a mixture of Zn(OTf)$_2$, N-methylephedrine 194 and alkyne 55. Unfortunately, despite the reported success in the literature, the reaction did not work in our hands.

Scheme 56: Proposed One-pot Oxidation-Grignard Addition Reaction.

This set-back prompted us to search the literature for alternative procedures. In 1999, the anti-selective addition of triisopropoxytitanium acetylide 200 to aldehyde 199 was published. It was reported that this alkyne addition afforded the anti-product 201 in 98% yield and as a single diastereoisomer (Scheme 57).[^93] The improved procedure is analogous to that employed previously without success in Scheme 56. The only major difference was the use of chloroisopropoxytitanium (IV). Unfortunately, the reaction was not successful and NMR spectroscopy of the isolated compound showed it not to be the desired product.

Scheme 57: Addition of Triisopropoxytitanium Acetylide 200 to Chiral Aldehyde 199.
2.6.2 One-Pot Oxidation-Alkyne Coupling

The failure of the alkyne to couple to the aldehyde under titanium or zinc-promoted conditions drove us to consider an alternative metal counterion during the addition process. It was discovered in our laboratory that treatment of alkyne 203 with ethylmagnesium bromide at $-78 \, ^\circ C$ did not proceed to generate the expected product. On its addition to the aldehyde 204, it gave instead the ethyl addition product 205 (Scheme 58).[[75]

\[
\text{H}_3\text{CO} \quad \text{H}_3\text{CO}
\]

Scheme 58: Addition of Acetylide 203 to Aldehyde 204. Reagents and Conditions: (a) EtMgBr, THF, $-78 \, ^\circ C$, 94%.

However, when the alkyne was treated with ethylmagnesium bromide at room temperature, the required magnesium acetylide was generated. Trapping of the aldehyde 204 afforded the alkynol product 206 in 88% yield (50:50 mixture of diastereoisomers) (Scheme 59).[[75]

\[
\text{H}_3\text{CO} \quad \text{H}_3\text{CO}
\]

Scheme 59: Trapping of Acetylide 203 with Aldehyde 204. Reagents and Conditions: (a) EtMgBr, THF, rt, 88%.

Thus, alkyne 55 was treated with ethylmagnesium bromide at room temperature and was then added to crude aldehyde 197. It was pleasing to see that the coupling did take place and the desired product 198 was obtained in 30% yield as a mixture of diastereoisomers (Scheme 60). It is worth pointing out that this
yield was for an initial, test-scale reaction and so it is fair to say that some material could potentially have been lost during work-up or purification. TLC analysis however proved the reaction to be efficient, with the clean conversion of the alcohol to the aldehyde and then to the final product.

Scheme 60: One-Pot Oxidation Alkyne Coupling. Reagents and Conditions: (a) EtMgBr, THF, rt, 3 h; (b) (COCl)$_2$, DMSO, Et$_3$N, THF, $-78^\circ C \rightarrow$ rt; (c) 55, THF, $-78^\circ C \rightarrow$ rt, 18 h, 30%.

Though the success of this reaction was appreciated and the gaining of the C$_1$—C$_{10}$ skeleton was welcomed, it was not advantageous to have an inseparable mixture of diastereoisomers. As can be appreciated, the $^1$H and $^{13}$C NMR spectra of such a compound is very complex and the ratio of diastereoisomers is not determinable. It can be postulated that a mixture is obtained due to the stereocentre α (alpha) to the aldehyde not being sufficient to fully direct the addition to the expected face. From the Felkin-Anh model, the outcome of the nucleophilic addition to the carbonyl compound can be predicted. When the large group is placed perpendicular to the carbonyl group, the expected face is the addition of the alkyne unit between the two hydrogen atoms (the two small groups and the least hindered trajectory). The syn-product is the expected product, while the anti-product is formed when the addition occurs between the large group and hydrogen of the aldehyde. In order to progress forward, the situation was reluctantly accepted and it was understood that NMR analysis of subsequent compounds would be difficult. Time was of the essence and we knew we could not afford the time at this stage to go back and test further enantioselective conditions.
2.7 Isomerisation Attempts

In the preparation of carbon-carbon double bonds, the isomerisation of a mixture of Z- and E-olefins to the geometrically pure E-isomer is highly significant and valuable. Over time, radical,[94] photochemical[95] and organometallic[96] reagents have been part of the conditions developed to isomerise olefins. Though successful, they are not without their disadvantages. Radical and photochemical techniques often require harsh conditions and in a number of photochemical reactions the reverse isomerisation is seen.

Recently, Yu and co-workers[97] prepared E-arylkenes via a mild, palladium(II)-catalysed isomerisation of Z-arylalkenes (Scheme 61). The method was limited to double bonds conjugated to aromatic systems, but this wasn’t a hindrance as the double bond to be isomerised in our case is conjugated to an aromatic unit. What made the method even more attractive was that the reaction required only 10% loading of the chosen palladium catalyst, bis(acetonitrile)palladium(II) chloride, which is also commercially available and relatively inexpensive. The authors found that cis- and trans-methyl styrenes and styrenes with more bulky substituents were converted to the trans-isomer in good yield.

\[
\begin{align*}
\text{Ar} & \quad \text{R} \quad \overset{10 \text{ mol}\% \text{ PdCl}_2(\text{MeCN})_2}{\xrightarrow{\text{CH}_2\text{Cl}_2, \text{ r.t.}}} \quad \text{Ar} \quad \text{R} \\
\end{align*}
\]

Scheme 61: Yu’s Palladium(II)-Catalysed Isomerisation of E-arylalkenes.

In 2007, Jung and colleagues[98] reported their efforts into the development of mild and efficient methods for olefin isomerisation, to generate geometrically pure E-alkenes using palladium acetate, tributyltinhydride and triethylamine (Scheme 62).

\[
\begin{align*}
\text{R} & \quad \text{R'} \quad \overset{5 \text{ mol}\% \text{ Pd(OAc)}_2, \text{ Bu}_3\text{SnH}}{\xrightarrow{\text{Et}_3\text{N, CH}_2\text{Cl}_2, \text{ reflux}}} \quad \text{R} \quad \text{R'} \\
\end{align*}
\]

Scheme 62: Jung’s Palladium(II)-Catalysed Isomerisation of Olefins.

Jung found his conditions to be general for the isomerisation of Z-alkenes with allylic hydrogens and conjugated Z-arylalkenes. The authors found that the
nature of the alkene substituents controlled the result of the isomerisation, for example, stabilisation by a phenyl group facilitated the reaction. The authors proposed a possible mechanism (Scheme 63) for the isomerisation and postulated that the Pd(0), formed by reduction of palladium(II) acetate with tributyltinhydride, would serve as an active catalyst for the isomerisation. The oxidative addition of tributyltinhydride to Pd(0) affords the palladium-tin complex which undergoes insertion. The $E$-olefin is generated following β-H elimination and Pd(0) is regenerated from Bu$_3$Sn—Pd—H.

Scheme 63: Proposed Mechanism of Pd-Catalysed Isomerisation with Bu$_3$SnH. Adapted from Reference 98.

The fact that the Wittig olefination gave a 3:2 mixture of isomers, presented an opportunity for us to attempt an olefin isomerisation. If successful, the Wittig reaction could be scaled up with the knowledge that the $E$:Z-mixture of isomers could be readily isomerised into the geometrically pure $E$-isomer. Hence, Jung's conditions were tried on a simple model system 185 (Scheme 64). Due to the fact that the isomers were inseparable, it made it difficult to follow the reaction by TLC. To monitor the reaction it became necessary to take an aliquot of reaction mixture, allow it to cool, filter it through Celite$^\circledR$ to remove the solids and concentrate it before running a $^1$H NMR to observe any isomerisation to the $E$-isomer. After 45 hours under reflux it became apparent that no further isomerisation of the $Z$-isomer to the $E$-isomer was occurring so the above work-up was performed, followed by column purification and analysis by NMR. Although not wholly successful, some isomerisation had taken place and from the spectra the mixture was now 4.8:2 from 3:2 ($E$:Z).
Scheme 64: Isomerisation attempts. Reagents and Conditions: (a) Pd(OAc)$_2$ (5 mol%), Bu$_3$SnH, Et$_3$N, CH$_2$Cl$_2$, reflux, 45 h, 33%; (b) Pd(OAc)$_2$ (5 mol%), Bu$_3$SnH, Et$_3$N, CHCl$_3$, reflux, 50 h then rt, 74 h, 54%.

A second test reaction attempt was run, treating alcohol 196 under the same conditions, but switching the solvent to chloroform. Taking into account the prolonged reaction time needed for this kind of transformation, on this occasion the reaction mixture was heated under reflux for 50 hours and then cooled to room temperature, with stirring continued for a further 74 h. Again the same problem of inseparable isomers was encountered, rendering TLC analysis ineffective. The $^1$H NMR spectrum showed a slight improvement from 1.4:1 to 2:1 ($E$:Z).

The failure of the palladium(II) catalysed isomerisation conditions to generate geometrically pure $E$-olefins meant that we had to seriously rethink our synthetic strategy to LL-Z1640-2. Whilst the Wittig olefination allowed us to garner material to test conditions for ensuing reactions in our proposed synthesis, it was becoming clear that this particular olefination to form the $C_1$—$C_2$ double bond in the trans-configuration was not suitable and another, significantly improved method was required.

2.8 Additional Studies

2.8.1 Cross-coupling Reactions

At this point a fellow PhD student in the research group found that a cross-metathesis between vinylboronic acid pinacol ester 207 and alkene 208 was achievable (Scheme 65). He found that Grubbs first or second generation
catalyst afforded alkene 209 in 71% or 73% yield respectively, as a 4:1 separable mixture of E:Z-isomers. Aside from proceeding with the desired Suzuki coupling, the success opened up the possibility of using alkene 208 as a partner in other Grubbs-mediated cross-metathesis reactions.

![Scheme 65: Successful Cross-metathesis of Alkene 208. Reagents and Conditions: (a) Grubbs second generation catalyst (5 mol%), CH₂Cl₂, reflux, 13 h, 73%; (b) Grubbs first generation catalyst (5 mol%), CH₂Cl₂, reflux, 13 h, 71%.](image)

My fellow PhD student then went on to investigate the possibility of a cross-metathesis reaction between aromatic alkene 210 and alkene 208. Following intense screening and optimisation, he found that the best reaction conditions were using Hoveyda-Grubbs second generation catalyst, with 30% loading and a ratio of 1:2 of aromatic alkene 210 and alkene 208 respectively (Scheme 66). The desired heterodimer 186 was obtained as a 9:1 mixture of E:Z. The additional formation of the homodimer could not be prevented and was isolated in an amount proportional to the success of formation of the heterodimer.

![Scheme 66: Successful Cross-metathesis of Aromatic Alkene 210 and Alkene 208. Reagents and Conditions: (a) Hoveyda-Grubbs second generation (30 mol%), CH₂Cl₂, reflux, 48 h, 73%.](image)

My colleague was able to protect the free hydroxyl of 186 as its MOM ether 211 and remove the silyl ether protecting group to reveal the free alcohol 212 (Scheme 67), at which stage the isomers became separable. Due to time constraints enforced upon my colleague, the project was left at this stage, but a synthetic path of this type is highly attractive and something that would be worthwhile pursuing.
2.8.2 Continuation of the Synthesis Towards LL-Z1640-2

Taking into account all the investigations carried out towards the total synthesis of LL-Z1640-2 thus far, it was necessary to decide on a suitable path to follow. It was known from one angle that the Wittig olefination wasn’t going to be productive in carrying the synthesis forward, due to the difficulties with the poor selectivity. Whilst all the possibilities for producing products with excellent E-selectivity had by no means been exhausted, we were now aware of the success with Grubbs-mediated cross-metathesis between alkenes 210 and 208.[75]

2.9 New Synthetic Route to LL-Z1640-2

For completeness, it is necessary to highlight the routes that have already been established towards aromatic alkene 210 and alkene 208. They are similar to those already described, but in order to present the revised synthesis towards LL-Z1640-2 in its entirety they will be discussed further.

2.9.1 Synthesis of the New Aromatic Fragment, 210

Aromatic fragment 210 was synthesised following the approach initially developed by Dr M. N. Robertson, a fellow member of the research group (Scheme 68).[49a,75,98]
2,4,6-Trihydroxybenzoate 114 was selectively methylated to afford diphenol 117. Diol 117 was then mono-protected to generate silyl ether 118. The remaining hydroxyl group was converted to the corresponding triflate 119, under carefully controlled conditions.\cite{75} The triflate was then subjected to Stille coupling\cite{99} with vinyltributyltin. This proceeded in good yield to afford 120, but also partially cleaved the silyl ether protecting group, giving phenol 210. A decision was taken to treat the mixture of 120 and 210 with TBAF to deprotect fully the TBS group, affording aromatic fragment 210 in 74% yield over two steps.

### 2.9.2 Synthesis of the Alkene Coupling Fragment, 208

2-Deoxy-d-ribose 179 was ketal protected using 2-methoxypropene (Section 2.3). Wittig olefination of lactol 144 using methyltriphenylphosphonium iodide proceeded to give terminal alkene 213 in an acceptable 60% yield.\cite{76} The primary alcohol was protected as its TBS silyl ether in 87% yield under standard conditions to give the desired alkene cross-metathesis coupling partner 208.
2.9.3 Olefin Metathesis

Olefin metathesis is one of the most powerful synthetic methods in organic chemistry. The definition of metathesis is change position, \textit{meta} meaning change and \textit{thesis} meaning position. In metathesis reactions double bonds are broken and made between carbon atoms in ways that cause atom groups to change places. In the 1950s, Du Pont, Standard Oil and Phillips Petroleum reported catalysed metathesis reactions when propene led to ethylene and 2-butenes on heating with molybdenum.\cite{100}

Olefin cross-metathesis is the intermolecular mutual exchange of alkylidene (or carbene) fragments between two olefins promoted by metal-carbene complexes (Scheme 70).\cite{101} The process is catalytic, typically requiring 1-5 mol\% of catalyst, with high yields readily achievable.

\begin{equation}
\begin{array}{c}
\text{R} \quad \Delta \\
\text{R'}
\end{array}
\quad 
\begin{array}{c}
\text{R} \quad \Delta \\
\text{R'}
\end{array}
\quad 
\begin{array}{c}
\text{R} \quad \Delta \\
\text{R'}
\end{array}
\end{equation}

\textbf{Scheme 70: General Scheme of Cross-Metathesis.}\cite{101}

In 1971, Chauvin and Hérisson published their widely accepted transition metal alkene metathesis mechanism (Scheme 71).\cite{102} The reaction is reversible, but the gaseous ethylene produced drives the reaction to completion. A [2+2] cycloaddition between olefin B and a transition metal carbene A forms a metallocyclobutane intermediate C. This collapses in a productive fashion to afford the first olefin product D and a new metal alkylidene E. This metal alkylidene can react with a molecule of F via metallocyclobutane G to yield A, which re-enters the catalytic cycle.
In 2005, the Nobel Prize in Chemistry was jointly awarded to Yves Chauvin, Robert H. Grubbs and Richard R. Schrock, "for the development of the metathesis method in organic synthesis."[103] They each contributed to the field of metathesis in their own way. To summarise, in 1971 Chauvin explained how metatheses reactions function and types of metal compound that act as catalysts, in 1990 Schrock was the first to produce an efficient metal-compound catalyst for metathesis (Figure 20, 214) and in 1992 Grubbs reported his development of a superior ruthenium catalyst (Figure 20, 215) for metathesis. Modifications of his catalysts came in 1995 (First Generation) and 1999 (Second Generation) (Figure 20, 216 and 217 respectively). Their research and findings combined allowed synthetic methods that were more efficient, simpler to use and more environmentally friendly.

Figure 20: Commonly Used Metathesis Catalysts.
2.9.4 Coupling of Fragments 210 and 208

The cross-coupling between the aromatic alkene 210 and alkene 208 was attempted using Hoveyda-Grubbs second generation catalyst (Figure 21) under the established conditions (Scheme 72).[^75]

![Hoveyda-Grubbs Second Generation Catalyst](image)

With a 30 mol% loading of catalyst and a 2:1 ratio of 208 to 210, the desired product 186 was obtained in 65% yield after refluxing in the dark for 48 h in dichloromethane. Despite repeated attempts the yield obtained was not quite as high as reported previously in the group[^75], though more than acceptable to proceed. The product was still a mixture of E- and Z- isomers, but had vastly improved to 9:1 (E:Z), as opposed to 3:2 obtained following the Wittig olefination.

![Cross-metathesis of 210 with 208](image)

**Scheme 72:** Cross-metathesis of 210 with 208. Reagents and Conditions: (a) Hoveyda-Grubbs second generation catalyst (30 mol%), CH₂Cl₂, reflux, 48 h, 65%.

From earlier work, a TBS silyl ether positioned on the aryl ring was found to be labile and as such was ruled out as the choice of protecting group for the aromatic hydroxyl. In addition, there was a TBS group already present in the molecule which could potentially make the mono-deprotection slightly troublesome. A MOM ether was chosen as the protecting group for the phenolic alcohol of coupled product 186. It was envisaged that the MOM group would stay in place throughout the remainder of the synthesis, while its cleavage could be performed simultaneously with the acetonide protecting group at the end of
the synthesis. The MOM group was introduced, using MOMBr and Hunig’s base, \cite{76} generating 211 in 60% yield (Scheme 73). This lower than expected yield was a surprise and it was originally assumed that the MOMBr could also be damaging the substrate. Removal of the TBS group with TBAF generated the free alcohol 212, which could be used directly in our previously established one-pot alkyne coupling reaction.

Scheme 73: Formation of Alcohol 212. Reagents and Conditions: (a) MOMBr, DIPEA, CH$_2$Cl$_2$, 0 °C $\rightarrow$ rt, 18 h, 60%; (b) TBAF, THF, 0 °C $\rightarrow$ rt, 1.5 h, 93%.

2.10 Synthesis of the Seco-Acid

2.10.1 Retrosynthetic Analysis of 2-{(E)-3-[(4S,5S)-5-((Z)-(S-5-Hydroxy-1-triisopropylsilyloxy-hex-2-enyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl}-4-methoxy-6-methoxymethylbenzoic acid, 218

As demonstrated in the retrosynthetic analysis shown in Scheme 74, seco-acid 218 was envisioned as originating from the base-catalysed hydrolysis of ester 219. Compound 219 would be the result of PMB deprotection at the terminus of the structure. Z-Alkene 220 can be gained via selective hydrogenation of the alkyne 221. Alkynol 222 comes from the one pot oxidation-acetylide addition of 212 and 223.
2.10.2 Synthesis of 2-\{(E)-3-[(4S,5S)-5-((Z)-(S)-5-Hydroxy-1-triisopropylsilanyloxy-hex-2-enyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-propeny]-4-methoxy-6-methoxymethylbenzoic acid, 218

Alcohol 212 was subjected to the same one-pot Swern oxidation-Grignard acetylide coupling as described previously. This time it was decided to use an alternative protecting group for the hydroxyl group of the alkyne unit. The experiences encountered with cleavage of previous TBS groups under regular reaction conditions prompted us to change our strategy with regards to orthogonal protection. It was assumed that the more stable PMB ether would withstand the conditions employed in the three reactions up to its cleavage.

As shown in Scheme 75, lithium acetylide complex was coupled with (S)-(+)propylene oxide to afford alcohol 190. The crude alcohol was then protected as the PMB ether to afford alkyne 223 in 40% over two steps.
Alkyne 223 was treated with ethylmagnesium bromide and the resulting anion was added directly to a solution of freshly generated aldehyde 224 in THF. It was pleasing to see that once again the Grignard acetylide had added cleanly to the aldehyde, affording 222 in an acceptable 65% yield, as an inseparable mixture of diastereoisomers (Scheme 76).

**Scheme 76: Synthesis of Seco-Acid 218.** Reagents and Conditions: (a) (COCl)₂, DMSO, Et₃N, –78 °C → rt; (b) THF, –78 °C → rt, 14 h, 65%; (c) TIPSCI, imidazole, DMF, rt, 24 h, 83% (based on starting material consumed); (d) H₂, Pd/BaSO₄, quinoline, MeOH, rt, 4 h, 85%; (e) DDQ, CH₂Cl₂, pH 7 buffer, rt, 20 h, 79%; (f) 2 N KOH, EtOH, 80 °C, 48 h, 57%.

Having successfully introduced the alkyne unit, a triisopropylsilyl (TIPS) ether was chosen as the protection group for the newly created secondary alcohol 222. In 1974, Ogilvie and colleagues[104] reported their experiments aimed at selective protection and deprotection of OH groups using the TIPS group. Due to its bulk, the isopropyl units of the TIPS group provide steric screening for the silicon they are attached to (and the atom to which the silicon is connected),[105] but also slow down reactions at silicon compared to TMS or TBDMS groups.

The TIPS ether was expected to remain in place for the duration of our synthesis until its cleavage in readiness for the final oxidation to the ketone. TIPS is more resistant to fluoride than TBS, but can be removed using standard conditions such as TBAF, so we didn’t foresee any issues with its removal.[106] Protection of secondary alcohol 222 using TIPSCI and imidazole proceeded slowly as expected
and did not go to completion despite multiple attempts. Fortunately, the transformation was clean and no other products were formed. In 2000, a group published their findings in the efficient and selective protection of alcohols and phenols with TIPS-Cl/imidazole using microwave irradiation. The method is solventless, so the alcohol 222, imidazole and TIPS-Cl were added to a dry reaction vessel and subjected to microwave irradiation. The pattern of irradiation is shown below in Table 1.

<table>
<thead>
<tr>
<th>Round</th>
<th>Irradiation Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time (s)</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
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<tr>
<td>3</td>
<td>30</td>
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<tr>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>90</td>
</tr>
</tbody>
</table>

Table 1: Irradiation Conditions for the TIPS Protection of Alcohol 222.

After each irradiation a sample of the reaction mixture was taken and TLC analysis performed. After the second round of irradiation, the desired product was observed (run against an authentic sample), with the reaction having progressed approximately 30%. After round three, the reaction had progressed further but after round four, the situation had changed. The reaction had progressed further still but there were three visible spots by TLC, starting material 222, product 221 and a previously unseen spot. We continued with round five and it was found that the starting material had still not been consumed, the formation of the unknown had increased and there was no distinct change in the desired product. It was postulated that proceeding with microwave irradiation would have only increased the percentage of the unknown, with no guaranteed consumption of alcohol 222. With these findings we reverted back to our standard protection conditions.

With the fully protected compound 221 in hand we turned our attention to the selective hydrogenation of the alkyne to generate the cis-alkene. Usual
palladium catalysts are so effective in promoting the addition of hydrogen to both triple and carbon-carbon bonds that the alkene intermediate formed by hydrogen addition to an alkyne cannot be isolated. Lindlar's catalyst\cite{107} is a less efficient catalyst and allows the isolation of the intermediate alkene. The addition of hydrogen is syn and the alkene formed has the cis-configuration. Hydrogenation of alkyne 222 using Pd/BaSO$_4$ poisoned with lead(II) acetate and quinoline under a hydrogen atmosphere generated the Z-olefin 220 in variable yields of 77-85%.

Removal of the PMB protecting group, to generate 219, was successfully achieved using DDQ, in a yield of 77%. However, some problems were encountered and on occasion the reaction did not proceed and it was necessary to work-up the reaction mixture and repeat the procedure. For this reason attempts were made to remove the PMB ether under different conditions.

In 2000, Yu and co-workers reported the chemo- and regio-selective cleavage of the PMB group at low temperature in the presence of tin(IV) chloride and thiophenol.\cite{108} With the authors statement of the reaction being fast and high yielding and with further encouragement from the fact that these conditions had been employed successfully already in our group\cite{109} we proceeded to test the reagents for the removal of the PMB group of 220. Unfortunately, $^1$H NMR of the crude residue suggested that the desired product had not been formed and it was not deemed fruitful to continue with any purification. Alternatively, it is well known that CAN (ammonium cerium(IV) nitrate) can be used to oxidatively cleave PMB ethers.\cite{110} The reaction was continuously monitored by TLC and after 20 minutes it was clear that the reaction was progressing cleanly, with the formation of only one new spot. Disappointingly, over the course of 7 hours, additional new spots began to appear and the decision was taken to work-up the reaction without the complete consumption of starting material. It was disappointing to see that after purification, the desired deprotected product 219 was obtained in only 16% yield. The additional spots formed were isolated but found to be unidentifiable by NMR. Consequently, it was decided to continue with the use of DDQ as other PMB removal conditions reported in the literature were deemed unsuitable, based on the functionality present in our substrate.
For our first attempt at saponification of the ester we chose to use 2 N KOH in ethanol\[111\] and found that the reaction proceeded well over the course of 48 hours under reflux to generate the seco-acid 218 in 57% yield. Taking guidance from reports where other groups have used base-catalysed ester saponification on large molecules, the yield gained was comparable and no optimisation attempts were performed.

2.11 Completion of the Synthesis

With a robust and reliable synthesis to seco-acid 218 established and subjected successfully to scale-up, we could now proceed with the key macrolactonisation step. The construction of macrocyclic structures is a recurrent and testing problem in synthesis. Macrocyclic systems can be generated by cyclisation of open, long chain precursors, but the ring closure is disfavoured entropically, due to loss of entropy associated with the formation of the usually more rigid, cyclic structure. There are two methods which are frequently used for macrolactonisation, acid activation and alcohol activation. Studies carried out by Illuminati and colleagues\[112\] and Stoll and colleagues\[113\] showed that for successful ring formation there are two types of energy to take into account, the enthalpy and entropy. For medium ring formation entropy<enthalpy and for large ring formation entropy>enthalpy. The most difficult ring size to form is $n = 8-11$.

Over time, new synthetic methods have been developed which readily allow the formation of macrolides. The methods that appeal most in respect to our synthesis are discussed accordingly.

2.11.1 Retrosynthetic Analysis for the Final Steps to LL-Z1640-2

As demonstrated in Scheme 77, the final step to the natural product LL-Z1640-2 is achieved through global deprotection. The protected compound 225 is a direct result of oxidation of the secondary alcohol 226, itself formed from the deprotection of the TIPS ether. Compound 227 is the product of the macrolactonisation.
Scheme 77: Retrosynthetic Analysis to LL-Z1640-2 from Seco-Acid 218.

### 2.11.2 Towards the Total Synthesis of LL-Z1640-2

The first attempt at forming macrocycle 227 was made using the well known Yamaguchi esterification. The Yamaguchi esterification allows the synthesis of highly functionalised esters and lactones via the alcoholyis of the corresponding mixed anhydrides. The conditions are mild, making it compatible with compounds which may have sensitive functionalities. The high catalytic activity of DMAP in acyl transfer reactions attracted the attention of the authors and they used it in esterifications with mixed anhydrides to investigate the synthesis of macrocyclic lactones. They found that 2,4,6-trichlorobenzoyl chloride and DMAP under high dilution was the best combination to give a high reaction rate and yield.

Yamaguchi took an acid sensitive seco-acid and treated it with 2,4,6-trichlorobenzoyl chloride in the presence of triethylamine, removing the triethylamine hydrochloride by-product. The mixed anhydride was diluted with
toluene and slowly added to a refluxing solution of DMAP in toluene via syringe pump in high dilution (0.002 M). The macrolactone was seen to form with no decomposition product. The mechanism for forming a macrolactone is shown in Scheme 79, using simplified models to demonstrate the order of events. The first step (Equation [1]) is the addition of the carboxylate A to the carboxylic acid chloride B, forming the tetrahedral intermediate C, which on addition of triethylamine eliminates triethylamine hydrochloride to form the mixed anhydride D. In Equation [2], DMAP E attacks at the least hindered carbonyl site of D. As it is a stronger nucleophile than the alcohol, the newly formed intermediate is less hindered and DMAP E leaves, generating the product H.

Scheme 79: General Mechanism of the Yamaguchi Macrolactonisation.

With the success experienced by other groups in utilising the Yamaguchi protocol for forming macrolactones, we were confident that this procedure would be more than suitable for use with our seco-acid. Treatment of seco-acid 218 under standard Yamaguchi conditions afforded the desired macrolactone 227 in 37% yield (Scheme 80). This was an excellent result for a first attempt and for a reaction performed on a test scale.
In an attempt to increase the macrolactonisation yield, we explored the use of MNBA. 2-Methyl-6-nitrobenzoic anhydride (MNBA, Figure 22) is an effective condensation reagent for the DMAP promoted lactonisation of \( \omega \)-hydroxycarboxylic acids, as reported by Shiina and co-workers.\(^{116}\) The reagents can produce comparable yields to the Yamaguchi conditions\(^{117}\) but the experimental procedure is far simpler. Unfortunately, cyclisation of seco-acid 218 to 227 could only be achieved in 28% yield using MNBA (Scheme 80).

There are other potential methods that would allow the macrolactonisation of seco-acid 218. The Keck coupling\(^{118a}\) uses a combination of a dialkyl carbodiimide, an amine hydrochloride and an amine base under high dilution to form the activated ester intermediate which then macrolactonises, generating \( N, N' \)-dialkyurea as a by-product.

Another alternative is the Corey-Nicolaou macrolactonisation.\(^{118b}\) This is a double activation method which forms the lactone from its seco-acid via 2-pyridinethiol esters. The reaction occurs under neutral and aprotic conditions.
and under high dilution to keep the undesired intermolecular ester formation low (Scheme 82).

Scheme 82: General Formula for the Corey-Nicolaou Macrolactonisation.

Mukaiyama’s lactonisation conditions\textsuperscript{[37]} (Scheme 83) were employed by Tatsuta and colleagues\textsuperscript{[36]} in the final stages of their total synthesis of LL-Z1640-2 to generate the lactone from the seco-acid (Chapter 1, Scheme 7). 1-Methyl-2-chloropyridinium iodide (4 eq.) in anhydrous acetonitrile is stirred and a solution of seco-acid and triethylamine (8 eq.) in acetonitrile added over 8 hours under high dilution.

Scheme 83: General Formula for the Mukaiyama Macrolactonisation.

The Mitsunobu reaction is a versatile and effective reaction used extensively in organic synthesis (Scheme 84). It was reported in 1967\textsuperscript{[44]} that secondary alcohols could be acylated with carboxylic acid in the presence of DEAD and triphenylphosphine and later that optically active secondary alcohols underwent complete inversion of configuration under the conditions. Currently, the Mitsunobu reaction is widely known and described as the substitution of primary and secondary alcohols with nucleophiles in the presence of a dialkyl azodicarboxylate and a trialkylphosphine.

Scheme 84: General Scheme for the Mitsunobu Reaction.
The first step of the assumed mechanism for the lactonisation is the irreversible addition of triphenylphosphine to DEAD (Scheme 85, Equation [1], A). The phosphine adds to the weak N=N π bond to give an anion stabilised by one of the ester groups. The zwitterionic adduct B formed is basic enough to then be able to abstract a proton from the carboxylic acid of hydroxy acid C, which substitutes as the strong nucleophile, to form products D and E.

\[
\text{[1]} \quad \text{[2]}
\]

Scheme 85: General Mechanism of Macrolactonisation via a Mitsunobu Reaction.

Oxygen and phosphorus have a strong affinity and so the alcohol of E immediately attacks the positively charged phosphorus atom of D (Scheme 85, Equation [2]). The anion of the nucleophile attacks the phosphorus derivative of the alcohol G in a normal S_{N}2 reaction at carbon, with phosphine oxide as the leaving group. This furnishes the lactone product H with inversion of the methyl group and phosphine oxide as the side-product.

Sellès and Lett\[^{[41]}\] used a Mitsunobu reaction to carry out the macrolactonisation of their hydroxy acid. At room temperature at 0.007 M the desired macrolide was obtained in a good yield of 67%. Importantly there was complete inversion of configuration at C_{10}, with no change of configuration at C_{6} (MPM protected in their case). The simple experimental procedure associated with the Mitsunobu reaction makes it attractive and it was considered useful to attempt the reaction with our hydroxy acid to test the procedure in our hands. Treatment of seco-acid 218 under Mitsunobu conditions afforded the desired macrolide 228 in
71% yield (Scheme 86). Despite being run on a small scale there was enough material to progress with and test the following transformations.

![Chemical structures](image)

**Scheme 86: Final Steps to LL-Z1640-2.** Reagents and Conditions: (a) DEAD, PPh₃, toluene, 0 °C → rt, 30 min, 71%; (b) TBAF, THF, 0 °C → rt, 1.25 h, 100%; (c) PCC, CH₂Cl₂, rt, 3.5 h, 20%; (d) 1 N HCl, MeOH, rt, 46 h.

Removal of the TIPS ether was undertaken with TBAF, cleanly generating secondary alcohol 229 in quantitative yield. Due to the small scale and from the relatively clean ¹H NMR spectrum, it was decided not to proceed with any purification and the crude product was carried directly to the next step. Turning our attention to the oxidation of the secondary alcohol 229, we chose to firstly attempt the reaction using pyridinium chlorochromate (PCC). Chromium (IV) reagents are conveniently used to oxidise alcohols to their corresponding aldehydes or ketones. They are convenient to use as they are soluble in dry organic solvents, usually dichloromethane for PCC, under anhydrous conditions. Alcohol 229 was treated with PCC and careful TLC analysis mapped the reaction, showing it to be progressing well over time, with the disappearance of the starting material and the gradual appearance of ketone 230. Following purification, ketone 230 was isolated in 20% yield. Regrettably, the lack of material prevented the acquisition of a full data set to absolutely confirm the product.

It was envisaged from the beginning that the MOM ether and acetonide protecting groups could be cleaved simultaneously under mild acidic conditions, with literature precedent reinforcing this theory. Keck and co-workers[^120] have reported using DOWEX-H⁺ resin in methanol at 70 °C to remove MOM and acetonide groups. Though they had experienced success previously, they found...
that in the reported case the conditions did not achieve the deprotection, even under higher temperatures and longer reaction times. They went on to find that BF$_3$·OEt$_2$ in CH$_2$Cl$_2$ was effective at removing both groups (Scheme 87).

Scheme 87: Keck’s Removal of Acetonide and MOM Protection Using DOWEX-H$^+$. 

Andrus and Shih$^{[121]}$ also reported their use of DOWEX resin in methanol, but at room temperature, to achieve the one step removal of both groups (Scheme 88).


In 2002, Kiyota, Ley and co-workers$^{[122]}$ reported, as part of their efforts to the synthesis, structure revision and absolute configuration of (+)-didemniserinolipid B, the simultaneous removal of the acetonide, BDA, Boc and MOM protecting groups. This was accomplished in one step using 1 N HCl in ethanol at 45 °C to obtain the fully deprotected target compound (Scheme 89).

Scheme 89: Kiyota and Ley’s Simultaneous Removal of Acetonide, BDA, Boc and MOM Protection Using 1 N HCl.
In his total synthesis of aigialomycin D, Danishefsky successfully performed the final global acidic deprotection (two MOM functions and an acetonide) using 0.5 N HCl in methanol.\textsuperscript{[76]} Vu also used HCl in methanol for global deprotection of the same compound, in his approach to the natural product.\textsuperscript{[100]} The reaction was slow and extended into days for completion, but ultimately was successful with Danishefsky reporting a yield in excess of 90\% (Scheme 90).

![Scheme 90: Generation of Aigialomycin D via Global Acidic Deprotection.](image)

For our first attempt at the global deprotection of 230, we chose the milder conditions of 1 N HCl in methanol at room temperature. Acutely aware of the long reaction time that may be required for the completion of the deprotection, it was thought responsible to start out with the mildest conditions, which may allow us to see clearly the deprotection proceeding by TLC. It also gave us the option of heating the reaction to accelerate a slow rate. Over the course of 46 hours, careful TLC analysis showed disappearance of the protected compound 230 and appearance of two new spots. It was presumed that cleavage of one protecting group was occurring faster than the other. Unfortunately, the small scale of the reaction and the lack of material prevented us from performing FCC to isolate each spot and hence determine the structure of the compound corresponding to each spot. Likewise, the lack of material prevented the acquisition of adequate NMR spectra for analysis.

It goes without saying that for a total synthesis to a natural product to be as successful as possible, as many methods as possible affording the best reliability and yields need to incorporated. With this in mind and taking into account the outcome of the Mitsunobu reaction, it naturally prompted us to seriously review our strategy as it became clear that a minor change in our already established synthesis could enable the very successful Mitsunobu reaction to be integrated into the route to LL-Z1640-2. Although we were able to generate the required product with the correct stereochemistry at C\textsubscript{10}, \textit{via} the Yamaguchi protocol in
acceptable yield and later via a procedure using MNBA in lower yield, we were disappointed that our pivotal step was not as fruitful as first hoped. The Mitsunobu protocol has several distinct advantages over other macrolactonisation methods:

1. Fast reaction time
2. Simple procedure
3. High dilution
4. High yield
5. Clean conversion
6. No side-products
7. Complete inversion of stereochemistry

2.12 Final Synthetic Route to LL-Z1640-2

The stereochemistry at C$_{10'}$ is introduced as a direct result of the one pot Swern oxidation-Grignard acetylide addition of alkyne 223. The Mitsunobu reaction later in the synthesis then serves to completely invert the stereochemistry of the methyl group at C$_{10'}$. Quite reasonably, if the stereochemistry of 223 was changed from $S$ to $R$, then the already proven higher yielding Mitsunobu lactonisation would not only generate the macrolide, but in doing so would simultaneously invert the stereochemistry to afford the desired $S$-configuration. TIPS ether cleavage, oxidation and global deprotection would complete the total synthesis of LL-Z1640-2.

The synthesis of the seco-acid epimer 239 began with lithium acetylide ethylenediamine, which was treated with $(R)$-$(+)$-propylene oxide 232 to afford the crude alcohol 233 (Scheme 91). The crude alcohol was then immediately protected to generate terminal alkyne 234 in 40% over two steps. We chose to continue with the PMB protecting group due to its proven stability throughout the remainder of the synthesis and its relative ease of cleavage.

![Scheme 91: Synthesis of 1-Methoxy-4-((R)-1-methyl-but-3-ynloxy)methyl)-benzene.](image)

Reagents and conditions: (a) lithium acetylide ethylenediamine complex, DMSO, 0 $^\circ$C $\rightarrow$ rt, 48 h; (b) NaH (60% in mineral oil), PMBCl, DMF, 0 $^\circ$C $\rightarrow$ rt, 17 h, 40% (over 2 steps).
Alkyne 234 was deprotonated with ethylmagnesium bromide and the resulting anion was added directly to a solution of freshly generated aldehyde (212→224) at −78 °C. Pleasingly, the Grignard acetylide added cleanly to the aldehyde, affording propargylic alcohol 235 in 75% yield, an increase of 10% from the previous addition. Similarly, the product was an inseparable mixture of diastereoisomers (Scheme 92). A TIPS ether was again used as the protecting group for the newly formed secondary alcohol as it had proven to be stable to later conditions and was easily removed using TBAF. Protection of alcohol 235 using TIPSCI and imidazole proceeded slowly like before and did not go to completion despite multiple attempts and a "recycling" procedure was employed. With the fully protected compound 236 in hand, selective hydrogenation was performed to generate the $\text{Z}$-olefin 237 in an excellent 89% yield. Removal of the PMB protecting group with DDQ in CH$_2$Cl$_2$ and pH 7 buffer at room temperature afforded alcohol 238 in 87% yield, which was a much more acceptable yield than the 77% gained previously. Saponification of the ester was again achieved using 2 N KOH in ethanol and after 48 hours under reflux, seco-acid 239 was generated in 61% yield.
Scheme 92: Final Synthesis to LL-Z1640-2. Reagents and Conditions: (a) (COCl)$_2$, DMSO, Et$_3$N, –78 °C → rt; (b) 234, THF, –78 °C → rt, 16 h, 75%; (c) TIPSCl, imidazole, DMF, rt, 19 h, 80%; (d) H$_2$, Pd/BaSO$_4$, quinoline, MeOH, rt, 2 h, 89%; (e) DDQ, CH$_3$Cl$_2$, pH 7 buffer, rt, 18 h, 87%; (f) 2 N KOH, EtOH, 80 °C, 48 h, 61%; (g) DEAD, PPh$_3$, toluene, 0 °C → rt, 10 min, 73%; (h) TBAF, THF, 0 °C → rt, 1 h; (i) PCC, CH$_3$Cl$_2$, rt, 18 h, 34%; (j) 1 N HCl, MeOH, rt, 5 d.

Mitsunobu macrolactonisation of seco-acid 239 afforded the macrocyclic lactone 227 in 73% yield. Cleavage of the TIPS ether was undertaken using TBAF to unmask the secondary alcohol 226, which was used without further purification. Oxidation of 226 with PCC generated lactone 225 in 34% yield, but once again the small quantities of material obtained prevented the attainment of a complete data set. This extreme lack of material meant that treatment of lactone 225 with 1 N HCl was not fruitful. It could be seen by TLC that a reaction was occurring, with two new spots forming like before, but the reaction did not go to completion. $^1$H NMR was not able to clarify if any of the globally deprotected product 15 had formed. Due to time constraints we were unable to synthesise more compound 225 and had to relinquish the opportunity to test the global deprotection further.
2.13 Further Investigation and Additional Studies

2.13.1 Alternative Retrosyntheses to LL-Z1640-2

As an alternative retrosynthesis to that shown in Scheme 74, we hypothesised that following the one-pot oxidation-alkyne coupling, the free hydroxyl of 242 could be oxidised readily to ketone 243. This could be followed by saponification of the ester to afford acid 241 (Scheme 93). The reduction of the alkyne and removal of the PMB ether would afford the seco-acid 240, which after macrolactonisation would yield the desired macrocycle with the lactone already in place. All that would remain would be removal of the MOM ether and acetonide protection groups, achievable in one step. The only concern was regarding whether the saponification would proceed in the presence of the ketone as deprotonation may occur at the position α to the ketone.

![Scheme 93: First Possible Route.](image)

In the second possible route (Scheme 94) it was envisaged that the free hydroxyl of 242 could be oxidised readily to the ketone 243, after which the proceeding transformations would take place, culminating in the saponification of the ester to the carboxylic acid 240. This seco-acid would then undergo macrolactonisation and the enone would already be in place.
Both methods described above are advantageous. The benefits of oxidising the alcohol at position C$_6$ earlier on in the synthesis, include the loss of a stereocentre and simplification of the NMR spectra.

The final option is the direct saponification of secondary alcohol 242. There were concerns about this method in the guise of whether the secondary alcohol could be oxidised in the presence of a carboxylic acid. There was also some apprehension regarding the possibility of spontaneous cyclisation of the alcohol moiety onto the acid functionality.

### 2.13.2 Practical Studies

Oxidation of secondary alcohol 198 or 222 to ketone 245 or 246 respectively, proceeded smoothly and quantitatively under Swern oxidation conditions, with no need for any purification following work-up (Scheme 95). In the $^1$H and $^{13}$C NMR spectra both showed clearly the disappearance of the alcohol and the newly formed carbonyl function of the ketone. Ester hydrolysis was then attempted.
Scheme 95: Oxidation then Saponification Method. Reagents and Conditions: (a) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, 2 h, –78 °C → rt, quant..

Alkali metal trimethylsilanolates (TMSO$^-\text{M}^+$) have been used widely for the efficient conversion of methyl esters to their acid salts under mild, non-aqueous conditions. In comparison with other oxygen anions they are advantageous in that they have good solubility in organic solvents, such as dichloromethane and diethyl ether. Encouraged by this and also the work published by Still and co-workers$^{[123]}$ which shows the hydrolysis of esters using TMSOK. Unfortunately the saponification of ketone 245 was unsuccessful under TMSOK conditions. A characteristic colour change was observed on addition of TMSOK, but after prolonged stirring at room temperature no product 247 was witnessed. This was confirmed after work-up when $^1$H NMR analysis still showed the clear presence of the methyl ester signal at 3.87 ppm. Treatment of ester 246 under basic hydrolysis conditions (aq. KOH) also failed to hydrolyse the group to form 248. Despite this, it was pleasing to see that the TBS ether was unaffected by both sets of conditions and remained in place throughout.

We tested whether the ester functionality of the newly generated secondary alcohol 222 can be directly saponified to allow the acid to be in place throughout the future transformations (Scheme 96). Even after 48 hours under reflux there was no reaction observed, likewise there was no appearance of spontaneous cyclisation or side reactions and the unreacted starting material was recovered.
During the studies described thus far we have simultaneously been considering and reviewing each step of the synthesis in order to determine whether it could be improved upon. The routes to aromatic fragment 210 and alkene 208 are well established and robust and although the cross-metathesis step between the two is successful, there are disadvantages associated with it:

- Long reaction time, 48 hours
- Difficult and time consuming purification requiring two successive flash column chromatography steps
- High catalyst loading
- High cost of catalyst

It has been found when repeating the reaction that the yields were not consistent and so this step was identified as holding potential for improvement. We did not wish to deviate from our original synthesis too much, so bearing this in mind we envisaged a Stille coupling between tin derivative 250 and aromatic unit 257. The tin derivative is easily prepared in four steps from alkene 208, which has already been efficiently made. A version of the aromatic fragment has already been made and only simple deviation from the original route is necessary.

### 2.13.3 Stille Coupling

The Stille reaction is one of the most influential synthetic tools in organic chemistry. First reported in 1978,\textsuperscript{[124]} the Stille coupling is the coupling between an organostannane and an organic electrophile to form a new C–C sigma bond and has been widely used for the palladium(0)-catalysed coupling of both aromatic and vinylic units (Scheme 97).
There are numerous advantages associated with the Stille coupling including the mild conditions and the fact that the precursor organotin compounds tolerate a wide variety of functional groups and are not sensitive to moisture or oxygen. On the other hand there is a distinct disadvantage due to their toxicity and the difficulty in removing all traces of tin from the reaction mixture and also the major side reaction of homocoupling of the organostannane reagent.

The detailed mechanism is still prone to discussion but the basic catalytic cycle (Figure 23) was proposed in 1979.\textsuperscript{[125]} Oxidative addition of the vinyl/aromatic triflate/halide gives a palladium(II) intermediate, which undergoes transmetallation with the prepared organostannane. This gives an organopalladium intermediate which then undergoes a reductive elimination step, releasing the product and palladium(0) catalyst.

Triflates are often used due to their ease of preparation, but typically lithium chloride is added to the reaction mixture because the triflate is a counter ion and is not bound to the metal as a ligand (Scheme 98). If transmetallation is to occur another ligand must be added to give the necessary square coplanar geometry. The catalyst is a 14 e\textsuperscript{−}, Pd(0) complex and those used commonly are Pd(PPh\textsubscript{3})\textsubscript{4}, Pd(dba)\textsubscript{2} and Pd(II) catalysts such as Pd(OAc)\textsubscript{2}, PdCl\textsubscript{2}(MeCN)\textsubscript{2} and PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} can also be used as precursors.
2.13.4 Retrosynthetic Analysis to tert-Butyl-[(4R,5S)-2,2-dimethyl-5-((E)-3-tributylstannyl-allyl)-[1,3]-dioxolan-4-ylmethoxy]-dimethylsilane, 250

As demonstrated in Scheme 99, it was hypothesised that vinylstannane could come from hydrostannylation of alkyne 70 which is the product of a Corey-Fuchs procedure from aldehyde 252 via dibromoolefin 251. Aldehyde 252 is the direct result of ozonolysis of alkene 208.

2.13.5 Synthesis of tert-Butyl-[(4R,5S)-2,2-dimethyl-5-((E)-3-tributylstannyl-allyl)-[1,3]-dioxolan-4-ylmethoxy]-dimethylsilane, 250

As discussed previously, silyl-protected alkene 208 can be made readily in three steps from 2-deoxy-d-ribose 179. Continuation of the synthesis from alkene 208 is shown in Scheme 100.
Scheme 100: Synthesis of tributylstannane 250. Reagents and Conditions: (a) O₃, CH₂Cl₂, −78 °C, 15 min then DMS, −78 °C → rt, h, 100%; (b) CBr₄, PPh₃, Zn dust, CH₂Cl₂, rt, 1.5 h, 100%; (c) nBuLi, THF, −78 °C, 2 h then H₂O, −78 °C → 0 °C–rt, 61%; (d) PdCl₂(PPh₃)₂, Bu₃SnH, THF, 30 min, rt, 79%.

The first step following formation of the alkene is the formation of the aldehyde unit 252. A classic method of transforming terminal olefins to aldehydes is through ozonolysis. Ozonolysis is a 1,3-diolar cycloaddition, which cleaves π bonds oxidatively so two carbonyl groups are formed. The procedure uses ozone which is a symmetrical molecule with a positively charged oxygen and two terminal oxygen atoms which share a negative charge (Figure 24).

Mechanistically, the first step involves a 1,3-dipolar cycloaddition to generate molozonide. The unstable molozonide decomposes instantly by a reverse 1,3-dipolar cycloaddition (Scheme 101, Equation [1]). The newly formed 1,3-dipole adds to the aldehyde in a second cycloaddition step to generate an ozonide. Dimethylsulfide is typically used to reduce the ozonide to give DMSO and two molecules of aldehyde (Scheme 101, Equation [2]).
Ozonolysis of alkene 208 gave the desired aldehyde 252 with no need for purification, based on $^1$H analysis of the crude material. The ozonolysis has been carried out on both milligram and multigram scales, with the unstable ozonide quenched with dimethylsulfide. This was a lengthy process and required a high excess of DMS (approximately 450-500 equivalents), added periodically over a prolonged period (typically 3-5 days), in order for complete conversion to the aldehyde. With aldehyde 252 in hand the next step was the transformation into terminal alkyne 70, utilising the well-known and reliable Corey-Fuchs reaction.[126]

The Corey-Fuchs conversion of an aldehyde into a terminal alkyne calls for two steps, initial generation of the dibromoolefin and the sequential elimination of HBr and reduction of the bromoalkyne. The first step can be achieved in two possible ways: (1) the aldehyde is added to a mixture of PPh$_3$ and CBr$_4$ in CH$_2$Cl$_2$ at 0 ºC; (2) zinc dust, PPh$_3$ and CBr$_4$ are mixed together in CH$_2$Cl$_2$ at ambient temperature and then the aldehyde is added to this mixture. This first step is comparable to the Wittig reaction and yields are generally high (80-90%).

The second step of the procedure is the conversion of the dibromoolefin to the terminal alkyne which is achieved by treatment with $n$BuLi in THF at $-78$ ºC to promote lithium-halogen exchange. This firstly rapidly forms the lithio derivative of the alkyne (lithium acetylide) which upon protonation produces the desired terminal alkyne.

Scheme 102, Equation [1] shows the first steps of the mechanism in which the phosphorus ylide is generated and then Equation [2] shows reaction of this ylide with the aldehyde in a manner analogous to the Wittig reaction. The mechanism for the conversion of the dibromoolefin to the alkyne is for the most part unknown but is thought to proceed as shown in Equation [3]. The sequential attack of two equivalents of $n$BuLi forms the lithium acetylide which after hydrolysis generates the terminal alkyne.
To begin with, an aldehyde model system was used to test and establish the conditions required for formation of the alkyne. Gratifyingly, the Corey-Fuchs reaction of the model system 253 proceeded cleanly to generate alkyne 255, via the dibromoolefin 254 (Scheme 103).\[^{[127]}\]

![Scheme 102: Mechanism of the Corey-Fuchs Reaction.](image1)

![Scheme 103: Test Corey-Fuchs Reaction.](image2)

Unfortunately, under the same conditions, aldehyde 252 proved slightly more troublesome than expected and required a little optimisation. However, treatment of aldehyde 252 under the zinc-mediated olefination conditions\[^{[128]}\] afforded the dibromoolefin 251 in quantitative yield. The newly generated dibromoolefin was treated with nBuLi to generate alkyne 70 in 61% yield after purification. It is worth mentioning that column purification is not required in every instance. The decision on whether to perform FCC was taken after viewing the \(^1\)H NMR spectrum of the crude residue.
2.13.6 Hydrostannylation

Organostannanes are of tremendous synthetic utility as building blocks in organic chemistry due to the considerable number of C–C bond forming reactions these intermediates undergo. There are three main ways of forming a carbon-tin (C–Sn) bond:

1. Reaction of a tin-metal compound ($R_3$-SnM) with an alkyl halide
2. Reaction of an organometallic with a tin halide
3. Overall addition of a tin-hydride to an alkyne, alkene or allene.

Method three is widely used due to the mild, neutral conditions and consequently there are multiple ways for addition of tin hydride:

1. Hydrostannylation under free-radical conditions
2. Stannylation-protonation of an alkyne or alkene
3. Metal-catalysed hydrostannylation of an alkyne or alkene.

Tributyltinhydride was first synthesised in 1947 by Finholt\textsuperscript{129} and has since become one of the most popular organometallic and hydrostannation reagents in organic synthesis for the formation of vinyl- and allyl- stannanes, mainly due to its price and reactivity.\textsuperscript{130} The main problems for the stannylation of alkynes are the regio- and stereo-controls of the addition of the stannyl residue to the triple bond. $Bu_3$SnH is commercially available or can be prepared \textit{in situ} from $Bu_3$SnCl and Et$_3$SiH in the presence of Lewis acid catalysts.\textsuperscript{131}

Beginning from commercially available 2-deoxy-D-ribose, alkyne 70 can be readily obtained in six robust steps in 47% overall yield. With the desired alkyne in hand it was thought that it could undergo hydrostannylation to afford the \textit{E}-vinylstannane 250 (Scheme 104).

![Scheme 104: Formation of E-Vinylstannane 250.](image-url)
Disappointingly and frustratingly, this proved to be more problematic than initially anticipated and as a result various reaction conditions were attempted (Table 2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AIBN Bu₃SnH</td>
<td>Toluene</td>
<td>95 °C</td>
<td>24 h</td>
<td>85% E:Z + alkene 208</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh₃)₄ Bu₃SnH</td>
<td>CH₂Cl₂</td>
<td>0 °C to rt</td>
<td>20 min</td>
<td>68% E:Z + alkene 208</td>
</tr>
<tr>
<td>3</td>
<td>PdCl₂(PPh₃)₂ Bu₃SnH</td>
<td>THF</td>
<td>Room Temperature</td>
<td>20 min</td>
<td>79% E:Z</td>
</tr>
</tbody>
</table>

Table 2: Attempted Conditions for the Formation of (E)-Vinylstannane 250.

Radical hydrostannylation has been greatly studied and in general gives a mixture of stereoisomers with the regiochemistry controlled by the relative stability of the two possible intermediate β-stannyl radicals (Scheme 105).[^129] The method is now less employed for the hydrostannylation of alkynes as the regio- and stereo-selectivities cannot be anticipated in advance, but it is still a popular radical cyclisation reaction.[^130]

![Scheme 105: Radical Hydrostannylation](image)

Addition of azobis(isobutylxtrinitrile) (AIBN) and tributyltinhydride (Bu₃SnH) to alkyne 70 resulted in the formation of an E:Z-mixture of vinylstannane 250 and an unknown compound, later found to be alkene 208. The isomers and the alkene were inseparable, although the yield was a reasonable 85%, suggesting no loss of product through side reactions or degradation.

Stannylmetallation of alkynes can be separated into stoichiometric stannylcupration and stannymetallation in the presence of a transition-metal catalyst (Scheme 106, Equation [1]). In the case of alkynes, metal-catalysed
hydrostannylation usually occurs with \textit{cis}-stereoselectivity and good regioselectivity. Palladium is the most widespread catalyst for the hydrostannylation and under the reaction conditions, palladium(II) complexes are reduced to the catalytically active palladium(0) species (Scheme 106, Equation [2]).

\[
\begin{align*}
\text{[1]} & \quad R^1 \equiv R^2 & \rightarrow & \quad R_3^1 \text{SnH} & \quad \text{metal catalyst, solvent} \\
\text{[2]} & \quad \text{Pd(II)} & \quad 2R_3^1 \text{SnH} & \quad \rightarrow & \quad \text{Pd(0)} & \quad (R_3^1 \text{Sn})_2 & \quad \text{H}_2
\end{align*}
\]

Scheme 106: General Equation for the Hydrostannylation of Alkynes.

In the first instance, stannylation of alkyne 70 was attempted using tributyltinhydride (Bu$_3$SnH) and tetrakis(triphenylphosphine)palladium(0) (Pd(PPh$_3$)$_4$). This also resulted in an inseparable \textit{E}:\textit{Z}-mixture of product 250 and alkene 208, in slightly lower yield of 68%. Additionally, PdCl$_2$(PPh$_3$)$_2$ was utilised as the catalyst and Bu$_3$SnH added. By this stage, after intense investigation, a solvent system had been found to enable the separation of the \textit{E}:\textit{Z}-product 250 from the alkene 208. As a result, a final yield of 79% was obtained.

2.13.7 Synthesis of Methyl 4-methoxy-2-(methoxymethoxy)-6-(trifluoromethylsulfonyloxy)benzoate, 257

With the kind provision of gram quantities of fully protected aromatic compound 119 by Dr M. N. Robertson we were able to by-pass the initial stages of the synthesis. Deprotection of silyl ether 119 under standard conditions afforded phenol 256 in high yield (Scheme 107). Reprotection of the alcohol as its MOM ether, using MOMBr and Hunig’s base, was extremely fruitful and the desired fully protected aromatic unit 257 was obtained in 90% yield.

\[
\begin{align*}
\text{119} & \quad \xrightarrow{a} \quad \text{256} \quad \xrightarrow{b} \quad \text{257}
\end{align*}
\]

Scheme 107: Synthesis of Aromatic Fragment 257. Reagents and Conditions: (a) TBAF, THF, 0 °C $\rightarrow$ rt, 2 h, 83%; (b) MOMBr, DIPEA, CH$_2$Cl$_2$, 0 °C $\rightarrow$ rt, 18 h, 90%.
Despite the mixture obtained as result of hydrostannylation of alkyne 70, it was decided that, rather than disregard the material, it would be used in an attempt to couple the triflate 257 (Scheme 108). In 2004, Baldwin[132] reported that combining copper(I) iodide and cesium fluoride can significantly enhance the Stille reaction coupling with aryl halides and triflates. These conditions were employed for our coupling partners, but despite promising TLC analysis, filtration of the reaction through Celite® was non-trivial and the subsequent ¹H NMR spectrum of the crude material showed no coupled product. Disappointingly, none of the other attempted modified procedures gave any of the desired product. In addition, the attempted coupling of triflate 257 and vinylstannane 250 with Pd(PPh₃)₄ and lithium chloride in 1,4-dioxane at 100 °C, was also unsuccessful.

![Scheme 108: Attempted Stille Coupling of Triflate 257 and Vinylstannane 250.](image)

Faced with a rapidly depleting supply of alkyne 70, we chose to use 3-butyln-1-ol 258 as a model system. The primary alcohol was protected as its TBS silyl ether under standard conditions in 82% yield (Scheme 109). TBS alkyne 259 was then subjected to a number of conditions to introduce the stannyl unit (Table 3).

![Scheme 109: Synthesis of E-Vinylstannane 260.](image)

The most successful conditions were using AIBN and Bu₃SnH (Table 3, Entry 5) giving vinylstannane 260 as an E:Z-ratio of 79:21 and quantitative yield. This result is comparable to the literature,[133] where the authors achieved an inseparable 90:10 mixture of the E- and Z-vinylstannanes.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>CuCN, nBuLi, Bu$_3$SnH</td>
<td>THF</td>
<td>-78 °C</td>
<td>~2 h total</td>
<td>![SnBu$_3$OTBS]</td>
</tr>
<tr>
<td>2</td>
<td>Bistributyl tin, CuCN, nBuLi, MeOH</td>
<td>THF</td>
<td>-78 °C</td>
<td>18 h</td>
<td>No product</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh$_3$)$_4$, Bu$_3$SnH</td>
<td>CH$_2$Cl$_2$</td>
<td>Room Temperature</td>
<td>10 min</td>
<td>Mix 3 products</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh$_3$)$_4$, Bu$_3$SnH</td>
<td>THF</td>
<td>Room Temperature</td>
<td>10 min</td>
<td>Mix 3 products</td>
</tr>
<tr>
<td>5</td>
<td>AIBN, Bu$_3$SnH</td>
<td>Toluene</td>
<td>80 °C</td>
<td>1.5 h</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>79:21 E:Z</td>
</tr>
</tbody>
</table>

Table 3: Attempts at the Synthesis of 260.

When palladium-catalysed conditions were employed (Table 3, Entry 3 and 4), a quick reaction time was observed. Unfortunately, the crude $^1$H NMR spectrum showed a mixture of three products 261, 262 and 263 (Figure 25).

![Figure 25: Products Obtained When Using Palladium-Catalysed Conditions.](image)

The stannylcupration of acetylenes was first discovered in 1981 when Piers and colleagues found that a trimethylstannyl copper or cuprate reagent added to acetylenic esters.$^{[134]}$ Reaction of (trialkylstannyl)cuprates with terminal alkynes proceeds with high regio- and stereoselectivity via a vinylcopper intermediate. Stannylcupration of terminal alkyne 259 with the mixed organocuprate Bu$_3$Sn(Bu)CuCNLi$_2$,$^{[130]}$ using two different reaction conditions gave mixed results. Both methods are involved and intricate procedures and while CuCN, nBuLi and Bu$_3$SnH in THF gave exclusively 262, CuCN, nBuLi, bistributyltin and methanol in THF gave no product whatsoever. Despite this, ongoing thought and investigation led to the attempt of the Stille coupling of vinylstannane 260 with aromatic triflate 119.
The reaction proceeded with 3 mol% of Pd(PPh₃)₄ in 1,4-dioxane at 100 °C over four days. The product was obtained as the pure E-isomer but disappointingly, the yield of product 263 was only 21%. However, we were optimistic about the potential of the conditions. As well as using triflates for palladium(0) catalysed couplings, iodides are also widely used. With this in mind, studies commenced into determining whether the corresponding aryl iodide would be a more effective coupling partner than the aryl triflate 119. Aryl triflates can be readily converted into iodides through treatment with NaI in DMF at 80 °C.\[^{135}\]

Upon applying these conditions to aryl triflate 119, the TBS protecting group was also cleaved during the transformation. Taking advantage of this, phenol 264 was protected as its MOM ether 18 in 98% yield (Scheme 111).

Both PdCl₂(PPh₃)₄ and Pd(PPh₃)₄ were used in our attempts to couple iodide 18 and vinylstannane 260 (Scheme 112). Progression of the reactions was followed by TLC analysis and to begin with there appeared to be the formation of a new product with the slow consumption of starting materials. Despite the promising beginning, after work-up and subsequent FCC to isolate the newly formed spot, no desired product was identified.
2.13.8 Sonogashira Couplings

An alternative to using a Stille coupling involved the use of a Sonogashira coupling.\[^{[39]}\] This would directly couple alkyne \(70\) to aryl triflate \(257\) (Scheme 113).

We were extremely hopeful about the Sonogashira coupling as there is ample literature precedence demonstrating its usefulness in coupling terminal alkynes and aryl/vinyl halides (Scheme 114).

The Sonogashira coupling is catalysed by two catalysts; a palladium(0) complex and a copper(I) co-catalyst. The palladium complex activates the organic halides by oxidative addition into the carbon-halogen bond. The copper co-catalyst reacts with the terminal alkyne and produces copper(I) acetylide, which acts as an activated species for the coupling reactions. The reaction conditions must be anhydrous, although newer procedures have been developed that increase its versatility. Liang and co-workers,\[^{[136]}\] have developed a copper-free procedure where the Sonogashira coupling takes place with PdCl\(_2\) in water under...
aerobic conditions. Mori’s procedure\textsuperscript{[137]} on the other hand, is carried out in aqueous ammonia, PdCl$_2$(PPh$_3$)$_2$ and copper iodide in THF. So as to neutralise the hydrogen halide by-product the reaction must be basic. Triethylamine and diethylamine are often used as solvents, though DMF and diethyl ether are also suitable.

The mechanistic cycle of the Sonogashira coupling is shown in Scheme 115. The first step involves the oxidative addition of palladium(0) A with the aryl halide/triflate to generate the Pd(II) complex B. The complex reacts in a transmetallation with the copper acetylide (produced in the copper cycle) to complex C, ejecting the copper halide F. Trans-cis isomerisation of the ligands form complex D.

\[ \text{Scheme 115: Mechanism of the Sonogashira Coupling.}\textsuperscript{[138]} \]

Regrettably, all coupling attempts using alkyne 70 and aryl triflate 257 failed to yield any of the desired product (Scheme 113). Interestingly, the Sonogashira coupling of the silyl-protected alkyne model system 259, with either aryl triflate 119 or aryl iodide 267, proved futile (Scheme 116). It served only to afford unreacted starting materials.
Scheme 116: Sonogashira Coupling of Aryl Triflate 119 or Aryl Iodide 267 and Terminal Alkyne 259. Reagents and Conditions: PdCl$_2$(PPh$_3$)$_2$, Cul, Et$_3$N, CH$_3$CN, rt.

The fact that the Stille couplings were more promising than the Sonogashira couplings, made us hopeful that a tributylstannane might prove more reactive. Treatment of alkyne 259 with nBuLi and Bu$_3$SnCl gave the desired stannane 269, which was found to be unstable and had to be used immediately in the next step (Scheme 117).

Scheme 117: Activation of Alkyne 259 and Subsequent Coupling Attempt. Reagents and Conditions: (a) nBuLi, THF, 0 °C, 1 h then Bu$_3$SnCl, 0 °C → rt, 19 h, 69%; (b) LiCl, Pd(PPh$_3$)$_4$, 1,4-dioxane, 100 °C, 4.5 h, 33%.

Stannane 269 was successfully coupled with aryl triflate 119 to afford the desired coupled product 268 in 33% yield. Despite the relatively low yield, the result was both pleasing and encouraging. With this product in hand, our attention could now turn to reduction of the triple bond to the E-double bond. Unfortunately, literature searches did not yield any procedures for doing this. A possibility was to use Na/NH$_3$, but due to the functionality already present and the nature of the compound this was not deemed suitable. As an alternative, the triple bond could be reduced to the Z-alkene using Lindlar's catalyst. Once the Z-double bond has been generated, a double bond isomerisation could be performed. Once again we elected to use a model substrate in order to test the reaction conditions (Scheme 118). 3-Iodoanisole 270 was coupled with propargyl alcohol 271 in the presence of PdCl$_2$(PPh$_3$)$_2$, copper(I) iodide and triethylamine to afford the desired internal alkyne 272 in 82% yield.
Scheme 118: Synthesis of Alkynol 272. Reagents and Conditions: (a) 271, PdCl₂(PPh₃)₂, CuI, Et₃N, CH₃CN, rt, 16 h, 82%.

The reduction of alkynol 272 proved to be slightly more complicated than originally expected. Treatment of alkynol 272 with Pd/BaSO₄ and quinoline led to over-reduction to give the completely saturated product 273 (Scheme 119). Reduction of alkynol 272 using Pd(OAc)₂, NaOMe and PPh₃ also failed to give any of the desired product.[141]

Scheme 119: Over-reduction of Alkynol 272 to Alkane 273. Reagents and Conditions: (a) H₂, Pd/BaSO₄, quinoline, MeOH, 2 h, 72%.

Seeking to remove the risk of the hydroxyl group coordinating to the palladium and aiding in the over-reduction, the hydroxyl group was protected as its silyl ether (Scheme 120). Hydrogenation of the silyl ether 274 was then carried out in two simultaneous reactions. One reaction was stopped after 30 minutes and the other after 60 minutes. After 30 minutes, the ¹H NMR spectrum showed an inseparable mixture of starting alkyne 274, desired alkene 275 and alkane 276. After 60 minutes alkane 276 was the only product.

Scheme 120: Protection of Alkynol 272 and Reduction of Alkyne 274. Reagents and Conditions: (a) TBDMSCl, DMAP, Et₃N, CH₂Cl₂, rt, 18 h, 78%; (b) H₂, Pd/BaSO₄, quinoline, MeOH, 30 min or 1 h.
Despite being a mixture, the reaction material isolated following the 30 minute procedure was taken in order to attempt isomerisation reactions (Scheme 121).

Scheme 121: Double bond Isomerisation of Alkene 275.

None of the conditions tried (PdCl₂(CH₃CN)₂ and Pd(OAc)₂/Bu₃SnH/Et₃N) were successful and didn't provide much scope for using this method as part of our synthesis. The C₁—C₂ double bond has been successfully isomerised successfully by Tatsuta and co-workers[^36] in their synthesis of LL-Z1640-2, though the palladium catalyst employed is expensive and time constraints prevented us from attempting this procedure.

As we had our Sonogashira product 268 in hand, we wanted to proceed and attempt the hydrogenation (Scheme 122). Treatment of alkyne 268 with Lindlar's catalyst afforded Z-olefin 278 in 52% yield, as confirmed by ^1^H and HRMS.

Scheme 122: Reduction of Alkyne 268. Reagents and Conditions: (a) H₂, Pd/BaSO₄, quinoline, MeOH, rt, 2 h, 52%.

At this point in the investigation, this particular route seemed to have hit a stumbling block due to the failure of the isomerisation reaction and so it was necessary to investigate alternative ways of introducing the E-double bond. Although Sonogashira product 268 can be achieved, the yield is low and it was postulated whether the aromatic ring may be too substituted. To test this theory, iodobenzoate 280 was synthesised from 2-iodobenzoic acid 279 using Fischer esterification[^142] and then coupled with alkyne 259 via a Sonogashira
coupling. The desired coupled product 281 was obtained in 71% yield (Scheme 123).

![Scheme 123: Formation of Iodobenzoate 280 and Subsequent Coupling. Reagents and Conditions: (a) H₂SO₄, MeOH, reflux, 7 h, 82%; (b) PdCl₂(PPh₃)₂, CuI, Et₃N, MeCN, rt, 2 h, 71%.

Takano and co-workers[143] showed that LiAlH₄ could selectively transform their alkyne 282 into the corresponding E-olefin 283 (Scheme 124). In our case, this would reduce the ester functionality, but if the alkyne could be reduced selectively then the formed alcohol could be converted back to the ester. In our hands the procedure wasn’t successful, with only trace amounts of alcohol 284 recovered from the reaction. The desired E-olefin 285 was not generated.

![Scheme 124: Alkyne Reduction Using LiAlH₄. Reagents and Conditions: (a) LiAlH₄, THF, reflux, 75 min; (b) LiAlH₄, THF, reflux, 24 h.

It was at this stage that time restraints were encountered and with no additional progress having been made, the focus turned to areas which could be further investigated and the practical work that could be pursued in the future.

2.14 Future Work

As noted previously, Carreira and colleagues published their facile synthesis of optically active propargylic alcohols 195 from aldehydes, using N-
methylephedrine 194 as the chiral additive, with 99% e.e. and good yields.\cite{91} When we came to employ these conditions for the addition of alkyne 55, we encountered problems regarding the stability of aldehyde 197. This was solved and overcome with the development of the one-pot procedure. The one pot oxidation-Grignard addition procedure, allowing the addition of the required alkyne unit to the freshly generated aldehyde, was highly successful but the $^1$H NMR spectra for this and subsequent reactions were rather complicated to interpret and assign. An ideal situation would be to enhance and improve the total synthesis by exploring further methods that would allow an asymmetric synthesis of propargylic alcohol 235. Following a search of the literature we became interested in two methods.\cite{144}

In 2005, Yamashita\cite{144a} published their findings based on the catalytic asymmetric alkynylation of aldehydes with terminal alkyynes by chiral alcohol (1$R$,2$R$)-2-(dimethylamino)-1,2-diphenylethanol 286 (Figure 26), which forms a more stable bimetallic complex 287 (than (+/-)$N$-methylephidrine) with no steric interactions.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure26.png}
\caption{Structure of (1$R$,2$R$)-2-(dimethylamino)-1,2-diphenylethanol 286 and its Bimetallic Complex 287.}
\end{figure}

The authors concluded that by employing a straightforward procedure and using 0.22 equivalents of chiral amino alcohol 286, zinc triflate (0.2 eq.) and triethylamine (0.5 eq.) in toluene at room temperature, they could bring about the asymmetric addition with the enantioselectivity reaching up to 98% (Scheme 125).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme125.png}
\caption{Example of Chiral Amino Alcohol Mediated Catalytic Asymmetric Alkynylation.}
\end{figure}
In 1994, Fujisawa\cite{144b} reported the use of zinc(II) bromide in the highly diastereoselective addition of acetylide to a chiral aldehyde. It is postulated that we could potentially apply the method to using our chiral terminal alkyne and aldehyde. The bromozinc acetylide is prepared from the lithium acetylide via transmetalation with ZnBr$_2$. The authors report a reaction time of 15 h, with an isolated yield of 81% and $>99:1$ syn:anti. Additionally, we would seek to investigate Carreira’s method further in the hope that optimisation would allow the reaction to proceed.

It was touched upon in 2.13.1 and 2.13.2 that the free hydroxyl of 242 could be oxidised readily to the ketone, after which the proceeding transformations would take place, culminating in the saponification of the ester to the carboxylic acid. This seco-acid would then undergo macrolactonisation and the enone would already be in place. As time and quantities of material didn’t allow the trial of this method but it would advantageous to attempt this in order to determine whether the enone can be in place throughout the following transformations. This would mean that when the seco-acid is subjected to macrolactonisation the product already has the enone in place and all that remains is the global deprotection.
3 Experimental

3.1 General Methods

All reactions were performed under an inert argon atmosphere unless otherwise noted. Reagents and starting materials were obtained from commercial sources and used as received, unless otherwise specified.

Anhydrous dichloromethane (DCM), diethyl ether, toluene and tetrahydrofuran (THF) were freshly obtained from in-house solvent purification system, Pure Solv 400-5MD (Innovative Technology, Inc). Anhydrous dimethylformamide (DMF) and triethylamine (TEA) were purchased from Aldrich Chemical Company. Petroleum ether refers to that with boiling fraction 40–60 °C. Solutions worked up were concentrated under reduced pressure at < 45 °C using a Buchi Rotavapor.

Melting points were determined using Stuart Scientific Melting Point SMP1 apparatus.

Optical rotations were determined as solutions irradiating with the sodium D line (λ = 598 nm) using an AA series automatic polarimeter. \([\alpha]_D\) values are given in units 10\(^{-1}\) deg cm\(^2\) g\(^{-1}\).

Infrared (IR) spectra were recorded as thin films on sodium chloride (NaCl) plates using a JASCO FTIR 410 spectrometer. Only significant absorptions (\(\nu_{\text{max}}\)) are reported in wavenumbers (cm\(^{-1}\)).

Proton magnetic resonance spectra (\(^1\)H NMR) were recorded at 400 MHz using a Bruker DPX-400 spectrometer for sample solutions in CDCl\(_3\), unless otherwise indicated. Chemical shifts (\(\delta_H\)) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The order of citation in parentheses is (1) number of equivalent nuclei (by integration) (2) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext. = sextet, oct. = octet, m = multiplet, br = broad) (3) coupling constant (\(J\)) quoted in Hertz to the nearest 0.1 Hz and (4) proton assignment. For relevant compounds, the OH signal was identified by D\(_2\)O exchange.
Carbon magnetic resonance spectra ($^{13}$C NMR) were recorded at 100 MHz using a Bruker DPX-400 spectrometer for sample solutions in CDCl$_3$, unless otherwise indicated. Chemical shifts ($\delta_C$) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. For larger, more complex compounds, the structure is shown with numbered carbon atoms to assist with the $^{13}$C assignment.

Mass spectra were obtained using a JEOL JMS-700 spectrometer.

TLC was performed on aluminium backed plates pre-coated with silica gel 60 (Kieselgel 60 F$_{254}$ aluminium plates, Merck) with A, petroleum ether-ethyl acetate (8:2); B, petroleum ether-ethyl acetate (7:3); C, petroleum ether-ethyl acetate (6:4); D, petroleum ether-ethyl acetate (9:1); E, petroleum ether-ethyl acetate (9.5:0.5); F, petroleum ether-diethyl ether (9.5:0.5); G, toluene-ethyl acetate (8:2); H, petroleum ether-ethyl acetate (2:8); I, petroleum ether-ethyl acetate (5:5); J, petroleum ether-ethyl acetate (3:7); K, chloroform-ethyl acetate (6:4); L, petroleum ether (10:0); M, petroleum ether-ethyl acetate (4:6); N, petroleum ether-diethyl ether (7:3); O, petroleum ether-ethyl acetate (2:8); P, petroleum ether-diethyl ether (9:1); Q, hexanes (10:0); R, petroleum ether-diethyl ether (8:2); S, petroleum ether-diethyl ether (5:5) as developers and detection under UV light ($\lambda_{\text{max}}$ 254 nm) and/or by staining with anisaldehyde, unless otherwise specified, followed by heating.

Flash column chromatography (FCC) was performed using Apollo Scientific silica gel 60 (0.040-0.063 mm), with the appropriate eluting solvent and elution gradient, shown in square brackets as part of the procedure, e.g. purification by FCC [petroleum ether-ethyl acetate (85:15)$\rightarrow$(75:25)$\rightarrow$(60:40)$\rightarrow$(50:50)] of the crude residue....

The following chemicals were used at the concentrations given, unless otherwise stated:

- tetra-Butylammonium fluoride (TBAF), 1 M in tetrahydrofuran
- Oxalyl chloride, 2 M in dichloromethane
- Ethyl Magnesium Bromide (EtMgBr), 3 M in diethyl ether
- Potassium bis(trimethylsilyl)amide (KHMDS), 0.5 M in toluene
- n-Butyllithium (nBuLi), 2.5 M in hexanes.
3.2 Synthesis and Characterisation of Compounds

**Methyl 2,4-Dihydroxy-6-methylbenzoate 169[^145a]**

Sodium hydride (5.16 g, 129 mmol, 60% dispersion in mineral oil) was washed with petroleum ether (2×10 cm³), suspended in anhydrous THF (50 cm³) and then cooled to 0 °C under an argon atmosphere. Methyl acetoacetate (9.3 cm³, 86.1 mmol) was then added dropwise, the solution cooled to −78 °C and nBuLi (32.7 cm³, 81.8 mmol) was added. The reaction mixture was then allowed to warm up to room temperature overnight. The mixture was heated under reflux for 24 h, cooled to room temperature and acidified to pH 1-2 with 6 M aqueous hydrochloric acid. The mixture was stirred overnight and the biphasic mixture was extracted with ethyl acetate (3×50 cm³). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (85:15)→(75:25)→(60:40)→(50:50)] of the crude residue afforded 169 (5.1 g, 65%) as a pale yellow solid; mp 130-132 °C (rec. from petroleum ether-ethyl acetate) (lit.,[^145a] 136-138 °C); δ_H (400 MHz; CDCl₃) 2.44 (3 H, s, CH₃), 3.90 (3 H, s, CO₂CH₃), 6.05 (1 H, s, HCCCH₃), 9.40 (1 H, s, OH) and 11.80 (1 H, s, OH). The spectral data matches that reported in the literature.[^145a]

Also isolated was 2,4-dihydroxy-6-methyl benzoic acid (1.8 g, 25%) as a yellow solid; δ_H (400 MHz; CDCl₃) 2.46 (3 H, s, CH₃), 6.20 (1 H, s, HCCCH₃), 9.45 (1 H, s, OH), 11.80 (1 H, s, OH) and 12.70 (1 H, s, COOH).

**Methyl 2-hydroxy-4-methoxy-6-methylbenzoate 168[^145b]**

To a stirred solution of phenol 169 (1.3 g, 7.32 mmol) in a mixture of chloroform/methanol (3:1, 35 cm³) at 0 °C was added (trimethylsilyl)diazomethane (4.4 cm³, 8.78 mmol, 2 M in diethyl ether) under an argon atmosphere. The solution was stirred at 0 °C for 3 h and then allowed to
warm up to room temperature overnight. The solution was recooled to 0 °C and a second aliquot of (trimethylsilyl)diazomethane (2.2 cm³, 4.39 mmol, 2 M in diethyl ether) was added. After 2 h at 0 °C, the solution was allowed to warm to room temperature overnight and the solvent was removed in vacuo. Purification by FCC [petroleum ether-ethyl acetate (95:5)] of the crude residue afforded methyl ether 168 (0.97 g, 89%) as a white solid; mp 130-132 °C (rec. from petroleum ether-ethyl acetate); ν max(film)/cm⁻¹ 3594 (OH), 1671 (C=O) and 1601 (C=C); δH(400 MHz; CDCl₃) 2.51 (3 H, s, CH₃), 3.74 (3 H, s, OCH₃), 3.93 (3 H, s, CO₂CH₂), 6.30 (1 H, dd, J 0.4 and 2.4, HCOH), 6.34 (1 H, d, J 2.8, CH) and 11.78 (1 H, s, OH); δC(100 MHz; CDCl₃) 22.1 (CH₃), 52.1 (COOCH₃), 55.7 (OCH₃), 101.0 (HCOH), 105.3 (C(OCOCH₃)), 111.2 (HCCCH₃), 142.9 (HCCCH₃), 164.5 (COH), 162.6 (COCH₃) and 170.3 (C=O); MS (EI) m/z 197 [M+H]⁺; HRMS m/z 197.0816 (197.0814 calcd for C₁₀H₁₃O₄, M+H⁺). The spectral data matches that reported in the literature.⁴⁴⁵b

Methyl 2-acetoxy-4-methoxy-6-methylbenzoate 167[¹⁴⁶]

To a solution of methyl ether 168 (1.74 g, 8.89 mmol) in dry dichloromethane (45 cm³) at 0 °C, was added sequentially pyridine (0.93 cm³, 1.56 mmol), acetic anhydride (1.26 cm³, 13.3 mmol) and dimethylaminopyridine (0.54 g, 4.44 mmol). The reaction mixture was stirred under argon for 2 h and then allowed to warm to room temperature, whereafter the solvent was removed in vacuo. Purification by FCC [petroleum ether-ethyl acetate (70:30)] of the crude residue afforded acetate 167 (2.05 g, 97%) as a pale yellow oil; Rf 0.31 (solvent A); ν max(film)/cm⁻¹ 1777 (C=O), 1609 (C=C), 1280 and 1151; δH(400 MHz; CDCl₃) 2.30 (3 H, s, OCOCH₃), 2.44 (3 H, s, CH₃), 3.30 (3 H, s, OCH₃), 3.88 (3 H, s, COOCCH₃), 6.49 (1 H, d, J 2.4, CH) and 6.67 (1 H, d, J 2.4, CH); δC(100 MHz; CDCl₃) 20.1 (H₂CC=O), 22.1 (CH₃), 52.7 (C=OOCCH₃), 55.9 (OCH₃), 108.8 (CH), 110.4 (CH), 114.7 (CC=OOCCH₃), 140.1 (CCH₃), 151.4 (CO=OCH₃), 161.6 (COCH₃), 165.7 (CO=OCOCH₃) and 169.8 (C=O). All spectral data matches that reported in the literature.⁴⁴⁶
Methyl 2-acetoxy-6-bromomethyl-4-methoxybenzoate 166[147]

To a stirred solution of acetate 167 (2.05 g, 8.62 mmol) in carbon tetrachloride (200 cm³) was added 1,3-dibromo-5,5-dimethylhydantoin (1.43 g, 4.99 mmol) and benzoyl peroxide (0.21 g, 0.86 mmol). The solution was heated under reflux under an argon atmosphere for 3.5 h and then cooled to room temperature, filtered and the solvent concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (95:5)→(90:10)→(85:15)] of the crude residue afforded bromide 166 (2.58 g, 95%) as a yellow oil, which solidifies upon freezing; Rf 0.41 (solvent A); mp 49-51 °C (rec. from petroleum ether-ethyl acetate); δH (400 MHz; CDCl₃) 2.30 (3 H, s, OCOC₃H₃), 3.86 (3 H, s, OC₃H₃), 3.93 (3 H, s, COOC₃H₃), 4.71 (2 H, s, CH₂Br), 6.61 (1 H, d, J 2.5, CH) and 6.89 (1 H, d, J 2.5, CH); δC (100 MHz; CDCl₃) 20.3 (H₃C=O), 30.9 (CH₂Br), 52.4 (C=OOC₃H₃), 55.7 (OCH₃), 108.9 (CH), 110.4 (CH), 114.6 (CC=OOC₃H₃), 140.1 (CCH₂Br), 151.1 (COC=OCH₃), 161.6 (COCH₃), 165.5 (COC=OCH₃) and 169.1 (C=OOC₃H₃). All spectral data matches that reported in the literature.[147]

Methyl 2-acetoxy-6-(diethoxy-phosphorylmethyl)-4-methoxybenzoate 189

Bromide 166 (350 mg, 1.10 mmol) was dissolved carefully in triethyl phosphite (0.23 cm³, 1.35 mmol) and then heated in the microwave at 180 °C for 26 min. After cooling down to room temperature, water (10 cm³) was added and then the solution was extracted with ethyl acetate (5×15 cm³). The combined organic layers were washed with saturated sodium chloride (2×15 cm³), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Short pass distillation removed excess triethyl phosphite from the crude residue to afford phosphonate 189 (193 mg, 58%) as a yellow oil; Rf 0.41 (solvent B); νmax(film)/cm⁻¹ 2982, 1773, 1720, 1612 (C=C), 1192 (P=O) and 1151; δH (400 MHz; CDCl₃) 1.20 (3 H, t, J 7.0 , CH₂CH₃), 1.30 (3 H, t, J 7.0, CH₂CH₃), 2.24 (3 H, s, OC=OCH₃), 3.50 (2 H, d, ₂J₁₂₀ 22.5, CH₂), 3.79 (3 H, s, OCH₃), 3.83 (3 H, s,
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COOCH₃, 3.98 (2 H, q, J 7.0, CH₂CH₃), 4.07 (2 H, q, J 7.0, CH₂CH₃), 6.52 (1 H, d, J 1.8, CH) and 6.78 (1 H, d, J 1.8, CH); δ(100 MHz; CDCl₃) 14.5 (2 × CH₂C₃H₅), 19.3 (CH₃C=OO), 30.4 (CH₂), 50.3 (COOCH₃), 53.8 (OCH₃), 60.4 (2 × CH₂CH₃), 104.4 (CHAr), 106.0 (CHAr), 116.4 (CCOOCH₃), 138.9 (CCH₂), 149.2 (CO), 159.5 (COCH₃), 164.3 (CH₃C=O) and 167.2 (C=OOCCH₃); MS (EI) m/z 374 [M]+; HRMS m/z 374.1125 (374.1131 calcd for C₁₆H₂₃O₈P, M⁺)

(3-Acetoxy-5-methoxy-2-methoxycarbonylbenzyl)-triphenylphosphonium bromide [147]

To a stirred solution of bromide 166 (2.08 g, 6.56 mmol) in toluene (33 cm³) was added triphenylphosphine (1.89 g, 7.21 mmol) and the reaction mixture heated to 110 °C for 24 h under argon. After allowing the reaction to cool down to room temperature, the solid was filtered under vacuum, washed with petroleum ether and allowed to air dry to afford phosphonium salt 165 (2.48 g, 65%) as a cream solid; mp 183-186 °C (rec. from petroleum ether); δ(400 MHz; CDCl₃) 2.20 (3 H, s, OCOC₂H₃), 3.37 (3 H, s, OCH₃), 3.70 (3 H, s, COOC₂H₃), 5.90 (2 H, d, 2JₚH 15.1, CH₂), 6.55 (1 H, t, J 2.4, CHCCH₂), 7.38 (1 H, t, J 2.7, CH) and 7.60-7.80 (15 H, m, 3×Ph); δ(100 MHz; CDCl₃) 20.1 (OCOCH₃), 54.5 (CO₂CH₃), 55.7 (OCH₃), 60.0 (CH₂), 102.9 (CH), 110.0 (CH), 112.4 (CCO₂CH₃), 128.6 (9×CH), 136.1 (6×CH), 137.8 (3×P-C), 139.9 (CCH₂), 151.0 (CCOCH₃), 165.6 (COCH₃), 169.0 (OCOCH₃) and 171.2 (CO₂CH₃); δP 24.1. All spectral data matches that reported in the literature.[147]

2-Deoxy-3,4-O-isopropylidene-β-pentopyranose [51]

Under an argon atmosphere, a −10 °C stirred solution of 2-deoxy-β-ribose (3.0 g, 22.4 mmol) in ethyl acetate (150 cm³) was treated with 2-methoxypropene (2.8 cm³, 29.1 mmol) and pyridinium p-toluenesulfonate (224 mg, 0.694 mmol). The solution was allowed to stir at −10 °C for 2.5 h before allowing it to warm up to room temperature overnight. The reaction was quenched with triethylamine (1.5 cm³) and then concentrated in vacuo. Purification by FCC [petroleum
ether-ethyl acetate (90:10)→(80:20)→(70:30)→(50:50)] of the crude residue afforded ketal 144 (2.39 g, 62%) as a white solid; \( R_f 0.30 \) (Solvent \( M \)); \( [\alpha]_{D}^{20} \) -29.3 (c 1.1, CHCl\(_3\) (lit., \( [\alpha]_{D}^{21} \) -46.0 (c 0.1, water); \( \nu_{\text{max}} \)(film)/cm\(^{-1}\) 2984 (OH), 2938, 1663, 1369; \( \delta_{H} \)(400 MHz; CDCl\(_3\)) (major \( \alpha \) anomer) 1.31 (3 H, s, CH\(_3\)), 1.48 (3 H, s, CH\(_3\)), 1.75 (1 H, ddd, \( J \) 4.2, 7.0 and 14.8, CH\(_2\)CHOH), 2.22 (1 H, dt, \( J \) 4.2 and 14.8, CH\(_2\)CHOH), 3.67 (1 H, dd, \( J \) 3.6 and 12.7, CH\(_2\)), 3.94 (1 H, dd, \( J \) 3.6 and 12.7, CH\(_2\)), 4.12-4.16 (1 H, m, CHOC), 4.41-4.47 (1 H, m, CHOC) and 5.23 (1 H, dd, \( J \) 4.2 and 7.2, CHO\(_H\)); \( \delta_{C} \)(100 MHz; CDCl\(_3\)) (major \( \alpha \) anomer) 25.4 (C\(_H\)\(_3\)), 27.3 (C\(_H\)), 32.1 (C\(_H_2\)), 62.1 (C\(_H_2\)COH), 70.8 (CH), 71.6 (CH), 90.9 (COH) and 108.8 (C(CH\(_3\))\(_2\)); MS (EI) \( m/z \) 197 [M]\(^{+}\); HRMS \( m/z \) 197.0772 (197.0784 calcd for C\(_8\)H\(_{14}\)NaO\(_4\), M\(^{+}\)); \( \delta_{H} \)(400 MHz; CDCl\(_3\)) (minor \( \beta \) anomer) 1.32 (3 H, s, CH\(_3\)), 1.57 (3 H, s, CH\(_3\)), 2.10 (2 H, t, \( J \) 3.8, CH\(_2\)CHOH), 3.65-3.71 (1 H, m, CH\(_2\)), 3.95-4.02 (1 H, m, CH\(_2\)), 4.13-4.23 (1 H, m, CHOC), 4.43-4.45 (1 H, m, CHOC) and 5.09 (1 H, m, CHOH). All spectral data matches that reported in the literature.\(^{[51]}\)

**Methyl 2-hydroxy-6-\{\(E/Z\)-3-\{\(4S,5R\)-5-hydroxymethyl-2,2-dimethyl\-[1,3\]dioxolan-4-yl\}-propenyl\}-4-methoxybenzoate 185**

![Methyl 2-hydroxy-6-\{\(E/Z\)-3-\{\(4S,5R\)-5-hydroxymethyl-2,2-dimethyl\-[1,3\]dioxolan-4-yl\}-propenyl\}-4-methoxybenzoate](image)

**Procedure A**

Sodium hydride (60% in mineral oil, 0.27 g, 6.65 mmol) was washed with petroleum ether (2×5 cm\(^3\)), suspended in dry tetrahydrofuran (13 cm\(^3\)) and added via cannula to a solution of phosphonium bromide 165 (3.70 g, 6.43 mmol) in dry tetrahydrofuran/dimethylformamide (5:1, 18:3.5 cm\(^3\)), all under an argon atmosphere. Stirring was continued for 45 min and then a solution of lactol 144 (0.75 g, 4.29 mmol) in dry tetrahydrofuran (13 cm\(^3\)) was added and the mixture heated at 80 °C for 30 min. The solution was allowed to cool down to room temperature and then sodium methoxide (25% solution in methanol, 1.02 cm\(^3\), 4.72 mmol) was added and the stirring continued for a further 15 min. The reaction mixture was diluted with water (50 cm\(^3\)) and extracted with ethyl acetate (3×50 cm\(^3\)). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated \textit{in vacuo}. Purification by FCC
[petroleum ether-ethyl acetate (80:20)→(70:30)→(60:40)] of the crude residue afforded diol 185 (0.61 g, 40%) as a yellow oil and as a 3:2 (E:Z) inseparable mixture of isomers; \( [\alpha]_D^{24} -1.2 \) (c 1.0, CHCl\(_3\)); \( \delta_t(400 \text{ MHz}; \text{CDCl}_3) \) (E-isomer) 1.38 (3 H, s, CCH\(_2\)), 1.50 (3 H, s, CCH\(_3\)), 2.41-2.50 (2 H, m, CH\(_2\)), 3.71 (2 H, d, J 6.2, CH\(_2\)OH), 3.80 (3 H, s, OCH\(_3\)), 3.93 (3 H, s, OOCH\(_3\)), 4.12-4.19 (1 H, m, CH=CHCH\(_2\)OH), 4.33 (1 H, q, J 6.2, CH\(_2\)CH), 5.89-5.98 (1 H, m, CH=CHCH\(_2\)), 6.39 (1 H, d, J 2.6, CHAr), 6.46 (1 H, d, J 2.6, CHAr), 7.02 (1 H, d, J 15.5, CH=CHCH\(_2\)) and 11.58 (1 H, s, OH); Z-isomer (inter alia) 5.61-5.67 (1 H, m, CH=CHCH\(_2\)) and 6.76 (1 H, d, J 11.4, CH=CHCH\(_2\)); \( \delta_c(100 \text{ MHz}; \text{CDCl}_3) \) (E-isomer) 25.5 (2\( \times \)CH\(_3\)), 32.9 (CH\(_2\)), 52.2 (O=OOCH\(_3\)), 55.5 (OCH\(_3\)), 61.6 (CH\(_2\)OH), 77.8 (CH=CHCH\(_2\)CHO and OCHCH\(_2\)OH), 99.8 (CAR), 99.9 (CAR), 108.3 (CC=O), 108.6 (OCO), 127.8 (CCH=CH), 132.9 (CCH=CH), 140.4 (CCH=CH), 162.9 (COH), 164.3 (COCH\(_3\)) and 171.5 (C=O); MS (FAB) \( m/z \) 353.5 [M+H]+; HRMS \( m/z \) 353.1591 (353.1600 calcd for C\(_{18}\)H\(_{25}\)O\(_7\), M+H+).

Procedure B

To a stirred solution of diol 185 (106 mg, 299 \( \mu \)mol) in dry dichloromethane (10 cm\(^3\)) was added palladium(II)acetate (Pd(OAc)_2) (3.4 mg, 14.9 \( \mu \)mol) and triethylamine (0.01 cm\(^3\), 47.9 \( \mu \)mol) at room temperature under argon. To this mixture was added tributyltinhydride (70 \( \mu \)L, 0.258 mmol) dropwise and the reaction solution was heated under reflux for 45 h. The reaction was cooled down to room temperature, filtered through Celite\textsuperscript{®} and the solvent concentrated carefully in vacuo. Purification by FCC [chloroform-ethyl acetate, (80:20)→(70:30)] of the crude residue afforded phenol 185 (35 mg, 33%); \( R_t \) 0.41 (solvent K); \(^1\)H NMR spectroscopy showed a slight Z to E isomerisation of the double bond from 3:2 to 4.8:2; \( \delta_t(400 \text{ MHz}; \text{CDCl}_3) \) (E-isomer) 1.38 (3 H, s, CCH\(_3\)), 1.50 (3 H, s, CCH\(_3\)), 2.34-2.40 (2 H, m, CH\(_2\)), 3.71 (2 H, d, J 6.2, CH\(_2\)OH), 3.79 (3 H, s, OCH\(_3\)), 3.93 (3 H, s, OOCH\(_3\)), 4.11-4.16 (1 H, m, CH=CHCH\(_2\)CH), 4.33 (1 H, q, J 6.2, CHCH\(_2\)OH), 5.87-5.93 (1 H, m, CH=CHCH\(_2\)), 6.38 (1 H, d, J 2.6, CHAr), 6.47 (1 H, d, J 2.6, CHAr), 7.02 (1 H, d, J 15.5, CH=CHCH\(_2\)) and 11.58 (1 H, s, OH); Z-isomer (inter alia) 5.60-5.65 (1 H, m, CH=CHCH\(_2\)) and 6.74 (1 H, d, J 11.4, CH=CHCH\(_2\)).
To a stirred solution of alcohol 185 (536 mg, 1.52 mmol) in dry dimethylformamide (30 cm$^3$) under argon was added tert-butyldimethylsilyl chloride (252 mg, 1.67 mmol) and imidazole (207 mg, 3.04 mmol). The solution was stirred for 3 h at room temperature and then diluted with distilled water (50 cm$^3$) and extracted with 50% diethyl ether in petroleum ether (3×150 cm$^3$). The combined organic layers were washed with water (50 cm$^3$), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (90:10)] of the crude residue afforded silyl ether 186 (377 mg, 55%; 65% based on starting material consumed) as a thick, colourless oil (recovered starting material 102 mg) and as a 7:5 (E:Z) mixture of isomers; $R_f$ 0.56 (Solvent D); $[\alpha]_{D}^{20}$ -1.2 (c 1.0, CHCl$_3$); $\nu_{\text{max}}$(film)/cm$^{-1}$ 2953 (OH), 2930, 1655 (C=O), 1610 (C=C), 1329, 1254, 1157 (O-Si) and 1074; $\delta_h$(400 MHz; CDCl$_3$) $(E$-isomer) 0.02 (6 H, s, Si(CH$_3$)$_2$), 0.80 (9 H, s, SiC(CH$_3$)$_3$), 1.25 (3 H, s, CCH$_3$), 1.46 (3 H, s, CCH$_3$), 2.35-2.50 (2 H, m, C$_2$H$_3$), 3.65 (2 H, d, J=6.2, C$_2$H$_2$OTBS), 3.73 (3 H, s, OCH$_3$), 3.81 (3 H, s, COOCH$_3$), 3.96-4.05 (1 H, m, CH=CHCH$_2$C), 4.18-4.22 (1 H, m, CHCH$_2$OTBS), 5.89-5.96 (1 H, m, CH=CHCH$_2$), 6.39 (1 H, d, J=2.6, CHAr), 6.42 (1 H, d, J=2.6, CHAr), 6.94 (1 H, d, J=15.5, CH=CHCH$_2$) and 11.57 (1 H, s, OH); $Z$-isomer (inter alia) 5.61 (1 H, m, CH=CHCH$_2$) and 6.68 (1 H, d, J=11.6, CH=CHCH$_2$); $\delta_c$(100 MHz; CDC$_3$) $(E$-isomer) -5.7 (Si(CH$_3$)$_2$), 18.2 (SiC(CH$_3$)$_3$), 25.5 (2×CH$_3$), 25.9 (SiC(CH$_3$)$_3$), 32.9 (CH$_2$), 52.2 (O=COCH$_3$), 55.5 (OCH$_3$), 61.6 (CH$_2$OH), 77.8 (2×CO), 99.8 (C=O), 99.9 (C=O), 108.3 (C=O), 108.6 (OCO), 127.8 (CCH=CH), 132.9 (CCH=CH), 140.4 (CCH=CH), 162.9 (COH), 164.3 (COCH$_3$) and 171.5 (C=O); MS (FAB) m/z 489.6 [M+Na]$^+$; HRMS m/z 489.2279 (489.2284 calcd for C$_{24}$H$_{38}$NaO$_7$Si, M+Na$^+$).
Methyl 2-\{(E/Z)-3-[(4S,5S)-5-(tert-butyl-dimethyl-silanyloxy)methyl]-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl\}-4-methoxy-6-(4-methoxybenzyloxy)-benzoate 187

Alcohol 186 (377 mg, 0.808 mmol) was dissolved in anhydrous dimethylformamide (60 cm$^3$) and potassium carbonate (168 mg, 1.21 mmol), p-methoxybenzyl chloride (0.12 cm$^3$, 0.889 mmol) and tetra-butylammonium iodide (30 mg, 0.0808 mmol) were added sequentially at room temperature. The resulting yellow solution was heated at 80 °C overnight after which time TLC analysis showed the reaction to be complete. After cooling down to room temperature, the reaction mixture was diluted with diethyl ether (50 cm$^3$) and quenched with water (50 cm$^3$). The organic layer was separated, washed with water (3 × 80 cm$^3$), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether:ethyl acetate (80:20)] of the crude residue afforded PMB ether 187 (426 mg, 90%) as a thick, pale yellow oil and as a 6:4 (E:Z) mixture of isomers; $R_f$ 0.34 (solvent A); $[\alpha]_D^{22} - 1.5$ (c 0.9, CHCl$_3$); $\nu_{\text{max}}$(film)/cm$^{-1}$ 2932, 1728 (C=O), 1599 (C=C), 1514, 1250, 1159 (O-Si) and 1099; $\delta_h$(400 MHz; CDCl$_3$) (E-isomer) 0.02 (6 H, s, Si(CH$_3$)$_2$), 0.81 (9 H, s, Si(C(CH$_3$)$_3$)), 1.23 (3 H, s, CH$_3$), 1.37 (3 H, s, CH$_3$), 2.34-2.50 (2 H, m, CH$_2$), 3.55-3.61 (2 H, m, CH$_2$OTBS), 3.71 (3 H, s, OCH$_3$), 3.79 (3 H, s, COOCH$_3$), 3.82 (3 H, s, OCH$_2$ArOCH$_3$), 3.96-4.19 (2 H, m, 2×CHO), 4.92 (2 H, d, J 3.3, OCH$_2$), 5.73-5.79 (1 H, m, CH=CH), 6.30-6.39 (2 H, m, 2×CHAr), 6.84 (1 H, d, J 15.4, CH=CH) and 7.20-7.26 (4 H, m, 4×CHAr); (Z-isomer) (inter alia) 5.72-5.81 (1 H, m, CH=CHCH$_2$) and 6.80 (1 H, d, J 11.5, CH=CHCH$_2$); $\delta_c$(100 MHz; CDCl$_3$) (E-isomer) - 5.4 (Si(CH$_3$)$_2$), 18.3 (SiC(CH$_3$)$_3$), 25.9 (SiC(CH$_3$)$_3$), 28.1 (C(CH$_3$)$_2$), 33.3 (CH$_2$), 52.1 (CO$_2$CH$_3$), 55.3 (2×OCH$_3$), 61.9 (CH$_2$OTBS), 70.4 (OCH$_2$), 77.1 (HCH$_2$OTBS), 77.7 (C=CH$_2$CH), 99.4 (CH), 101.9 (CH), 106.5 (CCO$_2$CH$_3$), 108.0 (C(CH$_3$)$_2$), 113.9 (2×CH(Ph)), 128.3 (C=C), 128.6 (OCH$_2$C and 2×CH(Ph)), 130.3 (C=C), 137.5 (CC=C), 157.1 (C(Ph)OCH$_3$), 159.3 (COPMB), 161.2 (COCH$_3$) and 168.5 (C=O); MS (FAB) m/z 609.7 [M+Na]$^+$; HRMS m/z 609.2859 (609.2860 calcd for C$_{32}$H$_{46}$O$_8$SiNa, M+Na$^+$).
Methyl 2-{((E/Z)-3-[(4S,5R)-5-hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl]-4-methoxy-6-(4-methoxybenzyloxy)-benzoate 196

Procedure A

A solution of silyl ether 187 (426 mg, 0.725 mmol) in tetrahydrofuran (5 cm³) was cooled to 0 °C and tert-butylammonium fluoride (1.45 cm³, 1.5 mmol) was added. After 10 min, the ice-water bath was removed and stirring was continued for 2 h. Diethyl ether (50 cm³) and water (50 cm³) were then added and the layers separated. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether:ethyl acetate, (30:70)] of the crude residue removed the slight, unidentifiable impurity and afforded alcohol 196 (324 mg, 94%) as a thick yellow oil and as a 7:5 (E:Z) mixture of isomers; \( R_\ell \) 0.5 (solvent \( H \)); \([\alpha]_{D}^{20} +12.0 \text{ (c 1.0, CHCl}_3\)); \( \nu_{\text{max}}\text{ (film)/cm}^{-1} \) 2933 (OH), 1652 (C=O), 1607, 1254, 1156 and 1040 (C-O); \( \delta_H \) (400 MHz; CDCl\(_3\)) (E-isomer) 1.26 (3 H, s, CH\(_3\)), 1.38 (3 H, s, CH\(_3\)), 2.29-2.39 (2 H, m, CH=CH\(_2\)), 3.60 (2 H, d, \( J_{5.6} \), CH\(_2\)OH), 3.70 (3 H, s, OCH\(_3\)), 3.73 (3 H, s, COOCH\(_3\)), 3.85 (3 H, s, OCH\(_2\)ArOCH\(_3\)), 4.02-4.21 (2 H, m, 2×CHO), 4.90 (2 H, s, OCH\(_2\)), 6.05-6.12 (1 H, m, CH=CH), 6.31 (1 H, d, \( J_{2.2} \), CHAr), 6.33 (1 H, d, \( J_{2.2} \), CHAr), 6.79 (1 H, d, \( J_{15.7} \), CH=CH) and 7.18-7.22 (4 H, 2×d, \( J_{6.0} \), 4×CHAr); (Z-isomer) (inter alia) 5.66-5.71 (1 H, m, HC=CHCH\(_2\)), 6.89 (1 H, d, \( J_{11.4} \), HC=CHCH\(_2\)); \( \delta_C \) (100 MHz; CDCl\(_3\)) (E-isomer) 25.4 (OC\(_3\)), 28.1 (OC\(_3\)), 33.2 (CH=CHCH\(_2\)), 52.3 (COOCH\(_3\)), 55.3 (2×OCH\(_3\)), 61.6 (CH\(_2\)OH), 70.4 (OCH\(_2\)), 77.8 (CHO), 77.8 (CHO), 99.4 (CHAr), 102.2 (CHAr), 106.4 (CCOOCH\(_3\)), 108.4 (OC(CH\(_3\))\(_2\)), 113.9 (2×CHAr), 128.6 (CH=CH, CCH\(_2\)O, 2×CHAr), 129.2 (CH=CH), 137.5 (CCH=CH), 157.3 (COCH\(_3\)), 159.3 (COCH\(_2\)), 161.3 (COCH\(_3\)) and 168.1 (C-O); \( \text{MS (FAB) m/z 473.4 [M+H] }^+\); HRMS m/z 473.2171 (473.2175 calcd for C\(_{26}\)H\(_{33}\)O\(_8\), M+Na\(^+\)).

Procedure B

To a stirred solution of PMB ether 196 (55.6 mg, 117 µmol) in chloroform (7 cm³) was added palladium(II) acetate (Pd(OAc)\(_2\)) (1.3 mg, 58.8 µmol) and
triethylamine (10 µL, 47.9 µmol) at room temperature under argon. To this mixture was added tributyltinhydride (0.07 cm$^3$, 0.258 mmol) dropwise and the reaction solution was heated under reflux for 50 h. The reaction was cooled down to room temperature and stirred for a further 74 h. The solvent was concentrated slowly in vacuo, then potassium fluoride (4 eq., 27 mg, 0.470 mmol), water (4 eq. 0.01 cm$^3$) and ethyl acetate (3 cm$^3$) were added and the reaction mixture stirred overnight. The potassium fluoride/tributyltinfluoride solid was filtered through Celite® with a little MgSO$_4$ added to absorb the water. The solvent was concentrated carefully in vacuo and the work-up procedure repeated on the now orange solution for 2 h. FCC [petroleum ether-ethyl acetate, (100:0)→(70:30)] of the residue afforded 196 (30 mg, 54%); $^1$H NMR spectroscopy showed a slight Z to E isomerisation of the double bond from 7:5 to 2:1.

Methyl 2-[(E/Z)-3-[(4$S$,5$S$)-5-formyl-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl]-4-methoxy-6-(4-methoxybenzyloxy)-benzoate 197

To a −78 °C solution of oxalyl chloride (0.10 cm$^3$, 0.203 mmol) in anhydrous dichloromethane (0.1 cm$^3$) was added dimethylsulfoxide (0.03 cm$^3$, 0.406 mmol). After stirring for 1 h, a solution of alcohol 196 in dichloromethane (0.7 cm$^3$) was added and stirring continued for a further 1 h. Triethylamine (0.08 cm$^3$, 0.609 mmol) was added and the reaction allowed to warm up to room temperature. The reaction was diluted with dichloromethane (7 cm$^3$), quenched with 1 M hydrochloric acid (7 cm$^3$) and then extracted with dichloromethane (2×10 cm$^3$). The combined organic layers were washed with saturated aqueous sodium chloride (10 cm$^3$), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford aldehyde 197 as an unstable yellow oil; $\delta_{\text{H}}$(400 MHz; CDCl$_3$) 9.72 (CHO).
A stirred suspension of lithium acetylide ethylenediamine complex (4.74 g, 51.6 mmol) in anhydrous dimethylsulfoxide (100 cm³) at 0 °C was treated with a solution of S-(+)-propylene oxide (3.0 cm³, 43.0 mmol) dropwise. The reaction was then allowed to warm up to room temperature where it was stirred for 48 h. The suspension was poured onto ice (100 cm³) and extracted with diethyl ether (4 × 70 cm³). The combined ether extracts were washed with brine (6 × 30 cm³), water (2 × 30 cm³) and dried over anhydrous magnesium sulfate. Careful evaporation of the solvent under atmospheric pressure yielded the crude alcohol 190 (3.6 g, 100%) as a colourless liquid, which was taken on without any further purification; [α]D²2 +16.5 (c 1.0, CHCl₃) (lit., [89] [α]D²6 +17.8 (c 0.2, CHCl₃)); νmax(film)/cm⁻¹ 3379 (OH), 3280 (C≡C) and 2340; δH(400 MHz; CDCl₃) 1.26 (3 H, d, J 6.0, CH₃), 2.08 (1 H, t, J 2.7, HC≡C), 2.33 (1 H, ddd, J 2.7, 5.3 and 16.0, CH₂), 2.42 (1 H, ddd, J 2.7, 6.2 and 16.0, CH₂) and 3.99-4.04 (1 H, m, HCOH). All spectral data matches that reported in the literature. [89]

A solution of alcohol 190 (3.6 g, 42.8 mmol) and imidazole (5.83 g, 85.6 mmol) in dimethylformamide (215 cm³) under argon was treated with tert-butyldimethylsilyl chloride (7.09 g, 47.1 mmol) and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with water (70 cm³) and the product extracted with diethyl ether (3 × 50 cm³). The combined ether extracts were washed with brine (3 × 50 cm³) and dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-diethyl ether (90:10)] of the crude residue afforded silyl ether 55 (6.6 g, 78%) as a colourless liquid; [α]D¹² +0.9 (c 1.0, CHCl₃) (lit., [148] [α]D¹⁰ -1.2 (c 10.0, CHCl₃); νmax(film)/cm⁻¹ 3309 (C≡C) and 1040 (C-O); δH(400 MHz; CDCl₃) 0.06 (6 H, s Si(CH₃)₂), 0.90 (9 H, s, Si(CH₃)₃), 1.22 (3 H, d, J 6.1, CH₃), 2.00 (1 H, t, J 2.7, HC≡C), 2.23 (1 H, ddd, J 2.7, 7.0 and 16.5, CH₂), 2.33 (1 H, ddd, J 2.7, 5.5 and 16.5, CH₂) and 3.98-4.03 (1 H, m, HCOH); δC(100 MHz; CDCl₃) -5.0 (Si(CH₃)₂), 18.2 (Si(CH₃)₃), 25.0 (CH₃), 25.8
Methyl 2-(3-{(4S,5R)-5-[(R)-5-(tert-butyldimethylsilanyloxy)-1-hydroxy-hex-2-ynyl]-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl)-4-methoxy-6-(4-methoxy-benzyloxy)-benzoate 198

A solution of alkyne 55 (29 mg, 0.155 mmol) in THF (1 cm³) at room temperature was treated with ethylmagnesium bromide (0.04 cm³, 0.124 mmol) and the resulting light brown mixture was stirred for 3 h.

Whilst the above deprotonation was being carried out, a −78 °C solution of oxalyl chloride (0.10 cm³, 0.207 mmol) in tetrahydrofuran (1 cm³) at −78 °C was treated with dimethylsulfoxide (0.03 cm³, 0.414 mmol). After stirring at −78 °C for 30 min, a solution of alcohol 196 (49 mg, 0.103 mmol) in tetrahydrofuran (0.5 cm³) was added and stirring continued for 1 h. Triethylamine (0.12 cm³, 0.829 mmol) was added and the reaction was allowed to warm up to room temperature. After 30 min at room temperature the reaction mixture was cooled back down to −78 °C and the deprotonated alkyne solution was added. The resulting mixture was allowed to warm up to room temperature and was stirred overnight. The reaction was then quenched with saturated aqueous ammonium chloride (10 cm³) and extracted with ethyl acetate (3×15 cm³). The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (60:40)] of the crude residue afforded alcohol 198 (20 mg, 30%) as a thick, yellow oil and as an inseparable mixture of diastereoisomers; Rf 0.57 (solvent I); νmax(film)/cm⁻¹ 2925 (OH), 2841, 1732 (C=O), 1596 (C=C), 1258 and 1112 (O-Si); δH (400 MHz; CDCl₃) 0.00 (6 H, s, Si(CH₃)_2), 0.79 (9 H, s, SiC(CH₃)_3), 1.18 (3 H, s, CH₃), 1.38 (3 H, s, CCH₃), 1.54 (3 H, s, CCH₃), 2.17-2.22 (2 H, m, CH₂), 2.42-2.48 (2 H, m, CH₂), 3.83-3.87 (1 H, m, CHOTBS), 3.79 (3 H, s, OCH₂PhOCH₃), 3.82 (3 H, s, OCH₃), 3.87 (3 H, s, CO₂CH₃), 4.24-4.35 (2 H, m, 2×OCH), 4.44-4.50 (3 H, m, CHO and OCH₂PhOCH₃), 6.21-6.29 (1 H, m, CH=CH), 6.42-6.49 (1 H, m, CH=CH), 6.63 (1 H, s, CH), 6.71 (1 H, s, CH), 6.90 (2 H, d, J 8.5, 2×CH) and 7.30
\[ \delta_0 \text{C}_{(100 \text{ MHz} ; \text{CDCl}_3)} 4.8 \ (\text{Si}(\text{CH}_3)_2), 17.9 \ (\text{Si}(\text{CH}_3)_3), 19.7 \ (\text{C}28), 25.3 \ (\text{C}20), 25.9 \ (\text{Si}(\text{CH}_3)_3), 26.9 \ (\text{C}26), 27.7 \ (\text{C}21), 31.3 \ (\text{C}31), 33.5 \ (\text{C}17), 52.0 \ (\text{C}29), 55.3 \ (\text{C}1), 55.6 \ (\text{C}12), 62.4 \ (\text{C}22), 70.5 \ (\text{C}23), 73.0 \ (\text{C}8), 73.3 \ (\text{C}27), 79.9 \ (\text{C}18), 80.1 \ (\text{C}25), 84.5 \ (\text{C}24), 100.9 \ (\text{C}10), 103.8 \ (\text{C}13), 108.8 \ (\text{C}19), 113.7 \ (\text{C}3 \text{ and C}4), 128.7 \ (\text{C}16), 129.3 \ (\text{C}15), 129.3 \ (\text{C}18), 130.2 \ (\text{C}5 \text{ and C}6), 137.6 \ (\text{C}14), 155.6 \ (\text{C}2), 161.3 \ (\text{C}9), 168.2 \ (\text{C}11) \text{ and } 171.3 \ (\text{C}30); \text{MS (CI) } m/z \ 668 \ [\text{M}]^+; \text{HRMS} \ m/z \ 668.3375 \ (668.3381 \text{ calcd for C}_{37} \text{H}_{52} \text{O}_9 \text{Si, M}^+). \]

Methyl 2-((E/Z)-3-[(4S,5S)-5-[(R)-5-(tert-butyldimethylsilyloxy)hex-2-ynoyl]-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl)-4-methoxy-6-(4-methoxybenzoyloxy)benzoate 245

A solution of oxalyl chloride (30 \mu L, 59.8 \mu mol) in anhydrous dichloromethane (0.6 cm\(^3\)) was treated with dimethylsulfoxide (10 \mu L, 0.119 mmol) at \(-78^\circ C\). After stirring at \(-78^\circ C\) for 30 min, a solution of alcohol 198 (20 mg, 29.9 \mu mol) in anhydrous dichloromethane (0.3 cm\(^3\)) was added and stirring continued for 1 h. Triethylamine (0.03 cm\(^3\), 0.239 mmol) was added and the reaction was allowed to warm up to room temperature. After 30 min at room temperature the reaction mixture was diluted with dichloromethane (10 cm\(^3\)) and separated with 1 N hydrochloric acid (10 cm\(^3\)). The organic layers were washed with saturated aqueous sodium hydrogen carbonate (20 cm\(^3\)), dried over anhydrous sodium sulfate, filtered and concentrated \textit{in vacuo} to afford 245 (20 mg, 100\%) as an off-white oil requiring no further purification; \( R_t \ 0.77 \ (\text{Solvent I}) \); \( \delta_0 \text{H} \ (400 \text{ MHz}; \text{CDCl}_3) \ 0.05 \ (6 \text{ H, s, Si(CH}_3)_2), 0.86 \ (9 \text{ H, s, Si(CH}_3)_3), 1.22 \ (3 \text{ H, s, CH}_3), 1.39 \ (3 \text{ H, s, CCH}_3), 1.54 \ (3 \text{ H, s, CCH}_3), 2.30-2.55 \ (4 \text{ H, m, 2}\times\text{CH}_2), 3.79 \ (6 \text{ H,}
2×s, OCH₂PhOCH₃ and OCH₃), 3.84 (3 H, s, CO₂CH₃), 3.98-4.04 (1 H, m, CHOTBS),
4.24-4.35 (2 H, m, 2×OCH), 5.00 (2 H, s, OCH₂PhOCH₃), 5.78-5.82 (1 H, m,
CH=CH), 6.18-6.22 (1 H, m, CH=CH), 6.40 (1 H, s, CH), 6.62 (1 H, s, CH), 6.90 (2
H, d, J 8.5, 2×CH) and 7.30 (2 H, d, J 8.5, 2×CH); δC (100 MHz; CDCl₃) -4.8
(Si(CH₃)₂), 17.9 (SiC(CH₃)₃), 19.7 (C28), 25.3 (C20), 25.9 (SiC(CH₃)₃), 26.8 (C26),
27.7 (C21), 31.2 (C31), 33.6 (C17), 52.0 (C29), 55.3 (C1), 55.8 (C12), 62.4 (C22),
73.1 (C8), 73.3 (C27), 79.9 (C18), 80.0 (C25), 84.5 (C24), 101.0 (C10), 103.7
(C13), 108.8 (C19), 113.9 (C3 and C4), 128.8 (C16), 129.3 (C15), 129.4 (C18),
130.0 (C5 and C6), 137.8 (C14), 155.7 (C2), 161.3 (C9), 168.1 (C11), 170.9.3(C30)
and 185.7 (C23).

Methyl 2-(tert-butyldimethylsilanyloxy)-4-methoxy-6-vinyl-benzoate 120

Lithium chloride (430 mg, 10.1 mmol) was dissolved in anhydrous
dimethylformamide (24 cm³) and then tri-2-furylphosphine (125 mg, 0.534 mmol)
and tris[dibenzyldieneacetone]dipalladium(0) (Pd₂(dba)₃) (62 mg, 0.0675 mmol)
were added sequentially at room temperature followed by a solution of triflate
119 (1.5 g, 3.37 mmol) in anhydrous dimethylformamide (10 cm³). The resulting
reaction mixture was stirred for 30 min before tributylvinyl tin (1.2 cm³, 4.05
mmol) was added. The reaction solution was heated to 60 °C for 3 h after which
it was cooled down to room temperature, diluted with dichloromethane (40 cm³)
and water (40 cm³). The aqueous layer was removed and the organic phase
washed with 1 M potassium fluoride aqueous solution (3×50 cm³). The reaction
mixture was shaken in a separatory funnel for 1 minute each wash. After the
first wash solid tributyltinfluoride precipitate formed at the interface and was
filtered out through Celite®. The combined organic layers were washed with
brine (50 cm$^3$), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (100:0)$\rightarrow$(95:5) then petroleum ether-diethyl ether (100:0)$\rightarrow$(95:5)] of the crude residue afforded an inseparable mixture of alkenes 120; $R_f$ 0.60 (Solvent A) and 210; $R_f$ 0.59 (Solvent A) (736 mg) as a white solid.

Silylated compound 120: $\delta_H$(400 MHz; CDCl$_3$) 0.01 (6 H, s, Si(CH$_3$)$_2$), 0.76 (9 H, s, SiC(CH$_3$)$_3$), 3.82 (3 H, s, CH$_3$), 3.91 (3 H, s, COOCH$_3$), 5.21 (1 H, dd, J 1.6 and 10.8, CH=CH$_2$), 5.45 (1 H, dd, J 1.6 and 17.1, CH=CH$_2$), 6.30 (1 H, d, J 2.4, CH(OTBS)), 6.42 (1 H, d, J 2.4, CH(COCH$_3$)) and 6.68-6.75 (1 H, m, CH$_2$); $\delta_C$(100 MHz; CDCl$_3$) -4.3 (Si(CH$_3$)$_2$), 17.8 (SiC(CH$_3$)$_3$), 25.8 (SiC(CH$_3$)$_3$), 52.0 (CO$_2$CH$_3$), 55.9 (OCH$_3$), 100.3 (CH), 103.5 (CH), 108.7 (CO$_2$CH$_3$), 115.9 (HC=CH$_2$), 138.4 (HC=CH$_2$), 143.9 (CH=CH$_2$), 164.3 (COH), 165.0 (COCH$_3$) and 171.8 (C=O).

Desilylated compound 210: $\delta_H$(400 MHz; CDCl$_3$) 3.78 (3 H, s, CH$_3$), 3.87 (3 H, s, COOCH$_3$), 5.18 (1 H, dd, J 1.5 and 10.8, CH=CH$_2$), 5.42 (1 H, dd, J 1.5 and 17.1, CH=CH$_2$), 6.36 (1 H, d, J 2.6, CH(OH)), 6.46 (1 H, d, J 2.6, CH(COCH$_3$)), 7.23-7.30 (1 H, m, CH=CH$_2$) and 11.61 (1 H, s, OH).

**Methyl 2-hydroxy-4-methoxy-6-vinylbenzoate 210**

A solution of alkenes 120 and 210 (736 mg, 2.28 mmol) in anhydrous tetrahydrofuran (10 cm$^3$) was cooled down to 0 °C. tetra-Butylammonium fluoride (4.5 cm$^3$, 4.56 mmol) was added and the ice-water bath was removed after 10 min, whereafter the reaction was allowed to warm up to room temperature. After 2 h, the reaction mixture was diluted with diethyl ether (30 cm$^3$) and diluted with water (30 cm$^3$). The organic layer was dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude residue was passed through a pad of silica gel which was eluted with 20% diethyl ether-petroleum ether to remove excess TBS. The fractions were concentrated under reduced pressure to afford phenol 210 (517 mg, 74% over two steps) as a white solid; $R_f$ 0.56 (Solvent A); mp 78-80 °C (from diethyl ether-petroleum ether) (lit.,$^{[149]}$ 75-76 °C); $\nu_{\text{max}}$(film)/cm$^{-1}$ 2925, 2854, 1733 (C=O), 1648 (C=C), 1437,
1328, 1257, 1159; δ_H (400 MHz; CDCl_3) 3.78 (3 H, s, OCH_3), 3.87 (3 H, s, COOCH_3), 5.18 (1 H, dd, J 1.6 and 10.8, CH=CH_2), 5.42 (1 H, dd, J 1.6 and 17.1, CH=CH_2), 6.36 (1 H, d, J 2.6, CH), 6.46 (1 H, d, J 2.6, CH), 7.23-7.33 (1 H, m, CH=CH_2) and 11.61 (1 H, s, OH); δ_C (100 MHz; CDCl_3) 52.1 (CO_2C_H_3), 55.5 (OCH_3), 100.3 (CH), 103.9 (CH), 108.3 (CCO_2C_H_3), 115.8 (HC=CH_2), 138.4 (HC=CH_2), 143.6 (CH=CH_2), 164.3 (COH), 165.1 (COCH_3) and 171.7 (C=O); MS (EI) m/z 208.0 [M]+; HRMS m/z 208.0734 (208.0736 calcd for C_{11}H_{12}O_4, M+). All spectral data matches that reported in the literature. [149]

((4S,5R)-5-Allyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol 213[76]

Potassium bis(trimethylsilyl)amide (32 cm^3, 16.1 mmol) was added to a −78 °C stirred suspension of methyl triphenylphosphonium iodide (8.74 g, 21.5 mmol) in anhydrous tetrahydrofuran (40 cm^3). The reaction was warmed up to 0 °C and stirred for 30 min before cooling back down to −78 °C. A solution of acetonide 144 (937 g, 5.38 mmol) in anhydrous tetrahydrofuran (10 cm^3) was added and the yellow solution was warmed up to room temperature overnight. The reaction was quenched with saturated aqueous ammonium chloride (50 cm^3) and extracted with ethyl acetate (3×50 cm^3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated \textit{in vacuo}. Purification by FCC [petroleum ether-ethyl acetate (100:0)→(70:30)→(60:40)] of the crude residue afforded alcohol 213 (557 g, 60%) as a yellow oil; R_f 0.54 (Solvent M); [α]_D^{25} -15.7 (c 1.0, CHCl_3) (lit., [76] [α]_D^{25} +54.8 (c 0.26, CHCl_3); ν_{max} (film)/cm\(^{-1}\) 3450 (OH), 2987, 2853, 1643, 1457, 1379, 1235, 1217, 1045 (C-O); δ_H (400 MHz; CDCI_3) 1.37 (3 H, s, CH_3), 1.48 (3 H, s, CH_3), 2.23-2.32 (1 H, m, CH_2), 2.36-2.46 (1 H, m, CH_2), 3.64 (2 H, t, J 5.8, CH_2), 4.17 (1 H, q, J 5.9, CHCH_2), 4.25 (1 H, q, J 5.9, CHCH_2OH), 5.09-5.18 (2 H, m, CH_2=CH) and 5.78-5.90 (1 H, m, CH_2=CH); δ_C (100 MHz; CDCl_3) 25.4 (CH_3), 28.0 (CH_3), 33.5 (CH_2), 61.3 (CH_2OH), 76.2 (CH), 77.8 (CH), 108.1 (C(CH_3)_2), 117.2 (HC=CHCH_2) and 134.2 (HC=CHCH_2); MS (CI) m/z 173 [M+H]+; HRMS m/z 173.1174 (173.1178 calcd for C_{9}H_{17}O_3, M+). All spectral data matches that reported in the literature.[76]
((4S,5S)-5- Allyl-2, 2-dimethyl-[1, 3]dioxolan-4-ylmethoxy)-tert-butyldimethylsilane 208

Alcohol 213 (446 mg, 2.59 mmol) was dissolved in anhydrous dichloromethane (13 cm³) and triethylamine (0.65 cm³, 4.66 mmol) and dimethylaminopyridine (32 mg, 0.259 mmol) were added sequentially at room temperature. The reaction mixture was stirred for 5 min and then tert-butyldimethylsilyl chloride (507 mg, 3.37 mmol) was added. After 18 h, the reaction was quenched with saturated aqueous ammonium chloride (10 cm³) and extracted with dichloromethane (3×10 cm³). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (95:5)] of the crude residue afforded silyl ether 208 (643 mg, 87%) as an orange oil; Rf 0.83 (Solvent A); [α]D23 -0.4 (c 1.0, CHCl₃); νmax (film)/cm⁻¹ 2954, 1643 (C=C), 1472, 1257 (Si-CH₃); δH (400 MHz; CDCl₃) 0.06 (6 H, s, Si(CH₃)₂), 0.89 (9 H, s, Si(CH₃)₃), 1.34 (3 H, s, CH₃), 1.43 (3 H, s, CH₃), 2.29-2.46 (2 H, m, CH₂), 3.59-3.71 (2 H, m, CH₂OTBS), 4.03-4.07 (1 H, m, CHCH₂), 4.18-4.22 (1 H, m, CHCH₂OTBS), 5.00-5.16 (2 H, m, CH₂=CH) and 5.83-5.95 (1 H, m, CH₂=CH); δC (100 MHz; CDCl₃) -5.5 (SiCH₃), -5.4 (SiCH₃), 18.3 (C(CH₃)₃), 25.5 (CH₃), 25.9 (3×CH₃), 28.1 (CH₃), 33.8 (CH₂), 61.9 (CH₂OTBS), 76.7 (CH), 77.8 (CH), 107.9 (C(CH₃)₂), 116.8 (CH=CHCH₂) and 135.2 (CH=CHCH₂); MS (Cl) m/z 287.1 [M+H]+; HRMS m/z 287.2047 (287.2042 calcd for C₁₅H₃₁O₃Si, M+H⁺).

2-{(E)-3-[(4S,5S)-5-(tert-butyldimethylsilanyloxymethyl)-2,2-dimethyl-methyl [1,3]dioxolan-4-yl]-propenyl}-6-hydroxy-4-methoxybenzoate 186

A stirred solution of styrene 210 (966 mg, 4.64 mmol) and alkene 208 (2.66 g, 9.28 mmol) in anhydrous dichloromethane (75 cm³) was treated with Hoveyda-Grubbs second generation catalyst (872 mg, 1.39 mmol) and the resulting mixture was heated to reflux in the dark for 48 h. The reaction mixture was allowed to cool down to room temperature and was filtered through silica gel
and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (95:5)→(90:10)] of the crude residue afforded alkene 186 (1.4 g, 65%) as a colourless oil; \( R_f \) 0.53 (Solvent N); \( [\alpha]_D^{23} \) -1.3 (c 1.0, CHCl₃); \( \nu_{\text{max}}\text{(film)}/\text{cm}^{-1} \) 2930 (OH), 2856, 1655 (C=C), 1437, 1327, 1213, 1159 and 1097 (O-Si); \( \delta_\text{H} \) (400 MHz; CDCl₃) 0.00 (6 H, s, Si(CH₃)₂), 0.82 (9 H, s, SiC(CH₃)₃), 1.27 (3 H, s, CH₃), 1.37 (3 H, s, CH₃), 2.35-2.50 (2 H, m, CH₂), 3.55-3.69 (2 H, m, CH₂), 3.80 (3 H, s, OCH₃), 3.89 (3 H, s, COOC₂H₅), 4.12-4.30 (2 H, m, 2×O), 5.98 (1 H, dt, \( J \) 6.9 and 15.5, CH=C(CH₃)CH₂), 6.36 (1 H, d, \( J \) 2.5, CH(Ar)), 6.48 (1 H, d, \( J \) 2.5, CH(Ar)), 7.01 (1 H, d, \( J \) 15.5, CH=CH) and 11.61 (1 H, s, OH); \( \delta_\text{C} \) (100 MHz; CDCl₃) -5.3 (SiCH₃), -5.2 (SiCH₃), 18.4 (SiC(CH₃)₃), 25.7 (CH), 26.0 (SiC(CH₃)₃), 28.3 (CH), 33.2 (CH₂), 52.1 (CO₂CH₃), 55.5 (OCH₃), 62.0 (CH₂OTBS), 77.3 (CH(O)), 77.8 (CH(O)), 99.9 (CH(Ar)), 103.8 (CH(Ar)), 108.1 (CO₂CH₃), 116.6 (C(CH₃)₂), 129.2 (HC=CHCH₂), 133.0 (HC=CHCH₂), 143.2 (CH=CHCH₂), 164.1 (COH), 165.1 (COCH₃) and 171.9 (C=O); MS (Cl) \( m/z \) 467 [M+H]+; HRMS \( m/z \) 467.2466 (467.2465 calcd for C₂₄H₃₉O₇Si, M+H⁺).

**Methyl 2-{(E)-3-[4S,5S]-5-(tert-butyldimethylsilanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl}-4-methoxy-6-methoxymethyl-benzoate 211**

Phenol 186 (263 mg, 0.565 mmol) was dissolved in anhydrous dichloromethane (6 cm³) and \( N,N' \)-diisopropylethylamine (DIPEA) (0.30 cm³, 1.60 mmol) was added at room temperature. The reaction mixture was cooled down to 0 °C and bromomethyl methyl (MOMBr) ether (0.10 cm³, 1.13 mmol) was slowly added. The ice-water bath was removed after 10 min and the reaction allowed to warm up to room temperature and stirred for 18 h. After this time, starting material was still present, so the above procedure was repeated and the reaction left for another 18 h. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (40 cm³) and extracted with ethyl acetate (3×40 cm³). The combined organic layers were washed with water (50 cm³), then brine (50 cm³), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-diethyl ether (80:20)→(70:30)] of the crude residue afforded MOM ether 211 (170 mg, 60%) as a colourless oil; \( R_f \) 0.26
Methyl 2-[(E)-3-((4S,5R)-5-hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-propenyl]-4-methoxy-6-methoxymethylbenzoate 212

MOM ether 211 (373 mg, 0.730 mmol) was dissolved in anhydrous tetrahydrofuran (5 cm$^3$) and cooled down to 0 °C before the addition of tetra-butylammonium fluoride (1.5 cm$^3$, 1.46 mmol). After 10 min, the ice-water bath was removed and the reaction allowed to warm up to room temperature. After 1.5 h, the reaction was diluted with ethyl acetate (10 cm$^3$) and water (10 cm$^3$) was added. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (30:70)] of the crude residue afforded alcohol 212 (268 mg, 93%) as an off white oil; $R_f$ 0.40 (Solvent O); $[\alpha]_D^{20}$ -6.0 (c 1.1, CHCl$_3$); $\nu_{\max}$ (film)/cm$^{-1}$ 2988, 2937, 1601 (C=O), 1433; $\delta_{\text{H}}$ (400 MHz; CDCl$_3$) 1.35 (3 H, s, OCC$_3$), 1.48 (3 H, s, OCCH$_3$), 2.37-2.47 (1 H, m, CH=CHCH$_2$), 2.49-2.58 (1 H, m, CH=CHCH$_2$), 3.45 (3 H, s, OCH$_2$OCH$_3$), 3.67 (2 H, t, J 5.8, CH$_2$OH), 3.79 (3 H, s, OCH$_3$), 3.88 (3 H, s, COOCH$_3$), 4.20 (1 H, q, J 5.8, CH$_2$CH), 4.28 (1 H, dt, J 5.8 and 8.0, CH$_2$OH), 5.13 (2 H, s, OCH$_2$OCH$_3$), 6.18 (1 H, ddd, J 6.1, 7.8 and 15.6, CH=CHCH$_2$), 6.43 (1 H, d, J 15.6, CH=CHCH$_2$), 6.59 (1 H, d, J 2.1, CH(Ar)) and
6.69 (1 H, d, J 2.1, CH(Ar)); δ(C(100 MHz; CDCl₃) 25.4 (C(CH₃)), 28.0 (C(CH₃)), 33.2 (CH₂), 52.2 (CO₂CH₃), 55.4 (OCH₃), 56.1 (OCH₂OCH₃), 61.3 (CH₂OH), 76.3 (CH(O)), 77.8 (CH(O)), 94.7 OCH₂OCH₃), 100.6 (CHAr), 103.6 (CHAr), 108.2 (CCO₂CH₃), 116.2 (C(CH₃)₂), 128.8 (HC=CHCH₂), 129.6 HC=CHCH₂), 137.3 (HC=CHCH₂), 155.5 COCH₂OCH₃), 161.2 (COCH₃) and 168.3 (C=O); MS (EI) m/z 396 [M]+; HRMS m/z 396.1787 (396.1784 calcd for C₂₀H₂₈O₈, M⁺).

1-Methoxy-4-((S)-1-methyl-but-3-nyloxy methyl)-benzene 223[150]

To a suspension of 60% NaH in mineral oil (2.51 g, 62.9 mmol) in anhydrous dimethylformamide (70 cm³) at 0 °C was added a solution of the freshly generated crude alcohol 190 (4.81 g, 57.2 mmol) in anhydrous dimethylformamide (70 cm³). The reaction mixture was stirred for 15 min, then p-methoxybenzyl chloride (11.6 cm³, 85.8 mmol) was added and the reaction mixture allowed to warm up to room temperature and stirred for 17 h. The reaction mixture was poured onto brine (400 cm³) and extracted with diethyl ether (3×100 cm³). The combined organic layers were concentrated under reduced pressure, then washed with brine (300 cm³), dried over anhydrous magnesium sulfate, filtered through cotton wool and the solvent removed under vacuum. Purification by FCC [petroleum ether-ethyl acetate (95:5)] of the crude residue afforded PMB ether 223 (5.26 g, 45%) as a colourless oil; [α]D²⁰ -8.8 (c 1.0, CHCl₃) (lit.,[150] [α]D²⁶ +6.5 (c 1.04, CHCl₃); νmax(film)/cm⁻¹ 3294 (C≡C), 1511 (C=C), 1243 and 1033 (C-O); δH(400 MHz; CDCl₃) 1.34 (3 H, d, J 6.0, CH₃), 2.08 (1 H, s, HC), 2.35-2.42 (1 H, m, HCC₂H₂), 2.51-2.58 (1 H, m, HCC₂H₂), 3.71 (1 H, app. sext, J 6.0 and 12.3, CH₃), 3.82 (3H, s, OCH₃), 4.53 (2 H, s, OCH₂), 6.91 (2 H, d, J 8.6, 2×CHAr) and 7.32 (2 H, d, J 8.6, 2×CHAr); δ(C(100 MHz; CDCl₃) 19.5 (CH₃), 26.0 (CH₂), 55.2 (OCH₃), 70.1 (CHCH₃), 70.3 (HCCCH₂), 72.8 (OCH₂), 81.3 (HCCCH₂), 113.8 (2×CHAr), 129.3 (2×CHAr), 130.6 (OCH₂C) and 159.2 (COCH₃). All ¹H and ¹³C data matches that reported in the literature.[150]
A solution of alkyne 223 (466 mg, 2.43 mmol) in anhydrous tetrahydrofuran (9.5 cm$^3$) was treated with ethylmagnesium bromide (0.76 cm$^3$, 2.27 mmol) at room temperature and the resulting solution was stirred for 5 h.

Whilst the above deprotonation was being carried out, a $-78 \degree$C solution of oxalyl chloride (1.52 cm$^3$, 3.03 mmol) in anhydrous tetrahydrofuran (15 cm$^3$) was treated with dimethyl sulfoxide (0.47 cm$^3$, 6.06 mmol). After 30 min, a solution of alcohol 212 (560 mg, 1.52 mmol) in anhydrous tetrahydrofuran (7 cm$^3$) was added and the reaction was stirred at $-78 \degree$C for 1 h. After this time, triethylamine (1.69 cm$^3$, 12.1 mmol) was added and the reaction was allowed to warm up to room temperature. After 30 min, the reaction was cooled back down to $-78 \degree$C and a solution of the deprotonated alkyne was added. The reaction mixture was allowed to warm to room temperature and stirring continued for 14 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (30 cm$^3$) and extracted with ethyl acetate ($2 \times 40$ cm$^3$). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (50:50)] of the crude residue afforded propargylic alcohol 222 (585 mg, 65%) as a thick, yellow oil and as an inseparable mixture of diastereoisomers; $R_f$ 0.33 (Solvent I); $\left[\alpha\right]_{D}^{19} -0.9$ (c 1.0, CHCl$_3$); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2928, 1728 (C=O), 1601 (C=C), 1250, 1153 and 1034 (C-O); $\delta_{\text{H}}$ (400 MHz; CDCl$_3$) 1.30 (3 H, s, C$_3$H$_3$), 1.38 (3 H, s, CCH$_3$), 1.54 (3 H, s, CCH$_3$), 2.39-2.78 (4 H, m, 2$\times$CH$_2$), 3.50 (3 H, s, OCH$_2$OCH$_3$), 3.69-3.71 (1 H, m, CHOPMB), 3.81 (3 H, s, OCH$_2$ArOCH$_3$), 3.83 (3 H, s, OCH$_3$), 3.91 (3 H, s, CO$_2$CH$_3$), 4.10-4.18 (1 H, m, OCH), 4.24-4.35 (1 H, m, OCH), 4.45-4.55 (3 H, m, CH$_2$OH and OCH$_2$ArOCH$_3$), 5.18 (2 H, s, OCH$_2$OCH$_3$), 6.19-6.29 (1 H, m, CH=CH), 6.49 (1 H, d, J 15.7, C=CH), 6.62 (1 H, s, CH), 6.71 (1 H, s, CH), 6.89 (2 H, d, J 8.5, 2$\times$CH) and 7.27 (2 H, d, J 8.5, 2$\times$CH); $\delta_{\text{C}}$ (100 MHz; CDCl$_3$) 19.8 (C22), 25.5 (C14), 26.5 (C20), 27.6 (C15), 31.0 (C33), 33.3 (C11), 52.3 (C31), 55.3 (C30), 55.5 (C6), 56.2 (C1), 62.1 (C16), 70.4 (C17), 72.9
(C23), 73.1 (C21), 79.7 (C12), 80.4 (C19), 84.5 (C18), 94.8 (C2), 100.7 (C4), 103.8 (C7), 108.6 (C13), 113.8 (C27 and C28), 128.7 (C10), 129.2 (C9), 129.3 (C24), 130.2 (C25 and C26), 137.6 (C8), 155.6 (C29), 161.3 (C3), 168.0 (C5) and 171.1 (C32); MS (FAB) m/z 599.3 [M+H]+; HRMS m/z 599.2862 (599.2856 calcd for C33H43O10, M+H+).

A solution of oxalyl chloride (0.19 cm³, 0.376 mmol) in anhydrous dichloromethane (2 cm³) was treated with dimethylsulfoxide (0.06 cm³, 0.752 mmol) at −78 °C. After 30 min, a solution of alcohol 222 (112 mg, 0.188 mmol) in anhydrous dichloromethane (1 cm³) was added and the reaction mixture stirred at −78 ° for 1 h. After this time, triethylamine (0.21 cm³, 1.50 mmol) was added and the reaction was allowed to warm to room temperature, where it was stirred for a further 30 min. The reaction mixture was diluted with dichloromethane (10 cm³) and quenched with 1 N hydrochloric acid (10 cm³). The phases were separated and the organic layer was washed with saturated aqueous sodium hydrogencarbonate (20 cm³), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (50:50)] of the crude residue afforded ketone 246 (95 mg, 85%) as a thick, yellow oil; Rf 0.53 (Solvent I); [α]D 3.1 (c 1.1, CHCl3); νmax (film)/cm⁻¹ 2203, 1714 (C=O), 1575 (C=C) and 1100; δH(400 MHz; CDCl3) 1.23 (3 H, d, J 6.1, CH₃), 1.32 (3 H, s, CCH₃), 1.56 (3 H, s, CCH₃), 2.27-2.66 (4 H, m, 2×CH₂), 3.39 (3 H, s, OCH₂OCH₃), 3.71 (3 H, s, OCH₂ArOCH₃), 3.65-3.73 (1 H, m,
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CHOPMB), 3.74 (3 H, s, OCH), 3.81 (3 H, s, CO₂CH₃), 4.36-4.43 (3 H, m, OCH and OCH₂ArOCH₃), 4.50 (1 H, d, J 7.3, OCH), 5.08 (2 H, s, OCH₂OCH₃), 6.08-6.18 (1 H, m, CH=CH), 6.38 (1 H, d, J 15.8, CH=CH), 6.54 (1 H, s, CH), 6.61 (1 H, s, CH), 6.79 (2 H, d, J 8.5, 2×CH) and 7.19 (2 H, d, J 8.5, 2×CH); δc(100 MHz; CDCl₃) 18.89 (C₂₂), 24.3 (C₁₅), 25.9 (C₂₀), 26.0 (C₁₄), 33.0 (C₁₁), 51.2 (C₃₁), 54.23 (C₃₀), 54.4 (C₆), 55.1 (C₁), 69.6 (C₂₃), 71.3 (C₂₁), 76.9 (C₁₂), 80.5 (C₁₉), 82.1 (C₁₆), 93.8 (C₁₈), 95.2 (C₂), 99.7 (C₄), 102.8 (C₇), 109.8 (C₃₃), 112.8 (C₂₇ and C₂₈), 115.5 (C₁₃), 128.0 (C₁₀), 128.2 (C₂₅ and 26), 128.3 (C₉), 129.1 (C₂₄), 136.2 (C₈), 154.5 (C₂₉), 158.2 (C₃), 160.2 (C₅), 167.3 (C₃₂) and 185.5 (C₁₇); MS (FAB) m/z 597.3 [M+H]⁺; HRMS m/z 597.2712 (597.2699 calcd for C₃₃H₄₁O₁₀, M+H⁺).

Methyl 4-methoxy-2-(((E)-3-[(4(S),5S)-5-[(R)-5-(4-methoxybenzyl)oxy]-1-triisopropylsilanyloxy-hex-2-ynyl]-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl)-6-methoxymethylbenzoate 221

To a solution of alcohol 222 (585 mg, 0.977 mmol) in anhydrous dimethylformamide (10 cm³) was added imidazole (199 mg, 2.93 mmol) and stirred until homogenous. Triisopropylsilyl chloride (0.25 cm³, 1.17 mmol) was then added at room temperature and the reaction was stirred for 16 h. The reaction mixture was then diluted with ethyl acetate (30 cm³) and quenched with water (40 cm³). The organic phase was washed with water (4×100 cm³), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (60:40)] of the crude residue afforded silyl ether 221 (386 mg, 52%, 83% based on starting material consumed) as a yellow oil (recovered starting material 216 mg); Rf 0.66 (Solvent I); [α]D²⁴ -
27.0 (c 1.0, CHCl₃); ν_{max}(film)/cm⁻¹ 2942, 2865, 1731 (C=O), 1600 (C=C), 1247, 1152 and 1048 (C-O); δ_{H}(400 MHz; CDCl₃) 1.01 (21 H, m, 3×SiCH(CH₃)₂), 1.12 (21 H, m, 3×SiC₃H₃), 1.29 (3 H, d, J 6.1, CH₃), 1.37 (3 H, s, CCH₃), 1.50 (3 H, s, CCH₃), 2.34 (1 H, dd, J 7.6 and 16.5, C≡CCH₂), 2.51-2.74 (3 H, m, CH=CHC₂H₂ and C≡CCH₂), 3.46 (3 H, s, OCH₂OCH₃), 3.60-3.67 (1 H, m, CHOPMB), 3.76 (3 H, s, OCH₂ArOC₃H₃), 3.81 (3 H, s, OC₃H₃), 4.09-4.29 (2 H, m, 2×CO), 4.48 (2 H, d, J 6.7, OCH₂ArOCH₃), 4.53 (1 H, d, J 6.8, HCOTIPS), 5.14 (2 H, s, OCH₂OCH₃), 6.18-6.25 (1 H, m, CH=CCH₂), 6.40 (1 H, dd, J 4.4 and 15.6, CH=CH), 6.60 (1 H, s, CH(Ar)), 6.69 (1 H, d, J 3.3, CH(Ar)), 6.87 (2 H, t, J 6.8, 2×CH(Ar)) and 7.24-7.28 (2 H, m, 2×CH(Ar)); δ_{C}(100 MHz; CDCl₃) 12.3 (C₃₄), 17.7 (C₃₅), 19.8 (C₂₂), 25.7 (C₁₅), 26.5 (C₂₀), 27.8 (C₁₄), 34.0 (C₁₁), 52.2 (C₃₁), 55.3 (C₃₀), 55.5 (C₆), 56.2 (C₁), 62.7 (C₁₇), 70.3 (C₂₃), 73.2 (C₂₁), 77.3 (C₁₂), 80.4 (C₁₆), 80.7 (C₁₉), 83.9 (C₁₈), 94.8 (C₂), 100.7 (C₄), 103.5 (C₇), 108.6 (C₃₃), 109.0 (C₁₃), 113.8 (C₂₇ and C₂₈), 128.2 (C₉), 129.2 (C₂₅ and C₂₆), 130.9 (C₂₄), 131.0 (C₁₀), 137.1 (C₈), 156.1 (C₂₉), 159.0 (C₃), 161.2 (C₅) and 168.0 (C₃₂); MS (FAB) m/z 777.3 [M+Na]⁺; HRMS m/z 777.4014 (777.4010 calcd for C₄₂H₆₂NaO₁₀Si, M+Na⁺).

A solution of alkyne 221 (270 mg, 0.357 mmol) in methanol (7 cm³) was treated with a catalytic amount of Pd/BaSO₄ catalyst and poisoned with quinoline (0.05 cm³, 0.45 mmol). The flask was evacuated and after purging three times with hydrogen gas via a balloon, the mixture was stirred under an atmosphere of hydrogen for 4 h at room temperature. TLC analysis deemed the reaction
complete and the solution was filtered through a pad of Celite® to remove the catalyst and the solvent concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (60:40)] of the crude residue afforded alkene 220 (225 mg, 83%) as a pale yellow oil; *R*$_f$ 0.72 (Solvent I); [α]$_D^{24}$ +26.7 (c 1.0, CHCl$_3$); ν$_{max}$(film)/cm$^{-1}$ 2963, 2918, 2851, 2363, 1969, 1734 (C=O), 1259,1014 and 793; δ$_H$(400 MHz; CDCl$_3$) 1.04 (3 H, s, 3×SiCH(CH$_3$)$_2$), 1.09 (18 H, s, 3×SiCH(CH$_3$)$_2$), 1.23 (3 H, d, J 6.1, CH$_3$), 1.32 (3 H, s, CCH$_3$), 1.42 (3 H, s, CCH$_3$), 2.22-2.69 (4 H, m, 2×CH$_2$), 3.45 (3 H, s, OCH$_2$OCH$_3$), 3.58-3.63 (1 H, m, CHOPMB), 3.77 (3 H, s, OCH$_2$ArOCH$_3$), 3.81 (3 H, s, OCH$_3$), 3.87 (3 H, s, COOCH$_3$), 3.92-4.16 (2 H, m, 2×CHO), 4.36-4.52 and 4.61-4.70 (3 H, m, OCH$_2$ArOCH$_3$ and HCOTIPS), 5.14 (2 H, s, OCH$_2$OCH$_3$), 5.48-5.68 (2 H, m, CH=CH), 6.20-6.30 (1 H, m, CH=CH), 6.44-6.47 (1 H, m, CH=CH) 6.59 (1 H, s, CH(Ar)), 6.74 (1 H, s, CH(Ar)), 6.85 (2 H, t, J 6.7, 2xCH(Ar)) and 7.24-7.27 (2 H, m, 2xCH(Ar)); δ$_C$(100 MHz; CDCl$_3$) 12.3 (C34), 17.7 (C35), 19.8 (C22), 25.6 (C15), 26.9 (C20), 27.4 (C14), 33.7 (C11), 52.0 (C31), 55.3 (C30), 55.4 (C6), 56.2 (C1), 60.4 (C17), 70.2 (C23), 74.3 (C21), 77.8 (C12), 80.5 (C16), 94.8 (C2), 99.2 (C4), 107.6 (C33), 107.8 (C7), 113.8 (C27 and C28), 117.3 (C13), 127.9 (C9), 129.2 (C25 and C26), 130.9 (C24), 131.0 (C19), 131.5 (C10), 132.3 (C18), 142.4 (C8), 155.5 (C29), 159.1 (C3), 161.2 (C5) and 168.7 (C32); MS (FAB) *m/z* 781.2 [M+Na]$^+$; HRMS *m/z* 779.4157 (779.4169 calcd for C$_{42}$H$_{64}$NaO$_{10}$Si, M+Na$^+$).
Methyl 2-{[(E)-3-[(4S,5S)-5-((Z)-(S)-5-hydroxy-1-triisopropylsilanyloxy-hex-2-enyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl]-4-methoxy-6-methoxymethylbenzoate 219

To a solution of PMB ether 220 (246 mg, 0.325 mmol) in dichloromethane (7 cm$^3$) and pH 7 buffer (7 cm$^3$) at 0 °C was added dichlorodicyanobenzoquinone (96 mg, 0.422 mmol). The reaction was allowed to warm to room temperature over 16 h. The reaction was then diluted with dichloromethane (30 cm$^3$) and quenched with saturated aqueous sodium hydrogencarbonate (30 cm$^3$). The aqueous layer was extracted with dichloromethane (3×30 cm$^3$) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated \textit{in vacuo}. Purification by FCC [petroleum ether-ethyl acetate (70:30)] of the crude residue afforded free alcohol 219 (160 mg, 77%) as a thick, yellow oil; $R_f$ 0.24 (Solvent B); $[\alpha]_D^{24} -19.0$ (c 0.9, CHCl$_3$); $\nu_{max}$ (film)/cm$^{-1}$ 2928, 2867, 1732 (C=O), 1601 (C=C), 1464, 1264, 1154 and 1048 (O-Si); $\delta$H(400 MHz; CDCl$_3$) 0.93 (3 H, s, 3×SiC$_3$H$_2$), 1.07 (18 H, s, 3×SiCH(CH$_3$)$_2$), 1.19 (3 H, dd, J 3.9 and 6.1, CH$_3$), 1.32 (3 H, s, CH$_3$), 1.40 (3 H, s, CH$_3$), 2.14-2.70 (4 H, m, 2CH$_2$), 3.46 (3 H, s, OCH$_2$OCH$_3$), 3.75 (3 H, s, OCH$_3$), 3.86 (3 H, s, COOCH$_3$), 3.91-4.19 (3 H, m, 2×CHO and CHOH), 4.66-4.78 (1 H, m, CHOTIPS), 5.12 (2 H, s, OCH$_2$OCH$_3$), 5.48-5.71 (2 H, m, CH=CH), 6.25-6.28 (1 H, m, CH=CH), 6.38-6.42 (1 H, m, CH=CH), 6.41 (1 H, d, J 2.2, CH(Ar)), and 6.54 (1 H, d, J 2.2, CH(Ar)); $\delta$C(100 MHz; CDC$_3$) 12.4 (C26), 18.2 (C27), 23.4 (C22), 25.5 (C15), 27.1 (C20), 27.5 (C14), 33.5 (C11), 52.0 (C23), 55.4 (C6), 56.2 (C1), 66.4 (C17), 68.1 (C21), 77.9 (C12), 80.4 (C16), 94.9 (C2), 99.2 (C4), 107.6 (C25), 108.1 (C7), 116.6 (C13), 127.0 (C9), 128.7 (C19), 132.2 (C10), 134.7 (C18), 142.4 (C8), 155.5 (C3), 161.2 (C5), and 168.1 (C24); MS (FAB) m/z 637.2 [M+H]$^+$; HRMS m/z 637.3768 (637.3772 calcd for C$_{34}$H$_{57}$O$_9$Si, M+H$^+$).
A solution of ester 219 (80 mg, 0.125 mmol) in ethanol (1 cm³) was treated with the dropwise addition of 2 N potassium hydroxide (1 cm³). The reaction mixture was heated under reflux for 48 h then cooled down to room temperature, diluted with water (5 cm³) and acidified to pH 1 with 6 N hydrochloric acid. The organics were extracted with ethyl acetate (2×10 cm³) and the combined organic phases were washed with water (7 cm³) then brine (7 cm³) and dried over anhydrous sodium sulfate. The solution was filtered and concentrated in vacuo. Purification by FCC [ethyl acetate (100)] of the crude residue afforded acid 218 (33 mg, 57%) as a thick, yellow oil; \( R_f \) 0.1 (Solvent I); \( [\alpha]_{D}^{22} -18.2 \) (c 1.0, CHCl₃); \( \nu_{\text{max}}\) (film)/cm⁻¹ 2940, 1591, 1447, 1253 and 1148; \( \delta_{H} \) (400 MHz: CDCl₃) 0.95 (3 H, s, 3×SiC₄H₁₂(CH₃)₂), 1.04 (18 H, s, 3×SiCH(CH₃)₂), 1.18 (3 H, dd, J 3.9 and 6.1, CH₃), 1.33 (3 H, s, CCH₃), 1.43 (3 H, s, CCH₃), 2.16-2.81 (4 H, m, 2xCH₂), 3.48 (3 H, s, OCH₂OCH₃), 3.82 (3 H, s, OCH₃), 3.97-4.36 (3 H, m, 2xCHO and CHO), 4.70-4.76 (1 H, m, CHOTIPS), 5.20 (2 H, s, OCH₂OCH₃), 5.59-5.71 (2 H, m, CH=CH), 6.12-6.23 (1 H, m, CH=CH), 6.44-6.47 (1 H, m, CH=CH), 6.51 (1 H, s, CH(Ar)), and 6.72 (1 H, s, CH(Ar)); \( \delta_{C} \) (100 MHz; CDCl₃) 12.9 (C25), 18.2 (C26), 23.1 (C22), 25.8 (C15), 27.8 (C17), 29.7 (C14), 34.0 (C11), 37.9 (C20), 55.6 (C6), 56.5 (C1), 67.9 (C21), 77.4 (C12), 80.3 (C16), 95.4 (C2), 100.9 (C4), 105.6 (C24), 108.7 (C7), 113.4 (C13), 127.1 (C9), 129.9 (C19), 130.3 (C10), 132.4 (C18), 139.9 (C8), 156.0 (C3), 161.7 (C5), and 168.2 (C23); MS (El) \( m/z \) 271.1 [H₃CCH(OH)CH₂CH=CHCH(OTIPS)]⁺.
Trichlorobenzoyl chloride (4.5 µL, 28.7 µmol) was added to a mixture of seco-acid 218 (17.9 mg, 28.7 µmol) and triethylamine (4.4 µL, 31.5 µmol) and the reaction mixture stirred at room temperature under argon for 2 h. The resulting mixture was filtered through a short pad of Celite® dilutrd with toluene (15 cm$^3$) and added to a refluxing solution of dimethylaminopyridine (21 mg, 0.172 mmol) in toluene (15 cm$^3$) over a period of 6 h. The reaction was then cooled down to room temperature, then diluted with diethyl ether (15 cm$^3$) and washed sequentially with 1 N hydrochloric acid (15 cm$^3$), saturated aqueous sodium hydrogen carbonate (2×15 cm$^3$) and brine (15 cm$^3$). The solution was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (70:30)] of the crude residue afforded lactone 227 (6.5 mg, 37%) as a thick, yellow oil; $R_f$ 0.61 (Solvent 1); $[^{13}C]_{D}$ -1.8 (c 1.0, CHCl$_3$); $\nu_{\text{max}}$(film)/cm$^{-1}$ 2935, 1269 and 1089 (O-Si); $\delta_H$(400 MHz; CDCl$_3$) 0.09 (3 H, s, 3×SiCH(CH$_3$)$_2$), 1.05 (18 H, s, 3×SiCH(CH$_3$)$_2$), 1.22-1.24 (3 H, m, CH$_3$), 1.32 (3 H, s, CCH$_3$), 1.48 (3 H, s, CCH$_3$), 2.18-2.21 (2 H, m, CH$_2$), 2.47-2.54 (2 H, m, CH$_2$), 3.42 (3 H, s, OCH$_2$OCH$_3$), 3.83 (3 H, s, OCH$_3$), 3.94-4.05 (3 H, m, 2×CHO and CHCH$_3$), 4.74-4.78 (1 H, m, CHOTIPS), 5.20 (2 H, s, OCH$_2$OCH$_3$), 5.61-5.76 (2 H, m, CH=CH), 6.44-6.47 (1 H, m, CH=CH), 6.65-6.69 (1 H, m, CH=CH), 6.61 (1 H, d, $J$ 2.1, CH), and 6.78 (1 H, s, CH); $\delta_C$(100 MHz; CDCl$_3$) 12.8 (C25), 18.3 (C26), 23.8 (C22), 26.4 (C15), 28.9 (C17), 29.7 (C14), 30.4 (C11), 38.7 (C20), 55.4 (C6), 76.1 (C16), 94.8 (C19), 111.4 (C18), 118.4 (C21), 120.4 (C1), 126.1 (C3), 126.8 (C13), 128.3 (C4), 135.6 (C5), 151.8 (C6), 157.8 (C7), 160.0 (C8), 164.1 (C9), 171.9 (C10), 189.3 (C12).
56.2 (C1), 68.2 (C21), 77.4 (C12), 81.4 (C16), 94.7 (C2), 100.6 (C4), 104.9 (C24),
107.8 (C7), 113.7 (C13), 128.8 (C9), 130.1 (C19), 131.0 (C10), 132.5 (C18), 137.8
(C8), 156.1 (C3), 161.4 (C5), and 167.8 (C23). The compound failed to ionise
under all mass spectrometry conditions attempted.

![Image of 13C Assignment]

Procedure B

A mixture of 2-methyl-6-nitrobenzoic anhydride (15.2 mg, 44 µmol),
dimethylaminopyridine (16.2 mg, 132 µmol) and powdered activated 4Å
molecular sieves in dry toluene (10 cm³) was stirred at room temperature for 30
min. A solution of seco-acid 218 (18.4 mg, 29 µmol) in dry toluene (6 cm³) was
then added slowly over 4 h. After the addition was complete, the reaction
mixture was stirred for 2 h at room temperature. The mixture was then diluted
with ethyl acetate (5 cm³), passed through a pad of Celite® and then washed
with saturated aqueous sodium hydrogen carbonate (10 cm³), water (10 cm³) and
brine (10 cm³). The solution was dried over anhydrous sodium sulfate, filtered
and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate
(80:20)] of the crude residue afforded lactone 227 (5 mg, 28%) as a thick, yellow
oil; Rf 0.57 (Solvent C). ¹H and ¹³C match that reported for Procedure A.

(2E,11Z)-(5S,9S,14R)-20-Methoxy-18-methoxymethyl-7,7,14-trimethyl-10-
triisopropylsilanyloxy-6,8,15-trioxa-tricyclo[15.4.0.0₅,₉]henicosa-
1(21),2,11,17,19-pentaen-16-one 228

To a solution of seco-acid 218 (27.5 mg, 44.1 µmol) in anhydrous toluene (6.3
cm³) was added triphenylphosphine (23 mg, 88.3 µmol) and the solution stirred
until dissolved. The mixture was cooled to 0 °C and diethyl azodicarboxylate
(DEAD) (14 μL, 88.3 μmol) was added slowly. After 5 min, the ice-water bath was removed and the reaction allowed to warm up to room temperature. After 30 min, the reaction was diluted with toluene (10 cm$^3$) and the solvent then evaporated slowly under vacuum to leave an orange viscous mass. Purification by FCC [petroleum ether–ethyl acetate (50:50)] of the residue afforded lactone 228 (19 mg, 71%) as a yellow oil; $R_f$ 0.67 (Solvent M); $[\alpha]_{D}^{22} +2.0$ (c 1.1, CHCl$_3$); $\nu_{\max }$(film)/cm$^{-1}$ 2929, 1262, 1089 (O-Si) and 1028; $\delta_{H}$(400 MHz; CDCl$_3$) 0.94 (3 H, s, 3×SiCH(CH$_3$)$_2$), 1.26 (3 H, d, $J$ 7.0, CH$_3$), 1.38 (3 H, s, CCH$_3$), 1.45 (3 H, s, CCH$_3$), 1.50-2.05 (2 H, 2×m, CH$_2$), 2.40-2.60 (2 H, m, CH$_2$), 3.44 (3 H, s, OCH$_2$OCH$_3$), 3.78 (3 H, s, OCH$_3$), 3.90-4.00 (2 H, m, 2×CHO), 4.22 (1 H, dd, $J$ 1.7 and 7.0, CHCH$_3$), 4.52 (1 H, dd, $J$ 8.2 and 9.3, CHOTIPS), 5.12 (2 H, s, OCH$_2$OCH$_3$), 5.42-5.90 (4 H, m, 2×CH=CH), 6.34 (1 H, d, $J$ 2.2, CH), and 6.54 (1 H, d, $J$ 2.2, CH); $\delta_{C}$(100 MHz; CDCl$_3$) 12.6 (C25), 18.1 (C26), 24.6 (C22), 26.9 (C15), 28.1 (C17), 29.6 (C14), 29.9 (C11), 36.7 (C20), 55.4 (C6), 56.2 (C1), 68.9 (C21), 77.3 (C12), 81.3 (C16), 94.6 (C2), 99.4 (C4), 107.4 (C24), 107.5 (C7), 116.9 (C13), 128.5 (C9), 130.5 (C19), 131.3 (C10), 132.5 (C18), 141.2 (C8), 155.3 (C3), 161.0 (C5), and 167.6 (C23). The compound failed to ionise under all mass spectrometry conditions attempted.

![12C Assignment](attachment:12C_assignment.png)

(2E,11Z)-(5S,9R,14R)-10-Hydroxy-20-methoxy-18-methoxymethyl-7,7,14-trimethyl-6,8,15-trioxa-tricyclo[15.4.0.05,9]henicosa-1(21),2,11,17,19-pentaen-16-one 229

Tetra-butylammonium fluoride (60 µL, 62.4 µmol) was added to a solution of TIPS ether 228 (19 mg, 31.2 µmol) in anhydrous tetrahydrofuran (1 cm$^3$). The reaction mixture was stirred at 0 °C for 10 min and was then allowed to warm up
to room temperature. After 1.25 h the reaction was diluted with diethyl ether (5 cm³) and quenched with water (5 cm³). The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to yield alcohol 229 as a yellow, thick oil; $\alpha$D +2.5 (c 1.0, CHCl₃); $\nu_{\text{max}}$ (film)/cm⁻¹ 1670 (C=O), 1159 and 1012; $\delta_H$(400 MHz; CDCl₃) 1.24 (3 H, d, CH₃), 1.35 (3 H, s, CCH₃), 1.44 (3 H, s, CCH₃), 1.80-2.05 (2 H, m, CH₂), 2.50-2.80 (2 H, m, CH₂), 3.45 (3 H, s, OCH₂OCH₃), 3.77 (3 H, s, OCH₃), 3.90-4.04 (2 H, m, 2×CHO), 4.27-4.29 (2 H, m, CHCH₃ and CHO), 5.12 (2 H, s, OCH₂OCH₃), 5.20-5.50 (2 H, m, CH=CH), 5.70-5.99 (2 H, m, CH=CH), 6.34 (1 H, d, J 2.0, CH) and 6.53 (1 H, d, J 2.0, CH); $\delta_C$(100 MHz; CDCl₃) 24.3 (C22), 26.3 (C15), 28.2 (C17), 29.3 (C14), 29.7 (C11), 35.2 (C20), 55.4 (C6), 56.2 (C1), 68.9 (C21), 77.6 (C12), 80.4 (C16), 94.5 (C2), 99.2 (C4), 107.4 (C24), 107.9 (C7), 116.9 (C13), 128.5 (C9), 130.1 (C19), 131.7 (C10), 132.1 (C18), 141.3 (C8), 154.9 (C3), 161.0 (C5), and 167.6 (C23).

A solution of pyridinium chlorochromate (16 mg, 77.4 µmol) in anhydrous dichloromethane (1 cm³) was treated with a solution of alcohol 229 (16.7 mg, 37.2 µmol) in anhydrous dichloromethane (1 cm³) at room temperature. After 3.5 h, the reaction mixture was diluted with dichloromethane (2 cm³) and passed through a short column of SiO₂, eluting with dichloromethane. The solvent was concentrated in vacuo to leave enone 230 (3.3 mg, 20%) as a thick, orange viscous mass; $R_f$ 0.71 (Solvent M); $\delta_H$(400 MHz; CDCl₃) 1.24 (3 H, d, J 6.4, CH₃),
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1.38 (3 H, s, CCH3), 1.45 (3 H, s, CCH3), 2.08-2.12 (2 H, m, CH2), 2.46-2.50 (2 H, m, CH2), 3.40 (3 H, s, OCH3OCH3), 3.73 (3 H, s, OCH3), 4.30-4.55 (2 H, m, CCH3 and CH2CHO), 4.72 (2 H, s, OCH3OCH3), 5.00-5.03 (1 H, m, CHO), 5.37-5.43 (2 H, m, CH=CH), 6.05-6.12 (2 H, m, CH=CH), 6.17 (1 H, d, J 2.8, CH), and 6.23 (1 H, d, J 2.8, CH). The lack of material prevented the acquisition of a full data set.

\[13^C\text{ Assignment}\]

(R)-(−)-Pent-4-yn-2-ol 233

A stirred suspension of lithium acetylide ethylenediamine complex (5.7 g, 62.0 mmol) in anhydrous dimethylsulfoxide (110 cm\(^3\)) at 0 °C was treated dropwise with \(R\)-(+)\)-propylene oxide (3.6 cm\(^3\), 51.6 mmol). The reaction was then allowed to warm up to room temperature, where it was stirred for 48 h. The suspension was poured onto ice (100 cm\(^3\)) and extracted with diethyl ether (4×80 cm\(^3\)). The combined ether extracts were washed with brine (6×30 cm\(^3\)), water (2×30 cm\(^3\)) and dried over anhydrous magnesium sulfate. Careful evaporation of the solvent at atmospheric pressure yielded the crude alcohol 233 which was taken on without any purification; \([\alpha]_{D}^{22}\) -18.0 (c 1.0, CHCl3); \(\nu_{\text{max}}\)\(\text{(film)/cm}^{-1}\) 3340 (OH), 3301 (C≡C) and 2360; \(\delta_{\text{H}}\)\(\text{(400 MHz; CDCl}_3\)) 1.20 (3 H, d, J 6.0, CH3), 2.10 (1 H, t, J 2.7, HC≡C), 2.33 (1 H, ddd, J 2.7, 5.3 and 16.0, CH2), 2.42 (1 H, ddd, J 2.7, 6.2 and 16.0, CH2) and 4.02-4.04 (1 H, m, HCOH); \(\delta_{\text{C}}\)\(\text{(100 MHz; CDCl}_3\)) 24.7 (CH3), 32.8 (CH2), 67.2 (HCOH), 71.1 (HC≡C) and 85.1 (HC=C); MS (Cl) \(m/z\) 67 [M-OH]\(^+\); HRMS \(m/z\) 67.0550 (67.0548 calcd for C5H7, M-OH\(^+\)).

1-Methoxy-4-((R)-1-methyl-but-3-ynloxy)methyl)-benzene 234

A suspension of 60% in mineral oil NaH (2.27 g, 56.7 mmol) at 0 °C, was diluted with anhydrous dimethylformamide (65 cm\(^3\)) and a solution of the freshly
generated crude alcohol 233 (4.34 g, 51.6 mmol) in anhydrous dimethylformamide (65 cm³) was added. The reaction mixture was stirred for 15 min, then p-methoxybenzyl chloride (10.5 cm³, 77.4 mmol) was added and the reaction mixture was allowed to warm up to room temperature and stirred for 17 h. The solution was then poured onto brine (400 cm³) and extracted with diethyl ether (3×100 cm³). The combined organic layers were concentrated under reduced pressure, then washed with brine (300 cm³), dried over anhydrous magnesium sulfate, filtered and the solvent concentrated. Purification by FCC [petroleum ether-ethyl acetate (95:5)] of the crude residue afforded PMB ether 234 (4.13 g, 40%) as a colourless oil; Rf 0.69 (Solvent A); [α]D 19 +11.2 (c 1.1, CHCl₃); νmax (film)/cm⁻¹ 2253, 911 and 739; δH (400 MHz; CDCl₃) 1.32 (3 H, d, J 6.0, CH₃), 2.04 (1 H, t, J 2.6, HC≡C), 2.38 (1 H, ddd, J 2.6, 7.0 and 16.6, CH₂), 2.52 (1 H, ddd, J 2.6, 4.9 and 16.6, CH₂), 3.70 (1 H, sext., J 6.0, CH), 3.86 (3 H, s, OCH₃), 4.53 (2 H, s, OCH₂), 6.91 (2 H, d, J 8.6, Ar) and 7.31 (2 H, d, J 8.6, Ar); δC (100 MHz; CDCl₃) 19.5 (CCH₃), 26.0 (CH₂), 55.3 (OCH₃), 69.9 (CH), 70.3 (HC≡C), 72.8 (OCH₂), 81.3 (HC≡C), 113.8 (2×CH), 129.2 (2×CH), 130.6 (C) and 159.1 (COCH₃); MS (EI) m/z 204.04 [M⁺]; HRMS m/z 204.1146 (204.1150 calcd for C₁₃H₁₆O₂, M⁺).

Methyl 2-((E)-3-[(4S,5R)-5-[(S)-1-hydroxy-5-(4-methoxybenzyl oxy)-hex-2-ynyl]-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl)-4-methoxy-6-methoxymethylbenzoate 235

A solution of alkyne 234 (82.4 mg, 0.403 mmol) in anhydrous tetrahydrofuran (2 cm³) was treated with ethyl magnesium bromide (0.13 cm³, 0.378 mmol) at room temperature and the resulting solution was stirred for 5.5 h.

Whilst the above deprotonation was being carried out, a −78 °C solution of oxalyl chloride (0.25 cm³, 0.504 mmol) in anhydrous tetrahydrofuran (3 cm³) was added dimethylsulfoxide (70 µL, 1.00 mmol). After stirring for 30 min a solution of alcohol 212 (100 mg, 0.252 mmol) in anhydrous tetrahydrofuran (1.5 cm³) was added and stirring continued for 1 h at −78 °C. After this time, triethylamine (0.28 cm³, 2.02 mmol) was added and the reaction allowed to warm up to room
temperature. After 30 min the reaction was cooled back down to $-78^\circ C$ and a solution of the deprotonated alkyne was added. The mixture was then allowed to warm up to room temperature overnight. The reaction was then quenched with saturated aqueous ammonium chloride (10 cm$^3$) and extracted with ethyl acetate (3×20 cm$^3$). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (50:50)] of the crude residue afforded propargylic alcohol 235 (113 mg, 75%) as a pale yellow oil and as an inseparable mixture of diastereoisomers; $R_f$ 0.27 (Solvent I); [α]$^\text{D}_{(25)}$ +0.04 (c 0.9, CHCl$_3$); $\nu_{\text{max}}$(film)/cm$^{-1}$ 3434, 3019, 1720 (C=O), 1602 (C=C), 1215, 765, 669; $\delta_{\text{H}}$(400 MHz; CDCl$_3$) 1.30 (3 H, s, CH$_3$), 1.38 (3 H, s, CCH$_3$), 1.54 (3 H, s, CCH$_3$), 2.39-2.78 (4 H, m, 2×CH$_2$), 3.50 (3 H, s, OCH$_2$OCH$_3$), 3.60-3.70 (1 H, m, CHOPMB), 3.81 (3 H, s, OCH$_3$ArOCH$_3$), 3.83 (3 H, s, OCH$_3$), 3.91 (3 H, s, CO$_2$CH$_3$), 4.20-4.30 (1 H, m, OCH), 4.43-4.47 (1 H, m, OCH), 4.45-4.55 (3 H, m, CHOH and OCH$_2$ArOCH$_3$), 5.18 (2 H, s, OCH$_2$OCH$_3$), 6.23-6.29 (1 H, m, CH=CH), 6.49 (1 H, d, J 15.7, CH=CH), 6.62 (1 H, s, CH), 6.71 (1 H, s, CH), 6.89 (2 H, d, J 8.5, 2×CH) and 7.27 (2 H, d, J 8.5, 2×CH); $\delta_{\text{C}}$(100 MHz; CDCl$_3$) 19.8 (C22), 25.5 (C14), 26.5 (C20), 27.6 (C15), 31.0 (C33), 33.3 (C11), 52.3 (C31), 55.3 (C30), 55.5 (C6), 56.2 (C1), 62.1 (C16), 70.4 (C17), 72.9 (C23), 73.1 (C21), 79.7 (C12), 80.4 (C19), 84.5 (C18), 94.8 (C2), 100.7 (C4), 103.8 (C7), 108.6 (C13), 113.8 (C27 and C28), 128.7 (C10), 129.2 (C9), 129.3 (C24), 130.2 (C25 and C26), 137.6 (C8), 155.6 (C29), 161.3 (C3), 168.0 (C5) and 171.1 (C32); MS (FAB) m/z 599.3 [M+H]$^+$; HRMS m/z 599.2843 (599.2857 calcd for C$_{33}$H$_{43}$O$_{10}$, M+H$^+$).
Propargylic alcohol 235 (113 mg, 0.188 mmol) was dissolved in anhydrous dimethylformamide (2 cm³), imidazole (38 mg, 0.566 mmol) added and the solution was stirred until homogenous. Triisopropylsilyle chlorid (0.05 cm³, 0.226 mmol) was then added at room temperature and the reaction left to stir overnight. The reaction mixture was diluted with ethyl acetate (10 cm³) and quenched with water (10 cm³). The organic layer was separated, extracted with water (3×30 cm³), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (50:50)] of the crude residue afforded TIPS ether 236 (114 mg, 80%) as a yellow oil; R̅f 0.60 (Solvent I); [α]D⁰ +2.2 (c 1.13, CHCl₃); ν max (film)/cm⁻¹ 2943, 2866, 1725 (C=O), 1601 (C=C), 1513, 1266, 1215, 1154, 757; δH (400 MHz; CDCl₃) 1.01-1.12 (21 H, m, TIPS), 1.29 (3 H, s, CH₃), 1.37 (3 H, s, CCH₃), 1.50 (3 H, s, CCH₃), 2.34 (1 H, dd, J 7.6 and 16.5, C≡CH₂ and C≡CH₂), 3.46 (3 H, s, OCH₂OC₃H₃), 3.61-3.67 (1 H, m, CH=CH₂ and C≡CH₂), 3.64 (3 H, s, OCH₂ArOC₃H₃), 3.81 (3 H, s, OCH₃), 3.88 (3 H, s, COOCH₃), 4.09-4.29 (2 H, m, 2×CHO), 4.48 (2 H, d, J 6.7, OCH₂PhOCH₃), 4.53 (1 H, d, J 6.4, HCOTIPS), 5.14 (2 H, s, OCH₂OCH₃), 6.22-6.31 (1 H, m, CH=CH), 6.40 (1 H, dd, J 4.4 and 15.6, CH=CH), 6.60 (1 H, s, CH(Ar)), 6.69 (1 H, d, J 3.3, CH(Ar)), 6.87 (2 H, t, J 6.8, 2×CH(Ph)) and 7.22-7.27 (2 H, m, 2×CH(Ph)); δC (100 MHz; CDCl₃) 12.3 (C₃₄), 17.7 (C₃₅), 19.8 (C₂₂), 25.7 (C₁₅), 26.5 (C₂₀), 27.8 (C₁₄), 34.0 (C₁₁), 52.2 (C₃₁), 55.3 (C₃₀), 55.5 (C₆), 56.2 (C₁), 62.8 (C₁₇), 70.3 (C₂₃), 73.2 (C₂₁), 77.3 (C₁₂), 80.5 (C₁₆), 80.7 (C₁₉), 83.7 (C₁₈), 94.8 (C₂), 100.7 (C₄), 103.6 (C₇), 108.5 (C₃₃), 109.0 (C₁₃), 113.8 (C₂₇ and C₂₈), 128.3 (C₉), 129.2 (C₂₅ and C₂₆), 130.9 (C₂₄), 131.0 (C₁₀), 137.1 (C₈), 156.1 (C₂₉), 159.0 (C₃), 161.2 (C₅) and 168.0 (C₃₂); MS (FAB) m/z 777.7 [M+Na]+; HRMS m/z 777.4019 (777.4012 calcd for C₄₂H₆₂NaO₁₀Si, M+Na⁺).
Methyl 4-methoxy-2-((E)-3-{{(4S,5S)-5-[(Z)-(R)-5-(4-methoxy-benzyloxy)-1-triisopropylsilyloxy-hex-2-enyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-propenyl)-6-methoxymethylbenzoate 237

A solution of TIPS ether 236 (59 mg, 0.0779 mmol) in methanol (1.5 cm³) was treated with a catalytic amount of Pd/BaSO₄ catalyst and poisoned with quinoline (0.01 cm³, 97.3 µmol). The flask was evacuated and after purging three times with hydrogen gas via a balloon, the mixture was stirred under an atmosphere of hydrogen for 2 h at room temperature. TLC analysis deemed the reaction complete and the solution was filtered through a pad of Celite® to remove the catalyst and the solvent concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (60:40)] of the crude residue afforded alkene 237 (53 mg, 89%) as a pale yellow oil; Rf 0.68 (Solvent I); [α]D²⁶ -2.4 (c 0.9, CHCl₃); νmax(film)/cm⁻¹ 2943, 2865, 1729 (C=O), 1602 (C=C), 1513; δH(400 MHz; CDCl₃) 1.04 (3 H, s, 3×CH(CH₃)₂), 1.09 (18 H, s, 3 CH(CH₃)₂), 1.23 (3 H, d, J 6.1, CH₃), 1.32 (3 H, s, CCH₃), 1.42 (3 H, s, CCH₃), 2.22-2.69 (4 H, m, 2×CH₂), 3.45 (3 H, s, OCH₂OCH₃), 3.56-3.60 (1 H, m, CH₂OPMB), 3.77 (3 H, s, OCH₂ArOC₃H₃), 3.81 (3 H, s, OCH₃), 3.87 (3 H, s, COOCH₃), 3.92-4.16 (2 H, m, 2×CHO), 4.36-4.52 (2 H, m, OCH₂ArOCH₃), 4.61-4.70 (1 H, m, HCOTIPS), 5.14 (2 H, s, OCH₂OCH₃), 5.48-5.68 (2 H, m, CH=CH), 6.25-6.31 (1 H, m, CH=CH), 6.43-6.47 (1 H, m, CH=CH) 6.59 (1 H, s, CH(Ar)), 6.74 (1 H, s, CH(Ar)), 6.85 (2 H, d, J 6.7, 2×CH(Ar)) and 7.24-7.27 (2 H, m, 2×CH(Ar)); δC(100 MHz; CDCl₃) 12.8 (C34), 17.7 (C35), 19.8 (C22), 25.6 (C15), 27.0 (C20), 27.5 (C14), 34.0 (C11), 52.1 (C31), 55.3 (C30), 55.5 (C6), 56.2 (C1), 68.1 (C17), 70.1 (C23), 74.3 (C21), 77.6 (C12), 80.3 (C16), 94.8 (C2), 100.7 (C4), 108.2 (C33), 108.3 (C7), 113.8 (C27 and C28), 117.0 (C13), 128.2 (C9), 129.2 (C25 and C26), 130.9 (C24), 131.0 (C19), 131.2 (C10), 132.3
(C18), 142.4 (C8), 155.5 (C29), 159.1 (C3), 161.2 (C5) and 168.7 (C32); MS (FAB) m/z 779.7 [M+Na]+; HRMS m/z 779.4168 (779.4169 calcd for C_{42}H_{64}NaO_{10}Si, M+Na+).

Methyl 2-{[(E)-3-[(4S,5S)-5-[(Z)-(R)-5-hydroxy-1-triisopropylsilanyloxy-hex-2-enyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl]-4-methoxy-6-methoxymethylbenzoate 238

PMB ether 237 (148 mg, 0.195 mmol) was dissolved in a mixture of dichloromethane (2 cm³) and pH 7 buffer (2 cm³) and cooled to 0 °C. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (58 mg, 25.4 µmol) was then added with vigorous stirring and the reaction allowed to warm up to room temperature overnight. After this time, the reaction was re-cooled to 0 °C and further 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (58 mg, 25.4 µmol) was added. After allowing the reaction to warm up to room temperature overnight, the reaction mixture was diluted with dichloromethane (15 cm³) and quenched with saturated aqueous sodium hydrogen carbonate (15 cm³). The aqueous layer was separated and extracted with dichloromethane (3×40 cm³). The combined organic layers were washed with brine (40 cm³), dried over anhydrous Na_{2}SO_{4}, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (60:40)] of the crude residue afforded alcohol 238 (108 mg, 87%) as a yellow oil; R_{f} 0.52 (Solvent I); [α]_{D}^{26} -0.03 (c 1.4, CHCl_{3}); ν_{max}(film)/cm⁻¹ 3450, 2942, 2865, 1721 (C=O), 1598, 1150; δ_{H}(400 MHz; CDCl_{3}) 0.93 (3 H, s, 3×CH(CH_{3})_{2}), 1.06 (18 H, s, 3×CH(CH_{3})_{2}), 1.18 (3 H, d, J 6.1, CH_{3}), 1.31 (3 H, s, CCH_{3}), 1.46 (3 H, s, CCH_{3}), 2.12-2.18 (1 H, m, CH_{2}), 2.23-2.32 (1 H, m, CH_{2}), 2.45-2.63 (2 H, m, CH_{2}),
3.45 (3 H, s, OCH$_2$OCH$_3$), 3.80 (3 H, s, OCH$_3$), 3.86 (3 H, s, COOCH$_3$), 3.96-4.02 (1 H, dd, $J$ 5.6 and 8.9, CHO), 4.22-4.29 (1 H, m, CHOH), 4.73 (1 H, t, $J$ 8.5, CHOTIPS), 5.12 (2 H, s, OCH$_2$OCH$_3$), 5.56-5.67 (2 H, m, CH=CH), 6.23-6.30 (1 H, m, CH=CH), 6.40 (1 H, d, $J$ 15.7, CH=CH), 6.57 (1 H, d, $J$ 2.2, CH(Ar)) and 6.71 (1 H, d, $J$ 2.2, CH(Ar)); $\delta$$_C$(100 MHz; CDCl$_3$) 12.9 (C26), 18.2 (C27), 23.8 (C22), 26.1 (C15), 28.1 (C17), 29.7 (C14), 34.4 (C11), 38.7 (C20), 52.1 (C23), 55.4 (C6), 56.2 (C1), 66.7 (C21), 77.7 (C12), 80.3 (C16), 94.8 (C2), 100.7 (C4), 103.7 (C25), 108.8 (C7), 116.5 (C13), 128.7 (C9), 129.9 (C19), 130.4 (C10), 133.8 (C18), 137.5 (C8), 155.5 (C3), 161.2 (C5), and 168.4 (C24); MS (EI) m/z 636.6 [M]$^+$; HRMS m/z 636.3699 (636.3694 calcd for C$_{34}$H$_{56}$O$_9$Si, M$^+$).

$^{13}$C Assignment

2-[(E)-3-[(4S,5S)-5-((Z)-(R)-5-Hydroxy-1-triisopropylsilanyloxy-hex-2-enyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl]-4-methoxy-6-methoxymethylbenzoic acid 239

Methyl ester 238 (79 mg, 0.124 mmol) was dissolved in ethanol (1.5 cm$^3$) and 2 N potassium hydroxide (1.5 cm$^3$) was added dropwise. A colour change from yellow to orange was observed after the addition of base. The reaction was heated under reflux for 48 h whereafter it was cooled down to room temperature and diluted with water (10 cm$^3$). The solution was acidified to pH 1-2 using 6 N hydrochloric acid and was then extracted with ethyl acetate (3×15 cm$^3$). The combined organic layers were washed with water (20 cm$^3$), then brine (20 cm$^3$), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (80:20)] of the crude residue afforded seco-acid 239 (47 mg, 61%) as a thick, pale orange oil; $R_t$ 0.17 (Solvent I); $[\alpha]_D^{21}$ -0.1 (c 1.0, CHCl$_3$); $\nu$$_{max}$(film)/cm$^{-1}$ 3447, 2941, 2866, 2359,
1724 (C=O), 1604 (C=C), 1248, 1155 and 1041 (C-O); δH(400 MHz; CDCl₃) 0.94 (3 H, s, 3×CH(CH₃)₂), 1.02 (18 H, s, 3×CH(CH₃)₂), 1.21 (3 H, d, J 6.1, CH₃), 1.30 (3 H, s, CCH₃), 1.47 (3 H, s, CCH₃), 2.08-2.45 (2 H, m, CH₂), 2.80-3.00 (2 H, m, CH₂), 3.52 (3 H, s, OCH₂OCH₃), 3.82 (3 H, s, OCH₃), 3.94-4.20 (3 H, m, 2×CHO and CHOH), 4.63-4.67 (1 H, m, CHOTIPS), 5.23 (2 H, s, OCH₂OCH₃), 5.59-5.71 (2 H, m, CH=CH), 6.20-6.27 (1 H, m, CH=CH), 6.42-6.48 (1 H, m, CH=CH), 6.51 (1 H, s, CH(Ar)), and 6.72 (1 H, s, CH(Ar)); δC(100 MHz; CDCl₃) 12.5 (C25), 18.2 (C26), 23.5 (C22), 26.0 (C15), 28.0 (C17), 29.7 (C14), 34.4 (C11), 38.7 (C20), 55.4 (C6), 56.5 (C1), 67.0 (C21), 77.5 (C12), 80.3 (C16), 95.3 (C2), 100.7 (C4), 105.5 (C24), 108.9 (C7), 114.0 (C13), 128.7 (C9), 130.2 (C19), 131.0 (C10), 133.0 (C18), 139.7 (C8), 156.2 (C3), 161.7 (C5), and 169.0 (C23); MS (FAB) m/z 645.6 [M+Na]+; HRMS m/z 645.3436 (645.3437 calcd for C₃₃H₅₄NaO₉Si, M+Na⁺).

(2E,11Z)-(5S,9S,14S)-20-Methoxy-18-methoxymethyl-7,7,14-trimethyl-10-triisopropylsilylanylox-6,8,15-trioxa-tricyclo[15.4.0.0⁵,⁹]henicosa-1(21),2,11,17,19-pentaen-16-one 227

Seco-acid 239 (45 mg, 72.4 µmol) was dissolved in anhydrous toluene (10 cm³) and triphenylphosphine (38 mg, 145 µmol) was added at room temperature. The mixture was stirred until homogenous and then the reaction mixture was cooled down to 0 °C at which stage, diethyl azodicarboxylate (20 µL, 145 µmol) was added dropwise. The ice-water bath was removed after 5 min and after a further 5 min, TLC analysis (solvent M) showed the total consumption of starting material. The solvent was then carefully evaporated in vacuo. Purification by FCC [petroleum ether - ethyl acetate (70:30)] of the crude residue afforded lactone 227 (31 mg, 73%) as a yellow oil; Rf 0.87 (Solvent M); [α]D₂¹ -1.6 (c 1.0,
CHCl$_3$; $\nu_{\text{max}}$(film)/cm$^{-1}$ 3439, 2941, 2866, 1725 (C=O), 1606 (C=C), 1249; $\delta_H$(400 MHz; CDCl$_3$) 0.80 (3 H, s, 3×CH(CH$_3$)$_2$), 0.99 (18 H, s, 3×CH(CH$_3$)$_2$), 1.18 (3 H, s, CH$_3$), 1.26 (3 H, s, CCH$_3$), 1.42 (3 H, s, CCH$_3$), 2.02-2.70 (4 H, m, 3×CH$_2$), 3.38 (3 H, s, OCH$_2$OCH$_3$), 3.70 (3 H, s, OCH$_3$), 3.75q4.05 (3 H, m, 2×CHO and CHCH$_3$), 4.73q4.76 (1 H, m, CH$_3$OTIPS), 5.08 (2 H, s, OCH$_2$OCH$_3$), 5.47q5.76 (2 H, m, CH=CH), 6.07q6.13 (1 H, m, CH=CH), 6.25-6.29 (1 H, m, CH=CH), 6.45 (1 H, s, CH), and 6.51 (1 H, s, CH); $\delta_C$(100 MHz; CDCl$_3$) 12.8 (C$_{25}$), 18.3 (C$_{26}$), 23.8 (C$_{22}$), 26.4 (C$_{15}$), 28.9 (C$_{17}$), 29.7 (C$_{14}$), 30.4 (C$_{11}$), 38.7 (C$_{20}$), 55.5 (C$_6$), 56.2 (C$_1$), 68.2 (C$_{21}$), 77.2 (C$_{12}$), 81.4 (C$_{16}$), 94.7 (C$_2$), 100.6 (C$_4$), 104.9 (C$_{24}$), 107.8 (C$_7$), 113.7 (C$_{13}$), 128.8 (C$_9$), 130.1 (C$_{19}$), 131.0 (C$_{10}$), 132.5 (C$_{18}$), 137.8 (C$_8$), 156.1 (C$_3$), 161.4 (C$_5$), and 167.8 (C$_{23}$); MS (FAB) m/z 627 [M+Na]$^+$; HRMS m/z 627.3324 (627.3329 calcd for C$_{33}$H$_{52}$NaO$_8$Si, M+Na$^+$).

Lactone 227 (31 mg, 51.9 µmol) was dissolved in anhydrous tetrahydrofuran (2 cm$^3$) and the solution was cooled down to 0 °C. tetra-Butylammonium fluoride (0.1 cm$^3$, 0.104 mmol) was added and the ice-water bath removed after 10 min. After 1 h, the reaction mixture was diluted with ethyl acetate (10 cm$^3$) and water (10 cm$^3$). The organic layer was separated and dried over anhydrous sodium sulfate, filtered and concentrated in vacuo, to afford alcohol 226 which was used without any further purification; $R_f$ 0.18 (Solvent C); $[\alpha]_D^{14} -2.8$ (c 1.0, CHCl$_3$); $\nu_{\text{max}}$(film)/cm$^{-1}$ 3360 (OH), 2922, 2851, 1720 (C=O), 1661 (C=C), 1468, 1155 and 1043 (C-O); $\delta_H$(400 MHz; CDCl$_3$) 1.16 (3 H, s, CH$_3$), 1.22 (3 H, s, CCH$_3$),
1.40 (3 H, s, CCH₃), 2.00-2.63 (4 H, m, 2×CH₂), 3.38 (3 H, s, OCH₂OCH₃), 3.68 (3 H, s, OCH₃), 3.75-4.00 (3 H, m, 2×CHO and CHCH₃), 4.33-4.37 (1 H, m, CHOH), 5.10 (2 H, s, OCH₂OCH₃), 5.47-5.76 (2 H, m, 2×CH=CH), 5.90-6.10 (2 H, m, 2×CH=CH), 6.45 (1 H, s, CH), and 6.51 (1 H, s, CH); δc (100 MHz; CDCl₃) 23.8 (C22), 26.5 (C15), 28.9 (C17), 29.7 (C14), 30.4 (C11), 38.8 (C20), 55.4 (C6), 56.2 (C1), 68.2 (C21), 77.2 (C12), 81.4 (C16), 94.7 (C2), 100.6 (C4), 104.9 (C24), 107.9 (C7), 113.7 (C13), 128.8 (C9), 130.1 (C19), 131.0 (C10), 132.5 (C18), 137.8 (C8), 156.1 (C3), 161.4 (C5), and 168.0 (C23).

Pyridinium chlorochromate (29 mg, 132 µmol) was dissolved in anhydrous dichloromethane (1.6 cm³) and a solution of alcohol 226 (30 mg, 66 µmol) in anhydrous dichloromethane (1.6 cm³) was added at room temperature. The reaction was stirred for 18 h and then decanted into a clean flask and the residue washed with dichloromethane (2×10 cm³). The solvent was concentrated in vacuo and the residual material diluted with diethyl ether (20 cm³). The suspension was filtered through cotton wool to remove the chromium salts. The ethereal component was washed with 1 M sodium hydroxide (15 cm³), then brine (15 cm³) and dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to leave an orange/brown residue. Purification by FCC [petroleum ether - ethyl acetate (50:50)] of the crude residue afforded protected LLqZ1640q 225 (10 mg, 34%); Rf 0.38 (Solvent C); [α]D₉₀° -0.16 (c 1.0, CHCl₃); νmax (film)/cm⁻¹ 2952 (C-H), 1760 (C=O), 1599 (C=C), 1019 and 979; δH (400 MHz; CDCl₃) 1.24 (6...
H, s, 2×CH₃), 1.32 (3 H, d, J 12.6, CH₃), 2.45-2.70 (4 H, m, 2×CH₂), 3.43 (3 H, s, OCH₂OCH₃), 3.75 (3 H, s, OCH₃), 4.41-4.43 (1 H, m, CH₂CHO), 4.53-4.56 (1 H, m, HCCCH₃), 4.63 (1 H, d, J 7.8, CHO), 5.08-5.15 (1 H, m, CH=CH), 5.29 (2 H, s, OCH₂OCH₃), 5.43-5.48 (1 H, m, CH=CH(C=O)), 6.01-6.05 (1 H, m, CH=CH(C=O)), 6.30-6.54 (2 H, m, CH=CH and CH) and 6.54 (1 H, m, CH). The lack of material prevented the acquisition of a full data set.

2-[(4S,5S)-5-((tert-Butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl]acetaldehyde 252

Alkene 208 (620 mg, 2.16 mmol) was dissolved in dichloromethane (15 cm³) and ozone was bubbled through the solution at −78 °C until the blue colour persisted (15 min). The reaction was quenched with dimethylsulfide (500 eq., 80 cm³, 1.08 mol; added periodically in 20 cm³ aliquots) and the resulting solution warmed up to room temperature and stirred until the disappearance of the ozonide (approx. 4 d). The reaction mixture was washed with water (25 cm³) and the organic layers separated. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford aldehyde 252 (650 mg, 100%) as a colourless oil; Rf 0.44 (Solvent E); [α]D²³ +1.9 (c 1.0, CHCl₃) (lit.,[151] [α]D²³ +2.2 (c 5.0, CHCl₃); δH(400 MHz; CDCl₃) 0.00 (6 H, s, Si(CH₃)₂), 0.82 (9 H, s, SiC(CH₃)₃), 1.30 (3 H, s, CH₃), 1.36 (3 H, s, CH₃), 2.68 (1 H, dd, J 7.8 and 16.8, CH₂), 2.80 (1 H, dd, J 5.6 and 16.8, CH₂), 3.52-3.56 (2 H, m, CH₂OTBS), 4.11 (1 H, dd, J 5.6 and 12.1, CHCH₂), 4.65 (1 H, dd, J 6.2 and 12.6, CHCH₂OTBS) and 9.74 (1 H, s, CHO); δC(100 MHz; CDCl₃) -5.5 (Si(CH₃)₂), 18.2 (Si-C), 25.3 (CH₃), 25.8 (SiC(CH₃)₃), 27.9 (CH₃), 43.7 (CH₂), 61.5 (CH₂OTBS), 71.9 (CH), 108.3 (C(CH₃)₂) and 200.1 (C=O). All spectral data matches that reported in the literature.[151]
**tert-Butyl[(4S,5S)-5-(3,3-dibromoallyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy]dimethylsilane 251**

A solution of aldehyde 252 (656 mg, 2.18 mmol) in anhydrous dichloromethane (27 cm³) at room temperature was treated sequentially with carbon tetrabromide (2.9 g, 8.73 mmol), zinc dust (571 mg, 8.73 mmol) and triphenylphosphine (2.3 g, 8.73 mmol). The addition of triphenylphosphine was done in portions so as to keep the reaction temperature at 25 °C. Over the reaction time, the colour changed from a green solution to a pinkish brown colour. After 1.5 h, the reaction was diluted with hexanes (100 cm³), passed through a pad of silica gel and washed with diethyl ether. The solvent was concentrated *in vacuo* to afford dibromide 251 (995 mg, 100%) as a colourless oil, which was used without any further purification; *Rf* 0.79 (Solvent A); [α]$_D^{20}$ -0.14 (c 1.4, CHCl₃); $\nu_{max}$ (film)/cm$^{-1}$ 2486, 2071, 1193 and 1121 (C=O); $\delta$(400 MHz; CDCl₃) 0.05 (6 H, s, Si(CH$_3$)$_2$), 0.85 (9 H, s, SiC(CH$_3$)$_3$), 1.31 (3 H, s, CH$_3$), 1.41 (3 H, s, CH$_3$), 2.22-2.30 (1 H, m, CH$_2$), 2.36-2.43 (1 H, m, CH$_2$), 3.64 (2 H, d, J 6.0, CH$_2$OTBS), 4.10 (1 H, q, J 6.0, CHCH$_2$), 4.18-4.23 (1 H, m, CHCH$_2$OTBS) and 6.54 (1 H, t, J 6.8, CH=Br$_2$); $\delta$(100 MHz; CDCl₃) -2.5 (Si(CH$_3$)$_2$), 19.1 (SiC(CH$_3$)$_3$), 26.3 (2×CH$_3$), 26.5 (SiC(CH$_3$)$_3$), 36.3 (CH$_2$), 64.7 (CH$_2$OTBS), 71.8 (CH), 75.9 (CH), 90.1 (C=CBr$_2$), 108.0 ((C(CH$_3$)$_2$) and 137.6 (C=CBr$_2$); MS (Cl) m/z 310.2 [M-OTBS]$^-$; HRMS m/z 310.9284 (310.9282 calcd for C$_9$H$_{13}$Br$_2$O$_2$, M-OTBS$^-$).

**tert-Butyl[(4S,5S)-2,2-dimethyl-5-prop-2-ynyl-[1,3]-dioxolan-4-ylmethoxy]-dimethylsilane 70**

Dibromoolefin 251 (1.0 g, 2.19 mmol) was dissolved in anhydrous tetrahydrofuran (27 cm³), cooled down to −78 °C and treated with nBuLi (1.6 M in hexanes, 2.7 cm³, 4.38 mmol). The reaction was kept at −78 °C for 2 h and then quenched with water (40 cm³). The mixture was stirred for 15 min at −78 °C and then allowed to warm up slowly to 0 °C and then room temperature. The reaction mixture was extracted with ethyl acetate (3×40 cm³) and the combined
organics were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether - ethyl acetate (97:3)] of the crude residue afforded alkyne 70 (395 mg, 61%) as a yellow oil; $R_f$ 0.57 (Solvent D); $\left[\alpha\right]_{D}^{20} -0.2$ (c 1.0, CHCl$_3$); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2477 (C≡C), 2051, 1201 and 1120 (C=O); $\delta_H$(400 MHz; CDCl$_3$) 0.15 (6 H, s, Si(CH$_3$)$_2$), 0.88 (9 H, s, SiC(CH$_3$)$_3$), 1.34 (3 H, s, CH$_3$), 1.45 (3 H, s, CH$_3$), 2.02 (1 H, t, J 2.6, C≡CH), 2.44-2.62 (2 H, m, CH$_2$), 3.71 (2 H, dd, $J$ 5.0 and 6.8, CH$_2$OTBS), 4.15 (1 H, q, J 6.0, CH$_2$CH$_2$OTBS) and 4.30-4.34 (1 H, m, CH$_2$CH$_3$); $\delta_C$(100 MHz; CDCl$_3$) $q_{5.4}$ (Si(CH$_3$)$_2$), 20.1 (SiC(CH$_3$)$_3$), 25.4 (CH$_2$), 25.9 (SiC(CH$_3$)$_3$), 27.8 (CH$_3$), 29.7 (CH$_3$), 61.5 (CH$_2$OTBS), 69.7 (HC≡C), 75.7 (HC≡CCH$_2$C), 77.4 (CCH$_2$OTBS), 81.2 (HC≡C) and 108.6 (C(CH$_3$)$_2$); MS (CI) $m/z$ 153.1 [M+OTBS$^+$]; HRMS $m/z$ 153.0912 (153.0916 calcd for C$_9$H$_{13}$O$_2$, M+OTBS$^+$).

tert-Butyl-[(4S,5S)-2,2-dimethyl-5-((E/Z)-3-tributylstannyl-allyl)-[1,3]-dioxolan-4-ylmethoxy]-dimethylsilane 250

Procedure A

A solution of alkyne 70 (40 mg, 0.135 mmol) and bis(triphenylphosphine)palladium dichloride ((Ph$_3$P)$_2$PdCl$_2$) (catalytic amount) in anhydrous tetrahydrofuran (2 cm$^3$) at room temperature, was treated by the slow addition of a solution of tributyltinhydride (40 µL, 142 µmol) in tetrahydrofuran (0.2 cm$^3$). Upon addition, the colour of the solution changed from pale yellow to orange-brown. After 20 min, the now brown coloured reaction was complete and the mixture was concentrated in vacuo. Purification by FCC [petroleum ether-diethyl ether (95:5)] of the crude residue afforded stannane 250 (62 mg, 79%) as a colourless oil and as an inseparable trans:cis mixture; $R_f$ 0.83 (Solvent E); $\left[\alpha\right]_{D}^{20} -1.8$ (c 0.7, CHCl$_3$); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2928, 2362 and 1255; $\delta_H$(400 MHz; CDCl$_3$) (trans) 0.04 (6 H, s, Si(CH$_3$)$_2$), 0.80-0.92 (24 H, m, SiC(CH$_3$)$_3$, (CH$_3$)$_3$, (CH$_2$)$_3$), 1.20-1.36 (9 H, m, CH$_3$, (CH$_2$)$_3$), 1.38 (3 H, s, CH$_3$), 1.40-1.60 (6 H, m, (CH$_2$)$_3$), 2.22-2.45 (2 H, m, (CH$_2$)$_3$), 3.53-3.70 (2 H, m, CH$_2$OTBS), 4.03-4.09 (1 H, m, CHCH$_2$OTBS), 4.14-4.20 (1 H, m, CHCH$_2$), 5.05 (1 H, d, $J$ 19.0, CH≡CH) and 5.81-5.83 (1 H, m, CH≡CH); (cis) (inter alia) 5.08 (1 H, d,
**J 11.5, (CH=CH).** MS (Cl) m/z 291.3 [Bu3Sn]+, 361.5 [Bu3SnCH=CHCH2CH2OH], 461.4 [M-TBS]+ and 577.6 [M+H]+.

**Procedure B**

Alkyne 70 (41.6 mg, 0.1403 mmol) in toluene (5 cm³) was treated with 2,2'-azobis(2-methyl)propionitrile (AIBN) (1.2 mg, 7 µmol) and Bu3SnH (0.04 cm³, 0.154 mmol) under argon. The mixture was heated to 95 °C for 24 h. The reaction mixture was then cooled down to room temperature and the solvent evaporated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (100:0)→(98.5:1.5)] of the crude residue afforded an inseparable mixture of E:Z-stannane 250 and alkene 208 (70 mg, 85%) as a colourless oil; Rf 0.54 (Solvent E). The spectral data matches that for Procedure A.

**Methyl 2-hydroxy-4-methoxy-6-(trifluoromethylsulfonyloxy)benzoate 256**

A solution of triflate 119 (1.23 g, 2.77 mmol) in anhydrous tetrahydrofuran (15 cm³) at 0 °C, was treated with tetra-butylammonium fluoride (5.5 cm³, 5.53 mmol) and the ice-water bath was removed after 10 min. After 2 h, the reaction mixture was diluted with ethyl acetate (20 cm³) and quenched with water (20 cm³). The phases were separated and the aqueous layer was extracted with ethyl acetate (20 cm³). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (80:20)] of the crude residue afforded phenol 256 (754 mg, 83%) as a white solid; Rf 0.62 (Solvent A); mp 35-38 °C (from petroleum ether-ethyl acetate); v_max (film)/cm⁻¹ 3367, 1671 (C=O), 1635 (C=C), 1570, 1427, 1341, 1219; δ_H(400 MHz; CDCl3) 3.74 (3 H, s, OCH₃), 3.88 (3 H, s, CO₂CH₃), 6.25 (1 H, s, CH), 6.39 (1 H, s, CH) and 11.59 (1 H, s, OH); δ_C(100 MHz; CDCl₃) 52.5 (CO₂CH₃), 56.0 (OCH₃), 100.3 (CCOH), 100.9 (CO₂CH₃), 103.2 (HCCOTf), 149.5 (COTf), 164.5 (COH), 165.3 (COCH₃) and 168.8 (CO₂CH₃); MS (Cl) m/z 331.2 [M+H]+; HRMS m/z 331.0100 (331.0100 calcd for C₁₀H₁₀F₃O₇S, M+H⁺).
Methyl 4-methoxy-2-(methoxymethyl)-6-(trifluoromethylsulfonyloxy)-benzoate 257

Phenol 256 (412 mg, 1.25 mmol) was dissolved in anhydrous dichloromethane (7 cm³) and N,N-diisopropylethylamine (0.65 cm³, 3.74 mmol) was added at room temperature. The reaction mixture was cooled to 0 °C and bromomethyl methyl ether (0.2 cm³, 2.50 mmol) was added. After 10 min, the ice-water bath was removed and the reaction mixture allowed to warm up to room temperature overnight. The now yellow solution was poured into saturated aqueous sodium hydrogen carbonate (30 cm³) and extracted with ethyl acetate (3 × 40 cm³). The combined organic layers were washed sequentially with brine (30 cm³) then water (30 cm³), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether–ethyl acetate (80:20)] of the crude residue afforded MOM ether 257 (421 mg, 90%) as a pale yellow solid; R_f 0.24 (Solvent A); mp 26-28 °C (from petroleum ether–ethyl acetate); \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 3434, 1630, 1425; \( \delta_{\text{H}}(400 \text{ MHz; CDCl}_3) \) 3.53 (3 H, s, OCH₂OCH₃), 3.86 (3 H, s, OCH₃), 3.94 (3 H, s, CO₂CH₃), 5.24 (2 H, s, CH₂), 6.52 (1 H, s, CH) and 6.79 (1 H, s, CH); \( \delta_{\text{C}}(100 \text{ MHz; CDCl}_3) \) 52.5 (CO₂CH₃), 55.9 (OCH₂OCH₃), 56.5 (OCH₃), 95.2 (OCH₂OCH₃), 101.0 (CCO₂CH₃), 101.5 (2 × CH(Ar)), 149.3 (COTf), 157.5 (COCH₂OCH₃), 157.4 (COCH₃) and 162.3 (C=O); MS (CI) m/z 375.3 [M+H]^+; HRMS m/z 375.0359 (375.0362 calcd for C₁₂H₁₄F₃O₈S, M+H^+).

tert-Butyl-but-3-ynyloxy-dimethylsilane 259

A solution of 3-butyn-1-ol (2.0 g, 28.5 mmol) in dichloromethane (140 cm³) at room temperature, was treated with dimethylaminopyridine (348 mg, 2.85 mmol) and triethylamine (7 cm³, 51.3 mmol). After 5 min, tert-butyldimethylsilyl chloride (5.6 g, 37.1 mmol) was added and the colourless solution was stirred for 18 h. The reaction was quenched with saturated aqueous ammonium chloride (100 cm³) and extracted with dichloromethane (3 × 20 cm³). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-diethyl ether (90:10)] of the crude residue afforded 259 (4.3 g, 82%) as a
colourless oil; \( R_f \) 0.87 (Solvent A); \( \delta_H (400 \text{ MHz}; \text{CDCl}_3) \) 0.06 (6 H, s, Si(CH\(_3\))\(_2\)), 0.88 (9 H, s, SiC(CH\(_3\))\(_3\)), 1.94 (1 H, t, J 2.6, H), 2.39 (2 H, dt, J 2.4 and 7.2, CH\(_2\)) and 3.71 (2 H, t, J 7.2, CH\(_2\)OTBS). All spectral data matches that reported in the literature.\(^{[152]}\)

tert-Butyl-[(E/Z)-4-(dibutylethylstannanyl)-but-3-enyloxy]-dimethylsilane \( 260^{[133]} \)

A neat mixture of alkyne \( 259 \) (103 mg, 0.559 mmol) and 2,2'-azobis(2-methyl)propionitrile (AIBN) (5 mg, 27.9 \( \mu \text{mol} \)) under argon was heated to 80 \(^{\circ} \text{C} \) for 1.5 h. The reaction mixture was then cooled down to room temperature and the excess alkyne \( 259 \) was removed under high vacuum to yield (265 mg) as an \( E:Z \)-mixture (79:21) of stannane \( 260 \) in quantitative yield and as a colourless oil. No separation was necessary and the mixture was used in the next step without any further purification; \( R_f \) 0.89 (Solvent D); \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 2924, 2855, 1464 and 1100 (O-Si); \( \delta_H (400 \text{ MHz}; \text{CDCl}_3) \) (E-isomer) 0.05 (6 H, s, Si(CH\(_3\))\(_2\)), 0.89 (9 H, s, SiC(CH\(_3\))\(_3\)), 1.21-1.34 (9 H, m, 3\( \times \)CH\(_3\)), 1.42-1.55 (18H, m, 9\( \times \)CH\(_2\)), 2.34-2.36 (2 H, m, CH\(_2\)), 3.64 (1 H, t, J 6.8, CH\(_2\)OTBS) and 5.93 (2 H, s, HC=CH); (Z-isomer) 0.06 (6 H, s, Si(CH\(_3\))\(_2\)), 0.91 (9 H, s, SiC(CH\(_3\))\(_3\)), 1.21-1.34 (9 H, m, 3\( \times \)CH\(_3\)), 2.24-2.27 (2 H, m, CH\(_2\)), 3.66 (1 H, t, J 7.0, CH\(_2\)OTBS), 5.89 (1 H, dt, J 1.2 and 12.4, HC=CH) and 6.53 (1 H, dt, J 6.8 and 12.8, HC=CH); MS (CI) \( m/z \) 419 [M-C(CH\(_3\))\(_3\)]\(^+\); HRMS \( m/z \) 419.1800 (419.1792 calcd for C\(_{18}\)H\(_{39}\)OSiSn, M-C(CH\(_3\))\(_3\)]\(^+\)). All spectral data matches that reported in the literature.\(^{[133]}\)

Methyl 2-((tert-butyldimethylsilanyloxy)-6-[(E)-4-(tert-butyldimethylsilanyloxy)-but-1-enyl]-4-methoxybenzoate \( 263 \)

A solution of triflate \( 119 \) (127 mg, 286 \( \mu \text{mol} \)) in dioxane (6 cm\(^3\)) was treated with stannane \( 260 \) (163 mg, 343 \( \mu \text{mol} \)), lithium chloride (36 mg, 857 \( \mu \text{mol} \)) and tetrakis(triphenylphosphine)palladium(0) (Pd(PPh\(_3\))\(_4\)) (10 mg, 8.57 \( \mu \text{mol} \)). The mixture was heated to 100 \(^{\circ} \text{C} \) for 24 h and then treated with a further portion of lithium chloride (36 mg, 857 \( \mu \text{mol} \)) and Pd(PPh\(_3\))\(_4\) (10 mg, 8.57 \( \mu \text{mol} \)). The reaction mixture was then heated under reflux for 3 d and then cooled down to room temperature and concentrated \textit{in vacuo}. Purification by FCC [petroleum
ether - diethyl ether (100:0)→(97:3)→(95:5)] of the crude residue afforded alkene 263 (29 mg, 21%) as colourless oil; Rf 0.5 (Solvent R); νmax(film)/cm⁻¹ 2931, 1730 (C=O) and 1257; δH (400 MHz; CDCl₃) 0.04 (6 H, s, Si(CH₃)₂), 0.20 (6 H, s, Si(CH₃)₂), 0.89 (9 H, s, SiC(CH₃)₃), 0.94 (9 H, s, SiC(CH₃)₃), 2.40 (2 H, q, J 6.7, CH₂), 3.69 (2 H, t, J 6.7, CH₂OTBS), 3.77 (3 H, s, OCH₃), 3.83 (3 H, s, CO₂CH₃), 6.15-6.18 (1 H, m, HC=CH), 6.25 (1 H, d, J 2.0, CH), 6.39 (1 H, d, J 15.7, HC=CH), 6.60 (1 H, d, J 7.0, CH); δC (100 MHz; CDCl₃) -5.3 (Si((CH₃)₂(CH₂OTBS)), 18.0 (Si((CH₃)₂(CH₂OTBS)), 18.3 (Si((CH₃)₂(CH₂OTBS)), 25.5 (SiC(CH₃)₃(CH₂OTBS)), 25.9 (SiC(CH₃)₃(OTBS)), 36.7 (CH₂), 52.0 (CO₂CH₃), 55.3 (OCH₃), 62.8 (CH₂OTBS), 102.8 (CH), 104.5 (CH), 118.3 (CCOOCH₃), 128.4 (HC=CH), 130.4 (HC=CH), 137.9 (CHC=CH), 154.0 (OTBS), 160.8 (COCH₃) and 168.6 (C=O); MS (EI) m/z 480.16 [M⁺]; HRMS m/z 480.2725 (480.2727 calcd for C₂₅H₄₄O₅Si₂, M⁺), 481.2775 (481.2806 calcd for C₂₅H₄₅O₅Si₂, M⁺).

tert-Butyldimethyl-(3-(tributylstanny1)but-3-enyloxy)silane 262[¹⁵³]

To a suspension of copper cyanide (194 mg, 2.17 mmol) in anhydrous tetrahydrofuran (8.5 cm³) was added nBuLi (1.6 M in hexanes, 2.8 cm³, 4.54 mmol) at −78 °C. The solution was warmed up to −40 °C and stirred for 10 min (pale yellow colour). The mixture was cooled back down to −78 °C and tributyltinhydride (1.2 cm³, 4.54 mmol) was added. The solution was warmed up to −40 °C and stirred for 10 min (yellow/gold colour). The solution was cooled back down to −78 °C and a solution of alkyne 259 (200 mg, 1.08 mmol) in anhydrous tetrahydrofuran (1 cm³) was added. The reaction mixture was allowed to warm up to −30 °C for 1 h and was then poured into a saturated aqueous ammonium chloride solution (10 cm³) at −10 °C. After 30 min, the reaction mixture was extracted with diethyl ether. The combined organic layers were washed with brine (20 cm³), dried over magnesium sulfate, filtered and the solvent concentrated in vacuo to afford stannane 262 quantitatively as a colourless oil; Rf 0.66 (Solvent E); δH (400 MHz; CDCl₃) 0.00 (6 H, s, Si(CH₃)₂), 0.72-0.92 (24 H, m, SiC(CH₃)₃, (CH₃)₃, (CH₂)₃), 1.20-1.30 (6 H, m, (CH₂)₃), 1.39-1.49 (6 H, m, (CH₂)₃), 2.28-2.30 (2 H, m, CH₂), 3.60 (2 H, t, J 7.2, CH₂OTBS) and 5.90 (2 H, s, C=CH₂). All spectral data matches that reported in the literature.[¹⁵³]
**tert-Butyl-dimethyl-(4-tributylstannanyl-but-3-ynyloxy)-silane 269**

Alkyne 259 (225 mg, 1.22 mmol) was dissolved in anhydrous tetrahydrofuran (10 cm$^3$) and cooled to 0 °C. nBuLi (0.9 cm$^3$, 1.46 mmol) was then added and the reaction mixture stirred for 10 min before it was allowed to warm up to room temperature, where it was stirred for 1 h. After this time, the reaction was cooled back down to 0 °C and tributyltinchloride (0.4 cm$^3$, 1.46 mmol) added. The pale yellow solution was stirred overnight at room temperature and then diluted with dichloromethane (20 cm$^3$). The mixture was washed with water (20 cm$^3$) and the phases separated and dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [hexanes (100) then ethyl acetate (100)] of the crude residue afforded alkyne 269 (397 mg, 69%) as a yellow oil; $R_f$ 0.07 (Solvent Q); $\delta_n$(400 MHz; CDCl$_3$) 0.08 (6 H, s, Si(CH$_3$)$_2$), 0.85-0.91 (24 H, m, SiC(CH$_3$)$_3$ and (CH$_3$)$_3$ and (CH$_2$)$_3$), 1.22-1.27 (6 H, m, (CH$_2$)$_3$), 1.46-1.49 (6 H, m, (CH$_2$)$_3$), 2.39 (2 H, t, J 7.3, CH$_2$) and 3.66 (2 H, t, J 7.3, CH$_2$OTBS). All spectral data matches that reported in the literature.$^{[139]}$

**Methyl 2-(**tert**-butyl-dimethyl-silanyloxy)-6-[4-(**tert**-butyl-dimethyl-silanyloxy)-but-1-ynyl]-4-methoxybenzoate 268**

A mixture of triflate 119 (310 mg, 0.699 mmol), lithium chloride (89 mg, 2.10 mmol), stannane 269 (397 mg, 0.838 mmol) and tetraakis(triphenylphosphine)palladium(0) (Pd(PPh$_3$)$_4$) (24 mg, 20.9 µmol) in 1,4-dioxane (15 cm$^3$) was heated at 100 °C for 4.5 h. The reaction was then cooled down to room temperature and the solvent was removed under reduced pressure. Initial purification by FCC [petroleum ether - diethyl ether (90:10)] followed by a second purification by FCC [petroleum ether - diethyl ether (95:5)] afforded alkyne 268 (111 mg, 33%) as a yellow oil; $R_f$ 0.6 (Solvent P); $\nu_{max}$(film)/cm$^{-1}$ 2931, 1732 (C=O) and 1265; $\delta_n$(400 MHz;CDCl$_3$) 0.00 (6 H, s, Si(CH$_3$)$_2$), 0.12 (6 H, s, Si(CH$_3$)$_2$), 0.82 (9 H, s, SiC(CH$_3$)$_3$), 0.88 (9 H, s, SiC(CH$_3$)$_3$), 2.52 (2 H, t, J 7.4, CH$_2$), 3.68 (3 H, s, OCH$_3$), 3.70 (2 H, t, J 7.8, CH$_2$OTBS), 3.76 (3 H, s, CO$_2$CH$_3$), 6.24 (1 H, d, J 2.1, CH) and 6.50 (1 H, d, J 2.1, CH); $\delta_c$(100 MHz;CDCl$_3$) -5.3 (Si(CH$_3$)$_2$ from CH$_2$OTBS), -4.4 (Si(CH$_3$)$_2$ from OTBS), 18.1 (SiC
from OTBS), 18.4 (SiC(CH)3 from CH2OTBS), 23.9 (CH2), 25.5 (SiC(CH)3 from OTBS), 25.9 (SiC(CH)3 from CH2OTBS), 52.1 (CO2CH3), 55.4 (OCH3), 61.9 (CH2OTBS), 79.8 (C≡C(CH)2), 90.1 (C≡C(CH)2), 106.5 (CH), 109.8 (CH), 121.9 (C(O2CH3)), 123.6 (C(C≡C)), 153.2 (C(OTBS)), 160.7 (C(OCH3)) and 167.3 (CO2CH3); MS (CI) m/z 479.4 [M+H]+; HRMS m/z 479.2644 (479.2650 calcd for C25H43O5Si2, M+H+).

Methyl 2-(tert-butyl-dimethyl-silyloxy)-6-[(Z)-4-(tert-butylidimethylsilanyloxy)-but-1-enyl]-4-methoxybenzoate 278

A solution of alkyne 268 (111 mg, 0.232 mmol) in methanol (2 cm³) was treated with a catalytic amount of Pd/BaSO4 catalyst and poisoned with quinoline (30 µL, 289 µmol). The flask was evacuated and after purging three times with hydrogen gas via a balloon, the mixture was stirred under an atmosphere of hydrogen for 2 h at room temperature. TLC analysis deemed the reaction complete and the solution was filtered through silica gel to remove the catalyst and the solvent concentrated in vacuo. Purification by FCC [petroleum ether-diethyl ether (95:5)→(90:10)] of the crude residue afforded (Z)-alkene 278 (58 mg, 52%) as a yellow oil; Rf 0.63 (Solvent R); νmax (film)/cm⁻¹ 3055, 1734 (C=O) and 1255; δH(400 MHz;CDCl3) 0.02 (6 H, s, Si(CH3)2), 0.20 (6 H, s, Si(CH3)2), 0.87 (9 H, s, SiC(CH3)3), 0.95 (9 H, s, SiC(CH3)3), 2.38 (2 H, q, J 6.5, CH2), 3.62 (2 H, t, J 6.5, CH2OTBS), 3.75 (3 H, s, OCH3), 3.79 (3 H, s, CO2CH3), 5.67-5.73 (1 H, m, HC=CH), 6.24 (1 H, d, J 2.0, CH), 6.43-6.49 (2 H, d, J 11.0, HC=CH); δC(100 MHz;CDCl3) -5.3 (Si(CH3)2 (CH2OTBS), -4.4 (Si(CH3)2 (OTBS), 18.1 (SiC(CH3)3), 18.4 (SiC(CH3)3), 25.5 (SiC(CH3)3 (CH2OTBS), 26.0 (SiC(CH3)3 (OTBS), 32.2 (CH2), 51.9 (CO2CH3), 55.3 (OCH3), 62.8 (CH2OTBS), 104.0 (CH), 108.5 (CH), 118.9 (CCOOCCH3), 128.1 (HC=CH), 130.7 (HC=CH), 137.9 (CHC=CH), 154.0 (OTBS), 160.6 (COCH3) and 168.4 (C=O); MS (FAB) m/z 481.3 [M+H]+; HRMS m/z 481.2810 (481.2806 calcd for C25H45O5Si2, M+H+).
3-(Methoxy-phenyl)-prop-2-yn-1-ol 272

3-idoanisole (1.0 g, 4.27 mmol) in anhydrous acetonitrile (40 cm³) was treated with PdCl₂(PPh₃)₂ (375 mg, 0.534 mmol), copper iodide (203 mg, 1.07 mmol) and triethylamine (3 cm³, 21.3 mmol). To this was added propargyl alcohol (287 mg, 5.12 mmol) and the reaction stirred in the dark for 16 hours at room temperature. The solids were removed by filtration, washed with diethyl ether (2×60 cm³) and the solvent concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (70:30)] of the crude residue afforded alkynol 272 (567 mg, 82%); Rf 0.31 (Solvent S); δH (400 MHz;CDCl₃) 1.71 (1 H, s, OH), 3.80 (3 H, s, OCH₃), 4.49 (2 H, s, CH₂OH), 6.88 (1 H, ddd, J 0.6, 2.8 and 8.4, CH), 6.98 (1 H, dd, J 1.2 and 2.4, CH), 7.03 (1 H, dt, J 0.8 and 7.6, CH) and 7.21 (1 H, dd, J 0.8 and 8.0, CH). The spectral data matches that reported in the literature.

3-(3-Methoxy-phenyl)-propan-1-ol 273

Alkynol 272 (114 mg, 0.703 mmol) was dissolved in methanol (10 cm³) and was treated with a catalytic amount of Pd/BaSO₄ catalyst and poisoned with quinoline (0.10 cm³, 0.879 mmol). The flask was evacuated and after purging three times with hydrogen gas via a balloon, the mixture was stirred under an atmosphere of hydrogen for 2 h at room temperature. TLC analysis deemed the reaction complete and the solution was filtered through a pad of silica gel and the solvent concentrated in vacuo. Purification by FCC [diethyl ether (100)] of the crude residue afforded alkane 273 (83 mg, 72%) as a pale yellow oil; Rf 0.23 (Solvent A); δH (400 MHz;CDCl₃) 1.80 (1 H, br s, OH), 2.39 (2 H, dd, J 6.4 and 14.2, CH₂CH₂CH₂), 3.19 (2 H, t, J 6.4, CH₂CH₂CH₂), 4.17 (2 H, t, J 6.4, CH₂CH₂CH₂), 4.29 (3 H, s, OCH₃), 7.20-7.32 (2 H, m, CH₁ and CH₃), 7.68 (1H, t, J 7.6, CH₂) and 7.74 (1 H, s, CH₄); MS (EI) m/z 166 [M]+; HRMS m/z 166.0996 (166.0994 calcd for C₁₀H₁₄O₂, M+). All spectral data matches that reported in the literature.
Alkynol 272 (200 mg, 1.23 mmol) was dissolved in dichloromethane (10 cm³) at room temperature and dimethylaminopyridine (15 mg, 0.123 mmol) and triethylamine (0.31 cm³, 2.22 mmol) were added successively. tert-Butyldimethylsilyl chloride (242 mg, 1.60 mmol) was added and the reaction stirred at room temperature for 18 h. The cloudy, yellow solution was quenched with saturated aqueous ammonium chloride (20 cm³) and extracted with dichloromethane (3×20 cm³). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. Purification by FCC [petroleum ether - diethyl ether (80:20)] of the crude residue afforded alkyne 274 (264 mg, 78%) as a pale orange oil; R₆ 0.67 (Solvent A); ν_max(film)/cm⁻¹ 2928 and 1257; δ_H(400 MHz; CDCl₃) 0.17 (6 H, s, Si(CH₃)₂), 0.93 (9 H, s, SiC(CH₃)₃), 3.80 (3 H, s, CH₃), 4.52 (2 H, s, CH₂), 6.85 (1 H, d, J 8.3, CH1), 6.93 (1 H, s, CH4), 7.00 (1 H, d, J 7.5, CH3) and 7.19 (1 H, t, J 8.0, CH2); δ_C(100 MHz; CDCl₃) -5.0 (Si(CH₃)₂), 18.3 (SiC(CH₃)₃), 25.9 (SiC(CH₃)₃), 52.3 (CH₂OTBS), 55.3 (OCH₃), 84.8 (C≡C), 87.8 (C≡C), 114.8 (C1 and C3), 116.5 (C4), 124.2 (CC≡CCH₂OTBS), 129.3 (C2) and 159.3 (COCH₃); MS (EI) m/z 276.1 [M]+, 261.0 [M-CH₃]⁺, 145.0 [M-OTBS]⁺; HRMS m/z 276.1543 (276.1546 calcd for C₁₆H₂₄O₂Si, M⁺), 277.1483 (277.1625 calcd for C₁₆H₂₅O₂Si, M+H⁺).
Methyl 2-(\textit{tert}-Butyldimethylsilanyloxy)-6-iodo-4-methoxybenzoate \textbf{267}

A dry flask was charged with triflate \textbf{119} (242 mg, 0.544 mmol) and sodium iodide (163 mg, 1.09 mmol). The reaction flask was flushed with argon and dry dimethylformamide (5 cm$^3$) was injected. The heterogeneous solution was heated to 80 °C for 17.5 h. After cooling down to room temperature, the reaction was poured into a mixture of saturated sodium thiosulphate (20 cm$^3$) and ethyl acetate (20 cm$^3$). The organic layer was separated and then washed with water (2×40 cm$^3$) and brine (30 cm$^3$), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated \textit{in vacuo}. Purification by FCC [petroleum ether – diethyl ether (80:20)] of the crude residue afforded \textbf{267} (99 mg, 43%) as a colourless oil; $R_f$ 0.43 (Solvent $R$); $\nu_{\text{max}}$(film)/cm$^{-1}$ 1265; $\delta_{\text{H}}$(400 MHz; CDCl$_3$) 0.00 (6 H, s, Si(CH$_3$)$_2$), 0.82 (9 H, s, SiC(CH$_3$)$_3$), 3.75 (3 H, s, OCH$_3$), 3.88 (3 H, s, CO$_2$CH$_3$), 6.32 (1 H, d, J 2.4, CH) and 6.47 (1 H, d, J 2.4, CH); $\delta_{\text{C}}$(100 MHz; CDCl$_3$) -3.6 (Si((CH$_3$)$_2$), 18.1 (SiC(CH$_3$)$_3$), 25.7 (SiC(CH$_3$)$_3$), 52.5 (CO$_2$CH$_3$), 56.0 (OCH$_3$), 100.0 (Cl), 100.9 (HCCOTBS), 103.3 (HCl), 133.7 (CCOOCH$_3$), 164.7 (COTBS), 165.4 (C=O) and 168.9 (COCH$_3$). The compound failed to ionise under all mass spectrometry conditions attempted.

t\textit{tert}-Butyl-[3-(3-methoxyphenyl)-allyloxy]-dimethylsilane \textbf{276}

Alkyne \textbf{274} (130 mg, 0.470 mmol) was dissolved in methanol (6 cm$^3$) and was treated with a catalytic amount of Pd/BaSO$_4$ catalyst and poisoned with quinoline (0.07 cm$^3$, 0.588 mmol). The flask was evacuated and after purging three times with hydrogen gas via a balloon, the mixture was stirred under an atmosphere of hydrogen for 1 h at room temperature. TLC analysis deemed the reaction complete and the solution was filtered through a pad of Celite\textsuperscript{®} and the solvent concentrated \textit{in vacuo}. Purification by FCC [diethyl ether (100)] of the crude residue afforded alkane \textbf{276} (92 mg, 70%) as a pale yellow oil; $R_f$ 0.23 (Solvent $A$); $\nu_{\text{max}}$(film)/cm$^{-1}$ 2951, 2857, 1258 and 1100 (O-Si); $\delta_{\text{H}}$(400 MHz; CDCl$_3$) 0.09 (6 H, s, Si(CH$_3$)$_2$), 0.91 (9 H, s, SiC(CH$_3$)$_3$), 1.78-1.82 (2 H, m, CH$_2$CH$_2$CH$_2$), 2.62 (2 H, t, J 7.6, CH$_2$CH$_2$CH$_2$), 3.61 (2 H, t, J 6.3, CH$_2$CH$_2$CH$_2$),
3.76 (3 H, s OCH₃), 6.70 (1 H, d, J 7.7, CH1), 6.73 (1 H, s, CH4), 6.78 (1 H, dd, J 7.7, CH3) and 7.20 (1 H, t, J 7.7, CH2); δ_C (100 MHz; CDCl₃) 5.3 (Si(CH₃)₂), 18.3 (SiC(CH₃)₃), 25.9 (SiC(CH₃)₃), 32.2 (CH₂CH₂CH₂OTBS), 34.4 (CH₂CH₂CH₂OTBS), 55.1 (OCH₃), 62.4 (CH₂CH₂CH₂OTBS), 111.0 (C1), 114.2 (C4), 121.1 (C3), 128.7 (C2), 142.0 (C) and 162.2 (COCH₃); MS (CI) m/z 281 [M+H]+; HRMS m/z 281.1934 (281.1937 calcd for C₁₆H₂₉O₂Si, M+H⁺).

![Chemical Structure](image)

**1H and 13C Assignment**

tert-Butyl-[(Z)-3-(3-methoxyphenyl)-allyloxy]-dimethylsilane 275

Alkyne 274 (130 mg, 0.470 mmol) was dissolved in methanol (6 cm³) and was treated with a catalytic amount of Pd/BaSO₄ catalyst and poisoned with quinoline (0.07 cm³, 0.588 mmol). The flask was evacuated and after purging three times with hydrogen gas via a balloon, the mixture was stirred under an atmosphere of hydrogen for 30 min at room temperature. TLC analysis deemed the reaction complete and the solution was filtered through a pad of Celite® and the solvent concentrated in vacuo. Purification by FCC [petroleum ether - diethyl ether (90:10)] of the crude residue afforded 274 and 275 and 276 (114 mg, 87%, 4:89:7) as an inseparable mixture and as a yellow oil; Rₕ 0.61 (Solvent P₁); δ_H (400 MHz; CDCl₃) (Z-alkene) 0.05 (6 H, s, Si(CH₃)₂), 0.87 (9 H, s, SiC(CH₃)₃), 3.78 (3 H, s, OCH₃), 4.43 (2 H, d, J 5.9, CH₂), 5.80 (1 H, dt, J 5.9 and 11.8, CH=CHCH₂), 6.41 (1 H, d, J 11.8, CH=CH), 6.69-6.80 (3 H, m, 3×CH) and 7.15-7.21 (1 H, m, CH); (alkane) 0.09 (6 H, s, Si(CH₃)₂), 0.91 (9 H, s, SiC(CH₃)₃), 1.77-1.81 (2 H, m, CH₂CH₂CH₂), 2.62 (2 H, t, J 7.6, CH₂CH₂CH₂), 3.61 (2 H, t, J 6.3, CH₂CH₂CH₂), 3.76 (3 H, s OCH₃), 6.69-6.80 (3 H, m, 3×CH) and 7.15-7.21 (1 H, m, CH).
**Methyl 2-iodo-benzoate 280**

![Chemical结构式](image)

To a solution of 2-iodobenzoic acid (1.0 g, 4.03 mmol) in methanol (4 cm³) was added concentrated sulphuric acid (0.24 cm³). The reaction mixture was heated under reflux for 7 h, then cooled down to room temperature, diluted with water (10 cm³) and extracted several times with chloroform (5×30 cm³). The combined organic layers were washed with water (40 cm³), 5% saturated aqueous sodium hydrogen carbonate (2×40 cm³), water (40 cm³) and brine (2×40 cm³), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether–diethyl ether (70:30)] of the crude residue afforded iodide 280 (868 mg, 82%) as a colourless oil; R_f 0.43 (Solvent R); \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 1725 (C=O), 1582 (C=C), 1430, 1249, 1100 and 1013; \( \delta_{\text{H}}(400 \text{ MHz}; \text{CDCl}_3) \) 3.96 (3 H, s, CH₃), 7.18 (1 H, dt, \( J \) 1.8 and 7.8, H1), 7.44 (1 H, dt, \( J \) 1.2 and 7.6, H3), 7.82 (1 H, dd, \( J \) 1.7 and 7.8, H4) and 8.04 (1 H, dd, \( J \) 1.1 and 8.0, H1); \( \delta_{\text{C}}(100 \text{ MHz}; \text{CDCl}_3) \) 52.5 (C(CH₃)), 94.1 (C-I), 127.9 (C2), 130.9 (C1), 132.6 (C3), 135.1 (C(CO₂CH₃)), 141.3 (C4) and 166.9 (C=O); MS (Cl) m/z 262 [M+H]^+; HRMS m/z 262.9566 (262.9569 calcd for C₈H₈IO₂, M+H^+). All spectral data matches that reported in the literature.\(^{[155]}\)

**¹H and ¹³C Assignment**

**Methyl 2-[4-(tert-Butyldimethylsilyloxy)-but-1-ynyl]-benzoate 281**

![Chemical结构式](image)

To a mixture of iodobenzoate 280 (300 mg, 1.14 mmol), alkyne 259 (253 mg, 1.37 mmol), bis(triphenylphosphine)palladium dichloride (PdCl₂(PPh₃)₂) (80 mg, 0.114 mmol) and copper iodide (22 mg, 0.114 mmol) in anhydrous acetonitrile (11 cm³) under argon was added triethylamine (0.80 cm³, 5.72 mmol) at room temperature. The reaction mixture was stirred in the dark for 2 h, then filtered through Celite® to remove the solids and washed with diethyl ether. The solvent was concentrated in vacuo. Purification by FCC [petroleum ether - diethyl ether
(90:10) of the crude residue afforded 281 (260 mg, 71%) as a yellow oil; $R_f$ 0.39 (Solvent $R$); $v_{\text{max}}$(film)/cm$^{-1}$ 2929, 1728 (C=O) and 1255; $\delta_H$(400 MHz; CDCl$_3$) 0.09 (6 H, s, Si(CH$_3$)$_2$), 0.90 (9 H, s, SiC(CH$_3$)$_3$), 2.68 (2 H, t, J 7.3, CH$_2$), 3.84 (2 H, t, J 7.3, CH$_2$OTBS), 3.89 (3 H, s, CH$_3$), 7.31 (1 H, dt, J 1.4 and 7.8, H2), 7.41 (1 H, dt, J 1.4 and 7.8, H3), 7.50 (1 H, dd, J 1.1 and 7.7, H4) and 7.88 (1 H, dd, J 1.1 and 7.7, H1); $\delta_C$(100 MHz; CDCl$_3$) -5.3 (Si(CH$_3$)$_2$), 18.3 (SiC(CH$_3$)$_3$), 24.2 (C≡CCH$_2$), 25.9 (SiC(CH$_3$)$_3$), 52.0 (COOCH$_3$), 61.9 (CH$_2$OTBS), 80.2 (C≡C), 92.5 (C≡C), 124.2 (CCOOCCH$_3$), 127.3 (C2), 130.2 (C1), 131.5 (C3), 132.2 (C≡C), 134.3 (C4) and 167.21 (C=O); MS (FAB) $m/z$ 319.2 [M+H]$^+$; HRMS $m/z$ 319.1727 (319.4906 calcd for C$_{18}$H$_{27}$O$_3$Si, M+H$^+$).

$^1$H and $^{13}$C Assignment

[2-(4-(tert-Butyldimethylsilyloxy)but-1-ynyl)phenyl]-methanol 284

To a solution of alkyne 281 (91 mg, 0.286 mmol) in anhydrous tetrahydrofuran (3 cm$^3$) was added lithium aluminium hydride (17 mg, 0.457 mmol) under argon. The resulting grey solution was heated under reflux for 23 h. The reaction mixture was cooled down to room temperature and then 0 °C, before the careful addition of diethyl ether (3 cm$^3$) and then water dropwise with stirring. As a white precipitate was formed, the water was added more quickly until approximately 10 cm$^3$ had been added. The resulting mixture was left to stir for 20 min at 0 °C, until no grey lithium aluminium hydride was visible. The entire solution was poured into a separating funnel and washed with 1 M sodium hydroxide (20 cm$^3$). The aqueous layer was separated and extracted with diethyl ether (2×15 cm$^3$). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and the solvent concentrated in vacuo. Purification by FCC [petroleum ether - diethyl ether (90:10)] of the crude residue afforded alcohol 284 (4.3 mg) as an oil and an unknown compound (8.1 mg).
Alcohol 284: \( R_f 0.2 \) (Solvent \( R \)); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 3365 (OH), 2929, 1265 and 1105 (O-Si); \( \delta \) (400 MHz; CDCl\(_3\)) 0.10 (6 H, s, Si(CH\(_3\))\(_2\)), 0.89 (9 H, s, SiC(CH\(_3\))\(_3\)), 2.65 (2 H, t, \( J \) 6.7, CH\(_2\)), 3.62 (2 H, t, \( J \) 6.7, CH\(_2\)OTBS), 4.77 (2 H, d, \( J \) 5.4, CH\(_2\)OH) and 7.19-7.46 (4 H, m, 4 \( \times \) CH); \( \delta \) (100 MHz; CDCl\(_3\)) 5.2 (Si(CH\(_3\))\(_2\)), 18.4 (SiC(CH\(_3\))\(_3\)), 24.0 (CH\(_2\)), 25.9 (SiC(CH\(_3\))\(_3\)), 62.0 (CH\(_2\)OTBS), 64.3 (CH\(_2\)OH), 79.8 (C≡C), 92.5 (C≡C), 122.1 (C2), 127.5 (C4), 128.1 (C6), 132.1 (C5), 139.2 (C3) and 142.8 (C1); MS (Cl) \( m/z \) 291.1 [M+H]\(^+\); HRMS \( m/z \) 291.1779 (291.1781 calcd for C\(_{17}\)H\(_{27}\)O\(_2\)Si, M+H\(^+\)).

Unknown: \( R_f 0.8 \) (Solvent \( R \)); \( \delta \) (400 MHz; CDCl\(_3\)) 0.09 (6 H, s, Si(CH\(_3\))\(_2\)), 0.88 (9 H, s, SiC(CH\(_3\))\(_3\)), 2.55 (1 H, t, \( J \) 7.2), 2.64 (1H, t, \( J \) 7.2), 3.75 (2 H, dt, \( J \) 7.2 and 12.5), 7.23-7.32 (2 H, m), 7.43 (1 H, d, \( J \) 7.0) and 7.50 (1 H, t, \( J \) 7.0).

**Methyl 2-hydroxy-6-iodo-4-methoxybenzoate 264**

![Chemical structure](image)

A dry flask was charged with triflate 119 (447 mg, 1.00 mmol) and sodium iodide (301 mg, 2.01 mmol). The reaction flask was flushed with argon and anhydrous dimethylformamide (10 cm\(^3\)) was injected. The heterogeneous solution was heated to 80 °C for 4 h. After cooling down to room temperature, the reaction was poured into a mixture of saturated sodium thiosulphate (20 cm\(^3\)) and ethyl acetate (20 cm\(^3\)). The organic layers were washed with water (2×40 cm\(^3\)) and brine (30 cm\(^3\)), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether - diethyl ether (80:20)] of the crude residue afforded iodide 264 (99 mg, 43%) as a colourless oil; \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 1739 (C=O) and 520; \( \delta \) (400 MHz; CDCl\(_3\)) 3.88 (3 H, s, OCH\(_3\)), 4.02 (3 H, s, CO\(_2\)CH\(_3\)), 6.38 (1 H, s, CH) and 6.53 (1 H, d, \( J \) 2.2, CH) and 7.29 (1 H, s, OH); \( \delta \) (100 MHz; CDCl\(_3\)) 52.5 (CO\(_2\)CH\(_3\)), 56.0 (OCH\(_3\)), 100.0 (Cl), 101.9 (HCCOH), 103.9 (HCCI), 133.6 (CCOOCH\(_3\)), 164.9 (COH), 165.4 (C=O) and 168.9 (COCH\(_3\)). The compound failed to ionise under all mass spectrometry conditions attempted.
Methyl 2-iodo-4-methoxy-6-methoxymethylbenzoate \textbf{18}\textsuperscript{[36]}

Phenol \textbf{264} (160 mg, 0.519 mmol) was dissolved in dichloromethane (5 cm\textsuperscript{3}) and \textit{N},\textit{N}-diisopropylethylamine (0.27 cm\textsuperscript{3},1.56 mmol) was added at room temperature. The reaction mixture was cooled down to 0 °C and bromomethyl methyl ether (0.10 cm\textsuperscript{3}, 1.04 mmol) was added. After 10 min, the ice-water bath was removed and the reaction allowed to warm to room temperature overnight. After this time, further \textit{N},\textit{N}'-diisopropylethylamine (0.27 cm\textsuperscript{3},1.56 mmol) and bromomethyl methyl ether (0.10 cm\textsuperscript{3}, 1.04 mmol at 0 °C) were added. After 2 h, the reaction mixture was poured into saturated aqueous sodium hydrogen carbonate (20 cm\textsuperscript{3}) and extracted with ethyl acetate (3×20 cm\textsuperscript{3}). The combined organic layers were washed with water (20 cm\textsuperscript{3}), then brine (20 cm\textsuperscript{3}), dried over anhydrous sodium sulfate, filtered and concentrated in \textit{vacuo}. Purification by FCC [petroleum ether – diethyl ether (80:20)] of the crude residue afforded MOM ether \textbf{18} (179 mg, 98%) as a colourless oil; \textit{Rf} 0.11 (Solvent \textit{R}); \textit{V}_{max}(\text{film})/\text{cm}^{-1} 1737 (C=O), 1620 (C=C), 1213, 1149, 1024 and 513; \textit{\delta}_{H}(400 MHz; CDCl\textsubscript{3}) 3.49 (3 H, s, OCH\textsubscript{2}OCH\textsubscript{3}), 3.81 (3 H, s, OCH\textsubscript{3}), 3.90 (3 H, s, CO\textsubscript{2}CH\textsubscript{3}), 5.19 (2 H, s, OCH\textsubscript{2}OCH\textsubscript{3}), 6.47 (1 H, d, J 2.2, CH) and 6.73 (1 H, d, J 2.2, CH); \textit{\delta}_{C}(100 MHz; CDCl\textsubscript{3}) 52.3 (CO\textsubscript{2}CH\textsubscript{3}), 56.0 (OCH\textsubscript{2}OCH\textsubscript{3}), 56.6 (OCH\textsubscript{3}), 95.2 (OCH\textsubscript{2}OCH\textsubscript{3}), 101.0 (C-I), 101.5 (CH), 110.8 (CH), 147.5 (COCH\textsubscript{3}), 157.5 (CO\textsubscript{2}H\textsubscript{2}OCH\textsubscript{3}), 162.4 (CCO\textsubscript{2}CH\textsubscript{3}) and 163.1 (C=O); \textit{MS} (Cl) \textit{m/z} 375.2 [M+Na]\textsuperscript{+}; \textit{HRMS} \textit{m/z} 374.9700 (374.9705 calcd for \textit{C}\textsubscript{11}H\textsubscript{13}INaO\textsubscript{5}, M+Na\textsuperscript{+}). All spectral data matches that reported in the literature.\textsuperscript{[36]}
4 Introduction

4.1 Natural Products

A natural product can be described as a chemical compound or substance that is created by a living organism. In the pharmaceutical industry, these compounds are often isolated and characterised, with specific focus on whether they possess any biological activity, which would render them of interest as a potential drug lead.

For many years numerous compounds have been isolated through tissue extraction of plants, animals and microorganisms. Through the use of highly specialised techniques, their novel chemical structures have been elucidated and solved.

Most biologically active natural products are secondary metabolites with highly complex structures hence; the construction of natural products synthetically provides challenges, both intellectually and practically. Since the synthesis of urea and acetic acid in the early 1800’s, chemistry has evolved so that highly complex targets are now achievable.

4.2 Alkaloids

The alkaloids are a family of naturally occurring heterocyclic organic compounds which contain nitrogen and an alkaline pH. Alkaloids can be produced by plants, bacteria, fungi or animals and many have been found to exert pharmacological effects and are now used as medicines, for example morphine, or in some cases as recreational drugs such as cocaine. The alkaloids have been further classified by way of their structure, chemical features, biological origin and the biogenetic origin if known, culminating in a quite exhaustive classification:

- Pyridine group
- Pyrrolidine group
- Tropane group
- Indolizidine
- Quinoline
- Isoquinoline
• Phenanthrene
• Phenethylamine
• Indole
• Purine
• Terpenoid
• Quaternary
• Miscellaneous

Some well known examples are caffeine, which is a purine alkaloid and further classified as a xanthine and ephedrine, a phenethylamine alkaloid (Figure 27).

![Structure of Caffeine 288 and Ephedrine 289.]

The total synthesis of alkaloids is prevalent in the literature and some of these often fascinating and hugely important, complex molecules have been synthesised and re-synthesised to take advantage of new synthetic developments. In addition, molecules that were previously resistant, have at long last succumbed to total synthesis.

### 4.3 Spirocyclic Pyrans and Piperidines

A number of natural products and biologically important compounds contain spirocyclic pyran and piperidine ring systems as part of their overall structures. In the past it was common that the difficulty in achieving the total synthesis of such natural products was the formation of the spirocyclic core structures. As a result, numerous synthetic approaches have been developed towards their generation, however most of these tend to be substrate specific and afford a limited number of functional handles from which synthetic diversification can take place.

### 4.4 Pinnaic Acid

In 1996, Uemura reported the isolation of pinnaic acid and tauropinnaic acid from the Okinawan bivalve *Pinna muricata* (Figure 28).
These compounds were the first members of a novel class of alkaloids, characterised by an azaspiro[4.5]decane ring system (highlighted in red). Subsequent research showed that pinnaic acid and tauropinnaic acid were found to exhibit inhibitory activity towards cytosolic phospholipase A\textsubscript{2} (cPLA\textsubscript{2}). The phospholipase A\textsubscript{2} (PLA\textsubscript{2}) family consists of lipolytic enzymes whose constituents catalyse the hydrolysis of intra- and extra-cellular membrane phospholipids.\textsuperscript{[159]} Cytosolic phospholipase A\textsubscript{2} (cPLA\textsubscript{2}) is an 85 kDa phospholipase which is important in the family as it has a significant role in the generation of free arachidonic acid from cellular phospholipids in mammalian cells.\textsuperscript{[160]} This acid can then go on to mediate the biosynthesis of, for example, prostaglandins and thromboxanes. These biological messengers influence cell proliferation and inflammatory responses and it is for this reason that selective cPLA\textsubscript{2} inhibitors are potential targets for the development of novel anti-inflammatory drugs. Pinnaic acid inhibits cPLA\textsubscript{2} \textit{in vitro}, with an IC\textsubscript{50} of 0.2 mM and as a result of this anti-inflammatory activity, suspicion arose that pinnaic acid may be a potential drug for the treatment of inflammation.\textsuperscript{[158,161]}

Shortly after its isolation in 1996, the configuration at C\textsubscript{14} of pinnaic acid was assigned to be \textit{R}, \textit{via} magnetic resonance methods, though this was never conclusive. The stereochemistry at C\textsubscript{17} was not assigned at all.\textsuperscript{[158]} The isolation process yielded only several milligrams of the natural material, preventing further pharmacological and structural studies meaning only total synthesis of the natural product would provide a resolution to the initial speculation over the assignment, as well as determining the configuration at C\textsubscript{17}.

There have been numerous research groups who have become intensely motivated to study the synthetic chemistry of pinnaic acid, with the work summarised in a review published in 2005 by Clive and colleagues.\textsuperscript{[162]} By this
stage there were three total syntheses of pinnaic acid$^{[159,163-165]}$ and two further formal syntheses of this alkaloid$^{[166,167,168]}$.\[4.4.1 Danishefsky's Total Synthesis of Pinnaic Acid\]

In 2001, Danishefsky and co-workers published the first total synthesis of pinnaic acid.$^{[159,164]}$ The synthesis is neat and concise and begins from Meyers' lactam (Scheme 126). Meyers' lactam 292 was asymmetrically allylated to give bicyclic lactam 293. After N-protection (Boc), stereoselective alkylation of the lithium enolate of 295 with methyl iodide gave 296. Base-induced hydrolysis of 296 and reduction of the anhydride intermediate gave alcohol 298 as the major product. Subsequent protection gave the protected amino alcohol 299.

\[\text{Scheme 126: Danishefsky's Synthesis of Pinnaic Acid. Reagents and Conditions: (a) Me}_3\text{SiCH}_2\text{CH=CH}_2, \text{TiCl}_4, \text{CH}_2\text{Cl}_2, –78 ^\circ\text{C} \rightarrow \text{rt}, 18 \text{ h}, 98\%; (b) Na, EtOH, NH}_3/\text{THF}, –33 ^\circ\text{C}, 1 \text{ h}, 88\%; (c) Boc}_2\text{O, DMAP, THF, rt, 18 h, 93\%; (d) LiHMDS, hexanes/THF, –78 ^\circ\text{C} \rightarrow –40 ^\circ\text{C}, 1.5 \text{ h, then MeI, –40} ^\circ\text{C}, 1 \text{ h; (e) LiOH, THF/H}_2\text{O, rt, 18 h; (f) CICO}_2\text{Et, Et}_3\text{N, THF, –10} ^\circ\text{C, 1 h, then NaBH}_4, \text{MeOH, 0} ^\circ\text{C} \rightarrow \text{rt}, 1 \text{ h, 39\% over three steps; (g) TBDPSCl, Et}_3\text{N, DMAP, 0} ^\circ\text{C} \rightarrow \text{rt, 96\%.}\]

The next series of transformations culminated in the generation of the azaspiro core. The alkylborane of 299 was coupled with vinyl iodide 306, itself generated from the corresponding vinyl stannane, to give 300 in 75% yield (Scheme 127). The removal of the Boc protecting group enabled the free amine 301 to undergo a base-induced cyclisation to afford desired piperidine 302 with good diastereoselectivity and as the exclusive E-isomer at C$_2$–C$_3$.\[14\]
Following removal of the TBDPS protecting group, the free alcohol 304 was subjected to oxidation conditions, but as the authors report, this was troublesome and the desired aldehyde could not be generated. It was eventually found that continued nitrogen protection was necessary, protection that would not be affected by proceeding transformations, but likewise would be readily removed at a later stage. In the end, the authors settled on the trifluoroacetyl derivative and created 303, following which the TBDPS protection was removed using HF-pyridine. The free alcohol 304 was then readily oxidised to aldehyde 305 in 84% yield using TPAP and NMO.

Base-mediated reaction of 305 with phosphonate 307 produced an inseparable mixture of product 308 and starting aldehyde 305. Despite this, the authors advanced with the mixture and following reduction with either R- or S-alpine borane, the alcohol was gained in 30% isolated yield over two steps (Scheme 128). Silyl deprotection gave diol 309 and cleavage of the TFA (→310) and ethyl ester functions gave what the authors believed to be pinnaic acid (PAI). The signals in the high field of the NMR spectrum were comparable with Uemura’s, but the lack of authentic natural product was a disadvantage as the synthetic and natural compounds could not be directly compared by NMR.
Shrewdly, the authors took 308 and reduced the carbonyl to the alcohol 311 using NaBH₄ (Scheme 129). This was then used to generate a different form of pinnaic acid which differed only in the configuration at C₁₄. Alcohol 311 was desilylated (→309) and the TFA (→310) and ester groups removed. This new pinnaic acid, PAII, exhibited an NMR spectrum which was vastly different in the high field area to the spectrum of natural pinnaic acid (from Uemura’s work).

After additional synthetic studies (not discussed here), the authors had strong evidence that compound PAI matched the natural pinnaic acid, making the configuration at C₁₄ S. To determine the configuration at C₁₇, diol 310 was exposed to acetic anhydride/pyridine and catalytic DMAP for two hours at room temperature (Scheme 130). This capped the free hydroxyls (→312) and
subsequent ozonolysis of the C_{15}=C_{16} bond gave chloroaldehyde 313. Reduction (→314) followed by acetylation afforded 315. The degradation product 315 was consistent with the R configuration at C_{17}.

Scheme 130: Danishefsky's Synthesis of Pinnaic Acid. Reagents and Conditions: (a) Ac₂O, pyridine, DMAP, rt, 2 h, 80%; (b) O₃, MeOH, −40 °C, then Me₂S; (c) NaBH₄, CeCl₃·H₂O, MeOH; (d) Ac₂O, Et₃N, rt, 35% over three steps.

4.4.2 Uemura's Asymmetric Synthesis of Pinnaic Acid

In 2007, Uemura and co-workers reported their asymmetric total synthesis of pinnaic acid.\textsuperscript{[169]} The synthesis began from a chiral cyclopentanone, developed especially for the investigation, with the overall route being neat and concise, incorporating impressive and intricate transformations.

In Uemura's synthesis, (R)-(+)−pulegone 316 was transformed into chiral compound 317 in five steps, with an overall yield of 41%.\textsuperscript{[169]} Enone 317 then underwent a key Pd-TMM (trimethylenemethane) [3+2]-cyclisation in high yield and high stereoselectivity to afford the anti-adduct 319 (Scheme 131).
Scheme 131: Uemura’s Asymmetric Synthesis of Pinnaic Acid. Reagents and Conditions: (a) Pd(OAc)$_2$, (iPrO)$_3$P, THF, reflux, 80%; (b) 4Å MS, alumina, CH$_2$Cl$_2$, rt, 43% (100% based on recovered starting material); (c) O$_3$, MeOH, –78 °C; then Me$_2$S, –78 °C, 82%; (d) TsNHNH$_2$, MeOH, 50 °C; (e) NaBH$_4$CN, TsOH, THF, reflux, 60% over two steps; (f) NaH, CbzCl, THF, reflux, 87%; (g) NaBH$_4$, LiBr, THF, 50 °C, quant.; (h) TBDPSCl, DMAP, Et$_3$N, CH$_2$Cl$_2$, rt; (i) CAN, MeCN/H$_2$O (1:1), 0 °C, 76% over two steps; (j) SO$_3$·pyridine, Et$_3$N, DMSO, rt; (k) 326, Et$_3$N, LiCl, THF, 30 °C, quant. in two steps.

Lactam 321 was obtained from lactone 319 through a Beckman rearrangement using O-mesitylsulfonylhydroxylamine (MSH, 320). Ozonolysis of the exo-olefin, hydrazone formation and deoxygenation gave 322. Alcohol 324 was obtained following amide protection (→323) and reductive opening of lactam 322. Interestingly, Uemura reported that no racemisation had occurred from cyclopentanone 317. Silyl protection of the primary alcohol, followed by PMP ether removal gave alcohol 325. Oxidation of alcohol 325 into the corresponding aldehyde, followed by a HWE reaction with phosphonate 326 furnished enone 327 as the $E$-isomer.

To construct the piperidine ring with the correct configuration at C$_5$ the authors use an innovative tandem hydrogenation-cyclisation procedure. This consists of four, one-pot transformations: (1) alkene saturation; (2) Cbz removal; (3) intramolecular cyclic imine and/or enamine formation and (4) stereoselective reduction of imine/enamine intermediate (Scheme 132).
Piperidine 328 was formed by reaction of enone 327 with 20 mol% palladium catalyst. Protection of the amino group (→329) and selective deprotection of the TBS group followed by a Grieco elimination[170] led to olefin 330.

Installation of the side chain was completed successfully via cross-metathesis of olefin 330 using Hoveyda-Grubbs second generation catalyst, with ethyl methacrylate as the solvent (Scheme 133). Hence, trisubstituted alkene 331 was obtained exclusively as the E-isomer.

Treatment of 331 with HF-pyridine afforded the terminal alcohol, which upon a second Grieco elimination gave terminal alkene 332. In this strategy the authors installed the C₁₇ centre as part of 333 and then introduced it to the spirocyclic core, via cross-metathesis. As expected, the terminal olefins were more reactive than the internal double bonds and the cross-metathesis proceeded in 69% yield to furnish 334 as the single trans-isomer (C₁₅—C₁₆ bond).
After removal of the two silyl groups, TFA amide and the ethyl ester, the chiral pinnaic acid was obtained as its sodium salt. \(^1\)H NMR comparison of this and the racemic form proved to be identical.

The method developed by Uemura and colleagues is advanced and relies heavily on the success of some intricate and complex reactions. Despite this, all the stereochemistry (apart from C\(_{17}\)) can be efficiently controlled from the methyl group in cyclopentone.

### 4.5 Halichlorine

In 1996, as well as reporting the isolation of pinninic acid, Uemura also isolated the novel marine alkaloid, halichlorine, from the Japanese black marine sponge *Halichondria okadai* (Figure 29).\(^{[158]}\) It is an interesting compound in that it shares the same azaspiro[4.5]decane core with pinninic acid.

![Figure 29: Structure of Halichlorine 336.](image)

Halichlorine is a crystalline compound and its structure was assigned only after extensive NMR studies; structurally it possesses 23 carbon atoms and five stereocentres. Halichlorine selectively inhibits induced expression of vascular cell adhesion molecule-1 (VCAM-1) with an IC\(_{50}\) of 7 µg/mL. VCAM-1 is a member of the immunoglobulin superfamily and is expressed on the surface of endothelium cells. VCAM-1 monitors and regulates leukocyte recruitment into inflamed tissue.\(^{[163,171]}\) Since leukocyte recruitment is involved in allergic inflammatory disorders, VCAM-1 has been identified as a target for drug discovery.
4.5.1 First Total Synthesis of (+)-Halichlorine

With its interesting biological profile, halichlorine was the subject of study in numerous groups but it wasn’t until three years after its isolation that it finally succumbed to total synthesis. In 1999, Danishefsky and colleagues discussed their studies towards and most importantly, the first total synthesis of halichlorine.\textsuperscript{[171-173]} In their initial publication\textsuperscript{[171]} they discussed the stereoselective, asymmetric synthesis of the spiroquinolizidine subunit 344, which contains 17 out of the 23 carbon's and four of the five stereocentres. Danishefsky's synthesis began with Meyers lactam 292 which was made by heating racemic carboxylic acid 337 with D-(−)-phenylglycinol 338 (Scheme 134). Treatment of the Meyers lactam 292 with allyl TMS in the presence of Lewis acid gave bicyclo lactam 293. After debenzylation (→294) and nitrogen protection, the bicyclic N-Boc-lactam 295 was stereoselectively methylated from the convex face to afford 296. This compound was hydrolysed (→297) and then reduced. The resulting primary alcohol 298 was protected to afford silyl ether 299.

At this juncture, three of the stereogenic centres had been introduced and the next stage was the formation of the C\textsubscript{5} stereocentre. Hydroboration of alkene 299 and subsequent palladium mediated Suzuki coupling of the resulting borane with Z-3-iodoacrylate allowed elongation of the allylic side chain to generate

\begin{center}
\textbf{Scheme 134: Danishefsky’s Synthesis of the Spiroquinolizidine Core of Halichlorine.}
\end{center}

Reagents and Conditions: (a) PhMe, reflux, 95%; (b) allyl TMS, TiCl\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2}, –78 °C → rt, 99%; (c) Na, NH\textsubscript{3}, THF, EtOH, –78 °C, 92%; (d) Boc\textsubscript{2}O, DMAP, THF, 96%; (e) (i) LiHMDS, THF, –40 °C; (ii) MeI, –78 °C → 0 °C, 90%; (f) LiOH, THF, H\textsubscript{2}O, 89%; (g) (i) CICOEt, Et\textsubscript{3}N, THF; (ii) NaBH\textsubscript{4}, MeOH, 82%; (h) TBDPSCI, Et\textsubscript{3}N, DMAP, CH\textsubscript{2}Cl\textsubscript{2}, 95%; (i) (i) 9-BBN, THF; (ii) Z-I-CH=CH=COOMe, Pd(dppf)Cl\textsubscript{2}, AsPh\textsubscript{3}, Cs\textsubscript{2}CO\textsubscript{3}, DMF, H\textsubscript{2}O; (j) (i) TFA, CH\textsubscript{2}Cl\textsubscript{2}; (ii) H\textsubscript{2}O, K\textsubscript{2}CO\textsubscript{3}, 77%.
unsaturated ester 339. Deprotection of the amino function and basification allowed an intramolecular Michael addition to take place and generate piperidine 340. The authors discuss the stereochemical control of this transformation as originating from the chair-conformation transition state, whereby the larger substituent adopts a pseudoequatorial position.

As shown in Scheme 135, crossed Claisen condensation of 340 with tert-butyl acetate produced the β-keto ester 341. Quinolizidine ring closure was then effected by a Mannich reaction with formaldehyde. Tricycle 342 was then converted into the α,β-unsaturated ester 343, which after deprotection gave spiroquinolizidine 344.

![Scheme 135](image)

**Scheme 135: Danishefsky’s Synthesis of the Spiroquinolizidine Core of Halichlorine.** Reagents and Conditions: (a) tBuOAc, LiHMDS, THF, –50 °C → rt, 86%; (b) H2CO, EtOH, 73%; (c) (i) LiHMDS, THF, 0 °C; (ii) Cp2Zr(H)Cl, rt, 91%; (d) HF-pyridine, THF, 94%.

Alcohol 344 was oxidised to aldehyde 345 using TPAP/NMO and then treated with Gilbert’s reagent[174] to produce alkyne 346 in reasonable yield. Hydrozirconation, followed by transmetallation gave zincate 347, which was then coupled to aldehyde 349 (aldehyde 349 was prepared from the known Weinreb amide 348[175]). The reaction was carried out in the presence of amino alcohol 350, which led to a 4:1 mixture of the desired 17R epimer 351. Treatment of the mixture with TBSOTf generated both the silyl ester of the carboxylic acid and the protection of the secondary alcohol (→352). Simultaneous cleavage of the carboxyl and primary silyl groups (→353) was brought about by the addition of ammonium fluoride in aqueous methanol. Crucially, the secondary TBS group remained intact. Macrolactonisation under Keck conditions enabled the formation of 17-TBS-halichlorine 354 and importantly allowed the separation of the 17R and 17S epimers. The final step entailed deprotection at C17 with HF-pyridine to afford halichlorine 336. The spectral data of the 17R synthetic material matched that of an authentic specimen.
Scheme 136: Completion of Danishefsky's Synthesis of Halichlorine. Reagents and Conditions: (a) TPAP, NMO, MeCN, rt; (b) N_{2}CHP(O)(OMe)_{2}, KO'Bu, THF, −78 °C, 57% over two steps; (c) (i) [Cp_{2}Zr(H)Cl], CH_{2}Cl_{2}; (ii) Zn_{2}Me, heptane, −65 °C; (iii) 350 (10 mol%), −65 °C → −30 °C; (iv) 349, −30 °C → rt, 67% overall; (d) DIBAH, PhMe, CH_{2}Cl_{2}, −78 °C, 82%; (e) TBSOTf, 2,6-lutidine, CH_{2}Cl_{2}, −78 °C → rt; (f) NH_{4}F, MeOH, H_{2}O, 66% overall from 351; (g) EDCI, DMAP, DMAP·HCl, CHCl_{3}, THF, reflux, 54%; (h) HF-pyridine, pyridine, THF, 95%.

4.6 Christie and Heathcock's Total Synthesis of (±)-Pinnaic Acid and (±)-Halichlorine

In 2004, PNAS published a fascinating report by Christie and Heathcock in which they reported the synthesis of both pinnaic acid and halichlorine, from a common late-stage intermediate.

As shown in Scheme 137, acylimmonium precursor 353 was prepared from keto-alcohol 352. Condensation of ketone 352 with benzyl carbamate gave the cis-fused bicyclic carbamate 353 as a 6:1 ratio of diastereoisomers. The structure was epimeric at C_{14}, with the major compound being the isomer with the methyl group on the convex face.
Scheme 137: Christie and Heathcock’s Synthesis. Reagents and Conditions: (a) Benzyl carbamate, Amberlyst-15, benzene, reflux, 2 h, 91%; (b) TiCl₄, H₂C=CHCH₂SiMe₃, CH₂Cl₂, –50 °C → –20 °C, 7 h, 53%; (c) (i) recrystallise as the hydroacetate salt; (ii) CbzCl, NaOH, H₂O, 15 h; (iii) MeOH, K₂CO₃, overnight; (d) Ac₂O, DMAP, Et₃N, CH₂Cl₂, rt, 1 h; (e) Grubbs second generation catalyst, CH₂Cl₂, 40 °C, 3.5 h; (f) 55 psi H₂, Pd/C, EtOAc, rt, 50 h.

Carbamate 353 was treated with allyl TMS and TiCl₄ to afford alcohol 354 in 53% yield, together with free amine 355. Amine 355 could be reprotected hence, increasing the allylation yield to 65%. Acetylation of the primary hydroxyl of 354 afforded 357, which underwent cross-metathesis with Nazarov ester 358 in the presence of Grubbs second generation catalyst, to produce enone 359. Reduction of enone 359 generated piperidine 360 as a single isomer at C₅.

With the core in place, the focus turned to functionalisation of the side chains. Protection of the nitrogen atom and C₅ side chain function was achieved through treatment of amino acid (obtained from amino ester 360) with the modified Mukaiyama reagent 369 (Scheme 138).

Cleavage of the acetate group of β-lactam 361, gave alcohol 362, which was then oxidised to aldehyde 363. Aldehyde 363 was then treated with phosphorane 370 to yield dienone 364 in 77% yield.
Reduction of ketone 364 gave alkenol 365 as a 5:2 mixture of diastereoisomers, which upon TES protection gave the fully protected compound 366. Cleavage of the β-lactam proceeded best when using “Red-Alp”, a pyrrolidine-modified Red-Al reagent,\(^{[177]}\) to enable the formation of aldehyde 368 via the decomposition of enamine 367 on silica gel. This amino aldehyde became the precursor for both pinnaic acid and halichlorine.

### 4.6.1 Completion of Pinnaic Acid

HWE reaction of aldehyde 368 afforded the entire carbon skeleton of pinnaic acid, in 54% yield. The authors make no mention of the obtained E:Z-selectivity in their publication. The silicon protecting groups were readily removed under standard conditions to afford diol 372 in 85% yield. Ester hydrolysis afforded the carboxylate salt 335, which upon treatment with pH 7 buffer allowed its purification as its zwitterion 290 by reverse-phase HPLC.
4.6.2 Completion of Halichlorine

To enable the conversion of aldehyde 368 into halichlorine 336, a new 6-membered ring fused to the spirocyclic core had to be created as well as the generation of the 15-membered macrocycle. Aldehyde 368 was treated with trimethyl phosphonoacrylate and lithium thiophenoxide to afford a mixture of the desired E:Z-thioether 373. Interestingly, when the E-isomer was treated with excess thiophenoxide a mixture was obtained that contained predominantly the Z-isomer. Heating of either the E:Z-mixture or the pure Z-isomer in a basic thiophenoxide solution resulted in the formation of dehydroquinolizidine 375. By allowing the nitrogen atom to add to the unsaturated ester of intermediate 374, addition/elimination of thiophenoxide could occur to form the dehydroquinolizidine. The silyl protecting groups were cleaved using TBAF (→376) and the resulting ester was saponified to give the sodium salt. Application of Keck’s macrolactonisation conditions allowed the formation of (±)-halichlorine 336. The NMR spectra of the synthetic material were identical to that of the authentic material.
Scheme 140: Completion of the Synthesis of Halichlorine. Reagents and Conditions: (a) Trimethyl phosphonoacrylate, PhSLi, THF, 0 °C → rt, 12 h, 71%; (b) K₂CO₃, PhSH, DMF, 55 °C, 35 h, 48-61%; (c) TBAF, THF, 0 °C, 3 h, 77%; (d) NaOH, MeOH, H₂O, 55 °C, 2 h, then rt, overnight; (e) N-(3-methylaminopropyl)-N'-ethylcarbodiimide hydrochloride, N-dimethylaminopyridine·HCl, CHCl₃, THF, reflux, 10 h, 32%.

4.7 Kibayashi’s Synthesis of (±)-Pinnaic Acid and (±)-Halichlorine

Kibayashi’s laboratory reported the efficient synthesis of ketone 381 incorporating the azaspirobicyclic core, via the 6-azaspiro[4.5]decane skeleton 380 (Scheme 141).[178] In a subsequent publication by the same authors,[166] ketone 381 was able to be used as a precursor in the synthesis of Danishefsky intermediate 303 and 401 (the ethyl ester of Danishefsky intermediate 344), to further enable a formal total synthesis of (±)-halichlorine and (±)-pinnaic acid.

Scheme 141: Summary of the Synthesis to Kibayashi’s Common Precursor 381.

Addition of allylmagnesium bromide to ketone 381 gave the tertiary alcohol 382. The allylation is directed to the less hindered face by the N-benzyloxy group. Oxidative cleavage of alkene 382 gave carboxylic acid 383, which upon cleavage of the benzyl group (→384), followed by lactam cyclisation gave the hydroxy tricyclic lactam 385. Dehydration of lactam 385 yielded a 2:1
mixture of the $\alpha$, $\beta$- and $\beta$, $\gamma$-lactams 386 and 387 respectively. Catalytic hydrogenation of the mixture gave the tricyclic lactam 388 as a single product. Removal of the silyl group afforded alcohol 389 which upon $C_7$ methylation from the $\beta$-face gave 390 and 391 with 15:1 selectivity.

Scheme 142: Kibayashi’s Synthesis towards Pinnaic Acid. Reagents and Conditions: (a) $H_2C\equiv CHCH_2MgBr$, THF, 0 °C, 99%; (b) OsO$_4$, NaIO$_4$, $H_2O$, THF, rt, 82%; (c) NaClO$_2$, NaH$_2$PO$_4$, 2-methyl-2-butene, $H_2O$, $t$-BuOH, rt, 95%; (d) $H_2$, Pd-C, EtOH, 97%; (e) ClCO$_2$CH$_2$CHMe$_2$, Et$_3$N, toluene, rt, 90%; (f) SOCl$_2$, Et$_3$N, CH$_2Cl_2$, 0 °C, 92%; (g) $H_2$, Pd-C, MeOH, 99%; (h) 1 M HCl, THF, rt, 99%; (i) Mel, LDA, THF, −78 °C, 78%.

Protection of the primary alcohol 390 as the benzyl ether 392, was followed by lactam cleavage to produce amino ester 394 using methyl triflate (Scheme 143), via iminium intermediate 393. The 1,7-disubstituted spirobicyclic compound underwent ester reduction to yield alcohol 395, which was converted to 396 by TBDPS protection, $N$-trifluoroacetylation and $O$-debenzylation. Dess–Martin oxidation of alcohol 396 gave the corresponding aldehyde 397, which after HWE homologation provided the TBDPS-protected Danishefsky intermediate 303. This intermediate had previously been converted to pinnaic acid (see Section 4.4.1) and thus constituted a formal synthesis of (+)-pinnaic acid by Kibayashi and co-workers.
Wittig methylation, N-protection and introduction of the alkenyl chain into the secondary amine allowed the azaspirobicyclic aldehyde 397 to be converted into diene 399 (Scheme 144). Ring-closing metathesis with Grubbs second generation catalyst enabled the formation of 400 in high yield. Finally, removal of the silyl protection furnished intermediate 401 (the ethyl ester of Danishefsky intermediate 344). Similarly this intermediate had been transformed into halichlorine (see Section 4.5.1) and so a formal synthesis of racemic halichlorine had also been achieved by Kibayashi and co-workers.

4.8 Investigation of Alternative Routes to the Spirocyclic Core of Pinnaic Acid and Halichlorine

The unique azaspiro[4.5]decane core structure present in both pinnaic acid and halichlorine has imparted challenges to synthetic chemists, who have strived for an easily accessible and reliable route to the core structure. As a consequence
many authors have described their synthetic approaches.\textsuperscript{[178-183]} In addition to those methods already described herein, it is not feasible and in the scope of this thesis to discuss every approach in depth. However, the work of many groups is portrayed in the informative review by Clive, Yu, Wang, Yeh and Kang in 2005.\textsuperscript{[162]}

4.9 The Achmatowicz and aza-Achmatowicz Oxidative Rearrangement

Hexoses have been successfully synthesised by routes which incorporate oxidative rearrangement of furylcarbinols 402 to pyranones 403, with chirality at the furylic position being conserved during the rearrangement (Scheme 145). This transformation has been termed the Achmatowicz rearrangement as a result of the pioneering work of O. Achmatowicz.\textsuperscript{[184]}

\[ \text{Hexoses} \]

\[ 402 \xrightarrow{[\text{O}]} 403 \]

Scheme 145: The Achmatowicz Rearrangement.

\( m \text{CPBA} \) is most commonly used as the peracid needed for the rearrangement to take place, though other reagents such as vanadyl acetylacetonate (\( \text{VO(acac)}_2 \)) and \( N \)-bromosuccinimide (\( \text{NBS} \)) have also been reported as suitable. In a quest for 2-(1-hydroxyalkyl)-3(2H)-furanones Ho and Sapp\textsuperscript{[185]} investigated the epoxidation of 2-furancarbinols 404 with \textit{tert}-butyl hydroperoxide in the presence of \( \text{VO(acac)}_2 \). It was expected that the double bond linked directly to the hydroxyalkyl chain would undergo the reaction regioselectively, with the resultant dioxabicyclo(3.1.0)hexane derivative rearranging to furanone 408 (Scheme 146). Oxidation was reasonably rapid and the 3(2H)-pyranones were obtained in acceptable yield.

\[ 404 \xrightarrow{} 405 \xrightarrow{} 406 \xrightarrow{} 407 \xrightarrow{} 408 \]

Scheme 146: Formation of Furanones 408 from 2-Furancarbinols.
These compounds underwent epoxide ring opening in a direction governed by the relative stability of the cyclic vanadate intermediate 409. Vanadates derived from the vic-glycol systems are the most favourable (Figure 30).

Figure 30: Cyclic Vanadate Intermediate 409.

Efforts to develop new routes to nitrogen bearing substances have been of considerable interest to synthetic chemists for some time. The aza-Achmatowicz rearrangement emerged in the 1980s in response to the synthetic problems the indolizidine and quinolizidine structures posed. Ciufolini and Wood\cite{186} reasoned that ketone 412 may be accessible from the enone 411. Enone 411 is in turn accessible through an aza-Achmatowicz rearrangement, starting from a substrate such as 410 (Scheme 147).

Scheme 147: The aza-Achmatowicz Rearrangement.

A hypothesis emerged that if similarly protected furfurylamines could be oxidised to nitrogen heterocycles, then they could be used as building blocks to readily incorporate nitrogen-containing heterocycles into natural product synthesis. Ciufolini reported that carbamate protected furfurylamines were unstable and readily hydrolysed to 3-hydroxypyridines under oxidation conditions. Further investigation by Zhou\cite{187} and Altenbach\cite{188} established that sulphonamide protection was well-suited under aza-Achmatowicz oxidation conditions and consequently the N-tosyl group is regularly used as a protecting group.

Since its conception, the aza-Achmatowicz reaction has been further developed and applied to the synthesis of a number of classes of compounds including piperidine alkaloids, azasaccharides and izidines. For the scope of this thesis it is not appropriate to discuss all of the synthetic situations in which the aza-
Achmatowicz has been used, but nevertheless some important and interesting examples are highlighted below.

### 4.9.1 Formation of Substituted Piperidines via the aza-Achmatowicz Rearrangement

In 2002, Harris and Padwa published their short and concise route to 2,5,6-trisubstituted piperidines, which incorporated an aza-Achmatowicz oxidation.\[^{189}\]

They postulated that this specific reaction could be used to prepare indolizidine systems such as 413 from furylamides 416 and subsequently a variety of piperidines-based alkaloids (Scheme 148).

\[
\begin{align*}
\text{R}_3 & \quad \text{R}_4 & \quad \text{R}_5 & \quad \text{R}_6 \\
\text{N} & \quad \text{O} & \quad \text{O} & \quad \text{H} \\
\text{Ts} & \quad \text{Ts} & \quad \text{Ts} & \quad \text{Ts}
\end{align*}
\]

Scheme 148: Padwa's Synthesis of 2,5,6-Trisubstituted Piperidines 413.

To enable the formation of systems such as 413, a 1,4-conjugate addition to 415 is necessary to introduce the R₃ substituent. To investigate the stereochemical aspects of this addition, 418 was prepared from furyl sulphonamide 417 and from NOE evaluation was assigned as the cis-isomer (Scheme 149). The authors reason that the "exclusive formation of 418 can be rationalised by assuming that A[^{1,3}]-strain between the two substituents and the tosyl group forces the methoxy and methyl groups to adopt a pseudoaxial orientation."\[^{189}\]

\[
\begin{align*}
\text{Nu} & \quad \text{Nu} & \quad \text{Nu} & \quad \text{Nu} \\
\text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3 \\
\text{Ts} & \quad \text{Ts} & \quad \text{Ts} & \quad \text{Ts}
\end{align*}
\]

Scheme 149: Padwa's Synthesis of 2,5,6-Trisubstituted Piperidines. Reagents and Conditions: (a) mCPBA, CH₂Cl₂, 2 h, rt, 85%; (b) (MeO)₃CH, BF₃·OEt₂, CH₂Cl₂, 0 °C, 3 h, 85%; (c) cuprate reagent, 85-90%; (d) allyl TMS, BF₃·OEt₂, CH₂Cl₂, 0 °C.

When enone 418 was treated with various cuprate reagents the reaction proved to be stereospecific, providing the corresponding Michael adducts in pure diastereomeric form. The stereochemistry is a result of axial attack from the face that is opposite to the diaxial substituents at C₂ and C₆. This may occur due to steric hindrance between the pseudoaxial 2,6-substituents and the equatorial
approach of the nucleophile, thus forming the kinetically favoured 1,4-adduct. Following this, the pyridinone ring can be functionalised at C6 by treatment of 419 with allyl trimethylsilane and BF3·OEt2 at 0 °C. The product 420 is a single diastereoisomer with 2,6-cis-disubstituted stereochemistry as dictated by the tosyl group which shields the opposite face of the molecule as a result of the A1,3-strain between the tosyl and methyl groups. The size of the tosyl group directs nucleophile attack on the iminium ion to the side of the C2 methyl, generating the cis-product.

In 2003, Padwa applied his methodology towards trisubstituted piperidines, which culminated in the synthesis of 6-epi-indolizidine 223A. A number of indolizidine alkaloids have been isolated from neotropical frogs, with a new subclass called 223A identified in 1997, after its extraction from a skin extract of the frog Dendrobatidae. The actual structure of 223A was finally elucidated in 2002 and was shown to contain an atypical 5,6,8-trisubstituted indolizidine ring (Figure 31).

A taxing problem in the synthesis of indolizidine alkaloids is the creation of the correct stereocentres in the piperidine ring, but Padwa envisioned that the aza-Achmatowicz reaction could be utilised to solve this issue and enable a synthesis of 6-epi-indolizidine 223A. At the outset of their work the revised structure had not been published, so the synthesis is directed towards the originally proposed structure 421.

The more complex dihydro-2H-pyridone 426 was synthesised from benzophenone-derived imine 423, which was alkylated, hydrolysed and the amine treated with tosyl chloride to generate 424 (Scheme 150). Oxidative rearrangement of 424 using mCPBA gave the desired 6-hydroxy-2,6-dihydropyridinone 425 as a single diastereoisomer, which was then transformed into alkene 426 through reaction with allylsilane.
The synthesis afforded 6-epi-indolizidine 223A in eight further steps, making the total synthesis thirteen steps long; with an overall yield of 13.1%. The incorporation of the aza-Achmatowicz oxidative rearrangement allows the 5,6,8-trisubstituted core structure to be easily obtainable, from which further functionalisation can take place.

4.9.2 Towards Hydroxylated Piperidine Alkaloids

In 2004, Cassidy and Padwa[^193] utilised the aza-Achmatowicz oxidative rearrangement as the crucial step in their synthesis of cis-2,3,6-trisubstituted piperidines. Padwa then proceeded to demonstrate its use in the synthesis of the biologically active alkaloids (+)-azimic acid and (+)-deoxocassine. Both compounds are 2,6-disubstituted piperidin-3-ol alkaloids, with azimic acid 434 being a product of the hydrolysis of azimine 433. Azimic acid, azimine and deoxocassine 435 (Figure 32) have attracted a great deal of attention since their isolation.
In Padwa’s synthesis of (±)-azimic acid and (±)-deoxocassine,[189] furyl sulphonamide 417 was oxidatively ring expanded with mCPBA, followed by treatment with trimethyl orthoformate and BF₃·OEt₂ to generate aminal 418 (Scheme 151). Reduction under Luche conditions gave the cis-alcohol 436 as a single diastereoisomer. Following TBS protection (→437), addition of methyl 3-(trimethylsilyl)-4-pentenoate, led to the formation of piperidine intermediate 438. The cis-substitution can be explained by assuming that the steric bulk of the tosyl group directs the allylsilane attack on the iminium ion to the side of the C₂-methyl group, leading to cis-stereochemistry.

To complete the synthesis of deoxocassine, ester 439 was converted to the Weinreb amide 440 in high yield (Scheme 152). Treatment of amide 440 with 6-heptenyllithium gave ketone 441. Ketone reduction via the corresponding tosylhydrazone afforded 442. Hydrogenation, followed by global deprotection, resulted in the formation of deoxocassine 435 in an excellent 92% over the final three steps.
The synthesis of azimic acid began from the same precursor 439 (Scheme 153). Ester 439 was reduced with LAH and the resulting alcohol 443 was converted to the mesylate before cyanide displacement resulted in the formation of nitrile 444. Hydrolysis of the nitrile, with consequential TBS cleavage, generated carboxylic acid 445. Finally, removal of the tosyl group afforded azimic acid 434.

The routes reported provide an efficient synthesis of two hydroxlated piperidine alkaloids. They both rely on the aza-Achmatowicz rearrangement as the pivotal step to provide the key N-tosyl-O-methylaminal from which the necessary functionalisation can take place.

### 4.10 Polymaxenolide

A coelenterate is an invertebrate of the phylum Coelenterata, which has a saclike body with a single mouth, which occurs in polyp and medusa forms. The group includes jellyfish, sea anemones and corals. A cnidarian is any coelenterate of the subphylum Cnidaria and the soft corals are a group of cnidarians that make up a large part of the biomass in tropical reefs. A good number of soft corals are of the genus Sinularia, which are inclined to form large
monospecific ‘carpets’ of up to 10 m². It is known that the soft corals produce multiple classes of unique secondary metabolites such as sesquiterpenes and diterpenes, with a broad range of carbon skeletons and biological activities.

The effects of natural hybridisation on secondary metabolite production and diversification has been largely ignored in marine organisms, despite the fact that it appears to be a widespread occurrence, having a bearing on the evolution of marine organisms. In 2004, Kamel and co-workers discovered hybridisation between *Sinularia maxima* and *Sinularia polydactyla* and reported the isolation (from Piti bomb holes in Guam) of a novel metabolite they termed polymaxenolide. Later, in 2009, Kamel and colleagues further examined the CH₂Cl₂/MeOH extracts and isolated additional related metabolites, 7E-polymaxenolide, 7E-5-epipolymaxenolide and polymaxenolides A–C.

The structure of polymaxenolide was resolved via mass spectrometry, IR spectrometry and extensive and intricate 1D and 2D NMR experiments. Fortunately for the authors, the isolated compound was in solid form, so x-ray crystallography was used to further determine the structure. The outcome of this investigation revealed that polymaxenolide 446 was composed of a fusion of a cembrane diterpene with an africanane-type sesquiterpene with the skeleton joined via a C–C bond (Figure 33).

![Figure 33: Structure of Polymaxenolide 446. The spirocyclic core structure is highlighted in red.](image-url)

Other than the accounts documenting its isolation and structural determination, there have been no biological or synthetic studies of polymaxenolide reported. Therefore, as a result of our interest in the synthesis of the spirocyclic piperidine and spirocyclic pyran core of natural products, we believed that we could use our prior synthetic experience and knowledge to establish a route to the spirocyclic core of polymaxenolide.
In our proposed approach, Lewis acid mediated ring-closing of 448 enables the formation of spirocyclic structure 447 (Scheme 154). Spirocycle 448 is the result of Achmatowicz rearrangement of TMS alkene 449, which itself is a product of Grubbs-mediated cross-metathesis of allyl TMS with terminal alkene 450. The known alkene 450 can be easily accessible from furan 453 in three steps.

Scheme 154: Retrosynthetic Analysis to Polymaxenolide 446.

In conclusion, the Achmatowicz and aza-Achmatowicz rearrangement reactions have become integral steps in the synthesis of natural products. With this in mind, we hope to build upon prior knowledge from our own laboratories and the chemistry community, to allow the use of this powerful rearrangement in our efforts towards the synthesis of the azaspiro cores of pinnaic acid and halichlorine, with the potential to develop a total synthesis of these alkaloids. We also believe that the rearrangement can be used to reach the spirocyclic core of polymaxenolide, with the view to then focus on a first total synthesis of this natural product.
5 Results and Discussion

At the outset of this project we envisioned that the work would ultimately lead towards a total synthesis of the marine natural product, pinnaic acid.

5.1 Retrosynthetic Analysis to Pinnaic Acid

As shown in Scheme 155, we envisaged pinnaic acid as having originated from spirocyclic piperidine 454, which could be obtained from the Nozaki coupling of vinyl iodide 455 and aldehyde 456. Vinyl iodide 455 is derived from conjugated ester 457. The fundamental spiropiperidine core 457 is thought to originate from aza-Achmatowicz rearrangement-intramolecular cyclisation sequence of allylsilane 458. This allylsilane could be generated from amino furan 459.

![Scheme 155: Retrosynthetic Analysis to Pinnaic Acid 290.](image)

5.2 Previous Work

The aza-Achmatowicz rearrangement has been explored in recent times by groups such as Ciufolini, Nelson and Padwa\textsuperscript{[193,196,197]} as a method of generating aza-saccharides and polysubstituted piperidine units. The generation of the enantiomerically pure furanyl alcohol limits the use of the rearrangement and though various approaches have been broached, we chose to take advantage of readily available oxynitrilases to introduce the desired hydroxyl functionality. It has formerly been demonstrated within the Marquez group that trimethylsilyl
Cyanohydrins can be treated with ammonia and transformed into their amine derivatives with complete inversion of configuration. We tentatively hypothesised that amino unit 462 could be obtained in a single step from aldehyde 480 by introduction of the appropriate ammonium salt into the enzymatic step (Scheme 156).

Scheme 156: Conversion of TMS Cyanohydrins into their Corresponding Amino Units.
Reagents and Conditions: (a) (S)-Oxynitrilase, HCN; (b) TMSCl, Et3N, DMAP, CH2Cl2; (c) NH3.

In addition, it has previously been demonstrated in our laboratory that highly functionalised spirocyclic pyrans can be obtained via the Achmatowicz rearrangement of furyl carbinols (Scheme 157).[157] This methodology, which takes advantage of the different rates of reaction for epoxidation and nucleophilic addition, has allowed spirocyclic units of different sizes to be selectively generated with complete stereocontrol.

Scheme 157: Synthesis of Highly Functionalised Spirocyclic Pyrans via Achmatowicz Rearrangement.

It is thought that the methodology established can be applied to the synthesis of both natural and unnatural spirocyclic piperidines beginning from the corresponding furfuryl amines (Scheme 158). Although it had been formerly shown that the rearrangement of α-hydroxyfurans could take place in the presence of olefins, there were concerns about the rearrangement of α-amino furans in the presence of double bonds.

Scheme 158: Proposed Synthesis of Spirocyclic Piperidines from Furfuryl Amines.
5.3 Synthesis of the Spirocyclic Core

5.3.1 Retrosynthetic Analysis

Before progressing to the commencement of reactions that involved compounds that necessitated the incorporation of stereochemistry, the decision was made to work with racemic material first, to test procedures and conditions and to allow evaluation of the results. A suitable retrosynthetic analysis was devised and is revealed in Scheme 159.

![Scheme 159: Retrosynthetic Analysis to Spirocyclic Piperidine Core 470 via a Racemic Route.](image)

Retrosynthetically, spirocyclic compound 470 could be achieved via a Grubbs-mediated ring-closing metathesis of 471, itself generated from diastereoselective allylation of 472 with allyl TMS. Hemi-aminol 472 is the product of the aza-Achmatowicz rearrangement of 473, which is flexible in having an alkyl side-chain which can vary in length and nature. Tosylate 474 could be generated through nitrogen protection of amine 475, the result of conversion from TMS-cyanohydrin 476. Cyanohydrin 476 can be formed directly from 2-furaldehyde or via cyanohydrin 477, itself made from 2-furaldehyde 460. The presence of CN as a leaving group allows the introduction of a yet to be determined side-chain. The proposed route is novel, flexible and versatile and we aimed to demonstrate improvement over existing methodologies. Following the ring-closing metathesis step there is the opportunity to form spirocyclic cores with different ring sizes.
5.3.2 Studies Towards the Synthesis of the Spirocyclic Core

The synthesis began with the commercially available and inexpensive starting material, 2-furaldehyde which was treated with 10% aqueous sodium hydrogen sulphite solution and 20% sodium cyanide solution. NaHSO$_3$ is a nucleophile which adds to aldehydes to give the bisulfite addition compound 479 via the mechanism detailed in Scheme 160. Nucleophilic attack of the sulphur lone pair on the carbonyl group of 460, leaves a positively charged sulphur atom which upon proton transfer leads to the bisulfite addition compound 479. When sodium cyanide is added, the formation of the bisulfite compound is reversed. Bisulfite then provides the single proton required to re-install the hydroxyl group of 484 at the end of the reaction.

Scheme 160: Mechanism for the Formation of Cyanohydrin 484. Adapted from Reference 119.

After 2 hours, the reaction had reached completion, but flash column purification proved to be troublesome due to crude product insolvability. Pre-adsorption onto silica gel also failed to yield any product. Modification of the work-up isolation allowed normal flash column chromatography to be carried out, affording the desired cyanohydrin 484 as a viscous, brown oil in 94% yield (Scheme 161). Protection of the alcohol as its TMS ether (476) using TMSCl failed to achieve completion, hence an alternative method was found.
Scheme 161: Synthesis of the Protected Amine. Reagents and Conditions: (a) 10% aq. NaHSO₃, 10% aq. NaCN, 0 °C → rt, 3.5 h, 94%; (b) TMSCl, pyridine, Et₂O, 0 °C, 22 h; (c) TMSCN, Et₃N, 1.5 h, 99%; (d) 2 M NH₃, EtOH, 40 °C, 2 h, 61%; (e) TsCl, DMAP, Et₃N, CH₂Cl₂, 0 °C → rt, 18 h, 12% or BnBr, DMAP, Et₃N, CH₂Cl₂, 0 °C → rt, 16 h, 27%.

2-Furaldehyde was treated carefully with TMSCN, which showed complete conversion after 2 hours. However, column chromatography proved troublesome and no desired product could be retrieved from the column. The reaction was repeated and the crude ¹H NMR spectra showed that other than excess triethylamine being present, the required product was clean, requiring no purification. The triethylamine was simply evaporated off the residue, yielding the TMS cyanohydrin 476 in 99%. This procedure was advantageous due to the fact that the starting aldehyde could be directly transformed into the TMS-cyanohydrin in one step,\(^{[198]}\) avoiding the intermediate cyanohydrin altogether.

In terms of the mechanism (Scheme 162) the reaction is a nucleophilic addition reaction to the carbonyl group. As the reaction is run with TMSCN, the TMS is present in the reaction mixture, which is then able to be attacked by the alkoxide 487, to generate the final TMS-cyanohydrin 476.

Scheme 162: Mechanism for the Formation of TMS-Cyanohydrin 476.

With TMS-cyanohydrin 476 in hand, conversion to the amino cyanohydrin was attempted. Treatment of TMS-cyanohydrin 476 with ammonia in ethanol generated amino cyanohydrin 475, with ¹H NMR spectroscopy of the crude residue showing that no further purification was necessary. A tosylate protecting group was chosen to mono-protect the nitrogen. It was found by Ciufolini\(^{[186,197,199]}\) that carbamate protected furfurylamines were unstable and readily hydrolysed to 3-hydroxypyridines under typical oxidation conditions. Sulphonamide protecting groups don't display this instability and are compatible
with the aza-Achmatowicz oxidation reaction. Amine 475 was treated with tosyl chloride and the desired protected compound 485 was isolated in 14% yield. Following a published procedure, the crude material was treated to precipitate any remaining impurities, affording tosyl amine 485 with only slight improvement in purity. This result was disappointing due to the relative simplicity of the reaction and on further attempts at protection with other groups similar results were also obtained. Some improvement was noted when using a benzyl ether protection, with mono-benzyl protected 486 isolated in 27% yield, a two-fold improvement in yield compared to the tosyl protection. Boc protection and benzoyl mono-protection of amine 475 was unsuccessful in both cases. At this stage it was clear that the protection step was hindering the synthesis, certainly insufficient product was always obtained which meant that the synthesis could not go forward as first planned.

Having had no success with the cyanohydrin approach, a new strategy was devised to generate the desired furfuryl amine. It has been reported that aldehydes can be aminoallylated using ammonia and allylating agents to give homoallylic primary amines with high chemoselectivity (amine vs. alcohol) (Scheme 163). This method affords α-amino furan units such as 488, while simultaneously incorporating a useful synthetic handle onto which further functionality could be added. This method is also advantageous as it avoids the use and handling of cyanide and cyano-containing compounds.

![Scheme 163: α-Aminoallylation Using Ammonia.](image)

Ammonia is a versatile and inexpensive nitrogen source and has been used as a nucleophile to incorporate nitrogen into organic molecules. The α-aminoalkylation of carbonyl compounds using ammonia has been reported, however, low yields have been the norm. Kobayashi and colleagues utilised the potential of ammonia and investigated α-aminoallylation of carbonyl compounds, using allylating agents as the carbon nucleophiles. It was Kobayashi who first described the novel three-component reactions of aldehydes, ammonia and
allylboronates to yield homoallylic primary amines with high chemoselectivities and stereoselectivities (Scheme 164).^{[201]}

\[
\begin{align*}
\text{Scheme 164: } \alpha\text{-Aminoallylation of Aldehydes.}
\end{align*}
\]

Kobayashi reported that since solvent has no effect in the reaction outcome, ethanol was chosen for its high solubility of ammonia and limited environmental impact. Variations of the allylboronated species also had little effect and pinacol allylboronate 489 was selected due to its high stability. Experimentally, Kobayashi found that a large excess of liquid ammonia was necessary to obtain high chemoselectivity of amine versus alcohol.

In subsequent communications Kobayashi reported the use of aqueous ammonia for the $\alpha$-aminoallylation, making it an easy and convenient procedure.\(^{[202]}\) Although initial results had shown that the use of aqueous ammonia led to a decrease in chemoselectivity (84:3 to 80:8, amine vs. alcohol). The inclusion of dodecylbenzenesulfonic acid (DBSA, Figure 34) as an additive was effective in improving the chemoselectivity. Since toluenesulfonic acid demonstrated much lower activity, it was thought that the hydrophobic element of DBSA played an important role.\(^{[202]}\) Further optimisation by the authors determined that $\alpha$-aminoallylations carried out with 10 mol% of DBSA in aqueous ammonia at room temperature for 6-12 hours, provided the best yields and selectivity.

\[
\begin{align*}
\text{Figure 34: Structure of Dodecylbenzenesulfonic acid. The hydrophobic and acidic elements are highlighted.}
\end{align*}
\]

In our hands, the $\alpha$-aminoallylation of 2-furaldehyde turned out to be an exceptionally reliable reaction, with identical yields obtained every time the reaction was carried out. The homoallylic amine 490 was reliably obtained in 55% yield and the matching alcohol side-product 491 in 3% yield (Scheme 165).
Despite the disappointing result with mono-tosylation of amine 475, we were optimistic about the chances of success with protection of homoallylic amine 490. Treatment of amine 490 with tosyl chloride gave a spot to spot conversion to yield tosyl amine 492 in quantitative yield. NMR spectroscopy confirmed the product as being extremely clean and impurity free.

We were delighted with the successful \(\alpha\)-aminoallylation reaction as it meant we were now in a strong position to proceed with the pivotal aza-Achmatowicz rearrangement.\(^{[184]}\) We were extremely pleased when treatment of tosyl amine 492 with \(m\)CPBA afforded the desired enone 493 in 59% yield. To our knowledge, this is the first example of a successful aza-Achmatowicz rearrangement in the presence of an olefin, the mechanism for which is demonstrated in Scheme 166.

Attempts to optimise the rearrangement yields by using purified \(m\)CPBA\(^{[204]}\) failed to increase the yield of the reaction. Also, it has been found through multiple reactions on similar scales that the yield is not consistent and fluctuates between 26% and 48%.

It was hypothesised that replacing the tosyl group on the amine with an electron donating group might improve the overall efficiency of the rearrangement. Treatment of amine 490 with benzyl bromide afforded the mono-protected
amine 494 in 43% yield, together with 10% of di-benzylated product 495 (Scheme 167). Interestingly, aza-Achmatowicz rearrangement of 494 gave dione 496, rather than the expected enone. The yield for the transformation was 26%, with the product being confirmed by NMR and mass spectrometry.

Knowing that the rearrangement was viable without affecting the terminal double bond, our attention focused on introducing the functionality at position C5 of the furyl ring. It was envisaged that deprotonation of 492 and addition of the appropriate bromoalkene would lead to addition product 497. The length of the chain introduced would dictate the final obtained ring size of product 498, following ring-closing metathesis (Scheme 168).

Hence, tosyl amine 492 was treated with nBuLi for 24 hours before being quenched with 6-bromo-1-hexene. After 24 hours the reaction afforded the desired disubstituted furan in 19% yield (48% based on starting material consumed). Unfortunately, despite extensive experimentation, which took into account equivalents, reaction times and bases, the reaction yield failed to improve.

Due to these difficulties an alternative route to 497 was explored, whereby the C5 side chain would be installed first (→501), followed by the introduction of the aldehyde at the C2 position (→500) by deprotonation and trapping with DMF.
As shown in Scheme 169, this then sets the molecule up for the reactions that have already been performed and shown to work.

Scheme 169: Alternative Route to 497.

Treatment of furan 453 with nBuLi and quenching with 4-bromo-1-butene afforded the desired alkenyl furan 501, $n=2$ in a disappointing 12% yield after purification. The low yield observed is presumably due to the relative volatility of the compound and the fact that two purification procedures were required. Similarly, freshly distilled furan was treated with nBuLi and 5-bromo-1-pentene to generate alkenyl furan 501, $n=3$. A decision was taken not to purify the crude residue as the $^1$H NMR spectrum showed it to be sufficiently clean to be taken on to the next step.

The Bouveault synthesis of aldehydes\cite{205} is well known (Scheme 170) and following a procedure reported by Marshall and colleagues,\cite{206} formylation of the furfuryl alkene was attempted. Unfortunately, treatment of alkenes 501 ($n=1$ and $n=3$) with sBuLi and quenching with DMF failed to generate the desired aldehydes. Alternative procedures were explored in the alkenes were treated with nBuLi and quenched with ethyl formate. However, despite repeated attempts no product could be detected, with the starting material remaining unaffected.

Scheme 170: Bouveault Synthesis of Aldehydes.

To check that deprotonation was taking place and the effect of the C$_5$ substituent in the reaction, freshly distilled furan was treated with nBuLi then quenched with DMF. NMR analysis of the crude reaction mixture showed that 2-
furaldehyde had been formed by the appearance of the characteristic aldehyde signal at 9 ppm (together with an unknown side-product). Likewise, when freshly distilled furan was treated with \( n\text{BuLi} \) and quenched with freshly distilled ethyl formate, NMR analysis of the crude product once again showed the presence of 2-furaldehyde. From these particular results it seemed that the procedure employed was suitable for the installation of the aldehyde at the \( C_2 \) position and perhaps it was the presence of the side chain at \( C_5 \) that was causing the reaction not to proceed. Additionally, the fact that the material was used crude in some cases, may have an impact on the success of the reaction.

As the main problem seemed to be the addition of the \( C_5 \) alkenyl chain, a new strategy had to be devised which would allow for the effective introduction of both side chains (Scheme 171). In a new approach, the disubstituted furan 497 originates from the tosyl protection of amine 499, itself a result of \( \alpha \)-aminoallylation of aldehyde 500. The aldehyde 500 is a product of oxidation of primary alcohol 502 which is the result of TBS cleavage of 503. Silyl ether 503 is the product of alkenyl chain addition onto 504 which comes from the TBS protection of the readily available furfuryl alcohol 505.

![Scheme 171: New Retrosynthesis to Furfuryl Compound 497.](image)

The first step of the synthesis (shown in Scheme 172) is the straightforward TBS protection of furfuryl alcohol 505 which was achieved in quantitative yield after only 10 minutes, to afford the silyl ether 504. There was no need for further purification.
The introduction of the C₅ alkenyl substituent was attempted using conditions which had been successfully employed for the synthesis of 2-(5-(allyl)-furylmethanol 509.\textsuperscript{[207]} Hence, TBS ether 504 was treated with nBuLi and quenched with freshly distilled allyl bromide. \textsuperscript{1}H NMR analysis of the crude residue showed the formation of a clean product but a short column was undertaken to remove the excess silyl product remaining from the protection step. This meant that the desired compound 506 was isolated in an excellent 91\% yield. Switching the solvent from tetrahydrofuran to diethyl ether resulted in an incomplete conversion of starting material to product. TBAF deprotection of the TBS ether proved not as reliable as expected and the desired primary alcohol 509 was isolated in 54\%. The addition of 1\% triethylamine to the column eluent failed to improve the yield. Switching the fluoride source from TBAF to hydrogen fluoride in pyridine was more successful, affording alcohol 509 in 61\% yield after purification. Swern oxidation of alcohol 509 afforded the crude aldehyde 512 in 87\%. The potential instability of this compound and the clean nature of the \textsuperscript{1}H NMR spectrum, showing the characteristic aldehyde signal at 9.49 ppm, meant that the product was not purified and taken on crude to the next step. With great satisfaction we now had the alkenyl chain in place at position C₅ and the aldehyde at the C₂ furan position, which left us in prime position to perform the α-aminoallylation. Due to the reliable success of this transformation previously, we were confident that the reaction would provide us with the correct adduct. This indeed turned out to be the case, with the reaction proceeding smoothly to afford the required amine 513 in 76\% yield, with no purification required. Surprisingly, the tosylation of amine 513 only gave the required nitrogen protected compound 514 in a mere 35\%. With this we could now proceed with the aza-Achmatowicz rearrangement of 514 (Scheme 173). In anticipation of the planned synthesis being successful, we synthesised
the additional compounds 507 and 508 with varying chain length at the C₅ position. The TBS ether was removed in each case using TBAF to afford the corresponding alcohols 510 and 511 (Scheme 172).

Scheme 173: aza-Achmatowicz Rearrangement of 515.

A number of different oxidative conditions and methods were attempted, including vanadyl acetoacetone (VO(acac)₂),[208] however, none of them yielded the desired product 515. It was postulated that a possible reason why the rearrangement was not working could be due to the multiple double bonds present in the molecule. In order to test this hypothesis, the decision was made to remove the double bond on the C₂ substituent of 492. Synthetically, this meant reverting back to a modified version of a previously attempted synthesis, whereby the C₅ substituent is installed and then rearrangement performed. Hydrogenation of furan 492 using palladium on carbon was extremely successful, giving the required alkane 516 in 99% yield (Scheme 174). Deprotonation using nBuLi and trapping of the resulting lithiate with allyl bromide gave the diq-substituted furan 517 in good yield, together with 44% of unreacted starting material.

Scheme 174: Hydrogenation of Furan 492. Reagents and Conditions: (a) H₂, Pd/C, MeOH, 40 min, rt, 99%; (b) allyl bromide, nBuLi, THF, 16 h, 0 °C → rt, 66% based on starting material consumed; (c) ‘oxidative conditions’.

Unfortunately, the same problems with the rearrangement were encountered, with mCPBA, VO(acac)₂/²BuOOH and NBS all failing to promote the desired rearrangement to generate spirocyclic piperidine 518. We were particularly disappointed as NBS has been reported to give good yields via a very simple procedure. Although NBS has been successfully used, as the oxidative reagent for the Achmatowicz rearrangement, in synthesis by Couladouros[209] and O’Doherty,[210,211] their reported conditions were unsuccessful in our hands.
Faced with this lack of success, we sought to remove the remaining terminal olefin of 517 to discover whether the dialkyl derivative 519 would then be able to oxidise successfully. Hydrogenation of alkene 517 proceeded in 98% yield to yield dialkane 519, which was subjected to the oxidative conditions. Once again there was no positive outcome, with no formation of 520.

![Scheme 175: Hydrogenation of 517 and attempted aza-Achmatowicz Rearrangement.](image)

Reagents and Conditions: (a) H₂, Pd/C, MeOH, 45 min, rt, 98%; (b) mCPBA, CH₂Cl₂, 0 °C → rt.

Although until this point the assumption had been made that the oxidative conditions used were not rearranging our substrates, there was also the possibility that the desired aminal might be formed under our conditions, but not able to withstand work-up and purification. For this reason it was decided to cap the aminal’s hydroxyl group with a methyl unit. Reactions of this type have been demonstrated successfully by Padwa[^189], so furyl sulphonamide 517 was oxidatively rearranged with mCPBA and the crude residue treated with trimethyl orthoformate and BF₃·OEt (Scheme 176). Unfortunately, TLC analysis showed no clear appearance of product 521 and resulted in the eventual degradation of all starting material.

Intriguingly, there are reports of the aza-Achmatowicz oxidative rearrangement being performed at elevated temperatures (up to 60 °C). Following helpful discussions with Dr D. P. Furkert[^212] a solution of furyl sulphonamide 521 in chloroform was treated with mCPBA at 55 °C. After 6 hours, the starting material seemed to have been consumed by TLC, together with the faint appearance of a possible product. Taking precedent from work by Padwa[^190] the crude product was treated with allyl trimethylsilane and BF₃·OEt₂. NMR spectroscopy of the crude residue was not conclusive and at this stage time did not permit repeated attempts at this transformation as we wished to progress to trial supplementary ideas. This area of investigation is worth revisiting in the future with respect to applying efforts towards optimising reaction conditions.
The findings thus far, suggested that the rearrangement proceeded well in the presence of the alkenyl chain at the C₂ position as long as there were no substituents at C₅. Substitution at both C₂ and C₅ caused the oxidative aza-Achmatowicz rearrangement to not proceed. Furthermore, hydrogenation of one or both of the terminal olefins did not aid the rearrangement in either case. As a result, we contemplated whether the oxidation would come about if the C₅ substitution was in place but the C₂ substitution was simplified. This would require the synthesis of the simplified analogue 524 (Scheme 177).

Synthetically, furfurylamine 526 was monoprotected in quantitative yield and the resulting tosylate 525 was treated sequentially with nBuLi and allyl bromide (Scheme 178). Gratifyingly, allyl furan 524 was obtained in 88% yield, with no need for purification. Treatment of tosyl amine 524 with excess mCPBA consumed the starting material, however the ¹H NMR showed that no desired product 523 was present.
Out of interest, the terminal olefin was removed using palladium on carbon to generate 528 in 92% yield with no column purification needed. Once again the aza-Achmatowicz reaction let us down and the rearrangement product 529 was not formed. Rearrangement of protected amine 525 also failed, with no reaction occurring the simple starting material was recovered after work-up.

Additionally, protected amine 525 was taken and deprotonated at C₅ to enable the addition of 4-bromo-1-butene to form 530 in 43% yield, which was then treated with mCPBA, but again the reaction failed (Scheme 179).

An attempt was also made with the Boc protected amine (Scheme 180). Oxidative rearrangement of Boc protected furfuryl amine 532 with mCPBA also caused the starting material to disappear by TLC, although ¹H NMR spectra showed a mixture of unknown signals.
The most interesting set of results were obtained when methyl furfurylamine was used as our starting substrate (Scheme 181). Methyl furfurylamine 534 was protected to afford the desired mono-tosylated product 535 in quantitative yield after purification. Tosyl amine 535 was treated with mCPBA under similar conditions to those used for all the previous rearrangement attempts. On this occasion we were delighted to see the successful aza-Achmatowicz reaction product 536, which was isolated in quantitative yield after work-up. $^1$H NMR analysis showed that no purification was required. Simultaneously, methyl furfurylamine was protected as the Boc amine 537 in quantitative yield. The rearrangement proceeded well by TLC but surprisingly; the product 538 was not easily isolated and after work-up NMR spectroscopy showed a significant number of additional signals that could not be attributed to any other realistic compound. Due to the great success of the tosylated compound the Boc analogue was abandoned.

Though we were thrilled with this success, we were intrigued as to why the rearrangement would now proceed with presence of a methyl group at C5, when it would not proceed with a longer chain or no substituent at all. To supplement our existing knowledge, the same process was executed with 5-methylfuraldehyde (Scheme 182).

5-Methylfuraldehyde 539 was subjected to the same α-aminoallylation reaction in aqueous ammonia described previously, which provided homoallylic amine 540 in 77% yield. Amine 540 was then monoprotected as either the tosyl amine 541 or Boc amine 543 in 93% yield and 81% yield respectively.
Treatment of amines 541 and 543 under the same oxidative rearrangement conditions led to the clean formation of enones 542 and 544 in 99% yield and 88% yield respectively, with no need for further purification. No additional products were seen by $^1$H NMR spectroscopy proved the result, with no need for any purification.

5.4 Efforts Towards the Synthesis of the Tricyclic Core of Halichlorine

5.4.1 Retrosynthetic Analysis

We envisaged that the results and information gained, as part of the previous studies described above, could be utilised to develop a short, concise route to the tricyclic core of halichlorine (Figure 35).

A retrosynthetic route was devised as shown in Scheme 183. It was hypothesised that the basic, initial tricyclic core 545, from which further functionalisation could be introduced, is the product of ring-closing metathesis of diene 546. Diene 546 was thought of as being a product of treatment of 547 with
allylstannane. Bicyclic structure 547 is generated from the reduction of dicarbonyl 548. This dicarbonyl is afforded after removal of the hydroxyl function of 549 using triethylsilane and a Lewis acid. 549 is a result of the aza-Achmatowicz oxidative rearrangement of 550, which in turn is gained from ring-closing metathesis of diene 551. Diene 551 could in turn be obtained through the protection of previously generated homoallylic amine 490, itself obtained via α-aminoallylation of 2-furaldehyde.

Scheme 183: Retrosynthetic Analysis to Tricyclic Core 545.

5.4.2 Initial Synthetic Investigations

Our synthesis began with homoallylic amine 490, which was prepared using the procedure described previously. Homoallylic amine 490 was treated with acryloyl chloride to generate amide 551 in a non-reproducible 63% yield after purification (Scheme 184). We were surprised that the yield was not higher for such a simple transformation, but a minor modification of the reaction conditions allowed us to obtain vastly improved and reliable quantitative yields.

Scheme 184: Synthesis of Bicyclic Structure 549. Reagents and Conditions: (a) allylboronic acid pinacol ester, DBSA, 25wt% aq. NH₃, rt, 2 h, 55%; (b) CH₂=CHCOCl, DIPEA, CH₂Cl₂, rt, 2 h, 100%; (c) Grubbs first generation catalyst (10 mol%), CH₂Cl₂, reflux, 18 h, 84%; (d) mCPBA, CHCl₃, 60 °C, 3.5 h then rt, 18 h, 70%.

Ring-closing metathesis of diene 551 using Grubbs first generation catalyst afforded lactam 550 in reproducible 76-84% yields. Disappointingly, aza-
Achmatowicz rearrangement of 550 failed to generate the desired product under a variety of conditions. We were delighted when the reaction was run with mCPBA at 60 °C in chloroform. In this case, the desired bicyclic lactam 549 was isolated in 70% yield, together with traces of unreacted starting material 550. Unfortunately, this reaction could not be repeated to reproduce the successful result and for the most part, no reaction was seen to occur at all.

Out of interest, to determine the effect of the double bond on the success of the reaction, the double bond of 550 was hydrogenated using palladium on activated carbon to generate 552 in 70% yield (Scheme 185). Regrettably, time constraints meant that only one attempt was made at the rearrangement to form 553 and it was disappointing to see no observed reaction and the starting material was recovered.

Scheme 185: Attempted Rearrangement of 662. Reagents and Conditions: (a) H₂, Pd/C, MeOH, 35 min, rt, 70%; (b) mCPBA, CHCl₃.

5.5 Efforts Towards the Synthesis of the Spirocyclic Core of Polymaxenolide

5.5.1 Retrosynthetic Analysis

As a result of our continued interest in the synthesis of the spirocyclic cores of natural products, we believed that we could utilise our learned knowledge and apply it further. Drawing from our synthetic experience thus far, we wanted to establish a route to the spirocyclic unit of polymaxenolide 446 (Figure 36), a route that would incorporate the Achmatowicz rearrangement.
Figure 36: Structure of Polymaxenolide 446. The spirocyclic unit is highlighted in red.

It was visualised that the spirocyclic unit 447 could be the product of Lewis acid-mediated ring-closing of 448, itself a product of the Achmatowicz rearrangement of 449 (Scheme 186). Grubbs-mediated cross-metathesis of alcohol 450 with allyltrimethylsilane could afford 449, with the alcohol a result of the silyl group removal in 451. The C₅ addition of an alkenyl chain of varying length to 452 gives 451, while 452 is prepared from the addition of isobutyraldehyde to furan 453, followed by silyl protection.

Scheme 186: Retrosynthetic Analysis to 447.

5.5.2 Initial Synthetic Investigations

The synthesis began with 2-lithiofuran which was trapped with isobutyraldehyde to generate the furfuryl alcohol 554 in 96% yield. Alcohol 554 was then protected as its corresponding TBS ether to give the desired protected compound 452 in 84% yield.
Deprotonation of 452 at C₅ with nBuLi, followed by the addition of 4-bromo-1-butene enabled the formation of 451 in excellent yield. Removal of the silyl protection group with TBAF then afforded the corresponding secondary alcohol 450 in 81% yield. Cross-metathesis of alkene 450 with allyltrimethylsilane in the presence of Grubbs second generation catalyst[214] converted the terminal double bond into the allylsilane 449 in 52% yield (Entry 2, Table 4). ¹H NMR analysis showed that 449 was formed as an inseparable mixture of E:Z-isomers (6.15:1). The remainder of the yield can be attributed to the formation of the homodimer. Efforts to improve the yield of the cross-metathesis reaction using alternative catalysts concluded in mixed results (Table 4).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Grubbs 1st Gen. (5 mol%)</td>
<td>Allyl TMS (3 eq.) CH₂Cl₂, reflux, 48 h</td>
<td>43%</td>
</tr>
<tr>
<td>2</td>
<td>Grubbs 2nd Gen. (5 mol%)</td>
<td>Allyl TMS (3 eq.) CH₂Cl₂, reflux, 48 h</td>
<td>52%</td>
</tr>
<tr>
<td>3</td>
<td>Hoveyda-Grubbs 2nd Gen. (5 mol%)</td>
<td>Allyl TMS (3 eq.) CH₂Cl₂, reflux, 48 h</td>
<td>27%</td>
</tr>
</tbody>
</table>

Table 4: Cross-Metathesis of 450 with Allyltrimethylsilane.

The Achmatowicz rearrangement of alkene 449 was initially attempted with the addition of mCPBA in two portions. Initially, the TLC of the reaction mixture gave cause to be optimistic about the success of the reaction, with the appearance of a major new spot thought to be the desired rearranged product. However, after work-up a second precautionary TLC showed the appearance of additional spots, bringing the total number to seven spots, with one being a
trace amount of remaining starting material. The spot thought to be the product was still the major spot and FCC was performed to isolate as many as possible. Unfortunately, even though the isolation was successful, $^1$H NMR spectroscopy showed a compound that had clearly degraded. As an alternative oxidising agent, VO(acac)$_2$ was used and this proved to be a significant improvement. TLC analysis showed a clean, spot to spot conversion with the only other spot being a faint showing at the baseline. FCC of the residue afforded the desired product 448 in 9% yield. It was postulated that degradation may be occurring on the silica column, therefore the feasibility of a one-pot, two-step procedure was investigated.

It was known from TLC analysis that the rearrangement product 448 was being formed cleanly as the major product. It was tentatively thought that filtering the reaction through Celite® would not greatly affect the compound. Therefore, a second method was tried in which 448 was not purified but used immediately in the second cyclisation procedure (Scheme 188). With the knowledge that VO(acac)$_2$ was the superior oxidising agent for the Achmatowicz rearrangement, the same procedure was carried out as described above. The reaction was filtered through Celite® and the solvent was concentrated to approximately 1 cm$^3$ and then fresh, anhydrous CH$_2$Cl$_2$ added and the solution cooled to $-78$ °C. The BF$_3$ complex, BF$_3$·OEt$_2$, was slowly added and then the stirring continued for 30 minutes at $-78$ °C. Disappointingly, the yield was very low (~1%) and only $^1$H NMR spectroscopy was able to be performed on such a small amount. Despite this, we believe that the desired product was indeed formed and isolated.

**Scheme 188: One-pot, two-step Procedure.** Reagents and Conditions: (a) VO(acac)$_2$, TBHP, CH$_2$Cl$_2$, 0 °C, 2 h, 9%; (b) BF$_3$·OEt$_2$, CH$_2$Cl$_2$, $-78$ °C, 30 min, ~1%.

Due to time restraints this method was only carried out once, but we believe that we have identified a novel route to the spirocyclic structure of polymaxenolide 447, incorporating the Achmatowicz rearrangement as the key
In addition we consider the one-pot method to be the correct reaction for the transformations and reason that further investigation will optimise the yield.

In addition to carrying out the above investigation into the synthesis of the spirocyclic core of polymaxenolide, we simultaneously began the synthesis of the additional units that would be needed. In readiness for the synthesis of spirocyclic core units with different ring sizes the appropriate compounds were prepared as shown below in Scheme 189, with no difficulties encountered. Once again, an inseparable $E$:$Z$-mixture of isomers of allylsilanes $561$ and $562$ was obtained.

We are encouraged by all of the progress that has been made in the three areas of our interest in spirocyclic piperidines and pyrans, but realise that further investigation is necessary in each area in order to progress further. This will mostly involve the testing of new reagents and optimisation of reaction conditions.

**Scheme 189: Synthesis of Compounds with Different C$_5$ Substitution.** Reagents and Conditions: (a) $n$BuLi, allyl bromide, THF, $0 \degree C \rightarrow rt$, 16 h, 92%; (b) $n$BuLi, 5-bromo-1-pentene, THF, $0 \degree C \rightarrow rt$, 16 h, 86%; (c) $n$BuLi, 6-bromo-1-hexene, THF, $0 \degree C \rightarrow rt$, 16 h, 100%; (d) TBAF, THF, $0 \degree C \rightarrow rt$, 19 h, 87%; (e) TBAF, THF, $0 \degree C \rightarrow rt$, 19 h, 81%; (f) TBAF, THF, $0 \degree C \rightarrow rt$, 19 h, 80%; (g) Grubbs second generation catalyst, allyl TMS, CH$_2$Cl$_2$, reflux, 48 h, 36%; (h) Grubbs second generation catalyst, allyl TMS, CH$_2$Cl$_2$, reflux, 48 h, 45%.
5.6 Future Work

5.6.1 Enantioselective α-Aminoallylation

The enantioselective synthesis of homoallylic primary amines has been reported.\textsuperscript{[202]} The synthesis is based on asymmetric 2-azonia-Cope rearrangement (Scheme 190). The authors term this transfer aminoallylation as "both the amino and the allyl groups are incorporated into the product".

\[
\begin{align*}
\text{NH}_2 & \quad \text{R}_2 \\
\text{R}_1 & \quad \text{O} \\
\text{NH}_2 & \quad \text{R}_2 \\
\text{R}_1 & \quad \text{O} \\
\text{NH}_2 & \quad \text{R}_2 \\
\text{R}_1 & \quad \text{O} \\
\text{NH}_2 & \quad \text{R}_2 \\
\text{R}_1 & \quad \text{O} \\
\end{align*}
\]

Scheme 190: Transfer Aminoallylation.

α-Aminoketone 564 was readily synthesised from (1R)-camphorquinone 563 in 80%, with >99% d.e. and then used for the transfer aminoallylation of 2-furaldehyde (Scheme 191).\textsuperscript{[202]} The desired optically active amine was obtained in 60% yield and 97% e.e.. It would be interesting to carry out this transfer aminoallylation on 2-furaldehyde to obtain the primary amine 565, which after mono-tosylation (\(\rightarrow\)566) could be subjected to the aza-Achmatowicz rearrangement. This would generate lactone 567.
5.6.2 Pinnaic Acid

It has been determined in the studies described that the *aza*-Achmatowicz rearrangement is highly successful for compounds that have either no substitution or methyl substitution at position $C_5$. This holds true for tosyl (or Boc) protected compounds with a terminal olefin, produced as a result of an $\alpha$-aminoallylation reaction, or for the simpler tosyl protected amine (Figure 37).

![Figure 37: $C_5$ Substitution Enabling a Successful *aza*-Achmatowicz Rearrangement.](image)

For clarification it is vital that the rearrangement of 514 is further investigated. From experience in trying various conditions for a variety of rearrangements, there is the belief that from the analysis of TLC's of various reactions, the rearrangement may be occurring and it is the work-up that is causing the product to be destroyed. Another possibility is that the product is extremely unstable and begins to decompose before it can be properly identified. In the future the solvent should not be evaporated to dryness unless the compound is stable. It was thought that 515 would be stable due to the hemiaminal being substituted. It is also possible that the residue may be undergoing rapid decomposition due to the peroxide reacting further with the hemiaminal.

Therefore, a sensible course of action would be to fully and rigorously investigate this particular reaction. This would involve complete examination of:

*Reagents* - with care taken to distill/purify any commercial reagents before use

*Equivalents* - trialling a range of equivalents from small to large, adding equivalents in one portion and/or portionwise

*Temperature* - adding reagents at a temperature lower/higher than room temperature, changing temperature throughout the course of the reaction, heating for prolonged period
Time - allowing a reaction to run its course to allow full consumption of starting material, seemingly dormant reactions should be left for prolonged periods to ensure that they are not just slow running. Particular care and attention must be made to TLC analysis must be made in these cases.

Following oxidative rearrangement it would be necessary to either:

Perform work-up - followed by reduction of the reaction solvent to ~1 cm³ and then carry out the Lewis acid mediated addition of allyltrimethylsilane to generate 522. The first wash after this reaction would be a sat. aq. NaHCO₃/NaSO₃ to remove any residual peroxide.

Not perform work-up - followed by reduction of the reaction solvent to ~1 cm³ and then carry out the Lewis acid mediated addition of allyltrimethylsilane. The first wash after this reaction would be a sat. aq. NaHCO₃/NaSO₃ to remove any residual peroxide.

If may also be necessary to perform the ring-closing metathesis immediately after the Lewis acid mediated addition, with careful work-up and no column purification (Scheme 192). If successful, the procedure could be applied to compounds with longer substitution at C₅, in order to generate larger ring sizes. Appropriate functionalisation could then take place utilising the terminal olefin.

Scheme 192: Proposed Three-Step Procedure to 568.

5.6.3 Halichlorine

It is difficult to know how to progress with this area in as much as the conditions which worked once do not enable a repeat result. A possibility is to investigate an alternative oxidising agent such as dimethyldioxirane (DMDO), which should be more reactive than mCPBA. DMDO is easily generated\textsuperscript{[215]} and used as a solution in acetone, with the products being only the oxidised compound and acetone. In 1991, Adger and colleagues reported their use of DMDO for the
oxidation of furans.\cite{216} With 1 equivalent of DMDO in acetone at room temperature they were able to successfully oxidise furfuryl alcohol 505 to 2H-pyran-3(6H)-one 569 and the substituted furfuryl alcohols 570 and 572 to their corresponding pyranones 571 and 573 respectively. No mention of yields is made in the publication.

\[ \text{Scheme 193: Oxidation of Furfuryl Alcohol with DMDO. Reagents and Conditions: DMDO (1 eq.) in acetone (0.05 mol dm}^{-3}, \text{acetone, rt.} \]

### 5.6.4 Polymaxenolide

There is a desire to further develop the one-pot, two-step reaction sequence in order to generate the bicyclic core 447 in higher yield (Scheme 194). Although it has been shown that the Lewis acid, BF$_3$:OEt$_2$ is effective to promote the cyclisation, there is a wish to perform a Lewis acid screen to test the effectiveness of other Lewis acids beginning with: EtAlCl$_2$, Et$_2$AlCl, SnCl$_4$, TiCl$_3$(O$i$Pr), TiCl$_2$(O$i$Pr)$_2$ and TiCl(O$i$Pr)$_3$. In addition there would be an investigation into the effect of temperature on the reaction.

\[ \text{Scheme 194: Generation of 447.} \]
6 Experimental

6.1 General Methods

All reactions were performed under an inert argon atmosphere unless otherwise noted. Reagents and starting materials were obtained from commercial sources and used as received, unless otherwise specified.

Anhydrous dichloromethane (DCM), diethyl ether, toluene and tetrahydrofuran (THF) were freshly obtained from in-house solvent purification system, Pure Solv 400-5MD (Innovative Technology, Inc). Anhydrous dimethylformamide (DMF) and triethylamine (TEA) were purchased from Aldrich Chemical Company. Petroleum ether refers to that with boiling fraction 40–60 °C. Solutions worked up were concentrated under reduced pressure at < 45 °C using a Buchi Rotavapor.

Melting points were determined using Stuart Scientific Melting Point SMP1 apparatus.

Optical rotations were determined as solutions irradiating with the sodium D line (\(\lambda = 598\) nm) using an AA series automatic polarimeter. \([\alpha]_D\) values are given in units \(10^1\) deg cm\(^2\) g\(^{-1}\).

Infrared (IR) spectra were recorded as thin films on sodium chloride (NaCl) plates using a JASCO FTIR 410 spectrometer. Only significant absorptions (\(\nu_\text{max}\)) are reported in wavenumbers (cm\(^{-1}\)).

Proton magnetic resonance spectra (\(^1\)H NMR) were recorded at 400 MHz using a Bruker DPX-400 spectrometer for sample solutions in CDCl\(_3\), unless otherwise indicated. Chemical shifts (\(\delta_H\)) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The order of citation in parentheses is (1) number of equivalent nuclei (by integration) (2) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext. = sextet, oct. = octet, m = multiplet, br = broad) (3) coupling constant (\(J\)) quoted in Hertz to the nearest 0.1 Hz and (4) proton assignment. For relevant compounds, the OH signal was identified by D\(_2\)O exchange.
Carbon magnetic resonance spectra ($^{13}$C NMR) were recorded at 100 MHz using a Bruker DPX-400 spectrometer for sample solutions in CDCl$_3$, unless otherwise indicated. Chemical shifts ($\delta_C$) are quoted in parts per million (ppm) and are referenced to the residual solvent peak.

For convenient $^1$H and $^{13}$C NMR spectroscopy characterisation, furanyl compounds have been labelled as shown below:

![Furanyl Compound Labeling]

Mass spectra were obtained using a JEOL JMS-700 spectrometer.

TLC was performed on aluminium backed plates pre-coated with silica gel 60 (Kieselgel 60 F$_{254}$ aluminium plates, Merck) with A, petroleum ether-ethyl acetate (8:2); B, petroleum ether-ethyl acetate (7:3); C, petroleum ether-ethyl acetate (6:4); D, petroleum ether-ethyl acetate (9:1); E, petroleum ether-ethyl acetate (9.5:0.5); F, petroleum ether-diethyl ether (9.5:0.5); G, toluene-ethyl acetate (8:2); H, petroleum ether-ethyl acetate (2:8); I, petroleum ether-ethyl acetate (5:5); J, petroleum ether-ethyl acetate (3:7); K, chloroform-ethyl acetate (6:4); L, petroleum ether (10:0); M, petroleum ether-ethyl acetate (4:6); N, petroleum ether-diethyl ether (7:3); O, petroleum ether-ethyl acetate (2:8); P, petroleum ether-diethyl ether (9:1); Q, hexanes (10:0); R, petroleum ether-diethyl ether (8:2); S, petroleum ether-diethyl ether (5:5) as developers and detection under UV light ($\lambda_{max}$ 254 nm) and/or by staining with anisaldehyde, unless otherwise specified, followed by heating.

Flash column chromatography (FCC) was performed using Apollo Scientific silica gel 60 (0.040-0.063 mm), with the appropriate eluting solvent and elution gradient, shown in square brackets as part of the procedure, e.g. purification by FCC [petroleum ether-ethyl acetate (85:15)→(75:25)→(60:40)→(50:50)] of the crude residue....

The following chemicals were used at the concentrations given, unless otherwise stated:
• *tetra*-Butylammonium fluoride (TBAF), 1 M in tetrahydrofuran
• Oxalyl chloride, 2 M in dichloromethane
• Ethyl Magnesium Bromide (EtMgBr), 3 M in diethyl ether
• Potassium bis(trimethylsilyl)amide (KHMD), 0.5 M in toluene
• *n*-Butyllithium (*n*BuLi), 2.5 M in hexanes.
6.2 Synthesis and Characterisation of Compounds

Furan-2-yl-hydroxy-acetonitrile 477\[217\]

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

A mixture of 2-furaldehyde (1.00 g, 10.4 mmol) and 10% aqueous NaHSO\textsubscript{3} (15.6 cm\textsuperscript{3}) was stirred in diethyl ether at 0 \degree C for 1 h. 20% aqueous sodium cyanide (4.16 cm\textsuperscript{3}) was added and stirring continued, allowing the reaction to warm to room temperature over 2.5 h. The reaction was diluted with ethyl acetate (30 cm\textsuperscript{3}) and water (30 cm\textsuperscript{3}) was added. The phases were separated and the aqueous layer extracted with ethyl acetate (3×20 cm\textsuperscript{3}). The combined organic extracts were washed with brine (30 cm\textsuperscript{3}), dried over anhydrous sodium sulfate, filtered and concentrated \textit{in vacuo}. Purification by FCC [petroleum ether-ethyl acetate, (80:20)→(70:30)→(60:40)] of the crude residue gave cyanohydrin 477 (1.20 g, 94%) as a thick brown oil; \(R_f\) 0.71 (solvent C); \(\nu_{\text{max}}\) (film)/cm\textsuperscript{-1} 3360 (OH) and 2252 (C≡N); \(\delta_h\) (400 MHz; CDCl\textsubscript{3}) 5.21 (1 H, s, \(CH\textsubscript{CN}\)), 6.30 (1 H, dd, \(J\) 1.9 and 3.3, \(CH=CO\)), 6.48 (1 H, d, \(J\) 3.3, \(CHCO\)) and 7.40 (1 H, d, \(J\) 1.9, \(CHO\)). The spectral data matches that reported in the literature.\[217\]

Furan-2-yl-trimethylsilyloxy-acetonitrile 476\[198\]

\[
\begin{align*}
&\text{TMS} \\
&\text{CN}
\end{align*}
\]

A stirred solution of 2-furaldehyde (2.00 g, 20.8 mmol) in triethylamine (1.45 cm\textsuperscript{3}, 10.4 mmol) at room temperature was treated by the careful dropwise addition of trimethylsilylcyanide (2.86 cm\textsuperscript{3}, 22.8 mmol). The reaction mixture was kept at room temperature for 1.5 h and the triethylamine was then evaporated under vacuum to afford TMS ether 476 (4.00 g, 99%) as a thick brown oil, with no need for further purification; \(R_f\) 0.82 (solvent A, PMBA); \(\nu_{\text{max}}\) (film)/cm\textsuperscript{-1} 2960, 1669 (C=C) and 1394; \(\delta_h\) (400 MHz; CDCl\textsubscript{3}) 0.00 (9 H, s, \(3\times CH\textsubscript{3}\)), 5.35 (1 H, s, \(CH\text{CN}\)), 6.20 (1 H, dd, \(J\) 1.9 and 3.3, \(CH=CO\)), 6.35 (1 H, d, \(J\) 3.3, \(CHCO\)) and 7.25 (1 H, d, \(J\) 1.9, \(CHO\)); \(\delta_c\) (125 MHz; CDCl\textsubscript{3}) 57.0 (CHCN), 108.8 (CHCO), 109.7 (CH=CO), 116.9 (CN), 142.7 (CHO) and 147.4 (CO); MS (EI) \(m/z\) 68.0 [M-C\textsubscript{3}H\textsubscript{9}ONSi]\textsuperscript{+}, 106.0 [M-C\textsubscript{3}H\textsubscript{9}OSi]\textsuperscript{+}, 180.0 [M-N]\textsuperscript{+}; HRMS \(m/z\) 195.0715 (195.0716 calcd for C\textsubscript{9}H\textsubscript{13}O\textsubscript{2}NSi, \(M^+\)). The spectral data matches that reported in the literature.\[198\]
Silyl ether 476 (1.50 g, 7.68 mmol) was dissolved in 2 M ammonia in ethanol (4.6 cm³, 9.22 mmol) at room temperature and the reaction mixture was stirred at 40 °C for 2 h. The reaction was quenched with CHCl₃ (75 cm³) and water (75 cm³). The phases were separated and the organic layer was acidified with 1 M hydrochloric acid (50 cm³). To the acid layer 2 M sodium hydroxide (200 cm³) was added, followed by extraction with chloroform (3×75 cm³). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give amine 475 (0.58 g, 61%) as a thick brown oil, with no need for further purification; Rₚ 0.12 (solvent B); δ_H(400 MHz; CDCl₃) 1.95 (2 H, br s, NH₂), 4.90 (1 H, s, CHCN), 6.30 (1 H, d, J 1.9 and 3.3, CH=CO), 6.40 (1 H, d, J 3.3, CHCO) and 7.40 (1 H, d, J 1.9, CHO).

N-(Cyano-furan-2-yl-methyl)-4-methyl-benzenesulfonamide 485

A solution of amine 475 (50 mg, 0.387 mmol) in anhydrous CH₂Cl₂ (7 cm³) at 0 °C, was treated with triethylamine (0.08 cm³, 0.580 mmol), dimethylaminopyridine (14 mg, 0.116 mmol) and p-toluenesulfonyl chloride (111 mg, 0.580 mmol) successively. The reaction mixture was warmed to room temperature and stirred for 18 h, after which further portions of dimethylaminopyridine were added (0.116 mmol then 0.058 mmol) due to the slow progress of the reaction. The reaction was diluted with diethyl ether (10 cm³) and the organic layer was washed sequentially with water (10 cm³), saturated aqueous sodium hydrogen carbonate (10 cm³) and dried over anhydrous sodium sulfate. The solution was filtered and concentrated in vacuo to give a crude residue which was purified by FCC [petroleum ether-ethyl acetate, (80:20)] to give tosylamine compound 485 (14 mg, 12%) together with a non-separable impurity. NMR spectrum shows required product plus impurity; Rₚ 0.44 (solvent C); δ_H(400 MHz; CDCl₃) 1.60 (1 H, br s, NH), 2.44 (3 H, s, CH₃), 5.23 (1 H, s, CHCN), 6.52 (1 H, dd, J 1.8 and 3.4, CH=CO), 6.82 (1 H, dd, J 0.7 and 3.4, CHCO), 7.32 (2 H, d, J 8.4, 2×CH), 7.53 (1 H, dd, J 0.7 and 1.8, CHO) and
7.81 (2 H, d, J 8.4, 2×CH). The spectral data matches that reported in the literature.\textsuperscript{[218]}

**Benzylamino-furan-2-yl-acetonitrile 486**

\[
\text{NH}_{\text{Bn}} \quad \text{CN}
\]

A solution of amine 475 (165 mg, 1.35 mmol) in anhydrous dichloromethane (7 cm\(^3\)) was cooled to 0 °C and treated with triethylamine (0.41 cm\(^3\), 2.97 mmol) and dimethylaminopyridine (99 mg, 0.811 mmol). The reaction was stirred at 0 °C for 10 min before the addition of benzyl bromide (0.18 cm\(^3\), 1.49 mmol). The solution was kept at 0 °C for 20 min and then was allowed to warm up to room temperature. The reaction was stirred for 16 h and then was diluted with dichloromethane (20 cm\(^3\)). The layers were separated and the organic layer was washed sequentially with water (2×20 cm\(^3\)), saturated aqueous sodium hydrogen carbonate (2×20 cm\(^3\)), dried over anhydrous sodium sulfate and concentrated in vacuo. Purification of the crude residue by FCC [petroleum ether-ethyl acetate, (90:10)→(85:15)] gave the benzyl protected amine 486 (76 mg, 27%); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2245 (C≡N), 1608 (C=C) and 1595; \(\delta_r\) (400 MHz; CDCl\(_3\)) 3.50 (2 H, s, CH\(_2\)), 5.02 (1 H, s, CH), 6.18 (1 H, dd, J 1.6 and 3.2, CH=CO), 6.30 (1 H, dd, J 0.7 and 3.2, CHCO), 7.17-7.35 (5 H, m, ArCH) and 7.60 (1 H, dd, J 0.7 and 1.6, CHO); \(\delta_c\) (100 MHz; CDCl\(_3\)) 45.0 (CH\(_2\)), 49.8 (CH), 106.4 (ArCH), 111.1 (ArCH), 118.2 (C≡N), 127.1 (PhpCH), 127.5 (2×PhCH), 128.2 (2×PhCH), 141.9 (CH\(_2\)C), 139.0 (ArCH) and 152.2 (OC); MS (EI) \(m/z\) 213 [M+H]\(^+\); HRMS \(m/z\) 213.1031 (213.1028 calcd for C\(_{13}\)H\(_{13}\)N\(_2\)O, M+H\(^+\)).

**1-Furan-2-yl-but-3-enylamine 490\textsuperscript{[202]}**

\[
\text{NH}_{\text{H}_2}
\]

A mixture of allylboronate pinacol ester (1.17 cm\(^3\), 6.24 mmol) and dodecylbenzenesulfonic acid (0.17 cm\(^3\), 0.520 mmol) in 25 wt% aqueous ammonia (10.4 cm\(^3\)) was stirred at room temperature for 30 min. To this suspension was added 2-furaldehyde (0.43 cm\(^3\), 5.20 mmol) and the reaction mixture was stirred vigorously at room temperature for 2 h. The reaction mixture was acidified to pH 1-2 with 3 N hydrochloric acid and extracted with dichloromethane (3×50 cm\(^3\)). The combined organic phases were dried over
anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford the crude alcohol 491 (14.4 mg, 2%); *Rt* 0.59 (solvent B). The aqueous layer was basified to pH 12-13 with 6 N sodium hydroxide and extracted with dichloromethane (3×50 cm³). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield amine 490 (392 mg, 55%) as an orange oil, with no need for further purification; *Rf* 0.21 (solvent B); \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} 2917, 1640 (\text{C=C}), 1438 \) and 1148; \( \delta_{\text{H}}(400 \text{ MHz; CDCl}_3) 1.80 (2 \text{ H, br s, NH}_2), 2.20-2.30 (1 \text{ H, m, CH}_2), 2.40-2.50 (1 \text{ H, m, CH}_2), 3.85 (1 \text{ H, dd, J 5.9 and 7.2, CHN}), 4.90-5.05 (2 \text{ H, m, CH=CH}_2), 5.55-5.70 (1 \text{ H, m, CH=CH}_2), 6.0 (1 \text{ H, dd, J 0.9 and 3.2, CH=CO}), 6.15 (1 \text{ H, d, J 3.2, CHCO}) \) and 7.20 (1 \text{ H, d, J 0.9, CHO}); \( \delta_{\text{C}}(100 \text{ MHz; CDCl}_3) 40.9 (\text{CH}_3), 49.2 (\text{CNH}_2), 104.4 (\text{CH=CO}), 110.0 (\text{CHCO}), 118.0 (\text{HC=CH}_2), 141.3 (\text{CCHN}) \) and 158.5 (CHO); MS (Cl) \( m/z 96.97 [\text{M-CH}_2\text{CH=CH}_2]^+, 138.11 [\text{M+H}]^+ \); HRMS \( m/z 138.0917 \) (138.0920 calcd for \( \text{C}_8\text{H}_{12}\text{NO, M+H}^+ \)).

\[
\begin{align*}
\text{N-(1-Furan-2-yl-but-3-enyl)-4-methyl-benzenesulfonamide 492}^{[219]} \\
\end{align*}
\]

To a solution of allylic amine 490 (100 mg, 0.729 mmol) in anhydrous dichloromethane (7 cm³) at 0 °C was added triethylamine (0.22 cm³, 1.60 mmol), dimethylaminopyridine (53 mg, 0.437 mmol) and tosyl chloride (210 mg, 1.09 mmol). The reaction mixture was stirred at 0 °C for 30 min, then allowed to warm to room temperature and was then stirred for a further 18 h. The reaction was diluted with diethyl ether (20 cm³) and the layers were separated. The organic phase was washed with water (2×20 cm³) followed by saturated aqueous sodium hydrogen carbonate (2×20 cm³). The solution was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford tosylamine 492 (212 mg, 100%) as a brown crystalline solid with no need for further purification; *Rt* 0.64 (solvent C); mp 83-85 °C (from diethyl ether) (lit.,\^[219]\] 86.6-88.6 °C); \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} 3272, 1642 (\text{C=C}), 1430, 1328, 1158 \) and 1092; \( \delta_{\text{H}}(400 \text{ MHz; CDCl}_3) 2.22 (3 \text{ H, s, CH}_3), 2.28-2.43 (2 \text{ H, m, CH}_2), 4.50 (1 \text{ H, q, J 6.8, CHN}), 5.02-5.07 (2 \text{ H, m, CH=CH}_2), 5.53-5.58 (1 \text{ H, m, CH=CH}_2), 5.97 (1 \text{ H, d, J 3.2, CHCO}), 6.15 (1 \text{ H, dd, J 2.0 and 3.2, CH=CO}), 7.17 (1 \text{ H, dd, J 0.4 and 2.0, CHO}), 7.21 (2 \text{ H, d, J 8.4, 2×CH}) \) and 7.63 (2 \text{ H, d, J 8.4, 2×CH}); \( \delta_{\text{C}}(100 \text{ MHz; CDCl}_3) 21.5 (\text{CH}_3), 39.0 (\text{CH}_2), 50.9 (\text{CHN}), 107.1 (\text{CH=CO}), 110.0 (\text{CHCO}), 119.3 (\text{CH=CH}_2), 127.0 (\text{CH}),
129.4 (CH), 132.6 (CH=CH2), 137.5 (CCHN), 141.9 (CHO), 143.1 (C) and 152.8 (C); MS (FAB) m/z 292.2 [M+H]+; HRMS m/z 292.1004 (292.1007 calcd for C15H18NO3S, M+H+). Spectral data matches that reported in the literature.\textsuperscript{[219]}

2-Allyl-6-hydroxy-1-(toluene-4-sulfonyl)-1,6-dihydro-2H-pyridin-3-one \textsuperscript{493}

Homoallylic amine \textsuperscript{492} (100 mg, 0.343 mmol) was dissolved in dry dichloromethane (1.7 cm\textsuperscript{3}) and cooled to 0 °C before being treated with \textit{meta}-chloroperoxybenzoic acid (mCPBA) (84.4 mg, 0.489 mmol). The reaction was stirred at 0 °C for 30 min and then allowed to warm to room temperature where it was stirred for 18 h. The reaction was quenched by stirring with saturated aqueous sodium hydrogen carbonate (10 cm\textsuperscript{3}) for 1 h and was then diluted with dichloromethane (10 cm\textsuperscript{3}). The layers were separated and the organic phase was washed with saturated aqueous sodium hydrogen carbonate (2×10 cm\textsuperscript{3}), water (2×10 cm\textsuperscript{3}) and dried over anhydrous sodium sulfate. The solvent was evaporated \textit{in vacuo} and FCC of the crude residue [petroleum ether-ethyl acetate, (80:20)→(70:30)→(65:35)] afforded hemi-aminal \textsuperscript{493} (50.2 mg, 48%; 59% based on starting material consumed) as a yellow oil; R\textsubscript{f} 0.39 (solvent C); \nu_{\text{max}}(\text{film})/\text{cm}^{-1} 3460 (OH), 2926, 1687, 1332, 1161, 1033 and 729; \delta_{\text{H}}(400 MHz; CDCl\textsubscript{3}) 2.30 (3 H, s, CH\textsubscript{3}), 2.51-2.60 (1 H, m, CH\textsubscript{2}), 2.66-2.75 (1 H, m, CH\textsubscript{2}), 3.40 (1 H, d, J 4.5, OH), 4.35 (1 H, t, J 7.4, CH(N)), 5.00-5.10 (2 H, m, CH=CH\textsubscript{2}), 5.71-5.82 (1 H, m, CH=CH\textsubscript{2}), 5.77 (1 H, s, CH(OH)), 5.88 (1 H, dd, J 1.2 and 10.4, CH=CH), 6.70 (1 H, dd, J 4.4 and 10.4, CH=CH), 7.20 (2 H, d, J 6.6, 2×CH) and 7.50 (2 H, d, J 6.6, 2×CH); \delta_{\text{C}}(100 MHz; CDCl\textsubscript{3}) 21.5 (CH\textsubscript{3}), 40.0 (CH\textsubscript{2}), 61.0 (CH(N)), 73.4 (CH(OH)), 118.9 (CH=CH\textsubscript{2}), 126.7 (2×CH), 126.8 (CH=CH), 130.1 (2×CH), 133.2 (CH=CH\textsubscript{2}), 136.6 (C), 143.0 (CH=CH), 144.3 (C) and 193.6 (C=O); MS (CI) m/z 290.3 [M-OH]+, 308.3 [M+H]+; HRMS m/z 308.0959 (308.0956 calcd for C\textsubscript{15}H\textsubscript{18}NO\textsubscript{3}S, M+H+).
Benzyl-(1-furan-2-yl-but-3-enyl)-amine 494

A mixture of homoallylic amine 490 (100 mg, 0.728 mmol), dimethylaminopyridine (53.4 mg, 0.437 mmol) and triethylamine (0.32 cm$^3$, 2.33 mmol) in anhydrous dichloromethane (7 cm$^3$) was stirred at 0 °C for 30 min before being treated with benzyl bromide (0.13 cm$^3$, 1.12 mmol). The reaction mixture was then allowed to warm to room temperature and was stirred for a further 18 h. The reaction was quenched with water (10 cm$^3$). The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (90:10)→(85:15)] of the crude residue afforded benzyl amine 494 (71 mg, 43%); $R_f$ 0.57 (solvent B); $\nu_{\text{max}}$(film)/cm$^{-1}$ 908 and 734; $\delta_H$(400 MHz; CDCl$_3$) 1.65 (1 H, br s, NH), 2.42-2.50 (2 H, m, CH$_2$), 3.52 (2 H, d, J 13.2, CH$_2$Ph), 3.66-3.69 (1 H, m, CHN), 4.92-5.04 (2 H, m, CH=CH$_2$), 5.57-5.70 (1 H, m, CH=CH$_2$), 6.09 (1 H, d, J 3.1, CH=CO), 6.24 (1 H, dd, J 1.8 and 3.1, CHCO), 7.11-7.25 (5 H, m, Ph) and 7.31 (1 H, dd, J 0.5 and 1.8, CHO); MS (Cl) $m/z$ 228.20 [M+H]$^+$; HRMS $m/z$ 228.1394 (228.1389 calcd for C$_{15}$H$_{18}$NO, M+H$^+$). Spectral data matches that reported in the literature.[220]

The di-protected compound 495 was also isolated (16 mg, 10%); $R_f$ 0.83 (solvent B); $\delta_H$(400 MHz; CDCl$_3$) 2.47-2.52 (1 H, m, CH$_2$), 2.50-2.55 (1 H, m, CH$_2$), 3.01 (2 H, d, J 13.9, CH$_2$Ph), 3.55-3.59 (3 H, m, CHN and CH$_2$Ph), 4.88-4.97 (2 H, m, CH=CH$_2$), 5.60-5.73 (1 H, m, CH=CH$_2$), 6.07 (1 H, d, J 3.1, CH=CO), 6.30 (1 H, dd, J 1.9 and 3.1, CHCO), 7.40 (1 H, d, J 1.9, CHO) and 7.01-7.35 (10 H, m, 2×Ph).

6-Allyl-1-benzyl-1,6-dihydropyridine-2,5-dione 496

$meta$-Chloroperoxybenzoic acid (mCPBA) (76 mg, 0.338 mmol) was added to a 0 °C solution of amine 494 (70 mg, 0.307 mmol) in anhydrous dichloromethane (1.5 cm$^3$). The reaction was stirred at 0 °C for 30 min before allowing it to warm
up to room temperature and stirring overnight. The reaction was then diluted with dichloromethane (5 cm$^3$) and quenched with saturated aqueous sodium hydrogen carbonate (5 cm$^3$). The organic layer was separated and was washed sequentially with saturated aqueous sodium hydrogen carbonate (2×10 cm$^3$) and water (10 cm$^3$). The solution was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (90:10)→(85:15)→(80:20)→(70:30)] of the crude residue afforded benzyl protected dione 496 (19.4 mg, 26%); $R_f$ 0.34 (solvent B); $\nu_{\max}(\text{film})$/cm$^{-1}$ 2924, 1643, 1456, 1296, 1139, 1010 and 733; $\delta_H$ (400 MHz; CDCl$_3$) 2.82-2.89 (1 H, m, CH$_2$), 3.20-3.29 (1 H, m, CH$_2$), 5.04 (1 H, t, J 7.5, CH(N)), 5.11 (1 H, br d, J 10.3, CH=CH$_2$), 5.25 (1 H, dd, J 1.4 and 17.1, CH=CH$_2$), 5.79 (1 H, ddt, J 10.3 and 17.1, CH=CH$_2$), 6.40 (1 H, dd, J 1.8 and 3.2, CH=CHCO), 6.56 (1 H, d, J 3.2, CH=CH(CO)), 7.38-7.45 (5 H, m, Ph) and 8.21-8.23 (2 H, m, CH$_2$Ph); $\delta_C$(100 MHz; CDCl$_3$) 29.7 (CH$_2$CH=CH$_2$), 35.1 (CH$_2$Ph), 73.3 (HCN), 119.0 (CH=CH$_2$), 128.5 (2× CH(Ph)), 128.8 (2× CH(Ph)), 130.3 (C(Ph)), 130.5 (CH(Ph)), 132.7 (CH=CH), 133.7 (CH=CH$_2$), 143.1 (CH=CH), 149.8 (O=C-N) and 191.0 (C=O); MS (Cl) m/z 242 [M+H]$^+$; HRMS m/z 242.1179 (242.1181 calcd for C$_{15}$H$_{16}$NO$_2$, M+H$^+$).

$N$-[1-(5-But-3-enyl-furan-2-yl)-but-3-enyl]-4-methyl-benzensulfonamide 497, ($n$=2)

Procedure A

A solution of tosyl amine 492 (126 mg, 0.432 mmol) in anhydrous tetrahydrofuran (2.2 cm$^3$) was cooled to −20 °C and nBuLi (0.18 cm$^3$, 0.454 mmol) was slowly added. The solution was stirred for 30 min at −20 °C before being cooled to −78 °C. The reaction was stirred for 45 min before being treated with tBuLi (1.7 M in pentane, 0.28 cm$^3$, 0.475 mmol) and the resulting reaction was stirred at −78 °C for 1 h. The reaction was warmed up to −20 °C and was then treated with 4-bromo-1-butene (0.06 cm$^3$, 0.562 mmol). After 1 h at −20 °C, the reaction mixture was warmed to 0 °C and then room temperature where it was left to stir for 48 h. The reaction was quenched by pouring onto ice (20 cm$^3$) and diluting with diethyl ether (10 cm$^3$). The phases were separated and the organic layer was washed with water (2×10 cm$^3$), saturated
aqueous sodium chloride (2×10 cm³) and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo and the crude residue was purified by FCC [petroleum ether-ethyl acetate (90:10→85:15→80:20)] to yield diene 497, \( n=2 \) (20.6 mg, 17%) as a yellow oil; \( R_f \) 0.60 (solvent A); \( \nu_{\text{max}} \) (film)/cm⁻¹ 2935, 1350, 1171 and 1020; \( \delta_{\text{H}} \) (400 MHz; CDCl₃) 1.82-1.95 (1 H, m, CH₂CH₂), 2.10-2.20 (1 H, m, CH₂CH₂), 2.35 (3 H, s, CH₃), 2.48-2.52 (1 H, m, CH₂CH=CH₂), 2.64-2.70 (1 H, m, CH₂CH=CH₂), 2.96-3.04 (2 H, m, CH₂CH₂), 4.72-5.07 (5 H, m, 2×CH=CH₂ and CHN), 5.47-5.70 (2 H, m, 2×CH=CH₂), 6.01 (1 H, d, J 3.2, CH=CO), 6.20 (1 H, d, J 3.2, CHCO) and 7.20 (2 H, d, J 8.2, 2×CH) and 7.65 (2 H, d, J 8.2, 2×CH); \( \delta_{\text{C}} \) (100 MHz; CDCl₃) 22.7 (CH₃), 27.7 (H₂C=CHCH₂CH₂), 29.1 (H₂C=CHCH₂), 41.4 (CH₂CH=CH₂), 55.1 (HCNH), 108.9 (2×CH), 117.8 (2×H₂C=CH), 127.4 (2×PhCH), 129.4 (2×PhCH), 134.2 (CH=CH₂), 136.7 (CCH₃), 138.5 (H₂C=CH), 140.5 (SO₂C), 147.8 (CCHNH) and 151.0 (H₂C=CH(CH₂)₂C); MS (Cl) m/z 346.2 [M+H]+; HRMS m/z 346.1480 (346.1477 calcd for C₁₉H₂₄NO₃S, M+H⁺).

Procedure B

A solution of homoallylic amine 492 (112 mg, 0.384 mmol) in anhydrous tetrahydrofuran (2.0 cm³) was cooled to —20 °C and nBuLi (0.16 cm³, 403 µmol) was slowly added. The solution was stirred for 30 min at —20 °C and then tBuLi (1.7 M in pentane, 0.25 cm³, 0.422 mmol) was added. The reaction was stirred at —20 °C for 1 h and then warmed to 0 °C before 4-bromo-1-butene (50 µL, 0.499 mmol) was added. After 1 h at 0 °C the reaction mixture was warmed to room temperature and stirred for 48 h. The reaction was quenched by pouring onto ice (20 cm³) and diluting with diethyl ether (10 cm³). The phases were separated and the organic layer was washed with water (2×10 cm³) and saturated aqueous sodium chloride (2×10 cm³). The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (90:10→85:15→80:20)] of the crude residue yielded 497, \( n=2 \) (11.3 mg, 9%) as a yellow oil; \( R_f \) 0.68 (solvent A). The spectroscopic data obtained matches that for Procedure A.
**N-[1-(5-Hex-5-enyl-furan-2-yl)-but-3-enyl]-4-methyl-benzenesulfonamide 497, n=4**

A solution of homoallylic amine 492 (106 mg, 0.363 mmol) in anhydrous THF (1.8 cm³) was treated with nBuLi (0.15 cm³, 0.363 mmol) at room temperature and the resulting solution was stirred for 24 h. 6-Bromo-1-hexene (0.049 cm³, 0.363 mmol) was then added and the reaction mixture was stirred for a further 24 h. The reaction was quenched by pouring onto ice (20 cm³) and diluting with diethyl ether (20 cm³). The phases were separated and the organic layer was washed with water (2 × 10 cm³) and saturated aqueous sodium chloride (2 × 10 cm³). The solution was dried over anhydrous sodium chloride, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate, (90:10) → (80:20)] of the crude residue gave diene 497, n=4 (25.5 mg, 19%; 48% based on starting material consumed); Rf 0.65 (solvent B); ν max (film)/cm⁻¹ 2937, 1346, 1173 and 1020; δH (400 MHz; CDCl₃) 1.00-1.50 (8 H, m, 4 × CH₂), 1.70-2.01 (2 H, m, CHNCH₂), 2.34 (3 H, s, CH₃), 4.05 (1 H, q, J 7.1, CHN), 4.58-5.0 (4 H, m, 2 × CH=CCH₂), 5.56-5.58 (2 H, m, 2 × CH=CH₂), 6.00 (1 H, d, J 3.2, CH=CO), 6.17 (1 H, dd, J 1.6 and 3.2, CHCO), 7.20 (2 H, d, J 8.2, 2 × CH) and 7.66 (2 H, d, J 8.2, 2 × CH); δC (100 MHz; CDCl₃) 22.6 (CH₃), 27.7 (H₂C=CHCH₂CH₂CH₂CH₂H₂), 27.9 (H₂C=CHCH₂CH₂CH₂CH₂H₂), 28.5 (H₂C=CHCH₂CH₂CH₂CH₂H₂), 29.1 (H₂C=CHCH₂CH₂CH₂CH₂H₂), 41.3 (CH₂CH=CH₂), 55.1 (HCNH), 108.9 (2 × CH), 117.6 (2 × H₂C=CH), 127.4 (2 × PhCH), 129.4 (2 × PhCH), 134.3 (CH=CH₂), 136.9 (CH₃), 138.4 (H₂C=CH), 140.5 (SO₂C), 147.8 (CCHNH) and 151.1 (H₂C=CH(CH₂)₂C); MS (Cl) m/z 374.1 [M+H⁺]; HRMS 374.1786 (374.1790 calcd for C₂₁H₂₈NO₃S, M+H⁺).

**tert-Butyl-(furan-2-ylmethoxy)-dimethyl-silane 504[207]**

To anhydrous dimethylformamide (10 cm³) was added furfuryl alcohol 505 (1.00 g, 10.1 mmol) at room temperature and the resulting solution was stirred for 10 min. Imidazole (2.08 g, 30.5 mmol) was then added and the mixture stirred until clear. tert-Butyldimethylsilyl chloride (2.30 g, 15.2 mmol) was added, with TLC analysis showing that the reaction was complete after 10 min. The mixture was diluted with diethyl ether (35 cm³) and quenched with water (50 cm³). The organic layer was washed with water (4 × 100 cm³), dried over anhydrous sodium...
sulphate, filtered and concentrated in vacuo, to afford silyl ether 504 (1.59 g, 74%) as a colourless oil with no further purification, although excess, inseparable Si signals are seen in the NMR spectrum which equate to 570 mg, 26% of the obtained total mass of 2.16 g; \( R_f \) 0.80 (solvent B); \( \delta_H (400 \text{ MHz;} \text{ CDCl}_3) 0.00 (6 \text{ H, s, Si(CH}_3)_2), 0.83 (9 \text{ H, s, SiC(CH}_3)_3), 4.56 (2 \text{ H, s, CH}_2), 6.14 (1 \text{ H, d, J 3.1 Hz, CH=CO}), 6.23 (1 \text{ H, dd, J 1.8 and 3.1, CHCO}) and 7.28 (1 \text{ H, d, J 1.8, CHO}). The spectral data matches that reported in the literature.\(^{[207]}\)

(5-Allyl-furan-2-ylmethoxy)-\textit{tert}-butyl-dimethyl-silane 506

A solution of crude silyl ether 504 (1.00 g, 4.70 mmol) in anhydrous tetrahydrofuran (23.5 cm\(^3\)) was stirred for 10 min before being cooled down to 0 °C and treated with \( n \text{BuLi} \) (2.25 cm\(^3\), 5.17 mmol). The resulting mixture was stirred at 0 °C for 15 min and then it was allowed to warm up to room temperature. The reaction was stirred at room temperature for 15 min and then cooled back down to 0 °C, where it was stirred for a further 15 min. Freshly distilled allyl bromide (0.49 cm\(^3\), 5.65 mmol) was then added and the reaction allowed to warm up to room temperature. After 18 h, the reaction mixture was diluted with diethyl ether (20 cm\(^3\)) and quenched with water (30 cm\(^3\)). The layers were separated and the organic phase was dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to afford diene 506 (1.07 g, 91%) with no need for further purification; \( R_f \) 0.66 (solvent F); \( \nu_{\text{max}} \text{(film)}/\text{cm}^{-1} 2929, 2858, 1255 \text{ and } 1078 \text{ (OqSi);} \delta_H (400 \text{ MHz;} \text{ CDCl}_3) 0.00 (6 \text{ H, s, Si(CH}_3)_2), 0.81 (9 \text{ H, s, SiC(CH}_3)_3), 3.30 (2 \text{ H, dd, J 1.0 and 6.6, CH}_2\text{CH=CH}_2), 4.51 (2 \text{ H, s, CH}_2), 5.02-5.08 (2 \text{ H, m, CH=CH}_2), 5.79-5.90 (2 \text{ H, m, CH=CH}_2 \text{ and CH=CO}) \text{ and } 6.07 (1 \text{ H, d, J 3.1, CHCO}); \delta_C (100 \text{ MHz;} \text{ CDCl}_3) -5.2 \text{ (Si(CH}_3)_2), 18.4 \text{ (SiC(CH}_3)_3), 25.8 \text{ (SiC(CH}_3)_3), 32.7 \text{ (CH}_2), 58.2 \text{ (CH}_2\text{OTBS)}, 106.1 \text{ (CH), 108.1 \text{ (CH), 116.8 \text{ (H}_2\text{C=CH)_2, 134.0 \text{ (H}_2\text{C=CH)}}, 152.0 \text{ (CO) and 154.0 \text{ (CCH}_2\text{OTBS); MS (El) } m/z 121 [\text{M-OTBS}^+]\text{;} \text{ HRMS } m/z 121.0656 (121.0653 \text{ calcd for C}_8\text{H}_9\text{O, M-OTBS}^{+})\text{.}

2-(5-Allyl)furyl methanol 509

A solution of TBS ether 506 (2.73 g, 9.73 mmol) in anhydrous tetrahydrofuran (45 cm\(^3\)) and pyridine (20 cm\(^3\)) was treated with hydrogen fluoride in pyridine
(10 cm$^3$) and the reaction stirred for 2 h at room temperature. The reaction was quenched by the careful addition of saturated aqueous sodium hydrogen carbonate (350 cm$^3$) with vigorous stirring. The mixture was stirred until the fizzing had subsided. After a further precautionary 30 min stirring, the reaction mixture was extracted with dichloromethane (2×70 cm$^3$) and the combined organic layers washed with water (100 cm$^3$), dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. Pyridine was azeotroped from the crude residue with toluene (3×10 cm$^3$). Purification by FCC of the crude residue [petroleum ether-ethyl acetate (85:15)] afforded alcohol 509 (0.812 g, 61%) as a yellow oil; $R_f$ 0.13 (solvent A), $\delta_H$(400 MHz; CDCl$_3$) 2.00 (1 H, br s, OH), 3.42 (2 H, dd, $J$ 0.7 and 6.6, CH$_2$CH=CH$_2$), 4.58 (2 H, s, CH$_2$), 5.12-5.22 (2 H, m, CH=CH$_2$), 5.89-6.03 (2 H, m, CH=CH$_2$ and CH=CO) and 6.20 (1 H, d, $J$ 3.1, CHCO); MS(EI) $m/z$ 138.1 [M]$^+$, 121.1 [M-OH]$^+$, 107.1 [M-CH$_2$OH]$^+$; HRMS $m/z$ 138.0685 (138.0681 calcd for C$_8$H$_{10}$O$_2$). The spectral data matches that reported in the literature.$^{[207]}$

**5-Allyl-furan-2-carbaldehyde 512$^{[221]}$**

![5-Allyl-furan-2-carbaldehyde](image)

To a $-78 \degree$C solution of oxalyl chloride (0.17 cm$^3$, 2.00 mmol) in dry dichloromethane (10 cm$^3$) was added a solution of dimethylsulfoxide (0.28 cm$^3$, 4.00 mmol) in dichloromethane (1 cm$^3$). After 20 min at $-78 \degree$C, a solution of alcohol 509 (184.4 mg, 1.33 mmol) in dichloromethane (6.7 cm$^3$) was added and the reaction was stirred at $-78 \degree$C for a further 1 h, whereafter triethylamine (0.93 cm$^3$, 6.67 mmol) was added. The reaction was warmed up to 0 $\degree$C and stirred for 30 min. The reaction was then diluted with dichloromethane (10 cm$^3$) and treated with 1 M hydrochloric acid (10 cm$^3$). The layers were separated and the organic layer was washed sequentially with saturated aqueous sodium chloride (20 cm$^3$) and saturated aqueous sodium hydrogen carbonate (20 cm$^3$). The solution was dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to afford aldehyde 512 (158.3 mg, 87%) as a brown oil with no further purification carried out; $R_f$ 0.69 (solvent C); $\delta_H$(400 MHz; CDCl$_3$) 3.32 (2 H, d, $J$ 7.2, CH$_2$), 5.09-5.12 (2 H, m, CH$_2$=CH), 5.82-5.90 (1 H, m, CH$_2$=CH), 5.92 (1 H, d, $J$ 3.3, CH=CO), 6.21 (1 H, d, $J$ 3.3, CHCO) and 9.49 (1 H, s, CHO). The spectral data matches that reported in the literature.$^{[221]}$
1-(5-Allyl-furan-2-yl)-but-3-enylamine 513

A mixture of allylboronic acid pinacol ester (0.14 cm$^3$, 0.759 mmol) and dodecylbenzenesulfonic acid (20 µL, 63.2 µmol) in 25 wt% ammonia (1.3 cm$^3$) was stirred at room temperature for 30 min before aldehyde 512 (86.2 mg, 0.632 mmol) was added. After stirring for 2 h, the reaction mixture was acidified to pH 1-2 with 3 N hydrochloric acid and extracted with dichloromethane (3×20 cm$^3$). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to afford the crude alcohol; $R_f$ 0.84 (solvent B). The aqueous layer was basified to pH 12-13 with 6 N sodium hydroxide and extracted with dichloromethane (3×20 cm$^3$). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to afford homoallylic amine 513 (86.1 mg, 76%) as a pale yellow oil with no further purification required; $R_f$ 0.09 (solvent B); $\nu_{max}$(film)/cm$^{-1}$ 2999, 2931 and 1029; $\delta_H$(400 MHz; CDCl$_3$) 1.90 (2 H, br s, $NH_2$), 2.29-2.35 (1 H, m, CH(NH$_2$)C$H_2$), 2.48-2.52 (1 H, m, CH(NH$_2$)C$H_2$), 3.28 (2 H, d, $J$ 6.5, C$H_2$), 3.88 (1 H, dd, $J$ 5.6 and 7.6, CH$_2$N), 5.00-5.11 (4 H, m, 2×CH=C$H_2$), 5.65-5.72 (1 H, m, CH(NH$_2$)CH$C=CH_2$), 5.81-5.91 (1 H, m, $CH=CH_2$), 5.85 (1 H, d, $J$ 3.0, $CH=CO$) and 5.96 (1 H, d, $J$ 3.0, CHCO); $\delta_C$(100 MHz; CDCl$_3$) 29.1 (H$_2$C=CHCH$_2$), 41.0 (CH$_2$), 49.3 (CHNH$_2$), 104.4 (CH=CO), 110.0 (CHCO), 118.0 (2×HC=CH$_2$), 134.6 (2×HC=CH$_2$), 141.5 (CCHN) and 158.5 (CHO); MS (Cl) $m/z$ 178 [M+H]$^+$; HRMS $m/z$ 178.1235 (178.1232 calcd for C$_{11}$H$_{16}$NO, M+H$^+$).

N-[1-(5-Allyl-furan-2-yl)-but-3-enyl]-4-methyl-benzenesulfonamide 514

A solution of homoallylic amine 513 (26.5 mg, 0.149 mmol) in dry dichloromethane (1 cm$^3$) was stirred at 0 °C for 30 min before triethylamine (0.05 cm$^3$, 0.328 mmol), dimethylaminopyridine (11 mg, 0.0897 mmol) and p-toluenesulfonyl chloride (43 mg, 0.224 mmol) were sequentially added. After 30 min at 0 °C, the reaction was allowed to warm up to room temperature and stirred overnight. The reaction mixture was diluted with diethyl ether (5 cm$^3$) and H$_2$O (10 cm$^3$) and the layers separated. The organic layer was washed with water (2×10 cm$^3$), saturated aqueous sodium hydrogen carbonate (2×10 cm$^3$)
and dried over anhydrous sodium sulphate. The solution was concentrated in vacuo to afford crude tosylate 514 (17.4 mg, 35%) with no further purification carried out; \( R_f \) 0.78 (solvent C); \( \nu_{\text{max}} \)(film)/cm\(^{-1} \) 2926, 1371, 1172 and 1010; \( \delta_\text{H} \)(400 MHz; CDCl\(_3\)) 2.35 (3 H, s, CH\(_3\)), 2.50-2.60 (1 H, m, CH(NHTs)CH\(_2\)), 2.63-2.72 (1 H, m, CH(NHTs)CH\(_2\)), 3.50 (1 H, dd, J 7.1 and 16.4, H\(_2\)C=CHCH\(_2\)), 3.71 (1 H, dd, J 5.4 and 16.4, H\(_2\)C=CHCH\(_2\)), 4.88-5.09 (5 H, m, CH=C\(_2\)H, CH\(_2\)=CH, HCNHTs)), 5.47-5.57 (1 H, m, CH\(_2\)=CHCH\(_2\)), 5.60-5.72 (1 H, m, (NHTs)CH\(_2\)CH=CH\(_2\)), 6.02 (1 H, dd, J 0.6 and 3.2, CH=CO), 6.17 (1 H, dd, J 1.8 and 3.2, CHCO), 7.18 (2 H, d, J 8.3, 2\( \times \)CH) and 7.64 (2 H, d, J 8.3, 2\( \times \)CH); \( \delta_\text{C} \)(100 MHz; CDCl\(_3\)) 21.4 (CH\(_3\)), 29.5 (H\(_2\)C=CHC\(_2\)H), 39.0 (CH\(_2\)), 51.0 (CHN), 107.3 (CH=CO), 110.0 (CHCO), 119.3 (CH=CH\(_2\)), 118.5 (H\(_2\)C=CH), 127.0 (CH), 129.4 (CH), 132.8 (CH=CH\(_2\)), 133.9 (H\(_2\)C=CH), 137.5 (CHCHN), 141.9 (CHO), 143.1 (C) and 152.8 (C) MS (CI) \([\text{m/z}]\) 332.2 [M+H]; HRMS \([\text{m/z}]\) 332.1323 (332.1321 calcd for C\(_{18}\)H\(_{22}\)O\(_3\)NS, M+H\(^+\)).

**tert-Butyl-dimethyl-(5-pent-4-enyl-furan-2-ylmethoxy)-silane 507**

A solution of furan 504 (322.2 mg, 1.52 mmol) in anhydrous tetrahydrofuran (8 cm\(^3\)) at 0 °C was treated with nBuLi (0.73 cm\(^3\), 1.67 mmol). After 15 min at 0 °C the reaction mixture was allowed to warm to room temperature where it was stirred for a further 15 min. The solution was recooled to 0 °C and 5-bromo-1-pentene (0.22 cm\(^3\), 1.82 mmol) was added. After 15 min at 0 °C, the reaction mixture was allowed to warm up to room temperature and stirred for 18 hours. The reaction was diluted with diethyl ether (10 cm\(^3\)) and partitioned with water (10 cm\(^3\)). The layers were separated and the organic layer was dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to afford alkene 507 (337 mg, 79%) as an oil; \( R_f \) 0.72 (solvent F); \( \nu_{\text{max}} \)(film)/cm\(^{-1} \) 2929, 2858, 1701, 1253 and 1078 (O-Si); \( \delta_\text{H} \)(400 MHz; CDCl\(_3\)) 0.02 (6 H, s, Si(CH\(_3\))\(_2\)), 0.83 (9 H, s, SiC(CH\(_3\))\(_3\)), 1.63-1.66 (2 H, m, CH\(_2\)CH\(_2\)CH\(_2\)), 2.05-2.10 (2 H, m, CH\(_2\)CH\(_2\)CH\(_2\)), 2.54-2.56 (2 H, m, CH\(_2\)CH\(_2\)CH\(_2\)), 4.51 (2 H, s, CH\(_2\)OTBS), 4.90-4.99 (2 H, m, CH\(_2\)=CH), 5.70-5.75 (1 H, m, CH\(_2\)=CH), 5.80 (1 H, d, J 3.0, CH=CO) and 6.02 (1 H, d, J 3.0, CHCO); \( \delta_\text{C} \)(100 MHz; CDCl\(_3\)) 5.9 (Si(CH\(_3\))\(_2\)), 17.9 (SiC(CH\(_3\))\(_3\)), 25.8 (SiC(CH\(_3\))\(_3\)), 27.1 (CH\(_2\)CH\(_2\)CH\(_2\)), 28.9 (CH\(_2\)CH\(_2\)CH\(_2\)), 37.2 (CH\(_2\)CH\(_2\)CH\(_2\)), 60.7 (CH\(_2\)OTBS), 106.6 (HC), 109.6 (HC), 115.0 (H\(_2\)C=CH), 137.6 (H\(_2\)C=CH), 152.2
(CCH₂OH) and 156.5 (C); MS (Cl) m/z 149.1 [M-OTBS]*; HRMS m/z 149.0965 (149.0966 calcd for C₁₀H₁₃O₂, M-OTBS*).

(5-Pent-4-enyl-furan-2-yl)-methanol 510

A 0 °C solution of silyl ether 507 (337 mg, 1.20 mmol) in tetrahydrofuran (10 cm³) was added tetra-butylammonium fluoride (2.4 cm³, 2.40 mmol) and the reaction was stirred at 0 °C for 15 min before allowing it to warm up to room temperature. After 1.5 h at room temperature the reaction mixture was diluted with diethyl ether (20 cm³) and quenched with water (20 cm³). The organic layer was separated, dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (80:20)→(75:25)] of the crude residue afforded alcohol 510 (60.4 mg, 30%) as a yellow oil; Rᶠ 0.09 (solvent F); νmax(film)/cm⁻¹ 3470 (OH), 2852, 1260; δH (400 MHz; CDCl₃) 1.71-1.80 (2 H, m, CH₂C₂H₂CH₂), 2.65 (2 H, t, J 7.6, CH₂CH₂H₂), 4.59 (2 H, d, J 5.8, CH₂OH), 5.00-5.07 (2 H, m, CH₂=C), 5.80-5.89 (1 H, m, CH₂=CH), 6.21 (1 H, d, J 3.0, CH=CO); δC (100 MHz; CDCl₃) 27.1 (CH₂CH₂CH₂), 27.5 (CH₂CH₂CH₂), 33.2 (CH₂CH₂CH₂), 57.7 (CH₂OH), 105.6 (HC), 108.6 (HCCCH₂OH), 115.0 (H₂C=CH), 138.2 (H₂C=CH), 152.2 (HCCCH₂OH) and 156.5 (HCC); MS (EI) m/z 82.96 [M-CH₂OH-CH₂=CHCH₂]+, 111.07 [M-CH₂OH-CH₂]+, 124.08 [M-CH₂OH-CH₂]+, 135.11 [M-CH₂OH]+; HRMS m/z 166.0996 (166.2170 calcd for C₁₀H₁₄O₂, M⁺).

tert-Butyl-(5-hex-5-enyl-furan-2-ylmethoxy)-dimethyl-silane 508

A 0 °C solution of silyl ether 504 (266.2 mg, 1.25 mmol) in anhydrous tetrahydrofuran (6.5 cm³) was treated with nBuLi (0.73 cm³, 1.67 mmol). After 15 min at 0 °C, the reaction mixture was allowed to warm up to room temperature and was stirred for a further 15 min, before being recooled back to 0 °C. 5-Bromo-1-hexene (0.2 cm³, 1.50 mmol) was then added and the reaction was stirred for 15 min. The reaction mixture was allowed to warm up to room temperature and stirred for 18 h. The reaction was diluted with diethyl ether (10 cm³) and quenched with water (10 cm³). The layers were separated and the organic layer was dried over anhydrous sodium sulphate, filtered and
concentrated in vacuo to afford alkene 508 (231 mg, 63%) as a colourless oil with no further purification required; $R_f$ 0.69 (solvent $F$); $\nu_{\text{max}}$(film)/cm$^{-1}$ 2934, 2860, 1699, 1258, 1159 and 1111; $\delta_H$(400 MHz; CDCl$_3$) 0.00 (6 H, s, (Si(CH$_3$)$_2$)$_2$), 0.83 (9 H, s, SiC(CH$_3$)$_3$), 1.33-1.62 (4 H, m, CH$_2$CH$_2$CH$_2$CH$_2$), 2.00 (2 H, qn, $J$ 6.7 and 13.8, CH$_2$=CHCH$_2$), 3.33 (2 H, t, $J$ 6.8, (CH$_2$)$_3$CH$_2$), 4.51 (2 H, s, CH$_2$OTBS), 4.85-4.94 (2 H, m, CH$_2$=CH), 5.67-5.75 (1 H, m, CH$_2$=CH), 5.82 (1 H, d, $J$ 2.9, CH=CO) and 6.02 (1 H, d, $J$ 2.9 Hz, CHCO); $\delta_C$(100 MHz, CDCl$_3$) q5.0 (Si(CH$_3$)$_2$), 15.5 (SiC(CH$_3$)$_3$), 25.9 (SiC(CH$_3$)$_3$), 25.9 (CH$_2$CH$_2$CH$_2$CH$_2$), 27.6 (CH$_2$CH$_2$CH$_2$CH$_2$), 32.4 (CH$_2$CH$_2$CH$_2$CH$_2$), 33.1 (CH$_2$CH$_2$CH$_2$CH$_2$), 68.2 (CH$_2$OTBS), 105.6 (HC), 108.2 (HCCCH$_2$OTBS), 115.3 (H$_2$C=CH), 138.3 (H$_2$C=CH), 152.7 (HCCCH$_2$OTBS) and 156.2 (HCC); MS (CI) $m/z$ 163 [M+OTBS$^+$]; HRMS $m/z$ 163.1120 (163.1123 calcd for C$_{11}$H$_{15}$O, M+OTBS$^+$).

(5-Hex-5-enyl-furan-2-yl)-methanol 511

A 0 °C solution of silyl ether 508 (231.8 mg, 0.787 mmol) in tetrahydrofuran (5 cm$^3$) was treated with tetra-$\text{butylammonium fluoride}$ (1.57 cm$^3$, 1.57 mmol) and the resulting reaction was stirred at 0 °C for 15 min, before being warmed up to room temperature. After 1.5 h at room temperature, the reaction mixture was diluted with diethyl ether (20 cm$^3$) and quenched with water (20 cm$^3$). The organic layer was separated, dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (80:20)$\rightarrow$(75:25)] of the crude residue afforded alcohol 511 (89.1 mg, 63%) as a yellow oil; $R_f$ 0.50 (solvent $C$); $\delta_H$(400 MHz; CDCl$_3$) 1.32-1.38 (2 H, m, CH$_2$=CH(CH$_2$)CH$_2$), 1.53-1.61 (2 H, m, CH$_2$=CHCH$_2$CH$_2$), 1.95-2.01 (2 H, m, CH$_2$=CHCH$_2$), 2.51 (2 H, t, $J$ 7.5, CH$_2$=CH(CH$_2$)CH$_2$), 4.45 (2 H, d, $J$ 5.9, CH$_2$OH), 4.82-4.90 (2 H, m, CH$_2$=CH), 5.66-5.73 (1 H, m, CH$_2$=CH), 5.82 (1 H, d, $J$ 3.1, CH=CO) and 6.08 (1 H, d, $J$ 3.1 Hz, CHCO); $\delta_C$(100 MHz, CDCl$_3$) 25.9 (CH$_2$CH$_2$CH$_2$CH$_2$), 26.2 (CH$_2$CH$_2$CH$_2$CH$_2$), 32.7 (CH$_2$CH$_2$CH$_2$CH$_2$), 33.2 (CH$_2$CH$_2$CH$_2$CH$_2$), 60.2 (CH$_2$OH), 105.6 (HC), 108.2 (HC), 115.3 (H$_2$C=CH), 138.3 (H$_2$C=CH), 152.2 (CCH$_2$OH) and 156.2 (C); MS (CI) $m/z$ 163.2 [M-OH$^+$]; HRMS $m/z$ 163.1126 (163.1123 calcd for C$_{11}$H$_{15}$O, M-OH$^+$).
1-(5-Methyl-furan-2-yl)-but-3-enylamine 540

A mixture of allylboronic acid pinacol ester (2.04 cm$^3$, 10.8 mmol) and dodecylbenzenesulfonic acid (0.3 cm$^3$, 0.90 mmol) in 25% aqueous ammonia (18 cm$^3$) was stirred for 30 min, before being treated with 5-methylfuraldehyde 539 (0.90 cm$^3$, 9.08 mmol) at room temperature. After 2 h, the reaction mixture was acidified to pH 1-2 with 3 N hydrochloric acid and extracted with dichloromethane (3×30 cm$^3$). The combined organic phases were dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to afford the crude alcohol; $R_f$ 0.68 (solvent A). The aqueous layer was basified to pH 12-13 with 6 N sodium hydroxide and extracted with dichloromethane (3×40 cm$^3$). The combined organic phases were dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to yield amine 540 (1.05 g, 77%) as yellow oil with no need for further purification; $R_f$ 0.16 (solvent A); $\delta_H$ (400 MHz; CDCl$_3$) 2.20 (3 H, s, CH$_3$), 2.33-2.40 (1 H, m, CH$_2$), 2.51-2.56 (1 H, m, CH$_2$), 3.90 (1 H, t, $J$ 6.1, CHN), 5.03-5.10 (2 H, m, CH=CH$_2$), 5.68-5.79 (1 H, m, CH=CH$_2$), 5.82 (1 H, d, $J$ 2.4, CH=CO) and 5.96 (1 H, d, $J$ 2.4, CHCO); $\delta_C$ (100 MHz; CDCl$_3$) 13.5 (CH$_3$), 40.9 (CH$_2$), 49.2 (CHN), 105.1 (CH), 105.8 (CH), 117.8 (CH=CH$_2$), 134.9 (CH=CH$_2$), 150.8 (CCHN) and 156.6 (CCH$_3$); MS (Cl) m/z 152.23 [M + H]$^+$; HRMS m/z 152.1074 (152.1075 calcd for C$_9$H$_{14}$NO, M+ H$^+$).

4-Methyl-N-[(1-(5-methyl-furan-2-yl)-but-3-enyl)]-benzenesulfonamide 541

A solution of homoallylic amine 540 (200 mg, 1.32 mmol) in dichloromethane (7 cm$^3$) was cooled to 0 °C and treated with dimethylaminopyridine (97 mg, 0.79 mmol) and triethylamine (0.41 cm$^3$, 2.90 mmol). After stirring for 10 min, p-toluenesulfonyl chloride (265 mg, 1.38 mmol) was added to the reaction mixture and the ice-water bath removed after a further 10 min. After 1 h, the reaction mixture was diluted with dichloromethane (10 cm$^3$) and quenched with water (10 cm$^3$). The phases were separated and the organic layer was washed with saturated aqueous sodium hydrogen carbonate (2×10 cm$^3$), dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. The crude residue was passed through a pad of silica gel (eluting with solvent C) to afford tosyl amine...
541 (376 mg, 93%) as a yellow oil; \( \nu_{\text{max}} \)(film)/cm\(^{-1} \) 3054, 2986, 1598, 1265 and 1160; \( \delta \)(400 MHz; CDCl\(_3 \)) 2.00 (3 H, s, CH\(_3 \)), 2.31 (3 H, s, CH\(_3\)(Ar)), 2.35-2.50 (2 H, m, CH\(_2 \)), 4.36 (1 H, q, \( J \) 6.9, CH\(_2\)NH), 5.00-5.02 (2 H, m, CH=CH\(_2 \)), 5.49-5.58 (1 H, m, CH=CH\(_2 \)), 7.12 (2 H, d, \( J \) 8.0, 2\( \times \)CH) and 7.57 (2 H, d, \( J \) 8.0, 2\( \times \)CH); \( \delta \)(C)(100 MHz; CDCl\(_3 \)) 13.3 (CH\(_3\)(Ar)), 21.5 (CH\(_3 \)), 39.1 (CH\(_2 \)), 51.2 (CHN), 105.8 (CH), 108.0 (CH), 119.1 (CH=CH\(_2 \)), 127.1 (2\( \times \)CH), 129.3 (2\( \times \)CH), 133.0 (CH=CH\(_2 \)), 137.7 (CH\(_3 \)), 143.0 (C), 150.6 (CCHN) and 151.6 (CH\(_3\)CO); MS (CI) \( m/z \) 306.3 [M+H]\(^+ \); HRMS \( m/z \) 306.1165 (306.1164 calcd for C\(_{16}\)H\(_{20}\)NO\(_3\)S, M+H\(^+ \)).

2-Allyl-6-hydroxy-6-methyl-1-(toluene-4-sulfonyl)-1,6-dihydro-2H-pyridin-3-one 542

\[ \text{HC-} \text{NTs}-\text{CH} \]

To a room temperature solution of tosyl amine 541 (103 mg, 0.337 mmol) in dichloromethane (1.7 cm\(^3 \)) was added \textit{meta}-chloroperoxybenzoic acid (mCPBA) (91 mg, 0.404 mmol). After stirring for 2 h, 10% aqueous sodium hydrogen carbonate (5 cm\(^3 \)) was added to the pale yellow solution and the resulting mixture was stirred for 40 min. The biphasic mixture was transferred to a separating funnel and dichloromethane (10 cm\(^3 \)) was added. The phases were separated and the organic layer was washed with saturated aqueous sodium hydrogen carbonate (4\( \times \)15 cm\(^3 \)), dried over anhydrous sodium sulphate, filtered and concentrated \textit{in vacuo} to afford hemi-aminal 542 (107 mg, 99%) as a pale yellow oil; \( R_f \) 0.10 (solvent A); \( \nu_{\text{max}} \)(film)/cm\(^{-1} \) 2254, 1701, 1265 and 1164; \( \delta \)(400 MHz; CDCl\(_3 \)) 2.12 (3 H, s, CH\(_3 \)), 2.43-2.50 (2 H, m, CH\(_2 \)), 2.45 (3 H, s, CH\(_3\)(Ar)), 4.02-4.05 (1 H, m, CH(N)), 4.89-4.99 (2 H, m, CH=CH\(_2 \)), 5.21 (1 H, d, \( J \) 7.6, CH=CH(C=O)), 5.41-5.51 (1 H, m, CH=CH\(_2 \)), 6.30 (1 H, app. s, CH=CH(C=O)) and 7.21 (2 H, d, \( J \) 8.0, 2\( \times \)CH) and 7.62 (2 H, d, \( J \) 8.0, 2\( \times \)CH); \( \delta \)(C)(100 MHz; CDCl\(_3 \)) 21.6 (CH\(_3\)(Ar)), 29.6 (CH\(_3 \)), 36.0 (CH\(_2 \)), 60.6 (CH(N)), 119.9 (CH=CH\(_2 \)), 127.2 (2\( \times \)CH), 129.8 (2\( \times \)CH), 131.5 (CH=CH\(_2 \)), 132.6 (CH=CH(CO)), 137.0 (C), 138.4 (C), 143.8 (CH=CH(CO)), 199.3 (C=O), plus one unresolved carbon; MS (Cl) \( m/z \) 322.2 [M+H]\(^+ \); HRMS \( m/z \) 322.1114 (322.1114 calcd for C\(_{16}\)H\(_{20}\)NO\(_3\)S, M+H\(^+ \)).
[1-(5-Methyl-furan-2-yl)-but-3-enyl]-carbamic acid tert-butyl ester 543

To a stirred, room temperature solution of homoallylic amine 540 (200 mg, 1.32 mmol) in water (1.5 cm$^3$) was added di-tert-butyl dicarbonate ((Boc)$_2$O) (317 mg, 1.45 mmol). The pale yellow solution was stirred at 30 min after which water (5 cm$^3$) was added and the mixture extracted with ethyl acetate (2×10 cm$^3$). The combined organic phases were dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to afford Boc amine 543 (269 mg, 81%) as a colourless oil with further purification needed; $R_f$ 0.67 (solvent A); $\nu_{\max}$ (film)/cm$^{-1}$ 1709, 1498, 1265 and 1168; $\delta_H$(400 MHz; CDCl$_3$) 1.45 (9 H, s, 3×CH$_3$), 2.27 (3 H, s, CH$_3$), 2.53-2.57 (2 H, m, CH$_2$), 4.80-4.83 (1 H, m, CHN), 5.05-5.12 (2 H, m, CH=CH$_2$), 5.65-5.73 (1 H, m, CH=CH$_2$), 5.88 (1 H, dd, J 1.0 and 3.0, CH=CO) and 6.03 (1 H, d, J 3.0, CHCO); $\delta_C$(100 MHz; CDCl$_3$) 28.4 (3×CH$_3$), 38.7 (CH$_2$), 48.3 (CHN), 85.2 (C(CH$_3$)$_3$), 105.9 (CH), 106.6 (CH), 118.1 (CH=CH$_2$), 133.9 (CH=CH$_2$), 146.7 (CHCN), 151.3 (CH$_3$C) and 155.2 (C=O); MS (Cl) $m/z$ 252.2 [M+H]$^+$; HRMS $m/z$ 252.1602 (252.1599 calcd for C$_{14}$H$_{22}$NO$_3$, M+H$^+$).

2-Allyl-6-hydroxy-6-methyl-3-oxo-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester 544

To a solution of Boc amine 543 (102 mg, 0.405 mmol) in dichloromethane (2 cm$^3$) at room temperature, was added meta-chloroperoxybenzoic acid (mCPBA) (109 mg, 0.486 mmol) at room temperature. After stirring for 1 h, 10% aqueous sodium hydrogen carbonate (5 cm$^3$) was added and the pale yellow biphasic solution was stirred for 1 h before being transferred to a separating funnel. Dichloromethane (10 cm$^3$) was added and the organic layer separated. The organic layer was washed with saturated aqueous sodium hydrogen carbonate (4×15 cm$^3$), dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to afford Boc aminal 544 (94.6 mg, 88%) as a white oil; $R_f$ 0.18 (solvent A); $\nu_{\max}$(film)/cm$^{-1}$ 3431 (OH), 2983, 2254, 1702 (C=O), 1165 and 907; $\delta_H$(400 MHz; CDCl$_3$) 1.44 (9 H, s, 3×CH$_3$), 2.21 (3 H, s, CH$_3$), 2.37-2.42 (1 H, m, CH$_2$), 2.58-2.64 (1 H, m, CH$_2$), 4.37-4.41 (1 H, m, NCH), 5.02-5.09 (2 H, m, CH=CH$_2$), 5.60-5.71 (1 H, m, CH=CH$_2$), 6.32 (2 H, m, CH=CH); $\delta_C$(100 MHz; CDCl$_3$) 28.2 (3×CH$_3$),
29.7 (CH₃), 35.5 (CH₂), 58.5 (NCH), 80.0 (COH), 85.2 (C(CH₃)₃), 119.6 (CH=CH₂), 130.1 (CH=CH(C=O)), 133.2 (CH=CH₂), 146.7 (CH=CH(C=O)), 155.5 (N(C=O)OᵗBu) and 200.6 (C=O); MS (CI) m/z 268.3 [M+H]+; HRMS m/z 268.1548 (268.1549 calcd for C₁₄H₂₂NO₄, M+H⁺).

**N-Furan-2-ylmethyl-4-methyl-benzenesulfonamide 525**[[222,223]]

To a stirred solution of furfurylamine (500 mg, 5.14 mmol) in dichloromethane (25 cm³) at 0 °C, was added triethylamine (1.6 cm³, 11.3 mmol) and dimethylaminopyridine (377 mg, 3.08 mmol). After 10 min, p-toluenesulfonyl chloride (1.03 g, 5.40 mmol) was added, following which, an immediate colour change from colourless to yellow was observed. The ice-water bath was then removed after 10 min and the reaction mixture was allowed to warm up to room temperature. After 1 h, the reaction was diluted with dichloromethane (20 cm³), washed with water (2×20 cm³) followed by saturated aqueous sodium hydrogen carbonate (2×20 cm³). The solution was then dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to afford tosyl amine 525 (1.29 g, 100%) as a yellow solid; R_f 0.35; mp 110-112 °C (from dichloromethane) (lit.,¹² 111-112 °C); δ_H(400 MHz; CDCl₃) 2.35 (3 H, s, CH₃), 4.09 (2 H, s, CH₂), 6.02 (1 H, dd, J 0.8 and 3.3, CH=CO), 6.15 (1 H, dd, J 1.9 and 3.3, CHCO), 7.18 (1 H, dd, J 0.8 and 1.9, CHO), 7.20 (2 H, d, J 8.3, 2×CH) and 7.65 (2 H, d, J 8.3, 2×CH). The spectral data matches that reported in the literature.[222,223]

**N-((5-allylfuran-2-yl)methyl)-4-methylbenzenesulfonamide 524**

A solution of tosyl amine 525 (259 mg, 1.02 mmol) in tetrahydrofuran (5 cm³) was stirred for 10 min and then cooled to 0 °C before being treated with nBuLi (0.49 cm³, 1.13 mmol). The resulting light brown solution was stirred at 0 °C for 15 min before being allowed to warm up to room temperature and stirred for 15 min. The solution was recooled down to 0 °C and allyl bromide (0.11 cm³, 1.23 mmol) was added. The reaction was stirred for 10 min and the ice-water bath was removed to allow the reaction mixture to warm up to room temperature. After 20 h, the reaction mixture was diluted with diethyl ether (10 cm³) and quenched with water (10 cm³). The organic layer was separated, dried over
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anhydrous sodium sulphate, filtered and concentrated in vacuo to afford alkene 524 (264 mg, 88%) as a dark brown thick oil; Rf 0.52 (solvent A); v_max(film)/cm\(^{-1}\) 2253, 1159, 1093 and 908; \(\delta_H\) (400 MHz; CDCl\(_3\)) 2.28 (3 H, s, CH\(_3\)), 3.62 (2 H, d, J 6.4, CH\(_2\)(CH=CH\(_2\)), 4.25 (2 H, s, CH\(_2\)), 4.98-5.03 (2 H, m, CH=CH\(_2\)), 5.45-5.57 (1 H, m, CH=CH\(_2\)), 6.00 (1 H, dd, J 0.6 and 3.2, CH=CO), 6.12 (1 H, dd, J 1.8 and 3.2, CHCO), 7.11 (2 H, d, J 8.2, 2×CH) and 7.53 (2 H, d, 2×CH); \(\delta_C\) (100 MHz; CDCl\(_3\)) 21.5 (CH\(_3\)), 42.7 (CH\(_2\)=CHC\(_H_2\)), 49.6 (CH\(_2\)N), 109.5 (CH), 110.3 (CH), 119.2 (CH\(_2\)=CH), 127.3 (2×CH), 129.5 (2×CH), 132.5 (CH\(_2\)=CH), 137.6 (CCH\(_3\)), 142.4 (CS), 143.1 (CH\(_2\)=CHCH\(_2\)) and 149.7 (CCH\(_2\)); MS (CI) m/z 292.2 [M+H]+; HRMS m/z 292.1006 (292.1007 calcd for C\(_{15}\)H\(_{18}\)NO\(_3\)S, M+H+).

4-Methyl-N-((5-propylfuran-2-yl)methyl)benzenesulfonamide 528

A solution of alkene 524 (174 mg, 0.598 mmol) in methanol (3 cm\(^3\)) was treated with a catalytic amount of 10% palladium on activated carbon. The flask was evacuated and after purging three times with hydrogen gas via a balloon, the mixture was stirred under an atmosphere of hydrogen for 45 min at room temperature. TLC analysis deemed the reaction complete and the solution was filtered through a pad of Celite\(^{\circ}\) to remove the catalyst and the solvent concentrated in vacuo to afford tosyl amine 528 (161 mg, 92%) as a thick, orange oil; Rf 0.52 (solvent A); v_max(film)/cm\(^{-1}\) 2254, 1334, 1158 and 908; \(\delta_H\) (400 MHz; CDCl\(_3\)) 0.72 (3 H, t, J 7.4, CH\(_2\)C\(_H_3\)), 1.49 (2 H, sext., J 7.4, CH\(_2\)CH\(_3\)), 2.35 (3 H, s, CH\(_3\)), 3.00 (2 H, dd, J 7.4 and 9.2, CH\(_2\)CH\(_2\)CH\(_3\)), 4.31 (2 H, s, CH\(_2\)), 6.07 (1 H, dd, J 8.1, 2×CH) and 7.57 (2 H, d, J 8.1, 2×CH); \(\delta_C\) (100 MHz; CDCl\(_3\)) 11.0 (CH\(_3\)), 21.5 (CH\(_3\)), 21.3 (CH\(_3\)Ar)), 21.5 (CH\(_3\)CH\(_2\)), 43.7 (CH\(_3\)CH\(_2\)CH\(_2\)), 49.2 (CH\(_2\)), 109.3 (CH), 110.4 (CH), 127.2 (2×CH), 129.5 (2×CH), 137.0 (CCH\(_3\)), 142.4 (CS), 143.0 (CHCH\(_2\)) and 149.9 (CH\(_2\)CH); MS (Cl) m/z 292.2 [M+H]+; HRMS m/z 294.1161 (296.1164 calcd for C\(_{15}\)H\(_{20}\)NO\(_3\)S, M+H+).

N-((5-(But-3-enyl)furan-2-yl)methyl)-4-methylbenzenesulfonamide 530

A solution of amine 525 (650 mg, 2.58 mmol) in tetrahydrofuran (10 cm\(^3\)) was stirred for 10 min, then cooled to 0 °C and treated with nBuLi (1.19 cm\(^3\), 2.84
mmol). The resulting dark orange solution was stirred at this temperature for 15 min before being warmed up to room temperature and stirred for 15 min. The solution was recooled to 0 °C and 4-bromobutene (0.32 cm³, 3.10 mmol) was added. After 10 min, the ice-water bath was removed to allow the reaction mixture to warm up to room temperature. After 20 h, TLC analysis showed there to be considerable remaining starting material, so the above procedure was repeated to add the same amount of reagents for a second time. After 8 h, the reaction had not proceeded, so the reaction mixture was diluted with diethyl ether (20 cm³) and water (20 cm³). The organic layer was separated, dried over anhydrous sodium sulphate, filtered and concentrated in vacuo.

Purification by FCC [petroleum ether-ethyl acetate (70:30)] of the residue afforded alkene 530 (340 mg, 43%) as an orange oil; ν max (film)/cm⁻¹ 913; δ H (400 MHz; CDCl₃) 2.05 (2 H, q, J 7.2, CH₂=CHCH₂), 2.25 (3 H, s, CH₃), 3.03 (2 H, t, J 7.2, CH₂=CHCH₂CH₂), 4.22 (2 H, s, CH₂), 4.82-4.88 (2 H, m, CH₂=CH), 5.51-5.62 (1 H, m, CH₂=CH), 6.00 (1 H, dd, J 0.6 and 3.2, CH=CO), 6.12 (1 H, dd, J 1.9 and 3.2, CHCO), 7.10 (2 H, d, J 8.4, 2×CH) and 7.51 (2 H, d, J 8.4, 2×CH); δ C (100 MHz; CDCl₃) 21.5 (CH₃), 32.8 (CH₂CH₂), 43.9 (CH₂CH₂), 46.9 (CH₂), 109.4 (CH), 110.4 (CH), 117.0 (CH₂=CH), 127.3 (2×CH), 129.5 (2×CH), 134.7 (CCH₃), 142.4 (CH₂=CH), 143.0 (CS), 149.8 (CCH₂), plus one unresolved carbon; MS (CI) m/z 306.2 [M+H]+; HRMS m/z 306.1165 (306.1164 calcd for C₁₆H₂₀NO₃S, M+H⁺).

4-Methyl-N-(5-methylfuran-2-ylmethyl)-benzenesulfonamide 535

To a stirred solution of methylfurfurylamine 534 (300 mg, 2.69 mmol) in dichloromethane (13 cm³) at 0 °C was added triethylamine (0.83 cm³, 5.93 mmol) and dimethylaminopyridine (198 mg, 1.61 mmol). After 10 min, p-toluenesulfonyl chloride (540 mg, 2.83 mmol) was added, following which an immediate colour change from colourless to yellow was observed. The cooling bath was removed after 10 min and the reaction mixture allowed to warm up to room temperature. After 1 h, the reaction was diluted with dichloromethane (20 cm³), washed with water (2×20 cm³) followed by saturated aqueous sodium hydrogen carbonate (2×20 cm³). The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. The residue was passed through a pad of silica gel to afford tosyl amine 535 (715 mg, 100%) as a yellow solid; Rf 0.31; mp 85-86 °C (from dichloromethane) (lit.,[224] 82-83 °C; δ H(400
MHz; CDCl₃) 2.16 (3 H, s, CH₃), 2.46 (3 H, s, CH₃(Ph)), 4.13 (2 H, s, CH₂), 5.80 (1 H, d, J 3.0, CH=CO), 5.99 (1 H, d, J 3.0, CHCO), 7.30 (2 H, d, J 8.0, 2×CH) and 7.74 (2 H, d, J 8.0, 2×CH); δ(100 MHz; CDCl₃) 13.4 (C CH₃), 21.5 (C H₃(Ph)), 40.3 (C H₂), 106.2 (CH), 109.1 (CH), 127.2 (2×CH), 129.6 (2×CH), 136.9 (C CH₃), 143.4 (C S), 147.5 (C CH₂) and 152.3 (O C(CH₃)); MS (CI) m/z 266.2 [M+H]⁺; HRMS m/z 266.0850 (266.0852 calcd for C₁₃H₁₆NO₃S, M+H⁺). The spectral data matches that reported in the literature.[224]

6-Hydroxy-6-methyl-1-(toluene-4-sulfonyl)-1,6-dihydro-2H-pyridin-3-one 536

To a 0 °C solution of amine 535 (360 mg, 1.35 mmol) in dichloromethane (7 cm³) was added meta-chloroperoxybenzoic acid (mCPBA) (365 mg, 1.62 mmol) and the ice-water bath was removed after 10 min. The yellow reaction mixture was allowed to warm up to room temperature and quenched after 4 h with water (10 cm³). The solution was transferred to a separating funnel and dichloromethane (15 cm³) and water (10 cm³) were added. The phases were separated and the organic layer was washed with water (10 cm³) and saturated aqueous sodium hydrogen carbonate (4×15 cm³), dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to afford 536 (381 mg, 100%) as a pale yellow oil; Rₜ 0.13 (solvent G); v_max(film)/cm⁻¹ 2253, 1160, 1090 and 910; δ_H(400 MHz; CDCl₃) 2.19 (3 H, s, CH₃), 2.36 (3 H, s, CH₃), 3.90 (2 H, s, J 5.2, CH₂), 5.23 (1 H, t, J 5.1, OH), 6.15 (1 H, d, J 11.9, CH=CH(CH₃=C=O)), 6.35 (1 H, d, J 11.9, CH=CH(CH₃=C=O)), 7.23 (2 H, d, J 8.2, 2×CH) and 7.66 (2 H, d, 2×CH); δ_C(100 MHz; CDCl₃) 21.6 (CH₃), 29.7 (CH₃COH), 51.5 (CH₂), 77.0 (COH), 127.1 (2×CH), 129.8 (2×CH), 133.2 (CH=CH(CH₃=C=O)), 136.2 (CS), 137.3 (CCH₃), 143.9 CH=CH(CH₃=C=O)) and 196.9 (C=O); MS (Cl) m/z 282.2 [M+H]⁺; HRMS 282.0807 (282.0800 calcd for C₁₃H₁₆NO₄S, M+H⁺).

Furan-2-ylmethyl-carbamic acid tert-butyl ester 532[225]

To a stirred mixture of furfuryl amine 526 (0.36 cm³, 4.11 mmol) in water (4.2 cm³) was added di-tert-butyl dicarbonate ((Boc)₂O) (988 mg, 4.43 mmol) at room temperature. After 40 min, the reaction was complete and was diluted with
water (10 cm$^3$) and extracted with ethyl acetate (2×10 cm$^3$). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to afford Boc amine 532 (785 mg, 97%) as a clear oil; $R_f$ 0.71; $\delta_H$ (400 MHz; CDCl$^3$) 1.45 (9 H, s, 3×CH$_3$), 4.30 (2 H, d, $J$ 5.4, CH$_2$), 6.20 (1 H, d, $J$ 2.8, CH=CO), 6.31 (1 H, dd, $J$ 1.8 and 2.8, CHCO) and 7.32 (1 H, dd, $J$ 0.8 and 1.8, CHO); $\delta_C$ (100 MHz; CDCl$^3$) 28.4 (3×CH$_3$), 37.7 (CH$_2$), 79.6 (CCH$_3$), 110.3 (2×CH), 142.0 (CHO), 146.7 (CCH$_2$) and 155.6 (C=O). The spectral data matches that reported in the literature.$^{[225]}$

(5-Methyl-furan-2-ylmethyl)-carbamic acid tert-butyl ester 537

To a stirred mixture of methylfurfurylamine 534 (150 mg, 1.34 mmol) in water (1.35 cm$^3$) was added di-tert-butyl dicarbonate ((Boc)$_2$O) (324 mg, 1.48 mmol) at room temperature. Soon after, transparent liquid droplets were observed on the walls of the reaction vessel. After 40 min, water (5 cm$^3$) was added to the pale yellow solution and the reaction mixture extracted with ethyl acetate (2×5 cm$^3$). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to yield Boc amine 537 (233 mg, 82%) as a yellow oil; $R_f$ 0.53 (solvent A); $\nu_{\text{max}}$(film)/cm$^{-1}$ 1701 and 1110; $\delta_H$ (400 MHz; CDCl$^3$) 1.48 (9 H, s, 3×CH$_3$), 2.27 (3 H, s, CH$_3$), 4.23 (2 H, d, $J$ 5.2, CH$_2$), 5.88 (1 H, dd, $J$ 0.8 and 2.9, CH=CO) and 6.08 (1 H, d, $J$ 2.9, CHCO); $\delta_C$ (100 MHz; CDCl$^3$) 13.5 (CH$_3$), 28.4 (3×CH$_3$), 37.8 (CH$_2$), 79.5 (C(CH$_3$)$_3$), 106.1 (CH), 107.8 (CH), 150.0 (CCH$_3$), 151.7 (CCH$_2$) and 155.6 (C=O); MS (EI) $m/z$ 211 [M]$^+$; HRMS $m/z$ 211.1210 (211.2108 calcd for C$_{11}$H$_{17}$NO$_3$, M$^+$).

$N$-(1-furan-2-yl-butyl)-4-methyl-benzenesulfonamide 516

To a solution of homoallylic amine 492 (275 mg, 0.943 mmol) in methanol (5 cm$^3$) was treated with a catalytic amount of 10% palladium on activated carbon. The flask was evacuated and after purging three times with hydrogen gas via a balloon, the mixture was stirred under an atmosphere of hydrogen for 40 min at room temperature. TLC analysis deemed the reaction complete and the solution was filtered through a pad of Celite® to remove the catalyst and the solvent concentrated in vacuo to afford alkane 516 (275 mg, 99%) as a white crystalline
solid; \( R_f \) 0.59 (solvent \( B \)); mp 94-96 °C (from methanol); \( \delta_H (400 \text{ MHz}; \text{CDCl}_3) \) 0.78 (3 H, t, \( J \) 7.4, \( \text{CH}_2\text{CH}_3 \)), 1.10-1.28 (2 H, m, \( \text{CH}_2\text{CH}_3 \)), 1.67 (2 H, q, \( J \) 7.6, \( \text{CH}_2\text{CH}_2 \)), 2.30 (3 H, s, \( \text{CH}_3 \) (Ph)), 4.32 (1 H, t, \( J \) 7.6, \( \text{CHN} \)), 5.80 (1 H, d, \( J \) 3.2, \( \text{CH}==\text{CO} \)), 6.03 (1 H, dd, \( J \) 1.8 and 3.2, \( \text{CHCO} \)), 7.06 (1 H, dd, \( J \) 0.6 and 1.8, \( \text{CHO} \)), 7.11 (2 H, d, \( J \) 8.1, 2×\( \text{CH} \)) and 7.53 (2 H, d, \( J \) 8.1, 2×\( \text{CH} \)); \( \delta_C (100 \text{ MHz}; \text{CDCl}_3) \) 13.5 (\( \text{CH}_2\text{CH}_3 \)), 18.9 (\( \text{CH}_2\text{CH}_3 \)), 21.5 (\( \text{CH}_3 \)), 37.1 (\( \text{CH}_2\text{CH}_2 \)), 51.5 (\( \text{CHN} \)), 106.8 (\( \text{CH}==\text{CO} \)), 109.9 (\( \text{CHCO} \)), 127.0 (\( \text{CH} \)), 129.4 (\( \text{CH} \)), 137.7 (\( \text{CCHN} \)), 141.8 (\( \text{CHO} \)), 143.0 (C) and 153.0 (C); MS (EI) \( m/z \) 293.1 [M]+, 250.1 [M-CH\(_2\text{CH}_2\text{CH}_3\)]+, 155.0 [M-(HTs)CH\(_2\text{CH}_2\text{CH}_3\)]+; HRMS \( m/z \) 293.1084 (293.1086 calcd for \( \text{C}_{15}\text{H}_{19}\text{NO}_3\text{S} \), M+).

\( N-[1-(5\text{-Allyl-furan-2-yl})\text{-butyl}]-4\text{-methyl-benzenesulfonamide} \) 517

To a solution of amine 516 (704.8 mg, 2.40 mmol) in tetrahydrofuran (10 cm\(^3\)) at 0 °C, was added \( \text{nBuLi} \) (1.2 cm\(^3\), 2.88 mmol). After stirring for 10 min at 0 °C and then 15 min at room temperature, the now yellow solution was recooled to 0 °C and allyl bromide (0.25 cm\(^3\), 2.88 mmol) was added. After 15 min at 0 °C, the reaction mixture was allowed to warm up to room temperature once again and stirred for 16 h. The reaction was diluted with diethyl ether (10 cm\(^3\)) and water (10 cm\(^3\)) was added to separate the layers. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated \( \text{in vacuo} \). Purification by FCC [petroleum ether-ethyl acetate (85:15)→(80:20)] of the crude residue afforded alkene 517 (294 mg, 66% based on starting material consumed); \( R_f \) 0.65 (solvent \( A \)); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 2910, 2849, 1699 (C=C), 1455, 1262 and 1090; \( \delta_H (400 \text{ MHz}; \text{CDCl}_3) \) 0.85 (3 H, t, \( J \) 7.4, \( \text{CH}_3 \)), 1.22-1.39 (2 H, m, \( \text{CH}_2\text{CH}_3 \)), 1.71-1.87 (2 H, m, \( \text{CH}_2\text{CH}_2 \)), 2.34 (3 H, s, \( \text{CH}_3 \)), 3.46 (1 H, dd, \( J \) 7.6 and 16.4, \( \text{CH}_2\text{CH}_3 \)), 3.06-3.70 (1 H, m, \( \text{CH}_2 \)), 4.87-5.00 (3 H, m, \( \text{CH}_2\text{CH}==\text{CH} \) and \( \text{CHN} \)), 5.47-5.55 (1 H, m, \( \text{CH}_2==\text{CH} \)), 5.98 (1 H, dd, \( J \) 0.6 and 3.2, \( \text{CH}==\text{CO} \)), 6.15 (1 H, dd, \( J \) 1.8 and 3.2, \( \text{CHCO} \)), 7.18 (2 H, d, \( J \) 8.4, 2×\( \text{CH} \)) and 7.63 (2 H, d, \( J \) 8.4, 2×\( \text{CH} \)); \( \delta_C (100 \text{ MHz}; \text{CDCl}_3) \) 13.7 (\( \text{CH}_3 \)), 19.5 (\( \text{CH}_2\text{CH}_3 \)), 21.5 (\( \text{CH}_3 \)), 33.9 (\( \text{CH}_2\text{CH}_2 \)), 47.1 (\( \text{CH}_2\text{CHCH}_2 \)), 55.1 (\( \text{CHN} \)), 108.5 (\( \text{CH}==\text{CO} \)), 110.1 (\( \text{CHCO} \)), 116.8 (\( \text{CH}_2==\text{CH} \)), 127.5 (2×\( \text{CH} \)), 129.2 (2×\( \text{CH} \)), 135.6 (\( \text{CHN} \)), 137.9 (\( \text{CCHN} \)), 141.8 (\( \text{CH}_2==\text{CH} \)), 142.9 (C) and 152.8 (C); MS (Cl) \( m/z \) 290.2 [M-\( \text{CH}_2\text{CH}_2\text{CH}_3 \)]+, 334.3 [M+H]+; HRMS \( m/z \) 334.1481 (334.1478 calcd for \( \text{C}_{18}\text{H}_{24}\text{O}_3\text{NS} \), M+).
4-Methyl-N-[(1-(5-propylfuran-2-yl)butyl)]benzenesulfonamide 519

To a solution of amine 517 (106 mg, 0.31 mmol) in methanol (2 cm³) was treated with a catalytic amount of 10% palladium on activated carbon. The flask was evacuated and after purging three times with hydrogen gas via a balloon, the mixture was stirred under an atmosphere of hydrogen for 45 min at room temperature. TLC analysis deemed the reaction complete and the solution was filtered through a pad of Celite® to remove the catalyst and the solvent concentrated in vacuo to afford alkane 519 (104 mg, 98%) as an orange oil with no further purification performed; $R_f$ 0.58 (solvent A); $\nu_{\text{max}}$(film)/cm$^{-1}$ 2254, 1160 and 908; $\delta_{\text{H}}$(400 MHz; CDCl$_3$) 0.64 (3 H, t, $J$ 7.4, CH$_3$), 0.84 (3 H, t, $J$ 7.4, CH$_3$), 1.20-1.40 (4 H, m, 2×CH$_2$CH$_3$), 1.63-1.71 (1 H, m, NCHCH$_2$), 1.83-1.91 (1 H, m, NCHCH$_2$), 2.43 (3 H, s, CH$_3$), 2.75-2.80 (1 H, m, CH$_2$), 2.88-2.97 (1 H, m, CH$_2$), 4.90 (1 H, t, $J$ 7.7, NCH), 5.92 (1 H, d, $J$ 3.3, CH=CO), 6.13 (1 H, dd, $J$ 1.9 and 3.3, CHCO), 7.17 (2 H, d, $J$ 8.0, 2×CH) and 7.61 (2 H, d, $J$ 8.0, 2×CH); $\delta_{\text{C}}$(100 MHz; CDCl$_3$) 11.3 (CH$_3$), 13.8 (HNCHCH$_2$CH$_2$CH$_3$), 19.7 (HNCHCH$_2$CH$_2$CH$_3$), 21.5 (PhCH$_3$), 23.8 (H$_3$CCH$_2$), 34.2 (H$_3$CCH$_2$CH$_2$), 46.5 (HNCHCH$_2$CH$_2$CH$_3$), 55.0 (HNCHCH$_2$CH$_2$CH$_3$), 108.2 (CH), 110.1 (CH), 127.4 (2×CH), 129.2 (2×CH), 138.2 (CCH$_3$), 141.8 (SO$_2$C), 142.7 (CCHNH) and 153.0 (CH$_3$CH$_2$CH$_2$C); MS (Cl) m/z 336.4 [M+H$^+$]; HRMS m/z 336.1637 (336.1634 calcd for C$_{18}$H$_{26}$NO$_3$S, M+H$^+$).

N-(1-Furan-2-yl-but-3-enyl)acrylamide 551

To a stirring, room temperature, solution of acryloyl chloride (70 µL, 0.801 mmol) and diisopropylethylamine (0.14 cm$^3$, 0.801 mmol) in dry dichloromethane (4 cm$^3$) under argon, was added a solution of amine 490 (100 mg, 0.729 mmol) and diisopropylethylamine (0.13 cm$^3$, 0.729 mmol) in dry dichloromethane (7 cm$^3$). The resulting bright yellow solution was stirred for 2 h, whereafter it was quenched with saturated aqueous ammonium chloride (15 cm$^3$) and diluted with dichloromethane (15 cm$^3$). The organic layer was separated and dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate, (60:40)] of the crude residue afforded amide 551 (139 mg, 100%) as a pale yellow oil; $R_f$ 0.52
(solvent I); $\delta_H$ (400 MHz; CDCl$_3$) 2.61 (2 H, t, $J = 6.9$, CH$_2$), 5.06-5.13 (2 H, m, CH=CH$_2$), 5.26-5.30 (1 H, m, CHN), 5.62-5.76 (2 H, m, CH$_2$CH=CH$_2$ and COCH=CH$_2$), 6.09-6.14 (1 H, m, COCH=CH$_2$), 6.20 (1 H, dd, $J = 0.6$ and 3.0, CH=CO), 6.28 (1 H, d, $J = 1.4$, CHCO), 6.31 (1 H, dd, $J = 1.4$ and 3.0, COCH=CH$_2$) and 7.33 (1 H, d, $J = 0.9$, CHO). The spectral data matches that reported in the literature.$^{[226]}$

6-Furan-2-yl-5,6-dihydro-1H-pyridin-2-one 550

![Chemical Structure]

A solution of amide 551 (316 mg, 1.65 mmol) in dry dichloromethane (17 cm$^3$) under argon was treated with Grubbs first generation catalyst (136 mg, 0.165 mmol). The reaction mixture was heated under reflux in the dark for 18 h, then concentrated under reduced pressure and the residue passed through a short column of silica gel, eluting with ethyl acetate, to give cyclic amide 550 (226 mg, 84%) as a brown solid with no further purification necessary; R$_f$ 0.07 (solvent C); mp 96-98 °C (from ethyl acetate) (lit.$^{[226]}$ 98-99 °C); $\delta_H$ (400 MHz; CDCl$_3$) 2.68-2.71 (2 H, m, CH$_2$), 4.80 (1 H, t, $J = 7.5$, CHN), 5.97 (1 H, d, $J = 10.0$, CH=CHCH$_2$), 6.25 (1 H, d, $J = 3.2$, CH=CO), 6.34 (1 H, dd, $J = 1.8$ and 3.2, CHCO), 6.61 (1 H, dt, $J = 4.2$ and 10.0, CH=CHCH$_2$) and 7.39 (1 H, s, CHO); $\delta_C$ (100 MHz; CDCl$_3$) 27.6 (CH$_2$), 47.2 (CHN), 104.8 (CH), 108.9 (CH), 122.8 (CH=CHCH$_2$), 138.1 (CH=CHCH$_2$), 140.7 (CHO), 151.6 (C) and 164.2 (C=O); MS (Cl) m/z 164.2 [M+H]$^+$; HRMS 164.0710 (164.0712 calc for C$_9$H$_9$NO$_2$, M+H$^+$). The spectral data matches that reported in the literature.$^{[226]}$

6-Furan-2-yl-piperidin-2-one 552$^{[186]}$

![Chemical Structure]

To a solution of amide 550 (56 mg, 0.345 mmol) in methanol (2 cm$^3$) was treated with a catalytic amount of 10% palladium on activated carbon. The flask was evacuated and after purging three times with hydrogen gas via a balloon, the mixture was stirred under an atmosphere of hydrogen for 35 min at room temperature. TLC analysis deemed the reaction complete and the solution was filtered through a pad of Celite$^\text{®}$ to remove the catalyst and the solvent
concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate, (20:80)] of the crude residue afforded lactam 552 (40 mg, 79%) as a white solid; \( R_f \) 0.24 (ethyl acetate); \( \delta_H (400 \text{ MHz}; \text{CDCl}_3) 1.76-1.87 \) (1 H, m, OC\( \text{CH}_2\text{CH}_2\)), 1.91-2.02 (2 H, m, OC\( \text{CH}_2\text{CH}_2\) and OC\( \text{CH}_2\text{CH}_2\text{CH}_2\)), 2.11-2.20 (1 H, m, OC\( \text{CH}_2\text{CH}_2\)), 2.42-2.48 (2 H, m, OC\( \text{CH}_2\)), 4.67 (1 H, t, \( J = 6.0 \), \( \text{CHNH} \)), 6.25 (1 H, d, \( J = 3.2 \), \( \text{CH=CO} \)), 6.38 (1 H, dd, \( J = 1.9 \) and 3.2, \( \text{CHCO} \)) and 7.40 (1 H, d, \( J = 1.9 \), \( \text{CHO} \)); MS (CI) \( m/z \) 166.25 [M+H]+; HRMS \( m/z \) 166.0864 (166.0868 calcd for \( \text{C}_9\text{H}_{12}\text{NO}_2, \text{M+H}^+ \)). The spectral data matches that reported in the literature.\[^{[186]}\]

**4-Hydroxy-9,9a-dihydro-4H-quinolizine-1,6-dione 549**

![Image of molecule]

A solution of lactam 550 (46 mg, 0.218 mmol) in chloroform (10 cm\(^3\)) was treated with meta-chloroperoxybenzoic acid (mCPBA) (139 mg, 0.620 mmol) in one portion at room temperature. The reaction mixture was heated to 60 °C for 3.5 h, then cooled down to room temperature and stirred overnight. The reaction mixture was diluted with dichloromethane (10 cm\(^3\)) and saturated aqueous sodium hydrogen carbonate (10 cm\(^3\)) added. The organic layer was washed with a further amount of saturated aqueous sodium hydrogen carbonate (15 cm\(^3\)), water (15 cm\(^3\)) and saturated aqueous sodium chloride (15 cm\(^3\)). The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate, (30:70)] of the crude residue afforded the bicyclic lactam 549 (40 mg, 70%) as a yellow oil; \( R_f \) 0.40 (solvent J); \( \delta_H (400 \text{ MHz}; \text{CDCl}_3) 2.70-2.75 \) (2 H, m, \( \text{H}_2\text{CCH}=\text{CH} \)), 4.44 (1 H, t, \( J = 8.1 \), \( \text{HCN} \)), 5.90 (1 H, dt, \( J = 1.9 \) and 10.0, \( \text{H}_2\text{CCH}=\text{CH} \)), 6.09 (1 H, d, \( J = 10.1 \), \( \text{O}=\text{CCH}=\text{CHCHOH} \)), 6.14 (1 H, d, \( J = 4.9 \), \( \text{O}=\text{CCH}=\text{CHCHOH} \)), 6.55-6.60 (1 H, m, \( \text{H}_2\text{CCH}=\text{CH} \)) and 6.99 (1 H, dd, \( J = 4.9 \) and 10.1, \( \text{O}=\text{CCH}=\text{CHCHOH} \)); \( \delta_C (100 \text{ MHz}; \text{CDCl}_3) 22.7 \) (\( \text{CH}_2 \)), 56.5 (\( \text{CHN} \)), 74.8 (\( \text{HOCH} \)), 122.9 (\( \text{CH}_2\text{CH}=\text{CH} \)), 126.9 (\( \text{HOCHCH}=\text{CH} \)), 138.5 (\( \text{CH}_2\text{CH} \)), 142.8 (\( \text{HOCHCH} \)), 157.9 (\( \text{NCO} \)) and 192.7 (\( \text{C}=\text{O} \)); MS (CI) \( m/z \) 162.19 [M-\text{OH}]+, 180.21 [M+H]+; HRMS 180.0675 (180.0660 calcd for \( \text{C}_9\text{H}_{12}\text{NO}_3, \text{M+H}^+ \)).
1-Furan-2-yl-2-methyl-propan-1-ol 554

To a solution of furan (5.0 g, 73.4 mmol) in diethyl ether (150 cm$^3$) at 0 $^\circ$C, was added $N,N,N',N'$-tetramethylethlenediamine (11.0 cm$^3$, 73.4 mmol), followed by nBuLi (32.3 cm$^3$, 80.7 mmol). The reaction mixture was stirred at 0 $^\circ$C for 1 h, then warmed up to room temperature and stirred for a further 1 h. After this time, the reaction mixture was cooled to -78 $^\circ$C and isobutyraldehyde (7.33 cm$^3$, 80.7 mmol) was added. After 3 h at -78 $^\circ$C, the reaction was diluted with diethyl ether (50 cm$^3$) and quenched with water (50 cm$^3$). The organic layer was separated, washed with water (3×50 cm$^3$), dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. Purification by FCC [diethyl ether-petroleum ether (30:70)] of the crude residue afforded furfuryl alcohol 554 (9.82 g, 96%) as a pale yellow oil; $\delta_H$ (400 MHz; CDCl$_3$) 0.86 (3 H, d, $J$ 6.8, CH$_3$), 1.02 (3 H, d, $J$ 6.8, CH$_3$), 1.94 (1 H, br s, OH), 2.10-2.13 (1 H, m, CH(CH$_3$)$_2$), 4.37 (1 H, d, $J$ 6.8, CHO), 6.27 (1 H, d, $J$ 3.2, CH=CO), 6.33 (1 H, dd, $J$ 1.8 and 3.2, CHCO) and 7.30 (1 H, d, $J$ 1.8, CHO). The spectral data matches that reported in the literature.[207]

tert-Butyl-(1-furan-2-yl-2-methyl-propoxy)-dimethyl-silane 452

To a solution of furfuryl alcohol 554 (5.90 g, 42.1 mmol) in dichloromethane (210 cm$^3$) at 0 $^\circ$C, was added triethylamine (17.6 cm$^3$, 126.3 mmol) and the reaction mixture was stirred for 10 min. tert-Butyldimethylsilyl chloride (9.52 g, 63.1 mmol) and dimethylaminopyridine (2.57 g, 21.1 mmol) were added successively and the reaction was warmed up to room temperature. After 16 h, further portions of triethylamine (17.6 cm$^3$, 126.3 mmol), dimethylaminopyridine (2.57 g, 21.1 mmol) and tert-butyldimethylsilyl chloride (9.52 g, 63.1 mmol) were added and the mixture stirred for a further 24 h. The reaction was quenched with 1% hydrochloric acid (40 cm$^3$) and extracted with dichloromethane (50 cm$^3$). The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate (50 cm$^3$), water (2×50 cm$^3$) and saturated aqueous sodium chloride (50 cm$^3$). The solution was then dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification
by FCC [diethyl ether-petroleum ether (20:80) then (5:95) then (0:100)] of the crude residue afforded silyl ether 452 (8.97 g, 84%) as a colourless oil; \( R_f \) 0.62 (solvent L); \( \delta_H (400 \text{ MHz}; \text{CDCl}_3) -0.18 \) (3 H, s, Si(CH\(_3\)_2)), 0.00 (3 H, s, Si(CH\(_3\)_2)), 0.77 (3 H, d, J 6.7, CH\(_3\)), 0.85 (9 H, s, SiC(CH\(_3\)_3), 0.93 (3 H, d, J 6.7, CH\(_3\)), 1.98-2.01 (1 H, m, CH), 4.29 (1 H, d, J 6.8, OCH), 6.11 (1 H, d, J 3.1, CH=CO), 6.27 (1 H, dd, J 1.8 and 3.1, CHCO) and 7.30 (1 H, d, J 1.8, CHO); \( \delta_C (100 \text{ MHz}; \text{CDCl}_3) -5.9 \) (Si(CH\(_3\)_2)), 18.0 (SiC(CH\(_3\)_3), 18.5 (CHCH\(_3\)), 19.0 (CHCH\(_3\)), 25.9 (SiC(CH\(_3\)_3), 35.2 (CH(CH\(_3\)_2), 76.8 (CHOTBS), 108.8 (CH=CO), 109.7 (CHCO), 152.5 (CCHOTBS) and 155.5 (C); MS (EI) \( m/z \ 123.1 \ [\text{M+OTBS}] \); HRMS \( m/z \ 123.0813 \ (123.0810 \text{ calcd for } C_{8}H_{11}O, \text{M-OTBS}^+).\)

\[ \text{[1-(5-Allyl-furan-2-yl)-2-methyl-propoxy]-tert-butyldimethylsilane 555} \]

To a solution of silyl ether 452 (1.0 g, 3.93 mmol) in anhydrous tetrahydrofuran (20 cm\(^3\)) at 0 °C was added \( nBuLi \) (2.36 cm\(^3\), 5.89 mmol). The resulting yellow solution was stirred at 0 °C for 15 min and then allowed to warm up to room temperature and stirred for 15 min. After recooling down to 0 °C, allyl bromide (0.41 cm\(^3\), 4.71 mmol) was added and the mixture was stirred for 15 min. The reaction was allowed to warm up to room temperature and after 16 h, the reaction was diluted with diethyl ether (30 cm\(^3\)) and quenched with water (50 cm\(^3\)). The phases were separated and the organic phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford alkene 555 (1.06 g, 92%) as a yellow oil with further purification necessary; \( R_f \) 0.70 (solvent L); \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \ 2981, 1610 \ (\text{C=C}) \text{ and } 1145 \ (\text{O-Si}) \); \( \delta_H (400 \text{ MHz}; \text{CDCl}_3) -0.16 \) (3 H, s, Si(CH\(_3\)_2)), 0.00 (3 H, s, Si(CH\(_3\)_2)), 0.77 (3 H, d, J 6.7, CHCH\(_3\)), 0.88 (9 H, s, SiC(CH\(_3\)_3), 0.93 (3 H, d, J 6.7, CHCH\(_3\)), 1.94-2.02 (1 H, m, CH(CH\(_3\)_2)), 3.33 (2 H, d, J 6.4, CH\(_2\)), 4.22 (1 H, d, J 6.9, CCHOTBS), 5.05-5.12 (2 H, m, CH\(_2=CH\)), 5.85-5.95 (1 H, m, CH=CH\(_2\)), 5.89 (1 H, d, J 3.1, CH=CO) and 6.02 (1 H, d, J 3.1, CHCO); \( \delta_C (100 \text{ MHz}; \text{CDCl}_3) -5.2 \) (Si(CH\(_3\)_2)), -4.9 (Si(CH\(_3\)_2)), 18.2 (SiC(CH\(_3\)_3), 18.4 (CHCH\(_3\)), 18.9 (CHCH\(_3\)), 25.8 (SiC(CH\(_3\)_3), 32.6 (CH\(_2\)), 34.2 (CH(CH\(_3\)_2), 74.2 (CCHOTBS), 105.8 (CH=CO), 107.0 (CHCO), 116.5 (CH\(_2=CH\)), 134.3 (CH\(_2=CH\)), 152.3 (CCHOTBS) and 155.5 (CH\(_2=CHCH\(_2\)C); MS (CI) \( m/z \ 163 \ [\text{M-OTBS}^+] \); HRMS \( m/z \ 163.1119 \ (163.1123 \text{ calcd for } C_{11}H_{15}O, \text{M-OTBS}^+).\)
1-(5- Allyl furan-2-yl)-2-methyl propan-1-ol 558

To a solution of silyl ether 555 (1.06 g, 4.19 mmol) in anhydrous tetrahydrofuran (20 cm^3) at 0 °C, was added tetra-nbutylammonium fluoride (8.4 cm^3, 8.38 mmol). The ice-water bath was removed after 10 min and the reaction was left to stir overnight. The reaction mixture was then diluted with diethyl ether (30 cm^3) and water (30 cm^3) was added. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (80:20)] of the crude residue afforded alcohol 558 (513 mg, 87%) as a colourless oil; Rf 0.26 (solvent D); \( \nu_{\text{max}} \)(film)/cm\(^{-1}\) 3550 (OH), 2968, 2940 and 1459; \( \delta_H \)(400 MHz; CDCl\(_3\)) 0.75 (3 H, d, J 6.7, CHCH\(_3\)), 0.91 (3 H, d, J 6.7, CHCH\(_3\)), 1.71 (1 H, d, J 5.2, OH), 1.98 (1 H, oct., J 6.8, CH(CH\(_3\))\(_2\)), 3.28 (2 H, dd, J 0.7 and 6.5, CH\(_2\)=CHCH\(_2\)), 4.19 (1H, dd, J 5.2 and 7.0, CHO\(_H\)), 4.98-5.06 (2 H, m, CH\(_2\)=CH), 5.78-5.89 (1 H, m, CH\(_2\)=CH), 5.85 (1 H, d, J 3.1, CH=CO) and 6.03 (1 H, d, J 3.1, CHCO); MS (El) m/z 163 [M-OH]^+; HRMS m/z 181.1225 (181.1229 calcd for C\(_{11}\)H\(_{17}\)O\(_2\), M+H^+). The spectral data matches that reported in the literature.[157]

[1-(5-But-3-enyl furan-2-yl)-2-methyl propoxy]-tert-butyl dimethyl silane 451

To a solution of silyl ether 452 (1.2 g, 4.71 mmol) in anhydrous tetrahydrofuran (25 cm^3) at 0 °C, was added nBuLi (2.82 cm^3, 7.06 mmol). The resulting yellow solution was stirred at 0 °C for 15 min and then allowed to warm up to room temperature. The solution was stirred at room temperature for 15 min and then recooled back down to 0 °C, before 4-bromo-1-butene (0.59 cm^3, 5.65 mmol) was added. The reaction was stirred for 15 min at 0 °C and then allowed to warm up to room temperature. After 16 h, the reaction was diluted with diethyl ether (40 cm^3) and water (60 cm^3), the organic layers were separated and dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford alkene 451 (1.32 g, 91%) as a yellow oil; Rf 0.72 (solvent L); \( \nu_{\text{max}} \)(film)/cm\(^{-1}\) 2969, 1621 and 1152 (O-Si); \( \delta_H \)(400 MHz; CDCl\(_3\)) -0.14 (3 H, s, Si(CH\(_3\))\(_2\)), 0.00 (3 H, s, Si(CH\(_3\))\(_2\)), 0.79 (3 H, d, J 6.7, CHCH\(_3\)), 0.86 (9 H, s, SiC(CH\(_3\))\(_3\)), 0.93 (3 H, d,
1-(5-But-3-enyl-furan-2-yl)-2-methyl-propan-1-ol 450

To a solution of silyl ether 451 (1.3 g, 4.21 mmol) in anhydrous tetrahydrofuran (20 cm³) was added tetra-butylammonium fluoride (8.4 cm³, 8.42 mmol) at 0 °C. The ice-water bath was removed after 10 min and the reaction was left to stir overnight at room temperature. The reaction mixture was then diluted with diethyl ether (30 cm³) and water (30 cm³) was added. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (80:20)] of the crude residue afforded alcohol 450 (818 mg, 81%) as a colourless oil; Rf 0.26 (solvent D); δH (400 MHz; CDCl₃) 0.71 (3 H, d, J 6.7, CH₃), 0.89 (3 H, d, J 6.7, CH₃), 1.67 (1 H, d, J 5.1, OH), 1.96 (1 H, oct., J 6.8, CH(3)₂), 2.25 (2 H, q, J 7.6, CH₂=CHCH₂), 2.58 (2 H, t, J 7.6, CH₂=CHCH₂CH₂), 4.16 (1 H, dd, J 5.2 and 7.1, CHOH), 4.82-4.94 (2 H, m, CH₂=CH), 5.65-5.75 (1 H, m, CH₂=CH), 5.80 (1 H, d, J 3.0, CH=CO) and 6.02 (1 H, d, J 3.0, CHCO); δC(100 MHz; CDCl₃) 18.4 (CH-C), 18.8 (CH-CH₃), 27.6 (CH₂=CHCH₂), 32.1 (CH₂=CHCH₂CH₂), 33.3 (CH(3)₂), 73.6 (CHOH), 105.4 (CH=CO), 107.1 (CHCO), 115.3 (CH₂=CH), 137.5 (CH₂=CH), 154.3 (CH(OH)) and 154.9 (CH₂=CHCH₂CH₂C); MS (EI) m/z 177.0 [M-CH₃]+; HRMS m/z 177.1281 (177.1279 calcd for C₁₂H₁₇O, M-CH₃⁺). The spectral data matches that reported in the literature.¹⁵⁷
[1-(5-Pent-4-enyl-furan-2-yl)-2-methyl-propoxy]-tert-butyl-dimethyl-silane 556

To a solution of silyl ether 452 (1.0 g, 3.93 mmol) in anhydrous tetrahydrofuran (20 cm³) at 0 °C, was added nBuLi (2.35 cm³, 5.89 mmol). The resulting yellow solution was stirred at 0 °C for 15 min and then allowed to warm up to room temperature. The solution was stirred at room temperature for 15 min and then recooled back down to 0 °C, before 5-bromo-1-pentene (0.56 cm³, 4.71 mmol) was added. The reaction was stirred for 15 min at 0 °C and then allowed to warm up to room temperature. After 16 h, the reaction was diluted with diethyl ether (40 cm³) and water (50 cm³), the organic layers were separated and dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford alkene 556 (1.09 g, 86%) as a yellow oil with no further purification carried out; Rf 0.71 (solvent L); δH(400 MHz; CDCl₃) 0.12 (3 H, s, Si(CH₃)₂), 0.00 (3 H, s, Si(CH₃)₂), 0.79 (3 H, d, J 6.7, CH(CH₃)₂), 0.86 (9 H, s, SiC(CH₃)₃), 0.93 (3 H, d, J 6.7, CHCH₂), 1.87-1.92 (2 H, m, CH₂=CHCH₂CH₂), 1.97-2.03 (1 H, m, CH(CH₃)₂), 2.18-2.21 (2 H, m, CH₂=CHCH₂), 2.92-2.97 (2 H, m, CH₂=CHCH₂CH₂), 4.20 (1 H, d, J 7.0, CHOTBS), 5.03-5.12 (2 H, m, CH₂=CH), 5.85-5.90 (1 H, m, CH₂=CH), 5.88 (1 H, d, J 3.2, CH=CO) and 6.02 (1 H, d, J 3.2, CHCO); δC(100 MHz; CDCl₃) -5.1 (Si(CH₃)₂), -4.8 (Si(CH₃)₂), 18.3 (SiC(CH₃)₃), 18.5 (CHCH₂), 19.0 (CH(CH₃)₂), 25.5 (C(CH₃)₃), 29.9 (CH₂=CHCH₂), 32.6 (CH₂=CHCH₂), 34.2 (CH(CH₃)₂), 38.4 (CH₂=CHCH₂), 74.0 (CHOTBS), 105.5 (CH=CO), 107.2 (CHCO), 116.6 (CH₂=CH), 134.5 (CH₂=CH), 152.1 (CHOTBS) and 155.4 (CH₂=CHCH₂C); MS (Cl) m/z 191 [M-OTBS⁺]; HRMS m/z 191.1433 (191.1436 calcd for C₁₃H₁₉O, M-OTBS⁺).

2-Methyl-1-(5-pent-4-enyl-furan-2-yl)-propan-1-ol 559

To a solution of silyl ether 556 (1.0 g, 3.10 mmol) in anhydrous tetrahydrofuran (15 cm³) was added tetra-butylammonium fluoride (6.2 cm³, 6.20 mmol) at 0 °C. The ice-water bath was removed after 10 min and the reaction left to stir overnight at room temperature. The reaction mixture was then diluted with diethyl ether (25 cm³) and water (25 cm³) was added. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford alcohol 559 (0.83 g, 68%) as a clear oil with no further purification carried out; Rf 0.7 (solvent L); δH(400 MHz; CDCl₃) 0.00 (3 H, s, Si(CH₃)₂), 0.02 (3 H, s, Si(CH₃)₂), 0.80 (9 H, s, SiC(CH₃)₃), 0.93 (3 H, d, J 6.7, CH(CH₃)₂), 1.89 (2 H, m, CH₂=CHCH₂), 2.88 (2 H, m, CH₂=CHCH₂CH₂), 2.92 (2 H, m, CH₂=CHCH₂CH₂), 5.03-5.12 (2 H, m, CH₂=CH), 5.85-5.90 (1 H, m, CH₂=CH), 6.00 (1 H, d, J 3.2, CH=CO) and 6.02 (1 H, d, J 3.2, CHCO); δC(100 MHz; CDCl₃) -8.1 (Si(CH₃)₂), -4.8 (Si(CH₃)₂), 18.3 (SiC(CH₃)₃), 18.5 (CHCH₂), 19.0 (CH(CH₃)₂), 25.5 (C(CH₃)₃), 29.9 (CH₂=CHCH₂), 32.6 (CH₂=CHCH₂), 34.2 (CH(CH₃)₂), 38.4 (CH₂=CHCH₂), 74.0 (CHOTBS), 105.5 (CH=CO), 107.2 (CHCO), 116.6 (CH₂=CH), 134.5 (CH₂=CH), 152.1 (CHOTBS) and 155.4 (CH₂=CHCH₂C); MS (Cl) m/z 191 [M-OTBS⁺]; HRMS m/z 191.1433 (191.1436 calcd for C₁₃H₁₉O, M-OTBS⁺).
vacuo. Purification by FCC [petroleum ether-ethyl acetate (90:10)→(85:15)] of the crude residue afforded alcohol 559 (514 mg, 80%) as a pale yellow oil; $R_f$ 0.45 (solvent A). Also obtained was a mixture of alcohol 559 and silyl ether 452 of which approximately 15% was silyl ether 452; $\delta_H$ (400 MHz; CDCl$_3$) 0.75 (3 H, d, $J$ 6.8, CH$_3$), 0.93 (3 H, d, $J$ 6.8, CH$_3$), 1.64 (2 H, q, $J$ 7.6, CH$_2$=CHCH$_2$H$_2$), 1.93-2.06 (3 H, m, CH$_2$=CHCH$_2$ and CH(CH$_3$)$_2$), 2.51 (2 H, t, $J$ 7.6, CH$_2$=CHCH$_2$CH$_2$CH$_2$), 4.19 (1 H, dd, $J$ 3.6 and 6.4, CHOH), 4.86-4.97 (2 H, m, CH$_2$=CH), 5.68-5.76 (1 H, m, CH$_2$=CH), 5.81 (1 H, d, $J$ 3.0, CH=CO) and 6.00 (1 H, d, $J$ 3.0, CHCO); $\delta_C$ (100 MHz; CDCl$_3$) 18.4 (CH$_3$C$_6$H$_3$), 18.8 (CH$_3$C$_6$H$_3$), 27.2 (CH$_2$=CHCH$_2$CH$_2$), 27.4 (CH$_2$=CHCH$_2$), 33.2 (CH(CH$_3$)$_2$), 33.3 (CH$_2$=CHCH$_2$CH$_2$CH$_2$), 73.6 (CHOH), 105.3 (CH=CO), 107.1 (CHCO), 115.0 (CH$_2$=CH), 138.2 (CH$_2$=CH), 154.3 (CCHOH) and 155.3 (CH$_2$=CHCH$_2$CH$_2$CH$_2$C); MS (EI) $m/z$ 191 [M-OH]$^+$; HRMS $m/z$ 191.1433 (191.1436 calcd for C$_{13}$H$_{19}$O, M-OH$^+$).

[1-(5-Hex-5-enyl-furan-2-yl)-2-methyl-propoxy]-tert-butyl-dimethylsilane 557

To a solution of silyl ether 452 (1.0 g, 3.93 mmol) in anhydrous tetrahydrofuran (20 cm$^3$) at 0°C, was added nBuLi (2.36 cm$^3$, 5.89 mmol). The resulting yellow solution was stirred at 0°C for 15 min and then allowed to warm up to room temperature. The solution was stirred at room temperature for 15 min and then recooled back down to 0°C, before 6-bromo-1-pentene (0.63 cm$^3$, 4.71 mmol) was added. The reaction was stirred for 15 min at 0°C and then allowed to warm up to room temperature. After 16 h, the reaction was diluted with diethyl ether (30 cm$^3$) and water (40 cm$^3$), the organic layers were separated and dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford alkene 557. $^1$H NMR spectroscopy of the crude residue showed that approximately 19% of starting material 452 remained, which was inseparable from the product ($R_f$ 0.58 (solvent L)) by FCC. Therefore alkene 557 was taken on crude to the next step; $\nu_{\text{max}}$(film)/cm$^{-1}$ 2929, 2857, 2251, 1676 (C=C), 1254 and 1068 (O-Si); $\delta_H$ (400 MHz; CDCl$_3$) 0.17 (3 H, s, Si(CH$_3$)$_2$), -0.09 (3 H, s, Si(CH$_3$)$_2$), 0.76 (3 H, d, $J$ 6.8, CH$_3$), 0.82 (9 H, s, Si(CH$_3$)$_3$), 0.94 (3 H, d, $J$ 6.8, CH$_3$), 1.40 (1 H, dt, $J$ 7.5 and 15.1, CH$_2$=CHCH$_2$H$_2$), 1.60 (1 H, dt, $J$ 7.5 and 15.1, CH$_2$=CHCH$_2$CH$_2$), 1.95-2.10 (3 H, m, CH(CH$_3$)$_2$ and CH$_2$=CHCH$_2$), 2.57 (2
H, t, J 7.5, CH2=CHCH2CH2CH2, 4.20 (1 H, d, J 7.1, CHOTBS), 4.88-5.01 (2 H, m, CH2=CH), 5.72-5.80 (1 H, m, CH2=CH), 5.83 (1 H, d, J 3.0, CH=CO) and 5.97 (1 H, d, J 3.0, CHCO); δ$_{C}$(100 MHz; CDCl$_3$) 18.4 (CHC(CH$_3$)$_3$), 18.8 (CHC(CH$_3$)$_3$), 24.5 (CH$_2$=CHCH$_2$CH$_2$), 27.9 (CH$_2$=CH(CH$_2$)$_2$CH$_2$), 28.4 (CH$_2$=CHCH$_2$), 33.3 (CH(CH$_3$)$_2$), 33.5 (CH$_2$=CH(CH$_2$)$_3$CH$_2$), 73.6 (CHOH), 105.1 (CH=CO), 107.1 (CHCO), 114.5 (CH$_2$=CH), 138.7 (CH$_2$=CH), 154.1 (CCHOH) and 155.7 (CH$_2$=CH(CH$_2$)$_4$C); MS (EI)

1-(5-Hex-5-enyl-furan-2-yl)-2-methyl-propan-1-ol 560

![Structure](https://example.com/structure.png)

To a stirred solution of silyl ether 557 (1.32 g, 3.91 mmol) in anhydrous tetrahydrofuran (20 cm$^3$) at 0 °C, was added tetraν-butylammonium fluoride (7.82 cm$^3$, 7.82 mmol). The ice-water bath was removed after 10 min and the reaction allowed to warm up to room temperature, whereafter it was stirred for 16 h. Due to the remainder of some starting material, further tetraν-butylammonium fluoride (1.10 cm$^3$, 1.10 mmol, 0.3 eq.) was added at 0 °C. After a further 4 h, there was still incomplete consumption of starting material so work up was carried out. The reaction was diluted with diethyl ether (30 cm$^3$) and water (30 cm$^3$), the organic layer was separated and dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by FCC [petroleum ether-diethyl ether (90:10)→(85:15)] of the crude residue afforded 560 (494 mg, 57%) as a colourless oil; R$_f$ 0.25 (solvent D); ν$_{max}$(film)/cm$^{-1}$ 3387 (OH), 2931, 2870, 1643 (C=C), 1180, 1010 and 910; δ$_{H}$(400 MHz; CDCl$_3$) 0.74 (3 H, d, J 6.8, CHC(CH$_3$)$_3$), 0.92 (3 H, d, J 6.8, CHCH$_3$), 1.33 (2 H, qn, J 7.6, CH$_2$=CH(CH$_2$)$_2$CH$_2$), 1.52 (2 H, qn, J 7.6, CH$_2$=CHCH$_2$CH$_2$), 1.69 (1 H, d, J 5.1, CH(CH$_3$)$_2$), 1.98 (2 H, q, J 7.5, CH$_2$=CHCH$_2$), 2.50 (2 H, t, J 7.6, CH$_2$=CH(CH$_2$)$_3$CH$_2$), 4.19 (1 H, dd, J 5.3 and 7.2, CHOH), 4.81-4.92 (2 H, m, CH$_2$=CH), 5.64-5.75 (1 H, m, CH$_2$=CH), 5.80 (1 H, d, J 3.0, CH=CO) and 6.00 (1 H, d, J 3.0, CHCO); δ$_{C}$(100 MHz; CDCl$_3$) 18.4 (CHCH$_3$), 18.8 (CHCH$_3$), 24.5 (CH$_2$=CHCH$_2$CH$_2$), 27.9 (CH$_2$=CH(CH$_2$)$_2$CH$_2$), 28.4 (CH$_2$=CHCH$_2$), 33.3 (CH(CH$_3$)$_2$), 33.5 (CH$_2$=CH(CH$_2$)$_3$CH$_2$), 73.6 (CHOH), 105.1 (CH=CO), 107.1 (CHCO), 114.5 (CH$_2$=CH), 138.7 (CH$_2$=CH), 154.1 (CCHOH) and 155.7 (CH$_2$=CH(CH$_2$)$_4$C); MS (EI)
m/z 222.1 [M]+; HRMS m/z 222.1618 (222.1620 calcd for C\textsubscript{14}H_{22}O\textsubscript{2}, M+). The spectral data matches that reported in the literature\textsuperscript{[157]}

\((E/Z)-2\text{-Methyl-1-}(5-(4-(\text{trimethylsilyl})\text{-but-2-enyl})\text{furan-2-yl})\text{propan-1-ol} \text{ 561}\)

Anhydrous dichloromethane (5 cm\textsuperscript{3}) was added to a mixture of alkene 558 (107 mg, 0.764 mmol) and allyltrimethylsilane (0.36 cm\textsuperscript{3}, 2.29 mmol). The reaction mixture was heated to reflux under an argon atmosphere after which Grubbs second generation catalyst (32 mg, 0.0382 mmol) was added. The reaction mixture was heated under reflux in the dark for 48 h, cooled to room temperature and the solvent concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (90:10)] of the crude residue afforded allylsilane 561 (72 mg, 36%) as a yellow oil and as an inseparable E:Z mixture (7:2); \(R_f\) 0.61; \(\nu_{\text{max}}\,\text{(film)}/\text{cm}^{-1}\) 3433 (OH), 2962, 1681 (C=C), 1249 and 1018 (O-Si); \(\delta\,\text{H}\) (400 MHz; CDCl\textsubscript{3}) (E isomer) 0.01 (9 H, s, Si(C\textsubscript{3}H\textsubscript{3})) 0.86 (3 H, d, J 6.8, CHCH\textsubscript{3}), 1.03 (3 H, d, J 6.8, CHCH\textsubscript{3}), 1.46 (2 H, dd, J 1.2 and 8.0, CH\textsubscript{2}TMS), 1.78 (1 H, d, J 5.2, OH), 2.05-2.15 (1 H, m, CH(CH\textsubscript{3})\textsubscript{2}), 3.32 (2 H, dd, J 6.8 and 11.8, CH\textsubscript{2}), 4.30 (1 H, dd, J 5.2 and 7.2, CHOH), 5.30-5.60 (2 H, m, \(J\textsc{trans}\) 15.1, CH=CH), 5.99 (1 H, d, J 3.3, CH=CO) and 6.12 (1 H, d, J 3.3, CHCO); \(\delta\,\text{C}\) (100 MHz; CDCl\textsubscript{3}) -1.5 (3\times CH\textsubscript{3}), 15.5 (2\times CH\textsubscript{3}), 24.3 (TMSCH\textsubscript{2}), 31.8 (CH\textsubscript{2}), 35.0 (HC(CH\textsubscript{3})\textsubscript{2}), 74.5 (HCOH), 106.8 (CH), 109.1 (CH), 127.8 (CH=CH), 144.5 (CH=CH\textsubscript{2}) and 151.1 (CHCOH); MS (FAB) m/z 249 [M-OH]+; HRMS m/z 249.1670 (249.1675 calcd for C\textsubscript{15}H\textsubscript{25}OSi, M-OH+).

\(2\text{-Methyl-1-}[5-(\text{(E/Z)-5-trimethylsilanyl-pent-3-enyl})\text{-furan-2-yl}]\text{-propan-1-ol} \text{ 449}\)

Anhydrous dichloromethane (5 cm\textsuperscript{3}) was added to a mixture of alkene 450 (123 mg, 0.632 mmol) and allyltrimethylsilane (0.30 cm\textsuperscript{3}, 1.89 mmol) and the reaction heated to reflux after which Grubbs second generation catalyst (27 mg, 0.0316 mmol) was added. The reaction mixture was heated under reflux in the dark for 48 h, cooled and the solvent concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (90:10)] of the crude residue afforded allylsilane 449 (92 mg, 52%) as a yellow oil and as an inseparable mixture E:Z-mixture.
(6.15:1); ν\textsubscript{max}(film)/cm\textsuperscript{-1} 3441 (OH), 2955, 1689 (C=C), 1250 and 1041 (O-Si); δ\textsubscript{H}(400 MHz; CDCl\textsubscript{3}) 0.04 (9 H, s, (Si(CH\textsubscript{3})\textsubscript{3}), 0.88 (3 H, d, J 6.8, CHCH\textsubscript{3}), 1.07 (3 H, d, J 6.8, CHCH\textsubscript{3}), 1.42 (2 H, d, J 7.9, CH\textsubscript{TMS}T), 2.12 (1 H, sext., J 6.8, CH(CH\textsubscript{3})\textsubscript{2}), 2.34 (2 H, q, J 7.0, CH\textsubscript{2}CH\textsubscript{2}), 2.67 (2 H, t, J 7.0, CH\textsubscript{2}CH\textsubscript{2}), 4.32-4.34 (1 H, m, CHOH), 5.24-5.50 (2 H, m, J\textsuperscript{trans} 15.0, CH=CH\textsubscript{2}), 5.94 (1 H, d, J 3.1, CH=CO) and 6.13 (1 H, d, J 3.1, CHCO); δ\textsubscript{C}(100 MHz; CDCl\textsubscript{3}) q1.7 (3 × CH\textsubscript{3}), 15.8 (2 × CH\textsubscript{3}), 24.3 (TMS\textsubscript{CH\textsubscript{2}}), 28.5 (CH\textsubscript{2}CH\textsubscript{2}), 31.9 (CH\textsubscript{2}CH\textsubscript{2}), 35.0 (HC(CH\textsubscript{3})\textsubscript{2}), 74.5 (HCOH), 106.8 (CH), 109.1 (CH), 127.8 (CH=CH), 149.5 (CH\textsubscript{2}C) and 151.6 (CHCOH); MS (Cl) m/z 263.3 [M-OH]\textsuperscript{+}, 279.3 [M-H]\textsuperscript{+}; HRMS m/z 280.1763 (280.1859 calcd for C\textsubscript{16}H\textsubscript{28}O\textsubscript{2}Si, M\textsuperscript{+}).

2-Methyl-1-[5-((E/Z)-6-trimethylsilyl-hex-4-enyl)-furan-2-yl]-propan-1-ol

Anhydrous dichloromethane (5 cm\textsuperscript{3}) was added to 559 (200 mg, 0.960 mmol) and allyltrimethylsilane (0.53 cm\textsuperscript{3}, 3.36 mmol) and the reaction heated to reflux after which Grubbs second generation catalyst (41 mg, 0.048 mmol) was added. The reaction mixture was heated under reflux in the dark for 48 h, cooled and the solvent concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (90:10)] of the crude residue afforded 562 (127 mg, 45%) as a yellow oil and as an inseparable E:Z mixture (2:1); R\textsubscript{f} 0.52 (Solvent A); ν\textsubscript{max}(film)/cm\textsuperscript{-1} 3394 (OH), 2955, 1249, 1010 (O-Si) and 964; δ\textsubscript{H}(400 MHz; CDCl\textsubscript{3}) 0.00 (9 H, s, (Si(CH\textsubscript{3})\textsubscript{3}), 0.86 (3 H, d, J 6.8, CH(CH\textsubscript{3})), 1.03 (3 H, d, J 6.8, CH(CH\textsubscript{3})), 1.42 (2 H, t, J 7.0, CH\textsubscript{2}), 1.62-1.79 and 2.00-2.20 (6 H, 2 × m, 3 × CH\textsubscript{2}), 2.59-2.65 (1 H, m, CH(CH\textsubscript{3})\textsubscript{2}), 4.27-4.32 (1 H, m, CHOH), 5.20-5.29 (1 H, m, CH=CH), 5.38-5.44 (1 H, m, CH=CH), 5.91 (1 H, d, J 3.0, CH=CO) and 6.10 (1 H, d, J 3.0, CHCO); δ\textsubscript{C}(100 MHz; CDCl\textsubscript{3}) -1.7 (3 × CH\textsubscript{3}), 16.0 (2 × CH\textsubscript{3}), 24.4 (TMS\textsubscript{CH\textsubscript{2}}), 28.6 (CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 29.4 (CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 34.8 (HC(CH\textsubscript{3})\textsubscript{2}), 38.6 (CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 74.8 (HCOH), 106.6 (CH), 109.0 (CH), 127.8 (CH=CH), 149.4 (CH\textsubscript{2}C) and 151.6 (CHCOH); MS (Cl) m/z 263.3 [M-OH]\textsuperscript{+}, 279.3 [M-H]\textsuperscript{+}; HRMS m/z 280.1763 (280.1859 calcd for C\textsubscript{16}H\textsubscript{28}O\textsubscript{2}Si, M\textsuperscript{+})

2-Methyl-1-[5-((E/Z)-6-trimethylsilyl-hex-4-enyl)-furan-2-yl]-propan-1-ol

Anhydrous dichloromethane (5 cm\textsuperscript{3}) was added to 559 (200 mg, 0.960 mmol) and allyltrimethylsilane (0.53 cm\textsuperscript{3}, 3.36 mmol) and the reaction heated to reflux after which Grubbs second generation catalyst (41 mg, 0.048 mmol) was added. The reaction mixture was heated under reflux in the dark for 48 h, cooled and the solvent concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (90:10)] of the crude residue afforded 562 (127 mg, 45%) as a yellow oil and as an inseparable E:Z mixture (2:1); R\textsubscript{f} 0.52 (Solvent A); ν\textsubscript{max}(film)/cm\textsuperscript{-1} 3394 (OH), 2955, 1249, 1010 (O-Si) and 964; δ\textsubscript{H}(400 MHz; CDCl\textsubscript{3}) 0.00 (9 H, s, (Si(CH\textsubscript{3})\textsubscript{3}), 0.86 (3 H, d, J 6.8, CH(CH\textsubscript{3})), 1.03 (3 H, d, J 6.8, CH(CH\textsubscript{3})), 1.42 (2 H, t, J 7.0, CH\textsubscript{2}), 1.62-1.79 and 2.00-2.20 (6 H, 2 × m, 3 × CH\textsubscript{2}), 2.59-2.65 (1 H, m, CH(CH\textsubscript{3})\textsubscript{2}), 4.27-4.32 (1 H, m, CHOH), 5.20-5.29 (1 H, m, CH=CH), 5.38-5.44 (1 H, m, CH=CH), 5.91 (1 H, d, J 3.0, CH=CO) and 6.10 (1 H, d, J 3.0, CHCO); δ\textsubscript{C}(100 MHz; CDCl\textsubscript{3}) -1.7 (3 × CH\textsubscript{3}), 16.0 (2 × CH\textsubscript{3}), 24.4 (TMS\textsubscript{CH\textsubscript{2}}), 28.6 (CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 29.4 (CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 34.8 (HC(CH\textsubscript{3})\textsubscript{2}), 38.6 (CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 74.8 (HCOH), 106.6 (CH), 109.0 (CH), 127.8 (CH=CH), 149.4 (CH\textsubscript{2}C) and 151.6 (CHCOH); MS (Cl) m/z 263.3 [M-OH]\textsuperscript{+}, 279.3 [M-H]\textsuperscript{+}; HRMS m/z 280.1763 (280.1859 calcd for C\textsubscript{16}H\textsubscript{28}O\textsubscript{2}Si, M\textsuperscript{+}).
6-Hydroxy-2-isopropyl-6-((E)-5-trimethylsilyl-pent-3-enyl)-6H-pyran-3-one

Procedure A

To a solution of alcohol 449 (64 mg, 0.228 mmol) in anhydrous dichloromethane (5 cm³) was added meta-chloroperoxybenzoic acid (mCPBA) (56 mg, 0.251 mmol) at 0 °C. The reaction was allowed to warm up to room temperature and left to stir overnight. An extra portion of meta-chloroperoxybenzoic acid (mCPBA) (28 mg, 0.125 mmol) was added and the solution was stirred overnight. The reaction mixture was diluted with dichloromethane (5 cm³) and saturated aqueous sodium hydrogen carbonate (5 cm³). The organic layer was separated and washed with water (5 cm³), brine (5 cm³) and dried over anhydrous sodium sulfate. The solution was then filtered and concentrated in vacuo. Purification by FCC [petroleum ether-ethyl acetate (80:20)] of the crude residue caused product degradation. Product 448 seen at Rf 0.34 (Solvent B).

Procedure B

To a solution of alcohol 449 (44.4 mg, 0.158 mmol) in dry dichloromethane (1.5 cm³) at 0 °C, was added vanadyl acetylacetonate (VO(acac)₂) (4.2 mg, 0.0158 mmol). The solution turned instantly green and tert-butyl hydroperoxide (TBHP) (40 µL, 0.237 mmol) was then added dropwise. The now dark red reaction mixture was stirred for 2 h at 0 °C, then filtered through a pad of Celite® and the filtrate concentrated in vacuo. Purification of the crude residue by FCC [petroleum ether-ethyl acetate (80:20)] afforded pyrone 448 (4.1 mg, 8.7%); Rf 0.42 (Solvent A); νmax(film)/cm⁻¹ 3423, 2960, 1686, 1248 and 841; δH (400 MHz, CDCl₃) 0.00 (9 H, s, Si(CH₃)₃), 0.82 (3 H, d, J 6.7, CH(CH₃)), 1.05 (3 H, d, J 6.7, CH(CH₃)), 1.42-1.44 (2 H, m, CH₂), 1.90 (2 H, t, J 2.8, CH=CHCH₂CH₂), 2.42-2.50 (2 H, m, CH=CHCH₂CH₂), 4.33-4.38 (1 H, m, (CO)CH), 5.32-5.40 (1 H, m, CH=CH), 5.49-5.53 (1 H, m, CH=CH), 6.03-6.08 (1 H, m, CH=CH(CO)) and 6.74-6.80 (1 H, m, CH=CH(CO)); δC(100 MHz; CDCl₃) -1.5 (3×CH₃), 18.5 (2×CH₃), 21.6
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(\text{HC=CHCH}_2\text{CH}_2), 25.2 (\text{CH}_2), 28.6 (\text{C(CH}_3_2)), 45.0 (\text{HC=CHCH}_2\text{CH}_2), 90.5 (\text{HCO}), 93.4 (\text{COH}), 126.0 (\text{HC=CH and HC=CHCO}), 144.3 (\text{HC=CHCO}) and 196.9 (\text{C=O}); \text{MS (Cl) } m/z 297.3 [M+H]^+; \text{HRMS } m/z 297.1888 (297.1886 \text{ calcd for } C_{16}H_{29}O_3\text{Si, M+H}^+)\).

\text{7-Isopropyl-1-vinyl-6-oxa-spiro[4.5]dec-9-en-8-one 447}

To a stirred solution of allylsilane 449 (90 mg, 0.321 mmol) in dry dichloromethane (3 cm$^3$) was added vanadyl acetylacetonate (VO(acac)$_2$) (8.5 mg, 0.0321 mmol) at 0 °C. The solution turned instantly green and tert-butyl hydroperoxide (TBHP) (0.08 cm$^3$, 0.481 mmol) was added dropwise. The dark red solution was stirred for 1.5 h at 0 °C then allowed to warm up to room temperature and filtered through Celite®. The solvent was concentrated \textit{in vacuo} to ~1 cm$^3$ and then dry dichloromethane (2 cm$^3$) was added and the solution cooled down to −78 °C. Boron trifluorodiethyletherate (BF$_3$·OEt$_2$) (0.12 cm$^3$, 0.962 mmol) was added slowly and stirring continued for 30 min at −78 °C. The reaction mixture was allowed to warm up to room temperature and was then quenched with saturated aqueous ammonium chloride (5 cm$^3$) and extracted with dichloromethane (2×7 cm$^3$). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (10 cm$^3$), water (10 cm$^3$) and saturated aqueous ammonium chloride (10 cm$^3$), then dried over anhydrous sodium sulfate, filtered and concentrated \textit{in vacuo}. Purification by FCC [petroleum ether-ethyl acetate (95:5) then (50:50)] of the crude residue afforded bicyclic pyran 447 (5.4 mg, −1%); $\nu_{\text{max}}$(film)/cm$^{-1}$ 2973, 2253, 1737, 1265 and 1095; $\delta_H$(400 MHz; CDCl$_3$) 0.76 (3 H, d, $J$ 6.8, CH$_3$), 1.10 (3 H, d, $J$ 6.8, CH$_3$), 0.80-1.04 and 1.16-1.76 (6 H, 2×m, 3×CH$_2$), 2.12-2.64 (2 H, m, CH(CH$_3$)$_2$ and HCCH=CH$_2$), 4.05 (1 H, dd, $J$ 2.8 and 4.4, (OCH)), 5.04 (2 H, dd, $J$ 7.7 and 13.5, CH=CH$_2$), 5.60-5.68 (1 H, m, CH=CH$_2$), 5.91 (1 H, d, $J$ 10.0, CH=CH(CO)) and 6.70 (1 H, d, $J$ 10.0, CH=CH(CO)); $\delta_C$(100 MHz; CDCl$_3$) 18.4 ((CH$_3$)$_2$), 23.6 (CH$_2$CH$_2$CH$_2$), 28.4 (CH$_3$CH$_2$CH$_2$), 28.9 (C(CH$_3$)$_2$), 39.2 (CH$_2$CH$_2$CH$_2$), 51.5 (CCH=CH), 80.9 (C), 94.1 (CC(CH$_3$)$_2$), 116.9 (CH=CH), 132.6 (HC=CHCO), 138.0 (CH=CH), 147.1 (HC=CHCO) and 196.1 (C=O).
List of References


34. K. Yoshimura, M. Yamane and S. Harada, JP 08040893


49. (a) N. Henry, M. N. Robertson and R. Marquez, *Tetrahedron Lett.*, 2007, 48, 6088-6091; (b) N. Henry, personal communication


53. www.mims.co.uk, accessed 10th February 2010


59. www.nhs.co.uk, accessed 16th March 2010

60. F. Bulkwill and A. Mantovani, *Lancet*, 2002, 357, 539-545


103. www.nobelprize.org, accessed 3rd October 2009


140. S. J. Hobson, PhD Thesis, University of Glasgow, 2010


185. T-L. Ho and S. G. Sapp, *Synthetic Communications*, 1983, 13, 297-211


212. (a) D. P. Furkert and S. M. Husbands, Proceedings of the 18th RSC Lakeland Symposium on Heterocyclic Chemistry, Grasmere, 2007; (b) D. P. Furkert and S. M. Husbands, Org. Lett., 2007, 9, 3769-3771


